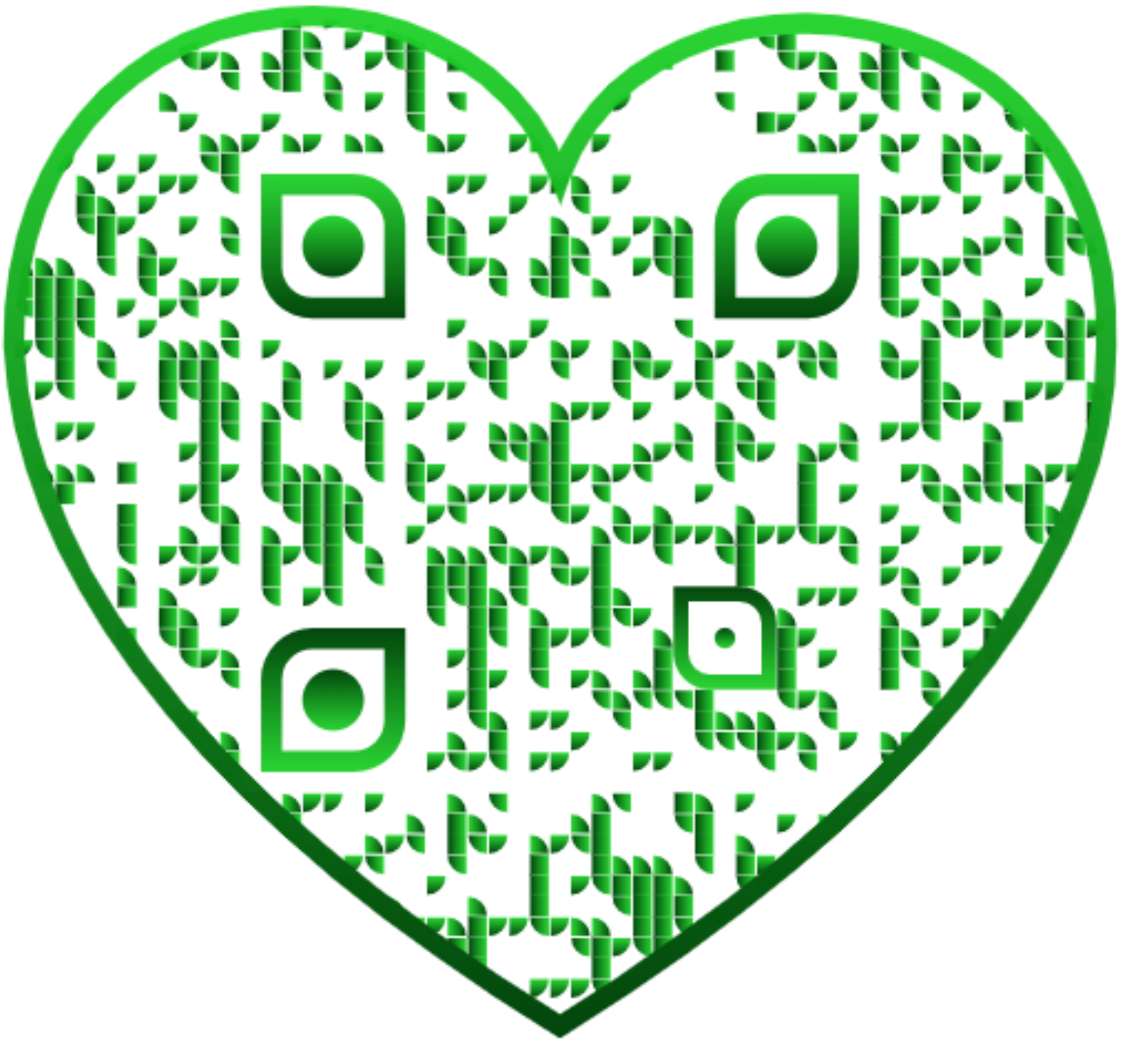
ELEVENTH EDITION

PHARMACOTHERAPY

A Pathophysiologic Approach

Joseph T. DiPiro • Gary C. Yee • L. Michael Posey
Stuart T. Haines • Thomas D. Nolin • Vicki Ellingrod

Mc Graw Hill



PAST EDITORS OF *PHARMACOTHERAPY*

Peggy E. Hayes, PharmD

Editions 1 and 2

Gary R. Matzke, PharmD, FCP, FCCP, FASN, FNAP

Editions 2–10

Robert L. Talbert, PharmD, FCCP, BCPS, FAHA

Editions 1–10

Barbara G. Wells, PharmD, FCCP, FASHP

Editions 3–10

11 TH EDITION

PHARMACOTHERAPY

A PATHOPHYSIOLOGIC APPROACH

Editors

Joseph T. DiPiro, PharmD
Dean and Professor, Archie O. McCalley Chair
School of Pharmacy, Virginia Commonwealth University
Richmond, Virginia

Gary C. Yee, PharmD, FCCP
Associate Vice Chancellor for Academic Affairs
Professor, Department of Pharmacy Practice and Science
University of Nebraska Medical Center
Omaha, Nebraska

L. Michael Posey, BSPharm, MA
President, PENS Pharmacy Editorial & News Services
Santa Rosa, California

Stuart T. Haines, PharmD, BCPS, BCACP
Professor, Department of Pharmacy Practice
Director, Pharmacy Professional Development
School Pharmacy, University of Mississippi School
Jackson, Mississippi

Thomas D. Nolin, PharmD, PhD, FCCP, FCP, FASN
Associate Professor
Department of Pharmacy and Therapeutics,
Center for Clinical Pharmaceutical Sciences
Department of Medicine, Renal-Electrolyte Division
Schools of Pharmacy and Medicine, University of Pittsburgh
Pittsburgh, Pennsylvania

Vicki L. Ellingrod, PharmD, FCCP
Associate Dean for Research and Graduate Education
John Gideon Searle Professor of Pharmacy, College of Pharmacy
Professor of Psychiatry, Medical School
University of Michigan
Ann Arbor, Michigan

New York Chicago San Francisco Athens London Madrid Mexico City Milan New Delhi Singapore Sydney Toronto

Copyright © 2020 by McGraw Hill. All rights reserved. Except as permitted under the United States Copyright Act of 1976, no part of this publication may be reproduced or distributed in any form or by any means, or stored in a database or retrieval system, without the prior written permission of the publisher.

ISBN: 978-1-26-011682-3
MHID: 1-26-011682-4

The material in this eBook also appears in the print version of this title: ISBN: 978-1-26-011681-6, MHID: 1-26-011681-6.

eBook conversion by codeMantra
Version 1.0

All trademarks are trademarks of their respective owners. Rather than put a trademark symbol after every occurrence of a trademarked name, we use names in an editorial fashion only, and to the benefit of the trademark owner, with no intention of infringement of the trademark. Where such designations appear in this book, they have been printed with initial caps.

McGraw-Hill Education eBooks are available at special quantity discounts to use as premiums and sales promotions or for use in corporate training programs. To contact a representative, please visit the Contact Us page at www.mhprofessional.com.

Notice

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular,

readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

TERMS OF USE

This is a copyrighted work and McGraw-Hill Education and its licensors reserve all rights in and to the work. Use of this work is subject to these terms. Except as permitted under the Copyright Act of 1976 and the right to store and retrieve one copy of the work, you may not decompile, disassemble, reverse engineer, reproduce, modify, create derivative works based upon, transmit, distribute, disseminate, sell, publish or sublicense the work or any part of it without McGraw-Hill Education's prior consent. You may use the work for your own noncommercial and personal use; any other use of the work is strictly prohibited. Your right to use the work may be terminated if you fail to comply with these terms.

THE WORK IS PROVIDED "AS IS." McGRAW-HILL EDUCATION AND ITS LICENSORS MAKE NO GUARANTEES OR WARRANTIES AS TO THE ACCURACY, ADEQUACY OR COMPLETENESS OF OR RESULTS TO BE OBTAINED FROM USING THE WORK, INCLUDING ANY INFORMATION THAT CAN BE ACCESSED THROUGH THE WORK VIA HYPERLINK OR OTHERWISE, AND EXPRESSLY DISCLAIM ANY WARRANTY, EXPRESS OR IMPLIED, INCLUDING BUT NOT LIMITED TO IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. McGraw-Hill Education and its licensors do not warrant or guarantee that the functions contained in the work will meet your requirements or that its operation will be uninterrupted or error free. Neither McGraw-Hill Education nor its licensors shall be liable to you or anyone else for any inaccuracy, error or omission, regardless of cause, in the work or for any damages resulting therefrom. McGraw-Hill Education has no responsibility for the content of any information accessed through the work. Under no circumstances shall McGraw-Hill Education and/or its licensors be liable for any indirect, incidental, special, punitive, consequential or similar damages that result from the use of or inability to use the work, even if any of them has been advised of the possibility of such damages. This limitation of liability shall apply

to any claim or cause whatsoever whether such claim or cause arises in contract, tort or otherwise.

Dedication

To our patients and students, who have challenged and inspired us and given meaning to all our endeavors.

To practitioners who continue to improve patient health outcomes and thereby serve as role models for their colleagues and students while clinging tenaciously to the highest standards of practice.

To our mentors, whose vision provided educational and training programs that encouraged our professional growth and challenged us to be innovators in our patient care, research, and education.

To our faculty colleagues for their efforts and support for our mission to provide a comprehensive and challenging educational foundation for the pharmacists of the future.

And finally to our families for the time that they have sacrificed so that this 11th edition would become a reality.

—The Editors

In Memoriam—Brian S. Decker, MD, PharmD, MS

Brian S. Decker (1963-2018), a coauthor of the "Hemodialysis and Peritoneal Dialysis" chapter in *Pharmacotherapy* since its eighth edition in 2012, received his BS in Wildlife Sciences and Pharmacy and PharmD degrees from Purdue University. He received his MD degree from Indiana University School of Medicine in 2003, and he completed a residency in Internal Medicine and Fellowships in Nephrology and Clinical Pharmacology at IU.

In 2007, Brian joined the faculty in the Indiana University School of Medicine in the Divisions of Nephrology and Clinical Pharmacology, and he simultaneously served as an Affiliate Faculty member in the Purdue University College of Pharmacy. During his time as a faculty member, he earned a MS in clinical research. Brian was an avid teacher of nephrology, pharmacology, and pharmacogenomics to trainees from both IU and Purdue.

Brian directed the Nephrology Fellowship Training Program, fostered Nephrology student interest groups, and was an active member of the IU Academy of Teaching Scholars. He was also very active locally and nationally in Nephrology and Pharmacology societies and in the local community.

Brian's knowledge of pharmacy and medicine was evident through his ability to further our understanding of nephrology. His unique perspective was apparent in his contribution to the Hemodialysis and Peritoneal Dialysis chapter where he provided key treatment details in a manner that was understandable and clinically relevant. As his coauthors, we will miss his knowledge, clinical experience, and perspective.

Kevin M. Sowinski, PharmD, FCCP
Mariann D. Churchwell, PharmD, FCCP

Contents

Contributors
Foreword
Preface

SECTION 1 Foundation Issues

Section Editor: *Stuart T. Haines, L. Michael Posey, and Thomas D. Nolin*

1. The Patient Care Process
   Stuart T. Haines, Mary Ann Kliethermes, and Todd Sorensen

e2. Health Literacy and Medication Use
   Oralia V. Bazaldua, DeWayne A. Davidson, Ashley Zurek, and Sunil Kripalani

e3. Cultural Competency
   Jeri J. Sias, Amanda M. Loya, José O. Rivera, and Jessica M. Shenberger-Trujillo

e4. Medication Safety Principles and Practices
   Robert J. Weber

e5. Clinical Pharmacokinetics and Pharmacodynamics
   Larry A. Bauer

e6. Pharmacogenetics
   Larisa H. Cavallari and Y. W. Francis Lam

e7. Clinical Toxicology
   Bryan D. Hayes and Peter A. Chyka

SECTION 2 Common Health Problems

Section Editor: *L. Michael Posey, Joseph T. DiPiro, and Vicki L. Ellingrod*

e8. Fever
Jamal Brown and Jenay Kyles

e9. Pain and Headache
Ryan Costantino, Christopher D. Kearney, and Kathryn A. Walker

e10. Minor Ophthalmic Disorders
Jared Ostroff

e11. Minor Otic Disorders
Lea S. Eiland

e12. Cough and Other Nonspecific Respiratory Symptoms
Brandon James Sucher

e13. Allergic Rhinitis
J. Russell May

e14. Oral Health and Systemic Conditions
Lisa M. Palmisano and Jennifer L. Mazan

e15. Oral Hygiene and Minor Oral Disorders
Anna Milone, Kristyn Williamson, and Maren Hall

e16. Skin Care and Minor Dermatologic Conditions
Rebecca M. Law and Howard I. Maibach

e17. Travel Health
Douglas Slain and Scott E. Kincaid

18. Contraception
Shareen Y. El-Ibiary, Sarah P. Shrader, and Kelly R. Ragucci

SECTION 3 Special Populations

Section Editor: *L. Michael Posey and Thomas D. Nolin*

e19. Pediatrics: General Topics in Pediatric Pharmacotherapy
Milap C. Nahata and Carol Taketomo

e20. Pediatrics: Oral Nutrition and Rehydration of Infants and Children
Katherine H. Chessman

e21. Pediatrics: Neonatal Critical Care
Kirsten H. Ohler and Jennifer T. Pham

e22. Geriatrics: The Aging Process in Humans and Its Effects on Physiology
Krista L. Donohoe, Elvin T. Price, Tracey L. Gendron, and Patricia W. Slattum

e23. Prescribing in the Older Adult
Emily R. Hajjar, Lauren R. Hersh, and Shelly L. Gray

e24. Assessing Health and Delivering HealthCare to Older Adults
Leigh Ann Mike, Zachary A. Marcum, and Shelly L. Gray

e25. Critical Care: General Topics in Critical Care
Adrian Wong and Sandra L. Kane-Gill

e26. Critical Care: Pain, Agitation, and Delirium
Gilles L. Fraser and Richard R. Riker

e27. Critical Care: Considerations in Drug Selection, Dosing, Monitoring, and Safety
Erin F. Bareto and Amy L. Dzierba

e28. Palliative Care
Nina M. Bemben and Mary Lynn McPherson

SECTION 4 Cardiovascular Disorders

Section Editor: *Stuart T. Haines*

e29. Assessment of the Cardiovascular System
Brent N. Reed, Kristin E. Watson, and Gautam Ramani

30. Hypertension
Eric J. MacLaughlin and Joseph J. Saseen

31. Dyslipidemia
Dave L. Dixon and Daniel M. Riche

32. Stable Ischemic Heart Disease
Paul Dobesh, Robert J. DiDomenico, and Kelly C. Rogers

33. Acute Coronary Syndrome
Robert J. DiDomenico, Paul P. Dobesh, and Shannon W. Finks

e34. Peripheral Arterial Disease
Zachary Stacy and Sheryl Chow

35. Chronic Heart Failure
Robert B. Parker, Jean M. Nappi, and Larisa H. Cavallari

36. Acute Decompensated Heart Failure
Brent N. Reed and Jo E. Rodgers

37. Venous Thromboembolism
Daniel M. Witt, Nathan Clark, and Sara R. Vazquez

38. Stroke
Melody Ryan and Melissa Nestor

39. The Arrhythmias
Jessica J. Tilton, Cynthia Sanoski, and Jerry L. Bauman

40. Cardiac Arrest
Jeffrey F. Barletta

41. Shock Syndromes
Seth R. Bauer, Robert MacLaren, and Brian L. Erstad

SECTION 5 Respiratory Disorders

Section Editor: *Stuart T. Haines*

e42. Evaluation of Respiratory Function
Maria I. Velez, Tamara D. Simpson, Stephanie M. Levine, and Jay I. Peters

43. Asthma
Kathryn V. Blake and Jason E. Lang

44. Chronic Obstructive Pulmonary Disease
Sharya V. Bourdet and Dennis M. Williams

45. Pulmonary Arterial Hypertension
Rebecca Moote, Rebecca L. Attridge, and Deborah J. Levine

46. Cystic Fibrosis
Chanin C. Wright and Yolanda Vera

e47. Drug-Induced Pulmonary Diseases
Hengameh H. Raissy and Michelle S. Harkins

SECTION 6 Gastrointestinal Disorders

Section Editor: *Joseph T. DiPiro*

e48. Evaluation of the Gastrointestinal Tract
Keith M. Olsen and Rachael V. McCaleb

49. Gastroesophageal Reflux Disease
Dianne May, Michael L. Thiman, and Satish S.C. Rao

50. Peptic Ulcer Disease and Related Disorders
Bryan L. Love and Phillip L. Mohorn

51. Inflammatory Bowel Disease
Brian A. Hemstreet

52. Nausea and Vomiting
Leigh Anne Hylton Gravatt, Krista L. Donohoe, and Mandy L. Gatesman

53. Diarrhea, Constipation, and Irritable Bowel Syndrome
Patricia H. Fabel and Kayce Shealy

54. Portal Hypertension and Cirrhosis
Julie M. Sease and Alyson G. Wilder

e55. Drug-Induced Liver Disease
William R. Kirchain and Rondall E. Allen

56. Pancreatitis
Scott Bolesta and Patricia A. Montgomery

57. Viral Hepatitis
Paulina Deming

58. Celiac Disease
Priti N. Patel and Robert A. Mangione

SECTION 7 Renal Disorders

Section Editor: *Thomas D. Nolin*

e59. Evaluation of Kidney Function
Thomas C. Dowling

60. Acute Kidney Injury
Jenana Halilovic Maker, Lauren Roller, and William E. Dager

61. Chronic Kidney Disease
Joanna Q. Hudson, Lori D. Wazny, and Paul Komenda

62. Hemodialysis and Peritoneal Dialysis
Kevin M. Sowinski, Mariann D. Churchwell, and Brian S. Decker

63. Drug-Induced Kidney Disease
Thomas D. Nolin and Mark A. Perazella

64. Glomerular Diseases
Jonathan J. Hogan and Alan H. Lau

65. Drug Therapy Individualization for Patients with Chronic Kidney Disease
Marisa Battistella and Thomas D. Nolin

66. Disorders of Sodium and Water Homeostasis
Katherine H. Chessman and Jason S. Haney

67. Disorders of Calcium and Phosphorus Homeostasis
Amy Barton Pai and Angela L. Bingham

68. Disorders of Potassium and Magnesium Homeostasis
Rachel W. Flurie

69. Acid–Base Disorders
John W. Devlin and Thomas D. Nolin

SECTION 8 Neurologic Disorders

Section Editor: *Vicki L. Ellingrod*

e70. Evaluation of Neurologic Illness
Melody Ryan and Stephen J. Ryan

71. Alzheimer Disease
Emily P. Peron, Kristin M. Zimmerman, Ericka L. Crouse, Patricia W. Slattum, and Sarah E. Hobgood

72. Multiple Sclerosis
Jacquelyn L. Bainbridge, Augusto Miravalle, Pei Shieen Wong, and Matthew J. Makelky Sr.

73. Epilepsy
Viet-Huong V. Nguyen, Sunita Dergalust, and Edward Chang

74. Status Epilepticus
Stephanie J. Phelps and James W. Wheless

75. Acute Management of the Brain Injury Patient
Bradley A. Boucher and G. Christopher Wood

76. Parkinson Disease
Jack J. Chen and Khashayar Dashtipour

77. Pain Management
Chris M. Herndon, James B. Ray, and Courtney M. Kominek

78. Headache Disorders
T. Kristopher Harrell and Deborah S. Minor

SECTION 9 Psychiatric Disorders

Section Editor: *Vicki L. Ellingrod*

e79. Evaluation of Psychiatric Disorders
Mark E. Schneiderhan, Leigh Anne Nelson, Jeffrey R. Bishop and Steven Bauer

80. Attention Deficit/Hyperactivity Disorder
Julie A. Dopheide, Danielle L. Stutzmann, and Steven R. Pliszka

81. Eating Disorders
Steven C. Stoner, Valerie L. Ruehter, and Melissa C. Palmer

82. Substance Use Disorders I: Depressants, Stimulants, and Hallucinogens
Robin Moorman Li, Patrick Leffers, and Paul L. Doering

83. Substance-Related Disorders II: Alcohol, Nicotine, and Caffeine
Robin Moorman Li, Lori Dupree, and Paul L. Doering

84. Schizophrenia
M. Lynn Crismon, Tawny Smith, and Peter F. Buckley

85. Major Depressive Disorder
Amy M. VandenBerg

86. Bipolar Disorder
Shannon J. Drayton and Christopher S. Fields

87. Anxiety Disorders: Generalized Anxiety, Panic, and Social Anxiety Disorders
Sarah T. Melton and Cynthia K. Kirkwood

88. Posttraumatic Stress Disorder and Obsessive-Compulsive Disorder
Kristen N. Gardner, Jolene R. Bostwick, and Ericka L. Crouse

89. Sleep–Wake Disorders
John M. Dopp and Bradley G. Phillips

90. Intellectual and Developmental Disabilities: Down Syndrome and Autism Spectrum Disorder
Steven R. Erickson

SECTION 10 Endocrinologic Disorders

Section Editor: *Stuart T. Haines*

91. Diabetes Mellitus

Jennifer Trujillo and Stuart T. Haines

92. Thyroid Disorders
Michael P. Kane and Gary Bakst

93. Adrenal Gland Disorders
Steven M. Smith, Scott G. Garland, and John G. Gums

e94. Pituitary Gland Disorders
Joseph K. Jordan, Amy Heck Sheehan, and Kashif M. Munir

SECTION 11 Gynecologic and Obstetric Disorders

Section Editor: *Vicki L. Ellingrod*

95. Pregnancy and Lactation: Therapeutic Considerations
Julie J. Kelsey and Kristina E. Ward

96. Menstruation-Related Disorders
Kai I. Cheang and Elena M. Umland

97. Endometriosis
Kathleen Vest and Sarah E. Lynch

98. Hormone Therapy in Women
Devra K. Dang, Kathryn E. Wheeler, and Judy T. Chen

SECTION 12 Urologic Disorders

Section Editor: *L. Michael Posey*

99. Erectile Dysfunction
Mary Lee and Roohollah Sharifi

100. Benign Prostatic Hyperplasia
Mary Lee and Roohollah Sharifi

101. Urinary Incontinence
Eric S. Rovner, Jean F. Wyman, and Sum Lam

SECTION 13 Immunologic Disorders

Section Editor: *Gary C. Yee and Thomas D. Nolin*

e102. Function and Evaluation of the Immune System
Daniel A. Zlott and Geoffrey M. Thiele

103. Systemic Lupus Erythematosus
Beth H. Resman-Targoff

e104. Drug Allergy
Christopher M. Bland and Bruce M. Jones

105. Solid-Organ Transplantation
Douglas L. Jennings and Heather J. Johnson

SECTION 14 Rheumatologic Disorders

Section Editor: *L. Michael Posey and Thomas D. Nolin*

106. Osteoarthritis
Lucinda M. Buys and Sara A. Wiedenfeld

107. Rheumatoid Arthritis
Stephanie Gruber, Bianca Lezcano, and Susan Hylland

108. Osteoporosis
Mary Beth O'Connell, Jill S. Borchert, Erin M. Slazak, and Joseph P. Fava

109. Gout and Hyperuricemia
Michelle A. Fravel and Michael E. Ernst

SECTION 15 Ophthalmic Disorders

Section Editor: *L. Michael Posey*

110. Glaucoma
Richard G. Fiscella, Timothy S. Lesar, Ohoud A. Owaidhah, and Deepak P. Edward

111. Age-Related Macular Degeneration
Alisa K. Escano and Casey S. Washington

e112. Drug-Induced Ophthalmic Disorders
Rena Gosser

SECTION 16 Dermatologic Disorders

Section Editor: *L. Michael Posey*

113. Acne Vulgaris
Debra Sibbald

114. Psoriasis
Rebecca M. Law and Wayne P. Gulliver

115. Atopic Dermatitis
Rebecca M. Law, Wayne P. Gulliver, and Poh Gin Kwa

116. Alopecia
Rebecca M. Law, Le Hanh Dung Do, and Howard I. Maibach

e117. Dermatologic Drug Reactions, Contact Dermatitis, and Common Skin Conditions
Rebecca M. Law, David T.S. Law, and Howard I. Maibach

SECTION 17 Hematologic Disorders

Section Editor: *Gary C. Yee*

118. Anemias
Kristen M. Cook and Devon M. Greer

119. Coagulation Disorders
Heidi Trinkman, Timothy L. McCavit, and Lauren Duran

120. Sickle Cell Disease
C. Y. Jennifer Chan and Melissa Frei-Jones

e121. Drug-Induced Hematologic Disorders
Elisa M. Greene and Tracy M. Hagemann

SECTION 18 Infectious Diseases

Section Editor: *Joseph T. DiPiro*

e122. Laboratory Tests to Direct Antimicrobial Pharmacotherapy
Brian J. Werth, Katie E. Barber, Jordan R. Smith, and Michael J. Rybak

123. Antimicrobial Regimen Selection
Grace C. Lee and David S. Burgess

124. Central Nervous System Infections
Christina Koutsari , Thomas J. Dilworth, Jessica Holt, Ramy Elshaboury, and John C. Rotschafer

125. Lower Respiratory Tract Infections
Evan J. Zasowski and Martha Blackford

126. Upper Respiratory Tract Infections
Christopher R. Frei and Bradi L. Frei

127. Influenza
Jessica Njoku

128. Skin and Soft-Tissue Infections
Douglas N. Fish

129. Infective Endocarditis
Daniel B. Chastain and Angie Veverka

130. Tuberculosis
Rocsanna Namdar and Charles Peloquin

131. Gastrointestinal Infections and Enterotoxigenic Poisonings
Andrew M. Roecker and Brittany N. Bates

132. Intra-Abdominal Infections
Alan E. Gross and Keith M. Olsen

e133. Parasitic Diseases
Jason M. Cota

134. Urinary Tract Infections and Prostatitis
Julianna M. Fernandez and Elizabeth A. Coyle

135. Sexually Transmitted Infections
Bryson Duhon and Yvonne J. Burnett

136. Bone and Joint Infections
Scott J. Bergman and Edward P. Armstrong

137. Sepsis and Septic Shock
S. Lena Kang-Birken and Sul R. Jung

138. Superficial Fungal Infections
Thomas E. R. Brown and Linda Dresser

139. Invasive Fungal Infections
Peggy L. Carver

140. Infections in Immunocompromised Patients
Scott W. Mueller and Douglas N. Fish

141. Antimicrobial Prophylaxis in Surgery
Salmaan Kanji

142. Vaccines and Immunoglobulins
Mary S. Hayney

143. Human Immunodeficiency Virus Infection
Peter L. Anderson, Jenna Yager, and Courtney V. Fletcher

SECTION 19 Oncologic Disorders

Section Editor: *Gary C. Yee*

144. Cancer Treatment and Chemotherapy
Lisa M. Cordes and Stacy S. Shord

145. Breast Cancer
Bonnie Lin Boster, Neelam K. Patel, and Laura Boehnke Michaud

146. Lung Cancer
Val R. Adams and Keith A. Hecht

147. Colorectal Cancer
Lisa M. Holle, Jessica M. Clement, and Lisa E. Davis

148. Prostate Cancer
LeAnn B. Norris

149. Lymphomas
Alexandre Chan, Chia Jie Tan, and Jolynn Sessions

150. Ovarian Cancer
Emily B. Borders and Judith A. Smith

151. Acute Leukemias
David DeRemer and Tara Higgins

152. Chronic Leukemias
Patrick J. Kiel and Meagan Grove

153. Multiple Myeloma
Amy M. Pick and Kamakshi V. Rao

e154. Myelodysplastic Syndromes
Jill S. Bates

e155. Renal Cell Carcinoma
Daniel J. Crona and Amber B. Cipriani

156. Melanoma
Cindy L. O'Bryant, Jamie C. Poust, and Christina M. Davis

157. Hematopoietic Stem Cell Transplantation
Susanne Liewer and Janelle Perkins

SECTION 20 Nutritional Disorders

Section Editor: *Thomas D. Nolin*

158. Assessment of Nutrition Status and Nutrition Requirements
Katherine H. Chessman and Vanessa J. Kumpf

159. Parenteral Nutrition
Todd W. Mattox and Catherine M. Crill

160. Enteral Nutrition
Vanessa J. Kumpf and Diana W. Mulherin

161. Obesity
Amy Heck Sheehan, Judy T. Chen, and Jack A. Yanovski

Index

SI unit conversions were produced by Ed Randell, PhD, DCC, FCACB, Division

Chief and Professor of Laboratory Medicine, Department of Laboratory Medicine, Eastern Health Authority and Faculty of Medicine, Memorial University of Newfoundland, St. John’s, Newfoundland, Canada

Conflict of Interest Disclosure and Mitigation

Contributors to *Pharmacotherapy: A Pathophysiologic Approach* must disclose relevant financial and other interests with entities that produce, market, sell, or distribute medications, health products, or services related to the medication use process. All contributors will complete, sign, and submit a conflict of interest (COI) disclosure statement to the Editors. Starting with the 11th edition, the COI disclosure must be submitted after an invitation has been extended and before a contributor agreement is signed.

After reviewing the COI disclosure statement submitted by a contributor, the Editors will develop and approve a plan to mitigate any and all potential COI's that might be reasonably perceived by the readers of *Pharmacotherapy: A Pathophysiologic Approach* to unduly influence the contributor's favorable or unfavorable portrayal of any product or service. The mitigation plan may include, but is not limited to, assigning a coauthor with no COI's to work with the contributor, subjecting the contribution to external peer review, or asking the contributor to divest the interest(s).

No contributor may receive a payment or services from a third party (commercial entity, government agency, professional organization, private foundation, etc.) for any work product submitted to *Pharmacotherapy: A Pathophysiologic Approach.* Starting with the 11th edition, potential contributors who are employees of a commercial entity that produces, markets, sells, or distributes medications or healthcare products generally will not be invited or re-invited to contribute.

COI disclosures for all contributors to *Pharmacotherapy: A Pathophysiologic Approach* will be made available to readers online. The internet address for the COI disclosure page will be published in the Contributors section of the text.

Contributors

Val R. Adams, PharmD, FCCP, BCOP
Associate Professor
Department of Pharmacy Practice and Science,
College of Pharmacy
University of Kentucky
Lexington, Kentucky
Chapter 146

Rondall E. Allen, BS, PharmD
Dean and Professor
School of Pharmacy and Health Professions
University of Maryland Eastern Shore
Princess Anne, Maryland
Chapter e55

Peter L. Anderson, PharmD
Professor
Skaggs School of Pharmacy and Pharmaceutical Sciences
University of Colorado Anschutz Medical Campus
Aurora, Colorado
Chapter 143

Edward P. Armstrong, PharmD
Professor Emeritus
Department of Pharmacy Practice and Science
College of Pharmacy
University of Arizona

Tucson, Arizona
Chapter 136

Rebecca L. Attridge, PharmD, BCPS
Professor
Department of Pharmacy Practice
University of the Incarnate Word Feik School of Pharmacy
San Antonio, Texas
Chapter 45

Jacquelyn L. Bainbridge, PharmD, FCCP
Professor
University of Colorado
Anschutz Medical Campus
School of Pharmacy
Department of Clinical Pharmacy and Neurology
Aurora, Colorado
Chapter 72

Gary Bakst, MD
Head
Division of Community Endocrinology
Albany Medical Center
Albany, New York
Chapter 92

Katie Barber, PharmD
Assistant Professor
Department of Pharmacy Practice
University of Mississippi School of Pharmacy
2500 North State Street
Jackson, Mississippi
Chapter 124

Erin F. Baretto, PharmD, MSc

Assistant Professor of Medicine and Pharmacy
Mayo Clinic
Rochester, Minnesota
Chapter e27

Jeffrey F. Barletta, PharmD
Professor and Vice Chair of Pharmacy Practice
College of Pharmacy
Midwestern University
Glendale, Arizona
Chapter 40

Jill S. Bates, PharmD, MS, BCOP, FASHP
PHASeR Pharmacy Program Manager
Durham VA Health Care System
Associate Professor of Clinical Education
University of North Carolina Eshelman School of Pharmacy
Durham, North Carolina
Chapter e154

Brittany N. Bates, PharmD, BCPS
Assistant Professor of Pharmacy Practice
Ohio Northern University
Lima, Ohio
Chapter 131

Marisa Battistella, PharmD, ACPR
Pharmacy Clinician Scientist
Associate Professor
Leslie Dan Faculty of Pharmacy
University of Toronto
Clinical Pharmacist-Nephrology
University Health Network
Toronto, Ontario, Canada
Chapter 65

Steven Bauer, MD
Board Certified Psychiatrist
Essentia Health and St. Luke's Hospital
Duluth, Minnesota
Chapter e79

Seth R. Bauer, PharmD, BCCCP
Clinical Specialist
Department of Pharmacy
Cleveland Clinic
Cleveland, Ohio
Chapter 41

Larry A. Bauer, PharmD, FCP, FCCP
Professor (Retired)
Department of Pharmacy
School of Pharmacy
Adjunct Professor
Department of Laboratory Medicine
School of Medicine
University of Washington
Seattle, Washington
Chapter e5

Jerry L. Bauman, PharmD, FCCP, FACC
Dean Emeritus and Distinguish Emeritus Professor
College of Pharmacy
University of Illinois at Chicago
Chicago, Illinois
Chapter 39

Oralia V. Bazaldua, PharmD, FCCP, BCPS, BCACP
Professor
Department of Family and Community Medicine
University of Texas Health Science Center at San Antonio

San Antonio, Texas
Chapter e2

Nina M. Bemben, PharmD, BCPS
Assistant Professor
Department of Pharmacy Practice and Science
University of Maryland School of Pharmacy
Baltimore, Maryland
Chapter e28

Scott J. Bergman, PharmD, FCCP, FIDSA, BCPS, BCIDP
Pharmacy Coordinator, Antimicrobial Stewardship
Nebraska Medicine
Clinical Associate Professor
College of Pharmacy
University of Nebraska Medical Center
Omaha, Nebraska
Chapter 136

Angela L. Bingham, PharmD, BCPS, BCNSP, BCCCP, FASPEN
Associate Professor of Clinical Pharmacy
PGY2 Critical Care Residency Program Director
Philadelphia College of Pharmacy
University of the Sciences
Philadelphia, Pennsylvania
Chapter 67

Jeffrey R. Bishop, PharmD, MS, BCPP, FCCP
Associate Professor
Department of Experimental and Clinical Pharmacology (ECP)University of Minnesota College of Pharmacy
Minneapolis, Minnesota
Chapter e79

Martha Blackford, PharmD, BCPS

Clinical Pharmacologist and Toxicologist
Clinical Pharmacology and Toxicology, Division of Critical Care
Department of Pediatrics
Akron Children's Hospital
Akron, Ohio
Chapter 125

Kathryn V. Blake, PharmD, BCPS, FCCP

Director
Center for Pharmacogenomics and Translational Research
Nemours Children's Health System
Jacksonville, Florida
Chapter 43

Christopher M. Bland, PharmD, FCCP, FIDSA, BCPS

Clinical Associate Professor
Clinical and Administrative Pharmacy
College of Pharmacy
University of Georgia
Clinical Pharmacy Specialist
St. Joseph's/Candler Health System, Inc.
Savannah, Georgia
Chapter e104

Scott Bolesta, PharmD, BCPS, FCCM, FCCP

Associate Professor
Department of Pharmacy Practice
Nesbitt College of Pharmacy
Wilkes University
Wilkes-Barre, Pennsylvania
Visiting Investigator
Center for Pharmacy Innovation and Outcomes
Geisinger Health System
Danville, Pennsylvania
Chapter 56

Jill S. Borchert, PharmD, BCACP, BCPS, FCCP
Professor and Vice Chair
Pharmacy Practice, Midwestern University
Chicago College of Pharmacy
Chicago, Illinois
Chapter 108

Emily B. Borders, PharmD, MS, BCOP
Assistant Professor
Department of Pharmacy Practice
College of Pharmacy
Southwestern Oklahoma State University
Weatherford, Oklahoma
Chapter 150

Bonnie Lin Boster, PharmD, BCOP
Clinical Pharmacy Specialist – Breast Medical Oncology
Division of Pharmacy
University of Texas MD Anderson Cancer Center
Houston, Texas
Chapter 145

Jolene R. Bostwick, PharmD, BCPS, BCPP
Assistant Dean for Students
Clinical Professor
Department of Clinical Pharmacy
University of Michigan College of Pharmacy
Ann Arbor, Michigan
Chapter 88

Bradley A. Boucher, PharmD, FCCP, MCCM
Professor of Clinical Pharmacy and Translational Science
Associate Dean
Strategic Initiatives and Operations
University of Tennessee, Health Sciences Center

Memphis, Tennessee
Chapter 75

Sharya V. Bourdet, PharmD, BCPS
Associate Clinical Professor
Department of Clinical Pharmacy
University of California, San Francisco School of Pharmacy
San Francisco, California
Chapter 44

Jamal Brown, PharmD, BCGP
Associate Professor of Pharmacy Practice
Florida A&M University College of Pharmacy and Pharmaceutical Sciences
Institute of Public Health
Tampa, Florida
Chapter e8

Thomas E. R. Brown, PharmD
Associate Professor
Leslie Dan Faculty of Pharmacy
University of Toronto
Toronto, Ontario
Chapter 138

Peter F. Buckley, MD
Interim CEOVCU Health System
Interim Senior Vice President
VCU Health Sciences
Dean
VCU School of Medicine
Executive Vice President for Medical Affairs
VCU Health System
Richmond, Virginia
Chapter 84

David S. Burgess, PharmD, FCCP
Professor and Chair
University of Kentucky College of Pharmacy
Department of Pharmacy Practice and Science
Lexington, Kentucky
Chapter 123

Yvonne J. Burnett, PharmD, BCIDP
Assistant Professor of Pharmacy Practice
St. Louis College of Pharmacy
St. Louis, Missouri
Chapter 135

Lucinda M. Buys, PharmD, BCACPS
Clinical Services Director
Adjunct Associate Professor
University of Iowa, College of Pharmacy
Siouxland Medical Education Foundation
Sioux City, Iowa
Chapter 106

Peggy L. Carver, PharmD, FCCP
Associate Professor of Pharmacy
Department of Clinical Pharmacy
University of Michigan College of Pharmacy
Ann Arbor, Michigan
Chapter 139

Larisa H. Cavallari, PharmD
Associate Professor
Department of Pharmacotherapy and Translational Research
University of Florida College of Pharmacy
Gainesville, Florida
Chapters e6 and 35

Alexandre Chan, PharmD, MPH, FCCP, FISOPP, BCPS, BCOP

Professor and Founding Chair
Department of Clinical Pharmacy Practice
Susan & Henry Samueli College of Health Sciences
University of California Irvine
Irvine, California
Chapter 149

C. Y. Jennifer Chan, PharmD, BCPPS

Clinical Assistant Professor of Pharmacy
Pharmacotherapy Education and Research Center
University of Texas at Austin—College of Pharmacy
Adjunct Associate Professor of Pediatrics
Department of Pediatrics
University of Texas Health Science Center
San Antonio, Texas
Chapter 120

Edward Chang, MD

Professor of Neurological Surgery
University of California San Francisco
Weill Institute for Neurosciences
Co-Director
The Center for Neural Engineering and Prostheses
University of California San Francisco and University of California Berkeley
California
Chapter 73

Daniel B. Chastain, PharmD, BCIDP, AAHIVP

Clinical Assistant Professor
University of Georgia College of Pharmacy, SWGA Clinical Campus
1000 Jefferson Street
Albany, Georgia
Chapter 129

Kai I. Cheang, PharmD, MS, BCPS, FCCP
Affiliate Associate Professor of Pharmacotherapy and Outcomes Science
Virginia Commonwealth University
Richmond, Virginia
Chapter 96

Annie Cheang, PharmD, MS, BCPS, FCCP
Freelance Medical Writer
Scientific Value, LLC
Scottsdale, Arizona

Jack J. Chen, PharmD
Principal Consultant Accreditation and Education Science
Chino Hills
California
Chapter 76

Judy T. Chen, PharmD, BCPS, BCACP, CDCES, FNAP
Clinical Associate Professor of Pharmacy Practice
Purdue University College of Pharmacy
Indianapolis, Indiana
Chapters 98 and 161

Katherine H. Chessman, PharmD, FPPA, FCCP, BCPS, BCNSP
Professor and Interim Chair
Clinical Pharmacy and Outcomes Sciences
Residency Program Director
PGY2 Pediatric Pharmacy Residency
Medical University of South Carolina College of Pharmacy
Clinical Pharmacy Specialist, Pediatrics/Pediatric Surgery
MUSC Shawn Jenkins Children's Hospital
Charleston, South Carolina
Chapters e20, 66, and 158

Sheryl Chow, PharmD

Associate Professor, Department of Pharmacy Practice and Administration
Western University of Health Sciences
Pomona, California
Chapter e34

Mariann D. Churchwell, PharmD, BCPS, FCCP
Associate Professor
University of Toledo
College of Pharmacy and Pharmaceutical Sciences
Toledo, Ohio
Chapter 62

Peter A. Chyka, PharmD, FAACT, DABAT
Professor Emeritus
College of Pharmacy
University of Tennessee Health Science Center
Knoxville, Tennessee
Chapter e7

Amber B. Cipriani, PharmD, BCOP
Precision Medicine Pharmacy Coordinator
University of North Carolina Medical Center
Clinical Assistant Professor
Division of Pharmacotherapy and Experimental Therapeutics
University of North Carolina Eshelman School of Pharmacy
Chapel Hill, North Carolina
Chapter e155

Nathan Clark, PharmD, BCPS
Clinical Pharmacy Supervisor
Anticoagulation and Anemia Service
Kaiser Permanente
Aurora, Colorado
Chapter 37

Jessica M. Clement, MD
Medical Director
Oncology Research
Hartford HealthCare Cancer Institute
Hartford, Connecticut
Chapter 147

Kristen M. Cook, PharmD, BCPS
Clinical Associate Professor
Department of Pharmacy Practice and Science
College of Pharmacy
University of Nebraska Medical Center
Omaha, Nebraska
Chapter 118

Lisa M. Cordes, PharmD, BCACP, BCOP
Oncology Clinical Pharmacy Specialist and Educator
National Institutes of Health
Bethesda, Maryland
Chapter 144

Ryan Costantino, PharmD, MS, BCPS, BCGP
Branch Chief
Data Innovation, Defense Health Agency
San Antonio, Texas
Chapter e9

Jason M. Cota, PharmD, MS
Vice Chair and Professor of Pharmacy Practice
University of the Incarnate Word Feik School of Pharmacy
San Antonio, Texas
Chapter e133

Elizabeth A. Coyle, PharmD, FCCM, BCPS
Assistant Dean for Academic Affairs

Clinical Professor
University of Houston College of Pharmacy
Houston, Texas
Chapter 134

Catherine M. Crill, PharmD, FCCP, BCNSP
Associate Professor
Departments of Clinical Pharmacy and Translational Science and Pediatrics
Director of Experiential Learning and International Programs
College of Pharmacy
University of Tennessee Health Science Center
Memphis, Tennessee
Chapter 159

M. Lynn Crismon, PharmD
Administrative Dean
Center for Health IPE
Dean
College of Pharmacy
University of Texas at Austin
Austin, Texas
Chapter 84

Daniel J. Crona, PharmD, PhD
Clinical Pharmacist Practitioner
Genitourinary Malignancies
University of North Carolina Medical Center
Assistant Professor
Division of Pharmacotherapy and Experimental Therapeutics
University of North Carolina Eshelman School of Pharmacy
Chapel Hill, North Carolina
Chapter e155

Ericka L. Crouse, PharmD, BCPP, CGP, FASCP
Clinical Pharmacy Specialist of Psychiatry and Clinical Associate Professor of

Pharmacy and Psychiatry
Virginia Commonwealth University, College of Pharmacy
Richmond, Virginia
Chapters 71 and 88

William E. Dager, PharmD, BCPS, MCCM, FCCP, FASHP, FCSHP

Pharmacist Specialist
University of California Davis Medical Center
Clinical Professor of Pharmacy
UC San Francisco School of Pharmacy
Clinical Professor of Medicine
UC Davis School of Medicine
Sacramento, California
Chapter 60

Devra K. Dang, BCPS, CDE, FNAP

Associate Clinical Professor of Pharmacy Practice
Department of Pharmacy Practice
University of Connecticut, College of Pharmacy
Storrs, Connecticut
Chapter 98

Khashayar Dashtipour, MD, PhD

Associate Professor, Neurology
School of Medicine
Associate Professor
Pharmacy Practice
Loma Linda University
Loma Linda, California
Chapter 76

DeWayne A. Davidson, PharmD, BCACP, BC-ADM

Clinical Assistant Professor
Division of Pharmacotherapy

University of Texas at Austin College of Pharmacy
Austin, Texas
Adjoint Assistant Professor
Department of Family and Community Medicine
University of Texas Health Science Center at San Antonio
San Antonio, Texas
Chapter e2

Christina M. Davis, PharmD, BCOP

Clinical Oncology Pharmacy Specialist
Department of Pharmacy
University of Colorado Anschutz Medical Campus
Aurora, Colorado
Chapter 156

Lisa E. Davis, PharmD, BCPS, BCOP

Professor
Department of Pharmacy Practice and Science
College of Pharmacy
University of Arizona
Tucson, Arizona
Chapter 147

Brian S. Decker, MD, PharmD, MS

Associate Professor of Clinical Medicine
Nephrology Fellowship Training Program Director
Division of Nephrology
Department of Medicine
Indiana University School of Medicine
Indianapolis, Indiana
Chapter 62

Paulina Deming, PharmD

Associate Professor
College of Pharmacy

University of New Mexico Health Sciences Center
Albuquerque, New Mexico
Chapter 57

David DeRemer, PharmD, BCOP, FCCP, FHOPA
Clinical Associate Professor
Department of Pharmacotherapy and Translational Research
College of Pharmacy
University of Florida
Gainesville, Florida
Chapter 151

Sunita Dergalust, PharmD, BCPS
Clinical Pharmacist
Neurology/Neurosurgery
West LA VA Healthcare Center
Los Angeles, California
Chapter 73

John W. Devlin, PharmD, BCCCP, MCCM, FCCP
Professor, Department of Pharmacy and Health Systems Sciences
Bouve College of Health Sciences
Northeastern University
Research Scientist, Division of Pulmonary and Critical Care Medicine
Brigham and Women's Hospital
Boston, Massachusetts
Chapter 69

Robert J. DiDomenico, PharmD, BCPS (AQ Cardiology)
Associate Professor of Pharmacy Practice
University of Illinois at Chicago College of Pharmacy
Chicago, Illinois
Chapters 32 and 33

Thomas J. Dilworth, PharmD

Pharmacy Coordinator, Infectious Diseases
Department of Pharmacy Services, Advocate Aurora Health
Aurora St. Luke's Medical Center
Milwaukee, Wisconsin
Chapter 124

Dave L. Dixon, PharmD, BCPS, BCACP, CDCES, CLS

Associate Professor
Department of Pharmacotherapy and Outcomes Science
Virginia Commonwealth University School of Pharmacy
Richmond, Virginia
Chapter 31

Le Hanh Dung Do, MD

Attending Physician
Hiep Loi Cosmetic Surgery Hospital
Ho Chi Minh City, Vietnam
Chapter 116

Paul Dobesh, PharmD, BCPS, BCCP

Professor
Department of Pharmacy Practice and Science
University of Nebraska Medical Center College of Pharmacy
Omaha, Nebraska
Chapters 32 and 33

Paul L. Doering, MS

Distinguished Service Professor Emeritus
Department of Pharmacotherapy and Translational Research
University of Florida College of Pharmacy
Gainesville, Florida
Chapters 82 and 83

Krista L. Donohoe, PharmD, BCPS, BCGP

Associate Professor

Department of Pharmacotherapy and Outcomes Science, School of Pharmacy
Virginia Commonwealth University
Richmond, Virginia
Chapters e22 and 52

Julie A. Dopheide, PharmD, BCPP
Professor of Clinical Pharmacy
University of Southern California
College of Pharmacy
Chapter 80

John M. Dopp, PharmD, MS
Associate Professor and Vice Chair
Pharmacy Practice Division
University of Wisconsin, School of Pharmacy
Madison, Wisconsin
Chapter 89

Thomas C. Dowling, PharmD, PhD, FCCP
Professor and Assistant Dean
Director, Office of Research and Sponsored Programs
College of Pharmacy
Ferris State University
Grand Rapids, Michigan
Chapter e59

Shannon J. Drayton, PharmD, BCPP
Associate Professor
Clinical Pharmacy and Outcome Science
Medical University of South Carolina, College of Pharmacy
Charleston, South Carolina
Chapter 86

Linda Dresser, PharmD, FCSHP
Pharmacotherapy Specialist- Antimicrobial Stewardship

University Health Network
Assistant Professor (status)
Leslie Dan Faculty of Pharmacy
University of Toronto
Toronto, Ontario
Chapter 138

Bryson Duhon, PharmD, BCPS
Assistant Dean for Student Success / Clinical Assistant Professor
University of Texas College of Pharmacy
Austin, Texas
Chapter 135

Lori Dupree, PharmD, BCPS
Clinical Assistant Professor
Department of Pharmacotherapy and Translational Research
University of Florida College of Pharmacy
Gainesville, Florida
Chapter 83

Lauren Duran, PharmD, MBA, BCPPS
Clinical Pharmacist
Hematology/Oncology and Stem Cell Transplantation
Cook Children's Medical Center
Fort Worth, Texas
Chapter 119

Amy L. Dzierba, PharmD, FCCM, FCCP, BCCCP
Clinical Pharmacy Manager
Adult Critical Care
New York-Presbyterian Hospital
Columbia University Irving Medical Center
New York, New York
Chapter e27

Deepak P. Edward, MD, FACS
Professor of Ophthalmology and Pathology
University of Illinois at Chicago
Chicago, Illinois
Chapter 110

Lea S. Eiland, PharmD, BCPS, BCPPS, FASHP, FPPA
Clinical Professor and Associate Department Head
Department of Pharmacy Practice
Auburn University Harrison School of Pharmacy
Auburn, Alabama
Chapter e11

Shareen Y. El-Ibiary, PharmD, FCCP, BCPS
Professor and Chair, Department of Pharmacy Practice
Midwestern University College of Pharmacy
Glendale, Arizona
Chapter 18

Ramy Elshaboury, PharmD, BCPS AQ-ID
Clinical Pharmacy Coordinator—Infectious Diseases
Massachusetts General Hospital
Boston, Massachusetts
Chapter 124

Steven R. Erickson, PharmD
Associate Professor of Clinical Pharmacy
University of Michigan College of Pharmacy
Ann Arbor, Michigan
Chapter 90

Michael E. Ernst, PharmD, BCGP, FCCP
Clinical Professor
Department of Pharmacy Practice and Science
Department of Family Medicine

University of Iowa
Iowa City, Iowa
Chapter 109

Brian L. Erstad, PharmD, BCPS
Professor and Head
Department of Pharmacy Practice and Science
University of Arizona College of Pharmacy
Tucson, Arizona
Chapter 41

Alisa K. Escano, PharmD, BCPS
Assistant Professor
Department of Pharmacotherapy and Outcomes Science
Virginia Commonwealth University School of Pharmacy
Inova Campus
Falls Church, Virginia
Chapter 111

Patricia H. Fabel, PharmD, BCPS
Clinical Associate Professor
University of South Carolina College of Pharmacy
Columbia, South Carolina
Chapter 53

Joseph P. Fava, PharmD, BCACP
Clinical Assistant Professor
Department of Pharmacy Practice
Eugene Applebaum College of Pharmacy and Health Sciences
Wayne State University
Detroit, Michigan
Chapter 108

Julianna M. Fernandez, PharmD, BCPS, BCGP
Clinical Associate Professor

Assistant Chair of Pharmacy Practice and Translational Research
University of Houston
Houston, Texas
Chapter 134

Christopher S. Fields, MD
Assistant Professor
Department of Psychiatry and Behavioral Sciences
Medical University of South Carolina
College of Medicine
Charleston, South Carolina
Chapter 86

Shannon W. Finks, PharmD, BCPS, BCCP
Professor, Department of Clinical Pharmacy and Translational Science
University of Tennessee Health Science Center
Memphis, Tennessee
Chapter 33

Richard G. Fiscella, PharmD, MPH
Clinical Professor Emeritus
Department of Pharmacy Practice
University of Illinois at Chicago
Chicago, Illinois
Chapter 110

Douglas N. Fish, PharmD, BCPS AQ-ID, FCCP, FCCM
Professor and Chair
Department of Clinical Pharmacy
Skaggs School of Pharmacy and Pharmaceutical Sciences
Aurora, Colorado
Chapters 128 and 140

Courtney V. Fletcher, PharmD
Professor and Director

Antiviral Pharmacology Laboratory
UNMC Center for Drug Discovery
University of Nebraska Medical Center
Omaha, Nebraska
Chapter 143

Rachel W. Flurie, PharmD, BCPS
Assistant Professor
Department of Pharmacotherapy and Outcomes Science
Virginia Commonwealth University School of Pharmacy
Richmond, Virgina
Chapter 68

Gilles L. Fraser, PharmD, MCCM
Professor of Medicine
Tufts University School of Medicine
Boston, Massachusetts
Clinical Pharmacy Specialist in Critical Care
Departments of Pharmacy and Critical Care Services
Maine Medical Center
Portland, Maine
Chapter e26

Michelle A. Fravel, PharmD, BCPS
Clinical Associate Professor
Department of Pharmacy Practice and Science
University of Iowa College of Pharmacy
Clinical Pharmacy Specialist, Ambulatory Care
Department of Pharmaceutical Care
University of Iowa Health Care
Iowa City, Iowa
Chapter 109

Bradi L. Frei, PharmD, MS, BCPS, BCOP
Professor, Pharmacy Practice

Feik School of Pharmacy
University of the Incarnate Word
San Antonio, Texas
Chapter 126

Christopher R. Frei, PharmD, MS, FCCP, BCPS
Professor, Pharmacotherapy Division
College of Pharmacy, University of Texas at Austin
San Antonio, Texas
Chapter 126

Melissa Frei-Jones, MD, MSCI
Associate Professor
Department of Pediatrics
Division of Hematology/Oncology
UT Long School of Medicine
San Antonio, Texas
Chapter 120

Kristen N. Gardner, PharmD, BCPP
Clinical Pharmacy Specialist-Behavioral Health
Kaiser Permanente Colorado
Denver, Colorado
Chapter 88

Scott G. Garland, PharmD
Clinical Assistant Professor
College of Medicine
Florida State University and Bay Care Health System
Winter Haven, Florida
Chapter 93

Mandy L. Gatesman, PharmD, BCOP
Clinical Pharmacy Specialist, Hematology and Oncology
Virginia Commonwealth University Health System

Richmond, Virginia
Chapter 52

Tracey L. Gendron, MS, PhD
Chair and Associate Professor, Gerontologist
Department of Gerontology, School of Pharmacy
Virginia Commonwealth University
Richmond, Virginia
Chapter e22

Rena Gosser, PharmD, BCPS
Clinical Manager
Ambulatory Pharmacy
UW Medicine-Harborview Medical Center
Clinical Assistant Professor
University of Washington School of Pharmacy
Seattle, Washington
Chapter e112

Leigh Anne Hylton Gravatt, PharmD, BCPS
Associate Professor
Department of Pharmacotherapy and Outcomes Science
Virginia Commonwealth University School of Pharmacy
Richmond, Virginia
Chapter 52

Shelly L. Gray, PharmD, MS
Shirley & Herb Bridge Endowed Professor
Director
Plein Center for Geriatric Pharmacy Research, Education & Outreach
School of Pharmacy
University of Washington
Seattle, Washington
Chapters e23 and e24

Elisa M. Greene, PharmD, BCACP
Associate Professor
Department of Pharmacy Practice
College of Pharmacy, Belmont University
Clinical Pharmacist – Siloam Health
Nashville, Tennessee
Chapter e121

Devon M. Greer, PharmD, BCOP
Clinical Specialist Pharmacist
Medical Oncology
Department of Pharmacy
Barnes-Jewish Hospital
St. Louis, Missouri
Chapter 118

Alan E. Gross, PharmD, BCPS, BCIDP
Clinical Associate Professor
University of Illinois at Chicago, College of Pharmacy
Infectious Diseases Pharmacist
University of Illinois Hospital and Health Sciences System
Chicago, Illinois
Chapter 132

Meagan Grove, PharmD, BCOP
Hematology/Bone Marrow Transplant Clinical Pharmacist
Indiana University Health—Melvin and Bren Simon Cancer Center
Indianapolis, Indiana
Chapter 152

Stephanie Gruber, PharmD, BCACP
Clinical Pharmacy Specialist
Internal Medicine Service
William S. Middleton Memorial Veterans Hospital
Madison, Wisconsin

Chapter 107

Wayne P. Gulliver, MD, FRCPC
Professor of Dermatology and Medicine
Memorial University of Newfoundland
St. John's, Newfoundland and Labrador, Canada
Chapters 114 and 115

John G. Gums, PharmD, FCCP
Professor of Pharmacy
Department of Pharmacotherapy and Translational Research
Associate Dean for Clinical and Administrative Affairs
University of Florida College of Pharmacy
Gainesville, Florida
Chapter 93

Tracy M. Hagemann, PharmD, FCCP, FPPA
Associate Dean, Nashville
Professor
Department of Clinical Pharmacy
College of Pharmacy
University of Tennessee Health Sciences Center
Chapter e121

Stuart T. Haines, PharmD, BCPS, BCACP
Professor
Department of Pharmacy Practice
University of Mississippi School of Pharmacy
Jackson, Mississippi
Chapters 1 and 91

Emily R. Hajjar, PharmD, MS, BCPS, BCAP, BCGP
Associate Professor
Department of Pharmacy Practice
Jefferson College of Pharmacy

Thomas Jefferson University
Philadelphia, Pennsylvania
Chapter e23

Maren Hall, DDS
Clinical Assistant Professor
School of Dentistry
University of Minnesota
Minneapolis, Minnesota
Chapter e15

Jason S. Haney, PharmD, BCPS, BCCCP
Associate Professor
Department of Clinical Pharmacy and Outcomes Sciences
Medical University of South Carolina College of Pharmacy
Medication Safety Director
Charleston Patient Safety Center of Inquiry
Ralph H. Johnson VA Medical Center
Charleston, South Carolina
Chapter 66

Michelle S. Harkins, MD
Professor and Chief, Division of Pulmonary and Critical Care Medicine
University of New Mexico, School of Medicine
Albuquerque, New Mexico
Chapter e47

T. Kristopher Harrell, PharmD
Associate Dean for Academic Affairs,
Professor of Pharmacy Practice
University of Mississippi, College of Pharmacy
Chapter 78

Bryan D. Hayes, PharmD, DABAT, FAACT, FASHP
Attending Pharmacist

Emergency Medicine and Toxicology
Massachusetts General Hospital
Assistant Professor of Emergency Medicine
Harvard Medical School
Boston, Massachusetts
Chapter e7

Mary S. Hayney, PharmD, MPH, FCCP, BCPS

Professor of Pharmacy
Division of Pharmacy Practice
University of Wisconsin—Madison School of Pharmacy
Madison, Wisconsin
Chapter 142

Keith A. Hecht, PharmD, BCOP

Associate Professor
Department of Pharmacy Practice
School of Pharmacy
Southern Illinois University Edwardsville
Edwardsville, Illinois
Chapter 146

Brian A. Hemstreet, PharmD, FCCP, BCPS

Assistant Dean for Student Affairs and Professor
University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences
Aurora, Colorado
Chapter 51

Chris M. Herndon, BCPS, CPE

Associate Professor, Pharmacy Practice
Southern Illinois University Edwardsville, School of Pharmacy
Chapter 77

Lauren R. Hersh, MD

Assistant Professor
Department of Family and Community Medicine
Thomas Jefferson University
Philadelphia, Pennsylvania
Chapter e23

Tara Higgins, PharmD, BCPPS
Pediatric Hematology/Oncology Clinical Pharmacy Specialist
UF Health Shands Hospital
Gainesville, Florida
Chapter 151

Sarah E. Hobgood, MD
Associate Professor
Department of Internal Medicine
Division of Geriatric Medicine
Virginia Common Wealth University, School of Medicine
Chapter 71

Jonathan J. Hogan, MD
Assistant Professor of Medicine
Division of Nephrology, Hypertension and Electrolytes
Clinical Director
Penn Glomerular Disease Center
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 64

Lisa M. Holle, PharmD, BCOP, FHOPA, FISOPP
Associate Clinical Professor
Department of Pharmacy Practice
School of Pharmacy
University of Connecticut
Storrs, Connecticut

Chapter 147

Jessica Holt, PharmD, BCPS (AQ-ID)

Infectious Diseases Coordinator
PGY2 Infectious Diseases Residency Program Director
Abbott Northwestern Hospital, part of Allina Health
Minneapolis, Minnesota
Chapter 124

Joanna Q. Hudson, PharmD, BCPS, FASN, FCCP, FNKF

Professor of Clinical Pharmacy and Translational Science and Medicine (Nephrology)
University of Tennessee Health Science Center
Memphis, Tennessee
Chapter 61

Susan Hylland, MD, FACR

Rheumatology Attending
William S. Middleton Memorial Veterans Hospital
Rheumatologist
University of Wisconsin Hospitals
Madison, Wisconsin
Chapter 107

Douglas L. Jennings, PharmD, FACC, FAHA, FCCP, FHFSA, BCPS

Associate Professor of Pharmacy
Clinical Pharmacist, Heart Transplant and LVAD Team
Arnold & Marie Schwartz College of Pharmacy and Health Sciences
Long Island University
New York-Presbyterian Hospital
Columbia University Irving Medical Center
New York, New York
Chapter 105

Heather J. Johnson, PharmD, BCPS
Assistant Professor
Department of Pharmacy and Therapeutics
University of Pittsburgh School of Pharmacy
Clinical Specialist-Transplant
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania
Chapter 105

Bruce M. Jones, PharmD, BCPS
Infectious Diseases Clinical Pharmacy Specialist
St. Joseph's/Candler Health System, Inc.
Clinical Adjunct Assistant Professor
College of Pharmacy
University of Georgia
Savannah, Georgia
Chapter e104

Joseph K. Jordan, PharmD, BCPS
Professor
Department of Pharmacy Practice
Butler University College of Pharmacy and Health Sciences
Indianapolis, Indiana
Chapter e94

Sul R. Jung, PharmD, BCPS, BCCCP
Critical Care Pharmacist
Ventura County Medical Center
Ventura, California
Chapter 137

Michael P. Kane, PharmD, BCPS, BCACP
Professor
Department of Pharmacy Practice
Albany College of Pharmacy and Health Sciences

Albany, New York
Chapter 92

Sandra L. Kane-Gill, PharmD, MSc, FCCM, FCCP
Professor
Department of Pharmacy and Therapeutics
Department of Critical Care Medicine and the Clinical Translational Science Institute
University of Pittsburgh Schools of Pharmacy and Medicine
Pittsburgh, Pennsylvania
Chapter e25

S. Lena Kang-Birken, PharmD, FCCP, AAHIVP
Associate Professor
Thomas J Long School of Pharmacy and Health Sciences
University of the Pacific
Stockton, California
Chapter 137

Salmaan Kanji, PharmD
Clinical Pharmacy Specialist
The Ottawa Hospital
Associate Scientist, Clinical Epidemiology Program
The Ottawa Hospital Research Institute
Assistant Professor
Department of Medicine, Division of Critical Care
University of Ottawa
Associate Professor
Faculty of Pharmacy, University of Montreal
Assistant Professor
School of Epidemiology and Public Health
Faculty of Medicine, University of Ottawa
Ottawa, Ontario, Canada
Chapter 141

Christopher D. Kearney, MD, FAAHPM
Medical Director of Palliative Medicine
MedStar Health
Baltimore, Maryland
Chapter e9

Julie J. Kelsey PharmD
Clinical Pharmacist
Department of Pharmacy Services
University of Virginia Health System
Charlottesville, Virginia
Chapter 95

Patrick J. Kiel, PharmD, BCPS, BCOP, FHOPA
Clinical Pharmacy Specialist
Hematology/Oncology—Precision Genomics Program
Indiana University Health—Melvin and Bren Simon Cancer Center
Indianapolis, Indiana
Chapter 152

Scott E. Kincaid, PharmD, BCPS
Professor of Pharmacy Practice
LECOM School of Pharmacy
Bradenton, Florida
Chapter e17

William R. Kirchain, PharmD, CDE
Director
Xavier University Health and Wellness Center
Xavier University of Louisiana
New Orleans, Louisiana
Chapter e55

Cynthia K. Kirkwood
Executive Associate Dean for Academic Affairs and Professor

Department of Pharmacotherapy and Outcomes Science
Virginia Commonwealth University, College of Pharmacy
Richmond, Virginia
Chapter 87

Mary Ann Kliethermes, PharmD
Director of Medication Safety and Quality
American Society of Health System Pharmacists
Bethesda, Maryland
Chapter 1

Paul Komenda, MD, FRCPC, MHA, CHE
Associate Professor of Medicine
Section of Nephrology
University of Manitoba
Research Director
Chronic Disease Innovation Centre
Seven Oaks General Hospital
Winnipeg, Manitoba, Canada
Chapter 61

Courtney M. Kominek, PharmD, BCPS, CPE
Clinical Pharmacy Specialist Pain Management
Harry S. Truman Memorial Veterans' Hospital
Columbia, Boone County, Missouri
Chapter 77

Christina Koutsari, PharmD PhD BCPS BCIDP
Infectious Disease and Antimicrobial Stewardship Pharmacist
Children's Hospitals and Clinics of Minnesota
Minneapolis/St Paul, Minnesota
Chapter 124

Sunil Kripalani, MD, MSc, SFHM
Professor of Medicine, Director of the Center for Clinical Quality and

Implementation Research
Co-Director of the Center for Effective Health Communication
Vanderbilt University
Nashville, Tennessee
Chapter e2

Vanessa J. Kumpf, PharmD, BCNSP, FASPEN

Clinical Pharmacist Specialist
Center for Human Nutrition
Vanderbilt University Medical Center
Nashville, Tennessee
Chapters 158 and 160

Poh Gin Kwa, MD

Pediatrician
Department of Pediatrics, Eastern Health
St. John's, Newfoundland and Labrador
Canada
Chapter 115

Jenay Kyles, PharmD

PGY1 Community Pharmacy Resident
Baylor Scott & White Health
Temple, Texas
Chapter e8

Y. W. Francis Lam, PharmD, FCCP

Professor
Department of Pharmacology
University of Texas Health Science Center at San Antonio
San Antonio, Texas
Chapter e6

Sum Lam, PharmD, BCGP, BCPS

Associate Clinical Professor

Department of Clinical Health Professions
St. John's University
Queens, New York
Chapter 101

Jason E. Lang, MD, MPH
Associate Professor of Pediatrics
Duke University School of Medicine
Durham, North Carolina
Chapter 43

Alan H. Lau, PharmD, FCCP, FNAP
Professor, Department of Pharmacy Practice
Director, International Clinical Pharmacy Education
College of Pharmacy
University of Illinois at Chicago
Chicago, Illinois
Chapter 64

Rebecca M. Law, PharmD
Associate Professor
School of Pharmacy and Discipline of Family Medicine, Faculty of Medicine
Memorial University of Newfoundland
St. John's, Newfoundland and Labrador, Canada
Chapters e16, 114, 115, 116, and e117

David T. S. Law, BSc, MD, PhD, CCFP
Assistant Professor
Department of Family and Community Medicine, Faculty of Medicine
University of Toronto
Staff
Department of Family Practice
Scarborough Hospital and Rouge Valley Health System
Scarborough, Ontario, Canada
Chapter e117

Mary Lee, PharmD, BCPS, FCCP

Professor of Pharmacy Practice
Chicago College of Pharmacy
Midwestern University
Downers Grove, Illinois
Chapters 99 and 100

Grace C. Lee, PharmD, PhD, BCPS

Assistant Professor
College of Pharmacy
University of Texas at Austin
Austin, Texas
Pharmacotherapy Education and Research Center, School of Medicine
University of Texas Health Science Center at San Antonio
San Antonio, Texas
Chapter 123

Patrick Leffers, PharmD

Toxicology/Emergency Medicine Fellow
Florida/USVI Poison Information Center-Jacksonville
UF Health Jacksonville
University of Florida
Gainesville, Florida
Chapter 82

Timothy S. Lesar, PharmD

Director of Clinical Pharmacy Services
Patient Care Services Director
Department of Pharmacy
Albany Medical Center
Albany, New York
Chapter 110

Deborah J. Levine, MD

Professor of Medicine in Pulmonary and Critical Care Medicine

University of Texas Health Science Center at San Antonio
San Antonio, Texas
Chapter 45

Stephanie M. Levine, MD
Professor of Medicine in Pulmonary and Critical Care Medicine
University of Texas Health Science Center at San Antonio
San Antonio, Texas
Chapter e42

Bianca Lezcano, PharmD
Clinical Pharmacy Specialist
Rheumatology Service
William S. Middleton Memorial Veterans Hospital
Madison, Wisconsin
Chapter 107

Robin Moorman Li, PharmD, BCACP, CPE
Clinical Associate Professor and Assistant Director of Jacksonville Campus
University of Florida College of Pharmacy
Chapters 82 and 83

Susanne Liewer, PharmD, BCOP, FHOPA
Clinical Associate Professor
Department of Pharmacy Practice and Science
College of Pharmacy
University of Nebraska Medical Center
Omaha, Nebraska
Chapter 157

Bryan L. Love, PharmD, MPH, FCCP, BCPS-AQ ID
Associate Professor
Department of Clinical Pharmacy and Outcomes Sciences
University of South Carolina College of Pharmacy
Columbia, South Carolina

Chapter 50

Amanda M. Loya, PharmD, BCPS

Clinical Associate Professor
School of Pharmacy
University of Texas at El Paso
Adjunct Clinical Assistant Professor
Department of Family and Community Medicine
Texas Tech University Health Sciences Center–El Paso
El Paso, Texas

Chapter e3

Sarah E. Lynch, PharmD, BCACP

Clinical Assistant Professor
Director of Skills Education at Binghamton University
College of Pharmacy
Binghamton, New York

Chapter 97

Robert MacLaren, PharmD, MPH

Professor
Department of Clinical Pharmacy
University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences
Aurora, Colorado

Chapter 41

Eric J. MacLaughlin, PharmD, BCPS

Professor and Chair, Department of Pharmacy Practice
Texas Tech University Health Sciences Center Jerry H. Hodge School of Pharmacy
Amarillo, Texas

Chapter 30

Howard I. Maibach, MD

Professor
Department of Dermatology
School of Medicine
University of California San Francisco
San Francisco, California
Chapters e16, 116, and e117

Matthew J. Makelky Sr., PharmD
Postdoctoral Fellowship in Clinical Neurology
Skaggs School of Pharmacy and Pharmaceutical Sciences
University of Colorado
Denver, Colorado
Chapter 72

Jenana H. Maker, PharmD, BCPS
Professor of Pharmacy Practice
University of the Pacific School of Pharmacy
Stockton, California
Chapter 60

Robert A. Mangione, PharmD
Provost Emeritus and Professor of Pharmacy
College of Pharmacy and Health Sciences
Department of Pharmacy Administration and Public Health
St. John's University
Queens, New York
Chapter 58

Zachary A. Marcum, PharmD, PhD, BCPS
Assistant Professor
School of Pharmacy
Bailey Faculty Fellow, Assistant Director for Research
Plein Center for Geriatric Pharmacy Research, Education & Outreach
University of Washington
Seattle, Washington

Chapter e24

Todd W. Mattox, PharmD, BCNSP, FASPEN
Medical and Surgical Clinical Pharmacist
Moffitt Cancer Center
Tampa, Florida
Chapter 159

J. Russell May, PharmD
Clinical Professor
Department of Clinical and Administrative Pharmacy
University of Georgia College of Pharmacy
Augusta, Georgia
Chapter e13

Dianne May, PharmD, FCCP, BCPS
Clinical Professor
Department of Clinical and Administrative Pharmacy
Campus Director for Pharmacy Practice Experiences
Division of Experience Programs
University of Georgia College of Pharmacy
Augusta, Georgia
Chapter 49

Jennifer L. Mazan, PharmD
Associate Professor
Department of Pharmacy Practice
Midwestern University, Chicago College of Pharmacy
Downers Grove, Illinois
Chapter e14

Rachael McCaleb, PharmD
Assistant Professor
School of Pharmacy
University of Arkansas for Medical Sciences

Little Rock, Arkansas
Chapter e48

Timothy L. McCavit, MD, MS
Staff Hematologist
Director, Bleeding Disorder Program
Cook Children's Medical Center
Fort Worth, Texas
Chapter 119

Mary Lynn McPherson, PharmD, MA, BCPS, CPE
Professor, Executive Director
Advanced Post-Graduate Education in Palliative Care
Department of Pharmacy Practice and Science
University of Maryland School of Pharmacy
Baltimore, Maryland
Chapter e28

Sarah T. Melton, PharmD, BCPP, BCACP, CGP, FASCP
Professor of Pharmacy Practice
East Tennessee State University
Gatton College of Pharmacy
Johnson City, Tennessee
Chapter 87

Laura Boehnke Michaud, PharmD, FASHP, BCOP, CMQ
Associate Director – Quality and Regulatory
Division of Pharmacy
Clinical Pharmacy Services
University of Texas MD Anderson Cancer Center
Houston, Texas
Chapter 145

Leigh Ann Mike, PharmD, BCPS, BCGP
Clinical Associate Professor

Assistant Director for Education
Plein Center for Geriatric Pharmacy Research, Education & Outreach
School of Pharmacy
University of Washington
Seattle, Washington
Chapter e24

Anna Milone, PharmD, BCPS

Teaching Specialist
Pharmacy Learning Collaborative
College of Pharmacy
University of Minnesota
Pharmacist
School of Dentistry
University of Minnesota
Minneapolis, Minnesota
Chapter e15

Deborah S. Minor, PharmD

Professor
University of Mississippi Medical Center
School of Medicine
Jackson, Mississippi
Chapter 78

Augusto Miravalle, MD

Associate Clinical Professor
Department of Neurology
University of Colorado, School of Medicine
Aurora, Colorado
Chapter 72

Phillip L. Mohorn, PharmD, BCPS, BCCCP

Clinical Pharmacy Specialist-Emergency Medicine
Northeast Georgia Health System

Gainesville, Georgia
Chapter 50

Patricia A. Montgomery, PharmD, FCSHP
Director of Quality
Mercy General Hospital
Full Clinical Professor
University of California, San Francisco
Sacramento, California
Chapter 56

Rebecca Moote, PharmD, MSc, BCPS
Clinical Associate Professor of Pharmacotherapy
University of Texas at Austin, College of Pharmacy
Austin, Texas
Chapter 45

Scott W Mueller, PharmD, BCCCP
Associate Professor
Department of Clinical Pharmacy
University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences
Aurora, Colorado
Chapter 140

Diana Wells Mulherin, PharmD, BCNSP, BCCCP
Clinical Pharmacist Specialist, Nutrition Support
Center for Human Nutrition and Department of Pharmaceutical Services
Vanderbilt University Medical Center
Nashville, Tennessee
Chapter 160

Kashif M. Munir, MD
Associate Professor, Division of Endocrinology, Diabetes, and Nutrition
University of Maryland School of Medicine

Baltimore, Maryland
Chapter e94

Milap C. Nahata, MS, PharmD, FCCP, FAPhA, FASHP, FPPA
Director, Institute of Therapeutic Innovations and Outcomes
Professor Emeritus of Pharmacy, Pediatrics and Internal Medicine
Colleges of Pharmacy and Medicine
Ohio State University and Nationwide Children's Hospital
Columbus, Ohio
Chapter e19

Rocsanna Namdar, PharmD, BCPS, FCCP
Inpatient Pharmacy Supervisor
New Mexico VA Health Care System
Albuquerque, New Mexico
Chapter 130

Jean M. Nappi, PharmD
Professor of Clinical Pharmacy and Outcome Sciences
Medical University of South Carolina
Charleston, South Carolina
Chapter 35

Leigh Anne Nelson, PharmD, BCPP
Professor
School of Pharmacy
University of Missouri—Kansas City
Kansas City, Missouri
Chapter e79

Melissa Nestor, PharmD
Assistant Professor, Department of Pharmacy Practice and Science
University of Kentucky College of Pharmacy
Lexington, Kentucky
Chapter 38

Viet-Huong V. Nguyen, PharmD, MPH, MS, BCPS
Assistant Professor
Department of Pharmacy Practice
Chapman University, School of Pharmacy
Irvine, California
Chapter 73

Jessica Njoku, PharmD, MPH, BCPS
System Clinical Pharmacy Manager
Harris Health System
Houston, Texas
Chapter 127

Thomas D. Nolin, PharmD, PhD, FCCP, FCP, FASN
Associate Professor
Department of Pharmacy and Therapeutics
Center for Clinical Pharmaceutical Sciences
Department of Medicine, Renal-Electrolyte Division
University of Pittsburgh Schools of Pharmacy and Medicine
Pittsburgh, Pennsylvania
Chapters 63, 65, and 69

LeAnn B. Norris, PharmD, FCCP, BCPS, BCOP
Clinical Associate Professor
Department of Clinical Pharmacy and Outcomes Sciences
College of Pharmacy
University of South Carolina
Columbia, South Carolina
Chapter 148

Mary Beth O'Connell, PharmD, BCPS, FASHP, FCCP, FNAP, AGSF
Professor
Department of Pharmacy Practice
Eugene Applebaum College of Pharmacy and Health Sciences

Wayne State University
Detroit, Michigan
Chapter 108

Kirsten H. Ohler, PharmD, BCPS, BCPPS
Clinical Associate Professor, Pharmacy Practice
Program Director, PGY1 Pharmacy Residency
Clinical Pharmacy Specialist, NICU
University of Illinois at Chicago
Chicago, Illinois
Chapter e21

Keith M. Olsen, PharmD, FCCP, FCCM
Dean and Professor
College of Pharmacy
University of Nebraska Medical Center
Omaha, Nebraska
Chapter e48

Jared Ostroff, PharmD, BCACP, BCGP
Ambulatory Pharmacy Anticoagulation Coordinator
Baystate Health
Springfield, Massachusetts
Chapter e10

Ohoud A. Owaidhah, MD
Chair
Glaucoma Division
Consultant, King Khaled Eye Specialist Hospital
Riyadh, Kingdom of Saudi Arabia
Chapter 110

Cindy L. O'Bryant, PharmD, BCOP, FCCP, FHOPA
Professor
Department of Clinical Pharmacy

University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences
University of Colorado Anschutz Medical Campus
Aurora, Colorado
Chapter 156

Amy Barton Pai, PharmD, BCPS, FASN, FCCP, FNKF
Associate Professor
Department of Clinical Pharmacy
College of Pharmacy
University of Michigan
Ann Arbor, Michigan
Chapter 67

Melissa C. Palmer, PharmD, BCPS
Clinical Assistant Professor
School of Pharmacy
University of Missouri—Kansas City
Chapter 81

Lisa M. Palmisano, PharmD, BCACP
Assistant Professor
Department of Pharmacy Practice
Midwestern University, Chicago College of Pharmacy
Downers Grove, Illinois
Chapter e14

Robert B. Parker, PharmD
Professor
Department of Clinical Pharmacy and Translational Science
University of Tennessee Health Science Center College of Pharmacy
Memphis, Tennessee
Chapter 35

Neelam K. Patel, PharmD, BCOP

Clinical Pharmacy Specialist—Breast Medical Oncology
Division of Pharmacy
University of Texas MD Anderson Cancer Center
Houston, Texas
Chapter 145

Priti N. Patel, PharmD, BCPS
Clinical Associate Professor
University of Florida College of Pharmacy
Gainesville, Florida
Chapter 58

Charles Peloquin, PharmD, FCCP
Professor
College of Pharmacy, and Emerging Pathogens Institute
University of Florida
Gainesville, Florida
Chapter 130

Mark A. Perazella, MD, FACP
Professor of Medicine
Yale University School of Medicine
Section of Nephrology
Department of Internal Medicine
Medical Director, Acute Dialysis Program
Yale-New Haven Hospital
New Haven, Connecticut
Chapter 63

Janelle Perkins, PharmD, BCOP
Professor
Department of Pharmacotherapeutics and Clinical Research
Taneja College of Pharmacy
University of South Florida
Tampa, Florida

Chapter 157

Emily P. Peron, PharmD, MS, BCPS, FASCP, FCCP
Associate Professor
Department of Pharmacotherapy and Outcomes Science
Virginia Commonwealth University, School of Pharmacy
Richmond, Virginia
Chapter 71

Jay I. Peters, MD
Professor and Chief, Division of Pulmonary Critical Care
University of Texas Health Science Center
San Antonio, Texas
Chapter e42

Jennifer T. Pham, PharmD, BCPS, BCPPS
Clinical Pharmacist—Neonatal Intensive Care Unit
University of Illinois Hospital & Health Sciences System
Children's Hospital University of Illinois
Clinical Assistant Professor
University of Illinois at Chicago College of Pharmacy
Chicago, Illinois
Chapter e21

Stephanie J. Phelps, BSc Pharm, PharmD
Associate Dean of Academic Affairs and Professor
Clinical Pharmacy and Pediatrics
University of Tennessee, Health Science Center
Memphis, Tennessee
Chapter 74

Bradley G. Phillips, PharmD, BCPS, FCCP
Department Head and Milliken-Reeve Professor
Department of Clinical Administrative Pharmacy
University of Georgia, College of Pharmacy

Augusta, Georgia
Chapter 89

Amy M. Pick, PharmD, BCOP
Assistant Dean for Experiential Education
Office of Experiential Programs
College of Pharmacy
University of Nebraska Medical Center
Omaha, Nebraska
Chapter 153

Steven R. Pliszka, MD
Board-Certified in Child and Adolescent Psychiatry
University of Texas Health Science Center at San Antonio
San Antonio, Texas
Chapter 80

Jamie C. Poust, PharmD, BCOP
Clinical Oncology Specialist
Department of Pharmacy
University of Colorado Anschutz Medical Campus
Aurora, Colorado
Chapter 156

Elvin T. Price, PharmD, PhD, FAHA
Director of Geriatric Pharmacotherapy Program
Associate Professor
Department of Pharmacotherapy and Outcomes Science, School of Pharmacy
Virginia Commonwealth University
Richmond, Virginia
Chapter e22

Kelly R. Ragucci, PharmD, FCCP, BCPS, CDE
Professor and Chair Departments of Clinical Pharmacy and Outcomes Sciences
Professor of Family Medicine

Medical University of South Carolina, College of Pharmacy
Charleston, South Carolina
Chapter 18

Hengameh H. Raissy, PharmD
Research Professor and Vice Chair of Research
Department of Pediatrics
University of New Mexico, School of Medicine
Albuquerque, New Mexico
Chapter e47

Gautam Ramani, MD
Associate Professor of Medicine
University of Maryland—Baltimore
Baltimore, Maryland
Chapter e29

Kamakshi V. Rao, PharmD, BCOP, FASHP
Clinical Pharmacist Practitioner
Bone Marrow Transplant
University of North Carolina Medical Center
Associate Professor of Clinical Education
University of North Carolina Eshelman School of Pharmacy
Chapel Hill, North Carolina
Chapter 153

Satish S.C. Rao, MD, PhD, FRCP
Professor of Medicine
Medical College of Georgia
Augusta University
Augusta, Georgia
Chapter 49

James B. Ray, PharmD, CPE
James A Otterbeck One Point Patient Care Professorship in Hospice and

Palliative Care
Department of Pharmacy Practice and Science / Division of Applied Clinical Sciences
University of Iowa, College of Pharmacy
Iowa City, Iowa
Chapter 77

Brent N. Reed, PharmD, BCPS, BCCP

Associate Professor, Department of Pharmacy Practice and Science
University of Maryland School of Pharmacy
Baltimore, Maryland
Chapters e29 and 36

Beth H. Resman-Targoff, PharmD, FCCP

Clinical Professor
Department of Pharmacy
Clinical and Administrative Sciences
College of Pharmacy
University of Oklahoma
Oklahoma City, Oklahoma
Chapter 103

Daniel M. Riche, PharmD, BCPS, CLS

Professor
Department of Pharmacy Practice
University of Mississippi School of Pharmacy
Jackson, Mississippi
Chapter 117

Richard R. Riker, MD, FCCM

Professor of Medicine
Tufts University School of Medicine
Boston, Massachusetts
Neuroscience Institute and Department of Critical Care Medicine
Maine Medical Center

Portland, Maine
Chapter e26

José O. Rivera, PharmD
Founding Dean and Professor
University of Texas at El Paso School of Pharmacy
Adjunct Professor, Texas Tech University Health Sciences Center
El Paso, Texas
Chapter e3

Jo E. Rodgers, PharmD, BCPS, BCCP
Clinical Professor
Department of Pharmacotherapy and Experimental Therapeutics
University of North Carolina Eshelman School of Pharmacy
Chapel Hill, North Carolina
Chapter 36

Andrew M. Roecker, PharmD, BCPS
Professor and Chair
Department of Pharmacy Practice
Director of Continuing Education
Raabe College of Pharmacy
Ohio Northern University
Ada, Ohio
Chapter 131

Kelly C. Rogers, PharmD, BCCP
Professor, Clinical Pharmacy and Translational Science
University of Tennessee College of Pharmacy
Memphis, Tennessee
Chapter 32

Lauren Roller, PharmD
Assistant Professor
Department of Clinical Sciences

College of Pharmacy
Touro University
Vallejo, California
Chapter 60

John C. Rotschafer, PharmD, FCCP
Professor
University of Minnesota
College of Pharmacy
Minneapolis, Minnesota
Chapter 124

Eric S. Rovner, MD
Professor of Urology
Department of Urology
Medical University of South Carolina
Charleston, South Carolina
Chapter 101

Valerie L. Ruehter, PharmD, BCPP
Clinical Associate Professor and Director of Experiential Education
University of Missouri Kansas City, School of Pharmacy
Kansas City, Missouri
Chapter 81

Stephen J. Ryan, MD
Professor of Neurology
University of Kentucky, College of Medicine
Lexington, Kentucky
Chapter e70

Melody Ryan, PharmD, MPH, BCPS, BCGP
Professor, Department of Pharmacy Practice and Science
University of Kentucky College of Pharmacy
Lexington, Kentucky

Chapters 38 and e70

Michael J. Rybak, PharmD, MPH, PhD
Professor of Pharmacy and Medicine
Anti-Infective Research Laboratory
Department of Pharmacy Practice
Eugene Applebaum College of Pharmacy & Health Sciences
Wayne State University
Detroit, Michigan
Chapter e122

Cynthia Sanoski, PharmD, BCPS
Chair and Associate Professor
Department of Pharmacy Practice
Jefferson College of Pharmacy
Philadelphia, Pennsylvania
Chapter 39

Joseph J. Saseen, PharmD, BCPS, BCACP
Professor and Vice Chair
Department of Clinical Pharmacy
University of Colorado Anschutz Medical Campus
Aurora, Colorado
Chapter 30

Mark E. Schneiderhan, PharmD, BCPP
Associate Professor
Department of Pharmacy Practice and Pharmaceutical Sciences
University of Minnesota, College of Pharmacy
Minneapolis, Minnesota
Chapter e79

Julie M. Sease, Pharm D, FCCP, BCPS, CDE, BCACP
Senior Associate Dean and Clinical Professor
University of South Carolina College of Pharmacy

Columbia, South Carolina
Chapter 54

Jolynn Sessions, PharmD, BCOP
Clinical Pharmacist in Oncology
Mission Health System
Associate Professor of Clinical Education
University of North Carolina Eshelman School of Pharmacy
Asheville, North Carolina
Chapter 149

Roohollah Sharifi, MD, FACS
Professor of Surgery/Urology, University of Illinois at Chicago
College of Medicine
Chicago, Illinois
Chapters 99 and 100

Kayce Shealy, PharmD, BCPS, BCACP, CDE
Associate Professor
Department of Pharmacy Practice
Presbyterian College School of Pharmacy
Clinton, South Carolina
Chapter 53

Amy Heck Sheehan, PharmD
Associate Professor of Pharmacy Practice
Purdue University College of Pharmacy
Indianapolis, IN
Chapters e94 and 161

Jessica M. Shenberger-Trujillo, PhD
Clinical Assistant Professor
Associate Dean of Assessment, Accreditation, and Strategic Planning
University of Texas at El Paso
El Paso, Texas

Chapter e3

Stacy S. Shord, PharmD, FCCP, BCOP
Associate Director for Labeling
Office of Oncologic Diseases
Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Silver Spring, Maryland
Chapter 144

Sarah P. Shrader, PharmD
Professor of Pharmacy
Department of Pharmacy Practice
University of Kentucky, College of Pharmacy
Lexington, Kentucky
Chapter 18

Jeri J. Sias, PharmD, MPH
Clinical Professor
University of Texas at El Paso School of Pharmacy
Adjunct Clinical Faculty
Department of Family and Community Medicine
Paul L. Foster School of Medicine
Texas Tech University Health Sciences Center—El Paso
El Paso, Texas
Chapter e3

Debra Sibbald, BScPhm, RPh, ACPR, MA, PhD
Senior Lecturer
Division of Pharmacy Practice
Leslie Dan Faculty of Pharmacy
University of Toronto
Toronto, Ontario, Canada
Chapter 113

Tamara D. Simpson, MD
Clinical Associate Professor
Division of Pulmonary Diseases and Critical Care Medicine
University of Texas Health Science Center at San Antonio
San Antonio, Texas
Chapter e42

Douglas Slain, PharmD, BCPS, FCCP, FASHP
Professor and Chair
Department of Clinical Pharmacy
Infectious Diseases Clinical Specialist
SOP Global Affairs Liaison
West Virginia University
Morgantown, West Virginia
Chapter e17

Patricia W. Slattum, PharmD, PhD, BCGP
Professor Emeritus
Department of Pharmacotherapy and Outcomes Science
School of Pharmacy
Virginia Commonwealth University
Richmond, Virginia
Chapters e22 and 71

Erin M. Slazak, PharmD, BCPS, BCACP
Clinical Assistant Professor
Department of Pharmacy Practice
University at Buffalo School of Pharmacy and Pharmaceutical Sciences
Buffalo, New York
Chapter 108

Tawny Smith, PharmD, BCPP
Associate Professor
Department of Psychiatry University of Texas at Austin, Dell Medical School
Austin, Texas

Chapter 84

Steven M. Smith, PharmD, MPH
Assistant Professor
Department of Pharmacotherapy and Translational Research
University of Florida
Gainesville, Florida
Chapter 93

Judith A. Smith, PharmD, BCOP, CPHQ, FCCP, FISOPP, FHOPA
Associate Professor
Director, Women's Health Integrative Medicine Research Program
Division of Gynecologic Oncology
Department of Obstetrics, Gynecology, and Reproductive Sciences
University of Texas Health Science Center McGovern Medical School
Houston, Texas
Chapter 150

Jordan Smith, PharmD
Assistant Professor of Clinical Sciences
High Point University School of Pharmacy
High Point, North Carolina
Chapter e122

Todd D. Sorensen, PharmD
Professor
Department of Pharmaceutical Care and Health Systems
University of Minnesota College of Pharmacy
Minneapolis, Minnesota
Chapter 1

Kevin M. Sowinski, PharmD, FCCP
Professor and Associate Head for Faculty Affairs
Department of Pharmacy Practice

Purdue University, College of Pharmacy
Adjunct Professor
Indiana University, School of Medicine
Indianapolis, Indiana
Chapter 62

Zachary Stacy, PharmD, MS, BCPS
Pharmacotherapy Specialist
Barnes-Jewish West County Hospital
St. Louis, Missouri
Chapter e34

Steven C. Stoner, PharmD, BCPP
Chair and Clinical Professor
Division of Pharmacy Practice and Administration
University of Missouri Kansas City, College of Pharmacy
Kansas City, Missouri
Chapter 81

Danielle L. Stutzmann, PharmD, BCPP
Psychiatric Pharmacist
Children's Hospital Colorado
Greater Denver Area, Colorado
Chapter 80

Brandon James Sucher, PharmD, BCACP, CDCES, AE-C
Professor
Department of Pharmacy Practice
Regis University School of Pharmacy
Denver, Colorado
Chapter e12

Carol Taketomo, PharmD
Director of Pharmacy and Clinical Nutrition
Children's Hospital of Los Angeles

Adjunct Assistant Professor of Pharmacy Practice
School of Pharmacy
University of Southern California
Los Angeles, California
Chapter e19

Chia Jie Tan, BScPharm(Hons), BCOP
Pharmacist and Doctoral Candidate
Department of Pharmacy
National University of Singapore
Singapore
Chapter 149

Geoffrey M. Thiele, PhD
Professor
Division of Rheumatology and Immunology
Department of Medicine
College of Medicine
University of Nebraska Medical Center
Omaha, Nebraska
Chapter e102

Michael L. Thiman, PharmD, BCPS, BCACP
Clinical Assistant Professor
Department of Clinical and Administrative Pharmacy
University of Georgia College of Pharmacy
Athens, Georgia
Chapter 49

Jessica J. Tilton, PharmD, BCACP
Clinical Assistant Professor
Department of Pharmacy Practice
University of Illinois at Chicago, College of Pharmacy
Chicago, Illinois
Chapter 39

Heidi Trinkman, PharmD

Pediatric Clinical Pharmacy Specialist
Hematology/Oncology and Stem Cell Transplantation
Cook Children's Medical Center
Fort Worth, Texas
Chapter 119

Jennifer Trujillo, PharmD, BCPS, BC-ADM, CDCES

Professor
Department of Clinical Pharmacy
University of Colorado Anschutz Medical Campus
Aurora, Colorado
Chapter 91

Elena M. Umland, PharmD

Associate Provost for Interprofessional Practice and Education
Associate Dean of Academic Affairs
Professor of Pharmacy
Jefferson College of Pharmacy
Philadelphia, Pennsylvania
Chapter 96

Amy M. Vandenberg, PharmD, BCPP

Clinical Pharmacist Specialist in Psychology and Neurology
PGY2 Psychiatry Residency Program Director
Adjunct Clinical Associate Professor in Pharmacy
University of Michigan, College of Pharmacy
Ann Arbor, Michigan
Chapter 85

Sara R. Vazquez, PharmD, BCPS

Clinical Pharmacist
Department of Pharmacy Services
University of Utah Health Care
Salt Lake City, Utah

Chapter 37

Maria I. Velez, MD
Associate Director
Interventional Pulmonary Program
University of Texas Health Science Center at San Antonio
San Antonio, Texas
Chapter e42

Yolanda Vera, PharmD, BCPS, BCPPS
Pediatric Patient Care Pharmacist
McLane Children's Hospital
Baylor Scott & White Healthcare
Temple, Texas
Chapter 46

Kathleen Vest, PharmD, CPE
Professor of Pharmacy Practice
Chicago College of Pharmacy
Downers Grove, Illinois
Chapter 97

Angie Veverka, PharmD, BCPS
Director, Live Teaching
Clinical Pharmacist Educator
RxPrep, Inc.
El Segundo, California
Chapter 129

Kathryn A. Walker, PharmD, BCPS, CPE
Senior Clinical and Scientific Director of Palliative Care
MedStar Health
Baltimore, Maryland
Chapter e9

Kristina E. Ward, PharmD, BCPS
Clinical Professor and Director of Drug Information Services
University of Rhode Island, College of Pharmacy
Kingston, Rhode Island
Chapter 95

Casey S. Washington, PharmD, BCPS
Assistant Professor
Department of Pharmacotherapy and Outcomes Science
Virginia Commonwealth University School of Pharmacy
Inova Campus
Falls Church, Virginia
Chapter 111

Kristin E. Watson, PharmD, BCPS, BCCP
Associate Professor
Department of Pharmacy Practice and Science
University of Maryland School of Pharmacy
Baltimore, Maryland
Chapter e29

Lori D. Wazny, BSc (Pharm), PharmD, EPPh
Clinical Pharmacist, Manitoba Renal Program
Clinical Assistant Professor
College of Pharmacy
University of Manitoba
University of Florida Working Professional PharmD program
Department of Pharmaceutical Services
Health Sciences Centre
Winnipeg, Manitoba, Canada
Chapter 61

Robert J. Weber, PharmD, MS
Administrator and Chief Pharmacy Officer
Department of Pharmacy

Ohio State University Wexner Medical Center
Columbus, Ohio
Chapter e4

Brian Werth, PharmD
Associate Professor of Pharmacy
University of Washington School of Pharmacy
Seattle, Washington
Chapter e122

Kathryn E. Wheeler, PharmD
Associate Dean of Academic Affairs and Associate Clinical Professor of Pharmacy Practice
University of Connecticut, School of Pharmacy
Storrs, Connecticut
Chapter 98

James W. Wheless, MD
Professor and Chief of Pediatric Neurology
LeBonheur Chair in Pediatric Neurology
University of Tennessee Health Science Center
Memphis, Tennessee
Chapter 74

Sara A. Wiedenfeld, PharmD, BCPS
Clinical Assistant Professor
Department of Pharmacy Practice and Science
Division of Applied Clinical Sciences
College of Pharmacy
University of Iowa
Iowa City, Iowa
Chapter 106

Alyson G. Wilder, PharmD, BCPS, BCCCP
Clinical Pharmacy Specialist

Prisma Health Richland
Columbia, South Carolina
Chapter 54

Dennis M. Williams, PharmD, BCPS, AE-C

Associate Professor
Division of Pharmacotherapy and Experimental Therapeutics
University of North Carolina Eshelman School of Pharmacy
Chapel Hill, North Carolina
Chapter 44

Kristyn Williamson, PharmD, BCACP

Teaching Specialist
Pharmacy Learning Collaborative
College of Pharmacy
University of Minnesota
Pharmacist
School of Dentistry
University of Minnesota
Minneapolis, Minnesota
Chapter e15

Daniel M. Witt, PharmD, BCPS

Professor and Chair
Department of Pharmacotherapy
University of Utah College of Pharmacy
Salt Lake City, Utah
Chapter 37

Pei Shieen Wong, PharmD

Principal Pharmacist at Singapore General Hospital
Outram Rd, Singapore
Chapter 72

Adrian Wong, PharmD, MPH, BCPS, BCCCP

Assistant Professor of Pharmacy Practice
MCPHS University
Clinical Pharmacist, Medical Intensive Care Unit
Beth Israel Deaconess Medical Center
Boston, Massachusetts
Chapter e25

G. Christopher Wood, PharmD, FCCP, FCCM, BCPS

Professor
Department of Clinical Pharmacy
University of Tennessee, Health Science Center
Memphis, Tennessee
Chapter 75

Chanin C. Wright, PharmD

Director of Pharmacy and Nutrition, McLane Children's Hospital
Baylor Scott & White Healthcare
Temple, Texas
Chapter 46

Jean F. Wyman, MN, PhD

Professor
Cora Meidl Siehl Chair in Nursing Research, Adult and Gerontological Health Cooperative, School of Nursing
University of Minnesota
Minneapolis, Minnesota
Chapter 101

Jenna Yager, PharmD

Postdoctoral Fellow
University of Colorado Anschutz Medical Campus
Skaggs School of Pharmacy and Pharmaceutical Sciences
Aurora, Colorado
Chapter 143

Jack A. Yanovski, MD, PhD

Chief, Section on Growth and Obesity
Associate Scientific Director for Translational Medicine
Division of Intramural Research
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, Maryland
Chapter 161

Evan J. Zasowski, PharmD, MPH, BCPS, BCIDP

Assistant Professor
Department of Clinical Sciences
Touro University California College of Pharmacy
Vallejo, California
Chapter 125

Kristin M. Zimmerman, PharmD, CGP

Associate Professor
Department of Pharmacotherapy and Outcomes Science
Virginia Commonwealth University, School of Pharmacy
Richmond, Virginia
Chapter 71

Daniel A. Zlott, PharmD, BCOP

Vice President
Professional Education Resources
American Pharmacists Association
Washington, D.C.
Chapter e102

Ashley Zurek, PharmD, BCGP

Clinical Pharmacist
Internal Medicine Service
San Antonio Military Medical Center

Fort Sam Houston, Texas
Chapter e2

Foreword

The 11th edition of *Pharmacotherapy: A Pathophysiologic Approach* becomes available over 30 years after the first edition was released in 1988. Pharmacy education and practice have seen many changes over this same period. Throughout this time, *Pharmacotherapy: A Pathophysiologic Approach* has been the most adopted textbook used by colleges and schools of pharmacy in the United States to prepare students to provide a strong foundation for the provision of their patient-centered care. Moreover, with a growing acceptance in clinical care by pharmacist in other countries, *Pharmacotherapy: A Pathophysiologic Approach* has experienced a growing international audience in this same time period.

The conversion of the entry level degree required for licensure to practice pharmacy in the United States from the 5-year Bachelor of Science degree to the 6-year Doctor of Pharmacy (PharmD) occurred with the entry level pharmacy classes in the year 2000. I began my tenure as the Executive Director of the now Accreditation Council for Pharmacy Education (ACPE; https://www.acpe-accredit.org/) in the summer of 1999 and retired this past year after 20 years of service. The original all PharmD Standards in 2000 (Standards 2000) were followed by subsequent revisions, Standards 2007 and Standards 2016. The editions of *Pharmacotherapy: A Pathophysiologic Approach* during this time period paid careful attention to the evolving ACPE standards. The 11th edition is no exception.

ACPE is an affiliate member of the Joint Commission of Pharmacy Practitioners (JCPP; https://jcpp.net/). In 2013, the then 11 members of JCPP approved the following vision statement for the profession of pharmacy in the United States:

> Patients achieve optimal health and medication outcomes with pharmacists as essential and accountable providers within patient-centered, team-based healthcare.

This vision statement formed the basis of ACPE Standards 2016. New elements of Standards 2016 were the expansion of the educational outcomes required of new graduates, via the adoption of the American Association of

Colleges of Pharmacy's Center for the Advancement of Pharmacy Education (CAPE) Educational Outcomes (http://www.aacp.org/resources/education/cape/Pages/default.aspx), The educational outcomes address:

- Foundational Knowledge
- Essentials for Practice and Care
- Approach to Practice and Care
- Personal and Professional Development

The 11th edition of *Pharmacotherapy: A Pathophysiologic Approach* offers excellent information to address aspects of all four of these educational outcomes. Recognizing the need for a consistent process in the delivery of patient care across the profession, the Joint Commission of Pharmacy Practitioners (JCPP) in 2014 released the *Pharmacists' Patient Care Process (PPCP).* The process is applicable to any practice setting where pharmacists provide patient care and for any patient care service provided by pharmacists. ACPE Standards 2016 incorporated the *PPCP* as a required component of the curriculum. The 11th edition of *Pharmacotherapy: A Pathophysiologic Approach* provides a new chapter fully describing the PPCP's purpose and components. In a unique and very innovative approach the new edition provides a "patient care process box" for the clinical conditions addressed. Each "box" focuses on the collection and assessment of information relevant to the clinical condition, the development of a plan of treatment and its implementation, as well as how to monitor and evaluate the success of the plan. This new feature should make the 11th edition of *Pharmacotherapy: A Pathophysiologic Approach* stand out from any other clinical textbook for pharmacy students.

Although I have focused this foreword primarily as a textbook for faculty and students in the United States, as a site visitor for ACPE's International Services Program I became aware of how much previous editions of *Pharmacotherapy: A Pathophysiologic Approach* have been adopted in other countries and the positive reactions from our international faculty and student colleagues. Likewise, because of the new edition's focus on the PPCP and the detail with which it is applied to various clinical conditions that pharmacists face in practice, I believe the 11th edition of *Pharmacotherapy: A Pathophysiologic Approach* will prove to be an outstanding source for the continuing professional development of pharmacists in all practice settings.

Peter H. Vlasses, PharmD, DSc (Hon), FCCP
Executive Director Emeritus
Accreditation Council for Pharmacy Education (ACPE)

Preface

As 2020 dawns, the professions of pharmacy and medicine mark the 200th anniversary of an important event in the history of the use of medications in management of human disease and ailments: the founding of the United States Pharmacopeia (USP) in Philadelphia in 1820. This was the first effort to compile a formal, accepted list of the ingredients in common use in the fledgling United States and standardize the acceptable quality of the products, most of which were botanical in origin.

The founding of USP led quickly to the maturation of both pharmacy and medicine. While two medical schools had been formed in the United States in the late 1700s, pharmacy remained an apprentice-based profession. Immediately after the USP founding, pharmacy began establishing schools for educating new members of the profession, starting with the Philadelphia College of Pharmacy in 1821. The *American Journal of Pharmacy* was established soon thereafter in 1825. Formal organizations of physicians and pharmacists were founded in this era, including the British Medical Association in 1832, the American Medical Association in 1847, and the American Pharmaceutical Association in 1852.

As *Pharmacotherapy: A Pathophysiologic Approach* enters its 11th edition, these events from 200 years ago are important and relevant, for they illustrate the long-standing professional partnership between pharmacists and physicians to ensure the appropriate and optimal use of medications in the prevention and treatment of disease. These events also provide clear evidence of the importance and role of published works in establishing consensus and driving positive changes in healthcare.

As Dr. Peter Vlasses writes eloquently in the foreword to this edition, *Pharmacotherapy* has been an influential factor over the past three decades in the maturation and recognition of the clinical practice of pharmacy as a patient-oriented specialty separate from the product-oriented tasks that consumed the bulk of pharmacists' time in the past. In this 11th edition, we sought to ensure that this work continued to provide evidence-based and comprehensive information about pathophysiology of disease states and how diseases can be prevented or treated. Like those who met in Philadelphia in 1820, we also examined trends in healthcare and considered the advice of others in the field.

In doing so, we first considered the Joint Commission for Pharmacy Practitioners (JCPP) framework for providing clinically oriented patient care services, the Pharmacist's Patient Care Process. This framework is directly relevant to the educational and practice process supported by the material in this work. As noted in Chapter 1, "The *patient care process* is a fundamental series of actions that guide the activities of health professionals. All health professionals who provide direct patient care should use a systematically and consistently applied *process of care* in their practice."

When we met to plan this edition in January 2017, we felt this process of care is so congruent to our content that we made substantive changes to the online materials. By adding Patient Care Process boxes to key chapters and posting the material in Chapter 1 of this edition as an online supplemental chapter to the 10th edition, we took our first steps toward making major changes to the online content between the printing of editions. The 11th edition was built online over many months before the print version was typeset and sent to print.

The 11th edition of *Pharmacotherapy* was also informed by the 2016 version of the American College of Clinical Pharmacy Pharmacotherapy Didactic Curriculum Toolkit. We identified several conditions not covered in our 10th edition, including cardinal symptoms of disease such as pain and fever that are typically managed by the patient using over-the-counter medications and other nonprescription products.

Another trend we noted is the increasing number of specialties recognized by the Board of Pharmacy Specialties (BPS). The first edition of *Pharmacotherapy* was used as important evidence in the petition to recognize pharmacotherapy as a specialty in the late 1980s. Over the years, we have had added chapters covering areas later recognized as specialties. For this 11th edition, we realized the time had come to provide a greater level of depth for special populations in specialty areas not adequately addressed in our disease-focused, organ system approach to pharmacotherapy.

In making decisions based on these developments, our intent remains the same as in our first edition: to provide both students and practitioners with the tools they need for the contemporary practice of pharmacotherapy. Bringing these threads together, the following are the key changes and new content included in the 11th edition of *Pharmacotherapy.*

- All disease-focused chapters have one or more Patient Care Process boxes that summarize considerations for each step.
- Preclass and postclass engaged learning activities are new to the 11th

edition to support new teaching methods now commonly used in higher education.

- A new Common Health Problems section presents information on cardinal symptoms of disease that are typically managed through self-care. In addition to coverage of symptoms such as pain, fever, and cough, chapters have been added that recognize the importance of oral health to overall health and prepare pharmacists and other primary care professionals to assist patients with their daily oral health needs. Other new chapters in this section cover minor otic, ophthalmic, and dermatologic disorders.
- In a new Special Populations section, Pediatrics and Geriatrics chapters have been expanded into three-chapter units that present a greater depth of information for those practicing in these areas, which are now recognized as BPS specialties.
- Likewise, a critical care section is new in the Special Populations section that presents basic information about this specialty and points users to the relevant chapters in other parts of the book for conditions often managed in the intensive care setting.
- Within the organ-based sections of the book, new chapters have been added on age-related macular degeneration, drug-induced ophthalmic disorders, and alopecia. Other refinements and chapter consolidations are apparent in other parts of the book, especially in the Cardiovascular, Respiratory, Renal, Neurologic, Psychiatric, Endocrinologic, Gynecologic/Obstetric, and Nutritional Disorders sections.

We wish to thank our retiring editors—Barbara Wells, Robert Talbert, and Gary Matzke—who worked on the text for decades and helped make *Pharmacotherapy* the gold standard in the profession. Continuing editors DiPiro, Yee, and Posey are pleased to welcome our new editors to the team: Vicki L. Ellingrod, Stuart T. Haines, and Thomas D. Nolin.

We acknowledge the many hours that *Pharmacotherapy's* more than 300 authors—including numerous writers contributing since the first edition—have devoted to this labor of love. Without their dedication to the cause of improving pharmacotherapy and maintaining the accuracy, clarity, and relevance of their chapters, this text would unquestionably not be possible.

A special thanks goes to Michael Weitz and Juanita Thompson of McGraw Hill and Ruma Khurana of MPS Limited for leading us into the new world of online authoring tools implemented with this edition and providing the path to a 21st-century workflow. While at times our impulses bordered on those of the

Luddites, we recognize the importance of moving *Pharmacotherapy* to a world in which content can be continually updated as new data become available.

Many thanks to Terry Schwinghammer for his insights during our editor meetings and continued devotion to the *Pharmacotherapy Casebook: A Patient-Focused Approach* companion to this work and the tools, chapter updates, and innovations he has shepherded onto the Access Pharmacy website. Finally, we thank James Shanahan, Peter Boyle, and their colleagues at McGraw Hill for their consistent support of the *Pharmacotherapy* family of resources, insights into trends in publishing and higher education, and the critical attention to detail so necessary in pharmacotherapy.

The Editors
March 2020

SECTION 1 FOUNDATION ISSUES

1

The Patient Care Process

Stuart T. Haines, Mary Ann Kliethermes, and Todd D. Sorensen

KEY CONCEPTS

1. A professional patient care practice is built on three essential elements: a philosophy of practice, a patient care process, and a practice management system.
2. A professional patient care practice is predicated on a patient-practitioner relationship established through respect, trust, and effective communication. Patients, and when appropriate caregivers and family, are actively engaged in decision making.
3. Adopting a uniform patient care process—a consistently implemented set of methods and procedures—serves as a framework for each patient encounter, increases quality and accountability, and creates shared language and expectations.
4. The patient care process includes five essential steps: collecting subjective and objective information about the patient; assessing the collected data to identify problems and set priorities; creating an individualized care plan that is evidence-based and cost-effective; implementing the care plan; and monitoring the patient over time during follow-up encounters to evaluate the effectiveness of the plan and modify it as needed.
5. The patient care process is supported by three inter-related elements: communication, collaboration, and documentation. Interprofessional teamwork and information technology facilitate the effective and efficient delivery of care.
6. A practice management system includes the infrastructure to deliver care. This includes physical space, documentation systems, payment for services, and qualified support personnel.

Preclass Engaged Learning Activity

For an overview of the importance of applying a consistent process of care in practice, listen to the following PharmacyForward podcast episodes:

- Pharmacists Patient Care Process - Episode I (Dr. Todd Sorensen) https://tinyurl.com/y2y8lht7
- Pharmacists Patient Care Process - Episode II (Dr. Mary Ann Kliethermes) https://tinyurl.com/y4jp56py
- Pharmacists Patient Care Process - Episode III (Dr. Kristina Butler) https://tinyurl.com/y3uuhwqb

INTRODUCTION

The *patient care process* is a fundamental series of actions that guide the activities of health professionals. All health professionals who provide direct patient care should use a systematically and consistently applied *process of care* in their practice.[1] Until recently, the language to describe the process for delivering comprehensive medication management services was ill-defined. In 2014, the Joint Commission for Pharmacy Practitioners (JCPP)—representing 11 national pharmacy organizations—endorsed a framework for providing clinically oriented patient care services called the Pharmacist's Patient Care Process.[2] However, the framework and the language to describe the process are not unique to the profession of pharmacy. Indeed, medicine, nursing, and dentistry all follow a putatively similar process of care[3] (see **Table 1-1**). For example, the American Nursing Association outlines the nursing process with steps that include assessment, diagnosis, outcomes/planning, implementation, and evaluation.[4] The Academy of Nutrition and Dietetics collapses these general steps into four steps, outlining the nutrition care process to include nutrition assessment, diagnosis, intervention, and monitoring/evaluation.[5] Although the care process is similar across disciplines, each health profession brings a unique set of knowledge, skills, attitudes, and values to the patient encounter.

TABLE 1-1 Professional Standards of Care and Their Domains

Primary Care IPC-2[6,7]	Dieticians: Nutrition Care Process[8]	Specialty Nursing: Standards of Practice[9]	Physical Therapists[10]
Symptoms, complaints	Nutrition assessment	Assessment	Examination
Diagnostic screening, prevention	Nutrition diagnosis	Diagnosis	Evaluation
Treatment, procedures, medication	Nutrition intervention	Outcomes identification	Diagnosis
Test results	Nutrition monitoring and evaluation	Develops plan of care	Prognosis
Administrative		Implements plan	Plan of care
Other		• Co-coordination of care • Health teaching and promotion • Prescriptive authority and treatment	Reexamination
Diagnoses, diseases		Evaluation	Discharge/ Discontinuation summary

Health professionals who provide direct patient care are often called *practitioners*. To *practice* is what health professionals do to bring their unique knowledge and skills to patients. A practice is not a physical location or simply a list of activities. Rather, a professional practice requires three essential elements: (1) a philosophy of practice, (2) a process of care, and (3) a practice management system.[3] These three inter-related concepts make the delivery of patient-centered care possible.

Health professionals have an ethical obligation to promote the health and well-being of the patients they serve. Thus, a philosophy—the moral purpose and a commonly held set of values that guides the profession—is the critical foundation on which the practices of pharmacy, medicine, nursing, and dentistry are built.[11] A philosophy of practice is often formally articulated in the professional code of ethics endorsed by professional organizations and an oath

that is recited by members of the profession during rituals and ceremonies. In addition to a code of ethics, most professions have an informal set of beliefs and values that also inform the self-proclaimed and societal expectations. For example, the concept of *pharmaceutical care* is not formally included in the code of ethics for the profession of pharmacy or the oath of a pharmacist.[12,13] However, informally, pharmacists understand they have a unique responsibility for addressing the drug-related needs of patients and should be held accountable for preventing, identifying, and resolving drug therapy problems.[14] Similarly, dentistry, nursing, and medicine have both formal and informal expectations that guide their professional practice.

A process of care that is systematically and consistently applied during each patient encounter increases the likelihood that optimal health outcomes are achieved.[15] The patient care process used throughout this book includes five essential steps: (1) collecting subjective and objective information about the patient; (2) assessing the collected data to identify problems, determine the adequacy of current treatments, and set priorities; (3) creating an individualized care plan that is evidence-based and cost-effective; (4) implementing the care plan; and (5) monitoring the patient over time during follow-up encounters to evaluate the effectiveness of the plan and modify it as needed (see **Fig. 1-1**). In addition to the five fundamental steps, a patient-centered approach to decision-making is essential.[16] To be patient-centered requires effective communication and seeking to understand the patient's needs, preferences, and values. It also requires interprofessional collaboration — working with other health professionals to development and implement a shared plan of care.[17] Each step of the process must be documented. These steps are interdependent and completing all five steps is necessary to achieve the greatest impact. While the process of care is common to all, each profession has a unique body of knowledge and skills they bring to bear when assessing the data and formulating plans.[3]

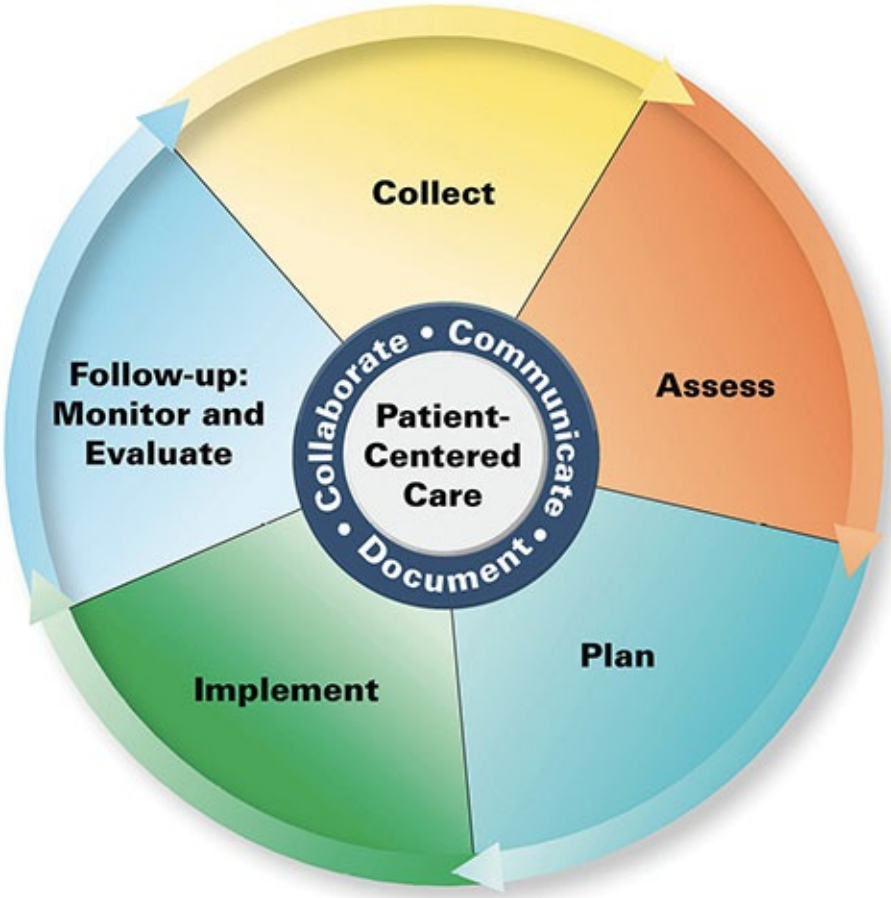


FIGURE 1-1 The Pharmacist's Patient Care Process endorsed by the Joint Commission for Pharmacy Practitioners (2014).

A practice must also have a practice management system that supports the efficient and effective delivery of services.[3] Without a well-defined practice management system, the practice would not be sustainable. This includes the infrastructure—the physical, financial, and human resources—as well as policies and procedures to carry out the patient care work. Successful practices have a clear mission statement that defines who the practice serves, the organizational values, and what they hope to accomplish. Furthermore, to achieve its mission, a practice must implement quality improvement methods that measure, evaluate, and improve the actions of practitioners (individually) and the practice (collectively).

While every practice is built on three essential elements—a philosophy of practice, a well-defined patient care process, and a practice management system—the focus of this chapter is to describe the patient care process applied to drug therapy management and explore some environmental issues that are influencing the adoption and application of this process by pharmacists.

IMPORTANCE OF A STANDARD CAREPORTANCE OF A STANDA PROCESS

It is well understood that healthcare is a complex business. Since the turn of the twenty-first-century, much effort has focused on gaining control of a disparate, disjointed, costly health system that is not adequately producing desired patient outcomes despite the healthcare workforce laboring harder than ever. Spurred by the Institute of Medicine's *Crossing the Quality Chasm* report from 2001,[18] which set the framework for redesigning healthcare delivery, healthcare institutions and practitioners have embraced the Triple Aim[19] with a focus on patient-centeredness, safety, and quality improvement (see **Fig. 1-2**). The Triple Aim can only be achieved with significant transformations in the delivery of care and by adopting payment models based on value.

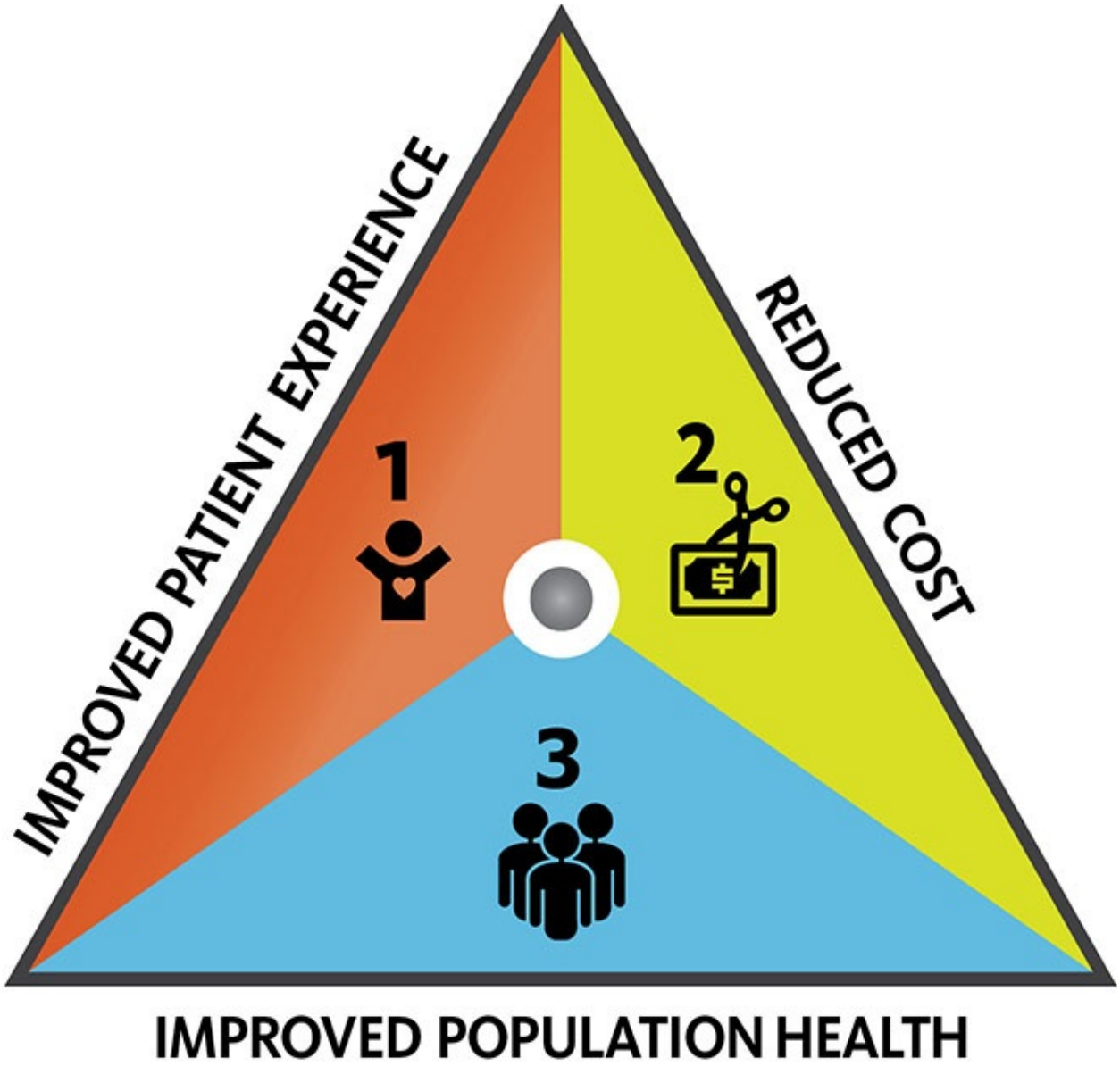


FIGURE 1-2 The Triple Aim in Healthcare.

To accelerate the requisite redesign of healthcare delivery, the Institute for Healthcare Improvement has developed guiding principles or "rules" for workforces and healthcare communities. Among these principles is to standardize what works in order to reduce unnecessary variation. Standardization is important because healthcare systems are embedded in a network that reaches well beyond traditional walls.[20] A lack of a standard process of care creates an environment that may result in unacceptable gaps in care. For a specific patient care service to be widely adopted and valued, it is imperative that clarity exists both in the execution of care and the terminology used to describe the care.

The stimulus for developing the patient care process for pharmacy was the wide variation observed as pharmacists provided direct patient care, often using the same terminology to describe diverse services or conversely, the same service is described using different terminology. As patient care services provided by pharmacists, physicians, and any other healthcare practitioner cannot operate in a silo, the services must be clearly articulated and well understood by patients, their caregivers, payers, and other members of the care team. Without a consistent patient care process, it has been challenging for the pharmacy profession to communicate the pharmacist's role to groups external to the profession and establish the distinct value pharmacists bring to an interprofessional care team. Moreover, the patient must know and understand what is to be delivered and to determine how best to receive the care provided. Likewise, other members of the healthcare team must determine how best to integrate the pharmacist's work into their efforts caring for the patient.

Creating a standardized process of care is not unique to pharmacy. It is well recognized in healthcare that setting standards encourage providers to approach patient care in a consistent manner. Systematically implementing a framework for care that is consistently applied assures no important step is overlooked and actions that may lead to greater harm than benefit are reduced or eliminated. Defining the standards of care enables the generation of outcome data that can be compared and used to demonstrate the value of a service. In a rapidly changing environment, the structure is essential to maintain consistency. In the hospital setting, care pathways and standard order sets are examples of standardized care processes that have been used for many years. Creating a standardized patient care process is not intended to re-invent "the wheel" but set a common framework.

A process of care must be built on a set of fundamental steps that can address the wide range of complexity that exists among patients. The process needs to be adaptable to varied settings, diverse populations, and different acuity levels. The process described throughout this text provides a unifying and comprehensible approach that is universally recognized.

PATIENT CARE PROCESS TO OPTIMIZE PHARMACOTHERAPY

There are two aspects that typically differentiate a profession-specific process of care. First, the application of the care process is defined within the context of the profession's knowledge and expertise. For pharmacy, the patient care process is

focused on a patient's medication-related needs and their experience with medication therapy.[3] Dentists and dental hygienists employ a patient care process that is focused on a patient's oral health needs.[21] The nursing care process is applied to provide a holistic approach to a patient's health needs and include physical and mental health, sociocultural issues, spirituality, as well as economic and lifestyle factors.[4] The general approach to providing care to an individual patient in each of these disciplines is similar; however, the focus of the process is distinct.

The second way in which each profession uniquely addresses a patient's needs is the manner in which patient-specific information is assessed. When assessing information collected from a patient (eg, history of present illness, physical examination, laboratory data), physicians employ a clinical reasoning process called "differential diagnosis" to weigh the probability of one disease versus other diseases that possibly account for the patient's signs and symptoms. In the case of dental hygienists, the American Dental Hygienists Association notes that an assessment not only includes a health history and clinical assessment, but also a "risk assessment" that includes 11 areas of evaluation.[5] For pharmacists providing comprehensive medication management, the assessment step involves a systematic examination of the indication, effectiveness, safety, and adherence for each of the patient's medications. This is a unique way of approaching a patient's health needs. No other discipline applies a systematic assessment process to a patient's medications and their medication experience in this manner.

Several publications and resources have outlined elements of the patient care process to deliver comprehensive medication management services.[2,6,11,17,22,23] There is relative consistency between these sources regarding the core elements. What varies is the specificity of the operational definition of each of the process components. Detailed operational definitions help to establish consistency across all practitioners applying the patient care process.[23] It is important to note that this care process is not specific to a care setting—the process can be applied in any setting when providing comprehensive medication management. What often varies is the information collected and its source as well as the duration of time to complete the process. For example, in an ambulatory care clinic the patient is often the most important source of information but in a critical care unit of a hospital there is a greater reliance on laboratory tests and special diagnostic studies. Similarly, the process of care unfolds in hours or days in acute care settings but may extend over weeks or months in chronic care environments.

Collect Information

When initiating the patient care cycle, a practitioner assures the collection of the necessary subjective and objective information about the patient and is responsible for analyzing the data in order to understand the relevant medical needs, medication-related problems, and clinical status of the patient. In some cases, this information will be directly collected by interviewing the patient or reviewing a medical record. In other cases, the practitioner may rely on other personnel to collect the information that will be used in the assessment. This may include a blood pressure determined by a clinical assistant or a list of active medications recorded by a nurse. However, it is ultimately the practitioner's responsibility to assure that all of the necessary information is collected and that the data is accurate, regardless of the source. This information is critical to the ability of the practitioner to complete an assessment that will appropriately address all of a patient's medication-related needs (see **Table 1-2**).

TABLE 1-2 Collect Patient-Specific Information

Functional Definition[23]

The practitioner assures the collection of the relevant and necessary subjective and objective information about the patient and is responsible for analyzing the data in order to understand the relevant medical/medication history and clinical status of the patient.

Operational Definition

1. Review the electronic health record to collect and organize relevant information (eg, patient demographics, active medical problem list, admission and discharge notes, office visit notes, laboratory values, diagnostic tests, medication lists).
2. Conduct a comprehensive medication review with the patient. When conducting a comprehensive medication review:
   - Inquire as to whether the patient has any questions or concerns for the visit.
   - Inquire about use of alcohol, tobacco, caffeine, as needed.
   - Inquire about immunizations.
   - Inquire about history of allergies and adverse effects.
   - Obtain and document a complete medication list that includes all prescription and nonprescription medications as well as complementary and alternative medicine the patient is taking (eg, name, indication, strength and formulation, dose, frequency, duration, and response to medication).
   - Gather past medication history, if pertinent.
   - Collect information pertaining to the patient's medication experience (eg, beliefs, expectations, and cultural considerations related to medications).
   - Determine the patient's personal goals of therapy.
   - Determine if patient is able to appropriately use/administer medication(s)
   - Inquire about the patient's ability to access medications, considering the ability to pick up medications and ability to afford medications.
   - Inquire as to whether the patient independently manages his/her medications or if they have help at home.
   - Inquire as to how the process of managing medications works at home (eg, pillboxes, calendars, reminders).
   - Inquire about the patient's adherence to his/her medications.
   - Inquire about the patient's appropriate use of his/her medications.
   - If nonadherence or misuse is a problem, explore reasons.
   - Gather any additional information that may be needed (eg, physical assessment, review of systems, home-monitored blood glucose, and/or blood pressure readings).
3. Analyze and synthesize subjective and objective information gathered prior to and during the visit in preparation for formulating an assessment of the patient's active medical problems and medication therapy problems.

Assess Information and Formulate a Medication Therapy Problem List

Once all of the information deemed necessary to conduct a comprehensive assessment of the patient and their medication-related needs has been collected, the assessment is organized into a problem list consisting of the patient's active medical problems and medication therapy problems. Once identified, problems are prioritized to make decisions regarding the patient's medication therapy in order to offer the best opportunity to achieve the patient's overall health goals. In doing so, the practitioner reviews each medical condition and medication to make sure that each current medication is *indicated* (or necessary) for the condition for which it is being taken and that each condition that requires drug therapy is being appropriately treated. Then the practitioner determines whether each medication the patient is taking is *effective*, achieving the intended outcome. This includes assuring the medication is the most appropriate option for the patient and is at a dose that is expected to achieve the intended effect. Next, the practitioner considers the *safety* of each medication, assuring that the patient is not experiencing or being exposed to an unnecessary risk of adverse effects or an unintended interaction. Finally, the practitioner then evaluates each medication for *adherence*-related concerns. This includes assuring the patient can take the medication as intended, considering issues such as access and affordability as well as sufficient knowledge and ability to appropriately administer the medication. Throughout the assessment process, practitioners must keep the patient's goals for therapy at the forefront of their decision-making. Table 1-3 outlines the assessment process applied when optimizing pharmacotherapy.

TABLE 1-3 Assess Patient-Specific Information to Determine Health-Related Needs

***Functional Definition*[23]**

The practitioner assesses the information collected and formulates a problem list consisting of the patient's active medical problems and medication therapy problems in order to prioritize medication therapy recommendations to achieve the patient's overall health goals.

Operational Definition

1. Assess the patient's active medical conditions taking into account clinical and patient goals of therapy.
2. Assess the **indication** of each medication the patient is taking. When assessing the indication of each medication, consider the following:
   - Does the patient have an indication for the medication?
   - Is the medication appropriate for the medical condition being treated?
   - Does the patient have an untreated medical condition that requires therapy, but is not being treated or prevented?
3. Assess the **effectiveness** of each medication the patient is taking. When assessing the effectiveness of each medication, consider the following:
   - Is the patient meeting both clinical and personal goals of therapy?
   - Is the most effective drug product being used for the medical condition?
   - Is the dose and duration appropriate for the patient?
   - Are laboratory test needed to monitor the effectiveness of medication therapy, but have not been obtained?
4. Assess the **safety** of each medication the patient is taking. When assessing the safety of each medication, consider the following:
   - Is the patient experiencing an adverse event from a medication?
   - Is the dose too high for the patient?
   - Do safer alternatives exist?
   - Are there any pertinent drug-disease, drug-drug, or drug-food interactions?
   - Are laboratory test needed to monitor the safety of medication therapy, but have not been obtained?
5. Assess **adherence** and the patient's ability to take (eg, administration, access, affordability) each medication. When assessing adherence, consider the following:
   - Is the patient able to access the medications, and, if not, why?
   - Is the patient able to afford the medication(s), and, if not, why?
   - Are the medications taken at times during the day that are appropriate to optimize effectiveness and minimize harm, but also are convenient for the patient?
   - Is the patient taking the medication as prescribed/instructed or are doses missed? If doses are missed, why?
   - Is the formulation appropriate for the patient (eg, can the patient swallow it)?
6. Formulate a medication therapy problem list, classifying the patient's medication therapy problems based on indication, effectiveness, safety, and adherence.
7. Prioritize the patient's medication therapy problems.

It is critical that the practitioner completes their assessment and defines a problem list considering indication, effectiveness, safety, and adherence *in this order*. This order of assessment ensures that the most relevant issue affecting the patient is identified. For example, there is a great deal of emphasis placed on improving patient adherence to medications, with nonadherence rates reported to range from 28% to 65%.[24,25] However, if a patient is prescribed a medication that is not indicated or is causing an adverse effect, focusing time and attention toward improving medication adherence is misguided and does not address the most important medication therapy problem. Selection of the most appropriate medication for the indication is the primary medication-related need that must be resolved.

The output of the assessment is a medication therapy problem list, prioritized in the order of importance from both the patient's and practitioner's perspective. Typically, the problem list is framed in a categorical system of medication therapy problems. A nationally recognized system for categorizing the output of a practitioner's assessment is now recognized by the Pharmacy Quality Alliance (see **Table 1-4**). There are ten medication therapy problem categories and these align with the four areas of medication use assessment.[26]

TABLE 1-4 Medication Therapy Problem Categories Framework[26]

Medication-Related Needs	Medication Therapy Problem Category
Indication	Unnecessary medication therapy
	Needs additional medication therapy
Effectiveness	Ineffective medication
	Dosage too low
	Needs additional monitoring
Safety	Adverse medication event
	Dosage too high
	Needs additional monitoring
Convenience	Adherence
	Cost

When this assessment approach is applied, a relatively consistent pattern of medication therapy problems emerges.[27-29] The categories identified with the greatest frequency are "needs additional therapy" and "dose too low" followed

by “adherence.” The other categories are observed less frequently. It should be noted that these reported trends all come from the application of this assessment process in ambulatory care settings. It is likely that the distribution of medication therapy problems would differ in acute care settings.

Develop the Care Plan

Upon completion of the assessment and establishing a prioritized list of medication therapy problems, an individualized patient-centered care plan that is evidence-based and as affordable as possible for the patient is created. The plan should be developed in collaboration with the patient or caregiver to ensure that it meets with the patient’s expectations and priorities. It also should be developed in collaboration with other healthcare professionals to ensure that all healthcare providers involved with the patient’s care agree and support the plan.

The care plan will include goals of therapy and outline contingencies to adjust medications, doses, or delivery as well as monitoring parameters. It will establish time frames for follow-up and clearly state who will be responsible for each component of the care plan. The steps for developing a patient-centered care plan are outlined in **Table 1-5**.

TABLE 1-5 Develop the Care Plan

Functional Definition[23]

The practitioner develops an individualized patient-centered care plan, in collaboration with other healthcare professionals and the patient or caregiver that is evidence-based and as affordable as possible for the patient.

Operational Definition

1. Develop a care plan to manage the patient's active medical conditions and resolve the identified medication therapy problems.
   - Coordinate care with the primary care provider and other healthcare team members to reach consensus on the proposed care plan, when needed.
2. Identify the monitoring parameters important to assess ongoing effectiveness, safety, and adherence, including frequency of follow-up monitoring.
3. Design personalized education and interventions.
4. Review and reconcile all medication lists (eg, from the medical record, patient, pharmacy) to arrive at an accurate and updated medication list.
5. Determine who will implement components of the care plan (ie, patient, pharmacist, other providers).
6. Determine the appropriate time frame for patient follow-up.
7. Determine the appropriate mode for follow-up (eg, phone, face-to-face).

Implement the Care Plan

Once a care plan is established, the practitioner implements the plan designed to prevent and resolve medication therapy problems. The care plan will likely include activities that the patient and other healthcare providers will be responsible; however, it is the duty of the practitioner to ensure that each of the elements of the plan has been implemented in a time frame that is reasonable and effective (see Table 1-6).

TABLE 1-6 Implement the Care Plan

***Functional Definition*[23]**

The practitioner implements the care plan in collaboration with other healthcare professionals and the patient or caregiver.

Operational Definition

1. Discuss the care plan with the patient.
2. Educate the patient on his/her medications and goals of therapy.
3. Ensure patient understanding of and agreement with plan.
4. Implement those recommendations that you have the ability to implement in your scope of practice.
5. If the practitioner cannot independently implement a recommendation(s), communicate the care plan to the rest of the care team, indicating where implementation of the plan is required by another member of the team.
6. Document the encounter in the electronic health record (eg, assessment, medication therapy care plan, rationale, monitoring, and follow-up).
7. Arrange patient follow-up based on determined time frame.
8. Communicate instructions for follow-up with the patient. Determine the appropriate mode for follow-up (ie, phone, face-to-face).

There are many tools and resources that may be used to support a patient and/or their caregivers to successfully implement the care plan. It is in this part of the patient care process where practitioners will employ strategies such as patient education, motivational interviewing techniques, tools that support medication adherence, and patient self-monitoring technologies. Each of these tools and resources are approaches to best meet the needs of the patient and their medication-related goals.

Follow-up with the Patient

After the initial implementation of a care plan, ongoing monitoring and follow-up to evaluate the effectiveness and safety of the plan are essential. The plan should be modified as needed in collaboration with other healthcare professionals and the patient or caregiver. This process of follow-up is critical and demonstrates the practitioner has assumed responsibility for the patient's medication-related needs. While a practitioner who serves as a consultant may not follow up to determine if the problem has been resolved, this is inconsistent with the expectations of a comprehensive medication management practice or the patient care process. As a healthcare practitioner who has assumed an important role in a patient's care, it is a responsibility of the practitioner to determine the outcome of drug therapy and take additional action if necessary.

This process of follow-up can occur through a variety of mechanisms including face-to-face encounters, phone calls, electronic health record messaging, and telehealth technologies (see Table 1-7).

TABLE 1-7 Follow-Up with the Patient

***Functional Definition*[23]**

The practitioner provides ongoing monitoring and follow-up to evaluate the effectiveness and safety of the care plan, and modifies the plan, when needed, in collaboration with other healthcare professionals and the patient or caregiver.

Operational Definition

1. Provide targeted follow-up and monitoring (whether in person, electronically, or via phone) to the patient, where needed, to monitor response to therapy and/or refine the care plan to achieve patient and clinical goals of therapy (ie, quick check-ins to monitor blood sugar or blood pressure, adjust insulin, check INRs, provide education).
2. Repeat a comprehensive medication management (CMM) follow-up visit at least once within 1 year of the CMM initial visit, whereby all steps of the CMM Patient Care Process are repeated to ensure continuity of care and ongoing medication optimization.
3. Refer the patient back to the provider (and document accordingly) if all medication therapy problems identified on previous visits have been resolved, no new problems are identified, and it is determined that the patient no longer needs CMM services.

The frequency to which follow-up occurs varies from setting to setting. A practitioner practicing in an acute care environment will possibly transfer responsibility for follow-up to other providers, including another pharmacist, when the patient transitions to another setting. In the ambulatory care setting, a practitioner should ensure that a patient has a comprehensive evaluation of their medications and health status annually, at a minimum. In some cases, the nature of the patient's medication therapy problems may be resolved to the degree to which the patient no longer requires ongoing monitoring. In such cases, the patient is referred back to the primary care provider for ongoing follow-up and monitoring.

ENVIRONMENTAL ISSUES

The third critical element of practice is a practice management system. The specifics of any practice management system are based on fundamental business

principles and the requirements of the particular type of healthcare setting where the practice exists.[30] In today's healthcare environment there are essential aspects of managing a practice that practitioners must consider—the metrics to ensure patient health outcomes are being achieved; efficient workflow; communication and documentation using the power of information technology (IT); and data that accurately reflects the attribution and value the practitioner brings to patient care.

Quality Metrics

Dr. Avedis Donabedian, considered the father of quality improvement in healthcare, defined standards as the desired and achievable performance related to a given parameter—an objective, definable, and measurable characteristic of the structure, the process, or the outcome of the care.[31] In order to determine quality, there must be a standard to measure the level of quality against. The patient care process sets a standard of achievable performance by defining the parameters of the process that can be measured. With the movement toward outcome-based healthcare models and value-based payment systems, it is critical to objectively measure the impact a patient care service has on a patient's health and well-being. This allows the linkage from the standard process, such as what health problems were identified and how they were addressed during the patient encounter, to the desired outcomes. For the process to be measurable, each element must be clearly defined and performed in a similar manner during each patient encounter. The lack of clarity and consistency has been the Achilles heel in the evidence to support the value of pharmacists' patient care services.[32] The standard process gives pharmacists an opportunity to show value on a large scale because the services are comparable and clearly understood across practice settings.

Workflow, Documentation, and Information Systems

The generation and analysis of data regarding the care provided and the resulting health outcomes are becoming increasingly important not only to organizations but to individual providers as well. Healthcare systems are rapidly embracing the power of technology to analyze information to gain important insights. This technology is only useful if clinical care is robustly documented, collected, and managed. Data is optimally collected as part of the workflow process using IT tools. Creating the requisite tools, however, requires a standard process to build cohesive systems with uniform data sets. This allows the reporting of

comparable information to providers and others.

The uniform patient care process sets a standard for the workflow that allows IT systems to capture and extract data for analysis and sharing. Imagine a patient encounter with a practitioner in any setting. The practitioner often has some patient information available prior to encounter; however, the practitioner will most likely collect new information. This work can now be electronically captured in the collect phase of the workflow. The practitioner will then assess the information and identify new or unresolved medication-related problems. Likewise, this work is captured in the assessment phase of the visit. The practitioner will then update or add to the team's plan of care for the patient and the information can be electronically captured in the planning phase. During the encounter, the practitioner may be able to implement some or all of the plan, and the tasks or services performed are captured during the implementation phase. During the follow-up and monitoring phase, the resolution of the identified problems and the results are documented. The information collected can now be exchanged, extracted, and analyzed at the provider, population, organizational, and payer levels because it is defined and collected in a uniform manner.

The ability to capture clinical data is currently available through a number of coding systems (see **Table 1-8**). The Pharmacy Health Information Technology Collaborative has been at the forefront in assuring pharmacist patient care services are part of the IT systems being developed for the healthcare system in the United States.[33] The collaborative has developed several documents demonstrating how the patient care process and Systematic Nomenclature of Medicine—Clinical Terms (SNOMED - CT) codes may be used to document a patient interaction and linked to patient outcomes attributable to the pharmacist-provided care. The documents are easily accessible on the Pharmacy Health Information Technology (HIT) website (http://pharmacyhit.org/). It is not necessary for practitioners to know each of the codes, but to understand how they operate behind the scenes when performing and documenting their clinical activities. This will enable practitioners to assist information technologists to effectively design systems to accurately document the elements of the process that can produce the data on medication-related outcomes.

TABLE 1-8 Clinical Coding Systems

System Name	Contents
International Classification of Disease (ICD)	Coding for medical procedures and encounters. Currently in its 10th edition with the 11th edition expected in 2018
Systematized Nomenclature of Medicine—Clinical Terms (SNOMED-CT)	A coding system of clinical terminology representing the full scope of clinical information in healthcare
Logical Observation Identifiers Names and Codes (LOINC)	Vocabulary database of universal identifiers for laboratory and clinical test results
Healthcare Common Procedural Coding System (HCPCS)	CMS established billing codes for Medicare for medical procedures that include CPT as well as codes not covered by CPT
Current procedure terminology (CPT)	Coding system for medical procedures developed and maintained by the American Medical Association primarily used for billing services
RxNorm	Standardized nomenclature for clinical drugs created by the National Library of Medicine

Documentation, Attribution, and Payment

Payment to healthcare providers for patient care services in the United States has traditionally been based on the documentation and reporting of standard processes of care. Rules and guidance from Medicare and the Center for Medicare and Medicaid Services (CMS) are considered the billing and payment standard for healthcare providers both for governmental and commercial payers. Eligible Medicare Part B providers such as physicians, nurse practitioners, and physician assistants must follow standards set forth in the CMS Documentation Guidelines for Evaluation and Management Services.[34] Pharmacists are familiar with these standards because they often use the SOAP (Subjective, Objectives, Assessment, and Plan) note format when documenting care including the patient's chief complaint, history of present illness, past medical history, social history, family history, review of systems, physical examination, assessment, and plan. Built on top of the standard documentation requirement is the reporting of the complexity of the care provided. This added layer of documentation is determined by the number of required elements in each documentation domain. A billing code can then be assigned to that patient care encounter which, in turn,

equates to a payment commensurate with the level of care provided. While this process is the basis for the current fee-for-service payment structure, it is likely the general format that will remain in any new payment model. Similarly, other providers such as dieticians and physical therapists have standard processes, workflow, and documentation that enable the payment structures in their practice model.

Pharmacists have traditionally used the SOAP note format when documenting care for patients. This is particularly appropriate when providing services incident to an eligible Medicare Part B provider. It is the standard documentation required in that circumstance. However, some elements for the SOAP note, which are required when using certain billing codes, are not routinely performed by pharmacists (eg, comprehensive physical examination). The pharmacist patient care process establishes a standard framework that reflects the pharmacist's work. Using a standard care process accompanied with a standard documentation framework will result in efficiencies of practice, enable appropriate and accurate billing, and facilitate the attribution of care to desired patient outcomes needed in value-based payment models.

CONCLUSION

A standard process of care provides the structure that all practitioners should follow and, when implemented correctly and consistently, can improve the quality of care. It provides a common language that defines roles, responsibilities, and expectations. Comprehensive medication management involves a five-step process: collect, assess, plan, implement, and follow-up. A standard process of care informs the creation of quality metrics and is the foundation of practitioner workflow, the structure of health information systems, and billing for patient care services.

Postclass Engaged Learning Activity

Pick three chapters in this textbook that include a Patient Care Process Box. Compare and contrast the structure and basic elements of each patient care process. What do these processes appear to have in common beyond the five key steps (eg, Collect, Assess, Plan, Implement, and Follow-up: Monitor and Evaluate)? How are they different? Don't focus too much on the details (eg, what specific laboratory tests are needed) but rather general elements. For example, is physical examination data important information to collect in all

or just some of these diseases? Is patient education a key element in every process of care or just some? Is the follow-up time frame similar or different? Based on your analysis, create a table with four rows and three columns, like this:

Chapter Title	Common Elements of Patient Care Process	Unique Elements of Patient Care Process

REFERENCES

1. Harris IM, Phillips B, Boyce E, et al. Clinical pharmacy should adopt a consistent process of direct patient care. *Pharmacotherapy*. 2014;34(8):e133–e148. doi:10.1002/phar.1459.
2. Joint Commission of Pharmacy Practitioners. *Pharmacists' Patient Care Process*. May 29, 2014. Available at: https://jcpp.net/wp-content/uploads/2016/03/PatientCareProcess-with-supporting-organizations.pdf.
3. Cipolle JR, Strand L, Morley P. Pharmaceutical care as the professional practice for patient-centered medication management services. In: Cipolle JR, Strand L, Morley P, eds. *Pharmaceutical Care Practice: The Patient Centered Approach to Medication Management*. 3rd ed. New York, NY: McGraw-Hill Companies; 2012;37–72.
4. American Nurses Association. The Nursing Process. https://www.nursingworld.org/practice-policy/workforce/what-is-nursing/the-nursing-process/. Accessed October 3, 2018.
5. Writing Group of the Nutrition Care Process/Standardized Language Committee. Nutrition care process and model Part I: The 2008 update. *J Am Diet Assoc*. 2008;108(7):1113–1117. doi:10.1016/j.jada.2008.04.027.
6. Phillips RLJ, Klinkman M, Green LA. *Conference Report: Harmonizing Primary Care Clinical Classification and Data Standards*. Washington, DC; 2007. http://www.graham-

center.org/content/dam/rgc/documents/publications-reports/monographs-books/harmonizing-primary-care.pdf. Accessed July 27, 2017.

7. ICPC Primary Health Care Classification Consortium. International Classification of Primary Care (ICPC-2) Process Codes update 2016. http://www.ph3c.org/4daction/w3_CatVisu/en/icpc.html?wCatIDAdmin=1106. Accessed July 27, 2017.
8. Lacey K, Pritchett E. Nutrition care process and model: ADA adopts road map to quality care and outcomes management. *J Am Diet Assoc*. 2003;103(8):1061–1072. doi:10.1053/jada.2003.50564.
9. Tomajan K, Barker CR, Canariato S V, et al. *Recognition of a Nursing Specialty, Approval of a Speciality Nursing Scope of Practice Statement, and Acknowledgment of Specialty Nursing Standards of Practice*. Silver Spring, MD; 2010. http://www.nursingworld.org/MainMenuCategories/ThePracticeofProfessic S-Booklet.pdf. Accessed July 27, 2017.
10. American Physical Therapy Association. *Guidelines: Physical Therapy Documentation of Patient/Client Management*. Alexandria, VA: 2009. https://www.apta.org/uploadedFiles/APTAorg/About_Us/Policies/BOD/Pra Accessed July 27, 2017.
11. Cipolle RJ, Strand L, Morley P. Toward a philosophy of pharmaceutical care practice. In: Cipolle RJ, Strand L, Morley P, eds. *Pharmaceutical Care Practice: The Patient-Centered Approach to Medication Management Services*. 3rd ed. New York, NY: McGraw-Hill Companies; 2012;94–100.
12. American Pharmacists Association. Code of Ethics for Pharmacists. Published 1994. http://www.pharmacist.com/code-ethics. Accessed October 3, 2018.
13. American Pharmacists Association. Oath of a Pharmacist. Published 2007. http://www.pharmacist.com/oath-pharmacist. Accessed October 3, 2018.
14. American Society of Hospital Pharmacists. ASHP Statement on Pharmaceutical Care. *Am J Hosp Pharm*. 1993;50:1720–1723.
15. Donabedian A. The quality of care: How can it be assessed? *JAMA*. 1988;260(12):1743–1748. doi:10.1001/jama.1988.03410120089033.
16. Epstein RM, Street RL, Jr. The values and value of patient-centered care. *Ann Fam Med*. 2011;9(2):100–103. doi:10.1370/afm.1239.
17. American College of Clinical Pharmacy. Standards of practice for clinical pharmacists. *Pharmacotherapy*. 2014;34(8):794–797.

doi:10.1002/phar.1438.

18. Institute of Medicine. *Crossing the Quality Chasm: A New Health System for the 21th Century*. Washington, DC: National Academies Press; 2001. doi:10.17226/10027.
19. Berwick DM, Nolan TW, Whittington J. The triple aim: Care, health, and cost. *Health Aff*. 2008;27(3):759–769. doi:10.1377/hlthaff.27.3.759.
20. Loehrer S, Feeley D, Berwick D. 10 New rules to accelerate healthcare redesign. Bold aspirations to guide healthcare organizations during an era of reform. *Healthc Exec*. 30(6):66, 68–69.
21. American Dental Hygienists' Association. *Standards for Clinical Dental Hygiene Practice*. Chicago, IL: American Dental Hygienists' Association; 2016. https://www.adha.org/resources-docs/2016-Revised-Standards-for-Clinical-Dental-Hygiene-Practice.pdf
22. McInnis T, Strand L, Webb CE. *Integrating Comprehensive Medication Management to Optimize Patient Outcomes: Resource Guide*. 2nd ed. 2012. https://www.pcpcc.org/sites/default/files/media/medmanagement.pdf.
23. The Patient Care Process for Delivering Comprehensive Medication Management (CMM): Optimizing Medication Use in Patient-Centered, Team-Based Care Settings. CMM in Primary Care Research Team. July 2018. Available at: http://www.accp.com/cmm_care_process.
24. Briesacher BA, Andrade SE, Fouayzi H, Chan KA. Comparison of drug adherence rates among patients with seven different medical conditions. *Pharmacotherapy*. 2008;28(4):437–443. doi:10.1592/phco.28.4.437.
25. Yeaw J, Benner JS, Walt JG, Sian S, Smith DB. Comparing adherence and persistence across 6 chronic medication classes. *J Manag Care Pharm*. 2009;15(9):728–740. doi:10.18553/jmcp.2009.15.9.728.
26. Pharmacy Quality Alliance. *Medication Therapy Problem Categories Framework for PQA Measures*. Alexandria, VA: Pharmacy Quality Alliance; 2017. https://www.pqaalliance.org/assets/Measures/PQA%20MTP%20Categories Accessed October 3, 2018.
27. Sorensen TD, Pestka DL, Brummel AR, Rehrauer DJ, Ekstrand MJ. Seeing the forest through the trees: Improving adherence alone will not optimize medication use. *J Manag Care Spec Pharm*. 2016;22(5):598–604. doi:10.18553/jmcp.2016.22.5.598.
28. Isetts BJ, Schondelmeyer SW, Artz MB, et al. Clinical and economic

outcomes of medication therapy management services: The Minnesota experience. *J Am Pharm Assoc*. 2008;48(2):203–214. doi:10.1331/JAPhA.2008.07108.

29. Ramalho de Oliveira D, Brummel AR, Miller DB. Medication therapy management: 10 years of experience in a large integrated health care system. *J Manag Care Pharm*. 2010;16(3):185–195. doi:10.18553/jmcp.2010.16.3.185.
30. Harris IM, Baker E, Berry T, et al. Developing a business-practice model for pharmacy services in ambulatory settings. *Pharmacotherapy*. 2008;28(2):285. doi:10.1592/phco.28.2.285.
31. Donabedian A. Criteria, norms and standards of quality: What do they mean? *Am J Public Health*. 1981;71(4):409–412.
32. Viswanathan M, Kahwati LC, Golin CE, et al. Medication therapy management interventions in outpatient settings. *JAMA Intern Med*. 2015;175(1):76. doi:10.1001/jamainternmed.2014.5841.
33. Pharmacy Health Information Technology Collaborative. http://pharmacyhit.org/. Accessed October 3, 2018.
34. Centers for Medicare and Medicaid Services. *Evaluation and Management Services Guide*. Rockville, MD: Department of Health and Human Services; 2016. https://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNProducts/Downloads/eval-mgmt-serv-guide-ICN006764.pdf. Accessed October 3, 2018

Health Literacy and Medication Use

Oralia V. Bazaldua, DeWayne A. Davidson, Ashley Zurek, and Sunil Kripalani

KEY CONCEPTS

1. Limited health literacy is common and must be considered when providing medication management services.
2. Some groups of people are at higher risk for having limited literacy skills, but in general, you cannot tell by looking.
3. Patients with limited health literacy are more likely to misunderstand medication instructions and have difficulty demonstrating the correct dosing regimen.
4. Limited health literacy is associated with increased healthcare costs and worse health outcomes, including increased mortality.
5. Despite numerous efforts to improve safe medication practices, current strategies have been inadequate, and this may have a larger impact in patients with limited literacy.
6. Most printed materials are written at higher comprehension levels than most adults can read.
7. The United States Pharmacopeia has set new standards for prescription medication labeling to minimize patient confusion.
8. Several instruments exist to measure health literacy, but some experts advocate “universal precautions” under which all patients are assumed to benefit from plain language and clear communication.
9. Obtaining a complete medication history and providing medication counseling are vital components in the medication management of patients with limited health literacy.

Preclass Engaged Learning Activity

Watch the YouTube video, "Health Literacy Fun with Wayne State & DMC," available online at https://www.youtube.com/watch?v=p5ErA71YsFE, and the TEDx Talk, "Are You Confused About Health Information? You're Not Alone," online at https://www.youtube.com/watch?v=-x6DLqtaK2g.

INTRODUCTION

Every day, thousands of patients are not taking their medications correctly. Some take too much. Others take too little. Some use a tablespoon instead of a teaspoon. Parents pour an oral antibiotic suspension in their child's ear instead of giving it by mouth because it was prescribed for an ear infection. Others are in the emergency department because they did not know how to use their asthma inhaler. It is not a deliberate revolt against the doctor's orders but rather a likely and an unfortunate result of a hidden risk factor—limited health literacy.

1 *Literacy*, at the basic level, is simply the ability to read and write. When these skills are applied to a health context, it is called *health literacy*, but health literacy is more than just reading and writing. *Health literacy*, as defined by the Institute of Medicine (IOM), is "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions." A growing body of evidence associates low health literacy with less understanding, worse outcomes, and increased cost. These poor outcomes have led this topic to receive national attention. Health literacy has been made "a priority area for national action" by the IOM[1,2] and Healthy People 2020.[3] As a result, federal policy initiatives promoting health literacy continue to be highlighted in Healthy People 2020, the Patient Protection and Affordable Care Act of 2010, and the Plain Writing Act of 2010.[4] A National Action Plan to Improve Health Literacy (**Table e2-1**) has also been developed by the Department of Health and Human Services (HHS).[5] Likewise, the Agency for Healthcare Research and Quality (AHRQ),[6,7] the National Institutes of Health (NIH),[8] and Centers for Disease Control and Prevention (CDC)[9] have each dedicated Websites to this topic and have provided funding to support studies and interventions that are specifically relevant to health literacy. Additionally, state and private sector organizations, such as America's Health Insurance Plans (AHIP) and the American College of Physicians (ACP) Foundation, have led efforts to improve health literacy

following the IOM's call to action.[10] Indeed, health literacy should be a national priority for the medical community as its consequences are far-reaching and cross-cutting.

More than one of every three American adults has difficulty understanding and acting on health information.[11] Patients with limited health literacy have less knowledge about how to manage their disease[12]; they misunderstand dosing instructions and warning labels on medication containers[13,14]; they are less likely to read or even look at medication guides[15]; their ability for medication management is limited as these persons are less able to identify or distinguish their medications from one another[16,17]; and they are less able to use a metered-dose inhaler (MDI) properly.[18] Limited health literacy skills have also been documented in caregivers of seniors[19] and in parents of children.[20] There is no question that limited health literacy is associated with adverse health outcomes[21] including an increased mortality rate[22] and increased healthcare costs.[23]

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

Cultural Competency

Jeri J. Sias, Amanda M. Loya, José O. Rivera, and Jessica M. Shenberger-Trujillo

KEY CONCEPTS

1. Healthcare providers should strive toward cultural competency to improve care and access unique resources for patients and communities from diverse cultures and backgrounds.
2. Changes in demographics in the United States, health disparities, and patient safety are among the reasons that cultural competency should be emphasized in healthcare.
3. A variety of models recognize cultural competency as a process, not an achievement.
4. Legal and regulatory issues surrounding cultural competency include understanding and interpreting accreditation standards for healthcare organizations and Title VI of the Civil Rights Act.
5. Patients may enter the healthcare setting with a different explanation of their illnesses than found in the Western biomedical model (WBM).
6. Cultural values and beliefs influence decisions and attitudes about healthcare, including race, ethnicity, age, gender, sexual orientation, and religious beliefs.
7. Developing communication skills to interact with diverse population involves recognizing personal styles and cultural values of communication as well as barriers to patient understanding.
8. Linguistic competency encompasses understanding the capacity of organizations and providers to communicate well with diverse populations such as patients with limited English proficiency (LEP), low literacy, or hearing impairments.
9. Before practitioners can understand other cultures, they should strive to

understand personal and organizational values and beliefs.

10 Skills for working with patients from diverse cultures include being able to listen to the patient's perception of health, acknowledging differences, being respectful, and negotiating treatment options.

Preclass Engaged Learning Activity

Select any one of the patients from diverse backgrounds introduced at the beginning of the chapter. What are the factors that influence their health that are based on genetics? Individual and family choices? Community influences? Larger city and policy structures? Based on the information provided, what social identity and acculturation characteristics are involved? Look up information about healthcare beliefs and values based on how the patient self-identifies with religion and race or ethnicity. If approached by one of the patients, providers may argue that "we can't solve everything in healthcare. I only have so much time during a visit." How might you respond to those statements? What changes can be made at a provider level, clinic/hospital level, and at a larger system-wide level to improve care across cultures?

CULTURE, COMMUNITY, AND SOCIAL DETERMINANTS OF HEALTH

Culture defines us.[1] Although our genetic makeup, that is largely nonmodifiable and affects our physical state of being, **social determinants of health** are also of great influence. Determinants of health describe the factors that affect the health of individuals. At the core of each person are their inherited traits as well as the choices that they make about their lifestyles (eg, diet, exercise, leisure activities). Their health is further marked by their exposure to healthy or risky behaviors based on the places where they live, work, worship, or go during the day and their built environment (eg, sidewalks, exposure to clean air, policies for healthy choices).[2] Basically, our socioeconomic status, race and ethnicity, gender, age, and communities (environments), as part of our cultures, shape us.[3]

Consider the following brief descriptions of three individuals and the determinants of health that influence them. Patient 1 is a 42-year-old bilingual Vietnamese American, Buddhist woman living on the West Coast whose family

immigrated to the United States 35 years ago. Her lifestyle choices include a vegetarian diet, gardening, and daily meditation. She lives in a suburban community with her husband and three children, drives a hybrid electric/gas car to her work as a school teacher, and purchases food from a local farmer's market. She has health insurance and her city public policy includes no indoor smoking in public places and state policies include special low-emission requirements on vehicles. Weekend activities with the family include sports and dance for the kids along with others from the community center that serves a number of Asian-American families.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

Medication Safety Principles and Practices

Robert J. Weber

KEY CONCEPTS

1. Medication errors (MEs) are defined as any mistake at any stage of the medication-use process; adverse drug events (ADEs) are the result of an injury as a result of an ME.
2. All MEs can be prevented, while ADEs can be categorized as preventable and potential.
3. MEs occur at an alarmingly high rate, with some ADEs having fatal outcomes for patients.
4. MEs can occur at any step of the medication-use process: selection and procurement, storage, ordering and transcribing, preparing and dispensing, administration, or monitoring.
5. Determining the actual and potential root causes of MEs helps to correct future errors in the medication-use system.
6. Quality improvement methods that prevent MEs and thereby minimize ADEs include identifying the ME and/or ADE, understanding the reasons for the ME and/or ADE, designing and implementing changes to prevent an ADE or ME, and checking the outcome of that change.
7. Healthcare organizations have implemented various measures to reduce the incidence of MEs and ADEs, such as computerized physician order entry (CPOE), automated drug distribution systems, bar-code scanning, and “smart” infusion pumps with decision support and where information is passed in a bidirectional manner between the pump and the patient’s electronic medical record (EMR).
8. Medication reconciliation or comparing a patient’s current medication

orders to all of the medications that the patient had been taking before any care transition (hospital admission, transfer, or discharge) is a vital process in preventing MEs and ADEs.

9. Promoting a "Just Culture" of medication safety cultivates trust in the workplace that makes personnel feel comfortable sharing safety information (eg, unsafe situations) and assuming personal responsibility and accountability for complying with safe medication practices.

INTRODUCTION

Medical errors are not a new phenomenon. Medical errors causing harm may lead to devastating effects on patients. In 1991, the Harvard Medical Practice Study showed that a significant number of people are victims of medical errors, and a subset experienced medication errors (MEs). This landmark study reviewed the incidence of adverse events and negligence in hospitalized patients in the state of New York showing that almost 4% of patients experienced an iatrogenic injury (one caused by healthcare practices or procedures), prolonging their hospital stays.[1] Importantly, nearly 14% of those mistakes were fatal. Examples of mistakes noted in the Harvard study included renal failure from angiographic dye and a missed diagnosis of colon cancer. Drug complications were the most common type of outcome attributed to negligence, accounting for 19% of these preventable adverse events.[1]

The goal of medication therapy is achieving defined therapeutic goals to improve a patient's quality of life while minimizing harm.[2] Known and unknown risks are associated with the therapeutic use of prescription and nonprescription drugs and drug administration devices.[3] Mishaps related to medication therapy include both adverse drug events (ADEs) and MEs.[4]

Medication errors negatively affect patients' confidence in the healthcare system and increase healthcare costs. Research conducted by the American Society of Health-System Pharmacists (ASHP) showed that 61% of patients surveyed reported that they were "very concerned" about being given the wrong medicine during a hospital stay.[5] MEs are also very costly—to healthcare systems, patients and their families, and healthcare workers. The emotional cost of an ME is also significant, including the burden on the family for grieving loss or stress for the healthcare worker (often referred to as the "second victim") involved in an ME that caused harm.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

Clinical Pharmacokinetics and Pharmacodynamics

Larry A. Bauer

KEY CONCEPTS

1. Clinical pharmacokinetics is the discipline that describes the absorption, distribution, metabolism, and elimination of drugs in patients requiring drug therapy.
2. Clearance is the most important pharmacokinetic parameter because it determines the steady-state concentration for a given dosage rate. Physiologically, clearance is determined by blood flow to the organ that metabolizes or eliminates the drug and the efficiency of the organ in extracting the drug from the bloodstream.
3. The volume of distribution is a proportionality constant that relates the amount of drug in the body to the serum concentration. The volume of distribution is used to calculate the loading dose of a drug that will immediately achieve a desired steady-state concentration. The value of the volume of distribution is determined by the physiologic volume of blood and tissues and how the drug binds in blood and tissues.
4. Half-life is the time required for serum concentrations to decrease by one-half after absorption and distribution are complete. It is important because it determines the time required to reach steady state and the dosage interval. Half-life is a dependent kinetic variable because its value depends on the values of clearance and volume of distribution.
5. The fraction of drug absorbed into the systemic circulation after extravascular administration is defined as its *bioavailability.*
6. Most drugs follow linear pharmacokinetics, whereby steady-state serum drug concentrations change proportionally with long-term daily dosing.

7. Some drugs do not follow the rules of linear pharmacokinetics. Instead of steady-state drug concentration changing proportionally with the dose, serum concentration changes more or less than expected. These drugs follow nonlinear pharmacokinetics.
8. Pharmacokinetic models are useful to describe data sets, to predict serum concentrations after several doses or different routes of administration, and to calculate pharmacokinetic constants such as clearance, volume of distribution, and half-life. The simplest case uses a single compartment to represent the entire body.
9. Factors to be taken into consideration when deciding on the best drug dose for a patient include age, gender, weight, ethnic background, other concurrent disease states, and other drug therapy.
10. Cytochrome P450 is a generic name for the group of enzymes that are responsible for most drug metabolism oxidation reactions. Several P450 isozymes have been identified, including CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.
11. Membrane transporters are protein molecules concerned with the active transport of drugs across cell membranes. The importance of transport proteins in drug bioavailability, elimination, and distribution is continuing to evolve. A principal transport protein involved in the movement of drugs across biologic membranes is P-glycoprotein. P-glycoprotein is present in many organs, including the gastrointestinal (GI) tract, liver, and kidney. Other transport protein families include the organic cation transporters, the organic anion transporters, and the organic anion transporting polypeptides.
12. When deciding on initial doses for drugs that are renally eliminated, the patient's kidney function should be assessed. A common, useful way to do this is to measure the patient's serum creatinine concentration and convert this value into an estimated creatinine clearance ($CL_{cr\ est}$). For drugs that are eliminated primarily by the kidney (more than or equal to 60% of the administered dose), some agents will need minor dosage adjustments for $CL_{cr\ est}$ between 30 and 60 mL/min (0.50 and 1.00 mL/s), moderate dosage adjustments for $CL_{cr\ est}$ between 15 and 30 mL/min (0.25 and 0.50 mL/s), and major dosage adjustments for $CL_{cr\ est}$ less than 15 mL/min (0.25 mL/s). For drugs approved after 2010, renal drug dosing adjustments may also include recommendations using estimated glomerular filtration rate (eGFR) in addition to $CL_{cr\ est}$. Supplemental doses of some medications also may

be needed for patients receiving hemodialysis if the drug is removed by the artificial kidney or for patients receiving hemoperfusion if the drug is removed by the hemofilter.

13. When deciding on initial doses for drugs that are hepatically eliminated, the patient's liver function should be assessed. The Child-Pugh score can be used as an indicator of a patient's ability to metabolize drugs that are eliminated by the liver. In the absence of specific pharmacokinetic dosing guidelines for a medication, a Child-Pugh score equal to 8 or 9 is grounds for a moderate decrease (~25%) in the initial daily drug dose for agents that are metabolized primarily hepatically (more than or equal to 60%), and a score of 10 or greater indicates that a significant decrease in the initial daily dose (~50%) is required for drugs that are metabolized mostly hepatically.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

Pharmacogenetics

Larisa H. Cavallari and Y. W. Francis Lam

KEY CONCEPTS

1. Genetic variation contributes to pharmacokinetic and pharmacodynamic drug properties.
2. Genetic variation occurs for drug metabolism, drug transporter, and drug target proteins, as well as disease-associated proteins that may impact drug response.
3. Single-nucleotide polymorphisms are the most common gene variations associated with drug response.
4. Genetic polymorphisms may influence drug effectiveness and risk for toxicity.
5. Pharmacogenetics is the study of the impact of genetic polymorphisms on drug response.
6. The goals of pharmacogenetics are to optimize drug efficacy and limit drug toxicity based on an individual's DNA.
7. Gene therapy aims to cure disease caused by genetic defects by changing gene expression.
8. Inadequate gene delivery and expression and serious adverse effects are obstacles to successful gene therapy.

Preclass Engaged Learning Activity

Visit the https://tinyurl.com/wdjr6xd website. Enter one of the following drugs in the search box: warfarin, codeine, paroxetine, clopidogrel, or carbamazepine. Review available dosing guidelines, labeling information, and one of the clinical annotations. This website is useful to enhance student

understanding of available resources for pharmacogenetic information.

INTRODUCTION

Great variability exists among individuals in response to drug therapy, and it is difficult to predict how effective or safe a medication will be for a particular patient. For example, when treating a patient with hypertension, it may be necessary to try several agents or a combination of agents before achieving adequate blood pressure control with acceptable tolerability. A number of clinical factors are known to influence drug response, including age, body size, kidney and liver function, and concomitant drug use. However, considering these factors alone is often insufficient in predicting the likelihood of drug efficacy or safety for a given patient. For example, identical antihypertensive therapy in two patients of similar age, sex, race, and with similar medical histories and concomitant drug therapy may produce inadequate blood pressure reduction in one patient and symptomatic hypotension in the other.

[1][2] The observed interpatient variability in drug response may result largely from genetically determined differences in drug metabolism, drug distribution, and drug target proteins. The influence of heredity on drug response was demonstrated as early as 1956 with the discovery that an inherited deficiency of glucose-6-phosphate dehydrogenase (G6PD) was responsible for hemolytic reactions to the antimalarial drug primaquine (**Fig. e6-1**). Variations in genes encoding cytochrome P450 (CYP) and other drug-metabolizing enzymes are now well recognized as causes of interindividual differences in plasma concentrations of certain drugs. These variations may have serious implications for narrow-therapeutic-index drugs such as warfarin, phenytoin, and mercaptopurine. Other variations associated with drug response occur in genes for drug transporters such as the solute carrier organic anion transporter (OAT) family member 1B1 (SLCO1B1) and organic cation transporter 1 (OCT1), as well as drug targets such as receptors, enzymes, and proteins involved in intracellular signal transduction. Genetic variations for drug metabolizing enzymes and drug transporter proteins may influence drug disposition, thus altering pharmacokinetic drug properties. Drug target genes may alter pharmacodynamic mechanisms by affecting sensitivity to a drug at its target site. Finally, genes associated with disease severity have been correlated with drug efficacy despite having no direct effect on pharmacokinetic or pharmacodynamic mechanisms.

PHARMACOGENETICS: A DEFINITION

[3] [4] Pharmacogenetics involves the search for genetic variations that lead to interindividual differences in drug response. The term *pharmacogenetics* often is used interchangeably with the term *pharmacogenomics.* However, pharmacogenetics generally refers to monogenetic variants that affect drug response, whereas pharmacogenomics refers to the entire spectrum of genes that interact to determine drug efficacy and safety. For example, a pharmacogenetic study would be one that examines the influence of the *CYP2C9* gene on warfarin dose requirements. A pharmacogenomic study might examine the interaction between the *CYP2C9*, vitamin K oxidoreductase complex subunit 1 (*VKORC1*), and *CYP4F2* genes on warfarin dose requirements. Given that multiple proteins are involved in determining the ultimate response to most drugs, many investigators are taking a more pharmacogenomic approach to elucidating genetic contributions to drug response. However, most examples of pharmacogenetic testing in clinical practice involve single genes. For simplicity, this chapter treats pharmacogenetics and pharmacogenomics as synonymous.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

Clinical Toxicology

Bryan D. Hayes and Peter A. Chyka

KEY CONCEPTS

1. Poisoning can result from exposure to excessive doses of any chemical, with medicines being responsible for most childhood and adult poisonings.
1. The total number and rate of poisonings have been increasing, but preventive measures, such as child-resistant containers, have reduced mortality in young children.
3. Immediate first aid may reduce the development of serious poisoning, and consultation with a poison control center may indicate the need for further therapy.
4. The use of ipecac syrup, gastric lavage, whole bowel irrigation, and cathartics has fallen out of favor as routine therapies, whereas activated charcoal remains useful for gastric decontamination of appropriate patients.
5. Antidotes can prevent or reduce the toxicity of certain poisons, but symptomatic and supportive care is essential for all patients.
6. Acute acetaminophen poisoning produces severe liver injury and occasionally kidney failure. A determination of serum acetaminophen concentration may indicate whether there is risk of hepatotoxicity and the need for acetylcysteine therapy.
7. Anticholinesterase insecticides may produce life-threatening respiratory distress and paralysis by all routes of exposure and can be treated with symptomatic care, atropine, and pralidoxime.
8. An overdose of calcium channel antagonists will produce severe hypotension and bradycardia and can be treated with supportive care, calcium, and insulin with supplemental dextrose.
9. Poisoning with iron-containing drugs produces vomiting, gross gastrointestinal bleeding, shock, metabolic acidosis, and coma, and can be

treated with supportive care and deferoxamine.

10. Acute opioid poisoning and overdose can produce life-threatening respiratory depression that can be treated with assisted ventilation and naloxone.

11. Chemicals can be used for mass poisonings by acts of terrorism and warfare and typically produce life-threatening effects within minutes to hours, which warrant emergency preparedness at healthcare facilities and communities.

Preclass Engaged Learning Activity

Watch the video entitled "Toxicology—The National Emergency Medicine Board Review Course" https://tinyurl.com/samzf2f up to minute 21:00. Dr. William "Billy" Mallon, an emergency medicine physician, provides an overview of some general toxicology principles covered in this chapter including GI decontamination, enhanced elimination, and antidotes. The video is useful to enhance student understanding of foundational concepts while also providing insight into the types of topics taught to related disciplines such as emergency medicine.

INTRODUCTION

Poisoning is an adverse effect from a chemical that has been taken in excessive amounts. The body can tolerate and, in some cases, detoxify a certain dose of a chemical; however, toxicity ensues once a critical exposure threshold is exceeded. Poisoning can produce minor local effects that may be treated readily in the outpatient setting or systemic life-threatening effects that require intensive medical intervention. Virtually any chemical can become a poison when taken in sufficient quantity, but the potency of some compounds leads to serious toxicity with small quantities (**Table e7-1**). Poisoning by chemicals includes exposure to drugs, industrial chemicals, household products, plants, venomous animals, agrochemicals, and weapons for warfare and terrorism. This chapter describes some examples of the spectrum of toxicity, outlines means to recognize poisoning risk, and presents principles of treatment.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

SECTION 2 COMMON HEALTH PROBLEMS

Fever

Jamal Brown and Jenay Kyles

KEY CONCEPTS

1. Fever can be a by-product of various infectious or pathologic processes, vaccinations, medications, and environmental exposure, or of vigorous activity.
2. Normal body temperature fluctuates and is regulated in the thermoregulatory center of the anterior hypothalamus. During a fever, prostaglandins cause an increase in the hypothalamic temperature set point and thereby increase production of heat in the periphery.
3. In a community setting, pharmacists should COLLECT key information on medications, medical history, immunizations, recent travel, social history, barriers of care, and course of fever.
4. Using the gathered data, pharmacists should ASSESS information to differentiate symptoms from surrounding conditions, determine appropriateness for self-care, evaluate history for causes of fever, and consider most appropriate medication for fever.
5. Goals of therapy include relieving discomfort, reducing body temperature, and when appropriate treating the underlying cause of fever.
6. Nondrug treatments include the use of cooling blankets, which should only be used along with antipyretics. Appropriate hydration and the use of fans also contribute to decreasing body temperature.
7. Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce fever, but they can adversely affect the gastrointestinal tract and platelets. For this reason, acetaminophen is the preferred agent to reduce fever in most patients. Therapy with NSAIDs and acetaminophen combinations can be used in most but not all patients.
8. Medical evaluation should be sought if symptoms of fever do not resolve

with over-the-counter treatment within 24 hours in children younger than 2 years, 48 hours in other children and 3 days in adults. Also, medical evaluation should occur in patients with alarming symptoms regardless of their temperature.

Preclass Engaged Learning Activity

In a small group, create a drug treatment table of over-the-counter products for fever. Consider appropriate age, mechanism of action, dosing schedule, disease interactions, drug interactions, and cost. Compare and contrast these agents based on these factors and create an "optimal" situation to use each medication. Also, create a list of conditions that mimic symptoms of fever. This will assist you during the Assess phase of the patient care process.

INTRODUCTION

Pharmacists and other primary care providers are often the first point of contact for patients who present with nonspecific symptoms that can be transient and self-limiting or that indicate the presence of serious disease. Collecting the information needed to assess these symptoms and make a recommendation to patients is a common and important activity of health professionals as they provide direct patient care.

Elevated body temperature is one of these cardinal manifestations of disease. Fever and elevated temperatures can be associated with many etiologies related to recent travel, illnesses, activity, and environmental factors. Pharmacists have an opportunity and responsibility to decipher information to help patients find appropriate treatment to decrease temperatures and alleviate associated symptoms or to seek more extensive medical evaluations.

A systematic process for assessing elevated temperatures includes asking the patient or caregiver for specific facts about the condition, examining the patient and measuring the body temperature, assessing the collected information, developing and implementing a treatment plan (including referring the patient when red flags to self-treatment are present), and scheduling appropriate follow-up. This chapter reviews the causes of fever in a clinic or pharmacy setting and appropriate evidence-based treatment to alleviate symptoms.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

Pain and Headache

Ryan Costantino, Christopher D. Kearney, and Kathryn A. Walker

KEY CONCEPTS

1. A comprehensive pain symptom analysis should be performed on each patient reporting pain to determine the type of pain condition.
2. A patient's self-report of pain is the most reliable indicator of the intensity and presence of pain.
3. Appropriateness of self-care options to manage pain must be determined after careful review of red flag indicators.
4. The topical route of administration is preferred to oral analgesics whenever feasible to limit systemic drug exposure.
5. Goals focused on quality of life and function in addition to traditional pain scores are preferred.

Preclass Engaged Learning Activity

Watch the video entitled "Emergency Room HD" on YouTube by Brian Regan. This 8-minute comedic video provides humor, as well as insight into a patient's experience having their pain assessed. The video is meant to enhance a students' understanding of the challenges clinicians face COLLECTING and ASSESSING pain using the patient care process.

INTRODUCTION

Relief of suffering is a central tenant of the oath we take upon assuming our roles as healthcare professionals.[1] Thus, we are all bound by duty to commit ourselves to the understanding of pain and caring for those experiencing it. The

International Association for the Study of Pain (IASP) defines pain as: “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.”[2] Despite being a top reason patients access the medical system, many patients will attempt to self-treat their pain with nonprescription medications.[3,4] This gives pharmacists unique opportunities to improve the health, wellness, and medication use among patients experiencing pain.

EPIDEMIOLOGY AND ETIOLOGY

The Institute of Medicine released a landmark report in 2011 stating that more than 100 million persons in the United States live with chronic pain.[5] In 2012, the National Health Interview Study reported 25.3 million adults suffer from daily pain.[6] While the true incidence and prevalence is difficult to determine, painful disorders have a significant burden on our society. Chronic pain alone is estimated to cost the United States more than US$600 billion each year in medical treatment and lost productivity.[7] Unfortunately, our healthcare system has historically struggled to provide medical professionals with adequate education and training to sufficiently diagnose and treat those suffering from pain.[5,8]

Headache and musculoskeletal disorders are two common etiologies of pain for which there are nonprescription treatment options available for patients to self-treat. Worldwide, almost half of the population with headache are self-treating without a formal diagnosis, according to available estimates.[9] This is concerning as many of the medications commonly used to treat painful conditions carry with them serious side effects (ie, bleeding with NSAIDs). Furthermore, one study demonstrated approximately half of our patients may not be aware of the potential side effects of their medication and many patients are under the impression OTC medications are safer or carry less risk than their equivalent prescription product.[10]

All healthcare professionals have a role to play in educating and assisting with the care of patients with painful disorders by screening for red flag symptoms (see **Table e9-1**) and referring patients to a primary care physician or specialist when appropriate. If a patient is appropriate to self-treat, pharmacists can provide guidance on the most appropriate drug given a patient’s symptoms and encourage safe use (eg, dosing, duration of use, and monitoring parameters).

ANATOMY AND MECHANISM OF DISEASE

Pain can contribute to suffering but can also serve as an essential protective mechanism used to maintain homeostasis in the body. For a detailed review of the pathogenesis of pain, see Chapter 77. For the purposes of self-care, it is helpful to classify pain into subcategories to align treatment modalities.

Pain is often classified as nociceptive, neuropathic, or mixed (see **Table e9-2**). Nociceptive pain occurs in response to harmful, or potentially harmful stimuli when signals are sent to the brain through the process of transduction, conduction, transmission, perception, and modulation. It is typically characterized as either somatic, or visceral in nature. Somatic and visceral pain often respond to primary analgesics available through self-care (eg, acetaminophen or NSAIDs), whereas neuropathic pain will often require a referral and evaluation for prescription analgesics. However, products containing capsaicin or lidocaine are available over-the-counter and may be beneficial in the initial treatment of patients experiencing neuropathic pain (see Table e9-2).

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

Minor Ophthalmic Disorders

Jared Ostroff

KEY CONCEPTS

1. Pharmacists are often the first healthcare provider that patients will seek with various eye complaints.
2. It is crucial to understand the various products available over-the-counter to provide appropriate recommendations.
3. Pharmacists should also be familiar with eye conditions that do require referral to a medical provider for further evaluation.

Preclass Engaged Learning Activity

Working with a partner, create a list of the various products available over-the-counter for patients with contact lenses. Consider cost, contact lens type, and instructions for use. Create a chart of potential recommendations for patients presenting to the pharmacist for assistance with daily contact lens cleaning and care. This will help you PLAN potential recommendations for optimal patient care.

INTRODUCTION

1 Within the pharmacy setting, patients seek out the pharmacist's expertise on a variety of medical conditions. When it comes to ophthalmic complaints, there are many considerations and other causes to rule out prior to making a pharmacologic recommendation. Patients will sometimes present in the pharmacy or primary care setting with dry eyes, burning eyes, or obstructed vision, or for help selecting appropriate contact lens solutions. While patients

may seek a quick cure, the pharmacist must also realize that a full assessment is encouraged for each patient complaining of symptoms to determine if it is appropriate to use nonpharmacologic or pharmacologic treatments that are available without a prescription or refer to another provider.

This chapter reviews some of the common eye complaints within the pharmacy or clinic setting and how to make the best evidence-based recommendations for their management.

DRY EYES

Collect. Dry eye disease, or keratoconjunctivitis sicca, is one of the most common complaints when patients visit the eye doctor, and its prevalence is estimated between 7% and 33%.[1] Risk factors for the development of dry eyes include increasing age and female sex.[2] While onset of dry eyes is often unpredictable, it may correlate with exposure to various changes in environment and current medications.

Patients with dry eyes may present with or without redness of the eyes with various complaints that will need a review of their current medical history and other predisposing factors. Factors such as weather, current medications, recent exposure, and previous experience with the condition are essential in triage and making recommendations for therapy.

Assess. The first step in evaluating a patient with dry eyes is to evaluate the complaints and medical history including any current medications or environmental triggers. Patients may not always recognize that environmental factors could play a role so it is essential to ask for that information. Since dry eyes may be caused by a variety of medications, perform a medication reconciliation with the patient's current medication list. Some of the medications to check for include antihistamines, decongestants, antidepressants, and hormone replacement therapy.[3] While this is not the only mechanism that can cause dry eyes, medications are frequently implicated. If offending medications are identified during reconciliation, advise the patient to stop using if appropriate and recommend an alternative product that would minimize the potential for dry eyes to return.

Plan. Once a thorough medication reconciliation is complete, rule out for any red flags such as complaints of any discharge, blurry vision, or difficulty with vision. Patients with those symptoms should be referred to a medical provider for further evaluation.

Implement. If there are no red flags or urgent symptoms needing further

evaluation, the choice of best initial option should be discussed with the patient. A number of factors contribute to selection of an initial treatment option. These may include cost, dosage form (suspension vs solution), administration times, previous experience with a product, and any potential drug or nondrug allergies.

2 When considering OTC treatment for dry eyes, the first-line recommendation is artificial tears, which may include cellulose, polyethylene glycol, and a preservative. Each of these ingredients have a specific role in dry eye treatment and many come in a variety of forms such as liquid, gel, and ointment. Preservative-free forms are also available; these are preferred in patients who wear contact lenses.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

Minor Otic Disorders

Lea S. Eiland

KEY CONCEPTS

1. The most common pathogens in acute otitis externa (AOE) are *Pseudomonas aeruginosa* and *Staphylococcus aureus*.
2. Topical antimicrobials are the medication and route of choice for the treatment of AOE.
3. Systemic antimicrobials are not warranted for the initial treatment of diffuse, uncomplicated AOE.
4. Pain should be assessed in all patients and therapy recommended based upon severity.
5. Appropriate counseling points for otic administration of medication should be provided to each patient.
6. Cerumen production is a naturally occurring process of the body.
7. Cerumen impaction may cause discomfort, itching, hearing loss, or tinnitus.
8. Cotton swabs should not be used as they can worsen cerumen impaction or cause trauma to the tympanic membrane.
9. Home-treatment options for cerumen impaction include cerumenolytic agents and/or irrigation.
10. Foreign objects such as pen caps, tweezers, or paper clips should not be inserted in the ear canal.

Preclass Engaged Learning Activity

1. Otic administration of medications: Working individually or in teams, develop a handout or short video for patients and caregivers to teach them

how to administer medication into the ear of a child or an adult. Be creative in the education models used for patient education!

2. Cerumenolytics: Which one to recommend first? Working individually or in teams, research the various cerumenolytic agents available for patient use and develop a selection algorithm. The algorithm should clearly state which product (with the respective dosing regimen) would be the first they recommend to a patient, the second, and so forth.

ACUTE OTITIS EXTERNA—INTRODUCTION

Acute otitis externa (AOE) is a diffuse inflammation of the external ear canal secondary to infection.[1] The tympanic membrane or pinna may also be involved in this infectious process. AOE may occur at any age but is uncommon in children younger than 2 years.

The hallmark sign of diffuse AOE is intense tenderness of the pinna when pulled, tragus when pushed, or both, which can be inconsistent with signs observed visually, such as redness or areas of cellulitis. Diagnosis of AOE requires a rapid onset (<48 hours) of signs and symptoms of ear canal inflammation within the past 3 weeks.[1] The signs of inflammation include tenderness of the pinna, tragus, or both or diffuse canal edema, erythema, or both. Signs may also include otorrhea, regional lymphadenitis, erythema of the tympanic membrane, or cellulitis of the pinna and adjacent skin.

Symptoms of inflammation include otalgia (70%), itching (60%), or fullness (22%), with or without jaw pain or hearing loss (32%).[1] Pain best correlates with the severity of the disease.[2]

This chapter focuses on AOE, but patients sometimes present with other types of otitis externa. Chronic otitis externa is defined as otitis externa occurring for 3 months or longer. Necrotizing or malignant otitis externa is defined as the AOE infection extending to the temporal bone causing osteomyelitis. This primarily occurs in patients who are older, have diabetes mellitus, or are immunocompromised.

Epidemiology and Etiology

Patients with AOE commonly seek treatment from healthcare providers in the outpatient setting. In 2007, 2.4 million patients received a diagnosis of AOE in the ambulatory care or emergency department setting (8.1 visits per 1,000

population).[3] In ambulatory care visits in the years 2003 to 2007 for AOE, 18.6% were for children 5 to 9 years of age, 15.8% were for children 10 to 14 years of age, and 53% were for adults 20 years of age or older. One study found a peak incidence of AOE in patients 7 to 12 years of age.[4] Ambulatory care clinicians spend approximately 600,000 hours treating patients with AOE, and annual direct healthcare costs for the nonhospitalized setting in the United States are up to $500 million.[1]

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

Cough and Other Nonspecific Respiratory Symptoms

Brandon James Sucher

KEY CONCEPTS

1. Cough is classified as acute, subacute, or chronic based on duration of symptoms.
2. Cough is an essential component for lung health maintenance, but persistent or excessive cough ceases to be protective, is bothersome, and adversely affects quality of life.
3. Although cough is associated with a variety of diseases, the duration of cough helps narrow the potential etiologies for cough symptoms.
4. The presence of dyspnea, red flag symptoms, and/or symptoms suggestive of acute bacterial rhinosinusitis indicates the need for referral to the patient's primary care physician.
5. Treatment trials (eg, intranasal corticosteroids, first-generation antihistamines, treatments for gastroesophageal reflux disease) can help rule out common causes of chronic cough.

Preclass Engaged Learning Activity

Create a flow chart that outlines the sequence of therapeutic approaches for the four most common causes of chronic cough. Indicate the name of the medication class that may be used for a therapeutic trial when available as an over-the-counter medication. When a therapeutic trial of an over-the-counter medication is not appropriate, indicate referral to the patient's primary care physician for each of the respective causes of chronic cough.

INTRODUCTION

1 2 Cough is the most common symptom patients report as the reason for seeking healthcare in ambulatory care settings.[1] Cough is defined clinically as expiration associated with a characteristic sound.[2] Cough is classified as acute, subacute, or chronic based on duration of symptoms (**Table e12-1**).[3] As a defense mechanism, cough protects the airways from aspiration and clears secretions such as mucus, foreign substances, and infectious organisms.[4,5] However, when cough is excessive or persists, it can be detrimental to patients through adverse consequences such as syncope, urinary incontinence, vomiting, chest pain, rib fractures, sleep disturbances, relationship difficulties, social embarrassment, and depression.[4–6] An increased frequency of cough also adversely affects health-related quality of life.[6]

EPIDEMIOLOGY AND ETIOLOGY

The prevalence of cough depends on environmental and genetic factors, comorbidities, and the type of questionnaire used.[2] Estimates of the prevalence of cough vary and range between 9% and 33%.[5,7] Chronic cough is more common in women and more commonly occurs in patients aged 50 to 70 years old with increased onset of chronic cough occurring near menopause.[7,8] Additionally, patients who continue to smoke are three times as likely to have a chronic cough compared to nonsmokers.[5] Results from the ACHOO study revealed the burden associated with acute cough and/or cold symptoms. Fifty-two percent of the survey respondents indicated that their daily lives were affected “a fair amount” or “a lot” when they had a cough and/or cold. Participants also reported a decrease of 26% in their perceived productivity when they were experiencing cough and/or cold symptoms, and 45% of respondents reported missing at least 1 day of work or school.[6]

The etiology of cough may occur anywhere within the realm of the vagus nerve, which is the longest nerve of the autonomic nervous system. Therefore, cough may arise from a variety of systems (eg, respiratory, cardiovascular, gastrointestinal).[2] Viral upper respiratory tract infections are the most common cause of acute cough, followed by exacerbations of underlying diseases [eg, asthma, chronic obstructive pulmonary disease (COPD), upper airway cough syndrome (UACS), bronchiectasis] and pneumonia.[3,4] The most common cause of subacute cough is postinfectious cough followed by exacerbations of

underlying diseases.[3,5,9] Asthma (including cough-variant asthma), UACS, nonasthmatic eosinophilic bronchitis (NAEB), and GERD are the most common causes of chronic cough in adult nonsmokers.[3,10,11] Additional causes of chronic cough are included in **Table e12-2**.[3–5,7,9,12,13]

RELEVANT ANATOMY AND MECHANISMS OF DISEASE

Physiology of Cough

Cough is a host defense mechanism. The cough reflex prevents introduction of particulate matter in the lower airways. The respiratory epithelial cells are covered with beating cilia and mucus. The beating cilia propel the overlying mucous layer upward toward the larynx. When mucociliary clearance is impaired due to damage of cilia (eg, smoking), coughing serves as a compensatory mechanism to help clear aspirated material, excess secretions, and foreign bodies.[14]

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

Allergic Rhinitis

J. Russell May

KEY CONCEPTS

1. Allergic rhinitis is a common disease. Prevention measures and treatment are justified in most cases because of the potential for complications.
2. Because an immune response to allergens results in release of inflammatory mediators that cause allergic rhinitis symptoms, patients must understand the rationale for proper timing and administration of prophylactic regimens.
3. Avoidance of allergens is difficult and it may be impractical to expect full success.
4. Antihistamines offer an effective option for treating both seasonal and persistent allergic rhinitis.
5. Intranasal steroids are highly effective in patients who use them properly.
6. While immunotherapy is the only disease-modifying treatment of allergic rhinitis, expense, potential risks, and the major time commitment required make patient selection critical.

Preclass Engaged Learning Activity

Perform a PubMed search to identify the latest national guidelines for the treatment of allergic rhinitis. Describe the drug classes considered to be first-line treatment and consider when second-line agents may be appropriate. This activity is intended to develop literature searching skills in identifying the latest treatment recommendations.

INTRODUCTION

Allergic rhinitis involves inflammation of the nasal mucous membrane. In a sensitized individual, allergic rhinitis occurs when inhaled allergenic particles contact mucous membranes and elicit a specific response mediated by immunoglobulin E (IgE). This acute response involves the release of inflammatory mediators and is characterized by sneezing, nasal itching, and watery rhinorrhea, often associated with nasal congestion. Itching of the throat, eyes, and ears frequently accompanies allergic rhinitis.

Allergic rhinitis may be regarded as seasonal allergic rhinitis, commonly known as *hay fever*, or persistent allergic rhinitis (formerly known as perennial rhinitis). Seasonal rhinitis occurs in response to specific allergens usually present at predictable times of the year, during plants' pollination (typically the spring or fall). Seasonal allergens include pollen from trees, grasses, and weeds. Persistent allergic rhinitis is a year-round disease caused by nonseasonal allergens, such as house dust mites, animal dander, and molds, or multiple allergic sensitivities. It typically results in less variable, chronic symptoms. Many patients have a combination of these two types of allergic rhinitis, with symptoms year-round and seasonal exacerbations.

EPIDEMIOLOGY AND ETIOLOGY

1 Allergic rhinitis is one of the most common diseases affecting adults and is the most common chronic disease in children in the United States, generating $2 to $5 billion in direct healthcare cost each year.[1] Prevalence rates are 14% in adults and 13% in children when using a physician-confirmed diagnosis.[2] Actual sensitization to inhaled allergens is likely higher and is increasing with estimates of 15% to 30% in the United States.[3] Patients may be limited in their ability to carry out normal daily functions; higher levels of general fatigue, mental fatigue, anxiety, depressive disorders, and learning disabilities (secondary to sleep loss and fatigue) are possible.

In addition, the impact of allergic rhinitis goes well beyond these CNS issues. Allergic rhinitis is associated with several other serious medical conditions, including asthma, chronic rhinosinusitis, otitis media, nasal polyposis, respiratory infections, and orthodontic malocclusions.

The development of allergic rhinitis is determined by genetics, allergen exposure, and the presence of other risk factors. A family history of allergic rhinitis, atopic dermatitis, or asthma suggests that rhinitis is allergic. The risk of developing allergic disease appears to increase if one parent is atopic and further increases if two are allergic; however, small sample sizes and the lack of

reproducibility prevent generalization.[4]

Allergen exposure is another necessary factor. For allergic rhinitis to occur, an individual must be exposed over time to a protein that elicits the allergic response in that individual. Many potential sufferers never develop symptoms because they do not come into contact with the allergen that would produce symptoms in them.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

Oral Health and Systemic Conditions

Lisa M. Palmisano and Jennifer L. Mazan

KEY CONCEPTS

1. Oral health is a growing global concern because of its effect on quality of life, morbidity, and mortality.
2. Dental caries and periodontal disease are examples of oral health conditions that have significant impact on patients' overall health status.
3. Tooth loss, periodontal disease, dental caries, and denture use have associations with morbidity and mortality risk.
4. Chronic hyperglycemia may cause various acute or chronic oral complications that may increase risk of worsening glycemic control or developing other systemic complications of diabetes.
5. Diabetes and periodontal disease have a bidirectional relationship on glycemic control and periodontal disease.
6. Medications used in treatment of cardiovascular diseases have adverse effects that can affect oral health.
7. Periodontal disease is shown to increase inflammatory markers that may worsen the progression of a patient's cardiovascular status, but no profound association can be made on the reduction of cardiovascular risk with the treatment of periodontal disease.
8. Patients with respiratory conditions such as asthma and COPD are at an increased risk of dental caries, periodontal disease, dental erosion, and oral candidiasis.
9. Xerostomia, acidity of saliva and the oral biofilm, and the deposition of added lactose in inhalers contribute to poor oral health of patients with respiratory conditions.
10. Patients with mental health conditions are more likely to suffer from dental caries, tooth loss, and oral lesions.

11 Poor oral health in patients with mental health conditions may result from poor oral hygiene, lack of motivation, cost, and barriers to accessing dental care.

12 Oral health disparities are noted across patients' lifespans as a result of age, access to dental coverage, income, education, and race/ethnicity.

13 National and local initiatives have been created to increase awareness, education, and access for oral healthcare for all Americans.

14 Nondental healthcare professionals, including pharmacists, can play an integral role in educating patients on oral health as it pertains to oral health diseases, systemic diseases, and medication-related adverse effects.

Preclass Engaged Learning Activity

Test your baseline knowledge on various oral health topics using the online short quizzes below:
General website (http://www.mouthhealthy.org/en/az-topics/quiz-time)
Specific short oral health quizzes:

1. What causes dry mouth?
2. Is all tobacco bad?
3. Kids' dental health
4. Teen dental health
5. Adults under 40 dental health
6. Adults 40–60 dental health
7. Adults over 60 dental health

INTRODUCTION TO ORAL HEALTH

1 Oral health encompasses health in the oral tissues, dentition, mastication ability, tongue movement along with the absence of chronic oral-facial pain, cancers, oral lesions, or other oral conditions or diseases that affect the oral, dental, or craniofacial tissues.[1,2] Poor oral health can result in physical oral dysfunction, malnutrition, sociopsychological impairment, cognitive decline, and a reduced overall quality of life.[2,3] Oral health is a global concern given the

disparities to access oral health providers and the growing evidence as a modifiable risk factor for chronic systemic conditions as well as oral diseases.[1,2,4–6] The manifestation of oral symptoms such as xerostomia, candida infections, and ulcerations are just examples of potential indicators of chronic conditions such as diabetes, cardiovascular disease (CVD), autoimmune disease, and others.[5,6] Furthermore, medical condition(s) and medication treatment can negatively affect a person's oral health. The call for action to improve oral healthcare has been emphasized by the World Health Organization, US Surgeon General, and other healthcare organizations.[1,4,5,7,8]

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

Oral Hygiene and Minor Oral Disorders

Anna Milone, Kristyn Williamson, and Maren Hall

KEY CONCEPTS

1. Dental caries is one of the most common chronic health conditions in both children and adults. Dental caries stems from an imbalance in saliva defense, microbial load, and lifestyle habits. Modifiable risk factors include oral hygiene practices and lifestyle factors. Dental caries can lead to tooth sensitivity, cause oral pain, and have implications for overall health.
2. For oral health maintenance, teeth should be brushed twice daily with fluoride toothpaste. Patients should floss daily and follow recommended technique for brushing and flossing. Oral health maintenance also includes the use of athletic mouthguards, denture care, and regular dental care by an oral healthcare professional.
3. Toothpaste contains fluoride as its primary active ingredient to prevent tooth decay and gum disease. Other active ingredients, such as potassium salts, may be added for tooth sensitivity, as well as abrasives and carbamide peroxide for tooth whitening.
4. The first-line treatment for dental pain is nonsteroidal anti-inflammatory drugs (NSAIDs), with or without acetaminophen.
5. Benzocaine is available over the counter in numerous products for adults, children, and infants as a local anesthetic for oral pain. While widely available, benzocaine has significant safety concerns and should not be used for teething pain in children younger than 2 years of age.
6. Canker sores are one of the most common ulcerative conditions of the mouth. Treatment options include pain management with topical agents and eliminating irritating food and drink from the diet.

7. Cold sores are recurrent oral lesions resulting from infection with herpes simplex virus type 1. Referral of patients to their primary care physician is likely warranted, as the most effective treatment options are available as prescription only products.
8. Xerostomia or dry mouth is a common oral condition often caused by medical conditions, medications, or medical treatments. Treatment of xerostomia greatly depends on the cause of the condition, but can be treated symptomatically with a number of OTC products.
9. Dentistry has few true emergencies; however, dental trauma where a permanent tooth is displaced or avulsed constitute a dental emergency, and immediate referral to an oral healthcare provider or urgent care center is warranted.
10. Fluoride is effective in preventing dental caries by inhibiting the demineralization of tooth enamel, enhancing the remineralization of enamel, and inhibiting bacterial enzymes involved in the metabolism of carbohydrates by cariogenic bacteria. Sources of fluoride include toothpaste, fluoridated drinking water, professionally applied topical fluorides, and oral fluoride supplementation.

Preclass Engaged Learning Activity

Explore the oral health section of either the Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/OralHealth/index.html), or the oral health portion of http://healthychildren.org by the American Academy of Pediatrics (AAP): https://www.healthychildren.org/English/healthy-living/oral-health/Pages/default.aspx). You can explore overview topics, Question and Answer sections, or topics that stimulate your interest. Find at least one topic that relates directly to community pharmacy practice or the primary care setting, such as the use of OTCs or educating patients. What areas of oral health do you feel knowledgeable in, and in what areas do you have gaps in knowledge? You may wish to reflect on any patient questions you have received on oral health topics. You may also wish to explore (either online or in person) the oral health section of a pharmacy. How large are these sections, and what products are available?

INTRODUCTION

Dentists and other members of the dental community are actively encouraging the involvement of additional health professionals in identification, referral, and in some cases treatment of patients with oral health conditions. Pharmacists, particularly community and health-system pharmacists, are the most accessible health professionals for patients presenting with oral health issues or questions. Furthermore, community pharmacies carry many products for oral health ranging from toothbrushes and mouthguards to rinses and pain relievers. Patients with oral pain, poorly fitting dentures, or a need for an athletic mouth guard often first enter a pharmacy seeking a solution, making the pharmacist the first healthcare professional they meet. It is important for the pharmacist and other primary care providers to have an understanding of the dental products available and be able to provide referrals and recommendations regarding oral health. Pharmacists and other primary care providers are integral parts of the collaborative interprofessional healthcare team, and dentists, dental hygienists, dental assistants, and dental therapists are also important and sometimes unrecognized members of this team.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

e16

Skin Care and Minor Dermatologic Conditions

Rebecca M. Law and Howard I. Maibach

KEY CONCEPTS

1. The skin is the largest organ of the human body. It performs vital functions such as (a) protecting the body against injury, physical agents, and ultraviolet radiation; (b) regulating body temperature; (c) preventing dehydration, thus helping to maintain fluid balance; (d) acting as a sense organ; and (e) acting as an outpost for immune surveillance. Skin also has a role in vitamin D production and absorption.
2. Age-related factors affect the epidermis, dermis, and subcutis. Pediatric skin is thinner, which enhances topical drug absorption and potential drug toxicities. Neonates, particularly premature neonates, are especially susceptible due to an incomplete skin barrier. Skin of older adults is drier, thinner, and more friable, which may predispose them to external insults and loss of the skin barrier function.
3. Examination of a patient's skin involves assessing skin color (degree of pigmentation, pallor, carotenemia, jaundice), skin temperature (warm, cool, clammy), skin surface characteristics (dryness, seborrhea, turgor, excessive or reduced sweating, texture), and the degree of photoaging.
4. Signs that a mole (nevus) may be dysplastic include: size >5 mm, irregular shape, variable/different pigmentation, indistinct borders; and they may be totally flat or flat with a central elevation.
5. Skin hydration is especially important for people with dry skin conditions. This involves an appropriate daily skin care routine and adequate daily fluid intake.
6. Management of diaper dermatitis includes frequent diaper changes, air drying (removing the diaper for as long as practical), gentle cleansing

(preferably with nonsoap cleansers and lukewarm water), and the use of barriers such as zinc oxide 40% ointment. After healing, a barrier such as zinc oxide 10% should be used with each diaper change as prophylaxis.

7 Due to the many negative effects and skin disorders relating to sun damage, sun protection at all times is critical, and this should be emphasized to patients, whether they are on medications with a photosensitivity potential or not. Sun protection includes sunscreens, sun avoidance, shading, long sleeve clothing, and wide brim hats or hats with a flap that covers the ears and neck. Sunscreens should always be used except in infants <6 months of age.

Preclass Engaged Learning Activity

Review the anatomy and physiology of the skin as described in this chapter of *Pharmacotherapy*. Audiovisual presentations of this material are available online, including a video on the components of the skin video on the components of the skin from the National Library of Medicine.

INTRODUCTION

The novelist Deen Ferrell has equated skin to life: “Life is too much like skin. It molds to the core of who you are and whether you dress it up, or try to keep busy so you don’t have to think about it, it doesn’t go away.”[1] Too often, we neglect to think about our skin or pay attention to changes on our skin that don’t go away. We allow our skin to get so dry it itches, cracks, and hurts. We ignore bumps and lesions on our skin because they are often painless and always present, so we do not notice when slow or subtle changes occur, which may be innocuous—or life threatening. It is easy to grow accustomed to something that is always there. We need to pay attention and teach our patients to pay attention.

1 Although not commonly thought of as such, skin is a vital organ with important functions. In fact, skin is the human body’s largest organ, with an average surface area of about 1.8 m^2.[2] The organ system that includes the skin is known as *the integumentary system*.

The human skin consists of an outer epidermis and an inner dermis, with subcutaneous fat. The epidermis (in 4 layers) primarily provides protection from the environment and performs a critical barrier function—keeping in water and

other vital substances and keeping out foreign elements. The dermis is a connective tissue layer that primarily provides resiliency and support for various skin structures and appendages such as sweat glands, sebaceous glands, hair, and nails. It also provides support for nerves and blood vessels. The subcutis (subcutaneous tissue) is a fatty layer below the dermis that helps to maintain the body temperature stable and protect bones and muscles from damage. It also allows nerves and blood vessels from the dermis to pass through and reach the muscles (**Fig. e16-1**). See “Structure and Functions of the Skin” section of this chapter for further discussion.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

Travel Health

Douglas Slain and Scott E. Kincaid

KEY CONCEPTS

1. Travelers should consult practitioners with travel health expertise when going to tropical or developing countries.
2. For the pretravel consultation recommendations, travelers should be given written material in their language to reinforce and supplement verbal instructions.
3. The pretravel screening appointment should include a discussion of items that should be contained in a travel medical kit.
4. Pregnant travelers should consult obstetric and travel medicine experts prior to traveling to developing countries.
5. Immunocompromised patients may need longer periods of pretravel preparatory time to allow for adequate immunization, given their sometimes blunted antibody responses to vaccines.
6. Travelers to sub-Saharan Africa, Southern Asia, Central and South America, and the Caribbean experience higher rates of infection than those traveling to other parts of the world.
7. Prophylactic antibiotic use may reduce the risk of traveler's diarrhea but is generally not recommended, primarily because of the risk of developing drug resistance or *Clostridium difficile* infection.
8. Prevention strategies are essential for limiting vector-borne infections during travel.
9. The mainstay of therapy in all altitude-related illnesses is descent to a lower altitude (typically at least a 300-meter reduction in altitude).
10. Patients who have previously been diagnosed with depression should continue their prescribed medications and minimize alcohol consumption while traveling.

Preclass Engaged Learning Activity

Design a medication kit for a family of four (2 adults and 2 preteen children) taking a 10-day trip to Aruba.

INTRODUCTION

Global (international) travel has increased dramatically over the past 20 years. A sizable proportion of this increased travel can be explained by individuals traveling from developed countries to developing countries.[1] Reasons for travel to developing countries are variable, but include work-related travel, leisure travel, medical tourism, adventure travel, medical mission or outreach, and study abroad programs.

Travel to distant lands has always been associated with risks to mental and physical health. Twenty-two percent to 64% of travelers experience health problems while traveling.[2] Travel to developing and/or tropical countries can be associated with even higher risks to traveler health than travel to developed or temperate countries. Many health problems arising during travel are self-limiting or not bothersome enough for travelers to seek medical care. However, approximately 10% of travelers seek help from physicians either during or soon after traveling.[3] In addition to infectious and noninfectious health problems, global travelers face potential dangers from vehicle and pedestrian traffic accidents, drowning, animal attacks, and assaults. This chapter focuses on health risks and diseases that affect global travelers, with primary emphasis on travel from developed countries to developing or tropical countries. Some travel-related information is included in other chapters, and readers will be referred accordingly.

PRETRAVEL PREPARATION

1 Travelers should review information about their destinations and itinerary and consider potential self-care options for health issues that may arise during travel. Pretravel preparation often involves the assistance of healthcare providers, which is typically more important for patients with chronic health conditions and those traveling internationally, especially to the developing

world. Travelers from North American and Europe heading to developing countries seek pretravel health advice 35% to 50% of the time.[4] Of these, only about 10% to 20% of travelers consult travel medicine experts or travel clinics. Informed primary care providers without extensive travel health expertise can provide adequate advice to travelers en route to low-risk destinations, but travelers should consult practitioners with travel health expertise when going to tropical or developing countries.[4]

Travel clinics and travel health experts are often underutilized.[4] Global travelers may not seek specialty travel advice because health insurance often does not cover expenses associated with pretravel care.[5] In addition, immigrants living in developed countries, going back to their home countries to visit friends and relatives (VFR) often believe they are immune to local diseases and do not feel the need to seek advice.[6] Unfortunately, VFR travelers often display some of the highest rates of travel health problems.[4,6] US residents traveling on global VFR trips make up about 33% of all travelers.[7] Other global travelers may not seek travel expert advice for travel to resorts in nearby countries. For example, Caribbean travel was associated with a higher proportion of travelers who did not seek pretravel advice among ill-returning travelers than travelers to other regions.[8] Even travelers staying at all-inclusive Caribbean resorts are subject to travel health issues.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

18

Contraception

Shareen Y. El-Ibiary, Sarah P. Shrader, and Kelly R. Ragucci

KEY CONCEPTS

1. Unintended pregnancy is a public health issue. A majority of unintended pregnancies that occur are due to inconsistent use or nonuse of contraceptives.
2. Contraception implies the prevention of pregnancy.
3. The following must be considered when selecting a contraceptive method: the effectiveness of the method, the noncontraceptive benefits and side effects of the method, attitude of the patient and of the sexual partner toward a contraceptive method, the ability to use the method correctly (which may alter the effectiveness of the method), and the ability to pay for the method.
4. Patient-specific factors (eg, frequency of intercourse, age, smoking status, desire for return to fertility, concomitant diseases, medications, and drug–drug interactions) must be evaluated when selecting a contraceptive method.
5. A variety of contraceptive methods are available. Nonhormonal methods include fertility awareness, barriers, spermicides, and the copper intrauterine device. Hormonal methods include estrogen/progestin products or progestin-only methods.
6. Adverse effects or difficulties in using the selected method should be monitored carefully and managed in consideration of patient-specific factors.
7. Some medications may alter the effects of hormonal contraceptives or vice versa; therefore, a patient's concomitant medications should be assessed for drug–drug interactions with hormonal contraceptives.
8. Accurate and timely counseling on the management of missed doses is

critical for contraceptive effectiveness.

9 Counseling on the optimal use of the contraceptive method and providing strategies for minimizing sexually transmitted infections/diseases (STIs/STDs) must be provided to all patients being initiated on contraceptives and for those also using contraception on an ongoing basis.

10 Emergency contraception (EC) may prevent pregnancy after unprotected intercourse or when regular contraceptive methods have failed.

11 Mifepristone, misoprostol, and methotrexate may be used in regimens for medical abortion.

Preclass Engaged Learning Activity

Watch the video entitled "The Menstrual Cycle" on YouTube from Osmosis. This is a 9-minute video that gives an overview of the menstrual cycle and discusses the cycle phases, ovulation, and the hormones involved. This video is helpful in serving as a quick refresher of the menstrual cycle physiology. Clear understanding of the menstrual cycle is important to understand the mechanisms of action for contraceptive products.

Watch the video entitled "Contraceptive CHOICE Project" on YouTube from Washington University in St. Louis. This is a 4-minute video that provides brief information regarding unintended pregnancy rates, along with an overview of long-acting reversible contraceptives and their benefits. It also discusses the effects of cost, access, and education, which are important considerations for contraceptive effectiveness and choice.

INTRODUCTION

1 Unintended pregnancy is a significant public health issue. In the United States, approximately 6 million women become pregnant each year.[1] The most recent data reveal that 45% of pregnancies are unintended, with the highest rates occurring in women aged 20 to 24 years.[2] About half of all unintended pregnancies end in abortion, and 41% occur in sexually active couples who claim they used some method of contraception.[2] If the goal of contraception—for pregnancies to be planned and desired—is to be realized, education on the use and effectiveness of contraceptive methods must be improved and provided.

EPIDEMIOLOGY

2 3 Contraception implies the prevention of pregnancy by inhibiting viable sperm from coming into contact with a mature ovum (ie, methods that act as barriers or prevent ovulation) or by preventing a fertilized ovum from implanting successfully in the endometrium (ie, mechanisms that create an unfavorable uterine environment). These methods differ in their relative effectiveness, safety, and patient acceptability (Tables 18-1 and 18-2).[3,4]

TABLE 18-1 Pregnancy and Continuation Rates for Various Pharmacologic Contraceptive Methods

Method	Pregnancy Typical Use	Pregnancy Ideal Use	Continuation After 1 Year
Combined oral contraceptive	7%	<1%	67%
Combined hormonal transdermal contraceptive patch	7%	<1%	--
Combined hormonal vaginal contraceptive ring	7%	<1%	--
Depo-medroxyprogesterone acetate	4%	<1%	56%
Copper IUD	<1%	<1%	78%
Levonorgestrel IUD	<1%	<1%	80%
Progestin-only implant	<1%	<1%	89%

Data from Reference 3.

TABLE 18-2 Comparison of Methods of Nonhormonal Contraception

				Percent of Women with Pregnancy[a]	
Method	**Absolute Contraindications**	**Advantages**	**Disadvantages**	**Perfect Use**	**Typical Use**
Condoms, male	Allergy to latex or rubber	Inexpensive STI/STD protection, including HIV (latex only)	High user failure rate Poor acceptance Possibility of breakage Efficacy decreased by oil-based lubricants Possible allergic reactions to latex in either partner	2	13
Condoms, female	Allergy to polyurethane History of TSS	Can be inserted just before intercourse or ahead of time STI/STD protection, including HIV	High user failure rate Dislike ring hanging outside vagina Cumbersome	5	21
Diaphragm with spermicide	Allergy to latex, rubber, or spermicide Recurrent UTIs History of TSS Abnormal gynecologic anatomy	Low cost Decreased incidence of cervical neoplasia Some protection against STIs/STDs	High user failure rate Decreased efficacy with increased frequency of intercourse Increased incidence of vaginal yeast UTIs, TSS Efficacy decreased by oil-based lubricants Cervical irritation	16	17
Cervical cap (FemCap)	Allergy to spermicide History of TSS Abnormal gynecologic anatomy Abnormal papanicolaou smear	Low cost Latex-free Some protection against STIs/STDs FemCap reusable for up to 2 years	High user failure rate Decreased efficacy with parity Cannot be used during menses	9	16[b]
Spermicides alone	Allergy to spermicide	Inexpensive	High user failure rate Must be reapplied before each act of intercourse May enhance HIV transmission No protection against STI/STDs	16	21
Sponge (Today)	Allergy to spermicide Recurrent UTIs History of TSS Abnormal gynecologic anatomy	Inexpensive	High user failure rate Decreased efficacy with parity Cannot be used during menses No protection against STIs/STDs	9[c]	14[d]

HIV, human immunodeficiency virus; STI/STD, sexually transmitted infection/disease; TSS, toxic shock syndrome; UTI, urinary tract infection.

[a]Failure rates in the United States during first year of use.

[b]Failure rate with FemCap reported to be 24% per package insert.

[c]Failure rate with Today sponge reported to be 20% in parous women.

[d]Failure rate with Today sponge reported to be 27% in parous women.

Data from Reference 3.

The actual effectiveness of any contraceptive method is difficult to determine because many factors affect contraceptive failure. Failure rates (eg, patient had an unintended pregnancy) can be described in two ways: perfect-use failure or typical-use failure. A failure in a patient who used the contraceptive agent properly is considered a method failure or perfect-use failure. User failure or typical-use failure rates take into account the perfect-use failure rate plus the user's ability to follow directions correctly and consistently and is usually higher.[3,4] The typical-use failure rate is used most often, because it is comprehensive including both the method and user failure rates.

ETIOLOGY AND PATHOPHYSIOLOGY

Comprehension of the hormonal regulation of the normal menstrual cycle is essential to understanding contraception in women (**Fig. 18-1**). The cycle of menstruation begins with menarche, usually around age 12 years, and continues to occur in nonpregnant women until menopause, usually around age 50 years. Factors such as race, body weight, medical conditions, and family history can affect the menstrual cycle.[3,4] The cycle includes the vaginal discharge of sloughed endometrium called *menses.* The menstrual cycle comprises three phases: (1) follicular (or preovulatory), (2) ovulatory, and (3) luteal (or postovulatory).

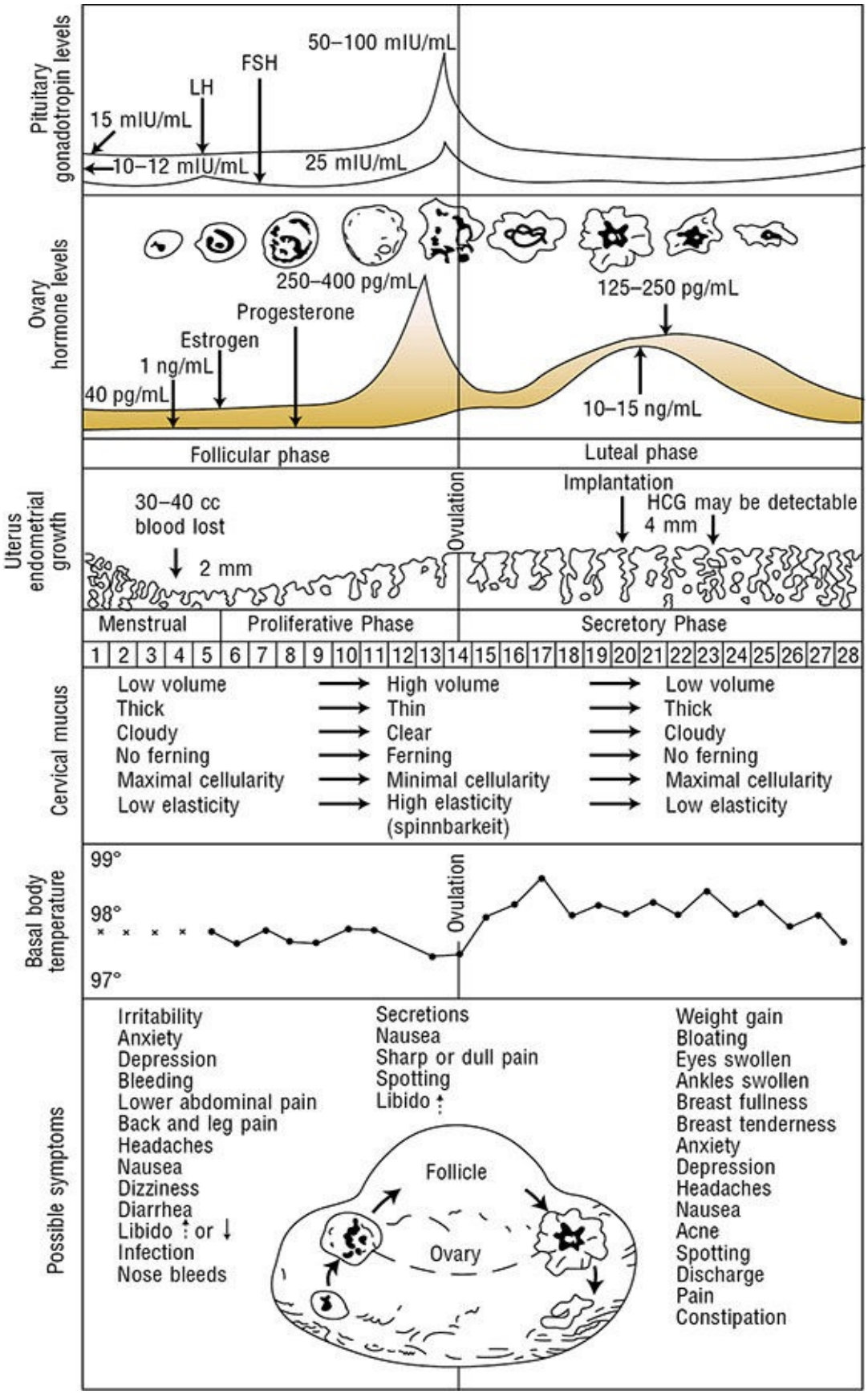

Pituitary gonadotropin levels
50–100 mIU/mL
FSH
LH
15 mIU/mL
10–12 mIU/mL
25 mIU/mL
Ovary hormone levels
250–400 pg/mL
125–250 pg/mL
Progesterone
Estrogen
1 ng/mL
40 pg/mL
10–15 ng/mL
Follicular phase
Luteal phase
Uterus endometrial growth
30–40 cc blood lost
2 mm
Ovulation
Implantation
HCG may be detectable
4 mm
Menstrual
Proliferative Phase
Secretory Phase
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
Cervical mucus
Low volume → High volume → Low volume
Thick → Thin → Thick
Cloudy → Clear → Cloudy
No ferning → Ferning → No ferning
Maximal cellularity → Minimal cellularity → Maximal cellularity
Low elasticity → High elasticity (spinnbarkeit) → Low elasticity
Basal body temperature
99°
98°
97°
Ovulation
Possible symptoms
Irritability
Anxiety
Depression
Bleeding
Lower abdominal pain
Back and leg pain
Headaches
Nausea
Dizziness
Diarrhea
Libido ↑ or ↓
Infection
Nose bleeds
Secretions
Nausea
Sharp or dull pain
Spotting
Libido ↑
Follicle
Ovary
Weight gain
Bloating
Eyes swollen
Ankles swollen
Breast fullness
Breast tenderness
Anxiety
Depression
Headaches
Nausea
Acne
Spotting
Discharge
Pain
Constipation

FIGURE 18-1 Menstrual cycle events, idealized 28-day cycle (FSH, follicle-stimulating hormone; HCG, human chorionic gonadotropin; LH, luteinizing hormone).
LH: 15 mIU/mL = 15 IU/L; 50–100 mIU/mL = 50100 IU/L.
FSH: 10-12 mIU/mL = 10-12 IU/L; 25 mIU/mL = 25 IU/L.
Estrogen: 40 pg/mL = ~150 pmol/L; 250-400 pg/mL = ~920-1,470 pmol/L; 125-250 pg/mL = ~460-920 pmol/L.
Progesterone: 1 ng/mL = 3 nmol/L; 10-15 ng/mL = ~30-50 nmol/L.
Temperatures: 99°F = 37.2°C; 98°F = 36.7°C; 97°F = 36.1°C.
(*From Reference 3. This figure may be reproduced at no cost to the reader*.)

The Menstrual Cycle

The first day of menses is referred to as *day 1 of the menstrual cycle* and marks the beginning of the follicular phase.[3] The follicular phase continues until ovulation, which typically occurs on day 14. The time after ovulation is referred to as the *luteal phase*, which lasts until the beginning of the next menstrual cycle. The median menstrual cycle length is 28 days, but it can range from 21 to 40 days. Generally, variation in length is greatest in the follicular phase, particularly in the years immediately after menarche and before menopause.[3]

The menstrual cycle is influenced by the hormonal relationships among the hypothalamus, anterior pituitary, and ovaries.[3] The hypothalamus secretes gonadotropin-releasing hormone (GnRH) in a pulsatile fashion.[3] These GnRH bursts stimulate the anterior pituitary to secrete bursts of gonadotropins, follicle-stimulating hormone (FSH), and luteinizing hormone (LH). FSH and LH direct events in the ovarian follicles that result in the production of a fertile ovum.

Follicular Phase

In the first 4 days of the menstrual cycle, FSH levels rise and allow the recruitment of a small group of follicles for continued growth and development (see Fig. 18-1).[3] Between days 5 and 7, one follicle becomes dominant and later ruptures, releasing the oocyte. The dominant follicle develops increasing amounts of estradiol and inhibin, which cause a negative feedback on the hypothalamic secretion of GnRH and pituitary secretion of FSH, causing atresia of the remaining follicles recruited during the cycle.

Once the follicle has received FSH stimulation, it must receive continued FSH stimulation or it will die.[3] FSH allows the follicle to enlarge and synthesize

estradiol, progesterone, and androgen. Estradiol stops the menstrual flow from the previous cycle, thickening the endometrial lining of the uterus to prepare it for embryonic implantation. It is responsible for increased production of thin, watery cervical mucus, which will enhance sperm transport during fertilization. FSH regulates the aromatase enzymes that convert androgens to estrogens in the follicle. If a follicle has insufficient aromatase, the follicle will not survive.

Ovulation

When estradiol levels remain elevated for a sustained period of time, the pituitary releases a mid-cycle LH surge (see Fig. 18-1).[3] This LH surge stimulates the final stages of follicular maturation and ovulation (follicular rupture and release of the oocyte). On average, ovulation occurs 24 to 36 hours after the estradiol peak and 10 to 16 hours after the LH peak. The LH surge, which occurs 28 to 32 hours before a follicle ruptures, is the most clinically useful predictor of approaching ovulation. After ovulation, the oocyte is released and travels to the fallopian tube, where it can be fertilized and transported to the uterus for embryonic implantation. Conception is most successful when intercourse takes place from 2 days before ovulation to the day of ovulation.

Luteal Phase

After rupture of the follicle and release of the ovum, the remaining luteinized follicles become the corpus luteum, which synthesizes androgen, estrogen, and progesterone (see Fig. 18-1).[3] Progesterone helps to maintain the endometrial lining, which sustains the implanted embryo and maintains the pregnancy. It also inhibits GnRH and gonadotropin release, preventing the development of new follicles. If pregnancy occurs, human chorionic gonadotropin prevents regression of the corpus luteum and stimulates continued production of estrogen and progesterone secretion to maintain the pregnancy until the placenta is able to fulfill this role.

If fertilization or implantation does not occur, the corpus luteum degenerates, and progesterone production declines.[3] The life span of the corpus luteum depends on the continuous presence of small amounts of LH, and its average duration of function is 9 to 11 days. As progesterone levels decline, endometrial shedding (menstruation) occurs, and a new menstrual cycle begins. At the end of the luteal phase, when estrogen and progesterone levels are low, FSH levels start to rise, and follicular recruitment for the next cycle begins.

CLINICAL PRESENTATION

3 4 Most health maintenance annual visits should include assessment of and counseling about reproductive health. Clinicians may use this opportunity to provide contraception and educate patients on prevention of STIs/STDs. Traditionally, hormonal contraception was provided subsequent to breast and pelvic examinations. However, the need for the physical examination may delay access to contraception and it reinforces the incorrect perception that these methods of contraceptives are harmful. Therefore, the American College of Obstetricians and Gynecologists (ACOG) allows provision of hormonal contraception after a simple medical history and blood pressure measurement.[5] Other preventive measures, such as pelvic and breast examinations, provision of the human papillomavirus vaccine, and screening for cervical neoplasia, can be accomplished during routine annual office visits.

TREATMENT

Desired Outcomes

The desired goal of treatment with all methods of contraception is to prevent pregnancy. However, many health benefits are associated with various contraceptive methods, including prevention of STIs/STDs (with condoms), improvements in menstrual cycle regularity (with hormonal contraceptives), improvements in certain health conditions (with hormonal contraceptives), and management of perimenopause (with hormonal contraceptives).[3,6]

General Approach to Treatment

Nonpharmacologic Therapy

3 4 5 **Fertility Awareness-based Methods** Motivated couples may use fertility awareness-based methods that entail avoiding sexual intercourse during the days of the menstrual cycle when conception is likely to occur. These typically include calendar-based methods such as the standard days or rhythm methods. In addition, there are symptoms-based methods that are based on observed physiologic changes, such as basal body temperature and cervical mucus to determine the fertile period. There are many technology apps available for these methods; however, the Food and Drug Administration (FDA) approved

the first app in this category (Natural Cycles) in 2018.[7] The major drawbacks of these methods are the relatively high pregnancy rates and avoidance of intercourse for several days during each menstrual cycle.[3]

3 4 5 9 **Barrier Techniques** The effectiveness of barrier methods depends almost exclusively on motivation to use them consistently and correctly.[3] These methods include condoms, diaphragms, cervical caps, and sponges (see Table 18-2). A major disadvantage is higher failure rates than most hormonal contraceptives; thus, provision of counseling and an advanced prescription for emergency contraception (EC) are recommended for all patients using barrier methods as their primary means of contraception.

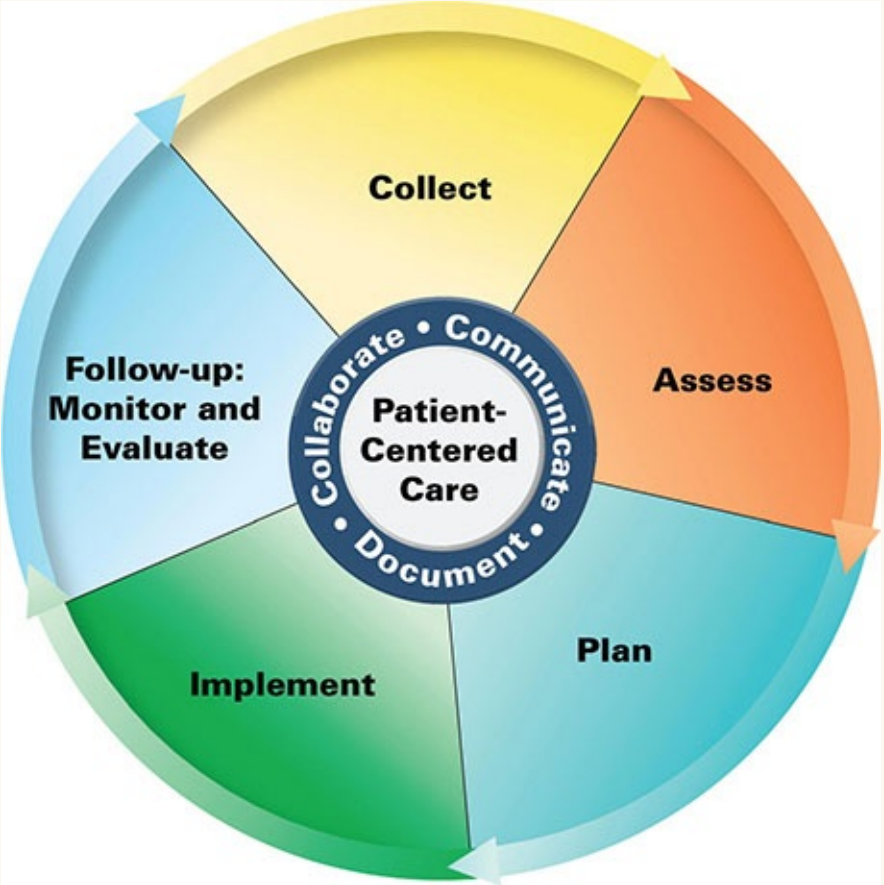
Male condoms create a mechanical barrier, preventing direct contact of the vagina with semen, genital lesions, and infectious secretions.[3] Most condoms in the United States are made of latex, which is impermeable to viruses. A small proportion of condoms are made from lamb intestine, which are permeable to viruses and should not be used to prevent STIs/STDs. Synthetic condoms manufactured from polyurethane are another option that are latex-free, and protect against viruses. Condoms are used worldwide as protection from STIs/STDs including human immunodeficiency virus (HIV). When condoms are used in conjunction with any other barrier method, their effectiveness theoretically approaches 98%. Spillage of semen or perforation and tearing of the condom can occur, but proper use minimizes these problems. Mineral oil–based vaginal drug formulations (eg, Cleocin, Premarin, and Monistat), lotions, or lubricants can decrease the barrier strength of latex and are not recommended, thus making water-soluble lubricants (eg, Astroglide and K-Y Jelly) the preferred choice. Condoms sold with prelubricated spermicides are no longer recommended because they do not provide additional protection against pregnancy or STIs/STDs and may increase vulnerability to HIV.[3,8,9]

The female condom is a prelubricated, loose-fitting polyurethane sheath, closed at one end, with flexible rings at both ends.[3] This method will protect against viruses, including HIV. Properly positioned, the ring at the closed end covers the cervix, and the sheath lines the walls of the vagina. The outer ring remains outside the vagina, covering the labia. The pregnancy rate of the female condom is reported to be higher when compared to male condoms. Male and female condoms should not be used together, as slippage and device displacement may occur.

The diaphragm, a reusable dome-shaped rubber cap with a flexible rim that is inserted vaginally, fits over the cervix in order to decrease access of sperm to the

ovum. The diaphragm requires a prescription from a clinician who has fitted the patient for the correct size.[3] Its efficacy is increased when it is used in conjunction with spermicidal cream or jelly. The diaphragm may be inserted up to 6 hours before intercourse and must be left in place for at least 6 hours afterward. However, leaving it in place for more than 24 hours is not recommended due to the potential for toxic shock syndrome (TSS). With subsequent acts of intercourse, the diaphragm should be left in place, and a condom should be used for additional protection.

The cervical cap (FemCap) is a soft, deep cup with a firm round rim that is smaller than a diaphragm and fits over the cervix like a thimble.[3] The cervical cap is available in three sizes and requires a prescription from a clinician who has fitted the patient for the correct size. It should be filled with spermicide prior to insertion. The cervical cap can be inserted 6 hours prior to intercourse and should not be removed for at least 6 hours after intercourse. It can remain in place for multiple episodes of intercourse without adding more spermicide but should not be worn for more than 48 hours at a time to reduce the risk of TSS. Failure rates with the cervical cap are higher than with other methods. Diaphragms and cervical caps do not protect against some STI/STDs including HIV; thus, condoms should also be used.



Patient Care Process for Contraception

Collect

- Patient characteristics (eg, age, sex, date of last menstrual period, pregnant, recently postpartum, breastfeeding, desire for pregnancy/return to fertility)
- Patient medical history (personal and family)
- Medication allergies
- Social history (eg, tobacco/ethanol use, relationships, sexual history)
- Current medications including over-the-counter (OTC), herbal products, dietary supplements
- Previous or current use of contraceptives
- Objective data: blood pressure (BP), height, weight

Assess

- Pregnancy status
- Effectiveness of previous contraceptive methods used (Tables 18-1 and 18-2)
- Blood pressure
- Weight and optimal method for use
- Precautions and contraindications to various types of contraceptives utilizing the CDC Medical Eligibility for Contraceptive Use, 2016 (see Table 18-6)
- Venous thromboembolism (VTE) risk factors (eg, recent surgery, plaster casting of lower extremity, cancer, prolonged immobility, recent hospitalization, recently postpartum)
- Drug interactions with various forms of contraception (see Table 18-6 for a select listing of drug interactions)
- Patient ability/willingness to use, adhere, or pay for various forms of contraception (Tables 18-1 and 18-2)

Plan*

- Drug therapy regimen including specific contraceptive dosage forms, dose, route, frequency, and duration (see Table 18-3 for select examples)
- Monitoring parameters including effectiveness and safety (eg, ACHES, abdominal pain, chest pain, headaches, eye problems, and severe leg pain) (Tables 18-4 and 18-5)

Implement*

- Provide patient education regarding all elements of contraceptive plan (eg, adherence, missed doses, side effects)
- Schedule appropriate follow-up to assess side effects, adherence issues, access to contraceptive

Follow-up: Monitor and Evaluate

- Presence of adverse effects (Tables 18-3, 18-4, and 18-5)
- For intrauterine devices, appropriate placement (eg, checking for strings)
- Changes in medical history (eg, increase in blood pressure, migraines, VTE risk, body mass index [BMI], new medications)
- Patient adherence to treatment plan using multiple sources of information

** Collaborate with patient, caregivers, and other healthcare professionals.*

Pharmacologic Therapy

Spermicides and Spermicide-Implanted Barrier Techniques

3 4 5 Spermicides, most of which contain nonoxynol-9, are chemical surfactants that destroy sperm cell walls and act as barriers that prevent sperm from entering the cervical os.[3] They are available as creams, films, foams, gels, suppositories, sponges, and tablets. Spermicides offer no protection against STI/STDs. In fact, when used frequently (more than two times per day), nonoxynol-9 may increase the risk of transmission of HIV by causing small disruptions in the vaginal epithelium.[3,8,9] The World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) do not promote products containing nonoxynol-9 for protection against STIs/STDs.

3 4 5 The vaginal contraceptive sponge (Today) contains 1 g of the spermicide nonoxynol-9.[3] It has a concave dimple on one side to fit over the cervix and a loop on the other side to facilitate removal. After being moistened with water, the sponge is inserted into the vagina up to 6 hours before intercourse. The sponge provides protection for 24 hours, regardless of the frequency of intercourse during this time. After intercourse, the sponge must be left in place for at least 6 hours before removal and should not be left in place for more than 24 to 30 hours to reduce the risk of TSS. Sponges should not be reused; after removal, they should be discarded. The sponge comes in one size and is available over-the-counter.

Hormonal Contraception

3 4 5 Hormonal contraceptives contain a combination of estrogen and progestin or a progestin alone. Oral contraceptive (OC) preparations first became available in the 1960s, but options have expanded to include a transdermal patch, a vaginal contraceptive ring, and long-acting injectable, implantable, and intrauterine contraceptives.

Combined hormonal contraceptives (CHCs) contain both estrogen and progestin and work primarily before fertilization to prevent conception. Progestins provide most of the contraceptive effect by thickening cervical mucus to prevent sperm penetration, slowing tubal motility, delaying sperm transport,

and inducing endometrial atrophy. Progestins block the LH surge, therefore inhibiting ovulation. Estrogens suppress FSH release from the pituitary, which may contribute to blocking the LH surge and preventing ovulation. However, the primary role of estrogen in hormonal contraceptives is to stabilize the endometrial lining and provide cycle control.[3,4]

Estrogens Three synthetic estrogens found in hormonal contraceptives available in the United States are ethinyl estradiol (EE), mestranol, and estradiol valerate. Ethinyl estradiol is the most commonly used estrogen in hormonal contraceptive products.[3,4] Most combined OCs, transdermal patch, and vaginal ring contain estrogen at doses of 20 to 50 mcg of EE.[4]

Progestins Progestin is a term used for a synthetic progesterone. A variety of progestins are available in the United States, and they vary in their progestational activity and differ with respect to inherent estrogenic, antiestrogenic, and androgenic effects.[3,4] Estrogenic and antiestrogenic properties are secondary to the extent of progestins' metabolism to estrogenic substances. Androgenic activity depends on two variables: the presence of sex hormone (testosterone)-binding globulin (SHBG-TBG) and the androgen-to-progesterone activity ratio. If the amount of SHBG-TBG is decreased, free testosterone levels increase, and androgenic side effects are more prominent.[4]

3 4 5 **Oral Contraceptives** With perfect-use OCs have a 99% efficacy rate, but with typical-use up to 7% of users may become pregnant (see Table 18-1).[3,4] The OCs currently available are modifications of the original products introduced in the 1960s and contain significantly less estrogen and progestin. High-dose formulations were associated with vascular and embolic events, cancers, and significant side effects, but reductions in hormone doses have been associated with fewer complications.

Monophasic OCs contain the same amounts of estrogen and progestin for 21 days, followed by 7-day placebo phase. Multiphasic pills (biphasic, triphasic, or quadriphasic) contain variable amounts of estrogen and progestin for 21 days, also followed by a 7-day placebo phase. There are no published data demonstrating increased safety or efficacy with the multiphasic tablets compared to monophasic tablets.[3,10,11] Extended-cycle tablets and continuous combination regimens may offer some benefits for patients in terms of side effects and convenience. With combination OCs, the types and doses of estrogen and progestin remain constant during the 21 to 24 days that active tablets are taken, though the doses and ratios of estrogens and progestins vary from one

preparation to another. The inclusion of 3 additional days of active pills to shorten the pill-free interval is thought to reduce hormone fluctuation between menstrual cycles. With extended use of OCs, active combination tablets are taken continuously for 84 days or longer followed by 7 days of inactive pills or estrogen-only pills.[4] **Table 18-3** lists available OC products by brand name and specifies hormonal composition.[3,4,12] Progestin-only "minipills" (28 days of active hormone per cycle) are also available options. Progestin-only OCs are less effective than combination OCs and are associated with irregular and unpredictable menstrual bleeding.[3,4] Minipills must be taken every day of the menstrual cycle at approximately the same time to maintain contraceptive efficacy. If a progestin-only OC is taken more than 3 hours late, patients should use a backup method of contraception for 48 hours.[4] Minipills may not block ovulation (nearly 40% of women continue to ovulate normally), so the risk of ectopic pregnancy is higher with their use than with other hormonal contraceptives.

TABLE 18-3 Pregnancy and Continuation Rates for Various Pharmacologic Contraceptive Methods

Product	Estrogen	Micrograms[b]	Progestin	Milligrams[b]	Spotting and Breakthrough Bleeding (%)
50 mcg Estrogen					
Ogestrel 0.5/50	Ethinyl estradiol	50	Norgestrel	0.5	4.5
Zovia 1/50	Ethinyl estradiol	50	Ethynodiol diacetate	1	13.9
Sub-50 mcg Estrogen Monophasic					
Afirmelle, Aubra, Aubra EQ, Aviane, Balcoltra, Delyla, Falmina, Larissia, Lessina, Lutera, Orsythia, Sronyx, Vienva, levonorgestrel/EE	Ethinyl estradiol	20	Levonorgestrel	0.1	26.5
Brevicon, Necon 0.5/35, Nortrel 0.5/35, Norminest Fe, Wera	Ethinyl estradiol	35	Norethindrone	0.5	24.6
Zovia 1/35, Kelnor 1/35	Ethinyl estradiol	35	Ethynodiol diacetate	1	37.4
Apri, Cyred, Desogen, desogestrel/EE, Emoquette, Enskyce, Isibloom, Juleber, Reclipsen	Ethinyl estradiol	30	Desogestrel	0.15	13.1
Altavera, Chateal, Kurvelo, Levora, Lillow, Marlissa, Portia	Ethinyl estradiol	30	Levonorgestrel	0.15	14
Aurovela 1/20, Aurovela Fe 1/20, Hailey Fe 1/20, Junel 1/20, Junel Fe 1/20, Loestrin 1/20; Fe 1/20, Melodetta 24 Fe (chewable) Microgestin 1/20; Microgestin Fe 1/20, norethindrone/EE, norethindrone/EE Fe, Tarina Fe 1/20	Ethinyl estradiol	20	Norethindrone	1	26.5
Aurovela 1.5/30-21, Aurovela 1.5/30-28, Aurovela Fe 1.5/30, Hailey Fe 1/20, Gildess Fe 1.5/30, Junel 1.5/30, Junel Fe 1.5/30, Larin (Fe) 1.5/30, Loestrin Fe 1.5/30, Microgestin 1.5/30, Microgestin Fe 1.5/30	Ethinyl estradiol	30	Norethindrone acetate	1.5	25.2
Cryselle, Elinest, Low-Ogestrel	Ethinyl estradiol	30	Norgestrel	0.3	9.6
Alyacen 1/35, Cyclafem 1/35, Dasetta 1/35, Necon 1/35, Norinyl 1+35, Nortrel 1/35, Ortho-Novum 1/35, Pirmella 1/35	Ethinyl estradiol	35	Norethindrone	1	14.7
Estarylla, Femynor, Norgestimate/ethinyl estradiol,Ortho-Cyclen, Mono-Linyah, Mononessa, Previfem, Sprintec	Ethinyl estradiol	35	Norgestimate	0.25	14.3
Balziva, Briellyn, Femcon Fe chewable, Zenchent, Gildagia, Nexesta Fe, Philith, Vyfemla, Wymzya Fe chewable, Zenchant, Zenchant Fe chewable	Ethinyl estradiol	35	Norethindrone	0.4	11
drosperinone/EE, Ocella, Safyral[c], Syeda, Tydemy[c], Yasmin, Zarah	Ethinyl estradiol	30	Drospirenone	3	14.5
Generess Fe chewable, Layolis Fe, Kaitlib Fe, norethindrone/EE	Ethinyl estradiol	25	Norethindrone	0.8	14.5
Sub-50 mcg Estrogen Monophasic Extended Cycle (longer than 21 days of active tablets)					
Lo Loestrin-24 FE[d]	Ethinyl estradiol	10	Norethindrone	1	50[e]
Aurovela 24 Fe, Junel Fe 24, Larin (Fe) 1/20, Larin 24 Fe, Minastrin 24 Fe chewable, norethindrone/EE/Fe, Taytulla (capsules)	Ethinyl estradiol	20	Norethindrone	1	50[e]
Amethia Lo, Camrese Lo, levonorgestrel/EE, LoSeasonique	Ethinyl estradiol	20/10	Levonorgestrel	0.1	50[e]
Amethyst	Ethinyl estradiol	20	Levonorgestrel	0.09	52[e]
Introvale, levonorgestrel/EE, Jolessa, Quasense Setlakin[f]	Ethinyl estradiol	30	Levonorgestrel	0.15	58.5[e]
Amethia, Ashlyna, Camrese, Daysee, levonorgesterel/EE Seasonique	Ethinyl estradiol	30/10	Levonorgestrel	0.15	50[e]
Quartette, Rivelsa	Ethinyl estradiol	20/25/30/10	Levonorgestrel	0.15	50[e]
Beyaz[c], drospirenone/EE, Gianvi, Loryna, Nikki, Rajani[c], Vestura, Yaz[d]	Ethinyl estradiol	20	Drospirenone	3	52.5[e]
Sub-50 mcg Estrogen Multiphasic					
Caziant, Cyclessa, Velivet	Ethinyl estradiol	25 (7)	Desogestrel	0.1 (7)	11.1
		25 (7)		0.125 (7)	
		25 (7)		0.15 (7)	
Tilia Fe, Tri-Legest Fe	Ethinyl estradiol	20 (5)	Norethindrone acetate	1 (5)	21.7
	Ethinyl estradiol	30 (7)	Norethindrone acetate	1 (7)	
	Ethinyl estradiol	35 (9)	Norethindrone acetate	1 (9)	
Azurette, Bekyree, desogestrel/EE, Kariva, Kimidess, Mircette, Pimtrea, Viorele	Ethinyl estradiol	20 (21)	Desogestrel	0.15 (21)	19.7
	Ethinyl estradiol	10 (5)	Desogestrel		

Necon 10/11	Ethinyl estradiol	35 (10)	Norethindrone	0.5 (10)	17.6
	Ethinyl estradiol	35 (11)	Norethindrone	1 (11)	
Alyacen 7/7/7, Cyclafem 7/7/7, Dasetta 7/7/7, Necon 7/7/7, Nortrel 7/7/7, Ortho-Novum 7/7/7, Pirmella 7/7/7	Ethinyl estradiol	35 (7)	Norethindrone	0.5 (7)	14.5
	Ethinyl estradiol	35 (7)	Norethindrone	0.75 (7)	
	Ethinyl estradiol	35 (7)	Norethindrone	1 (7)	
Ortho Tri-Cyclen, Tri-Estarylla, Tri-Femynor, Tri-Linyah, TriNessa, Tri-Previfem, Tri-Sprintec, Norgestimate/EE	Ethinyl estradiol	35 (7)	Norgestimate	0.18 (7)	17.7
	Ethinyl estradiol	35 (7)	Norgestimate	0.215 (7)	
	Ethinyl estradiol	35 (7)	Norgestimate	0.25 (7)	
Ortho Tri-Cyclen Lo, Norgestimate/EE Tri-Lo Estarylla, Tri-Lo-Marzia, Tri-Lo-Sprintec, TriNessa Lo	Ethinyl estradiol	25 (7)	Norgestimate	0.18 (7)	11.5
	Ethinyl estradiol	25 (7)	Norgestimate	0.215 (7)	
	Ethinyl estradiol	25 (7)	Norgestimate	0.25 (7)	
Aranelle, Leena, Tri-Norinyl	Ethinyl estradiol	35 (7)	Norethindrone	0.5 (7)	25.5
	Ethinyl estradiol	35 (9)	Norethindrone	1 (9)	
	Ethinyl estradiol	35 (5)	Norethindrone	0.5 (5)	
Enpresse, Trivora, levonorgestrel/EE, Levonest, Myzilra	Ethinyl estradiol	30 (6)	Levonorgestrel	0.05 (6)	
	Ethinyl estradiol	40 (5)	Levonorgestrel	0.075 (5)	
	Ethinyl estradiol	30 (10)		0.125 (10)	
Natazia	Estradiol valerate	3 (2)	Dienogest	0 (2)	
		2 (22)		2 (5)	
		1 (2)		3 (17)	
				0 (4)	
Progestin Only					
Camila, Deblitane, Errin, Heather, Incassia, Jencycla Jolivette, Lyza, Ortho Micronor, Nora-BE, Norlyda, Norlyroc, Orthor Micronor, Sharobel,Tulana, norethindrone	Ethinyl estradiol	–	Norethindrone	0.35	42.3

[a]28-day regimens (21-day active pills, then 7-day pill-free interval) unless otherwise noted.

[b]Number in parentheses refers to the number of days the dose is received in multiphasic oral contraceptives.

[c]Also contains levomefolate calcium 0.451 mg in all 28 tablets.

[d]28-day regimen (24-day active pills, then 4-day pill-free interval).

[e]Percent reporting after 6 to 12 months of use.

[f]91-day regimen (84-day active pills, then 7-day pill-free interval).

Data from References 3, 4, and 12.

8 ***Initiating an Oral Contraceptive*** Oral contraceptives may be initiated by several different methods, including on the first day of bleeding during the menstrual cycle, on the first Sunday after the menstrual cycle begins, or using the quick start method. The first day method is when the woman starts the OC on the first day of her menstrual cycle. The women should be instructed to use a second method of contraception (typically recommend condoms) for at least 7 days after initiation for maximum effectiveness though some sources state that no backup contraceptive method is required for the first day of menses start method.[13] The "Sunday start" method is to begin pills on the first Sunday after the menstrual cycle begins, as this may provide for weekends free of menstrual periods.[3,4,13,14] Women should also be instructed to use a second method of contraception (typically recommend condoms) for at least 7 days after initiation for maximum effectiveness. It may be preferable to have women use additional contraception for the entire first cycle, due to user failure in the first month. In the "quick start" method for initiating OCs, the patient takes the first tablet on the day of her office visit. Women should be instructed to use a second method of contraception for at least 7 days and potentially until she begins her next menstrual cycle to ensure optimal effectiveness. The woman should be informed that the menstrual period will be delayed until completion of the active tablets in the current OC pack. This method has been shown to be more successful in getting women to start OCs and to continue using OCs through the third cycle of use.[3] The Centers for Disease Control and Prevention (CDC) recommends that women start or resume hormonal contraception no sooner than 5 days after use of the emergency contraceptive ulipristal acetate to maximize the effectiveness of both products (use of the two products together may decrease effectiveness). Long-acting reversible contraceptive (LARC) methods such as the intrauterine device and implant, however, can be started at the time of ulipristal acetate use.[14]

3 4 5 ***Choice of Oral Contraceptive*** Because all combined OCs are similarly effective in preventing pregnancy (see Table 18-1), the initial choice is based on the hormonal content and dose, preferred formulation, and coexisting medical conditions (see Table 18-6).[4,12,14] In women without coexisting medical conditions, an OC containing 35 mcg or less of EE is recommended (see Table 18-3).[4,12] This strategy is based on evidence that complications and side effects from CHC (ie, VTE, stroke, or MI) result from excessive hormonal content. With nonadherence to OCs, the risk of pregnancy may be greater in women taking OCs containing less than 35 mcg of EE. Women with oily skin, acne, or hirsutism should be given low androgenic OCs.[4] Choice of an agent based upon coexisting medical conditions can be found in Table 18-6.[14]

It may be easier to identify/manage side effects and easier to manipulate to alter the timing of the menstrual cycle in patients taking monophasic OCs.[3,4] Continuous combination OCs either eliminate or reduce the number of menstrual cycles per year, leading to less premenstrual symptoms and dysmenorrhea. Commercially available continuous combination OCs are available, or monophasic 28 day OCs can be cycled by skipping the 7-day placebo phase. With continued use of extended-cycle or continuous combination OCs for 1 year, no significant changes in adverse effects have been noted. However, long-term studies have not been performed to assess the risk of cancer, venous thromboembolism (VTE), or changes in fertility. Extended-cycle regimens provide a shortened pill-free interval, from the traditional 7 days to 2 to 4 days. These various extended-cycle and continuous regimens may be beneficial for women with symptoms such as dysmenorrhea, severe premenstrual syndrome, or menstrual migraines.

6 ***Managing Oral Contraceptive Side Effects*** Many side effects occurring with early OC use (eg, nausea, bloating, breakthrough bleeding) improve spontaneously by the third cycle of use after adjusting to the altered hormone levels.[3,4,13,14] Women should be counseled to continue their OC for 2 to 3 months before a change is made to adjust the hormonal content unless a serious adverse effect is present. Despite the 2 to 3 month adjustment period, a large majority of women who discontinue OCs do so because of the side effects. Patient education and early reevaluation within 3 to 6 months are necessary to identify and manage adverse effects, in an effort to improve adherence. The most common adverse effect is irregular bleeding. Women on extended-cycle regimens should be counseled to expect this during the first 6 months. For women experiencing bleeding irregularities beyond the recommended time frame, the estrogen or progestin content may need to be adjusted.[4,13,14] Early breakthrough bleeding is typically due to insufficient estrogen and late breakthrough bleeding is due to insufficient progestin. Nausea may occur due to the estrogenic effects of these hormonal contraceptives. Skin breakouts occur more often in products with higher androgenic effects. Serious adverse effects that may occur with the use of CHCs are listed in **Table 18-4**, and common side effects along with recommended monitoring are reviewed in **Table 18-5**.[3,4,13] Patients should be instructed to consult with their provider immediately and likely should discontinue CHCs if they experience serious warning signs, described as ACHES (Abdominal pain, Chest pain, Headaches, Eye problems, and Severe leg pain).[3,4]

TABLE 18-4 Symptoms of a Serious or Potentially Serious Nature Associated with Combined Hormonal Contraception

Symptom	Possible Cause
SERIOUS: Stop immediately	
Loss of vision, proptosis, diplopia, papilledema	Retinal artery thrombosis
Unilateral numbness, weakness or tingling	Hemorrhagic or thrombotic stroke
Severe pains in chest, left arm or neck	Myocardial infarction
Hemoptysis	Pulmonary embolism
Severe pains, tenderness or swelling, warmth or palpable cord in legs	Thrombophlebitis or thrombosis
Slurring of speech	Hemorrhagic or thrombotic stroke
Hepatic mass or tenderness	Liver neoplasm
POTENTIALLY SERIOUS: May continue with caution while being evaluated	
Absence of menses	Cervical endometrial or vaginal cancer
Spotting or breakthrough bleeding	Cholecystitis, cholelithiasis, or liver neoplasm
Breast mass, pain or swelling	Pituitary adenoma
Right upper-quadrant pain	Cholestatic jaundice
Mid-epigastric pain	B6 deficiency
Migraine headache	Leiomyomata, adenomyosis
Severe nonvascular headache	
Galactorrhea	
Jaundice, pruritus	
Depression, sleepiness	
Uterine size increase	

Data from References 3 and 4.

TABLE 18-5 Drug Monitoring Table for Hormonal Contraception

Drug (or Drug Class)	Adverse Drug Reactions	Monitoring Parameter	Comments
Combined hormonal contraception	Nausea/vomiting Breast tenderness Weight gain Acne, oily skin Depression, fatigue Breakthrough bleeding/spotting Application site reaction (transdermal) Vaginal irritation (vaginal ring)	Patient symptoms Patient symptoms Weight Visual inspection Depression screening Menstrual symptoms Visual inspection Patient symptoms	Typically improves after two to three cycles; consider changing to lower estrogenic Consider changing to lower androgenic Data are limited and conflicting Consider changing to higher estrogenic
Depo-medroxyprogesterone acetate	Menstrual irregularities[a] Weight gain Acne Hirsutism Depression Decreased bone density	Menstrual symptoms Weight Visual inspection Visual inspection Depression screening BMD	Typically improves after 6 months Data are limited and conflicting Do not routinely screen with DXA
Levonorgestrel IUD	Menstrual irregularities[a] Insertion-related complications Expulsion Pelvic inflammatory disease	Menstrual symptoms Cramping, pain Cramping, pain, spotting, dyspareunia, missing strings Lower abdominal pain, unusual vaginal discharge, fever	Typically spotting, amenorrhea Prophylactic nonsteroidal anti-inflammatory drugs (NSAIDs) or local anesthetic may reduce occurrence IUD strings should be checked regularly by women to ensure IUD properly placed Overall risk of developing is rare, but counseling on STI/STD prevention is important
Copper IUD	See levonorgestrel IUD above	See levonorgestrel IUD above	Menstrual irregularities are typically heavier menses with copper IUD
Progestin-only implant	Menstrual irregularities[a] Insertion-site reactions	Menstrual symptoms Pain, bruising, skin irritation, erythema, pus, fever	Typically well-tolerated and resolve without treatment; infection is rare

[a]Suggested management of irregular bleeding may include use of NSAIDs for 5 to 7 days; hormonal treatment (if medically eligible) with COC or estrogen therapy for 10 to 20 days of treatment.

Data from References 3 and 13.

4 6 7 ***Managing Oral Contraceptive Drug Interactions*** The effectiveness of an OC is sometimes limited by drug interactions that interfere with GI absorption, increase intestinal motility by altering gut bacteriologic flora, and alter the metabolism, excretion, or binding of the OC.[2] The lower the dose of hormone in the OC, the greater the risk that a drug interaction will compromise its effectiveness. Women should be instructed to use an additional method of contraception if there is a possibility of a drug interaction altering the effectiveness of the OC.[4] Although less well documented, these recommendations generally apply to patients receiving transdermal and vaginal

CHC products.

Of all antibiotics, rifampin is the one with a true documented pharmacokinetic interaction.[3,13] Pharmacokinetic studies of other antibiotics have not shown any consistent interaction, but case reports of individual patients have shown a reduction in EE levels when OCs are taken with tetracyclines and penicillin derivatives. The mechanism of action is likely the inhibition of enterohepatic recirculation, but the clinical significance in most women is questionable. Women receiving concomitant rifampin (or derivatives) and OCs should be counseled on the possibility for decreased efficacy and to use an additional nonhormonal form of contraception while on the combination and for at least 7 days after the rifampin therapy has been discontinued; however, it has been recommended by some OC manufacturers to use a backup method for 28 days after use of any enzyme inducer such as rifampin.[13,15] It may be prudent to inform women of the slight risk of decreased effectiveness with other antimicrobials as well; however, it is not necessarily supported with strong evidence. If a woman is going to be receiving an interacting medication for more than 2 months, it is suggested to switch oral contraception to depot medroxyprogesterone acetate (DMPA) or an intrauterine device to avoid the interaction and eliminate the need for long-term additional nonhormonal contraception.

7 Women receiving certain anticonvulsants for a seizure disorder should be offered another form of contraception such as DMPA or LARC methods rather than OCs (see **Table 18-6**).[14] Some anticonvulsants (mainly phenobarbital, carbamazepine, phenytoin) induce the metabolism of estrogen and progestin, inducing breakthrough bleeding and potentially reducing contraceptive efficacy. In addition, some anticonvulsants are known teratogens. Use of combined OCs with lamotrigine may decrease the effectiveness of lamotrigine and increase the possibility of worsening the seizure disorder.

TABLE 18-6 U.S. Medical Eligibility Criteria for Contraceptive Use: Classifications for Combined Hormonal Contraceptives

Category 4: Unacceptable health risk (method not to be used)

- Breastfeeding or non-breastfeeding <21 days postpartum
- Current breast cancer
- Severe (decompensated) cirrhosis
- Current deep venous thrombosis/pulmonary embolism
- History/higher risk of deep venous thrombosis/pulmonary embolism (not on anticoagulant therapy)
- History/higher risk of deep venous thrombosis/pulmonary embolism (established on anticoagulant therapy for 3 months or greater)
- Thrombogenic mutations
- Major surgery with prolonged immobilization
- Migraines with aura, any age
- Systolic blood pressure ≥160 mm Hg or diastolic ≥100 mm Hg
- Hypertension with vascular disease
- Current and history of ischemic heart disease
- Benign hepatocellular adenoma or malignant liver tumor
- Peripartum cardiomyopathy, moderately or severely impaired cardiac function; normal or mildly impaired cardiac function <6 months
- Smoking ≥15 cigarettes per day and age ≥35
- Complicated solid organ transplantation
- History of cerebrovascular accident
- SLE; positive or unknown antiphospholipid antibodies
- Complicated valvular heart disease

Category 3: Theoretical or proven risks usually outweigh the advantages

- Breastfeeding 21-30 days postpartum with or without risk factors for VTE
- Breastfeeding 30-42 days postpartum with risk factors for VTE
- Non-breastfeeding 21-42 days postpartum with other risk factors for VTE
- Past breast cancer and no evidence of disease for 5 years
- History of DVT/PE (not on anticoagulant therapy or established on anticoagulant therapy for at least 3 months), but lower risk for recurrent DVT/PE
- Current gallbladder disease, symptomatic and medically treated
- History of bariatric surgery; malabsorptive procedures (*COCs only, vaginal ring/transdermal patch category 1)*
- History of cholestasis, past COC-related
- Hypertension; systolic blood pressure 140-159 mm Hg or diastolic 90-99 mm Hg
- Adequately controlled hypertension
- Peripartum cardiomyopathy, normal or mildly impaired cardiac function ≥6 months
- Smoking <15 cigarettes per day and age ≥35
- Use of fosamprenavir
- Use of certain anticonvulsants (phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine, and lamotrigine)
- Use of rifampicin or rifabutin therapy
- Diabetes with vascular disease or >20 years duration (*possibly category 4 depending upon severity*)
- Multiple risk factors for arterial cardiovascular disease (older age, smoking, diabetes, low HDL, high LDL, or high triglycerides and hypertension) (*possibly category 4 depending on category and severity*)
- Acute flare of viral hepatitis (*possibly category 4 depending on severity(initiation)*)
- Multiple sclerosis with prolonged immobility
- Current or history of superficial venous thrombosis

Category 2: Advantages generally outweigh theoretical or proven risks

- Age ≥40 (in the absence of other comorbid conditions that increase CVD risk)
- Sickle cell disease
- Undiagnosed breast mass
- Cervical cancer and awaiting treatment; cervical intraepithelial neoplasia
- Family history (first-degree relatives) of DVT/PE
- Major surgery without prolonged immobilization
- Diabetes mellitus (type 1 or type 2), nonvascular disease
- Gallbladder disease; symptomatic and treated by cholecystectomy or asymptomatic
- Migraines without aura
- History of pregnancy-related cholestasis
- History of high blood pressure during pregnancy
- Benign liver tumors; focal nodular hyperplasia
- Obesity
- Breastfeeding 30-42 days without other VTE risk factors
- Breastfeeding 42 days or more postpartum
- Non-breastfeeding 21-42 days postpartum without risk factors for VTE
- Rheumatoid arthritis on or off immunosuppressive therapy
- Smoking and <35 years old
- Uncomplicated sold organ transplantation
- Stable SLE without antiphospholipid antibodies
- Unexplained vaginal bleeding before evaluation
- Uncomplicated valvular heart disease
- Use of antiretrovirals other than fosamprenavir (*category 1 or 2 depending on agent*)
- Use of St. John's wort
- Inflammatory bowel disease (*possibly category 3 for those with increased risk of VTE*)
- Acute flare of viral hepatitis occurring during use of product (*continuation, category 3 or 4 for initiation of product)*

Category 1: No restriction (method can be used)

- Thalassemia, iron deficiency anemia
- Mild compensated cirrhosis
- Benign ovarian tumors
- Benign breast disease or family history of cancer
- Family history of cancer
- Schistosomiasis
- Cystic fibrosis
- Cervical ectropion
- Viral hepatitis (carrier/chronic)
- Minor surgery without immobilization
- Depression
- Gestational diabetes mellitus
- Endometrial cancer/hyperplasia, endometriosis
- Epilepsy
- Gestational trophoblastic disease
- Nonmigrainous headaches
- History of bariatric surgery; restrictive procedures
- History of pelvic surgery
- HIV infected or high risk
- Malaria
- Multiple sclerosis without prolonged immobility
- Ovarian cancer
- Past ectopic pregnancy
- Parity, parous, or nulliparous
- PID
- Postabortion
- Non-breastfeeding >42 days postpartum
- Severe dysmenorrhea
- Sexually transmitted infections
- Varicose veins
- Vaginal bleeding-irregular pattern without heavy bleeding or heavy, prolonged bleeding
- Thyroid disorders
- Tuberculosis
- Uterine fibroids
- Use of SSRIs
- Use of broad-spectrum antibiotics, antifungals, and antiparasitics

CHC, combined hormonal contraception; CVD, cardiovascular disease; HIV, human immunodeficiency virus; PE, pulmonary embolism; PID, pelvic inflammatory disease; VTE, venous thromboembolism.

Data from Reference 14.

Other medications that may affect OCs include HIV antiretrovirals such as protease inhibitors which, depending on the HIV medication, may decrease OC effectiveness or the OC may possibly alter the levels of protease inhibitor.[14] In addition, monitoring of potassium levels may be needed in women who take medications that increase potassium with drospirenone-containing OCs. Drospireneone is a derivative of spironolactone, a potassium-sparing diuretic, that also has anti-mineralocorticoid activity. Caution may be warranted in patients with a history of hyperkalemia or in patients taking concomitant medications that increase potassium levels or in high-risk patients taking strong inhibitors of CYP3A4.[15] Women should also be counseled that an over-the-counter herbal product, St. John's wort, may also possibly decrease OC effectiveness. Because there are several possible drug interactions that could affect the levels of OCs, it is recommended to assess all patient medications for possible interactions with OCs.[14]

9 ***Patient Instructions with Oral Contraceptives*** Many women who take OCs are not educated properly on the appropriate use of these medications. Women should be given the package insert that accompanies all products and instructed to read it. The written patient information should be supplemented with verbal information describing the mechanism of the medication, both common and serious side effects (ie, ACHES symptoms), and management of these side effects. Although several transient self-limiting side effects often occur, the patient should be aware of the danger signals that require immediate medical attention (see Table 18-4). The benefits and risks should be discussed, including the fact that OCs provide no physical barrier to the transmission of STIs/STDs, including HIV. Detailed instructions on when to start taking the OC should be provided. Patients should be told the importance of routine daily administration to ensure consistent plasma concentrations and improve adherence.

8 ***Missed Doses of Oral Contraceptives*** Specific instructions should be given regarding what to do if a tablet is missed.[13] For women who routinely have difficulty with adhering to daily dosing, counseling regarding other options such as the vaginal ring, transdermal patch, DMPA, implants, or IUDs should be provided. If warranted, suggesting EC may also be necessary.

For combined hormonal OCs, if one tablet is missed or late then take the tablet as soon as remembered and continue taking the rest of the tablets as prescribed (for most women that means two tablets taken on the same day). Typically no additional nonhormonal contraception methods are warranted. If

two or more consecutive tablets are missed then take one missed tablet as soon as remembered and discard the missed tablets. Continue taking the OC tablets as scheduled which means two tablets may need to be taken on the same day (ie, one of the missed tablets and one of the regularly scheduled tablets). If tablets were missed in the last week of hormonal tablets, finish the remaining active tablets (tablets with hormone) and then omit the hormone-free interval (skip taking the placebo tablets) and start a new pack of tablets. For both of these scenarios, counsel patients to use additional nonhormonal contraception until tablets of active hormone have been taken for 7 consecutive days. For all scenarios when two or more consecutive tablets are missed, consider counseling on use of EC if warranted. It is important to remember that handling missed or late doses of progestin-only OCs is different (see progestin-only pills section). In this case, if a woman is 3 hours late in taking her progestin-only tablet, then additional nonhormonal contraception should be used for 48 hours.[13]

6 9 ***Vomiting and Severe Diarrhea While on Oral Contraceptives*** Efficacy of OCs may be decreased when vomiting or severe diarrhea occurs, and recommendations for dosing OCs in this situation have been developed.[13] The recommendations are based on theoretical concerns and are identical to missed tablet instructions. If vomiting or diarrhea occurs for less than 48 hours then no redosing of OCs is warranted. If vomiting or diarrhea persists greater than 48 hours then continue taking tablets. If this scenario occurs during the last week of the hormonal tablets, then finish the tablets, skip the hormone-free tablets, and begin a new pack. Patients should be instructed to use additional nonhormonal contraception until tablets have been taken for 7 consecutive days after the vomiting or diarrhea subsides and counsel patients on use of EC if warranted.

Discontinuing Oral Contraceptives and Return of Fertility There is no evidence that OC use decreases subsequent fertility; there are similar findings with the transdermal patch and vaginal ring.[3] The average delay in ovulation after discontinuing OCs is 1 to 2 weeks. However, delayed ovulation is more common in women with a history of irregular menses. If amenorrhea does continue beyond 6 months, women should be counseled to see a physician for further fertility workup.[3,4] In the past, women were counseled to allow two to three normal menstrual periods before becoming pregnant to permit the reestablishment of menses and ovulation. However, in several large cohort and case-control studies, infants conceived in the first month after discontinuation of an OC had no greater chance of miscarriage or being born with a birth defect than those born in the general population.

Transdermal Contraceptives A CHC is available as a transdermal patch (Xulane, originally marketed as Ortho Evra), which includes 0.75 mg of EE and 6 mg of norelgestromin, the active metabolite of norgestimate.[3,4] Comparative trials have shown the transdermal patch to be as effective as combined OCs in patients weighing less than 90 kg. Of the 15 pregnancies reported in the clinical trials, five were among women weighing more than 90 kg; therefore, this product is not recommended as a first-line option for these women.[3,4,16]

Some patients experience application-site reactions, but other side effects are similar to those experienced with OCs (eg, breast discomfort, headache, and nausea).[4] A warning from the manufacturer states that women using the patch are exposed to approximately 60% more estrogen than from a typical OC containing 35 mcg of EE. Evidence suggests that higher exposure to estrogen may lead to increased thromboembolic risk, and the labeling for the contraceptive patch now contains a warning of this risk.[17]

The patch should be applied to the abdomen, buttocks, upper torso, or upper arm at the beginning of the menstrual cycle and replaced weekly for 3 weeks (the fourth week is patch-free).[3,4] The patch is designed to provide EE (estrogen) and norelgestromin (progestin) for 7 days. The patch should be changed weekly on the same day of week, which is known as the “Patch Change Day.” One patch should be worn at a time. According to the manufacturer, if the patch detaches and is off less than 24 hours, the detached patch or a new patch can be reapplied, and no additional hormone contraception necessary. If there is delayed application for more than 24 hours, a new patch must be applied as soon as possible, and additional nonhormonal contraception should be utilized until the patch has been worn for 7 consecutive days. This will also be a new “Patch Change Day” for the woman.[17] If the delayed application or detachment occurs in the third patch week, the hormone-free week should be omitted and a new patch should be applied immediately.[9,13,17]

Instructions vary if a woman forgets to change the patch based on where she is in the cycle.[17] If she forgets to apply a new patch after the hormone-free week, she will need to use a backup method of nonhormonal contraception until she has worn the patch for 7 days. If she forgets to apply a new patch in weeks 2 or 3 (left an active hormone patch on and forgot to replace it with a new one) and the delayed application is for only 1 or 2 days (up to 48 hours), a new patch should be applied immediately.[17] The next patch should be changed on the same “Patch Change Day,” and no backup contraception is needed. If the delayed application

for a new patch (old one is still on) is longer than 2 days (more than 48 hours), then she will need to start a new 4-week cycle of patches and use a backup nonhormonal method of contraception until a new patch has been placed for 7 days.[17] If the woman forgets to remove her patch for the hormone-free week, she should remove it as soon as she remembers and start the next cycle of patches on the regular "Patch Change Day" (day after Day 28 of the cycle). No backup contraceptive method is required in this situation. There should not be more than 7 days where a patch is not worn. If this occurs, the woman must use a backup nonhormonal contraceptive method until a new patch has been applied for 7 days.[17] Users have demonstrated greater adherence with the patch than with an OC, but whether this results in reduced pregnancy rates remains to be seen. The benefits of adherence must be weighed against the risk of increased estrogen exposure and possibility of VTE.

3 4 5 **Vaginal Rings** The vaginal contraceptive ring (NuvaRing) contains EE and etonogestrel.[18] It is a 54-mm flexible ring, 4 mm in thickness. Over a 3-week period, the vaginally inserted ring releases approximately 15 mcg/day of EE and 120 mcg/day of etonogestrel. Comparative trials have shown the vaginal ring to be as effective as combined OCs.

8 9 On the first cycle of use, the ring should be inserted on or before the fifth day of the menstrual cycle, remain in place for 3 weeks, then removed for 1 week to allow for withdrawal bleeding. The new ring should be inserted on the same day of the week as it was during the last cycle, similar to starting a new OC pack or transdermal patch on the same day of the week.

In contrast to diaphragms and cervical caps, precise placement is not an issue because the hormones are absorbed anywhere in the vagina. Women should be in a comfortable position, and compress the ring between the thumb and index finger and push it into the vagina. There is no danger of inserting the ring too far because the cervix will prevent it from traveling up the genital tract. Removal of the ring is performed in a similar manner, pulling it out and discarding into the foil patch (the ring should not be flushed down the toilet).[18] Patients should be discouraged from douching, but other vaginal products, including antifungal creams and spermicides, can be used.[4,18]

According to the manufacturer, if the ring has been displaced for less than 3 hours, a new ring should be inserted as soon as possible and kept in until the scheduled removal day, with no additional nonhormonal contraception necessary. If there is a delay of 3 or more hours, a new ring should be inserted immediately and either additional nonhormonal contraception should be utilized,

or intercourse should be avoided until the ring has been in place for 7 consecutive days. If the delayed reinsertion occurs during the third week of ring use, a new ring can be reinserted right away to start the next 21 day cycle. There may be some spotting or vaginal bleeding.

If a woman forgets to remove the ring after the third week, and there has been prolonged use of the ring for up to one extra week (not more than 4 weeks in place), she will still be protected and no backup protection will be necessary. The ring should be removed for the ring-free week, and a new ring can be inserted after the ring-free week. If the ring has been left in place longer than 4 weeks, the ring should be removed. The woman should check for possible pregnancy. Once pregnancy has been ruled out, a new cycle of the vaginal ring with 7 days of a nonhormonal contraceptive method may be started.[18]

6 Side effects, precautions, and contraindications for use of the vaginal ring are similar to those for all CHCs. The most commonly reported reasons for discontinuation of use were device-related issues, such as foreign-body sensation, device expulsion, and vaginal symptoms.[18] Cycle control with the vaginal ring appears to be equal or better than with combined OCs, with a low incidence of breakthrough bleeding and spotting after the second cycle of use. Patient acceptability of the delivery system has been studied, and the majority of women do not complain of discomfort in general or during intercourse.[4,18] A potential concern is the possibility of increased VTE (8 cases per 10,000 per year vs 6 cases with most CHCs) since etonogestrel is a metabolite of desogestrel, which may be associated with increased risk.[19]

3 4 5 Considerations with Combined Hormonal Contraceptive Use

When selecting a CHC, clinicians are challenged by weighing the benefits and risks associated with the many formulations available. The clinician must determine if the form of contraception is appropriate based upon the patient's lifestyle and potential adherence. A complete medical examination and papanicolaou (Pap) smear are not necessary before a CHC is prescribed. Based on American College of Obstetricians and Gynecologists (ACOG) recommendations, a medical history and blood pressure measurement should be obtained before prescribing a CHC, along with a discussion of the benefits, risks, and adverse effects with each patient.[3,5,13,14] For example, OCs are associated with noncontraceptive benefits, including relief from menstruation-related problems (eg, decreased menstrual cramps, decreased ovulatory pain [mittelschmerz], and decreased menstrual blood loss), improvement in menstrual regularity, alleviating acne and premenstrual dysphoric disorder, and decreased

iron deficiency anemia.[6] Women who take combination OCs have a reduced risk of ovarian and endometrial cancer. There is a 50% reduction in risk in women who have used OCs for 5 years or more, and protection may persist for more than 10 years post-use.[6] Combination OCs may also reduce the risk of ovarian cysts, ectopic pregnancy, pelvic inflammatory disease (PID), endometriosis, uterine fibroids, and benign breast disease. The CHC transdermal patch and vaginal ring are other combined hormonal options that may be more convenient for women than taking a tablet each day.

3 4 6 9 Adverse effects may hinder adherence and therefore efficacy, so they should be discussed prior to initiating a hormonal contraceptive agent.[13,14] Excessive or deficient amounts of estrogen and progestin are related to the most common adverse effects.[3,13] An important concern regarding the use of CHCs is the lack of protection against STI/STDs. Because of their high efficacy in preventing pregnancy, patients may choose not to use condoms. In addition to public health awareness, clinicians must encourage patients to use condoms for prevention of STI/STDs. OCs have an extensive history of safety concerns, which traditionally were related to high-dose estrogen tablets. Overall, the health risks associated with pregnancy, the specific health risks associated with CHCs, and the noncontraceptive benefits of CHCs should be factored into risk-to-benefit considerations. To replace the traditional absolute and relative contraindications to the use of OCs, the CDC developed a graded list of precautions for clinicians to consider when initiating CHCs (Table 18-6).[13,14]

Women Older than 35 Years Use of a CHC in women older than 35 is controversial. Older women, especially women in their 40s, retain a level of fertility even in the perimenopausal state and can use hormonal contraception to prevent pregnancy. Formulations with lower doses of estrogen (less than 30 mcg) have increased the use of CHCs in these women. In addition to the benefit of pregnancy prevention, they may improve or decrease the chance of developing perimenopausal and menopausal symptoms and increase bone mineral density (BMD). However, the benefits of using CHCs must be weighed against the risks in women older than 35. The increased risk of VTE should be considered especially in perimenopausal women older than 40. Older data suggest an increased risk of myocardial infarction (MI) in older women using CHCs, although many women in these studies were current smokers and used older formulations containing higher doses (greater than 50 mcg) of estrogen. More recent data do not support the increased risk of cardiovascular disease when low-dose formulations of CHCs are used in healthy, nonobese women.

Other concerns include the increased risk of ischemic stroke in women with migraines and the increased risk of breast cancer in older women.[4,14]

The risks and benefits of using CHCs in women greater than 35 must be considered on an individual basis. It is recommended that use of CHCs (with less than 50 mcg of estrogen) may be considered in healthy nonsmoking women. CHCs should not be recommended in women older than 35 years with migraine (with aura), uncontrolled hypertension, smoking, or diabetes with vascular disease.[4,14]

Smoking In early studies, OCs with 50 mcg EE or more were associated with MI in women who smoked cigarettes.[3,4] The United States case-control studies have found that both nonsmoking and smoking women, regardless of age, taking OCs with less than 50 mcg EE did not have an increased risk of MI or stroke. However, these studies included few women older than 35 years who were smokers. European studies, with a higher population of older smoking women, demonstrated an increased risk of MI in this population. Therefore, practitioners should prescribe CHC with caution, if at all, to women older than 35 years who smoke. Smoking 15 or more cigarettes per day by women in this age group is a contraindication to CHCs, and the risks generally outweigh the benefits of CHCs in those who smoke fewer than 15 cigarettes per day.[14] Progestin-only or nonhormonal contraceptive methods should be considered for women in this group.

Hypertension CHCs can cause small increases (ie, 6-8 mm Hg) in blood pressure, regardless of estrogen dosage.[4,14] This has been documented in both normotensive and mildly hypertensive women given a 30 mcg EE OC. In case-control studies of women with hypertension, OCs have been associated with an increased risk of MI and stroke. Use of low-dose CHC is acceptable in women younger than 35 years with well-controlled and frequently monitored hypertension. If a CHC-related increase in blood pressure occurs, discontinuing the CHC usually restores blood pressure to pretreatment values within 3 to 6 months.[4] Systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg is considered a contraindication to the use of CHCs. Hypertensive women who have a systolic blood pressure of 140 to 159 or diastolic blood pressure of 90 to 99 mm Hg should also avoid CHCs as the risks generally outweigh the benefits. Risks versus benefits should be considered for women who have additional cardiovascular risk factors along with hypertension. Women with hypertension who are taking potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, or aldosterone

antagonists may have increased serum potassium concentrations if they are also using an OC-containing drospirenone, which has anti-aldosterone properties.[4]

Dyslipidemia Generally, synthetic progestins may adversely affect lipid metabolism by decreasing high-density lipoprotein (HDL) and increasing low-density lipoprotein (LDL).[4,14] Estrogens tend to have more beneficial effects by enhancing removal of LDL and increasing HDL levels. Estrogens may moderately increase triglycerides. Much of the information on CHCs and impact on lipid profiles is from several years ago and dosing may have been a factor. Today as a net result, most low-dose CHCs have no significant impact on HDL, LDL, triglycerides, or total cholesterol. Although the lipid effects of CHCs theoretically can influence cardiovascular risk, the mechanism of increased cardiovascular disease in CHC users is believed to be due to thromboembolic and thrombotic changes, not atherosclerosis. It is generally acceptable to use CHCs in women with dyslipidemia as the single cardiovascular risk factor. However, careful consideration should be taken in women with dyslipidemia along with other cardiovascular risk factors and in many cases alternative methods of contraception may be recommended.

Diabetes Any effect of CHCs on carbohydrate metabolism is thought to be due to the progestin component.[4,14] However, most products used today with formulations containing low doses of progestins do not significantly alter insulin, glucose, or glucagon release or daily insulin requirements. CHCs do not appear to alter the hemoglobin A_{1C} values or accelerate the development of microvascular complications in women with diabetes. Therefore, nonsmoking women younger than 35 years with diabetes but no associated vascular disease can safely use CHCs. Diabetic women with vascular disease (eg, nephropathy, retinopathy, neuropathy, or other vascular disease) or diabetes of more than 20 years duration should not use CHCs.[4,14]

Migraine Headaches Women with migraine headaches may experience a decreased or an increased frequency of migraine headaches when using CHCs.[4,14,20] Studies have demonstrated a higher risk of stroke in women experiencing migraine with aura compared to women with simple migraine. In population-based studies, the risk of stroke in women with migraines has been elevated twofold to threefold. However, given the low absolute risk of stroke in young women (age less than 35 years), CHCs in healthy, nonsmoking women with migraine headaches without aura may still be considered.[14] Likewise, women with nonmigrainous headaches may also use CHCs without restriction.

Women of any age who have migraine with aura should not use CHC,[14] and women who develop migraines with aura while receiving CHC should discontinue use and consider a progestin-only option. Women developing migraines without aura while receiving CHCs should have their headaches evaluated to determine severity, evaluate for signs of an aura, and to discuss the risk versus benefit of CHC use.[14]

Breast Cancer Worldwide epidemiologic data from 54 studies in 25 countries (many of which studied high-dose OCs) were collected to assess the relationship between OCs and breast cancer.[4] Overall, investigators noted a small increase in the relative risk of having breast cancer diagnosed while combined OCs are taken and for up to 10 years following discontinuance. There is no increased excess risk of diagnosis 10 years or more after OCs are discontinued. A 2010 analysis of data from the Nurses' Health Study also found that women who used OCs had a slight increase in breast cancer risk.[21] In 2017, a large prospective Danish study reported breast cancer risks associated with more recent formulations of OCs.[22] Overall, women who were using or had recently discontinued using hormonal contraception had a modest (20%) increase in the relative risk of breast cancer compared with women who had never used hormonal contraception. The risk increased the longer the hormones were used and in women over the age of 40. If hormones are discontinued, the breast cancer risk returns to the same levels seen for women who never used them, although it may take longer for those who had taken for more than 5-10 years. For healthy young women, the benefits of hormonal contraception in preventing unwanted pregnancies and associated other benefits outweigh any risks. For those over the age of 40 or those who have an elevated risk of breast cancer because of family history or other factors, alternatives may be considered. The choice to use CHCs should not be affected by the presence of benign breast disease or a family history of breast cancer with either mutation. In women identified with BRCA1 or BRCA2 mutations, increased risk of breast cancer with OCs has been controversial. The results of two large, case-controlled studies have found conflicting results. Until additional data refutes or affirms these studies, it is important to understand these risks and assure they are discussed with patients as even a small increase in risk may be clinically important.[23,24] Women with current or past history of breast cancer should not use CHCs.[3,4,14]

Thromboembolism Estrogens increase hepatic production of factor VII, factor X, and fibrinogen in the coagulation cascade, therefore increasing the risk of

thromboembolic events (eg, deep vein thrombosis and pulmonary embolism). These risks are increased in women who have underlying hypercoagulable states (eg, deficiencies in antithrombin III, protein C, and protein S; factor V Leiden mutations, prothrombin G2010 A mutations) or who have acquired conditions (eg, obesity, pregnancy, immobility, trauma, surgery, and certain malignancies) that predispose them to coagulation abnormalities.[4,14] The incidence of thromboembolism and mortality is increased threefold in current OC users compared to nonusers. However, this risk is still less than the risk of VTE incurred during pregnancy. OCs containing new progestins such as third-generation progestins (eg, desogestrel and norgestimate) and a fourth-generation progestin (eg, drospirenone) have been associated with a slightly higher risk of thromboembolism.[3,4] Although the mechanisms for this increased risk is unclear, mechanisms underlying this increased risk may include: (a) a greater effect on the procoagulant, anticoagulant, and fibrinolytic pathways than earlier generation progestins; (b) an increased resistance to the anticoagulant effect of activated protein C; (c) increased levels of sex hormone-binding globulin; and (d) antiandrogenic effects of drospirenone make the CHC more estrogenic.[2,3,25,26] It is also thought that continuous, higher exposure to estrogen seen with the transdermal patch or vaginal ring is the reason for an increased thromboembolic risk with these agents as well.[25] An advisory committee to the FDA decided to change the product labeling of the transdermal patch as well as products containing drospirenone to include additional information about the increased risk of thromboembolism.[15,17] In addition, the vaginal ring also has an additional precaution in the product labeling.[18] Therefore, for women who are at an increased risk of thromboembolism (eg, older than 35 years, obesity, smoking, personal or family history of venous thrombosis, prolonged immobilization), it would be prudent to first consider low-dose oral estrogen contraceptives containing older progestins, progestin-only contraceptive methods, or barrier methods. A recent systematic review of progestin-only contraceptives did not suggest an overall significant increase in venous or arterial events.[27] Limited evidence suggests slight increases in thromboembolism in those using these for therapeutic indications or in those with other thromboembolic risk factors. Any slight increase in risk likely translates to a small increase in absolute numbers of thrombotic events at the population level.

Weighing the risks versus benefits of using CHCs containing third- and fourth-generation progestins, transdermal patch, and vaginal ring to determine their place in therapy is controversial. The overall risk of VTE with older low-dose agents is 6 per 10,000 women per year (compared with 2-3 per 10,000 in

nonusers). The risk increases to 10 to 15 per 10,000 women per year with drospirenone-containing OCs. Risk of VTE is also higher with the transdermal patch (10-15 per 10,000 women per year) and possibly with the vaginal ring (8 per 10,000 women per year). It is thought that continuous, higher exposure to estrogen seen with these formulations may be the cause of this increased risk. It is important to remember that regardless of contraceptive product, the risk is still lower than the risk of thromboembolism during pregnancy (17 per 10,000 women per year).[25]

Obesity The prevalence of obesity continues to rise each year among all age groups including women of childbearing age. It has been hypothesized that women with increased body weight have increased basal metabolic rates and induction of hepatic enzymes, leading to increased hormonal clearance and decreased serum concentrations of hormonal contraceptives. In addition, women who are obese have more adipose tissue, increasing hormonal sequestration, and decreased free hormone serum concentrations resulting in lower efficacy.[3,4] It is estimated that there is an additional two to four pregnancies per 100 woman-years of use in overweight or obese users.[16,28] Regardless of body weight, intrauterine devices (IUDs), implants, and DMPA have very low failure rates, and progestin-only contraceptives are considered safe in obese women.[14] In addition, the CDC states that the advantages of using an estrogen-containing contraceptive method (pill, patch, ring) generally outweigh the risks.[13,14] It should be noted that DMPA is associated with more weight gain than other methods.[3] With regard to EC, the copper IUD is the most reliable method in obese women. Oral EC products may be less effective and the effectiveness of levonorgestrel, in particular, is diminished.[29]

Obese women are also at risk of VTE, although studies evaluating the incidence of thromboembolism in obese women taking hormonal contraceptives have produced conflicting results. With low-dose estrogen containing products, the incidence increases from 5 to 10 cases in nonusers to 15 to 30 cases in users per 10,000 women per year. At baseline, obesity doubles the risk of thromboembolism compared to someone with a normal BMI. The American College of Obstetricians and Gynecologists suggests that progestin-only hormonal contraception may be more appropriate for obese women over the age of 35 years, although the CDC considers the benefits of estrogen-containing contraceptives to outweigh the risks as well.[14,16] Women should be counseled on any risks and consider alternative contraceptive methods on an individual basis.[16] Again, it should be noted that the risk of thromboembolism during

pregnancy and in the peripartum period is significantly greater than the risk with any hormonal contraceptive agent.

Postpartum Use of CHCs In the postpartum phase, there is concern about use of CHCs because of the mother's hypercoagulability and the effects on lactation. In the first 21 days postpartum (when the risk of thrombosis is higher), estrogen-containing hormonal contraceptives should be avoided (see Table 18-6).[14] If contraception is required during this period, progestin-only contraceptive methods may be acceptable alternatives. It is recommended that women who are breastfeeding avoid CHCs for the first 42 days postpartum in those with risk factors for VTE and for 30 days in those without risk factors. In those women who are not breastfeeding, CHCs should be avoided for up to 42 days postpartum in those with risk factors for VTE.[14] After 42 days postpartum, there is no restriction to the use of CHCs.

Systemic Lupus Erythematosus Contraception is important in women with systemic lupus erythematosus (SLE) because the risks associated with pregnancy are high in this population. Historically, clinicians have thought that CHCs exacerbated the symptoms of SLE,[4] postulating that estrogen may cause cutaneous lupus to progress to systemic lupus by promoting B-cell hyper-responsiveness and inducing or increasing autoimmunity.[4] Trials have shown that OCs with less than 50 mcg ethinyl estradiol do not increase the risk of flare among women with stable SLE and without antiphospholipid/anticardiolipin antibodies. Therefore, CHCs should be avoided in women with SLE and antiphospholipid antibodies or vascular complications and the risks outweigh the benefits of progestin-only contraceptive use in patient population. The copper intrauterine device may be the best option in this situation.[14] For patients with SLE without antiphospholipid antibodies or vascular complications, progestin-only contraceptives or the copper intrauterine device may be an alternative to CHCs; however, those with SLE and severe thrombocytopenia should avoid the copper intrauterine device and depot medroxyprogesterone acetate injection.[14]

Injectable Progestins Steroid hormones provide longer-term contraception when injected into the skin. Sustained progestin exposure blocks the LH surge, thus inhibiting ovulation. Should ovulation occur, progestins reduce ovum motility in the fallopian tubes. Even if fertilization occurs, progestins thin the endometrium, reducing the chance of implantation. Progestins also thicken the cervical mucus, producing a barrier to sperm penetration. This method of contraception does not provide any protection from STIs/STDs.[3,4]

Women who may benefit from injectable progestins are those who are breastfeeding, those who are intolerant to estrogens (ie, have a history of estrogen-related headache, breast tenderness, or nausea) or those with concomitant medical conditions or contraindications in which estrogen is not recommended (see Table 18-6). In addition, injectable progestins are beneficial for women with adherence issues; they have lower failure rates than CHC methods (see Table 18-1).[3,12,14]

Depot Medroxyprogesterone Acetate Depo-Provera (DMPA) is similar in structure to naturally occurring progesterone and is administered every 3 months either by deep intramuscular injection in the gluteal or deltoid muscle or subcutaneously in the abdomen or thigh within 5 days of onset of menstrual bleeding.[30,31] With perfect use, the efficacy of DMPA is more than 99%; however, with typical use, 3% of women experience unintended pregnancy.[3] The primary mechanism of action is suppression of ovulation. Depo-Provera is available as a 150 mg/mL injection vial or prefilled syringe for IM injection, and Depo-SubQ Provera 104 mg is available as a prefilled syringe.[30,31] Administration of both formulations of DMPA requires a medical office visit; however, studies of patient self-administration of subcutaneous DMPA have demonstrated positive results.[32,33]

Depo-Provera may be administered at any time as long as it is reasonably certain that the woman is not pregnant.[1,30,31] If it is administered between days 1 and 7 of the menstrual cycle in women who have not previously used hormonal contraception then no backup method is needed.[13] If it is administered at any other time of the menstrual cycle, then it is recommended to use an additional nonhormonal contraceptive backup method for 7 days. Additional recommendations on initiating the implant when switching from other methods of contraception are included in the package insert.[30,31] Although these injections may inhibit ovulation for up to 14 weeks, the dose should be repeated every 3 months (12 weeks) to ensure continuous contraception. The manufacturer recommends confirming the patient is not pregnant if there is a lapse of more than 13 weeks between injections for the intramuscular formulation or 14 or more weeks between injections for the subcutaneous formulation. However, CDC recommendations differ and state for either formulation, and pregnancy should be excluded in women with a lapse of 15 or more weeks.[13]

As with other contraceptive agents, concomitant conditions should be evaluated prior to use of DMPA. Although no adverse effects have been

documented in infants exposed to DMPA through breast milk, the manufacturer recommends not initiating DMPA until 6 weeks postpartum in breastfeeding women.[30,31] However, the CDC cites a lack of evidence supporting this claim and classifies DMPA use during this time frame as a category 1 or 2 suggesting that the benefit may outweigh the theoretical risk.[14] Women who are not breastfeeding but require contraception can receive DMPA immediately postpartum.[14] It is contraindicated in women with a current diagnosis of breast cancer due to potential hormonally sensitive tumors, and should be used with precaution in women with a past history of breast cancer, vascular, cardiovascular, or cerebrovascular disease, multiple risk factors for cardiovascular disease, and lupus. There is some concern that the impact of DMPA on lipids (potentially decreased HDL) and the hypoestrogenic pharmacologic effects may increase the risk of a vascular event. However, the risks with DMPA are much lower than with CHCs so risks and benefits should be weighed on an individual basis.[14] Women with sickle cell disease are good candidates for DMPA, as studies have demonstrated a reduction in sickle cell pain crises in women using DMPA.[14] In addition, women with seizure disorders may experience fewer seizures when taking DMPA for contraception, and there is not a concern with anticonvulsants reducing the contraceptive efficacy of DMPA.[3,14] Because return of fertility may be delayed after discontinuation of DMPA, it should not be recommended to women desiring pregnancy in the near future. The median time to conception from the first omitted dose is 10 months and 68% of women will be able to conceive within 12 months, 83% within 15 months, and 93% within 18 months of the last injection.[3,30,31]

6 Menstrual irregularities are the most frequent adverse effects of both formulations of DMPA and are most common in the first year of use. These irregularities include spotting, prolonged bleeding, and amenorrhea; counseling women on these possibilities is important before initiation of the method.[13,14] Women who cannot tolerate prolonged bleeding may benefit from a short course of NSAIDs (for 5-7 days) during the bleeding, and in addition, a short course of estrogen (if no contraindications are present) for approximately 10 to 20 days. Examples of estrogen regimens to help prolonged bleeding during DMPA include one pack of low-dose combined OCs or 1 mg of oral estradiol.[11] The incidence of irregular bleeding decreases from 30% to 50% in the first two years to 10% thereafter, and after 12 months of therapy, 55% of women report amenorrhea, with the incidence increasing to 68% after 2 years.[30,31]

Other adverse effects, including breast tenderness and depression, occur less

commonly. Weight gain is a concern for many women using DMPA, and the incidence and amount gained vary widely. It has been reported that weight gain averages 1 kg annually and may not resolve until 6 to 8 months after the last injections. In clinical trials 38% of patients reported a weight gain of > 10 lbs (4.5 kg) at 24 months.[3,4,30,31] However, use of DMPA in obese patients should not be excluded. Appropriate consideration of multiple factors should be evaluated for obese women and individualized decisions made for each patient. For all patients it is suggested that weight and BMI be monitored for patients receiving DMPA.[13,14]

Depot medroxyprogesterone acetate has been associated with short-term bone loss in younger women of reproductive age. This potential side effect may be due to lower ovarian estrogen production that occurs when gonadotropin secretion is suppressed.[3,34] Because longitudinal studies demonstrated effects on bone mineral density (BMD), the FDA issued a black box warning for DMPA in 2004.[30,31] It states that DMPA should be continued for more than 2 years, only if other contraceptive methods are inadequate. It also states that the loss of BMD seems to be greater with increasing duration of use and may not be completely reversible. However, the majority of clinicians view the effects of DMPA on BMD (which in the majority of cases is reversible) as a surrogate marker and there are no clear data that demonstrate the effects of DMPA on fracture risk.[34,35] The ACOG and CDC continue to recommend that for most patients the benefits of DMPA outweigh the risks even when used beyond 2 years of use.[10,32] It is not routinely recommended to use DMPA in women on long-term corticosteroids (eg, patients with rheumatoid arthritis) with a history or high risk of fractures.[14] While the ACOG does not recommend the routine screening of BMD in most patients,[34] a discussion regarding the risks and benefits of this contraceptive option is recommended prior to initiation and with prolonged use.

Long-acting Reversible Contraception (LARC) It refers to a category of hormonal and nonhormonal contraceptives that include IUDs and implants. This type of contraception is highly efficacious in preventing pregnancy, but the effects are quickly reversible upon removal.[36] As LARC does not require effort or adherence by the patient once they are inserted, perfect-use and typical-use efficacy rates do not differ, and the efficacy rate is similar to that of surgical options such as tubal ligation (see Table 18-1).[3,36] When compared to other methods of hormonal contraception, especially OCs, LARC methods are not used as frequently in the United States; however, increased education campaigns are demonstrating effectiveness. The use of LARC has increased to 14% of all

women between the ages of 15 to 44,[37] and all women should be considered potential candidates for this method.[31,33] In the past, many clinicians offered LARC only when adherence was an issue or in women with contraindications to estrogen. Project CHOICE was a prospective study in women age 14 to 45 that provided a choice of any reversible contraceptive method along with education at no cost. The majority of women chose a LARC method and had higher continuation rates at 2 years. There was also an observed decline in teen abortion rates during the study period.[38] Due to the high efficacy rates and emerging evidence of LARC methods, many advocates propose that increased use may decrease unintended pregnancy rates.[34]

3 4 5 ***Subdermal Progestin Implants*** Nexplanon (formerly called Implanon in the United States) is a single 4-cm-long implant, containing 68 mg of etonogestrel, which releases etonogestrel at a rate of 60 mcg daily for the first month, then decreases to an average of 30 mcg daily at the end of the 3 years of recommended use. The etonogestrel implant is placed under the skin of the upper arm using a preloaded inserter,[3,39] and clinicians must receive training from the manufacturer prior to insertion or removal of the device. The primary mechanism of action is suppression of ovulation. When ovulation is not suppressed, etonogestrel still is effective as the progestin thickens the cervical mucus and produces an atrophic endometrium. With both perfect and typical use, the efficacy rate is over 99%.[3,39] However, in overweight and obese women weighing more than 130% of their ideal body weight, the manufacturer states the possibility of decreased efficacy. However, it is noted that overweight women were excluded from studies, and recent small studies have not demonstrated any decreased effects.[39]

9 The etonogestrel implant can be inserted at any time as long as it is reasonably certain that the woman is not pregnant.[13,39] If the implant is inserted between days 1 and 5 of the menstrual cycle in women who have not previously used hormonal contraception then no backup method is needed.[13,39] If it is inserted at any other time of the menstrual cycle, then it is recommended to use an additional nonhormonal contraceptive backup method for 7 days. Additional recommendations on initiating the implant when switching from other methods of contraception are included in the package insert.[39] After removal, fertility returns within 30 days.

6 The major adverse effect associated with Nexplanon is irregular menstrual bleeding, which led to discontinuation of the implant in 11% of patients in clinical trials.[36,39] Women should be counseled about the risk of irregular

bleeding patterns so that patients will not request early removal of Nexplanon. Some women (22%) became amenorrheic with continued use, but many continued to have prolonged bleeding and spotting (18% and 34%, respectively) and frequent bleeding (7%).[13,39] Women who cannot tolerate prolonged bleeding may benefit from a short course of NSAIDs (for 5-7 days) during the bleeding. In addition, a short course of estrogen (if no contraindications are present) for approximately 10 to 20 days.[14] Insertion and removal complications are rare (less than 2%).[39] Nexplanon is radio opaque, making it easy to locate for removal by conducting an x-ray if needed.[13] Information from the manufacturer suggests using precaution when there is potential for drug interactions in the presence of potent CYP450 inducers (eg, rifampin, phenytoin, and carbamazepine).[39] This information conflicts with CDC recommendations which classify combining those medications with Nexplanon as a category 2, and suggest that the benefits may outweigh the theoretical risks. However, the CDC does still recommend use of additional nonhormonal contraception or switching to DMPA or an IUD as the preferred methods of managing these potential drug interactions.[14]

3 4 5 **Intrauterine Devices** Currently, five IUDs are available, all are T-shaped and are medicated, one with copper (ParaGard T 380A, many times referred to as ParaGard) and four with levonorgestrel (Mirena, Skyla, Liletta, and Kyleena), and clinicians must receive training from the manufacturer prior to insertion or removal of the IUDs. These IUDs have several possible mechanisms of action, including inhibition of sperm migration, damaging ovum or disrupting transport, and possibly damaging the fertilized ovum.[3] Due to the presence of local progestin, the Mirena, Skyla, Liletta, and Kyleena IUDs have additional mechanisms of endometrial suppression and thickening cervical mucus. The most recent evidence regarding the mechanisms of action demonstrates that the contraceptive activity of IUDs occurs before implantation.[3,36] Efficacy rates with IUDs are greater than 99% with both perfect and typical use,[3,36] and should not be inserted in the presence of current pregnancy, current pelvic inflammatory disease (PID), current STI/STD, puerperal or postabortion sepsis, purulent cervicitis, undiagnosed abnormal vaginal bleeding, malignancy of genital tract, uterine anomalies or fibroids distorting uterine cavity, allergy to an IUD component, or Wilson's disease (for copper IUD).[40,41] If an IUD is already in place and the patient contracts an STI/STD, the IUD in most cases can remain in place while the STI/STD is being treated.[3,14] The risk of PID among IUD users is low and there are no long-term

effects on fertility, and average time to return of fertility is similar to oral contracpetives.[36] The influence of drug interactions on the efficacy of IUDs is not a primary concern based on manufacturer and CDC recommendations.[40–44]

6 9 ParaGard is a highly effective IUD that can be left in place for 10 years.[3,40] A disadvantage of ParaGard is increased menstrual blood flow and dysmenorrhea; average monthly blood loss among users increased by 35% in clinical trials. Mirena, Skyla, Liletta, and Kyleena are the more recently approved IUDs in the United States and contain the progestin levonorgestrel.[40–44] Mirena and Liletta release 20 mcg of levonorgestrel daily decreasing over time and can be used for 5 years.[40,42] Kyleena releases 17.5 mcg of levonorgestrel daily decreasing over time and can also be used for 5 years.[44] Skyla releases 14 mcg of levonorgestrel daily decreasing over time and can be used for 3 years.[43] For all of the levonorgestrel IUDs, the systemic absorption of the progestin is minimal and considerably less than with OCs. There are no direct comparisons of safety or efficacy; when used appropriately all are highly effective and well tolerated.

9 Intrauterine devices can be inserted at any time as long as it is reasonably certain that the woman is not pregnant.[13] If the IUD is inserted between days 1 and 7 of the menstrual cycle in women who have not previously used hormonal contraception then no backup method is needed. If it is inserted at any other time of the menstrual cycle, then it is recommended to use an additional nonhormonal contraceptive backup method for 7 days. Additional recommendations on initiating an IUD when switching from other methods of contraception are included in the package inserts.

Concerns about pain and infection upon insertion of the IUD are common; however for most patients, insertion-pain is minimal and is not prolonged. If needed, common over-the-counter pain relievers such as NSAIDs or acetaminophen may be helpful. Pre-medicating women with misoprostol or paracervical lidocaine blocks have been studied,[13] but based on the evidence, misoprostol is not recommended for most women due to lack of efficacy. Paracervical lidocaine blocks may be recommended for pain reduction, but it is not a commonly accepted standard of care. Risk of infection upon IUD insertion is minimal, and it is not recommended to prophylactically treat women with antibiotics.[13] Women with current PID or STI/STD should delay having their IUD inserted. In contrast, women with an IUD in place that develop PID or an STI/STD should treat the infection, but it is not typically recommended to remove the IUD. It is recommended that women who have not been screened for

STI/STDs according to CDC guidelines be screened at the same time as insertion; if results come back positive then the STI/STD can be treated at that time.[13]

6 The major adverse effect associated with IUDs is irregular menstrual bleeding. The levonorgestrel IUD produces its effects locally via suppression of the endometrium, causing a reduction in menstrual blood loss over time. In contrast to the copper IUD, menstrual flow in users of the levonorgestrel IUD is decreased, and development of amenorrhea has been observed in 20% of users in the first year and 60% in the fifth year. Mirena specifically has an additional indication for treatment of heavy menstrual bleeding (menorrhagia).[40] A disadvantage of the levonorgestrel IUD is increased spotting in the first 6 months of use; women should be counseled that the spotting will decline gradually over time.[3,40] Women who cannot tolerate prolonged bleeding may benefit from a short course of NSAIDs (for 5-7 days) during the bleeding. In addition, a short course of estrogen (if no contraindications are present) could be used for approximately 10 to 20 days.[13]

Historically, IUD use in nulliparious and adolescent women was considered a precaution. However, recent evidence, clinical experience, and expert opinion do not preclude use in these populations. Risks versus benefits should be considered, and the woman must be counseled on the efficacy and potential adverse effects.[36,45] Strong consideration of an IUD is appropriate in this population due to high efficacy rates and low complication rates.[45] In addition, Skyla and Liletta included adolescent patients less than 18 years of age in clinical trials.[42,44]

10 **Emergency Contraception** Emergency contraception (EC) is used to prevent unintended pregnancy after unprotected or inadequately protected sexual intercourse (eg, no contraception, condom breakage, contraceptive mishap, or nonadherence, sexual assault). Pregnancy occurs when the fertilized egg is implanted into the endometrial lining. After intercourse, implantation of the fertilized egg typically takes approximately 5 days.[46] Progestin-only and progesterone receptor modulator products are approved by the FDA and recommended as first-line EC options.[3,4,46] Insertion of ParaGard (copper IUD) or prescribing higher doses of combined OCs (Yuzpe method) are other options.

Currently, the progestin-only formulation containing levonorgestrel 1.5 mg tablet × 1 dose (currently marketed in a variety of products, including Aftera, AfterPill, EContra One-Step, Fallback Solo, My Way, New Day, Next Choice One Dose, Opcicon One-Step, React and Plan B One Step, Take Action) is

approved specifically for EC in the United States.[12] Studies support that the primary mechanism of action of progestin-only EC is inhibiting or delaying ovulation.[46] The levonorgestrel-containing EC formulation is the regimen of choice due to availability, improved tolerability, and potentially increased efficacy rates. All formulations are now offered as one-dose options, to be given within 72 hours (3 days) of unprotected intercourse. However, the earlier the medication is given, the greater the efficacy and less chance of a pregnancy. Notably, there is some evidence that this regimen may be effective for up to 5 days after unprotected intercourse; but consideration of ulipristal or the copper IUD may be a better option if a woman can get access in time.[46] Levonorgestrel-containing EC products are available without a prescription to patients of all ages in the United States.[46]

10 Ulipristal acetate (ella) was approved for use as an EC by the FDA in 2010 and is a selective progesterone receptor modulator with mixed progesterone agonist and antagonist properties.[46,47] Its mechanism of action depends on the timing of administration relative to the woman's menstrual cycle.[48] However, the primary mechanism of action appears to be delay of ovulation. Ulipristal acetate is available by prescription only as a single dose of 30 mg taken within 120 hours (5 days) after unprotected intercourse with evidence supporting that it maintains efficacy for the full 120-hour window.[46,47] Data also exist to support noninferiority of ulipristal acetate compared to levonorgestrel-containing EC.[49]

Ulipristal acetate is not recommended for use in breastfeeding women. Ulipristal acetate affects progesterone receptors and may interfere with ongoing hormonal contraception. A reliable barrier method is recommended for intercourse that occurs in the same menstrual cycle with ulipristal acetate use, even if the patient is on a regular hormonal contraceptive. In addition, the woman should avoid using a hormonal contraceptive method or initiating a new hormonal contraceptive for at least 5 days after ulipristal acetate administration.[50] Taking hormonal contraception sooner may alter the effect of ulipristal acetate as well as may compromise the effect of the hormonal contraceptive.[50]

10 Determining the exact effectiveness rate of EC is difficult; however, the range has been reported to be between 59% and 94%.[46] Evidence reported that EC may prevent an average of 75% of expected pregnancies when taken appropriately. It is recommended that women have an advanced prescription on hand or access to an OTC formulation to maximize the effectiveness of EC.

Controversy exists regarding the potential for decreased efficacy of oral EC (both levonorgestrel and ulipristal) in overweight or obese women. No large-scale studies have been designed to fully resolve the controversy, and data from randomized trials have suggested an association with increased body weight and decreased efficacy of oral EC.[51,52] However, data demonstrate that there may be a decline in efficacy of levonorgestrel in women weighing greater than 75 kg. As oral EC is the most widely used EC method due to its accessibility, this issue is controversial. In 2016, the FDA announced that there was not enough evidence to change levonorgestrel labeling and encouraged further studies.[52] There is no effect of increased body weight on efficacy of a copper IUD.

6 Common adverse effects of EC include nausea, vomiting, and irregular bleeding.[46] Nausea and vomiting occur significantly less when progestin-only and progesterone receptor modulator EC is administered. Many women will experience irregular bleeding regardless of which EC method is used, with the menstrual period usually occurring 1 week before or after the expected time. Routine screening prior to or after receiving progestin-only and progesterone receptor modulator EC is not recommended. If a pregnancy already exists, the oral EC will not disrupt or harm the embryo. In addition, there are no contraindications to the use of these methods of EC (for the Yuzpe and copper IUD methods clinicians must adhere to their contraindications and precautions). No current data regarding the safety of repeated-use EC are available, but current consensus suggests that the risks are low, and women can receive multiple regimens if warranted, though use of a regular ongoing contraceptive should be encouraged. Appropriate counseling should be provided regarding timing of the dose, common adverse effects, and use of a regular contraceptive method (additional nonhormonal contraceptive methods should be used after EC for at least 7 days).

11 **Pregnancy Termination** For various reasons, medications may be needed for pregnancy termination. There are a variety of protocols and considerations that will not be covered in depth within this chapter. Medications used in early pregnancy (≤70 days) termination include mifepristone, misoprostol, and methotrexate, with misoprostol typically being used in combination with either mifepristone or methotrexate, or used alone.

Mifepristone is a steroid that binds progesterone receptors and causes abortion by blocking progesterone, softening the cervix, and increasing prostaglandin synthesis.[3,53] Progesterone is needed to maintain the corpus luteum during pregnancy. Softening of the cervix and increasing prostaglandins

also affects the pregnancy by stimulating contractions. Mifepristone is usually administered orally.[3,54] Prescribing of mifepristone is restricted to a prescriber that has met the training and qualifications of the manufacturer, and it is only dispensed out of the prescriber's facility. Although it is only used short-term for pregnancy termination, current practice still encourages monitoring for drug interactions as it is a major substrate and metabolized by the CYP450 3A4 system. Therefore, caution should be taken when administered with strong inhibitors or inducers of that system.[55]

Boxed warnings for mifepristone include infection and bleeding.[55] Bacterial infections and sepsis may occur without findings upon pelvic examination after the abortion or without signs of infections such as bacteremia and fever. Excessive bleeding may occur and could be a sign of incomplete abortion or other complications and needs prompt medical attention.[55] Prescribers need to inform patients of these risks prior to use and also educate patients on what to do if they feel they experience these events by discussing a patient agreement created by the manufacturer. When used as an abortifacient, mifepristone is contraindicated in patients with bleeding disorders or on anticoagulants.[55]

Misoprostol is a prostaglandin E1 analog, currently marketed as a protective agent in patients at risk for gastric ulcers that also causes softening of the cervix and stimulates uterine contractions. Off-label uses include abortion, labor induction, preventing and treating postpartum hemorrhage, cervical ripening for medical procedures, and treatment of early pregnancy loss.[53] Side effects of misoprostol may include stomach upset, diarrhea, headache, dizziness, and fever.[3,53,54] There are a variety of dosage forms available, including oral, vaginal, buccal, and sublingual. The vaginal, buccal, and sublingual dosage forms have more of an effect on the uterus than the oral form along with less gastrointestinal side effects.[53] Misoprostol may be used alone, but is more effective when used in combination with mifepristone.[3]

Methotrexate is an immunodulator that has a variety of uses. It works by inhibiting dihydrofolate reductase and ultimately inhibits DNA synthesis, repair, and cell replication.[54] This medication affects the rapidly dividing cells in the placenta causing abortion. In combination with misoprostol, methotrexate is effective as an abortifacient through the first 7 weeks of a pregnancy.[3] Side effects of the regimen include nausea, vomiting, diarrhea, chills, weakness, and fever.

Abortion regimens include mifepristone-misoprostol (most common), misoprostol-methotrexate, or misoprostol alone. The mifepristone-misoprostol

regimen approved for use by the FDA includes mifepristone 600 mg on day 1 and then misoprostol 400 mcg administered orally 48 hours after the mifepristone dose.[3,53,54] The efficacy of this regimen has been reported as 92% in pregnancies up to 49 days.[53] Efficacy is higher if the regimen is used earlier in the pregnancy. The mifepristone-misoprostol regimen works faster and is more effective in later gestational ages.[53] Either combination is more effective than misoprostol alone.[3,53]

In all cases, further assessment by the treating provider is required in the days that follow medication administration to ensure complete abortion and to assess for any complications. Abdominal cramps and bleeding are common after medical abortion.[3,53] A woman should be counseled that she will likely have heavy menstrual bleeding.[53] It is important for the woman to recognize if there is too much bleeding. Women experiencing bleeding that soaks two maxi pads per hour for 2 consecutive hours, should contact their health care provider promptly. Acetaminophen or NSAIDs such as ibuprofen may be used to help relieve pain and cramping.[3,53] Use of NSAIDs inhibit new prostaglandins but will not affect the use of misoprostol in pregnancy termination.

EVALUATION OF THERAPEUTIC OUTCOMES

9 Selecting a contraceptive method should involve the patient and clinician using a shared decision-making model. Contraceptive pharmacotherapy should be personalized for each patient, taking into account desired outcomes from a contraceptive and noncontraceptive perspective. Factors to consider include effectiveness, presence of coexisting medical conditions or medications, safety, adverse effects, cost, return to fertility time, and patient preference of the contraceptive method (eg, long-acting, short-acting, hormonal, oral, nonoral, barrier). Patients should receive both verbal and written instructions on the chosen method of contraception. In addition, access to timely contraception is important. The ACOG favors many strategies to improve comprehensive contraception, including full coverage by the Affordable Care Act in the United States, over-the-counter access for certain hormonal contraceptives, and advanced provision or counseling regarding EC.[56] In addition, a few states have (or are in the process of obtaining) expanded scope of practice to include provision of hormonal contraception by a pharmacist.[57] Follow-up appointments with a pharmacist or other provider can increase adherence and provide opportunities to address other health maintenance issues. The contraceptive

outcome of pregnancy prevention can be assessed when needed by obtaining a serum or urine pregnancy test.

Monitoring of the Pharmaceutical Care Plan

[3] [4] [5] [8] Contraceptive users should receive an annual well woman exam that may include a cytologic screening (as appropriate) and pelvic and breast examination. Consultation should provide routine health maintenance screening and to assess for clinical problems or adverse effects related to contraception (see Tables 18-4, 18-5, and 18-6). It is important to note that these annual screenings do not have to occur prior to prescribing hormonal contraception.

Annual blood pressure monitoring is recommended for all users of CHC. When a patient with a history of glucose intolerance or diabetes mellitus begins or discontinues the use of hormonal contraception, glucose levels must be monitored. Monitoring for the presence of adverse effects related to hormonal content or the presence of coexisting medical conditions is recommended for women using CHCs. Women using the etonorgestrel implant should be monitored annually for menstrual cycle disturbances, local inflammation, or infection at the implant site, acne, breast tenderness, headaches, and hair loss. Women using DMPA should be asked at 3-month follow-up visits about weight gain, menstrual cycle disturbances, and fractures. Women using IUDs should be asked at 1- to 3-month follow-up visits about IUD placement (checking for IUD strings to assure the IUD is still in the proper position), changes in menstrual bleeding patterns, and symptoms and protection against STI/STDs. Clinicians should check for proper IUD positioning and symptoms of upper genital tract infection.

Finally, clinicians should monitor and when indicated screen for HIV and STIs/STDs. All women should receive counseling about healthy sexual practices including the use of condoms to prevent the transmission of STIs/STDs when necessary.

CONCLUSION

A variety of contraceptive methods are available. Selection of a contraceptive method depends on many factors. Patient preference, method effectiveness, medical history, contraceptive side effects, desire for a return to fertility, and available access to products all play a role in choosing the best contraception method for a patient. Clinicians play a critical role in helping patients carefully

select an appropriate contraceptive method, monitoring side effects, and providing education on optimal use, effectiveness, and STI/STD prevention that can help reduce STI/STDs and unintended pregnancies.

Postclass Engaged Learning Activity

Download a copy of the Centers for Disease Control and Prevention (CDC) Medical Eligibility Criteria for Contraception Use, 2016 (MEC) from the CDC website. Utilize the CDC MEC document to determine recommendations for the following scenarios:

1. A patient with systemic lupus erythematosus with antiphospholipid antibodies who is requesting to use a combined hormonal contraceptive product
2. A patient who has had bariatric surgery and would like to use an intrauterine device
3. A patient with a history of severe decompensated cirrhosis who would like to use the progestin-only implant

Do some research on the Internet and find which states allow pharmacists to prescribe contraceptives and go to the individual state boards of pharmacy and download protocols to examine differences.

ABBREVIATIONS

ACOG	American College of Obstetrics and Gynecology
BMD	bone mineral density
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CHC	combined hormonal contraception
DMPA	depot medroxyprogesterone acetate
EC	emergency contraception
EE	ethinyl estradiol
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GnRH	gonadotropin-releasing hormone
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
IUD	intrauterine device
LARC	long-acting reversible contraception
LDL	low-density lipoprotein
LH	luteinizing hormone
MI	myocardial infarction
NSAID	nonsteroidal anti-inflammatory drug
OC	oral contraceptive
OTC	over the counter
Pap	papanicolaou (smear)
SHBG-TBG	sex hormone (testosterone) binding globulin
SLE	systemic lupus erythematosus
STI/STD	sexually transmitted infection/disease
TSS	toxic shock syndrome
VTE	venous thromboembolism
WHO	World Health Organization

REFERENCES

1. Finer LB, Zolna MR. Declines in unintended pregnancy in the United States, 2008-2011. *N Engl J Med*. 2016;374:843–852.
2. Guttmacher Institute. Unintended pregnancy in the United States: Fact sheet. September 2016. Available at: https://www.guttmacher.org/fact-sheet/unintended-pregnancy-united-states. Accessed October 23, 2018.
3. Hatcher RA, Trussell J, Nelson AL, et al. *Contraceptive Technology*. 21st

ed. New York: Ardent Median, Inc.; 2018.

4. Dickey RP.*Managing Contraceptive Pill Patients*. 15th ed. Fort Collins, CO: EMIS Inc.; 2014.
5. American College of Obstetricians and Gynecologists. Screening for cervical cancer. Practice Bulletin No.131. *Obstet Gynecol*. 2012;120:1239–1242.
6. American College of Obstetricians and Gynecologists. Noncontraceptive uses of hormonal contraceptives. Practice Bulletin No. 110. *Obstet Gynecol*. 2010;115:206–218.
7. Natural Cycles App. Available at: https://www.naturalcycles.com/en. Accessed August 18, 2018.
8. Grimes DA, Lopez LM, Raymond EG, et al. Spermicide used alone for contraception. *Cochrane Database Syst Rev*. 2013;(12):CD005218.
9. Wilkinson D, Ramjee G, Tholandi M, Rutherford GW. Nonoxynol-9 for preventing vaginal acquisition of HIV infection by women from men. *Cochrane Database Syst Rev*. 2002;(3):CD003936.
10. Van Vliet HAAM, Grimes DA, Helmerhorst FM, Schulz KF. Biphasic versus monophasic oral contraceptives for contraception. *Cochrane Database Syst Rev*. 2006;(3):CD002032.
11. Van Vliet HAAM, Grimes DA, Helmerhorst FM, Schulz KF. Triphasic versus monophasic oral contraceptives for contraception. *Cochrane Database Syst Rev*. 2011;3:CD003553.
12. Pharmacist's Letter Detail-Document: Comparison of oral contraceptives and non-oral alternatives. *Pharmacist's Letter/Prescriber's Letter*. Vol. 34. February 2018.
13. Curtis KM, Jatlaoui TC, Tepper NK, et al. U.S. Selected practice recommendations for contraceptive use, 2016. *MMWR Recomm Rep*. 2016;65(No. RR-4):1–66. doi:http://dx.doi.org/10.15585/mmwr.rr6504a1.
14. Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. Medical eligibility criteria for contraceptive use, 2016. *MMWR Recomm Rep*.2016;65(No. RR-3):1–104. doi:http://dx.doi.org/10.15585/mmwr.rr6503a1.
15. Yaz Package Insert, 2015. Whippany NJ: Bayer HealthCare Pharmaceuticals, Inc. Available at: http://labeling.bayerhealthcare.com/html/products/pi/fhc/YAZ_PI.pdf. Accessed January 17, 2019.
16. Artal R.ACOG women and obesity. Available at:

http://www.acog.org/About-ACOG/ACOG-Districts/District-II/Women-and-Obesity.

17. Xulane Package Insert, 2017. Morgantown, WV: Mylan Pharmaceuticals Inc.
18. NuvaRing Package Insert, 2018. Whitehouse Station, NJ: Merck & Co., Inc. Available at: http://www.merck.com/product/usa/pi_circulars/n/nuvaring/nuvaring_pi.pd Accessed January 15, 2019.
19. Pharmacist's Letter Detailed-Document: Hormonal Contraceptives and the Risk of Thrombosis. *Pharmacist's Letter/Prescriber's Letter*. Vol. 28. August 2012.
20. MacGregor EA. Contraception and headache. *Headache*. 2013;53:247–276.
21. Bhupathiraju SN, Grodstein F, Stampfer MJ, et al. Exogenous hormone use: oral contraceptives, postmenopausal hormone therapy, and health outcomes in the Nurses' health study. *Am J Public Health*. 2016;106(9):1631–1637.
22. Morch LS, Skovlund CW, Hannaford PC, et al. Contemporary hormonal contraception and the risk of breast cancer. *N Engl J Med*. 2017;377(23):2228–2239.
23. Figueiredo JC1, Haile RW, Bernstein L, et al. Oral contraceptives and postmenopausal hormones and risk of contralateral breast cancer among BRCA1 and BRCA2 mutation carriers and noncarriers: The WECARE Study. *Breast Cancer Res Treat*. 2010 Feb;120(1):175–183.
24. Kotsopoulos J1, Lubinski J, Moller P, et al. Hereditary Breast Cancer Clinical Study Group. Timing of oral contraceptive use and the risk of breast cancer in BRCA1 mutation carriers. *Breast Cancer Res Treat*. 2014 Feb;143(3):579–586.
25. Lidegaard OM, Nielsen LH, Skovlund CW, Lokkegaard E. Venous thromboembolism in users of non-oral hormonal contraception: Follow-up study, Denmark 2001–2010. *BMJ*. 2012;344:e2990.
26. Jick SS, Hernandez RK. Risk of non-fatal thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: Case-control study using United States claims data. *BMJ*. 2011;342:d2151.
27. Tepper NK, Whiteman MK, Marchbanks PA. Progestin-only contraception and thromboembolism: A systematic review. *Contraception*.

2016;94(6):678–700.
28. Dinger J, Minh TD, Buttmann N, Bardenheuer K. Effectiveness of oral contraceptive pills in a large U.S. cohort comparing progestogen and regimen. *Obstet Gynecol*. 2011;117:33–40.
29. Kapp N, Abitbol JL, Mathe H, et al. Effect of body weight and BMI on the efficacy of levonorgestrel emergency contraception. *Contraception*. 2015;91:97–107.
30. Depo-Provera Package Insert, 2010. New York: Pfizer. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020246s036lbl Accessed August 17, 2018.
31. Depo-SubQ Provera 104 Package Insert, 2016. New York: Pfizer. Available at: http://labeling.pfizer.com/ShowLabeling.aspx?id=549. Accessed August 18, 2018.
32. Beasley A, White K, Cremers S, Westhoff C. Randomized clinical trial of self versus clinical administration of subcutaneous depot medroxyprogesterone acetate. *Contraception*. 2014;89:352–356.
33. Kohn JE, Simons HR, Della Badia L, et al. Increased 1-year continuation of DMPA among women randomized to self-administration: Results from a randomized controlled trial at Planned Parenthood. *Contraception*. 2018;97:198–204.
34. American College of Obstetricians and Gynecologists. Committee Opinion No. 602 (reaffirmed 2017). Depot medroxyprogesterone acetate and bone effects. *Obstet Gynecol*. 2014;123:1398–1402.
35. Lopez LM, Chen M, Mullins Long S, et al. Steroidal contraceptives and bone fractures in women: Evidence from observational studies. *Cochrane Database Syst Rev*. 2015;(7):CD009849. doi.10.1002/14651858.CD009849.pub3.
36. American College of Obstetricians and Gynecologists. Long-acting reversible contraception: Implants and intrauterine devices. Practice Bulletin No. 186. *Obstet Gynecol*. 2017;130:e251–e269.
37. Kavanaugh M, Jerman J. Contraceptive method use in the United States: Trends and characteristics between 2008, 2012, and 2014. *Contraception*. 2018;97:14–21.
38. Birgisson BS, Zhao Q, Secura GM, et al. Preventing unintended pregnancy: The contraceptive choice project. *J Womens Health*. 2015;24:349–353.
39. Nexplanon Package Insert, 2017. Whitehouse Station, NJ: Merck & Co.,

Inc. Available at: http://www.merck.com/product/usa/pi_circulars/n/nexplanon/nexplanon_pi Accessed August 18, 2018.

40. ParaGard T380A Package Insert, 2018. Sellersville, PA: Teva Pharmaceuticals USA, Inc. Available at: http://paragard.com/Pdf/ParaGard-PI.pdf. Accessed August 17, 2018.
41. Mirena Package Insert, 2017. Whippany, NJ: Bayer Healthcare Pharmaceuticals, Inc. Available at: http://labeling.bayerhealthcare.com/html/products/pi/Mirena_PI.pdf. Accessed August 17, 2018.
42. Liletta Package Insert, 2018. Parsippany, NJ: Actavis Pharma, Inc. Available at: http://pi.actavis.com/data_stream.asp?product_group=1960&p=pi&language=E. Accessed February 2, 2019.
43. Skyla Package Insert, 2018. Whippany, NJ: Bayer Healthcare Pharmaceuticals, Inc. Available at: http://labeling.bayerhealthcare.com/html/products/pi/Skyla_PI.pdf. Accessed February 2, 2019.
44. Kyleena Package Insert, 2018. Whippany, NJ: Bayer Helathcare Pharmaceuticals, Inc. Available at: http://labeling.bayerhealthcare.com/html/products/pi/Kyleena_PI.pdf. Accessed February 2, 2019.
45. American College of Obstetricians and Gynecologists. Adolescents and long-acting reversible contraception: Implants and intrauterine devices. Committee Opinion No. 735. *Obstet Gynecol*. 2018;131:e130–e139.
46. American College of Obstetricians and Gynecologists. Emergency contraception. Practice Bulletin No. 152. *Obstet Gynecol*. 2015;126:e1–e11.
47. Brache V, Cochon L, Jesam C, et al. Immediate pre-ovulatory administration of 30 mg ulipristal acetate significantly delays follicular rupture. *Hum Reprod*. 2010;25:2256–2263.
48. Shrader SP, Hall LN, Ragucci KR, Rafie S. Updates in hormonal emergency contraception. *Pharmacotherapy*. 2011;31:887–895.
49. Glasier AF, Cameron ST, Fine PM, et al. Ulipristal acetate versus levonorgestrel for emergency contraception: A randomized non-inferiority trial and meta-analysis. *Lancet*. 2010;375:555–579.
50. ella Package Insert, 2018. Charleston, SC: Afaxys Pharma, LLC. Available at: https://www.ellanow.com/. Accessed November 27, 2018.

51. Glasier A, Cameron ST, Blithe D, et al. Can we identify women at risk of pregnancy despite using emergency contraception? Data from randomized trials of ulipristal acetate and levonorgestrel. *Contraception*. 2011;84:363–367.
52. Trussell J, Raymond EG, Cleland K. Emergency contraception: A last chance to prevent unintended pregnancy. Available at: https://ec.princeton.edu/questions/ec-review.pdf. Accessed November 27, 2018.
53. American College of Obstetricians and Gyencologists and Society of Family Planning. Medical management of first-trimester abortion. Practice Bulletin No. 143. March 2014. Available at: https://www.acog.org/-/media/Practice-Bulletins/Committee-on-Practice-Bulletins----Gynecology/Public/pb143.pdf. Accessed January 18, 2019.
54. Lexicomp. Misoprostol and Methotrexate: Lexi-Drugs. Riverwoods, IL: Wolters Kluwer Clinical Drug Information; 2019. Available at: http//:online.lexi.com. Accessed January 15, 2019.
55. Mifeprex package insert, 2004. New York: Danco Laboratories, LLC. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/020687s010-lbl.pdf. Accessed January 22, 2019.
56. American College of Obstetricians and Gynecologists. Access to contraception. Committee Opinion No. 615. *Obstet Gynecol.* 2015;125:250–255.
57. Stewart-Lynch A, Griffin B. Hormonal contraceptive prescribing by pharmacists: A brief overview. Available at: https://www.pharmacytimes.com/news/hormonal-contraceptive-prescribing-by-pharmacists-a-brief-overview. Accessed November 27, 2018.

SECTION 3 SPECIAL POPULATIONS

Pediatrics: General Topics in Pediatric Pharmacotherapy

Milap C. Nahata and Carol Taketomo

KEY CONCEPTS

1. Children are not just "little adults," and lack of data on important pharmacokinetic and pharmacodynamic differences has led to several disastrous situations in pediatric care.
2. Variations in absorption of medications from the gastrointestinal tract, intramuscular injection sites, and skin are important in pediatric patients, especially in premature and other newborn infants.
3. The rate and extent of organ function development and the distribution, metabolism, and elimination of drugs differ not only between pediatric versus adult patients but also among pediatric age groups.
4. The effectiveness and safety of drugs may vary among age groups and from one drug to another in pediatric versus adult patients.
5. Concomitant diseases may influence dosage requirements to achieve a targeted effect for a specific disease in children.
6. Use of weight-based dosing of medications for obese children may result in suboptimal drug therapy.
7. The myth that neonates and young infants do not experience pain has led to inadequate pain management in this pediatric population.
8. Special methods of drug administration are needed for infants and young children.
9. Many medicines needed for pediatric patients are not available in appropriate dosage forms; thus, the dosage forms of drugs marketed for adults may require modification for use in infants and children, necessitating assurance of potency and safety of drug use.

10 The pediatric medication-use process is complex and error prone because of the multiple steps required in calculating, verifying, preparing, and administering doses.

Preclass Engaged Learning Activity

Visit the US Food and Drug Administration website and navigate to the New Pediatric Labeling Information Database. The website provides comprehensive up-to-date information related to pediatric drug labeling changes. Explore available drugs, review recent labeling information for one drug of interest, and summarize the label changes. This website is useful to enhance student understanding of available resources for pediatric drug dosing information.

INTRODUCTION

Remarkable progress has been made in the clinical management of diseases in pediatric patients. This chapter highlights important principles of pediatric pharmacotherapy that must be considered when the diseases discussed in other chapters of this book occur in pediatric patients, defined as those younger than 18 years. Newborn infants born before 37 weeks of gestational age are termed *premature;* those between 1 day and 1 month of age are *neonates;* 1 month to 1 year are *infants;* 1 to 11 years are *children;* and 12 to 16 years are *adolescents*. This chapter covers notable examples of problems in pediatrics, pharmacokinetic differences in pediatric patients, drug efficacy and toxicity in this patient group, and various factors affecting pediatric pharmacotherapy. Specific examples of problems and special considerations in pediatric patients are cited to enhance understanding.

1 Infant mortality up to 1 year of age has declined from 200 per 1,000 births in the 19th century to 75 per 1,000 births in 1925 and to 5.9 per 1,000 births in 2016.[1] This success has resulted largely from improvements in identification, prevention, and treatment of diseases once common during delivery and the infancy period. Although most marketed drugs are used in pediatric patients, less than one-half of the drugs approved by the US Food and Drug Administration (FDA) are labeled for use in the pediatric population. Data on the pharmacokinetics, pharmacodynamics, efficacy, and safety of drugs in infants

and children are scarce. Lack of this type of information led to disasters such as gray baby syndrome from chloramphenicol, phocomelia from thalidomide, and kernicterus from sulfonamide therapy. Gray baby syndrome was first reported in two neonates who died after excessive doses of chloramphenicol (100-300 mg/kg/day); the serum concentrations of chloramphenicol immediately before death were 75 and 100 mcg/mL (mg/L; 232 and 309 µmol/L). Patients with gray baby syndrome usually have abdominal distension, vomiting, diarrhea, a characteristic gray color, respiratory distress, hypotension, and progressive shock.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

Pediatrics: Oral Nutrition and Rehydration of Infants and Children

Katherine H. Chessman

KEY CONCEPTS

1. Human milk is the preferred source of nutrition for almost all neonates and infants, including those born prematurely.
2. An infant formula is a nutritionally complete substitute if human milk is not available.
3. All infant formulas sold in the United States are required to meet FDA standards.
4. Cow milk–based formulas are used by most US non-breastfeeding infants.
5. Formulas for premature infants are designed to supply nutrients needed to promote growth and body composition changes that mimic those of a normal fetus at the same gestational age.
6. Some infants will require formulas with altered macronutrients, such as extensively hydrolyzed protein (*semi-elemental*) formulas, due to cow milk and soy protein sensitivities or other conditions.
7. Two nutrients of significant importance in infant nutrition are iron and vitamin D.
8. Enteral products are available for children who need supplemental nutrition beyond a regular toddler diet in most of the infant formula categories discussed and used for similar indications.
9. Expressed human milk and infant formulas must be handled and stored properly.
10. Oral rehydration therapy (ORT) is a mainstay of treatment for mild-to-moderate dehydration; severe dehydration requires intravenous rehydration.

Preclass Engaged Learning Activity

Visit the American Family Physician website and review the article titled "Infant Formula" at https://tinyurl.com/tpbj88a. The website is useful to enhance student understanding of the available infant formulas and their place in therapy.

INTRODUCTION

Infancy is a period of rapid growth followed by continued growth and development throughout childhood. Healthy term infants will double their birth weight in 4 months and triple it by 12 months. Adequate nutrient intake, absorption, and utilization is vital to ensure that growth and development progress normally. All practitioners providing healthcare for infants and children should be knowledgeable about pediatric nutrition to be able to quickly identify opportunities for intervention. Dietary Reference Intakes (DRIs)[1] established by the Food and Nutrition Board of the National Research Council for energy, protein, fat, trace element, vitamin, electrolyte, and mineral requirements and methods to estimate them are discussed in Chapter 158. This chapter will review the various formulas that are available for infants and children and their appropriate usage. Adolescents will typically use feeding formulations appropriate for adults when needed (see Chapter 160). The use of oral rehydration solutions will also be discussed.

INFANT NUTRITION

A term newborn's stomach has a capacity of 20 to 90 mL. Gastric capacity increases to 90 to 180 mL by 1 month of age. Too rapidly advancing oral or enteral nutrition intake can lead to emesis. Frequent feedings (every 2-3 hours) are needed early in life due to the stomach's limited capacity and the infant's high-metabolic demand (see **Table e20-1**). Human milk empties from the stomach at a faster rate than formula; thus, breastfed infants fed ad libitum (ad lib) may demand feeding more often. Nutritive sucking ability develops at approximately 34 weeks gestational age; before that time, tube feedings will be required. The ability to coordinate sucking, swallowing, and breathing when the respiratory rate is elevated also may necessitate tube feeding.

Human Milk

Human milk is the preferred source of nutrition for almost all neonates and infants, including those born prematurely. However, human milk does not fully meet the nutritional needs of all premature infants, and fortification may be required. The American Academy of Pediatrics (AAP)[2] and the World Health Organization (WHO)[3] recommend exclusive breastfeeding (or use of human milk if tube- or bottle-fed) for 6 months, and the use of iron-fortified formula when human milk is not available. After 6 months, complementary foods can be introduced; however, continued breastfeeding or provision of expressed human milk or iron-fortified formula is recommended until the infant is 12 months of age or as long as desired.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

Pediatrics: Neonatal Critical Care

Kirsten H. Ohler and Jennifer T. Pham

KEY CONCEPTS

1. Pharmacokinetic parameters are altered across the age spectrum of the neonatal population (ie, preterm to term) because of developmental maturation and the effect of various disease states on these processes. Therefore, medication selection and monitoring is of utmost importance in this population.
2. Treatment guidelines for neonatal resuscitation have been extrapolated from studies in older children and adults which may not be optimal because of differences in the pathophysiology of cardiopulmonary arrest among these populations.
3. Neonatal sepsis can be categorized as either early-onset sepsis (EOS) or late-onset sepsis (LOS). Pathogens associated with neonatal sepsis vary depending on the onset of sepsis (EOS vs LOS).
4. Empiric antibiotic therapy should be initiated in infants with suspected sepsis and should target the most common pathogens.
5. Patent ductus arteriosus occurs commonly in preterm neonates and, if hemodynamically significant, requires pharmacologic (with a cyclooxygenase inhibitor) or surgical closure.
6. In certain congenital heart defects (eg, tetralogy of Fallot, hypoplastic left heart syndrome, transposition of the great arteries), it is imperative that the ductus arteriosus remains patent. Prostaglandin E1 (alprostadil) is the drug of choice in these cases.
7. Neonatal hypotension can result in impaired cerebral perfusion and ischemic damage if left untreated. Because there is no clear consensus on the definition of neonatal hypotension, clinical judgment and review of the physiological parameters of the infant are important when making

diagnosis and treatment.

8. Pharmacologic therapy should be selected based on the etiology of hemodynamic instability and may include fluid bolus, vasopressors (such as dopamine, dobutamine, epinephrine, and norepinephrine), hydrocortisone, and vasopressin. Dopamine is the preferred initial vasopressor agent for hemodynamic support in neonates with hypotension.
9. Assessment of the degree of pain and sedation in the preverbal neonatal population is difficult. Assessment tools should be used, but it is important to recognize the population and pain type for which each tool has been validated.
10. Opioids and benzodiazepines are commonly used to provide analgesia and sedation for critically ill neonates; however, there are concerns about their effects on long-term neurodevelopment.

Preclass Engaged Learning Activity

Watch the video titled "Healthcare Heroes – NICU episode." https://tinyurl.com/t2d2noh. This 8-minute video provides a brief overview of the initial assessment and treatment of a critically ill neonate admitted to the neonatal intensive care unit. The video will enhance the student's understanding of the role of a multidisciplinary team in the complex care of an NICU patient. After watching the video, the student's reflection should include identification of the roles a pharmacist can play in the management of an unstable neonate. The ASSESS and PLAN steps of the patient care process will be developed through this exercise.

INTRODUCTION

Healthcare providers working in the neonatal intensive care unit (NICU) care for a wide range of patients—from those born prematurely to term newborns, newly born infants to infants who have spent months to years in the NICU, those with acute illnesses to those with chronic morbidities associated with prematurity. A large proportion of NICU patients are born prematurely. In the United States, almost 1 in 10 births is premature.[1] Preterm birth occurs when a neonate is born before 37 completed weeks of gestation.[2] Prematurity can be further categorized

as late preterm (ie, 34-37 weeks), moderate preterm (ie, 32-34 weeks), very preterm (ie, 28-32 weeks), and extremely preterm (ie, less than 28 weeks).[2] Neonates born prematurely can have multiple complications including respiratory distress syndrome, intraventricular hemorrhage (IVH), seizures, necrotizing enterocolitis (NEC), and sepsis, among others. Survivors of preterm birth often have morbidities such as bronchopulmonary dysplasia (BPD), neurodevelopmental delay, and cerebral palsy.[1,3] Despite medical advances, mortality in this population, especially those born extremely premature, remains high (30%-50%).[3]

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

Geriatrics: The Aging Process in Humans and Its Effects on Physiology

Krista L. Donohoe, Elvin T. Price, Tracey L. Gendron, and Patricia W. Slattum

KEY CONCEPTS

1. The population of people 65 years and older is increasing.
2. Age-related changes in physiology affect the functions of various organ systems and contribute to the onset of diseases.
3. Age-related changes in physiology can affect the pharmacokinetics and pharmacodynamics of numerous medications.
4. Successful aging is determined by individually defined measures of well-being that include maximizing health span and socio-environmental engagement.

Preclass Engaged Learning Activity

Brainstorm a list of age-related changes that occur in the human physiology and the effects they may have on pharmacokinetics/pharmacodynamics of medications in older adults.

INTRODUCTION

Medications can cure or palliate medical conditions in older adults, however, they can also cause a number of drug-related problems. Prevention of drug-related problems requires that health professionals be knowledgeable about the changes that occur with aging and the implications this has on prescribing,

monitoring, and evaluating medication regimens in older adults. This chapter will focus on the epidemiology of aging, mechanisms of aging, physiologic changes due to aging with an emphasis on the age-related changes in pharmacokinetics and pharmacodynamics of medications, and successful aging to maximize health span and quality of life.

EPIDEMIOLOGY OF AGING

1 The proportion of persons 65 years and older is increasing worldwide. In 2015, the percentage of people 65 years and older in the world was 8.5% and is projected to increase to 16.7% in 2050. In the United States, the population of older adults has changed from a pyramidal shape to a pillar. The rectangular shape will be top heavy in 2050 due to the baby boomer population. In 2015, 14.9% of the population was considered geriatric in the United States, and in 2050 it is projected to be 22.1%.[1] In 2035, the older adult population will outnumber children under 18 years old for the first time in US history.[2]

The population is aging due to people having fewer children and living longer. In the United States, the life expectancy in 2014 at birth for men is 76.4 years and 81.2 years for women. At age 65 and 85 years old, respectively, men are projected to live an additional 18 and 5.9 years, compared to 20.5 and 7 years for women.[3] The US life expectancy is down for the second year in a row from 78.7 in 2015 to 78.6 years in 2016. This may be attributed to an increase in drug overdose deaths and suicide rates in younger adults.[4]

Older adults often have multiple chronic conditions and thus need to see a number of specialists and healthcare providers. In 2013 to 2014, the highest reported chronic health conditions in the United States for adults 65 and older were hypertension (55.9%), arthritis (49%), heart disease (29.4%), cancer (23.4%), diabetes (20.8%), asthma (10.6%), chronic bronchitis or emphysema (8.1%), and stroke (7.9%). Women have a higher prevalence of arthritis and asthma, while men have higher rates of heart disease, cancer, and diabetes.[3] Data from the 2014 National Health Interview Survey (NHIS) revealed that 62% of adults above the age of 65 had at least two chronic conditions.[5] The six leading causes of death among persons 65 years and older were: heart disease, cancer, chronic lower respiratory diseases, stroke, Alzheimer’s disease, unintentional injuries, and influenza and pneumonia. Heart disease and cancer were the top two leading causes of death.[3]

Older adults have a high prevalence of chronic diseases along with

polypharmacy. The increased number of medications can lead to potential drug-related problems, such as drug-drug interactions.[6–8] To provide the best pharmacotherapy for this diverse and heterogeneous population of older adults it will be important to understand the mechanisms, pharmacokinetic, and pharmacodynamic changes that occur with aging, especially with respect to the common chronic conditions and medications that are used to treat them.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

Prescribing in the Older Adult

Emily R. Hajjar, Lauren R. Hersh, and Shelly L. Gray

KEY CONCEPTS

1. Improving and maintaining functional status is a cornerstone of care for older adults.
2. Adverse drug reactions in older adults are common and cause considerable morbidity.
3. Inappropriate prescribing is a major concern and is guided by the Beer's criteria.
4. Polypharmacy can be defined in various ways and is a common occurrence in older adults.
5. Underutilization of medications also occurs and can be improved by using the START criteria.
6. Pharmacists can play a major role in optimizing drug therapy and preventing adverse consequences of medications in older adults.
7. Deprescribing should be considered to reduce medications in older adults.
8. Practitioners may consider targeting high-risk older adults to implement comprehensive management strategies.

Preclass Engaged Learning Activity

Read the current American Geriatrics Society Beers Criteria®[16] and discuss the impact of the recommendations on medication use in older adults.

INTRODUCTION

1 Pharmacotherapy for older adults can cure or palliate disease as well as enhance health-related quality of life (HRQOL). HRQOL considerations for older adults include focusing on improvements in physical functioning (eg, activities of daily living), psychological functioning (eg, cognition, depression), social functioning (eg, social activities, support systems), and overall health (eg, general health perception).[1] Despite the benefits of pharmacotherapy, HRQOL can be compromised by drug-related problems. The clinical response to a medication in an older adult is the result of the interaction of a number of complex processes, including pharmacokinetics, pharmacodynamics, concurrent medications, comorbidities, and frailty. Age-related changes in physiology can affect drug pharmacokinetics and pharmacodynamics.[2] When applying general knowledge of pharmacokinetic and pharmacodynamic alterations in an older adult in the clinical setting, it is necessary to consider the patient's overall condition, age, diseases, frailty status, and concurrent medications. Prevention of drug-related problems in older adults requires that health professionals become knowledgeable about a number of age-specific issues. To address these knowledge needs, this chapter discusses the epidemiology of adverse consequences of medications in older adults and an approach to optimizing medication use through the provision of a comprehensive geriatric assessment.

ADVERSE CONSEQUENCES OF MEDICATION USE

Although medications used by older adults can lead to improvement in HRQOL, adverse outcomes caused by drug-related problems are considerable.[3] Adverse drug reactions (ADRs) and negative consequences of drug therapy are major threats to the HRQOL of outpatient older adults and account for a significant portion of healthcare expenditures.[4] Estimates are that more than $520 billion was spent in 2016 for prescription-associated morbidity and mortality from nonoptimized medications.[4]

ADVERSE DRUG REACTIONS

2 ADRs are a major public health problem for older adults in all settings.[5] ADRs are defined as "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function" and excludes

therapeutic failure and adverse drug withdrawal events.[6] Approximately 9% of hospitalizations in older adults are caused by ADRs.[7] Moreover, ADRs occur frequently in community-dwelling older adults (10%-35% yearly). Transitions of care are often high-risk times for ADRs.[8] For example, one study found that 19% of older adults experienced an adverse drug event within 45 days of hospital discharge. Some medication classes, such as anticoagulants, antidiabetic agents, and opioids, are especially problematic for causing serious ADRs in older adults.[9] Interestingly, use of potentially inappropriate medications (eg, Beers criteria drugs) only cause a small proportion of ADRs.[7–9] Number of medications is a consistent risk factor for ADRs.[7,10]

Inappropriate Prescribing

3 Inappropriate prescribing is defined broadly as prescribing medications outside the bounds of accepted medical standards. However, inappropriate prescribing is challenging to define and operationalize. Furthermore, "appropriateness" of prescribing is viewed differently in people with multiple chronic conditions or in those who are frail.[11] Inappropriate prescribing is associated with adverse drug events, falls, hospitalizations, and increased healthcare costs.[12–14]

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

Assessing Health and Delivering Healthcare to Older Adults

Leigh Ann Mike, Zachary A. Marcum, and Shelly L. Gray

KEY CONCEPTS

1. The population of older adults in the United States is increasing and is expected to become more racially and ethnically diverse.
2. The primary goal of care for older adults is to maximize the amount of time they can live independently.
3. Living arrangements of older adults are tied to health and functional status, presence of disabilities, and caregiver ability, rather than chronological age.
4. Geriatric assessment is a multidisciplinary, multifaceted approach to promote wellness and prolong independence.
5. Geriatric syndromes are multifactorial clinical conditions that are linked with poor health outcomes.
6. Pharmacists can play an important role in identifying medications that may be contributing to geriatric syndromes.
7. Transitions of care are common and risky for older adults.
8. Optimal care transitions require teamwork, and the pharmacist's primary role on the care transitions team is to identify and address current and potential medication-related problems.

INTRODUCTION

The population of older adults age 65 years or older is growing both globally and in the United States. This is due to increased life expectancy associated with advances in science and technology in early detection of diseases, therapeutic

interventions that increase survival, and overall improved healthcare delivery to the general public such as vaccinations, access to care, and multiple treatment options.[1]

As people are living longer, they are likely to experience multiple chronic medical conditions. The fraction of older adults using healthcare resources will increase, primarily due to the aging of the “Baby Boomer” generation. Despite the development of chronic medical conditions, many older adults lead full, active lives with functional abilities largely preserved. This is contrary to the myth that older age is linked with sickness and disability or poor functional status. Many of these older adults either have few chronic conditions or have them well-controlled. The healthcare needs for an active 65-year-old person are very different from an octogenarian living in a skilled-nursing facility. Additionally, with the advances in cancer treatment, and the emergence of new therapies that have transformed diseases such as hepatitis C and acquired immunodeficiency syndrome into chronic conditions, it is likely that the healthcare resources used by older adults will include treatment of advanced diseases, life-prolonging measures, and general health maintenance.

The goal of providing optimal healthcare to older adults is to promote and maintain independence, which has a direct effect on quality of life. To achieve and maintain independence, healthcare providers can target interventions and approaches to promote and maintain functional status. The functional status of older adults is impacted by disease, accidents, age-related changes (eg, decreased muscle mass or bone density), and frailty; it is independent of chronological age. Because of this, there has been a shift in focus in older adults from managing health conditions alone to incorporating functional status into the assessment of health and wellness. This requires a holistic, multidisciplinary approach.

In addition to the anticipated growth in numbers, the older American population is also expected to become more racially and ethnically diverse. An increasingly large body of literature describes differences across various ethnic groups and patient populations with regard to body composition, risk for developing certain diseases, assessment approaches, threshold for interventions, and treatment goals. From the pharmacotherapeutics standpoint, it is also important to understand the predictors of efficacy and adverse drug reactions in different patient populations. Some of these factors may include diet, lifestyle, and genetics. Equally important is the understanding of the patient’s values and believes in their acceptance of interventions. Collectively, these factors help clinicians develop and implement a personalized health management plan that is

more likely to reach the mutually defined goals established by both the older adults and their healthcare providers.

This chapter will discuss the epidemiology of aging as well as various threads of wellness and illness, independence, functional status, and disability that are relevant for clinical practice. In addition, housing options for older adults, geriatric syndromes, and some of the most common models of care delivery will be introduced. This chapter concludes with a summary of transitions of care for older adults.

EPIDEMIOLOGY OF AGING

In 2050, 21.3% of the global population will be at least 60 years old.[2] The US population will experience similar trends. By 2030, as the "Baby Boomers" age, approximately 20% of the US population will be 65 years old. Those aged ≥85 years will reach 4.3% of the total population by 2050.[3] Nearly half of older adults in the 50- to 54-year-old age range self-report their health as "excellent" or "very good." This decreases with age to 28% of those aged 85 and older.[4] Many older adults report that they receive assistance with Instrumental Activities of Daily Living (IADLs) or Activities of Daily Living (ADLs); more than half of those who have reached 85 years of age report receiving no assistance or supervision with functionally-related activities.[4]

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

Critical Care: General Topics in Critical Care

Adrian Wong and Sandra L. Kane-Gill

KEY CONCEPTS

1. Pharmacists are one member of the interdisciplinary patient care team; other members include physicians, nurses, advanced providers, physical therapists, and respiratory therapists.
2. There are numerous types of ICUs that pharmacists can work in such as burn, cardiovascular, medical, neurology, surgical, trauma, and tele-ICU. Patients in each of these units will have specific care needs.
3. Fundamental activities of a critical care pharmacist include evaluation of medications for appropriate indication, dose, and general appropriateness; monitoring of medications and identification of ADEs.
4. The management of ICU patients may lead to long-term cognitive effects in survivors.
5. Medication errors and ADEs are more common in the ICU than general care units. Medication errors can lead to ADEs, which are often preventable.
6. Management of renally-excreted and nephrotoxic drugs is important to avert unwanted adverse effects and possibly prevent disease progression.
7. Critical care pharmacists' participation in patient care rounds decreases the rate of ADEs.
8. One-third of total hospital drug costs are attributed to drug use in the ICU, so pharmacoeconomic analyses are important to make informed decisions about drug selection.

Preclass Engaged Learning Activity

Watch the video “ICU episode 1, season 1” at https://tinyurl.com/stcvm9b. This short video provides insight into the complexity of care provided in a contemporary intensive care setting, as well as the differences in the care required of critically ill patients compared to patients in general care units. The video is useful to enhance student understanding regarding the COLLECT and ASSESS steps in the patient care process.

INTRODUCTION

A clinician’s initial exposure to critically ill patients within the intensive care unit (ICU) is challenging. Critically ill patients commonly have multiple lines in place and are attached to life-support machines (eg, mechanical ventilation, continuous renal replacement therapy), which may appear foreign and/or difficult to manage. This chapter provides a brief overview of the complexity of care and the role of a pharmacist in the care provided in a contemporary intensive care setting.

HISTORY OF CRITICAL CARE PHARMACY

Clinical pharmacy services began in the 1970s and are currently considered an essential resource for ICU patient care.[1,2] This is unique as few disciplines have documented the positive value of pharmacists as clearly as critical care medicine. Despite this, a survey in 2006 found that only 62.2% of respondents (n=382) in the United States had a dedicated ICU pharmacist.[3] Similarly, only 74.4% of respondents (n=168) to an international survey indicated a dedicated pharmacist attended daily rounds.[4]

Over the past three decades, critical care pharmacy has evolved considerably. Select examples of notable advances include the following:

- Creation of the Clinical Pharmacy and Pharmacology section within the Society of Critical Care Medicine (SCCM; 1989)
- Creation of the Critical Care Practice and Research Network within the American College of Clinical Pharmacy (1992)
- Critical care pharmacists recognized as integral member of the

interdisciplinary team (2001)

- Appointment of the first pharmacist to serve as the president of SCCM (2010)
- Appointment of the first pharmacist to serve as the president of the Neurocritical Care Society (2017)
- Numerous pharmacists being awarded the designation of the Fellow or Master of the American College of Critical Care Medicine
- Pharmacist serving on critical care medicine guideline committees, including as first and senior authors

Additional advances have been made in the areas of training and certification. Critical care pharmacy residencies have increased dramatically. In 2005, there were 39 American Society of Health-System Pharmacists-accredited residencies, which increased to 145 as of this edition.[5] Moreover, board certification in critical care pharmacy became available in 2015 through the Board of Pharmacy Specialties. Since that time, over 2,100 pharmacists have been board certified.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

Critical Care: Pain, Agitation, and Delirium

Gilles L. Fraser and Richard R. Riker

KEY CONCEPTS

1. The primary goal of pain, agitation, and delirium (PAD) management is to provide patient comfort and safety with secondary goals to prevent immediate and long-term adverse physical and psychological outcomes.
2. PAD are interrelated and can confound efforts to provide intensive care including mobility, sleep, participation in care and in shared patient/caregiver decisions about appropriate levels of care.
3. It is important to systematically evaluate PAD with validated tools for timely identification and correction of inciting clinical issues.
4. Preventative measures and nonpharmacologic strategies for PAD management should be initiated as early as possible.
5. A multifaceted, multidisciplinary approach to PAD management impacts care and clinical outcomes.
6. Pain is an important cause of agitation in the intensive care unit (ICU) and should be assessed and treated before administration of sedatives.
7. No proven pharmacologic strategies limit the severity and duration of ICU delirium.
8. Sedative choice (dexmedetomidine or propofol) and depth of sedation may have an important impact on patient assessments and outcomes.

Preclass Engaged Learning Activity

Watch the video entitled “CAM-ICU Delirium Test”

https://tinyurl.com/ubl8br2. This brief 3-minute video is useful to enhance student understanding of a common and valid method of screening for delirium in critically ill adults who are unable to verbalize.

INTRODUCTION

The ICU is an inhumane environment where pain, agitation, and delirium are considered the most common clinical conditions confronting patients and their caregivers on a daily basis. These issues are stressful for patients as well as families and are often precipitated by factors that are frequently seen in the critically ill; hemodynamic instability, inadequate oxygenation, metabolic derangements, pain, the inability to communicate, immobility, sleep deprivation, the need for invasive instrumentation, and loss of autonomy all occurring in an unfamiliar and threatening environment.

1 Short-term patient goals for PAD management include the provision of comfort and safety. It is also important to consider newly recognized long-term outcomes in critical care survivors that affect their quality of life such as the inability to return to baseline physiologic and cognitive function and a high frequency (50%) of unemployment for a year or longer after discharge from the hospital.[1,2] In addition, postdischarge posttraumatic stress disorder (PTSD) and depression are experienced by 7% and 30% of ICU survivors respectively at one year.[3]

All of these outcomes are impacted by our choice of therapeutics for PAD management. For example, the provision of inadequate pain relief can be regarded as inhumane, but conversely, overaggressive opioid therapy continued in the outpatient setting represents an obvious and avoidable risk factor in this era of opioid abuse.[4] The complexity of the pharmacologic and nonpharmacologic management of pain, agitation, and delirium requires knowledge of the risks and benefits of each option and necessitates a standardized, but flexible evidence-based approach[5] (**Table e26-1**).

Although we will be discussing pain, agitation, and delirium in this chapter as discrete clinical issues, the reader should appreciate that they are inter-related.[6] The interwoven nature of PAD is well demonstrated by a patient with unrelieved pain (a risk factor for delirium) who develops agitation. This agitation can result in patient harm or injury, but attempts to control these dangerous behaviors with sedatives can in turn precipitate delirium all the while without controlling the inciting problem of pain.

DEFINITIONS AND CONSEQUENCES OF PAD

Pain

Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.”[5] Healthcare providers readily accept and anticipate that ICU patients will have pain associated with surgery, trauma, pancreatitis, or with invasive procedures, but less frequently recognize that pain is provoked by routine ICU care such as repositioning, endotracheal suctioning, and arterial gas determinations.[7,8]

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

Critical Care: Considerations in Drug Selection, Dosing, Monitoring, and Safety

Erin F. Barreto and Amy L. Dzierba

KEY CONCEPTS

1. Intensive care units are designed to support the complex needs of critically ill patients with acute organ dysfunction in need of a higher level of monitoring and treatment.
2. The four phases of critical illness include rescue, optimization, stabilization, and de-escalation, each of which can affect drug selection, dosing, and monitoring.
3. Ideal medications for use in the ICU have predictable bioavailability, fast onset, rapid titratability, and a wide therapeutic window.
4. Critically ill patients exhibit a uniquely complex pharmacokinetic profile and response to therapies that needs to be considered when individualizing drug regimens.
5. Acute changes to end-organ function occur more commonly in the ICU and affect drugs in a dynamic way.
6. Perfusion deficits and iatrogenic exposures can decrease enteral, subcutaneous, and intramuscular drug bioavailability which makes the intravenous route preferred in acutely ill unstable patients in the ICU.
7. The use of advanced organ support devices is common in the ICU and each device differentially affects the pharmacokinetics and pharmacodynamics of medications.
8. Key properties of drugs susceptible to sequestration in the ECMO circuit include high percentage of protein binding and high degree of lipophilicity.

9. Highly protein bound drugs are readily cleared by MARS and TPE, but not efficiently cleared by renal replacement therapies.
10. Many patient, provider, and environmental factors increase an ICU patient's vulnerability to medical errors, adverse drug events, and their related consequences, relative to their noncritically ill counterparts.

Preclass Engaged Learning Activity

Watch the first 12-minutes of the video "Right dose, right now: customizing drug dosing for the critically ill patient". This video briefly overviews some of the key pharmacokinetic and pharmacodynamic changes present in critically ill patients and the potential impact on anti-infective effectiveness and safety in the ICU.

INTRODUCTION

Epidemiology of Critical Illness

Since the poliomyelitis epidemic of the 1950s when mechanical ventilation was first introduced, significant advancements have been made in our understanding of the pathophysiology of syndromes of critical illness and the interventions needed to improve patient outcomes.[1] Only recently, however, have we begun to quantify the true global burden of critical illness. In the United States, 27% of all hospitalizations or 4.6 million stays annually include an intensive care unit (ICU) admission.[2] Short-term mortality for ICU patients is 8% to 22%, but can be much higher in patients with sepsis, acute respiratory distress syndrome, shock, or those in the developing world, where mortality still reaches 50% to 60% in some studies.[3] Although surviving critical illness is a short-term goal, survivors can experience long-term physical, psychological, and cognitive consequences, collectively termed "post-intensive care syndrome." When considering these sequelae, care of critically ill patients is estimated to cost $121 to $263 billion annually in the United States, on par with the financial burden of cancer care or cardiovascular disease.[4] It is essential that clinicians and scientists seek new ways to more effectively prevent and treat critical illness to improve patient outcomes and limit the global health burden.

The Dynamic Trajectory of Critical Illness

Critical care medicine is a diverse discipline that integrates aspects of medicine, surgery, and anesthesia. Broadly, contemporary ICU patients include those with acute organ dysfunction in need of resuscitation or organ support and those in need of monitoring after a major event or intervention who are at high risk for complications (eg, surgical procedure, trauma, bleed).[5]

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

Palliative Care

Nina M. Bemben and Mary Lynn McPherson

KEY CONCEPTS

1. Palliative care may be provided to any patient with a serious illness, at any point in the course of the illness, including while a patient receives curative or disease-focused therapy.
2. Hospice is a form of palliative care, which has been defined by Medicare to encompass care solely focused on comfort and quality of life during the last 6 months of a patient's life.
3. Pain is a common symptom among patients receiving palliative care and may be managed safely and effectively using nonopioid, adjuvant, and/or opioid therapies.
4. Opioids are the drug of choice for the management of dyspnea.
5. Constipation, nausea, vomiting, anxiety, and delirium are common symptoms among patients receiving palliative care and may be managed effectively with drug and nondrug therapies.
6. End-of-life care can be provided to patients in the last days of their lives through palliative or hospice care, and provides management of common terminal symptoms.
7. Identifying a patient's goals and structuring care to achieve those goals is a key component of palliative care. Identifying a patient's goals of care involves communication with patients, their families and/or caregivers, as well as other healthcare professionals.
8. Addressing nonphysical needs, such as spirituality and faith, are key components of providing quality palliative care.

Preclass Engaged Learning Activity

Navigate to the website http://www.graduate.umaryland.edu/palliative, then click on “Palliative Care Chat Podcast” on the left hand side. Scroll down to Episode 15: “Ten Tips Palliative Care Pharmacists Want the Palliative Care Team to Know When Caring for Patients.” Select any two tips discussed in the podcast and critically think through why the tip is an important one for the rest of the hospice or palliative care team. This podcast is useful to enhance your understanding regarding the PLAN and MONITORING and FOLLOW-UP steps in the patient care process.

INTRODUCTION

1 Palliative care, or palliative medicine, is specialized care provided to patients with serious illness with a goal of managing symptoms and helping patients to cope with their illnesses.[1] It is provided by an interdisciplinary team of healthcare professionals, including physicians, pharmacists, nurses, nurse practitioners, social workers, chaplains, and others.[2] Palliative care is appropriate for any patient with a serious or potentially life-limiting illness, at any point during the time course of that illness. Common diseases for which palliative care is appropriate include cancer, heart failure, advanced lung disease such as chronic obstructive pulmonary disease (COPD), organ failure such as liver or renal failure, and neurologic diseases such as dementia and Parkinson disease.[2] Patients may receive palliative care throughout the course of a serious illness, including while the patient receives treatment aimed at managing or curing the disease. If or when the serious illness progresses and disease-focused therapies are no longer helpful or desired, palliative care continues to be provided to manage symptoms and maximize quality of life.

Provision of palliative and hospice care to patients with limited prognoses has been shown to improve patient and caregiver satisfaction,[3–5] reduce healthcare utilization,[3,4] and decrease healthcare costs.[3,4,6] In addition to providing symptom management, improving patient and caregiver satisfaction, and reducing healthcare costs, early integration of palliative care has been shown to increase survival among patients with advanced cancer.[7,8]

Because of the evidence supporting the benefits of palliative care, clinical practice guidelines for serious illnesses incorporate palliative care into treatment recommendations. The American Society of Clinical Oncology and National

Comprehensive Cancer Network both recommend palliative care as a component of oncology management.[9,10] In addition, the American College of Cardiology Foundation/American Heart Association practice guideline for the management of heart failure supports the incorporation of palliative care into the management of patients with advanced heart failure due to its effectiveness in increasing quality of life.[11]

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

SECTION 4 CARDIOVASCULAR DISORDERS

Assessment of the Cardiovascular System

Brent N. Reed, Kristin E. Watson, and Gautam Ramani

KEY CONCEPTS

1. Many cardiovascular disorders develop over years to decades. Evaluation of the patient with or at risk for cardiovascular disease (CVD) must therefore include a comprehensive patient (or caregiver) interview to identify modifiable and nonmodifiable risk factors for CVD. Along with other key information (eg, vital signs, laboratory values), these data can be used to determine an individual patient's risk for future cardiovascular events.
2. Changes in the frequency, duration, and severity of cardiac-related symptoms (eg, ischemic chest pain, dyspnea) are essential to the assessment of CVD and often guide the urgency of intervention as well as the specific pharmacologic strategies selected. A comprehensive patient interview can also be useful for discerning CVD from noncardiac disorders that share similar symptomology.
3. Obtaining an accurate blood pressure measurement is paramount to the evaluation and treatment of several cardiovascular disorders. Guidelines for appropriate measurement technique include recommendations on patient preparation and position, cuff and stethoscope use, and blood pressure documentation.
4. Several cardiovascular disorders, such as heart failure (HF) and peripheral arterial disease, warrant physical examination of areas that are more distal from the heart, including the neck (eg, carotid arteries, jugular venous pressure, abdominojugular reflux) and lower extremities (eg, peripheral pulses, edema). Abnormal findings can prompt further evaluation or alterations in pharmacologic therapy.
5. Auscultation of the chest provides key information on valvular structure

and function. Abnormal heart sounds can be used to guide the need for further evaluation.

6. Two key cardiac-specific laboratory tests are cardiac troponin and brain natriuretic peptide (BNP). Elevations in cardiac troponin may indicate the presence of a myocardial infarction and can be used to guide both pharmacologic and nonpharmacologic interventions. A normal BNP concentration in a patient with dyspnea excludes the presence of HF whereas elevations are correlated with disease severity as well as long-term morbidity and mortality.

7. An electrocardiogram (ECG) records the pattern of electrical activity across the heart and each segment corresponds to an event in the cardiac cycle. The ECG provides an electrical map of the heart, which can be used to locate areas of ischemia or other pathology. Alterations in the ECG such as QT-interval prolongation can be drug-related and may place patients at risk for arrhythmias.

8. Stress testing remains the most common initial strategy for evaluating chest pain suspicious for myocardial ischemia. The two main modalities for testing are inducing stress via exercise or the administration of a pharmacologic agent such as dobutamine or adenosine. The information provided by a stress test is often combined with echocardiography and radionuclide myocardial perfusion imaging.

9. Echocardiography uses sound waves to create an image of the heart, providing important information on the structure and function of heart valves and chambers. Although a transthoracic echocardiogram (TTE) is less invasive and provides the key information necessary for most clinical decisions, a transesophageal echocardiogram (TEE) may be required to visualize structures located in posterior areas of the heart (eg, mitral valve, left atrial appendage).

10. Left heart catheterization (LHC) is an invasive procedure in which a catheter is inserted into a large artery and advanced to the left side of heart. The most common indication for LHC is coronary angiography, in which radiocontrast dye is used to visualize the coronary anatomy, often for the purposes of percutaneous coronary intervention.

11. Right heart catheterization (RHC) involves advancing a catheter through a large vein and into the right side of the heart, where information on pulmonary and intracardiac hemodynamics can be obtained. Key parameters obtained during RHC include pulmonary artery pressures

(including pulmonary capillary wedge pressure), cardiac output, and systemic vascular resistance, and these can be used to guide pharmacologic therapies in patients with HF or pulmonary hypertension.

12. Cardiac computed tomography (CCT) and cardiovascular magnetic resonance (CMR) imaging are noninvasive tests used to construct three-dimensional images of the heart. CCT can be used as an alternative to cardiac catheterization for performing coronary angiography, and CMR is commonly used to elucidate the etiology of HF.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

30

Hypertension

Eric J. MacLaughlin and Joseph J. Saseen

KEY CONCEPTS

1. The risk of cardiovascular (CV) morbidity and mortality is directly correlated with blood pressure (BP).
2. Evidence from clinical trials definitively demonstrates that antihypertensive drug therapy substantially reduces the risks of CV events and death in patients with high BP.
3. Essential hypertension is usually an asymptomatic disease. A diagnosis cannot be made based on one elevated BP measurement. An elevated BP value from the average of two or more BP measurements, present during two or more clinical encounters, is required to establish a diagnosis of hypertension.
4. The overall goal of treating hypertension is to reduce associated morbidity and mortality from CV events. Antihypertensive drug therapy should be selected based on evidence demonstrating CV event reduction.
5. A goal BP of <130/80 mm Hg is appropriate for most patients with hypertension.
6. The magnitude of BP elevation should be used to guide the number of antihypertensive agents to start when implementing drug therapy. Most patients with stage 1 hypertension should start on one medication as initial therapy. Most patients presenting with stage 2 hypertension should be started on two medications as initial therapy.
7. Lifestyle modifications should be prescribed to all patients, especially those with elevated BP and hypertension.
8. Angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), and thiazides are preferred firstline antihypertensive agents for most patients with

hypertension. These first-line options are for patients with hypertension who do not have a compelling indication for a specific antihypertensive drug class.

9. For most patients with hypertension, a β-blocker is not an appropriate first-line treatment because it will not reduce CV events as much as has been demonstrated with an ACEi, an ARB, a CCB, or thiazide.
10. Compelling indications are comorbid conditions where specific antihypertensive drug classes have been shown in clinical trials to reduce CV events in patients with the specific comorbidity.
11. Older patients are often at higher risk for orthostatic hypotension related to antihypertensive medications. While antihypertensive drug therapy selection should be the same as in younger patients, lower initial doses should be used to minimize the risk of orthostatic hypotension in older patients.
12. Patients have resistant hypertension when they fail to achieve goal BP while adherent to a regimen that includes three antihypertensive agents (one of which includes a diuretic) at full doses, or when four or more antihypertensive agents are needed to treat hypertension regardless of goal BP achievement.
13. Alternative antihypertensive agents should only be used in combination with first-line antihypertensive agents to provide additional BP lowering because they do not have sufficient evidence demonstrating CV event reduction.
14. Hypertensive *urgency* is ideally managed by adjusting current antihypertensive drug therapy or by adding a new antihypertensive medication. This provides a gradual reduction in BP, which is a safer treatment approach than rapid reductions in BP. On the other hand, hypertensive emergency requires acute care in an emergency department or hospital where intravenous antihypertensive drug therapy can be administered.

Preclass Engaged Learning Activity

CLINICAL INTERACTION: PATIENT WITH HYPERTENSION

Prepare for this activity by completing the following tasks:

- View the instructional video “Manual Method for Measuring Blood Pressure” at: https://tinyurl.com/y5d938zd
- Identify a patient with hypertension that has been prescribed two or more antihypertensive agents.

Complete the activity by doing the following:

- Manually measure a patient’s BP using the technique demonstrated in the video.
- Engage in a brief discussion with your patient and address the following topics related to hypertension:
  - How long has the patient had hypertension?
  - What strategies does the patient use to take their antihypertensive medications regularly?
  - What does the patient believe are the benefits of the current antihypertensive drug regimen?
  - What does the patient identify as some of the risks of their current antihypertensive drug regimen?
  - How well does the patient think the drug therapy regimen is working?
  - What is the patient’s goal BP?
  - Has the patient taken any other antihypertensive medications in the past and how did he/she respond to them?
  - What lifestyle modifications does the patient engage in to help control BP?
- At the end of this interview, write some brief notes about this patient encounter for the postclass activity.

INTRODUCTION

Hypertension is a common disease that is simply defined as persistently elevated arterial blood pressure (BP). Although elevated BP was perceived to be “essential” for adequate perfusion of vital organs during the early and middle 1900s, it has been identified as one of the most significant risk factors for cardiovascular (CV) disease for decades. Increasing awareness and diagnosis of hypertension, and improving control of BP with appropriate treatment are

considered critical public health initiatives to reduce CV morbidity and mortality.

The 2017 American College of Cardiology/American Heart Association (ACC/AHA) Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults is the most recent evidence-based clinical guideline in the United States for the management of hypertension.[1] It is the first comprehensive evidence-based hypertension guideline since the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) published in 2003.[2] The 2017 ACC/AHA guideline updates numerous areas including the definition of high BP, diagnosis, patient evaluation, treatment goals, management in various patient populations and additional strategies to improve BP control. This chapter incorporates relevant components of the 2017 ACC/AHA high BP guideline and additional evidence from clinical trials and meta-analyses, with a focus on the pharmacotherapy of hypertension.

The National Health and Nutrition Examination Survey and the National Center for Health Statistics regularly assess hypertension in the United States. Pooled data from 2011 to 2014 indicate that approximately 103.3 million Americans aged 20 years and above met the definition of hypertension according to the 2017 ACC/AHA guideline.[3] More than half (53.4%) of US adults taking antihypertensive medications had a BP above treatment goal. Considering the health consequences associated with high BP, there remain many opportunities for clinicians to improve the care of patients with hypertension.

EPIDEMIOLOGY

The definition of hypertension changed with the 2017 ACC/AHA guideline from a BP of ≥140/90 mm Hg to ≥130/80 mm Hg. Hence, the prevalence of hypertension has increased considerably. Almost half (46%) of American adults age 20 years and older have hypertension according to the ACC/AHA definition.[3] Although the overall prevalence has increased, only 1.9% would require additional drug therapy as the majority of newly diagnosed patients would require nonpharmacologic therapy only.[3]

The overall incidence of hypertension is similar between men and women but varies depending on age. The prevalence of high BP is higher in men than women before the age of 65 and is similar between the ages 65 and 74. However, after the age of 74, more women have high BP than men.[1,4] Prevalence rates are

highest in non-Hispanic blacks (59% in men, 56% in women), followed by non-Hispanic whites (47% in men, 41% in women), non-Hispanic Asians (45% in men, 36% in women), and Hispanics (45% in men, 42% in women).[1]

BP values increase with age, and hypertension (persistently elevated BP values) is very common in older patients. The lifetime risk of developing hypertension among those 55 years of age and older who are normotensive is higher than 90%.[1] Most patients have elevated BP before they are diagnosed with hypertension, with most diagnoses occurring between the third and fifth decades of life.

ETIOLOGY

In most patients, hypertension results from unknown pathophysiologic etiology (*essential* or *primary hypertension*). This form of hypertension cannot be cured, but it can be controlled. A smaller percentage of patients have a specific cause of their hypertension (*secondary hypertension*). There are many potential secondary causes that either are concurrent medical conditions or are endogenously induced. If identified, hypertension in these patients can be mitigated or potentially be cured.

Primary Hypertension

Most individuals with high BP (over 90%) have essential or primary hypertension.[1] Numerous potential mechanisms have been identified that contribute to the pathogenesis of essential hypertension, so identifying the exact underlying abnormality is not possible. Genetic factors may play a role in the development of essential hypertension by affecting sodium balance or other BP regulating pathways.

Secondary Hypertension

Secondary hypertension, where either a comorbid disease or a drug (or other product) is responsible for elevating BP (see **Table 30-1**), is much less common than primary hypertension (up to 10%).[1] In most of these cases, renal dysfunction resulting from severe chronic kidney disease (CKD) or renovascular disease is the most common secondary cause. Certain agents (drugs or other products), either directly or indirectly, can increase BP and cause or exacerbate hypertension. The most common agents are listed in Table 30-1. When a

secondary cause is identified, removing the offending agent (when feasible) or treating/correcting the underlying comorbid condition should be the first step in management.[5]

TABLE 30-1 Secondary Causes of Hypertension*

Diseases

- Chronic kidney disease
- Cushing's syndrome
- Coarctation of the aorta
- Obstructive sleep apnea
- Parathyroid disease
- Pheochromocytoma
- Primary aldosteronism
- Renovascular disease
- Thyroid disease

Medications

- Amphetamines (eg, amphetamine, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, methylphenidate, phendimetrazine, phentermine)
- Antivascular endothelin growth factor agents (bevacizumab, sorafenib, sunitinib)
- Corticosteroids (cortisone, dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone)
- Calcineurin inhibitors (cyclosporine, tacrolimus)
- Decongestants (pseudoephedrine, ocular phenylephrine)
- Ergot alkaloids (ergonovine, dihydroergotamine, methysergide)
- Erythropoiesis-stimulating agents (erythropoietin, darbepoetin)
- Estrogen-containing oral contraceptives
- Nonsteroidal anti-inflammatory drugs—cyclooxygenase-2 selective (celecoxib) and nonselective (aspirin [at higher doses], choline magnesium trisalicylate, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, naproxen sodium, oxaprozin, piroxicam, salsalate, sulindac, tolmetin)
- Testosterone
- Others: desvenlafaxine, venlafaxine, bupropion

Special Situations with Medications

- β-blocker or centrally acting α-agonists (when abruptly discontinued)
- β-blocker without α-blocker first when treating pheochromocytoma
- Use of a monoamine oxidase inhibitor (isocarboxazid, phenelzine, tranylcypromine) with tyramine-containing foods or certain drugs

Street Drugs and Other Products

- Cocaine and cocaine withdrawal
- Methamphetamine
- Ephedra alkaloids (eg, Ma huang), "herbal ecstasy," other analogues
- Anabolic steroids
- Ergot-containing herbal products
- St. John's wort

Excessive Consumption of Food Substances

- Sodium
- Ethanol
- Licorice

*Agents of most clinical importance.

PATHOPHYSIOLOGY

Multiple physiologic factors control BP and abnormalities of these factors are potential contributing components in the development of essential hypertension. These include malfunctions in either humoral (ie, the renin–angiotensin–aldosterone system [RAAS]) or vasodepressor mechanisms, abnormal neuronal mechanisms, defects in peripheral autoregulation, and disturbances in sodium, calcium, and natriuretic hormones. Many of these factors are cumulatively affected by the multifaceted RAAS, which ultimately regulates arterial BP. It is probable that no one factor is solely responsible for essential hypertension.

Arterial BP

Arterial BP is the pressure in the arterial wall measured in millimeters of mercury (mm Hg). The two arterial BP values are *systolic BP* (SBP) and *diastolic BP* (DBP). SBP represents the peak value, which is achieved during cardiac contraction. DBP is achieved after contraction when the cardiac chambers are filling, and represents the nadir value. The absolute difference between SBP and DBP is called the pulse pressure and is a measure of arterial wall tension. Mean arterial pressure (MAP) is the average pressure throughout the cardiac contraction cycle. It can be used clinically to represent overall arterial BP, especially in hypertensive emergency. During a cardiac cycle, two-thirds of the time is spent in diastole and one-third in systole. Therefore, the MAP is calculated by using the following equation:

$$\text{MAP} = \left(\text{SBP} \times \frac{1}{3}\right) + \left(\text{DBP} \times \frac{2}{3}\right)$$

Arterial BP is hemodynamically generated by the interplay between blood flow and the resistance to blood flow. It is mathematically defined as the product of cardiac output (CO) and total peripheral resistance (TPR) according to the following equation:

$$\text{BP} = \text{CO} \times \text{TPR}$$

CO is the major determinant of SBP, whereas TPR largely determines DBP. In turn, CO is a function of stroke volume, heart rate, and venous capacitance. **Table 30-2** lists physiologic causes of increased CO and TPR and correlates

them to potential mechanisms of pathogenesis.

TABLE 30-2 Potential Mechanisms of Pathogenesis

Blood pressure (BP) is the mathematical product of cardiac output and peripheral resistance. Elevated BP can result from increased cardiac output and/or increased total peripheral resistance.

Increased cardiac output	*Increased cardiac preload:* • Increased fluid volume from excess sodium intake or renal sodium retention *Venous constriction:* • Excess stimulation of the renin–angiotensin–aldosterone system (RAAS) • Sympathetic nervous system overactivity
Increased peripheral resistance	*Functional vascular constriction:* • Excess stimulation of the RAAS • Sympathetic nervous system overactivity • Genetic alterations of cell membranes • Endothelial-derived factors *Structural vascular hypertrophy:* • Excess stimulation of the RAAS • Sympathetic nervous system overactivity • Genetic alterations of cell membranes • Endothelial-derived factors • Hyperinsulinemia

Under normal physiologic conditions, arterial BP fluctuates throughout the day following a circadian rhythm. BP decreases to its lowest values during sleep followed by a sharp rise starting a few hours prior to awakening, with the highest values occurring midmorning. BP is also increased acutely during physical activity or emotional stress.

Classification

The classification of BP in adults (age 18 years and older) is based on the average of two or more properly measured BP values from two or more clinical encounters (Table 30-3).[1] According to ACC/AHA, there are four BP categories: normal, elevated, stage 1 hypertension, and stage 2 hypertension. Elevated BP is not a disease category, but is associated with an increased CV risks compared to patients with normal BP.[6] It identifies patients whose BP is likely to progress to hypertension in the future, and thus for whom lifestyle modifications should be

enacted to attenuate this progression.

TABLE 30-3 Classification of Blood Pressure in Adults (Age ≥18 Years)*

Classification	Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)
Normal	<120	and	<80
Elevated	120-129	and	<80
Stage 1 hypertension	130-139	or	80-89
Stage 2 hypertension	≥140	or	≥90

*Classification determined based on the average of two or more properly measured seated BP values from two or more clinical encounters. Out-of-office measurements should be used to confirm diagnosis. If systolic and diastolic BP values yield different classifications, the highest category is used for the purpose of determining a classification.

Hypertensive crises are clinical situations where patients have extreme BP elevations, typically >180/120 mm Hg. They are categorized as either *hypertensive emergency* or *hypertensive urgency*. Hypertensive emergencies are extreme BP elevations that are accompanied by acute or progressing end-organ damage. Hypertensive urgencies are extreme BP elevations without acute or progressing end-organ injury.

Cardiovascular Risk and Blood Pressure

1 Epidemiologic data demonstrate a strong correlation between BP and CV morbidity and mortality.[7] Risk of hypertensionassociated complications (eg, stroke, myocardial infarction [MI], angina, heart failure [HF], kidney failure, early death from a CV causes) is directly correlated with BP. Starting at a BP of 115/75 mm Hg, the risk of CV disease doubles with every 20/10 mm Hg increase.[1] Even patients with elevated BP have an increased risk of CV disease.

2 Treating patients with hypertension with antihypertensive drug therapy provides significant clinical benefits. Evidence from large-scale placebo-controlled clinical trials has repeatedly shown that the increased risks of CV events and death associated with elevated BP are reduced substantially by antihypertensive drug therapy (see the section “Treatment”).[8–10]

SBP is a stronger predictor of CV disease than DBP in adults aged 50 years and older; it is the most important BP parameter for most patients.[1] Patients are considered to have *isolated systolic hypertension* when their SBP values are elevated (ie, ≥130 mm Hg) and DBP values are not (ie, <80 mm Hg). Isolated

systolic hypertension is believed to result from pathophysiologic changes in the arterial vasculature consistent with aging. These changes decrease the compliance of the arterial wall and portend an increased risk of CV morbidity and mortality. A wider than normal pulse pressure (SBP minus DBP) is believed to reflect the extent of atherosclerotic disease in older patients and is a measure of increased arterial stiffness. Higher pulse pressure values seen in those with isolated systolic hypertension are directly correlated with risk of CV mortality.

Humoral Mechanisms

Several humoral abnormalities involving the RAAS, natriuretic hormone, and hyperinsulinemia may be involved in the development of essential hypertension.

The Renin–Angiotensin–Aldosterone System

The RAAS is a complex endogenous system that is involved with most regulatory components of arterial BP. Activation and regulation are primarily governed by the kidney (see **Fig. 30-1**). The RAAS regulates sodium, potassium, and blood volume. Therefore, this system significantly influences vascular tone and sympathetic nervous system activity, and is the most influential contributor to the homeostatic regulation of BP.

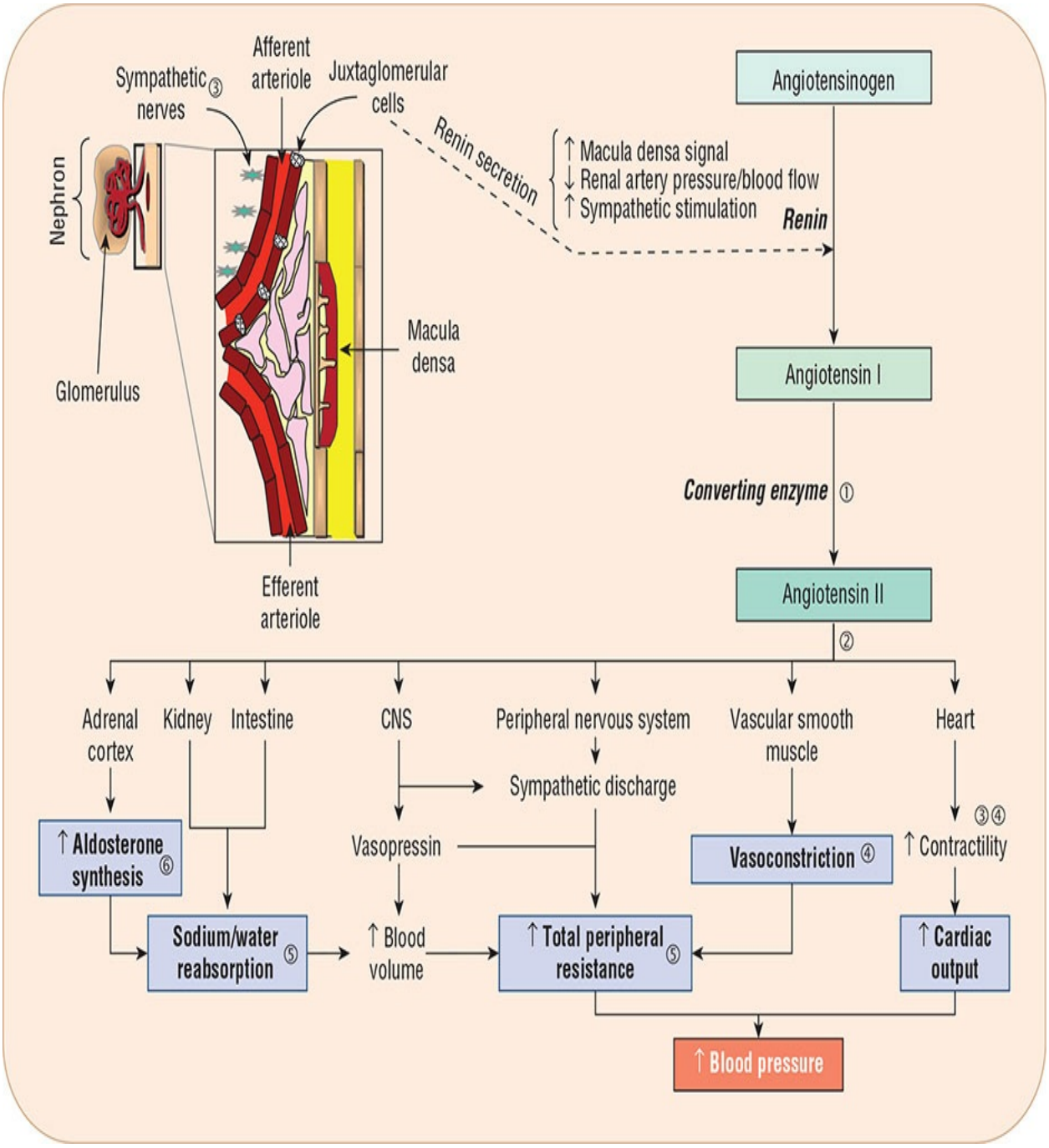


FIGURE 30-1 Diagram representing the renin–angiotensin–aldosterone system. The interrelationship between the kidney, angiotensin II, and regulation of blood pressure is depicted. Renin secretion from the juxtaglomerular cells in the afferent arterioles is regulated by three major factors that trigger conversion of angiotensinogen to angiotensin 1. The primary sites of action for major antihypertensive agents are included: 1 ACE inhibitor; 2 angiotensin II receptor blocker; 3 β-blocker; 4 calcium channel blocker; 5 thiazide; 6

mineralocorticoid receptor antagonist.

Renin is an enzyme that is stored in the juxtaglomerular cells, which are located in the afferent arterioles of the kidney. The release of renin is modulated by several factors: intrarenal factors (eg, renal perfusion pressure, catecholamines, angiotensin II) and extrarenal factors (eg, sodium, chloride, potassium).

Juxtaglomerular cells function as a baroreceptor-sensing device. Decreased renal artery pressure and kidney blood flow are sensed by these cells and stimulate secretion of renin. A decrease in sodium and chloride delivered to the distal tubule stimulates renin release. Catecholamines increase renin release probably by directly stimulating sympathetic nerves on the afferent arterioles that in turn activate the juxtaglomerular cells.

Renin catalyzes the conversion of angiotensinogen to angiotensin I in the blood. Angiotensin I is then converted to angiotensin II by angiotensin-converting enzyme (ACE). After binding to specific receptors (classified as either angiotensin II type 1 [AT_1] or angiotensin II type 2 [AT_2] subtypes), angiotensin II exerts biologic effects in several tissues. The AT_1 receptor is located in the brain, kidneys, myocardium, peripheral vasculature, and the adrenal glands. These receptors mediate most responses that are critical to CV and kidney function. The AT_2 receptor is located in adrenal medullary tissue, uterus, and brain. Stimulation of the AT_2 receptor does not influence BP regulation.

Circulating angiotensin II can elevate BP through pressor and volume effects. Pressor effects include direct vasoconstriction, stimulation of catecholamine release from the adrenal medulla, and centrally mediated increases in sympathetic nervous system activity. Angiotensin II also stimulates aldosterone synthesis from the adrenal cortex, leading to sodium and water reabsorption that increases plasma volume, TPR, and ultimately BP. Aldosterone also has a deleterious role in the pathophysiology of other CV diseases (eg, HF, MI, kidney disease) by promoting tissue remodeling leading to myocardial fibrosis and vascular dysfunction. Clearly, any disturbance in the body that leads to activation of the RAAS could explain chronic hypertension.

The heart and brain contain a local RAAS. In the heart, angiotensin II is also generated by angiotensin I convertase (human chymase). This enzyme is not blocked by ACE inhibition. Activation of the myocardial RAAS increases cardiac contractility and stimulates cardiac hypertrophy. In the brain, angiotensin II modulates the production and release of hypothalamic and pituitary hormones

and enhances sympathetic outflow from the medulla oblongata.

Natriuretic Hormone

Natriuretic hormone inhibits sodium and potassium ATPase and thus interferes with sodium transport across cell membranes. Inherited defects in the kidney's ability to eliminate sodium can cause increased blood volume. A compensatory increase in the concentration of circulating natriuretic hormone theoretically could increase urinary excretion of sodium and water. However, this hormone might block the active transport of sodium out of arteriolar smooth muscle cells. The increased intracellular sodium concentration ultimately increases vascular tone and BP.

Neuronal Regulation

Central and autonomic nervous systems are intricately involved in the regulation of arterial BP. Many receptors that either enhance or inhibit norepinephrine release are located on the presynaptic surface of sympathetic terminals. The α and β presynaptic receptors play a role in negative and positive feedback to the norepinephrine-containing vesicles. Stimulation of presynaptic α-receptors (α_2) exerts a negative inhibition on norepinephrine release. Stimulation of presynaptic β-receptors facilitates norepinephrine release.

Sympathetic neuronal fibers located on the surface of effector cells innervate the α- and β-receptors. Stimulation of postsynaptic α-receptors (α_1) on arterioles and venules results in vasoconstriction. There are two types of postsynaptic β-receptors, β_1 and β_2. Both are present in all tissues innervated by the sympathetic nervous system. However, in some tissues β_1-receptors predominate (eg, heart), and in other tissues β_2-receptors predominate (eg, bronchioles). Stimulation of β_1-receptors in the heart increases heart rate (chronotropy) and force of contraction (inotropy), whereas stimulation of β_2-receptors causes vasodilation in arteries and veins.

The baroreceptor reflex system is the major negative feedback mechanism that controls sympathetic activity. Baroreceptors are nerve endings lying in the walls of large arteries, especially in the carotid arteries and aortic arch. Changes in arterial BP rapidly activate baroreceptors that then transmit impulses to the brain stem through the ninth cranial nerve and vagus nerve. In this reflex system, a decrease in arterial BP stimulates baroreceptors, causing reflex vasoconstriction, increased heart rate, and increased force of cardiac contraction.

Baroreceptor reflex mechanisms may be less responsive in older patients and those with diabetes.

Stimulation of specific areas within the central nervous system (eg, nucleus tractus solitarius, vagal nuclei, vasomotor center, area postrema) can either increase or decrease BP. For example, α_2-adrenergic stimulation within the central nervous system decreases BP through inhibitory effects on the vasomotor center. However, angiotensin II increases sympathetic outflow from the vasomotor center, which increases BP.

The purpose of these neuronal mechanisms is to regulate BP and maintain homeostasis. Pathologic disturbances in any of the four major components (autonomic nerve fibers, adrenergic receptors, baroreceptors, central nervous system) could chronically elevate BP. These systems are physiologically interrelated. A defect in one component may alter normal function in another. Therefore, cumulative abnormalities may explain the development of essential hypertension.

Peripheral Autoregulatory Components

Abnormalities in renal or tissue autoregulatory systems could cause hypertension. Renal defects in sodium excretion may develop, which can then cause resetting of tissue autoregulatory processes resulting in a higher BP. The kidney usually maintains a normal BP through a volume–pressure adaptive mechanism. When BP drops, the kidneys respond by increasing retention of sodium and water, which leads to plasma volume expansion that increases BP. Conversely, when BP rises above normal, renal sodium and water excretion are increased to reduce plasma volume and CO.

Local autoregulatory processes maintain adequate tissue oxygenation. When tissue oxygen demand is normal to low, the local arteriolar bed remains relatively vasoconstricted. However, increased metabolic demand triggers arteriolar vasodilation that lowers peripheral vascular resistance (PVR) and increases blood flow and oxygen delivery.

Intrinsic defects in renal adaptive mechanisms could lead to plasma volume expansion and increased blood flow to peripheral tissues, even when BP is normal. Local tissue autoregulatory processes that vasoconstrict would then be activated to offset the increased blood flow. This effect would result in increased PVR and, if sustained, would also result in thickening of the arteriolar walls. This pathophysiologic component is plausible because increased TPR is a common underlying finding in essential hypertension.

Vascular Endothelial Mechanisms

Vascular endothelium and smooth muscle play important roles in regulating blood vessel tone and BP. Regulating functions are mediated by vasoactive substances that are synthesized by endothelial cells. It has been postulated that a deficiency in local synthesis of vasodilating substances (eg, prostacyclin and bradykinin) or excess vasoconstricting substances (eg, angiotensin II and endothelin I) contributes to essential hypertension, atherosclerosis, and other CV diseases.

Nitric oxide is produced in the endothelium, relaxes the vascular epithelium, and is a very potent vasodilator. The nitric oxide system is an important regulator of arterial BP. Patients with hypertension may have an intrinsic nitric oxide deficiency, resulting in inadequate vasodilation.

Electrolytes

Excess sodium intake is associated with hypertension. Populationbased studies demonstrate that high-sodium diets are associated with a high prevalence of stroke and hypertension. Conversely, lowsodium diets are associated with a lower prevalence of hypertension. Clinical studies have shown that dietary sodium restriction lowers BP in many (but not all) patients with elevated BP. The exact mechanisms by which excess sodium leads to hypertension are not known.

Alterations in calcium and potassium may also play an important role in the pathogenesis of hypertension. A lack of dietary calcium hypothetically can disturb the balance between intracellular and extracellular calcium, resulting in an increased intracellular calcium concentration and alterations in vascular smooth muscle function. Dietary potassium intake is inversely related to BP, and may blunt the effect of sodium on BP.[1] Potassium depletion may also increase PVR, but the clinical significance of small serum potassium concentration changes in relation to BP is unclear. While altered calcium and potassium may play a role in the development of hypertension, data demonstrating reduced CV risk with supplementation are very limited.

CLINICAL PRESENTATION

Hypertension

General: May appear healthy or may have additional CV risk factors:

- Age (≥55 years for men, ≥65 years for women)
- Diabetes (type 1 or type 2)
- Dyslipidemia
- Albuminuria
- Family history of premature CV disease
- Overweight (body mass index [BMI] 25-29.9 kg/m^2) or obesity (BMI ≥30 kg/m^2)
- Physical inactivity
- Tobacco use

Symptoms: Usually none related to elevated BP.

Signs: Previous BP (SBP or DBP) values in the elevated or the hypertension category.

Routine laboratory tests: Blood urea nitrogen (BUN)/serum creatinine with estimated glomerular filtration rate (using modification in diet in renal disease [MDRD] equation), lipid panel, fasting blood glucose, serum electrolytes (sodium, potassium, calcium), hemoglobin and hematocrit, and electrocardiogram. May have normal values and still have hypertension.

However, some may have abnormal values consistent with either additional CV risk factors or hypertension-related damage.

Other tests: Echocardiogram, spot urine albumin-to-creatinine ratio, uric acid.

Hypertension-related complications: The patient may have a previous medical history or diagnostic findings that indicate the presence of hypertension-associated complications:

- **Brain** (stroke, transient ischemic attack, dementia)
- **Eyes** (retinopathy)
- **Heart** (left ventricular hypertrophy [LVH], angina, prior MI, prior coronary revascularization, HF)
- **Kidney** (chronic kidney disease [CKD]
- **Peripheral vasculature** (peripheral arterial disease [PAD])

CLINICAL PRESENTATION

Diagnostic Considerations

3 Hypertension is called the *silent killer* because most patients do not have symptoms. The primary physical finding is persistently elevated BP. The diagnosis of hypertension cannot be made based on one elevated BP measurement. The average of two or more BP measurements taken during two or more clinical encounters is required to diagnose hypertension.[1] This BP average should be used to establish a diagnosis, and then classify the stage of hypertension using Table 30-3. Out-of-office measurements should be used to confirm elevated readings.

Measuring BP

The measurement of BP is a medical screening tool and should be conducted at every healthcare encounter.[1]

Cuff Measurement The most common method to measure BP in clinical practice is the indirect measurement of BP using an oscillometric device or sphygmomanometry. The appropriate procedure to indirectly measure BP is described by the AHA.[11] It is imperative that the measurement equipment (ie, inflation cuff, stethoscope, and manometer) meet national standards to ensure maximum quality and precision with measurement.

The AHA stepwise technique is recommended:

1. Patients should ideally refrain from nicotine and caffeine ingestion for 30 minutes, have emptied his/her bladder, and sit with lower back supported in a chair. Their bare arm should be supported and rest near heart level. Feet should be flat on the floor (with legs not crossed). The measurement environment should be relatively quiet and ideally provide privacy. Measuring BP in a position other than seated (supine or standing position) may be required under special circumstances (eg, suspected orthostatic hypotension, dehydration).
2. Measurement should begin only after a 5-minute period of rest.
3. Neither the patient nor the clinician measuring the BP should talk during measurement.
4. A properly sized cuff (pediatric, small, regular, large, or extra-large) should be used. The inflatable rubber bladder should be at least 80% of arm circumference and a width that is at least 40% of arm circumference.
5. The palpatory method should be used to estimate the SBP:
    a. Place the cuff on the upper arm with the bottom resting 2 to 3 cm

above the antecubital fossa and attach it to the manometer.

b. Close the inflation valve and inflate the cuff to 70 mm Hg. Palpate the radial pulse with the index and middle fingers of the opposite hand.
c. Inflate further in increments of 10 mm Hg until the radial pulse can no longer be palpated.
d. Note the pressure at which the radial pulse is no longer palpated. This is the estimated SBP.
e. Rapidly release the pressure in the cuff by opening the valve.

6. The stethoscope (either diaphragm or bell) should be placed on the bare skin of the antecubital fossa, directly over where the brachial artery is palpated. The stethoscope earpieces should be inserted appropriately. The valve should be closed and then the cuff inflated to 30 mm Hg above the estimated SBP from the palpatory method. The valve should then be slightly opened to slowly release pressure at a rate of approximately 2 mm Hg/second.
7. The clinician should listen for Korotkoff sounds with the stethoscope. The first phase of Korotkoff sounds is the initial presence of clear tapping sounds. Note the pressure at the first recognition of these sounds. This is the SBP. As pressure deflates, note the pressure when all sounds disappear, right at the last sound. This is the DBP.
8. Measurements should be rounded up to the nearest 2 mm Hg (eg, 145 mm Hg rounded up to 146 mm Hg).
9. A second measurement should be obtained after at least 1 minute. If the two measurements (SBP and/or DBP) differ by more than 5 mm Hg, additional measurement(s) should be obtained.
10. When first establishing care with a patient, BP should be measured in both arms. If consistent inter-arm differences exist, the arm with the higher value should be used.

Inaccuracies with indirect measurements result from inherent biologic variability of BP, errors related to incorrect technique, and the white coat effect.[11] Variations in BP occur with environmental temperature, the time of day and year, meals, physical activity, posture, alcohol, nicotine, and emotions. In the clinic setting, standard BP measurement procedures (eg, appropriate rest period, correct technique, right cuff size) are often not followed, which results in poor estimation of true BP. In addition, variations may occur between individuals measuring BP. Due to these factors, use of oscillometric devices is generally

preferred.

Approximately 15% to 20% of patients have *white coat hypertension*, where BP values rise in a clinical setting but are normal in nonclinical environments as measured with home or ambulatory BP (ABP) monitors.[11] Interestingly, the rise in BP dissipates gradually after leaving the clinical setting. It may or may not be precipitated by other stresses in the patient's daily life. This is in contrast to *masked hypertension*, where a decrease in BP occurs in the clinical setting.[12] With masked hypertension, home BP is much higher than the inoffice BP measurement. This situation may lead to undertreatment or lack of treatment for hypertension. While white coat hypertension is associated with a minimal increase in CV events, masked hypertension increases the risk similar to those with sustained hypertension. Moreover, patients with either white coat or masked hypertension are at higher risk of progressing to sustained hypertension.[13]

Pseudohypertension is a falsely elevated BP measurement. It may be seen in older patients, those with long-standing diabetes, or those with CKD due to rigid, calcified brachial arteries.[11] In these patients, the true arterial BP when measured directly with intraarterial measurement (the most accurate measurement of BP) is much lower than that measured using the indirect cuff method. The Osler's maneuver has been proposed as a method to test for pseudohypertension. In this maneuver, the BP cuff is inflated above peak SBP. If the radial artery remains palpable, the patient has a positive Osler's sign (rigid artery), which may indicate pseudohypertension. However, the diagnostic accuracy and reliability of this maneuver is questionable, and therefore is not recommended.

Older patients with a wide pulse pressure may have an auscultatory gap that can lead to underestimated SBP or overestimated DBP measurements.[11] In this situation, as the cuff pressure falls from the true SBP value, the Korotkoff sound may disappear (indicating a false DBP measurement), reappear (a false SBP measurement), and then disappear again at the true DBP value. When an auscultatory gap is present, Korotkoff sounds are usually heard when pressure in the cuff first starts to decrease after inflation. This may be eliminated by raising the arm overhead by 30 seconds before bringing it to the proper position and inflating the cuff. This maneuver decreases the intravascular volume and improves inflow thereby allowing Korotkoff sounds to be heard.[11]

Ambulatory and Home BP Monitoring Ambulatory BP (ABP) monitoring using an automated device records BP at frequent time intervals (eg, every 15-30 minutes) throughout a 24-hour period.[11] Home BP monitoring is performed by

patients or a caregiver, preferably in the morning, using a home monitoring device. Home BP monitoring values and ABP values are often lower than clinicmeasured values; the difference is greater in patients with stage 1 and stage 2 hypertension.[1] For example, a clinic BP of 130/80 mm Hg corresponds to home BP reading of 130/80 mm Hg and 24-hour ABP of 125/75 mm Hg. However, a clinic BP of 140/90 mm Hg corresponds to a home BP monitoring value of 135/85 mm Hg and 24-hour ABP value of 130/80 mm Hg.

Neither ABP nor home BP monitoring is needed for the diagnosis of hypertension, but they are recommended. These modalities can enhance the ability to identify patients with white coat and masked hypertension.[1] In addition, ABP monitoring may be a stronger pre dictor of all-cause and CV mortality than clinic measurements.[14] The 2017 ACC/AHA guideline recommends out-of-office measurements for diagnostic confirmation and to assist in titrating antihypertensive medication.[1] ABP monitoring may be helpful for patients with apparent drug resistance, hypotensive symptoms while on antihypertensive therapy, episodic hypertension (eg, white coat hypertension), autonomic dysfunction, and in identifying “nondippers” whose BP does not decrease by >10% during sleep and who may portend an increased risk of hypertension-associated complications.

Limitations of ABP and home BP measurements include the complexity of use, costs, and lack of prospective outcome data describing normal ranges for these measurements. Although home BP monitoring is less complicated and less costly than ambulatory monitoring, patients may omit or fabricate readings, or have poor technique (eg, not resting for an adequate period, improper placement, wrong cuff size). Therefore, patients should be educated on appropriate selection of a home BP device (eg, validated machine, ideally has a memory feature, correct cuff size) and how to use it correctly.

Clinical Evaluation

Frequently, the only sign of essential hypertension is elevated BP. The rest of the physical examination may be completely normal. However, a complete medical evaluation (including a comprehensive medical history, physical examination, and laboratory and/or diagnostic tests) is recommended after diagnosis to (a) identify secondary causes, (b) identify other CV risk factors or comorbid conditions that may define prognosis and/or guide therapy, and (c) assess for the presence or absence of hypertension-associated complications. All patients with hypertension should have the tests described in the “CLINICAL

PRESENTATION: HYPERTENSION" box prior to initiating antihypertensive drug therapy.[1] For patients without a history of atherosclerotic cardiovascular disease (ASCVD), left ventricular dysfunction, or diabetes, it is also important to estimate future risk of ASCVD. The 10-year clinical ASCVD (defined as coronary death or nonfatal myocardial infarction, or fatal or nonfatal stroke) risk calculator is based on the Pooled Cohort Equations and lifetime risk prediction tools can be found at http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/.

Secondary Causes

The most common secondary causes of hypertension are listed in Table 30-1. A complete medical evaluation should provide clues for identifying secondary hypertension. Patients with secondary hypertension might have signs or symptoms suggestive of the underlying disorder. Patients with pheochromocytoma may have a history of paroxysmal headaches, sweating, tachycardia, and palpitations. Over half of these patients suffer from episodes of orthostatic hypotension. In primary hyperaldosteronism, symptoms related to hypokalemia usually include muscle cramps and muscle weakness. Patients with Cushing's syndrome may complain of weight gain, polyuria, edema, menstrual irregularities, recurrent acne, or muscular weakness and have several classic physical features (eg, moon face, buffalo hump, hirsutism). Patients with coarctation of the aorta may have higher BP in the arms than in legs and diminished or even absent femoral pulses. Patients with renal artery stenosis may have an abdominal systolic–diastolic bruit.

Laboratory tests may also help identify secondary hypertension. Baseline hypokalemia may suggest mineralocorticoid-induced hypertension. Protein, red blood cells, and casts in the urine may indicate renovascular disease. Some laboratory tests are used specifically to diagnose secondary hypertension. These include plasma norepinephrine and urinary metanephrine for pheochromocytoma, plasma and urinary aldosterone concentrations for primary hyperaldosteronism, and plasma renin activity, captopril stimulation test, renal vein renin, and renal artery angiography for renovascular disease.

Certain drugs and other products can increase BP (see Table 30-1). For some patients, the addition of these agents can be the cause of hypertension or can exacerbate underlying hypertension. Identifying a temporal relationship between starting the suspected agent and developing elevated BP is most suggestive of drug-induced BP elevation.

Natural Course of Disease

The onset of hypertension is usually preceded by increased BP values that are in the elevated BP category. BP values may fluctuate between elevated and normal levels for a period of time. As the disease progresses, PVR increases, and BP elevation becomes chronic.

Hypertension-Associated Complications

Several complications can result as a consequence of high BP in patients with hypertension (see “CLINICAL PRESENTATION: HYPERTENSION” box). CV events (eg, MI, cerebrovascular events, kidney failure) are the primary causes of CV morbidity and mortality in patients with hypertension. The probability of CV events and CV morbidity and mortality in patients with hypertension is directly correlated with the severity of BP elevation.

Hypertension accelerates the development of atherosclerosis and stimulates left ventricular and vascular dysfunction. These pathologic changes are thought to be secondary to both a chronic pressure overload and a variety of nonhemodynamic stimuli. Several nonhemodynamic disturbances have been implicated in these effects (eg, the adrenergic system, RAAS, increased synthesis and secretion of endothelin I, decreased production of prostacyclin and nitric oxide). Atherosclerosis in hypertension is accompanied by the proliferation of smooth muscle cells, lipid infiltration into the vascular endothelium, and enhancement of vascular calcium accumulation.

Cerebrovascular disease is a consequence of hypertension. Either gross neurologic deficits or a slight hemiparesis with some incoordination and hyperreflexia are indicative of cerebrovascular disease. Stroke can result from lacunar infarcts caused by thrombotic occlusion of small vessels or intracerebral hemorrhage resulting from ruptured microaneurysms. Transient ischemic attacks secondary to atherosclerosis in the carotid arteries can also develop in patients with hypertension.

Retinopathies can occur in hypertension and may manifest as a variety of different findings. A funduscopic examination can detect hypertensive retinopathy, which manifests as arteriolar narrowing, focal arteriolar constrictions, arteriovenous crossing changes (nicking), retinal hemorrhages and exudates, and disk edema. Focal arteriolar narrowing, retinal infarcts, and flame-shaped hemorrhages usually are suggestive of an accelerated or malignant phase of hypertension (seen in some hypertensive emergencies). Papilledema (swelling of the optic disk) is usually only present in hypertensive emergencies.

Heart disease is a commonly identified complication of hypertension. A thorough cardiac and pulmonary examination can identify cardiopulmonary abnormalities. Clinical manifestations include LVH, coronary artery disease (angina, prior MI, and prior coronary revascularization), and HF. These complications may lead to cardiac arrhythmias, angina, MI, and sudden death. Coronary artery disease (also called *coronary heart disease*) and associated CV events are the most common causes of death in patients with hypertension.

The kidney damage caused by hypertension is characterized pathologically by hyaline arteriosclerosis, hyperplastic arteriosclerosis, arteriolar hypertrophy, fibrinoid necrosis, and atheroma of the major renal arteries. Glomerular hyperfiltration and intraglomerular hypertension are early stages of hypertensive nephropathy. Persistent albuminuria is followed by a gradual decline in renal function. The primary renal complication in hypertension is nephrosclerosis, which is secondary to arteriosclerosis. Atheromatous disease of a major renal artery may give rise to renal artery stenosis. Overt kidney failure is an important cause of end-stage kidney disease, especially in African Americans, Hispanics, and Native Americans.

The peripheral vasculature is a target organ affected by hypertension. Physical examination of the vascular system can detect evidence of atherosclerosis, which may present as arterial bruits (aortic, abdominal, or peripheral), distended veins, diminished or absent peripheral arterial pulses, or lower extremity edema. Peripheral arterial disease (PAD) is a clinical condition that can result from atherosclerosis. Other CV risk factors (eg, smoking) can increase the likelihood of PAD as well as all other complications.

TREATMENT

Overall Goal of Treatment

4 The overall goal of treating hypertension is to reduce morbidity and mortality from CV events (eg, coronary events, cerebrovascular events, HF) and kidney disease. Therefore, the specific selection of antihypertensive drug therapy should be based on evidence demonstrating a reduction in morbidity and mortality, not merely a reduction in BP.

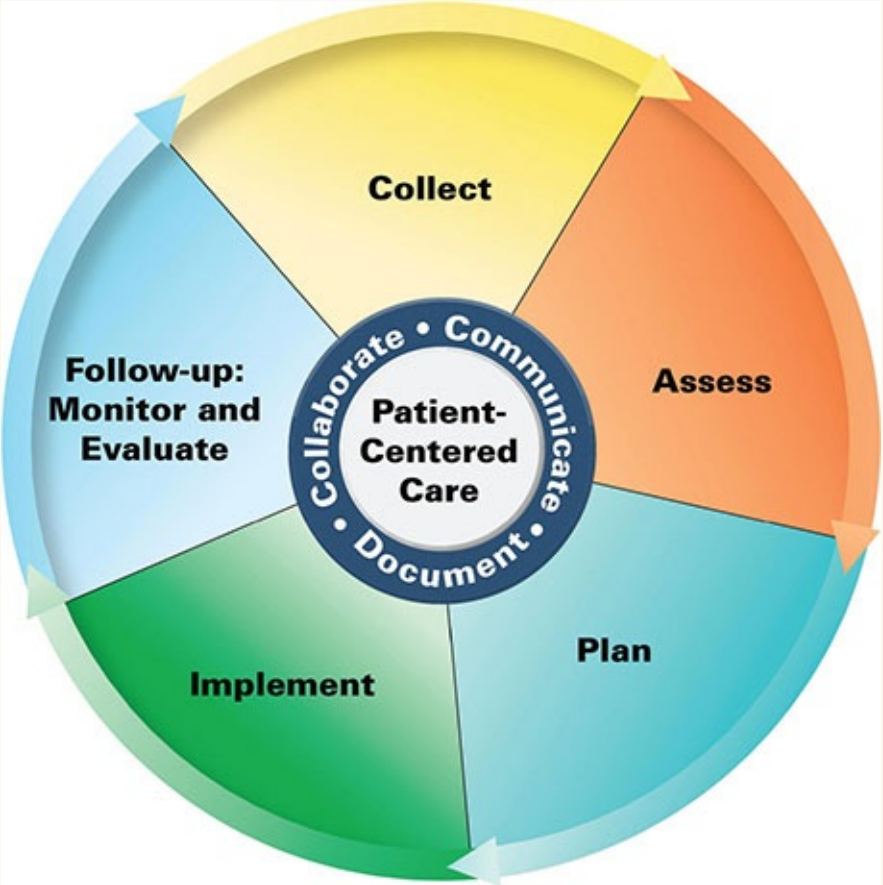
Surrogate Targets—Blood Pressure Goals

Treating patients with hypertension to achieve a desired goal BP is a surrogate

goal of therapy. Reducing BP to goal does not guarantee prevention of hypertension-associated complications, but is associated with a lower risk. Targeting a goal BP is how clinicians evaluate response to therapy. It is the primary method that is used to determine the need for titration and regimen modification.

The 2017 ACC/AHA guideline recommends a goal BP of <130/80 mm Hg for the management of hypertension in most patients (see "DESIRED OUTCOMES: GOAL BP FOR CHRONIC TREATMENT" box).[1] The American Diabetes Association recommends a goal of <140/90 mm Hg for most patients with diabetes, with a lower goal of <130/80 mm Hg for certain individuals (eg, those at high risk of ASCVD) if achieved without undue treatment burden.[15] The Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend a BP goal of ≤140/90 mm Hg for patients with hypertension and CKD (nondialysis), with a lower BP goal of ≤130/80 mm Hg only for those patients who have persistent albuminuria (≥30 mg urine albumin excretion per 24 hours or equivalent) as a therapeutic option.[16,17]

Historically, most patients with hypertension were treated to a goal BP of <140/90 mm Hg. However, evidence demonstrates significantly lower risk of CV events with lower BP goals, particularly in those with or at high risk of ASCVD. Some of the strongest data supporting the lower BP goals comes from the Systolic Blood Pressure Intervention Trial (SPRINT). The SPRINT evaluated a systolic BP goal of <120 mm Hg versus <140 mm Hg in patients with hypertension at high CV risk but without diabetes.[18] The study was stopped early after a median follow-up of 3.3 years due to a significantly lower risk of the primary composite outcome (MI, other acute coronary syndromes, stroke, HF, or death from CV causes) and allcause mortality in patients treated to the lower BP goals. While there was an increased risk of adverse events in the intensive treatment group (eg, hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure), the significant benefits outweighed these risks.



Patient Care Process for the Management of Hypertension

Collect

- Patient characteristics (eg, age, race, sex, pregnant)
- Patient history (past medical, family, social—dietary habits, tobacco use)
- Home blood pressure (BP) readings
- Current medications and prior antihypertensive medication use
- Objective data (see “CLINICAL PRESENTATION: HYPERTENSION” box)
  - BP, heart rate (HR), height, weight, and BMI
  - Labs (eg, serum electrolytes, Scr, BUN)
  - Other diagnostic tests when indicated (eg, ECG)

Assess

- Presence of compelling indications (eg, coronary artery disease, chronic kidney disease; see Fig. 30-3)
- Hypertension-related complications (eg, albuminuria, retinopathy; see "CLINICAL PRESENTATION: HYPERTENSION" box)
- Ten-year atherosclerotic cardiovascular disease (ASCVD) risk when indicated
- Current medications that may contribute to or worsen hypertension
- BP goal and whether goal has been achieved (see "DESIRED OUTCOMES: GOAL BP FOR CHRONIC TREATMENT" box)
- Appropriateness and effectiveness of current antihypertensive regimen
- For resistant hypertension if taking three or more antihypertensive medications (see Table 30-8)

Plan*

- Tailored lifestyle modifications (eg, diet, exercise, weight management; see Table 30-4)
- Drug therapy regimen including specific antihypertensive(s), dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Tables 30-5, 30-6, 30-7, and 30-9)
- Monitoring parameters including efficacy (eg, BP, cardiovascular events, kidney health), safety (medicationspecific adverse effects), and time frame (see Table 30-11)
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug therapy)
- Self-monitoring of BP, HR, and weight—where and how to record results
- Referrals to other providers when appropriate (eg, physician, dietician)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Determine BP goal attainment
- Presence of adverse effects
- Occurrence of CV events and development/progression of kidney impairment
- Patient adherence to treatment plan using multiple sources of information

** Collaborate with patient, caregivers, and other healthcare professionals.*

Desired Outcomes: Goal BP for Chronic Treatment

Most patients (including patients with clinical ASCVD [secondary prevention], diabetes, or CKD; primary prevention patients regardless of 10-year ASCVD risk score):

- <130/80 mm Hg

Older ambulatory, community dwelling patients:

- SBP <130 mm Hg

Institutionalized older patients, those with high disease burden and comorbidities, or limited life-expectancy:

- Consider a relaxed SBP goal of at least <150 mm Hg; <140 mm Hg in some patients if tolerated
- Use a team-based decision process weighing patient preferences, risks, and benefits

In addition to the SPRINT, several other systematic reviews and meta-analysis demonstrate that lower BP goals improve clinical outcomes better than higher BP goals.[19–23] In a systematic review and meta-analysis of 19 trials involving 44,989 patients, intensive treatment (mean BP 133/76 mm Hg) was associated with a reduced risk of major CV events, MI, stroke, albuminuria, and retinopathy progression compared to less intensive BP-lowering (mean BP 140/81 mm Hg).[20] The risk of serious adverse events with intensive therapy was low and did not differ significantly compared to less-intensive treatment, though severe hypotension was more frequent.

Evidence Supporting Lower BP Goals in Diabetes BP goal values for patients with diabetes have been a subject of debate for a number of years. A BP goal of

<130/80 mm Hg was historically recommended for patients with diabetes by multiple organizations. The primary evidence supporting this recommendation was from the Hypertension Optimal Treatment (HOT) study, which compared diastolic BP goals of <90 mm Hg, <85 mm Hg, or <80 mm Hg on CV outcomes.[24] Only the subgroup of patients with diabetes (*n* = 1,501) had a lower risk of major CV events in the <80 mm Hg group versus the <90 mm Hg group.

However, the NHLBI-sponsored Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD-BP) study questioned the benefit of lower BP goals for patients with diabetes.[25] The ACCORD-BP was an open-label, factorial study that randomized 4,733 patients with type 2 diabetes to a SBP of <120 mm Hg, or to a SBP <140 mm Hg. After a mean follow-up of 4.7 years, there was no significant difference in the annual rate of the primary endpoint (nonfatal MI, nonfatal stroke, or CV death) between the two groups. However, the annual incidence of the secondary end point of stroke was significantly lower with the <120 mm Hg goal, and this was the only prespecified end point that was different between the two groups.

Based on these data, the American Diabetes Association changed their recommendation to a goal BP of <140/90 mm Hg for most patients with hypertension and diabetes.[15] However, there are important limitations to ACCORD-BP that should be considered. First, ACCORD-BP was underpowered, as only half of the expected primary composite endpoint events occurred during the study. It was also a factorial study design. A recent post-hoc analysis of ACCORD-BP that examined CV outcomes for participants with CVD risk factors that would have been eligible for the SPRINT found very similar CV event rates and adverse effect rates as seen in the SPRINT.[26] Also, the evidence-based review performed for the 2017 ACC/AHA guideline found a lower risk of fatal or nonfatal stroke with lower BP goals in patients with diabetes.[19] Therefore, patients with diabetes should generally be treated to a BP of <130/80 mm Hg.

Avoiding Clinical Inertia

Although hypertension is one of the most common medical conditions, BP control rates are poor. *Clinical inertia* in hypertension is defined as an office visit for which no therapeutic move was made to lower BP in a patient with uncontrolled hypertension.[27] Clinical inertia is not the entire reason why many patients with hypertension do not achieve goal BP values. However, it is certainly a major reason that can be remedied simply through more aggressive

antihypertensive drug therapy. This strategy can include initiating, titrating, or changing drug therapy.

General Approach to Treatment

All patients with elevated blood pressure, stage 1 hypertension, and stage 2 hypertension should be engaged in lifestyle modifications. For patients with elevated blood pressure and those with stage 1 hypertension who are at low risk of ASCVD (ie, primary prevention with a 10-year ASCVD risk <10%), lifestyle modification alone is an appropriate initial treatment. The threshold when drug therapy should be started for these low-risk patients is when the BP is ≥140/90 mm Hg with a goal BP of <130/80 mm Hg. For patients with stage 1 or 2 hypertension who already have ASCVD (secondary prevention) or who have an elevated 10-year ASCVD risk ≥10% (including most patients with diabetes and most patients with CKD), the threshold for starting drug therapy is ≥130/80 mm Hg with a goal BP of <130/80 mm Hg.

6 The choice of initial antihypertensive drug therapy depends on the degree of BP elevation and presence of compelling indications (see the section "Pharmacotherapy"). A single first-line antihypertensive drug should be started as an initial therapy in most patients with newly diagnosed hypertension presenting with stage 1 hypertension. Combination drug therapy, preferably with two firstline antihypertensive drugs, should be started as an initial therapy in patients with newly diagnosed hypertension presenting with more severe BP elevation (stage 2 hypertension). This general approach to an initial therapy is outlined in **Fig. 30-2**. There are several compelling indications where specific antihypertensive drug classes have evidence showing unique benefits in patients with hypertension (see **Fig. 30-3**). Under these circumstances, selection of antihypertensive drug therapy should follow an evidence-based order.

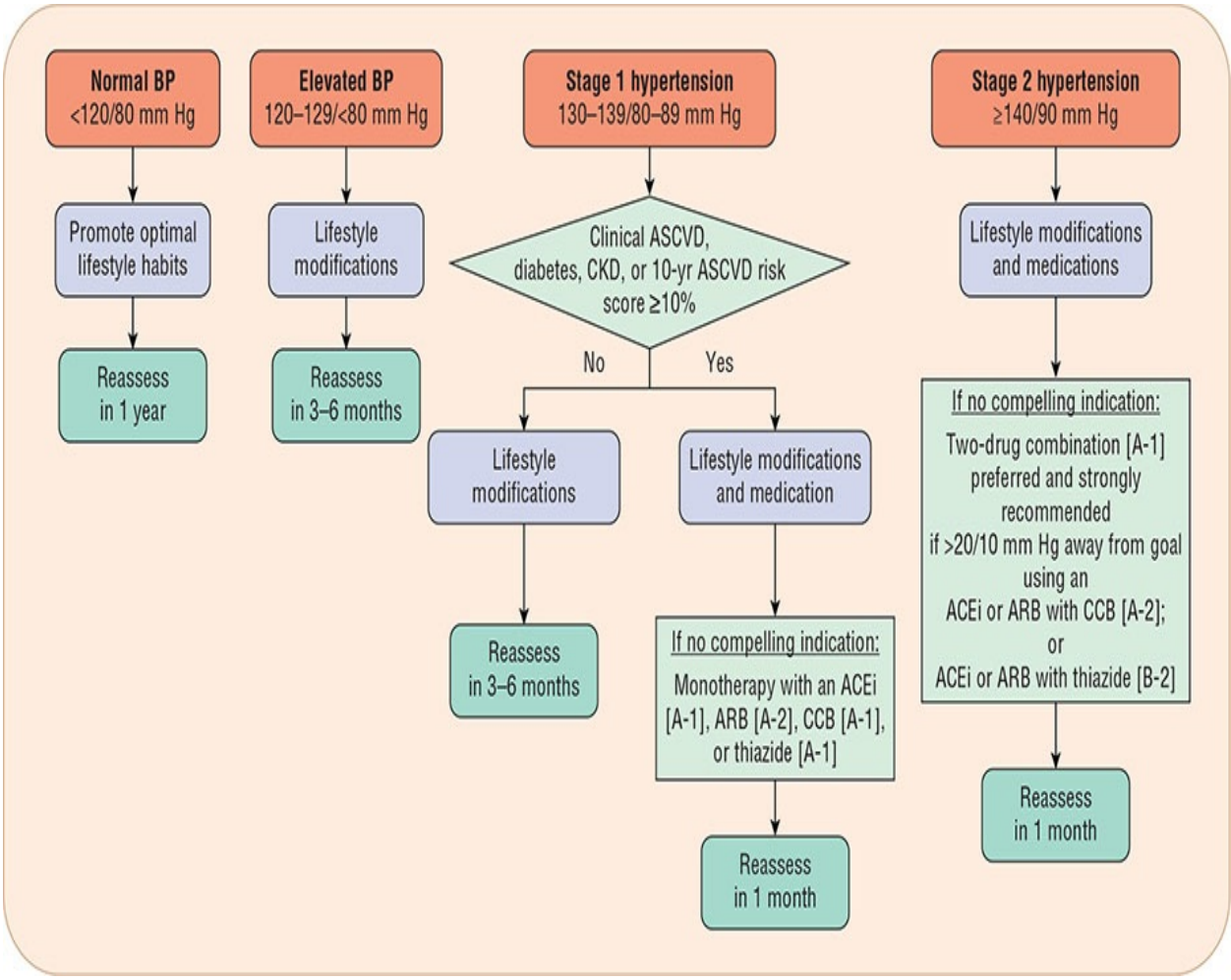


FIGURE 30-2 Algorithm for treatment of elevated BP and hypertension based on BP category at initial diagnosis. Drug therapy recommendations are graded with strength of recommendation and quality of evidence in brackets. Strength of recommendations: A, B, and C are good, moderate, and poor evidence to support recommendation, respectively. Quality of evidence: (1) evidence from more than one properly randomized controlled trial; (2) evidence from at least one well-designed clinical trial with randomization, from cohort or case-controlled studies, or dramatic results from uncontrolled experiments or subgroup analyses; (3) evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.

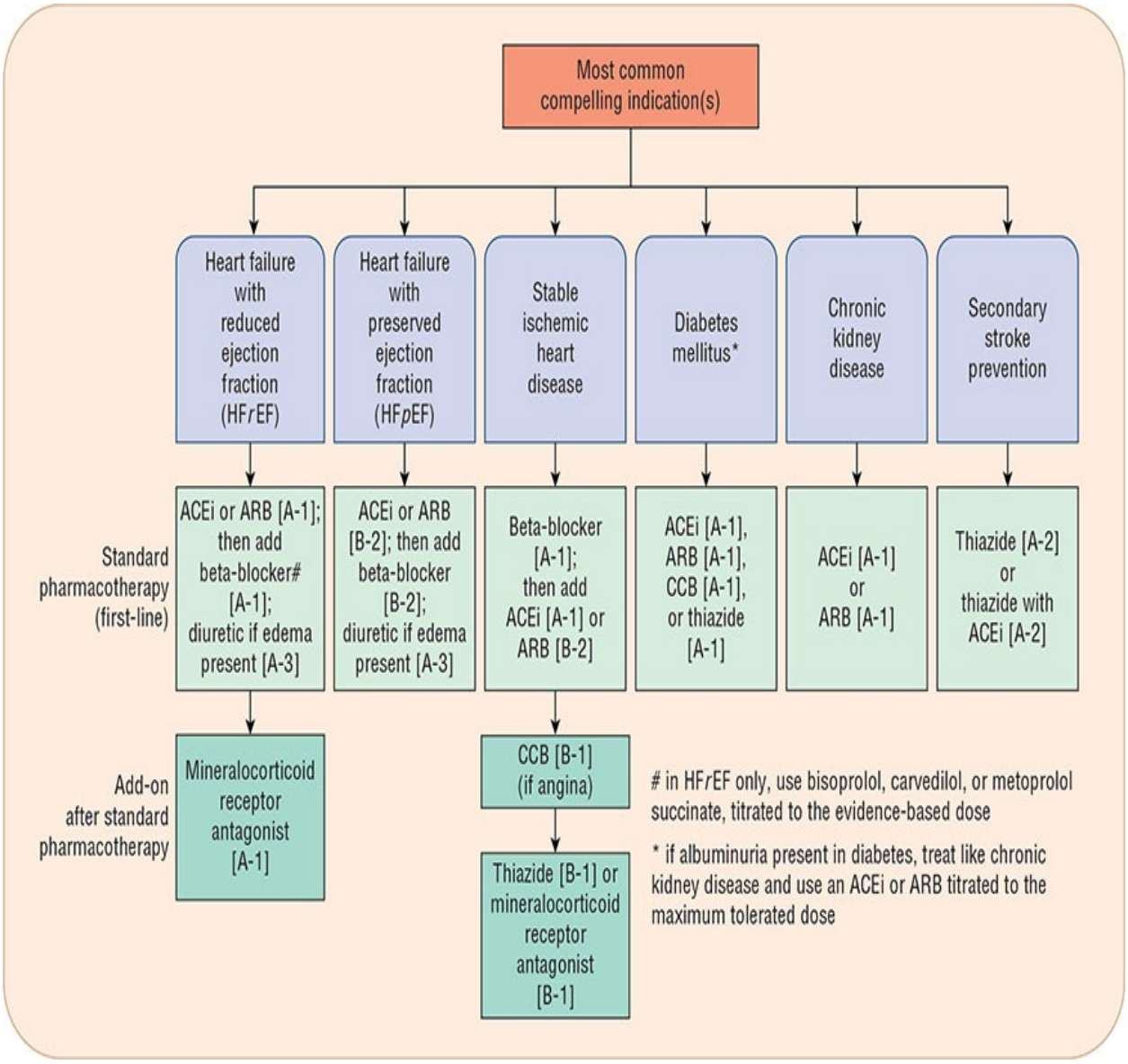


FIGURE 30-3 Compelling indications for individual drug classes. Compelling indications for specific drugs are evidence-based recommendations from outcome studies or existing clinical guidelines. The order of drug therapies serves as a general guidance that should be balanced with clinical judgment and patient response. Add-on pharmacotherapy recommendations are when additional agents are needed to lower BP to goal values. Blood pressure control should be managed concurrently with the compelling indication. Drug therapy recommendations are graded with strength of recommendation and quality of evidence in brackets. Strength of recommendations: A, B, and C are good, moderate, and poor evidence to support recommendation, respectively. Quality of evidence: (1) evidence from more than one properly randomized controlled trial; (2) evidence from at least one well-designed clinical trial with

randomization, from cohort or case-controlled analytic studies or multiple time series, or dramatic results from uncontrolled experiments or subgroup analyses; (3) evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.

Nonpharmacologic Therapy

7 All patients with elevated blood pressure and hypertension should be prescribed lifestyle modifications. However, they should never be used as a replacement for antihypertensive drug therapy for patients with hypertension who are not at goal BP. Recommended modifications that have been shown to lower BP are listed in **Table 30-4**.[1] Lifestyle modifications can provide small-to-moderate reductions in SBP. Aside from reducing BP in patients with known hypertension, strict adherence to lifestyle modification can decrease the progression to hypertension in patients with elevated BP values.

TABLE 30-4 Lifestyle Modifications to Prevent and Manage Hypertension

Modification	Recommendation	Approximate SBP Reduction (mm Hg)*	
		With Hypertension	Without Hypertension
Weight loss	Maintain normal body weight (body mass index, 18.5-24.9 kg/m^2), but aim for at least ≥1 kg weight reduction. Approximate 1 mm Hg BP reduction noted per 1 kg weight loss	5	2-3
DASH-type dietary patterns	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	11	3
Reduced salt intake	Reduce daily dietary sodium intake as much as possible, ideally to 1.5 g/day sodium (3.8 g/day sodium chloride)	5-6	2-3
Physical activity	90-150 min/wk of aerobic or dynamic resistance training, and involving moderate to vigorous intensity†	5-8 aerobic 4 dynamic	2-4 aerobic 2 dynamic
Moderation of alcohol intake	Limit consumption to ≤2 drink equivalents per day in men and ≤1 drink equivalent per day in women and lighter-weight persons‡	4	3

*Effects of implementing these modifications are time- and dose-dependent and could be greater for some patients.

†Aerobic exercise at 65%-75% heart rate reserve; dynamic resistance consisting of 6 exercises, 3 sets/exercise, 10 repetitions/set at 50%-80% of 1 rep maximum.

‡One drink equivalent is equal to 1.5 oz (~45 mL) of 80-proof distilled spirits (eg, whiskey), a 5 oz (~150 mL) glass of wine (12%), or 12 oz (~350 mL) of beer.

Source: Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.Hypertension. 2018;71(6):e13–e115.

A sensible dietary program is one that is designed to reduce weight gradually (for overweight and obese patients) and restricts sodium intake with only moderate alcohol consumption (for patients who consume alcohol). Successful implementation of dietary and lifestyle modifications by patients requires aggressive promotion by clinicians through patient education, encouragement, and continued reinforcement. Weight loss, as little as 5% of body weight, can decrease BP significantly in overweight or obese patients. Diets rich in fruits and vegetables and low in saturated fat have been shown to lower BP in patients with hypertension. Most people experience BP lowering with sodium restriction.

The Dietary Approaches to Stop Hypertension (DASH) eating plan is a diet that is rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat. It is recommended as a reasonable and feasible diet that has proven to lower BP. Intake of sodium should be minimized as much as possible, ideally to 1.5 g/day, although an interim goal of a 1 g/day reduction may be reasonable considering the challenges in achieving low sodium intake. Patients should be aware of the multiple sources of dietary sodium (eg, processed foods, soups, table salt) so that they may implement restriction. Potassium intake should be encouraged through fruits and vegetables with high content (ideally 3.5-5 g/day) in those with normal kidney function or without impaired potassium excretion. Excessive alcohol use can either cause or worsen hypertension. Patients with hypertension who drink alcoholic beverages should restrict their daily intake.

Physical activity consisting of aerobic or dynamic resistance training of 90 to 150 minutes per week (eg, 3-4 sessions per week, lasting on average 40 minutes per session) and involving moderate-to-vigorous intensity should be encouraged when possible. Studies have shown that physical activity, and in particular aerobic activity, can reduce BP, even in the absence of weight loss. Patients should consult their physicians before starting an exercise program, especially those with hypertension-associated complications.

Smoking (tobacco or other products) is not a secondary cause of essential hypertension. Therefore, smoking cessation is not a recommended strategy to control BP. However, smoking is a major, independent, modifiable risk factor for CV disease. Patients with hypertension who smoke should be counseled regarding the additional health risks that result from smoking. Moreover, the potential benefits that smoking cessation can provide should be explained to encourage cessation.

Pharmacotherapy

8 An ACEi, ARB, CCB, or a thiazide are the preferred first-line antihypertensive agents for most patients (Table 30-5).[1] These agents should be used to treat the majority of patients with hypertension because of evidence demonstrating CV event reduction. Several of these medications have subclasses where significant differences in mechanism of action, clinical use, side effects, or evidence from outcome studies exist. β-Blocker therapy should be reserved to either treat a specific compelling indication or used in combination with one or more of those mentioned above first-line antihypertensive agents for patients without a compelling indication. Other antihypertensive drug classes are considered alternative drug classes that may be used in select patients after implementing first-line agents (Table 30-6).

TABLE 30-5 Most Common First-Line and Other Antihypertensive Agents

Class	Subclass	Medication (Brand Name)	Usual Dose Range (mg/day)	Daily Frequency	Comments
ACEi		Benazepril (Lotensin)	10-40	1 or 2	May cause hyperkalemia in patients with chronic kidney disease or in those receiving a potassium-sparing diuretic, mineralocorticoid receptor antagonist, ARB, or direct renin inhibitor; can cause acute kidney injury in patients with severe bilateral renal artery stenosis or severe stenosis in artery to solitary kidney; contraindicated in pregnancy or in patients with a history of angioedema; starting dose should be reduced 50% in patients who are on a thiazide, are volume depleted, or are very elderly due to risks of hypotension
		Captopril (Capoten)	12.5-150	2 or 3	
		Enalapril (Vasotec)	5-40	1 or 2	
		Fosinopril (Monopril)	10-40	1	
		Lisinopril (Prinivil, Zestril)	10-40	1	
		Moexipril (Univasc)	7.5-30	1 or 2	
		Perindopril (Aceon)	4-16	1	
		Quinapril (Accupril)	10-80	1 or 2	
		Ramipril (Altace)	2.5-10	1 or 2	
		Trandolapril (Mavik)	1-4	1	
ARB		Azilsartan (Edarbi)	40-80	1	May cause hyperkalemia in patients with chronic kidney disease or in those receiving a potassium-sparing diuretic, mineralocorticoid receptor antagonist, ACEi, or direct renin inhibitor; can cause acute kidney injury in patients with severe bilateral renal artery stenosis or severe stenosis in artery to solitary kidney; do not cause a dry cough like an ACEi may; contraindicated in pregnancy; starting dose should be reduced 50% in patients who are on a thiazide, are volume depleted, or are very elderly due to risks of hypotension
		Candesartan (Atacand)	8-32	1 or 2	
		Eprosartan (Teveten)	600-800	1 or 2	
		Irbesartan (Avapro)	150-300	1	
		Losartan (Cozaar)	50-100	1 or 2	
		Telmisartan (Micardis)	20-40	1	
		Olmesartan (Benicar)	20-80	1	
		Valsartan (Diovan)	80-320	1	
Calcium channel blocker	Dihydropyridine	Amlodipine (Norvasc)	2.5-10	1	Do not use immediate-release nifedipine or immediate-release nicardipine; dihydropyridines are more potent arterial vasodilators than nondihydropyridines and may cause more peripheral edema; may cause reflex sympathetic discharge (tachycardia); have additional benefits in Raynaud's syndrome
		Felodipine (Plendil)	5-20	1	
		Nifedipine long-acting (Afeditab CR Adalat CC, Nifediac CC, Nifedical XL, Procardia XL)	30-90	1	
		Nisoldipine (Sular)	10-40	1	
	Nondihydropyridine	Diltiazem sustained release (Cardizem CD, Cartia XT, Dilacor XR, Diltia XT, Tiazac, Taztia XT)	120-480	1	Use extended-release products for hypertension; these agents block the A-V node, reduce heart rate, and may produce heart block, especially in combination with β-blockers; not all products are not AB rated as interchangeable on an equipotent milligram-per-milligram basis due to different release mechanisms and bioavailability; Cardizem LA, Matzim LA, and Verelan PM have delayed drug release for several hours after dosing and can provide chronotherapeutic drug delivery, but this does not have any clinical advantages; have additional benefits in patients with atrial tachyarrhythmia
		Diltiazem extended release (Cardizem LA, Matzim LA)	180-480	1 (morning or evening)	
		Verapamil sustained release (Calan SR, Isoptin SR, Verelan)	180-420	1 or 2	
		Verapamil chronotherapeutic oral drug absorption system (Verelan PM)	100-400	1 (in the evening)	
Diuretic	Thiazide	Chlorthalidone (Thalitone)	12.5-25	1	Hydrochlorothiazide is a "thiazide-type" while chlorthalidone, indapamide, and metolazone are "thiazide-like." Dose in the morning to avoid nocturnal diuresis; thiazides are more effective antihypertensives than loop diuretics in most patients; use usual doses to avoid adverse metabolic effects; hydrochlorothiazide, chlorthalidone, and indapamide are preferred; chlorthalidone is approximately 1.5 times as potent as hydrochlorothiazide; have additional benefits in osteoporosis; use with caution in patients with a history of gout
		Hydrochlorothiazide (Microzide)	12.5-50	1	
		Indapamide (Lozol)	1.25-2.5	1	
		Metolazone (Zaroxolyn)	2.5-10	1	
	Loop	Bumetanide (Bumex)	0.5-4	2	Dose in the morning and late afternoon (when twice daily) to avoid nocturnal diuresis; higher doses may be needed for patients with severely decreased glomerular filtration rate or HF; preferred over thiazides in patient with severe kidney dysfunction and resistant hypertension
		Furosemide (Lasix)	20-80	2	
		Torsemide (Demadex)	5-10	1	
	Potassium sparing	Amiloride (Midamor)	5-10	1 or 2	Weak diuretics that are used in combination with a thiazide to minimize hypokalemia; do not significantly lower BP unless used with a thiazide; should be reserved for patients experiencing diuretic-induced hypokalemia; avoid in patients with severe chronic kidney disease (estimated glomerular filtration rate <30 mL/min/1.73 m²); may cause hyperkalemia, especially in combination with a mineralocorticoid receptor antagonist, ACEi, ARB, direct renin inhibitor, or potassium supplements
		Amiloride/hydrochlorothiazide (Moduretic)	5-50	1	
		Triamterene (Dyrenium)	50-100	1 or 2	
		Triamterene/hydrochlorothiazide (Dyazide, Maxide)	37.5-75/25-50	1	
	Mineralocorticoid receptor antagonist	Eplerenone (Inspra)	50-100	1 or 2	Dose in the morning and late afternoon (when twice daily) to avoid nocturnal diuresis; eplerenone contraindicated in patients with an estimated creatinine clearance <50 mL/min (0.84 mL/s), elevated serum creatinine (>1.8 mg/dL [159 µmol/L] in women, >2 mg/dL [177 µmol/L] in men), or type 2 diabetes with albuminuria; often used as an add-on therapy in resistant hypertension; avoid in patients with severe chronic kidney disease (estimated glomerular filtration rate <30 mL/min/1.73 m²); may cause hyperkalemia, especially in combination with an ACEi, an ARB, direct renin inhibitor, or potassium supplements
		Spironolactone (Aldactone, CaroSpir)	25-50	1 or 2	

Class	Subclass	Medication (Brand Name)	Usual Dose Range (mg/day)	Daily Frequency	Comments
β-blocker	Cardio-selective	Atenolol (Tenormin)	25-100	1 or 2	Abrupt discontinuation may cause rebound hypertension; have additional benefits in patients with atrial tachyarrhythmia or preoperative hypertension; in general, cardioselective agents inhibit β_1-receptors at low-to-moderate dose, higher doses may also block β_2-receptors (especially metoprolol); additional vasodilation with nebivolol does not result in more orthostatic hypotension; nonselective agents inhibit β_1- and β_2-receptors at all doses, can exacerbate asthma, and have additional benefits in patients with essential tremor, migraine headache, portal hypertension, thyrotoxicosis. Agents with intrinsic sympathomimetic activity (acebutolol and pindolol) partially stimulate β-receptors while blocking against additional stimulation; no role in the management of hypertension and are contraindicated in patients with stable ischemic heart disease. Mixed α- and β-blockers produce vasodilation and have more orthostatic hypotension
		Betaxolol (Kerlone)	5-20	1	
		Bisoprolol (Zebeta)	2.5-10	1	
		Metoprolol tartrate (Lopressor)	100-200	2	
		Metoprolol succinate extended release (Toprol XL)	50-200	1	
		Nebivolol (Bystolic)	5-20	1	
	Nonselective	Nadolol (Corgard)	40-120	1	
		Propranolol (Inderal)	160-480	2	
		Propranolol long acting (Inderal LA, Inderal XL, InnoPran XL)	80-320	1	
		Timolol (Blocadren)	10-40	1	
	Mixed α- and β-blockers	Carvedilol (Coreg)	12.5-50	2	
		Carvedilol phosphate (Coreg CR)	20-80	1	
		Labetalol (Normodyne, Trandate)	200-800	2	

TABLE 30-6 Alternative Antihypertensive Agents

Class	Medication (Brand Name)	Usual Dose Range (mg/day)	Daily Frequency	Comments
α_1-Blocker	Doxazosin (Cardura)	1-8	1	Give first dose at bedtime; patients should rise from sitting or lying down slowly to minimize risk of orthostatic hypotension; additional benefits in men with benign prostatic hyperplasia
	Prazosin (Minipress)	2-20	2 or 3	
	Terazosin (Hytrin)	1-20	1 or 2	
Direct renin inhibitor	Aliskiren (Tekturna)	150-300	1	May cause hyperkalemia in patients with chronic kidney disease and diabetes or in those receiving a potassium-sparing diuretic, mineralocorticoid receptor antagonist, ACEi, or ARB; may cause acute kidney failure in patients with severe bilateral renal artery stenosis or severe stenosis in artery to solitary kidney; do not use in pregnancy
Central α_2-agonist	Clonidine (Catapres)	0.1-0.8	2	Abrupt discontinuation may cause rebound hypertension; most effective if used with a thiazide to diminish fluid retention; clonidine patch is replaced once per week
	Clonidine patch (Catapres-TTS)	0.1-0.3	1 weekly	
	Methyldopa (Aldomet)	250-1,000	2	
Direct arterial vasodilator	Minoxidil (Loniten)	10-40	1 or 2	Should be used with a thiazide and β-blocker to diminish fluid retention and reflex tachycardia
	Hydralazine (Apresoline)	20-100	2 to 4	

Historical Evidence Supporting Thiazide Therapy

Landmark placebo-controlled clinical trials demonstrate that thiazide therapy irrefutably reduces the risk of CV morbidity and mortality. The Systolic Hypertension in the Elderly Program (SHEP),[9] Swedish Trial in Old Patients with Hypertension (STOPHypertension),[8] and Medical Research Council (MRC) studies showed significant reductions in stroke, MI, all-cause CV disease, and mortality with thiazide-based therapy versus placebo. These trials used β-blockers as an add-on therapy for BP control. Agents such as an ACEi, an ARB, and a CCB were not available at the time of these studies. However, subsequent clinical trials have compared these antihypertensive agents with a thiazide and have demonstrated similar long-term benefits.[28–34]

The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) The results of the ALLHAT were the deciding evidence that the JNC7 used to justify thiazide therapy as a first-line therapy.[28] It was designed to test the hypothesis that newer antihypertensive agents (an α-blocker, an ACEi, or a dihydropyridine CCB) would be superior to thiazide-based therapy. The primary objective was to compare the combined end point of fatal CHD and nonfatal MI. Other hypertension-related complications (eg, HF, stroke) were evaluated as secondary end points. This was the largest prospective hypertension trial ever conducted and included 42,418 patients aged 55 and older with hypertension and one additional CV risk factor. This double-blind trial randomized patients to chlorthalidone-, amlodipine-, doxazosin-, or lisinoprilbased therapy for a mean of 4.9 years.

The doxazosin treatment arm was terminated early when a significantly higher risk of HF versus chlorthalidone was observed.[35] The other arms were continued as scheduled and no significant differences in the primary endpoint were seen between the chlorthalidone and lisinopril or amlodipine treatment groups at the end of the trial. However, chlorthalidone had statistically fewer secondary endpoints than amlodipine (HF) and lisinopril (combined CV disease, HF, and stroke). The study conclusions were that chlorthalidonebased therapy was superior in preventing one or more major forms of CV disease and was less expensive than amlodipineor lisinoprilbased therapy.

The ALLHAT was designed as a superiority study with the hypothesis that amlodipine, doxazosin, and lisinopril would be better than chlorthalidone.[36] It did not prove this hypothesis. Several subgroup analyses of specific populations (eg, black patients, CKD, diabetes) from the ALLHAT have been conducted to assess response in certain unique patient populations.[37–39] Surprisingly, none of

these analyses demonstrated superior CV event reductions with lisinopril or amlodipine versus chlorthalidone. Overall, thiazides remain unsurpassed in their ability to reduce CV morbidity and mortality in most patients.

Like the JNC7 guideline, the 2017 ACC/AHA high BP guideline recommends a thiazide as a first-line therapy for most patients.[1] However, an ACEi, an ARB, and a CCB are also comparable first-line options. Contrary to the historical preference to use a thiazide as preferred for treating most patients with hypertension, they are simply one of four first-line drug therapy options. Figure 30-2 displays the algorithm for the treatment of hypertension and highlights four first-line antihypertensive options for patients without a compelling indication for a specific drug class.

ACEi, ARB, and CCB as First-Line Agents

Clinical trial data cumulatively demonstrate that ACEi-, CCB-, and ARB-based antihypertensive therapy reduce CV events. These agents are first-line options for patients without a compelling indication. The Blood Pressure Lowering Treatment Trialists' Collaboration has evaluated the incidence of major CV events and death among different antihypertensive drug classes from 29 major randomized trials in 162,341 patients.[40] In placebo-controlled trials, major CV events were significantly lower with ACEiand CCB-based regimens versus placebo. Although there were minor differences in the incidence of certain CV events in some comparisons, there were no differences in total major CV events when an ACEi, a CCB, or a thiazide was compared with each other. In studies evaluating ARB-based therapy to control regimens, the incidence of major CV events was lower with ARB-based therapy. However, the control regimens used in these comparisons included both antihypertensive drug therapies and placebo. These results were largely consistent with the network meta-analysis conducted for the 2017 ACC/AHA guideline, which found that an ACEi, an ARB, a CCB, and a thiazide were all similar as first-line treatment for hypertension.[19]

Data from meta-analyses that incorporate high-quality randomized controlled trials provide more robust data than any single trial alone. High-quality meta-analyses provide clinically useful data that support using ACEi-, CCB-, or ARB-based treatment for hypertension as first-line antihypertensive agent. Clinicians should use meta-analyses data as supporting evidence when selecting a firstline antihypertensive regimen for hypertension in most patients.

Other major consensus guidelines recommend several firstline drug therapy options for treating hypertension in most patients. The 2013 European Society of Hypertension/European Society of Cardiology guidelines and the 2011 UK's

National Institute for Health and the Clinical Excellence guidelines recommend an ACEi, an ARB, a CCB, or a thiazide as first-line treatment.[41,42] The European Society of Hypertension/European Society of Cardiology guidelines are founded on the principle that CV risk reduction is a function of BP control that is largely independent of specific antihypertensives.[41] The UK guideline stratifies patients based on age and race; they recommend an ACEi or ARB first-line for patients under the age of 55 years, and a CCB first-line for patients age 55 years or older or for black patients.[42]

9 **β-Blocker Versus First-Line Agents** Clinical trial data and meta-analyses cumulatively suggest that treatment with a β-blocker may not reduce CV events to the extent that an ACEi, an ARB, a CCB, or particularly a thiazide does.[1] In the systematic review and network analysis conducted for the 2017 ACC/AHA guideline, β-blockers were less effective for the prevention of stroke and CV events than diuretics.[19]

Meta-analyses data evaluating β-blockers and their ability to reduce CV events have limitations. Most studies that were included in these analyses used atenolol as the β-blocker studied. Therefore, it is possible that atenolol is inferior and is the only β-blocker that does not reduce CV events as much as other first-line antihypertensive drug classes. A recent network meta-analysis comparing the effects of different β-blockers found a decreased risk of mortality and CV events with lipophilic agents (metoprolol, propranolol, and oxprenolol) compared to hydrophilic agents (atenolol).[43] However, due to challenges in the interpretation of meta-analyses of β-blockers compared to other first-line agents (eg, trials conducted at different times, use of different beta-blockers, changes in the efficacy of agents, etc.), most guideline recommendations do not differentiate between the β-blocker drug class.[41,42] In the absence of a compelling indication, the 2011 UK guideline recommends a β-blocker as a fourth-line therapy, only after other first-line antihypertensive agents (ACEi or ARB, CCB, thiazide) have been used.[42] These findings also call into question the validity of results from prominent prospective, controlled clinical trials evaluating antihypertensive drug therapy that used β-blocker–based therapy, especially atenolol, as the primary comparator.[30,32] These studies used once-daily atenolol, which in addition to being hydrophilic, may have been inadequately dosed based on the short half-life of this agent.

β-Blocker–based antihypertensive therapy does not increase the risk of CV events; β-blocker–based therapy reduces the risk of CV events compared with no antihypertensive therapy. Using a β-blocker as a first-line antihypertensive agent

is an option when an ACEi, an ARB, a CCB, or a thiazide cannot be used. β-Blockers also have an important role as an add-on therapy to first-line agents to reduce BP in patients with hypertension but without compelling indications.

Many of the clinical trials included in the meta-analyses that suggest β-blocker–based therapy may not reduce CV events as well as these other agents, used atenolol dosed once daily.[44] Atenolol has a half-life of 6 to 7 hours and is nearly always dosed once daily, while immediate-release forms of carvedilol and metoprolol have half-lives of 6 to 10 and 3 to 7 hours, respectively, and are dosed at least twice daily.[44] It is also, hydrophilic, which may not penetrate the brain and cell membrane as easily as lipophilic agents, and has been shown to be inferior to lipophilic agents (metoprolol, propranolol, and oxprenolol).[43] Therefore, it is possible that these findings might only apply to atenolol, particularly dosed once daily instead of twice daily. Based on available evidence, metoprolol succinate or carvedilol are the preferred β-blockers if a β-blocker is to be used.

Patients with Compelling Indications

10 Compelling indications represent specific comorbid conditions where evidence from clinical trials supports using specific antihypertensive classes to treat both the compelling indication and hypertension. Antihypertensive medication recommendations typically consist of combination drug therapy (see Fig. 30-3). Data from clinical trials have demonstrated a reduction in CV morbidity and/or mortality that justify use for patients with hypertension and with such a compelling indication.

Heart Failure with Reduced Ejection Fraction Five drug classes have compelling indications for HF with reduced ejection fraction (HF*r*EF), also known as systolic HF or left ventricular dysfunction.[45] The primary physiologic abnormality in HF*r*EF is decreased CO resulting from a decreased left ventricular ejection fraction. An evidence-based pharmacotherapy regimen for HF*r*EF, called *guideline-directed medical therapy*, consists of three to four drugs: an ACEi or ARB plus diuretic therapy, followed by the addition of an evidence-based β-blocker (ie, bisoprolol, carvedilol, metoprolol succinate) and possibly a mineralocorticoid receptor antagonist.

Evidence from clinical trials shows that ACEi therapy significantly modifies disease progression by reducing morbidity and mortality. Although HF*r*EF was the primary disease in these studies, ACEi therapy will also control BP in these patients with concomitant hypertension. An ARB is an acceptable alternative for

patients who cannot tolerate an ACEi. An ACEi or ARB should be started using a low dose in HF*r*EF, especially in patients with an acute exacerbation of HF. Acute HF exacerbation induces a compensatory highrenin condition, so starting an ACEi or ARB under these conditions can cause a pronounced first-dose effect and possible orthostatic hypotension.

Diuretics are a component of standard pharmacotherapy, primarily to provide symptomatic relief of edema by inducing diuresis. Loop diuretics are often needed, especially for patients with more advanced HF and/or CKD. However, some patients with well-controlled HF and without significant CKD may be managed with a thiazide.

β-Blocker therapy modifies disease in HF*r*EF and is a component of standard treatment for these patients. For patients on an initial regimen of a diuretic with an ACEi or ARB, add-on β-blocker therapy has been shown to reduce CV morbidity and mortality.[46] It is of paramount importance that β-blockers be dosed appropriately due to the risk of inducing an acute exacerbation of HF. They must be started in very low doses (much lower than that used to treat hypertension), and titrated slowly to high doses based on tolerability. Bisoprolol, carvedilol, and metoprolol succinate are the only β-blockers that are proved to be beneficial in HF*r*EF.

After implementation of a standard three-drug regimen (diuretic, ACEi or ARB, and evidence-based β-blocker), other agents may be added to further reduce CV morbidity and mortality, and reduce BP if needed. The addition of a mineralocorticoid receptor antagonist (e.g. spironolactone) can reduce CV morbidity and mortality in HF*r*EF.[46] For patients self-described as African Americans, addition of a fixed-dose combination of isosorbide dinitrate and hydralazine to the standard three-drug regimen (diuretic, ACEi or ARB, and evidence-based β-blocker) is a recommended option to improve CV outcomes.[45]

Heart Failure with Preserved Ejection Fraction Approximately 50% of patient with HF have a preserved ejection fraction (HF*p*EF). In HF*p*EF, patients have signs and symptoms of HF such as dyspnea, fatigue, and possibly edema, but they have a preserved left ventricular ejection fraction (≥50%).

Unlike interventions using GDMT in HF*r*EF that have been shown to decrease morbidity and mortality in HF, trials using the same medications in HF*p*EF have not shown similar benefits.[46] Therefore, treatment should be targeted at any underline symptoms, appropriate management of any underlying coronary artery disease, and attainment of goal BP to prevent progression of HF. Patients should use a β-blocker or an ACEi or ARB for treatment of

hypertension, but if signs and symptoms of edema are present, they should receive a diuretic.[1]

Stable Ischemic Heart Disease Chronic stable angina and a history of acute coronary syndrome (unstable angina or acute MI) are forms of stable ischemic heart disease (aka, coronary artery disease).[1] These are the most common forms of hypertension-associated complications. Patients with ischemic heart disease are at high risk for a CVD event.

β-Blocker therapy has been a standard of care for treating patients with stable (and unstable) ischemic heart disease and hypertension for decades. β-Blockers are first-line therapy in stable ischemic heart disease and can reduce BP and improve angina symptoms by decreasing myocardial oxygen consumption and demand.[1] They also decrease cardiac adrenergic stimulation and have been shown in clinical trials to reduce the risk of a subsequent MI and sudden cardiac death. β-Blocker therapy seems to be most effective in reducing the risk of CV events in patients with recent MI and/or ischemic symptoms. While data are available that indicates that the long-term risk of CV events and mortality may not be reduced with β-blocker therapy in patients with very stable coronary artery disease (ie, do not have ischemic symptoms or have a distant history of MI),[47] β-blockers should be used for treatment of hypertension in patients with stable ischemic heart disease.[1] An ACEi (or an ARB as an alternative) has been shown to improve cardiac remodeling and cardiac function and to reduce CV events in stable ischemic heart disease as an add-on to a β-blocker.

A long-acting nondihydropyridine CCB is an alternative to a β-blocker (diltiazem and verapamil) in stable ischemic heart disease.[48] The International Verapamil–Trandolapril Study (INVEST) demonstrated no difference in CV risk reduction when β-blocker– based therapy was compared with nondihydropyridine CCB-based treatment in this population.[49] Nonetheless, the preponderance of data is with β-blockers, and they remain the therapy of choice.[1,48]

A dihydropyridine CCB (eg, amlodipine, felodipine) is recommended as an add-on therapy in stable ischemic heart disease patients who have ongoing ischemic symptoms (aka, angina or chest pain).[48] CCBs (especially nondihydropyridine CCBs) and β-blockers provide anti-ischemic effects; they lower BP and reduce myocardial oxygen demand in patients with hypertension and stable (and unstable) ischemic heart disease. However, cardiac stimulation may occur with dihydropyridine CCBs (particularly immediate release formulations) or β-blockers with intrinsic sympathomimetic activity (ISA),

making these agents less desirable. Moreover, β-blockers with ISA should be avoided due to these deleterious effects.

Once ischemic symptoms are controlled with β-blocker and/or CCB therapy, other antihypertensive drugs can be added to provide additional CV risk reduction. Clinical trials have demonstrated that the addition of an ACEi further reduces CV events in patients with stable ischemic heart disease.[48] ARB therapy may provide similar benefits but have not been as extensively studied as ACEi therapy. Therefore, in stable ischemic heart disease, an ARB is generally considered an alternative to an ACEi. Thiazides can be added after that to provide additional BP lowering and to reduce CV risk further. However, thiazides do not provide anti-ischemic effects.

Diabetes Mellitus The primary cause of mortality in patients with diabetes is CV disease, and hypertension management is an important risk reduction strategy.[1] All four first-line antihypertensive agents (ACEi, ARB, CCB, thiazides) have been shown to reduce CV events in patients with diabetes (see Fig. 30-3).[1] The evidence-based review performed for the 2017 ACC/AHA guideline found no difference in all-cause mortality, CV mortality, HF, or stroke between ACEi-, ARB-, CCB-, and thiazide-based regimens in patients with diabetes.[19]

Traditionally, an ACEi or ARB was considered as a preferred antihypertensive agent for patients with diabetes.[2] The reasons for this were that pharmacologically both of these agents should provide nephroprotection due to vasodilation in the efferent arteriole of the kidney. Moreover, ACEi therapy has strong data demonstrating CV risk reduction in patients with established forms of heart disease. Evidence from clinical studies have demonstrated reductions in both CV risk (mostly with an ACEi) and reduction in risk of progressive kidney dysfunction (mostly with ARBs) in patients with diabetes.[15,50] However, data indicate that an ACEi or ARB does not confer significantly better CV risk reduction compared to CCBs, thiazides, or β-blockers in patients with diabetes.[51] In addition, the risk of kidney disease progression is low in absence of albuminuria (urine albumin-to-creatinine ratio ≥30 mg/g [3.4 mg/mmol creatinine]),[15] and many of the studies evaluating the ability of an ACEi or ARB to slow progression of kidney dysfunction were placebo controlled.[51] Therefore, an ACEi or ARB is recommended similarly to a CCB or thiazide in patients with diabetes and hypertension that do not have persistent albuminuria.[15]

After first-line antihypertensives (ACEi, ARB, CCB, thiazide), a β-blocker is a useful add-on therapy for BP control for patients with diabetes, or to treat

another compelling indication (eg, stable ischemic heart disease). A β-blocker (especially nonselective agents) can possibly mask the signs and symptoms of hypoglycemia in patients with tightly controlled diabetes because most of the symptoms of hypoglycemia (eg, tremor, tachycardia, and palpitations) are mediated through the sympathetic nervous system. Sweating, a cholinergically mediated symptom of hypoglycemia, still occurs during a hypoglycemic episode despite β-blocker therapy. Patients may also have a delay in hypoglycemia recovery time because compensatory recovery mechanisms need the catecholamine inputs that are antagonized by β-blocker therapy. Finally, unopposed α-receptor stimulation during the acute hypoglycemic recovery phase (due to endogenous epinephrine release intended to reverse hypoglycemia) may result in acutely elevated BP due to vasoconstriction. Despite these potential problems, β-blockers can be safely used for patients with diabetes.

Based on the weight of all evidence, any first-line agent can be used for controlling hypertension for patients with diabetes in the absence of albuminuria. Regardless of what agent is initially chosen, most patient will require combination therapy, which typically will include an ACEi or ARB with a CCB or thiazide.

Chronic Kidney Disease Hypertension can damage the renal tissue (parenchyma) and/or the renal arteries.[16] CKD in patients with hypertension initially presents as moderately increased albuminuria (urine albumin-to-creatinine ratio 30 to 299 mg/g [3.4 to 34 mg/mmol creatinine] on a spot urine sample or ≥30 mg albumin in a 24-hour urine collection) that can progress to overt kidney failure. The rate of kidney function deterioration is accelerated when both hypertension and diabetes are present. Patients with significant CKD (eg, GFR <60 mL/min/1.73 m^2 and/or albuminuria) have increased risk of CV disease and further progression to severe CKD.[1] BP control can slow the decline in kidney function and reduce the risk of a CV event in patients with CKD.

In addition to lowering BP, ACEi and ARB therapies can reduce intraglomerular pressure, which can theoretically provide additional benefits by further reducing the decline in kidney function. ACEi or ARB therapy has been shown to slow progression of CKD in patients with diabetes[17,50] and those without diabetes.[52] It is difficult to differentiate whether the kidney protection benefits are from RAAS blockade versus BP lowering. A meta-analysis failed to demonstrate any unique long-term kidney protective effects of RAAS-blocking drugs compared with other antihypertensive drugs, suggesting that benefits may be attributed to BP lowering.[53] Moreover, a subgroup analysis of patients from

the ALLHAT stratified by different baseline GFR values also did not show a difference in long-term outcomes with chlorthalidone versus lisinopril among patients with significant CKD.[37]

Patients may experience a rapid and profound drop in BP or acute kidney injury when initially starting an ACEi or ARB. The potential to produce acute kidney injury is particularly problematic in patients with significant bilateral renal artery stenosis or a solitary functioning kidney with stenosis. Patients with renal artery stenosis are usually older, and this condition is more common in patients with diabetes or those who smoke. Patients with renal artery stenosis do not always have evidence of kidney disease unless specific tests are performed. Starting with low dosages and evaluating serum creatinine soon after starting either an ACEi or ARB can minimize this risk.

Secondary Stroke Prevention Ischemic stroke (not hemorrhagic stroke) and transient ischemic attack (TIA) are considered hypertension-associated complications. More than two-thirds of patients who have had an ischemic stroke or TIA have hypertension.[1] Achieving goal BP values in patients who have experienced an ischemic stroke is considered a primary modality to reduce the risk of a second stroke or TIA. A thiazide, either in combination with an ACEi or as monotherapy, is an evidence-based antihypertensive regimen for patients with a history of stroke or transient ischemic attack.[1,54,55] ARB-based therapy has also been studied in this population.[56,57] Antihypertensive drug therapy should only be implemented after patients have stabilized following an acute cerebrovascular event, typically a few days after the event.[1] Moreover, the threshold for starting antihypertensive drug therapy in patients with a history of stroke is when BP is above 140/90 mm Hg.[1] Once antihypertensive therapy is initiated, these patients should be treated to a goal of <130/80 mm Hg.

Alternative Drug Treatments

It is sometimes necessary to use other agents such as a direct renin inhibitor, an α-blocker, a central α_2-agonist, an adrenergic inhibitor, or an arterial vasodilator in some patients. Although these agents are effective in lowering BP, they either do not have convincing evidence showing reduced morbidity and mortality in hypertension or have a high incidence of adverse effects that significantly hinders tolerability. Alternative agents are generally reserved for patients with resistant hypertension or as an add-on therapy with multiple other first-line antihypertensive agents.

Special Populations

Selection of drug therapy should follow the recommendations provided by evidence-based guidelines, which are summarized in Figs. 30-2 and 30-3.[1] These should be maintained as the guiding principles of drug therapy. However, there are some patient populations where the approach to drug therapy may be slightly altered or utilize recommended agents using tailored dosing strategies. In some cases, this is because other agents have unique properties that benefit a coexisting condition, but may not be based on evidence from outcome studies in hypertension.

Hypertension in Older People Hypertension often presents as isolated systolic hypertension in older patients.[1] Epidemiologic data indicate that CV morbidity and mortality are more directly correlated to SBP than to DBP for patients aged 50 and older. This population is also at high risk for hypertension-associated complications.[1] Although several placebo-controlled trials have specifically demonstrated risk reduction in this population, many older people with hypertension are either not treated or treated but not to goal BP.

The SHEP was a landmark double-blind, placebo-controlled trial that evaluated chlorthalidone-based treatment for isolated systolic hypertension.[9] A 36% reduction in total stroke, a 27% reduction in coronary artery disease, and 55% reduction in HF were demonstrated versus placebo. The Systolic Hypertension in Europe (Syst-Eur) trial was another placebo-controlled trial that evaluated treatment with a long-acting dihydropyridine CCB.[10] Treatment resulted in a 42% reduction in stroke, 26% reduction in coronary artery disease, and 29% reduction in HF. These data demonstrate reductions in CV morbidity and mortality in older patients with isolated systolic hypertension, especially with thiazides and long-acting dihydropyridine CCBs.

The “very elderly” population (80 years of age and older) were underrepresented in the SHEP and Syst-Eur studies. Historically, this population often was not treated to goal either because of a fear of side effects or because of limited evidence demonstrating benefit. However, the Hypertension in the Very Elderly Trial (HYVET) provided definitive evidence that antihypertensive drug therapy provides significant clinical benefits in these patients.[58] The HYVET was a prospective controlled clinical trial that randomized patients 80 years and older with hypertension to placebo or antihypertensive drug therapy. It was stopped early after a median of only 1.8 years because the incidence of death was 21% higher in placebo-treated patients. Based on these results, hypertension should be treated in patients age 80 years and older.

Thiazide or β-blocker therapy has been compared with either an ACEi or CCB in older patients with either systolic hypertension, diastolic hypertension, or both in the Swedish Trial in Old Patients with Hypertension-2 (STOP-2) study.[59] In this trial, no significant differences in the primary CV event endpoint were seen between conventional drugs and either an ACEi or CCB. These data support that overall treatment may be more important than specific antihypertensive agents in this population.

Older patients are more sensitive to volume depletion and sympathetic inhibition than younger patients. This may lead to orthostatic hypotension (see the next section). In older patients, this can increase the risk of falls due to the associated dizziness. Centrally acting agents and α_1-blockers should generally be avoided or used with caution in older patients because they are frequently associated with dizziness and orthostatic hypotension. First-line antihypertensives provide significant benefits and can safely be used in older patients, especially those age 80 years and older, but smaller-thanusual initial doses must be used for initial therapy.

The most appropriate BP goal for older patients has been a matter of significant debate. In 2003 the JNC7 recommended the same general BP goal of <140/90 mm Hg regardless of age.[2] However, in 2014 the panel members appointed to the Eighth Joint National Committee (JNC 8) recommended a less strict BP goal of <150/90 mm Hg in patients older than 60 years.[60] This recommendation sparked substantial disagreement and debate, with panel members appointed to the JNC8 who disagreed with this recommendation publishing a “minority view” citing concerns with the impact on public health and interpretation of the evidence.[61]

The best evidence for lower BP goals in older patients comes from the SPRINT-Senior trial, which was a prespecified subanalysis of patients 75 years and older who were enrolled in the SPRINT study.[62] In this cohort, older (mean age 79.9 years), communitydwelling patients without dementia and an expected life expectancy of 3 or more years who were treated to a SBP of <120 mm Hg compared a SBP of <140 mm Hg experienced a 34% reduced risk of the primary composite outcome of CVD and 33% reduced risk of all-cause mortality. While the lower SBP goal was associated with an increased risk of hypotension and electrolyte abnormalities, there was no difference in serious adverse events. The benefits of lower BP goals in older patients significantly outweighed the risk, though careful monitoring is essential to ensure safe medication use. A recent meta-analysis examining the risks and benefits of lower BP compared to a “relaxed” goal of <150 mm Hg found similar results.[63] Therefore, based on the

totality of evidence, older, ambulatory patients should be treated to a SBP goal of <130 mm Hg.[1]

The treatment of hypertension in older patients should follow the same principles that are outlined for general care of hypertension. However, in patients with multiple comorbidities or disease states, or in whom the benefit of therapy may be less established (eg, nursing home resident, dementia, etc.), the risks and benefits of using a lower BP goal should be considered, taking into account patient preference and using a team-based approach. In these patients, a relaxed SBP goal of at least <150 mm Hg (<140 mm Hg in some patients if tolerated) should be considered appropriate. Also, while the general approach to treatment is similar compared to younger patients, initial drug doses may be lower, and dosage titrations over a longer period are usually needed to minimize the risk of hypotension.

11 **Patients at Risk for Orthostatic Hypotension** Orthostatic hypotension is a significant drop in BP when standing and can be associated with dizziness and/or fainting. It is defined as a SBP decrease of >20 mm Hg or DBP decrease of >10 mm Hg when changing from supine to standing.[1] The risk of orthostatic hypotension is increased in older patients (especially those with isolated systolic hypotension, or those age 80 years or older) and those with long-standing diabetes, severe volume depletion, baroreflex dysfunction, autonomic insufficiency (eg, diabetes), and concomitant use of medications that cause venodilation (α-blockers, mixed α-/β-blockers, nitrates, and phosphodiesterase inhibitors). For patients with these risk factors, antihypertensive agents, especially a thiazide, an ACEi, or an ARB should be started in low doses.

Hypertension in Children and Adolescents Detecting hypertension in children requires customized evaluation. Hypertension is defined as SBP or DBP that is >95th percentile for sex, age, and height on at least three occasions for children.[64] BP values between the 90th and 95th percentile, or >120/80 mm Hg in adolescents, is considered elevated BP. Hypertensive children often have a family history of high BP, and many are overweight or obese, predisposing them to insulin resistance and associated CV risk. Unlike hypertension in adults, secondary hypertension is more common in children and adolescents. An appropriate workup for secondary causes is required if elevated BP is identified. Kidney disease (eg, pyelonephritis, glomerulonephritis) is the most common cause of secondary hypertension in children.

Nonpharmacologic treatment (eg, weight loss if overweight or obese, healthy diet, sleep, physical activity) is the cornerstone of therapy for essential

hypertension in children.[64] The goal is to reduce the BP to <90th percentile for sex, age, and height and <130/80 mm Hg in adolescents age 13 years and older.[64] An ACEi, an ARB, a β-blocker, a CCB, and a thiazide are all acceptable choices in children and have data supporting their use.[64] If an ACEi or ARB is to be used in adolescents girls of childbearing age, it is important to counsel regarding the risk of fetal injury and death since these agents are teratogenic and an alternative antihypertensive may be considered. As with adults, selection of initial agents should be based on the presence of compelling indications or concurrent conditions that may warrant their use.

Pregnancy Hypertension during pregnancy is a major cause of maternal and neonatal morbidity and mortality.[1] Hypertension during pregnancy is categorized as preeclampsia-eclampsia, chronic hypertension (of any cause), chronic hypertension superimposed preeclampsia, and gestational hypertension.[65] *Preeclampsia* is defined as hypertension (elevated BP ≥140/90 mm Hg on more than two occasions at least 4 hours apart after 20 weeks' gestation or ≥160/110 mm Hg confirmed within a short interval) in association with thrombocytopenia, impaired liver function, new-onset renal insufficiency, pulmonary edema, or new-onset cerebral or visual disturbances. It can lead to life-threatening complications for both mother and fetus. *Eclampsia*, the onset of convulsions in preeclampsia, is a medical emergency. Chronic hypertension is hypertension that predates pregnancy; superimposed preeclampsia is chronic hypertension associated with preeclampsia. *Gestational hypertension* is defined as new-onset hypertension arising after 20 weeks of gestation in the absence of proteinuria or other systemic findings (eg, thrombocytopenia, renal insufficiency, pulmonary edema, cerebral or visual disturbances).

It is controversial whether treating mild-to-moderate hypertension in pregnancy is beneficial. However, women with chronic hypertension prior to pregnancy are at increased risk of a number of complications including superimposed preeclampsia, preterm delivery, fetal growth restriction or demise, placental abruption, HF, and acute kidney failure.[65] In an open, international, multicenter study of nonproteinuric preexisting or gestational hypertension, tighter DBP goals (<85 mm Hg) were not associated with decreased rates of the primary composite outcome of pregnancy loss or highlevel neonatal care compared to less-tight control (DBP <100 mm Hg).[66] However, severe hypertension (≥160/110 mm Hg) developed less often in patients randomized to the tight control group compared to less-tight control (40.6% vs 27.5%).

Definitive treatment of preeclampsia is delivery. Labor induction is indicated

if pending or frank eclampsia is present. Otherwise, management consists of restricting activity, bed rest, and close monitoring. Salt restriction, or any other measures that contract blood volume, should not be employed. Antihypertensive agents are used before induction of labor if DBP is greater than 105 mm Hg with a target DBP of 95 to 105 mm Hg. Intravenous (IV) hydralazine is most commonly used, and IV labetalol is also effective. Immediaterelease oral nifedipine has been used in the past but is not approved by the FDA for hypertension, and untoward fetal and maternal effects (hypotension with fetal distress) have been reported.

Many agents can be used to treat chronic hypertension in pregnancy (**Table 30-7**). Unfortunately, there are few data regarding the most appropriate therapy in pregnancy. Labetalol, long-acting nifedipine, or methyldopa is recommended as a first-line agent due to favorable safety profile.[65] Other β-blockers (not atenolol) and CCBs are also reasonable alternatives. An ACEi, an ARB, and a direct renin inhibitor are known teratogens and are absolutely contraindicated.

TABLE 30-7 Treatment of Chronic Hypertension in Pregnancy

Medication/Class	Comments
Methyldopa	Long-term follow-up data support safety; considered a preferred agent
β-blockers	Generally safe, but intrauterine growth retardation reported (mostly with atenolol)
Labetalol	Increasingly used over methyldopa because of fewer side effects; considered a first-line agent
Clonidine	Limited data available; mainly an option in the third trimester
CCB	Limited data available; no increase in major teratogenicity with exposure (except immediate-release oral nifedipine should not be used); long-acting nifedipine considered a preferred agent
Thiazide	Not first-line agents but probably safe in low doses if started prior to conception when treating essential hypertension
ACEi, ARB, direct renin inhibitor	Contraindicated; major teratogenicity reported with exposure (fetal toxicity and death)

African Americans Hypertension affects African American patients at a disproportionately higher rate, and hypertension-associated complications are

more prevalent than in other populations.[1] Reasons for these differences are not fully understood but may be related to differences in underlying physiologic alterations. Hypertension is also more difficult to control in African Americans and usually requires two or more antihypertensives to reach a goal of <130/80 mm Hg.[1]

BP-lowering effects of antihypertensive medication classes vary in African Americans. However, these differences are only relevant when monotherapy treatment is utilized. CCBs and thiazides are most effective at lowering BP in African Americans and should be used first-line in the absence of a compelling indication.[1] When either of these two classes (especially thiazides) are used in combination with a β-blocker, an ACEi, or an ARB (which are three classes known to be less effective at lowering BP in African Americans), the antihypertensive response is significantly increased. This may be due to the low-renin pattern of hypertension in African Americans, which can result in less BP lowering with a β-blocker, an ACEi, or an ARB when used as monotherapy compared with white patients. Interestingly, African Americans have a higher risk of angioedema from an ACEi compared with whites.[1]

Despite potential differences in antihypertensive effects with monotherapy treatment, drug therapy selection should be based on evidence, no different from what is recommended for the hypertensive population in general. Medications recommended for specific compelling indications should be used when such compelling indications are present, even if the antihypertensive effect may not be as great as with another drug class (eg, use a β-blocker first-line for hypertension in an African American with stable ischemic heart disease or an ACE or ARB in an African American with CKD).

Other Conditions

Most patients with hypertension have some other coexisting conditions that may influence selection of drug therapy. The influence of comorbid conditions should only be complementary to, and never in replacement of, drug therapy choices recommended to treat a compelling indication. Under some circumstances, these considerations are helpful in deciding on a particular antihypertensive agent when more than one antihypertensive class is recommended. In some cases, an agent should be avoided because it may aggravate a concomitant disorder. In other cases, an antihypertensive can be used to treat hypertension, and another concomitant condition. These are briefly summarized in Table 30-5.

Pulmonary Disease and Peripheral Arterial Disease β-Blockers, especially

nonselective agents, have generally been avoided for patients with hypertension and reactive airway disease (asthma or chronic obstructive pulmonary disease [COPD] with a reversible obstructive component) due to a fear of inducing bronchospasm. However, cardioselective β-blockers can safely be used in patients with asthma or COPD.[1] Therefore, cardioselective β-blockers should be used to treat a compelling indication (ie, stable ischemic heart disease, or HF) for patients with reactive airway disease.

PAD is a noncoronary form of ASCVD. Patients with PAD are at an increased risk of stroke and CV events.[1,67] While β-blockers can theoretically be problematic for patients with PAD due to possible decreased peripheral blood flow secondary to unopposed stimulation of α_1-receptors that results in vasoconstriction, available data indicate that β-blockers do not worsen claudication symptoms or cause functional impairment.[67] Antihypertensive treatment for patients with PAD should follow the same general principles as patients without PAD.[1]

Metabolic Syndrome Metabolic syndrome is a cluster of multiple cardiometabolic risk factors.[1] It has been defined as the presence of three of the following five criteria: abdominal obesity, elevated triglycerides, low HDL cholesterol, elevated BP (or receiving drug treatment for high BP), and elevated fasting blood glucose.[68] Despite the debate regarding whether the metabolic syndrome is a true "disease" or simply a cluster of conditions, it is widely accepted that patients with metabolic syndrome are at increased risk of developing CV disease and/or type 2 diabetes. The cornerstone of treatment involves lifestyle modification (eg, weight loss if overweight or obese, exercise, dietary modifications). There are no definitive evidence that any first-line antihypertensive medication class is better or worse than another in reducing CV events in patients with metabolic syndrome.[1] While thiazides have been associated with a small increase in blood glucose and faster progression to diabetes, a subgroup analysis of the ALLHAT found that CV events were reduced more with chlorthalidone when compared to lisinopril in patients with impaired fasting glucose.[38] Therefore, any first-line antihypertensive can be used for patients with metabolic syndrome.

Erectile Dysfunction Most antihypertensive agents, particularly β-blockers, and mineralocorticoid receptor antagonists, have been associated with erectile dysfunction in men. However, it is not clear if erectile dysfunction associated with antihypertensive treatment is solely a result of drug therapy or rather a

symptom of underlying vascular disease. β-Blockers have historically been labeled as agents that cause significant sexual dysfunction. However, evidence supporting this notion are limited. A systematic review of 15 studies involving 35,000 patients assessing β-blocker use for MI, HF, and hypertension found only a very slight increased risk for erectile dysfunction.[69] In addition, prospective long-term data from the Treatment of Mild Hypertension Study (TOMHS) and the Veterans Administration cooperative trial show no difference in the incidence of erectile dysfunction between a thiazide and β-blocker versus an ACEi and CCB.[70,71] Centrally acting agents are associated with higher rates of sexual dysfunction and should be avoided in men with erectile dysfunction.

Hypertensive men frequently have ASCVD, which frequently results in erectile dysfunction. Therefore, erectile dysfunction is associated with chronic arterial changes resulting from elevated BP, and lack of control may increase the risk of erectile dysfunction. These changes are even more pronounced in hypertensive men with diabetes.

Resistant Hypertension

12 Resistant hypertension is defined as failure to achieve goal BP with the use of three or more antihypertensive drugs with complementary mechanisms of action (ideally using optimal doses, one of which is a diuretic) or when four or more antihypertensive drugs are needed to achieve BP control.[1,72] Using the previous BP goal of <140/90 mm Hg, it has been estimated that 12% of patients with hypertension fall under this definition.[4] With the new BP goal of <130/80 mm Hg, an additional 4% of patients (18% total) may meet criteria for resistant hypertension.[1] Patients with newly diagnosed hypertension or who are not receiving drug therapy should not be considered to have resistant hypertension. Difficult-to-control hypertension is persistently elevated BP despite treatment with two or three drugs, which fails to meet the criteria for resistant hypertension.

Several causes of resistant hypertension are listed in **Table 30-8**. Volume overload is a common cause, thus highlighting the importance of diuretic therapy in the management of hypertension. Pseudoresistance should also be ruled out by assuring adherence with prescribed therapy and possibly use of out-of-office BP measurements (by using a self-monitoring device or 24-hour ABP monitor).[1] Patients should be closely evaluated to see if any of these causes can be reversed.

TABLE 30-8 Causes of Resistant Hypertension

Improper BP measurement
Volume overload:
• Excess sodium intake
• Volume retention from kidney disease
• Inadequate diuretic therapy
Drug-induced or other causes:
• Nonadherence
• Inadequate doses
• Agents listed in Table 30-1
Associated conditions:
• Obesity, excess alcohol intake, obstructive sleep apnea
• Secondary hypertension

Treatment of patients with resistant hypertension should ultimately follow the principles of drug therapy selection from the 2017 ACC/AHA guideline. Compelling indications, if present, should guide selection assuming these patients are on a thiazide or other type of diuretic. However, there are treatment philosophies that are germane to the management of resistant hypertension: (a) assuring adequate diuretic therapy, (b) appropriate use of combination therapy, and (c) using alternative antihypertensive agents when needed.

Assuring Appropriate Diuretic Therapy

Diuretics have a large role in the pharmacotherapy of resistant hypertension. Thiazides are first-line antihypertensive agents, but chlorthalidone (thiazide-like) should be preferentially used ahead of hydrochlorothiazide, especially for patients with resistant hypertension, because it is more potent on a milligram-per-milligram basis.[1,73] Clinicians should identify that chlorthalidone, like all thiazides, has dose-dependent metabolic side effects (hypokalemia and hyperglycemia) and that appropriate monitoring should be implemented. However, it does not seem as though side effects are more common with chlorthalidone versus hydrochlorothiazide. Though less commonly used, indapamide (similar to chlorthalidone as “thiazide like”) is also a more potent antihypertensive agent than hydrochlorothiazide at commonly prescribed doses, and evidence does not demonstrate a higher risk of metabolic side effects.[74]

A mineralocorticoid receptor antagonist (eg, spironolactone) is also highly effective as an add-on agent.[1] Data indicate that many patients with resistant hypertension have some degree of underlying hyperaldosteronism, justifying the role of adding a mineralocorticoid receptor antagonist. Spironolactone has been compared to an α-blocker and a β-blocker as an add-on therapy for resistant

hypertension in the PATHWAY-2 study.[75] The BP-lowering effect of spironolactone was approximately double that of doxazosin and bisoprolol, reinforcing the benefits of blocking aldosterone by using a mineralocorticoid receptor antagonist in managing resistant hypertension.

Clinicians may consider using a loop diuretic, even in place of a thiazide, for patients with resistant hypertension who have very compromised kidney function (estimated GFR <30 mL/min/1.73 m^2).[1] Torsemide can be dosed once daily while furosemide must be dosed twice daily or three times daily.

First-Line Antihypertensive Agents

Angiotensin-Converting Enzyme Inhibitors (ACEi) An ACEi is a first-line therapy option in most patients with hypertension.[1] The ALLHAT demonstrated less HF and stroke with chlorthalidone versus lisinopril,[28] while another outcome study demonstrated similar, if not better, outcomes with an ACEi versus hydrochlorothiazide.[34] It is possible that the different thiazides have different abilities to reduce CV events. Nonetheless, strong evidence demonstrates that ACEi therapy overall reduces CV events comparably to other firstline antihypertensive agents.

ACE facilitates production of angiotensin II that has a major role in arterial BP regulation as depicted in Fig. 30-1. ACE is distributed in many tissues and is present in several different cell types, but its principal location is in endothelial cells. Therefore, the major site for angiotensin II production is in the blood vessels, not the kidney. An ACEi blocks the ACE, thus inhibiting the conversion of angiotensin I to angiotensin II. Angiotensin II is a potent vasoconstrictor that stimulates aldosterone secretion, causing an increase in sodium and water reabsorption with accompanying potassium loss. By blocking the ACE, vasodilation and a decrease in aldosterone occur.

An ACEi also blocks degradation of bradykinin and stimulates the synthesis of other vasodilating substances (prostaglandin E_2 and prostacyclin). Because an ACEi lowers BP in patients with normal plasma renin activity, bradykinin and perhaps tissue production of ACE are important in hypertension. Increased bradykinin enhances the BP-lowering effects of an ACEi, but also is responsible for the side effect of a dry cough. An ACEi may effectively prevent or regress LVH by reducing direct stimulation of angiotensin II on myocardial cells.

There are many evidence-based indications for an ACEi (see Fig. 30-3). An ACEi reduces CV morbidity and mortality in patients with HF*r*EF and decreases progression of CKD. They are first-line as disease-modifying therapy in all of

these patients unless contraindicated. An ACEi is a first-line option for patients with diabetes and hypertension because of demonstrated CV disease and kidney benefits. A regimen including an ACEi with a thiazide is first-line in recurrent stroke prevention based on benefits demonstrated from the PROGRESS trial showing a reduced risk of secondary stroke.[33] As an add-on to β-blocker therapy, evidence indicates that an ACEi further reduces CV risk in patients with stable ischemic heart disease, especially in patients post-MI.[76–78] These benefits of an ACEi occur in patients with ASCVD even in the absence of LV dysfunction and may reduce the development of new-onset type 2 diabetes.[79] Most ACEi medications can be dosed once daily for hypertension (Table 30-5). In some patients, especially when higher doses are used, twice-daily dosing is needed to maintain 24-hour effects with enalapril, benazepril, moexipril, quinapril, and ramipril.

ACEi therapy is generally well tolerated. Because they decrease aldosterone, an increase in potassium serum concentrations can occur. While this increase is usually small, hyperkalemia is possible. Patients with CKD or those taking potassium supplements, potassium-sparing diuretics, mineralocorticoid receptor antagonists, ARBs, or a direct renin inhibitor are at highest risk for hyperkalemia. Judicious monitoring of serum potassium and creatinine values within 4 weeks of starting or increasing the dose of an ACEi can often identify abnormalities early before they evolve into serious adverse events.

The most worrisome adverse effect of ACEi therapy is acute kidney injury. This serious adverse effect is uncommon, and the development of severe acute kidney failure is very rare, occurring in less than 1% of patients. Preexisting kidney disease increases the risk of this side effect. Severe bilateral renal artery stenosis or unilateral stenosis of a solitary functioning kidney renders patients dependent on the vasoconstrictive effect of angiotensin II on the efferent arteriole of the kidney, thus explaining why these patients are particularly susceptible to acute kidney injury from an ACEi. Slow titration of the ACEi dose and judicious kidney function monitoring can minimize risk and allow for early detection of patients with renal artery stenosis.

It is important to note that GFR does decrease somewhat in patients when started on an ACEi.[1] This is attributed to the inhibition of angiotensin II vasoconstriction on the efferent arteriole. This decrease in GFR often increases serum creatinine, and small increases should be anticipated when monitoring patients newly started on an ACEi. Either modest elevations of ≤35% (for baseline creatinine values ≤3 mg/dL [265 μmol/L]) or absolute increases <1 mg/dL (88 μmol/L) do not warrant changes. If larger increases occur, ACEi

therapy should be stopped or the dose reduced.

Angioedema is a serious potential complication of ACEi therapy. It occurs in <1% of the population, and is more likely in African Americans and smokers. Symptoms include lip and tongue swelling and possibly difficulty breathing. Drug withdrawal is appropriate for treating patients with angioedema. However, angioedema associated with laryngeal edema and/or pulmonary symptoms occasionally occurs and requires additional treatment with a bradykinin B2 receptor antagonist (eg, icatibant), fresh frozen plasma, and/or emergent intubations to support respiration. A history of angioedema, even if not from an ACEi, precludes the use of another ACEi (it is a contraindication). Cross-reactivity between an ACEi and an ARB does not appear to be a significant concern. The Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects with Cardiovascular Disease (TRANSCEND) trial enrolled 75 patients with a history of ACEi–induced angioedema, and randomized these patients to either placebo or ARB therapy.[80] There were no cases of repeat angioedema among these patients. These data suggest the cross-reactivity is very low. Hence, an ARB can be used in a patient with a history of ACEi– induced angioedema when it is needed. However, clinicians should monitor for repeat occurrences, since idiopathic angioedema may still occur.

A persistent dry cough may develop in up to 20% of patients treated with an ACEi. It is pharmacologically explained by the inhibition of bradykinin breakdown. This cough does not cause pulmonary disease but is annoying and can compromise adherence. It should be differentiated from a wet cough due to pulmonary edema, which may be a sign of uncontrolled HF and not ACEi–induced cough.

An ACEi (as well as an ARB or direct renin inhibitor) is absolutely contraindicated in pregnancy. Female patients of childbearing age should be counseled regarding effective forms of birth control as ACEi therapy is fetotoxic.[1] Fetopathy (group of conditions that include renal failure, renal dysplasia, hypotension, oligohydramnios, pulmonary hypotension, hypocalvaria, and death) has occurred with ACEi exposure in the second and third trimesters. Similar to a thiazide, an ACEi can increase lithium serum concentrations in patients on lithium therapy. Concurrent use of an ACEi with a potassium-sparing diuretic, potassium supplements, mineralocorticoid receptor antagonist, ARB, or direct renin inhibitor may result in hyperkalemia.

Starting doses of an ACEi should be low, with even lower doses for patients at risk for orthostatic hypotension or severe renal dysfunction (eg, elderly patients, those with CKD). Acute hypotension may occur at the onset of ACEi

therapy. Patients who are sodium or volume depleted, in an HF exacerbation, very elderly, or on concurrent vasodilators or thiazide therapy, are at high risk for this effect. It is important to start with half the normal dose of an ACEi for all patients with these risk factors and to use slow dose titration.

Angiotensin Receptor Blockers (ARBs) Angiotensin II is generated by two enzymatic pathways: the RAAS, which involves ACE, and an alternative pathway that uses other enzymes such as chymase (aka “tissue ACE”). An ACEi inhibits only the effects of angiotensin II produced through the RAAS, whereas ARBs inhibit the effects of angiotensin II from all pathways. It is unclear how these differences affect tissue concentrations of ACE.

ARB therapy directly blocks the AT_1 receptor that mediates the known effects of angiotensin II in humans: vasoconstriction, aldosterone release, sympathetic activation, antidiuretic hormone release, and constriction of the efferent arterioles of the glomerulus. They do not block the AT_2 receptor. Therefore, beneficial effects of AT2 receptor stimulation (vasodilation, tissue repair, and inhibition of cell growth) remain intact with ARB use. Unlike an ACEi, an ARB does not block the breakdown of bradykinin. Therefore, some of the beneficial effects of bradykinin (eg, vasodilation, regression of myocyte hypertrophy and fibrosis, increased levels of tissue plasminogen activator) are not present with ARB therapy.

An ARB is a first-line therapy option in most patients with hypertension.1 ARB therapy has been directly compared with ACEi therapy in patients with high CV risk.[81] The Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial (ON-TARGET) was a double-blind trial that randomized 25,620 patients (69% with a history of hypertension-based historical standards, mean BP of 142/82 mm Hg) to ACEi–based therapy, ARBbased therapy, or the combination of an ACEi with an ARB. The primary endpoint was a composite endpoint of CV death or hospitalization for HF. After a median follow-up of 56 months, there was no difference in the primary endpoint between any of the three treatment groups. Therefore, these data establish that the CV event–lowering benefits of ARB therapy is similar to ACEi therapy. Moreover, the combination of an ACEi with an ARB had no additional CV event lowering but was associated with a higher risk of side effects (renal dysfunction, hypotension). Therefore, there is no reason to use an ACEi with an ARB for the management of hypertension.

For patients with type 2 diabetes and CKD, the progression of kidney disease has been shown to be significantly reduced with ARB therapy.[50] Some benefits

appear to be independent of BP lowering, suggesting that the pharmacologic effects of ARBs on the efferent arteriole may result in attenuated progression of kidney disease. For patients with HF*r*EF, ARB therapy has been shown to reduce the risk of hospitalization for HF when used as an alternative therapy in ACEi-intolerant patients.[46]

ARBs have been compared head-to-head with CCBs. The Morbidity and Mortality After Stroke: Eprosartan Versus Nitrendipine in Secondary Prevention (MOSES) trial demonstrated that eprosartan reduced the risk of recurrent stroke greater than nitrendipine in patients with a past medical history of cerebrovascular disease.[56] These data support the common notion that ARBs may have cerebroprotective effects that may explain CV event reductions. Another outcome study, the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial, showed that valsartan-based therapy is equivalent to amlodipine-based therapy for the primary composite outcome of first CV event in patients with hypertension and additional CV risk factors.[32] However, the occurrence of certain components of the primary endpoint (stroke and MI) and new-onset type 2 diabetes was lower in the valsartan group. Although patients treated with amlodipine had slightly lower mean BP values than valsartan-treated patients, there was no difference in the primary endpoint.

The addition of a CCB or thiazide to an ARB significantly increases antihypertensive efficacy. Similar to an ACEi, most ARBs have long enough half-lives to allow for once-daily dosing. However, candesartan, eprosartan, losartan, and valsartan have the shortest half-lives and may require twice-daily dosing for sustained BP lowering.

ARB therapy has the lowest incidence of side effects compared with other antihypertensive agents.[82] ARBs do not affect bradykinin and do not elicit a dry cough like an ACEi. While referred to as an “ACEi without a cough,” pharmacologic differences between an ARB and ACEi highlight that they could have very different effects on vascular smooth muscle and myocardial tissue that can correlate to different effects. Regardless, they are first-line options for hypertension, and they are reasonable alternatives for patients that fail to tolerate ACEi therapy because of a cough. Due to their excellent tolerability, safety profile, and generic availability, ARBs are increasingly preferred by clinicians over an ACEi for hypertension.

An ARB may cause renal insufficiency, hyperkalemia, and orthostatic hypotension in a manner identical to that of an ACEi. The same precautions that apply to ACEi therapy regarding suspected bilateral renal artery stenosis, concomitant medications that can raise potassium, and/or increase in the risk of

hypotension also apply to ARBs. As previously discussed, patients with a history of ACEi angioedema can be treated with an ARB when needed.[83] An ARB should never be used in pregnancy.

Calcium Channel Blockers (CCBs) Both dihydropyridine CCBs and nondihydropyridine CCBs are first-line therapies for hypertension.[1] CCBs also have compelling indications in stable ischemic heart disease. However, with this compelling indication, they are primarily used as an add-on therapy to other antihypertensive drug classes.

Contraction of cardiac and smooth muscle cells requires an increase in free intracellular calcium concentrations from the extracellular fluid. When cardiac or vascular smooth muscle is stimulated, voltage-sensitive channels in the cell membrane are opened, allowing calcium to enter the cells. The influx of extracellular calcium into the cell releases stored calcium from the sarcoplasmic reticulum. As intracellular free calcium concentration increases, it binds to a protein, calmodulin, which then activates myosin kinase enabling myosin to interact with actin to induce contraction. CCBs work by inhibiting the influx of calcium across the cell membrane. There are two types of voltage-gated calcium channels: a high-voltage channel (L-type) and a low-voltage channel (T-type). Currently available CCBs only block the L-type channel, which leads to coronary and peripheral vasodilation.

The two subclasses, dihydropyridines and nondihydropyridines (see Table 30-5), are pharmacologically very different from each other. Antihypertensive effectiveness is similar with both, but they differ somewhat in other pharmacodynamic effects. Nondihydropyridines (verapamil and diltiazem) decrease heart rate and slow atrioventricular nodal conduction. Similar to a β-blocker, these drugs may also treat supraventricular tachyarrhythmias (eg, atrial fibrillation). Verapamil (and diltiazem to a lesser extent) produces negative inotropic and chronotropic effects that are responsible for its propensity to precipitate or cause systolic HF in high-risk patients. All CCBs (except amlodipine and felodipine) have negative inotropic effects. Dihydropyridines may cause a baroreceptormediated reflex tachycardia because of their potent peripheral vasodilating effects. This effect appears to be more pronounced with the first-generation dihydropyridines (eg, nifedipine) and is significantly diminished with the newer agents (eg, amlodipine) and when given in sustained-release dosage forms. Dihydropyridines do not alter conduction through the atrioventricular node and thus are not effective agents in supraventricular tachyarrhythmias.

Dihydropyridine CCBs have been extensively studied in hypertension. In the

ALLHAT there was no difference in the primary outcome between chlorthalidone and amlodipine, and only the secondary outcome of HF was higher with amlodipine.[28] A subgroup analysis of the ALLHAT directly compared amlodipine with lisinopril and demonstrated that there was no difference in the primary outcome.[84] However, amlodipine was superior to lisinopril for BP control in black patients, and for stroke reduction in black patients and women. There was a lower risk of HF in the lisinopril group. As discussed previously, the VALUE study also showed no difference between valsartan and amlodipine in the primary outcome of first CV event in high-risk patients.[32]

Dihydropyridine CCBs are very effective in older patients with isolated systolic hypertension. The placebo-controlled Syst-Eur trial demonstrated that a long-acting dihydropyridine CCB reduced the risk of CV events markedly in isolated systolic hypertension.[10] A long-acting dihydropyridine CCB, similar to a thiazide, should be strongly considered as preferred therapy in a patient with isolated systolic hypertension and no other compelling indications.

Among dihydropyridine CCBs, short-acting nifedipine may rarely cause an increase in the frequency, intensity, and duration of angina in association with acute hypotension. This effect is most likely due to reflex sympathetic stimulation and is likely obviated by using sustained-release formulations of nifedipine. For this reason, all other dihydropyridines have an intrinsically long half-life or are sustained-release formulations. Immediate-release nifedipine has been associated with an increased incidence of adverse CV effects, is not approved for treatment of hypertension, and should never be used to treat hypertension. Other side effects of dihydropyridine CCBs include dizziness, flushing, headache, gingival hyperplasia, peripheral edema, mood changes, and various GI complaints. Side effects due to vasodilation such as dizziness, flushing, headache, and peripheral edema occur more frequently with all dihydropyridine CCBs than with the nondihydropyridine CCBs because they are less potent vasodilators.

Diltiazem and verapamil are nondihydropyridine CCBs that can cause cardiac conduction abnormalities such as bradycardia or atrioventricular block. These problems occur mostly with high doses or when used for patients with preexisting cardiac conduction abnormalities. HF has been reported in otherwise healthy patients due to negative inotropic effects. Both drugs can cause peripheral edema and hypotension. Verapamil causes constipation in about 7% of patients. This side effect also occurs with diltiazem, but to a lesser extent.

Verapamil and diltiazem are considered moderate cytochrome P450 3A4

isoenzyme system inhibitors and can cause drug interactions. These medications can increase serum concentrations of other drugs that are metabolized by this isoenzyme system (eg, cyclosporine, digoxin, lovastatin, simvastatin, tacrolimus, theophylline). Verapamil and diltiazem should be given very cautiously with a β-blocker because there is an increased risk of heart block with these combinations. When a CCB is needed in combination with a β-blocker for BP lowering, a dihydropyridine should be selected because it will not increase the risk of heart block. The hepatic metabolism of CCBs, especially felodipine, nicardipine, nifedipine, and nisoldipine, may be inhibited by ingesting large quantities of grapefruit juice (eg, ≥1 quart [or 1 L] daily).

Many different formulations of verapamil and diltiazem are currently available (see Table 30-5). Although certain individual sustained-release verapamil and diltiazem products contain the same active drug, they are usually not AB-rated by the FDA as interchangeable on a milligram-per-milligram basis due to different biopharmaceutical release mechanisms. However, the clinical significance of these differences is likely negligible.

Two nondihydropyridine CCBs, sustained-release verapamil (Verelan PM) and long-acting diltiazem (Cardizem LA), are designed to target the circadian BP rhythm. When dosed in the evening, drug is released during the early morning hours when BP first starts to increase. Targeting medication release at specific times of day is termed chronotherapy. The rationale behind chronotherapy in hypertension is that blunting the early morning BP surge may result in greater reductions in CV events than dosing of conventional antihypertensive products in the morning. However, evidence from the Controlled Onset Verapamil Investigation of Cardiovascular End-Points (CONVINCE) trial showed that chronotherapeutic verapamil was similar to, but not better than, a thiazide–β-blocker– based regimen with respect to CV events.[29] Therefore, there is no specific advantage for the use of chronotherapeutic CCBs in treating hypertension.

Thiazides and other Diuretics There are four subclasses of diuretics: thiazides, loops, potassium-sparing agents, and mineralocorticoid receptor antagonists (see Table 30-5).[73] A thiazide is the preferred diuretic for hypertension and is considered a first-line therapy option in most patients.[1] The best available evidence justifying this recommendation is from the ALLHAT.[28] Moreover, when combination therapy is needed in hypertension to control BP, a thiazide as an add-on agent, but not necessarily the second agent, is very effective in augmenting BP lowering.

Loop diuretics are more potent agents for inducing diuresis, but are not ideal antihypertensive agents unless treating edema is also needed. In general, loop diuretics are sometimes required over a thiazide for hypertension in patients with severe CKD when estimated GFR is <30 mL/min/1.73 m^2, especially when edema is present.[73] However, many patients with an estimated GFR of <30 mL/min/1.73 m^2, but not on dialysis, will still have antihypertensive effects with thiazides. This is especially true with chlorthalidone.[73]

Potassium-sparing diuretics are very weak antihypertensive agents when used alone and provide minimal additive effect when used in combination with a thiazide or loop diuretic. Their use in hypertension is in combination with another diuretic to counteract the potassium-wasting properties of the other diuretic agent.

Mineralocorticoid receptor antagonists (spironolactone and eplerenone) inhibit aldosterone activity and are sometimes considered potassium-sparing diuretics. However, they are more potent as antihypertensives and should be viewed as an independent class due to evidence supporting different compelling indications. Mineralocorticoid receptor antagonists are most commonly used to treat resistant hypertension, as elevated aldosterone concentrations are prevalent in this setting. They are also used as an add-on agent in patients with HF*r*EF with or without concomitant hypertension.

The exact antihypertensive mechanism of action of diuretics is not known but has been well hypothesized. The drop in BP seen when diuretics are first started is caused by an initial diuresis. Diuresis causes reductions in plasma and stroke volume, which decreases CO and BP. This initial drop in CO causes a compensatory increase in PVR. With chronic diuretic therapy, extracellular fluid and plasma volume return to near pretreatment values. However, PVR decreases to values that are lower than the pretreatment baseline. This reduction in PVR is responsible for persistent antihypertensive effects.

With thiazides, additional actions may further explain their antihypertensive effects. They mobilize sodium and water from arteriolar walls. This effect would lessen the amount of physical encroachment on the lumen of the vessel created by the excessive accumulation of intracellular fluid. As the diameter of the lumen relaxes and increases, there is less resistance to the flow of blood and PVR further drops. High dietary sodium intake can blunt this effect and a low salt intake can enhance this effect. Thiazides are also postulated to cause direct relaxation of vascular smooth muscle.

Diuretics should be dosed in the morning when given once daily and in the morning and late afternoon when dosed twice daily to minimize nocturnal

diuresis. However, with chronic use, thiazides, potassium-sparing diuretics, and mineralocorticoid receptor antagonists rarely cause a pronounced diuresis.

The major pharmacokinetic differences between the different thiazide medications are serum half-life and duration of diuretic effect. The clinical relevance of these differences is unknown because the serum half-life of most antihypertensive agents does not correlate with the hypotensive duration of action. Moreover, diuretics lower BP primarily through extrarenal mechanisms. Hydrochlorothiazide and, to a greater extent, chlorthalidone are the two most frequently used thiazides in landmark clinical trials that have demonstrated reduced morbidity and mortality. Hydrochlorothiazide is considered a “thiazide-type” agent while chlorthalidone is a “thiazide-like” agent. These agents are not equipotent on a milligram-per-milligram basis; chlorthalidone is 1.5 to 2 times more potent than hydrochlorothiazide.[73] This is likely attributed to a longer half-life (45-60 hours vs 8-15 hours) and longer duration of effect (48-72 hours vs 16-24 hours) with chlorthalidone.

Thiazides are effective in lowering BP, especially when used in combination with most other antihypertensives. This additive response is explained by two independent pharmacodynamic effects. First, when two drugs cause the same overall pharmacologic effect (BP lowering) through different mechanisms of action, their combination usually results in an additive or synergistic effect. This is especially relevant when a β-blocker, an ACEi, or an ARB is indicated in an African American but does not elicit sufficient antihypertensive effect. Adding a thiazide, similar to a CCB, in this situation can often significantly lower BP. Second, a compensatory increase in sodium and fluid retention may be seen with antihypertensive agents. This problem is counteracted with the concurrent use of a thiazide.

Side effects of a thiazide include hypokalemia, hypomagnesemia, hypercalcemia, hyperuricemia, hyperglycemia, dyslipidemia, and sexual dysfunction. Many of these side effects were identified when high doses of thiazides were used in the past (eg, hydrochlorothiazide up to 200 mg/day). Current guidelines recommend dosing hydrochlorothiazide up to 50 mg/day or chlorthalidone up to 25 mg/day, which markedly reduces the risk for most metabolic side effects. However, these doses, which are most effective for BP lowering, increases the risk of hypokalemia.[85] Loop diuretics may cause the same side effects. Although the effect on serum lipids and glucose is even less significant, hypokalemia is more pronounced, and hypocalcemia may occur.

Hypokalemia and hypomagnesemia may cause muscle fatigue or cramps. However, serious cardiac arrhythmias can occur in patients with severe

hypokalemia and hypomagnesemia. Lowdose therapy (ie, 25 mg hydrochlorothiazide or 12.5 mg chlorthalidone daily) causes less electrolyte disturbances than higher doses. However, because the most effective doses of these two thiazides are hydrochlorothiazide 50 mg daily and chlorthalidone 25 mg daily, efforts should be made to keep potassium in the therapeutic range by careful monitoring, especially when higher doses are used.

Thiazide-induced hyperuricemia can precipitate gout. This side effect may be especially problematic for patients with a previous history of gout and is more common with thiazides. However, acute gout is unlikely in patients with no previous history of gout. If gout does occur in a patient who requires thiazide therapy, allopurinol can be given to prevent gout and will not compromise the antihypertensive effects of the thiazide. High doses of thiazide and loop diuretics may increase fasting glucose and serum cholesterol values. These effects, however, usually are transient and often inconsequential.[73]

Potassium-sparing diuretics can cause hyperkalemia, especially in patients with CKD or diabetes and in patients receiving concurrent treatment with a mineralocorticoid receptor antagonist, ACEi, ARB, direct renin inhibitor, or potassium supplements. Hyperkalemia is especially problematic for the mineralocorticoid receptor antagonist eplerenone, which is a very selective antagonist of aldosterone. Due to this increased risk of hyperkalemia, eplerenone is contraindicated for patients with impaired kidney function or type 2 diabetes with proteinuria (see Table 30-5). While spironolactone may cause gynecomastia in up to 10% of patients, this rarely occurs with eplerenone.

A thiazide can be used safely with most other agents. However, concurrent administration with lithium may result in increased lithium serum concentrations and can predispose patients to lithium toxicity.

β-Blockers β-Blockers have been used in several large outcome trials in hypertension. However, in most of these trials, a thiazide was the first-line agent with a β-blocker added for additional BP lowering. For patients with hypertension but without compelling indications, a β-blocker should not be used as the initial first-line agent. This recommendation is based on meta-analyses that suggest β-blocker–based therapy may not reduce CV events as well as these other agents when used as the initial drug to treat patients with hypertension who do not have a compelling indication for a β-blocker.[1]

A β-blocker is only an appropriate first-line agent in hypertension when used to treat specific compelling indications (eg, ischemic heart disease, HF*r*EF). Numerous trials have shown a reduced risk of CV events when β-blockers are used following an MI, during an acute coronary syndrome, or in patients with

chronic stable angina with ischemic symptoms. Although once contraindicated in HF, studies have shown that bisoprolol, carvedilol, and metoprolol succinate reduce mortality in patients with HF*r*EF who are treated with a diuretic and ACEi.

Several mechanisms of action have been proposed for β-blockers, but none alone has been shown to be consistently associated with a reduction in arterial BP. β-Blocker therapy has negative chronotropic and inotropic effects that reduce CO, which explains some of the antihypertensive effects. However, CO falls equally for patients treated with a β-blocker regardless of BP lowering. Additionally, β-blockers with ISA do not reduce CO, yet they lower BP and decrease peripheral resistance.

β-Adrenoceptors are also located on the surface membranes of juxtaglomerular cells, and a β-blocker inhibits these receptors and thus the release of renin. However, there is a weak association between plasma renin and antihypertensive efficacy of β-blocker therapy. Some patients with low plasma renin concentrations do respond to β-blocker therapy. Therefore, additional mechanisms likely also account for the antihypertensive effect of a β-blocker.

There are important pharmacodynamic and pharmacokinetic differences among β-blockers, but all agents provide a similar degree of BP lowering. There are three pharmacodynamic properties of β-blocker therapy that differentiate this class: cardioselectivity, ISA, and membrane-stabilizing effects. β-Blocker agents that possess a greater affinity for β_1-receptors than for β_2-receptors are *cardioselective*.

β_1-Adrenoceptors and β_2-adrenoceptors are distributed throughout the body, but they concentrate differently in certain organs and tissues. There is a preponderance of β_1-receptors in the heart and kidney, and a preponderance of β_2-receptors in the lungs, liver, pancreas, and arteriolar smooth muscle. β_1-Receptor stimulation increases heart rate, contractility, and renin release. β_2-Receptor stimulation results in bronchodilation and vasodilation. A cardioselective β-blocker is not likely to provoke broncho- spasm and vasoconstriction. Insulin secretion and glycogenolysis are mediated by β_2-receptors. Blocking β_2-receptors may reduce these processes and increase blood glucose or blunt recovery from hypoglycemia.

Cardioselective β-blockers (eg, bisoprolol, metoprolol, nebivolol) have clinically significant advantages over nonselective agents (eg, propranolol, nadolol), and are preferred when using a β-blocker to treat hypertension. Cardioselective agents are safer than nonselective agents for patients with

asthma or diabetes who have a compelling indication for a β-blocker. However, cardioselectivity is a dose-dependent phenomenon; at higher doses, some cardioselective agents lose their relative selectivity for β_1-receptors and block β_2-receptors as effectively as they block β_1-receptors. The dose at which cardioselectivity is lost varies from patient to patient and may not occur with highly selective β-blockers (eg, bisoprolol).

Some β-blockers (eg, acebutolol, pindolol) have ISA and act as partial β-receptor agonists. When they bind to the β-receptor, they stimulate it, but far less than a pure β-agonist. If the sympathetic tone is low, as it is during resting states, β-receptors are partially stimulated by ISA β-blockers. Therefore, resting heart rate, CO, and peripheral blood flow are not reduced when these types of β-blockers are used. Theoretically, ISA agents appear to have advantages over a non-ISA β-blockers in certain patients with HF or sinus bradycardia. Unfortunately, they do not appear to reduce CV events as well as other β-blockers. In fact, they may increase CV risk in patients with stable ischemic heart disease. Thus, agents with ISA are rarely needed and have no role in the management of hypertension.

All β-blockers exert a *membrane-stabilizing action* on cardiac cells when large doses are given. This activity is needed when β-blockers are used as an antiarrhythmic agent, but not for hypertension.

Pharmacokinetic differences among β-blockers relate to firstpass metabolism, route of elimination, the degree of lipophilicity, and serum half-lives. Propranolol and metoprolol undergo extensive first-pass metabolism, so the dose needed to attain β-blockade with either drug varies from patient to patient. Atenolol and nadolol are renally excreted. The dose of these agents may need to be reduced for patients with moderate-to-severe CKD.

β-Blockers, especially those with high lipophilic properties, penetrate the central nervous system and may cause other effects. Propranolol is the most lipophilic, and atenolol is the least lipophilic. Therefore, higher brain concentrations of propranolol compared with atenolol are seen after equivalent doses are given. It is thought that higher lipophilicity is associated with more central nervous system side effects (dizziness, drowsiness). However, the lipophilic properties provide better effects for non-CV conditions such as migraine headache prevention, essential tremor, and thyrotoxicosis. BP lowering is equal among β-blockers regardless of lipophilicity.

Most side effects of β-blockers are extensions of their ability to antagonize β-adrenoceptors. β-Blockade in the myocardium can be associated with bradycardia, atrioventricular conduction abnormalities (eg secondor third-degree

heart block), and the development of acute HF. The decrease in heart rate may benefit certain patients with atrial arrhythmias (atrial fibrillation, atrial flutter) and hypertension by both providing rate control and BP lowering. β-Blocker therapy usually only produces HF if used in high initial doses for patients with preexisting left ventricular dysfunction or if started in these patients during an acute HF exacerbation. Blocking β_2-receptors in arteriolar smooth muscle may cause cold extremities and may aggravate intermittent claudication or Raynaud's phenomenon as a result of decreased peripheral blood flow. Also, there is an increase of sympathetic tone during periods of hypoglycemia in patients with diabetes that may result in a significant increase in BP because of unopposed α-receptormediated vasoconstriction.

Abrupt cessation of β-blocker therapy can produce cardiac ischemia (aka, angina or chest pain), a CV event, or even death in patients with coronary artery disease. Abrupt cessation may also lead to rebound hypertension (a sudden increase in BP to or above pretreatment values). To avoid this, β-blockers should always be tapered gradually over 1 to 2 weeks before eventually discontinuing the drug. This acute withdrawal syndrome is believed to be secondary to progression of underlying coronary disease, hypersensitivity of β-adrenergic receptors due to upregulation, and increased physical activity after withdrawal of a drug that decreases myocardial oxygen requirements. For patients without coronary disease, abrupt discontinuation may present as tachycardia, sweating, and generalized malaise in addition to increased BP.

Like a thiazide, β-blocker therapy has been shown to increase serum cholesterol and glucose values, but these effects are transient and of little-to-no clinical significance. For patients with diabetes, the reduction in CV events was as great with β-blocker therapy as with an ACEi in the United Kingdom Prospective Diabetes Study (UKPDS)[86] and far superior to placebo in the SHEP trial.[9] In the Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial, patients with diabetes and hypertension who were randomized to metoprolol tartrate had an increase in hemoglobin A1C values, while patients randomized to carvedilol did not.[87] This suggests that mixed αand β-blocking effects of carvedilol may be preferential to metoprolol for patients with uncontrolled diabetes. However, differences in hemoglobin A1C values were small.

Nebivolol is a third-generation β-blocker. Similar to carvedilol and labetalol, this β-blocker results in vasodilation. However, carvedilol and labetalol cause vasodilation because of their ability to block α_1-receptors, while nebivolol causes vasodilation through the release of nitric oxide. There are no proven long-

term clinical benefits of the nitric oxide effects seen with nebivolol, but this might explain a lower risk of β-blocker–associated fatigue, erectile dysfunction, and metabolic side effects (eg, hyperglycemia) with this agent.

13 **Alternative Agents** Alternative antihypertensive agents may be used as an add-on therapy to provide additional BP lowering in patients who are already treated with combination therapy consisting of first-line antihypertensives.

α_1-Blocker Selective α_1-receptor blockers (doxazosin, prazosin, and doxazosin) work in the peripheral vasculature and inhibit the uptake of catecholamines in smooth muscle cells resulting in vasodilation and BP lowering.

Doxazosin was one of the original treatment arms of the ALLHAT. However, it was stopped prematurely when more secondary endpoints of stroke, HF, and CV events were seen with doxazosin compared with chlorthalidone.[35] There were no differences in the primary endpoint of fatal coronary heart disease and nonfatal MI. These data demonstrated that thiazides are superior to α_1-blockers in preventing CV events in patients with hypertension. Therefore, α_1-blockers should only be used in combination with first-line antihypertensive agents.

An α_1-blocker can provide symptomatic benefits in men with benign prostatic hypertrophy. These agents block postsynaptic $\alpha_1$adrenergic receptors located on the prostate capsule, causing relaxation and decreased resistance to urinary outflow. However, when used to lower BP, they should only be in addition to first-line antihypertensive agents.

A potentially severe side effect of an α_1-blocker is a “first-dose” phenomenon that is characterized by transient dizziness or faintness, palpitations, and even syncope within 1 to 3 hours of the first dose. This adverse reaction can also happen after dose increases. These episodes are accompanied by orthostatic hypotension and can be mitigated by taking the first dose and subsequent first increased doses at bedtime. Because orthostatic hypotension and dizziness may persist with chronic administration, these agents should be used very cautiously in older patients that are at an increased risk of falls. Even though antihypertensive effects are achieved through a peripheral α_1-receptor antagonism, these agents cross the blood– brain barrier and may cause central nervous system side effects such as lassitude, vivid dreams, and depression. α_1-Blocker therapy also may cause priapism. Sodium and water retention can occur with higher doses, and sometimes even with chronic administration of low doses. Therefore, these agents are most effective when given in combination with a thiazide to maintain antihypertensive efficacy and minimize potential

edema.

Aliskiren Aliskiren is the only direct renin inhibitor. This drug blocks the RAAS at its point of activation, which results in reduced plasma renin activity and BP lowering.

The role of this drug class in the management of hypertension is very limited. Aliskiren is approved as monotherapy or in combination therapy. Since aliskiren is a RAAS blocker, it should not be used in combination with an ACEi or ARB because of a higher risk of serious adverse effects without providing additional reduction in CV events.[1]

Many of the cautions and adverse effects observed with an ACEi or ARB applies to aliskiren. Aliskiren should never be used in pregnancy due to the known teratogenic effects of using other drugs that block the RAAS system. Angioedema has also been reported in patients treated with aliskiren, as have increases in serum creatinine and serum potassium values. The mechanisms of these adverse effects are likely similar to those with an ACEi or ARB. It is reasonable to utilize similar monitoring strategies by measuring serum creatinine and serum potassium in patients treated with aliskiren.

Central α_2-Agonist Clonidine, guanfacine, and methyldopa lower BP primarily by stimulating α_2-adrenergic receptors in the brain. This stimulation reduces sympathetic outflow from the vasomotor center in the brain and increases vagal tone. It is also believed that peripheral stimulation of presynaptic α_2-receptors may further reduce sympathetic tone. Reduced sympathetic activity together with enhanced parasympathetic activity can decrease heart rate, CO, TPR, plasma renin activity, and baroreceptor reflexes. Clonidine is often used in resistant hypertension, and methyldopa is commonly used for pregnancy-induced hypertension.

Chronic use of a centrally acting α_2-agonist results in sodium and water retention, which is most prominent with methyldopa. Low doses of clonidine and guanfacine can be used to treat hypertension without the addition of a thiazide. However, methyldopa should be given in combination with a thiazide to avoid the blunting of an antihypertensive effect that happens with prolonged use when used to treat chronic hypertension (but not in pregnancy). Sedation and dry mouth are common anticholinergic side effects that typically improve with chronic use of low doses, but they are more troublesome in older patients. As with other centrally acting antihypertensives, depression can occur, especially with high doses. The incidence of orthostatic hypotension and dizziness is higher

than with other antihypertensive agents, so they should be used very cautiously in the elderly. Lastly, clonidine has a relatively high incidence of anticholinergic side effects (sedation, dry mouth, constipation, urinary retention, and blurred vision). Thus, it should generally be avoided for chronic antihypertensive therapy in older patients.

Abrupt cessation of a central α_2-agonist may lead to rebound hypertension. This effect is thought to be secondary to a compensatory increase in norepinephrine release after abrupt discontinuation. In addition, other effects such as nervousness, agitation, headache, and tremor can also occur, which may be exacerbated by concomitant β-blocker use, particularly with clonidine. Thus, if clonidine is to be discontinued, it should be tapered. For patients who are receiving concomitant β-blocker therapy, the β-blocker should be gradually discontinued first several days before gradual discontinuation of clonidine.

Methyldopa can cause hepatitis or hemolytic anemia, although this is rare. Transient elevations in serum hepatic transaminases are occasionally seen with methyldopa therapy but are only clinically relevant if greater than three times the upper limit or normal. Methyldopa should be quickly discontinued if persistent increases in serum hepatic transaminases or alkaline phosphatase are detected because this may indicate the onset of fulminant life-threatening hepatitis. A Coombs-positive hemolytic anemia occurs in <1% of patients receiving methyldopa, although 20% exhibit a positive direct Coombs test without anemia. For these reasons, methyldopa has limited use in routine management of hypertension, except in pregnancy.

Direct Arterial Vasodilator Hydralazine and minoxidil directly relax arteriolar smooth muscle resulting in vasodilation and BP lowering. They exert little to no venous vasodilation. Both agents cause potent reductions in perfusion pressure that activate baroreceptor reflexes. Activation of baroreceptors results in a compensatory increase in sympathetic outflow, which leads to an increase in heart rate, CO, and renin release. Consequently, tachyphylaxis (loss of antihypertensive effect) can develop with continued use. This compensatory baroreceptor response can be counteracted by concurrent use of a β-blocker.

All patients receiving hydralazine or minoxidil for chronic therapy should first receive both a thiazide and a β-blocker. Direct arterial vasodilators can precipitate angina in patients with stable ischemic heart disease unless the baroreceptor reflex mechanism is blocked with a β-blocker. Nondihydropyridine CCBs (diltiazem and verapamil) can be used as an alternative to β-blockers, but a β-blocker is preferred. The side effect of sodium and water retention is significant but is minimized by using a thiazide concomitantly.

One side effect unique to hydralazine is a dose-dependent druginduced lupus-like syndrome. Hydralazine is eliminated by hepatic *N*-acetyltransferase. This enzyme displays genetic polymorphism, and "slow acetylators" are especially prone to develop drug-induced lupus with hydralazine. This syndrome is more common in women and is reversible on discontinuation. Drug-induced lupus may be avoided by using less than 200 mg of hydralazine daily. Because of side effects, hydralazine has limited clinical use for chronic management of hypertension. However, it is especially useful for patients with severe CKD and in kidney failure. Hydralazine, when used in combination with isosorbide dinitrate, has been shown to reduce the risk of CV events in black patients with HF*r*EF when added to a standard regimen of a diuretic, ACEi or ARB, and evidence-based β-blocker therapy.[46]

Minoxidil is a more potent vasodilator than hydralazine. Therefore, the compensatory increases in heart rate, CO, renin release, and sodium retention are even more dramatic. Due to significant water retention, a loop diuretic is often more effective than a thiazide in patients treated with minoxidil. A troublesome side effect of minoxidil is hypertrichosis (hirsutism), presenting as increased hair growth on the face, arms, back, and chest. Hypertrichosis usually ceases when the drug is discontinued. Other minoxidil side effects include pericardial effusion and a nonspecific T-wave change on the electrocardiogram. Minoxidil is reserved for resistant hypertension and for patients requiring hydralazine that experience druginduced lupus.

Combination Therapy

13 Initial therapy with a combination of two antihypertensive drugs is recommended for patients with stage 2 hypertension particularly if BP is >20/10 mm Hg away from goal.[1] Using a fixeddose combination product is an option for these types of patients and has been shown to improve adherence. Initial two-drug combination therapy may also be appropriate for patients with multiple compelling indications for different antihypertensive agents. Moreover, combination therapy is often needed to control BP in patients who are already treated with drug therapy because most patients require two or more agents.[1]

Long-term safety and efficacy of initial two-drug therapy for hypertension has been evaluated in the ACCOMPLISH trial.[88] This was a prospective, randomized, double-blind trial in 11,506 patients with hypertension and other CV risk factors. All of these patients either had stage 2 hypertension or were on antihypertensive drug therapy at enrollment. Patients were randomized to receive

either benazepril-with-hydrochlorothiazide or benazepril-with-amlodipine as initial drug therapy. Treatment was titrated to a goal BP of <140/90 mm Hg for most patients and <130/80 mm Hg for patients with diabetes or CKD.

The trial was terminated early after a mean of 36 months because the incidence of CV events was 20% lower in the benazepril-with-amlodipine group compared with the benazeprilwith-hydrochlorothiazide group. What is most important for clinical practice is that this trial established that initial two-drug therapy for stage 2 hypertension, as has been consistently recommended in guidelines dating back to 2003 (the JNC 7), was safe and highly effective in lowering BP. Mean BP measurements were 132/73 and 133/74 mm Hg in the benazepril-with-amlodipine and the benazepril-with-hydrochlorothiazide groups, respectively. However, rates of attaining a BP of <140/90 mm Hg were 75.4% and 72.4% (benazepril-with-amlodipine and benazepril-withhydrochlorothiazide, respectively).

The ACCOMPLISH trial established initial two-drug antihypertensive therapy as an evidence-based strategy to treat hypertension. Clinicians should consider this study as justification for implementing initial two-drug therapy antihypertensive regimens in appropriate patients. Moreover, The ACCOMPLISH trial demonstrated that the combination of an ACEi with a dihydropyridine CCB was more effective in reducing CV events than the combination of an ACEi with hydrochlorothiazide. However, thiazides are very effective at lowering BP, particularly chlorthalidone and indapamide, especially when used in combination with other agents, and hydrochlorothiazide is available in many fixed-dose combination products.

Optimal Use of Combination Therapy

Clinicians should anticipate the need for combination therapy to control BP in most patients. Using low-dose combinations also provides greater reductions in BP compared with high doses of single agents, with fewer drug-related side effects.[71] Contrary to popular myth, appropriately increasing the number of antihypertensive medications to attain goal BP values does not increase the risk of adverse effects. The American Society of Hypertension has recommended three categories of combination therapy (see “AMERICAN SOCIETY OF HYPERTENSION RECOMMENDATIONS FOR COMBINATION THERAPY” box).[89] Preferred combinations are ideal for lowering BP, have complementary mechanisms of action, and use evidence-based first-line agents. Acceptable combinations may not provide all of the benefits that preferred combinations do, and may have additive side effect profiles. Less effective

combinations are limited in their overall benefits, and should only be used when necessary, except when treating compelling indication.

American Society of Hypertension Recommendations for Combination Therapy[89]

Preferred	Acceptable	Less Effective
ACEi/CCB	β-Blocker/thiazide	ACEi/β-blocker
ARB/CCB	CCB (dihydropyridine)/ β-blocker	ARB/β-blocker
ACEi/thiazide	CCB/thiazide	CCB (nondihydropyridine)/ β-blocker
ARB/thiazide	Thiazide/potassium-sparing diuretic	Centrally acting agent/β-blocker

Some combinations should be avoided when treating hypertension. As previously discussed, the ON-TARGET demonstrated that the use of an ACEi with an ARB in the management of hypertension resulted in no additional reduction in the incidence of CV events.[90] Moreover, this combination resulted in a higher risk of adverse events that was also demonstrated in other trials. These same negative effects are seen when aliskiren is used in combination with an ARB.[91] These combinations (using two RAAS blockers together) should be avoided in the management of hypertension.[1] Other combinations such as a thiazide with a potassium-sparing diuretic, both of which appear to have overlapping mechanisms of action, should be implemented only to minimize side effects and not for additional BP lowering. The combination of two CCBs, a dihydropyridine with a nondihydropyridine, can provide additional BP lowering but has limited use in the routine management of most patients. Under no circumstance should two drugs from the exact same class of medications be used to treat hypertension.

Fixed-Dose Combination Products Many fixed-dose combination products are commercially available, and many are generic (see **Table 30-9**). Most of these products contain a thiazide and have multiple dose strengths available. Individual dose titration is more complicated with fixed-dose combination products, but this strategy can reduce the number of daily tablets/capsules and can simplify regimens to improve adherence by decreasing pill burden. This alone may increase the likelihood of achieving or maintaining goal BP values and is a recommended strategy to improve adherence.[1] Depending on the

product, some may be less expensive to patients and health systems. Nonadherence rates are 24% lower when fixed-dose combination products are used to treat hypertension compared with using free drug components (separate pills) to treat hypertension.[92]

TABLE 30-9 Fixed-Dose Combination Products

Combination	Medication (Brand Name)
ACEi with CCB	Amlodipine/benazepril (Lotrel) Perindopril/amlodipine (Prestalia) Trandolapril/verapamil (Tarka)
ARB with CCB	Amlodipine/olmesartan (Azor) Telmisartan/amlodipine (Twynsta) Valsartan/amlodipine (Exforge)
ACEi with a thiazide	Benazepril/hydrochlorothiazide (Lotensin HCT) Captopril/hydrochlorothiazide (Capozide) Enalapril/hydrochlorothiazide (Vaseretic) Fosinopril/hydrochlorothiazide (Monopril HCT) Lisinopril/hydrochlorothiazide (Prinizide, Zestoretic) Moexipril/hydrochlorothiazide (Uniretic) Quinapril/hydrochlorothiazide (Accuretic)
ARB with a thiazide	Azilsartan/chlorthalidone (Edarbyclor) Candesartan/hydrochlorothiazide (Atacand HCT) Eprosartan/hydrochlorothiazide (Teveten HCT) Irbesartan/hydrochlorothiazide (Avalide) Losartan/hydrochlorothiazide (Hyzaar) Olmesartan/hydrochlorothiazide (Benicar HCT) Telmisartan/hydrochlorothiazide (Micardis HCT) Valsartan/hydrochlorothiazide (Diovan HCT)
β-blocker with a thiazide	Atenolol/chlorthalidone (Tenoretic) Bisoprolol/hydrochlorothiazide (Ziac) Metoprolol succinate/hydrochlorothiazide (Dutoprol) Metoprolol tartrate/hydrochlorothiazide (Lopressor HCT) Nadolol/bendroflumethiazide (Corzide) Propranolol/hydrochlorothiazide (Inderide)
β-Blocker with an ARB	Nebivolol/valsartan (Byvalson)
Direct renin inhibitor with thiazide	Aliskiren/hydrochlorothiazide (Tekturna HCT)
Direct renin inhibitor with CCB	Aliskiren/amlodipine (Tekamlo)
Mineralocorticoid receptor antagonist with thiazide	Spironolactone/hydrochlorothiazide (Aldactazide)
ARB with CCB with a thiazide	Amlodipine/valsartan/hydrochlorothiazide (Exforge HCT) Olmesartan/amlodipine/hydrochlorothiazide (Tribenzor)
Direct renin inhibitor with CCB with a thiazide	Aliskiren/amlodipine/hydrochlorothiazide (Amturnide)

Pharmacoeconomic Considerations

The cost of effectively treating hypertension is substantial, with estimated annual healthcare expenditures of approximately $2,000 more for patients with hypertension than without hypertension.[93] The average annual direct and indirect cost of hypertension from 2013 to 2014 was $53.2 billion, with direct costs alone estimated to grow to $220.9 billion by 2035.[4] Costs of care, though, are offset by savings that would be realized by reducing CV morbidity and mortality. Cost related to treating CV events (eg, MI, end-stage kidney failure) can drastically increase healthcare costs.

Antihypertensive drug costs are not a major portion of the total cost of hypertensive care. Most antihypertensives including an ACEi, an ARB, a CCB, and a thiazide are generic, with many available on discount formularies, including even generic fixed-dose combinations.

It is crucial to identify ways to control the cost of care without increasing the morbidity and mortality associated with uncontrolled hypertension. Using evidence-based pharmacotherapy will save costs. An ACEi, an ARB, a CCB, and a thiazide are all first-line treatment options in most patients without compelling indications, and are inexpensive, with few exceptions. Utilizing generic agents, either as monotherapy or in combination, is appropriate under nearly all circumstances in hypertension management. Use of once-daily and fixed-dose generic combination antihypertensives that are economical is preferred.[1]

Team-Based Collaborative Care

Team-based care for patients with cardiovascular disease is highly recommended in the comprehensive care of patients.[1] A collaborative approach to management of hypertension is a proven strategy that improves goal BP attainment rates.[1] Ideal patient care models are interprofessional and utilize physicians, pharmacists, nurses, and other healthcare professionals.

With the advent of healthcare reform, collaborative team-based approaches to chronic diseases are viewed as high-quality and costeffective improvement modalities. Within these models, pharmacists have been proven to be an effective component of team-based models not only in community pharmacy or ambulatory clinic settings[94] but also in community outreach sites such as black-owned barbershops.[95] In addition to optimizing selection and implementation of

antihypertensive drug therapy and increased attainment of goal BP, clinical interventions by pharmacists have been proven to reduce the risk of adverse drug events and medication errors in ambulatory patients with CV disease.[96] Clinical pharmacists have a substantial effect in a wide variety of roles in clinical settings, largely through optimization of drug use, avoidance of adverse drug events, and transitional care activities focusing on medication reconciliation and patient education.[97]

Hypertensive Urgencies and Emergencies

Both hypertensive urgencies and emergencies are characterized by the presence of very elevated BP, typically >180/120 mm Hg.[1] However, the need for urgent or emergent antihypertensive therapy must be determined based on the presence of acute or immediately progressing end-organ injury, not elevated BP alone. Urgencies are not associated with acute or immediately progressing end-organ injury, while emergencies are. Examples of acute end-organ injury include encephalopathy, intracranial hemorrhage, acute left ventricular failure with pulmonary edema, dissecting aortic aneurysm, unstable angina, acute renal failure, and eclampsia.

14 **Hypertensive Urgency** A common error with hypertensive urgency is implementing overly aggressive antihypertensive drug therapy. The classification terminology “urgency” has likely perpetuated this treatment. Hypertensive urgencies are ideally managed by adjusting maintenance therapy, by adding a new antihypertensive agent, by increasing the dose of a current medication, or by treating anxiety as applicable.[1] Using this approach is preferred as it provides a more gradual reduction in BP. Very rapid reductions in BP to goal values should be discouraged due to potential risks of adverse events. Because autoregulation of blood flow in patients with hypertension occurs at a much higher range of pressure than in normotensive persons, the inherent risks of reducing BP too precipitously include cerebrovascular accidents, MI, and acute kidney failure. Hypertensive urgency requires BP reductions with oral antihypertensive agents to stage 2 over a period of several hours to days. All patients with hypertensive urgency should be reevaluated within and no later than 7 days (preferably after 1-3 days).

Acute administration of a short-acting oral antihypertensive (eg, captopril, clonidine, labetalol) followed by careful observation for several hours to assure a gradual reduction in BP is an option for treatment of hypertensive urgency. However, no data support this approach as being absolutely needed. Oral

captopril is one of the agents of choice and can be used in doses of 25 to 50 mg at 1to 2-hour intervals. The onset of action of oral captopril is 15 to 30 minutes, and a marked fall in BP is unlikely to occur if no hypotensive response is observed within 30 to 60 minutes. For patients with hypertensive rebound following withdrawal of clonidine, 0.2 mg can be given initially, followed by 0.2 mg hourly until the DBP falls below 110 mm Hg or a total of 0.7 mg clonidine has been administered. A single dose may be all that is necessary. Labetalol can be given in a dose of 200 to 400 mg, followed by additional doses every 2 to 3 hours.

Oral or sublingual immediate-release nifedipine has been used for acute BP lowering in the past but is dangerous. This approach produces a rapid reduction in BP. Immediate-release nifedipine should never be used for hypertensive urgencies due to risk of causing severe adverse events (eg, MI, stroke).

Hypertensive Emergency Hypertensive emergencies are rare situations that require immediate BP reduction with one of the parenteral agents listed in **Table 30-10** to limit new or progressing end-organ damage (see Classification under Arterial BP above). The rate of BP reduction is dependent upon whether the patient has aortic dissection, severe preeclampsia or eclampsia, or pheochromocytoma with hypertensive crisis. In these life-threatening situations, patients should be cared for in the intensive care unit, and SBP should be reduced immediately to <140 mm Hg in the first hour, with additional BP lowering to <120 mm Hg for patients with an aortic dissection.[1] For patients with a hypertensive emergency that do not have an aortic dissection, severe preeclampsia or eclampsia, pheochromocytoma with hypertensive crisis, the goal is not to lower BP to <130/80 mm Hg; rather, the initial target is a reduction in MAP of up to 25% within over the first hour. If the patient is then stable, BP can be reduced to 160/100-110 mm Hg within the next 2 to 6 hours.[1] Precipitous drops in BP may lead to end-organ ischemia or infarction. If patients tolerate this reduction well, additional gradual decreases toward goal BP values can be attempted after 24 to 48 hours. The exception to this guideline is for patients with an acute ischemic stroke where maintaining an elevated BP is needed for a longer period.

TABLE 30-10 Parenteral Antihypertensive Agents for Hypertensive Emergency

Medication	Dose	Onset (minutes)	Duration (minutes)	Adverse Effects	Special Indications
Clevidipine	1-2 mg/hr (32 mg/hr maximum)	2-4	5-15	Headache, nausea, tachycardia, hypertriglyceridemia	Most hypertensive emergencies except acute HF; caution with coronary ischemia; contraindicated in soy or egg allergy, defective lipid metabolism, and severe aortic stenosis
Enalaprilat	1.25-5 mg IV every 6 hours	15-30	360-720	Precipitous fall in pressure in high-renin states; variable response	Acute left ventricular heart failure; avoid in acute myocardial infarction, eclampsia
Esmolol hydrochloride	250-500 mcg/kg/min IV bolus, and then 50-100 mcg/kg/min IV infusion; may repeat bolus after 5 minutes or increase infusion to 300 mcg/min	1-2	10-20	Hypotension, nausea, asthma, first-degree heart block, HF	Aortic dissection; perioperative; avoid in patients treated with a β-blocker, bradycardic, or decompensated HF
Fenoldopam mesylate	0.1-0.3 mcg/kg/min IV infusion	<5	30	Tachycardia, headache, nausea, flushing	Most hypertensive emergencies; caution with glaucoma
Hydralazine hydrochloride	12-20 mg IV 10-50 mg intramuscular	10-20 20-30	60-240 240-360	Tachycardia, flushing, headache, vomiting, aggravation of angina	Eclampsia
Labetalol hydrochloride	20-80 mg IV bolus every 10 minutes; 0.5-2 mg/min IV infusion	5-10	180-360	Vomiting, scalp tingling, bronchoconstriction, dizziness, nausea, heart block, orthostatic hypotension	Most hypertensive emergencies except acute HF or heart block
Nicardipine hydrochloride	5-15 mg/hr IV	5-10	15-30, may exceed 240	Tachycardia, headache, flushing, local phlebitis	Most hypertensive emergencies except acute HF; caution with coronary ischemia
Nitroglycerin	5-100 mcg/min IV infusion	2-5	5-10	Headache, vomiting, methemoglobinemia, tolerance with prolonged use	Coronary ischemia
Sodium nitroprusside	0.25-10 mcg/kg/min IV infusion (requires special delivery system)	Immediate	1-2	Nausea, vomiting, muscle twitching, sweating, thiocyanate and cyanide intoxication	Most hypertensive emergencies; caution with high intracranial pressure, azotemia, or in chronic kidney disease

The clinical situation should dictate which IV medication is used to treat hypertensive emergencies. Regardless, therapy should be provided in a hospital intensive care unit or emergency room setting with intra-articular BP monitoring. Table 30-10 lists special indications for agents that can be used.

Nitroprusside is widely considered the agent of choice for most cases, but it can be problematic for patients with CKD. It is a direct-acting vasodilator that decreases PVR but does not increase CO unless left ventricular failure is present. Nitroprusside can be given to treat most hypertensive emergencies, but in aortic dissection, propranolol should be given first to prevent reflex sympathetic activation. Nitroprusside is metabolized to cyanide and then to thiocyanate, which is eliminated by the kidneys. Therefore, serum thiocyanate levels should be monitored when infusions are continued for longer than 72 hours. Nitroprusside should be discontinued if the concentration exceeds 12 mg/dL (~2 mmol/L). The risk of thiocyanate accumulation and toxicity is increased for patients with impaired kidney function. The use of nitroprusside is limited by a recent and significant increase in the cost of this agent.

IV nitroglycerin dilates both arterioles and venous capacitance vessels, thereby reducing both cardiac afterload and cardiac preload, which can decrease myocardial oxygen demand. It also dilates collateral coronary blood vessels and improves perfusion to ischemic myocardium. These properties make IV nitroglycerin ideal for the management of hypertensive emergency in the presence of myocardial ischemia and/or acute pulmonary edema. IV nitroglycerin is associated with tolerance when used over 24 to 48 hours and can cause a severe headache.

Fenoldopam, nicardipine, and clevidipine are newer agents. Fenoldopam is a dopamine-1 agonist. It can improve renal blood flow and may be especially useful for patients with kidney insufficiency. Nicardipine and clevidipine are dihydropyridine CCBs that provide arterial vasodilation and can treat cardiac ischemia similar to nitroglycerin, but they may provide more predictable reductions in BP.

The hypotensive response of hydralazine is less predictable than with other parenteral agents. Therefore, its major role is in the treatment of eclampsia or hypertensive encephalopathy associated with renal insufficiency.

EVALUATION OF THERAPEUTIC OUTCOMES

Monitoring the Pharmacotherapy Plan

Routine, ongoing monitoring to assess the desired effects of antihypertensive therapy (efficacy, including BP goal attainment), undesired adverse effects (side effects and toxicity), and disease progression is needed in all patients treated with antihypertensive drug therapy.

Efficacy

The most important strategy to prevent CV morbidity and mortality in hypertension is BP control to goal (see “DESIRED OUTCOMES: GOAL BP FOR CHRONIC TREATMENT” box). Treating to a goal BP of <130/80 mm Hg should be attained in older patients and those with isolated systolic hypertension, but actual BP lowering can occur at a more gradual pace to avoid orthostatic hypotension. Modifying other CV risk factors (eg, smoking, dyslipidemia, diabetes) is also essential.

Both clinic-based and self-measurement home BP monitoring are important components for monitoring and managing hypertension. Patients should be encouraged to obtain a validated home BP monitor, record the results, and send or bring them to follow-up clinic visits. BP response should be evaluated in the clinic 4 weeks after initiating or making changes in therapy and results compared to home BP readings. Once goal BP is attained, assuming no signs or symptoms of acute end-organ damage are present, clinic BP monitoring can be done every 3 to 6 months. More frequent evaluations are required for patients with a history of poor control, nonadherence, progressive end-organ damage, or symptoms of adverse drug effects.

Automated ABP monitoring can be useful clinically to establish effective 24-hour control. This type of monitoring may become the standard of care in the future because evolving data have demonstrated significant benefits of using these types of measurements to diagnose hypertension, confirm white coat or masked uncontrolled hypertension, and could be a stronger predictor of CVD.[1]

For patients self-measuring their BP at home, it is important that they measure during the early morning hours, taking at least two measurements 1 minutes apart before taking antihypertensive medications for most days and then in the evening on alternate days of the week using appropriate technique.[1] BP measurements should be recorded daily, or ideally, a monitor with a built-in memory should be used. Patients should be instructed to bring their actual measurements and/or BP monitor with built-in memory to follow-up clinic appointments, and any changes to drug therapy should be based on an average BP reading from two or more occasions.[1]

Side Effects and Toxicity

Patients should be monitored routinely for adverse drug effects. The most common side effects associated with each class of antihypertensive agents were discussed in the previous "Individual Antihypertensive Agents" section, and laboratory parameters for first-line agents are listed in **Table 30-11**. Laboratory monitoring should typically occur 4 weeks after starting a new agent or dose increase, and then every 6 to 12 months in stable patients. Additional disease-specific monitoring might be needed (eg, diabetes, dyslipidemia, gout) depending on which agents are used. Moreover, patients treated with a mineralocorticoid receptor antagonist (eplerenone or spironolactone) should have potassium concentrations and kidney function assessed within 3 days of initiation and again at 1 week to detect potential hyperkalemia. The occurrence of an adverse drug event may require dosage reduction or substitution with an alternative antihypertensive agent.

TABLE 30-11 Routine Monitoring for Select Antihypertensive Agents

Class	Parameters
ACEi	BP; BUN/serum creatinine; serum potassium
ARB	BP; BUN/serum creatinine; serum potassium
β-Blocker	BP; heart rate
Calcium channel blocker	BP; heart rate
Mineralocorticoid receptor antagonist	BP; BUN/serum creatinine; serum potassium
Thiazide	BP; BUN/serum creatinine; serum electrolytes (potassium, magnesium, sodium); uric acid (for thiazides)

Disease Progression

Patients should be monitored for signs and symptoms of hypertension-associated complications. A careful history for ischemic chest pain (or pressure), palpitations, dizziness, dyspnea, orthopnea, headache, sudden change in vision, one-sided weakness, slurred speech, and loss of balance should be taken to determine the presence of CV and cerebrovascular disease. Other monitoring parameters that may be used include funduscopic changes on eye exam, LVH on electrocardiogram, albuminuria, and changes in kidney function by calculating estimated GFR. These parameters should be monitored periodically because any sign of deterioration requires additional assessment and follow-up.

Adherence and Persistence

Poor medication use behaviors and lack of persistence with antihypertensive pharmacotherapy is a major problem and associated with significant increases in costs due to development of complications. Since hypertension is a relatively asymptomatic disease, poor adherence is frequent, particularly in newly treated patients. Up to 25% of patients do not fill their initial prescription for antihypertensive medication and during the first year of treatment an average patient possesses their BP medication only half of the time.[1] Long-term risk of CV events can be significantly reduced when patients are adherent to their antihypertensive drug therapy. Therefore, it is imperative to assess patient adherence and medication taking behavior on a regular basis.

Improving adherence to antihypertensive treatment and hypertension control requires a multifactorial approach.[1] These include interventions aimed at the patient, provider, and healthsystem level. Examples can include (a) focusing on clinical outcomes (eg, following national guidelines, use of once-daily antihypertensives and combination rather than free individual components, encouraging self-monitoring of BP), (b) empowering informed activated patients (eg, behavioral and motivational strategies, use of pill boxes, systems to prompt patients to refill prescriptions), (c) implementing a team approach (eg, collaborative interprofessional models of care), (d) use of telehealth strategies (eg, transmission of data from self-monitored BP to assist in BP management), and (e) advocating for health policy reform (eg, use of performance measures, reduce patient copayments for healthcare services and medications, provide financial incents to providers for improved performance).

After identifying less than optimal adherence in a patient with hypertension, appropriate patient education, counseling, and intervention should occur. Once-daily regimens are recommended in most patients to improve adherence. Some patients may incorrectly believe that aggressive treatment may negatively impact the quality of life and thus result in nonadherence. However, several studies have found that most patients feel better once their BP is controlled, and patients should be made aware of this. Patients on antihypertensive therapy should be questioned periodically about changes in their general health perception, physical functioning, and overall satisfaction with treatment. Lifestyle modifications should always be recommended to augment antihypertensive drug therapy and provide other potential health benefits. Persistence with lifestyle modifications should also be continually encouraged.

CONCLUSION

Hypertension is a very common medical condition in the United States with significant health consequence if not controlled. Treatment of patients with hypertension should include both lifestyle modifications and pharmacotherapy. Evidence from outcome-based clinical trials has definitively demonstrated that treating hypertension reduces the risk of CV events and subsequently reduces morbidity and mortality. Moreover, evidence evaluating individual drug classes has resulted in an evidence-based approach to selecting pharmacotherapy in an individual patient. An ACEi, an ARB, a CCB, and a thiazide are all first-line agents. Data suggest that using a β-blocker first-line to treat patients with hypertension, without the presence of a compelling indication, may not be as beneficial in reducing the risk of CV events compared with ACEi-, ARB-, CCB-, or thiazide-based therapy. Therefore, they are not first-line therapy options unless an appropriate compelling indication is present.

Patients should be treated to a goal BP value. In addition to selecting an appropriate antihypertensive regimen, attaining a goal BP is also of paramount importance to ensure a maximum reduction in risk for CV events is provided. A BP goal of <130/80 mm Hg is recommended for most patients with hypertension. Most patients with hypertension require more than one drug to attain goal BP values; therefore, combination therapy should be anticipated.

Optimizing hypertension management can be achieved in many ways. Team-based approaches to implementing care and attain goal BP values are effective. Judicious use of cost-effective medications and fixed-dose combination products should always be considered to improve the sustainability of treatment. Lastly, interventions to reinforce adherence and lifestyle modifications are needed for comprehensive management of hypertension.

Postclass Engaged Learning Activity

Review the following materials on iForumRx.org website:

- Read “Ten Things Every Clinician Should Know About the 2017 Hypertension Guidelines” available at: https://tinyurl.com/yxbrsctq
- Listen to the embedded podcast.

CLINICAL INTERACTION: PATIENT WITH HYPERTENSION
Complete the activity by doing the following:

- Reevaluate the patient with hypertension that you identified for the PRECLASS engaged learning activity (prescribed two or more antihypertensive agents) based on the information that you collected during the activity.
- Assess the patient's hypertension and determine if it is controlled.
- Assess the patient's antihypertensive drug therapy regimen and determine if the medications are appropriate for the patient, considering safety and efficacy.
- Identify any barriers to adherence to either medications or lifestyle modifications that are present in the patient and formulate solutions for these barriers.
- Determine what recommendations you would have for this patient's antihypertensive drug therapy regimen and any changes to monitoring.
- Provide education regarding lifestyle modifications, antihypertensive drug therapy, and self-monitoring.

ABBREVIATIONS

ABP	ambulatory blood pressure
ACC	American Heart Association
ACCOMPLISH	Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension
ACCORD-BP	Action to Control Cardiovascular Risk in Diabetes Blood Pressure
ACE	angiotensin-converting enzyme
AHA	American Heart Association
ALLHAT	Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial
ARB	angiotensin II receptor blocker
ASCVD	atherosclerotic cardiovascular disease
AT_1	angiotensin II type 1
AT_2	angiotensin II type 2
BP	blood pressure
BUN	blood urea nitrogen
CCB	calcium channel blocker
CKD	chronic kidney disease
CO	cardiac output
CONVINCE	Controlled Onset Verapamil Investigation of Cardiovascular End-Points
COPD	chronic obstructive pulmonary disease
CV	cardiovascular
DASH	Dietary Approaches to Stop Hypertension
DBP	diastolic blood pressure
GEMINI	Glycemic Effects in Diabetes Mellitus: Carvedilol–Metoprolol Comparison in Hypertensives
GFR	glomerular filtration rate

HOT	Hypertension Optimal Treatment
HF	Heart Failure
HF*p*EF	Heart Failure with preserved Ejection Fraction
HF*r*EF	Heart Failure with reduced Ejection Fraction
HYVET	Hypertension in the Very Elderly Trial
INVEST	International Verapamil–Trandolapril Study
ISA	intrinsic sympathomimetic activity
KDIGO	Kidney Disease Improving Global Outcomes
LVH	left ventricular hypertrophy
MAP	mean arterial pressure
MDRD	modification of diet in renal disease
MI	myocardial infarction
MOSES	Morbidity and Mortality After Stroke: Eprosartan Versus Nitrendipine in Secondary Prevention
MRC	Medical Research Council
NHLBI	National Heart, Lung, and Blood Institute
ON-TARGET	Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial
PAD	Peripheral arterial disease
PATHWAY-2	Prevention and Treatment of Hypertension with Algorithm Based Therapy-2
PVR	peripheral vascular resistance
RAAS	renin–angiotensin–aldosterone system
SBP	systolic blood pressure
SHEP	Systolic Hypertension in the Elderly Program
SPRINT	Systolic Pressure Intervention Trial
STOP-2	Swedish Trial in Old Patients with Hypertension-2
STOP-Hypertension	Swedish Trial in Old Patients with Hypertension
Syst-Eur	Systolic Hypertension in Europe
TOMHS	Treatment of Mild Hypertension Study
TPR	total peripheral resistance
TRANSCEND	Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects with Cardiovascular Disease
UKPDS	United Kingdom Prospective Diabetes Study
VALUE	Valsartan Antihypertensive Long-Term Use Evaluation

REFERENCES

1. Whelton JR, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.. *Hypertension*. 2018;71(6):e13–e115.
2. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42(6):1206–1252.
3. Muntner P, Carey RM, Gidding S, et al. Potential U.S. population impact of the 2017 ACC/AHA High Blood Pressure Guideline. *J Am Coll Cardiol*. 2018;71(2):109–118. doi: 10.1016/j. jacc.2017.10.073.
4. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics—2018 update: A report from the American Heart Association. *Circulation*. 2018;137(12):e67–e492. doi: 10.1161/CIR.0000000000000558.
5. Wilson L, Saseen JJ. Hypertension. *Drug-Induced Diseases: Prevention, Detection, and Management*. Bethesda, MD: American Society of Health-Systems Pharmacists, Inc.: chap 27. In press.
6. Guo X, Zhang X, Guo L, et al. Association between pre-hypertension and cardiovascular outcomes: A systematic review and meta-analysis of prospective studies. *Curr Hypertens Rep*. 2013;15(6):703–716. doi: 10.1007/s11906-013-0403-y.
7. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies C. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360(9349):1903–1913.
8. Dahlof B, Lindholm LH, Hansson L, Schersten B, Ekbom T, Wester PO. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet*. 1991;338(8778):1281–1285.
9. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA*. 1991;265(24):3255–3264.

10. MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. *BMJ*. 1992;304(6824):405–412.
11. Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals: part 1: Blood pressure measurement in humans: A statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Circulation*. 2005;111(5):697–716.
12. Pickering TG, Davidson K, Gerin W, Schwartz JE. Masked hypertension. *Hypertension*. 2002;40(6):795–796.
13. Mancia G, Bombelli M, Facchetti R, et al. Long-term risk of sustained hypertension in white-coat or masked hypertension. *Hypertension*. 2009;54(2):226–232. doi: 10.1161/HYPERTENSIONAHA.109.129882.
14. Banegas JR, Ruilope LM, de la Sierra A, et al. Relationship between clinic and ambulatory blood-pressure measurements and mortality. *N Engl J Med*. 2018;378(16):1509–1520. doi: 10.1056/NEJMoa1712231.
15. American Diabetes Association. Cardiovascular disease and risk management: Standards of medical care in diabetes 2018. *Diabetes Care*. 2018;41(Suppl 1):S86–S104. doi: 10.2337/dc18-S009.
16. Kidney Disease Improving Global Outcomes. Chapter 3: Blood pressure management in CKD ND patients without diabetes mellitus. *Kidney Int Suppl* (2011). 2012;2(5):357–362. doi: 10.1038/kisup.2012.53.
17. Kidney Disease Improving Global Outcomes. Chapter 4: Blood pressure management in CKD ND patients with diabetes mellitus. *Kidney Int Suppl* (2011). 2012;2(5):363–369. doi: 10.1038/kisup.2012.54.
18. The SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373(22):2103–2116. doi: 10.1056/NEJMoa1511939.
19. Reboussin DM, Allen NB, Griswold ME, et al. Systematic review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2017;71:e116–e135. doi: 10.1161/hyp.0000000000000067.

20. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: Updated systematic review and meta-analysis. *Lancet*. 2016;387(10017):435–443. doi: 10.1016/s0140-6736(15)00805-3.
21. Bundy JD, Li C, Stuchlik P, et al. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: A systematic review and network meta-analysis. *JAMA Cardiol*. 2017;2(7):775–781. doi: 10.1001/jamacardio.2017.1421.
22. The Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: A metaanalysis of individual patient data. *Lancet*. 2014;384(9943):591–598. doi:10.1016/s0140-6736(14)61212-5.
23. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 7. Effects of more vs. less intensive blood pressure lowering and different achieved blood pressure levels—updated overview and meta-analyses of randomized trials. *J Hypertens*. 2016;34(4):613–622. doi:10.1097/hjh.0000000000000881.
24. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: Principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet*. 1998;351(9118):1755–1762.
25. The ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362(17):1575–1585. doi: 10.1056/NEJMoa1001286.
26. Buckley LF, Dixon DL, Wohlford GFt, Wijesinghe DS, Baker WL, Van Tassell BW. Intensive versus standard blood pressure control in SPRINT-eligible participants of ACCORD-BP. *Diabetes Care*. 2017;40(12):1733–1738. doi: 10.2337/dc17-1366.
27. O'Connor PJ. Overcome clinical inertia to control systolic blood pressure. *Arch Intern Med*. 2003;163(22):2677–2678.
28. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and LipidLowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288(23):2981–2997.
29. Black HR, Elliott WJ, Grandits G, et al. Principal results of the Controlled

Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. *JAMA*. 2003;289(16):2073–2082.

30. Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): A randomised trial against atenolol. *Lancet*. 2002;359(9311):995–1003.
31. Dahlof B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): A multicentre randomised controlled trial. *Lancet*. 2005;366(9489):895–906.
32. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: The VALUE randomised trial. *Lancet*. 2004;363(9426):2022–2031.
33. PROGRESS Collaborative Group. Randomised trial of a perindoprilbased blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet*. 2001;358(9287):1033–1041.
34. Wing LM, Reid CM, Ryan P, et al. A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med*. 2003;348(7):583–592.
35. Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Collaborative Research Group. Diuretic versus alphablocker as first-step antihypertensive therapy: Final results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Hypertension*. 2003;42(3):239–246.
36. Davis BR, Cutler JA, Gordon DJ, et al. Rationale and design for the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). ALLHAT Research Group. *Am J Hypertens*. 1996;9(4 Pt 1):342–360.
37. Rahman M, Pressel S, Davis BR, et al. Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a diuretic: A report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med*. 2005;165(8):936–946.
38. Whelton PK, Barzilay J, Cushman WC, et al. Clinical outcomes in

antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and LipidLowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med*. 2005;165(12):1401–1409.

39. Wright JT Jr., Dunn JK, Cutler JA, et al. Outcomes in hypertensive black and nonblack patients treated with chlorthalidone, amlodipine, and lisinopril. *JAMA*. 2005;293(13):1595–1608.
40. Turnbull F. Effects of different blood-pressure-lowering regimens on major cardiovascular events: Results of prospectively-designed overviews of randomised trials. *Lancet*. 2003;362(9395):1527–1535.
41. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34(28):2159–2219. doi: 10.1093/eurheartj/eht151.
42. National Institute for Health and Clinical Excellence (NICE) Clinical Guideline. Hypertension in adults: Diagnosis and management. https://www.nice.org.uk/guidance/cg127. Accessed May 29, 2018.
43. Zhang Y, Sun N, Jiang X, Xi Y. Comparative efficacy of beta-blockers on mortality and cardiovascular outcomes in patients with hypertension: A systematic review and network meta-analysis. *J Am Soc Hypertens*. 2017;11(7):394–401. doi: 10.1016/j.jash.2017.05.001.
44. Ripley TL, Saseen JJ. Beta-blockers: A review of their pharmacological and physiological diversity in hypertension. *Ann Pharmacother*. 2014;48(6):723–733. doi: 10.1177/1060028013519591.
45. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136(6): e137–e161. doi: 10.1161/CIR.0000000000000509.
46. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: Executive summary—a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128(16):1810–1852. doi: 10.1161/CIR.0b013e31829e8807.
47. Bangalore S, Steg G, Deedwania P, et al. Beta-blocker use and clinical

outcomes in stable outpatients with and without coronary artery disease. *JAMA*. 2012;308(13):1340–1349. doi: 10.1001/jama.2012.12559.

48. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2014;130(19):1749–1767. doi: 10.1161/CIR.0000000000000095.
49. Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International VerapamilTrandolapril Study (INVEST): A randomized controlled trial. *JAMA*. 2003;290(21):2805–2816.
50. American Diabetes Association. Microvascular complications and foot care: Standards of medical care in diabetes—2018. *Diabetes Care*. 2018;41(Suppl 1):S105–S118. doi: 10.2337/dc18-S010.
51. Bangalore S, Fakheri R, Toklu B, Messerli FH. Diabetes mellitus as a compelling indication for use of renin angiotensin system blockers: Systematic review and meta-analysis of randomized trials. *BMJ*. 2016;352:i438. doi: 10.1136/bmj.i438.
52. Wright JT Jr., Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: Results from the AASK trial. *JAMA*. 2002;288(19):2421–2431.
53. Casas JP, Chua W, Loukogeorgakis S, et al. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: Systematic review and meta-analysis. *Lancet*. 2005;366(9502):2026–2033.
54. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(7):2160–2236. doi: 10.1161/STR.0000000000000024.
55. Rashid P, Leonardi-Bee J, Bath P. Blood pressure reduction and secondary prevention of stroke and other vascular events: A systematic review.

Stroke. 2003;34(11):2741–2748. doi: 10.1161/01.STR.0000092488.40085.15.

56. Schrader J, Luders S, Kulschewski A, et al. Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention: Principal results of a prospective randomized controlled study (MOSES). *Stroke*. 2005;36(6):1218–1226.
57. Yusuf S, Diener HC, Sacco RL, et al. Telmisartan to prevent recurrent stroke and cardiovascular events. *N Engl J Med*. 2008;359(12): 1225–1237. doi: 10.1056/NEJMoa0804593.
58. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med*. 2008;358(18): 1887–1898. doi: 10.1056/NEJMoa0801369.
59. Hansson L, Lindholm LH, Ekbom T, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: Cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet*. 1999;354(9192):1751–1756.
60. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the eighth joint national committee (JNC 8). *JAMA*. 2014;311(5):507–520. doi: 10.1001/jama.2013.284427.
61. Wright JT Jr, Fine LJ, Lackland DT, Ogedegbe G, Dennison Himmelfarb CR. Evidence supporting a systolic blood pressure goal of less than 150 mm Hg in patients aged 60 years or older: The minority view. *Ann Intern Med*. 2014;160(7):499–503. doi: 10.7326/M13-2981.
62. Williamson JD, Supiano MA, Applegate WB, et al. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥75 years: A randomized clinical trial. *JAMA*. 2016;315(24): 2673–2682. doi: 10.1001/jama.2016.7050.
63. Bavishi C, Bangalore S, Messerli FH. Outcomes of intensive blood pressure lowering in older hypertensive patients. *J Am Coll Cardiol*. 2017;69(5):486–493. doi: 10.1016/j.jacc.2016.10.077.
64. Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. 2017;140(3): pii: e20171904. doi: 10.1542/peds.2017-1904.
65. American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the

American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol*. 2013;122(5):1122–1131. doi: 10.1097/01.AOG.0000437382.03963.88.

66. Magee LA, von Dadelszen P, Rey E, et al. Less-tight versus tight control of hypertension in pregnancy. *N Engl J Med*. 2015;372(5):407–417. doi: 10.1056/NEJMoa1404595.
67. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2017;69(11):e71–e126. doi: 10.1016/j.jacc.2016.11.007.
68. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and international association for the Study of Obesity. *Circulation*. 2009;120(16):1640–1645. doi:10.1161/CIRCULATIONAHA.109.192644.
69. Ko DT, Hebert PR, Coffey CS, Sedrakyan A, Curtis JP, Krumholz HM. Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *JAMA*. 2002;288(3):351–357.
70. Grimm RHJr., Grandits GA, Prineas RJ, et al. Long-term effects on sexual function of five antihypertensive drugs and nutritional hygienic treatment in hypertensive men and women. Treatment of Mild Hypertension Study (TOMHS). *Hypertension*. 1997;29(1 Pt 1):8–14.
71. Materson BJ, Reda DJ, Cushman WC, et al. Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *N Engl J Med*. 1993;328(13):914–921. doi: 10.1056/NEJM199304013281303.
72. Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: Diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Hypertension*. 2008;51(6):1403–1419. doi: 10.1161/HYPERTENSIONAHA.108.189141.
73. Ernst ME, Moser M. Use of diuretics in patients with hypertension. *N Engl J Med*. 2009;361(22):2153–2164. doi: 10.1056/NEJMra0907219.

74. Roush GC, Ernst ME, Kostis JB, Tandon S, Sica DA. Head-tohead comparisons of hydrochlorothiazide with indapamide and chlorthalidone: Antihypertensive and metabolic effects. *Hypertension*. 2015;65(5):1041–1046. doi: 10.1161/HYPERTENSIONAHA.114.05021.
75. Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): A randomised, doubleblind, crossover trial. *Lancet*. 2015;386(10008):2059–2068. doi: 10.1016/S0140-6736(15)00257-3.
76. Smith SC Jr., Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease—2011 update: A guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation*. 2011;124(22):2458–2473. doi: 10.1161/CIR.0b013e318235eb4d.
77. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the management of patients with non-ST-elevation acute coronary syndromes: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64(24):e139–e228. doi: 10.1016/j.jacc.2014.09.017.
78. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;61(4):e78–e140. doi: 10.1016/j.jacc.2012.11.019.
79. Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensinconverting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: A combined analysis of three trials. *Lancet*. 2006;368(9535):581–588.
80. Yusuf S, Teo K, et al. Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensinconverting enzyme inhibitors: A randomised controlled trial. *Lancet*. 2008;372(9644):1174–1183. doi: 10.1016/S0140-6736(08)61242-8.

81. Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358(15):1547–1559. doi: 10.1056/NEJMoa0801317.
82. Abraham HM, White CM, White WB. The comparative efficacy and safety of the angiotensin receptor blockers in the management of hypertension and other cardiovascular diseases. *Drug Saf*. 2015;38(1):33–54. doi: 10.1007/s40264-014-0239-7.
83. Yusuf S, Teo K, Anderson C, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet*. 2008;372(9644):1174–1183. doi: 10.1016/S0140-6736(08)61242-8.
84. Leenen FH, Nwachuku CE, Black HR, et al. Clinical events in high-risk hypertensive patients randomly assigned to calcium channel blocker versus angiotensin-converting enzyme inhibitor in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. *Hypertension*. 2006;48(3):374–384.
85. Messerli FH, Makani H, Benjo A, Romero J, Alviar C, Bangalore S. Antihypertensive efficacy of hydrochlorothiazide as evaluated by ambulatory blood pressure monitoring: a meta-analysis of randomized trials. *J Am Coll Cardiol*. 2011;57(5):590–600. doi: 10.1016/j.jacc.2010.07.053.
86. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *BMJ*. 1998;317(7160):713–720.
87. Bakris GL, Fonseca V, Katholi RE, et al. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: A randomized controlled trial. *JAMA*. 2004;292(18):2227–2236.
88. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med*. 2008;359(23):2417–2428. doi: 10.1056/NEJMoa0806182.
89. Gradman AH, Basile JN, Carter BL, Bakris GL. Combination therapy in hypertension. *J Am Soc Hypertens*. 2010;4(1):42–50. doi: 10.1016/j.jash.2010.02.005.
90. ONTARGET Investigators; Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358(15):1547–1559. doi: 10.1056/NEJMoa0801317.

91. Parving HH, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med*. 2012;367(23):2204–2213. doi: 10.1056/NEJMoa1208799.
92. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: A meta-analysis. *Am J Med*. 2007;120(8):713–719. doi: 10.1016/j.amjmed.2006.08.033.
93. Kirkland EB, Heincelman M, Bishu KG, et al. Trends in healthcare expenditures among US adults with hypertension: national estimates, 2003–2014. *J Am Heart Assoc*. 2018;7(11):pii: e008731. doi: 10.1161/JAHA.118.008731.
94. Santschi V, Chiolero A, Colosimo AL, et al. Improving blood pressure control through pharmacist interventions: A meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2014;3(2):e000718. doi: 10.1161/JAHA.113.000718.
95. Victor RG, Lynch K, Li N, et al. A cluster-randomized trial of blood-pressure reduction in black barbershops. *N Engl J Med*. 2018;378(14):1291–1301. doi: 10.1056/NEJMoa1717250.
96. Murray MD, Ritchey ME, Wu J, Tu W. Effect of a pharmacist on adverse drug events and medication errors in outpatients with cardiovascular disease. *Arch Intern Med*. 2009;169(8):757–763. doi: 10.1001/archinternmed.2009.59.
97. Dunn SP, Birtcher KK, Beavers CJ, et al. The role of the clinical pharmacist in the care of patients with cardiovascular disease. *J Am Coll Cardiol*. 2015;66(19):2129–2139. doi: 10.1016/j.jacc.2015.09.025.

31

Dyslipidemia

Dave L. Dixon and Daniel M. Riche

KEY CONCEPTS

1. Lipid abnormalities increase the risk for coronary heart disease (CHD) and cerebrovascular morbidity and mortality.
2. Low-density-lipoprotein cholesterol (LDL-C) is the primary target for lipid-lowering therapy.
3. Genetic abnormalities and environmental factors are involved in the development of dyslipidemia.
4. Therapeutic lifestyle change is first-line therapy for any lipoprotein disorder.
5. If therapeutic lifestyle changes are insufficient, lipid-lowering agents should be chosen based on which lipid is at an undesirable level and the degree to which it is expected to increase the risk of atherosclerotic cardiovascular disase (ASCVD).
6. Statins are the drugs of choice for dyslipidemia because of potency and cost-effectiveness.
7. If statin monotherapy is insufficient, patients may be treated with evidence-based combination therapy but should be monitored closely for drug–drug interactions.
8. Reducing total cholesterol and LDL-C reduces CHD and total mortality.
9. Lipid-lowering therapies that reduce ASCVD event rates are cost-effective.
10. Several novel medications including antisense oligonucleotide inhibitors of apoB, microsomal triglyceride transport protein inhibitors, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are now available to treat familial hypercholesterolemia. These medications can be used as an adjunct therapy or in lieu of statin therapy.

Preclass Engaged Learning Activity

Watch these YouTube videos to learn about cholesterol basics as well as the physiology of lipoprotein cholesterol and metabolism:

- Cholesterol Good and Bad https://tinyurl.com/yx6a5ufj by the US National Library of Medicine
- Physiology of Lipoprotein Cholesterol https://tinyurl.com/hcy239y by Armando Hasudungan
- Physiology of Lipoprotein Metabolism by National Heart, Blood, Lung Institute https://tinyurl.com/pwo856o

INTRODUCTION

Cholesterol, triglycerides, and phospholipids are the major lipids that combine with proteins to be transported as complexes of lipid and proteins known as lipoproteins. Lipids, such as cholesterol and triglycerides, are insoluble in plasma, which is why the lipoproteins are required for transportation (**Fig. 31-1**).[1,2]

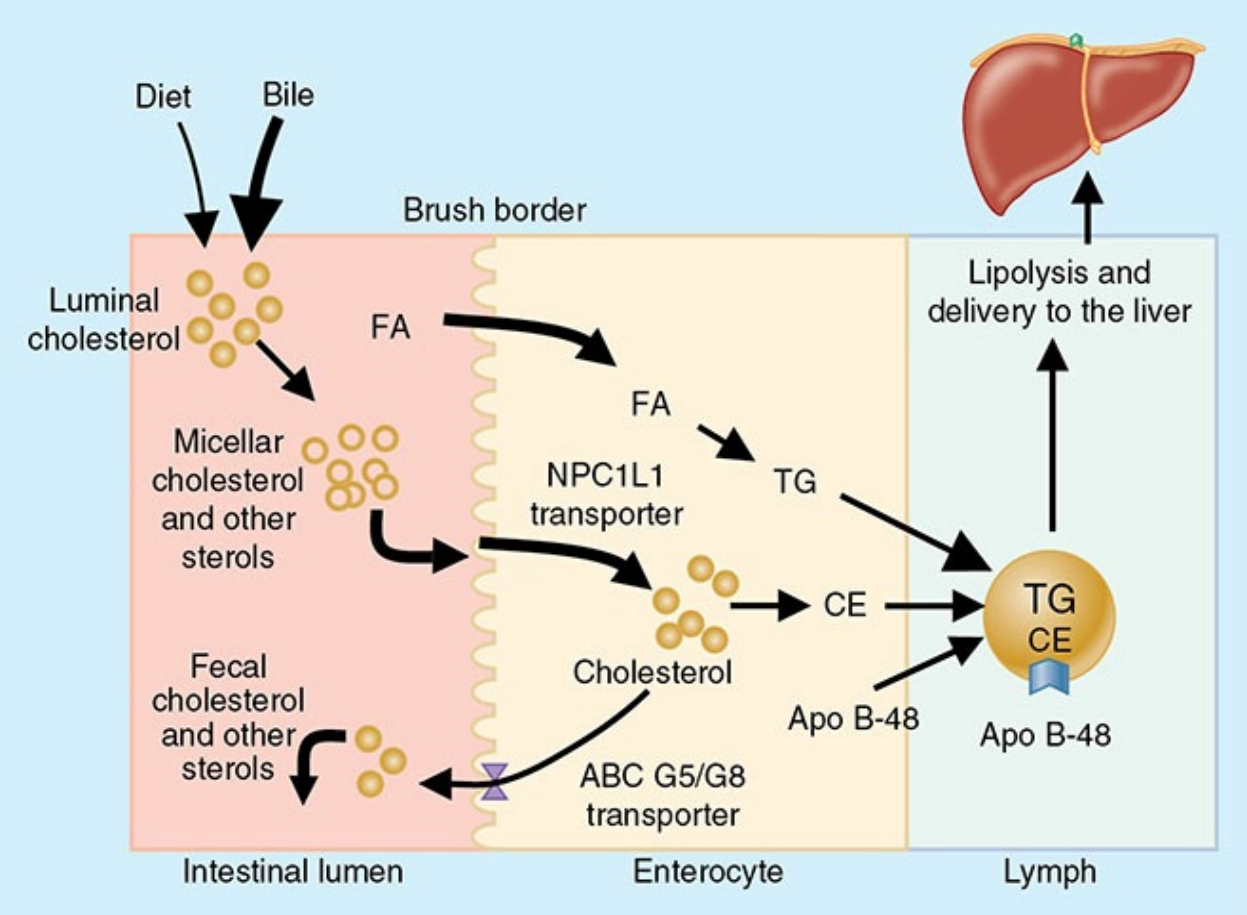


FIGURE 31-1 Intestinal cholesterol absorption and transportation. Cholesterol from food and bile enters the gut lumen and is emulsified by bile acids into micelles. Micelles bind to intestinal enterocytes and cholesterol, and other sterols are transported from the micelles to the enterocytes by sterol transporters. Triglycerides (TG) synthesized by absorbed fatty acids (FA) are incorporated into chylomicrons. Chylomicrons are released into lymphatic circulation and converted to chylomicron remnants (by losing triglyceride), and are then taken up by hepatic LDL-receptor–related protein. (Apo, apolipoprotein; ABC, ATP-binding cassette; CE, cholesterol ester; FA, fatty acid; NPC1L1, Niemann-Pick C1-Like1 protein; TG, triglyceride.) (*Reproduced with permission from Chisholm-Burns MA, Schwinghammer TL, Malone PM, Kolesar JM, Bookstaver PB, Lee KC, eds. Pharmacotherapy Principles & Practice. 5th ed. New York: McGraw-Hill; 2019.*)

There are three major classes of lipoproteins in the serum. These include low-density lipoproteins (LDL), high-density lipoproteins (HDL), and very low-density lipoproteins (VLDL). VLDL is the primary carrier of triglycerides (TG) in the circulation. Intermediate-density lipoprotein (IDL) is between VLDL and

LDL and is included in LDL-C measurement (**Fig. 31-2**).[3]

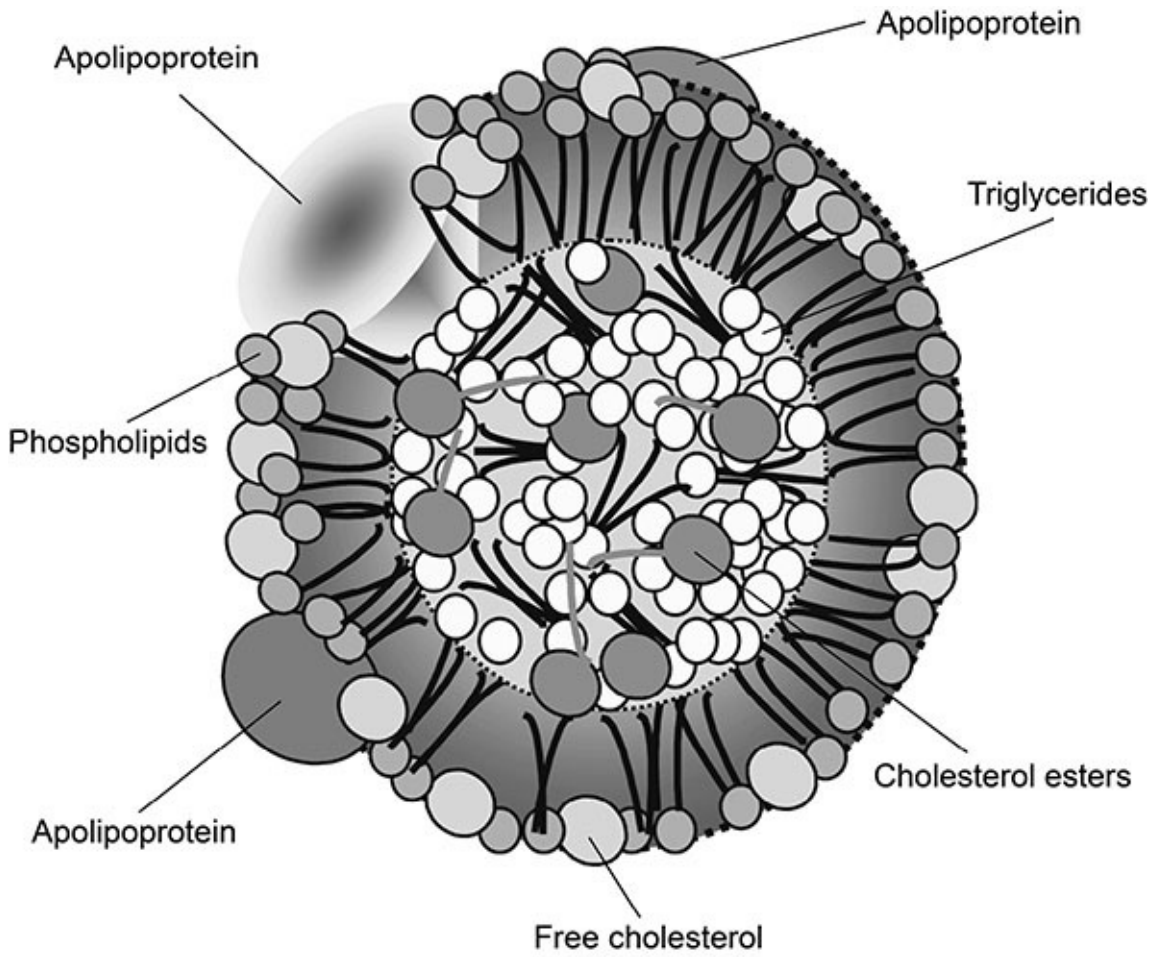


FIGURE 31-2 Lipoprotein structure, which contains variable amounts of core cholesterol esters and triglycerides and have varying numbers and types of surface apolipoproteins.

1 2 Lipid abnormalities increase the risk of coronary, cerebrovascular, and peripheral vascular arterial disease collectively known as atherosclerotic cardiovascular disease (ASCVD). The ASCVD-risk assessment evaluates a 10-year atherosclerotic cardiovascular disease incident. Developing a first ASCVD event is defined as nonfatal myocardial infarction or coronary heart disease (CHD) death, or fatal or nonfatal stroke, over a 10-year period. Premature coronary atherosclerosis is the most common and significant consequence of dyslipidemia. The 2014 guidelines from the American Heart Association (AHA) and American College of Cardiology (ACC) state there is not sufficient evidence to recommend treating to specific lipid targets but suggests four statin benefit patient populations instead. Low-density lipoprotein cholesterol (LDL-C) is the

primary target of lipid lowering therapy. Methods for risk assessment were also updated, which increases the number of patients that would qualify for therapy. Primary and secondary CHD prevention measures are provided as well.[4–7]

There are several subtypes of dyslipidemias, including hypertriglyceridemia, low HDL cholesterol (HDL-C), and diabetic dyslipidemia. Hypertriglyceridemia can lead to pancreatitis when very high TG levels (>500 mg/dL [5.65 mmol/L]) are seen. High serum triglycerides should primarily be treated by achieving desirable body weight, consumption of low saturated fat and cholesterol diet, regular exercise, smoking cessation, and restriction of alcohol.[3,4] In patients with borderline-high TG but with accompanying risk factors of established congenital heart disease, family history of premature CHD, concomitant LDL-C elevation or low HDL-C, and genetic forms of hypertriglyceridemia associated with CHD, lipid-lowering therapy should be considered.[8–10]

Low HDL-C is another dyslipidemia subtype that can occur due to insulin resistance, physical inactivity, diabetes, cigarette smoking, high carbohydrate intake, and some medications. In patients with low HDL-C, the primary target remains LDL-C, but an emphasis on weight loss, increased physical activity, and smoking cessation are recommended. No randomized controlled trials (RCT) have shown a reduction in ASCVD risk by raising HDL-C levels.[3,11] Hypertriglyceridemia, low HDL-C, and minimally elevated LDL-C characterize diabetic dyslipidemia. Because the primary target is LDL-C in diabetic dyslipidemia, statins are considered the drugs of choice.[3,4,12,13]

EPIDEMIOLOGY

Total cholesterol and LDL-C increase throughout life in both men and women. According to AHA estimates, approximately 45% of American adults aged 20 or older have total cholesterol levels exceeding 200 mg/dL (5.17 mmol/L).[14] The prevalence of elevated total cholesterol in adults has remained the same over the past decade but has improved in children. Westernized societal diets high in cholesterol are a strong contributor to the increase in total and LDL-C cholesterol. In 2011, CHD caused one in every seven deaths in the United States. More than half of individuals at borderline-high risk remain unaware that they have dyslipidemia, and fewer than half of the highest risk persons (those with symptomatic CHD) are receiving lipid-lowering treatment. About one-third of treated patients are achieving their LDL-C goal; fewer than 20% of CHD patients are at their LDL-C goal. Estimates from the National Cholesterol Education Program (NCEP) state that only 26% of patients have an optimal

LDL-C (<100 mg/dL [2.59 mmol/L]), and that large numbers of patients are either untreated or undertreated. Patients at highest risk are less likely to be treated to desirable LDL-C values.[15–17] When patients who are at risk but who have not yet experienced initial cardiovascular (eg, myocardial infarction [MI]) or cerebrovascular (eg, ischemic stroke) events are treated, it is termed primary prevention. Treatment for those with manifest ASCVD is termed secondary prevention.[17] Studies, such as the Framingham Heart study, show that risk for developing cardiovascular disease is related to the degree of LDL-C elevation in a continuous fashion.[3] Hypercholesterolemia, cigarette smoking, hypertension, diabetes, and low HDL-C levels are all additive risk factors for CHD. Risk of MI increases five to seven times with any pre-existing CHD or previous MI compared to patients with no history of these. Patients with a history of CHD or MI should be screened, identified, and treated for dyslipidemias. Fifty percent of all MIs and 70% of all deaths due to CHD occur in patients with known CHD.

ETIOLOGY

3 Genetitc abnormalities and environmental factors are involved in the development of dyslipidemia. The underlying causes of dyslipidemias can be categorized into two types: primary or secondary. Genetic factors that increase lipid levels can be inherited and cause primary or familial dyslipidemia. By contrast, lifestyles, diseases, medications, and diet can all lead to abnormal lipid levels and cause secondary or “acquired” dyslipidemia.

Primary or Familial Dyslipidemias

Primary or familial dyslipidemias account for a large number of cases of increased total cholesterol, LDL-C, TGs, or decreased HDL-C. There are certain familial or genetic defects that can contribute. Genetic disorders can cause an increase or decrease in different lipoproteins. Primary dyslipidemias result in an increased risk of premature ASCVD due to significant elevations in cholesterol levels. There are different types of familial dyslipidemias, including hypercholesterolemia, hypertriglyceridemia, combined hyperlipidemia, and disorders of HDL-C metabolism and an excess of lipoproteins. Two other primary disorders include homozygous familial hypercholesterolemia (HoFH) and heterozygous familial hypercholesterolemia (HeFH). HeFH is more common with one case per 250 people versus HoFH with one case per one million people. In familial hypertriglyceridemia, TGs are elevated in the range of

200 to 500 mg/dL (2.26 to 5.65 mmol/L), but at times can be greater than 1,000 mg/dL (11.3 mmol/L). Patients presenting with TG concentrations greater than or equal to 500 mg/dL (5.65 mmol/L) can have eruptive xanthomas and/or acute pancreatitis. Heterozygous gene dysfunction usually causes elevations in LDL-C between 250 and 450 mg/dL (6.47 to 11.64 mmol/L), and homozygous patients may present with LDL-C concentrations above 500 mg/dL (12.93 mmol/L). Tendon xanthomas are thick cholesterol deposits. Xanthelasmas and arcus cornea can also occur, and these are cholesterol deposits in the eyelids and around the corneal rim.[18–21]

Secondary or Acquired Dyslipidemias

Secondary or acquired dyslipidemias can accompany genetic disorders or cause lipid imbalances. “The 4D classification” of secondary causes of dyslipidemia include, diet, drugs, disorder, and diseases.[19] Regarding diet, an increase in cholesterol can be caused from excessive alcohol use, anorexia, weight gain, excessive carbohydrate intake, and high saturated fat intake. Certain medications can also contribute. For example, some medications that can increase both LDL-C and TGs include atypical antipsychotics, diuretics, beta blockers, glucocorticoids, oral estrogen and progestin, tacrolimus, and cyclosporine.

Certain metabolism disorders can contribute to cholesterol imbalances. Nephrotic syndrome, renal failure, biliary obstruction, hypothyroidism, and pregnancy can all potentially contribute. Comorbid conditions or diseases such as hypothyroidism, pregnancy, obesity, polycystic ovarian syndrome (PCOS), uncontrolled diabetes, liver disease, chronic kidney disease can also play a role.

Although we classify the lipid disorders into primary and secondary dyslipidemias based on etiologies, most dyslipidemias are a result of a combination of both.[4,19]

PATHOPHYSIOLOGY

Lipoproteins and Cholesterol Synthesis

There are four types of lipoproteins: chylomicrons, VLDL, LDL, and HDL. These lipoproteins vary in content of lipid and protein. The ratio of protein and lipid in these lipoproteins contribute to the function of each. Chylomicrons contain the most lipid and very little protein. HDL contains the most protein and a small amount of lipids. The small amount of lipid, and in turn cholesterol, in

HDL lipoproteins gives HDL the role of picking up extra cholesterol from the tissue. LDL is not necessarily “bad” cholesterol, but in excess, this generates the problem. We need cholesterol for the transportation of fats that are absorbed in our diet and delivered to our tissues. Chylomicrons are not normally in plasma during periods of fasting. In the small intestine, fats are digested and emulsified into micelles. Cholesterol is also absorbed. Fatty acids, cholesterol, and proteins or apoproteins are packaged and form the chylomicrons. The chylomicrons circulate around the body and deliver lipids and TGs to tissues in need. The remaining chylomicrons are transported to the liver and bind to LDL receptors. Glucose that has also been absorbed from our diet is delivered to the liver. In the liver, glucose is converted to pyruvate and then to acetyl-CoA. Acetyl-CoA is eventually converted to cholesterol through 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. HMG-CoA reductase is a target for statins, thus stopping cholesterol synthesis. Glycolysis also synthesizes glycerol. Combining glycerol and one fatty acid forms monoacylglycerol, and two more fatty acids form triglycerides. Triglycerides and apoproteins are packed through the Golgi apparatus and form lipoproteins. Lipoproteins contain proteins, apoproteins, TGs, phospholipids, and cholesterol. The liver does not make all lipoproteins. In fact, only empty HDL and VLDL are made in the liver. VLDL has more TGs and lipids than HDL. VLDL transports these lipids and TGs to tissues in need of energy or storage. Adipose tissue stores fat, and many tissues use fatty acids for energy. VLDL is transported across lipase, which changes the VLDL to IDL or intermediate-density lipoproteins. IDL can then be converted to LDL. LDL mainly transports cholesterol to body tissues, which is why LDL contains the most cholesterol. Tissues need cholesterol to make hormones and maintain cell membrane integrity. Once LDL gives these tissues cholesterol, it returns to the liver. LDL binds to LDL receptors and is then either recycled to make more lipoproteins or excreted into the bile. Any excess cholesterol is excreted into the bile, so the body maintains cholesterol balance. HDL or empty HDL plays a role in picking up any or excess cholesterol and returning it to the liver. The full HDL containing the picked up cholesterol binds to scavenger receptors. They are then either recycled or excreted depending on how much cholesterol is needed.[22]

Lipid Metabolism and Transport

Cholesterol is water-insoluble so it cannot circulate through blood without help. Lipoproteins are large carrier proteins to help with transport because they are water-soluble. This allows major lipids to be circulated through the blood.

Lipoproteins vary in characteristics depending on the amount of cholesterol, TG, and apolipoproteins. All lipoproteins also have something called apolipoproteins on its surface. The purpose of apolipoproteins is the assembly and secretion of lipoproteins. They are also major structural components of lipoproteins that have ligands for binding to receptors or cell surfaces. These are the cofactors for the activation of enzymes. Apolipoproteins have various functions that transport lipids from sites of absorption to sites where they are used. Apolipoprotein B containing lipoproteins, known as non-HDL, make up the lipid-delivery pathway. Apolipoprotein A-1 or HDL participates in reverse cholesterol transport. ApoB containing lipoproteins arise from two sources, one being intestinal ApoB-48 and the other hepatic ApoB-100 lineage. ApoB containing lipoproteins are secreted from the intestine or liver into the plasma. Apolipoproteins E, C-II, and C-III are secreted with them. These also may be acquired from HDL. Apolipoprotein remodeling begins, and ApoC-II activates lipoprotein lipase (LPL), which hydrolyzes the lipoprotein core TGs into free fatty acids. The fatty acids exit and the lipoproteins become smaller and smaller. Remodeling of the ApoB-100 hepatic lipoprotein, another step by hepatic lipase (HL) is needed to convert IDL to LDL. Most ApoB remnants are recycled to the liver by the LDL-receptor–related protein (LRP). They can have other metabolic requirements, too. Excess ApoB particles can invade arterial walls and become oxidized. Once oxidized, they are taken up by macrophage scavenger receptors creating foam cells that lead to atheroma.

ApoA-1 or HDL pathways are believed to protect our bodies from atherogenesis. HDL has two major protective roles in preventing atherogenesis. Reverse cholesterol transport is the transfer of excess cholesterol from peripheral tissues by HDL. ApoA-1 is secreted from the liver or intestine and is transported to the cells to remove excess cholesterol. HDL has several cholesterol removing mechanisms. Upregulation of the ATP-binding cassette transporter or ABCA-1 transporter is triggered by excess cholesterol in the macrophages. ABCA-1 harvests free cholesterol and delivers it to the cell membrane. The free cholesterol is esterified by lecithin-cholesterol acyltransferase or LCAT. The cholesterol ester moves to the core of the lipoprotein forming the mature HDL3. Further removal of cholesterol by HDL3 occurs through scavenger receptor class B type 1, or SR-B1 receptors and is acted on by LCAT, which expands to HDL2. ABCA-1 and SR-B1 are key for cholesterol efflux. HDL2 cholesterol is transferred to ApoB containing lipoproteins. HDL now has one of three options: HDL triglycerides may be hydrolyzed by HL back into HDL3; HDL2 can return to the liver and through SR-B1 converted back to HDL3; or HDL2 may be catabolized by the liver. All of these systems work together to maintain

cholesterol homeostasis (**Figs. 31-3** and **31-4**).[23]

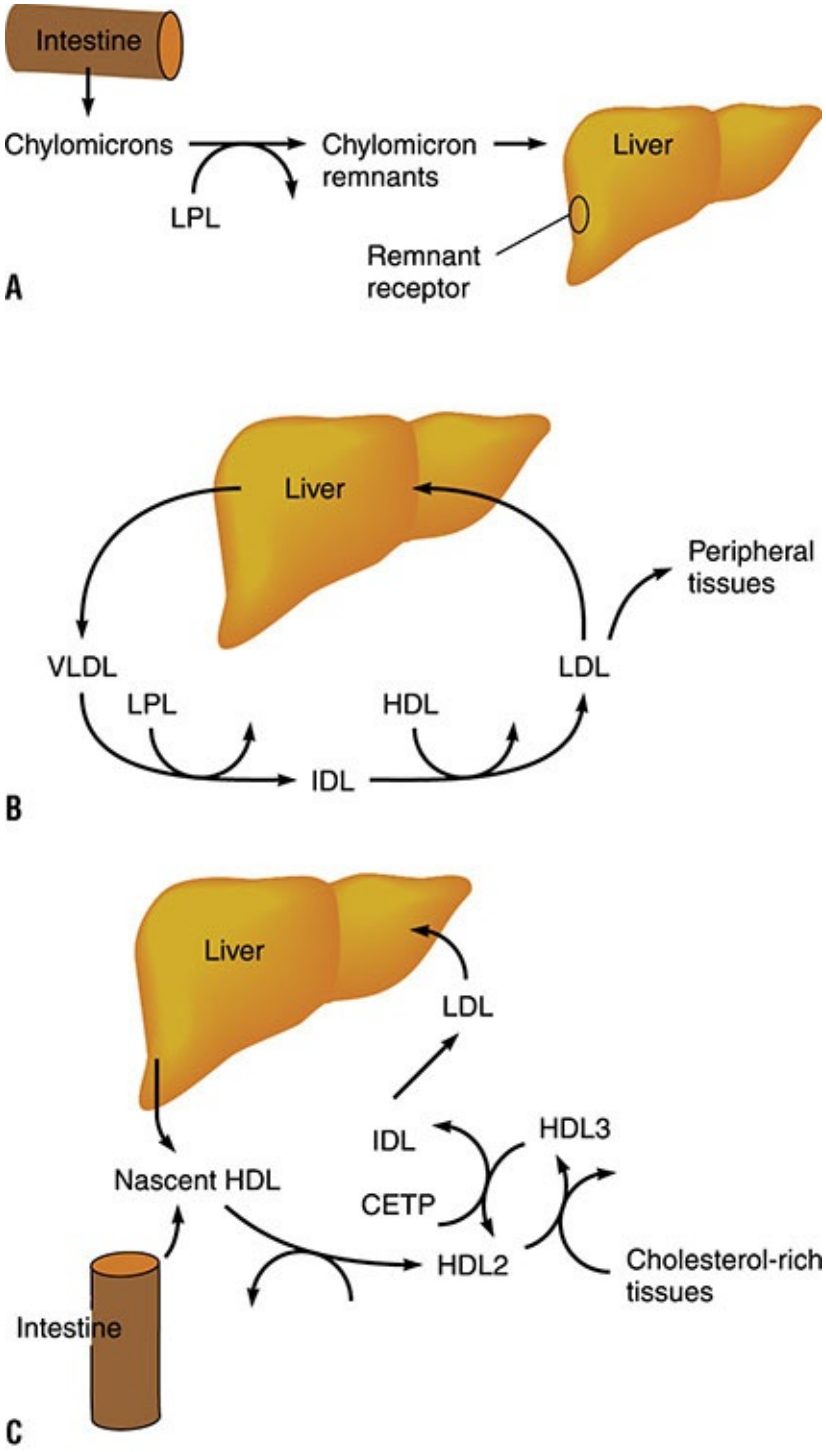


FIGURE 31-3 Biosynthetic pathway for cholesterol. The rate-limiting enzyme in this pathway is 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase). (CETP, cholesterol ester transfer protein; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density

lipoprotein; LPL, lipoprotein lipase; VLDL, very-low-density lipoprotein.) (*A*) Exogenous pathway; (*B*) Endogenous pathway; (*C*) Reverse cholesterol transport. (*Adapted from Breslow JL. Genetic basis of lipoprotein disorders. J Clin Invest 1989;84:373.*)

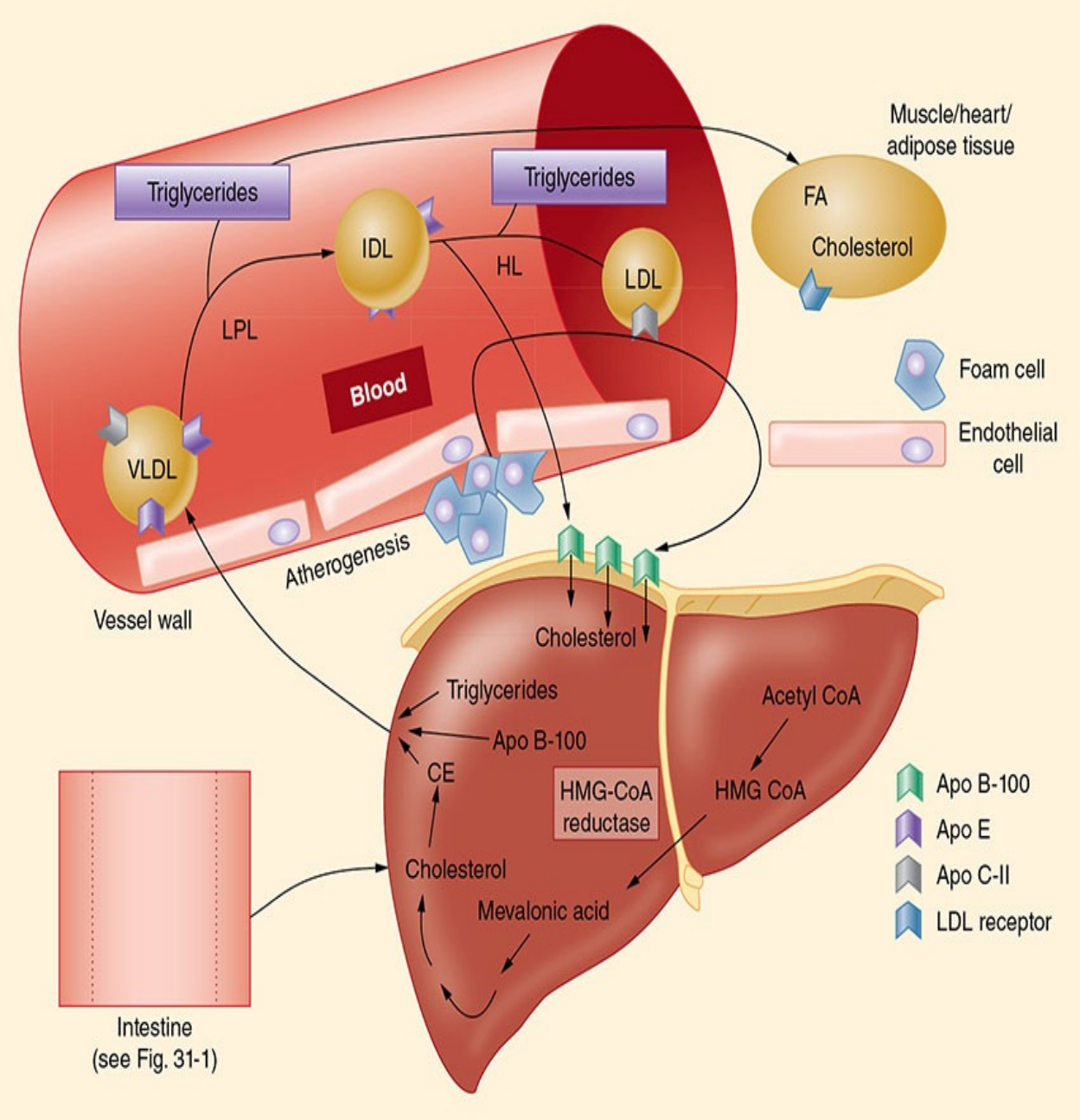


FIGURE 31-4 Endogenous lipoprotein metabolism. In the liver, the cholesterol and triglycerides are packed into VLDL particles and sent into the blood. They are then converted into IDL, which can be cleared by hepatic IDL receptor or metabolized into LDL. LDL can be cleared by LDL receptors or it can enter the

arterial walls and contribute to the development of atherosclerotic plaques and cardiovascular disease. HDL-C is responsible for transporting cholesterol and phospholipids from the arterial cell wall or other extrahepatic tissues back to the liver. Cholesterol that is returned back to the liver can then be excreted into the bile. This process is known as reverse cholesterol transport. (Apo, apolipoprotein; CE, cholesteryl ester; FA, fatty acid; HMG-CoA, β-Hydroxy β-methylglutaryl-CoA; HL, hepatic lipase; LDL, low-density lipoprotein; LPL, lipoprotein lipase; VLDL, very low-density lipoprotein) (*Reprinted with permission from Marrs JC. Pathophysiology of Atherosclerotic Cardiovascular Disease. In: Wiggins BS, Saseen JJ, eds. Pharmacist's Guide to Lipid Management. 2nd ed. Lenexa, KS: American College of Clinical Pharmacy, 2014:2.*)

Familial Hypercholesterolemia

Familial hypercholesterolemia is characterized by (a) a selective elevation in the plasma level of LDL; (b) deposition of LDL-derived cholesterol in tendons (xanthomas) and arteries (atheromas); and (c) inheritance as an autosomal dominant trait with homozygotes more severely affected than heterozygotes. The primary defect in familial hypercholesterolemia is the inability to bind LDL to the LDL receptor (LDL-R) or, rarely, a defect of internalizing the LDL-R complex into the cell after normal binding. This leads to lack of LDL degradation by cells and unregulated biosynthesis of cholesterol, with total cholesterol and LDL-C being inversely proportional to the deficit in LDL receptors. Homozygotes (prevalence 1 in 1,000,000) have severe hypercholesterolemia (650-1,000 mg/dL [16.8-25.9 mmol/L]), with the early appearance of cutaneous xanthomas and fatal CHD generally before the age of 20 and have essentially no functional LDL receptors. Heterozygotes have only about one-half of the normal number of LDL receptors, total cholesterol levels in the range of 300 to 600 mg/dL (7.76-15.52 mmol/L) and cardiovascular events beginning in the third and fourth decades of life.

Secondary causes of dyslipidemia exist and that several drugs and conditions may contribute to abnormal lipid levels (**Table 31-1**). These secondary forms of dyslipidemia should be managed by addressing the underlying abnormality, including modification of drug therapy when appropriate.

TABLE 31-1 Secondary Causes of Lipoprotein Abnormalities

Hypercholesterolemia	• Hypothyroidism • Obstructive liver disease • Nephrotic syndrome • Anorexia nervosa • Acute Intermittent Porphyria • Drugs: progestins, thiazide diuretics, glucocorticoids, beta-blockers, isotretinoin, protease inhibitors, cyclosporine, mirtazapine, sirolimus
Hypertriglyceridemia	• Obesity • Diabetes mellitus • Lipodystrophy • Glycogen storage disease • Ileal bypass surgery • Sepsis • Pregnancy • Acute Hepatitis • Systemic lupus erythematosus • Monoclonal gammopathy: multiple myeloma, lymphoma • Drugs: Alcohol, estrogens, isotretinoin, beta blockers, glucocorticoids, bile-acid resins, thiazides, asparaginase, interferons, azole antifungals, mirtazapine, anabolic steroids, sirolimus, bexarotene
Hypercholesterolemia	• Malnutrition • Malabsorption • Myeloproliferative diseases • Chronic infectious diseases: human immunodeficiency virus (HIV), tuberculosis • Monoclonal gammopathy • Chronic Liver Disease
Low HDL	• Malnutrition • Obesity • Drugs: non-ISA beta-blockers, anabolic steroids, probucol, isotretinoin, progestins

Pathogenesis of Atherosclerotic Cardiovascular Disease

The “response-to-injury” hypothesis states that risk factors such as oxidized LDL, mechanical injury to the endothelium, excessive homocysteine, immunologic attacks, or infection-induced changes in endothelial and intimal function lead to endothelial dysfunction and a series of cellular interactions that culminate in atherosclerosis. C-reactive protein (CRP) is an acute phase reactant and a marker for inflammation. Measuring one’s CRP levels by means of a high-sensitivity CRP may be useful in identifying patients at risk for developing CAD. Lipid abnormalities increase the risk for CHD and cerbrovascular morbidity and mortality. The eventual outcomes of this atherogenic cascade are clinical events such as angina, MI, arrhythmias, stroke, peripheral arterial

disease, abdominal aortic aneurysm, and sudden death. Atherosclerotic lesions are thought to arise from transport and retention of plasma LDL-C through the endothelial cell layer into the extracellular matrix of the subendothelial space. Once in the artery wall, LDL-C is chemically modified through oxidation and nonenzymatic glycation. Mildly oxidized LDL-C then recruits monocytes into the artery wall, which become transformed into macrophages. Macrophages have tremendous potential for accelerating LDL-C oxidation and apolipoprotein B accumulation and altering the receptor-mediated uptake of LDL-C into the artery wall from the usual LDL-R to a "scavenger receptor" not regulated by cell content of cholesterol. Oxidized LDL-C increases plasminogen inhibitor levels (promotion of coagulation), induces the expression of endothelin (vasoconstrictive substance), inhibits the expression of nitric oxide (a vasodilator and platelet inhibitor), and is toxic to macrophages if highly oxidized. As oxidation of biologically active lipids proceeds, other lipids breakdown products of fatty acids and oxysterol are formed, which continue the reaction within the tissue. These events lead to a massive accumulation of cholesterol. The cholesterol-laden macrophages become foam cells; foam cells are the earliest recognized cells of the arterial fatty streak. Oxidized LDL-C provokes an inflammatory response, which is mediated by a number of chemoattractants and cytokines. The process of aging may lead to lipoproteins that are more susceptible to oxidation and have longer resident time in the vascular compartment. Repeated injury and repair within an atherosclerotic plaque eventually leads to fibrous cap protecting the underlying core of lipids, collagen, calcium, and inflammatory cells such as T-lymphocytes. Maintenance of the fibrous plaque is critical to prevent plaque rupture and subsequent coronary thrombosis.[24] An imbalance between plaque synthesis and degradation may lead to a weakened or vulnerable plaque prone to rupture. The fibrous cap may become weakened through decreased synthesis of the extracellular matrix or increased degradation of the matrix (**Fig. 31-5**).

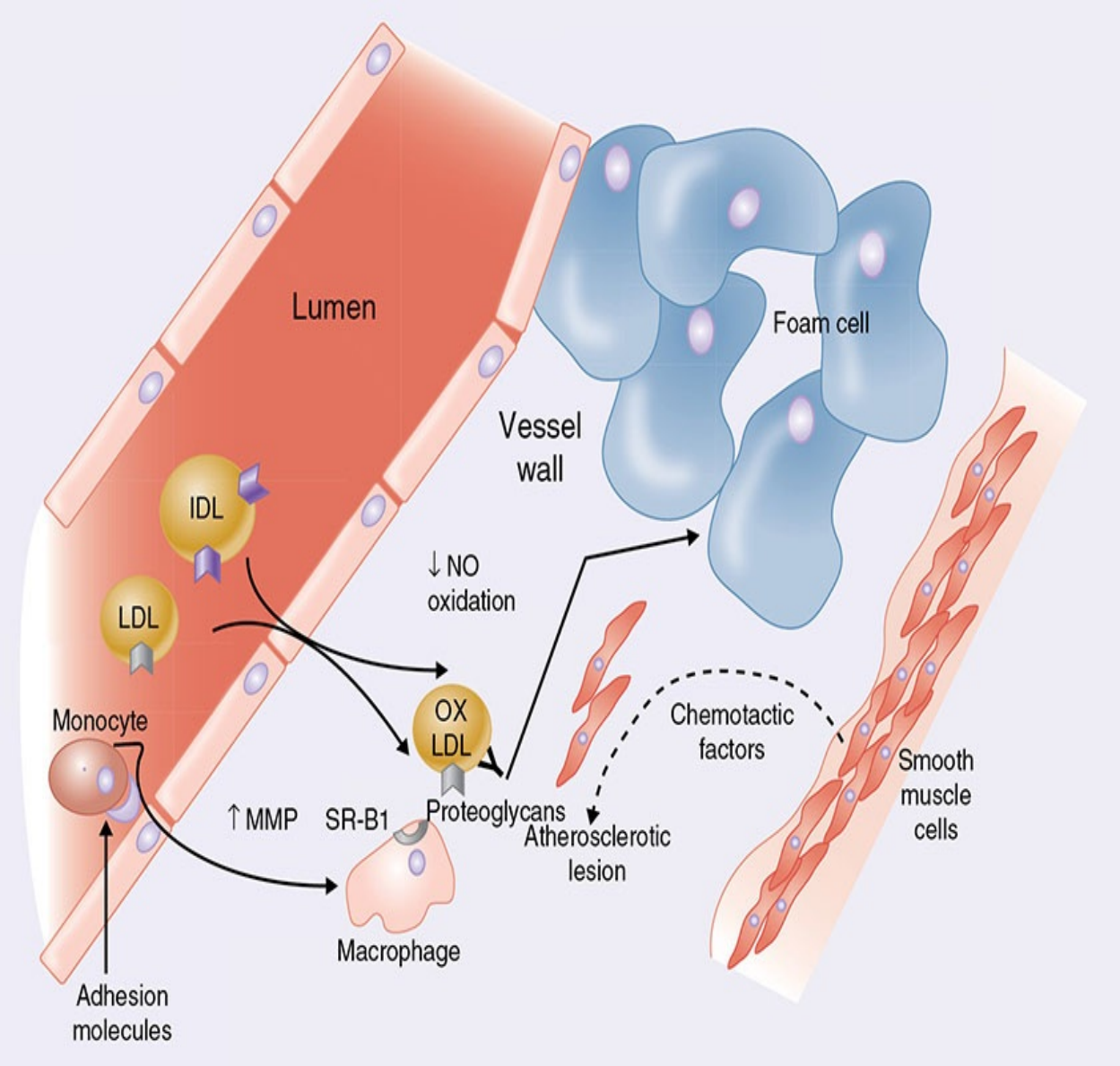


FIGURE 31-5 Atherogenesis is initiated by the migration of LDL and remnant lipoprotein particles into the vessel walls. These particles undergo oxidation and are taken up by macrophages in an unregulated fashion, which induces endothelial cell dysfunction. This, in turn, reduces the ability of the endothelium to dilate the artery and cause a prothrombotic state. Unregulated uptake of cholesterol by macrophages leads to foam cell formation, and thus the development of atherosclerotic plaques. Macrophages eventually produce and secrete matric metalloproteinases, which degrade the collagen matrix of the plaques and cause them to be unstable. This can potentially lead to a myocardial infarction. This is a progressive process. (IDL, intermediate density lipoprotein; LDL, low-density lipoprotein; MMP, matrix metalloproteinase; NO, nitric oxide; SR-B1, scavenger receptor class B type 1) (*Reproduced with permission from*

Chisholm-Burns MA, Schwinghammer TL, Malone PM, Kolesar JM, Bookstaver PB, Lee KC, eds. Pharmacotherapy Principles & Practice. 5th ed. New York: McGraw-Hill; 2019.)

CLINICAL PRESENTATION

Dyslipidemias

General

- Most patients are asymptomatic for years before they develop ASCVD; the initial presentation may be sudden death due to a CHD event.
- Many patients with dyslipidemia also present with one or more of the following abnormalities*:
  - Abdominal obesity
  - Atherogenic dyslipidemia
  - Increased blood pressure
  - Insulin resistance and/or glucose intolerance
  - Prothrombotic or proinflammatory state
- *Patients with three or more of these abnormalities are considered to have the metabolic syndrome

Symptoms of ASCVD

- Chest pain
- Palpitations
- Sweating
- Anxiety
- Shortness of breath
- Loss of consciousness
- Difficulty with speech or movement
- Abdominal pain

Signs

- Abdominal pain
- Pancreatitis

- Eruptive xanthomas
- Peripheral polyneuropathy

Laboratory Tests

- Elevated total cholesterol, LDL-C, TGs, apolipoprotein B, hsCRP
- Decreased HDL-C

Other Diagnostic Tests

- Screenings for manifestations of vascular disease, including carotid ultrasound, coronary calcium score, ankle-brachial index, and heart catheterization.

TREATMENT

Desired Outcomes

Desired levels of TC, LDL-C, HDL-C, and TG are provided in **Table 31-2** for adults and **Table 31-3** for children. While abnormalities in these surrogate markers may impart an increased risk for ASCVD events, the goal of treatment is to not merely correct lab abnormalities but prevent the development and progression of ASCVD. Thus, the desired outcome is to prevent ASCVD-related morbidity and mortality, including revascularization procedures, MI, and ischemic stroke. Initiation of lipid-lowering therapies primarily involves the use of those agents shown in RCT to reduce ASCVD risk.[20,25]

TABLE 31-2 Classification of Total-, LDL-, HDL-Cholesterol, and Triglycerides in Adults

Total Cholesterol	
<200 mg/dL (5.17 mmol/L)	Desirable
200-239 mg/dL (5.17-6.20 mmol/L)	Borderline high
≥240 mg/dL (6.21 mmol/L)	High
Low-Density Lipoprotein Cholesterol	
<100 mg/dL (2.59 mmol/L)	Optimal
100-129 mg/dL (2.59-3.35 mmol/L)	Near or above optimal
130-159 mg/dL (3.36-4.13 mmol/L)	Borderline high
160-189 mg/dL (4.14-4.90 mmol/L)	High
≥190 mg/dL (4.91 mmol/L)	Very high
High-Density Lipoprotein Cholesterol	
<40 mg/dL (1.03 mmol/L)	Low (Men)
<50 mg/dL (1.3 mmol/L)	Low (Women)
Triglycerides	
<150 mg/dL (1.70 mmol/L)	Normal
150-199 mg/dL (1.70-2.25 mmol/L)	Borderline high
200-499 mg/dL (2.26-5.64 mmol/L)	High
≥500 mg/dL (5.65 mmol/L)	Very high

TABLE 31-3 Classification of Total-, LDL-, HDL-Cholesterol and Triglycerides in Children

Total Cholesterol	
<170 mg/dL (4.4 mmol/L)	Acceptable
170-199 mg/dL (4.4-5.2 mmol/L)	Borderline
≥200 mg/dL (5.2 mmol/L)	High
Low-Density Lipoprotein Cholesterol	
<110 mg/dL (2.8 mmol/L)	Acceptable
110-129 mg/dL (2.8-3.3 mmol/L)	Borderline
≥130 mg/dL (3.4 mmol/L)	High
High-Density Lipoprotein Cholesterol	
<40 mg/dL (1 mmol/L)	Low
40-45 mg/dL (1-1.2 mmol/L)	Borderline
>45 mg/dL (1.2 mmol/L)	Acceptable
Triglycerides	
0-9 years	
<75 mg/dL (0.8 mmol/L)	Acceptable
75-99 mg/dL (0.8-1.1 mmol/L)	Borderline
≥100 mg/dL (1.1 mmol/L)	High
10-19 years	
<90 mg/dL (1 mmol/L)	Acceptable
90-129 mg/dL (1-1.5 mmol/L)	Borderline
≥130 mg/dL (1.5 mmol/L)	High

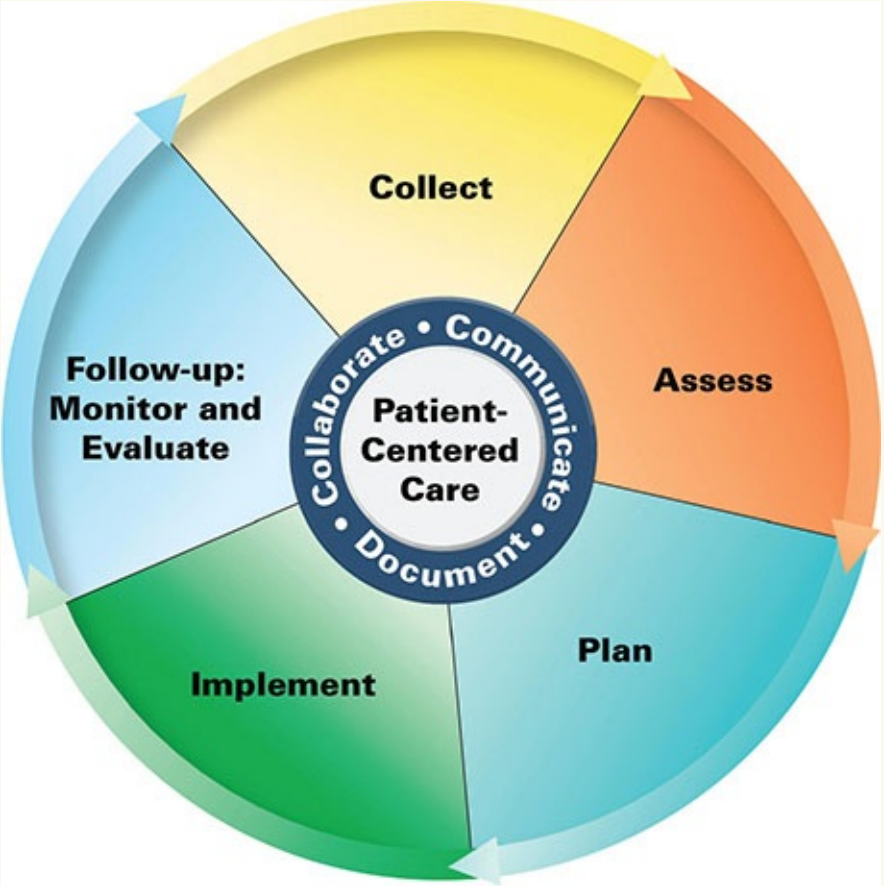
Data from Daniels SR, Benuck I, Christakis DA, et al. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: Full report, 2011. National Heart Lung and Blood Institute.

Available at: www.nhlbi.nih.gov/files/docs/guidelines/peds_guidelines_full.pdf

General Approach

6 A comprehensive approach to treating dyslipidemia and all modifiable major risk ASCVD factors is required to significantly reduce the risk of first and recurrent ASCVD events. Therapeutic lifestyle change is the first-line therapy for any lipoprotein disorder. A healthy lifestyle should be implemented in all patients with the general components including a reduction in the percent of calories from saturated and *trans* fats, increased intake of soluble fiber, weight reduction if overweight or obese, increased physical activity, and avoiding or quitting tobacco use.[25] Additionally, patients with a diagnosis of hypertension should achieve optimal blood pressure control based on the 2017 ACC/AHA Guidelines for control of hypertension (see Chapter 30, “Hypertension”).[26]

Persons with diabetes mellitus, especially those with established ASCVD, should receive glucose-lowering therapies that have been shown to reduce ASCVD risk (see Chapter 91, “Diabetes Mellitus”).[27]



Patient Care Process for the Management of Dyslipidemias

Collect

- Patient characteristics (eg, age, race, gender, pregnant)
- Patients history: Past medical (eg, HTN), family (eg, early-onset coronary heart disease), social
- Current medications (including over-the-counter [OTC]) and prior lipid-lowering medication use
- Socioeconomic factors that may affect access to treatment or other aspects of care

- Lifestyle assessment: smoking status, exercise, diet, and alcohol intake
- Symptoms indicative of ischemic injury (eg, chest pain)
- Objective data
  - Height, weight, BMI, and blood pressure
  - Lipoprotein concentrations (eg, Total Cholesterol/LDL-C/HDL-C/Triglycerides)
  - Labs (eg, AST/ALT, urinalysis, TSH, glucose, Serum Creatinine, and BUN at baseline)

Assess

- Potential secondary causes (eg, diabetes mellitus, alcohol abuse, renal dysfunction, liver disease, drug-induced, thyroid disorder)
- Special needs of specific patient populations such as children/adolescents, pregnant or menopausal women, older adults, ethnic/racial groups, or high-risk conditions/residual risks (eg, patients with rheumatoid arthritis or residual risk despite statin and lifestyle therapy)
- Presence of high-risk comorbid conditions: diabetes mellitus, peripheral arterial disease, coronary artery disease, chronic kidney disease, carotid artery stenosis, abdominal aortic aneurysm
- Dyslipidemia-related complications (eg, heart disease, stroke)
- Ten-year atherosclerotic cardiovascular disease (ASCVD)-risk assessment (only if primary prevention)
- Current medications that may contribute to dyslipidemia
- LDL-C reduction based on statin benefit group, if applicable (see Table 31-4)
- Appropriateness and effectiveness of current lipid-lowering therapy (if any)

Plan*

- Tailored therapeutic lifestyle changes (eg, diet and nutrition)
- Drug therapy regimen including specific lipid-lowering medication, dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Table 31-4)
- Monitoring parameters including efficacy (eg, lipid panel, cardiovascular events), safety (medication-specific adverse effects), and time frame (3-

month initial follow-up intervals, followed by 6-12 month intervals once at goal)

- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug therapy)
- Self-monitoring of weight, exercise, diet, drug adherence/adverse effects
- Referrals to other providers when appropriate for coordination of care (eg, physician, dietician)

Implement*

- Provide patient education regarding all elements of the treatment plan, including self-management training
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up and time frame to achieve goals of therapy

Follow-up: Monitor and Evaluate

- Determine response to lipid-lowering therapy and weight-loss goals
- Presence of medication-induced adverse effects (eg, elevated transaminases or myalgia on statins)
- The occurrence of cardiovascular (CV) events
- Patient adherence to treatment plan using multiple sources of information

** Collaborate with patient, caregivers, and other healthcare professionals.*

5 If therapeutic lifestyle changes are insufficient, lipid-lowering agents should be chosen based on which lipid is at an undesirable level and the degree to which it is expected to increase the risk of ASCVD. The decision to initiate lipid-lowering therapy in the management of dyslipidemia should be based on an individual's ASCVD risk and not merely plasma levels of atherogenic lipoproteins (such as LDL-C) alone.[28] Patients with established ASCVD are at highest risk and most likely to benefit from select lipid-lowering therapies (such as statins). Risk assessment in patients without established ASCVD is more of an art that requires careful consideration of traditional (eg, age, hypertension) and nontraditional (eg, autoimmune diseases, socioeconomic status) risk factors, the risks of lipid-lowering therapy, and patient preference. For patients between 40 and 79 years of age and no history of ASCVD, the ASCVD Risk Estimator

Plus (available at: www.tools.acc.org/ascvd-risk-estimator-plus) should be used to facilitate a clinician-patient discussion regarding the benefit and risks of lipid-lowering therapy, especially in patients whose 10-year risk is 7.5% or greater (see **Table 31-4**). The Risk Estimator is comprised of the patient's age, gender, race, TC, HDL-C, blood pressure, diabetes status, smoking status, and use of antihypertensives, statins, and aspirin. Importantly, the Risk Estimator is based on data from large population studies of mostly African-American and non-Hispanic white men and women. The Risk Estimator can be used for other ethnic groups if they are designated as non-Hispanic white; however, the Risk Estimator will underestimate the risk of American Indians and Asian Americans of South Asian ancestry, while overestimating the risk of Asian Americans of East Asian ancestry and some Hispanics (eg, Mexican Americans).[28] An estimated lifetime risk for ASCVD can also be performed for patients between age 20 and 39, yet these results should only be used to justify the need for lifestyle change and not the initiation of lipid-lowering therapy. Additional tools for ASCVD-risk assessment include high-sensitivity C-reactive protein (hsCRP), apolipoprotein B, and lipoprotein(a) [Lp(a)] levels that may be obtained to inform decision making in low-intermediate risk patients or those with recurrent ASCVD events despite appropriate lipid-lowering therapy.[28]

TABLE 31-4 Key Recommendations to Reduce the Risk of Atherosclerotic Cardiovascular Disease (ASCVD) in Adults

Recommendations (ACC/AHA COR and LOE)

Heart-healthy lifestyle for everyone

Statin Benefit Groups—Patient groups likely to benefit from statin therapy

1. Clinical ASCVD[i]
   a. Very high-risk[ii]
      - High-intensity or maximally tolerated statin therapy **(Class I)**
   b. Not at very high-risk
      - Age <75 years: High-intensity statin therapy **(Class I)**
        - If high-intensity not tolerated, use moderate-intensity statin therapy **(Class I)**
      - Age >75 years: Initiation of moderate- or high-intensity statin is reasonable **(Class IIa)**

2. Primary prevention—Severe Hypercholesterolemia (LDL-C ≥190 mg/dL [4.91 mmol/L])
   a. Rule out secondary causes of dyslipidemia
   b. Age 20-75 years: Maximally tolerated statin therapy **(Class I)**

3. Primary prevention—Diabetes 40-75 years and LDL-C 70-189 mg/dL (1.81 - 4.89 mmol/L)
   a. Moderate-intensity statin therapy regardless of 10-year ASCVD risk **(Class I)**
   b. High-intensity statin therapy is reasonable in patients with diabetes and multiple ASCVD-risk factors **(Class IIa)**
   c. It is reasonable to continue statin therapy in adults ≥75 years with diabetes previously taking statin therapy **(Class IIa)**
   d. It is reasonable to initiate statin therapy in adults ≥75 years with diabetes after a discussion of risks and benefits **(Class IIb)**
   e. It is reasonable to initiate statin therapy in adults 20-30 years with diabetes if any of the following apply: **(Class IIb)**
      - Long duration of diabetes (≥10 years for type 2 diabetes; ≥20 years for type 1 diabetes)
      - Albuminuria (≥30 mg/g albumin/mg creatinine [3.4 mg/mmol creatinine])
      - Estimated glomerular filtration rate <60 mL/min/1.73 m^2
      - Retinopathy
      - Neuropathy
      - Ankle-brachial index <0.9

4. Primary prevention—no diabetes, 40-75 years and LDL-C 70-189 mg/dL (1.81 - 4.89 mmol/L)
   1. Emphasize heart-healthy lifestyle and address other risk factors
   2. Estimate 10-year ASCVD-risk score based on Pooled Cohort Equation
      - High Risk (≥20%): Initiate high-intensity statin therapy **(Class I)**
      - Intermediate Risk (≥7.5% to <20%): If risk enhancers[iii] present, consider moderate-intensity statin therapy **(Class I)**
        - If risk decision is uncertain, consider measuring CAC in selected adults
          - Consider no statin if CAC = 0 unless patient has diabetes or significant family history of ASCVD
          - Consider initiating statin therapy if CAC 1-99, especially if age >55 years
          - Initiate statin therapy if CAC ≥100
      - Borderline Risk (5% to <7.5%): If risk enhancers[iii] present, risk discussion regarding moderate-intensity statin therapy **(Class IIb)**
      - Low Risk (<5%): Emphasize heart-healthy lifestyle **(Class I)**

5. Primary prevention—no diabetes, 20-39 years and LDL-C 70-189 mg/dL (1.81 - 4.89 mmol/L)
   a. Estimate lifetime ASCVD-risk based on Pooled Cohort Equation to encourage lifestyle to reduce ASCVD risk
   b. Consider statin therapy if family history of premature ASCVD and LDL-C ≥160 mg/dL (4.14 mmol/L)

[i]Clinical ASCVD includes nonfatal MI, CHD death, and nonfatal and fatal stroke, TIA or peripheral arterial disease presumed to be of atherosclerotic origin.

[ii]Very high risk include history of >1 major ASCVD events including recent ACS (past 12 months), history of MI, ischemic stroke, or peripheral arterial disease; OR one major ASCVD event plus multiple high-risk conditions: >65 years, familial hypercholesterolemia, history of coronary bypass graft surgery, diabetes mellitus, hypertension, CKD, current smoking, LDL-C >100 mg/dL (2.59 mmol/L) despite maximally tolerated statin and ezetimibe, or history of heart failure.

[iii]Risk Enhancers include: LDL-C 160-189 mg/dL (4.14-4.89 mmol/L), family history of premature ASCVD, metabolic syndrome, chronic kidney disease, chronic inflammatory conditions (eg, rheumatoid arthritis), premature menopause (before age 40), preeclampsia, high-risk race/ethnicities (eg, South Asian), triglycerides ≥175 mg/dL (1.98 mmol/L), hs-CRP ≥2 mg/L, lipoprotein(a) ≥50 mg/dL (0.5 g/L), apoB ≥130 mg/dL, (1.3 g/L) or ankle-brachial index <0.9.

ABI, ankle brachial index; ACC/AHA, American College of Cardiology/American Heart Association; ASCVD, Atherosclerotic cardiovascular disease; CAC, coronary artery calcium; COR, Class of recommendation; hsCRP, high-sensitivity C reactive protein; LDL-C, low-density lipoprotein cholesterol; LOE, Level of evidence; NYHA, New York Heart Association.

6 7 The HMG-CoA reductase inhibitors or “statins” are the drugs of choice for most patients with dyslipidemia.[20] A large body of evidence from randomized, double-blind, placebo-controlled trials has demonstrated the effectiveness of statins on reducing first and recurrent cardiovascular events, cardiovascular mortality, and all-cause mortality.[29] The 2018 ACC/AHA Blood Cholesterol Guideline identified four statin benefit groups where the data from RCT demonstrate clear evidence that the benefit of statin therapy outweighs the potential risks (Table 31-4).[20] Nonstatin lipid-lowering therapies (such as ezetimibe) play a supportive role in the management of dyslipidemia and are primarily used in combination with statins when adequate LDL-C lowering cannot be achieved with statins alone, or in patients unable to tolerate the recommended dose of a statin (**Table 31-5**).[30]

TABLE 31-5 Key Recommendations on Role of Nonstatin Therapies to Reduce ASCVD Risk in Adults

Recommendations	Threshold for considering nonstatin therapies	
	LDL-C (mg/dL)	non-HDL-C (mg/dL)
1. Clinical ASCVD without comorbidities[i] on maximally tolerated statin a. Consider ezetimibe[ii] first b. Consider adding or replacing with PCSK9 inhibitor[iii] second	≥70 (1.81 mmol/L)	≥100 (2.59 mmol/L)
2. Clinical ASCVD with comorbidities on maximally tolerated statin a. Consider ezetimibe or PCSK9 inhibitor as initial therapy and addition of another agent if necessary	≥70 (1.81 mmol/L)	≥100 (2.59 mmol/L)
3. Clinical ASCVD and baseline LDL-C >190 mg/dL (4.91 mmol/L) on maximally tolerated statin a. Consider ezetimibe or PCSK9 inhibitor as initial therapy and addition of another agent if necessary	≥70 (1.81 mmol/L)	≥100 (2.59 mmol/L)
4. Primary prevention and baseline LDL-C >190 mg/dL (4.91 mmol/L) on maximally tolerated statin a. Consider ezetimibe or PCSK9 inhibitor as initial therapy and addition of another agent if necessary	≥100 (2.59 mmol/L)	≥130 (3.36 mmol/L)
5. Primary prevention (age 40-75 years) with diabetes and baseline LDL-C 70-189 mg/dL (1.81-4.89 mmol/L) on maximally tolerated statin a. Consider ezetimibe	≥100 (2.59 mmol/L)	≥130 (3.36 mmol/L)

[i]Comorbidities include diabetes, recent ASCVD event (<3 months), ASCVD event while on a statin, poorly controlled ASCVD-risk factors, elevated lipoprotein(a), chronic kidney disease, symptomatic heart failure, maintenance hemodialysis, baselines LDL-C >190 mg/dL (4.91 mmol/L), age >65 years, prior MI or nonhemorrhagic stroke, current daily cigarette smoking, symptomatic peripheral artery disease with prior history of heart attack or stroke, history of nonmyocardial infarction–related coronary revascularizations, low HDL-C, high-sensitivity C-reactive protein >2 mg/L, or metabolic syndrome.

[ii]Ezetimibe is preferred if <25% additional LDL-C needed, patients <3 months postacute coronary syndrome, cost considerations, patient preference.

[iii]PCSK9 inhibitor is preferred if >25% additional LDL-C needed and patient willing to administer subcutaneous injections.

Clinical ASCVD includes nonfatal MI, CHD death, and nonfatal and fatal stroke, TIA or peripheral arterial disease presumed to be of atherosclerotic origin.

ASCVD, Atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; PCSK9, proprotein subtilisin/kexin type 9.

Data from Reference 20.

8 Numerous clinical outcome trials have been performed to determine whether lipid-lowering therapies reduce ASCVD risk in primary and secondary prevention populations. Reducing total cholesterol and LDL-C reduces CHD and total mortality. It is beyond the scope of this chapter to discuss each of these trials in significant detail. **Table 31-6** summarizes select trials supporting the use of statins and select nonstatins (ezetimibe and PCSK9 inhibitors) to reduce ASCVD risk. Most of the primary and secondary prevention studies were double-blinded, randomized, and placebo-controlled, lasting 2 to 7 years, and most had sufficient patient numbers to be meaningful. The body of evidence supporting the role of statin therapy to reduce ASCVD is significant and meta-analysis data confirms these agents as the first-line therapy in dyslipidemia management.[31] As mentioned previously in this chapter, not all lipid-lowering

therapies have translated to reducing ASCVD risk, despite having favorable effects on the lipid profile.

TABLE 31-6 Selected Landmark Clinical Trials with Lipid-Lowering Drugs

Trial	Follow-Up (yr)	*N*	Intervention	Control Events (%)	Intervention Events (%)	*p-value*	RRR (%)	ARR (%)	NNT
Primary Prevention									
AFCAPS/TexCAPS	5	6,605	Lovastatin 20-40 mg	5.5	3.5	<0.001	36.4	2.0	50
WOSCOPS	4.9	6,595	Pravastatin 40 mg	7.8	5.5	<0.001	29.5	2.3	43
CARDS	4	2,838	Atorvastatin 10 mg	9.0	5.8	0.001	37	3.2	32
JUPITER	1.9	17,802	Rosuvastatin 20 mg	2.82	1.59	0.00001	44	1.2	82
Secondary Prevention									
HPS	5	20,536	Simvastatin 40 mg	14.7	12.9	0.0003	13	1.8	56
TNT	4.9	10,001	Atorvastatin 10 mg vs 80 mg	10.9	8.7	<0.001	22	2.2	45
IMPROVE-IT	7	18,144	Ezetimibe + Statin	34.7	32.7	0.016	6	2	50
FOURIER	2.2	27,564	Evolocumab + Statin	11.3	9.8	<0.001	15	1.5	67

ARR, absolute risk reduction; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study[107]; CARDS, Collaborative Atorvastatin Diabetes Study[12]; FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients with Elevated Risk[32]; HPS, Heart Protection Study[106]; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trail[33]; JUPITER, Justification for the Use of Statins in Prevention[34]; NNT, Number Needed to Treat; RRR, relative risk reduction; TNT, Treat to New Targets Trial[108]; WOSCOPS, The West of Scotland Coronary Prevention Study.[109]

Nonpharmacologic Therapy

Lifestyle modification is the cornerstone of ASCVD-risk reduction and is recommended in all patients, including those receiving lipid-lowering therapy. Weight and body mass index (BMI) should be determined at each visit and lifestyle patterns to induce a weight loss of 5% to 10% should be discussed in persons who are overweight or obese. Moderate-to-vigorous intensity physical activity is recommended three to four times per week with each session lasting 40 minutes on average. All patients should also be counseled to stop smoking and avoid tobacco products altogether.[25]

It is important to recognize that there is no single diet suitable for every patient. Instead, advise patients to reduce the percent of calories from saturated and *trans* fats by following a dietary pattern that emphasizes vegetables, fruits, whole grains, low-fat dairy, poultry, fish, legumes, and nuts; while limiting the intake of sweets, sugary beverages, and red meat. Plans that closely mirror this dietary pattern and effectively lower LDL-C include DASH, the USDA Food

Pattern, and AHA Diet. Although the Mediterranean-style diet has no consistent effect on LDL-C levels, it has been shown to reduce major cardiovascular events among persons at high cardiovascular risk when compared to a control diet. Any recommended dietary pattern should be adapted to a patient's caloric requirements, cultural food preferences, and for other medical conditions (eg, diabetes mellitus). Individualized diet counseling that provides acceptable substitutions for unhealthy foods and ongoing reinforcement by a registered dietitian are necessary for maximal effect. It is also important to involve all family members, especially if the patient is not the primary person preparing food.[25]

Less than one-third of Americans meet the 2015-2020 Dietary Guidelines for Americans limit of less than 10% of calories from saturated fats.[35] In patients with lipid disorders, the 2013 AHA/ACC Lifestyle Management Guideline recommended only 5% to 6% of total calories from saturated fat.[25] This can be achieved by recommending patients limit or avoid fast food, high-fat dairy products, and sweets. Previous dietary guideline recommendations to limit dietary cholesterol to 300 mg/day was omitted in 2015. However, it is still recommended that individuals limit their daily dietary cholesterol intake. A dietary pattern low in saturated and *trans* fats will typically result in a reduction in dietary cholesterol since foods high in saturated and *trans* fats are often high in cholesterol. A 12-week trial of lifestyle modification is generally recommended before considering lipid-lowering therapy in patients without evidence of ASCVD, diabetes, or other high-risk features. Importantly, lifestyle modification alone is inappropriate for patients with established ASCVD or diabetes given the benefit of statins in these high-risk patients.

Dietary Supplements

Select dietary supplements may be useful to augment diet and lipid-lowering therapy. Increased intake of soluble fiber in the form of oat bran, pectins, certain gums, and psyllium products can reduce total and LDL-C, but have little or no effect on HDL-C or TG levels. Soluble fiber binds cholesterol and bile acids in the small intestine, which decrease absorption and reabsorption. Total daily fiber intake should be about 25 g/day, yet most Americans average only half of the recommended amount.[36] Dietary supplements containing fiber may be used to supplement the diet and achieve the recommended daily intake. An intake of 3 to 12 g/day show reductions in total and LDL-C of 10 mg/dL (0.26 mmol/L) and 12 mg/dL (0.31 mmol/L), respectively, compared to control.[30] It remains unknown if soluble fiber supplements have any impact on cardiovascular morbidity and

mortality. Although seemingly safe, patients should be advised to stay well hydrated to avoid gastrointestinal distress. These products may also be useful in managing constipation associated with the bile acid sequestrants.

In epidemiologic studies, ingestion of large amounts of oily, cold-water fish (such as salmon) is associated with a reduction in ASCVD risk. Modest consumption (1-2 servings per week) reduces the risk of cardiovascular death and total mortality.[37] The American Heart Association recommends eating oily fish at least twice a week; however, there are concerns with some types of fish (such as tuna) that often have high levels of environmental contaminants. There are also concerns about environmental sustainability. Fish oil supplementation is an alternative option that provides a consistent daily intake of omega-3 PUFA such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Fish oil supplementation significantly reduces TG levels and VLDL-C, but may increase total cholesterol and LDL-C. Other potentially favorable cardiovascular effects of fish oil supplementation include antiarrhythmic, antiplatelet, and anti-inflammatory properties. Despite this, a meta-analysis of 10 RCT found no benefit with low doses (less than 2 g/day) of omega-3 PUFA supplementation.[38] Still, current recommendations suggest low-dose omega-3 PUFA supplementation is reasonable to consider in secondary prevention patients with heart failure or at high risk of sudden cardiac death.[39] Low dose omega-3 PUFA supplementation is not recommended in primary prevention patients, especially those with diabetes who do not have established ASCVD.[39,40] Additional details regarding prescription omega-3 PUFA products are further discussed under drug therapy.

Phytosterols, including plant sterols and stanols isolated from vegetable oils, also reduce LDL-C levels. Ingestion of 2 g/day will reduce LDL-C by 5% to 15%, while doses above 3 g/day confer no additional LDL-C lowering.[28] The efficacy of plant sterols and plant stanols is considered to be comparable. The mechanism by which phytosterols reduce LDL-C remains unclear but may decrease the transport of cholesterol in the intestinal brush border membrane and affect cholesterol uptake via Niemann-Pick C1-Like 1 (NPC1L1) and other transporters. Because lipids are needed to solubilize stanol/sterol esters, they are usually available in commercial butter-like spreads (such as Benecol®). The presence of plant stanols/sterols is listed on the food label. Phytosterols should be administered 2 to 4 hours before or after bile acid sequestrants to avoid binding of phytosterols in the gut. Although phytosterols are generally recognized as safe (GRAS) in the United States, they can cause gastrointestinal distress and should be avoided in patients with sitosterolemia, a rare genetic

disorder characterized by 50- to 100-fold increase in plant sterol levels and rapid onset of atherosclerosis.[41] The effects of long-term phytosterol supplementation on ASCVD risk remains unknown.

Red yeast rice is a commonly used dietary supplement in the United States that originates from Chinese medicine. The active ingredient of red yeast rice is monacolin K, which is chemically identical to lovastatin. This leads some patients to believe red yeast rice is a “natural” statin and, therefore, safer than statins currently available only by prescription; however, the active ingredient in over-the-counter (OTC) red yeast rice products vary by over 120-fold. Many products contain little to no monacolin.[42] Conversely, case reports of rhabdomyolysis, liver toxicity, and renal failure have raised concerns about some red yeast rice formulations containing significantly higher levels of monacolin K than described on the label.[43] Red yeast rice is not recommended as a suitable alternative to statins. However, if patients choose to take red yeast rice, it is recommended they purchase it from a reputable supplier and avoid concurrent use with prescription statins.

Pharmacologic Therapy

9 There are numerous randomized, double-blinded clinical trials demonstrating that reduction of LDL-C reduces ASCVD-event rates in the setting of primary and secondary prevention.[27] Epidemiological studies suggest that every 38 mg/dL (0.98 mmol/L) reduction in LDL-C produces a 21% reduction in ASCVD event rates over 5 years.[44] Additional findings from large prospective cohort studies and Mendelian randomization studies have also demonstrated a dose-dependent log-linear association between LDL-C and ASCVD risk[45] and that lower levels of LDL-C achieve significant reductions in ASCVD risk. These studies provide a strong rationale for attempting to lower plasma cholesterol and LDL-C in patients at risk for ASCVD.[45] It should be noted, however, that not all lipid-lowering agents that reduce LDL-C have resulted in a reduction in ASCVD events (eg, CETP inhibitors). Thus, LDL-C lowering alone should not be the sole basis for selecting an appropriate agent.[20,28] Lipid-lowering drugs can be broadly divided into agents that primarily decrease atherogenic cholesterol-containing lipoprotein particles (such as statins) and those that primarily decrease TG levels (such as fibrates).

Treatment of Specific Dyslipidemia Subtypes

Familial Hypercholesterolemia

Individuals with familial hypercholesterolemia (FH) have a very high lifetime risk of developing ASCVD. Compared to the general population, FH is associated with a 24-fold higher risk of developing acute MI before age 40.[46] FH should be suspected in adults with untreated LDL-C levels of 190 mg/dL (4.91 mmol/L) or greater or non-HDL cholesterol levels of 220 mg/dL (5.69 mmol/L) or greater who have a family history of high cholesterol or ASCVD in first-degree relatives. Physical findings (such as xanthomas or corneal arcus) may be present in some patients with FH, but their absence does not rule out a diagnosis of FH. In clinical practice, one of several validated tools, including the Dutch Lipid Clinic Network, US Make Early Diagnosis Prevent Early Death (MEDPED), and Simon-Broome Registry, are used to make a formal diagnosis of FH. Genetic testing is available but is only necessary when the diagnosis is uncertain or if it is needed to obtain prior authorization for select lipid-lowering therapies, such as PCSK9 inhibitors. Approximately 20% of patients with clinically definite FH will not have an identifiable mutation; therefore, a negative genetic test does not exclude FH.[47] Importantly, cascade screening of all first-degree relatives of diagnosed FH patients is highly recommended as an effective strategy to identify previously undiagnosed FH patients.

10 Mipomersen and lomitapide are orphan drugs indicated for use in patients with HoFH and reduce LDL-C levels by ~25% and ~40%, respectively.[48] Mipomersen is an oligonucleotide inhibitor of apolipoprotein B-100 synthesis administered via subcutaneous injection, while the orally administered lomitapide is a microsomal triglyceride transfer protein, or microsomal TG transfer protein inhibitor, which reduces the level of cholesterol that the liver and intestines assemble and secrete into the circulation. Mipomersen is associated with injection site pain and reactions, while both mipomersen and lomitapide have a black box warning for severe hepatotoxicity and are only available through restricted Risk Evaluation and Mitigation Strategy (REMS) programs.[48] Other treatment options for HoFH patients include LDL apheresis (a process similar to dialysis that removes LDL from the blood) and liver transplant.[46]

Hypertriglyceridemia

Elevated TG levels are strongly associated with an increased risk of ASCVD; however, the direct role of TG in the development of ASCVD remains debatable.[49] All patients with elevated TG levels (see Tables 31-1 and 31-2) should be advised to implement lifestyle interventions shown to reduce TG

levels, including a 5% to 10% reduction in body weight, reducing consumption of sugar and refined carbohydrates, increasing physical activity, smoking cessation, and restricting alcohol. Secondary causes of hypertriglyceridemia should also be identified and addressed. Uncontrolled diabetes and chronic kidney disease are common causes of elevated TG levels, along with certain medications (such as protease inhibitors and atypical antipsychotics). The best approach to managing patients whose TG levels remain elevated after optimizing lifestyle interventions and addressing secondary causes remains unclear, but statins are generally considered first line given they can reduce TG levels by up to 30% at higher doses and help achieve desired levels of LDL-C.[50] The role of TG-lowering therapies such as fibrates and omega-3 PUFA in patients with TG of 200 to 499 mg/dL (2.26 5.64 mmol/L) is less clear. Clinical trials are underway to determine if fibrates and omega-3 PUFA reduce ASCVD risk in this population.[51]

Fasting TG levels exceeding 500 mg/dL (5.65 mmol/L) are more commonly associated with pancreatitis and other consequences of hyperchylomicronemia (such as eruptive xanthomas). At this level of elevated TG, a genetic form of hypertriglyceridemia often coexists with other causes of elevated triglycerides such as diabetes. Dietary fat restriction is a basic element of treatment as this reduces the synthesis and entry of additional chylomicrons into the circulation. Lipid-lowering therapies that primarily lower TG levels (such as fibrates, omega-3 PUFA, and niacin) are recommended as first-line agents.[50] Statins may be reasonable first-line options in those patients with an ASCVD risk of 7.5% or greater. If TG levels are persistently over 500 mg/dL (5.65 mmol/L), it is reasonable to consider adding omega-3 PUFA or fibrate therapy. Success in treatment is defined as a reduction in triglycerides below 500 mg/dL (5.65 mmol/L) and preventing pancreatitis.

Low HDL Cholesterol

Low HDL-C is a strong independent risk predictor of ASCVD.[52] Low HDL-C is defined as less than 40 mg/dL (1.03 mmol/L) for men and less than 50 mg/dL (1.29 mmol/L) for women, but there is no specified goal for HDL-C raising. Low HDL-C may be a consequence of insulin resistance, physical inactivity, diabetes, cigarette smoking, very high carbohydrate intake, and certain drugs. In patients with low HDL-C levels, the primary target remains LDL-C. Niacin has the potential for the greatest increase in HDL-C compared to other lipid-lowering therapies and the effect is more pronounced with regular or immediate-release forms than with sustained-release forms. However, no RCT data have

shown a reduction in ASCVD risk by raising HDL-C.[53,54] Additionally, several CETP inhibitors capable of raising HDL-C levels as much as 135% were evaluated in randomized, placebo-controlled trials but no additional benefit was found when these drugs were added to background statin therapy.[52] Due to the lack of pharmacological agents demonstrating an improvement in clinical outcomes by focusing on raising HDL-C, lifestyle modification (such as smoking cessation and increasing physical activity) remains the preferred approach. Although alcohol consumption has been shown to increase HDL-C, it is not acceptable to recommend this to patients who do not already consume alcohol.

Medications That Primarily Lower Atherogenic Cholesterol

HMG-CoA Reductase Inhibitors (Statins)

Statins (such as atorvastatin) are considered the first-line lipid-lowering therapies for managing dyslipidemia due to robust evidence from multiple RCTs demonstrating that statins significantly decrease the risk of first (primary prevention) and recurrent (secondary prevention) cardiovascular events.[20,44] Statins significantly reduce LDL-C levels (20%-60%), modestly increase HDL-C (6%-12%) and decrease TG levels (10%-29%).[55] Statins interrupt the conversion of HMG-CoA to mevalonate, the rate-limiting step in de novo cholesterol biosynthesis, by inhibiting HMG-CoA reductase (see Fig. 31-4). Metabolic studies with statins in normal volunteers and patients with hypercholesterolemia suggest a reduced synthesis of LDL-C, as well as enhanced catabolism of LDL mediated through LDL receptors, as the principal mechanisms for lipid-lowering effects. Statin selection is primarily based on the patients individual ASCVD risk and indicated intensity (see **Tables 31-4** and **31-7**). Currently available products in order of decreasing LDL-C lowering potency, include rosuvastatin, atorvastatin, pitavastatin, simvastatin, lovastatin, pravastatin, and fluvastatin.[55] The plasma half-lives for all the statins are relatively short (1-3 hours) except for atorvastatin, pitavastatin, and rosuvastatin, which may account for their potency.[55] Statins are generally well tolerated but are not without adverse effects. However, discontinuation rates due to adverse effects in randomized, double-blind, placebo-controlled trials have often been similar between statin and placebo.[56]

TABLE 31-7 Intensity of Statin Therapy by Drug and Dose

High-intensity Statin Therapy	Moderate-intensity Statin Therapy	Low-intensity Statin Therapy
Daily dose lowers LDL on average by ≥50%	Daily dose lowers LDL on average by 30% to <50%	Daily dose lowers LDL on average by <30%
Atorvastatin 40-80 mg	**Atorvastatin 10-20 mg**	Simvastatin 10 mg
Rosuvastatin 20-40 mg	**Rosuvastatin 5-20 mg**	**Pravastatin 10-20 mg**
	Simvastatin 20-40 mg[i]	**Lovastatin 20 mg**
	Pravastatin 40-80 mg	Fluvastatin 20-40 mg
	Lovastatin 40 mg	Pitavastatin 1 mg
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg BID	
	Pitavastatin 2-4 mg	

[i]Simvastatin is not recommended by the FDA to be started at 80 mg/day due to increased risk of myopathy and rarely rhabdomyolysis.

Boldface type indicates medications that have cardiovascular outcome data from RCTs when given in the specified dose.

FDA, Food and Drug Administration; RCT, Randomized clinical trials.

Statin-associated muscle symptoms (SAMS) are reported by 10% to 25% of statin users and are frequently reported by patients as a reason for statin discontinuation.[57] While various definitions of SAMS exist, the clinical diagnosis of SAMS is one of subjective clinical assessment. Myalgia is the most commonly reported muscle-related adverse effect with statin therapy and refers to bilateral muscle achiness, weakness, or cramps affecting larger muscle groups (such as thighs and back). Myopathy is often used interchangeably with myalgia, but myopathy is a general term used for any muscle-related symptoms. The most concerning of SAMS is rhabdomyolysis, which is a rapid breakdown of skeletal muscle resulting in creatine kinase (CK) elevations greater than 10 times the upper limit of normal. The release of myoglobin from damaged muscle tissue may also compromise renal function and lead to acute kidney injury. Patients presenting with rhabdomyolysis will often describe their urine as dark or “tea-colored” and present with nausea, vomiting, confusion, coma, cardiac arrhythmias, electrolyte disturbances, and even death. Fortunately, rhabdomyolysis in statin-treated patients is exceedingly rare occurring in only 0.1% of patients in RCT compared to 0.04% of patients receiving placebo. Rhabdomyolysis is not only caused by statins but can also be induced by extreme physical exercise, certain metabolism disorders (eg, diabetic ketoacidosis), other drugs (eg, colchicine), toxins, and infection.

Certain risk factors are known to increase the risk of developing SAMS and

recognition of these risk factors at the time of statin initiation may minimize the risk of SAMS. Known risk factors include advanced age, female gender, low body mass index, frequent heavy exercisers, comorbidities (eg, kidney disease, hypothyroidism), and increased serum statin concentrations due to drug–drug interactions.[57] A lower dose might be necessary for patients with multiple risk factors for SAMS, and once the starting dose is tolerated, the dose can be titrated to the desired potency. Avoiding major drug–drug interactions is a significant modifiable risk factor for SAMS that pharmacists can directly impact. Nearly 80% of all medications are metabolized in the liver by the cytochrome P450 system (CYP) with CYP3A4 being the most predominant.[58] Statins are no different as nearly all statins, except pravastatin, are metabolized to some degree by CYP isoenzymes. Lovastatin, simvastatin, and atorvastatin are associated with more significant drug–drug interactions since they are predominantly metabolized by CYP3A4, while fluvastatin, pitavastatin, and rosuvastatin rely on other CYP isoenzymes (eg, CYP2C9, CYP2C8, CYP2C19).[59] The co-prescribing of medications that compete with or inhibit the same CYP isoenzyme (such as verapamil) can increase serum statin concentrations and the risk for SAMS. The concurrent use of medications such as gemfibrozil that interfere with statin glucuronidation, which is responsible for statin clearance, increase the risk of SAMS.

The management of SAMS requires a multifaceted approach. Documentation of the patients' reported symptoms and determining the probability of SAMS is an important first step. A Statin Intolerance App (available at: http://www.acc.org/statinintoleranceapp) created by the ACC is a helpful resource that can be used to determine the possibility of SAMS and provide guidance on managing patients with possible SAMS. Statin therapy should be generally discontinued in patients with intolerable symptoms. If symptoms resolve, initiate a different statin at a lower dose.[57,60] Additionally, hydrophilic statins (such as atorvastatin and rosuvastatin) may be better tolerated than lipophilic statins (such as simvastatin). In patients where symptoms do not improve, other potential causes of muscle pain should be excluded, including hypothyroidism and vitamin D deficiency, before a statin rechallenge.[60] Alternative dosing strategies (eg, every other day) using statins with long half-lives (atorvastatin, rosuvastatin, and likely pitavastatin) may also be considered. Nonstatin therapies may be considered in patients who fail multiple statins. While routine CK monitoring is not recommended, a CK measurement prompted by patient symptoms can be used to exclude rhabdomyolysis and can assist with identifying those with definite myalgia. Importantly, patients should be reassured

that statins are effective and safe, and SAMS is reversible with statin discontinuation.

Other notable adverse effects of statins include mild elevations in serum transaminase levels (primarily alanine aminotransferase [ALT]). Liver enzymes are not, however, an accurate measure of liver function and there is no causal relationship between statin use and liver failure. Therefore, routine periodic monitoring of liver enzymes is not required, but liver enzyme tests should be obtained before starting statin therapy to have a baseline value for comparison if liver enzymes are later discovered to be elevated. Other potential causes for elevated liver enzymes, including excessive alcohol intake, infection, and select medications should also be evaluated. Statins may be initiated in patients with chronic liver disease, compensated cirrhosis, and nonalcoholic fatty liver disease; however, statins are contraindicated in patients with decompensated cirrhosis or acute liver failure.[60]

Statin use is also associated with a small increased risk of new-onset diabetes.[57] This was first observed in the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial, where the number of new-onset diabetes cases was 0.6% higher in those receiving rosuvastatin 20 mg/day compared to placebo.[34] Subsequent meta-analyses of statin trials have also found a modest increase in the number of new-onset diabetes cases among statin-treated patients compared to placebo, but the absolute risk increase is <1%.[61,62] Common attributes of statin users who develop new-onset diabetes include receiving higher doses of statins and having other risk factors for diabetes, including obesity, impaired fasting glucose, HbA1c >6% (0.06; 42 mmol/mol Hb) or metabolic syndrome.[63] Mechanisms to explain the association between statin use and new-onset diabetes remains unclear. However, observational data suggest that higher cholesterol levels are protective against developing diabetes. This may be attributable to changes at the cellular level involving disruption of cholesterol-sensitive cellular functions that affect insulin secretion and insulin sensitivity.[57] Ultimately, the benefit of statin therapy greatly outweighs the risk of new-onset diabetes as statin use in patients at high ASCVD risk will prevent approximately three ASCVD events for every new case of diabetes.

Cholesterol Absorption Inhibitors

Ezetimibe is a preferred adjunct therapy given it has been shown to modestly reduce the risk of recurrent cardiovascular events in a secondary prevention

population when used in combination with statin therapy.[33] The primary lipid-lowering effect of ezetimibe is a modest reduction in LDL-C of 15% to 24%; with higher reductions achievable when used in combination with statin therapy.[33,64] Ezetimibe reduces LDL-C by inhibiting the NPC1L1 protein, an important transporter of cholesterol absorption in the small intestine and hepatocytes.[64] Known polymorphisms of *NPC1L1* are associated with lower LDL-C levels and decreased ASCVD risk; thus, providing a rational why ezetimibe reduces ASCVD risk.[65] Other than mild gastrointestinal complaints (such as diarrhea) and postmarketing reports of myalgia and mild ALT elevations when used in combination with statins, ezetimibe is generally well tolerated. Previous concerns over a potential increased risk of cancer have been nullified given recent prospective clinical trial data showing there is no increased risk of cancer with ezetimibe use.[33] Ezetimibe has no effects on the CYP450 enzyme system; however, concomitant use with cyclosporine can lead to increased exposure to both ezetimibe and cyclosporine.[64]

The bile acid sequestrants (BAS), such as colesevelam, modestly reduce LDL-C (13%-20%) and reduce cardiovascular events when used as monotherapy.[66] There is currently no data to determine if the benefits observed with BAS monotherapy translate to its use in combination with statin therapy. As such, BAS are generally used as adjunct therapy with statins when desired LDL-C levels are not achieved with statins alone. Importantly, BAS are considered first line during pregnancy since they are not systemically absorbed and pose no risk to the fetus. The primary action of BAS is to bind bile acids in the intestinal lumen, with a concurrent interruption of enterohepatic circulation of bile acids and a markedly increased excretion of acidic steroids in the feces. This decreases the bile acid pool size and stimulates the hepatic synthesis of bile acids from cholesterol. Depletion of the hepatic pool of cholesterol results in an increase in cholesterol biosynthesis and an increase in the number of LDL-R on the hepatocyte membrane. The increased number of receptors stimulates an enhanced rate of catabolism from plasma and lowers LDL-C levels. The increase in hepatic cholesterol biosynthesis may be paralleled by increased hepatic VLDL production and, consequently, BAS may aggravate hypertriglyceridemia and should be avoided in those with TG levels exceeding 300 mg/dL (3.39 mmol/L).[30]

One of the main barriers to BAS is their poor tolerability profile. Early BAS (such as cholestyramine) were developed as powders that require mixing with water or juice to create a slurry for oral administration. Gastrointestinal complaints of constipation, bloating, epigastric fullness, nausea, and flatulence

are commonly reported with these formulations.[30] These adverse effects can be minimized by increasing fluid intake, modifying the diet to increase bulk, and using stool softeners. Tablet forms of BAS (such as colesevelam) are generally better tolerated than resin powders and associated with lower overall discontinuation rates.[67] Other potential adverse effects include impaired absorption of fat-soluble vitamins A, D, E, and K; gastrointestinal obstruction; and reduced bioavailability of other drugs such as warfarin, levothyroxine, and phenytoin.[30] Drug–drug interactions may be avoided by taking other medications 1 hour before or 4 hours after the BAS.[30] Colesevelam is not only approved as a lipid-lowering agent but also as an antihyperglycemic that modestly lowers glucose levels in patients with type 2 diabetes mellitus.[68] Given the better safety and tolerability profile of ezetimibe, BAS should be reserved only for those patients unable to tolerate ezetimibe who need additional LDL-C lowering despite maximally tolerated statin therapy.[30]

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors

The PCSK9 inhibitors (e.g. alirocumab) reduce LDL-C by as much as 60% when added to background statin therapy. Inhibiting PCSK9 promotes LDL-R recycling to the cell surface, which increases LDL-C clearance from the circulation. Both alirocumab and evolocumab are fully human monoclonal antibodies to PCSK9 and were approved by the FDA in 2015.[30] Randomized, double-blind clinical trials have also shown these agents effectively reduce recurrent cardiovascular events in patients following an acute coronary event and secondary prevention populations when added to background statin therapy.[32,69]Alirocumab and evolocumab are both administered by subcutaneous injection. Although this may be a barrier for some patients, PCSK9 inhibitors can be administered bi-weekly or once-monthly. The most common adverse effect reported are injection site reactions, which can be minimized by allowing the injection to come to room temperature before use and icing the site before injecting. Some patients may also report “flu-like” symptoms after the injection. There were initial concerns over a potential increased risk for neurocognitive adverse effects; however, a randomized trial found no difference in cognitive function between those randomized to evolocumab *versus* placebo over 19 months of follow-up.[70] Furthermore, those patients who reach very low levels of LDL-C (less than 20 mg/dL [0.53 mmol/L]) do not appear to be an increased risk of adverse events.[71] Despite this favorable data, the long-term effects of

achieving very low levels of LDL-C with PCSK9 inhibitors remains unknown. Despite their LDL-C lowering potency and favorable safety profile, PCSK9 inhibitor use has been limited due to their high cost. Although PCSK9 inhibitors should primarily be used in combination with maximally tolerated statins in high-risk patients unable to achieve desired LDL-C levels with a statin alone, evolocumab is FDA-approved for use as monotherapy in patients with primary hyperlipidemia (such as heterozygous familial hypercholesterolemia).[30,72]

Drug That Primarily Lower Triglycerides

Fibric Acid Derivatives (Fibrates)

Although fibrates, such as gemfibrozil, have been shown to reduce cardiovascular events when used as monotherapy, there is less evidence to support their use in combination with statin therapy.[49,50] Fibrates are primarily used in patients with TG levels that exceed 500 mg/dL (5.65 mmol/L) to reduce the risk of acute pancreatitis. The two available fibrates, gemfibrozil and fenofibrate, are potent TG-lowering therapies (20%-50%), but may cause a modest reciprocal rise in LDL-C in patients with severely elevated TG levels.[51] Plasma HDL-C concentrations may rise 10% to 15% or more with fibrates. Gemfibrozil increases the activity of LPL and reduces to a lesser extent the synthesis or secretion of VLDL from the liver into the plasma. Fenofibrate increases LPL activity and reduces apoprotein C-III (an inhibitor of LPL) by activating peroxisome proliferator-activated receptor α (PPARα), which regulates the expression of genes involved in the regulation of lipids and other metabolic processes.

Fibrates are generally well tolerated, but gastrointestinal complaints and transient elevations in transaminase levels have been reported.[73] Both gemfibrozil and fenofibrate require dose adjustments for significant renal impairment and fenofibrate has been reported to worsen renal function, although this is usually transient and self-limiting.[20,74] Muscle-related adverse effects can occur with both gemfibrozil and fenofibrate alone but is more common when used in combination with statins to manage complex dyslipidemia or elevated TG levels. Gemfibrozil, and its glucuronide metabolite, has potent effects on CYP450 enzymes (such as CYP3A4), intestinal, hepatic, and renal transporters making it highly prone to significantly increase serum statin concentrations and the risk of SAMS.[59] For this reason, current guidelines do not recommend gemfibrozil to be initiated in patients receiving statin therapy; fenofibrate is

favored instead.[20] Fenofibrate and gemfibrozil and may enhance the formation of gallstones, but this occurs rarely.[75] Fibrates may potentiate the effects of warfarin and the international normalized ratio (INR) should be monitored very closely with this combination.[76]

Omega-3 Polyunsaturated Fatty Acids (PUFA)

High doses of omega-3 fatty PUFA (2-4 g/day of EPA/DHA) significantly reduce TG and VLDL cholesterol levels (20%-50%) with lesser effects on other lipoproteins.[51] The mechanisms by which omega-3 PUFA reduce TG levels include increasing hepatic oxidation of free fatty acids, increasing LDL hydrolysis by activating PPARα and inhibiting apoprotein C-III. The omega-3 PUFA formulations approved by the FDA for treating TG levels of 500 mg/dL (5.65 mmol/L) or greater include an omega-3-acid ethyl ester of EPA/DHA (Lovaza®), omega-3-carboxylic acid of EPA/DHA (Epanova®), and ethyl ester of EPA only (Vascepa®). DHA and EPA have different effects on LDL-C as EPA prevents LDL oxidation and promotes LDL clearance, whereas DHA does not; however, the clinical significance of this remains unclear.[77] Prescription omega-3 PUFA products contain approximately 1 g of EPA/DHA per capsule, whereas the EPA/DHA content of OTC “fish oil” supplements is often less than 300 mg per capsule and are not regulated by the FDA. Unless patient affordability is an issue, prescription omega-3 PUFA are preferred to minimize pill burden and ensure product quality. Randomized clinical trials of omega-3 PUFA have shown mixed results due to the lack of generalizability due to the population studied, the background lipid-lowering therapy used, and dose taken.[51,77] The recently published REDUCE-IT study, a landmark trial, evaluated the effects of icosapent ethyl (4g/day), a high-potency EPA derivative, used as add-on therapy to statins.[78] At baseline, patients enrolled in the REDUCE-IT study had a median TG level of 216 mg/dL (2.44 mmol/L) and the majority had a history of ASCVD. Icosapent ethyl reduced the rate of ischemic events by 25% and significantly reduced the risk of cardiovascular death when compared to placebo. However, icosapent ethyl also increased the risk of hospitalization for atrial fibrillation or flutter. The REDUCE-IT study was released shortly after the 2018 ACC/AHA guidelines were published and, thus, icosapent ethyl was not discussed or recommended. Future guidelines should bring clarity to the role of icosapent ethyl for the treatment of hypertriglyceridemia in patients at high risk of ASCVD events.

Gastrointestinal complaints (such as abdominal pain and “fishy burps”) are

common with OTC omega-3 PUFA products but may be minimized by refrigerating the capsules. However, they should not be kept frozen in the freezer. Caution is advised in patients with known sensitivities or allergies to fish or shellfish. Drug–drug interactions are minimal with omega-3 PUFA, although caution is advised when used concomitantly with antiplatelet agents or anticoagulants since omega-3 PUFA may prolong bleeding time.

Niacin

Niacin (nicotinic acid) increases HDL-C (5%-30%), and lowers TG (20%-50%) and LDL-C (5%-20%). Despite these favorable changes in the lipid profile, niacin has not been shown to improve cardiovascular outcomes in patients on background statin therapy with relatively well-controlled lipids at baseline.[53,54] Niacin primarily lowers TG levels by inhibiting lipolysis with a decrease in free fatty acids in plasma and decreased hepatic esterification of TG. It also significantly raises HDL-C by reducing its catabolism and selectively decreasing hepatic removal of HDL apoA-I but not the removal of cholesterol esters, thereby increasing the capacity of retained apoA-I to augment reverse cholesterol transport in isolated hepatic cells. Niacin also reduces the hepatic synthesis of VLDL, which, in turn, leads to a reduction in the synthesis of LDL. However, the modest decrease in serum LDL-C levels is dose-dependent.

Niacin has many adverse drug reactions that frequently limit its use. Cutaneous flushing and itching appear to be prostaglandin mediated and can be reduced by administering aspirin 325 mg given shortly before niacin ingestion.[79] Flushing seems to be related to rising plasma concentrations of niacin and the use of immediate-release formulations; taking the dose with meals and slowly titrating the dose upward may also minimize these effects. Extended- or sustained-release products may minimize these complaints in some patients. The only legend form of niacin, Niaspan® (Abbott), is an extended-release form of niacin with pharmacokinetics intermediate between immediate- and sustained-release products that are sold as food supplements rather than legend products. In controlled trials, Niaspan® is reported to have fewer dermatologic reactions and has a lower risk for hepatoxicity.[79] Potentially important laboratory abnormalities occurring with niacin therapy include elevated liver function tests, hyperuricemia, and hyperglycemia. With less than 3 g/day, the degree of liver function test elevation is generally not marked and often transient, and a temporary reduction in dosage frequently corrects the problem. Pre-existing gout and diabetes may be exacerbated by niacin; these patients should be monitored more closely and their medication titrated appropriately.[80,81] Niacin is

contraindicated in patients with active liver disease and active peptic ulcer disease. Concomitant alcohol and hot beverages may magnify flushing and pruritus with niacin and they should be avoided at the time of ingestion. Nicotinamide should not be used in the treatment of hyperlipidemia, as it does not effectively lower cholesterol or TG levels.

Special Populations

Older Adults

Dyslipidemia is an independent risk factor for ASCVD in older adults (greater than 65 years old), as it is in the younger patient.[82] The attributable risk, which is the difference in absolute rates of cardiovascular events between segments of the population with higher or lower serum cholesterol levels, increases with age. Drug therapy in principle differs little from younger patients, and older patients respond to lipid-lowering therapies as well as younger patients. The gain in life expectancy may be small depending on the age at the start of treatment and the magnitude of LDL-C reduction. The benefits of moderate-to-high intensity statin therapy in older adults for secondary prevention is quite clear, while the benefit of statins in older adults for primary prevention is more controversial.[82] This is especially true in individuals greater than 75 years of age since this age group is poorly represented in RCTs.[20] Primary prevention in younger patients requires about 2 years before reduction in ASCVD risk is apparent, and this lag time should be taken into consideration, along with life expectancy, in patient selection for statin therapy in older adults. To help address this gap in the evidence, the ongoing Statin Therapy for Reducing Events in the Elderly (STAREE) trial (NCT02099123) is evaluating the efficacy of atorvastatin 40 mg/day for primary prevention in those 70 years or older without diabetes.

The risks of statin therapy in older adults must also be considered. Changes in body composition, renal function, and other physiologic changes of aging may make older patients more susceptible to the adverse effects of lipid-lowering drug therapy.[82] Older adults are more prone to developing SAMS and the effects of SAMS on the risk of falls and functional status remains unclear.[77] There is also concern regarding the potential negative effects of statins on cognitive function; however, data from meta-analyses has suggested statins are not associated with adverse cognitive effects.[83,84] Statin use has also been associated with increased risk of cataracts, which is highly prevalent among older adults, yet a meta-analysis found no clear evidence showing statins increase the risk of

cataracts.[85] Older adults are also more likely to develop type 2 diabetes and the impact of statin therapy on new-onset diabetes in older adults is a concern warranting further study.

Children

While cardiovascular events rarely occur in those under 18 years of age, the process of atherosclerosis often begins during childhood.[86] Early identification and management of risk factors is critical for primordial prevention of ASCVD. Dyslipidemia in children can develop from secondary causes, similar to adults, or may present as primary dyslipidemia (such as FH). Universal lipid screening is recommended between age 9 and 11 as this is a stable time for lipid assessment before the onset of puberty, which decreases cholesterol levels 10% to 20%.[86] Lipid screening before age 9 is only recommended in children with a significant family history of premature ASCVD, known first-degree relatives with dyslipidemia, or other cardiovascular risk factors (such as diabetes, obesity, or hypertension).[86]

Drug therapy in children is not recommended until the age of 10 years or older and the guidelines for initiation of therapy and acceptable levels of cholesterol and lipoproteins are quite different that adults (see Table 31-3).[86] Children younger than 10 years should only receive drug therapy if they have a genetic lipid disorder (such as FH) or high-risk ASCVD condition (such as diabetes); these children should be referred to a pediatric lipid specialist.[86] Lifestyle interventions are generally the mainstay of therapy, yet children with FH will often require drug therapy. Pravastatin may be used in children as young as 8 years old, while all other statins are indicated for use in children 10 years of age and older.[86] Start with the lowest available statin dose and titrate every 3 months as necessary to achieve treatment goals. Appropriate contraception strategies are recommended in females taking statins who are sexually active. Ezetimibe and BAS also have data suggesting they are safe and effective to use in children 10 years or older. At this time, evolocumab is the only PCSK9 inhibitor with safety and efficacy data in children 13 years or older with HoFH.[72] The safety and efficacy of fibrates and omega-3 PUFA have not been established.

Women

The leading cause of death in women is ASCVD and as many women as men die of ASCVD annually. This is mostly due to a longer average life expectancy and

a higher lifetime risk of ischemic stroke than men.[87] Age is an important factor when estimating cardiovascular risk in women as most ASCVD events occur in postmenopausal women. The decline in estrogen levels that occurs during menopause is associated with increased cardiovascular risk, yet hormone replacement therapy is not recommended as studies have shown it does not reduce cardiovascular risk.[88,89] Other age-related changes, including increases in blood pressure and LDL-C, play a significant role as well in both women and men. Women have been underrepresented in RCT of lipid-lowering therapies; however, a meta-analysis of 27 RCTs found statin therapy is equally effective in men and women.[90] Nonstatin therapies also appear to be equally effective except for fenofibrate, which is associated with an increased ASCVD risk in women when combined with simvastatin.[91] This finding was not, however, observed in another RCT comparing fenofibrate to placebo.[92] The clinical significance of this subgroup finding remains unknown.

Pregnancy is associated with a progressive rise in cholesterol and TG levels, yet dietary therapy is the mainstay of treatment, with emphasis on maintaining a nutritionally balanced diet as per the needs of pregnancy.[93] If the patient is very high risk or has FH, a BAS may be considered during pregnancy since there is no systemic drug exposure.[93] Statins are pregnancy category X and contraindicated due to potential teratogenic effects. Women of childbearing age who are on statin therapy and are sexually active should use a reliable form of contraception to prevent pregnancy. Women who plan to become pregnant should discontinue the statin 1 to 2 months before pregnancy is attempted. Ezetimibe and niacin are pregnancy category C drugs but no data are available in humans. Increased intake of omega-3 PUFA, particularly DHA, during pregnancy is important for fetal brain development; however, prescription omega-3 PUFA products are pregnancy category C.[94] There is currently no information on the safety of PCSK9 inhibitors in pregnant women.

Patients with Diabetes

Diabetes is a major risk factor for ASCVD and persons with diabetes are at greater risk of morbidity and mortality following an ASCVD event.[20] The dyslipidemia commonly found in persons with diabetes is often characterized by hypertriglyceridemia, low HDL-C, and modestly elevated, but dense, LDL-C that are highly atherogenic.[95] Despite the modest elevation in LDL-C observed in these patients, statins are the first-line therapy given the significant body of evidence from RCT demonstrating that statins reduce ASCVD events and

mortality in persons with diabetes.[20] However, individual risk among those with diabetes who have no history of ASCVD is not homogenous, so the 10-year ASCVD-risk score may be used to determine the appropriate statin intensity (see Table 31-4).[20] High-intensity statin therapy is preferred in those with diabetes and a history of ASCVD (secondary prevention) given these patients are at very high risk of recurrent ASCVD events.

The role of nonstatin therapies in persons with diabetes is complex but has become clearer in recent years. In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) the benefit of adding ezetimibe to simvastatin was significantly enhanced in those with diabetes compared to patients without diabetes.[96] The addition of evolocumab to background statin therapy in the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial was equally effective in those with, and without, diabetes.[97] Given the mixed dyslipidemia associated with diabetes, there has been considerable interest in the potential of fibrates to reduce ASCVD risk. However, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) the combination of fenofibrate and a statin in patients with type 2 diabetes did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke compared to simvastatin alone.[91] Subgroup analyses from two RCTs have suggested a potential benefit with fenofibrate in those with TG levels >204 mg/dL (2.31 mmol/L) and HDL-C <34 mg/dL (0.88 mmol/L), but this has not been evaluated in a prospective RCT.[91,92] Additionally, fenofibrate appears to reduce the progression of diabetic retinopathy, as well as the need for laser treatment.[98] The BAS colesevelam is FDA-approved to improve both glycemic and lipid control, but it can exacerbate hypertriglyceridemia, which is commonly observed in those with diabetes.[51] Niacin modestly increases fasting plasma glucose (~4%-5%) and HbA1c levels (~0.25%).[80] As such, niacin should not be routinely used in persons with diabetes especially given the lack of evidence to support its use.

Patients with Kidney Disease

Dyslipidemia is highly prevalent among patients with kidney disease.[99] The dyslipidemia pattern in patients with kidney disease includes hypertriglyceridemia, slightly elevated total cholesterol and LDL-C and low HDL-C levels.[99] These abnormalities are thought to be caused by a deficiency in apolipoprotein C-II, perhaps as a result of sustained use of heparin during hemodialysis and depletion of LPL, carbohydrate-induced obesity and

hypertriglyceridemia, loss of carnitine during hemodialysis, use of acetate buffer (acetate is a precursor to fatty acid synthesis) during hemodialysis, and decreased LCAT activity during hemodialysis.[100] Dialysis does not correct the lipid abnormalities. Renal transplantation may correct lipid abnormalities in some patients; however, in others, the use of transplantation-related medications, such as corticosteroids and cyclosporine may aggravate lipid abnormalities.[100]

Statins effectively reduce LDL-C in patients with kidney disease, yet the cardiovascular event reduction is less robust in patients kidney disease.[99] Notably, rosuvastatin failed to prevent cardiovascular events in a RCT of patients undergoing hemodialysis suggesting statins should not be initiated in this population.[101] Statins are generally continued, however, in patients who are on statins before progressing to end-stage renal disease and requiring dialysis.[99] Moderate-intensity statins are generally preferred in patients with kidney disease to minimize the risk of adverse effects (such as SAMS).[99] Kidney transplant recipients are at considerably high risk of future cardiovascular events and should receive statin therapy; however, appropriate statin selection is important given the potential for drug–drug interactions with antirejection therapies (such as cyclosporine).[99] Ezetimibe may also be used in combination with statin therapy based on RCT evidence showing this combination reduces cardiovascular events compared to placebo in patients at various stages of advanced kidney disease.[102] Current guidelines do not advocate for routine use of other nonstatin therapies at this time given the paucity of efficacy data and safety concerns.[99]

Patients with Chronic Inflammatory Disorders and HIV

It is well established that the chronic inflammation and immune activation seen with chronic inflammatory disorders (eg, rheumatoid arthritis, lupus) and human immunodeficiency virus (HIV) accelerate the development and progression of atherosclerosis. These nontraditional risk factors are not included in the ASCVD-risk estimator, but they should be considered when assessing individual ASCVD risk. After a 3- to 6-month trial of lifestyle interventions, these patients should have their 10-year ASCVD risk estimated. In those with a 10-year ASCVD risk of 5% or greater, it is reasonable to initiate moderate-intensity statin therapy.

In addition to considering statin therapy, there are additional considerations with the treatments used for chronic inflammatory disorders and HIV. Long-term

use of antiretroviral therapy, for example, has been shown to mediate atherosclerosis progression and development in patients with HIV. With that said, many antiretrovirals (eg, protease inhibitors) can significantly increase TG levels. Anti-inflammatory therapies (eg, tociluzimab, methotrexate) used in the management of rheumatoid arthritis have produced mixed results in terms of their effects on lipid levels and ASCVD risk.

EVALUATION OF THERAPEUTIC OUTCOMES

Short-term evaluation of therapy for dyslipidemia is based on a complete lipid panel obtained 4 to 12 weeks after initiation or following a dose adjustment of lipid-lowering therapy to evaluate therapeutic response.[20] This is especially important with statin therapy given there are numerous pharmacokinetic and pharmacodynamic differences among statins that give rise to variable response to therapy.[103] Long-term evaluation is based on a repeat lipid panel obtained every 3 to 12 months to ensure adherence to lipid-lowering therapy and maintenance of desired levels of LDL-C.[20] It should be noted that although total cholesterol (TC) HDL-C, and TG levels are directly measured, LDL-C is typically estimated using the Friedewald equation, LDL-C = TC – HDL-C – (TG/5) (or LDL-C = TC – HDL-C – (TG/2.2) when lipid levels are all expressed in mmol/L), which does not provide an accurate estimate of VLDL-C.[104] As such, the Friedewald equation can underestimate LDL-C in patients with high TG levels as well as those with very low LDL-C levels. Given VLDL-C concentrations are typically small in comparison to LDL-C, the inaccuracy of VLDL-C has previously been accepted. However, given the increased prevalence of obesity, metabolic syndrome, and diabetes, more patients have elevated levels of VLDL-C. Useful alternatives in these patients include non-HDL-C (TC minus HDL-C) and direct LDL-C measurements, which are more accurate than estimated LDL-C using the Friedewald equation.[104] A nonfasting lipid panel is generally acceptable, except in patients with hypertriglyceridemia, where a fasting lipid panel is preferred to minimize interference from chylomicrons.[105] Routine safety monitoring of hepatic function and CK levels is not recommended in statin-treated patients, but these may be obtained if the patient has signs or symptoms suggestive of liver or muscle injury.[20] Patients taking niacin, on the other hand, should have hepatic function tests performed at baseline, after each dosage increase, and every 6 months thereafter while taking a stable dose.[20] Periodic monitoring of A1c is warranted in persons with diabetes receiving niacin and patients treated with statins who are at high risk for

developing diabetes.[20]

In patients treated with lipid-lowering therapy for secondary prevention, symptoms such as angina or intermittent claudication may improve over months to years. If patients have xanthomas or other external manifestations of dyslipidemia, these lesions should regress with therapy.[46] Modifiable risk factors such as hypertension, smoking, exercise and weight control, and glycemic control in persons with diabetes should also be monitored and evaluated.[20,28] Dietary therapy is an important part of treating dyslipidemia and a dietitian should be consulted to perform an initial evaluation with periodic follow-up thereafter if the goals of therapy are not achieved.[25] Use of food diaries and recall surveys enable the collection of information about diet in a systematic manner and may improve patient adherence to dietary recommendations.

Postclass Engaged Learning Activity

Watch the video entitled “Strategies for Optimizing Statin Therapy: Focus on Drug Interactions” from Pharmacy Times by Mary Bridgeman. This 14-minute video provides a detailed overview of potential drug–drug interactions that can occur with statin therapy through the CYP3A4 pathway. Create a table of the strong CYP3A4 inhibitors and inducers, the effect each would have on a patient’s statin concentrations, and what potential side effects could occur from those interactions. This information will help students be prepared to participate in the PLAN and FOLLOW-UP steps in the patient care process.

- Link to video: https://bit.ly/2OaHiWG

ABBREVIATIONS

Apo	apolipoprotein
ASCVD	atherosclerotic cardiovascular disease
ALT	alanine transaminase
AST	aspartate transaminase
ATP	adenosine triphosphate
BAS	bile acid sequestrants
BMI	body mass index
BUN	blood urea nitrogen
CE	cholesterol ester
CETP	cholesterol ester transfer protein
CHD	coronary heart disease
CKD	chronic kidney disease
CVD	cardiovascular disease
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
HbA1c	glycosylated hemoglobin A1c
HDL-C	high-density lipoprotein-cholesterol
HIV	human immunodeficiency virus
HMG CoA	β-hydroxy β-methylglutaryl coenzyme A
HTN	hypertension
IDL-C	intermediate-density lipoprotein-cholesterol
LCAT	lecithin-cholesterol acyltransferase
LDL-C	low-density lipoprotein-cholesterol
LPL	lipoprotein lipase
LRP	LDL-receptor-related protein
NPC1L1	Niemann-Pick C1-like1
OTC	over-the-counter
PCOS	polycystic ovarian syndrome
PSCK9	proprotein convertase subtilisin/kexin type 9
PUFA	polyunsaturated fatty acid
RCT	randomized controlled trial
SAMS	statin-associated muscle symptoms
T2DM	type 2 diabetes mellitus
TC	total cholesterol
TG	triglyceride
TSH	thyroid stimulating hormone
UA	urinalysis
VLDL-C	very low-density lipoprotein-cholesterol

REFERENCES

1. Rosenson R. Lipoprotein classification, metabolism, and role in atherosclerosis. *UpToDate*. May 5, 2017.
2. Wiggins BS, Saseen JJ. *Pharmacist's Guide to Lipid Management*. 2nd. Lenexa, KS: American College of Clinical Pharmacy; 2014.
3. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP). (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
4. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the national cholesterol education program adult treatment panel III guidelines. *Circulation*. 2004;110:227–239.
5. Smith SC Jr, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: Endorsed by the National Heart, Lung, and Blood Institute. *Circulation*. 2006;113:2363–2372.
6. Mosca L, Banka CL, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 Update. *Circulation*. 2007;115:1481–1501.
7. Fletcher B, Berra K, Ades P, et al. Managing abnormal blood lipids: A collaborative approach. *Circulation*. 2005;112:3184–3209.
8. Yuan G, Al-Shali KZ, Hegele RA. Hypertriglyceridemia: Its etiology, effects, and treatment. *CMAJ Can Med Assoc J*. 2007;176:1113–1120.
9. Mckenney JM, Sica D. Prescription Omega-3 fatty acids for the treatment of hypertriglyceridemia. *Am J Health Syst Pharm*. 2007;64:595–605.
10. Oh RC, Lanier JB. Management of hypertriglyceridemia. *Am Fam Physician*. 2007;75:1365–1371.
11. Mckenney J. New perspectives on the use of niacin in the treatment of lipid disorders. *Arch Intern Med*. 2004;164:697–705.
12. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre randomised placebo-controlled trial. *Lancet*. 2004;364:685–696.
13. Collins R, Armitage J, Parish S, et al. Heart protection study collaborative G. effects of cholesterol-lowering with simvastatin on stroke and other

major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. *Lancet*. 2004;363:757–767.

14. Ford ES, Mokdad AH, Giles WH, Mensah GA. Serum total cholesterol concentrations and awareness, treatment, and control of hypercholesterolemia among US adults: Findings from the National Health and Nutrition Examination Survey, 1999 to 2000. *Circulation*. 2003;107(17):2185–2189.
15. Foley Ka, Denke MA, Kama-Bahl S, et al. The impact of physician attitudes and beliefs on treatment decisions: Lipid therapy in high-risk patients. *Med Care*. 2006;44:421–428.
16. Arnett DK, Jacobs RD Jr, Luepker RV, et al. Twenty-year trends in serum cholesterol, hypercholesterolemia, and cholesterol medication use: The minnesota heart survey, 1980-1982 to 2000-2002. *Circulation*. 2005;112:3884–3891.
17. Mozaffarian D, Benjamin EJ, Go AS, et al. Executive summary: Heart disease and stroke statistics—2015 update: A report from the American Heart Association. *Circulation*. 2015;131:434–441.
18. Menotti A, Lanti M, Nedeljkovic S, et al. The relationship of age, blood pressure, serum cholesterol, and smoking habits with the risk of typical and atypical coronary heart disease death in the European Cohorts of seven countries study. *Int J Cardiol*. 2006;106:157–163.
19. Stone NJ. Secondary causes of hyperlipidemia. *Med Clin North Am*. 1994;78:117–141.
20. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/ Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. Nov 2018;1097:S1. doi: 10.1016/j.jacc.2018.11.003.
21. Yuan F, Wang J, Hegele RA. Heterozygous familial hypercholesterolemia: an underrecognized cause of early cardiovascular disease. *CMAJ*. 2006;174:1124–1129.
22. Hasudungan, Armando. “Physiology of Lipoproteins Cholesterol.” *YouTube*. June 1, 2015. Available at: https://www.youtube.com/watch?v=PkKH8lTxvzA.
23. “Physiology of Lipoprotein Metabolism.” YouTube. August 17, 2009. Available at: https://www.youtube.com/watch?v=97uiV4RiSAY.

24. Libby P. How our growing understanding of inflammation has reshaped the way we think of disease and drug development. *Clin Pharmacol Ther*. 2010;87:389–391.
25. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk. *J Am Coll Cardiol*. 2014;53(25):2960–2984.
26. Whelton PK, Carey RM, Aronow WS. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. *J Am Coll Cardiol*. 71(19):e127–e248. doi: 10.1016/j.jacc.2017.11.006.
27. American Diabetes Association. 2018 Standards of Medical Care in Diabetes. *Diabetes Care*. 2018.
28. Goff DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA Guideline on the assessment of cardiovascular risk: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25):2935–2959.
29. Navarese EP, Robinson JG, Kowalewski M, et al. Association between baseline LDL-C level and total and cardiovascular mortality after LDL-C lowering: A systematic review and meta-analysis. *JAMA*. 2018;319(15):1566–1579.
30. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2017 Focused update on the 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-Cholesterol lowering in the management of atherosclerotic cardiovascular disease risk. *J Am Coll Cardiol*. 2017;70(14):1785–1822.
31. Cholesterol Treatment Trialists Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: A meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670–1681.
32. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376(18):1713–1722.
33. Cannon CP, Blazing mA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015; 372:2387–2397.
34. Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent

vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359(21):2195–2207.

35. U.S. Department of Health and Human Services and U.S. Department of Agriculture. *2015-2020 Dietary Guidelines for Americans*. 8th ed. December 2015. Available at: http://health.gov/dietaryguidelines/2015/guidelines.
36. Hoy MK, Goldman JD. Fiber intake of the U.S. population: What we eat in America, NHANGES 2009-2010. Food Surveys Research Group Dietary Data Brief No. 12. September 2014.
37. Mozaffarian D, Rimm EB. Fish intake, contaminants and human health: Evaluating the risks and benefits. *JAMA*. 2006;296(15):1885–1899.
38. Aung T, Halsey J, Kromhout D, et al. Associations of Omega-3 fatty acid supplement use with cardiovascular disease risks: Meta-analysis of 10 trials involving 77,917 individuals. *JAMA Cardiol*. 2018;3(3):225–234.
39. Siscovick DS, Barringer TA, Fretts AM, et al. Omega-3 polyunsaturated fatty acid (Fish Oil) supplementation and the prevention of clinical cardiovascular disease: A science advisory from the american heart association. *Circulation*. 2017;135:e867–e884.
40. Bowman L, Mafham M, Wallendszus K, et al. ASCEND Study Collaborative Group. Effects of n-3 fatty acid supplements in diabetes mellitus. *N Engl J Med*. 2018;379(16):1540–1550.
41. Yoo EG. Sitosterolemia: A review and update of pathophysiology, clinical spectrum, diagnosis, and management. *Ann Pediatr Endocrinol Metab*. 2016;21(1):7–14.
42. Cohen PA, Avula B, Khan IA. Variability in strength of red yeast rice supplements purchased from mainstream retailers. *Eur J Prev Cardiol*. 2017;24(13):1431–1434.
43. Dujovne CA. Red yeast rice preparations: Are they suitable substitutions for statins? *Am J Med*. 2017;130(10):1148–1150.
44. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: Prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins. *Lancet*. 2005;366:1267–1278.
45. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur H J*.

2017;38(32):2459–2472.

46. Robinson JG, Goldberg AC. Treatment of adults with Familial Hypercholesterolemia and evidence for treatment: Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol*. 2011;5:S18–S29.
47. Hopkins PN, Toth PP, Ballantyne CM. Rader DJ national lipid association expert panel on familial hypercholesterolemia. Familial hypercholesterolemias: Prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol*. 2011;5(3 Suppl):S9–S17.
48. Dixon DL, Sisson EM, Butler M, et al. Lomitapide and Mipomersen: Novel lipid-lowering therapies for the management of familial hypercholesterolemia. *J Cardiovasc Nurs*. 2014;29(5):E7–E12.
49. Miller M, Stone NJ, Ballantyne C, et al. Triglycerides and cardiovascular disease: A Scientific Statement from the American Heart Association. *Circulation*. 2011;123(20):2292–2333.
50. Jacobson TA, Ito MK, Maki KC, et al. National lipid association recommendations for patient-centered management of dyslipidemia: Part 1—full report. *J Clin Lipidol*. 2015;9:129–169.
51. Kelly MS, Beavers C, Bucheit JD, et al. Pharmacologic approaches for the management of patients with moderately elevated triglycerides (150–499 mg/dL). *J Clin Lipidol*. 2017;11:872–879.
52. Toth PP, Barter PJ, Rosenson RS, et al. High-density lipoproteins: A consensus statement from the National Lipid Association. *J Clin Lipidol*. 2013;7(5):484–525.
53. Landray MJ, Haynes R, Hopewell JC, et al. HPS2-THRIVE Collaborative Group. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med*. 2014;371(3):203–212.
54. Boden WE, Probstfield JL, Anderson T, et al. AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med*. 2012;365(24):2255–2267.
55. Schachter M. Chemical, pharmacokinetics and pharmacodynamic properties of statins: An update. *Fundam Clin Pharmacol*. 2005;19(1):117–125.
56. Tobert JA, Newman CB. Statin tolerability: In defense of placebo-controlled trials. *Eur J Prev Cardiol*. 2016;23:891–896.
57. Thompson PD, Panza G, Zaleski A, Taylor B. Statin-Associated side

effects. *J Am Coll Cardiol*. 2016;67(20):2396–2410.

58. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: Regulation of gene expression, enzyme activities, and impact of genetic variation. *Pharmacol Ther*. 2013;138(1):103–141.
59. Wiggins BS, Saseen JJ, Page RL, et al. Recommendations for management of clinically significant drug-drug interactions with statins and select agents used in patients with cardiovascular disease. *Circulation*. 2016;134(21):e468–e495.
60. Rosenson RS, Baker SK, Jacobson TA, et al. An assessment by the statin muscle safety task force: 2014 Update. *J Clin Lipidol*. 2014;8(3):S58–S71.
61. Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: A meta-analysis. *JAMA*. 2011;305:2556–2564.
62. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: A collaborative meta-analysis of randomised statin trials. *Lancet*. 2010;375:735–742.
63. Ridker PM, Pradhan A, MacFadyen JG, et al. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: An analysis from the JUPITER trial. *Lancet*. 2012;380(9841):565–571.
64. Ezetimibe (Zetia®) [package insert]. Whitehouse Station, NJ: Merck & Co., Inc; 2007.
65. The Myocardial Infarction Genetics Consortium Investigators. Inactivating mutations in *NPC1L1* and protection from coronary heart disease. *N Engl J Med*. 2014;371:2072–2082.
66. The lipid research clinics coronary primary prevention trial results. I. Reduction in incidence of coronary heart disease. *JAMA*. 1984;251(3):351–364.
67. Brunetti L, DeSantis EH. Patient tolerance and acceptance of colesevelam hydrochloride: Focus on type-2 diabetes mellitus. *Pharmacy and Therapeutics*. 2015;40(1):62–67.
68. Fonseca VA, Handelsman Y, Staels B. Coleseveal lowers glucose and lipid levels in type 2 diabetes: The clinical evidence. *Diabetes Obes Metab*. 2010;12(5):384–392.
69. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med*. November 29, 2018;379(22):2097–2107.

70. Giugliano RP, Mach F, Zavitz K, et al. Cognitive function in a randomized trial of evolocumab. *N Engl J Med*. 2017;377:633–643.
71. Giugliano RP, Pedersen TR, Park JG, et al. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: A prespecified secondary analysis of the FOURIER trial. *Lancet*. 2017;390:1692–1671.
72. Evolocumab (Repatha®) [package insert]. Thousand Oaks, CA: Amgen; 2015.
73. Fenofibrate (Tricor®) [package insert]. North Chicago, IL: Abbott Laboratories; 2010.
74. Mychaleckyj JC, Craven T, Nayak U, et al. Reversibility of fenofibrate therapy-induced renal function impairment in ACCORD type 2 diabetic participants. *Diabetes Care*. 2012;35(5):1008–1014.
75. Caroli-Bosc FX, Le Gall P, Pugliese P, et al. Role of fibrates and HMG-CoA reductase inhibitors in gallstone formation. *Digestive Diseases and Sciences*. 2001;46(3):540–544.
76. Dixon DL, Williams VG. Interaction between gemfibrozil and warfarin: Case report and review of the literature. *Pharmacotherapy*. 2009;29(6):744–748.
77. Bradberry JC, Hilleman DE. Overview of Omega-3 fatty acid therapies. *Pharmacy and Therapeutics*. 2013;38(11):681–691.
78. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N Engl J Med*. 3, 2019;380(1):11–22. doi: 10.1056/NEJMoa1812792.
79. Jacobson TA. A “Hot” topic in dyslipidemia management—”How to Beat a Flush”: Optimizing niacin tolerability to promote long-term treatment adherence and coronary disease prevention. *Mayo Clin Proc*. 2010;85(4):365–379.
80. Goldberg RB, Jacobson TA. Effects of niacin on glucose control in patients with dyslipidemia. *Mayo Clin Proc*. 2008 Apr;83(4):470–478.
81. Salem CB, Slim R, Fathallah N, Hmouda H. Drug-induced hyperuricemia and gout. *Rheumatology*. 2017;56(5):679–688.
82. Dixon DL, Donohoe KL, Ogbonna KC, Barden SM. Current drug treatment of hyperlipidemia in older adults. *Drugs Aging*. 2015;32:127–138.
83. Swiger KJ, Manalac RJ, Blumenthal RS, et al. Statins and cognition: A

systematic review and meta-analysis of short- and long-term cognitive effects. *Mayo Clin Proc*. 2013;88(11):1213–1221.

84. Ott BR, Daiella LA, Dahabreh IJ, et al. Do statins impair cognition? A systematic review and meta-analysis of randomized controlled trials *J Gen Intern Med*. 2015;30(3):348–358.
85. Yu S, Chu Y, Li G, et al. Statin use and the risk of cataracts: A systematic review and meta-analysis. *J Am Heart Assoc*. 2017;6(3):pii: e004180. doi: 10.1161/JAHA.116.004180.
86. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: Summary report. *Pediatrics*. 2011;128(suppl 5):S213–S256.
87. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics-2018 update: A report from the American Heart Association. *Circulation*. 2018;137(12):e67–e492.
88. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med*. 2003;349:523–534.
89. Hulley S, Grady D, Bush T, et al. For the heart and estrogen/progestin replacement study (HERS) research group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA*. 1998;280:605–613.
90. Cholesterol Treatment Trialists Collaboration. Efficacy and safety of LDL-lowering therapy among men and women: Meta-analysis of individual data from 174 000 participants in 27 randomised trials. *Lancet*. 2015;385:1397–1405.
91. Ginsberg HN, Elam MB, Lovato LC, et al. Effects of combination lipid therapy in Type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1563–1574.
92. Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): Randomised controlled trial. *Lancet*. 2005;366(9500):1849–1861.
93. Wild R, Weedin EA, Wilson D. Dyslipidemia in pregnancy. *Cardiol Clin*. 2015;33:209–215.
94. Coletta JM, Bell SJ, Roman AS. Omega-3 fatty acids and pregnancy. *Rev Obstet Gynecol*. 2010;3(4):163–171.
95. Goldberg IJ. Diabetic dyslipidemia: Causes and consequences. *J Clin*

Endocrinol Metab. 2001;86(3):965–971.

96. Giugliano RP, Cannon CP, Blazing MA, et al. Benefit of adding ezetimibe to statin therapy on cardiovascular outcomes and safety in patients with versus without diabetes mellitus: Results from IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). *Circulation*. 2018;137(151):1571–1582.
97. Sabatine MS, Leiter LA, Wiviott SD, et al. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: A prespecified analysis of the FOURIER randomised controlled trial. *Lancet Diabetes Endocrinol*. 2017;5(12):941–950.
98. Chew EY, Ambrosius WT, Davis MD, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med*. 2010;363(3):233–244.
99. Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. Clinical practice guidelines for lipid management in CKD: summary of recommendation statements and clinical approach to the patient. *Kindey Int Suppl*. 2013;3(3):259–305.
100. Vaziri ND. Dyslipidemia of chronic renal failure: The nature, mechanisms, and potential consequences. *Am J Physiol Renal Physiol*. 2006;290(2):F262–F272.
101. Fellstrom BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med*. 2009;360:1395–1407.
102. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of heart and renal protection): A randomized placebo-controlled trial. *Lancet*. 2011;377(9784):2181–2192.
103. Karlson BW, Wiklund O, Palmer MK, et al. Variability of low-density lipoprotein cholesterol response with different doses of atorvastatin, rosuvastatin, and simvastatin: Results from VOYAGER. *Eur Heart J Cardiovasc Pharmacother*. 2016;2(4):212–217.
104. Martin SS, Blaha MJ, Elshazly MB, et al. Friedewald-estimated versus directly measured low-density lipoprotein cholesterol and treatment implications. *J Am Coll Cardiol*. 2013;62(8):732–739.
105. Nordestgaard BG, Langsted A, Mora S, et al. Fasting is not routinely required for determination of a lipid profile: Clinical and laboratory

implications including flagging at desirable concentration cut-points-a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. *Eur Heart J*. 2016;37(25):1944–1958.

106. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360(9326):7–22. 12114036.
107. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA*. 1998;279(20):1615–1622.
108. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352(14):1425–1435.
109. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med*. 1995;333(20):1301–1307.

32

Stable Ischemic Heart Disease

Paul Dobesh, Robert J. DiDomenico, and Kelly C. Rogers

KEY CONCEPTS

1. Stable ischemic heart disease (SIHD) is caused by an obstructive atherosclerotic plaque in one or more epicardial coronary arteries. Increases in myocardial oxygen demand in the setting of a fixed decrease in myocardial oxygen supply result in myocardial ischemia. Some patients with SIHD may have a component of vasospasm that requires a slightly different pharmacologic approach.
2. Chest pain (angina) from exertion is the cardinal symptom of myocardial ischemia in patients with SIHD.
3. Assessment of successful treatment of angina includes reducing the number of episodes, enabling patients to participate in activities that provide a high-level quality of life, and decreasing mortality by using guideline-directed medical therapy (GDMT).
4. Management of modifiable atherosclerotic risk factors is key to improving the quantity of life in patients with SIHD.
5. Aspirin, angiotensin-converting enzyme inhibitors, and statins play an important role in preventing adverse cardiovascular events in patients with SIHD.
6. β-blockers are typically regarded as first-line therapy in the management and control of episodes of angina in patients with SIHD.
7. Calcium channel blockers, long-acting nitrates, and ranolazine are often used as additional therapy for angina. Calcium channel blockers and nitrates are first-line therapies in vasospastic disease.
8. All patients with SHID should receive sublingual nitroglycerin for acute treatment and should receive education regarding its proper use.
9. Revascularization procedures may provide a survival advantage over

GDMT in SIHD patients with more extensive atherosclerotic disease but have not demonstrated a clear advantage over GDMT in those with less extensive disease.

Preclass Engaged Learning Activity

To better understand the normal physiology of the heart and the pathophysiology of coronary artery disease (CAD) please watch the following videos:

1. Pathophysiology of CAD—What is Coronary Artery Disease? Khan Academy: https://tinyurl.com/y3cjyb8v
2. Myocardial oxygen supply—University of British Columbia, UBC Anesthesiology: https://tinyurl.com/yxjouoh3
3. Myocardial oxygen demand—University of British Columbia, UBC Anesthesiology: https://tinyurl.com/y5488brm

INTRODUCTION

Coronary artery disease (CAD) is the leading cause of ischemic heart disease and is typically the result of atherosclerotic plaques in the epicardial vessels. The process of atherosclerosis begins early in life, with fatty steaks developing in many people in their teenage years or early twenties. These plaques grow over decades and start to become pathologic in a person's fifth decade of life and beyond. In addition to CAD, atherosclerosis also manifests in other vascular beds leading to cerebrovascular disease (stroke) and peripheral arterial disease. Ischemic heart disease may present as an acute coronary syndrome (ACS), which includes unstable angina, non-ST-segment myocardial infarction (MI), or ST-segment elevation MI. It may also present as stable ischemic heart disease (SIHD), which typically manifest as either chronic stable exertional angina or ischemia without clinical symptoms (silent ischemia). Less common causes of SIHD include microvascular angina, which is due to atherosclerosis in endocardial instead of epicardial vessels. Microvascular angina is more common in women and those with metabolic syndrome. Coronary vasospasm represents a form of angina that results from an increase in coronary vascular tone that can occur in either normal or diseased vessels. Prinzmetal's angina is a form of vasospastic angina that does not involve atherosclerotic plaque. Inappropriate,

insufficient, or untreated SIHD cannot only lead to MI and cardiac death, but also the development of heart failure (HF), arrhythmias, and valvular disease. The American College of Cardiology (ACC) and American Heart Association (AHA) have published guidelines for the diagnosis and management of SIHD.[1]

EPIDEMIOLOGY

According to AHA statistics, in 2014 an estimated 92.1 million (36.6%) adult Americans had at least one form of cardiovascular disease (CVD), which includes CAD, HF, stroke, and hypertension (HTN).[2] Among patients with CVD, approximately 16.5 million adult Americans had CAD, corresponding to an estimated prevalence of 6.3%. The prevalence of CAD is higher in men and increases with age. Among patients with CAD, the total number of patients with SIHD is difficult to determine. Statistics from the AHA estimate that approximately 8.7 million Americans have angina pectoris while the prevalence of MI among adult Americans is approximately 7.9 million, together approximating the prevalence of CAD.[2] Stable angina is the initial manifestation of ischemic heart disease in approximately one-half of all patients who eventually have an MI.

The mortality and costs associated with CAD are enormous. In 2015, CVD was the number one cause of death in the United States with CAD being the most common cause of CVD death, accounting for almost 400,000 deaths—44% of all CVD-related mortality.[2] Adjusting for age, death rates per 100,000 are highest among black patients compared to those of white and Hispanic ancestry and among men compared to women within each racial demographic. Estimated direct and indirect cost of CAD was $205 billion in 2014, with costs expected to double by 2030.[2]

The prognosis of patients with SIHD is related to the extent of atherosclerotic disease, the presence of left ventricular (LV) dysfunction, and the presence of other comorbidities. The severity of angina symptoms may also be useful in determining the prognosis.[3] In a study of 8,908 Veterans Administration patients with CAD, the risk of death increased with the degree of self-reported physical limitation due to angina.[4] It is thought that the degree of physical limitation reflects the extent of underlying atherosclerotic disease. In addition to mortality, SIHD leads to significant morbidity. Most patients will eventually need to be hospitalized for ACS. Patients often have a reduced quality of life due to their inability to perform activities of daily living without chest pain.[5,6] There is also a

significant amount of lost time from work and lost productivity that have a large indirect cost to patients and society. Data from the Bypass Angioplasty Revascularization Investigation suggest that approximately 15% to 20% of patients rate their health as fair or poor despite revascularization, and 30% of patients are never able to return to work.[7]

ETIOLOGY AND PATHOPHYSIOLOGY

1 Angina pectoris is most often the result of an imbalance between myocardial oxygen supply and myocardial oxygen demand (MVO_2). The process of maintaining adequate coronary blood flow to meet the metabolic demands of the myocytes is complex. Multiple factors influence the supply/demand equation.

The pathophysiology of SIHD is driven by an increase in MVO_2 in the setting of a fixed decrease in myocardial oxygen supply.[8] The etiology of the fixed decrease in supply is long-standing, well-developed atherosclerotic plaque. These plaques grow over several decades. The extent and rate of growth are related to risk factors such as smoking, dyslipidemia, hypertension (HTN), diabetes mellitus (DM), and genetics. The process and development of atherosclerosis are covered in Chapter 31 (Dyslipidemia). Unlike ACS, the episodes of angina in patients with SIHD are not caused by ruptured atherosclerotic plaque which leads to thrombus formation and a rapid reduction in coronary blood flow.[9,10] Rather, the atherosclerotic plaques are stable, have a reduced lipid core, and a firm calcified covering. Since the vessel lumen size does not acutely change, the atherosclerotic plaque produces a relatively fixed decrease in myocardial oxygen supply.

Determinants of Myocardial Oxygen Demand

The major determinants of MVO_2 include heart rate (HR), myocardial contractility, and intramyocardial wall tension. A twofold increase in any of these determinants requires an approximate 50% increase of coronary flow to maintain the myocardial oxygen supply. Intramyocardial wall tension is the leading contributor to increased MVO_2 and is directly related to the radius or size of the ventricular cavity and blood pressure (BP), and indirectly related to the ventricular muscle mass. The larger the size of the ventricular cavity, the more energy or myocardial work is needed for myocardial contraction (systole). During early systole, myocardial work peaks when the pressure in the LV

overcomes the pressure outside the aortic valve. The aortic valve is then pushed open and blood is ejected into the systemic circulation. The higher the blood pressure outside the aortic valve, the more MVO_2 needed. Increased ventricular muscle mass should make myocardial work easier and reduce MVO_2. For example, some athletes have increased ventricular muscle mass and their heart works more efficiently. Unfortunately, left ventricular hypertrophy results in dysfunctional myocytes that do not improve MVO_2. Left ventricular hypertrophy can worsen the supply/demand balance because the blood vessel development (supply) is less than the native myocardium.

The rate-pressure product, or double product, is a common non-invasive measure of MVO_2. To determine the rate-pressure product, multiply the HR and systolic BP. However, changes in contractility or volume loading of the LV are not accounted for in this calculation. An increase in MVO_2 requirements commonly stems from the release of norepinephrine by adrenergic nerve endings in the myocardium and vascular bed as part of the physiologic response to exertion, emotion, or mental stress. The rate of increase of MVO_2, which correlates to the speed at which a physical task is carried out, can be as important as the total amount of MVO_2. A rapid increase in physical exertion is particularly likely to precipitate angina. Tasks involving motion of the hands over the head can also provoke chest pain. Mental and emotional stress may precipitate angina, presumably by increasing adrenergic tone and reducing vagal activity. Sexual activity may precipitate angina due to the combination of physical exertion and emotional stimulation. Similarly, anger can produce constriction of coronary arteries. Other precipitates of angina include physical exertion after a heavy meal and excessive metabolic demands imposed by chills, fever, exposure to cold, thyrotoxicosis, hypoglycemia, and other causes of tachycardia.

Determinants of Myocardial Oxygen Supply

Coronary Blood Flow

Meeting the metabolic demands of the myocardium is centered on the ability to maintain adequate coronary blood flow and coronary arterial pressure. Resting coronary blood flow under normal conditions averages 0.7 to 1.0 mL/min/g of myocardium.[11] The coronary vasculature is made up of larger epicardial vessels, also referred to as R_1 or conductance vessels, and smaller endocardial vessels

called R_2 or resistance vessels (**Fig. 32-1**).[12] Resistance to coronary blood flow is the sum of the resistance in the R_1 and R_2 vessels. The larger epicardial vessels typically offer little resistance to blood flow and can accommodate large increases in coronary blood flow without producing a significant change in pressure. These vessels primarily serve a conduit function. In healthy coronary arteries, resistance to flow is controlled by smaller endocardial (R_2) vessels. These vessels will contract and dilate to maintain blood flow based on the metabolic demands of the myocardium. When a person is at rest or not engaged in physical activity, MVO_2 is low and endocardial vessels constrict. The need for blood flow is low. When there is physical exertion or emotional stress, MVO_2 increases and the endocardial vessels dilate to increase myocardial oxygen supply in proportion to the increase in MVO_2 (Fig. 32-1). The process of constricting and dilating the resistance vessels based on MVO_2 is called autoregulation.[8,12] In response to increased MVO_2, several vasodilatory substances (eg, nitric oxide, prostacyclin, bradykinin) are secreted and this can increase coronary blood flow four- to fivefold over normal resting conditions.[8] The increase in coronary flow above resting conditions is the coronary flow reserve.

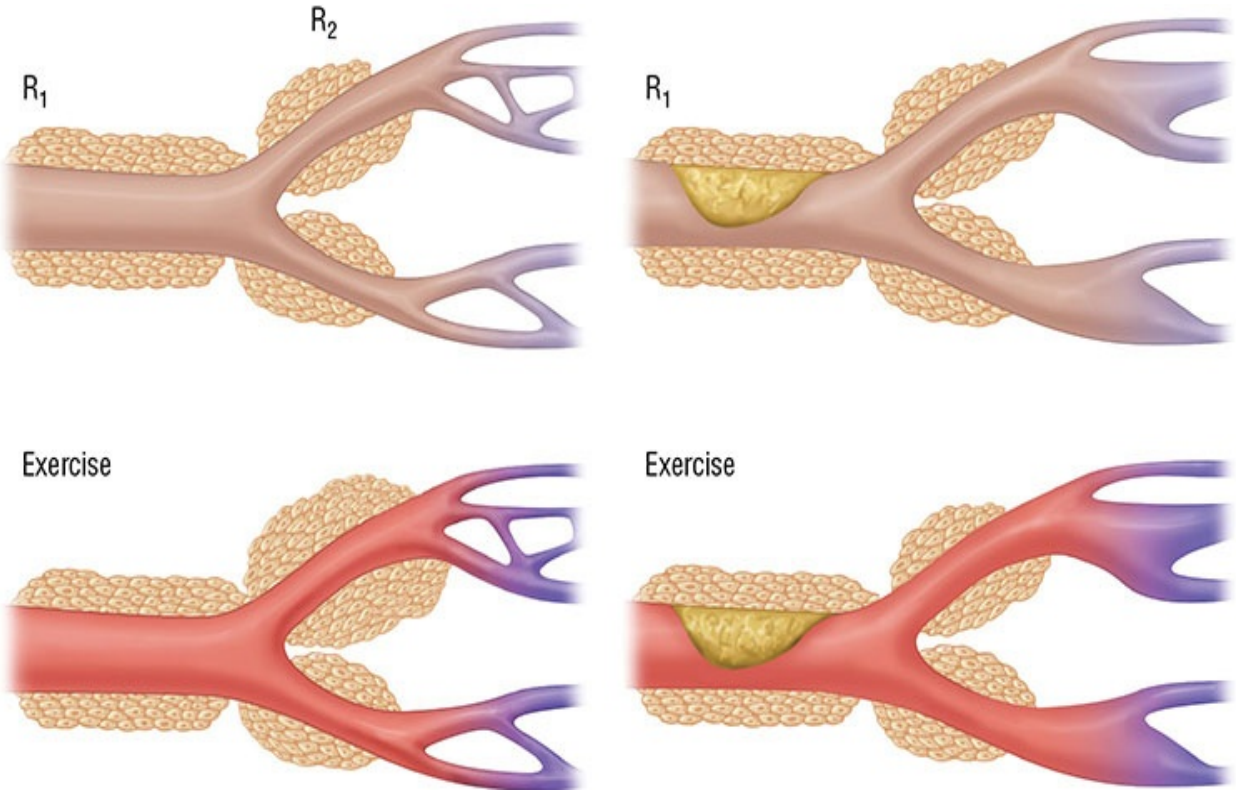


FIGURE 32-1 The coronary circulation with large epicardial conductance vessels (R_1) and intramyocardial resistance arterioles (R_2). Resistance to flow equals $R_1 + R_2$. R_2 resistance is normally much greater than R_1; hence flow is equal to the driving pressure across the coronary bed divided by the resistance in R_2. Dilation in R_2 normally occurs in response to exercise or increased myocardial oxygen demand. When an atherosclerotic lesion narrows the conductance vessel, the arterioles dilate under resting conditions to prevent ischemia. However, during period of exertion, the vasodilator reserve is limited. (*Reproduced, with permission, from Epstein SE, O'Cannon R, Talbot TL. Hemodynamic principles in the control of coronary blood flow. Am J Cardiol. 1985;56:4E-10E.*)

Coronary atherosclerotic plaques typically develop in the larger epicardial vessels. As plaques grow and cause luminal narrowing, resistance to blood flow in epicardial vessels transforms from minimal to considerable. This continues to a point where the resistance from the epicardial vessels becomes dominant. Through autoregulation, the increase in resistance from the R_1 or conductance vessels is offset by vasodilation in the R_2 or resistance vessels to maintain flow.[12]

The luminal diameter occupied by the atherosclerotic plaque determines the drop in pressure and blood flow after the stenosis. The most important determinant of resistance for any given level of flow is the minimum stenosis cross-sectional area.[8] Because resistance is inversely proportional to the square of the cross-sectional area, small dynamic changes in the luminal area caused by atherosclerotic plaque size, thrombus creation, or vasospasm can lead to large changes in the stenosis pressure-flow relationship and reduce maximal perfusion during vasodilation.[8]

Coronary plaques that occupy less than 50% to 70% of the vessel luminal diameter are often referred to as "nonobstructive". They rarely produce ischemia or angina.[12] These smaller plaques do not produce symptoms, and therefore, the patient and clinician typically have no idea they exist. Small plaques have a rich lipid core and thin fibrous cap, they are more prone to rupture and provoke acute thrombus formation, making them potentially lethal (see Chapter 33 "Acute Coronary Syndromes").[9,10]

Once the epicardial vessel is narrowed by 70% or more of the luminal diameter, the endocardial vessels must fully dilate in order to maintain normal coronary resistance. These larger plaques are considered "obstructive."[8,12] At

this point, much of the coronary flow reserve has been used and minimal physical exertion exhausts any remaining capacity. Further increases in exercise intensity are no longer accompanied by decreases in endocardial (R_2) resistance. Blood flow cannot increase to accommodate the demand and autoregulation has reached its ceiling. The resulting flow deficit causes myocardial ischemia and, frequently, angina. The amount of exertion a patient can endure is largely based on the extent of vessel stenosis and the remaining coronary flow reserve. The endocardial flow reserve is exhausted when the epicardial stenosis severity exceeds 90%. Narrowing of the luminal diameter by 90% or more is called a critical stenosis.

Heart Rate and Systole

Increasing HR not only increases MVO_2 but also reduces myocardial oxygen supply. While most tissues and organs are perfused during systole, the heart is the only organ that is perfused during diastole, the phase of myocardial relaxation. There are two physiologic explanations.[8] First, the pressure created in the ventricles during systole creates an increase in pressure in the coronary circulation well above the pressure for coronary perfusion (50-60 mm Hg). Only during diastole do the pressures drop sufficiently to allow coronary flow. Second, the physical compression force of the myocardium that occurs during systole squeezes the coronary vessels closed, preventing blood flow. During a typical cardiac cycle with a normal resting HR, the myocardium spends twice as much time in diastole compared to systole. When the HR increases, time spent in diastole is reduced while time in systole remains relatively unchanged. During times of exertion and increased HR, the ratio of time spent in diastole to systole is reduced from 2:1 to as little as 1:1. This reduces the time for myocardial perfusion, and thus, myocardial oxygen supply is significantly diminished.[8]

Oxygen Extraction and Oxygen Carrying Capacity

Two additional determinants to myocardial oxygen supply are myocardial oxygen extraction and oxygen carrying capacity. Coronary carrying capacity of oxygen is relatively fixed under normal circumstances and not capable of changing in response to increased MVO_2. Therefore, during exertion, the ability to increase oxygen delivery to myocytes is limited mainly through increasing oxygen extraction from the arterial blood. However, this compensatory mechanism only provides little additional oxygen as myocardial arterial oxygen extraction is already approximately 75% under normal circumstances.[13]

Arterial oxygen content is related to hemoglobin concentration and oxygen saturation. Consequently, patients with anemia (low hemoglobin) or hypoxia (low oxygen saturation) have lower than normal oxygen carrying capacity. Anemia is thought to impact total oxygen carrying capacity to a greater degree than hypoxia until the oxygen saturation falls below 50% (0.50). This explains why patients with SIHD often require transfusions when hemoglobin concentrations fall below 9 to 10 g/dL (90 to 100 g/L; 5.59 to 6.21 mmol/L), whereas patients without SIHD can tolerate hemoglobin concentrations as low as 6 g/dL (60 g/L; 3.72 mmol/L). Most patients have an arterial oxygen saturation between 95% and 100% (0.95 and 1.0) so oxygen therapy would not improve oxygen delivery. Therefore, there is little opportunity to improve myocardial oxygen supply by improving myocardial oxygen extraction or oxygen-carrying capacity, leaving increased myocardial blood flow as the principal mechanism for increasing myocardial oxygen supply.

Coronary Collateral Circulation

In the setting of SIHD, pre-existing collateral vessels develop in a process termed arteriogenesis. When a coronary stenosis exceeds 70%, endocardial vessel pressure falls due to maximized autoregulation. This extent of stenosis also contributes to the severity and duration of the episodes of exertion-induced ischemia. The ischemic episodes stimulate nitric oxide synthase and lead to the production of vascular endothelial growth factor and basic fibroblast growth factor. The combination of altered coronary pressure, growth factors, and endogenous vasodilators (eg, nitrous oxide, prostacyclin) changes native collateral vessels of approximately 200 μm in existing epicardial anastomoses into mature vessels that can reach 1 to 2 mm in diameter.[14] While most functional collateral flow develops from the process of arteriogenesis, collateral perfusion can also occur from the development of new collateral vessels in a process called angiogenesis. The process of angiogenesis is also driven by physical forces and growth factors but produces smaller, capillary-like vessels. These vessels can provide collateral flow in the border between ischemic and nonischemic regions of the myocardium.[14] Capillary angiogenesis may also occur within the ischemic region and can reduce the intercapillary distance for oxygen delivery.

Other Factors

While atherosclerotic coronary stenosis is the leading etiology in the development of SIHD and angina, there are additional pathophysiologic

mechanisms that also contribute to disease onset and progression. These mechanisms include endothelial dysfunction, microvascular dysfunction, vasospasm, platelet activation and coagulation, as well as inflammation.[14] A reduction in nitric oxide-mediated vasodilation leads to endothelial dysfunction. This can be due to impaired nitric oxide synthesis or availability. Reduced vasodilator response may lead to ischemia at lower levels of exertion. There can also be impairments that reduced microvascular response to endogenous vasodilators or exaggerate the response to vasoconstrictors.[14]

Patients with an ACS event have ruptured atherosclerotic plaque with platelet accumulation and coagulation response producing an acute reduction in myocardial oxygen supply.[9,10] While this is not the pathophysiology of ischemia in patients with SIHD, there can be smaller plaques (30%-50% stenosis) that rupture and produce a limited platelet and coagulation response that does not produce an acute compromise in myocardial oxygen supply. Instead, the thrombotic process is arrested and the thrombus undergoes re-endothealialization.[9] This greatly accelerates plaque accumulation. Finally, inflammation plays a role in the pathophysiology of SIHD. Macrophages and T lymphocytes produce and secrete cytokines, chemokines, and growth factors that activate endothelial cells, increase vasoreactivity, and proliferation of vascular smooth muscle cells.[14,15] C-reactive protein, a marker of inflammation, has been shown to be elevated in patients with SIHD and correlates to adverse CV events. Statin therapy in patients with elevated C-reactive protein and normal cholesterol levels reduces the risk of CV events.[16] While an obstructive atherosclerotic plaque contributes to ischemia and angina in patients with SIHD, the pathophysiology involves multiple mechanisms that can be used as therapeutic targets.

Coronary Vasospasm and Prinzmetal's Angina

Most patients with SIHD have an obstructive coronary stenosis and exertion-induced ischemia. Since the size of the obstructive lesion does not change acutely, the amount of exertion needed to induce ischemia and angina is often predictable in an individual patient. For example, the patient knows that working in the garden for 20 minutes or walking five blocks at a certain pace will produce chest pain. Patients with this pattern of angina have a fixed angina threshold. Some patients have variable-threshold angina. In these patients, the amount of exertion needed to provoke chest pain differs from day to day. An example would be the patient who could walk six blocks before experiencing

angina yesterday, but today can only walk one block before becoming symptomatic. These patients have an obstructing atherosclerotic plaque leading to a fixed decrease in myocardial oxygen supply, but they also have transient vasospasm superimposed at the site of the obstructing plaque.[12,14] The vasospasm at or distal to the location of atherosclerotic plaque is typically induced by endothelial damage. Damaged endothelial cells produce less than normal amounts of vasodilator substances such as endothelium-derived relaxing factor (EDRF) and often have an exaggerated response to vasoconstrictors during exercise.[14] Patient symptoms will differ based on the extent of the underlying fixed obstruction and the degree of dynamic change in coronary arterial tone. The changing pattern of ischemia in these patients reflects varying amounts of vasospasm. Angina episodes are typically more common in the morning hours due to the circadian release of vasoconstrictors. Exposure to cold temperature, emotion, and mental stress may also lower the angina threshold in patients with variable threshold angina.

Some patients have variant angina, also known as Prinzmetal's angina. Patients with variant angina usually do not have flow-obstructing atherosclerotic plaques in their coronary arteries, but instead, have vasospasm in epicardial vessels.[8,14] The vasospasm is due to reduced production of vasodilators and an exaggerated response to endogenous vasoconstrictors. Patients with Prinzmetal's angina also have a different clinical presentation when compared to patients with SIHD due to an obstructive coronary plaque. Patients with Prinzmetal's angina are typically younger, may experience chest pain at rest, often in the early morning, and have transient ST-segment elevation on the electrocardiogram (ECG).

CLINICAL PRESENTATION

2 A thorough patient history is key to the clinical assessment of a patient with SIHD. Exertional chest pain is the classic presenting symptom of patients with SIHD. The differential diagnosis of "chest" pain is broad (**Table 32-1**). Therefore, it is important to determine if symptoms are due to a cardiac or noncardiac pathology. The patient's description of chest pain can be helpful in determining if the pain is more likely SIHD or ACS. The PQRST pneumonic is commonly used when conducting the patient interview to gather important aspects of the chest pain story (**Table 32-2**).

TABLE 32-1 Differential Diagnosis of Episodic Chest Pain Resembling

Angina Pectoris

	Duration	Quality	Provocation	Relief	Location	Comment
Effort angina	5-15 minutes	Visceral (pressure)	During effort or emotion	Rest, NTG	Substernal, radiates	First episode vivid
Rest angina	5-15 minutes	Visceral (pressure)	Spontaneous	NTG	Substernal, radiates	Often nocturnal
Mitral prolapse	Minutes to hours	Superficial (rarely visceral)	Spontaneous (no pattern)	Time	Left anterior	No pattern, variable
Esophageal reflux	10 minutes-1 hour	Visceral	Spontaneous, cold liquids, exercise, lying down	Foods, antacids, H_2 blockers, proton pump inhibitors, NTG	Substernal, radiates	Mimics angina
Peptic ulcer	Hours	Visceral, burning	Lack of food, "acid" foods	Foods, antacids, H_2 blockers, proton pump inhibitors	Epigastric, substernal	
Biliary disease	Hours	Visceral (wax and wane)	Spontaneous, food	Time, analgesia	Epigastric, radiates	Colic
Cervical disk	Variable (gradually subsides)	Superficial	Spontaneous, food	Time, analgesia	Arm, neck	Not relieved by rest
Hyperventilation	2-3 minutes	Visceral	Emotion, tachypnea	Stimulus removed	Substernal	Facial paresthesia
Musculoskeletal	Variable	Superficial	Movement, palpation	Time, analgesia	Multiple	Tenderness
Pulmonary	Minutes to hours	Visceral (pressure)	Often spontaneous	Rest, time bronchodilator	Substernal	Dyspneic

NTG, nitroglycerin.

TABLE 32-2 PQRST Approach to Assessment of a Patient's Chest Pain

Factor	Presentation in Stable Ischemic Heart Disease	Questions to Ask
Precipitating factors	Typically brought on by some level of exercise or exertion	What were you doing when the pain started? What brought on this chest pain?
Palliative measures	Relieved by rest with or without a sublingual nitroglycerin in 5-10 minutes	Is there anything that helps the pain go away? If you rest does the pain get better? Does your sublingual nitroglycerin help?
Quality of the pain	Described as a continuous squeezing, heaviness, or tightness	How would you describe the pain? Does the pain change when you breathe in and out?
Region	Substernal	Where is the pain located? Can you point to where the pain seems to originate?
Radiation	Left or right arm, back, down into the abdomen, up into the neck	Does the pain seem to radiate or go to other locations?
Severity	While pain is subjective, those who have pain report a 5 or higher on a 10-point scale	On a scale from 1 to 10, with 1 being no pain, and 10 being the worst pain you have ever had, how would you rate this pain?
Temporal pattern (timing)	Pain lasts less than 20 minutes and is usually relieved in 5-10 minutes	How long did the pain last? How long before the pain went away? After you started to rest, how long before the pain went away?

The chest pain in a patient with SIHD is often precipitated by exertion, such as walking, gardening, sexual activity, or activities of daily living such as showering, cleaning house, or doing laundry. In this setting, the exertion produces an increase in MVO_2 that exceeds what can be provided by the fixed decrease in myocardial oxygen supply from the obstructive atherosclerotic plaque. Typically, rest or the use of sublingual nitroglycerin (SL NTG) relieves the symptoms. As the patient rests for a few minutes, the HR and BP comes

down, re-establishing a balance between myocardial oxygen supply and demand, relieving their chest pain. Use of SL NTG provides acute relief by increasing myocardial oxygen supply through vasodilation of epicardial vessels and a reduction in preload.

Cardiac chest pain is often described as squeezing, crushing, heaviness, or tightness in the chest. It can also be described as a numbness or burning in the chest. Chest pain that is described as sharp, increases with inspiration or expiration, or is reproducible with palpation is less likely to be cardiac in origin. The pain is often substernal and may radiate to the right or left shoulder, right or left arm (left more commonly than right), neck, back, or abdomen. Cardiac chest pain rarely radiates above the mandible (jaw) or below the umbilicus (belly button). The severity of cardiac chest pain can be difficult to quantify since pain is subjective, but most patients will state the pain is severe and rate it five or higher on a ten-point scale. The duration of the chest pain in patients with SIHD is less than 20 minutes, usually only 5 to 10 minutes. Other symptoms that may be present during times of ischemia include diaphoresis, nausea, vomiting, and dyspnea.

1 It is helpful to connect the pathophysiology with the clinical presentation. In SIHD, ischemia is produced by an increase in MVO_2 in the setting of a fixed decrease in supply. The exertion exhausts autoregulation and coronary flow reserve. The patient experiences chest pain. When the patient rests for 5 to 10 minutes or uses an SL NTG, the MVO_2 decreases to a point in which myocardial supply and demand are back in balance—the pain and other symptoms go away. The major differences between the pain with SIHD compared to ACS would be the precipitating factors and the duration of the chest pain. The patient with an ACS typically has angina at rest that lasts longer than 20 minutes. The pathophysiology in a patient with an ACS is an abrupt decrease in myocardial oxygen supply precipitated by a plaque rupture.

The severity of chest pain and the impact of SIHD on daily activities are often evaluated using the Canadian Cardiovascular Society (CCS) classification system (**Table 32-3**).[17] The CSS system evaluates the level of activity needed to produce angina. All of the current severity scores are limited by the subjective nature of a patient's pain as well as the reliability and reproducibility of patient observations.

TABLE 32-3 Classification of Total-, LDL-, HDL-Cholesterol and Triglycerides in Children

Class	Description of Stage
Class I	Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation
Class II	Slight limitation or ordinary activity. Angina occurs on walking or climbing stairs rapidly, on walking uphill, on walking or stair climbing after meals, in cold, in wind, under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal condition
Class III	Marked limitations of ordinary physical activity. Angina occurs on walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace
Class IV	Inability to carry on any physical activity without discomfort—anginal symptoms may be present at rest

Source: Reproduced, with permission, from Campeau L. Grading of angina pectoris. Circulation 1976;54:522-523.

Not all patients have a typical chest pain presentation.[1] "Typical" angina is comprised of three components: (1) substernal chest discomfort with a characteristic quality and duration, which is (2) provoked by exertion or emotional stress, and (3) relieved by rest or NTG. Patients with "atypical" angina meet two of the three criteria. Patients meeting one or none of the typical angina characteristics likely have non-cardiac causes of chest pain. Patient groups more likely to present with atypical angina include women and the elderly. Patients with DM may also have decreased sensation of pain due to neuropathy.[14] Features of atypical angina or angina equivalents include symptoms such as midepigastric discomfort, effort intolerance, dyspnea, and excessive fatigue. One study found that 65% of women with ischemia present with atypical symptoms.[18]

After a description of the chest pain has been obtained, a review of the patient's CAD risk factors should be performed. Non-modifiable risk factors include the patient's age, sex, and a family history of premature atherosclerotic cardiovascular disease (ASCVD) in first-degree relatives (onset in a male before age 55 or a female before age 65). Modifiable risk factors including HTN, DM, dyslipidemia, and cigarette smoking should also be explored. In addition to considering traditional risk factors, markers of inflammation, such as high sensitive C-reactive protein, may also be obtained. The evidence regarding the utility of C-reactive protein in the setting of primary prevention is growing but

its value in guiding therapy in the setting of established CAD (secondary prevention) is less certain. Due to the systemic nature of atherosclerotic cardiovascular disease (ASCVD), patients with a history of cerebrovascular or peripheral arterial disease are also at high risk for CAD. It is likely that patients who have atherosclerosis in cerebral or peripheral arteries also have atherosclerosis in their coronary arteries even if it has not yet led to episodes of angina.

The physical examination of a patient with SIHD usually produces nonspecific findings. At the time of an angina episode, patients may have tachycardia, diaphoresis, and shortness of breath. Patients may also have symptoms of nausea, vomiting, and lightheadedness. Other physical findings may relate to cardiovascular risk factors including an increased BP or a fourth heart sound reflecting long-standing HTN. Other findings may include pulmonary crackles, a displaced point of maximal impulse, or a third heart sound in patients with HF with reduced ejection fraction (HFrEF).

Diagnostic and Prognostic Testing

Several noninvasive and invasive testing can be done to assist in the diagnosis and evaluation of patients with SIHD. A detailed discussion of these tests and when they should be used can be found in the ACC/AHA SIHD guidelines.[1] More information on how each test is performed is available in Chapter e29.

The results of cardiac testing can provide prognostic information, may help guide pharmacotherapy, and identify patients who need a revascularization procedure. All patients with angina symptoms should receive a 12-lead electrocardiograph (ECG). In the resting state, the ECG will be normal in ≥50% of patients with SIHD. In SIHD patients with a normal ECG at rest, about 50% will develop ischemic ST-T wave changes during an episode of angina. These changes can be observed on the ECG conducted during an exercise stress test. Exercise stress testing is a relatively easy and inexpensive method for detecting CAD. Since many patients cannot physically endure an exercise stress test, the myocardium can also be stressed pharmacologically with adenosine, regadenoson, dipyridamole, or dobutamine. Stress testing can provide important diagnostic and prognostic information, especially when conducted with a nuclear imaging study to evaluate myocardial perfusion.

Coronary angiography is the most accurate test for the diagnosis and assessment of patients with CAD and is considered the “gold standard.” Unfortunately, coronary angiography is an invasive technique that requires

arterial access. Coronary angiography in patients with SIHD routinely reveal that approximately 25% of patients have single-vessel disease, 25% have double-vessel disease, and 25% have triple-vessel disease, with 5% to 10% presenting with left main coronary disease and another 15% with no detectable critical vessel obstruction.

Coronary angiography is also useful in determining the fractional flow reserve in patients with obstructive coronary stenosis. Fractional flow reserve (FFR) is an indirect index determined by measuring the driving pressure of microcirculatory flow distal to the area of stenosis relative to the coronary driving pressure available in the absence of stenosis.[19] The FFR is attractive for clinical use in that it can immediately assess the physiologic significance of an intermediate stenosis to help guide decisions regarding coronary intervention. Moreover, the FFR is unaffected by alterations in resting flow. Data currently suggest that patients with an FFR of less than or equal to 0.80 may have a better outcome with a revascularization procedure compared to medical therapy, but more studies are needed to determine the best use of this index.[19,20]

Additional noninvasive diagnostic tests may be used to establish the diagnosis of CAD or follow the progression of disease in patients with SIHD. Myocardial perfusion imaging (eg, nuclear imaging studies) involves administration of an intravenous radioactive tracer before and after a stressor (exercise or pharmacologic). Uptake of the radioactive tracer is proportional to coronary blood flow in normal myocytes and the resulting images can detect perfusion defects. Cardiac magnetic resonance combined with physiologic or pharmacologic stressors can also detect the presence of perfusion defects as well as wall motion abnormalities. Coronary artery calcium scoring using computed tomography (CT), often called “ultra-fast CT” or electron beam CT, multislice or multidetector CT, and CT angiography can also be used to detect the presence of CAD.

Biomarkers

Cardiac troponin concentrations are released when there is myocyte death (infarction) and hence are not typically elevated in patients with SIHD. One study of patients undergoing percutaneous coronary intervention (PCI) for treatment of SIHD found that 6% of patients had an elevated troponin before PCI.[21] After adjusting for demographic, clinical, angiographic, and procedural factors, patients with an elevated pre-procedure troponin were more likely to have an MI or die in-hospital when compared to patients without an elevated

troponin (13.4% vs 5.6%). The differences in these outcomes were still significant 1 year later.[21] The study was conducted at multiple sites and, given the lack of a single reference range, no specific troponin value designating increased risk could be determined. The reasons why troponin predicted these outcomes is not completely understood but may be due to increased cardiac cell membrane permeability with repeated ischemia.

TREATMENT

Treatment recommendations from the ACC/AHA guidelines use a Class of Recommendation (COR) system, which estimates the size of the treatment effect, balancing efficacy and safety. Each recommendation is also based on a Level of Evidence (LOE), which describes the quality, quantity, and consistency of supporting data. **Table 32-4** describes the ACC/AHA recommendations and the levels of evidence.[1]

TABLE 32-4 The American College of Cardiology and American Heart Association Evidence Grading System[1]

Recommendation Class	Level of Evidence
I. Conditions for which there is evidence or general agreement that a given procedure or treatment is useful and effective	A. Data derived from multiple randomized clinical trials with large numbers of patients
II. Conditions for which there is conflicting evidence or a divergence of opinion that the usefulness/efficacy of a given procedure or treatment is useful and effective a. The weight of evidence/opinion is in favor or usefulness/efficacy b. Usefulness/efficacy is less well established by evidence/opinion	B. Data derived from a limited number of randomized trials with small numbers of patients, careful analyses of nonrandomized studies, or observational registries
III. Conditions for which there is evidence or general agreement that a given procedure or treatment is not useful/effective and in some cases may be harmful	C. Expert consensus was the primary basis for the recommendation

The treatment of patients with SIHD typically involves two complementary strategies.[1] See **Figure 32-2**. The first strategy is directed toward slowing the

progression of atherosclerosis and preventing complications such as MI, HF, stroke, and death (either sudden cardiac death or progression of underlying CVD). This strategy focuses on risk-factor modification and providing vasculoprotection therapies. See **Table 32-5**. While these therapies have demonstrated the ability to reduce mortality, and therefore, the quantity of life, they have minimal impact on improving symptoms and the functional limitations caused by angina, or the quality of life. The second strategy is focused on reducing the number of ischemic episodes as well as increasing the amount of exertion or exercise a patient can accomplish before chest pain occurs. See **Table 32-6**. Therapies used in this approach rarely have demonstrated a survival benefit but improve the quality of life through a reduction in symptoms.

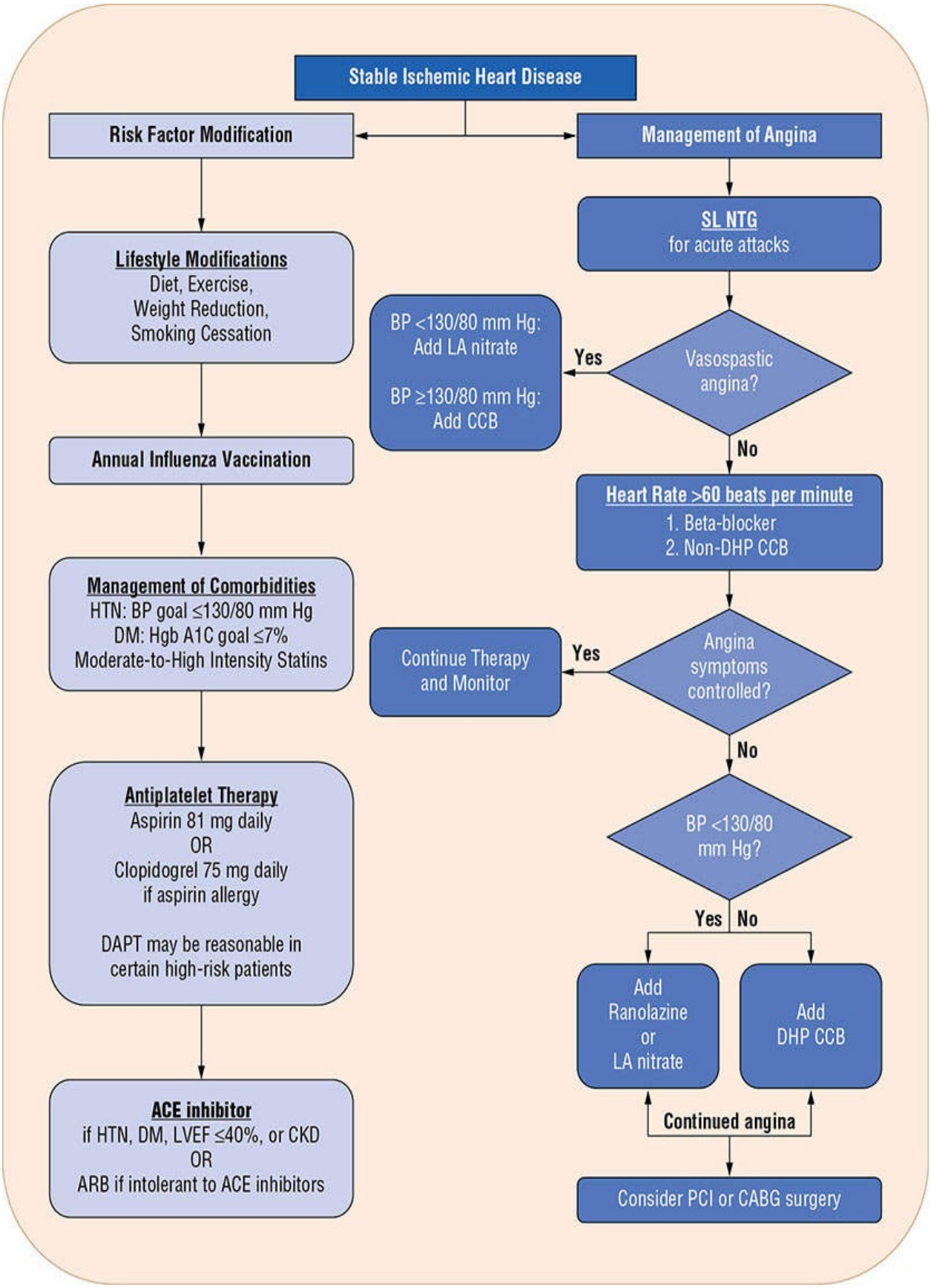

Stable Ischemic Heart Disease
Risk Factor Modification
Management of Angina
Lifestyle Modifications
Diet, Exercise,
Weight Reduction,
Smoking Cessation
SL NTG
for acute attacks
BP <130/80 mm Hg:
Add LA nitrate
BP ≥130/80 mm Hg:
Add CCB
Yes
Vasospastic angina?
No
Annual Influenza Vaccination
Heart Rate >60 beats per minute
1. Beta-blocker
2. Non-DHP CCB
Management of Comorbidities
HTN: BP goal ≤130/80 mm Hg
DM: Hgb A1C goal ≤7%
Moderate-to-High Intensity Statins
Continue Therapy and Monitor
Yes
Angina symptoms controlled?
No
Antiplatelet Therapy
Aspirin 81 mg daily
OR
Clopidogrel 75 mg daily
if aspirin allergy
DAPT may be reasonable in certain high-risk patients
BP <130/80 mm Hg?
Yes
No
Add Ranolazine or LA nitrate
Add DHP CCB
Continued angina
ACE inhibitor
if HTN, DM, LVEF ≤40%, or CKD
OR
ARB if intolerant to ACE inhibitors
Consider PCI or CABG surgery

FIGURE 32-2 Treatment algorithm for stable ischemic heart disease (guideline-directed medical therapy). The Hgb A1c goal of ≤7% is equivalent to 53 mmol/mol Hgb. (ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; DHP, dihydropyridine; DM, diabetes mellitus; HTN, hypertension; LA, long-acting; LVEF, left ventricular ejection fraction; SL NTG, sublingual nitroglycerin).

TABLE 32-5 Risk Factor Modification: ACC/AHA Recommendations[1,48,49,51,62]

Lipid Management

Class I

1. Lifestyle modifications, including daily physical activity and weight management, are strongly recommended for all patients with SIHD.
2. Dietary therapy for all patients should include reduced intake of saturated fats (to <7% of total calories), *trans* fatty acids (to <1% of total calories), and cholesterol (to <200 mg/day).
3. In addition to therapeutic lifestyle changes, a high-intensity statin should be prescribed, in the absence of contraindications or documented adverse effects.
4. In patients who are >75 years of age or cannot tolerate high-intensity statin therapy, moderate-intensity statins should be used if tolerated.
5. For patients who cannot tolerate high-intensity statins or do not attain a 50% decrease in LDL-C (or LDL remains >70-100 mg/dL [1.81-2.59 mmol/L]), the addition of ezetimibe first and PCSK-9 inhibitors second is reasonable.
6. Referral to a lipid specialist should be considered.

Blood Pressure Management

Class I

1. All patients should be counseled about the need for lifestyle modification: weight control; increased physical activity; alcohol moderation; sodium reduction; and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products.
2. In patients with SIHD with BP 130/80 mm Hg or higher, antihypertensive drug therapy should be instituted in addition to or after a trial of lifestyle modifications.
3. The specific medications used for treatment of HTN in SIHD patients should be based on compelling indications (eg, prior MI, angina, HFrEF) and may include beta blockers, ACE inhibitors, or ARBs with addition of other drugs, such as thiazide diuretics, dihydropyridine calcium channel blockers, or aldosterone antagonists, if needed to achieve a goal of BP less than 130/80 mm Hg.
4. For patients with angina and persistent uncontrolled HTN, it is recommended to add dihydropyridine CCBs to beta blockers.

Class IIa

1. For patients who have had an ACS, it is reasonable to continue beta blockers long-term if needed for treatment of HTN.

Diabetes Management

Class IIa

1. For selected individual patients, such as those with a short duration of diabetes mellitus and a long life expectancy, a goal A1c of 7% (53 mmol/mol Hgb) or less is reasonable.
2. A goal A1c <8% (64 mmol/mol Hgb) is reasonable for certain patients according to age, history of hypoglycemia, the presence of microvascular or macrovascular complications, or presence of coexisting medical conditions.

Class IIb

1. Initiation of pharmacotherapy interventions to achieve target A1c might be reasonable.

Influenza Vaccination

Class I

1. Annual influenza vaccinations are recommended for patients with SIHD.

Physical Activity

Class I

1. For all patients, the clinician should encourage 30-60 minutes of moderate-intensity aerobic activity, such as brisk walking, at least 5 days and preferably 7 days per week, supplemented by an increase in daily lifestyle activities (eg, walking breaks at work, gardening, household work) to improve cardiorespiratory fitness and move patients out of the least-fit, least-active, high-risk cohort (bottom 20%).
2. For all patients, risk assessment with a physical activity history and/or an exercise test is recommended to guide prognosis and prescription.
3. Medically supervised programs (cardiac rehabilitation) and physician-directed, home-based programs are recommended for at-risk patients at first diagnosis.

Class IIa

1. It is reasonable for the clinician to recommend complementary resistance training at least 2 days per week.

Weight Management

Class I

1. BMI and/or waist circumference should be assessed at every visit, and the clinician should consistently encourage weight maintenance or reduction through an appropriate balance of lifestyle, physical activity, structured exercise, caloric intake, and formal behavioral programs when indicated to maintain or achieve a BMI between 18.5 and 24.9 kg/m^2 and a waist circumference less than 102 cm (40 in.) in men and less than 88 cm (35 in.) in women (less for certain racial groups).
2. The initial goal of weight loss therapy should be to reduce body weight by approximately 5%-10% from baseline. With success, further weight loss can be attempted if indicated.

Smoking Cessation Counseling

Class I

1. Smoking cessation and avoidance of exposure to environmental tobacco smoke at work and home should be encouraged for all patients with SIHD. Follow-up, referral to special programs, and pharmacotherapy are recommended along with a systematic strategy for smoking cessation (Ask, Advise, Assess, Assist, Arrange, Avoid).

Management of Psychological Factors

Class IIa

1. It is reasonable to consider screening of SIHD patients for depression and to refer or treat when indicated.

Class IIb

1. Treatment of depression has not been shown to improve cardiovascular disease outcomes but might be reasonable for its other clinical benefits.

Alcohol Consumption

Class IIb

1. In patients with SIHD who use alcohol, it might be reasonable for nonpregnant women to have one drink (4 ounces [~120 mL] of wine, 12 ounces [355 mL] of beer, or 1 ounce [30 mL] of spirits) a day and for men to have one or two drinks per day, unless alcohol is contraindicated (such as in patients with a history of alcohol abuse or dependence or with liver disease).

Avoiding Exposure to Air Pollution

Class IIa

1. It is reasonable for patients with SIHD to avoid exposure to increased air pollution to reduce the risk of cardiovascular events.

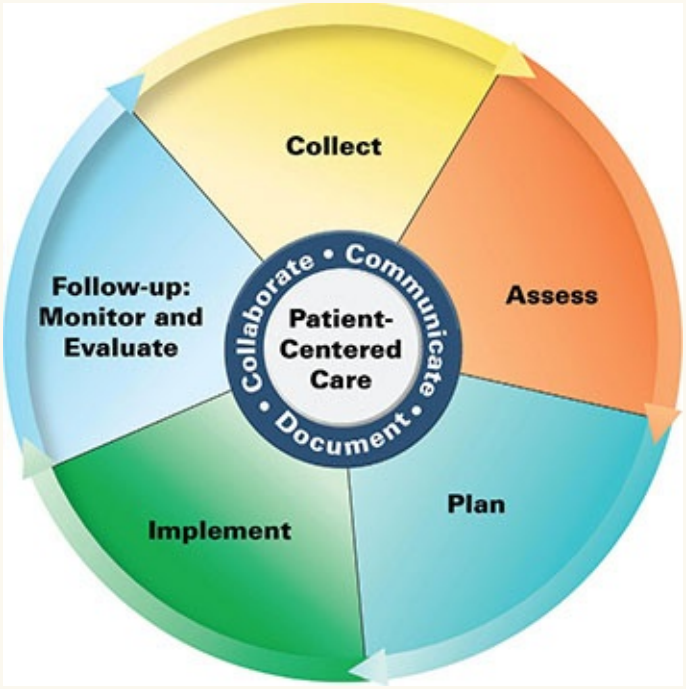
TABLE 32-6 ACC/AHA Class of Recommendations for Pharmacotherapy to Relieve Symptoms[1]

Class I

1. β-blockers should be prescribed as initial therapy for relief of symptoms in patients with SIHD (LOE B).
2. Calcium channel blockers or long-acting nitrates should be prescribed for relief of symptoms when β-blockers are contraindicated or cause unacceptable side effects in patients with SIHD (LOE B).
3. Calcium channel blockers or long-acting nitrates, in combination with β-blockers, should be prescribed for relief of symptoms when initial treatment with β-blockers is unsuccessful in patients with SIHD (LOE B).
4. Sublingual nitroglycerin or nitroglycerin spray is recommended for immediate relief of angina in patients with SIHD (LOE B).

Class IIa

1. Treatment with a long-acting nondihydropyridine calcium channel blocker (verapamil or diltiazem) instead of a β-blocker as initial therapy for relief of symptoms is reasonable in patients with SIHD (LOE B).
2. Ranolazine can be useful when prescribed as a substitute for β-blockers for the relief of symptoms in patients with SIHD if initial treatment with β-blockers leads to unacceptable side effects or is ineffective or if initial treatment with β-blockers is contraindicated (LOE B).
3. Ranolazine in combination with β-blockers can be useful when prescribed for relief of symptoms when initial treatment with β-blockers is not successful in patients with SIHD (LOE A).



Patient Care Process for Acute Coronary Syndrome

Collect

- Patient characteristics (eg, age, sex, pregnant)
- Description of chest discomfort and/or related symptoms (eg, quality, location, severity, radiation, precipitating factors, palliative measures, time of onset, duration of symptoms)
- Patient medical (personal and family) and social histories (eg, tobacco/ethanol, drugs of abuse [eg, cocaine])
- Current medications with particular attention to phosphodiesterase-5 inhibitors, over-the-counter medications (eg, aspirin-containing medications), and herbals/dietary supplement use
- History of allergy or intolerance to medications
- Objective data
  - Blood pressure, heart rate, respiratory rate, height, weight, O_2-saturation, physical exam
  - Labs: cardiac troponin (cTn), creatinine, potassium, hemoglobin, platelets, lipid profile

- Diagnostic tests: 12-lead electrocardiogram (ECG); coronary angiogram and stress testing as necessary

Assess

- Description of chest discomfort to determine differential diagnosis and classification of ACS
- Presence of provoking factors (eg, exertion, mental/emotional stress, tachyarrhythmia, high adrenergic state including the use of stimulant medications, exposure to cold)
- Presence/control of risk factors for coronary artery disease (CAD) (eg, hypertension, dyslipidemia, diabetes, smoking, obesity, family history of premature CAD)
- Presence of ACS-related complications (eg, heart failure [HF], cardiogenic shock, arrhythmias, heart block, stroke)
- Previous/recent revascularization procedures (eg, percutaneous coronary intervention [PCI] with/without stenting, coronary artery bypass graft surgery [CABG])
- Presence of ST-segment elevation or equivalent on 12-lead ECG
- Risk for major adverse cardiac events (MACE) (eg, perform risk stratification [see Table 33-1])
- Contraindications or intolerance to medications used to treat/prevent angina symptoms and MACE
- Barriers that may impair adherence to the care plan

Plan*

- Initiate antithrombotic therapy to treat and prevent intracoronary thrombosis as well as drug therapy to alleviate angina symptoms and prevent MACE including specific drug(s), dose, route, frequency, and duration (see Figs. 33-1 and 33-2; Tables 33-2, 33-3, 33-4, 33-5, 33-7, and 33-9).
- Monitoring parameters: efficacy (eg, resolution of signs and symptoms of angina and ACS-related complications) and adverse effects; frequency and timing of follow-up
- Patient education: purpose of treatment, lifestyle modifications, planned procedures, drug-specific information (eg, indication, dose, route, frequency, adverse effects)

- Self-monitoring for recurrent angina symptoms, signs and symptoms of ACS-related complications, adverse effects, when to seek emergency medical attention
- Address barriers to adherence to medications and lifestyle modification
- Referrals to other providers (eg, primary care provider, endocrinologist, dietician, smoking cessation)

Implement*

- Provide patient education regarding all elements of treatment plan as described above.
- Use motivational interviewing and coaching strategies to maximize adherence.
- Schedule follow-up (eg, usually within 1-2 weeks but no later than 6 weeks after discharge).

Follow-up: Monitor and Evaluate

- Presence of angina symptoms, exercise tolerance, presence/control of CAD risk factors, presence/control of ACS-related complications
- Appropriate use and doses of evidence-based pharmacotherapy for ACS
- Presence of adverse effects and drug–drug interactions
- Patient adherence to treatment plan using multiple sources of information

* *Collaborate with patient, caregivers, and other healthcare professionals.*

Desired Outcomes

4 In addition to reducing the risk of CV events and mortality, the ACC/AHA SIHD guidelines state that a goal of therapy should be the complete, or nearly complete, elimination of chest pain and return to normal activities with a functional capacity of CCS class I angina.[1]

Pharmacologic Therapy

Providing guideline-directed medical therapy (GDMT), also referred to as optimal medical therapy, reduces the risk of mortality in patients with SIHD.[1] In the absence of proximal CAD, multivessel CAD, or acute ischemia, GDMT

reduces the rate of death and MI similar to revascularization therapy for most patients with SIHD. Most of the evidence-based GDMT target risk-factor modification (Table 32-5), but also include aspirin and angiotensin-converting enzyme (ACE) inhibition.

Antiplatelet Therapy

5 Aspirin produces an antiplatelet effect by irreversibly blocking cyclooxygenase-1 (COX-1) activity (~95%) for the life of the platelet, thereby inhibiting thromboxane A_2 production. The reduction in thromboxane A_2 leads to reduced platelet activation and aggregation. Aspirin doses as small as 30 mg daily effectively inhibit COX-1. Aspirin doses above 75 to 100 mg provide little additional antiplatelet activity.[22] Aspirin may also provide benefits through some non-platelet mediated effects. Higher doses of aspirin (≥325 mg daily) significantly impair endothelial secretion of prostacyclin, which is a natural vasodilator. Low dose aspirin does not have this deleterious effect. Although aspirin may inhibit prostacyclin secretion, the effects on the endothelium are reversible, unlike its effect on platelets.[23] After unbound aspirin has been removed from the circulation (half-life is about 30 minutes), prostacyclin secretion and its vasodilation effects are restored. Aspirin may also attenuate the synthesis of cytokines such as interleukin-2, interleukin-6, and interferon in leukocytes as well as prevent leukocyte rolling and macrophage-induced endothelial activation.[23] The extent to which these pharmacologic properties contribute to the clinical benefits from aspirin is unknown.

Evidence supporting the effectiveness of aspirin in patients with SIHD first came from a subgroup analysis of the Physicians Health Study.[24] The trial was a double-blind evaluation of the efficacy of aspirin (325 mg every other day) compared to placebo in the primary prevention of MI, stroke, or CV death. Of the 22,071 patients enrolled in the trial, only 333 had a history of SIHD. After the five-year follow-up period, the patients with SIHD who took aspirin had an 87% reduction in first MI.[24] This benefit came with a significant increase in hemorrhagic stroke, although none of the strokes were fatal.

The beneficial effects of aspirin were confirmed in the more robust SAPAT (Swedish Angina Pectoris Aspirin Trial).[24] The SAPAT trial randomized 2,035 patients with controlled angina on sotalol to 75 mg of aspirin daily or matching placebo. At the end of the 50-month follow-up period, patients receiving aspirin had a 34% reduction in first MI or sudden death. There was no difference in major bleeding or stroke between the groups.

Some patients are nonresponsive to the antiplatelet effects of aspirin, and therefore, do not receive a clinical benefit. In patients with CAD, the risk of recurrent CV events was more than threefold higher in patients with aspirin non-responsiveness.[25] The rate of aspirin non-responsiveness was estimated to be 24% in one meta-analysis, but the range reported in the included studies was wide (0%-57%).[26] In studies that used light transmission aggregotomy induced with arachidonic acid (the gold standard test) or measured serum thromboxane B_2, the rate of aspirin non-responsiveness is only 6%.[26] These results are similar to the findings of the ASPECT (Aspirin-Induced Platelet Effects) trial, in which aspirin non-responsiveness defined by COX-1-nonspecific methods was 27%, compared to only 6% when COX-1-specific methods were used.[27] The ASPECT investigators also reported no difference in aspirin non-responsiveness between patients receiving 81 mg, 162 mg, or 325 mg daily.[27] A lack of dose-response is consistent with the findings of the Antithrombotic Trialists' Collaboration meta-analysis which found a similar reduction in vascular events regardless if patients were receiving low dose (75-150 mg daily), moderate dose (160-325 mg daily), or high dose (500-1500 mg daily) aspirin.[22]

Aspirin non-responsiveness may occur because of changes to the COX-1 enzyme, such as changes to the enzyme structure, or temporary blockade of the active site on the enzyme. Of particular concern is the potential for non-steroidal anti-inflammatory drug (NSAID) therapy to block the COX-1 enzyme. Naproxen and ibuprofen have shown to interfere with aspirin's antiplatelet effect when coadministered by competing for the site of action.[23] The timing of coadministration appears to be an important factor. The effect of aspirin on platelet aggregation is impaired when ibuprofen is given 2 hours before aspirin, but when aspirin is given first, antiplatelet activity is retained.

While aspirin non-responsiveness does exist, the incidence is probably not as high as once believed. Although patients with aspirin non-responsiveness are more likely to have ischemic events, routinely testing patients is not recommended. Given that increasing the dose of aspirin does not impact responsiveness or improve clinical outcomes, the only effective strategy would be to change to or add an alternative antiplatelet agent.

For patients unable to take aspirin due to allergy or intolerance, clopidogrel represents a suitable alternative antiplatelet agent to prevent MI and death in patients with CAD.[1] While clopidogrel significantly reduced the incidence of stroke, MI, or vascular death in patients with ASCVD compared to aspirin in the CAPRIE (The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial, the absolute difference between the two strategies was small (0.5%;

number needed to treat = 200).[23] Given the small magnitude of benefit and potential for non-responsiveness to clopidogrel, it remains a second line choice in patients with CAD. When used in patients with SIHD, clopidogrel should be given 75 mg per day.

Dual antiplatelet therapy (DAPT) with aspirin plus a $P2Y_{12}$ inhibitor, such as clopidogrel, has a clear benefit in patients after a PCI with coronary stent placement and following treatment for ACS. The role of DAPT in patients with SIHD who have not received PCI with stent placement or experienced a recent ACS event is less clear. In the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial, the combination of aspirin plus clopidogrel for 28 months did not reduce the risk of death, MI, stroke, or coronary revascularization when compared to aspirin alone but increased the risk of moderate bleeding.[28] However, in those patients with established vascular disease at study entry receiving aspirin plus clopidogrel, there was a significant reduction in the risk of death, MI and stroke compared to aspirin alone (7.3% vs 8.8%).[29] In patients with a history of MI at least 1 year prior, the combination of ticagrelor 60 mg twice daily plus aspirin reduced the risk of cardiac events compared to aspirin alone but more than doubled the risk of major bleeding complications.[30]

Patient responsiveness to clopidogrel is highly variable and the antiplatelet activity follows a bell-shaped curve.[31] There are several tests that have been used to evaluate clopidogrel's antiplatelet activity and there are different definitions of non-responsiveness. Thus, estimates of non-responsiveness to clopidogrel range from 5% to 44%.[32,33] Several trials have correlated clopidogrel non-responsiveness with poor clinical outcomes.

It is unclear what to do if a patient is found to have a lack of appropriate response to clopidogrel. The most common cause of non-responsiveness is poor adherence. Even a small number of missed doses will result in an inadequate response to clopidogrel. Data from the PREMIER (Prospective Registry Evaluating Myocardial Infarction: Events and Recovery) registry provides evidence that poor adherence is associated with increased ischemic events, as well as important insight into patient predictors of poor adherence.[34]

Conversion of clopidogrel to its active compound is a two-step process. While numerous cytochrome P450 (CYP) enzymes may play a role, the CYP2C19 enzyme seems to be the major contributor in both steps. This has led some to suggest a role for CYP2C19 genotype testing to identify potential non-responders to clopidogrel therapy.[35] Genetic polymorphisms to CYP2C19 may

contribute to a lack of response to clopidogrel therapy, but do not explain a lack of response in most patients. CYP2C19 polymorphisms only explain 12%-15% of the variability in clopidogrel response.[36,37] Many patients with “wild-type” CYP2C19 still do not achieve an adequate antiplatelet response to clopidogrel. Genetic testing is not recommended to identify poor responders to clopidogrel therapy.

A lack of adequate response to clopidogrel may also be due to drug-drug interactions involving CYP2C19. All proton pump inhibitors are metabolized by CYP2C19. These are the most widely prescribed medications worldwide and a number of trials evaluating the impact of proton pump inhibitors on clopidogrel activity have been conducted. Both pharmacodynamic and observational cohort trials have suggested that patients receiving a proton pump inhibitor, most often omeprazole, concurrently with clopidogrel have reduced antiplatelet activity and more ischemic events.[38,39] However, the only prospective, randomized clinical trial conducted to date failed to find a change in clinical event rates in patients given clopidogrel plus omeprazole.[40]

Recommendations from the ACC/AHA for the use of antiplatelet agents in the management of SIHD include a Class I recommendation for the use of aspirin 75 to 162 mg daily.[1] Aspirin should be continued indefinitely in the absence of contraindications (LOE A). Clopidogrel is considered an appropriate alternative when aspirin is contraindicated (LOE B). The guidelines state that treatment with aspirin (75-162 mg daily) and clopidogrel 75 mg daily might be reasonable in certain high-risk patients with SIHD (Class IIb, LOE B recommendation).

Angiotensin-Converting Enzyme (ACE) Inhibitors

6 In the setting of ASCVD, ACE inhibitors stabilize coronary plaque, provide restoration or improvement in endothelial function, inhibit vascular smooth muscle cell growth, decrease macrophage migration, and possibly prevent oxidative stress. They may also possess some antithrombotic properties by inhibiting platelet aggregation and augmenting the endogenous fibrinolytic system. However, ACE inhibitors have not been shown to improve symptomatic ischemia or chest pain episodes.[24]

The role of ACE inhibitors in patients at high risk for CV events was evaluated in the HOPE (Heart Outcomes Prevention Evaluation) trial.[41] The HOPE trial investigators randomized patients with normal LV function and either ASCVD (history of CAD, stroke, peripheral arterial disease) or its

equivalent (eg, DM with at least one additional risk factor) to placebo or ramipril 10 mg daily. Approximately 80% of the patients had a history of CAD and 55% had a history of SIHD. After the 5-year follow-up period, patients who received ramipril were significantly less likely to experience one of the primary endpoints (CV death, MI, or stroke).[41] These impressive benefits were seen despite a minimal reduction in BP with the use of ramipril. Benefits were consistent across all groups of patients enrolled, regardless of the location of ASCVD.

Subsequent trials have produced conflicting results. In the EUROPA (European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease) trial, perindopril 8 mg daily significantly reduced the incidence of CV death, MI, or cardiac arrest compared to placebo in patients with SIHD.[42] In contrast, the addition of trandolapril 4 mg daily to standard therapy in patients with documented CAD did not significantly reduce the incidence of CV death, MI, or coronary revascularization in the PEACE (Prevention of Events with Angiotensin Converting Enzyme Inhibitors) trial.[43] A meta-analysis of 7 trials with 33,960 patients demonstrated a 14% reduction in mortality in patients with CAD treated with an ACE inhibitor.[44] Based on the well-established benefits, it is appropriate to use ACE inhibitors in patients with SIHD who have HTN, DM, HFrEF, or following an MI.[1]

Trials have evaluated the role of angiotensin receptor blockers (ARB) to determine if they provide a similar benefit as ACE inhibitors in the setting of CAD. In ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial), patients with pre-existing CV disease or DM with end-organ damage treated with either the ACE inhibitor ramipril 10 mg daily or the ARB telmisartan 80 mg daily appeared to have a similar benefit.[45] However, there was no added benefit from combining the two agents. There were significantly more adverse effects of hypotension, syncope, and renal dysfunction in patients treated with combination therapy. In a second trial, telmisartan failed to demonstrate a CV benefit over placebo in patients who were intolerant to ACE inhibitors.[46] Based on these conflicting data, an ARB may be considered if the patient cannot tolerate ACE inhibitor therapy, and combination therapy should be avoided.

Recommendations from the ACC/AHA include a Class I recommendation to use ACE inhibitors in all patients with SIHD who also have HTN, DM, HFrEF, or chronic kidney disease, unless contraindicated (LOE A).[1] ARBs are recommended for the same patient populations if they are intolerant to ACE inhibitors (LOE A). It is a Class IIa recommendation to use ACE inhibitors in patients with both SIHD and other vascular diseases (LOE B), and ARBs in

these patients if intolerant to ACE inhibitors (LOE B).

Lipid Management

7 Multiple studies have demonstrated a continuous increase in coronary events with increasing low-density lipoprotein cholesterol (LDL-C) in men and women with and without SIHD. Statin therapy significantly lowers LDL-C and reduces CV event rates. The Cholesterol Treatment Trialist Collaborators found a 10% reduction in all-cause mortality and 20% reduction in cardiac mortality for every 40 mg/dL (1.03 mmol/L) reduction in LDL-C.[47] Statin therapy also reduces the risk of MI, stroke, and need for coronary revascularization. Higher dose and high potency statin regimens are more effective than lower dose, low-potency regimens.[47]

Current guidelines recommend that all patients with known ASCVD, such as SIHD, should receive high-intensity statin therapy to achieve a 50% or more reduction in LDL-C.[48] Patients over the age of 75 years, or those who cannot tolerate high-intensity statin therapy, should receive moderate-intensity statin therapy to achieve a 30% to 50% reduction in LDL-C. In patients with clinical ASCVD who do not achieve a 50% reduction in LDL-C or who have an LDL ≥100 mg/dL (2.59 mmol/L) on high-intensity statin therapy, the additional non-statin therapies such as ezetimibe, bile-acid sequestrates, or PCSK9-inhibitors may be considered.[49] In patients with clinical ASCVD with DM, a recent ASCVD event, CKD, or poorly controlled risk factors, targeting an LDL-C less than 70 mg/dL (1.81 mmol/L) or non–HDL-C less than 100 mg/dL (2.59 mmol/L) may be considered.[49]

High-intensity statin options include atorvastatin 40 or 80 mg daily or rosuvastatin 20 or 40 mg daily. It should be noted that atorvastatin 80 mg is considered the preferred dose. The 40 mg dose of atorvastatin was only used in one trial in patients who could not tolerate the 80 mg dose.[50] Also, rosuvastatin 20 mg daily is the preferred regimen based on the trial evidence, with the 40 mg daily dose being recommended because it is also an approved dose. Moderate-intensity statin regimens include once-daily atorvastatin 10 to 20 mg, rosuvastatin 5 to 10 mg, simvastatin 20 to 40 mg, pravastatin 40 to 80 mg, lovastatin 40 mg, pitavastatin 2 to 4 mg, fluvastatin extended release 80 mg, or twice daily fluvastatin 40 mg.[48]

Regular physical activity, dietary changes, and weight management should also be implemented (Table 32-5). Dietary approaches to lowering LDL-C include replacing saturated and *trans* fatty acids with dietary carbohydrates or

unsaturated fatty acids and reducing dietary cholesterol. A diet low in saturated fat and cholesterol typically lowers LDL-C by 10% to 15%. The addition of plant stanols/sterols (2g/d) can lower LDL-C by 5% to 15%. Viscous fiber (>10 g/d) reduces LDL-C by 3% to 5%. A 10 lb (4.5 kg) weight loss reduces LDL-C by 5% to 8%. Regular physical exercise improves cardiac fitness and facilitates weight loss but does not reliably lower LDL-C.

Blood Pressure Management

A number of observational trials have demonstrated a continuous relationship between BP and risk of CV events. The risk of vascular death increases linearly over the BP range of 115/75 mm Hg to 185/115 mm Hg. The risk doubles for every 20 mm Hg increase in systolic BP or 10 mm Hg increase in diastolic BP.[51] Clinical trials have evaluated when to initiate therapy and attempted to define the target BP goal for patients with HTN. However, the specific BP target for patients with and without SIHD has been debated. Clinical trials and meta-analyses support the current guidelines which recommend initiating pharmacotherapy in patients with SIHD with a BP of 130/80 mm Hg or higher and treating to a BP goal of less than 130/80 mm Hg.[51–53]

Reduction of BP should consist of lifestyle modifications as well as pharmacotherapy (Table 32-5). This includes a diet rich in fruits, vegetables, and low-fat dairy products, regular physical exercise, a reduction in dietary sodium, and limited alcohol consumption. Lifestyle modifications can also contribute to weight loss. A 10 kg weight loss can reduce systolic BP by 5 to 20 mm Hg.

Drugs used to treat HTN in patients with SIHD commonly include agents that can be used to treat the symptoms of the disease. β-blockers are often used to control angina symptoms and they also lower BP. Patients may also be on ACE inhibitors to reduce CV risk. Therefore, most patients with SIHD will receive these two classes of agents for the treatment of HTN. If additional therapy is needed, dihydropyridine (DHP) calcium channel blocker (CCBs) are often added because they treat both HTN and reduce angina symptoms. If the patient's angina symptoms are well controlled, thiazide diuretics may be considered as add-on therapy for HTN. They are considered a first-line treatment in most populations and do not appear to be detrimental when used by patients with SIHD.[51]

Smoking Cessation

The relationship between tobacco use and increased risk of CVD is well

documented.[54] Cigarette smoking promotes and accelerates ASCVD through a number of mechanisms including increased platelet adhesion, elevated fibrinogen concentrations, endothelial dysfunction, altered serum lipids, and vasoconstriction.[55] Smoking is perhaps the most important cause of preventable CVD and death.[2,54] Compared to those who never smoked, smokers lose approximately 10 years of life expectancy and early cessation is associated with an approximate 90% reduction in mortality and improved quality of life.[56] Therefore, abstinence and smoking cessation are key components of lifestyle modifications for patients with SIHD.

Advice from a clinician recommending and discussing the importance of smoking cessation significantly increases the likelihood that a patient will quit. Clinicians should approach smoking cessation by using the 6 A's framework:[1]

1. Ask each patient about tobacco use at every visit
2. Advise each smoker to quit
3. Assess each smoker's willingness to make a quit attempt
4. Assist each smoker in making a quit attempt by offering medication and referral for counseling
5. Arrange for follow-up
6. Avoid exposure to environmental tobacco smoke

Several pharmacologic agents are available over the counter or with a prescription and are all more effective than placebo.[57] Nicotine replacement therapy is available in a number of dosage forms without a prescription to fit the patient's lifestyle including patches, tablets, gum, lozenges, and nasal spray. Sustained-release bupropion and the partial agonist of the $\alpha_4\beta_2$ nicotinic receptor, varenicline, are also first-line medications to treat tobacco dependence in adults. Cardiovascular safety of all three pharmacotherapies has been demonstrated in the Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES).[58] There was no evidence of serious CVD or CV adverse events in a general population of 8,058 patients receiving smoking cessation medications. Nonpharmacologic methods for smoking cessation are just as important as pharmacotherapy. Self-help programs, telephone counseling, behavioral therapy, and exercise all can be used to help patients quit smoking.

Diabetes Management

8 DM is a strong risk factor for the development of CV disease. Patients with

type 1 DM have a 10-fold increased risk of having a CV event and patients with type 2 DM have a two- to sixfold risk of CV death compared to those without DM. In fact, 80% of all deaths in patients with DM are associated with ASCVD.[2]

Like HTN, the glycemic target for patients with DM, including those with SIHD, is the subject of considerable debate. Studies have found that achieving an A1c of less than 7% (53 mmol/mol Hgb) reduces microvascular complications from DM such as retinopathy, nephropathy, and neuropathy.[59] While subgroup analyses of larger trials have suggested lower rates of ischemic events in patients randomized to intensive glycemic control (A1c less than 7% [53 mmol/mol Hgb]), macrovascular events were not significantly reduced in trials comparing intensive to more lenient glycemic control in high-risk patients with DM, including those with pre-existing CVD.[59] In these trials, patients in the intensive glycemic control groups had higher rates of adverse events including severe hypoglycemia, CVD death, and overall mortality.[59] In patients with SIHD, current AHA/ACC recommendations target an A1c of less than 7% (53 mmol/mol Hgb) for patients with DM of short duration and a long life expectancy (Class IIa, LOE B) but a more lenient goal (A1c <8% [64 mmol/mol Hgb]) for frail or high-risk patients (Class IIa, LOE C; Table 32-5).[1]

Metformin is the drug of first choice for the treatment of DM type 2, including patients with SIHD. While sulfonylureas provide a similar reduction in A1c, their potential to induce hypoglycemia and weight gain make metformin a more attractive option. Although debate remains regarding the effect of metformin and sulfonylureas on CV events, a recent meta-analysis did not find a significant association between the use of either therapy and CV outcomes.[59] In recent years, several clinical trials have demonstrated that newer therapies for the treatment of DM type 2 significantly reduce the risk of CV events, including all-cause mortality.[60] In a recent meta-analysis, the risk of death was reduced by 20% (hazard ratio [HR] 0.80, 95% credible interval [CrI] 0.71-0.89) in patients treated with sodium-glucose-cotransporter 2 (SGLT-2) inhibitors and by 12% (HR 0.88, 95% CrI 0.81-0.94) in patients treated with glucagon-like peptide 1 (GLP-1) agonists compared to patients in the control groups.[61] Cardiovascular mortality was also lower in patients treated with either SGLT-2 inhibitors or GLP-1 agonists compared to control subjects.[61] The risk of adverse event rates leading to discontinuation was higher with GLP-1 agonists compared to SGLT-2 inhibitors and dipeptidyl peptidase 4 inhibitors.[61] Consequently, updated guidelines for the treatment of DM now recommend using agents proven to reduce CV events (eg, empagliflozin, canagliflozin, liraglutide) as add-on

therapy with metformin in patients with DM type 2 and ASCVD whose blood glucose remain uncontrolled.[62]

Influenza Vaccination

Patients with cardiac disease who develop seasonal influenza are at high risk for complications and more likely to die. Patients with SIHD should receive an annual influenza vaccination to prevent morbidity and mortality.[1]

Pharmacotherapy to Relieve Symptoms Recommendations

β-blockers

9 β-adrenergic blocking agents are commonly used in the management of patients with SIHD and reduce both symptomatic and silent episodes of myocardial ischemia. β-adrenergic blocking agents competitively inhibit the effects of circulating catecholamines on β-adrenoceptors. The predominant adrenergic receptor type in the heart is the β_1-receptor, and competitive blockade minimizes the influence of endogenous catecholamines on the chronotropic and inotropic state of the myocardium. β-blockers also produce a moderate reduction in BP through competitive inhibition of β1-receptors in the kidney, leading to a reduction in renin release. By reducing HR, myocardial contractility, and intramyocardial wall tension through BP reduction, β-blockers impact all major contributing factors to MVO_2.[63] Reductions in heart rate may also improve myocardial oxygen delivery by prolonging diastole filling time and increasing myocardial perfusion.

β_1-selectivity does not improve the efficacy of β-blockers for the treatment of SIHD and all agents appear equally effective. β_1-selective agents would be preferred in patients with chronic obstructive pulmonary disease, peripheral arterial disease, DM, dyslipidemias, and sexual dysfunction, where blockage of the β_2-adrenergic receptor may be problematic. It should be noted that even β_1-selective agents lose their selectivity at higher doses. β-blockers with combined α_1 and β-blockade are also effective in the management of angina. β-blockers with intrinsic sympathomimetic activity cause a slight to moderate activation of the β-receptor, in addition to competing with endogenous catecholamines. Due to this unique pharmacologic property, they do not affect resting HR but do modestly lower HR when catecholamine concentrations are increased during

exercise. While agents with intrinsic sympathomimetic activity may be useful for patients with peripheral arterial disease and dyslipidemia, they are not preferred in patients with CAD. Selection of a β-blocker in patients with SIHD should be guided by the presence of comorbid diseases, preferred dosing frequency, and cost.

Most side effects experienced with the use of β-blockers are an extension of their pharmacologic activity. Patients receiving β-blockers may experience bradycardia, hypotension, heart block, impaired glucose metabolism, and altered serum lipids. β-blockers may alter the lipid profile by increasing triglycerides and decreasing HDL-C. They have no impact on LDL-C. Changes in the lipid profile are greater with non-selective β-blockers but are usually transient. Central nervous system adverse effects such as fatigue, depression, insomnia, and general malaise are usually mild but among the most common reasons for treatment discontinuation. Impotence has been reported in approximately 1% of men receiving β-blockers. Patients with a history of airway disease may suffer from bronchospasm and patients with HFrEF may become fluid overloaded. Patients without these preexisting disease states usually do not suffer from these adverse effects and it is important to note that even patients at risk for adverse effects receive significant benefit from the use of β-blockers. β-blockers are absolutely contraindicated in patients with pre-existing bradycardia, 2nd or 3rd degree atrioventricular block, a history of uncontrolled reactive airway disease (asthma), severe peripheral arterial disease (critical limb ischemia), hypotension, HFrEF with unstable fluid status, and patients with DM who have frequent episodes of hypoglycemia. All patients should receive a β-blocker following an MI unless there is an absolute contraindication. A patient with SIHD who has never had an ACS, especially acute MI, and who has concurrent chronic obstructive pulmonary disease can be treated with an appropriate CCB or a β-blocker.

If β-blocker therapy needs to be discontinued, doses need to be tapered over 2 to 3 weeks to prevent abrupt withdrawal. During β-blocker therapy, β-receptors become up-regulated in the myocardium. With abrupt withdrawal, these new receptors, along with all of the blocked receptors, are now stimulated by endogenous catecholamines. This can produce a significant increase in MVO_2, induce ischemia, and even MI. If for some reason β-blockers cannot be tapered, patients should be instructed to avoid exertion as much as possible and manage angina episodes with SL NTG. Using a non-DHP CCB would be the preferred second-line choice if β-blockers are contraindicated or must be discontinued.

Calcium Channel Blockers

[7] CCBs effectively reduce the frequency and duration of angina episodes in patients with SIHD. All CCBs reduce MVO_2, as well as provide some increase in supply by inducing coronary vasodilation and preventing vasospasm. CCB modulate calcium entry into the myocardium and vascular smooth muscle, as well as other tissues. This leads to a reduction in the cytosolic concentration of calcium responsible for activation of the actin-myosin complex leading to contraction of vascular smooth muscle and myocardium.

Calcium channel blockers should be considered as two separate classes of drugs. While all CCBs inhibit the influx of calcium ions, the location of the inhibition differs based on the chemical structure of the agents. The DHP CCBs, such as nifedipine, amlodipine, isradipine, and felodipine, primarily block calcium receptors in vascular smooth muscle cells, such as arterioles, with minimal effect on the myocardium. In contrast, the phenylalkylamine (verapamil) and benzothiazepine (diltiazem) agents, commonly referred to as non-DHP CCBs, block calcium ion entry mostly in the myocardium, with minimal effect on vascular smooth muscle. Verapamil has the greatest impact on myocardial calcium channels. Diltiazem has an intermediate effect.

All CCBs reduce MVO_2 by reducing wall tension by lowering arterial blood pressure, and to a minor extent, depressing cardiac contractility. Like β-blockers, non-DHP CCBs also reduce HR and contractility through blockade of myocardial calcium channels. The DHP CCBs slightly reduction cardiac contractility and produce either a neutral or increase in HR due to reflex tachycardia from direct arterial dilation. The effect on contractility and reflex tachycardia are not uniform across the class of DHP CCBs. Agents such as nifedipine produce more impairment of LV function than amlodipine and felopidine. Due to their propensity to cause reflex tachycardia, short-acting DHP CCBs should be avoided when treating SIHD, chronic HTN, hypertensive crisis, or during an ACS event. Reflex tachycardia from longer acting DHP CCBs can be prevented with concurrent β-blocker therapy.

Common side effects of CCBs vary between the two classes. Patients taking non-DHP CCBs may experience bradycardia, hypotension, atrioventricular block, and symptoms of LV depression. Non-DHP CCBs should not be used in patients who have contraindications or cannot tolerate β-blockers due to these same effects. Non-DHP CCBs should be avoided in patients with concomitant HFrEF due to their negative inotropic effects but can provide benefit to patients in atrial fibrillation with a rapid ventricular response due to their negative

dromotropic effects. Verapamil has also been reported to cause constipation in up to 8% of patients. Patients taking DHP CCBs may experience reflex tachycardia, hypotension, headache, gingival hyperplasia, and peripheral edema. While most DHP CCBs are contraindicated in patients with HFrEF, amlodipine, and felodipine are considered safe options in patients with HFrEF and concomitant SIHD or HTN.

Calcium channel blockers undergo hepatic oxidative biotransformation via the cytochrome P450 isoenzyme 3A4 and other isoenzymes. Verapamil and diltiazem inhibit clearance of other substrates for the 3A4 isoenzyme such as carbamazepine, cyclosporine, lovastatin, simvastatin, and benzodiazepines. The DHP CCBs do not produce a clinically meaningful interaction with these medications. Verapamil, and to a lesser extent diltiazem, also inhibit P-glycoprotein mediated drug transport. This interaction is partially responsible for increases in serum concentrations of agents such as digoxin and cyclosporine. Verapamil also decreases the clearance of digoxin, requiring close monitoring if these agents are used together. Agents that induce the P450 3A4 isoenzyme can reduce the effectiveness of all CCBs. Potential pharmacodynamic interactions also need to be monitored in patients taking CCBs. Patients receiving verapamil or diltiazem concurrently with other agents that reduce HR and atrioventricular nodal conduction (β-blockers, digoxin, and amiodarone) should be monitored for the development of bradycardia or heart block.

Nitrates

7 Organic nitrates were found to have antianginal properties over one hundred years ago when Murrell first reported in 1879 the ability of a 1% nitroglycerin solution administered orally to relieve and prevent angina attacks. Organic nitrates are prodrugs that require biotransformation into the active compounds. This process leads to denitration of the nitrate and the release of nitric oxide, also known as EDRF. Nitric oxide increases concentrations of cyclic guanosine monophosphate in the vascular endothelium leading to a reduction in cytoplasmic calcium and subsequent vasodilation. Vasodilation occurs predominantly on the venous side of the vascular system thereby reducing preload, myocardial wall tension, and MVO_2. As doses are increased, arterial vasodilation also occurs. Arterial vasodilation can produce reflex tachycardia that can negate some of the anti-angina benefits. Patients on adequate doses of β-blockers will not have reflex tachycardia, making this an effective combination for controlling a patient’s acute and chronic angina symptoms.

Nitrates also vasodilate stenotic vessels as well as the intracoronary

collaterals. Given that blood flow is exponentially related to the degree of stenosis, small increases in vasodilation in these narrowed vessels can produce significant increases in myocardial oxygen supply to ischemic areas of the myocardium. Nitrate-induced coronary vasodilation occurs predominately in epicardial vessels, with minimal effect on the coronary microcirculation. This explains why nitrates do not cause coronary steal similar to other vasodilators like dipyridamole or sodium nitroprusside. In coronary steal, there is vasodilation in coronary vessels without atherosclerotic disease but coronary vessels with disease are not dilated. Therefore, more blood flow is shifted, or "stolen", to non-diseased vessels away from vessels with disease that have reduced blood flow. Nitrates may also have anti-aggregant effects on platelets, but the clinical impact is negligible.

Common side effects from nitrate therapy include headache, flushing, nausea, postural hypotension, and syncope. While the hypotension is usually not severe, patients who are volume depleted may experience paradoxical bradycardia if they attempt to rapidly stand. Headache will usually resolve after about 2 weeks when nitrates are used for chronic therapy. It is important to note that this does not represent tolerance or loss of antianginal effectiveness. Acetaminophen is effective in managing nitrate-induced headache during the initial weeks of therapy. Patients using transdermal nitroglycerin may experience skin erythema and inflammation. Initiating therapy with smaller doses and rotating the application site can mitigate some of the adverse effects of transdermal NTG

8 Several formulations of nitrates are available for acute and chronic use (**Table 32-7**). All patients with CAD should have access to SL NTG tablets or spray for the treatment of acute episodes of angina. Patient education is critical to ensure appropriate SL NTG use (**Table 32-8**). The SL route of administration avoids gastrointestinal absorption and hepatic first-pass metabolism. SL NTG 300 to 400 mcg typically provides relief of angina within 5 minutes of administration. SL NTG can also relieve symptoms even if the patient is chronically taking long-acting nitrates. The side effects of flushing, headache, and postural hypotension can appear rapidly and the patient should be aware of this potential. SL NTG can also be used to prevent acute episodes of angina. When patients want to participate in activities which they know lead to angina, they can take a dose of SL NTG 2 to 5 minutes in advance. This prophylactic dose provides up to 30 minutes of protection and allows patients to participate in activities that they might otherwise be unable. Due to its longer half-life, sublingual isosorbide dinitrate provides protection for up to one hour.

TABLE 32-7 Nitrate Products

Product	Onset (minutes)	Duration	Initial Dose
Nitroglycerin			
IV	1-2	3-5 minutes	5 mcg/min
Sublingual/lingual	1-3	30-60 minutes	0.3-0.4 mg
Oral	40	3-6 hours	2.5-9 mg three times a day
Ointment	20-60	2-8 hours	0.5-1 in.
Patch	40-60	>8 hours	1 patch
Isosorbide dinitrate			
Sublingual/chewable	2-5	1-2 hours	2.5-5 mg three times a day
Oral	20-40	4-6 hours	5-20 mg three times a day
Isosorbide mononitrate			
Immediate-release	30-60	6-8 hours	20 mg twice a day
Extended-release	30-60	12-24 hours	30-60 mg daily

TABLE 32-8 Appropriate Use of Sublingual Nitroglycerin

Education Point	Rationale
Keep in original dark glass container	SL NTG will interact with plastic and can lose potency when exposed to light. This is why it is packaged in a dark glass container.
Do not store in a larger plastic vial with child-resistant safety cap	During an episode of angina, you do not want the patient struggling to figure out how to open the safety cap.
Do not store in the bathroom	SL NTG will degrade in moisture and tablets will lose their integrity and potency.
Keep SL NTG close by at all times; may need multiple vials	SL NTG does not do the patient any good if they do not have it with them at the time of an episode of angina. The patient should consider having one at home, at work, in garage, etc.
The patient should be sitting down and rest while taking tablet	While the SL NTG tablets are small, the dose is not. It is likely the patient will have some flushing, may get a headache, and even become a little light-headed. They need to know this can happen.
Describe how to use a sublingual tablet	The SL NTG is administered under the tongue in order to provide rapid absorption and avoid first-pass metabolism. The patient needs to keep the tablet under the tongue until dissolved. Avoid swallowing the tablet.
Once opened, tablets need to be refilled every 6 months and spray every 3 years	Due to the instability of SL NTG tablets, they are typically only good for 6 months after the bottle is opened.[a] Shelf-life of the spray is longer. Patients need to be advised to refill SL NTG even if all doses have not been taken.
Remove the cotton plug from the bottle	Larger quantity bottles commonly have a cotton plug. During an episode of angina, you do not want the patient to be struggling with trying to get the cotton plug out of the bottle.
May be taken in advance of events known to cause chest pain	SL NTG can be used to prevent episodes of angina if taken before partaking in an exertional event known to precipitate angina/chest discomfort.
Contact 911 if first SL NTG does not relieve angina[b]	Most episodes of angina are relieved within 5-10 minutes of rest and a single SL NTG. If pain persists, the episode may be an acute coronary syndrome, not stable ischemic heart disease. This requires rapid medical attention.

[a]Product specific.

[b]May be patient specific base on their known experience with SL NTG and angina episodes.

SL NTG, sublingual nitroglycerin.

The development of nitrate tolerance must be considered when chronically using long-acting nitrate therapy for SIHD. Several trials have shown that continuous nitrate therapy for more than 24 hours leads to a reduction or loss of the hemodynamic and antianginal effects of nitrates. In a large study in patients receiving 24 hours of transdermal NTG, almost all of the patients lost control of their angina symptoms within 24 hours to 1 week, which cannot be overcome with higher doses.[64]

Nitrate tolerance is not an “all or none” phenomenon. Responsiveness is reduced in some patients while others experience a total loss of efficacy. Despite continued use of nitrates and a loss of antianginal effect, plasma volume remains expanded and some hemodynamic effects are maintained. Chronic administration of nitrates produces a state of oxidative stress leading to dysfunction of mitochondrial aldehyde dehydrogenase, the enzyme responsible for converting nitrates to the active agent NO.[65,66] Consequentially, the dysfunctional enzyme in unable to produce active NO and the angina relieving effect of nitrate agents is reduced or lost.

Why nitrate tolerance develops remains unknown but several pharmacologic approaches have been developed to manage and prevent it. One thought is that tolerance is due to an exhausting of sulfhydryl groups needed to use organic nitrates.[65] Based on this hypothesis, acetylcysteine and ACE inhibitors such as captopril, which supply sulfhydryl groups, have been investigated as a potential strategy for preventing nitrate tolerance. Unfortunately, both of these agents have provided inconsistent results. ACE inhibitors may prevent nitrate tolerance through other mechanisms. The inhibition of angiotensin II production can reduce superoxide anion production, leading to reduced nitrate degradation, as well as a reduction in protein kinase C and endothelin leading to a reduction in vasoconstriction. Unfortunately, none of these approaches have shown to be effective in maintaining the antianginal effects of continuous nitrate therapy.

The preferred management of nitrate tolerance for patients with CAD is to ensure a 10 to 14 hour nitrate-free interval every day. This approach has been shown to maintain antianginal efficacy with the use of chronic nitrates. The rationale for this approach is based on the observation that although nitrate tolerance develops rapidly, it also is reversed rapidly. Unfortunately, this approach does not provide the patient anti-ischemic coverage for a full 24 hours and places the patient at risk for angina episodes. Typically, the nitrate-free interval is provided during the nighttime hours when the patient is sleeping and, in most cases, has lower MVO_2. Several trials have used chronic nitrates with a

daily nitrate-free interval and demonstrated increased exercise time, reduced exercise-induced ischemic events, and reduced need for SL NTG. Despite these benefits, a nitrate-free interval would not provide protection to the 20% to 30% of patients with SIHD that experience nocturnal episodes of angina. Moreover, it is well documented that angina episodes and MI commonly occur in the morning hours, immediately before or after awakening. Patients using chronic nitrate therapy are unlikely to have taken or applied their nitrate therapy for the day during this critical time period. Therefore, nitrates should not be routinely used as monotherapy in patients with SIHD due to the lack of 24-hour coverage, lack of protection against circadian-related ischemic events, and potential for reflex tachycardia. Trials have shown that patients taking intermittent transdermal NTG did not experience rebound ischemia during the nitrate-free interval when β-blockers or diltiazem were concurrently used.

7 There are number of potential nitrate preparations that can be used for chronic long-term prevention of angina episodes. Transdermal patches and isosorbide mononitrate (ISMN) are the most commonly prescribed chronic nitrates. Although isosorbide dinitrate is effective, the three times daily dosing regimen requires patients to take a dose every 4 to 5 hours in order to provide an adequate nitrate-free interval. Two of the ISMN preparations are dosed twice daily. The twice-daily preparations should be dosed 7 hours apart, such as 7 am and 2 pm. It is critical to be specific about the times each dose should be taken so that patients do not take the doses 12 hours apart, thus compromising the nitrate-free interval. One ISMN preparation is dosed once daily. It is an extended-release preparation that provides 12 hours of nitrate exposure. This should be followed by a 12-hour nitrate-free interval. Transdermal NTG patches are typically prescribed as “on in the am and off in the pm.” It is best to provide specific times for application and remove (eg, apply at 8 am and removed at 8 pm). Patients who work evening or night shifts need to have the timing of their nitrate doses adjusted to coincide with when they are active during the day.

Ranolazine

Unlike other agents used for angina, ranolazine does not impact HR, BP, the inotropic state, or coronary blood flow. Animal studies have demonstrated that ranolazine has little affinity for α_1, β_1, and β_2 adrenoreceptors and has minimal calcium channel blocking activity. Ranolazine reduces ischemic episodes by selective inhibition of late sodium current (I_{Na}). Total sodium entry during an action potential is comprised of an early (fast) and late (slow) component. Under

normal conditions, late I_{Na} constitutes only 1% of total I_{Na}. A number of preclinical studies have observed an increase in late I_{Na} in ischemic and failing hearts.[67] It is not fully appreciated if this increase in late I_{Na} is due to an increase in density of the late Na^+ channels or a dysfunction of these channels. The increase in intracellular Na^+ triggers an increase in the influx of Ca^{2+} through the reverse mode of the Na^+/Ca^{2+} exchanger, resulting in intracellular Ca^{2+} overload and eventually myocardial stunning.[67] Therefore, it is not the intracellular Na^+ concentration that produces ischemic damage, but its recognized role in Ca^{2+} accumulation via Na^+/Ca^{2+} exchange.[67] By inhibiting late I_{Na}, ranolazine produces a reduction in intracellular Na^+. The reduction in intracellular Na^+ contributes to a reduction in the magnitude of ischemia-induced Ca^{2+} overload and improves myocardial function as well as myocardial perfusion.[67]

Ranolazine is available as a sustained-release preparation dosed twice daily. With a half-life of approximately 7 hours, ranolazine achieves steady state within 3 days. While 1000 mg twice daily is significant better than 500 mg twice daily in terms of improving exercise tolerance, the difference between the 1000 mg twice daily dose and the 1500 mg twice daily dose is minimal. The incidence of adverse events is greater with the 1500 mg twice daily regimen and, therefore, the 1000 mg twice daily dose is preferred. When ranolazine is added to atenolol (50 mg daily), diltiazem (180 mg daily), or amlodipine (5 mg or 10 mg daily), there was an increase in exercise duration, time to angina, time to 1 mm ST-depression, and a reduction in the number of angina episodes and SL NTG tablets used per week compared to placebo.[68,69] In these trials, the magnitude of increase in exercise duration during testing was associated with a 25% reduction in the weekly number of angina episodes and SL NTG use over placebo and almost a 50% reduction from baseline.[69,70] The improvement in exercise duration demonstrated with ranolazine is consistent with results produced with β-blockers, CCBs, and chronic nitrates.[8,71]

Patients should be initiated on ranolazine 500 mg twice daily, with the dose increased to 1000 mg twice daily within the next 1 to 2 weeks if tolerated. Ranolazine is primarily cleared by CYP3A4 (70%-85%) and CYP2D6 (10%-15%) in the liver and is a substrate for P-glycoprotein, making it prone to a number of clinically important drug interactions. Potent inhibitors of CYP3A4 and P-glycoprotein such as ketoconazole, itraconazole, protease inhibitors, clarithromycin and nefazodone will significantly increase ranolazine drug concentrations. Conversely, potent CYP3A4 inducers such as phenytoin, phenobarbital, carbamazepine, rifampin, rifabutin, rifapentine, and St. John’s

wort significantly decrease ranolazine drug concentrations. Concurrent use of these strong inhibitors and inducers with ranolazine is contraindicated. Moderate inhibitors of CYP3A4, such as diltiazem, verapamil, erythromycin, and fluconazole, can be used with ranolazine, but the dose should not exceed 500 mg twice daily. Due to inhibition of CYP3A4 by ranolazine, doses of simvastatin should not exceed 20 mg daily if coadministered. Ranolazine increases digoxin 1.4- to 1.6-fold at trough and 2-fold at peak plasma concentrations, likely through competition for intestinal and renal P-glycoprotein. Digoxin doses may need to be reduced to avoid toxicity. Agents that are potent inhibitors of P-glycoprotein, such as cyclosporine, may increase ranolazine concentrations and side effects. The dose of ranolazine should be reduced.

Ranolazine and metformin compete for renal clearance through the organic cation transporter 2, which has the potential to increase metformin drug concentrations and increase the risk of lactic acidosis. This interaction is only clinically meaningful when both full dose ranolazine (1,000 mg twice daily) and full dose metformin (1,000 mg twice daily) are used together. In this setting, the metformin dose should be reduced to 850 mg twice daily. Patients on ranolazine 500 mg twice daily do not need to alter their metformin doses. Ranolazine produces reductions in A1c by 0.6% to 0.7% (7 to 8 mmol/mol Hgb).[69,72] Reductions in blood glucose were observed in patients with or without diabetes, without causing hypoglycemia. While ranolazine is not a treatment for DM, clinicians may find this property useful.

The most common adverse effects from ranolazine use are constipation, nausea, dizziness, and headache. At therapeutic doses ranolazine produces a modest prolongation of QTc (15 msec or less). A linear relationship exists between ranolazine plasma concentration and the QTc interval, with a 2.6 msec increase in QTc per 1,000 ng/mL (µg/L). Patients should not receive doses of more than 1,000 mg twice daily and caution should be used in patients receiving concomitant QTc-prolonging agents.

While ranolazine is safe and effective for treating angina episodes, it would only be an option as monotherapy in patient with SIHD who cannot tolerate traditional anti-angina agents due to hemodynamic or other adverse effects. Ranolazine is also recommended as add-on therapy to traditional anti-angina agents. In patients who have achieved HR and BP targets on maximally tolerated doses of traditional agents but continue to have exertional angina symptoms, ranolazine is a reasonable choice because it does not impact these hemodynamic parameters.

Nonpharmacologic Therapy (Revascularization)

Surgical revascularization plays an important role in the treatment of SIHD. The most common revascularization procedures are coronary artery bypass grafting (CABG) surgery or percutaneous coronary intervention (PCI) with or without stent placement. According to the AHA, approximately 480,000 PCI procedures are done in the United States annually with half performed in patients with SIHD.[2] Stents are placed in over 90% of patients undergoing PCI, with drug-eluting stents (DES) accounting for 82% of all stents. Bare metal stent (BMS) are placed less commonly (18%). Approximately 371,000 CABG surgeries are performed annually.[2] Other revascularization options are under development.

9 The primary goal of revascularization is to prolong life and, secondarily, to eliminate or reduce symptoms. Circumstances when revascularization is recommended (Class I) over medical therapy as initial management of SIHD are described in **Table 32-9**.[1] Whereas most of the pharmacologic approaches reduce MVO_2, revascularization increases myocardial oxygen supply in vessels with critical stenosis. This is accomplished by opening the vessel (PCI) or using alternative transplanted vessels to bypass a critical stenosis (CABG). While both of these procedures are highly effective and have advantages in certain groups of patients over pharmacologic approaches, both have limitations.

TABLE 32-9 Revascularization: ACC/AHA Class I Recommendations[1]

Revascularization to Improve Survival

Left Main CAD Revascularization

Class I

1. CABG to improve survival is recommended for patients with significant (≥50% diameter stenosis) left main coronary artery stenosis. (LOE B)

Non-Left Main CAD Revascularization

Class I

1. CABG to improve survival is beneficial in patients with significant (≥70% diameter) stenosis in three major coronary arteries with or without involvement of the proximal LAD artery or in the proximal LAD artery plus one other major coronary artery. (LOE B)
2. CABG or PCI to improve survival is beneficial in survivors of sudden cardiac death with presumed ischemia-mediated ventricular tachycardia caused by significant (≥70% diameter) stenosis in a major coronary artery. (LOE C)
3. CABG is recommended in preference to PCI to improve survival in patients with multivessel CAD and diabetes mellitus, particularly if a LIMA graft can be anastomosed to the LAD artery. (LOE B)

Revascularization to Improve Symptoms

Class I

1. CABG or PCI to improve symptoms is beneficial in patients with one or more significant (≥70% diameter) coronary artery stenoses amenable to revascularization and unacceptable angina despite GDMT. (LOE A)

Percutaneous Coronary Intervention (PCI)

The term PCI encompasses the use of balloon angioplasty with stent placement as well as other less commonly performed intracoronary procedures such as rotational atherectomy and aspiration thrombectomy. During a PCI, a catheter is guided into the coronary blood vessels through either the femoral or radial arterial. A sheath is placed in either the femoral or radial artery to maintain access during the procedure. A guide catheter is then introduced through the sheath and advanced to the ostium of the coronary arteries. A guide wire is then advanced through the guide catheter and across the stenosis in the coronary vessel. The deflated balloon is then slid along the guide wire and to the site of the coronary stenosis. The balloon is then inflated. The inflated balloon expands the coronary lumen by stretching and tearing the atherosclerotic plaque. (See Chapter 33 for detailed review). Most elective PCI procedures are completed in 30 to 60 minutes.

Abrupt vessel closure is a potential complication of balloon angioplasty.

Abrupt vessel closure is provoked by physical disruption of the plaque on the vessel walls during the procedure. In the past, this complication occurred in 5% to 8% of cases and required emergency CABG surgery in 3% to 5% of patients. A second complication from PCI is restenosis which can lead to recurrent symptoms and the need for another revascularization procedure in approximately 30% to 50% of patients within a year.[73] Today these complications have been dramatically reduced with the use of antithrombotic therapy and intracoronary stents.

Stents are a stainless steel scaffold placed within coronary arterials that can prevent acute vessel closure and restenosis. The stent is placed over the deflated balloon and advanced to the area of coronary stenosis. When the balloon is inflated, the stent expands into the coronary vascular wall. The balloon is then deflated, leaving the expanded stent permanently in the diseased coronary vessel. While stents have had a dramatic effect of reducing restenosis, and therefore repeat revascularization procedures, they do not prevent death or MI more effectively than balloon angioplasty alone.

Restenosis is a phenomenon characterized by a greater than 50% diameter loss in the vessel lumen at the site of the intervention. Restenosis most often occurs within the first 3 to 6 months following the procedure. The pathophysiology of restenosis involves a complex cascade of various growth factors and cytokines that promote smooth muscle cell proliferation and result in a progressive loss of luminal diameter.[73] Restenosis typically occurs through the following mechanisms: early vessel recoil, late constrictive remodeling, and neointimal proliferation.[73]

Elastic recoil is a nearly instantaneous phenomenon, occurring during the first hour after successful dilation of the vessel. As the vessel is stretched during balloon angioplasty, the endothelium lining the vessel becomes damaged. In response to the stretching, the fibers begin to recoil back to their previous size.[73] Late constrictive remodeling, also referred to as negative remodeling, is mediated by myofibroblasts of the adventitia layer of the coronary vessel. Balloon-induced injury often results in exposure of the adventitia to the lumen. Cell proliferation begins as activated fibroblasts contribute to the enlargement of the adventitia. In time, these activated fibroblasts differentiate into myofibroblasts that are involved in the profibrotic and remodeling effects of the vessel.[73] As the adventitia becomes thick and fibrotic, a decrease in arterial cross-sectional area results.

The scaffold-like properties of a BMS prevent restenosis by controlling elastic recoil and negative remodeling. Restenosis rates dropped from 30% to

50% with balloon angioplasty alone to 15% to 30% with the use of BMS. However, stent-induced vessel injury and inflammatory reactions around the stent struts trigger a set of events that promote neointimal hyperplasia, a normal response to vascular damage.[73] The anti-proliferative drugs used in DES target neointimal hyperplasia. DES are coated with sirolimus, paclitaxel, zotarolimus, or everolimus. These agents interrupt the cell cycle to prevent neointimal proliferation and reduce restenosis rates to 5% to 10%.[73]

Although stents can effectively reduce restenosis, the exposed stent struts can provoke thrombosis. Stent thrombosis is driven by the implantation of the stent into an atherosclerotic plaque, exposing platelet adhering proteins to the stent surface. Patients remain at risk for stent thrombosis until a thin layer of endothelial tissue can grow around the stent struts. This process is called re-endothelialization and typically occurs in 2 to 4 weeks after BMS deployment, with most adverse events occurring within the first 2 weeks. The process of re-endothelialization is significantly prolonged with the use of DES. The drugs in a DES prevent smooth muscle, neointimal, and endothelial cell growth. Therefore, while DES effectively reduce neointimal proliferation and the risk of restenosis, they also increase the period of risk for stent thrombosis.

Stent thrombosis is uncommon (<5% of cases) but catastrophic when it occurs. Stent thrombosis results in a large MI or death in two-thirds of cases. The mortality rate from stent thrombosis ranges from 20% to 45%. Stent thrombosis can be largely prevented by using dual antiplatelet therapy (DAPT).

Pharmacotherapy with PCI

The physical damage imposed on the atherosclerotic plaque during PCI with stent placement induces platelet recruitment and activation, leading to the potential for thrombus formation. Therefore, antithrombotic therapy with antiplatelet and anticoagulant agents are necessary to produce a successful outcome. Antiplatelet therapy is also used after the procedure to reduce the risk of stent thrombosis.

All patients without a contraindication should receive aspirin before PCI and thereafter continued for life. Patients already on chronic aspirin therapy should take an additional 75 to 325 mg before PCI. Aspirin-naive patients should be given a dose of 325 mg at least 2 hours but preferably 24 hours before PCI. Chronic treatment with aspirin 81 mg daily is recommended after PCI. Patients receiving a stent should also receive a $P2Y_{12}$ inhibitor (eg, clopidogrel) before PCI. The ACC/AHA guidelines recommend against stent placement if it is believed the patient will not tolerate or comply with the recommended duration

of DAPT.[1]

After elective PCI, DAPT should be continued to reduce the risk of stent thrombosis. Patients who receive a BMS, a minimum of one month of DAPT is sufficient.[74] In patients at high risk of bleeding, a minimum of 2 weeks can be given, as most re-endothelialization of the stent surface occurs within 2 weeks. Patients receiving a DES should receive at least 6 months of DAPT due to the delayed and somewhat unknown duration of the re-endothelialization process.[73,74] However, it is reasonable for those patients who receive a DES and are high risk of bleeding or develop significant bleeding to stop the $P2Y_{12}$ inhibitor after only 3 months of therapy.[74]

The results of the DAPT (Dual Antiplatelet Therapy Trial) found that a longer duration of DAPT (up to 30 months) provides a greater reduction in CV adverse events when compared to 12 months of treatment.[75] Therefore, the guidelines state that a longer treatment regimen for both BMS and DES can be considered in patients who have tolerated therapy, are not at high risk of bleeding, nor have experienced any bleeding complications. This longer duration of DAPT for patients receiving a DES is a Class IIb recommendation.[74]

PCI Versus Medical Management

Despite advancements in PCI technique and stent technology, no study to date has demonstrated that PCI in patients with SIHD improves survival. This is most likely due the advancements in pharmacotherapy and use of GDMT. Early studies found PCI resulted in fewer angina episodes when compared to medical therapy, but PCI in these trials rarely included the use of stents and medical therapy did not include the use of high-intensity statins or ACE inhibitors.[76]

Contemporary PCI and GDMT have been compared in recent clinical trials. In the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial, patients were randomized to GDMT alone or PCI with GDMT.[77] Medication adherence, based on patient self-reports, was excellent with more than 90% of patients taking aspirin, β-blocker, and ACE inhibitor therapies. The rate of death and MI in the two treatment groups was not different after a median follow up of 4.6 years (19.0% in PCI group vs 18.5% in GDMT group). While more patients were angina-free in the PCI group compared to the GDMT group at one year (66% vs 58%), there was no difference at the 5-year follow-up time point (74% vs 72%). The need for revascularization after 5 years was lower in the PCI group (21.1% vs 32.6%). This trial confirms that even in modern day practice, PCI with GDMT does not

lower the risk of death and MI compared to GDMT alone, and PCI should be reserved for patients with SIHD refractory angina after receiving optimal GDMT. A 12 year follow-up of the COURAGE trial participants failed to show a difference in mortality between the two groups (25% vs 24%).[78] These data underscore the importance of aggressive, goal-oriented, pharmacotherapy in patients with SIHD. While one-third of patients in the COURAGE study randomized to the GDMT group did need to receive PCI during the 5-year study, two-thirds did not. Thus, based on the available evidence, PCI cannot be supported as the initial management strategy in most patients with SIHD.

While the COURAGE and others trials suggest that PCI in SIHD should be reserved for patients with chest pain despite optimal GDMT, the early use of PCI remains common and controversial. The ISCHEMIA trial (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) is currently ongoing in an attempt to bring a final answer to this question. An important outcome will be a quality of life assessment. The results of this study are projected to be available in 2020.

Coronary Artery Bypass Graft Surgery

9 While PCI is the most common form of revascularization, CABG surgery is recommended to prolong survival or relieve refractory symptoms of angina in select patients (Table 32-9).[1,79,80] In the majority of CABG surgeries, a sternotomy and division of the sternum is done to provide the surgeons direct access to the heart. Thus, it is often referred to as “open heart surgery”. Once the heart is exposed, vascular conduits surgically harvested from other areas of the body are used to “bypass” the atherosclerotic plaque. The most commonly used vascular conduits are the saphenous vein grafts (SVG) from the leg and the left internal mammary artery (LIMA) from the chest wall. The radial and gastroepiploic arteries are also occasionally used. When a LIMA graft is performed, the distal portion is detached from its insertion point behind the sternum and an anastomosis is made distal to the atherosclerotic plaque of the diseased coronary artery to restore blood flow beyond the blockage. The other vascular conduits (eg, SVG) are considered “free grafts” and are anastomosed distal to atherosclerotic plaques of the other diseased coronary arteries. The proximal ends of the free grafts are then anastomosed to the aorta restoring blood flow distal to the blockage. Prior to and during the anastomoses of the bypass grafts, patients are often placed on cardiopulmonary bypass which redirects blood from the heart to a bypass machine. In the bypass machine, venous blood is oxygenated and then returned to the systemic circulation to

maintain myocardial and systemic perfusion during the surgery. The heart is then arrested allowing the surgeons to perform the surgery without the heart actively beating. After the bypass grafts have been installed, the patient is weaned from cardiopulmonary bypass machine, the heart and lung resume their normal functioning, the cannulas are removed, and the sternum and incisions are closed.

While a critical obstruction of a native coronary vessel due to atherosclerosis usually takes five or more decades, the lifespan of a SVG is significantly shorter. This may be due to the higher BP in arterial circulation compared to venous pressures. Endothelial damage and LDL-C accumulation significantly accelerates the atherosclerotic process. The use of arterial grafts provides greater long-term graft patency compared to SVG. Arterial grafts are more prone to vasospasm and require longer surgical times to harvest.

Despite the advancements in technique and patient care, CABG surgery is associated with several complications. Death, neurological impairment, MI, major bleeding, acute kidney injury, atrial fibrillation, and surgical wound infections are all potential complications following CABG surgery. Early mortality within 30 days is generally low (1%-2%) but is higher in emergent or high-risk cases (eg, multiple comorbidities, elderly).[81] Neurological complications such as stroke (1%-3%), delirium (8%-50%), and cognitive deficits can occur due to hypoxia, emboli, hemorrhage, or a metabolic abnormality during or shortly after the surgery.[81] Patients with advanced age, previous stroke or transient ischemic attack, HTN, ASCVD, atrial fibrillation, and prolonged cardiopulmonary bypass duration are at higher risk of neurological complications. Atrial fibrillation occurs in as many as 30% of patients undergoing CABG surgery but is often transient. An infection of the sternum, known as mediastinitis, occurs in 0.5%-3% of patients and may prolong hospital stays, increase recovery time, and result in repeat surgical intervention.[81] MI, major bleeding requiring surgical re-exploration, and acute kidney injury requiring hemodialysis each occur in 1% to 4% of patients following CABG surgery.[81]

New approaches to CABG surgery have been developed in an attempt to minimize complications. One of these approaches is the off-pump bypass coronary surgery that is performed while the heart is beating. By reducing the need for cardiopulmonary bypass and aortic clamping, rates of adverse neurologic and renal events are significantly lower.[81] Another approach to surgical revascularization is the use of minimally invasive direct coronary artery bypass during which a small left anterior thoracotomy is done in lieu of a sternotomy. Due to the small incision and technical difficulty of the surgery, only

patients with single-vessel disease in either the left anterior descending or right coronary artery currently are candidates for the procedure. Although postoperative pain is often increased, clinical outcomes of minimally invasive direct coronary artery bypass are similar to conventional CABG but recovery time is quicker.[81]

In suitable surgical candidates, CABG surgery is the preferred revascularization strategy in several clinical scenarios (Table 32-9). In patients with left main CAD (≥50% stenosis) "unprotected" by collateral coronary blood flow or patent bypass grafts, 2-vessel CAD (≥70% stenosis in the proximal left anterior descending coronary artery and one additional major coronary artery), and multivessel CAD (≥ 70% stenosis in three or more major coronary arteries) including patients with diabetes for whom a LIMA graft can be used to bypass the left anterior descending coronary artery, CABG surgery is preferred to PCI and medical management because it is associated with prolonged survival.[79–81] CABG surgery is also recommended to decrease mortality in patients who survived an episode of sudden cardiac death due to ischemia from significant (≥70% stenosis) CAD in one or more arteries. In patients with SIHD whose symptoms are refractory to GDMT, CABG surgery may be considered.[1,80] However, because it is less invasive than CABG surgery, PCI is often the preferred strategy in this setting.

Pharmacotherapy with CABG

Prior to CABG surgery, attention to pharmacotherapeutic needs is important to minimize postoperative complications. Patients should receive aspirin 100-325 mg daily preoperatively to reduce the risk of graft closure. To reduce the risk of CABG-related major bleeding, $P2Y_{12}$ inhibitors should be discontinued well in advance of an elective CABG surgery (5 days for clopidogrel and ticagrelor; 7 days for prasugrel) and at least 24 hours prior to urgent CABG surgery, if possible. Unless contraindicated, β-blockers should be initiated at least 24 hours prior to CABG surgery to reduce the risk of postoperative atrial fibrillation.

Pharmacotherapy after CABG surgery includes aspirin, lipid-lowering therapy, β-blockers, and the continuation of ACE inhibitors (ACC/AHA Class I recommendations).[1] Aspirin 100 to 325 mg daily should be resumed or initiated within 6 hours of CABG surgery and continued indefinitely to reduce the risk of graft closure during the first year after surgery. Aspirin should also be prescribed for the primary or secondary prevention of acute MI. If patients are truly aspirin allergic, clopidogrel is an acceptable alternative. Due to the accelerated atherosclerotic process in the bypass grafts, high-intensity statin therapy should

be resumed or initiated in all patients following CABG surgery.[48,80] Although data from clinical trials suggest no benefit, large observational studies of perioperative and postoperative β-blocker use are associated with lower mortality following CABG surgery. Therefore, β-blockers should be initiated after CABG surgery and continued after discharge.[80] The safety and efficacy of initiating ACE inhibitors following CABG surgery is uncertain and may increase the risk of hypotension and acute kidney injury, particularly if administered during the early postoperative period.[80] However, continuation of previous ACE inhibitor therapy following CABG surgery is associated with a significant reduction in nonfatal cardiac, cerebral, and renal events whereas ACE inhibitor withdrawal following CABG surgery is associated with increased event rates.[82] Therefore, for patients taking ACE inhibitors or ARBs prior to CABG surgery, these therapies should be resumed following surgery once patients have demonstrated stable hemodynamics and renal function.[80] For ACE inhibitor-naïve patients, initiation of an ACE inhibitor should be considered in stable patients with compelling indications (eg, HFrEF, HTN, DM, chronic kidney disease).[80] For symptomatic relief of chest pain episodes, patients need access to SL NTG after surgery. Smoking cessation and cardiac rehabilitation are also critical to successful postoperative outcomes.

Management of Fixed-Threshold Angina

8 Medical management of angina episodes follows a stepwise approach (see Figure 32-2 and Table 32-6). All patients should have access to SL NTG for treatment of an episode of angina. Patients need to be adequately educated on appropriate use and storage, assuring consistent access to the tablets or spray (Table 32-8). This may require patients to have multiple vials or canisters that are in areas that they spend time (eg, home, work, car, garage). While some patients may only need SL NTG for infrequent attacks, many patients with SIHD will need chronic therapy to prevent angina episodes. Patients experiencing frequent angina episodes, or in whom angina is impacting quality of life, should receive chronic therapy. The goal of chronic therapy is to provide complete or nearly complete elimination of angina episodes while having the patient take part in normal activities.

Either a β-blocker or a non-DHP CCB (verapamil or diltiazem) can be used for the initial chronic management of angina. The goal is to lower the patient's resting HR to 50 to 60 beats per minute and an exercise HR of less than 100 beats per minutes. It should be noted that not all patients, especially elderly

patients, can tolerate a HR in this range, and therefore the goal HR would be as low as the patient can tolerate above 50 beats per minute. β-blockers or a non-DHP CCB can improve exercise duration and reduce the number of weekly angina episodes.[71]

6 β-blockers are currently recommended over CCBs as initial therapy for control of angina episodes in patients with SIHD.[1] This recommendation is based on improved survival demonstrated with the use of β-blockers in patients after MI and with HFrEF. It should be noted that only carvedilol, metoprolol succinate, and bisoprolol should be used in patients with HFrEF, starting with low doses and titrating up in a slow and set regimen. Neither of the non-DHP CCBs have demonstrated similar benefits in patients following an MI or with HFrEF. In the absence of HFrEF or bradycardia, patients with contraindications or intolerable side effects to β-blocker therapy unrelated to HR lowering should use verapamil or diltiazem as initial therapy. In patients without a history of MI or HF, the use of β-blocker therapy does not provide a survival advantage and is used purely for control of ischemic episodes and symptoms of angina.[71]

5 If angina symptoms are controlled once the HR goal is achieved, no additional anti-angina therapy is necessary and patients are monitored for continued efficacy and side effects. Regardless of whether a β-blocker or non-DHP CCB are selected as initial therapy, many patients will require combination therapy to attain adequate control of their symptoms. If additional therapy is required, the need for additional antihypertensive agents should be considered in the next step. Patients who continue to have elevated BP above the goal of 130/80 mm Hg should be prescribed a DHP CCB. Unlike long-acting nitrates and ranolazine, DHP CCBs decrease both MVO_2 and BP. While not commonly combined, DHP CCB and non-DHP CCB target different calcium channels and are a rational regimen for patients with SIHD. It is important to monitor the patient for peripheral edema and signs and symptoms of reduced cardiac output.

7 In patients with continued angina episodes despite achieving BP and HR goals, a long-acting nitrate or ranolazine should be added to the regimen. Both agents have demonstrated efficacy when used in combination with SL NTG and medications to control HR and BP. While long-acting nitrates are not optimal agents when used as monotherapy due reflex tachycardia, this is attenuated in patients who are taking a β-blocker or non-DHP CCB. Ranolazine does not reduce HR or BP, making it an option in patients who have already achieved their HR and BP goals, but still have exertional angina. The selection of a long-acting nitrate or ranolazine should be based on patient preferences, tolerability, and cost. Long-acting nitrates do not provide 24-hour angina protection, but this

may not be an issue for all patients. While ranolazine provides 24 hours protection and has a more attractive side effect profile compared to long-acting nitrates, it is significantly more expensive.

Patients who are unable to fully participate in the activities that bring them joy in life because of inadequate control of chest pain symptoms, despite the use of maximally tolerated therapies, have refractory angina. Some patients may have refractory angina while taking relatively fewer anti-angina medications or lower doses due to intolerances or contraindications. Patients with refractory angina should be referred for revascularization therapy.

Management of Variable-Threshold Angina and Prinzmetal's Angina

Patients with variable-threshold angina require pharmacotherapy that targets vasospasm. While β-blockers are typically the agents of first choice in patients with fixed-threshold angina, they are less useful in patients with vasospasm. Although not all studies report increased chest pain episodes with β-blockers in patients with vasospasm, they can induce coronary vasoconstriction and prolong ischemia. Worsening angina is most likely due to unopposed α1-adrenergic receptor stimulation during β-blockade. A similar phenomenon may occur in patients with SIHD treated with β-blockers who also abuse cocaine.

Both nitrates and calcium channel blockers reduce vasospasm. Most patients respond well to SL NTG for acute attacks. While long-acting nitrates can be used in the treatment of vasospasm, the high doses typically needed for adequate symptom control are not well tolerated. Therefore, CCBs are often used. There is no preference to which agent is selected first, but CCBs are dosed less frequently and a single agent may be sufficient to manage symptoms. Nifedipine, verapamil, and diltiazem are all equally effective for the initial management of coronary vasospasm. Dose titration is important to maximize the response with CCBs. Patients unresponsive to calcium antagonists alone may add long-acting nitrates.

EVALUATION OF THERAPEUTIC OUTCOMES

The therapeutic goals in the management of patients with SIHD are to prolong life, reduce symptoms of angina, and improve quality of life. Improving the patient's quality of life requires careful attention to the potential adverse effects from medications. Surrogate endpoints such as BP goal attainment, use of high-

intensity statin, A1c goal attainment, smoking cessation, and achieving a health weight should be used to determine progress toward the ultimate goal — reduced risk of mortality and major cardiovascular events. Patients should be evaluated every 1 to 2 months until goals are achieved. Follow up every 6 to 12 months thereafter is appropriate.

3 Monitoring for improvements in symptoms related to angina should include asking the patients about the number of angina episodes and weekly SL NTG use as well as inquiring about exercise capacity or duration of exertion needed to induce angina. It is important to ask the patient about their ability to engage in activities they want to do. It is not uncommon for patients to report reduced or no episodes of angina because they have stopped engaging in activities that bring on angina. Once patients have received optimal medical therapy, symptoms should improve in 2 to 4 weeks and remain stable until the disease progresses. Instruments such as the Seattle Angina Questionnaire and CCS Angina Grading Scale can be used to improve the assessment of symptoms.[1] While objective tests such as an exercise tolerance test with or without cardiac imaging can be obtained to assess the adequacy of treatment, they are primarily performed in patients who do not achieve adequate symptom control. Following a revascularization procedure, the patients' symptoms should be assessed every 6 to 12 months.

Postclass Engaged Learning Activity

Perform a literature search looking for research manuscripts that examine the differences between optimal medical therapy versus revascularization in patients with stable ischemic heart disease (SIHD). Create a table that describes the components of optimal medical therapy in these trials. The table should address what was defined as optimal medical therapy for the following therapeutic approaches:

- Antiplatelet therapy
- Angiotensin-converting enzyme inhibitors
- Beta-blockers and other antianginal agents
- Heart rate and/or blood pressure goals
- Lipid lowering therapy
- Lipid panel goals
- Diet management

Diabetes mellitus goals
Physical activity
Smoking cessation

ABBREVIATIONS

ACC	American College of Cardiology
ACE	angiotensin converting enzyme
ACS	acute coronary syndrome
AHA	American Heart Association
ARB	angiotensin receptor blocker
ASCVD	atherosclerotic cardiovascular disease
BMS	bare metal stent
BP	blood pressure
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CCS	Canadian Cardiovascular Society
CCB	calcium channel blocker
COR	class of recommendation
COX	cyclooxygenase
CT	computer topography
CVD	cardiovascular disease
CYP	cytochrome P450
DES	drug-eluting stent
DHP	dihydropyridine
DM	diabetes mellitus
ECG	electrocardiogram
EDRF	endothelium-derived relaxing factor
FFR	fractional flow reserve
GDMT	guideline-directed medical therapy
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HR	heart rate
HTN	hypertension
ISMN	isosorbide mononitrate

LDL-C	low-density lipoprotein cholesterol
LIMA	left internal mammary artery
LOE	level of evidence
LV	left ventricle
MI	myocardial infarction
MVO_2	myocardial oxygen demand
PCI	percutaneous coronary intervention
SIHD	stable ischemic heart disease
SL NTG	sublingual nitroglycerin
SVG	saphenous vein graft

REFERENCES

1. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association of Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012;60:e44–e164.
2. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics-2018 update: A report from the American Heart Association. *Circulation*. 2018;137:e67–e492.
3. Steg PG, Greenlaw N, Tendera M, et al. Prevalence of angina symptoms and myocardial ischemia and their effect on clinical outcomes in outpatients with stable coronary artery disease: Data from the International Observational CLARIFY Registry. *JAMA Intern Med*. 2014;174:1651–1659.
4. Mozaffarian D, Bryson CL, Spertus JA, et al. Anginal symptoms consistently predict total mortality among outpatients with coronary artery disease. *Am Heart J*. 2003;146:1015–1022.
5. Five-year clinical and functional outcome comparing bypass surgery and angioplasty in patients with multivessel coronary disease: A multicenter randomized trial. Writing Group for the Bypass Angioplasty Revascularization Investigation (BARI) Investigators. *JAMA*. 1997;277:715–721.

6. Boini S, Briancon S, Guillemin F, Galan P, Hercberg S. Occurrence of coronary artery disease has an adverse impact on health-related quality of life: A longitudinal controlled study. *Int J Cardiol*. 2006;113:215–222.
7. Hlatky MA, Rogers WJ, Johnstone I, et al. Medical care costs and quality of life after randomization to coronary angioplasty or coronary bypass surgery. Bypass Angioplasy Revascularization Investigation (BARI) Investigators. *N Engl J Med*. 1997;336:92–99.
8. Tarkin JM, Kaski JC. Pharmacological treatment of chronic stable angina pectoris. *Clin Med*. 2013;13:63–70.
9. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary heart disease and the acute coronary syndrome (first of two parts). *N Engl J Med*. 1992;326:242–250.
10. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary heart disease and the acute coronary syndrome (second of two parts). *N Engl J Med*. 1992;326:310–318.
11. Canty JMJR, Duncker DJ. Coronary blood flow and myocardial ischemic. In: Mann DL, Zipes DP, Libby P, Bonow RO, eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 10th ed. Philadelphia, PA: Elsevier Saunders; 2015;1029–1056.
12. Epstein SE, Cannon RO III, Talbot TL. Hemodynamic principles in the control of coronary blood flow. *Am J Cardiol*. 1985;56:4E–10E.
13. Laughlin MH, Davis MJ, Secher NH, et al. Peripheral circulation. *Compr Physiol*. 2012;2:321–447.
14. Marzilli M, Merz CNB, Boden WE, et al. Obstructive coronary atherosclerosis and ischemic heart disease: An elusive link!. *J Am Coll Cardiol*. 2012;60:951–956.
15. Pepine CJ, Douglas PS. Rethinking stable ischemic heart disease: is this the beginning of a new era? *J Am Coll Cardiol*. 2012;60:957–959.
16. Ridker PM, Danielson E, Fonseca FAH, et al. JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359:2195–2207.
17. Campeau L. Grading of angina pectoris (letter). *Circulation*. 1976;54:522–523.
18. Pepine CJ, Balaban RS, Bonow RO, et al. Women's Ischemic Syndrome Evaluation: Current status and future research directions: Report of the National Heart, Lung and Blood Institute workshop. October 2-4, 2002; Section 1: diagnosis of stable ischemia and ischemic heart disease.

Circulation. 2004;109:e44–e46.

19. Gould KL, Johnson NP, Bateman TM, et al. Anatomic versus physiologic assessment of coronary artery disease: Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making. *J Am Coll Cardiol*. 2013;62:1639–1653.
20. van de Hoef TP, Echavarría-Pinto M, van Lavieren MA, et al. Diagnostic and prognostic implications of coronary flow capacity: A comprehensive cross-modality physiological concept in ischemic heart disease. *J Am Coll Cardiol Intv*. 2015;8:1670–1680.
21. Jeremias A, Kleiman NS, Nassif D, et al. EVENT Registry Investigators. Prevalence and prognostic significance of preprocedural cardiac troponin elevation among patients with stable coronary artery disease undergoing percutaneous coronary intervention: Results from the Evaluation of Drug Eluting Stents and Ischemic Events Registry. *Circulation*. 2008;118:632–638.
22. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324:71–86.
23. Dobesh PP, Varnado S, Doyle M. Antiplatelet agents in cardiology: A report on aspirin, clopidogrel, prasugrel, and ticagrelor. *Cur Pharm Des*. 2016;22:1918–1932.
24. Rousan TA, Mathew ST, Thadani U. Drug therapy for stable angina pectoris. *Drugs*. 2017;77:265–284.
25. Sofi F, Marcucci R, Gori AM, Abbate R, Gensini GF. Residual platelet reactivity on aspirin therapy and recurrent cardiovascular events—at meta-analysis. *Int J Cardiol*. 2008;128:166–171.
26. Hovens MMC, Snoep JD, Eikenboom JCJ, van der Bom JG, Mertens BJA, Huisman MV. Prevalence of persistent platelet reactivity despite use of aspirin: A systematic review. *Am Heart J*. 2007;153:175–181.
27. Gurbel PA, Bliden KP, DiChiara J, et al. Evaluation of dose-related effects of aspirin on platelet function: Results from the Aspirin-Induced Platelet Effect (ASPECT) study. *Circulation*. 2007;115:3156–3164.
28. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med*. 2006;354:1706–1717.

29. Bhatt DL, Flather MD, Hacke W, et al. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. *J Am Coll Cardiol*. 2007;49:1982–1988.
30. Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015;372:1791–1800.
31. Serebruany VL, Steinhubl SR, Berger PB, et al. Variability in platelet responsiveness to clopidogrel among 544 individuals. *J Am Coll Cardiol*. 2005;45:246–251.
32. Wismann PP, Roest M, Asselbergs FW. Platelet-reactivity tests identify patients at secondary risk of secondary cardiovascular events: A systematic review and meta-analysis. *J Thromb Haemost*. 2014;12:736–747.
33. Bonello L, Tantry US, Marcucci R, et al. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. *J Am Coll Cardiol*. 2010;56:919–933.
34. Spertus JA, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. *Circulation*. 2006;113:2803–2809.
35. Scott SA, Sangkuhl K, Stein CM, et al. Clinical pharmacogenetics implementation consortium guidelines for cytochrome P450-2C19 (CYP2C19) genotype and clopidogrel therapy: 2013 update. *Clin Pharmacol Ther*. 2013;94:317–323.
36. Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *JAMA*. 2009;302:849–857.
37. Hochholzer W, Trenk D, Fromm MF. Impact of cytochrome P450 2C19 loss-of-function polymorphism and of major demographic characteristics on residual platelet function after loading and maintenance treatment with clopidogrel in patients undergoing elective coronary stent placement. *J Am Coll Cardiol*. 2010;55:2427–2434.
38. Gilard M, Arnaud B, Cornily J-C, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin. The randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. *J Am Coll Cardiol*. 2008;51:256–260.
39. Norgard NB, Mathews KD, Wall GC. Drug-drug interaction between

clopidogrel and the proton pump inhibitors. *Ann Pharmacother*. 2009;43:1266–1274.

40. Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med*. 2010;363:1909–1917.
41. HOPE Investigators. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high risk patients. *N Engl J Med*. 2000;342:145–153.
42. The European trial on reduction of cardiac events with perindopril in stable coronary artery disease investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: Randomised, double-blind, placebo-controlled, multicenter trial (the EUROPA study). *Lancet*. 2003;362:782–788.
43. PEACE Trial Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med*. 2004;351:2058–2068.
44. Danchin N, Cucherat M, Thuillez C, Durand E, Kadri Z, Steg PG. Angiotensin-converting enzyme inhibitors in patients with coronary artery disease and absence of heart failure or left ventricular systolic dysfunction: An overview of long-term randomized controlled trials. *Arch Intern Med*. 2006;166:787–796.
45. The ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358:1547–1559.
46. The TRANSCEND Investigators. Effects of angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: A randomised controlled trial. *Lancet*. 2008;372:1174–1183.
47. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: A meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670–1681.
48. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *Circulation*. 2014;129(Suppl 2):S1–S45.
49. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-

cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol*. 2016;68:92–125.

50. Pedersen TR, Faergeman O, Kastelein JJP, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: A randomized controlled trial. *JAMA*. 2005;294:2445.
51. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults—a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;71:e127–e248.
52. The SPRINT Research Group. A randomized trial of intensive versus standard blood pressure control. *N Engl J Med*. 2015;373:2103–2116.
53. Reboussin DM, Allen NB, Griswold ME, et al. Systematic review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults—a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;71:2176–2198.
54. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. The health consequences of smoking-50 years of progress: A report of the Surgeon General. http://www.ncbi.nlm.nih.gov/pubmed/24455788. Published 2014; accessed June 13, 2018.
55. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: An update. *J Am Coll Cardiol*. 2004;43:1731–1737.
56. Jha P, Ramasundarahettige C, Landsman V, et al. 21st-century hazards of smoking and benefits of cessation in the United States. *N Engl J Med*. 2013;368:341–350.
57. Anthenelli RM, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): A double-blind, randomised,

placebo-controlled clinical trial. *Lancet*. 2016;387(10037):2507.

58. Benowitz NL, Pipe A, West R, et al. Cardiovascular safety of varenicline, buproprion, and nicotine patch in smokers: A randomized clinical trial. *JAMA Intern Med*. 2018;178:622–631.
59. Hong KN, Fuster V, Rosenson RS, Rosendorff C, Bhatt DL. How low to go with glucose, cholesterol, and blood pressure in primary prevention of CVD. *J Am Coll Cardiol*. 2017;70:2171–2185.
60. Lee G, Oh S-W, Hwang S-S, et al. Comparative effectiveness of oral antidiabetic drugs in preventing cardiovascular mortality and morbidity: A network meta-analysis. *PLoS ONE*. 2017;12:e0177646. https://doi.org/10.1371/journal.pone.0177646.
61. Zheng SL, Roddick AJ, Aghar-Jaffar R, et al. Association between use of sodium-glucose-cotransporter 2 inhibitors, glucagon-like peptide 1 agonists, and dipeptidyl peptidase 4 inhibitors with all-cause mortality in patients with type 2 diabetes: A systematic review and meta-analysis. *JAMA*. 2018;319:1580–1591.
62. American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment: Standards of medical care in diabetes—2018. *Diabetes Care*. 2018;41(Suppl 1):S73–S85.
63. Messerli FH, Bangalore S, Yao SS, Steinberg JS. Cardioprotection with beta-blockers: Myths, facts and Pascal's wager. *J Intern Med*. 2009;266:232–241.
64. Steering Committee Transdermal Nitroglycerin Cooperative Study. Acute and chronic antianginal efficacy of continuous twenty-four-hour application of transdermal nitroglycerin. *Am J Cardiol*. 1991;68:1263–1273.
65. Munzel T, Daiber A, Mulsch A. Explaining the phenomenon of nitrate tolerance. *Circ Res*. 2005;97:618–628.
66. Daiber A, Oelze M, Wenzel P, et al. Nitrate tolerance as a model of vascular dysfunction: Roles for mitochondrial aldehyde dehydrogenase and mitochondrial oxidative stress. *Pharmacol Rep*. 2009;61:33–48.
67. Dobesh PP, Trujillo TC. Ranolazine: A new option in the management of chronic stable angina. *Pharmacotherapy*. 2007;27:1659–1676.
68. Chaitman BR, Skettino SL, Parker JO, et al., for the MARISA Investigators. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. *J Am Coll Cardiol*. 2004;43:1375–1382.

69. Chaitman BR, Pepine CJ, Parker JO, et al. CARISA Investigators. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina. A randomized controlled trial. *JAMA*. 2004;291:309–316.
70. Stone PH, Gratsiansky NA, Blokhin A, Huang I-Z, Meng L. Antianginal efficacy of ranolazine when added to treatment with amlodipine. The ERICA (Efficacy of Ranolizine in Chronic Angina) Trial. *J Am Coll Cardiol*. 2006;48:566–575.
71. Mody P, Sidhu MS, Brilakis ES, Sacco JD, Banerjee S, Boden WE. Antianginal agents for the management for stable ischemic heart disease: A review. *Card Rev*. 2016;24:177–189.
72. Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, et al. , for the MERLIN-TIMI 36 Trial Investigators. Effects of Ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes: The MERLIN-TIMI 36 randomized trial. *JAMA*. 2007;297:1775–1783.
73. Dobesh PP, Stacy ZA, Ansara AJ, Enders JM. Drug-eluting stents: A mechanical and pharmacologic approach to coronary artery disease. *Pharmacotherapy*. 2004;24:1554–1577.
74. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2016;68:1082–1115.
75. Mauri L, Kereiakes DJ, Yeh RW, et al., for the DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med*. 2014;371:2155–2166.
76. Stergiopoulos K, Boden WE, Hartigan P, et al. Percutaneous coronary intervention outcomes in patients with stable obstructive coronary artery disease and myocardial ischemia: A collaborative meta-analysis of contemporary randomized clinical trials. *JAMA Intern Med*. 2014;174:232–240.
77. Boden WE, O'Rourke RA, Teo KK, et al. COURAGE Trial Research Group.Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356:1503–1516.
78. Sedlis SP, Hartigan PM, Teo KK, et al. COURAGE Trial Investigators. Effects of PCI on long-term survival in patients with stable ischemic heart

disease. *N Engl J Med*. 2015;373:1937–1946.

79. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guidelines for the diagnosis and management of patients with stable ischemic heart disease. *J Am Coll Cardiol*. 2014;64:1929–1949.
80. Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery. *J Am Coll Cardiol*. 2011;58:e123–e210.
81. Head SJ, Milojevic M, Taggart DP, Puskas JD. Current practice of state-of-the-art surgical coronary revascularization. *Circulation*. 2017;136:1331–1345.
82. Drenger B, Fontes ML, Miao Y, et al. Patterns of use of perioperative angiotensin-converting enzyme inhibitors in coronary artery bypass graft surgery with cardiopulmonary bypass—effects on in-hospital morbidity and mortality. *Circulation*. 2012;126:261–269.

33

Acute Coronary Syndrome

Robert J. DiDomenico, Paul P. Dobesh, and Shannon W. Finks

KEY CONCEPTS

1. The predominant cause of acute coronary syndrome (ACS) in more than 90% of patients is the acute rupture, fissure, or erosion of an unstable atherosclerotic plaque followed by subsequent thrombus formation that impairs distal blood flow resulting in acute myocardial ischemia.
2. Patients with symptoms of myocardial ischemia suspected of having ACS should undergo risk stratification that incorporates their past medical history, presenting signs and symptoms, 12-lead electrocardiogram (ECG), and cardiac troponin (cTn); dynamic elevation in serial cTn values confirms the diagnosis of myocardial infarction (MI).
3. Intravenous (IV) nitroglycerin (NTG) should be considered to alleviate anginal pain and/or treat acute comorbidities such as uncontrolled hypertension (HTN) or heart failure (HF), oxygen should be administered to patients with hypoxia (oxygen saturation less than 90% [0.90]), and IV morphine may be considered in patients with refractory anginal pain.
4. In the absence of contraindications, an oral β-blocker should be initiated for all patients with ACS and continued for at least 1 and up to 3 years or more to reduce the risk of major adverse cardiac events (MACE); calcium channel blockers (CCBs) may be considered in patients with vasospasm and those refractory to or with contraindications or intolerance to β-blockers.
5. Reperfusion of the infarct-related artery in ST-segment elevation myocardial infarction (STEMI) with primary percutaneous coronary intervention (PCI) within 90 minutes of first medical contact is preferred to fibrinolytic therapy, which should be considered if primary PCI cannot be performed within 120 minutes of presentation.
6. Antiplatelet therapy is a central component to the acute and chronic

management of patients with ACS to reduce MACE, frequently includes aspirin plus a $P2Y_{12}$ inhibitor, and requires careful attention be paid to the clinical scenario to select the regimen that optimizes efficacy and safety.

7. Use of parenteral anticoagulant agents (unfractionated heparin [UFH], low-molecular-weight heparin [LMWH], fondaparinux, bivalirudin) during hospitalization have the ability to reduce MACE in patients with ACS and requires knowledge of the diagnosis, selected management strategy, and other factors to select the drug and dosing regimen that optimize efficacy and safety.
8. Dual antiplatelet therapy (DAPT) with aspirin plus a $P2Y_{12}$ receptor inhibitor is indicated for all patients post ACS for a minimum of 12 months regardless of whether the patient is managed with an ischemia-driven approach or if the patient undergoes revascularization.
9. All patients post ACS should receive maximally tolerated statin therapy to reduce the risk of MACE; patients with low-density lipoprotein cholesterol (LDL-C) of 70 mg/dL (1.81 mmol/L) or greater on maximally tolerated statin therapy should be considered for the addition of nonstatin therapies (eg, ezetimibe, proprotein convertase subtilisin kexin 9 [PCSK9] inhibitor).
10. To reduce the risk of MACE, all post-MI patients should receive oral treatment with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) unless contraindicated and a mineralocorticoid receptor antagonist if the left ventricular ejection fraction (LVEF) is 40% (0.40) or less and HF symptoms or diabetes mellitus (DM) are also present.

Preclass Engaged Learning Activity

To better understand the pathophysiology of acute coronary syndrome (ACS) and the rationale for pharmacotherapy to treat ACS, please watch the following videos:

1. Thrombotic cascade in ACS—Acute coronary syndrome (ACS) pathology—Thrombosis Advisor https://tinyurl.com/y23cmrzh (Duration 1:48 minutes)
2. Pathophysiology of ACS—Heart attack (myocardial infarction) pathophysiology—Khan Academy: https://tinyurl.com/y68h3nrl (Duration

11:48 minutes)

3. Myocardial healing and remodeling—Healing after a heart attack (myocardial infarction)—Khan Academy https://tinyurl.com/yxjzkuff (Duration 7:42 minutes)
4. Complications from ACS—Complications after a heart attack (myocardial infarction)—Khan Academy https://tinyurl.com/y3arf66z (Duration 9:07 minutes)

INTRODUCTION

Acute coronary syndrome (ACS) is an acute manifestation of coronary artery disease (CAD) and, for many patients, is the first indication they have CAD. Patients with ACS typically experience an acute reduction in coronary blood flow most often due to a ruptured atherosclerotic plaque and subsequent formation of an intracoronary thrombus. The reduction in coronary blood flow produces myocardial ischemia and, if left untreated, may lead to myocardial infarction (MI).

Patients with ACS typically experience acute chest discomfort similar to those with stable ischemic heart disease (SIHD) but the symptoms are often more severe and prolonged or refractory despite medical interventions. Like patients with SIHD, those experiencing ACS are at risk for complications such as MI, heart failure (HF), ventricular arrhythmias, and death. The spectrum of ACS includes ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA). The American College of Cardiology (ACC) and the American Heart Association (AHA) have published guidelines for the diagnosis and management of patients with STEMI and non-ST-segment elevation acute coronary syndrome (NSTE-ACS), which includes NSTEMI and UA.[1,2]

EPIDEMIOLOGY

The AHA estimates that every 40 seconds an American will experience a MI.[3] There is a direct relationship between age and the prevalence of both CAD and CAD-related events such as MI. More than 1 million persons are discharged from the hospital annually with a primary or secondary diagnosis of an ACS.[3] Myocardial infarction accounts for more than 70% of these hospitalizations, the majority are the first occurrence of a coronary event.[3] The presentation of MI

has changed over the last two decades. Between 1999 and 2008, the proportion of all patients with MI experiencing a NSTEMI and STEMI were 67% and 33%, respectively.[4] However, the incidence of STEMI declined by 62% over that time period (47% in 1999, 22.9% in 2008, $p < 0.001$), while the age- and sex-adjusted incidence of NSTEMI was largely unchanged over the same period.[4] While many patients who experience a MI experience symptoms prompting emergent care, an estimated 170,000 Americans will suffer a MI with minimal or no symptoms (eg, "silent MI") that may go undetected, placing them at high risk for major adverse cardiovascular events (MACE).[3]

Patients who experience ACS are at high risk for developing complications. The 1-year and 5-year mortality rates for patients experiencing MI are estimated at 18% to 23% and 36% to 47% for males and females, respectively.[3] Patients experiencing STEMI have a greater short-term (eg, 30 days) risk of complications, including death, compared to patients experiencing NSTEMI, whereas NSTEMI is associated with a greater long-term (eg, 2 years) risk.[3] In addition to death, patients experiencing ACS are also at risk for developing HF, cardiogenic shock, and ventricular arrhythmias, each of which contribute to the mortality associated with this disease state. Fortunately, declines in STEMI prevalence and overall severity of MI coupled with therapeutic advances have contributed to a reduction in complications associated with ACS globally. For example, the incidence of HF following MI has declined more than 40% over the last two decades and the risk of death has similarly declined.[3] Lower rates of in-hospital death and MACE have been associated with increased utilization of percutaneous coronary intervention (PCI) and optimal medical therapy in patients treated for MI.[3] Therefore, the use of evidence-based therapies to treat ACS, the focus of this chapter, improves outcomes in these patients and should be prioritized in care plans.

The treatment of ACS is associated with significant healthcare resource utilization and related costs. For patients hospitalized for ACS, the mean and median length of stay (LOS) were 5.5 and 4 days, respectively, in a recent analysis.[5] Over the last two decades, hospital LOS decreased by approximately 20% for patients hospitalized for MI who were not treated with coronary artery bypass graft (CABG) surgery.[6] Frequent hospitalizations and utilization of revascularization therapies (eg, PCI, CABG) leads to high costs associated with treating patients with ACS. In the United States, the mean cost of treating patients hospitalized for UA was $7,916 (median cost $7,841) while the average cost of a hospitalization for MI was $24,695 (median cost $26,749).[7] In fact, MI ranks among the top 10 most expensive conditions treated in the United States.[3]

Despite the decline in hospital LOS, hospital costs have increased by 10% in patients with MI treated with PCI and approximately 20% in those treated with CABG surgery between 2001 and 2011.[6]

ETIOLOGY

Endothelial dysfunction, inflammation, and the formation of fatty streaks contribute to the formation of atherosclerotic coronary artery plaques, the underlying cause of CAD.[7] The predominant cause of ACS in more than 90% of patients is the acute rupture, fissure, or erosion of an unstable atherosclerotic plaque followed by subsequent thrombus formation that impairs distal blood flow resulting in acute myocardial ischemia. If myocardial ischemia persists sufficiently long, MI can occur. This presentation of MI is classified as a type 1 MI.[8] Less commonly, ACS may occur due to an acute mismatch between oxygen supply and demand (eg, coronary vasospasm, coronary embolism, coronary artery dissection, concomitant condition that acutely increases oxygen demand). When the latter results in myocardial injury, it is classified as a type 2 MI.[8] Other classifications of MI include patients who suffer cardiac death with symptoms suggestive of myocardial ischemia for whom biomarker detection is not possible (type 3), MI associated with PCI-related myocardial injury (type 4), and MI associated with CABG surgery (type 5).[8]

PATHOPHYSIOLOGY

The “Vulnerable Plaque”

The basic pathophysiologic process leading to an ACS event typically involves rupture of an atherosclerotic plaque and subsequent thrombus formation. This thrombus formation produces an abrupt decrease in myocardial blood flow and oxygen supply leading to ischemia and potentially death of myocytes and infarction.[9] The development of atherosclerotic plaques is complex and discussed in detail in Chapter 31, “Dyslipidemia.” It is important to note that the atherosclerotic plaques that produce demand-driven angina in patients with SIHD are different than those that produce an ACS. The atherosclerotic plaques in patients with SIHD typically have thicker fibrous caps, and rarely rupture. The atherosclerotic plaques that rupture in patients with ACS typically have thin fibrous caps.[10] The plaques in patients with ACS also have a

larger cholesterol necrotic core while those in patients with SIHD are more likely to be solidified with calcium deposits. Atherosclerotic plaques that rupture in patients with ACS tend to be “nonobstructive”, occluding less than 70% of the luminal diameter. Thus, patients with nonobstructive plaques may not experience angina symptoms prior to plaque rupture due to adequate autoregulation to maintain blood flow and oxygen supply in times of increased myocardial oxygen demand (coronary autoregulation is discussed in Chapter 32, “Stable Ischemic Heart Disease”). Therefore, patients are often unaware they have atherosclerotic plaques until the ACS event occurs.

The fibrous cap of an atherosclerotic plaque is what separates its lipid core from circulating platelets and coagulation factors in blood. The cap initially is normal arterial intima or thickened intima tissue. As the atherosclerotic plaque grows this is replaced and expanded by fibrous tissue with high amounts of type 1 collagen.[11] As previously discussed, thinner fibrous caps are often referred to as “vulnerable plaques” that are more prone to rupture and produce an ACS. One study demonstrated the mean thickness of the fibrous cap in ruptured plaques to be only 23 μm, with 95% of fibrous caps being less than 65 μm. Fibrous caps 80 μm or more almost never rupture. The thinning of the fibrous cap involves both an increased breakdown of collagen in the fibrous matrix, and a reduction in collagen production to restore the structure of the fibrous cap. Inflammatory processes are involved with both mechanisms.

The reduction in collagen production originates from a reduction in the number of secretory smooth muscle cells within the plaque, and a reduction in the synthesis within these cells.[11,12] Alteration of collagen synthesis and breakdown by macrophages and T cells demonstrates the significant role inflammation plays in thinning and weakening of the fibrous cap and increasing potential for plaque rupture triggering an ACS event.[11–13] Altering the role of these inflammatory processes continues to be an active area of investigation to prevent and treat patients with atherosclerosis and ACS.

A thinning fibrous cap by itself does not usually produce plaque rupture. There is typically a connection to physiological or psychological stress which enhances the likelihood of an acute event.[14,15] Approximately two-thirds of ACS events occur in the morning. This is likely related to circadian rhythm activation of the sympathetic nervous system and catecholamine release that produces an increase in heart rate, blood pressure, and vasoconstriction. An increase in catecholamines may occur due to physical and emotional stress. These changes in conjunction with a thin fibrous cap place patients at risk for ruptured atherosclerotic plaque and subsequent ACS.

Plaque Rupture and Clot Formation

The process of thrombus formation at the site of the ruptured atherosclerotic plaque is complex. Thrombus formation involves platelets and the coagulation cascade. While these two components of thrombus formation are often described separately, they are intertwined and each depends on the other.[16] These components do not contribute equally to thrombus formation in all vascular types. In venous thrombosis, the coagulation cascade dominates thrombus formation and platelets play a more minor role. In arterial thrombosis, such as ACS, platelets dominate, with the coagulation process having less contribution. This is evident by the use of pharmacotherapy in each vascular type. Prevention and treatment of venous thrombosis utilizes anticoagulant agents almost exclusively, while patients with arterial thrombosis are treated with two, and sometimes three, antiplatelet agents and only a short duration of a single anticoagulant agent.

Upon plaque rupture, the barrier between the necrotic core of the plaque and blood components is breached.[16] Circulating platelets are initially attracted and adhere to the area of injury. The adhesion of these initial platelets occurs via platelet glycoprotein (GP) VI receptors binding to collagen within the damaged fibrotic cap, as well as platelet GP Ib-IX receptors and von Willebrand factor. Platelets may then be activated by numerous substances including collagen, thrombin, thromboxane A_2, adenosine diphosphate (ADP), epinephrine, and serotonin. These substances have different potency in their ability to activate platelets, with thrombin (from the clotting cascade) and collagen being the strongest activators. Each of these activators has individual receptors found on the platelet surface (eg, $P2Y_{12}$ receptor for ADP, protease-activated receptor [PAR]-1 for thrombin).

Once an activator binds to its specific receptor a chain reaction is initiated within the platelet with an influx of calcium leading to multiple changes in the platelet.[16] During platelet activation, the platelet changes shape from a disc-like structure to a polymorphic structure with protruding arms that significantly increases the surface area of the platelet. Granules with high concentrations of platelet activators (eg, thromboxane A_2, ADP, serotonin) make their way to the surface of the platelet and release their contents into the circulation. This leads to additional localized activation of platelets that have not adhered to the area of vascular injury. The activated platelet is also the location of the assembly of the tenase and prothrombinase complex that produce most of the activated factor Xa and IIa (thrombin) in the coagulation cascade. Therefore, this represents the

interface between platelets and the clotting cascade in thrombosis. Finally, platelet activation leads to expression of active GP IIb/IIIa receptors. On a resting platelet there are approximately 40,000 to 50,000 GP IIb/IIIa receptors in a dormant form.[16] Upon platelet activation, an additional pool of these receptors converts from intracellular to extracellular, providing a total of 90,000 to 100,000 GP IIb/IIIa receptors, making it the most abundant receptor found on any cell in the body. Through activation, the GP IIb/IIIa receptors undergo a conformational change that exposes the binding site. The main ligand that binds to this receptor is fibrinogen, a linear molecule with a binding site for GP IIb/IIIa on each side. Therefore, each fibrinogen can bind to a GP IIb/IIIa receptor on different platelets, linking those platelets together. The linking of platelets together via the GP IIb/IIIa receptors and fibrinogen is the process of platelet aggregation. Hence, the process of platelet adhesion, activation, and aggregation produce a platelet plug in the area of atherosclerotic plaque rupture.

The platelet plug by itself is rarely enough to significantly occlude myocardial blood flow and oxygen supply.[14] A fibrin meshwork then forms within and on top of the platelet plug that more completely traps cellular components such as red blood cells and produces the abrupt reduction in myocardial blood flow. The formation of this fibrin meshwork involves activation of the clotting cascade.

Initiation of the clotting cascade begins with the interaction and activation of factor VII and tissue factor.[16] Tissue factor is found in endothelial cells, as well as on macrophages at the site of the ruptured fibrous cap. This tissue factor–factor VIIa complex is able to activate small amounts of factor X, which then can activate small amounts of thrombin (factor IIa). The amount of thrombin produced during this initiation phase of coagulation is not enough to promote thrombosis. However, this initial amount of thrombin activates factor VIII. Activated factor VIII (factor VIIIa), with factor IXa (produced from the tissue factor–factor VIIa complex as well as factor XIa), creates the tenase complex on the platelet surface which activates large amounts of factor X. The initial thrombin produced also activates factor V. Activated factor V (factor Va) and activated factor X (factor Xa produced from the tenase complex) create the prothrombinase complex on the surface of the activated platelet where the majority of the thrombin involved in thrombosis is produced. Thrombin is now able to convert fibrinogen into fibrin, which creates the meshwork in the thrombosis and solidifies the clot. Thrombin also activates factor XIII, which provides additional clot stability, continues the positive feedback with creation of factors VIIIa and Va, as well as provides significant platelet activation via PAR-1

receptors.

Thrombus formation in the area of atherosclerotic plaque rupture produces an abrupt reduction in myocardial blood flow and oxygen supply. This abrupt blockage produces ischemia and, if untreated, potentially infarction which results in myocyte necrosis and cell death.[10,14,15] Therefore, early recognition and prompt initiation of treatment can limit ACS-related sequelae. Determinants on the progression to infarction and even the extent of infarction depends on a number of factors. These may include both the location and size of the thrombus, activity of the endogenous fibrinolytic system, as well as the extent of collateral circulation.[14,15]

Ventricular Remodeling After MI

In the setting of MI, acute and chronic adaptations occur to prevent hemodynamic collapse that may also lead to ventricular remodeling and the development of post-MI complications. Similar to what occurs locally within the infarct-related artery, inflammation at the site of myocardial injury plays a key role in ventricular remodeling. In addition, stimulation of the neurohormonal systems occurs and contributes to this process.

In patients who experience a decrease in cardiac output following MI, stimulation of both the sympathetic nervous system (SNS) and renin–angiotensin–aldosterone system (RAAS) occurs to compensate for the decrease in cardiac output similar to what is observed in patients with acute and chronic heart failure (see Chapter 35, “Chronic Heart Failure” and Chapter 36, “Acutely Decompensated Heart Failure”). Activation of the SNS is immediate, resulting in increased contractility, heart rate, and peripheral resistance.[17] However, because synthesis of components of the RAAS are dependent on an increase in mRNA and protein levels, the response is slower.[17] Stimulation of the RAAS results in sodium and water retention as well as peripheral vasoconstriction in an attempt to maintain adequate hemodynamics and perfusion. Vasopressin and endothelin are also released following MI but play a lesser role.[17]

Following MI, some patients experience chronic hyperactivity of either or both the SNS and RAAS, both of which contribute to adverse cardiac remodeling.[17] Chronic hyperactivation of the SNS leads to desensitization and downregulation of β_1-adrenergic receptors, modification of the excitation–contraction coupling mechanism, ventricular hypertrophy, and further impairment of contractility and cardiac output. Likewise, increased production of both angiotensin II and aldosterone via chronic hyperactivation of the RAAS

leads to ventricular hypertrophy. Angiotensin II also increases oxidative stress, release of inflammatory mediators, and collagen deposition, each of which contributes to myocardial fibrosis, or scarring. While myocardial fibrosis is essential for tissue repair following MI, its development impairs ventricular contraction and elasticity. This can lead to the thinning of the left ventricular wall and eventually to the development of a dilated cardiomyopathy.

Complications

Depending on the extent and area of ischemia, various complications are possible in patients with ACS, particularly those with MI, which can manifest hours to weeks after the index event.[18] Electrophysiologic disturbances including ventricular arrhythmias, bradyarrhythmias, and heart block are possible and may occur either in the acute phase of the ischemic event due to electrical instability generated during myocyte destruction or in the recovery phase due to ventricular remodeling. Heart failure is possible depending on the extent of myocardial necrosis and subsequent impairment of ventricular contractility. In fact, approximately 5%–6% of patients with STEMI develop cardiogenic shock, an acute, severe form of heart failure associated with hypotension, systemic hypoperfusion, and poor outcomes.[18] Myocardial rupture of the papillary muscle, ventricular septum, or free wall of the ventricle are possible within the first 10 days of infarction due to extensive myocyte necrosis in those areas.[18] Thromboembolism, including stroke, is also possible due to embolization of left ventricular thrombi that can form due to infarct-related ventricular aneurysm or left ventricular dysfunction. Pericarditis, an autoimmune-mediated inflammation of the pericardium, can occur weeks after an MI, particularly after a large infarct.[18] Many patients with ACS develop depression during the convalescent period.

Signs and Symptoms

2 The symptoms and clinical presentation of ACS are similar to those of stable angina (see Chapter 32). The “classic” presentation of ACS is abrupt onset of substernal chest pain often described as a sensation of squeezing, heaviness, or tightness in the chest that may radiate, typically to either or both arms or shoulders (radiation to the left side is more common), the neck, or the jaw. Patients with ACS may also experience diaphoresis, nausea, vomiting, and dyspnea. Many patients—as many as one-third—with ACS may present with

atypical symptoms that do not include chest pain.[1] Atypical symptoms include epigastric pain, indigestion, stabbing, or pleuritic chest pain, and increasing exertional dyspnea, the latter representing the most common “angina equivalent.”[2] Older adults (75 years of age or older), women, and patients with diabetes mellitus (DM), impaired renal function, and dementia are more likely to present with atypical features.[2]

2 Features that differentiate ACS from stable angina include symptom severity and duration. Unlike SIHD, patients with ACS often experience symptom durations lasting 10 minutes or longer.[2] New or worsening symptoms or a change in symptom pattern (eg, acute increase in frequency or severity, occurring at rest or minimal exertion, longer duration) may be indicative of ACS.[1,2]

On physical examination, there are no specific findings indicative of ACS. In fact, the physical examination may be normal in many patients. Acute myocardial ischemia can cause a S_4 or paradoxical splitting of S_2 on auscultation, but these are nonspecific findings. Rather, clinicians should evaluate for the presence of complications of MI (eg, HF, new murmur of mitral regurgitation due to papillary muscle dysfunction) which, if present, should expedite the evaluation and therapeutic interventions.[2]

12-Lead Electrocardiogram

2 The presenting electrocardiogram (ECG) is critical for expeditious risk stratification and triage of patients presenting with ACS. Patients with possible ACS should have a 12-lead ECG performed and interpreted within 10 minutes of presentation to an emergency department (ED).[2] Ideally, a 12-lead ECG should be performed by emergency medical services (EMS) providers and communicated to the ED staff prior to hospital arrival in order to expedite reperfusion, if necessary.[1] Electrocardiographic changes suggestive of acute ischemia include ST-segment elevation or ST-segment depression of 0.05 mm or greater and T-wave inversion of at least 1 mm in at least two contiguous leads (**Fig. 33-1**).[2,8] Except for leads V_2-V_3 where greater ST-segment elevation is required, when ST-segment elevation of at least 1 mm is present in patients suspected of having ACS, the presumptive diagnosis of STEMI is made and the patient should be considered for emergent reperfusion therapy (Fig. 33-1).[1,8] In addition, the presence of new left bundle–branch block (LBBB) in patients suspected of having ACS is strongly suggestive of acute MI and has been

considered a STEMI equivalent.[1] However, because new LBBB occurs infrequently, a prior 12-lead ECG should be reviewed, if available, to determine if the LBBB is new or old. Patients with a high suspicion of ACS but with a normal ECG on presentation should have serial ECGs performed (eg, every 15–30 minutes for the first hour) to detect ischemic changes.[2] In approximately 1%–6% of patients with ACS, often those with occlusions of the left circumflex or right coronary arteries, the 12-lead ECG may be normal or “electrically silent.” Therefore, appropriate evaluation and risk stratification for patients with ACS must incorporate the evaluation of the patient’s medical history, presenting symptoms, ECG findings, and biomarkers.

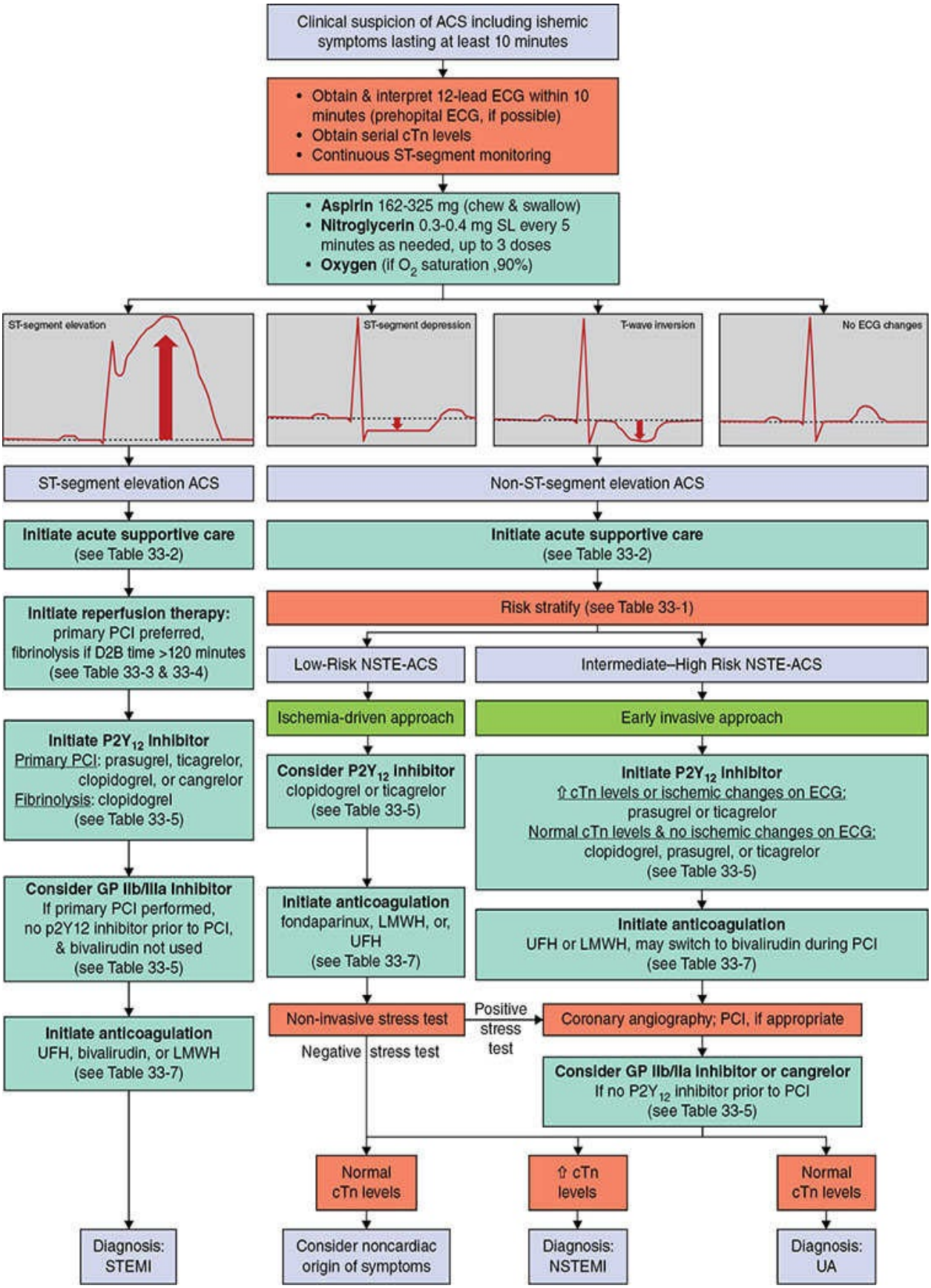

Clinical suspicion of ACS including ischemic symptoms lasting at least 10 minutes
• Obtain & interpret 12-lead ECG within 10 minutes (prehopital ECG, if possible)
• Obtain serial cTn levels
• Continuous ST-segment monitoring
• Aspirin 162-325 mg (chew & swallow)
• Nitroglycerin 0.3-0.4 mg SL every 5 minutes as needed, up to 3 doses
• Oxygen (if O2 saturation ,90%)
ST-segment elevation
ST-segment depression
T-wave inversion
No ECG changes
ST-segment elevation ACS
Non-ST-segment elevation ACS
Initiate acute supportive care (see Table 33-2)
Initiate acute supportive care (see Table 33-2)
Initiate reperfusion therapy: primary PCI preferred, fibrinolysis if D2B time >120 minutes (see Table 33-3 & 33-4)
Risk stratify (see Table 33-1)
Low-Risk NSTE-ACS
Intermediate–High Risk NSTE-ACS
Ischemia-driven approach
Early invasive approach
Initiate P2Y12 inhibitor
Primary PCI: prasugrel, ticagrelor, clopidogrel, or cangrelor
Fibrinolysis: clopidogrel
(see Table 33-5)
Consider P2Y12 inhibitor
clopidogrel or ticagrelor
(see Table 33-5)
Initiate P2Y12 inhibitor
⇧ cTn levels or ischemic changes on ECG:
prasugrel or ticagrelor
Normal cTn levels & no ischemic changes on ECG:
clopidogrel, prasugrel, or ticagrelor
(see Table 33-5)
Consider GP IIb/IIa inhibitor
If primary PCI performed, no p2Y12 inhibitor prior to PCI, & bivalirudin not used
(see Table 33-5)
Initiate anticoagulation
fondaparinux, LMWH, or, UFH
(see Table 33-7)
Initiate anticoagulation
UFH or LMWH, may switch to bivalirudin during PCI
(see Table 33-7)
Initiate anticoagulation
UFH, bivalirudin, or LMWH
(see Table 33-7)
Non-invasive stress test
Positive stress test
Coronary angiography; PCI, if appropriate
Negative stress test
Consider GP IIb/IIa inhibitor or cangrelor
If no P2Y12 inhibitor prior to PCI
(see Table 33-5)
Normal cTn levels
⇧ cTn levels
Normal cTn levels
Diagnosis: STEMI
Consider noncardiac origin of symptoms
Diagnosis: NSTEMI
Diagnosis: UA

FIGURE 33-1 Evaluation and initial management of patients with suspected ACS.
(ACS, acute coronary syndrome; CABG, coronary artery bypass graft; cTn, cardiac troponin; D2B, door-to-balloon; ECG, electrocardiogram; GP, glycoprotein; LMWH, low-molecular-weight heparin; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; SL, sublingual; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina; UFH, unfractionated heparin.)

Cardiac Troponin

The cardiac troponins (cTn) are part of the contractile apparatus of myocardial cells and are the most sensitive and specific biomarkers for detecting myocardial injury.[2,8] Within 2–4 hours of myocyte injury or necrosis, these proteins are released into the bloodstream resulting in elevated blood levels (exceed the 99th percentile of the upper reference limit).[2,8] The emerging high-sensitivity cTn assays are capable of measuring relatively low concentrations much earlier in the clinical course of myocardial injury that could not be detected with traditional cTn assays. The use of high-sensitivity cTn assays likely increases the frequency of NSTEMI diagnosis. Elevations in cTn may persist for several days and remain elevated as long as 2 weeks.[2]

CLINICAL PRESENTATION:

Acute Coronary Syndrome

General

- The patient is typically in acute distress and may develop or present with hypertensive crisis, acute heart failure, cardiogenic shock, or cardiac arrest.

Symptoms

- The classic symptom of ACS is abrupt-onset substernal chest pain or discomfort often described as a squeezing, heaviness, or tightness that persists for 10 minutes or longer. Symptoms may radiate to the arms, shoulders, back, abdomen, or jaw. Nausea, vomiting, diaphoresis, or

shortness of breath may also be present.

- Patients likely to present with atypical symptoms include older adults aged 75 years or greater, women, and patients with diabetes, impaired renal function, and dementia.

Signs

- No physical findings are specific for ACS. Nonspecific findings include S_4 or paradoxical splitting of S_2 on auscultation.
- Patients with ACS may present with signs of acute decompensated HF including jugular venous distention, pulmonary edema, and an S_3 on auscultation.
- Patients with ischemia-related papillary muscle dysfunction may present with a new murmur of mitral regurgitation.
- Patients may also present with arrhythmias, including tachycardia or bradycardia, as well as heart block.
- Hemodynamic abnormalities may include hypertension and hypotension or shock.

Laboratory Tests

- Cardiac troponin (cTn, either cTnI or cTnT) is measured at the time of presentation and repeated 3 to 6 hours later to detect myocardial injury; elevated levels in a patient with ACS symptoms, ischemic changes on ECG, or other diagnostic evidence of ischemia confirm the diagnosis of MI. Additional cTn levels should be obtained beyond 6 hours after symptom onset in patients intermediate to high-risk features of ACS but normal cTn levels during serial measurements.
- For patients with ACS symptoms who do not have ST-segment elevation on ECG but an elevated cTn, NSTEMI is the appropriate diagnosis. Patients' ACS symptoms with ischemic changes on ECG but normal cTn may have unstable angina (UA) or an alternative diagnosis.
- Blood chemistry tests are performed with particular attention given to potassium and magnesium, which may affect heart rhythm.
- SCr is measured and CrCl is used to identify patients who are at high risk of morbidity and mortality—dosage adjustments for renally cleared medications may be necessary.
- Baseline complete blood count (CBC) and coagulation tests (aPTT or anti-

Xa levels, INR) should be obtained; most patients will receive antithrombotic therapy and these tests are useful in monitoring for complications related to antithrombotic therapy, including bleeding.

- Fasting lipid panel.

Other Diagnostic Tests

- The 12-lead ECG is the first step in evaluating a patient with ACS. Patients are risk-stratified into two groups: those with ST-segment elevation or its equivalent (STEMI) and those without (NSTE-ACS). Patients with NSTE-ACS may have other ischemic ECG changes including ST-segment depression or T-wave inversion.
- Patients with STEMI, intermediate- to high-risk ACS, and those with recurrent chest discomfort are likely to undergo coronary angiography via a left heart catheterization to diagnose CAD and may be treated with PCI during the procedure.
- Prior to hospital discharge, an assessment of left ventricular (LV) function via echocardiogram or equivalent modality should be performed to identify patients with LV dysfunction (LV ejection fraction [LVEF] less than 40% [0.40]) who are at high risk of death and candidates for guideline-directed medical therapy and device therapy.
- Selected low-risk patients may undergo early stress testing.

Risk Stratification

- A risk assessment that incorporates the clinical presentation, past medical history, ECG, and cTn should be performed to identify high-risk patients and guide therapeutic interventions. One or more of the validated risk estimators (see Table 33-1) should be used for this purpose.

2 There are several nonischemic causes of myocardial injury (eg, HF, myocarditis, Takotsubo syndrome, chronic kidney disease) that result in elevated cTn, particularly if high-sensitivity cTn assays are used.[2,8] Therefore, clinical context is required to establish the diagnosis of ACS. Myocardial injury is considered acute if there is a dynamic rise and/or fall by 20% or more in serial cTn values.[8] In contrast, when using a high-sensitivity cTn assay, the absolute change (in ng/L), rather than a relative change, increases diagnostic accuracy and may be useful is distinguishing an MI from other causes of cTn elevation.[8]

Attention must be paid to the units of measure between traditional and high-sensitivity cTn; they are not interchangeable. When acute myocardial injury is detected (eg, dynamic elevation of cTn) in a patient presenting with ACS symptoms, ischemic changes on ECG, or other diagnostic evidence of ischemia (eg, imaging that demonstrates loss of myocardium or new regional wall motion abnormality, coronary thrombus detected during angiography or autopsy), the diagnosis of MI is appropriate.[8] Classification of MI is made based on the presenting ECG findings. For patients with dynamic cTn elevations whose presenting ECG demonstrated ST-segment elevation of at least 1 mm in two contiguous leads or new LBBB, the diagnosis of STEMI is confirmed.[8] In contrast, for patients with symptoms of ACS without at least 1 mm ST-segment elevation on the ECG at presentation but with dynamic elevation of cTn, the diagnosis of NSTEMI is appropriate.[2,8] Patients with symptoms consistent with ACS but in whom the cTn is not elevated may have UA or an alternative diagnosis.[8]

Given that dynamic changes in cTn are needed to establish the diagnosis of MI, serial cTn levels should be obtained when the patient presents to the emergency department and again 3-6 hours after symptom onset.[2] If the time of symptom onset is unclear from the patient's history, the time of presentation to the ED should be considered the time of symptom onset.[2] For patients with intermediate- to high-risk features of ACS (eg, ECG changes, clinical presentation) but normal cTn values during serial measurements, additional measurement of cTn after the 6 hours may be warranted.[2]

Risk Stratification

2 For patients with ACS, acute risk stratification is essential to determine which patients may benefit from reperfusion therapy, an early invasive approach, or medical management (Fig. 33-1).[1,2] Initial evaluation of risk should include the clinical presentation, past medical history, and both ECG and cTn upon presentation. For example, because STEMI has the highest short-term risk of death, patients with ACS who present with significant ST-segment elevation on ECG should be considered for emergent reperfusion therapy; confirmation of elevated cTn should not delay treatment.

Several risk scoring tools have been developed that predict both short-term and long-term event rates, such as mortality, in patients with ACS (**Table 33-1**).[19–22] Because they have been well-studied and can be easily applied in the clinical setting, the most common among these risk calculators are the

Thrombolysis in Myocardial Infarction (TIMI) risk score for NSTE-ACS and the Global Registry of Acute Coronary Events (GRACE) score. Each of the risk assessment tools incorporates the patient's symptoms, past medical history, ECG, and cTn, while the GRACE score also includes additional clinical indicators. The History, ECG, Age, Risk factors, and Troponin (HEART) score is another tool that can be used to quickly assess the risk of patients presenting to the hospital with chest pain. For each risk estimator, there is a linear relationship between increasing score and the risk of MACE. For example, in patients with NSTE-ACS, the incidence of MACE through 14 days was 4.7% to 8.3%, 13.2% to 19.9%, and 26.2% to 40.9% in the low (TIMI risk score 0–2), intermediate (TIMI risk score 3–4), and high (TIMI risk score 5–7) risk groups, respectively.[19] Compared to both the TIMI and GRACE risk estimators, the HEART score is better at identifying patients who present to the hospital with suspected ACS at low risk of MACE.[23] While this prognostic information is useful, the ability of the risk scoring tools to identify patients with ACS who may benefit from specific therapeutic interventions described below makes them particularly useful in the development of the treatment plan.

TABLE 33-1 Tools to Assess Risk of Major Adverse cardiac Events in Patients with Acute Coronary Syndrome

TIMI Risk Score (STEMI)[21]	TIMI Risk Score (NSTE-ACS)[19]	GRACE Risk Score[20]	HEART Score[22]
Component (points)	**Each component worth 1 point**	**Points for each component vary based on value**	**Component (points)**
Age <65 years (1)	Age ≥65 years	Age	History highly suspicious (2),
Age 65-74 years (2)	≥3 CAD risk factors*	Killip class	moderately suspicious (1),
Age ≥75 years (3)	Known CAD†	Systolic BP	slightly suspicious (0)
HTN, DM, or angina‡ (1)	Aspirin use within 7 days	Heart rate	ECG: significant ST
Systolic BP <100 mm Hg (3)	≥2 angina episodes within 24 hours	Serum creatinine	depression (2), nonspecific
Heart rate >100 bpm (2)	Transient STE or ST depression	Cardiac arrest on admission	repolarization disturbance (1),
Killip class II–IV (2)	Elevated biomarkers (eg, cTn)	Elevated biomarkers (eg, cTn)	normal (0)
Weight <67 kg (1)		ST deviation§	Age: ≤65 years (2), 45-65 years (1),
Anterior STE or LBBB (1)			<45 years (0)
Time to treatment >4 hours (1)			Risk factors for CAD: ≥3 (2),
			1-2 (1), no risk factors (0)
			Troponin: ≥2x ULN (2),
			1-2x ULN (1), ≤ULN (0)
Calculate point total and determine risk for major adverse cardiac events			
Low risk: 0-3 points	Low risk: 0-2 points	Low risk: <109 points	Low risk: 0-3 points
Intermediate risk: 4-5 points	Intermediate risk: 3-4 points	Intermediate risk: 109-140 points	Intermediate risk: 4-6 points
High risk: ≥6 points	High risk: ≥5 points	High risk: >140 points	High risk: ≥7 points

*Risk factors include family history of coronary artery disease, hypertension, hypercholesterolemia, diabetes, and current smoker.

†Prior coronary stenosis ≥50%.

‡History of angina.

§Includes transient ST-segment elevation ≥ 1 mm, ST-segment depression ≥ 1 mm, new T wave inversions ≥ 1 mm, pseudo-normalization of previously inverted T waves, new Q waves, new R wave > S wave in lead V_1, new left bundle branch block.

BP, blood pressure; CAD, coronary artery disease; DM, history of diabetes; cTn, cardiac troponin; ECG, electrocardiogram; GRACE, Global Registry of Acute Coronary Events; HEART, History, Electrocardiogram (ECG), Age, Risk factors, Troponin; HTN, history of hypertension; LBBB, left bundle branch block; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; ST, ST-segment; STE, ST-segment elevation; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; ULN, upper limit of normal.

Online calculator available for TIMI Risk Score (STEMI) at: https://www.mdcalc.com/timi-risk-score-stemi

Online calculator available for TIMI Risk Score (NSTE-ACS) at: http://www.timi.org/index.php?page=calculators

Online calculator available for GRACE score at: http://www.outcomes-umassmed.org/grace/acs_risk/acs_risk_content.html

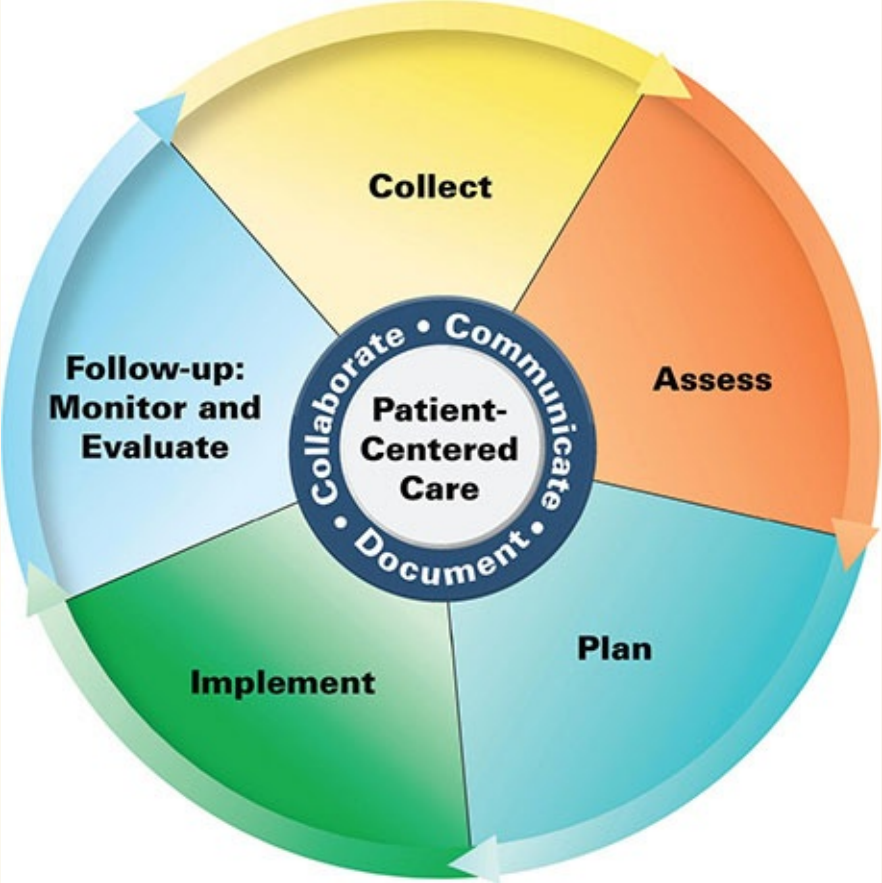
TREATMENT

Treatment decisions for patients with ACS are made based on the initial and

ongoing risk stratification (Fig. 33-1). Rapid identification and delineation of ACS subtype (STEMI, NSTE-ACS) is imperative as treatment goals and timeframes for intervention differ slightly based upon the clinical presentation and subsequent risk of death or complications from the index event (eg, patient with STEMI). When ACS is suspected, the patient should be immediately referred to an ED, chest pain unit, or equivalent facility for evaluation which should include 12-lead ECG and cTn such that expeditious treatment can be initiated.[1,2] Patients with possible ischemic symptoms, particularly if high-risk features (persistent chest pain, severe dyspnea, syncope or presyncope, or palpitations) are present, should be educated to activate the EMS system (eg, call 9-1-1) and seek transport via ambulance as EMS personnel are equipped to treat cardiac arrest should it occurs and this approach is associated with earlier initiation of reperfusion therapy.

Desired Outcomes

In patients with ACS, treatment is aimed at achieving both short-term and long-term outcomes. Short-term desired outcomes in a patient with ACS are as follows: (a) early restoration of blood flow to the infarct-related artery to prevent infarct expansion (in the case of MI) or prevent complete occlusion and MI (in UA); (b) prevention of death and other MI complications; (c) prevention of coronary artery reocclusion; and (d) relief of ischemic chest discomfort. Long-term desired outcomes are control of CAD risk factors, prevention of additional MACE, including reinfarction, stroke, and HF, and improvement in quality of life.



Patient Care Process for Acute Coronary Syndrome

Collect

- Patient characteristics (eg, age, sex, pregnant)
- Description of chest discomfort and/or related symptoms (eg, quality, location, severity, radiation, precipitating factors, palliative measures, time of onset, duration of symptoms)
- Patient medical (personal and family) and social histories (eg, tobacco/ethanol, drugs of abuse [eg, cocaine])
- Current medications with particular attention to phosphodiesterase-5 inhibitors, over-the-counter medications (eg, aspirin-containing medications), and herbals/dietary supplement use
- History of allergy or intolerance to medications
- Objective data

- Blood pressure, heart rate, respiratory rate, height, weight, O_2-saturation, physical exam
- Labs: cardiac troponin (cTn), creatinine, potassium, hemoglobin, platelets, lipid profile
- Diagnostic tests: 12-lead electrocardiogram (ECG); coronary angiogram and stress testing as necessary

Assess

- Description of chest discomfort to determine differential diagnosis and classification of ACS
- Presence of provoking factors (eg, exertion, mental/emotional stress, tachyarrhythmia, high adrenergic state including the use of stimulant medications, exposure to cold)
- Presence/control of risk factors for coronary artery disease (CAD) (eg, hypertension, dyslipidemia, diabetes, smoking, obesity, family history of premature CAD)
- Presence of ACS-related complications (eg, heart failure [HF], cardiogenic shock, arrhythmias, heart block, stroke)
- Previous/recent revascularization procedures (eg, percutaneous coronary intervention [PCI] with/without stenting, coronary artery bypass graft surgery [CABG])
- Presence of ST-segment elevation or equivalent on 12-lead ECG
- Risk for major adverse cardiac events (MACE) (eg, perform risk stratification [see Table 33-1])
- Contraindications or intolerance to medications used to treat/prevent angina symptoms and MACE
- Barriers that may impair adherence to the care plan

Plan*

- Initiate antithrombotic therapy to treat and prevent intracoronary thrombosis as well as drug therapy to alleviate angina symptoms and prevent MACE including specific drug(s), dose, route, frequency, and duration (see Figs. 33-1 and 33-2; Tables 33-2, 33-3, 33-4, 33-5, 33-7, and 33-9).
- Monitoring parameters: efficacy (eg, resolution of signs and symptoms of

angina and ACS-related complications) and adverse effects; frequency and timing of follow-up
- Patient education: purpose of treatment, lifestyle modifications, planned procedures, drug-specific information (eg, indication, dose, route, frequency, adverse effects)
- Self-monitoring for recurrent angina symptoms, signs and symptoms of ACS-related complications, adverse effects, when to seek emergency medical attention
- Address barriers to adherence to medications and lifestyle modification
- Referrals to other providers (eg, primary care provider, endocrinologist, dietician, smoking cessation)

Implement*

- Provide patient education regarding all elements of treatment plan as described above.
- Use motivational interviewing and coaching strategies to maximize adherence.
- Schedule follow-up (eg, usually within 1-2 weeks but no later than 6 weeks after discharge).

Follow-up: Monitor and Evaluate

- Presence of angina symptoms, exercise tolerance, presence/control of CAD risk factors, presence/control of ACS-related complications
- Appropriate use and doses of evidence-based pharmacotherapy for ACS
- Presence of adverse effects and drug–drug interactions
- Patient adherence to treatment plan using multiple sources of information

* *Collaborate with patient, caregivers, and other healthcare professionals.*

General Approach to Treatment

The general treatment approach to ACS includes rapid diagnostic triage to determine an appropriate management strategy (Fig. 33-1). Patients with STEMI are of the highest priority and should be emergently referred to the cardiac catheterization lab for primary PCI with the goal of mechanically restoring blood flow to the infarct-related artery as quickly as possible. Patients with NSTE-ACS

will undergo additional risk stratification to determine the best approach, which is usually an early invasive approach (eg, PCI) for intermediate- and high-risk patients or a more conservative, ischemia-guided management plan without planned PCI for those with either the lowest risk for coronary event or contraindications to the invasive procedure itself (Fig. 33-1). Regardless of treatment strategy planned (early invasive approach or ischemia-guided approach), general treatment measures for intermediate- and high-risk patients include admission to the hospital, oxygen administration (if oxygen saturation is <90% [0.90]), bed rest with continuous multi-lead ST-segment monitoring for arrhythmias and ischemia, frequent measurement of vital signs, ischemic pain relief, and prompt initiation of antithrombotic therapy.

Acute Supportive Care

Historically, clinicians and educators have used the mnemonic MONA (Morphine, Oxygen, Nitroglycerin, Aspirin) as a reminder for acute supportive care interventions to be considered in patients with ACS. However, in recent years, recommendations for the routine use of some of these therapies (eg, morphine, oxygen) have been tempered. Further, MONA ignores other potentially useful interventions to consider in the early phase of ACS treatment. Thus, the mnemonic THROMBINS$_2$ (Thienopyridine, Heparin, Renin-angiotensin-aldosterone system, Oxygen, Morphine, β-blocker, Intervention [eg, PCI], Nitroglycerin, Statin/Salicylate [eg, aspirin]) has been developed as a more contemporary reminder for early interventions to consider in patients with ACS.[24] Acute supportive therapies used to treat patients with ACS are summarized in **Table 33-2**.

TABLE 33-2 Acute Supportive Care Medications Initiated During the Initial 24 Hours of ACS Treatment[1,2,25,26,27]

Drug	Indication (Class of Recommendation)*	Contraindication/Caution	Dose/Administration	Adverse Effects
Morphine	Refractory pain (IIb)	Known hypersensitivity Hypotension Bradycardia Lethargic or moribund patient	STEMI: 4-8 mg IV × 1 (lower dose in elderly), then 2-8 mg IV every 5-15 minutes PRN NSTE-ACS: 1-5 mg IV every 5–30 minutes PRN	Constipation, nausea, vomiting, hypotension, respiratory depression
Oxygen	Oxygen saturation <90% [0.90] (I)	Chronic obstructive pulmonary disease Carbon dioxide retention	2-4 L/min, increasing rate and/or changing to face mask PRN	Increased coronary vascular resistance, decreased coronary blood flow, increased mortality
Nitroglycerin (NTG)	Angina (I) Uncontrolled hypertension (I) Acute heart failure (I)	SBP less than 90 mm Hg or greater than 30 mm Hg below baseline Avoid if recent PDE_5 inhibitor use: Avanafil: within 12 hours Sildenafil: within 24 hours Vardenafil: within 24 hours Tadalafil: within 48 hours Use with caution if RV infarct suspected Avoid abrupt cessation of IV NTG; wean gradually	SL: 0.3-0.4 mg every 5 minutes, up to 3 doses PRN IV: 10 mcg/min titrated to symptom relief and desired blood pressure	Flushing, headache, hypotension, tachycardia
β-blockers	All patients without contraindications (I) *Associated with mortality reduction, especially in patients with HFrEF*	Signs of heart failure Low cardiac output state Risk factors for cardiogenic shock: Age 70 years or greater SBP less than 120 mm Hg Sinus tachycardia (HR greater than 110 bpm) Sinus bradycardia (HR less than 60 bpm) Killip class III Prolonged time from symptom onset High-grade AV block Active asthma or reactive airway disease	Carvedilol 6.25 mg twice daily; target dose is 25 mg twice daily as tolerated Metoprolol Oral: 25-50 mg every 6-12 hours for 2-3 days, then once (metoprolol succinate) or twice daily (metoprolol tartrate); target dose is 200 mg daily IV: 5 mg every 5 min as tolerated up to 3 doses, titrated to BP and HR; should only be considered if BP is uncontrolled or refractory symptoms Continue therapy for at least 3 years, indefinitely in patients with concomitant HFrEF Other β-blockers may be considered; in patients with HFrEF, use either metoprolol succinate, carvedilol, or bisoprolol	Hypotension, heart failure, bradycardia, cardiogenic shock, AV block, exacerbation of asthma or reactive airway disease
Calcium channel blockers	Angina, normal LVEF, and contraindication or intolerance to β-blocker (I) Angina refractory to β-blocker and normal LVEF (I) Coronary vasospasm (I)	Signs of heart failure Low cardiac output state Risk factors for cardiogenic shock: Age 70 y or greater SBP less than 120 mmHg, sinus tachycardia (HR greater than 110 bpm) Sinus bradycardia (HR less than 60 bpm) Killip class III Prolonged time from symptom onset High-grade AV block	Diltiazem 120-360 mg/day orally† Verapamil 240-480 mg/day orally† Amlodipine 5-10 mg orally once daily Nicardipine 60-120 mg/day orally† Nifedipine ER 30-120 mg orally once daily	Hypotension Diltiazem and verapamil: heart failure, cardiogenic shock, bradycardia, AV block

ACS, acute coronary syndrome; AV, atrioventricular; BP, blood pressure; ER, extended release; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; IV, intravenous; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; PDE5, phosphodiesterase-5; PRN, as needed; RV, right ventricular; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction.

*AHA/ACC class of recommendations: I, benefit far outweighs the risk, treatment should be administered; IIb, benefit is equal to or exceeds the risk, additional studies with broad objectives are needed, treatment may be considered.

†Dose and frequency may differ based on formulation.

Nitroglycerin

Nitrates, including nitroglycerin (NTG), are effective anti-ischemic medications and are routinely recommended as part of the initial management of patients with ACS.[1,2] Nitrates promote the release of nitric oxide from the endothelium, which results in venous and arterial vasodilation. Venodilation, the predominant effect, decreases preload, reducing ventricular wall tension and myocardial oxygen demand. The effects on arterial vasodilation are less prominent but may lower systemic vascular resistance and blood pressure at higher doses, thus reducing myocardial oxygen demand. Nitrates also dilate coronary arteries and increase collateral blood flow.

However, the rationale for treating ACS patients with nitrates is extrapolated from an understanding of the pathophysiology of ACS, pharmacology of nitrates, numerous uncontrolled studies, and clinical experience—not their ability to reduce MACE.[2] In the pre-reperfusion era, IV nitrates, including IV NTG, were one of the primary therapeutic interventions and were associated with a 35% reduction in the risk of death.[28] However, there is a paucity of data demonstrating that nitrate administration to patients with ACS in the reperfusion era is effective in providing symptom relief or reducing the incidence of MACE. In two studies randomizing more than 77,000 patients with suspected MI, neither IV NTG (for 24 hours) followed by daily transdermal NTG nor daily isosorbide mononitrate reduced the incidence of MACE.[29,30] Post-infarction angina and cardiogenic shock was lower with the IV followed by transdermal NTG approach but not with the isosorbide mononitrate strategy. More recently, the use of IV sodium nitrite in 229 patients with STEMI treated with primary PCI had no effect on infarct size.[31]

3 Because NTG is effective in relieving angina symptoms, it is often utilized in patients with ACS with ongoing angina who are not hypotensive.[1,2] The recommended use for NTG in patients with ACS is provided in Table 33-2. Initially, SL NTG should be administered every 5 minutes for up to three doses as needed for angina. Patients with persistent angina despite SL NTG, IV NTG should be considered, particularly in patients with uncontrolled HTN or evidence of HF on presentation. Because NTG dilates coronary arteries, it is useful in treating ACS related to vasospasm, particularly if cocaine intoxication is thought to be contributory. In fact, in patients with cocaine-induced chest pain, IV NTG is often the initial anti-ischemic medication recommended, especially if uncontrolled HTN is present.[32] Intravenous NTG should be continued until

symptoms have resolved, blood pressure is controlled, and heart failure symptoms have subsided. Hemodynamic tolerance to IV NTG can occur, requiring higher doses with prolonged therapy. Because abrupt cessation of IV NTG can precipitate angina symptoms, the infusion should be gradually weaned.[33] The most significant adverse effects of nitrates are flushing, headache, hypotension, and tachycardia. Because a synergistic reduction in blood pressure can occur leading to hypotension, nitrate administration is contraindicated in patients who have recently taken oral phosphodiesterase-5 inhibitors (Table 33-2).[1,2,34]

Morphine

Intravenous morphine is a potent analgesic and anxiolytic agent that also causes venodilation and increases vagal tone which reduces heart rate.[1,2] The analgesic and anxiolytic effects may improve patient comfort while the hemodynamic effects may reduce oxygen demand thereby making IV morphine an attractive treatment option in patients with ACS. However, randomized clinical trials have not been conducted to determine the optimal dose nor evaluate the safety and efficacy of IV morphine in patients with ACS.

The results of observational studies have called into question the safety of routinely using IV morphine to treat ACS. One analysis of registry data from 57,039 patients found that patients treated for NSTE-ACS with IV morphine had higher rates of in-hospital death. More recently, while the use of IV morphine had no effect on in-hospital outcomes in patients with STEMI, it was associated with longer hospital stays and larger infarct sizes in patients with NSTEMI in an observational analysis of 3,027 patients.[35]

A proposed mechanism for the adverse outcomes associated with IV morphine in patients with ACS is the presence of a drug–drug interaction with $P2Y_{12}$ inhibitors. Morphine stimulates opioid receptors in the GI tract leading to inhibition of gastric emptying, which may slow the absorption of the antiplatelet.[36] Additionally, common side effects of morphine include nausea and vomiting. Studies have demonstrated that coadministration of IV morphine and $P2Y_{12}$ inhibitors prolongs the time to peak concentrations, decreases total drug exposure, and produces less platelet inhibition.[36]

3 Currently, there is uncertainty regarding the role of IV morphine in patients with ACS. In patients with STEMI, current guidelines state that IV morphine is the drug of choice for pain relief but do not provide a class recommendation.[1] In NSTE-ACS, the use of IV morphine is recommended only

in patients refractory to treatment with other anti-ischemic medications (Class IIb recommendation).[2] If IV morphine is used to treat patients with ACS, doses between 1 and 5 mg every 5-30 minutes are recommended (Table 33-2).[1,2] While nausea and vomiting are common, the most serious adverse effects to monitor are hypotension and respiratory depression.

Oxygen

Although routine oxygen is often administered to patients with ACS, it should be reserved for a minority of patients, particularly those with oxygen saturation less than 90% [0.90].[1,2] Emerging data suggest that routine use of oxygen may adversely affect patients with ACS by increasing coronary vascular resistance and reducing coronary blood flow.[1,2] A recent pooled Cochrane review of five studies revealed that routine use of supplemental oxygen to patients treated for MI was of no benefit with signals suggesting infarct size may be increased.[37]

β-Blockers

Because β-blockers not only possess beneficial anti-ischemic effects but also lower the risk of MACE, their use is recommended for all patients with ACS without contraindications.[1,2] β-Blockers antagonize the β_1-adrenergic receptors causing a decrease in heart rate, contractility, blood pressure, and, subsequently, myocardial oxygen demand. Additionally, the reduction in heart rate increases diastole, prolonging myocardial perfusion time. β-Blockers increase coronary blood flow to ischemic myocardium by increasing coronary collateral resistance, preventing the shunting of blood away from ischemic areas.[38] The reduction in myocardial oxygen demand coupled with improved coronary blood flow to ischemic areas make β-blockers effective anti-ischemic medications in patients with ACS.

The anti-ischemic effects described above also contribute to the reduction in risk of MACE observed in patients with ACS treated with β-blockers. The risk of reinfarction and post-infarction angina is reduced in patients with MI treated with β-blockers.[39,40] Additionally, β-blockers have been shown to improve survival in patients with MI, although this benefit has been questioned in recent years. Propranolol was studied in one of the earliest, large-scale clinical trials to demonstrate that the long-term use of β-blockers reduced mortality.[41] However, like many β-blocker trials in MI, this study was conducted in the pre-reperfusion era. A contemporary trial conducted in the reperfusion era randomized 45,852

patients with MI to early IV followed by oral metoprolol in a 2x2 factorial design that also compared DAPT to aspirin alone.[42] Although metoprolol was associated with reductions in reinfarction, ventricular fibrillation, and arrhythmic death, all-cause mortality and the composite endpoint of death, reinfarction, ventricular fibrillation, or other arrest were not different between the metoprolol and placebo groups through a mean follow-up of 15 days. Consistent with this theme, a meta-analysis of 60 trials (102,003 patients) evaluating β-blockers in MI found a modest mortality benefit for studies conducted during the pre-reperfusion era but no benefit was observed in studies completed during the reperfusion era.[39] Some of the uncertainty regarding the mortality stems from variations in the duration of therapy and follow up in many of the trials. One meta-analysis found β-blockers had no influence on the odds of death in short-term trials (up to 6 weeks of treatment) but were associated with a 23% lower risk in long-term trials (treatment durations of 6-48 months).[40] A recent observational study of 2,753 patients with MI found that for patients treated with β-blockers at hospital discharge 5-year mortality was approximately 30% lower; however, the benefits were no longer statistically significant for those continuing therapy beyond one year.[43]

4 Although the mortality benefit of β-blockers in the reperfusion era is uncertain, because they reduce the risk of MI, angina, and arrhythmias, in the absence of contraindications, current guidelines recommend the initiation of oral β-blockers within the first 24 hours of presentation and continuation of therapy for at least 3 years (Table 33-2).[1,2,25] Although several β-blockers have been studied in the setting of ACS, the most commonly used agents are metoprolol and carvedilol largely due to the mortality benefit associated with their use in the treatment of HF, a common complication of ACS. The most serious adverse effects observed in patients with ACS treated with β-blockers include HF, hypotension, bradycardia, and cardiogenic shock.[42] Therefore, in patients with evidence of or risk of developing these complications, β-blocker therapy should be withheld and initiation reassessed later during hospitalization.[1,2] Advanced age (70 years or older), presenting systolic blood pressure less than 120 mm Hg, sinus tachycardia (heart rate greater than 110 bpm) or bradycardia (heart rate less than 60 bpm) upon presentation, Killip class III (eg, pulmonary edema), and prolonged time from symptom onset are patient characteristics associated with an increased risk of cardiogenic shock for whom β-blocker initiation should be postponed.[1,2,42] While β-blocker initiation should be avoided in patients with ACS and decompensated HF due to left ventricular dysfunction, commencement of β-blocker therapy prior to discharge once HF symptoms have been stabilized

is safe, has been associated with lower mortality, and should be considered for all patients with ACS and compensated HF with reduced ejection fraction (HFrEF).[2,44] For patients with ACS and acute intoxication with cocaine or methamphetamine, β-blockers should be avoided unless a concomitant coronary vasodilator is also used to minimize the risk of causing or potentiating coronary vasospasm via unopposed α_1-adrenergic stimulation.[2,32,45] Because early initiation of IV β-blockers has been associated with an increased risk of heart failure and cardiogenic shock, parenteral therapy should be reserved for patients with STEMI who have acute, uncontrolled HTN or refractory symptoms and no contraindications.[1] For patients with ACS and concomitant left ventricular dysfunction (left ventricular ejection fraction [LVEF] less than 40% [0.40]), β-blocker therapy is often lifelong, whereas the recommended duration of therapy for patients with ACS and normal LVEF is at least three years.[1,25]

Calcium Channel Blockers

Calcium channel blockers (CCBs) possess beneficial anti-ischemic effects and are recommended for some patients with ACS, particularly those who are unable to take β-blockers.[1,2] CCBs cause arterial vasodilation, including coronary vasodilation, decreasing peripheral resistance, afterload, blood pressure, and myocardial oxygen demand.[38] All CCBs are also negative inotropes. However, because dihydropyridine (DHP) CCBs are potent peripheral vasodilators, they cause a baroreceptor-mediated increase in sympathetic activity that negates their negative inotropic effect.[38] Non-DHP CCBs decrease sinoatrial node activity and slow atrioventricular node conduction resulting in a decreased heart rate.[38]

4 Although CCBs are effective as anti-ischemic agents, reports of harm, lack of consistent benefit in clinical trials, and the robust data supporting β-blockers have narrowed the indications for CCBs in patients with ACS. While individual trials have found diltiazem and verapamil lower the risk of reinfarction and post-infarction angina, a systematic review of 28 trials (19,000 patients) investigating CCBs for the treatment of ACS failed to demonstrate a beneficial effect on mortality, MI, or recurrent MI.[26,27,46] Consequently, current guidelines recommend non-DHP CCBs (eg, diltiazem, verapamil) to treat angina symptoms in patients with ACS who have a contraindication, have intolerance, or are refractory to β-blockers in the absence of left ventricular dysfunction, risk factors for cardiogenic shock, and atrioventricular conduction defects (Table 33-2).[1,2] Because of their ability to dilate coronary arteries, long-acting CCBs are recommended in patients with ACS with known or suspected vasospasm.[2]

However, if vasospasm is secondary to cocaine intoxication, the use of CCBs should be considered only after treatment with IV NTG and benzodiazepines.[32,45] Although long-acting formulations may be reasonable, immediate release nifedipine should be avoided as it has been associated with an increased mortality risk in patients with CAD, including those with ACS.[2,47] The most common adverse effects associated with the use of non-DHP CCBs in patients with ACS include heart block, bradycardia, hypotension, and GI disturbances.

Treatment Strategies in STEMI

The widespread use of reperfusion during ACS is responsible for the dramatic decrease in MI-related mortality over the past three decades in the United States.[48] Reperfusion strategies include fibrinolytics and mechanical intervention via PCI with or without stenting, both with the aim of restoring blood flow to the infarct-related artery. Appropriate choice and timing of reperfusion in ACS to facilitate revascularization are critical in STEMI to improve outcomes. Strategies to reduce delays in reperfusion include prehospital assessment of the initial ECG by EMS, early anti-ischemic medication administration, and transport to a hospital with PCI capable facilities.

Primary PCI

5 In STEMI, the degree of myonecrosis is curvilinear, with the maximum amount of damage occurring in the first few hours of infarction.[49] Therefore, prompt efforts to restore blood flow to the infarct-related artery are paramount. During PCI, mechanical reperfusion is performed using intracoronary balloons, stents, and other devices. The reader is referred to Chapter 32 for a more detailed description of both coronary angiography and PCI. Compared to reperfusion with fibrinolysis, primary PCI improves survival, establishes consistent revascularization to the infarct-related artery, significantly reduces the risk of stroke and intracranial hemorrhage, and reduces reinfarction and recurrent ischemia. More rapid performance of primary PCI can result in superior clinical outcomes for patients with STEMI.[1,50,51] In a study of 29,222 patients with STEMI treated with primary PCI from the National Registry of Myocardial Infarction, the adjusted odds ratio for in-hospital death was 1.42 (95% confidence interval 1.24-1.62) when the door-to-balloon time was more than 90 minutes compared to 90 minutes or less.[52] In the United States, quality improvement programs have reduced mean door-to-balloon times from 120

minutes to 87 minutes, decreasing the in-hospital mortality rate from 8.3% to 6.6%.[53] Therefore, early reperfusion with primary PCI is of upmost importance and is preferred by guidelines for patients presenting with STEMI, with the goal of reperfusion within 90 minutes from time of first medical contact.[1] However, in the United States, only 39% of all hospitals can perform PCI.[54] Given the benefits of primary PCI, it is recommended that patients presenting with STEMI to a hospital unable to perform PCI be transferred to a PCI-capable hospital to achieve reperfusion within 120 minutes of the first medical contact.[1] Every minute delay results in additional myocardial cell damage that may be irreversible. Patients with STEMI undergoing primary PCI also require adjunctive antiplatelet and anticoagulant therapy which is discussed in greater detail later in this chapter.[1]

Fibrinolysis

5 When primary PCI for patients with STEMI is not possible within a timely fashion, fibrinolysis is an important means of reperfusion and prevents 30 early deaths per 1000 patients treated within 6 hours of symptom onset.[55] Based on mortality data from a propensity-matched observational study of more than 19,000 STEMI patients, the mortality advantage of primary PCI over fibrinolysis is lost when primary PCI is delayed more than 121 minutes.[56] While an exact time frame is debatable, recent guidelines state that fibrinolysis is indicated and should be administered when PCI cannot be performed within 120 minutes.[1] Situations where this may apply include when patients have immediate contraindications to receiving contrast dye, or in cases where patients present to a facility unable to perform PCI and transfer time would exceed 120 minutes, or when patients present at off-peak hours when the catherization laboratory is not adequately staffed. Non-PCI-capable hospitals should aspire to transfer patients with STEMI to a PCI-capable hospital within 30 minutes of arrival (door-in-door-out goal).[1] Yet, when the anticipated time to PCI is expected to exceed 120 minutes, fibrinolytic therapy should be given within 30 minutes of hospital arrival provided no contraindications are present.[1] In fact, for patients with STEMI, the time from hospital presentation until the start of fibrinolytic therapy (door-to-needle time) is a quality performance measure of timely and effective care.[57] In a recent analysis evaluating the timeliness of reperfusion for patients with STEMI, the median door-to-needle time for patients treated with fibrinolytics was approximately 24 minutes with approximately 60% meeting the goal of less than 30 minutes.[58] A coordinated approach among EMS, ED,

cardiology, and pharmacy personnel are needed in order to improve this further.

Indications and contraindications to fibrinolytic therapy are outlined in **Table 33-3**. Fibrinolytic therapy is associated with a slight but statistically significant risk for stroke, largely attributed to intracranial hemorrhage (ICH), which occurs in 0.9%-1.0% of patients.[59] Significant predictors for ICH include advanced age, lower total body weight, female sex, pre-existing cerebrovascular disease, and systolic and diastolic HTN at time of presentation.[59]

TABLE 33-3 Indications and Contraindications to Fibrinolytic Therapy for STEMI[1]

Indications	Absolute Contraindications	Relative Contraindications
Symptoms of acute coronary syndrome with an onset within 12 hours of first medical contact	Any prior hemorrhagic stroke	BP >180/110 mm Hg on presentation or history of chronic poorly controlled hypertension
ST-segment elevation of 1 mm or greater in two contiguous leads or new left bundle branch block on a 12-lead ECG	Ischemic stroke within 3 months (except in past 4.5 hours)	History of ischemic stroke greater than 3 months before
Anticipated that primary PCI cannot be performed within 120 minutes of first medical contact	Intracranial neoplasm or arteriovenous malformation	Recent major surgery (less than 3 weeks before)
	Active internal bleeding	Traumatic or prolonged CPR (greater than 10 minutes)
	Aortic dissection	Recent internal bleeding (within 2-4 weeks)
	Considerable facial trauma or closed-head trauma in past 3 months	Active peptic ulcer
	Intracranial or intraspinal surgery within 2 months	Noncompressible vascular punctures
	Severe, uncontrolled hypertension (unresponsive to emergency therapy)	Pregnancy
	For streptokinase,* treatment within previous 6 months (if considering streptokinase again)	Known intracranial pathology (dementia)
		Oral anticoagulant therapy

BP, blood pressure; CPR, cardiopulmonary resuscitation; ECG, electrocardiogram.

*Streptokinase is no longer marketed in the United States but is available in other countries.

Relative contraindications to fibrinolytic therapy should be mitigated where possible (eg, giving antihypertensive medications to reduce blood pressure to less than 185/110 mm Hg) to reduce the risk for major bleeding, including ICH, prior to administration. Patients at high risk for major bleeding (including a history of ICH) presenting with an absolute contraindication should not receive fibrinolytic therapy and should be transferred to a hospital capable of performing PCI. It is important to weigh the potentially life-saving effect against life-threatening potential for adverse event in those with contraindications to fibrinolytic therapy, taking into consideration alternative options such as delayed PCI. The mortality benefit of fibrinolysis is highest when administered early after symptom onset but is negligible if administered to patients with symptom durations exceeding 12 hours. The use of fibrinolytics between 12 and 24 hours after symptom onset should be limited to patients with clinical and/or

electrocardiographic evidence of ongoing ischemia.[1] Noncerebral bleeding from fibrinolysis has been reported to be as high as 13%.[59]

When fibrinolytic therapy is indicated, a fibrin-specific agent (alteplase, reteplase, or tenecteplase) is recommended over a non-fibrin-specific agent (eg, streptokinase) because of greater reperfusion success and less systemic bleeding with fibrin-specific agents.[1] Any fibrin-specific agent is acceptable as no drug has demonstrated superiority over the others with regard to the mortality benefit.[60] However, a recent meta-analysis demonstrated a trend toward lower risk of major bleeding with tenecteplase compared to other fibrin-specific agents.[60] Therefore, safety considerations along with ease of administration or formulary restrictions may dictate the institutional preference of one agent over another. All hospitals should have protocols addressing fibrinolysis eligibility, dosing, and monitoring. Dosing considerations for the use of fibrinolytics in STEMI are provided in **Table 33-4**.

TABLE 33-4 Fibrinolytic Therapy Dosing in Patients with STEMI[1]

Drug	Dosing Considerations	Comments
Alteplase (tPA)	15 mg IVP over 1-2 minutes, then 0.75 mg/kg (maximum 50 mg) IV over 30 minutes, then 0.5 mg/kg (maximum 35 mg) IV over 60 minutes; total dose not to exceed 100 mg	"Accelerated" 90-minute weight-based infusion
Reteplase (rPA)	10 units IVP over 2 minutes x 2 doses given 30 minutes apart	Double bolus, separated by 30 minutes
Tenecteplase (TNK-tPA)	<60 kg: 30 mg IVP; 60-69 kg: 35 mg IVP; 70-79 kg: 40 mg IVP; 80-89 kg: 45 mg IVP; >90 kg: 50 mg IVP	Single, weight-based (~0.5 mg/kg) bolus administered over 5 seconds*

IVP, intravenous push.

Please refer to Tables 33-4 and 33-5 for appropriate adjunctive antiplatelet and anticoagulant therapy for patients with STEMI treated with fibrinolytics.

*In patients 75 years or older, the dose may be reduced by 50% to decrease the risk of intracranial hemorrhage.[61]

As with primary PCI, antiplatelet therapy and parenteral anticoagulation should be given concomitantly in patients treated with fibrinolytic therapy to

improve vessel patency and to prevent reocclusion.[1] Adjunctive antiplatelet and anticoagulant therapies are discussed later in this chapter.

Despite data suggesting benefit and feasibility of pre-hospital fibrinolysis, administration of fibrinolytic therapy by EMS personnel to patients during transport to the hospital is not routine practice in the United States. Early angiography after fibrinolytic therapy, a practice referred to as a pharmacoinvasive approach, has shown promise in reducing cardiovascular events compared to patients transferred for immediate PCI, yet increased rates of ICH have been implicated with this approach.[48,61] Transfer to a PCI-capable facility for possible "rescue PCI" after fibrinolysis is appropriate for those who fail fibrinolytic therapy and those patients with acute, severe HF or cardiogenic shock.[1]

Treatment Strategies in NSTE-ACS

Early Invasive Approach

While patients presenting with STEMI benefit from immediate reperfusion of the infarct-related artery due to complete arterial occlusion, patients presenting with NSTE-ACS typically have a partially occluded coronary artery with some residual perfusion and, therefore, the need for and urgency to perform PCI is not as critical. With an early invasive approach, the patient has a diagnostic angiography performed early in the hospital course, typically within the first 24 hours, with the intent to perform revascularization if appropriate, depending on the coronary anatomy.[2] An early invasive strategy improves cardiovascular outcomes in patients presenting with NSTE-ACS with the greatest benefits achieved in those patients with the highest risk for MACE. Risk stratification is, therefore, essential in NSTE-ACS to determine which patients will derive the most benefit from an early invasive approach. The benefit of routine invasive therapy is superior to an ischemia-guided approach (a more conservative watch and wait approach) usually in patients with advanced age (older than age 70), previous MI or revascularization, ST-segment changes, HF (especially with left ventricular dysfunction), elevated cTn, DM, and in those with positive results from noninvasive stress tests. Most recent practice guidelines recommend an early invasive strategy in those with an elevated risk for death or MI (eg, GRACE score greater than 140 [see Table 33-1]), those with refractory angina, acute HF, other symptoms of cardiogenic shock, or arrhythmias.[2,62]

Ischemia-Guided Approach ("Medical Management")

In contrast to an early invasive approach, a more conservative management strategy for those with the lowest risk is referred to as an ischemia-guided approach, or "medical management," where antiplatelet and anticoagulant medications are administered and PCI is not initially planned. The patient is evaluated for signs and symptoms of recurrent ischemia or hemodynamic instability and taken for coronary angiography and possible PCI only if recurrent symptoms develop. This strategy is appropriate for those with TIMI risk scores of 0-1, and GRACE score less than 109, for those with serious comorbidities or contraindications to angiography/PCI (eg, renal failure), or when the risks of the procedure outweigh the benefits of revascularization.[2] The ischemia-driven approach is also preferred by guidelines for those with a low likelihood of ACS, in women without troponin elevation, and in those who do not consent for revascularization.[2]

Antithrombotic Therapy

Due to the role of thrombus formation in the setting of ACS, timely and appropriate antithrombotic therapy is an important component of optimal pharmacotherapy. Antithrombotic therapy consists of antiplatelet and anticoagulant therapy. While platelets dominate the pathophysiologic process in arterial thrombosis, the central role of thrombin in both platelet activation and coagulation make both types of therapy necessary in the acute phase of treatment in a patient with ACS. After hospital discharge, most patients are typically continued on long-term antiplatelet therapy only, although evidence for use of long-term anticoagulant therapy after ACS is emerging for some high-risk groups.

One of the most challenging aspects to the use of antithrombotic therapy in patients with ACS is that not all agents have been studied across the spectrum of ACS and its different management strategies. While some agents may have data in the setting of NSTE-ACS, they may not have data in STEMI. For patients with NSTE-ACS, data are different for patients being managed with an ischemia-driven approach compared to those receiving PCI.[2] Some agents may have data in the setting of primary PCI in STEMI, but not with the use of fibrinolytics in STEMI.[1] Lastly, agents may have data in these different settings, but the doses may differ depending on the diagnosis or management strategy.

Therefore, clinicians must know the evidence on appropriate antithrombotic drug use, dose, and duration based on the patient's diagnosis and management strategy to optimize patient outcomes and prevent adverse events.

Antiplatelet Therapy

The use and dosing of antiplatelet therapies for the treatment of ACS are summarized in **Table 33-5**.

TABLE 33-5 Antiplatelet Drug Use and Dosing Across the Spectrum of ACS and Management Strategy[1,2]

	STEMI		NSTE-ACS	
Drug	**Primary PCI**	**Fibrinolytic Reperfusion**	**Early Invasive Strategy**	**Ischemia-Driven Strategy**
Aspirin				
Loading dose	162-325 mg	162-325 mg	162-325 mg	162-325 mg
Maintenance dose	81 mg daily	81 mg daily	81 mg daily	81 mg daily
$P2Y_{12}$ inhibitors				
Clopidogrel				
Loading dose	600 mg	300 mg Age greater than 75 years: No loading dose given	600 mg	300 mg
Maintenance dose	75 mg daily	75 mg daily	75 mg daily	75 mg daily
Prasugrel		No recommendation		No recommendation*
Loading dose	60 mg		60 mg	
Maintenance dose	10 mg daily Weight less than 60 kg: 5 mg daily		10 mg daily Weight less than 60 kg: 5 mg daily	
Ticagrelor		No recommendation		
Loading dose	180 mg		180 mg	180 mg
Maintenance dose	90 mg twice daily		90 mg twice daily	90 mg twice daily
Cangrelor	30 mcg/kg IV bolus, followed by 4 mcg/kg/min IV infusion for at least 2 hours or duration of PCI	No recommendation	30 mcg/kg IV bolus, followed by 4 mcg/kg/min IV infusion for at least 2 hours or duration of PCI	No recommendation
GP IIb/IIIa inhibitor				
Abciximab†	0.25 mg/kg IV bolus, followed by 0.125 mcg/kg/min (maximum 10 µg/min) IV infusion for 12 hours after PCI, OR 0.25 mg/kg IC bolus only	No recommendation	0.25 mg/kg IV bolus, followed by 0.125 mcg/kg/min IV infusion for 12 hours after PCI	No recommendation
Eptifibatide	180 mcg/kg IV bolus x 2 given 10 minutes apart, followed by 2 mcg/kg/min IV infusion started after first bolus and continued for 18-24 hours after PCI CrCl less than 50 mL/min (0.83 mL/s): Reduce infusion by 50% Hemodialysis: Avoid use	No recommendation	180 mcg/kg IV bolus x 2 given 10 minutes apart, followed by 2 mcg/kg/min IV infusion started after first bolus and continued for 18-24 hours after PCI CrCl less than 50 mL/min (0.83 mL/s): Reduce infusion by 50% Hemodialysis: Avoid use	No recommendation
Tirofiban	25 mcg/kg IV bolus, followed by 0.15 mcg/kg/min CrCl less than 60 mL/min (1.0 mL/s): Reduce infusion by 50%	No recommendation	25 mcg/kg IV bolus, followed by 0.15 mcg/kg/min CrCl less than 60 mL/min (1.0 mL/s): Reduce infusion by 50%	No recommendation

CrCl, creatinine clearance; GP, glycoprotein; IC, intracoronary; IV, intravenous; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

*Not mentioned in the ACC/AHA guidelines, but evidence of noninferiority compared to clopidogrel exists. Prasugrel dosing was a 30 mg loading dose followed by 10 mg daily. Patients weighing less than 60 kg or age 75 years or more received a maintenance dose of 5 mg daily.

†Abciximab is no longer available in the United States and Canada; international availability is also very limited.

Aspirin Aspirin, or acetylsalicylic acid, has been a standard part of the treatment of ACS for several decades. Aspirin provides its antiplatelet effect by acetylating a hydroxyl group of serine 530 on the cyclooxygenase (COX)-1 enzyme on platelets, and thereby preventing the conversion of arachidonic acid into a number of prostaglandins, and eventually thromboxane A_2.[63] Thromboxane A_2 produces platelet activation as well as vasoconstriction. While unbound aspirin has a half-life of only about 15-20 minutes, the irreversible binding of aspirin to the platelet COX-1 enzyme inhibits thromboxane A_2–induced platelet activation for the life of the platelet (7–10 days).

6 Aspirin is recommended for all patients with ACS without contraindications, regardless of the type of ACS or the management strategy. The initial dose of aspirin should be 162 to 325 mg (non-enteric coated) given as soon as possible.[1,2] Typically, this is given as 2 to 4 "baby" aspirin (81 mg in the United States) to be chewed and swallowed. The process of chewing allows for faster dissolution time and platelet inhibition in less than 30 minutes compared to about 60 minutes when tables are consumed whole.[63] Patients undergoing PCI for NSTE-ACS or STEMI already receiving chronic aspirin doses of 81 mg daily should be given an additional dose of 81–325 mg before the procedure.[1,2]

After the initial dose of aspirin, daily doses of aspirin should be 81 mg daily and continued indefinitely.[1,2] In a trial of over 25,000 patients with ACS, higher daily maintenance doses of aspirin (300–325 mg) provided no reduction in CV death, MI, or stroke compared to lower daily maintenance doses (75–100 mg), but did produce a significantly higher incidence of gastrointestinal (GI) bleeding with the higher dose regimen.[64]

Contraindications to aspirin include a hypersensitivity to aspirin and major GI intolerance. In these rare cases, clopidogrel with a loading dose followed by a maintenance dose should be used as an alternative.[1,2] While ticagrelor may also be considered, there are no direct comparative data to aspirin available. The main adverse effects of aspirin include dyspepsia and GI bleeding, which is an extension of its inhibition of prostaglandins responsible for GI protection.[63] The use of low-dose and/or enteric-coated aspirin can provide a reduction in these adverse effects. Aspirin with antacid, known as "buffered aspirin," does not provide GI protection. Although most surgical procedures can be conducted with patients on aspirin, it should be discontinued approximately 5 days before the procedure if desired.

6 **P2Y12 Inhibitors** Aspirin is rarely used as the sole antiplatelet agent in

patients with ACS and is typically combined with an oral $P2Y_{12}$ inhibitor as part of dual antiplatelet therapy (DAPT). There are currently three orally administered $P2Y_{12}$ inhibitors (clopidogrel, prasugrel, and ticagrelor) and one intravenous (IV) agent (cangrelor), and their pharmacology is summarized in Table 33-6. Clopidogrel and prasugrel both belong to the chemical class of thienopyridines that are prodrugs requiring hepatic activation. Both agents have a thiol ring that must be opened to expose the sulfur atom. This sulfur then interacts with the sulfur within the $P2Y_{12}$ receptor creating an irreversible disulfide bond. The binding of the thienopyridine agent to the receptor prevents the receptor's ability to be activated by adenosine diphosphate and subsequent platelet activation and aggregation.

TABLE 33-6 $P2Y_{12}$ Inhibitor Pharmacology Comparisons[63,65]

Property	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Brand name	Plavix	Effient	Brilinta	Kengreal
Drug class	Thienopyridine	Thienopyridine	Cyclopentyltriazolopyrimidine	ATP analogue
Absorption	≥50%	80%	36%	100%
Tmax	2 hours	30 minutes	60 minutes	2 minutes
Onset of action	75 mg: 3-5 days			2 minutes
	300 mg: 6-8 hours	10 mg: 3 days	90 mg: 2-3 days	
	600 mg: 2-4 hours	60 mg: 30-60 minutes	180 mg: 60 minutes	
Metabolism (CYP isoenzymes)	Hepatic (2C19, 3A4, 1A2, 2B6)	Hepatic (2B6, 3A4, 2C9, 2C19)	Hepatic (3A4, 2C9)	ATPases in vascular endothelium
Prodrug	Yes	Yes	No	No
$P2Y_{12}$ Binding	Irreversible	Irreversible	Reversible	Reversible
Half-life	6 hours	7 hours	12 hours	3-5 minutes
Platelet recovery after cessation of therapy	~5 days	~7 days	~3 days	1-2 hours

ATP, adenosine triphosphate; CYP, cytochrome p450.

Ticagrelor and cangrelor are not thienopyridines, and therefore do not require hepatic activation to provide their antiplatelet effect. Cangrelor is an adenosine triphosphate analogue and ticagrelor belongs to the chemical class of a cyclopentyltriazolopyrimidine that has structural components similar to adenosine triphosphate. While adenosine diphosphate is a known activator of platelets through the $P2Y_{12}$ receptor, adenosine triphosphate is a known inhibitor

of this receptor. Ticagrelor and cangrelor do not form an irreversible bond with the $P2Y_{12}$ receptor as thienopyridines, but instead bind reversibly in a different location. With ticagrelor and cangrelor, adenosine diphosphate is allowed to bind to the $P2Y_{12}$ receptor, but the signal is blocked and does not lead to platelet activation and aggregation. Hence, ticagrelor and cangrelor are $P2Y_{12}$ receptor inhibitors, just by a different mechanism than thienopyridines. Due to the reversible binding of ticagrelor to the $P2Y_{12}$ receptor, it requires twice daily dosing and cangrelor is given by a continuous infusion.

6 Bleeding risk in patients treated with a $P2Y_{12}$ inhibitors undergoing major surgery is of concern. In patients with ACS treated with a clopidogrel-based DAPT regimen, the risk of CABG-related major bleeding was approximately 50% higher in clopidogrel-treated patients when surgery was performed within 5 days of clopidogrel cessation compared to patients treated with aspirin alone.[66] The risk of CABG-related major bleeding in ACS patients treated with DAPT is more than four times higher with prasugrel than clopidogrel.[67] Consequently, clopidogrel and ticagrelor should be held for at least 5 days and prasugrel should be held for 7 days prior to elective surgery (eg, CABG surgery).[1,2] Because of its short duration of action, cangrelor can be continued until just a few hours before surgery, which is a favorable property of this agent.[65] Given the known bleeding risk associated with $P2Y_{12}$ inhibitor use and CABG, preloading patients with NSTE-ACS with a $P2Y_{12}$ inhibitor prior to PCI is controversial given that some may require CABG surgery. However, the need for urgent or emergent CABG surgery (eg, within 5–7 days) is relatively low (1%–2%). Thus, preloading with $P2Y_{12}$ inhibitors is reasonable, especially in patients with STEMI undergoing primary PCI since CABG surgery is uncommon in these patients.

Clopidogrel Conversion of clopidogrel to its active compound takes two cytochrome P 450 (CYP) enzyme steps.[63] While multiple CYP enzymes take part in this conversion, CYP2C19 is responsible for at least 50% of this conversion. Patients with loss of function alleles (*2 or *3) have demonstrated a reduced ability to convert clopidogrel to its active form and have less platelet inhibition compared to patients with wild-type CYP2C19 (*1). It has also been demonstrated that up to 40% of patients receiving clopidogrel fail to achieve an optimal antiplatelet effect.[68] While there is a fair amount of variability in how the antiplatelet effect is determined, patients who fail to respond adequately to clopidogrel have greater risk for MACE compared to patients with an adequate antiplatelet response. While genetic polyphormisms of CYP2C19 contribute to

the inadequate response to clopidogrel, CYP2C19 status only explains 12%–15% of the variability demonstrated with clopidogrel.[68] Consequentially, lack of response to clopidogrel is multifaceted and can occur in patients with wild-type CYP2C19. Since trials have not demonstrated improved CV outcomes in patients receiving genetic or platelet function testing to date, obtaining this information is not recommended in current guidelines.[1,2] Since proton pump inhibitors are known inhibitors of CYP2C19, concern has been raised about increased risk for MACE in patients receiving these agents with clopidogrel. While the clopidogrel labeling information lists omeprazole and esomeprazole as being contraindicated, clinical evidence supporting this interaction is inconsistent.[68]

Clopidogrel has been extensively evaluated in patients with ACS. The CURE trial (Clopidogrel in Unstable Angina to Prevent Recurrent Events) compared aspirin alone to clopidogrel given as a 300 mg loading dose, followed by 75 mg daily for up to 12 months.[66] Patients receiving DAPT demonstrated a significant reduction in CV death, MI, and stroke compared to aspirin alone. This trial not only demonstrated the efficacy of clopidogrel, but also established DAPT as the standard of care for patients presenting with ACS. Since 80% of the patients in this trial were medically managed, this dosing regimen is used in patients undergoing an ischemia-driven approach for NSTE-ACS.

A 600-mg loading dose provides more potent and faster onset of antiplatelet activity and has demonstrated better efficacy in patients undergoing PCI compared to initially receiving a 300-mg loading dose of clopidogrel. These data come from the results of a large trial (n = 25,086) where the approximately 70% of patients who received PCI benefited from the 600-mg loading dose over the 300-mg loading dose.[64] Patients who received an ischemia-driven approach did best with a 300-mg loading dose as in the CURE trial in regards to efficacy and safety outcomes. These data support the 600-mg clopidogrel loading dose in patients undergoing PCI for NSTE-ACS and STEMI.

Finally, clopidogrel is the only $P2Y_{12}$ inhibitor to be evaluated in large clinical trials in patients with STEMI receiving reperfusion with fibrinolytic therapy. Two trials have demonstrated the efficacy and safety of clopidogrel as part of DAPT in these patients.[69,70] Due to the increased concern of ICH in patients receiving fibrinolytics, only a 300 mg loading dose is used, and patients aged 75 or older do not receive any loading dose.

Prasugrel Prasugrel must also be converted to an active compound through hepatic conversion, but the conversion of prasugrel is more efficient, requiring a

single CYP enzyme step, and multiple enzymes are capable of making the conversion.[38] Consequentially, the ability of prasugrel to be converted to its active compound is not limited and leads to faster and more potent platelet inhibition compared to clopidogrel. Prasugrel was compared to clopidogrel as part of DAPT with aspirin in patients undergoing PCI for NSTE-ACS or STEMI.[67] Prasugrel provided a significant reduction in CV death, MI, or stroke compared to clopidogrel. The benefit of prasugrel was similar in the first few days of therapy, and after the first few days out to 1 year. Therefore, the reduction in these MACE were due to not only more potent early antiplatelet therapy, but also sustained potent antiplatelet therapy.

6 Greater efficacy, however, came at a cost of more non-CABG major bleeding and fatal bleeding. Upon further evaluation of the net clinical benefit (CV death, MI, stroke, and major bleeding), patients entering the trial with a history of stroke or transient ischemic attach were at greater risk for harm from prasugrel. Therefore, these patients have an absolute contraindication to receiving prasugrel. Patients over the age of 75 years and those weighing less than 60 kg also had more bleeding with prasugrel compared to clopidogrel, but the overall net clinical benefit was neutral. Prasugrel should generally be avoided in patients over the age of 75 years. Exceptions may be made for patients who present with prior MI or DM, as the benefit in these patients outweighed the harm. Finally, in patients weighing less than 60 kg, the 60 mg loading dose of prasugrel is still given, but a 5 mg maintenance dose is recommended instead of the typical 10 mg dose although the safety and efficacy of this dose has not been established.

Prasugrel has been compared to clopidogrel in patients undergoing an ischemia-driven approach.[71] Although there was no increased risk of bleeding with prasugrel in this trial, there was also no difference in efficacy. The use of prasugrel in these patients is not mentioned in the current guidelines.[2] Prasugrel has also not been evaluated in patients with STEMI receiving reperfusion therapy with fibrinolytics.

6 ***Ticagrelor*** As with prasugrel, ticagrelor provides faster and more potent inhibition of platelets compared to clopidogrel.[72] Although ticagrelor does not require hepatic activation, it is metabolized by CYP3A4. Therefore, ticagrelor is contraindicated in patients receiving strong CYP3A4 inhibitors such as azole antifungals and protease inhibitors, as well as strong inducers of this enzyme such as carbamazepine, phenytoin, rifamycins, and St. John’s Wort. Patients on ticagrelor should not receive doses of simvastatin or lovastatin higher than 40

mg daily. Due to competition for P-glycoprotein, ticagrelor can increase digoxin concentrations by 30% to 50%.

Ticagrelor has been compared to clopidogrel as part of DAPT with aspirin in patients undergoing PCI (NSTE-ACS or STEMI) or undergoing an ischemia-driven approach for NSTE-ACS in a large clinical trial (n = 18,624).[73] Patients receiving ticagrelor demonstrated a significant reduction in CV death, MI, or stroke compared to clopidogrel. While this reduction was evident within the first 30 days of therapy, two-thirds of the benefit was demonstrated after the first 30 days out to 1 year. As with prasugrel, the benefit of ticagrelor was not simply due to more potent antiplatelet therapy early, but also sustained potent antiplatelet therapy. The magnitude of benefit was also similar in patients receiving an ischemia-driven approach to those receiving PCI. There was also a significant 21% reduction in CV mortality demonstrated with the use of ticagrelor over clopidogrel, which has not been seen in other trials of $P2Y_{12}$ inhibitors. In the trial it was observed that higher doses of aspirin attenuated the benefit of ticagrelor compared to clopidogrel, and that only patients receiving low-dose aspirin (daily dose of 100 mg or less) received benefit.[74] Based on these data, ticagrelor is contraindicated in patients receiving chronic aspirin daily doses of more than 100 mg. The mechanism of this interaction remains unknown. Although non-CABG major bleeding was significantly increased, there was no increase in fatal bleeding. While ticagrelor has been found to be noninferior to clopidogrel for major bleeding risk in patients with STEMI receiving reperfusion with fibrinolytics, clopidogrel is the only $P2Y_{12}$ inhibitor with specific recommendations as an adjunct to fibrinolytic therapy in patients with STEMI.[75]

While all antiplatelet agents have the adverse effect of bleeding, the unique structure of ticagrelor produces additional adverse effects. In the trial mentioned above, significantly more patients receiving ticagrelor complained of dyspnea (13.8%) compared to those receiving clopidogrel (7.8%).[73] Symptoms of dyspnea are typically mild to moderate, require no specific therapy or workup, and usually dissipate within 2-4 weeks. Coaching of the patient through these episodes is often successful as the need to discontinue therapy due to dyspnea in the clinical trial was necessary in less than 1% of patients. Use of ticagrelor was also associated with an increase in asymptomatic ventricular pauses, increases in uric acid, and small increases in serum creatinine. In addition to its antiplatelet effects, preclinical studies have also demonstrated that ticagrelor can interfere with adenosine degradation and increase adenosine concentrations via inhibition of adenosine uptake by erythrocytes.[72] This interaction most likely occurs

through inhibition of the sodium-independent equilibrative nucleoside transporter (ENT)-1. Erythrocyte ENT-1 is responsible for uptake of adenosine into the cell where it is metabolized by multiple mechanisms. The ability of ticagrelor to inhibit adenosine's uptake via ENT-1 is likely due to the adenosine core of ticagrelor.[72] This interaction produces an increase in adenosine exposure that likely explains these unique adverse effects.

Cangrelor Cangrelor is currently the only available intravenously administered $P2Y_{12}$ inhibitor. Similar to ticagrelor, cangrelor is a reversible inhibitor of the $P2Y_{12}$ receptor and binds to the receptor at a different location than adenosine diphosphate. Despite currently recommended loading doses, oral $P2Y_{12}$ inhibitors take a minimum of 1 to 2 hours to obtain maximum platelet inhibition, and 3 to 7 days for platelet recovery after discontinuation.[65] Cangrelor achieves maximum platelet inhibition within approximately 2 minutes of an IV bolus dose, with restoration of normal platelet reactivity within 1 to 2 hours of cessation of the infusion.[65] Cangrelor has an elimination half-life of less than 9 minutes and is metabolized by ATPases in the blood. Therefore, hepatic or renal dysfunction are not likely to impact the pharmacokinetics of cangrelor.[65] The fast return to normal platelet function may provide safety advantages for cangrelor over other $P2Y_{12}$ inhibitors in the context of bleeding or transition to CABG surgery.

The use of cangrelor in patients with ACS is not well defined. In a clinical trial evaluating the efficacy and safety of cangrelor (n = 11,145), patients received a cangrelor bolus dose followed by an infusion of about 2 hours before PCI or a clopidogrel loading dose (300 or 600 mg) after PCI.[76] After the 2 hour infusion of cangrelor, patients were loaded with clopidogrel and received a maintenance dose of 75 mg daily thereafter. Patients with ACS comprised a total of 44% of the total PCI patients in the trial (26% NSTE-ACS and 18% STEMI). At 48 hours after PCI, cangrelor provided a significant reduction in MACE with an increase in minor bleeding, but not major bleeding. Since the chemical structure is similar to ticagrelor, dyspnea was reported more with the use of cangrelor, but the shorter drug exposure time likely contributed to a lower incidence (1.2%) and discontinuation rate (0.1%) compared to ticagrelor in a large randomized trial (13.8% and 0.9%, respectively).[76,77] The utility of cangrelor in patients pre-loaded with clopidogrel is unknown, as well as how it might compare to faster acting and more potent prasugrel and ticagrelor.

Cangrelor may interfere with binding of the active metabolites of clopidogrel and prasugrel. Studies have demonstrated that when clopidogrel is given with

cangrelor, the ability of the thienopyridines to irreversibly inhibit platelet function was reduced.[77,78] It is suspected that the reversible inhibitor cangrelor directly prevents binding of the short-lived but irreversible active metabolite. Once the infusion is discontinued, no impact on the pharmacodynamic effect of clopidogrel was seen. This same interaction would be expected with prasugrel. Therefore, it is important that if cangrelor is used, the loading dose of the thienopyridine not be given until the cangrelor infusion has been discontinued. This interaction does not exist with ticagrelor.

Switching Antiplatelet Agents Situations may occur after initial DAPT is chosen whereby therapy needs to change based upon some unique clinical scenario. Switching of therapy can be described as an escalation of therapy whereby clopidogrel is switched to a more potent $P2Y_{12}$ inhibitor such as ticagrelor or prasugrel. Reasons for escalation include cases of heightened risk for a coronary event or stent thrombosis, development of drug interaction, intolerance or nonadherence, identification of a genetic polymorphism to clopidogrel, or confirmation of inadequate platelet inhibition. In contrast, de-escalation typically refers to switching from a more potent $P2Y_{12}$ inhibitor to clopidogrel. Need for a de-escalation of $P2Y_{12}$ inhibitor therapy may be needed in response to bleeding, when there is a new indication to concurrently use an oral anticoagulant, or in cases of when cost is limiting medication access or leading to less than optimal adherence. Data on switching antiplatelet therapies is limited and is primarily based on pharmacodynamic studies. The efficacy and safety of switching agents during the first 12 months following ACS, therefore, is not fully known. But clinical decisions based on the reason for switching (ie, escalation versus de-escalation) and the timing from index event (ie, acute/early phase within the first 30 days versus later) must be weighed. One international consensus panel recommends that no loading dose be given when de-escalating therapy due to bleeding.[79] Loading doses are generally not needed when de-escalating therapy except when being when switching from ticagrelor to another $P2Y_{12}$ inhibitor.[79] Any escalation in therapy should be accompanied by a loading dose of the new agent regardless of time of last $P2Y_{12}$ inhibitor dose, followed by maintenance therapy 24 hours after last $P2Y_{12}$ inhibitor dose.[79] Finally, when switching between $P2Y_{12}$ inhibitors within 30 days of the index event, loading doses are recommended in most cases, except when the reason for switching is because of bleeding.[79] In general, the switch should occur 24 hours after the last dose of previous $P2Y_{12}$ inhibitor.[79]

Glycoprotein IIb/IIIa Inhibitors Binding of fibrinogen to activated GP IIb/IIIa receptors represents the final step in platelet aggregation, making inhibition of this receptor an ideal target in patients with ACS. Each of the agents are only available as an IV infusion. Abciximab is a chimeric human-murine monoclonal antibody Fab fragment that blocks the GP IIb/IIIa receptor–fibrinogen binding. Abciximab demonstrates irreversible binding to the GP IIb/IIIa receptor, with platelet function recovery occurring over approximately 24 hours after discontinuation of the infusion. Due to the strong binding of abciximab to the GP IIb/IIIa receptor, the drug to receptor ration is approximately 2:1.[80] Therefore, platelet transfusions can absorb the excess abciximab, and would be effective in management of a major bleeding episode.

Eptifibatide and tirofiban are commonly referred to as "small molecule" GP IIb/IIIa inhibitors, as they are peptide and nonpeptide inhibitors of the GP IIb/IIIa receptor, respectively, and have a much smaller molecular weight compared to abciximab. These agents have reversible binding of the GP IIb/IIIa receptor. Therefore, platelet function recovery occurs in 2 to 4 hours after discontinuation of the infusion. The reversible binding of the small molecule agents requires that they overwhelm the ability of fibrinogen to bind to the GP IIb/IIIa receptor with high concentrations and a drug to receptor ratio that is approximately 500 to 1000:1.[80] Consequently, platelet transfusion would not be able to absorb excess drug and would not be helpful in the management of bleeding with eptifibatide or tirofiban.

Besides bleeding, GP IIb/IIIa inhibitors can also cause significant thrombocytopenia in about 1% of patients receiving abciximab and 0.5% with eptifibatide and tirofiban.[80] Given that GP IIb/IIIa inhibitors should be administered with a heparin, it is important to differentiate GP IIb/IIIa inhibitor–induced thrombocytopenia from heparin-induced thrombocytopenia (HIT).[81] Thrombocytopenia from a GP IIb/IIIa inhibitor occurs more rapidly (within hours) and the platelet count nadir is typically lower (about 20,000) compared to HIT. Contrary to patients with HIT, if thrombocytopenia occurs with abciximab, platelet transfusion can be administered. While the efficacy of platelet transfusion for thrombocytopenia from eptifibatide or tirofiban is limited, it would unlikely be harmful as in HIT.[81]

Although GP IIb/IIIa inhibitors have demonstrated a significant reduction in MACE in several trials, the majority of these trials were conducted before DAPT became standard of care and before the more potent $P2Y_{12}$ inhibitors prasugrel and ticagrelor were available. In the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 2 (ISAR-REACT 2) trial,

patients receiving PCI for NSTE-ACS and a 600 mg loading dose of clopidogrel randomized to abciximab with heparin had a significant reduction in MACE compared to heparin alone.[82] Interestingly, the benefit was only demonstrated in patients who had an elevated cTn (13.1% vs. 18.3%; $p = 0.02$), with no difference in patients without elevated cTn (4.6% in both groups).[82] Therefore, GP IIb/IIIa inhibitors provide added benefit in the setting of early DAPT, but should be reserved for high-risk patients with elevated cTn. The ability of GP IIb/IIIa inhibitors to reduce MACE in patients receiving prasugrel or ticagrelor remains unknown. Trials comparing a strategy of GP IIb/IIIa inhibitors plus heparin to bivalirudin alone in patients with ACS undergoing PCI demonstrated no difference in MACE, but significantly less major bleeding with bivalirudin alone.[83,84] While these trials have many limitations, clinicians have consistently used less GP IIb/IIIa inhibitors over the last decade.

Patients with NSTE-ACS undergoing an ischemia-driven approach do not derive benefit from GP IIb/IIIa inhibitors and should not be used in these patients.[2] Patients with STEMI receiving reperfusion with fibrinolytics have significant increases in major bleeding and ICH when GP IIb/IIIa inhibitors are used concomitantly and they should be avoided in these patients as well.[1]

6 While the use of GP IIb/IIIa inhibitors has been diminishing over the years, the patient for whom GP IIb/IIIa inhibitors may provide the most benefit is one receiving PCI for NSTE-ACS with elevated cTn, (eg, suffering MI) or STEMI who has not been preloaded with a P2Y12 inhibitor and is not being treated with bivalirudin. Guidelines also state that it is reasonable to use a GP IIb/IIIa inhibitor in patients who are preloaded with clopidogrel based on the results of the ISAR-REACT 2 trial.[1,2,62,82] In this setting, consensus guidelines recommend the use of either a bolus followed a 12-hour infusion (abciximab) or an 18–24-hour infusion (eptifibatide and tirofiban) but the contemporary use of these drugs continues to evolve. These agents should always be given with unfractionated heparin (UFH) or a low-molecular-weight heparin (LMWH) that should be discontinued immediately following the PCI procedure to reduce risk of major bleeding.

Anticoagulants

Although patients with ACS are typically on at least two antiplatelet agents for at least a year, usually a single anticoagulant is used in these patients and the duration is abbreviated (typically the initial few days of hospitalization).[1,2] Currently available anticoagulants inhibit the production of thrombin by

inhibiting factor Xa, inhibit thrombin itself, or a combination of these. While the use of oral anticoagulants may be common for other thromboembolic disease states, all of the current evidence in the acute management of ACS is with injectable agents. The use and dosing of anticoagulant therapies for the treatment of ACS are summarized in **Table 33-7**.

TABLE 33-7 Anticoagulant Drug Use and Dosing Across the Spectrum of ACS and Management Strategy[1,2]

	STEMI		NSTE-ACS	
Drug	**Primary PCI**	**Fibrinolytic reperfusion**	**Early invasive strategy**	**Ischemia-driven strategy**
Bivalirudin	0.75 mg/kg IV bolus, followed by 1.75 mg/kg/hr IV infusion until completion of PCI CrCl less than 30 mL/min (0.5 mL/s): Reduce infusion to 1 mg/kg/hr	No recommendation	0.10 mg/kg IV bolus, followed by 0.25 mg/kg/hr IV infusion continued until completion of PCI	No recommendation
Enoxaparin	0.5 mg/kg one time IV bolus*	30 mg IV bolus, followed by 1 mg/kg SC every 12 hours for up to 8 days or hospital discharge SC doses should be initiated within 15 minutes of the IV bolus. The first two SC doses should be capped at 100 mg CrCl less than 30 mL/min (0.5 mL/s): 30 mg IV bolus, followed by 1 mg/kg SC every 24 hours. The first SC dose should be capped at 100 mg Age 75 years or more: No IV bolus. Initiate at 0.75 mg/kg SC every 12 hours The first two SC doses should be capped at 75 mg CrCl less than 30 mL/min (0.5 mL/s) AND age 75 years or more: No IV bolus. Initiate at 1 mg/kg every 24 hours The first dose should be capped at 100 mg	1 mg/kg SC every 12 hours until PCI A 0.3 mg/kg IV bolus should be given if PCI occurs before two SC doses have been given, or if the last dose was given 8 hours or more prior to PCI CrCl less than 30 mL/min (0.5 mL/s): 1 mg/kg SC every 24 hours An initial 30 mg IV bolus can be given	1 mg/kg SC every 12 hours for duration of hospitalization An initial 30 mg IV bolus can be given CrCl less than 30 mL/min (0.5 mL/s): 1 mg/kg SC every 24 hours
Fondaparinux	No recommendation	2.5 mg IV first dose, followed by 2.5 mg SC daily for up to 8 days or hospital discharge	2.5 mg SC daily until PCI At time of PCI: No GP IIb/IIIa: IV UFH 85 units/kg† With GP IIb/IIIa: IV UFH 60 units/kg†	2.5 mg SC daily for up to 8 days or duration of hospitalization
Unfractionated heparin	No GP IIb/IIIa: 70-100 units/kg IV bolus to achieve a therapeutic ACT† GP IIb/IIIa: 50-70 units/kg IV bolus to achieve a therapeutic ACT†	60 units/kg (maximum initial bolus: 4000 units) IV bolus, followed by 12 units/kg/hr (maximum initial infusion rate: 1000 units/hr)	60 units/kg (maximum initial bolus: 4000 units) IV bolus, followed by 12 units/kg/hr (maximum initial infusion rate: 1000 units/hr)†	60 units/kg (maximum initial bolus: 4000 units) IV bolus, followed by 12 units/kg/hr (maximum initial infusion rate: 1000 units/hr)

ACT, activated clotting time; CrCl, creatinine clearance; GP, glycoprotein; IV, intravenous; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; SC, subcutaneous; STEMI, ST-segment elevation myocardial infarction; UFH, unfractionated heparin.

*Not mentioned in the ACC/AHA guidelines, but evidence exists

†Additional IV boluses of UFH may be needed to maintain a therapeutic ACT

Unfractionated Heparin Unfractionated heparin has been widely used in the management of patients with ACS for several decades. The UFH molecule is a highly sulfated polysaccharide. Unfractionated heparin provides its anticoagulant activity by binding to the endogenous anticoagulant antithrombin (AT) via a unique pentasaccharide sequence, increasing its affinity for clotting factor inhibition by 1000-fold.[85] These UFH–AT complexes can then inhibit clotting factors IXa, Xa, XIa, XIIa, and thrombin, with most of the impact provided through inhibition of factor Xa and thrombin. Inhibition of thrombin requires a tertiary binding between the UFH–AT and thrombin molecules. This requires that the chain length of the inhibitory molecule be at least 18 saccharides long.[85] This additional binding is not necessary for inhibition of factor Xa. Since most UFH molecules are approximately 45-50 saccharides long, UFHs can inhibit factor Xa and thrombin in an equal 1:1 ratio.[85]

The anticoagulant effect of UFH has significant interpatient variability.[85] This is due to additional binding of UFH with endothelial cells, plasma protein, and ingestion by macrophages. As a result of the unpredictable anticoagulant response of UFH, therapy needs to be monitored with an activated partial thromboplastin time (aPTT). The aPTT should be measured every 6 hours until two consecutive readings are within the therapeutic range, as determined by the individual institutional protocols, then every 24 hours for the duration of UFH therapy. Although goal ranges for aPTT vary by institution based on the assays used, an aPTT goal of 1.5-2 times the institution's control value is recommended.[1] If a dose adjustment is made, the same monitoring schedule should be restarted. Due to the short duration of anticoagulant therapy in patients with ACS, it is not uncommon for the UFH to be discontinued before the patient ever achieves two consecutive therapeutic aPTT measurements. Platelet counts should also be monitored daily or every other day to monitor for HIT. While HIT typically presents 5 days or more after UFH exposure, it can occur within hours if the patient has been exposed to heparin in the last 3 months.[81] If HIT is suspected, UFH should be discontinued and anticoagulation with an IV direct thrombin inhibitor should be provided.

7 Based on experience, UFH can be used across the spectrum of ACS and regardless of the management strategy.[1,2] The recommended dosing of UFH has changed several times over the past decades in an attempt to maximize efficacy and minimize bleeding. Currently, the recommended dose of UFH is an IV bolus of 60 units/kg (initial maximum total dose of 4000 units) and an initial infusion rate of 12 units/kg/hr (initial maximum 1000 units/hr). This is the recommended

dose regardless of the ACS diagnosis or management strategy.[1,2] After initiation of heparin, dosage adjustments can exceed the recommended maximums as necessary to achieve the aPTT goal. Bolus doses of 2000 to 5000 units can also be given in the cardiac catheterization laboratory at the time of PCI to maintain an adequate activated clotting time (ACT). In a meta-analysis of six trials (1,353 patients) comparing the use of heparin plus aspirin to aspirin alone in patients with NSTE-ACS, the risk of death or MI was reduced by 33% in heparin-treated patients.[86] Because of the long-standing experience and use of UFH in patients with ACS, it is the standard-of-care comparison in clinical trials.

Low-Molecular-Weight Heparins Similar to UFHs, LMWHs must first bind to AT to provide their anticoagulant activity. LMWHs are created through chemical or enzymatic depolymerization of UFH molecules.[85] This creates a mixture of lower molecular weight fragments compared to the larger intact UFH molecule. Most of these fragments are less than 18 saccharides long. Consequently, LMWH's anticoagulant activity results mostly from inhibition of factor Xa with only the few larger fragments able to inhibit thrombin. The ratio of factor Xa to thrombin inhibition with a LMWH is typically 3:1 or 4:1, depending on the process of depolymerization.[85]

Compared to UFHs, LMWHs provide a predicable anticoagulant dose response with no need for routine therapeutic monitoring. While most patients receiving a LMWH do not require therapeutic monitoring, an anti-Xa level may be desired in certain patient populations.[85] Patient groups where anti-Xa monitoring may be helpful would be pediatrics, pregnancy, obesity (greater than 190 kg), and patients with severe renal insufficiency (eg, creatinine clearance [CrCl] less than 30 mL/min [0.5 mL/s]). While pediatric and pregnant patients rarely have ACS, obesity and severe renal insufficiency are more common in patients with ACS. The target peak anti-Xa level is 0.3 to 0.7 IU/mL (kIU/L) drawn 4 hours after the third dose. Since patients with ACS typically receive anticoagulant therapy for only a few days, the utility of anti-Xa monitoring in these patients is limited. There is also a lower incidence of HIT with the use of LMWHs (less than 2%) compared to UFH (2%–5%).[81] Even though the risk of HIT is lower with LMWH, the monitoring of platelet counts is still warranted. Due to the 90% cross-reactivity between HIT antibodies from LMWH and UFH, LMWH is not considered a safe alternative in patients who develop HIT from UFH and vice versa.[81]

While other LMWHs are available, enoxaparin is the most widely studied agent in patients with ACS, and is the only LMWH recommended in the

ACC/AHA guidelines.[1,2] Data supporting the use of enoxaparin exist in patients with NSTE-ACS and STEMI regardless of the management or reperfusion strategy used. Unfortunately, the dosing of enoxaparin varies across these different settings, requiring careful attention to assure the right dose is used in the right patient to maximize efficacy and safety (Table 33-7).

7 In patients with NSTE-ACS undergoing an ischemia-driven approach, use of subcutaneous (SC) enoxaparin at 1 mg/kg every 12 hours for up to 3 days is supported by two clinical trials that demonstrated a significant reduction in MACE compared to IV UFH without increasing major bleeding.[87] In patients with NSTE-ACS treated with an early invasive strategy, SC enoxaparin (1 mg/kg every 12 hours) was compared to IV UFH in a trial of 10,027 patients.[88] The overall results demonstrated similar efficacy between the agents but more major bleeding with enoxaparin. This trial was complicated by a large number of patients receiving both anticoagulants during the trial. Interestingly, in the approximately 5,800 patients who were treated with either enoxaparin or IV UFH alone, those randomized to enoxaparin demonstrated a 17% reduction in the risk of death or MI at 30 days and at 6 months without a significant increase in major bleeding comapred to IV UFH. Based on these data, either UFH or enoxaparin is recommended in patients with NSTE-ACS. Patients who arrive at PCI and have received less than two SC doses should receive a supplemental IV enoxaparin bolus dose of 0.3 mg/kg to provide sufficient anticoagulation during the procedure.[2] Patients who have received at least two SC doses and arrive at PCI within 8 hours of their last dose do not require any additional anticoagulation for PCI.[2,88] Patients having PCI performed within 8-12 hours of their last dose should also receive the supplemental IV enoxaparin bolus dose.[2,88] Patients with a CrCl less than 30 mL/min (0.5 mL/s) should receive enoxaparin 1 mg/kg every 24 hours instead of every 12 hours.

7 In patients with STEMI receiving reperfusion with fibrinolytics, enoxaparin has demonstrated a significant 17% reduction in death and MI compared to UFH.[89] Major bleeding was increased, but there was no increase in ICH which occurred in less than 1% of patients. Dosing of enoxaparin in this trial used a 30 mg IV bolus followed immediately by 1 mg/kg SC every 12 hours. The bolus dose is necessary in the setting of STEMI due to the rapid need for reperfusion therapy. Patients aged 75 years or greater and those with a CrCl less than 30 mL/min (0.5 mL/s) need to receive altered dosing to reduce the risk of bleeding in these higher-risk patients (Table 33-7). Trials in patients receiving primary PCI for STEMI have used a single IV dose of 0.5 mg/kg of enoxaparin. A meta-analysis of trials evaluating this dose of enoxaparin in primary PCI

demonstrate a reduction in mortality and significantly less major bleeding compared to UFH.[90] Despite these data, a definitive clinical trial has not been conducted with enoxaparin in this setting.

Fondaparinux Fondaparinux is a synthetic molecule existing of only the five saccharides needed to bind to and potentiate the activity of AT.[85] While others have been investigated, fondaparinux is the only available pentasaccharide worldwide. Due to the small size of the molecule, once it binds to AT it can only inhibit factor Xa and has no activity against thrombin. Similar to LMWH, fondaparinux also provides a predicable anticoagulant dose response and no need for therapeutic monitoring.[85] While case reports of fondaparinux-induced thrombocytopenia have been reported, the incidence is thought to be extremely rare.[81] Based on the lack of antibody cross-reactivity, it is reasonable to consider use of fondaparinux in patients with a history of HIT.[81] Based on the long half-life of fondaparinux, the SC dose (2.5 mg) is only given once daily. Fondaparinux is contraindicated in patients with a CrCl of less than 30 mL/min (0.5 mL/s) due to the significant degree of renal elimination. There can also be accumulation in patients with a CrCl between 30 and 60 mL/min (0.5 and 1.0 mL/s), but this is typically not a factor with the short duration of therapy in patients with ACS.[91]

7 The use of fondaparinux in patients with ACS has been evaluated in two large trials.[92,93] The trial in NSTE-ACS evaluated patients receiving either an ischemia-driven or invasive management strategy. Results of the trial demonstrated similar efficacy between fondaparinux and enoxaparin, with significantly less major bleeding in patients receiving fondaparinux.[92] There were a number of issues in the trial that may have explained this bleeding difference such as anticoagulation being continued after PCI, large doses of UFH given at the time of PCI with enoxaparin, and the longer duration of therapy (about 8 days) than what is typically seen in the United States. Regardless, fondaparinux can be considered in patients undergoing an ischemia-driven approach at high risk of bleeding.[2] Patients undergoing PCI demonstrated a significant increase in catheter-related thrombosis if they received fondaparinux compared to enoxaparin.[92] Due to this concern, supplemental doses of IV UFH must be given if a patient receiving fondaparinux who requires PCI.[2] Consequently, fondaparinux is rarely used and not currently recommended in the United States for patients with NSTE-ACS receiving an invasive management approach.[62]

7 The trial utilizing fondaparinux in STEMI evaluated patients receiving

reperfusion with either fibrinolytics or primary PCI.[93] In this trial, fondaparinux was compared to UFH. Similar to the NSTE-ACS trial, patient receiving primary PCI demonstrated significantly higher rates of catheter-related thrombosis if they received fondaparinux compared to UFH.[1,93] As in NSTE-ACS, fondaparinux use has been constrained by this limitation and is not recommended in patients receiving primary PCI.[62] In patients receiving fibrinolytics, the use of fondaparinux demonstrated similar efficacy and safety compared to UFH.[93] Based on the lack of benefit over UFH, and the benefit demonstrated with enoxaparin over UFH in this population, fondaparinux is rarely used in patients with STEMI.

Bivalirudin Bivalirudin is an intravenously administered direct thrombin inhibitor. Being a "direct" inhibitor means bivalirudin does not have to first bind to AT to provide its anticoagulant effect.[85] Because of the lack of AT binding, bivalirudin can inhibit not only free or soluble thrombin, similar to UFH and LMWH, but also fibrin-bound thrombin. Fibrin-bound thrombin is still enzymatically active, but the large AT–anticoagulant complexes are unable to gain access and, therefore, exert anticoagulant activity.[85] The clinical benefit of bivalirudin's inhibition of this larger pool of thrombin is difficult to quantify.

7 Bivalirudin has not been evaluated in patients with NSTE-ACS undergoing an ischemia-driven approach or in patients with STEMI receiving reperfusion with fibrinolytics. Therefore, bivalirudin is only used in patients with ACS who receive PCI and can be monitored with an ACT in the catheterization laboratory.[1,2,85] In one NSTE-ACS trial evaluating anticoagulation as part of an early invasive approach, patients received a heparin derivative (UFH or enoxaparin) with a GP IIb/IIIa inhibitor, bivalirudin with a GP IIb/IIIa inhibitor, or bivalirudin alone.[83] There was no difference in efficacy or safety in patients receiving a heparin with a GP IIb/IIIa inhibitor compared to bivalirudin with a GPII/IIIa inhibitor. Consequently, because of the lack of benefit and increased cost associated with the combination of bivalirudin and a GP IIb/IIIa inhibitor, this regimen is not recommended in patients with NSTE-ACS undergoing PCI. Patients receiving bivalirudin alone demonstrated similar efficacy but significantly less major bleeding compared to a heparin with a GP IIb/IIIa inhibitor. It should be noted that patients who were not preloaded with clopidogrel in the trial had significantly more MACE if they received bivalirudin alone.[2,83] Therefore, bivalirudin may not be as protective in patients who do not receive a $P2Y_{12}$ inhibitor prior to PCI. Similar to the study in NSTE-ACS, bivalirudin alone demonstrated similar efficacy with significantly less major

bleeding compared to UFH with a GP IIb/IIIa in patients undergoing primary PCI for STEMI.[84] Although the definition of some of the endpoints and results in the high-risk patients in both of these studies raised some controversy, these data led to a significant reduction in the use of GP IIb/IIIa inhibitors. Over the last several years, additional trials have suggested that bivalirudin does not offer efficacy or safety benefit over UFH alone in the setting of primary PCI for STEMI, particularly as vascular access to perform PCI has moved from a predominantly femoral arterial approach associated with higher rates of bleeding to a radial artery approach associated with less bleeding.[94–96] While the role of bivalirudin in these patients is recommended in the guidelines, many cardiologists have come full circle and often use UFH for primary PCI for patients with STEMI instead of bivalirudin.

Oral Anticoagulants The addition of an oral anticoagulant or thrombin antagonist to single or dual antiplatelet therapy reduces the risk of MACE in those with established CVD or at high risk for ASCVD but increases the risk of bleeding. Consequently, the use of chronic anticoagulation following ACS is not routine. Additional study in this area is of paramount importance because of continued thrombotic risk in patients post-ACS, yet the best efficacy and safety profile has yet to be determined.

Secondary Prevention of Ischemic Events

For most patients, the initial 24 hours of ACS care are focused on reperfusion (if appropriate), antithrombotic therapy, and acute supportive measures. After a diagnosis of ACS, patients are considered to have atherosclerotic cardiovascular disease (ASCVD) and should be treated aggressively because they are at the highest risk of recurrent MACE. Secondary prevention strategies proved to accomplish these goals typically include anti-ischemic, antiplatelet, lipid-lowering, and antihypertensive therapies (**Table 33-8**).[1,2,25] Specific pharmacotherapy proved to decrease mortality, HF, reinfarction or stroke, and stent thrombosis should be initiated prior to hospital discharge in all patients without contraindications. Medication reconciliation at discharge should include assessment for DAPT, β-blocker, angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), and statin therapy unless a contraindication exists (**Fig. 33-2**). In addition, short-acting NTG should be prescribed as needed for any subsequent episode of acute angina for patients not taking phosphodiesterase-5 inhibitors. Select patients may also meet criteria for benefit from an aldosterone antagonist.

TABLE 33-8 Chronic Medications to Reduce Risk of MACE and Control Symptoms Following ACS[1,2,97,98]

Drug	Indication in ACS Patients (Class of Recommendation)*	Contraindication/Caution	Dose (All doses are oral unless indicated)	Adverse Effects
Aspirin	All patients without contraindications	Hypersensitivity to aspirin or NSAID History of asthma, rhinitis, and nasal polyps History of upper GI bleeding Bleeding disorder/active bleeding	81 mg once daily	Dyspepsia, GI bleeding
$P2Y_{12}$ inhibitors	All patients without contraindications	Thienopyridine hypersensitivity Bleeding disorder/active bleeding Previous intracranial hemorrhage Prasugrel: prior TIA or stroke Ticagrelor: aspirin doses greater than 100 mg daily; strong CYP3A4 inhibitors or inducers	Clopidogrel 75 mg once daily Prasugrel 10 mg once daily; weight less than 60 kg: 5 mg daily Ticagrelor 90 mg twice daily	Bleeding, rash Ticagrelor: dyspnea, ventricular pauses, bradycardia
β-Blockers	All patients without contraindications	Signs of heart failure Low cardiac output state High-grade AV block Active asthma or reactive airway disease	Carvedilol 6.25 mg twice daily; target dose (in patients with HFrEF): 25 mg twice daily as tolerated Metoprolol 25-50 mg every 6-12 hours for 2-3 days, then once (metoprolol succinate) or twice daily (metoprolol tartrate); target dose (in patients with HFrEF): 200 mg daily Continue therapy for at least 3 years, indefinitely in patients with concomitant HFrEF Other β-blockers may be considered; in patients with HFrEF, use either metoprolol succinate, carvedilol, or bisoprolol	Hypotension, heart failure, bradycardia, cardiogenic shock, AV block, exacerbation of asthma or reactive airway disease
Statins	All patients without contraindications	Active liver disease Pregnancy Breastfeeding Concomitant use of fibrate	Atorvastatin 80 mg daily Rosuvastatin 20-40 mg daily	GI discomfort, arthralgia, myalgia, musculoskeletal pain, hepatotoxicity
Nonstatin therapies for cholesterol management	Patients with very high risk ASCVD (eg, post-ACS) with LDL-C greater than 70 mg/dL (1.81 mmol/L) on maximally tolerated statin therapy	Hypersensitivity Simvastatin/ezetimibe: strong CYP3A4 inhibitors	Ezetimibe 10 mg daily Simvastatin 40 mg/ezetimibe 10 mg Alirocumab 75 mg SC every 2 weeks	Ezetimibe and combination: GI discomfort, arthralgia, myalgia, musculoskeletal pain Alirocumab: injection site pain, hypersensitivity
ACE inhibitors	All patients without contraindications	Hypotension Renal failure Hyperkalemia	Lisinopril 2.5-5 mg daily; target dose: 10-40 mg daily Captopril 6.25-12.5 mg three times daily; target dose: 25-50 mg three times daily Ramipril 2.5 mg twice daily; target dose: 5 mg twice daily Trandolapril 0.5-1 mg daily; target dose: 4 mg daily	Hypotension, hyperuricemia, hyperkalemia, worsening renal function, chronic cough, angioedema
ARBs	Patients intolerant to ACE inhibitors	Hypotension Renal failure Hyperkalemia	Valsartan 20 mg twice daily; target dose: 160 mg twice daily	Hypotension, hyperuricemia, hyperkalemia, worsening renal function
Aldosterone antagonist	Patients with LVEF 40% (0.40) or less and either DM or symptoms of HF	Elevated serum creatinine Men: 2.5 mg/dL (221 µmol/L) or greater Women: 2.0 mg/dL (177 µmol/L) or greater CrCl 30 mL/min (0.5 mL/s) or less Serum potassium 5.0 mEq/L (mmol/L) or greater	Eplerenone 25 mg daily; target dose: 50 mg daily Spironolactone 12.5-25 mg daily; target dose: 25-50 mg daily	Hyperkalemia, worsening renal function
Nitroglycerin (NTG)	All patients without contraindications	Hypotension Avoid if recent PDE_5 inhibitor use Avanafil: within 12 hours Sildenafil: within 24 hours Vardenafil: within 24 hours Tadalafil: within 48 hours	SL: 0.3-0.4 mg every 5 minutes, up to 3 doses PRN	Flushing, headache, hypotension, tachycardia

ACS, acute coronary syndrome; AV, atrioventricular; ASCVD, atherosclerotic vascular disease; CrCl, creatinine clearance; CYP3A4, cytochrome p450 isoenzyme 3A4; DM, diabetes mellitus; GI, gastrointestinal; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NSAID, nonsteroidal anti-inflammatory drug; PDE5, phosphodiesterase-5; PRN, as needed; SC, subcutaneously; TIA, transient ischemic attack.

*AHA/ACC class of recommendations: I, benefit far outweighs the risk, treatment should be administered; IIb, benefit is equal to or exceeds the risk, additional studies with broad objectives are needed, treatment may be considered.

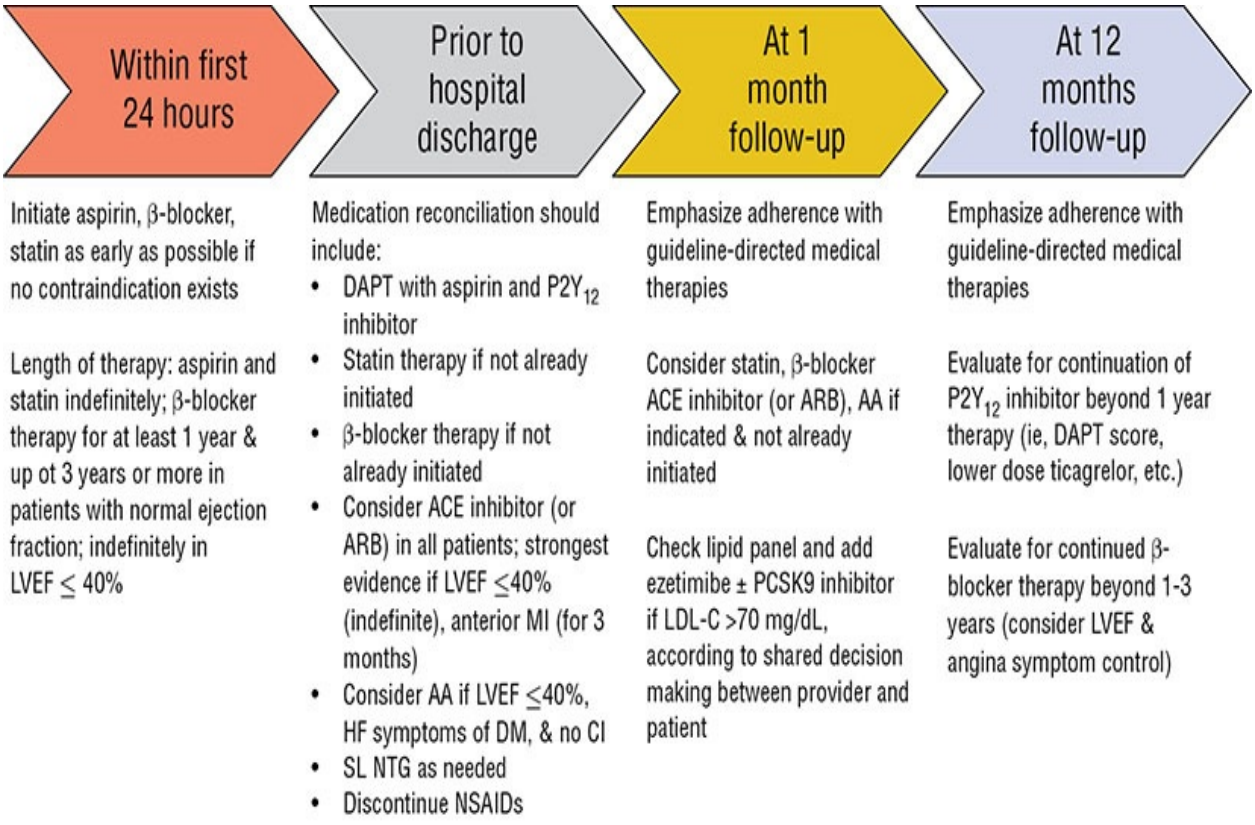


FIGURE 33-2 Secondary prevention of ischemic events over time.[1,2,97] (AA, aldosterone antagonist; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CI, contraindications; DAPT, dual antiplatelet therapy; DM, diabetes mellitus; HF, heart failure; LDL-C, Low Density Lipoprotein Cholesterol (70 mg/dL is expressed in SI units as 1.81 mmol/L); LVEF, left ventricular ejection fraction (40% is expressed in SI units as a fraction, ie, 0.40); MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; PCSK9, proprotein convertase subtilisin-kexin type 9; SL NTG, sublingual nitroglycerin.)

In addition to evaluating patients for the use of medications proved to reduce the risk of MACE or recurrent symptoms of angina, additional interventions may be appropriate to optimize outcomes and improve safety. Aggressive risk factor modification strategies such as increased physical activity, dietary modification, weight loss, blood pressure modification, and smoking cessation should be communicated to all patients, initiated, and continued indefinitely.[99] Proton pump inhibitors provide a protective benefit in patients at highest risk for GI

bleeding from DAPT and may be considered for select patients (eg, history of GI bleeding, triple therapy with DAPT, and an oral anticoagulant with or without a history of GI bleeding).[2] All patients should refrain from chronic use of nonsteroidal anti-inflammatory drugs with high degree of cyclo-oxygenase-2 selectivity as they are associated with increased cerebrovascular and cardiovascular events.[1,2]

Duration of Dual Antiplatelet Therapy (DAPT)

8 The ACC/AHA has published guidelines specifically related to dosing, initiation, and duration of DAPT after ACS, including situations when therapy should be discontinued.[1,2,100] In general, shorter durations of DAPT are appropriate for those patients with a lower ischemic risk who may have a high bleeding risk. Conversely, longer durations of DAPT may be reasonable in patients at higher ischemic risk if bleeding risk is not unacceptably high. No randomized trials have compared different durations of DAPT specifically in the ACS setting. Yet, because the ischemic risk following ACS is considered high, DAPT with aspirin plus a $P2Y_{12}$ receptor inhibitor is indicated for most patients treated for ACS for a minimum of 12 months regardless of whether the patient was medically managed or if the patient undergoes some type of revascularization.[1,2,100] For patients with STEMI treated with fibrinolysis, the minimum recommended duration of DAPT is 14 days.[1,100] Every patient receiving DAPT should understand the benefit as well as risks associated with the therapy and the importance of maintaining adherence with therapy for the appropriate duration of therapy.

Continuation of DAPT beyond 12 months may be reasonable for patients at higher ischemic risk provided they also have a lower bleeding risk. This should be an individualized decision, considering both ischemic and bleeding risks. The DAPT risk score has been derived from the DAPT study and is supported by guidelines to aid in making decisions regarding prolonging DAPT beyond 12 months (**Table 33-9**).[101] A risk score of two or more suggests that prolonging therapy is favorable and would reduce ischemic events with perhaps only a modest increase in bleeding risk. Conversely, for those with a DAPT less than two, the risk for bleeding is anticipated to be greater than an ischemic benefit and the $P2Y_{12}$ inhibitor should be discontinued. It is important to realize that the DAPT score was developed from a study comparing standard DAPT (12 months) to an extended duration of 30 months of therapy in patients who had PCI with intracoronary stenting for either SIHD or ACS and is not appropriate

for determining DAPT durations shorter than 12 months. Further, 65% patients enrolled in this study were administered clopidogrel and 35% were treated with prasugrel; ticagrelor was not used. Other risk prediction models are being developed and evaluated.

TABLE 33-9 Factors Used to Calculate DAPT Score and Predict Ischemic and Bleeding Events[100,101]

Points	+2	+1	−1	−2
Clinical variables	CHF or LVEF less than 30% (0.30) Saphenous vein graft PCI	Current tobacco user Diabetes mellitus NSTEMI or STEMI at presentation Prior MI or PCI Stent diameter less than 3 mm Paclitaxel-eluting stent	Age 65-74	Age ≥75 years

Risk factors ordered from left to right include those with highest ischemic risk and highest point accrual to those with the highest bleeding risk and negative point accrual. A score of ≥2 favors prolonged DAPT; a score of <2 is of unfavorable risk/benefit. Total score ranges from −2 to 10.

Continued use of DAPT with ticagrelor beyond 12 months after ACS can be considered. One trial compared standard dose ticagrelor to a reduced dose of 60 mg twice daily in combination with low-dose aspirin to aspirin alone in patients who had suffered an MI 1 to 3 years prior.[102] This study demonstrated continued DAPT with either dose of ticagrelor decreased the composite of CV death, MI, or stroke compared to aspirin alone. While major bleeding was increased in patients treated with ticagrelor compared to aspirin alone, there were fewer bleeds in the low-dose ticagrelor group compared to the standard dose. It is important to note that the lower dose of ticagrelor (60 mg twice daily) has not been studied in the first 12 months after ACS; therefore, only the 90 mg twice daily is appropriate for the first year after index event.

Cholesterol Management

9 **Statins** Following ACS, statins reduce total mortality, CV mortality, MI, and stroke. Results from landmark clinical trials have unequivocally demonstrated the value of statins in secondary prevention following MI and provide an

approximate 1% reduction in risk of ASCVD event per 1% reduction in low-density lipoprotein cholesterol (LDL-C) over time.[97] Further, clinical trial results confirm the benefit of high-intensity statins initiated 1 to 10 days after ACS presentation. A meta-analysis of randomized controlled clinical trials in almost 18,000 patients with recent ACS (less than 14 days) found that statin therapy reduces mortality by 19%, with benefits observed after approximately 4 months of treatment.[103] Therefore, high-intensity statin therapy should be initiated during the index hospitalization once the patient has been stabilized and continued indefinitely. Risk reductions from high-intensity statin therapy occur regardless of cholesterol concentrations at presentation. Therefore, all patients with ACS should receive the highest dose of maximally tolerated statin.[1,2,97]

In those patients who are already taking low- or moderate-intensity statin therapy at time of ACS presentation, consideration should be given to switching to a high-intensity statin. For ACS patients with a history of statin intolerance or those at high risk for statin-related adverse effects (elderly, drug interaction, etc.), the use of moderate-intensity statins or lower doses of high-intensity statins may be considered.[97] Patients aged greater than 75 years may be prescribed a moderate-intensity statin as initial therapy because they are at higher risk of adverse drug effects and the data using high-dose statins in this patient subgroup are less robust.[97]

A lipid panel should be reassessed 4-6 weeks after initiation of therapy with the goal of a 50% reduction in LDL-C from baseline. Baseline lipid concentrations should be drawn as early as possible, ideally within the first 24 hours of ACS presentation, as phasic changes may occur that falsely lower total cholesterol, LDL-C, and high-density lipoprotein cholesterol. Triglycerides may be falsely elevated during this immediate period of ACS. See Chapter 31 for a more detailed discussion on the management of patients with dyslipidemia.

Other Cholesterol-Lowering Therapies Recently, nonstatin therapies have been shown to lower the risk of MACE in patients with ACS already receiving statin therapy and may be considered as add-on therapy in select patients. The IMPproved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) study compared the combination of simvastatin and ezetimibe, a nonstatin, to moderate-dose simvastatin in patients with recent (within 10 days) ACS and an LDL-C level between 50 and 100 mg/dL (1.29 and 2.59 mmol/L).[104] At 7 years, there was a modest reduction (6.4% relative risk reduction) in the rate of MACE in the simvastatin/ezetimibe group compared to simvastatin alone. Event rates were lower in patients who achieved lower LDL-

C, suggesting a direct relationship between LDL-C and benefit. More recently, a new class of potent, injectable cholesterol-lowering drugs, the proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors, has also been shown to lower the risk of MACE in patients with ACS. In a trial of nearly 19,000 patients with recent ACS (within 1-12 months), alirocumab added to high-intensity statin therapy reduced LDL-C by approximately 60% and the risk of MACE at 4 years by 15% compared to high-intensity statin therapy alone.[98] However, at the current cost of approximately $14,000 annually, the cost-effectiveness of PCSK9 inhibitors in this setting remains uncertain.[97] Nevertheless, for patients with clinical ASCVD treated with maximally tolerated statin therapy at very high risk (eg, recent ACS event) and persistently elevated LDL-C (70 mg/dL [1.81 mmol/L]or greater), current guidelines suggest adding ezetimibe.[97] If LDL-C remains elevated despite maximally tolerated statin therapy and ezetimibe, addition of a PCSK9 inhibitor is reasonable.[97]

ACE Inhibitors or Angiotensin Receptor Blockers

10 Following MI, the benefit of ACE inhibitors has been demonstrated through reductions in mortality, reinfarction rates, and HF, most likely through prevention of adverse cardiac remodeling.[1,2,105,106] While the use of IV enalaprilat within 24 hours of MI should be avoided due to increased risk of adverse events, early administration (within 48 hours of presentation) of ACE inhibitors is associated with lower mortality within the first month of therapy with additional benefit observed during longer treatment durations.[105,106] Data for use of ACE inhibitors is strongest for those with left ventricular dysfunction (LVEF 40% [0.40] or less) or in those who developed HF symptoms in the early phase of ACS.[105] Therefore, treatment with ACE inhibitor is recommended in all patients with MI and concomitant HFrEF, HTN, DM, or stable chronic kidney disease.[1,2,25] For patients without those comorbidities who suffer an MI, treatment with an ACE inhibitor is also reasonable.[1,25] Because they have been shown to have comparable benefit to ACE inhibitors in patients with MI, an ARB may be prescribed for those who cannot tolerate an ACE inhibitor.[1,2,25,107]

Although ACE inhibitors and ARBs are generally well-tolerated, it is important to monitor closely for the development of noteworthy adverse effects. The most common adverse effects associated with ACE inhibitors and ARBs are worsening renal function and hypotension. Hyperkalemia is also possible and is more likely in patients who develop acute kidney injury. Therefore, close monitoring of renal function, potassium levels, and blood pressure are warranted

1-2 weeks following initiation and dose adjustments. Although angioedema and chronic cough are possible with each of these therapies, both adverse effects are more common with ACE inhibitors and occur infrequently with ARBs.

Aldosterone Antagonists

10 To reduce mortality, administration of an aldosterone antagonist, either eplerenone or spironolactone, should be considered within the first 14 days following MI in all patients treated with both an ACE inhibitor (or ARB) and β-blocker with left ventricular dysfunction (LVEF of 40% [0.40] or less) and either HF symptoms or DM.[1,2,25] Aldosterone antagonists have been shown in experimental and human studies to attenuate the adverse hemodynamic and metabolic effects from chronic excessive aldosterone production as well as the cardiac remodeling that occurs in patients with MI.[108] A recent meta-analysis of 11 randomized clinical trials (11,258 patients) demonstrated treatment of post-MI patients with aldosterone antagonists resulted in significantly higher LVEF, 26% lower risk for new or worsening HF, and an 18% reduction in the risk of both all-cause mortality and CV mortality.[108] Although mortality was lower in patients with and without HF treated with aldosterone antagonists, the difference was only significant in patients with HF.

Both eplerenone and spironolactone block the mineralocorticoid receptor to which aldosterone binds. Spironolactone is a nonspecific steroid hormone receptor antagonist that also binds progesterone and androgen receptors and can cause gynecomastia in men and menstrual irregularities in women.[38] In contrast, eplerenone is selective for the mineralocorticoid receptor, thereby minimizing the risk of gynecomastia, sexual dysfunction, and menstrual irregularities.[38] In post-MI clinical trials, aldosterone antagonists have been associated with a more than twofold increase in the risk of hyperkalemia with an overall incidence of 11.6%.[108] Therefore, post-MI patients with serum potassium concentrations greater than 5 mmol/L (mEq/L) should not receive an aldosterone antagonist.[2] Additional contraindications for aldosterone antagonists in post-MI patients include a serum creatinine greater than 2.5 mg/dL (221 µmol/L) for men or 2 mg/dL (177 µmol/L) for women, or CrCl less than 30 mL/min (0.5 mL/s).[2] Because of the increased risk of hyperkalemia, especially in patients with chronic kidney disease, both serum potassium and renal function should be monitored diligently: 3 days and 1 week after initiation or dose titration, then monthly for the first 3 months, and every 3 months thereafter. Currently, there are no data to support that the more selective, more expensive eplerenone is

superior to, or should be preferred to, the less expensive generic spironolactone unless a patient has experienced gynecomastia, breast pain, or impotence while receiving spironolactone.

Nitroglycerin

All patients should be prescribed and instructed on the appropriate use of short-acting NTG, either sublingual tablets or lingual spray, to relieve acute anginal symptoms on an as needed basis.[1,2] Appropriate patient education for patients prescribed short-acting NTG is provided in Chapter 32. Chronic long-acting nitrate therapy has not been shown to reduce MACE following ACS and its role is typically limited to the prevention of recurrent symptoms of angina for ACS patients with significant coronary stenoses not amenable to revascularization who experience symptomatic SIHD. For patients with ACS for whom vasospasm is believed to be contributory, long-acting nitrates are recommended to treat and reduce the frequency of anginal episodes.[2]

EVALUATION OF THERAPEUTIC OUTCOMES

Evaluation of short-term efficacy focuses on restoration or preservation of coronary blood flow, symptom relief, and prevention of MACE. Restoration of blood flow and relief of ischemia can be detected by resolution of the ischemic changes on ECG at the time of presentation, which should occur soon after revascularization. Although cTn levels may remain elevated for several days, for patients with MI, cTn levels should peak within 12 to 24 hours and should decline steadily thereafter once ischemia is relieved. More importantly, if blood flow is restored or preserved and the angina is managed effectively, the patients should have resolution of symptoms rather quickly. In terms of MACE, monitoring for the development of complications from ACS (eg, HF, arrhythmias) should occur frequently. Lastly, assuring that evidence-based therapies shown to reduce the risk of MACE following ACS have been initiated in appropriate patients is critical.

Long-term evaluation of outcomes is directed largely at functional capacity and continued focus on risk reduction. Returning to and maintaining a high quality of life is an important goal following an ACS hospitalization. Patients should eventually be able to return to their activities of daily living, perhaps following a cardiac rehabilitation program to assist them with this goal. Additionally, patients should be monitored at every healthcare encounter for the development of adverse effects from ACS pharmacotherapy (**Table 33-10**). If

patients show signs of adverse effects or intolerance, particularly serious adverse events such as bleeding or hypotension, the offending agent(s) may need to be discontinued until the symptoms have resolved. Oral antiplatelet agents are a leading cause of hospitalizations and ED visits for adverse drug reactions among senior citizens.[109] Patients should be counseled on the risks and sites of potential bleeding and should be told to seek medical care immediately if significant bleeding is noticed. If bleeding occurs while on chronic therapy, the patient should be referred to the prescribing physician as the severity of bleed and the timing since index event (and presence of stent placement) may influence supportive measures and cessation of therapy.

TABLE 33-10 Therapeutic Drug Monitoring of Pharmacotherapy for ACS

Drug	Adverse Effects	Monitoring
Fibrinolytics	Bleeding (ICH)	Clinical signs of bleeding;[a] baseline aPTT, INR; Hgb, Hct, platelet count at baseline then daily; mental status every 2 hours for signs of ICH
Aspirin	Dyspepsia, GI bleeding	Clinical signs of bleeding;[a] GI upset; Hgb, Hct, and platelet count at baseline & every 6 months
$P2Y_{12}$ inhibitors	Bleeding, rash	Clinical signs of bleeding;[a] evidence of rash; Hgb, Hct, platelet count at baseline and every 6 months
	Ticagrelor: dyspnea, ventricular pauses, bradycardia	Ticagrelor: dyspnea, heart rate, telemetry during hospitalization
Glycoprotein IIb/IIIa inhibitors	Bleeding, thrombocytopenia (can be profound with abciximab)	Clinical signs of bleeding;[a] Hgb, Hct, and platelet count at baseline, 2 hours, then daily
		Eptifibatide and tirofiban: serum creatinine at baseline then daily
Anticoagulants	Bleeding	Clinical signs of bleeding;[a] baseline aPTT, INR; Hgb, Hct, platelet count at baseline then daily
	Unfractionated heparin and LMWH: heparin-induced thrombocytopenia	Unfractionated heparin: aPTT every 6 hours until two consecutive aPTT values are at goal, then every 24 hours; ACT during PCI
		Enoxaparin, bivalirudin, and fondaparinux: serum creatinine at baseline then daily
		Enoxaparin: may consider steady-state anti-Xa levels in special populations
β-Blockers	Hypotension, heart failure, bradycardia, cardiogenic shock, AV block, exacerbation of asthma or reactive airway disease	Continuous telemetry (while hospitalized); blood pressure, heart rate, signs and symptoms of heart failure; monitor every 5 minutes before each IV bolus dose; monitor every shift while hospitalized then at each healthcare encounter after discharge
Nitroglycerin	Flushing, headache, hypotension, tachycardia	Blood pressure and heart rate; monitor every 5-15 minutes following dosage adjustment of intravenous nitroglycerin then every 1-2 hours; monitor every 5 minutes following administration of short-acting nitroglycerin
Morphine	Hypotension, respiratory depression, sedation, hypersensitivity	Blood pressure, heart rate, respiratory rate, sedation level 5 minutes after administration then every 1-2 hours for 4 hours after the last dose
Calcium channel blockers	Hypotension	Blood pressure, heart rate, every shift while hospitalized then at each healthcare encounter after discharge
	Verapamil and diltiazem: heart failure, cardiogenic shock, bradycardia, AV block	Verapamil and diltiazem: continuous telemetry (while hospitalized); signs and symptoms of heart failure every shift while hospitalized then at each healthcare encounter after discharge
Statins	GI discomfort, arthralgia, myalgia, musculoskeletal pain, hepatotoxicity	Liver function tests at baseline (prior to discharge) and if signs or symptoms of hepatotoxicity develop; creatinine kinase if severe myalgia or musculoskeletal symptoms occur; LDL-C at baseline, 4-12 weeks after initiation or dose adjustment, then every 3-12 months
Nonstatin therapies for cholesterol management	Ezetimibe and combination: GI discomfort, arthralgia, myalgia, musculoskeletal pain	Simvastatin/ezetimibe: liver function tests at baseline (prior to discharge) and if signs or symptoms of hepatoxicity develop; creatinine kinase if severe myalgia or musculoskeletal symptoms occur; LDL-C at baseline, 4-12 weeks after initiation or dose adjustment, then every 3-12 months
	Alirocumab: injection site pain, hypersensitivity	Alirocumab: LDL-C at baseline and 4-8 weeks after initiation or dose adjustment; evaluation of injection site if injection site pain develops, signs and symptoms of hypersensitivity with each healthcare encounter
ACE inhibitors	Hypotension, hyperuricemia, hyperkalemia, worsening renal function, chronic cough, angioedema	Blood pressure every shift while hospitalized, 1-2 weeks after initiation or dose adjustment, then with each healthcare encounter; serum creatinine and potassium at baseline, 1-2 weeks after initiation, then every 6-12 months; signs and symptoms of angioedema or cough with each healthcare encounter
ARBs	Hypotension, hyperuricemia, hyperkalemia, worsening renal function	Blood pressure every shift while hospitalized, 1-2 weeks after initiation or dose adjustment, then with each healthcare encounter; serum creatinine and potassium at baseline, 1-2 weeks after initiation, then every 6-12 months
Aldosterone antagonist	Hyperkalemia, worsening renal function	Blood pressure every shift while hospitalized, 1-2 weeks after initiation or dose adjustment, then with each healthcare encounter; serum creatinine and potassium at baseline, after initiation or dose adjustment: at 3 days, 1 week, monthly for 3 months, then every 3 months

ACT, activated clotting time; aPTT, activated partial thromboplastin time; GI, gastrointestinal; Hct, hematocrit; Hgb, hemoglobin; ICH, intracranial hemorrhage; INR, international normalized ratio; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention.

[a] Clinical signs of bleeding include bloody stools, melena, hematuria, hematemesis, bruising, and oozing from arterial or venous puncture sites.

Modified with permission from DiPiro JT, Talbert RL, Yee GC, et al. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2018:165-192.

For long-term risk reduction, the focus centers on control of CAD risk factors and the appropriate use of and adherence to an evidence-based medication regimen known to reduce the risk of MACE. Lifestyle modifications should be reinforced during each healthcare encounter. Similarly, control of CAD risk factors should be assessed and interventions made to improve risk factor control, if necessary. Finally, it is important to reassess the evidence-based regimen to determine the need to either escalate (eg, add additional evidence-based ACS therapies or increase their doses) or de-escalate therapy (eg, consider discontinuation of $P2Y_{12}$ inhibitor after 12 months or β-blocker after 3 years in a post-MI patient with a normal LVEF).

Medication adherence must also be assessed during each healthcare encounter. Despite evidence to support mortality reduction with secondary prevention strategies, typically less than 50% of patients remain adherent at 1 year.[110] Because nonadherence with secondary prevention medications following ACS leads to poor CV outcomes, it is paramount that patients receive thorough medication counseling (including counseling prior to hospital discharge) and be monitored for medication persistence.[1,2,99] Counseling should include assessments of health literacy level, barriers to adherence, access to medications, and understanding of instructions.[99] Additionally, patients and their caregivers should be provided written and verbal instructions about the purpose of each medication, changes to previous medication regimen, optimal time to take each medication, new allergies or medication intolerances, need for timely prescription fill after discharge, anticipated duration of therapy, consequences of nonadherence, common and/or serious adverse reactions that may develop, and drug–drug and drug–food interactions.[99] Early follow-up (within 6 weeks) after discharge has been associated with improved medication adherence and, for this reason, post-discharge follow-up is often scheduled within 1 to 2 weeks.[111]

CONCLUSION

For the majority of patients, the pathophysiology of ACS involves an acute disruption of an atherosclerotic plaque followed by platelet activation and aggregation followed by intracoronary thrombus formation. Myocardial ischemia ensues due to an acute imbalance between myocardial oxygen supply and demand and may lead to MI depending on the severity and duration of thrombotic occlusion. Therefore, the acute pharmacotherapeutic management of ACS is focused on antiplatelet, anticoagulation, and anti-ischemic therapies.

Appropriate selection of these agents depends upon patient presentation (eg, STEMI or NSTE-ACS), the decision for reperfusion (eg, PCI, fibrinolysis, or no reperfusion), and individual considerations for efficacy and safety associated with individual agents (eg, pharmacokinetic alterations, drug–drug interactions, contraindications). High-intensity statins should be initiated early and continued indefinitely for all patients with ACS without contraindications to lower LDL-C and stabilize atherosclerotic plaques. Long-term use of DAPT lowers the risk of MACE after ACS and maintains stent patency in patients who had intracoronary stent implantation during PCI. Neurohormonal blocking drugs such as β-blockers and inhibitors of the RAAS system are also associated with lower risk of MACE and should be initiated prior to hospital discharge in appropriate patients. The pharmacist plays an important role in the patient care process for ACS, collecting and analyzing clinical information, collaborating in the development and implementation of the care plan, and evaluating therapeutic outcomes.

Postclass Engaged Learning Activity

Consider the following scenarios in which patients with recent ACS hospitalizations present to the community pharmacy. Write a brief summary of the community-based interventions the pharmacist should consider, including patient counselling points.

Scenario 1: While picking up new prescriptions for aspirin 81 mg daily and prasugrel 10 mg daily, a patient asks the pharmacist for recommendations for a nonsteroidal anti-inflammatory drug (NSAID) to treat his chronic osteoarthritis. The patient states he was just discharged from the hospital for a “heart attack” and had a stent placed.

Scenario 2: A patient presents to the community pharmacy with new prescriptions for aspirin 81 mg daily and ticagrelor 90 mg twice daily stating she was just discharged from the hospital for a myocardial infarction. She also requests a refill of apixaban 5 mg twice daily which she was prescribed 6 months ago for atrial fibrillation.

Scenario 3: A patient presents to the community pharmacy requesting refills for metoprolol succinate and nitroglycerin sublingual tablets, stating he’s overdue to refill these since his discharge 6 weeks ago for a “heart attack.” When reviewing the medication profile, the pharmacist notes that the patient was also prescribed aspirin 81 mg daily and clopidogrel 75 mg daily and that neither has been refilled since the hospital discharge.

ABBREVIATIONS

ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
ACT	activated clotting time
ADP	adenosine diphosphate
AHA	American Heart Association
aPTT	activated partial thromboplastin time
ARB	angiotensin receptor blocker
ASCVD	atherosclerotic cardiovascular disease
AT	antithrombin
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CCB	calcium channel blocker
COX	cyclooxygenase
CrCl	creatinine clearance
cTn	cardiac troponin
CV	cardiovascular
CYP	cytochrome P450
DAPT	dual antiplatelet therapy
DHP	dihydropyridine
DM	diabetes mellitus
ECG	electrocardiogram
ED	emergency department
EMS	emergency medical services
ENT	equilibrative nucleoside transporter
GI	gastrointestinal
GP	glycoprotein
GRACE	Global Registry of Acute Coronary Events
HEART	History, ECG, age, risk factors, and troponin
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HIT	heparin-induced thrombocytopenia
HTN	hypertension
ICH	intracranial hemorrhage
IV	intravenous
LBBB	left bundle branch block
LDL-C	low-density lipoprotein cholesterol
LMWH	low-molecular-weight heparin
LOS	length of stay
LVEF	left ventricular ejection fraction
MACE	major adverse cardiovascular events
MI	myocardial infarction
MONA	morphine, oxygen, nitroglycerin, aspirin
NSTE-ACS	non-ST-segment elevation acute coronary syndromes
NSTEMI	non-ST-segment elevation myocardial infarction
NTG	nitroglycerin
PAR	protease-activated receptor
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin-kexin type 9
RAAS	renin–angiotensin–aldosterone system
SIHD	stable ischemic heart disease
SNS	sympathetic nervous system
STEMI	ST-segment-elevation myocardial infarction
SC	subcutaneous
TIMI	thrombolysis in myocardial infarction
UA	unstable angina
UFH	unfractionated heparin

REFERENCES

1. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;61:e78–e140.
2. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64:e139–e228.
3. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics-2018 update: A report from the American Heart Association. *Circulation*. 2018;137:e67–e492.
4. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med*. 2010;362:2155–2165.
5. Tickoo S, Bhardwaj A, Fonarow GC, Liang L, Bhatt DL, Cannon CP. Relation between hospital length of stay and quality of care in patients with acute coronary syndromes (from the American Heart Association's Get with the Guidelines—coronary artery disease data set). *Am J Cardiol*. 2016;117:201–205.
6. Sugiyama T, Hasegawa K, Kobayashi Y, Takahashi O, Fukui T, Tsugawa Y. Differential time trends of outcomes and costs of care for acute myocardial infarction hospitalizations by ST elevation and type of intervention in the United States, 2001-2011. *J Am Heart Assoc*. 2015;4:e001445.
7. Nicholson G, Gandra SR, Halbert RJ, Richhariya A, Nordyke RJ. Patient-level costs of major cardiovascular conditions: a review of the international literature. *Clinicoecon Outcomes Res*. 2016;8:495–506.
8. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol*. 2018. doi: 10.1016/j.jacc.2018.08.1038.
9. Ford TJ, Berry C, De Bruyne B, et al. Physiological predictors of acute coronary syndromes: Emerging insights from the plaque to the vulnerable patient. *JACC Cardiovasc Interv*. 2017;10:2539–2547.

10. Crea F, Liuzzo G. Pathogenesis of acute coronary syndromes. *J Am Coll Cardiol*. 2013;61:1–11.
11. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. *N Engl J Med*. 2013;368:2004–2013.
12. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. *Circ Res*. 2014;114:1852–1866.
13. Libby P, Tabas I, Fredman G, Fisher EA. Inflammation and its resolution as determinants of acute coronary syndromes. *Circ Res*. 2014;114:1867–1879.
14. Crea F, Libby P. Acute coronary syndromes: The way forward from mechanisms to precision treatment. *Circulation*. 2017;136:1155–1166.
15. Fuster V, Kovacic JC. Acute coronary syndromes: Pathology, diagnosis, genetics, prevention, and treatment. *Circ Res*. 2014;114:1847–1851.
16. Furie B, Furie BC. Mechanisms of thrombus formation. *N Engl J Med*. 2008;359:938–949.
17. Gabriel-Costa D. The pathophysiology of myocardial infarction-induced heart failure. *Pathophysiology*. 2018;25:277–284.
18. Reed GW, Rossi JE, Cannon CP. Acute myocardial infarction. *Lancet*. 2017;389:197–210.
19. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA*. 2000;284:835–842.
20. Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med*. 2003;163:2345–2353.
21. Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An intravenous nPA for treatment of infarcting myocardium early II trial substudy. *Circulation*. 2000;102:2031–2037.
22. Six AJ, Backus BE, Kelder JC. Chest pain in the emergency room: Value of the HEART score. *Neth Heart J*. 2008;16:191–196.
23. Poldervaart JM, Langedijk M, Backus BE, et al. Comparison of the GRACE, HEART and TIMI score to predict major adverse cardiac events in chest pain patients at the emergency department. *Int J Cardiol*. 2017;227:656–661.

24. Kline KP, Conti CR, Winchester DE. Historical perspective and contemporary management of acute coronary syndromes: From MONA to THROMBINS2. *Postgrad Med*. 2015;127:855–862.
25. Smith SCJr, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: A guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. *J Am Coll Cardiol*. 2011;58:2432–2446.
26. Effect of verapamil on mortality and major events after acute myocardial infarction (the Danish Verapamil Infarction Trial II–DAVIT II). *Am J Cardiol*. 1990;66:779–785.
27. Gibson RS, Boden WE, Theroux P, et al. Diltiazem and reinfarction in patients with non-Q-wave myocardial infarction. Results of a double-blind, randomized, multicenter trial. *N Engl J Med*. 1986;315:423–429.
28. Yusuf S, Collins R, MacMahon S, Peto R. Effect of intravenous nitrates on mortality in acute myocardial infarction: An overview of the randomised trials. *Lancet*. 1988;1:1088–1092.
29. GISSI-3: Effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. *Lancet*. 1994;343:1115–1122.
30. ISIS-4: A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. *Lancet*. 1995;345:669–685.
31. Siddiqi N, Neil C, Bruce M, et al. Intravenous sodium nitrite in acute ST-elevation myocardial infarction: A randomized controlled trial (NIAMI). *Eur Heart J*. 2014;35:1255–1262.
32. McCord J, Jneid H, Hollander JE, et al. Management of cocaine-associated chest pain and myocardial infarction: A scientific statement from the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. *Circulation*. 2008;117:1897–1907.
33. Figueras J, Lidon R, Cortadellas J. Rebound myocardial ischaemia following abrupt interruption of intravenous nitroglycerin infusion in patients with unstable angina at rest. *Eur Heart J*. 1991;12:405–411.

34. Ventimiglia E, Capogrosso P, Montorsi F, Salonia A. The safety of phosphodiesterase type 5 inhibitors for erectile dysfunction. *Expert Opin Drug Saf*. 2016;15:141–152.
35. McCarthy CP, Bhambhani V, Pomerantsev E, Wasfy JH. In-hospital outcomes in invasively managed acute myocardial infarction patients who receive morphine. *J Interv Cardiol*. 2018;31:150–158.
36. Kubica J, Kubica A, Jilma B, et al. Impact of morphine on antiplatelet effects of oral P2Y12 receptor inhibitors. *Int J Cardiol*. 2016;215:201–208.
37. Cabello JB, Burls A, Emparanza JI, Bayliss SE, Quinn T. Oxygen therapy for acute myocardial infarction. *Cochrane Database Syst Rev*. 2016;12:CD007160.
38. Brunton LL, Hilal-Dandan R, Knollmann BC. *Goodman & Gilman's : The Pharmacological Basis of Therapeutics*. 13th ed. New York, NY: McGraw-Hill Education; 2018. eds.http://accesspharmacy.mhmedical.com.proxy.cc.uic.edu/content.aspx?bookid=2189§ionid=170270669. Accessed December 6, 2018.
39. Bangalore S, Makani H, Radford M, et al. Clinical outcomes with beta-blockers for myocardial infarction: A meta-analysis of randomized trials. *Am J Med*. 2014;127:939–953.
40. Freemantle N, Cleland J, Young P, Mason J, Harrison J. Beta blockade after myocardial infarction: Systematic review and meta regression analysis. *BMJ*. 1999;318:1730–1737.
41. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. *JAMA*. 1982;247:1707–1714.
42. Chen ZM, Pan HC, Chen YP, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: Randomised placebo-controlled trial. *Lancet*. 2005;366:1622–1632.
43. Park JJ, Kim SH, Kang SH, et al. Effect of beta-blockers beyond 3 years after acute myocardial infarction. *J Am Heart Assoc*. 2018;(7):e007567.
44. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: The CAPRICORN randomised trial. *Lancet*. 2001;357:1385–1390.
45. Agrawal PR, Scarabelli TM, Saravolatz L, et al. Current strategies in the evaluation and management of cocaine-induced chest pain. *Cardiol Rev*. 2015;23:303–311.
46. Held PH, Yusuf S, Furberg CD. Calcium channel blockers in acute

myocardial infarction and unstable angina: An overview. *BMJ*. 1989;299:1187–1192.

47. Furberg CD, Psaty BM, Meyer JV. Nifedipine. Dose-related increase in mortality in patients with coronary heart disease. *Circulation*. 1995;92:1326–1331.
48. Bagai A, Dangas GD, Stone GW, Granger CB. Reperfusion strategies in acute coronary syndromes. *Circ Res*. 2014;114:1918–1928.
49. Gersh BJ, Stone GW, White HD, Holmes DR Jr. Pharmacological facilitation of primary percutaneous coronary intervention for acute myocardial infarction: Is the slope of the curve the shape of the future? *JAMA*. 2005;293:979–986.
50. Bagai A, Jollis JG, Dauerman HL, et al. Emergency department bypass for ST-Segment-elevation myocardial infarction patients identified with a prehospital electrocardiogram: A report from the American Heart Association Mission: Lifeline program. *Circulation*. 2013;128:352–359.
51. Ting HH, Krumholz HM, Bradley EH, et al. Implementation and integration of prehospital ECGs into systems of care for acute coronary syndrome: A scientific statement from the American Heart Association Interdisciplinary Council on Quality of Care and Outcomes Research, Emergency Cardiovascular Care Committee, Council on Cardiovascular Nursing, and Council on Clinical Cardiology. *Circulation*. 2008;118:1066–1079.
52. McNamara RL, Wang Y, Herrin J, et al. Effect of door-to-balloon time on mortality in patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol*. 2006;47:2180–2186.
53. Gibson CM, Pride YB, Frederick PD, et al. Trends in reperfusion strategies, door-to-needle and door-to-balloon times, and in-hospital mortality among patients with ST-segment elevation myocardial infarction enrolled in the National Registry of Myocardial Infarction from 1990 to 2006. *Am Heart J*. 2008;156:1035–1044.
54. Langabeer JR, Henry TD, Kereiakes DJ, et al. Growth in percutaneous coronary intervention capacity relative to population and disease prevalence. *J Am Heart Assoc*. 2013;2:e000370.
55. Bonnefoy E, Lapostolle F, Leizorovicz A, et al. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: A randomised study. *Lancet*. 2002;360:825–829.
56. Pinto DS, Frederick PD, Chakrabarti AK, et al. Benefit of transferring ST-

segment-elevation myocardial infarction patients for percutaneous coronary intervention compared with administration of onsite fibrinolytic declines as delays increase. *Circulation*. 2011;124:2512–2521.

57. Jneid H, Addison D, Bhatt DL, et al. 2017 AHA/ACC clinical performance and quality measures for adults With ST-elevation and non-ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *Circ Cardiovasc Qual Outcomes*. 2017;70(16):2048–2090.
58. Dasari TW, Roe MT, Chen AY, et al. Impact of time of presentation on process performance and outcomes in ST-segment-elevation myocardial infarction: A report from the American Heart Association: Mission Lifeline program. *Circ Cardiovasc Qual Outcomes*. 2014;7:656–663.
59. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39:119–177.
60. Jinatongthai P, Kongwatcharapong J, Foo CY, et al. Comparative efficacy and safety of reperfusion therapy with fibrinolytic agents in patients with ST-segment elevation myocardial infarction: A systematic review and network meta-analysis. *Lancet*. 2017;390:747–759.
61. Armstrong PW, Gershlick AH, Goldstein P, et al. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med*. 2013;368:1379–1387.
62. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol*. 2011;58:e44–e122.
63. Dobesh PP, Varnado S, Doyle M. Antiplatelet agents in cardiology: A report on aspirin, clopidogrel, prasugrel, and ticagrelor. *Curr Pharm Des*. 2016;22:1918–1932.
64. Current-Oasis Investigators. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *N Engl J Med*. 2010;363:930–942.
65. Akers WS, Oh JJ, Oestreich JH, Ferraris S, Wethington M, Steinhubl SR. Pharmacokinetics and pharmacodynamics of a bolus and infusion of

cangrelor: a direct, parenteral P2Y12 receptor antagonist. *J Clin Pharmacol*. 2010;50:27–35.

66. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345:494–502.
67. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001–2015.
68. Tantry US, Bonello L, Aradi D, et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. *J Am Coll Cardiol*. 2013;62:2261–2273.
69. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: Randomised placebo-controlled trial. *Lancet*. 2005;366:1607–1621.
70. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med*. 2005;352:1179–1189.
71. Roe MT, Armstrong PW, Fox KA, et al. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. *N Engl J Med*. 2012;367:1297–1309.
72. Dobesh PP, Oestreich JH. Ticagrelor: Pharmacokinetics, pharmacodynamics, clinical efficacy, and safety. *Pharmacotherapy*. 2014;34:1077–1090.
73. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045–1057.
74. Mahaffey KW, Wojdyla DM, Carroll K, et al. Ticagrelor compared with clopidogrel by geographic region in the Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation*. 2011;124:544–554.
75. Berwanger O, Nicolau JC, Carvalho AC, et al. Ticagrelor vs clopidogrel after fibrinolytic therapy in patients with ST-elevation myocardial infarction: A randomized clinical trial. *JAMA Cardiol*. 2018;3:391–399.
76. Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med*. 2013;368:1303–1313.
77. Steinhubl SR, Oh JJ, Oestreich JH, Ferraris S, Charnigo R, Akers WS.

Transitioning patients from cangrelor to clopidogrel: Pharmacodynamic evidence of a competitive effect. *Thromb Res*. 2008;121:527–534.

78. Dovlatova NL, Jakubowski JA, Sugidachi A, Heptinstall S. The reversible P2Y antagonist cangrelor influences the ability of the active metabolites of clopidogrel and prasugrel to produce irreversible inhibition of platelet function. *J Thromb Haemost*. 2008;6:1153–1159.
79. Angiolillo DJ, Rollini F, Storey RF, et al. International expert consensus on wwitching platelet P2Y12 receptor-inhibiting therapies. *Circulation*. 2017;136:1955–1975.
80. Dobesh PP, Latham KA. Advancing the battle against acute ischemic syndromes: A focus on the GP IIb-IIIa inhibitors. *Pharmacotherapy*. 1998;18:663–685.
81. Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e495S–e530S.
82. Kastrati A, Mehilli J, Neumann FJ, et al. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: The ISAR-REACT 2 randomized trial. *JAMA*. 2006;295:1531–1538.
83. Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med*. 2006;355:2203–2216.
84. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med*. 2008;358:2218–2230.
85. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e24S–e43S.
86. Oler A, Whooley MA, Oler J, Grady D. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. *JAMA*. 1996;276:811–815.
87. Antman EM, Cohen M, Radley D, et al. Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction. TIMI 11B-ESSENCE meta-analysis. *Circulation*. 1999;100:1602–1608.

88. Ferguson JJ, Califf RM, Antman EM, et al. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: Primary results of the SYNERGY randomized trial. *JAMA*. 2004;292:45–54.
89. Antman EM, Morrow DA, McCabe CH, et al. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med*. 2006;354:1477–1488.
90. Navarese EP, De Luca G, Castriota F, et al. Low-molecular-weight heparins vs. unfractionated heparin in the setting of percutaneous coronary intervention for ST-elevation myocardial infarction: A meta-analysis. *J Thromb Haemost*. 2011;9:1902–1915.
91. Turpie AG, Lensing AW, Fuji T, Boyle DA. Pharmacokinetic and clinical data supporting the use of fondaparinux 1.5 mg once daily in the prevention of venous thromboembolism in renally impaired patients. *Blood Coagul Fibrinolysis*. 2009;20:114–121.
92. Fifth Organization to Assess Strategies in Acute Ischemic Syndromes I, Yusuf S, Mehta SR, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med*. 2006;354:1464–1476.
93. Yusuf S, Mehta SR, Chrolavicius S, et al. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: The OASIS-6 randomized trial. *JAMA*. 2006;295:1519–1530.
94. Kastrati A, Neumann FJ, Mehilli J, et al. Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. *N Engl J Med*. 2008;359:688–696.
95. Schulz S, Richardt G, Laugwitz KL, et al. Prasugrel plus bivalirudin vs. clopidogrel plus heparin in patients with ST-segment elevation myocardial infarction. *Eur Heart J*. 2014;35:2285–2294.
96. Shahzad A, Kemp I, Mars C, et al. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): An open-label, single centre, randomised controlled trial. *Lancet*. 2014;384:1849–1858.
97. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/ guideline on the management of blood cholesterol: A report of the American College of Cardiology/American Heart Association Task Force

on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018. https://doi.org/10.1016/j.jacc.2018.11.003.

98. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med*. 2018;379:2097–2107.
99. Wiggins BS, Rodgers JE, DiDomenico RJ, Cook AM, Page RLII. Discharge counseling for patients with heart failure or myocardial infarction: A best practices model developed by members of the American College of Clinical Pharmacy's Cardiology Practice and Research Network based on the Hospital to Home (H2H) Initiative. *Pharmacotherapy*. 2013;33:558–580.
100. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2016;68:1082–1115.
101. Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA*. 2016;315:1735–1749.
102. Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015;372:1791–1800.
103. Hulten E, Jackson JL, Douglas K, George S, Villines TC. The effect of early, intensive statin therapy on acute coronary syndrome: A meta-analysis of randomized controlled trials. *Arch Intern Med*. 2006;166:1814–1821.
104. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372:2387–2397.
105. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA*. 1995;273:1450–1456.
106. Rodrigues EJ, Eisenberg MJ, Pilote L. Effects of early and late administration of angiotensin-converting enzyme inhibitors on mortality after myocardial infarction. *Am J Med*. 2003;115:473–479.

107. Lee VC, Rhew DC, Dylan M, Badamgarav E, Braunstein GD, Weingarten SR. Meta-analysis: Angiotensin-receptor blockers in chronic heart failure and high-risk acute myocardial infarction. *Ann Intern Med*. 2004;141:693–704.
108. Bossard M, Binbraik Y, Beygui F, et al. Mineralocorticoid receptor antagonists in patients with acute myocardial infarction: A systematic review and meta-analysis of randomized trials. *Am Heart J*. 2018;195:60–69.
109. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med*. 2011;365:2002–2012.
110. Kumbhani DJ, Steg PG, Cannon CP, et al. Adherence to secondary prevention medications and four-year outcomes in outpatients with atherosclerosis. *Am J Med*. 2013;126:693–700e1.
111. Faridi KF, Peterson ED, McCoy LA, Thomas L, Enriquez J, Wang TY. Timing of first postdischarge follow-up and medication adherence after acute myocardial infarction. *JAMA Cardiol*. 2016;1:147–155.

Peripheral Arterial Disease

Zachary Stacy and Sheryl Chow

KEY CONCEPTS

1. The prevalence of peripheral arterial disease (PAD) is related to age and the presence of atherosclerotic risk factors for cardiovascular disease (CVD).
2. Despite significant morbidity and mortality, PAD awareness remains low resulting in many undiagnosed and untreated patients.
3. The clinical presentation of PAD is variable and includes a range of symptoms. The two most common characteristics of PAD are intermittent claudication (IC) and pain at rest in the lower extremities.
4. The ankle-brachial index (ABI) is a simple, noninvasive, quantitative test that is a highly sensitive and specific tool to diagnose PAD.
5. Several atherosclerotic risk factors play an important role in the development and progression of PAD. Many of these risk factors are modifiable using various nonpharmacologic and pharmacologic interventions.
6. Nonpharmacologic interventions, such as a supervised exercise program, can improve a patient's quality of life and reduce leg symptoms.
7. Antiplatelet therapy, such as aspirin or clopidogrel, is recommended to reduce myocardial infarction, stroke, and vascular death in patients with PAD.
8. In addition to exercise therapy and risk factor modification, cilostazol is an effective medication to reduce leg symptoms and increase walking distance in patients with IC.

Preclass Engaged Learning Activity

Watch a *Patient Stories* video from the nonprofit organization Vascular Cures' website (http://vascularcures.org/video-library/). These 3-minute testimonial videos describe the symptoms and limitations patients experience due to peripheral arterial disease, and the interventions responsible for the improvement in their quality of life. The video is useful to enhance your understanding regarding the COLLECT and ASSESS steps in the patient care process.

Self-Guided Questions:

1. What are the typical and atypical symptoms reported by patients in these testimonial videos?
2. Based on the patient stories, how would you assess their symptoms using the Fontaine and Rutherford classification systems?
3. What types of pharmacological and nonpharmacological interventions did these patients receive for their PAD?

INTRODUCTION

Peripheral arterial disease (PAD), the most common form of peripheral vascular disease, is a manifestation of progressive narrowing of arteries due to atherosclerosis.[1] PAD is associated with elevated risk of cardiovascular disease (CVD) morbidity and mortality, even in the absence of history of acute myocardial infarction (AMI), stroke, or other manifestations of CVD.[2] Patients with PAD have approximately the same relative risk of death from CVD as do patients with a history of coronary or cerebrovascular disease, and PAD should be considered a surrogate marker of subclinical coronary artery disease (CAD) and other vascular territories. The treatment of PAD focuses on minimizing cardiovascular risk factors and decreasing the functional impairment caused by symptoms of intermittent claudication (IC) through nonpharmacologic and pharmacologic therapy.[3]

EPIDEMIOLOGY

1 PAD affects approximately 8.5 million Americans age 40 years or older with an overall prevalence of 2.69%.[1] One estimate predicted the overall world

prevalence in 2010 to be over 200 million people.[4] The prevalence of PAD is highly dependent on age, being infrequent in younger individuals and common in older individuals (**Fig. e34-1**). In age- and gender-adjusted logistic regression analyses, black race/ethnicity (odds ratio [OR] 2.39), current smoking (OR 4.23), diabetes (OR 2.08), hypertension (HTN; OR 1.75), hypercholesterolemia (OR 1.67), and impaired renal function (estimated glomerular filtration rate <60 mL/min/1.73 m^2) (OR 2.17) were associated with more prevalent PAD.[5] Individuals with PAD are also more likely to have a self-reported history of any CAD or CVD but, interestingly, no association with elevated body mass index. The reported relative risk of death from CVD in patients with PAD is reported to range from 2 to 5.1 in patients with or without CVD and 2.9 to 5.7 in patients without known CVD.[6] The risk of death is approximately the same in men and women and is elevated even in asymptomatic patients. Annual mortality significantly increases as the ankle-brachial index (ABI) decreases, with one study demonstrating a significant decline in survival with each 0.1 decrement in ABI.[7,8]

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

Chronic Heart Failure

Robert B. Parker, Jean M. Nappi, and Larisa H. Cavallari

KEY CONCEPTS

1. Heart failure (HF) is a progressive clinical syndrome that can result from any changes in cardiac structure or function that impair the ability of the ventricle to fill with or eject blood. HF may be caused by an abnormality in systolic function, diastolic function, or both. The leading causes of HF are coronary artery disease and hypertension. The primary manifestations of the syndrome are dyspnea, fatigue, and fluid retention.
2. In heart failure with reduced ejection fraction (HFrEF), there is a decrease in cardiac output resulting in activation of a number of compensatory responses that attempt to maintain adequate cardiac output. These responses include activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS). These compensatory mechanisms are responsible for the symptoms of HFrEF and contribute to disease progression.
3. Our current understanding of HFrEF pathophysiology is best described by the neurohormonal model. Activation of endogenous neurohormones including norepinephrine, angiotensin II, aldosterone, vasopressin, and numerous proinflammatory cytokines play an important role in ventricular remodeling and the subsequent progression of HF. Importantly, pharmacotherapy targeted at antagonizing this neurohormonal activation slows the progression of HFrEF and improves survival.
4. Most patients with HFrEF should be routinely treated with guideline-directed medical therapy (GDMT) that includes an angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), or angiotensin II blocker/neprilysin inhibitor and an evidence-based β-blocker. Selected patients should also receive aldosterone antagonists, loop diuretics, or hydralazine/nitrates. The benefits of these medications on

slowing HF progression, reducing morbidity and mortality, and/or improving symptoms are clearly established.

5. In patients with HFrEF, ACE inhibitors improve survival, slow disease progression, reduce hospitalizations, and improve quality of life. The doses for these agents should be targeted at those shown in clinical trials to improve survival. ARBs are recommended for patients intolerant to ACE inhibitors due to angioedema or cough. In symptomatic patients receiving an ACE inhibitor or ARB, replacement with the combination ARB/neprilysin inhibitor is recommended.

6. The β-blockers carvedilol, metoprolol succinate, and bisoprolol prolong survival, decrease hospitalizations and need for transplantation, and promote “reverse remodeling” of the left ventricle. These agents are recommended for all patients with HFrEF unless contraindicated. Therapy must be instituted at low doses, with slow upward titration to the target dose.

7. Although chronic loop diuretic therapy frequently is used in patients with HFrEF or HFpEF, it is not mandatory. Diuretic therapy along with sodium restriction is required only in those patients with peripheral edema and/or pulmonary congestion. Many patients will need continued diuretic therapy to maintain euvolemia after fluid overload is resolved.

8. Aldosterone antagonists reduce mortality in patients with HFrEF and New York Heart Association (NYHA) class II to IV symptoms and thus should be strongly considered in these patients provided that potassium and renal function can be carefully monitored. Aldosterone antagonists may be considered to reduce the risk of hospitalization in patients with HFpEF.

9. The combination of hydralazine and nitrates improves the composite endpoint of mortality, hospitalizations for HF, and quality of life in African Americans receiving standard therapy for HFrEF. Current guidelines recommend the addition of hydralazine and nitrates to self-described African Americans with HFrEF and moderate-to-severe symptoms that are receiving GDMT with ACE inhibitors and β-blockers. Hydralazine and a nitrate might be reasonable in patients unable to tolerate either an ACE inhibitor or ARB because of renal insufficiency, hyperkalemia, or possibly hypotension.

10. Digoxin does not improve survival in patients with HFrEF but does provide symptomatic benefits. Digoxin doses should be adjusted to achieve plasma concentrations of 0.5 to 0.9 ng/mL (mcg/L; 0.6-1.2 nmol/L); higher plasma

concentrations are not associated with additional benefits but may be associated with increased risk of toxicity.

11 Treatment of heart failure with preserved ejection fraction (HFpEF) should be targeted at symptom reduction as well as underlying cause. Patients with HFpEF are often treated differently than those with HFrEF.

Preclass Engaged Learning Activity

Watch the two videos below.

1. Congestive heart failure (CHF) - systolic, diastolic, left side, right side, & symptoms by Osmosis. https://tinyurl.com/jb8fcqx. This video provides an overview of the pathophysiology of heart failure due to both systolic and diastolic dysfunction. It also explains how heart failure symptoms relate to the underlying pathophysiology of this disorder. A thorough understanding of heart failure pathophysiology and symptoms are key for students understanding how pharmacotherapy affects symptoms and improves overall outcomes. This will assist student understanding of the COLLECT and ASSESS steps in the patient care process.
2. Chronic Management of Heart Failure A Guideline Approach by Myung Park, MD. https://tinyurl.com/uklfrmf. This video covers guideline-directed medical therapy for heart failure with reduced ejection fraction (HFrEF). It is useful to increase student understanding of the PLAN and IMPLEMENT steps in the patient care process.

INTRODUCTION

1 2 Heart failure (HF) is a progressive clinical syndrome that can result from any abnormality in cardiac structure or function that impairs the ability of the ventricle to fill with or eject blood.[1] HF may be caused by an abnormality in systolic function, diastolic function, or both. Making the distinction is important because the treatment of HF may be quite different depending on whether the predominant mechanism of the disorder is systolic or diastolic dysfunction. HF is the final common pathway for numerous cardiac disorders including those affecting the pericardium, heart valves, and myocardium. Diseases that adversely affect ventricular diastole (filling), ventricular systole (contraction), or both can

lead to HF.

For many years it was believed that reduced myocardial contractility, or systolic dysfunction (ie, reduced left ventricular ejection fraction [LVEF]), now referred to as heart failure with reduced ejection fraction (HFrEF), was the sole disturbance in cardiac function responsible for HF. However, it is now recognized that large numbers of patients with the HF syndrome have a relatively normal systolic function (ie, normal LVEF). This condition is now referred to as HF with preserved LVEF (HFpEF) and is believed to be primarily due to diastolic dysfunction of the heart.[1] Approximately 50% of patients with HF have preserved LVEF with disturbances in relaxation (lusitropic) properties of the heart, or diastolic dysfunction.[1,2] However, regardless of the etiology of HF, the underlying pathophysiologic process and principal clinical manifestations (fatigue, dyspnea, and often volume overload) are similar and appear to be independent of the initial cause. This chapter will focus on the treatment of patients with chronic HFrEF and HFpEF. Chapter 36, "Acute Decompensated Heart Failure," discusses the treatment of acute decompensated HF.

EPIDEMIOLOGY

HF is an epidemic public health problem in the United States.[2] Approximately 6.5 million Americans have HF with 1,000,000 new cases diagnosed each year.[2] Unlike most other cardiovascular diseases, the incidence and prevalence of HF are increasing and are expected to continue to increase over the next few decades as the population ages. A large majority of patients with HF are elderly, with multiple comorbid conditions that influence morbidity and mortality.[2] Improved survival from treatment of comorbidities such as hypertension and coronary artery disease as well as more widespread use of device therapy including implantable cardioverter-defibrillators and cardiac resynchronization therapy are likely contributors to the increased incidence and prevalence of HF.[2,3] Annual hospital discharges for HF are approximately 900,000 and HF is a common hospital discharge diagnosis in individuals over age 65.[2] The disorder also has a tremendous economic impact, with this expected to increase markedly as the baby-boom generation ages. The annual expenditures for HF were over $30 billion, with estimates approaching $70 billion by 2030.[2] Thus, HF is a major medical problem, with a substantial economic impact that is expected to become even more significant as the population ages.

Despite prodigious advances in our understanding of the etiology, pathophysiology, and pharmacotherapy of HF, the prognosis for patients with this disorder remains grim. Although the mortality rates have declined over the last 50 years, the overall 5-year survival remains approximately 42% for all patients with a diagnosis of HF, with mortality increasing with symptom severity.[1,2] Death is classified as sudden in about 40% of patients, implicating serious ventricular arrhythmias as the underlying cause.[1] Factors affecting the prognosis of patients with HF include, but are not limited to, age, gender, LVEF, renal function, natriuretic peptide plasma concentrations, diabetes, metabolic syndrome, the extent of underlying coronary artery disease, blood pressure (BP), HF etiology, and drug or device therapy. Recent models incorporating these and other factors enable clinicians to develop reliable estimates of an individual patient's prognosis.[1]

ETIOLOGY

1 2 HF can result from any disorder that affects the ability of the heart to contract (systolic function) and/or relax (diastolic dysfunction); common causes of HF are shown in **Table 35-1**.[4] HF with reduced systolic function (ie, reduced LVEF) is the classic, more familiar form of the disorder and is now referred to as heart failure with reduced ejection fraction (HFrEF). Up to 50% of patients with HF have preserved left ventricular systolic function with presumed diastolic dysfunction, now termed heart failure with preserved ejection fraction (HFpEF).[5] Patients with HFpEF typically are elderly, female, and obese, and have hypertension (HTN), atrial fibrillation, or diabetes.[6] Mortality is lower in patients with HFpEF compared to patients with HFrEF, despite HFpEF patients being older.[6] Patients with HFpEF are more likely to have hypertension but less likely to have coronary disease (41% vs 55%, respectively).[6]

TABLE 35-1 Causes of Chronic Heart Failure

Heart failure with reduced ejection fraction (HFrEF)

- Coronary artery disease (eg, myocardial infarction or ischemia)
- Dilated cardiomyopathies (eg, drug-induced, viral infections, postpartum)
- Pressure overload (eg, systemic or pulmonary hypertension, aortic or pulmonic valve stenosis)
- Volume overload (eg, valvular regurgitation, shunts, high-output states)

Heart failure with preserved ejection fraction (HFpEF)

- Increased ventricular stiffness
  - Ventricular hypertrophy (eg, hypertrophic cardiomyopathy, hypertension)
  - Infiltrative myocardial diseases (eg, amyloidosis, sarcoidosis, endomyocardial fibrosis)
  - Myocardial infarction or ischemia
- Mitral or tricuspid valve stenosis
- Pericardial disease (eg, pericarditis, pericardial tamponade)

Data from Reference 4.

1 Coronary artery disease is the most common cause of HFrEF, accounting for up to 75% of cases.[4] MI leads to a reduction in muscle mass due to the death of affected myocardial cells. The degree to which contractility is impaired depends on the size of the infarction. To attempt to maintain cardiac output (CO), the surviving myocardium undergoes a compensatory remodeling, thus beginning the maladaptive process that initiates the HF syndrome and leads to further injury to the heart. This is discussed in greater detail in Pathophysiology below. Myocardial ischemia and infarction also affect the diastolic properties of the heart by increasing ventricular stiffness and slowing ventricular relaxation. Thus, MI frequently results in systolic and diastolic dysfunction.

Impaired systolic function is a cardinal feature of dilated cardiomyopathies. Although the cause of reduced contractility frequently is unknown, abnormalities such as interstitial fibrosis, cellular infiltrates, cellular hypertrophy, and myocardial cell degeneration are seen commonly on histologic examination. Inherited forms of dilated as well as hypertrophic cardiomyopathies may also occur.[1,4]

Pressure or volume overload causes ventricular hypertrophy, which attempts to return contractility to a near-normal state. If the pressure or volume overload persists, the remodeling process results in alterations in the geometry of the hypertrophied myocardial cells and is accompanied by increased collagen deposition in the extracellular matrix. Thus, both systolic and diastolic functions may be impaired.[7] Examples of pressure overload include systemic or pulmonary HTN and aortic or pulmonic valve stenosis.

HTN remains an important cause and/or contributor to both HFrEF and HFpEF in many patients, particularly women, the elderly, and African Americans.[1,4] The role of HTN should not be underestimated because it is an important risk factor for ischemic heart disease and present in a high percentage of patients with coronary artery disease. HF is a largely preventable disorder such that appropriate management of lifestyle risk factors (eg, HTN, coronary heart disease, smoking, obesity, physical activity, diabetes) is key to minimize the risk of HF development.

PATHOPHYSIOLOGY

Normal Cardiac Function

To understand the pathophysiologic processes in HF, a basic understanding of normal cardiac function is necessary. CO is defined as the volume of blood ejected per unit time (L/min) and is the product of heart rate (HR) and stroke volume (SV):

$$CO = HR \times SV$$

The relationship between CO and mean arterial pressure (MAP) is:

$$MAP = CO \times \text{systemic vascular resistance (SVR)}$$

HR is controlled by the autonomic nervous system. SV, or the volume of blood ejected during systole, depends on preload, afterload, and contractility.[7] As defined by the Frank-Starling mechanism, the ability of the heart to alter the force of contraction depends on changes in preload. As myocardial sarcomere length is stretched, the number of cross-bridges between thick and thin myofilaments increases, resulting in an increase in the force of contraction. The length of the sarcomere is determined primarily by the volume of blood in the ventricle; therefore, left ventricular end-diastolic volume (LVEDV) is the primary determinant of preload. In normal hearts, the preload response is the primary compensatory mechanism such that a small increase in end-diastolic volume results in a large increase in CO. Because of the relationship between pressure and volume in the heart, left ventricular end-diastolic pressure (LVEDP) is often used in the clinical setting to estimate preload. The hemodynamic measurement used to clinically estimate LVEDP is the pulmonary capillary wedge pressure (PCWP), also known as the pulmonary artery occlusion pressure

(PAOP). Afterload is a more complex physiologic concept that can be viewed pragmatically as the sum of forces preventing active forward ejection of blood by the ventricle. Major components of afterload are ejection impedance, wall tension, and regional wall geometry. In patients with left ventricular systolic dysfunction, an inverse relationship exists between afterload (estimated clinically by SVR) and SV such that increasing afterload causes a decrease in SV (**Fig. 35-1**). Contractility is the intrinsic property of cardiac muscle describing fiber shortening and tension development.

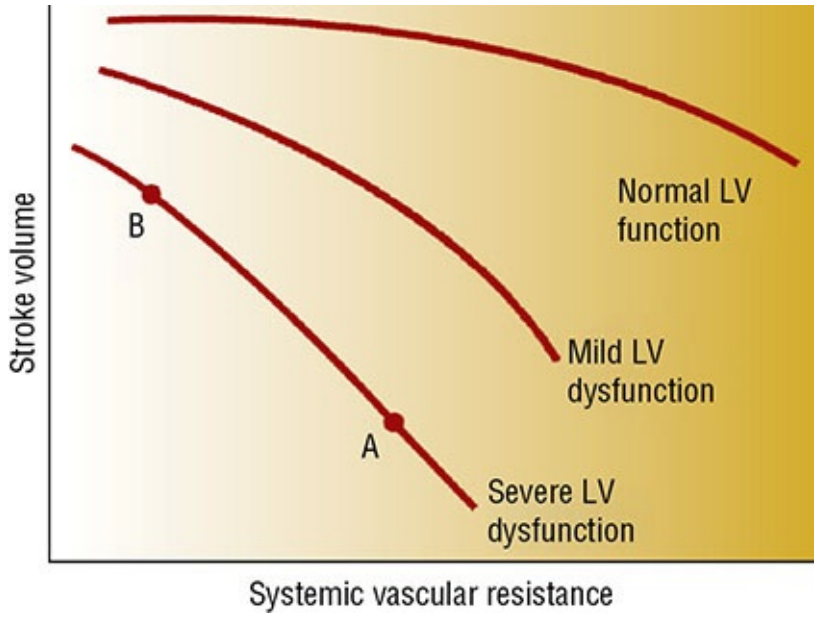


FIGURE 35-1 Relationship between stroke volume and systemic vascular resistance. In an individual with normal left ventricular (LV) function, increasing systemic vascular resistance has little effect on stroke volume. As the extent of LV dysfunction increases, the negative, inverse relationship between stroke volume and systemic vascular resistance becomes more important (B to A).

Heart Failure with Preserved Ejection Fraction

This disorder can be defined as a condition in which myocardial relaxation and filling are impaired and incomplete. The ventricle is unable to accept an adequate volume of blood from the venous system, does not fill at low pressure, and/or is unable to maintain normal SV. In its most severe form, HFpEF results in overt symptoms of HF. In modest HFpEF, symptoms of dyspnea and fatigue occur only during stress or activity, when HR and end-diastolic volume increase. In its mildest form, HFpEF can be manifested as a slow or delayed pattern of relaxation and filling with little or no elevation in diastolic pressure and few or

no cardiac symptoms. The congestive symptoms that occur with HFpEF are a manifestation of increased pulmonary venous pressures. HFpEF is caused by impaired myocardial relaxation and/or increased diastolic stiffness. When HF is caused by a predominant abnormality in diastolic function, the ventricular chamber is not enlarged, and EF may be normal or even elevated.[8] **Figure 35-2** shows the pressure-volume relationship in a patient with normal versus abnormal diastolic function. Changes in the myocardium are associated with a shift upward and to the left of the pressure-volume curve so that for any increase in LV volume, diastolic pressure rises to a much greater level than normally would occur. Clinically, patients present with reduced exercise tolerance and dyspnea when they have elevated LV diastolic pressures. Patients with HFpEF have a predominant abnormality in diastolic function, whereas patients with HFrEF have a predominant abnormality in systolic function of the LV.

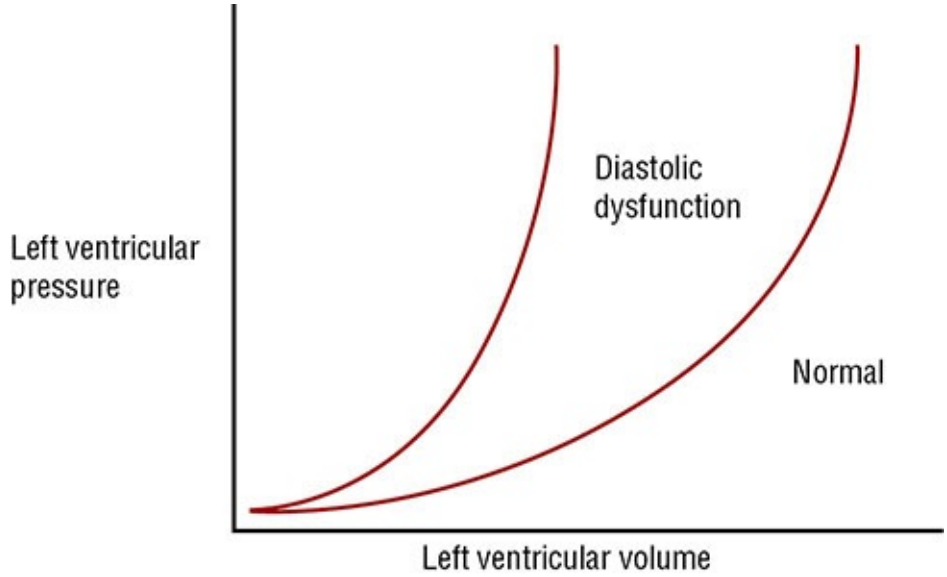


FIGURE 35-2 Diastolic pressure-volume relationship in a normal patient (right trace) and a patient with diastolic dysfunction (left trace).

HFpEF may represent a collection of syndromes because there is significant variability in morphology and functional presentation.[9] Some feel that a systemic inflammatory state and microvascular endothelial dysfunction play a role.[5] Although CAD is a common comorbidity, the symptoms of heart failure are often disproportionate to the severity of coronary artery disease. Obesity, hypertension, and diabetes are proinflammatory and are frequent comorbidities in patients with HFpEF. During physical exertion, CO increases through integrated enhancements in venous return, contractility, HR, and peripheral vasodilation. The vasodilation that normally occurs during exercise is impaired

in HFpEF.[9] Pulmonary HTN is also a common finding. Abnormalities in each of these components of normal exercise reserve function have been identified in HFpEF and all may contribute to pathophysiology in individual patients.[5,8]

Compensatory Mechanisms in HFrEF

2 HFrEF is a progressive disorder initiated by any event that impairs the ability of the heart to contract and sometimes relax resulting in a decrease in CO. The index event may have an acute onset, as with MI, or the onset may be slow, as with long-standing HTN. Regardless of the index event, a decrease in CO results in activation of compensatory responses to maintain the circulation.[7,10] These compensatory responses include: (a) tachycardia and increased contractility through sympathetic nervous system (SNS) activation, (b) the Frank-Starling mechanism, whereby an increase in preload results in an increase in SV, (c) vasoconstriction, and (d) ventricular hypertrophy and remodeling. Compensatory responses evolved to provide short-term support to maintain circulatory homeostasis after acute reductions in BP or renal perfusion. However, the persistent decline in CO in HF triggers long-term activation of these compensatory responses resulting in the complex functional, structural, biochemical, and molecular changes important for the development and progression of HF. The beneficial and detrimental effects of these compensatory responses are described below and are summarized in **Table 35-2**.

TABLE 35-2 Beneficial and Detrimental Effects of the Compensatory Responses in Heart

Compensatory Response	Beneficial Effects of Compensation	Detrimental Effects of Compensation
Increased preload (through Na^+ and retention)	Optimizes stroke volume via Frank-Starling mechanism	Pulmonary and systemic congestion and edema formation Increased MVO_2
Vasoconstriction	Maintains BP in face of reduced CO Shunts blood from nonessential organs to brain and heart	Increased MVO_2 Increased afterload decreases stroke volume and further activates the compensatory responses
Tachycardia and increased contractility (due to SNS activation)	Helps maintain CO	Increased MVO_2 Shortened diastolic filling time β_1-receptor downregulation, decreased receptor sensitivity Precipitation of ventricular arrhythmias Increased risk of myocardial cell death
Ventricular hypertrophy and remodeling	Helps maintain CO Reduces myocardial wall stress Decreases MVO_2	Diastolic dysfunction Systolic dysfunction Increased risk of myocardial cell death Increased risk of myocardial ischemia Increased arrhythmia risk Fibrosis

BP, blood pressure; CO, cardiac output; MVO2, myocardial oxygen demand; SNS, sympathetic nervous system.

Tachycardia and Increased Contractility

The increase in HR and contractility that rapidly occurs in response to a drop in CO is primarily due to the release of norepinephrine (NE) from adrenergic nerve terminals, although parasympathetic nervous system activity is also diminished.[10] Loss of atrial contribution to ventricular filling also can occur (atrial fibrillation, ventricular tachycardia), reducing ventricular performance even more. Because ionized calcium is sequestered into the sarcoplasmic reticulum and pumped out of the cell during diastole, the shortened diastolic time with increases in HR also results in a higher average intracellular calcium concentration during diastole, increasing actin-myosin interaction, augmenting

the active resistance to fibril stretch, and reducing lusitropy. Conversely, the higher average calcium concentration translates into greater filament interaction during systole, generating more tension.[7] Increasing HR also increases myocardial oxygen demand. If ischemia is induced or worsened, both diastolic and systolic functions may become impaired, and SV can drop precipitously.

Fluid Retention and Increased Preload

Augmentation of preload is another compensatory response that is rapidly activated in response to decreased CO. Renal perfusion in HF is reduced due to both depressed CO and redistribution of blood away from nonvital organs. The kidney interprets the reduced perfusion as an ineffective blood volume, resulting in activation of the renin-angiotensin-aldosterone system (RAAS) in an attempt to maintain BP and increase renal sodium and water retention. Reduced renal perfusion and increased sympathetic tone also stimulate renin release from juxtaglomerular cells in the kidney. As shown in **Fig. 35-3**, renin is responsible for conversion of angiotensinogen to angiotensin I. Angiotensin I is converted to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II may also be generated via non–ACE-dependent pathways. Angiotensin II stimulates aldosterone release from the adrenal gland, thereby providing an additional mechanism for renal sodium and water retention. As intravascular volume increases secondary to sodium and water retention, left ventricular volume and pressure (preload) increase, sarcomeres are stretched, and the force of contraction is enhanced.[7] While the preload response is the primary compensatory mechanism in normal hearts, the chronically failing heart usually has exhausted its preload reserve.[7] As shown in **Fig. 35-4**, increases in preload will increase SV only to a certain point. Once the flat portion of the curve is reached, further increases in preload will only lead to pulmonary or systemic congestion, a detrimental result.[7] Figure 35-4 also shows that the curve is flatter in patients with left ventricular dysfunction. Consequently, a given increase in preload in a patient with HF will produce a smaller increment in SV than in an individual with normal ventricular function.

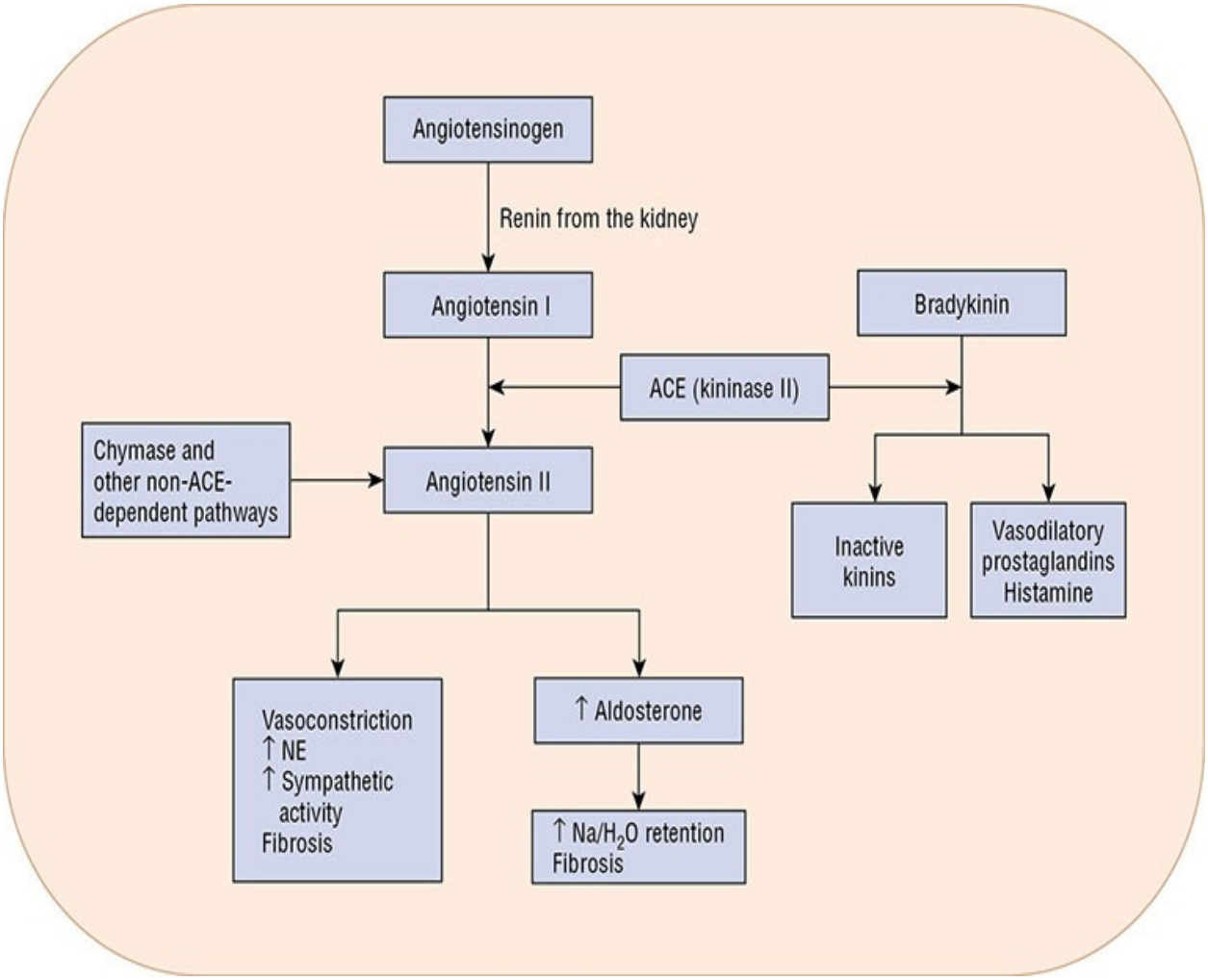


FIGURE 35-3 Physiology of the renin-angiotensin-aldosterone system. Renin produces angiotensin I from angiotensinogen. Angiotensin I is cleaved to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II has a number of physiologic actions that are detrimental in heart failure. Note that angiotensin II can be produced in a number of tissues, including the heart, independent of ACE activity. ACE is also responsible for the breakdown of bradykinin. Inhibition of ACE results in accumulation of bradykinin that, in turn, enhances the production of vasodilatory prostaglandins.

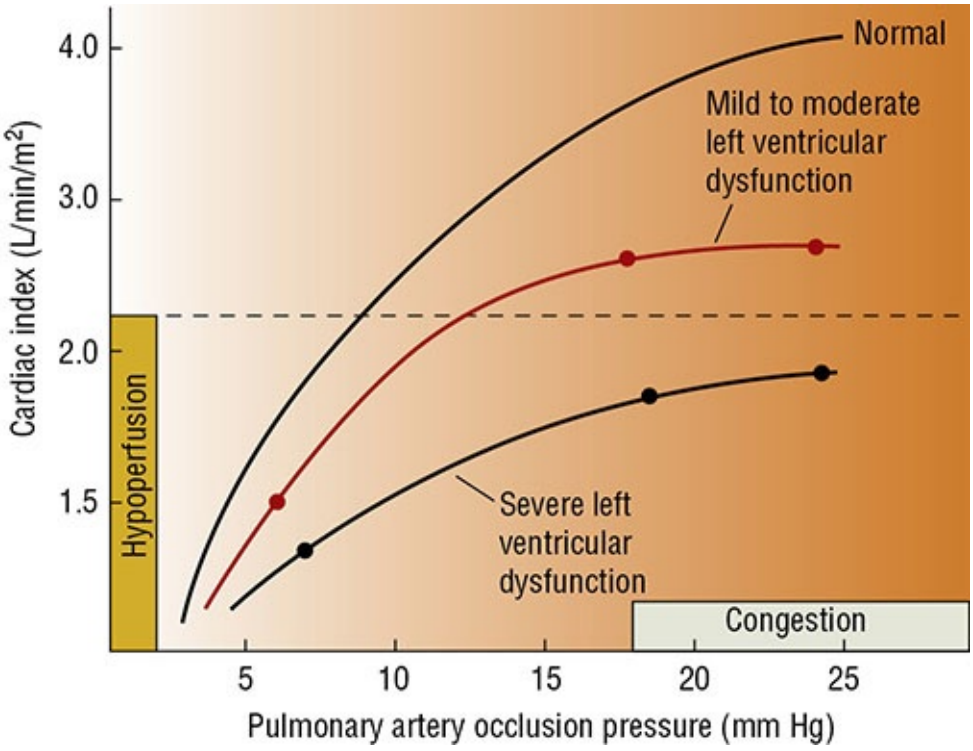


FIGURE 35-4 Relationship between cardiac output (shown as cardiac index which is CO/BSA) and preload (shown as pulmonary artery occlusion pressure).

Vasoconstriction and Increased Afterload

Vasoconstriction occurs in patients with HFrEF to help redistribute blood flow away from nonessential organs to coronary and cerebral circulations to support BP, which may be reduced secondary to a decrease in CO (MAP = CO × SVR).[7] A number of neurohormones likely contribute to the vasoconstriction, including NE, angiotensin II, endothelin-1 (ET-1), neuropeptide Y, urotensin II, and arginine vasopressin (AVP).[7,10] Vasoconstriction impedes forward ejection of blood from the ventricle, further depressing CO and heightening the compensatory responses. The failing ventricle is exquisitely sensitive to changes in afterload (Fig. 35-1). Thus, increases in afterload often potentiate a vicious cycle of continued worsening and downward spiraling of the HF state.

Ventricular Hypertrophy and Remodeling

3 While the signs and symptoms of HF are closely associated with the items described above, the progression of HF appears to be independent of the patient's hemodynamic status. It is now recognized that left ventricular hypertrophy and remodeling are key components in the pathogenesis of

progressive myocardial failure.[7] *Ventricular hypertrophy* is a term used to describe an increase in ventricular muscle mass. *Cardiac or ventricular remodeling* is a broader term describing changes in both myocardial cells and the extracellular matrix that result in changes in the size, shape, structure, and function of the heart.[11] These progressive changes in ventricular structure and function ultimately result in a change in the shape of the left ventricle from an ellipse to a sphere. This change in ventricular size and shape serves to further depress the mechanical performance of the heart, increases regurgitant flow through the mitral valve, and, in turn, fuels the continued progression of remodeling. Ventricular hypertrophy and remodeling can occur in association with any condition that causes myocardial injury.[11] The onset of the remodeling process precedes the development of HF symptoms.

Cardiac remodeling is a complex process that affects the heart at the molecular and cellular levels.[7,11] Key elements in the process are shown in **Fig. 35-5**. Collectively, these events result in progressive changes in myocardial structure and function such as cardiac hypertrophy, myocyte loss, and alterations in the extracellular matrix. The progression of the remodeling process leads to reductions in myocardial systolic and/or diastolic function that, in turn, results in further myocardial injury, perpetuating the remodeling process and the decline in left ventricular performance. Angiotensin II, NE, ET, aldosterone, vasopressin, and numerous inflammatory cytokines, as well as substances under investigation, that are activated both systemically and locally in the heart and vasculature play an important role in initiating the signal transduction cascade responsible for ventricular remodeling. Although these mediators produce harmful effects on the heart, their increased circulating and tissue concentrations are also toxic to other organs and serve as an important reminder that HF is a systemic as well as a cardiac disorder.[7,10,11]

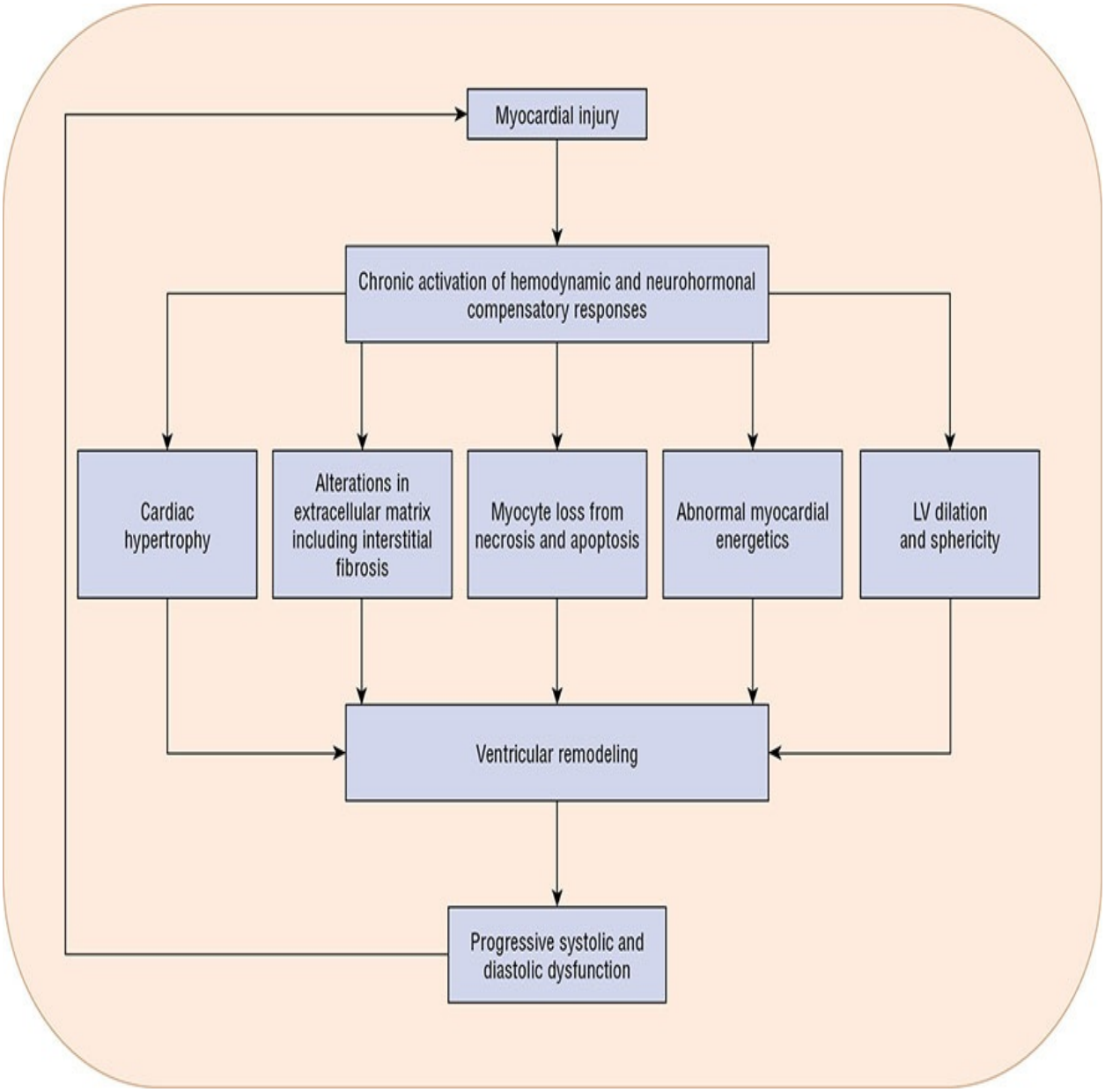


FIGURE 35-5 Key components of the pathophysiology of cardiac remodeling. Myocardial injury (eg, myocardial infarction) results in the activation of a number of hemodynamic and neurohormonal compensatory responses in an attempt to maintain circulatory homeostasis. Chronic activation of the neurohormonal systems results in a cascade of events that affect the myocardium at the molecular and cellular levels. These events lead to the changes in ventricular size, shape, structure, and function known as ventricular remodeling. The alterations in ventricular function result in further deterioration in cardiac systolic and diastolic functions that further promotes the remodeling process.

Pressure overload (and probably hormonal activation) associated with HTN

produces concentric hypertrophy (increase in the ventricular wall thickness without chamber enlargement), that is often found in HFpEF.[8] Conversely, eccentric left ventricular hypertrophy (myocyte lengthening with increased chamber size with minimal increase in wall thickness) characterizes the hypertrophy seen in patients with systolic dysfunction or previous MI. As the myocytes undergo change, so do various components of the extracellular matrix. For example, collagen degradation may lead to myocyte slippage, fibroblast proliferation, and increased fibrillar collagen synthesis, resulting in fibrosis and stiffening of the entire myocardium. Thus, a number of important ventricular changes that occur with remodeling include alterations in the geometry of the heart from an elliptical to a spherical shape, increases in ventricular mass (from myocyte hypertrophy), and changes in ventricular composition (especially the extracellular matrix) and volumes, all of which contribute to the impaired cardiac function. If the event producing cardiac injury is acute (eg, MI), the ventricular remodeling process begins immediately. However, it is the progressive nature of this process that results in continual worsening of the HF state, and thus is now the major focus for identification of therapeutic targets. In fact, HF pharmacotherapy associated with decreased mortality, and/or slowing the progression of the disease, produce these effects largely by slowing or reversing ventricular remodeling, a process often referred to as *reverse remodeling*.

Neurohormonal Model of Heart Failure

2 3 The current paradigm used to describe HF pathogenesis is the *neurohormonal model*.[7] This model recognizes an initiating event (eg, MI, long-standing HTN) that leads to decreased CO and begins the “HF state.” The problem then moves beyond the heart, and it becomes a systemic disease whose progression is mediated largely by neurohormones and autocrine/paracrine factors that drive myocyte injury, oxidative stress, inflammation, and extracellular matrix remodeling. While the former paradigms still guide us to some extent in the symptomatic management of the disease (eg, diuretics and digoxin), it is this latter paradigm that helps us understand disease progression and, more importantly, the ways to slow disease progression. In the sections that follow, key neurohormones and autocrine/paracrine factors, collectively termed biomarkers, are described with respect to their role in HF and its progression. The benefits of current and investigational drug therapies can be better understood through a solid understanding of the neurohormones they regulate.

Although the neurohormonal model provides a logical framework for our current understanding of HF progression and the role of various medications in attenuating this progression, it must be emphasized that this model does not completely explain HF progression.

Angiotensin II

Of the neurohormones and autocrine/paracrine factors that play an important role in HFrEF pathophysiology, angiotensin II is probably the best understood.[7,12] Angiotensin II has multiple actions that contribute to its detrimental effects. It is a potent vasoconstrictor mediated by binding to the angiotensin type 1 (AT1) receptor in the vasculature and it also causes a release of AVP and ET-1. Angiotensin II facilitates the release of NE from adrenergic nerve terminals, heightening SNS activation. It promotes sodium retention through direct effects on the renal tubules and by stimulating aldosterone release. Its vasoconstriction of the efferent glomerular arteriole helps to maintain renal perfusion pressure in patients with severe HF or impaired renal function. Finally, angiotensin II, and many of the neurohormones released in response to angiotensin II plays a central role in stimulating ventricular hypertrophy, remodeling, myocyte apoptosis, oxidative stress, inflammation, and alterations in the myocardial extracellular matrix. Clinical trials showing that attenuating angiotensin II-mediated effects with ACE inhibitors or ARBs improve hemodynamics, symptoms, hospitalizations, and survival highlight the importance of angiotensin II in HF pathophysiology.[1]

Norepinephrine

NE plays a central role in the tachycardia, vasoconstriction, and increased contractility and plasma renin activity in HFrEF.[10] Plasma NE concentrations are elevated in correlation with the degree of HF, and patients with the highest plasma NE concentrations have the poorest prognosis.[7] Excessive SNS activation causes downregulation of β_1-receptors, with a subsequent loss of sensitivity to receptor stimulation. Excess catecholamines increase the risk of arrhythmias and can cause myocardial cell loss by stimulating both necrosis and apoptosis. Finally, NE contributes to ventricular hypertrophy and remodeling. The beneficial effects of β-blockers on outcomes in patients with HFrEF support the critical role of sympathetic nervous system activation and NE in the pathophysiology of the HF state.[1,4]

Aldosterone

Aldosterone-mediated sodium retention and its key role in volume overload and edema have long been recognized as important components of the HF syndrome.[7] Circulating aldosterone is increased in HF due to stimulation of its synthesis and release from the adrenal cortex by angiotensin II and due to decreased hepatic clearance from reduced hepatic perfusion. The direct effects of aldosterone on the heart that may be even more important than sodium retention in HF pathophysiology. Aldosterone produces interstitial cardiac fibrosis through increased collagen deposition in the extracellular matrix of the heart. By increasing the stiffness of the myocardium, cardiac fibrosis may decrease systolic function and impair diastolic function. Extra-adrenal production of aldosterone in the heart, kidneys, and vascular smooth muscle also contributes to the progressive nature of HF through target organ fibrosis and vascular remodeling. Induction of a systemic proinflammatory state, increased oxidative stress, wasting of soft tissues and bone, secondary hyperparathyroidism, and mineral/micronutrient dyshomeostasis are other important pathologic actions of aldosterone that directly contribute to ventricular remodeling and HF progression.[7,12] Clinical trials with the aldosterone antagonists spironolactone[13] and eplerenone[14,15] showing significant reductions in morbidity and mortality in patients with HFrEF provide compelling evidence of the important role of aldosterone in HFrEF initiation and progression. Although not studied as extensively as in HFrEF, aldosterone antagonists also show benefit in patients with HFpEF.[16,17]

Natriuretic Peptides

The natriuretic peptide family has three members, atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP).[18] Of these, BNP is the most useful in the diagnosis and management of HF.[18,19] BNP and its related biologically inactive peptide, NT-proBNP, are synthesized and released from the ventricle in response to pressure or volume overload. BNP or NT-proBNP plasma concentrations are elevated in patients with HF functioning to increase natriuresis and diuresis and attenuate activation of the RAAS and SNS. A recent clinical trial showing that neprilysin-mediated inhibition of natriuretic peptide breakdown improves outcomes in patients with HFrEF supports the importance of these peptides in HF pathophysiology.[20]

The development of easily performed commercial assays for BNP and NT-proBNP resulted in widespread interest in the role of these peptides as a

biomarker for prognostic, diagnostic, and therapeutic use. In patients with chronic HFrEF, the degree of elevation in BNP concentrations is closely associated with poor outcomes.[18,19] Accurate diagnosis of acute decompensated HF is often difficult since many of the symptoms (eg, dyspnea) mimic those of other disorders such as pulmonary disease or obesity. The most well-established clinical application of BNP testing is in the urgent care setting where the BNP or NT-proBNP assay is useful when combined with clinical evaluation for differentiating dyspnea secondary to either HFrEF or HFpEF from other causes.[1,19]

Studies evaluating the role of serial BNP measurement to guide drug therapy have not shown consistent improvement in long-term outcomes compared with standard medical therapy, particularly in patients with HFpEF.[18,19] As a result, current guidelines reflect this uncertainty and do not support the routine use of serial BNP measurement in chronic HF management.[1,19]

Arginine Vasopressin

AVP is a pituitary peptide hormone that regulates renal water excretion and plasma osmolality.[7] Plasma concentrations of AVP are elevated in patients with HF, supporting its role in the pathophysiology of this disorder. The physiologic effects of AVP are mediated through the V_{1a}, V_{1b}, and V_2 receptors. Stimulation of these receptors by increased circulating AVP results in several maladaptive responses including: (a) increased renal free water reabsorption in the face of plasma hypoosmolality resulting in volume overload and hyponatremia; (b) increased arterial vasoconstriction that contributes to reduced CO; and (c) stimulation of remodeling by cardiac hypertrophy and extracellular matrix collagen deposition.

Given the importance of AVP in HF, recent efforts have focused on the development of AVP antagonist drugs for the treatment of acute and chronic HF. By blocking the AVP receptor, these agents primarily increase free water excretion (ie, an “aquaretic” effect). Although clinical trials with the AVP antagonists tolvaptan and conivaptan demonstrate improvements in acute symptoms and increases in serum sodium and urine output without affecting HR, BP, renal function, or other electrolytes, no improvements in morbidity and mortality were seen.[21]

Factors Precipitating/Exacerbating Heart Failure

Although significant advances have been made in treatment, symptom exacerbation, to the point that hospitalization is required, is a common and growing problem in patients with chronic HF. Hospitalization for HF exacerbation consumes large amounts of healthcare dollars and significantly impairs the patient's quality of life. Thus, there is great interest in identifying and then remedying factors that increase the risk of decompensation. Appropriate therapy can often maintain patients in a "compensated" state, indicating that they are relatively symptom-free. However, there are many aggravating or precipitating factors that may cause a previously compensated patient to develop worsened symptoms necessitating hospitalization. Often, these precipitating factors are reversible or treatable, such that a thorough evaluation for their presence is imperative.

Cardiac events are a frequent cause of worsening HF.[1] Myocardial ischemia and infarction are potentially reversible causes that must be carefully considered since nearly 70% of patients with HF patients have coronary artery disease. Revascularization should be considered in appropriate patients. Atrial fibrillation is a common comorbidity in patients with HF and is associated with increased morbidity and mortality.[22] Control of ventricular response, maintenance of sinus rhythm in appropriate patients, and prevention of thromboembolism are important elements in the treatment of patients with concomitant HF and atrial fibrillation. Uncontrolled HTN is also an important contributing factor and should be treated according to current guidelines.[23]

Noncardiac events are also associated with HF decompensation. Pulmonary infections frequently cause worsening HF. Many of these events would be preventable with the more widespread use of the pneumococcal and influenza vaccines. Pulmonary embolus, diabetes, chronic kidney disease, hypothyroidism, and hyperthyroidism should also be considered.

Nonadherence with prescribed HF medications or with dietary recommendations (eg, sodium intake and fluid restriction) is also a common cause of HF exacerbation.[1] Polypharmacy is common in patients with HF. Thus, nonadherence is an important contributor to poor outcomes and socioeconomically disadvantaged patients appear to be disproportionately affected.

A number of drugs can precipitate or exacerbate HF by one or more of the following mechanisms: (a) negative inotropic effects; (b) direct cardiotoxicity; or (c) increased sodium and/or water retention (**Table 35-3**).[24] The resulting symptoms are typically those associated with volume overload, but in more severe cases hypoperfusion may also be present. Nonsteroidal anti-inflammatory

drugs (NSAIDs) are increasingly recognized for their ability to exacerbate HF and increase risk of hospitalization and mortality through volume retention, decreased renal function, and increased BP.[24]

TABLE 35-3 Drugs That May Precipitate or Exacerbate Heart Failure

Negative inotropic effect
Antiarrhythmics (disopyramide, dronedarone, flecainide, propafenone, sotalol)
Beta-blockers (eg, propranolol, metoprolol, carvedilol)
Calcium channel blockers (eg, verapamil, diltiazem)
Itraconazole
Cardiotoxic
Doxorubicin, daunorubicin, epirubicin, idarubicin
Daunomycin
Cyclophosphamide
Pertuzamab
Trastuzumab
Bevacizumab
Mitoxantrone
Ifosfamide
Mitomycin
Lapitinib
Sunitinib
Sorafenib
Imatinib
Carbamazepine
Ethanol
Amphetamines (eg, cocaine, methamphetamine)
Sodium and water retention
NSAIDs
Cyclooxygenase-2 (COX-2) inhibitors
Rosiglitazone and pioglitazone
Glucocorticoids
Androgens and estrogens
Salicylates (high dose)
Sodium-containing drugs (eg, carbenicillin disodium, ticarcillin disodium)
Uncertain mechanism
TNF-α inhibitors (eg, adalimumab, infliximab, etanercept)
Dipeptidyl peptidase-4 (DPP-4) inhibitors (eg, saxagliptin)

What should be evident is that many of the precipitating factors are preventable, particularly through appropriate healthcare professional intervention. Specifically, patient education and counseling by a pharmacist

should be able to identify and address inadequate HF therapy, detect medication nonadherence, and administration of drugs or the presence of drug-drug interactions that may worsen HF (Table 35-3).[25,26] A careful medication history is an important aspect of evaluating the cause(s) of HF exacerbation. Discontinuation of medications known to exacerbate HF may help prevent hospitalizations. Use of medications such as antiarrhythmic agents, particularly disopyramide, dronedarone, and flecainide, and nondihydropyridine calcium channel blockers are important precipitants of exacerbations. The widespread use of NSAIDs, particularly the nonprescription agents that many patients perceive as having a low risk of adverse effects, is also problematic and should be discouraged. Thus, many of the factors precipitating HF exacerbations are amenable to pharmacist intervention. Attention to these factors may make important contributions to reducing the risk of adverse cardiovascular outcomes and improving the patient's quality of life.

CLINICAL PRESENTATION

Signs and Symptoms

2 11 The primary manifestations of both HFrEF and HFpEF are dyspnea and fatigue, which lead to exercise intolerance, and fluid overload, which can result in peripheral edema and pulmonary congestion.[1,27] The presence of these signs and symptoms may vary considerably from patient to patient such that some patients have dyspnea but no signs of fluid retention, whereas others may have marked volume overload with few complaints of dyspnea or fatigue. However, many patients have both dyspnea and volume overload. Clinicians should remember that symptom severity often does not correlate with the degree of LV dysfunction. Patients with a low LVEF (less than 20%-25% [0.20-0.25]) may be asymptomatic, whereas those with preserved LVEF may have significant symptoms. Symptoms can vary considerably over time in a given patient, even in the absence of changes in ventricular function or medications.

Systemic congestion is associated with a number of signs and symptoms. Jugular venous distension (JVD) is the simplest and most reliable sign of fluid overload. Examination of the right internal jugular vein with the patient at a 45° angle is the preferred method for assessing JVD. The presence of JVD more than 4 cm above the sternal angle suggests systemic venous congestion. In patients with mild systemic congestion, JVD may be absent at rest, but the application of pressure to the abdomen will cause an elevation of JVD (hepatojugular reflux).

Peripheral edema is a cardinal finding in HF. Edema usually occurs in dependent parts of the body, and thus is seen as ankle or pedal edema in ambulatory patients, although it may be manifested as sacral edema in bedridden patients. Adults typically have a 10-lb (4.5 kg) fluid weight gain before trace peripheral edema is evident; therefore, patients with acute decompensated HF may have no clinical evidence of systemic congestion except weight gain. Body weight is thus an excellent short-term endpoint for evaluating fluid status. Nonfluid weight gain and loss of muscle mass due to cardiac cachexia are potential confounders for long-term use of weight as a marker for fluid status. Hepatomegaly and ascites are other signs of systemic congestion.

Patients with HFrEF may exhibit signs and symptoms of low CO alone or in addition to volume overload. The primary complaint associated with hypoperfusion is fatigue. Objective indicators of low CO include worsening renal function, cool extremities, altered mental status, resting tachycardia, low systolic blood pressure, and narrow pulse pressure.

Diagnosis

No single test is available to confirm the diagnosis of HF—it is a clinical syndrome associated with a variety signs and symptoms.[1,27] Because HF can be caused or worsened by multiple cardiac and noncardiac disorders, some of which may be treatable or reversible, accurate diagnosis is essential for the development of therapeutic strategies. HF is often initially suspected in a patient based on symptoms. However, signs and symptoms lack sensitivity for diagnosing HF since they are frequently found with many other disorders. Even in patients with known HF, there is poor correlation between the presence or severity of symptoms and the hemodynamic abnormality. With few exceptions, HFpEF cannot be distinguished from HFrEF on the basis of the history, physical examination, chest x-ray, and ECG alone.[5] Patients with HFpEF are often elderly, with multiple comorbidities.[5] A proposed scoring system to help clinicians diagnose HFpEF, called the H2FPEF (**H**eavy, **H**ypertensive, Atrial **F**ibrillation, **P**ulmonary hypertension, **E**lderly, **F**illing pressure) score uses body mass index (2 points), taking two or more medications for hypertension (1 point), paroxysmal or persistent atrial fibrillation (3 points), pulmonary hypertension (1 point), age greater than 60 years (1 point), and Doppler echocardiographic E/e greater than 9 (1 point).[28] Patients with scores 0-1, 2-5 and 6-9 have a low, intermediate, and high probabilities of having HFpEF. Those patients with intermediate scores may require additional testing.

CLINICAL PRESENTATION

Heart Failure

General

- Patient presentation may range from asymptomatic to cardiogenic shock

Symptoms

- Dyspnea, particularly on exertion
- Orthopnea
- Paroxysmal nocturnal dyspnea
- Exercise intolerance
- Cough
- Fatigue
- Nocturia
- Hemoptysis
- Abdominal pain
- Anorexia
- Nausea
- Bloating
- Poor appetite, early satiety
- Weight gain or loss

Signs

- Ascites
- Pulmonary rales
- Pulmonary edema
- Tachypnea
- S_3 gallop, mitral regurgitant murmur
- Cool extremities
- Pleural effusion
- Cheyne-Stokes respiration

- Tachycardia
- Narrow pulse pressure
- Cardiomegaly
- Peripheral edema
- Jugular venous distention
- Hepatojugular reflux
- Hepatomegaly
- Venous stasis changes
- Lateral displacement of apical impulse
- Cachexia
- Mental status changes

Laboratory tests

- BNP >100 pg/mL (ng/L; 29 pmol/L)
- NT-proBNP >300 pg/mL (ng/L; 35 pmol/L)
- Electrocardiogram may be normal or it could show numerous abnormalities including acute ST-T wave changes from myocardial ischemia, atrial fibrillation, bradycardia, left ventricular hypertrophy
- Serum creatinine: It may be increased due to hypoperfusion. Preexisting renal dysfunction can contribute to volume overload.
- Complete blood count useful to determine if heart failure due to reduced oxygen carrying capacity
- Chest x-ray: Useful for detection of cardiac enlargement, pulmonary edema, and pleural effusions
- Echocardiogram: Used to assess LV size, valve function, pericardial effusion, wall motion abnormalities, and ejection fraction
- Hyponatremia: Serum sodium <130 mEq/L (mmol/L) is associated with reduced survival and may indicate worsening volume overload and/or disease progression

A complete history and physical examination targeted at identifying cardiac or noncardiac disorders or behaviors that may cause or hasten HF development or progression are essential in the initial patient evaluation. A careful medication

history should also be obtained with a focus on the use of medications that can precipitate or exacerbate heart failure (Table 35-3).[24]

Particular attention should be paid to cardiovascular risk factors and to other disorders that can cause or exacerbate HF such as HTN, diabetes, atrial fibrillation, dyslipidemia, tobacco use, sleep-disordered breathing, and thyroid disease. Since coronary artery disease is the cause of HF in many patients, evaluation of the possibility of coronary disease is essential, especially in men. If coronary artery disease is detected, appropriate revascularization procedures may then be considered. The patient's volume status should be documented by assessing the body weight, JVD, and presence or absence of pulmonary congestion and peripheral edema. Laboratory testing may assist in the identification of disorders that cause or worsen HF. The initial evaluation should include a complete blood count, serum electrolytes (including calcium and magnesium), assessment of renal and hepatic function, urinalysis, lipid profile, hemoglobin A1C, thyroid function tests, iron studies, chest x-ray, and 12-lead ECG. There are no specific ECG abnormalities associated with HF, but findings may help detect coronary artery disease or conduction abnormalities that could affect prognosis and guide treatment decisions. Measurement of BNP or NT-proBNP may also assist in differentiating dyspnea caused by HF from other causes.

Although the history, physical examination, and laboratory tests provide important insight into the underlying cause of HF, the echocardiogram is the single most useful test in the evaluation of the patient. The echocardiogram is used to assess abnormalities in cardiac structure and function and should include evaluation of the pericardium, myocardium, and heart valves, and quantification of the LVEF to determine if systolic or diastolic dysfunction is present.

TREATMENT

Of Chronic Heart Failure

Desired Outcomes

The goals of therapy in the management of chronic HF are to improve the patient's quality of life, relieve or reduce symptoms, prevent or minimize hospitalizations, slow progression of the disease, and prolong survival. Pharmacotherapy plays a key role in achieving these goals.[1] In addition,

identification of risk factors for HF development and recognition of its progressive nature have led to increased emphasis on preventing the development of this disorder. With this in mind, the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the evaluation and management of HF utilize a staging system that not only recognizes the evolution and progression of the disorder but also emphasizes risk factor modification and preventive treatment strategies (**Fig. 35-6**).[1] The four stages of this system differ from the NYHA functional classification (**Table 35-4**) with which most clinicians are familiar. The NYHA system is primarily intended to classify symptoms according to the clinician's subjective evaluation and does not recognize preventive measures or the progression of the disorder. A patient's symptoms can change frequently over a short period of time due to changes in medications, diet, intercurrent illnesses, etc. For example, a patient with ACC/AHA Stage C HF with NYHA class IV symptoms such as marked volume overload could rapidly improve to class I or II with aggressive diuretic therapy. In contrast, a patient's ACC/AHA HF stage could not improve (eg, go from Stage C to Stage B) even though the patient's symptoms could fluctuate between NYHA functional classes over time.

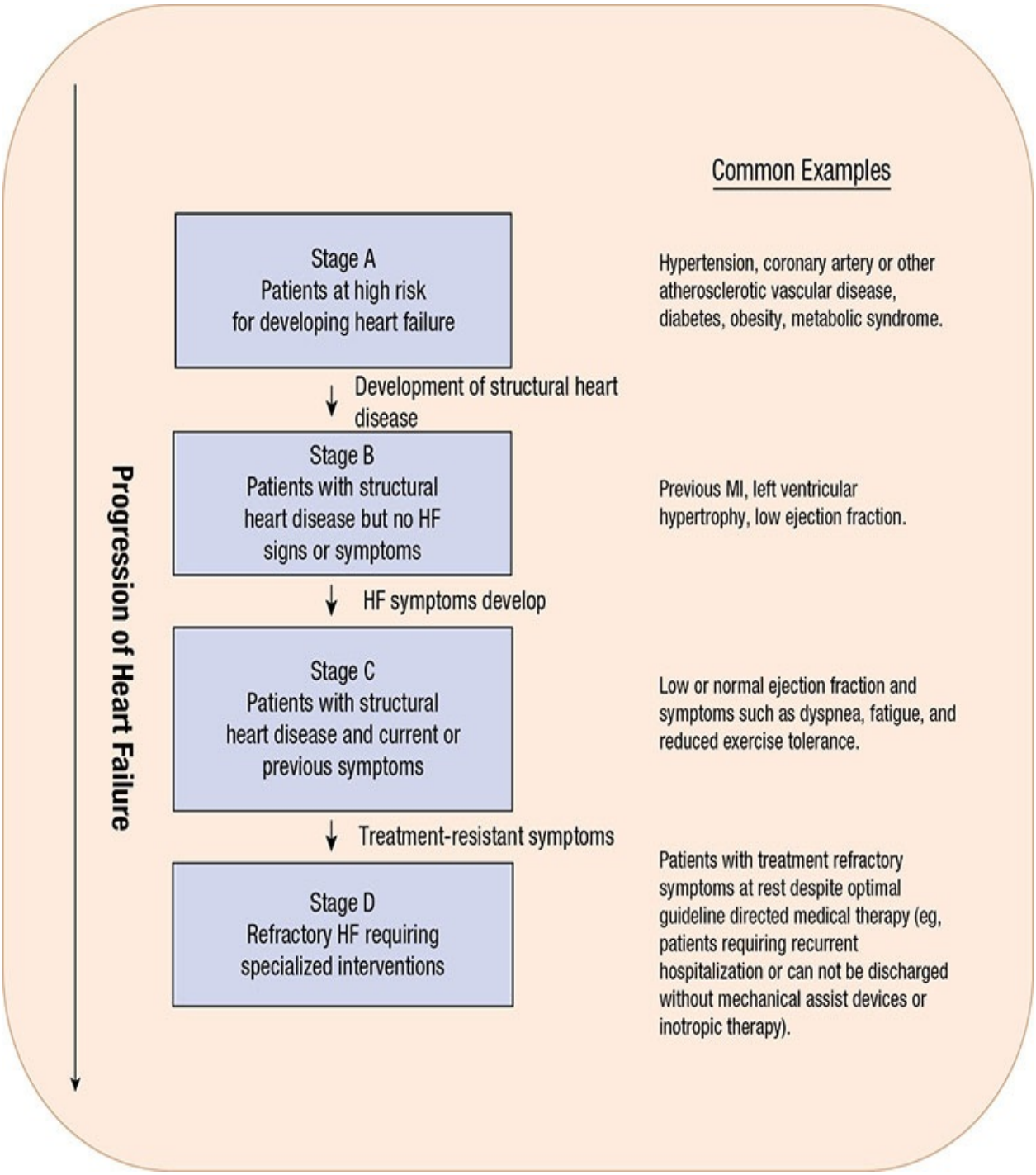


FIGURE 35-6 ACC/AHA heart failure staging system.
Data from Reference 1.

TABLE 35-4 New York Heart Association Functional Classification

Functional Class
I. Patients with cardiac disease but without limitations of physical activity. Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.
II. Patients with cardiac disease that results in slight limitations of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.
III. Patients with cardiac disease that results in marked limitation of physical activity. Although patients are comfortable at rest, less than ordinary activity will lead to symptoms.
IV. Patients with cardiac disease that results in an inability to carry on physical activity without discomfort. Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.

The general principles used to guide the treatment of HFrEF are based on numerous large, randomized, double-blind, multicenter trials. Until recently, no such randomized trials had been performed in patients with HFpEF. Consequently, the guidelines for the management of HFpEF are based primarily on clinical investigations in relatively small groups of patients, clinical experience, and concepts based on the knowledge and understanding of the pathophysiology of the disease process. Treatment of HFpEF is directed at alleviation of congestion with diuretics, managing precipitating factors (ischemia, hypertension, or atrial fibrillation) and addressing underlying microvascular inflammation.[6] The treatment regimen outlined in **Table 35-5** applies to patients with HFpEF who have clear manifestations of congestion either at rest or with exertion. In general, the typical therapies used for HFrEF have not shown a significant benefit for patients with HFpEF.

TABLE 35-5 Targeted Approach to Treatment of HFpEF

Symptom-targeted Treatment	Rationale	Agent
Decrease pulmonary venous pressure	Reduce left ventricular volume	Diuretics, salt restriction
Decrease myocardial oxygen consumption	Reduce heart rate Control blood pressure	β-blockers, diltiazem, verapamil, ACE inhibitors, ARBs, calcium channel blockers
Maintain atrial contraction	Restore and/or maintain sinus rhythm	Cardioversion of atrial fibrillation
Improve exercise tolerance	As above	Use positive inotropic agents with caution
Disease-targeted treatment		
Prevent/treat myocardial ischemia		β-blockers, diltiazem, verapamil, nitrates
Prevent/regress ventricular hypertrophy		Antihypertensive therapy
Mechanism-targeted treatment		
Modify myocardial and extramyocardial mechanisms		Possibly ACE inhibitors or ARBs, diuretics, spironolactone
Modify intracellular and extracellular mechanisms		Possibly ACE inhibitors or ARBs, spironolactone

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HFpEF, heart failure with preserved ejection fraction.

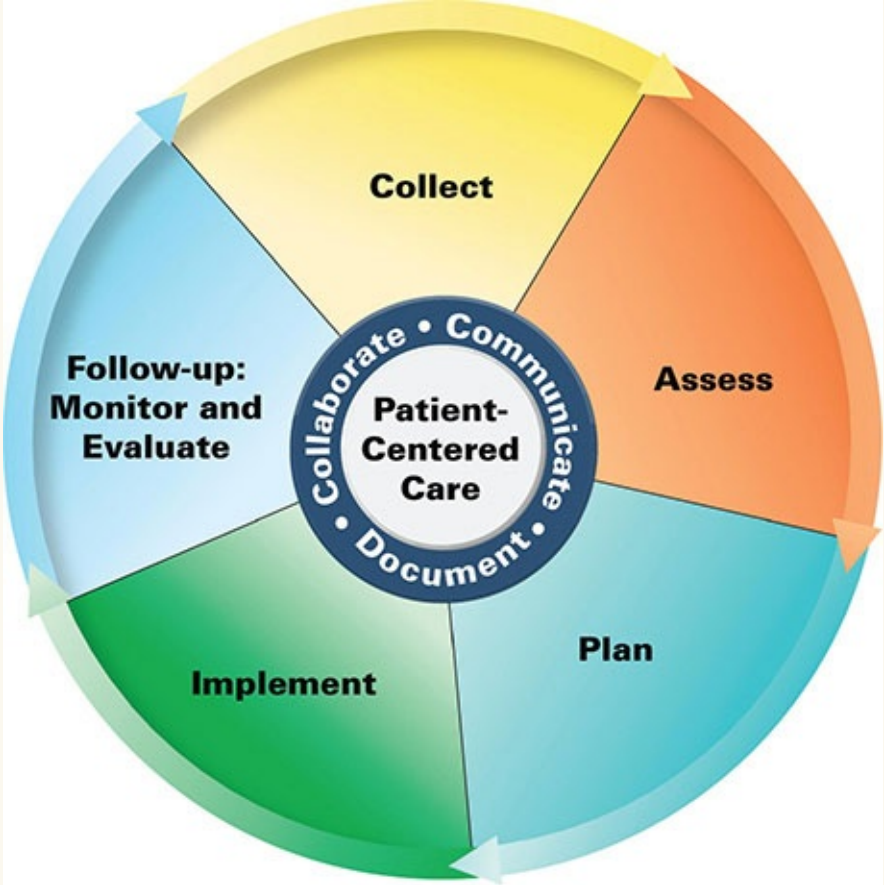
General Approach to Treatment

The complexity of the HF syndrome necessitates a comprehensive approach to management that includes accurate diagnosis, identification, and treatment of risk factors, elimination or minimization of precipitating factors, appropriate pharmacologic and nonpharmacologic therapy, and close monitoring and follow-up.

The first step in the management of chronic HF is to determine the etiology (see Table 35-1) and/or any precipitating factors. Appropriate treatment of underlying disorders (eg, hyperthyroidism, valvular heart disease) may obviate the need for specific HF treatment. Revascularization or anti-ischemic therapy in patients with coronary disease may reduce HF symptoms. Drugs that aggravate HF (see Table 35-3) should be discontinued if possible.

Restriction of dietary sodium and fluid intake is an important lifestyle intervention for both HFrEF and HFpEF. Mild (<3 g/day) to moderate (<2 g/day) sodium restriction, in conjunction with daily measurement of weight, should be implemented to minimize volume retention and allow the use of lower and safer diuretic doses. Patients should avoid adding salt to prepared foods and eliminate foods high in sodium (eg, salt-cured meats, salted snack foods, pickles, soups, delicatessen meats, and processed foods). In patients with hyponatremia (serum Na <130 mEq/L [mmol/L]) or those with persistent volume retention despite high diuretic doses and sodium restriction, daily fluid intake should be limited to

2 L/day from all sources. However, both sodium and fluid restriction must be done with care in patients with HFpEF. Excessive restriction can lead to hypotension, low-output state, and/or renal insufficiency. Daily weights may help assess volume status. Dietary and lifestyle factors that decrease the risk of development of CAD and HTN should be encouraged. Although guidelines indicate sodium restriction is reasonable to minimize congestion, proven benefits on clinical outcomes are lacking.



Patient Care Process for Heart Failure with Preserved Ejection Fraction (HFpEF)

Collect

- Patient characteristics (eg, age, gender)
- Patient medical history (personal and family)
- Social history (eg, tobacco/ethanol use) and dietary habits including intake

of sodium-containing foods and fluid

- Current medications including OTC use, herbal products, dietary supplements
- Objective data
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2-saturation, ejection fraction
  - Labs including complete blood count, comprehensive metabolic panel, BNP or NT-pro-BNP

Assess

- Hemodynamic stability (eg, systolic BP <90 mm Hg, HR >110 bpm, O_2-saturation <90% [0.90], RR)
- Presence of comorbidities (eg, diabetes mellitus, hypertension, atrial fibrillation)
- Presence of volume overload (eg, weight gain, rales, neck vein distension, peripheral edema, hepatomegaly)
- Presence of exertional dyspnea, orthopnea, fatigue
- Emotional status (eg, presence of anxiety, depression)

Plan*

- Drug therapy regimen including diuresis if the patient is hypervolemic (Tables 35-5, 35-6, and 35-7)
- Management of comorbidities such as hypertension, atrial fibrillation, and diabetes
- Monitoring parameters including efficacy (eg, shortness of breath) and safety (eg, sign and symptoms of worsening renal function); frequency and timing of follow-up
- Patient education (eg, the purpose of treatment, dietary and lifestyle modification, invasive procedures, drug-specific information, medication administration)
- Referrals to other providers when appropriate (eg, heart failure specialist, behavioral health, dietician)

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (eg, SCr, electrolytes, adherence assessment)

Follow-up: Monitor and Evaluate

- Resolution of heart failure symptoms (eg, shortness of breath)
- Presence of adverse effects (eg, SCr, electrolytes, BP, HR)
- Patient adherence to treatment plan using multiple sources of information

* *Collaborate with patient, caregivers, and other healthcare professionals.*

Other important general measures include patient and family counseling on the signs and symptoms of HF, detailed written instructions on the importance of appropriate medication use and compliance, activity level, diet, discharge medications, weight monitoring, continuity of care, and the need for close monitoring and follow-up to reinforce compliance and minimize the risk of HF exacerbations and subsequent hospitalization.[1,29]

4 The ACC/AHA treatment guidelines are organized around the four identified stages of HF, and the treatment recommendations are summarized in **Figs. 35-7** and **35-8**.[1,23,29] These guidelines primarily focus on HFrEF, although discussions of acute decompensated HF and management of patients with comorbid diseases often encountered in this population are included.

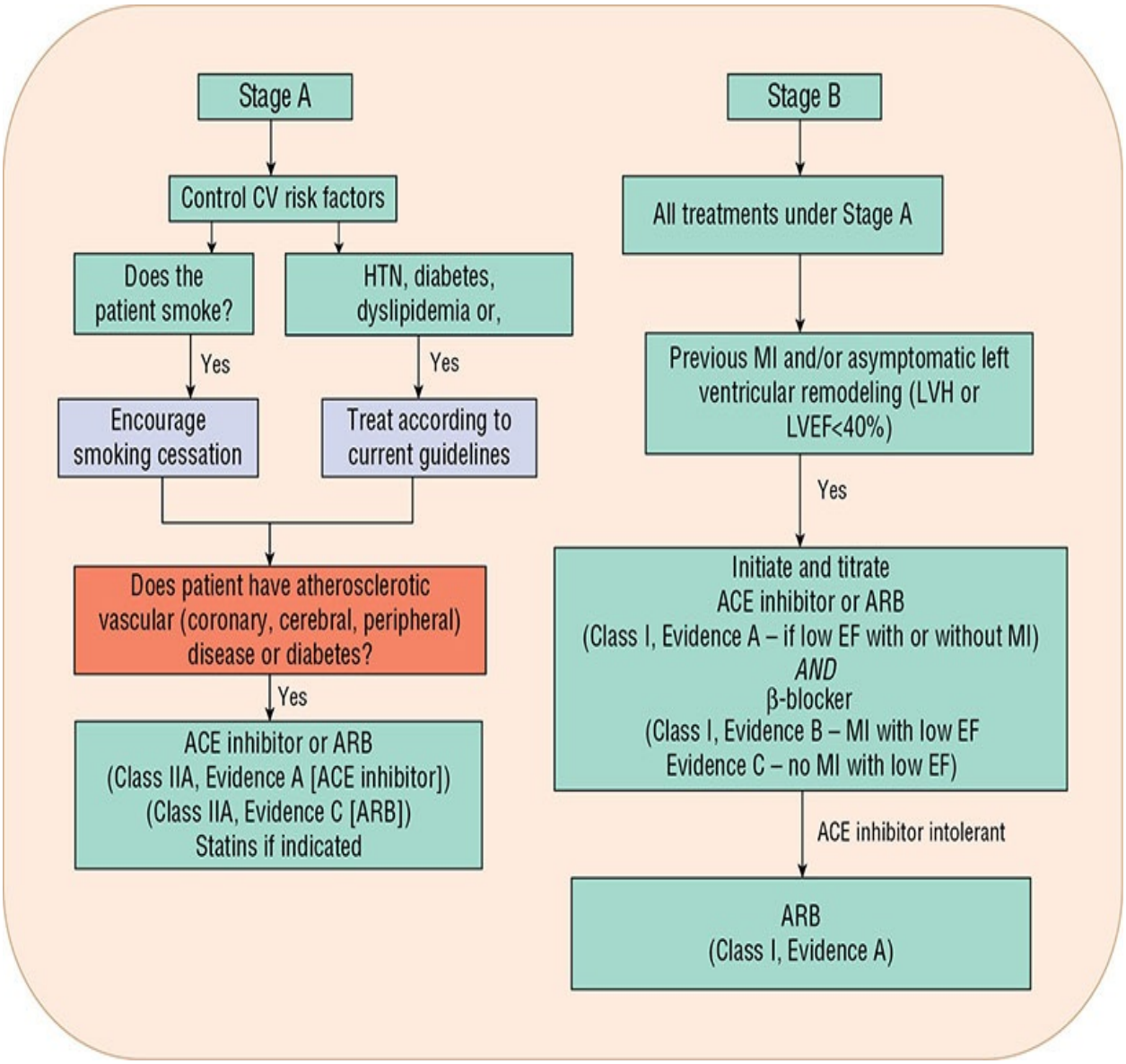


FIGURE 35-7 Treatment algorithm for patients with ACC/AHA Stage A and B heart failure.
Data from Reference 1.

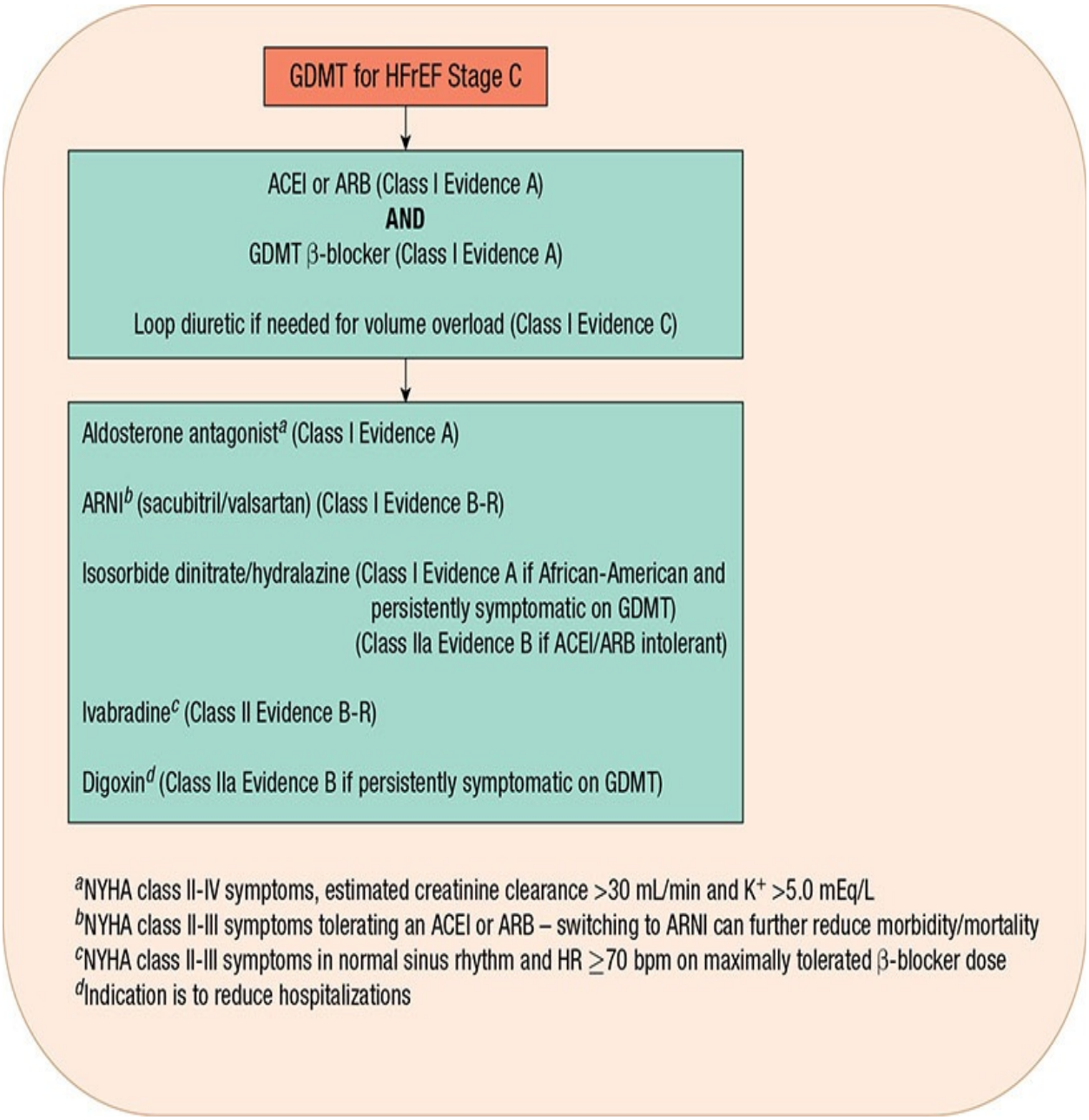


FIGURE 35-8 Guideline-directed treatment algorithm for patients with ACC/AHA Stage C heart failure with reduced ejection fraction.
Data from References 1 and 23.

Less information on the treatment of HFpEF is available. This relative paucity of evidence is reflected in guidelines for the diagnosis and management of HFpEF published by the ACC/AHA, the ESC, and the HFSA.[1,30,31] In general, all three guidelines recommend treating comorbid conditions by controlling HR and BP, alleviating causes of myocardial ischemia, reducing volume, and restoring and maintaining sinus rhythm in patients with atrial

fibrillation. Table 35-6 summarizes the therapeutic recommendations.

TABLE 35-6 Pharmacotherapy for Heart Failure with Preserved Ejection Fraction

Recommendations
Diuretics
A loop or a thiazide diuretic should be considered for patients with volume overload. However, with more severe volume overload or inadequate response to a thiazide, a loop diuretic should be implemented. Caution is warranted not to lower preload excessively, which may reduce stroke volume and cardiac output.
ACE inhibitors
ACE inhibitors may be considered in all patients.
ACE inhibitors should be considered in all patients who have symptomatic atherosclerotic cardiovascular disease or diabetes and one additional risk factor.
Angiotensin receptor blockers
Angiotensin receptor blockers may be considered in all patients.
In patients who are intolerant of ACE inhibitors, an angiotensin receptor blocker can be considered as an alternative.
Aldosterone antagonists
Aldosterone antagonists can reduce the risk of hospitalization in patients that do not have contraindications or are at risk for hyperkalemia.
Aldosterone antagonists may be beneficial for those patients with elevated BNP or NT-proBNP.
β-Blockers
β-blockers should be considered in patients with one or more of the following conditions: • Myocardial infarction • Hypertension • Atrial fibrillation requiring ventricular rate control
Calcium channel blockers
In patients with atrial fibrillation warranting ventricular rate control who either are intolerant to or have not responded to a β-blocker, diltiazem or verapamil should be considered.
A nondihydropyridine or dihydropyridine calcium channel blocker can be considered for symptom-limiting angina.
A nondihydropyridine or dihydropyridine calcium channel blocker can be considered for hypertension.

ACE, angiotensin-converting enzyme.

As the management of HF has become increasingly complex, disease management programs that include HF specialty clinics, home-based interventions, structured telephone support, and close patient follow-up are frequently used. Most are multidisciplinary and may include physicians, advanced practice nurses, dieticians, and pharmacists. In general, the programs focus on optimization of drug and nondrug therapy, patient and family education and counseling, exercise and dietary advice, intense follow-up by telephone or home visits, improving adherence to medications and lifestyle recommendations, encouragement of self-care, and early recognition of and management of volume

overload.[1] Such programs have typically focused on patients with more severe HF who are at high risk for hospital admission. In general, multidisciplinary disease management programs improve quality of life and reduce HF and all-cause hospitalizations and costs, although these benefits are not consistently demonstrated in all studies.

Treatment of Stage A Heart Failure

Patients in Stage A have no structural heart disease or HF symptoms but are at high risk for developing HF because of the presence of risk factors (Fig. 35-7). The emphasis in these patients is on risk factor identification and modification to prevent the development of structural heart disease and subsequent HF. Commonly encountered risk factors include HTN, dyslipidemia, diabetes, obesity, metabolic syndrome, smoking, and coronary artery disease. Although each of these disorders individually increases risk, they frequently coexist in many patients and act synergistically to foster the development of both HFrEF and HFpEF.[3] Effective blood pressure control reduces the risk of developing HF by approximately 50%; thus, current HTN-treatment guidelines should be followed.[1] Obesity, diabetes, and metabolic syndrome also importantly contribute to the risk of developing HF.[3] Appropriate management of coronary disease and its associated risk factors are also important. Although treatment must be individualized, ACE inhibitors or ARBs and statins are recommended for HF prevention in patients with multiple vascular risk factors.[1]

Treatment of Stage B Heart Failure

Patients in Stage B have structural heart disease, but do not have HF symptoms (Fig. 35-7). This group includes patients with left ventricular hypertrophy, recent or remote MI, valvular disease, or LVEF <40% (0.40). These individuals are at risk for developing HF, and treatment is targeted at minimizing additional injury and preventing or slowing the remodeling process. In addition to the treatment measures outlined in Stage A, all patients with a reduced LVEF should receive an ACE inhibitor or ARB and an evidence-based β-blocker to prevent development of HF, whether or not they have had an MI.[1] Patients with a previous MI and reduced LVEF should also receive an ACE inhibitor or ARB, evidence-based β-blockers, and a statin.[1]

Treatment of Stage C Heart Failure

4 5 6 7 8 9 10 11 Patients with structural heart disease and previous

or current symptoms are classified in Stage C and include both HFrEF and HFpEF. In addition to treatments in Stages A and B, patients with HFrEF in Stage C should be routinely treated with GDMT that includes an ACE inhibitor, ARB, or angiotensin receptor-neprilysin inhibitor (valsartan/sacubitril, ARNI) together with an evidence-based β-blocker, and aldosterone antagonists in eligible patients to reduce morbidity and mortality (Fig. 35-8).[23] Loop diuretics, hydralazine-isosorbide dinitrate (ISDN), digoxin, and ivabradine are also used in selected patients. Nonpharmacologic therapy with devices such as an implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy (CRT) with a biventricular pacemaker is also indicated in certain patients with HFrEF in Stage C (see "Nonpharmacologic Therapy" section below).

Dozens of trials evaluated pharmacotherapy in patients with HFrEF, but few focused on patients with HFpEF. In fact, most published HF studies specifically excluded patients with preserved EF. The results of some key HFpEF clinical trials as well as ongoing studies are summarized in **Table 35-7**. Most trials targeting the renin-angiotensin-aldosterone system have been disappointing. Phosphodiesterase inhibitors and isosorbide mononitrate are ineffective.[5,32] Angiotensin receptor blockers/neprilysin inhibitors, ranolazine, interleukin-1 blockade, iron repletion, and monitoring pulmonary artery pressures, are some of the other strategies being investigated in this patient population.

TABLE 35-7 Key Clinical Trials for HFpEF

Trial (No. of Patients)	Treatment	Inclusion Criteria	Primary Endpoint	Results
CHARM-Preserved[38] (*n* = 3,023)	Candesartan vs placebo for a mean of 36.6 months. Patients continued their background HF medications: ACE inhibitor (19%), β-blocker (55%), diuretics (75%), spironolactone (11%).	EF >40% (0.40), NYHA II-IV, ≥1 hospitalization for CV reason	Composite of CV mortality or HF hospitalization	No significant difference was found in the primary endpoint between treatment groups or in CV deaths. Compared with placebo, candesartan use was associated with statistically significant fewer HF admissions.
I-Preserve[39] (*n* = 4,128)	Irbesartan vs placebo for 2 years. ACE inhibitor can be used for any indication other than HTN.	Clinical criteria for HF or hospitalized within 6 months for HF, age ≥60 years, NYHA II-IV, EF ≥45% (0.45)	Composite of all-cause mortality or CV hospitalization	No significant difference was found in the primary endpoint between treatment groups, overall death rates, or CV hospitalization rate.
TOPCAT[17] (*n* = 3,345)	Spironolactone vs placebo for 2 years	Clinical criteria for HF, age ≥50 years, EF ≥45% (0.45), ≥1 hospitalization for HF, controlled SBP	CV mortality, aborted cardiac arrest, HF hospitalization	With a mean follow-up of 3.3 years, the primary outcome occurred in 18.6% of the spironolactone group and 20.4% in the placebo group. Only hospitalizations were significantly reduced by 17%. A post hoc analysis showed a significant benefit in the primary outcome in those patients enrolled in the Americas as compared to those enrolled in Russia and Georgia.
PARAGON-HF (*n* = 4,822)	Sacubitril/valsartan vs valsartan	NYHA class II-IV with EF>45% (0.45)	Composite of CV death and total HF hospitalization	Estimated completion in 2019. https://clinicaltrials.gov/ct2/show/NCT01920711

ACE, angiotensin-converting enzyme; CHARM, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; CV, cardiovascular; DIG, Digitalis Investigation Group.

Treatment of Stage D HFrEF

Stage D HF includes patients receiving maximally tolerated GDMT that have persistent symptoms. This is often referred to as advanced, refractory, or end-stage HF. These patients often undergo recurrent hospitalizations or cannot be discharged from the hospital without special interventions, have a poor quality of life, and are at high risk for morbidity and mortality. These individuals have the most advanced form of HF and should be referred to HF management programs so that specialized therapies including mechanical circulatory support,

continuous IV positive inotropic therapy, and cardiac transplantation can be considered in addition to standard treatments outlined in Stages A to C.[1,33] Discussions with the patient and family members regarding prognosis, patient priorities for minimizing symptoms versus prolonging survival, options for additional treatments, and end-of-life and hospice care should be initiated.[33] The approach to the treatment of patients with Stage D HF is discussed in more detail in Chapter 36.

Nonpharmacologic Therapy

Sudden cardiac death, primarily due to ventricular tachycardia and fibrillation, is responsible for 40% to 50% of the mortality in patients with HFrEF. Implantation of an ICD prevents sudden cardiac death and is an effective primary prevention to reduce the risk of mortality in selected patients with HFrEF.[1] Guidelines recommend use of an ICD for primary prevention in patients receiving GDMT with NYHA class II-III symptoms and an LVEF <35% (0.35) that are expected to live for at least one year.[1] In patients with NYHA class I symptoms and an LVEF <30% (0.30), an ICD is also recommended for primary prevention if life expectancy exceeds one year.[1]

Delayed electrical activation of the left ventricle, characterized on the ECG by a QRS duration that exceeds 120 ms, occurs in approximately one-third of patients with moderate-to-severe HFrEF. Since the left and right ventricles normally activate simultaneously, this delay results in asynchronous contraction of the ventricles and contributes to the hemodynamic abnormalities of HF. Implantation of a specialized biventricular pacemaker (CRT) to restore synchronous activation of the ventricles improves ventricular function and hemodynamics and is associated with reverse remodeling and increased LVEF. Use of CRT improves exercise capacity, symptoms, quality of life, hospitalizations, and mortality in patients with HRrEF.[1] Guidelines recommend CRT in patients receiving GDMT that have NYHA class II-III or ambulatory class IV symptoms and with a QRS duration >150 ms and LVEF <35% (0.35).[1] CRT can also be considered in selected patients with a QRS duration between 120 and 149 ms. Combined CRT and ICD devices are used if the patient meets the indications for both devices.

In patients with stage D HFrEF receiving GDMT, the use of mechanical circulatory support with a left ventricular assist device (LVAD) can be considered in certain patients.[1] Although the criteria for use of these devices continue to rapidly evolve, they are frequently used to bridge patients to cardiac

transplant or as destination therapy in patients ineligible for transplant and their use in these settings is associated with better survival and improved functional capacity.[1,34]

Pharmacologic Therapy

Pharmacologic Therapy for HFpEF

11 With a few notable exceptions, many of the drugs used to treat HFrEF are the same as those for treatment of HFpEF. However, the rationale for their use, the pathophysiologic process that is being altered by the drug, and the dosing regimen may be different. For example, β-blockers are recommended for the treatment of both HFrEF and HFpEF. In HFrEF, chronic therapy with β-blockers improves morbidity and mortality. In HFpEF, however, β-blockers are used to decrease HR, increase diastolic duration, and modify the hemodynamic response to exercise. Diuretics also are used in the treatment of both HFrEF and HFpEF. However, the doses of diuretics used to treat HFpEF are, in general, much lower than those used to treat HFrEF. Antagonists of the RAAS are useful in lowering BP and reducing LVH. Some drugs, however, are used to treat either HFrEF or HFpEF, but not both. Calcium channel blockers such as diltiazem, amlodipine, and verapamil have little utility in the treatment of HFrEF. In contrast, each of these drugs has been proposed as being useful in the treatment of HFpEF.

Pharmacologic Therapy for Stages B–D HFrEF

4 5 6 7 8 9 10 A treatment algorithm for the management of patients with Stage C HFrEF is shown in Fig. 35-8. In general, these patients should receive combined therapy with an ACE inhibitor, ARB, or ARNI along with an evidence-based β-blocker, plus an aldosterone antagonist in selected patients.[23] A diuretic should be administered if there is evidence of fluid retention. Other therapies including digoxin, ivabradine, or the combination of hydralazine-nitrates can be considered in selected patients.[1] Drug dosing and monitoring are summarized in **Tables 35-8** and **35-9**.

TABLE 35-8 Guideline Recommended Drug Therapies and Doses for HFrEF

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Comments
Loop Diuretics					
Furosemide	Lasix®	20-40 mg once or twice daily	20-160 mg once or twice daily	Cl_{cr} 20-50 mL/min (0.33-0.83 mL/s): 160 mg once or twice daily Cl_{cr} <20 mL/min (0.33 mL/s): 400 mg daily	Single doses exceeding those listed are unlikely to elicit additional response
Bumetanide	Bumex®	0.5-1.0 mg once or twice daily	1-2 mg once or twice daily	Cl_{cr} 20-50 mL/min (0.33-0.83 mL/s): 2 mg once or twice daily Cl_{cr} <20 mL/min (0.33 mL/s): 8-10 mg daily	Single doses exceeding those listed are unlikely to elicit additional response
Torsemide	Demadex®	10-20 mg once daily	10-80 mg once daily	Cl_{cr} 20-50 mL/min (0.33-0.83 mL/s): 40 mg once daily Cl_{cr} <20 mL/min (0.33 mL/s): 200 mg daily	Single doses exceeding those listed are unlikely to elicit additional response
ACE Inhibitors					
Captopril	Capoten®	6.25 mg three times daily	50 mg three times daily[a]		
Enalapril	Vasotec®	2.5 mg twice daily	10-20 mg twice daily[a]		
Lisinopril	Zestril®, Prinivil®	2.5-5.0 mg once daily	20-40 mg once daily[a]		
Quinapril	Accupril®	5 mg twice daily	20-40 mg twice daily		
Ramipril	Altace®	1.25-2.5 mg once daily	10 mg once daily[a]		
Fosinopril	Monopril®	5-10 mg once daily	40 mg once daily		Undergoes both hepatic and renal elimination
Trandolapril	Mavik®	1.0 mg once daily	4 mg once daily[a]		Undergoes both hepatic and renal elimination
Perindopril	Aceon®	2 mg once daily	8-16 mg once daily		Undergoes both hepatic and renal elimination
Angiotensin Receptor Blockers					
Candesartan	Atacand®	4-8 mg once daily	32 mg once daily[a]		
Valsartan	Diovan®	20-40 mg twice daily	160 mg twice daily[a]		
Losartan	Cozaar®	25-50 mg once daily	150 mg once daily[a]		
Angiotensin Receptor Blocker/Neprilysin Inhibitor					
Sacubitril/valsartan	Entresto®	49/51 mg sacubitril/valsartan twice daily	97/103 mg sacubitril/valsartan twice daily[a]		For patients taking a low dose of or not taking an ACE inhibitor or ARB or if eGFR is <30 mL/min/1.73m², the starting dose is 24/26-mg sacubitril/valsartan twice daily
Beta-blockers					
Bisoprolol	Zebeta®	1.25 mg once daily	10 mg once daily[a]		
Carvedilol	Coreg®	3.125 mg twice daily	25 mg twice daily[a]	Target dose for patients weighing >85 kg is 50 mg twice daily	Should be taken with food
Carvedilol phosphate	Coreg CR®	10 mg once daily	80 mg once daily		Should be taken with food
Metoprolol succinate CR/XL	Toprol-XL®	12.5-25 mg once daily	200 mg once daily[a]		
Aldosterone Antagonists					
Spironolactone	Aldactone®	eGFR >50 mL/min/1.73m²: 12.5-25 mg once daily	25-50 mg once daily[a]	eGFR 30-49 mL/min/1.73m²: 12.5 mg once daily or every other day	The risk of hyperkalemia increases if serum creatinine is >1.6 mg/dL (141 µmol/L). Avoid if baseline potassium is >5 mEq/L (mmol/L)
Eplerenone	Inspra®	eGFR >50 mL/min/1.73m²: 25 mg once daily	50 mg once daily[a]	eGFR 30-49 mL/min/1.73m²: 25 mg every other day	The risk of hyperkalemia increases if serum creatinine is >1.6 mg/dL (141 µmol/L). Avoid if baseline potassium is >5 mEq/L (mmol/L)

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Comments
Other					
Hydralazine-Isosorbide Dinitrate	Bidil®	Hydralazine 37.5 mg three times daily Isosorbide dinitrate 20 mg three times daily	Hydralazine 75 mg three times daily[a] Isosorbide dinitrate 40 mg three times daily[a]		Indicated in conjunction with standard heart failure therapy to improve survival and reduce hospitalizations in self-identified African-American patients
Digoxin	Lanoxin®	0.125-0.25 mg once daily	0.125-0.25 mg once daily	Reduce dose in elderly, patients with low lean body mass, and patients with impaired renal function	Target plasma concentration range is 0.5-0.9 ng/mL (mcg/L; 0.6-1.2 nmol/L). Does not improve survival in patients with HFrEF
Ivabradine	Corlanor®	5 mg twice daily	5-7.5 mg twice daily	Avoid if resting heart rate <60 BPM before treatment	Indicated to reduce the risk of hospitalization in patients with HFrEF with a resting heart rate >70 BPM receiving maximally tolerated beta-blocker doses. Take with meals

Cl_{cr}, creatinine clearance; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction.

[a]Regimens proven in large clinical trials to reduce mortality.

Data from References 23 and 35.

TABLE 35-9 Drug Monitoring

Drug Class	Adverse Effect	Monitoring Parameters	Comments
ACE inhibitors	Angioedema, cough, hyperkalemia, hypotension, renal dysfunction	BP, electrolytes, BUN, and creatinine	Contraindicated in patients with bilateral renal artery stenosis, history of angioedema, or pregnancy. Assess BP, BUN, creatinine, and electrolytes at baseline and 1-2 weeks after initiation or increase in dose. Goal is target dose from clinical trials or highest tolerated.
ARBs	Hyperkalemia, hypotension, renal dysfunction	BP, electrolytes, BUN, and creatinine	Contraindicated in patients with bilateral renal artery stenosis or pregnancy. Assess BP, BUN, creatinine, and electrolytes at baseline and 1-2 weeks after initiation or increase in dose. Use with caution in patients with a history of ACE inhibitor-associated angioedema. Goal is target dose from clinical trials or highest tolerated.
Sacubitril/ valsartan	Angioedema, hyperkalemia, hypotension, dizziness, renal dysfunction	BP, electrolytes, BUN, and creatinine	Contraindicated in patients with a history of angioedema associated with ACE inhibitor or ARB therapy or in pregnancy. Assess BP, BUN, creatinine, and electrolytes at baseline and 1-2 weeks after initiation or dose increase. Start with a low dose and double the dose every 2-4 weeks as tolerated based on BP, serum potassium, and renal function. Goal is target dose from clinical trials or highest tolerated.
Aldosterone antagonists	Gynecomastia/breast tenderness/ menstrual irregularities (spironolactone), hyperkalemia, worsening renal function	BP, electrolytes, BUN, and creatinine	Assess BP, BUN, creatinine, and electrolytes at baseline. Check potassium 3 days and 1 week after initiation and then monthly for the first 3 months. Change to eplerenone if gynecomastia develops with spironolactone.
β-blockers	Bradycardia, heart block, bronchospasm, hypotension, worsening HF	BP, HR, ECG, signs and symptoms of worsening HF, blood glucose	Start with low dose and titrate upward no more often than every 2 weeks as tolerated based on BP, HR, and symptoms. Goal is target dose from clinical trials or highest tolerated. Patients may feel worse before they feel better.
Digoxin	GI and CNS adverse effects, brady- and tachyarrhythmias. See Table 35-11	Electrolytes, BUN, creatinine, ECG, serum digoxin concentration	Target serum digoxin concentration 0.5-0.9 ng/mL (mcg/L; 0.6-1.2 nmol/L)
Ivabradine	Bradycardia, hypertension, atrial fibrillation, luminous phenomena (phosphenes, transiently enhanced brightness in a portion of the visual field	BP, HR, ECG	Start with 5 mg twice daily and after 2 weeks adjust dose to achieve a resting HR 50-60 BPM. Only use in patients in sinus rhythm.
Diuretics	Hypovolemia, hypotension, hyponatremia, hypokalemia, hypomagnesemia, hyperuricemia, renal dysfunction, thirst	BP, electrolytes, BUN, creatinine, glucose, uric acid, changes in weight, JVD	Dose should be adjusted based on volume status, renal function, electrolytes, and BP. Reassess these parameters 1-2 weeks after dose changes. Goal is lowest dose that maintains euvolemia.
Hydralazine	Hypotension, headache, rash, arthralgia, lupus, tachycardia	BP, HR	
Nitrates	Hypotension, headache, lightheadedness	BP, HR	

7 **Diuretics** The compensatory mechanisms in HF stimulate excessive sodium and water retention, often leading to pulmonary and systemic congestion.[35] Diuretic therapy, in addition to sodium restriction, is recommended in all patients with clinical evidence of fluid retention. Once fluid overload has been resolved, many patients require chronic diuretic therapy to maintain euvolemia. Among the drugs used to manage HF, diuretics are the most rapid in producing symptomatic benefits. However, diuretics do not prolong survival or alter disease progression, and therefore are not considered mandatory therapy. Thus, patients who do not have fluid retention would not require diuretic therapy.

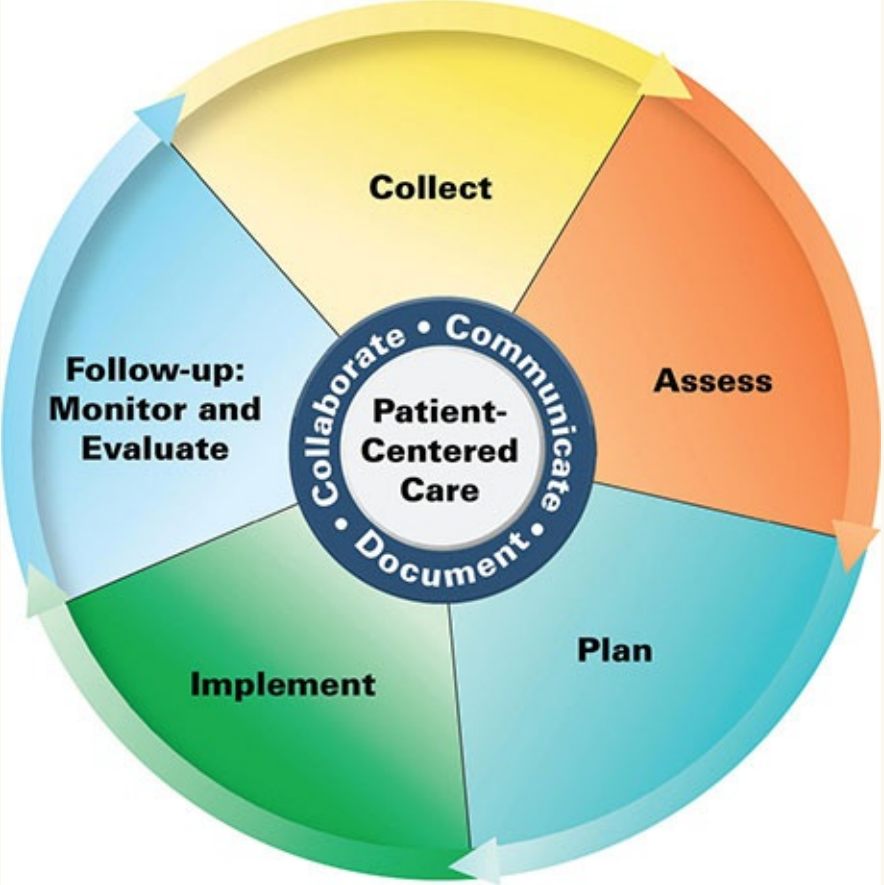
The primary goals of diuretic therapy are to reduce symptoms associated with fluid retention, improve exercise tolerance and quality of life, and reduce hospitalizations from HF. Diuretics accomplish this by decreasing pulmonary and peripheral edema through reduction of preload. Although preload is a determinant of CO, the Frank-Starling curve (see Fig. 35-4) shows that patients with congestive symptoms have reached the flat portion of the curve. A reduction in preload improves symptoms but has little effect on the patient's SV or CO until the steep portion of the curve is reached. However, diuretic therapy must be used judiciously because over-diuresis can lead to a reduction in CO, renal perfusion, and symptoms of volume depletion.

Diuretic therapy is usually initiated in low doses in the outpatient setting, with dosage adjustments based on symptom assessment and daily body weight. Change in body weight is a sensitive marker of fluid retention or loss, and it is recommended that patients monitor their status by taking daily morning body weights. Patients who gain 1 lb/day (~0.5 kg/day) for several consecutive days or 3 to 5 lb (1.4-2.3 kg) in a week should contact their healthcare provider for instructions (which often will be to increase the diuretic dose temporarily). Such action often will allow patients to prevent a decompensation that requires hospitalization. Patients may be directed to self-adjust their diuretic dose based on changes in HF symptoms and daily body weight. Hypotension or worsening renal function (eg, increases in serum creatinine) may be indicative of volume depletion and necessitates a reduction in the diuretic dose. Assessing volume status is particularly important before ACE inhibitor or β-blocker initiation or dose titration as over-diuresis may predispose patients to hypotension and other adverse effects with these agents.

11 In patients with HFpEF, diuretic treatment should be initiated at low doses in order to avoid hypotension and fatigue. Hypotension can be a significant problem in the treatment of HFpEF because patients have a very steep LV diastolic pressure-volume curve such that a small change in volume causes a

large change in filling pressure and CO. After the acute treatment of HFpEF has been completed, long-term treatment should include small-to-moderate oral doses of diuretics (furosemide 20-40 mg/day, chlorthalidone 25-50 mg/day, or hydrochlorothiazide 12.5-25 mg/day).

Thiazide Diuretics Thiazide diuretics such as hydrochlorothiazide block sodium reabsorption in the distal convoluted tubule (approximately 5%-8% of filtered sodium). The thiazides, therefore, are relatively weak diuretics and infrequently used alone in HF. However, thiazides or the thiazide-like diuretic metolazone can be used in combination with loop diuretics to promote a very effective diuresis. In addition, thiazide diuretics may be preferred in patients with only mild fluid retention and elevated BP because of their more persistent antihypertensive effects compared with loop diuretics.



Patient Care Process for Heart Failure with Reduced Ejection Fraction (HFrEF)

Collect

- Patient characteristics (eg, age, sex)
- Patient medical history (personal and family)
- Social history (eg, tobacco/ethanol use) and dietary habits including intake of sodium-containing foods and fluid
- Current medications including over-the-counter (OTC), herbal products, dietary supplements
- Etiology of heart failure (Table 35-1)
- Objective data
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, left ventricular ejection fraction, echocardiogram, chest x-ray
  - Labs including complete blood count, comprehensive metabolic panel (eg, serum Na, K, BUN, creatinine), urinalysis, liver function tests, thyroid stimulating hormone, brain natriuretic peptide (BNP) or NT-pro-BNP, electrocardiogram (ECG)
  - Physical examination (eg, signs/symptoms of volume overload [see Clinical Presentation Box])

Assess

- Hemodynamic stability (eg, systolic BP <90 mm Hg, signs/symptoms of hypotension or poor perfusion)
- Presence of comorbidities (eg, coronary artery disease, hypertension, diabetes, atrial fibrillation)
- Presence of volume overload (eg, weight gain, rales, jugular vein distension, peripheral edema)
- Presence of exertional dyspnea, orthopnea, fatigue
- Emotional status (eg, presence of anxiety, depression)

Plan*

- Initiate and titrate guideline-directed medical therapy with ACEI, ARB, or ARNI + β-blocker (Fig. 35-8, Tables 35-8 and 35-9). Add diuretics if the patient is volume overloaded
- Add additional drug therapy as indicated based on patient characteristics (eg, aldosterone antagonists, isosorbide/hydralazine, ivabradine [Fig. 35-8,

Tables 35-8 and 35-9])

- Monitoring parameters including efficacy (eg, shortness of breath, lower extremity edema) and safety (eg, worsening renal function, hypotension, bradycardia); follow-up frequency and timing
- Patient education (eg, the purpose of treatment, dietary and lifestyle modification, invasive procedures, drug-specific information, medication administration)
- Self-monitoring for heart failure symptoms (eg, daily weights, sodium, and fluid intake)
- Referrals to other providers when appropriate (eg, heart failure specialist, dietician)

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (eg, serum creatinine, electrolytes, vital signs, adherence assessment)

Follow-up: Monitor and Evaluate

- Resolution of heart failure signs and symptoms (eg, JVD, weight, shortness of breath)
- Presence of adverse effects (eg, serum creatinine, electrolytes, BP, HR)
- Patient adherence to treatment plan using multiple sources of information

* *Collaborate with patient, caregivers, and other healthcare professionals.*

Loop Diuretics Loop diuretics are usually necessary to restore and maintain euvolemia in HF. They act by inhibiting a Na–K–2Cl transporter in the thick ascending limb of the loop of Henle, where 20% to 25% of filtered sodium normally is reabsorbed. Loop diuretics also induce a prostaglandin-mediated increase in renal blood flow, which contributes to their natriuretic effect. Coadministration of NSAIDs, including cyclooxygenase-2 inhibitors, blocks this prostaglandin-mediated effect and can diminish diuretic efficacy. Excessive dietary sodium intake may also reduce the efficacy of loop diuretics. Unlike thiazides, loop diuretics maintain their effectiveness in the presence of impaired

renal function, although higher doses may be necessary to obtain adequate delivery of the drug to the site of action.

There are currently three loop diuretics available that are used routinely: furosemide, bumetanide, and torsemide.[35] They share many similarities in their pharmacodynamics, with their differences being largely pharmacokinetic in nature. Relevant information on the loop diuretics is shown in Tables 35-8 and 35-9. Following oral administration, the peak effect with all the agents occurs in 30 to 90 minutes, with a duration of 4 to 8 hours (longer for torsemide). Following IV administration, the diuretic effect begins within minutes. All three drugs are highly (>95%) bound to plasma proteins, and reach the tubular lumen by active transport via the organic acid transport pathway. The magnitude of the effect is determined by the peak concentration achieved in the nephron, and there is a threshold concentration that must be achieved before any diuresis occurs. Competitors for the organic acid transport pathway (probenecid or organic by-products of uremia) can inhibit delivery of loop diuretics to their site of action and decrease effectiveness.

The greatest difference between the agents is bioavailability. Bioavailability of bumetanide and torsemide is essentially complete (80%-100%), whereas furosemide bioavailability exhibits marked intrapatient and interpatient variability.[35] Furosemide bioavailability ranges from 10% to 100%, with an average of 50%. Thus, if bioequivalent IV and oral doses are desired, oral furosemide doses should be approximately double that of the IV dose, whereas IV and oral doses are the same for torsemide and bumetanide. Coadministration of furosemide and bumetanide with food can decrease bioavailability significantly, whereas food has no effect on the bioavailability of torsemide. The intra-abdominal congestion that can occur in HF also may slow the rate (and thus decrease the peak concentration) of furosemide, which can reduce its efficacy. Thus, furosemide is most problematic with respect to rate and extent of absorption and the factors that influence it, whereas torsemide has the least variable bioavailability.

Data suggest that these differences in bioavailability and variability may have clinical implications. For example, several studies suggest that torsemide is absorbed reliably and may be associated with better outcomes than the more variably absorbed furosemide.[35] Torsemide may modulate neurohormonal levels resulting in attenuation of cardiac remodeling. Torsemide is preferred in patients with persistent fluid retention despite high doses of other loop diuretics. While the costs of torsemide exceed those of furosemide, pharmacoeconomic analyses suggest that the costs of care are similar or less with torsemide.

Heart failure is one of the disease states in which the maximal response to loop diuretics is reduced. This is believed to result from a decrease in the rate of diuretic absorption and/or increased proximal or distal tubule reabsorption of sodium, possibly due to increased activity of the Na–K–2Cl transporter.[35] As a consequence, loop diuretics exhibit a ceiling effect in HF, meaning that once the ceiling dose is reached, no additional diuretic response is achieved by increasing the dose. Thus, when this dose is reached, additional diuresis can be achieved by giving the drug more often (twice daily or occasionally three times daily) or by giving combination diuretic therapy. Multiple daily dosing achieves a more sustained diuresis throughout the day. When dosed two or three times daily, the first dose is usually given first thing in the morning and the final dose in the late afternoon/early evening. The appropriate chronic dose of a loop diuretic is that which maintains the patient at a stable dry weight without symptoms of dyspnea. Ranges of doses of loop diuretics and recommended ceiling doses are shown in Table 35-8.

Diuretics cause a variety of metabolic abnormalities, with severity related to the potency of the diuretic.[4,35] The reader is referred to Chapter 36 (Acute Decompensated Heart Failure) for a detailed discussion on the adverse effects of diuretic therapy. Hypokalemia is the most common metabolic disturbance with thiazide and loop diuretics, which in HF patients may be exacerbated by hyperaldosteronism. Hypokalemia increases the risk for ventricular arrhythmias in HF and is especially worrisome in patients receiving digoxin. It is often accompanied by hypomagnesemia. Since adequate magnesium is necessary for entry of potassium into the cell, co-supplementation with both magnesium and potassium may be necessary to correct the hypokalemia. Concomitant ACE inhibitor (or ARB) and/or aldosterone antagonist therapy may help minimize diuretic-induced hypokalemia because these drugs tend to increase serum potassium concentration through their inhibitory effect on aldosterone secretion. Nonetheless, the serum potassium concentration should be monitored closely in HF patients and supplemented appropriately when needed.

5 **ACE Inhibitors** ACE inhibitors are a key component of the pharmacotherapy of patients with HFrEF.[1] By blocking the conversion of angiotensin I to angiotensin II by ACE, the production of angiotensin II and, in turn, aldosterone is decreased. This decrease in angiotensin II and aldosterone attenuates many of the deleterious effects of these neurohormones that drive HF initiation and progression. ACE inhibitors also inhibit the breakdown of bradykinin that increases vasodilation and also leads to cough. The evidence that ACE inhibitors improve symptoms, slow disease progression, and decrease

mortality in patients with HFrEF is unequivocal. As a result, current guidelines recommend that all patients with HFrEF, regardless of whether or not symptoms are present, should receive ACE inhibitors to reduce morbidity and mortality, unless there are contraindications.[1,23]

Numerous placebo-controlled clinical trials in both symptomatic and asymptomatic patients with reduced LVEF have documented the favorable effects of ACE inhibitor therapy on symptoms, heart failure progression, hospitalizations, and quality of life.[1,23] ACE inhibitors improve survival by 20% to 30% compared with placebo and these benefits are maintained with continued therapy.[1,23] The benefits of ACE inhibitor therapy are independent of the etiology of HF (ischemic vs nonischemic) and are greatest in patients with the most severe symptoms. As efficacy has been demonstrated with numerous agents, the improved outcomes are a “class effect” of ACE inhibitors.[1,23]

ACE inhibitor therapy should be started with low doses followed by gradual titration as tolerated to the target or maximally tolerated doses.[1,29] Dose titration is usually accomplished by doubling the dose every 2 weeks. Higher doses further reduce the risk of hospitalization, but not mortality, compared to lower doses.[1] Blood pressure, renal function, and serum potassium should be evaluated at baseline and within 1 to 2 weeks after therapy is started and after each dose increase. Although symptoms may improve within a few days of initiating therapy, it may take weeks to months before the full benefits are apparent. Even if symptoms do not improve, long-term ACE inhibitor therapy should be continued to reduce the risk of mortality and hospitalization.

A number of ACE inhibitors are currently available; those commonly used in the treatment of patients with HF are summarized in Table 35-8. Although ACE inhibitors vary in their chemical structure (eg, sulfhydryl vs non–sulfhydryl-containing agents) and tissue affinity, all ACE inhibitors studied improve symptoms and mortality in patients with HFrEF.[1,23] However, it seems most prudent to use those agents documented to reduce morbidity and mortality because the dose required for these endpoints has been determined.[1]

The primary adverse effects of ACE inhibitors are secondary to their major pharmacologic action of suppressing angiotensin II and increasing bradykinin. The most common adverse effects with these agents are hypotension, renal dysfunction, and hyperkalemia. ACE inhibitors reduce BP in nearly all patients, with hypotension becoming problematic when symptoms such as dizziness, light-headedness, blurred vision, presyncope, or syncope are observed. Hypotension occurs most frequently soon after therapy is started, after an increase in dose, or in patients that are volume depleted from diuretics. An often

overlooked solution to hypotension is to space the administration times of vasoactive medications (eg, diuretics and β-blockers) throughout the day so that these medications are not all administered at or near the same time.

Functional renal insufficiency causes increases in serum creatinine and blood urea nitrogen (BUN). As CO and renal blood flow decline, renal perfusion is maintained by the vasoconstrictor effect of angiotensin II on the efferent arteriole. Patients most dependent on this system for maintenance of renal perfusion (and therefore most likely to develop renal insufficiency with ACE inhibitors) are those with severe HF, hypotension, hyponatremia, volume depletion, bilateral renal artery stenosis, and concomitant use of NSAIDs.[1,29] Increases in serum creatinine of >0.5 mg/dL (44 μmol/L) if the baseline creatinine is <2 mg/dL (177 μmol/L) or of >1 mg/dL (88 μmol/L) if the creatinine is >2 mg/dL (177 μmol/L) should prompt clinicians to reduce the dose of ACE inhibitors or reconsider ACE therapy and evaluate potential causes for the abrupt decline in renal function. Since renal dysfunction with ACE inhibitors is secondary to alterations in renal hemodynamics, it is almost always reversible on discontinuation of the drug.

Hyperkalemia is most likely to occur in patients with renal insufficiency, in elderly patients, and in those taking concomitant potassium supplements, potassium-containing salt substitutes, or potassium-sparing diuretic therapy (including an aldosterone antagonist), especially if they have diabetes.[36] Patiromer or sodium zirconium cyclosilicate can be used to treat or prevent hyperkalemia in these patients.[36]

A dry, nonproductive cough is the most common reason for discontinuation of ACE inhibitors, occurring in up to 15% to 20% of patients with a similar frequency with all the agents.[1] The cough usually occurs within the first few months of therapy, resolves within 1 to 2 weeks of drug discontinuation, and reappears with rechallenge. Because cough is a bradykinin-mediated effect, replacement of ACE inhibitor therapy with an ARB is reasonable. Angioedema is a potentially life-threatening complication that is also due to bradykinin accumulation and occurs in approximately 1% of patients receiving an ACE inhibitor. It occurs more frequently in patients over 65 years of age, African Americans, women, and patients with histories of drug rashes or seasonal allergies.[37] Use of ACE inhibitors is contraindicated in patients with a history of angioedema. Caution should be exercised if ARBs are used as an alternative therapy in patients with ACE inhibitor-induced angioedema, as cross-reactivity is reported.[1] ACE inhibitors are contraindicated in pregnancy due to the increased risk of fetal renal failure, intrauterine growth retardation, and other

congenital defects.

5 **Angiotensin II Receptor Blockers** The crucial role of the RAAS in HF development and progression is well established as are the benefits of inhibiting this system with ACE inhibitors. However, angiotensin II can be formed in a number of tissues, including the heart, through non–ACE-dependent pathways (eg, chymase, cathepsin, and kallikrein).[7] By blocking the angiotensin II receptor subtype, AT_1, ARBs attenuate the deleterious effects of angiotensin II on ventricular remodeling, regardless of the site of origin of the hormone. Since ARBs do not inhibit the ACE enzyme, these agents do not affect bradykinin, which is linked to ACE inhibitor cough and angioedema.

ARBs are now a guideline-recommended alternative in patients who are unable to tolerate an ACE inhibitor due to cough or angioedema.[1,23] Numerous ARBs are currently available but only three agents, candesartan, valsartan, and losartan, are recommended in the treatment guidelines.[1] The efficacy of these agents is supported by clinical trial data that document a target dose associated with improved survival and other important outcomes in patients with decreased EF.[1] The specific drugs and doses proven to be effective in clinical trials should be used (Table 35-8). The clinical use of ARBs is similar to that of ACE inhibitors. Therapy should be initiated at low doses and then titrated to target doses (Table 35-8).[1] Blood pressure, renal function, and serum potassium should be evaluated within 1 to 2 weeks after initiation of therapy and after increases in dose and these monitoring, parameters should be used to guide subsequent dose changes.

11 The role of ARBs in the treatment of HFpEF is less clear. The CHARM-Preserved trial was the first large prospective study to demonstrate some benefit (reduction in hospitalizations for HF) of an ARB in patients with HFpEF receiving standard background treatment, although no improvement in cardiovascular death was observed.[38] Adverse effects of candesartan in this study were frequent; 22% of candesartan-treated patients discontinued therapy because of hypotension, increased serum creatinine, or hyperkalemia. In the Irbesartan in Heart Failure with Preserved EF (I-PRESERVE) trial, irbesartan was compared with placebo in over 4,000 patients with symptoms of HF and an LVEF of at least 45% (0.45).[39] There was no significant difference between irbesartan and placebo with regard to death or hospitalization for cardiovascular causes. No benefit was seen in quality-of-life measures. There was a high discontinuation rate of the study drug in this trial (33%), as well as a high rate of post-randomization initiation of ACE inhibitors (20%) and spironolactone

(10%), which may have contributed to the outcome in this trial.

The major adverse effects of ARBS are related to the suppression of the RAAS. The incidence of and risk factors for developing hypotension, impaired renal function, and hyperkalemia with the ARBs are similar to those with ACE inhibitors.[1] Thus, ARBs are not alternatives in patients who develop these complications from ACE inhibitors. Careful monitoring is required when an ARB is used with another inhibitor of the RAAS (eg, ACE inhibitor or aldosterone antagonist) as this combination increases the risk of these adverse effects. Since ARBs do not affect bradykinin, they are not associated with cough and have a lower risk of angioedema than ACE inhibitors.[37] However, because of reports of recurrences of angioedema after ARB use in patients with a history of ACE inhibitor-related angioedema, ARBs should be used with caution in any patient with a history of angioedema as cross-reactivity may occur.[37] Similar to the ACE inhibitors, the ARBs are contraindicated in pregnancy.

Angiotensin II Receptor Blocker/Neprilysin Inhibitor (ARNI)

The first angiotensin receptor/neprilysin inhibitor approved for the treatment of patients with HFrEF is valsartan/sacubitril. It is a crystalline complex composed of the ARB valsartan and sacubitril, a neprilysin inhibitor prodrug. After ingestion, sacubitril dissociates from the complex and is cleaved into its active form LBQ657, which inhibits the action of neprilysin that degrades natriuretic peptides (NPs), bradykinin, and other endogenous vasodilator and natriuretic peptides.[40] By reducing the neprilysin-mediated breakdown of these compounds, vasodilation, diuresis, and natriuresis are enhanced and renin and aldosterone secretion is inhibited.

The PARADIGM-HF study compared sacubitril/valsartan to enalapril in patients with NYHA Class II-IV HFrEF.[20] The primary outcome of the trial was a composite of death from cardiovascular causes or first hospitalization for heart failure. There was a statistically significant 20% relative risk reduction in the primary outcome for patients receiving sacubitril/valsartan (21.8%) compared to enalapril (26.5%). A similar reduction was seen in each component of the primary endpoint. Death from any cause was also significantly reduced in the sacubitril/valsartan-treated patients. Hypotension occurred more frequently in patients randomized to sacubitril/valsartan compared to enalapril. However, more patients receiving enalapril experienced cough and hyperkalemia greater than 6.0 mEq/L (mmol/L). Angioedema was rare in either treatment group.

Sacubitril/valsartan was studied in patients with HFpEF in the phase II PARAMOUNT trial, where NT-proBNP levels were significantly reduced after 12 weeks of therapy when compared to valsartan alone.[41] This trial formed the basis of the phase III study PARAGON, which is intended to enroll over 4,800 patients with a preserved EF. Results are anticipated in 2019.

In patients with HFrEF and NYHA class II-III symptoms tolerating an ACE inhibitor or ARB, current guidelines recommend replacement by ARNI to further reduce morbidity and mortality.[23] ACE inhibitors should be discontinued 36 hours prior to initiating ARNI; no waiting period is needed in patients receiving an ARB. The initial starting dose for most patients being treated for HFrEF is 49/51 mg sacubitril/valsartan twice daily and titrated to the target dose of 97/103 mg sacubitril/valsartan twice daily after 2 to 4 weeks. A reduced dose of 24/26 mg sacubitril/valsartan is available for patients taking a low dose of either an ACE inhibitor or an ARB prior to initiation or those with severe renal dysfunction (eGFR <30 mL/min/1.73m^2). Blood pressure, serum potassium, and renal function should be closely monitored after the start of therapy and after each titration step. The valsartan component of the combination product is 40% to 60% more bioavailable than conventional valsartan tablets. Thus, the 24-mg sacubitril /26-mg valsartan tablet is equivalent to 40 mg of valsartan.[42]

The most common adverse reactions and risk factors for their development are similar to those with ACE inhibitors or ARBs and include hypotension, dizziness, hyperkalemia, worsening renal function, and cough. Angioedema occurred more frequently with sacubitril/valsartan compared to enalapril (0.5% vs 0.2%, respectively).[20] The risk of angioedema is fourfold higher in African-American patients.[42] Sacubitril/valsartan is contraindicated in patients with a history of angioedema associated with an ACE inhibitor or ARB. Sacubitril/valsartan is also contraindicated in pregnancy and should not be used concurrently with ACE inhibitors or other ARBs.

6 **β-Blockers** β-Blockers antagonize the detrimental effects of the SNS in HF and slow disease progression. Favorable effects of β-blockers in HF include antiarrhythmic effects, attenuation or reversal of ventricular remodeling, reduction in myocyte death from catecholamine-induced necrosis or apoptosis, improvement in left ventricular systolic function, reductions in HR and ventricular wall stress thereby reducing myocardial oxygen demand, and inhibition of plasma renin release.[1] There is overwhelming clinical trial evidence that β-blockers reduce morbidity and mortality in patients with HFrEF. As such, the ACC/AHA guidelines on the management of HF recommend that β-blockers

should be used in all stable patients with HFrEF in the absence of contraindications or a clear history of β-blocker intolerance.[1] Patients should receive a β-blocker even if their symptoms are mild or well controlled with diuretic and ACE inhibitor therapy. Importantly, it is not essential that ACE inhibitor doses be optimized before a β-blocker is started because the addition of a β-blocker is likely to be of greater benefit than an increase in ACE inhibitor dose.[1] β-Blockers are also recommended for asymptomatic patients with a reduced left ventricular EF (Stage B) to decrease the risk of progression to HF.[1]

Three β-blockers, in particular, have been shown to reduce morbidity and mortality compared with placebo in randomized, controlled trials: carvedilol, metoprolol succinate (CR/XL), and bisoprolol. Each was studied in a large population with the primary endpoint of mortality, and in each case, the trial was stopped early because of significant survival benefit with the β-blocker. The US Carvedilol Heart Failure Study demonstrated a 65% reduction in the risk of death with the addition of carvedilol to standard therapy, including an ACE inhibitor, digoxin, and diuretic.[43] In MERIT-HF, treatment with metoprolol succinate (Toprol-XL®) was associated with a 34% reduction in total mortality, a 41% reduction in sudden death, and a 49% reduction in death from worsening HF compared to placebo.[44] Bisoprolol was studied in the Cardiac Insufficiency Bisoprolol Study II (CIBIS II), which demonstrated a 34% reduction in total mortality, 44% reduction in sudden death, and a 26% reduction in death due to worsening HF with bisoprolol compared with placebo.[45] Multiple post hoc subgroup analyses of the MERIT-HF and CIBIS II trials suggest that the benefits of β-blockade occur regardless of HF etiology or disease severity.

In contrast to earlier trials in which the majority of participants had either NYHA class II or class III HFrEF, the COPERNICUS trial examined the efficacy and safety of β-blockers in clinically stable patients with class IV HF who had symptoms at rest or with minimal exertion.[46] Like the other studies, COPERNICUS was stopped early after carvedilol produced a 35% relative reduction in mortality. Carvedilol was well tolerated in this population, with fewer participants receiving carvedilol compared with placebo requiring discontinuation of study medication.

In addition to improving survival, β-blockers improve multiple other endpoints. Clinical trials demonstrate 15% to 20% reductions in all-cause hospitalization and 25% to 35% reductions in hospitalizations for worsening HF with β-blocker therapy.[45,47,48] Increases in LVEF of 5 to 10 units (eg, from an EF of 20%-25% [0.20-0.25] or 30% [0.30]) have been observed after several weeks to months of therapy. β-Blockers have also been shown to decrease ventricular

mass, improve the sphericity of the ventricle, and reduce systolic and diastolic volumes (left ventricular end-systolic volume and LVEDV).[1,4] These effects are often collectively called *reverse remodeling*, referring to the fact that they return the heart toward more normal size, shape, and function. β-Blockers are also associated with improvements in NYHA functional class, patient symptom scores or quality-of-life assessments, and exercise performance, as assessed by the 6-minute walk test.

Data from a study of carvedilol in post-MI patients with a decreased left ventricular EF support the use of β-blockers in asymptomatic patients with left ventricular systolic dysfunction (Stage B).[49] While the primary endpoint of all-cause mortality or hospital admission for cardiovascular problems was similar in the carvedilol and placebo groups, carvedilol significantly reduced all-cause mortality alone compared with placebo. Cardiovascular mortality and nonfatal MI were also lower among carvedilol-treated patients.

6 The benefits of β-blockers in HFrEF are not a class effect, therefore, one of the three agents with proven survival benefits (metoprolol succinate, carvedilol, or bisoprolol) should be used.[1,4] Metoprolol and bisoprolol selectively block the β_1-receptor, while carvedilol blocks the β_1-, β_2-, and α_1-receptors and also possesses antioxidant effects. The smallest commercially available tablet of bisoprolol is a scored 5-mg tablet. Since the recommended starting dose of 1.25 mg/day is not readily available, bisoprolol is the least commonly used of the three agents and, in fact, is not approved by the Food and Drug Administration (FDA) for use in HFrEF. Thus, therapy is generally limited to either carvedilol or metoprolol succinate, and there is no compelling evidence that one drug is superior to the other. While one trial found a lower mortality rate in patients treated with carvedilol 25 mg twice daily compared to immediate release metoprolol 50 mg twice daily,[50] concerns regarding the formulation (immediate release vs sustained release) and dose (100 vs 200 mg/day) of metoprolol used limit the conclusions that can be drawn from the trial. The efficacy of the immediate-release formulation in reducing mortality in HF has not been proven. Metoprolol succinate provides more consistent plasma concentrations over a 24-hour period and appears to provide more favorable effects on HR variability, autonomic balance, and BP, suggesting that this formulation might be superior to immediate-release metoprolol. More recent data from heart failure registries suggest that metoprolol succinate and carvedilol are similarly effective.[51,52] A controlled-release formulation of carvedilol (carvedilol CR) that allows once-daily dosing is available, and pharmacokinetic studies demonstrate similar degrees of drug exposure with the controlled- and

immediate-release formations of the drug.

Pharmacologic differences between β-blockers may aid in the selection of a specific agent. Carvedilol is expected to have greater antihypertensive effects than the other agents because of its α-receptor blocking properties and may be preferred in patients with poorly controlled BP. Conversely, metoprolol or bisoprolol may be preferred in patients with low BP or dizziness and in patients with significant airway disease.

Most participants in β-blocker trials were on ACE inhibitors at baseline since the benefits of these agents were proven prior to β-blocker trials. Whether the approach of starting a β-blocker prior to an ACE inhibitor or ARB is safe and effective is not clear. The risk for decompensation during β-blocker initiation may be greater in the absence of preexisting ACE inhibitor or ARB therapy. Thus, ACE inhibitors or ARBs should be started first in most patients. Initiating a β-blocker first may be advantageous for patients with evidence of excessive SNS activity (eg, tachycardia) and may also be appropriate for patients whose renal function or potassium concentrations preclude starting an ACE inhibitor (or ARB) at that time.

Components that are critical for successful β-blocker therapy include appropriate patient selection, drug initiation and titration, and patient education. β-Blockers should be initiated in stable patients who have no or minimal evidence of fluid overload.[1] While β-blockers are typically started in the outpatient setting, initiation of a β-blocker prior to discharge in patients who are hospitalized for decompensated HF increases β-blocker usage compared with outpatient initiation without increasing the risk of serious adverse effects.[56,57] However, β-blockers should not be started in patients who are hospitalized in the intensive care unit or recently required IV inotropic support. In unstable patients, other HF therapy should be optimized and then β-blocker therapy reevaluated once stability is achieved.

Initiation of a β-blocker at normal doses in patients with HF may lead to symptomatic worsening or acute decompensation owing to the drug's negative inotropic effect. For this reason, β-blockers are listed as drugs that may exacerbate or worsen HF (see Table 35-3). To minimize the likelihood for acute decompensation, β-blockers should be started in very low doses with slow upward dose titration and close monitoring. β-Blocker doses should be doubled no more often than every 2 weeks, as tolerated, until the target or maximally tolerated dose is reached. Uptitration should be avoided if the patient experiences signs of worsening HF, including volume overload and poor perfusion. Fluid overload may be asymptomatic and manifest solely as an

increase in body weight. Mild fluid overload may be managed by intensifying diuretic therapy. Once the patient has been stabilized, dose titration may continue as tolerated until the target or highest tolerated dose is reached. According to current guidelines, target doses are those associated with reductions in mortality in placebo-controlled clinical trials.[1] The starting and target doses achieved in clinical trials are described in Table 35-8. Data with both metoprolol and carvedilol suggest that HR may serve as a guide to the degree of β-blockade, with greater magnitude of HR reduction associated with greater improvement in survival. Thus, lower β-blocker doses might be considered reasonable if the reduction in HR indicates a good response to β-blocker therapy.[53]

Guidelines recommend continuing β-blocker therapy during hospitalization for HF whenever possible.[1] Despite their negative inotropic effects, continuing β-blocker therapy during hospitalization for acute decompensated HF appears to neither worsen symptoms nor delay clinical improvement. In fact, β-blocker withdrawal may increase the risk of mortality after hospital discharge.[54] Further, stopping β-blocker therapy during acute decompensation may lead to lower chronic β-blocker use due to failure to reinstitute β-blocker therapy once the patient has stabilized.[55]

Good communication between the patient and the healthcare provider(s) is particularly important for successful therapy. It is important to educate patients that β-blocker therapy is expected to positively influence disease progression and survival even if there is little to no symptomatic improvement. Patients should understand that dose titration is a long, gradual process. Patients should also be aware that response to therapy may be delayed and that HF symptoms may actually worsen during the initiation period. In the event of worsening symptoms, patients who understand the potential benefits of long-term β-blocker therapy may be more likely to continue treatment.

11 In patients with HFpEF, β-blockers may help to lower and maintain low pulmonary venous pressures by decreasing HR and increasing the duration of diastole. Tachycardia is poorly tolerated in patients with HFpEF for several reasons. First, rapid HRs cause an increase in myocardial oxygen demand and a decrease in coronary perfusion time. This can promote ischemia even in the absence of epicardial CAD. Second, incomplete relaxation between cardiac cycles may result in an increase in diastolic pressure relative to volume. Third, a rapid rate reduces diastolic filling time and ventricular filling. Thus, many clinicians use β-blockers (and nondihydropyridine calcium channel blockers) to prevent excessive tachycardia and produce a relative bradycardia in patients with diastolic dysfunction. However, excessive bradycardia can result in a fall of CO

despite an increase in LV filling.[2] Such considerations underscore the need for individualizing therapeutic interventions that affect HR. In general, it is not necessary to start at an extremely low dose and titrate the β-blocker in a slow, progressive fashion in HFpEF as it is in HFrEF. However, because patients tend to be older, have numerous comorbidities, and take many concomitant medications, it is prudent to start with a moderate dose of β-blockers. A meta-analysis examining the effects of β-blocker therapy on clinical outcomes in patients with HFpEF found lower all-cause mortality but no significant reduction for HF hospitalizations in observational studies.[60] These findings were not replicated in two small randomized trials. However, those studies were underpowered and many patients were lost to follow-up. An individual patient-level meta-analysis found no benefit of β-blocker therapy in patients with HFpEF (EF>50% [0.50]) in normal sinus rhythm as compared to patients with reduced (EF<40% [0.40]) or mid-range EF (40%-49% [0.40-0.49]).[61]

Possible adverse effects with β-blocker use in HF include bradycardia or heart block, hypotension, fatigue, impaired glycemic control in diabetic patients, bronchospasm in patients with asthma, and worsening HF. Clinicians should monitor vital signs and carefully assess for signs and symptoms of worsening HF during β-blocker initiation and titration. Hypotension is more common with carvedilol due to its α_1-receptor blocking properties. Bradycardia and hypotension generally are asymptomatic and require no intervention; however, β-blocker dose reduction is warranted in symptomatic patients. Fatigue usually resolves after several weeks of therapy, but sometimes requires dose reduction. In diabetic patients, β-blockers may worsen glucose tolerance and can mask the tachycardia and tremor (but not sweating) that accompany hypoglycemia. In addition, nonselective agents such as carvedilol may prolong insulin-induced hypoglycemia and slow recovery from a hypoglycemic episode. Despite this, there is evidence that carvedilol may improve insulin sensitivity and that β-blockers are well tolerated and significantly reduce morbidity and mortality in patients with diabetes and HFrEF. Thus, while β-blockers should be used cautiously in patients with recurrent hypoglycemia, concerns of masking symptoms of hypoglycemia or worsening glycemic control should not preclude β-blocker use in patients with diabetes. Patients with diabetes should be warned of these potential adverse effects and blood glucose should be monitored when initiating, adjusting, and discontinuing β-blocker therapy. Adjustment of hypoglycemic therapy may be necessary with concomitant β-blocker use in diabetics.

Absolute contraindications to β-blocker use include uncontrolled

bronchospastic disease, symptomatic bradycardia, advanced heart block without a pacemaker, and acute decompensated HF. However, β-blockers may be tried with caution in patients with asymptomatic bradycardia, COPD, or well-controlled asthma. Particular caution is warranted in patients with marked bradycardia (<55 bpm) or hypotension (systolic BP <80 mm Hg).

8 **Aldosterone Antagonists** Spironolactone and eplerenone are aldosterone antagonists that work by blocking the mineralocorticoid receptor, the target site for aldosterone, and, thus, they are also referred to as mineralocorticoid receptor antagonists. In the kidney, aldosterone antagonists inhibit sodium reabsorption and potassium excretion. While the diuretic effects with low doses of aldosterone antagonists are minimal, the potassium-sparing effects can have significant consequences as discussed below. In the heart, aldosterone antagonists inhibit cardiac extracellular matrix and collagen deposition, thereby attenuating cardiac fibrosis and ventricular remodeling.[62] Aldosterone antagonists also attenuate the systemic proinflammatory state, atherogenesis, and oxidative stress caused by aldosterone. Thus, as with ACE inhibitors and β-blockers, the data on aldosterone antagonists also support the neurohormonal model of HF. In addition, there is evidence that aldosterone antagonists may attenuate aldosterone-induced calcium excretion and reductions in bone mineral density and protect against fractures in HF.[62]

Three randomized, placebo-controlled trials have evaluated low-dose aldosterone antagonism in patients with HFrEF or post-MI and left ventricular dysfunction. In each trial, the aldosterone antagonist was added to standard therapy, which included an ACE inhibitor and diuretic. While the initial trial was conducted before the benefits of β-blockers were fully appreciated, participants in the latter two trials received β-blockers. All three trials excluded patients with significant renal dysfunction (eg, serum creatinine above 2.5 mg/dL [221 μmol/L]) and elevated serum potassium (eg, above 5 mEq/L [mmol/L]) at baseline.

The RALES trial was the first to examine the efficacy of aldosterone antagonism in HFrEF. Patients with current or recent NYHA class IV HFrEF were randomized to spironolactone 25 mg/day or placebo.[13] The study was stopped prematurely because of a significant 30% reduction in the primary endpoint of total mortality with spironolactone. Spironolactone reduced mortality due to both progressive HF and sudden cardiac death. It also produced a 35% reduction in hospitalizations for worsening HF and significant symptomatic improvement, as assessed by changes in NYHA functional class.

The EPHESUS trial evaluated the effect of selective antagonism of the mineralocorticoid receptor with eplerenone in patients with left ventricular dysfunction after MI.[14] Patients with evidence of HF or diabetes were randomized within 3 to 14 days of MI to eplerenone, titrated to 50 mg/day, or placebo. Treatment with eplerenone was associated with a significant 15% relative reduction in the risk of death from any cause and a 15% reduction in the risk of hospitalization from HF. Most recently, the EMPHASIS-HF trial demonstrated significant improvements in clinical outcomes with eplerenone, titrated to 50 mg/day (mean dose of 39 mg/day), in patients with NYHA class II HF and an LVEF of 35% [0.35] or less.[15] Eligible patients were hospitalized for a cardiovascular reason within 6 months of study entry or had a plasma BNP of at least 250 pg/mL (ng/L; 72 pmol/L) or an N-terminal proBNP of at least 500 pg/mL (ng/L; 59 pmol/L) in men and 750 pg/mL (ng/L; 89 pmol/L) in women. Eplerenone treatment reduced the primary endpoint of cardiovascular death or HF hospitalization by 37%, all-cause and cardiovascular mortality by 24%, and hospitalization for HF by 42%. A post hoc analysis of the data also showed a reduction in the incidence of new-onset atrial fibrillation or flutter with eplerenone.

The TOPCAT trial examined the effect of spironolactone in patients with HFpEF.[17] TOPCAT randomized 3,445 patients with symptomatic heart failure and an ejection fraction of 45% (0.45) or greater to spironolactone up to 45 mg/day (mean dose of 25 mg/day) or placebo. As an additional criterion for inclusion, patients had to either have a hospitalization within one year in which heart failure management was a major component or a BNP of at least 100 pg/mL (ng/L; 29 pmol/L) (or N-terminal proBNP of at least 360 pg/mL [ng/L; 42 pmol/L]) within 60 days of study entry. The primary outcome was the composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for heart failure. After a mean follow-up of 3.3 years, there was no difference in the primary outcome or in the secondary outcomes of all-cause mortality, hospitalization for any reason, myocardial infarction, or stroke between groups. However, there was a significant 17% reduction in the risk for hospitalization for heart failure with spironolactone compared to placebo. Prespecified subgroup analysis showed a benefit with spironolactone among those enrolled on the basis of an elevated natriuretic peptide level, but not in those enrolled on the basis of the hospitalization criterion. There also appeared to be a difference in outcomes by region of enrollment. Approximately 51% of patients were enrolled from the Americas (the United States, Canada, Argentina, and Brazil), and the remainder were enrolled from Eastern Europe (Russia and the Republic of Georgia). Post

hoc analysis showed a greater reduction in the primary outcome with spironolactone among patients from the Americas, but not in those from Eastern Europe.[16] While the prespecified test for interaction between region and study arm was not significant, differences in baseline characteristics by region and the lower event rate overall in patients from Eastern Europe confound the interpretation of the study results.

Current guidelines recommend adding a low-dose aldosterone antagonist to standard therapy to improve symptoms, reduce the risk of HF hospitalization, and increase survival in select patients provided that potassium and renal function can be carefully monitored.[1] Based on the clinical trial data in HFrEF, low-dose aldosterone antagonists are appropriate for two groups of patients: those with mild to moderately severe HFrEF (NYHA class II to IV) who are receiving standard therapy and those with left ventricular dysfunction and either acute HF or diabetes early after MI.[1] Among patients with mild HFrEF (NYHA class II), aldosterone antagonists should be considered in those with a prior hospitalization for cardiovascular reasons or an elevated plasma BNP or N-terminal proBNP level. On the basis of findings from TOPCAT, guidelines recommend adding an aldosterone antagonist to decrease the risk for hospitalization for heart failure in patients with HFpEF, especially if plasma natriuretic peptide levels are elevated.[23]

Aldosterone antagonist use in clinical trials was associated with significant increases in serum potassium and creatinine. Most trials demonstrated a higher rate of hyperkalemia (serum potassium ≥5.5 mEq/L [mmol/L] or ≥6.0 mEq/L [mmol/L]) with the aldosterone antagonist compared to placebo.[14,15,17] However, hyperkalemia occurs more commonly in clinical practice than in clinical trials.[63] Risk factors for hyperkalemia include impaired renal function, high potassium concentrations, failure to decrease or stop potassium supplements when starting aldosterone antagonists, diabetes, inadequate laboratory monitoring, high potassium intake, and concomitant use of both ACE inhibitors and ARBs or NSAIDs. The ACC/AHA recommended strategies to minimize the risk for hyperkalemia with aldosterone antagonists in HF and are summarized in **Table 35-10**.[1] Chief among these recommendations is to avoid aldosterone antagonists in patients with renal dysfunction or elevated serum potassium. Serum creatinine may overestimate renal function in the elderly and in patients with decreased muscle mass, in whom creatinine clearance should serve as a guide for the appropriateness of aldosterone antagonist therapy. The risk for hyperkalemia is dose-dependent, and the morbidity and mortality reductions with aldosterone antagonists in clinical trials occurred at low doses

(ie, spironolactone 25 mg/day and eplerenone 50 mg/day). Therefore, the doses of aldosterone antagonists should be limited to those associated with beneficial effects in order to decrease the risk for hyperkalemia. Initiation of every-other-day dosing is appropriate for patients with marginal renal function or who are otherwise at high risk for hyperkalemia. Spironolactone also interacts with androgen and progesterone receptors, which may lead to gynecomastia, impotence, and menstrual irregularities in some patients. Such adverse effects are less frequent with eplerenone owing to its low affinity for the progesterone and androgen receptors.

TABLE 35-10 Recommended Strategies for Reducing the Risk for Hyperkalemia with Aldosterone Antagonists

- Avoid starting aldosterone antagonists in patients with any of the following:
  - Serum creatinine concentration >2.0 mg/dL (177 µmol/L) in women or >2.5 mg/dL (221 µmol/L) in men or a creatinine clearance <30 mL/min/1.73m²(0.29 mL/s/m²)
  - Recent worsening of renal function
  - Serum potassium concentration >5.0 mEq/L (mmol/L)
  - History of severe hyperkalemia
- Start with low doses (12.5 mg/day for spironolactone and 25 mg/day for eplerenone) especially in the elderly and in those with diabetes or a creatinine clearance <50 mL/min/1.73m² (0.48 mL/s/m²).
- Decrease or discontinue potassium supplements when starting an aldosterone antagonist.
- Avoid concomitant use of NSAIDs or COX-2 inhibitors.
- Avoid concomitant use of high-dose ACE inhibitors or ARBs.
- Avoid triple therapy with an ACE inhibitor, ARB, and aldosterone antagonist.
- Monitor serum potassium concentrations and renal function within 3 days and 1 week after the initiation or dose titration of an aldosterone antagonist or any other medication that could affect potassium homeostasis. Thereafter, potassium concentrations and renal function should be monitored monthly for the first 3 months, and then every 3 months.
- If potassium exceeds 5.5 mEq/L (mmol/L) at any point during therapy, discontinue any potassium supplementation or, in the absence of potassium supplements, reduce or stop aldosterone antagonist therapy.
- Counsel patients to:
  - limit intake of high potassium-containing foods and salt substitutes.
  - avoid the use of over-the-counter NSAIDs.
  - temporarily discontinue aldosterone antagonist therapy if diarrhea develops or diuretic therapy is interrupted.

Data from Reference 1.

Other Treatments for HFrEF in Select Patients

9 **Nitrates and Hydralazine** Nitrates and hydralazine were originally combined in the treatment of HFrEF because of their complementary hemodynamic actions. Nitrates, by serving as nitric oxide donors, activate guanylate cyclase to increase cyclic guanosine monophosphate (cGMP) in vascular smooth muscle resulting in venodilation and decreased preload. Hydralazine is a direct-acting arterial vasodilator causing a decrease in SVR and resultant increases in SV and CO (Fig. 35-1). However, the beneficial effects of hydralazine and nitrates extend beyond their hemodynamic actions and are likely related to attenuating the biochemical processes driving HF progression.

Based on the results of initial clinical trials showing ISDN and hydralazine were more effective in African Americans, the African-American Heart Failure Trial (A-HeFT) enrolled self-identified African Americans with NYHA class III or IV HFrEF receiving standard heart failure therapy and compared outcomes in patients randomized to the fixed-dose combination of hydralazine/Isosorbide dinitrate (BiDil®) or placebo. The trial was terminated early because of a significant 43% reduction in all-cause mortality in patients receiving hydralazine/isosorbide compared with placebo. Based on these results, BiDil® was approved by the FDA to treat HFrEF in African Americans.

Guidelines recommend the addition of hydralazine/ISDN to self-described African Americans with HFrEF and NYHA class III-IV symptoms treated with ACE inhibitors or ARBs and β-blockers.[1] Hydralazine/ISDN can also be useful in patients unable to tolerate either an ACE inhibitor or ARB because of renal insufficiency, hyperkalemia, or possibly hypotension.[1]

Despite its efficacy, the use of hydralazine/ISDN is limited by the need for three times daily dosing and frequent adverse effects including dizziness, headache, and GI distress. Because of cost, some clinicians use generic hydralazine and ISDN as separate agents, rather than BiDil®. Although the generic and brand name products are not bioequivalent as determined in healthy volunteer studies, it is unknown if these pharmacokinetic differences impact clinical outcomes.

HFpEF In contrast to the beneficial effects of hydralazine/ISDN in patients with HFrEF, the effects in patients with HFpEF are less clear. Nitrates are frequently used in patients with HFpEF to improve exercise tolerance, although their actual benefits are poorly understood. A recent study determined the effect of increasing doses of isosorbide mononitrate (30-120 mg daily) on exercise

tolerance in 110 patients with HFpEF.[32] Compared to placebo, a dose-dependent reduction in activity levels was found in patients receiving isosorbide mononitrate.[32] In addition, isosorbide mononitrate did not improve quality of life or plasma NT-proBNP concentrations. Adverse events, including worsening HF and presyncope/syncope, were more frequent with isosorbide treatment. These findings suggest that in the absence of another indication for nitrate therapy (eg, angina), nitrates provide no benefits to patients with HFpEF.

Ivabradine Ivabradine is a new agent that reduces heart rate and is used in the treatment of HFrEF.[64] Ivabradine selectively inhibits the I_f current responsible for controlling the depolarization rate of the sinus node.[64] By blocking this current, ivabradine slows the spontaneous depolarization of the sinus node resulting in a dose-dependent slowing of the heart rate. Ivabradine does not affect AV conduction, blood pressure, or myocardial contractility.[64]

Elevated resting heart rate (>70-80 BPM) is emerging as an important independent risk factor for adverse outcomes in patients with HFrEF and is associated with increased hospital admissions, disease progression, and mortality.[58] New approaches to address increased heart rate in these patients are needed because, for a variety of reasons, β-blockers are frequently underdosed in clinical practice and the benefits of β-blockers are associated with the degree of heart rate reduction and the dose administered.[58,59] In the SHIFT trial, ivabradine reduced the risk of hospitalization for worsening heart failure in patients with HFrEF in sinus rhythm.[65] As a result, guidelines recommend the use of ivabradine in patients with HFrEF (EF <35% [0.35]) in sinus rhythm who have a resting heart rate >70 bpm and are receiving maximally tolerated β-blocker doses.[23]

The starting dose of ivabradine in most patients is 5 mg twice daily with meals. After 2 weeks of treatment, the resting heart rate should be evaluated and if between 50 and 60 bpm, the dose should be continued. If the heart rate is >60 bpm, the dose can be increased to the maximum of 7.5 mg twice daily. If at any point, the heart rate is <50 bpm or if the patient has symptomatic bradycardia, the dose should be reduced by 2.5 mg twice daily. In this case, if the patient is receiving only 2.5 mg twice daily, then ivabradine should be discontinued. Because of the clear benefits of β-blockers on mortality and that many patients treated with β-blockers are under-dosed, clinicians should remember to titrate to the maximum tolerated doses before determining the need for ivabradine. The most common adverse effects associated with ivabradine were bradycardia, atrial fibrillation, and visual disturbances.

10 Digoxin The benefits of digoxin in HF are related to its neurohormonal modulating activity.[66] These effects occur at low plasma concentrations and little inotropic effect is seen. Digoxin attenuates the excessive SNS activation present in HF patients. Chronic HF is also marked by autonomic dysfunction, most notably suppression of the parasympathetic (vagal) system. Digoxin increases parasympathetic activity in HF patients and leads to a decrease in HR, thus enhancing diastolic filling. The vagal effects also result in slowed conduction and prolongation of AV node refractoriness, thus slowing the ventricular response in patients with atrial fibrillation. This leads to a decrease in HR, which enhances diastolic filling. Because atrial fibrillation is a common complication of HF, the combined neurohormonal and negative chronotropic effects of digoxin may be beneficial for such patients.

The Digitalis Investigation Group (DIG) trial examined the effects of digoxin on survival and hospitalization in patients with HF symptoms, an LVEF of <45% [0.45], and in sinus rhythm.[67] Most patients received background therapy with diuretics and ACE inhibitors. No significant differences in all-cause mortality were found between patients receiving digoxin and placebo. Digoxin reduced hospitalizations for worsening HF by 28% compared with placebo. Among patients with an LVEF greater than 45% [0.45] (HFpEF) who were enrolled in an ancillary DIG trial, there was no apparent benefit of digoxin on hospitalizations or mortality.[68]

The DIG trial was the first study to show that a positive inotropic agent does not increase mortality and actually decreases morbidity in patients with HFrEF. An analysis of the trial database found that lower serum digoxin concentrations (SDCs) were associated with decreased mortality, whereas higher concentrations were not.[69] Specifically, compared with placebo, SDCs of 0.5 to 0.9 ng/mL (mcg/L; 0.6-1.2 nmol/L) 1 month after digoxin initiation were associated with lower mortality, all-cause hospitalizations, and HF hospitalizations. Serum concentrations greater than or equal to 1 ng/mL (mcg/L; 1.3 nmol/L) were associated with lower HF hospitalizations with no effect on mortality. Based on these data, for most patients, the target SDC should be 0.5 to 0.9 ng/mL (mcg/L; 0.6-1.2 nmol/L).[1] This more conservative target may also decrease the risk of adverse effects from digoxin toxicity. In most patients with normal renal function, this serum concentration range can be achieved with a daily dose of 0.125 mg. Patients with decreased renal function or low body weight, the elderly, or those receiving interacting drugs (eg, amiodarone) should receive 0.125 mg daily or every other day. Routinely measuring SDCs is not necessary unless digoxin toxicity is suspect or there are other conditions that may significantly

affect SDC such as worsening renal function or the initiation of an interacting drug. In patients with atrial fibrillation, digoxin alone is often ineffective to control ventricular response in patients with atrial fibrillation and increasing the dose only increases the risk of toxicity. Digoxin combined with a β-blocker or amiodarone is superior to either agent alone for controlling ventricular response in patients with atrial fibrillation and HF.[1] Therefore, target SDCs are the same regardless of whether the patient is in sinus rhythm or atrial fibrillation. Several equations and nomograms have been proposed to estimate digoxin maintenance doses based on estimated renal function for a particular patient and population pharmacokinetic parameters. These methods are extensively reviewed elsewhere.[70]

The DIG trial was conducted prior to the proven benefits and widespread use of β-blockers in HF. Observational studies have reexamined digoxin in the context of contemporary HF therapy and shown either neutral effects or reductions in hospitalizations with digoxin and either neutral or detrimental effects of the drug on mortality.[71–73] Post-hoc analysis of the DIG trial suggested that discontinuation of digoxin may be detrimental, but whether this is true in the presence of β-blocker therapy is unknown.[74] Based on the totality of data, digoxin is not considered a first-line agent in HF but a trial may be considered in conjunction with GDMT, including ACE inhibitors or ARBs, β-blockers, and diuretics, in patients with symptomatic HFrEF to improve symptoms and reduce hospitalizations.[1] Digoxin may also be considered to help control ventricular response rate in patients with HFrEF and supraventricular arrhythmias, although β-blockers are generally more effective rate control agents, especially during exercise. Digoxin withdrawal may be considered for asymptomatic patients who have significant improvement in systolic function with optimal ACE inhibitor and β-blocker treatment.

There is no established role for digoxin in HFpEF when patients are in normal sinus rhythm. Digoxin may be of benefit in patients with concomitant HFpEF and atrial fibrillation.[75]

Digoxin pharmacokinetics are well described.[70] There is a long “distribution phase” after administration of oral or IV digoxin, resulting in a lag time before a maximum pharmacologic response is observed. Transiently elevated SDCs during the distribution phase are not associated with increased therapeutic or adverse effects, although they can mislead the clinician who is unaware of the timing of blood sampling relative to the previous digoxin dose. Consequently, blood samples for measurement of SDCs should be collected at least 6 hours and preferably 12 hours or more after the last dose. The drug efflux transporter P-

glycoprotein (P-gp) plays an important role in the bioavailability, renal and nonrenal clearance, and drug interactions with digoxin. Clinically important pharmacokinetic/pharmacodynamic drug interactions are summarized in **Table 35-11**.

TABLE 35-11 Selected Digoxin Drug Interactions

Drugs	Mechanism/Effect	Suggested Management
Amiodarone, dronedarone	Inhibits P-glycoprotein resulting in decrease in renal and nonrenal clearance; can increase SDC by 70%-100%	Monitor SDC and adverse effects; anticipate the need to reduce the dose by 30%-50%
Antacids	Concurrent administration may decrease digoxin bioavailability by 20%-35%	Space doses at least 2 hours apart or avoid concurrent use if possible
Cholestyramine, Colestipol	Bind digoxin in gut and decrease bioavailability 20%-35%; may also decrease enterohepatic recycling	Space doses at least 2 hours apart or avoid concurrent use if possible
Cyclosporine	Inhibits P-glycoprotein resulting in decreased clearance	Monitor SDC and adverse effects; anticipate the need to reduce the dose
Diuretics	Thiazides or loop diuretics may cause hypokalemia and hypomagnesemia, thereby increasing the risk of digitalis toxicity	Monitor and replace electrolytes if necessary
Erythromycin, clarithromycin, tetracycline	Alter gut bacterial flora; bioavailability and SDC increase 40%-100% in about 10% of patients who extensively metabolize digoxin in the gut, may also be due to inhibition of P-glycoprotein by macrolides	Monitor SDC and anticipate the need to reduce the dose; avoid concurrent use if possible
Ketoconazole, itraconazole	Decrease in renal and nonrenal clearance by inhibition of P-glycoprotein; SDC may increase by 50%-100%	Monitor SDC and anticipate the need to reduce the dose by 50%
Kaolin-pectin	Large dose (30-60 mL) may decrease digoxin bioavailability by about 60%	Space doses at least 2 hours apart or avoid concurrent use if possible
Metoclopramide	Increase in gut mobility may decrease the bioavailability of slow dissolving tablets; unknown significance	Effect is minimized by administration of digoxin capsules
Neomycin, sulfasalazine	Decrease in bioavailability by 20%-25%	Space doses at least 2 hours apart or avoid concurrent use if possible
Propafenone	Decrease in renal clearance; SDC may increase 30%-40%	Monitor SDC and anticipate the need to reduce the dose
Ranolazine	Inhibits P-glycoprotein; SDC may increase by 50%	Monitor SDC
Ritonavir, telaprevir	Inhibits P-glycoprotein and may increase SDC	Monitor SDC and anticipate the need to reduce the dose
Quinidine	Inhibits P-glycoprotein resulting in a decrease in renal and nonrenal clearance; also the displacement of digoxin from tissue binding sites with a decrease in the volume of distribution; SDC generally increases about twofold.	Monitor SDC and adverse effects; anticipate the need to reduce dose by 50%
Spironolactone	Decrease in renal and nonrenal clearance; also interference with some digoxin assays, thus increasing apparent SDC	Monitor SDC and anticipate the need to reduce dose; check assay for interference
Verapamil	Inhibits P-glycoprotein resulting in a decrease in renal and nonrenal clearance, SDC may increase 70%-100%	Monitor SDC and anticipate the need to reduce the dose by 50%; consider using another calcium channel blocker

SDC, serum digoxin concentration.

Digoxin can produce a variety of cardiac and noncardiac adverse effects, but it is usually well tolerated by most patients (**Table 35-12**).[66] Noncardiac adverse effects frequently involve the CNS or GI systems but also may be nonspecific

(eg, fatigue or weakness). Cardiac manifestations include numerous different arrhythmias caused by the drug's multiple electrophysiologic effects. Rhythm disturbances are of particular concern because patients with chronic HF are already at increased risk for sudden cardiac death, presumably due to ventricular arrhythmias. Patients at increased risk of toxicity include those with impaired renal function, decreased lean body mass, the elderly, and those taking interacting drugs. Hypokalemia, hypomagnesemia, and hypercalcemia will predispose patients to cardiac manifestations of digoxin toxicity. Thus, concomitant therapy with diuretics may lead to electrolyte abnormalities and increase the likelihood of cardiac arrhythmias. Similarly, hypothyroidism, myocardial ischemia, and acidosis will also increase the risk of cardiac adverse effects. Although digoxin toxicity is commonly associated with plasma concentrations greater than 2 ng/mL (mcg/L; 2.6 nmol/L), toxicity may occur at lower concentrations and clinicians should remember that digoxin toxicity is based on the presence of symptoms rather than a specific plasma concentration.[70] Usual treatment of digoxin toxicity includes drug withdrawal or dose reduction and treatment of cardiac arrhythmias and electrolyte abnormalities. In patients with life-threatening digoxin toxicity, purified digoxin-specific Fab antibody fragments should be administered.

TABLE 35-12 Signs and Symptoms of Digoxin Toxicity

Noncardiac (mostly CNS) adverse effects

- Anorexia, nausea, vomiting, abdominal pain
- Visual disturbances
  - Halos, photophobia, problems with color perception (ie, red-green or yellow-green vision), scotomata
- Fatigue, weakness, dizziness, headache, neuralgia, confusion, delirium, psychosis

Cardiac adverse effects[a,b]

- Ventricular arrhythmias
- Premature ventricular depolarizations, bigeminy, trigeminy, ventricular tachycardia, ventricular fibrillation
- Atrioventricular (A-V) block
- First degree, second degree (Mobitz type I), third degree
- A-V junctional escape rhythms, junctional tachycardia
- Atrial arrhythmias with slowed A-V conduction or A-V block
- Particularly paroxysmal atrial tachycardia with A-V block
- Sinus bradycardia

[a]Some adverse effects may be difficult to distinguish from the signs/symptoms of heart failure.

[b]Digoxin toxicity has been associated with almost every known rhythm abnormality (only the more common manifestations are listed).

Data from Eichorn EJ, Gheorghiade M. *Prog Cardiovasc Dis.* 2002;44:251-266.

11 **Calcium Channel Blockers** Calcium channel blockers can provide symptom-targeted treatment in patients with HFpEF by decreasing HR and increasing exercise tolerance. They can also provide disease-targeted therapy by treating HTN and coronary artery disease. However, the beneficial effect of these agents on exercise tolerance is not always paralleled by improved LV diastolic function or increased relaxation rate.

Of the calcium channel blockers, the nondihydropyridines (verapamil and diltiazem) are the most effective because they lower heart rate in addition to lowering BP. Nondihydropyridines are also frequently used to treat the comorbidities of hypertension and atrial fibrillation in patients with HFpEF. Sustained-release nifedipine, because of its strong vasodilator properties, tends to cause hypotension, reflex tachycardia, and peripheral edema. These characteristics make it less useful in HFpEF. Amlodipine may be effective because it reduces BP. Initial daily doses are verapamil 120 to 240 mg, diltiazem 90 to 120 mg, and amlodipine 2.5 mg.

Heart block is a contraindication for the nondihydropyridines. The most common adverse effects are bradycardia and heart block (for the nondihydropyridines). Peripheral edema and headache also are common.

Nondihydropyridines exacerbate the bradycardic effects of β-blockers, and verapamil raises digoxin serum concentrations by 70%. Diltiazem increases cyclosporine, tacrolimus, and sirolimus serum concentrations. Generic formulations, but not necessarily generic equivalents to the original brand names, are available for some of the calcium channel blockers.

Special Populations

HF is often accompanied by other disorders whose natural history or therapy may affect morbidity, mortality, and treatment approach. Optimal management of these concomitant disorders in the context of the patient's HF is an important consideration in the overall care of the patient.

Hypertension Although ischemic heart disease has replaced HTN as the most common cause of HF, up to 90% of patients with HF have current or a previous history of HTN.[3] HTN directly contributes to the development of both HFrEF and HFpEF as well as indirectly by increasing the risk of coronary artery disease. Effective treatment of HTN markedly reduces the risk of developing HF.[3] Pharmacotherapy of HTN in patients with HFrEF should initially involve agents that can treat both disorders such as ACE inhibitors, ARBs, or ARNI, β-blockers, aldosterone antagonists, and diuretics. If control of HTN is not achieved after optimizing treatment with these agents, the addition of ISDN/hydralazine or a dihydropyridine calcium channel blocker such as amlodipine should be considered. Calcium channel blockers with negative inotropic effects (eg, verapamil, diltiazem) should be avoided in patients with HFrEF. Target levels of BP should be less than 130/80 mm Hg, consistent with current guidelines (see Chapter 30, "Hypertension").[23,76]

In patients with HFpEF, both verapamil and diltiazem can be safely used. However, clinicians should remember that HFpEF is associated with HTN and aging, making it a common diagnosis in elderly women. Because these women often are frail and have low muscle mass, their creatinine clearance and renal function may be compromised. Special care must be taken when selecting and titrating doses of drugs such as diuretics, ACE inhibitors, and ARBs and close attention paid to monitoring serum creatinine and electrolytes.

Angina Coronary artery disease is the most common cause of HFrEF. Appropriate management of coronary disease and its risk factors is thus an important strategy for the prevention and treatment of HF (see Chapter 32, "Stable Ischemic Heart Disease"). Coronary revascularization should be strongly considered in patients with both HF and angina.[1] Pharmacotherapy of angina in

patients with HF should utilize drugs that can effectively treat both disorders. Nitrates and β-blockers are effective antianginals and are the preferred agents for patients with both disorders since they may improve hemodynamics and clinical outcomes. It should be noted that the antianginal effectiveness of these agents may be significantly limited if fluid retention is not controlled with diuretics. Similar to their use in HTN, both amlodipine and felodipine appear to be safe to use in this setting. Optimization of treatments for secondary prevention of coronary and atherosclerotic vascular disease should also be considered.[3]

Atrial Fibrillation Atrial fibrillation is the most frequently encountered arrhythmia and it is commonly found in patients with HF (both HFrEF and HFpEF), affecting 5% to 50% of patients with the prevalence increasing in parallel to the severity of HF.[1,22] The high incidence of atrial fibrillation in these patients is not surprising since each disorder predisposes to the other and they share many risk factors including coronary artery disease, diabetes, obesity, and HTN. The presence of atrial fibrillation in patients with HF is associated with a worse long-term prognosis.[22] Moreover, HF exacerbations and atrial fibrillation are closely linked causes of hospitalization and it is often difficult to determine which disorder caused the other. Thus, optimal management according to established guidelines is required with careful attention paid to control of ventricular response, symptoms, and anticoagulation for stroke prevention.[22,75]

Digoxin is frequently used to slow ventricular response in patients with HF and atrial fibrillation. However, it is more effective at rest than with exercise and it does not affect the progression of HF. In addition, the potential for digoxin to increase mortality in patients with atrial fibrillation is a growing concern.[77] β-Blockers are more effective than digoxin and have the added benefits of improving morbidity and mortality in patients with HFrEF. Combination therapy with digoxin and a β-blocker may be more effective for rate control than either agent used alone. Calcium channel blockers with negative inotropic effects such as verapamil or diltiazem should be avoided in patients with HFrEF but are effective in patients with HFpEF.

There appear to be no differences in outcomes between the rhythm-(restoration and maintenance of sinus rhythm) and rate-control approaches to atrial fibrillation in patients with HF.[22,75] Rhythm control is often reserved for patients in whom the rate cannot be controlled or who remain symptomatic. In general, amiodarone is the preferred agent if the rhythm control approach is taken. Although it has many noncardiac toxicities, amiodarone does not have cardio-depressant or significant proarrhythmic effects and appears to be safe in

HFrEF. Dofetilide also appears to be safe and effective in this population.[1,75] Class I antiarrhythmics and dronedarone should be avoided. Because of the limited efficacy and potential for serious adverse effects with antiarrhythmic drugs, there is a growing interest in the use of catheter ablation for restoring sinus rhythm in these patients.[22]

Diabetes 11 Diabetes is a common comorbid condition in patients with HF, present in 25% to 40% of patients.[3] As an important risk factor for coronary artery disease, diabetes directly contributes to the development of HF. Importantly, diabetes is also a risk factor for developing HF, particularly in women, independent of coronary artery disease or HTN.[3] Diabetes is associated with more rapid HF progression and is a significant predictor of morbidity and mortality in patients with HF.[3] In HFpEF, diabetes increases cardiomyocyte hypertrophy and stiffness through hyperinsulinemia and microvascular endothelial inflammation. Diabetes worsens left ventricular diastolic dysfunction through larger and stiffer cardiomyocytes. Cardiomyocyte death is more common in HFrEF. Clinical trials should differentiate HFrEF versus HFpEF when evaluating diabetes management.[3]

Pharmacotherapy of diabetes in patients with HF should be targeted to control hyperglycemia according to current guidelines, although it remains uncertain if this approach reduces the risk of HF development or outcomes in patients with established HF.[1,3] Some medications used to treat diabetes can have important adverse effects in patients with HF (see Chapter 91, “Diabetes Mellitus”). Because the TZDs (pioglitazone and rosiglitazone) are associated with fluid retention, these medications should not be used in patients with NYHA class II-IV HF.[1] Use of metformin in patients with HF has been contraindicated because of the purported risk of lactic acidosis. However, a growing body of data demonstrates that not only is metformin safe in HF, but it may also be associated with improved morbidity and mortality.[3] Nevertheless, careful monitoring of volume status and renal function is still needed when metformin is used in these patients. The use of the dipeptidyl peptidase 4 (DPP-4) inhibitors or glucagon-like peptide-1 agonists in patients with HF remains controversial with clinical trials showing associations between some of these agents with increased risk of developing HF, whereas other studies show no increased risk.[3] The sodium glucose cotransporter-2 inhibitors lower serum glucose by blocking renal tubular reabsorption, thereby increasing glucosuria. Recent trials have shown canagliflozin, dapagliflozin, and empaglifozin decreasing hospitalizations for heart failure by approximately 35%.[3]

EVALUATION OF THERAPEUTIC OUTCOMES

Although mortality is an important endpoint, it does not give a complete measure of the overall impact of HF because many patients are repeatedly hospitalized for HF exacerbations and continue to survive, albeit with a significantly reduced quality of life. Thus, some of the more important therapeutic outcomes in HF management, such as prolonged survival or prevention or slowing of the progression of HF, are difficult to quantify in an individual patient. However, after appropriate diagnostic evaluation to determine the etiology of HF, ongoing clinical assessment of patients typically focuses on the evaluation of three general areas: (a) functional capacity, (b) volume status, and (c) laboratory monitoring.

The evaluation of functional capacity should focus on the presence and severity of symptoms the patient experiences during activities of daily living and how his or her symptoms affect these activities. Questions directed toward the patient's ability to perform specific activities may be more informative than general questions about what symptoms the patient may be experiencing. For example, patients should be asked if they could exercise, climb stairs, get dressed without stopping, check the mail, go shopping, or clean the house. Another important component of the assessment of functional capacity is to ask patients what activities they would like to do but are now unable to perform.

Assessment of volume status is a vital component of the ongoing care of patients with HF. This evaluation provides the clinician important information about the adequacy of diuretic therapy. Since the cardinal signs and symptoms of HF are caused by excess fluid retention, the efficacy of diuretic treatment is readily evaluated by the disappearance of these signs and symptoms. The physical examination is the primary method for the evaluation of fluid retention, and specific attention should be focused on the patient's body weight, the extent of JVD, presence of hepatojugular reflux, presence, and severity of pulmonary congestion, and peripheral edema. Specifically, in a patient with pulmonary congestion, monitoring is indicated for resolution of rales and pulmonary edema and improvement or resolution of DOE, orthopnea, and PND. For patients with systemic congestion, a decrease or disappearance of peripheral edema, JVD, and hepatojugular reflux is sought. Other therapeutic outcomes include an improvement in exercise tolerance and fatigue, decreased nocturia, and a decrease in HR. Clinicians also will want to monitor BP and ensure that the patient does not develop symptomatic hypotension as a result of drug therapy. Body weight is a sensitive short-term marker of fluid loss or retention, and

patients should be counseled to weigh themselves daily, reporting changes of 3 to 5 lb (1.4 to 2.3 kg) to their healthcare provider so that adjustments can be made in diuretic doses. Patients and healthcare providers should be aware that HF progression may be slowed even though symptoms have not resolved.

Routine monitoring of serum electrolytes and renal function is required in patients with HF. Assessment of serum potassium and magnesium is especially important because hypokalemia and hypomagnesemia are common adverse effects of diuretic therapy and are associated with an increased risk of arrhythmias and digoxin toxicity (hypokalemia). Serum potassium monitoring is also required because of the risk of hyperkalemia associated with ACE inhibitors, ARBs, ARNI, and aldosterone antagonists. A serum potassium ≥4 mEq/L (mmol/L) should be maintained with some evidence suggesting it should be ≥4.5 mEq/L (mmol/L).[78] Assessment of renal function (BUN and serum creatinine) is also an important endpoint for monitoring diuretic and RAAS inhibitor therapy. Common causes of worsening renal function in patients with HF include over-diuresis, adverse effects of RAAS inhibition, and hypoperfusion.

An excellent overview on approaches to initiating and titrating evidence-based therapies, monitoring parameters, therapeutic endpoints, improving adherence, and solutions to frequently encountered problems when evaluating and treating patients with HFrEF was recently published by American College of Cardiology Task Force on expert consensus decision pathways.[29]

Postclass Engaged Learning Activity

Diabetes is a common comorbidity in patients with both HFrEF and HFpEF. A number of new hypoglycemic agents are available that can affect cardiovascular outcomes in patients with diabetes. Conduct a literature search and identify a primary research manuscript involving a hypoglycemic agent published in the last 1 to 2 years that evaluates the impact of the drug on heart failure outcomes. Write a brief summary of the study methods, the major findings, and how (or if) this new information might change clinical practice. This activity is intended to build your literature evaluation skills and the ability to critically appraise research manuscripts.

ABBREVIATIONS

ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
AHA	American Heart Association
ANP	atrial natriuretic peptide
ARB	angiotensin receptor blocker
ARNI	angiotensin-receptor blocker/neprilysin inhibitor
AVP	arginine vasopressin
BNP	B-type natriuretic peptide
BP	blood pressure
BPM	beats per minute
BUN	blood urea nitrogen

cAMP	cyclic adenosine monophosphate
CNP	C-type natriuretic peptide
CO	cardiac output
COX-2	cyclooxygenase-2
CRT	cardiac resynchronization therapy
ET	endothelin
GDMT	guideline-directed medical therapy
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HFSA	Heart Failure Society of America
HR	heart rate
HTN	hypertension
IABP	intra-aortic balloon pump
ICD	implantable cardioverter-defibrillator
JVD	jugular venous distension
LVAD	left ventricular assist device
LVEDV	left ventricular end diastolic volume
LVEDP	left ventricular end diastolic pressure
LVEF	left ventricular ejection fraction
MI	myocardial infarction
NE	norepinephrine
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
PCWP	pulmonary capillary wedge pressure
P-gp	P-glycoprotein
RAAS	renin–angiotensin–aldosterone system
SDC	serum digoxin concentration
SNS	sympathetic nervous system
SVR	systemic vascular resistance
TNF-α	tumor necrosis factor-α
TZD	thiazolidinedione

REFERENCES

1. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62:e147–e239.

2. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics—2018 Update: A report from the American Heart Association. *Circulation*. 2018;137:e67–e492.
3. Bozkurt B, Aguilar D, Deswal A, et al. Contributory risk and management of comorbidities of hypertension, obesity, diabetes mellitus, hyperlipidemia, and metabolic syndrome in chronic heart failure: A scientific statement from the American Heart Association. *Circulation*. 2016;134:e535–e578.
4. Mann DL. Management of patients with heart failure with reduced ejection fraction. In: Zipes DP, Libby P, Bonow RO, Mann DL, Tomaselli GF, Braunwald E,eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 11th ed. Philadelphia, PA: Elsevier; 2019:490–522.
5. Zakeri R, Cowie MR. Heart failure with preserved ejection fraction: Controversies, challenges and future directions. *Heart*. 2018;104:377–384.
6. Lam CSP, Voors AA, de Boer RA, Solomon SD, van Veldhuisen DJ. Heart failure with preserved ejection fraction: From mechanisms to therapies. *Eur Heart J*. 2018;39:2780–2792.
7. Hasenfuss G, Mann DL. Pathophysiology of heart failure. In: Zipes DP, Libby P, Bonow RO, Mann DL, Tomaselli GF, Braunwald E,eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 11th ed. Philadelphia, PA: Elsevier; 2019:442–461.
8. Borlaug BA. The pathophysiology of heart failure with preserved ejection fraction. *Nature Reviews Cardiology*. 2014;11:507–515.
9. Lewis GA, Schelbert EB, Williams SG, et al. Biological phenotypes of heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2017;70:2186–2200.
10. Lymperopoulos A, Rengo G, Koch WJ. Adrenergic nervous system in heart failure: Pathophysiology and therapy. *Circ Res*. 2013;113:739–753.
11. Heusch G, Libby P, Gersh B, et al. Cardiovascular remodelling in coronary artery disease and heart failure. *Lancet*. 2014;383:1933–1943.
12. Hartupee J, Mann DL. Neurohormonal activation in heart failure with reduced ejection fraction. *Nature Reviews Cardiology*. 2017;14:30–38.
13. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341:709–717.

14. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348:1309–1321.
15. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364:11–21.
16. Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the treatment of preserved cardiac function heart failure with an aldosterone antagonist (TOPCAT) trial. *Circulation*. 2015;131:34–42.
17. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370:1383–1392.
18. Maisel AS, Choudhary R. Biomarkers in acute heart failure-state of the art. *Nature Reviews Cardiology*. 2012;9:478–490.
19. Chow SL, Maisel AS, Anand I, et al. Role of biomarkers for the prevention, assessment, and management of heart failure: A scientific statement from the American Heart Association. *Circulation*. 2017;135:e1054–e1091.
20. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993–1004.
21. Houston BA, Kalathiya RJ, Kim DA, Zakaria S. Volume overload in heart failure: An evidence-based review of strategies for treatment and prevention. *Mayo Clin Proc*. 2015;90:1247–1261.
22. Verma A, Kalman JM, Callans DJ. Treatment of patients with atrial fibrillation and heart failure with reduced ejection fraction. *Circulation*. 2017;135:1547–1563.
23. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136:e137–e161.
24. Page RL 2nd, O'Bryant CL, Cheng D, et al. Drugs that may cause or exacerbate heart failure: A scientific statement from the American heart association. *Circulation*. 2016;134:e32–e69.
25. Milfred-LaForest SK, Chow SL, DiDomenico RJ, et al. Clinical pharmacy services in heart failure: An opinion paper from the Heart Failure Society of America and American College of Clinical Pharmacy Cardiology

Practice and Research Network. *Pharmacotherapy*. 2013;33:529–548.

26. Stough WG, Patterson JH. Role and value of clinical pharmacy in heart failure management. *Clin Pharmacol Ther*. 2017;102:209–212.
27. Januzzi JL, Mann DL. Approach to the patient with heart failure. In: Zipes DP, Libby P, Bonow RO, Mann DL, Tomaselli GF, Braunwald E,eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 11th ed. Philadelphia, PA: Elsevier; 2019:403–417.
28. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation*. 2018;(9):861–870.
29. Yancy CW, Januzzi JL Jr, Allen LA, et al. 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: Answers to 10 pivotal issues about heart failure with reduced ejection fraction: A report of the American College of Cardiology Task Force on expert consensus decision pathways. *J Am Coll Cardiol*. 2018;71:201–230.
30. Lindenfeld J, Albert NM, Boehmer JP, et al. HFSA 2010 comprehensive heart failure practice guideline. *J Card Fail*. 2010;16:e1–e194.
31. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37:2129–2200.
32. Redfield MM, Anstrom KJ, Levine JA, et al. Isosorbide mononitrate in heart failure with preserved ejection fraction. *N Engl J Med*. 2015;373:2314–2324.
33. Fang JC, Ewald GA, Allen LA, et al. Advanced (stage D) heart failure: A statement from the Heart Failure Society of America Guidelines Committee. *J Card Fail*. 2015;21:519–534.
34. Sajgalik P, Grupper A, Edwards BS, et al. Current status of left ventricular assist device therapy. *Mayo Clin Proc*. 2016;91:927–940.
35. Ellison DH, Felker GM. Diuretic treatment in heart failure. *N Engl J Med*. 2017;377:1964–1975.
36. Sarwar CM, Papadimitriou L, Pitt B, et al. Hyperkalemia in heart failure. *J Am Coll Cardiol*. 2016;68:1575–1589.
37. Kostis WJ, Shetty M, Chowdhury YS, Kostis JB. ACE inhibitor-induced angioedema: A review. *Curr Hypertens Rep*. 2018;20:55.

38. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: The CHARM-Preserved trial. *Lancet*. 2003;362:777–781.
39. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med*. 2008;359:2456–2467.
40. Vardeny O, Miller R, Solomon SD. Combined neprilysin and renin-angiotensin system inhibition for the treatment of heart failure. *JACC Heart Fail*. 2014;2:663–670.
41. Solomon SD, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: A phase 2 double-blind randomised controlled trial. *Lancet*. 2012;380:1387–1395.
42. King JB, Bress AP, Reese AD, Munger MA. Neprilysin inhibition in heart failure with reduced ejection fraction: A clinical review. *Pharmacotherapy*. 2015;35:823–837.
43. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med*. 1996;334:1349–1355.
44. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL randomised intervention trial in congestive heart failure (MERIT-HF). *Lancet*. 1999;353(9169):2001–2007.
45. The cardiac insufficiency bisoprolol study II (CIBIS-II): A randomised trial. *Lancet*. 1999;353:9–13.
46. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001;344:1651–1658.
47. Hjalmarson A, Goldstein S, Fagerberg B, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: The Metoprolol CR/XL randomized intervention trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. *Jama*. 2000;283:1295–1302.
48. Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: Results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation*. 2002;106:2194–2199.
49. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: The CAPRICORN randomised

trial. *Lancet*. 2001;357:1385–1390.

50. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol or Metoprolol European Trial (COMET): Randomised controlled trial. *Lancet*. 2003;362:7–13.
51. Frohlich H, Zhao J, Tager T, et al. Carvedilol compared with metoprolol succinate in the treatment and prognosis of patients with stable chronic heart failure: Carvedilol or metoprolol evaluation study. *Circulation Heart failure*. 2015;8:887–896.
52. Pasternak B, Svanstrom H, Melbye M, Hviid A. Association of treatment with carvedilol vs metoprolol succinate and mortality in patients with heart failure. *JAMA Intern Med*. 2014;174:1597–1604.
53. McAlister FA, Wiebe N, Ezekowitz JA, Leung AA, Armstrong PW. Meta-analysis: Beta-blocker dose, heart rate reduction, and death in patients with heart failure. *Ann Intern Med*. 2009;150:784–794.
54. Prins KW, Neill JM, Tyler JO, Eckman PM, Duval S. Effects of beta-blocker withdrawal in acute decompensated heart failure: A systematic review and meta-analysis. *JACC Heart Fail*. 2015;3:647–653.
55. Jondeau G, Neuder Y, Eicher JC, et al. B-CONVINCED: Beta-blocker CONtinuation Vs. INterruption in patients with Congestive heart failure hospitalizED for a decompensation episode. *Eur Heart J*. 2009;30:2186–2192.
56. Willenheimer R, van Veldhuisen DJ, Silke B, et al. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: Results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. *Circulation*. 2005;112:2426–2435.
57. Gattis WA, O'Connor CM, Gallup DS, Hasselblad V, Gheorghiade M. Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure: Results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial. *J Am Coll Cardiol*. 2004;43:1534–1541.
58. Bhatt AS, DeVore AD, DeWald TA, Swedberg K, Mentz RJ. Achieving a maximally tolerated beta-blocker dose in heart failure patients: Is there room for improvement? *J Am Coll Cardiol*. 2017;69:2542–2550.
59. Greene SJ, Butler J, Albert NM, et al. Medical therapy for heart failure with reduced ejection fraction: The CHAMP-HF registry. *J Am Coll*

Cardiol. 2018;72:351–366.

60. Bavishi C, Chatterjee S, Ather S, Patel D, Messerli FH. Beta-blockers in heart failure with preserved ejection fraction: A meta-analysis. *Heart Fail Rev*. 2015;20:193–201.
61. Cleland JGF, Bunting KV, Flather MD, et al. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: An individual patient-level analysis of double-blind randomized trials. *Eur Heart J*. 2018;39:26–35.
62. Flatt DM, Brown MC, Mizeracki AM, King BJ, Weber KT. Mineralocorticoid receptor antagonists in the management of heart failure and resistant hypertension: A review. *JAMA Cardiol*. 2016;1:607–612.
63. Trevisan M, de Deco P, Xu H, et al. Incidence, predictors and clinical management of hyperkalaemia in new users of mineralocorticoid receptor antagonists. *Eur J Heart Fail*. 2018;20:1217–1226.
64. Koruth JS, Lala A, Pinney S, Reddy VY, Dukkipati SR. The clinical use of Ivabradine. *J Am Coll Cardiol*. 2017;70:1777–1784.
65. Swedberg K, Komajda M, Bohm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): A randomised placebo-controlled study. *Lancet*. 2010;376:875–885.
66. Ambrosy AP, Butler J, Ahmed A, et al. The use of digoxin in patients with worsening chronic heart failure: Reconsidering an old drug to reduce hospital admissions. *J Am Coll Cardiol*. 2014;63:1823–1832.
67. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med*. 1997;336:525–533.
68. Ahmed A, Rich MW, Fleg JL, et al. Effects of digoxin on morbidity and mortality in diastolic heart failure: The ancillary digitalis investigation group trial. *Circulation*. 2006;114:397–403.
69. Ahmed A, Rich MW, Love TE, et al. Digoxin and reduction in mortality and hospitalization in heart failure: A comprehensive post hoc analysis of the DIG trial. *Eur Heart J*. 2006;27:178–186.
70. Schentag J, Bang A, Kozinski-Tober J. Digoxin. *Applied Pharmacokinetics and Pharmacodynamics*. 4th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2006;411–439.
71. Allen LA, Fonarow GC, Simon DN, et al. Digoxin use and subsequent outcomes among patients in a contemporary atrial fibrillation cohort. *J Am Coll Cardiol*. 2015;65:2691–2698.

72. Lam PH, Bhyan P, Arundel C, et al. Digoxin use and lower risk of 30-day all-cause readmission in older patients with heart failure and reduced ejection fraction receiving beta-blockers. *Clin Cardiol*. 2018;41:406–412.
73. Freeman JV, Yang J, Sung SH, Hlatky MA, Go AS. Effectiveness and safety of digoxin among contemporary adults with incident systolic heart failure. *Circ Cardiovasc Qual Outcomes*. 2013;6:525–533.
74. Ahmed A, Gambassi G, Weaver MT, Young JB, Wehrmacher WH, Rich MW. Effects of discontinuation of digoxin versus continuation at low serum digoxin concentrations in chronic heart failure. *Am J Cardiol*. 2007;100:280–284.
75. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation*. 2014;130:e199–e267.
76. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;71:2199–2269.
77. Vamos M, Erath JW, Hohnloser SH. Digoxin-associated mortality: A systematic review and meta-analysis of the literature. *Eur Heart J*. 2015;36:1831–1838.
78. Weiss JN, Qu Z, Shivkumar K. Electrophysiology of hypokalemia and hyperkalemia. *Circ Arrhythm Electrophysiol*. 2017;10(3):pii: e004667.

36

Acute Decompensated Heart Failure

Brent N. Reed and Jo E. Rodgers

KEY CONCEPTS

1. Patients presenting to the hospital with acute decompensated heart failure (ADHF) can be categorized into four hemodynamic subsets based on volume status (euvolemic or "dry" vs volume overloaded or "wet") and cardiac output (adequate cardiac output or "warm" vs hypoperfusion or "cold"). Patients may be warm and dry, warm and wet, cold and dry, or cold and wet.
2. While invasive hemodynamic monitoring using a pulmonary artery (PA) catheter does not alter outcomes in a broad population of ADHF patients, it may be considered in those who are refractory to initial therapy, whose volume status is unclear, or in those with clinically significant hypotension (ie, systolic blood pressure < 80 mm Hg) or worsening renal function despite standard therapy.
3. Key hemodynamic parameters monitored with a PA catheter include pulmonary capillary wedge pressure (PCWP; reflecting fluid status or "preload"), cardiac output or cardiac index (CI; often used to reflect the innate contractility of the heart), and systemic vascular resistance (SVR; reflecting vascular tone or "afterload"). Although a normal PCWP (6–12 mm Hg) is desirable in healthy patients, higher ventricular filling pressures (15–18 mm Hg) are often necessary in patients with heart failure (HF).
4. Treatment goals for ADHF include relief of congestive symptoms, restoration of systemic tissue perfusion via improved cardiac output, and minimization of further cardiac damage and other adverse effects.
5. Optimizing oral chronic HF therapy in the setting of ADHF may assist with improving cardiac output, relieving congestion, and preventing hospital readmission.
6. Pharmacologic therapies used in the management of ADHF can be broadly

classified according to whether they improve volume overload and/or low cardiac output. No therapy studied to date has conclusively been shown to reduce mortality and some may worsen outcomes.

7. Intravenous (IV) loop diuretics are considered first-line therapy for the management of ADHF associated with volume overload refractory to orally administered diuretics. Administration as a bolus or continuous infusion appears to be equally effective and safe when selected as initial therapy, although high-dose loop diuretic therapy (ie, 2.5-times the oral regimen prior to admission) is associated with greater volume removal. The addition of a thiazide-type diuretic may be considered in patients with diuretic resistance. If patients continue to be refractory to, or experience worsening of renal function with diuretic therapy, IV vasodilators and/or inotropes may be indicated. Placement of a PA catheter may be helpful in guiding therapy in such patients.

8. Vasopressin antagonists such as tolvaptan may be considered in patients with severe euvolemic or hypervolemic hyponatremia. Therapy should only be initiated in a hospital setting to allow for monitoring of volume status and serum sodium concentrations, as rapid correction of serum sodium may result in adverse neurological sequelae.

9. Ultrafiltration may be considered in patients with diuretic resistance or those with worsening renal impairment despite IV vasodilator and/or inotrope therapy.

10. Intravenous vasodilators may be added to diuretics for rapid resolution of congestive symptoms, especially in patients with acute pulmonary edema or severe hypertension. Such therapy may also be considered in patients who fail to respond to aggressive treatment with diuretics. In the absence of hypotension (systolic blood pressure <90 mm Hg or symptomatic hypotension) or reduced left ventricular filling pressures, IV vasodilators should also be considered prior to IV inotropes in patients with ADHF and evidence of low cardiac output. Frequent blood pressure monitoring is necessary to ensure their safe use.

11. Intravenous inotropes are recommended for maintaining systemic perfusion and end-organ function in hypotensive patients with evidence of severe left ventricular dysfunction and low cardiac output. Inotropic therapy may also be considered in patients who do not tolerate or respond to IV vasodilators or in patients with worsening renal function despite standard therapy. Patients receiving IV inotropes should be monitored continuously for

arrhythmias.

12. Temporary mechanical circulatory support (MCS) is indicated in select patients with severe ADHF or those with advanced HF who are refractory to pharmacologic therapy. The intra-aortic balloon pump (IABP) is the most common type of temporary MCS but provides the least amount of hemodynamic support. Other types of temporary MCS include temporary ventricular assist devices (VADs) and extracorporeal membrane oxygenation (ECMO).

13. Cardiac transplantation remains the only definitive therapy for advanced HF. Given the extended wait time for identifying suitable donors, implantation of a durable VAD may be considered for patients who are eligible for cardiac transplantation (ie, “bridge to transplant”) or in whom transplantation is not an option (ie, “destination therapy”).

Preclass Engaged Learning Activity

For an introduction to the signs and symptoms of acute decompensated heart failure (ADHF), watch this video (https://www.youtube.com/watch?v=4qd7fwcBwek) from the American Heart Association on YouTube. As you read the textbook chapter, match each of these signs and symptoms to the hemodynamic subset in which you would expect to find them (ie, warm and wet, cold and dry, cold and wet). Also think about what additional data (eg, physical examination findings, laboratory values) you might also expect to find in each hemodynamic subset as well as the general treatment approach (ie, volume removal and/or improved tissue perfusion).

INTRODUCTION

The clinical course of heart failure (HF) manifests as periods of relative stability with increasingly frequent episodes of decompensation as the disease progresses.[1] Several terms have been used to characterize worsening HF requiring hospitalization. Patients with persistent symptoms requiring specialized interventions (eg, surgery) despite guideline-directed medical therapy (GDMT) are classified as having advanced HF or Stage D according to the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) system.[2] Due to the presence of HF symptoms with minimal

activity or at rest, these patients are also typically classified as New York Heart Association (NYHA) class III or IV, respectively. The terms *acute decompensated heart failure* (ADHF) or *exacerbation of heart failure* refer to those patients with new or worsening signs or symptoms of HF (often as a result of volume overload and/or low cardiac output [CO]) requiring medical intervention such as an emergency department visit or hospitalization. The term *acute heart failure* may be misleading as it more often refers to patients with a sudden onset of HF signs or symptoms following previously normal cardiac function (eg, following myocardial infarction [MI]). This chapter focuses on the management of patients with ADHF, which may include those with heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF).

Despite the considerable morbidity and mortality associated with ADHF, few randomized controlled trials have been conducted in this patient population. For those studies that have been published, the heterogeneity of patients enrolled often limits clinical application. Nonetheless, clinical practice guidelines for HF issued by ACCF/AHA include sections specifically focused on the management of advanced HF and ADHF; these will be referenced where relevant throughout this chapter.[2]

EPIDEMIOLOGY

An estimated 5.7 million American adults have HF and projections indicate another 3 million will develop HF by 2030, a 50% increase in prevalence from prior estimates.[3,4] The growing number of patients living with HF has led to substantial increases in hospitalization rates for ADHF. Recent data indicate that over 1 million patients are hospitalized for HF annually, contributing to significant increases in morbidity and mortality and adding substantial burden to the healthcare system.[3,5] Hospitalization for HF has been independently associated with increases in subsequent hospitalization as well as decreased survival, which may explain why the mortality rate at 5 years remains 50%.[3,5,6] The cost of HF is projected to approach $70 billion by 2030, an increase thought to be driven primarily by the costs of acute care.[4]

ETIOLOGY AND PATHOPHYSIOLOGY

The underlying etiology of ADHF varies and is often multifactorial. De novo HF

may occur due to left ventricular dysfunction following a large MI or sudden elevation in blood pressure; such cases represent approximately 25% of admissions.[7] However, the majority of hospitalizations for ADHF (70%) are comprised of patients experiencing an acute worsening of chronic HF[7]; readers are referred to (Chapter 35, "Chronic Heart Failure") for a more detailed discussion of the etiology and pathophysiology of chronic HF including precipitating factors. Patients can become refractory to oral therapies and decompensate after even a relatively mild insult (eg, dietary indiscretion, nonsteroidal anti-inflammatory drug use), medication nonadherence, or concurrent noncardiac illness (eg, infection). New or worsening cardiac processes, such as MI, atrial or ventricular arrhythmias, hypertensive crises, myocarditis, or acute valvular insufficiency, may also produce ADHF in an otherwise stable patient. Emerging evidence indicates that exacerbations of chronic HFrEF and HFpEF occur in approximately equal numbers.[2] A minority of patients (5%) present with gradual, progressive worsening of CO and refractoriness to therapy due to advanced left ventricular systolic dysfunction.[7]

Several studies have provided a better understanding of the prognostic factors associated with ADHF. Data from the Acute Decompensated Heart Failure National Registry (ADHERE) found elevated blood urea nitrogen (BUN) to be the best individual predictor of in-hospital mortality, followed by low systolic blood pressure and elevated serum creatinine.[8] Hyponatremia, elevations in troponin I, ischemic etiology, and poor functional capacity are also negative prognostic factors.[5] In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) Registry, low blood pressure and poor renal function were found to be negative prognostic markers for subsequent readmission or death.[9] Use of GDMT at discharge and coronary angiography or implantable cardioverter-defibrillator placement during hospitalization were associated with improved prognosis, suggesting that optimal management during hospitalization can yield beneficial effects on subsequent prognosis.[9]

CLINICAL PRESENTATION

1 A careful history and physical examination are key components of an ADHF diagnosis. The history should focus on potential etiologies of ADHF, the presence of precipitating factors, onset, duration, and severity of symptoms, and a careful medication history. Hemodynamic status should also be ascertained in

order to guide initial therapy. Patients presenting with ADHF may be categorized into one of four hemodynamic subsets based on volume status (euvolemic or "dry" vs volume overloaded or "wet") and CO (adequate CO or "warm" vs hypoperfusion or "cold"). The corresponding subsets are warm and dry (subset I), warm and wet (subset II), cold and dry (subset III), or cold and wet (subset IV) (**Fig. 36-1**). The term *cardiogenic shock* may also be used to describe patients in subsets III and IV who present with low blood pressure and evidence of tissue hypoperfusion. In addition to guiding therapeutic decision-making, these four hemodynamic profiles are also predictive of clinical outcomes. Compared to dry-warm patients, patients in the wet-warm and wet-cold subsets have a 2-fold and 2.5-fold greater risk of death at 1 year, respectively.[10]

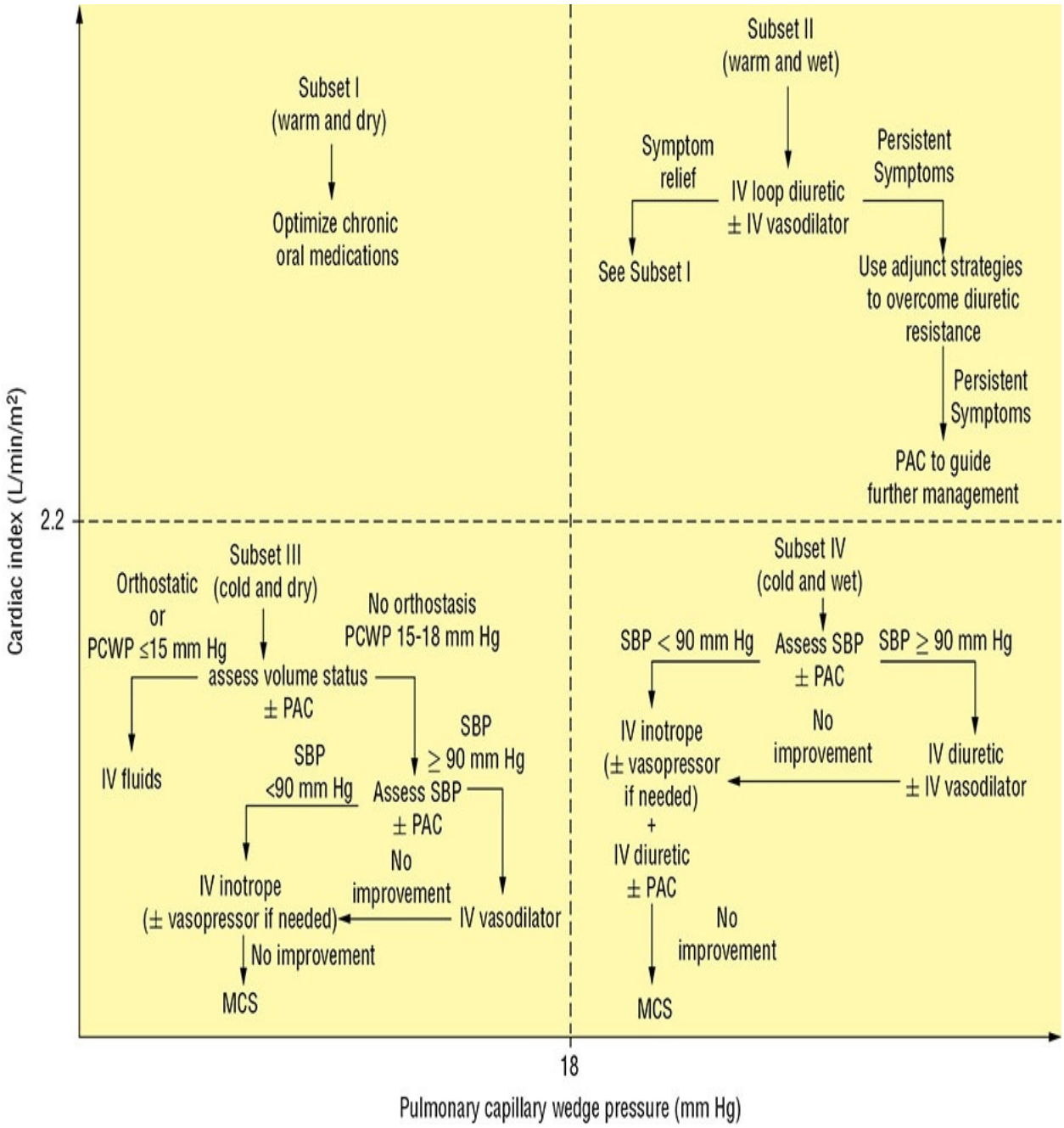


FIGURE 36-1 General management algorithm for acute decompensated heart failure based on clinical presentation. Patients may be categorized into a hemodynamic subset based on signs and symptoms or invasive hemodynamic monitoring. Adjunct strategies for overcoming diuretic resistance include increasing the dose of loop diuretic; switching to a continuous infusion; adding a diuretic with an alternative mechanism of action, an IV vasodilator, or an IV inotrope; and in select patients, adding MCS. (IV, intravenous; MCS, mechanical circulatory support; PAC, pulmonary artery catheter; PCWP, pulmonary capillary wedge pressure; SBP, systolic blood pressure.).

Although hemodynamic status can be determined in a majority of patients based on signs and symptoms, a small subset of patients may require invasive hemodynamic monitoring to guide therapy. In this latter population, measurement of the pulmonary capillary wedge pressure (PCWP) and cardiac index (CI) may be used to categorize patients by volume status and CO, respectively. A PCWP greater than 18 mm Hg often reflects volume overload and is generally used to distinguish "wet" from "dry" subsets, whereas a CI less than 2.2 L/min/m^2 (0.037 L/s/m^2) is often used to distinguish "cold" from "warm" subsets; use of these invasive hemodynamic parameters will be discussed in further detail later in this chapter.

CLINICAL PRESENTATION

General

- Patients with ADHF typically present in one of four hemodynamic subsets (Fig. 36-1) based on the presence of volume overload (ie, congestion) and/or low cardiac output (ie, tissue hypoperfusion).
- Hemodynamic status can be ascertained in most patients based on a history and physical examination; a subset may require invasive hemodynamic monitoring.

Symptoms

- Volume overload: dyspnea, orthopnea, paroxysmal nocturnal dyspnea, ascites, gastrointestinal symptoms (poor appetite, nausea, early satiety), peripheral edema, weight gain.
- Low output: altered mental status, fatigue, gastrointestinal symptoms (similar to volume overload), decreased urine output.

Signs

- Volume overload: pulmonary crackles (or rales), elevated jugular venous pressure, abdominojugular reflux, S3 gallop, peripheral edema.
- Low output: tachycardia, hypotension (more commonly) or hypertension, narrow pulse pressure, cool extremities, pallor, cachexia.

Laboratory Values

- Volume overload: B-type natriuretic peptide < 100 pg/mL (ng/L; 29

pmol/L)and N-terminal B-type natriuretic peptide < 300 pg/mL (ng/L; 35 pmol/L)are negatively predictive for congestive ADHF; serum sodium concentration < 130 mEq/L (mmol/L); elevated alkaline phosphatase; elevated gamma-glutamyl transferase.

- Low cardiac output: evidence of end-organ injury due to impaired perfusion, such as elevated liver transaminases and serum creatinine; mixed venous oxygen concentration < 60% (0.60); elevated serum lactate.

Hemodynamic Monitoring

- Volume overload: pulmonary capillary wedge pressure > 18 mm Hg; other pressures (eg, right atrial pressure, pulmonary artery diastolic pressure) also commonly elevated.
- Low cardiac output: cardiac index < 2.2 L/min/m^2 (0.037 L/s/m^2), with or without systemic vascular resistance > 1400 dyne·sec·cm^{-5} (140 MPa·sec·m^{-3}).

Hospitalization for ADHF should be considered based on the clinical findings listed in **Table 36-1**. Most patients do not require admission to an intensive care unit and may be admitted to a monitored unit or general medical floor. If a patient experiences hemodynamic instability necessitating frequent monitoring of vital signs, invasive hemodynamic monitoring, or rapid titration of IV medications (with concurrent monitoring), admission to an intensive care unit may be required to ensure optimal outcomes.

TABLE 36-1 Indications for Hospitalization in Patients Presenting with ADHF

Presenting Features	Clinical Findings
Evidence of fluid overload	• Weight gain > 10 kg (consider if >5 kg) • Symptoms of congestion (eg, dyspnea on exertion or at rest, orthopnea, PND, and early satiety*) • Signs of congestion (eg, tachypnea with oxygen saturation < 90% (0.90), JVD, crackles, hepatomegaly, and lower extremity edema)
Evidence of low cardiac output	• Extreme fatigue • Hypotension, narrow pulse pressure • Cool extremities
Evidence of organ hypoperfusion	• Worsening renal or hepatic function • Altered mental status
Concomitant cardiovascular diseases that could compromise hemodynamic status	• Uncontrolled hypertension • Myocardial ischemia or infarction • Valvular disease • Arrhythmia (eg, atrial fibrillation with rapid ventricular response, ventricular tachycardia, and repeated ICD shocks)
Other conditions that could compromise hemodynamic status	• Severe electrolyte deficiency (potassium and magnesium) • Acute exacerbation of pulmonary disease (eg, asthma, COPD, or pulmonary embolus) • Infection such as pneumonia or urosepsis • Symptomatic hypothyroidism or hyperthyroidism • Use of medications with negative inotropic effects (eg, nondihydropyridine calcium antagonists) • Use of medications that promote fluid retention (eg, NSAIDs, steroids, thiazolidinediones, and pregabalin)

COPD, chronic obstructive pulmonary disease; ICD, implantable cardioverter defibrillator; JVD, jugular venous distension; NSAIDs, nonsteroidal anti-inflammatory agents; PND, paroxysmal nocturnal dyspnea.

*Early satiety may also be a symptom of low cardiac output.

Signs and Symptoms

Important elements of the physical examination include assessment of vital signs and weight, cardiac auscultation for heart sounds and murmurs, pulmonary auscultation for crackles, presence and severity of peripheral edema, and evidence of end-organ dysfunction. The most common presentation of ADHF is severe volume overload. Symptoms consistent with pulmonary congestion include orthopnea and dyspnea with minimal exertion, and those associated with systemic congestion include gastrointestinal (GI) discomfort, ascites, and peripheral edema. Orthopnea is the symptom that best correlates with elevated pulmonary pressure, whereas jugular venous pressure is the most reliable sign of volume status, warranting evaluation at admission as well as throughout the acute hospitalization as an indicator of diuretic efficacy.[10] An S3 gallop,

suggestive of increased volume in the left ventricle, has high diagnostic specificity for ADHF.[10] Other physical findings, such as pulmonary crackles and lower extremity edema, have low specificity and sensitivity for the diagnosis of ADHF.

Signs and symptoms of low CO are often nonspecific and may include generalized fatigue, cool extremities, and pallor. Manifestations of impaired end-organ perfusion may also be present, such as altered mental status (decreased perfusion to the central nervous system) or decreased urine output (decreased renal perfusion). Hypotension and narrow pulse pressure may also suggest low CO. Gastrointestinal symptoms, such as poor appetite, nausea, and early satiety, may be a sign of poor perfusion to the GI tract, abdominal congestion, or both. Many patients will present with signs and symptoms of both wet and cold subsets; in these patients, symptoms of low CO may not be obvious until congestion has been optimally treated.

Laboratory Findings

Plasma B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) concentrations are positively correlated with the degree of left ventricular dysfunction and HF, and are now frequently used to assist in the differential diagnosis of dyspnea (HF vs asthma, chronic obstructive pulmonary disease, or infection). A low BNP concentration, often defined as less than 100 pg/mL (ng/L; 29 pmol/L), has a 96% predictive value for excluding HF as an underlying etiology for dyspnea.[10] An NT-proBNP concentration of less than 300 pg/mL (ng/L; 35 pmol/L) is similarly predictive for excluding HF. In addition, an elevated BNP concentration prior to discharge is associated with an increased risk of poor long-term outcomes. However, some limitations exist. For example, any disease process that increases right heart pressures will elevate BNP, such as pulmonary emboli, chronic obstructive lung disease, and pulmonary arterial hypertension. In addition, BNP concentrations may be mildly increased with advanced age, female gender, and renal dysfunction, and may be lower in the setting of obesity.[10] Although the role of BNP in HF remains an area of ongoing research, guidelines currently recommend obtaining a BNP or NT-proBNP in order to assist with clinical decision-making when the diagnosis of ADHF is uncertain and for determining the prognosis or severity of disease.[2]

A number of other laboratory tests should also be obtained to identify precipitating factors for ADHF (eg, thyroid function tests, complete blood count to assess for infection). In particular, cardiac enzymes should be obtained to

exclude the presence of myocardial ischemia. Routine serum chemistries (eg, serum creatinine, liver function tests) should also be obtained to assess end-organ perfusion. Profound volume overload may also contribute to aberrations in serum markers of end-organ function due to venous congestion. Other helpful laboratory tests include markers of peripheral tissue perfusion, such as venous oxygenation saturation and serum lactate concentrations.

Invasive Hemodynamic Monitoring

2 Invasive hemodynamic monitoring should be reserved for select patients with ADHF. It is usually performed with a flow-directed pulmonary artery (PA) catheter (also known as Swan-Ganz catheter) placed percutaneously into a central vein and advanced through the right side of the heart and into the PA. This process may also be referred to as right heart catheterization (in contrast to left heart catheterization, which is often used to visualize the coronary arteries). In a clinical trial assessing routine PA catheter use in patients with ADHF, no impact on survival was observed, although those with a clear indication for its use (eg, titration of IV inotropes) were excluded.[11] Based on these results, the routine use of invasive hemodynamic monitoring in patients with ADHF is not currently recommended.[2] However, it often provides important information in patients whose clinical status is unclear or complicated, or as a guide for titrating rapidly acting medications (eg, IV vasodilators). As a consequence, invasive hemodynamic monitoring should be considered in patients who are refractory to initial therapy, those in whom volume status is unclear, or those who have clinically significant hypotension (eg, systolic blood pressure <80 mm Hg) or worsening renal function (WRF) despite appropriate initial therapy. Hemodynamic assessment is also required in patients being evaluated for mechanical circulatory support (MCS) or cardiac transplantation; in the latter case, adequate reversal of pulmonary hypertension in response to vasodilator challenge must be documented before listing for transplant. Finally, documentation of an adequate hemodynamic response to IV inotropic therapy is often necessary in order to obtain approval for reimbursement for chronic outpatient inotropic therapy.[2]

3 Several important hemodynamic parameters can be obtained from a PA catheter. Inflation of a balloon proximal to the end port allows the catheter to be “wedged” inside a pulmonary capillary, yielding the PCWP. In the absence of an intracardiac shunt, mitral valve disease, or severe pulmonary disease, the PCWP may be used to estimate left ventricular end-diastolic pressure, or “preload.”

Preload refers to the stretch incurred by cardiac myocytes in response to increased volumetric pressure. Thus, PCWP can be a useful marker of volume status; elevated PCWP is often indicative of volume overload whereas reduced PCWP indicates dehydration or inadequate ventricular filling pressure. The relationship between preload (or PCWP) and CO is described by the Frank–Starling mechanism, which is depicted in **Fig. 36-2A**. Due to the much flatter curve observed in patients with HF, increases in preload do not confer the same improvements in CO observed in patients with normal cardiac function. As a consequence, higher pressures (ie, 15–18 mm Hg, compared to a normal range of 6–12 mm Hg) are often required in patients with HF in order to optimize CO. Excess preload (PCWP >18 mm Hg) manifests as signs and symptoms of congestion. Fortunately, PCWP can be lowered to 15 to 18 mm Hg with relatively little decrease in CO due to the flatter shape of the Frank–Starling curve in HF. Extreme elevations in PCWP (representing profound volume overload) are also thought to worsen cardiac function, although a precise mechanism for this phenomenon is unknown.

A PA catheter may also be used to determine CO, or the volume of blood being pumped by the heart (particularly by the left ventricle) over a unit of time. CO is often normalized for body surface area to yield CI, which allows measurements to be made without considering the body size. Using parameters derived from the PA catheter, CO is calculated based on one of two methods. The thermodilution method for determining CO is performed by releasing cooled fluid from a proximal port on the PA catheter and measuring the resulting change in temperature at a downstream thermistor over a period of time. In the Fick method, blood flow is calculated using the difference between arterial and venous oxygen concentration, oxygen-carrying capacity of hemoglobin, and a population constant for oxygen consumption over time. The preferred method for determining CO varies by clinician, although the presence of certain comorbid conditions (eg, valvular abnormalities and pulmonary disease) may make one method more or less accurate in an individual patient.

The systemic vascular resistance (SVR) can also be calculated using parameters measured by the PA catheter, including CO, mean arterial pressure (MAP), and central venous pressure (CVP). Also referred to as total peripheral resistance or arterial impedance, SVR reflects “afterload,” or the total sum of forces impeding ejection of blood from the left ventricle. Vasoconstriction (ie, decreased diameter of arterial vessel lumen) increases vascular resistance, whereas vasodilation decreases it. Although SVR is inversely related to CO, patients with normal left ventricular function can often withstand relatively high

elevations in SVR, as shown in **Fig. 36-2B**. However, in patients with HF, even a moderately elevated SVR can compromise left ventricular performance. Elevated SVR is common in untreated HF and generally responsive to oral or IV vasodilators. Conversely, a reduction in resistance is consistent with vasodilatory shock (eg, sepsis) and is routinely managed with IV vasopressor therapy (see Chapter 41,"Pharmacotherapy in Shock").

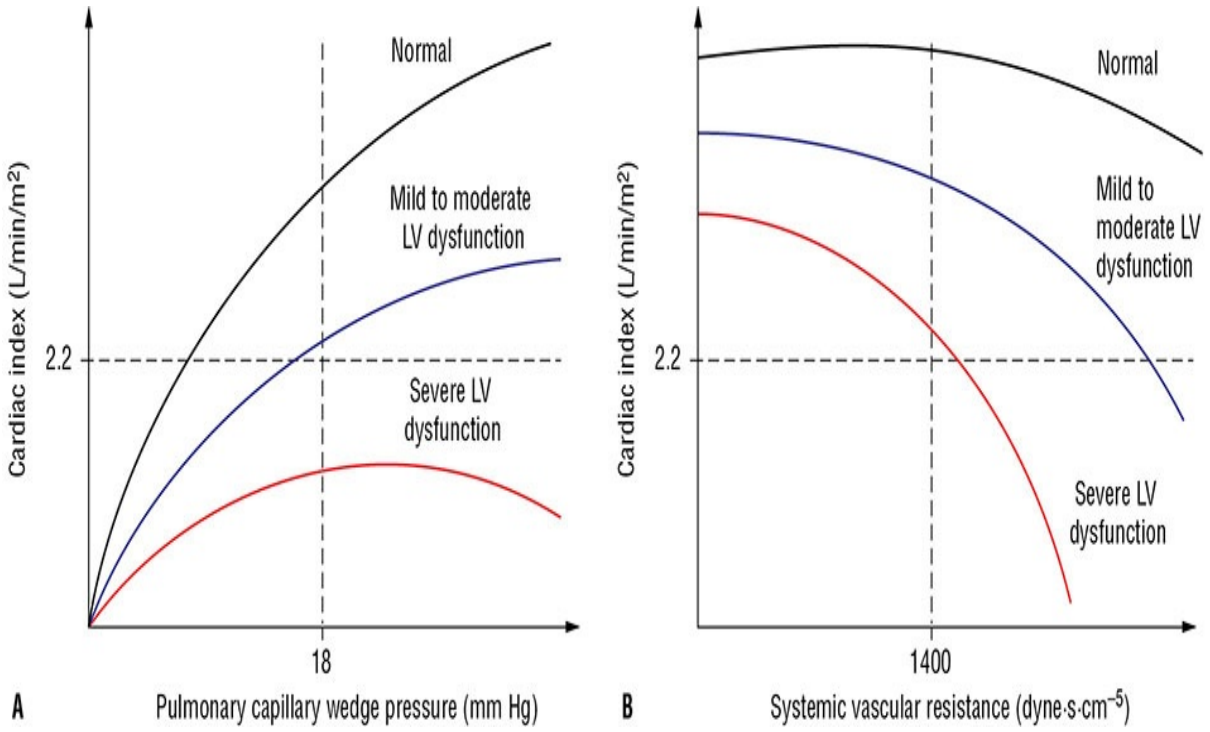


FIGURE 36-2 Hemodynamic alterations in heart failure. For cardiac index expressed in SI units of $L/s/m^2$ multiply values expressed in units of $L/min/m^2$ by 0.0167. For systemic vascular resistance expressed in SI units of $MPa \cdot s \cdot m^{-3}$ multiply values expressed in units of $dyne \cdot s \cdot cm^{-5}$ by 0.1. **(A)** An illustration of the relationship between cardiac output (displayed as cardiac index, which is cardiac output normalized for body surface area) and preload (displayed as pulmonary capillary wedge pressure) according to severity of left ventricular function. (B) An illustration of the corresponding relationship between cardiac output and afterload (displayed as systemic vascular resistance). (LV, left ventricular.).

When heart rate is held constant, CO reflects stroke volume, or the volume of blood being pumped by the heart (particularly by the left ventricle) with each beat. Although stroke volume is in part determined by cardiac contractility, it is also influenced by preload and afterload, and alterations in CO (or CI) should

therefore be interpreted in the context of PCWP and SVR. For example, a low CI (< 2.2 L/min/m^2 [0.037 L/s/m^2]) in the setting of a low PCWP (< 6 mm Hg) may represent decreased preload due to hypovolemia rather than impaired contractility (Fig. 36-2A). Similarly, a low CI in the setting of high SVR (> 1400 dyne·sec·cm^{-5} [140 MPa·sec·m^{-3}]) may represent impaired left ventricular performance due to excess afterload (Fig. 36-2B). In both of these cases, CI could be increased directly (via inotropic therapy, for example) but a more optimal strategy would be to first address the aberrations in PCWP or SVR contributing to low CI.

A PA catheter can also be used to measure pulmonary vascular resistance (PVR), which represents the impedance of blood flow from the right ventricle to the pulmonary circulation. Pulmonary hypertension and pulmonary edema are two common causes of elevated PVR. As described previously, patients with elevated pulmonary pressure must have proven reversibility (in response to vasodilator challenge) prior to being listed for heart transplantation. Otherwise, if elevations in PVR are irreversible, isolated right ventricular failure is likely to occur immediately following heart transplantation. Just as SVR is calculated using MAP, PVR is calculated using the mean PA pressure, which incorporates the PA systolic and diastolic pressures. The PA diastolic pressure may also be useful if the PA catheter fails to wedge (making it impossible to obtain PCWP). If the PCWP and PA diastolic pressure have been correlated prior to the failure to wedge, then the PA diastolic pressure may be followed as a surrogate marker of volume status. Normal values for the aforementioned hemodynamic parameters are listed in **Table 36-2**.

TABLE 36-2 Normal Hemodynamic Values

Central Venous (Right Atrial) Pressure, mean, CVP	<5 mm Hg
Right Ventricular Pressure (Systolic/Diastolic)	25/0 mm Hg
Pulmonary Artery Pressure (Systolic/Diastolic), PAS/PAD	25/10 mm Hg
Pulmonary Arterial Pressure, mean, PAP	<18 mm Hg
Pulmonary Capillary Wedge Pressure, PCWP	<12 mm Hg*
Systemic Arterial Pressure (Systolic/Diastolic), SBP/DBP	120/80 mm Hg
Mean Arterial Pressure, MAP = (DBP+[1/3 (SBP-DBP])	70–110 mm Hg
Cardiac Output, CO	4–6 L/min
Cardiac Index, CI = CO/BSA	2.8–4.2 L/min/m^2 (0.047-0.070 L/s/m^2)
Systemic Vascular Resistance, SVR = ([MAP–CVP]*80)/(CO)	900–1,400 dyne·sec·cm^{-5} (90-140 MPa·s·m^{-3})
Pulmonary Vascular Resistance, PVR = ([PAP–CVP]*80)/(CO)	150–250 dyne·sec·cm^{-5} (15-25 MPa·s·m^{-3})
Arterial Oxygen Saturation	90%–94% (0.90-0.94)
Mixed Venous Oxygen Saturation	60%–80% (0.60-0.80)

BSA, body surface area.

*A higher than normal pulmonary capillary wedge pressure (ie, 15–18 mm Hg) is often accepted in patients with heart failure. See text for details.

TREATMENT

Desired Outcomes

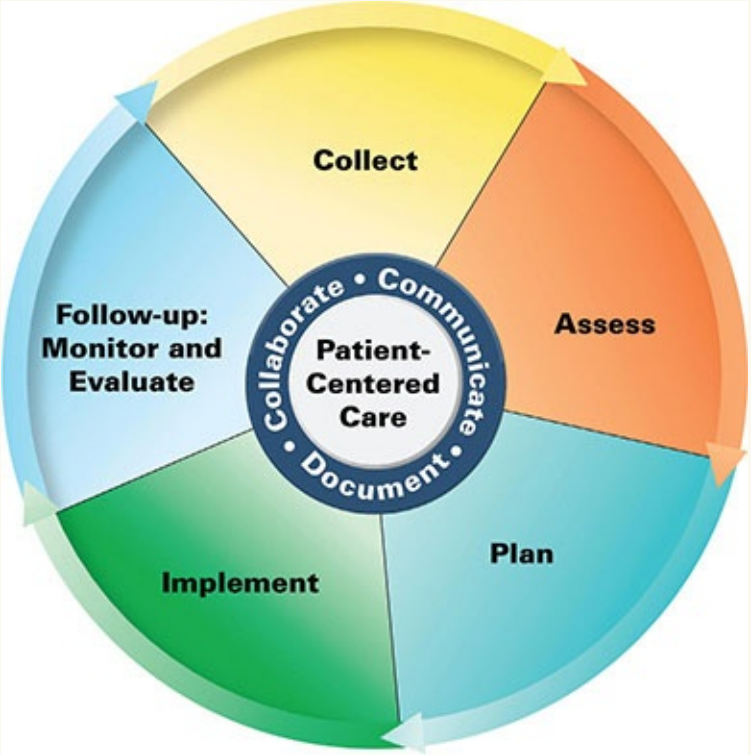
4 The overall goals of therapy in ADHF are to relieve symptoms, improve hemodynamic stability (ie, restore end-organ perfusion if compromised), and reduce short-term mortality, so that a patient can be discharged in a stable compensated state on oral drug therapy. Although IV diuretic, vasodilator, and inotropic therapy can be very effective at achieving these goals, their efficacy must be balanced against the potential for serious adverse effects. All patients should also be evaluated for precipitating factors of ADHF, including arrhythmias, hypertension, myocardial ischemia or infarction, anemia, and

thyroid disorders. Patients who may benefit from coronary revascularization should also be identified. Medications (including noncardiac medications) that may worsen cardiac function should also be evaluated. Prior to discharge, optimization of chronic oral therapy and patient education are critical to preventing rehospitalization. When available and appropriate, patients should be referred to an HF disease management program.[2]

General Approach to Treatment

5 An important step in the management of ADHF is to first assess medications being taken prior to admission and determine whether adjustment or discontinuation is required. If fluid retention is evident on physical examination, aggressive diuresis should be pursued. Although increasing the dose of oral diuretic therapy may be effective in some cases, the use of IV diuretics is recommended.[2] In the absence of cardiogenic shock or symptomatic hypotension, every effort should be made to continue all GDMT for HF. β-Blocker therapy may be temporarily held or dose-reduced if recent initiation or up-titration is responsible for acute decompensation. Otherwise, β-blocker discontinuation is discouraged as it has been associated with worse outcomes in patients with ADHF.[12,13] Appropriateness of initiating β-blockers prior to discharge will be discussed later in this chapter.

Select GDMT may also need to be temporarily held in the setting of renal dysfunction, especially if oliguria or hyperkalemia is present (eg, ACE inhibitors, angiotensin receptor blockers, angiotensin receptor-neprilysin inhibitors, aldosterone antagonists). Therapies that may cause WRF (eg, ACE inhibitor) should only be initiated or up-titrated cautiously during aggressive volume removal with IV diuretic therapy. In addition, serum potassium concentrations should be monitored closely as IV diuretic therapy is transitioned to oral diuretic therapy, especially if an aldosterone antagonist has been initiated during the hospital stay; this ensures therapy can be tolerated on the intended oral diuretic dose prescribed at discharge. Most patients may continue to receive digoxin at doses targeting a trough serum concentration of 0.5 to 1 ng/mL (mcg/L; 0.6 to 1.3 nmol/L).[6] Discontinuation of digoxin is generally discouraged as an association between withdrawal of therapy and worsening HF has been well-documented.[14,15] Digoxin should only be discontinued if serum concentrations cannot be safely maintained within the desirable range (eg, fluctuating renal function).



Patient Care Process for Acute Decompensated Heart Failure (ADHF)

Collect

- Patient characteristics (eg, age, sex, pregnancy status)
- Patient medical history (personal and family)
- Social history (eg, tobacco, ethanol, illicit drug use) and dietary habits, including fluid intake and sodium-containing foods
- Current medications including nonprescription (especially nonsteroidal anti-inflammatory drug and decongestant use), herbal products, and dietary supplements
- Subjective data
  - Signs/symptoms of fluid overload (eg, weight changes, dyspnea on exertion or at rest, orthopnea, paroxysmal nocturnal dyspnea, abdominal fullness, lower extremity edema, early satiety)
  - Signs/symptoms of low cardiac output (eg, fatigue, dyspnea on exertion, early satiety)

- Signs/symptoms associated with precipitating factors (eg, chest pain, palpitations, presyncope, and syncope)
- Distance patient is able to walk on a flat surface and incline, ability to climb one to two flights of stairs
- Ability to complete activities of daily living
- Additional diuretic doses taken
- Home recording of weight and vital signs if available

- Objective data
  - Weight on admission and daily throughout hospital stay (standing weight preferred if not bedridden)
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), and arterial oxygen saturation every 1 to 6 hours depending on the severity of illness
  - Continuous telemetry monitoring, especially if administering intravenous inotropes or if concerned for arrhythmias
  - Pertinent laboratory values, especially sodium, potassium, serum creatinine, BUN, liver function tests, B-type natriuretic peptide
  - Additional laboratories depending on the severity of illness and other comorbid conditions
  - Various diagnostic tests depending on presumed etiology of acute decompensation, the severity of illness, and drug therapy selection
    - Echocardiogram if symptoms suggest disease progression
    - Electrocardiogram if symptoms suggest new onset or worsening arrhythmia
    - Left heart catheterization if symptoms suggest new or worsening myocardial ischemia
    - Right heart catheterization (ie, placement of a pulmonary artery catheter) to guide use of intravenous vasodilators and inotropes (in select patients) or to evaluate for advanced therapies

Assess

- Volume status (eg, increase in weight, signs/symptoms of fluid overload)
- Perfusion status (eg, complaints of fatigue, objective data consistent with low cardiac output)

- Ability/willingness to pay for newer guideline-directed medical therapies for heart failure (eg, sacubitril/valsartan)
- Ability/willingness to obtain laboratory monitoring tests (eg, follow-up potassium following initiation of an aldosterone antagonist)
- Emotional status (eg, presence of anxiety, depression)

Plan*

- Drug therapy regimen, including guideline-directed medical therapies for heart failure such as angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARB) as well as dose, route, frequency, and duration
- Monitoring parameters for efficacy (eg, weight to maintain euvolemia, surrogate markers of end-organ function) and safety (eg, orthostasis); frequency and timing of follow-up
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug-specific information, medication administration)
- Referrals to other providers when appropriate (eg, electrophysiology for implantable cardioverter defibrillator [ICD] placement, upgrade of ICD to chronic resynchronization therapy [CRT])

Implement*

- Provide patient education regarding all elements of treatment plan (eg, self-monitoring of weight, sodium and fluid dietary restriction, self-titration of diuretic dose in select patients)
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up in 3 to 7 days following hospital discharge

Follow-up: Monitor and Evaluate

- Resolution of symptoms of fluid overload or low cardiac output
- Presence of adverse effects (eg, orthostasis due to over-diuresis or excess vasodilation)
- Obtain laboratory monitoring data (eg, potassium, magnesium, BUN/serum creatinine [diuretics]; potassium and serum creatinine [ACE inhibitor, ARB]; blood pressure [ACE inhibitor, ARB, β-blocker]; and heart rate [β-blocker])

- Patient adherence to treatment plan using multiple sources of information
- Re-evaluate need for escalation of guideline-directed medical therapy (up-titration or initiation of additional therapies) or referral for nonpharmacologic therapies (eg, ICD, CRT) or advanced therapies (eg, ventricular assist device, transplant) every 1 to 3 months depending on the severity of illness

** In collaboration with the patient, caregivers, and other healthcare professionals.*

6 The acute management of ADHF is based primarily on hemodynamic status. The hemodynamic subsets described previously were first proposed for patients with left ventricular dysfunction following acute MI but are also applicable to patients with ADHF due to other causes.[16] Patients with underlying HFrEF may present in any of the four hemodynamic subsets, whereas those with HFpEF usually only present in subset II. Two general approaches exist for determining hemodynamic status. One is to use simple clinical parameters (eg, signs and symptoms, blood pressure, and organ function) and the other is to use these in conjunction with invasive hemodynamic monitoring. A management algorithm based on hemodynamic subset is depicted in Fig. 36-1. The hemodynamic effects exerted by pharmacologic therapies used in the management of ADHF are illustrated in **Fig. 36-3**.

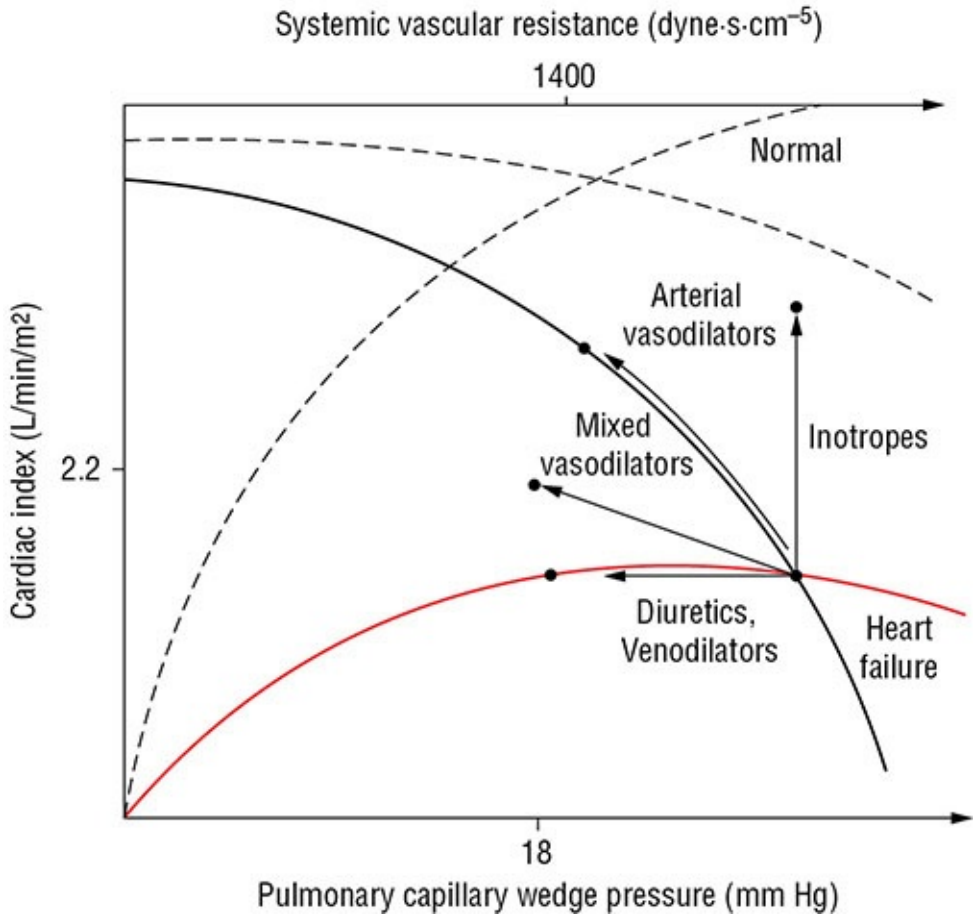


FIGURE 36-3 Hemodynamic effects of pharmacologic therapy in acute decompensated heart failure. Pharmacologic agents used in the management of acute decompensated heart failure exert important effects on cardiovascular hemodynamics. Although diuretics and venodilators reduce preload, this does not substantially reduce cardiac output in patients with heart failure and adequate filling pressures due to a flatter Frank–Starling curve. Arterial vasodilators reduce afterload, producing an increase in cardiac output as a consequence of improved left ventricular performance. Vasodilators with effects on both venous and arterial tissue may reduce both preload and afterload. Inotropes improve contractility directly, although some agents (eg, milrinone) may exert salutary effects on afterload via vasodilation. For cardiac index expressed in SI units of $L/s/m^2$ multiply values expressed in units of $L/min/m^2$ by 0.0167.

Subset I (Warm and Dry)

Patients in subset I generally do not have signs and symptoms of volume overload or hypoperfusion and usually have CI and PCWP values within appropriate ranges. Patients in this subset have the lowest risk of mortality and

do not require immediate intervention other than optimization of GDMT for HF. Patients with significant left ventricular dysfunction may still present in subset I because normal compensatory mechanisms and/or drug therapy may at least partially correct an otherwise abnormal hemodynamic profile.

Subset II (Warm and Wet)

Patients in subset II are likely to present with signs and symptoms of congestion (eg, orthopnea and peripheral edema) due to increased hydrostatic pressure in the pulmonary and systemic circulation, but without evidence of peripheral hypoperfusion. As a consequence, they often have adequate CO but a PCWP greater than 18 mm Hg. The primary goal of therapy in these patients is to relieve symptoms of congestion by lowering PCWP to an acceptable range (ie, 15–18 mm Hg). Considerably greater reductions should generally be avoided, as these could compromise CO, increase heart rate, or provoke neurohormonal activation.

Intravenous agents that reduce preload via diuresis and/or direct venodilation (eg, loop diuretics) are the most appropriate initial therapy for patients presenting in subset II. Although symptomatic improvement may occur within minutes of IV loop diuretic administration, significant relief of congestive symptoms may require several hours in select patients. Resistance to loop diuretics may occur, requiring dose escalation or addition of thiazide-type diuretics. For those with refractory symptoms despite diuretic therapy, IV vasodilators with effects on primarily the venous vasculature (eg, nitroglycerin) may be utilized for rapid venodilation (see Fig. 36-3), which can aid in acutely improving hypoxia. IV vasodilators should especially be considered in patients with acute pulmonary edema or severe hypertension but avoided in patients with symptomatic hypotension. Continuous blood pressure monitoring should be performed during IV vasodilator use. If symptomatic hypotension occurs with vasodilator therapy, the dose should be reduced or the agent discontinued. Failure to respond to the above therapies or WRF may indicate the presence of impaired CO, and IV inotropic therapy (with or without PA catheter insertion) should be considered.

Patients in subset II should also be placed on a sodium restriction (<2 g daily). In patients with moderate hyponatremia (<130 mEq/L [mmol/L]), fluid restriction (<2 L daily) should be considered, and in patients with worsening or severe hyponatremia (<125 mEq/L [mmol/L]), stricter fluid restriction may be necessary.[2] Arginine vasopressin (AVP) antagonists may also be considered for severe euvolemic or hypervolemic hyponatremia, particularly if neurologic

symptoms emerge. Finally, supplemental oxygen should be administered as needed for hypoxemia (arterial oxygen saturation < 90% [0.90]).

Subset III (Cold and Dry)

Patients in subset III present with evidence of peripheral hypoperfusion (eg, weakness, decreased urine output, and weak pulses) but no signs or symptoms of congestion. They often present with a CI of less than 2.2 L/min/m^2 (0.037 L/s/m^2)(but no abnormal elevation in PCWP. The mortality rate of patients in subset III is higher than that of patients with adequate perfusion.[16] Although the treatment goal is to alleviate signs and symptoms of hypoperfusion by increasing CI and perfusion to essential organs, therapy may differ based on initial presentation. If evidence of hypovolemia exists (eg, orthostatic hypotension) or PCWP is below 15 mm Hg, IV fluids should be cautiously administered to provide a more optimal left ventricular filling pressure (ie, 15–18 mm Hg), consequently improving CI (see Fig. 36-1). As this presentation most often occurs in the setting of overly aggressive diuresis, diuretic therapy should be withheld and fluid restriction liberalized; these interventions alone may obviate the need for IV fluids.

In patients whose CI remains low despite restoration of optimal left ventricular filling pressures, IV positive inotropic agents (eg, dobutamine and milrinone) and/or IV arterial vasodilators (eg, nitroprusside) may be necessary to achieve adequate CI (see Fig. 36-3). As with vasodilators, IV inotrope administration requires frequent blood pressure monitoring as well as continuous monitoring for arrhythmias. If arrhythmias occur, dose reduction or discontinuation of inotropic therapy should be performed. IV inotropes should also be avoided in patients with low left ventricular filling pressure. In general, inotropic therapy should be reserved for patients with evidence of severely low CO who are not candidates for IV vasodilators (ie, hypotension). They may also be used to “bridge” patients to MCS or heart transplantation, or as palliative therapy to improve functional status and quality of life in patients who are ineligible for definitive therapies.

Subset IV (Cold and Wet)

Patients in subset IV present with signs and symptoms of both volume overload and peripheral hypoperfusion, and often have a PCWP exceeding 18 mm Hg and a CI of less than 2.2 L/min/m^2 (0.037 L/s/m^2). This subset is characterized by the worst prognosis of all four and represents the most common hemodynamic

profile for patients with end-stage HF. Given the severity of HF, patients in subset IV cannot maintain adequate CI despite elevated left ventricular filling pressure and increased myocardial fiber stretch. Treatment goals for these patients include alleviation of signs and symptoms of congestion and hypoperfusion by increasing CI to above 2.2 L/min/m^2 (0.037 L/s/m^2) and reducing PCWP to 15 to 18 mm Hg while maintaining adequate MAP. Therapy often involves a combination of agents used in subsets II and III (ie, combination of IV diuretic plus vasodilator or inotrope). These targets may be difficult to achieve and often necessitate careful monitoring and individualization of drug therapy. In the presence of significant hypotension and low MAP (and SVR is low to normal or unknown), vasodilators should be avoided. In some cases, even the vasodilating effects of inotropic therapy may compromise MAP, requiring that combined inotrope and vasopressor therapy (eg, dobutamine plus norepinephrine) or an inotrope with vasopressor activity (eg, dopamine) be used to achieve adequate end-organ perfusion. Once peripheral perfusion has been restored, therapy can then be adjusted to obtain the desired clinical response (see Fig. 36-1).

PHARMACOLOGIC THERAPY

Despite advances in the care of patients with heart failure, none of the therapies used in the treatment of ADHF confer long-term improvements in morbidity and mortality, and some may cause harm when used indiscriminately. Therefore, the primary role of pharmacologic therapy in ADHF is to relieve acute symptoms and stabilize patients so that GDMT may be safely initiated or titrated; in those with advanced disease who are unable to tolerate GDMT, it may also be used as a bridge to definitive therapy (eg, cardiac transplantation).

Loop Diuretics

7 The IV loop diuretics furosemide and bumetanide are the mainstay of therapy for relieving congestion in the setting of ADHF (**Table 36-3**), and furosemide remains the most widely studied and used in this setting. Bolus administration reduces preload within 5 to 15 minutes by functional venodilation and later (>20 minutes) via sodium and water excretion, thereby improving pulmonary congestion. Although patients with HFrEF can tolerate significant reductions in preload without compromising stroke volume, excessive diuresis (ie, PCWP <15 mm Hg) can lead to a decline in CO (see Fig. 36-3). Excessive

reductions in venous return may also compromise CO in other conditions, including diastolic dysfunction, intravascular volume depletion, or patients in whom CO is significantly dependent on adequate filling pressure (ie, preload-dependent). Reflex increases in neurohormonal activation (ie, elevation of renin, norepinephrine, and AVP) may result in arteriolar and coronary vasoconstriction, tachycardia, and increased myocardial oxygen consumption. Unlike arterial vasodilators and positive inotropic agents, diuretics do not cause an upward shift in the Frank–Starling curve or significantly increase CO in most patients (see Fig. 36-3). In some cases, patients with severe congestion may experience improvements in CO as PCWP approaches the normal range (see Fig. 36-3), which may explain why renal function occasionally improves in the setting of diuresis. Alternatively, improvements in renal function may reflect the relief of congestive nephropathy.

TABLE 36-3 Diuretics Commonly Utilized for the Management of ADHF

	Furosemide	Bumetanide	Torsemide	Metolazone	Hydrochlorothiazide	Chlorothiazide
Mechanism	Loop diuretic	Loop diuretic	Loop diuretic	Thiazide-type diuretic	Thiazide-type diuretic	Thiazide-type diuretic
Oral bioavailability	10%–100% (mean 50%)	80%–90%	80%–100%	40%–65%	65%–75%	N/A
Dose equivalence (IV)	20–40 mg	0.5–1 mg	10–20 mg	N/A	N/A	N/A
Usual intermittent dose (maximum)	40–160 mg IV once to three times daily (200 mg/dose)	0.5–4 mg IV once to three times daily (5 mg/dose)	IV no longer available	2.5–5 mg PO once daily (20 mg/day)	25–50 mg PO once daily (100 mg/day)	500 mg–1 g IV once or twice daily (2 g/day)
Usual continuous infusion dose (maximum)	5–20 mg/hr (40 mg/hr)	0.5–2 mg/hr (4 mg/hr)	IV no longer available	N/A	N/A	N/A
Onset of action (Peak effect)	30–60 min PO, 5 mins IV (2 hrs)	30–60 min PO, 2–3 mins IV (1–2 hrs)	1 hr PO (1–2 hrs)	2–3 hrs (6–8 hrs)	2 hrs (4 hrs)	15 mins IV (30 mins IV)
Duration of action	4–6 hrs	4–6 hrs	18–24 hrs	12–24 hrs	5–15 hrs	6–12 hrs

CrCl, creatinine clearance; IV, intravenous; N/A, not applicable; PO, oral.

Current guidelines recommend the use of IV loop diuretics as first-line therapy for patients with ADHF and volume overload.[2] Although the oral bioavailability of furosemide is relatively unchanged in patients with HF who have adequate GI perfusion, the rate of absorption is prolonged by approximately twofold and peak concentrations are reduced by approximately half. Because loop diuretics have a sigmoidal-shaped concentration-response

curve, prolonged absorption may result in concentrations that fail to reach the threshold necessary for producing diuresis, necessitating the use of IV therapy.

Low doses (ie, doses equivalent to IV furosemide 20–40 mg) should initially be selected in patients with ADHF who are naïve to loop diuretics. For patients taking loop diuretics prior to admission, a total daily dose of 1- to 2.5-times their home dose is recommended.[2,17] Higher doses are associated with more rapid relief of congestive symptoms but may also increase the risk of transient worsening of renal function (WRF).[17] However, transient WRF in ADHF improves with adjustments to diuretic therapy (eg, decreases in dose, temporary interruptions in therapy) and does not worsen long-term renal outcomes.[17,18]

Importantly, guidelines indicate that doses may be administered as either an IV bolus (ie, divided every 12 hours) or continuous IV infusion.[2] In a prospective randomized trial comparing furosemide administered as a continuous infusion or intermittent IV bolus every 12 hours, no differences in relief of symptoms, urine output, weight loss, or long-term outcomes were observed between the two methods of administration.[17] Of note, patients receiving IV bolus therapy were more likely to require a dose increase or the addition of a thiazide-type diuretic, which may explain the equivocal results in the two groups. Similarly, several smaller studies suggest a greater natriuretic effect with no difference in metabolic adverse effects when continuous infusion furosemide is compared to the same total daily dose given by IV bolus.[19,20] In a prospective trial consisting exclusively of patients with HFpEF, continuous infusion furosemide was associated with an increase in WRF compared to IV bolus administration; however, the study was underpowered and dosing information was not described, making these results difficult to interpret.[21,22] Consequently, the appropriate method of administration for loop diuretic therapy in ADHF remains an area of controversy.

Most patients tolerate at least a 2-L per day net negative diuresis. However, intravascular volume depletion may occur if diuresis exceeds the rate at which fluid migrates from the interstitial space back into the systemic vasculature (ie, transcapillary refill rate). Patients who are malnourished due to the early satiety commonly observed in advanced HF (as a consequence of abdominal edema and/or reduced perfusion to the GI tract) may be especially sensitive to rapid shifts in intravascular volume due to decreased oncotic pressure resulting from hypoalbuminemia. Due to these and other factors, diuretic therapy must be highly individualized in order to obtain the desired improvement in congestive symptoms while avoiding a reduction in CO, symptomatic hypotension, or WRF. Hence, some patients with advanced HF may only tolerate a 1-L per day net

negative diuresis. Electrolyte depletion (eg, potassium, magnesium) should also be monitored closely, especially when high doses or combination diuretic therapy is utilized.

Occasionally, patients respond less optimally to escalating doses of loop diuretics, a phenomenon known as diuretic resistance. The mechanisms responsible for diuretic resistance in patients with HF are thought to be both pharmacokinetic and pharmacodynamic in nature.[23] In addition to the limits with oral absorption described previously, resistance is also observed with IV administration, suggesting an equally important pharmacodynamic contribution to this phenomenon. The decreased responsiveness in patients with HF may be explained in part by compensatory reabsorption in the distal convoluted tubule in response to the high concentrations of sodium resulting from blocked reabsorption in the loop of Henle. Over time, the distal tubule may also undergo hypertrophy, thereby enhancing its ability to reabsorb sodium. Finally, neurohormonal activation, impaired CO, reduced renal perfusion, and decreased drug delivery to the kidney may also contribute to resistance.

Several strategies may be employed to overcome diuretic resistance. Current guidelines recommend one of two pharmacologic options in patients who do not initially respond to diuretic therapy: increased doses of loop diuretics or addition of an alternative diuretic with a different mechanism of action (eg, thiazide-type diuretics).[2] Higher doses of loop diuretics are more likely to achieve concentrations near the top of the concentration-response curve and may improve diuresis at the expense of increasing the risk of WRF.[17] Transitioning to continuous infusion loop diuretics may also be considered, as higher doses may be administered via this method and its use compared to IV bolus administration has not been studied in patients with diuretic resistance.

Other pharmacologic strategies for relieving congestion in ADHF include the adjunct use of vasopressin antagonists, ultrafiltration, and IV vasodilators, and each of these will be discussed in greater detail in the sections to follow. In patients with worsening renal perfusion due to low CO, IV inotropes or arterial vasodilators may improve diuresis by improving central hemodynamics (also discussed in detail later in this chapter).

One strategy for enhancing diuresis that has fallen out of favor is the administration of low doses of dopamine (ie, 2–5 mcg/kg/min), as recent studies indicate minimal, if any, improvement in diuresis.[24–26] Despite an initial prospective randomized trial suggesting dopamine might offer renal protection during aggressive diuresis, more recent investigations assessing low doses in conjunction with IV loop diuretics demonstrated no improvements in urine

output, renal protection, or symptom relief, and increased rates of tachycardia.[24–26] Given the evidence of β-mediated effects at lower infusion rates, dopamine may not provide any advantages over a traditional inotrope when used in this setting.

Adjunct Diuretics

A second strategy for overcoming diuretic resistance recommended in the guidelines is to add a second diuretic with a different mechanism of action.[2] Based on the results of several retrospective cohort studies, combining a loop diuretic with a distal tubule blocker such as oral metolazone, oral hydrochlorothiazide, or IV chlorothiazide (see Table 36-3) can produce a synergistic diuretic effect. Inhibition of sodium reabsorption in the loop of Henle increases sodium delivery to (and reabsorption in) the distal convoluted tubule, which can be subsequently blocked by a thiazide-type diuretic. Sequential nephron blockade with a loop and thiazide-type diuretic should generally be reserved for hospitalized patients, as profound diuresis with severe electrolyte and intravascular volume depletion may occur. If used in the outpatient setting, very low doses or infrequent administration (eg, one to three times weekly) of a thiazide-type diuretic should be recommended. Patients should also receive close follow-up (eg, weight, vital signs, serum potassium, and assessment for orthostatic hypotension) to avoid serious adverse events.

Vasopressin Antagonists

Physiologic fluid balance depends on relative concentrations of sodium and water. An abnormally low serum sodium concentration, or *hyponatremia*, is commonly defined as less than 125 mmol/L and can be classified as hypovolemic, euvolemic (urine sodium <30 mmol/L), or hypervolemic (urine sodium >30 mmol/L) in nature. Heart failure is most commonly associated with hypervolemic hyponatremia, although excess diuretic administration may result in hypovolemic hyponatremia. Other causes of hyponatremia include syndrome of inappropriate diuretic hormone (SIADH), cirrhosis with ascites, and medications.

Hyponatremia is often characterized by inappropriately elevated concentrations of AVP or antidiuretic hormone. In the setting of HF, reduced CO leads to excess stimulation of arterial baroreceptors, which in turn enhances AVP secretion and consequently, net water retention. While the prevalence of

hyponatremia in patients with HF varies by definition, as many as one in five patients hospitalized for acute HF present with serum sodium concentrations less than 136 mmol/L.[27] Furthermore, the presence of hyponatremia has been associated with increased mortality in this population.[28]

While many cases of hyponatremia are mild, asymptomatic, and self-limited, prompt diagnosis and management is critical for the less common but life-threatening presentation, which may include lethargy, confusion, respiratory arrest, cerebral edema, seizures, coma, or death. Treatment is specific to the underlying etiology, as well as the duration and severity of symptoms. Strategies for managing hypervolemic hyponatremia include removal of the underlying cause, fluid restriction, or administration of diuretics (with or without hypertonic saline), vasopressin antagonists, or other therapies. Importantly, while neurological sequelae may occur if treatment is not initiated promptly, overly rapid correction of hyponatremia (>12 mmol/L per 24 hours) may be just as detrimental.

8 The two currently available vasopressin receptor antagonists, tolvaptan and conivaptan, inhibit one or two AVP receptors, V_{1A} or V_2. Stimulation of V_{1A} receptors, which are present in vascular smooth muscle and myocardium, results in vasoconstriction as well as myocyte hypertrophy, coronary vasoconstriction, and positive inotropic effects. V_2 receptors are located in the renal tubules where they regulate water reabsorption. Tolvaptan selectively binds to and inhibits the V_2 receptor, whereas conivaptan nonselectively inhibits both V_{1A} and V_2 receptors. Tolvaptan is orally bioavailable and indicated for the management of hypervolemic and euvolemic hyponatremia in patients with SIADH, cirrhosis, or HF. Tolvaptan is typically initiated at 15 mg daily and then titrated to 30 mg or 60 mg as needed for resolution of hyponatremia. Importantly, tolvaptan is a substrate of cytochrome P450 3A4 and is contraindicated with potent inhibitors of this enzyme. Conivaptan is an IV agent indicated for hypervolemic and euvolemic hyponatremia resulting from a variety of causes; however, because it is not indicated in patients with HF, conivaptan will not be discussed in further detail here. Patients receiving vasopressin antagonists must be monitored closely to avoid an overly rapid rise in serum sodium, which may result in hypotension or hypovolemia, requiring that therapy be discontinued. Therapy may be restarted at a lower dose if hyponatremia recurs or persists and/or adverse effects resolve.

The role of vasopressin antagonists in the long-term management of HF remains unclear at this time. In a trial comprised entirely of patients hospitalized with HF, tolvaptan was associated with significant improvement in hyponatremia

compared to placebo.[29] In addition, patients receiving tolvaptan experienced an improvement in diuresis and symptoms of congestion. However, the study failed to demonstrate an improvement in long-term outcomes including morbidity and mortality. More recently, another trial randomized patients with ADHF presenting within 24 hours of hospitalization to tolvaptan or placebo.[30] At 72 hours, WRF was observed in significantly more tolvaptan-treated patients. Overall, these two trials do not support routinely using tolvaptan in patients with ADHF and thus it should be reserved for management of severe hyponatremia.[2]

Overall, tolvaptan is well tolerated; common side effects include dry mouth, thirst, urinary frequency, constipation, and hyperglycemia. While tolvaptan is orally available, therapy in clinical trials was initiated in the inpatient setting, where serum sodium and volume status could be closely monitored. Because of the adverse consequences of rapid changes in serum sodium concentrations or fluid balance, initiation and titration of therapy should occur primarily in the inpatient setting, allowing for close surveillance of serum sodium concentrations.

Vasodilators

9 Current guidelines focus on the role of IV vasodilators as an adjunct treatment for refractory congestive symptoms,[2] but they may also be helpful for restoring tissue perfusion in select patients with low CO. Vasodilators are commonly classified according to their most prominent site of action (ie, arterial or venous circulation). As described in the section on patients in subset II, venodilators act as preload reducers by increasing venous capacitance, thus reducing symptoms of pulmonary congestion in patients with high ventricular filling pressures. Arterial vasodilators exert their beneficial effects by counteracting the peripheral vasoconstriction and impaired CO that can result from activation of the sympathetic nervous system, renin–angiotensin–aldosterone system, and other neurohormonal mediators in both acute and chronic HF. In these patients, arterial vasodilators act as impedance-reducing agents, reducing afterload and causing a reflexive improvement in left ventricular performance and thus an increase in CO. Mixed vasodilators act on both resistance and capacitance vessels, reducing congestive symptoms while increasing CO.

Intravenous vasodilators should, therefore, be considered prior to positive inotropic therapy in patients with low CO and elevated SVR (or elevated blood pressure in those without a PA catheter). For patients in whom blood pressure or SVR is already low, including those receiving GDMT with vasodilating effects

(eg, ACE inhibitors) or those with advanced HF, hypotension may preclude the use of IV vasodilators. In patients with advanced HF and limited contractile reserve, increases in left ventricular performance may not fully compensate for reductions in afterload, leading to worsening hypotension. In addition, IV vasodilators have not been extensively studied in patients with HFpEF, where a sudden drop in preload may compromise existing defects in ventricular filling, leading to decreased CO.[31]

The most commonly used IV vasodilators in ADHF are nitroglycerin and sodium nitroprusside, which differ according to their effects on arterial and venous circulation (**Table 36-4**). Nitroglycerin is primarily a venodilator (except at high doses) whereas sodium nitroprusside is a mixed venous and arterial vasodilator. Nesiritide, a third vasodilator formerly used in ADHF, has since been discontinued by the manufacturer.

TABLE 36-4 Vasodilators Commonly Utilized for the Management of ADHF*

Drug (Vasodilatory effect)	Onset, Half-life	Elimination	Dose	HR	MAP	PCWP	CO	SVR
Nitroglycerin (venous > arterial)	Immediate, <4 mins	Inactive metabolites in urine	10–20 mcg/min and titrate 10–20 mcg/min q10–20 mins, max 200 mcg/kg/min	0/↑	0/↓	↓	0/↑	0/↓
Nitroprusside (venous = arterial)	Immediate, 2 mins	Cyanide (hepatic), thiocyanate (renal)	0.1–0.2 mcg/kg/min, titrate 0.1–0.2 mcg/kg/min q10–20 mins, max 3 mcg/kg/min	0/↑	0/↓	↓	↑	↓
Furosemide (venous only)	1 hr (PO)/ 5 mins (IV), 2 hrs	Urine	Variable†	0	0/↓	↓	0	0
Enalaprilat (arterial > venous)	<15 mins, 11 hrs	Urine	1.25–2.5 mg q6–8h	0	0/↓	↓	↑	↓

*See text for a more detailed description of the interpatient variability in response.

†Intravenous bolus administered <0.4 mg/min.

↑, increase; ↓, decrease; 0, no change; HR, heart rate; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; CI, continuous infusion; CO, cardiac output; IVB, intravenous bolus; SVR, systemic vascular resistance.

Nitroglycerin

Intravenous nitroglycerin is often preferred for preload reduction in patients with ADHF, especially those with evidence of pulmonary congestion. Because of its short half-life (1–3 minutes), IV nitroglycerin is administered by continuous infusion. Its major hemodynamic effects are reductions in preload and PCWP via functional venodilation and mild arterial vasodilation that is particularly evident

in patients with HF and elevated SVR or when given in doses exceeding 100 mcg/min (see Table 36-4). At higher doses, nitroglycerin displays potent coronary vasodilating properties, exerting beneficial effects on myocardial oxygen demand and supply and making it the vasodilator of choice for patients with severe HF and ischemic heart disease.

Nitroglycerin should be initiated at a dose of 5 to 10 mcg/min (0.1 mcg/kg/min) and increased every 5 to 10 minutes as tolerated. Hypotension and an excessive decrease in PCWP are important dose-limiting side effects. Maintenance doses usually vary from 35 to 200 mcg/min (0.5–3 mcg/kg/min). While tolerance to the hemodynamic effects of nitroglycerin may develop over 12 to 72 hours of continuous administration, some patients experience a sustained response. Nitroglycerin should not be used in the presence of elevated intracranial pressure because it may worsen cerebral edema in this setting.

Only one prospective randomized controlled trial has evaluated nitroglycerin in patients with ADHF.[32] Compared to nesiritide, nitroglycerin was similarly efficacious at improving dyspnea at 3 hours after administration but was less effective at reducing PCWP. Neither agent improved global clinical status compared to placebo.

Sodium Nitroprusside

As a result of its balanced effects in arterial and venous tissue, sodium nitroprusside increases CI to a similar degree as dobutamine and milrinone despite having no direct inotropic activity; however, greater decreases in PCWP, SVR, and blood pressure are generally observed. MAP may remain fairly constant due to reflexive improvements in stroke volume and CO but can decrease based on the extent of arterial smooth muscle relaxation. Patients with normal left ventricular function do not experience an increase in stroke volume when SVR falls because the normal ventricle is fairly insensitive to changes in afterload. Consequently, these patients may experience a significant decrease in blood pressure in response to arterial vasodilators. These differences explain why sodium nitroprusside is a potent antihypertensive agent in patients without HF but causes less hypotension and reflex tachycardia in the presence of left ventricular dysfunction (see Fig. 36-2B). Nonetheless, hypotension remains an important dose-limiting effect of sodium nitroprusside and its use should be primarily reserved for patients with elevated SVR. Close monitoring of therapy is warranted, as even modest increases in heart rate can have adverse consequences in patients with underlying ischemic heart disease and/or resting tachycardia.

Sodium nitroprusside is an effective strategy for short-term management of patients with severe HF across a variety of settings (e.g., acute MI, valvular regurgitation, postcoronary bypass surgery, and ADHF). Generally, sodium nitroprusside does not worsen, and may even improve, the balance between myocardial oxygen demand and supply by lowering both left ventricular wall tension (thus reducing oxygen demand) and end-diastolic pressure (thereby increasing subendocardial blood flow). However, an excessive decrease in systemic arterial pressure may reduce coronary perfusion and worsen ischemia due to coronary steal.

Sodium nitroprusside has a rapid onset of action but its effects last less than 10 minutes, necessitating administration by continuous IV infusion. Its short duration of action also allows precise dose-titration based on clinical and hemodynamic response. As with nitroglycerin, sodium nitroprusside should be initiated at low doses (0.1–0.2 mcg/kg/min) to avoid excessive hypotension and increased by small increments (0.1–0.2 mcg/kg/min) every 5 to 10 minutes as tolerated. Effective doses usually range from 0.5 to 3 mcg/kg/min. A rebound phenomenon, which may be due to reflex neurohormonal activation during sodium nitroprusside therapy, has been reported following abrupt withdrawal in patients with HF. Therefore, therapy should be tapered slowly when transitioning patients to oral medications. As with nitroglycerin, sodium nitroprusside should be avoided in the presence of elevated intracranial pressure as it may worsen cerebral edema in this setting. Given the potent pulmonary vasodilatory effects of sodium nitroprusside as well as its short half-life, it is frequently used to determine reversibility of pulmonary hypertension in patients being evaluated for heart transplantation.

Following IV administration, sodium nitroprusside interacts with hemoglobin to release cyanide, which undergoes hepatic conversion to thiocyanate before it is eliminated renally. As a consequence, sodium nitroprusside can cause cyanide and thiocyanate toxicity, but these effects are unlikely when doses less than 3 mcg/kg/min are administered for less than 3 days, except in patients with significant renal impairment (ie, serum creatinine concentration >3 mg/dL (265 µmol/L).

Unfortunately, no prospective randomized controlled trials have investigated the use of sodium nitroprusside in patients with ADHF. However, in a small retrospective study, patients with a reduced CI (ie, ≤2 L/min/m^2 [0.033 L/s/m^2]) treated with sodium nitroprusside experienced improved hemodynamics compared to patients who did not receive sodium nitroprusside.[33] All-cause mortality was also lower in patients who received sodium nitroprusside, likely

due to improved use of GDMT in this group. At baseline, patients receiving nitroprusside tended to have higher MAP, increased cardiac filling pressures, and lower CI, but the observed improvements in mortality remained even after including only those patients who had initial MAP less than or equal to 85 mm Hg.

Inotropes

10 Patients in subsets III and IV ("cold" subsets) require prompt correction of low CO in order to restore peripheral tissue perfusion and preserve end-organ function. Although IV inotropes can improve peripheral hypoperfusion by directly enhancing cardiac contractility, their association with adverse outcomes necessitates that they be reserved for select patients with refractory ADHF, particularly those unable to tolerate vasodilators due to hypotension. Current guidelines recommend that inotrope therapy be considered only as a temporizing measure for maintaining end-organ perfusion in patients with cardiogenic shock or evidence of severely depressed CO and low systolic blood pressure (ie, ineligible for IV vasodilators) until definitive therapy can be initiated, as a "bridge" for those with advanced HF who are eligible for MCS or cardiac transplantation, or for palliation of symptoms in patients with advanced HF who are not eligible for MCS or cardiac transplantation.[2]

Much of the concern regarding use of IV inotrope therapy in patients with ADHF is based on data from the ADHERE Registry, which compared in-hospital mortality among patients receiving IV nitroglycerin, nesiritide, or the inotropes milrinone or dobutamine.[34] After adjusting for baseline parameters known to predict in-hospital mortality, both dobutamine- and milrinone-treated patients experienced higher in-hospital mortality compared to those receiving either nitroglycerin or nesiritide. Only one randomized controlled trial has prospectively evaluated the use of IV inotropic therapy as a strategy for improving clinical outcomes in patients with ADHF but without evidence of hypoperfusion. In patients with ADHF randomized to a 48-hour infusion of milrinone or placebo, no difference in length of stay was observed and adverse events were more common in the milrinone group, including sustained hypotension requiring intervention and new onset of atrial fibrillation or flutter.[35]

Select populations with advanced HF may require placement of an indwelling IV catheter for continuous outpatient administration of inotropic therapy. This approach may be used to "bridge" patients awaiting durable MCS or cardiac transplantation, or as a palliative approach to facilitate discharge in patients who

are not candidates for advanced therapies but also cannot be weaned from inotropic support. Therapy in this latter group should only be considered after multiple unsuccessful attempts have been made to maximize oral therapy and discontinue IV inotropes. Although this strategy may be effective for symptom palliation, the risk of mortality is likely increased.

Importantly, IV inotropes rarely, if ever, produce a single cardiovascular action. Even when intended for a specific purpose (eg, positive inotropic effects), other cardiovascular effects (tachycardia, vasodilation, or vasoconstriction) may either add to the therapeutic effect of the drug, or cause adverse effects that negate or even outweigh its intended therapeutic benefit. How an individual patient will respond to an intervention is often difficult to anticipate. For this reason, hemodynamic monitoring with a PA catheter may be useful.

The two IV inotropic agents most commonly used for the management of ADHF are dobutamine and milrinone. Although both drugs increase intracellular concentrations of cAMP, they do so by different mechanisms. Dobutamine activates adenylate cyclase through direct stimulation of β-adrenergic receptors, thus catalyzing the conversion of adenosine triphosphate to cAMP, whereas milrinone reduces degradation of cAMP by inhibiting phosphodiesterase type 3. Increased intracellular cAMP enhances phospholipase (and subsequently phosphorylase) activity, increasing the rate and extent of calcium influx during systole and thus enhancing contractility. In addition, cAMP enhances reuptake of calcium by the sarcoplasmic reticulum during diastole, improving active relaxation. Comparisons between dobutamine and milrinone indicate that the two agents generally produce similar hemodynamic effects, although dobutamine is usually associated with more pronounced increases in heart rate and milrinone is associated with greater relaxation in arterial smooth muscle. Differences in the pharmacologic effects of the two agents may confer advantages or disadvantages in an individual patient; these and other clinical considerations for their use in the management of ADHF will be reviewed in the sections to follow.

Digoxin has a limited role in hemodynamically unstable patients due to its limited inotropic effects. In patients who take digoxin as chronic therapy, discontinuation or dose-adjustment during an acute decompensation is generally unnecessary unless changes in renal function increase the risk of toxicity. As discussed previously in this chapter, discontinuation should be discouraged in the absence of toxicity, given the potential for digoxin withdrawal.[14,15]

Dobutamine

The receptor activities of dobutamine and other adrenergic agonists are summarized in **Table 36-5**. Dobutamine, a synthetic catecholamine, is a β_1- and β_2-receptor agonist with some α_1-agonist effects. Unlike dopamine, dobutamine does not result in the release of norepinephrine from nerve terminals. Consequently, the positive inotropic effects of dobutamine are attributed to its effects on β_1-receptors. Stimulation of cardiac β_1-receptors by dobutamine does not generally produce a significant change in heart rate, thus explaining its more modest chronotropic effects compared with dopamine. Modest peripheral β_2-receptor-mediated vasodilation tends to offset minor α_1-receptor-mediated vasoconstriction. In addition, the increase in CO often results in a reflexive decline in SVR. As a consequence, the net hemodynamic effect of dobutamine, particularly at low doses, is usually vasodilation.

TABLE 36-5 Inotropes Commonly Utilized for the Management of ADHF*

Drug	Onset, Half-life	Dose	Receptor Affinity ($\alpha_1/\beta_1/\beta_2/DA_1$)	HR	MAP	PCWP	CO	SVR
Dobutamine	<10 mins, 2 mins	1–2 mcg/kg/min, titrate 1–2 mcg/kg/min q10–20 mins, max 20 mcg/kg/min	↑/↑↑↑↑/↑↑/0	0/↑	0	↓	↑	↓
Milrinone	5–15 min, 1–4 hr, (prolonged if renal dysfunction)	0.1–0.2 mcg/kg/min, titrate 0.1 mcg/kg/min q4–16 hrs (titrate slowly in renal dysfunction), max 0.75 mcg/kg/min (IVB dose generally avoided)	Phosphodiesterase inhibition	0/↑	0/↓	↓	↑	↓
Dopamine	< 5 mins, 2 mins	0.5–3 mcg/kg/min	0/0/0/↑↑	0	0	0	0/↑	↓
		3–10 mcg/kg/min	0/↑↑↑↑/↑↑/↑↑	↑	↑	0	↑	0
		10–20 mcg/kg/min	↑↑↑↑/↑↑↑↑/↑↑/↑↑	↑	↑	↑	↑	↑

*See text for a more detailed description of the dose-dependent hemodynamic effects.

The effects of dobutamine are observed within minutes, but its peak effects may take up to 10 minutes to occur. Initial doses of 2.5 to 5 mcg/kg/min may be increased progressively to 20 mcg/kg/min based on clinical and hemodynamic responses. Cardiac index is increased due to inotropic stimulation, arterial vasodilation, and a variable increase in heart rate. Because of offsetting changes in arteriolar resistance and CI, dobutamine usually causes relatively little change in MAP, unlike the more consistent increases observed with dopamine. The vasodilating action of dobutamine usually reduces PCWP, making it particularly useful in the presence of low CI and an elevated left ventricular filling pressure;

conversely, these effects may be detrimental in the presence of a reduced filling pressure. Although its impact on heart rate is variable, the major adverse effects of dobutamine are tachycardia and ventricular arrhythmias. Potentially detrimental increases in oxygen consumption have also been observed. While concerns exist regarding the attenuation of its effects during prolonged administration, changes in receptor expression require that dobutamine be slowly tapered rather than abruptly discontinued.

Milrinone

Milrinone is a bipyridine derivative that inhibits phosphodiesterase III, an enzyme responsible for the breakdown of cAMP to adenosine monophosphate (AMP). Milrinone has supplanted the use of its prototype amrinone due to less frequent occurrence of thrombocytopenia. Because both inotropic and vasodilating effects contribute to its therapeutic effects in ADHF, milrinone is often referred to as an inodilator. The relative balance of these pharmacologic effects may vary with dose and underlying cardiovascular pathology.

During IV administration, milrinone produces an increase in stroke volume (and therefore CO) with minimal change in heart rate (see Table 36-5). Despite an increase in CI, MAP may remain constant due to a concomitant decrease in arteriolar resistance. However, the vasodilating effects of milrinone may predominate, leading to a decrease in blood pressure and reflex tachycardia. Like dobutamine, milrinone lowers PCWP by venodilation and thus is particularly useful in patients with a low CI and an elevated left ventricular filling pressure. Such a reduction in preload, however, can be hazardous for patients without excessive filling pressure (especially those in subset III), thus blunting the improvement in CO produced by the positive inotropic and arterial dilating actions of milrinone. Furthermore, milrinone should be used cautiously in severely hypotensive patients because it does not increase, and may even decrease, arterial blood pressure.

Milrinone has a longer elimination half-life than other vasoactive agents. In healthy subjects, the half-life of milrinone is about 1 hour but may be as long as 3 to 6 hours in patients with renal dysfunction. The long elimination half-life of milrinone presents several disadvantages in this patient population, including the inability to perform minute-to-minute titrations based on hemodynamic changes and persistence of adverse effects (eg, arrhythmias or hypotension) following drug discontinuation. Although a loading dose is still listed in the product labeling for milrinone (50 mcg/kg administered over 10 minutes), this practice is uncommon due to an increased risk of hypotension. Most patients are started on

a maintenance infusion of 0.1 to 0.3 mcg/kg/min (up to 0.75 mcg/kg/min). Milrinone is excreted unchanged in the urine, and thus, its infusion rate should be decreased by 50% to 70% in patients with significant renal impairment.

The most notable adverse effects associated with milrinone are arrhythmia, hypotension, and thrombocytopenia. Although the incidence of thrombocytopenia is rare, patients should still have platelet counts measured before and during therapy.

Inotrope Selection

Although inotrope selection is often clinician-dependent, certain characteristics may make one agent more ideal in an individual patient. Dobutamine should be considered when a significant decrease in MAP might further compromise hemodynamic function, as this is more common with the initiation of milrinone. Selection of an inotropic drug should also take into account whether patients are receiving chronic β-blocker therapy and whether a β_1-selective agent (eg, metoprolol succinate) or mixed α, β-blocking agent (eg, carvedilol) is used. Traditionally, milrinone has been advocated in patients who are receiving chronic β-blocker therapy because its inotropic effects do not involve β-receptor stimulation. However, this is not supported by evidence. In fact, the hemodynamic effects of dobutamine may persist in the presence of β-blocker therapy, particularly with β_1-selective agents as a result of β-receptor upregulation or selective activation of β_2-receptors by dobutamine.[36] Similar effects are not observed in the presence of carvedilol, which may inhibit the hemodynamic benefits of dobutamine entirely. Concomitant β-blocker therapy may augment the hemodynamic effects of milrinone based on studies with a structurally similar phosphodiesterase inhibitor, enoximone.[36]

The combination of dobutamine and milrinone is likely to produce additive effects on CO and PCWP, suggesting that this regimen may be considered in patients who have dose-limiting adverse effects with either drug class. However, whether this combination provides a therapeutic advantage over the combined use of a positive inotrope and a traditional vasodilator (eg, sodium nitroprusside) is unclear.

Agents with Combined Inotropic and Vasopressor Activity

Although therapies that can increase SVR are generally avoided in ADHF,

agents with combined inotropic and vasopressor activity, such as norepinephrine or dopamine, may be required in select scenarios where marked systemic hypotension may preclude the use of traditional IV inotropes (eg, septic shock, refractory cardiogenic shock). Alternatively, these agents may be used in combination with traditional inotropes so that adjustments can be made to each agent independently in order to achieve the desired hemodynamic response. Although these strategies are common in clinical practice, minimal data exist to support their use.

Norepinephrine is an endogenous catecholamine that exerts its hemodynamic effects via direct stimulation of α_1- and β_1-adrenergic receptors. Its effects on β_1-adrenergic receptors in myocardial tissue are thought to confer improvements in CO as a result of increases in heart rate and cardiac contractility. However, despite having similar affinity for α_1- and β_1-adrenergic receptors, enhanced vasoconstriction via activation of peripheral α_1-receptors appears to be the predominant hemodynamic effect observed clinically. The limited impact of norepinephrine on CO may be due to its lack of affinity for β_2-receptors, which would both enhance cardiac contractility and balance its effects on α_1-receptors in vascular smooth muscle. In contrast with dopamine, the affinity of norepinephrine for adrenergic receptors does not appreciably differ based on dose.

Dopamine is an endogenous precursor of norepinephrine and exerts its effects by directly stimulating adrenergic receptors as well as causing release of norepinephrine from adrenergic nerve terminals. Dopamine produces dose-dependent hemodynamic effects as a result of its relative affinity for α_1-, β_1-, β_2-, and D_1- (vascular dopaminergic) receptors (see Table 36-5).

The positive inotropic effects of dopamine are mediated primarily by β_1-receptors and become more prominent at doses of 2 to 5 mcg/kg/min. Cardiac index is increased because of an increase in stroke volume and a variable increase in heart rate, which is also partially dose-dependent. Minimal changes in SVR occur, presumably because neither vasodilation (D_1- and β_2-receptor-mediated) nor vasoconstriction (α_1-receptor-mediated) predominates. However, at doses between 5 and 10 mcg/kg/min, chronotropy and α_1-receptor-mediated vasoconstriction become more prominent. MAP is usually raised as a result of increases in both CI and SVR (see Table 36-5).

The vasoconstriction observed with higher doses of norepinephrine and dopamine may limit improvements in CI by concomitantly increasing afterload

and preload. As a consequence, they should generally be reserved for patients with low CO and low systolic blood pressure despite adequate ventricular filling pressures, or as an adjunct to inotrope therapy when hypotension precludes the use of inotrope therapy alone. At higher doses, agents with vasopressor activity may alter several parameters that increase myocardial oxygen demand (eg, increased heart rate, contractility, and systolic pressure) and potentially decrease myocardial blood flow (eg, coronary vasoconstriction and increased wall tension), which may worsen ischemia in patients with coronary artery disease. As with dobutamine and milrinone, arrhythmogenesis is also more common at higher doses, although this risk appears to be greater with dopamine than with norepinephrine.[37]

Nonpharmacologic Therapy

Several nonpharmacologic therapies are routinely used in ADHF. All patients with congestive symptoms should be placed on a sodium restriction (< 2 g daily), and fluid restriction should also be considered for those with refractory symptoms. Noninvasive ventilation may be considered in patients with respiratory distress due to acute pulmonary edema, particularly those at risk for intubation. Although most patients with limited mobility should receive pharmacologic thromboprophylaxis with unfractionated heparin or low-molecular-weight heparin, mechanical thromboprophylaxis with intermittent pneumatic compression devices may be considered in patients at high risk for bleeding complications.

Most of the nonpharmacologic therapies used in ADHF are primarily reserved for patients who have failed pharmacologic therapy. Ultrafiltration and wireless invasive hemodynamic monitoring (W-IHM) may be used in the management of congestive symptoms whereas MCS (temporary or durable devices) and cardiac transplantation may be considered in those with advanced disease.[2]

Ultrafiltration

11 Renal impairment is common among patients with ADHF, and advanced forms may warrant the use of renal replacement therapy (eg, hemodialysis). Ultrafiltration has emerged as another strategy for rapid fluid removal, where salt and water may be eliminated at rates of up to 500 mL/h. It reduces PCWP and increases diuresis without adversely affecting hemodynamics. Potential candidates for ultrafiltration include patients demonstrating diuretic resistance,

renal impairment following diuretic administration, or continued renal impairment despite inotropic therapy. Complications of ultrafiltration include those associated with central venous access (eg, infection), rapid volume removal, and intravascular depletion, although electrolyte depletion is generally minimal.

Small studies suggest that ultrafiltration represents an effective strategy for fluid removal in HF patients and that early initiation prior to IV diuretics reduces hospital length of stay and readmission rates. In a study comparing early ultrafiltration to IV diuretics in patients with ADHF and evidence of fluid overload, ultrafiltration resulted in greater weight loss at 48 hours (5 kg vs 3.1 kg) as well as net fluid loss (4.6 L vs 3.3 L), although no differences in dyspnea scores were observed.[38] Several additional endpoints were improved among patients in the ultrafiltration group, but a more recent study has challenged these findings.[39] Patients with ADHF, worsened renal function, and persistent congestion were randomized to a strategy of stepped pharmacologic therapy or ultrafiltration. Ultrafiltration was inferior to pharmacologic therapy with respect to the bivariate endpoint of change from baseline in serum creatinine and body weight at 96 hours, primarily due to WRF in the ultrafiltration group. There was also no significant difference in weight loss and more patients in the ultrafiltration group experienced a serious adverse event. Subsequently, use of ultrafiltration has received greater scrutiny and ongoing trials are attempting to determine its role in managing volume overload.

Wireless Implantable Hemodynamic Monitoring

Increases in cardiac filling pressures often precede the development of congestive symptoms, and W-IHM has recently emerged as a strategy for using early hemodynamic changes to adjust therapy and thus prevent ADHF in high-risk patients. The CardioMEMS Heart Failure System (Abbott; Lake Bluff, IL) consists of a wireless sensor implanted into the PA during a right heart catheterization and an electronic capturing system that collects information on PA systolic, diastolic, and mean pressures. In addition to guiding therapy adjustments during acute hospitalization, W-IHM can also be telemonitored after patients are discharged from the hospital, permitting further titration of diuretic therapy and GDMT. In a randomized controlled trial of patients with a recent hospitalization for ADHF, the CardioMEMS device was associated with a significant reduction in the absolute risk of HF hospitalization at 6 months.[40] Despite these benefits, widespread use of W-IHM has been limited due to

concerns regarding the long-term durability and cost-effectiveness of the device.

Temporary Mechanical Circulatory Support

12 For patients with refractory ADHF, temporary MCS may be considered for hemodynamic stabilization until the underlying etiology of cardiac dysfunction resolves or has been corrected (“bridge to recovery”) or until evaluation for definitive therapy (eg, durable MCS or cardiac transplantation) can be completed (“bridge to decision”).[2] Due to the invasive nature of MCS and its potential complications, therapy should be reserved for patients who are refractory to maximally tolerated pharmacologic therapy. Intravenous vasodilators and inotropic agents may also be used in conjunction with temporary MCS to maximize hemodynamic and clinical benefits or to facilitate device removal. Regardless of the modality selected, systemic anticoagulation is required to prevent device thrombosis. Temporary MCS should generally be avoided in patients with irreversible advanced HF and no plan for definitive management, those with contraindications to anticoagulation therapy, and those with comorbid conditions or anatomical abnormalities that preclude device implantation. The three most common modalities of temporary MCS are the intra-aortic balloon pump (IABP), ventricular assist device (VAD), and extracorporeal membrane oxygenation (ECMO) (**Fig. 36-4**). Unique features, contraindications, and complications of each type of device will be discussed in the sections to follow.

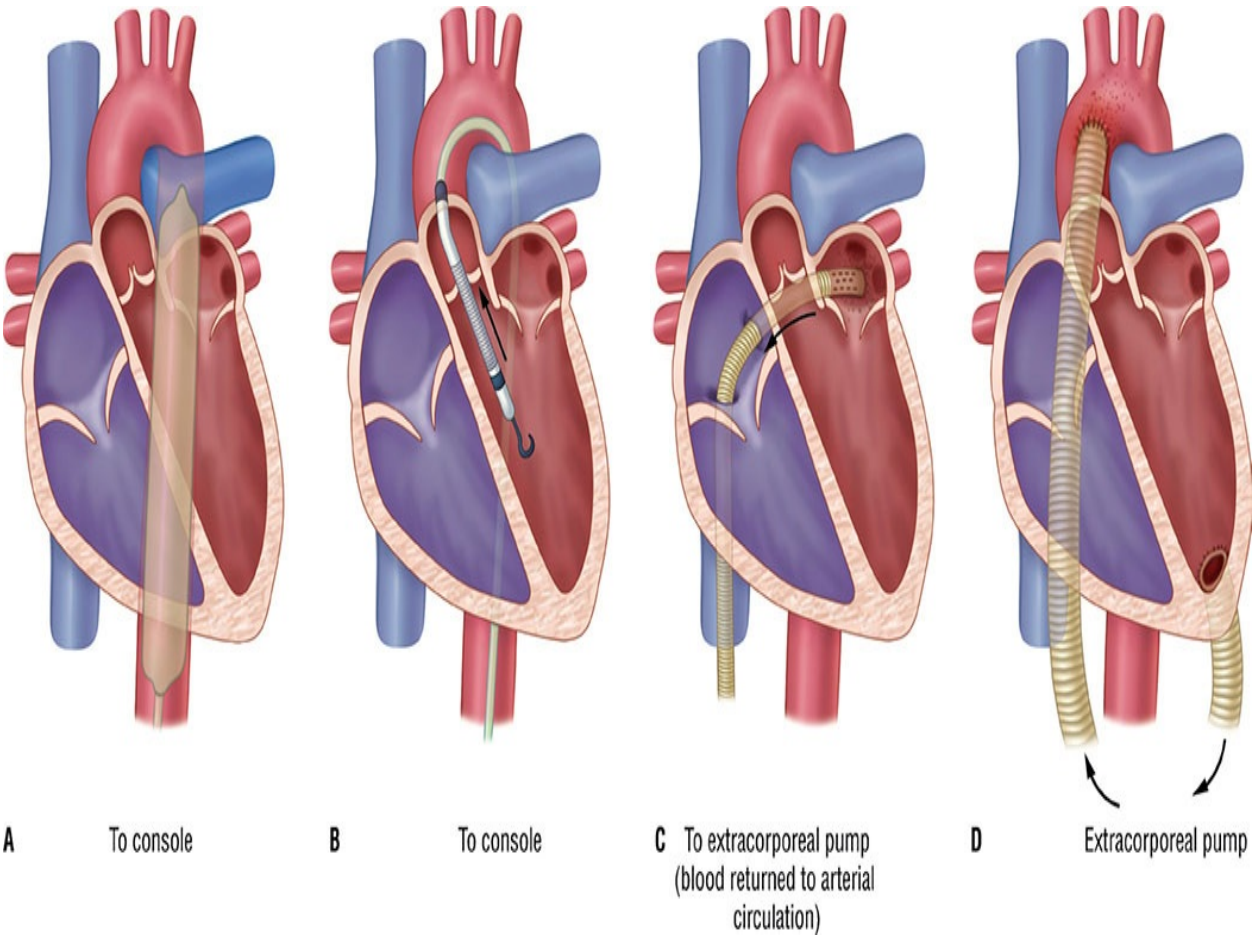


FIGURE 36-4 Common types of temporary mechanical circulatory support. (A) An intra-aortic balloon pump (IABP) is advanced into the descending aorta where it inflates during diastole (shown), displacing blood and improving coronary filling. During systole (not shown), the IABP deflates, producing a vacuum-like effect that reduces peripheral resistance. (B) An example of an Impella percutaneous ventricular assist device (VAD). An Impella device is advanced through the aortic valve, where blood is transferred from the left ventricle to the aorta by an axial flow pump. (C) The TandemHeart device, which is inserted percutaneously into a large peripheral vein and advanced across the intra-atrial septum. Blood is removed from the left atrium and propelled by an extracorporeal centrifugal flow pump back into the systemic circulation (not shown). (D) The cannula of a CentriMag VAD. An inflow cannula is surgically inserted into the apex of the left ventricle, where blood is transferred to an extracorporeal centrifugal flow pump (not shown), where it is returned to the systemic circulation via an outflow cannula surgically inserted into the aorta. In extracorporeal membrane oxygenation (ECMO) (not shown), the inflow and outflow cannula are inserted into peripheral vessels.

Intra-aortic Balloon Pump

An IABP consists of a polyethylene balloon mounted on a catheter that is inserted percutaneously into the femoral artery and advanced into the descending thoracic aorta (see Fig. 36-4A). During counterpulsation, the balloon is synchronized with the electrocardiogram (or alternatively, changes in pressure) so that it inflates during diastole and displaces blood to the proximal aorta, thus increasing diastolic pressure and coronary perfusion. The balloon deflates just prior to the opening of the aortic valve during systole, which causes a sudden "vacuum-like" decrease in aortic pressure, allowing the left ventricle to pump against reduced arterial impedance. Although the IABP is the most commonly employed modality of temporary MCS due to its ease of use, it only provides an estimated 1.0 L/min of CO. As a consequence, the primary benefits of an IABP are enhanced coronary perfusion, increased myocardial oxygen supply, and reduced myocardial oxygen demand. It may be particularly useful for patients with myocardial ischemia complicated by cardiogenic shock, although it has not been shown to improve mortality in this setting.[41] Systemic anticoagulation is generally recommended, although cases of IABP use without anticoagulation have been reported.[42] Complications of the IABP include vascular injury, thrombocytopenia, and renal impairment due to obstruction of the splanchnic circulation by balloon malposition. Use should be avoided in patients with severe peripheral vascular disease.

Ventricular Assist Devices

A VAD provides hemodynamic support by assisting and, in some cases, replacing the pumping functions of the right and/or left ventricles. Compared to an IABP, temporary VADs confer greater hemodynamic improvements but no differences in long-term survival.[43] A left ventricular assist device (LVAD) propels blood from the left ventricle or left atrium to the ascending aorta whereas a right VAD propels blood from the right ventricle or right atrium to the PA. A right VAD may be used alone or in conjunction with an LVAD; this latter configuration is known as a biventricular assist device. All VADs are preload-dependent, meaning that adequate intra-ventricular filling pressure (ie, volume) is required to optimize blood flow. As with the native ventricle in HF, VADs are also afterload-sensitive, meaning that excess peripheral resistance can impair blood flow. Complications of VAD implantation include bleeding, infections, and risks associated with the specific implantation technique. In addition, the devices can cause thrombosis, renal and hepatic dysfunction, and arrhythmias.

Right ventricular failure is a unique complication of LVAD implantation as a result of increased venous return, persistently elevated pulmonary pressures, and changes in right ventricular geometry.

Percutaneous VADs include the Impella series (Abiomed, Danvers, MA) and TandemHeart (CardiacAssist, Pittsburgh, PA). Impella devices are inserted percutaneously into a large peripheral artery and advanced in a retrograde fashion across the aortic valve, where blood is advanced from the left ventricle to the ascending aorta via axial flow (see Fig. 36-4B). The amount of CO augmented by the Impella device depends on the model used; for example, the Impella 2.5 and 5.0 models supply 2.5 L and 5.0 L/min of flow, respectively. Hemolysis is a common complication of Impella use due to the axial flow facilitated by the device. The TandemHeart device consists of an inflow cannula placed percutaneously into a large peripheral vein and advanced transseptally into the left atrium (see Fig. 36-4C). Blood is withdrawn from the left atrium by an extracorporeal pump and propelled via an outflow cannula placed percutaneously into a large artery. Up to 5.0 L/min of flow can be provided by the TandemHeart. Due to its placement across the intra-atrial septum, perforation and shunt formation are potential complications with this device.

The most common surgically implanted temporary VAD is the CentriMag (Thoractec Corp., Pleasanton, CA), which can provide right, left, or biventricular support and up to 10 L/min of CO. The CentriMag device consists of a centrifugal flow extracorporeal pump and surgically placed inflow and outflow cannula supporting the affected ventricle (see Fig. 36-4D). Given the surgical technique required for placement of the CentriMag device, tissue injury is its most common complication.

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation may be venoarterial or venovenous in nature. In venoarterial ECMO, deoxygenated blood is transported from the venous circulation to an extracorporeal oxygenator and centrifugal flow pump and returned as oxygenated blood to the arterial circulation. In contrast, venovenous ECMO consists of only extracorporeal oxygenation; hemodynamic support is provided by native cardiac function. As a consequence, venoarterial ECMO is more common in the management of refractory ADHF, where up to 8 L/min of cardiac support can be provided. Complications of ECMO include bleeding, infections, and organ dysfunction. Serum drug concentrations can also be significantly impacted as a result of increased volume of distribution, decreased elimination due to hepatic and/or renal impairment, and sequestration

of drugs in the ECMO circuit.

ADVANCED THERAPIES

No consensus definition exists for advanced HF or the stage at which patients should be considered for definitive therapies such as durable MCS and heart transplantation. Nonetheless, evaluation for these advanced therapies is commonly initiated during an admission for ADHF, particularly if hospitalization is accompanied by severe symptoms at rest, intolerance of GDMT, decline in organ function, refractory arrhythmias, or an inability to be successfully weaned from inotropic or temporary MCS support. Because of the complexity of care, potential risks, and resource implications of durable MCS and heart transplantation, patients with advanced HF must undergo a rigorous interdisciplinary evaluation before becoming eligible candidates. Components of this evaluation commonly include past medical, surgical, and psychosocial history, medication and adverse event history, adherence to medications and medical care, comorbid conditions, risks for postoperative complications, and health insurance coverage. Relative contraindications to the use of advanced therapies include excess perioperative risk, irreversible pulmonary hypertension, inability to manage postoperative care (eg, medication therapy, monitoring), and concurrent survival-limiting diseases (eg, malignancy).

Durable Mechanical Circulatory Support

The most common indications for durable MCS are temporary device implantation in patients awaiting heart transplantation who are unlikely to survive the duration of time required for identifying a suitable donor (“bridge to transplantation”) and permanent device implantation in patients who are ineligible for heart transplantation due to advanced age or comorbid conditions (“destination therapy”). Although far less common than with temporary MCS, durable VADs may be implanted in patients who are likely to become eligible transplant candidates (“bridge to decision”) but evaluation is incomplete or has been delayed until certain requirements can be satisfied (eg, smoking cessation). Durable MCS is almost exclusively comprised of LVAD implantation, although select patients may remain hospitalized with right VAD or biventricular support while awaiting transplantation.

Durable LVADs are implanted by inserting an inflow cannula into the apex of the left ventricle, which is connected to an intracorporeal pumping unit; blood is

returned to the systemic circulation via an outflow cannula inserted into the aorta. Whereas previous devices provided hemodynamic support via pulsatile flow, newer-generation devices utilize a continuous flow mechanism, allowing them to be smaller in size, less subject to deterioration over time, and conferring an improvement in event-free survival.[44] Research suggests that prolonged unloading of the left ventricle with an LVAD in combination with drug therapy can produce sustained recovery in LV function, amelioration of symptoms, and in some cases, device explantation.[45] The three continuous flow LVADs currently approved for use in the United States are the axial flow HeartMate II LVAD (Abbott; Lake Bluff, IL) and centrifugal flow HeartMate 3 LVAD (Abbott) and HeartWare Ventricular Assist Device (HVAD) (HeartWare, Inc; Framingham, MA). All three devices are capable of providing up to 10 L/min of CO. For complete heart replacement therapy, total artificial heart systems continue to be investigated, although size and embolic complications limit widespread use.

Complications following durable LVAD placement are similar as those described for temporary devices. Device malfunction may occur with long-term use but has become rare with advances in technology. The most perplexing challenge in the care of LVAD patients remains identifying a chronic antithrombotic regimen that balances the risk of device thrombosis and bleeding. Antithrombotic regimens most often include a vitamin K antagonist and antiplatelet agent, although the goal international normalized ratio (INR) range and antiplatelet agents selected (eg, aspirin, dipyridamole, clopidogrel) may vary significantly by center. Suspected pump thrombosis should be promptly evaluated, although no consensus exists on an appropriate treatment strategy (eg, enhanced antiplatelet or anticoagulant therapy, thrombolysis, or pump exchange).[46]

Heart Transplantation

13 Orthotopic heart transplantation remains the optimal management strategy for patients with irreversible advanced HF, as 10-year survival rates approach 60% among patients transplanted after 2001.[47] Unfortunately, the shortage of acceptable donor hearts has prolonged waiting times and many patients succumb to their disease prior to transplantation. Another significant percentage of patients are deemed ineligible for heart transplantation because of age, concurrent illnesses, psychosocial factors, or other reasons. The shortage of donor hearts has prompted the development of new surgical strategies, including

ventricular aneurysm resection, mitral valve repair, and myocardial cell transplantation, which have resulted in variable degrees of improvement. Further development of these and other techniques may offer additional options in patients who are not eligible for VAD implantation or heart transplantation. For a more detailed discussion of heart transplantation, see Chapter 105 “Solid Organ Transplantation.”

EVALUATION OF THERAPEUTIC OUTCOMES

Daily monitoring to assess the efficacy of drug therapy is critical to assuring optimal outcomes and should include weight, strict measurement of fluid intake and output, and HF signs and symptoms (**Table 36-6**). Foley catheter placement is not recommended unless close monitoring of urine output is not otherwise possible. Safety endpoints such as monitoring for electrolyte depletion, symptomatic hypotension, and renal dysfunction should be assessed frequently. While many safety parameters can be monitored daily, some will need to be monitored more frequently based on the patient’s clinical status. Vital signs should be assessed multiple times throughout the day at a frequency that is appropriate for the patient’s degree of stability. Orthostatic blood pressure should be assessed at least once daily.

TABLE 36-6 Monitoring Recommendations for Patients Hospitalized with ADHF

Parameter	Frequency	Notes
Weight	Daily	Assess after voiding in the morning
		Utilize same scale each day, if possible
		Account for increase or decrease in food intake
Fluid balance	Daily*	Strict intake and output
Vital signs	More than daily	Blood pressure and heart rate including signs/symptoms of orthostatic hypotension, rhythm (continuous)
Signs of congestion and/or low output	Daily*	Jugular venous distension, crackles, hepatomegaly, splenomegaly, hepatojugular reflux, ascites, lower extremity edema, hypotension, narrow pulse pressures, cool extremities, altered mental status, worsening renal or hepatic function
Symptoms of congestion and/or low output	Daily*	Dyspnea on exertion or at rest, orthopnea, paroxysmal nocturnal dyspnea, nausea/vomiting, early satiety, fatigue, lightheadedness, chest pain, palpitations
Electrolytes	Daily*	Potassium, magnesium, sodium
Renal function	Daily*	Blood urea nitrogen and serum creatinine including ratio to assess volume status (ie, over-diuresis)
Hepatic function	Variable*	Alk Phos and GGT primarily for fluid overload, AST and ALT primarily for hypoperfusion
BNP, NT-proBNP	Admission, discharge	Admission for diagnosis, discharge for prognosis
Other	Variable	Troponin and other cardiac enzymes if myocardial strain
		Arterial blood gas if hypoxic
		Lactate if hypoperfusion present

Alk Phos, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BNP, B-type natriuretic peptide; GGT, gamma-glutamyltransferase; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*Daily unless change in clinical status warrants more frequent assessment.

Patients with ADHF may have critically reduced CO, usually with low arterial blood pressure and systemic hypoperfusion resulting in organ system dysfunction (ie, cardiogenic shock). They may also have pulmonary edema with hypoxemia, respiratory acidosis, and markedly increased work of breathing. With cardiopulmonary support, response to interventions should be assessed promptly to allow for timely adjustments in treatment. Continuous telemetry monitoring, continuous pulse oximetry, urine flow, and automated blood pressure recordings are standards of care for critically ill patients with cardiopulmonary decompensation. Peripheral or femoral arterial catheters may be utilized for continuous and accurate assessment of arterial pressure.

Preparing for Discharge

Patients should not be discharged until optimal volume status is achieved and

they have been successfully transitioned from an IV to an oral diuretic regimen and IV inotropes and vasodilators have been discontinued for at least 24 hours. Efforts should also be made to optimize GDMT in hemodynamically stable patients without contraindications, including the reinitiation of therapies held earlier in the admission. Low-dose β-blocker therapy may be safely initiated at discharge without increasing the risk of readmission,[48] and transitioning eligible patients to the angiotensin receptor neprilysin inhibitor (ARNI) sacubitril/valsartan may also be considered.[49] If relevant, smoking cessation must be addressed to avoid delay in consideration for advanced therapies. The following should be documented in the medical record: left ventricular ejection fraction and ACE inhibitor and β-blocker use (for patients with reduced LVEF) or intolerance to such.[50]

Prior to discharge, patients and caregivers should be counseled on dietary sodium restriction as well as monitoring body weight daily and parameters for when to titrate diuretics or call a healthcare provider for further instruction (eg, 3-lb weight gain in 24 hours). Medication changes (initiation, discontinuation, dose change) should be clearly conveyed verbally and in writing and financial coverage for all medication assured. The importance of dietary and medication adherence should be emphasized. Appropriate follow-up should be scheduled, including an appointment at 7 to 10 days post discharge and a nurse visit or phone call at 3 days for select patients. Pertinent follow-up labs (eg, potassium, serum creatinine) should also be scheduled, including other medication-related labs (eg, INR for warfarin, serum digoxin concentration). All patients should be considered for referral to a formal disease management program.

Multidisciplinary disease management programs and other specialized interventions involving pharmacists have been associated with a wide range of benefits including reduced HF readmissions.[51] A recent systematic review of multidisciplinary teams involving a pharmacist showed reductions in all-cause and HF hospitalizations.[52] The American Heart Association recently published a statement describing transitional care interventions acknowledging that of the transition of care programs for patients with HF (n = 20); 75% used a collaborative, multidisciplinary team that included pharmacists.[53]

CONCLUSION

Several recent clinical trials have addressed many controversies in the management of ADHF, including the appropriate dosing of diuretics and use of vasodilators and vasopressors (eg, dopamine) in patients with volume overload.

Still, many unanswered questions remain, including inotrope selection in low CO and optimal use of GDMT in the setting of ADHF. Many advances in MCS have extended the lives of patients awaiting transplant; however, limited evidence exists to guide management of this patient population, including how to avoid and manage complications associated with these devices. Finally, ideal management of patients with ADHF includes optimization of GDMT, optimal communication with patients, caregivers, and other healthcare providers with each care transition, and outpatient follow-up with a collaborative, multidisciplinary team.

Postclass Engaged Learning Activity

Pair up with a classmate and create a series of flash cards, in which you describe a patient in one of the four hemodynamic subsets on one side (ie, signs, symptoms, physical examination findings, laboratory values) and the appropriate classification and treatment approach on the other side. Present your partner with the case and ask him or her to recommend an initial treatment and monitoring plan. Ensure that at least one of each of the four hemodynamic subsets is represented in your stack of cards, but also try varying the complexity and severity of each case. For example, start with a simple case of fluid overload (ie, subset II or "warm and wet") and ask your partner to recommend an intravenous diuretic regimen based on the patient's home diuretic dose. Later, progress to patient scenarios with subset III ("cold and dry") and IV ("cold and wet"). For each case, ask your partner to list patient-specific factors that might influence the treatment approach (eg, hypotension when deciding between a vasodilator and inotrope) as well as monitoring parameters for the therapies selected. For an extra challenge, add in some cases where you provide values from a pulmonary artery catheter or have a patient who develops diuretic resistance. Compare and contrast your partner's recommendations with those you wrote on the back of the card.

Finally, after you have determined an acute management strategy for each case, go back through the cards and imagine that each patient has recovered and is being prepared for discharge. Develop a plan to optimize their guideline-directed medical therapy as well as any needed follow-up monitoring. Practice how you would educate a patient about these changes with your partner.

ABBREVIATIONS

ACCF	American College of Cardiology Foundation
ACE	angiotensin-converting enzyme
ADHF	acute decompensated heart failure
AHA	American Heart Association
AMP	adenosine monophosphate
AVP	arginine vasopressin
BNP	B-type natriuretic peptide
BUN	blood urea nitrogen
cAMP	cyclic adenosine monophosphate
cGMP	cyclic guanosine monophosphate
CI	cardiac index
CO	cardiac output
CVP	central venous pressure
DT	destination therapy
ECMO	extracorporeal membrane oxygenation
GDMT	guideline-directed medical therapy
GI	gastrointestinal
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HVAD	HeartWare Ventricular Assist Device
IABP	intra-aortic balloon pump
INR	international normalized ratio
IV	intravenous
JVD	jugular venous distension
LVAD	left ventricular assist device
MAP	mean arterial pressure
MCS	mechanical circulatory support
MI	myocardial infarction
NYHA	New York Heart Association
PA	pulmonary artery
PCWP	pulmonary capillary wedge pressure
PVR	pulmonary vascular resistance
SIADH	syndrome of inappropriate diuretic hormone
SVR	systemic vascular resistance
VAD	ventricular assist device
W-IHM	wireless invasive hemodynamic monitoring
WRF	worsening renal function

REFERENCES

1. Gheorghiade M, De Luca L, Fonarow GC, Filippatos G, Metra M, Francis GS. Pathophysiologic targets in the early phase of acute heart failure syndromes. *Am J Cardiol*. 2005;96(6A):11G–17G.
2. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62(16):e147–e239.
3. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics—2018 update: A report from the American Heart Association. *Circulation*. 2018;137(12):e67–e492.
4. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: A policy statement from the American Heart Association. *Circ Heart Fail*. 2013;6(3):606–619.
5. Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: Lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol*. 2014;63(12):1123–1133.
6. Weintraub NL, Collins SP, Pang PS, et al. Acute heart failure syndromes: Emergency department presentation, treatment, and disposition: Current approaches and future aims: A scientific statement from the American Heart Association. *Circulation*. 2010;122(19):1975–1996.
7. Felker GM, Adams KF, Konstam MA, O'Connor CM, Gheorghiade M. The problem of decompensated heart failure: Nomenclature, classification, and risk stratification. *Am Heart J*. 2003;145(2 Suppl): S18–S25.
8. Fonarow GC, Adams KF, Abraham WT, et al. Risk stratification for in-hospital mortality in acutely decompensated heart failure: Classification and regression tree analysis. *JAMA*. 2005;293(5):572–580.
9. O'Connor CM, Abraham WT, Albert NM, et al. Predictors of mortality after discharge in patients hospitalized with heart failure: An analysis from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J*. 2008;156(4):662–673.
10. Nohria A, Mielniczuk LM, Stevenson LW. Evaluation and monitoring of patients with acute heart failure syndromes. *Am J Cardiol*. 2005;96(6A):32G–40G.

11. Binanay C, Califf RM, Hasselblad V, et al. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: The ESCAPE trial. *JAMA*. 2005;294(13):1625–1633.
12. Fonarow GC, Abraham WT, Albert NM, et al. Influence of beta-blocker continuation or withdrawal on outcomes in patients hospitalized with heart failure: Findings from the OPTIMIZE-HF program. *J Am Coll Cardiol*. 2008;52(3):90–199.
13. Jondeau G, Neuder Y, Eicher J-C, et al. B-CONVINCED: Beta-blocker CONtinuation Vs. INterruption in patients with Congestive heart failure hospitalizED for a decompensation episode. *Eur Heart J*. 2009;30(18):2186–2192.
14. Packer M, Gheorghiade M, Young JB, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. RADIANCE Study. *N Engl J Med*. 1993;329(1):1–7.
15. Uretsky BF, Young JB, Shahidi FE, Yellen LG, Harrison MC, Jolly MK. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: Results of the PROVED trial. PROVED Investigative Group. *J Am Coll Cardiol*. 1993;22(4):955–962.
16. Forrester JS, Diamond G, Chatterjee K, Swan HJ. Medical therapy of acute myocardial infarction by application of hemodynamic subsets (first of two parts). *N Engl J Med*. 1976;295(24):1356–1362.
17. Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med* 2011;364(9):797–805.
18. Aronson D, Burger AJ. The relationship between transient and persistent worsening renal function and mortality in patients with acute decompensated heart failure. J Card Fail. Jul 2010;16(7):541–547. 20610229.
19. Dormans TP, van Meyel JJ, Gerlag PG, Tan Y, Russel FG, Smits P. Diuretic efficacy of high dose furosemide in severe heart failure: Bolus injection versus continuous infusion. *J Am Coll Cardiol*. 1996;28(2):376–382.
20. Thomson MR, Nappi JM, Dunn SP, Hollis IB, Rodgers JE, Van Bakel AB. Continuous versus intermittent infusion of furosemide in acute decompensated heart failure. *J Card Fail*. 2010;16(3):88–193.
21. Sharma K, Vasihnav J, Kalathiya R, et al. Randomized evaluation of heart failure with preserved ejection fraction patients with acute heart failure

and dopamine: The ROPA-DOP trial. *JACC Heart Fail*. 2018;6(10):859–870.

22. Reed BN, Gottlieb SS. Diuretic strategies and renal dysfunction in heart failure with preserved ejection fraction. *JACC Heart Fail*. 2018;6(12):1049–1050.
23. Cleland JGF, Coletta A, Witte K. Practical applications of intravenous diuretic therapy in decompensated heart failure. *Am J Med*. 2006;119(12 Suppl 1):S26–S36.
24. Chen HH, Anstrom KJ, Givertz MM, et al. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: The ROSE acute heart failure randomized trial. *JAMA*. 2013;310(23):2533–2543.
25. Giamouzis G, Butler J, Starling RC, et al. Impact of dopamine infusion on renal function in hospitalized heart failure patients: Results of the Dopamine in Acute Decompensated Heart Failure (DAD-HF) Trial. *J Card Fail*. 2010;16(12):922–930.
26. Triposkiadis FK, Butler J, Karayannis G, et al. Efficacy and safety of high dose versus low dose furosemide with or without dopamine infusion: The Dopamine in Acute Decompensated Heart Failure II (DAD-HF II) Trial. *Int J Cardiol*. 2014;172(1):15–121.
27. Gheorghiade M, Gattis WA, O'Connor CM, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: A randomized controlled trial. *JAMA*. 2004;291(16):1963–1971.
28. Lee WH, Packer M. Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure. *Circulation*. 1986;73(2):257–267.
29. Gheorghiade M, Konstam MA, Burnett JC, et al. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: The EVEREST Clinical Status Trials. *JAMA*. 2007;297(12):1332–1343.
30. Felker GM, Mentz RJ, Cole RT, et al. Efficacy and safety of tolvaptan in patients hospitalized with acute heart failure. *J Am Coll Cardiol*. 2017;69(11):1399–1406.
31. Schwartzenberg S, Redfield MM, From AM, Sorajja P, Nishimura RA, Borlaug BA. Effects of vasodilation in heart failure with preserved or reduced ejection fraction implications of distinct pathophysiologies on response to therapy. *J Am Coll Cardiol*. 2012;59(5):442–451.
32. Publication Committee for the VMAC Investigators (Vasodilatation in the

Management of Acute CHF). Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: A randomized controlled trial. *JAMA*. 2002;287(12):1531–1540.

33. Mullens W, Abrahams Z, Francis GS, et al. Sodium nitroprusside for advanced low-output heart failure. *J Am Coll Cardiol*. 2008;52(3):200–207.
34. Abraham WT, Adams KF, Fonarow GC, et al. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: An analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). *J Am Coll Cardiol*. 2005;46(1):57–64.
35. Cuffe MS, Califf RM, Adams KF, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: A randomized controlled trial. *JAMA*. 2002;287(12):1541–1547.
36. Metra M, Nodari S, D'Aloia A, et al. Beta-blocker therapy influences the hemodynamic response to inotropic agents in patients with heart failure: A randomized comparison of dobutamine and enoximone before and after chronic treatment with metoprolol or carvedilol. *J Am Coll Cardiol*. 2002;40(7):1248–1258.
37. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med*. 2010;362(9):779–789.
38. Costanzo MR, Guglin ME, Saltzberg MT, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol*. 2007;49(6):675–683.
39. Bart BA, Goldsmith SR, Lee KL, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med*. 2012;367(24):2296–2304.
40. Abraham WT, Adamson PB, Bourge RC, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: A randomised controlled trial. *Lancet*. 2011;377(9766):658–696.
41. Thiele H, Zeymer U, Neumann F-J, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med*. 2012;367(14):1287–1296.
42. Pucher PH, Cummings IG, Shipolini AR, McCormack DJ. Is heparin needed for patients with an intra-aortic balloon pump? *Interact Cardiovasc Thorac Surg*. 2012;15(1):36–139.

43. Cheng JM, den Uil CA, Hoeks SE, et al. Percutaneous left ventricular assist devices vs. intra-aortic balloon pump counterpulsation for treatment of cardiogenic shock: A meta-analysis of controlled trials. *Eur Heart J*. 2009;30(17):2102–2108.
44. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med*. 2009;361(23):2241–2251.
45. Birks EJ, Tansley PD, Hardy J, et al. Left ventricular assist device and drug therapy for the reversal of heart failure. *N Engl J Med*. 2006;355(18):1873–1884.
46. Goldstein DJ, John R, Salerno C, et al. Algorithm for the diagnosis and management of suspected pump thrombus. *J Heart Lung Transplant*. 2013;32(7):667–670.
47. Lund LH, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-second Official Adult Heart Transplantation Report-2015; Focus Theme: Early Graft Failure. *J Heart Lung Transplant*. 2015;34(10):1244–1254.
48. Gattis WA1, O'Connor CM, Gallup DS, Hasselblad V, Gheorghiade M; IMPACT-HF Investigators and Coordinators. Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure: results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial. *J Am Coll Cardiol*. 2004;43(9)1534–1541.
49. Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med*. https://doi.org/10.1056/NEJMoa1812851. Accessed December 22, 2018.
50. Wiggins BS, Rodgers JE, DiDomenico RJ, Cook AM, Page RL. Discharge counseling for patients with heart failure or myocardial infarction: A best practices model developed by members of the American College of Clinical Pharmacy's Cardiology Practice and Research Network based on the Hospital to Home (H2H) Initiative. *Pharmacotherapy*. 2013;33(5):558–580.
51. Milfred-LaForest SK, Chow SL, DiDomenico RJ, et al. Clinical pharmacy services in heart failure: An opinion paper from the Heart Failure Society of America and American College of Clinical Pharmacy Cardiology Practice and Research Network. *Pharmacotherapy*. 2013;33(5):529–548.
52. Koshman SL, Charrois TL, Simpson SH, McAlister FA, Tsuyuki RT.

Pharmacist care of patients with heart failure: A systematic review of randomized trials. *Arch Intern Med*. 2008;168(7):687–694.

53. Albert NM, Barnason S, Deswal A, et al. Transitions of care in heart failure: A scientific statement from the American Heart Association. *Circ Heart Fail*. 2015;8(2):384–409.

37

Venous Thromboembolism

Daniel M. Witt, Nathan Clark, and Sara R. Vazquez

KEY CONCEPTS

1. VTE is often associated with identifiable risk factors.
2. The diagnosis of suspected VTE should be confirmed by objective testing.
3. During hospitalization, patients should receive VTE prophylaxis based on the risk factors present and the anticipated duration of risk.
4. Initial VTE treatment should include a rapid-acting anticoagulant.
5. For VTE treatment, injectable anticoagulants should be overlapped with warfarin for at least 5 days and until the patient's international normalized ratio is ≥2.0 for at least 24 hours.
6. Direct oral anticoagulants (DOACs) such as rivaroxaban, apixaban, dabigatran, edoxaban, and betrixaban are a significant advancement in VTE prevention and treatment.
7. Most patients with uncomplicated DVT or PE can be safely treated as outpatients.
8. Most patients with VTE should receive 3 months of anticoagulation therapy; treatment beyond 3 months should be based on the risk of VTE recurrence and bleeding as well as patient preferences.
9. Optimal anticoagulant therapy management requires knowledge of pharmacologic and pharmacokinetic characteristics as well as a systematic management approach with ongoing patient education.

Preclass Engaged Learning Activity

Access the following website: https://tinyurl.com/y5qtehec and read the VTE

stories of at least five different patients. These stories are useful to enhance student understanding regarding the impact of VTE and its treatment on the lives of patients and their families.

INTRODUCTION

VTE is a potentially fatal disorder and significant health problem in our aging society.[1] VTE results from clot formation within the venous circulation and is manifested as deep vein thrombosis (DVT) and/or pulmonary embolism (PE) (**Fig. 37-1**).[1] DVT is rarely fatal, but PE can result in death within minutes of symptom onset, before effective treatment can be given. Beyond the symptoms produced by the acute event, VTE complications, such as the postthrombotic syndrome and chronic thromboembolic pulmonary hypertension (CTPH), also cause substantial disability and suffering.[1] Identifying VTE risk factors is important for targeting patients at high risk for VTE who would most benefit from VTE prevention strategies.[2–4]

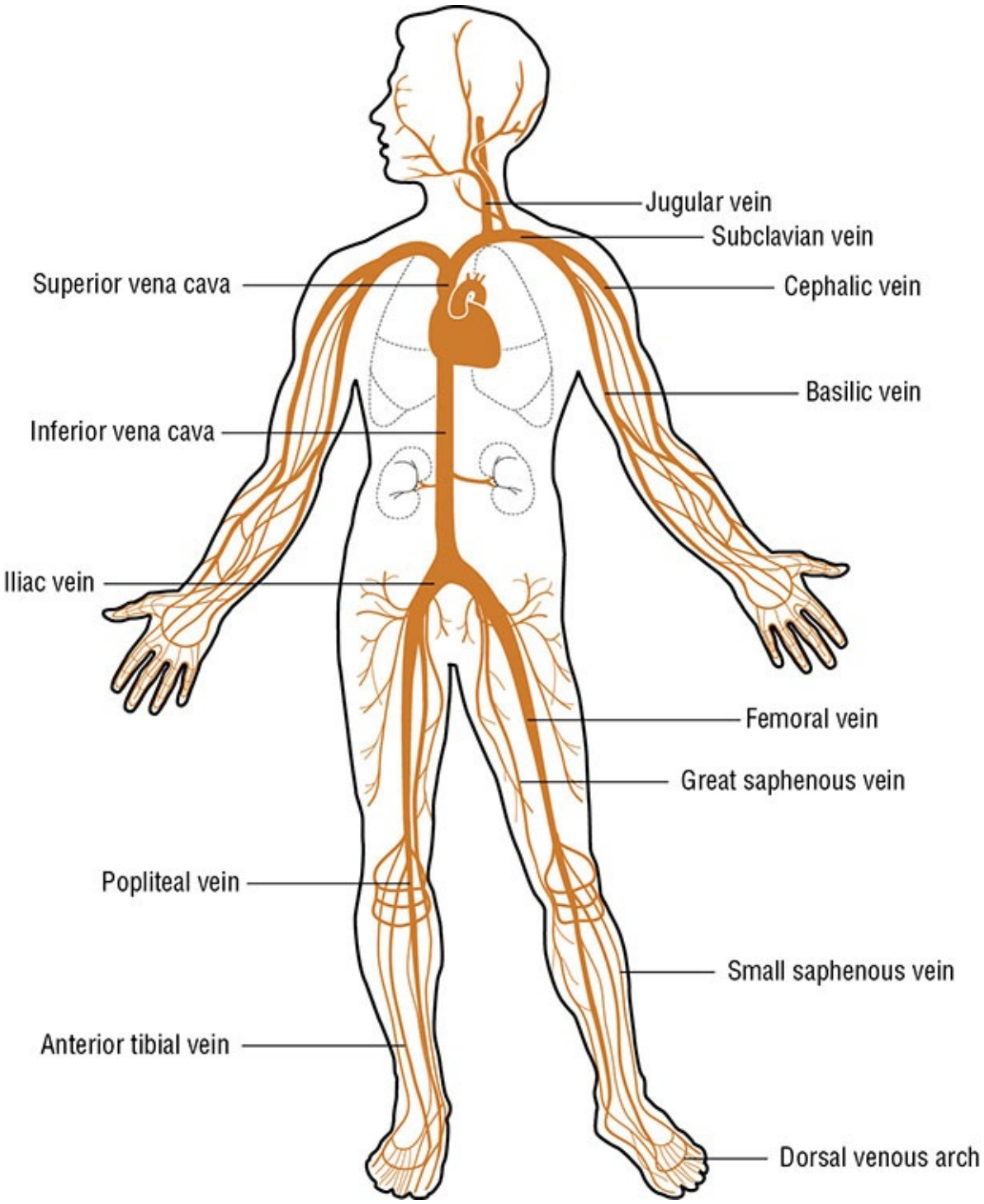


FIGURE 37-1 Venous circulation.

Rapid and accurate diagnosis is critical to making appropriate treatment decisions when VTE is suspected.[5] Optimal prevention and treatment of VTE using anticoagulant drugs requires an in-depth knowledge of their pharmacology and pharmacokinetic properties, and a comprehensive approach to patient

management.[6] Bleeding is a common and serious complication of anticoagulant therapy.[2–4]

EPIDEMIOLOGY

VTE is associated with significant global disease burden.[7] The incidence rate of symptomatic first VTE is estimated at 132 per 100,000 patient-years and occurs more frequently in women (55.6%).[8] When standardized by age, Asians appear to have the lowest VTE incidence (122 per 100,000 patient-years) followed by whites (191) and blacks (203).[8] Recurrent VTE rates are highest in the 180 days following the initial event and decline slowly over the next 4 to 10 years. In the absence of secondary prophylaxis, the 10-year cumulative recurrent VTE risk is approximately 25.0%.[8]

ETIOLOGY

1 A number of identifiable factors increase VTE risk (**Table 37-1**). Many risk factors fall into categories constituting what is known as Virchow's triad: blood stasis, vascular injury, and hypercoagulability.

TABLE 37-1 Risk Factors for Venous Thromboembolism

Risk Factor	Comments/Examples
Age	Incidence of VTE in adults age 75 and older is seven to ten times higher than adults younger than 55 years, with risk increasing even more over age 85
Prior VTE History	Potent risk factor for recurrence, risk is highest during the first 180 days after VTE
Blood stasis	Acute medical illness requiring hospitalization Surgery (especially general anesthesia >30 minutes) Paralysis (eg, status post stroke, spinal cord injury) Immobility (eg, plaster casts, status post stroke, or spinal cord injury) Polycythemia vera Obesity
Vascular injury	Major orthopedic surgery (eg, knee or hip replacement) Trauma (especially fractures of the pelvis, hip, or leg) Indwelling venous catheters
Hypercoagulability	Malignancy Factor V Leiden (homozygous >>heterozygous) Prothrombin (G20210A) gene mutation Protein C deficiency Protein S deficiency Antithrombin deficiency Factor VIII excess (>90th percentile) Factor XI excess (>90th percentile) Antiphospholipid antibodies Lupus anticoagulant Anticardiolipin antibodies (IgG and/or IgM >99th percentile) Anti-β_2-glycoprotein I antibodies (IgG and/or IgM >99th percentile) Inflammatory bowel disease Nephrotic syndrome Paroxysmal nocturnal hemoglobinuria Pregnancy or up to 6 weeks postpartum Drug therapy (eg, estrogen-containing contraceptives, estrogen replacement therapy, tamoxifen, raloxifene, cancer therapy, heparin-induced thrombocytopenia)

VTE, venous thromboembolism.

Source: Data from Bates et al.,[9] Kahn et al.,[2] Gould et al.,[3] Falck-Ytter et al.,[4] Johnson et al.[10], and Anderson et al.[11]

Blood Stasis

Blood stasis favors clotting in part through concentrating the elements responsible for blood clot formation.[12] Contraction of the calf and thigh muscles coupled with one-way valves in leg veins facilitate blood flow back to the heart and lungs; thus, damage to venous valves and prolonged immobility result in venous stasis.[13] Blood stasis in the venous system partly explains why numerous medical conditions and surgical procedures are associated with an increased

VTE risk (Table 37-1).

Vascular Injury

Intact vascular endothelial cells separate flowing blood from subendothelial vessel wall components. These subendothelial components are responsible for preventing blood loss through clot formation (see detailed description in section "Pathophysiology"). Vascular injury (eg, surgery, trauma) disrupts this protective barrier initiating blood clot formation.[14]

Hypercoagulability

Several inherited and acquired disorders as well as drugs have been linked to blood hypercoagulability (Table 37-1). Estrogen-containing contraception, estrogen replacement therapy, and selective estrogen receptor modulators are all linked to VTE risk.[9] Women with inherited hypercoagulability disorders are at particularly high risk of developing VTE during pregnancy and while taking estrogen.[9]

In many cases, VTE results from converging combinations of inherited and acquired thrombotic risk factors. Thus, an individual with a congenital hypercoagulable condition may experience VTE only after being placed in high-risk situations such as surgery, immobilization, the use of estrogen-containing oral contraceptives, or pregnancy. Approximately a third of VTEs are provoked by identifiable risk factors.[8]

PATHOPHYSIOLOGY

Hemostasis is the process responsible for maintaining circulatory system integrity following blood vessel damage (**Fig. 37-2**).[14] Hemostatic clots remain localized to the vessel wall and do not greatly impair blood flow. In contrast, pathologic clots like those causing VTE result in blood flow impairment and often cause complete vessel occlusion.[14]

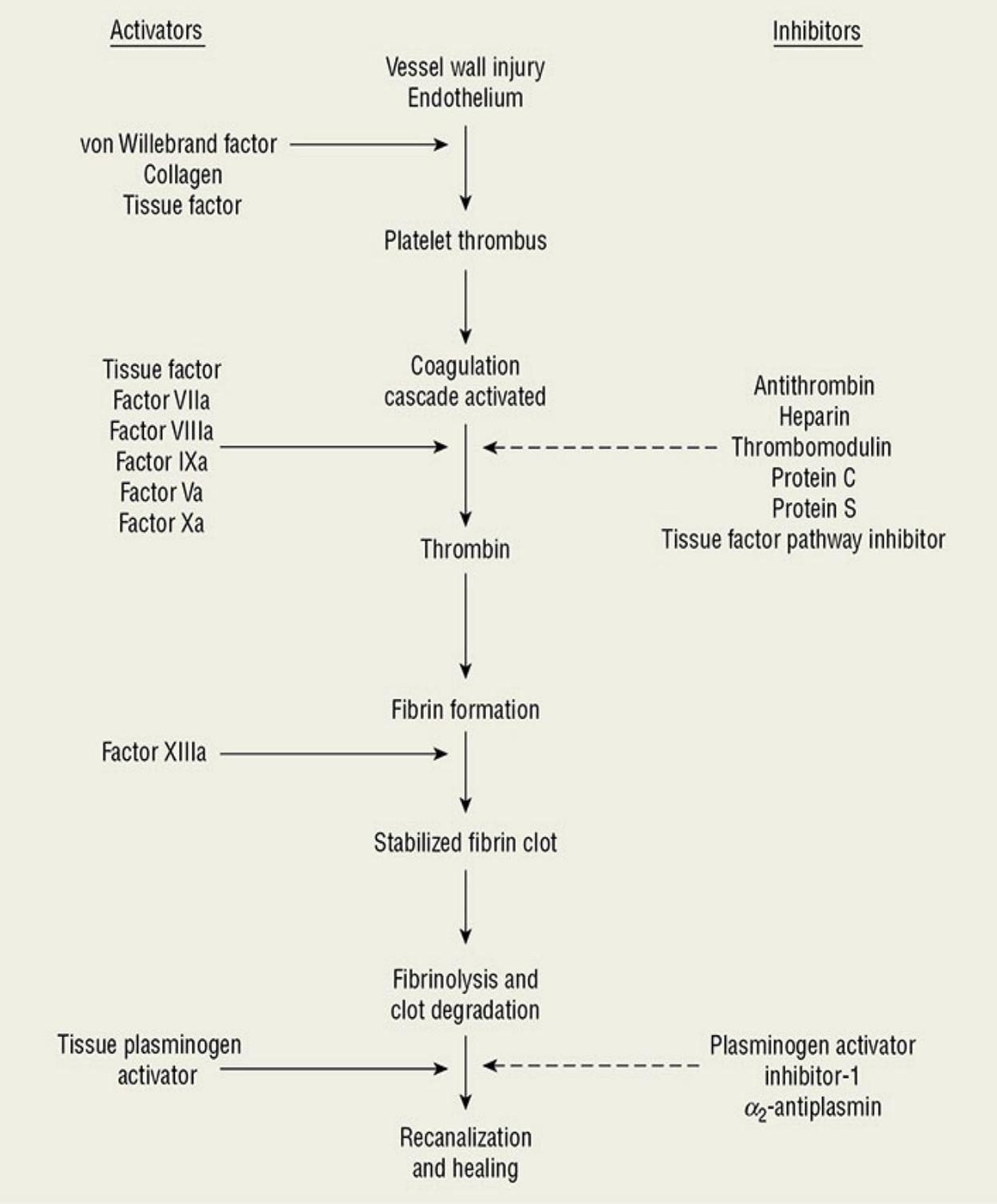


FIGURE 37-2 Overview of hemostasis.

Collagen and tissue factor (TF) form a hemostatic barrier around blood vessels and organs. Under normal circumstances, endothelial cells lining the vessel wall physically separate collagen and TF from circulating platelets and

clotting factors (namely, activated factor VII [VIIa]). Vessel injury results in platelet activation and TF-mediated clotting factor cascade initiation culminating in thrombin formation and ultimately fibrin clot, which seals the breach (Fig. 37-2).[14] In contrast to physiologic hemostasis, pathologic VTE often occurs without gross vessel wall damage and may be triggered by TF brought to the growing thrombus by circulating microparticles. Venous clots are mainly composed of fibrin, platelets, and trapped red blood cells and often occur in areas of disturbed blood flow, like deep leg vein valve cusps.[14]

Platelet and coagulation cascade activation occurs nearly simultaneously. Platelets become actively involved in thrombus formation after binding to adhesion proteins like von Willebrand factor and collagen when blood is exposed to damaged vessel endothelium.[14] A platelet thrombus grows as activated platelets recruit additional platelets, some of which also become activated while others remain loosely associated without undergoing activation and ultimately break away from the growing thrombus. Activated platelets change shape and release components critical for sustaining further thrombus formation into the environment surrounding the developing clot.[14] Activated platelets accumulating in the thrombus also express P-selectin, an adhesion molecule that facilitates capture of blood-borne TF bearing microparticles resulting in fibrin clot formation via the coagulation cascade (**Fig. 37-3**).[14] Activated platelets provide phospholipid-rich surfaces necessary for coagulation cascade reactions.[14]

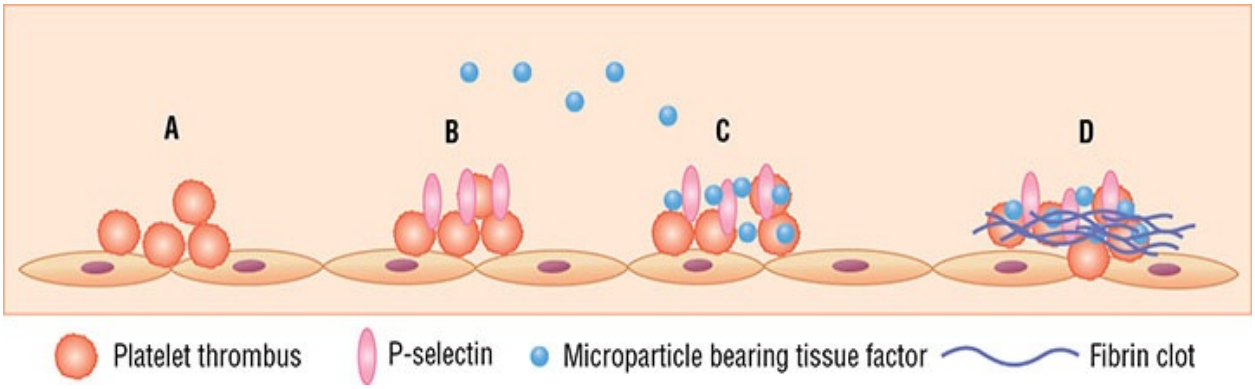


FIGURE 37-3 Model of pathologic thrombus formation: (*A*) activated platelets adhere to vascular endothelium; (*B*) activated platelets express P-selectin; (*C*) pathologic microparticles express active tissue factor and are present at a high concentration in the circulation—these microparticles accumulate, perhaps by binding to activated platelets expressing P-selectin; (*D*) tissue factor can lead to thrombin and fibrin generation. (*Adapted from De Caterina R, et al. General*

mechanisms of coagulation and targets of anticoagulants (Section I). Position Paper of the ESC Working Group on Thrombosis--Task Force on Anticoagulants in Heart Disease. Thromb Haemost. 2013;109:569-579.)

The conceptual model for the coagulation cascade has evolved from the classic depiction of extrinsic, intrinsic, and common pathways (**Fig. 37-4**) to a more modern notion whereby highly regulated reactions take place on cell surfaces in three overlapping phases: initiation, amplification, and propagation. The cascade starts on TF-bearing cells and continues on the surfaces of activated platelets (**Fig. 37-5**).[14]

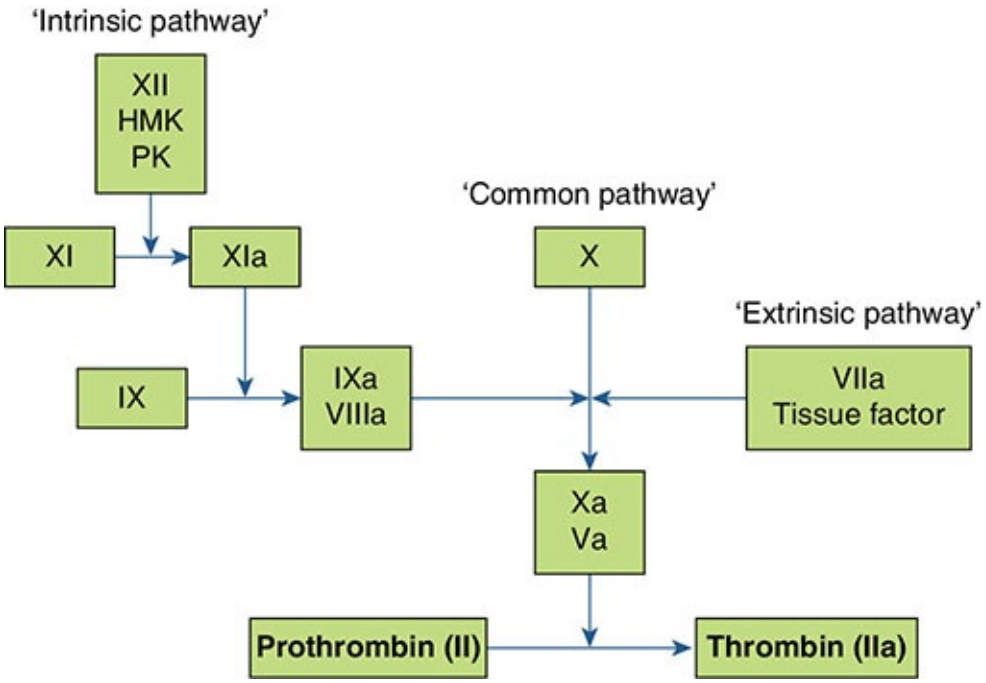


FIGURE 37-4 Classic depiction of the coagulation cascade. (HMK, High-molecular-weight kininogen; PK, Prekallikrein.)

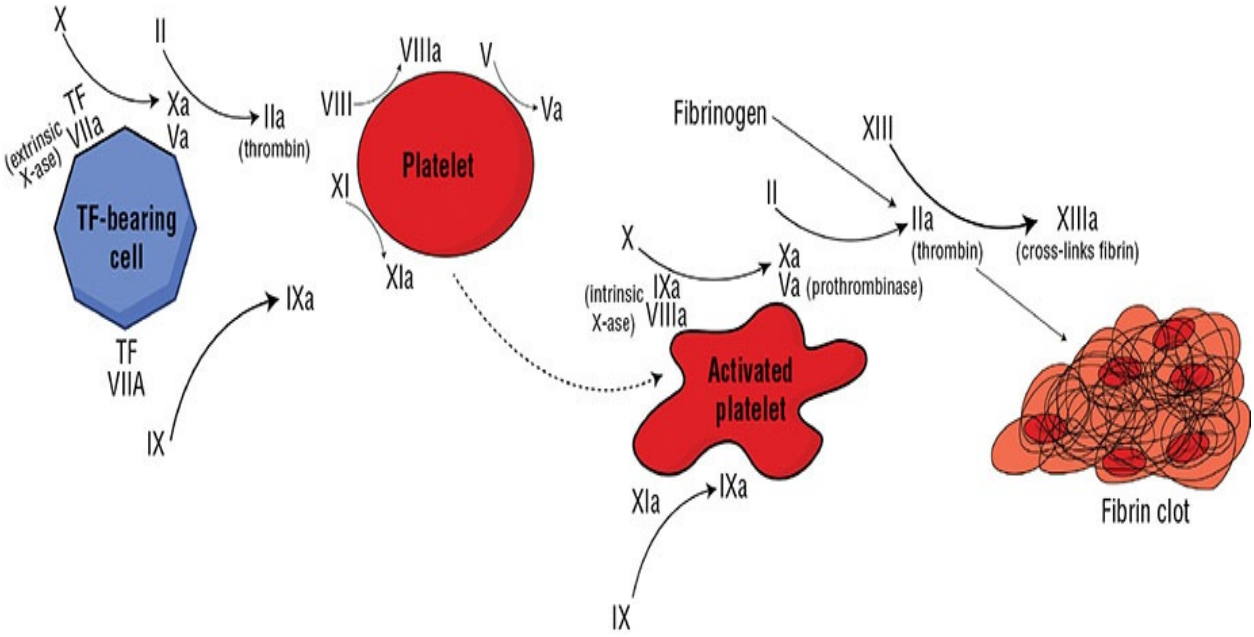


FIGURE 37-5 Cellular coagulation cascade model. (*Adapted from De Caterina R, et al. General mechanisms of coagulation and targets of anticoagulants (Section I). Position Paper of the ESC Working Group on Thrombosis--Task Force on Anticoagulants in Heart Disease. Thromb Haemost. 2013;109:569-579.*)

The initiation phase takes place on TF-bearing cells exposed after vessel injury or captured via P-selectin (Fig. 37-3). The TF/VIIa complex (known as extrinsic tenase) activates limited amounts of factors IX and X. Factor Xa then associates with factor Va to form the prothrombinase complex, which cleaves prothrombin (factor II) to generate a small (picomolar) amount of thrombin (factor IIa) (Fig. 37-5). Factor IXa moves from TF-bearing cells to the surface of activated platelets in the growing platelet thrombus. Tissue factor pathway inhibitor (TFPI), an important regulator of TF/FVIIa-induced coagulation, rapidly terminates the initiation phase.[14]

In the amplication phase the small amount of thrombin produced during the initiation phase activates factors V and VIII, which bind to platelet surfaces and support the large-scale thrombin generation occuring during the propagation phase. Platelet-bound factor XI is also activated by thrombin during this phase.[14]

A burst of thrombin generation occurs during the propagation phase as the VIIIa/IXa (known as “intrinsic tenase”) promotes factor Xa formation and prothrombinase complexes assemble on the surface of activated platelets accelerating thrombin generation. Thrombin generation is further supported by factor XIa bound to the platelet surface, which activates factor IX to form

additional intrinsic tenase.[14]

Thrombin generated during the propagation phase converts fibrinogen to fibrin monomers that precipitate and polymerize to form fibrin strands. Factor XIIIa, which is also activated by the action of thrombin, covalently bonds these strands to one another (Fig. 37-5) to form an extensive meshwork that surrounds and encases the aggregating platelet thrombus and red blood cells to form a stabilized fibrin clot.[14] Clot formation eventually terminates when the expanding meshwork of platelets and fibrin "paves over" the initiation site and activated factors are unable to diffuse through the overlying clot layer.

A number of tempering mechanisms control coagulation (Fig. 37-2). Without effective self-regulation, thrombus formation results in vascular occlusion. Intact endothelium adjacent to the damaged tissue actively produce several antithrombotic substances.[12] Thrombomodulin modulates thrombin activity by converting protein C to its active form (aPC). When joined with its cofactor protein S, aPC inactivates factors Va and VIIIa regulating the functionality of the prothrombinase and tenase complexes, respectively.[12] aPC and protein S prevent coagulation reactions from spreading to healthy, uninjured vessel walls. Antithrombin is a circulating protein that inhibits thrombin and factor Xa. Heparan sulfate, a heparin-like compound secreted by endothelial cells, exponentially accelerates antithrombin activity.[12] As described previously, TFPI plays an important role by regulating the initiation phase.[14] When these self-regulatory mechanisms are intact, fibrin clot is limited to the vessel injury zone. However, disruptions in the system can result in hypercoagulability.[15]

The fibrinolytic system is responsible for blood clot dissolution.[16] Inactive plasminogen is converted by tissue plasminogen activator (tPA) to active plasmin, an enzyme that degrades fibrin mesh into soluble end products collectively known as fibrin degradation products including D-dimer which is a marker of thrombosis used when diagnosing VTE.[16] The fibrinolytic system is also under the control of a series of stimulatory and inhibitory substances (Fig. 37-2). Plasminogen activator inhibitor-1 inhibits tPA and α_2-antiplasmin inhibits plasmin activity. Impaired functioning of the fibrinolytic system has also been linked to hypercoagulability and thrombotic complications.[16]

Although VTE can form in any part of the venous circulation, most begin in the leg(s). Thrombus isolated in calf veins is unlikely to break loose (embolize), but thrombus involving the popliteal and larger veins above it are more likely to embolize and travel through the right side of the heart and cause PE by lodging in the pulmonary artery or one of its branches, occluding blood flow to the lung,

and impairing gas exchange. Without treatment, the affected portion of the lung becomes necrotic and oxygen delivery to other vital organs decreases, potentially resulting in fatal circulatory collapse.[1]

Inherited and Acquired Hypercoagulability Disorders

Disturbances in hemostatic regulation may result in hypercoagulability. Hypercoagulability can be inherited or acquired.[15] aPC resistance increases the risk of VTE approximately threefold and is the most common inherited hypercoagulability disorder with a prevalence rate in Caucasians of 2.0% to 7.0%.[15] aPC resistance most often results from a gene mutation that renders factor V resistant to degradation by aPC. This mutation is known as factor V Leiden, named after Leiden, Holland, where the defect was first described.[15]

The prothrombin G20210A mutation is the second most frequent inherited hypercoagulability disorder, occurring in about 2.0% to 4.0% of Caucasians and imparting about a threefold increased VTE risk.[15] This mutation increases circulating prothrombin, and enhanced thrombin generation has been observed, but the mechanism whereby this disorder increases VTE risk is not completely understood.[11] The prevalence of factor V Leiden and prothrombin G20210A mutation in the general population results in some patients inheriting multiple genetic defects greatly increasing the lifetime VTE risk.[15]

Although accurate VTE risk estimates associated with inherited protein C, protein S, and antithrombin deficiencies (present in <1% of the population) are not known, many experts believe the lifetime risk is high, perhaps sevenfold higher than patients without such disorders. Many patients with protein C, protein S, or antithrombin deficiency suffer VTE prior to age 60.[11]

Acquired disorders of hypercoagulability may result from malignancy, the presence of antiphospholipid antibodies, or estrogen use. A strong link between cancer and thrombosis has long been recognized.[17] Tumor cells secrete procoagulant substances that activate the coagulation cascade, and patients with cancer often have suppressed protein C, protein S, and antithrombin levels. Cancer cells use thrombotic mechanisms to recruit a blood supply, metastasize, and create barriers against host defense mechanisms.[17]

Antiphospholipid antibodies are a heterogeneous group of antibodies targeting proteins that bind phospholipids.[11] These include antibodies that prolong phospholipid-based clotting assays, known as lupus anticoagulants, as well as anticardiolipin and β_2-glycoprotein (β_2-gp) I antibodies.

Antiphospholipid antibodies are found in up to 5% of normal healthy populations but are more common in patients with autoimmune disorders such as systemic lupus erythematosus and inflammatory bowel disease. The precise mechanism by which antiphospholipid antibodies provoke thrombosis remains to be definitively determined. Contributing factors include complement activation, protein C and fibrinolysis inhibition, platelet activation, and increased TF expression.[11]

CLINICAL PRESENTATION (INCLUDING DIAGNOSTIC CONSIDERATIONS)

2 The symptoms of DVT or PE are nonspecific and objective tests are required to confirm or exclude the diagnosis. Patients with DVT frequently present with unilateral leg pain and swelling. Postthrombotic syndrome, a long-term complication of DVT caused by damage to the venous valves, may also result in chronic lower extremity swelling, pain, tenderness, skin discoloration, and, in the most severe cases, ulceration. PE typically presents with chest pain, shortness of breath, tachypnea, and tachycardia, which in some cases may result in cardiopulmonary collapse.[5,18]

Given that VTE can be debilitating or fatal, it is important to treat quickly and aggressively. Conversely, because major bleeding induced by anticoagulant drugs can be equally harmful, it is important to avoid treatment when the diagnosis is not a reasonable certainty. Assessment of the patient's status should focus on the search for risk factors in the patient's medical history (Table 37-1). Even in the presence of mild, seemingly inconsequential symptoms, VTE should be strongly suspected in those with multiple risk factors.[18]

Clinical assessment significantly improves the diagnostic accuracy of noninvasive tests such as compression ultrasound (CUS), computed tomography pulmonary angiography (CTPA), and D-dimer. Simple clinical assessment checklists such as the Wells score can be used to determine if a patient is "likely" or "unlikely" to have DVT or PE (**Figs. 37-6** and **37-7**).[19] Patients with a likely probability of VTE have >60% chance of VTE, compared with <10% chance for patients with an unlikely probability.[20] In general, patients with an unlikely probability of VTE should first have their D-dimer tested. If the D-dimer result is below the defined cutoff point, VTE is ruled out; if above the cutoff point, the patient should have appropriate diagnostic imaging (either CUS for suspected DVT or CTPA for suspected PE).

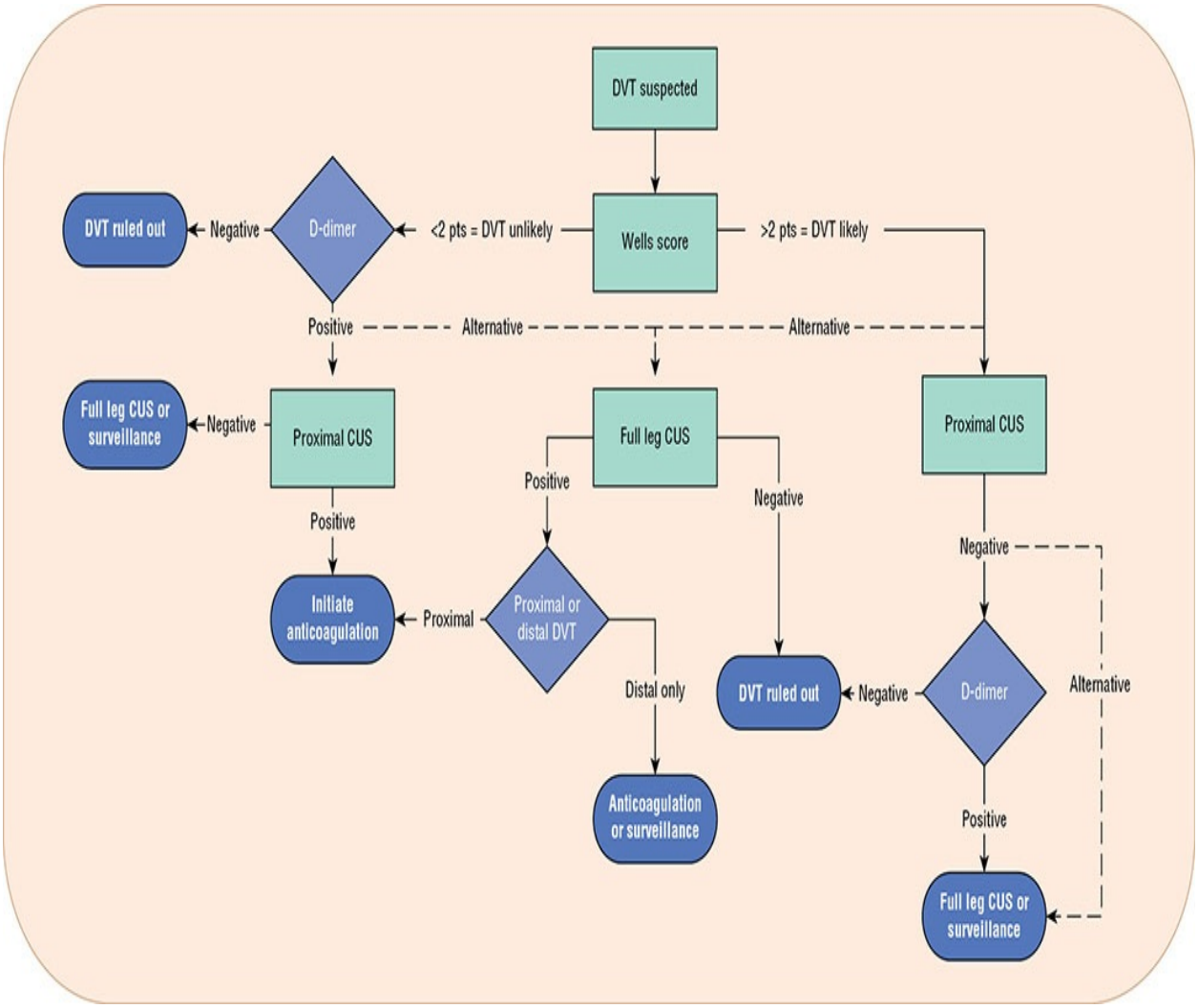


FIGURE 37-6 Deep vein thrombosis diagnostic algorithm. (CUS, compression ultrasound; DVT, deep vein thrombosis; Surveillance, follow-up CUS in 7-14 days to assess for proximal DVT; Wells score: 1 pt each for: active cancer, paralysis or recent plaster cast, immobilization >3 days or surgery in previous 12 weeks, tenderness along the venous system, entire leg swollen, calf swelling >3 cm, pitting edema, collateral superficial veins, history of DVT. Alternate diagnosis as likely as DVT, subtract 2 pts.) (*Data from References* 19, 20 *and* 22.)

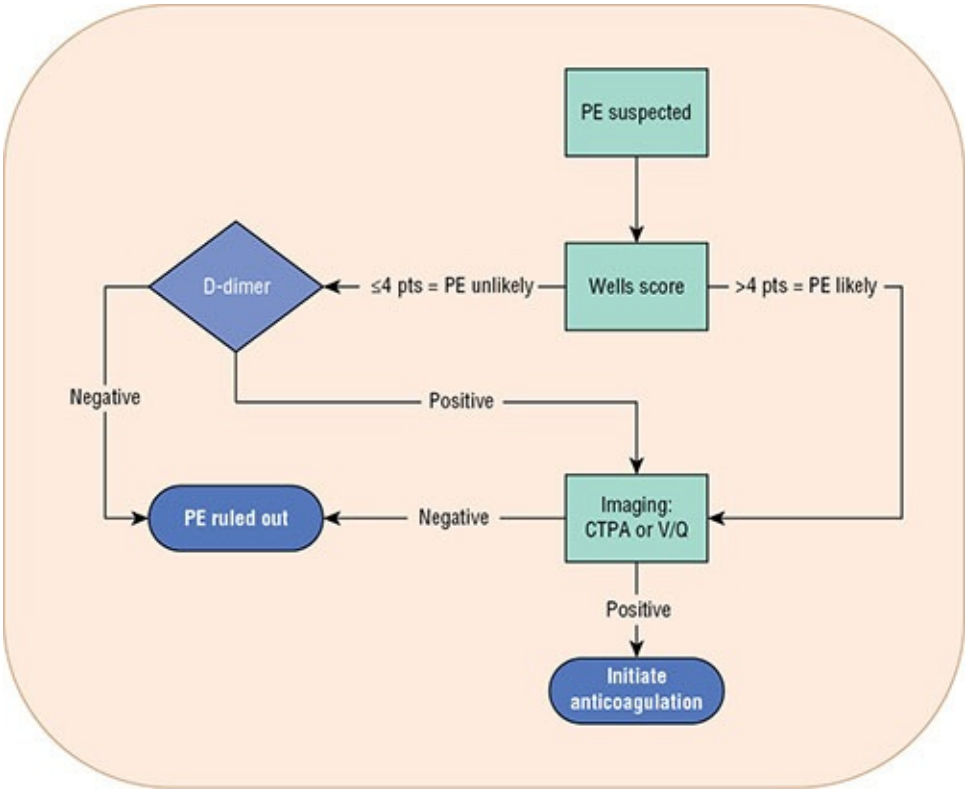


FIGURE 37-7 Pulmonary embolism diagnostic algorithm. (CTPA, computed tomography pulmonary angiograph; PE, pulmonary embolism; V/Q, ventilation/perfusion scanning; Simplified Wells PE Score, signs/symptoms of DVT, alternative diagnosis less likely than PE [3 pts each], HR >100 bpm, immobile >3 days in past 4 weeks, history of DVT/PE [1.5 pts each], hemoptysis or malignancy [1 pt each].) (*Data from References* 18 *and* 23.)

D-dimer is a fibrin clot degradation product and levels are significantly elevated in patients with acute thrombosis. Although D-dimer is a very sensitive marker of clot formation, it is not sufficiently specific. A variety of conditions are associated with D-dimer elevations, including recent surgery or trauma, pregnancy, advanced age, and cancer; therefore, a positive D-dimer test is not conclusive evidence of VTE diagnosis. However, a *negative* D-dimer, for most assays defined as <500 ng/mL (mcg/L), can be useful in ruling out the diagnosis of VTE.[20] Two strategies to improve the utility of D-dimer include (1) adjusting the threshold for a negative result for advanced age and (2) using clinical probability scores for VTE.

Advanced age is known to elevate D-dimer levels, and a proposed strategy involves multiplying patient age by 10 to obtain an age-adjusted D-dimer threshold (eg, an 80-year-old patient's D-dimer threshold would be 800 ng/mL (mcg/L), meaning a result less than 800 ng/mL (mcg/L) reasonably excludes

VTE). A second proposed strategy involves using a higher threshold (1000 ng/mL [mcg/L]) for patients with low clinical probability of VTE, and standard threshold (500 ng/mL [mcg/L]) for those with moderate clinical probability. A retrospective comparison of the two methods found the clinical-probability adjusted strategy performed better at ruling out VTE, but larger prospective studies need to be performed before a recommendation can be made about the optimal strategy for D-dimer interpretation.[21] Appropriate use of D-dimer should include initial risk stratification using a validated clinical assessment tool.[20]

Radiographic contrast studies (venography and pulmonary angiography) are the most accurate VTE diagnostic methods, but are expensive invasive procedures technically difficult to perform and evaluate. Severely ill patients are often unable to tolerate these procedures, and many develop hypotension and cardiac arrhythmias. The contrast medium is also nephrotoxic and irritating to vessel walls which may paradoxically precipitate VTE.[19] For these reasons, less invasive tests, such as CUS (either full leg or proximal segments only) and CTPA are most commonly used in clinical practice for the initial evaluation of patients with suspected VTE. In patients with allergy to contrast media, renal impairment, or high radiation exposure risk, the ventilation–perfusion (V/Q) scan is an alternative PE diagnostic test.[20]

All patients with a likely probability of DVT should receive either proximal (popliteal, femoral, and iliac veins) or full leg CUS. A normal full leg ultrasound rules out DVT, whereas a normal proximal ultrasound requires additional testing with D-dimer, full leg ultrasound, or repeat proximal ultrasound surveillance in 1 week. Patients with CUS indicating proximal DVT should receive anticoagulant treatment. Evidence of distal vein DVT (anterior and posterior tibial, peroneal, gastrocnemius veins) after full leg ultrasound may be treated with anticoagulants or have repeated ultrasound surveillance to assess for propagation into the proximal deep veins of the leg (Fig. 37-6). Patients with a likely probability of PE should receive imaging with either CTPA or V/Q scan. A negative imaging result rules out PE, whereas a positive imaging result indicates need for anticoagulant treatment (Fig. 37-7).[18–20]

CLINICAL PRESENTATION

Deep Vein Thrombosis

General

DVT most commonly develops in patients with identifiable risk factors (see Table 37-1). Some may have asymptomatic disease.

Symptoms

The patient may complain of leg swelling, pain, or warmth. Symptoms are nonspecific and objective testing must be performed to establish the diagnosis

Signs

The patient's superficial veins may be dilated and a "palpable cord" may be felt in the affected leg. The patient may experience pain in back of the knee when the examiner dorsiflexes the foot of the affected leg (Homan's sign).

Laboratory tests

Serum concentration of D-dimer, a by-product of fibrin degradation, is nearly always elevated. D-dimer values <500 ng/mL (mcg/L) combined with clinical decision rules are useful in ruling out the diagnosis of DVT.

Diagnostic tests

Compression ultrasound is the most commonly used test to diagnose DVT. It is a noninvasive test that can visualize clot formation in veins of the legs. It cannot reliably detect small blood clots in calf veins. Coupled with a careful clinical assessment, it can rule in or out the diagnosis in the majority of cases Venography is the gold standard for the diagnosis of DVT. However, it is an invasive test that involves injection of radiopaque contrast dye into a foot vein. It is expensive and can cause anaphylaxis and nephrotoxicity.

CLINICAL PRESENTATION

Pulmonary Embolism

General

Pulmonary embolism (PE) most commonly develops in patients with risk factors for venous thromboembolism (see Table 37-1) during or following a hospitalization. Although many patients develop a symptomatic deep vein thrombosis prior to developing a PE, some do not. Patients may die suddenly from cardiogenic shock and circulatory collapse before effective treatment can be initiated.

Symptoms

The patient may complain of cough, chest pain, chest tightness, shortness of breath, or palpitation. The patient may spit or cough up blood (hemoptysis). When PE is massive, the patient may complain of dizziness or light-headedness. Symptoms may be confused with myocardial infarction, requiring objective testing to establish the diagnosis.

Signs

The patient may have tachypnea, tachycardia, and appear diaphoretic. The patient's neck veins may be distended. In massive PE, the patient may appear cyanotic and become hypotensive. In such cases, oxygen saturation by pulse oximetry or arterial blood gas will likely indicate that the patient is hypoxic. In the worse cases, the patient may go into cardiogenic shock and die within minutes.

Laboratory tests

Serum concentration of D-dimer, a by-product of fibrin degradation, is nearly always elevated. D-dimer values <500 ng/mL (mcg/L) combined with clinical decision rules are useful in ruling out the diagnosis of PE.

Diagnostic tests

Computerized tomography pulmonary angiography (CTPA) is the most commonly used test to diagnose PE, but some centers still use the ventilation–perfusion (V/Q) scan. A V/Q scan measures the distribution of blood and airflow in the lungs. When there is a large mismatch between blood and airflow in one area of the lung, there is a high probability that the patient has a PE.

Pulmonary angiography is the gold standard for the diagnosis of PE. However, it is an invasive test that involves injection of radiopaque contrast dye into the pulmonary artery. The test is expensive and associated with a significant risk of mortality

PREVENTION AND TREATMENT

Unfortunately, there is little public awareness of the life-threatening nature of DVT and PE. A global survey conducted by the International Society of Thrombosis and Hemostasis suggests that half of patients surveyed have little or

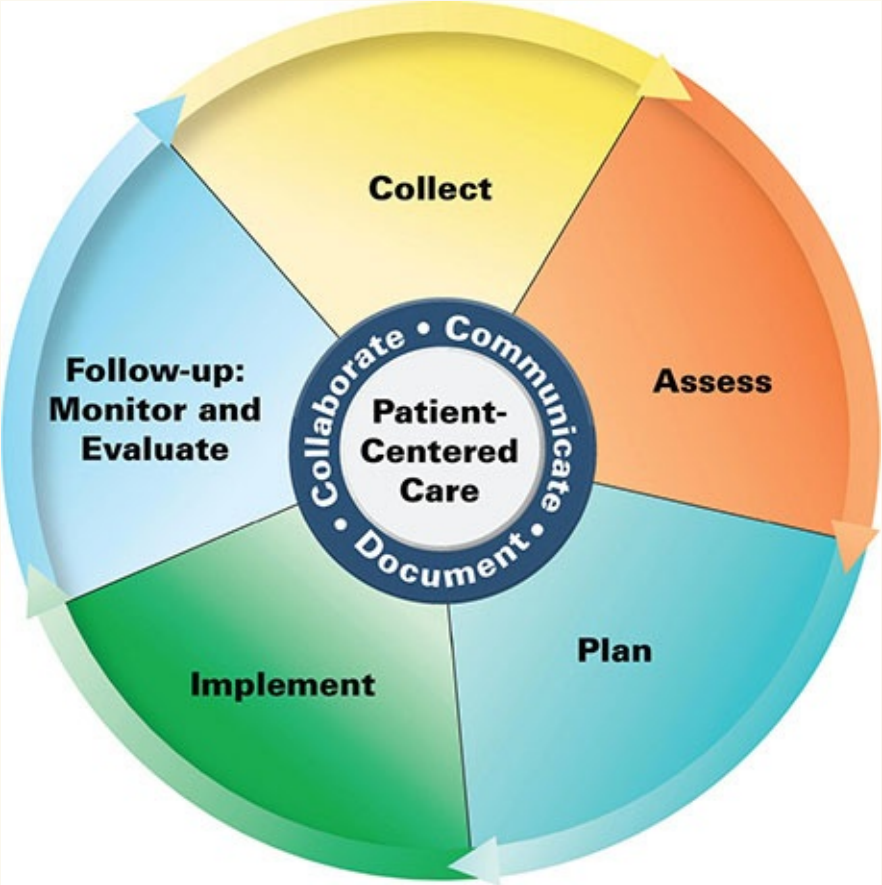
no awareness of VTE, and less than half of respondents could identify VTE risk factors.[24] VTE awareness was substantially lower than for other disease states like stroke, heart attack, and breast cancer, each of which have major public awareness campaigns. This underscores the need to increase knowledge of the risks, signs, and symptoms of VTE through increased media visibility.

Desired Outcomes

Prevention strategies in at-risk populations positively impact patient outcomes because VTE is potentially fatal and costly to treat.[25] Treatment of VTE is aimed at preventing thrombus extension and embolization, reducing recurrence risk, and preventing long-term complications such as the postthrombotic syndrome and CTPH. Carefully managed anticoagulant drug use is important to reduce the risk of bleeding associated with these agents.

General Approach to the Prevention of Venous Thromboembolism

Effective prophylaxis can reduce the risk of fatal PE in high-risk surgical and medical populations. Early ambulation is often sufficient for those at low risk of VTE.[26] Educational programs and clinical decision support systems have been shown to improve the appropriate use of VTE prevention methods.[27]



Patient Care Process for the Prevention of Venous Thromboembolism

Collect

- Patient characteristics (eg, age, sex, active cancer, pregnant)
- Patient history (past medical [eg, bleeding history], family, social—dietary habits including intake of vitamin K containing foods (see Table 37-13), tobacco/ethanol use)
- Current medications including aspirin/OTC NSAID use and prior anticoagulant medication use
- Objective data
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), O_2-saturation, height, weight
  - Labs (eg, Hgb, Scr, platelets, aPTT, PT)

Assess

- Presence of VTE risk factors (see Tables 37-1 and 37-2); consider using Padua Prediction Score for medical patients or the Caprini Score for surgery patients (excludes orthopedic surgery)
- Presence of active bleeding and/or bleeding risk factors (see Table 37-10)
- Presence of medications that increase VTE risk (eg, estrogen)
- Presence of contraindications to anticoagulation therapy
- Ability/willingness to self-inject LMWH/fondaparinux if extended parenteral therapy being considered
- Ability/willingness to pay for various anticoagulation therapy options if extended therapy being considered
- Ability/willingness to obtain appropriate laboratory monitoring if extended therapy being considered (eg, INR for warfarin)

Plan*

- Drug therapy regimen including specific anticoagulant(s), dose, route, frequency, and duration; (see Fig. 37-10, Tables 37-6 and 37-11)
- Monitoring parameters including efficacy (eg, INR results, signs and symptoms of VTE), safety (bleeding, platelet count [heparin]), and timing of assessments
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug therapy; see Table 37-5)
- Self-monitoring for VTE symptoms, occurrence of bleeding, when to seek emergency medical attention

Implement

- Ensure appropriate VTE prevention is initiated based on patient-specific VTE/bleeding risk
- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence if extended therapy being considered
- Schedule follow-up (eg, INR tests [warfarin], bleeding risk assessment, duration of therapy assessment)

Follow-up: Monitor and Evaluate

- Occurrence of VTE symptoms (eg, shortness of breath, chest pain, leg or arm swelling, redness, pain)
- Presence of adverse effects (eg, bleeding, GI upset [dabigatran], HIT [heparin])
- INR results (adjust warfarin dose as needed to keep within target range)
- Patient adherence to treatment plan if extended therapy
- Inquire whether the patient is ambulatory and/or weight-bearing (following orthopedic surgery)

* *Collaborate with patient, caregivers, and other healthcare professionals.*

3 Despite ongoing efforts to minimize hospital-acquired VTE, up to one-third of hospitalized patients at high VTE risk without contraindications to anticoagulant therapy still do not receive appropriate prophylaxis.[28] The American College of Chest Physicians' *Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: Evidence-Based Clinical Practice Guidelines* (AT9) as well as the United Kingdom's National Institute for Health and Care Excellence (NICE) Guidelines provide evidence-based recommendations for VTE prevention and treatment.[18] A summary of AT9 VTE prophylaxis recommendations can be found in **Table 37-2**. Pharmacologic and mechanical methods are effective for preventing VTE and can be used alone or in combination.[2–4]

TABLE 37-2 Guidelines for the Prevention of Venous Thromboembolism

Patients Admitted to Hospital for a Medical Illness[2]

For acutely ill hospitalized medical patients at increased risk of thrombosis, thromboprophylaxis with low-molecular-weight heparin (LMWH), low-dose unfractionated heparin (LDUH) twice or thrice daily, or fondaparinux is recommended (Grade 1B).[a] Betrixaban is also approved for this indication.

For acutely ill hospitalized medical patients at low risk of thrombosis, use of pharmacologic prophylaxis or mechanical prophylaxis is not recommended (Grade 1B).

For acutely ill hospitalized medical patients who are bleeding or at high risk for bleeding, anticoagulant thromboprophylaxis is not recommended (Grade 1B).

For acutely ill hospitalized medical patients at increased risk of thrombosis who are bleeding or at high risk for major bleeding, optimal use of mechanical thromboprophylaxis with graduated compression stockings or intermittent pneumatic compression (IPC) is suggested (Grade 2C). When bleeding risk decreases, and if venous thromboembolism (VTE) risk persists, substitution of pharmacologic thromboprophylaxis for mechanical thromboprophylaxis is suggested (Grade 2B).

For critically ill patients, thromboprophylaxis with LMWH or LDUH is suggested over no prophylaxis (Grade 2C).

For critically ill patients who are bleeding, or are at high risk for major bleeding, mechanical thromboprophylaxis with graduated compression stockings or IPC is suggested (Grade 2C). When bleeding risk decreases, substitution of pharmacologic thromboprophylaxis for mechanical thromboprophylaxis is suggested (Grade 2C).

In outpatients with cancer who have no additional risk factors for VTE, routine prophylaxis is not recommended with LMWH or LDUH (Grade 2B) or warfarin (Grade 1B).

Routine thromboprophylaxis is not recommended for chronically immobilized persons residing at home or at a nursing home (Grade 2C).

For long-distance travelers at increased risk of VTE (including previous VTE, recent surgery or trauma, active malignancy, pregnancy, estrogen use, advanced age, limited mobility, severe obesity, or known thrombophilia disorder), frequent ambulation, calf muscle exercise, sitting in an aisle seat or below-the-knee graduated compression stockings providing 15-30 mm Hg (2-4 kPa) pressure at the ankle are suggested (Grade 2C).

In persons with thrombophilia but no previous history of VTE, the long-term daily use of mechanical or pharmacologic thromboprophylaxis to prevent VTE is not recommended (Grade 1C).

Patients Undergoing a Surgical Procedure (Excluding Orthopedic Surgery)[3]

For general and abdominal–pelvic surgery patients at very low risk for VTE, no specific pharmacologic (Grade 1B) or mechanical (Grade 2C) prophylaxis other than early ambulation is recommended.

For patients at low risk of VTE after abdominal–pelvic surgery or cardiac surgery with an uncomplicated course, mechanical prophylaxis, preferably with IPC, over no prophylaxis is suggested (Grade 2C).

For patients at moderate VTE risk after general, abdominal–pelvic, or thoracic surgery, or cardiac surgery with a prolonged course not at high risk for major bleeding complications, LMWH or LDUH (Grade 2B), or mechanical prophylaxis, preferably with IPC (Grade 2C), is suggested over no prophylaxis.

For patients at moderate risk for VTE after general, abdominal–pelvic surgery, thoracic surgery, or cardiac surgery who are at high risk for major bleeding complications or those in whom the consequences of bleeding are thought to be particularly severe, mechanical prophylaxis, preferably with IPC, is suggested over no prophylaxis (Grade 2C).

For patients at high risk for VTE after general, abdominal–pelvic, and thoracic surgery who are not at high risk for major bleeding complications, pharmacologic prophylaxis with LMWH (Grade 1B) or LDUH (Grade 1B) is suggested over no prophylaxis. Combination with graduated compression stockings or IPC is also suggested (Grade 2C).

For high-VTE-risk general, abdominal–pelvic, and thoracic surgery patients who are at high risk for major bleeding complications or those in whom the consequences of bleeding are thought to be particularly severe, the use of mechanical prophylaxis, preferably with IPC, is suggested over no prophylaxis until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated (Grade 2C).

For high-VTE-risk patients undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk for major bleeding complications, extended-duration pharmacologic prophylaxis (4 weeks) with LMWH is recommended over shorter-duration prophylaxis (Grade 1B).

For general and abdominal–pelvic surgery patients at high risk for VTE in whom both LMWH and LDUH are contraindicated or unavailable and who are not at high risk for major bleeding complications, low-dose aspirin (Grade 2C), fondaparinux (Grade 2C), or mechanical prophylaxis, preferably with IPC (Grade 2C), is suggested over no prophylaxis.

For general and abdominal–pelvic surgery patients, an inferior vena cava (IVC) filter is not recommended for primary VTE prevention (Grade 2C).

Patients Undergoing an Orthopedic Surgery[4]

In patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA), use of one of the following for a minimum of 10-14 days is recommended: LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, LDUH, adjusted-dose warfarin, aspirin (all Grade 1B), or IPC (Grade 1C) Rivaroxaban for up to 5 days following surgery followed by aspirin 81 mg daily for 9 days (TKA) and 30 days (THA) is also an option.

In patients undergoing hip fracture surgery (HFS), use of one of the following is recommended: antithrombotic prophylaxis for a minimum of 10-14 days, LMWH, fondaparinux, LDUH, adjusted-dose warfarin, aspirin (all Grade 1B), or IPC (Grade 1C).

For patients undergoing major orthopedic surgery (THA, TKA, HFS) and receiving LMWH as thromboprophylaxis, starting either 12 hours or more preoperatively or 12 hours or more postoperatively is recommended over starting within 4 hours or less preoperatively or 4 hours or less postoperatively (Grade 1B).

In patients undergoing THA, TKA, or HFS, irrespective of the concomitant use of IPC or length of treatment, the use of LMWH is suggested over other recommended alternatives, including fondaparinux, apixaban, dabigatran, rivaroxaban, LDUH (all Grade 2B), adjusted-dose warfarin, or aspirin (all Grade 2C).

For patients undergoing major orthopedic surgery, extending thromboprophylaxis in the outpatient period for up to 35 days from the day of surgery is suggested (Grade 2B).

In patients undergoing major orthopedic surgery, dual prophylaxis with an antithrombotic agent and IPC is suggested during the hospital stay (Grade 2C).

In patients undergoing major orthopedic surgery who decline injections or IPC, apixaban or dabigatran (alternatively rivaroxaban or adjusted-dose warfarin) is recommended over alternative forms of prophylaxis (all Grade 1B).

For primary prevention of VTE after major orthopedic surgery, no thromboprophylaxis is suggested over placement of an IVC filter in patients with an increased bleeding risk or contraindications to both pharmacologic and mechanical thromboprophylaxis (Grade 2C).

The use of screening compression ultrasound in asymptomatic patients following major orthopedic surgery is not recommended (Grade 1B).

No prophylaxis is suggested rather than pharmacologic thromboprophylaxis in patients with isolated lower leg injuries requiring leg immobilization (Grade 2C).

For patients undergoing knee arthroscopy without a history of prior VTE, no thromboprophylaxis is suggested (Grade 2B).

[a]Recommendations are graded as strong (Grade 1) or weak (Grade 2) based on high-quality (Grade A), moderate-quality (Grade B), or weak-quality (Grade C) evidence.

Nonpharmacologic Therapy

Compression stockings and intermittent pneumatic compression (IPC) devices prevent VTE by increasing the velocity of venous blood flow through graded pressure application. IPC devices utilize a series of cuffs wrapped around the patient's legs that inflate in continuous 1- to 2-minute cycles from the ankles to the knees or thighs. IPC devices should be worn at least 18 hr/day for optimal effectiveness.

Graduated compression stockings do not reliably reduce VTE in medically ill patients.[2] However, they reduce the incidence of VTE (including asymptomatic and distal DVT) by approximately 65% when used after orthopedic surgery, cardiac surgery, gynecologic surgery, or neurosurgery.[3] IPC reduces the risk of VTE by more than 60% following general surgery, neurosurgery, and orthopedic surgery.[3] Both modalities can be used in combination with anticoagulation to maximize VTE prevention.[29]

Mechanical methods do not increase bleeding risk, which makes them attractive for postoperative VTE prophylaxis, especially in patients with contraindications to pharmacologic therapies. However, they are not risk-free, as discomfort, skin breakdown, and ulceration can occur.[2]

Inferior vena cava (IVC) filters can provide short-term protection against PE in very high-risk patients by blocking embolization of thrombus formed below the filter.[30] Percutaneous insertion of an IVC filter is a minimally invasive procedure performed using fluoroscopic imaging to verify placement. Limited nonrandomized data support the effectiveness and long-term safety of IVC filters for PE prevention. Frequently "retrievable" IVC filters are never retrieved, increasing risk for long-term complications such as DVT, filter migration, IVC occlusion, and insertion site thrombosis.[3] As such, IVC filters should be reserved for patients at highest VTE risk in whom other prophylactic strategies cannot be used. IVC filters should be removed when VTE risk has passed or when anticoagulation is no longer contraindicated.[30]

Pharmacologic Therapy

Pharmacologic options for preventing VTE have been extensively evaluated in randomized clinical trials and significantly reduce the risk of VTE following hip and knee replacement, hip fracture repair, general surgery, myocardial infarction, ischemic stroke, and in selected hospitalized medical patients.[2–4] The optimal

agent and dose for VTE prevention must be based on an assessment of VTE and bleeding risk, as well as cost and availability.

Medical Patients

Several risk assessment models have been developed to identify hospitalized and critically ill patients at high VTE risk likely to benefit from thromboprophylaxis. The Padua Prediction Score is a prospectively validated VTE risk assessment tool for hospitalized medical patients.[2] Three points each are assigned for active cancer, previous VTE, reduced mobility, and thrombophilia; 2 points are assigned for trauma and/or surgery within the last month; and 1 point each is assigned for age ≥70 years, heart and/or respiratory failure, acute myocardial infarction or ischemic stroke, acute infection and/or rheumatologic disorder, body mass index ≥30 kg/m^2, or ongoing hormonal treatment. Among high-risk patients (score ≥4 points) not receiving prophylaxis, VTE occurred in 11.0% within 90 days compared with just 0.3% of low-risk patients.[2]

Recommendations for preventing VTE during medical illness are summarized in Table 37-2. Compared with placebo, low-dose unfractionated heparin (LDUH), low-molecular-weight heparin (LMWH), and fondaparinux all reduce symptomatic VTE and fatal PE among high-risk medical patients.[2] Betrixaban is the only DOAC-approved for extended prophylaxis in acutely ill medical patients at high risk of VTE.[31] Hospitalized and acutely ill medical patients at high VTE risk and low bleeding risk should receive pharmacologic prophylaxis with LDUH, LMWH, fondaparinux, or betrixaban during hospitalization or until fully ambulatory. Routine pharmacologic prophylaxis is not warranted in low-VTE-risk medical patients. Mechanical prophylaxis is preferred over anticoagulation therapy in medical patients at high bleeding risk (eg, active gastric or duodenal ulcer, history of bleeding within 90 days, or platelet count <50 × 10^9/L).[2] Mechanical prophylaxis should also be considered if more than one of the following are present: Age 85 years or more, hepatic failure, renal failure (creatinine clearance [CrCL] <30 mL/min [0.5 mL/s]), admission to intensive care or cardiac care units, central venous catheter, rheumatic disease, active cancer, or male sex.[2] Patients with severe hepatic insufficiency are not adequately protected from VTE even if baseline INR is elevated. This population is particularly challenging as they are at risk for VTE without prophylaxis and bleeding with pharmacologic prophylaxis.[32,33]

Surgical Patients

General recommendations for reducing perioperative VTE risk include using regional, rather than general anesthesia, whenever possible.[18] The Caprini score can be used to estimate VTE risk after general surgery. The Caprini score awards points for patient-specific risk factors (eg, age, body mass index, VTE history) and procedure-related risk factors including minor or major surgery, laparoscopic or open procedures, and elective arthroplasty. Summing risk factor points yields VTE risk categorized as very low (0-1 point), low (2 points), moderate (3-4 points), or high (≥5 points).[3] Estimating surgical bleeding risk is challenging due to the wide variety of surgery types, the effect of surgical technique, and the lack of a validated bleeding predication rule. Table 37-2 summarizes the AT9 recommendation for preventing VTE following nonorthopedic surgery. In general, patients at high VTE risk but low bleeding risk should receive LDUH or LMWH prophylaxis in addition to graduated compression stockings or IPC. Patients at high bleeding risk should receive IPC if VTE risk is moderate or high. Low risk patients able to ambulate early after surgery do not routinely require VTE prophylaxis.[3]

Total joint arthroplasty is associated with very high postoperative VTE risk.[4] Recommended pharmacologic agents for VTE prevention following joint replacement surgery include aspirin, adjusted-dose warfarin, low-dose UFH, LMWH, fondaparinux, dabigatran, apixaban, and rivaroxaban for a minimum of 10 days postsurgery.[4] Head-to-head trials fail to reliably demonstrate differences in clinically relevant outcomes such as symptomatic VTE, fatal PE, major hemorrhage, and surgical site complications between agents.[4]

AT9 suggests using LMWHs preferentially over other agents after total joint arthroplasty based on favorable pharmacologic properties and extensive clinical use.[4] One consideration in the use of LMWH is bleeding risk as it relates to the timing of thromboprophylaxis initiation. LMWH administration within 2 hours preoperatively or postoperatively increases bleeding risk by as much as fivefold compared with starting 12 hours after surgery.[4]

Warfarin remains a commonly prescribed agent for VTE prevention after total joint arthroplasty due to low acquisition cost and oral administration.[34] AT9 recommends “dose-adjusted warfarin” without specific guidance on target INR and American Academy of Orthopaedic Surgery guidelines also no longer recommend a specific INR target.[4,35]

DOACs offer convenient oral administration and fixed dosing without need for routine coagulation testing. The safety and efficacy of DOACs are similar to enoxaparin after total joint replacement, but studies after hip fracture surgery are

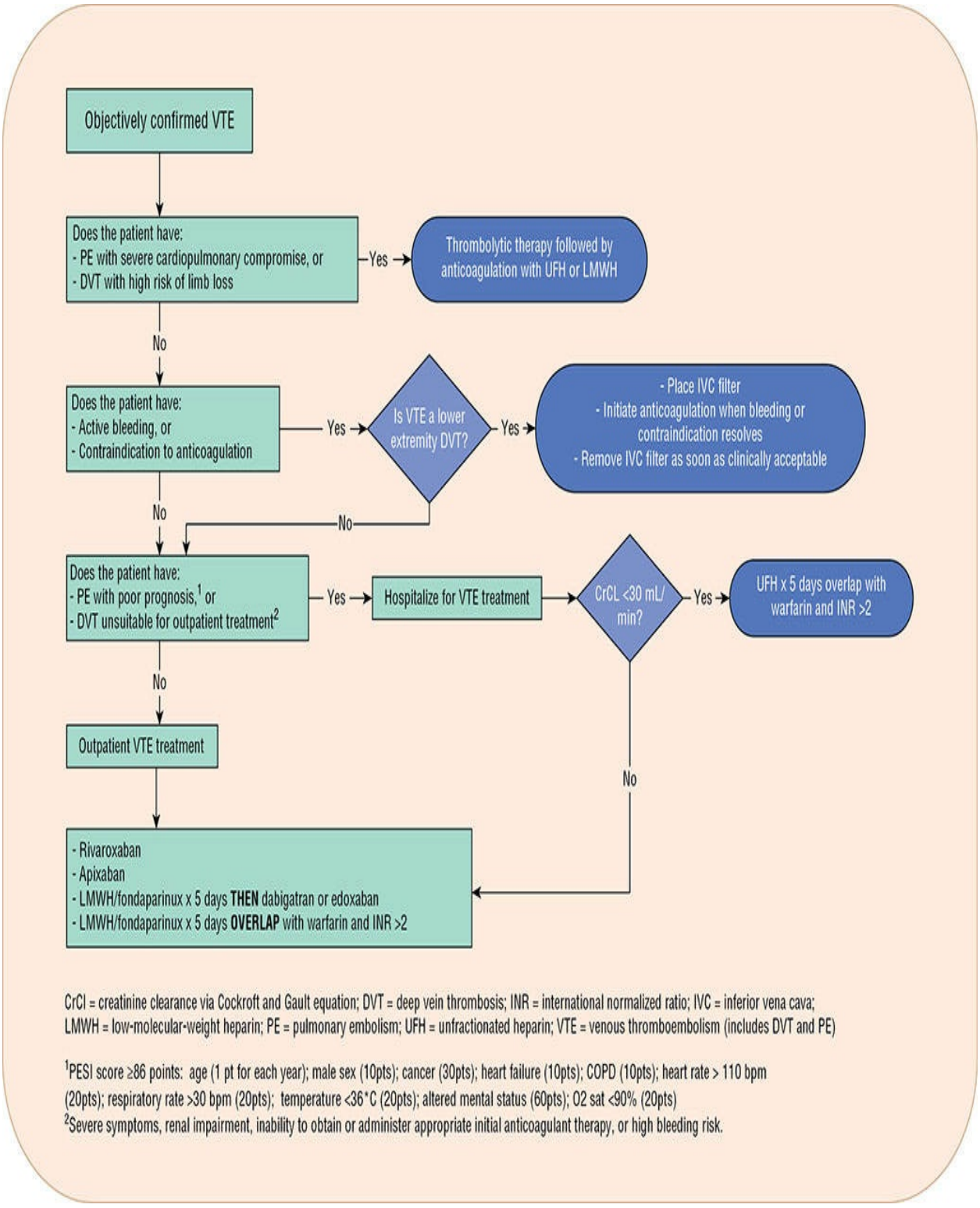
lacking.[4] AT9 expresses a preference for apixaban, dabigatran, or warfarin in patients unwilling to use LMWH injections.[4] Another option is a short course (eg, 5 days) of DOAC therapy followed by aspirin.[36] This approach may optimally balance the use of an anticoagulant to prevent early postoperative thrombosis when the risk is highest, and a low-cost oral option (aspirin) that can be easily administered after hospital discharge. In addition, it avoids the inconvenience of subcutaneous injections.

Duration of Therapy

Optimal VTE prophylaxis duration following surgery is not well established. Prophylaxis should be given throughout the period of increased VTE risk. For general surgical procedures once patients are able to ambulate regularly and other risk factors are no longer present, prophylaxis can be discontinued.[2,3] Because of relatively high VTE incidence in the month following hospital discharge among patients undergoing lower extremity orthopedic procedures, extended prophylaxis appears to be beneficial.[4] Most clinical trials support the use of antithrombotic prophylaxis for 15 to 42 days following total knee or hip replacement surgery.[4]

General Approach to the Treatment of Venous Thromboembolism

Anticoagulation therapies remain the mainstay of VTE treatment. DVT and PE are manifestations of the same disease process and are treated similarly (**Figs. 37-8** and **37-9**, **Table 37-3**). Before prescribing anticoagulation therapy for VTE treatment, establishing an accurate diagnosis is imperative to prevent unnecessary bleeding risk and expense to the patient.[5] Patients with a likely VTE probability may need rapid-onset anticoagulation therapy while awaiting diagnostic testing results, whereas patients with unlikely probability but positive D-dimer may need rapid-onset anticoagulation only if diagnostic testing will be delayed more than 4 hours.[18]



CrCl = creatinine clearance via Cockroft and Gault equation; DVT = deep vein thrombosis; INR = international normalized ratio; IVC = inferior vena cava; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; UFH = unfractionated heparin; VTE = venous thromboembolism (includes DVT and PE)

[1]PESI score ≥86 points: age (1 pt for each year); male sex (10pts); cancer (30pts); heart failure (10pts); COPD (10pts); heart rate > 110 bpm (20pts); respiratory rate >30 bpm (20pts); temperature <36°C (20pts); altered mental status (60pts); O2 sat <90% (20pts)

[2]Severe symptoms, renal impairment, inability to obtain or administer appropriate initial anticoagulant therapy, or high bleeding risk.

FIGURE 37-8 Decision algorithm: Acute treatment of VTE. (CrCl, creatinine clearance via Cockroft and Gault equation; DVT, deep vein thrombosis; INR, international normalized ratio; IVC, inferior vena cava; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; UFH, unfractionated heparin; VTE,

venous thromboembolism [includes DVT and PE].) (*Adapted from ref Wells, et al.*[37] *and Meyer et al.*[39])

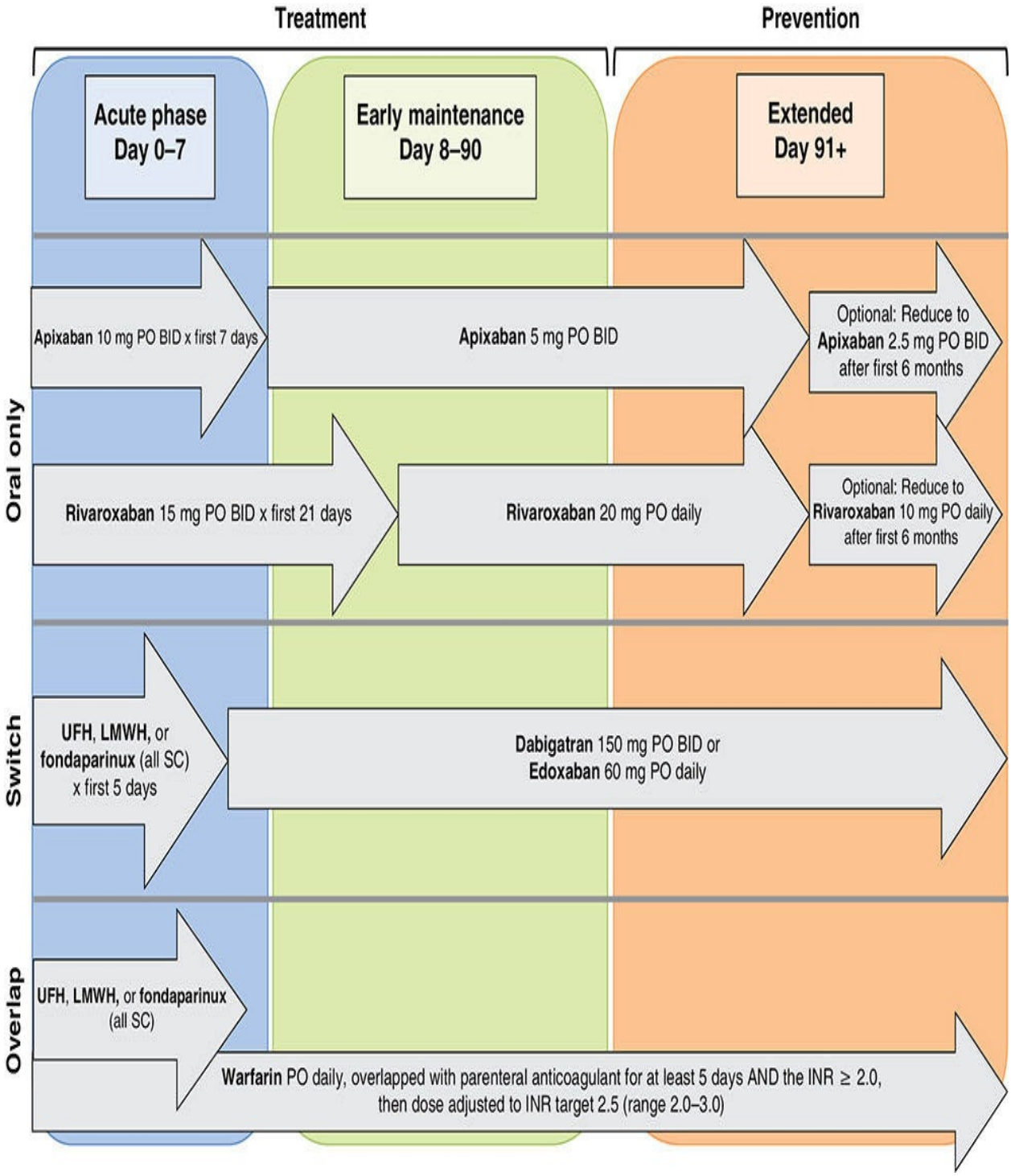


FIGURE 37-9 Overview of VTE treatment strategies: Acute, early maintenance, and extended treatment phases.

TABLE 37-3 Guidelines for the Treatment of Venous Thromboembolism

Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE)

In patients with acute DVT of the leg or PE, a DOAC (dabigatran, rivaroxaban, apixaban, or edoxaban) is suggested over warfarin therapy (Grade 2B).[a]
In patients with acute DVT of the leg or PE treated with warfarin therapy, initial treatment with LMWH, fondaparinux, IV UFH, or SC UFH is recommended (Grade 1B).
In patients with acute DVT of the leg or PE, early initiation of warfarin (eg, same day as parenteral therapy is started) over delayed initiation, and continuation of parenteral anticoagulation for a minimum of 5 days and until the international normalized ratio (INR) is 2 or above for at least 24 hours are recommended (Grade 1B).
In patients with acute DVT of the leg or PE, LMWH or fondaparinux is suggested over IV UFH (Grade 2C [2B for fondaparinux in PE]) and over SC UFH (Grade 2B for LMWH; Grade 2C for fondaparinux).
In patients with proximal DVT of the leg or PE provoked by surgery, treatment with anticoagulation for 3 months is recommended over treatment of a shorter period (Grade 1B), treatment of a longer time-limited period (eg, 6 or 12 months) (Grade 1B), or extended therapy (Grade 1B regardless of bleeding risk).
In patients with proximal DVT of the leg or PE provoked by a nonsurgical transient risk factor, treatment with anticoagulation for 3 months is recommended over treatment of a shorter period (Grade 1B), treatment of a longer time-limited period (eg, 6 or 12 months) (Grade 1B), and extended therapy if there is a high bleeding risk (Grade 1B); anticoagulation for 3 months is suggested over extended therapy if there is a low or moderate bleeding risk (Grade 2B).
In patients with a first unprovoked DVT of the leg or PE, treatment with anticoagulation for at least 3 months is recommended over treatment of a shorter duration (Grade 1B); after 3 months of treatment, the risk-to-benefit ratio of extended therapy should be evaluated; for patients with low or moderate bleeding risk, extended anticoagulant therapy is suggested over 3 months of therapy (Grade 2B); for patients with high bleeding risk, 3 months of anticoagulant therapy is recommended over extended therapy (Grade 1B).
In patients with recurrent unprovoked VTE, extended anticoagulant therapy is recommended over 3 months of therapy in those with low bleeding risk (Grade 1B), and suggested in those with moderate bleeding risk (Grade 2B); in patients with high bleeding risk, 3 months of therapy is suggested over extended therapy (Grade 2B).
In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).
In patients with DVT of the leg or PE who are treated with warfarin, a therapeutic INR range of 2-3 (target INR of 2.5) is recommended for all treatment durations (Grade 1B).
In patients with DVT of the leg or PE and no cancer and not treated with a DOAC, warfarin therapy is suggested over LMWH for long-term therapy (Grade 2C).
In patients with DVT of the leg or PE and cancer, LMWH or a DOAC is suggested over warfarin therapy (DOACs should be used with caution in patients with cancer of the gastrointestinal tract).
In patients with DVT of the leg or PE who receive extended therapy, there is no need to change the choice of anticoagulant after the first 3 months unless patient circumstances dictate a change in therapy (Grade 2C).
In patients with acute DVT of the leg or PE, the use of an inferior vena cava (IVC) filter in addition to anticoagulants is not recommended (Grade 1B) unless anticoagulation therapy is contraindicated (Grade 1B); a conventional course of anticoagulant therapy is suggested if the risk of bleeding resolves (Grade 2B).
In patients who are incidentally found to have asymptomatic DVT of the leg or PE, the same initial and long-term anticoagulation as for comparable patients with symptomatic DVT of PE is suggested (Grade 2B).
In patients with unprovoked proximal DVT of the leg or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, aspirin is suggested over no aspirin to prevent recurrent VTE (Grade 2C).
In patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a low risk for recurrent VTE, clinical surveillance is suggested over anticoagulation (Grade 2C); if high risk for recurrent VTE anticoagulation is suggested over clinical surveillance (Grade 2C).
In patients with recurrent VTE while on warfarin therapy (in the therapeutic range) or on DOAC (and believed to be compliant), switching to treatment with LMWH at least temporarily is suggested (Grade 2C).
In patients who have recurrent VTE while on long-term LMWH (and are believed to be compliant), increasing the LMWH dose by about one-quarter to one-third is suggested (Grade 2C).

DVT Specific

In patients with acute DVT of the leg and whose home circumstances are adequate, initial treatment at home is recommended over treatment in hospital (Grade 1B).
In patients with acute DVT of the leg, early ambulation is suggested over initial bed rest (Grade 2C).
In patients with acute proximal DVT of the leg, anticoagulant therapy alone is suggested over catheter-directed thrombolysis (Grade 2C).
In patients with acute symptomatic DVT of the leg, the routine use of graduated compression stockings for the purpose of preventing postthrombotic syndrome is not suggested (Grade 2B).

PE Specific

In patients with low-risk PE and whose home circumstances are adequate, treatment at home or early discharge is suggested over standard discharge (eg, after first 5 days of treatment) (Grade 2B).
In patients with acute PE associated with hypotension (eg, systolic BP < 90 mm Hg) who do not have a high bleeding risk, systemically administered thrombolytic therapy is suggested (Grade 2B).
In most patients with acute PE not associated with hypotension, systemically administered thrombolytic therapy is not recommended (Grade 1B).
In selected patients with acute PE who deteriorate after starting anticoagulant therapy but have yet to develop hypotension and who have a low bleeding risk, systemically administered thrombolytic therapy is suggested over no therapy (Grade 2C).
In patients with acute PE who are treated with a thrombolytic agent, systemically administered thrombolytic therapy is suggested over catheter directed thrombolysis (Grade 2C); when a thrombolytic agent is used, short infusion times (eg, a 2-hour infusion) are suggested over prolonged infusion times (eg, a 24-hour infusion) (Grade 2C); thrombolytic administration through a peripheral vein is suggested over a pulmonary artery catheter (Grade 2C).
In patients with acute PE associated with hypotension and who have high bleeding risk, failed systemic thrombolysis, or shock that is likely to cause death before systemic thrombolysis can take effect (eg, within hours), catheter-assisted thrombus removal is suggested over no such intervention if appropriate expertise and resources are available (Grade 2C).
In patients with chronic thromboembolic pulmonary hypertension (CTPH), extended anticoagulation is recommended over stopping therapy (Grade 1B); in selected patients with CTPH who are identified by an experienced thromboendarterectomy team, pulmonary thromboendarterectomy is suggested (Grade 2C).

Upper Extremity DVT

In patients with acute upper extremity DVT (UEDVT) involving the axillary or more proximal veins, acute treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH) is recommended over no such acute treatment (Grade 1B); LMWH or fondaparinux is suggested over IV UFH (Grade 2C) and over SC UFH (Grade 2B); anticoagulant therapy alone is suggested over thrombolysis (Grade 2C).
In patients with UEDVT who undergo thrombolysis, the same intensity and duration of anticoagulant therapy as in similar patients who do not undergo thrombolysis is recommended (Grade 1B).
In most patients with UEDVT associated with a central venous catheter, not removing the catheter is suggested if it is functional and there is an ongoing need for the catheter (Grade 2C).
In patients with UEDVT involving the axillary or more proximal veins, a minimum duration of anticoagulation of 3 months is suggested over a shorter period (Grade 2B); in patients who have UEDVT that is not associated with a central venous catheter or with cancer, 3 months of anticoagulation is recommended over a longer duration of therapy (Grade 1B); in patients who have UEDVT that is associated with a central venous catheter that is not removed, anticoagulation that continues as long as the central venous catheter remains is recommended over stopping after 3 months of treatment in patients with cancer (Grade 1C), and is suggested in patients with no cancer (Grade 2C).[a]

[a]Recommendations are graded as strong (Grade 1) or weak (Grade 2) based on high-quality (Grade A), moderate-quality (Grade B), or weak-quality (Grade C) evidence.

Source: Data from Kearon et al.[5,33]

Strict bed rest was traditionally recommended following acute DVT based on the assumption that leg movement would dislodge the clot, resulting in PE. However, ambulation in conjunction with graduated compression stockings results in faster reduction of pain and swelling with no apparent increase in embolization rate. Patients should be encouraged to ambulate as much as symptoms permit. If ambulation increases pain and swelling, the patient should be instructed to lie down and elevate the affected leg until symptoms subside.

IVC filters have a limited role in the management of acute VTE and should only be used when anticoagulants are contraindicated due to active bleeding.[22] As soon as the bleeding resolves, patients should receive a conventional course of anticoagulant therapy and have the filter removed within 90 to 120 days of implantation.[5,18,30] In life- or limb-threatening circumstances, elimination of the obstructing thrombus may be warranted and the use of thrombolysis or thrombectomy considered.[5,37]

4 7 Once the diagnosis of VTE has been objectively confirmed (see details regarding Clinical Presentation and Diagnosis above), anticoagulant therapy with a rapid-acting anticoagulant should be instituted as soon as possible. Available anticoagulants can be administered in the outpatient setting in most patients with DVT and in carefully selected hemodynamically stable patients with PE. Given the predictable response and reduced need for laboratory monitoring with LMWH and DOACs, stable patients with DVT or PE who have normal vital signs, low bleeding risk, and no other uncontrolled comorbid conditions requiring hospitalization can be discharged early or treated entirely on an outpatient basis (**Table 37-4**).[38] Not all patients are appropriate candidates for outpatient VTE treatment. At a minimum, patients must be reliable or have adequate caregiver support and be willing and active participants in outpatient VTE management. Important patient education aspects for outpatient VTE treatment are summarized in **Table 37-5**. Hemodynamically unstable patients with PE should be admitted for anticoagulation therapy initiation. The decision to initiate outpatient therapy should be based on institutional resources and patient-specific variables.[37,39]

TABLE 37-4 Outpatient Treatment Suggestions for Deep Venous Thrombosis and Pulmonary Embolism

Inclusion: Patients with objectively diagnosed VTE
Relative exclusion: Patients who are hemodynamically unstable
Exclusion: Arterial thromboembolism or patients who are currently receiving dialysis, actively bleeding, have had recent (within 2 weeks) major surgery/trauma, or have other severe uncompensated comorbid conditions
Suggested procedure may vary depending on the patient's clinical condition
Confirm diagnosis of VTE by objective testing

Day 1

Baseline laboratory evaluation
- International normalized ratio (INR)—if use of warfarin anticipated
- Serum creatinine (SCr)
- Complete blood count (CBC) with platelets

Medication—see Fig. 37-9
Patient education
- Clinical pharmacy/nursing
  - Educate patient regarding the importance of proper monitoring of anticoagulation therapy (if applicable) and warning signs that should prompt additional medical evaluation; document activities in the medical record
  - If applicable, teach patient how to self-administer LMWH/fondaparinux (if patient or family member unwilling or unable to self-administer injection, visiting nurse services should be arranged or consider single oral anticoagulant approach); initial injection should be administered in the medical office or hospital
  - Instruct patient regarding local therapy: elevation of affected extremity, localized heat, anti-embolic exercises (flexion–extension of ankle for lower extremity VTE, or hand squeezing–relaxation for upper extremity VTE)
- Dispensing pharmacy
  - Reinforce patient education regarding indication, use, monitoring, side effects, and drug interactions with antithrombotic therapy
  - Screen patient's pharmacy profile for potential drug–drug interactions with anticoagulation therapy
  - Dispense anticoagulant therapy
  - Verify anticoagulation service enrollment

Days 3-4

Laboratory evaluation if on warfarin: check INR
Assess for symptoms of pulmonary embolism
Medications: continue anticoagulant medication(s) as directed
Anticoagulation service
- If on warfarin interpret results of INR and adjust dose of warfarin to achieve a target INR of 2.5
- Patient activity: continue reduced activity as long as pain persists (when possible, elevate extremity); increase activity as tolerated
- Document activities in medical record

Day 5

Laboratory evaluation if on warfarin: check INR
Assess for symptoms of pulmonary embolism
Medications: continue anticoagulant medication(s) as directed
Anticoagulation service
- If on warfarin interpret results of INR and adjust dose of warfarin to achieve a target INR of 2.5 (stop LMWH if INR $\geq$2.0)
- Patient activity: no restriction; if pain increases, contact primary care provider
- Document activities in medical record

Day 6 (Dabigatran or Edoxaban)

Medications: transition from parenteral to oral medication
Assess for symptoms of pulmonary embolism
Anticoagulation service
- Verify adherence, affordability, and tolerability of oral medication
- Patient activity: no restriction; if pain increases, contact primary care provider
- Review key education points (eg, keep in original container [dabigatran])
- Document activities in medical record

Day 8 (Apixaban)

Medications: Decrease apixaban dose
Anticoagulation service
- Patient activity: no restrictions; if pain increases contact primary care provider
- Verify adherence, affordability, and tolerability of oral medication
- Document activities in medical record

Day 22 (Rivaroxaban)

Medications: Decrease riaroxaban dose
Anticoagulation service
- Verify adherence, affordability, and tolerability of oral medication
- Patient activity: no restriction; if pain increases, contact primary care provider
- Review key education points (eg, take with food [rivaroxaban])
- Document activities in medical record

TABLE 37-5 Patient Education for Outpatient Venous Thromboembolism Therapy

General Information Regarding VTE and the Goals of Treatment

- Anticoagulant medications (injections and warfarin tablets, injections and dabigatran or edoxaban, or rivaroxaban or apixaban) have been prescribed to prevent your blood clot from growing larger so that the body can begin to dissolve the clot.
- Your body may be able to completely dissolve the clot, but in some cases the clot never goes completely away; even with adequate anticoagulation therapy, some people will have chronic pain and swelling in the affected limb; people who have had one clot are at increased risk of having future clots.
- Warfarin tablets take several days to begin to work, so at first LMWH or fondaparinux injections and warfarin tablets are used together.
- When the warfarin has become effective, you will be able to stop the LMWH or fondaparinux injections; you will continue to take warfarin tablets for 3 months or longer to prevent blood clots from returning.
- It is important for you to administer your LMWH or fondaparinux and warfarin exactly as directed.
- It is important not to use LMWH at the same time as dabigatran or edoxaban—first use LMWH then switch to dabigatran or edoxaban.

Subcutaneous Injection Technique (If Needed)

- You must learn to give yourself an injection of LMWH or fondaparinux under the skin; alternatively, you may have a family member or visiting nurse give it to you.
- If your LMWH or fondaparinux syringes were filled by the manufacturer, they can be stored at room temperature; if your syringes were filled by the pharmacy, they should be stored in the refrigerator; if you were instructed to fill your own syringes, you should prepare the syringe immediately prior to injecting its contents.
- If you see a bubble in the syringe, do not try to get it out; you may accidentally squirt out part of your dose.
- Choose an injection site on your abdomen; clean the area with alcohol, and then position an uncapped syringe at a 90° angle; pinch the skin, stick the needle in as far as it will go, and gently but firmly push the plunger down; this will inject the medicine into the skin; when all the medication has been injected, remove the needle and dispose of it in an appropriate container.
- You will likely experience a burning sensation when the medication is injected; this will go away after a few minutes.
- Rotate injection sites from side to side; do not inject into the same site more than once; avoid the area around your navel; do not inject into any bruises.

Blood Test Monitoring

- If you are taking warfarin, regular blood tests are required to make sure your medication is working properly.
- The prothrombin time tells how quickly your blood forms a clot; it is used to tell how well warfarin is working.
- The INR is a way to standardize the prothrombin time between laboratories; your goal INR range is between 2 and 3; if your INR is less than 2, you are at higher risk for clotting; if your INR is greater than 3, you are at higher risk for bleeding; your dose of warfarin will be adjusted based on the results of this test.
- If you are taking LMWH, fondaparinux, dabigatran, edoxaban, rivaroxaban, or apixaban you need to have a blood test to determine how well your kidneys are working.

Warfarin Information

- Each strength of warfarin has a unique color; each time you refill your prescription, make sure your new tablets are the same color as the ones you have been taking; if not, ask your pharmacist why.
- Warfarin should be taken at approximately the same time each day.
- The most common and serious side effect of warfarin is bleeding; you should be careful to avoid situations or activities that increase your risk of injury; apply direct pressure to control bleeding from superficial cuts.
- Warfarin has many drug interactions; always check with your provider before taking any new medications (including nonprescription medications and dietary supplements).
- Foods rich in vitamin K (dark green leafy vegetables, etc.) may interfere with warfarin; do not avoid foods rich in vitamin K, but try to maintain consistent dietary habits.
- Alcohol can increase your risk for bleeding and interfere with warfarin therapy; drink alcohol in moderation (one to two drinks per day); avoid binge drinking.
- If you need to have a surgery or diagnostic procedure, talk to your provider to make a plan for how to take your anticoagulant medication before and after the procedure. Do not stop taking your anticoagulant medication without first talking to your provider.

Dabigatran, Edoxaban, Rivaroxaban, and Apixaban Information

- Take rivaroxaban 15- or 20-mg doses with food to make sure the medication is well absorbed from your stomach.
- It is very important that you take each dose of your medication. These medications leave your body within hours; so missing a dose of medication may place you at a higher risk of blood clots.
- If you need to have a surgery or procedure, talk to your provider to make a plan for how to take your anticoagulant medication before and after the procedure. Do not stop taking your anticoagulant medication without first talking to your provider.
- There are a few drug interactions with dabigatran, edoxaban, rivaroxaban, and apixaban; always check with your provider before taking any new medications (including nonprescription medications and dietary supplements).

Contact Your Provider If You Experience

- Prolonged bleeding from a cut or scrape
- Blood in your urine
- Blood in your stool
- Prolonged nose bleeding (longer than 30 minutes)
- Increased swelling or pain where the blood clot was

Go to the Emergency Department If You Experience

- Sudden onset of shortness of breath
- Chest pain
- Coughing up blood
- Black tarry-appearing stool
- Severe headache of sudden onset
- Drooping of one side of your face
- Weakness in one of your arms
- Slurred speech

INR, international normalized ratio; LMWH, low-molecular-weight heparin.

8 The appropriate initial duration of anticoagulation therapy to effectively treat an acute first episode of VTE for all patients is 3 months.[38] To prevent new VTE episodes not directly related to the preceding episode, continuing anticoagulation therapy may be required.[1] Individually tailoring anticoagulation therapy duration therapy beyond 3 months requires careful consideration of the circumstances surrounding the initial thromboembolic event, the presence of ongoing thromboembolic risk factors, bleeding risk, and patient preference.[38]

The most important considerations in determining recurrent VTE risk are whether the initial thrombotic event was associated with a major transient or reversible risk factor (eg, surgery, plaster cast leg immobilization, or hospitalization in the month prior to VTE) and the presence of active cancer.[38] The estimated cumulative risk of recurrent VTE after stopping anticoagulant therapy for VTE provoked by surgery is 1% after 1 year and 3% after 5 years, and that for VTE provoked by a nonsurgical reversible risk factor is 5% after 1 year and 15% after 5 years. Three months of anticoagulation therapy is recommended in these situations.[5] Patients with a first unprovoked (idiopathic) VTE have approximately 10% recurrence risk in the first year and approximately 30% and 50% over 5 and 10 years, respectively. These patients should be considered for extended anticoagulation therapy when feasible.[38] Extended therapy refers to continuing anticoagulation beyond 3 months without a scheduled stop date, but stopping therapy if there is a subsequent increase in bleeding risk or change in patient preference for anticoagulation.[38] For patients with a second idiopathic VTE episode, extended anticoagulation is recommended.[38] Anticoagulation is rarely stopped in patients with VTE and active cancer because of high recurrence risk.[38] Factors that may lead to the decision to stop anticoagulation therapy after 3 months include noncompliance with therapy, initial clot isolated in calf veins (even if idiopathic), or moderate-to-high bleeding risk.[38]

Important risk factors for bleeding include age>75 years, previous noncardioembolic stroke, history of gastrointestinal bleeding, renal or hepatic impairment, anemia, thrombocytopenia, concurrent antiplatelet use (avoid if possible), noncompliance, poor anticoagulant control (for patients on warfarin), serious acute or chronic illness, and the presence of structural lesions (eg, tumor, recent surgery) that could bleed. One to two bleeding risk factors suggest moderate bleeding risk while three or more suggests high bleeding risk.[5]

Various risk prediction rules aimed at identifying patients with very low

recurrence risk after a first idiopathic VTE have evaluated whether safe withdrawal of anticoagulation therapy may be possible after 3 months. Some factors that may predict lower recurrence risk include female sex, low D-dimer levels one month after stopping anticoagulation therapy, absence of residual clot on ultrasound, absence of hereditary and acquired thrombophilia, and absence of the postthrombotic syndrome. Risk assessment derived from combining several independent recurrence risk factors has also been investigated.[5] Further validation is needed before any one factor or prediction rule using a combination of factors can justify stopping anticoagulation. The decision to continue extended anticoagulation therapy should be reassessed periodically. Patients should be involved in any decision to continue therapy with consideration given to long-term prognosis, risk of bleeding, ability to adhere to anticoagulation therapy instructions, financial resources, lifestyle, and quality of life.[5] When anticoagulation therapy is stopped, there is a similar risk of recurrence whether patients have been treated for 3 months or longer.[38]

Patients with VTE are often tested for hereditary and acquired hypercoagulable states (thrombophilia). The available evidence does not support a strong association between genetically transmitted thrombophilia (especially factor V Leiden and prothrombin G20210A) and higher recurrent VTE rates.[11] For this reason, routine testing for thrombophilia is not recommended.[18]

For patients with proximal DVT, wearing graduated compression stockings does not reduce the risk of developing the postthrombotic syndrome.[40] However, for patients with persistent leg pain and swelling, graduated compression stockings can be suggested for symptomatic relief.

Pharmacologic Therapy

The anticoagulant drugs used to treat VTE are the same as those used for VTE prevention. However, there are important differences in the approach to VTE treatment in terms of the doses used and duration of therapy.

Direct Oral Anticoagulants

Clinical trials have demonstrated that single-drug therapy with rivaroxaban or apixaban produce similar rates of recurrent VTE when compared to the traditional approach of initiating warfarin overlapped with enoxaparin for both acute DVT and PE.[41–43] The rate of major bleeding was lower with rivaroxaban in the PE trial,[42] but not in the DVT trial.[43] Apixaban was associated with

significantly fewer major bleeding episodes than traditional therapy.[41] Both drugs are initiated with a higher dose and subsequently reduced to a maintenance dose (Fig. 37-9). Neither drug requires routine coagulation monitoring. Patients with CrCL <25-30 mL/min (0.42-0.5 mL/s), active cancer, and those requiring thrombolytic therapy were excluded from these clinical trials.[41–43] Until further data are available, traditional anticoagulation therapy should be used in these patient populations. Replacing the effective but cumbersome combination warfarin overlapped with an injectable anticoagulant with a single-drug regimen simplifies VTE treatment. However, the higher acquisition cost of rivaroxaban and apixaban may be a barrier for some patients.

6 Oral dabigatran 150 mg twice daily and oral edoxaban 60 mg once daily have each been compared with traditional therapy in randomized, double-blind, noninferiority trials involving patients with acute VTE.[44,45] In these trials, all patients were initially given at least 5 days of parenteral anticoagulation therapy (unfractionated heparin [UFH] or LMWH) and then randomized to study treatment. Both dabigatran and edoxaban were noninferior to warfarin following the use of a parenteral anticoagulant. Dabigatran caused similar rate of major bleeding[44] and edoxaban significantly fewer major bleeding events when compared to warfarin.[45] Similar to the other DOACs, patients with hemodynamically unstable PE or at high bleeding risk were excluded and should not receive treatment with dabigatran or edoxaban until further data are available. Patients with CrCL <30 mL/min (0.5 mL/s) should not receive dabigatran, but for patients with a CrCL 15-50 mL/min (0.25-0.83 mL/s), the dose of edoxaban can be reduced from 60 to 30 mg once daily.[45] The requirement for parenteral anticoagulation prior to initiation of dabigatran or edoxaban therapy is a disadvantage compared with single-drug approaches to VTE treatment. DOACs are preferred over traditional anticoagulation therapy approaches for the treatment of VTE in the *American College of Chest Physician 10th edition* guidelines and edoxaban and rivaroxaban may be reasonable alternatives to LMWH monotherapy for patients with cancer-associated VTE.[38,46]

Low-Molecular-Weight Heparin

LMWH given subcutaneously in fixed, weight-based doses (**Table 37-6**) is at least as effective as UFH given intravenously for the treatment of VTE.[6] UFH is preferred as the initial anticoagulant for unstable patients in case thrombolytic therapy or embolectomy are needed.[47] Among patients without cancer treated

initially with LMWH, acute treatment with LMWH is generally transitioned to long-term warfarin therapy after about 5 to 10 days. Long-term LMWH monotherapy is preferred for patients with cancer-associated VTE.

TABLE 37-6 FDA-Approved Venous Thromboembolism Indications and Doses for Low-Molecular-Weight Heparins

Indications	Enoxaparin	Dalteparin
Hip replacement surgery (prophylaxis)	30 mg SC q 12 hr *Or* 40 mg SC q 24 hr Extended prophylaxis may be given for up to 3 weeks	Postoperative start: 2,500 units SC given after surgery, and then 5,000 units SC q 24 hr *Or* Preoperative start (evening before surgery): 5,000 units SC followed by 5,000 units SC 4-8 hr after surgery, and then 5,000 units SC q 24 hr *Or* Preoperative start (day of surgery): 2,500 units SC 2 hr before surgery, then 2,500 units given 4-8 hr after surgery, and then 5,000 units SC q 24 hr
Knee replacement surgery (prophylaxis)	30 mg SC q 12 hr	
Abdominal surgery (prophylaxis)	40 mg SC q 24 hr	2,500 units SC q 24 hr or 5,000 units SC q 24 hr or 2,500 units SC followed by 2,500 units SC 12 hr later and then 5,000 units subcutaneous q 24 hr
Acute medical illness (prophylaxis)	40 mg SC q 24 hr	5,000 units SC q 24 hr
Deep vein thrombosis treatment (with or without pulmonary embolism)	1 mg/kg SC q 12 hr *Or* 1.5 mg/kg SC q 24 hr	
Venous thromboembolism treatment in patients with cancer		200 units/kg SC q 24 hr for 30 days, followed by 150 units SC q 24 hr

Fondaparinux

Fondaparinux has been shown to be a safe and effective alternative to LMWH for acute VTE treatment.[5] It is dosed once daily via weight-based subcutaneous injection as follows: 5 mg if <50 kg, 7.5 mg if 50 to 100 kg, and 10 mg if>100 kg.[48] Compared with weight-based LMWH dosing, this flexible dosing scheme may be particularly useful with obese patients and those whose weight falls between commercially available prefilled LMWH syringes. Careful attention should be paid to renal function as fondaparinux is contraindicated if CrCL is <30 mL/min (0.5 mL/s).[48]

Unfractionated Heparin

UFH may be administered subcutaneously or by continuous intravenous infusion (Table 37-7). The anticoagulant response to UFH is highly variable when given intervenously and it is a standard practice to adjust the dose based on coagulation test results. The activated partial thromboplastin time (aPTT) and antifactor Xa concentration are the two most commonly used tests to monitor the UFH anticoagulant effect. The therapeutic aPTT range at each institution should be adapted to the responsiveness of the reagent and instrument used.[6] Weight-based UFH dosing by IV infusion is preferred to fixed UFH doses (eg, 5,000 unit bolus followed by 1,000 units/h continuous infusion). However, failure to give a sufficient intravenous UFH dose has been shown to increase VTE recurrence risk.[6] If a sufficient dose of UFH is administered subcutaneously (initial dose 333 units/kg followed by 250 units/kg twice daily), aPTT-guided dose titration may be unnecessary.[6] Intravenous UFH requires hospitalization with frequent aPTT monitoring and dose adjustment. Despite these efforts, some patients still fail to achieve an adequate response to UFH therapy.[6] Consequently, UFH has largely been replaced by LMWH, fondaparinux, and DOACs for management of acute VTE. However, because the clearance of LMWH, fondaparinux, and DOACs is dependent on renal function, UFH continues to have a role for acute VTE treatment in patients with CrCL <30 mL/min (0.5 mL/s) and unstable patients.[5,38,49]

TABLE 37-7 Weight-Based[a] Dosing for Unfractionated Heparin Administered by Continuous IV Infusion for Acute VTE

Initial Bolus Dose	Initial Infusion Rate
80 units/kg (Maximum = 10,000 units)	18 units/kg/hr (Maximum = 2,300 units/hr)
Maintenance Infusion Rate	
Activated Partial Thromboplastin Time (seconds)	***Dose Adjustment***
<37 (or anti-factor Xa <0.20 unit/mL [kU/L])	80 units/kg bolus, and then increase infusion by 4 units/kg/hr
37-47 (or anti-factor Xa 0.20-0.29 unit/mL [kU/L])	40 units/kg bolus, and then increase infusion by 2 units/kg/hr
48-71 (or anti-factor Xa 0.30-0.70 unit/mL [kU/L])	No change
72-93 (or anti-factor Xa 0.71-1 unit/mL [kU/L])	Decrease infusion by 1-2 units/kg/hr
>93 (or anti-factor Xa >1 unit/mL [kU/L])	Hold infusion for 1 hr, and then decrease by 3 units/kg/hr

[a]Use actual body weight for all calculations. Adjusted body weight may be used for obese patients (>130% of ideal body weight).

Source: Data from Garcia et al.[6]

Warfarin

5 Warfarin monotherapy is unacceptable for acute VTE treatment because the slow onset of effect is associated with high incidence of recurrent thromboembolism. However, warfarin is effective in the long-term VTE management provided it is started concurrently with rapid-acting injectable anticoagulant therapy.[5] Injectable anticoagulation should overlap with warfarin therapy for at least 5 days and until an INR ≥2 has been achieved for at least 24 hours.[5] The initial dose of warfarin should be 5 to 10 mg for most patients and periodically adjusted to achieve and maintain an INR between 2 and 3 (**Fig. 37-10**).

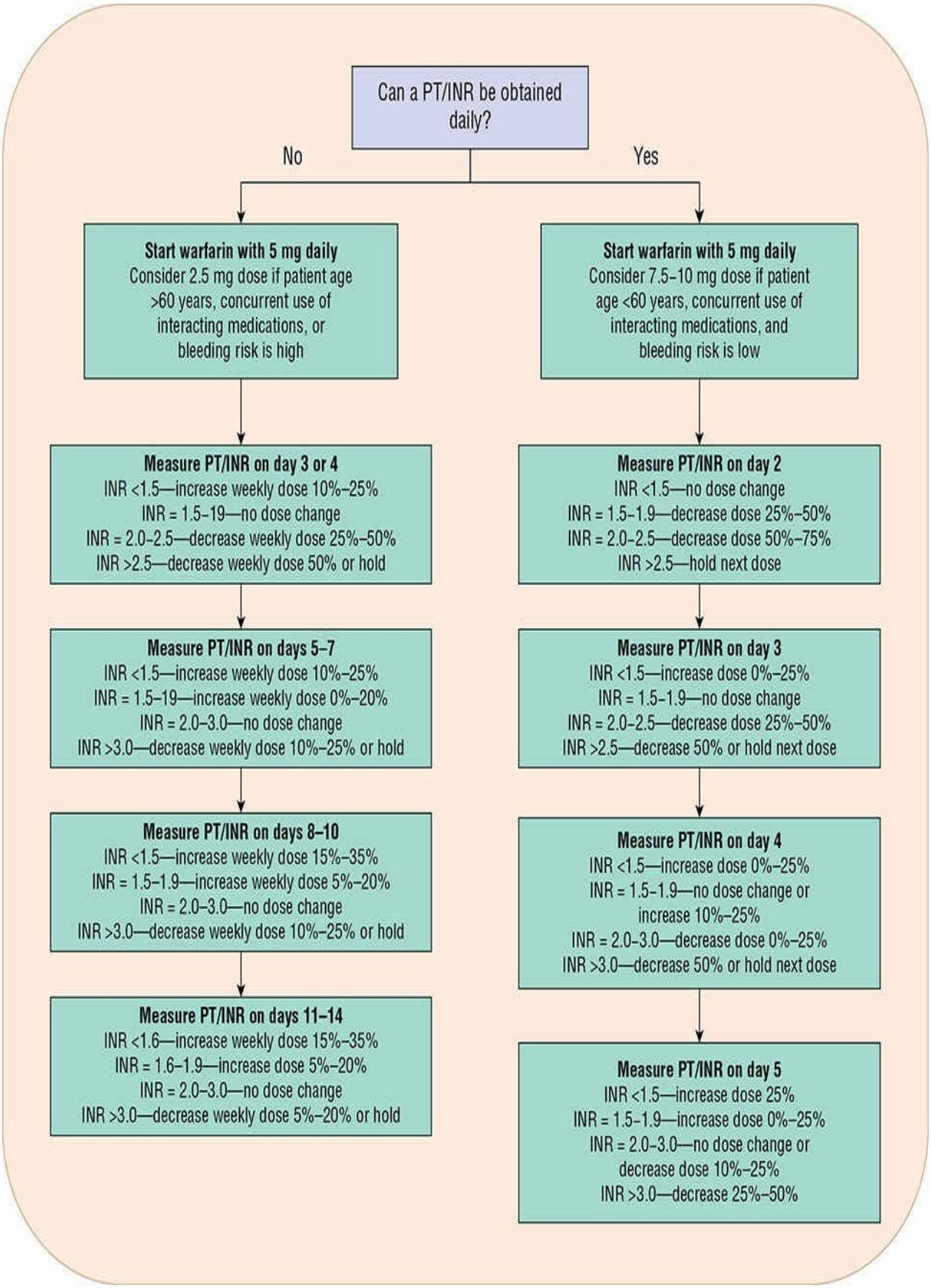

Can a PT/INR be obtained daily?
No
Yes
Start warfarin with 5 mg daily
Consider 2.5 mg dose if patient age >60 years, concurrent use of interacting medications, or bleeding risk is high
Measure PT/INR on day 3 or 4
INR <1.5—increase weekly dose 10%–25%
INR = 1.5–19—no dose change
INR = 2.0–2.5—decrease weekly dose 25%–50%
INR >2.5—decrease weekly dose 50% or hold
Measure PT/INR on days 5–7
INR <1.5—increase weekly dose 10%–25%
INR = 1.5–19—increase weekly dose 0%–20%
INR = 2.0–3.0—no dose change
INR >3.0—decrease weekly dose 10%–25% or hold
Measure PT/INR on days 8–10
INR <1.5—increase weekly dose 15%–35%
INR = 1.5–1.9—increase weekly dose 5%–20%
INR = 2.0–3.0—no dose change
INR >3.0—decrease weekly dose 10%–25% or hold
Measure PT/INR on days 11–14
INR <1.6—increase weekly dose 15%–35%
INR = 1.6–1.9—increase dose 5%–20%
INR = 2.0–3.0—no dose change
INR >3.0—decrease weekly dose 5%–20% or hold
Start warfarin with 5 mg daily
Consider 7.5–10 mg dose if patient age <60 years, concurrent use of interacting medications, and bleeding risk is low
Measure PT/INR on day 2
INR <1.5—no dose change
INR = 1.5–1.9—decrease dose 25%–50%
INR = 2.0–2.5—decrease dose 50%–75%
INR >2.5—hold next dose
Measure PT/INR on day 3
INR <1.5—increase dose 0%–25%
INR = 1.5–1.9—no dose change
INR = 2.0–2.5—decrease dose 25%–50%
INR >2.5—decrease 50% or hold next dose
Measure PT/INR on day 4
INR <1.5—increase dose 0%–25%
INR = 1.5–1.9—no dose change or increase 10%–25%
INR = 2.0–3.0—decrease dose 0%–25%
INR >3.0—decrease 50% or hold next dose
Measure PT/INR on day 5
INR <1.5—increase dose 25%
INR = 1.5–1.9—increase dose 0%–25%
INR = 2.0–3.0—no dose change or decrease dose 10%–25%
INR >3.0—decrease 25%–50%

FIGURE 37-10 Initiation of warfarin therapy. (INR, international normalized ratio; PT, prothrombin time.)

Alternative Treatment

Most VTE cases require only anticoagulation therapy. In select cases, removing the occluding thrombus by pharmacologic or surgical means may be warranted.[22,50] Thrombolytic agents are proteolytic enzymes that enhance conversion of plasminogen to plasmin.[5] Thrombolytic therapy for DVT improves early venous patency, but this does not necessarily translate into improved long-term outcomes.[22] If thrombolytic therapy is pursued, systemic administration via peripheral vein is preferred to catheter-directed thrombolysis.[22] Patients with extensive proximal DVT presenting within 14 days of symptom onset, with good functional status, low bleeding risk, and a life expectancy of a year or more are thrombolysis candidates (**Table 37-8**). Catheter-based thrombus fragmentation, with or without thrombus fragment aspiration, can be combined with catheter-directed thrombolysis; however, this approach has not been shown to be superior to anticoagulation therapy alone in preventing postthrombotic syndrome and increases the risk of major bleeding.[50] The same anticoagulation therapy duration and intensity is recommended as for patients with DVT not receiving thrombolysis.[5] Patients with DVT involving the iliac and common femoral veins are at highest risk for postthrombotic syndrome and may have the greatest potential to benefit from thrombus removal strategies. In patients with impending venous gangrene despite optimal anticoagulant therapy, thrombus removal is indicated; for all other patients with acute DVT, AT9 suggests anticoagulation therapy alone over either catheter-directed or systemic thrombolysis.[5]

TABLE 37-8 Thrombolysis for the Treatment of Venous Thromboembolism

- The majority of patients with VTE do not require thrombolytic therapy
- Thrombolytic therapy for DVT should be reserved for patients who present with extensive proximal DVT (eg, ileofemoral) within 14 days of symptom onset, have good functional status, and are at low risk of bleeding
- Thrombolytic therapy should be administered to patients with massive PE with evidence of hemodynamic compromise (hypotension or shock) unless contraindicated by bleeding risk
- Thrombolytic therapy should be considered for selected high-risk patients with PE without hypotension provided the risk of bleeding is acceptable
- Factors associated with high risk for adverse PE outcomes include:
  - Ill-appearing patients with marked dyspnea, anxiety, and low oxygen saturation
  - Elevated troponin levels
  - Right ventricular dysfunction on echocardiography
  - Right ventricular enlargement on chest CT
- Factors that increase the risk of bleeding must be evaluated before thrombolytic therapy is initiated (ie, recent surgery, trauma or internal bleeding, uncontrolled hypertension, recent stroke or intracranial hemorrhage)
- Baseline labs should include CBC and blood typing in case transfusion is needed
- Alteplase 100 mg infused via peripheral vein over 2 hours is the most commonly used thrombolytic for patients with PE
- Before thrombolytic therapy for PE, IV UFH should be administered in full therapeutic doses
- During thrombolytic therapy it is acceptable to either continue or suspend IV UFH (suspending UFH is the most common practice in the United States)
- aPTT should be measured following the completion of thrombolytic therapy
  - If aPTT is <80 seconds, UFH infusion should be started and adjusted to maintain aPTT in therapeutic range
  - If aPTT is>80 seconds, measure every 2-4 hours and start UFH infusion when aPTT is <80 seconds
- Avoid phlebotomy, arterial puncture, and other invasive procedures during thrombolytic therapy to minimize the risk of bleeding

aPTT, activated partial thromboplastin time; CBC, complete blood cell count; DVT, deep vein thrombosis; PE, pulmonary embolism; UFH, unfractionated heparin.

Source: Data from Kearon et al.[22] and Goldhaber and Bounameaux.[1]

In acute PE successful clot dissolution with thrombolytic therapy reduces elevated pulmonary artery pressure and normalizes right ventricular dysfunction. However, the risk of death from PE should outweigh the risk of serious bleeding associated with thrombolytic therapy. Patients being considered for thrombolytic

therapy should be screened carefully for contraindications relating to bleeding risk (Table 37-8).[5,51] Thrombolytic therapy is considered necessary in addition to aggressive interventions such as volume expansion, vasopressor therapy, intubation, and mechanical ventilation for patients with massive PE accompanied by shock and cardiovascular collapse (about 5% of patients with PE).[5,51] Thrombolytic therapy in these patients should be administered without delay to reduce risk of progression to multisystem organ failure and death. While lifesaving in the acute phase of massive PE with hypotension, the hemodynamic benefit of thrombolysis is comparable to that of UFH after a few days.[52]

The benefit of thrombolytic therapy in patients with PE without hemodynamic compromise is less clear and rapid risk stratification is required to determine whether patients may benefit from thrombolysis or embolectomy in addition to anticoagulation therapy.[47] Risk stratification helps determine the initial treatment intensity. Low-risk patients can be discharged early or managed as outpatients and high-risk patients should be admitted to an intensive care unit for surveillance and/or advanced therapies such as thrombolysis.[53] Key components of risk stratification are clinical evaluation, determination of cardiac biomarker levels such as troponin, and assessment of right ventricular size and function.[5] The Pulmonary Embolism Severity Index (PESI) is a prognostic tool utilizing 11 routinely available clinical parameters: demographics (age and gender), comorbid illnesses (cancer, heart failure, and chronic lung disease), and clinical findings (pulse, systolic blood pressure, respiratory rate, temperature, mental status, and arterial oxygen saturation). PESI stratifies patients into five risk classes with classes I and II considered low risk.[53] AT9 suggests that patients with acute PE presenting without hypotension be risk stratified by signs that indicate clinical instability including decrease in systolic blood pressure but>90 mm Hg, tachycardia, elevated jugular venous pressure, clinical evidence of poor tissue perfusion, hypoxemia, and failure to improve on anticoagulant therapy.[5] Patients with one or more of these clinical features are at high risk for PE-related morbidity and mortality and may benefit from thrombolytic therapy, provided bleeding risk is acceptable, even in the absence of hemodynamic compromise (Table 37-8).[5,22]

In rare circumstances surgical thrombectomy for extensive ileofemoral DVT may be necessary, but catheter-directed thrombolysis is preferred if bleeding risk is acceptable.[22] For acute PE treatment, catheter-based embolectomy might be suitable in settings where the necessary expertise and resources are available for patients who have contraindications to thrombolytic therapy, have failed thrombolytic therapy, or in whom death is likely before thrombolytic onset.[22] In

the absence of contraindications, catheter-based PE embolectomy is usually combined with thrombolytic therapy unless the bleeding risk is high.[5] Surgical embolectomy is reserved for massive PE and hemodynamic instability when thrombolysis is contraindicated, and for when thrombolysis has failed clinically or will not have sufficient time to take effect.[5] In chronic PE cases—where persistent emboli produce CTPH, hypoxemia, and right-sided heart failure—surgical pulmonary thromboendarterectomy offers greater benefit than anticoagulants and may be the treatment of choice if performed by an experienced surgical team.[22] A permanent IVC filter is usually inserted before or during the procedure and long-term anticoagulation therapy is needed.[5]

Special Populations

Some patient populations with VTE require special consideration due to increased risk for recurrence, adverse events, or altered anticoagulant pharmacokinetics.

Pregnancy

Anticoagulation therapy is commonly used for the prevention and treatment of VTE during pregnancy.[9] UFH and LMWH do not cross the placenta and are preferred during pregnancy (**Table 37-9**).[9] Warfarin crosses the placenta and can result in fetal bleeding, central nervous system abnormalities, and embryopathy and should not be used for VTE treatment during pregnancy.[9] Women of childbearing age taking warfarin must be counseled regarding fetal risks and need for effective contraception. DOACs should be avoided in pregnancy until more information regarding their safety is available.[54–57] Fondaparinux has not been extensively studied in pregnancy and may cross the placenta.[48] However, fondaparinux may be considered in pregnant patients intolerant to LMWH or those with a history of heparin-induced thrombocytopenia.[58]

TABLE 37-9 Anticoagulant Use During Pregnancy and Delivery[9]

Acute treatment[a]	LMWH • Enoxaparin 1 mg/kg SC q 12 hr or 1.5 mg/kg q 24 hr *Or* • Dalteparin 100 units/kg SC q 12 hr *Or* UFH • Initiate using weight-based IV therapy and adjust dose to achieve therapeutic anti-Xa level for at least 5 days • Transition to SC adjusted-dose UFH administered q 8-12 hr with mid-interval anti-Xa activity adjusted to achieve an anti-Xa level of 0.3-0.7 unit/mL [kU/L][b]
Long-term treatment[c]	LMWH • Maintain initial LMWH dose regimen throughout pregnancy *Or* Alter LMWH dose in proportion to any weight change (usually gain) *Or* UFH • Obtain anti-Xa level at the midpoint of the dosing interval and adjust UFH dose to achieve an anti-Xa level of 0.3-0.7 unit/mL [kU/L]
Issues at the time of delivery	Elective induction of labor • Discontinue UFH or LMWH 24 hr prior to induction • Initiate therapeutic doses of UFH by IV infusion and discontinue 4-6 hr prior to expected time of delivery if risk of recurrent VTE is deemed high Spontaneous labor • For LMWH, if there is a reasonable expectation that significant anticoagulant effect will be present at time of delivery: (a) epidural should be avoided and (b) reversal with protamine sulfate may be considered • For UFH, monitor the aPTT and reverse with protamine sulfate if aPTT is prolonged near the time of delivery Postpartum • Commence UFH or LMWH as soon as safely possible (usually 12 hr following delivery) • Concurrently initiate warfarin therapy and discontinue UFH or LMWH when the INR is 2 or greater • Continue anticoagulants for at least 6 weeks following delivery • Warfarin can be safely used by women who are breast-feeding

[a]Twice-daily LMWH preferred during pregnancy due to increased clearance.

[b]Anti-Xa monitoring preferred as the relationship between aPTT and heparin levels differs in pregnant compared with nonpregnant patients.

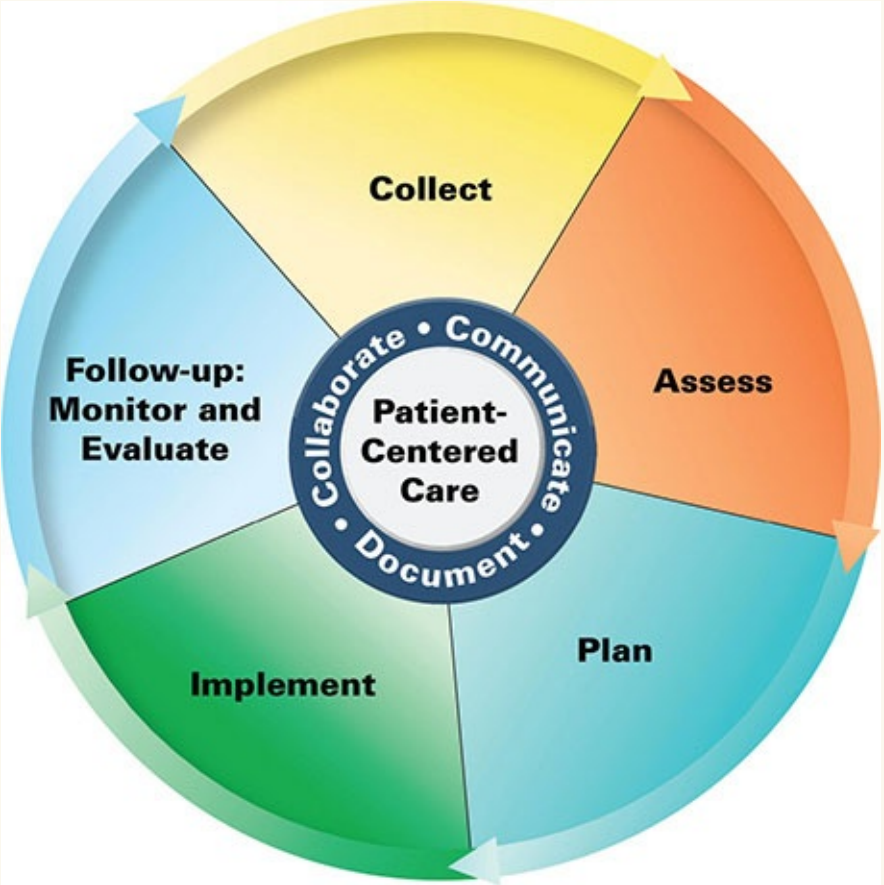
[c]As pregnancy progresses the volume of distribution of LMWH changes, glomerular filtration rate increases, and most women gain weight.

aPTT, activated partial thromboplastin time; INR, international normalized ratio; LMWH, low-molecular-weight heparin; SC, subcutaneously; UFH, unfractionated heparin; VTE, venous thromboembolism.

Pregnant women with a history of VTE should receive VTE prophylaxis for 6 weeks after delivery.[59] Antenatal prophylaxis may also be indicated in women with a history of multiple VTE, VTE associated with pregnancy or estrogen therapy, or known thrombophilia. Anticoagulation for acute VTE during pregnancy should continue for at least 6 weeks postpartum and a minimum total duration of 3 months.[9] Warfarin, UFH, and LMWH are safe during breast-feeding.[6,60] It is not known if DOACs are excreted in human milk and breast-feeding is not recommended.[54–57]

Pediatric Patients

VTE in pediatric patients is increasing secondary to prematurity, cancer, trauma, surgery, congenital heart disease, and systemic lupus erythematosus. Pediatric patients rarely experience unprovoked VTE, but often develop DVTs associated with indwelling central venous catheters.[61] Recommendations for anticoagulant therapy in pediatric patients are largely extrapolated from data from clinical trials in adults. However, there are important pharmacokinetic and pharmacodynamic differences that should be taken into consideration. The majority of literature supporting pediatric recommendations is derived from uncontrolled studies, case reports, or in vitro experiments. When possible, a pediatric hematologist with experience treating VTE should manage pediatric patients.[61]



Patient Care Process for the Treatment of Venous Thromboembolism

Collect

- Patient characteristics (eg, age, sex, pregnant)
- Patient history (past medical, family, social—dietary habits including intake of vitamin K containing foods (see Table 37-13), tobacco/ethanol use)
- Current medications including aspirin/OTC NSAID use and prior anticoagulant medication use
- Objective data
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), O_2-saturation, height, weight
  - Labs (eg, Hgb, Scr, platelets, aPTT, PT)

- Do NOT order hypercoagulability tests
- Objective confirmation of VTE (see Figs. 37-6 and 37-7)

Assess

- Hemodynamic instability (eg, SBP<90 mm Hg, HR>110 bpm, O_2-sat<90% [0.90]), evidence of limb ischemia
- Presence of active bleeding and/or bleeding risk factors (see Table 37-10)
- Presence of VTE provoking factors (eg, recent surgery, plaster casting of lower extremity, indwelling catheter, cancer, pregnancy, estrogen use, prolonged immobility, recent hospitalization)
- Ability/willingness to self-inject LMWH/fondaparinux
- Ability/willingness to pay for various anticoagulation therapy options
- Ability/willingness to obtain appropriate laboratory monitoring (eg, INR for warfarin)
- Emotional status (eg, presence of anxiety, depression)

Plan*

- Drug therapy regimen including specific anticoagulant(s), dose, route, frequency, and duration; (see Figs. 37-8 and 37-9, Tables 37-3, 37-4, 37-6, 37-8, and 37-9)
- Monitoring parameters including efficacy (eg, INR results, pain control, limb swelling, shortness of breath), safety (bleeding, VTE recurrence), and timing of assessments
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, invasive procedures, drug therapy; see Table 37-5)
- Self-monitoring for resolution of VTE symptoms, occurrence of bleeding, when to seek emergency medical attention
- Referrals to other providers when appropriate (eg, thrombosis specialist, behavioral health, dietician)

Implement

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence

- Schedule follow-up (eg, INR tests [warfarin], Scr [DOACs], adherence assessment, bleeding risk assessment, duration of therapy assessment)

Follow-up: Monitor and Evaluate

- Resolution of VTE symptoms (eg, shortness of breath, chest pain, swelling, redness, pain)
- Presence of adverse effects (eg, bleeding, GI upset [dabigatran])
- INR results (adjust warfarin dose as needed to keep between 2 and 3)
- Patient adherence to treatment plan using multiple sources of information
- Duration of therapy after 90 days

* *Collaborate with patient, caregivers, and other healthcare professionals.*

Anticoagulation with UFH and warfarin remains the most frequently used approach for VTE treatment in pediatric patients and the recommended target aPTT and INR ranges as well as the duration of therapy are extrapolated from studies conducted in adults.[61] The recommended initial bolus dose of UFH is 75 to 100 units/kg given intravenously over 10 minutes followed by a maintenance infusion of 28 units/kg/hr for infants 2 to 12 months of age and 20 units/kg/hr for children aged 1 year or older.[61] Subsequent infusion rate adjustments should be made every 4 to 6 hours to maintain the aPTT within the institution-specific therapeutic range. The usual warfarin starting dose is 0.2 mg/kg with a maximum of 10 mg. Infants require higher warfarin doses per kilogram to maintain a target INR of 2.0 to 3.0 compared with teenagers and adults (mean dose 0.33 mg/kg, 0.09 mg/g, and 0.04-0.08 mg/kg, respectively).[61] The INR target range for VTE treatment in children is 2.0 to 3.0. Frequent INR monitoring and warfarin dose adjustments are typically required. When compared with adults, only 10% to 20% of pediatric patients can be safely monitored with once monthly INRs.[61] Obtaining blood for coagulation monitoring tests in pediatric patients is challenging because many have poor venous access; some clinicians recommend using finger-stick blood samples with portable point-of-care INR monitors.[61] Despite the need for daily injections, LMWH is an attractive alternative for pediatric patients due to low potential for drug–drug interactions and less frequent laboratory testing. Most experts recommend anti-Xa activity monitoring with goal anti-factor Xa levels between 0.5 and 1.0 unit/mL (kU/L) 4 to 6 hours following subcutaneous injection. Compared with adults, children younger than 3 months or weighing <5

kg have higher per-kilogram dose requirements to achieve a “therapeutic” anti-Xa response. The LMWH dose for older children is generally similar to weight-adjusted doses used in adults.[61] Warfarin can be initiated concurrently with UFH or LMWH therapy. Similar to adults, therapy should be overlapped for a minimum of 5 days and until the INR is therapeutic. Warfarin should be continued for at least 3 months for provoked VTE and 6 months for unprovoked VTE.[61] DOACs are attractive alternatives in pediatric patients due to oral administration and no need for routine coagulation monitoring; however, safety, effectiveness, and dosing in this population have not been established.[54–57] Thrombolysis and thrombectomy have been successfully employed in pediatric patients, but published data are very limited—routine use is not recommended.[61]

Patients with Cancer

Cancer-related VTE is associated with threefold higher rates of recurrent VTE and up to sixfold higher rates of bleeding. In addition, warfarin-based approaches are less effective for the treatment VTE in patients with active cancer.[62] Warfarin therapy in cancer patients is often complicated by drug interactions (eg, chemotherapy and antibiotics) and the need to interrupt therapy for invasive procedures. Maintaining stable INR control is also more difficult in this patient population because of nausea, anorexia, and vomiting.[5]

Treatment of cancer-related VTE with LMWH monotherapy rather than traditional warfarin-based therapy decreases recurrent VTE rates without increasing bleeding risk. Consensus guideline panels recommend LMWH monotherapy for VTE treatment in patients with cancer.[5,17,63,64] Advantages of LMWH over warfarin for VTE treatment in cancer are expected to be greatest in those with one or more of the following: metastatic disease, treatment with aggressive chemotherapy, extensive VTE at presentation, liver dysfunction, poor or unstable nutritional status, or desire to avoid frequent blood draws for coagulation monitoring.[5]

For patients with cancer and VTE receiving LMWH, therapy should continue for 3 to 6 months after which the LMWH can be continued or warfarin or DOAC therapy substituted. Anticoagulation therapy should continue for as long as the cancer is “active” and while the patient is receiving antitumor therapy.[5] A risk-to-benefit assessment should be performed on a regular basis considering overall clinical status, bleeding risk, quality of life, and life expectancy.[5] For patients with cancer who experience a VTE recurrence despite receiving anticoagulant therapy, LMWH appears to be more effective than warfarin-based therapy in

preventing further recurrences and increasing the anticoagulant intensity may not be necessary in this situation.[62]

A meta-analysis evaluated the outcomes of the subset of patients with cancer within the phase III VTE treatment trials comparing DOACs and traditional therapy with LMWH followed by warfarin.[65] There were similar recurrent VTE and major bleeding rates in the two groups suggesting DOACs are not inferior to conventional warfarin therapy for cancer-associated VTE management.[65] Edoxaban and rivaroxaban have been compared to dalteparin monotherapy for treatment of cancer-related VTE and were as effective as dalteparin for preventing VTE recurrence but caused more bleeding.[66,67] Excess DOAC-related bleeding often occurred in the gastronintestinal tract in patients with gastrointestinal malignancy.[66] Thus, DOACs may be an important alternative to LMWH for cancer-related VTE given the limited tolerability of long-term LMWH.

Patients with Renal Insufficiency

Patients with acute or chronic kidney disease often require anticoagulation for VTE prevention or treatment. With the exception of warfarin and UFH, most anticoagulants require adequate renal function for their elimination. Accumulation of drug is possible during treatment with LMWH, fondaparinux, and DOACs.[6,60] In addition, patients with chronic kidney disease are at increased risk of bleeding, regardless of how the drug is eliminated.[68]

LMWHs are renally eliminated and should be used with caution in patients with severe renal impairment.[69] Enoxaparin has specific labeling for patients with CrCL <30 mL/min (0.5 mL/s), but supporting evidence is limited to pharmacokinetic modeling analyses.[70] Bleeding and recurrent VTE outcomes for patients with CrCL <30 mL/min (0.5 mL/s) receiving enoxaparin 1mg/kg once daily for acute VTE treatment was comparable to patients with normal renal function in one retrospective study.[49] However, UFH remains preferred for acute VTE treatment in this setting until further evidence becomes available.[5]

DOACs are eliminated to varying degrees through the kidney and require dose adjustment for renal impairment.[54–57] Use of these anticoagulants in patients with CrCL <30 mL/min (0.5 mL/s) (<25 mL/min [0.42 mL/s] for apixaban) should be avoided.

Patients Undergoing Invasive Procedures

Patients scheduled to undergo invasive procedures often require temporary discontinuation of anticoagulation therapy.[71] The decision to withhold anticoagulation therapy should be based on the type of surgical procedure being performed and the patient's bleeding and thromboembolic risk. In most cases, anticoagulation therapy should be continued in patients undergoing minimally invasive procedures such as dental work, cataract surgery, or minor dermatologic procedures.[72] If the bleeding risk from the procedure is considerable, near-normal hemostasis should be achieved prior to the procedure. For DOACs the time required for restoration of normal hemostasis after interrupting therapy is dependent on renal function and medication half-life. Stopping DOACs 2 days prior to invasive procedures is usually sufficient to restore near normal hemostasis for patients with normal renal function. Additional days off therapy may be required for patients with impaired renal function.[54–57] The anticoagulant effect of dabigatran can be rapidly reversed with idarucizumab for patients requiring urgent surgical interventions.[73] Up to 5 days may be required for restoration of normal hemostasis after warfarin discontinuation. Patients at high thromboembolic risk (ie, DVT or PE in the previous month) may be considered for so-called "bridge therapy" with UFH or a LMWH given before and after the procedure.[72] Bridge therapy has been associated with increased major bleeding without offering additional recurrent VTE risk reduction in low-to-moderate risk patients; therefore, most patients with VTE can safely interrupt warfarin for invasive procedures without using bridge therapy.[71]

DRUG CLASS INFORMATION

9 Optimal use of anticoagulant therapies requires knowledge of pharmacologic and pharmacokinetic characteristics as well as systematic management and ongoing patient education to reduce the risks of bleeding and therapeutic failure (**Table 37-10**).

TABLE 37-10 Risk Factors for Major Bleeding While Taking Anticoagulation Therapy

Higher anticoagulation intensity
Initiation of therapy (first few days and weeks)
Unstable anticoagulation response
Age>65 years
Concurrent aspirin or other antiplatelet therapy
Concurrent nonsteroidal anti-inflammatory drug use
History of gastrointestinal tract bleeding
Recent surgery or trauma
High risk for fall/trauma
Heavy alcohol use
Renal failure
Cerebrovascular disease
Malignancy

Source: Data from Schulman et al.[68]

Direct Oral Anticoagulants

Shortcomings with warfarin, LMWH, fondaparinux, and UFH have driven the search for replacements with rapid anticoagulant onset and oral administration without the need for monitoring. The DOACs represent a major advance in VTE prevention and treatment.

Pharmacology/Mechanism of Action

Rivaroxaban, apixaban, edoxaban, and betrixaban are potent and selective inhibitors of both free and clot-bound factor Xa and do not require antithrombin to exert their anticoagulant effect.[31,54,56,57] Dabigatran is a selective, reversible, direct factor IIa inhibitor.[55]

Pharmacokinetics

Rivaroxaban, apixaban, and edoxaban have good oral bioavailability (greater than 60%), whereas dabigatran is formulated as a prodrug (dabigatran etexilate) to overcome poor oral bioavailability.[54–57] Betrixaban has reduced oral bioavailability of 34% and should be given with food.[31] All DOACs reach peak plasma concentrations in less than 4 hours. Each drug is renally eliminated to a variable extent, as low as 7% for betrixaban and as high as 80% for dabigatran, with terminal half-lives of 9 to 12 hours for rivaroxaban, apixaban, and

edoxaban, and 14 to 17 hours for dabigatran.[54–57] Betrixaban is the DOAC with the longest half-life, 19 to 27 hours.[31] DOACs should be used with caution in patients with renal dysfunction.[74] Rivaroxaban and apixaban are substrates of cytochrome p450 (CYP) 3A4, and the P-glycoprotein (P-gp) transporter.[54,56] Edoxaban and dabigatran do not undergo significant CYP 3A4 metabolism, but all are P-gp substrates.[55,57] Inhibitors and inducers of CYP 3A4 enzymes or P-gp may cause changes in DOAC exposure and increase risk of bleeding or VTE events.[54–57]

Efficacy

DOACs are noninferior to warfarin therapy overlapped with LMWH for VTE treatment.[54–57] For patients who are at high risk of VTE recurrence who require extended anticoagulant therapy beyond 6 months, rivaroxaban and apixaban at either the treatment or prophylactic dose were superior to low-dose aspirin or placebo, respectively.[75,76] Similarly, when compared to LMWH, rivaroxaban and apixaban are noninferior for preventing VTE following hip or knee replacement surgery.[54–56] Extended-duration betrixaban reduced VTE incidence compared to standard-duration enoxaparin in hospitalized medically ill patients at-risk for VTE.[31] Approved DOAC indications for prevention and treatment of VTE are summarized in **Table 37-11**.

TABLE 37-11 Approved Indications and Dosing for the Direct Oral Anticoagulants

	VTE Prophylaxis	Acute VTE Treatment	Reduction in the Risk of Recurrence of DVT/PE in Patients at Continued Risk
Dabigatran	110 mg PO first day after hip replacement surgery, then 220 mg once daily for 28-35 days	150 mg PO twice daily with or without food FOLLOWING at least 5 days of parenteral anticoagulant therapy	150 mg PO twice daily with or without food
Rivaroxaban	10 mg PO once daily continuing for 12-35 days post-hip or knee replacement surgery	15 mg PO twice daily with food for Days 1-21, then 20 mg PO once daily with food beginning on day 22	10 mg PO once daily with or without food
Apixaban	2.5 mg PO twice daily with or without food for 12-35 days (hip replacement) or 12 days (knee replacement)	10 mg PO twice daily with or without food for days 1-7, then 5 mg PO twice daily with or without food beginning on day 8	2.5 mg PO twice daily with or without food
Edoxaban	Not approved for use	60 mg PO once daily with or without food FOLLOWING at least 5 days of parenteral anticoagulant therapy; 30 mg once daily for patients with CrCL 15-50 mL/min [0.25-0.83 mL/s] or body weight less than or equal to 60 kg or who use certain P-gp inhibitors	Not approved for use
Betrixaban	For hospitalized patients with acute medical illness initial single dose of 160 mg PO, followed by 80 mg once daily continuing for 35-42 days	Not approved for use	Not approved for use

PO, by mouth; VTE, venous thromboembolism

Source: Data from references 54–57.

Adverse Effects

The most common adverse effect associated with DOAC therapy is bleeding.[54–57] The International Society for Thrombosis and Haemostasis defines major bleeding as fatal bleeding, any bleeding into a critical anatomic space (eg, intracranial bleeding, hemarthrosis, pericardial bleeding, or intraocular bleeding), bleeding that requires transfusion of two or more units of whole blood or red cells, or bleeding that leads to a greater than 2 g/dL (20 g/L; 1.24 mmol/L) drop in hemoglobin concentration. Bleeding that does not meet the major bleeding criteria but requires medical intervention or alteration of therapy is sometimes termed clinically relevant nonmajor bleeding. All other bleeding is considered minor and is common during anticoagulation therapy even in the most expertly managed patients. Patients presenting with significant bleeding during DOAC therapy should receive routine supportive care (fluid resuscitation, blood transfusion, maintenance of renal function, bleeding source identification, and surgical intervention if needed), and discontinuation of anticoagulation therapy.[77] Because DOACs have relatively short half-lives, these measures may

control bleeding in many patients, especially those with normal renal function.[77] Activated charcoal may provide some benefit if drug intake occurred within the previous 2 hours and hemodialysis may be of benefit for reversal of dabigatran.[77] Idarucizumab is a humanized monoclonal antibody fragment that rapidly reverses the dabigatran anticoagulant effect following IV administration.[73] Idarucizumab can be used during emergency situations such as life-threatening bleeding and when there is need for urgent surgical intervention. Andexanet is a recombinant Factor Xa molecule that binds the Factor Xa inhibitors rivaroxaban and apixaban without having intrinsic antithrombotic activity. It can be used for the reversal of life-threatening bleeding in patients taking rivaroxaban or apixaban. Ciraparantag is a synthetic molecule in development for the urgent reversal of UFH, LMWH, and the DOACs (**Table 37-12**). If traditional hemostatic measures fail or drug-specific reversal agents are not available in a life-threatening bleeding situation, it may be reasonable to consider the use of prothrombin complex concentrates (PCCs) (3-factor, 4-factor, or activated PCCs) or recombinant Factor VIIa, while weighing the associated risk for thrombotic events. Animal, in vitro, and healthy volunteer studies have shown that these agents reverse coagulation laboratory parameters, but controlled studies of these agents in bleeding patients taking DOACs are not available. Fresh-frozen plasma (FFP) is unlikely to provide clinical benefit.[77] The most frequent nonbleeding adverse events in clinical trials of DOACs were gastrointestinal complaints.[54–57]

TABLE 37-12 Reversal Agents for the Direct Oral Anticoagulants

Reversal Agent	Target	Outcomes and Current Status
Idarucizumab (monoclonal antibody fragment)	Dabigatran	Reversed anticoagulant effect of dabigatran in patients with serious bleeding or needing urgent reversal for a procedure Approved by the FDA in October 2015
Andexanet (modified recombinant Factor Xa)	Rivaroxaban, Apixaban	Reversed anticoagulant effect of rivaroxaban and apixaban in patients with intracranial hemorrhage Approved by the FDA in May 2018
Ciraparantag (synthetic molecule)	UFH, LMWH, Rivaroxaban, Apixaban, Edoxaban, Dabigatran	Reversed anticoagulant effect of Rivaroxaban, Apixaban, Edoxaban, and Dabigatran in animal studies Reversed anticoagulant effect of Rivaroxaban, Apixaban, and Edoxaban in human in vitro studies Reversed anticoagulant effect of Enoxaparin and Edoxaban in healthy volunteers Phase III trials not yet begun

Source: Data from Pollack,[73] Greinacher,[78] Tornkvist,[79] and Ansell.[80]

Drug–Drug and Drug–Food Interactions

Adding aspirin to DOAC therapy nearly doubles bleeding rates and should be avoided in most patients with VTE. All DOACs are P-gp substrates and subject to changes in anticoagulant effect when coadministered with P-gp inhibitors or inducers. Rivaroxaban and apixaban are subject to interactions involving inhibitors or inducers of CYP 3A4.[54–57] During DOAC therapy, concurrent use of interacting drugs should be avoided because the anticoagulant effect cannot be easily monitored. When interacting drugs cannot be avoided it may be best to switch to warfarin for dose adjustment guided by INR monitoring.

Dosing and Administration

Rivaroxaban and apixaban can be used in a single-drug approach for acute VTE treatment, whereas at least 5 days of parenteral anticoagulant therapy is required prior to initiating edoxaban or dabigatran for acute VTE (Fig. 37-9). The 15- and 20-mg doses of rivaroxaban and the 40- and 80-mg doses of betrixaban should be taken with food to enhance oral absorption, but all other DOACs can be taken irrespective of food.[54–57] Dosing information for VTE prevention and treatment is summarized in Table 37-11.

Low-Molecular-Weight Heparin

LMWH fragments produced by either chemical or enzymatic depolymerization of UFH are heterogeneous mixtures of sulfated glycosaminoglycans with approximately one-third the mean molecular weight of UFH.[6] Advantages of LMWH over UFH include predictable anticoagulation dose response, improved subcutaneous bioavailability, dose-independent clearance, longer biologic half-life, lower incidence of thrombocytopenia, and reduced need for routine laboratory monitoring.[6]

Pharmacology/Mechanism of Action

LMWH prevents thrombus growth and propagation by enhancing and accelerating the activity of antithrombin.[6] The principal difference in the pharmacologic activity of LMWH and UFH is their relative inhibition of factor Xa and thrombin. Because of smaller chain lengths, LMWH has limited activity against thrombin (**Fig. 37-11**). The ratio of anti-factor Xa:IIa activity varies between 4:1 and 2:1. By comparison, UFH has an anti-factor Xa:IIa activity ratio of 1:1.[6]

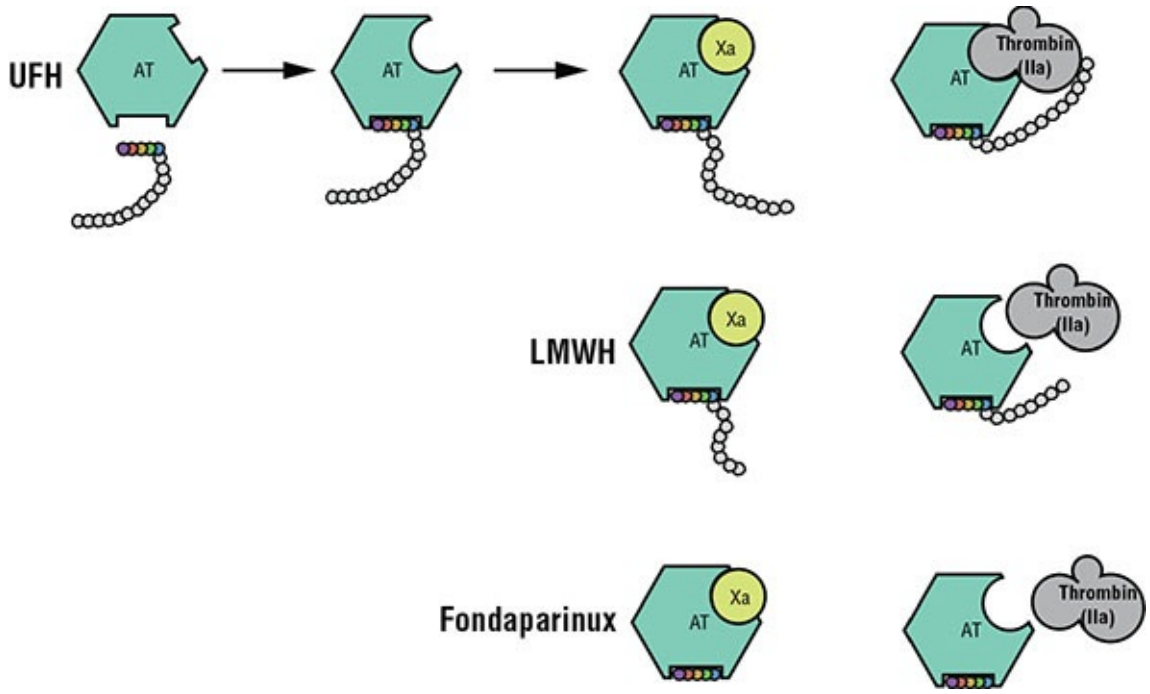


FIGURE 37-11 Pharmacologic activity of unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs), and fondaparinux.

Pharmacokinetics

Compared with UFH, LMWH has a more predictable anticoagulation response. The improved pharmacokinetic profile of LMWH is the result of reduced binding to proteins and cells.[6] The bioavailability of LMWH is about 90% when administered subcutaneously. The peak anticoagulation effect is seen within 3 to 5 hours of subcutaneous LMWH injection and the predominant mode of elimination for LMWH is renal. Consequently, biologic half-life may be prolonged in patients with renal impairment.[6] The plasma half-life of LMWH preparations is 3 to 6 hours. Unlike UFH, the clearance of LMWH is independent of dose.[6]

Efficacy

The efficacy of LMWH for prevention of VTE was established in clinical trials in comparison to low-dose UFH and placebo. For treatment of VTE, the efficacy of fixed weight-based LMWH was compared to aPTT-adjusted intravenous UFH; all patients were transitioned to warfarin for long-term therapy.[70,81]

Adverse Effects

As with other anticoagulants, bleeding is the most common LMWH adverse effect.[68] The frequency of major bleeding may be less with LMWH than with UFH, but this has not been consistently demonstrated in clinical trials.[68] Although there is no proven method for reversing LMWH anticoagulation if major bleeding occurs, intravenous protamine sulfate can be administered. However, because of limited binding to the shorter LMWH chains, protamine sulfate neutralizes only around 60% to 75% of LMWH anticoagulant activity.[6] The recommended dose of protamine sulfate is 1 mg/1 mg of enoxaparin or 1 mg/100 anti-factor Xa units of dalteparin administered in the previous 8 hours. A second protamine sulfate dose of 0.5 mg/1 mg or 100 anti-factor Xa units can be given if bleeding continues. Smaller doses of protamine sulfate can be used if the LMWH dose was given in the previous 8 to 12 hours. The use of protamine sulfate is not recommended if LMWH was administered more than 12 hours earlier.[6] Two reversal agents may have an important role in the future of management of LMWH-related bleeding. Andexanet is a recombinant modified Factor Xa molecule that lacks enzymatic activity while binding to anticoagulant medications and ciraparantag, currently in development, may have utility in rapidly reversing LMWH.[82]

Although thrombocytopenia can occur with LMWH use, the incidence of heparin-induced thrombocytopenia (HIT) is one-third of that observed with UFH, perhaps due to the reduced propensity of LMWH to bind to platelets.[6] However, LMWH exhibits nearly 100% cross-reactivity with UFH antibodies in vitro and thus LHWH should be avoided in patients with an established diagnosis or history of HIT.[6] The risk of osteoporosis appears to be lower with LMWH than with UFH, but both agents have been associated with osteopenia.[6]

Drug–Drug Interactions

The concurrent use of drugs that enhance bleeding risk should be avoided during LMWH therapy if possible. This includes aspirin or other antiplatelet agents, nonsteroidal anti-inflammatory drugs, dipyridamole, or sulfinpyrazone.[70,81]

Dosing and Administration

LMWH is given in fixed or weight-based doses based on the product and indication (Table 37-6). Doses should be based on actual body weight and dose capping (ie, a fixed, maximum daily dose) is not recommended.[69] The dose for enoxaparin is expressed in milligrams, whereas dalteparin doses are expressed in units of anti-factor Xa activity. LMWH is given by subcutaneous injection, as

described in Table 37-5.

Significant LMWH accumulation is possible in patients with severe renal impairment.[6] The enoxaparin dose should be reduced or the dosing interval extended to once daily in patients with CrCL <30 mL/min (0.5 mL/s).[70] Dalteparin is less reliant upon renal elimination than enoxaparin, however its pharmacokinetics are insufficiently characterized in renal insufficiency.[83] LMWH use in patients with end-stage renal disease receiving hemodialysis is poorly understood; thus, UFH is preferred for these patients.[6] Some experts recommend measuring anti-factor Xa activity if LMWH therapy is continued for more than a few days in patients with severe renal disease.[6] For patients with CrCL <30 mL/min (0.5 mL/s) who require VTE prophylaxis, enoxaparin 30 mg once daily is recommended.[6]

Fondaparinux

Fondaparinux is a synthetic molecule consisting of the five critical saccharide units that bind specifically, but reversibly, to antithrombin. Unlike UFH or LMWH, fondaparinux inhibits only factor Xa activity.[6]

Pharmacology/Mechanism of Action

Fondaparinux prevents thrombus generation and clot formation by indirectly inhibiting factor Xa activity through its interaction with antithrombin (Fig. 37-11). Fondaparinux is not destroyed during this process and is released to bind other antithrombin molecules.[6]

Pharmacokinetics

Fondaparinux is rapidly and completely absorbed following subcutaneous administration achieving peak plasma concentrations approximately 2 hours after a single dose and 3 hours with repeated once-daily dosing. At therapeutic concentrations fondaparinux does not bind to red blood cells or other plasma proteins.[6] Fondaparinux is primarily eliminated unchanged in the urine and its terminal elimination half-life is 17 to 21 hours.[6] The anticoagulant effect of fondaparinux persists for 2 to 4 days following discontinuation of the drug in patients with normal renal function.

Efficacy

The efficacy of fondaparinux for prevention of VTE was established in several

clinical trials in comparison to LMWH. For the treatment of VTE, the efficacy of fixed weight-based dosing of fondaparinux was compared to weight-based dosing of LMWH; all patients were transitioned to warfarin for long-term therapy.[48]

Adverse Effects

The primary adverse effect associated with fondaparinux therapy is bleeding.[48] Fondaparinux should be used with extreme caution with neuraxial anesthesia or following spinal puncture because of the risk for spinal or epidural hematoma formation.[48] Some case reports have implicated fondaparinux as a cause of HIT, while others have documented successful HIT treatment with fondaparinux.[84] A specific antidote to reverse the antithrombotic activity of fondaparinux is not currently available.[6]

Drug–Drug Interactions

Fondaparinux has no known pharmacokinetic drug interactions; other drugs with anticoagulant, fibrinolytic, or antiplatelet activity increase the risk of bleeding.[48]

Dosing and Administration

The dose of fondaparinux for VTE prevention is 2.5 mg injected subcutaneously once daily following surgery if hemostasis has been established. It is important to avoid initiating fondaparinux too soon because there is a significant relationship between first dose timing and major bleeding risk.[6] Patients weighing less than 50 kg should not receive VTE prophylaxis with fondaparinux.[48] The usual duration of prophylaxis is 5 to 9 days, but extended prophylaxis for up to 35 days following a lower extremity orthopedic procedure may be used.[4] For the treatment of DVT or PE, the dose of fondaparinux is 5 mg for patients up to 50 kg, 7.5 mg for 50 to 100 kg, and 10 mg for >100 kg.[48]

Unfractionated Heparin

UFH has been used for VTE prevention and treatment for decades. Commercially available UFH preparations are derived from bovine lung or porcine intestinal mucosa. Although some differences exist between the two sources, no differences in antithrombotic activity have been demonstrated.[6]

Pharmacology/Mechanism of Action

UFH is a heterogeneous mixture of sulfated mucopolysaccharides of variable lengths and pharmacologic properties.[6] The anticoagulant profile and clearance of each UFH molecule varies based on its length. Smaller chains are cleared less rapidly than their longer counterparts.[6]

The anticoagulant effect of UFH is mediated through a specific pentasaccharide sequence that binds to antithrombin, provoking a conformational change (Fig. 37-11). Only one-third of the UFH molecules possess the unique pentasaccharide sequence with affinity for antithrombin. The UFH–antithrombin complex is 100 to 1,000 times more potent as an anticoagulant compared with antithrombin alone. Antithrombin inhibits factor IXa, Xa, XIIa, and IIa activity. UFH prevents thrombus growth and propagation allowing endogenous thrombolytic systems to lyse the clot.[6]

Thrombin and Xa are most sensitive to UFH–antithrombin complex inhibition. To inactivate thrombin, the heparin molecule must form a ternary complex bridging between antithrombin and thrombin (Fig. 37-11).[6] Only molecules containing more than 18 saccharides are able to bind to both antithrombin and thrombin simultaneously. Smaller heparin molecules cannot facilitate the interaction between antithrombin and thrombin. In contrast, the inactivation of factor Xa does not require UFH to form a bridge with antithrombin, but requires only UFH binding to antithrombin via the specific pentasaccharide sequence. UFH molecules with as few as five saccharide units are able to catalyze the inhibition of factor Xa. After it has produced its effect UFH uncouples from antithrombin and quickly recouples with another antithrombin molecule.[6]

Pharmacokinetics

UFH is not reliably orally absorbed as a result of its large molecular size and anionic structure. The bioavailability and biologic activity of UFH is limited by a propensity to bind plasma proteins, platelet factor-4, macrophages, fibrinogen, lipoproteins, and endothelial cells. This may explain the substantial interpatient and intrapatient variability observed in the anticoagulation response to UFH.[6]

The onset of anticoagulant effect after subcutaneous injection is 1 to 2 hours, peaking at 3 hours.[6] Continuous infusion is preferred for intravenous UFH administration.[5] Intramuscular administration is discouraged because of the risk of large hematoma formation.

UFH has a dose-dependent half-life of approximately 30 to 90 minutes.[6] There are two primary mechanisms for UFH elimination, a rapid, but saturable zero-order process involving enzymatic inactivation of heparin molecules bound to endothelial cells and macrophages, and renal elimination via a slower, nonsaturable first-order process. With typical therapeutic UFH regimens the zero-order process predominates.[6]

Efficacy

The clinical effectiveness of UFH for prevention and treatment of VTE has been determined through many years of clinical use.

Adverse Effects

Low-dose subcutaneous UFH is associated with a minimal risk of major bleeding, while rates for patients receiving therapeutic UFH doses range from 0% to 2%.[68] Close monitoring for bleeding signs and symptoms during UFH therapy is crucial.[6,68] When major bleeding occurs, UFH should be discontinued and the underlying bleeding source identified and treated. Protamine sulfate in a dose of 1 mg per 100 units of UFH (maximum of 50 mg) can be administered via slow intravenous infusion to reverse the anticoagulant effects of UFH.[6] Protamine sulfate neutralizes UFH in 5 minutes, and persists for 2 hours. Multiple doses or prolonged infusion of protamine sulfate may be necessary if bleeding continues.[6]

HIT is a rare drug-induced immunologic reaction requiring immediate intervention.[85] The most common complication of HIT is VTE; arterial thromboembolic events occur less frequently. Approximately 5% to 10% of patients with HIT die, usually from thrombotic complications.[85] Thrombocytopenia (defined as a platelet count $<150 \times 10^3/mm^3$ [$150 \times 10^9/L$]) is the most common clinical HIT manifestation. HIT should be suspected if platelet counts decrease by 30% to 50% but remain above $150 \times 10^3/mm^3$ ($150 \times 10^9/L$).[85] The characteristic onset of falling platelet count occurs in the first 5 to 10 days after initiation of UFH (Day 0 being the first day of UFH), particularly when administered perioperatively.[85] Thrombocytopenia alone is not sufficient for diagnosing HIT; serologic confirmation of heparin antibodies using an assay available only in a few specialty laboratories is required.[85] Falsely diagnosing HIT can have serious consequences including unnecessary anxiety, unnecessary UFH withdrawal, and the use of alternative anticoagulants with higher bleeding risk. One decision analysis found that strict adherence to platelet monitoring for

HIT could, at best, prevent one thrombosis per 1,000 patients screened at the cost of one major bleeding event.[85] For these reasons, AT9 suggests monitoring platelet counts every 2 to 3 days from Day 4 to 14 of UFH only in populations where the expected HIT risk exceeds 1%.[85] The use of a clinical prediction rule, such as the four Ts score (***T***hrombocytopenia, ***T***iming of platelet count fall or thrombosis, ***T***hrombosis, o***T***her explanation for thrombocytopenia) can improve the predictive value of platelet count monitoring and heparin antibody testing.[85,86] A four Ts score should be calculated when HIT is suspected in patients receiving heparin (UFH or LMWH). If the four Ts score is low (3 or less), no further workup is needed, whereas, further HIT workup including serologic testing should be undertaken if the four Ts score is moderate (4-5) or high (6-8).[87] In the setting of new thrombosis occurring in conjunction with falling platelets and a moderate or high four Ts score all sources of heparin should be discontinued. Alternative anticoagulation with a direct thrombin inhibitor should then be initiated. If warfarin therapy is being used it should be discontinued and reversed with vitamin K; once platelet counts have recovered warfarin can be resumed so long as it is overlapped with direct thrombin inhibitor until the INR is ≥2.0.[85]

Using UFH in doses ≥20,000 units/day for more than 6 months, especially during pregnancy, is associated with significant bone loss and may lead to osteoporosis.[6]

Drug–Drug and Drug–Food Interactions

Few drug interactions are reported with UFH, but concurrent use with other anticoagulants, thrombolytics, and antiplatelet agents increases bleeding risk.[6]

Dosing and Administration

UFH dose is expressed in units of activity. For VTE prevention, UFH is given by subcutaneous injection in the abdominal fat layer. The typical prophylaxis dose is 5,000 units every 8 to 12 hours. When immediate and full anticoagulation is required, an intravenous bolus dose followed by a continuous infusion is preferred (Table 37-7).[6] Subcutaneous UFH (initial dose of 333 units/kg followed by 250 units/kg every 12 hours) also provides adequate therapeutic anticoagulation for the treatment of acute VTE.[6]

Warfarin

Because of its narrow therapeutic index, predisposition to drug and food interactions, and propensity to exacerbate bleeding, warfarin requires frequent monitoring and extensive patient education to achieve optimal outcomes.[60]

Pharmacology/Mechanism of Action

Warfarin exerts its anticoagulation effect by inhibiting the enzymes responsible for the cyclic vitamin K interconversion in the liver.[60] Vitamin K in its reduced form is a required cofactor for vitamin K–dependent carboxylation of factors II, VII, IX, and X, as well as the endogenous anticoagulant proteins C and S. Hepatic carboxylation of the N-terminal region of these proteins is required for biologic activity. By inhibiting the reduced vitamin K supply used in the production of these proteins, warfarin therapy produces partially carboxylated and decarboxylated coagulation proteins with reduced activity.[60] Warfarin has no direct effect on previously circulating clotting factors or previously formed thrombus. The time required for warfarin to achieve its pharmacologic effect is dependent on coagulation protein elimination half-lives (6 hours for factor VII and 72 hours for prothrombin).[60] Full antithrombotic effect is not achieved for at least 6 days after warfarin therapy initiation. By suppressing fully functional clotting factor production, warfarin prevents initial thrombus formation and propagation.[60]

Pharmacokinetics

Warfarin is a racemic mixture of *R* and *S* isomers, with *S*-warfarin being 2.7 to 3.8 times more potent than *R*-warfarin.[60] Warfarin is rapidly and extensively absorbed from the GI tract (bioavailability>90%) and reaches peak plasma concentration within 4 hours of oral administration. Warfarin is 99% bound to plasma proteins and undergoes stereoselective metabolism via CYP 1A2, 2C9, 2C19, 2C8, 2C18, and 3A4 isoenzymes in the liver, with 2C9 being the main enzyme to modulate the elimination of *S*-warfarin.[88] Warfarin pharmacokinetics varies substantially between individuals leading to large interpatient differences in dose requirements. Genetic variations in the 2C9 isoenzyme and vitamin K epoxide reductase (VKOR) have been shown to correlate with warfarin dose requirements.[60] Given the greater potency of *S*-warfarin, coadministration of drugs that induce or inhibit the CYP 2C9 isoenzyme is more likely to cause clinically significant interactions.[60]

Efficacy

The clinical effectiveness of warfarin for prevention and treatment of VTE has been determined through many years of clinical use.

Adverse Effects

Warfarin's primary adverse effect is bleeding that can range from mild to life threatening.[60] Although warfarin does not cause bleeding per se, it exacerbates bleeding from existing lesions and can enable massive bleeding from ordinarily minor sources.[60] Anticoagulation therapy intensity is an important bleeding risk factor; the likelihood of bleeding rises with increasing INR values.[60] Therefore, maintaining the INR within the target range is important to reduce bleeding risk. For INR>4.5 without evidence of bleeding, AT9 suggests withholding warfarin, decreasing the warfarin dose, and/or providing a small dose of vitamin K to shorten the time required to return to normal INR.[89] Vitamin K can be administered parenterally or orally; the oral route is preferred in the absence of serious bleeding. Most patients with asymptomatic INR elevations can be safely managed by withholding warfarin alone. AT9 suggests against routine vitamin K use if the INR is between 4.5 and 10 and no bleeding is present as it has not been shown to affect the risk of developing subsequent bleeding or thromboembolism compared with simply withholding warfarin alone. For INRs>10 without evidence of bleeding, oral vitamin K 2.5 mg is suggested.[89] Vitamin K should be used cautiously in patients at high thromboembolism risk due to the possibility of INR overcorrection. Conversely, simply withholding warfarin therapy may not lower high INRs quickly enough in patients at high bleeding risk or in situations associated with prolonged INR elevations such as drug interactions and intentional overdoses.

Patients with warfarin-associated major bleeding require supportive care. AT9 suggests rapid reversal of anticoagulation with four-factor PCCs (rather than FFP) and 5 to 10 mg of vitamin K–administered via slow intravenous injection.[89]

Other adverse effects associated with warfarin are uncommon, but can be serious.[60] The etiology of the "purple toe syndrome" is unknown, but is thought to be the result of cholesterol microembolization into the arterial circulation of the toes.[60] If recognized early, complete resolution can be achieved by simply substituting warfarin for a different anticoagulant.[90] Warfarin-induced skin necrosis is a serious dermatologic reaction usually manifesting in the first week of therapy as a painful maculopapular rash and ecchymosis or purpura that subsequently progresses to necrotic gangrene. Areas of the body rich in

subcutaneous fat, such as the breasts, thighs, buttocks, and abdomen are most commonly affected.[60] If skin necrosis is suspected, warfarin therapy should be discontinued immediately and reversed with FFP or PCC and vitamin K, and full-dose UFH or LMWH therapy initiated. Patients with a history of skin necrosis should restart warfarin with extreme caution, if at all, using small doses and gradual titration under full-dose UFH or LMWH coverage until a therapeutic INR is achieved.[60]

Drug–Food and Drug–Drug Interactions

The pharmacokinetic and pharmacodynamic properties of warfarin predispose to numerous clinically important food and drug interactions.[91] Vitamin K can reverse warfarin's pharmacologic activity, and many foods contain sufficient vitamin K to reduce the anticoagulation effect if consumed in large portions or repetitively within a short period of time.[60] Patients should be instructed to maintain a relatively consistent intake of vitamin K–rich foods (**Table 37-13**). It is important to stress consistency rather than abstinence.

TABLE 37-13 Vitamin K Content of Select Foods[a]

Very High (>200 mcg)	High (100-200 mcg)	Medium (50-100 mcg)	Low (<50 mcg)
Brussel sprouts	Basil	Apple, green	Apple, red
Chickpeas	Broccoli	Asparagus	Avocado
Collard greens	Chive	Cabbage	Beans
Coriander	Coleslaw	Cauliflower	Breads, grains
Endive	Cucumber (with peel)	Mayonnaise	Carrot
Kale	Canola oil	Nuts, pistachio	Cereal
Lettuce, red leaf	Green onion/scallion	Squash, summer	Celery
Parsley	Lettuce, butterhead		Coffee
Spinach	Mustard greens		Corn
Swiss chard	Soybean oil		Cucumber (without peel)
Tea, green			Dairy products
Tea, black			Eggs
Turnip greens			Fruit (varies)
Watercress			Lettuce, iceberg
			Meats, fish, poultry
			Pasta
			Peanuts
			Peas
			Potato
			Rice
			Tomato

[a]Approximate amount of vitamin K per 100 g (3.5 oz) serving.

Source: Data from Booth and Centurelli.[92]

Pharmacokinetic drug interactions with warfarin primarily result from alterations in hepatic metabolism. Drugs inhibiting or inducing CYP 2C9, 1A2, and 3A4 isoenzymes have the greatest potential to significantly alter warfarin therapy response.[60] Drugs altering hemostasis or platelet function (eg, aspirin, clopidogrel) can increase bleeding risk without altering warfarin pharmacokinetics or impacting the INR.[60] Clinicians should advise patients on warfarin to report potential interactions to their anticoagulation provider whenever a drug product, dietary supplement, or herbal product is initiated or stopped, whether prescribed or available over the counter. If there is a known drug interaction or doubt about potential to alter the warfarin response, more

frequent INR testing is recommended with warfarin dose adjustments as needed to maintain INRs in the target range.[91]

Dosing and Administration

The dose of warfarin is individualized based on the desired target INR range and anticoagulant response by periodically measuring the prothrombin time and calculating the INR.[60] The pharmacodynamic response and pharmacokinetic disposition of warfarin between and within patients are highly variable. Therefore, the dose of warfarin must be individualized based on frequent clinical and laboratory monitoring.[60]

The average weekly warfarin dose is between 25 and 55 mg. Some patients require lower than usual dose requirement including patients who are of advanced age (>65 years), have an elevated baseline INR, poor nutritional status, liver disease, genetic polymorphisms in CYP 2C9 and VKOR, and concurrent use of medications known to enhance the effect of warfarin.[60] Higher than usual dose requirements are also necessary in some patients including concurrent use of medications known to induce the metabolism of warfarin such as rifampin and carbamazepine, high dietary vitamin K intake, and genetic polymorphisms in CYP 2C9. It is important to collect a complete medication history, including use of herbal and nutritional products as these can influence warfarin's metabolism, dose requirements, and the risk of bleeding.[60]

Initiating warfarin therapy with 5 to 10 mg daily and adjusting the dose based on the INR response will produce therapeutic INRs in 4 to 5 days for most patients (Fig. 37-10). Lower starting doses may be acceptable based on patient-related factors such as advanced age, malnutrition, liver disease, or heart failure. Starting doses>10 mg should be avoided.[60] When warfarin therapy is initiated in the outpatient setting the INR should be measured every 1 to 3 days until stabilized. For patients with acute VTE, a parenteral, rapid acting anticoagulant such as UFH, LMWH, or fondaparinux should be overlapped with warfarin therapy for at least 5 days regardless of whether the target INR has been achieved earlier.[5,60]

It is important to allow sufficient time for changes in the INR to occur when adjusting the dose of warfarin. In general, maintenance dose changes should not be made more frequently than every 3 days. When adjusting maintenance warfarin doses the weekly dose should be reduced or increased by 5% to 25% of the weekly dose; the full effect of dose changes may not become evident for 5 to 7 days or longer.[60] Patients demonstrating a stable response to warfarin as

evidenced by consistently therapeutic INR results on the same warfarin dose can have INRs checked as infrequently as every 8 to 12 weeks, although most stable patients are tested approximately every 4 to 6 weeks.[89]

Therapeutic Considerations

Prevention Versus Treatment of VTE

Lower doses of LMWH and DOACs are used for VTE prevention than during VTE treatment. Warfarin may be targeted to a traditional INR range (2.0-3.0) or reduced intensity (1.5-2.5) for VTE prophylaxis. Orthopedic surgeons frequently prefer the lower INR range due to perceived lower bleeding risk. VTE prophylaxis in high-risk hospitalized patients is typically discontinued at discharge. In contrast, after major orthopedic surgery VTE prophylaxis continues following discharge for up to 35 days.

VTE treatment requires full therapeutic anticoagulant doses for at least 3 months. Patients unwilling to self-administer LMWH or fondaparinux injections may prefer apixaban or rivaroxaban which are taken orally. The duration of anticoagulant therapy after acute VTE is principally determined by whether the clot was provoked, unprovoked, or recurrent. Three months of therapeutic anticoagulation is sufficient following a first episode of VTE provoked by major transient risk factors such as surgery, pregnancy, or trauma. Appropriately selected patients with unprovoked or recurrent VTE should receive long-term anticoagulation for secondary VTE prevention. Patients selected for long-term secondary anticoagulation traditionally receive standard therapeutic doses. In patients for whom there is clinical equipoise regarding anticoagulation continuation, prophylactic doses of apixaban and rivaroxaban are as effective as full therapeutic doses after 6 months of treatment has been completed.[75,76] However, prophylactic doses were not clearly safer than therapeutic doses as the risk of major bleeding was low for both options. Switching to aspirin for long-term secondary VTE prevention is also an option, but is less effective than continuing anticoagulation therapy.[93,94]

Renal Function

Periodic renal function assessment is important during long-term DOAC therapy, especially for patients with CrCL <50 mL/min (0.83 mL/s). DOACs should not be used in patients with CrCL <25 mL/min (0.42 mL/s) (apixaban) or 30 mL/min (0.5 mL/s) (rivaroxaban and dabigatran) and warfarin is preferred in this

setting. Edoxaban dosing is reduced to 30 mg once daily in patients with CrCL 15 to 50 mL/min (0.25-0.83 mL/s).[54–57] LMWHs also rely upon renal elimination and UFH remains preferred in patients with severe renal compromise (eg, CrCL <30mL/min [0.5 mL/s]).[22]

Weight

Patients at extremes of body weight were underrepresented in DOAC VTE treatment trials. There is speculation regarding whether very obese or very small patients receive equivalent anticoagulant effects with DOAC when compared to other patients. DOACs should be used with caution in very obese or very small patients until additional information substantiating equivalent outcomes becomes available. The International Society of Thrombosis and Haemostasis recommends avoiding the use of DOACs in patients weighing more than 120 kg or with a body mass index of greater than 40 kg/m^2.[95]

LMWH dosing in obesity frequently causes concern. Patients weighing more than 90 kg would exceed the maximum dose specified in approved labeling for dalteparin (18,000 units).[81] However, evidence supports similar anti-Xa exposure to LMWH and no increase in bleeding risk compared to nonobese patients when doses based on actual body weight without capping are administered.[96] Fondaparinux is a convenient option for obese patients as the 10 mg dose is suitable for acute VTE treatment in patients>100 kg.[48] Obese patients requiring VTE prophylaxis may need higher than normal LMWH doses. For example enoxaparin 40 mg subcutaneously twice daily may be more effective than usual VTE prophylaxis doses for patients undergoing bariatric surgery.[97]

Response to Previous Therapy

Other than bleeding, anticoagulants are generally well tolerated. However, adverse reactions, treatment failure, or allergies during previous therapy may necessitate preferential use of one anticoagulant over another.

Warfarin allergy is rare and often related to dyes or tablet excipients rather than the active ingredient. Warfarin 10 mg tablets contain no dye and can be considered when allergy is suspected. Patients experiencing dabigatran-related dyspepsia can try taking the dose with a full glass of water or food. Transitioning to another DOAC or warfarin may be necessary.

Cost is an important aspect of personalizing anticoagulant therapy for VTE prevention and treatment. For patients unable to afford DOACs, warfarin remains a cost-effective option.

Patients suspected of having a recurrent VTE during anticoagulant therapy should have their adherence to therapy assessed and imaging compared to historical data to ensure the clot is in fact new. Determining and correcting the causes of poor medication adherence to anticoagulation therapy should occur before pursuing alternate anticoagulant therapy. Malignancy should be considered when treatment adherence appears to be good. Switching to a LMWH is recommended for breakthrough VTE occurring during oral anticoagulation therapy.[22] Patients having breakthrough VTE during LMWH should be switched to twice daily injections (if receiving once daily LMWH) and considered for dose escalation of 25% to 33%.[22] Switching to an oral factor Xa inhibitor may also be an option given the comparable efficacy of edoxaban and dalteparin for the treatment of cancer-related VTE; however, less is known regarding their use in breakthrough VTE.

Drug Interactions

Although the DOACs have far fewer drug interactions than warfarin, when critical drug interactions are unavoidable, the DOACs are not preferred because coagulation tests with known reference ranges and dosing recommendations to adjust DOAC therapy are not available. Which drug interactions must be avoided is matter of debate. Potent inducers of P-gp and CYP3A4 enzymes such as carbamazepine and rifampin should be avoided. Caution should be used with concurrent use of potent P-gp or combination P-gp/CYP3A4 inhibitors with a DOAC, particularly in the setting renal insufficiency.[54–57]

Pharmacogenomics

CYP2C9 is the hepatic microsomal enzyme responsible for metabolism of the more potent S-enantiomer of warfarin. Polymorphisms in CYP2C9 and the gene coding for VKOR (known as vitamin K epoxide reductase complex 1) explain a substantial proportion of warfarin dose variability between patients. Dosing algorithms using CYP2C9 and VKOR pharmacogenomics, as well as clinical and drug interaction information, have been developed to assist providers more accurately select initial warfarin doses based upon a predicted maintenance warfarin dose for an individual patient (see www.warfarindosing.org). The Food and Drug Administration (FDA) updated the warfarin package label to include use of pharmacogenetic testing in 2007.[88]

There are several barriers to the widespread application of pharmacogenomic testing for warfarin. First, and most important, is the prothrombin time /INR.

The ability to rapidly assess a patient's physiologic response to warfarin using an inexpensive and widely available test limits the need for pharmacogenomic information. Second is the timeliness of receiving pharmacogenomic test results. Pharmacogenomic information is most valuable when selecting the first 3 or 4 warfarin doses. However, pharmagenomic testing outside of clinical trials may require several days or longer before results become available. Delaying warfarin initiation is rarely safe, thus pharmacogenomic test results are only meaningful if they are available in the first 2 to 3 days after treatment initiation. Although poor metabolizing CYP2C9 subtypes have been associated with increased risk of bleeding compared to the wild-type, clinical trials have not demonstrated improved bleeding or thromboembolic outcomes with the routine use of pharmacogenomic information to guide warfarin dosing when compared to usual care.[98,99] As a result, the clinical utility and cost-effectiveness of warfarin pharmacogenomics remains ill-defined and AT9 suggests against routine use.[89]

Evaluation of Therapeutic Outcomes

Warfarin dose titration based on INR monitoring and UFH dose titration based on aPTT monitoring allow a degree of personalized therapy not available with other anticoagulants. The intensity of warfarin or UFH therapy can be easily titrated in high-risk situations such as invasive procedures, accidental or intentional overdose, suspected nonadherence, or concomitant therapy with interacting drugs. Titrating DOAC therapy cannot be accomplished due to lack of readily available quantitative coagulation assays and dosing guidelines in these clinical scenarios.[100]

While laboratory coagulation monitoring is unnecessary during DOAC therapy, clinical surveillance is likely beneficial. In clinical trials comparing DOACs to warfarin, patients receiving DOAC therapy had contact with healthcare provider every 4 weeks to screen for bleeding, changes in renal or hepatic function, drug adherence, potential drug interactions, and plan for invasive procedures. A study performed in patients with atrial fibrillation taking dabigatran found that pharmacist involvement during initial drug selection, patient education, and follow-up contacts improved drug adherence.[101] Adherence is essential to preventing recurrent VTE during DOAC therapy due to their short half-lives. Pharmacist involvement during DOAC initiation may be especially important to ensure proper transitions from LMWH to dabigatran or edoxaban or from initiation to maintenance dosing with rivaroxaban or apixaban.

An ABCDEF checklist may be helpful when monitoring patients on DOACs: A-Adherence with therapy, B-Bleeding Risk Assessment, C-Creatinine clearance/renal function monitoring, D-Drug interaction evaluation, E-Examination for adverse events and therapeutic effectiveness, and F-Final assessment and recommendations regarding the need for ongoing DOAC therapy.[102] What remains unclear is how frequently patient monitoring should be performed for patients on DOACs, and whether it should be performed for all patients taking DOACs or only those at highest-risk.

Because LMWH anticoagulant response is predictable when given subcutaneously, routine laboratory monitoring is unnecessary.[6] Prior to LMWH initiation, baseline complete blood cell counts with platelets and serum creatinine should be obtained. The complete blood cell count can be checked every 5 to 10 days during the first 2 weeks of LMWH therapy and every 2 to 4 weeks thereafter to monitor for occult bleeding. If neuraxial anesthesia has been used, patients should be closely monitored for signs and symptoms of neurologic impairment.[70]

Anti-factor Xa activity is the most widely used test to monitor the anticoagulant effect of LMWH in clinical practice. Routine anti-factor Xa activity measurement is unnecessary in uncomplicated patients who are stable.[6] Measuring anti-factor Xa activity may be considered in patients who have significant renal impairment (eg, CrCL <30 mL/min [0.5 mL/s]), are morbidly obese, or are pregnant.[6] However, many laboratories do not standardize the measurement of anti-actor Xa levels for specific LMWH products. For this reason and because the correlation between anti-factor Xa levels and adverse outcomes is uncertain, some experts recommend against measuring anti-factor Xa activity in these situations.

When anti-factor Xa activity is used to monitor LMWH therapy, the sample should be drawn during the peak anti-factor Xa activity—once steady state has been achieved (after the second or third dose) and approximately 4 hours after the subcutaneous injection.[6] The anti-factor Xa activity therapeutic range is not well-defined and has not been clearly correlated with efficacy or the risk of bleeding. For the treatment of VTE, an acceptable target range for the peak anti-Xa level for twice-daily enoxaparin dosing is 0.6 to 1 unit/mL (kU/L). For once daily dosing, peak targets>1 unit/mL (kU/L) for enoxaparin and 1.05 units/mL (kU/L) for dalteparin have been suggested.[6] The target range for peak anti-Xa concentrations during cancer-associated VTE treatment with dalteparin is 0.5 to 1.5 units/mL(kU/L).[81]

Prior to initiating fondaparinux, baseline kidney function should be

determined as fondaparinux is contraindicated when CrCL is <30 mL/min (0.5 mL/s).[48] Signs and symptoms of bleeding should be monitored daily, particularly in patients with a baseline CrCL between 30 and 50 mL/min (0.5 and 0.83 mL/s). If neuraxial anesthesia has been used, patients should be closely monitored for signs and symptoms of neurologic impairment.[48] Fondaparinux does not alter coagulation tests such as the aPTT and PT. The role of anti-factor Xa monitoring during fondaparinux is not well-defined, but routine coagulation testing is not required.[48]

Administration of UFH requires close monitoring because each patient's anticoagulant response is unpredictable.[6] Although the aPTT has several limitations, most experts advocate using the aPTT to monitor UFH provided that institution-specific therapeutic ranges are defined.[6] The aPTT should be measured prior to the initiation of therapy to determine the patient's baseline. With intravenous infusion, the aPTT response to UFH therapy should be measured 6 hours after initiation or dose changes. UFH doses should be adjusted based on patient response and the institution-specific aPTT therapeutic range (Table 37-7).[6]

The prothrombin time (PT) measures the biologic activity of factors II, VII, and X and has been used for decades to monitor the anticoagulation effects of warfarin. The PT is performed by measuring the time required for clot formation after adding calcium and thromboplastin to citrated plasma.[60] Interpreting the PT is problematic because thromboplastins of differing sensitivity produce substantially different results, some of which could lead to inappropriate dosing decisions. The World Health Organization (WHO) addressed the need for standardization in the late 1970s by developing a reference thromboplastin and recommending the use of the INR to monitor warfarin therapy.[60] The INR attempts to correct for differences in thromboplastin reagents through the following formula:

$$\mathrm{INR} = \left(\frac{\mathrm{PT}^{\mathrm{patient}}}{\mathrm{PT}^{\mathrm{control}}} \right)^{\mathrm{ISI}}$$

The International Sensitivity Index (ISI) is a measure of thromboplastin responsiveness compared with the WHO reference standard.[60] Although the INR system has a number of limitations, it remains the preferred method for monitoring warfarin therapy.[60]

Anticoagulation therapy management services can optimize the care of

patients who take warfarin therapy by providing structured care, comprehensive patient education, and evaluation of outcomes. When anticoagulation management services are not available, individual clinicians should strive to implement similar structured care processes.[89]

Portable finger-stick INR devices are available for monitoring warfarin therapy. These devices permit clinicians to do “real-time” therapeutic INR monitoring and enable patients to engage in self-testing at home.[89] Patients who engage in INR self-testing and warfarin self-management have fewer thromboembolic complications, report high levels of satisfaction with care, and maintain INRs within the therapeutic range slightly more frequently than those managed by “usual care.” However, home INR testing and self-management is not for everyone and requires careful patient selection and considerable patient education.[89] Finger-stick INR devices are relatively expensive, but some patients qualify for insurance coverage for the monitor and testing supplies.

CONCLUSION

VTE is a significant public health issue, yet there is little public awareness of the life-threatening nature of this commonly occurring condition. Given the number and variety of clinical circumstances that place individuals at risk for VTE, improvements in VTE prevention and care have the potential to benefit many patients. Over the past decade, the focus on quality healthcare has included systematic measures to improve the use of effective VTE prophylaxis and evidence-based VTE treatments. The concerted efforts of government and accrediting agencies working with hospitals and other healthcare institutions will hopefully reduce VTE rates. Systematic approaches to this problem are needed at every level, starting with increased public and health practitioner awareness, continuing with the uniform use of effective prophylactic strategies in patients at risk, and concluding with the application of high-quality VTE treatment strategies.

Postclass Engaged Learning Activity

Conduct a literature search and identify a primary research study that has been published in the past 12 months regarding the treatment of VTE. If the study is regarding a new patient care process, write a brief summary about the process, how feasible you believe the process would be to implement in

practice, and what setting(s) the process would be best suited (eg, community pharmacy, ambulatory clinic, long-term care facility, hospital). If the study is regarding a medication that is discussed in this chapter, write a brief summary about the study methods, the major findings, and how this new information might change current practice. If the study is regarding a new medication that is not described in the chapter, write a brief summary about the medication's mechanisms of action, how it is administered, and one potential advantage or disadvantage of this new medication compared to the current standard of care. This activity is intended to build your literature evaluation skills and ability to critically appraise research manuscripts.

ABBREVIATIONS

aPC	activated protein C
aPTT	activated partial thromboplastin time
AT9	*Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: Evidence-Based Clinical Practice Guidelines* published by the American College of Chest Physicians
β_2-gp	β_2-glycoprotein
CrCL	creatinine clearance
CTPA	computed tomography pulmonary angiography
CTPH	chronic thromboembolic pulmonary hypertension
CUS	compression ultrasound
CYP	cytochrome P450
DOAC	direct acting oral anticoagulant
DVT	deep vein thrombosis
FFP	fresh-frozen plasma
HIT	heparin-induced thrombocytopenia
INR	international normalized ratio
IPC	intermittent pneumatic compression
ISI	International Sensitivity Index
IVC	inferior vena cava
LDUH	low-dose unfractionated heparin
LMWH	low-molecular-weight heparin
NICE	National Institute for Health and Care Excellence
PCCs	prothrombin complex concentrates
PE	pulmonary embolism
PESI	Pulmonary Embolism Severity Index
P-gp	P-glycoprotein
PT	prothrombin time
TF	tissue factor
TFPI	tissue factor pathway inhibitor
tPA	tissue plasminogen activator
UFH	unfractionated heparin
V/Q	ventilation–perfusion
VKOR	vitamin K epoxide reductase
VTE	venous thromboembolism
WHO	World Health Organization

REFERENCES

1. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. *Lancet*. 2012;379:1835–1846.
2. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e195S–e226S.
3. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e227S–e277S.
4. Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e278S–e325S.
5. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e419S–e494S.
6. Garcia DA, Baglin TP, Weitz JI, Samama MM, American College of Chest P. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e24S–e43S.
7. Day ISCfWT. Thrombosis: A major contributor to the global disease burden. *J Thromb Haemost*. 2014;12:1580–1590.
8. Martinez C, Cohen AT, Bamber L, Rietbrock S. Epidemiology of first and recurrent venous thromboembolism: A population-based cohort study in patients without active cancer. *Thromb Haemost*. 2014;112:255–263.
9. Bates SM, Greer IA, Middeldorp S, et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e691S–e736S.
10. Johnson SA, Eleazer GP, Rondina MT. Pathogenesis, diagnosis, and treatment of venous thromboembolism in older adults. *J Am Geriatr Soc*. 2016;64:1869–1878.
11. Anderson JA, Weitz JI. Hypercoagulable states. *Critical Care Clinics*. 2011;27:933–952,vii.

12. Turpie AG, Esmon C. Venous and arterial thrombosis: Pathogenesis and the rationale for anticoagulation. *Thromb Haemost*. 2011;105:586–596.
13. Reitsma PH, Versteeg HH, Middeldorp S. Mechanistic view of risk factors for venous thromboembolism. *Arterioscler Thromb Vasc Biol*. 2012;32:563–568.
14. De Caterina R, Husted S, Wallentin L, et al. General mechanisms of coagulation and targets of anticoagulants (Section I). Position Paper of the ESC Working Group on Thrombosis: Task Force on Anticoagulants in Heart Disease. *Thromb Haemost*. 2013;109:569–579.
15. Margaglione M, Grandone E. Population genetics of venous thromboembolism. A narrative review. *Thromb Haemost*. 2011;105:221–231.
16. Rijken DC, Lijnen HR. New insights into the molecular mechanisms of the fibrinolytic system. *J Thromb Haemost*. 2009;7:4–13.
17. Khorana AA. Cancer and coagulation. *Am J Hematol*. 2012;87 (Suppl 1):S82–S87.
18. Chong LY, Fenu E, Stansby G, Hodgkinson S, Guideline Development G. Management of venous thromboembolic diseases and the role of thrombophilia testing: summary of NICE guidance. *BMJ*. 2012;344:e3979.
19. Bates SM, Jaeschke R, Stevens SM, et al. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e351S–e418S.
20. Le Gal G, Righini M. Controversies in the diagnosis of venous thromboembolism. *J Thromb Haemost*. 2015;13(Suppl 1):S259–S265.
21. Takach Lapner S, Julian JA, Linkins LA, Bates S, Kearon C. Comparison of clinical probability-adjusted D-dimer and age-adjusted D-dimer interpretation to exclude venous thromboembolism. *Thromb Haemost*. 2017;117:1937–1943.
22. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest*. 2016;149:315–352.
23. Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: Increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost*. 2000;83:416–420.
24. Wendelboe AM, McCumber M, Hylek EM, et al. Global public awareness

of venous thromboembolism. *J Thromb Haemost*. 2015;13:1365–1371.

25. Mahan CE, Holdsworth MT, Welch SM, Borrego M, Spyropoulos AC. Deep-vein thrombosis: A United States cost model for a preventable and costly adverse event. *Thromb Haemost*. 2011;106:405–415.
26. Guyatt GH, Eikelboom JW, Gould MK, et al. Approach to outcome measurement in the prevention of thrombosis in surgical and medical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e185S–e194S.
27. Gray J, Razmus I. Improving venous thromboembolism prevention processes and outcomes at a community hospital. *Jt Comm J Qual Patient Saf*. 2012;38:61–66.
28. Schiro TA, Sakowski J, Romanelli RJ, et al. Improving adherence to best-practice guidelines for venous thromboembolism risk assessment and prevention. *Am J Health Syst Pharm*. 2011;68:2184–2189.
29. Zareba P, Wu C, Agzarian J, Rodriguez D, Kearon C. Meta-analysis of randomized trials comparing combined compression and anticoagulation with either modality alone for prevention of venous thromboembolism after surgery. *Br J Surg*. 2014;101:1053–1062.
30. Rajasekhar A, Streiff MB. Vena cava filters for management of venous thromboembolism: A clinical review. *Blood Rev*. 2013;27:225–241.
31. Portola Pharmaceuticals I. Betrixaban prescribing information. 2018. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208383s000lbl Accessed May 19, 2018.
32. Reichert JA, Hlavinka PF, Stolzfus JC. Risk of hemorrhage in patients with chronic liver disease and coagulopathy receiving pharmacologic venous thromboembolism prophylaxis. *Pharmacotherapy*. 2014;34:1043–1049.
33. Ali M, Ananthakrishnan AN, McGinley EL, Saeian K. Deep vein thrombosis and pulmonary embolism in hospitalized patients with cirrhosis: A nationwide analysis. *Digestive Diseases and Sciences*. 2011;56:2152–2159.
34. Anderson FAJr., Huang W, Friedman RJ, et al. Prevention of venous thromboembolism after hip or knee arthroplasty: Findings from a 2008 survey of US orthopedic surgeons. *J Arthroplasty*. 2012;27:659–666. e5.
35. Mont MA, Jacobs JJ, Boggio LN, et al. Preventing venous

thromboembolic disease in patients undergoing elective hip and knee arthroplasty. *J Am Acad Orthop Surg*. 2011;19:768–776.

36. Anderson DR, Dunbar M, Murnaghan J, et al. Aspirin or Rivaroxaban for VTE Prophylaxis after Hip or Knee Arthroplasty. *N Engl J Med*. 2018;378:699–707.
37. Wells PS, Forgie MA, Rodger MA. Treatment of venous thromboembolism. *JAMA*. 2014;311:717–728.
38. Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: Results of a randomized trial (SELECT-D). *J Clin Oncol*. 10, 2018;36(20):2017–2023. doi: 10.1200/JCO.2018.78.8034.
39. Meyer G, Planquette B, Sanchez O. Pulmonary embolism: Whom to discharge and whom to thrombolyze? *J Thromb Haemost*. 2015;13(Suppl 1):S252–S258.
40. Kahn SR, Shapiro S, Wells PS, et al. Compression stockings to prevent post-thrombotic syndrome: A randomised placebo-controlled trial. *Lancet*. 2014;383:880–888.
41. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369:799–808.
42. Investigators E-P, Buller HR, Prins MH, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366:1287–1297.
43. Investigators E, Bauersachs R, Berkowitz SD, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363:2499–2510.
44. Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation*. 2014;129:764–772.
45. Hokusai VTEI, Buller HR, Decousus H, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013;369:1406–1415.
46. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med*. 15, 2018;378(7):615–624. doi: 10.1056/NEJMoa1711948.
47. Goldhaber SZ. Advanced treatment strategies for acute pulmonary embolism, including thrombolysis and embolectomy. *J Thromb Haemost*.

2009;7(Suppl 1):322–327.
48. GlaxoSmithKline. Arixtra Prescribing Information 2018.
49. Martinez K, Kosirog E, Billups SJ, Clark NP, Delate T, Witt DM. Clinical outcomes and adherence to guideline recommendations during the Initial treatment of acute venous thromboembolism. *Ann Pharmacother*. 2015;49:869–875.
50. Vedantham S, Goldhaber SZ, Julian JA, et al. Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis. *N Engl J Med*. 2017;377:2240–2252.
51. Wang TF, Squizzato A, Dentali F, Ageno W. The role of thrombolytic therapy in pulmonary embolism. *Blood*. 2015;125:2191–2199.
52. Baglin T. What happens after venous thromboembolism? *J Thromb Haemost*. 2009;7(Suppl 1):287–290.
53. Aujesky D, Hughes R, Jimenez D. Short-term prognosis of pulmonary embolism. *J Thromb Haemost*. 2009;7(Suppl 1):318–321.
54. Bristol Myers Squibb C. Eliquis Prescribing Information. 2018. Available at http://packageinserts.bms.com/pi/pi_eliquis.pdf. Accessed May 19, 2018.
55. Boehringer-Ingelheim. Pradaxa Prescribing Information. 2018. Available at http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing%20Information/PIs/Pradaxa/Pra Accessed May 19, 2018.
56. Janssen Pharmaceuticals I. Xarelto Prescribing Information. 2015. Available at https://www.xareltohcp.com/shared/product/xarelto/prescribing-information.pdf. Accessed August 30, 2015.
57. Daiichi Sankyo I. Savaysa Prescribing Information. 2018. Available at http://dsi.com/prescribing-information-portlet/getPIContent?productName=Savaysa&inline=true. Accessed May 19, 2018.
58. Knol HM, Schultinge L, Erwich JJ, Meijer K. Fondaparinux as an alternative anticoagulant therapy during pregnancy. *J Thromb Haemost*. 2010;8:1876–1879.
59. Kamel H, Navi BB, Sriram N, Hovsepian DA, Devereux RB, Elkind MS. Risk of a thrombotic event after the 6-week postpartum period. *N Engl J Med*. 2014;370:1307–1315.
60. Ageno W, Gallus AS, Wittkowsky A, et al. Oral anticoagulant therapy:

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e44S–e88S.

61. Monagle P, Chan AK, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e737S–e801S.
62. Schulman S, Zondag M, Linkins L, et al. Recurrent venous thromboembolism in anticoagulated patients with cancer: Management and short-term prognosis. *J Thromb Haemost*. 2015;13:1010–1018.
63. Easaw JC, Shea-Budgell MA, Wu CM, et al. Canadian consensus recommendations on the management of venous thromboembolism in patients with cancer. Part 2: Treatment. *Curr Oncol*. 2015;22:144–155.
64. Farge D, Debourdeau P, Beckers M, et al. International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *J Thromb Haemost*. 2013;11:56–70.
65. Vedovati MC, Germini F, Agnelli G, Becattini C. Direct oral anticoagulants in patients with VTE and cancer: A systematic review and meta-analysis. *Chest*. 2015;147:475–483.
66. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med*. 2018;378:615–624.
67. Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: Results of a randomized trial (SELECT-D). *J Clin Oncol*. 2018;36(20):2017–2023.
68. Schulman S, Beyth RJ, Kearon C, Levine MN, American College of Chest P. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133:257S–298S.
69. Clark NP. Low-molecular-weight heparin use in the obese, elderly, and in renal insufficiency. *Thromb Res*. 2008;123(Suppl 1):S58–S61.
70. Sanofi-Aventis. Lovenox Prescribing Information. 2018. Available at http://products.sanofi.us/lovenox/lovenox.html. Accessed May 29, 2018.
71. Clark NP, Witt DM, Davies LE, et al. Bleeding, recurrent venous thromboembolism, and mortality risks during warfarin interruption for invasive procedures. *JAMA Intern Med*. 2015;175:1163–1168.

72. Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e326S–e350S.
73. Pollack CVJr., Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med*. 2015;373:511–520.
74. Yeh CH, Gross PL, Weitz JI. Evolving use of new oral anticoagulants for treatment of venous thromboembolism. *Blood*. 2014;124:1020–1028.
75. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med*. 2013;368:699–708.
76. Weitz JI, Lensing AWA, Prins MH, et al. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. *N Engl J Med*. 2017;376:1211–1222.
77. Weitz JI, Pollack CVJr. Practical management of bleeding in patients receiving non-vitamin K antagonist oral anticoagulants. *Thromb Haemost*. 2015;114.
78. Greinacher A, Thiele T, Selleng K. Reversal of anticoagulants: An overview of current developments. *Thromb Haemost*. 2015;113:931–942.
79. Tornkvist M, Smith JG, Labaf A. Current evidence of oral anticoagulant reversal: A systematic review. *Thromb Res*. 2018;162:22–31.
80. Ansell JE, Bakhru SH, Laulicht BE, et al. Use of PER977 to reverse the anticoagulant effect of edoxaban. *N Engl J Med*. 2014;371:2141–2142.
81. PfizerLabs. Fragmin Prescribing Information. 2018. Available at http://labeling.pfizer.com/ShowLabeling.aspx?id=2293. Accessed May 19, 2018.
82. Crowther M, Crowther MA. Antidotes for novel oral anticoagulants: Current status and future potential. *Arterioscler Thromb Vasc Biol*. 2015;35:1736–1745.
83. Park D, Southern W, Calvo M, et al. Treatment with dalteparin is associated with a lower risk of bleeding compared to treatment with unfractionated heparin in patients with renal insufficiency. *J Gen Intern Med*. 2016;31(12):182–187.
84. Blackmer AB, Oertel MD, Valgus JM. Fondaparinux and the management of heparin-induced thrombocytopenia: The journey continues. *Ann Pharmacother*. 2009;43:1636–1646.

85. Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e495S–e530S.
86. Crowther MA, Cook DJ, Albert M, et al. The 4Ts scoring system for heparin-induced thrombocytopenia in medical-surgical intensive care unit patients. *J Crit Care*. 2010;25:287–293.
87. Cuker A, Gimotty PA, Crowther MA, Warkentin TE. Predictive value of the 4Ts scoring system for heparin-induced thrombocytopenia: A systematic review and meta-analysis. *Blood*. 2012;120:4160–4167.
88. Bristol Myers Squibb C. Coumadin Prescribing Information. 2018. Available at http://packageinserts.bms.com/pi/pi_coumadin.pdf. Accessed May 19, 2018.
89. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e152S–e184S.
90. Cakebread HE, Knight HM, Gajendragadkar PR, Cooper JP. Warfarin-induced purple toe syndrome successfully treated with apixaban. *BMJ Case Rep*. 2014; 2014. doi:10.1136/bcr-2014-205320.
91. Clark NP, Delate T, Riggs CS, et al. Warfarin interactions with antibiotics in the ambulatory care setting. *JAMA Internal Medicine*. 2014;174:409–416.
92. Booth SL, Centurelli MA. Vitamin K: A practical guide to the dietary management of patients on warfarin. *Nutr Rev*. 1999;57:288–296.
93. Becattini C, Agnelli G, Schenone A, et al. Aspirin for preventing the recurrence of venous thromboembolism. *N Engl J Med*. 2012;366:1959–1967.
94. Brighton TA, Eikelboom JW, Mann K, et al. Low-dose aspirin for preventing recurrent venous thromboembolism. *N Engl J Med*. 2012;367:1979–1987.
95. Martin K, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of the direct oral anticoagulants in obese patients: Guidance from the SSC of the ISTH. *J Thromb Haemost*. 2016;14:1308–1313.
96. Al-Yaseen E, Wells PS, Anderson J, Martin J, Kovacs MJ. The safety of dosing dalteparin based on actual body weight for the treatment of acute

venous thromboembolism in obese patients. *J Thromb Haemost*. 2005;3:100–102.

97. Parker SG, McGlone ER, Knight WR, Sufi P, Khan OA. Enoxaparin venous thromboembolism prophylaxis in bariatric surgery: A best evidence topic. *Int J Surg*. 2015;23:52–56.
98. Pirmohamed M, Burnside G, Eriksson N, et al. A randomized trial of genotype-guided dosing of warfarin. *N Engl J Med*. 2013;369:2294–2303.
99. Kimmel SE, French B, Kasner SE, et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. *N Engl J Med*. 2013;369:2283–2293.
100. Cuker A, Siegal DM, Crowther MA, Garcia DA. Laboratory measurement of the anticoagulant activity of the non-vitamin K oral anticoagulants. *J Am Coll Cardiol*. 2014;64:1128–1139.
101. Shore S, Ho PM, Lambert-Kerzner A, et al. Site-level variation in and practices associated with dabigatran adherence. *JAMA*. 2015;313:1443–1450.
102. Gladstone DJ, Geerts WH, Douketis J, Ivers N, Healey JS, Leblanc K. How to Monitor Patients Receiving Direct Oral Anticoagulants for Stroke Prevention in Atrial Fibrillation: A Practice Tool Endorsed by Thrombosis Canada, the Canadian Stroke Consortium, the Canadian Cardiovascular Pharmacists Network, and the Canadian Cardiovascular Society. *Ann Intern Med*. 2015;163:382–385.

38

Stroke

Melody Ryan and Melissa Nestor

KEY CONCEPTS

1. Stroke can be either ischemic (87%) or hemorrhagic (13%) and the two types are treated differently.
2. Transient ischemic attacks (TIAs) require urgent intervention to reduce the risk of stroke, which is known to be highest in the first few days after TIA.
3. In patients with an ischemic stroke and a blood pressure (BP) <220/120 mmHg without comorbid conditions requiring acute hypertensive treatment, the acute lowering of BP in the first 48 to 72 hours after stroke onset does not improve survival or the level of dependency. In patients with intracranial hemorrhage and elevated systolic blood pressure (SBP) between 150 and 220 mmHg, the acute lowering of SBP to lower than 140 mmHg is safe and may improve functional outcomes.
4. Thrombectomy is strongly recommended for patients with anterior circulation arterial occlusion in the internal carotid artery (ICA) or the M1 segment of the middle cerebral artery (MCA) who are within 6 hours of symptom onset and may be considered in select patients within 6 to 24 hours of symptom onset.
5. In patients with ischemic stroke and 70% to 99% stenosis of the carotid artery, carotid endarterectomy or carotid stenting should be performed.
6. Early pharmacologic reperfusion (initiated less than 4.5 hours from symptom onset) with intravenous alteplase has been shown to improve functional ability after ischemic stroke.
7. Antiplatelet therapy is the cornerstone of antithrombotic therapy for the secondary prevention of noncardioembolic ischemic stroke.
8. Oral anticoagulation is recommended for the secondary prevention of cardioembolic stroke in moderate- to high-risk patients.

9. Elevated blood pressure is very common in ischemic stroke patients and treatment of hypertension in these patients is associated with a decreased risk of stroke recurrence
10. Statin therapy is recommended for all ischemic stroke patients, regardless of baseline cholesterol, to reduce stroke recurrence.

Preclass Engaged Learning Activity

Search the guidelines for stroke care published by the American Heart Association (AHA)/American Stroke Association (ASA) in the professional section of the AHA Website (www.heart.org). Read the executive summary regarding the most recent guideline for pharmacotherapy of stroke. Note the large number of guidelines and the frequency with which they are released. This activity is designed to improve your ability to locate the most current treatment standards for stroke and to help you understand the dynamic nature of stroke treatment recommendations.

INTRODUCTION

Stroke is the leading cause of disability among adults and the fifth leading cause of death in the United States, behind cardiovascular disease, cancer, unintentional injuries, and chronic lower respiratory diseases.[1] Although the incidence of stroke has been trending downward, approximately 795,000 strokes occurred in 2014 that resulted in 133,103 deaths.[2] Aggressive efforts to organize stroke care at the local and regional levels and increased utilization of evidence-based recommendations and national guidelines may have contributed to the improved outcomes.

EPIDEMIOLOGY

There are currently 7.2 million stroke survivors in the United States and stroke is the leading cause of adult disability, with women having worse outcomes than men.[2] Owing in part to the need for expensive posthospitalization rehabilitation and nursing home care, the annual cost of stroke in the United States is estimated to be $40.1 billion.[2]

Not all groups have benefitted equally from advances in care and prevention of stroke. African Americans have stroke rates that are 1.5 times those of whites, and the difference is up to four times at younger ages.[2] In addition, geographic disparity in stroke incidence exists, such that many states in the southeastern United States have stroke mortality rates 30% to 40% higher than the national average.[2] Lastly, case fatality due to hemorrhagic stroke has not declined in the past decade, with 30-day rates remaining around 46%.[2]

Etiology

1 Stroke is subdivided into either ischemic or hemorrhagic types (87% and 13%, respectively, of all strokes in the 2018 AHA report).[2] Hemorrhagic stroke includes subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH). SAH occurs when blood enters the subarachnoid space, which can occur due to trauma, rupture of an intracerebral aneurysm, or rupture of an arteriovenous malformation (AVM). ICH, however, occurs when bleeding occurs in the brain parenchyma itself, with the formation of a hematoma within the brain. Uncontrolled hypertension is the most common causative factor for ICH, but antithrombotic therapy, cerebral amyloid angiopathy, and some drugs of abuse are also associated with ICH.[3] Hemorrhagic stroke, though less frequent in occurrence, has a significantly higher mortality than ischemic stroke, with a mortality rate of nearly 50% versus slightly more than 25% for ischemic stroke.[4]

Ischemic stroke is caused by occlusion within a cerebral artery or emboli from a more proximal source resulting in occlusion of a cerebral artery. Atherosclerosis of large arteries, either intracranial or extracranial, as well as small artery damage, can give rise to ischemic stroke. Emboli can also arise centrally from the heart in patients with atrial fibrillation, valvular heart disease, or other prothrombogenic heart problems and are responsible for approximately 25% of ischemic stroke. Large artery atherosclerosis, small artery disease, and cardioembolism comprise the majority of ischemic stroke mechanisms though stroke cause is undetermined in some cases.[5] Determining if stroke mechanism is due to a cardiogenic mechanism as compared to other causes is important in order to select the most appropriate long-term pharmacotherapy in stroke patients.

Risk Factors

Risk factors for ischemic stroke can be described as nonmodifiable or

modifiable, with some risk factors more well-documented than others with respect to stroke risk. The main risk factors of ischemic stroke are listed in **Table 38-1**.[6] The risk of stroke doubles for each decade older than 55 years. Men are at a higher risk of ischemic stroke than women at a younger age, but women have a higher mortality and higher lifetime risk of ischemic stroke overall. African Americans, Asian-Pacific Islanders, and Hispanic individuals have higher rates of death from ischemic stroke as compared to Caucasians.[6] Recommendations for ischemic stroke prevention focus on aggressive management of modifiable, well-documented risk factors.

TABLE 38-1 Risk Factors for Ischemic Stroke[6]

Nonmodifiable risk factors
Age
Race
Sex
Low birth weight
Genetic Factors
Modifiable, well documented
Cigarette Smoking
Hypertension
Diabetes
Asymptomatic carotid stenosis
Dyslipidemia
Atrial fibrillation
Sickle cell disease
Poor diet
Obesity
Physical inactivity
Other cardiac diseases (coronary heart disease, heart failure, PAD)
Potentially modifiable, less well documented
Migraine
Metabolic syndrome
Drug and alcohol abuse
Inflammation and infection
Elevated lipoprotein (a)
Homocysteinemia
Sleep-disordered breathing

Source: Data from reference 6.

The most common modifiable, well-documented risk factors for ischemic stroke include hypertension, cigarette smoking, diabetes, atrial fibrillation, and dyslipidemia. Hypertension is the most common risk factor, affecting up to one

in three adults in the United States. Cardiac disease, including coronary artery disease, congestive heart failure, left ventricular hypertrophy, and particularly atrial fibrillation, is also a very important risk factor. Atrial fibrillation increases an individual's risk of ischemic stroke to 5% to 20% per year, depending on concomitant comorbidities. Diabetes mellitus, dyslipidemia, and cigarette smoking contribute to atherogenic disease and increase the risk of ischemic stroke.[6]

PATHOPHYSIOLOGY

Ischemic Stroke

Ischemic stroke is the manifestation of neurologic deficit due to occlusion of a cerebral artery, which causes a reduction in cerebral blood flow. The pathophysiologic mechanisms of ischemic stroke are given in **Fig. 38-1**. These arterial occlusions are most commonly due to artery-to-artery emboli, cardiac sources of emboli, or by vascular changes leading to occlusion of the cerebral artery itself. Cerebral blood flow is maintained at an average rate of 50 mL/100 g per minute over a wide range of blood pressure (mean arterial pressures of 50-150 mm Hg) by a process called cerebral autoregulation. Cerebral blood vessels dilate and constrict in response to changes in blood pressure, but this process can be impaired by atherosclerosis, chronic hypertension, and acute injury, such as stroke. Decrease in cerebral blood flow due to arterial occlusion can lead to infarction of cerebral tissue. Surrounding a core area of infarct is tissue that is ischemic but may maintain membrane integrity and is referred to as the ischemic penumbra.[7] This penumbra is the potentially salvageable area of brain tissue with urgent pharmacologic and endovascular interventions in acute ischemic stroke.

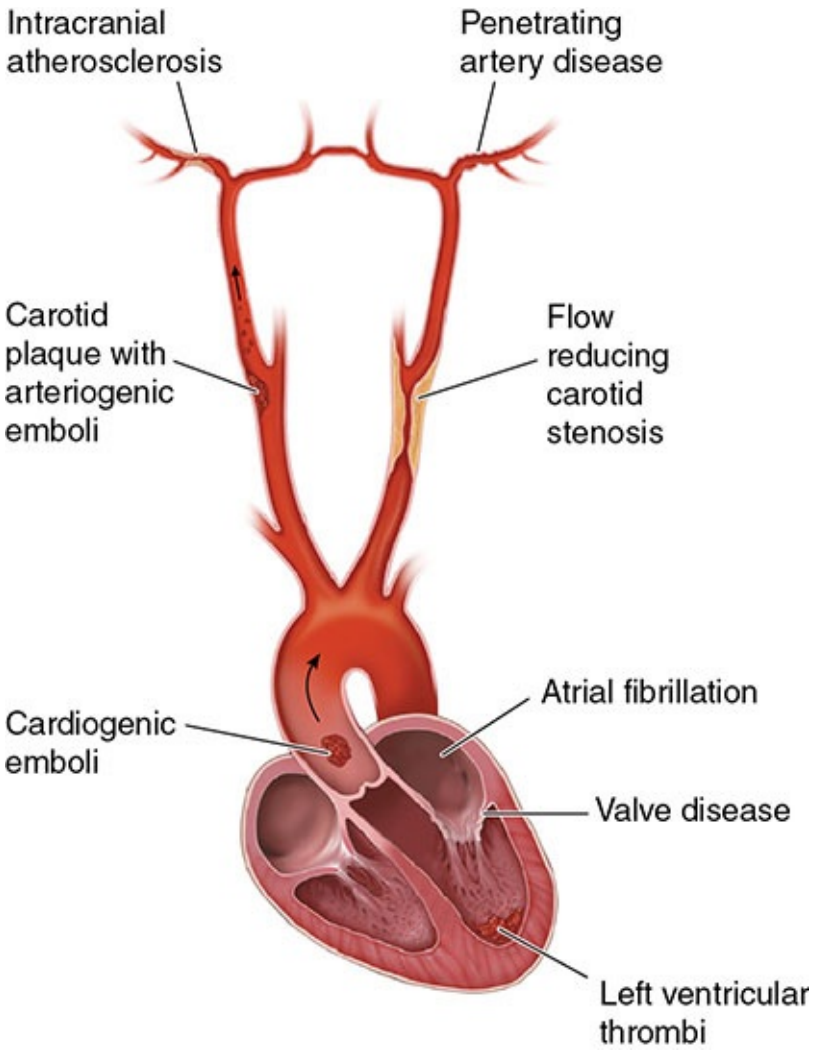


FIGURE 38-1 Pathophysiology of ischemic stroke. Diagram illustrating the three major mechanisms underlying ischemic stroke including occlusion of an intracranial vessel by an embolus that arises from a distant site (eg, cardiogenic embolus), in situ thrombosis of an intracranial vessel, typically affecting the small penetrating arteries, and hypoperfusion caused by flow-limiting stenosis of a major extracranial artery. (*Reproduced with permission from Smith WS, Johnston S, Hemphill J III. Ischemic stroke. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 20th ed. New York, NY: McGraw-Hill; 2018.*)

Insufficient oxygen supply in ischemic tissue leads to adenosine triphosphate (ATP) depletion with subsequent lactate accumulation due to anaerobic metabolism and accumulation of intracellular sodium and water, leading to cytotoxic edema and eventual cell lysis. There is also an influx of calcium intracellularly leading to activation of lipases and proteases resulting in protein

degradation and free fatty acid release from cellular membranes. Additionally, excitatory amino acids, such as glutamate and asparte, are released in ischemic tissue that perpetuate neuronal damage and production of damaging prostaglandins, leukotrienes, and reactive oxygen species. These processes occur within 2 to 3 hours from onset of ischemia and ultimately lead to cellular apoptosis and necrosis.[7]

CLINICAL PRESENTATION

Stroke

General

- The patient may not be able to reliably report the history due to cognitive or language deficits. A reliable history may have to come from a family member or witness.

Symptoms

- The patient may complain of weakness on one side of the body, inability to speak, loss of vision, vertigo, and/or falling. Ischemic stroke is not usually painful, but some patients may complain of headache. Pain and headache, often severe, are more common with hemorrhagic stroke.

Signs

- The specific areas of neurologic deficit are determined by the area of the brain involved.
- Hemiparesis or monoparesis occurs commonly, as does a hemisensory deficit.
- Patients with vertigo and double vision are likely to have posterior circulation involvement.
- Aphasia is seen commonly in patients with anterior circulation strokes.
- Patients may also suffer from dysarthria, visual field deficits, and altered levels of consciousness.

Laboratory Tests

- In acute stroke assessment of blood glucose, platelet count, and coagulation parameters (eg, prothrombin time, aPTT) are used to

determine treatment eligibility.

- Tests for hypercoagulable states (protein C/S deficiency, antiphospholipid antibody) should be done only when the cause of the stroke cannot be determined based on the presence of well-known risk factors.

Other Diagnostic Tests

- CT scan of the head will reveal an area of hyperintensity (white) in patients with hemorrhage and will be normal or hypointense (dark) in patients with infarction. It may take 24 hours before the CT scan will reveal the area of infarction.
- MRI of the head will reveal areas of ischemia with higher resolution and an MRI with diffusion-weighted imaging (DWI) will reveal an evolving infarct within minutes of stroke onset.
- Vascular imaging with CTA is recommended in patients with endovascular treatment indications. CTA can identify both acute treatment candidacy as well as identify intracranial and extracranial arterial stenosis.
- An ECG can help determine whether the patient is presenting in atrial fibrillation.
- TTE can identify cardiac valve abnormalities or wall-motion abnormalities as sources of emboli to the brain. A “bubble study” in which a solution with tiny bubbles is injected intravenously can be done to look for an intra-arterial shunt indicating an atrial-septal defect or a patent foramen ovale. The bubbles can be seen moving through the heart chambers during the TTE.
- In patients unable to undergo CTA, carotid Doppler (CD) and transcranial Doppler (TCD) can be used to determine extracranial carotid artery stenosis and intracranial artery stenosis.

Hemorrhagic Stroke

Hemorrhagic stroke causes neuronal damage by a variety of mechanisms and timelines. ICH hematoma causes primary injury and mechanical compression of the brain parenchyma itself. Early hematoma expansion, which may be seen in up to 38% of patients within 3 hours of ICH onset, is associated with worsened functional outcome and increased mortality. Hematoma volume is one indicator of prognosis and the ICH score is utilized to predict 30-day mortality rates. The

highest rates of mortality are associated with a low Glasgow Coma Score (GCS) on presentation (GCS 3-4), ICH volume greater than 30 cc (mL), intraventricular extension, brain stem location, and age greater than 80.[8] Secondary mechanisms of injury in ICH patients are mediated by subsequent inflammatory response, cerebral edema, and damage from blood product degradation.[3]

CLINICAL PRESENTATION

The term stroke describes patients with an episode of neurologic dysfunction caused by focal cerebral, spinal, or retinal infarction. The syndrome of arterial ischemia with transient symptoms (<24 hours) and without evidence of infarction is a transient ischemic attack or TIA. Appropriate patient history obtainment helps determine the nature of symptom onset and duration of neurologic dysfunction. The location of the central nervous system (CNS) injury and its reference to a specific arterial distribution in the brain are determined through neurologic examination and confirmed by imaging studies such as CT and MRI scanning. The main arterial supply to the cerebral hemispheres is illustrated in **Figs. 38-2** and **38-3**. Vascular imaging with CTA can aid clinicians in determining the cause of stroke and if there is an indication for urgent mechanical intervention.

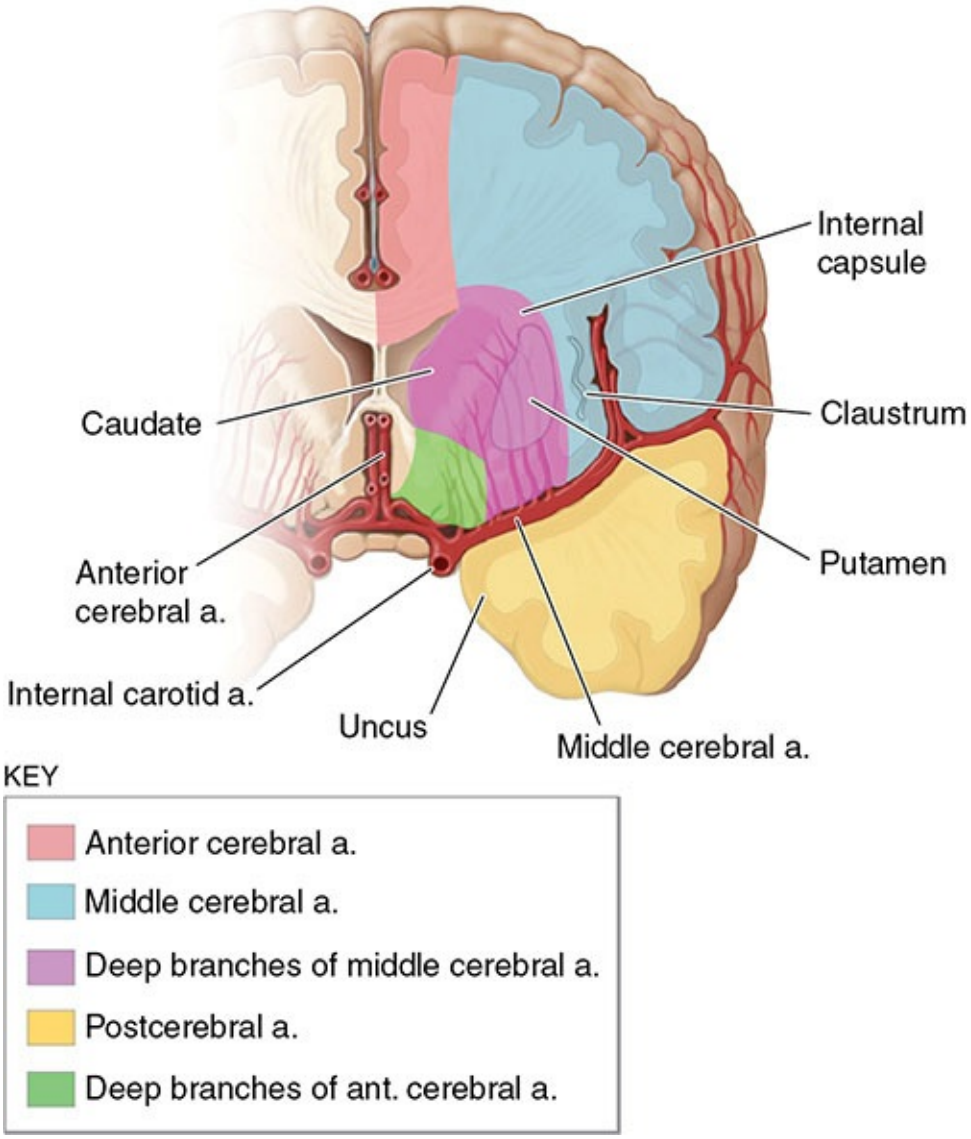


FIGURE 38-2 Diagram of a cerebral hemisphere in coronal section showing the territories of the major cerebral vessels branching from the internal carotid arteries. (*Reproduced with permission from Smith WS, Johnston S, Hemphill J III. Cerebrovascular Diseases. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 20th ed. New York, NY: McGraw-Hill; 2018.*)

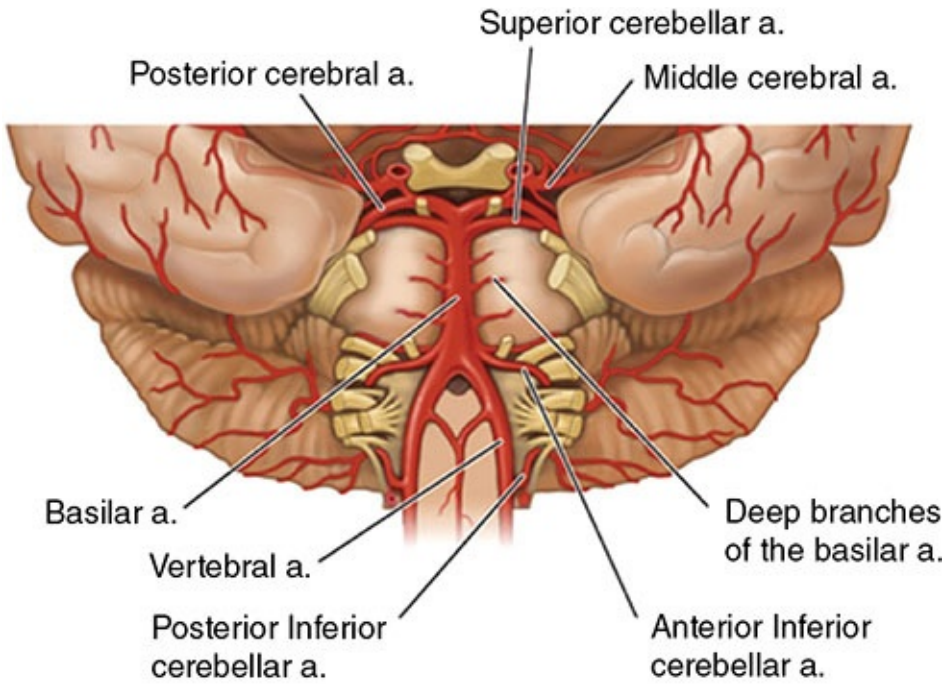


FIGURE 38-3 Diagram of the posterior circulation, showing the intracranial vertebral arteries forming the basilar artery that gives off the anterior inferior cerebellar, superior cerebellar, and posterior cerebral arteries. The posterior inferior cerebellar artery arises from each of the vertebral segments. The majority of brainstem blood flow arises from numerous deep branches of the basilar artery that penetrate directly into the brainstem. (*Reproduced with permission from Smith WS, Johnston S, Hemphill J III. Cerebrovascular Diseases. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 20th ed. New York, NY: McGraw-Hill 2018.*)

TREATMENT

Desired Outcomes

The goals of treatment of acute stroke are to (a) reduce the ongoing neurologic injury in the acute setting to reduce mortality and long-term disability, (b) prevent complications secondary to immobility and neurologic dysfunction, and (c) prevent stroke recurrence. Primary prevention of stroke is described elsewhere.[9]

General Approach to Treatment

2 3 For patients with presumed acute stroke, the initial approach is to first ensure the patient is stable from a respiratory and cardiac standpoint and then to quickly determine whether the injury is ischemic or hemorrhagic, which is determined by a CT scan. Ischemic stroke patients presenting within hours of symptom onset should be evaluated for pharmacologic and mechanical reperfusion therapy. Patients with TIA require urgent assessment and intervention to reduce the risk of stroke, which is highest in the first few days after TIA.[6] In patients with an ischemic stroke and a BP <220/120 mm Hg without comorbid conditions requiring acute hypertensive treatment, the acute lowering of blood pressure in the first 48 to 72 hours after ischemic stroke does not prevent death or improve the level of dependency. "Permissive hypertension" in these patients is often part of routine care. However, for patients who are alteplase-treatment candidates or those with comorbid conditions, such as aortic dissection, acute myocardial infarction, pulmonary edema, or hypertensive encephalopathy, treatment of hypertension may be required. If BP is treated, the use of short-acting and easily titrated agents, such as labetalol or nicardipine/clevidipine, is preferred. **Table 38-2** outlines current recommendations regarding the management of arterial hypertension in patients with ischemic stroke. In patients with ICH and elevated blood pressure, the acute lowering of SBP to 140 mm Hg has been shown to be safe and may improve functional outcome.[8] Once the patient is out of the hyperacute phase management efforts are focused on preventing worsening of stroke, minimizing complications, and instituting appropriate secondary prevention strategies. The acute phase of the stroke includes the first week after the event.[6,8,10]

TABLE 38-2 Blood Pressure Treatment Guidelines in Stroke[8,10]

Ischemic Stroke with Alteplase Treatment

- Pre-alteplase: lower BP to SBP <185 mm Hg and DBP <110 mm Hg
- Post-alteplase: maintain SBP <180 mm Hg and DBP <105 mm Hg for 24 hours

Ischemic Stroke without Alteplase Treatment

- Treatment benefit uncertain/not recommended unless BP >220/120 mm Hg
- Lowering BP by 15% is probably safe when required by comorbid conditions (such as concomitant acute coronary event, acute heart failure, aortic dissection, symptomatic intracranial hemorrhage, preeclampsia/eclampsia)

Intracranial Hemorrhage

- Treatment is reasonable for ICH patients with SBP >220 mm Hg
- For ICH patients with SBP 150-220 mm Hg, acute lowering of SBP to 140 mm Hg is safe

Pharmacologic Options for Blood Pressure Lowering in Acute Stroke

- Labetalol 10-20 mg IV over 1-2 minutes, may repeat
- Nicardipine 5 mg/hr IV, titrate up by 2.5 mg/hr every 5-15 minutes, maximum 15 mg/hr
- Clevidipine 1-2 mg/hr IV, titrate by doubling the dose every 2-5 minutes, maximum 21 mg/hr
- Other agents to consider: hydralazine, enalaprilat, nitroprusside IV infusion, labetalol IV infusion

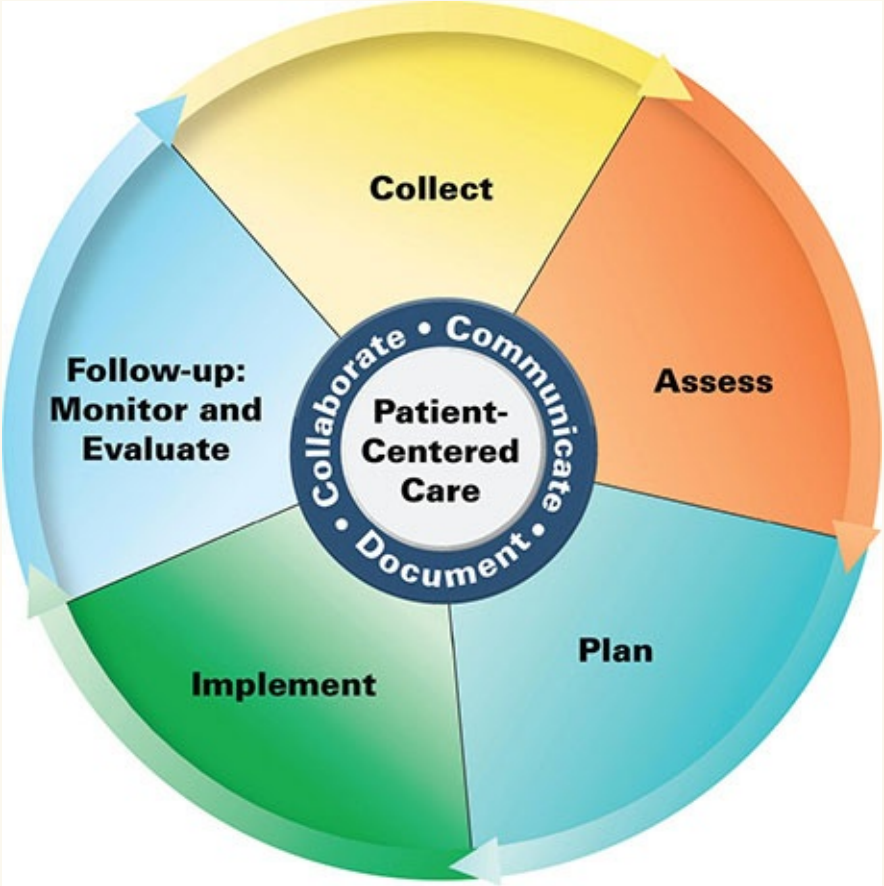
BP, blood pressure; DBP, diastolic blood pressure; ICH, intracerebral hemorrhage; IV, intravenous; SBP, systolic blood pressure.

Source: Data from references 8 and 10.

Nonpharmacologic Therapy

4 **Ischemic Stroke** Endovascular intervention and thrombectomy with retrievable stents to reperfuse ischemic brain tissue has been recommended by the AHA/ASA since 2015 based on data from several clinical trials.[10] Thrombectomy is strongly recommended for patients with anterior circulation arterial occlusion in the ICA or the M1 segment of the MCA who are within 6 hours of symptom onset and may be considered in select patients within 6 to 24 hours of symptom onset. Patients with ICA and M1 MCA arterial occlusions and symptom onset within 24 hours may be candidates for endovascular intervention if imaging studies suggest a significant area of salvageable penumbra is present. The benefit of mechanical thrombectomy with stent retrievers is less clear in patients with posterior circulation occlusions and should be considered in a case-by-case basis.[10] The availability of this mechanical intervention for stroke has

greatly increased the importance of early vascular diagnostic imaging followed by rapid transfer and escalation of care to centers with interventional capabilities in patients with these emergent large vessel occlusions.



Patient Care Process for Acute Ischemic Stroke

Collect

- Patient characteristics (eg, age, sex, race)
- Patient medical history (personal and family)
- Social history (eg, tobacco/ethanol use)
- Current medications including nonprescription aspirin/nonsteroidal anti-inflammatory drug (NSAID) use, herbal products, dietary supplements, and prior antiplatelet and anticoagulant medication use
- Medication allergies
- Objective data

- Blood pressure (BP), heart rate, respiratory rate, height, weight
- Labs including hemoglobin, platelets, serum creatinine, activated partial thromboplastin time (aPTT), prothrombin time, blood glucose, troponin
- Noncontrast computed tomography (CT) scan, magnetic resonance imaging (MRI), and/or computed tomography angiography (CTA) may be needed
- Neurologic examination (eg, National Institutes of Health Stroke Scale [NIHSS] score)
- Electrocardiogram (ECG) and, in some patients, transthoracic echocardiogram (TTE)

Assess

- Hemodynamic stability (eg, SBP <110 mm Hg, DBP <185 mm Hg, if tissue plasminogen activator candidate; blood pressure less than 220/120 mm Hg otherwise; O_2-sat >94% [0.94]; temperature <38ºC [102ºF])
- Blood glucose (<60 mg/dL [3.3 mmol/L] or >180 mg/dL [10.0 mmol/L] should be treated)
- Presence of active bleeding and/or bleeding risk factors (Table 38-8)
- Patient's candidacy for tissue plasminogen activator treatment (Table 38-4) or thrombectomy
- Presence of dysphagia (swallowing disorder)

Plan

- Aspirin within 24 to 48 hours unless contraindicated; delay for 24 hours if the patient has been given tissue plasminogen activator
- Antiplatelet drug therapy regimen including specific medication(s), dose, frequency, and duration OR oral anticoagulant, if the patient has atrial fibrillation (see Table 38-3)
- Evaluation for carotid endarterectomy or carotid stenting
- Prophylaxis for venous thromboembolism, if immobile
- Nutritional plan; if the patient has dysphagia, nutrition via nasogastric tube or percutaneous gastrostomy tube
- Treat and manage stroke risk factors (Table 38-1) (eg, blood pressure control [Tables 38-2 and 38-3], dyslipidemia, diabetes)
- Monitoring parameters including efficacy (eg, stroke symptoms) and safety

(eg, signs and symptoms of bleeding [all antiplatelets and oral anticoagulants], headache [dipyridamole]); frequency and timing of follow-up

- Patient education (eg, the purpose of treatment, dietary and lifestyle modification, invasive procedures, drug-specific information, medication administration)
- Self-monitoring for stroke recurrence, the occurrence of bleeding, and when to seek emergency medical attention
- Referrals to other providers when appropriate (eg, physical therapist, occupational therapist, behavioral health, dietician)

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Improvement of stroke symptoms; neurological examination
- Presence of adverse effects (eg, bleeding [all medications], gastrointestinal upset [aspirin], headache [dipyridamole], cerebral edema, seizures)
- Patient adherence to treatment plan using multiple sources of information
- Adherence to recommended follow-up appointments (eg, neurology, physical therapy)
- Assess for poststroke depression

**Collaborate with patient, caregivers, and other healthcare professionals.*

Large infarcts of the MCA are often devastating and in patients without recanalization via pharmacologic or mechanical intervention rates of morbidity and mortality are high. Decompressive hemicraniectomy is a surgical procedure that can be done to reduce intracranial pressure, typically due to cerebral edema, and can reduce mortality and improve functional outcome. In patients under 60 years of age with unilateral MCA infarcts and significant cerebral edema, surgical intervention with decompressive craniectomy has been shown to reduce

mortality by almost 50% and improve favorable neurologic outcomes at one year (18% of patients with modified Rankin score [mRS] of 2). This surgical intervention can be considered for patients over the age of 60 but the likelihood of favorable neurologic outcome is less robust. In patients with cerebellar infarction and significant swelling surgical decompression can be lifesaving. For all ischemic stroke patients coordinated care with a multidisciplinary approach to assessment and early rehabilitation is effective in reducing overall disability due to stroke.[10]

5 In secondary prevention, carotid endarterectomy of an ulcerated and/or stenotic carotid artery is a very effective way to reduce stroke incidence and recurrence in appropriate patients and in centers where the operative morbidity and mortality are low. In fact, in ischemic stroke patients with 70% to 99% stenosis of an ipsilateral ICA, recurrent stroke risk can be reduced by up to 48% compared with medical therapy alone when combined with aspirin 325 mg daily.[11] In patients younger than 70 years, carotid stenting is a less invasive alternative and can be effective in reducing recurrent stroke risk when combined with aspirin and clopidogrel therapy.[11,12] There are conflicting studies regarding efficacy and adverse effects when comparing the two procedures.[13] However, in patients with intracranial stenosis, aggressive medical management was shown to be superior to stenting in reducing recurrent stroke.[14]

Hemorrhagic Stroke SAH often arises from a ruptured intracranial aneurysm or AVM and intervention as early as possible with either surgical clipping or endovascular coiling of the vascular anomaly reduces the risk of rebleeding and improves mortality.[15] For patients with cerebellar ICH and neurologic deterioration, brainstem compression, and/or hydrocephalus from ventricular obstruction early surgical intervention and hematoma removal is recommended. For patients with cerebral ICH, the usefulness of surgical hematoma evacuation or use of minimally-invasive clot evacuation are not well established. Ventricular drainage with an extraventricular drain (EVD) is reasonable in patients with hydrocephalus causing decreased consciousness.[8]

Temperature Management

Fever worsens outcomes in patients with both hemorrhagic and ischemic stroke types. Identification of the source of fever and management is recommended to maintain patients within normothermia ranges. Pharmacologic and nonpharmacologic interventions can be considered and applied. Data are limited to support induced hypothermia and this intervention should be done only in a

controlled, clinical trial setting.[8,10]

Pharmacologic Therapy

Ischemic Stroke

Acute Treatment The stroke council of the American Stroke Association has created and published guidelines that address the management of acute ischemic stroke.[10] For acute treatment, the only two pharmacologic agents with class I recommendations are alteplase initiated within 4.5 hours of stroke onset and aspirin started within 24 to 48 hours of stroke onset (**Table 38-3**).[10]

TABLE 38-3 Recommendations for Pharmacotherapy of Ischemic Stroke

Acute treatment

Recommendation	Evidence Grade[1]
Alteplase 0.9 mg/kg IV (maximum 90 mg), 10% as a bolus with the remainder given over 1 hour in selected patients	
• Within 3 hours of onset[10]	IA
• Between 3 and 4.5 hours of onset[10]	IB
Aspirin 160-325 mg daily started within 48 hours of onset[10]	IA

Secondary prevention

Stroke Etiology	Recommendation	Evidence Grade[1]
Noncardioembolic	Antiplatelet therapy[10]	
	• Aspirin 50-325 mg daily	IA
	• Aspirin 25 mg + extended-release dipyridamole 200 mg twice daily	IB
	• Clopidogrel 75 mg daily	IIaB
Cardioembolic (especially atrial fibrillation)	Anticoagulant therapy[10]	
	• Vitamin K Antagonist (Warfarin) (INR = 2.5)	IA
	• Apixaban 5 mg twice daily	IA
	• Dabigatran 150 mg twice daily	IB
	• Edoxaban 60 mg daily[16]	Not graded in current guidelines
	• Rivaroxaban 20 mg daily	IIaB
Patient Characteristic	**Recommendation**	**Evidence Grade[1]**
Age ≤75	High-intensity statin therapy[19]	IA
Age >75	Moderate- or high-intensity statin therapy[19]	IIaB-R
BP >140/90[51]	BP reduction[10]	IB-R

[1]Classes: I, evidence or general agreement about usefulness and effectiveness; II, conflicting evidence about the usefulness; IIa, the weight of evidence in favor of the treatment; IIb, usefulness less well established; III, not useful and may be harmful. Levels of evidence: A, multiple randomized clinical trials; B, a single randomized trial or nonrandomized studies; C, expert opinion or case studies; B-R, moderate-quality evidence from one or more randomized controlled trials or meta-analyses of moderate-quality randomized controlled trials.

INR, international normalized ratio; IV, intravenous.

Data from References 10, 16, 19, and 51.

6 ***Alteplase*** Early pharmacologic reperfusion (initiated less than 4.5 hours from symptom onset) with IV alteplase has been shown to improve functional ability after ischemic stroke as compared to no intervention.[10] The National Institute of Neurologic Disorders and Stroke (NINDS) Recombinant Tissue-Type Plasminogen Activator (rt-PA) Stroke Trial, published in 1995, was the first large trial demonstrating the effectiveness of IV alteplase in the treatment of ischemic stroke.[17] In this trial, 624 patients were randomized 1:1 to receive either alteplase 0.9 mg/kg IV or placebo within 3 hours of the onset of stroke symptoms. At 3 months after enrollment, 39% of alteplase-treated patients achieved "excellent outcome" (defined as minimal to no disability on several neurologic scales, including mRS) as compared to 25% of placebo patients. This beneficial effect was noted despite a higher rate of symptomatic ICH in alteplase-treated patients (6.4% compared to 0.6% in placebo). Patients with severe symptoms at presentation (National Institutes of Health Stroke Scale [NIHSS] greater than 20) and early ischemic changes on CT scan were at highest risk for symptomatic intracranial hemorrhage but, despite this risk, these patients receiving alteplase still had better neurologic outcome at 90 days compared patients receiving placebo.[17]

Following the NINDS trial, the European Cooperative Acute Stroke Study (ECASS) III also demonstrated improved functional outcome at 3 months when alteplase was administered between 3 and 4.5 hours of stroke symptom onset when compared with placebo (52.4% vs 45.2%).[18] Based on these data the AHA/ASA guidelines were altered to extend the window for alteplase to up to 4.5 hours from symptom onset. It should be noted that there may be diminished benefit of alteplase in patients presenting within 3 to 4.5 hours from symptom onset and severe stroke (NIHSS>25 or evidence of more than one-third of MCA territory infarct on initial imaging).[10] Although the alteplase time window for administration is extended to 4.5 hours, for many patients early administration of alteplase is associated with improved outcomes, so delays in pharmacologic therapy should be minimized as much as possible.

Alteplase use is associated with a high risk for bleeding, including intracranial hemorrhage, and adherence to guideline-recommended protocol is essential to achieving a positive outcome and minimizing the risk. The essentials of this protocol can be summarized as (a) stroke team activation, (b) CT scan to rule out hemorrhage, (c) treatment as early as possible within 4.5 hours of symptom onset, (d) meeting inclusion and exclusion criteria (**Table 38-4**), (e) administration of alteplase 0.9 mg/kg total dose given as 10% as a bolus over 1

minute, remaining 90% over 1 hour, and maximum dose of 90 mg, (f) avoidance of antithrombotic therapy (anticoagulant or antiplatelet) for 24 hours after alteplase, (g) and close patient monitoring for elevated blood pressure, neurologic status, and hemorrhage. Endovascular intervention is not a contraindication to alteplase and patients eligible for alteplase should receive pharmacologic treatment in addition to mechanical thrombectomy.[10]

TABLE 38-4 Inclusion and Exclusion Criteria for Alteplase Use in Acute Ischemic Stroke[10]

Inclusion Criteria
Age ≥18 years
Clinical diagnosis of ischemic stroke with neurologic deficit
Time of symptom onset well established to be <4.5 hours from treatment initiation
Contraindications
Symptoms/Imaging consistent with subarachnoid hemorrhage or acute intracerebral hemorrhage
Current use of direct thrombin inhibitors or direct factor Xa inhibitors in prior 48 hours
Use of treatment-dose low molecular weight heparin in prior 24 hours
Infective endocarditis
Intra-axial, intracranial neoplasm
Aortic arch dissection
Active internal bleeding or coagulopathy (platelets <100,000/mm^3 [100 x 10^9/L], INR>1.7, aPTT>40s, PT>15s)
Severe head trauma in prior 3 months
Gastrointestinal malignancy or bleeding within prior 21 days
Warnings/Use Clinical Judgment
History of intracranial hemorrhage
History of ischemic stroke within prior 3 months
Unruptured/unsecured AVM or aneurysm >10 mm
Major surgery or nonhead trauma
History of bleeding diathesis
Extensive regions of clear hypoattenuation on initial CT scan

aPTT, activated partial thromboplastin time; AVM, arteriovenous malformation; CT, computed tomography; INR, international normalized ratio; PT; prothrombin time.

Source: Data from reference 10.

Aspirin Early aspirin therapy within 24 to 48 hours from symptom onset should be given to stroke patients unless allergy or other contraindication prevents the use. For patients receiving alteplase, aspirin and other antithrombotics are generally held for 24 hours after alteplase administration to reduce risk of

hemorrhage.[10]

Early use of aspirin in ischemic stroke patients is recommended by the AHA/ASA guidelines to reduce the long-term risk of death and disability with much of the support coming from two large randomized clinical trials, the International Stroke Trial (IST) and the Chinese Acute Stroke Trial (CAST), and systematic review.[10] Data are limited to describe acute use of nonaspirin antiplatelet agents in the acute stroke phase, apart from combination therapy investigations, but it may be reasonable to use an alternate antiplatelet agent in acute stroke patients who have an allergy or severe contraindication to aspirin.[20]

Aspirin exerts its antiplatelet effect by irreversibly inhibiting cyclooxygenase, which, in platelets, prevents the conversion of arachidonic acid to thromboxane A2 (TXA2), which is a powerful vasoconstrictor and stimulator of platelet aggregation. Platelets remain impaired for their life span (5-7 days) after exposure to aspirin. Aspirin also inhibits prostacyclin (PGI2) activity in the smooth muscle of vascular walls. PGI2 inhibits platelet aggregation, and the vascular endothelium can synthesize PGI2 such that the platelet antiaggregating effect is maintained.[22] There is probably a point at which lower doses of aspirin do not completely block TXA2, and recent studies indicate that the lowest effective dose may be in the range of 50 mg/day.[22] Upper gastrointestinal (GI) discomfort and bleeding are the most common adverse effects of aspirin and have been shown to be dose-related. The highest rates of GI bleeding (5%) have been reported in patients receiving 1,200 mg/day as compared with rates of 2% in patients taking the more commonly prescribed 300 mg/day. Upper GI symptoms are much more common than frank bleeding; however, with 40% of patients affected at 1,200 mg/day and 25% at 300 mg/day.[23] In the European Stroke Prevention (ESPS)-2 study, even 50 mg/day of aspirin was associated with a twofold increase in bleeding over the placebo group.[24]

The onset of the antiplatelet effect of aspirin is less than 60 minutes.[23] It has been reported, however, that some patients either have or develop “aspirin resistance” and can require higher doses to achieve the desired antiplatelet effect.[25] Several genetic polymorphisms, including those of cyclooxygenase (COX)-1, COX-2, glycoprotein IIb/IIIa, and adenosine diphosphate (ADP) receptors, may contribute to aspirin resistance.[26] Despite this, routine testing for aspirin resistance is not recommended. It was observed that administration of ibuprofen prior to the administration of a daily aspirin dose inhibits the aspirin from binding irreversibly to the cyclooxygenase and can decrease its antiplatelet effect.[27] Current recommendations are to administer aspirin at least 2 hours

before an NSAID or to wait at least 4 hours after an NSAID dose.

Blood Pressure Management In general, it is more common for patients with ischemic stroke to present with elevated or normal blood pressure. However, hypotension and hypovolemia, if present, should be corrected to maintain systemic perfusion and end organ function. Data are limited to recommend pharmacologic agents to increase blood pressure in acute ischemic stroke above the typical normal parameters. For patients with elevated blood pressure who are otherwise eligible for alteplase, the treatment of hypertension to a goal systolic blood pressure less than 185 mm Hg and diastolic blood pressure of less than 110 mm Hg is recommended before thrombolytic administration. While data are limited, it is also reasonable to maintain blood pressure less than 185/110 mm Hg for patients undergoing mechanical thrombectomy. For patients not requiring intravenous thrombolytic therapy or endovascular intervention, the use of "permissive hypertension" and allowing blood pressure to rise as high as 220/120 mmHg for the first 48 to 72 hours is often used as early initiation of antihypertensive therapy does not prevent death or dependency. For patients with comorbid conditions requiring blood pressure management, a reduction of 15% is probably safe. See Table 38-2 for a summary of these recommendations and pharmacotherapeutic options.[10] When treating hypertension in acute ischemic stroke it is typical to use intravenous drugs with faster time to onset and ability to titrate to patient response. Labetalol can be used as an intravenous bolus dose or as a continuous infusion and calcium channel antagonist infusions, such as nicardipine and clevidipine, are often first-line agents. In patients with refractory hypertension there may be a role for last-line agents such as sodium nitroprusside to achieve blood pressure goals.

Unfractionated Heparin Use of urgent anticoagulation (eg, unfractionated heparin or low-molecular-weight heparin) is not routinely recommended in the early phase of acute ischemic stroke treatment. There are data investigating the clinical benefit of urgent anticoagulation in the setting of nonocclusive intraluminal thrombus in acute stroke, but the data are limited. Restricted use on a case-by-case basis or in a clinical trial setting may be considered. Use and benefit of immediate anticoagulation for nonstroke indications (eg, prophylaxis for venous thromboembolism) should be weighed against the risk of intracranial hemorrhagic conversion in acute ischemic stroke patients.[10]

7 **Secondary Prevention** Antiplatelet therapy is the cornerstone of antithrombotic therapy for the secondary prevention of ischemic stroke and should be used in noncardioembolic strokes. Aspirin, extended-release

dipyridamole plus aspirin, and clopidogrel are all recommended for secondary stroke prevention.[6] In patients with atrial fibrillation and a presumed cardiac source of embolism, oral anticoagulation with either vitamin K antagonists (warfarin), apixaban, dabigatran, or rivaroxaban is recommended for secondary stroke prevention.[6] Other pharmacotherapy recommended for secondary prevention of stroke includes blood pressure lowering and statin therapy. Current recommendations regarding the acute treatment and secondary prevention of stroke are given in Table 38-3.

Antiplatelet Agents All patients who have had an acute ischemic stroke or TIA should receive long-term antithrombotic therapy for secondary prevention.[6] In patients with noncardioembolic stroke, this will be some form of antiplatelet therapy. In a comprehensive meta-analysis, the overall benefit of antiplatelet therapy in patients with atherothrombotic disorders was estimated to be 22%.[24] Aspirin is the best studied of the available agents, but published literature supports the use of the combination product extended-release dipyridamole plus aspirin and clopidogrel as alternative first-line agents for the secondary stroke prevention (**Table 38-5**).[6]

TABLE 38-5 Landmark Studies in Secondary Stroke Prevention

Study	Number and Type of Patients	Study Groups	Outcome Measures	Results
European Stroke Prevention Study 2 (ESPS-2)[34]	6,602 patients with prior ischemic stroke or TIA	• Aspirin 25 mg twice daily • Extended-release dipyridamole 200 mg twice daily • Aspirin/extended-release dipyridamole 25/200 mg twice daily • Placebo	Recurrent stroke or death	• Aspirin reduced stroke by 18% compared to placebo ($p = 0.013$) • Extended-release dipyridamole reduced stroke by 16% compared to placebo ($p = 0.039$) • Extended-release dipyridamole plus aspirin reduced stroke by 37% compared to placebo ($p<0.001$)
ESPRIT 2006[60]	2,739 patients with prior minor stroke or TIA	• Aspirin 30-325 mg daily • Extended-release dipyridamole 200 mg twice daily plus aspirin 30-325 mg daily	Death from all vascular causes, stroke, or myocardial infarction	13% of extended-release dipyridamole plus aspirin group met an outcome compared to 16% of the aspirin group (HR 0.8, 95% CI 0.55-0.98)
Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE)[32]	19,000 patients with myocardial infarction, stroke, peripheral arterial disease	• Aspirin 325 mg daily • Clopidogrel 75 mg daily	Death from all vascular causes, myocardial infarction, or stroke	Clopidogrel reduced the outcome by 8% compared to aspirin ($p= 0.043$)
Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS)[24]	20,332 patients with previous ischemic stroke	• Extended-release dipyridamole plus aspirin 200/26 mg twice daily • Clopidogrel 75 mg daily	Recurrent stroke	There was no difference in recurrent stroke in patients given extended-release dipyridamole plus aspirin (9%) and clopidogrel (8.8%)
Aspirin Plus Clopidogrel In the Management of ATherothrombosis with Clopidogrel in High-risk patients (MATCH)[37]	7,599 patients with ischemic stroke or TIA	• Clopidogrel 75 mg daily • Clopidogrel 75 mg daily plus aspirin 75 mg daily	Stroke, myocardial infarction, vascular death, rehospitalization for acute ischemia	There was no difference between the groups
Stroke Prevention in Subcortical Stroke (SPS)-3[38]	3,020 patients with lacunar stroke	• Aspirin 325 mg daily • Aspirin 325 mg daily plus clopidogrel 75 mg daily	Recurrent stroke	There was no difference between the groups
Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE)[39]	5,170 patients with mild ischemic stroke	• Aspirin 75 mg daily for 90 days • Clopidogrel 300 mg loading dose, then 75 mg daily for 90 days and aspirin 75 mg daily for 21 days	Recurrent stroke within 90 days	8.2% of subjects treated with the combination had a stroke 11.7% treated only with aspirin had a stroke ($p< 0.001$)
Triple vs guideline Antiplatelet therapy to prevent Recurrence after acute Ischaemic Stroke or transient ischaemic attack (TARDIS)[43]	3,096 patients with TIA or ischemic stroke	• Aspirin 300 mg loading dose followed by 50-150 mg daily plus sustained-release dipyridamole 200 mg twice daily plus and clopidogrel 300 mg loading dose followed by 75 mg daily for 30 days • Either clopidogrel or aspirin plus sustained-release dipyridamole for 30 days	Recurrent stroke	No difference in recurrent stroke between groups Increased risk of major bleeding in the triple therapy group ($p= 0.006$)
European Atrial Fibrillation Trial (EAFT)[42]	1,007 patients with atrial fibrillation and TIA or minor stroke	• Oral anticoagulants (warfarin) • Aspirin 300 mg daily • Placebo	Stroke, myocardial infarction, systemic embolism, or death from vascular disease	8% of anticoagulant group vs 15% of aspirin group vs 17% of placebo group experienced outcome (HR 0.53, 95% confidence interval 0.36-0.79)

HR, hazard ratio; TIA, transient ischemic attack.

Clopidogrel Clopidogrel has a unique platelet antiaggregatory effect in that it is an inhibitor of the ADP pathway of platelet aggregation through purinergic receptor P2Y, G-protein coupled 12 (P2Y12) receptor inhibition and inhibits known stimuli to platelet aggregation.[21,28,29] This effect causes an alteration of the platelet membrane and interference with the membrane–fibrinogenic interaction leading to a blocking of the platelet glycoprotein IIb/IIIa receptor. A time lag of 3 to 7 days before the antiplatelet effect is maximal should be expected.

Clopidogrel is a prodrug and requires activation by CYP4502C19 in order to achieve its antiplatelet effect. There is polymorphism of various alleles that code for this enzyme with *1 being the wild type, *17 leading to faster metabolism and *2 and *3 causing slower metabolism. Thus, individuals with one copy of *2 or *3 are classified as intermediate metabolizers and those with two copies of *2 or *3 or one copy of each (*2/*3) are termed poor metabolizers.[30] Poor metabolizers are found in about 2% of Caucasians, 4% of African Americans, and 14% of Chinese.[30] The 2013 Statement from the Clinical Pharmacogenetics Implementation Consortium and the 2017 Summary of Recommendations from the Dutch Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy both suggest pharmacogenetic testing prior to using clopidogrel.[30] The newest AHA/ASA guidelines for acute treatment of stroke do not suggest doing so.[10] Similarly, medicines that inhibit CYP4502C19 have a similar effect. Interactions with omeprazole and esomeprazole are of particular concern and their use should be avoided in patients taking clopidogrel. Opioids slow gastric emptying, and thus decrease exposure to the clopidogrel metabolites and decrease its efficacy.[31]

The efficacy of clopidogrel as an antiplatelet agent in atherothrombotic disorders was demonstrated in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial.[32] In the final analysis, clopidogrel was slightly (8% RRR) more effective than aspirin and had a similar incidence of adverse effects. The tolerability of clopidogrel 75 mg/day is at least as good as medium-dose (325 mg/day) aspirin, and there is less GI bleeding.[32] Clopidogrel is associated with an increased risk of diarrhea and rash, but discontinuation rates owing to adverse effects are similar to those with aspirin 325 mg/day (5.3% and 6%, respectively).[32] There is no excess neutropenia in patients taking clopidogrel, and rates of thrombotic thrombocytopenic purpura probably are no greater than background rate.

Extended-Release Dipyridamole Plus Aspirin Dipyridamole in high doses is thought to inhibit platelet aggregation by inhibiting phosphodiesterase, leading to accumulation of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) intracellularly, which prevent platelet activation. In addition, dipyridamole also enhances the antithrombotic potential of the vascular wall.[33] Early studies of the role of dipyridamole in stroke prevention failed to show a benefit over that realized by aspirin alone. The ESPS-2 demonstrated the efficacy of high-dose extended-release dipyridamole alone and in combination with aspirin in secondary stroke prevention.[34] In the ESPS-2, 25% of the patients who received combination dipyridamole and aspirin discontinued the therapy early, and the rate of discontinuation owing to headache was more than three times as common (10%) as in the aspirin-alone group (3%).[34] Even when patients were carefully educated and coached in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial, discontinuation due to headache was six times higher in the extended-release dipyridamole plus aspirin group (5.9% vs 0.9%).[24] The extended-release formulation of dipyridamole is important in that it allows twice-daily administration and higher doses to be tolerated in patients. The use of immediate-release generic dipyridamole in combination with regular aspirin, in order to reduce costs, is unproven and should be discouraged.

In the PRoFESS trial comparing extended-release dipyridamole plus aspirin with clopidogrel, the risk of recurrent stroke was similar for the two antiplatelet agents, but clopidogrel was better tolerated with less bleeding and headache.[24]

Ticagrelor Ticagrelor is a direct-acting ADP P2Y12 receptor inhibitor.[29] In the Acute Stroke or Transient Ischaemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) trial, 13,199 patients with noncardioembolic stroke who were not treated with alteplase were given ticagrelor with a loading dose of 180 mg then 90 mg twice daily for 90 days or aspirin 300 mg loading dose with 100 mg daily 90 days. Ticagrelor did not demonstrate superiority to aspirin in this trial.[35] However, in a subgroup analysis of patients with an atherosclerotic cause of stroke, there was a 32% lower risk of secondary stroke within 90 days in patients treated with ticagrelor.[36] Although this analysis was prespecified in the study protocol, it was considered exploratory and ticagrelor is not FDA approved for secondary stroke prevention.

Dual Antiplatelet Therapy In the Aspirin Plus Clopidogrel in the Management of Atherothrombosis with Clopidogrel in High-Risk Patients (MATCH) study, clopidogrel in combination with aspirin was no better than clopidogrel alone in

secondary stroke prevention, but the risk of life-threatening bleeding increased.[37] In the Stroke Prevention in Subcortical Stroke (SPS)-3 trial of patients with recent minor strokes, the arm of the trial studying the combination of clopidogrel and aspirin was stopped early because of excess mortality due to bleeding in this group.[38] However, the combination has been studied in patients with TIA or minor stroke in the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial, and short-term (3 weeks) use of the combination of clopidogrel and aspirin was associated with improved outcomes at 3 months.[39] There was no difference in subsequent hemorrhagic stroke between the groups. A major limitation of this study is that it was conducted entirely in China, a country with five times the stroke rate of the United States and with little genetic diversity.[39] A similar international study also found a reduction in stroke with the combination of aspirin and clopidogrel, but found an increase in hemorrhagic events in the combination group, causing the trial to be discontinued early.[40] Key differences between these studies that may have led to the higher bleeding risk include a higher loading dose of clopidogrel (600 vs 300 mg) and a longer duration of aspirin therapy in the combination group (90 vs 21 days). Most of the ischemic events in these trials occurred early while the hemorrhagic events were dispersed throughout the 90-day monitoring period, which agrees with the hypothesis that the duration of dual therapy may have been too long.[41] Of note, neither of these trials enrolled patients who had been given alteplase. A meta-analysis comparing short-term dual antiplatelet therapy (all studies <6 months, most <3 months of dual therapy) found this use was associated with a 35% risk reduction of recurrent stroke ($p< 0.00001$).[42]

The positive results of dual antiplatelet therapy led researchers to try triple antiplatelet therapy. One trial, the Triple versus guideline Antiplatelet therapy to prevent Recurrence after acute Ischaemic Stroke or transient ischaemic attack (TARDIS) trial, compared the combination of aspirin, sustained-release dipyridamole, and clopidogrel to a “guideline group” which received either clopidogrel or aspirin and sustained-release dipyridamole. This trial was stopped early because of a doubling of the risk of major bleeding in the triple therapy group. There was no difference in risk of recurrent stroke between the groups.[43]

8 **Oral Anticoagulants** Oral anticoagulation is the treatment of choice for the prevention of stroke in patients with atrial fibrillation.[6,44] In patients with atrial fibrillation and a recent history of stroke or TIA, the risk of recurrence places these patients in one of the highest risk categories known. The European Atrial Fibrillation Trial (EAFT) demonstrated a 53% reduction in risk with

anticoagulation.[42] Targeting an international normalized ratio (INR) of 2.5 prevents stroke with the lowest bleeding risk; therefore, a target INR of 2.5 is recommended in the secondary prevention of stroke.[6,10,44] Newer direct-acting oral anticoagulants (DOAC) including dabigatran (direct thrombin inhibitor), rivaroxaban, edoxaban, and apixaban (direct factor Xa inhibitors) have significant advantages over warfarin in terms of ease of dosing and less food and drug interactions. In addition, in the prevention of stroke in selected patients with atrial fibrillation, all three agents have been shown to be as effective as, and in some cases, superior to, warfarin in reducing recurrent events and intracranial hemorrhage.[45–47]

Before using DOAC the patient's renal function must be evaluated. For dabigatran, patients with a creatinine clearance of 15-30 mL/min (0.25-0.50 mL/s) should receive a reduced dose of 75 mg twice daily. In patients with a creatinine clearance of ≤50 mL/min (0.83 mL/s), rivaroxaban should be dosed at 15 mg daily with the evening meal. For apixaban, if patients have at least two of the following characteristics, they should be given 2.5 mg twice daily: age greater than or equal to 80 years, body weight less than or equal to 60 kg, or serum creatinine greater than or equal to 1.5 mg/dL (133 µmol/L). Edoxaban dosing should be reduced to 30 mg daily if creatinine clearance is between 15 and 50 mL/min (0.25-0.83 mL/s). However, edoxaban should not be given to patients with creatinine clearances above 95 mL/min because those patients had an increased risk of stroke when treated with edoxaban compared to warfarin. There is limited information on the use of these agents in patients with a body mass index over 40 kg/m^2.[48]

Timing of beginning oral anticoagulants has been in question. Older guidelines suggest waiting up to 14 days prior to beginning anticoagulation because of the risk of hemorrhagic transformation of the ischemic area. However, newer, small studies suggest that treatment as early as 3 to 5 days after a stroke in selected patients may be associated with no excess hemorrhage, but fewer recurrent strokes.[49]

9 ***Blood Pressure Management*** Elevated BP is very common in ischemic stroke patients, and treatment of hypertension in these patients is associated with a decreased risk of stroke recurrence.[50] The most recent hypertension guidelines have the following recommendations for BP control after ischemic stroke in order to prevent future strokes:

- Adults with previously treated hypertension who experience a stroke or

transient ischemic attack (TIA) should be restarted on antihypertensive treatment after the first few days of the index event to reduce the risk of recurrent stroke and other vascular events.

- For adults who experience a stroke or TIA, treatment with a thiazide diuretic, angiotensin-converting enzyme (ACE) inhibitor, or angiotensin receptor blocker, or combination treatment consisting of a thiazide diuretic plus ACE inhibitor, is useful. Selection of specific drugs should be individualized on the basis of patient comorbidities and agent pharmacological class.
- Adults not previously treated for hypertension who experience a stroke or TIA and have an established BP of 140/90 mm Hg or higher should be prescribed antihypertensive treatment a few days after the index event to reduce the risk of recurrent stroke and other vascular events.
- For adults who experience a stroke or TIA, a BP goal of less than 130/80 mm Hg may be reasonable.
- For adults with a lacunar stroke, a target SBP goal of less than 130 mm Hg may be reasonable.[51]

10 **Statins** Statin therapy is recommended for all ischemic stroke patients, regardless of baseline cholesterol, to reduce stroke recurrence. The statins have been shown to reduce the risk of stroke by approximately 30% in patients with coronary artery disease and elevated plasma lipids.[52] The Stroke Prevention by Aggressive Reduction in Cholesterol (SPARCL) study demonstrated that atorvastatin 80 mg daily reduced the risk of recurrent stroke by 16% and coronary events by 42% in patients with no cardiac history. Although the high-dose statin caused an increase in liver enzymes, there was no increase in myopathy.[53] It is now recommended that patients age 75 or younger experiencing ischemic stroke of presumed atherosclerotic origin be treated with high-intensity statin therapy for secondary stroke prevention with a target of achieving a 50% or greater reduction in low-density lipoprotein (LDL) cholesterol. For patients older than 75, moderate- or high-intensity statin therapy can be initiated as tolerated.[19] If the patient is on maximally tolerated statin therapy, but still has an LDL cholesterol ≥70 mg/dL (1.81 mmol/L), ezetimibe may be initiated. In very high-risk patients (multiple major atherosclerotic cardiovascular events or one major atherosclerotic cardiovascular event and multiple high-risk conditions) who are taking maximally tolerated statins and ezetimibe with LDL cholesterol ≥70 mg/dL (1.81 mmol/L), a proprotein

convertase subtilisin/kexin type 9 (PCSK9) inhibitor may be considered.[19]

Hemorrhagic Stroke

Acute Treatment The stroke council of the American Heart Association/American Stroke Association has published guidelines on the management of spontaneous intracerebral hemorrhage in 2015. While the usefulness of pharmacologic interventions is limited in this stroke type, the management of hypertension and reversal of coagulopathy in anticoagulant-associated ICH should be considered.

Blood Pressure Management Hypertension in patients with hemorrhagic stroke increases the risk of hematoma expansion. For patients with ICH presenting with a systolic blood pressure above 220 mmHg, aggressive lowering of blood pressure with continuous intravenous infusion medications is reasonable. Based on data from the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2 (INTERACT2) and Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH-2) trials, the acute lowering of systolic blood pressure to a goal of 140 mmHg is safe and may be effective to improve functional outcome.[8] For patients with SAH due to aneurysm rupture blood pressure control to at least a systolic blood pressure less than 160 mmHg is reasonable in the time period from symptom onset to aneurysm obliteration.[15] Refer to Table 38-2 for a summary of these recommendations and pharmacologic treatment options.

Anticoagulation Reversal When ICH occurs in a patient on anticoagulants, the use of reversal agents to correct the medication-induced coagulopathy should be considered. For patients on warfarin with elevated INR, reversal with vitamin K, typically intravenously, in combination with a four-factor prothrombin complex concentrate is recommended. Fresh frozen plasma can be used in place of a prothrombin complex concentrate, if necessary, but is not preferred.[8] Idarucizumab may be considered for reversing the effect of dabigatran specifically.[54] Factor Xa inhibitors, such as rivaroxaban and apixaban, may be reversed with andexanet alfa[55] (**Table 38-6**).

TABLE 38-6 Selected Anticoagulant Reversal

Drug	First-Line Reversal Recommendation	Alternate Treatment
Warfarin	Vitamin K 10 mg IV ×1 -and- 4-Factor Prothrombin Complex Concentrate (4PCC) INR 2 to <4: 25 units/kg, max 2,500 units INR 4-6: 35 units/kg, max 3,500 units INR >6: 50 units/kg, max 5,000 units	Vitamin K 10 mg IV ×1 -and- Fresh Frozen Plasma (FFP) 10-15 mL/kg
Dabigatran	Idarucizumab 5 gm IV ×1	Hemodialysis 4PCC 50 units/kg
Rivaroxaban ≤10 mg	Andexanet alfa 400 mg IV Bolus at rate of 30 mg/min, followed by 4 mg/min IV infusion up to 120 minutes	4PCC 50 units/kg
Rivaroxaban >10 mg or unknown dose	If <8 hours since last dose or unknown time andexanet alfa 800 mg IV bolus at rate of 30 mg/min, followed by 8 mg/min IV infusion up to 120 minutes If ≥8 hours since last dose Andexanet alfa 400 mg IV Bolus at rate of 30 mg/min, followed by 4 mg/min IV infusion up to 120 minutes	4PCC 50 units/kg
Apixaban ≤5 mg	Andexanet alfa 400 mg IV Bolus at rate of 30 mg/min, followed by 4 mg/min IV infusion up to 120 minutes	4PCC 50 units/kg
Apixaban >5 mg or unknown dose	If <8 hours since last dose or unknown time Andexanet alfa 800 mg IV bolus at rate of 30 mg/min, followed by 8 mg/min IV infusion up to 120 minutes If ≥8 hours since last dose Andexanet alfa 400 mg IV Bolus at rate of 30 mg/min, followed by 4 mg/min IV infusion up to 120 minutes	4PCC 50 units/kg
Edoxaban	Andexanet alfa not studied	4PCC 50 units/kg

FFP, fresh frozen plasma; IV, intravenous; 4PCC, 4-factor prothrombin complex concentrate; INR, international normalized ratio.

EVALUATION OF THERAPEUTIC OUTCOMES

Patients with acute stroke should be monitored intensely for the development of neurologic worsening (recurrence or extension of stroke), complications (venous thromboembolism or infection), and adverse effects from pharmacologic or nonpharmacologic interventions. The most common reasons for deterioration in a stroke patient are (a) extension of the original lesion—ischemic or hemorrhagic—in the brain, (b) development of cerebral edema and raised intracranial pressure, (c) hypertensive emergency, (d) infection (urinary and respiratory most common), (e) venous thromboembolism (DVT and pulmonary embolism), (f) electrolyte abnormalities and cardiac rhythm disturbances (can be associated with brain injury), and (g) recurrent stroke.

The approach to monitoring drug therapy in the hospitalized stroke patient is summarized in **Table 38-7**. The plan should be customized for individual patients based on the etiology of the stroke, their comorbidities, and ongoing disease processes.

TABLE 38-7 Monitoring Stroke Therapy in Hospitalized Patients

Drug	Adverse Effect	Monitoring Parameters	Comments
Alteplase	Bleeding	Neurologic examination, blood pressure	Every 15 minutes × 1 hour; every 30 minutes × 6 hours; every 1 hour × 17 hours; every shift after
Aspirin	Bleeding		Daily
Clopidogrel	Bleeding		Daily
Extended-release dipyridamole plus aspirin	Headache, bleeding		Daily
Direct-acting oral anticoagulants	Bleeding		Daily
Warfarin	Bleeding	PT/INR, hemoglobin, hematocrit	Daily

INR, international normalized ratio.

Bleeding is also a major adverse effect of antiplatelet agents and anticoagulants in the ambulatory setting. Several studies have been conducted to evaluate risk factors for bleeding for patients treated with oral anticoagulants.[55] Acronyms with scoring for bleeding risk factors have been developed from these studies (**Table 38-8**). S_2TOP-BLEED provides a 3-year risk of bleeding percentage when compared to a chart available in the publication.[55] For patients using oral anticoagulants, HAS-BLED is a useful assessment tool for determining bleeding risk.[56] A score ≥3 indicates high risk for bleeding and should be accompanied by more intensive patient monitoring.

TABLE 38-8 Acronyms for Scoring Bleeding Risk[58,59]

Antiplatelet Agents

S_2TOP-BLEED

Symbol	Risk Factor	Points to Award
S_2	Male **S**ex	2
	Smoking	1
T	**T**ype of antiplatelet agent: Aspirin ± extended-release dipyridamole or Aspirin + clopidogrel	1 5
O	**O**utcome on modified Rankin Scale ≥3	2
P	**P**rior stroke	1
B	High **B**lood pressure	1
L	**L**ower body mass index <20 kg/m² or	2
	20-25 kg/m²	1
E	**E**lderly: age 45-54 years	2
	55-64 years	4
	65-74 years	6
	75-84 years	9
	≥85 years	12
E	Asian **E**thnicity	1
D	**D**iabetes	1

Oral Anticoagulants

HAS-BLED

Symbol	Risk Factor	Points to Award
H	**H**ypertension (SBP >160 mm Hg)	1
A	**A**bnormal renal or liver function	1
		1
S	**H**istory of **S**troke	1
B	History of **B**leeding	1
L	**L**abile INRs	1
E	**E**lderly (age >65 years)	1
D	**D**rugs that promote bleeding or excess alcohol	1

SBP, systolic blood pressure.

Source: Data from references 58 and 59.

For survivors of noncardioembolic strokes, approximately 3% to 4% per year will experience another stroke.[57] One-third to one-half of these strokes occur while patients are on antiplatelet therapy to prevent stroke.[58] None of these agents reduces stroke risk to zero; some of the most important causes of breakthrough strokes are nonadherence, inappropriate dosing, reduced absorption, increased metabolism, drug-drug interactions, and genetic polymorphisms.[58] The healthcare practitioner is in a position to impact several of these factors. Nonadherence can have a root cause in a lack of understanding of therapy, adverse effects of the therapy, or the number of medications on discharge, among other factors.

CONCLUSION

Treatment of stroke requires a team approach to provide an accurate diagnosis to guide treatment and select therapies proven to improve outcomes. Careful patient selection for pharmacologic and nonpharmacologic therapies is paramount. Monitoring treatment helps assure goals of therapy are met.

Postclass Engaged Learning Activity

Conduct a literature search and identify a primary research manuscript that has been published in the past 12 months regarding the pharmacotherapy of stroke. If the manuscript is regarding a medication that is discussed in the book chapter, write a brief summary about the study methods, the major findings, and how this new information might change current practice. If the manuscript is regarding a new medication that is not described in the chapter, write a brief summary about the medication's mechanisms of action, how it is administered, and one potential advantage or disadvantage of this new medication compared to the current standard of care. This activity is intended to build your literature evaluation skills and the ability to critically appraise research manuscripts.

ABBREVIATIONS

ACE	angiotensin-converting enzyme
ADP	adenosine diphosphate
AHA	American Heart Association
aPTT	activated partial thromboplastin time
ATACH-2	Antihypertensive Treatment of Acute Cerebral Hemorrhage II
ATP	adenosine triphosphate
AVM	arteriovenous malformation
ASA	American Stroke Association
BP	blood pressure
cAMP	cyclic adenosine monophosphate
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events
CAST	Chinese Acute Stroke Trial
CD	carotid Doppler
cGMP	cyclic guanosine monophosphate
CHANCE	Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events
COX	cyclooxygenase
CNS	central nervous system
CT	scan computed tomography scan
CTA	computed tomography angiography
CYP2C19	cytochrome P4502C19
DBP	diastolic blood pressure
DCI	delayed cerebral ischemia
DOAC	direct-acting oral anticoagulants
DVT	deep vein thrombosis
DWI	diffusion-weighted imaging
EAFT	European Atrial Fibrillation Trial
ECASS	European Cooperative Acute Stroke Study
ECG	electrocardiogram
ESPS-2	European Stroke Prevention Study 2
EVD	external ventricular drainage
FFP	fresh frozen plasma
GCS	Glasgow Coma Score
GI	gastrointestinal
ICA	internal carotid artery
ICH	intracerebral hemorrhage
INR	international normalized ratio
INTERACT2	Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2
IPC	intermittent pneumatic compression
IST	International Stroke Trial
LDL	low-density lipoprotein

MATCH	Management of ATherothrombosis with Clopidogrel in High-risk patients
MCA	middle cerebral artery
MI	myocardial infarction
MRI	magnetic resonance imaging
mRS	modified Rankin score
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurologic Disorders and Stroke
NSAID	nonsteroidal anti-inflammatory drug
NVAF	nonvalvular atrial fibrillation
P2Y12	purinergic receptor P2Y, G-protein coupled 12
PAD	peripheral arterial disease
PCC	prothrombin complex concentrate
PCSK9	proprotein convertase subtilisin/kexin type 9
PGI2	prostacyclin
PRoFESS	Prevention Regimen for Effectively Avoiding Second Strokes
RRR	relative risk reduction
SAH	subarachnoid hemorrhage
SBP	systolic blood pressure
SOCRATES	Acute Stroke or Transient Ischaemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes
SPAF III	Stroke Prevention in Atrial Fibrillation
SPARCL	Stroke Prevention by Aggressive Reduction in Cholesterol
SPS	Stroke Prevention in Subcortical Stroke
TARDIS	Triple versus guideline Antiplatelet therapy to prevent Recurrence after acute Ischaemic Stroke or transient ischaemic attack
TCD	transcranial Doppler
TEE	transesophageal echocardiography
TIA	transient ischemic attack
TTE	transthoracic echocardiography
TXA2	thromboxane A2
VKORC1	Vitamin K epoxide reductase complex subunit 1

REFERENCES

1. Centers for Disease Control and Prevention. Leading causes of death and numbers of deaths by sex, race, and Hispanic origin: United States, 1980 and 2016. Available at: https://www.cdc.gov/nchs/data/hus/2017/019.pdf. Accessed July 11, 2018.
2. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics—2018 update: A report from the American Heart Association. *Circulation*. 2018;137: e67–e492.
3. Caceres JA, Goldstein JN. Intracranial hemorrhage. *Emerg Med Clin North Am*. 2012;30: 771–794.
4. Andersen KK, Olsen TS, Dehlendorff C, Kammersgaard LP. Hemorrhagic and ischemic strokes compared. *Stroke*. 2009;40: 2068–2072.
5. Kolominsky-Rabas PL, Weber M, Gefeller O, et al. Epidemiology of ischemic stroke subtypes according to TOAST criteria: Incidence, recurrence, and long-term survival in ischemic stroke subtypes: A population-based study. *Stroke*. 2001;32: 2735–2740.
6. Kernan WN, Ovbiogele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: A guidelines for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45: 2160–2236.
7. Xing C, Arai K, Lo EH, Hommel M. Pathophysiologic cascades in ischemic stroke. *Int J Stroke*. 2012;7: 378–385.
8. Hemphill JC, Greenberg SM, Anderson CS, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46: 2032–2060.
9. Meschia JF, Bushnell C, Boden-Albala B, et al. Guidelines for the primary prevention of stroke: A statement for health professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45: 3754–3832.
10. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: A guideline for professionals from the American Heart Association/American Stroke Association. *Stroke*. 2018;49: e46–e99.
11. Brott TG, Halperin JL, Abbara S, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS

guideline on the management of patients with extracranial carotid and vertebral artery disease: Executive summary. *Catheter Cardiovasc Interv*. 2013;81: E75–E123.

12. Brott TG, Hobson RW, Howard G, et al. Stenting versus endarterectomy for treatment of carotid artery stenosis. *N Engl J Med*. 2010;363: 11–23.
13. Noiphithak R, Leingudom A. Recent update on carotid endarterectomy versus carotid artery stenting. *Cerebrovascular Diseases*. 2017;43: 68–75.
14. Chimowitz MI, Lynn MJ, Derdeyn CP, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med*. 2011;365: 993–1003.
15. Connolly ES, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage. *Stroke*. 2012;43(6):1711–1737.
16. Rost NS, Giugliano RP, Ruff CT, et al. Outcomes with edoxaban versus warfarin in patients with previous cerebrovascular events findings from ENGAGE AF-TIMI 48 (Effective anticoagulation with factor Xa next generation in atrial fibrillation-thrombolysis in myocardial infarction 48). *Stroke*. 2016;47: 2075–2082.
17. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Eng J Med*. 1995;333: 1581–1587.
18. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359: 1317–1329.
19. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/ Guideline on the Management of Blood Cholesterol. A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2018. Article ahead of print.
20. Sandercock PA, Counsell C, Tseng MC, Cecconi E. Oral antiplatelet therapy for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2014; (3):Cd000029.
21. Lansberg MG, O'Donnell MJ, Khatri P, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141: e601S–e636S.
22. Food and Drug Administration. FDA Approves New Prescribed Uses for

Aspirin. FDA Talk Paper T98-76. 1998. Available at: www.fda.gov/bbs/topics/ANSWERS/ANS00919.html.

23. Serebruany VL, Malinin AI, Sane DC. Rapid platelet inhibition after a single capsule of Aggrenox: Challenging a conventional full-dose aspirin antiplatelet advantage? *Am J Hematol*. 2003;72: 280–281.
24. Sacco RL, Diener HC, Yusuf S, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med*. 2008;359: 1238–1251.
25. Eikelboom JW, Hankey GJ. Aspirin resistance: A new independent predictor of vascular events? *J Am Coll Cardiol*. 2003;41: 966–968.
26. Cai G, Zhou W, Lu Y, et al. Aspirin resistance and other aspirin-related concerns. *Neurol Sci*. 2016;37: 181–189.
27. Catella-Lawson F, Reilly MP, Kapoor SC, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med*. 2001;345: 1809–1817.
28. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischemic stroke or transient ischaemic attack in high-risk patients (MATCH): Randomized, double-blind, placebo-controlled trial. *Lancet*. 2004;364: 331–337.
29. Kubisa MJ, Jezewski MP, Gasecka A, et al. Ticagrelor—toward more efficient platelet inhibition and beyond. *Ther Clin Risk Manag*. 2018;14: 129–140.
30. Dean L, et al. Clopidogrel therapy and CYP2C19 genotype. *Medical Genetics Summaries*. Bethesda, MD: National Center for Biotechnology Information; 2018.
31. Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership. Plavix Product Information. Bridgewater, NJ: Author; 2018.
32. CAPRIE Steering Committee. A randomized, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1995;348: 1329–1339.
33. Eisert WG. Near-field amplification of antithrombotic effects of dipyridamole through vessel wall cells. *Neurology*. 2001;57(suppl 2):S20–S23.
34. Diener HC, Cunha L, Forbes C, et al. European Stroke Prevention Study 2: Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci*. 1996;143: 1–13.

35. Johnston SC, Amarenco P, Albers GW, et al. Ticagrelor versus aspirin in acute stroke or transient ischemic attack. *New Engl J Med*. 2016;375: 35–43.
36. Amarenco P, Albers GW, Denison H, et al. Efficacy and safety of ticagrelor versus aspirin in acute stroke or transient ischaemic attack of atherosclerotic origin: A subgroup analysis of SOCRATES, a randomised, double-blind, controlled trial. *Lancet Neurol*. 2017;16: 301–310.
37. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischemic stroke or transient ischaemic attack in high-risk patients (MATCH): Randomized, double-blind, placebo-controlled trial. *Lancet*. 2004;364: 331–337.
38. The SPS3 Investigators. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. *N Engl J Med*. 2012;367: 817–825.
39. Wang Y, Wang Y, Zhao X, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med*. 2013;369: 11–19.
40. Johnston SC, Easton JD, Ferrant M, et al. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. *N Engl J Med*. 2018;379: 215–225.
41. Liu Y, Fei Z, Wang W, et al. Efficacy and safety of short-term dual- versus mono-antiplatelet therapy in patients with ischemic stroke or TIA: A meta-analysis of 10 randomized controlled trials. *J Neurol*. 2016;263: 2247–2259.
42. European Atrial Fibrillation Trial Study Group. Secondary prevention in nonrheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet*. 1993;342: 1255–1262.
43. Bath PM, Woodhouse LJ, Appleton JP, et al. Triple versus guideline antiplatelet therapy to prevent recurrence after acute ischaemic stroke or transient ischaemic attack: The TARDIS RCT. *Health Technol Assess*. 2018;22(48):1–76.
44. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. *J Am College Cardiol*. 2014;61: e1–76.
45. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139–1151.
46. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981–992.
47. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in

nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883–891.

48. Martin K, Beyer-Westendorf J, Davidson BL, et al. Use of the direct oral anticoagulants in obese patients: Guidance from the SSC of the ISTH. *J Thromb Haemost*. 2016;14: 1308–1313.
49. Seiffge DJ, Werring DJ, Piciaroni M, et al. Timing of anticoagulation after recent ischaemic stroke in patients with atrial fibrillation. *Lancet Neurol*. 2018; online ahead of print.
50. Bath PM, Lidenstrom E, Boysen G, et al. Tinzaparin in acute ischaemic stroke (TAIST): A randomized, aspirin-controlled trial. *Lancet*. 2001;358: 702–710.
51. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: Executive summary. *Hypertension*. 2018;71: 1269–1324.
52. Hebert PR, Gaziano JM, Chan KS, Hennekens CH. Cholesterol lowering with statin drugs, risk of stroke, and total mortality: An overview of randomized trials. *JAMA*. 1997;278: 313–321.
53. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355: 549–559.
54. Pollack CV Jr, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal: Full cohort analysis. *N Engl J Med*. 2017;377: 431–441.
55. Connolly SJ, Gibson CM, Crowther M, et al. Andexanet alfa for factor Xa inhibitor reversal. *N Engl J Med*. 2016;375: 2499–500.
56. Hilkins NA, Algra A, Diener HC, et al. Predicting major bleeding in patients with noncardioembolic stroke on antiplatelets: S_2TOP-BLEED. *Neurology*. 2017;89: 936–943.
57. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: The Euro Heart Survey. *Chest*. 2010;138: 1093–1100.
58. Dhamoon MS, Sciacca RR, Rundek T, et al. Recurrent stroke and cardiac risks after first ischemic stroke: The Northern Manhattan Study. *Neurology*. 2006;66(5):641–646.
59. John S, Katzan I. Recurrent stroke while on antiplatelet therapy. *Neurol*

Clin. 2015;33: 475–489.

60. ESPRIT Study Group; Halkes PH, van Gijn J. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): Randomized controlled trial. *Lancet*. 2006;367: 1665–1673.
61. Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: Final results. *J Neurol Neurosurg Psychiatry*. 1991;54: 1044–1054.

39

The Arrhythmias

Jessica J. Tilton, Cynthia Sanoski, and Jerry L. Bauman

KEY CONCEPTS

1. The use of antiarrhythmic drugs (AADs) in the United States has declined because clinical trials have shown increased mortality with their use due to proarrhythmic side effects. AADs have been increasingly replaced by nonpharmacologic approaches such as ablation and the implantable cardioverter-defibrillator (ICD).
2. AADs frequently cause side effects and are complex in their pharmacokinetic characteristics. Close monitoring is required of all of these drugs to assess for adverse effects as well as potential drug interactions.
3. The most commonly prescribed AAD is amiodarone. This drug is effective in terminating and preventing a wide variety of symptomatic supraventricular and ventricular arrhythmias. However, amiodarone is plagued by frequent side effects and requires close monitoring. The most concerning toxicity is pulmonary fibrosis. The side effect profiles of the intravenous (IV) (acute, short-term) and oral (chronic, long-term) forms of amiodarone differ substantially.
4. In patients with atrial fibrillation (AF), therapy is traditionally aimed at controlling ventricular rate, preventing thromboembolic (TE) complications, and restoring and maintaining sinus rhythm (SR). Studies show there is no need to aggressively pursue strategies to maintain SR; rate control alone (leaving the patient in AF) is often sufficient in patients who can tolerate it. Nonetheless, chronic AAD therapy may still be needed in patients who continue to have symptoms despite adequate ventricular rate control.
5. Paroxysmal supraventricular tachycardia (PSVT) is usually a result of reentry in or proximal to the atrioventricular (AV) node or AV reentry incorporating an accessory pathway; common tachycardias can be

terminated acutely with AV nodal blocking drugs such as adenosine, and recurrences can be prevented by catheter ablation using radiofrequency current.

6. Patients with Wolff-Parkinson-White (WPW) syndrome may have several different tachycardias that are acutely treated by different strategies: orthodromic reentry (adenosine), antidromic reentry (adenosine or procainamide), and AF (procainamide or ibutilide). AV nodal blocking drugs are contraindicated in patients with WPW syndrome and AF.
7. Based on the results of the Cardiac Arrhythmia Suppression Trial (CAST) and other trials, AADs (with the exception of beta blockers) should no longer routinely be used in patients with prior myocardial infarction (MI) or left ventricular (LV) dysfunction and minor ventricular rhythm disturbances (eg, premature ventricular complexes [PVCs]).
8. Patients with hemodynamically significant ventricular tachycardia (VT) or ventricular fibrillation (VF) not associated with an acute MI who are successfully resuscitated (with electrical cardioversion, epinephrine, amiodarone, lidocaine) are at high risk for sudden cardiac death (SCD) and should receive an ICD ("secondary prevention").
9. Implantation of an ICD should be considered for the primary prevention of SCD in certain high-risk patient populations. High-risk patients include those with a history of MI and LV dysfunction (regardless of whether they have inducible sustained ventricular arrhythmias), as well as those with New York Heart Association (NYHA) class II or III heart failure with reduced ejection fraction (HF*r*EF) as a result of either ischemic or nonischemic causes.
10. Life-threatening drug-induced ventricular proarrhythmia generally takes two forms: sinusoidal or incessant monomorphic VT (class Ic AADs) and torsades de pointes (TdP) (class Ia or III AADs and many other noncardiac drugs).

Preclass Engaged Learning Activity

Watch the video entitled "Normal Sinus Rhythm on an EKG" in Khan Academy by Bianca Yoo. This 9-minute video provides a brief overview of the cardiac conduction system and how it translates to an electrocardiogram. The video is useful to enhance student understanding regarding the

COLLECT and ASSESS steps in the patient care process.

INTRODUCTION

The heart has two basic properties, namely, an electrical property and a mechanical property. The synchronous interaction between these two properties is complex, precise, and relatively enduring. The study of the electrical properties of the heart has grown at a steady rate, interrupted by periodic salvos of scientific breakthroughs. Einthoven's pioneering work allowed graphic electrical tracings of cardiac rhythm and probably represents the first of these breakthroughs. This discovery of the surface electrocardiogram (ECG) has remained the cornerstone of diagnostic tools for cardiac rhythm disturbances. Since then, intracardiac recordings and programmed cardiac stimulation have advanced our understanding of arrhythmias, and microelectrode, voltage clamping, and patch clamping techniques have allowed considerable insight into the electrophysiologic actions and mechanisms of AADs. The new era of molecular biology and mapping of the human genome promises even greater insights into mechanisms (and potential therapies) of arrhythmias. Noteworthy in this regard is the discovery of genetic abnormalities in the ion channels that control electrical repolarization (heritable long QT syndrome) or depolarization (Brugada syndrome).

1 There was some expectation that advances in AAD discovery would lead to a highly effective and nontoxic agent that would be effective for a majority of patients. Instead, significant problems with drug toxicity and proarrhythmia have resulted in a decline in the overall volume of AAD usage in the United States since 1989. The other phenomenon that has significantly contributed to the decline in AAD use is the development of extremely effective nonpharmacologic therapies. Technical advances have made it possible to permanently interrupt reentry circuits with radiofrequency ablation, which renders long-term AAD use unnecessary in certain arrhythmias. Furthermore, the impressive survival data associated with the use of ICDs for the primary and secondary prevention of SCD have led most clinicians to choose "device" therapy as the first-line treatment for patients who are at high risk for life-threatening ventricular arrhythmias. Both of these nonpharmacologic therapies have become increasingly popular for the management of arrhythmias so that the potential proarrhythmic effects and organ toxicities associated with AADs can be avoided.

PATHOPHYSIOLOGY

Normal Conduction

Electrical activity is initiated by the sinoatrial (SA) node and moves through cardiac tissue by a tree-like conduction network. The SA node initiates cardiac rhythm under normal circumstances because this tissue possesses the highest degree of automaticity or rate of spontaneous impulse generation. The degree of automaticity of the SA node is largely influenced by the autonomic nervous system in that both cholinergic and sympathetic innervations control the sinus rate. Most tissues within the conduction system also possess varying degrees of inherent automatic properties. However, the rates of spontaneous impulse generation of these tissues are less than that of the SA node. Thus, these latent automatic pacemakers are continuously overdriven by impulses arising from the SA node (primary pacemaker) and do not become clinically apparent.

From the SA node, electrical activity moves in a wave front through an atrial specialized conducting system and eventually gains entrance to the ventricle via the AV node and a large bundle of conducting tissue referred to as the bundle of His. The conducting tissues bridging the atria and ventricles are referred to as the junctional areas. Again, this area of tissue (junction) is largely influenced by autonomic input and possesses a relatively high degree of inherent automaticity (about 40 beats/min which is less than that of the SA node). From the bundle of His, the cardiac conduction system bifurcates into several (usually three) bundle branches: one right bundle and two left bundles. These bundle branches further arborize into a conduction network referred to as the Purkinje system. The conduction system as a whole innervates the mechanical myocardium and serves to initiate excitation–contraction coupling and the contractile process. After a cell or group of cells within the heart is electrically stimulated, a brief period of time follows in which those cells cannot again be excited. This time period is referred to as the refractory period. As the electrical wave front moves down the conduction system, the impulse eventually encounters tissue refractory to stimulation (recently excited) and subsequently dies out. The SA node subsequently recovers, fires spontaneously, and begins the process again.

Prior to cellular excitation, an electrical gradient exists between the inside and the outside of the cardiac cell membrane. At this time, the cell is polarized. In atrial and ventricular conducting tissues, the intracellular space is approximately −80 to −90 mV with respect to the extracellular environment. The electrical gradient just prior to excitation is referred to as the resting membrane potential (RMP) and is the result of differences in ion concentrations between the inside

and the outside of the cell. At RMP, the cell is polarized primarily by the action of active membrane ion pumps, the most notable of these being the sodium–potassium pump. For example, this specific pump (in addition to other systems) attempts to maintain the intracellular sodium concentration at 5 to 15 mEq/L (mmol/L), the extracellular sodium concentration at 135 to 142 mEq/L (mmol/L), the intracellular potassium concentration at 135 to 140 mEq/L (mmol/L), and the extracellular potassium concentration at 3 to 5 mEq/L (mmol/L).

Electrical stimulation (or depolarization) of the cell will result in changes in membrane potential over time or a characteristic action potential curve (**Fig. 39-1**). The action potential curve results from the transmembrane movement of specific ions and is divided into different phases. Phase 0 or initial, rapid depolarization of atrial and ventricular tissues is caused by an abrupt increase in the permeability of the membrane to sodium influx. This rapid depolarization more than equilibrates (overshoots) the electrical potential, resulting in a brief initial repolarization or phase 1. Phase 1 (initial repolarization) is caused by a transient and active potassium efflux (ie, the I_{Kto} current). Calcium begins to move into the intracellular space at about −60 mV (during phase 0), causing a slower depolarization. Calcium influx continues throughout phase 2 of the action potential (plateau phase) and is balanced to some degree by potassium efflux. Calcium entrance (only through L channels in myocardial tissue) distinguishes cardiac conducting cells from nerve tissue and provides the critical ionic link to excitation–contraction coupling and the mechanical properties of the heart as a pump. The membrane remains permeable to potassium efflux during phase 3, resulting in cellular repolarization. Phase 4 of the action potential is the gradual depolarization of the cell and is related to a constant sodium leak into the intracellular space balanced by a decreasing (over time) efflux of potassium. The slope of phase 4 depolarization determines, in large part, the automatic properties of the cell. As the cell is slowly depolarized during phase 4, an abrupt increase in sodium permeability occurs, allowing the rapid cellular depolarization of phase 0. The juncture of phase 4 and phase 0 where rapid sodium influx is initiated is referred to as the threshold potential of the cell. The level of threshold potential also regulates the degree of cellular automaticity.

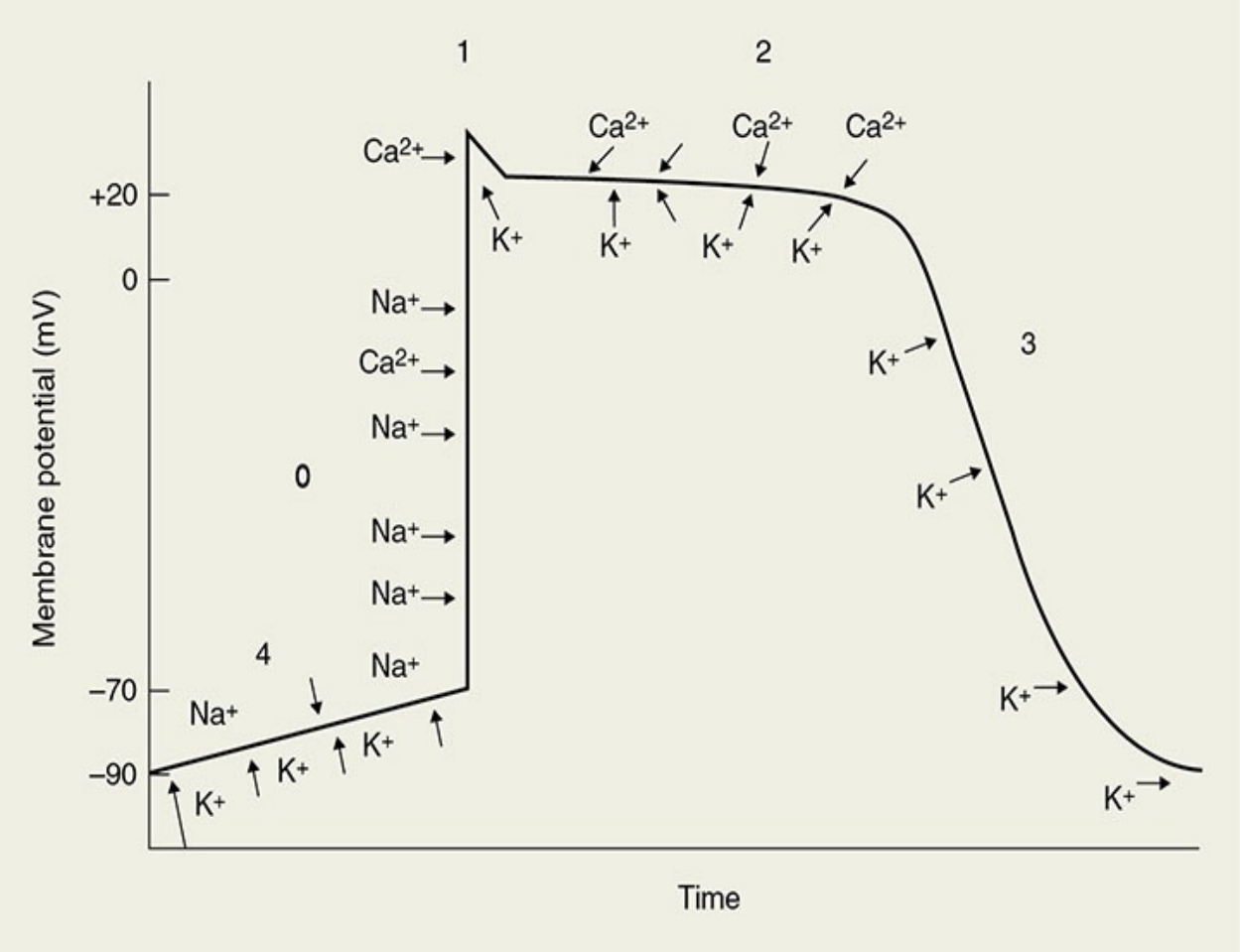


FIGURE 39-1 Purkinje fiber action potential showing specific ion flux responsible for the change in membrane potential. Ions outside of the line (eg, sodium) move from the extracellular space to the intracellular space and ions on the inside of the line (eg, potassium) move from the inside of the cell to the outside.

Not all cells in the cardiac conduction system rely on sodium influx for initial depolarization. Some tissues depolarize in response to a slower inward ionic current caused by calcium influx. These “calcium-dependent” tissues are found primarily in the SA and AV nodes (both L and T channels) and possess distinct conduction properties in comparison to “sodium-dependent” fibers. Calcium-dependent cells generally have a less negative RMP (−40 to −60 mV) and a slower conduction velocity. Furthermore, in calcium-dependent tissues, recovery of excitability outlasts full repolarization, whereas in sodium-dependent tissues, recovery is prompt after repolarization. These two types of electrical tissues also differ dramatically in how drugs modify their conduction properties.

Ion conductance across the lipid bilayer of the cell membrane occurs via the

formation of membrane pores or “channels” (**Fig. 39-2**). Selective ion channels probably form in response to specific electrical potential differences between the inside and the outside of the cell (voltage dependence). The membrane itself is composed of both organized and disorganized lipids and phospholipids in a dynamic sol-gel matrix. During ion flux and electrical excitation, changes in this sol-gel equilibrium occur and permit the formation of activated ion channels. Besides channel formation and membrane composition, intrachannel proteins or phospholipids, referred to as gates, also regulate the transmembrane movement of ions. These gates are thought to be positioned strategically within the channel to modulate ion flow. Each ion channel conceptually has two types of gates: an activation gate and an inactivation gate (see Fig. 39-2). The activation gate opens during depolarization to allow the ion current to enter or exit from the cell, and the inactivation gate later closes to stop ion movement. When the cell is in a rested state, the activation gates are closed and the inactivation gates are open. The activation gates then open to allow ion movement through the channel, and the inactivation gates later close to stop ion conductance. Thus, the cell cycles between three states: resting, activated or open, and inactivated or closed. Activation of SA and AV nodal tissue is dependent on a slow depolarizing current through calcium channels and gates, whereas the activation of atrial and ventricular tissues is dependent on a rapid depolarizing current through sodium channels and gates.

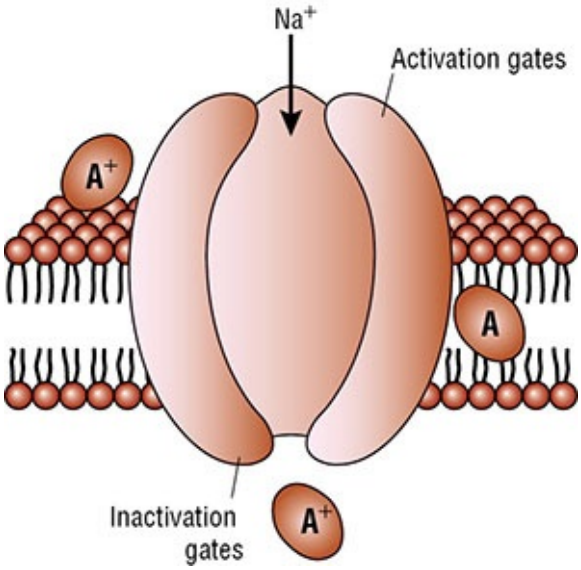


FIGURE 39-2 Lipid bilayer, sodium channel, and possible sites of action of the class I AADs (*A*). Class I AADs may theoretically inhibit sodium influx at an extracellular, intramembrane, or intracellular receptor site. However, all approved agents appear to block sodium conductance at a single receptor site by

gaining entrance to the interior of the channel from an intracellular route. Active ionized drugs block the channel predominantly during the activated or inactivated state and bind and unbind with specific time constants (described as fast on–off, slow on–off, and intermediate). (AADs, antiarrhythmic drugs.)

Abnormal Conduction

The mechanisms of tachyarrhythmias have been classically divided into two general categories: those resulting from an abnormality in impulse generation (“automatic” tachycardias) and those resulting from an abnormality in impulse conduction (“reentrant” tachycardias).

Automatic tachycardias depend on spontaneous impulse generation in latent pacemakers and may be a result of several different mechanisms. Drugs, such as digoxin or catecholamines, and conditions, such as hypoxia, electrolyte abnormalities (eg, hypokalemia), and fiber stretch (cardiac dilation), may lead to an increased slope of phase 4 depolarization in cardiac tissues other than the SA node. These factors that experimentally lead to abnormal automaticity are also known to be arrhythmogenic in clinical situations. The increased slope of phase 4 causes heightened automaticity of these tissues and competition with the SA node for dominance of cardiac rhythm. If the rate of spontaneous impulse generation of the abnormally automatic tissue exceeds that of the SA node, then an automatic tachycardia may result. Automatic tachycardias have the following characteristics: (a) the onset of the tachycardia is unrelated to an initiating event such as a premature beat; (b) the initiating beat is usually identical to subsequent beats of the tachycardia; (c) the tachycardia cannot be initiated by programmed cardiac stimulation; and (d) the onset of the tachycardia is usually preceded by a gradual acceleration in rate and termination is usually preceded by a gradual deceleration in rate. Clinical tachycardias resulting from the classic forms of enhanced automaticity already described are not as common as once thought. Examples are sinus tachycardia and junctional tachycardia.

Triggered automaticity is also a possible mechanism for abnormal impulse generation. Briefly, triggered automaticity refers to transient membrane depolarizations that occur during repolarization (early afterdepolarizations [EADs]) or after repolarization (delayed afterdepolarizations [DADs]) but prior to phase 4 of the action potential. Afterdepolarizations may be related to abnormal calcium and sodium influx during or just after full cellular repolarization. Experimentally, EADs may be precipitated by hypokalemia, class Ia AADs, or slow stimulation rates—any factor that blocks the ion channels (eg, potassium) responsible for cellular repolarization. EADs provoked by drugs that

block potassium conductance and delay repolarization are the underlying cause of TdP. DADs may be precipitated by digoxin or catecholamines and suppressed by non-dihydropyridine (non-DHP) calcium channel blockers (CCBs), and have been suggested as the mechanism for multifocal atrial tachycardia, digoxin-induced tachycardias, and exercise-provoked VT. Triggered automatic rhythms possess some of the characteristics of automatic tachycardias and some of the characteristics of reentrant tachycardias (description follows).

Reentry is a concept that involves indefinite propagation of the impulse and continued activation of previously refractory tissue. There are three conduction requirements for the formation of a viable reentrant focus: (1) two pathways for impulse conduction, (2) an area of unidirectional block (prolonged refractoriness) in one of these pathways, and (3) slow conduction in the other pathway (**Fig. 39-3**). Usually, a critically timed premature beat initiates reentry. This premature impulse enters both conduction pathways but encounters refractory tissue in one of the pathways at the area of unidirectional block. The impulse dies out because the tissue is still refractory from the previous (sinus) impulse. Although it fails to propagate in one pathway, the impulse may still proceed in a forward direction (antegrade) through the other pathway because of this pathway's relatively shorter refractory period. The impulse may then proceed through a loop of tissue and "reenter" the area of unidirectional block in a backward direction (retrograde). Because the antegrade pathway has slow conduction characteristics, the area of unidirectional block has time to recover its excitability. The impulse can proceed in a retrograde fashion through this previously refractory tissue and continue around the loop of tissue in a circular fashion. Thus, the key to the formation of a reentrant focus is crucial conduction discrepancies in the electrophysiologic characteristics of the two pathways. The reentrant focus may excite surrounding tissue at a rate greater than that of the SA node, leading to formation of a clinical tachycardia. The above model is anatomically determined in that there is only one pathway for impulse conduction with a fixed circuit length. Another model of reentry, referred to as a functional reentrant loop or leading circle model, may also occur (**Fig. 39-4**).[1] In a functional reentrant focus, the length of the circuit may vary depending on the conduction velocity and recovery characteristics of the impulse. The area in the middle of the loop is continually kept refractory by the inwardly moving impulse. The length of the circuit is not fixed but is the smallest circle possible, such that the leading edge of the wave front is continuously exciting tissue just as it recovers. It differs from the anatomic model in that the leading edge of the impulse is not preceded by an excitable gap of tissue, and it does not have an

obstacle in the middle or a fixed anatomic circuit. Clinically, many reentrant foci probably have both anatomic and functional characteristics. In the so-called figure eight model, a zone of unidirectional block is present, allowing for two impulse loops that join and reenter the area of block in a retrograde fashion to form a pretzel-shaped reentrant circuit. This model combines functional characteristics with an excitable gap. All of these theoretical models require a critical balance of refractoriness and conduction velocity within the circuit and as such have helped to explain the effects of drugs on terminating, modifying, and causing cardiac rhythm disturbances.

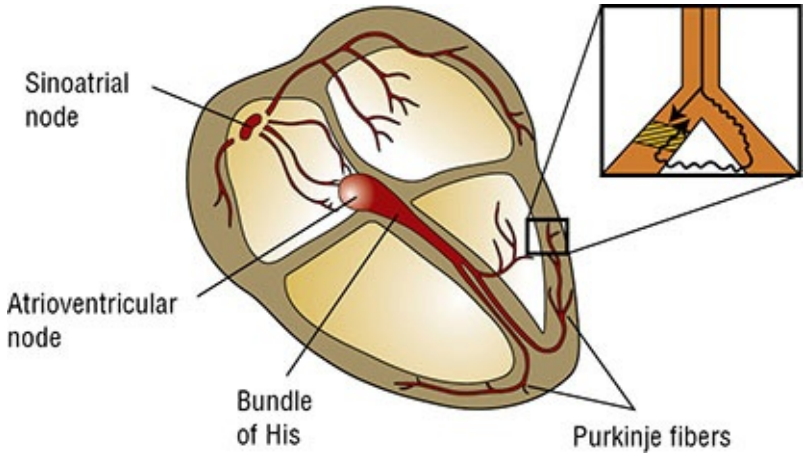


FIGURE 39-3 Conduction system of the heart. The magnified portion shows a bifurcation of a Purkinje fiber traditionally explained as the etiology of reentrant VT. A premature impulse travels to the fiber which is damaged by heart disease or ischemia. It encounters a zone of prolonged refractoriness (area of unidirectional block; *cross-hatched area*) but fails to propagate because the fiber remains refractory to stimulation from the previous impulse. However, the impulse may slowly travel (*squiggly line*) through the other portion of the Purkinje twig and will “reenter” the cross-hatched area if the refractory period is concluded and the fiber is now excitable. Thus, the premature impulse never meets refractory tissue; circus movement ensues. If this site stimulates the surrounding ventricle repetitively, clinical reentrant VT results. (VT, ventricular tachycardia.)

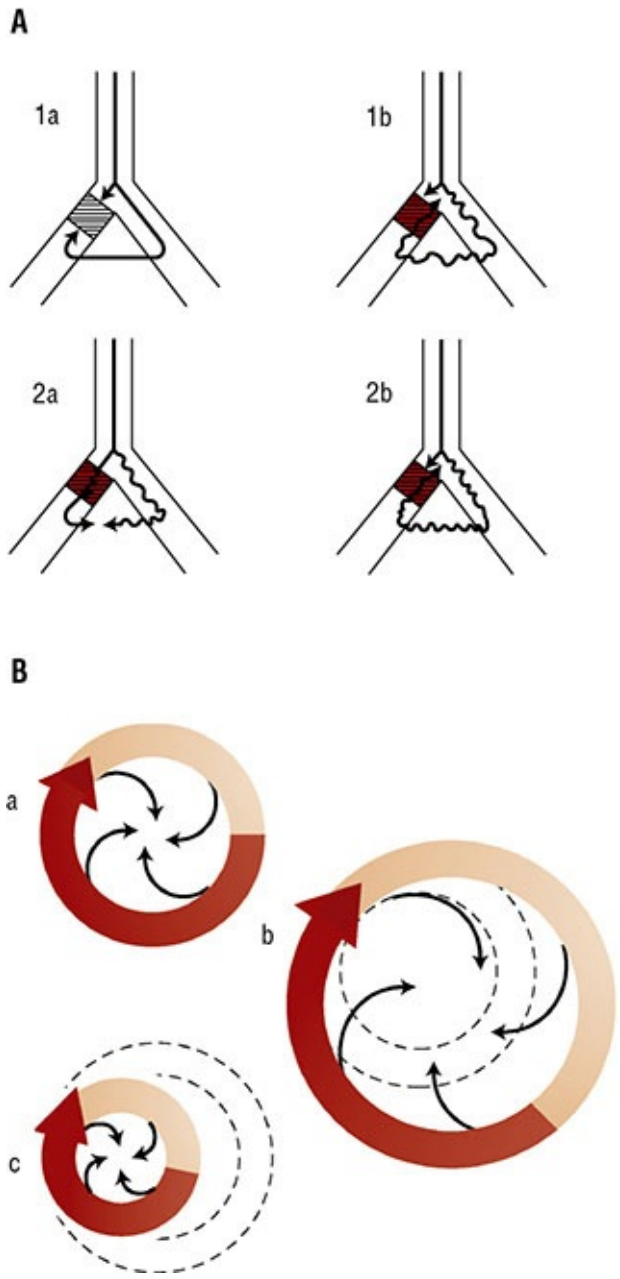


FIGURE 39-4 (*A*) Possible mechanism of proarrhythmia in the anatomic model of reentry. *1a.* Nonviable reentrant loop due to bidirectional block (*shaded area*). *1b.* Instance where a drug slows conduction velocity without significantly prolonging the refractory period. The impulse is now able to reenter the area of unidirectional block (*shaded area*) because slowed conduction through the antegrade pathway allows recovery of the block. A new reentrant tachycardia may result. *2a.* Nonviable reentrant loop due to a lack of a unidirectional block. *2b.* Instance where a drug prolongs the refractory period without significantly slowing conduction velocity. The impulse moving antegrade meets refractory tissue (*shaded area*) allowing for unidirectional block. A new reentrant

tachycardia may result. (*B*) Mechanism of reentry and proarrhythmia. *a.* Functionally determined (*leading circle*) reentrant circuit. This model should be contrasted with anatomic reentry; here the circuit is not fixed (it does not necessarily move around an anatomic obstacle) and there is no excitable gap. All tissue inside is held continuously refractory. *b.* Instance where a drug prolongs the refractory period without significantly slowing conduction velocity. The tachycardia may terminate or slow in rate as shown as a consequence of a greater circuit length. The *dashed lines* represent the original reentrant circuit prior to drug treatment. *c.* Instance where a drug slows conduction velocity without significantly prolonging the refractory period (ie, class Ic *antiarrhythmic drugs*) and accelerates the tachycardia. The tachycardia rate may increase (proarrhythmia) as shown as a consequence of a shorter circuit length. The dashed lines represent the original reentrant circuit prior to drug treatment. (*Reprinted, with permission, from McCollam PL, Parker RB, Beckman KJ, et al. Proarrhythmia: A paradoxic response to antiarrhythmic agents. Pharmacotherapy 1989;9:146.*)

What causes reentry to become clinically manifest? Reentrant foci may occur at any level of the conduction system: within the branches of the specialized atrial conduction system, within the Purkinje network, and even within portions of the SA and AV nodes. The anatomy of the Purkinje system appears to provide a suitable substrate for the formation of microreentrant loops and is often used as a model to facilitate the understanding of reentry concepts. Of course, because reentry does not usually occur in normal, healthy conduction tissue, various forms of heart disease or conduction abnormalities must usually be present before reentry becomes manifest. In other words, the various forms of heart disease (eg, coronary artery disease [CAD], LV dysfunction) can result in changes in conduction in the pathways of a suitable reentrant substrate. An often-used example is reentry occurring as a consequence of ischemic or hypoxic damage; with inadequate cellular oxygen, cardiac tissue resorts to anaerobic glycolysis for adenosine triphosphate production. As high-energy phosphate concentrations diminish, the activity of the transmembrane ion pumps declines and RMP rises. This rise in RMP causes inactivation in the voltage-dependent sodium channel, and the tissue begins to assume slow conduction characteristics. If changes in conduction parameters occur in a discordant manner due to varying degrees of ischemia or hypoxia, then a reentry circuit may become manifest. Furthermore, an ischemic, dying cell liberates intracellular potassium, which also causes a rise in RMP. In other cases, reentry may occur as a consequence of anatomic or functional variants in the normal

conduction system. For instance, patients may possess two (instead of one) conduction pathways near or within the AV node, or have an anomalous extranodal AV pathway that possesses different electrophysiologic characteristics from the normal AV nodal pathway. Reentry in these cases may occur within the AV node or encompass both atrial and ventricular tissues. Reentrant tachycardias have the following characteristics: (a) the onset of the tachycardia is usually related to an initiating event (ie, premature beat); (b) the initiating beat is usually different in morphology from subsequent beats of the tachycardia; (c) the initiation of the tachycardia can usually be incited with programmed cardiac stimulation; and (d) the initiation and termination of the tachycardia is usually abrupt without an acceleration or deceleration phase. There are many examples of reentrant tachycardias, including AF, atrial flutter (AFl), AV nodal reentrant tachycardia (AVNRT), AV reentrant tachycardia (AVRT), and recurrent VT.

PHARMACOLOGIC THERAPY

In a theoretical sense, drugs have antiarrhythmic activity by directly altering conduction in several ways. First, a drug may depress the automatic properties of abnormal pacemaker cells. A drug may do this by decreasing the slope of phase 4 depolarization and/or by elevating threshold potential. If the rate of spontaneous impulse generation of the abnormally automatic foci becomes less than that of the SA node, normal cardiac rhythm can be restored. Second, drugs may alter the conduction characteristics of the pathways of a reentrant loop.[1,2] A drug may facilitate conduction (shorten refractoriness) in the area of unidirectional block, allowing antegrade conduction to proceed. On the other hand, a drug may further depress conduction (prolong refractoriness) either in the area of unidirectional block or in the pathway with slowed conduction and a relatively shorter refractory period. If refractoriness is prolonged in the area of unidirectional block, retrograde propagation of the impulse is not permitted, causing a “bidirectional” block. In the anatomic model, if refractoriness is prolonged in the pathway with slow conduction, antegrade conduction of the impulse is not permitted. In either case, drugs that reduce the discordance and cause uniformity in conduction properties of the two pathways may suppress the reentrant substrate. In the functionally determined model, if refractoriness is prolonged without significantly slowing conduction velocity, the tachycardia may terminate or slow in rate as a consequence of a greater circuit length (see Fig. 39-4). There are other theoretical ways to stop reentry: (a) a drug may

eliminate the critically timed premature impulse that triggers reentry; (b) a drug may slow conduction velocity to such an extent that conduction is extinguished; or (c) a drug may reverse the underlying form of heart disease that was responsible for the conduction abnormalities that led to the arrhythmia (ie, “reverse remodeling”).

AADs have specific electrophysiologic actions that alter cardiac conduction in patients with or without heart disease. These actions form the basis of grouping AADs into specific categories based on their electrophysiologic actions in vitro. Vaughan Williams proposed the most frequently used classification system (**Table 39-1**).[2] This classification has been criticized for the following reasons: (a) it is incomplete and does not allow for the classification of drugs such as digoxin or adenosine; (b) it is not pure, and many agents have properties of more than one class of drugs; (c) it does not incorporate drug characteristics such as mechanisms of tachycardia termination/prevention, clinical indications, or side effects; and (d) drugs become “labeled” within a class, although they may be distinct in many regards. Despite these criticisms, the Vaughan Williams classification remains the most frequently used for categorizing the electrophysiologic actions of AADs.

TABLE 39-1 Classification of Antiarrhythmic Drugs

Class	Drug	Conduction Velocity[i]	Refractory Period	Automaticity	Ion Block
Ia	Quinidine Procainamide Disopyramide	↓	↑	↓	Sodium (intermediate) Potassium
Ib	Lidocaine Mexiletine	0/↓	↓	↓	Sodium (fast on–off)
Ic	Flecainide Propafenone[ii]	↓↓	0	↓	Sodium (slow on–off)
II[iii]	Beta blockers	↓	↑	↓	Calcium (indirect)
III	Amiodarone[iv] Dofetilide Dronedarone[iv] Sotalol[ii] Ibutilide	0	↑↑	0	Potassium
IV[iii]	Verapamil Diltiazem	↓	↑	↓	Calcium

[i]Variables for normal tissue models in ventricular tissue.

[ii]Also has beta-blocking actions.

[iii]Variables for sinoatrial (SA) and atrioventricular (AV) nodal tissue only.

[iv]Also has sodium, calcium, and beta-blocking actions; see Table 39-2 (for amiodarone).

The class Ia AADs, quinidine, procainamide, and disopyramide, slow conduction velocity, prolong refractoriness, and decrease the automatic properties of sodium-dependent (normal and diseased) conduction tissue. Although class Ia AADs are primarily considered sodium channel blockers, their electrophysiologic actions can also be attributed to blockade of potassium channels. In reentrant tachycardias, these drugs generally depress conduction and prolong refractoriness, theoretically transforming the area of unidirectional block into a bidirectional block. Clinically, class Ia drugs are broad-spectrum AADs that are effective for both supraventricular and ventricular arrhythmias. Procainamide is only available in the IV formulation as all of its oral formulations have been discontinued. These AADs tend not to be used frequently in clinical practice for the management of either supraventricular or ventricular arrhythmias primarily because of their limited efficacy and significant toxicities.

The class Ib AADs, lidocaine and mexiletine were historically categorized separately from quinidine-like drugs. This was a result of early work demonstrating that lidocaine had distinctly different electrophysiologic actions. In normal tissue models, lidocaine generally facilitates actions on cardiac

conduction by shortening refractoriness and having little effect on conduction velocity. Thus, it was postulated that these agents could improve antegrade conduction, eliminating the area of unidirectional block. Of course, arrhythmias do not usually arise from normal tissue, leading investigators to study the actions of lidocaine in ischemic and hypoxic tissue models. Interestingly, studies have shown lidocaine to possess class Ia quinidine-like properties in diseased tissues. Therefore, it is probable that lidocaine acts in a similar fashion to the class Ia AADs (ie, prolongs refractoriness in diseased ischemic tissues leading to bidirectional block in a reentrant circuit). Lidocaine and similar agents have accentuated effects in ischemic tissue caused by the local acidosis and potassium shifts that occur during cellular hypoxia. Changes in pH alter the time that local anesthetics occupy the sodium channel receptor, thereby affecting the agent's electrophysiologic actions. In addition, the intracellular acidosis that ensues as a consequence of ischemia could cause lidocaine to become "trapped" within the cell, allowing increased access to the receptor. The class Ib AADs are considerably more effective in ventricular arrhythmias than supraventricular arrhythmias. As a group, these drugs are relatively weak sodium channel blockers (at normal stimulation rates).

The class Ic AADs, propafenone and flecainide, are extremely potent sodium channel blockers, profoundly slowing conduction velocity while leaving refractoriness relatively unaltered. The class Ic AADs theoretically eliminate reentry by slowing conduction to a point where the impulse is extinguished and cannot propagate further. Although the class Ic AADs are effective for both ventricular and supraventricular arrhythmias, their use for ventricular arrhythmias has been limited by the risk of proarrhythmia.

Class I AADs are grouped together because of their common action in blocking sodium conductance. The receptor site for these AADs is probably inside the sodium channel so that, in effect, the drug plugs the pore. The AAD may gain access to the receptor either via the intracellular space through the membrane lipid bilayer or directly through the channel. Several principles are inherent in antiarrhythmic sodium channel receptor theories[3]:

1. Class I AADs have predominant affinity for a particular state of the channel (eg, during activation or inactivation). For example, lidocaine blocks sodium current primarily when the cell is in the inactivated state, whereas quinidine, flecainide, and propafenone are predominantly open (or activated)-channel blockers.
2. Class I AADs have specific binding and unbinding characteristics to the

receptor. For example, lidocaine binds to and dissociates from the channel receptor quickly ("fast on–off") but flecainide has very "slow on–off" properties. This explains why flecainide has such potent effects on slowing ventricular conduction, whereas lidocaine has little effect on normal tissue (at normal heart rates). In general, the class Ic AADs are "slow on–off," the class Ib AADs are "fast on–off," and the class Ia AADs are intermediate in their binding kinetics.

3. Class I AADs possess rate dependence (ie, sodium channel blockade and slowed conduction are greatest at fast heart rates and least during bradycardia). For "slow on–off" drugs, sodium channel blockade is evident at normal rates (60-100 beats/min), but for "fast on–off" agents, slowed conduction is only apparent at fast heart rates.
4. Class I AADs are weak bases with a pK_a >7 and block the sodium channel in their ionized form. Consequently, pH will alter these actions: acidosis accentuates and alkalosis diminishes sodium channel blockade.
5. Class I AADs appear to share a single receptor site in the sodium channel. It should be noted, however, that a number of class I AADs have other electrophysiologic properties. For instance, quinidine has potent potassium channel blocking activity (manifests predominantly at low concentrations) as does *N*-acetylprocainamide (manifests predominantly at high concentrations), the primary metabolite of procainamide. Additionally, propafenone has beta-blocking actions.

The beta blockers are classified as class II AADs. For the most part, the clinically relevant acute antiarrhythmic mechanisms of the beta blockers result from their antiadrenergic actions. Because the SA and AV nodes are heavily influenced by adrenergic innervation, beta blockers would be most useful in tachycardias in which these nodal tissues are abnormally automatic or are a portion of a reentrant loop. These drugs are also helpful in slowing ventricular response in atrial arrhythmias (eg, AF) by their effects on the AV node. Furthermore, some tachycardias are exercise-related or precipitated by states of high sympathetic tone (perhaps through triggered activity), and beta blockers may be useful in these instances. Beta-adrenergic stimulation results in increased conduction velocity, shortened refractoriness, and increased automaticity of the nodal tissues; beta blockers will antagonize these effects. In the nodal tissues, beta blockers interfere with calcium entry into the cell by altering catecholamine-dependent channel integrity and gating kinetics. In sodium-dependent atrial and ventricular tissues, beta blockers shorten repolarization

somewhat but otherwise have little direct effect. The antiarrhythmic properties of beta blockers observed with long-term, chronic therapy in patients with heart disease are less well understood. Although it is clear that beta blockers decrease the likelihood of SCD (presumably arrhythmic death) after MI, the mechanism for this benefit remains unclear but may relate to the complex interplay of changes in sympathetic tone, damaged myocardium, and ventricular conduction. In patients with HF, drugs such as beta blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers may prevent arrhythmias such as AF by attenuating the structural and/or electrical remodeling process in the myocardium.[4,5]

The class III AADs include those agents that specifically prolong refractoriness in atrial and ventricular tissues. This class includes amiodarone, dronedarone, sotalol, ibutilide, and dofetilide; these drugs share the common effect of delaying repolarization by blocking potassium channels. Amiodarone and sotalol are effective in most supraventricular and ventricular arrhythmias. Amiodarone displays electrophysiologic characteristics of all four Vaughan Williams classes; it is a sodium channel blocker with relatively “fast on–off” kinetics, has nonselective beta-blocking actions, blocks potassium channels, and has a small degree of calcium channel blocking activity (**Table 39-2**). At normal heart rates and with chronic use, its predominant effect is to prolong repolarization. With IV administration, its onset is relatively quick (unlike the oral form) and beta blockade predominates initially. Theoretically, amiodarone, like class I AADs, may interrupt the reentrant substrate by transforming an area of unidirectional block into an area of bidirectional block. However, electrophysiologic studies using programmed cardiac stimulation imply that amiodarone may leave the reentrant loop intact. The impressive effectiveness of amiodarone coupled with its low proarrhythmic potential has challenged the notion that selective ion channel blockade by AADs is preferable. Sotalol is a potent inhibitor of outward potassium movement during repolarization and also possesses nonselective beta-blocking actions. Unlike amiodarone and sotalol, dronedarone, ibutilide, and dofetilide are only approved for the treatment of supraventricular arrhythmias. Both ibutilide (only available IV) and dofetilide (only available orally) can be used for the acute conversion of AF or AFl to SR. Dofetilide can also be used to maintain SR in patients with AF or AFl of longer than 1 week’s duration who have been converted to SR. Dronedarone is approved to reduce the risk of hospitalization in patients with a history of paroxysmal or persistent AF who are currently in SR. Although structurally related to amiodarone, dronedarone’s structure has been modified through the

addition of a methylsulfonyl group and the removal of iodine. Dronedarone is also similar to amiodarone in exhibiting electrophysiologic characteristics of all four Vaughan Williams classes (sodium channel blocker with relatively "fast on–off" kinetics, nonselective beta blocker, potassium channel blocker, and calcium channel antagonist).

TABLE 39-2 Time Course and Electrophysiologic Effects of Amiodarone

				IV		Oral	
Class	**Mechanism**	**EP**	**ECG**	**Minutes–Hours**	**Hours–Days**	**Days–Weeks**	**Weeks–Months**
Class I	Na^+ block	↑HV	↑QRS	0	+	+	++
Class II	β-block	↑AH	↑PR ↓HR	++	++	++	++
Class III	K^+ block	↑VERP ↑AERP	↑QT	0	+	++	++++
Class IV	Ca^{2+} block[i]	↑AH	↑PR ↓HR	+	+	+	+

AERP, atrial effective refractory period; AH, atria–His interval; ECG, electrocardiographic effects; EP, electrophysiologic actions; HR, heart rate; HV, His–ventricle interval; IV, intravenous; VERP, ventricular effective refractory period.

[i]Rate-dependent.

There are a number of different potassium channels that function during normal conduction; all approved class III AADs inhibit the delayed rectifier current (I_K) responsible for phase 2 and phase 3 repolarization. Subcurrents make up I_K: an ultrarapid component (I_{Kur}), a rapid component (I_{Kr}), and the slow component (I_{Ks}). Sotalol, ibutilide, and dofetilide selectively block I_{Kr}, whereas amiodarone and dronedarone block both I_{Kr} and I_{Ks}. Potassium channel blockers (particularly those with selective I_{Kr} blocking properties) display "reverse use dependence" (ie, their effects on repolarization are greatest at low heart rates). Sotalol and drugs like it also appear to be much more effective in preventing VF (in dog models) than the traditional sodium channel blockers. These drugs also decrease defibrillation threshold in contrast to class I AADs which tend to increase this parameter. This feature could be important in patients with ICDs, as concurrent therapy with class I AADs may require more energy for successful cardioversion or may render the ICD ineffective in terminating the ventricular arrhythmia. The Achilles' heel of all class III AADs is an extension of their underlying ionic mechanism; that is, by blocking potassium channels and delaying repolarization, these medications may also cause proarrhythmia in the

form of TdP by provoking EADs.

The non-DHP CCBs, verapamil and diltiazem, are categorized as class IV AADs. At least two types of calcium channels are operative in SA and AV nodal tissues: a L-type channel and a T-type channel. Both L-type channel blockers (verapamil and diltiazem) and selective T-type channel blockers (mibefradil was previously approved but withdrawn from the market) will slow conduction, prolong refractoriness, and decrease automaticity (eg, due to EADs or DADs) of the calcium-dependent tissue in the SA and AV nodes. Therefore, these agents are effective in automatic or reentrant tachycardias which arise from or use the SA or AV nodes. In supraventricular arrhythmias (eg, AF or AFl), these drugs can slow ventricular response by slowing AV nodal conduction. Furthermore, because calcium entry seems to be integral to exercise-related tachycardias and/or tachycardias caused by some forms of triggered automaticity, these agents may be effective in the treatment of these types of arrhythmias. The DHP CCBs (eg, nifedipine) do not have significant antiarrhythmic activity as they do not affect AV nodal conduction.

2 All AADs currently available have an impressive side effect profile (**Table 39-3**). A considerable percentage of patients cannot tolerate long-term therapy with these drugs and will have to discontinue therapy because of side effects. Flecainide, propafenone, quinidine, procainamide, disopyramide, sotalol, and dronedarone may precipitate worsening HF in a significant number of patients with underlying LV systolic dysfunction; consequently, these drugs should be avoided in patients with HF*r*EF. The class Ib AAD, mexiletine, causes neurologic and/or gastrointestinal toxicity in a high percentage of patients. One of the most frightening side effects related to AADs is the aggravation of underlying ventricular arrhythmias or the precipitation of new (and life-threatening) ventricular arrhythmias.[6]

TABLE 39-3 Side Effects of Antiarrhythmic Drugs

Disopyramide	Anticholinergic symptoms (dry mouth, urinary retention, constipation, blurred vision), nausea, anorexia, TdP, HF, conduction disturbances, ventricular arrhythmias
Procainamide	Hypotension, TdP, worsening HF, conduction disturbances, ventricular arrhythmias
Quinidine	Cinchonism, diarrhea, abdominal cramps, nausea, vomiting, hypotension, TdP, worsening HF, conduction disturbances, ventricular arrhythmias, fever
Lidocaine	Dizziness, sedation, slurred speech, blurred vision, paresthesia, muscle twitching, confusion, nausea, vomiting, seizures, psychosis, sinus arrest, conduction disturbances
Mexiletine	Dizziness, sedation, anxiety, confusion, paresthesia, tremor, ataxia, blurred vision, nausea, vomiting, anorexia, conduction disturbances, ventricular arrhythmias
Flecainide	Blurred vision, dizziness, dyspnea, headache, tremor, nausea, worsening HF, conduction disturbances, ventricular arrhythmias
Propafenone	Dizziness, fatigue, blurred vision, bronchospasm, headache, taste disturbances, nausea, vomiting, bradycardia or AV block, worsening HF, ventricular arrhythmias
Amiodarone	Tremor, ataxia, paresthesia, insomnia, corneal microdeposits, optic neuropathy/neuritis, nausea, vomiting, anorexia, constipation, TdP (<1%), bradycardia or AV block (IV and oral use), pulmonary fibrosis, liver function test abnormalities, hypothyroidism, hyperthyroidism, photosensitivity, blue-gray skin discoloration, hypotension (IV use), phlebitis (IV use)
Dofetilide	Headache, dizziness, TdP
Dronedarone	Nausea, vomiting, diarrhea, serum creatinine elevations, bradycardia, worsening HF, hepatotoxicity, pulmonary fibrosis, acute renal failure, TdP (<1%)
Ibutilide	Headache, TdP, bradycardia or AV block, hypotension
Sotalol	Dizziness, weakness, fatigue, nausea, vomiting, diarrhea, bradycardia or AV block, TdP, bronchospasm, worsening HF

AV, atrioventricular; HF, heart failure; IV, intravenous; TdP, torsades de pointes.

3 Amiodarone has assumed a prominent place in the treatment of both acute

and chronic supraventricular and ventricular arrhythmias and is the most commonly prescribed AAD.[7] Once considered a drug of last resort, it is often the first AAD considered for the treatment of many arrhythmias. Yet amiodarone is a peculiar and complex drug, displaying unusual pharmacologic effects, pharmacokinetics, dosing regimens, and multiorgan side effects. Amiodarone has an extremely long elimination half-life (approximately 60 days) and large volume of distribution; consequently, its onset of action with the oral form is delayed (days to weeks) despite the use of a loading regimen, and its effects persist for a long period (months) after discontinuation. Amiodarone is a substrate of the cytochrome P450 (CYP) 3A4 isoenzyme, a moderate inhibitor of many CYP isoenzymes (eg, CYP2C9, CYP2D6, CYP3A4), and a P-glycoprotein (P-gp) inhibitor, all of which can result in the potential for numerous drug interactions. Amiodarone interacts with digoxin and warfarin and can significantly increase plasma concentrations of both drugs. By inhibiting P-gp, amiodarone can increase digoxin concentrations by approximately twofold; therefore, the digoxin dose should be empirically reduced by 50% when amiodarone is initiated. By inhibiting CYP2C9 and CYP3A4, amiodarone can increase warfarin concentrations and the international normalized ratio (INR). Consequently, when amiodarone and warfarin are initiated concurrently, warfarin should be started at a dose of 2.5 mg daily. When amiodarone is initiated in a patient already receiving warfarin, close INR monitoring is needed and the dose of warfarin may need to be reduced by approximately 30%.[8] Acute administration of amiodarone is usually well tolerated by patients; however, severe organ toxicities may result with chronic use. Severe bradycardia (sometimes requiring pacing to allow the patient to remain on amiodarone), hyperthyroidism, hypothyroidism, peripheral neuropathy, gastrointestinal discomfort, and photosensitivity are common. Fulminant hepatitis (uncommon) and pulmonary fibrosis (5%-10% of patients) have caused death.[9,10] Although amiodarone can cause corneal microdeposits (usually do not affect vision) in virtually every patient, it has also been associated with the development of optic neuropathy/neuritis which can lead to blindness. Even though amiodarone markedly prolongs the QT interval, the risk of proarrhythmia (ie, TdP) is rare. All of these side effects mandate close and continued monitoring (liver enzymes, thyroid function tests, eye examinations, chest radiographs, pulmonary function tests) and have led to a proliferation of “amiodarone clinics” designed just for patients receiving this drug on a chronic basis (**Table 39-4**).[11,12]

TABLE 39-4 Amiodarone Monitoring

Side Effect	Monitoring Recommendations	Management of Side Effect
Pulmonary fibrosis	Chest radiograph (baseline, and then every 12 months)	Discontinue amiodarone immediately; may consider corticosteroid therapy
	Pulmonary function tests (baseline, and then if symptoms develop)	
	High-resolution CT (if symptoms develop)	
Hypothyroidism	TFTs (baseline, and then every 6 months)	Thyroid hormone supplementation (eg, levothyroxine)
Hyperthyroidism	TFTs (baseline, and then every 6 months)	Antithyroid drugs (eg, methimazole, propylthiouracil) or corticosteroids; may need to discontinue amiodarone
Optic neuritis/neuropathy	Ophthalmologic examination (baseline [only if visual impairment present], and then if symptoms develop)	Discontinue amiodarone immediately
Corneal microdeposits	Slit-lamp examination (routine monitoring not necessary)	No treatment necessary
Hepatotoxicity	LFTs (baseline, and then every 6 months)	Lower the dose or discontinue amiodarone if LFTs >2× the upper limit of normal
Bradycardia/heart block	ECG (baseline, and then every 3-6 months)	Lower the dose, if possible, or discontinue amiodarone if severe (or continue amiodarone and implant permanent pacemaker)
Tremor, ataxia, peripheral neuropathy	History/physical examination (each office visit)	Lower the dose, if possible, or discontinue amiodarone if severe
Photosensitivity	History/physical examination (each office visit)	Lower the dose; advise patients to wear sunblock while outdoors

ECG, electrocardiogram; LFTs, liver function tests, TFTs, thyroid function tests.

With the addition of a methylsulfonyl group and the deletion of the iodine moiety, dronedarone is less lipophilic than amiodarone; consequently, dronedarone is supposed to be less likely to accumulate in tissues and cause various organ toxicities. Dronedarone also has a considerably shorter half-life (approximately 24 hours) when compared with amiodarone which allows for steady state to be achieved in 5 to 7 days without the need for loading doses. Like amiodarone, dronedarone is a substrate of the CYP3A4 isoenzyme and a moderate inhibitor of the CYP2D6 and CYP3A4 isoenzymes. Its use with potent CYP3A4 inhibitors or inducers should be avoided. Dronedarone may increase plasma concentrations of (*S*)-warfarin; therefore, the INR should be closely monitored with concurrent use of these drugs. Dronedarone also inhibits P-gp and can increase digoxin concentrations by about 2.5-fold. Consequently, when concomitantly using dronedarone and digoxin, the digoxin dose should be empirically reduced by 50%. Additionally, dronedarone can increase dabigatran concentrations in patients with renal impairment. To minimize the risk of

bleeding when concomitantly using dronedarone and dabigatran in patients with moderate renal impairment (creatinine clearance [CrCl] 30-50 mL/min [0.5-0.83 mL/s]), the dose of dabigatran should be reduced to 75 mg twice daily. The concomitant use of dronedarone and dabigatran should be avoided in patients with severe renal impairment (CrCl less than 30 mL/min [0.5 mL/s]). While it was initially believed that dronedarone would cause fewer organ toxicities with the deletion of the iodine moiety, several postmarketing reports have suggested that this AAD may be associated with several significant organ toxicities, including severe hepatic injury, interstitial lung disease (ie, pulmonary fibrosis), and acute kidney injury.[13–15]

Table 39-5 summarizes the pharmacokinetics of the AADs and **Table 39-6** lists recommended dosages of the oral dosage forms of the AADs. **Table 39-7** lists the dosing recommendations for the IV forms of various AADs.

TABLE 39-5 Pharmacokinetics of Antiarrhythmic Drugs

Drug	Primary Route of Elimination[i]	Substrate[ii]	Inhibitor[ii]
Disopyramide	H/R	CYP3A4 (M)	—
Procainamide	H/R	NAT CYP2D6 (M)	—
Quinidine	H	CYP3A4 (M) CYP2C9	CYP2D6 (S) CYP3A4 (S) CYP2C9 P-gp
Lidocaine	H	CYP3A4 (M) CYP2D6 (M) CYP1A2 CYP2C9	CYP1A2 (S) CYP2D6
Mexiletine	H	CYP2D6 (M) CYP1A2 (M)	CYP1A2 (S)
Flecainide	H/R	CYP2D6 (M) CYP1A2	CYP2D6
Propafenone[iii]	H	CYP2D6 (M) CYP1A2 CYP2D6	CYP1A2 CYP2D6
Amiodarone	H	CYP3A4 (M) CYP1A2 CYP2C19 CYP2D6	CYP2C9 CYP2D6 CYP3A4 CYP1A2 CYP2C19 P-gp
Dofetilide	R/H	CYP3A4	—
Dronedarone	H	CYP3A4	CYP2D6 CYP3A4
Ibutilide	H	—	—
Sotalol	R	—	—
Diltiazem	H	CYP3A4 (M) CYP2C9 CYP2D6	CYP3A4 CYP2C9 CYP2D6 P-gp
Verapamil	H	CYP3A4 (M) CYP1A2 CYP2C9	CYP3A4 CYP1A2 CYP2C9 CYP2D6 P-gp

[i]H, hepatic; R, renal.

[ii]CYP, cytochrome P450 isoenzyme; M, major; NAT, N -acetyltransferase; P-gp, P-glycoprotein; S, strong.

[iii]Variables for parent compound (not 5-OH-propafenone).

TABLE 39-6 Typical Maintenance Doses of Oral Antiarrhythmic Drugs

Drug	Dose	Dose Adjusted
Disopyramide	100-150 mg every 6 hours	HEP, REN
	200-300 mg every 12 hours (SR form)	
Quinidine	200-300 mg sulfate salt every 6 hours	HEP
	324-648 gluconate salt every 8-12 hours	
Mexiletine	200-300 mg every 8 hours	HEP
Flecainide	50-200 mg every 12 hours	HEP, REN
Propafenone	150-300 mg every 8 hours	HEP
	225-425 mg every 12 hours (SR form)	
Amiodarone	400 mg two to three times daily until	
	10 g total, and then 200-400 mg daily[i]	
Dofetilide	500 mcg every 12 hours	REN[ii]
Dronedarone	400 mg twice daily (with meals)[iii]	
Sotalol	80-160 mg every 12 hours	REN[iv]

HEP, hepatic impairment; REN, renal impairment; SR, sustained release.

[i]Usual maintenance dose for atrial fibrillation is 200 mg/day (may further decrease dose to 100 mg/day with long-term use if patient clinically stable in order to decrease risk of toxicity); usual maintenance dose for ventricular arrhythmias is 300-400 mg/day.

[ii]Dose should be based on creatinine clearance; should not be used when creatinine clearance <20 mL/min (0.33 mL/s).

[iii]Should not be used in severe hepatic impairment.

[iv]Should not be used for atrial fibrillation when creatinine clearance <40 mL/min (0.67 mL/s).

TABLE 39-7 IV Antiarrhythmic Dosing

Drug	Clinical Situation	Dose
Amiodarone	Pulseless VT/VF	300 mg IV/IO push (can give additional 150 mg IV/IO push if persistent VT/VF or if VT/VF recurs), followed by infusion of 1 mg/min for 6 hours, and then 0.5 mg/min × 18 hours
	Stable VT (with a pulse)	150 mg IV over 10 minutes, followed by infusion of 1 mg/min for 6 hours, and then 0.5 mg/min × 18 hours
	AF (termination)	150 mg IV over 10 minutes, followed by infusion of 1 mg/min for 6 hours, and then 0.5 mg/min × 18 hours
Diltiazem	PSVT; AF (rate control)	0.25 mg/kg IV over 2 minutes (may repeat with 0.35 mg/kg IV over 2 minutes), followed by infusion of 5-15 mg/hr
Ibutilide	AF (termination)	1 mg IV over 10 minutes (may repeat if needed)
Lidocaine	Pulseless VT/VF	1-1.5 mg/kg IV/IO push (can give additional 0.5-0.75 mg/kg IV/IO push every 5-10 minutes if persistent VT/VF [maximum cumulative dose = 3 mg/kg]), followed by infusion of 1-4 mg/min (1-2 mg/min if liver disease or HF)
	Stable VT (with a pulse)	1-1.5 mg/kg IV push (can give additional 0.5-0.75 mg/kg IV push every 5-10 minutes if persistent VT [maximum cumulative dose = 3 mg/kg]), followed by infusion of 1-4 mg/min (1-2 mg/min if liver disease or HF)
Procainamide	AF (termination); stable VT (with a pulse)	15-18 mg/kg IV over 60 minutes, followed by infusion of 1-4 mg/min
Verapamil	PSVT; AF (rate control)	2.5-5 mg IV over 2 minutes (may repeat up to maximum cumulative dose of 20 mg); can follow with infusion of 2.5-10 mg/hr

AF, atrial fibrillation; HF, heart failure; IO, intraosseous; IV, intravenous; PSVT, paroxysmal supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

SUPRAVENTRICULAR ARRHYTHMIAS

The common supraventricular tachycardias that often require drug treatment are: (a) AF or AFl; (b) PSVT; and (c) automatic atrial tachycardias. Other common supraventricular arrhythmias that usually do not require drug therapy include premature atrial complexes and sinus tachycardia. For example, premature atrial complexes rarely cause symptoms and never cause hemodynamic compromise; therefore, drug therapy is usually not indicated. Likewise, sinus tachycardia is usually caused by underlying metabolic or hemodynamic disorders (eg, infection, dehydration, hypotension), and therapy should be directed at the underlying cause, not the tachycardia. Of course, there are exceptions to these suggestions. For example, sinus tachycardia may be deleterious in patients after cardiac surgery or MI. Therefore, AADs, such as beta blockers, may be indicated in these situations. Stated in another way, although many arrhythmias generally do not require therapy, clinical judgment and patient-specific variables play an important role in this decision. AF, AFl, and PSVT tend to be the most common supraventricular arrhythmias seen in clinical practice; therefore, this discussion will focus only on these arrhythmias.

Atrial Fibrillation and Atrial Flutter

AF continues to be the most common sustained arrhythmia encountered in clinical practice, affecting between 2.7 and 6.1 million Americans.[16] The overall prevalence of AF is 0.4% to 1%, and this increases with age (eg, approximately an 8% prevalence in patients greater than 80 years old).[16,17] The prevalence of AF also appears to increase as patients develop more severe HF, increasing from 4% in asymptomatic NYHA class I patients to 50% in patients with NYHA class IV HF.[18] With the aging population, improved survival in patients with HF, CAD, and hypertension, and the increased frequency of surgical procedures being performed, it is expected that the prevalence of AF will dramatically increase to an estimated 12 to 15 million by the year 2030.[18,19] Based on data derived from the Framingham study cohort, the general lifetime risk for AF in men and women at least 40 years of age is estimated to be 1 in 4.[20]

AF and AFl may present as a chronic, established tachycardia, an acute tachycardia, or a self-terminating, paroxysmal form. The following semantics and definitions are sometimes used specifically for AF: acute AF (onset within 48 hours), paroxysmal AF (terminates spontaneously in less than 7 days),

recurrent AF (two or more episodes), persistent AF (duration longer than 7 days and does not terminate spontaneously), long-standing persistent AF (duration longer than 12 months), and permanent AF (patient and provider jointly decide to stop attempts to restore or maintain SR).[21] AF is characterized by extremely rapid (atrial rate of 400-600 beats/min) and disorganized atrial activation. With this disorganized atrial activity, there is a loss of the contribution of synchronized atrial contraction (atrial kick) to forward cardiac output. Supraventricular impulses penetrate the AV conduction system in variable degrees resulting in an irregular activation of the ventricles and an irregularly irregular pulse. The AV node will not conduct most of the supraventricular impulses, causing the ventricular response to be considerably slower than the atrial rate. It is sometimes stated that "AF begets AF," that is, the arrhythmia tends to perpetuate itself. Long episodes are more difficult to terminate perhaps because of tachycardia-induced changes in atrial function (mechanical and/or electrical "remodeling").

CLINICAL PRESENTATION

Supraventricular Tachycardias

Atrial Fibrillation/Flutter

General

- These arrhythmias are usually not directly life-threatening and do not generally cause hemodynamic collapse or syncope; 1:1 AFl (ventricular response approximately 300 beats/min) is an exception. Also, patients with underlying forms of heart disease who are heavily reliant on atrial contraction to maintain adequate cardiac output (eg, mitral stenosis, obstructive cardiomyopathy) display more severe symptoms of AF or AFl.

Symptoms

- Most often, patients complain of rapid heart rate/palpitations, chest pain, dyspnea, dizziness, and fatigue. Medical emergencies are severe HF (ie, pulmonary edema, hypotension) or AF occurring in the setting of acute MI.

Diagnostic tests/signs (ECG)

- AF is an irregularly irregular supraventricular rhythm with no discernible, consistent atrial activity (P waves). Ventricular rate is usually 90 to 170 beats/min and the pulse is irregular. AFl is (usually) a regular supraventricular rhythm with characteristic flutter waves (or sawtooth pattern) reflecting more organized atrial activity. Commonly, the ventricular rate is in factors of 300 beats/min (eg, 150, 100, or 75 beats/min).

Paroxysmal Supraventricular Tachycardia Caused by Reentry

General

- This arrhythmia can be transient, resulting in little, if any, symptoms.

Symptoms

- Patients can complain of intermittent episodes of rapid heart rate/palpitations that abruptly start and stop, usually without provocation (but occasionally as a result of exercise). Severe symptoms include syncope. Often (in particular, those with AV nodal reentry), patients complain of a chest pressure or neck sensation. This is caused by simultaneous AV contraction with the right atrium contracting against a closed tricuspid valve. Life-threatening symptoms (syncope, hemodynamic collapse) are associated with an extremely rapid heart rate (eg, greater than 200 beats/min) and AF associated with an accessory pathway.

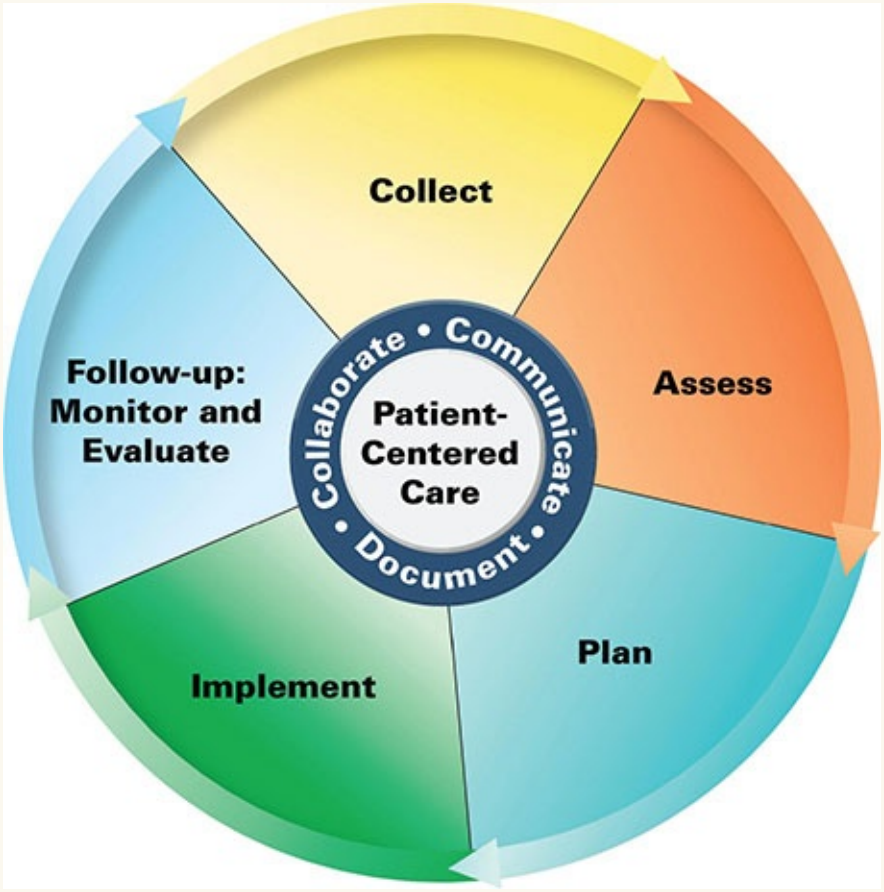
Diagnostic tests/signs (ECG)

- Most commonly, PSVT is a rapid, narrow QRS tachycardia (regular in rhythm) that starts and stops abruptly. Atrial activity, although present, is difficult to ascertain on surface ECG because P waves are “buried” in the QRS complex or T wave.

AFl occurs less frequently than AF but is similar in its precipitating factors, consequences, and drug therapy approach. This arrhythmia is characterized by rapid (atrial rate of 270-330 beats/min) but regular atrial activation. The slower and regular electrical activity results in a regular ventricular response that is in approximate factors of 300 beats/min (ie, 1:1 AV conduction = ventricular rate of 300 beats/min; 2:1 AV conduction = ventricular rate of 150 beats/min; 3:1 AV conduction = ventricular rate of 100 beats/min). AFl may be characterized as

“typical” or “atypical.” “Typical” flutter is the more common classic form with atrial rates of approximately 300 beats/min and the characteristic “sawtooth” pattern of atrial activation as shown by the surface ECG. “Atypical” flutter tends to be faster, being somewhat of a hybrid between “typical” AFl and AF. Although the ventricular response usually has a regular pattern with this arrhythmia, AFl with varying degrees of AV block or that occur with episodes of AF (“fib-flutter”) can cause an irregular ventricular rate.

It is generally accepted that the predominant mechanism of AF and AFl is reentry. AF appears to result from multiple atrial reentrant loops (or wavelets), whereas AFl is caused by a single, dominant, reentrant substrate (“typical” AFl counterclockwise or clockwise circus movement in the right atrium around the tricuspid annulus). AF or AFl usually occurs in association with various forms of structural heart disease (SHD) that cause left atrial distension, including myocardial ischemia or infarction, hypertensive heart disease, valvular disorders such as mitral stenosis or mitral insufficiency, congenital abnormalities such as septal defects, dilated or hypertrophic cardiomyopathy, and obesity. Disorders that cause right atrial stretch and are associated with AF or AFl include acute pulmonary embolism and chronic lung disease resulting in pulmonary hypertension and cor pulmonale. AF may also occur in association with states of high adrenergic tone such as thyrotoxicosis, surgery, alcohol withdrawal, sepsis, and excessive physical exertion. AF that develops in the absence of clinical, electrocardiographic, radiographic, and echocardiographic evidence of SHD is defined as lone AF. Other states in which patients are predisposed to episodes of AF are the presence of an accessory pathway and sinus node dysfunction (SND).



Patient Care Process for Atrial Fibrillation (AF)

Collect

- Patient characteristics (eg, age, sex)
- History of present illness (eg, signs/symptoms of AF, duration of AF symptoms) and patient medical history
- Social history (eg, tobacco/ethanol use) and dietary habits including intake of vitamin K–containing foods (for warfarin)
- Current and previous medications including prescription, over-the-counter, aspirin/nonsteroidal anti-inflammatory drugs, herbal products, and dietary supplements
- Objective data
  - Blood pressure (BP), ventricular rate (ie, heart rate), height, weight
  - Labs: electrolytes (potassium, magnesium), serum creatinine (SCr), hemoglobin, hematocrit, platelets, activated partial thromboplastin time,

prothrombin time (PT), international normalized ratio (INR), thyroid function tests

- 12-lead electrocardiogram and echocardiogram

Assess

- Hemodynamic instability (eg, systolic BP <90 mm Hg), evidence of decompensated heart failure, or angina
- Duration of AF symptoms (unknown, less than 48 hours, or greater than 48 hours)
- Left ventricular systolic function (ie, left ventricular ejection fraction)
- Risk of stroke (CHA_2DS_2-VASc score) and risk of bleeding (HAS-BLED score)
- Presence of potentially reversible causes of AF (eg, thyrotoxicosis, alcohol withdrawal, infection, electrolyte abnormalities [hypokalemia, hypomagnesemia])
- Ability/willingness to pay for anticoagulation treatment options
- Ability/willingness to obtain laboratory monitoring tests (eg, PT/INR [warfarin], SCr [direct oral anticoagulants (DOACs)])
- Potential drug interactions with rate control medications, anticoagulants, and/or antiarrhythmics

Plan

- Drug therapy regimen including rate control medication(s), anticoagulant, and/or antiarrhythmic as well as dose, route, frequency, and duration; see Figs. 39-5 and 39-6 and Table 39-9.
- Monitoring parameters including efficacy (eg, ventricular rate, rhythm, PT/INR [warfarin], signs/symptoms of stroke) and safety (eg, proarrhythmia [ventricular tachycardia, torsades de pointes], sign/symptoms of bleeding, SCr); frequency and timing of follow-up
- Patient education (eg, purpose of treatment, drug-specific information, monitoring/follow-up)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize

adherence

- Schedule follow-up (eg, PT/INR [warfarin], SCr [DOACs], adherence assessment (all medications), bleeding risk assessment [warfarin and DOACs], serum digoxin concentration [digoxin], pertinent laboratory/radiologic tests [amiodarone])

Follow-up: Monitor and Evaluate

- Ventricular rate and rhythm
- Symptoms
- Presence of adverse effects (eg, bradycardia [ventricular rate control medications], bleeding [warfarin and DOACs], organ toxicities [antiarrhythmics]) (See Table 39-3)
- INR [warfarin only] (adjust warfarin dose as needed to maintain target INR in range of 2-3) and determine time in therapeutic range (TTR)
- Patient adherence to treatment plan using multiple sources of information

**Collaborate with patient, caregivers, and other healthcare professionals.*

Patients with AF or AFl may experience the entire range of symptoms associated with other supraventricular tachycardias, although syncope as a presenting symptom is uncommon. Because left atrial kick is lost with the onset of AF, patients with HF*r*EF or HF with preserved ejection fraction (HF*p*EF) may develop worsening signs and symptoms of HF as they often depend on the contribution of their atrial kick to maintain an adequate cardiac output. TE events, resulting from atrial stasis and poorly adherent mural thrombi, are an additional complication of AF. Of course, the most devastating complication in this regard is the occurrence of an embolic stroke. The average rate of ischemic stroke in patients with AF who are not receiving antithrombotic therapy is approximately 5% per year.[22] Stroke can precede the onset of documented AF, probably as a result of undetected paroxysms prior to the onset of established AF. The risk of stroke significantly increases with age, with the annual attributable risk increasing from 1.5% in individuals 50 to 59 years of age to almost 24% in those 80 to 89 years of age.[23] The risk of stroke in patients with only AFl has been traditionally believed to be lower than AF. Although the role of antithrombotic therapy in patients with AFl has not been adequately studied in clinical trials, the most recent guidelines suggest that the same risk stratification scheme and antithrombotic recommendations used in patients with AF should

also be applied to those with AFl.[21]

General Approach to Treatment

4 The traditional approach to the treatment of AF can be organized into several sequential goals. First, evaluate the need for acute treatment (usually administering drugs that slow ventricular rate). Second, contemplate whether an attempt should be made to restore the patient to SR, taking into consideration the risks (eg, thromboembolism). Lastly, consider ways to prevent the long-term complications of AF such as arrhythmia recurrence and thromboembolism. Historically, one of the biggest controversies in the management of AF had been whether restoring and maintaining SR is a desirable goal for all patients. However, based on the results of numerous large-scale clinical trials, we now have a resolution to this controversy. A review of the management of AF and AFl, including a discussion of this controversy follows, organized according to the goals already outlined. **Figure 39-5** shows an algorithm for the management of AF and AFl. In addition, **Table 39-8** summarizes the recommendations for pharmacologically controlling ventricular rate and restoring and maintaining SR from the AF guidelines developed by the American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS).[21]

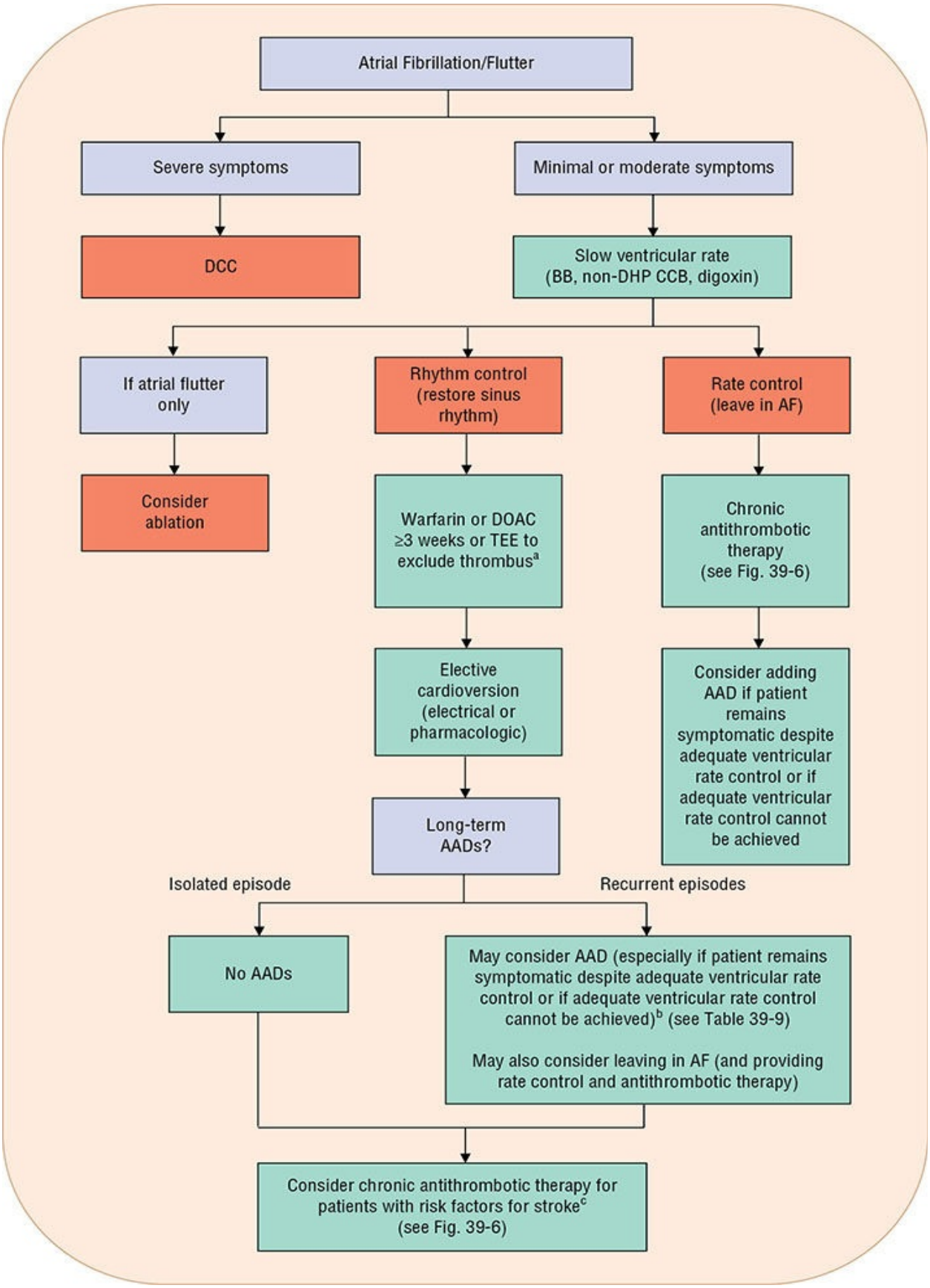

Atrial Fibrillation/Flutter
Severe symptoms
Minimal or moderate symptoms
DCC
Slow ventricular rate (BB, non-DHP CCB, digoxin)
If atrial flutter only
Rhythm control (restore sinus rhythm)
Rate control (leave in AF)
Consider ablation
Warfarin or DOAC ≥3 weeks or TEE to exclude thrombus[a]
Chronic antithrombotic therapy (see Fig. 39-6)
Elective cardioversion (electrical or pharmacologic)
Consider adding AAD if patient remains symptomatic despite adequate ventricular rate control or if adequate ventricular rate control cannot be achieved
Long-term AADs?
Isolated episode
Recurrent episodes
No AADs
May consider AAD (especially if patient remains symptomatic despite adequate ventricular rate control or if adequate ventricular rate control cannot be achieved)[b] (see Table 39-9)
May also consider leaving in AF (and providing rate control and antithrombotic therapy)
Consider chronic antithrombotic therapy for patients with risk factors for stroke[c] (see Fig. 39-6)

FIGURE 39-5 Algorithm for the treatment of AF and AFl. *a*If AF is less than 48 hours in duration, anticoagulation prior to cardioversion is unnecessary; initiate anticoagulation with unfractionated heparin, a low-molecular-weight heparin, apixaban, dabigatran, edoxaban, or rivaroxaban as soon as possible either before or after cardioversion for patients at high risk for stroke (this anticoagulant regimen or no antithrombotic therapy may be considered in low-risk patients). *b*Ablation may be considered for patients who fail or do not tolerate at least one AAD or as first-line therapy (before AAD therapy) for select patients with recurrent symptomatic paroxysmal AF or any classification of AF and heart failure with reduced left ventricular ejection fraction. *c*Chronic antithrombotic therapy should be considered in all patients with AF and risk factors for stroke regardless of whether or not they remain in sinus rhythm. (AAD, antiarrhythmic drug; AF, atrial fibrillation; AFl, atrial flutter; BB, beta blocker; non-DHP CCB, non-dihydropyridine calcium channel blocker; DCC, direct current cardioversion; DOAC, direct oral anticoagulant; TEE, transesophageal echocardiogram.)

TABLE 39-8 Evidence-Based Pharmacologic Treatment Recommendations for Controlling Ventricular Rate, Restoring Sinus Rhythm, and Maintaining Sinus Rhythm in Patients with Atrial Fibrillation

Treatment Recommendations	ACC/AHA/ ESC Guideline Recommendation
Ventricular rate control (acute setting)	
In the absence of an accessory pathway, an IV beta blocker or IV non-DHP CCB is recommended for patients without HF.	Class I
In the absence of an accessory pathway, IV digoxin or IV amiodarone is recommended to control the ventricular rate in patients with HF.	Class I
In the absence of an accessory pathway, an IV beta blocker is recommended to control the ventricular rate in patients with stable HF*r*EF.	Class I
In the absence of an accessory pathway, an IV non-DHP CCB is recommended to control the ventricular rate in patients with stable HF*p*EF.	Class I
In the absence of an accessory pathway, IV amiodarone is recommended to control the ventricular rate in critically ill patients.	Class IIa
IV amiodarone can be useful to control the ventricular rate when other measures are unsuccessful or contraindicated.	Class IIa
Digoxin, non-DHP CCBs, or IV amiodarone should not be used in patients with an accessory pathway.	Class III
IV beta blockers or IV non-DHP CCBs are not recommended in patients with decompensated HF.	Class III
Ventricular rate control (chronic setting)	
An oral beta blocker or non-DHP CCB is recommended to control the ventricular rate in patients with paroxysmal, persistent, or permanent AF.	Class I
An oral beta blocker or non-DHP CCB is recommended to control the ventricular rate in patients with persistent or permanent AF and compensated HF*p*EF.	Class I
Digoxin is effective for controlling resting heart rate in patients with HF*r*EF.	Class I
A combination of digoxin and a beta blocker is reasonable to control resting and exercise heart rate in patients with HF*r*EF.	Class IIa
A combination of digoxin and a non-DHP CCB is reasonable to control resting and exercise heart rate in patients with HF*p*EF.	Class IIa
Oral amiodarone can be used when the ventricular rate cannot be adequately controlled at rest and during exercise with an oral beta blocker, non-DHP CCB, and/or digoxin.	Class IIb
Oral non-DHP CCBs and dronedarone are not recommended to control the ventricular rate in patients with decompensated HF.	Class III
Dronedarone should not be used to control the ventricular rate in patients with permanent AF.	Class III
Restoration of sinus rhythm	
In the absence of contraindications, flecainide, dofetilide, propafenone, or ibutilide is recommended for pharmacologic cardioversion of AF.	Class I
Oral amiodarone is a reasonable option for pharmacologic cardioversion of AF.	Class IIa
The "pill-in-the-pocket" approach with flecainide or propafenone can be used to terminate persistent AF on an outpatient basis once the treatment has been used safely in the hospital, in patients without sinus or AV node dysfunction, bundle-branch block, QT interval prolongation, Brugada syndrome, or SHD (*Note*: AV node must be adequately blocked with beta blocker or non-DHP CCB therapy before initiating this therapy).	Class IIa
Dofetilide should not be initiated on an outpatient basis.	Class III
Maintenance of sinus rhythm	
The following AADs are recommended for maintaining SR, depending on underlying SHD and other comorbidities: amiodarone, dofetilide, dronedarone, flecainide, propafenone, and sotalol.	Class I
Because of its potential toxicities, amiodarone should only be used after consideration of its risks and when other agents have failed or are contraindicated.	Class I
The risk of the AAD, including proarrhythmia, should be considered before initiating treatment with that drug.	Class I
Antiarrhythmic therapy can be useful for maintaining SR for the treatment of tachycardia-induced cardiomyopathy.	Class IIa
It may be reasonable to continue current AAD therapy in the setting of infrequent, well-tolerated recurrences of AF when the drug has reduced the frequency or symptoms of AF.	Class IIb
An AAD should not be continued when the AF becomes permanent.	Class III
Dronedarone should not be used in patients with class III or IV HF or patients who have had an episode of decompensated HF in the last 4 weeks)	Class III

AAD, antiarrhythmic drug; ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association; AV, atrioventricular; CCB, calcium channel blocker; DHP, dihydropyridine; HF, heart failure; HF*p*EF, heart failure with preserved ejection fraction; HF*r*EF, heart failure with reduced ejection fraction; HRS, Heart Rhythm Society; IV, intravenous; SHD, structural heart disease; SR, sinus rhythm.

Data from January CT, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014;(64):e1–e76.

Acute Treatment

First, consider the patient with new-onset, symptomatic AF or AFl. Although uncommon, patients may present with signs and/or symptoms of hemodynamic instability (eg, severe hypotension, angina, or pulmonary edema), which qualifies as a medical emergency. In these situations, direct current cardioversion (DCC) is indicated as first-line therapy in an attempt to immediately restore SR (without regard to the risk of thromboembolism). AFl often requires relatively low energy levels of countershock (ie, 50 joules [J]), whereas AF often requires higher energy levels (ie, greater than 200 J).

If patients are hemodynamically stable, there is no emergent need to restore SR. Instead, the focus should be directed toward controlling the patient's ventricular rate. Achieving adequate ventricular rate control should be a treatment goal for all patients with AF. To achieve this goal, drugs that slow conduction and increase refractoriness in the AV node (eg, beta blockers, non-DHP CCBs, or digoxin) should be used as initial therapy. Although loading doses of digoxin have been historically recommended as first-line treatment to slow ventricular rate, use of this drug for this purpose, especially in patients with normal LV systolic function (left ventricular ejection fraction [LVEF] greater than 40% [0.40]), has declined.[7] Potential reasons for the declining use of digoxin in this patient population are its relatively slow onset and its inability to control the ventricular rate during exercise. Although an initial decrease in the ventricular rate can sometimes be observed within 1 hour of IV administration of digoxin, full control is usually not achieved for 24 to 48 hours. Digoxin also tends to be ineffective for controlling ventricular rate under conditions of increased sympathetic tone (ie, surgery, thyrotoxicosis) because it slows AV nodal conduction primarily through vagotonic mechanisms. Additionally, in several recent analyses, the use of digoxin in patients with AF has been associated with a significant increase in the risk of mortality.[24,25] In contrast, IV beta blockers and non-DHP CCBs have a relatively quick onset and can effectively control the ventricular rate at rest and during exercise. Beta blockers are also effective for controlling ventricular rate under conditions of increased sympathetic tone.

Based on the most recent AHA/ACC/HRS guidelines for the treatment of AF, the selection of a drug to control ventricular rate in the acute setting should be primarily based on the patient's LV function.[21] In patients with normal LV function (LVEF greater than 40% [0.40]), an IV beta blocker (propranolol,

metoprolol, esmolol) or non-DHP CCB (diltiazem or verapamil) is recommended as first-line therapy to control ventricular rate.[21] All of these drugs have proven efficacy in controlling the ventricular rate in patients with AF. Propranolol and metoprolol can be administered as intermittent IV boluses, whereas esmolol (because of its very short half-life of 5-10 minutes) must be administered as a series of loading doses followed by a continuous infusion. Likewise, because control of ventricular rate can be transient with a single bolus, verapamil or diltiazem can be given as an initial IV bolus followed by a continuous infusion.[26] These continuous infusions can be adjusted in monitored settings to the desired ventricular rate. In situations where AF or AFl is precipitated by states of increased sympathetic tone (ie, surgery, thyrotoxicosis), IV beta blockers can be highly effective and should be considered as first-line therapy.

In patients with HF*r*EF (LVEF less than or equal to 40% [0.40]), both IV diltiazem and verapamil should be avoided because of their potent negative inotropic effects.[21] IV beta blockers should be used with caution in this patient population and should be avoided if patients are in the midst of an episode of decompensated HF. In those patients who are having an exacerbation of HF symptoms, IV administration of either digoxin or amiodarone should be used as first-line therapy to achieve ventricular rate control. IV amiodarone can also be used in patients who are refractory to or have contraindications to beta blockers, non-DHP CCBs, and digoxin. However, clinicians should be aware that the use of amiodarone for controlling ventricular rate may also stimulate the conversion of AF to SR and place the patient at risk for a TE event, especially if the AF has persisted for at least 48 hours or is of unknown duration. In patients with stable HF*p*EF, either IV diltiazem or verapamil is recommended to acutely control ventricular rate; however, these agents should be avoided in these patients if they are experiencing decompensated HF.

Restoration of Sinus Rhythm

After treatment with AV nodal blocking drugs and a subsequent decrease in the ventricular rate, the patient should be evaluated for the possibility of restoring SR if AF persists. Within the context of this evaluation, several factors should be considered. First, many patients spontaneously convert to SR without intervention, obviating the need for therapy to achieve this goal. For instance, AF occurs frequently as a complication of cardiac surgery and often spontaneously reverts to SR without therapy. Second, restoring SR is not a necessary or realistic goal in some patients. The results of six landmark clinical

trials (Pharmacological Intervention in Atrial Fibrillation [PIAF], Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation [RACE], Atrial Fibrillation Follow-Up Investigation of Rhythm Management [AFFIRM], Strategies of Treatment of Atrial Fibrillation [STAF], How to Treat Chronic Atrial Fibrillation [HOT-CAFE], and Atrial Fibrillation and Congestive Heart Failure [AF-CHF]) have shed significant light on the comparative efficacy of rate-control (controlling ventricular rate; patient remains in AF) and rhythm-control (restoring and maintaining SR) treatment strategies in patients with AF.[27–32] The AFFIRM trial is the largest rate-control versus rhythm-control study to be conducted to date in patients with AF.[29] In this trial, patients with AF and at least one risk factor for stroke were randomized to either a rate-control or a rhythm-control group. Rate-control treatment involved AV nodal blocking drugs (digoxin, beta blockers, and/or non-DHP CCBs) first, and then nonpharmacologic treatment (AV nodal ablation with pacemaker implantation), if necessary. All patients in this group were anticoagulated with warfarin to achieve an INR of 2 to 3. In the rhythm-control group, class I or III AADs were used to maintain SR. The choice of AAD therapy was left up to each patient's physician; however, by the end of the trial, more than 60% of patients had received at least one trial of amiodarone and approximately 40% of patients had received at least one trial of sotalol. In this group, anticoagulation was encouraged but could be discontinued if SR had been maintained for at least 4 weeks. After a mean follow-up period of 3.5 years, overall mortality was not statistically different between the two strategies. The results of the PIAF, RACE, STAF, and HOT-CAFE trials were consistent with those of the AFFIRM trial.[27,28,30,31] In addition, a meta-analysis of the data from all of these trials demonstrated no significant difference in overall mortality between rate-control and rhythm-control strategies, which persisted even when the results from the AFFIRM trial were excluded from this analysis.[33]

Even though the results of the PIAF, RACE, STAF, HOT-CAFE, and AFFIRM trials collectively demonstrate that a rate-control strategy is a viable alternative to a rhythm-control strategy in patients with persistent AF, a significant limitation of these results is that they cannot be applied to patients with HF because only a small proportion of patients enrolled in these trials had LV systolic dysfunction. The AF-CHF trial was conducted to specifically evaluate the safety and efficacy of rate-control and rhythm-control strategies in patients with HF*r*EF.[32] In this trial, patients with an LVEF less than or equal to 35% [0.35], a history of HF (defined as NYHA class II to IV HF within the last 6 months, NYHA class I HF with a hospitalization for HF during the previous 6

months, or an LVEF less than or equal to 25%[0.25]), and a history of AF were randomized to either a rate-control or a rhythm-control group. Rate-control treatment involved concomitant therapy with a beta blocker and digoxin first, and then nonpharmacologic treatment (AV nodal ablation with pacemaker implantation), if necessary. In the rhythm-control group, amiodarone was the preferred AAD, whereas sotalol and dofetilide were considered alternatives (most of the patients ultimately received amiodarone). If patients in this group did not convert to SR within 6 weeks, electrical cardioversion was performed. Anticoagulation was recommended for all patients in both treatment groups. After a mean follow-up period of 37 months, no significant difference was observed between the treatment groups with regard to the primary end point of death from cardiovascular (CV) causes. Patients in the rhythm-control group tended to have more hospitalizations, primarily due to repeated cardioversions and adjustment of AAD therapy, compared with patients in the rate-control group; however, this difference was not statistically significant. It is important to note that the results of this trial should not be applied to patients with HF*p*EF. Nevertheless, the results of this trial are generally consistent with those of the PIAF, RACE, AFFIRM, STAF, and HOT-CAFE trials and suggest that a rhythm-control strategy does not confer any advantage over a rate-control strategy in patients with AF and HF*r*EF.

4 Clearly, these important findings temper the old approach of aggressively attempting to maintain SR. Because a rhythm-control strategy does not offer any significant advantage over a rate-control strategy in the management of patients with persistent or recurrent AF (including those with concomitant HF*r*EF), it is considered acceptable to allow patients to remain in AF, while being chronically treated with AV nodal blocking drugs (to achieve adequate ventricular rate control) and appropriate antithrombotic therapy (to prevent TE complications). The important question with this rate-control approach is: What defines “adequate” ventricular rate control? While adequate ventricular rate control was previously considered to be achieving a heart rate less than 80 beats/min at rest and less than 100 beats/min during exercise, evidence from the RACE II trial has suggested that employing a more lenient rate-control strategy (resting heart rate less than 110 beats/min) may be a reasonable approach for certain patients with AF.[34] In this trial, a lenient rate-control strategy (resting heart rate less than 110 beats/min) was considered to be noninferior to a strict heart rate-control strategy (resting heart rate less than 80 beats/min and heart rate during moderate exercise less than 110 beats/min) with regard to the primary end point of CV death, hospitalization for HF, stroke, systemic embolism, bleeding, and life-threatening

arrhythmic events. According to the most recent AHA/ACC/HRS guidelines for AF, this lenient rate-control strategy is recommended for those patients with persistent AF provided that patients are asymptomatic and have preserved LV systolic function (LVEF greater than 40% [0.40]).[21] In patients who are symptomatic or have LV systolic dysfunction (LVEF less than or equal to 40% [0.40]), a stricter rate-control approach (resting heart rate less than 80 beats/min) should be considered.

As in the acute setting, the selection of an AV nodal blocking drug to control ventricular rate in the chronic setting should be primarily based on the patient's LV function.[22] In patients with normal LV function (LVEF greater than 40% [0.40]) or in patients with stable HF*p*EF, an oral beta blocker or non-DHP CCB (diltiazem or verapamil) is preferred over digoxin because of their relatively quick onset and maintained efficacy during exercise. When adequate ventricular rate control cannot be achieved with one of these drugs, the addition of digoxin may result in an additive lowering of the heart rate. Verapamil and diltiazem should not be used in patients with HF*r*EF (LVEF less than or equal to 40% [0.40]). Instead, beta blockers (ie, metoprolol succinate, carvedilol, or bisoprolol) and digoxin are preferred in these patients. Specifically, in patients with NYHA class II or III HF, beta blockers should be considered over digoxin because of their survival benefits in patients with HF*r*EF. If patients are having an episode of decompensated HF (NYHA class IV), digoxin is preferred as first-line therapy to achieve ventricular rate control because of the potential for worsening HF symptoms with the initiation and subsequent titration of beta blocker therapy. If adequate ventricular rate control during rest and exercise cannot be achieved with beta blockers, non-DHP CCBs, and/or digoxin in patients with normal or depressed LV function, oral amiodarone can be used as alternative therapy to control the heart rate.

Because a rate-control strategy is now considered a reasonable initial approach for the chronic management of AF, the question that remains to be answered is, "In which patients should restoration of SR be considered?" Electrical or pharmacologic cardioversion should be considered for those patients with AF who remain symptomatic despite having adequate ventricular rate control or for those patients in whom adequate ventricular rate control cannot be achieved.[21] A rhythm-control strategy may also be considered in patients who are experiencing their first episode of AF if they are likely to convert to and remain in SR. Other factors that may lend themselves to the use of a rhythm-control strategy include younger age, presence of tachycardia-induced cardiomyopathy, AF precipitated by acute illness, and patient

preference.

In those patients in whom the decision has been made to restore SR, one must consider that this very act (regardless of whether an electrical or pharmacologic method is chosen) places the patient at risk for a TE event. The reason for this heightened risk is that the return of SR restores effective contraction in the atria, which may dislodge poorly adherent thrombi. Administering anticoagulant therapy prior to cardioversion not only prevents clot growth and the formation of new thrombi but also allows existing thrombi to become organized and well adherent to the atrial wall. It is a generally accepted principle that the risk of thrombus formation and a subsequent embolic event increases if the duration of the AF exceeds 48 hours. Therefore, it is vital for clinicians to estimate the duration of the patient's AF so that appropriate anticoagulant therapy can be administered prior to cardioversion if needed.

Two sets of recently updated guidelines provide recommendations regarding the use of appropriate anticoagulant therapy in patients with AF undergoing cardioversion based on whether the duration of AF is less than or greater than 48 hours (or of unknown duration): the American College of Chest Physicians (CHEST guidelines) and the 2019 AHA/ACC/HRS Focused Update of the 2014 AF guidelines.[35,36] For those patients undergoing elective cardioversion (electrical or pharmacologic) for AF lasting at least 48 hours or for an unknown duration, both sets of guidelines recommend that therapeutic anticoagulation with well-managed warfarin (INR target range 2 to 3) or a direct oral anticoagulant (DOAC) (apixaban, dabigatran, edoxaban, or rivaroxaban) should be given for at least 3 weeks before cardioversion is performed; this recommendation applies to patients regardless of their CHA_2DS_2-VASc score.[35,36]

If 3 weeks of therapeutic oral anticoagulant therapy is not feasible in these patients, there is an alternative regimen whereby the patient can undergo a screening transesophageal echocardiogram (TEE) prior to cardioversion to search for the presence of thrombus in the heart chambers (particularly the atria or atrial appendage). When the TEE-guided approach is performed in the inpatient setting, anticoagulant therapy with either IV unfractionated heparin (UFH) (to maintain an activated partial thromboplastin time prolongation that corresponds to plasma heparin levels of 0.3-0.7 IU/mL (kIU/L) anti-factor Xa activity) or a low-molecular-weight heparin (LMWH) (subcutaneously at treatment doses used for venous thromboembolism) should be initiated at the time the TEE will be performed.[35] If no thrombus is visualized on the TEE, cardioversion should then be performed within 24 hours of the TEE.

Alternatively, when the TEE-guided approach is performed on an outpatient basis, warfarin therapy (INR target 2.5; range 2-3) should be initiated with the TEE and cardioversion being scheduled 5 days later. Several studies have been conducted to compare the efficacy and safety of DOACs and warfarin in patients undergoing TEE-guided cardioversion.[37] Overall, no significant difference in the risk of ischemic stroke or systemic embolism was observed between DOACs and warfarin in these studies. However, because these trials were underpowered to demonstrate efficacy of the DOACs over warfarin in this setting, the DOACs were not "officially" included in the CHEST guideline recommendations for anticoagulant therapy for patients undergoing TEE-guided cardioversion.[35] Rather, these guidelines state that the DOACs "offer an alternative" in the outpatient setting prior to patients undergoing these procedures.

If cardioversion is successful (ie, patient is now in SR), therapeutic anticoagulation with warfarin (INR target range 2-3) or a DOAC (apixaban, dabigatran, edoxaban, or rivaroxaban) should be continued for at least 4 weeks, regardless of the patient's baseline risk of stroke.[35,36] The reason for continuing anticoagulation for this additional 4-week time period is that after restoration of SR, full atrial contraction does not occur immediately. Rather, it returns gradually to a maximum contractile force over a 3- to 4-week period. Decisions regarding long-term antithrombotic therapy after this 4-week time period should be primarily based on the patient's risk for stroke and not on whether he/she is in SR. If a thrombus is seen on TEE, cardioversion should not be performed and the patient should be anticoagulated for another 4 to 12 weeks.[35] If cardioversion is to be pursued after this time period, the decision regarding whether another TEE is performed should be individualized to the patient.

In patients with AF that is less than 48 hours in duration, a prolonged period of anticoagulation prior to cardioversion is unnecessary because there has not been sufficient time to form atrial thrombi. Recommendations regarding short-term anticoagulation therapy given immediately prior to cardioversion differ between the CHEST guidelines and the 2019 AHA/ACC/HRS Focused Update. According to the most recent CHEST guidelines, anticoagulant therapy with either UFH (IV) or LMWH (subcutaneously) (both at treatment doses used for venous thromboembolism) should be initiated at the time the patient presents with AF that is definitively known to be less than 48 hours in duration.[35] According to the 2019 AHA/ACC/HRS Focused Update, the anticoagulant regimen selected depends on the patient's risk of stroke. For those patients at high risk for stroke (ie, men with a CHA_2DS_2-VASc score of at least 2 or women with a CHA_2DS_2-VASc score of at least 3) (see discussion below on CHA_2DS_2-

VASc scoring system), UFH or a DOAC (apixaban, dabigatran, edoxaban, or rivaroxaban) is *reasonable* as soon as possible before cardioversion.[36] For those patients at low risk for stroke (ie, men or women with CHA_2DS_2-VASc score of 0 or 1, respectively), the use of UFH or a DOAC (apixaban, dabigatran, edoxaban, or rivaroxaban) *may be considered* prior to cardioversion.[36] If the patient is successfully cardioverted to SR, the CHEST guidelines recommend that therapeutic anticoagulation with warfarin (INR target range 2-3) or a DOAC (apixaban, dabigatran, edoxaban, or rivaroxaban) should be continued for at least 4 weeks, regardless of the patient's baseline risk of stroke.[35] Decisions regarding long-term antithrombotic therapy after this 4-week time period should be primarily based on the patient's risk for stroke and not on whether he/she is in SR. Based on the 2019 AHA/ACC/HRS Focused Update, recommendations regarding the need for long-term anticoagulation following cardioversion depend on the patient's risk of stroke.[36] For those patients at high risk for stroke (ie, men with a CHA_2DS_2-VASc score of at least 2 or women with a CHA_2DS_2-VASc score of at least 3), these guidelines recommend long-term anticoagulation therapy. However, no long-term anticoagulant therapy is recommended for patients at low risk for stroke (men or women with CHA_2DS_2-VASc score of 0 or 1, respectively).

After anticoagulation needs and/or TEE have been addressed, the process of restoring SR can be considered. There are two methods of restoring SR in patients with AF or AFl: pharmacologic cardioversion and DCC. The decision to use either of these methods is generally a matter of clinical preference. The disadvantages of pharmacologic cardioversion are the risk of significant side effects (eg, drug-induced TdP), the potential for drug–drug interactions (eg, digoxin–amiodarone), and the lower efficacy of AADs when compared with DCC. The advantages of DCC are that it is quick and more often successful (80%-90% success rate) compared to pharmacologic cardioversion. The disadvantages of DCC are the need for prior sedation/anesthesia and a risk (albeit small) of serious complications such as sinus arrest or ventricular arrhythmias.

Nonetheless, despite the relatively high success rate associated with DCC, clinicians often elect to use AADs first, and then resort to DCC in the event that these drugs fail. Pharmacologic cardioversion appears to be most effective when initiated within 7 days after the onset of AF.[21] According to the treatment guidelines for AF, there is relatively strong evidence for efficacy of the class III pure I_K blockers (ibutilide and dofetilide), the class Ic AADs (flecainide and

propafenone), and amiodarone (oral or IV) for cardioversion of AF.[21] Class Ia AADs have limited efficacy or have not been adequately studied in this setting. Sotalol is not effective for cardioversion of paroxysmal or persistent AF. Single, oral loading doses of propafenone (body weight greater than 70 kg: 600 mg; less than 70 kg: 450 mg) and flecainide (body weight greater than 70 kg: 300 mg; less than 70 kg: 200 mg) are effective compared with placebo for conversion of recent-onset AF and have been incorporated into the "pill-in-the-pocket" approach endorsed by the treatment guidelines.[21,38] With this method, outpatient, patient-controlled self-administration of a single, oral loading dose of flecainide or propafenone can be a relatively safe and effective approach for the termination of recent-onset AF in a selected patient population that does not have sinus or AV node dysfunction, bundle-branch block, or SHD.[38] This approach should be considered in patients who have previously been successfully cardioverted with these drugs on an inpatient basis.

Overall, when considering pharmacologic cardioversion, the selection of an AAD should be based on whether the patient has SHD (eg, LV dysfunction, CAD, valvular heart disease, LV hypertrophy).[21] In the absence of any type of SHD, the use of a single, oral loading dose of flecainide or propafenone is a reasonable approach for cardioversion. Ibutilide can also be used as an alternative in this patient population; however, use of this agent is restricted to a monitored setting in the hospital because it requires QT interval monitoring. In patients with underlying SHD, flecainide, propafenone, and ibutilide should be avoided because of the increased risk of proarrhythmia; amiodarone or dofetilide should be used instead. Although amiodarone can be administered safely on an outpatient basis because of its low proarrhythmic potential, dofetilide therapy can only be initiated in the hospital (for QT interval monitoring and assessment of renal function). Additionally, it should be remembered that a patient's ventricular rate should be adequately controlled with AV nodal blocking drugs prior to administering a class Ic AAD for cardioversion. The class Ic AADs may paradoxically increase ventricular response. The most likely mechanism for this effect is that by slowing atrial conduction, the class Ic AADs decrease the number of impulses reaching the AV node. Consequently, the AV node paradoxically allows more impulses to gain entrance to the ventricular conduction system, thereby increasing ventricular rate.

Chronic Treatment

There are two forms of therapy that the clinician must consider in each patient

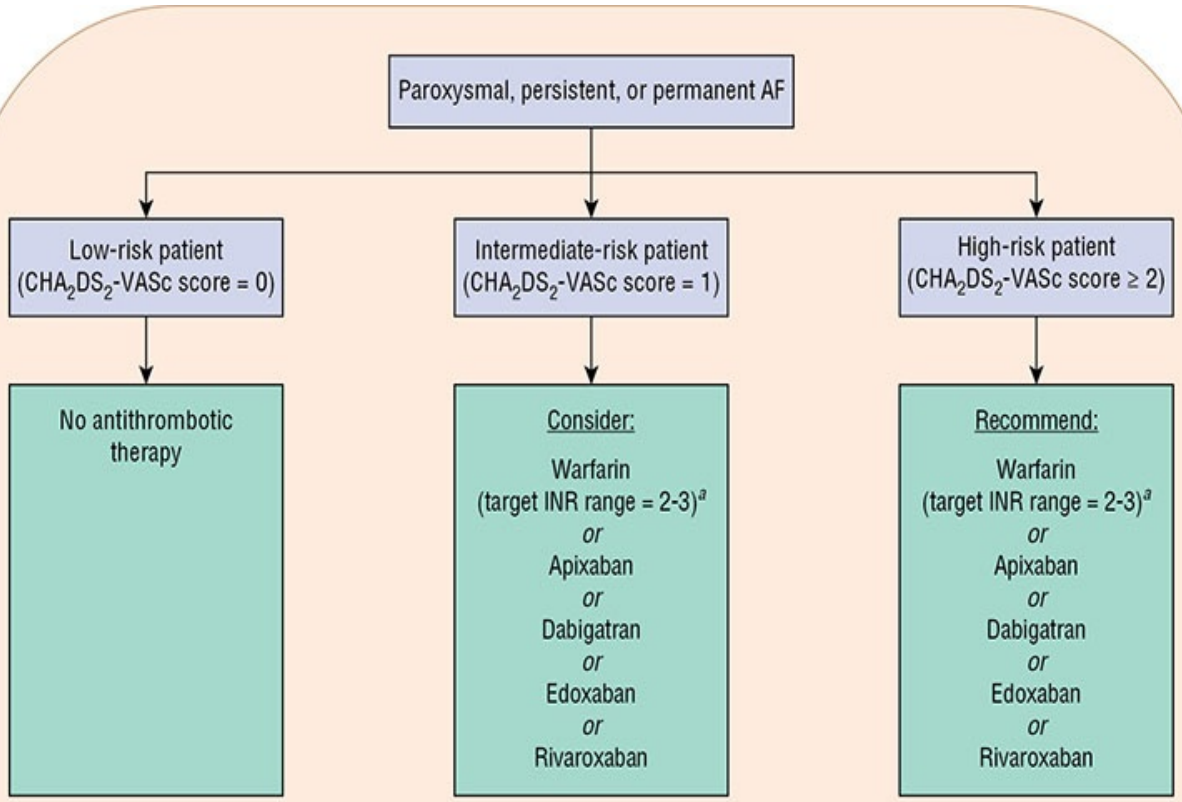
with AF: long-term antithrombotic therapy to prevent stroke and long-term AADs to prevent recurrences of AF.

Chronic Anticoagulation Therapy

Historically, warfarin has been the standard of care for stroke prevention in patients considered to be at moderate or high risk for stroke due to AF. However, while warfarin is undoubtedly effective in preventing strokes in patients with AF, its use can be associated with a number of potential limitations, including a narrow therapeutic window, requirement for routine INR monitoring, food and drug interactions, and pharmacogenetic influences. Over the past decade, several oral antithrombotic therapies have been approved by the Food and Drug Administration (FDA) for stroke prevention in patients with nonvalvular AF (without moderate-to-severe mitral stenosis or mechanical heart valve). These oral anticoagulant drugs, commonly referred to as DOACs include the direct thrombin inhibitor, dabigatran, and the factor Xa inhibitors, apixaban, edoxaban, and rivaroxaban.

When initiating chronic antithrombotic therapy in patients with AF, assessing the patient's risk for stroke becomes important for selecting the most appropriate regimen. Based on the most recent CHEST guidelines, the CHA_2DS_2-VASc risk scoring system has been recommended for stroke risk stratification in patients with AF.[35] With this risk index, patients with AF are given two points each if they have a history of a previous stroke, transient ischemic attack, or thromboembolism, or if they are at least 75 years old. Patients are given one point each for having hypertension, diabetes, congestive HF, vascular disease (eg, MI, peripheral arterial disease, or aortic plaque), being 65 to 74 years old, or being female. CHA_2DS_2-VASc is an acronym for each of these risk factors. The points are added up, and the total score is then used to determine the most appropriate antithrombotic therapy for the patient (**Fig. 39-6**). No antithrombotic therapy is recommended for males with a CHA_2DS_2-VASc score of 0 and females with a CHA_2DS_2-VASc score of 1, as these patients are considered to be at low risk for stroke.[35] For patients with one nonsex CHA_2DS_2-VASc stroke risk factor (ie, CHA_2DS_2-VASc score of 1 in males or 2 in females), oral anticoagulant therapy is suggested over aspirin monotherapy, concomitant aspirin and clopidogrel therapy, or no antithrombotic therapy. For patients with more than one nonsex CHA_2DS_2-VASc stroke risk factor (ie, CHA_2DS_2-VASc score of 2 or higher in males or 3 or higher in females), oral anticoagulant therapy is recommended over aspirin monotherapy, concomitant aspirin and

clopidogrel therapy, or no antithrombotic therapy.



High-risk patients:

- Have one of the following risk factors:
  - Prior ischemic stroke, transient ischemic attack, or systemic embolism
  - Age ≥ 75 years

OR

- Have ≥2 of the following risk factors:
  - Age 65-74 years
  - Hypertension
  - Diabetes mellitus
  - Congestive HF
  - Vascular disease (eg, MI, peripheral arterial disease, or aortic plaque)

Intermediate-risk patients

- Have only one of the following risk factors:
  - Age 65-74 years
  - Hypertension
  - Diabetes mellitus
  - Congestive HF
  - Vascular disease (eg, MI, peripheral arterial disease, or aortic plaque)

Low-risk patients

- Age <65 years with none of the conditions listed above in the high-or intermediate-risk categories

FIGURE 39-6 Algorithm for the prevention of thromboembolism in paroxysmal, persistent, or permanent AF. *a*The target INR for patients with prosthetic heart valves should be based on the type of valve that is present. (AF, atrial fibrillation; HF, heart failure; INR, international normalized ratio; MI, myocardial infarction.)

The efficacy and safety of dabigatran were compared with those of warfarin in patients with AF in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial.[39] In this study, patients were randomized to receive dabigatran 110 mg twice daily, dabigatran 150 mg twice daily or adjusted-dose warfarin. The median follow-up period was 2 years. For the primary end point of stroke or systemic embolism, both dabigatran groups were shown to be noninferior to warfarin. However, superiority was also assessed and the dabigatran 150-mg group was shown to be superior to warfarin in reducing this end point. The rate of major bleeding was similar between the dabigatran 150-mg and warfarin groups, while the rate of major bleeding was significantly lower in the dabigatran 110-mg group than in the warfarin group. The rate of intracranial hemorrhage was significantly lower in both dabigatran groups than in the warfarin group. Even though the 110- and 150-mg dosing regimens of dabigatran were evaluated in this trial, only the 150-mg dose was initially approved by the FDA for AF. A lower 75-mg dose was also initially approved for patients with a CrCl of 15 to 30 mL/min (0.25-0.5 mL/s) even though this dose has not been evaluated in a randomized, prospective clinical trial in patients with AF; this dose has only pharmacokinetic data to support its use.[40] It is important to note that the RE-LY trial excluded patients with a CrCl less than 30 mL/min (0.5 mL/s). A 110-mg dose of dabigatran was recently approved for prophylaxis of venous thromboembolism in patients following hip replacement surgery. Although this dose has not been FDA-approved for stroke prevention in AF, the CHEST guidelines suggest using this dose (or apixaban or edoxaban) in patients with a history of or who are at high risk of bleeding.[35] Dabigatran is contraindicated in patients with mechanical heart valves because its use in this population has been associated with an increased risk of TE complications and bleeding.[41]

The efficacy and safety of rivaroxaban were compared with those of warfarin in patients with AF in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF).[42] In this study, patients were randomized to receive rivaroxaban 20 mg daily or adjusted-dose warfarin.

The median follow-up period was 1.9 years. For the primary end point of stroke or systemic embolism, rivaroxaban was shown to be noninferior to warfarin. The rate of major and nonmajor clinically relevant bleeding was similar between the rivaroxaban and warfarin groups. Significantly fewer intracranial hemorrhages occurred in the rivaroxaban group compared with the warfarin group.

The efficacy and safety of apixaban were compared with those of warfarin in patients with AF in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial.[43] Overall, apixaban was shown to be noninferior and superior to warfarin with regard to the primary end point of stroke or systemic embolism. The rate of major bleeding in this trial was significantly lower in the apixaban group than in the warfarin group. Additionally, significantly fewer intracranial hemorrhages occurred in the apixaban group compared with the warfarin group.

The efficacy and safety of edoxaban were compared with those of warfarin in patients with AF in the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction (ENGAGE AF-TIMI) 48 trial.[44] In this study, patients were randomized to receive edoxaban 60 mg daily, edoxaban 30 mg daily or adjusted-dose warfarin. Overall, both doses of edoxaban were shown to be noninferior to warfarin with regard to the primary end point of stroke or systemic embolism. However, the edoxaban 60-mg dosing regimen was also shown to be superior to warfarin with regard to this end point. The rate of major bleeding and the risk of intracranial bleeding were significantly lower in both edoxaban groups than in the warfarin group. However, the risk of major gastrointestinal bleeding was significantly higher in the edoxaban 60-mg group, but significantly lower in the edoxaban 30-mg group when compared to the warfarin group.

The most recent CHEST guidelines provide recommendations regarding the use of various anticoagulant agents for stroke prevention in patients with AF.[35] Based on the results of several clinical trials, these guidelines recommend therapy with a DOAC (apixaban, dabigatran, edoxaban, or rivaroxaban) over warfarin. However, it is essential that anticoagulant therapy be individualized for each patient, with consideration given to drug cost, insurance coverage, INR monitoring options, patient preference, drug interaction potential, and anticipated adherence to medication therapy and necessary follow-up. Specifically with warfarin, the target INR range should be 2 to 3, and the goal time spent within this therapeutic range (ie, time in therapeutic range [TTR]) should ideally be greater than 70%.[35] The TTR is an important metric when evaluating the efficacy of warfarin therapy as the risk of TE events, major

bleeding, and death is lower in patients with a TTR of at least 65% compared to patients with a TTR of less than 65%.[45] The most recent CHEST guidelines have recommended the use of the SAMe-TT_2R_2 score to assist in the identification of patients who are likely or not likely to achieve good anticoagulation control with warfarin (ie, TTR of at least 65%).[35] With this scoring system, patients with AF are given 2 points each if they use tobacco or are of a non-white race. Patients are given one point each for being female, being younger than 60 years of age, having at least two of the specified medical conditions (hypertension, diabetes, CAD/MI, congestive HF, previous stroke, pulmonary disease, hepatic disease, or renal disease), or receiving treatment with a medication that interacts with warfarin. SAMe-TT_2R_2 is an acronym for each of these risk factors. Once the points for this scoring system are added up, a score of 0 to 2 suggests that patients are likely to achieve a TTR of at least 65%. Patients with a score of more than 2 are less likely to achieve a TTR of at least 65% and should be educated on strategies that could improve their TTR including more frequent INR monitoring and medication reviews, adherence counseling, and dietary guidance. Alternatively, these patients could be considered for DOAC therapy. Additionally, if a patient has previously taken warfarin, the time that his/her INR has been within the therapeutic range should also be considered before making the decision to switch the patient to a DOAC.

If a patient is unable to maintain a therapeutic INR while on warfarin, therapy with a DOAC is recommended. Strict adherence with the DOACs is important because missing a single dose could result in an increased risk of TE events.[46] If treatment with warfarin must be temporarily interrupted for the patient to undergo a medical procedure, coverage with a parenteral anticoagulant (eg, UFH, LMWH) should be considered. In these patients, the risks of stroke and bleeding must be evaluated to determine if bridging therapy is warranted. In patients with mechanical heart valves, warfarin is the anticoagulant of choice and the INR should be based on the type and location of the valve placed. Dabigatran, edoxaban, and rivaroxaban should be avoided in patients with a CrCl less than 15 mL/min (0.25 mL/s). In this particular population, anticoagulant options are warfarin and apixaban. Edoxaban should also be avoided in patients with a CrCl greater than 95 mL/min (1.58 mL/s) because of the potential for reduced efficacy.

Although it was previously an acceptable practice to continue antithrombotic therapy for only 4 weeks after successful cardioversion (with the belief that a patient's risk for thromboembolism had abated since he/she was in SR), data from the RACE and AFFIRM trials strongly suggest that patients with AF and

other risk factors for stroke continue to be at risk for stroke even when maintained in SR.[28,29] It is possible that these patients may be having undetected episodes of paroxysmal AF, placing them at risk for stroke. Consequently, the most recent AHA/ACC/HRS guidelines recommend that decisions regarding chronic antithrombotic therapy should be based on a patient's risk for stroke using the CHA_2DS_2-VASc scoring system.[21]

Chronic Antiarrhythmic Therapy

The second form of chronic therapy to be considered is AADs to prevent recurrences of AF. Historically, many clinicians have aggressively attempted to maintain SR by prescribing oral AADs (usually quinidine) to prevent AF recurrences despite the fact that only small studies with conflicting results existed evaluating this approach. To evaluate the efficacy of quinidine in preventing AF, a well-known meta-analysis of the existing literature was completed.[47] This meta-analysis demonstrated that indeed more patients remain in SR with quinidine therapy (compared with placebo); however, approximately 50% of patients have recurrences of AF within a year despite the use of quinidine. This reported effectiveness was at the cost of an associated increase in mortality (presumably due, in part, to proarrhythmia) in the quinidine-treated patients. These disturbing results (published soon after the CAST[48]) became widely quoted and highly visible, making clinicians question the wisdom of long-term prevention of recurrences of AF with AADs. These results coupled with the findings of the PIAF, RACE, AFFIRM, STAF, HOT-CAFE, and AF-CHF trials question the need to use AADs to prevent AF recurrences.[27–32] In fact, based on the results of these landmark trials, the use of AADs to maintain SR may be more reasonable to consider in patients who remain symptomatic despite having adequate ventricular rate control or for those patients in whom adequate ventricular rate control cannot be achieved.

According to the most recent AHA/ACC/HRS treatment guidelines for AF, the class Ic or III AADs are reasonable to consider to maintain patients in SR (**Table 39-9**).[21] The role of the class Ia AADs for maintenance of SR has been deemphasized throughout these guidelines as they are considered less effective or incompletely studied compared with the class Ic and III AADs. Interestingly, a systematic review of AADs for the maintenance of SR after cardioversion in patients with AF demonstrated that AF recurrences were significantly reduced with the use of class Ia, Ic, and III AADs. However, mortality was significantly increased with the class Ia drugs, in particular.[49]

TABLE 39-9 Guidelines for Selecting Antiarrhythmic Drug Therapy for Maintenance of Sinus Rhythm in Patients with Recurrent Paroxysmal or Recurrent Persistent Atrial Fibrillation

No structural heart disease[i] (absence of heart failure, coronary artery disease, or significant LVH)
First line[ii]: dofetilide, dronedarone, flecainide, propafenone, or sotalol
Second line:[iii] amiodarone

Heart failure[i]
First line[ii]: amiodarone or dofetilide
Second line: catheter ablation

Coronary artery disease[i]
First line[ii]: dofetilide, dronedarone,[iv] or sotalol[iv]
Second line[iii]: amiodarone

LVH, left ventricular hypertrophy.

[i]Drugs are listed alphabetically and not in order of suggested use.

[ii]Catheter ablation may also be considered first-line therapy in select patients with paroxysmal atrial fibrillation.

[iii]Catheter ablation may also be considered when patients are refractory or intolerant to at least 1 antiarrhythmic drug.

[iv]Should only be used in this situation if the patient has normal left ventricular systolic function.

The class Ic AADs, flecainide and propafenone, are effective for maintaining SR. However, because of the increased risk for proarrhythmia, these drugs should be avoided in patients with SHD.

Although all of the oral class III AADs have demonstrated efficacy in preventing AF recurrences, amiodarone is clearly the most effective agent and is the most frequently used AAD despite its potential for causing significant organ toxicity.[7] The superiority of amiodarone over other AADs for maintaining patients in SR has been demonstrated in a number of clinical trials. In the Canadian Trial of Atrial Fibrillation, amiodarone was significantly more effective than sotalol or propafenone in maintaining SR in patients with persistent or paroxysmal AF.[50] Furthermore, in a substudy of the AFFIRM trial, amiodarone appeared to be the most effective AAD in maintaining SR of those used in the study.[51] In the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial, amiodarone was significantly more effective than sotalol at maintaining SR in all patient subgroups, except for those with CAD where the efficacy of these two drugs was comparable.[52]

Although sotalol is not effective for conversion of AF, it is an effective drug for maintaining SR. Sotalol appears to be at least as effective as quinidine or

propafenone in preventing recurrences of AF.[50,53] However, treatment with either quinidine or sotalol is associated with a similar incidence of TdP. Because this form of proarrhythmia primarily occurs with higher doses of sotalol (quinidine usually causes TdP at low or therapeutic concentrations), it may be more easily predicted and therefore avoided. Nonetheless, sotalol may be similar to quinidine in increasing mortality in patients with AF; however, this finding requires further study.[54]

Dofetilide is effective in preventing AF recurrences but has not been directly compared with either amiodarone or sotalol. In a large, multicenter trial, dofetilide was more effective than placebo in maintaining SR (approximately 35%-50% at 1 year).[55] The efficacy of dofetilide for maintenance of SR has also specifically been demonstrated in patients with HF*r*EF.[56] Like sotalol and quinidine, dofetilide also has significant potential to cause TdP (in a dose-related fashion).

The safety and efficacy of dronedarone for the treatment of AF and AFl have been evaluated in several clinical trials. In the European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm and the American–Australian–African Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm, which were similar in design, dronedarone was more effective than placebo in maintaining SR in patients with paroxysmal or persistent AF or AFl.[57] In another trial, the use of dronedarone in patients with persistent or paroxysmal AF or AFl was associated with significantly fewer hospitalizations due to CV events or death when compared with placebo.[58] The safety and efficacy of dronedarone were also evaluated in a trial that included patients with NYHA class III or IV HF and an LVEF of 35% (0.35) or less.[59] This trial was prematurely terminated because all-cause mortality (primarily due to worsening HF) was significantly higher in the dronedarone group when compared with the placebo group. Consequently, based on these findings, dronedarone is contraindicated in and has received a black box warning for patients with advanced HF (NYHA class IV or NYHA class II or III with a recent hospitalization for decompensated HF). The efficacy and safety of dronedarone in patients with AF have been compared with those of amiodarone.[60] In this trial, dronedarone was shown to be significantly less effective than amiodarone in reducing AF recurrences; however, tolerability was significantly better in the dronedarone group than in the amiodarone group as evidenced by higher rates of premature drug discontinuation and adverse events in the amiodarone group. Most recently, a trial that enrolled patients with permanent AF and risk factors for major vascular events was terminated

prematurely after significantly more patients in the dronedarone group died (primarily from CV causes), were hospitalized for HF, and suffered a stroke when compared with the placebo group.[61] Based on the results of this trial, dronedarone is contraindicated in and has received a black box warning for patients with permanent AF.

Overall, the selection of an AAD to maintain SR should be primarily based on whether the patient has SHD.[21] However, other factors, including renal and hepatic function, concomitant disease states and drugs, and the AAD's side effect profile, also need to be considered. Based on the most recent AHA/ACC/HRS treatment guidelines for AF, dofetilide, dronedarone, flecainide, propafenone, or sotalol should be considered initially for those patients with no underlying SHD because these drugs have the most optimal long-term safety profile in this setting.[21] However, amiodarone could be used as alternative therapy if the patient fails or does not tolerate one of these initial AADs. In the presence of SHD, flecainide and propafenone should be avoided because of the risk of proarrhythmia. For those patients with HF*r*EF (LVEF less than or equal to 40% [0.40]), amiodarone or dofetilide should be considered the AADs of choice. At this time, only amiodarone and dofetilide have been shown to be mortality-neutral in patients with AF and HF*r*EF. Both dronedarone and sotalol should be avoided in patients with HF*r*EF because of the risk for increased mortality (dronedarone) or worsening HF (dronedarone and sotalol). In patients with CAD, dofetilide, dronedarone, or sotalol can be used initially. Again, dronedarone and sotalol should not be used if patients have concomitant HF*r*EF. Amiodarone could be used as an alternative therapy if the patient fails or does not tolerate one of these initial AADs. The presence of LV hypertrophy may predispose the myocardium to proarrhythmic events. Because of their low proarrhythmic potential, amiodarone or dronedarone should be considered first-line AAD therapy in these patients.

Nonpharmacologic forms of therapy, designed to maintain SR, are becoming increasingly popular treatment options for patients with AF or AFl. For patients who have "typical" AFl, not associated with concurrent AF, ablation of the reentrant substrate with radiofrequency current is highly effective (more than 90%) and should be first-line treatment of AFl to prevent recurrences.[62,63] Catheter ablation for patients with AF is much more technically difficult for a variety of reasons, including the lack of a single, identifiable, and ablatable reentrant focus (as in AFl). Nonetheless, progress has been made in this area. Patients with AF have been found to have arrhythmogenic foci that occur in atrial tissue near and within the pulmonary veins. The ablation procedure most

commonly used is a pulmonary vein isolation (PVI) ablation, where radiofrequency energy can be delivered to these areas in an attempt to abolish the foci. Historically, PVI ablation was often considered last-line therapy for patients who had failed all AADs, including amiodarone. However, in some of the recent trials, the use of PVI ablation in patients with AF has been associated with a significant reduction in recurrent episodes of AF and an improvement in quality of life when compared with AAD therapy.[64–66] In patients with AF and concomitant HF*r*EF who did not respond to, were intolerant of, or were unwilling to take AADs, the use of PVI ablation has been associated with a significant reduction in all-cause mortality or hospitalization for worsening HF.[67] There is also evidence to suggest that this procedure may be superior to AADs as first-line therapy of symptomatic AF.[68,69] According to the most recent AHA/ACC/HRS guidelines for AF, for those patients with symptomatic episodes of AF who fail or do not tolerate at least one class I or III AAD, PVI ablation is recommended for those with paroxysmal AF, reasonable for those with persistent AF, and may be considered for those with long-standing persistent AF.[21] For those patients with symptomatic episodes of AF who have not yet received treatment with a class I or III AAD, PVI ablation is reasonable for those with recurrent, paroxysmal AF and may be considered for persistent AF. This procedure is not without its risks, as major complications, such as pulmonary vein stenosis, TE events, cardiac tamponade, and new AFl, have been reported in 4.5% of patients.[70]

Paroxysmal Supraventricular Tachycardia

5 PSVT arising by reentrant mechanisms includes those arrhythmias caused by AV nodal reentry (ie, AVNRT), AV reentry incorporating an accessory pathway (ie, AVRT), SA nodal reentry, and intra-atrial reentry. AVNRT and AVRT are, by far, the most common of these tachycardias.

AVNRT is usually seen in middle-aged adults without heart disease and more than 60% of cases occur in females.[71] The ventricular rate can range from 110 beats/min to more than 250 beats/min. This arrhythmia can spontaneously occur or be provoked by exertion, coffee, tea or alcohol. Patients generally tolerate AVNRT well; however, its sudden onset could precipitate shortness of breath, dizziness, or neck pulsations.[63]

The underlying substrate of AVNRT is the functional division of the AV node into two (or more) longitudinal conduction pathways or “dual” AV nodal pathways.[72] It is clear that there are not two distinct anatomic pathways inside

the AV node itself; rather, it is likely that a fan-like network of perinodal fibers inserts into the AV node and represents the second pathway. The pathways possess key differences in conduction characteristics: one is a fast-conducting pathway with a relatively long refractory period (fast pathway) and the other is a slower-conducting pathway with a shorter refractory period (slow pathway). The presence of dual pathways does not necessarily imply that the patient will have clinical PSVT. In fact, it is estimated that between 10% and 50% of patients have discernible dual pathways, but the incidence of AVNRT is considerably lower.[72] Sustenance of the tachycardia depends on the critical electrophysiologic discrepancies and the ability of one pathway (usually the slow) to allow repetitive antegrade conduction, and the ability of the other pathway (usually the fast) to allow repetitive retrograde conduction. During SR, a patient with dual pathways conducts supraventricular impulses antegrade through both pathways. Electrical activity reaches the distal common pathway at the level of or above the His bundle and continues to depolarize the ventricles in an antegrade direction. Conduction proceeds via the two pathways but reaches the distal common pathway first through the fast AV nodal route (**Fig. 39-7**).

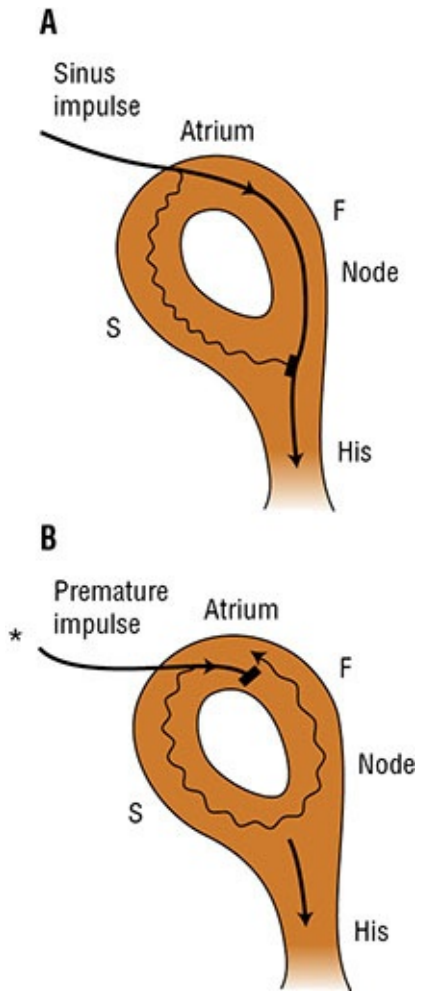


FIGURE 39-7 Reentry mechanism of dual AV nodal pathway PSVT. (*A*) Sinus rhythm: the impulse travels from the atrium through the fast pathway, *F*, and then to the His-Purkinje system (*His*). The impulse also travels through the slow pathway, *S*, but is stopped when refractory tissue is encountered. (*B*) Dual AV nodal reentry: a critically timed premature impulse, *, is stopped in the fast pathway, F (because of prolonged refractoriness) but is able to travel antegrade down the slow pathway, S, and retrograde through the fast pathway. (AV, atrioventricular; PSVT, paroxysmal supraventricular tachycardia.)

The mechanism behind AVNRT may occur by the following sequence of events. The occurrence of an appropriately timed premature impulse penetrates the AV node but is blocked in the fast pathway that is still refractory from the previous beat. However, the slow pathway, which has a shorter refractory period, permits antegrade conduction of the premature impulse. By the time the impulse has reached the distal common pathway, the fast pathway has recovered its excitability and now will permit retrograde conduction. The impulse reaches the

common proximal pathway, preceded by an excitable gap of tissue, and reenters the slow pathway. A reentrant circuit that does not require atrial or ventricular tissue is completed within the AV node, and a tachycardia is thereby initiated. The common form of this tachycardia uses the slow pathway for antegrade conduction and the fast pathway for retrograde conduction; an uncommon form exists in which the reentrant impulse travels in the opposite direction.

AVRT is generally seen in young adults, and like AVNRT, is generally well tolerated. However, it can be less benign than AVNRT as it can cause syncope and death. AVRT depends on the presence of an accessory pathway that bypasses the normal AV conduction pathway. Several different types of accessory pathways have been described, depending on the specific anatomic areas they connect (eg, AV or nodoventricular tracts). During SR (**Fig. 39-8**), patients with an accessory pathway that can conduct antegrade depolarize the ventricles simultaneously through both the AV nodal and accessory pathway, causing ventricular preexcitation and creating a fusion pattern on the early portion of the QRS complex (known as a delta wave). Patients may have an accessory pathway that is not evident on ECG, which is referred to as a “concealed” accessory pathway. These concealed accessory pathways are often incapable of antegrade conduction and can only accept electrical stimulation in a retrograde fashion. The electrocardiographic expression of a delta wave depends on the location of the accessory pathway, the distance from the wave front of sinus activation, and the conduction characteristics of the various structures involved. It should be noted that (similar to patients with dual AV nodal pathways) not all patients with preexcitation with an accessory AV pathway are capable of having clinical PSVT, characterized as WPW syndrome.

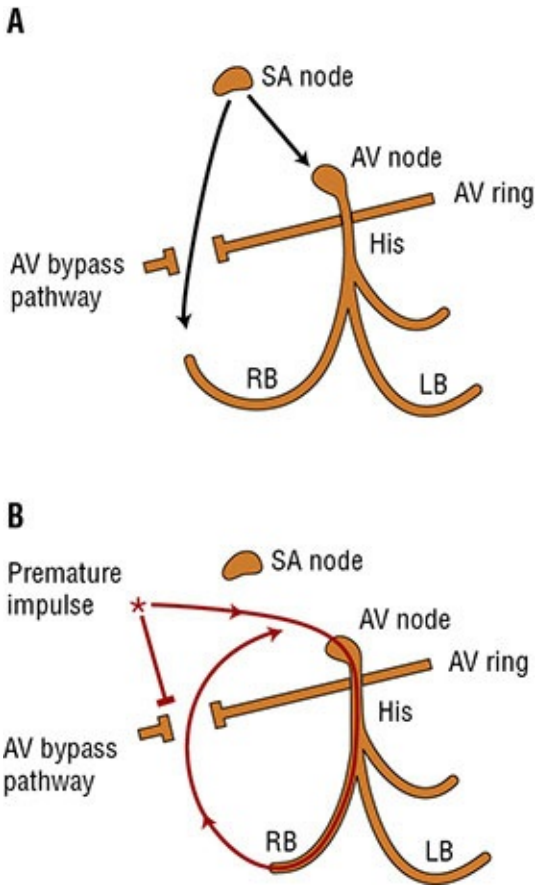


FIGURE 39-8 Reentry mechanism for AV accessory pathway PSVT in Wolff-Parkinson-White syndrome. (*A*) Sinus rhythm: the impulse travels from the atrium to the ventricle by two pathways—the AV node and an accessory bypass pathway. (*B*) AV reentry: a critically timed premature impulse (*) is stopped in accessory pathway (because of prolonged refractoriness) but travels antegrade through the AV node and retrograde through accessory pathway. (AV, atrioventricular; His, His-Purkinje system; LB, left bundle branch; PSVT, paroxysmal supraventricular tachycardia; RB, right bundle branch; SA, sinoatrial.)

6 Patients with an accessory AV pathway may have three forms of WPW syndrome: (a) orthodromic AVRT; (b) antidromic AVRT; and/or (c) AF. AVRT usually occurs by the following sequence of events. Analogous to AVNRT, two pathways (e.g. the normal AV nodal pathway and the accessory AV pathway) exist that have different electrophysiologic characteristics. The AV nodal pathway usually has a relatively slower conduction velocity and shorter refractory period, and the accessory pathway has a faster conduction velocity and a longer refractory period. A critically timed premature atrial impulse may be blocked in the accessory pathway because this area is still refractory from the

previous sinus beat. However, the AV nodal pathway, with a relatively shorter refractory period, may accept antegrade conduction of the premature atrial impulse. Meanwhile, the accessory pathway may recover its excitability and now allow retrograde conduction. A macroreentrant tachycardia is thereby initiated in which the antegrade pathway is the AV nodal pathway, the distal common pathway is the ventricle, the retrograde pathway is the accessory pathway, and the proximal common pathway is the atrium (see Fig. 39-8). Additionally, this macroreentrant tachycardia could also be initiated by a premature ventricular impulse that first conducts retrograde over the accessory pathway, then antegrade through the AV nodal pathway. This sequence of events (down the AV node, up the accessory pathway), termed *orthodromic AVRT*, is the common variety of reentry in patients with an accessory AV pathway, resulting in a narrow QRS tachycardia. In the uncommon variety, conduction proceeds in the opposite direction (down the accessory pathway, up the AV node), resulting in a wide QRS tachycardia, which is termed *antidromic AVRT*. Patients with WPW syndrome can have a third type of tachycardia, namely, AF. The occurrence of AF in the setting of an accessory AV pathway can be extremely serious. As AF is an extremely rapid atrial tachycardia, conduction can proceed down the accessory AV pathway, resulting in a very fast ventricular response or even VF and SCD. Unlike the AV nodal pathway, the refractory period of the accessory pathway shortens in response to rapid stimulation rates.

General Approach to Treatment

Both pharmacologic and nonpharmacologic methods have been used to treat patients with PSVT. Drugs used in the treatment of these arrhythmias can be divided into three broad categories: (a) those that directly or indirectly increase vagal tone to the AV node (eg, digoxin); (b) those that depress conduction through slow, calcium-dependent tissue (eg, adenosine, beta blockers, and non-DHP CCBs); and (c) those that depress conduction through fast, sodium-dependent tissue (eg, quinidine, procainamide, disopyramide, and flecainide). Drugs within these categories alter the electrophysiologic characteristics of the reentrant substrate so that PSVT cannot be sustained. In PSVT caused by AVNRT, class I AADs, such as flecainide, act primarily on the retrograde fast pathway. Digoxin and beta blockers may work on either the retrograde fast or the antegrade slow pathway. Verapamil, diltiazem, and adenosine prolong conduction time and increase refractoriness, primarily in the slow antegrade pathway of the reentrant loop. In PSVT caused by AVRT, class I AADs increase refractoriness in the fast accessory pathway or within the His-Purkinje system.

Beta blockers, digoxin, adenosine, and verapamil all act by their effects on the AV nodal (antegrade, slow) portion of the reentrant circuit. Regardless of the mechanism, treatment measures are directed first at terminating an acute episode of PSVT and then at preventing symptomatic recurrences of the arrhythmia.

Acute management (**Fig. 39-9**) for patients with AVNRT or orthodromic AVRT include vagal maneuvers and/or adenosine.[63] Vagal techniques, such as unilateral carotid sinus massage, Valsalva maneuver, ice water facial immersion, or induced retching, are about 20% successful in terminating these PSVTs, although carotid massage and Valsalva maneuver are the simplest, least obtrusive, and most frequently used of these techniques. Should these techniques and/or adenosine be ineffective or unfeasible in a hemodynamically unstable patient (ie, syncope, pre-syncope, angina, or severe HF), synchronized DCC is the next step. Even at low energy levels (such as 25 J), DCC is almost always effective in quickly restoring SR and correcting symptomatic hypotension. If vagal techniques and/or adenosine are ineffective or unfeasible in patients who are hemodynamically stable, the next course of action would be administration of IV beta-blockers or non-DHP CCBs (oral could be used with AVNRT). Approximately 80% to 98% of patients with a narrow QRS, regular arrhythmia (AVNRT or orthodromic AVRT) given adenosine (6-12 mg) will revert to SR within seconds; and, those given IV verapamil (5-10 mg), IV diltiazem (15-25 mg) will revert to SR within 5 minutes.[73] However, if AVNRT is unable to be corrected with these measures, IV amiodarone can be utilized.[63] For patients with AVRT, the next step would be synchronized cardioversion.

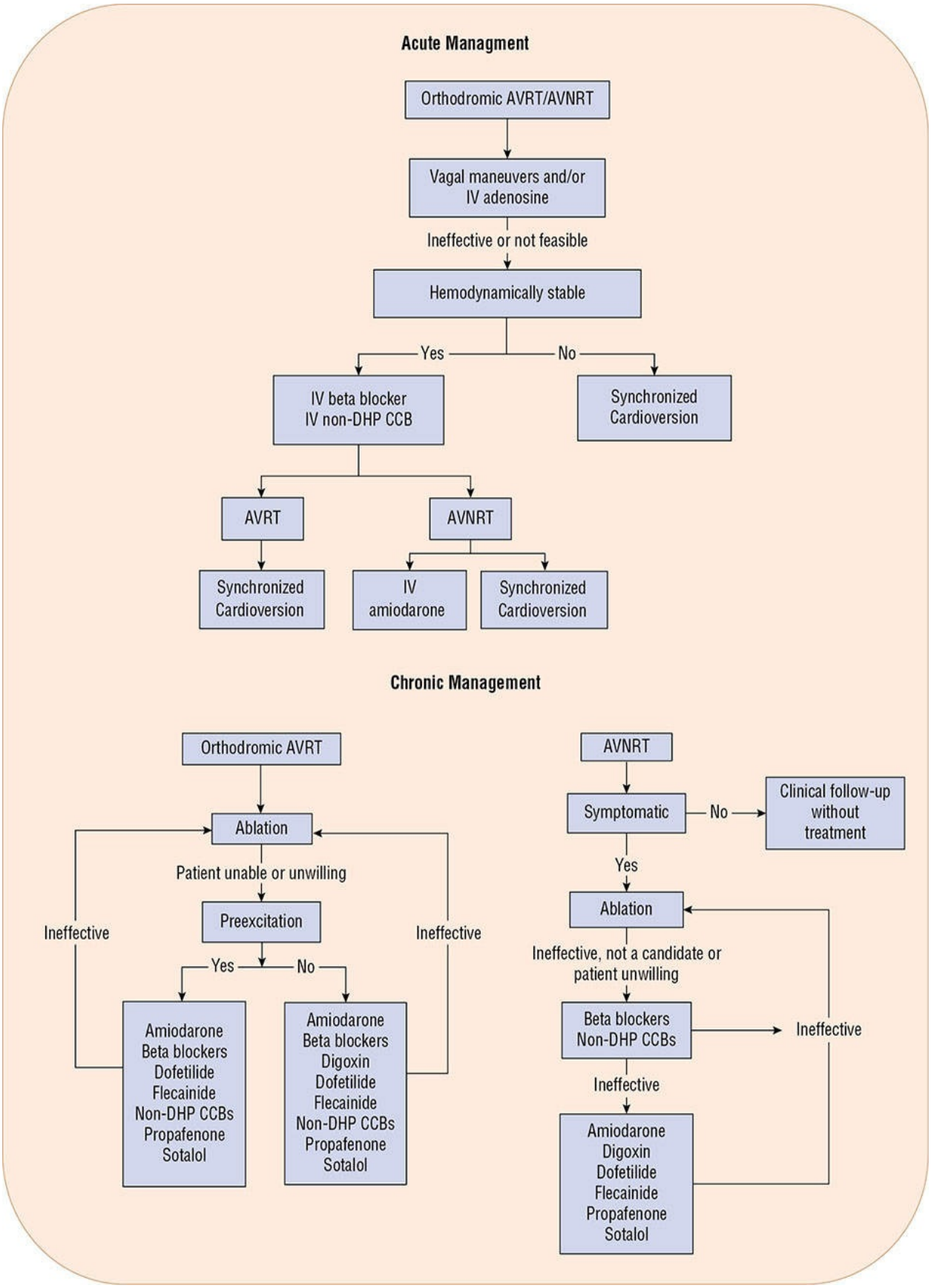

Acute Managment
Orthodromic AVRT/AVNRT
Vagal maneuvers and/or IV adenosine
Ineffective or not feasible
Hemodynamically stable
Yes
No
IV beta blocker IV non-DHP CCB
Synchronized Cardioversion
AVRT
AVNRT
Synchronized Cardioversion
IV amiodarone
Synchronized Cardioversion
Chronic Management
Orthodromic AVRT
Ablation
Patient unable or unwilling
Preexcitation
Ineffective
Ineffective
Yes
No
Amiodarone Beta blockers Dofetilide Flecainide Non-DHP CCBs Propafenone Sotalol
Amiodarone Beta blockers Digoxin Dofetilide Flecainide Non-DHP CCBs Propafenone Sotalol
AVNRT
Symptomatic
No
Clinical follow-up without treatment
Yes
Ablation
Ineffective, not a candidate or patient unwilling
Beta blockers Non-DHP CCBs
Ineffective
Ineffective
Amiodarone Digoxin Dofetilide Flecainide Propafenone Sotalol

FIGURE 39-9 Algorithm for the treatment of acute (*top panel*) orthodromic AVRT/AVNRT and chronic prevention of recurrences (*bottom panel*). (AVNRT, atrioventricular nodal reentrant tachycardia; AVRT, atrioventricular reentrant tachycardia; IV, intravenous; non-DHP CCBs, non-dihydropyridine calcium channel blockers.) *Note:* Drugs are listed in alphabetical order not preference.

Should a patient have preexcited AF, synchronized cardioversion should be used if hemodynamically unstable.[63] If the patient is hemodynamically stable, IV ibutilide or procainamide can be administered. IV digoxin, IV amiodarone, oral or IV beta blockers, diltiazem, and verapamil should be avoided in patients with preexcited AF as they may increase conduction over the accessory pathway leading to an increase in the ventricular rate and enhance the risk of provoking a life-threatening ventricular arrhythmia.

Once the acute episode of AVNRT or AVRT is terminated, a decision on long-term preventive therapy must follow. Preventive treatment is indicated if: (a) frequent episodes occur that necessitate therapeutic intervention (ie, emergency department visits) or cause symptoms that interfere with the patient's lifestyle; or (b) episodes are infrequent but cause severe symptoms. If preventive treatment is deemed necessary, either drug therapy or catheter ablation can be used.

AADs are no longer the treatment of choice to prevent recurrences of reentrant PSVT for the following reasons: (a) lifelong treatment is necessary in these generally young, but otherwise healthy, individuals; (b) there are few, if any, large controlled or comparative trials to assist the clinician in rationally choosing effective agents; and (c) most importantly, other nonpharmacologic treatments are clearly more effective. Nevertheless, drug therapy may occasionally be necessary in some patients, particularly those with mild symptoms and infrequent recurrences. A trial-and-error approach may be used, complemented by the use of ambulatory electrocardiographic recordings (Holter) or telephonic transmissions of cardiac rhythm (event monitors) to objectively document the efficacy or failure of the chosen drug regimen. Drugs known to be effective in preventing recurrences of these arrhythmias are the AV nodal blocking drugs (digoxin, beta blockers, non-DHP CCBs, and combinations of these agents) and the class Ic AADs (flecainide, propafenone).[63] Sotalol, dofetilide, and amiodarone can be considered alternatives. Although rarely used, digoxin is only indicated in orthodromic AVRT without preexcitation.

5 Catheter ablation using radiofrequency current on the PSVT substrate has dramatically altered the traditional treatment of these patients (**Fig. 39-10**). Radiofrequency energy delivered through an ablation catheter causes small,

discrete lesions through thermal energy. During invasive electrophysiologic studies, portions of the reentrant circuit can be located (or mapped) by the use of a number of catheters. Once this is completed, radiofrequency energy is applied, creating thermal injury in the tissue necessary for reentry. In this way, the substrate for reentry is destroyed, “curing” the patient of recurrent episodes of PSVT and obviating the need for chronic drug therapy. Complications, although unusual, include cardiac tamponade, pericarditis, valvular insufficiency, and AV block. Radiofrequency ablation is highly effective, preventing the recurrences of PSVT in more than 90% of patients.[74,75] The procedure was originally used in patients with WPW syndrome.[74] In these patients, the extranodal pathway is most often located at the left lateral free wall between the left atrium and ventricle at the level of the mitral valve (see Fig. 39-10). After the pathway is located, radiofrequency current is applied to this area resulting in irreversible thermal damage to the targeted tissue. Ablation of the extranodal connection occurs promptly, and evidence of preexcitation (delta waves) disappears. Thereafter, a similar approach was developed for patients with AVNRT, placing the catheter just anterior to the coronary sinus, below the His bundle and in the region of the slow pathway.[75] The preferred method in these individuals is to apply small amounts of radiofrequency current to the slow pathway of the reentrant circuit in order to modify its properties enough so that AVNRT cannot recur.

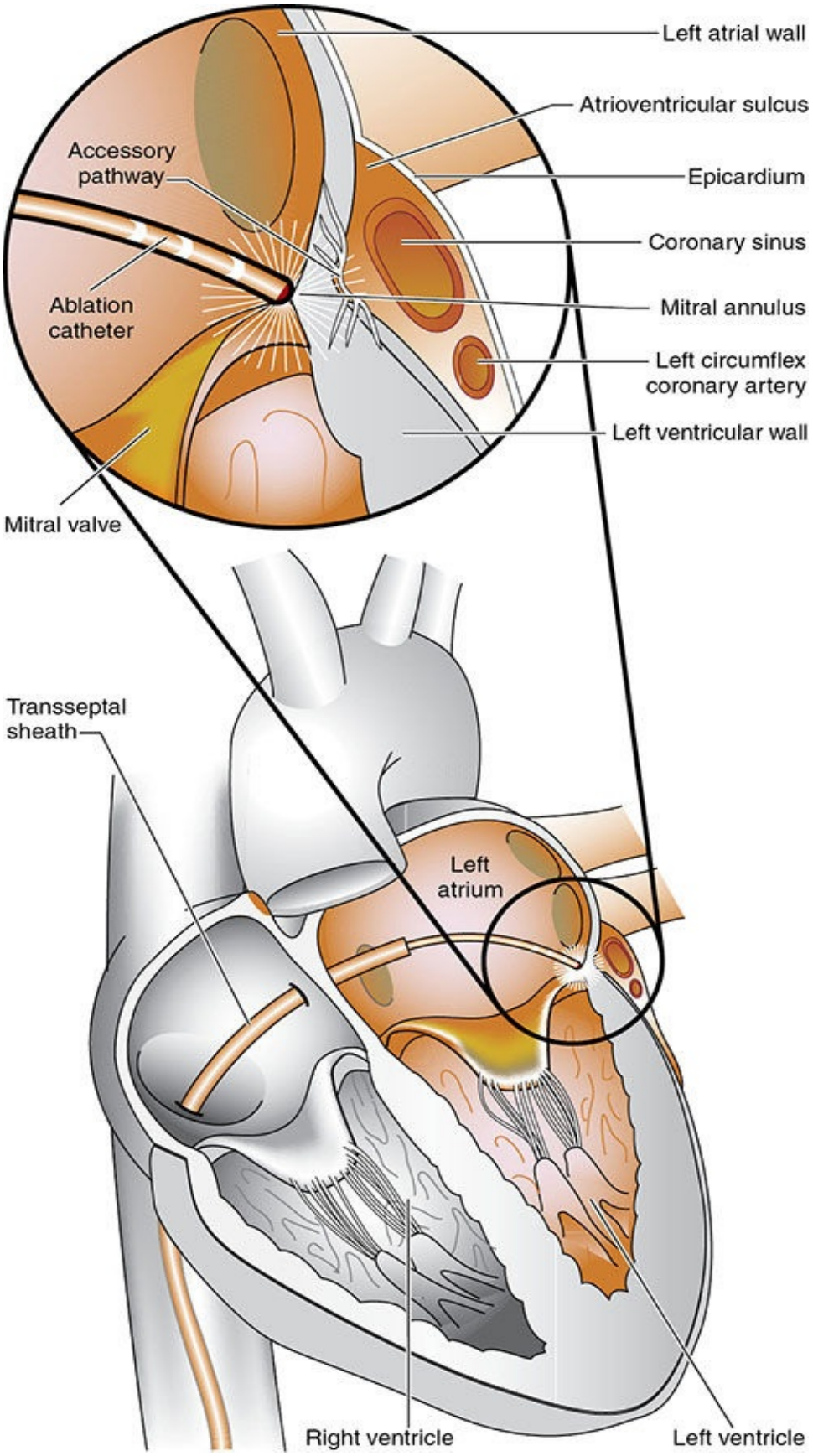

Left atrial wall
Atrioventricular sulcus
Accessory pathway
Epicardium
Coronary sinus
Ablation catheter
Mitral annulus
Left circumflex coronary artery
Left ventricular wall
Mitral valve
Transseptal sheath
Left atrium
Right ventricle
Left ventricle

FIGURE 39-10 Drawing showing catheter placement for radiofrequency ablation of a left lateral free wall accessory pathway. Here, a venous (atrial) transseptal puncture to gain access to accessory pathway is shown; a retrograde arterial approach has also been used. (*Data from Lerman BB, Basson CT. High risk patients with ventricular preexcitation: A pendulum in motion. N Engl J Med 2003;349:1787–1789. Copyright © 2003 Massachusetts Medical Society. All rights reserved.*)

Catheter ablation is the preferred treatment strategy (over AADs) for patients with symptomatic PSVT because the procedure is highly effective and curative, rarely results in complications, and obviates the need for chronic AAD therapy.[63] Catheter ablation is also a cost-effective approach (in the long term) because, if effective, the costs of drugs and repeated hospital visits are avoided. In one cost-effectiveness analysis, radiofrequency ablation improved quality of life and reduced lifetime medical expenditures by nearly $30,000 compared with chronic drug treatment.[76]

VENTRICULAR ARRHYTHMIAS

The common ventricular arrhythmias include (a) PVCs, (b) VT, and (c) VF. These arrhythmias may result in a wide variety of symptoms. PVCs often cause no symptoms or only mild palpitations. VT may be a life-threatening situation associated with hemodynamic collapse or may be totally asymptomatic. VF, by definition, is an acute medical emergency necessitating cardiopulmonary resuscitation (CPR).

Premature Ventricular Complexes and Sudden Cardiac Death

PVCs are very common ventricular rhythm disturbances that occur in patients with or without SHD. Experimental models show that PVCs may be elicited by abnormal automaticity, triggered activity, or reentrant mechanisms. It is well known that PVCs are commonly observed in apparently healthy individuals; in these patients, the PVCs seem to have little, if any, prognostic significance. PVCs occur more frequently and in more complex forms in patients with SHD than in healthy individuals. The prognostic meaning of PVCs has been well studied in patients with MI (acute or remote) with several consistent themes. Patients with some forms of PVCs (ie, multifocal or couplets) are at higher risk

for SCD than if they did not have these minor rhythm disturbances. SCD can be defined as unexpected death (without an obvious noncardiac cause) occurring in a patient within 1 hour of experiencing symptoms (witnessed episodes) or within 24 hours of last being observed in normal health (unwitnessed episodes).[77] Studies of patients who experienced SCD (and happened to be wearing an electrocardiographic monitor at the time) often demonstrate the cause to be VF preceded by a short run of VT and frequent PVCs.[78]

General Approach to Treatment

Historically, investigators promoted the concept that patients in the acute phase of MI may have types of PVCs that are predictive of VF and SCD. These types of PVCs were referred to as "warning arrhythmias" and included frequent ventricular ectopy (more than 5 beats/min), multiform configuration (different morphology), couplets (two in a row), and R-on-T phenomenon (PVCs occurring during the repolarization phase of the preceding sinus beat in the vulnerable period of ventricular recovery). However, as a result of using continuous electrocardiographic monitoring techniques, it has become apparent that almost all patients have warning arrhythmias in the acute MI setting. In those patients who experience VF, warning arrhythmias are no more common than in those without VF. Consequently, warning arrhythmias observed during acute MI are neither sensitive nor specific for determining which patients will have VF. Thus, there is little need to direct drug therapy specifically at PVC suppression in these particular patients. Studies show that effective prevention of VF in the acute MI setting may be achieved without the abolition of PVCs.

Conversely, data strongly imply that PVCs documented in the convalescence period of MI do carry important long-term prognostic significance.[79] PVCs occurring after an MI seem to be a risk factor for patient death that is independent of the degree of LV dysfunction or the extent of coronary atherosclerosis. Ruberman et al. employed the following classification of PVCs: simple or benign (infrequent and monomorphic) versus complex (at least 5 PVCs/min, couplets, R-on-T beats, and multiform).[79] These investigators found that the presence of complex (but not simple) ventricular ectopy in the setting of CAD was associated with a higher incidence of overall mortality and cardiac death.

Because PVCs without associated SHD in apparently healthy individuals carry little or no risk, drug therapy is unnecessary. However, because of the prognostic significance of complex PVCs in patients with SHD, the use of AAD

therapy to suppress them has been controversial. Historically, many supported the aggressive use of AAD therapy to suppress PVCs, based on the underlying premise of eliminating a risk factor for SCD in patients with CAD (namely, the presence of complex PVCs). However, others favored a more conservative approach and disregarded the use of AAD therapy in the absence of significant symptoms. An important study, the CAST, abruptly put an end to this debate in noteworthy fashion. This trial was conducted to determine if suppression of ventricular ectopy with encainide, flecainide, or moricizine could decrease the incidence of death from arrhythmia in patients who had suffered an MI.[48] In the trial, patients with an LVEF less than or equal to 55% (0.55)(if recruited within 90 days of the MI) or an LVEF less than or equal to 40% (0.40)(if recruited at least 90 days after the MI) were randomized to receive encainide, flecainide, moricizine, or placebo to decrease the incidence of death from arrhythmia. Patients with an LVEF less than 30% (0.30) were randomized only to encainide or moricizine. When compared with placebo, treatment with encainide or flecainide was associated with a significantly higher rate of total mortality and death due to arrhythmia, presumably caused by proarrhythmia. Analysis of the moricizine arm indicated neither harm nor benefit from this therapy; therefore, only this portion of the study was allowed to continue as CAST II.[80] However, CAST II was also prematurely discontinued because there was a trend toward an increase in mortality in moricizine-treated patients. The overall results of the two CASTs conclusively prove that the use of AAD therapy (beyond the general use of beta blockers) to suppress PVCs in patients after an MI does not improve survival and is most likely detrimental.

CLINICAL PRESENTATION

Ventricular Arrhythmias

PVCs

- PVCs are non–life-threatening and usually asymptomatic. Occasionally, patients will complain of palpitations or uncomfortable heartbeats. Since the PVC, by definition, occurs early and the ventricle contracts when it is incompletely filled, patients do not feel the PVC. Rather, the sinus beat following the PVC and a compensatory pause is usually responsible for the patient’s symptoms.

VT

- The symptoms of VT (monomorphic VT or TdP), if prolonged (ie, sustained), can vary from nearly completely asymptomatic to pulseless, hemodynamic collapse. Fast heart rates and underlying poor LV function will result in more severe symptoms. Symptoms of nonsustained, self-terminating VT also correlate with duration of episodes (eg, patients with 15-second episodes will be more symptomatic than those with three-beat episodes).

VF

- By definition, VF results in hemodynamic collapse, syncope, and cardiac arrest. Cardiac output and blood pressure are not recordable.

Even though the CAST was conducted more than two decades ago, it is considered one of the most important trials ever undertaken and has had a tremendous influence on the overall approach to the treatment of arrhythmias, as well as a far-reaching impact on AAD development. The results of the CAST have clearly had a negative influence on the long-term use of all AADs, causing a broad skepticism in the risk-versus-benefit analysis of this class of drugs. Consequently, pharmaceutical companies have shifted their drug discovery and investigative efforts away from potent sodium channel blockers. The findings of the CAST have also provided additional fuel for the pursuit of nonpharmacologic therapies for arrhythmias, such as catheter ablation and implantable devices.

Despite the discouraging results of the CAST, post-MI patients with complex ventricular ectopy remain at risk for death. Other drugs, besides the class Ic AADs, have been studied in this patient population, including sotalol. Sotalol is comprised of a racemic mixture of D- and L-isomers: both isomers are class III potassium channel blockers but the L-isomer also has beta-blocking actions. Chronic therapy with D-sotalol was studied in patients with a remote MI complicated by complex ectopy in the Survival with Oral D-Sotalol trial.[81] In this trial, D-sotalol treatment was not targeted at PVC suppression (unlike the CAST), yet (like the CAST) the trial was halted prematurely because of excessive mortality in the treatment arm. Again, the presumed reason for this observation was D-sotalol–related proarrhythmia. Currently, only two AADs have been shown *not* to increase mortality in post-MI patients with long-term use: amiodarone and dofetilide. A number of trials have shown amiodarone to decrease the incidence of sudden (or arrhythmic) death, but not total mortality, in post-MI patients with complex ventricular ectopy.[82,83] Clearly, because of its

impressive side effect profile and its inability to improve survival, amiodarone should not routinely be recommended in patients with heart disease such as remote MI and complex PVCs. Two randomized controlled trials have also shown that chronic therapy with dofetilide has no effect on overall mortality in post-MI patients with LV dysfunction.[84,85]

7 How should the clinician approach the patient with documented asymptomatic PVCs? Clearly, attempts to suppress asymptomatic PVCs should *not* be made with any AAD. Indeed, those patients who are at risk for arrhythmic death (recent MI, LV dysfunction, complex PVCs) should also *not* be routinely given *any* class I or III AAD.[86] If these patients have symptomatic PVCs, chronic drug therapy should be limited to the use of beta blockers. The use of beta blockers in post-MI patients is associated with a reduction in the incidence of total mortality and SCD, especially in the presence of LV dysfunction. Beta blockers can also be used in patients without underlying SHD to suppress symptomatic PVCs. Uncommonly, patients have such frequent PVCs that are either extremely bothersome or result in a decline in left ventricular function (usually when the PVCS greater than 20% of all beats). In these patients, ablation of the PVCs can be pursued.[97]

Ventricular Tachycardia

VT is a wide QRS tachycardia that may acutely occur as a result of metabolic abnormalities, ischemia, or drug toxicity, or chronically recur as a paroxysmal form. On the ECG, VT may appear as repetitive monomorphic or polymorphic ventricular complexes. The definition of VT is three or more consecutive PVCs occurring at a rate of greater than 100 beats/min. An acute episode of VT may be precipitated by severe electrolyte abnormalities (hypokalemia or hypomagnesemia), hypoxia, or digoxin toxicity, or (most commonly) may occur in patients presenting with acute MI or myocardial ischemia complicated by HF. In these cases, correction of the underlying precipitating factors will usually prevent further recurrences of VT. As an example, if VT occurs during the first 24 hours of an acute MI, it will probably not reappear on a chronic basis after the infarcted area has been reperfused or healed with scar formation. This form of acute VT may be caused by a transient reentrant mechanism within temporarily ischemic or dying ventricular tissue. In contrast, some patients have a chronic, recurrent form of VT that is almost always associated with some type of underlying SHD. Common examples are paroxysmal VT associated with idiopathic dilated cardiomyopathy or remote MI with an LV aneurysm. In

chronic, recurrent VT, microreentry within the distal Purkinje network and myocardium is responsible for the underlying substrate in a large majority of patients (see Fig. 39-3). Theoretically, electrophysiologic abnormalities occur as a result of structural damage and heart disease within the ventricular conducting system. The reentrant circuit may possess both anatomically determined and functional properties coursing through normal tissue, damaged (but not dead) tissue, and islands of necrosed tissue. In a minority of patients, macroreentrant circuits may be responsible for recurrent VT, including reentry incorporating the bundle branches. Patients with acute VT associated with a precipitating factor often suffer severe symptoms, requiring immediate treatment measures. Chronic, recurrent VT may also cause severe hemodynamic compromise but may also be associated with only mild symptoms that are generally well tolerated. The severity of symptoms is reliant upon the rate of the tachycardia and the patient's underlying heart disease and ventricular function.

Sustained VT is that which requires therapeutic intervention to restore a stable rhythm or persists for a relatively long time (usually more than 30 seconds). Nonsustained VT is that which self-terminates after a brief duration (usually less than 30 seconds). Patients who experience VT more frequently than SR (ie, VT is the dominant rhythm) are considered to have incessant VT. In monomorphic VT, the QRS complexes are similar in morphologic characteristics from beat to beat. In polymorphic VT, the QRS complexes vary in shape and/or size between beats. A characteristic type of polymorphic VT, in which the QRS complexes appear to undulate around a central axis and that is associated with evidence of delayed ventricular repolarization (long QT interval or prominent U waves), is referred to as TdP.

Most, but not all forms of recurrent VT occur in patients with extensive SHD. VT occurring in a patient without SHD is sometimes referred to as idiopathic VT and may take several forms including fascicular VT and ventricular outflow tract VT.[87–89] Fascicular VT arises from a fascicle of the left bundle branch (usually posterior) and is usually not associated with severe underlying SHD. Non-DHP CCBs (but not adenosine) are effective in terminating an acute episode of fascicular VT. Ventricular outflow tract VT (usually originating from the right ventricular outflow tract) originates from near the pulmonic valve (or uncommonly the aortic valve or LV outflow tract) and also occurs in patients with normal LV function without discernible SHD.[89] Unlike other forms of VT, right ventricular outflow tract VT often terminates with adenosine and may be prevented with beta blockers and/or non-DHP CCBs.

Some unusual forms of VT are congenital or heritable. TdP can be associated

with heritable defects in the flux of ions that govern ventricular repolarization. Although multiple syndromes and genetic mutations have been described, the more common examples are long QT syndrome 1 (depressed I_{Ks}), long QT syndrome 2 (depressed I_{Kr}), and long QT syndrome 3 (enhanced, inward sodium ion flux during repolarization).[90] Polymorphic VT (without a prolonged QT interval) or VF may also occur due to a heritable defect in the sodium channel. This is the case in Brugada syndrome, which is described as a typical ECG pattern (ST-segment elevation in leads V_1 to V_3) in SR that is associated with SCD, and commonly occurs in males of Asian descent.[91]

General Approach to Treatment

Consider the patient with the more common form of sustained monomorphic VT (ie, those with SHD, usually ischemic in nature). Like other rapid tachycardias, the initial management of an acute episode of VT (with a pulse) requires a quick assessment of the patient's signs and symptoms. If severe symptoms are present (ie, severe hypotension, angina, pulmonary edema), synchronized DCC should be delivered immediately to attempt to restore SR. An investigation should be made into possible precipitating factors which should be corrected if possible. The diagnosis of acute MI should always be entertained. If the episode of VT is thought to be an isolated electrical event associated with a transient initiating factor (such as acute myocardial ischemia or digoxin toxicity), there is no need for long-term AAD therapy once the precipitating factors are corrected (eg, an MI has been reperfused and healed and the patient is stable). Nevertheless, the patient should be monitored closely for possible recurrences of VT.

Patients presenting with an acute episode of VT (with a pulse) associated with only mild symptoms can be initially treated with AADs. The reader is referred to the 2010 AHA Guidelines for CPR and Emergency Cardiovascular Care (ECC) (no updated recommendations regarding treatment of VT [with a pulse] in 2018 Guidelines Update for CPR and ECC).[92] IV procainamide, amiodarone, or sotalol can be considered in this situation. Lidocaine can be considered as an alternative. In one small study, IV procainamide was shown to be associated with significantly fewer major cardiac adverse events and a higher termination rate when compared to IV amiodarone.[93] Synchronized DCC should be delivered if the patient's status deteriorates, VT degenerates to VF (would be unsynchronized in this situation), or drug therapy fails.

Once an acute episode of sustained VT has been successfully terminated by electrical or pharmacologic means and an acute MI has been ruled out, the

possibility of a patient having recurrent episodes of VT should be considered. Evidence for the possibility of VT recurrence can often be gleaned from invasive electrophysiologic studies using programmed ventricular stimulation. Because these patients are at extremely high risk for death, trial-and-error attempts to find effective therapy are unwarranted. To gain some objective evidence of a response to a specific AAD regimen, serial testing of these drugs using the following two surrogate end points has been used: (a) inability to induce sustained VT with programmed extrastimuli by invasive electrophysiologic studies; and (b) suppression of ventricular ectopic beats by serial 24-hour continuous electrocardiographic (Holter) monitoring. These two strategies have been compared but largely abandoned for several reasons.[94,95] First, the yield for finding an effective AAD is low. For instance, sustained monomorphic VT can be rendered noninducible or nonsustained by programmed stimulation protocols in only 20% to 25% of patients. Therefore, the clinician frequently must search for other therapeutic options or settle for other treatment end points such as slower and more tolerable inducible VT. Second, amiodarone is the most effective (approximately 50% effective after 2 years) AAD in patients with recurrent VT; however, electrophysiologic drug testing does not necessarily predict the clinical efficacy of amiodarone. Patients may have continued inducibility of VT on amiodarone despite long-term success. Indeed, empiric amiodarone has been compared with therapy (with other AADs) guided by electrophysiologic testing in patients at high risk for recurrent VT.[96] In this trial, amiodarone therapy without invasive testing was superior in preventing SCD and recurrences of severe ventricular arrhythmias at all-time points. Third, the recurrence rate of life-threatening VT is high (20%-50% per year depending on the AAD chosen), regardless of the method of acute drug testing. Fourth, as referred to previously, there is a substantial side effect profile of the class I and III AADs. Lastly, and perhaps most importantly, is the impressive demonstrated effectiveness of nonpharmacologic approaches to the treatment of recurrent VT/VF.[97] For instance, some forms of recurrent VT are amenable to catheter ablation therapy using radiofrequency current. This approach is highly effective (approximately 90%) in idiopathic VT (right ventricular outflow tract or fascicular VT), but less so in recurrent VT associated with a cardiomyopathic process or remote MI with LV aneurysm. In the latter patients, ablation is usually regarded as second-line therapy after other methods have failed.[98] Additionally, numerous trials have established the ICD as a superior treatment over AAD therapy not only for the prevention of SCD in patients who have been resuscitated from an episode of cardiac arrest or had sustained VT (“secondary

prevention") but also for the prevention of an initial episode of SCD in certain high-risk patient populations ("primary prevention").

Implantable Cardioverter-Defibrillator

8 The introduction of and advances in the ICD (**Fig. 39-11**) have obviated the need to rely solely on the use of AADs to prevent episodes of life-threatening ventricular arrhythmias.[99] Numerous advancements in device technology have allowed the ICD to become smaller, less invasive to implant, and programmable with advanced functions. Early ICDs required a thoracotomy to place the generator in the abdomen, whereas with the newer, smaller models, the leads are implanted transvenously with the generator placed into the pectoral region in a manner similar to cardiac pacemakers. Modern ICDs now employ a "tiered-therapy approach," meaning that overdrive or antitachycardia pacing (stimulates the heart to go faster than the rate induced by the VT) can be attempted first to terminate the tachyarrhythmia (no painful shock delivered), followed by low-energy cardioversion, and, finally, by high-energy defibrillation shocks. In addition, backup antibradycardia pacing and extended battery lives have made these newer devices much more attractive. All models store recordings during delivery of pacing shocks, which is extremely important in discerning appropriate shocks (ie, delivers shock for serious ventricular arrhythmia) from inappropriate shocks (ie, delivers shock for AF with rapid ventricular rate) and in documenting true recurrences of the patient's tachycardia.

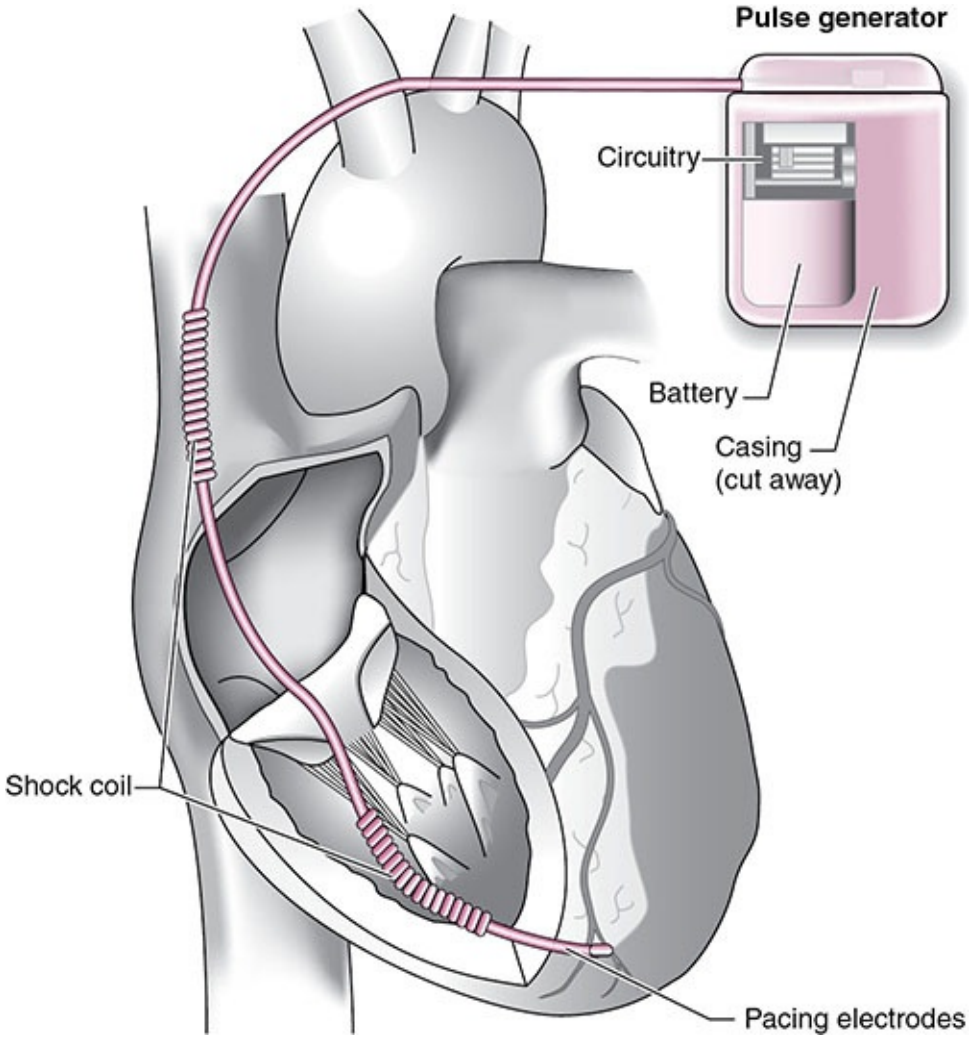


FIGURE 39-11 Drawing showing implantable cardioverter-defibrillator. (*Data from Pacifico A, et al. Prevention of implantable-defibrillator shocks by treatment with sotalol. N Engl J Med. 1999;340:1855–1862. Copyright © 2003 Massachusetts Medical Society. All rights reserved.*)

Although the ICD is a highly effective method for preventing SCD due to recurrent VT or VF, several problems remain. First, the device itself, the implantation procedure, electrophysiologic studies, hospitalization, and physician fees are costly. Given that the indications for receiving an ICD have significantly expanded over the past several years, the total cost associated with the implantation of this device is likely to place a great burden on the healthcare system. Second, many patients (as high as 70%) with ICDs end up receiving concomitant AAD therapy (usually amiodarone or sotalol).[100,101] AADs can be initiated in these patients for a number of reasons, including: (a) decreasing the frequency of VT/VF episodes to subsequently reduce the frequency of

appropriate shocks; (b) reducing the rate of VT so that it can be terminated with antitachycardia pacing; and (c) decreasing episodes of concomitant supraventricular arrhythmias (eg, AF, AFl) that may trigger inappropriate shocks. As a result of these potential benefits, the concomitant use of AADs can minimize patient discomfort and prolong the battery life of the ICD. The decision to initiate concomitant AAD therapy should be individualized, with treatment usually being reserved for those patients with frequent shocks because of VT or AF. If AADs are added to ICD therapy, one should note that many of these drugs alter defibrillation thresholds; consequently, the device may need to be reprogrammed to account for this alteration.[102]

Prevention of Sudden Cardiac Death The results of three trials, the Antiarrhythmics Versus Implantable Defibrillators (AVID), Cardiac Arrest Study Hamburg (CASH), and Canadian Implantable Defibrillator Study (CIDS), definitively support the ICD as first-line therapy for the secondary prevention of SCD.[103–105] Of these, the AVID trial was the largest, randomizing more than 1,000 patients with resuscitated VF, sustained VT with syncope, or hemodynamically significant sustained VT (with LVEF less than or equal to 40% [0.40]) to either an ICD or AADs (approximately 95% received amiodarone at discharge).[103] The trial was stopped early because of a demonstrated superiority of the ICD; patients in the ICD group had a better overall survival when compared with those in the AAD group (75% vs 64%, respectively, at 3 years). Although they were smaller trials, both CASH and CIDS demonstrated the efficacy of an ICD compared with amiodarone in patients with a history of sustained VT or VF, with the ICD reducing overall mortality by 20% to 25%.[104,105] Overall, the results of these three trials provide strong support for the aggressive use of the ICD in patients who are at high risk for recurrent, life-threatening ventricular arrhythmias.

One of the patient populations that appears to be at high risk for a first episode of SCD includes those with a prior MI, LV dysfunction, and nonsustained VT. The use of AADs to prevent SCD in this high-risk group has been significantly limited by the results of the CAST and other similar trials that have collectively demonstrated that these drugs may actually increase the risk of mortality in these patients. As a result of these trials, clinicians have sought a more clearly defined strategy for risk stratification in these patients before initiating drug therapy.

9 For patients with nonsustained VT, there are four treatment strategies based upon symptoms and underlying comorbidities: (a) conservative (ie, no

AAD treatment beyond beta blockers); (b) empiric amiodarone; (c) ablation; and (d) aggressive (ie, electrophysiologic studies with possible insertion of an ICD) (**Fig. 39-12**).[97] A number of early studies suggested that tests such as electrophysiologic studies could be used to determine long-term risk in patients with nonsustained VT.[106,107] For instance, Wilber et al. demonstrated that post-MI patients with nonsustained VT and inducible sustained VT after programmed stimulation were at increased risk for subsequent VT/VF or SCD compared with those in whom sustained VT could not be induced.[106] These data provided the basis for the Multicenter Automatic Defibrillator Implantation Trial (MADIT) and the Multicenter Unsustained Tachycardia Trial (MUSTT).[108,109] The MADIT was the first of these trials to be conducted to evaluate the efficacy of ICD therapy in this high-risk patient population. Specifically, this trial randomized patients with a previous MI, LVEF less than or equal to 35% (0.35), asymptomatic nonsustained VT, and inducible VT that was not suppressed with the use of IV procainamide to receive an ICD or conventional medical therapy (74% received amiodarone).[108] This trial was terminated prematurely after a significant survival benefit was detected in the ICD group. The findings of the MADIT were subsequently supported by those of the MUSTT. In the MUSTT, patients with a history of MI, LVEF less than or equal to 40% (0.40), asymptomatic nonsustained VT, and inducible sustained VT were randomized to a conservative approach (no AAD therapy beyond beta blockers) or electrophysiologically guided therapy (AADs and/or ICD).[109] The results showed that the conservative approach had a significantly higher event rate (cardiac arrest or death from arrhythmia). However, when the results of the electrophysiologically guided group were further stratified, those receiving only AADs (no ICD) were no different in terms of outcomes than those who received no treatment. In other words, only those treated with an ICD had a significantly lower event rate and greater survival. One problem with the MUSTT, however, is that, because the trial was initiated in 1989, nearly 50% of patients received class I AADs or drugs that are now known not to improve survival in patients with CAD, LV dysfunction, and ventricular arrhythmias; only 10% of patients received the most effective agent in this setting, amiodarone. Based on the results of the MADIT and MUSTT, it is reasonable for patients with CAD, LV dysfunction, and nonsustained VT to undergo electrophysiologic testing.[97] If these patients do have inducible sustained VT/VF, implantation of an ICD is warranted.

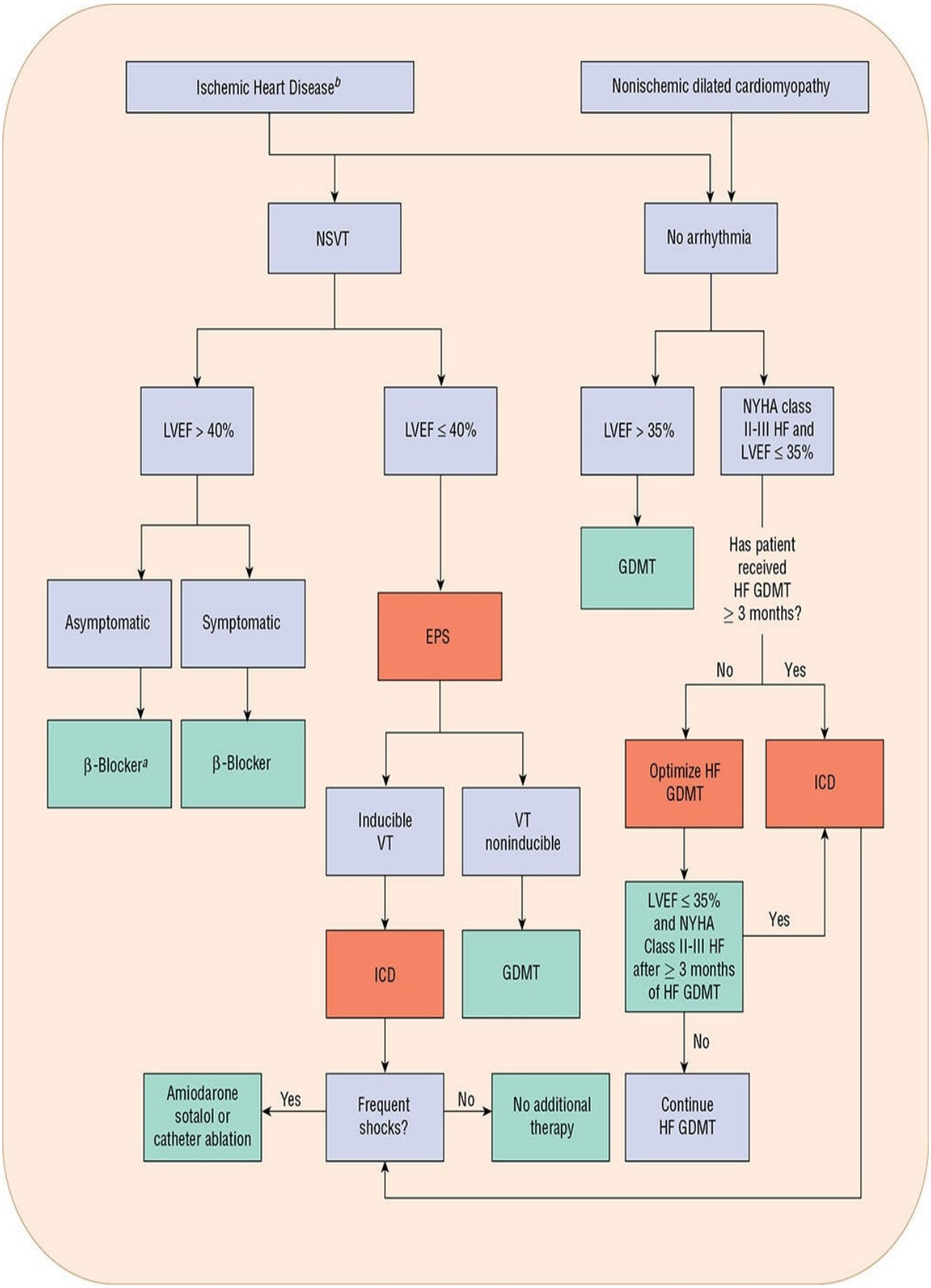

Ischemic Heart Disease[b]
Nonischemic dilated cardiomyopathy
NSVT
No arrhythmia
LVEF > 40%
LVEF ≤ 40%
LVEF > 35%
NYHA class II-III HF and LVEF ≤ 35%
Asymptomatic
Symptomatic
EPS
GDMT
Has patient received HF GDMT ≥ 3 months?
No
Yes
β-Blocker[a]
β-Blocker
Inducible VT
VT noninducible
Optimize HF GDMT
ICD
LVEF ≤ 35% and NYHA Class II-III HF after ≥ 3 months of HF GDMT
Yes
ICD
GDMT
No
Amiodarone sotalol or catheter ablation
Yes
Frequent shocks?
No
No additional therapy
Continue HF GDMT

FIGURE 39-12 Algorithm for the primary prevention of SCD in patients with a history of MI or with a nonischemic dilated cardiomyopathy. LVEF of 35% is equivalent to 0.35 expressed as a fraction. *a*In these patients, the β-blocker is being used to reduce post-MI mortality. *b*Patients should be >40 days post-MI and at least 90 days postrevacularization prior to insertion of the ICD. (EPS, electrophysiologic study; GDMT, guideline-directed medical therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSVT, nonsustained VT; SCD, sudden cardiac death; VT, ventricular tachycardia.)

Although the MADIT and MUSTT provide clinicians with important information regarding risk stratification, both of these trials targeted patients who had a history of nonsustained VT. The results of two landmark trials, the MADIT II and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), have provided clinicians with additional information regarding the treatment of other groups of high-risk patients who have no prior history of ventricular arrhythmia.[110,111] In the MADIT II, patients with a prior MI and LVEF less than or equal to 30% (0.30) were randomized to receive either an ICD or a conventional therapy (routine post-MI and HF therapy).[110] Neither a history of ventricular arrhythmia nor electrophysiologic testing was required for inclusion in this study. Patients in the ICD group experienced a significant reduction in mortality when compared with the conventional therapy group; the reduction in mortality in the ICD group was primarily due to a reduction in arrhythmic death. Whereas the MADIT, MUSTT, and MADIT II limited enrollment to patients with ischemic cardiomyopathy, the SCD-HeFT is the largest trial, to date, to evaluate the efficacy of an ICD in a nonischemic HF population. In this trial, patients with NYHA class II or III HF (of either ischemic or nonischemic etiology) and LVEF less than or equal to 35% (0.35) were randomized to receive placebo, amiodarone, or an ICD.[111] All patients were treated with appropriate HF therapies, as indicated. Implantation of an ICD resulted in a significantly lower mortality rate compared with treatment with either placebo or amiodarone (there was no difference between placebo and amiodarone). The survival benefits of the ICD were observed regardless of the etiology of the HF.

9 Overall, as the ICD trials have evolved over the past decade, the indications for implanting these devices have significantly expanded.[97,112] Based on the results of the MUSTT, MADIT, MADIT II, and SCD-HeFT, many patients will be eligible for an ICD.

Ventricular Proarrhythmia

All AADs have the potential to aggravate existing arrhythmias or to cause new arrhythmias. It is believed that AADs may cause proarrhythmia in nearly 30% of patients.[6] Many definitions for proarrhythmia have been proposed; however, in the simplest terms, it indicates the development of a significant new arrhythmia (such as VT, VF, or TdP) or worsening of an existing arrhythmia (episodes are longer, faster, or more frequent). As with all arrhythmias, the consequences of proarrhythmia are varied. Some patients who develop proarrhythmia may be totally asymptomatic, others may notice a worsening of symptoms, and some may die suddenly. The development of proarrhythmia results from the same mechanisms that cause arrhythmias in general (eg, quinidine-induced TdP due to EADs) or from an alteration in the underlying substrate due to the AAD (eg, development of an accelerated tachycardia caused by flecainide, which decreases conduction velocity without significantly altering the refractory period).[6] The diagnosis of proarrhythmia is sometimes difficult to make because of the variable nature of the underlying arrhythmias. However, in all cases, the AAD should be discontinued if proarrhythmia is detected or suspected.

Monomorphic Ventricular Tachycardia 10 The prototypical form of proarrhythmia caused by the class Ic AADs is a rapid, sustained, monomorphic VT with a characteristic sinusoidal QRS pattern that is often resistant to resuscitation with cardioversion or overdrive pacing. It is sometimes referred to as sinusoidal or incessant VT and is the result of excessive sodium channel blockade and slowed conduction. Sinusoidal VT caused by the class Ic AADs was thought to occur within the first several days of drug initiation. However, the results of the CAST indicate that the risk for this type of proarrhythmia may exist as long as the AAD is continued. Factors that can predispose a patient to this form of proarrhythmia include: (a) the presence of underlying ventricular arrhythmias; (b) CAD; and (c) LV dysfunction. Provocation of proarrhythmia by the class Ic AADs is sometimes reported during exercise, which is most likely a result of augmented slowed conduction at rapid heart rates (ie, rate-dependent sodium blockade). The incidence of proarrhythmia caused by class Ic AADs is greatest in patients with all three of the above risk factors (approximately 10%-20%) and extremely uncommon in those without these risk factors, such as patients with supraventricular tachycardias and normal LV function. Other factors that have a less well-defined association with proarrhythmia are elevated AAD serum concentrations and rapid dosage escalation of the AAD. It has been proposed that the presence of underlying ventricular conduction delays may also

pose a risk for proarrhythmia. As mentioned earlier, incessant monomorphic VT is often resistant to resuscitation; however, some have had success with lidocaine ("fast on–off" AAD, which successfully competes with a "slow on–off" agent such as flecainide for sodium channel receptor) or sodium bicarbonate (reverses the excessive sodium channel blockade).

10 **Torsades de Pointes** TdP is a rapid form of polymorphic VT (**Fig. 39-13**) that is associated with evidence of delayed ventricular repolarization (long QT interval or prominent U waves) on ECG. It is important to note that most forms of polymorphic VT occurring in the setting of a normal QT interval are similar to monomorphic VT in terms of etiology and treatment strategies (thus, a long QT interval is crucial to the diagnosis of TdP). Much has been learned about the underlying etiology of TdP. Basic defects (genetic, drugs, or diseases) that delay repolarization by influencing ion movement (usually by blocking potassium efflux) provoke EADs preferentially in cells deep in the heart muscle, which, in turn, trigger reentry and TdP. Drugs that cause TdP usually delay ventricular repolarization in an inhomogeneous way (termed *dispersion of refractoriness*), which facilitates the formation of multiple reentrant loops in the ventricle.[113] TdP may occur in association with hereditary syndromes or as an acquired form (ie, a result of drugs or diseases). The underlying etiology in both cases is delayed ventricular repolarization due to blockade of potassium conductance. It is possible, however, that some individuals have a partially expressed form of these congenital syndromes but never suffer TdP unless some other external factor (eg, drugs, diseases, electrolyte disturbances, abrupt heart rate changes) further delays ventricular repolarization. Specifically, acquired forms of TdP are associated with electrolyte disturbances (hypokalemia or hypomagnesemia), subarachnoid hemorrhage, myocarditis, liquid protein diets, arsenic poisoning, severe hypothyroidism, or, most commonly, drug therapy (notably phenothiazines, antibiotics, antihistamines, antidepressants, and AADs) (**Table 39-10**).

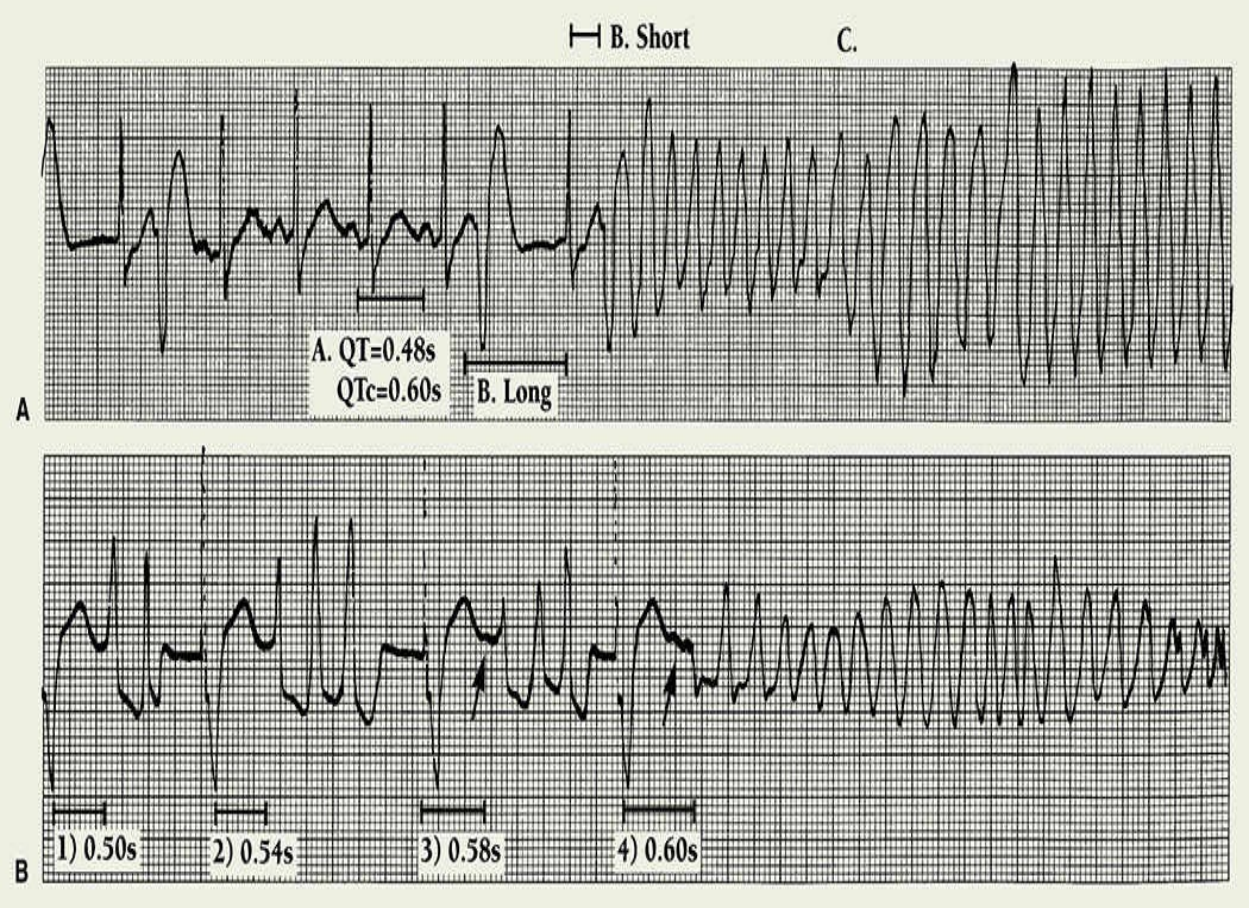


FIGURE 39-13 Panel A. Torsade de pointes due to high concentrations of N-acetyl procainamide in a patient with renal dysfunction receiving procainamide. Note the extremely long corrected QT (QTc) interval (A), characteristic long-short initiating sequence (B) and polymorphic configuration of the ensuing rapid ventricular tachycardia (C). Panel B. Torsade de pointes caused by quinidine. Note the presence of a couplet and two triplets following each extra systolic pause. The pause gets progressively longer until it is long enough to result in an episode of sustained torsade de pointes. Also, as the pause lengthens, discernible U waves (labeled ↑) begin to appear. The amplitude of the U wave is somewhat greater with the longest pause. (*Reprinted from Bauman JL. Drug safety: Cardiac arrhythmias. Antihistamine update symposium. Hosp Med 1995;31:24.*)

TABLE 39-10 Potential Causes of QT Interval Prolongation and Torsade de Pointes

Conditions

Congenital long QT syndromes
Heart failure
Hypokalemia
Hypomagnesemia
Myocardial ischemia/infarction
Myocarditis
Severe bradycardia (<50 beats/min)
Severe hypothermia
Severe starvation/liquid protein diets
Subarachnoid hemorrhage

Drugs

Antiarrhythmic drugs
- Amiodarone (<1%)
- Disopyramide
- Dofetilide
- Dronedarone
- Ibutilide
- Procainamide (also *N*-acetylprocainamide)
- Quinidine
- Sotalol

Antiinfectives
- Azole antifungals (e.g. fluconazole, voriconazole)
- Fluoroquinolones (e.g. levofloxacin, moxifloxacin, gemifloxacin)
- Macrolides
- Pentamidine

Cancer chemotherapy or biologic agents
- Ceritinib
- Crizotinib
- Dasatinib
- Degarelix
- Eribulin
- Lapatinib
- Leuprolide
- Nilotinib
- Oxaliplatin
- Pazopanib
- Sorafenib
- Sunitinib
- Toremifene
- Vandetanib
- Vemurafenib

Miscellaneous
- Chloroquine
- Methadone
- Ondansetron (IV)
- Tacrolimus

Psychotropics
- Atypical antipsychotics (eg, quetiapine, ziprasidone)
- Droperidol
- Haloperidol
- Phenothiazines (eg, thioridazine, chlorpromazine)
- Pimozide
- Tricyclic and tetracyclic antidepressants

Toxins
- Arsenic
- Organophosphate insecticides

IV, intravenous

Note: For a complete list, see www.crediblemeds.org.

The class Ia AADs (especially quinidine) and class III I_{Kr} blockers are most notorious for precipitating TdP; the class Ib and Ic AADs rarely, if ever, cause TdP as they do not appreciably delay repolarization. Most AADs with I_{Kr} blocking activity cause TdP in approximately 2% to 4% of patients, with the exceptions being amiodarone and dronedarone (less than 1%). Risk factors and associated features of drug-induced TdP have been identified and can be summarized as follows[114]: (a) high dosages or plasma concentrations of the offending drug ("dose-related") (except for quinidine-induced TdP, which tends to occur more frequently at low-to-therapeutic plasma concentrations); (b) concurrent SHD (eg, CAD, HF, and/or LV hypertrophy); (c) evidence of mild delayed repolarization (prolonged QT interval) at baseline; (d) evidence of a prolonged QT interval shortly after initiation of the offending drug; (e) concomitant electrolyte disturbances such as hypokalemia or hypomagnesemia; (f) female gender; and (g) a characteristic long–short initiating sequence (so-called "pause dependence") of the TdP episode (Fig. 39-13). However, none of these associations are absolute prerequisites to the development of drug-induced TdP. For instance, although TdP is usually documented early in the course of quinidine therapy, patients may develop this arrhythmia anytime during chronic treatment.[115] The reason for quinidine's relatively unique propensity for causing TdP at relatively low dosages and plasma concentrations requires explanation. Quinidine's ability to block I_{Kr} is clinically manifest at low plasma concentrations; at higher plasma concentrations, its sodium channel blocking properties predominate. Other drugs that block I_{Kr} usually do so in a concentration-dependent fashion. The observation that most patients who suffer drug-induced TdP have evidence of mildly delayed repolarization (long QT intervals) even before they are prescribed the offending drug has stimulated a search for a potential genetically linked risk. Indeed, it appears that at least some patients with acquired drug-induced TdP possess mutations of genes that encode for I_{Kr} or I_{Ks}.[114]

The common underlying electrophysiologic cause of TdP is a delay in ventricular repolarization (provoking EADs), which usually results from inhibition (drug-induced or genetic) of the I_K current and manifests as QT interval prolongation on the ECG. Therefore, the extent of QT interval prolongation has been used as a measurement of risk of TdP. However, considerable controversy exists regarding this practice. Amiodarone, for example, commonly causes significant QT prolongation but is a relatively

infrequent cause of TdP. Nonetheless, the QT interval should be measured and monitored in all patients prescribed drugs that have a high potential for causing TdP (see Table 39-10). Patients with a prolonged QT_c interval at baseline (QT interval corrected for heart rate, which can be calculated using Bazett's formula: QTc= QT measured/R − R Interval) (ie, greater than 450 msec in men; greater than 470 msec in women) should not be given drugs that have a high potential for causing TdP. The development of clinically significant QTc interval prolongation (ie, QTc interval greater than 500 msec or an increase in the QTc interval of more than 60 to 70 msec from baseline) after initiation of a drug is an indication to discontinue the agent or, at least, to reduce its dosage and carefully monitor.[116]

Drug-induced TdP has become an extremely visible hazard plaguing new drugs, sometimes resulting in public health disasters. For instance, several drugs (cisapride, astemizole, levomethadyl, grepafloxacin, sparfloxacin, terfenadine, and high-dose [32 mg] IV ondansetron) have been withdrawn from the market in the United States because of their significant potential for causing TdP. One of the most visible and striking examples of drug withdrawal due to TdP occurred with the popular nonsedating antihistamine, terfenadine. Terfenadine is a potent I_{Kr} blocker but is rapidly metabolized by CYP3A4 to an active moiety (fexofenadine) that is not associated with delayed repolarization. Consequently, in the presence of drugs that block the CYP3A4 isoenzyme (eg, ketoconazole, erythromycin, diltiazem), accumulation of the parent compound, terfenadine, causes clinically significant blockade of I_{Kr} that could result in TdP and even death.[117] Because of experiences like this, all new drug entities under investigation are screened for their ability to block I_K and cause significant QT prolongation.

Acute treatment of TdP is different than treatment for the more common acute monomorphic VT. For an acute episode of TdP, most patients will require and respond to DCC. However, TdP tends to be paroxysmal in nature and often will rapidly recur after DCC. Therefore, after the initial restoration of a stable rhythm, therapy designed to prevent recurrences of TdP should be instituted. AADs that further prolong repolarization such as IV procainamide are absolutely contraindicated. Lidocaine is usually ineffective. Although there are no true efficacy trials, IV magnesium sulfate, by suppressing EADs, is considered the drug of choice in preventing recurrences of TdP.[97] If IV magnesium sulfate is ineffective, treatment strategies designed to increase heart rate, shorten ventricular repolarization, and prevent the pause dependency should be initiated. Either temporary transvenous pacing (105-120 beats/min) or pharmacologic

pacing (isoproterenol) can be initiated for this purpose. All drugs that prolong the QT interval should be discontinued, and exacerbating factors (eg, hypokalemia or hypomagnesemia) should be corrected.

Ventricular Fibrillation

VF is electrical anarchy of the ventricle resulting in no cardiac output and CV collapse. Death will ensue rapidly if effective treatment measures are not taken. Patients who die abruptly (within 1 hour of initial symptoms) and unexpectedly (ie, "sudden death") usually have VF recorded at the time of death.[118] SCD accounts for more than 360,000 deaths per year in the United States.[16] It occurs most commonly in patients with CAD or LV dysfunction, but occasionally in those without associated heart disease (eg, Brugada syndrome). When a patient experiences sudden cessation of cardiac activity with no normal breath nor signs of circulation they are said to have sudden cardiac arrest. CPR, medications, and defibrillation can be corrective measures to prevent SCD. If the event is not associated with acute MI, sustained VT and/or VF during electrophysiologic studies are often inducible. These individuals are at high risk for the recurrence of VT and/or VF. In contrast, patients who have VF associated with acute MI (ie, within 48 hours of hospital presentation) usually have little risk of recurrence.

In the presence of acute coronary syndrome, CAD should be treated. The patient's LVEF should be reevaluated 40 days post-MI and 90 days post-revascularization.[97] If the LVEF is greater than 35% (0.35), the patient should be treated with medical management; however, if the LVEF is less than 35% (0.35), an ICD should be considered. Without acute coronary syndrome, the patient should be evaluated for SHD and inherited arrhythmia syndrome. Regardless, reversible causes should be eliminated and avoided. If no reversible cause is identified, an ICD can be considered.

Acute Management

A patient with pulseless VT or VF should be managed according to the most recent AHA guidelines for CPR and ECC.[119] A detailed discussion regarding the acute management of pulseless VT/VF can be found in Chapter 40, "Cardiopulmonary Arrest."

BRADYARRHYTHMIAS

For the most part, the symptoms of bradyarrhythmias result from a decline in

cardiac output. Because cardiac output decreases as heart rate decreases (to a point), patients with bradyarrhythmias may experience symptoms in association with hypotension, such as dizziness, syncope, fatigue, and confusion. If LV dysfunction exists, patients may experience worsening HF symptoms. Except in the case of recurrent syncope, symptoms associated with bradyarrhythmias are often subtle and nonspecific.

Sinus Bradycardia

Sinus bradyarrhythmias (heart rate less than 60 beats/min) are a common finding, especially in young, athletically active individuals, and usually are neither symptomatic nor in need of therapeutic intervention. On the other hand, some patients, particularly the elderly, have SND. This may be the result of underlying SHD and the normal aging process that attenuate SA nodal function over time resulting in symptomatic sinus bradycardia and/or periods of sinus arrest.[112] SND is usually reflective of diffuse conduction disease, and accompanying AV block is relatively common. Furthermore, symptomatic bradyarrhythmias may be accompanied by alternating periods of paroxysmal tachycardias such as AF. In this instance, AF sometimes presents with a rather slow ventricular response (in the absence of AV nodal blocking drugs) because of diffuse conduction disease. The occurrence of alternating bradyarrhythmias and tachyarrhythmias is referred to as the tachy-brady syndrome. The occurrence of paroxysmal AF in a patient with SND may be a result of underlying SHD with atrial dysfunction or atrial escape in response to reduced sinus node automaticity. In fact, because the rate of impulse generation by the sinus node is generally depressed or may fail altogether, other automatic pacemakers within the conduction system may “rescue” the sinus node. These rescue rhythms often present as paroxysmal atrial rhythms (eg, AF) or as a junctional escape rhythm.

The treatment of SND involves eliminating the symptomatic bradycardia and potentially managing alternating tachycardias such as AF. In general, the long-term therapy of choice is permanent pacemaker implantation.[112] Dual-chamber, rate-adaptive chronic pacing clearly improves symptoms and overall quality of life and decreases the incidence of paroxysmal AF and systemic embolism.[120] Drugs commonly employed to treat supraventricular tachycardias should be used with caution, if at all, in the absence of a functioning pacemaker. AADs prescribed to prevent AF recurrences may also suppress the escape or rescue rhythms that appear in severe sinus bradycardia or sinus arrest. Consequently, these drugs may transform an asymptomatic patient with bradycardia into a

symptomatic one. The addition of class I AADs can also affect pacemaker threshold and result in loss of capture if the pacemaker is not appropriately interrogated and adjusted. Other drugs that depress SA or AV nodal function, such as beta blockers, non-DHP CCBs, and ivabradine, may also significantly exacerbate bradycardia. Drugs with indirect sympatholytic actions, such as methyldopa and clonidine, may also worsen SND. The use of digoxin in these patients is controversial; however, in most cases, it can be used safely.

Another reason for paroxysmal bradycardia and sinus arrest, not directly due to SND, is carotid sinus hypersensitivity.[112] Again, this syndrome occurs commonly in the elderly with underlying SHD, and may precipitate falls and hip fractures. Symptoms occur when the carotid sinus is stimulated, resulting in an accentuated baroreceptor reflex. Often, however, symptoms are not well correlated with the obvious physical manipulation of the carotid sinus (in the lateral neck region). Patients may experience intermittent episodes of dizziness or syncope because of sinus arrest caused by increased vagal tone (the cardioinhibitory type), a drop in systemic blood pressure caused by sympathetic withdrawal (the vasodepressor type), or both (mixed cardioinhibitory and vasodepressor types). The diagnosis can be confirmed by performing carotid sinus massage with ECG and blood pressure monitoring in a controlled setting. Symptomatic carotid sinus hypersensitivity should be treated with permanent pacemaker therapy.[112] However, some patients, particularly those with a significant vasodepressor component, still experience syncope or dizziness even after pacemaker implantation. The choice of definitive drug therapy in this situation is marred by the lack of controlled trials, although alpha-adrenergic stimulants such as midodrine are often tried in addition to the pacemaker.[120]

Vasovagal syndrome, by causing bradycardia, sinus arrest, and/or hypotension, is the cause of syncope in many patients who present with recurrent fainting of unknown origin.[112] By history, many individuals can recount rare instances of fainting spells at times of duress or fear. These episodes are most often caused by vasovagal syncope. However, some patients have extremely frequent, unexpected syncopal episodes that interfere with the patient’s quality of life and cause physical danger (sometimes referred to as neurocardiogenic syncope syndrome or malignant vasovagal syndrome). Vasovagal syncope is presumed to be a neurally mediated, paradoxical reaction involving stimulation of cardiac mechanoreceptors (ie, Bezold-Jarisch reflex). Forceful contraction of the ventricle (eg, as with adrenergic stimulation) coupled with low ventricular volumes (eg, with upright posture or dehydration) provides a powerful stimulus for cardiac mechanoreceptors. Syncope results from the spontaneous

development of transient hypotension (sympathetic withdrawal) and bradycardia (vagotonia). However, the true mechanism of vasovagal syncope remains to be definitively determined. For instance, patients with denervated hearts (eg, heart transplant recipients) can still experience this form of syncope. Regardless, patients believed to have frequent episodes of vasovagal syncope have been evaluated and diagnosed using the upright body-tilt test, a potent stimulus for the development of vasovagal symptoms.[121] Although commonly used, the sensitivity and reproducibility of this test have been questioned.[122]

Traditionally, beta blockers, such as metoprolol, were frequently chosen as the drugs of choice in preventing episodes of vasovagal syncope. Although these drugs may seem inappropriate to treat a syndrome resulting from vasodilation and bradycardia, the therapeutic approach is designed to block an inappropriate vasovagal reaction (ie, they inhibit the sympathetic surge that causes forceful ventricular contraction and precedes the onset of hypotension and bradycardia). To most clinicians' surprise, most controlled trials of the use of beta blockers in patients with severe vasovagal syncope have shown no effect compared with placebo in preventing syncopal episodes.[123] Some trials have suggested that beta blockers are more effective and should be used in older patients (older than 40 years of age) with vasovagal syncope rather than the relatively young.[124] Other drugs that have been used successfully (with or without beta blockers) include mineralocorticoids as volume expanders (fludrocortisone), anticholinergic drugs (scopolamine patches, disopyramide), alpha-adrenergic agonists (midodrine), adenosine analogs (theophylline, dipyridamole), and selective serotonin receptor antagonists (sertraline, paroxetine).[125] Permanent pacing has been used with some success but should be reserved for drug-refractory patients.[112] Because of the questionable effectiveness of beta blockers and the paucity of controlled or comparative trials, there is not a true drug of choice for severe vasovagal syncope, and clinicians are left with choosing agents and judging clinical effectiveness in individual patients on a case-by-case basis.

Atrioventricular Block

Conduction delay or block may occur in any area of the AV conduction system: the AV node, the His bundle, or the bundle branches. AV block is usually categorized into three different types based on ECG findings (**Table 39-11**). First-degree AV block is 1:1 AV conduction with a prolonged PR interval. Second-degree AV block is divided into two forms: Mobitz I AV block (Wenckebach periodicity) is less than 1:1 AV conduction with progressively

lengthening PR intervals until a ventricular complex is dropped; Mobitz II AV block is intermittently dropped ventricular beats in a random fashion without progressive PR lengthening. Third-degree AV block is complete heart block where AV conduction is totally absent (AV dissociation). First-degree AV block usually represents prolonged conduction in the AV node. Mobitz I, second-degree AV block is also usually caused by prolonged conduction in the AV node. In contrast, Mobitz II, second-degree AV block is usually caused by conduction disease below the AV node (ie, His bundle). Third-degree AV block may be caused by disease at any level of the AV conduction system: complete AV nodal block, His bundle block, or trifascicular block. In this situation, the ventricle beats independently of the atria (AV dissociation), and the rate of ventricular activation and QRS configuration are determined by the site of the AV block. The usual degree of automaticity of ventricular pacemakers progressively declines as the site of impulse generation moves down the ventricular conduction system. Therefore, the ventricular escape rate in cases of trifascicular block will be significantly less than complete AV nodal block. Consequently, trifascicular block is a much more dangerous form of AV block. For instance, complete AV block at the level of the AV node usually results in the ventricular rhythm being controlled by the stable AV junctional pacemaker (rate approximately 40 beats/min). In contrast, in complete AV block due to trifascicular or His bundle block, a much less reliable pacemaker with slower rates below the site of block controls ventricular rhythm.

TABLE 39-11 Forms of Atrioventricular Block

Type	Criteria	Site of Block
First-degree block	Prolonged PR interval (>0.2 second) 1:1 AV conduction	Usually AVN
Second-degree block		
Mobitz I	Progressive PR prolongation until QRS is dropped; <1:1 AV conduction	AVN
Mobitz II	Random nonconducted beats (absence of QRS); <1:1 AV conduction	Below AVN
Third-degree block	AV dissociation; absence of AV conduction	AVN or below

AV, atrioventricular; AVN, atrioventricular node.

AV block may be found in patients without underlying SHD such as trained

athletes or during sleep when vagal tone is high. Also, AV block may be transient where the underlying etiology is reversible such as in myocarditis, myocardial ischemia, after CV surgery, or during drug therapy. Beta blockers, digoxin, or non-DHP CCBs may cause AV block, primarily in the AV nodal area. Class I AADs may exacerbate conduction delays below the level of the AV node (sodium-dependent tissue). In other cases, AV block may be irreversible, such as that caused by acute MI, rare degenerative diseases, primary myocardial disease, or congenital heart disease.

If patients with second-degree or third-degree AV block develop signs or symptoms of poor perfusion (eg, altered mental status, chest pain, hypotension, shock), IV atropine (0.5 mg given every 3-5 minutes, up to 3 mg total dose) should be administered.[92] If these patients do not respond to atropine, transcutaneous pacing can be initiated. Sympathomimetic infusions such as epinephrine (2-10 mcg/min) or dopamine (2-10 mcg/kg/min) can also be used in the event of atropine failure and are particularly effective in sinus bradycardia/arrest and AV nodal block. An isoproterenol infusion (2-10 mcg/min) may be considered if the patient does not respond to dopamine or epinephrine; however, this drug should be used with caution because of its vasodilating properties and ability to increase myocardial oxygen consumption (particularly during active MI). As would be expected, these drugs usually do not help when the site of AV block is below the AV node (eg, Mobitz II or trifascicular AV block) because their primary mechanism is to accelerate conduction through the AV node. If patients with bradycardia or AV block present with signs and symptoms of adequate perfusion, no acute therapy other than close observation is recommended.

Patients with chronic symptomatic AV block should be treated with the insertion of a permanent pacemaker.[112] Patients without symptoms can sometimes be followed closely without the need for a pacemaker. Patients with acute MI and evidence of new AV block or conduction disturbances will often require the insertion of a temporary transvenous pacemaker. AV block more commonly occurs as a complication of inferior wall MIs because of high vagal innervation at this site, and the coronary blood flow to the nodal areas usually supplies the inferior wall. However, the AV block may only be transient, obviating the need for permanent pacing.

EVALUATION OF THERAPEUTIC OUTCOMES

Generally, patients who suffer from tachyarrhythmias can be monitored for one

or several possible therapeutic outcomes. Obviously, the presence or recurrence of any arrhythmia can be documented by electrocardiographic means (eg, surface ECG, Holter monitor, or event monitor). Furthermore, patients may experience a decrease in blood pressure that may result in symptoms ranging from light-headedness to abrupt syncope, depending on the rate of the arrhythmia and the status of the underlying heart disease. For some patients, the potential alteration in hemodynamics may result in death if the arrhythmia is not detected and treated immediately. Besides these clinical outcomes, many patients with tachyarrhythmias experience alterations in quality of life as a result of recurrent symptoms of the arrhythmia or from side effects of therapy. And, finally, there are the economic considerations of medical or surgical intervention, continued medical care, and chronic drug or nonpharmacologic treatment.[126,127] Most of the studies are limited to the use of nonpharmacologic therapies such as the ICD or radiofrequency ablation.[76,128] Because that technology is rapidly evolving, what is not very cost-effective now may indeed be cost-effective in the next several years. For example, original cost-effectiveness analysis of the ICD showed it to be highly sensitive to the life of the generator, yet newer-generation devices have made significant advances not only in their size but also in their battery life. More recent data on the effect of the ICD on mortality coupled with the declining costs of an ICD imply that the device is indeed cost-effective in certain subsets of patients, which is similar to well-proven drug therapies used for other disorders.[128] Other nonpharmacologic treatments, such as catheter ablation for PSVT, not only improve quality of life but also save money on medical expenditures compared with chronic drug therapy.[76]

There are some therapeutic outcomes that are unique to certain arrhythmias. For instance, patients with AF or AFl need to be monitored for thromboembolism and for complications of antithrombotic therapy (bleeding, drug interactions). However, the most important monitoring parameters for most patients fall into the following categories: (a) mortality (total and sudden cardiac death); (b) arrhythmia recurrence (duration, frequency, symptoms); (c) hemodynamic consequences (heart rate, blood pressure, symptoms); and (d) treatment complications (side effects or need for alternative or additional drugs, devices, surgery) (**Table 39-12**). When evaluating the arrhythmia literature, care should be taken to consider real outcomes. For example, total mortality is more meaningful than SCD rates; it is possible an intervention prevents arrhythmic death but patients die from other causes, leaving all-cause mortality unaltered. Likewise, surrogate markers of drug efficacy (eg, noninducible tachycardia, suppression of minor arrhythmias) should be judged with a degree of skepticism.

One should ask: Did the treatment make patients live longer (reduce mortality)? Did the treatment make them feel better (improve humanistic outcomes or quality of life)? Was the treatment economically worth it (cost-effective)?

TABLE 39-12 Arrhythmia Outcomes

Mortality
Total, all cause mortality
Arrhythmia-related death (ie, sudden cardiac death)
Signs and symptoms
Recurrences documented by electrocardiogram
Time to recurrence
Frequency of recurrences
Exercise tolerance
Symptoms (eg, lightheadedness)
Blood pressure
Heart rate
Surrogate markers used to determine efficacy
Number of premature ventricular complexes per day
Inducibility of tachycardia with programmed stimulation
Necessity of nondrug interventions (eg, ICD)
ICD shocks
Side effects of drugs/treatment complications
Quality of life
Economics
Arrhythmia-specific (eg, systemic embolism in atrial fibrillation)

ICD, implantable cardioverter-defibrillator.

Postclass Engaged Learning Activity

A 71-year-old male presents to the electrophysiology clinic for interrogation of his ICD and follow-up. He complains of occasional fatigue that began a couple months ago. Otherwise, he denies chest pain, dizziness, blurred vision, headache, shortness-of-breath, palpitations, proxysymal noctural dyspnea, or orthopnea.

Past Medical History

Coronary artery disease; s/p MI and CABG × 3 vessels 2014
Hyperlipidemia
History of reflux esophagitis
Hypertension
Obstructive sleep apnea
Depression

Heart Failure s/p ICD for primary prevention

Current Medications

1. Aspirin 81mg daily
2. Carvedilol 25 mg twice daily
3. Lisinopril 20 mg daily
4. Omeprazole 40 mg daily
5. Paroxetine 10 mg daily
6. Simvastatin 40 mg qhs
7. Digoxin 125 mcg daily

Vitals BP 105/65 mmHg, HR 74 beats/min irregularly irregular, RR 23, Temp 99, IBW 75 kg

ECHO ejection fraction 30% (0.30); moderate-severely dilated left atrium, moderately dilated right atrium, mild LVH

ECG atrial fibrillation; HR 76 beats/min, QTc 432 ms

ICD interrogation in last 3 months 7 episodes of AF, longest episode 13 hours

Labs SCr = 1.6 mg/dL (141 µmol/L), CrCl = 35.38 mL/min (0.59 mL/s), K+ = 3.2 mEq/L (mmol/L), Mg = 1.8 mEq/L (0.90 mmol/L)

Impression: Newly diagnosed atrial fibrillation

Please answer the following questions regarding this case.

1. What classification of atrial fibrillation does this patient have?
2. List the risk factors for the development of atrial fibrillation in this case?
3. What is the patient's CHA_2DS_2-VASc score?
4. Does the patient need to be anticoagulated; if so, what is an appropriate treatment regimen?
5. The physician has decided to pursue rhythm control in this patient. Is rhythm control a good option for this patient? Explain your rationale.
6. For the following medications, determine if it would be APPROPRIATE or INAPPROPRIATE for the treatment of AF in this case: flecainide, dronedarone, dofetilide, and mexiletine.
7. The physician has decided to start amiodarone in this patient. What parameters need to be monitored and how often?
8. What patient education would you provide regarding amiodarone?

After 1 year of successful therapy with amiodarone, the patient develops fibrotic changes on chest x-ray. He is admitted to the hospital for dofetilide initiation. Two days later you are responding to a code that was called because he was found unconscious while in torsades de pointes.

1. What is the most likely cause of torsades de pointes in this case?
2. How should torsades de pointes be treated in this case?

ABBREVIATIONS

AAD	antiarrhythmic drug
ACC	American College of Cardiology
AF	atrial fibrillation
AF-CHF	Atrial Fibrillation and Congestive Heart Failure
AFFIRM	Atrial Fibrillation Follow-Up Investigation of Rhythm Management
AFl	atrial flutter
AHA	American Heart Association
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
AV	atrioventricular
AVNRT	atrioventricular nodal reentrant tachycardia
AVRT	atrioventricular reentrant tachycardia
AVID	Antiarrhythmics Versus Implantable Defibrillators
CAD	coronary artery disease
CASH	Cardiac Arrest Study Hamburg

CAST	Cardiac Arrhythmia Suppression Trial
CCB	calcium channel blocker
CIDS	Canadian Implantable Defibrillator Study
CPR	cardiopulmonary resuscitation
CrCl	creatinine clearance
CV	cardiovascular
CYP	cytochrome P450
DAD	delayed afterdepolarization
DCC	direct current cardioversion
DHP	dihydropyridine
DOAC	direct oral anticoagulants
EAD	early afterdepolarization
ECC	emergency cardiovascular care
ECG	electrocardiogram
ENGAGE AF-TIMI	Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction
FDA	Food and Drug Administration
HF	heart failure
HF*p*EF	heart failure with preserved ejection fraction
HF*r*EF	heart failure with reduced ejection fraction
HOT-CAFE	How to Treat Chronic Atrial Fibrillation
HRS	Heart Rhythm Society
ICD	implantable cardioverter-defibrillator
INR	international normalized ratio
IV	intravenous
J	joules
LMWH	low-molecular-weight heparin
LV	left ventricular
LVEF	left ventricular ejection fraction
MADIT	Multicenter Automatic Defibrillator Implantation Trial
MI	myocardial infarction
MUSTT	Multicenter Unsustained Tachycardia Trial
NYHA	New York Heart Association
P-gp	P-glycoprotein
PIAF	Pharmacological Intervention in Atrial Fibrillation
PSVT	paroxysmal supraventricular tachycardia
PVC	premature ventricular complex
PVI	pulmonary vein isolation
RACE	Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation
RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy
RMP	resting membrane potential
ROCKET-AF	Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
SA	sinoatrial
SCD	sudden cardiac death
SCD-HeFT	Sudden Cardiac Death in Heart Failure Trial
SHD	structural heart disease
SND	sinus node dysfunction
SR	sinus rhythm
STAF	Strategies of Treatment of Atrial Fibrillation
TdP	torsades de pointes
TE	thromboembolic
TEE	transesophageal echocardiography
TTR	time in therapeutic range
UFH	unfractionated heparin
VF	ventricular fibrillation
VT	ventricular tachycardia
WPW	Wolff-Parkinson-White

REFERENCES

1. Alice MA, Bonke FIM, Schopman FJG. Circus movement in rabbit atrial muscle as a mechanism of tachycardia III. The “leading circle” concept: A new model of circus movement in cardiac tissue without the involvement of an anatomic obstacle. *Circ Res*. 1977;41:9–18.
2. Vaughan Williams EM. A classification of antiarrhythmic actions reassessed after a decade of new drugs. *J Clin Pharmacol*. 1984;24:129–147.
3. Hondeghem LM, Katzung BG. Antiarrhythmic agents: The modulated receptor mechanism of action of sodium and calcium channel-blocking drugs. *Annu Rev Pharmacol Toxicol*. 1984;24:387–423.
4. Nasr IR, Bouzamondo A, Hulot JS, et al. Prevention of atrial fibrillation onset by beta-blocker treatment in heart failure: A meta-analysis. *Eur Heart J*. 2007;28:457–462.
5. Makkar KM, Sanoski CA, Spinler SA. Role of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and aldosterone antagonists in the prevention of atrial and ventricular arrhythmias. *Pharmacotherapy*. 2009;29:31–48.
6. Podrid PJ. Proarrhythmia, a serious complication of antiarrhythmic drugs. *Curr Cardiol Rep*. 1999;1:289–296.
7. Fang MC, Stafford RS, Ruskin JN, et al. National trends in antiarrhythmic and antithrombotic medication use in atrial fibrillation. *Arch Intern Med*. 2004;164:55–60.
8. Sanoski CA, Bauman JL. Clinical observations with the amiodarone/warfarin interaction: Dosing relationships with long-term therapy. *Chest*. 2002;121:19–23.
9. Camus P, Martin WJ, Rosenow EC. Amiodarone pulmonary toxicity. *Clin Chest Med*. 2004;25:65–75.
10. Babatin M, Lee SS, Pollak PT. Amiodarone hepatotoxicity. *Curr Vasc Pharmacol*. 2008;6:228–236.
11. Sanoski C, Schoen MD, Gonzalez RD, et al. Rationale, development and outcomes of a multidisciplinary clinic for patients receiving chronic oral amiodarone. *Pharmacotherapy*. 1998;18:1465–1515.
12. Epstein AE, Olshansky B. Naccarelli GV, et al. Practical management

guide for clinicians who treat patients with amiodarone. *Am J Med*. 2016;129:468–475.

13. Jahn S, Zollner G, Lackner C, Stauber B. Severe toxic hepatitis associated with dronedarone. *Curr Drug Saf*. 2013;8:201–202.
14. Siu CW, Wong MP, Ho CM, et al. Fatal lung toxic effects related to dronedarone use. *Arch Intern Med*. 2012;172:516–517.
15. Young C, Maruthappu M, Wayne RP, Leaver L. Reversible acute kidney injury requiring haemodialysis five days after starting dronedarone in a stable 71-year-old man at risk of cardiovascular polypharmacy. *J R Coll Physicians Edinb*. 2013;43:122–125.
16. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics - 2018 update: A report from the American Heart Association. *Circulation*. 2018;137:e67–e492.
17. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: The AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001;285:2370–2375.
18. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*. 2006;114:119–125.
19. Colilla S, Crow A, Petkun W, et al. Estimates of current and future incidence and prevalence of atrial fibrillation in the US adult population. *Am J Cardiol*. 2013;112:1142–1147.
20. Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for developing atrial fibrillation: The Framingham Heart Study. *Circulation*. 2004;110:1042–1046.
21. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014;(64):e1–e76.
22. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: Analysis of pooled data from five randomized controlled trials. *Arch Intern Med*. 1994;154:1449–1457.
23. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. *Stroke*. 1991;22:983–988.

24. Turakhia MP, Santangeli P, Winkelmayer WC, et al. Increased mortality associated with digoxin in contemporary patients with atrial fibrillation: Findings from the TREAT-AF Study. *J Am Coll Cardiol*. 2014;64:660–668.
25. Eisen A, Ruff CT, Braunwald E, et al. Digoxin use and subsequent clinical outcomes in patients with atrial fibrillation with or without heart failure in the ENGAGE AF-TIMI 48 Trial. *J Am Heart Assoc*. 2017;6(7). pii:e006035. doi:10.1161/JAHA.117.006035.
26. Phillips BG, Gandhi AJ, Sanoski CA, et al. Comparison of intravenous diltiazem and verapamil for the acute treatment of atrial fibrillation and flutter. *Pharmacotherapy*. 1997;17:1238–1245.
27. Hohnloser SH, Kuck KH, Lilienthal J. Rhythm or rate control in atrial fibrillation—Pharmacological Intervention in Atrial Fibrillation (PIAF): A randomised trial. *Lancet*. 2000;356:1789–1794.
28. Van Gelder IC, Hagens VE, Bosker HA, et al. The Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation Study Group. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med*. 2002;347:1834–1840.
29. The Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;347:1825–1833.
30. Carlsson J, Miketic S, Windeler J, et al. Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: The Strategies of Treatment of Atrial Fibrillation (STAF) study. *J Am Coll Cardiol*. 2003;41:1690–1696.
31. Opolski G, Torbicki A, Kosior DA, et al. Rate control vs rhythm control in patients with nonvalvular persistent atrial fibrillation: The results of the Polish How to Treat Chronic Atrial Fibrillation (HOT CAFE) Study. *Chest*. 2004;126:476–486.
32. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med*. 2008;358:2667–2677.
33. de Denus S, Sanoski CA, Carlsson J, Opolski G, Spinler SA. Rate vs rhythm control in patients with atrial fibrillation: A meta-analysis. *Arch Intern Med*. 2005;165:258–262.
34. Van Gelder IC, Groenveld HF, Crijns HJ, et al. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med*. 2010;362:1363–1373.

35. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. *Chest*. 2018;154:1121–1201.
36. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guidelines for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2019. doi:10.1161/CIR.0000000000000665.
37. Caldeira D, Costa J, Ferreira JJ, Lip GYH, Pinto FJ. Non-vitamin K oral anticoagulants in the cardioversion of patients with atrial fibrillation: systemic review and meta-analysis. *Clin Res Cardiol*. 2015;104:582–590.
38. Alboni P, Botto GL, Baldi N, et al. Outpatient treatment of recent-onset atrial fibrillation with the “pill-in-the-pocket” approach. *N Engl J Med*. 2004;351:2384–2391.
39. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151.
40. Liesenfeld KH, Lehr T, Dansirikul C, et al. Population pharmacokinetic analysis of the oral thrombin inhibitor dabigatran etexilate in patients with non-valvular atrial fibrillation from the RE-LY trial. *J Thromb Haemost*. 2011;9:2168–2175.
41. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med*. 2013;369:1206–1214.
42. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891.
43. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992.
44. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369:2093–2104.
45. Haas S, Ten Cate H, Accetta G, et al. Quality of vitamin K antagonist control and 1-year outcomes in patients with atrial fibrillation: A global perspective from the GARFIELD-AF registry. *PloS One*. 2016;11(10):e0164076. doi.10.1371/journal.pone.0164076.
46. Patel MR, Hellkamp AS, Lokhnygina Y, et al. Outcomes of discontinuing rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: Analysis from the ROCKET AF trial (Rivaroxaban Once-

Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation). *J Am Coll Cardiol*. 2013;61:651–658.

47. Coplen SE, Antman EM, Berlin JA, et al. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion: A meta-analysis of randomized control trials. *Circulation*. 1990;82:1106–1116.
48. Echt DS, Liebson PR, Mitchell B, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. *N Engl J Med*. 1991;324:781–788.
49. Lafuente-LaFuente C, Mouly S, Longás-Tejero MA, et al. Antiarrhythmic drugs for maintaining sinus rhythm after cardioversion of atrial fibrillation. *Arch Intern Med*. 2006;166:719–728.
50. Roy D, Talajic M, Dorian P, et al. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. *N Engl J Med*. 2000;324:913–920.
51. AFFIRM First Antiarrhythmic Drug Substudy Investigators. Maintenance of sinus rhythm in patients with atrial fibrillation: An AFFIRM substudy of the first antiarrhythmic drug. *J Am Coll Cardiol*. 2003;42:20–29.
52. Singh BN, Singh SN, Reda DJ, et al. Amiodarone versus sotalol for atrial fibrillation. *N Engl J Med*. 2005;352:1861–1872.
53. Juul-Moller S, Edvardsson N, Rehnqvist-Ahlberg N. Sotalol versus quinidine for the maintenance of sinus rhythm after direct current conversion of atrial fibrillation. *Circulation*. 1990;82:1932–1939.
54. Southworth MR, Zarembski D, Viana M, Bauman JL. Comparison of sotalol versus quinidine for maintenance of normal sinus rhythm in patients with chronic atrial fibrillation. *Am J Cardiol*. 1999;83:1629–1632.
55. Singh S, Zoble RG, Yellen L, et al. Efficacy and safety of oral dofetilide in converting and maintaining sinus rhythm in patients with chronic atrial fibrillation or atrial flutter. The Symptomatic Atrial Fibrillation Investigative Research on Dofetilide (SAFIRE-D) Study. *Circulation*. 2000;102:2385–2390.
56. Pedersen OD, Bagger H, Keller N, et al. Efficacy of dofetilide in the treatment of atrial fibrillation-flutter in patients with reduced left ventricular function, a Danish Investigation of Arrhythmia and Mortality on Dofetilide (DIAMOND) Substudy. *Circulation*. 2001;104:292–296.
57. Singh BN, Connolly SJ, Crijns HJGM, et al. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med*.

2007;357:987–999.

58. Hohnloser SH, Crijns HJGM, van Eickels M, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med*. 2009;360:668–678.
59. Køber L, Torp-Pedersen C, McMurray JJV, et al. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med*. 2008;358:2678–2687.
60. Le Heuzey JY, De Ferrari GM, Radzik D, et al. A short-term, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of dronedarone versus amiodarone in patients with persistent atrial fibrillation: The DIONYSOS study. *J Cardiovasc Electrophysiol*. 2010;21:597–605.
61. Connolly SJ, Camm AJ, Halperin JL, et al. Dronedarone in high-risk permanent atrial fibrillation. *N Engl J Med*. 2011;365:2268–2276.
62. Spector P, Reynolds MR, Calkins H, et al. Meta-analysis of ablation of atrial flutter and supraventricular tachycardia. *Am J Cardiol*. 2009;104:671–677.
63. Page RL, Joglar JA, Caldwell MA, et al. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2016;133:e506–e574.
64. Pappone C, Augello G, Sala S, et al. A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: The APAF Study. *J Am Coll Cardiol*. 2006;48:2340–2347.
65. Oral H, Pappone C, Chugh A, et al. Circumferential pulmonary-vein ablation for chronic atrial fibrillation. *N Engl J Med*. 2006;354:934–941.
66. Wilber DJ, Pappone C, Neuzil P, et al. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: A randomized controlled trial. *JAMA*. 2010;303:333–340.
67. Marrouche NF, Brachmann J, Andresen D, et al. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med*. 2018;378:417–427.
68. Morillo C, Verma A, Kuck A, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT 2): A randomized trial. *JAMA*. 2014;311:692–700.

69. Cosedis NJ, Johannessen A, Raatkainen P, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. *N Engl J Med*. 2012;367:1587–1595.
70. Cappato R, Calkins H, Chen SA, et al. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2010;3:32–38.
71. Porter MJ, Morton JB, Denman R, et al. Influence of age and gender on the mechanism of supraventricular tachycardia. *Heart Rhythm*. 2004;1:393–396.
72. Sung RJ, Lauer MR, Chun H. Atrioventricular node reentry: Current concepts and new perspectives. *Pacing Clin Electrophysiol*. 1994;17:1413–1430.
73. DiMarco JP, Miles W, Akhtar M, et al. Adenosine for paroxysmal supraventricular tachycardia: Dose ranging and comparison with verapamil. Assessment in placebo-controlled, multicenter trials. *Ann Intern Med*. 1990;1113:104–110.
74. Jackman WM, Wang Z, Friday KJ, et al. Catheter ablation of accessory atrioventricular pathways (Wolff-Parkinson-White syndrome) by radiofrequency current. *N Engl J Med*. 1991;324:1605–1611.
75. Jackman WM, Beckman KJ, McClelland JH, et al. Treatment of supraventricular tachycardia due to atrioventricular nodal reentry by radiofrequency catheter ablation of slow pathway conduction. *N Engl J Med*. 1992;327:313–318.
76. Cheng CH, Sanders GD, Hlatky MA, et al. Cost effectiveness of radiofrequency ablation for supraventricular tachycardia. *Ann Intern Med*. 2000;133:864–876.
77. Meyer L, Stubbs B, Fahrenbruch C, et al. Incidence, causes, and survival trends from cardiovascular related sudden cardiac arrest in children and young adults 0 to 35 years of age: A 30-year review. *Circulation*. 2012;126:1363–1372.
78. Bayes deLuna A, Coumel P, LeClercq IF. Ambulatory sudden cardiac death: Mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. *Am Heart J*. 1989;117:151–159.
79. Ruberman W, Weinblatt E, Goldberg JD, et al. Ventricular premature beats and mortality after myocardial infarction. *N Engl J Med*. 1977;297:750–757.
80. The Cardiac Arrhythmia Suppression Trial II Investigators. Effect of the

antiarrhythmic agent moricizine on survival after myocardial infarction. *N Engl J Med*. 1992;327:227–233.

81. Waldo AL, Camm AJ, deRuyter H, et al. Effect of d-sotalol on mortality in patients with left ventricular dysfunction and remote myocardial infarction. *Lancet*. 1996;348:7–12.
82. Julian DG, Camm AJ, Frangin G, et al. Randomized trial of effect of amiodarone on mortality in patients with left ventricular dysfunction after recent myocardial infarction: EMIAT. *Lancet*. 1997;349:667–674.
83. Cairns JA, Connolly SJ, Roberts R, et al. Randomized trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarizations: CAMIAT. *Lancet*. 1997;349:675–682.
84. Torp-Pederson C, Moller M, Bloch-Thomsen PE, et al. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. *N Engl J Med*. 1999;341:857–865.
85. Kober L, Block-Thomsen PE, Moller M, et al. Effect of dofetilide in patients with recent myocardial infarction and left ventricular dysfunction: A randomized trial. *Lancet*. 2000;356:2052–2058.
86. Hilleman DE, Bauman JL. Role of antiarrhythmic therapy in patients at risk for sudden cardiac death: An evidence-based review. *Pharmacotherapy*. 2001;21:556–575.
87. Edhouse J, Morris F. Broad complex tachycardia—Part I. *BMJ*. 2002;312:719–722.
88. Edhouse J, Morris F. Broad complex tachycardia—Part II. *BMJ*. 2002;324:776–779.
89. Cole CR, Marrouche NF, Natale A. Evaluation and management of ventricular outflow tract tachycardias. *Card Electrophysiol Rev*. 2002;6:442–447.
90. Modell SM, Lehmann MH. The long QT syndrome family of cardiac ion channelopathies: A HuGE review. *Genet Med*. 2006;8:143–155.
91. Antzelevitch C, Brugada P, Brugada J, et al. Brugada syndrome: 1992–2002: A historical perspective. *J Am Coll Cardiol*. 2003;41:1665–1671.
92. 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care science. *Circulation*. 2010;122:5640–5933.
93. Ortiz M, Martin A, Arribas F, et al. Randomized comparison of

intravenous procainamide vs. intravenous amiodarone for the acute treatment of tolerated wide QRS tachycardia: the PROCAMIO study. *Eur Heart J*. 2017;38:1329–1335.

94. Mason JW, Electrophysiologic Study Versus Electrocardiographic Monitoring Investigators. A comparison of electrophysiologic testing with Holter monitoring to predict antiarrhythmic drug efficacy for ventricular tachyarrhythmias. *N Engl J Med*. 1993;329:445–451.
95. Mason JW, Electrophysiologic Study Versus Electrocardiographic Monitoring Investigators. A comparison of seven antiarrhythmic drugs in patients with ventricular tachyarrhythmias. *N Engl J Med*. 1993;329:452–458.
96. The Cascade Investigators. Randomized antiarrhythmic drug therapy in survivors of cardiac arrest (the CASCADE Study). *Am J Cardiol*. 1993;72:280–287.
97. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2018;138:e272–e391.
98. Sapp JL, Wells GA, Parkash R, et al. Ventricular tachycardia ablation versus escalation of antiarrhythmic drugs. *N Engl J Med*. 2016;375:111–121.
99. DiMarco JP. Implantable cardioverter-defibrillators. *N Engl J Med*. 2003;349:1836–1847.
100. Pacifico A, Hohnloser SH, Williams JH, et al. Prevention of implantable-defibrillator shocks by treatment with sotalol. *N Engl J Med*. 1999;340:1855–1862.
101. Connolly SJ, Dorian P, Roberts RS, et al. Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: The OPTIC Study: A randomized trial. *JAMA*. 2006;295:165–171.
102. Dopp AL, Miller JM, Tisdale JE. Effects of drugs on defibrillation capacity. *Drugs*. 2008;68:607–630.
103. The AVID Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med*. 1997;337:1576–1583.

104. Connolly SJ, Gene M, Roberts TS, et al. Cardiac Implantable Defibrillator Study (CIDS): A randomized trial of the implantable cardioverter-defibrillator against amiodarone. *Circulation*. 2000;101:1297–1302.
105. Kuck KH, Cappato R, Siebels J, et al. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: The Cardiac Arrest Study Hamburg (CASH). *Circulation*. 2000;102:748–754.
106. Wilber DJ, Olshansky B, Moran JF, et al. Electrophysiological testing and nonsustained VT. Use and limitations in patients with coronary artery disease and impaired ventricular function. *Circulation*. 1990;82:350–358.
107. Buxton AE, Leek KL, DiCarlo L, et al. Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. Multicenter Unsustained Tachycardia Trial. *N Engl J Med*. 2000;342:1937–1945.
108. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *N Engl J Med*. 1996;335:1933–1940.
109. Buxton AE, Lee KL, Fisher JD, et al. A randomized study of the prevention of sudden death in patients with coronary artery disease. *N Engl J Med*. 1999;341:1882–1890.
110. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002;346:877–883.
111. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med*. 2005;352:225–237.
112. Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2013;61:e6–e75.
113. Antzelevitch C. Heterogeneity of cellular repolarization in LQTS: The role of M cells. *Eur Heart J*. 2001;3:K2–K16.
114. Roden DM. Long QT syndrome: Reduced repolarization reserve and the genetic link. *J Intern Med*. 2006;259:59–69.
115. Oberg KC, O'Toole MF, Gallastegui JL, Bauman JL. "Late"

proarrhythmia due to quinidine. *Am J Cardiol*. 1994;74:192–194.

116. Schwartz PJ, Woosley RL. Predicting the unpredictable: Drug-induced QT prolongation and torsades de pointes. *J Am Coll Cardiol*. 2016;67:1639–1650.
117. Bauman JL. The role of pharmacokinetics, drug interactions and pharmacogenetics in the acquired long QT syndrome. *Eur Heart J*. 2001;3:K93–K100.
118. Koplan BA, Stevenson WG. Ventricular tachycardia and sudden cardiac death. *Mayo Clin Proc*. 2009;84:289–297.
119. Panchal AR, Berg KM, Kudenchuk PJ, et al. 2018 American Heart Association focused update on advanced cardiovascular life support use of antiarrhythmic drugs during and immediately after cardiac arrest: An update to the American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2018(138):e740–e749.
120. Amin V, Pavri BB. Carotid sinus syndrome. *Cardiol Rev*. 2015;23:130–134.
121. Milstein S, Reyes WJ, Benditt DG. Upright body tilt for evaluation of patients with recurrent, unexplained syncope. *Pacing Clin Electrophysiol*. 1989;12:117–124.
122. Almquist A, Goldenberg I, Milstein S. Provocation of bradycardia and hypotension by isoproterenol and upright posture in patients with unexplained syncope. *N Engl J Med*. 1990;320:346–351.
123. Brignole M. Randomized clinical trials of neurally mediated syncope. *J Cardiovasc Electrophysiol*. 2003;14(Suppl):S64–S69.
124. Sheldon R, Connolly S, Rose S, for the POST Investigators. Prevention of Syncope Trial (POST). A randomized, placebo-controlled study of metoprolol in the prevention of vasovagal syncope. *Circulation*. 2006;113:1164–1170.
125. Armaganijan L, Morillo CA. Treatment of vasovagal syncope: An update. *Curr Treat Options Cardiovasc Med*. 2010;12:472–488.
126. Kupersmith J, Holmes-Novner M, Hogan A, et al. Cost-effectiveness analysis in heart disease, I: General principles. *Prog Cardiovasc Dis*. 1994;37:161–184.
127. Kupersmith J, Holmes-Novner M, Hogan A, et al. Cost-effectiveness analysis in heart disease, III: Ischemia, congestive heart failure, and arrhythmias. *Prog Cardiovasc Dis*. 1995;37:307–346.

128. Sanders GD, Hlatky MA, Owens DK. Cost-effectiveness of implantable cardioverter-defibrillators. *N Engl J Med*. 2005;353:1471–1480.

40

Cardiac Arrest

Jeffrey F. Barletta

KEY CONCEPTS

1. High-quality cardiopulmonary resuscitation with minimal interruptions in chest compressions should be delivered to all patients following cardiac arrest.
2. The AHA algorithm for basic life support emphasizes circulation, airway, and breathing, forming the mnemonic "CAB."
3. The purpose of using vasopressor therapy following cardiac arrest is to augment coronary and cerebral perfusion pressures.
4. Vasopressin appears to offer no benefit as a substitute for epinephrine.
5. Successful treatment of both pulseless electrical activity (PEA) and asystole depends on determining the underlying cause.
6. Intraosseous administration is the preferred alternative route when IV access cannot be achieved.

Preclass Engaged Learning Activity

Review the American Heart Association (AHA) algorithms for BLS and ACLS. Create a table which lists the medications that are recommended in the guidelines that might be used, when they might be used, and what the intended purpose of their use is. All guidelines for cardiopulmonary resuscitation and emergency cardiac care can be found at https://tinyurl.com/zy2efpq

INTRODUCTION

Cardiac arrest is defined as the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation (eg, a detectable pulse, unresponsiveness, and apnea).[1] While there is wide variation in the reported incidence of cardiac arrest, it is estimated that there are more than 350,000 people in the United States who are assessed by emergency medical services (EMS) for a suspected out-of-hospital cardiac arrest each year.[1] Survival to hospital discharge following out-of-hospital cardiac arrest is only 11.4% and survival with good neurologic function is even lower.[1] While there has been a minimal change over the last 40 years, the survival rate for out-of-hospital cardiac arrest improved slightly during the last reported observation period between 2005 and 2012.[2] This improvement was seen in both prehospital and in-hospital survival.

In-hospital cardiac arrests occur in roughly 209,000 patients in the United States annually.[1] Similar to out-of-hospital arrests, some progress has also been made over the past decade in in-hospital cardiac arrests, with survival rates to hospital discharge increasing from roughly 16% in 2000 to 24% in 2015.[1] Survival rates are substantially higher in victims with a shockable rhythm (ie, those that are treated with electrical defibrillation). One study reported survival rates of 49% compared to 11% with nonshockable rhythms.[3]

EPIDEMIOLOGY

Cardiac arrest can arise from either cardiac or noncardiac origins (eg, submersion, asphyxia, trauma, overdose, etc.). In adult patients, cardiac arrest usually results from the development of an arrhythmia. Historically, ventricular fibrillation (VF) and pulseless ventricular tachycardia (PVT) have been the most common initial rhythms seen in out-of-hospital arrests, but these are now seen in less than one-quarter of cases.[1] In fact, data from the Cardiac Arrest Registry to Enhance Survival (CARES) project reported asystole to be the most common presenting rhythm (47.3%), which is similar to other registry data whereby nonshockable rhythms (ie, asystole, PEA) were more prevalent.[4] It is unclear why there has been a change in the types of arrhythmias that most commonly lead to cardiac arrest. Possible explanations include the increasing incidence of noncardiac causes of arrest that present with apnea leading to bradycardia and then pulseless electrical activity (PEA) or asystole. A second explanation might be the increasing role of implantable pacemakers and defibrillators.[5] Finally, beta-blockers and ACE inhibitors may shorten the duration of VF, and the

expanded use of these drug classes for ischemic heart disease and heart failure may account for the increased occurrence of non-VF/PVT rhythms.[6] This change in the presenting rhythm types is concerning because survival rates to hospital discharge are substantially higher with shockable rhythms like VF and PVT (30%) compared to nonshockable rhythms like PEA and asystole (6%).[4]

A similar finding has been observed with in-hospital cardiac arrest. One study using the "Get with the Guidelines-Resuscitation" registry reported that 79% of patients had an initial rhythm of asystole or PEA and only 21% had VF or PVT.[7] Survival rates were 12.2% for asystole/PEA and 35% for VF/PVT.

In pediatric patients, cardiac arrest typically results from respiratory failure and asphyxiation. As such, the initial rhythm most often encountered in out-of-hospital arrest is PEA or asystole.[7] Survival rate with out-of-hospital pediatric arrests is roughly 13% and is lower in infants when compared to children and adolescents.[8] Survival following in-hospital cardiac arrest is much higher (45%) and most survivors have a favorable neurologic outcome (89%).[9] Similar to the adult population, risk-adjusted survival rates have increased over the past decade from 14% in 2000 to 43% in 2009.[10]

ETIOLOGY

The most common clinical finding in adult patients who suffer cardiac arrest is coronary artery disease, accounting for roughly 75% of sudden cardiac deaths.[11] Other causes of sudden cardiac death include cardiomyopathies, valvular heart disease, myocarditis, hypertrophy, primary electrical heart disease, and noncardiac causes. Unfortunately, in many patients (up to 69%), cardiac arrest is the first clinical sign of coronary artery disease with no preceding signs or symptoms.[11]

CLINICAL PRESENTATION

General: Cardiac arrest is characterized by the cessation of cardiac mechanical activity. General signs and symptoms are consistent with a sudden cessation of circulation.

Symptoms (occurring prior to the event)

- Anxiety
- Crushing chest pain

- Nausea
- Vomiting
- Diaphoresis

Signs

- Apnea
- Hypotension
- Lack of a detectable pulse
- Cyanosis
- Cold, clammy extremities

In pediatric patients, cardiac arrest is often the terminal event of respiratory failure or progressive shock.[12] Out-of-hospital arrests frequently are associated with trauma, sudden infant death syndrome, drowning, poisoning, choking, severe asthma, and pneumonia. In-hospital arrests, on the other hand, are associated with sepsis, respiratory failure, drug toxicity, metabolic disorders, and arrhythmias.

PATHOPHYSIOLOGY OF CARDIAC ARREST

There are two distinct pathophysiologic conditions associated with cardiac arrest. The first is primary cardiac arrest whereby arterial blood is fully oxygenated at the time of arrest. As forward blood flow ceases, arterial blood oxygenation remains normal for about 10 minutes and subsequently declines due to the lack of ventilation.[13] Alternatively, respiratory failure can lead to severe hypoxemia, hypotension, and secondary cardiac arrest. It is important to identify the underlying pathophysiology as different treatment approaches are required.[13]

TREATMENT

Desired Outcome

The global goals of resuscitation are to preserve life, restore health, relieve

suffering, limit disability, and respect the individual's decisions, rights, and privacy.[14] This can be accomplished via CPR by the return of spontaneous circulation (ROSC) with effective perfusion and ventilation as quickly as possible to minimize hypoxic damage to vital organs. Survival to hospital discharge with good neurologic function should be the primary treatment outcome sought by clinicians. Survival to hospital discharge in a vegetative or comatose state cannot be classified as a success and can impose a tremendous economic burden on the healthcare system.

The presence of a healthcare advanced directive allows patients to communicate their wishes and preferences regarding medical care and may lead to a "do not attempt resuscitation" order. These orders should explicitly state the resuscitation interventions that are to be performed and should have been clearly communicated by the patient, their family, or a surrogate decision-maker.

General Approach to Treatment

Cardiopulmonary Resuscitation

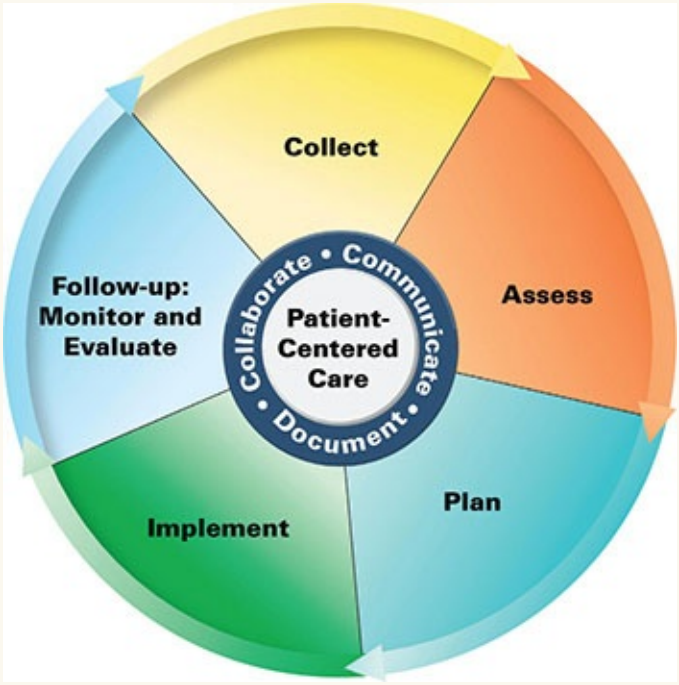
Resuscitation techniques have been studied for many years. In 1960, Kouwenhoven described positive outcomes in 14 of 20 patients with in-hospital cardiac arrest who were given closed chest compressions at a rate of 60 per minute.[15] Following the publication of this landmark article, chest compressions integrated with expired air ventilation (ie, mouth-to-mouth) became the fundamentals of basic life support known as the "ABC's."[16]

Cardiopulmonary resuscitation (CPR) employs chest compressions to restore threshold blood flows, particularly to the heart and brain. There are two proposed explanations to describe how chest compression improves blood flow during CPR.[17] The original explanation is known as the cardiac pump theory whereby compression of the heart between the sternum and vertebrae creates forward flow. However, echocardiography during chest compressions has revealed that the left ventricular size does not always change and the mitral valve may not close.[17] The second explanation is the thoracic pump theory whereby intrathoracic pressure changes during chest compressions and the heart merely acts as a passive conduit for flow. It is likely that both cardiac compression and intrathoracic pressure changes contribute.

In 1966, the American Heart Association (AHA) first published guidelines for the treatment of cardiac arrest.[18] Since then, national conferences and certification have played a major role in encouraging widespread competency in

CPR technique. There have been many revisions of the guidelines over the years, and this is particularly true of the most recent guidelines, published in 2015.[19] The 2015 guidelines represent a new era for the AHA Guidelines for CPR and Emergency Cardiovascular Care (ECC) because they have transitioned from a 5-year revision cycle to a web-based format that is continuously updated.[20] This will allow for the more rapid application of new research findings into patient care.

1 High-quality CPR continues to be emphasized in the latest guidelines published by the AHA. Clinicians must focus on proper technique, including adequate rate and depth of compressions, allowing full chest recoil after each compression, avoiding excessive ventilation, and minimizing interruptions.[21] There is an association between survival to hospital discharge and chest compression rate (optimally between 100 and 120 beats/minute), chest compression depth (optimally 40–54 mm), and chest compression fraction (optimally the proportion of resuscitation time without spontaneous circulation when chest compressions are administered should be ≥60%).[22] Unfortunately, the provision of CPR is frequently sub-optimal, particularly when rescuers become fatigued.[23] As a result, mechanical devices to provide consistent high-quality chest compressions have been developed. Animal studies have shown that cerebral blood flow is greater with these devices compared to manual compression but human studies have not demonstrated improvements in survival.[24] This could be due to time delays and a decrease in chest compression fraction when these devices are deployed. In addition to mechanical devices to deliver chest compressions, several devices can provide feedback in “real time” to assist with CPR quality. Data demonstrating improvement in survival, however, are lacking.[24]



Patient Care Process for Cardiac Arrest

Collect*

- Patient characteristics (eg, sex, age)
- Patient medical history (if available)
- Current and past medications that could have contributed to the arrest or serve as a clue to the underlying medical history
- Objective data
  - Presence of a pulse
  - Cardiac rhythm

Assess*

- Is the patient responsive?
- Is there a pulse present?
- Are the ECG leads correctly placed on the patient?
- Is the rhythm shockable?

Plan*

- Activate EMS and obtain an AED if one is nearby (for out-of-hospital arrest)
- Call for “code blue” and obtain crash cart (for in-hospital arrest)
- Immediately begin chest compressions and follow BLS algorithm
- Administer electrical therapy (ie, defibrillation) if indicated
- Drug therapy per advanced cardiac life support (ACLS) algorithm if indicated
- Monitor for the return of spontaneous circulation, cardiac rhythm, and pulse

Implement*

- Perform high-quality chest compressions with minimal interruptions
- Administer defibrillations and drug therapy as indicated by cardiac rhythm

Follow-up: Monitor and Evaluate*

- Monitor end-tidal CO_2 as an indicator of CPR quality
- Implement postresuscitative care plan consisting of therapeutic hypothermia if indicated
- ECG and PCI when an acute coronary syndrome is suspected
- Review patient history for identification of other contributors or underlying cause of the arrest
- Diligent monitoring of blood pressure, oxygen saturation, temperature, urine output, and glucose
- Evaluate and monitor for seizure

* *Collaborate with patient, caregivers, and other healthcare professionals.*

The 2015 guidelines continue to emphasize the “chain of survival” to highlight the treatment approach and illustrate the importance of a timely response. The updated guidelines, however, now include two separate chains: one for out-of-hospital cardiac arrest and another for in-hospital cardiac arrest.[25] This has been done to reflect the differences in the steps needed to respond to a cardiac arrest in the in-patient and out-patient settings. The five links in each chain of survival are as follows:

Out-of-hospital

1. Immediate recognition of cardiac arrest and activation of EMS
2. Early CPR with an emphasis on chest compressions
3. Rapid defibrillation
4. Effective advanced life support
5. Integrated postcardiac arrest care

In-hospital

1. Appropriate surveillance and prevention of cardiac arrest
2. Prompt notification and response by a multidisciplinary team of professional providers
3. High-quality CPR
4. Prompt defibrillation and advanced life support when appropriate
5. Integrated postcardiac arrest care

While all five links of the chain of survival are important, basic life support (BLS) is the foundation for saving lives after cardiac arrest (ie, immediate recognition, early CPR, and rapid defibrillation).[21] One large observational study compared the effects of BLS and advanced cardiac life support (ACLS) on outcomes. Survival to hospital discharge was greater among patients who received BLS (13.1% vs 9.2%).[26] CPR provides critical blood flow to the heart and brain, prolongs the time VF is present (prior to the deterioration to asystole), and increases the likelihood that a shock will terminate VF and result in a rhythm compatible with life.[21] For every minute that elapses before successful defibrillation can be administered, survival rates decrease by 7% to 10% if CPR is not provided.[27] With immediate CPR, the survival rates decline more gradually (down to 3%–4% per minute).[28] In effect, CPR can increase the likelihood of survival threefold from arrest to survival. Basic CPR alone, however, is not likely to terminate VF and lead to ROSC.

Basic Life Support 2 The mnemonic for the CPR sequence is “CAB” which stands for circulation, airway, and breathing. Historically, BLS and ACLS providers have been taught the mnemonic, “ABC.” This change was made to stress the importance of maintaining blood flow to the heart and brain and to avoid delays or interruptions to chest compressions.

When first encountering a victim, the initial action is to determine if the

patient is responsive. If there is no response, the rescuer should immediately activate the emergency medical response team, obtain (or call for) an automated external defibrillator (AED), and then immediately start CPR with chest compressions. A cardiac arrest victim will be unresponsive and it can be difficult for rescuers to determine if the victim is breathing normally. Thus, “look, listen, and feel” for respirations is not recommended as part of the initial assessment.[21] Similarly, pulse recognition is often inaccurate, and it is recommended that lay rescuers not check for a pulse. Healthcare providers could assess for a pulse but take no more than 10 seconds to do so. If one is not detected within this short time frame, then chest compressions should be immediately initiated.[21,29] Surprisingly, no study has ever shown the necessity of checking a pulse during ongoing CPR.

The prompt provision of chest compressions is of paramount importance, and rescuers should attempt them regardless of rescuer experience or skill. The teaching of BLS now focuses on delivering high-quality CPR at a rate of 100 to 120 compressions per minute, adequate depth (at least 2 in. [~50 mm] in an adult), and allowing full chest recoil while minimizing any interruptions.

The role of ventilation (ie, rescue breaths) has been deemphasized in recent years.[30] It is recommended that most lay rescuers should provide chest compression-only CPR for adults with out-of-hospital cardiac arrest. For lay rescuers trained in CPR using chest compressions and ventilation, it is reasonable to provide ventilation in addition to chest compressions. For EMS-delivered CPR, providers should perform CPR in cycles of 30 compressions and 2 breaths or alternatively 1 breath every 6 seconds for asynchronous ventilation during continuous chest compressions.

In all cases, CPR should continue until an AED arrives. The AED leads should be immediately placed on the victim so that the device can determine if the rhythm is shockable. If so, then one shock should be delivered and CPR immediately resumed for about 2 minutes or until prompted by the AED to allow for another rhythm check. If the rhythm is not shockable, CPR should resume immediately for about 2 minutes or until prompted by the AED. This cycle should be continued until advanced life support providers take over or the victim starts to move (**Figure 40-1**).

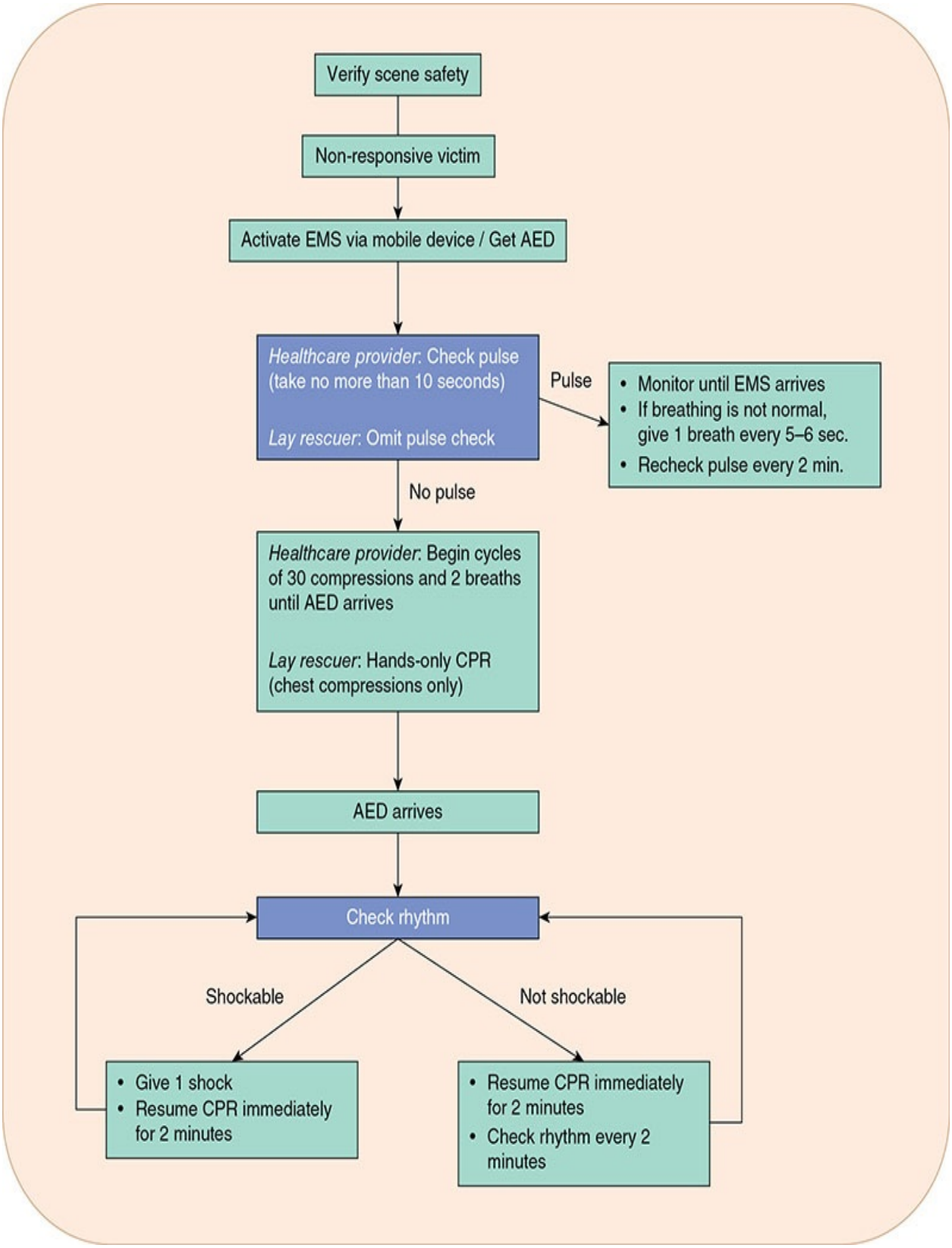


FIGURE 40-1 Treatment algorithm for adult cardiac arrest: Basic life support (BLS).

Despite widespread dissemination of CPR guidelines and the ongoing education of healthcare providers, the quality of chest compressions remains poor. Furthermore, only 40% of the time, bystanders provide CPR during out-of-hospital cardiac arrest in the United States.[4] This has led to additional educational initiatives in an attempt to improve the quality of CPR, and dispatchers now instruct callers to provide chest compression-only CPR until EMS arrives.[30]

Advanced Cardiac Life Support Once EMS or other ACLS certified providers arrive, additional therapy may be given. Either a bag-mask device or an advanced airway (eg, endotracheal tube, supraglottic device) may be utilized to provide ventilation. When this occurs, one provider can deliver 1 breath every 6 seconds while continuous chest compressions are being performed by a second provider.

Animal and human studies have shown that monitoring of end-tidal carbon dioxide, coronary perfusion pressure, and central venous oxygen saturation can provide valuable information that improves resuscitation success.[31] End-tidal carbon dioxide (ETCO2) is the concentration of carbon dioxide in exhaled air at the end of expiration. During cardiac arrest, the level of ETCO2 decreases because there is no flow through the pulmonary circulation. Thus, a persistently low ETCO2 (ie, <10 mm Hg [1.3 kPa]) during CPR in intubated patients makes ROSC unlikely.[31] One systematic review reported a mean ETCO2 of 26 mm Hg (3.5 kPa) in patients who achieved ROSC compared to 13 mm Hg (1.7 kPa) in those who did not.[32] In patients without ROSC and persistently decreased ETCO2, chest compression techniques should be evaluated. The latest guidelines recommend ETCO2 monitoring during CPR whenever possible.[31]

One shock should be administered to cardiac arrest victims who are in VF or PVT with the immediate resumption of chest compressions.[31] If there is still a shockable rhythm, then an additional shock should be delivered every 2 minutes. After 2 cycles, epinephrine is indicated. It is important that chest compressions continue while medications are being prepared and administered. This cycle is repeated until either a pulse is obtained with effective circulation, the rhythm changes, or the patient expires. If the cardiac rhythm is not deemed to be shockable, then the patient is likely to be in either asystole or PEA. In this circumstance, the rescuer must consider reversible causes. Nonetheless, CPR should be performed with epinephrine administration every 3 to 5 minutes (**Figure 40-2**).

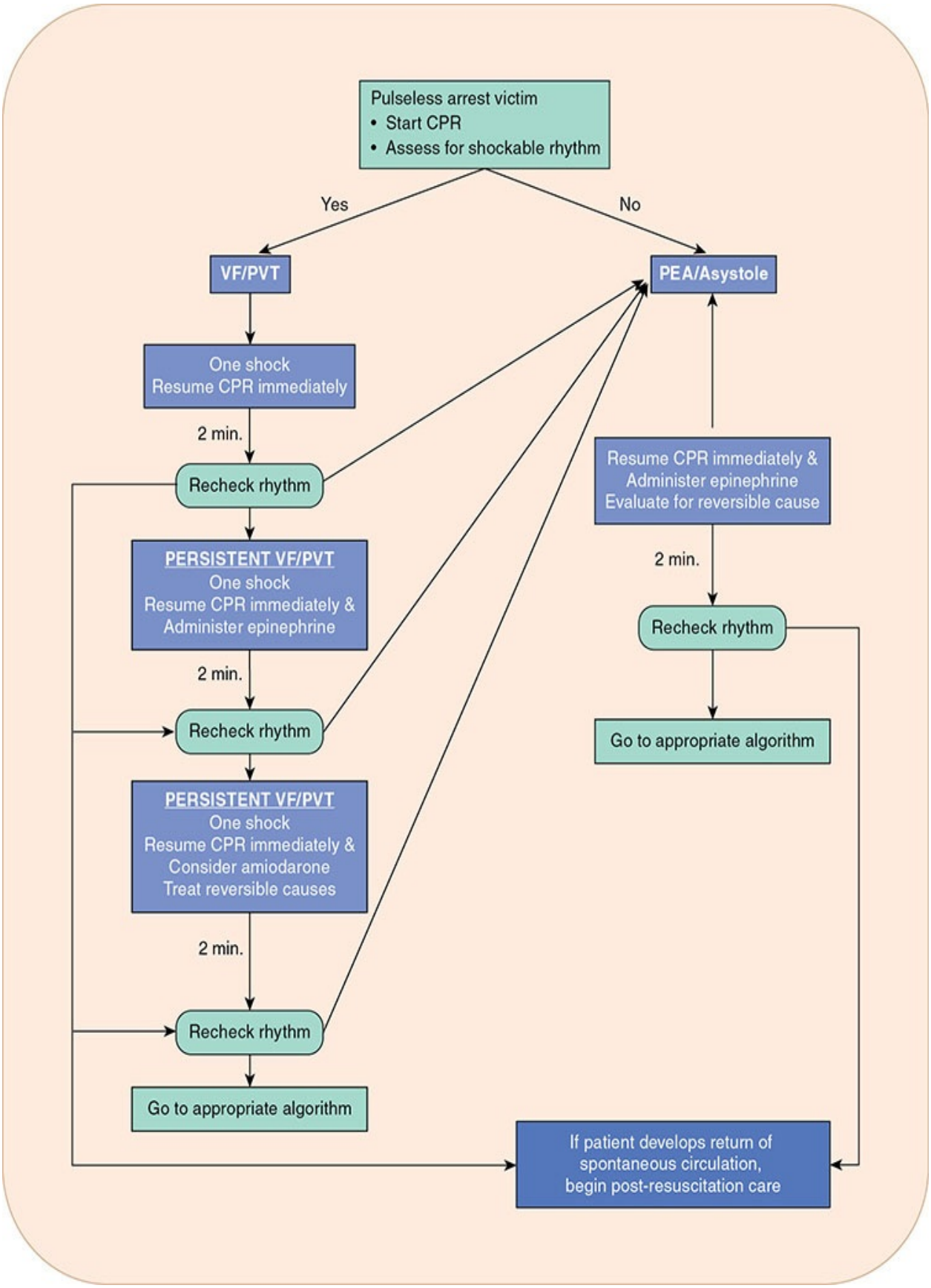

Pulseless arrest victim
• Start CPR
• Assess for shockable rhythm
Yes
No
VF/PVT
PEA/Asystole
One shock
Resume CPR immediately
2 min.
Recheck rhythm
PERSISTENT VF/PVT
One shock
Resume CPR immediately &
Administer epinephrine
2 min.
Recheck rhythm
PERSISTENT VF/PVT
One shock
Resume CPR immediately &
Consider amiodarone
Treat reversible causes
2 min.
Recheck rhythm
Go to appropriate algorithm
Resume CPR immediately &
Administer epinephrine
Evaluate for reversible cause
2 min.
Recheck rhythm
Go to appropriate algorithm
If patient develops return of
spontaneous circulation,
begin post-resuscitation care

FIGURE 40-2 Treatment algorithm for adult cardiac arrest: Advanced cardiac life support (ACLS).

Cardiocerebral Resuscitation

Cardiocerebral resuscitation (CCR) is an alternative approach for resuscitation that was developed largely because of the relative lack of progress with survival rates following an out-of-hospital cardiac arrest.[33] CCR has been embraced by the AHA guidelines and comprises three major components: a community component, an EMS component, and a hospital component.

The community component consists of prompt recognition (check), activation of EMS (call), and chest compression only CPR (compress). Chest compressions deliver a small but critical amount of oxygen to the brain and myocardium. Cerebral and coronary perfusion pressures, however, build up slowly once chest compressions are begun. These perfusion pressures are lost if chest compressions are stopped to deliver mouth-to-mouth ventilation. It has been noted that lay rescuers take approximately 16 seconds to deliver 2 breaths as recommended by earlier guidelines.[33] The loss of perfusion during this time period is extremely detrimental as ROSC is closely related to perfusion pressures generated during chest compressions.

The EMS component of CCR consists of a revised ACLS algorithm. This protocol is based on the 3-phase time-sensitive model of cardiac arrest.[34] The first phase is the electrical phase (0-5 minutes), where prompt defibrillation is the most important intervention. The second phase is the hemodynamic phase (5-15 minutes), where adequate coronary and cerebral perfusion pressures, before and after defibrillation, are crucial. Defibrillation prior to CPR in this phase commonly leads to asystole or PEA. This is likely due to the presence of global tissue ischemia and the need for blood flow (via chest compressions) to “flush out” deleterious metabolic factors that have accumulated during ischemia. The third phase is the metabolic phase (beyond 15 minutes) in which survival is very low and hypothermia may be the most beneficial approach. Therefore, the EMS protocol of CCR emphasizes prompt initiation of continuous chest compressions before and immediately after a single indicated direct current shock.[33] In situations where EMS personnel may have witnessed the arrest or if there is optimal continuous chest compressions in progress when EMS arrives, immediate defibrillation should be attempted.

The hospital component of CCR calls for aggressive postresuscitation care. This consists of the use of therapeutic hypothermia, emergent cardiac

catheterization, and percutaneous coronary intervention for patients with myocardial ischemia as a potential cause of their arrest. This requires the designation of cardiac receiving centers which are hospitals with a commitment and expertise in postresuscitative care.

Clinical studies evaluating CCR have demonstrated a significant improvement in survival compared to conventional CPR.[33] Pooled data from a systematic review demonstrated that the use of a CCR protocol was associated with an improved odds of survival to hospital discharge (odds ratio [OR] = 2.26; 95% confidence interval [CI] 1.64-3.12).[35] Patients with VF/PVT may fare even better (OR [95% CI] = 2.98 [1.92-4.62]).

Ventricular Fibrillation /Pulseless Ventricular Tachycardia

Nonpharmacologic Therapy

In patients with VF or PVT, electrical defibrillation is the only effective method of restoring a cardiac rhythm; therefore, it is a crucial link in the “chain of survival,” especially for a witnessed arrest.[31] Although early defibrillation is crucial for survival following cardiac arrest, several studies have suggested that CPR prior to defibrillation (consistent with the CCR model) may increase the likelihood of a successful outcome.[36–39] The latest guidelines state that for a witnessed adult cardiac arrest, when an AED is immediately available, the defibrillator should be used as soon as possible. When the arrest is not witnessed or when an AED is not immediately available, CPR should be initiated while the defibrillator is being retrieved and defibrillation attempted as soon as the device is ready for use.[21] For in-hospital cardiac arrest, if an AED is available, CPR should begin while the AED is being placed.

It is not necessary to check the victim’s pulse after defibrillation because there is most often myocardial stunning with poor perfusion and diminished cardiac output immediately after electrical therapy.[31] After 2 minutes of chest compressions, the rhythm should be rechecked and if there is still evidence of VF or PVT, pharmacologic therapy with repeat attempts at single-discharge defibrillation should be attempted.

Intravenous (IV) access and an advanced airway should be obtained when feasible, but not at the expense of stopping chest compressions.[21] There is no clear data showing an advantage using endotracheal intubation or other airway devices compared to bag-mask ventilation.[31] Intubation, therefore, is typically

reserved for scenarios where bag-mask ventilation cannot be adequately provided or as a stepwise approach to airway management. Once an airway is obtained, providers must be careful to not provide excessive ventilations.

Pharmacologic Therapy

Sympathomimetics Sympathomimetics continue to be the first pharmacologic agents administered in the setting of cardiac arrest despite limited evidence demonstrating that survival to hospital discharge is improved. Nevertheless, sympathomimetics have been associated with an increased rate of ROSC and play a major role in the pharmacotherapy of cardiac arrest.

3 The primary goal of sympathomimetic therapy is to augment low coronary and cerebral perfusion pressures encountered during CPR. Chest compressions can improve blood flow to the heart and the brain but it is only about 25% of normal.[40] Even with optimally performed chest compressions, coronary perfusion pressures are only 10 to 15 mm Hg and systolic arterial pressure is rarely above 80 mm Hg.[41] Clinical data have indicated that ROSC is unlikely when the coronary perfusion pressure is less than 15 mm Hg.[42,43] Sympathomimetics, therefore, work to increase these pressures through their vasoconstrictive properties.

Epinephrine continues to be a drug of first choice for the treatment of VF, PVT, asystole, and PEA. Epinephrine is an alpha- and beta-receptor agonist causing vasoconstriction as well as increasing the rate and forcefulness of heart contractions.[44]

Prospective data evaluating epinephrine in the setting of out-of-hospital cardiac arrest are limited. In one study, patients were randomized to receive standard ACLS with intravenous (IV) drug administration or standard ACLS without IV drug administration.[45] There were 851 patients analyzed and VF/PVT was the initial rhythm in 34%. Intravenous medications administered included epinephrine (79%), atropine (46%), and amiodarone (17%). A significant increase in ROSC and hospital admission was noted in patients who received IV drug therapy. This difference was primarily observed in patients with initial rhythms other than VF/PVT. The contribution of epinephrine (versus other IV medications) to these outcomes was not assessed. A second randomized, controlled trial compared epinephrine with placebo in 534 patients.[46] VF or PVT was the initial rhythm in slightly less than half of the participants. Return of spontaneous circulation and survival to hospital admission was significantly higher with epinephrine use but there was no difference in the rate of survival to

hospital discharge. While epinephrine was effective in achieving ROSC in both shockable and nonshockable rhythms, its effect was more pronounced in those with nonshockable rhythms.

Several large observational studies have evaluated the impact of epinephrine on survival. One large registry study of over 400,000 patients failed to demonstrate a survival benefit with prehospital administration of epinephrine.[47] Despite a significant improvement in ROSC with epinephrine, 1-month survival and survival with good neurologic function were both lower in patients who received epinephrine. A second study evaluated outcomes in patients with witnessed out-of-hospital cardiac arrest.[48] After propensity matching, epinephrine was associated with improvements in survival at 1 month or discharge (17% vs 13.4%) in patients with VF/PVT but there was no difference in neurologically intact survival.

The influence of the timing of epinephrine has been examined in several studies. Earlier administration appears beneficial.[49–52] One study found survival worsened when epinephrine administration was delayed.[53] Similarly, other studies have reported that for each minute increase in the time to epinephrine administration, the odds of survival and the odds of hospital discharge with good neurologic function are reduced.[49–52] Therefore, the time to epinephrine administration may be a key factor for survival.

Given these disparate results with epinephrine use, its role during cardiac arrest remains unclear. The negative impact of epinephrine observed in some studies may be related to its mechanism of action. Epinephrine causes alpha-mediated vasoconstriction which increases coronary perfusion but may also decrease perfusion to other vital organs. Animal research has linked epinephrine to a decrease in cerebral microvascular blood flow and increase in brain tissue ischemia during and after CPR.[54] One study in humans measured cerebral oxygenation in patients who experienced an in-hospital cardiac arrest, before-and-after epinephrine administration.[55] A small increase in cerebral oxygenation (1.4%) was noted but the clinical importance of this small change is questionable. Epinephrine also stimulates beta-receptors which can increase myocardial oxygen demand, impair lactate clearance, and contribute to postresuscitation myocardial dysfunction.[56] This has led some investigators to evaluate the simultaneous administration of an adrenergic antagonist with epinephrine therapy, thereby isolating the alpha-2 effects, in an animal model.[57] This approach has not been extensively studied in humans.

Several studies have compared epinephrine with other adrenergic agonists

such as pure alpha-1 agonists (phenylephrine and methoxamine) and agents with more potent alpha-activity (norepinephrine).[58] When compared to pure alpha-1 agonists, there is no advantage in terms of long-term survival. One potential reason could be the potent alpha-2 effects of epinephrine and the fact that these receptors lie extrajunctionally in the intima of the blood vessels making them more accessible to circulating catecholamines.[59] Furthermore, during ischemia, the number of postsynaptic alpha-1-receptors decreases which suggests a greater role for alpha-2 agonists during CPR.[60] Epinephrine has also been compared with norepinephrine, a potent alpha-agonist (both alpha-1 and alpha-2) with some beta-1 effects. In the only large-scale randomized, double-blind, prospective trial comparing epinephrine and norepinephrine use in patients with an out-of-hospital cardiac arrest, there were no significant differences in ROSC, hospital admission, or discharge.[61] A second, smaller study demonstrated higher resuscitation rates with norepinephrine compared to epinephrine (64% vs 32%) but no significant difference in survival to hospital discharge.[62] Since the use of epinephrine has been established for many decades in evidence-based guidelines, strong outcome-related data (eg, survival to hospital discharge with good neurologic function) would be required for an alternative to replace it. Consequently, epinephrine remains the first-line sympathomimetic in the setting of cardiac arrest.

The recommended dose for epinephrine is 1 mg administered by IV or intraosseous (IO) injection every 3 to 5 minutes[31] (**Table 40-1**). The recommended dose for epinephrine was derived from animal studies (0.1 mg/kg in a 10 kg dog) and equates to approximately 0.015 mg/kg for a 70 kg human.[63] Animal studies have demonstrated a positive dose–response relationship with epinephrine, suggesting that higher doses might improve hemodynamics and resuscitation success.[58] However, human studies have reported increased morbidity with high-dose epinephrine. The hemodynamic findings are consistent with catecholamine toxicity, including decreased cardiac indices, left ventricular dysfunction, and decreased oxygen delivery. This discrepancy between animal and human studies could be related to most victims of cardiac arrest having coronary artery disease, which is not encountered in an animal model. Additionally, atherosclerotic plaques in humans can aggravate the balance between myocardial oxygen supply and demand, and the interval from arrest to treatment is longer in human studies than that encountered in an animal model. Thus, high-dose epinephrine is not recommended for routine use in cardiac arrest.

TABLE 40-1 Evidence-Based Recommendations

Recommendations	Recommendation Grades[a]
Epinephrine	
Standard dose epinephrine (1 mg IV/IO every 3-5 minutes) may be reasonable for patients with cardiac arrest	Class IIb, LOE B-R
High-dose epinephrine is not recommended for routine use in cardiac arrest	Class III: No benefit, LOE B-R
It may be reasonable to administer epinephrine as soon as feasible after the onset of cardiac arrest due to an initial nonshockable rhythm	Class IIb, LOE C-LD
Vasopressin	
Vasopressin offers no advantage as a substitute over epinephrine	Class III: No benefit, LOE B-R
Vasopressin in combination with epinephrine offers no advantage as a substitute for standard dose epinephrine	Class IIb, LOE B-R
For in-hospital cardiac arrest, the combination of intra-arrest vasopressin, epinephrine, and methylprednisolone with post-arrest hydrocortisone may be considered	Class IIb, LOE C-LD
Amiodarone	
Amiodarone may be considered in patients with VF/PVT unresponsive to CPR, defibrillation, and a vasopressor	Class IIb, LOE B-R
Lidocaine	
Lidocaine may be considered as an alternative to amiodarone for VF/PVT that is unresponsive to CPR, defibrillation, and a vasopressor	Class IIb, LOE C-LD
Magnesium	
Magnesium is not routinely recommended for VF/PVT	Class III: No benefit, LOE B-R
Thrombolysis	
Thrombolysis may be considered when cardiac arrest is suspected to be caused by pulmonary embolism	Class IIb, LOE C-LD
Targeted Temperature Management	
Comatose adult patients with ROSC after cardiac arrest should have targeted temperature management	Class I, LOE B-R (VF/PVT); Class I, LOE C-EO (non-VF/PVT and in-hospital arrests)
A constant temperature between 32°C and 36°C should be maintained	Class I, LOE B-R
It is reasonable that targeted temperature management be maintained for at least 24 hours after achieving target temperature	Class IIa, LOE C-EO
Routine prehospital cooling of patients after ROSC with rapid infusion of cold intravenous fluids is not recommended	Class III: No benefit, LOE A
Miscellaneous	
Avoiding and immediately correcting hypotension (SBP <90 mm Hg or MAP <65 mm Hg) during postresuscitation care may be reasonable	Class IIb, LOE C-LD
The benefit of any specific target range of glucose management is uncertain	Class IIb, LOE B-R

CPR, cardiopulmonary resuscitation; IV, intravenous; IO, intraosseous; VF, ventricular fibrillation; PVT, pulseless ventricular tachycardia; SBP, systolic blood pressure; MAP, mean arterial pressure; LOE, level of evidence.

[a]Key for evidence-based classifications:
Class of recommendations:
- Class I (Strong). Benefit >>>Risk
- Class IIa (Moderate). Benefit >> Risk
- Class IIb (Weak). Benefit ≥ Risk
- Class III: No Benefit (Moderate). Benefit = Risk
- Class III: Harm (Strong). Risk > Benefit

Levels of Evidence (LOE):
- Level A: High-quality evidence from more than one RCT, meta-analyses of high-quality RCTs, one or more RCT corroborated by high-quality registry studies.
- Level B-R (Randomized): Moderate-quality evidence from one or more RCTs, meta-analyses of moderate-quality RCTs.
- Level B-NR (Nonrandomized): Moderate-quality evidence from one or more well-designed nonrandomized studies, observational studies, or registry studies, meta-analyses of such studies.
- Level C-LD (Limited data): Randomized or nonrandomized observational or registry studies with limitations of design or execution, meta-analyses of such studies, physiological or mechanistic studies in human subjects.
- Level C-EO (Expert opinion): Consensus of expert opinion based on clinical experience.

Vasopressin Vasopressin, also known as antidiuretic hormone, is a potent, nonadrenergic vasoconstrictor that increases blood pressure and systemic vascular resistance. Although it acts on various receptors throughout the body, its vasoconstrictive properties are due primarily to its effects on the V1 receptor. Measurement of vasopressin levels in patients undergoing CPR has shown a high correlation between the levels of endogenous vasopressin released and the potential for ROSC.[64] In one study, plasma vasopressin concentrations were approximately three times as high in survivors compared with nonsurvivors, suggesting that vasopressin is released as an adjunct to epinephrine in life-threatening events such as cardiac arrest.[65]

Vasopressin is proposed to have several advantages over epinephrine. First, the metabolic acidosis that frequently accompanies cardiac arrest can blunt the vasoconstrictive effect of adrenergic agents such as epinephrine. This effect does not occur with vasopressin. Second, the stimulation of beta-receptors caused by epinephrine can increase myocardial oxygen demand and complicate the postresuscitative phase of CPR. This is not seen with vasopressin use because it does not act on beta-receptors. Vasopressin also may have a beneficial effect on renal blood flow by stimulating V_2 receptors in the kidney, causing vasodilation and increased water reabsorption. With regard to splanchnic blood flow (ie, blood flow to the gastrointestinal tract), however, vasopressin has a detrimental effect when compared to epinephrine.[64]

Despite these theoretical advantages with vasopressin, clinical outcomes are not superior to that achieved with epinephrine alone.[66–71] The utility of a multidrug regimen that also included corticosteroids with vasopressin therapy has been evaluated in the setting of in-hospital cardiac arrest.[72,73] The rationale is based on the hemodynamic effects of steroids alone with their potential to impact the intensity of the postresuscitation systemic inflammatory response and organ dysfunction. In a single-center trial, patients were randomized to receive either epinephrine alone or 20 units of vasopressin plus 1 mg of epinephrine and 40 mg of methylprednisolone (followed by hydrocortisone in the postresuscitative phase).[73] Significant benefits were observed in ROSC (81% vs 52%, $p = 0.003$) and survival to hospital discharge (19% vs 4%, $p = 0.02$) with combination therapy including corticosteroids. A subsequent multi-center trial conducted at three centers using the same drug regimen also found a higher probability for ROSC (84% vs 66%, $p = 0.005$) and a higher probability for survival to hospital discharge with good neurologic function (14% vs 5%, $p = 0.02$).[72]

4 In summary, vasopressin appears to offer no benefit when used as a substitute for or in combination with epinephrine compared to standard dose epinephrine alone.[31] The combination of methylprednisolone, vasopressin, and epinephrine may be considered in the setting of in-hospital cardiac arrest but further studies are needed before this approach could be routinely recommended.

Antiarrhythmics The purpose of antiarrhythmic drug therapy following unsuccessful defibrillation and vasopressor administration is to prevent the development or recurrence of VF and PVT. However, clinical evidence demonstrating improved survival to hospital discharge is lacking.[74,75]

Amiodarone use may be considered in patients with VF or PVT, unresponsive to CPR, defibrillation, and vasopressor therapy. Amiodarone is classified as a class III antiarrhythmic but possesses electrophysiologic characteristics of all four Vaughn Williams classifications. A large, randomized, double-blind trial in patients with out-of-hospital cardiac arrest secondary to VF or PVT (known as the ARREST trial) reported a higher incidence of survival to hospital admission (44% vs 34%, $p = 0.03$) but no difference in survival to hospital discharge (13.4% vs 13.2%, p = NS).[76] This was the first trial to demonstrate the benefit of any antiarrhythmic agent over placebo in patients with out-of-hospital cardiac arrest. A subsequent trial (known as the ALIVE trial) compared amiodarone with lidocaine in patients with out-of-hospital cardiac arrest due to VF.[77] In this trial, amiodarone was associated with improved survival to hospital admission compared with lidocaine but there was no difference in survival to hospital discharge. The most recent trial (the ALPS study) compared amiodarone and lidocaine to placebo in patients with an out-of-hospital arrest with shock-resistant VF/PVT.[78] In this trial, no significant difference in survival to hospital discharge for amiodarone versus placebo, for lidocaine versus placebo, or amiodarone versus lidocaine was found.

Adverse effects of amiodarone encountered in a cardiac arrest include hypotension and bradycardia.[79] These effects are largely due to the intravenous vehicle, polysorbate 80 and benzyl alcohol. A formulation of amiodarone exists that does not contain these solvents and adverse hemodynamic effects appear to be minimized. Nevertheless, the administration of a vasoconstrictor prior to amiodarone can potentially prevent hypotension.

Lidocaine is currently recommended as an alternative to amiodarone, if amiodarone is not available.[31] Minimal evidence exists supporting lidocaine use for VF/PVT. In the only published case–control study, no significant difference was noted in ROSC, admission to the hospital, or survival to hospital discharge

between those who received lidocaine and those who did not.[80] In contrast, a retrospective analysis in patients with VF indicated that lidocaine was associated with a higher rate of ROSC and hospitalization ($p < 0.01$) but not an increase in the hospital discharge rate.[81] A prospective study comparing the effectiveness of lidocaine with standard-dose epinephrine failed to show a benefit and lidocaine appeared to promote asystole.[82]

Magnesium Severe hypomagnesemia has been associated with VF/PVT, but the routine administration of magnesium during a cardiac arrest has not demonstrated any benefit in clinical outcome. Two observation trials noted an improvement in ROSC in patients with arrests associated with torsades de pointes.[31] Therefore, magnesium should only be administered in the setting of torsades de pointe.

Thrombolytics Since most cardiac arrests are related to either myocardial infarction or pulmonary embolism, several investigators have evaluated the role of thrombolytics during CPR. Earlier smaller studies have demonstrated some benefit with their use, but in the two largest randomized controlled trials, no difference was noted.[79] In the most rigorous study performed to date, patients with out-of-hospital cardiac arrest were randomized to receive either tenecteplase or placebo.[83] After a blinded review by the data and safety monitoring board, criteria for futility were met and the study was terminated. Both ROSC and survival to hospital discharge were similar between groups. However, the incidence of intracranial hemorrhage was significantly greater with tenecteplase versus placebo (2.7% vs 0.4%, $p = 0.006$). Potential reasons for failure in this study include the omission of antiplatelet and antithrombin medication administration during CPR and poor delivery of the thrombolytic to the coronary arteries due to impaired flow and perfusion. Given these results, fibrinolytic therapy should not be used routinely in cardiac arrest. When pulmonary embolism is suspected, their use may be warranted.[84]

Pulseless Electrical Activity and Asystole

Nonpharmacologic Therapy

5 Pulseless electrical activity is defined as the absence of a detectable pulse and the presence of some type of electrical activity other than VF or PVT. Patients with PEA have mechanical cardiac contractions but they are too weak to produce a palpable pulse or blood pressure. Although PEA is classified as a

"rhythm of survival," the likelihood of successful resuscitation is much lower than seen with VF/PVT.[1] PEA is often caused by a treatable underlying cause and the resuscitation team must quickly identify and correct it if the resuscitation is to be successful (Table 40-2). Asystole occurs when there is a lack of electrical activity in the heart and appears as a flat line on the ECG. Asystole is often not amenable to treatment. Therefore, withdrawal of resuscitation efforts should be considered if there is no rapid ROSC.[79] Like PEA, successful treatment of asystole depends almost entirely on diagnosing the underlying cause.

TABLE 40-2 Underlying Causes of Pulseless Electrical Activity and Asystole

Condition	Clues	Treatment
Hypovolemia	History, flat neck veins	Intravenous fluids
Hypoxia	Cyanosis, blood gases, airway problems	Ventilation, oxygen
Hydrogen ion (acidosis)	History of bicarbonate-responsive preexisting acidosis	Sodium bicarbonate, hyperventilation
Hyper (Hypo) kalemia	History of renal failure, diabetes, recent dialysis, dialysis fistulas, medications	Calcium chloride, insulin, glucose, sodium bicarbonate, sodium polystyrene sulfonate, dialysis
Hypothermia	History of exposure to cold, central body temperature	Rewarming, oxygen, intravenous fluids
Hypoglycemia	History of diabetes	Glucose infusion
Toxin (Drug overdose)	Bradycardia, history of ingestion, empty bottles at the scene, pupils, neurologic exam	Drug screens, intubation, lavage, activated charcoal
Tamponade (Cardiac)	History (trauma, renal failure, thoracic malignancy), no pulse with CPR, vein distention, impending tamponade-tachycardia, hypotension, low pulse pressure changing to sudden bradycardia as terminal event	Pericardiocentesis
Tension pneumothorax	History (asthma, ventilator, chronic obstructive pulmonary disease, trauma), no pulse with CPR, neck vein distention, tracheal deviation	Needle decompression
Thrombosis, coronary	History, ECG, enzymes	PCI, thrombolytics, oxygen, nitroglycerin, heparin, aspirin, morphine
Thrombosis, pulmonary	History, no pulse with CPR, distended neck veins	Pulmonary arteriogram, surgical embolectomy, thrombolytics
Trauma	History, examination	Volume infusion, intracranial pressure monitoring, bleeding control, surgical intervention

Data from reference 31.

The algorithm for treating PEA and asystole are the same. Both conditions require CPR, airway control, and IV access. Asystole should be reconfirmed by

checking a second lead on the cardiac monitor. Defibrillation should be avoided in patients with asystole because the parasympathetic discharge that occurs with defibrillation may reduce the chance of ROSC and worsen the chance of survival. The emphasis in resuscitation is good quality CPR without interruption and identifying a correctable cause. Transcutaneous pacing can be attempted, if available.

Hypothermia may be used following ROSC. Metabolic parameters (eg, lactate and O_2 extraction) improve when post-arrest comatose adults are treated with hypothermia.[85] However, survival to hospital discharge with good neurologic function has not been favorably impacted.[86] This could be due to the relatively poor prognosis in this population.

Pharmacologic Therapy

The primary pharmacologic agent used in the treatment of asystole or PEA is epinephrine; vasopressin is no longer recommended. While studies evaluating these therapies in patients exclusively with asystole or PEA are limited, these rhythms were observed in a majority of patients included in the published research. In the largest observational trial evaluating the role of epinephrine in out-of-hospital arrest, 93% had either PEA or systole as the first documented rhythm.[47] In this study, epinephrine was associated with a significant improvement in ROSC, but 1-month survival and survival with good neurologic function were lower with epinephrine. A second study revealed similar findings but worse neurological outcomes were noted when the time to epinephrine administration exceeded 10 minutes.[87] In one study of more than 25,000 patients with in-hospital arrest and either asystole or PEA, a step-wise decrease in survival was observed with each incremental delay in epinephrine administration.[50] As with VF/PVT, time to epinephrine administration appears to be an important factor.

Another agent that is no longer recommended in the setting of PEA or asystole is atropine.[31] Atropine is an antimuscarinic agent that blocks the depressant effect of acetylcholine on both heart rate and atrioventricular nodal conduction, thus decreasing parasympathetic tone. During asystole, parasympathetic tone may increase because of the vagal stimulation that occurs secondary to intubation, the effects of hypoxia and acidosis, or alterations in the balance of parasympathetic and sympathetic control.[88] Nevertheless, there are no prospective controlled trials showing benefit from atropine for the treatment of asystole or PEA and the evidence is inconsistent in observational reports.

Therefore, atropine should not be routinely administered to patients with PEA or asystole.

Acid/Base Management

Acidosis seen during cardiac arrest results from decreased blood flow and inadequate ventilation. Chest compressions generate only approximately 25% of normal cardiac output, leading to inadequate organ perfusion, tissue hypoxia, and metabolic acidosis. In addition, the lack of ventilation causes retention of carbon dioxide, leading to respiratory acidosis. Acidosis produces not only reduced myocardial contractility but also lowers the fibrillation threshold. Maintaining adequate alveolar ventilation was once considered a mainstay of treatment during cardiac arrest to limit the accumulation of carbon dioxide and control the acid–base imbalance.[79] With the evolution to CCR, however, ventilations are avoided and evidence has not shown any deleterious effects with this practice in patients with primary cardiac arrest. With arrests of long duration, buffer therapy (eg, sodium bicarbonate) has sometimes been given to reduce the detrimental effects associated with acidosis (eg, reduced myocardial contractility), enhance the effect of epinephrine, and improve the rate of defibrillation. However, there is insufficient data to support its use.[89] In one propensity score-matched analysis, bicarbonate use was associated with a lower probability of favorable neurologic outcome (OR [95% CI] = 0.59 [0.39–0.88]).[90]

Sodium bicarbonate may have detrimental effects.[89] Sodium bicarbonate produces the following reaction: $[HCO_3^-] + [H^+] \leftrightarrow [H_2O] + [CO_2]$. When sodium bicarbonate is added to an acidic environment, the reaction will shift to the right, thereby increasing tissue and venous hypercarbia. The carbon dioxide generated by this reaction will diffuse into the cell and decrease intracellular pH. The accumulation of intracellular carbon dioxide, specifically within the myocardium, is inversely correlated with coronary perfusion pressure produced by CPR. Intracellular acidosis also will decrease myocardial contractility, further complicating the low-flow state associated with CPR. Furthermore, treatment with sodium bicarbonate often overcorrects extracellular pH because sodium bicarbonate has a greater effect when the pH is closer to normal.[91] The induced alkalosis causes an increase in the affinity of oxygen to hemoglobin (“left shift”), thus interfering with oxygen release into the tissues.

Sodium bicarbonate is not recommended for routine use in patients with cardiac arrest.[31]It can be considered in special circumstances such as patients

with hyperkalemia, tricyclic antidepressant overdose, or salicylate toxicity.

Postresuscitative Care

Following the ROSC from a cardiac arrest, patient management should be directed toward the postcardiac arrest syndrome.[92]There are four main components of the postcardiac arrest syndrome that highlight succinct pathophysiologic processes and potential areas for treatment: hypoxic brain injury, myocardial dysfunction, systemic ischemia-reperfusion response, and the underlying precipitating pathology (**Table 40-3**).[93,94]Many of the concepts within these four components surround the principles of basic ICU care (eg, adequate oxygenation, circulatory support, hemodynamic optimization, prevention of secondary brain injury, etc.). Post-arrest care has the significant potential to reduce mortality by addressing altered hemodynamics, multiple organ dysfunction, and central nervous system injury.[92,93]

TABLE 40-3 Postcardiac Arrest Syndrome

Syndrome	Pathophysiology	Clinical Manifestation
Hypoxic brain injury	• Impaired cerebrovascular autoregulation • Cerebral edema • Post-ischemic neurodegeneration	• Seizures • Coma • Myoclonus • Cognitive dysfunction • Cortical/Spinal Stroke • Brain death
Myocardial dysfunction	• Global hypokinesis • Acute coronary syndrome	• Reduced cardiac output • Cardiogenic shock • Dysrhythmias
Systemic ischemia-reperfusion response	• Systemic inflammatory response syndrome • Impaired vasoregulation • Hypercoagulability • Microcirculatory dysfunction • Adrenal suppression • Immunosuppression	• Tissue hypoxia • Hypotension • Fever • Hyperglycemia • Infection • Multi-system organ failure
Underlying precipitating pathology	• Cardiovascular disease • Pulmonary disease • Hypovolemia/ Hemorrhage • Stroke • Pulmonary embolism • Poisoning/overdose • Infection • Electrolyte disturbances	• Clinical manifestation will be specific to the underlying cause

Data from references 93 and 94.

After ROSC, it is imperative to ensure adequate airway and oxygenation. Re-arrest is common in the first minutes after resuscitation (occurring in roughly one of five cases). Hypoxia and hypotension are also frequently seen.[95] Both hypoxia and hyperoxia are associated with adverse outcomes after cardiac arrest.[95] Usually, 100% oxygen is used during the initial resuscitation effort and if ROSC is obtained (and the patient is placed on a mechanical ventilator), the healthcare team should titrate the oxygen fraction down as tolerated to maintain

an oxyhemoglobin saturation of at least 94% (0.94).[92] Overventilation can be a problem in the postresuscitation period; ETCO2 monitoring can avoid this pitfall.

Given that cardiac ischemia is the most common cause of cardiac arrest, a rapid search for electrocardiographic changes consistent with acute myocardial infarction should be undertaken immediately.[95] If an acute myocardial infarction is present, urgent revascularization should be performed. Other potential causes such as pulmonary embolism, hemorrhage, drug overdose, poisonings, sepsis, and anaphylaxis should be considered.

Following ROSC, cerebral hypoperfusion is common, lasting several hours to days after resuscitation. During this time, cerebral vascular resistance is increased and autoregulation is impaired. Increased perfusion pressures (ie, systemic blood pressure) are needed to maintain adequate blood flow to the brain. An optimal goal of mean arterial pressure (MAP) target has not been determined. Nevertheless, augmenting blood pressure to achieve a goal of MAP more than 80 mm Hg has been recommended.[93,95]

Therapeutic hypothermia, also called targeted temperature management, is currently considered an important component of postresuscitative care. Restoration of blood flow following cardiac arrest can lead to several chemical cascades and destructive enzymatic reactions that result in cerebral injury. These reactions include free-radical production, excitatory amino acid release, and calcium shifts which lead to mitochondrial damage and apoptosis (programmed cell death).[96] Hypothermia can protect against cerebral injury by suppressing these chemical reactions. Additionally, therapeutic hypothermia can decrease cerebral metabolism and oxygen consumption. For each 1°C drop in temperature, cerebral metabolism decreases by 6% to 10%.[96]

Early success with hypothermia was described in two pivotal trials published in 2002.[97,98] In the first trial, patients who had been resuscitated after cardiac arrest due to VF but remained comatose were assigned randomly to undergo therapeutic hypothermia, targeting a temperature of 32°C to 34°C, for 24 hours.[97] A favorable neurologic outcome was achieved in 55% of patients in the hypothermia group compared to 39% in the normothermia group. The second study targeted 33°C maintained for 12 hours.[98] Forty-nine percent of patients in the hypothermia group had good neurologic function at the time of hospital discharge (to either home or a rehabilitation facility) compared with 26% of patients in the normothermia group.

Recently, there have been several large trials that have challenged the role of

therapeutic hypothermia during postcardiac arrest care.[99–104] The first was a randomized controlled trial comparing targeted temperature management at 33°C versus 36°C for 36 hours.[99] There were no significant differences noted in all-cause, end of trial mortality, or poor neurologic function. A second randomized controlled trial assessed whether or not prehospital cooling improved survival.[100] The target temperature less than 34°C was reached approximately 1 hour sooner in the intervention group compared to controls. Prehospital cooling was not associated with increased survival to hospital discharge or improvement in neurological status. A third randomized controlled trial evaluated the relationship between duration of hypothermia and neurologic outcome in 351 patients.[101] In this study, the targeted temperature was 33°C, maintained for either 24 or 48 hours. The duration of targeted temperature management had no impact on neurologic outcomes assessed at 6 months. Lastly, a large cohort study used the "Get With the Guidelines-Resuscitation" registry and performed a matched propensity score analysis to compare survival to hospital discharge and favorable neurologic survival.[102] Therapeutic hypothermia was not associated with improved in-hospital survival (27% vs 29%) or more favorable neurological survival (17% vs 21%). This association was similar for both shockable and nonshockable cardiac arrest rhythms.

Two randomized controlled trials have recently evaluated the role of therapeutic hypothermia in children.[103,104] The first study was conducted in children after out-of-hospital arrest and randomized children to either hypothermia (target temperature 33°C for 48 hours) or normothermia (target temperature 36.8°C).[104] No difference was noted between groups (hypothermia, 20% vs normothermia, 12%). Similarly, a second study that included children following in-hospital arrest using similar temperature targets found no benefit.[103]

Collectively, these studies raise the question as to whether hypothermia or merely avoiding hyperthermia improves outcomes. In one of the earlier trials, there was no active temperature management in the control group. Mild fever occurred in some patients (average temperature was 37.8°C).[97] This is important because previous research has shown for each degree higher than 37°C, the risk of unfavorable neurologic recovery increases.[105] Nevertheless, despite recent data showing no improvement in outcomes, targeted temperature management should not be abandoned. Current guidelines recommend targeted temperature management for all comatose adult patients after ROSC.[92] The target temperature should be between 32°C and 36°C and maintained for at least 24 hours. It is also reasonable to actively prevent fever following targeted temperature management.

Several methods can be used to induce hypothermia. Surface cooling devices are noninvasive and include simple ice packs, cooling blankets/gel pads, ice water immersion, and nasopharyngeal evaporative cooling devices. Invasive cooling methods include ice-cold intravenous fluids, endovascular cooling catheters, body cavity lavage, extracorporeal circuits, and selective brain cooling. It is unknown which method produces optimal outcomes, but target temperatures should be reached as quickly as possible (eg, the induction phase).[95] During the maintenance phase, the core temperature should be tightly controlled with little or no fluctuations. The rewarming phase should be slow and controlled at a rate of 0.2°C to 0.5°C per hour.

Inducing hypothermia is not without risk. Shivering occurs during the induction phase, increasing metabolic rate and myocardial oxygen demand. Several strategies exist to blunt the thermoregulatory response to hypothermia and these measures should be implemented accordingly.[95,96] Coagulopathy, dysrhythmias, bradycardia, diuresis, electrolyte disorders, hyperglycemia, and infections have also been described.[95,96] Moreover, hypothermia can affect drug distribution and clearance.[96] Although the duration of hypothermia is typically short, careful patient monitoring is necessary, particularly with vasoactive agents, sedatives, and opiates.

Special Populations

Asthma

Asthma is a very common disorder, and despite modern therapies, there are still in excess of 2 million emergency room visits and 5,000 to 6,000 asthma-related deaths annually in the United States.[106] True cardiac arrest in asthma is infrequent, as the primary pathophysiology is respiratory compromise and poor ventilation.[107] Asthma exacerbations are a combination of bronchoconstriction, airway inflammation, and mucous plugging. This leads to severe air trapping, hyperinflation, and hemodynamic compromise. While wheezing is common in an asthma exacerbation, it does not correlate with the degree of airway obstruction. In contrast, with worsening disease (and subsequent decrease in airflow), wheezing may disappear. Further, several disease states cause wheezing, including pulmonary edema, pneumonia, anaphylaxis, foreign bodies, and tumors.[106]

Patients with life-threatening asthma need to be treated aggressively with bronchodilators and corticosteroids. Adjunctive therapies include

anticholinergics, magnesium sulfate, ketamine, helium/oxygen mixtures, or inhaled anesthetics.[108–112] Noninvasive ventilation can be attempted if the patient is deteriorating and still awake. This may prevent the need for mechanical ventilation.[113] The decision to intubate is a clinical judgment. However, the endotracheal tube will not solve the airway problem and aggressive asthma management needs to continue after intubation. In addition, intubation and positive airway pressure can trigger further bronchoconstriction or hemodynamic compromise.

The provision of BLS and standard ACLS measures should be followed in patients with acute asthma.[106] However, since the effect of auto-positive end-expiratory pressure, known as breath stacking, can be severe, a strategy of low respiratory rate and volume ventilation may be appropriate.[106] Similarly, for cardiac arrest in patients with acute asthma, especially when ventilation is difficult, tension pneumothorax should be strongly considered.[106]

Anaphylaxis

Anaphylaxis is a severe allergic reaction that can lead to airway obstruction and cardiovascular collapse.[106] It accounts for between 500 and 1000 deaths annually in the United States.[114] The initial signs can be nonspecific, but a “sense of impending doom” is common.[106] Rhinitis often leads to laryngeal edema with stridor in the upper airway. Bronchoconstriction often mimics an acute asthma attack.

Cardiovascular collapse is common in severe anaphylaxis due to vasodilation and increased capillary permeability. This can rapidly lead to myocardial hypoperfusion and ischemia and to full cardiac arrest. There are no randomized trials comparing strategies to manage arrest due to anaphylaxis.[106] Therefore, standard basic and advanced life support measures should be followed.

Early advanced airway management is recommended due to the potential for rapidly developing laryngeal edema. Epinephrine has been the mainstay of treatment for years.[106] The recommended dose is 0.2 to 0.5 mg and should be administered via intramuscular injection to all patients with signs of systemic allergy.[106] This can be repeated every 5 to 15 minutes if there is no clinical improvement. Vasopressin has been used successfully in patients who did not respond to standard therapy.[115] Fluid resuscitation is usually required for restoration of circulation and has been evaluated in one study where hypotension did not respond immediately to vasoactive drugs.[116] There are no prospective trials evaluating other agents in anaphylactic shock or arrest. Antihistamines,

inhaled beta-agonists, and intravenous corticosteroids have been used successfully in anaphylaxis and may be considered in cardiac arrest due to anaphylaxis.[106]

Pregnancy

Pregnancy is a unique situation where survival of both the fetus and the mother depends on CPR. Despite the fact that pregnant patients are younger than most cardiac arrest victims, the incidence of cardiac arrest during pregnancy appears to be on the rise in the United States.[84] Historically, survival has been poor but survival rates of nearly 60% have been recently reported.[117] Survival is largely dependent on the underlying etiology. The most common causes during pregnancy are anesthetic complications, accidents, bleeding, cardiovascular, drugs, embolism, fever, and hypertension.[118]

The best hope for survival of the fetus is maternal survival. High-quality chest compressions is essential and hand placement should be similar as in a nonpregnant patient. Because the vena cava and aorta can be obstructed by the uterus in the second and third trimesters during pregnancy, CPR procedures should be modified. Manual lateral uterine displacement (ie, pulling the uterus to the side)[84] is currently recommended. Alternatively, tilting the patient laterally by approximately 30 degrees can be used but the quality of chest compressions is compromised.[84]

Airway control is important in the pregnant patient. The airway may be smaller because of the hormonal changes and edema.[118] Similarly, because of increased intra-abdominal pressure exerted by the uterus, as well as hormonal changes that change the resting state of the gastroesophageal sphincter, there is an increased risk of aspiration. The rescuer may need to give smaller respiration volumes than normal.

The ACLS provider should follow the standard guidelines in the pregnant patient, including the same use of chest compressions, defibrillation, and medications.[118] Epinephrine remains the vasopressor of first choice despite concerns that it can diminish uterine blood flow. Amiodarone should be considered for refractory, shock-resistant VF/PVT. No medication should be withheld in the setting of cardiac arrest because of concerns about fetal teratogenicity. While there are clear changes in pharmacokinetic parameters (ie, the volume of distribution and clearance) during pregnancy, there are few data to justify alternative dosing strategies. Standard doses, therefore, are recommended.

While the etiology of arrest in pregnancy is often the same as in the

nonpregnant patient, there are several unique causes that need to be considered.[118] Excess magnesium sulfate administration (ie, iatrogenic from treating eclampsia) can prompt cardiac arrest. In such cases, the therapeutic administration of calcium can be lifesaving. An amniotic embolism can lead to complete cardiovascular collapse during labor and delivery. Pre-eclampsia/eclampsia developing after the 20th week of gestation can produce hypertension and multiple organ dysfunction, including cardiac arrest. Vascular events including acute coronary syndromes and acute pulmonary embolism can also be a cause.

It is paramount to remember that unless circulation is restored to the mother, both the mother and the fetus will succumb. The resuscitation leader should consider the need for emergent cesarean delivery if there is no immediate response after lateral uterine displacement and CPR.[84]

Hypothermia

Unintentional hypothermia (not therapeutic hypothermia used post-arrest) occurs when the body temperature is less than 30°C (86°F). It is associated with marked derangements in body function. Because it can depress virtually every body system, including pulse and respiration, the patient may appear to be dead. If the patient still has a perfusing rhythm, therapy is directed toward rewarming techniques. For mild hypothermia (ie, >34°C [93.2°F]), passive rewarming is recommended.[106] For moderate hypothermia (ie, 30°C–34°C [86°F–93.2°F]), active external rewarming is recommended, and for severe hypothermia (ie, <30°C [86°F]) active internal rewarming is recommended. Patients need to be manipulated very gently as VF is sometimes precipitated by movement.

If the patient is in cardiac arrest, then the standard BLS algorithm should be followed. Pulse and respiratory rates may be slow or difficult to detect and ECG may show asystole. If the victim displays no signs of life, then chest compressions and rescue breaths should ensue immediately. If the patient is in VF or PVT, electrical therapy should be given in a standard manner and CPR should immediately resume. Source of heat loss should be minimized (ie, removal of wet clothing, protection from the environment, etc.). The role for medications is unclear. Previous guidelines recommended withholding IV medications when the body temperature is less than 30°C. Current recommendations state it is reasonable to give epinephrine per standard ACLS practices.[106]

It is debatable when to stop resuscitative efforts in the hypothermic patient. Many authors have proposed that a patient should not be pronounced dead until

the core temperature has been restored to near normal.[106]

Trauma

Cardiac resuscitation of the trauma arrest patient should follow standard BLS and ACLS practices. Survival of an out-of-hospital cardiac arrest due to trauma is rare.[106] The rescuer needs to consider airway obstruction, pneumothorax, tracheobronchial injury, cardiac or large arterial injury, cardiac tamponade, severe head injury with secondary cardiac collapse, and other injuries specific to the particular trauma.[106] Survival is higher in young patients with treatable penetrating injuries.

Trauma patients often suffer head or cervical injuries; thus cervical spine precautions should be used. A jaw thrust maneuver is the preferred way to open the airway, with in-line stabilization during attempts at advanced airway placement.[106] Inadequate ventilation of one side is usually due to tube malposition, tension pneumothorax, or hemothorax. These conditions are usually treated by medical personnel at the hospital after transport.

Chest compressions should be performed in a standard manner. Ongoing hemorrhage must be controlled with either temporizing or definitive measures. Fluid resuscitation and restoration of blood volume is essential as resuscitation is unlikely if the patient has severe hypovolemia. Open thoracotomy for trauma-induced arrest may be indicated for select patients.[119] Open thoracotomy can allow relief of tamponade, control of major vessel hemorrhage, or direct repair. Open thoracotomy is a strong recommendation for patients who are pulseless but have signs of life after penetrating thoracic injury.[119] In the setting of penetrating extra-thoracic injury or blunt injury, open thoracotomy is a conditional recommendation.

A unique cause of cardiac arrest caused by a blow of the anterior chest or sternum during the repolarization part of the cardiac cycle is called “Commotio Cordis.”[120] These events are commonly seen in young athletes and can be caused by a fall or a baseball or hockey puck striking the sternum. Prompt recognition and rapid defibrillation is often lifesaving. Provision of BLS, the use of an AED, and standard ACLS procedures are appropriate for this type of arrest.

Drowning

Drowning is the result of primary respiratory impairment following

immersion/submersion in a liquid. It is a common, preventable cause of morbidity and mortality. Cardiac arrest in this setting is due to hypoxia. The most powerful predictor of outcome, therefore, is the duration of submersion. In one study the probability of a good outcome was only 2% when the submersion duration exceeded 10 minutes.[121] With submersion durations that exceed 25 minutes, resuscitation efforts may be futile.

Because hypoxia is the underlying etiology of cardiac arrest in drowning victims, the traditional A-B-C approach should be used instead of C-A-B.[106] Early care consists of immediate rescue breathing, even before they are removed from the water or liquid. Once the victim is removed from the water, immediate chest compressions should be started if they are pulseless. Drowning victims can present with any of the pulseless rhythms; standard guidelines for these rhythms should be followed. A “Drowning Chain of Survival” has been proposed to improve outcomes.[122]The five links in the chain are: prevent drowning, recognize distress, provide flotation, remove from water, and provide care as needed.

Electrocution/Lightning

There are many etiologies of electrical shock injuries including a lightning strike, high-tension current, or household current.[106] The severity of injury depends on the site, type of current, duration of contact, pathway, and the magnitude of delivered electricity.

Cardiac arrest is common in electrical injury due to the current passing through the heart during the “vulnerable period” of the cardiac cycle. In large-current events, such as lightning strike, the heart undergoes massive depolarization. In some cases, the intrinsic pacemaker can restore an organized cardiac electrical cycle. Injury to other muscles, however, particularly the thoracic musculature, and suppression of the respiratory center can lead to inadequate ventilations, hypoxia, and subsequent cardiac arrest. Ventilatory support, therefore, must be maintained after ROSC is achieved.

When approaching a victim of electrocution, the rescuer must first be certain of his or her own safety. Prompt CPR and ACLS, when available, is indicated. Electric shock is often associated with multiple trauma, including spinal injury, multiple injuries to the skeletal muscles, as well as fractures. These factors need to be evaluated by the resuscitation team.

Airway control may be difficult due to the edema that often accompanies electrical injuries; thus, an advanced airway early in the treatment process is

recommended.[106] With soft tissue swelling, there is often a need for aggressive fluid resuscitation in these patients. The underlying tissue, or visceral organ damage, is often worse than the external appearance. It is usually recommended that these patients be transferred to centers with expertise in dealing with these types of injuries.

Drug Administration

The routes of administration available for drug delivery during CPR include IV (both central and peripheral access), intraosseous (IO), and endotracheal. Each route represents a compromise between access and efficacy in introducing the drug into the central circulation. When selecting a route for drug administration, it is important to minimize any interruptions in chest compressions during CPR.

Central venous access will result in a faster and higher peak drug concentration than peripheral access but central line access is not needed in most resuscitation attempts. If a central line is already present, it should be the access site of choice. An appropriately trained provider may consider placing a central line if one is not present but CPR should not be interrupted. Central lines located above the diaphragm are preferable to those located below the diaphragm because of poor blood flow during CPR.[123] If IV access (either central or peripheral) has not been established, a large peripheral venous catheter should be inserted. It has been suggested that only one attempt at peripheral IV insertion should be made.[124]If unsuccessful, an IO device should be inserted. Peripheral drug administration yields a peak concentration in the major systemic arteries in roughly 1.5 to 3 minutes but this time can be shortened by up to 40% if the drug is followed by a 20-mL fluid bolus and elevating the extremity.[123]

6 IO is the preferred route for drug and fluid administration if IV access cannot be achieved.[79] The effectiveness and safety of the IO route have been widely documented in both adults and children.[125] Potential anatomic sites for insertion of an IO needle are the sternum, tibia, and humerus.[125,126] Pharmacokinetic data have demonstrated similar areas under the curve and times to peak concentration for sternal IO and central IV administration.[126]The need for cessation of chest compressions, however, along with the risk of injury to the heart or great vessels makes the sternum a less desirable site for insertion. As such, the proximal tibia is typically preferred because it is easy to locate, provides a flat, wide surface for insertion, has minimal subcutaneous layers overlying the bone, and doesn’t interfere with CPR. Several IO access devices are commercially available that allow for rapid insertion and are easy to use.

Clinical trials have documented success rates greater than 80% and placement times in 1 to 2 minutes.[125]

In the event that neither IV nor IO access can be established, a few drugs can be administered through an endotracheal tube. These drugs are atropine, lidocaine, epinephrine, naloxone, and vasopressin.[79] There are no data with amiodarone. Medications administered through the endotracheal route will have both a lower and delayed peak concentration than when drugs are administered by the IV or IO routes. Animal studies have suggested that the lower epinephrine concentrations seen after endotracheal administration may lead to vasodilation, and clinical trials in humans have also failed to demonstrate any benefit when using the endotracheal route.[127,128] In one clinical trial, lower rates of ROSC, hospital admission, and hospital discharge were observed with endotracheal drug administration compared to IV.[128] If the endotracheal route is to be used, the recommended medication dose is 2 to 2.5 times larger than the IV/IO dose. Providers should dilute the medication in 5 to 10 mL of either sterile water or normal saline. Better drug absorption may be achieved with sterile water.[79]

EVALUATION OF THERAPEUTIC OUTCOMES

The optimal outcome following CPR is an awake, responsive, spontaneously breathing patient. Patients must remain neurologically intact with minimal morbidity following the resuscitation if it is to be considered a success.

Monitoring during cardiac arrest includes both CPR performance and physiologic. CPR performance can be assessed using devices that provide real-time feedback on CPR quality. In many cases, rhythm assessment via ECG and pulse checks are the only physiologic parameters available to guide therapy. Palpating a pulse to determine the efficacy of blood flow during CPR, however, has not been shown to be useful. Invasive hemodynamic monitoring (eg, coronary perfusion pressure, central venous oxygenation) can provide useful information during CPR but these are seldom available. Arterial diastolic pressure may be a reasonable surrogate for coronary perfusion pressure; values less than 20 mm Hg are generally considered suboptimal and a goal of more than 25 mm Hg is suggested.[129] An arterial central venous oxygen saturation of less than 30% (0.30) is indicative of poor CPR quality.[79]

End-tidal carbon dioxide monitoring is a useful method to assess cardiac output during CPR and has been associated with ROSC. The main determinant of carbon dioxide excretion is the rate of delivery from the peripheral tissues to

the lungs. Increasing cardiac output through effective CPR will yield higher ETCO2 levels. Therefore, ETCO2 levels reflect the cardiac output generated by CPR. Persistently low ETCO2 values (<10 mm Hg [1.3 kPa]) during CPR in intubated patients suggest ROSC is unlikely.[31]The goal ETCO2 level during CPR should be at least 20 mm Hg (2.7 kPa).[129]

Evaluation of outcomes in the postresuscitative phase should be directed toward the components of the postcardiac arrest syndrome. The precipitating cause of the arrest should be identified and treated (eg, coronary angiography with prompt recanalization if indicated). Hemodynamics should be optimized with avoidance of hypotension (MAP <65 mm Hg or SBP <90 mm Hg).[92] Oxygenation should be closely monitored with the maintenance of arterial blood oxygen saturation above 94% (0.94).[96] Seizures can occur in up to 24% of adults and 47% of children following cardiac arrest, thus EEG monitoring is indicated.[95] Hyperthermia has been associated with poor outcomes and should be avoided.[92] Normoglycemia should be maintained. Because the postcardiac arrest syndrome can affect practically every organ-system, a review-of-systems approach for assessment (ie, “head-to-toe”) is strongly suggested.

CONCLUSION

Cardiac arrest is often fatal but rapid recognition and treatment can result in a favorable outcome. The “Chains of Survival” as described by the AHA provide a framework for treatment. Early recognition and response including high-quality chest compressions with minimal interruptions, early defibrillation, and postresuscitative care remain major hallmarks of therapy. Nevertheless, there are many areas of uncertainty such as the optimal approach for oxygenation and ventilation, the role of drug therapy (eg, epinephrine), the value of therapeutic hypothermia, resuscitation targets, the role of extracorporeal therapies (ie, cardiopulmonary bypass), and the value of neuroprotective agents.[130] A comprehensive research approach, consisting of randomized controlled trials, registry-based studies, pragmatic trials, and animal/laboratory research will be necessary to advance our understanding and improve outcomes.

Postclass Engaged Learning Activity

Watch the following video illustrating cardiocerebral resuscitation of an out-of-hospital cardiac arrest at https://tinyurl.com/y3gcljnn

ABBREVIATIONS

ACLS	advanced cardiac life support
AED	automated external defibrillator
AHA	American Heart Association
BLS	basic life support
CCR	cardiocerebral resuscitation
CI	confidence interval
CPP	coronary perfusion pressure
CPR	cardiopulmonary resuscitation
ECC	emergency cardiovascular care
ECG	electrocardiogram
EMS	emergency medical services
ETCO2	end-tidal carbon dioxide
IO	intraosseous
IV	intravenous
MAP	mean arterial pressure
OR	odds ratio
PCI	percutaneous coronary intervention
PEA	pulseless electrical activity
PE	pulmonary embolism
ROSC	return of spontaneous circulation
PVT	pulseless ventricular tachycardia
SBP	systolic blood pressure
VF	ventricular fibrillation

REFERENCES

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: a report from the American Heart Association. *Circulation*. 2017;135:e146–e603.
2. Chan PS, McNally B, Tang F, Kellermann A. Recent trends in survival from out-of-hospital cardiac arrest in the United States. *Circulation*. 2014;130:1876–1882.
3. Nolan JP, Soar J, Smith GB, et al. Incidence and outcome of in-hospital cardiac arrest in the United Kingdom National Cardiac Arrest Audit. *Resuscitation*. 2014;85:987–992.
4. Center for Disease Control and Prevention. 2016 Cardiac Arrest Registry

to Enhance Survival (CARES) National Summary Report. 2018. https://mycares.net/sitepages/uploads/2017/2016%20Non-Traumatic%20National%20Summary%20Report.pdf. Accessed January 25, 2018.

5. Weil MH, Fries M. In-hospital cardiac arrest. *Crit Care Med*. 2005;33:2825–2830.
6. Weil MH, Tang W. Rhythms and outcomes of cardiac arrest. *Crit Care Med*. 2010;38:310.
7. Atkins DL, Everson-Stewart S, Sears GK, et al. Epidemiology and outcomes from out-of-hospital cardiac arrest in children: the Resuscitation Outcomes Consortium Epistry-Cardiac Arrest. *Circulation*. 2009;119:1484–1491.
8. Atkins DL, Berger S. Improving outcomes from out-of-hospital cardiac arrest in young children and adolescents. *Pediatr Cardiol*. 2012;33:474–483.
9. Berg RA, Nadkarni VM, Clark AE, et al. Incidence and outcomes of cardiopulmonary resuscitation in PICUs. *Crit Care Med*. 2016;44:798–808.
10. Girotra S, Spertus JA, Li Y, Berg RA, Nadkarni VM, Chan PS. Survival trends in pediatric in-hospital cardiac arrests: an analysis from Get With the Guidelines-Resuscitation. *Circ Cardiovasc Qual Outcomes*. 2013;6:42–49.
11. Hayashi M, Shimizu W, Albert CM. The spectrum of epidemiology underlying sudden cardiac death. *Circ Res*. 2015;116:1887–1906.
12. Kleinman ME, Chameides L, Schexnayder SM, et al. Part 14: pediatric advanced life support: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2010;122:S876–908.
13. Ewy GA. Cardiocerebral and cardiopulmonary resuscitation—2017 update. *Acute Med Surg*. 2017;4:227–234.
14. Mancini ME, Diekema DS, Hoadley TA, et al. Part 3: ethical issues: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2015;132:S383–396.
15. Kouwenhoven WB, Jude JR, Knickerbocker GG. Closed-chest cardiac massage. *JAMA*. 1960;173:1064–1067.
16. Safar P. Community-wide cardiopulmonary resuscitation. *J Iowa Med Soc*.

1964;54:629–635.

17. Cooper JA, Cooper JD, Cooper JM. Cardiopulmonary resuscitation: history, current practice, and future direction. *Circulation*. 2006;114:2839–2849.
18. Cardiopulmonary resuscitation. Statement by the Ad Hoc Committee on Cardiopulmonary Resuscitation of the Division of Medical Sciences, National Academy of Sciences—National Research Council. *JAMA*. 1966;198:372–379. 10.1001/jama.1966.03110170084023.
19. Neumar RW, Shuster M, Callaway CW, et al. Part 1: executive summary: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2015;132:S315–367.
20. American Heart Association. Guidelines for CPR and emergency cardiovascular care. 2018. https://eccguidelines.heart.org/index.php/circulation/cpr-ecc-guidelines-2/. Accessed January 26, 2018.
21. Kleinman ME, Brennan EE, Goldberger ZD, et al. Part 5: adult basic life support and cardiopulmonary resuscitation quality: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2015;132:S414–435.
22. Harris AW, Kudenchuk PJ. Cardiopulmonary resuscitation: the science behind the hands. *Heart*. 2018.;104:1056–1061.
23. Soar J, Edelson DP, Perkins GD. Delivering high-quality cardiopulmonary resuscitation in-hospital. *Curr Opin Crit Care*. 2011;17:225–230.
24. Nassar BS, Kerber R. Improving CPR performance. *Chest*. 2017;152:1061–1069.
25. Kronick SL, Kurz MC, Lin S, et al. Part 4: systems of care and continuous quality improvement: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2015;132:S397–413.
26. Sanghavi P, Jena AB, Newhouse JP, Zaslavsky AM. Outcomes after out-of-hospital cardiac arrest treated by basic vs advanced life support. *JAMA Intern Med*. 2015;175:196–204.
27. Larsen MP, Eisenberg MS, Cummins RO, Hallstrom AP. Predicting survival from out-of-hospital cardiac arrest: a graphic model. *Ann Emerg Med*. 1993;22:1652–1658.
28. Link MS, Atkins DL, Passman RS, et al. Part 6: electrical therapies:

automated external defibrillators, defibrillation, cardioversion, and pacing: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2010;122:S706–719.

29. Eberle B, Dick WF, Schneider T, Wisser G, Doetsch S, Tzanova I. Checking the carotid pulse check: diagnostic accuracy of first responders in patients with and without a pulse. *Resuscitation*. 1996;33:107–116.
30. Kleinman ME, Goldberger ZD, Rea T, et al. 2017 American Heart Association focused update on adult basic life support and cardiopulmonary resuscitation quality: an update to the American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2018;137:e7–e13.
31. Link MS, Berkow LC, Kudenchuk PJ, et al. Part 7: adult advanced cardiovascular life support: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2015;132:S444–464.
32. Hartmann SM, Farris RW, Di Gennaro JL, Roberts JS. Systematic review and meta-analysis of end-tidal carbon dioxide values associated with return of spontaneous circulation during cardiopulmonary resuscitation. *J Intensive Care Med*. 2015;30:426–435.
33. Ewy GA, Bobrow BJ. Cardiocerebral resuscitation: an approach to improving survival of patients with primary cardiac arrest. *J Intensive Care Med*. 2016;31:24–33.
34. Weisfeldt ML, Becker LB. Resuscitation after cardiac arrest: a 3-phase time-sensitive model. *JAMA*. 2002;288:3035–3038.
35. Salmen M, Ewy GA, Sasson C. Use of cardiocerebral resuscitation or AHA/ERC 2005 guidelines is associated with improved survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. *BMJ Open*. 2012;2:e001273.
36. Cobb LA, Fahrenbruch CE, Walsh TR, et al. Influence of cardiopulmonary resuscitation prior to defibrillation in patients with out-of-hospital ventricular fibrillation. *JAMA*. 1999;281:1182–1188.
37. Garza AG, Gratton MC, Salomone JA, Lindholm D, McElroy J, Archer R. Improved patient survival using a modified resuscitation protocol for out-of-hospital cardiac arrest. *Circulation*. 2009;119:2597–2605.
38. Kellum MJ, Kennedy KW, Ewy GA. Cardiocerebral resuscitation improves survival of patients with out-of-hospital cardiac arrest. *Am J*

Med. 2006;119:335–340.

39. Wik L, Hansen TB, Fylling F, et al. Delaying defibrillation to give basic cardiopulmonary resuscitation to patients with out-of-hospital ventricular fibrillation: a randomized trial. *JAMA*. 2003;289:1389–1395.
40. Chamberlain D, Frenneaux M, Fletcher D. The primacy of basics in advanced life support. *Curr Opin Crit Care* 2009;15:198-202.
41. Robinson LA, Brown CG, Jenkins J, et al. The effect of norepinephrine versus epinephrine on myocardial hemodynamics during CPR. *Ann Emerg Med*. 1989;18:336–340.
42. Paradis NA, Martin GB, Rivers EP, et al. Coronary perfusion pressure and the return of spontaneous circulation in human cardiopulmonary resuscitation. *JAMA*. 1990;263:1106–1113.
43. Reynolds JC, Salcido DD, Menegazzi JJ. Conceptual models of coronary perfusion pressure and their relationship to defibrillation success in a porcine model of prolonged out-of-hospital cardiac arrest. *Resuscitation*. 2012;83:900–906.
44. Attaran RR, Ewy GA. Epinephrine in resuscitation: curse or cure? *Future Cardiol*. 2010;6:473–482.
45. Olasveengen TM, Sunde K, Brunborg C, Thowsen J, Steen PA, Wik L. Intravenous drug administration during out-of-hospital cardiac arrest: a randomized trial. *JAMA*. 2009;302:2222–2229.
46. Jacobs IG, Finn JC, Jelinek GA, Oxer HF, Thompson PL. Effect of adrenaline on survival in out-of-hospital cardiac arrest: A randomised double-blind placebo-controlled trial. *Resuscitation*. 2011;82:1138–1143.
47. Hagihara A, Hasegawa M, Abe T, Nagata T, Wakata Y, Miyazaki S. Prehospital epinephrine use and survival among patients with out-of-hospital cardiac arrest. *JAMA*. 2012;307:1161–1168.
48. Nakahara S, Tomio J, Takahashi H, et al. Evaluation of pre-hospital administration of adrenaline (epinephrine) by emergency medical services for patients with out of hospital cardiac arrest in Japan: controlled propensity matched retrospective cohort study. *BMJ* 2013;347:f6829.
49. Andersen LW, Berg KM, Saindon BZ, et al. Time to epinephrine and survival after pediatric in-hospital cardiac arrest. *JAMA*. 2015;314:802–810.
50. Donnino MW, Salciccioli JD, Howell MD, et al. Time to administration of epinephrine and outcome after in-hospital cardiac arrest with non-shockable rhythms: retrospective analysis of large in-hospital data registry.

Br Med J. 2014;348:g3028.

51. Ewy GA, Bobrow BJ, Chikani V, et al. The time dependent association of adrenaline administration and survival from out-of-hospital cardiac arrest. *Resuscitation*. 2015;96:180–185.
52. Koscik C, Pinawin A, McGovern H, et al. Rapid epinephrine administration improves early outcomes in out-of-hospital cardiac arrest. *Resuscitation*. 2013;84:915–920.
53. Dumas F, Bougouin W, Geri G, et al. Is epinephrine during cardiac arrest associated with worse outcomes in resuscitated patients? *J Am Coll Cardiol*. 2014;64:2360–2367.
54. Ristagno G, Tang W, Huang L, et al. Epinephrine reduces cerebral perfusion during cardiopulmonary resuscitation. *Crit Care Med*. 2009;37:1408–1415.
55. Deakin CD, Yang J, Nguyen R, et al. Effects of epinephrine on cerebral oxygenation during cardiopulmonary resuscitation: a prospective cohort study. *Resuscitation*. 2016;109:138–144.
56. Rivers EP, Wortsman J, Rady MY, Blake HC, McGeorge FT, Buderer NM. The effect of the total cumulative epinephrine dose administered during human CPR on hemodynamic, oxygen transport, and utilization variables in the postresuscitation period. *Chest*. 1994;106:1499–1507.
57. Huang L, Sun S, Fang X, Tang W, Weil MH. Simultaneous blockade of alpha1- and beta-actions of epinephrine during cardiopulmonary resuscitation. *Crit Care Med*. 2006;34:S483–485.
58. Larabee TM, Liu KY, Campbell JA, Little CM. Vasopressors in cardiac arrest: a systematic review. *Resuscitation*. 2012;83:932–939.
59. Ornato JP. Use of adrenergic agonists during CPR in adults. *Ann Emerg Med*. 1993;22:411–416.
60. Brown C, Wiklund L, Bar-Joseph G, et al. Future directions for resuscitation research. IV. Innovative advanced life support pharmacology. *Resuscitation*. 1996;33:163–177.
61. Callaham M, Madsen CD, Barton CW, Saunders CE, Pointer J. A randomized clinical trial of high-dose epinephrine and norepinephrine vs standard-dose epinephrine in prehospital cardiac arrest. *JAMA*. 1992;268:2667–2672.
62. Lindner KH, Ahnefeld FW, Grunert A. Epinephrine versus norepinephrine in prehospital ventricular fibrillation. *Am J Cardiol*. 1991;67:427–428.

63. Redding JS, Pearson JW. Evaluation of drugs for cardiac resuscitation. *Anesthesiology*. 1963;24:203–207.
64. Wenzel V, Raab H, Dunser MW. Role of arginine vasopressin in the setting of cardiopulmonary resuscitation. *Best Pract Res Clin Anaesthesiol*. 2008;22:287–297.
65. Lindner KH, Haak T, Keller A, Bothner U, Lurie KG. Release of endogenous vasopressors during and after cardiopulmonary resuscitation. *Heart*. 1996;75:145–150.
66. Aung K, Htay T. Vasopressin for cardiac arrest: a systematic review and meta-analysis. *Arch Intern Med* 2005;165:17-24.
67. Biondi-Zoccai GG, Abbate A, Parisi Q, et al. Is vasopressin superior to adrenaline or placebo in the management of cardiac arrest? A meta-analysis *Resuscitation*. 2003;59:221–224.
68. Layek A, Maitra S, Pal S, Bhattacharjee S, Baidya DK. Efficacy of vasopressin during cardio-pulmonary resuscitation in adult patients: a meta-analysis. *Resuscitation*. 2014;85:855–863.
69. Mentzelopoulos SD, Zakynthinos SG, Siempos I, Malachias S, Ulmer H, Wenzel V. Vasopressin for cardiac arrest: meta-analysis of randomized controlled trials. *Resuscitation*. 2012;83:32–39.
70. Sillberg VA, Perry JJ, Stiell IG, Wells GA. Is the combination of vasopressin and epinephrine superior to repeated doses of epinephrine alone in the treatment of cardiac arrest: a systematic review. *Resuscitation*. 2008;79:380–386.
71. Zhang Q, Liu B, Zhao L, et al. Efficacy of vasopressin-epinephrine compared to epinephrine alone for out of hospital cardiac arrest patients: a systematic review and meta-analysis. *Am J Emerg Med*. 2017;35:1555–1560.
72. Mentzelopoulos SD, Malachias S, Chamos C, et al. Vasopressin, steroids, and epinephrine and neurologically favorable survival after in-hospital cardiac arrest: a randomized clinical trial. *JAMA*. 2013;310:270–279.
73. Mentzelopoulos SD, Zakynthinos SG, Tzoufi M, et al. Vasopressin, epinephrine, and corticosteroids for in-hospital cardiac arrest. *Arch Intern Med* 2009;169:15-24.
74. Huang Y, He Q, Yang M, Zhan L. Antiarrhythmia drugs for cardiac arrest: a systemic review and meta-analysis. *Crit Care* 2013;17:R173.
75. Ong ME, Pellis T, Link MS. The use of antiarrhythmic drugs for adult cardiac arrest: a systematic review. *Resuscitation*. 2011;82:665–670.

76. Kudenchuk PJ, Cobb LA, Copass MK, et al. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med*. 1999;341:871–878.
77. Dorian P, Cass D, Schwartz B, Cooper R, Gelaznikas R, Barr A. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. *N Engl J Med*. 2002;346:884–890.
78. Kudenchuk PJ, Brown SP, Daya M, et al. Amiodarone, lidocaine, or placebo in out-of-hospital cardiac arrest. *N Engl J Med*. 2016;374:1711–1722.
79. Neumar RW, Otto CW, Link MS, et al. Part 8: adult advanced cardiovascular life support: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2010;122:S729–767.
80. Harrison EE. Lidocaine in prehospital countershock refractory ventricular fibrillation. *Ann Emerg Med*. 1981;10:420–423.
81. Herlitz J, Ekstrom L, Wennerblom B, et al. Lidocaine in out-of-hospital ventricular fibrillation. Does it improve survival? *Resuscitation*. 1997;33:199–205.
82. Weaver WD, Fahrenbruch CE, Johnson DD, Hallstrom AP, Cobb LA, Copass MK. Effect of epinephrine and lidocaine therapy on outcome after cardiac arrest due to ventricular fibrillation. *Circulation*. 1990;82:2027–2034.
83. Bottiger BW, Arntz HR, Chamberlain DA, et al. Thrombolysis during resuscitation for out-of-hospital cardiac arrest. *N Engl J Med*. 2008;359:2651–2662.
84. Lavonas EJ, Drennan IR, Gabrielli A, et al. Part 10: special circumstances of resuscitation: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2015;132:S501–518.
85. Hachimi-Idrissi S, Corne L, Ebinger G, Michotte Y, Huyghens L. Mild hypothermia induced by a helmet device: a clinical feasibility study. *Resuscitation*. 2001;51:275–281.
86. Donnino MW, Andersen LW, Berg KM, et al. Temperature management after cardiac arrest: an advisory statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care,

Perioperative and Resuscitation. *Resuscitation*. 2016;98:97–104.

87. Goto Y, Maeda T, Goto Y. Effects of prehospital epinephrine during out-of-hospital cardiac arrest with initial non-shockable rhythm: an observational cohort study. *Crit Care* 2013;17:R188.
88. Gonzalez ER. Pharmacologic controversies in CPR. *Ann Emerg Med*. 1993;22:317–323.
89. Velissaris D, Karamouzos V, Pierrakos C, Koniari I, Apostolopoulou C, Karanikolas M. Use of sodium bicarbonate in cardiac arrest: current guidelines and literature review. *J Clin Med Res*. 2016;8:277–283.
90. Kawano T, Grunau B, Scheuermeyer FX, et al. Prehospital sodium bicarbonate use could worsen long term survival with favorable neurological recovery among patients with out-of-hospital cardiac arrest. *Resuscitation*. 2017;119:63–69.
91. Bjerneroth G. Tribonat: a comprehensive summary of its properties. *Crit Care Med*. 1999;27:1009–1013.
92. Callaway CW, Donnino MW, Fink EL, et al. Part 8: post-cardiac arrest care: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2015;132:S465–482.
93. Madder RD, Reynolds JC. Multidisciplinary management of the post-cardiac arrest patient. *Cardiol Clin*. 2018;36:85–101.
94. Neumar RW, Nolan JP, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. *Circulation*. 2008;118:2452–2483.
95. Elmer J, Polderman KH. Emergency neurological life support: resuscitation following cardiac arrest. *Neurocrit Care*. 2017;27:134–143.
96. Nolan JP, Soar J, Cariou A, et al. European Resuscitation Council and European Society of Intensive Care Medicine 2015 guidelines for post-

resuscitation care. *Intensive Care Med*. 2015;41:2039–2056.

97. The Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002;346:549–556.
98. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002;346:557–563.
99. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. *N Engl J Med*. 2013;369:2197–2206.
100. Kim F, Nichol G, Maynard C, et al. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: a randomized clinical trial. *JAMA* 2014;311:45-52.
101. Kirkegaard H, Soreide E, de Haas I, et al. Targeted temperature management for 48 vs 24 Hours and neurologic outcome after out-of-hospital cardiac arrest: A randomized clinical trial. *JAMA*. 2017;318:341–350.
102. Chan PS, Berg RA, Tang Y, Curtis LH, Spertus JA. Association between therapeutic hypothermia and survival after in-hospital cardiac arrest. *JAMA*. 2016;316:1375–1382.
103. Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic hypothermia after in-hospital cardiac arrest in children. *N Engl J Med*. 2017;376:318–329.
104. Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in children. *N Engl J Med*. 2015;372:1898–1908.
105. Zeiner A, Holzer M, Sterz F, et al. Hyperthermia after cardiac arrest is associated with an unfavorable neurologic outcome. *Arch Intern Med*. 2001;161:2007–2012.
106. Vanden Hoek TL, Morrison LJ, Shuster M, et al. Part 12: cardiac arrest in special situations: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2010;122:S829–861.
107. McFadden ER, Jr., Warren EL. Observations on asthma mortality. *Ann Intern Med*. 1997;127:142–147.
108. Hess DR, Acosta FL, Ritz RH, Kacmarek RM, Camargo CA. The effect of heliox on nebulizer function using a beta-agonist bronchodilator. *Chest*.

1999;115:184–189.

109. Petrillo TM, Fortenberry JD, Linzer JF, Simon HK. Emergency department use of ketamine in pediatric status asthmaticus. *J Asthma*. 2001;38:657–664.
110. Rodrigo GJ, Castro-Rodriguez JA. Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis. *Thorax* 2005;60:740-6.
111. Schultz TE. Sevoflurane administration in status asthmaticus: a case report. *AANA J*. 2005;73:35–36.
112. Silverman RA, Osborn H, Runge J, et al. IV magnesium sulfate in the treatment of acute severe asthma: a multicenter randomized controlled trial. *Chest*. 2002;122:489–497.
113. Soroksky A, Stav D, Shpirer I. A pilot prospective, randomized, placebo-controlled trial of bilevel positive airway pressure in acute asthmatic attack. *Chest*. 2003;123:1018–1025.
114. Neugut AI, Ghatak AT, Miller RL. Anaphylaxis in the United States: an investigation into its epidemiology. *Arch Intern Med* 2001;161:15-21.
115. Schummer C, Wirsing M, Schummer W. The pivotal role of vasopressin in refractory anaphylactic shock. *Anesth Analg*. 2008;107:620–624.
116. Brown SG, Blackman KE, Stenlake V, Heddle RJ. Insect sting anaphylaxis; prospective evaluation of treatment with intravenous adrenaline and volume resuscitation. *Emerg Med J*. 2004;21:149–154.
117. Mhyre JM, Tsen LC, Einav S, Kuklina EV, Leffert LR, Bateman BT. Cardiac arrest during hospitalization for delivery in the United States, 1998-2011. *Anesthesiology*. 2014;120:810–818.
118. Jeejeebhoy FM, Zelop CM, Lipman S, et al. Cardiac arrest in pregnancy: a scientific statement from the American Heart Association. *Circulation*. 2015;132:1747–1773.
119. Seamon MJ, Haut ER, Van Arendonk K, et al. An evidence-based approach to patient selection for emergency department thoracotomy: a practice management guideline from the Eastern Association for the Surgery of Trauma. *J Trauma Acute Care Surg*. 2015;79:159–73.
120. Link MS, Maron BJ, Wang PJ, VanderBrink BA, Zhu W, Estes NA 3rd. Upper and lower limits of vulnerability to sudden arrhythmic death with chest-wall impact (commotio cordis). *J Am Coll Cardiol*. 2003;41:99–104.
121. Quan L, Mack CD, Schiff MA. Association of water temperature and

submersion duration and drowning outcome. *Resuscitation*. 2014;85:790–794.

122. Szpilman D, Webber J, Quan L, et al. Creating a drowning chain of survival. *Resuscitation*. 2014;85:1149–1152.
123. Vincent R. Drugs in modern resuscitation. *Br J Anaesth*. 1997;79:188–197.
124. Kellum MJ. Improving performance of emergency medical services personnel during resuscitation of cardiac arrest patients: the McMAID approach. *Curr Opin Crit Care*. 2009;15:216–220.
125. Weiser G, Hoffmann Y, Galbraith R, Shavit I. Current advances in intraosseous infusion: a systematic review. *Resuscitation*. 2012;83:20–26.
126. Hoskins SL, do Nascimento P, Jr., Lima RM, Espana-Tenorio JM, Kramer GC. Pharmacokinetics of intraosseous and central venous drug delivery during cardiopulmonary resuscitation. *Resuscitation*. 2012;83:107–112.
127. Niemann JT, Stratton SJ. Endotracheal versus intravenous epinephrine and atropine in out-of-hospital “primary” and postcountershock asystole. *Crit Care Med*. 2000;28:1815–1819.
128. Niemann JT, Stratton SJ, Cruz B, Lewis RJ. Endotracheal drug administration during out-of-hospital resuscitation: where are the survivors? *Resuscitation*. 2002;53:153–157.
129. Meaney PA, Bobrow BJ, Mancini ME, et al. Cardiopulmonary resuscitation quality: improving cardiac resuscitation outcomes both inside and outside the hospital. A consensus statement from the American Heart Association. *Circulation*. 2013;128:417–435.
130. Nolan JP, Berg RA, Bernard S, et al. Intensive care medicine research agenda on cardiac arrest. *Intensive Care Med*. 2017;43:1282–1293.

41

Shock Syndromes

Seth R. Bauer, Robert MacLaren, and Brian L. Erstad

KEY CONCEPTS

1. The presence of shock is indicated by inadequate global tissue perfusion. Low blood pressures represent states of poor tissue perfusion but are not required to define shock.
2. Shock is typically classified into one of four etiologic mechanisms: (1) hypovolemic, (2) cardiogenic, (3) obstructive, or (4) vasodilatory/distributive.
3. Shock syndromes can be differentiated based on evaluation of preload, cardiac output, and afterload or assessment of surrogate markers.
4. Inadequate oxygen delivery leads to organ damage in critical illness.
5. Blood lactate should be measured in all patients in whom shock is suspected.
6. Treatment of the patient with circulatory shock can be divided into four phases: salvage, optimization, stabilization, and de-escalation. Each phase has different but sometimes overlapping goals and therapeutic strategies.
7. Crystalloid solutions are the first-line fluid of choice for forms of circulatory insufficiency that are associated with hemodynamic instability.
8. Vasopressors and inotropes are required in patients with shock when volume resuscitation fails to maintain adequate blood pressure and tissues remain hypoperfused.
9. The choice of a particular vasopressor or inotrope agent depends on the underlying shock pathophysiology, goals of therapy, and clinical pharmacology.
10. Norepinephrine is the preferred initial vasopressor for shock.

Preclass Engaged Learning Activity

Develop a table that has two columns, one titled crystalloid solutions and one titled colloid solutions. In each column, list at least four potential advantages and four potential disadvantages of the solution. Note that there are a number of crystalloid and colloid solutions that are commercially available, so you will need to be specific about the solutions included in the table. The purpose of this exercise is to help students choose a preferred resuscitation fluid for a critically ill patient based on patient-specific data.

INTRODUCTION

Circulatory shock is a medical emergency requiring prompt recognition and treatment because it can quickly lead to serious pathophysiologic consequences, including patient death. Shock is a broad term for a heterogeneous group of syndromes that cause an acute, generalized form of circulatory failure associated with inadequate oxygen utilization by the cells.[1] Typically, shock is characterized as a systolic blood pressure (SBP) <90 mm Hg (or acute reduction of at least 40 mm Hg from baseline) or mean arterial blood pressure (MAP) <70 mm Hg with tachycardia and organ perfusion abnormalities.[2] The key feature of all shock syndromes is inadequate tissue and organ perfusion.

Learners are strongly encouraged to read Chapter e29 “Evaluation of Cardiovascular Function” and Chapter 137 “Sepsis and Septic Shock” to augment their understanding of the content in this chapter.

EPIDEMIOLOGY

Hemodynamic compromise necessitating vasopressors is common in the intensive care unit (ICU), with about one-third of critically ill patients receiving vasopressors during their clinical course.[3] Shock is not a reportable category by state and federal agencies that track causes of death and, thus, the true incidence is unknown. Reported mortality of patients with shock in clinical studies from the 1980s exceeded 70%, but now ranges from 20% to 55%.[4–7] However, estimates of deaths due to shock are complicated by differences in definitions and classification systems. Part of the problem is defining when progressive circulatory insufficiency results in the loss of normal compensatory responses by the body, which could reverse the processes leading to irreversible organ

dysfunction. This loss of appropriate compensation varies from patient to patient and is not always readily apparent during the initial patient presentation. Therefore, forms of shock, such as hemorrhagic shock, are often subsumed by more readily identifiable categories of death, such as accidental injuries and homicides.

ETIOLOGY

1 The presence of circulatory shock is indicated by inadequate global tissue perfusion. Circulatory shock develops when the cardiovascular system is unable to deliver an adequate oxygen supply to meet tissue oxygen demands, resulting in cellular dysfunction. This cellular dysoxia leads to a shift in cellular metabolism to anaerobic pathways and results in elevated blood lactate concentrations. Physiologically, tissue metabolic requirements are met by both adequate MAP and adequate oxygen delivery (DO_2). The MAP is the driving pressure for peripheral blood flow and end-organ perfusion. Tissue blood flow cannot be directly measured; therefore, MAP is used as a surrogate estimate. Because the components of blood pressure are cardiac output (CO) and systemic vascular resistance (SVR), and CO is a determinant of DO_2, blood pressure is integrally related to DO_2. However, compensatory mechanisms such as vasoconstriction may preserve blood pressure while tissue perfusion is inadequate. Therefore, while low blood pressure is commonly present in patients with shock, it is not required to define shock.[1]

2 Shock is typically classified into one of four etiologic mechanisms: (1) hypovolemic, (2) cardiogenic, (3) obstructive, or (4) vasodilatory/distributive. Vasodilatory/distributive is the most commonly encountered shock syndrome, which accounts for about two-thirds of all shock cases requiring vasopressors. Cardiogenic and hypovolemic shock are both encountered in about 16% of cases, while obstructive shock is rarely encountered (about 2% of cases).[2] Notably, patients may have components of more than one shock syndrome on presentation (the categories are not mutually exclusive) and patients can transition from one shock type to another (eg, a patient with cardiogenic shock may subsequently develop septic shock, or a patient with septic shock may develop cardiogenic shock from a myocardial infarction). Hypovolemic, cardiogenic, and obstructive shock are all characterized by low CO, but the mechanism for low CO is different in each shock state. Hypovolemic shock is caused by inadequate venous return, from internal or external loss of

intravascular fluids (eg, trauma, surgery, or hemorrhage), resulting in insufficient cardiac preload and decreased stroke volume. Cardiogenic shock results from a loss in pump function, either through decreased cardiac contractility (eg, myocardial infarction), acute valvular abnormality, or an arrhythmia (eg, ventricular tachycardia). Obstructive shock results from an extracardiac obstruction to blood flow into or out of the heart, such as tension pneumothorax, cardiac tamponade, or pulmonary embolism.

Vasodilatory/distributive shock is distinctly different than the other three forms of shock because it is characterized by a loss of vascular tone. Vasodilatory shock is a general term that describes tissue hypoperfusion due to a decrease in SVR (or hypoperfusion despite a normal or elevated CO). Technically, distributive shock is a subset of vasodilatory shock characterized by maldistribution of blood flow in the microcirculation (consisting of arterioles, capillaries, and venules) or at the organ level. However, since most cases of vasodilatory shock result in distributive shock the terms are often used interchangeably. Septic shock causes vasodilatory/distributive shock in 96% of cases, but this shock type can also be caused by a number of conditions, including neurogenic shock (typically secondary to acute spinal cord injury), immune-mediated (ie, anaphylactic) or nonimmunologic (ie, anaphylactoid) reactions, adrenal insufficiency, acute liver failure, or as a component of ischemia-reperfusion injury (eg, after cardiopulmonary bypass or return of spontaneous circulation after cardiac arrest).

PATHOPHYSIOLOGY

Each shock syndrome has a different etiology and resultant pathophysiology. However, since all shock syndromes lead to inadequate tissue perfusion and cellular dysoxia, they have the same effect on cellular metabolism. **Figure 41-1** provides a simplified view of the pathophysiology of circulatory insufficiency assuming the acute insult causing shock did not result in immediate patient death. Cell damage and death may occur from the primary insult or from ischemia-reperfusion injury. While the primary insult for shock leads to initial harm, the host response can also result in deleterious effects. Ischemia-reperfusion injury is a consequence of the host response to an abrupt decrease in tissue perfusion with subsequent restoration of perfusion, leading to a systemic inflammatory response syndrome with the release of a multitude of mediators that have complex interactions to further injury. In addition to edematous obstruction of capillaries and oxygen-free radical damage of cell membranes, a

number of cellular (eg, white blood cells and platelets) and humoral (eg, procoagulants, anticoagulants, complement, and kinins) components are activated, causing the release of other inflammatory mediators and the formation of microthrombi. The resulting reperfusion injury may range from readily reversible organ dysfunction to multiple-organ failure and death. Cells have varying responses to hypoxia, ranging from astrocytes that quit functioning almost immediately to other cells that may tolerate more prolonged periods of hypoperfusion. Left unmitigated, cell death occurs with prolonged injury and is usually heralded by vasodilation and acidosis.

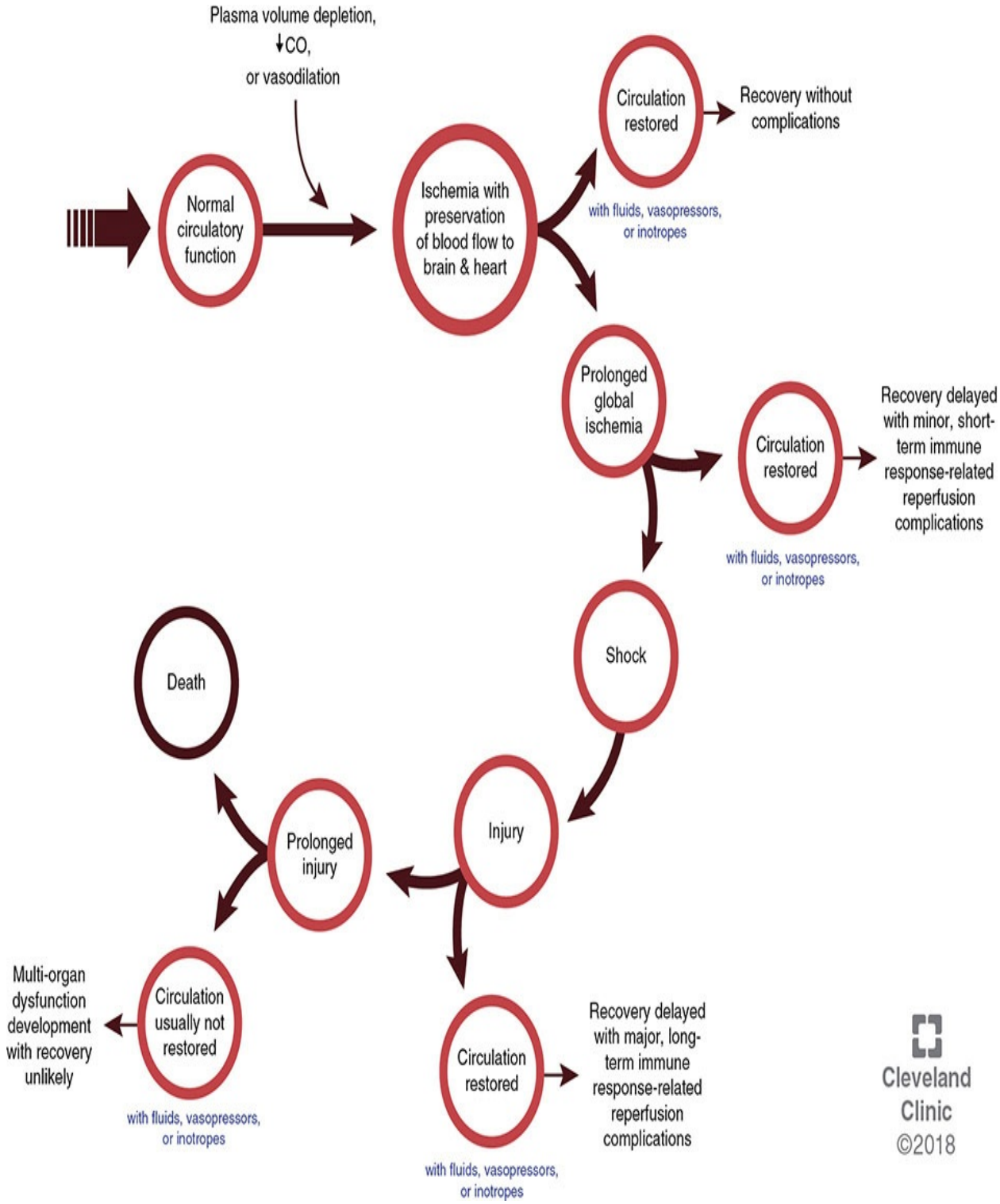


FIGURE 41-1 The pathophysiology of shock—detrimental outcomes versus recovery. (CO, cardiac output.) (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2018. All Rights Reserved.)

Most patients admitted to the ICU with circulatory shock have some level of

systemic inflammatory response syndrome, which is the body's response to tissue injury. This syndrome is defined by a number of hypermetabolic changes reflected in the patient's temperature, white blood cell count and differential, and respiratory and heart rates. The stress response involves complex interactions between the nervous system and immunomodulating substances and has similar (if not the same) harmful and helpful consequences described with reperfusion following shock. As part of the stress response, anti-inflammatory pathways are also activated to counterbalance the pro-inflammatory effects on local tissues. Vagal nerve-mediated release of acetylcholine leads to suppression of pro-inflammatory cytokines by macrophages.[8] Additionally, the renin-angiotensin-aldosterone and hypothalamic-pituitary-adrenocortical systems are activated, with angiotensin II, vasopressin, and cortisol released in order to maintain blood pressure through vasoconstriction and concomitantly retain sodium and water in the kidneys to increase cardiac preload. Cortisol and catecholamine release from the adrenal gland also inhibit pro-inflammatory cytokine production.[8] If the underlying problems are left untreated, the patient may develop multiple-organ dysfunction syndrome during the final stages of illness.

3 Conceptually, shock syndromes can be differentiated based on evaluation of preload, cardiac output, and afterload (**Fig. 41-2**).[2,9] For example, while hypovolemic and cardiogenic shocks both result in a decreased cardiac output, hypovolemic shock is caused by low cardiac preload and cardiogenic shock results in an elevated cardiac preload. Because cardiogenic shock and obstructive shock have the same profile in this conceptual model some experts consider the causes of obstructive shock to be etiologies of cardiogenic shock. Vasodilatory/distributive shock is typically described as a hyperdynamic shock state from low SVR, but a high cardiac output only develops after venous return is restored (typically with fluid resuscitation).[9,10] For this reason, vasodilatory/distributive shock may be divided into two stages; pre-resuscitation and post-resuscitation.

Shock State	Preload	CO	Afterload
Hypovolemic	↓	↓	↑
Cardiogenic	↑	↓	↑
Obstructive	↑	↓	↑
Vasodilatory/Distributive			
Pre-resuscitation	↓	↓	↓
Post-resuscitation	↑	↑	↓

FIGURE 41-2 Circles indicate primary dysfunction in shock state. (CO, cardiac output.)

Hypovolemic shock is extracellular volume depletion that may result from blood loss (plasma and red blood cells) due to trauma, surgery, or internal hemorrhage or from plasma loss due to fluid sequestered within the body or lost from the body. The body attempts to compensate for volume depletion beginning with autoregulatory vasoconstriction of smaller blood vessels. When the cause of circulatory insufficiency continues unabated, local mechanisms eventually fail to provide adequate compensation, and macrocirculatory changes ensue. With increasing volume depletion, blood flow to the heart (preload) is decreased, resulting in lower CO and subsequent activation of baroreceptors and chemoreceptors leading to sympathetic discharge. Also, fluid shifting from the interstitial space to the intravascular space occurs through a phenomenon known as transcapillary refill, and hormones (eg, adrenocorticotropic hormone, angiotensin, catecholamines, and vasopressin) that cause sodium and water retention by the kidneys are released. The phenomenon of transcapillary refill means that the body can have fluid losses exceeding normal plasma volume. These responses cause increases in stroke volume, heart rate, and systemic vascular resistance so that blood pressure and hence tissue perfusion can be maintained. However, if the initial insult is great enough the endogenous response is overcome and circulatory shock ensues. In the case of hemorrhage leading to hypovolemic shock (ie, hemorrhagic shock), prompt attention must be given to cellular as well as plasma losses. Red blood cells lost during the bleeding episode may compound ischemic damage in vital organs. Clotting factors and platelets are also lost in hemorrhage. The resulting bleeding problems may be aggravated by the dilutional effect of fluid resuscitation on clotting factor activity. This coagulopathy in hemorrhagic shock is typically

accompanied by acidosis and hypothermia and referred to as the lethal triad.

Cardiogenic shock is inadequate cardiac output from an intracardiac cause leading to tissue hypoperfusion. In about 80% of cases cardiogenic shock is caused by acute myocardial infarction leading to left ventricular dysfunction.[11] Mechanical irregularities complicating acute myocardial infarction, such as acute mitral regurgitation or ventricular septal or free wall rupture may also lead to cardiogenic shock. Less frequent causes include acute-on-chronic valvular heart disease, arrhythmias, and myocarditis. Isolated right ventricular cardiogenic shock is rare and will not be discussed. In the setting of acute myocardial infarction, coronary ischemia leads to an abrupt reduction in cardiac output, which causes a decrease in blood pressure and further impairs coronary perfusion. Sympathetic nervous system activation leads to compensatory tachycardia and vasoconstriction. While endogenous catecholamine release initially maintains blood pressure, it also increases myocardial oxygen demand, which can worsen ischemia and create a viscous cycle. As an adaptive mechanism, the left ventricle also dilates in order to maintain stroke volume. This leads to increased cardiac preload, pulmonary venous hypertension, and subsequent pulmonary edema. Patients with cardiogenic shock may also have cytokine-mediated vasodilation and microcirculatory dysfunction.[11,12]

The source of obstructive shock is an extracardiac obstruction to cardiovascular flow, which may lead to either impaired diastolic filling (eg, tension pneumothorax or cardiac tamponade) or impaired systolic contraction (eg, pulmonary embolism or acute-on-chronic pulmonary hypertension). In cases where diastolic filling is impaired, ventricular preload is decreased. However, in impaired systolic contraction ventricular afterload is abruptly increased, which leads to ventricular failure. Both etiologies of obstructive shock lead to decreased CO and similar compensatory mechanisms as with cardiogenic shock ensue.

Vasodilatory/distributive shock is caused by systemic vasodilation. This deficiency of vascular smooth muscle cell constriction may be from activation of vasodilatory mechanisms or a failure of vasoconstrictive pathways. In septic shock, the host response to the infecting pathogen leads to release of proinflammatory cytokines, which activate endothelial cells to increase expression of inducible nitric oxide synthase (iNOS) resulting in nitric oxide (NO) production. Nitric oxide subsequently causes vasodilation through the cyclic guanosine monophosphate pathway. Additionally, lactate and intracellular acidosis activate adenosine triphosphate (ATP)-sensitive potassium channels, which causes potassium efflux and cellular hyperpolarization. This

hyperpolarization impairs calcium influx through voltage-gated calcium channels even in the presence of vasoconstrictor ligands (eg, catecholamines, vasopressin, and angiotensin II), which in turn impedes cellular depolarization and vasoconstriction.[13] Consequently, the effectiveness of endogenous and exogenous vasoconstrictors is reduced. Prolonged exposure of vascular endothelial tissue to catecholamines may also promote receptor downregulation and "desensitization" to catecholamines. Systemic vasodilation causes ineffective circulating plasma volume through an increase in venous capacitance (venous pooling), which is exacerbated by loss of intravascular volume through capillary leak.[8,10] Decreased venous return leads to decreased cardiac preload and decreased CO. Fluid resuscitation and catecholamine administration can restore effective circulating plasma volume and a high CO state ensues in the setting of low left ventricular afterload. Some patients with septic shock may also have myocardial dysfunction after fluid resuscitation through mechanisms that are poorly understood (but not likely cytokine-mediated).[14,15] Furthermore, microthrombi and dysfunction of the microcirculation can lead to heterogeneous distribution of delivered oxygen and altered tissue perfusion despite macrocirculatory (eg, blood pressure and CO) goal attainment.[16]

4 Inadequate DO_2 leads to organ damage in critical illness. In normal individuals, oxygen consumption (VO_2) depends on DO_2 up to a certain critical level (VO_2 flow dependency). At this point, tissue oxygen requirements apparently are satisfied and further increases in DO_2 will not alter VO_2 (VO_2 flow independency). The point that VO_2 becomes dependent on DO_2 represents a pathologic transition from aerobic to anaerobic cellular metabolism and lactate production.[17,18] Although animal models of sepsis substantiate this relationship, studies in critically ill humans show a continuous, pathologic dependence relationship of VO_2 with DO_2. The apparent linear relationship between DO_2 and VO_2 has been questioned because both share variables, and this mathematical coupling can produce artifactual relationships between variables.[17] Inconsistent relationships between DO_2 and VO_2 are observed when VO_2 is measured independently by indirect calorimetry. While the systematic assessments of DO_2 and VO_2 and their dependence are rarely practiced, the concepts of ensuring adequate DO_2 are frequently applied. The DO_2 and VO_2 parameters are calculated as follows:

$$DO_2 = CO \times CaO_2$$

$$VO_2 = CO \times (CaO_2 - CvO_2)$$

where CO = cardiac output, CaO_2 = arterial oxygen content determined by hemoglobin concentration and arterial oxygen saturation, and CvO_2 = venous oxygen content determined by hemoglobin concentration and venous oxygen saturation (SvO_2).

Venous oximetry (ie, venous oxygen saturations) reflects the adequacy of tissue oxygenation.[18] SvO_2 and central venous oxygen saturation ($ScvO_2$) are the oxyhemoglobin saturation of venous blood obtained from the pulmonary artery and a central vein in the thorax, respectively, and are expressed as a percentage. When tissue oxygen demand exceeds supply, the oxygen extraction ratio (O_2ER) increases and values of SvO_2 and $ScvO_2$ are low. Rearranging the equations above shows that when hemoglobin, arterial oxygen saturation, and VO_2 are stable, SvO_2 or $ScvO_2$ values reflect CO. Thus, venous oximetry may be utilized as a surrogate for CO, and can be useful in shock state differentiation. Although SvO_2 and $ScvO_2$ are not equivalent, they correlate well in most circumstances and $ScvO_2$ is a reasonable approximation of SvO_2. Generally, SvO_2 values above 70% (0.70) are considered adequate and normal. However, SvO_2 values below 50% (0.50) are low and may approach the critical O_2ER where anaerobic metabolism will occur and lactate concentrations will increase. In isolation, firm conclusions about the O_2ER cannot be made from SvO_2 values between 50% (0.50) and 70% (0.70), and other markers of tissue perfusion should be utilized to interpret values in this range. High venous oximetry values (above 80% [0.80]) can represent a high CO, but may also be a poor prognostic sign indicating adequate DO_2 but poor capacity of tissues to extract oxygen.[18]

Hemodynamic parameters obtained from monitoring devices are critical to shock syndrome identification, therapeutic intervention selection, and monitoring a patient's response to therapy. Importantly, one hemodynamic parameter cannot show the complete hemodynamic profile, instead hemodynamics must be interpreted in the context of multiple parameters.[1] Also, a monitoring device by itself cannot improve patient-centered outcomes and the information obtained must be combined with evidence-based therapies. The type of shock may be clear based on the patient's presenting symptoms and physical exam. For example, a patient who presents after motor vehicle collision with frank blood loss most likely has hypovolemic shock (hemorrhagic shock

subtype). However, concomitant shock states may occur, such as cardiac tamponade due to hemopericardium from chest trauma in the above example. When further hemodynamic assessment is needed to initially evaluate the type of shock, echocardiography is suggested over more invasive methods (such as central venous or pulmonary artery catheters).[1] Critical care clinicians are frequently and increasingly trained to perform and evaluate transthoracic echocardiograms, which can lead to a rapid (within 5 minutes) and noninvasive diagnosis of the shock type.[16,19] A rapid assessment by cardiac echocardiography includes evaluation of left and right ventricular chamber size and function, pericardial appearance, and vena cava size with and without respiration. Additional assessments of valve structure/function and measurement of the left ventricular outflow tract velocity-time integral (which can be used to calculate stroke volume and CO) may also be performed.[2,19] Ventricular chamber size and function are the most crucial components for shock differentiation because they reflect ventricular filling and contractility, respectively.

Advanced hemodynamic monitoring may be necessary to augment the diagnosis or treatment of a patient with shock. Importantly, there is no high level evidence to support routine use of a central venous catheter in patients with shock. A central venous catheter placed in the internal jugular or subclavian vein may be used to measure the central venous pressure (CVP), to obtain venous samples for laboratory testing (including $ScvO_2$), and to administer drugs (including vasopressors) or fluids directly to the central circulation. A triple-lumen catheter frequently is used, whereby drugs with known incompatibility can be administered. The CVP may be used as an estimate of preload for shock state differentiation, but should not be utilized as a resuscitation goal.[1,20,21] In summary, estimates or surrogates for hemodynamic parameters that may be used include ventricular size on echocardiography or CVP as estimates for preload, and SvO_2, $ScvO_2$, or ventricular contractility on echocardiography as surrogates for CO.

The general goal of therapy during resuscitation from shock is to achieve and maintain MAP consistently above 65 mmHg while ensuring adequate perfusion to the critical organs.[1,2] Hemodynamic and perfusion monitoring can be categorized into two broad areas: global versus regional monitoring. Global parameters, such as systemic blood pressure, venous oximetry, and lactate, assess perfusion and oxygen utilization of the entire body. Regional monitoring techniques focus on tissue-specific oxygen delivery and subsequent changes in functional indices of individual organs. These measurements include coagulation

abnormalities (disseminated intravascular coagulation), altered renal and/or hepatic function, altered gastrointestinal perfusion, cool extremities, cardiac ischemia, and altered sensorium. Although none of these indices alone is a reliable indicator of adequate resuscitation, they offer immediate detection and may be prognostic of recovery when combined and defined at the level of organ function. As a result, these indices are frequently used as surrogate end points for the goals of resuscitation. While it is assumed that normalization of these parameters infers benefit, the clinician must first treat the patient rather than relying solely on data from continuous monitoring to guide therapy.

5 Blood lactate should be measured in all patients in whom shock is suspected.[1,2,22] Because lactate production is increased under anaerobic conditions, blood lactate concentration can be used as a diagnostic tool for tissue hypoperfusion.[23,24] However, not all lactate elevations are from Type A hyperlactatemia where oxygen demand exceeds supply. Type B hyperlactatemia is not related to tissue hypoxia, but instead is associated with an underlying disease (eg, malignancy or sepsis), a medication-related cause (eg, epinephrine, metformin, or linezolid), or inborn errors of metabolism.[24] Increased lactate production, reduced lactate elimination (commonly termed “clearance”), or the combination of these two mechanisms may lead to hyperlactatemia. Because lactate is predominantly metabolized by the liver, patients with severe liver dysfunction may have impaired lactate elimination accentuating lactate concentration elevations in shock. Additionally, regional tissue hypoperfusion (eg, arterial thrombosis leading to critical limb ischemia or mesenteric ischemia) may also produce elevated lactate concentrations. As such, if an elevated blood lactate concentration (>2 mmol/L) does not normalize after initial resuscitation the cause for the elevated concentration must be investigated and not assumed to be due to tissue hypoxia.

Blood pressures, CO, blood lactate, and venous oximetry parameters do not offer information about perfusion to individual organs. Organ-specific hypoxia may be evident by coagulopathy as indicated by thrombocytopenia (platelet count <100,000/L and/or prolonged clotting times [international normalized ratio >1.5 or activated partial thromboplastin time at least 1.5-fold the upper limit of normal]), impaired renal function with urine production <0.5 mL/kg/hr and/or increased serum concentrations of blood urea nitrogen and creatinine, altered hepatic function with substantially increased serum concentrations of transaminases and bilirubin, altered gastrointestinal perfusion manifested by ileus and diminished bowel sounds, cool extremities, cardiac ischemia with elevated troponin levels and electrocardiogram or echocardiography changes,

pulmonary ischemia with worsening partial pressure of arterial oxygen (PaO_2), and altered sensorium.[1,2,8] The success of resuscitation should be based on the combination of blood pressure, organ-specific parameters of regional perfusion, and global perfusion measurements.

The microcirculation plays a key role in tissue oxygenation because it is where oxygen release occurs. Microcirculatory blood flow is often altered in patients with shock (particularly in patients with septic shock) and improvements in microcirculatory blood flow are associated with improved patient outcomes.[25] Monitoring and resuscitation strategies have typically focused on global (macrocirculatory) hemodynamics, which cannot predict microcirculatory blood flow.[26] Microcirculatory evaluations (eg, sidestream darkfield imaging of sublingual blood flow) are typically not undertaken in clinical practice because proper measurements require user experience and time to analyze the results. With technical advances, though, markers of tissue perfusion may be used more commonly.

Receptor Pharmacology

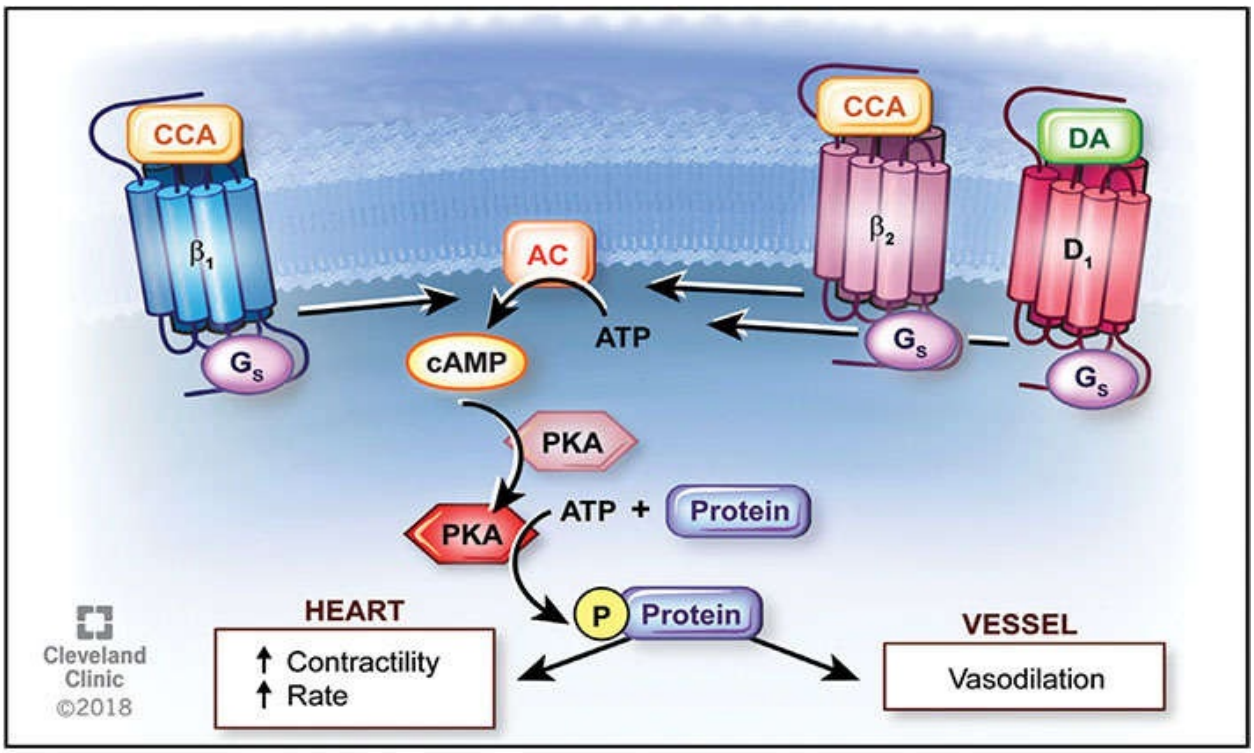
Comparative receptor activities of endogenous and exogenously administered catecholamines, vasopressin, and angiotensin II is summarized in **Table 41-1**.[27–34] Endogenous catecholamines are responsible for regulation of vascular and bronchiolar smooth muscle tone and myocardial contractility. These effects are mediated by sympathetic adrenergic receptors of the autonomic nervous system located in the vasculature, myocardium, and bronchioles. Postsynaptic adrenoceptors are located at or near the synaptic junction. These receptors can be activated by naturally circulating or exogenous catecholamines (eg, norepinephrine, epinephrine, and phenylephrine), whereas presynaptic adrenoceptors are stimulated by locally released neurotransmitters (eg, norepinephrine) and are controlled by a negative feedback mechanism.

TABLE 41-1 Adrenergic, Dopaminergic, Vasopressin, and Angiotensin Receptor Pharmacology and Organ Distribution

Effector Organ	Receptor Subtype	Physiologic Response
Heart		
Sinoatrial node	β_1, β_2, AT-1	Increased heart rate
Atria	β_1, β_2	Increased contractility Increased conduction velocity
Atrioventricular node	β_1, β_2, AT-1	Increased automaticity Increased conduction velocity
His-Purkinje system	β_1, β_2, AT-1	Increased automaticity Increased conduction velocity
Ventricles	α_1, AT-1 β_1, β_2	Increased contractility Increased contractility Increased conduction velocity Increased automaticity Increased rate idioventricular pacemaker cells
Arterioles		
Coronary	α_1, α_2, V1, AT-1; β_2, D1, V2 (via NO)	Constriction; dilation
Skin and mucosa	α_1, α_2, V1, AT-1	Constriction
Skeletal muscle	α_1, V1, AT-1; β_2, AT-2	Constriction; dilation
Cerebral	α_1, V1, AT-1; V2 (via NO)	Constriction (slight); dilation
Pulmonary	α_1; β_2, V2 (via NO)	Constriction; dilation
Abdominal viscera (mesentery)	α_1, V1; β_2, D1	Constriction; dilation
Renal	α_1, α_2, V1, AT-1; β_1, β_2, D1, AT-2	Constriction; dilation
Veins (systemic)	$\alpha_{1, \alpha 2; \beta 2}$	Constriction; dilation
Lungs		
Tracheal/bronchial smooth muscle	β_2	Relaxation
Bronchial glands	α_1; β_2	Decreased; increased secretion
Stomach		
Motility and tone	α_1, α_2, β_1, β_2	Decreased (usually)
Sphincter	α_1	Contraction (usually)
Secretions	α_2	Inhibition
Intestine		
Motility and tone	α_1, α_2, β_1, β_2; V_1	Decreased (usually)
Sphincters	α_1	Contraction
Secretions	α_2	Inhibition
Kidney		
Aldosterone secretion	AT-1	Increased
Renin secretion	α_1; β_1	Decreased; increased
Reabsorption of water	V2, AT-1	Increased
Sodium reabsorption and H^+ excretion	AT-1; AT-2	Increased; decreased
Skeletal muscle	β_2	Increased contractility, glyconeogenesis, K^+ uptake
Liver	α_1, β_2	Glycogenolysis and gluconeogenesis
Fat cells	α_1, β_1, β_2	Lipolysis (thermogenesis)
Pituitary	V1, AT-1	Adrenocorticotropic hormone secretion
Hypothalamus	AT-1	Vasopressin secretion
Nervous	AT-1	Enhanced norepinephrine secretion
Immune		
Pro-inflammatory cytokine release, macrophage and T-cell activation	AT-1; AT-2	Increased; decreased
Coagulation system		
	V1	Thromboxane synthesis (platelet aggregation)
	AT-1	Release of plasminogen activator inhibitor-1, platelet activation

AT, angiotensin; D, dopamine; NO, nitric oxide; V, vasopressin.

The signal transduction pathways associated with catecholamine-, vasopressin-, and angiotensin II-induced effects in the heart and blood vessels are illustrated in **Fig. 41-3**.[27–33] Agonists of β-adrenoceptors and dopamine (D_1) receptors stimulate adenylate cyclase by a G-protein (G_s)–dependent mechanism (Fig. 41-3, top). Adenylate cyclase generates cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). cAMP-dependent protein kinase A, which is activated by elevations in intracellular cAMP, phosphorylates target proteins to modify cellular function. Through these mechanisms, β_1-adrenoceptor activation exerts positive inotropic and chronotropic effects in the heart, and β_2-adrenoceptor and D_1-receptor activation induces vascular smooth muscle relaxation. Agonists of α_1-adrenoceptors stimulate phospholipase C-β (PLC-β) through a G-protein (G_q)–dependent process (Fig. 41-3, bottom). PLC-β produces inositol trisphosphate and diacylglycerol from cell membrane phosphatidylinositol bisphosphate. Diacylglycerol activates protein kinase C, an enzyme that phosphorylates several key proteins (eg, extracellular signal-regulated kinases, c-Jun NH_2-terminal kinases, and mitogen-activated protein kinases) that modify cellular function (eg, hypertrophy). Inositol trisphosphate elicits the release of calcium from intracellular stores, such as the sarcoplasmic reticulum. Calcium forms a complex with calmodulin, which then activates calcium/calmodulin-dependent protein kinases (CaMK). CaMKs phosphorylate target proteins to alter cellular function. Myosin light-chain kinase is an example of a CaMK. Its action of phosphorylating myosin light chain leads to vascular smooth muscle contraction.


CCA
β1
Gs
AC
ATP
cAMP
CCA
β2
Gs
DA
D1
Gs
PKA
PKA
ATP + Protein
P Protein
HEART
↑ Contractility
↑ Rate
VESSEL
Vasodilation
Cleveland Clinic ©2018

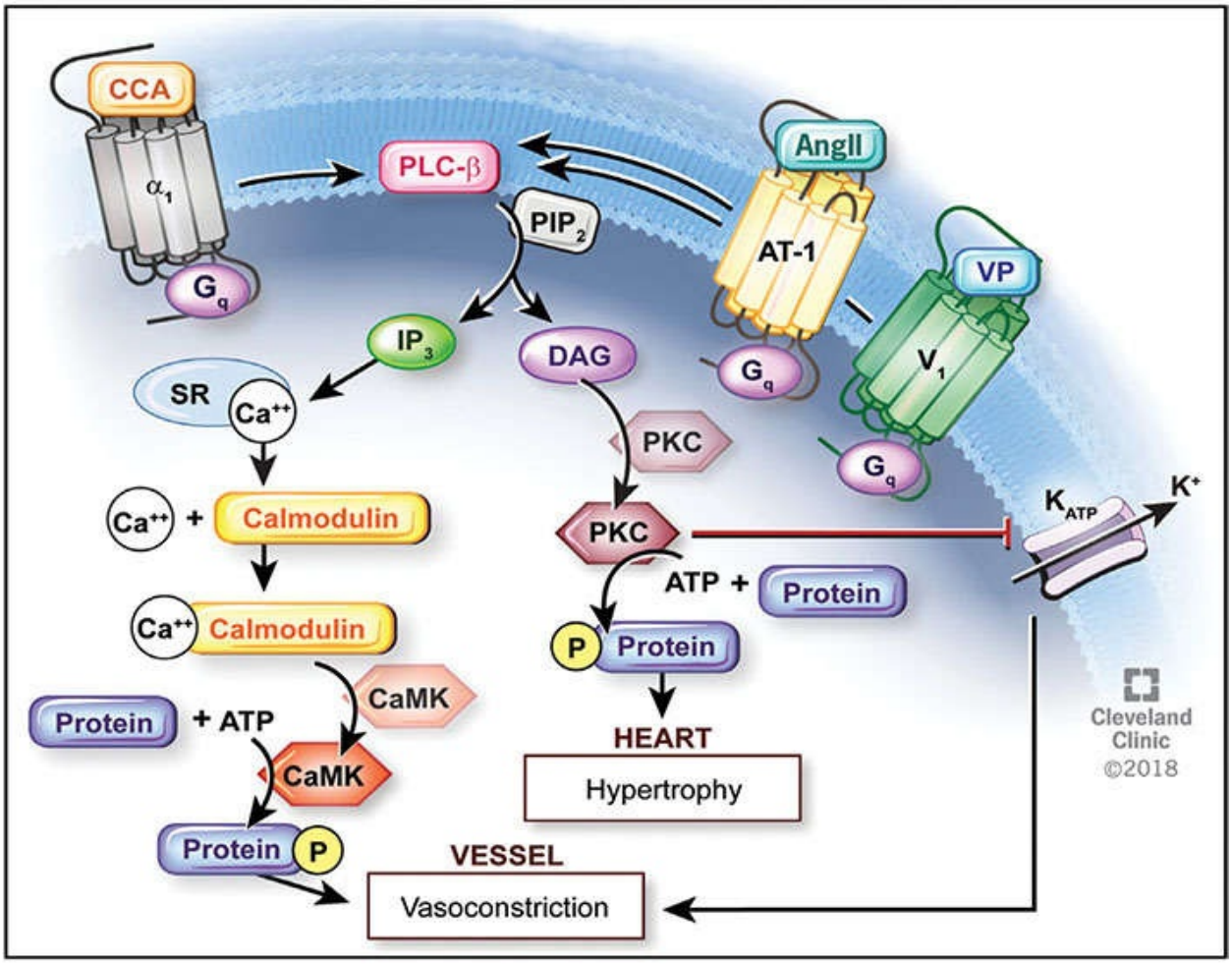

CCA
α1
Gq
PLC-β
PIP2
IP3
DAG
SR
Ca++
Ca++ + Calmodulin
Ca++ Calmodulin
CaMK
Protein + ATP
CaMK
Protein P
AngII
AT-1
Gq
VP
V1
Gq
PKC
PKC
ATP + Protein
P Protein
KATP
K+
HEART
Hypertrophy
VESSEL
Vasoconstriction
Cleveland Clinic ©2018

FIGURE 41-3 Top: Catecholamine (CCA)-induced effects mediated in heart (β_1) or vascular smooth muscle (β_2, D_1). (AC, adenylate cyclase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; PKA, cAMP-dependent protein kinase.) Bottom: CCA (α_1), angiotensin II (AngII), and vasopressin (VP)-induced actions in vascular smooth muscle. (Ca++, calcium ion; CaMK, calcium/calmodulin-dependent protein kinase; DAG, diacylglycerol; IP_3, inositol trisphosphate; K_{ATP}, ATP-sensitive potassium channel; P, phosphorus; PIP_2, phosphatidylinositol bisphosphate; PKC, protein kinase C; PLC-β, phospholipase C-β; SR, sarcoplasmic reticulum.) These pathways have been extensively simplified, and denoted cellular effects represent one of many produced. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2018. All Rights Reserved.)

The normal heart contains primarily postsynaptic β_1-receptors, which when stimulated cause increased rate and force of contraction. This effect is mediated by activation of adenylate cyclase and subsequent generation and accumulation of cAMP. Stimulation of postsynaptic cardiac α_1 receptors causes a significant increase in contractility without an increase in rate, an effect mediated by PLC rather than adenylate cyclase. The increased contractility is more pronounced at lower heart rates and has a slower onset and longer duration in comparison with β_1-mediated inotropic response. Presynaptic α_2-adrenoceptors also are found in the heart and appear to be activated by norepinephrine released by the sympathetic nerve itself. Their activation inhibits further norepinephrine release from the nerve terminal.

Both presynaptic and postsynaptic adrenoceptors are present in the vasculature. Postsynaptic α_1- and α_2-receptors mediate vasoconstriction, whereas postsynaptic β_2-receptors induce vasodilation. Presynaptic α_2 receptors inhibit norepinephrine release in the vasculature, also promoting vasodilation. Presynaptic β_1-adrenoceptors promote neurotransmitter release. Stimulation of peripheral D_1 receptors produces renal, coronary, and mesenteric vasodilation and a natriuretic response. Stimulation of D_2 receptors inhibits norepinephrine release from sympathetic nerve endings, sequesters prolactin and aldosterone, and may induce nausea and vomiting. D_1- and D_2-receptor stimulation also suppresses peristalsis and may precipitate ileus.

Vasopressin-induced vasoconstriction occurs through a variety of direct and indirect mechanisms.[29–31] Stimulation of vascular vasopressin (V_1)-receptors

causes vasoconstriction by receptor-coupled activation of PLC and calcium release from intracellular stores via secondary messengers similar to α_1-adrenergic stimulation (Fig. 41-3, bottom). Vasopressin also inhibits vascular potassium-sensitive ATP channels via activation of protein kinase C, indirectly leading to vasoconstriction (Fig. 41-3, bottom). V_1-receptor stimulation inhibits the actions of interleukin (IL)-1β and thereby further facilitates vasoconstriction. Vasopressin also increases the activity of adrenergic receptors. The greatest vasoconstriction occurs in the skin and soft tissue, skeletal muscle, fat tissue, pancreas, and thyroid gland. In contrast, vasopressin causes vasodilation in the cerebral, pulmonary, coronary, and selected renal vascular beds by enhancing endothelial NO release through V_1- and V_2-receptor stimulation in these tissues.[29–31] Vasopressin has minimal to no inotropic or chronotropic effects.

V_2 receptors located in the kidneys are responsible for the antidiuretic properties of vasopressin.[29–31] Stimulation of V_2 receptors facilitates integration of aquaporins into the luminal cell membrane of distal tubules and collecting duct capillaries to increase permeability and thus retain intravascular volume. However, vasopressin stimulation of V_1-receptors causes vasoconstriction of efferent arterioles and relative vasodilation of afferent arterioles to increase glomerular perfusion pressure and filtration rate to enhance urine production.

Vasopressin rapidly increases serum cortisol concentration by stimulating V_3 receptors in the pituitary gland to enhance the release of adrenocorticotropic hormone (ACTH).[29–31] Cortisol helps regulate pro-inflammatory states and increases blood pressure through several mechanisms, including inhibition of iNOS to reduce NO production, reversal of adrenergic receptor desensitization, and increased intravascular volume through retention of sodium and water.

Angiotensin II also causes vasoconstriction through both direct and indirect mechanisms.[32,33] When angiotensin II binds to angiotensin (AT)-1 receptors on arterioles, a G-protein (G_q)–dependent process with PLC-β activation is initiated, which results in vasoconstriction. This is a similar mechanism to α_1-adrenoceptor- and V_1-receptor–mediated vasoconstriction. Stimulation of AT-1 receptors in the hypothalamus and pituitary also leads to vasopressin and ACTH secretion, respectively, further enhancing vasoconstriction. AT-1 receptors are also present in the kidney and lead to multiple effects, including aldosterone secretion, sodium reabsorption, and H^+ excretion. In the renal vasculature, AT-1 receptors are present on efferent renal arterioles but not afferent renal arterioles, resulting in increased glomerular filtration pressure. Coagulation factors are also

affected by AT-1, with increased expression of plasminogen activator inhibitor-1 (leading to inhibition of the fibrinolytic pathway) and platelet activation.[32,33] Several immune mediators are also influenced by AT-1 stimulation, including pro-inflammatory cytokine release, and macrophage and T-cell activation. Some of the effects of AT-1 are counterbalanced by AT-2; stimulation of AT-2 receptors leads to vasodilation (including skeletal muscle and afferent renal arterioles) and anti-inflammatory activity.

Adrenoreceptor Function

Most of the work describing receptor function and associated clinical pharmacology has been performed in either animal models or human volunteers. In critically ill patients with shock, derangements in adrenergic receptor activity may result in resistance to exogenously administered catecholamine.[27–30] This "desensitization" frequently is characterized by myocardial and vascular hyporesponsiveness to high dosages of inotropes and vasopressor agents. Prolonged exposure of vascular endothelial tissue to vasopressor drugs (α-adrenergic agonists) or endogenous catecholamines may promote additional receptor downregulation.[28] Increased endogenous catecholamine concentrations have been reported in endotoxemic and other critically ill patients, suggesting an acquired adrenergic receptor defect and desensitization of adrenergic receptors and alteration in voltage-sensitive calcium channels. The problem in critically ill patients may be related to decreased receptor activity or density. However, in patients with septic shock, catecholamine concentrations are even higher, so abnormalities in adrenergic receptor function are greater, with associated reductions in the concentrations of intracellular signal transduction mediators. The worsened receptor abnormality may be explained by defects distal to the receptor site, such as uncoupling of adrenergic receptors from adenylate cyclase or PLC, or dysfunction in the regulatory G-protein unit of signal transduction pathways. Hypoxemia and acidosis may further worsen receptor adrenergic activity.

In addition to catecholamines, circulating inflammatory cytokines may be partly responsible for distal alterations.[28,30,31] Macrophage-derived IL-1 and tumor necrosis factor (TNF)-α produce impaired coupling of β-adrenoceptors to adenylate cyclase resulting in myocardial hyporesponsiveness to various vasopressors and inotropes.[16,28,31] Additionally, IL-1 and TNF-α suppress gene expression of α_1-adrenoceptors, resulting in fewer receptor proteins. Cytokine-mediated iNOS expression leads to overproduction of NO, which directly

contributes to vasodilation. NO also indirectly produces vasodilation by combining with superoxide to form peroxynitrite, a highly toxic reactive species that causes endothelial dysfunction, uncoupling of α_1-adrenoceptors to PLC, and deactivation of catecholamines. The result of inflammation is a system that promotes adrenergic receptor dysfunction to limit myocardial performance and accentuate vasodilation and shock.[16,28,31] However, the clinical response to vasopressors and possibly inotropic agents is variable over time because α- and β-adrenergic receptor derangements will change with the dynamic inflammatory process.[16,22,28–31] Therefore, these drugs should be dosed to clinical end points and not to arbitrary maximal dosages and high dosages are frequently required.

Vasopressin, Cortisol, and Angiotensin II

Endogenous arginine vasopressin, a peptide hormone also known as antidiuretic hormone, is important for osmoregulation under normal physiologic conditions. Vasopressin is produced in the hypothalamus, stored in the posterior pituitary, and released from magnocellular neurons of the hypothalamus.[30,31] Increased serum osmolality and hypovolemia are the major stimuli for vasopressin release.[31] Other stimuli commonly associated with shock are dopamine, histamine, angiotensin II, prostaglandins, pain, hypoxia, acidosis, hypotension, hypercarbia, and α_1-adrenergic receptor stimulation. Vasopressin release is inhibited by NO, natriuretic peptides, γ-aminobutyric acid, β-adrenergic receptor stimulation, and α_2-adrenergic receptor stimulation.[31]

Normal serum vasopressin concentrations are <4 pg/mL (3.7 pmol/L).[31] Serum vasopressin concentrations are elevated with hypotension. Vasopressin response in septic shock is biphasic. During the initial hours of septic shock, serum concentrations of vasopressin are appropriately high to help maintain blood pressure and organ perfusion. Thereafter, serum vasopressin concentrations decline dramatically over the next 96 hours to physiologically normal but inappropriately low values, resulting in a state of “relative deficiency.” A similar pattern has been observed in patients with hypovolemic (hemorrhagic) shock secondary to trauma.[35] In contrast, serum vasopressin concentrations remain elevated in patients with cardiogenic shock. Administration of vasopressin at 0.01 to 0.07 units/min produces concentrations similar to those observed in early septic shock and other shock states; however, the correlation between vasopressin concentrations and blood pressure is unclear.[31] Administration of vasopressin augments the decline of inflammatory

mediators and improves arterial pressure while minimizing the dosage of catecholamine vasopressors.[31,36]

The mechanism of vasopressin insufficiency in septic and hypovolemic shock is not well understood. Neurohypophyseal stores in the posterior lobe of the pituitary gland are depleted during shock, likely as a result of excessive and continuous baroreceptor stimulation that eventually exhausts the limited vasopressin secretory stores. In addition, secretion of vasopressin is inhibited by enhanced endothelial production of NO, high circulating concentrations of adrenergic agonists (both endogenous and exogenous), and tonic inhibition by stretch receptors in response to volume replacement and mechanical ventilation.[31]

As with vasopressin, during sepsis a state of "relative adrenal insufficiency" is produced by continuous activation of the hypothalamic-pituitary-adrenal axis by IL-1, IL-6, and TNF-α that causes depletion of cortisol in the adrenal glands.[37] Administration of corticosteroids improves arterial pressure while minimizing the dosage of catecholamine vasopressors. Current proposed mechanisms of the vasoconstrictor effect of corticosteroids include increasing the number and stimulating the function of α_1- and β-adrenergic receptors and attenuating the production of inflammatory mediators responsible for vasodilation.

The use of corticosteroids for treatment of septic shock has been a topic of controversy for many years. Interest in corticosteroid use is driven by the awareness of adrenocortical insufficiency in critically ill patients with septic shock. Relative adrenal insufficiency has been defined as a random cortisol concentration <10 mcg/dL (280 nmol/L) or an increase of <9 mcg/dL (250 nmol/L) following a dose of synthetic ACTH irrespective of the initial serum cortisol concentration.[38] Although absolute insufficiency is rare, relative adrenocortical insufficiency is present in 50% to 70% of patients with septic shock and is associated with a poor outcome.[38]

Conversely, an elevated random cortisol concentration (>34 mcg/dL [940 nmol/L]) is also a predictor of mortality.[38] Mortality is further increased if cortisol response to ACTH is <9 mcg/dL (250 nmol/L), suggesting that the risk of mortality is greatest in situations of adrenal gland "fatigue" (ie, degree of stress is not matched by sufficient cortisol production by the adrenal glands despite operating at maximal functional capacity).

Angiotensin II concentrations may also be low in patients with vasodilatory shock resulting in a "relative deficiency." Typically, angiotensin II

concentrations are elevated in patients with effective hypovolemia (ie, hypovolemic shock and vasodilatory shock) because of renin secretion. However, pro-inflammatory cytokines (eg, IL-1 and TNF-α) can lead to downregulation of AT-1, which leads to low aldosterone concentrations despite high concentrations of renin and angiotensin II.[33] Additionally, reduced sensitivity of AT-1 to angiotensin II as well as impaired conversion of angiotensin I to angiotensin II via angiotensin converting enzyme has been observed.[33]

CLINICAL PRESENTATION

The initial presentation of patients with circulatory shock can vary markedly. A patient's first contact with the healthcare setting is commonly as a result of the underlying etiology such as fever and malaise associated with infection or chest pain associated with acute myocardial infarction. However, patients may also present with overt signs of tissue hypoperfusion. Regardless of patient age or preexisting conditions, the initial monitoring of a patient with suspected circulatory shock should include the following noninvasive parameters: vital signs, urine production, mental status, and physical examination (**Fig. 41-4**). Clinical manifestations of tissue hypoperfusion may be apparent at the bedside, including neurologic (eg, confusion or obtundation), cutaneous (eg, warm skin in states of vasodilation and cool, clammy, or mottled skin in states of vasoconstriction), and renal (eg, low urine production) abnormalities. However, signs of tissue hypoperfusion must be interpreted in the context of concomitant therapies (eg, sedative administration) and the patient's history (eg, chronic end-stage renal disease with anuria).

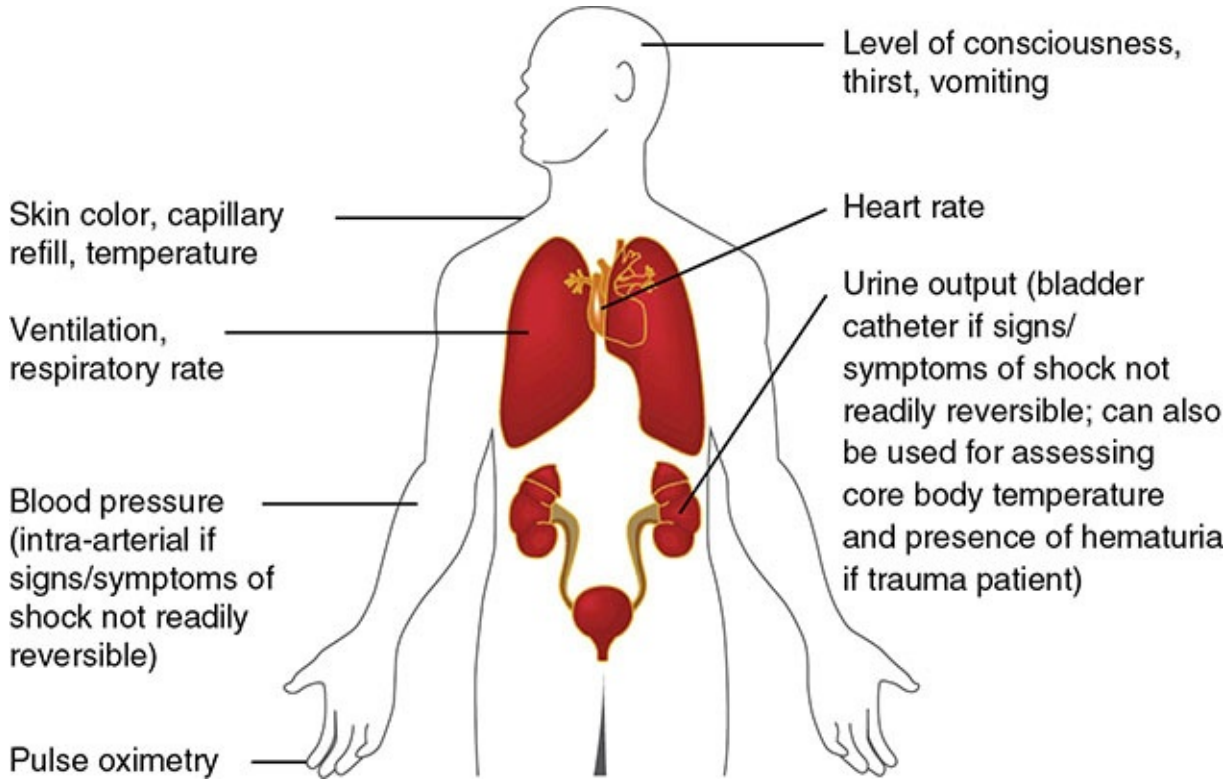


FIGURE 41-4 Clinical parameters—evaluation and monitoring of patients in shock.

Although the presenting signs and symptoms of circulatory insufficiency are variable, patients usually have decreased blood pressure, increased heart and respiratory rates, and a normal or low-normal temperature (eg, 36°C–37°C [96.8°F–98.6°F]) in the absence of infection, exposure to extremes of temperature, and medications that impair thermoregulation. However, patients with infection may have an elevated temperature (eg, above 38.3°C [101°F]). As mentioned earlier, recordings of vital signs must be interpreted in light of known or suspected baseline conditions. For example, alcohol, β-blockers, diuretics, and medications with anticholinergic effects may impair thermoregulation. Medications such as β-blockers and calcium channel blockers or disease states like cirrhosis may alter resting blood pressure and heart rate, as well as the subsequent response to therapeutic interventions. Although a blood pressure reading of 110/70 mm Hg (systolic/diastolic) may be acceptable in many patients, it may be inadequate in a patient with preexisting hypertension who normally has a blood pressure of 170/105 mm Hg. At the other extreme, patients with very low blood pressure may have inaudible or inaccurate determinations with cuff (sphygmomanometric) measurements. Chapters 1 and e29 detail blood pressure measurement (eg, cuff size, position). In this case, intra-arterial

monitoring is indicated. The respiratory rate may be elevated because of anxiety or as a compensatory mechanism for the metabolic acidosis caused by lactic acidosis. Pulse or arterial oxygen saturation may be decreased because of pulmonary edema.

Mental status changes associated with circulatory shock may range from subtle fluctuations in mood or mild confusion to unconsciousness. Although the latter finding typically is indicative of more severe tissue hypoperfusion, less dramatic findings should not be interpreted as indicating the absence of shock. Similar interpretation difficulties must be considered when performing the initial physical examination. While capillary refill (rapid return of blood flow to the extremity after removal of compression) is usually impaired, an orderly progression from warm, reddish skin with appropriate capillary refill to cold, cyanotic discoloration with impaired refill may not occur.

Although the kidneys continually produce urine, the bladder stores the urine for intermittent elimination. For the initial diagnosis and management of acute circulatory insufficiency, a catheter can be inserted into the bladder for measurement of urine production. In contrast to thirst, which is a relatively insensitive indicator of volume depletion, urine production is generally diminished with inadequate kidney perfusion and increases with appropriate resuscitation. This presumes, of course, that acute kidney insufficiency or medications such as diuretics are not altering the expected response. Adults should produce at least 0.5 to 1 mL/kg/hr of urine.

CLINICAL PRESENTATION

Shock Syndromes

General

- Initial presentation can vary markedly, but the symptoms are typically a result of the underlying etiology of shock.

Symptoms

- Patients may report dizziness, light-headedness, confusion, or low urine production.
- Symptoms consistent with underlying shock etiology, such as cough, fever, and malaise secondary to pneumonia or chest pain secondary to acute myocardial infarction, will be present.

Signs

- Increases in heart rate (eg, >120 beats/min) and respiratory rate (eg, >30 breaths/min)
- Low blood pressure (eg, systolic blood pressure <90 mm Hg) and low or normal body temperature (eg, 36°C–37°C [96.8°F–98.6°F]) in the absence of infection. If infection is present body temperature may be elevated (eg, above 38.3°C [101°F]).
- With severe hypoperfusion, altered mental status to the point of obtundation may be observed.

Laboratory tests

- Blood lactate concentration is typically elevated (>2 mmol/L).
- Evidence of end-organ hypoperfusion may be present (eg, elevated serum creatinine).
- Hemoglobin and hematocrit may be decreased in a bleeding patient.
- Elevated cardiac troponin concentration will be observed with acute myocardial infarction.

Diagnostic tests

- Rapid assessment by cardiac echocardiography is indicated when the shock etiology is unclear.
- Advanced hemodynamic monitoring (eg, central venous catheterization) may be needed for diagnosis or treatment.

Increased blood lactate concentration (above 2 mmol/L) is typically present. End organ dysfunction may be reflected in laboratory testing, such as elevated serum creatinine with renal dysfunction or elevated transaminase levels with hepatic dysfunction. The complete blood count can be variable. In the absence of infection it may be normal, but in septic shock the white blood cell count is usually increased (above 12,000 cells per microliter [12 x 10^9/L]). In hemorrhagic shock, hemoglobin, and hematocrit would decrease over time; septic shock may lead to a decrease in platelet count. In both hemorrhagic shock and septic shock the prothrombin time and international normalized ratio may increase over time. Cardiac troponin concentrations may be increased in the setting of myocardial ischemia.

TREATMENT

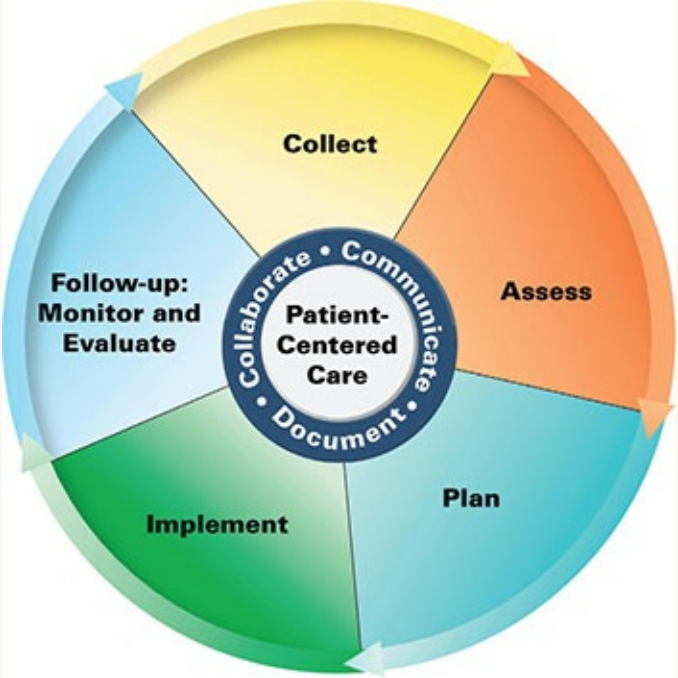
6 Treatment of the patient with circulatory shock can be divided into four phases, with each having different (but sometimes overlapping) goals of treatment and therapeutic strategies.[2] The first phase focuses on salvage, where a minimum perfusion pressure and CO must be obtained to ensure the patient's survival. Concomitant treatment of the underlying etiology of the shock state, which are lifesaving measures, should also be initiated at this time. Examples of these treatments include surgical/interventional hemostasis, antimicrobials and source control for sepsis, and coronary revascularization for acute myocardial infarction. The second phase is optimization, where the goals shift to ensuring adequate organ perfusion and DO_2. Stabilization is the third phase, where the goal is preventing (further) end-organ dysfunction. In the fourth phase of de-escalation, facilitation of patient recovery is targeted where goals include weaning (or cessation) of vasoactive medications and fluid elimination. Although this chapter focuses on the salvage and optimization phases, recognizing the phase of a patient's circulatory shock is necessary to establish treatment goals and corresponding therapeutic approaches. The desired outcome is to reduce morbidity and mortality by preventing organ damage and, to the extent possible, reserve or halt existing organ dysfunction.

General Approach to Treatment

Hospitalization is indicated for patients with circulatory insufficiency that does not readily respond to fluid resuscitation. If access to the circulatory system for administration of fluids and medication is not obtained prior to hospitalization, this should be a priority. Venous access generally is obtained during the preliminary examination process. Whenever large-volume fluid resuscitation is expected, as in hemorrhagic or septic shock, at least two IV catheters are desirable. Because flow is a function of tubing length and catheter diameter, large-bore peripheral IV lines are preferred over longer central lines for initial resuscitation. However, if vasopressors must be initiated they should preferentially be administered via a central venous catheter. Unfortunately, vascular access in some patients may be problematic, and other routes such as intraosseous infusion may be necessary. Prior to the last decade, use of intraosseous fluid and drug administration in the United States was mostly restricted to children with IV access issues, but it is increasingly being used in

adult patients as well. In the stabilization phase of circulatory shock treatment, proper attention must be paid to general supportive and preventative care measures that include appropriate assessment and management of pain, anxiety/agitation, delirium, immobility, sleep disturbances, nutrition, glycemic control, and thromboembolism prophylaxis.

Arterial blood pressure is the commonly used end point of therapy; however, restoration of adequate perfusion pressure is the primary criterion of effectiveness.[1,2,22] Profound hypotension (MAP <60 mm Hg) is associated with pressure-dependent decreases in coronary, cerebral, and renal blood flow and may rapidly produce myocardial, cerebral, and renal ischemia. Therefore, a goal MAP above 65 mm Hg is often targeted for shock to maintain perfusion; however, patient-specific characteristics must be considered in establishing a blood pressure goal and determining an adequate perfusion response to resuscitation. In order to limit further bleeding in patients with hemorrhagic shock, the blood pressure goal is SBP of 80 to 90 mm Hg with a restricted volume replacement strategy until major bleeding has been controlled.[1,39] If MAP or SBP remains below goal, then vasopressors should be initiated to ensure tissue perfusion.



Patient Care Process for Shock Syndromes

Collect

- Reason(s) for hospitalization
- History of present illness
- Patient characteristics (eg, age, sex, pregnant)
- Past medical history
- Social history (eg, tobacco/ethanol use)
- Medication history, including intravenous fluids that have been administered
- Review of systems and physical examination findings
- Objective data
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2-saturation
  - Labs including lactate, hemoglobin, platelets, serum creatinine, activated partial thromboplastin time, prothrombin time
  - Urine production if catheterized
  - Presence of visually evident bleeding
  - Other hemodynamic or advanced monitoring data (echocardiography) if available

Assess

- Hemodynamic stability/instability (eg, systolic BP <90 mm Hg, HR >110 bpm, O_2-sat <90% [0.90])
- Noninvasive measures of circulatory insufficiency (eg, skin color, capillary refill, and temperature; level of consciousness; urine production if catheterized)
- Dynamic markers of fluid responsiveness and advanced monitoring parameters if available
- Change in baseline organ function as evidenced by laboratory or other measures of circulatory insufficiency
- Risk for bleeding or ongoing bleeding based on objective data
- Need for vasopressors
- Goals and wishes of patient or healthcare surrogate decision maker’s goals and wishes for the patient if the patient cannot express their goals and

wishes

Plan

- Surgery or procedure if needed (eg, noncompressible bleeding, coronary revascularization, debridement of infected tissue)
- Initial focus on fluid resuscitation with type and amount of fluid based on patient-specific data
- Initiation of vasoactive medications when patient is not responding to fluid resuscitation as is commonly seen in patients with vasodilatory/distributive forms of shock
- Administer blood products as needed for hemorrhagic forms of shock
- Intra-aortic balloon pump or extracorporeal life support for cardiac output augmentation
- Referrals or consults to specialist providers (eg, infectious diseases providers, hematology providers) when appropriate

Implement*

- Ensure that all members of the interprofessional care team and patient's family/friends are aware of the plan for care
- Plan for transfer to step down unit or hospital ward after stabilization in ICU

Follow-up: Monitor and Evaluate

- Ongoing signs and symptoms of circulatory insufficiency (multiple times daily) and organ function status (at least once daily)
- Presence of adverse effects
- Schedule possible follow-up visit(s) based on status upon discharge

*Collaborate with patient, caregivers, and other healthcare professionals.

Blood pressure is an insensitive parameter of resuscitation because it is affected by several hemodynamic variables (eg, blood pressure may be within the goal range when CO is inadequate). As such, additional resuscitation goals should be utilized to ensure end-organ perfusion and DO_2 are optimized. Adequate DO_2 can be ensured through evaluating CO, SvO_2, or $ScvO_2$. Instead

of considering a specific CO, S_{VO_2}, or S_{CVO_2} value as high or low based on absolute values, it is best to interpret these values as adequate or inadequate or trend them relative to clinical response.[18] Adequacy is determined by concomitantly assessing markers of end-organ perfusion (eg, urine production) and lactate concentrations. Targeting absolute values of DO_2 or its surrogates in isolation is not recommended.[1] Serial lactate concentrations are recommended in the early phases of shock treatment because lactate clearance and normalization correspond with improved global tissue perfusion.[1,24] Since blood lactate measurement does not require invasive hemodynamic monitoring, targeting lactate clearance or normalization is an attractive end point.

After the salvage treatment phase, fluids should only be given to patients with ineffective tissue perfusion who are predicted or demonstrated to be fluid responsive. Because only about half of hemodynamically unstable patients respond to a fluid challenge,[20,21] the benefits of fluid administration (improved CO and tissue perfusion) must be balanced against the risks of fluid overload (eg, pulmonary edema). This risk/benefit determination is informed by determining fluid responsiveness, defined as demonstration or prediction of an increase in stroke volume or CO by >10% with a rapid fluid bolus.[20,21] Importantly, blood pressure change (or lack thereof) does not reliably indicate CO response to a fluid challenge.[21] Evaluating fluid responsiveness is most crucial in patients in whom the risk of detrimental fluid effects are not acceptable (eg, a patient with refractory hypoxemia) unless they have evidence of hypoperfusion and fluids are predicted to have benefit. Although commonly used, cardiac filling pressures (eg, CVP and pulmonary artery occlusion pressure [PAOP]) poorly predict fluid responsiveness; therefore, dynamic markers of fluid responsiveness should be utilized instead.[20–22] Dynamic markers of fluid responsiveness include assessments based on heart-lung interactions in mechanically ventilated patients (eg, pulse pressure variation, stroke volume variation, and inferior vena cava dimension variation) or response to the passive leg raising test (which can be used in all patients). Each of these dynamic markers have limitations to their reliability, which should be recognized prior to their employment.[21] If fluid administration is indicated, a fluid challenge technique should be utilized where the type of fluid, rate of administration, goals to be achieved, and safety limits are outlined prior to initiation.[22,40]

Nonpharmacologic Therapy

Nonpharmacologic therapy for shock is dependent on the inciting event,

although the basic life support measures such as a secure airway with appropriate oxygenation apply to all patients. For patients with hypovolemic shock, additional measures would include surgery (including stabilization of fractures), control of blood loss by physical compression, endoscopic, or surgical control, blood component transfusion, and prevention of heat loss since hypothermia may aggravate other problems such as coagulopathy and bleeding. For patients with heat exposure (eg, heat stroke), cooling measures are indicated. Patients with thermal injuries should have the wound sites covered with cool, moist sterile dressings until more definitive care can take place. Those with cardiogenic shock secondary to acute myocardial infarction should undergo emergent coronary revascularization and be considered for CO augmentation via mechanical device (eg, intra-aortic balloon pump or extracorporeal life support). Nonpharmacologic therapy is frequently the treatment of choice for obstructive shock, including pericardiocentesis or surgical evacuation of fluid for cardiac tamponade, and needle decompression and/or chest tube thoracostomy for tension pneumothorax. Surgical or catheter thrombectomy are also potential treatment options for obstructive shock secondary to pulmonary embolism. Patients with vasodilatory/distributive shock secondary to septic shock should have infectious source control and consideration should be given to fever control via external cooling. Those with immune-mediated shock should have the potentially offending agent(s) discontinued and, if possible, clearance augmented.

Pharmacologic Therapy

Intravenous Fluids and Blood Products

Because IV fluids are utilized as the initial treatment for most shock syndromes, they will be considered as pharmacologic agents for this discussion. The goal of administering IV fluids is to increase venous return in order to subsequently increase stroke volume, cardiac output, DO_2, and blood pressure. Intravenous fluids are typically classified as crystalloids or colloids, each with advantages and disadvantages. Blood products may also be administered to replace cellular and plasma losses with the added benefit of increasing venous return. This section reviews intravenous fluids and blood products, the relative advantages and disadvantages of each, and provides guidance for the clinical use of these agents.

Consensus statements for the treatment of shock and hemodynamic monitoring have been published by the European Society of Intensive Care

Medicine.[1] Recommendations for shock associated with trauma are available as part of the Advanced Trauma Life Support course (http://www.facs.org/trauma/atls/) and from the Eastern Association for the Surgery of Trauma.[41] Guidelines specific to the management of major bleeding and coagulopathy after trauma, and fluid therapy in neurointensive care patients are also available.[39,42] The Surviving Sepsis Campaign also has published international guidelines for the management of patients with sepsis and septic shock.[22] Other evidence relative to fluid choice for resuscitation is available from systematic reviews,[43–45] a consensus statement on colloid use in critically ill patients,[46] and a guideline pertaining to burn shock resuscitation.[47] Taken as a whole, the recommendations from all of these sources are consistent in that isotonic (or near isotonic) crystalloid solutions are the initial fluid of choice for resuscitation in patients with shock and large volumes should be administered (with the notable exception of patients with cardiogenic shock).

7 **Crystalloid solutions** Isotonic crystalloid (sodium-containing) solutions are the first-line fluid of choice for forms of circulatory insufficiency that are associated with hemodynamic instability. Solutions with sodium concentrations approximating normal serum sodium values usually are indicated because they cause greater expansion of the intravascular and interstitial spaces compared with dextrose solutions (**Table 41-2**). Lactated Ringer's and 0.9% sodium chloride ("normal saline") solutions are examples of such crystalloid solutions. Balanced salt solutions (eg, lactated Ringer's solution and multiple electrolytes injection [eg, Plasma-Lyte A; multiple products available]) and 0.9% sodium chloride have similar efficacy in expanding plasma volume but balanced salt solutions may be safer. Excess chloride administration with infusions of 0.9% sodium chloride may lead to hyperchloremic metabolic acidosis and possibly acute kidney injury, which may be less likely to occur with balanced salt solutions. Large pragmatic, cluster-randomized, multiple-crossover studies of critically ill and noncritically ill patients suggest that balanced salt solutions are less frequently associated with major adverse kidney events within 30 days (a composite outcome of death from any cause, new renal-replacement therapy, or serum creatinine level at least 200% of the baseline level).[50,51] In both studies the effect size of major adverse kidney events was small (about 1% absolute risk difference between groups) and no single component of the composite outcome was significantly different between groups. The study in 15,802 critically ill patients showed less renal dysfunction and numerically lower mortality with balanced crystalloids compared to 0.9% sodium chloride, although the effects

sizes were small for both outcomes.[51] Serum chloride concentrations were consistently lower and serum bicarbonate concentrations were consistently higher with balanced crystalloids over the first week of study. Despite the limitations of these studies, practice is shifting toward balanced salt solutions. Importantly, because balanced salt solutions may exacerbate cerebral edema in brain-injured patients, these solutions should be used cautiously in patients with this condition (Table 41-3). Additionally, concerns have been raised relative to the proinflammatory effects (eg, neutrophil activation) of the D-isomer form of lactate that is contained along with the L-isomer in commercially available racemic isomer solutions of lactated Ringer's solution. However, these concerns have not been substantiated in clinical trials.

TABLE 41-2 Fluid Distribution and Major Indications[a]

Fluid	Intracellular	Interstitial	Intravascular	Major Indication
0.9% sodium chloride, lactated Ringer's, or multiple electrolytes injection (eg, Plasma-Lyte A)	None	750 mL	250 mL	Intravascular volume expansion
3% sodium chloride	→	750 mL+	250 mL+	Small boluses (eg, 150-300 mL) and/or intermittent infusions used for patients with elevated intracranial pressure or those with symptomatic hyponatremia
5% dextrose / 0.45% sodium chloride	333 mL	500 mL	167 mL	Maintenance fluid in euvolemic or dehydrated (sodium and water loss) patients with mild signs/symptoms of volume depletion
5% dextrose	667 mL	250 mL	83 mL	Dehydration (primarily water loss) in patients with mild signs/symptoms of volume depletion
5% albumin	None	None	1,000 mL[b]	Intravascular volume expansion
25% albumin	→	→	1,000 mL+++[b]	Usually given by intermittent infusion to expand the intravascular volume via recruitment of volume from the interstitial space (eg, after large-volume paracentesis)

[a]Based on administration of 1 L of each solution *for comparative purposes only*. This amount of fluid, particularly for 3% saline and 25% albumin, would be inappropriate and likely harmful if given over a short period of time. Numbers are approximations and are likely not reflective of actual fluid distribution in critically ill patients; arrows indicate direction of fluid shift and plus signs indicate fluid pulled from other compartments.

[b]After distribution and attainment of steady-state conditions, 60% of albumin (and associated fluid) is in interstitial compartment and 40% is in intravascular compartment.

TABLE 41-3 Adverse Effects of Plasma Expanders

Balanced salt solutions (lactated Ringer's or multiple electrolytes injection [eg, Plasma-Lyte A])
- Primarily extensions of pharmacologic actions (eg, fluid overload, dilutional coagulopathy)
- Hyponatremia with lactated Ringer's (has 130 mEq/L [mmol/L] of sodium); because multiple electrolytes injection [eg, Plasma-Lyte A] has 140 mEq/L [mmol/L] of sodium this is not a concern with this solution)

0.9% sodium chloride ("normal saline")
- Primarily extensions of pharmacologic actions (eg, fluid overload, dilutional coagulopathy)
- Hyperchloremic metabolic acidosis (contains 154 mEq/L [mmol/L] of chloride)
- Hypernatremia (contains 154 mEq/L [mmol/L] of sodium)
- Acute kidney injury (from hyperchloremia)

3% sodium chloride ("hypertonic saline")
- Primarily extensions of pharmacologic actions (eg, fluid overload, dilutional coagulopathy; intracellular volume depletion)
- Hypernatremia (contains 513 mEq/L [mmol/L] of sodium)
- Hyperchloremia (contains 513 mEq/L [mmol/L] of chloride)

Albumin
- Primarily extensions of pharmacologic actions (eg, fluid overload; dilutional coagulopathy)
- Amino acid profile and catabolism alterations (clinical significance?); potential protein overload if given with exogenous protein (eg, parenteral nutrition)
- Anaphylactoid/anaphylaxis reactions (life-threatening reactions rare; higher in patients with immunoglobulin A deficiency)
- Infectious complications (all reported cases have been associated with improper handling by manufacturer or institution; no reported cases of human immunodeficiency virus or hepatitis transmission)
- Interactions with medications and nutrients (clinical significance varies)
- Metal loading, particularly aluminum (long-term administration in patients with renal failure)
- Negative inotropic effect; reductions in ionized calcium concentrations (not well documented)
- Pyrogenic reactions (not well documented)
- Renal dysfunction with hyperoncotic albumin

Although lactated Ringer's solution contains lactate, it does not cause substantial elevations in circulating lactate concentrations when used as a resuscitation solution.[52] Once adequate plasma volume has been restored by fluid administration, the body can readily clear the blood of the excess lactate

that has accumulated from both anaerobic metabolism and lactated Ringer's solution. However, blood samples for lactate determinations drawn through catheters (arterial and venous) that have not been cleared appropriately may have spurious increases or decreases in lactate concentrations because of retained lactated Ringer's and nonlactated solutions (eg, varying concentrations of dextrose-in-water or sodium chloride), respectively. Therefore, blood samples for lactate concentration determinations should be drawn from a catheter that has been cleared adequately (eg, 5 mL) of infusate after temporarily stopping the fluid infusion.

Alternative Fluid Treatments Hypertonic sodium chloride solutions have been studied as alternatives to isotonic crystalloid solutions for hypovolemic shock, particularly in patients with traumatic brain injuries. By causing redistribution (ie, pulling fluid) from the intracellular space, hypertonic solutions cause rapid expansion of the intravascular compartment, which is essential for vital organ perfusion. In head-injured patients, it has been postulated that this redistribution should decrease intracranial pressure because the vessels of the brain are more impermeable to sodium ions than are vessels in other areas of the body. Additionally, hypertonic sodium chloride solutions have beneficial immunomodulating actions when compared with more isotonic solutions in experiments with animals. Unfortunately, the theoretical benefits associated with hypertonic sodium chloride solutions have not translated into improved outcomes when used for the initial resuscitation of patients with shock.

From a safety standpoint, hypertonic sodium chloride is considered to be a high-risk concentrated electrolyte solution. Potential dosing and administration errors and related adverse events can occur when hypertonic sodium solution is ordered and administered by clinicians relatively unfamiliar with its use. Potential adverse events include cellular crenation and damage caused by the dramatic fluid shifts associated with hypernatremia, metabolic acidosis from hyperchloremia, and peripheral vein destruction from high osmolality. The osmolarity of 3% sodium chloride is 1,026 mOsm/L. Although there are some notable exceptions (eg, peripheral parenteral nutrition solutions often approach 1,000 mOsm/L), IV solutions with osmolarity values above 600 mOsm/L are usually recommended should be administered through a central line. In the limited number of studies conducted in humans to date, adverse effects have been uncommon when hypertonic (2-3%) sodium solutions have been administered through a peripheral line.

Larger-molecular-weight solutions (ie, >30,000 Da) known as *colloids* have been recommended in conjunction with or as replacements for crystalloid

solutions, although their use is controversial. The major theoretical advantage of these compounds is their prolonged intravascular retention time compared with crystalloid solutions. In contrast to isotonic crystalloid solutions that have substantial interstitial distribution within minutes of IV administration, colloids remain in the intravascular space for hours or days, depending on factors such as the size of the colloid molecules and capillary permeability. Examples of colloids used as plasma expanders in the United States include albumin, hydroxyethyl starch, and much less commonly, dextran. Albumin is known as a *monodisperse colloid* because all its molecules are of the same molecular size and weight, whereas hydroxyethyl starch and dextran solutions are *polydisperse compounds* with molecules of varying molecular size that are roughly proportional to molecular weight. In light of these differences, colloid comparisons are based on weight-averaged ([number of molecules at each weight × particle weight]/total weight of all molecules) or number-averaged (arithmetic mean of all particles' weights) molecular weight. The size and weight differences of the colloids have important implications for the distribution of the products because lower-molecular-weight substances are retained in the intravascular space for a shorter period of time as a result of more rapid leakage across the vessel membrane. The theoretical benefit common to all colloids is based on their increased molecular weight (average molecular weight in the case of hydroxyethyl starch and dextran) that corresponds to increased intravascular oncotic pressure leading to enhanced intravascular volume and longer retention time in the absence of increased capillary permeability compared with crystalloids.

Even in patients with intact capillary permeability, small and intermediate size colloid molecules such as albumin eventually will leak through capillary membranes with a few notable exceptions (eg, those in the central nervous system and glomeruli). In the case of albumin with a distribution half-life of 15 hours in normal subjects, approximately 60% of administered albumin molecules (and associated fluid) would be shifted to the interstitial space within 3 to 5 days of exogenous administration. In patients with altered vascular permeability (eg, sepsis), the leakage of albumin from the intravascular to the interstitial space may occur within hours, not days. The primary adverse effect concern of all colloids is fluid overload, which is an extension of their pharmacologic action. Excessive fluid administration has been shown to increase capillary permeability through disruption of the endothelial glycocalyx. Another adverse effect of increasing concern is renal dysfunction that seems to be related to hyperoncotic (eg, 25%) albumin and other starch and dextran products. The mechanism of this adverse effect may be related to alteration of normal glomerular oncotic pressure

differences or formation of lesions in the kidney.[53]

Albumin is available in the United States in 5% and 25% concentrations. Plasma protein fraction has oncotic actions similar to a 5% albumin solution, which is not surprising because albumin is the predominant protein in this product. When given in equipotent amounts, albumin is much more costly than crystalloid solutions. Additionally, the 5% and 25% albumin solutions typically are priced such that no cost saving is associated with dilution of the 25% product to make a 5% concentration. In general, dilution should be avoided because of the possibility of preparation errors; cases of hemolysis and death have occurred when 25% albumin was inappropriately diluted with sterile water for injection, causing a dramatic lowering of effective osmolarity. The 5% albumin solution is relatively *iso-oncotic*, which means that it does not pull fluid into the compartment in which it is contained. In contrast, 25% albumin is referred to as *hyperoncotic* albumin because it tends to pull fluid into the compartment containing the albumin molecules. In general, the 5% albumin solution is used for shock states with inadequate venous return. The 25% solution should not be used for acute circulatory insufficiency unless it is used in combination with other fluids or it is being used in patients with excess total body water but intravascular depletion as a means of pulling fluid into the intravascular space. An example of the latter condition is cirrhosis with ascites in which total body water is substantially increased, but the patient is hypotensive as a consequence of lack of intravascular volume. To justify this use of hyperoncotic albumin from a cost-effectiveness standpoint presumes that there is evidence of adverse effects associated with the excess water (eg, interstitial fluid accumulation in the lungs) and that the albumin remains in the intravascular space long enough to be of benefit. Albumin has a variety of functions beyond plasma expansion, such as binding properties, inflammatory gene modification, and antioxidant and free radical scavenging effects, which have been used to justify its administration instead of less expensive crystalloid or other colloid products. Although appealing theoretically, improved patient outcomes related to these properties have not been documented in adequately powered, randomized controlled trials. Additionally, the clinician must realize that the properties of commercially available albumin products are not biologically identical to those of native albumin. For example, denaturation of the products may lead to inefficient binding and decreased oncotic activity.

From a historical perspective, the so-called crystalloid versus colloid debate was intensified when a meta-analysis by the well-respected Cochrane group found an overall increase in mortality associated with albumin using pooled

results of randomized investigations.[54] With the notable exception of trauma patients, a subsequent and more comprehensive systematic review did not find increased mortality attributable to albumin.[55] These conflicting findings prompted the design and completion of a landmark investigation involving almost 7,000 critically ill patients, which did not detect a statistically significant difference in 28-day mortality between patients treated with either 0.9% sodium chloride or 4% albumin.[56] In a subset of patients with severe traumatic brain injury, mortality in those receiving albumin was significantly higher at 24 months, an effect that seemed to be confined to patients with severe injury.[57] This multicenter, randomized, double-blind investigation, referred to as the Saline versus Albumin Fluid Evaluation (SAFE) study, involved a heterogeneous group of ICU patients and was not sufficiently powered to look at various subsets, so clinicians must be cautious when extrapolating the results to more specific patient populations. Additionally, the assigned study fluid was used throughout the 28-day study period for volume expansion; therefore, this study was not exclusively an evaluation of the initial phase of fluid resuscitation and the implications of the study findings in that setting are unclear. The results of meta-analyses that include this large study are conflicting with regard to a survival benefit associated with colloid administration; however, they are in agreement that resuscitation with albumin achieves higher values of CVP and MAP more rapidly than crystalloid fluids with a lower overall fluid balance.[58–61] A recent randomized study of 1,818 patients with sepsis also showed that albumin 20% achieved higher MAP despite a lower net fluid balance compared to crystalloid solutions but mortality rates were similar.[62]

The colloids are expensive solutions and whether these beneficial outcomes confer cost-benefit over crystalloids has not been established. While the use of albumin in specific patient populations (eg, septic shock) is still debated, a systematic review and meta-analysis found that, when compared with alternative resuscitation solutions, hydroxyethyl starch was associated with increased mortality, increased acute kidney injury, and increased use of renal replacement therapy.[63] In light of these studies the US-product labeling of all medications in the class was changed to state they are contraindicated in critically ill patients; therefore, starch products should not be used for fluid resuscitation.

Blood Products In the case of a patient with hemorrhage, prompt attention must be given to cellular as well as plasma losses. Red blood cells lost during the bleeding episode may lead to ischemic damage in vital organs. Packed red blood cell transfusions may be needed to increase the oxygen-carrying capacity of the

blood because oxygen transport is a function not only of cardiac output but also of hemoglobin concentration and saturation, and of hemoglobin affinity for oxygen. Red blood cells contain hemoglobin that delivers oxygen to tissues. Neither crystalloids nor colloids perform this function. Although a small group of trauma patients respond to the initial fluid bolus and remain stable, most patients respond initially and then deteriorate. The latter patients, as well as patients with blood loss associated with surgery and those with gastrointestinal hemorrhage, frequently need blood components such as packed red blood cells (Table 41-4).

TABLE 41-4 General Indications and Concerns for Blood Products and Prothrombin Complex Concentrates[a]

Product	Major Indication	Major Concerns
Packed red blood cells	Increase oxygen-carrying capacity of blood. Usually indicated in patients with continued deterioration after volume replacement or obvious exsanguination	Hypocalcemia, hyperkalemia, hyperphosphatemia, circulatory overload, ARDS (lowest risk among blood products), immunomodulation, transfusion reactions, hypothermia, and virus transmission
Fresh frozen plasma	Replacement of clotting factors. Generally overused; indicated if ongoing hemorrhage in patients with PT/PTT >1.5 times normal, prolonged initial fibrin formation (R value) on viscoelastic testing, severe hepatic disease, or other bleeding diathesis	Hypocalcemia, circulatory overload, ARDS (highest risk among blood products, particularly transfusions from female donors), immunomodulation, transfusion reactions, hypothermia, and virus transmission
Platelets	Used for bleeding due to severe thrombocytopenia (ie, platelet count <20,000/μL [20 × 10^9/L]), rapidly dropping platelet counts as would occur with massive bleeding, or decreased clot strength (maximum amplitude value) on viscoelastic testing	Hypocalcemia, circulatory overload, ARDS, immunomodulation, transfusion reactions, hypothermia, and virus transmission
Cryoprecipitate	Contains concentrated fibrinogen, von Willebrand factor, factor VIII, and factor XIII. Generally not indicated in acute hemorrhage but rather used after specific deficiencies are identified (eg, decreased rate of clot formation [alpha value] on viscoelastic testing)	Hypocalcemia, circulatory overload, ARDS, immunomodulation, transfusion reactions, hypothermia, and virus transmission
Prothrombin complex concentrates (PCCs)	The most commonly used product contains inactivated factors II, VII, IX, and X, and Proteins C and S. Another product contains activate factors. Used for reversal of antithrombotic agents in the setting of acute major bleeding or prior to urgent surgery/invasive procedure.	Thrombosis (arterial and venous), anaphylactic reactions, and viral transmission. Some products contain heparin and should not be given to patients with heparin-induced thrombocytopenia

[a]Although whole blood can be used for large-volume blood loss, most hospitals use component therapy, and use crystalloids or colloids for plasma expansion.

ARDS, acute respiratory distress syndrome; PT, prothrombin time; PTT, partial thromboplastin time.

Administration of excessive blood products may be counterproductive. In the case of red blood cells, attempts to raise the hemoglobin to high–normal or supranormal concentrations may decrease oxygen delivery by increasing blood

viscosity. Stored red blood cells undergo biochemical alterations to reduce oxygen dissociation at the tissue level which may explain why studies do not demonstrate increased end organ DO_2. Additionally, there are concerns of hyperkalemia, hyperphosphatemia, and immunomodulation with red blood cell administration. Use of a more liberal transfusion strategy (transfusion threshold less than 10 g/dL [100 g/L; 6.21 mmol/L]) has been curtailed in many institutions with the publication of a randomized, multicenter trial involving critically ill patients that found 30-day mortality to be similar whether patients were transfused at a hemoglobin concentration less than 7 or 10 g/dL (70 or 100 g/L; 4.34 or 6.21 mmol/L).[64] Although the investigators were cautious about extrapolating the results of this investigation, subsequent studies performed in patients with acute upper gastrointestinal hemorrhage, septic shock, and those undergoing cardiac surgery found similar results with a restrictive transfusion strategy (transfusion threshold of hemoglobin concentration ≤7 g/dl [70 g/L; 4.34 mmol/L]).[65–67] In fact, liberal transfusion strategies were associated with increased bleeding in patients with acute upper gastrointestinal hemorrhage and higher mortality in critically ill patients with lower severity of illness. With the exception of the critically ill or perioperative patients with acute exsanguination, there is little justification for a liberal transfusion strategy based solely on hemoglobin concentrations.

Clotting factors may be lost from bleeding or consumed through hemostatic mechanisms requiring replacement. Laboratory parameters or viscoelastic testing (eg, thromboelastography) may guide blood product administration.[39] Blood products that contain clotting factors include fresh frozen plasma, platelets, and cryoprecipitate (Table 41-4). Concentrated products available as lyophilized powder for reconstitution (eg, prothrombin complex concentrates or fibrinogen concentrate) are increasingly used as alternatives to traditional blood products because they are not associated with hypervolemia or immunomodulation, but they may enhance the risk of thromboembolic events. Reversal agents for antithrombotic-associated bleeding may also be administered (eg, prothrombin complex concentrates for warfarin, idarucizumab for dabigatran, and andexanet alfa for rivaroxaban or apixaban).

Blood products have risks beyond immunomodulation. There is the rare but important risk of virus transmission (eg, human immunodeficiency virus and hepatitis). Citrate that is added to stored blood products to prevent coagulation may bind to calcium, resulting in hypocalcemia. In patients receiving large amounts of blood products, prophylactic calcium administration may be warranted until levels are available. Potassium and phosphate concentrations

often are elevated in stored packed red blood cells, particularly when hemolysis has occurred during storage. Additionally, blood product administration may be associated with acute respiratory distress syndrome (particularly with fresh frozen plasma and platelets) or circulatory overload. Other issues that must be considered with blood product administration include monitoring for transfusion-related reactions and attention to appropriate warming, particularly when large volumes are given to pediatric patients, because hypothermia is associated with increased fluid requirements and mortality.

Fluid Resuscitation in Distributive (Septic) Shock In patients with distributive shock the initial fluid challenge volume is unclear. While the Surviving Sepsis Campaign guidelines strongly recommend 30 mL/kg crystalloids given within the first 3 hours of shock recognition, the evidence to support this specific volume for administration is low quality.[22] Multiple approaches exist for fluid resuscitation during the first 6 hours of therapy. One initial approach includes liberal fluid administration (50-75 mL/kg) while reserving vasopressors, and another approach includes relatively restrictive initial fluid administration (≤30 mL/kg) with earlier use of vasopressors to maintain tissue perfusion. Both approaches have rationale, because early aggressive fluid resuscitation can restore effective venous return (and thus increase cardiac output) but can also contribute to edema within organs that impairs their function. A comparison of these initial resuscitation approaches is currently ongoing.[48] Greater than 30 mL/kg of crystalloid fluids in total may be needed to obtain goal MAP, reverse global hypoperfusion (lactate clearance, $S_{CV}O_2$ ≥70% [0.70]), or achieve clinical indication of regional organ-specific perfusion (eg, urine production). An isolated bolus (eg, 250-500 mL) in an adult patient with shock is unlikely to cause a substantial change in blood pressure or acid–base balance. Therefore, multiple fluid boluses are often needed in such patients to achieve hemodynamic stability. However, excessive fluid administration has been associated with higher mortality and overly aggressive fluid administration should be avoided,[53] especially in patients with heart failure or impending pulmonary edema. Also, intravenous medication diluents can contribute significantly to total fluid volume administration during a patient's ICU stay and, when 0.9% sodium is utilized, can contribute to hyperchloremia and possibly acute kidney injury.[49] Therefore, total fluid administration should be accounted for, and dynamic fluid response with clinical assessment should occur frequently following each fluid challenge.[22]

Fluid Resuscitation in Hypovolemic (Hemorrhagic/Traumatic) Shock The

need for immediate treatment of hemorrhagic shock with plasma expanders (ie, crystalloids or colloids) seems obvious, but no large, well-controlled trials conducted in humans have supported this practice. To the contrary, evidence suggests that fluid resuscitation beyond minimal levels (ie, mean arterial pressure ≥60 mm Hg) is harmful in patients with penetrating abdominal trauma due to hemodilution and clot destabilization. One prospective study involving 598 adult patients with gunshot or stab wound injuries to the torso and systolic blood pressure measurements of 90 mm Hg or less found that delayed fluid resuscitation until operation was associated with increased survival and discharge from the hospital.[68] Since concerns were expressed about the comparability of the immediate and delayed resuscitation groups, particularly because true randomization did not take place, a follow-up randomized trial was conducted to verify the findings. There were no differences in survival (four deaths in each group) in the second trial regardless of whether systolic blood pressure was titrated to ≥100 mm Hg or to 70 mm Hg.[69] Both studies were conducted in populated urban areas with approximately 2 hours from the time of injury to operation. Therefore, the results may not be applicable to rural areas with extended transport times. There also is a concern in applying the results of these investigations to patients with certain kinds of single-system injuries, particularly head trauma, where cerebral perfusion pressure is of primary importance.

The administration of hypertonic sodium chloride solutions requires less overall fluid than isotonic solutions; therefore, it stands to reason that concerns regarding the dilutional effect of isotonic solutions could be minimized with hypertonic saline solutions. In order to address ongoing questions of efficacy, the National Heart, Lung, and Blood Institute evaluated hypertonic sodium chloride solutions with or without a colloid (ie, 7.5% sodium chloride or 7.5% sodium chloride in 6% dextran 70) for prehospitalized trauma patients with shock and severe traumatic brain injury in two trials conducted by a network of sites known as the Resuscitation Outcomes Consortium. Both of the parallel trials were stopped when it was determined that the hypertonic sodium chloride solutions were no better than 0.9% sodium chloride (“normal saline”) and further enrollment would not change the 33 outcomes.[70,71] Therefore, isotonic crystalloids are the fluid of choice since they are equal in efficacy with a lower risk of adverse effects compared with hypertonic solutions that are high-risk electrolyte solutions. Lactated Ringer’s solution may be used as an alternative solution to 0.9% sodium chloride, but should be used cautiously in patients with traumatic brain injury because it may worsen cerebral edema. Given their

relatively poor intravascular expansion and association with poor outcome in animal models of closed head injury, hypotonic solutions should be avoided in this population.

Although the applicability of the aforementioned studies to other populations and settings is debatable, the *presumption* of benefits from immediate plasma expansion in all preoperative patients with circulatory insufficiency caused by hemorrhage is no longer valid. Instead, the initial priority should be surgical control of the bleeding source; until this is possible, fluids should be given in small aliquots to yield a palpable pulse and to maintain mean arterial pressures no more than 60 mm Hg and systolic pressures no more than 90 mm Hg based on accurate measurements (eg, arterial monitoring). Approaches also should be used to avoid or decrease acute traumatic coagulopathy, which is the result of the combination of bleeding-induced shock, tissue injury–related thrombin-thrombomodulin-complex generation, and activation of anticoagulant and fibrinolytic pathways.[39]

The periodic shortages, high costs, and adverse effect concerns related to blood products have prompted investigations of alternative “bloodless” strategies. In addition to the use of more restrictive transfusion thresholds, as mentioned previously, these strategies have included hemoglobin-based oxygen carriers and perfluorocarbon compounds to deliver oxygen to tissues. Other strategies have aimed at reducing blood loss through the use of improved procedural and surgical techniques, as well as the administration of hemostatic medications. Reversal of antithrombotic agents (eg, prothrombin complex concentrates for patients receiving warfarin) should be considered in the context of the patient’s degree of bleeding or operative plan and their indication for antithrombotic therapy. However, the only hemostatic medication with a proven mortality benefit is the antifibrinolytic agent tranexamic acid. The best evidence for efficacy was data from a multicenter trial involving more than 20,000 adult trauma patients with significant bleeding (or risk for significant bleeding) who were randomized to IV tranexamic acid 1 g over 10 minutes followed by 1 g over 8 hours by infusion or matching placebo within 8 hours of injury.[72] There was a significant reduction in all-cause mortality with tranexamic acid compared with placebo with no increase in vascular or other adverse events. A more in-depth review of the results of this trial suggest that the beneficial effects are most likely to occur if tranexamic acid is given within the first 3 hours of injury. While additional data are still needed in specific subpopulations such as patients with traumatic brain injuries, this study is relatively unique in that an intervention apart from surgery and blood product administration was

demonstrated to reduce mortality.

In the bleeding patient, once hemostasis has been achieved, a more restrictive transfusion strategy (ie, transfusion if hemoglobin ≤7 g/dL [70 g/L; 4.34 mmol/L]) is indicated unless a patient has active cardiac ischemia.[39] Additional blood product administration should be guided by laboratory parameters (eg, PT/INR and platelets) or viscoelastic testing (eg, thromboelastography).[39] Reversal of antithrombotic therapy (eg, prothrombin complex concentrates for warfarin) may also be utilized for severe bleeding.

Vasopressors and Inotropes

8 Vasopressors and inotropes are required in patients with shock when volume resuscitation fails to maintain adequate blood pressure (MAP ≥65 mm Hg) and organs and tissues remain hypoperfused.[1,2,8,22,29] In addition, vasopressors may be needed temporarily to treat life-threatening hypotension when tissue perfusion is inadequate despite ongoing aggressive fluid resuscitation. Inotropes are frequently used to optimize DO_2 in cases of septic shock and cardiac function in cases of cardiogenic shock.[1,2,11,12,22] The clinician must decide on the choice of agent, therapeutic end points, and safe and effective doses of vasopressors and inotropes to be used. This section provides guidance for the clinical use of adrenergic agents, optimization of pharmacotherapeutic outcomes, and minimization of adverse effects in critically ill patients with septic shock. Vasopressin, angiotensin II, and corticosteroids, as they relate to shock, also are emphasized because they have pharmacologic interactions with catecholamine vasopressors, possess hemodynamic effects, and are frequently used.

9 The choice of a particular vasopressor or inotrope agent depends on the underlying shock pathophysiology, goals of therapy, and clinical pharmacology of the agent(s).[29] In most shock syndromes, limited literature exists to guide optimal agent selection. Catecholamine vasopressors may result in adverse peripheral vasoconstrictive, metabolic, and dysrhythmogenic effects that limit or outweigh their positive effects on the central circulation.[28–31] Excessive peripheral vasoconstriction with catecholamine vasopressors may cause ischemia or necrosis of already poorly perfused tissues such as the skin and the mesenteric and splanchnic circulations. Some of these profound vasoconstrictive effects may be compounded by under-resuscitation with fluid administration prior to initiating the vasopressor. Vasopressor catecholamines also have the potential to cause extravasation-associated tissue damage if infusions infiltrate during peripheral administration. In the event of infiltration, an α-receptor

antagonist such as phentolamine (5 or 10 mg in 10 mL saline) should be injected intradermally or nitroglycerin paste applied topically to reverse local vasoconstriction. β_1 cardiac stimulation may produce myocardial ischemia and atrial and ventricular arrhythmias, especially in patients with coronary artery disease, atherosclerosis, cardiomyopathies, left ventricular hypertrophy, congestive heart failure, or underlying dysrhythmias. Table 41-5 lists potential adverse effects of commonly used vasopressors and inotropes.[28–31,74]

TABLE 41-5 Receptor Pharmacology and Adverse Events of Selected Vasopressor and Inotropic Agents Used in Shock[a]

Agent (Adverse Events)	α_1	α_2	β_1	β_2	D	V_1	V_2	AT-1	AT-2
Angiotensin II (5,000-10,000 ng/mL NS)	Tachycardia, thrombosis, peripheral ischemia, lactic acidosis, bronchospasm, infection								
1.25-80 ng/kg/min	0	0	0	0	0	0	0	++++	++++
Dobutamine (500-4,000 mcg/mL D_5W or NS)	Tachycardia, dysrhythmias, hypotension								
2-10 mcg/kg/min	+	0	++++	++	0	0	0	0	0
>10-20 mcg/kg/min	++	0	++++	+++	0	0	0	0	0
Dopamine (800-3,200 mcg/mL D_5W or NS)	Tachycardia, dysrhythmias, decreased PaO_2, mesenteric hypoperfusion, GI motility inhibition, T-cell inhibition								
1-3 mcg/kg/min	0	0	+	0	++++	0	0	0	0
3-10 mcg/kg/min	0/+	0	++++	+	++++	0	0	0	0
>10-20 mcg/kg/min	+++	0	++++	+	0	0	0	0	0
Epinephrine (8-16 mcg/mL D_5W or NS)	Tachycardia, dysrhythmias, mesenteric hypoperfusion, increased lactate, hyperglycemia, immunomodulation								
0.01-0.05 mcg/kg/min	++	++	++++	+++	0	0	0	0	0
0.05-3 mcg/kg/min	++++	++++	+++	+	0	0	0	0	0
Norepinephrine (16-64 mcg/mL D_5W or NS)	Mixed effects on myocardial performance and mesenteric perfusion, peripheral ischemia								
0.02-3 mcg/kg/min	++++	+++	+++	+/++	0	0	0	0	0
Phenylephrine (100-400 mcg/mL D_5W or NS)	Mixed effects on myocardial performance, peripheral ischemia								
0.5-9 mcg/kg/min	+++	+	+	0	0	0	0	0	0
Vasopressin (0.2-1 units/mL D_5W or NS)	Mixed effects on myocardial performance, mesenteric hypoperfusion, peripheral ischemia, thrombocytopenia, hyperbilirubinemia								
0.01-0.1 units/min	0	0	0	0	0	++++	++++	0	0

[a]Activity ranges from no activity (0) to maximal (++++) activity.

AT, angiotensin; D, dopamine; D_5W, dextrose 5% in water; GI, gastrointestinal; NS, normal saline (0.9% sodium chloride); PaO_2, arterial oxygen pressure; V, vasopressin.

10 Use of Vasopressors and Inotropes in Distributive (Septic) Shock

The Surviving Sepsis Campaign guidelines outline vasopressor and inotrope selection, and corticosteroid use for patients with septic shock.[22] Other evidence relative to vasopressor and inotrope choice is available from systematic reviews and meta-analyses.[73–78] Guidelines from the Society of Critical Care Medicine and European Society of Intensive Care Medicine also outline corticosteroid use in patients with septic shock,[38] and systematic reviews and meta-analyses also exist on the topic.[79,80] Overall, the recommendations from all of these sources support norepinephrine as the first-line vasopressor for shock.

In patients with vasodilatory/distributive shock, norepinephrine should be started when a MAP ≥65 mm Hg and/or adequate tissue perfusion is not achieved with fluid resuscitation. Norepinephrine infusions are initiated at 0.05 to 0.1 mcg/kg/min and rapidly titrated to preset blood pressure goals (usually MAP ≥65 mm Hg) and/or improvement in global and regional peripheral perfusion (eg, decrease blood lactate or restore urine production). Norepinephrine may be associated with tachydysrhythmias, with higher doses more likely to cause this adverse effect. The primary limitation to use is that norepinephrine is not commercially available as premixed ready-to-use solutions, so use requires preparation time. Institutions may stock compounded admixtures in preparation for administration but they must follow sterile compounding and storage regulations.

Epinephrine is considered second-line or as adjunctive therapy to norepinephrine because it is associated with tachydysrhythmias and lactate elevation.[28–30,73,82] In contrast to other vasopressors, lactate concentrations frequently rise during epinephrine therapy resulting in variable arterial pH values. The increase in lactate may be a result of worsened DO_2 to the liver (and subsequent anaerobic metabolism) or to the hepatosplanchnic circulation, direct increase in calorigenesis and breakdown of glycogen (enhanced aerobic lactate production via β_2-adrenergic receptor stimulation), or lactate mobilization. Of all the vasopressors, epinephrine exhibits the most pronounced capacity to induce hyperglycemia by increased gluconeogenesis and glycogenolysis with α-mediated suppression of insulin secretion. Despite the administration of high doses, epinephrine-associated clinically important dysrhythmias or cardiac ischemia occur at variable rates irrespective of age or underlying cardiac status.[28–30,73,82] Nevertheless, caution must be exercised before considering epinephrine for managing hypoperfusion in patients with inadequate CO in the setting of coronary artery disease, in whom ischemia, chest pain, or myocardial infarction may result. Epinephrine is commonly used in countries where other agents may not be readily available or are relatively expensive. It may also be

used as an inotrope after cardiac surgery, particularly in patients with revascularized coronary circulation. Like norepinephrine, epinephrine is not commercially available as premixed ready-to-use solution. Institutions may stock compounded admixtures in preparation for administration but they must follow sterile compounding and storage regulations.

All catecholamine vasopressors, but especially epinephrine, possess immunomodulatory actions, primarily mediated by β_2-adrenergic actions because almost all immune cells express this receptor.[83] In general, catecholamines inhibit the production of inflammatory cytokines (eg, IL-6, TNF-α), may enhance anti-inflammatory cytokines (eg, IL-4 and IL-10), suppress oxygen free radical production from neutrophils, and direct proapoptotic effects.[83] These anti-inflammatory effects may be either beneficial or deleterious by dampening harmful effects of oxygen free radical–mediated tissue injury or by reducing neutrophilic defense against bacteria. While epinephrine is most associated with the immunomodulatory actions, the clinical significance of these actions remain unknown.

Despite its purported use in refractory shock, little information is available regarding the clinical efficacy of phenylephrine. It improves myocardial performance in hyperdynamic, normotensive patients with sepsis but worsens myocardial performance in patients with cardiogenic shock as a result of a decrease in CO and an increase in SVR. Therefore, phenylephrine use warrants caution and should not be used as an initial vasopressor in shock patients with impaired myocardial performance. The available data on hemodynamics, oxygen-transport variables, and mortality with phenylephrine in shock patients may not be generalizable because of the small numbers of patients evaluated. Tachydysrhythmias are notably infrequent with phenylephrine, particularly when it is used as a single agent or at higher doses, because phenylephrine exerts little activity on β_1-adrenergic receptors. Whether the beneficial effects can be sustained with longer administrations of phenylephrine is unclear. Phenylephrine may be a particularly useful alternative in patients who cannot tolerate tachycardia or tachydysrhythmias with use of norepinephrine or epinephrine and in patients who are refractory to norepinephrine or epinephrine (because of β-adrenergic receptor desensitization).[22,73] Like norepinephrine and epinephrine, it is not commercially available as premixed ready-to-use solution. Institutions may stock compounded admixtures in preparation for administration but they must follow sterile compounding and storage regulations.

Use of dopamine as a first-line vasopressor is no longer recommended. Its clinical use frequently is hampered by tachycardia and tachydysrhythmias,

which may lead to myocardial ischemia.[4] Although tachydysrhythmias theoretically should not be expected to occur until administration of dopamine 5 to 10 mcg/kg/min, these β_1 effects are observed with dosages as low as 3 mcg/kg/min. While dopamine may improve hemodynamic function, the use of dopamine for shock is questionable because regional hemodynamics, oxygen-transport variables, and functional parameters of improved organ perfusion are not consistently enhanced in a sustained manner and may be negatively impacted.[6] Low-dose dopamine did not demonstrate improved renal function in a randomized, placebo-controlled study of 328 critically ill patients with early renal dysfunction.[84] A meta-analysis of 61 trials (N = 3359) confirmed that low-dose dopamine fails to enhance renal function or survival in critically ill patients.[85] The negative findings of low-dose dopamine use and the deleterious effects of inotropic and vasopressor dosages of dopamine on regional hemodynamics, oxygen transport, and functional performance of organ perfusion raise concern over whether dopamine should even be considered in patients with shock.[22,84,85] Unlike other vasopressor agents, however, dopamine is commercially available as premixed ready-to-use solutions of various concentrations that can be stored in automated dispensing systems for rapid initiation.

Current guidelines for patients with septic shock recommend a trial of dobutamine infusion up to 20 mcg/kg/min in the presence of myocardial dysfunction (elevated cardiac filling pressures, low CO, echocardiography displaying left ventricular dysfunction) or continued signs of global or regional hypoperfusion despite meeting volume and MAP goals.[22] Increased cardiac performance measures in response to adjunctive dobutamine therapy are predictive of survival during sepsis. However, administration of dobutamine purely to achieve a normal CO, DO_2, or $S_{CV}O_2$ in the absence of other signs of tissue hypoperfusion (eg, low urine production) is not recommended. The achievement of supranormal oxygen transport values with dobutamine is of little value compared with treatment to normal values. In addition, administration of dobutamine to achieve these high values may increase mortality rate and/or the incidence of adverse effects.

Dobutamine should be started at dosages ranging from 2.5 to 5 mcg/kg/min. Dosage increments of dobutamine beyond 20 mcg/kg/min are limited by complications of tachycardia, myocardial ischemia, hypertension, and tachydysrhythmias despite the absence of preexisting cardiac abnormalities. Although a dose response may be seen, evidence suggests that dosages >5 mcg/kg/min may provide limited beneficial effects on oxygen transport values

and hemodynamics and may increase adverse cardiac effects. If given to patients who are intravascularly depleted, dobutamine will result in hypotension and a reflexive tachycardia. Because dobutamine increases myocardial oxygen demand, it should be used cautiously in patients with cardiogenic shock, particularly those with acute myocardial infarction who have not undergone coronary revascularization.[11] Doses should be guided by clinical end points, echocardiography, and global perfusion goals. Dobutamine, like other inotropes, usually is given until improvement in myocardial function with resolution of the underlying etiology or dose-limiting side effects are observed. Dobutamine is commercially available as premixed ready-to-use solutions.

Additional vasoactive agents (eg, vasopressin and/or angio-tensin II and/or corticosteroids) may be added to improve MAP or decrease catecholamine requirements. However, specific catecholamine dosage thresholds indicating initiation of these adjunctive agents are unclear.

Adjunctive use of vasopressin for preventing dose escalation of adrenergic agents, decreasing norepinephrine dosage or increasing MAP should be considered in patients with vasodilatory/distributive shock. A meta-regression showed a negative correlation between vasopressin and norepinephrine dosages.[76] Small studies of septic shock patients demonstrate that initial therapy with vasopressin achieves blood pressure control as effectively as traditional catecholamine vasopressors but the response is delayed.[31] Therefore, vasopressin therapy should be used as add-on therapy to catecholamine adrenergic agents rather than as first-line therapy.[22,31] In patients with septic shock, dosages are generally fixed at 0.03 or 0.04 units/min with higher doses reserved for salvage therapy (norepinephrine dosage >0.6 mcg/kg/min).[22] The results of studies showed that vasopressin markedly reduced the requirements for adrenergic agents.[31,76,77,86] Therefore, vasopressin should be used when response to one or two adrenergic agents is inadequate or as a method for reducing the dosage of these therapies.[22] Increased arterial pressure should be evident within the first hour of vasopressin therapy, at which time the dose(s) of adrenergic agent(s) should be reduced while maintaining goal MAP. In patients with vasodilatory shock after cardiac surgery vasopressin is frequently titrated to the MAP goal with dosages up to 0.1 units/min.[87]

Mesenteric ischemia associated with vasopressin may be clinically relevant. Increased hepatic transaminases and total bilirubin concentrations may occur with vasopressin therapy, suggesting impaired hepatic blood flow or a direct effect on excretory hepatic function.[31,35] While mesenteric vasoconstriction occurs at vasopressin serum concentrations as low as 10 pg/mL (9 pmol/L), the

results of studies indicate that vasopressin dosages exceeding 0.04 units/min worsen gastric mucosal perfusion when it is added to low or high doses of catecholamine vasopressors.[31] The effect is additive with norepinephrine despite substantially reduced dosages of norepinephrine when vasopressin is initiated. Ischemic skin lesions have also been observed in several studies, with an occurrence rate as high as 30% after vasopressin was added to norepinephrine-resistant shock.[31] However, meta-analyses concluded there was no difference in adverse events between vasopressin and control.[76–78]

Several studies reported difficulty discontinuing vasopressin therapy. Because vasopressin is often used to replace a physiologic deficiency in patients with septic shock, it stands to reason that the requirement for vasopressin will subside with reversal of the septic process. Whether vasopressin should be stopped prior to or after catecholamine vasopressors is currently unclear.[35] Long-term administration of vasopressin may be associated with hyponatremia and thrombocytopenia. Vasopressin is not available as premixed ready-to-use solutions.

The optimal use of angiotensin II is currently unclear although it most likely will be used as an adjunctive therapy to catecholamines and vasopressin in the treatment of patients with vasodilatory/distributive shock. However, angiotensin II is associated with a number of adverse effects due to its action on receptors throughout the body. It increases the risk of thromboembolic events, particularly deep vein thrombosis. This adverse effect is likely due to release of plasminogen activator inhibitor-1 (resulting in inhibition of fibrinolysis) and platelet activation.[33,35] Because of this risk, concurrent thromboembolism prophylaxis should be utilized. Heart rate significantly increases after angiotensin II initiation, and this agent should be used cautiously in those who cannot tolerate an increase in heart rate (eg, older patients with coronary artery disease). Through unclear mechanisms, patients receiving angiotensin II have a higher risk for secondary infection, particularly fungal infection.[35,88] Angiotensin II has been associated with bronchospasm and should be avoided in patients with asthma or current bronchospasm.[33,35]

Therapy of septic shock with corticosteroids improves hemodynamic variables and lowers catecholamine vasopressor dosages with minimal effects on patient safety.[22,38] Corticosteroids should be considered when fluids and moderate- to high-dose vasopressors are unable to restore hemodynamic stability, or when weaning of vasopressor therapy proves futile.[38,79,80] They should also be started in cases of shock when adrenal insufficiency is suspected (eg, patients receiving long-term corticosteroid therapy for other indications

prior to the onset of shock); however, assessment of adrenal function to guide therapy is not recommended.[22,38] Adverse events with corticosteroids for shock are few because corticosteroids are administered for a finite period of time, usually 7 days. Studies to date suggest that short-term, low-dose corticosteroids do not alter the rates of gastrointestinal bleeding and superinfections, but increase the risk for hypernatremia and hyperglycemia, and may increase the risk of neuromuscular weakness.[79,80] Acutely elevated serum concentrations of blood urea nitrogen and white blood cell count may also occur. The reader is referred to Chapter 137 "Sepsis and Septic Shock" for further discussion of this topic.

Use of Vasopressors and Inotropes in Hypovolemic (Hemorrhagic/Traumatic) Shock Guidelines specific to the management of major bleeding and coagulopathy after trauma also outline vasopressor and inotrope use.[30,75] In contrast to other forms of shock such as vasodilatory/distributive, medications are a distant alternative to the primary therapy for hypovolemic shock, fluids. In hypovolemic shock, peripheral resistance is high due to compensatory mechanisms aimed at maintaining tissue perfusion. Early or overzealous use of vasopressors in lieu of fluids may exacerbate this resistance to the point that flow is stopped. Vasopressors are only used as a temporizing measure or as a last resort when all other measures to maintain perfusion have been exhausted.[29] Because vasopressors have such a limited role in hypovolemic shock, there are very few studies that compare various agents. However, norepinephrine is considered the first-line vasopressor of choice.

Comparative Studies of Vasoactive Agents The results of several observational and randomized studies support norepinephrine as the first-line vasopressor for most shock states, particularly septic shock.[22,29] A meta-analysis of 11 trials (N = 1,718) showed norepinephrine was associated with increased survival compared to dopamine.[73] Tachydysrhythmias were less common with norepinephrine. The results of one study contributed to the majority of data. The study randomized 1,679 patients with shock unresponsive to volume resuscitation to norepinephrine or dopamine and found similar 28-day mortality rates.[4] Despite the theoretical advantages of dopamine in patients with cardiogenic shock, dopamine was not superior to norepinephrine in patients with this shock type. Overall, patients receiving norepinephrine had fewer arrhythmic events and more vasopressor-free days. Limitations of this landmark study include the use of a relatively conservative definition of "shock unresponsive to fluid administration" (only 1 L of crystalloid or 0.5 L of colloid), the use of open-label

norepinephrine in patients with inadequate hemodynamic response to study drug regimens, and the lack of standardization of other shock therapies that affect hemodynamic variables (eg, corticosteroids, dobutamine, additional fluid administration). This study demonstrates that while there is no mortality benefit of norepinephrine over dopamine, it is more effective in increasing blood pressure and is safer.

Two randomized, double blind studies compared epinephrine with norepinephrine in 330 and 280 patients with shock, respectively.[81,82] Both studies found similar 28-day mortality rates and time to vasopressor withdrawal with epinephrine and norepinephrine. One study found more events of tachydysrhythmias with epinephrine leading to study discontinuation.[82] Both studies also showed that epinephrine was associated with lower arterial pH values and higher serum lactate concentrations over the first days of therapy. Another study compared norepinephrine and epinephrine in 57 patients with cardiogenic shock after acute myocardial infarction.[89] Cardiac index was higher with epinephrine over the first 4 hours of treatment, but there was no difference between groups over the 72-hour study period. The study was stopped early because of a higher incidence of refractory cardiogenic shock in patients receiving epinephrine. Survival was similar between study groups, but the study was not designed or statistically powered to evaluate this outcome. These data suggest that norepinephrine is preferred to epinephrine in patients with cardiogenic shock.

Taken together, these data suggest that norepinephrine is the primary vasopressor of choice in patients in most shock states because of its multiple benefits: (1) norepinephrine may decrease mortality in septic shock; (2) it reverses inappropriate vasodilation and low global oxygen extraction; (3) it attenuates myocardial depression at unchanged or increased CO and increased coronary blood flow; (4) it improves renal perfusion pressure and renal filtration; (5) it enhances splanchnic perfusion; and (6) it is less likely than many other vasopressors to cause tachydysrhythmias.[28–30,74]

Two meta-analysis (10 trials, $N = 1{,}134$ and 23 trials, $N = 3{,}088$, respectively) concluded that adjunctive vasopressin did not produce a survival benefit in patients with vasodilatory/distributive shock,[76,78] while a third meta-analysis (9 trials, $N = 998$) showed vasopressin reduced mortality.[77] Differences in trial inclusion for the meta-analyses and statistical techniques likely explain the differences in findings. The largest meta-analysis (23 trials, $N = 3088$) showed the addition of vasopressin to catecholamine vasopressors was associated with a lower risk for atrial fibrillation.[78] The results of one study contributed the

majority of the data for all meta-analyses. A randomized study of 776 patients with septic shock requiring catecholamine vasopressors showed that 28-day mortality rates were similar when titrated vasopressin 0.01 to 0.03 units/min or norepinephrine was added to open-label catecholamine therapy.[86] Subgroup analyses suggested a mortality benefit with vasopressin in patients with less severe shock. The adverse event profiles were similar between groups and vasopressin therapy expedited the discontinuation of catecholamine vasopressors. Although vasopressin helped preserve renal function in patients with acutely declining urine production,[90] a subsequent randomized study of early vasopressin in patients with septic shock (N = 409) did not detect a difference between norepinephrine and vasopressin in the number of kidney failure-free days.[91] At present, vasopressin should not be used for the sole purpose of improving or maintaining renal function.

A study compared norepinephrine and vasopressin in patients with vasodilatory/distributive shock after cardiac surgery (N = 300).[87] The incidence of a composite outcome of mortality or severe complications (stroke, requirement for mechanical ventilation for longer than 48 hours, deep sternal wound infection, reoperation, or acute kidney injury) was lower in patients receiving vasopressin. There was a lower incidence of acute kidney injury in patients receiving vasopressin but no difference between groups in mortality or other components of the composite outcome. This trial is limited by much higher incidence of atrial fibrillation than US national benchmarks, and norepinephrine doses exceeding those typically used in practice for the treatment of patients with shock after cardiac surgery. These data suggest vasopressin may be considered as a component of vasopressor therapy for patients with vasodilatory/distributive shock after cardiac surgery.

Few studies to date have evaluated angiotensin II as a therapy for shock. In one study 321 patients with vasodilatory shock (81% septic shock) requiring a norepinephrine dosage of at least 0.2 mcg/kg/min without evidence of a low CO were randomized to angiotensin II or placebo.[88] Compared with those receiving placebo, patients receiving angiotensin II more frequently achieved a MAP of at least 75 mm Hg without an increase in the dosage of open-label vasopressors after 3 hours. Angiotensin II was also associated with lower open-label vasopressor doses over 3 hours. There was no difference between groups in organ function after 48 hours or mortality at day 28. Limitations of this study include selection of a MAP goal higher than recommended by guidelines and study design not sufficient to evaluate patient-centered outcomes. Although a secondary analysis of the study suggested a mortality benefit with angiotensin II

in patients with acute kidney injury treated with renal replacement therapy at study enrollment,[92] at present angiotensin II should not be started exclusively for this indication.

Several randomized controlled trials of low-dose corticosteroids in vasopressor-dependent septic shock patients have been published.[79,80] The results of meta-analyses are conflicting with regard to a survival benefit associated with corticosteroid administration; however, they are in agreement that corticosteroid use improves hemodynamics with more rapid shock reversal and shorter durations of vasopressor support.[79,80] Discrepancies in survival between studies may be related to severity of illness of the enrolled patients. Studies that showed a mortality benefit included very ill patients requiring high-dose vasopressors (average norepinephrine dosages about 1 mcg/kg/min) while studies that did not detect a mortality benefit enrolled less ill patients (average norepinephrine dosages 0.5 mcg/kg/min or below). Additional discrepancies between studies include timing of enrollment (earlier enrollment in studies finding a mortality benefit) and administration method (continuous infusion in a large study that did not detect a mortality benefit vs intermittent bolus administration in studies showing a mortality benefit). These study discrepancies and conflicting results have led to ongoing debate about the optimal use of corticosteroids in patients with septic shock.

The receptor selectivity of clinically used vasopressors and inotropes and hemodynamic effects are listed in Table 41-5.[28–31,74]

Norepinephrine Norepinephrine has combined strong α_1-activity and less potent β_1-agonist effects while maintaining weak vasodilatory effects of β_2-receptor stimulation. It produces vasoconstriction primarily via its more prominent α-effects on all vascular beds, thus increasing SVR.[28–30,74] Norepinephrine administration produces a small (10%-15%) increase in stroke volume.[29] Several meta-analyses have demonstrated improved MAP and mortality in ICU patients with severe hypotension treated with norepinephrine either as first-line therapy or after therapeutic failure with fluid resuscitation treatment.[1,22,73,74]

Norepinephrine 0.05 to 2 mcg/kg/min reliably and predictably improves hemodynamic parameters to “normal” values in most patients with shock. As with other vasopressors, norepinephrine dosages exceeding those recommended by most references frequently are needed in critically ill patients with shock to achieve predetermined goals. A significant increase in MAP is caused by an increase in SVR. Heart rate generally decreases with norepinephrine because of reflex bradycardia from increased SVR.[28–30,74] Increasing norepinephrine doses

to maintain higher MAPs may increase heart rates, cardiac index, DO_2, and cutaneous blood flow but these results are inconsistent. Older patients may benefit from the combined α- and β-adrenergic effects of norepinephrine given the higher prevalence of coronary disease and compromised ventricles in this patient population. By virtue of restored MAP and hence coronary perfusion, cardiac index is increased in older patients, whereas in younger patients with less coronary artery disease and a higher cardiac index at baseline, norepinephrine acts primarily as a vasoconstrictor. Norepinephrine either does not influence or slightly increases cardiac filling pressures (eg, PAOP).

The effect of norepinephrine on oxygen transport parameters is variable and depends on baseline values and concurrently administered vasoactive agents. In most studies of norepinephrine alone, either an increase or no change in DO_2 is seen with no change in O_2ER, particularly when DO_2 values were "supranormal" prior to therapy. Splanchnic blood flow and fractional blood flow are higher with norepinephrine than either dopamine or epinephrine despite higher CO with the two latter agents.

Epinephrine Epinephrine exerts combined α- and β-agonist effects.[28–30,73] At low dosages (0.01-0.05 mcg/kg/min) β-adrenergic effects predominate with an increase in stroke volume and CO. For this reason low dosages of epinephrine may be utilized as an inotrope after cardiac surgery. When higher epinephrine dosages are used α-adrenergic effects are predominantly observed and SVR and MAP are increased. Epinephrine is an acceptable choice for hemodynamic support of patients with shock because of its combined vasoconstrictor and inotropic effects.[28–30,73,82] It is as effective as norepinephrine for MAP response in vasodilatory/distributive shock. Epinephrine dosages of 0.04 to 1 mcg/kg/min alone increase hemodynamic and oxygen-transport variables to "supranormal" values in shock patients without coronary artery disease. Large dosages (0.5-3 mcg/kg/min) often are required, particularly for patients with septic shock. Smaller dosages (0.1-0.5 mcg/kg/min) are effective when epinephrine is added to other vasopressors and inotropes. In addition, younger patients appear to respond better to epinephrine, possibly due to greater β-adrenergic reactivity.

Despite a linear dose-response curve with rapid improvement of hemodynamic variables and DO_2, epinephrine has deleterious effects on regional hemodynamics and oxygen utilization. Although DO_2 increases mainly as a function of increases in the CO and a more variable increase in SVR, VO_2 may not increase, and O_2ER may fall. A decrease in gastric mucosal perfusion may be

seen during epinephrine administration but this effect can be counteracted in part by dobutamine. This may be explained by the vasodilatory effect of dobutamine on gastric mucosal microcirculation resulting in a redistribution of blood flow toward the mucosa. When compared with a combination of norepinephrine and dobutamine, epinephrine preferentially decreases splanchnic DO_2 and increases systemic lactate concentration without increasing VO_2. The effects of epinephrine on absolute and fractional splanchnic blood flow are more pronounced during severe shock. However, evidence suggests that epinephrine, in contrast to dopamine, increases the proportion of total CO delivered to the splanchnic circulation, although VO_2 is not increased sufficiently. As a result, O_2ER values are usually lower with epinephrine than with other vasopressors but the concomitant administration of dobutamine helps maintain O_2ER.

Phenylephrine Phenylephrine is essentially a pure α_1-agonist and increases blood pressure primarily through vasoconstriction.[28–30,73] Given the presence of cardiac α_1-receptors, phenylephrine also may increase contractility and CO, although variable effects on CO are observed. It is a therapeutic option in hypotensive patients experiencing a tachyarrhythmia when a vasopressor with minimal to no β_1-agonist activity is indicated.[1,22]

Phenylephrine is an attractive agent for use in vasodilatory/distributive shock because of its selective α-agonism with primarily vascular effects.[28–30,73] As with other vasopressors, phenylephrine dosages required to achieve goals of therapy are significantly higher than dosages traditionally recommended for use. Phenylephrine 0.5 to 9 mcg/kg/min, used alone or in combination with dobutamine or low dosages of dopamine, improves blood pressure and myocardial performance in fluid-resuscitated patients with vasodilatory/distributive shock. Incremental doses of phenylephrine result in linear dose-related increases in SVR and MAP when administered alone as a single agent in stable, nonhypotensive but hyperdynamic, volume-resuscitated surgical ICU patients. In septic shock, phenylephrine does not significantly impair the cardiac index, PAOP, or peripheral perfusion. Phenylephrine improves MAP by increasing SVR and stroke index through enhanced venous return to the heart.

In septic shock, phenylephrine appears to increase global tissue oxygen use, although data regarding the relationship of the oxygen-transport variables with increases in MAP and cardiac index are conflicting. Increases in VO_2 appear to be dissociated from DO_2, representing an increase in O_2ER as the cardiac index

remains unchanged. Increases in VO_2 may result from redistribution of blood flow to previously underperfused areas, improving oxygen use as a result of changes in MAP and SVR. Evidence of globally improved peripheral tissue perfusion is observed as lactic acid concentration declines or remains unchanged and urine production increases significantly at increased or maximal VO_2. An increased O_2ER may contribute to improved tissue response.

Few data regarding the effect of phenylephrine on regional hemodynamics and oxygen-transport variables are available. When phenylephrine replaced norepinephrine in patients with septic shock, phenylephrine selectively reduced splanchnic blood flow and thus splanchnic DO_2 and splanchnic lactate uptake rate without changing the overall splanchnic VO_2. Concomitantly, arterial lactate concentrations increased. Because all of these parameters normalized when norepinephrine was reinstated, these data suggest that exogenous β-adrenergic stimulation (norepinephrine) may determine hepatosplanchnic perfusion and oxygen availability but not utilization in septic shock. Phenylephrine and norepinephrine demonstrate similar short-term hemodynamic profiles and indices of global and regional perfusion when used as an initial vasopressor in septic shock.[28–30]

Dopamine Dopamine has been described as having dose-related receptor activity at D_1-, D_2-, β_1-, and α_1-receptors.[28–31,74] This dose-response relationship has not been confirmed in critically ill patients. In patients with shock, great overlap of hemodynamic effects occur, even at dosages as low as 3 mcg/kg/min. Although it was historically frequently utilized dopamine is no longer considered a first-line therapy for shock.[22,29]

Dopamine is a natural precursor to norepinephrine and epinephrine and generally not as effective as these two agents for achieving goal MAP in patients with shock.[28–30,74] Most studies of patients with septic shock have shown that dopamine at dosages of 5 to 10 mcg/kg/min increases CO by improving contractility and heart rate, primarily from its β_1 effects. At higher dosages (>10 mcg/kg/min) it increases MAP as a result of both increased CO and SVR due to its combined β_1 and α_1 effects.

The clinical utility of dopamine as a vasopressor in the setting of shock is limited because large dosages are frequently necessary to maintain CO and MAP. At dosages exceeding 20 mcg/kg/min, further improvement in cardiac performance and regional hemodynamics is limited. The effect of dopamine on global oxygen-transport variables parallels the hemodynamic effects. Although

dopamine improves global DO_2, it may compromise O_2ER in the splanchnic and mesenteric circulations by α_1-mediated vasoconstriction. Splanchnic blood flow and DO_2 increase with dopamine, but with no preferential increase in splanchnic perfusion as a fraction of CO and systemic increases in DO_2. Large doses of dopamine cause a decrease or lack of change in regional VO_2 and a decrease in tissue O_2ER. Dopamine at low or vasopressor dosages directly impedes gastric motility in critical illness and may aggravate gut ischemia in shock. Similar to high-dose administration, low-dose dopamine increases splanchnic blood flow but lowers splanchnic VO_2 in sepsis. Therefore, dopamine at all dosages impairs hepatosplanchnic metabolism despite an increase in regional perfusion. Low dosages (eg, 2 mcg/kg/min) increase renal blood flow and glomerular filtration rate in studies of animals and healthy volunteers, but urine production is similar to placebo in critically ill patients.[84]

Dobutamine Dobutamine, a synthetic catecholamine, is primarily a selective β_1-agonist with mild β_2- and vascular α_1-activity, resulting in strong positive inotropic activity without concomitant vasoconstriction.[28–30] In comparison with dopamine, dobutamine produces a larger increase in CO and is less arrhythmogenic. α_1-Adrenoceptors in the heart are directly stimulated by the (−) isomer of dobutamine, but β_1 and β_2 activity resides in the (+) isomer. The strong inotropic action of dobutamine is a function of its structure, the additive effect of cardiac α_1- and β_1-agonist activity, and a relatively weak chronotropic effect limited to the (+) isomer action on the β-receptors. Clinically, β_2-induced vasodilation and the increased myocardial contractility with subsequent reflex reduction in sympathetic tone lead to a decrease in SVR. Optimal uses of dobutamine in shock are for patients with low CO and high filling pressures (eg, left ventricular dysfunction demonstrated with echocardiography) or ongoing signs of global or regional hypoperfusion despite adequate resuscitation; however, vasopressors may be needed to counteract arterial vasodilation.[22,29]

Dobutamine is an inotrope with vasodilatory properties (an “inodilator”).[28–30] It is used for treatment of septic and cardiogenic shock to increase the CO, typically by 25% to 50%. In septic shock, left and right ventricular function are depressed despite a high CO, whereas ventricular volumes and compliance are increased. Dobutamine increases stroke volume, left ventricular stroke work index, and thus cardiac index and DO_2 without increasing PAOP.[28–30] It also enhances chronotropy effect. The combination of dobutamine and

norepinephrine results in a lower increase in heart rate compared with use of epinephrine alone.

Dobutamine increases DO_2 without affecting VO_2, resulting in decreased O_2ER. Arterial lactate concentrations decrease significantly with norepinephrine and dobutamine compared with dopamine and epinephrine infusions. The addition of dobutamine to other vasopressors improves gastric mucosal perfusion even without increases in CO. The addition of dobutamine to norepinephrine or epinephrine treatment improves gastric mucosal perfusion. This effect may relate to blood flow redistribution toward gastric mucosa, due to either an increase in the fraction of CO distributed to the global hepatosplanchnic blood flow and/or a redistribution of blood flow within gastric wall layers toward the mucosa by "stealing" blood away from the muscularis potentially as a result of greater β_2-mediated vasodilation. Sublingual microcirculation improves after dobutamine is added to vasopressor-dependent septic shock patients in a manner unrelated to arterial pressure or CO, suggesting that enhanced perfusion is the result of the "steal" phenomenon. Of note, gastric mucosal perfusion and tissue oxygen utilization are most improved with concurrent norepinephrine and dobutamine therapies compared with other vasopressor combinations at the same level of MAP.

Vasopressin Initiating vasopressin in patients with vasodilatory/distributive shock increases SVR and arterial blood pressure, which allows for reductions in the dosage requirements of catecholamine adrenergic agents.[31,33,73,76,77,86,88] These effects are rapid and sustained. Vasopressin's strongest vasoconstrictive action occurs in the skin and soft tissues, skeletal muscles, and fat tissues.[31] Vasopressin decreases heart rate after initiation because of reflex bradycardia from increased SVR.[93] Unlike adrenergic receptor agonists, the vasoconstrictive effects of vasopressin are preserved during hypoxemia and severe acidemia, and pulmonary arterial pressures do not increase with vasopressin. After initiation of vasopressin, organ-specific vasodilation may preserve cardiac and renal function. Whereas V_2 stimulation promotes water retention from the distal tubules and collecting ducts, V_1-receptors cause vasoconstriction of efferent arterioles and relative vasodilation of afferent arterioles to increase glomerular perfusion pressure and filtration rate, enhancing urine production.[31,90]

Because vasopressin increases SVR through vasoconstriction it may be utilized as a component of therapy for patients with vasodilatory/distributive shock. Studies involving vasopressin infusion for management of septic shock show rapid and sustained improvement in blood pressure.[31,76,77,86] These effects

are evident with administration of dosages up to 0.04 units/min. Administration of dosages >0.04 units/min may be associated with negative changes in CO and mesenteric mucosal perfusion; however, these results are inconsistent in studies.[31,35] Cardiac ischemia and reductions in stroke volume appear to be rare when dosages of 0.04 units/min or lower are used.[35] However, higher dosages of vasopressin in patients with septic shock complicated by impaired left ventricular systolic function warrant extreme caution. Although vasopressin may have deleterious effects on mesenteric and skin perfusion, studies report vasodilation of cerebral, pulmonary, coronary, and some renal vasculature beds. The clinical outcomes associated with selective vasodilation are not yet known except for the possibility of enhanced urine production in patients not anuric at baseline.[90]

Angiotensin II Angiotensin II increases SVR and may be utilized for patients with vasodilatory/distributive shock. Blood pressure rapidly increases after initiation of angiotensin II in patients with low SVR (ie, those with vasodilatory/distributive shock). The starting dosage of angiotensin II is 10 to 20 ng/kg/min with rapid titration (as quickly as every 5 minutes) to MAP goal. In the first 3 hours of treatment the dosage may be increased up to 80 ng/kg/min; thereafter, the dosage should not exceed 40 ng/kg/min. The effects of angiotensin II on myocardial performance, oxygen transport parameters, and regional organ perfusion are unclear. However, because the risk of lactic acidosis and delirium are higher with angiotensin II, there may be a deleterious effect on regional tissue perfusion.[35,88] Angiotensin II has only been evaluated in patients without depressed CO so it should also be used with extreme caution in patients with impaired left ventricular systolic function. Angiotensin II also increases glomerular perfusion pressure and filtration, but its effects on kidney function are unclear.[35] Angiotensin II increases heart rate through unclear mechanisms, but likely due to activation of AT-1 receptors in the heart.[34,35]

EVALUATION OF THERAPEUTIC OUTCOMES

The initial goals of therapy are to restore effective tissue and organ perfusion. Priority should be placed on the ABCs of life support (ie, airway, breathing, and circulation), assessment of vital signs and mental status, and determination of tissue perfusion (eg, urine production after catheterization). The underlying cause of the patient's tissue hypoperfusion should be evaluated because this leads to the correct treatment approach. For example, in hemorrhagic shock due

to trauma, the most important intervention is surgical control of bleeding, and anything that delays this control is likely to increase, not decrease, mortality. If patients have signs of tissue hypoperfusion and their clinical syndrome is consistent with a shock state that is fluid responsive (eg, hypovolemic), an initial fluid challenge of at least 500 mL of crystalloid fluid should be administered.

Current recommendations for patients with sepsis are to measure blood lactate concentration and administer 30 mL/kg of crystalloid for hypotension within 3 hours of presentation and obtain MAP ≥65 mm Hg with vasopressors, reassess volume status, and re-measure serum lactate if the initial lactate was elevated within 6 hours of presentation.[22] Although protocolized initial treatment of patients with septic shock is not better than usual care, usual care must include rapid (ie, within 1 hour of recognition) antibiotic administration and aggressive fluid resuscitation.[22] **Figure 41-5** presents an algorithm for the management of patients with shock.[1,2,22,27–30,39] This algorithm suggests a stepwise approach to optimize MAP, first with crystalloid fluid resuscitation and using norepinephrine. Although crystalloids are the initial fluid type of choice and albumin cannot be recommended for the prevention or initial treatment of circulatory insufficiency, its use may be appropriate in patients who are not responding to crystalloids and are developing problems such as interstitial fluid accumulation. Patients with evidence of inadequate CO without fluid responsiveness should have an inotrope initiated or mechanical circulatory support considered. Inotropes may be added for shock states with low CO or left ventricular dysfunction. Occasionally, epinephrine and phenylephrine are used when necessary. Although this approach is empirical, it is used broadly in clinical practice and has been justified by the desire to avoid the adverse events associated with strong vasoconstriction. Developing a strategy to rapidly restore effective tissue perfusion reduces mortality. Goals of initial resuscitation should include crystalloid fluids if the patient is fluid responsive, vasopressor agents to achieve MAP at least 65 mm Hg (or SBP 80-90 mm Hg in trauma patients), and frequent clinical assessments to meet global and regional perfusion goals (eg, additional fluid challenge or inotropic therapy to achieve lactate clearance ≥20% or $ScvO_2$ ≥70% [0.70] or urine production ≥0.5 mL/kg/hr).[1,22] Patients who develop supranormal DO_2 and VO_2 values have lower mortality, but targeting these with exogenous administration of vasopressors/inotropes is not beneficial and cannot be recommended. Further work is required to better elucidate the differential effects of vasopressors on regional hemodynamic and oxygen-transport values as measures of local tissue perfusion.

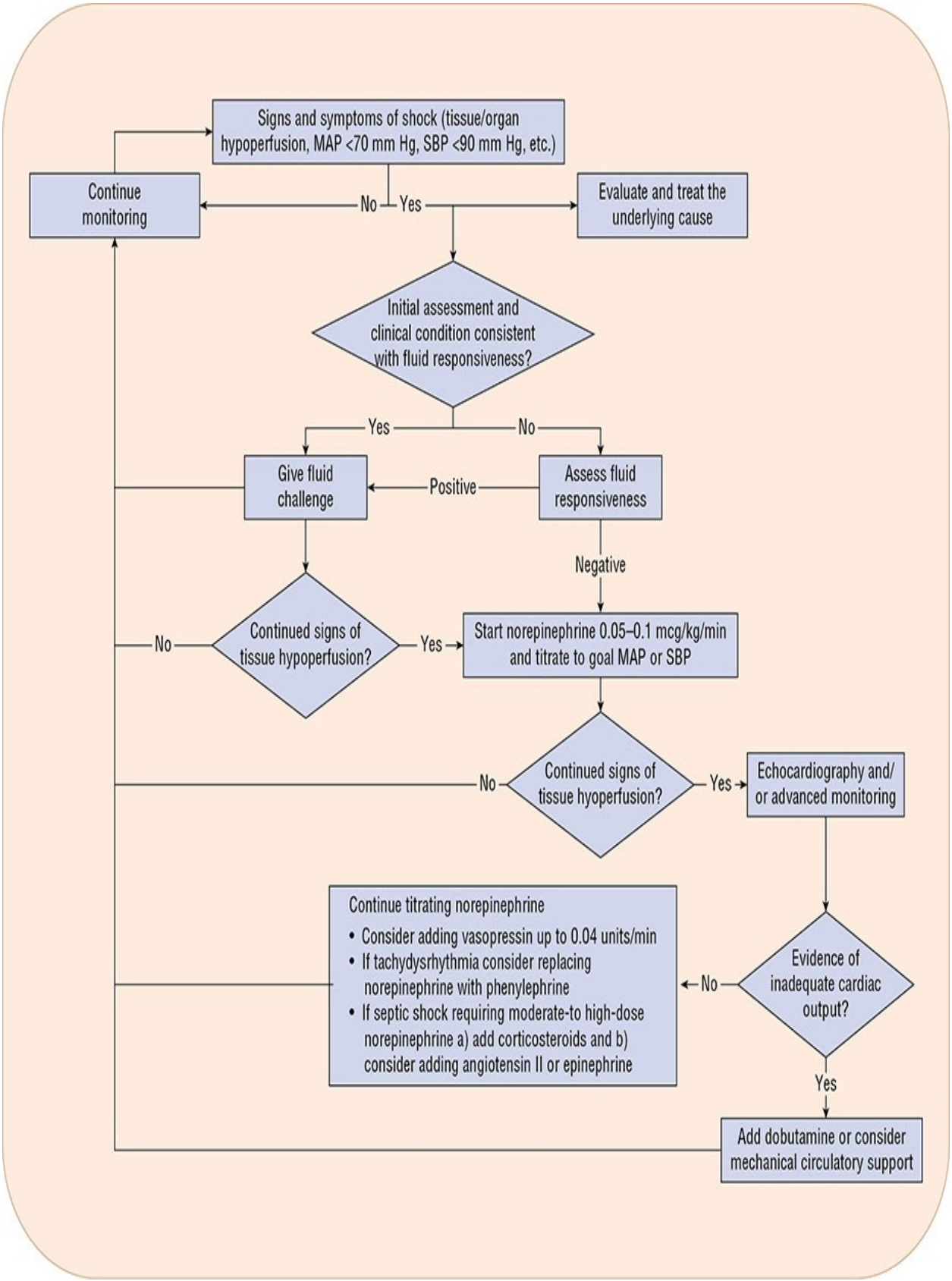

Signs and symptoms of shock (tissue/organ hypoperfusion, MAP <70 mm Hg, SBP <90 mm Hg, etc.)
Continue monitoring
No
Yes
Evaluate and treat the underlying cause
Initial assessment and clinical condition consistent with fluid responsiveness?
Yes
No
Give fluid challenge
Positive
Assess fluid responsiveness
Negative
No
Continued signs of tissue hypoperfusion?
Yes
Start norepinephrine 0.05–0.1 mcg/kg/min and titrate to goal MAP or SBP
No
Continued signs of tissue hyoperfusion?
Yes
Echocardiography and/or advanced monitoring
Continue titrating norepinephrine
• Consider adding vasopressin up to 0.04 units/min
• If tachydysrhythmia consider replacing norepinephrine with phenylephrine
• If septic shock requiring moderate-to high-dose norepinephrine a) add corticosteroids and b) consider adding angiotensin II or epinephrine
No
Evidence of inadequate cardiac output?
Yes
Add dobutamine or consider mechanical circulatory support

FIGURE 41-5 MAP, mean arterial pressure; SBP, systolic blood pressure.).

Vasopressors should be initiated if tissue perfusion is not responding to fluid challenges. Dosage titration and monitoring of vasopressor and inotropic therapy should be guided by the "best clinical response" and lactate clearance.[1,2,22,28–30,39] Clinically effective dosing of vasopressors and inotropes in shock often requires dosages much higher than recommended by most references.[1,2,22,28–30,39] These large doses must be tempered with the development of adverse effects. The goal is to use the lowest effective dosage while minimizing evidence of global hypoperfusion (lactate, $S_{CV}O_2$) and regional hypoperfusion such as myocardial (eg, tachydysrhythmias, electrocardiographic changes, troponin elevations), renal (decreased glomerular filtration rate and/or urine production), splanchnic/gastric (bowel ischemia, elevated transaminases), pulmonary (worsening PaO_2), or peripheral (cold extremities) ischemia. Therapy with catecholamine vasopressors and inotropes is continued until myocardial depression and/or vascular hyporesponsiveness (ie, blood pressure) of shock improve, usually measured in hours to days.[22,29]

Patients should be frequently monitored for their response to therapy. If perfusion is not restored with the initial treatment approach then echocardiography should be pursued with additional treatment options implemented based on the findings. Additional hemodynamic monitoring with a pulmonary artery catheter should be considered in complex patients (eg, those with mixed shock states) or when a clinician is questioning the validity of perfusion assessments or measurements from other monitoring devices. The pulmonary artery catheter (ie, a Swan-Ganz catheter) provides multiple cardiovascular parameters, including CVP, pulmonary artery pressure, PAOP (commonly called the "wedge pressure"), CO, SVR, and S_VO_2. However, because the pulmonary artery catheter is more invasive (leading to a higher risk of complications) than a central venous catheter and not associated with improved clinical outcomes, it should not be used routinely for patients with shock.[1,94] Semi-invasive and minimally invasive hemodynamic monitoring devices are increasingly utilized in patients with shock but are beyond the scope of this chapter.[95]

A number of laboratory tests are indicated for monitoring of shock in the ICU setting. These include assays for assessing possible electrolyte alterations and kidney perfusion (eg, blood urea nitrogen and creatinine). Among other things, a complete blood count will enable assessment of possible infection (white blood

cell count), oxygen-carrying capacity of the blood (hemoglobin, hematocrit), and ongoing bleeding (hemoglobin, hematocrit, and platelet count). In bleeding patients clotting factors are lost and diluted; therefore, concomitant monitoring of coagulation function through laboratory tests (eg, PT/INR and platelets) or viscoelastic tests (eg, thromboelastography) with corresponding measures of support should be initiated.[39] An increasing blood lactate concentration, an increasing arterial base deficit, or a decreasing bicarbonate concentration are global markers indicative of inadequate perfusion leading to anaerobic metabolism. The value of these surrogate markers for improving patient outcomes is controversial, but they are considered traditional end points of resuscitation, particularly trauma patients. Other tests may be indicated if organ dysfunction is likely. For example, when blood flow to the liver is interrupted because of sustained hypotension, a condition known as shock liver may occur. In this condition, the levels of transaminases on a liver panel may be markedly elevated in the first couple of days after marked hypotension, although the concentrations should decrease over time. Along with laboratory testing, a more extensive history can be obtained during the subacute monitoring period.

In patients responding to initial therapy discontinuation of vasopressor or inotropic therapy should be executed slowly; therapy should be "weaned" to avoid a precipitous worsening in regional and systemic hemodynamics. Careful monitoring of global and regional end points also should be geared toward discontinuation of vasopressors and inotropes as soon as the patient is hemodynamically stable. This requires constant observation. Because vasopressors and inotropes often are started while the patient is not yet optimally volume resuscitated, clinicians should reevaluate fluid responsiveness frequently so that the patient can be weaned from the vasopressor as soon as possible. Dosages should be titrated downward approximately every 10 minutes to determine if the patient can tolerate gradual withdrawal and eventual discontinuation of the vasopressor and/or inotrope. Discontinuation of agents may occur only minutes to hours after their initiation, or it may take days to weeks. Shock requiring vasopressor and/or inotropic support usually resolves within several days to 1 week.

This algorithmic approach (**Fig. 41-5**) is consistent with the recommendations made in the Surviving Sepsis Campaign guidelines and other reference documents for the monitoring and treatment of patients with shock.[1,2,16,22,27–30,39] Personalized pharmacotherapy for hemodynamic support of shock may be rational in certain situations (such as long-standing baseline hypertension, or home corticosteroid use) but may be difficult to achieve because patient response

is variable and the acute nature of emergent resuscitation often necessitates treatment before pharmacotherapy can be personalized. In the future, vasopressor therapies may be directed to pharmacogenomic profiles as recent research indicates effectiveness and safety may be influenced by gene polymorphisms.

CONCLUSION

The presence of circulatory shock is indicated by inadequate global tissue perfusion. Shock syndromes are typically classified into either hypovolemic, cardiogenic, obstructive, or vasodilatory/distributive shock. Differentiation of these syndromes is conceptually based on evaluation of preload, cardiac output, and afterload. Patients require close monitoring, including assessment of organ and tissue perfusion, adequate DO_2, and fluid responsiveness.

Crystalloids and norepinephrine are the recommended first-line fluid and vasopressor, respectively, for shock.[2,22,29,39] Balanced salt solutions may be preferred to 0.9% sodium chloride as the initial crystalloid solution. The choice of additional fluids, vasopressors, or inotropic agents should be made according to the clinical needs of the patient and the data obtained from hemodynamic and global and regional perfusion monitoring.[1,2,22,27–30,39]

Postclass Engaged Learning Activity

Conduct a literature search and find a randomized controlled trial that has been published in the past 24 months regarding the use of a balanced salt solution as a plasma expander in a critically ill patient population. Write a brief summary of the study and how the findings of the study might impact the type of fluid used for the resuscitation of a critically ill patient. In particular, describe the purported advantages of the balanced salt solution compared to the solution used in the control group. Assess the major limitations of the study and propose a design for a future study that has the potential to address these limitations.

ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
AT	Angiotensin
ATP	Adenosine triphosphate
BP	Blood pressure
CaMK	Calcium/calmodulin-dependent protein kinases
cAMP	Cyclic adenosine monophosphate
CaO_2	Arterial oxygen content
CI	Confidence interval
CO	Cardiac output
CvO_2	Venous oxygen content
CVP	Central venous pressure
D	Dopamine
DO_2	Oxygen delivery
HR	Heart rate
ICU	Intensive care unit
IL	Interleukin
iNOS	Inducible nitric oxide synthase
MAP	Mean arterial blood pressure
NO	Nitric oxide
O_2ER	Oxygen extraction ratio
PaO_2	Partial pressure of arterial oxygen
PAOP	Pulmonary artery occlusion pressure
PLC	Phospholipase C
RR	Respiratory rate
SBP	Systolic blood pressure
$ScvO_2$	Central venous oxygen saturation
SvO_2	(Mixed) venous oxygen saturation
SVR	Systemic vascular resistance
TNF	Tumor necrosis factor
V	Vasopressin
VO_2	Oxygen consumption

REFERENCES

1. Cecconi M, De Backer D, Antonelli M, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. *Intensive Care Med*. 2014;40(12):1795–1815.
2. Vincent JL, De Backer D. Circulatory shock. *N Engl J Med*.

2013;369(18):1726–1734.

3. Sakr Y, Vincent JL, Schuerholz T, et al. Early- versus late-onset shock in European intensive care units. *Shock*. 2007;28(6):636–643.
4. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med*. 2010;362(9):779–789.
5. Kadri SS, Rhee C, Strich JR, et al. Estimating ten-year trends in septic shock incidence and mortality in United States academic medical centers using clinical data. *Chest*. 2017;151(2):278–285.
6. Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. *JAMA*. 2014;311(13):1308–1316.
7. Thiele H, Akin I, Sandri M, et al. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. *N Engl J Med*. 2017;377(25):2419–2432.
8. Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med*. 2013;369(9):840–851.
9. Dellinger RP. Cardiovascular management of septic shock. *Crit Care Med*. 2003;31(3):946–955.
10. Funk DJ, Jacobsohn E, Kumar A. Role of the venous return in critical illness and shock: Part II-shock and mechanical ventilation. *Crit Care Med*. 2013;41(2):573–579.
11. Thiele H, Ohman EM, Desch S, Eitel I, de Waha S. Management of cardiogenic shock. *Eur Heart J*. 2015;36(20):1223–1230.
12. Reynolds HR, Hochman JS. Cardiogenic shock: Current concepts and improving outcomes. *Circulation*. 2008;117(5):686–697.
13. Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. *N Engl J Med*. 2001;345(8):588–595.
14. Landesberg G, Levin PD, Gilon D, et al. Myocardial dysfunction in severe sepsis and septic shock: No correlation with inflammatory cytokines in real-life clinical setting. *Chest*. 2015;148(1):93–102.
15. Vieillard-Baron A, Caille V, Charron C, Belliard G, Page B, Jardin F. Actual incidence of global left ventricular hypokinesia in adult septic shock. *Crit Care Med*. 2008;36(6):1701–1706.
16. De Backer D. Detailing the cardiovascular profile in shock patients. *Crit Care*. 2017;21(suppl 3):311.

17. Huang YC. Monitoring oxygen delivery in the critically ill. *Chest*. 2005;128(5 suppl 2):554S–560S.
18. Walley KR. Use of central venous oxygen saturation to guide therapy. *Am J Respir Crit Care Med*. 2011;184(5):514–520.
19. McLean AS. Echocardiography in shock management. *Crit Care*. 2016;20:275.
20. Marik PE, Cavallazzi R. Does the central venous pressure predict fluid responsiveness? An updated meta-analysis and a plea for some common sense. *Crit Care Med*. 2013;41(7):1774–1781.
21. Monnet X, Marik PE, Teboul JL. Prediction of fluid responsiveness: An update. *Ann Intensive Care*. 2016;6(1):111.
22. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. *Crit Care Med*. 2017;45(3):486–552.
23. Kraut JA, Madias NE. Lactic acidosis. *N Engl J Med*. 2014;371(24):2309–2319.
24. Suetrong B, Walley KR. Lactic acidosis in sepsis: It's not all anaerobic: Implications for diagnosis and management. *Chest*. 2016;149(1):252–261.
25. De Backer D, Donadello K, Sakr Y, et al. Microcirculatory alterations in patients with severe sepsis: Impact of time of assessment and relationship with outcome. *Crit Care Med*. 2013;41(3):791–799.
26. De Backer D, Hollenberg S, Boerma C, et al. How to evaluate the microcirculation: Report of a round table conference. *Crit Care*. 2007;11(5):R101.
27. Annane D, Ouanes-Besbes L, de Backer D, et al. A global perspective on vasoactive agents in shock. *Intensive Care Med*. 2018;44(6):833–846.
28. Bangash MN, Kong ML, Pearse RM. Use of inotropes and vasopressor agents in critically ill patients. *Br J Pharmacol*. 2012;165(7):2015–2033.
29. Hollenberg SM. Vasoactive drugs in circulatory shock. *Am J Respir Crit Care Med*. 2011;183(7):847–855.
30. Jentzer JC, Coons JC, Link CB, Schmidhofer M. Pharmacotherapy update on the use of vasopressors and inotropes in the intensive care unit. *J Cardiovasc Pharmacol Ther*. 2015;20(3):249–260.
31. Russell JA. Bench-to-bedside review: Vasopressin in the management of septic shock. *Crit Care*. 2011;15(4):226.
32. Antonucci E, Gleeson PJ, Annoni F, et al. Angiotensin II in refractory

septic shock. *Shock*. 2017;47(5):560–566.

33. Bissell BD, Browder K, McKenzie M, Flannery AH. A blast from the past: Revival of angiotensin II for vasodilatory shock. *Ann Pharmacother*. 2018;52(9):920–927.
34. Allen AM, Zhuo J, Mendelsohn FA. Localization of angiotensin AT1 and AT2 receptors. *J Am Soc Nephrol*. 1999;10(suppl 11):S23–29.
35. Bauer SR, Sacha GL, Lam SW. Safe use of vasopressin and angiotensin II for patients with circulatory shock. *Pharmacotherapy*. 2018;38(8):851–861.
36. Russell JA, Fjell C, Hsu JL, et al. Vasopressin compared with norepinephrine augments the decline of plasma cytokine levels in septic shock. *Am J Respir Crit Care Med*. 2013;188(3):356–364.
37. Marik PE, Pastores SM, Annane D, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: Consensus statements from an international task force by the American College of Critical Care Medicine. *Crit Care Med*. 2008;36(6):1937–1949.
38. Annane D, Pastores SM, Rochwerg B, et al. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Crit Care Med*. 2017;45(12):2078–2088.
39. Rossaint R, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: Fourth edition. *Crit Care*. 2016;20(1):100.
40. Vincent JL, Weil MH. Fluid challenge revisited. *Crit Care Med*. 2006;34(5):1333–1337.
41. Plurad DS, Chiu W, Raja AS, et al. Monitoring modalities and assessment of fluid status: A practice management guideline from the Eastern Association for the Surgery of Trauma. *J Trauma Acute Care Surg*. 2018;84(1):37–49.
42. Oddo M, Poole D, Helbok R, et al. Fluid therapy in neurointensive care patients: ESICM consensus and clinical practice recommendations. *Intensive Care Med*. 2018;44(4):449–463.
43. Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev*. 2013(2):CD000567.

44. Roberts I, Blackhall K, Alderson P, Bunn F, Schierhout G. Human albumin solution for resuscitation and volume expansion in critically ill patients. *Cochrane Database Syst Rev*. 2011(11):CD001208.
45. Lewis SR, Pritchard MW, Evans DJ, et al. Colloids versus crystalloids for fluid resuscitation in critically ill people. *Cochrane Database Syst Rev*. 2018;8:CD000567.
46. American Thoracic Society. Evidence-based colloid use in the critically ill: American Thoracic Society Consensus Statement. *Am J Respir Crit Care Med*. 2004;170(11):1247–1259.
47. Pham TN, Cancio LC, Gibran NS, American Burn A. American Burn Association practice guidelines burn shock resuscitation. *J Burn Care Res*. 2008;29(1):257–266.
48. Self WH, Semler MW, Bellomo R, et al. Liberal versus restrictive intravenous fluid therapy for early septic shock: Rationale for a randomized trial. *Ann Emerg Med*. 2018;72(4):457–466.
49. Magee CA, Bastin MLT, Laine ME, et al. Insidious harm of medication diluents as a contributor to cumulative volume and hyperchloremia: A prospective, open-label, sequential period pilot study. *Crit Care Med*. 2018;46(8):1217–1223.
50. Self WH, Semler MW, Wanderer JP, et al. Balanced crystalloids versus saline in noncritically ill adults. *N Engl J Med*. 2018;378(9):819–828.
51. Semler MW, Self WH, Wanderer JP, et al. Balanced crystalloids versus saline in critically Ill adults. *N Engl J Med*. 2018;378(9):829–839.
52. Didwania A, Miller J, Kassel D, Jackson EVJr, Chernow B. Effect of intravenous lactated Ringer's solution infusion on the circulating lactate concentration: Part 3. Results of a prospective, randomized, double-blind, placebo-controlled trial. *Crit Care Med*. 1997;25(11):1851–1854.
53. Finfer S, Myburgh J, Bellomo R. Intravenous fluid therapy in critically ill adults. *Nat Rev Nephrol*. 2018;14(9):541–557.
54. Cochrane Injuries Group Albumin R. Human albumin administration in critically ill patients: Systematic review of randomised controlled trials. *BMJ*. 1998;317(7153):235–240.
55. Choi PT, Yip G, Quinonez LG, Cook DJ. Crystalloids vs. colloids in fluid resuscitation: A systematic review. *Crit Care Med*. 1999;27(1):200–210.
56. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350(22):2247–2256.

57. SAFE Study Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group; Australian Red Cross Blood Service; George Institute for International Health; Myburgh J, Cooper DJ, Finfer S, et al. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med*. 2007;357(9):874–884.
58. Delaney AP, Dan A, McCaffrey J, Finfer S. The role of albumin as a resuscitation fluid for patients with sepsis: A systematic review and meta-analysis. *Crit Care Med*. 2011;39(2):386–391.
59. Patel A, Laffan MA, Waheed U, Brett SJ. Randomised trials of human albumin for adults with sepsis: Systematic review and meta-analysis with trial sequential analysis of all-cause mortality. *BMJ*. 2014;349:g4561.
60. Rochwerg B, Alhazzani W, Sindi A, et al. Fluid resuscitation in sepsis: A systematic review and network meta-analysis. *Ann Intern Med*. 2014;161(5):347–355.
61. Xu JY, Chen QH, Xie JF, et al. Comparison of the effects of albumin and crystalloid on mortality in adult patients with severe sepsis and septic shock: A meta-analysis of randomized clinical trials. *Crit Care*. 2014;18(6):702.
62. Caironi P, Tognoni G, Masson S, et al. Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med*. 2014;370(15):1412–1421.
63. Zarychanski R, Abou-Setta AM, Turgeon AF, et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: A systematic review and meta-analysis. *JAMA*. 2013;309(7):678–688.
64. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med*. 1999;340(6):409–417.
65. Holst LB, Haase N, Wetterslev J, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. *N Engl J Med*. 2014;371(15):1381–1391.
66. Mazer CD, Whitlock RP, Fergusson DA, et al. Restrictive or liberal red-cell transfusion for cardiac surgery. *N Engl J Med*. 2017;377(22):2133–2144.
67. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med*. 2013;368(1):11–21.

68. Bickell WH, Wall MJJr, Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med*. 1994;331(17):1105–1109.
69. Dutton RP, Mackenzie CF, Scalea TM. Hypotensive resuscitation during active hemorrhage: Impact on in-hospital mortality. *J Trauma*. 2002;52(6):1141–1146.
70. Bulger EM, May S, Brasel KJ, et al. Out-of-hospital hypertonic resuscitation following severe traumatic brain injury: A randomized controlled trial. *JAMA*. 2010;304(13):1455–1464.
71. Bulger EM, May S, Kerby JD, et al. Out-of-hospital hypertonic resuscitation after traumatic hypovolemic shock: A randomized, placebo controlled trial. *Ann Surg*. 2011;253(3):431–441.
72. Shakur H, Roberts I, et al. CRASH-2 trial collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): A randomised, placebo-controlled trial. *Lancet*. 2010;376(9734):23–32.
73. Avni T, Lador A, Lev S, Leibovici L, Paul M, Grossman A. Vasopressors for the treatment of septic shock: Systematic review and meta-analysis. *PLoS One*. 2015;10(8):e0129305.
74. De Backer D, Aldecoa C, Njimi H, Vincent JL. Dopamine versus norepinephrine in the treatment of septic shock: A meta-analysis. *Crit Care Med*. 2012;40(3):725–730.
75. Gamper G, Havel C, Arrich J, et al. Vasopressors for hypotensive shock. *Cochrane Database Syst Rev*. 2016;2:CD003709.
76. Polito A, Parisini E, Ricci Z, Picardo S, Annane D. Vasopressin for treatment of vasodilatory shock: An ESICM systematic review and meta-analysis. *Intensive Care Med*. 2012;38(1):9–19.
77. Serpa Neto A, Nassar APJ, Cardoso SO, et al. Vasopressin and terlipressin in adult vasodilatory shock: A systematic review and meta-analysis of nine randomized controlled trials. *Crit Care*. 2012;16(4):R154.
78. McIntyre WF, Um KJ, Alhazzani W, et al. Association of vasopressin plus catecholamine vasopressors vs catecholamines alone with atrial fibrillation in patients with distributive shock: A systematic review and meta-analysis. *JAMA*. 2018;319(18):1889–1900.
79. Rochwerg B, Oczkowski SJ, Siemieniuk RAC, et al. Corticosteroids in sepsis: An updated systematic review and meta-analysis. *Crit Care Med*. 2018;46(9):1411–1420.

80. Rygard SL, Butler E, Granholm A, et al. Low-dose corticosteroids for adult patients with septic shock: A systematic review with meta-analysis and trial sequential analysis. *Intensive Care Med*. 2018;44(7):1003–1016.
81. Annane D, Vignon P, Renault A, et al. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: A randomised trial. *Lancet*. 2007;370(9588):676–684.
82. Myburgh JA, Higgins A, Jovanovska A, Lipman J, Ramakrishnan N, Santamaria J. A comparison of epinephrine and norepinephrine in critically ill patients. *Intensive Care Med*. 2008;34(12):2226–2234.
83. Andreis DT, Singer M. Catecholamines for inflammatory shock: A Jekyll-and-Hyde conundrum. *Intensive Care Med*. 2016;42(9):1387–1397.
84. Bellomo R, Chapman M, Finfer S, Hickling K, Myburgh J. Low-dose dopamine in patients with early renal dysfunction: A placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. *Lancet*. 2000;356(9248):2139–2143.
85. Friedrich JO, Adhikari N, Herridge MS, Beyene J. Meta-analysis: Low-dose dopamine increases urine output but does not prevent renal dysfunction or death. *Ann Intern Med*. 2005;142(7):510–524.
86. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med*. 2008;358(9):877–887.
87. Hajjar LA, Vincent JL, Barbosa Gomes Galas FR, et al. Vasopressin versus Norepinephrine in patients with vasoplegic shock after cardiac surgery: The VANCS randomized controlled trial. *Anesthesiology*. 2017;126(1):85–93.
88. Khanna A, English SW, Wang XS, et al. Angiotensin II for the treatment of vasodilatory shock. *N Engl J Med*. 2017;377(5):419–430.
89. Levy B, Clere-Jehl R, Legras A, et al. Epinephrine versus norepinephrine for cardiogenic shock after acute myocardial infarction. *J Am Coll Cardiol*. 2018;72(2):173–182.
90. Gordon AC, Russell JA, Walley KR, et al. The effects of vasopressin on acute kidney injury in septic shock. *Intensive Care Med*. 2010;36(1):83–91.
91. Gordon AC, Mason AJ, Thirunavukkarasu N, et al. Effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock: The VANISH randomized clinical trial. *JAMA*. 2016;316(5):509–518.

92. Tumlin JA, Murugan R, Deane AM, et al. Outcomes in patients with vasodilatory shock and renal replacement therapy treated with intravenous angiotensin II. *Crit Care Med*. 2018;46(6):949–957.
93. Gordon AC, Wang N, Walley KR, Ashby D, Russell JA. The cardiopulmonary effects of vasopressin compared with norepinephrine in septic shock. *Chest*. 2012;142(3):593–605.
94. Rajaram SS, Desai NK, Kalra A, et al. Pulmonary artery catheters for adult patients in intensive care. *Cochrane Database Syst Rev*. 2013;(2):CD003408.
95. Teboul JL, Saugel B, Cecconi M, et al. Less invasive hemodynamic monitoring in critically ill patients. *Intensive Care Med*. 2016;42(9):1350–1359.

SECTION 5 RESPIRATORY DISORDERS

Evaluation of Respiratory Function

Maria I. Velez, Tamara D. Simpson, Stephanie M. Levine, and Jay I. Peters

KEY CONCEPTS

1. The function of the lungs is to maintain the arterial partial pressure of oxygen (PaO_2) and arterial partial pressure of carbon dioxide ($PaCO_2$) within normal ranges (ie, normal ventilation-perfusion ratio).
2. The air in the lung is divided into four compartments: tidal volume—air exhaled during non-exertional breathing; inspiratory reserve volume (IRV)—maximal air *inhaled* above tidal volume; expiratory reserve volume (ERV)—maximum air *exhaled* after tidal volume; and residual volume (RV)—air remaining in the lung after maximal exhalation. The sum of all four components is the total lung capacity (TLC).
3. Obstructive lung disease is defined as an inability to get air out of the lung. It is identified on spirometry when forced expiratory volume in the first second of expiration (FEV_1) compared to the forced vital capacity (FVC) (total amount of air that can be exhaled during a forced exhalation) (FEV_1/FVC) is less than 70% to 75% (0.70 to 0.75) in adults (or below the lower limit of normal (LLN) based on population studies).
4. An increase in FEV_1 of 12% (and greater than 0.2 L in adults) after an inhaled β-agonist suggests an acute bronchodilator response.
5. Restrictive lung disease is defined as an inability to get enough air into the lung and is best defined as a reduction in TLC (usually less than 80% of predicted).
6. Restrictive lung disease can be produced by a number of diseases, such as increased elastic recoil (interstitial lung disease), respiratory muscle weakness (myasthenia gravis), and mechanical restrictions (pleural effusion or kyphoscoliosis). It can also be the result of poor effort during the

pulmonary function tests (PFTs).

7. The shape of the flow–volume loop, which includes inspiratory and expiratory flow-volume curves, and the ratio of forced expiratory and inspiratory flow at 50% of VC ($FEF_{50\%}/FIF_{50\%}$ greater than 1) may be useful in the diagnosis of upper airway obstruction.
8. Cardiopulmonary exercise testing allows for the assessment of multiple organs involved in exercise.

Preclass Engaged Learning Activity

Watch this brief video about when and how to perform a spirometry: “Taking a Spirometry Test,”.

INTRODUCTION

The primary function of the respiratory system is to maintain normal arterial blood gases, that is, arterial partial pressure of oxygen (PaO_2) and arterial partial pressure of carbon dioxide ($PaCO_2$). To achieve this goal, several processes must be accomplished; including alveolar ventilation, pulmonary perfusion, ventilation–perfusion matching, and gas transfer across the alveolar–capillary membrane. Alveolar ventilation is achieved by the cyclic process of air movement in and out of the lung. During inspiration, the inspiratory muscles contract and generate a negative pressure in the pleural space. This pressure gradient between the mouth and the alveoli draws fresh air (tidal volume [V_T]) into the lung. Approximately one-third of the inspired gas stays in the conducting airways (dead space), and two thirds reach the alveoli.

1. The human lung contains a series of branching, progressively tapering airways that originate at the glottis and terminate in a matrix of thin-walled alveoli. Coursing through this matrix of alveoli is a rich network of capillaries that originates from the pulmonary arterioles and terminates in the pulmonary venules. The adequacy of respiration in each gas exchange unit depends on the apposition of a thin film of mixed venous blood with just the right amount of fresh alveolar gas. During “ideal” gas exchange, blood flow and ventilation are uniform; accordingly, there is no alveolar–arterial difference (or gradient) in the partial pressure of oxygen ($P[A–a]O_2$, sometimes called the A–a gradient).

However, gas exchange is not perfect, even in the normal lung. Normally, alveolar ventilation is less than pulmonary blood flow, and the overall ventilation–perfusion ratio is 0.8 (not 1.0).

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

43

Asthma

Kathryn V. Blake and Jason E. Lang

KEY CONCEPTS

1. Asthma is a highly prevalent disease that is a result of genetic predisposition and environmental interactions; it is one of the most common chronic diseases of childhood.
2. Asthma is primarily a chronic inflammatory disease of the airways of the lung for which there is no known cure or primary prevention; the immunohistopathologic features include cell infiltration by neutrophils, eosinophils, T-helper type 2 lymphocytes, mast cells, and epithelial cells.
3. Chronic asthma is characterized by either the intermittent or persistent presence of highly variable degrees of airflow obstruction from airway wall inflammation and bronchial smooth muscle constriction; in some patients, persistent changes in airway structure occur.
4. Variability in response to medications requires individualization of therapy within existing evidence-based guidelines for management. This is most evident in patients with severe asthma phenotypes.
5. Ongoing patient education, for a partnership in asthma care, is essential for optimal patient outcomes and includes trigger avoidance and self-management techniques.
6. The inflammatory process in asthma is treated most effectively with corticosteroids, with the inhaled corticosteroids (ICSs) having the greatest efficacy and safety profile for long-term management.
7. Bronchial smooth muscle constriction is prevented or treated most effectively with inhaled β_2-adrenergic receptor agonists.

Preclass Engaged Learning Activity

Watch the five short videos in the series Asthma Management Academy. These videos provide a brief overview of the following topics Module 1 Scope of Asthma, Module 2 Triggers, Module 3 Medications, Module 4 Medication Devices, Module 5 Monitoring and Assessment. The videos are useful to enhance student understanding regarding the COLLECT and ASSESS steps in the patient care process.

INTRODUCTION

Asthma has been known since antiquity, yet it is a disease that still defies precise definition. The word *asthma* is of Greek origin and means “panting.” More than 2,000 years ago, Hippocrates used the word *asthma* to describe episodic shortness of breath; however, the first detailed clinical description of the asthmatic patient was made by Aretaeus in the second century.[1]

The Global Initiative for Asthma (GINA) provides a practical asthma definition[2]: “Asthma is a *heterogeneous* disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation.” The National Institutes of Health, National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3 (EPR3), adds that the variable airflow obstruction is often reversible either spontaneously or with treatment, although reversibility may not be complete in some patients with asthma.[3]

The definitions encompass the important heterogeneity of the clinical presentation of asthma by describing the scientific and clinically accepted characteristics of asthma.

EPIDEMIOLOGY

An estimated 26.5 million persons in the United States have asthma (about 8.4% of the population).[4] Asthma is the most common chronic disease among children in the United States affecting overall health, with approximately 6 million children affected.[5,6] In the United States, as in other industrialized

countries, the prevalence of asthma has increased from 7.3% in 2001. Asthma prevalence is higher in persons with incomes below 100% of poverty level at 11.8% and in blacks 11.6% and Puerto Ricans 14.3%. Adults are five times more likely to die from asthma than children, with the highest death rates in females and non-Hispanic blacks (who have two to three times the death rate of whites or Hispanics).[5] Nearly 14 million school days are missed per year due to asthma, and asthma accounts for nearly half of school absences in children with little variation by sex, age (young vs adolescent), race and ethnicity, or poverty level.[5]

Influenza infection can result in serious complications in people with asthma, even those with mild disease and those who are well-controlled on medication. An annual influenza vaccination is an essential preventative measure in people with asthma. However, in 2015, only 47% of adults and 64% of children with asthma received the influenza vaccination, with the highest rate in children under 5 years at 80%, which is likely due to regular visits to the pediatrician.[5]

Approximately 60% of adults and children describe themselves as having persistent (vs intermittent) asthma yet only 40% of adults and children report using long-term control medications that are fundamental for the prevention and control of symptoms. Nearly 20% of children and 24% of adults report using a quick-relief medication (such as a short-acting inhaled β_2-agonist [SABA]) more than twice weekly, which is a marker for poorly controlled asthma.[5]

The estimated direct healthcare costs of asthma in the United States in 2015 US dollars was $80 billion in medical expenses, missed work or school, or death.[7] The societal burden of asthma (indirect medical expenditures: loss of productivity and death) in the United States was $5.9 billion. Prescription drugs were the largest single direct medical expenditure.[8]

The natural history of asthma is still not well defined. Although asthma can occur at any time, it is principally a pediatric disease, with most patients being diagnosed by 5 years of age and up to 50% of children having symptoms by 2 years of age.[3] Asthma is more common in boys but between 30% and 70% of children with asthma will improve markedly or become symptom-free by early adulthood; chronic disease persists in about 30% to 40% of patients, but becomes more common in adult women than men; generally 20% or less develop severe chronic disease.[3,9] Predictors of persistent adult asthma include atopy, onset during school age, and presence of bronchial hyper-responsiveness (BHR).[3] Diminished lung growth may occur in some children (approximately 10%) with asthma.[3]

In adults, most longitudinal studies have suggested a more rapid rate of

decline in lung function in asthmatics than in nonasthmatic people, primarily reflected in forced expiratory volume in 1 second (FEV_1).[3] However, the annual decline in FEV_1 is less than that in smokers or in patients with a diagnosis of emphysema. In general, individuals with less frequent asthma attacks and normal lung function on initial assessment have higher remission rates, whereas smokers have the lowest remission and highest relapse rates.[3] The level of BHR tends to predict the rate of decline in FEV_1, with a greater decline found with high levels of BHR.[3] Thus, airway obstruction in asthma may become irreversible and also worsen over time owing to airway remodeling (see below).[3] However, most patients do not die from long-term progression of their disease and their life span is not different from the general population.[3]

As with prevalence and morbidity, mortality from acute exacerbations of asthma worldwide has been relatively stable over the past 10 years, with a death rate of 0.19 per 1,000 persons with asthma reported in 2012.[10] However, those in the lowest sociodemographic groups bear the greatest risk of death from asthma which may be more than fivefold greater than those in the highest sociodemographic group.[9] Despite the relatively low number of asthma deaths, 80% to 90% are preventable.[3]

Most deaths from asthma occur outside the hospital, and death is rare after hospitalization. The most common cause of death from asthma is inadequate assessment of the severity of airway obstruction by the patient or healthcare professional and inadequate therapy. The most common cause of death in hospitalized patients is also inadequate or inappropriate therapy. Thus, the key to prevention of death from asthma, as advocated by both US NAEPP and GINA, is education.[2,3]

ETIOLOGY

1 Epidemiologic studies strongly support the concept of a genetic predisposition plus environmental interaction to the development of asthma, yet the picture remains complex and incomplete.[11] Genetic factors account for 60% to 80% of the susceptibility. Asthma represents a complex genetic disorder, in that the asthma phenotype is likely a result of polygenic inheritance or different combinations of genes. Initial searches focused on establishing links between atopy (genetically determined state of hypersensitivity to environmental allergens) and asthma Genome-wide searches have also found linkages with genes on chromosome 17q21 (such as *ZPBP2*, *GSDMB*, and *ORMDL3*) and

interleukin genes (*IL33*, *IL1RL1/IL18R1*, and *IL2RB9*) and HLA-DQ and SMAD3 that are associated with epithelial barrier function and innate and adaptive immune response abnormalities.[9] Although genetic predisposition to atopy is a significant risk factor for developing asthma, not all atopic individuals develop asthma, nor do all patients with asthma exhibit atopy. Disparate phenotypes of asthma (progressive or remodeled vs nonprogressive) are likely genetically determined.[11]

1 Environmental risk factors for the development of asthma include socioeconomic status, family size, exposure to secondhand tobacco smoke in infancy, and in utero, allergen exposure, ambient air pollution, urbanization, viral respiratory infections including respiratory syncytial virus (RSV) and rhinovirus, and decreased exposure to common childhood infectious agents.[12] The timing of, and exposure to, certain environmental factors during early childhood in genetically susceptible individuals is thought to predispose to the development of allergies and asthma by allowing the allergic immunologic system (T-helper cell type 2 [Th_2] [Th_2 high asthma] lymphocytes) to develop instead of the system to fight infections (T-helper type 1 [Th_1] [Th_2 low asthma] lymphocytes).[9,13] The first 2 years of life appear to be most important for the exposures to produce an alteration in the immune response system.[12]

Risk factors for early (less than 3 years of age) recurrent wheezing associated with viral infections include preterm birth, low birth weight, male gender, and parental smoking. However, this early pattern is due to smaller airways, and these risk factors are not necessarily risk factors for developing asthma in later life.[12] Atopy is the predominant risk factor for children to have continued asthma.[12] Asthma can begin in adults later in life. Occupational asthma in previously healthy individuals emphasizes the effect of environment on the development of asthma.[14] The heterogeneity of the asthma phenotype appears most obvious when listing the diverse protective and risk factors for asthma development (**Fig. 43-1**).[3,12,13] These various factors have relative degrees of importance from patient to patient. Environmental exposures are the most important precipitants of severe asthma exacerbations. Epidemics of severe asthma in cities have followed exposures to high concentrations of aeroallergens. Viral respiratory tract infections remain the single most significant precipitant of severe asthma in children and are an important trigger in adults as well.[15] Other possible factors precipitating exacerbations include air pollution, emotions, exercise,, occupational exposures, and drugs.

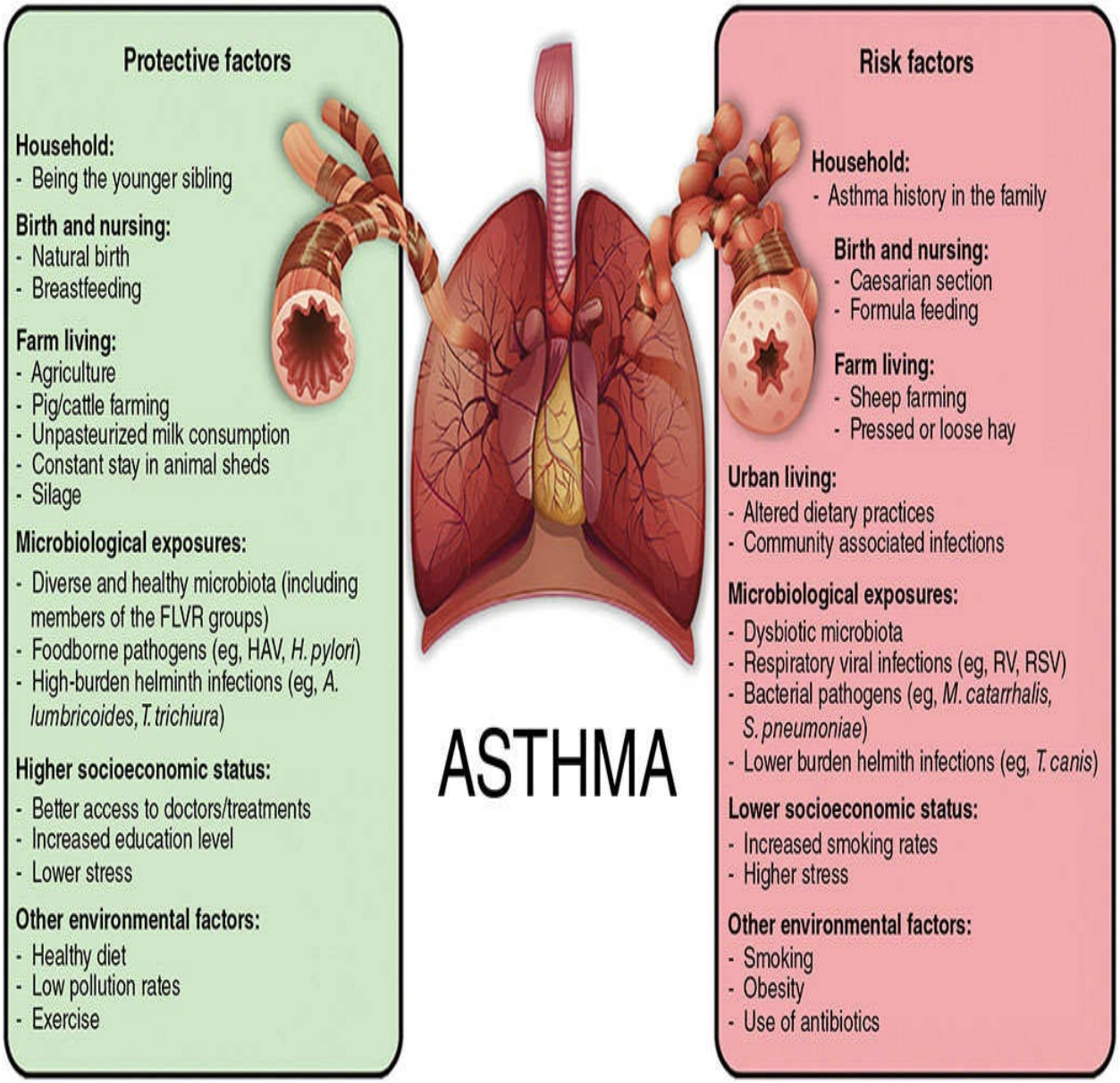


FIGURE 43-1 Factors that are associated with protecting against, or risk for, developing asthma. These various factors have relative degrees of importance from patient to patient. FLVR, Faecalibacterium, Lachnospira, Veillonella, and Rothia spp; HAV, hepatitis A; RV, rhinovirus; RSV, respiratory syncytial virus. (Reprinted, with permission, from van Tilburg Bernardes E, Arrieta MC. Hygiene hypothesis in asthma development: Is hygiene to blame? Arch Med Res. 2017;48:717–726.)

PATHOPHYSIOLOGY

2 Major characteristics of asthma include a variable degree of airflow

obstruction (related to smooth muscle bronchospasm, edema, and mucus hypersecretion), BHR, and airway inflammation (**Fig. 43-2**). To understand the pathogenetic mechanisms that underlie the many phenotypes of asthma, it is critical to identify factors that initiate, intensify, and modulate the inflammatory response of the airways and to determine how these processes produce the characteristic airway abnormalities.

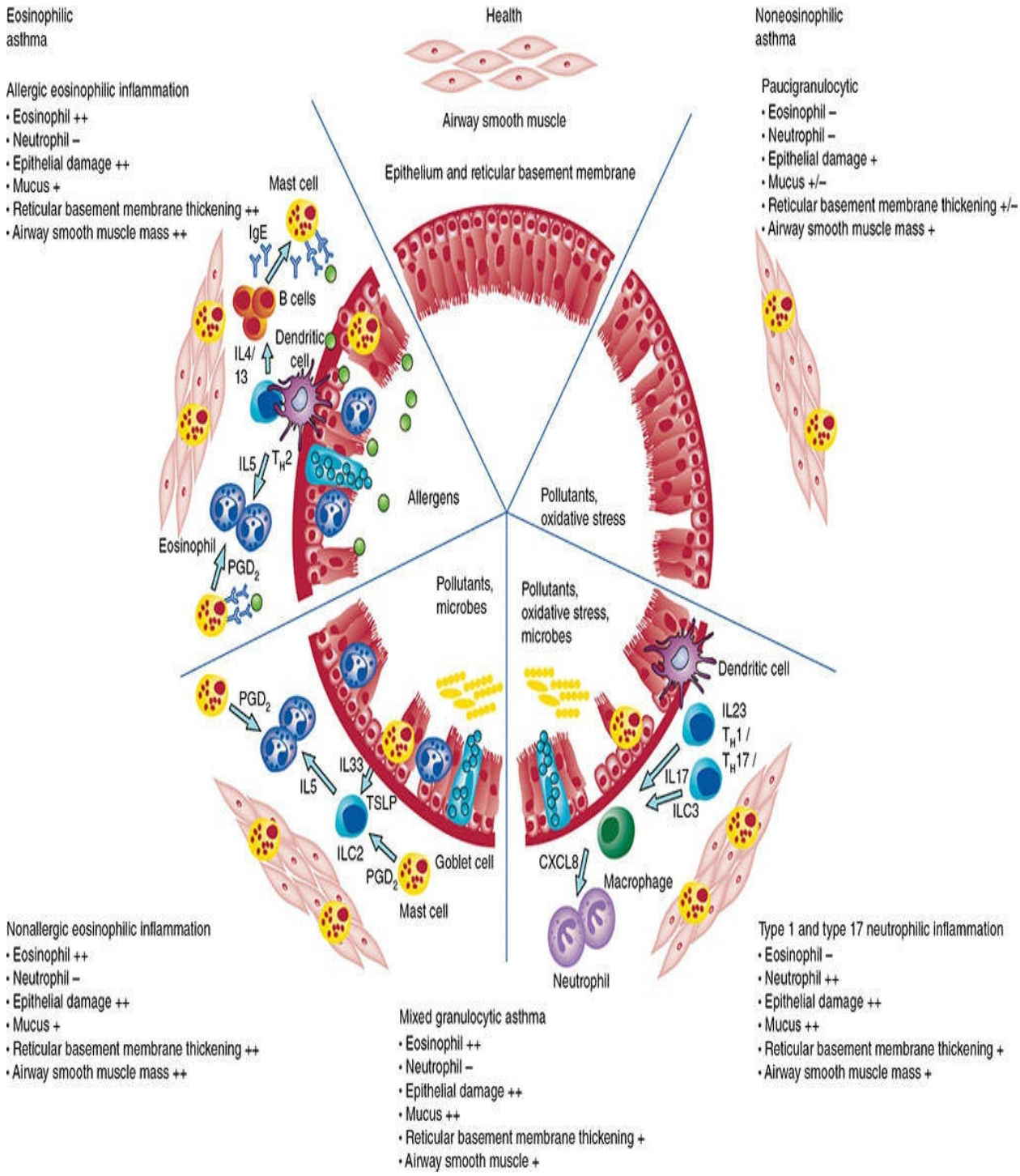


FIGURE 43-2 Diagrammatic presentation of the relationship between inflammatory cells, lipid and preformed mediators, inflammatory cytokines, and proposed pathogenesis and clinical presentation in asthma. See text for details (IL, interleukin; PG, prostaglandin; TSLP, thymic stromal lymphopoietin; CXCL8, C-X-C motif chemokine ligand 8; ILC2, type 2 innate lymphoid cells; Th, T helper). (Reprinted from Papi A, Brightling C, Pedersen SE, Reddel HK.

Asthma. Lancet. 2018;391:783-800.)

Acute and Chronic Inflammation

Inhaled allergen challenge models contribute most to our understanding of acute inflammation in asthma.[9] Inhaled allergen challenge in allergic patients leads to an early phase reaction that, in some cases, may be followed by a late-phase reaction. The activation of cells bearing allergen-specific immunoglobulin E (IgE) initiates the early phase reaction. It is characterized by the rapid activation of airway mast cells and macrophages leading to the rapid release of pro-inflammatory mediators such as histamine, eicosanoids, and reactive oxygen (O_2) species that induce contraction of airway smooth muscle, mucus secretion, and edema.[9] The bronchial microcirculation has an essential role in this inflammatory process. Inflammatory mediators induce microvascular leakage with exudation of plasma in the airways.[9] Acute plasma protein leakage induces a thickened, engorged, and edematous airway wall and a consequent narrowing of the airway lumen. Plasma exudation may compromise epithelial integrity, and the presence of plasma in the lumen may reduce mucus clearance.[9] Plasma proteins also may promote the formation of exudative plugs mixed with mucus and inflammatory and epithelial cells. Together these effects contribute to airflow obstruction (see Fig. 43-2).

The late-phase inflammatory reaction occurs 6 to 9 hours after allergen provocation and involves the recruitment and activation of eosinophils, $CD4^+$ thymically derived lymphocytes (T cells), basophils, neutrophils, and macrophages.[9] There is selective retention of airway T cells, the expression of adhesion molecules, and the release of selected pro-inflammatory mediators and cytokines involved in the recruitment and activation of inflammatory cells.[9] The activation of T cells after allergen challenge leads to the release of Th_2-related cytokines that may modulate the late-phase response.[9] The release of preformed cytokines by mast cells is the likely initial trigger for the early recruitment of inflammatory cells that then recruit and induce the more persistent involvement by T cells.[9] The enhancement of nonspecific BHR usually can be demonstrated after the late-phase reaction but not after the early phase reaction following allergen or occupational challenge.

Airway inflammation has been demonstrated in all forms of asthma, and an association between the extent of inflammation and the clinical severity of asthma has been demonstrated in selected studies.[9] It is accepted that both

central and peripheral airways are inflamed.

In asthma, all cells of the airways are involved and become activated (Fig. 43-2). Included are eosinophils, neutrophils, T cells, mast cells, alveolar macrophages and dendritic cells, epithelial cells, fibroblasts, and bronchial smooth muscle cells. These cells also regulate airway inflammation and initiate the process of remodeling by the release of cytokines and growth factors.[9,16]

Chronic inflammation is associated with nonspecific BHR and increases the risk of asthma exacerbations. Exacerbations are characterized by increased symptoms and worsening airway obstruction over a period of days or even weeks, and rarely hours. Hyper-responsiveness of the airways to physical, chemical, and pharmacologic stimuli is a hallmark of asthma.[3] BHR also occurs in some patients with chronic bronchitis and allergic rhinitis.[3] Normal healthy subjects also may develop a transient BHR after viral respiratory infections or ozone exposure. However, the degree of BHR in patients with asthma is quantitatively greater than in other populations. Bronchial responsiveness of the general population fits a unimodal distribution that is skewed toward increased reactivity; individuals with clinical asthma represent the extreme end of this distribution. The degree of BHR within asthma correlates with its clinical course and medication requirement necessary to control symptoms.[3] Patients with mild symptoms or in remission demonstrate lower levels of BHR.

The current understanding is that the BHR seen in asthma is at least in part due to and correlative with the extent of airway inflammation.[3] Airway remodeling also correlates somewhat with BHR.[16]

Inflammatory Cells

Epithelial Cells Bronchial epithelial cells participate in mucociliary clearance and removal of noxious agents; however, they also enhance inflammation by releasing eicosanoids, peptidases, matrix proteins, cytokines, chemokines, and nitric oxide (NO).[9] Epithelial cells can be activated by IgE-dependent mechanisms, viruses, pollutants, or histamine. In asthma, especially fatal asthma, extensive epithelial shedding occurs. The functional consequences of epithelial shedding may include heightened BHR, release of the chemokine eotaxin that attracts eosinophils, altered permeability of the airway mucosa, depletion of epithelial-derived relaxant factors, and loss of enzymes responsible for degrading pro-inflammatory neuropeptides. The integrity of airway epithelium may influence the sensitivity of the airways to various provocative stimuli. Epithelial cells also may be important in the regulation of airway remodeling and

fibrosis.[9,16]

Eosinophils Eosinophils play an effector role in asthma by releasing pro-inflammatory mediators, cytotoxic mediators, and cytokines.[9] Circulating eosinophils migrate to the airways by cell rolling, through interactions with selectins, and eventually adhere to the endothelium through the binding of integrins to adhesion proteins (vascular cell adhesion molecule 1 [VCAM-1] and intercellular adhesion molecule 1 [ICAM-1]). As eosinophils enter the matrix of the membrane, their survival is prolonged by interleukin 5 (IL-5) and granulocyte-macrophage colony-stimulating factor (GM-CSF). On activation, eosinophils release inflammatory mediators such as leukotrienes (LTs) and granule proteins to injure airway tissue.[9]

Lymphocytes Mucosal biopsy specimens from patients with asthma contain lymphocytes, many of which express surface markers of inflammation. There are two types of T-helper $CD4^+$ cells. Th_1 cells produce IL-2 and interferon-γ (IFN-γ), both essential for cellular defense mechanisms. Th_2 cells produce cytokines (IL-4, 5, and 13) that mediate allergic inflammation. It is known that Th_1 cytokines inhibit the production of Th_2 cytokines, and vice versa. It is hypothesized that allergic asthmatic inflammation results from a Th_2-mediated mechanism (an imbalance between Th_1 and Th_2 cells).[9] However, it has also been observed that there exists a low Th_2 cytokine phenotype of asthma in adults that appears more resistant to usual therapies for asthma.[17]

Th_1 and Th_2 Endotypes Th_2 high asthma is characterized by activation of mediators such as IL-25 and IL 33 which subsequently activate IL-4, IL-5, and IL-13, as well as non-interleukin-dependent factors such as thymic stromal lymphopoietin (TSLP).[18] Inflammation occurs as a result of exposure of the airway epithelium to inhaled allergens, microbes, and inhaled pollutants (thus encompassing allergic and nonallergic inflammation) and occurs in approximately half of all patients with asthma.[18] The effects of these mediators result in inflammatory cell activation and secretion of IgE as well as the airway epithelium and smooth muscle.

Th_2 low asthma is described as neutrophilic asthma or mixed, pauci-granulocytic asthma and is less well understood.[18] Patients are typically less responsive to corticosteroids, have fewer allergic symptoms, and are diagnosed later in life.

The T-cell population in the cord blood of newborn infants is skewed toward a Th_2 phenotype.[9,12] The extent of the imbalance between Th_1 and Th_2 cells (as indicated by diminished IFN-*γ* production) during the neonatal phase may predict the subsequent development of allergic disease, asthma, or both. It has been suggested that infants at high risk of asthma and allergies should be exposed to stimuli that upregulate Th_1-mediated responses in order to restore the balance during a critical time in the development of the immune system and the lungs.[12]

The basic premise of the Th_1 and Th_2 imbalance is that the newborn's immune system needs timely and appropriate environmental stimuli to create a balanced immune response. Factors that enhance Th_1-mediated responses include infection with *Mycobacterium tuberculosis*, measles virus, helminths, and hepatitis A virus; endotoxin exposure; increased exposure to infections through contact with older siblings; and daycare attendance during the first 6 months of life. Restoration of the balance between Th_1 and Th_2 cells may be impeded by frequent administration of oral antibiotics, with concomitant alterations in GI flora. Other factors favoring the Th_2 phenotype include residence in an industrialized country, urban environment exposure, diet, and sensitization to house dust mites and cockroaches.[12] Immune "imprinting" may begin in utero by transplacental transfer of allergens and cytokines.

Mast Cells Mast cell degranulation is important in the initiation of immediate responses following exposure to allergens.[3] Mast cells reside throughout the walls of the respiratory tract, and increased numbers of these cells (threefold to fivefold) have been described in the airways of allergic asthmatics.[9] Once binding of allergen to cell-bound IgE occurs, mediators such as histamine; eosinophil and neutrophil chemotactic factors; LTs C_4, D_4, and E_4; prostaglandins; platelet-activating factor (PAF); and others are released from mast cells (see Fig. 43-2). Histologic examination has revealed decreased numbers of granulated mast cells in the airways of patients who have died from acute asthma attacks, suggesting that mast cell degranulation is a contributing factor. Sensitized mast cells are also activated by osmotic stimuli to account for exercise-induced bronchospasm (EIB).[19]

Alveolar Macrophages The primary function of alveolar macrophages in the normal airway is to serve as "scavengers," engulfing and digesting bacteria and other foreign materials. Macrophages are found in large and small airways, ideally located for affecting the asthmatic response. A number of mediators

produced and released by macrophages have been identified, including pro-inflammatory and anti-inflammatory cytokines, reactive oxygen species, and eicosanoids.[12] In addition, alveolar macrophages are able to produce neutrophil chemotactic factor and eosinophil chemotactic factor, which in turn amplify the inflammatory process.

Neutrophils The role of neutrophils in the pathogenesis of asthma remains somewhat unclear because they reside in low numbers normally in the airway. Though they usually do not infiltrate tissues showing chronic allergic inflammation, they are instrumental in the inflammation arising from occupational exposures such as particulate matter, ozone, and diesel exhaust. Neutrophils can be involved in late-phase inflammatory reactions. However, high numbers of neutrophils have been observed in the airways of patients who died from sudden-onset fatal asthma and in those with severe disease.[20] This suggests that neutrophils may play a pivotal role in the disease process, at least in some patients with long-standing or corticosteroid-resistant asthma.[17,20] The neutrophil also can be a source for a variety of mediators, including PAF, prostaglandins, thromboxanes, and LTs, that contribute to BHR and airway inflammation.[20]

Fibroblasts and Myofibroblasts Fibroblasts are found frequently in connective tissue. Human lung fibroblasts may behave as inflammatory cells on activation by IL-4 and IL-13. The myofibroblast may contribute to the regulation of inflammation via the release of cytokines and to tissue remodeling. In asthma, myofibroblasts are increased in numbers beneath the reticular basement membrane, and there is an association between their numbers and the thickness of the reticular basement membrane.[9,16]

Inflammatory Mediators

Associated with asthma for many years, histamine is capable of inducing smooth muscle constriction and bronchospasm and is thought to play a role in mucosal edema and mucus secretion.[3] Lung mast cells are an important source of histamine. The release of histamine can be stimulated by exposure of the airways to a variety of factors, including physical stimuli (airway drying with exercise) and relevant allergens.[9] Histamine is involved in acute bronchospasm following allergen exposure; however, other mediators such as LTs are also involved.

Besides histamine release, mast cell degranulation releases ILs, proteases, and other enzymes that activate the production of other mediators of inflammation.

Several classes of important mediators, including arachidonic acid and its metabolites (ie, prostaglandins, LTs, and PAF), are derived from cell membrane phospholipids.

Once arachidonic acid is released, it can be metabolized by the enzyme cyclooxygenase to form prostaglandins. Prostaglandin D_2 is a potent bronchoconstricting agent; however, it is unlikely to produce sustained effects and its role in asthma remains to be determined. Similarly, prostaglandin $F_2\alpha$ is a potent bronchoconstrictor in patients with asthma and can enhance the effects of histamine.[3,9] However, its pathophysiologic role in asthma is unclear. Another cyclooxygenase product, prostacyclin (prostaglandin I_2), is known to be produced in the lung and may contribute to inflammation and edema owing to its effects as a vasodilator.

Thromboxane A_2 is produced by alveolar macrophages, fibroblasts, epithelial cells, neutrophils, and platelets within the lung.[9] It may have several effects, including bronchoconstriction, involvement in the late asthmatic response, and involvement in the development of airway inflammation and BHR.

The 5-lipoxygenase pathway of arachidonic acid metabolism is responsible for the production of the *cysteinyl LTs*.[9] LTC_4, LTD_4, and LTE_4 are released during inflammatory processes in the lung. LTs D_4 and E_4 share a common receptor (LTD_4 receptor) that, when stimulated, produces bronchospasm, mucus secretion, microvascular permeability, and airway edema, whereas LTB_4 is involved with granulocyte chemotaxis.

Thought to be produced by macrophages, eosinophils, and neutrophils within the lung, PAF is involved in the mediation of bronchospasm, sustained induction of BHR, edema formation, and chemotaxis of eosinophils.[9]

Adhesion Molecules

Adhesion molecules are glycoproteins that facilitate infiltration and migration of inflammatory cells to the site of inflammation. They have additional functions involved in the inflammatory process aside from promoting cell adhesion, including activation of cells and cell–cell communication, and promoting cellular migration and infiltration.[3] Many adhesion molecules are divided into families on the basis of their chemical structure. These families are the integrins, cadherins, immunoglobulin supergene family, selectins, vascular adressins, and carbohydrate ligands.[9] Those thought to be important in inflammation include the integrins, immunoglobulin supergene family, selectins, and carbohydrate

ligands, including ICAM-1 and VCAM-1.[9] Adhesion molecules are found on a variety of cells, such as neutrophils, monocytes, lymphocytes, basophils, eosinophils, granulocytes, platelets, endothelial cells, and epithelial cells, and can be expressed or activated by the many inflammatory mediators present in asthma.[9]

Mucus Production

The mucociliary system is the lung's primary defense mechanism against irritants and infectious agents. Mucus, composed of 95% water and 5% glycoproteins, is produced by bronchial epithelial glands and goblet cells.[9] The lining of the airways consists of a continuous aqueous layer controlled by active ion transport across the epithelium in which water moves toward the lumen along the concentration gradient. Catecholamines and vagal stimulation enhance the ion transport and fluid movement. Mucus transport depends on its viscoelastic properties. Mucus that is either too watery or too viscous will not be transported optimally. The exudative inflammatory process and sloughing of epithelial cells into the airway lumen impair mucociliary transport. The bronchial glands are increased in size and the goblet cells are increased in size and number in asthma. Expectorated mucus from patients with asthma tends to have a high viscosity. The mucous plugs in the airways of patients who died in status asthmaticus are tenacious and tend to be connected by mucous strands to the goblet cells. Asthmatic airways also may become plugged with casts consisting of epithelial and inflammatory cells. Although it is tempting to speculate that death from asthma attacks is a result of the mucous plugging resulting in irreversible obstruction, there is no direct evidence for this. Autopsies of asthmatics who died from other causes have shown similar pathology. In addition, some patients who have died of sudden severe asthma did not show the characteristic mucous plugging on necropsy.[9]

Airway Smooth Muscle

The airway smooth muscle extends from the trachea through the respiratory bronchioles. When expressed as a percentage of wall thickness, the smooth muscle represents 5% of the large central airways and up to 20% of the wall thickness in the bronchioles. Total smooth muscle mass decreases rapidly past the terminal bronchioles to the alveoli, so the contribution of smooth muscle tone to airway diameter in this region is relatively small. In the large airways of

asthmatics, smooth muscle may account for 11% of the wall thickness. It is possible that the increased smooth muscle mass of the asthmatic airways is important in magnifying and maintaining BHR in persistent disease. However, it appears that the hypertrophy and hyperplasia are secondary processes caused by chronic inflammation and are not the primary cause of BHR.[21]

Neural Control/Neurogenic Inflammation

The airway is innervated by parasympathetic, sympathetic, and nonadrenergic inhibitory nerves.[3] Parasympathetic innervation of the smooth muscle consists of efferent motor fibers in the vagus nerves and sensory afferent fibers in the vagus and other nerves.[21] Normal resting tone of human airway smooth muscle is maintained by vagal efferent activity. Maximum bronchoconstriction mediated by vagal stimulation occurs in the small bronchi and is absent in the small bronchioles. The nonmyelinated C fibers of the afferent system lie immediately beneath the tight junctions between epithelial cells lining the airway lumen.[21] These nerve endings probably represent the irritant receptors of the airways. Stimulation of these irritant receptors by mechanical stimulation, chemical and particulate irritants, and pharmacologic agents such as histamine produces reflex bronchoconstriction.[9]

The nonadrenergic, noncholinergic (NANC) nervous system has been described in the trachea and bronchi. Substance P, neurokinin A, neurokinin B, and vasoactive intestinal peptide (VIP) are the best characterized neurotransmitters in the NANC nervous system.[9] VIP is an inhibitory neurotransmitter. Inflammatory cells in asthma can release peptidases that can degrade VIP, producing exaggerated reflex cholinergic bronchoconstriction. NANC excitatory neuropeptides such as substance P and neurokinin A are released by stimulation of C-fiber sensory nerve endings. The NANC system may play an important role in amplifying inflammation in asthma by releasing NO.

Remodeling of the Airways

Acute inflammation is a beneficial, nonspecific response of tissues to injury and generally leads to repair and restoration of the normal structure and function. In contrast, asthma represents a chronic inflammatory process of the airways followed by healing that in some may result in altered structure referred to as *remodeling*.[16] Repair involves replacement of injured tissue by parenchymal cells of the same type and replacement by connective tissue and its maturation

into scar tissue. In asthma, remodeling presents as extracellular matrix fibrosis, an increase in smooth muscle and mucous gland mass, and angiogenesis.[16]

The precise mechanisms of remodeling of the airways are under intense study. Airway remodeling is of concern because it may represent an irreversible process that can have more serious sequelae such as the development of chronic obstructive pulmonary disease (COPD).[3,16] Observations in children with asthma indicate that some loss of lung function may occur during the first 5 years of life.[12] Importantly, no current therapies have been shown to alter either early decreased lung growth or later progressive loss of lung function.

Nitric Oxide

NO is produced by cells within the respiratory tract. It has been thought to be a neurotransmitter of the NANC nervous system.[22] Endogenous NO is generated from the amino acid L-arginine (L-Arg) by the enzyme NO synthase.[22] Three isoforms of NO synthase exist. One isoform is induced in response to pro-inflammatory cytokines, inducible NO synthase (iNOS), in airway epithelial cells and inflammatory cells of asthmatic airways.[22] NO produces smooth muscle relaxation in the vasculature and bronchials. However, it appears to amplify the inflammatory process and is unlikely to be of therapeutic benefit. Investigations measuring the fraction of exhaled NO (FeNO) concentrations have suggested that it may be a useful measure of ongoing allergic lower airway inflammation in patients with asthma and for guiding asthma therapy.[22,23]

Factors Contributing to Asthma Severity

Viral Respiratory Infections

Viral respiratory infections are primarily responsible for exacerbations of asthma, particularly in children under age 10.[15] Children aged 5 or younger may have wheezing (which may or may not be asthma) associated with upper respiratory tract infections up to six to eight times per year.[2] Infants are particularly susceptible to airway obstruction and wheezing with viral infections because of their small airways. Approximately 30% to 40% of infants who have severe RSV bronchiolitis will have recurrent wheezing but the subsequent prevalence of asthma is 5% to 10% in children.[15] The most common cause of exacerbations in both children and adults is the rhinovirus, which is the most frequent virus associated with the common cold and distributed worldwide.[15]

Other viruses isolated include RSV, parainfluenza virus, adenoviruses, coronavirus, and influenza viruses. Certain viruses (RSV and parainfluenza virus) are capable of inducing specific IgE antibodies, and rhinovirus can activate eosinophils directly in asthmatics.[15] The increase in asthma symptoms and BHR that occurs may last for days or weeks following resolution of the symptoms of the viral infection. Evidence does not support a beneficial effect of influenza vaccine for preventing asthma exacerbations from subsequent influenza infections.[3] However, patients with moderate-to-severe asthma should be vaccinated against influenza annually.[2]

Environmental and Occupational Factors

The development and heterogeneity of persistent asthma is driven by complex gene–environment interactions. Agents and events that are known to trigger asthma are listed in **Table 43-1**. The mechanisms for inducing symptoms are as varied as the exposure factor and include both IgE- and cell-mediated reactions.[2] The World Allergy Organization (WAO) predicts an increase in the incidence and prevalence of asthma due to environmental exposures from climate change.[24] Greater temperature variability, industrial pollution, more frequent forest fires, higher concentration of ground-level ozone, increased trans-boundary movement of respiratory infectious agents, and changes in aeroallergen distribution are all cited factors. Exposure to 0.2 ppm ozone for 2 to 3 hours can induce bronchoconstriction and increase BHR in asthmatics.[3,14] Sulfur dioxide in the ambient atmosphere is highly irritating and presumably induces bronchoconstriction through mast cell or irritant-receptor involvement.[3] Asthma produced by repeated prolonged exposure to industrial inhalants is a significant health problem. It has been estimated that occupational asthma accounts for 15% of all asthmatic persons.[2] An estimated 5% to 20% of new cases of adult-onset asthma can be attributed to occupational exposure.[2] Occupational asthma can be difficult to diagnose as the latency between exposure and symptom development can extend from months to years.[2] Persons with occupational asthma have the typical symptoms of asthma with cough, dyspnea, and wheeze. Typically, the symptoms are related to workplace exposure and improve on days off and during vacations.[14] Once occupational asthma has developed, the symptoms persist in most patients even after exposure is no longer present [GINA Appendix 2018].[2]

TABLE 43-1 List of Agents and Events Triggering Asthma Exacerbations

Respiratory infection
Respiratory syncytial virus (RSV), rhinovirus, influenza, parainfluenza, *Mycoplasma pneumonia*, *Chlamydia*, chronic rhinosinusitis

Allergens
Airborne pollens (grass, trees, weeds), house dust mites, animal dander, rodents, cockroaches, fungal spores

Environment
Cold air, fog, ozone, sulfur dioxide, nitrogen dioxide, tobacco smoke (including second and third hand), wood smoke, energy efficient buildings (increase indoor air pollution), meteorological conditions related to climate change, scented home products, cleaners, and perfumes

Emotions
Anxiety, stress, laughter

Exercise
Particularly in cold, dry climate

Drugs/preservatives
Acetaminophen, Aspirin, NSAIDs (cyclooxygenase inhibitors), sulfites, benzalkonium chloride, nonselective β-blockers, higher airway reversibility to beta2 agonist

Occupational stimuli
Bakers (flour dust); farmers (hay mold); spice and enzyme workers; occupational cleaners, printers (Arabic gum); chemical workers (azo dyes, anthraquinone, ethylenediamine, toluene diisocyanates, polyvinyl chloride); plastics, rubber, and wood workers (formaldehyde, western cedar, dimethylethanolamine, anhydrides)
Host factors: obesity, African American race, Hispanic ethnicity, low socioeconomic status

Stress, Depression, and Psychosocial Factors in Asthma

Observational studies demonstrate an association between increased stress and worsening asthma, but the role is not clearly defined.[3] Bronchoconstriction from psychological factors appears to be mediated primarily through excess parasympathetic input. Atropine has been shown to block experimental psychogenic bronchoconstriction. Persons with asthma are more likely to have depression than those without asthma. The episodic nature of both diseases may be related to abnormal expression of Th2 cytokines that have effects in the brain as well as the airway. It is most important to emphasize to both patients and parents that asthma is not an emotional disease. However, coping skills may benefit the patient who becomes emotionally distraught during an asthma attack.

Chronic Rhinosinusitis

Disorders of the upper respiratory tract, particularly rhinitis and sinusitis, have been linked with asthma for many years. As many as 40% to 50% of asthmatics have abnormal sinus radiographs.[3] The prevalence of allergic sensitization increases with asthma severity; nasal polyposis is often seen in those with allergic rhinitis. It has been postulated that transport of mucus chemotactic factors and inflammatory mediators from nasal passages during allergic rhinitis into the lungs may accentuate BHR. However, chronic sinusitis may just represent a nonbacterial coexisting condition with allergic asthmatics because the histologic changes in the paranasal sinuses are similar to those seen in the lung and nose.[3] Thus, it would seem that treatment of upper airway disease could optimize overall asthma control. However, a large study of children and adults found that treatment of chronic sinonasal disease with intranasal corticosteroids for 6 months improved neither asthma control nor BHR, suggesting that the treatment of sinus disease and asthma be managed separately.[25]

Gastroesophageal Reflux Disease

Symptoms of gastroesophageal reflux disease (GERD) as well as asymptomatic reflux are common in both children and adults who have asthma.[3] Nocturnal asthma may be associated with nighttime reflux.[3] Reflux of acidic gastric contents into the esophagus is thought to initiate a vagally mediated reflex bronchoconstriction.[3] Also of concern is that most medications that decrease airway smooth muscle tone may have a relaxant effect on gastroesophageal sphincter tone. There is no benefit from treating asymptomatic reflux in asthma.[2,26] Treatment with proton pump inhibitors does not improve asthma control even in those with documented reflux.[26] Symptomatic reflux should be treated for its general health benefits.[2]

Female Hormones and Asthma

Asthma symptoms may vary significantly during different stages of the menstrual cycle. Premenstrual worsening of asthma has been reported in 20% of women, whereas worsening of pulmonary functions has been reported even in women not aware of worsening symptoms.[15,27] Women with premenstrual symptoms tend to be older, have a higher body mass index, more severe asthma, and a longer duration of asthma.[2] The pathophysiology is uncertain because estrogen replacement in postmenopausal women has been shown to worsen

asthma, whereas estradiol and progesterone administration has been variably reported to improve or have no effect on asthma in women with premenstrual asthma.[27,28] The clinical significance of menstruation-related asthma is still unclear because some studies have reported that up to 50% of ED visits by women were premenstrual, whereas others have reported no association with menstrual phase.[27,28] Pregnancy may cause worsening, improvement, or no change in asthma symptoms, and the changes seem to occur with equal frequency. These changes are suspected to be related to altered sex hormones, stress, and fetal antigens.[28]

Foods, Drugs, Additives, and Vitamins

In the literature, documentation of food allergens as triggers for asthma is not available.[3] However, additives, specifically sulfites used as preservatives, can trigger life-threatening asthma exacerbations. Beer, wine, dried fruit, and open salad bars, in particular, have high concentrations of metabisulfites.[3] Severe oral corticosteroid-dependent patients should be warned about ingesting foods processed with sulfites.

Aspirin and other nonsteroidal anti-inflammatory drugs can cause severe asthma exacerbations (aspirin-exacerbated respiratory disease).[2] The mechanism is related to cyclooxygenase-1 (COX-1) inhibition, and inhaled corticosteroids (ICSs) are the primary preventive treatment although oral corticosteroids may be required; leukotriene receptor antagonists (LTRAs) may be useful.[2] The prevalence increases with age and severity of asthma.[3] The greatest frequency occurs in severe corticosteroid-resistant asthmatics in their fourth and fifth decades who also have perennial rhinitis and nasal polyposis (presence of several polyps).[3] Other drugs that do not precipitate bronchospasm but that prevent its reversal are the nonselective β-blocking agents.[2,3]

Children with vitamin D insufficiency have been considered at greater risk of uncontrolled asthma (increased hospitalizations, BHR, and eosinophil counts).[29] Vitamin D helps regulate T cells and improves their secretion of anti-inflammatory cytokines in response to corticosteroids.[29] In adults with asthma, evidence of benefit for vitamin D supplementation is inconclusive.[2] There are no published data evaluating Vitamin D treatment in children with asthma.

In a systematic review, fish oil supplementation or dietary intake of fish during pregnancy had no consistent effects of the risk of wheeze, asthma, or atopy in the child.[2]

Obesity

Epidemiologic data suggest that obesity increases the prevalence of asthma and may reduce asthma control, although it may be difficult to distinguish obesity-induced respiratory symptoms from true asthma symptoms particularly because obesity often precedes the onset of asthma.[30] Lung volume and tidal volume are reduced in obesity, promoting airway narrowing. Obesity also produces low-grade systemic inflammation that may act on the lung to worsen asthma.[30] The mechanism may be the release of adipose-derived pro-inflammatory mediators such as IL-6, IL-10, eotaxin, tumor necrosis factor-α, transforming growth factors-β_1, C-reactive protein, leptin, and adiponectin or a result of common predisposing dietary factors. Although not all studies find relationship between body mass index and asthma control, management of asthma in obese patients should include weight loss measures.[31] Additional comorbidities of obesity that may independently contribute to asthma symptoms include obstructive sleep apnea, GERD, and metabolic syndrome.[2]

Exposure to Tobacco Smoke

A thorough history that considers age, respiratory symptoms (onset, exacerbations, progression, variability, seasonality or periodicity, and persistence), past history, and previous diagnoses and treatment and response to treatment, and that includes discussion of social and occupational risk factors may identify relevant smoking history or exposure to environmental tobacco smoke. The clinician is then faced with distinguishing asthma from COPD. Some patients have clinical features of both, now termed asthma COPD Overlap Syndrome (ACOS).[2] Physical examination findings, lung function measures, and radiology data are then combined with the history, to confirm this syndromic diagnosis. GINA and the Global Initiative for Chronic Obstructive Lung Disease provide recommendations for initial therapy of ACOS, if the differential diagnosis is equally balanced between asthma and COPD.[32] Referral for expert advice and further diagnostic evaluation may be necessary. A recent literature review has been published to characterize the prevalence of ACOS and the effect of different disease definitions on these estimates, to help guide decision making for both refining the ACOS definition and trial design aimed at effective treatment.[33]

CLINICAL PRESENTATION

Chronic Asthma

3 Classic asthma is characterized by episodic and variable respiratory symptoms; however, the clinical presentation of asthma is as diverse as the number of triggering events (see "Clinical Presentation: Chronic Ambulatory Asthma" above). Although wheezing is the characteristic symptom of asthma, the medical literature is replete with the warning that "not all that wheezes is asthma." A wheeze is a high-pitched, whistling sound created by turbulent airflow through an obstructed airway, so any condition that produces significant obstruction can result in wheezing as a symptom. In addition, "all of asthma does not wheeze" is an equally justifiable warning. Patients may present with a chronic persistent cough (cough variant asthma) as their only symptom.[2,3]

There is no single diagnostic test for asthma. The diagnosis is based primarily on a good history.[2,3] The patient may have a family history of allergy or asthma or have symptoms of allergic rhinitis, or atopic dermatitis.[2,3] Reversibility of airway obstruction following administration of a short-acting inhaled β_2-agonist or excessive variability in twice daily PEF over 2 weeks are diagnostic criteria.[2] Patients with normal values of spirometry can be challenged by exercise or substances that produce bronchoconstriction, such as methacholine or mannitol, to determine if they have BHR, but, again, positive challenges are not diagnostic. Newer tests of inflammation in the airways such as induced sputum eosinophil and/or neutrophil counts and FeNO measurements are consistent with but not diagnostic of asthma.

GINA recommends confirmation of the diagnosis of asthma in patients already taking controller treatment using objective testing. The process depends on the patient's symptoms and lung function, and may include a trial of either a lower or a higher dose of controller treatment.[2]

CLINICAL PRESENTATION

Chronic Asthma

General

- Asthma is a disease of exacerbation and remission, so the patient may not have any signs or symptoms at the time of examination.

Symptoms

- The patient may complain of episodes of shortness of breath, chest tightness, coughing (particularly at night), wheezing, or a whistling sound from the chest when breathing. These often occur in association with exercise, but also occur spontaneously or in association with known allergens.

Signs

- Wheezing on auscultation (more typically on expiration), prolonged expiratory phase on auscultation dry hacking cough, or signs of atopy (allergic rhinitis and/or atopic dermatitis) may occur.

Laboratory

- Spirometry demonstrates obstruction (reduced FEV_1/forced vital capacity [FVC]) with reversibility following inhaled β_2-agonist administration (FEV_1 increases by more than 12% and 200 mL). The FEV_1/FVC ratio is normally more than 0.75 to 0.80 in adults, and more than 0.85 in children.

Other diagnostic tests

- Excessive variability in twice-daily peak expiratory flow (PEF) over 2 weeks (greater than 10% in adults and greater than 13% in children). A fall in FEV_1 of at least 10% following 6 minutes of near maximal exercise. Elevated eosinophil count and IgE concentration in blood. Elevated FeNO (greater than 20 ppb in children younger than 12 years of age and greater than 25 ppb in adults). Positive methacholine challenge (PC_{20} FEV_1 less than 12.5 mg/mL) or mannitol challenge (FEV_1 decrease of at least 15% from baseline after 635 mg or less).

Asthma has a widely variable presentation from chronic daily symptoms to only intermittent symptoms. The intervals between symptoms can be days, weeks, months, or years. Asthma also can vary as to its severity, the intrinsic intensity of the disease process. Severity is most easily and directly measured in a patient who is not currently receiving asthma treatment. The NAEPP has provided a means of classifying asthma severity that is divided into two domains: impairment and risk.[3] This classification system is individualized for three age groups (0-4, 5-11, and greater than or equal to 12 years) and summarized in **Table 43-2**. GINA has provided a means of determining chronic therapy for children and adults aged 6 years and older based on symptom control

and future risk of adverse outcomes, described later in this chapter.

TABLE 43-2 Classifying Asthma Severity for Patients Who Are Not Currently Taking Long-Term Control Medications

		Children 0-4 and 5-11 Years of Age			
			Persistent		
	Components	**Intermittent**	**Mild**	**Moderate**	**Severe**
Impairment	Symptoms	≤2 days/wk	>2 days/wk but not daily	Daily	Throughout the day
	Nighttime awakenings (0-4 years)	0	1-2 × month	3-4 × month	>1 × week
	5-11 years	≤2 × month	3-4 × month	>1 × week, but not nightly	Often 7 × week
	SABA use for Sx control	≤2 days/wk	>2 days/wk but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	FEV_1 > 80%	FEV_1 > 80%	FEV_1 60%-80%	FEV_1 < 60%
	5-11 years	FEV_1/FVC >85% (0.85)	FEV_1/FVC >80% (0.80)	FEV_1/FVC 75%-80% (0.75-0.80)	FEV_1/FVC <75% (0.75)
	Exacerbations	**Intermittent**	**Persistent**		
Risk	0-4 years	0-1/y	≥2 in 6 months or ≥4 wheezing episodes/1 year lasting >1 day		
	5-11 years	0-2/y	>2 in 1 year		
	Recommended step for initiating treatment	Step 1	Step 2	Step 3 and consider short course of oral corticosteroids	
		Youths ≥12 Years of Age and Adults			
			Persistent		
	Components	**Intermittent**	**Mild**	**Moderate**	**Severe**
Impairment	Symptoms	≤2 days/wk	>2 days/wk but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2 × month	3-4 × month	>1 × week, but not nightly	Often 7 × week
	SABA use for Sx control	≤2 days/wk	>2 days/wk, but not >1 × day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function[a]	FEV_1 >80%	FEV_1 >80%	FEV_1 60%-80%	FEV_1 <60%
		FEV_1/FVC normal	FEV_1/FVC normal	FEV_1/FVC reduced 5% (0.05)	FEV_1/FVC reduced >5% (0.05)
	Exacerbations	**Intermittent**	**Persistent**		
Risk		0-2/yr	>2 in 1 year		
	Recommended step for initiating treatment	Step 1	Step 2	Step 3 and consider short course of oral corticosteroids	Step 4 or 5 and consider course of oral corticosteroid

[a]Normal FEV1/FVC: 8-19 years 85% (0.85); 20-39 years 80% (0.80); 40-59 years 75% (0.75); 60-80 years 70% (0.70).

SABA, short-acting β-agonist.

The intermittent and/or chronic nature of symptoms does not necessarily determine the severity of symptoms during exacerbations. Asthma severity is determined by lung function, symptoms, nighttime awakenings, and interference with normal activity prior to therapy. Patients can present with a range from intermittent symptoms that require no medications or only occasional use of short-acting inhaled β_2-agonists to severe persistent asthma symptoms despite treatment with multiple medications.

Acute Severe Asthma

Uncontrolled asthma, with its inherent variability, can progress to an acute state where inflammation, airway edema, excessive mucus accumulation, and severe bronchospasm result in a profound airway narrowing that is poorly responsive to usual bronchodilator therapy[2,3] (see "Clinical Presentation: Acute Severe Asthma" above). Although this progression is the most common scenario, some patients experience rapid-onset or hyper-acute attacks.[2,3] Hyper-acute attacks are associated with neutrophilic as opposed to eosinophilic infiltration and resolve rapidly with bronchodilator therapy, suggesting that smooth muscle spasm is the major pathogenic mechanism.[20] In most cases, emergency department (ED) visits for acute severe asthma represent the failure of an adequate therapeutic regimen to control persistent asthma. Underutilization of anti-inflammatory drugs and excessive reliance on short-acting inhaled β_2-agonists are the major risk factors for severe exacerbations.[2,3] However, frequent exacerbations may represent a specific phenotype of asthma. A blunted perception of airway obstruction may predispose certain individuals to fatal asthma attacks.[3]

Exercise-Induced Bronchospasm

During vigorous exercise, pulmonary function measurements (FEV_1 and PEF) in patients with asthma increase during the first few minutes but then begin to decrease after 6 to 8 minutes (**Fig. 43-3**).[3] EIB is defined as a drop in FEV_1 of 10% or greater from baseline (pre-exercise value).[19] Most studies suggest that many patients with persistent asthma experience EIB.[3] The exact pathogenesis of EIB is unknown, but heat loss and/or water loss from the central airways appears to play an important role.[19] EIB is provoked more easily in cold, dry air, ambient ozone, and airborne particulate matter; alternatively, warm, humid air can blunt

or block it.[19] Studies have demonstrated increased plasma histamine, cysteinyl LTs, prostaglandins, and tryptase concentrations during EIB, suggesting a role for mast cell degranulation.[19] These findings led to the development of inhaled mannitol, an osmotic agent, as an indirect pharmacologic bronchoprovocation test to assist in the diagnosis of asthma.[34]

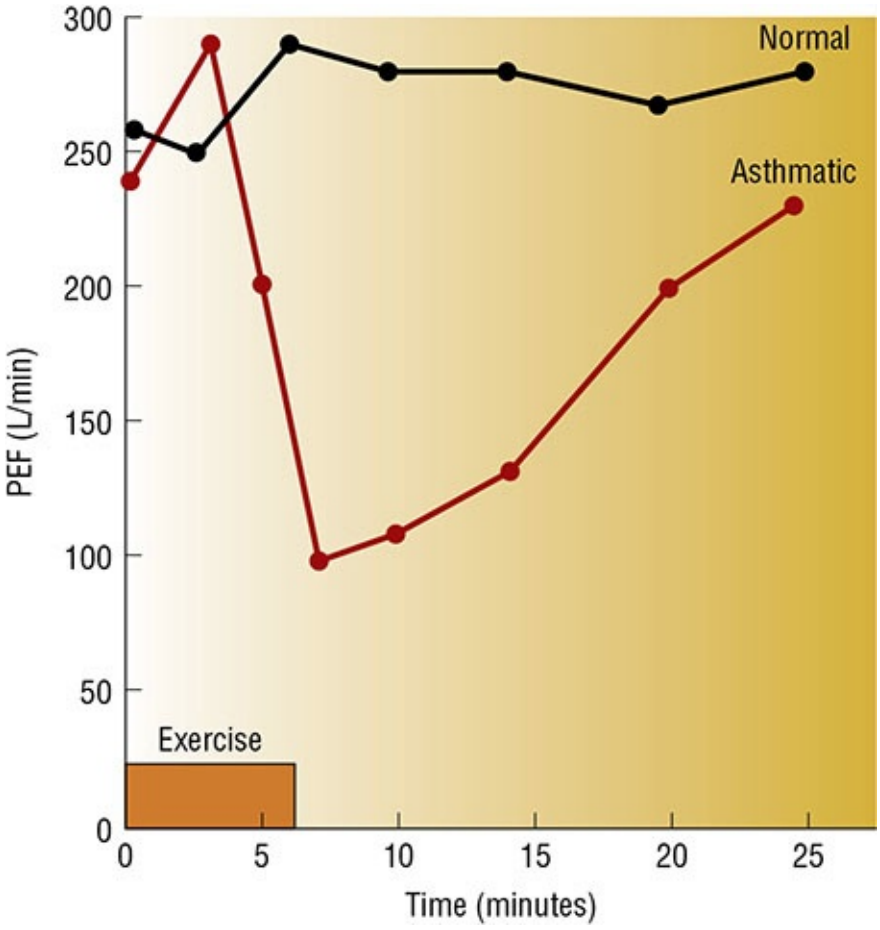


FIGURE 43-3 Typical responses to exercise in a normal subject and an asthmatic subject. Note the initial bronchodilation (PEF, peak expiratory flow).

A refractory period following EIB lasts up to 4 hours after exercise in some patients. During this period, repeat exercise of the same intensity produces either no decrease in pulmonary function or a drop of less than 50% of the initial response.[19] The refractory period is thought to be caused by an acute depletion of mast cell mediators and time required for their repletion.

EIB is believed to be a reflection of increased BHR associated with asthma. A correlation, though not perfect, exists between EIB and reactivity to histamine, methacholine, and mannitol.[19] Other patient groups with BHR (eg, after viral

infection, cystic fibrosis, or allergic rhinitis) show bronchoconstriction after exercise to a lesser degree (5%-10% drops) than patients with asthma (15%-40% drops).[19] Patients will not always demonstrate the same sensitivity. During periods of remission, a decreased sensitivity to the same degree of exercise is often observed. Finally, a number of children and adults with EIB are otherwise normal, without symptoms or abnormal pulmonary function except in association with exercise.[3] Elite athletes have a higher prevalence of EIB than the general population.[19]

CLINICAL PRESENTATION

Acute Severe Asthma

General

- An episode can progress over several days or hours (usual scenario) but can progress rapidly over 1 to 2 hours.

Symptoms

- The patient is anxious in acute distress and complains of severe dyspnea, shortness of breath, chest tightness, or burning. The patient is only able to say a few words with each breath. Symptoms are unresponsive to usual measures (short-acting inhaled β_2-agonist administration).

Signs

- Signs include expiratory and inspiratory wheezing on auscultation (breath sounds may be diminished with very severe obstruction), dry hacking cough, tachypnea, tachycardia, pale or cyanotic skin, hyper-inflated chest with intercostal and supraclavicular retractions, and hypoxic seizures if very severe.

Laboratory tests

- Peak expiratory flow and/or FEV_1 less than 40% of normal predicted values. Decreased arterial O_2 (PaO_2), and O_2 saturations by pulse oximetry (SaO_2 less than 90% [0.90] on room air is severe). Decreased arterial or capillary CO_2 if mild, but in the normal range or increased in moderate-to-severe obstruction.

Other diagnostic tests

- Blood gases to assess metabolic acidosis (lactic acidosis) in severe obstruction. Complete blood count if there are signs of infection (fever and purulent sputum). Serum electrolytes as therapy with β_2-agonist and corticosteroids can lower serum potassium, magnesium, and phosphate, and increase glucose. Chest radiograph if signs of consolidation on auscultation.

Nocturnal Asthma

3 Worsening of asthma during sleep is referred to as *nocturnal asthma*. Patients with nocturnal asthma exhibit significant falls in pulmonary function between bedtime and awakening.[3] Typically, their lung function reaches a nadir at 3 to 4 AM. Although the pathogenesis of this phenomenon is unknown, it has been associated with diurnal patterns of endogenous cortisol secretion and circulating epinephrine.[3] Direct evidence for an inflammatory component to nocturnal asthma includes increased circulating histamine and activated eosinophils and LT excretion at night associated with increased BHR to methacholine.[3]

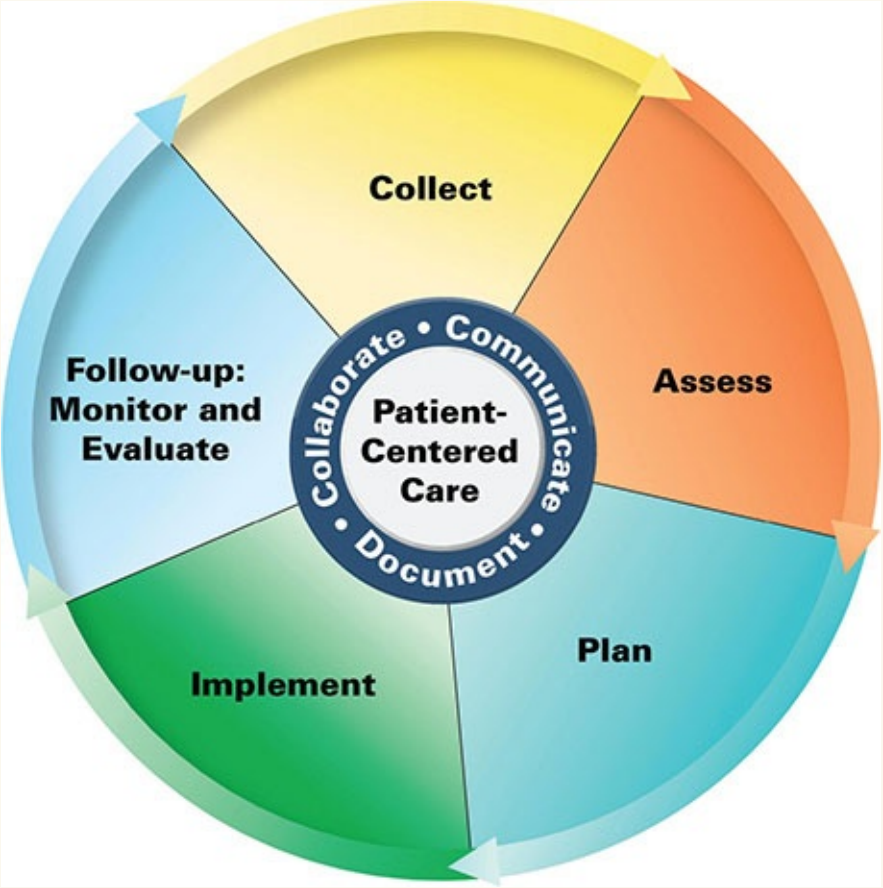
Numerous other factors that may affect nocturnal worsening of asthma, including allergies and improper environmental control, gastroesophageal reflux, obstructive sleep apnea, and sinusitis, also must be considered when evaluating these patients.[3] Experts consider nocturnal symptoms to be a sign of inadequately treated persistent asthma.[3] Awakening from nocturnal asthma is a sensitive indicator of both severity and inadequate control.[3]

TREATMENT

Desired Outcomes

GINA's long-term goals of asthma management are: (1) to achieve good control of symptoms and maintain normal activity levels and (2) to minimize future risk of exacerbations, fixed airflow limitation, and side effects.[2] The importance of eliciting the patient's own goals is emphasized, as is the development of a patient–healthcare provider partnership. Key components are strategies to both facilitate good communication and reduce the impact of impaired health

literacy.[2] Self-management education reduces asthma morbidity in both adults and children (Evidence A).[2] GINA recommends control-based asthma management, adjusting pharmacological and nonpharmacological treatment in a continuous cycle of assessment, treatment, and review. Assessment includes symptom control, risk factors, inhaler technique and adherence, and patient preferences. Response review includes symptoms, exacerbations, medication side effects, patient satisfaction, and lung function.[2] GINA does not recommend either sputum-guided treatment or FeNO-guided treatment for the general asthma population.[2]



Patient Care Process for the Management of Persistent Asthma

Collect

- Patient characteristics (eg, age, race/ethnicity, sex, pregnant)

- Patient history (eg, past medical, known triggers, psychosocial history, gastroesophageal reflux disease)
- Family history (eg, asthma, allergy, atopic dermatitis)
- Home/work environment (eg, environmental, occupational, tobacco smoke, carpet/bedding, pets) (see Table 43-1)
- Current medications and prior response to controller therapies (eg, ICS+/−LABA; montelukast; LAMA; biologic therapies)
- Subjective and objective data (see Table 43-2)
  - Symptoms (description and frequency)
  - Nocturnal awakenings
  - Albuterol use frequency for symptom control
  - Activity limitation
  - Exacerbation frequency
  - Peak expiratory flow readings

Assess

- Comorbid conditions (eg, allergies, rhinosinusitis, obesity, obstructive sleep apnea, gastroesophageal reflux, smoking)
- Symptom frequency including exercise tolerance (see Tables 43-2 and 43-3)
- Exacerbation history (eg, oral corticosteroid use, emergency department visits, hospitalization)
- Current medications that may contribute to or worsen asthma (eg, nonsteroidal anti-inflammatory drug [NSAID], aspirin) (see Table 43-1)
- Appropriateness and effectiveness of current medications in controlling symptoms and preventing exacerbations
- Inhaler technique (see Fig. 43-7) and adherence; potential barriers
- Socioeconomic barriers to obtain medications
- Adherence to nonpharmacologic recommendations (eg, allergen avoidance, environmental control)

Plan*

- Tailored environmental modifications (eg, pet removal, carpet removal, pillow and mattress covers, exercise pretreatment, occupational exposures)

(see Table 43-1)

- Medication therapy regimen: dose, route, frequency, duration, and MDI spacer; specify the continuation and discontinuation of existing therapies (see Tables 43-3, 43-4, 43-5, 43-6, 43-8, 43-9, and 43-13)
- Monitoring parameters including efficacy (eg, daily symptoms, nocturnal awakenings, albuterol use, exercise tolerance, peak expiratory flow [in selected patients]), and time frame (see Table 43-2)
- Patient/family education (eg, purpose of treatment, environmental modifications, drug therapies, inhaler technique)
- Self-monitoring of symptoms, albuterol use, peak expiratory flow (in selected patients)—where and how to record results (see Fig. 43-4)
- Referrals to other providers when appropriate (eg, specialist physician)

Implement*

- Provide patient/family education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up based on symptoms and medication changes

Follow-up: Monitor and Evaluate

- Determine symptom control and exacerbation outcomes
- Presence of adverse effects
- Patient adherence to treatment plan using multiple sources of information

*Collaborate with patient, caregivers, and other healthcare professionals.

GINA discriminates between preferred treatment options at a population level (based on efficacy, effectiveness, safety, and availability/cost at this level) versus choosing between asthma controller options for individual patients. A shared decision-making approach is recommended for the latter, to include preferred treatment, patient characteristics or phenotype,[2] patient/parent preference, and practical issues (inhaler technique, adherence, and cost).[2]

General Approach to Treatment

The NAEPP[3] and GINA[2] outline sound strategies for management and treatment

of asthma. However, the NAEPP Guidelines for the Diagnosis and Management of Asthma was last published in 2007 as the EPR3.[3] Since that time, clinical practice strategies have changed and new drugs have been approved for marketing by the Food and Drug Administration (FDA) that merit evaluation and inclusion as revision to the guidelines. At this time, a complete update to the guidelines is not planned. However, updates on selected topics will be published in 2020. The GINA guidelines are updated every few years, and thus, GINA is more current (updated in 2018), and describes levels of evidence used in their report.[2] Evidence level A provides a rich body of data consisting of randomized controlled trials (RCTs) and meta-analyses; evidence level B has a more limited body of data, but still relies on RCTs and meta-analyses; evidence C includes outcomes of nonrandomized trials or observational studies; and evidence D relies on panel consensus judgment. Therefore, the sections describing management of chronic and acute asthma largely reflect the GINA guidelines.

General Approach to the Management of Chronic Asthma

The current GINA recommendations for initial controller treatment in adults and adolescents with persistent asthma are summarized in **Table 43-3**.[2] Regardless of the long-term therapy, all patients need to have quick-relief medication in the form of short-acting inhaled β_2-agonists available for acute symptoms. Ensure that the patient can use both the reliever and controller delivery devices correctly. Schedule an appointment for a healthcare provider visit after 2 to 3 months, or earlier, depending on clinical urgency.

TABLE 43-3 GINA Recommendations for Initial Controller Treatment in Adults and Adolescents

Symptom Presentation	Preferred Treatment (Evidence Level)
Symptoms or need for SABA < 2×/mo; no waking due to asthma in last month; and no risk factors for exacerbations, including in prior year	No controller (D)
Infrequent symptoms, but patient has one or more risk factor for exacerbation, eg, low lung function, use of OCS in prior year, intensive care treatment for asthma ever	Low-dose ICS (D)
Symptoms or need for SABA between 2×/mo and 2×/wk, or patient wakes due to asthma ≥ 1 mo	Low-dose ICS (B)
Symptoms or need for SABA > 2×/wk	Low-dose ICS[a] (A)
Troublesome symptoms most days or waking ≥ 1×/wk, especially if any risk factors exist	Medium/high-dose ICS(A) or low-dose ICS/LABA[b] (A)
Symptoms consistent with severely uncontrolled asthma, or with an acute exacerbation	OCS short course AND start of high-dose ICS(A) or moderate-dose ICS/LABA[b] (D)

ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids; SABA, short-acting beta$_2$-agonist.

(A), (B), (C), (D) = grade of evidence with A as the highest grade and D as the lowest grade.

[a]Less effective options are LTRA or theophylline.

[b]Not recommended for initial controller treatment in children 6-11 years.

5 The ICSs are considered the preferred long-term control therapy for persistent asthma in all patients due to their potency and consistent effectiveness.[2] Low- to medium-dose ICSs reduce BHR, improve lung function, and reduce severe exacerbations leading to ED visits and hospitalizations. They are more effective than theophylline or the LTRAs.[2,35] In addition, the ICS is the only therapy that reduces the risk of dying from asthma.[2,3] In the low to medium doses recommended by GINA (**Table 43-4**), ICSs are safe for long-term administration (see below).[2,35] They do not appear to reduce airway remodeling and loss of lung function found in some patients with persistent asthma. The ICSs do not enhance lung growth in children with asthma, prevent the development of asthma in high-risk infants, or induce remission of asthma as

BHR and other measures of inflammation return to pretreatment levels on discontinuation of therapy.[36] The sensitivity and consequent clinical response to ICSs can vary among patients.[2,3]

TABLE 43-4 Inhaled Corticosteroid Products, Lung Delivery, and Comparative Daily Dosages

ICS	Product	Lung Delivery[a]
Beclomethasone dipropionate	40 and 80 mcg/actuation HFA[b] MDI[c]	50%-60%
Budesonide	90 or 180 mcg/dose DPI[d], Flexhaler	15%-30%
	200 and 500 mcg ampules, 1 mg	5%-8%
Ciclesonide	80 or 160 mcg/actuation HFA MDI	50%
Flunisolide	80 mcg/actuation HFA MDI	68%
Fluticasone furoate	100, 200 mcg/actuation DPI, Ellipta	80%-85%
Fluticasone propionate	44, 110, and 220 mcg/actuation HFA MDI	20%
	50, 100, and 250 mcg/dose DPI, Diskus	15%
Mometasone furoate	110 and 220 mcg/dose DPI, Twisthaler; 100 mcg and 200 mcg/actuation HFA MDI	11%

	Comparative Daily Dosages (mcg) of Inhaled Corticosteroids		
	Low Dose Child[a]/Adult	Medium Dose Child[a]/Adult	High Dose Child[a]/Adult
Beclomethasone dipropionate			
HFA MDI	80-160/80-240	>160-320/>240-480	>320/>480
Budesonide			
DPI	180-360/180-540	>360-720/>540-1,080	>720/>1,080
Nebules	500/unknown	1,000/unknown	2,000/unknown
Ciclesonide HFA MDI	80-160/160-320	>160-320/>320-640	>320/>640
Flunisolide HFA MDI	160/320	320/320-640	≥640/>640
Fluticasone furoate DPI		unknown/100	unknown/200
Fluticasone propionate			
HFA MDI	88-176/88-264	176-352/264-440	>352/>440
DPI	100-200/100-300	200-400/300-500	>400/>500
Mometasone furoate DPI	110/110-220	220-440/>220-440	>440/>440

[a]5 to 11 years of age, except for Budesonide Nebules, which is 2 to 11 years of age.

[b]Hydrofluoroalkane.

[c]Metered-dose inhaler.

[d]Dry powder inhaler.

Although studies of the alternative long-term control therapies (eg, LTRAs and theophylline) demonstrate improvement in symptoms, lung function, and as-needed, short-acting inhaled β_2-agonist use, they do not reduce BHR, suggesting minimal anti-inflammatory activity.[2,3] The evidence suggests minimal to no

differences in efficacy between these alternatives.

For those patients inadequately controlled on low-dose ICSs either an increased dose of the ICS or the combination of ICS and LABA is recommended in Step 3 to gain control of more moderate persistent asthma.[2] Alternatives could be the addition of LTRAs or theophylline to ICSs.[2] The addition of theophylline or LTRAs to ICSs is no more effective than doubling the dose of the ICS.[3] The combination of ICS/LABA is more effective at reducing severe asthma exacerbations than doubling the dose of ICS in moderate persistent asthma; increasing the dose of ICSs fourfold also will result in a significant reduction in exacerbations.[37,38] However, doses of ICSs in the high range significantly enhance the risk of toxicity.[39] Thus, high doses of ICSs plus LABA are reserved for patients with severe persistent asthma.[2,3]

Although the addition of a third controller medication is often used clinically in patients with severe persistent asthma uncontrolled on high-dose ICS/LABA, there are limited studies evaluating this practice.[2] LTRAs or theophylline added to high-dose combination ICS/LABA do not improve outcomes.[2] The addition of a biologic to therapy can reduce exacerbations by approximately 30% to 50%.[18,40] The addition of tiotropium bromide, however, to ICS/LABA does not confer a lower risk of exacerbations.[41]

Other therapies reserved for treatment of uncontrolled severe asthma after an optimal trial of high-dose ICSs in combination with LABA or long-acting muscarinic antagonist (LAMA) and/or biologic therapy includes bronchial thermoplasty and oral corticosteroids. Bronchial thermoplasty targets hypertrophied smooth muscle in the airways through delivery of thermal energy in a controlled manner to the airway wall to reduce the airway smooth muscle mass. This results in a reduced response to bronchoconstrictive stimuli. Oral corticosteroids are prescribed daily or every other day with the goal to maintain asthma control at the lowest dose possible due to significant adverse effects that occur with long-term use.

Patients with documented allergen sensitization with clinical symptoms may also be prescribed allergen immunotherapy given as subcutaneous injections or as sublingual allergen immunotherapy. Treatment must be administered in a clinical setting that is prepared to manage anaphylactic reactions. Because treatment may involve weekly appointments for several years, patients need to carefully consider the burden of treatment before initiating allergy immunotherapy.

GINA provides general principles for step-down of controller treatment.[2]

Consideration is warranted if symptoms have been well controlled and lung function has been stable for more than or equal to 3 months (Evidence Grade D). An appropriate time should be chosen (no respiratory infection, not travelling, not pregnant). Engage the patient in this therapeutic trial, monitor with symptoms and/or PEF, and schedule follow-up (Evidence Grade D). Stepping down ICS doses by 25% to 50% at 3 month intervals is considered feasible and safe for most patients (Evidence Grade B).

The GINA stepwise approach for control-based management is outlined in Table 43-5.[2] This GINA approach emphasizes three components[2]: ASSESS—documentation of symptom control and risk factors, and if these are uncontrolled, check inhaler technique and adherence, and consider whether symptoms are due to a comorbid condition such as allergic rhinitis, GERD, or obesity rather than asthma. ADJUST therapy (up or down)—both drug therapy and nonpharmacological strategies; treat modifiable risk factors. REVIEW RESPONSE—assess and optimize asthma control about every 3 months.

TABLE 43-5 GINA Stepwise Approach to Control Symptoms and Minimize Future Risk[7]

Step	Preferred Option (Evidence Level)	Other Recommended Options (Evidence Level)
1	As-needed SABA (A)	Consider low-dose ICS, in addition to as-needed SABA, to reduce the risk for exacerbations (B)
2	Low-dose ICS, plus as-needed SABA (A)	LTRA (A) Low-dose ICS/LABA (A) ICS started with symptoms of allergic asthma, for seasonal treatment only (D)
3	Low-dose ICS/LABA, plus as-needed SABA for adults/adolescents (A) OR low-dose ICS/formoterol as both maintenance and reliever (A) For children 6-11 years, mod. dose ICS, plus as-needed SABA	Medium-dose ICS, for adults/adolescents (A) Low-dose ICS plus LTRA (A) or low-dose, sustained release theophylline (B)
4	Medium-dose ICS/LABA, plus as-needed SABA for adults/adolescents (B) OR medium-dose ICS/formoterol as both maintenance and reliever (A) For children 6-11 years, refer child to asthma specialist	Add-on therapy with tiotropium for adults with exacerbation history (A) Sublingual allergen immunotherapy in adults with allergic rhinitis and house dust mite sensitization if FEV_1 is above 70% predicted
5	Referral to specialist and consideration of add-on treatment if asthma remains uncontrolled	Add-on anticholinergic (B): Tiotropium if ≥ 12 years Add-on anti-IgE (A): Omalizumab (subcutaneous) for moderate-to-severe allergic asthma if ≥ 6 years Add-on anti-interleukin-5 therapy (A): Mepolizumab if ≥12 years (subcutaneous); Reslizumab if ≥18 years) (intravenous) Add-on anti-interleukin 5 receptor (A): Benralizumab if ≥12 years (subcutaneous) Sputum-guided treatment adjusted by eosinophilia >3% (0.03)(A) Bronchial thermoplasty in some adults with severe asthma (B) Add-on low-dose OCS (≤7.5 mg/day prednisone equivalent) (B)

ICS, inhaled corticosteroids; LABA, long-acting $beta_2$-agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids; SABA, short-acting $beta_2$-agonist.

(A), (B) = grade of evidence with A as the highest grade.

6 Special Populations to Consider in the Management of Chronic Asthma

The management of asthma in children younger than 5 years of age follows the same stepwise approach as in older children and adults but many treatments have not been studied adequately. Thus, many of the recommendations in this age group are extrapolated from older children and adults.[2] The primary differences in management are that no controller treatment is necessarily indicated for Step 1 and the recommended treatment in Step 3 is doubling the dose of ICS rather than adding LABA as is recommended for older children and adults; ICS/LABA have not been shown to reduce the risk of exacerbation or improve symptom control compared to the same dose of ICS alone.[2] Most of the available ICS have been studied in young children but not all have marketing approval from the FDA in this age group. Lack of an approved indication in children under 5 years of age

could affect insurance coverage for specific products. ICSs are available as MDI, DPI, and nebulized formulations but the preferred method of delivery is by MDI with a valved spacer and facemask, if needed.[2] Smaller spacers (less than 350 mL) are preferred because 5 to 10 breaths after actuation are required to inhale the complete dose. It is also recommended to not change the spacer type once a child is stable on a specific dose of ICS due to large differences in delivery between devices.[2] ICS use, even with low doses, causes reductions in growth velocity in children that are clinically important.[42,43] Thus, the lowest effective should be used and height should be regularly measured during treatment.[42,43] Treatment of moderate-to-severe asthma exacerbations may require use of oral corticosteroids but high-dose nebulized budesonide administered intermittently (1 mg twice a day for 7 days) at early signs of upper respiratory tract infections was as effective at preventing severe episodes of wheezing in infants 12 to 53 months of age with recurrent wheezing as low-dose (0.5 mg daily) continuous therapy.[44]

The FDA approval for montelukast (an LTRA) in children younger than age 6 was based on safety and pharmacokinetic studies establishing doses but not on efficacy, although improvement in symptoms and as-needed bronchodilators was noted.[3] Based on data from older children, a small minority of children may respond better to montelukast than ICS.[3] ICSs are recommended as first-line therapy but the initial choice between a trial of ICS or montelukast should be based on shared decision making between the provider and caregiver.

The elderly are at highest risk from dying of asthma and there are multiple contributing factors.[2] As in very young children, there have been few prospective studies evaluating drug therapies.[2] In addition, the elderly have a high comorbidity burden which may impact response to therapies differently than with younger patients, and which contributes to the difficultly with adherence when multiple medications for different diseases are given daily. Control of comorbid conditions (obesity, smoking, depression, and rhinosinusitis) may be required to improve treatment outcomes.[45] Arthritis, vision impairment, and muscle weakness which may affect inspiratory flow should be considered when selecting inhaler devices.[2] In addition, the elderly may have difficulty distinguishing breathlessness due to ageing or cardiovascular disease from symptoms of asthma.[2] Owing to the increased risk of osteoporosis and cataracts in the elderly, patients requiring high doses of ICSs should have routine height measurements, bone mineral density determinations, and ophthalmic examinations.[2,3] Appropriate therapies for prevention of osteoporosis

should be instituted.[2,3] ICS use may contribute to skin bruising which is already common in the elderly.

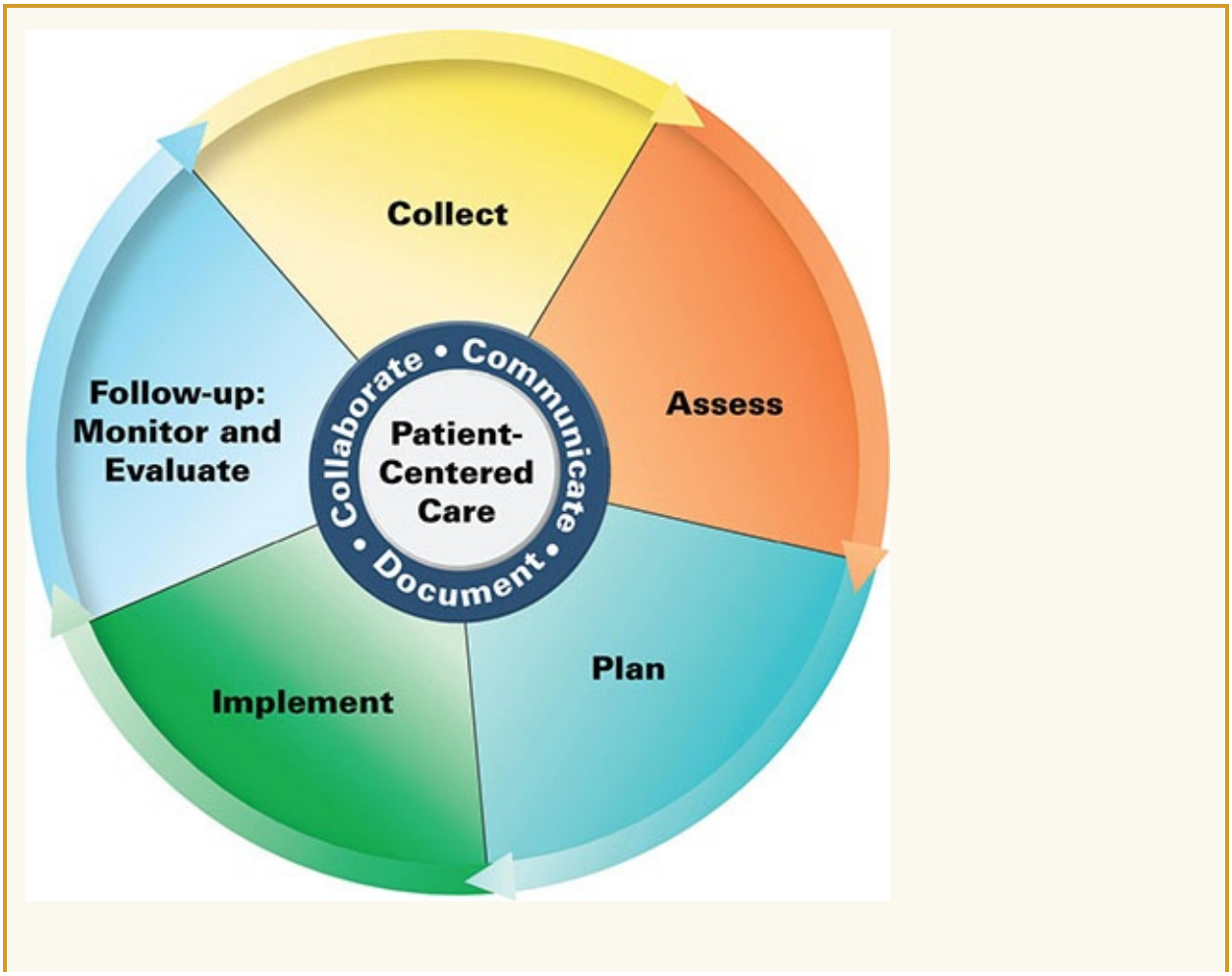
Asthma affects 8% of pregnant women, making it potentially the most common serious medical condition to complicate pregnancy.[46] Maternal asthma has been reported to increase the risk of perinatal mortality, preeclampsia, preterm birth, and low-birth-weight infants.[46] More severe asthma is associated with increased risks, whereas better-controlled asthma is associated with decreased risks. A systematic review of the evidence on the safety of asthma medications has concluded that it is safer for pregnant women with asthma to be treated with effective medications than for them to have exacerbations.[46] The safety of the newer biologic treatments in pregnancy is unknown.[47] Proper monitoring and control of asthma should enable a woman with asthma to maintain a normal pregnancy with little or no risk to mother or her fetus. Patients should be monitored monthly as exacerbations are more common in the second trimester and should include objective assessment of lung function and validated assessment of symptoms.[2,46]

A stepwise approach to managing asthma during pregnancy and lactation has been published, with low-dose ICSs recommended as preferred treatment for mild persistent asthma with the addition of a LABA if not adequately controlled.[28,46] Budesonide is considered the preferred ICS to initiate because it has the greatest amount of safety data, and the data are reassuring; however, patients who are well-controlled on a particular ICS should remain on current treatment as changing doses could jeopardize asthma control.[28,46] Stepping down treatment should not be initiated during pregnancy due to a risk of perturbations in asthma control.[2] Albuterol is considered the preferred rescue therapy.[46] Conditions that may aggravate asthma such as allergic rhinitis, sinusitis, and GERD should be aggressively treated.[48] Pregnant women are particularly susceptible to viral infections which may lead to exacerbations and worsening asthma symptoms, and should be aggressively treated to avoid fetal hypoxia.[2] Moderate-to-severe exacerbations should be treated per usual treatment guidelines with a target oxygen saturation of 95% (0.95).[2] Hyperventilation during labor may induce bronchoconstriction and should be treated with short-acting inhaled β_2-agonist.[2] Fentanyl, rather than morphine, should be used for pain control as morphine may induce histamine release and respiratory depression.[48]

General Approach to the Management of Acute

Severe Asthma

The primary goal is prevention of life-threatening asthma by early recognition of signs of deterioration and early intervention. Initial assessment includes history, physical examination, and objective assessments. It is important that therapy not be delayed, so the history and physical examination should be obtained while initial therapy is being provided. The brief history will assess for onset and causes of the exacerbation; severity of symptoms and if associated with anaphylaxis; medication use, adherence, and response to current therapy; and risk factors for asthma-related death. The asthma-related risk factors for death include: a history of near-fatal asthma requiring intubation and mechanical ventilation; hospitalization or emergency care in the past year; current or recent use of oral corticosteroids; no current use of ICSs; over use of short-acting inhaled β_2-agonist therapy (more than one canister per month); history of psychiatric disease or psychosocial problems; poor medication adherence; lack of a written asthma action plan; and food allergy.[2]



Patient Care Process for the Management of Acute Asthma

Collect

- Initial Assessments
  - **A**irway, **B**reathing, **C**irculation
  - If signs of extreme distress, drowsiness, confusion, silent chest → start SABA, oxygen, consult ICU, consider intubation
- Patient characteristics (eg, age, race/ethnicity, sex, pregnant)
- Patient history (eg, past medical, known triggers, psychosocial history)
- Past exacerbation history (eg, past need for hospitalization, intensive care, or intubation)
- History of food allergy
- Current medications and prior response to controller therapies (eg, ICS+/−LABA; montelukast; LAMA; biologic therapies)

Assess

- Degree of severity of exacerbation—MILD or MODERATE (see Fig. 43-5)
  - Can talk in phrases or sentences
  - Can sit up
  - Not agitated
  - Respiratory rate elevation mild to moderate
  - No sign of accessory muscle use
  - Oxygen saturation 90% to 95% (0.90 to 0.95)
  - PEF rate>50% of predicted (or previous best)
- Degree of severity of exacerbation—SEVERE (see Fig. 43-5)
  - Can only talk in single words
  - Hunched forward
  - Agitated
  - Respiratory rate elevation severe (>30/min for adults)
  - Accessory muscle use evidence

- Oxygen saturation <90% (0.90)
- PEF rate≤50% of predicted (or previous best)

Implement Acute Therapies

- If SEVERE, use team approach to immediately and simultaneously start SABA, oxygen, ICU involvement, and preparation for possible intubation (see Fig. 43-5)
  - Start SABA and ipratropium bromide
  - Titrate oxygen to keep 94% (0.94) or higher; use continuous oximetry and cardiac monitoring
  - IV corticosteroids (consider IV magnesium and high-dose ICS)
- If MILD-MODERATE (see Fig. 43-5)
  - Start SABA
  - Consider ipratropium bromide
  - Titrate oxygen to keep 94% (0.94) or higher
  - Oral corticosteroids

Follow-up: Monitor and Evaluate (see Fig. 43-5)

- Assess clinical changes frequently
- If continuing deterioration, consider intubation and ICU transfer
- Measure lung function in all patients 1 hour after initial treatment if able
- Disposition
  - If continued signs/symptoms of distress and FEV1 or PEF minimally improved, <60% predicted or personal best → continue treatment as above and reassess frequently
  - If significantly improved clinical signs/symptoms and FEV1 or PEF improved to 60% to 80% predicted or personal best → consider for discharge planning

The physical exam will assess vital signs and any complicating factors such as pneumonia or anaphylaxis as well as other comorbid conditions that could be causing acute shortness of breath such as inhaled foreign body, congestive heart failure, pulmonary infection, and pulmonary embolism.[2]

Objective assessments are keys to monitoring response to therapy and should

be made before initiation of oxygen or drug treatment. Lung function testing by PEF or FEV_1 should be measured before treatment if possible and thereafter at 1 hour after start of treatment and then periodically until response is achieved or no further improvement is evident.[2] Oxygen saturation is also monitored closely preferably by pulse oximetry and is a key parameter in young children who may not be able to perform lung function. Arterial blood gases are typically reserved for patients who are poorly responsive to initial treatment or deteriorating. A chest X-ray is rarely indicated unless there are physical signs of other or additional complicating features such as foreign body aspiration.

Oxygen therapy is initiated to achieve an arterial oxygen saturation of 93% to 95% (0.93-0.95) in adolescents and adults and 94% to 98% (0.94-0.98) in school-aged children and pregnant women or those with cardiac disease.[2,3] Oxygen therapy is continued until the patient has stabilized with continued use of pulse oximetry to monitor further oxygen need and response to medications.

The primary therapy of acute exacerbations is pharmacologic, which includes short-acting inhaled β_2-agonists and, depending on the severity, systemic corticosteroids, inhaled ipratropium, intravenous magnesium sulfate, and O_2. Treatments are typically administered concurrently to facilitate rapid improvement.[3] New evidence supports the use of heliox versus oxygen for nebulized β_2-agonist administration in patients with moderate-to-severe exacerbations who do not respond to standard therapy.[2,49] Heliox is a combination of helium and oxygen (often 70:30) that has a lower density than air which reduces resistance to flow and increases ventilation by converting turbulent flow to more efficient laminar flow.[50] Limited data suggest that the benefits with heliox therapy are apparent in those with severe exacerbations by improving PEF and reducing the risk of hospitalizations in both children and adults.[49]

A modest leukocytosis on complete blood count is common in asthma exacerbations due to viral infection or secondary to corticosteroid administration. Leukocytosis associated with corticosteroid administration does not cause a shift to the left as is seen in bacterial infections. Serum electrolytes should be monitored in patients who take diuretics regularly and in patients with coexistent cardiovascular disease, as short-acting inhaled β_2-agonists can produce transient decreases in potassium, magnesium, and phosphate.[3] The combination of high-dose β_2-agonists and systemic corticosteroids occasionally may result in excessive elevations of glucose and lactic acid.[50]

Initial response is measured 1 hour after the first three inhaled bronchodilator

treatments are administered and provides the best indicator for the need for hospitalization.[2] Indicators for hospitalization typically rely on the degree of respiratory distress, oxygen requirement, and frequency of need for inhaled β_2-agonists. Adjunctive indicators may include an initial FEV_1 less than 25% predicted or PEF that is less than 40% of their personal best, and post-treatment FEV_1 or PEF that is 40% to 60%.[2] Other indicators of severe asthma include monosyllabic speech, inaudible breath sounds, sitting hunched forward, and use of accessory muscles.[2] Patients with lung function that is 40% to 60% predicted *may* be considered for discharge after assessment of risk factors for death from asthma and the likelihood for follow-up care. Those with higher lung function can be discharged after risk factor and follow-up care assessment.[2]

Discharge planning after an ED visit or hospitalization includes arrangement for follow-up care within 1 week as well as review of strategies to improve asthma management. Referral to a specialist is suggested for those who have been hospitalized or frequently seek care in the ED despite having regular primary care. Strategies for preventing future urgent care visits includes ensuring the patient understands the cause of the exacerbation, how to modify risk factors, how to use medications correctly and for what purpose, and has a written asthma action plan that includes self-assessment of worsening symptoms and home PEF values.[2]

Figures 43-4 and **43-5** illustrate the recommended therapies for the treatment of acute asthma exacerbations in home and ED/hospital settings, respectively.[3] The dosages of the drugs for acute severe exacerbations are provided in **Table 43-6**.[3] Institutions should strongly consider developing critical pathways/treatment algorithms for their EDs because their implementation has been shown to improve outcomes and decrease the cost of care.[51]

Effective asthma self-management education requires:

- Self-monitoring of symptoms and/or lung function
- Written asthma action plan
- Regular medical review

	All patients	**If PEF or FEV_1 <60% of best, or not improving after 48 hours**
		Continue reliever
	Increase reliever	Continue controller
	Early increase in controller as below	Add prednisolone 40-50 mg/day
	Review response	Contact doctor

EARLY or MILD → LATE OR SEVERE

Medication	Short-term change (1-2 weeks) for worsening asthma	Evidence Level
Increase usual reliever:		
Short-acting beta2-agonist (SABA)	Increase frequency of SABA use For pMDI, add spacer	A A
Low dose ICS/formoterol*	Increase frequency of reliever use (maximum formoterol total 72 mcg/day	A
Increase usual controller:		
Maintenance and reliever ICS/formoterol*	Continue maintenance ICS/formoterol and increase reliever ICS/formoterol as needed* (maximum formoterol total 72 mcg/day)	A
Maintenance ICS with SABA as reliever	At least double ICS; consider increasing ICS to high dose (maximum 2000 mcg/day BDP equivalent)	B
Maintenance ICS/formoterol with SABA as reliever	Quadruple maintenance ICS/formoterol (maximum formoterol 72 mcg/day)	B
Maintenance ICS/other LABA with SABA as reliever	Step up to higher dose formulaion of ICS/other LABA, or consider adding a separate ICS inhaler (to maximum total 2000 mcg/day BDP equivalent)	D
Add oral corticosteroids (OCS) and contact doctor		
OCS (prednisone or prednisolone)	Add OCS for severe exacerbations (eg, PEF or FEV_1 <60% personal best or predicted), or patient not responding to treatment over 48 hours	A
	Adults: prednisolone 1mgk/kg.day (maximum 50 mg) usually for 5-7 days. *Children*: 1-2 mg/kg/day (maximum 40 mg) usually for 3-5 days	D
	Tapering is not needed if OCS are prescribed for < 2 weeks	B

BDP: beclomethasone dipropionate; FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroid; PEF: peak expiratory flow; SABA short-acting $beta_2$-agonist. Options are listed in order of evidence.

*ICS/formoterol maintenance and reliever regimen: lose dose budesonide or beclomethasone with formoterol. This regimen is not approved for children < 12 years in many countries.

FIGURE 43-4 Self-management of worsening asthma in adults and adolescents with a written asthma action plan. (Recreated from and with permission from Global Initiative for Asthma. Global strategy for asthma management and prevention, 2018. Available from: www.ginasthma.org.)

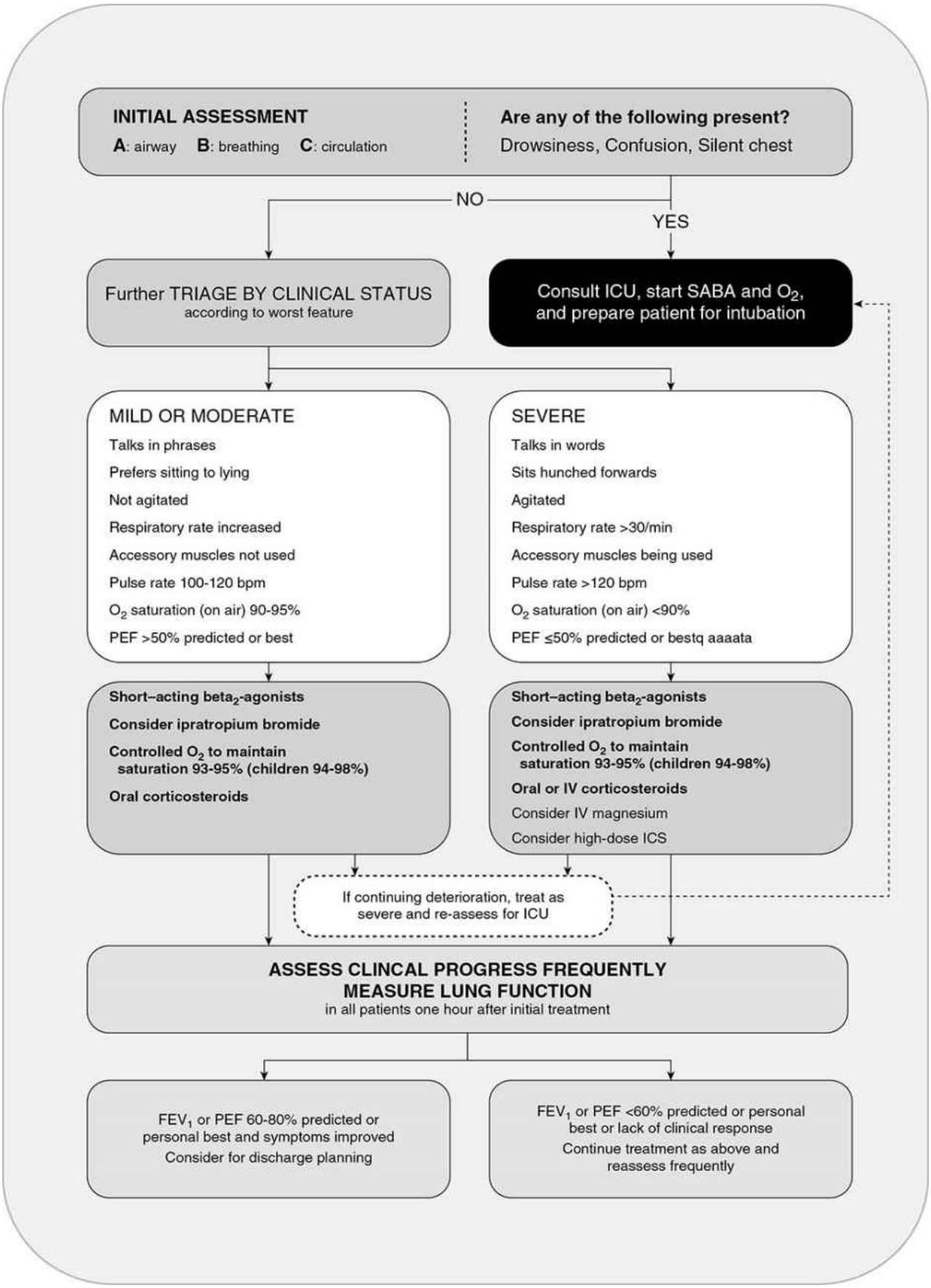

INITIAL ASSESSMENT
A: airway B: breathing C: circulation
Are any of the following present?
Drowsiness, Confusion, Silent chest
NO
YES
Further TRIAGE BY CLINICAL STATUS
according to worst feature
Consult ICU, start SABA and O_2, and prepare patient for intubation
MILD OR MODERATE
Talks in phrases
Prefers sitting to lying
Not agitated
Respiratory rate increased
Accessory muscles not used
Pulse rate 100-120 bpm
O_2 saturation (on air) 90-95%
PEF >50% predicted or best
SEVERE
Talks in words
Sits hunched forwards
Agitated
Respiratory rate >30/min
Accessory muscles being used
Pulse rate >120 bpm
O_2 saturation (on air) <90%
PEF ≤50% predicted or bestq aaaata
Short–acting beta$_2$-agonists
Consider ipratropium bromide
Controlled O_2 to maintain saturation 93-95% (children 94-98%)
Oral corticosteroids
Short–acting beta$_2$-agonists
Consider ipratropium bromide
Controlled O_2 to maintain saturation 93-95% (children 94-98%)
Oral or IV corticosteroids
Consider IV magnesium
Consider high-dose ICS
If continuing deterioration, treat as severe and re-assess for ICU
ASSESS CLINCAL PROGRESS FREQUENTLY
MEASURE LUNG FUNCTION
in all patients one hour after initial treatment
FEV_1 or PEF 60-80% predicted or personal best and symptoms improved
Consider for discharge planning
FEV_1 or PEF <60% predicted or personal best or lack of clinical response
Continue treatment as above and reassess frequently

FIGURE 43-5 Management of asthma exacerbations in acute care facility, for example, emergency department.

TABLE 43-6 Dosages of Drugs for Treatment of Acute Severe Exacerbations of Asthma

Medications	Dosages		
	≥12 Years Old	<12 Years Old	Comments
Inhaled β-Agonists			
Albuterol nebulizer solution (5 mg/mL, 0.63 mg/3 mL, 1.25 mg/3 mL, 2.5 mg/3 mL)	2.5-5 mg every 20 minutes for three doses, and then 2.5-10 mg every 1-4 hours as needed, or 10-15 mg/hr continuously if in the emergency department or hospitalized	0.15 mg/kg (minimum dose 2.5 mg) every 20 minutes for three doses, and then 0.15-0.3 mg/kg up to 10 mg every 1-4 hours as needed, or 0.5 mg/kg/hr by continuous nebulization if in the emergency department or hospitalized	Only selective β_2-agonists are recommended. For optimal delivery, dilute aerosols to minimum of 4 mL at gas flow of 6-8 L/min. Use face mask if <4 years
Albuterol MDI (90 mcg/puff)	4-8 puffs every 30 minutes up to 4 hours, and then every 1-4 hours as needed	4-8 puffs every 20 minutes for three doses, and then every 1-4 hours as needed	In patients in severe distress, nebulization is preferred; use VHC-type spacer with face mask if <4 years old
Levalbuterol nebulizer solution (0.31 mg/3 mL, 0.63 mg/3 mL, 2.5 mg/1 mL, 1.25 mg/3 mL)	Give one-half the milligram dose of albuterol above	Give one-half the milligram dose of albuterol above	The single isomer of albuterol is twice as potent on a milligram basis Not recommended
Levalbuterol MDI (45 mcg/puff)	See albuterol MDI dose above	See albuterol MDI dose above	See albuterol MDI dose one-half as potent as albuterol on a microgram basis Not recommended
Anticholinergics			
Ipratropium bromide nebulizer solution (0.25 mg/mL)	500 mcg every 30 minutes for three doses, and then every 2-4 hours as needed	250 mcg every 20 minutes for three doses, and then 250 mcg every 2-4 hours	May mix in same nebulizer with albuterol; only add to β_2-agonist therapy
Ipratropium bromide MDI (18 mcg/puff)	8 puffs every 20 minutes as needed for up to 3 hours	4-8 puffs as needed every 2-4 hours	Not to be continued once hospitalized
Corticosteroids[a]			
Prednisone, methylprednisolone, prednisolone	50 mg in one or two divided doses (prednisone equivalent)	1 mg/kg (maximum 40 mg/day) in two divided doses (prednisone equivalent)	For outpatient "burst" use 1-2 mg/kg/day, maximum 60 mg, for 3-5 days in children and 40-60 mg/day in one or two divided doses for 5-7 days in adults

[a]No advantage has been found for very-high-dose corticosteroids in acute severe asthma, nor is there any advantage for IV administration over oral therapy. The usual regimen is to continue the oral corticosteroid for duration of hospitalization. The final duration of corticosteroid therapy for an acute exacerbation may be from 3 to 10 days. If patients are then started on ICSs, there is no need to taper the systemic corticosteroid dose. ICSs can be started at any time during the exacerbation.

Data from Reference 3.

Special Populations to Consider in the Management of Acute Severe Asthma Infants and children younger than 5 years of age may be at greater risk of respiratory failure than older children and adults. Although treated with the

same drugs, these younger children require the use of a face mask as opposed to a mouthpiece for delivery of aerosolized medication. The face mask should be sized appropriately and should fit snugly over the nose and mouth. Use of the "blow-by" method, where the respiratory therapist or parent places the mask or extension tubing near the child's nose and mouth, should be discouraged because holding the mask as few as 2 cm from the patient's face reduces lung delivery of the aerosol by 80%.[3,52]

Children with severe exacerbations present with oxygen saturation of 92% (0.92) or less, speak in monosyllabic words, have increased heart rate (above 200 beats/min if 0-3 years or above 180 beats/min if 4-5 years), central cyanosis, and inaudible breath sounds which indicate minimal ventilation sufficient to cause wheezing.[2] Hypoxemia is treated with oxygen to achieve oxygen saturation of 94% to 98% (0.94-0.98). Avoidance of hypoxemia is critical and treatment should be initiated with nebulized β_2-agonists delivered by an oxygen-driven nebulizer. Treatment should begin immediately even if a full assessment has not been taken. Children with less severe symptoms can be treated with 2.5 mg of albuterol by nebulizer or two to six inhalations of albuterol with a spacer/facemask every 20 minutes for three doses with reassessment at the end of this treatment. Subsequent doses by nebulizer or two to three inhalations by spacer/facemask can be given every hour, but if symptoms do not resolve after 10 inhalations administered over 3 to 4 hours then a hospital admission is advised.[2] As in older children and adults, oral corticosteroids are administered at the time of inhaled β_2-agonists or systemically in children unable to swallow. Inhaled ipratropium bromide can be administered with β_2-agonist treatment but should not be continued for more than three doses in an hour. There is no evidence for continuing inhaled anticholinergics added to β_2-agonists in hospitalized children.[53] Nebulized magnesium sulfate may be administered as three doses in the first hour in children 2 years and older with severe exacerbations.[2] As in older children and adults, young children should be discharged with a prescription for oral corticosteroids for a 3- to 5-day treatment course and followed up within 7 days by a primary care provider.

General Principles of Aerosol Therapy for Asthma

4 5 aerosol delivery of drugs for asthma has the advantage of being site specific and thus enhancing the therapeutic ratio.[3,52] Inhalation of short-acting β_2-agonists provides more rapid bronchodilation than either parenteral or oral administration, as well as the greatest degree of protection against EIB and other

challenges.[3] ICSs have been developed with rapid oral and systemic clearance to enhance lung activity and reduce systemic activity. Specific agents (eg, formoterol, salmeterol, and ipratropium bromide) are only effective by inhalation.[3] Therefore, an understanding of aerosol drug delivery is essential to optimal asthma therapy. **Table 43-7** lists the factors determining lung deposition of therapeutic aerosols.

TABLE 43-7 Factors Determining Lung Deposition of Aerosols

Device	Device Factors	Patient Factors
Metered-dose inhaler (MDI)	Canister held inverted Formulation (solution or suspension) Actuator cleanliness Addition of a spacer device	Inspiratory flow (slow, deep) Breath-holding Tilting head back Coordinating actuation with inhalation Priming and shaking the device
Dry powder inhaler (DPI)	Device cleanliness Resistance to inhalation Humidity	Inspiratory flow (deep, forceful) Tilting head back Maintaining parallel to ground once activated
Jet nebulizer (small volume)	Volume fill (3-6 mL) Gas flow (6-12 L/min) Dead space volume Open vs closed system Thumb-activating valve Mouthpiece vs face mask	Inspiratory flow (slow, deep) Breath-holding Tapping nebulizer
Ultrasonic nebulizer	Volume fill Not effective for suspensions Mouthpiece vs face mask	Inspiratory flow (slow, deep) Breath-holding Tapping nebulizer
Spacer device	Volume (≥650 mL) One-way valves Holding chamber vs open-ended Antistatic lining Mouthpiece vs face mask	Inspiratory flow (slow, deep) Time between actuation and inhalation (<5 seconds) Cleaning with detergent to reduce static Multiple actuations (all at once) decrease delivery Coordination of actuation and inhalation for the simple open-tube spacers

Device Determinants of Delivery Devices used to generate therapeutic aerosols include jet nebulizers, ultrasonic nebulizers, metered-dose inhalers (MDIs), and dry powder inhalers (DPIs). The single most important device factor determining the site of aerosol deposition is particle size.[52] Devices for delivering therapeutic aerosols generate particles with mass median aerodynamic diameters (MMAD) from 0.5 to 35 μm.[52] Particles larger than 10 μm deposit in the oropharynx,

particles between 5 and 10 μm deposit in the trachea and large bronchi, particles 1 to 5 μm in size reach the lower airways, and particles smaller than 0.5 μm act as a gas and are exhaled. As a result of the Montreal Protocol of 1987, chlorofluorocarbon (CFC) propellants in MDIs were phased out and replaced with hydrofluoroalkane (HFA) propellants that do not have ozone-depleting properties.[52] The resultant MDIs, particularly for corticosteroid inhalers, are solution aerosols (vs suspensions) with extra-fine particle size distributions (MMAD of 1.1 μm) and high lung deposition.

In asthma, the airways, not the alveoli, are the target for delivery. Respirable particles are deposited in the airways by three mechanisms: (a) inertial impaction, (b) gravitational sedimentation, and (c) Brownian diffusion.[52] The first two mechanisms are the most important for therapeutic aerosols and probably are the only factors that can be manipulated by patients.

Each delivery device within a classification generates specific aerosol characteristics, so extrapolation of delivery data from one device cannot be applied to the other devices in the class. For instance, MDIs can deliver 15% to 50% of the actuated dose; DPIs, 10% to 30% of the labeled dose; and nebulizers 2% to 15% of the starting dose.[52] MDIs and DPIs are portable and convenient, unlike jet nebulizers. Small portable ultrasonic nebulizers have also been developed.

MDIs consist of a pressurized canister with a metering valve; the canister contains active drug, low-vapor-pressure propellants such as HFA, co-solvents, and/or surfactants.[52] With any change in the components of an MDI, the FDA considers it to be a new drug that requires stability, safety, and efficacy studies prior to approval. The MDI drug is either in solution or a suspended micronized powder. In order to disperse the suspension for accurate delivery, the canister must be shaken. The metering chamber measures a liquid volume, and, therefore, the device must be held with the valve stem downward so that the chamber is covered with liquid[52] (**Fig. 43-6**). If not used for a period of time the drug in the chamber evaporates which could lead to an inadequate therapeutic dose. Inhalers have to be primed before first use to fill the chamber and after an interval of nonuse.[52] When the canister is actuated, the device releases the propellant and drug in a forceful spray whose particles are large (MMAD = 45 μm)[52] (see Fig. 43-6). As evaporation occurs, the particle size is reduced to a final MMAD of 0.5 to 5.5 μm depending on the MDI. The aerosol cloud extends about 6 inches beyond the MDI at the lowest MMAD.[52] Each MDI has different conditions for storage, priming, and durations to expiration, so the clinician must become familiar with and counsel the patient on these factors.

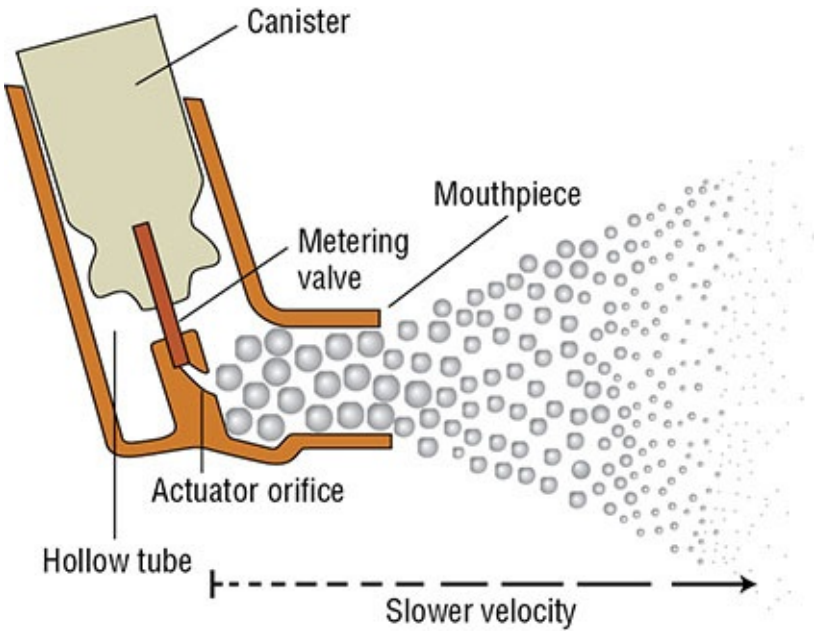


FIGURE 43-6 Illustration of a metered-dose inhaler demonstrating the particle size difference as the aerosol cloud extends outward.

Spacer devices are used frequently with an MDI to decrease oropharyngeal deposition and enhance lung delivery.[2,3] However, not all spacer devices produce similar effects. The design of spacers varies from simple open-ended tubes that separate the MDI from the mouth to valved holding chambers (VHC) with one-way valves that open during inhalation (the preferred system); some VHCs have a face mask to accommodate drug delivery in children 5 years or younger.[2] A VHC allows evaporation of the propellant prior to inhalation permitting a greater number of drug particles to achieve a respirable droplet size. VHC use also allows inhalation after actuation of the MDI, obviating the need for good hand–lung coordination.[52] Additionally, the large particles that normally would deposit in the oropharynx "rain out" in the spacer.[52] Spacer size may affect the amount of drug available for inhalation; a lower volume spacer (less than 350 mL) is advantageous in very young children.[2]

All the available spacers significantly reduce oropharyngeal deposition from MDIs, with the VHCs being superior to the open-ended tubes.[52] This reduction in oropharyngeal deposition is an important factor in reducing local adverse effects (eg, hoarseness and oropharyngeal candidiasis) from ICSs.[52] The change in lung delivery depends on both the MDI and the drug, where one spacer device may enhance delivery with one MDI preparation and decrease delivery with others.[52] Therefore, once a patient is stabilized on a drug and chamber combination, the chamber should not be substituted in order to avoid changes in

the dose delivered to the lungs. Finally, over time, holding chambers (eg, plastic) can build up static electricity that attracts small particles to the sides of the chamber, significantly reducing aerosol availability. Some spacers should be washed weekly with household detergent with a single rinse and allowed to drip dry.[3] Other VHCs have been developed with antistatic materials.

Dry micronized powders can be inhaled directly into the lungs. A number of DPIs are now available for use in the United States.[52] Currently, there are no generic DPIs as each drug plus device has its own patent. Each DPI has unique characteristics with advantages and disadvantages (**Table 43-8**). The primary advantage of DPIs is that they are breath actuated and require minimal hand–lung coordination, and it is thus easier to teach patients proper technique.[52] Some DPIs are more flow dependent than others.[52] Thus, similar to MDIs and spacers, delivery data from one DPI cannot be extrapolated to another.

TABLE 43-8 Characteristics of Commonly Used Inhalation Devices

Device	Drugs	Breath Activated	Dose Counter	Other Excipients	Disadvantages
MDI	All classes	No	No/yes	Propellants, surfactants, cosolvents	Requires coordination of actuation and inhalation. Large pharyngeal deposition. Difficult to teach
Pressair	Aclidinium	Yes	Yes	Lactose filler	Requires rapid inhalation to activate
Respiclick	Albuterol	Yes	Yes	Lactose filler	Requires rapid inhalation to activate
MDI plus valved holding chamber	All classes	No	No		More expensive than MDI alone; less portable; some payers will not pay; inconsistent effect on delivery; nonstatic preferred
Jet nebulizers	All classes	No	—	Preservatives in some solutions	Significant interbrand variability; expensive and time consuming; less efficient than MDIs; contamination possible; preparations may be light and temperature sensitive (short shelf life)
Ultrasonic nebulizer	Cromolyn solution, short-acting β_2-agonist solutions	No	—	Preservatives in some solutions	Same as for jet nebulizers and cannot be used for suspensions; battery operated are portable
Flexhaler	Budesonide	Yes	Yes	Lactose filler	Requires high inspiratory flow (60 L/min) Pharyngeal deposition Not approved for <6 years of age
Diskus	Fluticasone; salmeterol; fluticasone/ salmeterol	Yes	Yes	Lactose filler	Not approved for <4 years of age Requires inspiratory flow of 30-60 L/min
Ellipta	Fluticasone furoate Fluticasone/ vilanterol	Yes	Yes	Lactose filler	Not approved for <12 years of age (18 years for fluticasone/vilanterol) Requires inspiratory flow of 60 L/min
Aerolizer	Formoterol	Yes	—	Lactose filler	Single-dose capsules. Not approved for <5 years of age Requires flow of 30-60 L/min
Neohaler	Indacaterol	Yes	—	Lactose filler	Single-dose capsules. Not approved for children Requires flow of 60 L/min
Handihaler	Tiotropium	Yes	—	Lactose filler	Single-dose capsule. Not approved for children Requires flow of 20 L/min
Twisthaler	Mometasone	Yes	Yes	Lactose filler	Not approved for <4 years of age
Respimat	Tiotropium Albuterol/ Ipratropium Olodaterol	No	Yes	Preservative	Requires slow deep breath. Not approved for <12 years of age

Nebulizers come in two basic types, the jet nebulizer and the ultrasonic nebulizer. Jet nebulizers produce an aerosol from a liquid solution or suspension placed in a cup. A tube connected to a stream of compressed air or O_2 flows up through the bottom and draws the liquid up an adjacent open-ended tube.[52] The air and liquid strike a baffle, creating a droplet cloud that is then inhaled.[52] Ultrasonic nebulizers produce an aerosol by vibrating liquid lying above a transducer at speeds of about 1 mHz.[52] Both produce similar degrees of lung deposition, with the exception that ultrasonic nebulizers are ineffective for nebulizing currently available micronized suspensions.[52] The aerosol output and lung delivery vary significantly among the commercially available jet nebulizers even when operated in the same manner.[52] Increasing fill volume will increase the total amount of drug delivered. However, it also will take longer for the patient to nebulize the dose.[52] The MMAD of the droplets is related directly to the gas flow, with flows of 5 to 12 L/min providing an aerosol cloud with an MMAD of 4 to 8 μm for most jet nebulizers.[52] Each jet nebulizer comes with its optimal operating and cleaning instructions.

6 7 **Patient Determinants of Delivery** The most important patient factor determining aerosol deposition is inspiratory flow (see Table 43-7).[3,52] High inspiratory flows with MDIs increase the degree of deposition owing to impaction of particles of any size, thereby increasing deposition centrally (ie, throat and large airways) and decreasing peripheral deposition. Optimal inspiratory flow for most MDIs is slow and deep (approximately 30 L/min or 5 seconds for a full inhalation).[2,3] In general, DPIs require higher inspiratory flows (greater than or equal to 60 L/min) and a change in inhalation technique (ie, deep, forceful inspiration) for optimal dispersion of the powder, which, in turn, increases the amount of drug delivered to the larger central airways.[52] However, this difference in delivery may not produce clinically significant differences.[52] Patients should be cautioned not to exhale into DPIs because this causes loss of dose and moistens the dry powder, causing aggregation into larger particles. Patient factors that cannot be controlled include interpatient variability in airway geometry (particularly the differences between children and adults)[52] and the effects of bronchospasm, edema, and mucus hypersecretion. Mild obstruction increases aerosol deposition; however, severe obstruction probably leads to increased central deposition from impaction.[52] The absolute delivery to the lung is not as important as consistency of delivery, assuming that a sufficient dose to produce the desired therapeutic effect is achieved. No single inhalation device is the best for all patients. Table 43-8 lists the differing characteristics of inhalation

devices.

Appropriate inhalation technique is essential to achieve optimal drug delivery and therapeutic effect.[2,3] The components are illustrated in **Fig. 43-7**. Approximately 50% to 80% of a dose from MDIs and DPIs impacts on the oropharynx and is then swallowed; the rest is either left in the device or exhaled.[52] It is important that MDI actuation occurs during inhalation.[3,52] Although radiolabeled studies with MDIs indicate improved delivery by holding the actuator 2 to 3 cm in front of an open mouth to allow more evaporation and less impaction, physiologic studies with bronchodilators have failed to document an advantage for this method.[3,52] Many patients do not use their MDIs optimally, and patient instruction with demonstration is the most effective means of improving inhaler technique.[2,3] Even with instruction, up to 30% of patients, particularly young children and the elderly, cannot master the use of an MDI. For these patients, attachment of a VHC to the MDI can improve efficacy significantly.[3,52] However, addition of a VHC offers no advantage in patients who can use an MDI optimally alone.[52] Mouth rinsing following treatment with MDI- and DPI-ICSs is important to minimize local adverse effects and oral absorption.[3,52]

How To Use Your Metered-Dose Inhaler

Using an inhaler seems simple, but most patients do not use it the right way. When you use your inhaler the wrong way, less medicine gets to your lungs.

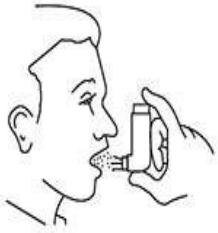
For the next few days, read these steps aloud as you do them or ask someone to read them to you. Ask your doctor or nurse to check how well you are using your inhaler.

Use your inhaler in one of the three ways pictured below. A or B are beast, but C can be used if you have trouble with A and B. Your doctor may give you other types of inhalers.

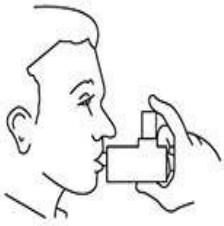
Steps for Using Your Inhaler

Getting ready	1. Take off the cap and shake the inhaler.
	2. Breath out all the way.
	3. Hold your inhaler the way your doctor said (A, B, or C below).
Breathe in slowly	4. As you start breathing in slowly throuch your mouth, press down on the inhaler one time. (If you use a holding chamber, first press down on the inhaler. within 5 seconds, begin to breathe in slowly.
	5. Keep breathing in slowly, as deeply as you can.
Hold your breath	6. Hold your breath as you count to 10 slowly, if you can.
	7. For inhaled quick-relief medicine (beta2-agonists), wait about 15–30 seconds between puffs. There is no need to wait between puffs for other meicines.

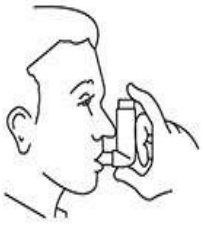
A. Hold inhaler 1 to 2 inches in front of your mouth (about the width of two fingers).



B. Use a spacer/holding chamber. These come in many shapes and can be useful to any patient.



C. Put the inhaler in your mouth. Do not use for steroids.



Clean your inhaler as needed, and know when to replace your inhaler. For instructions, read the package insert or talk to ypur doctor, other health care provider, or pharmacist.

FIGURE 43-7 Instructions for inhaler use from the NAEPP Expert Panel Report 3. (Source: National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. NIH Publication No. 07-4051. Revised August 2007.)

Delivery from high-resistance DPIs is more flow dependent than from low-resistance DPIs. Thus, younger children and possibly elderly adults will have more variability in delivery from high-resistance devices.[52] Most children younger than 4 years of age cannot generate a sufficient inspiratory flow to use DPIs. Young children (younger than 4 years) and infants generally require the use of a face mask attached to either an MDI plus VHC or a nebulizer. The use of a face mask results in a reduction in lung delivery due to the portion of the aerosol inhaled nasally, so the doses of drugs used in these patients are often not decreased.

Nonpharmacologic Therapy for Chronic and Acute Asthma

Chronic Asthma

Although the mainstay of the management of asthma is pharmacologic therapy, it is likely to fail without concurrent attention to relevant environmental control and management of comorbidities that may contribute to respiratory symptoms and poor quality of life. Nonpharmacologic therapies are incorporated into GINA's recommendations for initiation of regular daily controller treatment, as well as the stepwise approach for adjusting treatment in adults, adolescents, and children.[2] The guidelines were designed to give healthcare providers a framework with which to develop the proper approach to the individualized therapy of patients. The heterogeneity of asthma demands an individualized approach to therapy with the basic goals of therapy as primary outcome measures.[2] The focus of controller therapy is the reduction of airway inflammation, control of symptoms, and reduction of future risks. Thus, current therapeutic options in asthma consist of acute reliever (rescue) medications for as-needed relief of breakthrough symptoms and exacerbations, and long-term control medications used for the prevention of symptoms and exacerbations and the suppression of inflammation and reduction of BHR.[2] GINA emphasizes the importance of concurrently identifying and treating modifiable risk factors, such

as active smoking and exposure to tobacco smoke, obesity, major psychological problems, major socioeconomic problems, confirmed food allergy, and allergen exposure if sensitized.[2] Avoidance of occupational exposures, indoor allergens, and medications that may make asthma worse should be considered when relevant.

In patients with known allergic triggers for their asthma, allergen avoidance has resulted in an improvement in symptoms, a reduction in medication use, and a decrease in BHR.[3] A comprehensive approach to environmental control is advocated. For example, for patients with house dust mite allergy removing carpeting from bedrooms, washing sheets in hot water (greater than 54.4°C [greater than 130°F]), and using special dust-proof pillow and mattress covers can reduce symptoms and need for medications.[3] Obvious environmental triggers (eg, animal dander and cockroaches), if the patient is sensitive, should be avoided. Evidence for home air-filtering systems and chemicals for killing house dust mites is limited.[3]

Allergen-specific immunotherapy as either subcutaneous injections or sublingual administration may improve symptom scores and reduce medication use in patients with documented allergen sensitivity.[2] Allergen treatment should be directed to specific allergens to which the patient has documented sensitivity. Immunotherapy with multiple antigens tends to be less effective than with single allergens. The burden of frequent healthcare visits for immunotherapy administration must be considered before starting therapy as treatment will need to be continued for several years before there is sustained improvement in symptoms.

Acute Asthma

Infants and young children may be mildly dehydrated owing to increased insensible loss, vomiting, and decreased intake.[3] Unless dehydration has occurred, increased fluid therapy is not indicated in acute asthma management because the capillary leak from cytokines and increased negative intrathoracic pressures may promote edema in the airways.[3] Correction of significant dehydration is always indicated, and the physical examination and urine specific gravity may help to guide therapy in young children, in whom the state of hydration may be difficult to determine.[3] Chest physical therapy and mucolytics are not recommended in the therapy of acute asthma.[3] Sedatives should not be given because anxiety may be a sign of hypoxemia, which could be worsened by central nervous system depressants. Antibiotics also are not indicated routinely

because viral respiratory tract infections are the primary cause of asthma exacerbations.[3] Antibiotics should be reserved for patients who have signs and symptoms of pneumonia (eg, fever, pulmonary consolidation, and purulent sputum from polymorphonuclear leukocytes). *Mycoplasma* and *Chlamydia* are infrequent causes of severe asthma exacerbations but should be considered in patients with high O_2 requirements.[3,54]

Respiratory failure or impending respiratory failure as measured by rising $PaCO_2$ (greater than or equal to 45 mm Hg [6 kPa]) or failure to correct hypoxemia with supplemental O_2 therapy is treated first with noninvasive ventilation and eventually with intubation and mechanical ventilation, if needed.[2]

Patient Education

7 The development of a patient–healthcare provider partnership in care through patient education and the teaching of patient self-management skills should be the cornerstone of any treatment program.[2] There are a number of published self-management programs for children and adults available through the American Lung Association, as well as asthma treatment centers, and nationally through the NAEPP, GINA, and the Asthma and Allergy Foundation of America.[2,3] Asthma self-management programs have been shown to improve patient adherence to medication regimens, improve self-management skills, and improve use of healthcare services.[55,56]

Self-management programs instruct patients in the pathogenesis of asthma and the appropriate use of their medications but focus principally on teaching patients to recognize triggers for their asthma, how to recognize early signs of deterioration, and how to keep track of symptoms (with or without a diary), and take action.[2,3,55] Short-term home PEF monitoring can be used to assess response to treatment, assess a baseline for asthma action plans, or evaluate triggers (such as occupational triggers) and is typically recorded for about 2 weeks.[2] However, routine PEF monitoring is generally only recommended for those patients with severe asthma or poor symptom perception.[2]

The NAEPP has recommended a PEF monitoring system based on a traffic light scenario (based on percentage of normal predicted values or personal best values): the green zone is equal to 80% to 100%, the yellow zone is equal to 50% to 79%, and the red zone is less than 50%. The yellow zone is cautionary and requires increasing as-needed bronchodilator use and possibly beginning

prednisone if not improved, whereas the red zone warrants contacting the patient's healthcare provider.[3]

Patient education is essential before monitoring can be effective. It is successful regardless of the healthcare provider who provides it. The NAEPP and GINA advocate significant involvement of all points of patient care in the educational process.[2,3] The provision of written action plans enhances the success of education and is considered an essential component of care.[2,3] Samples of clinically tested written action plans that are PEF or symptom based are available from NAEPP and GINA guidelines and other sources.[2,3]

Pharmacologic Therapy

β_2-Agonists

5 6 The β_2-agonists are the most effective bronchodilators available. The β_2-adrenergic receptors are transmembrane proteins consisting of clusters of seven helices of amino acids that form the ligand-binding core.[57] This activation, in turn, decreases unbound intracellular calcium, producing smooth muscle relaxation, mast cell membrane stabilization, and skeletal muscle stimulation.[57] Despite the fact that β_2-agonists are potent inhibitors of mast cell degranulation in vitro, they do not inhibit the late asthmatic response to allergen challenge or the subsequent BHR.[3,57] Long-term administration of β_2-agonists does not reduce BHR, confirming a lack of significant anti-inflammatory activity. β_2-Adrenergic stimulation also activates Na^+-K^+-ATPase, produces gluconeogenesis, and enhances insulin secretion, resulting in a mild-to-moderate decrease in serum potassium concentration by driving potassium intracellularly.[51] The chronotropic response to β_2-agonists is mediated in part by baroreceptor reflex mechanisms as a result of the drop in blood pressure from vascular smooth muscle relaxation, as well as by direct stimulation of cardiac β_2-receptors and some β_1 stimulation at high concentrations.[51] Because β_1-receptor stimulation produces excessive cardiac stimulation, resulting in cardiac arrhythmias, and because the inotropic effect enhancing myocardial O_2 consumption leads to myocardial necrosis, there is no rationale for using non-β_2-selective agonists in the treatment of asthma.[3]

Table 43-9 compares the various short-, long-, and ultra-long-acting β-adrenergic agonists used in asthma in terms of onset and duration of action.[58,59]

The β_2-agonists are functional or physiologic antagonists, in that they relax airway smooth muscle regardless of the mechanism for constriction.[57] When administered in equipotent doses, all the short-acting drugs produce the same intensity of response; the only differences are in duration of action and cardiac toxicity.[3,57] The catecholamine derivatives all have the disadvantage of rapid inactivation of their 3,4-hydroxyl catechol group from catechol-*O*-methyltransferase located in the GI tract, rendering them orally inactive. In addition, catecholamines are taken up rapidly into tissues by secondary uptake mechanisms that limit their receptor occupancy and thus have a shorter duration of action.[57] All the β_2-agonists are more bronchoselective when administered by the aerosol route. Aerosol administration of the short-acting β_2-agonists provides more rapid response and greater protection against provocations that induce bronchospasm such as exercise and allergen challenges than does systemic administration.[3,57] Differences in myocardial effects are discernible between selective and nonselective agents even when administered as aerosols, particularly at the higher doses used for acute severe asthma. The β_2-agonists also differ in efficacy or ability to activate the β_2-adrenergic receptors. Full agonists include the catecholamines while the synthetic β_2-agonists all exhibit various levels of partial agonism.[57] Although partial agonists by definition cannot produce maximum dilation or protection as full agonists and can potentially block the effect of a full agonist, these differences have not been proven to be clinically significant.

TABLE 43-9 Onset and Duration of Action of *β*-Adrenergic Agonists

	Onset and Duration of Action[a]		
Agent	Bronchodilation (hours)	Protection (hours)[a]	Onset of bronchodilation
Isoproterenol	0.5-2	0.5-1	1-2 minutes
Albuterol/ levalbuterol	4-8	2-4	1-2 minutes
Formoterol	≥12	≥12	1-2 minutes
Salmeterol	≥12	≥12	10 minutes
Indacaterol	≥24	≥24	1-2 minutes
Olodaterol	≥24	≥24	1-2 minutes
Vilanterol	≥24	≥24	1-2 minutes

[a]Protection refers to the prevention of bronchoconstriction induced by exercise or nonspecific bronchial challenges.

The majority of synthetic β_2-agonists are 1:1 racemic mixtures of two mirror images (enantiomers) owing to an asymmetric or chiral carbon.[57] Since most physiologic functions (receptor occupancy and activation and enzymatic metabolism) are stereoselective, the (*R*)-enantiomers of the β_2-agonists are the most pharmacologically active isomer.[57] While it was felt initially that the (*S*)-enantiomers were essentially inactive owing to the 100- to 1,000-fold potency difference between the enantiomers, studies in animal models and isolated in vitro tissue preparations have suggested that the (*S*)-enantiomer of albuterol may be pro-inflammatory and could induce BHR.[57] However, evidence that this occurs consistently in humans or is clinically relevant is lacking.[57] The pharmacokinetics are stereoselective as well, although not predictable. (*R*)-Albuterol is metabolized more rapidly than (*S*)-albuterol, which could lead to accumulation of (*S*)-albuterol with continued dosing.[57] Levalbuterol tartrate is the (*R*)-enantiomer of albuterol, and is a comparable selective β_2-adrenergic receptor agonist.

Both the intensity and duration of response are dose dependent, and, more important, the dose–response relationship is dynamic.[57] At increasing levels of baseline bronchoconstriction (irrespective of the stimulus), the dose–response curve is shifted to the right, and the duration of bronchodilation is decreased.[57] This shift is reflected in the need for higher, more frequent doses in acute asthma exacerbations; the duration of protection against significant provocation is much less than the duration of bronchodilation in chronic stable asthma for short-

acting inhaled β_2-agonists (see Table 43-9).[57]

Chronic administration of β_2-agonists leads to downregulation (decreased number of β_2-receptors) and a decreased binding affinity (desensitization) for these receptors.[57] Systemic corticosteroid therapy can both prevent and partially reverse this phenomenon.[3,57] However, the use of ICSs appears to have minimal ability to prevent tolerance to β_2-agonists.[57] Tolerance primarily reduces duration of bronchodilation as opposed to peak response, although the latter can occur as well. A significantly greater tolerance develops in other tissues (eg, lymphocytes and cardiac and skeletal muscle) compared with the lung, primarily as a result of the surplus β_2-receptors found in respiratory smooth muscle.[57] Tolerance to the extra-pulmonary effects (cardiac stimulation and hypokalemia) may account for a lack of significant cardiac effects with retention of the bronchodilator response despite chronic-inhaled β_2-agonist therapy, whereas tolerance to mast cell stabilization may be a drawback to chronic use.[57] Thus, chronic β_2-agonist administration produces a tolerance of minimal clinical significance that is overcome easily by increasing the dose or by administering corticosteroids.[3,57] Most of the tolerance occurs within a week of regular administration and does not worsen with continued administration. As would be expected from a receptor phenomenon, tolerance is a cross-tolerance to all β_2-agonists.[57] Regular treatment (four times daily) does not improve symptom control over as-needed use and is not indicated.[2,3] Regular treatment with the long-acting inhaled β_2-agonists (LABAs) is discussed below.

In conclusion, the short-acting inhaled selective β_2-agonists are indicated for the as-needed treatment of intermittent episodes of bronchospasm. They are the first treatment of choice for acute severe asthma and EIB.[2,3,19] They inhibit EIB in a dose-dependent fashion and provide complete protection for a 2-hour period following inhalation with varying levels of patient-dependent protection over 4 hours.[19] Although the regular administration of β_2-agonists slightly decreases the protective effect, two inhalations prior to exercise still essentially block EIB completely (1% vs 5% drop in FEV_1).[19,57]

4 **Short-Acting β_2-Agonists** The short-acting inhaled β_2-agonists are the most effective bronchodilators and the treatment of first choice for the management of acute severe asthma.[2] In adults, administration as either continuous or intermittent (every 20 minutes for three doses) over 1 hour results in equivalent

improvement.[3] In the subset of more severely obstructed patients, continuous nebulization provides greater improvement in lung function and decreases the hospitalization rate and duration of hospitalization when compared with intermittent (hourly) nebulized albuterol in the same total dose.[3] Thus, continuous nebulization is recommended for patients having an unsatisfactory response (achieving less than 50% of normal FEV_1 or PEF) following the initial three doses (every 20 minutes) of aerosolized β_2-agonists and potentially for patients presenting initially with PEF or FEV_1 values of less than 30% of predicted normal.[3] Intravenous β_2-agonists have only a limited role in severe exacerbations.[2] Effective doses of aerosolized β_2-agonists can be delivered successfully through mechanical ventilator circuits to infants, children, and adults in respiratory failure secondary to severe airway obstruction.[52]

The doses of inhaled β_2-agonists for acute severe asthma exacerbations (see Table 43-6) have been derived empirically. The β_2-agonists follow a log-linear dose–response curve. In addition, the dose–response curve is shifted to the right by more severe bronchospasm or by increased concentrations of bronchospastic mediators, which is characteristic of functional antagonists.[60] The ability to increase the dose of the short-acting aerosolized β_2-agonists by as much as 5- to 10-fold over doses producing adequate bronchodilation in chronic stable asthma is what contributes to their efficacy in reversing the bronchospasm of acute severe exacerbations. The nebulizer dose of inhaled β_2-agonists for children often is listed on a weight basis (milligrams per kilogram). However, a fixed minimal dose (2.5 mg albuterol or equivalent), as opposed to a weight-adjusted dose, is more appropriate in younger children because children younger than 5 years of age receive a lower lung dose.[3] Adults dosed on a weight basis demonstrate excessive cardiac stimulation, so they have fixed maximal doses[3] (see Table 43-6). Initial doses of inhaled β_2-agonists can produce vasodilation, worsening ventilation–perfusion mismatch, slightly lowering O_2 saturation or PaO_2.[51] High doses of inhaled β_2-agonists can produce a decrease in serum potassium concentration, an increase in heart rate, and an increase in serum glucose and lactic acid concentration.[2] Electrolyte monitoring may be needed in patients with pre-existing heart disease who receive frequent doses for an acute exacerbation.[2] Hyperlactatemia is common but is not accompanied by metabolic acidosis and does not increase the risk of hospitalization.[50] Both children and adults receiving continuously nebulized β_2-agonists have demonstrated

decreased heart rate as their lung function improves.[3] Thus, an elevated heart rate is not an indication to use lower doses or to avoid using inhaled β_2-agonists.

There is no evidence to support the use of levalbuterol over albuterol for the treatment of acute severe exacerbations in either children or adults with respect to efficacy or adverse effects.[60] A meta-analysis that showed a lower risk for hospitalization in the levalbuterol-treated patients was driven by one study only.[60]

Inhaled epinephrine as Primatene Mist® MDI has been available without a prescription for over 50 until it was removed from the market in 2011 because the inhaler contained CFC propellants which are substances that deplete the ozone layer. It returned to the market in late 2018 as a reformulated MDI with a hydrofluoroalkane propellant. Primatene Mist® is only to be used for the temporary relief of mild symptoms of intermittent asthma in patients 12 years and older and if improvement is not seen within 20 minutes, it becomes worse, or more than 8 inhalations in a 24-hour period, or there are more than two episodes in a week, the patient should see a physician immediately. Primatene Mist® is less effective than prescription SABAs.

The inhaled β_2-agonists produce similar efficacy whether delivered by MDI plus VHC or nebulization in treating acute severe exacerbations in the ED and hospital; thus, the choice depends on the experience and comfort of the treating clinicians.[2] The DPIs are currently not indicated for the treatment of acute severe asthma exacerbations due to the higher inspiratory flows required for adequate drug delivery.[3]

Long-Acting Inhaled β_2-Agonists The two LABAs, formoterol and salmeterol, provide long-lasting bronchodilation (greater than or equal to 12 hours)[58] (see Table 43-9). Unlike the more water-soluble short-acting β_2-agonists, the long-acting agents are lipid soluble, readily partitioning into the outer phospholipid layer of the cell membrane.[58] In addition, ultra-LABAs (indacaterol, vilanterol, and olodaterol) have a 24-hour bronchodilator duration of effect. Vilanterol in combination with fluticasone furoate is available for once-daily dosing for asthma in adults aged 18 and older in the United States and for children and adults aged 12 and older in European countries. Currently, products containing indacterol and olodaterol are only indicated for COPD, but are being evaluated for asthma.

The LABAs and ultra-LABAs are more β_2-selective than albuterol and more bronchoselective by virtue of their property of remaining in the lung tissue cell

membrane, which produces its longer duration.[58] The LABAs have a duration of bronchodilator effect of about 12 hours and are dosed twice daily whereas the ultra-LABAs have extended bronchodilator characteristics and last up to 24 hours permitting once-daily dosing.[58] The onset of action (time required to increase FEV_1 by 12% over baseline) is similar to that of albuterol for LABAs and ultra-LABAs with the exception of salmeterol which has an onset of approximately 10 minutes. However, this difference is of little consequence as salmeterol, formoterol, and vilanterol are recommended for chronic therapy only in combination with ICSs in the United States (in European countries combination ICS with formoterol are also used on-demand for acute relief of symptoms).[2] LABAs are available as single entity and as fixed-dose combinations with ICSs (see below) though single-entity LABA products are FDA approved for use only with ICS. Patients need to be counseled to continue to use their short-acting inhaled β_2-agonists for acute exacerbations while receiving the ICS/LABA combination products.

The LABAs are preferred adjunctive therapy to ICSs in children 12 years and older and adults for step 3 and children 6 to 11 years of age for steps 4 and 5.[2] Combination treatment with ICS/LABA provides greater asthma control than increasing the dose of ICS alone, while at the same time reducing the frequency of mild and severe exacerbations.[2]

As with short-acting β_2-agonists, tolerance can occur with chronic administration of LABAs and seems to plateau after about 1 week of regular therapy but response recovers rapidly after only 3 days of nonuse.[58] Long-term trials have shown no diminution in bronchodilator response but a partial loss of the bronchoprotective effect against methacholine, histamine, and exercise challenge.[58] These effects do not seem to have a significant impact on the quality of asthma control with chronic daily use.

Concern for risks with long-acting β_2-agonist use began shortly after approval of the first available LABA, salmeterol, with reports of respiratory deaths in salmeterol users, and risks were evaluated in multiple meta-analyses which resulted in Boxed Warnings on the labeling of products containing an ICS/LABA.[61–64] In response to these findings, the FDA mandated conduct of several large clinical trials by the manufacturers to evaluate the risk of ICS/LABA therapy on serious asthma-related adverse effects. The results of these trials that included over 41,000 patients aged 12 and older, and a single trial in children 4 to 11 years old, indicate that there is no significantly increased risk of asthma-related hospitalizations, intubations, or asthma-related deaths with

ICS/LABA compared to ICS; the FDA has removed the Boxed Warning for ICS/LABA products but has retained it for single-ingredient LABA products[65]

Corticosteroids

4 The corticosteroids are the most effective anti-inflammatories available to treat asthma.[2,3] Actions useful in treating asthma include (a) increasing the number of β_2-adrenergic receptors and improving the receptor responsiveness to β_2-adrenergic stimulation, (b) reducing mucus production and hypersecretion, (c) reducing BHR, and (d) reducing airway edema and exudation.[3,66] The glucocorticoid receptor is found in the cytoplasm of most body cells, explaining the multiple effects of systemic corticosteroids. There is no difference between glucocorticoid receptors found throughout the body; however, genetic differences between glucocorticoid receptors from different individuals may determine some of the variations in response.[66] The corticosteroids are lipophilic, readily cross the cell membrane, and combine with the glucocorticoid receptor. The activated complex then enters the nucleus, where it acts as a transcription factor leading to gene activation or suppression.[67] This leads to specific mRNA production, resulting in increased production of anti-inflammatory mediators; suppression of several pro-inflammatory cytokines such as IL-1, GM-CSF, IL-4, IL-5, IL-6, and IL-8, reducing inflammatory cell activation, recruitment, and infiltration; and decreasing vascular permeability.[67] In addition, the activated glucocorticoid receptor complex can act directly with cytoplasmic transcription factors, nuclear factor-κB, and activating protein 1 to prevent the action of pro-inflammatory cytokines on the cell.[67]

Owing to the mechanism that modifies gene expression, the time required to see a particular effect depends on the time required for new protein synthesis, decreased formation of the particular mediator, and resolution of the inflammatory response.[67] Generally, the cellular and biochemical effects are immediate, but varying amounts of time are required to produce a clinical response. β_2-Receptor density increases within 4 hours of corticosteroid administration.[67] Improved responsiveness to β_2-agonists occurs within 2 hours.[67] In acute severe asthma, 4 to 12 hours may be required before any clinical response is noted.[67,68] Reversal of seasonally increased BHR requires at least 1 week of therapy.[67] The chronic use of corticosteroids does not induce a state of corticosteroid dependence, there is no evidence of tolerance produced by chronic administration.

The systemic and inhaled corticosteroids most commonly used in the treatment of asthma are compared in Table 43-10.[67,68]

TABLE 43-10 Pharmacodynamic/Pharmacokinetic Comparison of the Corticosteroids

Systemic	Anti-inflammatory Potency	Mineralocorticoid Potency	Duration of Biologic Activity (hours)
Hydrocortisone	1	1	8-12
Prednisone	4	0.8	12-36
Methylprednisolone	5	0.5	12-36
Dexamethasone	25	0	36-72
Inhaled	**Receptor Binding Affinity[a]**	**Oral Bioavailability (%)**	**Systemic Clearance (L/hr)**
Beclomethasone dipropionate/monoproprionate[b]	0.4/13.5	20/40	150/120
Budesonide	9.4	11	84
Ciclesonide/des-*ciclesonide*[b]	0.12/12	<1/<1	152/228
Flunisolide	1.8	20	58
Fluticasone proprionate	18	≤1	66
Mometasone furoate[c]	23	<1	53

[a]Receptor binding affinities are relative to dexamethasone equal to 1.

[b]Beclomethasone diproprionate and Ciclesonide are prodrugs that are activated in the lung to their active metabolites beclomethasone monopropionate and des-ciclesonide, respectively.

[c]Mometasone furoate studied in a different receptor system. Value estimated from relative values of beclomethasone dipropionate and fluticasone proprionate in that system.

Systemic Corticosteroids Systemic corticosteroids are indicated in all patients with acute severe asthma exacerbations not responding completely to initial inhaled β_2-agonist administration (every 20 minutes for three doses) and should be administered within 1 hour of presentation.[2,3] Clinical improvement is noted after approximately 4 hours. IV therapy offers no therapeutic advantage over oral administration except in patients who are too dyspneic to swallow, vomiting, or intubated.[2,3] This therapy usually is continued until hospital discharge. Tapering the systemic corticosteroid dose following discharge from the hospital appears unnecessary, provided that patients are prescribed ICSs for outpatient therapy.[3] Adults are effectively treated with a 5- to 7-day course of therapy but children typically require only 3 to 5 days.[2] It is recommended that a full dose of the corticosteroid be continued until the patient's PEF reaches 70% of predicted normal or personal best.[3] Dexamethasone as 1 or 2 days versus a 5-day course of

prednisone/prednisolone may be an option for children and has the benefit of causing less vomiting.[2,69]

Multiple daily dosing of systemic corticosteroids for the initial therapy of acute asthma exacerbations appears warranted because receptor binding affinities of lung corticosteroid receptors are decreased in the face of airway inflammation.[70] However, patients with less severe exacerbations may be treated adequately with once-daily administration. High-dose and very-high-pulse-dose corticosteroid regimens have not been shown to enhance the outcomes in severe acute asthma but are associated with a higher likelihood of side effects.[70]

ICSs initiated within 1 hour of presentation to the ED reduce hospitalization rate in those not treated with systemic corticosteroids.[2] However, current evidence suggests there is no rationale for combining inhaled and systemic therapy nor for replacing systemic with inhaled therapy.[2]

Besides acute severe asthma, systemic corticosteroids are also recommended for the treatment of impending episodes of severe asthma unresponsive to bronchodilator therapy.[2,3] The effects of corticosteroids in asthma are dose and duration dependent. This pattern is true for the adverse effects as well (**Table 43-11**). The clinician must continually balance the toxicity of chronic systemic corticosteroid therapy with control of asthma symptoms. Because short-term (1-2 weeks) high-dose corticosteroids (1-2 mg/kg/day of prednisone) do not produce serious toxicities, the ideal use is to administer the systemic corticosteroids in a short “burst” and then to maintain the patient on appropriate long-term control therapy with ICSs.[3] In general, therapy for more than 5 days at doses that exceed the usual physiologic endogenous cortisol production will cause temporary aberration in adrenal cortisol release.[67] However, this hypothalamic–pituitary–adrenal (HPA) axis suppression is short-lived (1-3 days) and readily reversible following short bursts (less than or equal to 10 days) of pharmacologic doses.[67] A maximum number of short bursts that a patient can receive probably exists, after which chronic corticosteroid side effects occur. Adult patients receiving at least eight bursts (more than or equal to 10 days each) have a similar decrease in trabecular bone density as patients on daily or alternate-day corticosteroids over 1 year.[66] Children who received four or more bursts per year of prednisone exhibited a subnormal response to hypoglycemic stress or adrenocorticotropic hormone (ACTH) administration.[67] Very short courses (3-5 days) have been effective in reducing hospitalization from acute exacerbations.[2,3] Use of the shorter-acting corticosteroids such as prednisone will produce less adrenal suppression than the longer-acting dexamethasone.[67]

TABLE 43-11 Adverse Effects of Chronic Systemic Glucocorticoid Administration

Hypothalamic–pituitary–adrenal suppression	Hypertension
Growth retardation	Skin striae
Skeletal muscle myopathy	Impaired wound healing
Osteoporosis/fractures	Inhibition of leukocyte and monocyte function
Aseptic necrosis of bone	Subcutaneous tissue atrophy
Pancreatitis	Glaucoma
Pseudotumor cerebri	Posterior subcapsular cataracts
Psychiatric disturbances	Moon facies
Sodium and water retention	Central redistribution of fat
Hypokalemia/hyperglycemia	

Inhaled Corticosteroids The principal advantage of the ICSs is their high topical potency to reduce inflammation in the lung and low systemic activity.[68] The ICSs have high anti-inflammatory potency, approximately 1,000-fold greater than endogenous cortisol, and differ from each other by as much as fourfold to sixfold.[68] However, potency differences, which are simply a measure of binding affinity to the receptor, can be overcome simply by giving different microgram dosages of drug (Table 43-10). Depending upon the microgram per inhalation, the potency differences between products will be reflected by the number of inhalations required to achieve the same therapeutic effect. Products that require more inhalations per dose or twice-daily versus once-daily treatment may result in poorer adherence.

Aerosol delivery of the preparations is remarkably variable, ranging from 10% to 60% of the nominal dose (ie, that dose which leaves an actuator for an MDI or, in the case of a DPI, which is released on actuation of the inhaler).[68] Different devices for the same chemical entity may result in twofold differences in delivery, so that delivery method can make a significant difference in the relative comparable dose or therapeutic index.[3,68]

The ICSs, beclomethasone dipropionate, budesonide, ciclesonide, flunisolide, fluticasone propionate, fluticasone furoate, and mometasone furoate, which are currently available for use, are compared and listed in Table 43-4. All are approved for once- or twice-daily dosing. The ICSs have pharmacokinetic differences that result in different topical/systemic activity.[68] Most evidence is consistent with log-linear dose–response curves for both indirect and direct responses. The log-linear nature of the dose–response curve for ICS activity raises the issue of how much of a difference in dose (or lung delivery) or potency

is detectable. The measures used to assess efficacy (lung function, BHR, symptoms, and as-needed short-acting inhaled β_2-agonist use) are downstream events from the anti-inflammatory activity. It takes a fourfold difference in potency or dose to detect clinically significant differences in efficacy.[38] The table of comparable ICS doses (see Table 43-4) is based on extensive clinical trial data.[2,68] Clinically comparable doses take into consideration drug potency differences as well as device delivery differences but not the potential for systemic activity.

Because the glucocorticoid receptors within the various tissues are the same, differences in the pharmacokinetic profile are required to produce differences in the topical/systemic effect ratio (therapeutic index).[68] Pharmacokinetic properties that enhance topical selectivity include rapid systemic clearance, poor oral bioavailability, and prolonged residence time in the lung.[68] Owing to their high lipophilicity, systemic clearance of the available ICSs is very rapid, approaching the rate of liver blood flow with the exception of ciclesonide, which is inactivated by blood esterases as well.[68] However, the ICSs differ markedly in their oral bioavailability, although they all undergo rather extensive first-pass metabolism to less active substances when absorbed.[68] The ICSs produce dose-dependent systemic effects, contributed by the orally absorbed fraction and the fraction absorbed from the lung.[3,68] (**Table 43-12**). Essentially, all the drug that reaches the lung is absorbed systemically; thus, a slow absorption from the lung results in an apparent long elimination half-life and enhances topical selectivity by lowering the systemic concentration.[68] Ciclesonide and beclomethasone dipropionate differ from the other ICSs, in that the parent compounds are prodrugs that are metabolized in the lung to the active compounds des-ciclesonide and beclomethasone monopropionate.[68] The potential advantage of the drugs with low oral bioavailability is obviated by using a spacer device with the MDI for the drugs with higher oral bioavailability because appropriate spacers reduce the oral amount delivered by 80%.[68] The use of VHCs also can increase systemic activity by increasing lung delivery of drugs not absorbed significantly orally.[68] If this increase in lung deposition is twofold or less, it will increase systemic activity without producing a clinically important increase in efficacy, thus decreasing the therapeutic index.[68] Mouth rinsing and spitting will also reduce the oral availability and are particularly useful for DPI devices.[3,68] Although ciclesonide and its active metabolite have rapid systemic clearance suggesting an improved therapeutic index, it has not yet been clearly established in clinical trials.[68]

TABLE 43-12 Effects of Inhaled Corticosteroids

Beneficial Effects	Potential Adverse Effects
Decrease eosinophil numbers	Hoarseness, dysphonia, thrush
Decrease mast cell numbers	Growth retardation, skeletal muscle myopathy
Decrease T-lymphocyte cytokine production	Osteoporosis, fractures, and aseptic necrosis of hip
Inhibit transcription of inflammatory genes in airway epithelium	Posterior subcapsular cataract formation and glaucoma
Reduce endothelial cell leak	Adrenal axis suppression, immunosuppression
Upregulate β_2-receptor production	Impaired wound healing, easy bruising, skin striae
Reduce airway epithelial subbasement membrane thickening	Hyperglycemia/hypokalemia, hypertension
	Psychiatric disturbances

The response to ICSs is somewhat delayed. Most patients' symptoms will improve in the first 1 to 2 weeks of therapy and will reach maximum improvement in 4 to 8 weeks.[3] Improvement in baseline FEV_1 and PEF may require 3 to 6 weeks for maximum improvement, whereas improvement in BHR requires 2 to 3 weeks and approaches maximum in 1 to 3 months but may continue to improve over 1 year.[3] Most of the improvement in these parameters occurs at low-to-medium doses, and there is a large variability in response, with 10% of patients not demonstrating an improvement in either parameter.[3] Significant decreases in FeNO occur within 1 to 2 days with maximum effect in 2 to 3 weeks. Sensitivity to exercise challenge decreases after 4 weeks of therapy.[19] Although single doses do not inhibit the immediate asthmatic response to antigen challenge or exercise, continued therapy for 1 week partially suppresses the response. The two latter effects are likely due to a reduction in mucosal mast cells.[3]

Local adverse effects from ICSs include oropharyngeal candidiasis and dysphonia that are dose dependent. The dysphonia (reported in 5%-20% of patients) appears to be due to a local corticosteroid-induced myopathy of the vocal cords.[3] The use of a spacer device with MDIs can decrease oropharyngeal deposition and thus decrease the incidence and severity of local side effects.[2,3] In infants who require ICS delivery through a face mask, the parent should clean the nasal–perioral area with a damp cloth following each treatment to prevent oropharyngeal candidiasis.

Systemic adverse effects can occur with any of the ICSs given in a

sufficiently high dose.[2,3] Long-term adverse effects of greatest concern include growth suppression in children, osteoporosis, cataracts, dermal thinning, and adrenal insufficiency and crisis.[3,68] Of these, only growth retardation occurs in low-to-medium doses. However, the growth reduction appears to be transient, in that growth velocity is reduced in the first 6 months to 2 years of therapy and then returns to normal.[3,68] The effect is small (1-2 cm total) and not cumulative, but does persist into adulthood.[71] The suppression of the HPA axis and decreased bone mineralization are dose dependent and do not appear to be significant clinically except at high doses.[39] The risks therefore depend on the therapeutic index of each ICS and its delivery device. The effect of delivery device is illustrated by fluticasone propionate, which has both the greatest therapeutic index when administered by DPI and the lowest therapeutic index when administered by MDI plus VHC.[68] Many of the ICSs, including fluticasone propionate, budesonide, ciclesonide, and mometasone furoate, are metabolized in the GI tract and liver by cytochrome (CYP) 3A4 isoenzymes. Potent inhibitors of CYP3A4 such as ritonavir and ketoconazole have the potential for increasing systemic concentrations of these ICSs by increasing oral availability and decreasing systemic clearance.[68] Some cases of clinically significant Cushing's syndrome and secondary adrenal insufficiency have been reported.[68]

Most patients with moderate disease can be controlled with twice-daily dosing of most ICSs.[2,3,68] In milder asthma, once-daily dosing is often sufficient to maintain control.[68] Once-daily dosing may be suitable, particularly in mild asthma, once initial control is established.[68] There is no specific pharmacologic or pharmacokinetic aspect of the current ICSs that allows for once-daily dosing because all the agents studied (both the older low-potency ICSs and newer high-potency ICSs) have been effective, provided that patients had relatively mild-to-moderate asthma.[68] More severe patients may require multiple daily dosing. The inflammatory response of asthma has been shown to inhibit corticosteroid-receptor binding.[68] Once asthma is controlled, many patients are able to reduce the ICS dose and maintain control.[68]

There has been interest in using ICSs as needed or intermittently alone or in combination with a LABA with mild persistent asthma. The available data indicate that as-needed use of ICS with or without a LABA has a similar effect on reducing exacerbations compared to regular ICS use but has a less beneficial effect on daily asthma control.[72–75] The as-needed regimen may reduce exposure to ICS by as much as 75% compared with the regular daily ICS regimen and this reduced ICS exposure and subsequent reduced medication cost may be an

attractive compromise to having less well-controlled daily symptoms for some patients.[73,74]

Anticholinergics

The anticholinergic agents have a long history of use for asthma, with an evolving role in the management of asthma.[2,3,76] Anticholinergics are competitive inhibitors of muscarinic receptors.[76] Unlike β_2-agonists, they are not functional antagonists; they only reverse cholinergic-mediated bronchoconstriction. Normal bronchial tone is maintained through parasympathetic innervation of the airways via the vagus nerve.[76] A number of the triggers and mediators of asthma (ie, histamine, prostaglandins, sulfur dioxide, exercise, and allergens) produce bronchoconstriction in part through vagal reflex mechanisms.[76] Studies consistently demonstrate that anticholinergics are effective bronchodilators in asthma. Anticholinergics attenuate but do not block allergen-induced asthma in a dose-dependent fashion and have no effect on BHR.[76] Anticholinergics attenuate but do not block EIB.[19] Five muscarinic receptor subtypes (M_1 through M_5), all inhibited by atropine, have been identified; M_1, M_2, and M_3 are the principal receptors in the airway.[76]

Ipratropium bromide is a nonselective antagonist of M_1, M_2, and M_3 receptors. Although ipratropium produces net bronchodilation, blockade of M_2 receptors allows further release of presynaptic acetylcholine, and may antagonize the bronchodilatory effect of blocking M_3, a possible basis of paradoxical bronchoconstriction.[76] Only the quaternary ammonium derivatives such as ipratropium bromide and tiotropium should be used because they have the advantage of little absorption across respiratory mucosa and do not penetrate the blood–brain barrier. This attribute contributes to negligible systemic effects with a prolonged local effect (ie, bronchodilation). In addition, the quaternary compounds do not appear to significantly alter mucociliary clearance or respiratory secretions.[76] Ipratropium bromide has duration of action of 4 to 8 hours. Both intensity and duration of action are dose dependent. Time to reach maximum bronchodilation for ipratropium is considerably slower than for aerosolized short-acting β_2-agonists (30-60 minutes vs 5-10 minutes). However, this difference is of little clinical consequence because some bronchodilation is seen within 30 seconds; 50% of maximum response occurs within 3 minutes.[76] Ipratropium bromide is only indicated as adjunctive therapy in acute severe asthma not completely responsive to β_2-agonists alone.[2,3]

Inhaled ipratropium bromide produces a further improvement in lung function of 10% to 15% over inhaled β_2-agonists alone in the management of acute asthma in the ED setting. In children and adults, multiple-dose ipratropium bromide added to initial therapy reduces hospitalization rate in the subset of patients with moderate-to-severe asthma exacerbations.[2] However, there is no benefit to continuing combined anticholinergic and β_2-agonist therapy during hospitalization on duration of stay or clinical outcomes.[53] Ipratropium bromide, a quaternary amine, is poorly absorbed and produces minimal or no systemic effects.[77] Care should be taken when administering ipratropium bromide by nebulizer. If a tight mask or mouthpiece is not used, the ipratropium bromide that deposits in the eyes may produce pupillary dilation and difficulty in accommodation.[3]

Tiotropium bromide, a long-acting inhaled anticholinergic with duration of 24 hours, has a higher affinity for muscarinic receptors than ipratropium; it dissociates from muscarinic receptors more slowly than ipratropium.[76] Tiotropium may be considered an add-on therapy in patients 12 years and older whose asthma is not well controlled with a medium-to-high dose of ICS and LABA combination therapy. The addition of tiotropium modestly improves lung function but, more importantly, increases the time to severe exacerbation requiring oral corticosteroid treatment.[2]

Leukotriene Modifiers

Two cysteinyl LTRAs (zafirlukast and montelukast) and one 5-lipoxygenase inhibitor (zileuton) are available in the United States.[78] In challenge studies, they reduce allergen-, exercise-, cold-air hyperventilation-, irritant-, and aspirin-induced asthma.[78] Clinical use of zileuton is limited due to the potential for elevated liver enzymes (especially in the first 3 months of therapy), and the potential inhibition of drugs metabolized by the CYP3A4 isoenzymes.[78] They are not preferred alternatives in mild persistent asthma or as an alternative add-on therapy for moderate persistent asthma (see Tables 43-3 and 43-5).[2]

These drugs improve pulmonary function tests (FEV_1 and PEF), decrease nocturnal awakenings and β_2-agonist use, and improve asthma symptoms.[78] A major advantage is that they are effective orally, and can be administered once or twice a day.[78] However, they are less effective in asthma than low doses of ICSs.[2,3,35] Although montelukast is approved for EIB in adults, it is significantly less effective than short-acting inhaled β_2-agonists.[19] In adults with severe

uncontrolled asthma they do not improve outcomes.[78] They are not as effective as LABAs when added to ICSs for moderate persistent asthma.[78] It is not yet possible to predict which patients respond best to LT modifiers, although there is some evidence that patients with aspirin-sensitive asthma do well, as predicted by studies showing increased cysteinyl LT production in these patients.[78] It is possible that genetic polymorphisms in the 5-lipoxygenase or LTC_4 synthase pathways or in cys-LT_1 receptors might predict better responders in the future.[78] LTRAs also have modest efficacy in allergic rhinitis.

In general, the LTD_4 receptor antagonists are well tolerated and do not appear to have serious class-specific effects.[3] An idiosyncratic syndrome similar to the Churg–Strauss syndrome, with marked circulating eosinophilia, heart failure, and associated eosinophilic vasculitis, has been reported in a small number of patients treated with zafirlukast and montelukast.[79] The majority of these patients had been receiving high-dose ICS or oral corticosteroids and were able to reduce the dose as a consequence of the LTD_4 receptor antagonists. It is unclear whether the increased reports are due to increased case findings among patients with asthma prescribed a new drug or whether the syndrome is related to corticosteroid dose reduction or an idiosyncratic effect of LTRAs in general. Whatever the cause, it appears to be a rare syndrome, with an estimated incidence of less than 1 case per 15,000 to 20,000 patient-years of treatment.[79]

Reports of adverse neuropsychiatric events caused the manufacturers of the LT inhibitors to revise their labeling in 2008. In children, the relative risk of neuropsychiatric adverse reactions associated with montelukast is 12 times greater than ICS.[80] The risks are greatest within a few weeks of starting therapy, resulting in approximately 16% of children discontinuing therapy. Therefore, patients should be closely monitored when initiating treatment with montelukast.[80] The most frequent reported reactions are irritability, aggressiveness, and sleep disturbance; suicidality, though rare, has also been reported.[80–82] Reports of fatal hepatic failure associated with zafirlukast have prompted a warning for patients to be made aware of signs and symptoms of hepatic dysfunction.[3]

Zileuton can be administered twice daily as controlled-release tablets.[3] Efficacy data are more limited, liver function monitoring is recommended, and drug interactions are reported with warfarin and theophylline.

Biologic Agents

Table 43-13 outlines the current biologic agents either FDA approved or in trials, as well as the biomarkers predicting therapeutic responses and the biomarkers modulated by therapy.[83–85] Omalizumab was approved by the FDA in 2003 and the newer biologics are the first new drugs for asthma in over a decade. These agents are targeting the IgE pathway (relevant to allergic asthma) or IL-4, IL-13, and IL-5 pathways (relevant to the Th2 pathway and eosinophilic disorders) and are indicated for patients with moderate or severe asthma (depending upon the drug) along with other biomarker or other clinical indicator associated with treatment response. One investigational product, tezepelumab, blocks TSLP and is potentially a first in class drug.

TABLE 43-13 Targeted Biologic Therapies for Asthma and Potential Biomarkers

Pathway	Biologic Agents Approved	Biomarkers Predicting Therapeutic Response	Route of Administration
IgE	Omalizumab (Xolair®)	FeNO Blood eosinophils	Subcutaneous
IL-5	Mepolizumab (Nucala®) Reslizumab (Cinqair®)	Blood eosinophils	Mepolizumab: subcutaneous Reslizumab: intravenous
IL-5Rα	Benralizumab (Fasenra®)	Blood eosinophils	Subcutaneous
IL-4Rα (IL-4/ IL-13)	Dupilumab (Dupixent®)	Blood eosinophils	Subcutaneous
	Biologic Agents in Trials (Phase 3)		
TSLP	Texepelumab	–	Subcutaneous
CRTh2	Fevipiprant	–	Oral
IL-25	ABN125	–	Intravenous

CRTh2, chemoattractant receptor-homologous molecule expressed on Th2 cells; FeNO, fraction of exhaled nitric oxide; Ig, immunoglobulin; IL, interleukin; R, receptor; TSLP, thymic stromal lymphopoietin.

Data from Reference 18.

These products are typically reserved for patients with moderate-to-severe persistent asthma who have been treated with dual therapy with ICS/LABA or triple therapy such as with ICS/LABA+LAMA and remain poorly controlled. Defining which patients have severe asthma and are candidates for biologic therapy consideration is important. The American Thoracic Society (ATS) defines refractory or severe asthma on the basis of two major and seven minor criteria.[86] To meet the ATS definition, patients must have one of the two major criteria (OCS for greater than 50% of past year or continuous high-dose ICS)

and two of the seven minor criteria (concurrent use of greater than or equal to 1 other controller, daily symptoms requiring SABA, FEV_1 less than 80% predicted, greater than or equal to 1 urgent care visits in past year, greater than or equal to three OCS bursts in past year, deterioration with decrease in corticosteroid dose of 25%, and history of near-fatal event). This definition of severe asthma may include patients with good disease control and focuses on the need of high doses of corticosteroids; the NLHBI Severe Asthma Research Program uses these criteria as do many of the pharmaceutical manufacturers developing drugs to meet the unmet need of the severe disease phenotype.[83] Gaps still remain about the determinants of severe asthma in children, and trials of novel therapeutic strategies for severe asthma in childhood populations are essential to guide therapy rather than reliance of extrapolation of results from trials conducted in adults.[87]

Anti-IgE (Omalizumab) Omalizumab is a recombinant anti-IgE antibody approved for the treatment of allergic asthma not well controlled on oral corticosteroids or ICSs.[88] It is a composite of 95% human and 5% antihuman murine IgE sequences. Omalizumab binds to the Fc portion of the IgE antibody preventing the binding of IgE to its high-affinity receptor (FcεRI) on mast cells and basophils. The decreased binding of IgE on the surface of mast cells leads to a decrease in the release of mediators in response to allergen exposure. Omalizumab also decreases FcεRI expression on basophils and airway submucosal mast cells over 8 to 12 weeks.[88]

Omalizumab is administered subcutaneously and the dosage is determined by the patient's baseline total serum IgE level (international units per milliliter [kIU/L]) and body weight (kilograms).[88] Doses range from 150 to 375 mg and are given at either 2- or 4-week intervals. No further adjustments for variations in total serum IgE are required, and patients receive a consistent dose for the duration of treatment.[86] Omalizumab is currently recommended for the treatment of patients greater than 6 years of age with moderate-to-severe asthma, which is not adequately controlled by ICS, ICS/LABA, and in some cases, OCS. Elevated levels of FeNO at 19.5 ppb or greater are predictive of an exacerbation rate reduction of approximately 50%.[40] In those with lower FeNO but eosinophil counts of at least 260 cell/μL (0.26×10^9/L), the exacerbation rate is reduced by approximately 30%.[40] Clinical trials that have included children less than 12 years with allergic asthma and poor disease control demonstrate nearly complete elimination of the spring and fall exacerbations.[40]

Anti-IL-5 (Mepolizumab, Reslizumab, Benralizumab) Mepolizumab and reslizumab target IL-5 that regulates the terminal differentiation of eosinophils as well as eosinophil activation and recruitment to the airway.[40] These drugs are monoclonal antibodies directed against IL-5 to block activation of the IL-5 receptor on eosinophils. Benralizumab binds to the alpha subunit of the IL-5 receptor of eosinophils and prevents binding of IL-5, thus mitigating downstream eosinophilic inflammation.[18]

Mepolizumab and benralizumab are approved for patients with severe asthma aged 12 years and older and are administered subcutaneously; reslizumab is approved for those with severe asthma 18 years and older and is administered intravenously. Mepolizumab and reslizumab are dosed every 4 weeks; benralizumab is dosed every 4 weeks for 3 months then every 8 weeks. Doses are to be administered in a healthcare setting by professionals who are prepared to manage anaphylaxis. Each of these drugs are indicated for patients with an "eosinophilic phenotype" which has not been formally defined by the FDA or any professional society. However, reductions in exacerbation rate of approximately 50% is observed when patients have a certain minimum peripheral blood eosinophil count that varies by drug.[18,40] Blood eosinophil counts correlate reasonably well with sputum (airway) eosinophil numbers (airway eosinophils are the ideal biomarker but difficult to measure clinically) in moderate persistent asthma, but correlate less well in patients who are on maintenance oral corticosteroids, indicating that additional mechanisms of inflammation are active in these patients.[18] Responsiveness to exacerbation reduction appears to be more likely with blood eosinophil levels above 150 cells/μL (0.15×10^9/L) with mepolizumab, above 400 cells/μL (0.4×10^9/L) with reslizumab, and above 300 cells/μL (0.3×10^9/L)for benralizumab.[18,40] Patients aged 50 years or older who are to be treated with mepolizumab should receive a recombinant zoster vaccination (preferably not live virus) 4 weeks prior to starting treatment.[18] Reslizumab labeling includes a Boxed Warning for anaphylaxis. Mepolizumab and benralizumab have been studied in patients who require daily oral corticosteroid therapy with benefits noted in reduced exacerbation rate while also having an oral corticosteroid sparing effect.[18]

Anti-IL-4/IL-13 (Dupilumab) Dupilumab targets the IL-4α receptor, thus blocking IL4 and IL-13 signaling which are key cytokines that promote IgE synthesis and inflammatory cell recruitment. Dupilumab is approved for patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype and is administered subcutaneously every 2 weeks. Unlike

mepolizumab, reslizumab, and benralizumab, FeNo levels above 25 ppb in addition to blood eosinophil levels of at least 150 cells/μL (0.15×10^9/L) is predictive of a response in reducing asthma exacerbation rate by approximately 50%; in those on maintenance oral corticosteroids, it reduces exacerbation rate and maintenance oral corticosteroid doses.[40]

Magnesium Sulfate

Intravenous and nebulized magnesium sulfate have been used in addition to standard therapies (β_2-agonists, systemic corticosteroids, anticholinergics, and oxygen) in children and adults with severe or life-threatening asthma. Magnesium sulfate is a moderately potent bronchodilator, producing relaxation of smooth muscle by blocking calcium ion influx into smooth muscles and it may have anti-inflammatory effects.[89] A meta-analysis found strong evidence that single infusion of 1.2 or 2 g magnesium sulfate administered to adults with moderate, severe, or life-threatening asthma who had not sufficiently responded to β_2-agonists, systemic corticosteroids, and oxygen reduced hospital admission rate (seven fewer admissions per 100 treated) and improved lung function.[90] Previous meta-analyses have shown inconsistent effects in adults on respiratory function and hospitalization rate when administered by the intravenous or nebulized route, but it was not clear if magnesium sulfate was given concurrently with standard therapy or after failure to respond to standard therapy.[91,92] There are fewer studies in children with severe or life-threatening asthma, though one meta-analysis found that intravenous use improved respiratory function and reduced hospitalizations but again it was not clear exactly when in the course of care magnesium was administered.[92] For patients with severe asthma exacerbations, current guidelines suggest that a single 2 g intravenous infusion can be helpful in reducing hospital admissions in adults who have a FEV_1 less than 25% to 30% predicted upon arrival in the ED, children and adults who have persistent hypoxemia after standard treatment, and children whose FEV_1 remains below 60% predicted after 1 hour of standard treatment.[2] The adverse effects of magnesium sulfate include hypotension, facial flushing, sweating, depressed deep tendon reflexes, hypothermia, cardiac, and CNS and respiratory depression.

Methylxanthines

Methylxanthines have been used for asthma therapy for more than 50 years, but

are rarely used owing to the high risk of severe life-threatening toxicity and numerous drug interactions, as well as decreased efficacy compared with ICSs, LABAs, and biologics.[93] Theophylline, the primary methylxanthine of interest, is a moderately potent bronchodilator with mild anti-inflammatory properties and is available for oral and intravenous administration.[3]

Theophylline has a log-linear dose–response curve and dosing requires monitoring of blood concentrations for both efficacy and toxicity (excessive blood concentrations can cause seizures and death).[2,3,79] See **Figure 43-8**. In addition, theophylline is eliminated primarily by metabolism via the hepatic CYP P450 mixed-function oxidase microsomal enzymes (primarily the CYP1A2 and CYP3A4 isozymes), and drug interactions affecting metabolism will significantly affect blood concentrations.[93,94] See **Table 43-14**.

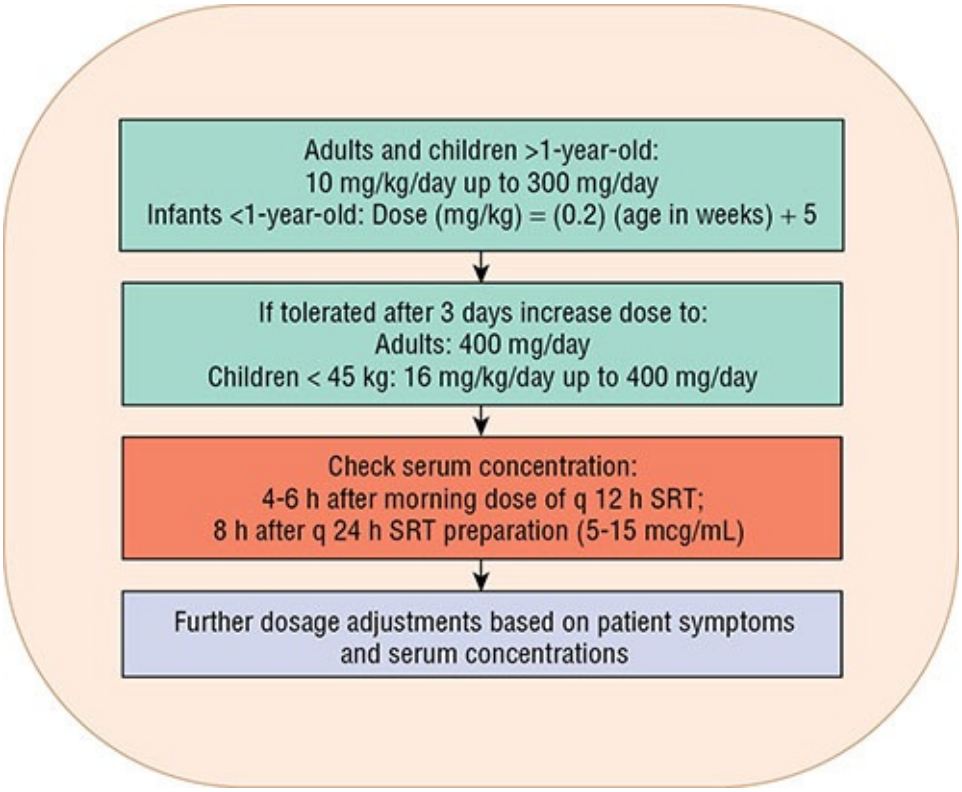


FIGURE 43-8 Algorithm for slow titration of theophylline dosage and guide for final dosage adjustment based on serum theophylline concentration measurement. For infants younger than 1 year of age, the initial daily dosage can be calculated by the following regression equation: Dose (mg/kg) = (0.2) (age in weeks) + 5. Whenever side effects occur, dosage should be reduced to a previously tolerated lower dose.

TABLE 43-14 Factors Affecting Theophylline Clearance

Decreased Clearance	% Decrease	Increased Clearance	% Increase
Cimetidine	−25 to −60	Rifampin	+53
Macrolides: erythromycin, TAO, clarithromycin	−25 to −50	Carbamazepine Phenobarbital Phenytoin	+50 +34 +70
Allopurinol	−20	Charcoal-broiled meat	+30
Propranolol	−30		
Quinolones ciprofloxacin, enoxacin, perfloxacin	−20 to −50	High-protein diet Smoking	+25 +40
Interferon	−50	Sulfinpyrazone	+22
Thiabendazole	−65	Moricizine	+50
Ticlopidine	−25	Aminoglutethimide	+50
Zileuton	−35		
Systemic viral illness	−10 to −50		

Alternative Therapies

The inhalational anesthetics halothane, isoflurane, and enflurane all have been reported to have a positive effect in children and adults with acute severe asthma on mechanical ventilation that is unresponsive to standard medical therapy.[95] The proposed mechanisms for inhalational anesthetics include β_2-adrenergic receptor stimulation, direct relaxation on bronchial smooth muscle, inhibition of airway reflexes, attenuation of histamine-induced bronchospasm, and alteration of the nitric oxide pathway in epithelial cells.[95] Well-controlled trials with these agents have not been completed.[95] Potential adverse effects include myocardial depression, vasodilation, arrhythmias, and depression of mucociliary function.[95] In addition, the practical problem of delivery and scavenging these agents in the intensive care environment as opposed to the operating room and the avoidance of environmental pollution to treating caregivers is a concern. The use of volatile

anesthetics cannot be recommended based on insufficient evidence of efficacy.

Ketamine has been recommended for rapid induction of anesthesia in patients with asthma who require intubation and mechanical ventilation.[96] In addition, intravenous ketamine has been used as a bolus followed by continuous infusion in both intubated and nonintubated patients with severe asthma exacerbations but controlled trials have not provided evidence of efficacy.[3] Purported mechanisms for beneficial effects in asthma include inhibition of histamine and acetylcholine-induced bronchoconstriction and acting as a sympathomimetic agent.[3] Ketamine has several significant adverse effects, including the anesthesia emergence reaction, which can alter mood and cause delirium. These emergence phenomena occur in at least 25% of patients over 16 years of age; the incidence seems to be much lower in younger patients.[3] Other adverse effects include hypertension and sinus tachycardia or hypotension and sinus bradycardia.

EVALUATION OF THERAPEUTIC OUTCOMES

The two key components of effective asthma control are “symptom control” and “future risk of adverse outcomes.”[2] Symptom control is assessed by inquiring about frequency of daytime and nighttime asthma symptoms, reliever medication use, and activity limitations; poor symptom control is also an indicator of future risk for exacerbations.[2] However, even when perceived symptom control is good, assessments of future risk of exacerbations, airflow limitation (which may be under-perceived by patients), and medication adverse effects need to be assessed.[2]

Future risk of adverse outcomes includes assessment of the risk of future exacerbations, fixed airflow limitation (and thus diminished response to therapy), and medication adverse effects.[2] To assess the risk for future exacerbations (with exacerbation defined as a worsening of asthma requiring the use of systemic corticosteroids or an increase in the use of systemic corticosteroids for patients on a stable maintenance dose to prevent a serious outcome), lung function should be measured before the start of treatment and then 2 months later when maximum response to controller medications is likely attained.[2,97,98] This benchmark of “personal best” can then be used for ongoing risk assessment. Other factors that affect future risk of exacerbations include exacerbation history in the previous year (one or more exacerbations requiring systemic corticosteroids is a risk factor) or intubation or intensive care unit stay for asthma as well as ED visits for urgent care.[2,98] Fixed airflow limitation can

be affected by lack of ICS treatment, smoking exposure, and low lung function. During ongoing care, spirometry should be measured yearly but PEF monitoring is typically reserved for those with severe asthma.[2] Adverse effect risks are influenced by oral and ICS dose and potential drug interactions with cytochrome P450 inhibitors.[2] In addition, poor inhaler technique (such as not rinsing and spitting after ICS use) can lead to oral candidiasis or an increase in the swallowed fraction of the dose that could influence linear growth in children.

There are several simple screening questionnaires that can be used to assess asthma symptom control quickly in a clinic setting. The Asthma Control Test is a validated simple five-question survey for patients 12 years and older that yields a numerical score; a score of 19 or less indicates poor asthma control and several institutions have incorporated the survey into the electronic health record in order to evaluate changes over time.[99,100] There is a companion Childhood Asthma Control Test survey for children 4 to 11 years.[99,100] A number of other validated questionnaires exist such as the Asthma Therapy Assessment Questionnaire (ATAQ) and the Asthma Control Questionnaire (ACQ).[99,100]

Patients should also be asked about exercise tolerance as perceived good exercise tolerance may be biased by a sedentary lifestyle adapted to the frequency of bothersome symptoms. All patients on inhaled drugs should have their inhalation delivery technique evaluated periodically—monthly initially and then every 3 to 6 months. Before stepping up therapy, adherence, environmental control, and comorbid conditions should be reviewed.[2]

Following initiation of anti-inflammatory therapy or an increase in dosage, most patients should begin experiencing a decrease in symptoms in 1 to 2 weeks and achieve maximum symptomatic improvement within 4 to 8 weeks. The use of higher ICS doses or more potent agents may accelerate the process. Improvement in FEV_1 and PEF should follow a similar time frame; however, a decrease in BHR, as measured by morning PEF, PEF variability, and exercise tolerance, may take longer and improve over 1 to 3 months.[2] Patients should be informed that following a viral respiratory infection, they may experience decreased exercise tolerance for up to 4 weeks.

Initial visits with the patient should focus on the patient's concerns, expectations, and goals of treatment. Basic education should focus on asthma as a chronic lung disease, the types of medications, and how they are to be used. Inhaler technique is taught, as is when to seek medical advice. Written action plans should be provided. Both peak flow-based or symptom-based self-monitoring can be effective, if taught and followed correctly.[2] The first follow-

up visit should include repetition of the educational messages from the first visit, as well as review of the patient's current medications, adherence, and any difficulties related to the therapy.

CONCLUSION

Asthma is a complex disease with a multitude of clinical presentations. The exact defect in asthma has not been defined, and it may be that asthma is a common presentation of a heterogeneous group of diseases. Asthma is defined and characterized by excessive reactivity of the bronchial tree to a wide variety of noxious stimuli. The reaction is characterized by bronchospasm, excessive mucus production, and inflammation. The central role of inflammation in inducing and maintaining BHR is now becoming widely appreciated. The goal of asthma therapy is to normalize, as much as possible, the patient's life and prevent chronic irreversible lung changes. Drugs are the mainstay of asthma management. The goal of drug therapy is to use the minimum amount of medications possible to control the disease. In persistent asthma, therapy should be aimed at both bronchospasm and inflammation in order to produce the best results. Patients should be followed and monitored diligently for toxicities. Although death from asthma is an uncommon event, the most common cause of death is under-estimating the severity of obstruction either by the patient or by the clinician; the next common cause is under-treatment. A cornerstone of therapy is education and the realization that most asthma deaths are avoidable.

Postclass Engaged Learning Activity

Identify the drug classes used as controller therapy in the treatment of asthma. Construct a table that describes the pathophysiologic mechanism that is targeted by each class in the treatment of asthma. Then provide a rationale for combining the different drugs (single, dual, triple, or more) in patients with moderate or severe persistent asthma. This exercise is designed to reinforce student understanding of the place in therapy for different therapeutic classes of asthma medications.

ABBREVIATIONS

ACOS	Asthma COPD Overlap Syndrome
ACQ	Asthma Control Questionnaire
ACTH	adrenocorticotropic hormone
Arg	arginine
ATAQ	Asthma Therapy Assessment Questionnaire
BHR	bronchial hyper-responsiveness
CFC	chlorofluorocarbon
COPD	chronic obstructive pulmonary disease
CYP	cytochrome P450
DPI	dry powder inhaler
ED	emergency department
EIB	exercise-induced bronchospasm
EPR3	Expert Panel Report 3
FeNO	fraction of exhaled nitric oxide
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GERD	gastroesophageal reflux disease
GINA	Global Initiative for Asthma
GM-CSF	granulocyte-macrophage colony-stimulating factor
HFA	hydrofluoroalkane
HPA	hypothalamic–pituitary–adrenal
ICAM-1	intercellular adhesion molecule 1
ICS	inhaled corticosteroid
IFN-γ	interferon-γ
IgE	immunoglobulin E
IL	interleukin
iNOS	inducible nitric oxide synthase
LABA	long-acting inhaled β_2-agonist
LAMA	long-acting muscarinic antagonist
LT	leukotriene
MDI	metered-dose inhaler
MMAD	mass median aerodynamic diameter
NAEPP	National Asthma Education and Prevention Program
NANC	nonadrenergic, noncholinergic
NO	nitric oxide
O_2	oxygen
PAF	platelet-activating factor
PEF	peak expiratory flow

RCT	randomized controlled trial
RSV	respiratory syncytial virus
SABA	short-acting beta-agonist
T cells	thymically derived lymphocytes
Th_1	type 1 T-helper cell
Th_2	type 2 T-helper cell
TSLP	thymic stromal lymphopoietin
VCAM-1	vascular cell adhesion molecule 1
VHC	valved holding chamber
VIP	vasoactive intestinal peptide

REFERENCES

1. Rosenblatt MB. History of bronchial asthma. In: Weiss EB, Segal MS, eds.*Bronchial Asthma: Mechanisms and Therapeutics*. 2nd ed. Boston: Little, Brown; 1976:5–17.
2. Global Initiative for Asthma. *Global Strategy for Asthma Management and Prevention;* 2018. Available at: http://www.ginasthma.org/. Accessed August 3, 2018.
3. *National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the diagnosis and management of asthma*. Bethesda, MD: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute, publication no. 08-4051; 2007.
4. Centers for Disease Control and Prevention. *Most Recent Asthma Data;* 2018. Available at: https://www.cdc.gov/asthma/most_recent_data.htm. Accessed November 15, 2018.
5. Centers for Disease Control and Prevention. *Data, Statistics, and Surveillance: Asthma Surveillance Data*; 2016. Available at: https://www.cdc.gov/asthma/asthmadata.htm. Accessed November 15, 2018.
6. Asher I, Pearce N. Global burden of asthma among children. *Int J Tuberc Lung Dis*. 2014;18:1269–1278.
7. Nurmagambetov T, Kuwahara R, Garbe P. The Economic Burden of Asthma in the United States, 2008–2013. *Ann Am Thorac Soc*. 2018;15:348–356.
8. American Lung Association, Epidemiology and Statistics Unit, RaHED.

Trends in Asthma Morbidity and Mortality. American Lung Association; 2015.

9. Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. *Lancet*. 2018;391:783–800.
10. Ebmeier S, Thayabaran D, Braithwaite I, Benamara C, Weatherall M, Beasley R. Trends in international asthma mortality: Analysis of data from the WHO Mortality Database from 46 countries (1993-2012). *Lancet*. 2017;390:935–945.
11. Melen E, Pershagen G. Pathophysiology of asthma: Lessons from genetic research with particular focus on severe asthma. *J Intern Med*. 2012;272:108–120.
12. Gelfand EW. Pediatric asthma: A different disease. *Proc Am Thorac Soc*. 2009;6:278–282.
13. van Tilburg Bernardes E, Arrieta MC. Hygiene hypothesis in asthma development: Is hygiene to blame? *Arch Med Res*. 2017;48:717–726.
14. Dykewicz MS. Occupational asthma: Current concepts in pathogenesis, diagnosis, and management. *J Allergy Clin Immunol*. 2009;123:519–528. quiz 29-30.
15. Jartti T, Gern JE. Role of viral infections in the development and exacerbation of asthma in children. *J Allergy Clin Immunol*. 2017;140:895–906.
16. Murdoch JR, Lloyd CM. Chronic inflammation and asthma. *Mutat Res*. 2010;690:24–39.
17. Gauthier M, Ray A, Wenzel SE. Evolving concepts of asthma. *Am J Respir Crit Care Med*. 2015;192:660–668.
18. McGregor MC, Krings JG, Nair P, Castro M. Role of biologics in asthma. *Am J Respir Crit Care Med*. 2018.
19. Parsons JP, Hallstrand TS, Mastronarde JG, et al. An official American Thoracic Society clinical practice guideline: Exercise-induced bronchoconstriction. *Am J Respir Crit Care Med*. 2013;187:1016–1027.
20. Fahy JV. Eosinophilic and neutrophilic inflammation in asthma: Insights from clinical studies. *Proc Am Thorac Soc*. 2009;6:256–259.
21. An SS, Bai TR, Bates JH, et al. Airway smooth muscle dynamics: A common pathway of airway obstruction in asthma. *Eur Respir J*. 2007;29:834–860.
22. Haccuria A, Michils A, Michiels S, Van Muylem A. Exhaled nitric oxide:

A biomarker integrating both lung function and airway inflammation changes. *J Allergy Clin Immunol*. 2014;134:554–559.

23. Wang Z, Pianosi PT, Keogh KA, et al. The diagnostic accuracy of fractional exhaled nitric oxide testing in asthma: A systematic review and meta-analyses. *Mayo Clin Proc*. 2018;93:191–198.
24. D'Amato G, Holgate ST, Pawankar R, et al. Meteorological conditions, climate change, new emerging factors, and asthma and related allergic disorders: A statement of the World Allergy Organization. *World Allergy Organ J*. 2015;8:25.
25. Dixon AE, Castro M, et al. American Lung Association-Asthma Clinical Research Centers' Writing Committee. Efficacy of nasal mometasone for the treatment of chronic sinonasal disease in patients with inadequately controlled asthma. *J Allergy Clin Immunol*. 2015;135:701–709. e5.
26. American Lung Association Asthma Clinical Research Centers, Mastronarde JG, Anthonisen NR, et al. Efficacy of esomeprazole for treatment of poorly controlled asthma. *N Engl J Med*. 2009;360:1487–1499.
27. Brenner BE, Holmes TM, Mazal B, Camargo CA, Jr. Relation between phase of the menstrual cycle and asthma presentations in the emergency department. *Thorax*. 2005;60:806–809.
28. National Institutes of Health, Lung, Blood Institute. NAEPP Expert Panel Report Managing Asthma During Pregnancy: Recommendations for Pharmacologic Treatment—Update 2004. NIH Publication No. 04-5246. 2004.
29. Brehm JM, Schuemann B, Fuhlbrigge AL, et al. Serum vitamin D levels and severe asthma exacerbations in the Childhood Asthma Management Program study. *J Allergy Clin Immunol*. 2010;126:52–58.e5.
30. Dixon AE, Holguin F, Sood A, et al. An official American Thoracic Society Workshop report: Obesity and asthma. *Proc Am Thorac Soc*. 2010;7:325–335.
31. Marcon A, Corsico A, Cazzoletti L, et al. Body mass index, weight gain, and other determinants of lung function decline in adult asthma. *J Allergy Clin Immunol*. 2009;123:1069–1074,74 e1-4.
32. *Diagnosis of Diseases of Chronic Airflow Limitation: Asthma, COPD, and Asthma: COPD Overlap Syndrome (ACOS)*; 2015. Available at: https://www.ginasthma.org/.
33. Woodruff PG, van den Berge M, Boucher RC, et al. American Thoracic

Society/National Heart, Lung, and Blood Institute Asthma: Chronic Obstructive Pulmonary Disease Overlap Workshop Report. *Am J Respir Crit Care Med*. 2017;196:375–381.

34. Anderson SD, Charlton B, Weiler JM, et al. Comparison of mannitol and methacholine to predict exercise-induced bronchoconstriction and a clinical diagnosis of asthma. *Respir Res*. 2009;10:4.
35. Chauhan BF, Ducharme FM. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. *Cochrane Database Syst Rev*. 2012;CD002314.
36. Strunk RC, Sternberg AL, Szefler SJ, et al. Long-term budesonide or nedocromil treatment, once discontinued, does not alter the course of mild to moderate asthma in children and adolescents. *J Pediatr*. 2009;154:682–687.
37. Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. *Cochrane Database Syst Rev*. 2010;CD005535.
38. Kelly HW. Inhaled corticosteroid dosing: double for nothing? *J Allergy Clin Immunol* 2011;128:278–281.e2.
39. Pedersen S. Clinical safety of inhaled corticosteroids for asthma in children: An update of long-term trials. *Drug Saf*. 2006;29:599–612.
40. Busse WW. Biological treatments for severe asthma: Where do we stand? *Curr Opin Allergy Clin Immunol*. 2018;18:509–518.
41. Sobieraj DM, Baker WL, Nguyen E, et al. Association of inhaled corticosteroids and long-acting muscarinic antagonists with asthma control in patients with uncontrolled, persistent asthma: A systematic review and meta-analysis. *JAMA*. 2018;319:1473–1484.
42. Zhang L, Prietsch SO, Ducharme FM. Inhaled corticosteroids in children with persistent asthma: Effects on growth. *Evid Based Child Health*. 2014;9:829–930.
43. Pruteanu AI, Chauhan BF, Zhang L, Prietsch SO, Ducharme FM. Inhaled corticosteroids in children with persistent asthma: Dose-response effects on growth. *Evid Based Child Health*. 2014;9:931–1046.
44. Zeiger RS, Mauger D, Bacharier LB, et al. Daily or intermittent budesonide in preschool children with recurrent wheezing. *N Engl J Med*. 2011;365:1990–2001.
45. Song WJ, Cho SH. Challenges in the management of asthma in the

elderly. *Allergy Asthma Immunol Res*. 2015;7:431–439.

46. Namazy JA, Schatz M. The safety of asthma medications during pregnancy: an update for clinicians. *Ther Adv Respir Dis*. 2014;8:103–110.
47. Schatz M, Krishnan JA, Chambers C. Implications of Changes in U.S. Food and Drug Administration Prescribing Information Regarding the Safety and Use of Asthma Biologics during Pregnancy. *Ann Am Thorac Soc*. 2018;15:1131–1136.
48. Maselli DJ, Adams SG, Peters JI, Levine SM. Management of asthma during pregnancy. *Ther Adv Respir Dis*. 2013;7:87–100.
49. Rodrigo GJ, Castro-Rodriguez JA. Heliox-driven beta2-agonists nebulization for children and adults with acute asthma: A systematic review with meta-analysis. *Ann Allergy Asthma Immunol*. 2014;112:29–34.
50. Rodrigo GJ. Advances in acute asthma. *Curr Opin Pulm Med*. 2015;21:22–26.
51. Schatz M, Kazzi AA, Brenner B, et al. Introduction. *Proc Am Thorac Soc*. 2009;6:353–356.
52. Dolovich MB, Dhand R. Aerosol drug delivery: Developments in device design and clinical use. *Lancet*. 2011;377:1032–1045.
53. Vezina K, Chauhan BF, Ducharme FM. Inhaled anticholinergics and short-acting beta(2)-agonists versus short-acting beta2-agonists alone for children with acute asthma in hospital. *Cochrane Database Syst Rev*. 2014;7:CD010283.
54. Guilbert TW, Denlinger LC. Role of infection in the development and exacerbation of asthma. *Expert Rev Respir Med*. 2010;4:71–83.
55. Boyd M, Lasserson TJ, McKean MC, Gibson PG, Ducharme FM, Haby M. Interventions for educating children who are at risk of asthma-related emergency department attendance. *Cochrane Database Syst Rev*. 2009;CD001290.
56. Janson SL, McGrath KW, Covington JK, Cheng SC, Boushey HA. Individualized asthma self-management improves medication adherence and markers of asthma control. *J Allergy Clin Immunol*. 2009;123:840–846.
57. Kelly HW. Risk versus benefit considerations for the beta(2)-agonists. *Pharmacotherapy*. 2006;26:164S–174SS.

58. Cazzola M, Page CP, Calzetta L, Matera MG. Pharmacology and therapeutics of bronchodilators. *Pharmacol Rev*. 2012;64:450–504.
59. Westbury GLM, Blais CM, Davis BE, Cockcroft DW. Bronchoprotective effect of vilanterol against methacholine-induced bronchoconstriction in mild asthmatics: A randomized three-way crossover study. *Ann Allergy Asthma Immunol*. 2018;121:328–332.
60. Jat KR, Khairwa A. Levalbuterol versus albuterol for acute asthma: A systematic review and meta-analysis. *Pulm Pharmacol Ther*. 2013;26:239–248.
61. Finkelstein FN. Risks of salmeterol? *N Engl J Med*. 1994;331:1314.
62. Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: Comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *BMJ*. 1993;306:1034–1037.
63. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM, Group SS. The Salmeterol Multicenter Asthma Research Trial: A comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest*. 2006;129:15–26.
64. McMahon AW, Levenson MS, McEvoy BW, Mosholder AD, Murphy D. Age and risks of FDA-approved long-acting beta(2)-adrenergic receptor agonists. *Pediatrics*. 2011;128:e1147–e1154.
65. *FDA Drug Safety Communication: FDA review finds no significant increase in risk of serious asthma outcomes with long-acting beta agonists (LABAs) used in combination with inhaled corticosteroids (ICS)*. Food and Drug Aministration; 2017. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm589587.htm. Accessed November 15, 2018.
66. Tse SM, Tantisira K, Weiss ST. The pharmacogenetics and pharmacogenomics of asthma therapy. *Pharmacogenomics J*. 2011;11:383–392.
67. Green RH, Wardlaw AJ. Systemic corticosteroids in asthma. In: Li J, ed. *Pharmacotherapy of Asthma*. New York: Taylor & Francis; 2005:233–262.
68. Raissy HH, Kelly HW, Harkins M, Szefler SJ. Inhaled corticosteroids in lung diseases. *Am J Respir Crit Care Med*. 2013;187:798–803.
69. Keeney GE, Gray MP, Morrison AK, et al. Dexamethasone for acute asthma exacerbations in children: A meta-analysis. *Pediatrics*. 2014;133:493–499.
70. Rowe BH, Edmonds ML, Spooner CH, Diner B, Camargo CA, Jr.

Corticosteroid therapy for acute asthma. *Respir Med*. 2004;98:275–284.

71. Kelly HW, Sternberg AL, Lescher R, et al. Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med*. 2012;367:904–912.
72. Sobieraj DM, Weeda ER, Nguyen E, et al. Association of inhaled corticosteroids and long-acting beta-agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma: A systematic review and meta-analysis. *JAMA*. 2018;319:1485–1496.
73. O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled combined budesonide-formoterol as needed in mild asthma. *N Engl J Med*. 2018;378:1865–1876.
74. Bateman ED, Reddel HK, O'Byrne PM, et al. As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. *N Engl J Med*. 2018;378:1877–1887.
75. Wang G, Zhang X, Zhang HP, et al. Corticosteroid plus beta2-agonist in a single inhaler as reliever therapy in intermittent and mild asthma: A proof-of-concept systematic review and meta-analysis. *Respir Res*. 2017;18:203.
76. Peters SP., et al. Anticholinergic therapies. In: Adkinson NF, Bochner BS, Burks AW, eds., et al. *Middleton's Allergy Principles and Practice*. 8th ed. Philadelphia, PA: Elsevier Health Sciences; 2014;1552–1566.
77. Lazarus SC. Clinical practice. Emergency treatment of asthma. *N Engl J Med*. 2010;363:755–764.
78. O'Byrne PM, Gauvreau GM, Murphy DM. Efficacy of leukotriene receptor antagonists and synthesis inhibitors in asthma. *J Allergy Clin Immunol*. 2009;124:397–403.
79. Kelly HW. Non-corticosteroid therapy for the long-term control of asthma. *Expert Opin Pharmacother*. 2007;8:2077–2087.
80. Benard B, Bastien V, Vinet B, Yang R, Krajinovic M, Ducharme FM. Neuropsychiatric adverse drug reactions in children initiated on montelukast in real-life practice. *Eur Respir J*. 2017;50.
81. Haarman MG, van Hunsel F, de Vries TW. Adverse drug reactions of montelukast in children and adults. *Pharmacol Res Perspect*. 2017;5.
82. Law SWY, Wong AYS, Anand S, Wong ICK, Chan EW. Neuropsychiatric events associated with leukotriene-modifying agents: A systematic review. *Drug Saf*. 2018;41:253–265.
83. Bell MC, Busse WW. Severe asthma: An expanding and mounting clinical

challenge. *J Allergy Clin Immunol Pract*. 2013;1:110–121. quiz 22.

84. Darveaux J, Busse WW. Biologics in asthma: The next step toward personalized treatment. *J Allergy Clin Immunol Pract*. 2015;3:152–160. quiz 61.
85. Legrand F, Klion AD. Biologic therapies targeting eosinophils: Current status and future prospects. *J Allergy Clin Immunol Pract*. 2015;3:167–174.
86. American Thoracic Society. Proceedings of the ATS workshop on refractory asthma: Current understanding, recommendations, and unanswered questions. *Am J Respir Crit Care Med*. 2000;162:2341–2351.
87. Guilbert TW, Bacharier LB, Fitzpatrick AM. Severe asthma in children. *J Allergy Clin Immunol Pract*. 2014;2:489–500.
88. Ledford DK. Omalizumab: Overview of pharmacology and efficacy in asthma. *Expert Opin Biol Ther*. 2009;9:933–943.
89. Powell CV. The role of magnesium sulfate in acute asthma: Does route of administration make a difference? *Curr Opin Pulm Med*. 2014;20:103–108.
90. Kew KM, Kirtchuk L, Michell CI. Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department. *Cochrane Database Syst Rev*. 2014;5:CD010909.
91. Powell C, Dwan K, Milan SJ, et al. Inhaled magnesium sulfate in the treatment of acute asthma. *Cochrane Database Syst Rev* 2012;12:CD003898.
92. Shan Z, Rong Y, Yang W, et al. Intravenous and nebulized magnesium sulfate for treating acute asthma in adults and children: A systematic review and meta-analysis. *Respir Med*. 2013;107:321–330.
93. Barnes PJ. Theophylline. *Am J Respir Crit Care Med*. 2013;188:901–906.
94. Sorkness CA, Blake KV. Asthma. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy: A Pathophysiologic Approach, 10e. New York, NY: McGraw-Hill Education; 2017.
95. Tobias JD. Inhalational anesthesia: Basic pharmacology, end organ effects, and applications in the treatment of status asthmaticus. *J Intensive Care Med*. 2009;24:361–371.
96. Jat KR, Chawla D. Ketamine for management of acute exacerbations of asthma in children. *Cochrane Database Syst Rev*. 2012;11:CD009293.

97. Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: Asthma control and exacerbations: Standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med*. 2009;180:59–99.
98. Fuhlbrigge A, Peden D, Apter AJ, et al. Asthma outcomes: Exacerbations. *J Allergy Clin Immunol*. 2012;129:S34–S48.
99. Bime C, Nguyen J, Wise RA. Measures of asthma control. *Curr Opin Pulm Med*. 2012;18:48–56.
100. Cloutier MM, Schatz M, Castro M, et al. Asthma outcomes: Composite scores of asthma control. *J Allergy Clin Immunol*. 2012;129:S24–S33.

44

Chronic Obstructive Pulmonary Disease

Sharya V. Bourdet and Dennis M. Williams

KEY CONCEPTS

1. Chronic obstructive pulmonary disease (COPD) is a treatable and preventable disease characterized by progressive airflow limitation that is not fully reversible and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases.
2. Mortality from COPD has increased steadily over the past three decades; it currently is the fourth leading cause of death in the United States.
3. The primary cause of COPD is cigarette smoking, implicated in 85% of diagnosed cases in the United States. Other risks include a genetic predisposition, environmental exposures (including occupational dusts and chemicals), and air pollution.
4. In patients with COPD, staging of airflow limitation (GOLD 1-4) is classified by spirometry measurements, while disease severity (Category A-D) is classified using a combined assessment of symptom score, as measured by validated questionnaire, and risk for future exacerbations.
5. Smoking cessation and avoidance of other known toxins are the only management strategies proven to slow the progression of COPD.
6. Oxygen therapy has been shown to reduce mortality in selected patients with COPD. Oxygen therapy is indicated for patients with a resting PaO_2 of less than 55 mm Hg (7.3 kPa) or a PaO_2 of less than 60 mm Hg (8.0 kPa) and evidence of right-sided heart failure, polycythemia, or impaired neurologic function.
7. Inhaled bronchodilators are the mainstay of drug therapy for COPD and are used to relieve patient symptoms, improve exercise tolerance and quality of

life. Guidelines recommend short-acting bronchodilators as initial therapy for patients with occasional symptoms and for all patients as rescue therapy for the relief of symptoms.

8. For patients experiencing persistent symptoms, either a long-acting β_2-agonist (LABA) or long-acting anticholinergic (LAMA) offers significant benefits and both are of comparable efficacy. If a patient has continued symptoms, combining long-acting bronchodilator agents (LABA plus LAMA) is recommended.
9. For patients at high risk for future exacerbations, either a long-acting β_2-agonist (LABA) or long-acting anticholinergic (LAMA) are effective at reducing exacerbation frequency. Anticholinergic agents are more effective at reducing exacerbation frequency and should be considered first-line. If a patient has continued exacerbations or has more severe disease (Category D) combining long-acting bronchodilator agents (LABA plus LAMA) is recommended.
10. The role of inhaled corticosteroid (ICS) therapy in COPD is controversial. Patients with frequent and severe exacerbations may benefit from ICS therapy, although the risk of pneumonia is increased.
11. Acute exacerbations of COPD have a significant impact on disease progression and mortality. Treatment of acute exacerbations includes intensification of bronchodilator therapy and a short course of systemic corticosteroids.
12. Antimicrobial therapy should generally be used during acute exacerbations of COPD if the patient exhibits at least two of the following: increased dyspnea, increased sputum volume, and increased sputum purulence. A C-reactive protein (CRP) test may be helpful to guide the decision to treat a COPD exacerbation with antibiotics.

Preclass Engaged Learning Activity

Watch the video entitled “Pathophysiology of Large and Small Airway Disease in COPD” in AccessPharmacy by Scott Stern, MD. This 5-minute video provides a visual explanation of pathophysiologic changes occurring in lungs of patients with COPD. This video assists with comprehension of physiologic changes and correlation with clinical presentation in COPD.

Watch the video “Gasping for Air: Life with COPD” (*The New York Times*,

July 31, 2008). This 6-minute video provides the perspective of a patient diagnosed with COPD. This video helps remind clinicians of patient experiences with the disease, how physiologic changes are correlated with symptoms and challenges to optimal diagnosis and treatment.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common lung disease characterized by airflow limitation that is not fully reversible, in contrast to the reversibility of airflow limitation in asthma. COPD is both chronic and progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases.[1] COPD is preventable and treatable and causes significant extrapulmonary effects that contribute to disease severity in a subset of patients.

In order to standardize the care of patients with COPD and present evidence-based recommendations, the National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO) launched the Global Initiative for Chronic Obstructive Lung Disease (GOLD) in 2001. This report was revised in December 2019.[1] The goals of the GOLD organization are to increase awareness of COPD and reduce morbidity and mortality associated with the disease. In addition to GOLD, other international organizations have developed consensus guidelines focusing on the prevention and management of acute exacerbations associated with COPD. The American College of Chest Physicians (ACCP) and the Canadian Thoracic Society collaborated on guidelines for the prevention of COPD exacerbations which were published in 2015.[2] In 2017, the American Thoracic Society and European Respiratory Society jointly published guidelines for both the prevention and management of acute exacerbations of COPD (AECOPD).[3,4]

International guidelines emphasize the terms *preventable* and *treatable* to support a positive approach to managing the patient with COPD. Support is also reflected in advocacy and availability of research funding to improve understanding about this disease and its management. Examples include NHLBI funding of Specialized Centers of Clinically Oriented Research (SCCOR) programs in COPD that promote multidisciplinary research and collaboration between the National Institutes of Health as well as the Centers for Disease Control and Prevention’s COPD National Action Plan, which outlines strategic goals for empowering patients and caregivers, preventing and managing disease,

supporting research initiatives, and developing educational and public health policies related to COPD.[5,6]

The term COPD has historically been used to describe a group of pulmonary diseases with a fixed airflow limitation. The two principal conditions are chronic bronchitis and emphysema, which are referred to as phenotypes. Chronic bronchitis is associated with chronic or recurrent excessive mucus secretion into the bronchial tree with cough that is present on most days for at least 3 months of the year for at least two consecutive years in a patient in whom other causes of chronic cough have been excluded.[1] While chronic bronchitis is defined in clinical terms, emphysema is defined in terms of anatomic pathology. Historically, emphysema was diagnosed based on histologic findings at autopsy. Given that this histologic definition has limited clinical value, emphysema also has been defined as abnormal permanent enlargement of the airspaces distal to the terminal bronchioles accompanied by destruction of their walls, without obvious fibrosis.[1]

Differentiating COPD as either chronic bronchitis or emphysema as descriptive subsets of COPD is no longer considered relevant. This is based on the observation that the majority of COPD is caused by a common risk factor (cigarette smoking) and most patients exhibit features of both chronic bronchitis and emphysema. Currently, emphasis is placed on the pathophysiologic features of small airways disease and parenchymal destruction as contributors to chronic airflow limitation. Chronic inflammation affects the integrity of the airways, causes damage, and promotes destruction of the parenchymal structures. The underlying problem is persistent exposure to noxious particles or gases that sustain the inflammatory response. The airways of both the lung and the parenchyma are susceptible to inflammation, and the result is the chronic airflow limitation that characterizes COPD (**Fig. 44-1**).

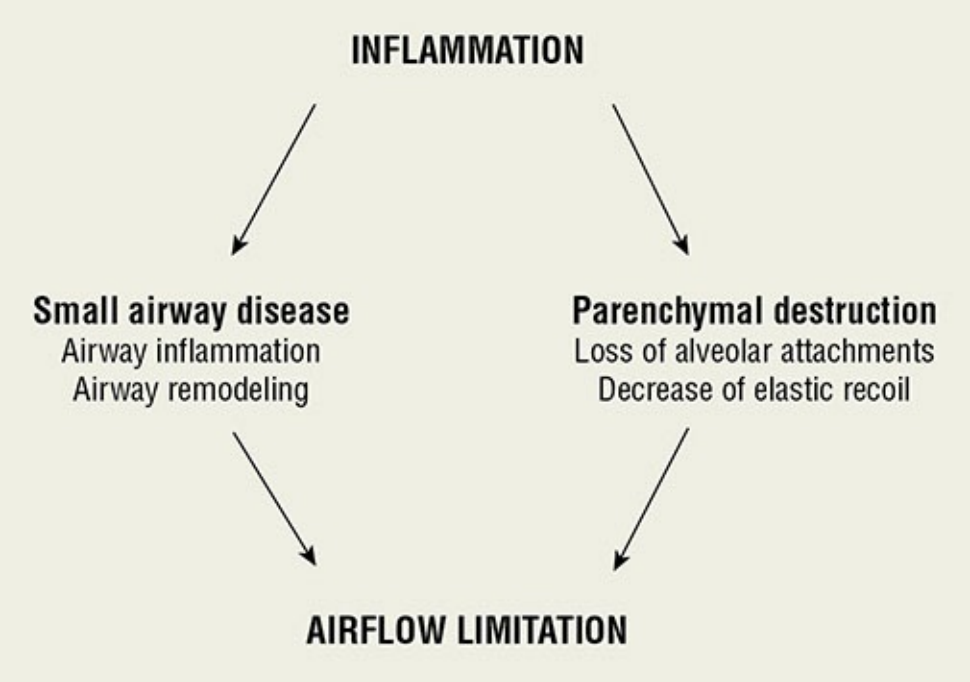


FIGURE 44-1 Mechanisms for developing chronic airflow limitation in COPD. (*Data from Reference 1.*)

EPIDEMIOLOGY

In the United States, approximately 16 million Americans are estimated to have COPD, although the true prevalence of people with chronic airflow obstruction as measured by spirometry may exceed 28 million.[7] Despite a decline in the rate of cigarette smoking among adults in the United States, the prevalence of airflow obstruction and COPD is not expected to significantly decrease in the near future. Approximately 15% of the population in the United States currently smoke.[8] Historically considered a disease primarily affecting men, women are now more likely to have a diagnosis of COPD than men, and the mortality rate is higher for women (52% vs 48%). Prevalence of COPD diagnosis varies among ethnic groups. American Indians/Alaskan Natives are more affected than others.[9]

Chronic obstructive pulmonary disease is the fourth leading cause of death in the United States, exceeded only by cancer, heart disease, and unintentional injuries. Over 130,000 deaths are attributed to COPD annually.[9,10] In contrast to other leading causes of death which have declining mortality rates, the mortality rate attributable to COPD has increased over the last 40 years. The trend of increasing COPD mortality likely reflects the long latency period between

smoking exposure and complications associated with COPD. Between 1969 and 1985, the mortality rate due to COPD increased for men and then plateaued between 1985 and 1999.[11] From 1999 to 2013, the mortality rate due to COPD decreased among men but remained unchanged among women.[11,12] The magnitude difference is likely reflective of changes in smoking status among women in the first decades of the 20th century.

While the mortality associated with COPD is significant, morbidity and costs associated with the disease also have a significant impact on patients, their families, and the healthcare system. Annually, patients with COPD account for over 15 million physician office visits and 700,000 hospitalizations. Surveys indicate that individuals with COPD are more likely to report physical activity limitations and be unable to work compared to individuals without COPD.[13] In the United States, an estimated $32 billion was spent on services related to COPD care in 2010, and these costs are expected to increase to $49 billion by the year 2020.[6] Costs associated with the disease are directly related to the severity of COPD and frequency of exacerbations.

ETIOLOGY

3 Cigarette smoking is the most common risk factor and accounts for 85% to 90% of cases of COPD in the United States.[1,6] Components of tobacco smoke activate inflammatory cells, which produce and release the inflammatory mediators characteristic of COPD. Smokers are 12 to 13 times more likely to die from COPD than nonsmokers.[14] Although the risk is lower in pipe and cigar smokers, it is still higher than in nonsmokers. Age of starting, total pack-years, and current smoking status are predictive of COPD mortality. Children and spouses of smokers have increased risk of developing significant pulmonary dysfunction through passive smoking, also known as environmental tobacco smoke or *secondhand smoke*.

Chronic obstructive pulmonary disease is attributed to a combination of risk factors that results in lung injury and tissue destruction, as evidenced by the fact that less than 50% of all smokers develop COPD, but not all smokers who have equivalent smoking histories develop the same degree of pulmonary impairment.[15] Risk factors can be divided into host factors and environmental factors (**Table 44-1**), and the interaction between these risks leads to expression of the disease. Host factors, such as genetic predisposition, may not be modifiable but are important for identifying patients at high risk of developing

the disease.

TABLE 44-1 Risk Factors for Development of Chronic Obstructive Pulmonary Disease (COPD)

Exposures	Host Factors
Environmental tobacco smoke	Genetic predisposition (AAT deficiency)
Occupational dusts and chemicals	Airway hyperresponsiveness
Air pollution	Impaired lung growth

Environmental factors, such as tobacco smoke, occupational dust, and chemicals are modifiable factors that, if avoided, may reduce the risk of disease development. Environmental exposures associated with COPD are particles that are inhaled by the individual, which result in inflammation and cell injury. Exposure to multiple environmental toxins increases the risk of COPD. Thus, the total burden of inhaled particles (eg, cigarette smoke as well as occupational and environmental particles and pollutants) plays a significant role in the development of COPD. It is helpful to assess an individual's total burden of inhaled particles. For example, an individual who smokes and works in a textile factory has a higher total burden of inhaled particles than an individual who smokes and has no occupational exposure.

In nonindustrialized countries, occupational exposures may be a more common risk than cigarette smoking. These exposures include dust and chemicals such as vapors, irritants, and fumes. Reduced lung function and deaths from COPD are higher for individuals who work in gold and coal mining, in the glass or ceramic industries with exposure to silica dust, and in jobs that expose them to cotton dust or grain dust, toluene diisocyanate, or asbestos. Other occupational risk factors include chronic exposure to open cooking or heating fires. It is unclear whether air pollution alone is a significant risk factor for the development of COPD in smokers and nonsmokers with normal lung function. However, in individuals with existing pulmonary dysfunction, significant air pollution worsens symptoms.

Individuals exposed to the same environmental risk factors do not have the same chance of developing COPD, suggesting that host factors play an important role in pathogenesis. Specific genes, such as matrix metalloproteinase 12 (MMP12), α_1-antitrypsin, and other genetic markers have been implicated with decline of lung function and potential risk of developing COPD.[1] However, only hereditary deficiency of α_1-antitrypsin (AAT) has been definitively shown to

correlate with development of emphysema and pulmonary dysfunction.[16] $Alpha_1$-antitrypsin-associated emphysema is an example of a pure genetic disorder inherited in an autosomal recessive pattern. A primary role of AAT, a plasma protein synthesized in hepatocytes, is to protect cells, especially those in the lung, from destruction by elastase released by neutrophils. Deficiency of AAT results in a protease–antiprotease imbalance and accelerated decline in lung function. Several types of AAT deficiency have been identified and are due to mutations in the AAT gene. True AAT deficiency accounts for less than 1% of COPD cases.[1]

Patients with AAT deficiency develop COPD at an early age (20-50 years) primarily owing to an accelerated decline in lung function. Compared with an average annual decline in forced expiratory volume in 1 second (FEV_1) of 25 mL/year in healthy nonsmokers, patients with homozygous AAT gene deficiency have been reported to have declines of 54 mL/year for nonsmokers and 108 mL/year for current smokers. Effective diagnosis is dependent on clinical suspicion, diagnostic testing of serum concentrations, and genotype confirmation.[16] Patients developing COPD at an early age or those with a strong family history of COPD should be screened for AAT deficiency.

Two additional host factors that may influence the risk of developing COPD include airway hyperresponsiveness and lung growth. Individuals with airway hyperresponsiveness, such as asthma, to various inhaled particles may have an accelerated decline in lung function compared with those without airway hyperresponsiveness. Additionally, individuals who do not attain maximal lung growth owing to low-birth-weight, prematurity at birth, or childhood illnesses may be at risk for COPD in the future.[1]

PATHOPHYSIOLOGY

Chronic obstructive pulmonary disease is characterized by chronic inflammatory changes that lead to destructive tissue changes and development of chronic airflow limitation. The inflammatory process is widespread and involves airways, pulmonary vasculature, and lung parenchyma. Exposure to noxious gas and particles activate inflammatory cells to release a variety of chemical mediators. While both asthma and COPD result from inflammatory responses, it is helpful to contrast the types of inflammatory cells and mediators involved because response to anti-inflammatory therapy differs between the two diseases. The inflammation seen in COPD is often referred to as *neutrophilic* in nature,

but macrophages and CD8+ lymphocytes also play major roles.[1,17] In a small subset of patients with COPD, there may be inflammation common to both COPD and asthma and such patients may be classified as having "asthma-COPD overlap syndrome."[18] Characteristics of inflammation for the two diseases are summarized in **Table 44-2**.

TABLE 44-2 Features of Inflammation in COPD Compared with Asthma

	COPD	Asthma
Cells	Neutrophils Large increase in macrophages Increase in CD8+ T lymphocytes	Eosinophils Small increase in macrophages Increase in CD4+ T lymphocytes Activation of mast cells
Mediators	LTB4 IL-8 TNF-α	LTD4 IL-4, IL-5 (Plus many others)
Consequences	Squamous metaplasia of epithelium Parenchymal destruction Mucus metaplasia Glandular enlargement	Fragile epithelium Thickening of basement membrane Mucus metaplasia Glandular enlargement
Response to treatment	Glucocorticosteroids have variable effect	Glucocorticosteroids inhibit inflammation

Other processes proposed to play a major role in the pathogenesis of COPD include increased oxidative stress and imbalance between destructive and protective defense systems in the lungs (proteases and antiproteases).[1,19] Altered interaction between airway oxidants and antioxidants is responsible for the increased oxidative stress present in COPD. Increases in oxidant markers (eg, hydrogen peroxide and nitric oxide) are seen in the epithelial lining fluid and are generated by cigarette smoke or noxious particles.[1] Oxidants react with and damage various proteins and lipids, leading to cell and tissue damage. Oxidants also promote inflammation directly and exacerbate the protease–antiprotease imbalance by inhibiting antiprotease activity.[19] These processes may be the result of ongoing inflammation or occur as a result of environmental pressures and exposures (**Fig. 44-2**).

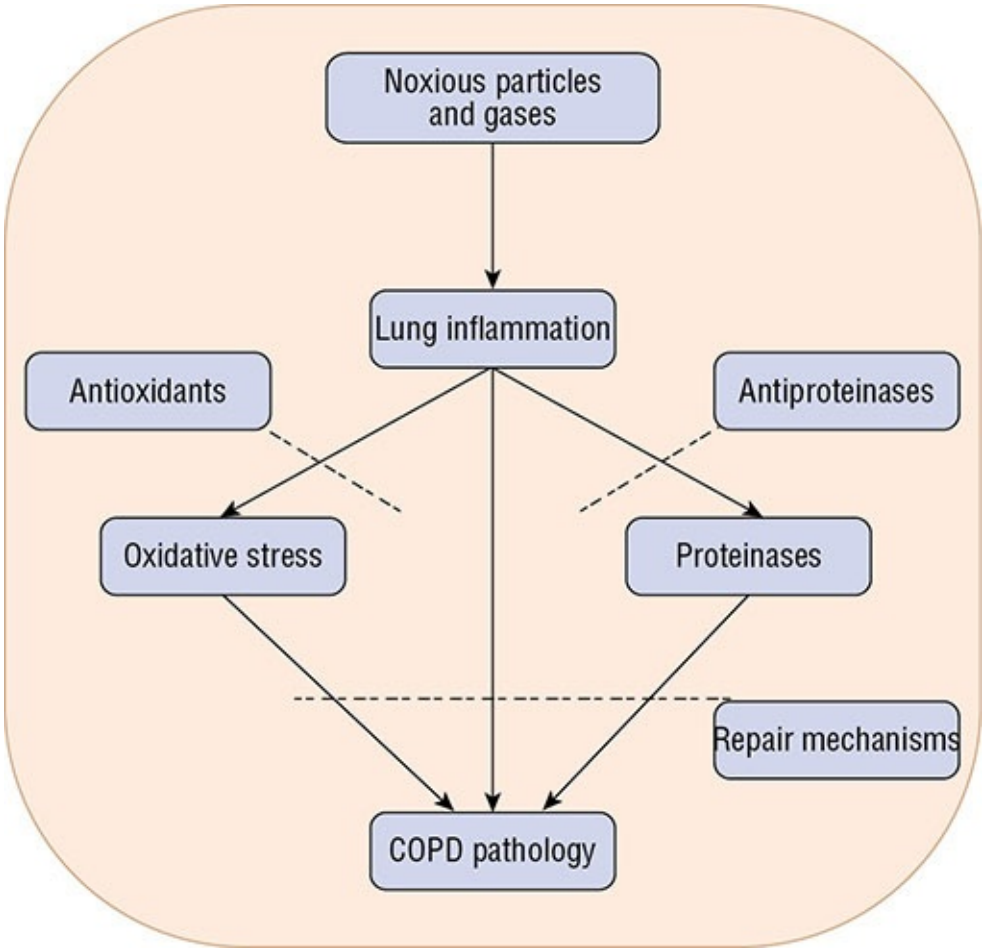


FIGURE 44-2 Pathogenesis of COPD.

Pathologic changes of COPD are widespread, affecting large and small airways, lung parenchyma, and the pulmonary vasculature.[1] An inflammatory exudate is often present that leads to an increase in the number and size of goblet cells and mucus glands. Mucus secretion is increased, and ciliary motility is impaired. There is also a thickening of smooth muscle and connective tissue in the airways. Inflammation is present in central and peripheral airways. The chronic inflammation results in a repeated injury and repair process that leads to scarring and fibrosis. Diffuse airway narrowing is present and is more prominent in smaller peripheral airways. Airflow obstruction is attributed to airway inflammation, while the blood gas abnormalities result from impaired gas transfer due to parenchymal damage and loss of alveolar-capillary networks.

Mucus hypersecretion is present early in the course of the disease and is associated with an increased number and size of mucus-producing cells. Presence of chronic inflammation perpetuates the process, although resulting airflow obstruction and chronic airflow limitation may be reversible or

irreversible. The various causes of airflow obstruction are summarized in **Table 44-3**.

TABLE 44-3 Etiology of Airflow Limitation in COPD

Reversible
Presence of mucus and inflammatory cells and mediators in bronchial secretions
Bronchial smooth muscle contraction in peripheral and central airways
Dynamic hyperinflation during exercise
Irreversible
Fibrosis and narrowing of airways
Reduced elastic recoil with loss of alveolar surface area
Destruction of alveolar support with reduced patency of small airways

Parenchymal changes affect the gas-exchanging units of the lungs, including the alveoli and pulmonary capillaries. As disease progresses, abnormalities in gas exchange lead to hypoxemia and/or hypercapnia, although there is not a strong correlation between pulmonary function and arterial blood gas (ABG). Significant changes in ABGs usually are not present until airflow limitation is very severe.[1] In such patients, hypoxemia, or low arterial oxygen tension (pressure exerted by oxygen gas in arterial blood [PaO_2] = 45-60 mm Hg [6.0-8.0 kPa]) and hypercapnia, or elevated arterial carbon dioxide tension (pressure exerted by carbon dioxide gas in arterial blood [$PaCO_2$] = 50-60 mm Hg [6.7-8.0 kPa]) can become chronic problems. Initially, when present, hypoxemia is associated with exertion. As disease progresses, hypoxemia develops at rest. Hypoxemia is attributed to hypoventilation (V) of lung tissue relative to perfusion (Q) of the area. This low (V/Q) ratio will progress over a period of several years, resulting in a consistent decline in the PaO_2. Some COPD patients lose the ability to increase the rate or depth of respiration in response to persistent hypoxemia.

As COPD progresses and gas exchange worsens, patients may exhibit chronic hypercapnia, and are referred to as carbon dioxide retainers. In such patients, central respiratory response to chronically increased $PaCO_2$ is blunted. These changes in PaO_2 and $PaCO_2$ are subtle and progress over a period of many years. As a result, serum pH usually is near normal because the kidneys compensate by retaining bicarbonate. If acute respiratory distress develops, such as seen with significant pneumonia or COPD exacerbation with respiratory failure, $PaCO_2$ may rise sharply, and the patient presents with a worsening respiratory acidosis.

The vascular changes of COPD include loss of pulmonary capillary beds, thickening of pulmonary vessels and vasoconstriction of pulmonary arteries in response to hypoxemia.[1,20] Chronic hypoxemia and permanent changes in pulmonary vasculature lead to increases in pulmonary pressures, especially during exercise. When elevated pulmonary pressures are sustained, right-sided heart failure, or cor pulmonale, develops and is characterized by right ventricle hypertrophy in response to increased pulmonary vascular resistance. Pulmonary hypertension is the most common cardiovascular complication of COPD and can result significant morbidity.

Thoracic over-inflation is a relevant feature in the pathophysiology of COPD, because it is a central factor in causing dyspnea. Chronic airflow obstruction leads to air trapping, resulting in thoracic hyperinflation that can be detected on chest radiograph. Hyperinflation results in several dynamic changes in the chest, including flattening of diaphragmatic muscles. Under normal circumstances, diaphragms are dome-shaped muscles tethered at the lung bases. When diaphragms contract, the muscles become shorter and flatter, creating the negative inspiratory force through which air flows into lungs during inspiration. With thoracic hyperinflation, diaphragmatic muscles are placed at a disadvantage and are less efficient muscles of ventilation. Increased work required by diaphragmatic contractions predisposes patients to muscle fatigue, especially during periods of exacerbations.

Another consequence of thoracic hyperinflation is the change in lung volumes. For patients with COPD exhibiting thoracic hyperinflation, there is an increase in functional residual capacity (FRC), which is the amount of air left in the lung after exhalation at rest. Therefore, these patients are breathing at higher lung volumes that perturb gas exchange. Increased FRC limits the inspiratory reserve capacity, which is the amount of air that the patient can inhale to fill the lungs. Increased FRC limits duration of inhalation time and has been associated with increased complaints of dyspnea by patients.[1] Pharmacotherapy for COPD, especially bronchodilators, can reduce thoracic hyperinflation by reducing airflow obstruction and air trapping. This explains symptom improvement reported by patients with COPD despite minimal improvements in expiratory lung function.

Another important systemic consequence of COPD is loss of skeletal muscle mass and general decline in the overall health status. These changes are partially attributed to systemic inflammation and can have devastating effects on overall health status and comorbidities. Systemic effects include cardiovascular events associated with ischemia, cachexia, weight loss, osteoporosis, anemia, and

muscle wasting.[1] There has been interest in measuring C-reactive protein as a marker to assess systemic inflammation and its correlation with disease severity; however, it is premature to recommend its use in practice for chronic management.[21] Instead, C-reactive protein may have a role in identifying patients with acute exacerbation of COPD who should receive treatment with antibiotics.

CLINICAL PRESENTATION

Chronic Obstructive Pulmonary Disease

Symptoms

- Chronic cough—may be intermittent; may be unproductive
- Chronic sputum production
- Dyspnea—worse with exercise; progressive over time
  - Decreased exercise tolerance or decline in physical activity
  - Chest tightness or wheezing

Risk Factors

- Tobacco smoke exposure
- Indoor air pollution (eg, burning wood and biofuel for cooking or heating)
- Occupational and environmental hazards (eg, organic and inorganic dusts, chemical fumes)
- α_1-Antitrypsin deficiency

Physical Examination

- Shallow breathing
- Increased resting respiratory rate
- Barrel chest due to hyperinflation of lungs
- Pursed lips during exhalation
- Use of accessory respiratory muscles
- Cyanosis of mucosal membranes (seen in later stages of disease)

Diagnostic Tests

- Spirometry with postbronchodilator testing
- Radiograph of chest (to rule out other diagnoses)
- Arterial blood gas (not routinely obtained in chronic management; has utility in acute decompensation). Lab abnormalities may include pH <7.35, PaO_2 <80 mmHg (10.0 kPa) mmHg (6.0 kPa), $PaCO_2$ >50 mmHg (6.7 kPa), and bicarbonate >26 mEq/L (mmol/L)

The diagnosis of COPD is made based on the patient's symptoms, history of exposure to risk factors, and confirmed by pulmonary function testing, such as spirometry. Patients may experience cough for several years before dyspnea develops and often will not seek medical attention until dyspnea is significant. A diagnosis of COPD should be considered for any patient, age 40 years or older, with persistent or progressive dyspnea, with chronic cough productive of sputum, and who exhibits an unusual or abnormal decline in activity, especially in the presence of exposure to environmental tobacco smoke. In addition, presence of genetic factors, including AAT deficiency, and occupational exposures should be evaluated as approximately 15% of patients with COPD do not have a history of cigarette smoking. Current preventative guidelines do not endorse routine screening tests for asymptomatic patients with risk factors for COPD, although some medical societies have advocated for proactively identifying patients early in the stages of the disease.[22]

Spirometry combined with physical examination improves the diagnostic accuracy of COPD.[1] Spirometry represents a comprehensive assessment of lung volumes and capacities. Patients with all levels of severity of COPD exhibit the hallmark finding of airflow obstruction; specifically, a reduction in FEV_1/FVC ratio to less than 70% (0.70). FVC is the total volume of air exhaled after maximal inhalation and FEV_1 is the total volume of air exhaled in one second. A fixed ratio of less than 70% (0.70) may be problematic because normal aging may affect this result; however, it continues to be the current standard. Previous criteria for the diagnosis of COPD included measuring the degree of airflow limitation before and after inhaled bronchodilator challenge. It is no longer recommended to obtain prebronchodilator values or to calculate the degree of reversibility in order to diagnose COPD (**Table 44-4**).[1] Postbronchodilator spirometry results should be used in assessing lung function in patients with COPD.

TABLE 44-4 Procedures for Postbronchodilator Testing

Preparation

Tests should be performed when patients are clinically stable and free from respiratory infection.

Patient must be able to participate with maximal effort during test.

Spirometry

Bronchodilators can be given by either metered-dose inhaler or nebulization.

Usual doses are 400 mcg of β-agonist, 160 mcg of anticholinergic, or the two combined.

FEV_1 should be measured 10-15 minutes after a short-acting β-agonist or 30-45 minutes after a short-acting anticholinergic or combination.

Results

Airflow limitation is confirmed by a postbronchodilator $FEV_1/FVC < 70\%$ (0.70).

Data from Reference 1.

Spirometry is useful to confirm presence of airflow limitation and to determine severity of obstruction.[23] Currently, GOLD consensus guidelines suggest a four-grade classification of airflow limitation (**Table 44-5**). Use of peak expiratory flow measurements as a diagnostic tool or to classify severity is not adequate for COPD due to low specificity and the high degree of effort dependence; however, a low peak expiratory flow is consistent with the clinical presentation of COPD. A comprehensive discussion about spirometry and interpretation can be found in Chapter e42, "Evaluation of Respiratory Function."

TABLE 44-5 Spirometric Grades: Classification of Severity of Airflow Obstruction Based on Postbronchodilator FEV^1

Spirometric Grade	FEV_1/FVC Ratio	Measured FEV_1 Compared to Predicted FEV_1 (%)	Symptoms
GOLD 1: mild	FEV_1/FVC <70% (0.70)	FEV_1 ≥80% (0.80) of predicted	May be without symptoms
GOLD 2: Moderate	FEV_1/FVC <70% (0.70)	FEV_1 between 50% (0.5) and 80% (0.8) of predicted	May be with or without symptoms
GOLD 3: Severe	FEV_1/FVC <70% (0.70)	FEV_1 between 30% (0.3) and 50% (0.5) of predicted	Symptoms generally present
GOLD 4: Very Severe	FEV_1/FVC <70% (0.70)	FEV_1 <30% (0.30) of predicted	Significant symptoms present

Dyspnea is typically the most troublesome complaint for patients with COPD and often is the stimulus for seeking medical attention. It can impair exercise performance and functional capacity and is frequently associated with depression and anxiety. Together, these have a significant effect on health-related quality of life.[1] As a subjective symptom, dyspnea is often difficult for the clinician to assess. Various tools are available to evaluate severity of dyspnea. The modified Medical Research Council (mMRC) scale is commonly employed and categorizes dyspnea grades from 0 to 4.[1] Patients with COPD may experience a variety of symptoms, not limited only to dyspnea. Therefore, impact of COPD on other measures of health status has been recognized and newer patient assessment tools, such as COPD assessment Test (CAT) and COPD Control Questionnaire (CCQ), include items related to overall symptoms and activities. Other patient assessment questionnaires, such as the Chronic Respiratory Questionnaire (CRQ) and St. George's Respiratory Questionnaire (SGRQ), are comprehensive measures of disease impact on health status and are used frequently in clinical trials; however, use in clinical practice is limited by their length and complexity. Currently, there are three patient assessment questionnaires amenable to use in routine clinical practice and recommended by international guidelines (**Table 44-6**).[1]

TABLE 44-6 Comparison of Patient Assessment Questionnaires Used in COPD

Name	Description of Scoring System	Link to Assessment Tool
COPD Assessment Test (CAT)	• Includes eight items related to health status and impact of COPD on daily activities • Each item scored 0-5 with additive total score of 40 • Score of <10 means less symptoms • Score of ≥10 means more symptoms	http://catestonline.org
Modified Medical Research Council Dyspnea Questionnaire (mMRC)	• Includes five descriptive statements related to dyspnea only • Patient chooses most appropriate statement • Each statement corresponds to score of 0-4 • Score of <2 means less symptoms • Score of ≥2 means more symptoms	http://www.goldcopd.org
COPD Control Questionnaire (CCQ)	• Includes 10 items in three domains related to symptoms, functional state, mental state • Assesses clinical control of disease in past week • Score weighted for each domain • Score <1 means less symptoms[a] • Score ≥1 means more symptoms[a]	http://www.ccq.nl

[a]Exact cut point values have not yet been established for this assessment questionnaire.

Classification Based on Severity

4 Previously, therapy guidelines have defined disease severity solely by spirometry. Observations that patients with similar spirometric parameters exhibit variations in symptom severity and risk of adverse health events, such as exacerbations, have led to a revision in severity classification. In order to incorporate multiple factors that contribute to disease risk, the revised GOLD

consensus guidelines recommend that spirometric severity (ie, GOLD spirometric grade 1-4, see Table 44-5) be separated from symptom and exacerbation assessment. A separate, combined "ABCD" classification system has been recommended for severity of symptoms and risk of future exacerbation (**Table 44-7**). This new classification system acknowledges that symptom management and prevention of exacerbations, rather than FEV_1 should be used to guide therapy. Classification of airflow limitation severity and spirometric grade remains useful for predicting disease outcomes such as mortality and exacerbations and is a consideration for other therapies such as lung reduction surgery or transplantation.

TABLE 44-7 Combined Assessment of COPD Severity

Patient Category	Description	Exacerbations in Last Year[a]	CAT	mMRC
A	Less symptoms; low risk	0-1	<10	0-1
B	More symptoms; low risk	0-1	≥10	≥2
C	Less symptoms; high risk	≥2	<10	0-1
D	More symptoms; high risk	≥2	≥10	≥2

[a]If one exacerbation requiring hospitalization, patient is automatically considered high risk despite less than 2 exacerbations occurring in one year (eg, Patient Category C or D).

Data from Reference 1.

Symptom assessment should be measured at baseline and then during routine visits using CAT or mMRC. Defined cut points for patients exhibiting "more symptoms" and "less symptoms" have been established for CAT and mMRC but are not as well defined for CCQ. Frequency of exacerbations can be assessed by a review of exacerbation history for the past 12 months. Patients with at least two exacerbations in the last 12 months, or one exacerbation requiring hospitalization, are considered high risk for future exacerbations (category C or D). Patients are then assigned to ABCD category based on these two assessments. Classifying patients according to ABCD categories helps inform treatment decisions as guideline-recommended initial and escalation therapy is based on ABCD category classification.

Prognosis

Patients with COPD are a heterogeneous group and multiple factors, such as airflow limitation, age, frequency and severity of exacerbations, and comorbidities, have been implicated in rate of disease progression and prognosis. Rate of COPD progression is variable and not easily predicted for individual patients. Several prognostic indices have been shown to be useful in predicting survival among populations of patients with COPD (**Table 44-8**).[24,25] Based on prognostic indices, mortality for patients with COPD increases with worsening airflow limitation (lower FEV_1 percent of predicted), greater age, lower body mass index, higher dyspnea score (mMRC), shorter 6-minute walk distance, continued smoking, frequent and severe exacerbations, and presence of selected comorbidities. The primary causes of death of patients with COPD include respiratory failure, cardiovascular events or diseases, and lung cancer.[1] Advanced directives, palliative care coordination and end-of-life care are appropriate options to consider for patients with significant progression and comorbidities.

TABLE 44-8 Selected Prognostic Indices Used in COPD

Name	Description of Tool
BMI, Obstruction, Dyspnea, Exercise (BODE) Index	• Composite score of body mass index, measured FEV_1, mMRC score, and 6MWT distance • Score provides estimate of 4-year survival • Well-known and validated tool
Age, Dyspnea, Obstruction (ADO) Index	• Composite score of age, mMRC score, and measured FEV_1 • Score provides estimate of 3-year survival • May be more useful in primary care if 6MWT not able to be measured
COPD Specific Comorbidity Test (COTE) Index	• Includes 12 comorbidities observed to contribute to mortality in COPD patients • Better predictive power if combined with ADO or BODE index

FEV_1, forced expiratory volume in one second; mMRC, modified Medical Research Council; 6MWT, 6-minute walk test.

TREATMENT

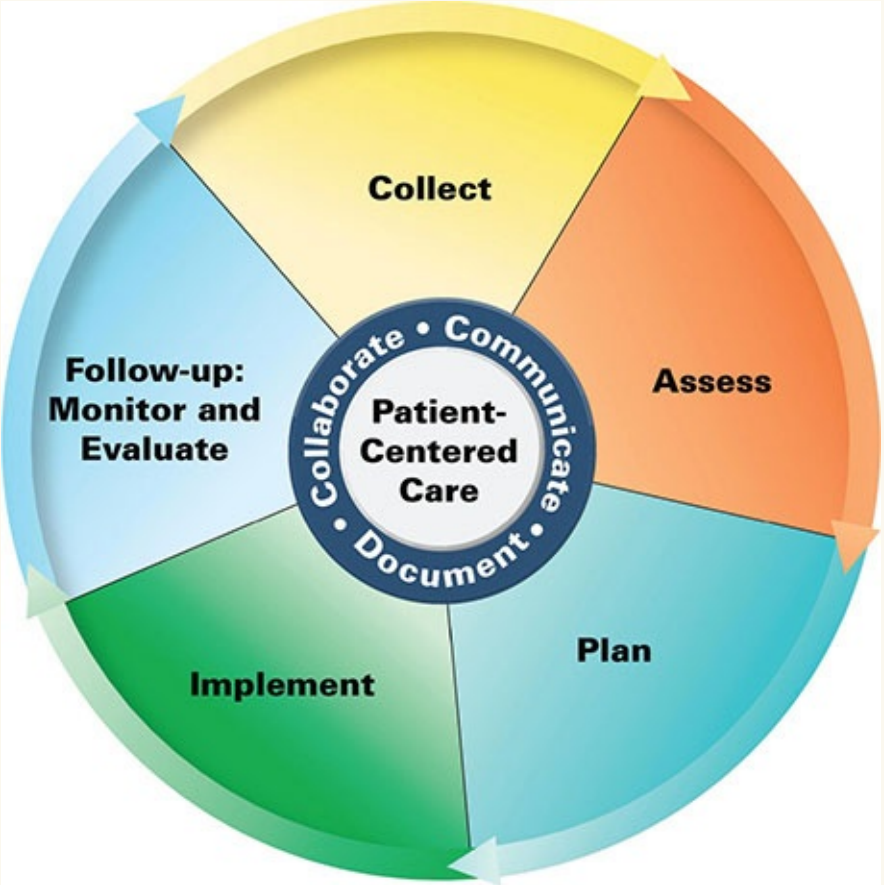
Chronic Obstructive Pulmonary Disease

Desired Outcome

Given the significant clinical and economic impact of COPD, a major focus in healthcare should be on its prevention in patients at risk of the disease. Limiting or eliminating exposure to tobacco smoke and other environmental irritants should be the goal of prevention efforts. For patients already with a diagnosis of COPD, the primary goal is to prevent or slow disease progression. Specific goals are listed in Table 44-9. Optimally, these goals can be accomplished with minimal risks or adverse effects. Therapy of the patient with COPD is multifaceted and includes pharmacologic and nonpharmacologic strategies.

TABLE 44-9 Goals of COPD Management

1. Prevent disease progression
2. Relieve symptoms
3. Improve exercise tolerance
4. Improve overall health status
5. Prevent and treat exacerbations
6. Prevent and treat complications
7. Reduce morbidity and mortality



Patient Care Process for the Management of Chronic Obstructive Pulmonary Disease (COPD)

Collect

- Patient characteristics (eg, age, gender)
- History of present illness including history of COPD exacerbations in last 12 months and management (eg, home, Primary Care Provider visit, Emergency Department visit or hospitalization)
- Patient history (past medical, family, social—environmental exposures, tobacco use, exercise tolerance, and capacity)
- Current medications including immunizations (eg, influenza, pneumococcus) and any prior pulmonary medication use
- Objective data (see Tables 44-5 to 44-7)
  - Symptom scores using validated questionnaire (eg, CAT, mMRC)

- Current and previous spirometry/pulmonary function tests (eg, FEV_1)

Assess

- Severity of symptoms (eg, “more symptoms” or “less symptoms” based on questionnaires, Table 44-6)
- Risk of future exacerbation (eg, high risk or low risk)
- Degree of airflow limitation (eg, GOLD spirometry group, Table 44-5)
- Patient category based on GOLD Combined Assessment (eg, Category ABCD, Table 44-7)
- Readiness to quit, if current tobacco use (see Tables 44-10 to 44-12)
- Appropriateness and effectiveness of current pulmonary medication regimen
- Ability to administer/participate with inhaled therapies (eg, dexterity, vision, coordination)
- Ability to pay for medications (eg, insurance, formulary considerations, self-pay)

Plan

- Patient-specific goals of therapy (see Tables 44-13 and 44-19)
- Drug therapy regimen including specific medication, dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Tables 44-13 and 44-14)
- Oxygen therapy, if severe airflow limitation
- Monitoring parameters including efficacy (eg, symptoms, exacerbations), safety (medication-specific adverse effects), and time frame
- Patient education (eg, purpose of medications, administration technique, recognition of exacerbations)
- Referrals to other providers when appropriate (eg, physician, pulmonary rehabilitation)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence

- Schedule follow-up

Follow-up: Monitor and Evaluate

- Determine goal attainment (eg, symptoms, exacerbations, complications)
- Presence of treatment-related adverse effects
- Patient adherence to treatment plan using multiple sources of information

** Collaborate with patient, caregivers, and other healthcare professionals.*

Unfortunately, most treatments for COPD have not been shown to improve survival or to slow the progressive decline in lung function. However, many therapies do improve pulmonary function and quality of life as well as reduce the risk of COPD exacerbations and duration of hospitalization. While earlier studies of COPD therapies focused primarily on relief of symptoms and improvements in pulmonary function measurements such as FEV_1, more recent studies also measure disease-specific quality-of-life and the frequency and severity of exacerbations. A reduction in exacerbation frequency is an important outcome to consider when evaluating the role and benefit of chronic therapies used in COPD management.

General Approach to Treatment

To be effective, clinicians should address four major components of management: assess and monitor the condition, avoid or reduce exposure to risk factors, manage stable disease, and treat exacerbations.[1] These components are addressed through a variety of nonpharmacologic and pharmacologic approaches.

Nonpharmacologic Therapy and Health Maintenance Strategies

Patients with COPD should receive education about their disease, treatment plans, and strategies to slow progression and prevent complications. Advising and counseling patients about smoking cessation are essential, if applicable, and should be addressed for patients in all stages of the disease. Because the natural course of the disease leads to respiratory failure, clinicians should address end-of-life decisions and advanced directives prospectively with the patient and family. Increasingly, palliative care services, which include both end-of-life and

hospice care for patients with all types of life-threatening acute and chronic illnesses, have been utilized for patients with severe COPD.[26]

Smoking Cessation 5 Smoking cessation represents the single most important intervention in preventing development, as well as progression, of COPD. A primary component of COPD management is avoidance of or reduced exposure to risk factors. Exposure to environmental tobacco smoke is a major risk factor, and smoking cessation is the most effective strategy to reduce the risk of developing COPD and to slow or stop disease progression. Smoking cessation leads to decreased symptomatology and slows the rate of decline of pulmonary function even after significant abnormalities in pulmonary function tests have been detected. As confirmed by the Lung Health Study, smoking cessation is the only intervention proven to affect long-term decline in FEV_1 and slow the progression of COPD.[27] In this 5-year prospective trial, smokers with early COPD were randomly assigned to one of the following three groups: smoking-cessation intervention plus inhaled ipratropium three times a day, smoking-cessation intervention alone, or no intervention. During an 11-year follow-up, the rate of decline in FEV_1 among subjects who continued to smoke was more than twice the rate in sustained quitters.[28] Smokers who underwent smoking-cessation intervention had fewer respiratory symptoms and a smaller annual decline in FEV_1 compared with smokers who had no intervention.

Tobacco cessation has mortality benefits beyond those related to COPD. A follow-up analysis of the Lung Health Study data conducted more than 14 years later demonstrated an 18% reduction in all-cause mortality in patients who received the intervention compared with usual care.[29] Intervention patients had lower death rates due to cardiovascular diseases (the leading cause of mortality) and lung cancer.

Every clinician has a responsibility to advise smokers regarding smoking-cessation and should take an active role in assisting patients with tobacco dependence in order to reduce the burden on the individual, their family, and healthcare system. Counseling that is provided by clinicians is associated with greater success rates than self-initiated efforts. A clinical practice guideline for treating tobacco dependence from the United States Public Health Service (USPHS) was last updated in 2008.[30] The major findings and recommendations of that report are summarized in **Table 44-10**. A more recent review of tobacco cessation strategies, including the potential role of electronic nicotine dispensing systems (eg, e-cigarettes), was published in 2015.[31] Since 2004, reports from the Surgeon General on the health consequences of smoking have emphasized the

detrimental effects of cigarette smoking on the general health of smokers and individuals exposed to secondhand smoke. It is estimated that over 20 million Americans have died prematurely from exposure to cigarette smoking since 1964.

TABLE 44-10 Key Guideline Recommendations Regarding Tobacco Use and Dependence

- Tobacco dependence is a chronic disease that often requires repeated intervention and multiple attempts to quit. Effective treatments are available that can significantly improve rates of long-term abstinence.
- Clinicians and healthcare delivery systems should consistently identify and document tobacco use status and treat every tobacco user.
- Tobacco-dependence treatments are effective over a broad range of populations. Clinicians should encourage every patient willing to make a quit attempt to use counseling treatments and medications recommended in the guideline.
- Brief tobacco-dependence treatments are effective. Clinicians should offer every patient who uses tobacco at least these brief treatments.
- Individual, group, and telephone counseling are effective, and their effectiveness increases with treatment intensity. Practical counseling (problem-solving and/or skills training) and social support are especially effective and should be employed as a part of treatment.
- There are numerous effective medications for tobacco dependence, and clinicians should encourage their use by patients during a quit attempt, except when medically contraindicated or with populations in which the evidence of effectiveness is insufficient (pregnancy, smokeless tobacco users, light smokers, and adolescents). Seven first-line medications (5 nicotine and 2 non-nicotine) consistently increase long-term abstinence rates. Clinicians should also consider the use of combinations as identified in the guideline.
- Counseling and medication are effective when used by themselves for treating tobacco dependence. The combination of the two is more effective than either alone. Patients should be encouraged to use both counseling and medication.
- Telephone quitline counseling is effective for diverse populations and offers the advantage of broad reach. Clinicians should ensure patient access to quitlines and promote quitline use.
- For a tobacco user who is currently unwilling to make a quit attempt, clinicians should use motivational treatments that have been shown to be effective in increasing future quit attempts.
- Tobacco-dependence treatments are both clinically effective and highly cost-effective relative to interventions for other clinical disorders. Providing coverage for these treatments increases quit rates. Insurers and purchasers should ensure that all insurance plans include the counseling and medications identified as effective in the guideline as covered benefits.

Data from References 30 and 31.

Evidence from long-term cessation trials show that tobacco cessation, either sustained or intermittent, is of benefit at any point. For patients with COPD, maximum benefit is seen with early and sustained cessation; however, incremental benefit is seen at all time points. Given that approximately 40% of patients with COPD continue to smoke, patients and clinicians should

understand it is never too late to quit and repeated attempts at cessation may be necessary. It is estimated that over 75% of smokers want to quit and one-third have made a serious effort. Yet complete and permanent tobacco cessation is difficult.[30,31] Rather than focusing on unsuccessful attempts or incomplete cessation, patients should be congratulated and encouraged for any behavior changes resulting in smoking reduction and exposure.

The USPHS guidelines recommend that clinicians take a comprehensive approach to smoking-cessation counseling. Advice should be given to smokers even if they have no symptoms of smoking-related disease or if they are receiving care for reasons unrelated to smoking. Clinicians should be persistent in their motivational efforts because relapse is common among smokers owing to the chronic nature of dependence. Brief interventions (3 minutes) of counseling have been shown to be effective. However, it must be recognized that the patient must be ready to stop smoking. There are several stages which influence patient decision making. Based on this, a five-step intervention program is proposed (**Table 44-11**).

TABLE 44-11 Five-Step Strategy for Smoking-Cessation Program (5 As)

Ask	Use systematic approach to identify all tobacco users.
Advise	Urge all tobacco users to quit.
Assess	Determine willingness to make a cessation attempt.
Assist	Provide support for the patient to quit smoking.
Arrange	Schedule follow-up and monitor for continued abstinence.

There is strong evidence to support use of pharmacotherapy to assist in smoking cessation and therapy should be offered to most patients as part of a cessation attempt. In general, available pharmacotherapies will double the effectiveness of a cessation effort. Agents considered first line are listed in **Table 44-12**. The usual duration of therapy is 8 to 12 weeks, although some individuals may require longer courses of treatment. Precautions to consider before using bupropion include a history of seizures or an eating disorder. Nicotine replacement therapies are contraindicated for patients with recent (less than 2 weeks) myocardial infarction or stroke. Varenicline, a nicotine acetylcholine receptor partial agonist, relieves physical withdrawal symptoms and reduces the rewarding properties of nicotine. Nausea and headache are the most frequent complaints associated with varenicline. Currently, varenicline has not been studied in combination with other tobacco cessation therapies. Second-line agents are less effective or associated with greater adverse effects; however, they

may be useful in selected clinical situations. These therapies include clonidine and nortriptyline, a tricyclic antidepressant. Given the significant increase in use of e-cigarettes and other electronic nicotine delivery systems (ENDS), there is interest in the potential role of these agents as a smoking cessation strategy. It is not clear if substituting ENDS for traditional cessation therapy produces similar or greater tobacco cessation rates and long-term safety outcomes of these systems have not been determined.[31] ENDS should not be recommended as part of a smoking-related strategy until additional evidence is available.

TABLE 44-12 First-Line Pharmacotherapies for Smoking Cessation

Agent	Usual Dose	Duration	Common Complaints
Bupropion SR	150 mg orally daily for 3 days, then twice daily	12 weeks, up to 6 months	Insomnia, dry mouth
Nicotine gum	2-4 mg gum prn, up to 24 pieces daily	12 weeks	Sore mouth, dyspepsia
Nicotine inhaler	6-16 cartridges daily	Up to 6 months	Sore mouth and throat
Nicotine nasal spray	8-40 doses daily	3-6 months	Nasal irritation
Nicotine patches	Various, 7-21 mg every 24 hours	Up to 8 weeks	Skin reaction, insomnia
Varenicline	0.5 mg daily orally for 3 days, then 0.5 mg twice daily for 4 days, then 1 mg twice daily	12 weeks	Nausea, sleep disturbances

Behavioral modification techniques or other forms of psychotherapy also may be helpful in assisting in smoking cessation. Programs that address triggers and issues associated with smoking (ie, learned behaviors, environmental influences, and chemical dependence) using a team approach are more likely to be successful. The role of alternative medicine therapies in smoking cessation is controversial. Hypnosis may aid in improving abstinence rates when added to a smoking-cessation program but appears to give little benefit when used alone.

Other Environmental Triggers Although cigarette smoke is by far the most

common risk for developing COPD in most patients, exposure to other environmental toxins also confers risks.[1] Exposures to occupational dusts and fumes have been implicated as a cause of COPD in 19% of smokers and 31% of nonsmokers with COPD in the United States. In the case of known environmental hazards, primary prevention is appropriate. Policies to limit airborne exposures in the workplace and outdoors, as well as education efforts of workers and policy makers, are recommended.

Pulmonary Rehabilitation Exercise training is beneficial in the treatment of COPD to improve exercise tolerance and to reduce symptoms of dyspnea and fatigue.[1] Pulmonary rehabilitation programs are an integral component in the management of COPD and should include exercise training along with smoking cessation, breathing exercises, optimal medical treatment, psychosocial support, and health education. Pulmonary rehabilitation has no direct effect on lung function or gas exchange. Instead, it optimizes other body systems so that impact of poor lung function is minimized. Exercise training reduces the CNS response to dyspnea, ameliorates anxiety and depression, reduces thoracic hyperinflation, and improves skeletal muscle function.[32]

High-intensity training (70% maximal workload) is possible even in advanced COPD patients, and level of intensity improves peripheral muscle and ventilatory function. Studies have demonstrated that pulmonary rehabilitation with exercise three to seven times per week can produce long-term improvement in activities of daily living, quality of life, exercise tolerance, and dyspnea for patients with moderate-to-severe COPD.[33] Improvements in dyspnea do not always result in improvements in spirometry. While rehabilitation programs vary based on length of program, and exercise frequency and intensity, those with longer length and more frequent sessions have demonstrated the best clinical benefit.

Long-Term Oxygen Therapy 6 Use of supplemental oxygen therapy increases survival in COPD patients with chronic hypoxemia at rest. Patients receiving oxygen therapy for at least part of the day have lower rates of mortality than those not receiving oxygen. Long-term oxygen therapy provides more benefit in terms of survival after at least 5 years of use and improves quality of life for patients by increasing walking distance, improving neuropsychological condition, and reducing time spent in the hospital.[1] Before patients are considered for long-term oxygen therapy, they should be stabilized in the outpatient setting, and pharmacotherapy should be optimized. Once optimized, long-term oxygen therapy should be instituted if either of the following two

conditions is observed and documented twice in a 3-week period:

1. A resting PaO_2 of less than 55 mm Hg (7.3 kPa) or SaO_2 less than 88% (0.88) with or without hypercapnia.
2. A resting PaO_2 between 55 and 60 mm Hg (7.3 and 8.0 kPa) or SaO_2 less than 88% (0.88)with evidence of right-sided heart failure, polycythemia, or pulmonary hypertension.

The most practical means of administering long-term oxygen is with the nasal cannula, at 1 to 2 L/min, providing 24% to 28% (0.24 to 0.28) fraction of inspired oxygen (FiO_2) with a goal to raise PaO_2 above 60 mm Hg (8.0 kPa). There are three different ways to deliver oxygen, including (a) in liquid reservoirs, (b) compressed into a cylinder, and (c) via an oxygen concentrator. Although conventional liquid oxygen and compressed oxygen are quite bulky, smaller, portable tanks are available to permit greater patient mobility. Oxygen concentrator devices separate nitrogen from room air and concentrate oxygen. These are the most convenient and the least expensive method of oxygen delivery. Oxygen-conservation devices are available that allow oxygen to flow only during inspiration, making the supply last longer. These may be particularly useful to prolong the oxygen supply for mobile patients using portable cylinders. However, devices are bulky and subject to failure. Patient education about flow rates and avoidance of flames (ie, smoking) is of the utmost importance.

Adjunctive Therapies In addition to supplemental oxygen, adjunctive therapies to consider as part of a pulmonary rehabilitation program are psychoeducational care and nutritional support. Psychoeducational care (such as relaxation) has been associated with improvement in the functioning and well-being of adults with COPD.[1] The role of nutritional support for patients with COPD is controversial. Several studies have shown associations of malnutrition, low body mass index (BMI), and impaired pulmonary status among patients with COPD. However, results from multiple studies suggest that the effect of nutritional support on physical and functional outcomes in COPD is small and may be most beneficial for malnourished patients.[34]

Immunizations Recommended vaccines can reduce the likelihood of respiratory infections that lead to COPD exacerbations. Because influenza is a common complication in COPD that can lead to exacerbations and respiratory failure, an annual vaccination with the inactivated intramuscular influenza vaccine is recommended. Immunization against influenza can reduce exacerbations,

hospitalization, all-cause death and respiratory death in COPD patients.[35] Influenza vaccine should be administered annually during each influenza season. Vaccination against influenza can begin as early as August, with most patients being vaccinated during regular medical visits or at vaccination clinics in October and November. COPD patients should receive an inactivated form of the influenza virus vaccine. The oral antiviral agent, oseltamivir, can be considered for patients with COPD during an outbreak for patients who have not been immunized; however, this therapy is less effective and causes more side effects.[36]

The Centers for Disease Control and Prevention (CDC) and the American Lung Association (ALA) recommend the 23-valent pneumococcal polysaccharide vaccine (PPSV23) for people from 2 to 64 years of age who have chronic lung disease and for all people older than 65 years.[36] In 2009, the CDC added smokers over the age of 18 years to the recommendations. Although evidence for the benefit of the polysaccharide pneumococcal vaccine in COPD is not strong, the argument for its use in patients with COPD is that the current vaccine provides coverage for 85% of pneumococcal strains causing invasive disease and the increasing rate of resistance of pneumococcus to selected antibiotics.[37] Current GOLD guidelines recommend immunization with PPSV23 for all COPD patients who are 65 years and older and for patients less than 65 years with comorbidities or FEV_1 less than 40% (0.40) predicted.[1] Repeated vaccination with the 23-valent product is not recommended for patients aged 2 to 64 years with chronic lung disease. However, revaccination is recommended for patients over 65 years of age if the first vaccination was more than 5 years earlier and the patient was younger than age 65. In 2014, the Advisory Committee on Immunization Practices (ACIP) recommended vaccination with the 13-valent pneumococcal conjugate vaccine (PCV13) for all adults aged 65 years or older. At age 65, it is recommended to administer PCV13 followed in 1 year with PPSV23, as long as at least 5 years have passed since the previous PPSV23.

Pharmacologic Therapy

In contrast to survival benefit conferred by supplemental oxygen therapy and tobacco cessation, there is no medication available for the treatment of COPD that has been conclusively shown to modify lung function decline or prolong survival.[1] There is some evidence that chronic treatment with pharmacotherapy may reduce the rate of lung function decline in a subset of patients, although

more definitive studies are needed to confirm these observations. The primary goal of pharmacotherapy is to improve patient symptoms, reduce the frequency and severity of exacerbations, and improve the patient's exercise tolerance.

Currently available therapies for COPD are summarized in **Tables 44-13** and **44-14**. International guidelines recommend a stepwise approach to the use of pharmacotherapy based on disease severity determined by symptom burden and exacerbation risk.[1] The impact of recurrent exacerbations on accelerating disease progression is increasingly recognized as an important factor to be considered. Currently, there is inadequate evidence to support the routine use of more aggressive pharmacotherapy early in the course of disease because of the lack of a disease-modifying benefit. Due to the progressive nature of COPD, pharmacotherapy tends to be chronic and cumulative. Step-down approaches in stable patients have not been successful. Patients exhibit varied responses to available therapies and the treatment approach must be individualized.

TABLE 44-13 Recommended Pharmacologic Therapy for Stable COPD and Evaluation of Therapeutic Outcomes

Patient Category	Initial Therapy	Assessment	Escalation Therapy
A (less symptoms, less risk)	Offer bronchodilator, either short or long acting depending on symptoms	Assess symptomatic benefit of therapy after initiation (ie, mMRC or CAT score) Assess exacerbation history Assess inhaler technique regularly Assess technique and adherence before modifying therapy Assess tobacco cessation readiness, if continued smoking Assess immunization status (influenza, pneumococcal)	Continue therapy if beneficial or if re-education needed Stop therapy if intolerable adverse effects and switch to alternate class for symptom control Combine bronchodilator classes for additional symptom control If patient experiences exacerbations, reassess goals (ie, low vs high risk for exacerbation) and follow escalation therapy as outlined in category C
B (more symptoms, less risk)	Start LAMA or LABA for symptom control	Assess symptomatic benefit of therapy after initiation (ie, mMRC or CAT score) Assess exacerbation history Assess inhaler technique regularly Assess technique and adherence before modifying therapy Assess tobacco cessation readiness, if continued smoking Assess immunization status (influenza, pneumococcal)	Continue therapy if beneficial or if re-education needed Add long-acting bronchodilator if persistent symptoms on monotherapy (LAMA/LABA) If dual bronchodilators do not improve symptoms, consider stepping back to monotherapy AFTER adherence and inhaler technique assessed If patient experiences exacerbations, reassess goals (ie, low vs high risk for exacerbation) and follow escalation therapy as outlined in category C
C (less symptoms, more risk)	Start long-acting bronchodilator for exacerbation prevention LAMA is preferred over LABA for initial therapy	Assess symptomatic benefit of therapy after initiation (ie, mMRC or CAT score) Assess exacerbation history Assess inhaler technique regularly Assess technique and adherence before modifying therapy Assess tobacco cessation readiness, if continued smoking Assess immunization status (influenza, pneumococcal)	Continue therapy if beneficial or if re-education needed Add long-acting bronchodilator if persistent symptoms on monotherapy (LAMA/LABA) If persistent exacerbations on long-acting bronchodilator monotherapy and eosinophil count $<300/\mu L$ ($0.3 \times 10^9/L$), add additional long-acting bronchodilator (LAMA/LABA); dual bronchodilators preferred due to better efficacy and lower risk of pneumonia If persistent exacerbations on long-acting bronchodilator monotherapy and eosinophil count $\geq 300/\mu L$ ($0.3 \times 10^9/L$) or ≥ 100 AND ≥ 2 moderate exacerbations/1 hospitalization, consider starting ICS/LABA instead of LAMA/LABA If persistent exacerbations on dual LAMA/LABA and eosinophil count $\geq 100/\mu L$ ($0.1 \times 10^9/L$), consider adding ICS If persistent exacerbations on dual LAMA/LABA and eosinophil count $<100/\mu L$ ($0.1 \times 10^9/L$), consider roflumilast for patients with FEV_1 $<50\%$ (0.50) and chronic bronchitis or azithromycin (nonsmokers or former smokers only) If persistent exacerbations on triple therapy (LAMA/LABA/ICS), consider roflumilast for patients with $FEV_1 < 50\%$ (0.50) and chronic bronchitis or azithromycin (nonsmokers or former smokers only) If recurrent exacerbations or pneumonia, consider withdrawal of ICS over 12 weeks
D (more symptoms, more risk)	Start long-acting bronchodilator for exacerbation prevention and symptom control LAMA is preferred over LABA for initial therapy If highly symptomatic (ie, CAT >20), consider dual long-acting bronchodilators (LAMA/LABA) If blood eosinophil count $\geq 300/\mu L$ ($0.3 \times 10^9/L$), consider starting ICS/LABA instead of LAMA/LABA	Assess symptomatic benefit of therapy after initiation (ie, mMRC or CAT score) Assess exacerbation history Assess inhaler technique regularly Assess technique and adherence before modifying therapy Assess tobacco cessation readiness, if continued smoking Assess immunization status (influenza, pneumococcal)	Continue therapy if beneficial or if re-education needed If persistent exacerbations, follow escalation therapy as outlined in category C If recurrent exacerbations or pneumonia, consider withdrawal of ICS over 12 weeks

CAT, COPD assessment test; ICS, inhaled corticosteroids; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonists; mMRC, modified Medical Respiratory Council questionnaire; SABA, short-acting beta-agonist; SAMA, short-acting muscarinic antagonists.

TABLE 44-14 COPD Medication Chart

	Active Ingredient	Dosage Form; Route	Usual Frequency	Proprietary Name	Device Type
Short-Acting Bronchodilators					
Short-acting beta agonist (SABA)	Albuterol sulfate	Aerosol, metered; inhalation	Four to six times a day as needed	Proventil-HFA; Ventolin-HFA; Proair HFA	MDI
	Albuterol sulfate	Solution; inhalation	Four to six times a day as needed	Accuneb; generic	Nebulization
	Levalbuterol hydrochloride	Solution; inhalation	Three to four times a day as needed	Xopenex; generic	Nebulization
	Levalbuterol tartrate	Aerosol, metered; inhalation	Three to four times a day as needed	Xopenex HFA	MDI
Short-acting anticholinergics (SAMA)	Ipratropium bromide	Aerosol, metered; inhalation	Four times a day as needed	Atrovent HFA	MDI
	Ipratropium bromide	Solution; inhalation	Four times a day as needed	generic	Nebulization
Long-Acting Bronchodilators					
Long-acting beta agonist (LABA)	Arformoterol tartrate	Solution; inhalation	Twice daily	Brovana	Nebulization
	Formoterol fumarate	Solution; inhalation	Twice daily	Perforomist	Nebulization
	Indacaterol maleate	Powder; inhalation	Once daily	Arcapta Neohaler	DPI
	Olodaterol hydrochloride	Spray metered; inhalation	Once daily	Striverdi Respimat	SMI
	Salmeterol xinafoate	Powder; inhalation	Twice daily	Serevent Diskus	DPI
Long-acting anticholinergics (LAMA)	Aclidinium bromide	Powder; inhalation	Twice daily	Tudorza Pressair	DPI
	Tiotropium bromide	Spray metered; inhalation	Once daily	Spiriva Respimat	SMI
	Tiotropium bromide	Powder; inhalation	Once daily	Spiriva Handihaler	DPI
	Glycopyrrolate	Solution; inhalation	Twice daily	Lonhala Magnair	Nebulization
	Glycopyrrolate	Powder; inhalation	Twice daily	Seebri Neohaler	DPI
	Umeclidinium bromide	Powder; inhalation	Once daily	Incruse Ellipta	DPI
	Revefenacin	Solution; inhalation	Once daily	Yupelri	Nebulization
Inhaled Corticosteroids					
Inhaled Corticosteroids (ICS)	Beclomethasone dipropionate	Aerosol, metered; inhalation	Twice daily	Qvar 40; Qvar 80	MDI
	Budesonide	Powder; inhalation	Twice daily	Pulmicort Flexhaler	DPI
	Budesonide	Suspension; inhalation	Once or twice daily	Pulmicort Respules; generic	Nebulization
	Flunisolide	Aerosol, metered; inhalation	Twice daily	Aerospan HFA; Aerobid	MDI
	Fluticasone propionate	Aerosol, metered; inhalation	Twice daily	Flovent HFA	MDI
	Mometasone furoate	Powder; inhalation	Twice daily	Asmanex Twisthaler	DPI
Combination Inhalers					
Dual Combination (SABA/SAMA)	Albuterol sulfate; ipratropium bromide	Solution; inhalation	Four to six times a day as needed	Duoneb; generic	Nebulization
	Albuterol sulfate; ipratropium bromide	Spray metered; inhalation	Four to six times a day as needed	Combivent Respimat	SMI
Dual Combination (LAMA/LABA)	Umeclidium bromide; vilanterol trifenatate	Powder; inhalation	Once daily	Anoro Ellipta	DPI
	Tiotropium bromide;olodaterol hydrochloride	Spray metered; inhalation	Once daily	Stiolto Respimat	SMI
	Glycopyrrolate; indacaterol maleate	Powder; inhalation	Twice daily	Utibron Neohaler	DPI
	Glycopyrrolate; formoterol fumarate	Aerosol, metered; inhalation	Twice daily	Bevespi Aerosphere	MDI
Dual Combination (ICS/LABA)	Budesonide; formoterol fumarate dihydrate	Aerosol, metered; inhalation	Twice daily	Symbicort	MDI
	Fluticasone furoate; vilanterol trifenatate	Powder; inhalation	Once daily	Breo Ellipta	DPI

	Fluticasone proprionate; salmeterol xinafoate	Powder; inhalation	Twice daily	Advair Diskus; Airduo Respiclick	DPI
	Fluticasone propionate; salmeterol xinafoate	Aerosol, metered; inhalation	Twice daily	Advair HFA	MDI
	Mometasone furoate; formoterol fumarate	Aerosol, metered; inhalation	Twice daily	Dulera	MDI
Triple Combination (ICS/LAMA/LABA)	Fluticasone furoate; umeclidinium bromide; vilanterol trifenatate	Powder; inhalation	Once daily	Trelegy Ellipta	DPI
Oral Medications					
	Roflumilast	Tablet; oral	Once daily	Daliresp	Oral
	Theophylline	Tablet; capsule; oral	Once or twice daily (extended release)	Theo-24; generic	Oral

Pharmacotherapy for COPD involves use of inhaled medications which require patient knowledge and skill using various inhalation devices. Several delivery devices are available (ie, metered-dose inhalers [MDIs], dry powder inhalers [DPIs], soft-mist inhalers [SMIs], nebulizers, and ancillary devices such as holding chambers), and instructions about proper use vary (see Chapter 43, “Asthma” for an information about inhalation devices). There is no clear advantage of one delivery system over another and all devices are associated with administration errors.[38] Comorbidities common for patients with COPD, including physical and cognitive impairments, can have a significant effect on the patient’s ability to use devices and it is recommended that patient-specific factors and preferences be considered.[1] Periodic and frequent reinforcement and observation by clinicians is required to assess optimal use and determine if alternative devices or therapy is needed.

Treatment regimens with multiple inhalation devices add complexity and may adversely impact adherence and disease management. In one cohort study, patients prescribed multiple types of inhalation devices had worse outcomes (increased exacerbations and rescue therapy use) compared to patients using devices of a similar type or administration technique.[39] For patients requiring therapy with multiple inhaled medications, clinicians should prescribe devices with a similar administration technique or containing combinations of medications. Formulary restrictions and healthcare payer reimbursement issues often make this recommendation difficult to apply in practice.

Bronchodilators

7 Bronchodilators represent the mainstay of drug therapy for COPD and are used to relieve patient symptoms, improve exercise tolerance, and quality of life. For patients with COPD, clinical benefits of bronchodilators include increased exercise capacity, decreased air trapping in lungs, and relief of symptoms such as dyspnea. However, use of bronchodilators does not produce significant improvements in pulmonary function measurements of expiratory airflow such as FEV_1. Bronchodilator classes available for the treatment of COPD include short- and long-acting β_2-agonists, short- and long-acting anticholinergics, and methylxanthines. Short-acting bronchodilators relieve symptoms and increase exercise tolerance. Long-acting bronchodilators relieve symptoms, reduce exacerbation frequency, and improve quality of life and health status. In general, adverse effects of bronchodilator medications are related to their pharmacologic effects and are dose dependent. Because COPD patients are older and more likely to have comorbid conditions, risk for adverse effects and drug interactions is higher compared with patients with asthma.

Short-Acting Bronchodilators Initial recommended therapy for COPD patients who experience occasional symptoms (category A) is a bronchodilator, either long or short acting (Table 44-13). Short-acting bronchodilators are also recommended for all patients for use as rescue or as needed therapy to manage symptoms (category A, B, C, D). Among short-acting bronchodilators, choices include short-acting β_2-agonist or short-acting anticholinergic agents. Both classes of agents have a relatively rapid onset of action, relieve symptoms, and improve exercise tolerance and lung function. Of note, short-acting bronchodilators do not reduce the frequency or severity of exacerbations in COPD. Both classes are equally effective for symptom management. When a patient does not achieve adequate management of symptoms with one agent, combination of a short-acting β_2-agonist and short-acting anticholinergic is reasonable.

Short-Acting Sympathomimetics (β_2-Agonists) β_2-agonists cause bronchodilation by stimulating adenyl cyclase to increase formation of cyclic adenosine monophosphate (cAMP), which is responsible for mediating relaxation of bronchial smooth muscle. In addition, β_2-agonists may improve mucociliary clearance within the airways. In COPD patients, short-acting β_2-agonists exert a rapid onset of effect, although response generally is less than that seen in asthma. Short-acting inhaled β_2-agonists cause only a small improvement in FEV_1 acutely but may improve respiratory symptoms and

exercise tolerance despite the small improvement in spirometric measurements.

Choices for short-acting, selective β_2-agonists are albuterol and levalbuterol. Racemic epinephrine is available as an over-the-counter product but is not appropriate for chronic treatment. Albuterol is the most frequently used short-acting β_2-agonist and is a racemic mixture of (*R*)-albuterol, which is responsible for the bronchodilator effect, and (*S*)-albuterol, which has no therapeutic effect. (*S*)-Albuterol is considered by some clinicians to be inert, whereas others believe that it may be implicated in worsening airway inflammation and antagonizing the response to (*R*)-albuterol. Levalbuterol is a single-isomer formulation of (*R*)-albuterol. Despite years of clinical use, there is no compelling evidence to suggest that levalbuterol offers a clear advantage in terms of clinical effectiveness or safety over albuterol, and it is more expensive.[40]

The preferred route of administration for short-acting, selective β_2-agonists is by inhalation. Use of oral and parenteral β-agonists in COPD is discouraged because they are no more effective than properly used inhalation devices, and the incidence of systemic adverse effects such as tachycardia and hand tremor is greater. Administration of β_2-agonists in outpatient and emergency room settings via inhalers (MDIs or DPIs) is at least as effective as nebulization therapy and usually favored for reasons of cost and convenience.[1,4] Chapter 43, includes information about the devices used for delivering aerosolized medication and a comparison of β_2-agonist therapies.

Inhaled β_2-agonists are generally well tolerated. They can cause sinus tachycardia and rhythm disturbances in predisposed patients, but these are rarely reported. Skeletal muscle tremors can occur initially but generally subside as tolerance develops. Older patients may be more sensitive and may experience palpitations, skeletal muscle tremors, and “jittery” feelings after β_2-agonist use.

Short-Acting Anticholinergics When given by inhalation, anticholinergics, also referred to as antimuscarinics, produce bronchodilation by competitively inhibiting muscarinic receptors, subtypes M_1, M_2, and M_3, in bronchial smooth muscle and mucus glands. This activity blocks acetylcholine, with the net effect being a reduction in cyclic guanosine monophosphate (cGMP), which normally acts to constrict bronchial smooth muscle, and decreased mucus secretion.

Ipratropium is the most commonly prescribed short-acting anticholinergic agent for COPD in the United States. Studies comparing ipratropium with inhaled β_2-agonists have generally reported similar improvements in pulmonary function, although ipratropium has a slower onset of action and a more

prolonged bronchodilator effect. Because of slower onset of effect (15-20 minutes compared with 5 minutes for albuterol), ipratropium may be less suitable for as-needed use; however, it is often prescribed in that manner. In contrast to albuterol, ipratropium exhibits a dose–response effect with increasing dose, rather than increasing frequency. Patients may experience additional symptom improvement with a higher number of inhalations (ie, 6 puffs Q6 hours, maximum 24 puffs/day); whereas, no additional improvement is seen with increasing the frequency (ie, more frequent than Q6 hours).[1]

Lack of systemic absorption of ipratropium greatly diminishes anticholinergic adverse effects such as blurred vision, constipation, urinary retention, nausea, and tachycardia associated with the prototype anticholinergic, atropine. The most frequent patient complaints with ipratropium are dry mouth, nausea, and an occasional metallic taste. In rare instances, inhaled anticholinergics may precipitate narrow-angle glaucoma symptoms. Compared to albuterol, ipratropium has a lower incidence of skeletal muscle tremor and tachycardia.

8 9 **Long-Acting Bronchodilators** For patients with COPD who experience persistent symptoms, or in whom short-acting therapies do not provide adequate relief, long-acting bronchodilator therapies are recommended (Table 44-13). Long-acting agents are also recommended for patients at high risk for exacerbation (category C and D). Long-acting inhaled bronchodilator therapy can be administered as an inhaled β_2-agonist (LABA) or an anticholinergic (LAMA). Compared with short-acting agents, long-acting inhaled bronchodilator therapy is more convenient for patients with persistent symptoms and has shown superior outcomes in improving lung function, relieving symptoms, and importantly reductions in exacerbation frequency and improved quality of life. For symptom management, both LABAs and LAMAs are equally effective. However, LAMAs appear to be slightly more effective at preventing exacerbations. Treatment selection should consider individual patient response, tolerability, adherence, and economic factors.

Long-Acting Inhaled β_2-Agonists Multiple LABAs are currently available in the United States (Table 44-14) and differ primarily by dosing frequency (twice daily vs once daily) and device type (SMI, DPI, nebulizer). One LABA, vilanterol, is currently available in the United States only in combination with an inhaled corticosteroid (fluticasone) or long-acting anticholinergic (umeclidinium). Arformoterol, formoterol, indacaterol, and olodaterol have an onset of action similar to albuterol (less than 5 minutes), whereas salmeterol has a slower onset (15-20 minutes); however, none of these agents are recommended

for acute relief of symptoms in COPD. There is no dose titration for any of these agents; the starting dose is the effective and recommended dose for all patients.

Clinical benefits of LABAs compared with short-acting bronchodilators include similar or superior improvements in lung function and symptoms, as well as reduced exacerbation rates and need for hospitalization.[41] The use of the long-acting agents should be considered for patients with frequent and persistent symptoms and those at higher risk for exacerbation (see Table 44-13). When patients require short-acting β_2-agonists on a scheduled basis, LABAs are more convenient based on dosing frequency but may be more expensive. In contrast to their use in asthma, LABA monotherapy for COPD is not associated with increased mortality and is recommended as part of international guidelines.

Long-acting β_2-agonists are similar with regards to impact on disease outcomes. Salmeterol and formoterol improve lung function, symptoms, exacerbation frequency, and associated hospitalizations.[1] Indacaterol improves symptoms, health status, and frequency of exacerbations.[1] Olodaterol also decreases symptoms and improves lung function, but evidence for exacerbation outcomes are more limited. Effect of olodaterol on exacerbation frequency has not been comparatively evaluated when used as monotherapy; however when used with tiotropium it moderately reduces exacerbations requiring systemic corticosteroids compared to tiotropium monotherapy alone.[42]

Long-Acting Anticholinergics Several LAMAs are currently available in the United States (Table 44-14) and differ in terms of dosing frequency (twice daily vs once daily) and device type (SMI, DPI, nebulizer). Long-acting anticholinergic agents are more selective than ipratropium at blocking important muscarinic receptors. They dissociate slowly from M_3 receptors, resulting in prolonged bronchodilation with once or twice a day dosing.[43] Aclidinium, glycopyrrolate, and umeclidinium have a faster onset of action (5-15 minutes) compared to tiotropium (80 minutes); however, none of these agents are recommended for acute relief of symptoms. There is no dose titration for any of these agents; the starting dose is the effective and recommended dose for all patients.

Clinical benefits of LAMAs compared with placebo or short-acting bronchodilators include superior improvements in lung function and symptoms, as well as reduced exacerbation rates and hospitalization.[43,44] Available in the United States since 2004, tiotropium is the most extensively studied LAMA with regards to comparative outcomes. In clinical trials, aclidinium and glycopyrrolate have been shown to have similar improvements in lung function

and symptoms compared to tiotropium and also reduce frequency of exacerbations.[45–48] Clinical benefits of umeclidinium have primarily been evaluated as part of combination bronchodilator regimens.

8 9 Long-acting anticholinergics provide similar improvement for symptoms and health status compared to long-acting β_2-agonists and either class is an appropriate choice for patients with persistent symptoms or those needing a step-up from short-acting agents. When evaluating exacerbation outcomes, LAMAs (primarily tiotropium) provide a greater reduction in exacerbation frequency compared to LABAs and should be considered as first-line monotherapy for patients at high risk for exacerbation (Table 44-13) Compared to combination therapy with ICS/LABA (fluticasone/salmeterol), tiotropium monotherapy showed similar reduction in exacerbation rate and less pneumonia events, although combination therapy was associated with a higher study completion.[49]

Long-acting anticholinergics have been evaluated in clinical trials to determine potential impact of bronchodilator therapy on progression of lung function decline. In the landmark clinical trial UPLIFT, patients were randomized to therapy with either placebo or inhaled tiotropium and lung function decline was followed for 4 years.[50] Tiotropium was not shown to have significant effect on lung function decline over time but was effective for reducing symptoms and frequency of exacerbations. Patients in this trial were in more advanced stages of COPD as reflected by the mean postbronchodilator FEV_1 of 1.32 L, corresponding to 48% of predicted FEV_1 or GOLD spirometric stage 3. More recently, tiotropium has again been evaluated for its effect on lung function, but this time in patients in earlier stages of the disease. In the Tie-COPD trial, patients with an FEV_1 >50% (0.50) of predicted (GOLD spirometric grade 1 or 2) were randomized to placebo or tiotropium and lung function decline followed for 2 years.[51] At the end of the trial, patients in the tiotropium group had a higher measured FEV_1 and slower annual decline compared to patients in the placebo group. Application of these results to clinical practice may be difficult given that current goals for inhaled therapy are targeted at patients with symptoms or those at high risk of future exacerbation. Slowing lung function has not yet been a therapeutic target with inhaled therapy. If used in early stage disease, it would require patients who do not yet have symptoms or experienced an exacerbation to commit to long-term maintenance therapy. Future studies are needed to determine optimal timing and length of therapy.

Previously, retrospective analyses have reported an increased risk of

cardiovascular events associated with ipratropium and tiotropium use.[52] However, the UPLIFT study, which was a prospective trial over 4 years, did not report an increased cardiovascular risk associated with tiotropium use.[50] Additionally, a prospective, noninferiority trial (TIOSPIR) has been published which compared the effects of tiotropium delivered via Handihaler or Respimat devices among 17,000 patients with COPD over a median 2.3-year period.[53] Primary outcomes in this trial were risk of death and risk of first COPD exacerbation. Secondary outcomes included cardiovascular safety. No significant differences were seen in any of the primary or secondary outcomes when comparing tiotropium delivery devices. Further studies are needed to evaluate the cardiovascular safety of ipratropium.

Combination Anticholinergics and β-Agonists (Dual Bronchodilators)
Combination regimens of bronchodilators are often used in the treatment of COPD as symptoms worsen over time. Combining bronchodilators with different mechanisms of action allows the lowest possible effective doses to be used and reduces potential adverse effects from individual agents.[1] Short-acting bronchodilators may be combined for patients experiencing persistent symptoms, although step up to long-acting bronchodilator monotherapy is usually preferred (Table 44-13).

Current clinical practice guidelines recommend combining long-acting bronchodilators for patients who have persistent symptoms or recurrent exacerbations on bronchodilator monotherapy (Table 44-13). Combination of long-acting bronchodilators (LAMA/LABA) provides significant improvement in lung function, symptoms, and quality-of-life measures compared with LABA or LAMA monotherapy.[1,54] In addition, dual long-acting bronchodilator therapy has been shown to decrease frequency of moderate-to-severe exacerbations compared to either LAMA or LABA monotherapy.

Methylxanthines Methylxanthines, including theophylline and aminophylline, may produce bronchodilation through numerous mechanisms, including (a) inhibition of phosphodiesterase, thereby increasing cAMP levels, (b) inhibition of calcium ion influx into smooth muscle, (c) prostaglandin antagonism, (d) stimulation of endogenous catecholamines, (e) adenosine receptor antagonism, and (f) inhibition of release of mediators from mast cells and leukocytes.[1] Chronic theophylline use for patients with COPD may offer improvements in lung function and gas exchange. Subjectively, theophylline has been shown to reduce dyspnea, increase exercise tolerance, and improve respiratory drive in COPD patients.[1]

Methylxanthines have been available for the treatment of COPD for at least five decades and at one time were considered first-line therapy. However, with availability of LABAs and LAMAs, the role of methylxanthine therapy has become more limited. Because of risk for drug interactions and significant intrapatient and interpatient variability in dosage requirements, theophylline therapy generally is considered for patients who are intolerant or unable to use an inhaled bronchodilator. Theophylline is still an alternative to commonly used inhaled therapies and systemic administration may have a beneficial effect on peripheral airways.[1]

Although theophylline is available in a variety of oral dosage forms, sustained-release preparations are most appropriate for the long-term management of COPD. These products have the advantages of improving medication adherence and achieving more consistent serum concentrations over rapid-release theophylline and aminophylline preparations. However, caution must be used in switching from one sustained-release preparation to another because there is considerable variability in their sustained-release characteristics.[55]

Therapy can be initiated at 200 mg twice daily and titrated upward every 3 to 5 days to the target dose. Most patients require daily doses of 400 to 900 mg. Dosage adjustments generally should be made based on serum concentration results. Traditionally, the therapeutic range of theophylline has been 10 to 20 mcg/mL (mg/L; 55 to 111 µmol/L); however, because of the frequency of dose-related adverse effects and a lack of a clear benefit when used in higher concentrations, a more conservative therapeutic range of 8 to 15 mcg/mL (mg/L; 44 to 83 µmol/L) is now targeted, especially in the elderly. When concentrations are measured, trough measurements should be obtained.

Once a dose is established, serum concentrations should be monitored once or twice a year unless the patient’s disease worsens, medications that interfere with theophylline metabolism are added to therapy, or toxicity is suspected. Adverse effects are dose related; however, there is an overlap between therapeutic and toxic ranges. Minor adverse effects include dyspepsia, nausea, vomiting, diarrhea, headache, dizziness, and tachycardia. More serious toxicities, which typically do not occur until concentrations exceed 20 mcg/mL (mg/L; 111 µmol/L), include arrhythmias and seizures.

Factors that decrease theophylline clearance and lead to reduced maintenance dose requirements include advanced age, bacterial or viral pneumonia, left or right ventricular failure, liver dysfunction, hypoxemia from acute decompensation, and use of drugs such as cimetidine, macrolides, and

fluoroquinolone antibiotics. Factors that may enhance theophylline clearance and result in the need for higher maintenance doses include tobacco and marijuana smoking, hyperthyroidism, and the use of such drugs as phenytoin, phenobarbital, and rifampin.

In summary, there are decades of experience with theophylline and other methylxanthine products in the management of patients with COPD. However, inhalation therapy is currently preferred based on superior efficacy and safety, as well as ease of use. Theophylline is a challenging medication to dose, monitor, and manage due to the significant intrapatient and interpatient variability in pharmacokinetics and the potential for drug interactions and toxicities.

Corticosteroids Anti-inflammatory mechanisms whereby corticosteroids exert their beneficial effect in COPD include (a) reduction in capillary permeability to decrease mucus, (b) inhibition of release of proteolytic enzymes from leukocytes, and (c) inhibition of prostaglandins. The benefits of chronic systemic corticosteroid therapy in the chronic management of COPD are not clear and risk of toxicity is significant. Long-term adverse effects associated with systemic corticosteroid therapy include osteoporosis, muscular atrophy, thinning of the skin, development of cataracts, and adrenal suppression and insufficiency. Therefore, chronic therapy with oral steroids should be avoided in COPD patients.[1] While a small number of COPD patients are responders to oral steroids, many of these patients actually may have an asthmatic, or reversible, component to their disease. Asthma-COPD Overlap (ACO) syndrome is now a recognized condition affecting both asthma and COPD patients, and patients exhibiting this syndrome may benefit from therapies traditionally considered for asthma alone.[18] Currently, appropriate situations to consider corticosteroids in COPD include as inhalation therapy for chronic stable COPD in patients at high risk of exacerbation (category C or D) and short-term systemic use for acute exacerbations (Tables 44-13 and 44-19).

10 It has been postulated that inhaled corticosteroid therapy might be beneficial in COPD to slow disease progression. Unfortunately, results of major clinical trials have failed to demonstrate any clear benefit from chronic treatment with ICS in modifying long-term decline in lung function.[1] However, ICS have been associated with other benefits in some patients, including a decrease in exacerbation frequency and improvements in lung function and health status.[1,56] Clinical benefits of ICS therapy in COPD have been observed with combination therapy, primarily as an addition to LABA monotherapy. Given lack of supporting evidence and in contrast to evidence in patients with asthma, ICS

monotherapy for patients with COPD is not recommended.

Although a dose–response relationship for ICS has not been demonstrated in COPD, major clinical trials employed moderate-to-high doses for treatment. At these doses, adverse effects must be considered with long-term therapy. Recent trials have reported an increased risk of pneumonia and mycobacterial pulmonary infections in patients with COPD.[56–58] Risk factors for developing pneumonia include age >55 years, body mass index (BMI) less than 25 kg/m^2, current smoker, history of exacerbation or pneumonia (last 12 months), or severe airflow limitation.[1] Other adverse effects include hoarseness, sore throat, oral candidiasis, and skin bruising. Severe adverse effects, such as adrenal suppression, osteoporosis, and cataract formation, have been reported less frequently than with systemic corticosteroids, but clinicians should monitor patients who are receiving high-dose chronic therapy.

There has been conflicting evidence supporting a dose relationship between ICS use and risk of fractures among patients with COPD. A recent nested, case-control analysis of over 200,000 patients observed an increased risk of fracture with higher daily doses of ICS and long-term use (>4 years).[59] Given this evidence, it appears prudent to treat patients with the lowest effective dose of ICS to minimize risk of fracture. Clinicians should also recommend adequate intake of calcium and vitamin D and consider periodic bone mineral density testing for patients at risk of osteopenia.

Currently, the recommended role of ICS therapy is for patients at high risk of exacerbation (category C and D) who have recurrent exacerbations despite optimal therapy with inhaled bronchodilators. Given the risks associated with long-term ICS therapy, clinicians should appropriately identify patients who will receive the best benefit. Evaluations of current practice have shown that many patients with COPD may be inappropriately prescribed an ICS (ie, not high risk for exacerbations), exposing them to unnecessary adverse effects.[60] In order to best target therapy, consensus guidelines now propose using blood eosinophil counts to identify patients with COPD who might benefit from chronic treatment with ICS (Table 44-13).

Given concern for increased pulmonary infections among patients treated with ICS and growing evidence for benefit of dual bronchodilator therapy, some clinicians have advocated for withdrawing ICS therapy.[61] Two recent trials have evaluated the impact of withdrawing ICS therapy in patients with moderate and severe COPD.[62,63] In the INSTEAD trial, patients with moderate COPD and low risk of exacerbations (eg, no exacerbation in the previous 12 months) were transitioned from salmeterol/fluticasone combination therapy to indacaterol

alone. At 12 weeks, there was no difference in lung function, symptoms or health status between treatment groups. Effect of therapy change on long-term risk of exacerbation was not evaluated.[62] In the WISDOM trial, patients with severe COPD receiving “triple therapy” (LAMA/LABA/ICS) had their ICS tapered over 12 weeks and then discontinued. Discontinuation of ICS therapy did not result in a significant increase in exacerbations. However, some patients experienced a decrease in FEV_1 or return of symptoms with ICS withdrawal.[63] These trials provide more information to clinicians who may wish to scale back ICS therapy due to observed adverse effects, such as recurrent pneumonia, or in patients who are not at high risk for exacerbations and can be maintained on long-acting bronchodilators alone.

Combination Therapy: Dual Therapy (LAMA/LABA or ICS/LABA) For patients with recurrent exacerbations despite optimal long-acting bronchodilator monotherapy, combination therapy with dual long-acting bronchodilators (LAMA/LABA) is preferred over combination therapy with ICS/LABA (Table 44-13).[1,64] This recommendation is based on results of the FLAME trial which reported superior efficacy with regards to exacerbation prevention with LAMA/LABA (glycopyrrolate/indacaterol) therapy compared to ICS/LABA (fluticasone/salmeterol) and a lower rate of pneumonia (3.2% for LAMA/LABA vs 4.8% for ICS/LABA).[65] Dual therapy with ICS/LABA may be considered instead of LAMA/LABA for patients with blood eosinophil ≥ 300 cells/μL (0.3×10^9/L) or ≥ 100 cells/uL and ≥ two moderate exacerbations or one exacerbation requiring hospitalization in the last year (high risk).[1]

A more recent study appears to contradict the superiority of LAMA/LABA over ICS/LABA for exacerbation prevention. In the IMPACT trial, which was a three-arm study designed to evaluate the benefit of escalation to triple therapy (LAMA/LABA/ICS) versus dual therapy with ICS/LABA or LAMA/LABA, exacerbation prevention was greater in the ICS/LABA group compared to the LAMA/LABA group.[66] While these results are in contrast to the outcomes of the FLAME trial, it is important to note that 70% of patients enrolled in the IMPACT trial were already receiving ICS prior to randomization and the run-in period after randomization was only 2 weeks. Thus, patients on ICS and randomized to the LAMA/LABA group effectively discontinued ICS therapy without tapering and may account for the higher number of exacerbations seen initially after randomization. Additionally, patients with asthma were not excluded from this study, which may account for the lower exacerbation rate observed in the ICS/LABA group compared to the LAMA/LABA group.

Combination Therapy: Triple Therapy (LAMA/LABA/ICS) For patients with persistent symptoms and recurrent exacerbations on dual inhaled therapy, triple therapy with LAMA/LABA/ICS is recommended as initial escalation therapy (Table 44-13). Evidence for the benefit of triple therapy has emerged from recent studies evaluating combination therapy within a single device and there is also limited evidence supporting triple therapy given by multiple devices.[66–69] Compared to dual therapy with either LAMA/LABA or ICS/LABA, triple therapy with LAMA/LABA/ICS provides additional benefit in reducing frequency of moderate-to-severe exacerbations in patients with COPD. Given the risk of adverse effects with ICS, clinicians may consider by-passing triple inhalation therapy (LAMA/LABA/ICS) for those patients with persistent exacerbations and lower blood eosinophil count (<100 cells/μL [0.1 x 10^9/L]) in favor of oral alternatives such as roflumilast or azithromycin.[1]

Phosphodiesterase Inhibitors

Phosphodiesterase 4 (PDE4) is the major phosphodiesterase found in airway smooth muscle cells and inflammatory cells and is responsible for degrading intracellular cAMP. Inhibition of PDE4 results in relaxation of airway smooth muscle cells and decreased activity of inflammatory cells and mediators such as TNF-α and IL-8. Roflumilast, an oral PDE4 inhibitor available in the United States, is recommended for patients with recurrent exacerbations despite treatment with triple inhalation therapy (LAMA/LABA/ICS) (Table 44-13).[1] It may also be considered as escalation therapy for patients with recurrent exacerbations on dual long-acting bronchodilators (LAMA/LABA) who are not candidates for ICS such as those with low blood eosinophil count (<100 cells/μL [0.1 x 10^9/L]) or who are at higher risk of adverse effects associated with ICS. Given both theophylline and roflumilast have similar mechanisms of action through inhibition of phosphodiesterases, both should not be used together for the management of COPD.

Roflumilast has bothersome adverse effects that may limit therapy in some patients.[70] Major effects include diarrhea, nausea, decreased appetite, weight loss, headache and neuropsychiatric effects such as suicidal thoughts, insomnia, anxiety, and new or worsened depression. Most symptoms such as diarrhea, nausea, and headache occur early after initiation and usually resolve over time. In order to avoid adverse effects and early discontinuation of therapy, it is recommended to start dosing at 250 mcg orally for 4 weeks and then increase to a maintenance dose of 500 mcg orally once a day. Weight loss (average of 2 kg) may be of concern in patients with low BMI and discontinuation may be

necessary if significant weight loss is observed. Use of roflumilast is cautioned in patients with a history of depression or suicidality. Both patients and family members should be counseled regarding the potential for mood and behavior changes and to alert healthcare providers if they occur.

Roflumilast is metabolized by CYP3A4 and 1A2 and coadministration with strong inducers of cytochrome P450 is not recommended due to potential for subtherapeutic plasma concentrations. Although there are no recommended dose adjustments, caution should also be used when administering roflumilast with strong inhibitors of cytochrome P450 due to potential for adverse effects.

Azithromycin

In certain pulmonary conditions such as cystic fibrosis and bronchiectasis, chronic therapy with macrolide antibiotics, specifically azithromycin, has proven clinical benefit. In a study evaluating chronic azithromycin in patients with COPD, patients were randomized to azithromycin (250 mg orally daily) or placebo in addition to maintenance therapy for COPD and were followed for 1 year.[71] Chronic azithromycin was associated with a lower rate of exacerbations and improved quality-of-life scores; however, more patients in the azithromycin group reported hearing deficits (25% vs 20% in the placebo group). Of note, patients who continued to smoke did not have a reduction in exacerbation frequency with azithromycin. Therapy with azithromycin was also associated with a higher rate of colonization with macrolide-resistant bacteria. Patients were carefully screened for hearing impairment and risk factors for QT prolongation prior to entering the study and were excluded if either was present.

In 2012, a retrospective, observational study reported an increase in cardiac events with short courses of azithromycin.[72] The FDA has since updated product labeling to include a precaution about QT prolongation. Given limited evidence supporting the use of long-term treatment (beyond 1 year) with azithromycin, it would be prudent to wait for more safety data before routinely recommending this therapy for patients with COPD who are at high risk for exacerbations. Current guidelines recommend to only consider the addition of chronic azithromycin for patients with recurrent exacerbations despite optimal therapy and who are not active smokers (Table 44-13). Clinicians may choose to consider azithromycin for individual patients at high risk for exacerbations but must carefully weigh the risks and benefits of therapy.

α_1-Antitrypsin Replacement Therapy

For patients with inherited AAT deficiency-associated emphysema, treatment focuses on reduction of risk factors such as smoking, symptomatic treatment with bronchodilators, and augmentation therapy with replacement AAT. Based on knowledge about the relationship between serum concentrations of AAT and the risk of developing emphysema, augmentation therapy is intended to maintain serum concentrations above the protective threshold throughout the dosing interval.[1,16] Augmentation therapy consists of weekly infusions of pooled human AAT to maintain AAT plasma levels over 10 μmol/L (0.54 g/L). Much of the data supporting the use of AAT replacement are based on evidence of biochemical efficacy (eg, administering the product and demonstrating protective serum concentrations of AAT).

Clinical evidence for slowing lung function decline or improving outcomes with augmentation therapy is sparse. Stated challenges to performing randomized clinical trials include the large sample size and long duration of follow-up required, and expense of conducting such a trial. One observational study followed patients in the National Registry of Severe AAT Deficiency over a period of several years and documented clinical outcomes. In this study, patients who received weekly augmentation therapy with purified AAT had slower declines in FEV_1 and decreased mortality compared with patients who never received augmentation therapy.[73] However, this was an observational study, not a randomized, placebo-controlled trial, and so direct cause-and-effect relationships cannot be concluded. One randomized, placebo-controlled study of patients with severe AAT deficiency (ZZ phenotype) did show a significant reduction in lung tissue loss as measured by computed tomographic (CT) scan for patients receiving augmentation therapy.[74] Other measures of lung function and mortality were not reported.

The recommended dosing regimen for replacement AAT is 60 mg/kg administered IV once a week at a rate of 0.08 mL/kg/min, adjusted to patient tolerance. Augmentation therapy can cost over $50,000 annually. In the absence of alternative treatments, it is difficult to assess the cost-effectiveness using conventional criteria. AAT replacement therapy is derived from pooled blood donors. There have been repeated problems with supply of this product due to production and contamination issues. Currently, there are several products available (Glassia [Kamada], Prolastin-C [Talecris], Aralast and Aralast-NP [Baxter], Zemaira [Aventis Behring]) which should minimize interruption in product supply in the future. Drug development research continues in the area of recombinant products and AAT replacement via inhalation.

Other Pharmacologic Considerations

A number of other treatments have been explored over the years. Among these therapies, either there is insufficient evidence to warrant recommending their use or they have been proven to not be beneficial in the management of COPD. A brief summary is provided because the clinician likely will encounter patients who are receiving or inquire about these treatments.

Expectorants and Mucolytics

Adequate water intake generally is sufficient to maintain hydration and assist in the removal of airway sections. Mucolytics and expectorants such as compounded saturated solutions of potassium iodide, ammonium chloride, N-acetylcysteine, and guaifenesin have been evaluated as adjunctive therapy for patients with COPD. In one trial, patients with moderate-to-severe COPD were randomized to either placebo or oral N-acetylcysteine 600 mg twice daily for 1 year. Patients were not required to be on ICS prior to randomization. N-acetylcysteine was associated with a significant decrease in exacerbation rate among patients with moderate disease only.[75] Strong evidence of clinical benefit is lacking for the routine use of mucolytics in the treatment of COPD.[76]

In 2011, FDA removed unapproved cough and cold preparations, including several containing guaifenesin, from the market due to safety and efficacy concerns. Two extended-release tablet formulations are currently approved by the FDA. Other approved formulations of guaifenesin contain dextromethorphan or pseudoephedrine and should not be used for COPD maintenance therapy.

Opioids

Systemic (oral and parenteral) opioids, especially morphine, can relieve dyspnea for patients with end-stage COPD. Nebulized therapy is sometimes used in clinical practice, although data about clinical benefit are lacking. Opioids should be used carefully, if at all, to avoid reducing ventilatory drive.

Investigational Therapies

Based on knowledge about the importance of neutrophilic inflammation in COPD and potential therapeutic benefit of inhibition of neutrophil activity, a number of anti-inflammatory compounds have been explored. Many studies of these strategies have been disappointing. Infliximab, a TNFα-blocker, failed to demonstrate any benefits on quality of life or secondary end-points including

lung function, exercise capacity, or exacerbation rates. The discontinuation rate due to adverse events was high (20%-27%) in the active treatment group.[77] Other current areas of investigation include p38 mitogen activated protein kinase inhibitors (MAPK), inhibitors of interleukin 1 and interleukin 5, epithelial growth factor receptor inhibitors, and neutrophil elastase inhibitors.[78]

The role of HMG-CoA reductase inhibitors for patients with COPD has garnered interest due to known pleiotropic effects statins and role of systemic inflammation in COPD. Retrospective and observational trials have reported previous associations with simvastatin therapy and reduction in exacerbation frequency, although this effect was not confirmed in a prospective, randomized trial.[79]

Complications of Progressive COPD

Pulmonary Hypertension

Pulmonary hypertension associated with COPD (PH-COPD) may occur in up to 30% of patients and is associated with increased mortality.[80] Given the management complexity of patients with pulmonary hypertension, referral to expert centers specializing in PH is recommended. Investigations of pharmacologic therapy typically used in the treatment of pulmonary arterial hypertension (ie, endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, prostacyclin analogs) for patients with PH-COPD are limited and provide conflicting results. Due to concerns of worsening gas exchange in patients with COPD, pulmonary vasodilators are not recommended outside of clinical trials or specialized pulmonary hypertension centers.

Cor Pulmonale

Cor pulmonale is right-sided heart failure secondary to pulmonary hypertension. Long-term oxygen therapy and diuretics are mainstays of therapy for cor pulmonale. Increasing PaO_2 above 60 mm Hg (8.0 kPa) with supplemental oxygen therapy decreases pulmonary hypertension and resistance against which the right ventricle has to work. While diuretics may help decrease fluid overload, caution should be used because patients with significant right-sided heart failure are highly dependent on preload for cardiac output. Digitalis glycosides have no role in the treatment of cor pulmonale.

Beta-blocker therapy is indicated to treat systolic heart failure including patients who have experienced a myocardial infarction. Beta-blocker therapy can

present unique challenges for patients with airway disease but are generally well tolerated by patients with COPD who do not exhibit bronchial hyperreactivity. Patients with COPD should be treated with β_1-selective agents. Use of beta-blocker therapy for patients with COPD and cardiac disease has been associated with improved overall survival.[81,82]

Polycythemia

Polycythemia secondary to chronic hypoxemia in COPD patients can be improved by either continuous oxygen therapy or periodic phlebotomy if oxygen therapy alone is not sufficient. Acute phlebotomy is indicated if the hematocrit is above 55% to 60% (0.55 to 0.60) and the patient is experiencing CNS effects suggestive of sludging from high blood viscosity. Long-term oxygen then can be used to maintain a lower hematocrit.

Surgical Intervention

Various surgical options have been employed in the management of COPD.[1] These include bullectomy, lung volume reduction surgery (LVRS), and lung transplantation. Presence of bullae may contribute to complaints of dyspnea, and their removal can improve lung function and reduce symptoms, although there is no evidence of a mortality benefit. Lung volume reduction surgery removes sections of lung to reduce hyperinflation and may improve survival in selected patients. Lung transplantation, either single or double, may improve exercise capacity and health status but median survival is only 5.5 years after transplant.[1]

COPD EXACERBATIONS

The natural history of COPD is characterized by recurrent acute exacerbations associated with increased symptoms and a decline in overall health status. An exacerbation is defined as a change in the patient's baseline symptoms (dyspnea, cough, or sputum production) beyond day-to-day variability sufficient to warrant a change in management.[1] Exacerbations have a significant impact on the natural course of COPD and occur more frequently in patients with advanced age, significant airflow limitation and comorbid conditions. Because many patients experience chronic symptoms, diagnosis of an exacerbation is based, in part, on subjective measures and clinical judgment; thus, it can be considered a syndrome. Exacerbations are significant events as they are associated with significant morbidity, including worsening health status, increased risk for acute

cardiovascular events, impairment of daily activities, and acceleration of lung function decline. Additionally, exacerbations, especially those requiring hospitalization, are associated with an increased mortality risk. Acute exacerbations have a significant impact of the economics of treating COPD as well, estimated at 35% to 45% of the total costs of the disease in some settings.[2–4]

There is limited data about pathophysiology of COPD exacerbation due to the chronic nature of the disease and the poor health of patients. Inflammatory mediators, including neutrophils and eosinophils, may be increased in sputum during an exacerbation. Airflow limitation may not change remarkably during an exacerbation compared to chronic baseline limitation.[1] Lung hyperinflation, if present, is worsened during an exacerbation, which contributes to increasing dyspnea and poor gas exchange.

The primary physiologic change is often a worsening of ABG values due to poor gas exchange and increased muscle fatigue. For a patient experiencing a severe exacerbation, profound hypoxemia and hypercapnia can be accompanied by respiratory acidosis and respiratory failure.

Criteria used to define acute exacerbation of COPD (AECOPD) among clinicians vary widely; however, most rely on a change in one or more of the following clinical findings: worsening symptoms of dyspnea, increase in sputum volume, or increase in sputum purulence (**Table 44-15**). With an exacerbation, patients using rapid-acting bronchodilators may report an increase in the frequency of use and may seek additional medical care. Acute exacerbations can range from mild to severe and are classified based on level of treatment and intervention required (**Table 44-16**).

TABLE 44-15 Staging Acute Exacerbations of COPD[a]

Mild (type 1)	One cardinal symptom[a] plus at least one of the following: URTI[b] within 5 days, fever without other explanation, increased wheezing, increased cough, increase in respiratory or heart rate >20% above baseline
Moderate (type 2)	Two cardinal symptoms[a]
Severe (type 3)	Three cardinal symptoms[a]

[a]Cardinal symptoms include worsening of dyspnea, increase in sputum volume, and increase in sputum purulence.

[b]URTI, upper respiratory tract infection.

TABLE 44-16 Classification of Acute Exacerbation of COPD

Severity	Definition
Mild	Treated with short-acting bronchodilators only No treatment with antibiotics or systemic corticosteroids required
Moderate	Treated with short-acting bronchodilators Treatment with antibiotics and/or systemic corticosteroids required
Severe	Treated with short-acting bronchodilators Treatment with antibiotics and/or systemic corticosteroids required Treatment requires hospitalization or visit to emergency department May be associated with acute respiratory failure

An important complication of a severe exacerbation is acute respiratory failure. In the emergency department or hospital, an ABG usually is obtained to assess the severity of an exacerbation. The diagnosis of acute respiratory failure in COPD is made based on an acute change in the ABGs. Defining acute respiratory failure as a PaO_2 of less than 50 mm Hg (6.7 kPa) or a $PaCO_2$ of greater than 50 mm Hg (6.7 kPa) often may be incorrect and inadequate because these values may not represent a significant change from a patient's baseline values. A more precise definition is an acute drop in PaO_2 of 10 to 15 mm Hg (1.3 to 2.0 kPa) or any acute increase in $PaCO_2$ that decreases the serum pH to 7.3 or less. Additional acute clinical manifestations of respiratory failure include restlessness, confusion, tachycardia, diaphoresis, cyanosis, hypotension, irregular breathing, miosis, and unconsciousness.

CLINICAL PRESENTATION

COPD Exacerbations

Symptoms

- Increased sputum volume
- Acutely worsening dyspnea
- Chest tightness
- Presence of purulent sputum
- Increased need for bronchodilators

- Malaise, fatigue
- Decreased exercise tolerance

Physical Examination

- Fever
- Wheezing, decreased breath sounds

Diagnostic Tests

- Sputum sample for Gram stain and culture
- Chest radiograph to evaluate for new infiltrates

Prognosis

Acute exacerbations of COPD are associated with significant morbidity and mortality. While mild exacerbations may be managed at home, mortality rates are higher for patients admitted to the hospital and range from 22% to 43% after 1 year, and 36% to 49% after 2 years.[83,84] COPD exacerbations contribute to in hospital mortality and deaths after discharge, in addition to hastening the decline of lung function. Many patients experiencing an exacerbation do not have a return to their baseline clinical status for several weeks, significantly affecting their quality of life.

As many as 50% of patients hospitalized for an exacerbation are readmitted within 6 months.[2–4] Risk factors for relapse and potential readmission include FEV_1 less than 50% (0.50) of predicted, severity of exacerbation, previous exacerbation frequency, presence of comorbidities and inadequate antibiotic therapy.[85] As part of the 2010 Affordable Care Act, the Hospital Readmission Reduction Program was established by the Centers for Medicare and Medicaid Services (CMS) which incentivizes healthcare organizations to reduce readmission rates for selected conditions, including COPD. The most important predictor for future exacerbation is past exacerbation history; thus, prevention of AECOPD is a major therapeutic goal for patients with a history of frequent exacerbations (ie, high risk).

TREATMENT

COPD Exacerbations

Desired Outcomes

11 Goals of therapy for patients experiencing acute exacerbations of COPD are to minimize the negative consequences of the acute exacerbation (ie, reduce symptoms, prevent hospitalization, shorten hospital stay, prevent acute respiratory failure or death) and prevent future exacerbations.[1] Factors that influence severity, and subsequently level of care required, include the severity of airflow limitation, presence of comorbidities, and history of previous exacerbations. Table 44-17 includes factors that warrant treatment in the hospital and Table 44-18 describes assessment of hospitalized patients for presence of acute respiratory failure.

TABLE 44-17 Factors Favoring Hospitalization for Treatment of COPD Exacerbation

Presence of high-risk comorbidity (eg, pneumonia, arrhythmia, CHF, diabetes, renal or hepatic failure)
Suboptimal response to outpatient management
Marked worsening of dyspnea
Inability to eat or sleep due to symptoms
Worsening hypoxemia or hypercapnia
Mental status changes
Lack of home support for care
Uncertain diagnosis

TABLE 44-18 Assessment of Patients Hospitalized for Acute Exacerbations of COPD

Assessment	Presentation
No respiratory failure	Respiratory rate 20-30 bpm No use of accessory muscles No changes in mental status Hypoxemia improved with supplemental oxygen No increase in $PaCO_2$
Acute respiratory failure—not life threatening	Respiratory rate >30 bpm Using accessory muscles No changes in mental status Hypoxemia improved with supplemental oxygen Increase in $PaCO_2$ compared to baseline or 50-60 mmHg (6.7 - 8.0 kPa)
Acute respiratory failure—life threatening	Respiratory rate >30 bpm Using accessory muscles Acute changes in mental status Hypoxemia not improved with supplemental oxygen or need for FIO_2 >40% (0.40) Increase in $PaCO_2$ compared to baseline or >60 mmHg (8.0 kPa) or acidosis (pH <7.25)

bpm, beats per minute.

Various therapeutic options for exacerbation management are summarized in Table 44-19. Pharmacotherapy consists of intensification of bronchodilator therapy and a short course of systemic corticosteroids. Antimicrobial therapy is indicated in the presence of selected symptoms. Since the frequency and severity of exacerbations are closely related to each patient's overall health status, all patients should receive optimal chronic treatment, including smoking cessation, appropriate pharmacologic therapy, and preventative therapy such as vaccinations.

TABLE 44-19 Therapeutic Options for Acute Exacerbations Exacerbations of COPD

Therapy	Comments
Antibiotics	Recommended if all three of the following cardinal symptoms are present: • Increased dyspnea • Increased sputum production • Increased sputum purulence Recommended if at least two of the following cardinal symptoms are present as long as one of the symptoms is increased sputum purulence: • Increased dyspnea • Increased sputum production • Increased sputum purulence Recommended for patients requiring mechanical ventilation (either noninvasive or invasive) regardless of symptoms present Recommended treatment duration is 5-7 days
Corticosteroids	Oral or IV therapy may be used for total duration of 5-7 days If IV is used, it should be changed to oral after improvement in pulmonary status If continued longer than 14 days, then the dose should be tapered to avoid HPA Axis suppression
Bronchodilators	MDIs and DPIs equal in efficacy to nebulization β-Agonists also may increase mucociliary clearance Long-acting β-agonists or long-acting antimuscarinics should not be used for quick relief of symptoms or on an as-needed basis
Controlled oxygen therapy	Titrate oxygen to desired oxygen saturation (>90% [0.90]) Monitor arterial blood gas for development of hypercapnia
Noninvasive mechanical ventilation	Consider for patients with acute respiratory failure Not appropriate for patients with altered mental status, severe acidosis, respiratory arrest, or cardiovascular instability

Nonpharmacologic Therapy

Controlled Oxygen Therapy

Oxygen therapy should be provided for patients with significant hypoxemia during an exacerbation (eg, oxygen saturation less than 90% [0.90]). Caution must be used, however, because many patients with COPD rely on mild

hypoxemia to trigger their drive to breathe. In healthy individuals, drive to breathe is triggered by carbon dioxide accumulation. For patients with COPD who retain carbon dioxide as a result of disease progression, hypoxemia rather than hypercapnia becomes the main trigger for respiratory drive. Overly aggressive administration of oxygen to patients with chronic hypercapnia may result in respiratory depression and respiratory failure. Oxygen therapy should be used to achieve a PaO_2 of greater than 60 mm Hg (8.0 kPa) or oxygen saturation of greater than 90% (0.90). An ABG should be obtained after oxygen initiation to monitor carbon dioxide retention resulting from hypoventilation.

Noninvasive Mechanical Ventilation

Noninvasive positive-pressure ventilation (NPPV) provides ventilatory support with oxygen and pressurized airflow using a face or nasal mask with a tight seal but without endotracheal intubation. There have been numerous trials reporting the benefits of NPPV for patients with acute respiratory failure due to COPD exacerbations. NPPV has been associated with lower mortality, lower intubation rates, and shorter hospital stays for COPD exacerbations. A recent analysis regarding NPPV in patients with respiratory failure in general included a subset of patients with COPD and reported that the risk of hospital-based mortality and long-term mortality was reduced by 56%.[86] Benefits seen with NPPV generally can be attributed to a reduction in the complications that often arise with invasive mechanical ventilation. Not all patients with COPD exacerbations are appropriate candidates for NPPV. Patients with altered mental status may not be able to protect their airway and thus may be at increased risk for aspiration. Patients with severe acidosis (pH <7.25), respiratory arrest, or cardiovascular instability should be not considered for NPPV. Patients failing a trial of NPPV or those considered poor candidates should be considered for intubation and mechanical ventilation if appropriate based on the patient's goals of care.

Pharmacologic Therapy

Bronchodilators

During exacerbations, intensification of bronchodilator regimens is used commonly. Short-acting β_2-agonists are preferred due to their rapid onset of action. The doses and frequency of bronchodilator administration can be increased to provide symptomatic relief. Anticholinergic agents may be added if symptoms persist despite increased doses of β_2-agonists. Combinations of these

agents are employed often, although data are lacking about their benefit versus using higher doses of a single agent. Bronchodilators may be administered via MDIs or nebulization with equal efficacy.[1] Nebulization may be considered for patients with severe dyspnea who are unable to hold their breath after actuation of an MDI. Evidence supporting the use of theophylline during exacerbations is lacking, and thus theophylline generally should be avoided due to concern for adverse effects.

Corticosteroids

Treatment with systemic corticosteroids in acute exacerbations of COPD (AECOPD) has been shown to improve oxygenation, recovery time, shorten hospitalization, and reduce risk of relapse.[4,87] Studies have varied with regards to severity of exacerbation (ie, moderate or severe), clinical setting (ie, outpatient management or hospitalization), and dosing regimen (ie, dose, route, frequency, and duration). Several trials including hospitalized patients have used high initial doses (often intravenous) before tapering to a lower oral dose to complete duration of therapy. Adverse effects such as hyperglycemia, insomnia, and hallucinations may occur at higher doses. Depending on clinical status of the patient, treatment may be initiated at a lower dose or tapered more quickly if these effects occur.

Optimal corticosteroid dosing regimen for each presentation of AECOPD is not known, although it appears that a regimen of prednisone 40 mg orally daily (or equivalent) for 5 days can be effective for most patients. The REDUCE trial evaluated a 5-day course of prednisone 40 mg versus 14 days in a noninferiority study.[88] Shorter treatment duration was noninferior to longer treatment duration for the primary outcome of time to next exacerbation and resulted in less systemic corticosteroid exposure. If steroid treatment is continued for greater than 2 weeks, a tapering oral schedule should be employed to avoid hypothalamic–pituitary–adrenal (HPA) axis suppression.

Antimicrobial Therapy

12 Most acute exacerbations of COPD are caused by viral or bacterial infections. However, as many as 30% of exacerbations are caused by unknown factors.[1] Data supporting the use of antibiotics for COPD exacerbations are remarkably sparse. In order to limit unnecessary use, antibiotics should be initiated in any of these clinical situations: (1) patients presenting with three cardinal symptoms of AECOPD, (2) patients presenting with two cardinal

symptoms as long as one is increased sputum purulence, and (3) patients requiring mechanical ventilation (noninvasive or invasive) regardless of symptoms (Table 44-19).[1,89] Utility of sputum Gram stain and culture is questionable, as some patients have chronic bacterial colonization of the bronchial tree between exacerbations.

C-reactive protein (CRP) has been evaluated as a potential biomarker to assist with decisions regarding the use of antimicrobial therapy for COPD exacerbations. An open-label randomized controlled trial evaluated the use of CRP measurement versus no CRP measurement when deciding on use of antibiotics for AECOPD. The primary outcome was percentage of antibiotic prescriptions issued within 4 weeks of initial exacerbation. Antibiotic prescriptions were issued less frequently when CRP levels were used to guide decisions compared to usual care. Moreover, patients in the CRP-guided group had improved COPD health status scores. The risk of hospitalization was similar in both groups. These results support the use of CRP measurements to guide antmicrobial decisions for AECOPD and is a reasonable approach to antimicrobial stewardship.[90]

Emergence of drug-resistant organisms has mandated that antibiotic regimens be chosen judiciously. Selection of empirical antimicrobial therapy should be based on the most likely organism(s) thought to be responsible for the infection based on the patient's presentation and site-specific sensitivities. The most common organisms for acute exacerbation of COPD are *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, and *Haemophilus parainfluenzae*. More virulent bacteria may be present for patients with more complicated acute exacerbations of COPD, including drug-resistant pneumococci, β-lactamase–producing *H. influenzae* and *M. catarrhalis*, and enteric gram-negative organisms, including *Pseudomonas aeruginosa*. **Table 44-20** summarizes recommended antimicrobial therapy for exacerbations of COPD and the most common organisms based on patient presentation. Therapy with antibiotics generally should be continued for at least 5 to 7 days. If the patient deteriorates or does not improve as anticipated, hospitalization may be necessary, and more aggressive attempts should be made to identify potential pathogens responsible for the exacerbation.

TABLE 44-20 Recommended Antimicrobial Therapy in Acute Exacerbations of COPD

Patient Characteristics	Likely Pathogens	Recommended Therapy
Uncomplicated exacerbations <4 exacerbations per year No comorbid illness	*S. pneumoniae* *H. influenzae* *M. catarrhalis* *H. parainfluenzae* Resistance uncommon	Macrolide (azithromycin, clarithromycin) Second- or third-generation cephalosporin Doxycycline Therapies not recommended[a]: TMP/SMX, amoxicillin, first-generation cephalosporins, and erythromycin
Complicated exacerbations Age ≥65 and >4 exacerbations per year Presence of comorbid illness	As above plus drug-resistant pneumococci, β-lactamase–producing *H. influenzae* and *M. catarrhalis*	Amoxicillin/clavulanate Fluoroquinolone with enhanced pneumococcal activity (levofloxacin, gemifloxacin, and moxifloxacin)
Presence of risk factors for colonization and infection with multi-drug resistant pathogens Need for chronic corticosteroid therapy Recent hospitalization (90 days) Recent antibiotic therapy (90 days) Resident of long-term care facility	Some enteric gram-negatives As above plus *P. aeruginosa*	Fluoroquinolone with enhanced pneumococcal and *P. aeruginosa* activity (levofloxacin) IV therapy if required: β-lactamase resistant penicillin with antipseudomonal activity 3rd- or 4th-generation cephalosporin with antipseudomonal activity

[a]TMP/SMX should not be used due to increasing pneumococcal resistance; amoxicillin and first-generation cephalosporins are not recommended due to β-lactamase susceptibility; and erythromycin is not recommended due to insufficient activity against *H. influenzae*.

DISCHARGE PREPARATION AND FOLLOW-UP

Patients hospitalized for acute exacerbations of COPD are at high-risk for relapse and readmission to the hospital; therefore, appropriate planning should take place prior to discharge to ensure therapy issues and postdischarge care coordination are clearly addressed. Patients should be initiated or restarted on appropriate maintenance therapy (such as long-acting bronchodilators) prior to discharge. Patient assessment and education regarding new or continuing therapy should also take place prior to discharge and reinforced during postdischarge follow-up. Some patients may require supplemental oxygen during their exacerbation and for a period of time after discharge. Continued need for long-term oxygen therapy should be assessed as part of postdischarge follow-up (**Table 44-21**). Other critical elements of discharge planning and follow-up include medication reconciliation, self-management plans, when to seek medical attention, assessment of symptoms and activities of daily living, and status of other comorbid conditions.

TABLE 44-21 Discharge Planning and Postdischarge Follow-up in Acute Exacerbations of COPD

Timeline	Assessment	Plans
Prior to Discharge	Assess maintenance therapy and optimize per therapeutic goals and patient factors Assess inhaler technique Assess technique and adherence before modifying therapy Assess tobacco cessation readiness, if continued smoking Assess immunization status (influenza, pneumococcal) Assess need for oxygen therapy after discharge Assess needed follow-up for comorbid conditions	Ensure patient will be able to obtain and afford prescriptions for therapy Utilize motivational interviewing and teach back for education and counseling Ensure understanding of medications to continue and/or stop (ie, antibiotics, systemic corticosteroids) Coordinate referral to outpatient tobacco cessation services, if indicated Provide immunizations while hospitalized Coordinate outpatient services for supplemental oxygen, if indicated Ensure follow-up care plans are communicated and appointments scheduled (ie, within 1-4 weeks postdischarge)
1-4 weeks Postdischarge	Assess symptoms (ie, mMRC or CAT score) Assess patient ability to cope in their usual environment Assess physical activity and ability to do activities of daily living (ADLs) Assess inhaler technique Assess technique and adherence before modifying therapy Assess tobacco cessation readiness, if continued smoking Assess immunization status (influenza, pneumococcal) Assess continued need for oxygen therapy, if continued after discharge Assess status of comorbidities	Ensure patient completes mMRC or CAT prior to or during visit Coordinate home care services for assistance with ADLs, if indicated Ensure patient will be able to obtain and afford prescriptions for therapy Utilize motivational interviewing and teach back for education and counseling Ensure understanding of medications Coordinate referral to outpatient tobacco cessation services, if indicated Provide immunizations, if appropriate Coordinate outpatient services for supplemental oxygen, if indicated Ensure follow-up care plans are communicated and appointments scheduled
12-16 weeks Postdischarge	Assess symptoms (ie, mMRC or CAT score) Assess patient ability to cope in their usual environment Assess physical activity and ability to do activities of daily living Assess airflow limitation via spirometry Assess inhaler technique Assess technique and adherence before modifying therapy Assess tobacco cessation readiness, if continued smoking Assess immunization status (influenza, pneumococcal) Assess continued need for oxygen therapy, if continued after discharge Assess status of comorbidities	Ensure patient completes mMRC or CAT prior to or during visit Coordinate home care services for assistance with ADLs, if indicated Refer patient for spirometry testing Ensure patient will be able to obtain and afford prescriptions for therapy Utilize motivational interviewing and teach back for education and counseling Ensure understanding of medications Coordinate referral to outpatient tobacco cessation services, if indicated Provide immunizations, if appropriate Coordinate outpatient services for supplemental oxygen, if indicated Ensure follow-up care plans are communicated and appointments scheduled

It is important to assess medication adherence, inhaler technique, optimal pharmacotherapy, tobacco cessation readiness, and immunization status prior to discharge. In acute care or ambulatory care settings, clinical pharmacists are often called on to educate patients, recommend appropriate therapy changes,

assist patients with formulary and insurance barriers, and complete prior authorization requests. Dedicated programs targeting recently discharged patients have shown improvements in health outcomes, such as readmissions, when combined with clinical pharmacy services.[91,92]

PALLIATIVE CARE, END-OF-LIFE CARE, AND HOSPICE

Based on the natural course of COPD, characterized by a progressive decline in lung function and the development of complications, it is important to periodically reconsider the goals of care, end-of-life decisions, and advanced directives.[1] Involvement of palliative care services is recommended once symptoms become significantly limiting or disabling or if repeated hospitalizations occur. An effective strategy to discuss end-of-life care involves the patient's participation in identifying advanced directives and goals of care. Patients should be assured that symptoms, including pain, will be managed and their dignity will be preserved. Specific issues that should be addressed include the location and provider for terminal care, desire to use or withhold mechanical ventilation, and involvement of other family members in decisions on behalf of the patient.

EVALUATION OF THERAPEUTIC OUTCOMES

To evaluate therapeutic outcomes of COPD, the practitioner must first delineate between chronic stable COPD and acute exacerbations. In chronic stable COPD, pulmonary function tests should be assessed annually as recommended by guidelines and following any treatment additions or discontinuations. Average rate of decline of FEV_1 is a useful objective measure to assess the course of COPD over time. However, patients with similar FEV_1 values may differ in the frequency and severity of symptoms and exacerbation history, thus emphasizing the need for a combined assessment for all patients. Average rate of decline in FEV_1 for healthy, nonsmoking patients attributable to age alone is 25 to 30 mL/year. The rate of decline in smokers is steeper, especially for heavy smokers compared with light smokers. The decline in pulmonary function is a curvilinear path. The more severely diminished the FEV_1 at diagnosis, the steeper the rate of decline. Greater numbers of years of smoking and number of cigarettes smoked also correlate with a steeper decline in pulmonary function.[1]

Objective improvements in PFTs often are minimal—therefore, subjective assessments are important. These include symptom scores and quality-of-life assessments. In addition, exacerbation rates, visits to the emergency department, and hospitalizations should be quantified and evaluated. During acute exacerbations of COPD, white blood cell count, vital signs, chest x-ray, and changes dyspnea, sputum volume, and sputum purulence should be assessed at the onset and throughout treatment of an exacerbation. In severe exacerbations, ABGs and oxygen saturation also should be monitored. As with any drug therapy, adherence, adverse effects, potential drug interactions should also be evaluated.

To date, there is limited evidence that any available pharmacotherapies for COPD impact disease progression. Removal of the primary causative factor for COPD (eg, cessation of cigarette smoking) does improve survival, as does supplemental oxygen therapy in a subset of patients. The most pertinent clinical outcomes that have emerged from clinical trials over the past decade are symptom improvement and reductions in exacerbation frequency. While it is important to continue to explore strategies to improve survival, consideration should be given to these two relevant and important outcome measures when initiating, continuing, and monitoring therapy.

Postclass Engaged Learning Activity

Prepare a journal club discussion reviewing a published manuscript of COPD treatment. Identify a clinical trial referenced in the chapter or another study published more recently that may affect practice. Prepare a brief summary of the important points of the manuscript using the following content areas: (1) Rationale for conducting the study (What question does the study try to address?), (2) Study design and methods (What type of study was this? How were the patients selected for inclusion? Which patients were excluded? Does it make sense why some patients were excluded?), (3) Study outcomes (Do the outcomes align with the study question being addressed? Are they clinically important? How were the outcomes evaluated? Was there adequate power to detect a clinically meaningful difference?), (4) Critical evaluation (What were the strengths and weaknesses of this study? If you were to redesign the study, what would you change?), (5) Application to practice (Were the results expressed in terms clinicians care about and can use in everyday practice? Should the results change practice? Give some patient cases or situations to illustrate your points). This activity is intended to build

your literature evaluation skills and ability to critically appraise research manuscripts.

ABBREVIATIONS

AAT	α_1-antitrypsin
ABG	arterial blood gas
ACCP	American College of Chest Physicians
ACIP	Advisory Committee on Immunization Practices
ACOS	asthma and COPD overlap syndrome
ATS	American Thoracic Society
BMI	body mass index
cAMP	cyclic adenosine monophosphate
CAT	COPD Assessment Test
CCQ	Clinical COPD Questionnaire
CDC	Centers for Disease Control and Prevention
cGMP	cyclic guanosine monophosphate
COPD	chronic obstructive pulmonary disease
COT	continuous oxygen therapy
CRQ	Chronic Respiratory Questionnaire
CT	computed tomography
DPI	dry powder inhaler
ENDS	electronic nicotine delivery systems
ERS	European Respiratory Society
FEV_1	forced expiratory volume in 1 second
FRC	functional residual capacity
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HPA	hypothalamic–pituitary–adrenal
ICS	inhaled corticosteroid
IL	interleukin
LABA	long-acting inhaled β_2-agonist
LTB_4	leukotriene B_4
LVRS	lung volume reduction surgery
MDI	metered-dose inhaler
MMP12	matrix metalloproteinase 12
mMRC	modified Medical Research Council
NETT	National Emphysema Treatment Trial
NHLBI	National Heart, Lung, and Blood Institute

NOT	nocturnal oxygen therapy
NPPV	noninvasive positive-pressure ventilation
$PaCO_2$	pressure exerted by carbon dioxide gas in arterial blood
PaO_2	pressure exerted by oxygen gas in arterial blood
PDE4	phosphodiesterase 4
PDE5	phosphodiesterase type 5
PHS	Public Health Service
PH-COPD	Pulmonary hypertension associated with COPD
SCCOPE	Systemic Corticosteroids in Chronic Obstructive Pulmonary Disease Exacerbations
SCCOR	Specialized Centers of Clinically Oriented Research
SGRQ	St. George's Respiratory Questionnaire
TNF-α	tumor necrosis factor-α
TORCH	Towards a Revolution in COPD Health
UPLIFT	Understanding Potential Long-Term Impacts on Function with Tiotropium
VC	vital capacity
WHO	World Health Organization

REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (GOLD). 2020. Available at: http://www.goldcopd.
2. Criner GJ, Bourbeau J, Diekemper RL, et al. Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline. *Chest*. 2015;147(4):894–942. doi:10.1378/chest.14-1676.
3. Wedzicha JA, Calverley PMA, Albert RK, et al. Prevention of COPD exacerbations: A European Respiratory Society/American Thoracic Society guideline. *Eur Respir J*. 2017;50:1602265. http://www.thoracic.org/statements/copd.php.
4. Papi A, Rabe KF, Rigau D, et al. Management of COPD exacerbations: A European Respiratory Society/American Thoracic Society guideline. *Eur Respir J*. 2017;49:1600791. http://www.thoracic.org/statements/copd.php.
5. Postow L, Punturieri A, Croxton TL, Weinmann GG, Kiley JP. A decade of National Heart, Lung, and Blood Institute programs supporting COPD

research and education. *J COPD F*. 2014;1(1):64–72. http://journal.copdfoundation.org.

6. U.S. Department of Health and Human Services. COPD National Action Plan. National Heart, Lung, and Blood Institute. Bethesda, MD. Publication NO. 17-HL-8031. Available at: http://copd.nih.gov.
7. Ford ES, Mannino DM, Wheaton AG, Giles WH, Presley-Cantrell LR, Croft JB. Trends in the prevalence of obstructive and restrictive lung function among adults in the United States: Findings from the National Health and Nutrition Examination Survey from 1988-1994 to 2007-2010. *Chest*. 2013;143(5):1395–1406.
8. Jamal A, Phillips E, Gentzke AS, et al. Current Cigarette Smoking Among Adults: United States, 2016. *MMWR*. 2018;67:53–59.
9. National Center for Health Statistics. *Health, United States, 2015: With Special Feature on Racial and Ethnic Health Disparities*. Hyattsville, MD: National Center for Health Statistics; 2016.
10. National Center for Health Statistics. *Mortality in the United States, 2016. NCHS Data Brief, no 293*. Hyattsville, MD: National Center for Health Statistics; 2017.
11. Ma J, Ward EM, Siegel RL, Jemal A. Temporal Trends in Mortality in the United States, 1969-2013. *JAMA*. 2015;314:1731–1739.
12. Ford ES, Croft JB, Mannino DM, Wheaton AG, Zhang X, Giles WH. COPD surveillance: United States, 1999–2011. *Chest*. 2013;144(1):284–305.
13. Wheaton AG, Cunningham TJ, Ford ES, Croft JB. Employment and activity limitations among adults with chronic obstructive pulmonary disease—United States, 2013. *MMWR*. 2015:64(11):290–295.
14. U.S. Department of Health and Human Services. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.
15. Rennard SI, Vestbo J. COPD: The dangerous underestimate of 15%. *Lancet*. Apr 15, 2006;367(9518):1216–1219. doi:10.1016/S0140-6736(06)68516-4.
16. Silverman EK, Sandhaus RA. Alpha1-antitrypsin deficiency. *N Engl J Med*. 2009;360:2749–2757.

17. Barnes PJ. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. *J Allergy Clin Immunol*. 2016;138:16–27.
18. Global Initiative for Asthma. Asthma, COPD and Asthma-COPD Overlap. 2017. Available at: http://www.ginasthma.org.
19. Domej W, Oettl K, Renner W. Oxidative stress and free radicals in COPD—Implications and relevance for treatment. *Int J Chron Obstruct Pulmon Dis*. 2014;9:1207–1224.
20. Sakao S, Voelkel NF, Tatsumi K. The vascular bed in COPD: Pulmonary hypertension and pulmonary vascular alterations. *Eur Respir Rev*. 2014;23:350–355.
21. Patel N, Belcher J, Thorpe G, Forsyth NR, Spiteri MA. Measurement of C-reactive protein, procalcitonin and neutrophil elastase in saliva of COPD patients and healthy controls: Correlation to self-reported well-being parameters. *Respir Res*. 2015;16:62–69.
22. Guirguis-Blake JM, Senger CA, Webber EM, Mularski RA, Whitlock EP. Screening for chronic obstructive pulmonary disease: Evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2016;315:1378–1393.
23. Dempsey TM, Scanlon PD. Pulmonary function tests for the generalist: A brief review. *Mayo Clin Proc*. 2018;93:763–771.
24. de Torres JP, Casanova C, Marín JM, et al. Prognostic evaluation of COPD patients: GOLD 2011 versus BODE and the COPD comorbidity index COTE. *Thorax*. 2014;69:799–804.
25. Morales DR, Flynn R, Zhang J, Trucco E, Quint JK, Zutis K. External validation of ADO, DOSE, COTE and CODEX at predicting death in primary care patients with COPD using standard and machine learning approaches. *Respir Med*. 2018;138:150–155.
26. Vermylen JH, Szmuilowicz E, Kalhan R. Palliative care in COPD: An unmet area for quality improvement. *Int J Chron Obstruct Pulmon Dis*. 2015;10:1543–1551.
27. Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline in FEV_1: The Lung Health Study. *JAMA*. 1994;272:1497–1505.
28. Anthonisen NR, Connett JE, Murray RP. Smoking and Lung Function of Lung Health Study participants after 11 Years. *Am J Respir Crit Care Med*. 2002;166:675–679.

29. Anthonisen NR, Skeans MA, Wise RA, et al. The effects of a smoking cessation intervention on 14.5-year mortality: A randomized clinical trial. *Ann Intern Med*. 2005;142:233.
30. Fiore MC, Jaén CR, Baker TB, et al. Treating tobacco use and dependence: 2008 Update. *Clinical Practice Guideline. Public Health Service*. Rockville, MD: U.S. Department of Health and Human Services; May 2008. Available at: www.surgeongeneral.gov/tobacco.
31. Patnode CD, Henderson JT, Thompson JH, Senger CA, Fortmann SP, Whitlock EP. Behavioral counseling and pharmacotherapy interventions for tobacco cessation in adults, including pregnant women: A review of reviews for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2015;163(8):608–621.
32. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2015;2:CD003793.
33. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: Key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med*. 2013;188(8):e13–e64.
34. Ferreira IMI, Brooks D, White J, Goldstein R. Nutritional supplementation for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2012;12:CD000998.
35. Bekkat-Berkani R, Wilkinson T, Buchy P, et al. Seasonal influenza vaccination in patients with COPD: A systematic literature review. *BMC Pulmonary Medicine*. 2017;17(1):79.
36. Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP) Adult Immunization Work Group. Advisory committee on immunization practices recommended immunization schedule for adults aged 19 years or older—United States 2015. *MMWR Morb Mortal Wkly Rep*. 2015;64(4):91–92.
37. Walters JA, Smith S, Poole P, Granger RH, Wood-Baker R. Injectable vaccines for preventing pneumococcal infection in patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2010; (11):CD001390.
38. Chrystyn H, van der Palen J, Sharma R, et al. Device errors in asthma and COPD: Systematic literature review and meta-analysis. *NPJ Primary Care Respiratory Medicine*. 2017;27:1–10.

39. Bosnic-Anticevich S, Chrystyn H, Costello R, et al. The use of multiple respiratory inhalers requiring different inhalation techniques has an adverse effect on COPD outcomes. *Int J Chron Obstruct Pulmon Dis*. 2016;12:59–71.
40. Asmus MJ, Hendeles L. Levalbuterol nebulizer solution: Is it worth five times the cost of albuterol? *Pharmacotherapy*. 2000;20:123–129.
41. Kew KM, Mavergames C, Walters JA. Long-acting beta2-agonists for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2013;10:CD010177.
42. Calverley PMA, Anzueto AR, Carter K, et al. Tiotropium and olodaterol in the prevention of chronic obstructive pulmonary disease exacerbations (DYNAGITO): A double-blind, randomised, parallel-group, active-controlled trial. *Lancet Respir Med*. 2018;6:337–344.
43. Melani AS. Long-acting muscarinic antagonists. *Expert Rev Clin Pharmacol*. 2015;8(4):479–501.
44. Cheyne L, Irvin-Sellers MJ, White J. Tiotropium versus ipratropium bromide for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2015;9:CD009552.
45. Ni H, Soe Z, Moe S. Aclidinium bromide for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2014;9:CD010509.
46. Wedzicha JA, Agusti A, Donaldson G, Chuecos F, Lamarca R, Garcia Gil E. Effect of aclidinium bromide on exacerbations in patients with moderate-to-severe COPD: A pooled analysis of five phase III, randomized, placebo-controlled studies. *COPD: J Chron Obstruct Pulmon Dis*. 2016;13:669–676.
47. Tashkin DP, Gross NJ. Inhaled glycopyrrolate for the treatment of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2018;13:1873–1888.
48. Chen W, Huang C, Sheu C, et al. Long-acting beta2-agonists versus long-acting muscarinic antagonists in patients with stable COPD: A systematic review and meta-analysis of randomized controlled trials. *Respirology*. 2017;22:1313–1319.
49. Wedzicha JA, Calverley PM, Seemungal TA, et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med*. 2008;177:19–26.
50. Tashkin DP, Celli B, Senn S, et al. A 4 year trial of tiotropium in chronic

obstructive pulmonary disease (UPLIFT). *N Engl J Med*. 2008;359:1543–1554.

51. Zhou Y, Zhong N, Li X, et al. Tiotropium in early-stage chronic obstructive pulmonary disease. *N Eng J Med*. 2017;377:923–935.
52. Celli B, Decramer M, Leimer I, Vogel U, Kesten S, Tashkin DP. Cardiovascular safety of tiotropium in patients with COPD. *Chest*. 2010;137:2–30.
53. Wise RA, Anzueto A, Cotton D, et al.; TIOSPIR Investigators. Tiotripium Respimat inhaler and the risk of death in COPD. *N Engl J Med*. 2013;369(16):1491–1501.
54. Oba Y, Sarva ST, Dias S. Efficacy and safety of long-acting β-agonist/long-acting muscarinic antagonist combinations in COPD: A network meta-analysis. *Thorax*. 2016;71:15.
55. Barnes PJ. Theophylline: New perspectives for an old drug. *Am J Respir Crit Care Med*. 2003;167:813–818.
56. Yang IA, Clarke MS, Sim EH, Fong KM. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2012;7:CD002991.
57. Kew KM, Seniukovich A. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2014;3:CD010115.
58. Brassard P, Suissa S, Kezouh A, Ernst P. Inhaled corticosteroids and risk of tuberculosis in patients with respiratory diseases. *Am J Respir Crit Care Med*. 2011;183:675–678.
59. Gonzalez AV, Coulombe J, Ernst P, Suissa S. Long-term use of inhaled corticosteroids in COPD and the risk of fracture. *Chest*. 2018;153:321–328.
60. Chalmers JD, Tebboth A, Galyle A, et al. Determinants of initial inhaled corticosteroid use in patients with GOLD A/B COPD: A retrospective study of UK general practice. *NPJ Prim Care Respir Med*. 2017;27(1):43.
61. Miravitlles M, Cosío BG, Arnedillo A, et al. A proposal for the withdrawal of inhaled corticosteroids in the clinical practice of chronic obstructive pulmonary disease. *Respiratory Research*. 2017;18(1):198.
62. Rossi A, van der Molen T, del Olmo R, et al. INSTEAD: A randomised switch trial of indacaterol versus salmeterol/fluticasone in moderate COPD. *Eur Respir J*. 2014;44(6):1548–1556.

63. Magnussen H, Disse B, Rodriguez-Rosin R, et al. Withdrawal of inhaled glucocorticoids and exacerbations of COPD (WISDOM). *N Engl J Med*. 2014;371:1285–1294.
64. Beeh KM, Burgel P, Franssen FME, et al. How do dual long-acting bronchodilators prevent exacerbations of chronic obstructive pulmonary disease? *Am J Respir Crit Care Med*. 2017;196:139–149.
65. Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD (FLAME). *N Eng J Med*. 2016;374:2222–2234.
66. Lipson DA, Barnhart F, Brealey N, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD (IMPACT). *N Eng J Med*. 2018;378:1671–1680.
67. Papi A, Vestbo J, Fabbri L, et al. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): A double-blind, parallel group, randomised controlled trial. *Lancet*. 2018;391:1076–1084.
68. Vestbo J, Papi A, Corradi M, et al. Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): A double-blind, parallel group, randomised controlled trial. *Lancet*. 2017;389:1919–1929.
69. Siler TM, Kerwin E, Sousa AR, Donald A, Ali R, Church A. Efficacy and safety of umeclidinium added to fluticasone furoate/vilanterol in chronic obstructive pulmonary disease: Results of two randomized studies. *Respir Med*. 2015;109(9):1155–1163.
70. Wedzicha JA, Calverley PM, Rabe KF. Roflumilast: A review of its use in the treatment of COPD. *Int J Chron Obstruct Pulmon Dis*. 2016;11:81–90.
71. Albert RK, Connett J, Bailey WD, et al. Azithromycin for prevention of exacerbation in COPD. *N Engl J Med*. 2011;365:689–698.
72. Ray WA, Murray KT, Hall K, et al. Azithromycin and the risk of cardiovascular death. *N Engl J Med*. 2012;366:1881–1890.
73. Alpha-1-Antitrypsin Deficiency Registry Study Group. Survival and FEV_1 decline in individuals with severe deficiency of alpha-1-antitrypsin. *Am J Respir Crit Care Med*. 1998;158:49–59.
74. Dirksen A, Dijkman JH, Madsen F, et al. A randomized clinical trial of alpha-1-antitrypsin augmentation therapy. *Am J Respir Crit Care Med*. 1999;160:1468–1472.

75. Zheng JP, Wen FQ, Bai CX, et al.; PANTHEON study group. Twice daily N-acetylcysteine 600 mg for exacerbations of chronic obstructive pulmonary disease (PANTHEON): A randomised, double- blind placebo-controlled trial. *Lancet Respir Med*. 2014;2(3):187–194.
76. Poole P, Black PN, Cates CJ. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2012;8:CD001287.
77. Rennard SI, Fogarty C, Kelsen S, et al. The safety and efficacy of infliximab in moderate to severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2007;175:926–934.
78. Babu KS, Morjaria JB. Emerging therapeutic strategies in COPD. *Drug Discov Today*. 2015;20(3):371–379.
79. Criner GJ, Connett JE, Voelker H. Simvastatin in moderate-to-severe COPD. *N Eng J Med*. 2014;371:970.
80. Grimminger J, Ghofrani HA, Weissmann N, Klose H, Grimminger F. COPD-associated pulmonary hypertension: Clinical implications and current methods for treatment. *Expert Rev Respir Med*. 2016;10:755–766.
81. Quint JK, Herrett E, Bhaskaran K, et al. Effect of beta blockers on mortality after myocardial infarction in adults with COPD: Population-based cohort study of UK electronic healthcare records. *BMJ*. 2013;347:16650.
82. Etminan M, Jafari S, Carleton B, Fitzgerald JM. Beta-blocker use and COPD mortality: A systematic review and meta-analysis. *BMC Pulm Med*. 2012;12:48–54.
83. Eriksen N, Vestbo J. Management and survival of patients admitted with an exacerbation of COPD: Comparison of two Danish cohorts. *Clin Respir J*. 2010;4(4):208–214.
84. Gudmundsson G, Ulrik CS, Gislason T, et al. Long-term survival in patients hospitalized for chronic obstructive pulmonary disease: A prospective observational study in the Nordic countries. *Int J Chron Obstruct Pulmon Dis*. 2012;7:571–576.
85. Mantero M, Rogliani P, DiPasquale M, et al. Acute exacerbations of COPD: Risk factors for failure and relapse. *Int J COPD*. 2017;12:2687–2693.
86. Cabrini L, Landoni G, Oriani A, et al. Noninvasive ventilation and survival in acute care settings: A comprehensive systematic review and meta-analysis of randomized controlled trials. *Crit Care Med*.

2014;43(4):880–888.

87. Hernandez JM, Edmonds M. Do systemic corticosteroids improve outcomes in chronic obstructive pulmonary disease exacerbations? *Ann Emerg Med*. 2016;67(2):258–259. doi:10.1016/j.annemergmed.2015.07.009.
88. Leuppi JD, Schuetz P, Bingisser R, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease. *JAMA*. 2013;309(21):2223–2231.
89. Wilson R, Sethi S, Anzueto A, Miravittles M. Antibiotics for treatment and prevention of exacerbations of chronic obstructive pulmonary disease. *J Infect*. 2013;67:497–515.
90. Butler CC, Gillespie D, White P, et al. C-reactive protein testing to guide antibiotic prescribing for COPD exacerbations. *N Engl J Med*. 11, 2019;381(2):111–120. doi:10.1056/NEJMoa1803185.
91. Cavanaugh JJ, Lindsey KN, Shilliday BB, Ratner SP. Pharmacist-coordinated multidisciplinary hospital follow-up visits improve patient outcomes. *J Manag Care Spec Pharm*. 2015;21:256–260.
92. Sanchez GM, Douglass MA, Mancuso MA. Revisiting project re-engineered discharge (RED): The impact of a pharmacist telephone intervention on hospital readmission rates. *Pharmacotherapy*. 2015;35:805–812.

45

Pulmonary Arterial Hypertension

Rebecca Moote, Rebecca L. Attridge, and Deborah J. Levine

KEY CONCEPTS

1. Pulmonary arterial hypertension (PAH) is defined as a mean pulmonary artery pressure (mPAP) ≥25 mm Hg at rest with a pulmonary wedge pressure or left ventricular end-diastolic pressure (LVEDP) ≤15 mm Hg and a pulmonary vascular resistance (PVR) >3 Wood units (WU) measured by right cardiac catheterization.
2. Patients with PAH present with exertional dyspnea, fatigue, weakness, and exertion intolerance. As the disease progresses, symptoms of right heart dysfunction and failure, such as dyspnea at rest, lower extremity edema, chest pain, and syncope, may be present.
3. The definitive diagnosis of PAH is done with a right heart catheterization. The right heart catheterization provides important prognostic information and can be used to assess pulmonary vasoreactivity prior to initiating therapy.
4. Goals of treatment are to alleviate symptoms; improve quality of life, functional class, and exercise capacity; slow disease progression; and improve survival.
5. Nonpharmacologic therapy, including counseling on pregnancy avoidance, immunizations, and low-sodium diets, should be provided to all patients with PAH.
6. Conventional therapy of PAH includes oral anticoagulants, diuretics, oxygen, and digoxin.
7. Prostacyclin analogs such as epoprostenol, treprostinil, and iloprost induce potent vasodilation of pulmonary vascular beds and are typically reserved for WHO functional class III and IV patients. Only epoprostenol has demonstrated improved survival.

8 Patients with WHO functional class II or III are commonly initiated on oral therapy for PAH. Options include endothelin-receptor antagonists, phosphodiesterase-5 inhibitors, riociguat, and selexipag. These agents have been shown to improve exercise capacity, functional class, and hemodynamics in PAH.

9 Calcium channel blockers are only considered in a small number of patients who have a positive response to acute vasoreactivity testing. A very small number of patients have a long-term response to calcium channel blockers.

10 Combination therapy may address more than one mechanism causing PAH. Combination therapy may be initiated sequentially or as the initial regimen in patients with worse functional classes. Evidence demonstrates that initial combination therapy is associated with a significant reduction in time to clinical failure and PAH hospitalizations.

Preclass Engaged Learning Activity

The mechanism of action of medications used in pulmonary arterial hypertension (PAH) is directly tied to the pathophysiology of the disease. Create a concept map of the site of action of the major drug classes utilized in PAH—prostacyclin analogs, endothelin-receptor antagonists, phosphodiesterase inhibitors, and guanylate cyclase stimulators. There is an excellent diagram published in the *New England Journal of Medicine* in 2004. While the information is slightly outdated, it is a great place to start creating a concept map. This activity is intended to prepare you for understanding the role of the medications in the treatment of PAH as well as to increase critical thinking skills related to evaluating side effects and monitoring parameters of these medications.

INTRODUCTION

1 Pulmonary arterial hypertension (PAH) is a group of conditions relating to elevated blood pressure measured within the pulmonary artery. Pulmonary hypertension is not a specific diagnosis; rather it is a complex group of disorders relating to the pulmonary circulation. Pulmonary hypertension is classified into five groups according to the World Health Organization (WHO); see **Table 45-**

1.[1] Pulmonary arterial hypertension (PAH) or Group 1 pulmonary hypertension is a progressive disease characterized by an elevation in pulmonary arterial pressure and pulmonary vascular resistance. PAH may be defined as a mean pulmonary artery pressure (mPAP) ≥25 mm Hg at rest, with a pulmonary capillary wedge pressure or left ventricular end-diastolic pressure [LVEDP]) ≤15 mm Hg and a pulmonary vascular resistance (PVR) >3 Wood units (WU) measured by cardiac catheterization.[2–4]

TABLE 45-1 World Health Organization Classification of Pulmonary Hypertension

Group 1—Pulmonary Arterial Hypertension (PAH)

- Idiopathic (IPAH)
- Heritable
  - BMPR-2
  - Other mutations: ALK-1, ENG, SMAD9, CAV1, KCNK3
- Drugs and toxins induced
- Associated with (APAH)
  - Connective tissue diseases
  - HIV infection
  - Portal hypertension
  - Congenital heart diseases
  - Schistosomiasis
- Pulmonary veno-occlusive disease and/or pulmonary capillary hemoangiomatosis
  - Idiopathic
  - Heritable
    - EIF2AK4 mutation
    - Other mutations
  - Drugs, toxins, and radiation-induced
  - Associated with:
    - Connective tissue disease
    - HIV infection
- Persistent pulmonary hypertension of the newborn

Group 2—Pulmonary Hypertension due to Left Heart Disease

- Left ventricular systolic dysfunction
- Left ventricular diastolic dysfunction
- Valvular disease
- Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
- Congenital/acquired pulmonary veins stenosis

Group 3—Pulmonary Hypertension due to Lung Diseases and/or Hypoxia

- Chronic obstructive pulmonary disease
- Interstitial lung disease
- Other pulmonary diseases with a mixed restrictive and obstructive pattern
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental abnormalities

Group 4—Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

- Chronic thromboembolic pulmonary hypertension
- Other pulmonary artery obstructions
  - Angiosarcoma
  - Other intravascular tumors
  - Arteritis
  - Congenital pulmonary arteries stenosis
  - Parasites (hydatidosis)

Group 5—Pulmonary Hypertension with Unclear and/or Multifactorial Mechanisms

- Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
- Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis
- Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

ALK-1, activin receptor-like kinase type-1; BMPR-2, bone morphogenetic protein receptor 2; CAV1, caveolin-1; ENG, endoglin; EIF2AK4, eukaryotic translation initiation factor 2 alpha kinase 4; HIV, human immunodeficiency virus.

Data from Reference 4.

PAH may occur in the setting of underlying medical conditions or as an idiopathic disease (idiopathic PAH [IPAH]). Historically, medical treatment of PAH has been limited due to lack of effective, targeted therapy. Without medical therapy, IPAH portends a poor prognosis (median survival 2.8 years) after diagnosis.[5] Prior to the availability of disease-specific therapy for IPAH, survival rates for 1, 3, and 5 years were 68%, 48%, and 34%, respectively.[6] Since the approval of epoprostenol in 1995, a number of new therapeutic options have been developed. An epidemiologic study demonstrated survival rates at 1 and 3 years were 85% and 68%, respectively, in patients with PAH, and 91% and 74%, respectively, in patients with IPAH.[7]

In addition, the same registry showed overall 5-year survival rates of 65.4% in previously diagnosed patients versus 61.2% in newly diagnosed patients with PAH.[8]

EPIDEMIOLOGY

The prevalence of PAH is estimated to be 15 to 26 patients per million individuals.[9] In a French registry study of more than 600 patient with PAH, Humbert found that the most common cause of PAH was IPAH (approximately 40%), followed by PAH associated with connective tissue diseases (15.3%), congenital heart disease (11.3%), portal hypertension (10.4%), and familial PAH (FPAH) (3.9%).[10] The US-based REVEAL registry (Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management) also provides helpful insight into the epidemiology of PAH. The registry includes over 3,500 patients and found that 46% of PAH was idiopathic while 25% was associated with connective tissue diseases and 10% was associated with congenital heart diseases.[11] However, the diagnosis of PAH is growing due to increased awareness and knowledge of the disease state, leading to earlier and improved evaluation and identification.

ETIOLOGY

PAH most often originates with a predisposing state and one or more inciting factors that could be genetic or environmental exposures.[12] Once a permissive environment exists, multiple mechanisms can be activated leading to vascular constriction, cellular proliferation, and a prothrombotic state resulting in PAH

and its sequelae.[13] PAH can be associated with numerous conditions as well as being an idiopathic condition (IPAH). The incidence of IPAH is estimated to be 2.0 to 7.6 per 1 million in North America and Europe, with a marked female predominance (male-to-female ratio, 1:1.7), and mean age at the time of recognition is approximately 37 years, although there is considerable variation.[1,2,14] Based on recent registry data, PAH is now being diagnosed more commonly in older patients, with a mean age at diagnosis ranging from 50 to 65 years old.[1,2,14] Although uncommon in the United States, the most common form of PAH worldwide is schistosomiasis followed by congenital heart disease and pulmonary hypertension of early childhood.[3] Rheumatologic diseases such as scleroderma, systemic lupus erythematosus, rheumatoid arthritis, and myositis are also associated with the development of PAH. Patients with scleroderma who develop PAH, estimated between 7% and 12% of patients, have markedly worse outcomes in comparison to other PAH subgroups. Patients with human immunodeficiency virus (HIV) infection can develop PAH with a prevalence of 0.5%. In patients with liver disease, portal hypertension may cause concurrent pulmonary hypertension in an estimated 2% to 6% of patients.[3] Multiple drugs and toxins have been associated with PAH but those that definitively precipitate PAH include anorexigens such as aminorex, fenfluramine, benfluorex, and dexfenfluramine.[1,4,14] Other definite precipitants include toxic rapeseed oil and selective serotonin reuptake inhibitors (SSRIs), specifically in newborns of pregnant patients exposed to SSRIs after 20 weeks of gestation.[3,4] Other drugs considered to be likely or possible causative agents for PAH include amphetamines, L-tryptophan, cocaine, interferon α and β, and certain chemotherapeutic agents (dasatanib, mitomycin C, carmustine, etoposide, cyclophosphamide, bleomycin).[3,4] Heritable PAH (HPAH) includes both IPAH with germline mutations and familial cases without an identified mutation. Germline mutations seen in PAH include bone morphogenetic protein receptor 2 (BMPR-2) and activin receptor-like kinase 1 (ALK-1). About 75% of patients with HPAH have BMPR-2 mutations.[2] Genetic testing for these mutations may be offered and professional genetic counseling should be provided at expert centers.[3]

PATHOPHYSIOLOGY

PAH is characterized by progressive vasoconstriction of the small pulmonary arteries that eventually leads to right ventricular hypertrophy and failure. The

right ventricle is thin-walled and accustomed to the much lower pressures of the pulmonary system and therefore does not have the reserve that the left ventricle does.[15] Regardless of etiology, all subgroups of PAH are based on similar clinical and pathologic physiology. The pathobiology of PAH involves several key biologic events, including endothelial cell dysfunction, thrombotic lesions, platelet activation, the gain of constricting factors, loss of relaxing factors, intimal proliferation, medial hypertrophy, fibrosis, and inflammation—all combining to produce progressive and deleterious vascular remodeling (**Fig. 45-1**).[16,17] Multiple genetic mutations are known to contribute to the pathophysiology of PAH, including BMPR-2, ALK-1, Caveolin-1, KCNK3, nitric oxide synthase (ec-NOS), and 5-hydroxytryptamine (serotonin [5-HT]) transporter (5-HTT).[3,16,18]

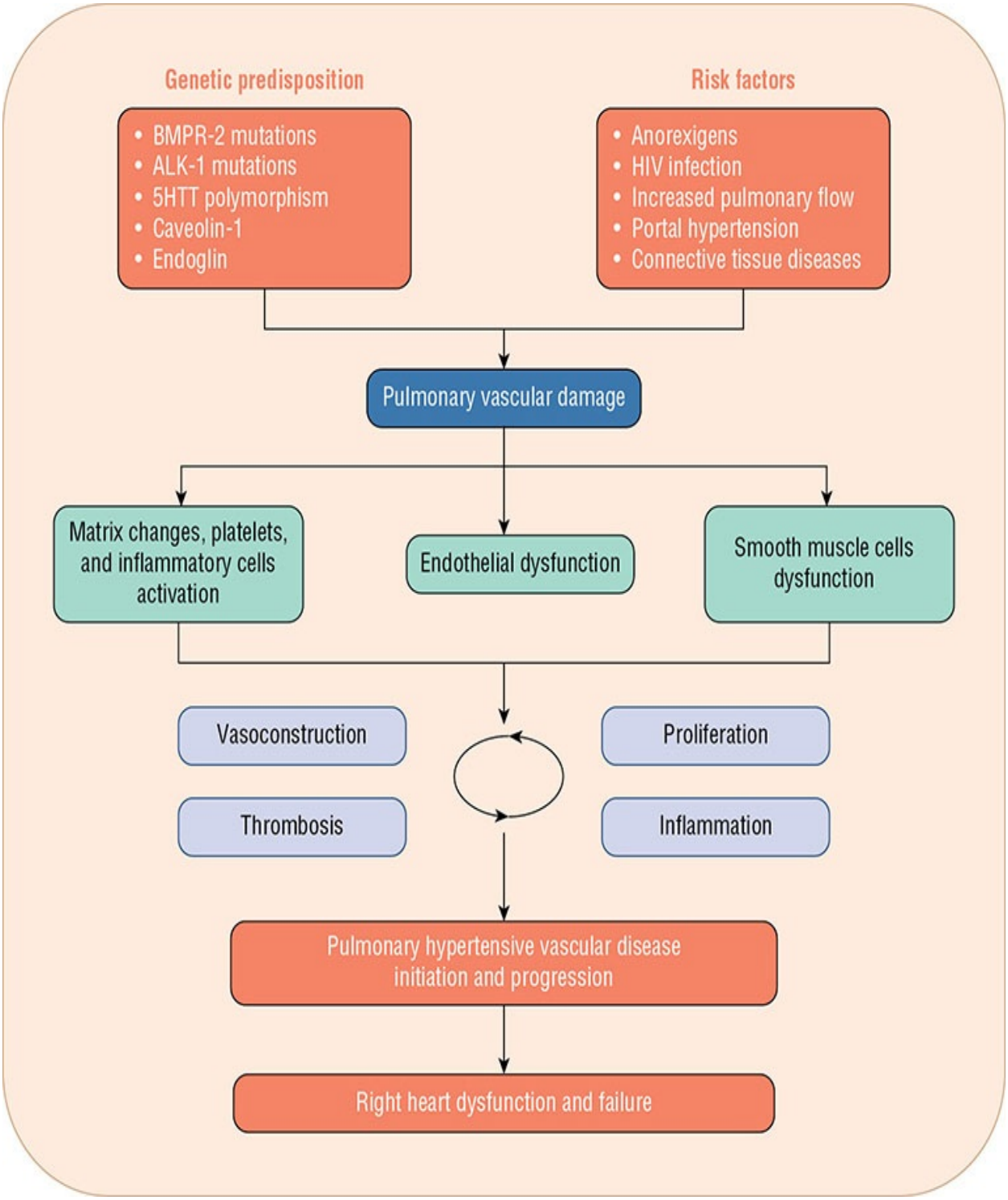


FIGURE 45-1 Pathophysiology of pulmonary arterial hypertension. Pulmonary arterial hypertension; potential pathogenetic and pathobiologic mechanisms. (5-HTT, serotonin transporter gene; ALK-1, activin receptor-like kinase 1 gene; BMPR-2, bone morphogenetic receptor 2 gene; HIV, human immunodeficiency virus.) (*Reproduced with permission from Galiè N, Torbicki A, Barst R, et al.*

*Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. Eur Heart J. 2004;25(24):*2243–2278.)

Molecular, cellular, and genetic mechanisms are mediated by a variety of biologically active compounds, including prostacyclin (PGI_2), endothelin-1 (ET-1), nitric oxide (NO), and 5-HT. PGI_2 is a vasodilatory and antiproliferative substance that is produced by the endothelial cells, and the synthesis of PGI_2 and its circulating levels are reduced in PAH. Furthermore, thromboxane, a vasoconstrictor, is increased in PAH. ET-1 is produced in the endothelium, and it possesses potent vasoconstrictor and mitogenic effects. ET-1 levels are increased in PAH and clearance is reduced. ET-1 acts via the endothelin receptors (ET_A and ET_B) to promote vascular smooth muscle proliferation and vasoconstriction.[17,19] Plasma levels of ET-1 are correlated with the severity of PAH and prognosis.[20] NO is produced in the endothelium via NO synthase and leads to vasodilation and opening of cell membrane potassium channels to allow potassium ion efflux, membrane depolarization, and calcium channel inhibition. In PAH there is evidence of decreased NO synthase expression, leading to vasoconstriction and cell proliferation.[21] Elevated 5-HT has been observed and vasoconstriction mediated via the increased expression of the $5\text{-}HT_{1B}$ receptor is seen in PAH.[3]

Autoantibodies, proinflammatory cytokines, and inflammatory infiltrates may also participate in the pathogenesis of PAH. Coagulation is disordered in PAH as evidenced by increased levels of von Willebrand factor, plasma fibrinopeptide A, plasminogen activator inhibitor-1, 5-HT, and thromboxane. Furthermore, tissue plasminogen activator, thrombomodulin, NO, and PGI_2 are decreased, leading to an imbalance favoring thrombosis. Endothelial dysfunction is the common denominator of mechanisms for PAH, and a variety of injuries, such as shear stress, inflammation, toxins, and hypoxia, are thought to be involved.[3,16]

2 The signs and symptoms of PAH are highly variable depending on the stage of the disease and comorbidities. The impact of these signs and symptoms on functional capacity can be generally described using the World Health Organization functional classification (**Table 45-2**). Symptoms are often related to right ventricular dysfunction and may include exertional dyspnea, fatigue, and weakness.[4] As the disease progresses, patients may experience dyspnea at rest, chest pain, presyncope, syncope, lower extremity edema, and abdominal bloating and distension. On physical exam, patients with PAH may have an

accentuated component of S_2 audible at the apex of the heart, midsystolic ejection murmur, palpable left parasternal lift, right ventricular S_4 gallop, and a prominent "a" wave.[3] Hepatojugular reflux, a diastolic murmur of pulmonary regurgitation, and a systolic murmur of tricuspid regurgitation may be present in advanced disease.[3] Patients with an increased risk of mortality are more likely to have a higher WHO functional class, older age, male gender, higher brain natriuretic peptide (BNP), higher right atrial pressure and lower cardiac output. In contrast, patients with a decreased risk of mortality are more likely to have a lower WHO functional class, higher 6-minute walk distance, lower BNP, and higher cardiac output.[13]

TABLE 45-2 World Health Organization Functional Classification of Pulmonary Arterial Hypertension

Class	Description
I	Patients with PAH in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnea, fatigue, chest pain, or presyncope
II	Patients with PAH who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope
III	Patients with PAH who have marked limitation of physical activity. There is no discomfort at rest, but less than normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope
IV	Patients with PAH who are unable to perform any physical activity at rest and who may have signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest, and symptoms are increased by almost any physical activity

Data from Badesch DB, Abman SH, Simonneau G, Rubin LJ, McLaughlin VV. Medical therapy for pulmonary arterial hypertension: Updated ACCP evidence-based *clinical practice guidelines. Chest 2007;131:1917-1928.*

3 Several comorbidities and environmental factors play a role in the development of PAH and must be evaluated when establishing an initial diagnosis of PAH (Fig. 45-2). In patients with a clinical suspicion of PAH, Doppler echocardiography should be performed as a noninvasive screening test that can detect increased pulmonary pressures, although this study cannot be

used to definitively diagnose PAH.[22] Echocardiography is also useful in evaluating specific causes of pulmonary hypertension, such as a cardiac shunt or left-sided heart disease. Echocardiography can also be used to assess treatment interventions and to follow disease progression.[3] However, right heart catheterization is the definitive study to diagnose PAH and evaluate patients who are worsening clinically.[18] Right heart catheterization can be used to assess pulmonary vasoreactivity in patients with idiopathic, heritable, or drug-induced PAH with the administration of fast-acting, short-duration vasodilators to determine the extent of vascular smooth muscle constriction and vasodilator response to calcium channel blockers (CCBs; I-C).[4] **Table 45-3** lists the classes of recommendations and levels of evidence, and **Table 45-4** lists commonly used agents and their dosages. The consensus definition of a positive response is defined as a reduction of mPAP by at least 10 mm Hg to a value of 40 mm Hg or less.[23] Patients with a positive vasoreactivity response (approximately 13% of patients on initial testing) are most likely to have a beneficial hemodynamic and clinical response. These patients may be able to be treated with CCBs. However, about half of these patients lose an acute vasodilator response when tested 1 year later.[24] Therefore, even this small group of patients who may be treated with CCBs must be followed closely for safety and efficacy. If the patient loses the acute vasodilator response, the patient needs to be switched to different PAH therapy. Patients who have a negative response on initial vasodilator testing are not candidates for treatment with CCBs.[3,25]

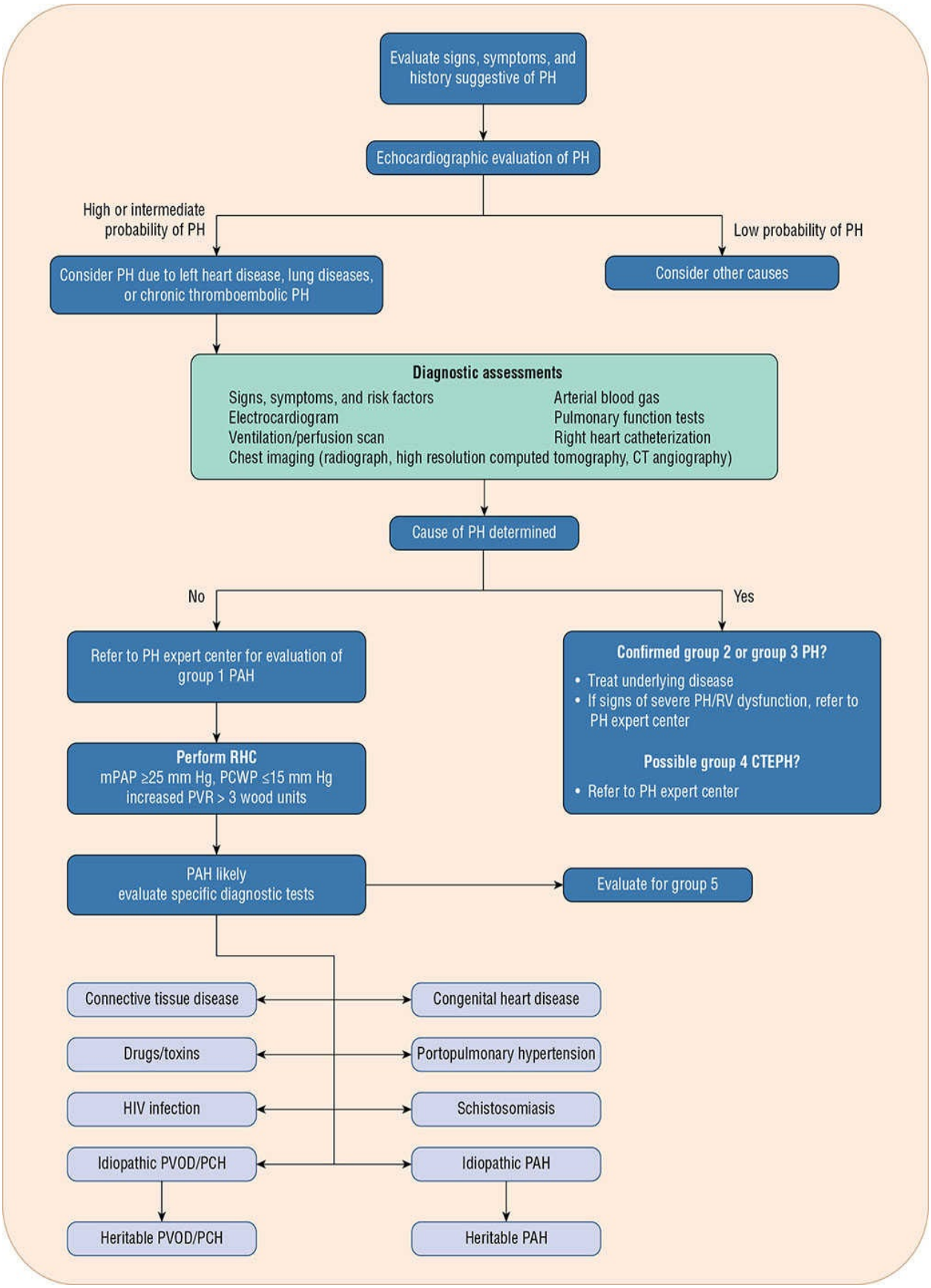

Evaluate signs, symptoms, and history suggestive of PH
Echocardiographic evaluation of PH
High or intermediate probability of PH
Low probability of PH
Consider PH due to left heart disease, lung diseases, or chronic thromboembolic PH
Consider other causes
Diagnostic assessments
Signs, symptoms, and risk factors
Electrocardiogram
Ventilation/perfusion scan
Chest imaging (radiograph, high resolution computed tomography, CT angiography)
Arterial blood gas
Pulmonary function tests
Right heart catheterization
Cause of PH determined
No
Yes
Refer to PH expert center for evaluation of group 1 PAH
Confirmed group 2 or group 3 PH?
• Treat underlying disease
• If signs of severe PH/RV dysfunction, refer to PH expert center
Possible group 4 CTEPH?
• Refer to PH expert center
Perform RHC
mPAP ≥25 mm Hg, PCWP ≤15 mm Hg
increased PVR > 3 wood units
PAH likely
evaluate specific diagnostic tests
Evaluate for group 5
Connective tissue disease
Congenital heart disease
Drugs/toxins
Portopulmonary hypertension
HIV infection
Schistosomiasis
Idiopathic PVOD/PCH
Idiopathic PAH
Heritable PVOD/PCH
Heritable PAH

FIGURE 45-2 Diagnostic algorithm of pulmonary arterial hypertension. (CTEPH, chronic thromboembolic pulmonary hypertension; HIV, human immunodeficiency virus; PVOD/PCH, pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis; RHC, right heart catheterization.) (*Adapted from Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERA Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2016;37(1):67-119.*)

TABLE 45-3 Classes of Recommendations and Levels of Evidence*

Classes of Recommendations	Definition	Suggested Wording to Use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended / Is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that a given treatment or procedures is not useful/effective, and in some cases may be harmful.	Is not recommended
Levels of Evidence	**Definition**	
A	Data derived from multiple randomized clinical trials or meta-analyses.	
B	Data derived from a single randomized clinical trial or large nonrandomized studies.	
C	The consensus opinion of the experts and/or small studies, retrospective studies, registries.	

*Classes of Recommendations and Levels of Evidence are consistent between the ESC/ERS Guidelines and the WHO Guidelines.

Data from Reference 4.

TABLE 45-4 Agents for Vasodilator Testing in Pulmonary Arterial Hypertension

	NO	Epoprostenol	Adenosine
Route	Inhaled	IV	IV
Dose range	10-80 ppm	2-10 ng/kg/min	50-250 mcg/kg/min
Dosing increments	10-80 ppm for 5 minutes	2 ng/kg/min every 15 minutes	50 mcg/kg/min every 2 minutes
Common side effects	None	Headache, flushing, nausea	Chest tightness, dyspnea

NO, nitric oxide.

Data from Reference 26.

Because PAH commonly occurs in the setting of connective tissue disease, serologic markers should be obtained to confirm or exclude these diagnoses.[3,27] Liver function tests (LFTs) should also be evaluated due to the increased risk for PAH in patients with cirrhosis and portal hypertension and as a baseline for certain PAH therapies. HIV is associated with an increased prevalence of PAH, and HIV testing should be done as part of the initial PAH workup.[3] Chronic thromboembolic pulmonary hypertension (CTEPH) should be evaluated with ventilation-perfusion lung scans and/or pulmonary angiography. Pulmonary function testing and arterial blood oxygenation should be evaluated. The diffusing capacity of carbon monoxide may be particularly helpful in systemic sclerosis and PAH.[3] In patients with PAH, serial determinations of functional class, exercise capacity (assessed by the 6-minute walk distance), and serial biomarkers (ie, BNP) provide benchmarks for disease severity, response to therapy, and progression.[3,27] These variables can be used to determine risk level in patients and may aid in prognosis. **Table 45-5** outlines the calculation of low, intermediate, and high-risk patients based on these factors. **Table 45-6** also provides guidelines for initial assessment and timing and when each assessment is indicated.

TABLE 45-5 Risk Assessment in Pulmonary Arterial Hypertension

Determinants of prognosis* (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5%-10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope†	Repeated syncope‡
WHO functional class	I, II	III	IV
6MWD	>440 m	165-440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 mL/min/kg (>65% pred.) Ve/VCO_2 slope <36	Peak VO_2 11-15 mL/min/kg (35%-65% pred.) Ve/VCO_2 slope 36-44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) Ve/VCO_2 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/L (14.5 pmol/L) NT-proBNP <300 ng/L (35.4 pmol/L)	BNP 50-300 ng/L (14.5-86.7 pmol/L) NT-proBNP 300-1,400 ng/L (35.4-165 pmol/L)	BNP >300 ng/L (86.7 pmol/L) NT-proBNP >1,400 ng/L (165 pmol/L)
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18-26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Hemodynamics	RAP <8 mm Hg CI ≥2.5 L/min/m^2 (0.042 L/s/m^2) SvO_2 >65% (0.65)	RAP 8-14 mm Hg CI 2.0-2.4 L/min/m^2 (0.033-0.040 L/s/m^2) SvO_2 60%-65% (0.60-0.65)	RAP >14 mm Hg CI ≤2.0 L/min/m^2 (0.033 L/s/m^2) SvO_2 <60% (0.60)

*Most of the proposed variables and cut-off values are based on expert opinion. They may provide prognostic information and may be used to guide therapeutic decisions, but applications to individual patients must be done carefully. One must also note that most of these variables have been validated mostly for IPAH and the cut-off values used above may not necessarily apply to other forms of PAH. Furthermore, the use of approved therapies and their influence on the variables should be considered in the evaluation of the risk.

†Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in the otherwise stable patient.

‡Repeated episodes of syncope, even with little or regular physical activity.

Data from Reference 4.

TABLE 45-6 Suggested Assessment and Timing for the Follow-Up of Patients with Pulmonary Arterial Hypertension

	At baseline	Every 3-6 months*	Every 6-12 months*	3-6 months after changes in therapy*	In case of clinical worsening
Medical assessment and determination of functional class	+	+	+	+	+
ECG	+	+	+	+	+
6MWT/Borg dyspnea score	+	+	+	+	+
CPET	+		+		+*
Echo	+		+	+	+
Basic lab†	+	+	+	+	+
Extended lab‡	+		+		+
Blood gas analysis§	+		+	+	+
Right heart catheterization	+		+‖	+¶	+¶

*Intervals to be adjusted according to patient needs.

†Basic lab includes blood count, INR (in patients receiving vitamin K antagonists), serum Creatinine, sodium, potassium, AST/ALT (in patients receiving ERAs), bilirubin and BNP/NT-proBNP

‡Extended lab includes TSH, troponin, uric acid, iron status (iron, ferritin, soluble transferrin receptor) and other variables according to individual patient need.

§From arterial or arterialized capillary blood; may be replaced by peripheral oxygen saturation in stable patients or if BGA is not available.

‖Some centers perform RHCs at regular intervals during follow-up.

¶Should be considered.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BGA, blood gas analysis; BNP, brain natriuretic peptide; CPET, cardiopulmonary exercise testing; Echo, echocardiography; ECG, electrocardiogram; ERAs, endothelin-receptor antagonists; FC, functional class; INR, international normalized ratio; lab, laboratory assessment; NT-proBNP, N-terminal pro-brain natriuretic peptide; RHC, right heart catheterization; TSH, thyroid stimulating hormone; 6MWT, 6-minute walking test.

Data from Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2016;37(10):67-119.

CLINICAL PRESENTATION

Pulmonary Arterial Hypertension

Symptoms

- Exertional dyspnea
- Fatigue
- Weakness
- Exertional chest pain
- Complaints of general exertion intolerance
- Dyspnea at rest as the disease progresses
- Syncope

- Lower extremity edema

Symptoms of Related Conditions

- Paroxysmal nocturnal dyspnea as a result of left-sided heart disease
- Raynaud's phenomenon, arthralgia, or swollen hands and other symptoms of connective tissue disease
- Orthopnea

Symptoms of Disease Progression

- Leg swelling
- Abdominal bloating and distension
- Anorexia
- Profound fatigue
- May develop as right ventricular dysfunction and tricuspid valve regurgitation evolve

Signs of Advanced Disease

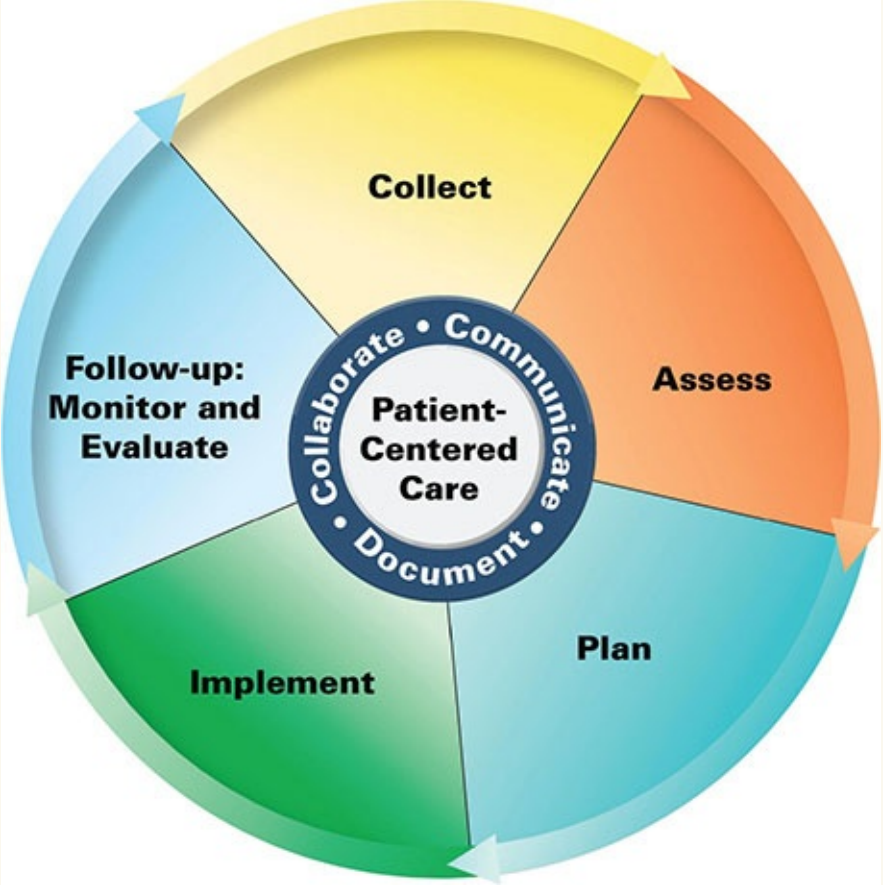
- Diastolic murmur of pulmonary regurgitation
- A pansystolic murmur of tricuspid regurgitation
- Hepatojugular reflux
- Right ventricular S_3 gallop
- Marked distension of jugular veins
- Peripheral edema
- Hypotension
- Cool extremities suggesting markedly reduced cardiac output and peripheral vasoconstriction

TREATMENT

Desired Outcomes

4 Specific goals in the treatment of PAH include achievement of good exercise capacity, improved right ventricular function, alleviation of symptoms,

improvement in quality of life, prevention of disease progression, and improvement in survival.[13] Trials in the PAH population have undergone a change over the last decade. In the past, outcomes were predominantly focused on improvement in hemodynamic parameters and exercise tolerance.[28,29] However, more recent studies have focused on clinical outcomes, particularly combined clinical worsening. This outcome may differ among clinical trials but typically includes outcomes such as hospitalization, progression of symptoms, treatment escalation to prostacyclin therapy, transplantation, atrial septostomy, and death.[28]



Patient Care Process for Pulmonary Arterial Hypertension

Collect

- Patient characteristics (eg, age, race, gender, pregnancy status)

- Patient history: past medical (eg, connective tissue diseases), family (eg, family history of pulmonary arterial hypertension), social (eg, use of cocaine and amphetamines)
- Current medications (eg, particularly anorexigen use such as fenfluramine)
- Immunization history (eg, influenza, pneumococcal vaccination)
- Socioeconomic factors that may affect access to treatment
- Lifestyle assessment: smoking status, exercise, diet, alcohol intake, sexual activity
- Symptoms (eg, exertional dyspnea or chest pain, syncope, volume overload) and WHO Functional Class
- Objective data
  - Height, weight, BMI, blood pressure, and heart rate
  - Echocardiography and electrocardiogram
  - Right heart catheterization (with acute vasoreactivity testing if idiopathic, heritable, or anorexigen-associated PAH)
  - Labs (eg, AST/ALT, BNP)

Assess

- Rule out secondary causes (eg, left heart disease [Group 2], lung diseases and/or hypoxia [Group 3], chronic thromboembolic pulmonary hypertension [Group 4], pulmonary hypertension with unclear multifactorial mechanisms [Group 5])
- Assess groups with special considerations such as pregnant women
- Presence of comorbid conditions: atrial tachyarrhythmias, depression, anxiety, anemia
- Current medications that may affect PAH-targeted therapy (eg, drug–drug interactions)
- Recommended treatment options based on WHO functional class (see Table 45-2)
- Appropriateness and effectiveness of current PAH therapy (eg, WHO functional class, exercise capacity, change in pulmonary pressures, if any)

Plan*

- Therapeutic lifestyle changes (eg, diet and nutrition)

- Drug therapy regimen including specific PAH medication, dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Table 45-7)
- Evaluate current therapy for drug–drug interactions at each visit (see Table 45-9)
- Monitoring parameters including efficacy (eg, WHO functional class, exercise capacity, change in pulmonary pressures), safety (medication-specific adverse effects), and time frame (3-month initial follow-up intervals, followed by 6-12 month intervals once at goal) (see Table 45-6)
- Patient education (eg, the purpose of treatment, dietary and lifestyle modification, drug therapy, immunizations, counseling on pregnancy and air travel)
- Self-monitoring of weight, exercise, diet, drug adherence/adverse effects
- Referral to PAH specialty center for coordination of care

Implement*

- Provide patient education regarding all elements of the treatment plan
- For parenteral prostacyclin analogs, coordinate with specialty company to ensure appropriate education on agents, including reconstitution, safety, back-up supplies
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up and time frame to achieve goals of therapy (eg, improvement in WHO functional class and exercise capacity, symptom improvement, euvolemia [see Table 45-6])
- Educate patient on when to seek medical care (eg, worsening edema or dyspnea)

Follow-up: Monitor and Evaluate

- Determine response to PAH therapy and volume management
- Presence of medication-induced adverse effects (eg, elevated transaminases on endothelin-receptor antagonists, headache, flushing, edema, pump issues with parenteral prostacyclin analogs [see Table 45-8])
- Routine pregnancy screening for females (especially if receiving endothelin-receptor antagonists or riociguat)

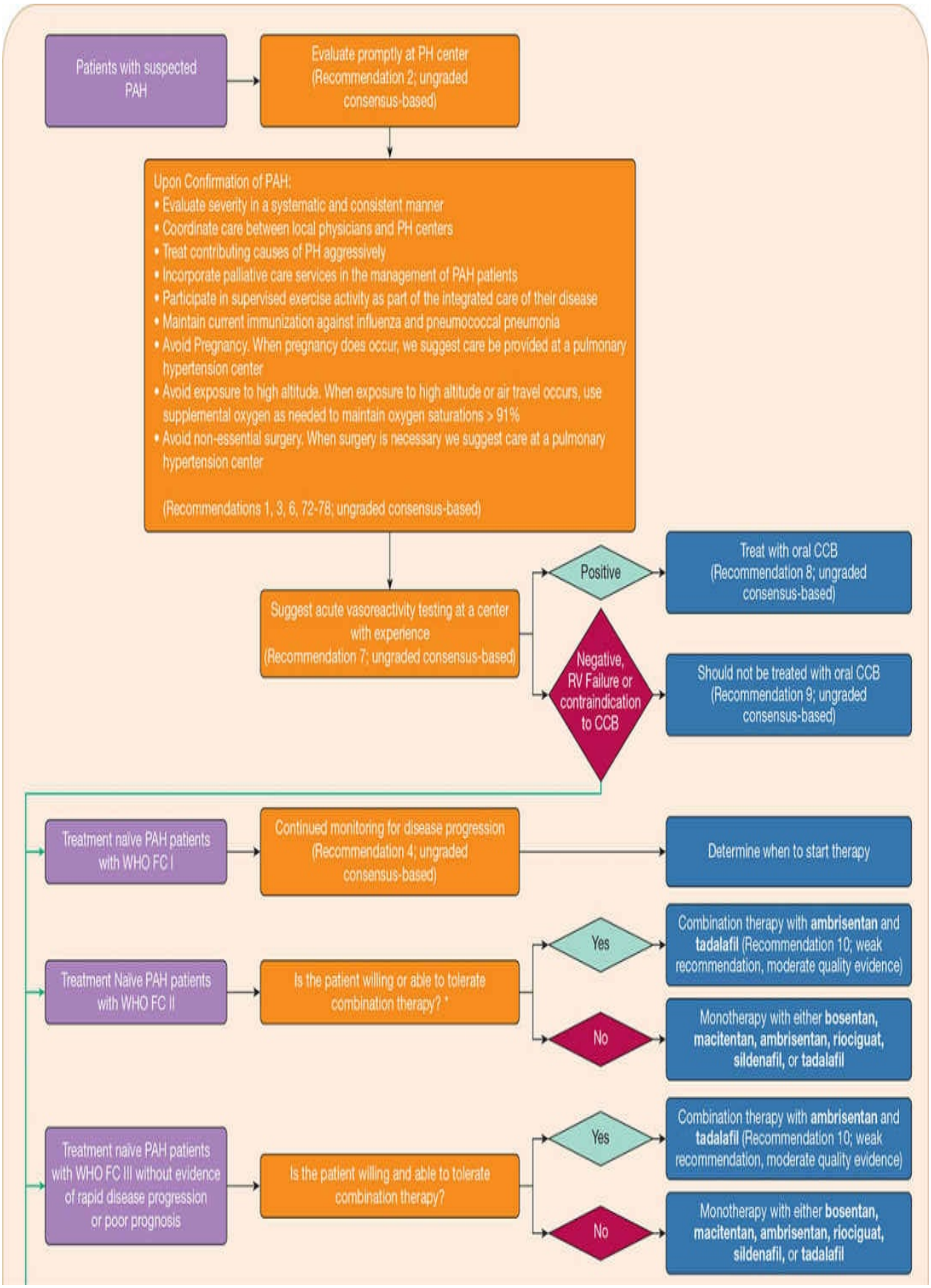
- The occurrence of PAH worsening (eg, worsening symptoms or hospitalizations for PAH)
- Patient adherence to the treatment plan

* *Collaborate with patient, caregivers, and other healthcare professionals.*

General Approach to Treatment

Treatment of PAH may be categorized into nonpharmacologic, pharmacologic, and surgical interventions. The principal endothelial abnormalities that are current pharmacologic therapeutic targets include: (1) supplementing endogenous vasodilators, (2) inhibiting endogenous vasoconstrictors, and (3) reducing endothelial platelet interaction and limiting thrombosis. Nonpharmacologic therapy can be quite broad and should be used when clinically appropriate. Surgical therapy is indicated in certain situations and includes atrial septostomy, pulmonary thromboendarterectomy for CTEPH, and lung or heart-lung transplantation (for disease that is not responsive to medical therapy). Bilateral lung and lung-heart transplantation has been shown to improve survival rates in patients with PAH.[1]

In January 2019, the American College of Chest Physicians (CHEST) released an updated guideline for PAH pharmacotherapy. The guideline focuses on new recommendations for combination therapy and provides visual algorithms to assist providers in selecting appropriate PAH therapies.[30] Combination therapy is recommended in treatment naïve PAH patients with functional class II or III and the new guideline recommends initial management with ambristenan and tadalafil, if able to tolerate combination therapy. See **Fig. 45-3** for the CHEST guideline treatment algorithms.


Patients with suspected PAH
Evaluate promptly at PH center (Recommendation 2; ungraded consensus-based)
Upon Confirmation of PAH:
• Evaluate severity in a systematic and consistent manner
• Coordinate care between local physicians and PH centers
• Treat contributing causes of PH aggressively
• Incorporate palliative care services in the management of PAH patients
• Participate in supervised exercise activity as part of the integrated care of their disease
• Maintain current immunization against influenza and pneumococcal pneumonia
• Avoid Pregnancy. When pregnancy does occur, we suggest care be provided at a pulmonary hypertension center
• Avoid exposure to high altitude. When exposure to high altitude or air travel occurs, use supplemental oxygen as needed to maintain oxygen saturations > 91%
• Avoid non-essential surgery. When surgery is necessary we suggest care at a pulmonary hypertension center
(Recommendations 1, 3, 6, 72-78; ungraded consensus-based)
Suggest acute vasoreactivity testing at a center with experience (Recommendation 7; ungraded consensus-based)
Positive
Treat with oral CCB (Recommendation 8; ungraded consensus-based)
Negative, RV Failure or contraindication to CCB
Should not be treated with oral CCB (Recommendation 9; ungraded consensus-based)
Treatment naïve PAH patients with WHO FC I
Continued monitoring for disease progression (Recommendation 4; ungraded consensus-based)
Determine when to start therapy
Treatment Naïve PAH patients with WHO FC II
Is the patient willing or able to tolerate combination therapy? *
Yes
Combination therapy with ambrisentan and tadalafil (Recommendation 10; weak recommendation, moderate quality evidence)
No
Monotherapy with either bosentan, macitentan, ambrisentan, riociguat, sildenafil, or tadalafil
Treatment naïve PAH patients with WHO FC III without evidence of rapid disease progression or poor prognosis
Is the patient willing and able to tolerate combination therapy?
Yes
Combination therapy with ambrisentan and tadalafil (Recommendation 10; weak recommendation, moderate quality evidence)
No
Monotherapy with either bosentan, macitentan, ambrisentan, riociguat, sildenafil, or tadalafil

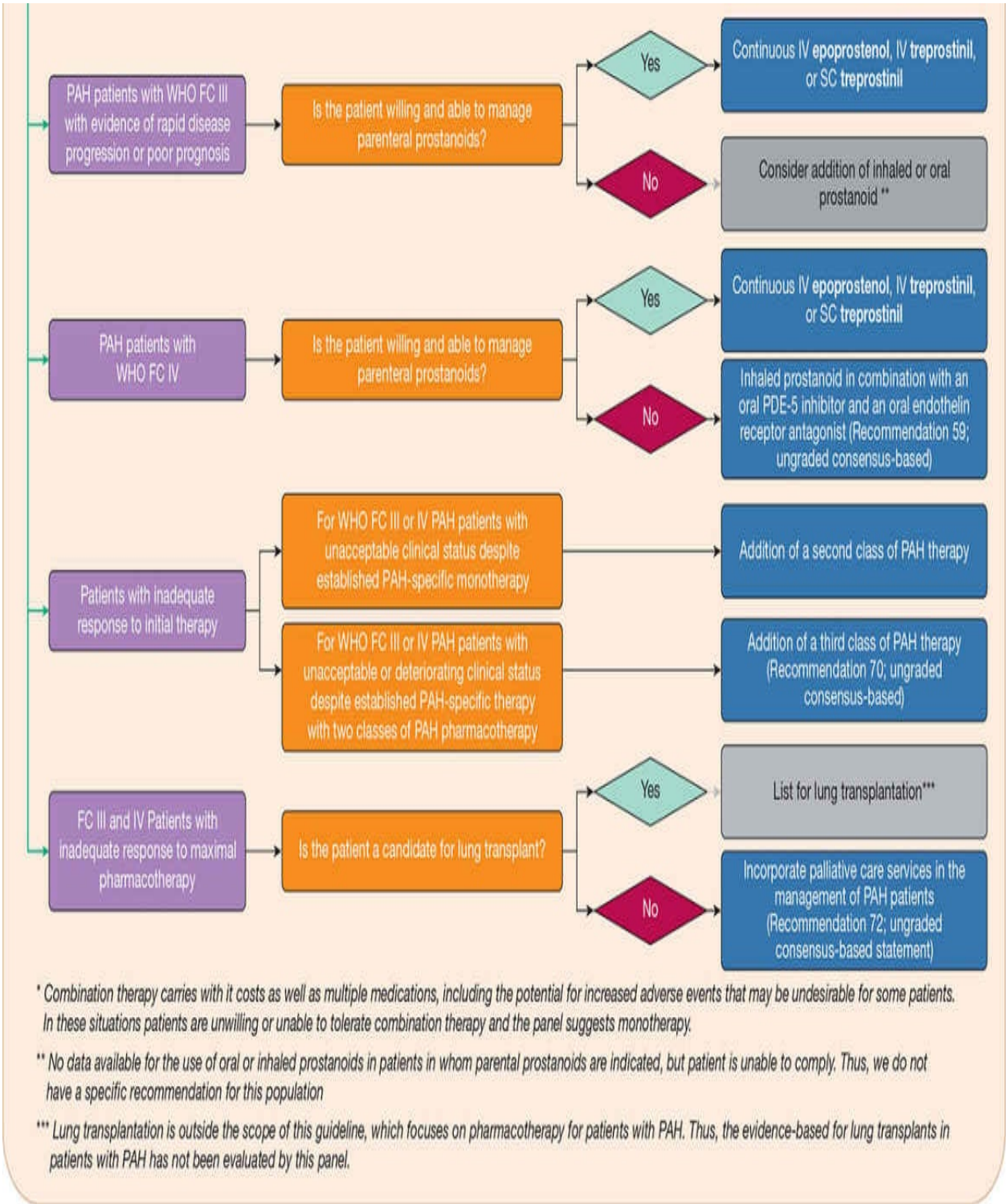


FIGURE 45-3 Guideline Algorithm for Pharmacologic Therapy for PAH in Adults. Where multiple options are provided, there is no comparative effectiveness data to suggest a greater benefit to one therapy over the other. In these situations, other factors, such as patient preference and values, costs, and insurance coverage may guide decision-making. (CCB, calcium channel blocker;

6MWD, 6-minute walk distance; FC, functional class; PAH, pulmonary artery hypertension; PH, pulmonary hypertension; RV, right ventricular; WHO, World Health Organization.) (*Reproduced with permission from Klinger JR, Elliott CG, Levine DJ, et al. Therapy for pulmonary arterial hypertension in adults: Update of the CHEST guideline and expert panel report. Chest. 2019 Mar;155(3):565–586.*)

Nonpharmacologic Therapy

5 Nonpharmacologic therapy is frequently used to address comorbid conditions that often accompany PAH. Patients with PAH should be counseled on several important points. Pregnancy should be avoided due to high morbidity and mortality rates in females with PAH during pregnancy and in the postpartum course (I-C).[5] Immunization against influenza and pneumococcal disease should be provided (I-C).[3] Hypoxemia may aggravate vasoconstriction in patients with PAH; therefore, PAH patients may require supplemental oxygen (IIa-C), particularly when using air travel.[4] Patients should adhere to a low-sodium diet to avoid fluid retention predisposing to right heart failure.[31] Cardiopulmonary rehabilitation improves functional status, exercise capacity, and quality of life in patients with PAH (IIa-B).[1]

Pharmacologic Therapy

The number of potential therapies for PAH has expanded dramatically in the last decade. In addition to adjunctive background therapy, multiple drugs have been developed specifically for the treatment of PAH. Figure 45-3 illustrates the currently recommended treatment algorithm based on the most recent guidelines.[4]

6 **Conventional Pharmacologic Treatment** Conventional therapy includes oral anticoagulants, diuretics, oxygen, and digoxin.[4] Anticoagulation with warfarin may be considered in patients with PAH, particularly if they have IPAH. The rationale for oral anticoagulants is based on the presence of traditional risk factors for venous thromboembolism, such as heart failure and immobility, as well as thrombotic changes in the pulmonary microcirculation. Meta-analyses of small cohort studies demonstrate a 31% mortality risk reduction with anticoagulation.[32] However, recent registry studies report conflicting results regarding the benefit of anticoagulation in IPAH and

APAH.[33,34] When used, the target international normalized ratio (INR) in most centers is 1.5 to 2.5.[3,23] Anticoagulation is recommended for patients with IPAH, HPAH, and PAH due to anorexigens (IIb-C) and may be considered on a case-by-case basis in patients with PAH associated with connective tissue diseases or congenital heart diseases (IIb-C).[4] It may also be recommended in patients on long-term intravenous prostaglandin therapy as these patients are at risk for catheter-associated thrombosis.[4] Anticoagulation is not recommended for patients with PAH associated with portal hypertension or HIV (III-C).[4] Of note, studies evaluating anticoagulation with direct-acting oral anticoagulants in patients with PAH are ongoing.[26]

Loop diuretics such as furosemide are helpful adjunctive therapy in patients with decompensated right heart failure and associated findings of increased central venous pressure, abdominal organ congestion, peripheral edema, and ascites.[3] Appropriate diuretic therapy in right heart failure and volume overload provides symptomatic and clinical benefits in patients with PAH (I-C).[4] Patients should be maintained at as close to a euvolemic state as possible.

Oxygen therapy with a goal oxygen saturation greater than 90% (0.90) may be beneficial in some patients with a PaO_2 <60 mm Hg (8.0 kPa), although no data exist regarding long-term benefit of oxygen treatment in PAH (I-C).[4] Oxygen treatment is controversial in patients with PAH associated with shunts (ie, Eisenmenger's syndrome).

Digoxin may be used for patients with PAH with right heart failure as adjunctive therapy along with diuretics to control symptoms as well as in patients with atrial arrhythmias (I-C).[1] There are no long-term trials and clinical benefit is uncertain. Optimal plasma concentrations are unknown; however, based on data for digoxin in left systolic dysfunction, the typical target concentration is between 0.5 and 0.8 ng/mL (µg/L; 0.64 and 1 nmol/L). Patients on digoxin should receive periodic monitoring of potassium.

Lastly, iron deficiency anemia is commonly reported in patients with PAH and may lead to decreased exercise capacity. Treatment of iron deficiency anemia with iron replacement is recommended in patients with PAH (II-b).[4]

Targeted Pharmacologic Therapy The first medication, epoprostenol, developed to specifically target the disease process causing PAH was approved in 1995. Since then, there has been a surge in the availability of drug therapy for the treatment of PAH with five classes of medications now available. Specific pharmacologic therapy targets the disease process while conventional therapy is used for the management of symptoms and/or comorbid conditions.

Synthetic Prostacyclin and Prostacyclin Analogs PGI_2 is produced predominantly by endothelial cells, inducing potent vasodilation of all vascular beds. It is also a potent inhibitor of platelet aggregation and possesses cytoprotective and antiproliferative activities. PGI_2 synthase expression is reduced in pulmonary arteries, and urinary excretion of PGI_2 metabolites is reduced in PAH. Epoprostenol is a synthetic analog of PGI_2 and has a short half-life of 3 to 5 minutes; consequently, it must be given by continuous IV infusion. Initiation of epoprostenol should be done in a hospital setting at low doses ranging from 2 to 4 ng/kg/min and increased at a rate limited by side effects (flushing, headache, diarrhea, jaw pain, backache, abdominal cramping, extremity pain, and hypotension). During initiation and initial titration of epoprostenol, patients may require inotropic and/or blood pressure support for hemodynamic stability.[35] The two available products, Flolan® (now available generic) and Veletri®, have unique stability and reconstitution parameters; both pharmacists and patients should be aware of the differences and follow the manufacturer recommendations. Due to the short half-life of the drug, it is recommended that the patient have a backup supply of the drug and infusion pump as interruption of epoprostenol may lead to life-threatening pulmonary vasoconstriction.[36] Because the drug must be administered by continuous infusion with a central venous catheter and pump, bacteremia and catheter obstruction are potential complications. A Centers for Disease Control and Prevention (CDC) study found that bloodstream infections occurred with epoprostenol and treprostinil in the range of 0.3 to 2.1 per 1,000 medicine days (approximately 1 infection every 3 years) when these drugs are given by the IV route.[37] The target dose for the first 2 to 4 weeks is around 10 to 15 ng/kg/min, and periodic dose increases are then required to maximize efficacy. Doses are variable but are often in the range of 25 to 80 ng/kg/min.[38,39] Multiple observational series have documented an improvement in survival in patients with IPAH.[39–41] Based on current guidelines, epoprostenol is indicated for WHO functional class III and IV (I-A).[1]

Treprostinil is a stable analog of PGI_2 given for subcutaneous (SC) or IV infusion approved for functional classes II, III, and IV.[39] The major advantages of treprostinil over epoprostenol include ease of use and increased safety due to a longer half-life, lowering the risk of rebound effects that may happen with drug interruption.[19] Treprostinil has been shown to improve 6-minute walk distance and hemodynamics with outcomes that are similar to epoprostenol.[42,43] In clinical trials, the greatest exercise improvement was observed in patients who

were more compromised at baseline and in patients who could tolerate doses in the upper quartile (>13.8 ng/kg/min). The initial dose for treprostinil is 1.25 ng/kg/min by either the SC or the IV route. If not tolerated, the dose should be reduced to 0.625 ng/kg/min and dose titration again attempted at 4 weeks. Infusion site pain is common with the SC route and can occur in up to 85% of patients, leading to discontinuation of treatment in 8% of patients and limiting upward dose titration.[38] Patients unable to tolerate SC can be transitioned to IV treprostinil.[23] Transitions between prostacyclin agents or routes should be performed inpatient at an expert referral center. Bloodstream infections, primarily due to gram-negative pathogens, are more likely with IV treprostinil than with IV epoprostenol.[44] Use of the diluent used for epoprostenol, which has a more basic pH, to reconstitute IV treprostinil may decrease rates of bloodstream infections to a rate similar to that seen with epoprostenol.[45] Other side effects are similar to epoprostenol. Based on international guidelines, treprostinil is recommended for functional class III (SC administration—I-B; IV administration—IIa-C), and functional class IV (SC and IV administration—IIb-C).[1]

In an effort to prevent complications and use of pumps and central venous catheters for PGI_2 analog administration, aerosolized formulations were developed. The first approved formulation, iloprost (Ventavis), is a PGI_2 analog that is given by inhalation using a dosing system provided by the manufacturer (ADD system) with the initial inhaled dose being 2.5 mcg six to nine times per day up to every 2 hours during waking hours. The dose should be titrated and maintained at 5 mcg/dose if tolerated. In a 3-month clinical trial, iloprost via inhalation provided at least a 10% improvement in 6-minute walking distance and improvement in functional class.[46] Inhaled iloprost can be cumbersome to use as each inhalation dose can take 4 to 10 minutes to administer and multiple inhalations are required for a full dose. Patients should also be instructed to have a backup supply as iloprost has a short half-life, similar to epoprostenol.[23] Adverse effects are similar to other PGI_2 analogs, including cough, headache, flushing and jaw pain. Inhaled iloprost is indicated for functional class III (I-B) and functional class IV (IIb-C), although many clinicians prefer using the IV or SC route in patients with more severe disease.[4]

The second aerosolized formulation, inhaled treprostinil, was approved by the FDA in July 2009 to improve exercise capacity in functional class III patients. In a clinical trial, patients receiving inhaled treprostinil experienced a 20-m improvement in 6-minute walk distance compared with those on placebo. All

patients included in the trial were concurrently receiving bosentan or sildenafil for at least 3 months.[47] An open-label extension of the trial found that inhaled treprostinil provided sustained benefit and was safe and efficacious over a 2-year period.[48] The approved dosing of inhaled treprostinil is three breaths (18 mcg each) four times daily during waking hours. The dose may be titrated based on patient tolerance at 1- to 2-week intervals to a maximum dose of nine breaths four times daily. Inhaled treprostinil requires less time to administer, but the formulation is more complicated to prepare than inhaled iloprost.[23] While inhaled treprostinil avoids the infusion-related complications of the other PGI_2 analogs, use is cautioned in patients with acute pulmonary infections or underlying lung disease. The most common adverse effects seen in clinical trials include throat irritation, cough, headache, nausea, dizziness, and flushing. Inhaled treprostinil may also cause systemic hypotension, and patients should be monitored carefully if they are concurrently on diuretics, antihypertensives, or other vasodilators. Inhaled treprostinil is indicated for patients with functional class III (I-B) and IV (IIb-C).[1]

Finally, the first oral prostacyclin analog, sustained-release treprostinil (Orenitram), was approved by the FDA in December 2013 for patients with functional class II and III PAH. Oral treprostinil monotherapy for 12 weeks was associated with a significant increase of 23 meters in 6-minute walk distance.[49] No differences were observed between treprostinil and placebo in time to clinical worsening or WHO functional class. Two randomized controlled trials followed evaluating the use of oral treprostinil in addition to endothelin-receptor antagonists and/or phosphodiesterase-5 inhibitors. Neither study demonstrated a significant improvement in 6MWD with oral treprostinil therapy.[50,51] The average increase in 6MWD did correspond to treprostinil dose, with patients receiving higher doses demonstrating more improvement. Adverse events in studies included headache, nausea, diarrhea, and jaw pain. Like other prostacyclin analogs, oral treprostinil inhibits platelet aggregation and may increase the risk of bleeding, especially in patients treated with anticoagulants. Oral treprostinil must be taken with food to improve absorption and cannot be crushed due to the osmotic release formulation. Oral treprostinil is indicated for patients with functional class III (IIb-B).[4]

Prostacyclin IP Receptor Agonist Selexipag is a novel prostacyclin IP receptor agonist that was approved for use in patients with WHO functional class II and III PAH in 2015.

Selexipag works by agonizing the prostacyclin IP receptor coupled with G_s

protein, leading to increased cyclic adenosine monophosphate and relaxation of vascular smooth muscle. This leads to pulmonary vasodilation, as well as antiproliferative effects on smooth muscle cells and inhibition of platelet aggregation. The initial clinical trial evaluating the use of selexipag showed efficacy in decreasing pulmonary vascular resistance and improving cardiac index and 6-minute walk distance.[52] A large clinical trial of 1,156 patients with IPAH and APAH treated with selexipag versus placebo demonstrated a decrease in disease progression, hospitalizations for PAH, and complications from PAH.[53] These outcomes were similar in patients on no background therapy and when added to background ERAs, phosphodiesterase-5 inhibitors, or both. This finding supports the use of triple oral combination therapy.[54] In addition, when a subgroup of patients with PAH associated with connective tissue diseases was evaluated, similar benefits were seen with selexipag.[55] Dose titration is similar to the prostacyclin analogs where the patient is initiated on a starting dose and titrated to the maximum tolerated dose. The initial starting dose is 200 mcg PO twice daily; this dose can be increased by 200 mcg twice daily increments to a maximum dose of 1600 mcg twice daily. The median dose tolerated was 1,000 mcg twice daily in the clinical trial.[53] Of note, patients with treatment interruptions greater than 3 days required re-titration of the drug. Adverse effects are very common, especially with dose titration, and similar to those caused by prostacyclin analogs, including flushing, headache, diarrhea, nausea, jaw pain, and myalgias. Selexipag may also cause anemia so a complete blood cell count should be monitored periodically. Selexipag has also been associated with an increased incidence of hyperthyroidism.

8 ***Endothelin-Receptor Antagonists (ERAs)*** ET-1, a peptide produced primarily by the vascular endothelial cells, is characterized as a powerful vasoconstrictor and mitogen for smooth muscle. Activation of the ET-1 system has been shown in both plasma and lung tissue of PAH patients. There are three FDA-approved oral endothelin-receptor antagonists (ERAs) available for the treatment of PAH—bosentan, ambrisentan, and macitentan. Bosentan is an orally active dual ET_A and ET_B receptor antagonist that improves exercise capacity, functional class, hemodynamics, echocardiographic and Doppler variables, and time to clinical worsening.[56,57] In one of the larger studies with bosentan, patients were started on 62.5 mg twice daily for 4 weeks followed by 125 or 250 mg twice daily for a minimum of 12 weeks. Both doses were better than placebo, and the higher dose provided greater improvement in 6-minute walking distance. Increases in hepatic aminotransferases occurred in 11% of patients and were

dose-dependent.[57] The mechanism of increased liver enzymes is thought to be competition by bosentan and its metabolites with the biliary excretion of bile salts, resulting in the retention of bile salts that can be cytotoxic to hepatocytes. Because of this toxicity, bosentan is only available through a distribution program.[23] Bosentan should be started at 62.5 mg twice daily in adults and adolescents for 4 weeks. After 4 weeks of therapy, the dose should be increased to 125 mg twice daily. If LFTs are confirmed to be in the range of three to five times the upper limit of normal, reduce the daily dose or interrupt treatment. If LFTs return to pretreatment levels, bosentan may be continued or reintroduced if indicated. LFTs should be monitored at baseline and monthly thereafter, and monthly pregnancy testing is required in females (US boxed warning for teratogenicity). A complete blood count should be monitored every 3 months as bosentan has been associated with anemia. Bosentan is indicated for WHO functional class II and III (I-A/B) as well as functional class IV (IIb-C).[4]

Ambrisentan is a once-daily selective ET_A receptor antagonist that improves exercise capacity and hemodynamics and delays clinical worsening in PAH.[58,59] Two large trials demonstrated a significant improvement in functional capacity with ambrisentan compared to placebo at doses of 2.5, 5, and 10 mg daily. However, a greater response was seen with increased doses. All doses were well tolerated, with no patients on therapy experiencing an increase in LFTs more than three times the upper limit of normal. Similar to bosentan, ambrisentan is teratogenic and should be avoided in pregnancy; it is only available through a distribution program.[23] Unlike bosentan, liver toxicity occurs very rarely with ambrisentan (0.8% in 12-week trials and 2.8% for up to 1 year).[40] Common side effects include peripheral edema, nasal congestion, flushing, anemia, and palpitations. Treatment should be initiated with 5 mg once daily and increased to 10 mg once daily if required. Ambrisentan is recommended for WHO functional class II and III (I-A/B) as well as functional class IV (IIb-C).[4]

Macitentan (Opsumit) is a once-daily dual ERA. Macitentan was approved based on the results of the Study with an Endothelin-Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome (SERAPHIN) trial.[60] Patients were randomized to placebo, macitentan 3 mg orally daily, or macitentan 10 mg orally daily. Patients could be on concomitant therapy, if at stable doses for 3 months, with oral or inhaled prostanoids, calcium channel blockers, or oral phosphodiesterase inhibitors. Patients on intravenous or subcutaneous prostacyclins were excluded. The majority of patients (>80%) were functional class II or III. Both macitentan doses demonstrated statistically significant decreases in composite events related to PAH or death compared to

placebo. Worsening of PAH was the most common event (defined as a decrease in 6-minute walk distance, worsening symptoms, and need for additional treatment). Increase in LFTs was similar across all groups, about 3.5%-4.5%. More patients in the macitentan groups experienced nasopharyngitis, headache, and anemia than with placebo. The FDA-approved dose is 10 mg by mouth daily. Macitentan is teratogenic and female patients must go through a REMS program to receive the drug. Macitentan is recommended for WHO functional class II and III (IB) as well as functional class IV (IIb-C).[4]

Phosphodiesterase Inhibitors There are two phosphodiesterase-5 inhibitors (PDE-5i) available for the treatment of PAH—sildenafil and tadalafil. Sildenafil is a potent and highly specific phos-phodiesterase-5 inhibitor that is approved for erectile dysfunction but also has been shown to reduce mPAP and improve functional class. Sildenafil exerts its pharmacologic effect by increasing the intracellular concentration of cyclic guanosine monophosphate, leading to vasorelaxation and antiproliferative effects on vascular smooth muscle cells. In a double-blind, placebo-controlled trial, sildenafil with conventional therapy significantly improved 6MWD and hemodynamic parameters at 12 weeks compared with placebo.[61] The FDA-approved dose is 20 mg by mouth three times per day; however, much higher doses are routinely used clinically. Common adverse effects include headaches, flushing, epistaxis, dyspepsia, and diarrhea. Sildenafil may also cause systemic hypotension. Changes in vision have been reported, including blue-tinted vision and sudden loss of vision. In the event of sudden loss of vision, the drug should be stopped. Concurrent administration of sildenafil and bosentan leads to a 50% decrease in sildenafil concentrations through cytochrome P450 3A4 induction, requiring dose adjustment of sildenafil. Nitrate therapy may lead to an excessive reduction in blood pressure and should be avoided with sildenafil. PDE-5 inhibitors should not be used with riociguat due to increased risk of hypotension. Based on the current guidelines, sildenafil is recommended for functional class II and III patients with PAH (I-A) in addition to functional class IV patients (IIb-C).[4]

Another phosphodiesterase-5 inhibitor, tadalafil, was approved by the FDA in 2009 for the treatment of PAH. In a 16-week study, tadalafil 40 mg daily significantly improved exercise capacity, quality of life, and time to clinical worsening. Fifty-three percent of patients in this study were also on background bosentan therapy. Treatment-naïve patients demonstrated not only greater improvement in exercise capacity than those on bosentan therapy but also greater improvement on all secondary outcomes. One possible explanation is decreased tadalafil levels as bosentan is a potent CYP450 3A4 inducer. Higher

doses of tadalafil may be required in patients on concurrent bosentan therapy.[62] The most commonly reported adverse events were headache, myalgia, and flushing. The recommended dose is 40 mg by mouth once a day.[63] Concurrent use with nitrate therapy should also be avoided with tadalafil. PDE-5 inhibitors should not be used with riociguat due to increased risk of hypotension. Current guidelines indicate tadalafil for functional class II and III (I-B) and functional class IV (IIb-C).[4]

Guanylate Cyclase Stimulator Riociguat is a soluble guanylate cyclase stimulator approved by the FDA in 2013. Riociguat works synergistically with nitric oxide and directly stimulates soluble guanylate cyclase. In the phase 3 study Pulmonary Arterial Hypertension Soluble Guanylate Cyclase-Stimulator Trial 1 (PATENT-1), riociguat 2.5 mg by mouth three times daily improved 6MWD, hemodynamic parameters, and WHO functional class.[64] Syncope occurred in 1% of riociguat patients compared to 4% in the placebo group. Of note, patients were continued on baseline therapy of endothelin-receptor antagonists or nonintravenous prostacyclin analogs. However, the use of riociguat with phosphodiesterase-5 inhibitors is contraindicated due to the additive risk of hypotension. The recommended starting dose is 1 mg by mouth three times daily (TID), titrated by 0.5 mg TID every 2 weeks to a maximum dose of 2.5 mg by mouth TID. Riociguat is teratogenic and female patients must go through a REMS program to receive the drug. Riociguat is recommended for WHO functional class II and III (I-B) as well as functional class IV (IIb-C).[4]

9 ***Calcium Channel Blockers*** Since such a small number of patients with IPAH, HPAH, or PAH induced by drugs or toxins have a positive response to acute vasodilator testing, calcium channel blockers (CCBs) are infrequently used in the management of PAH. Approximately 13% of patients with IPAH will demonstrate an acute vasodilator response and may be initiated on CCB therapy. However, the number responding to long-term therapy is low (7%).[24] CCBs should not be used in the absence of demonstrated acute vasoreactivity.[1] If used in patients without acute vasoreactivity, CCBs are associated with systemic hypotension leading to reflex tachycardia, sympathetic stimulation, and right ventricular ischemia, ultimately increasing patient morbidity.[5] If used, dihydropyridine CCBs are preferred as they lack the negative inotropic effects seen with verapamil. Diltiazem may be used in patients who also have tachycardia to slow heart rate through atrioventricular node blockade. If left ventricular systolic dysfunction is present, diltiazem and verapamil should not be used. Assessment of CCB therapy should occur soon after initiation, and if

improvement in functional class to class I or II is not seen, additional or alternative PAH therapy must be initiated. In acute responders, CCBs may be used in WHO functional classes I to IV (I-C).[1] Doses used for PAH are relatively high—that is, up to 20 to 30 mg/day for amlodipine, 120 to 240 mg/day for nifedipine and 240 to 720 mg/day for diltiazem—however, initial doses should be much lower and titrated upward to response.[5] The most common adverse effect is peripheral edema. Specific information concerning individual drugs used for PAH is shown in **Tables 45-7** to **45-9**.

TABLE 45-7 Dosing Recommendations for Common Treatments for Pulmonary Arterial Hypertension

Drug	Initial Dose	Usual Range	Other
Epoprostenol	2-4 ng/kg/min by IV infusion	Titrate up to 20-40 ng/kg/min	
Treprostinil (IV or SC)	1.25 ng/kg/min by continuous subcutaneous or IV infusion	Decrease to 0.625 ng/kg/min if not tolerated Increase by no more than 1.25 ng/kg/min weekly for the first 4 weeks of therapy and no more than 2.5 ng/kg/min weekly for the duration of therapy	
Treprostinil (inhaled)	Three inhalations (18 mcg) four times daily during waking hours (approximately 4 hours apart)	Reduce to one to two breaths if three breaths not tolerated; increase to three breaths when tolerance improves The goal maintenance dose is nine breaths (54 mcg) per treatment four times daily; titrate by increasing three breaths at 1- to 2-week intervals as tolerated	
Treprostinil (oral)	0.25 mg every 12 hours or 0.125 mg every 8 hours	Titrate dose in increments of 0.25 to 0.5 mg every 12 hours or 0.125 mg every 8 hours every 3 to 4 days The maximum dose is determined by tolerability Avoid abrupt discontinuation; if not tolerated, decrease dose stepwise in 0.25-0.5 mg increments	If unable to continue oral therapy temporarily while inpatient, consider initiation of IV or SC treprostinil; 1/5 of the total daily oral dose is an estimate of total daily parenteral dose
Iloprost	2.5 mcg inhaled six to nine times daily (dosing at ≥2-hour intervals while awake)	Titrate to 5 mcg per dose with a maximum daily dose of 45 mcg	
Bosentan	62.5 mg orally twice daily for 4 weeks	Increase to 125 mg orally twice daily	Available through Tracleer Access Program
Ambrisentan	5 mg orally daily	Titrate to maximum dose of 10 mg daily	Available through Letairis Education and Access Program
Macitentan	10 mg orally daily	Maximum dose of 10 mg orally daily	Available through Opsumit Risk Evaluation and Mitigation Strategy Program
Sildenafil	20 mg orally three times daily, taken at least 4-6 hours apart	Maximum FDA-approved dose is 20 mg orally three times a day; higher doses frequently used clinically	
Tadalafil	40 mg orally once daily, with or without food	40 mg orally once daily	Not recommended to divide the dose
Riociguat	0.5-1 mg orally three times daily	Maximum dose is 2.5 mg orally three times daily Titrate every 2 weeks to maximum tolerated dose; dose limited by hypotension	Use is contraindicated with PDE-5 inhibitors due to the risk of hypotension Available through Adempas Risk Evaluation and Mitigation Program
Selexipag	200 mcg orally twice daily	Titrate to maximally tolerated dose in 200 mcg increments; maximum dose 1,600 mcg orally twice daily	

TABLE 45-8 Monitoring Recommendations for Adverse Drug Reactions

Drug	Adverse Reaction	Monitoring Parameter	Comments
Synthetic Prostacyclin and Prostacyclin Analogs			
Epoprostenol and Treprostinil (IV/SC/oral)	Pain (chest and jaw), flushing, headache	Patient reported symptoms	Occurs with dose titration; titrate to balance efficacy and adverse effect
	GI (nausea, vomiting, diarrhea, anorexia)	Patient reported symptoms	
	Hypotension	Blood pressure	Occurs with dose titration; additive hypotensive effects with other antihypertensives, vasodilators, and diuretics
	Thrombocytopenia	Platelets; signs and symptoms of bleeding	Monitor with concurrent anticoagulant and antiplatelet agents
Treprostinil (SC-specific)	SC site pain	Local pain at SC administration site	Frequent site rotation may improve; may also use cool compresses, lidocaine-based creams or patches, or pluronic lecithin organogel (PLO) to relieve pain
Treprostinil (inhaled)	Cough and throat irritation	Patient reported symptoms	
Iloprost	Cough and throat irritation	Patient reported symptoms	
Prostacyclin IP Receptor Agonist			
Selexipag	Pain (chest and jaw), flushing, headache	Titrate to balance efficacy and adverse effect	Occurs with dose titration
	GI (nausea, diarrhea)	Patient reported symptoms	
	Anemia	Hemoglobin	Monitor at baseline and then periodically throughout treatment
	Hyperthyroidism	Thyroid stimulating hormone	May monitor if associated symptoms
Endothelin-Receptor Antagonists			
Bosentan and Ambrisentan and Macitentan	Anemia	Hemoglobin	Usually resolves after the first 3 months of therapy
	Edema	Edema on physical exam	May require a dose increase of diuretic therapy
Bosentan (specific)	Hepatotoxicity	Baseline and monthly liver function tests required	Black box warning for liver injury
Phosphodiesterase-5 Inhibitors			
Sildenafil and Tadalafil	Headache	Patient reported symptoms; occurs due to vasodilation	
	Nasal congestion	Patient reported symptoms	
	Hypotension	Blood pressure	Concurrent use with nitrates potentiates effects
	Visual changes	Consider baseline exam; repeat exam if visual changes occur	
Soluble Guanylate Cyclase Stimulator			
Riociguat	Headache	Patient reported symptoms	
	Hypotension	Blood pressure	
	Peripheral edema	Edema on physical exam	
	Major bleeding	Hemoglobin and hematocrit Signs and symptoms of bleeding	
	Gastroesophageal reflux disease (GERD)	Patient reported symptoms; heart burn / reflux symptoms	

TABLE 45-9 Potentially Significant Drug Interactions with Pulmonary Arterial Hypertension Drugs.

PAH drug	Mechanism of interaction	Interacting drug	Interaction
Ambrisentan	Unknown	Cyclosporine Ketoconazole	Caution is required in the coadministration of ambrisentan with ketoconazole and cyclosporine.
Bosentan	CYP3A4 inducer	Sildenafil	Sildenafil levels fall 50%; bosentan levels increase 50%. May not require dose adjustments of either drug.
	CYP3A4 substrate	Cyclosporine	Cyclosporine levels fall 50%; bosentan levels increase fourfold. Combination contraindicated.
	CYP3A4 substrate	Erythromycin	Bosentan levels increase. May not require dose adjustment of bosentan during a short course.
	CYP3A4 substrate	Ketoconazole	Bosentan levels increase twofold.
	CYP3A4 substrate + bile salt pump Inhibitor	Glibenclamide	Increase incidence of elevated aminotransferases. Potential decrease of hypoglycemic effect of glibenclamide. Combination contraindicated.
	CYP2C9 and CYP3A4 substrate	Fluconazole, amiodarone	Bosentan levels increase considerably. Combination contraindicated.
	CYP2C9 and CYP3A4 inducers	Rifampicin, phenytoin	Bosentan levels decrease by 50%. Need for dose adjustment uncertain.
	CYP2C9 inducer	HMG CoA reductase inhibitors	Simvastatin levels reduce 50%; similar effects likely with atorvastatin. Cholesterol level should be monitored.
	CYP2C9 inducer	Warfarin	Increases warfarin metabolism, may need to adjust warfarin dose. Intensified monitoring of warfarin recommended following initiation but dose adjustment usually unnecessary.
	CYPC9 and CYP3A4 inducers	Hormonal contraceptives	Hormone levels decrease. Contraception unreliable.
Macitentan			Not yet determined.
Selexipag			Not yet determined.
Sildenafil[44]	CYP3A4 substrate	Bosentan	Sildenafil levels fall 50%; bosentan levels increase 50%. May not require dose adjustments of either drug.
	CYP3A4 substrate	HMG CoA reductase inhibitors	May increase simvastatin/atorvastatin levels through competition for metabolism, Sildenafil levels may increase. Possible increased risk of rhabdomyolysis.
	CYP3A4 substrate	HIV protease inhibitors	Ritonavir and saquinavir increase sildenafil levels markedly.
	CYP3A4 inducer	Phenytoin	Sildenafil levels may fall.
	CYP3A4 substrate	Erythromycin	Sildenafil levels increase. May not require dose adjustment for a short course.
	CYP3A4 substrate	Ketoconazole	Sildenafil levels increase. May not require dose adjustment.
	CYP3A4 substrate	Cimetidine	Sildenafil levels increase. May not require dose adjustment.
	cGMP	Nitrates, Nicorandil Molsidomine	Profound systemic hypotension, combination contraindicated.
Tadalafil[45]	CYP3A4 substrate	Bosentan	Tadalafil exposure decreases by 42%, no significant changes in bosentan levels.[45] May not require dose adjustment.
	cGMP	Nitrates, Nicorandil	Profound systemic hypotension, combination contraindicated.
Riociguat[18]	cGMP	Sildenafil, other PDE-5 inhibitors	Hypotension, severe side effects, combination contraindicated.
	cGMP	Nitrates, Nicorandil	Profound systemic hypotension, combination contraindicated.

Data from Reference 4.

10 ***Combination Therapy*** Combination therapy is an attractive option to address the multiple pathophysiologic mechanisms in PAH, resulting in improvement in hemodynamics, symptoms, and exercise capacity. A significant portion of patients require combination therapy with either two or three-drug regimens. Two meta-analyses found that combination therapy decreased time to clinical worsening by 35% to 40%.[29,65] Sequential combination therapy is recommended for patients with inadequate clinical response to monotherapy and is a common clinical strategy. However, initial combination therapy may have a role for some patients.[28] **Tables 45-10** and **45-11** show current treatment recommendations for initial combination and sequential combination therapy, respectively.

TABLE 45-10 Recommendations for Efficacy of Initial Drug Combination Therapy for Pulmonary Arterial Hypertension (group 1) According to World Health Organization Functional Class.[c]

	Class[a]-Level[b]					
Treatment	**WHO-FC II**		**WHO-FC III**		**WHO-FC IV**	
Ambrisentan + tadalafil[d]	I	B	I	B	IIb	C
Other ERA + PDE-5i	IIa	C	IIa	C	IIb	C
Bosentan + sildenafil + iv epoprostenol	-	-	IIa	C	IIa	C
Bosentan + iv epoprostenol	-	-	IIa	C	IIa	C
Other ERA or PDE-5i + sc treprostinil			IIb	C	IIb	C
Other ERA or PDE-5i + other iv prostacyclin analogs			IIb	C	IIb	C

ERA, endothelin-receptor antagonist; iv, intravenous; PDE-5i, phosphodiesterase type 5 inhibitor; RCT, randomized controlled trial; sc, subcutaneous; WHO-FC, World Health Organization functional class.

[a]Class of recommendation.

[b]Level of evidence.

[c]Reference(s) supporting recommendations.

[d]Time to clinical failure as primary endpoint in RCTs or drugs with demonstrated reduction in all-cause mortality (prospectively defined).

TABLE 45-11 Recommendations for Efficacy of Sequential Drug Combination Therapy for Pulmonary Arterial Hypertension (group 1) According to World Health Organization Functional Class.[c]

Treatment	Class[a]-Level[b]					
	WHO-FC II		WHO-FC III		WHO-FC IV	
Macitentan added to sildenafil[d]	I	B	I	B	IIa	C
Riociguat added to bosentan	I	B	I	B	IIa	C
Selexipag[e] added to ERA and/or PDE-5i[d]	I	B	I	B	IIa	C
Sildenafil added to epoprostenol	-	-	I	B	IIa	B
Treprostinil inhaled added to sildenafil or bosentan	IIa	B	IIa	B	IIa	C
Iloprost inhaled added to bosentan	IIb	B	IIb	B	IIb	C
Tadalafil added to bosentan	IIa	C	IIa	C	IIa	C
Ambrisentan added to sildenafil	IIb	C	IIb	C	IIb	C
Bosentan added to epoprostenol	-	-	IIb	C	IIb	C
Bosentan added to sildenafil	IIb	C	IIb	C	IIb	C
Sildenafil added to bosentan	IIb	C	IIb	C	IIb	C
Other double combinations	IIb	C	IIb	C	IIb	C
Other triple combinations	IIb	C	IIb	C	IIb	C
Riociguat added to sildenafil or other PDE-5i	III	B	III	B	III	B

EMA, European Medicines Agendy; ERA, endothelin-receptor antagonist; PAH, pulmonary arterial hypertension; PDE-5i, phosphodiesterase type 5 inhibitor; RCT, randomized controlled trial; WHO-FC, World Health Organization functional class.

[a]Class of recommendation.

[b]Level of evidence

[c]Reference(s) supporting recommendations

[d]Time to clinical failure as primary endpoint in RCTs or drugs with demonstrated reduction in all-cause mortality (prospectively defined).

[e]This drug was not approved by the EMA at the time of publication of these guidelines.

The addition of nonparenteral prostanoid therapy to either ERAs or PDE-5 inhibitor therapy has demonstrated mixed results. Inhaled iloprost and oral treprostinil failed to demonstrate significant clinical improvements when added to background ERA, PDE-5i, or combination therapy. However, the GRIPHON study found a 40% decrease in clinical worsening with selexipag when added to background therapy. This improvement in outcomes was significant regardless of the type of background therapy (ERA, PDE-5i, or a combination).[53] Adding an ERA agent to PDE-5 inhibitor or prostanoid therapy has also been demonstrated to be effective. The addition of macitentan to PDE-5 inhibitor or nonparenteral prostanoid therapy delayed clinical worsening in the SERAPHIN trial.[60] However, this may not be a class effect. In the COMPASS trial, the addition of bosentan to sildenafil therapy did not demonstrate a benefit.[66] Use of

PDE-5 inhibitors or riociguat in combination with prostanoids or ERAs has demonstrated mixed results. Sildenafil added to epoprostenol provided significant improvements in clinical outcomes and delay in clinical worsening.[67] Riociguat combined with ERAs showed benefit at 12 weeks.[64] However, tadalafil combined with bosentan did not show a clinical improvement.[68]

The AMBITION trial compared initial combination therapy with ambrisentan and tadalafil versus either therapy alone. Initial combination therapy was associated with a significant reduction in time to clinical failure and PAH hospitalizations. Adverse effects such as peripheral edema, headache, nasal congestion, and anemia were more common in the combination group than either monotherapy group. However, there was no difference in drug discontinuation due to adverse events.[69] This initial combination is considered a I-B recommendation for WHO Class II and III patients and a IIb-C recommendation for WHO Class IV patients. The TRITON study, a randomized controlled trial, is ongoing to evaluate the benefit of initial triple therapy (macitentan, tadalafil, and selexipag) compared to initial dual therapy (macitentan and tadalafil).[70]

Special Populations

Pregnancy

Pregnancy confers an increased risk of mortality in PAH patients. Guidelines recommend encouraging PAH patients to actively avoid pregnancy.[4] There is no consensus on the best birth control method for PAH patients, but the use of two methods should be considered. Estrogen-containing products should be avoided. Patients who do become pregnant need to be referred as soon as possible to a pulmonary hypertension center where there are expert high-risk OB and PAH specialists who have experience in this area.[4] All ERAs (bosentan, ambrisentan, and macitantan) are teratogenic, as is riociguat. These medications should be discontinued immediately if a patient becomes pregnant and therapy needs to be adjusted. Monthly pregnancy tests are required for use of ERAs and riociguat. It is also important to note that bosentan may decrease the efficacy of oral birth control medications.

Evaluation of Therapeutic Outcomes

Response to treatment in PAH can be objectively measured by the 6-minute walk distance, echocardiography to assess pulmonary pressures, and right heart

catheterization to assess ventricular function and pulmonary pressures (see Table 45-6). The WHO functional classification system is clinically useful, but correlations to hemodynamics are imprecise. Other outcomes that are useful in clinical trials include hospitalization for exacerbations of PAH and the development of complications and death. Table 45-6 provides recommendations regarding specific baseline and follow-up assessments and when they should be performed.

CONCLUSION

Significant advances have been made in elucidating the pathogenesis of PAH as well as in the evaluation and treatment of these patients over the past three decades. With approved targeted therapies such as ERAs, phosphodiesterase-5 inhibitors, and PGI_2 analogs, clinical improvement is possible in most patients, leading to a higher quality of life and delay of disease progression. Patient education is important to improve acceptance of this disease and referral to specialty care centers may provide the best outcomes.

Postclass Engaged Learning Activity

Conduct a literature search and identify a primary research manuscript that has been published in the past 12 months regarding the treatment of pulmonary arterial hypertension. Focus your search on trials evaluating the role of combination therapy. Write a brief summary about the study methods, the major findings, and how this new information might change current practice. This activity is intended to build your literature evaluation skills and ability to critically appraise research manuscripts.

ABBREVIATIONS

ALK-1	activin receptor-like kinase 1
APAH	associated pulmonary arterial hypertension
BMPR-2	bone morphogenetic protein receptor 2
BNP	brain natriuretic peptide
CCB	calcium channel blocker
CTEPH	chronic thromboembolic pulmonary hypertension
NOS	nitric oxide synthase
ERA	endothelin-receptor antagonist
ET-1	endothelin-1
FPAH	familial pulmonary arterial hypertension
5-HT	serotonin
5-HTT	5-hydroxytryptamine transporter
HIV	human immunodeficiency virus
HPAH	heritable pulmonary arterial hypertension
INR	international normalized ratio
IPAH	idiopathic pulmonary arterial hypertension
LEAP	Letairis Education and Access Program
LFT	liver function test
LVEDP	left ventricular end-diastolic pressure
PAP	pulmonary artery pressure
NO	nitric oxide
PAH	pulmonary arterial hypertension
PGI_2	prostacyclin
SC	subcutaneous
WHO	World Health Organization

REFERENCES

1. Galiè N, Corris PA, Frost A, et al. Updated treatment algorithm of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2013;62(25):D60–D72. doi: 10.1016/j.jacc.2013.10.031.
2. Hoeper MM, Bogaard HJ, Condliffe R, et al. Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25):D42–D50. doi: 10.1016/j.jacc.2013.10.032.
3. McLaughlin VV, Shah SJ, Souza RHM. Management of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2015;65(18):1976–1997.
4. Galiè N, Humbert M, Vachiery J-L, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*.

2015;46:903–975. doi: 10.1093/eurheartj/ehv317.

5. Taichman DB, Ornelas J, Chung L, et al. Pharmacological therapy for pulmonary arterial hypertension in adults: CHEST guideline. *Chest*. 2014;146(2):449–475. doi: 10.1378/chest.14-0793.
6. D'Alonzo GE. Survival in patients with primary pulmonary hypertension. *Ann Intern Med*. 1991;115(5):343. doi: 10.7326/0003-4819-115-5-343.
7. Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: Insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation*. 2010;122(2):164–172. doi: 10.1161/CIRCULATIONAHA.109.898122.
8. Farber HW, Miller DP, Poms AD, et al. Five-year outcomes of patients enrolled in the REVEAL registry. *Chest*. 2015;148(4):1043–1054. doi: 10.1378/chest.15-0300.
9. McGoon MD, Benza RL, Escribano-Subias P, et al. Pulmonary arterial hypertension. *J Am Coll Cardiol*. 2013;62(25):D51–D59. doi: 10.1016/j.jacc.2013.10.023.
10. Humbert M, Sitbon O, Chaouat A, et al. Pulmonary arterial hypertension in France: Results from a national registry. *Am J Respir Crit Care Med*. 2006;173(9):1023–1030. doi: 10.1164/rccm.200510-1668OC.
11. Badesch DB, Raskob GE, Elliott CG, et al. Pulmonary arterial hypertension: Baseline characteristics from the REVEAL Registry. *Chest*. 2010;137(2):376–387. doi: 10.1378/chest.09-1140.
12. Yuan JX-J. Pathogenesis of pulmonary arterial hypertension: The need for multiple hits. *Circulation*. 2005;111(5):534–538. doi: 10.1161/01.CIR.0000156326.48823.55.
13. McGoon MD, Benza RL, Escribano-Subias P, et al. Pulmonary arterial hypertension: epidemiology and registries. *J Am Coll Cardiol*. 2013;62(25 Suppl):D51–D59. doi: 10.1016/j.jacc.2013.10.023.
14. McLaughlin VV, Shah SJ, Souza R, Humbert M. Management of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2015;65(18):1976–1997. doi: 10.1016/J.JACC.2015.03.540.
15. Shah SJ. Pulmonary hypertension. *JAMA*. 2012;308(13):1366. doi: 10.1001/jama.2012.12347.
16. Schermuly RT, Ghofrani HA, Wilkins MR, Grimminger F. Mechanisms of disease: Pulmonary arterial hypertension. *Nat Rev Cardiol*. 2011;8(8):443–455. doi: 10.1038/nrcardio.2011.87.

17. Olsson KM, Hoeper MM. Novel approaches to the pharmacotherapy of pulmonary arterial hypertension. *Drug Discov Today*. 2009;14(5-6):284–290. doi: 10.1016/j.drudis.2008.12.003.
18. Humbert M. Update in pulmonary hypertension 2008. *Am J Respir Crit Care Med*. 2009;179(8):650–656. doi: 10.1164/rccm.200901-0136UP.
19. Park MH. Advances in diagnosis and treatment in patients with pulmonary arterial hypertension. *Catheter Cardiovasc Interv*. 2008;71(2):205–213. doi: 10.1002/ccd.21389.
20. Rubens C, Ewert R, Halank M, et al. Big endothelin-1 and endothelin-1 plasma levels are correlated with the severity of primary pulmonary hypertension. *Chest*. 2001;120(5):1562–1569. Available at http://www.ncbi.nlm.nih.gov/pubmed/11713135. Accessed October 20, 2015.
21. Giaid A, Saleh D. Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. *N Engl J Med*. 1995;333(4):214–221. doi:10.1056/NEJM199507273330403.
22. Janda S, Shahidi N, Gin K, Swiston J. Diagnostic accuracy of echocardiography for pulmonary hypertension: a systematic review and meta-analysis. *Heart*. 2011;97(8):612 LP–622. Available at http://heart.bmj.com/content/97/8/612.abstract.
23. Bishop BM, Mauro VF, Khouri SJ. Practical considerations for the pharmacotherapy of pulmonary arterial hypertension. *Pharmacother J Hum Pharmacol Drug Ther*. 2012;32(9):838–855. doi:10.1002/j.1875-9114.2012.01114.x.
24. Olivier S, Marc H, Xavier J, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation*. 2005;111(23):3105–3111. doi:10.1161/CIRCULATIONAHA.104.488486.
25. O'Callaghan DS, Savale L, Montani D, et al. Treatment of pulmonary arterial hypertension with targeted therapies. *Nat Rev Cardiol*. 2011;8:526. Available at https://doi.org/10.1038/nrcardio.2011.104.
26. Calderone A, Stevens W, Prior D, et al. Multicentre randomised placebo-controlled trial of oral anticoagulation with apixaban in systemic sclerosis-related pulmonary arterial hypertension: The SPHInX study protocol. *BMJ Open*. 2016;6(12):e011028. http://bmjopen.bmj.com/content/6/12/e011028.abstract.
27. Agarwal R, Gomberg-Maitland M. Current therapeutics and practical management strategies for pulmonary arterial hypertension. *Am Heart J*.

2011;162(2):201–213. doi:10.1016/J.AHJ.2011.05.012.

28. Lajoie AC, Bonnet S, Provencher S. Combination therapy in pulmonary arterial hypertension: Recent accomplishments and future challenges. *Pulm Circ*. 2017;7(2):312–325. doi:10.1177/2045893217710639.
29. Fox BD, Shtraichman O, Langleben D, Shimony A, Kramer MR. Combination therapy for pulmonary arterial hypertension: a systematic review and meta-analysis. *Can J Cardiol*. 2016;32(12):1520–1530. doi:10.1016/j.cjca.2016.03.004.
30. Klinger JR, Elliott G, Levine DJ, et al. Therapy for pulmonary arterial hypertension in adults 2018: Update of the CHEST guideline and expert panel report. *CHEST*. 2019;155(3):565–586. doi: 10.1016/j.chest.2018.11.030.
31. McGoon M, Gutterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest*. 2004;126(1 Suppl):14S–34S. doi:10.1378/chest.126.1_suppl.14S.
32. Caldeira D, Loureiro MJ, Costa J, Pinto FJ, Ferreira JJ. Oral anticoagulation for pulmonary arterial hypertension: systematic review and meta-analysis. *Can J Cardiol*. 2014;30(8):879–887.
33. Preston IR, Roberts K, Miller DP. Effect of warfarin treatment on survival of patients with pulmonary arterial hypertension (PAH) in the registry to evaluate early and long-term PAH disease management (REVEAL). *Circulation*. 2015;132:2403–2411.
34. Olsson KM, Delcroix M, Ghofrani H-A. Anticoagulation and survival in pulmonary arterial hypertension: results from the comparative, prospective registry of newly initiated therapies for pulmonary hypertension (COMPERA). *Circulation2*. 2014;129(1):57–65.
35. Akagi S, Ogawa A, Miyaji K, Kusano K, Ito H, Matsubara H. Catecholamine support at the initiation of epoprostenol therapy in pulmonary arterial hypertension. *Ann Am Thorac Soc*. 2014;11(5):719–727. doi: 10.1513/AnnalsATS.201308-268OC.
36. Coons JC, Clarke M, Wanek MR, Bauer A, Bream-Rouwenhorst HR. Safe and effective use of prostacyclins to treat pulmonary arterial hypertension. *Am J Heal Pharm*. 2013;70(19):1716 LP–1723. http://www.ajhp.org/content/70/19/1716.abstract.
37. Kallen AJ, Lederman E, Trevino I, et al. Bloodstream infections in patients given treatment with intravenous prostanoids. *Infect Control Hosp*

Epidemiol. 2008;29(4):342–349.

38. Galiè N, Torbicki A, Barst R, et al. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. *Eur Heart J*. 2004;25(24):2243–2278. doi: 10.1016/j.ehj.2004.09.014.
39. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of. *J Am Coll Cardiol*. 2009;53(17):1573–1619. doi: 10.1016/j.jacc.2009.01.004.
40. Badesch DB, Tapson VF, McGoon MD, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. *Ann Intern Med*. 2000;132(6):425–434. http://www.ncbi.nlm.nih.gov/pubmed/10733441.
41. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: Prognostic factors and survival. *J Am Coll Cardiol*. 2002;40(4):780–788. http://www.ncbi.nlm.nih.gov/pubmed/12204511.
42. Simonneau G, Barst RJ, Galiè N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: A double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med*. 2002;165(6):800–804. doi: 10.1164/ajrccm.165.6.2106079.
43. Gomberg-Maitland M, Tapson VF, Benza RL, et al. Transition from intravenous epoprostenol to intravenous treprostinil in pulmonary hypertension. *Am J Respir Crit Care Med*. 2005;172(12):1586–1589. doi: 10.1164/rccm.200505-766OC.
44. Kitterman N, Poms A, Miller DP, Lombardi S, Farber HW, Barst RJ. Bloodstream infections in patients with pulmonary arterial hypertension treated with intravenous prostanoids: Insights from the REVEAL REGISTRY®. *Mayo Clin Proc*. 2012;87(9):825–834. doi: 10.1016/j.mayocp.2012.05.014.
45. Rich JD, Glassner C, Wade M, et al. The effect of diluent pH on bloodstream infection rates in patients receiving IV treprostinil for pulmonary arterial hypertension. *Chest*. 2012;141(1):36–42. doi:

10.1378/chest.11-0245.

46. Olschewski H, Simonneau G, Galiè N, et al. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med*. 2002;347(5):322–329. doi: 10.1056/NEJMoa020204.
47. McLaughlin VV, Benza RL, Rubin LJ, et al. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: A randomized controlled clinical trial. *J Am Coll Cardiol*. 2010;55(18):1915–1922. doi: 10.1016/J.JACC.2010.01.027.
48. Benza RL, Seeger W, McLaughlin VV, et al. Long-term effects of inhaled treprostinil in patients with pulmonary arterial hypertension: The TReprostinil sodium Inhalation Used in the Management of Pulmonary arterial Hypertension (TRIUMPH) study open-label extension. *J Hear Lung Transplant*. 2011;30(12):1327–1333. doi: 10.1016/J.HEALUN.2011.08.019.
49. Jing Z-C, Parikh K, Pulido T, et al. Efficacy and safety of oral treprostinil monotherapy for the treatment of pulmonary arterial hypertension. *Circulation*. 2013;127(5):624–633. doi: 10.1161/CIRCULATIONAHA.112.124388.
50. Tapson VF, Torres F, Kermeen F, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients on background endothelin receptor antagonist and/or phosphodiesterase type 5 inhibitor therapy (The FREEDOM-C Study): A randomized controlled trial. *Chest*. 2012;142(6):1383–1390. doi: 10.1378/CHEST.11-2212.
51. Tapson VF, Jing Z-C, Xu K-F, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients receiving background endothelin receptor antagonist and phosphodiesterase type 5 inhibitor therapy (The FREEDOM-C2 Study): A randomized controlled trial. *Chest*. 2013;144(3):952–958. doi: 10.1378/CHEST.12-2875.
52. Simonneau G, Torbicki A, Hoeper MM, et al. Selexipag: An oral, selective prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension. *Eur Respir J*. 2012;40(4):874 LP–880. http://erj.ersjournals.com/content/40/4/874.abstract.
53. Sitbon O, Channick RC, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med*. 2015;373(26):2522–2533. doi: 10.1056/NEJMoa1503184.
54. Coghlan JG, Channick R, Chin K, et al. Targeting the prostacyclin pathway with selexipag in patients with pulmonary arterial hypertension

receiving double combination therapy: Insights from the randomized controlled GRIPHON study. *Am J Cardiovasc Drugs*. 2018;18(1):37–47. doi: 10.1007/s40256-017-0262-z.

55. Gaine S, Chin K, Coghlan G, et al. Selexipag for the treatment of connective tissue disease-associated pulmonary arterial hypertension. *Eur Respir J*. 2017;50(2):1602493. doi: 10.1183/13993003.02493-2016.
56. Hoeper MM, Leuchte H, Halank M, et al. Combining inhaled iloprost with bosentan in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J*. 2006;28(4):691 LP–694. http://erj.ersjournals.com/content/28/4/691.abstract.
57. Humbert M, Barst RJ, Robbins IM, et al. Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. *Eur Respir J*. 2004;24(3):353 LP–359. http://erj.ersjournals.com/content/24/3/353.abstract.
58. Galié N, Badesch D, Oudiz R, et al. Ambrisentan therapy for pulmonary arterial hypertension. *J Am Coll Cardiol*. 2005;46(3):529–535. doi: 10.1016/j.jacc.2005.04.050.
59. Barst RJ. A review of pulmonary arterial hypertension: Role of ambrisentan. *Vasc Health Risk Manag*. 2007;3(1):11–22. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1994051&tool=pmcentrez&rendertype=abstract.
60. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med*. 2013;369(9):809–818. doi: 10.1056/NEJMoa1213917.
61. Galiè N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med*. 2005;353(20):2148–2157. doi: 10.1056/NEJMoa050010.
62. Abraham T, Wu G, Vastey F, Rapp J, Saad N, Balmir E. Role of combination therapy in the treatment of pulmonary arterial hypertension. *Pharmacotherapy*. 2010;30(4):390–404. doi: 10.1592/phco.30.4.390.
63. Galiè N, Brundage BH, Ghofrani HA, et al. Tadalafil therapy for pulmonary arterial hypertension. *Circulation*. 2009;119(22):2894–2903. doi: 10.1161/CIRCULATIONAHA.108.839274.
64. Ghofrani H-A, D'Armini AM, Grimminger F, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med*. 2013;369(4):319–329. doi: 10.1056/NEJMoa1209657.
65. Lajoie AC, Lauziere G, Lega J-C, et al. Combination therapy versus

monotherapy for pulmonary arterial hypertension: A meta-analysis. *Lancet Respir Med*. 2016;4(4):291–305.

66. McLaughlin V, Channick RN, Ghofrani HA, et al. Bosentan added to sildenafil therapy in patients with pulmonary arterial hypertension. *Eur Respir J*. 2015;46(2):405–413. doi: 10.1183/13993003.02044-2014.
67. Simonneau G, Rubin LJ, Galiè N, et al. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: A randomized trial. *Ann Intern Med*. 2008;149(8):521–530. http://www.ncbi.nlm.nih.gov/pubmed/18936500.
68. Barst RJ, Oudiz RJ, Beardsworth A, et al. Tadalafil monotherapy and as add-on to background bosentan in patients with pulmonary arterial hypertension. *J Hear Lung Transplant*. 2011;30(6):632–643. doi: 10.1016/J.HEALUN.2010.11.009.
69. Galiè N, Barberà JA, Frost AE, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med*. 2015;373(9):834–844. doi: 10.1056/NEJMoa1413687.
70. Actelion. The Efficacy and Safety of Initial Triple Versus Initial Dual Oral Combination Therapy in Patients with Newly Diagnosed Pulmonary Arterial Hypertension (TRITON). ClinicalTrials.gov. 2018:NCT02558231.

46

Cystic Fibrosis

Chanin C. Wright and Yolanda Vera

KEY CONCEPTS

1. Good nutrition with appropriate pancreatic enzyme and vitamin supplementation are essential in the management of cystic fibrosis (CF).
2. Airway clearance and anti-inflammatory therapies are key components to improve pulmonary health in CF patients.
3. Antipseudomonal agents are the cornerstone of antibiotic therapy for chronic lung infections in the CF patient.
4. Altered pharmacokinetics of CF patients can impact the dosing and clearance of pharmacologic therapy.

Preclass Engaged Learning Activity

Read Novak KJ. Chapter 33: Cystic Fibrosis: Blood, Sweat, Lungs and Gut Level II. In: Schwinghammer TL, Koehler JM, Borchert JS, Slain D, Park SK, eds. *Pharmacotherapy Case Book*, 10th Edition. New York, NY: McGraw-Hill Education, 2017.

This practice case gives a real-life example of a typical CF patient who might present to a clinic or hospital, the medications that are typically used, and monitoring that should be performed. This case will help develop the learner's understanding about the COLLECT, ASSESS, and PLAN steps in the patient care process.

INTRODUCTION

Cystic Fibrosis (CF) is a disease state resulting from a dysfunction in the cystic

fibrosis transmembrane conductance regulator (CFTR). It is the most common life-limiting genetic disorder in Caucasians with a prevalence of 30,000 affected individuals in the United States. Historically, the saying "Woe to that child which when kissed on the forehead tastes salty. He is bewitched and soon must die[1]" would describe the ill fate of an individual affected with CF in the Middle Ages. With available treatments, affected individuals currently have an expected life span of approximately 40 years. Multiple organ systems are affected in individuals with CF, especially the lungs, the digestive system, and the reproductive organs. Mortality is most commonly due to respiratory/cardiorespiratory causes and complications of organ transplant.[2]

EPIDEMIOLOGY

CF occurs in approximately 1 in 2,500 to 3,500 Caucasian newborns. Although CF occurs in all ethnicities, the frequencies in other populations is much lower: 1 in 17,000 African Americans and 1 in 31,000 Asians.[1] In the 1970s, patients only survived into their teen years. In 2013, progress in care had extended survival to 43 years. Initiating appropriate treatment at a young age impacts long-term survival. Hence, the timing of diagnosis and recognition of signs and symptoms are crucial.[2–7]

ETIOLOGY

CF is caused by a mutation of the *CFTR* gene. Extensive genetic studies have increased awareness regarding the large spectrum of mutations in the CF population. Over 2,000 mutations have been identified through the extensive collaboration between the CF Foundation and international researchers. The most common mutation identified in CF patients is *ΔF508*.[4]

CF is an autosomal recessive disease, in which one mutation present on each allele of the *CFTR* gene results in presentation of the disease. The presentation of a mutation on only one allele of the *CFTR* gene will prevent the full expression of CF. Genetic studies have increased the understanding of genotype–phenotype relationships. Various mutations in the *CFTR* gene can result in various pathologies such as primary lung disease to minor gastrointestinal (GI) involvement.

PATHOPHYSIOLOGY

To successfully treat CF, a good understanding of the disease's underlying pathophysiology is crucial. It is well established that gene mutations cause an abnormality in the CFTR. This initiates the sequence of events responsible for the manifestations of CF. Mucosal obstruction occurs in the distal airways of the lung and submucosal glands, which express the CFTR. The CFTR also performs numerous cellular functions, including the regulation of chloride transport across the cell membrane. Studies in genotype–phenotype relationships have shown that an abnormality on the CFTR contributes to the expression of other gene proteins involved with inflammatory responses, ion transport, and cell signaling. These various expressions result in differences in clinical severity among patients with the same mutations on the CFTR.[8–10]

Under normal conditions, the CFTR helps regulate ion transport and salt homeostasis in the sweat glands. Typically, the sodium ion is followed by the chloride ion and is reabsorbed from the lumen by the CFTR and amiloride-sensitive epithelial sodium channel (ENaC). As a result of the CFTR's malfunction in CF patients, chloride fails to be reabsorbed, which impacts the sodium ion reabsorption as well. This produces sweat that contains high level of salt. The endpoint of this process is a highly negatively charged lumen, which leads to an increased salt content in the sweat gland. This is known as the transepithelial potential difference, which is two to three times greater in CF patients than in patients without CF. These processes can lead to organ damage in the CF patient (**Fig. 46-1**).[7]

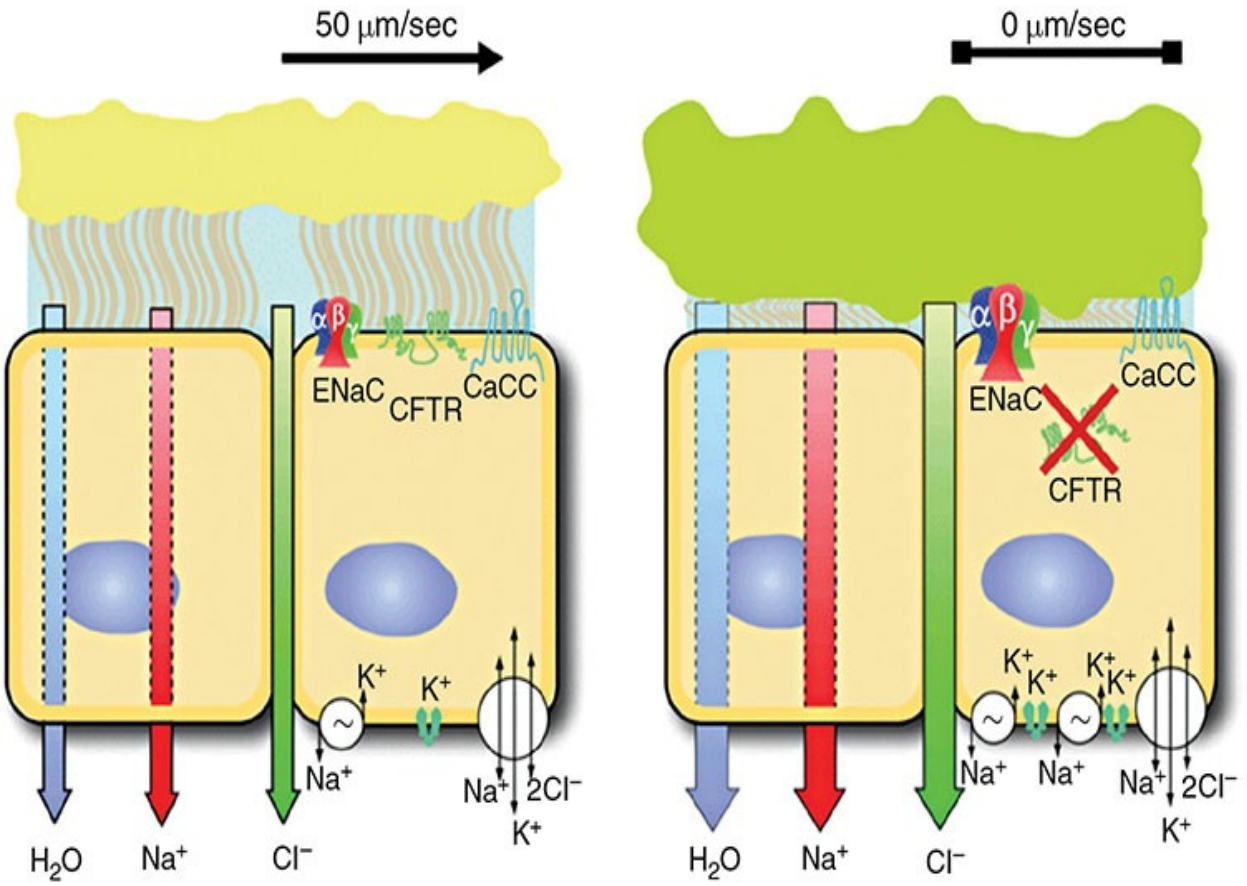


FIGURE 46-1 Comparison of ion transport properties of normal (left) and CF (right) airway epithelia. The vectors describe routes and magnitudes of Na^+ and Cl^- transport that is accompanied by osmotically driven water flow. The normal basal pattern for ion transport absorption of Na+ from the lumen via an amiloride-sensitive epithelial Na^+ channel (ENaC) composed of α, β, and γ ENaC subunits. This process is accelerated in CF. The capacity to initiate cyclic AMP–mediated Cl^- secretion is diminished in CF airway epithelia due to abnormal maturation/dysfunction of the CFTR Cl^- channel. The accelerated Na+ absorption in CF reflects the absence of CFTR inhibitory effects on Na^+ channels. A Ca^{2+}-activated Cl^- channel, likely a product of the TMEM16a gene, is expressed in normal and CF apical membranes and can be activated by extracellular ATP. Horizontal arrows depict the velocity of mucociliary clearance (μm/sec). (*Reproduced with permission from Chapter 259. Cystic Fibrosis. Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson J, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 18th ed. New York: McGraw-Hill; 2012.*)

One of the common causes of morbidity and mortality in CF patients is

mucosal obstruction of the exocrine glands. Mucosal obstruction causes the ducts to dilate, which results in the coating of lung surfaces by thick, viscous, neutrophil-dominated debris. These secretions initiate a cascade of events that lead to inflammation and formation of scar tissue in the lungs.[6] Other organ systems are impacted by the absence of CFTR activity as well. Approximately 10% of CF patients are born with meconium ileus, which is an intestinal obstruction that may be fatal if left untreated. Blockage of the pancreatic duct leads to complications such as chronic fibrosis and fatty replacement of the pancreatic gland. Bile duct obstruction causes cirrhosis of the liver, and male CF patients can experience infertility due to obstruction of the vas deferens in utero.[3]

CLINICAL PRESENTATION

Sinus and Pulmonary

CF patients will usually experience chronic infections and frequently develop polyps in the sinus cavity. Daily symptomatology includes shortness of breath and cough, with sputum production. A common finding in radiology chest films is a flat diaphragm with an increased chest diameter and air trapping. Pulmonary function tests will reflect a decrease in forced expiratory volume at 1 second (FEV_1). Older patients will experience digital clubbing, a deformity of the fingers and fingernails often associated with chronic hypoxia. Bacterial growth in the lungs will often drive CF patients to a state of exacerbation, resulting in increased cough, a reduction in pulmonary function, and increased sputum production with a change in color.

Gastrointestinal System

Pancreatic insufficiency occurs in 85% of those affected with CF.[2] Infants and children may present with meconium ileus, steatorrhea, and failure to thrive due to malabsorption. This presentation is due to the obstruction of the pancreatic ducts and intestinal tract and their inability to digest essential nutrients. Older patients may experience severe constipation and insulin deficiency.

Reproductive

As patients reach adolescent and adult ages, tests may show azoospermia due to

blockage of or the congenital bilateral absence of the vas deferens. Females may experience reduced fertility as cervical fluids have lower water content and decreased thinning during ovulation.[11]

Diagnostic Tests

All states require hospitals to perform CF newborn screening.[12] The screening test checks for immunoreactive trypsinogen (IRT), a chemical produced by the pancreas. The IRT tends to be high in babies with CF. A baby with a positive newborn screen, signs or symptoms of CF, and family history should then undergo sweat chloride testing. The quantitative pilocarpine iontophoresis sweat test (QPIT) or sweat chloride test was developed due to the risk of hyperpyrexia associated with older methods that utilized plastic body bags to make patients sweat. QPIT uses only a small area on the forearm, which is then stimulated to secrete sweat through the skin by iontophoresis of pilocarpine. Sweat from the stimulated area is then collected and analyzed for chloride content. Chloride concentrations are quantified as: normal: ≤29 mmol/L; intermediate: 30 to 59 mmol/L; and abnormal: ≥60 mmol/L. Values more than or equal to 60 mmol/L are consistently diagnostic of CF. It is suggested that samples from two sites will increase the reliability of the diagnosis.[4] If the chloride concentration is quantified as 30 to 59 mmol/L, further CFTR genetic analysis is required to confirm diagnosis. Identification of the CFTR mutation may then be used to determine functional impact.[3]

TREATMENT

The multidisciplinary team plays a vital role in assisting patients to reach short- and long-term goals. Since CF affects multiple organ systems, there are several therapeutic goals that must be addressed including nutritional, gastrointestinal, pulmonary, and psychosocial goals as well as the prevention and treatment of infectious diseases.[11]

General Approach to Treatment

Due to the complexity and multi-system involvement of CF, patients should be cared for by multiple specialties that work together to provide optimal care. CF patients are often cared for by Cystic Fibrosis centers where the interprofessional

CF team is comprised of a pulmonologist, respiratory therapist, gastroenterologist, dietician, physical therapist, psychologist, social worker, CF nurse, and pharmacist. Other specialties may be consulted depending on the patient's specific needs.

Once the patient has been diagnosed with CF, they will undergo a baseline assessment to determine the severity of the disease, as mutation differences and expression can lead to different clinical manifestations. Today, assessment of genetic information will also be used to determine if the patient is eligible to receive treatment with the newest class of medications : CFTR modulators. Depending on the patient's clinical presentation, each affected organ system must be addressed to reach the desired outcomes and goals established by the CF Foundation.

The pharmacist plays a unique role in selecting the initial treatment and evaluating the patient's current pharmacotherapy regimen to determine safety and efficacy. The inability to pay for CF medications often influences treatment adherence. Due to the complex social issues that impact CF patients, the social worker is an integral part of the CF team. Maintaining health insurance is a lifelong problem for CF patients as employment is difficult to maintain due to frequent work absences. Thus, many CF patients have low-paying jobs without health insurance coverage.

Building relationships and confiding in others about personal health issues can be intimidating and difficult for CF patients. Due to infection control guidelines, face-to-face meetings between CF patients are limited. The use of new technology now allows support groups via video conferencing and online discussion. The decision to marry and/or have children is complicated by an awareness of their abbreviated life span.[11,13]

Nonpharmacologic Therapy

1 In healthy individuals, the pancreas is vital to the absorption and digestion of essential nutrients for the body's growth and function. In pancreatic-insufficient CF individuals, the resulting inability to absorb these nutrients may lead to malnourishment. The focus of treatment lies in achieving and maintaining normal weight for adults and normal growth for children. This is primarily achieved by managing GI and pulmonary symptoms, monitoring nutrient and energy intake, and addressing psychosocial and financial issues. Optimal nutrition leads to healthy pulmonary function, including improved FEV_1, and increase in survival.

To help meet this desired outcome, the CF Foundation recommends energy intake greater than the standard for the general population to support weight gain and maintenance in children over 2 years and in adults. Data gathered from population-based studies have shown that an energy intake of 110% to 200% compared to the general population improves nutritional status in CF individuals. The CF Foundation has also established consensus-based assessment parameters to monitor nutritional status in CF individuals. These parameters and goals are listed in **Table 46-1**. For patients who consistently fail to meet weight goals, the clinician must consider the use of nutritional supplements that may be given orally or via percutaneous endoscopic gastrostomy (PEG) tube.

TABLE 46-1 Cystic Fibrosis Foundation Nutritional Assessment Parameters and Recommendations

- Age-appropriate body mass index (BMI) method should be utilized to assess weight and height.
- Better FEV_1 status at about 80% predicted or above was associated with BMI % at 50th percentile or higher.
- For children and adolescents aged 2–20 years, the CF Foundation recommends that weight-for-stature assessment uses the BMI percentile method and those children and adolescents maintain a BMI at or above the 50th percentile.
- For children diagnosed <2 years of age, the CF Foundation recommends that children reach a weight-for-length status of 50th percentile by 2 years.
- For adults 20 years and older, the CF Foundation recommends that weight-for-stature assessment use the BMI method and that women maintain a BMI ≥22, and men maintain a BMI ≥23.
- For adults 20 years and older, the CF Foundation recommends that unintentional weight loss be avoided. When encountered in patient care, unintentional weight loss should be evaluated in the context of the patient's usual weight and health status.

BMI, body mass index; CF, cystic fibrosis; FEV_1, forced expiratory volume at 1 second.

Pharmacologic Therapy

Pancreatic Enzyme Replacement Therapy

To meet the nutritional needs of patients with CF, pancreatic enzyme replacement therapy (PERT) is used to treat nutrient malabsorption due to

pancreatic insufficiency. PERT has a long track record of both safety and efficacy in improving nutritional status in CF patients and is recommended in addition to adequate dietary intake. Consensus-based guidelines recommend a dose of 500 to 2,500 lipase units per kilogram (kg) of body weight per meal; or 10,000 units per kg per day; or 4,000 units per gram of dietary fat per day. Enzyme supplement products are not bioequivalent; therefore, the CF Foundation does not recommend substitution.

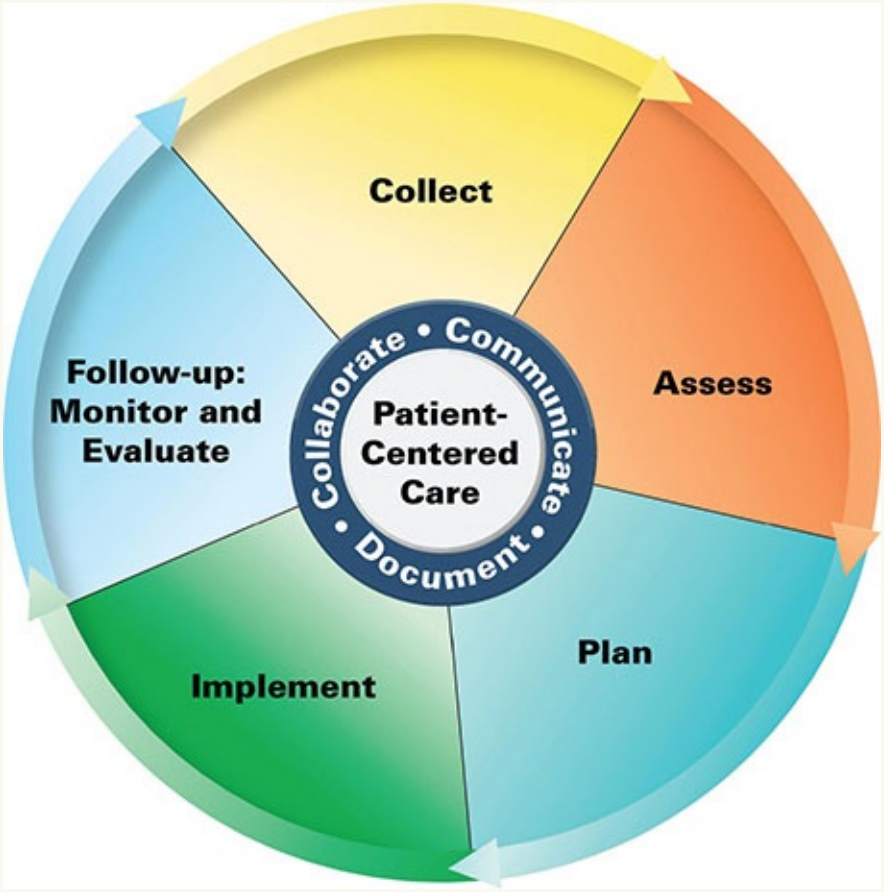
Most preparations are capsules containing enteric-coated microspheres or enteric-coated tablets designed to withstand the acidic environment in the stomach so that the enzymes are delivered to the small intestine. Frequently, CF patients require the addition of histamine receptor antagonists or proton-pump inhibitors in order to create an alkaline environment in the intestine. Enteric-coated capsules should not be crushed but may be opened and mixed with nonalkaline food. However, if allowed to sit in food for a prolonged amount of time, the enteric coating will be break down and enzymes inactivated. Enzymes are administered prior to meals, snacks, and fat-soluble vitamins.[8]

Patients who take greater than the guideline-recommended doses may develop fibrosing colonopathy, which leads to colonic strictures. This condition should be considered in individuals who have evidence of obstruction, bloody diarrhea, or ascites, as well as in patients who have abdominal pain, ongoing diarrhea, or poor weight gain. Risk factors for fibrosing colonopathy include: age less than 12 years; enzyme dosages more than 6,000 lipase units/kg/meal for more than 6 months; history of meconium ileus or distal intestinal obstruction syndrome (DIOS); history of any intestinal surgery; and inflammatory bowel disease.

Patients who experience fibrosing colonopathy should have the dose of enzyme supplements reduced and given oral laxatives or enemas. More severe cases may require surgical intervention.[9] Currently available enzyme preparations are shown in **Table 46-2**.[8]

TABLE 46-2 Pancreatic Enzyme Supplements

Trade Name	Manufacturer	Lipase Units	Protease Units	Amylase Units	Dosage Form	FDA Approval
Creon®	Abbott Laboratories	3,000 6,000 12,000 24,000 36,000	9,500 19,000 38,000 76,000 114,000	15,000 30,000 60,000 120,000 180,000	Delayed-release capsule, enteric-coated microspheres	Approved
Pancreaze®	Janssen Pharmaceuticals, Inc.	2,600 4,200 10,500 16,800 21,000	6,200 14,200 35,500 56,800 54,700	10,850 24,600 61,500 98,400 83,900	Delayed-release capsule, enteric-coated microtablets	Approved
Pertzye®	Digestive Care, Inc.	4,000 8,000 16,000	14,375 28,750 57,500	15,125 30,250 60,500	Delayed-release capsule, bicarbonate-buffered enteric-coated microspheres	Approved
Ultresa®	Aptalis Pharma US, Inc.	13,800 20,700 23,000	27,600 41,400 46,000	27,600 41,400 46,000	Delayed-release capsule, enteric-coated minitablets	Approved
Viokace	Aptalis Pharma US, Inc.	10,440 20,880	39,150 78,300	39,150 78,300	Tablet	Approved
Zenpep®	Aptalis Pharma US, Inc.	3,000 5,000 10,000 15,000 20,000 25,000 40,000	10,000 17,000 34,000 51,000 68,000 85,000 136,000	16,000 27,000 55,000 82,000 109,000 136,000 218,000	Delayed-release capsule, enteric-coated beads	Approved



Patient Care Process for Cystic Fibrosis

Collect

- Patient characteristics (eg, age, sex, pregnancy status)
- Patient medical history (personal and family) including genetic results, if available
- Social history (eg, tobacco/ethanol use, school, job, insurance)
- Eating habits (when and how much of what foods)
- Current medications including over-the-counter (OTC) use, herbal products, and dietary supplements
- Symptoms including
  - Respiratory symptoms (eg, cough, shortness of breath, sputum production)
  - Stooling frequency and description

- Objective data
  - Respiratory rate (RR), height, weight, oxygen saturation, and forced expiratory volume in 1 second (FEV_1) if available
  - Labs including: complete metabolic panel, complete blood count (CBC) with differential, serum creatinine (SCr), culture and sensitivity results

Assess

- Medication adherence (what, when, and how medications are taken)
- Nutritional status
- Exercise tolerance
- Financial ability to afford medications
- School / job performance and limitations
- Emotional status of patient and family caregivers

Plan

- Drug therapy regimen (including doses, route, formulation, frequency, duration, and timing with other medications and therapies)
- Order Labs (including sputum cultures, vitamin concentrations, and A1C)
- Obtain FEV_1 and bone mineral density scan
- Referrals to social work if needed

Implement

- Provide patient and caregiver education on the treatment plan
- Use coaching and teach back strategies to encourage adherence
- Schedule follow-up

Follow-up and Evaluate

- Results of sputum cultures
- Evaluate stool frequency and description and adjust enzyme therapy, if needed
- Patient adherence (check refill history and patient’s ability to describe regimen)
- Cough and FEV_1 including changes in symptoms

*Collaborate with patient, caregivers, and other healthcare professionals (Pulmonologist, Gastroenterologist, dietitian, social work, and respiratory therapist).

Bone Health and Vitamin Supplementation

Increased longevity in CF patients has revealed bone disease as an emerging complication. Many studies have observed that 50% to 75% of CF adults have low bone density and high rates of bone fractures. CF patients are especially at risk due to several contributing factors: malabsorption of vitamin D, poor nutritional status, physical inactivity, glucocorticoid therapy, delayed pubertal maturation, and early hypogonadism. Increased bone resorption and decreased bone formation are likely stimulated by elevated serum cytokine levels triggered by chronic pulmonary inflammation. Additionally, chronic infections lead to bone loss in patients regardless of pancreatic sufficiency. Pancreatic-insufficient CF patients lack the ability to absorb fat-soluble vitamins A, D, E, and K (ADEK). Decreased calcium absorption and intake can also compound this problem. As bone disease progresses, patient may no longer be eligible for a lung transplantation, which may prolong survival in CF patients.

Appropriate bone density monitoring for CF patients requires obtaining levels of fat-soluble vitamins yearly, as well as treatment with daily supplementation. Special multivitamin formulations contain high amounts of fat-soluble vitamins designed to deliver the appropriate doses required. Recommended vitamin D levels are a minimum of 30 ng/mL (75 nmol/L). Even with these precautions, adequate vitamin D levels may be difficult to maintain due to altered absorption, reduced fat mass, and minimal exposure to sun light. Medical management of CF patients can also contribute to bone disease by the administration of glucocorticoids, posttransplant immunosuppressant therapies, and antibiotic therapies that require protection from sunlight exposure.[10]

Pulmonary Health and Treatment

2 One of the fundamentals of pulmonary care in CF patients is airway clearance. CF patients, in general, have impaired mucociliary clearance that results in thick sputum, predisposing them to chronic infections and inflammation. Effective airway clearance involves the use of a bronchodilator, a mucolytic medication, and chest percussion. It is recommended that airway clearance therapy (ACT) be initiated within the first few months of life. Typical medications used in airway clearance are shown in **Table 46-3**. Choosing a

particular ACT routine for a patient is based on the patient's needs. There is no consensus on the optimal method of ACT. The regimen including duration or number of treatments per day may be changed in response to acute illness or exacerbations.

TABLE 46-3 Airway Clearance Therapies

Treatment	Dose
Albuterol	2 puffs prior to therapy 2-4 times a day
HyperSal® (hypertonic saline)	4 mL delivered via a nebulizer 2-4 times a day
Pulmozyme® (dornase alfa)	2.5 mg delivered via a nebulizer 1-2 times a day

Chest percussion was originally performed with a cupped hand pounding on the chest that generated percussion or vibration. Currently, the most convenient method is the use of a percussion vest. Aerobic exercise is also effective and recommended for improved airway clearance.[14]

The sequence of clearance therapy or the "pulmonary toilet" regimen is recommended for individuals ≥6 years and administered concurrently with percussion therapy in the following order:

- A bronchodilator: Albuterol is commonly used for this indication. It helps open up the airways and prevents bronchospasm.
- Hypertonic saline (HyperSal®): Hydrates the airway mucus secretions and facilitates mucociliary function.
- Dornase alfa (Pulmozyme®): Enzyme that cleaves extracellular DNA, which results in decreased viscosity of mucus.
- Aerosolized antibiotics (ie, Aztreonam [Cayston], tobramycin [TOBI®]): If this therapy is indicated based on severity of lung disease and sputum cultures, it is administered after the CF patient completes percussion therapy.

Bronchodilator therapy, hypertonic saline, and dornase alfa are strongly recommended by the CF Foundation for chronic use in patients 6 years and older. Bronchodilators should be used in patients who demonstrate bronchiole hyperresponsiveness or a bronchodilator response. Side effects may include

cough, wheezing, and hyperactivity.[15] The use of hypertonic saline helps restore airway hydration and enhance mucociliary function. A study conducted in Australia showed that CF patients who surfed had better pulmonary outcomes than other patients who did not.[16] Researchers believed that the inhalation of ocean water helped improve FEV_1 during this activity. Clearance and pulmonary function were measured during a 14-day period in 24 patients who were randomly assigned to receive a daily treatment of 7% hypertonic saline with or without pretreatment of a control. Results showed significant improvement in FEV_1 and forced vital capacity (FVC), as well as improvement of respiratory symptoms in hypertonic saline patients. The study also demonstrated that these patients were able to sustain mucus clearance for more than 8 hours. The use of hypertonic saline has shown an improvement in lung function and a 56% reduction in exacerbations. Known side effects during administration include irritation to the airways, which may lead to a drop in FEV_1, increased cough, sore throat, and chest tightness. In an attempt to ameliorate these symptoms, providers may use a lower concentration of 3% hypertonic saline.[15,16]

Dornase alfa (Pulmozyme®) is also recommended in all patients 6 years or older, and is strongly recommended in patients with moderate-to-severe lung disease, to improve lung function and reduce exacerbations. Results from three randomized controlled trials and a crossover trial involving 520 patients showed improvement in FEV_1 by 3.2% and reduction in exacerbations.[17]

Anti-inflammatory Therapies

Pulmonary inflammation begins early in life, as shown by the predominance of proinflammatory mediators that can be seen on bronchiolar lavage. A normal inflammatory response to bacteria becomes pathologic in CF patients who have both a prolonged and exaggerated reaction. Treatment of this inflammatory response is crucial to treating the CF patient.

Anti-inflammatory therapies must address the neutrophil response and inhaled therapies will target the endobronchial location, which is the site of inflammation. Using medications that terminate the inflammatory process may be effective. Airway clearance and antibiotics will help control the inflammatory stimulation. Steroids and nonsteroidal anti-inflammatory drugs (NSAIDs) are not widely used because of long-term safety concerns. High-dose ibuprofen (20-30 mg/kg of body weight twice daily) has proven efficacious in a study where patients showed less decline in pulmonary function when compared with patients given placebo. Patients on high-dose ibuprofen were able to maintain weight and

had less hospital admissions. The benefits of this regimen exceed the risks of GI complications and nephrotoxicity. The CF Foundation recommends the chronic use of oral ibuprofen for CF patients between the age of 6 and 17 years, and an FEV_1 ≥60% predicted. Plasma concentrations must be maintained at 50 to 100 mcg/mL (mg/L; 242 to 485 µmol/L) to slow the loss of lung function. For CF patients>18 years use of chronic ibuprofen is not recommended due to insufficient data.[15]

Studies with macrolides have shown an inhibition of the neutrophil migration and a decrease in production of proinflammatory mediators. It is unclear at this point if the anti-inflammatory effects of macrolides are a combination of antimicrobial and/or immunomodulatory mechanisms of action. Four randomized controlled trials have since demonstrated this effect with azithromycin (250-500 mg) given three times weekly, which has led to increased nutritional status and decreased pulmonary exacerbations.

Multiple studies comparing patients with and without pseudomonas colonization showed a certain decrease in pulmonary exacerbations but an unclear improvement in lung function in those patients not colonized with pseudomonas. Therefore, current recommendations suggest use of macrolides in individuals infected with pseudomonas to achieve highest net benefit. Patients should be screened for nontuberculous mycobacteria (NTM) prior to initiation of therapy as there is concern for the development of resistance with the chronic use of azithromycin.[15,18]

Infectious Diseases

3 Antibiotic therapy plays two integral roles in the treatment of CF patients: improving pulmonary function and preventing pulmonary failure. Oral, IV, and aerosolized antibiotic formulations are indicated and used in patients who experience acute pulmonary exacerbations, are chronically infected with *P. aeruginosa*, or require prevention of chronic *P. aeruginosa* infection. A major disadvantage of treatment in CF patients is that pathogens are not fully eradicated from the airways and will often develop resistance. Unfortunately, this limits antimicrobial selection, and can contribute to deterioration of pulmonary function (**Table 46-4**).

TABLE 46-4 Antimicrobial Agents Used in Cystic Fibrosis

Medication and Route of Administration	Pediatric Dose (mg/kg/day)	Adult Dose	Dosing Frequency	Pathogens
Oral				
Ciprofloxacin	40	750 mg	Q 12 H	*Pseudomonas, Alcaligenes*
Sulfamethoxazole/ Trimethoprim	15-20 mg of TMP	15-20 mg of TMP/kg/day	Q 6-8 H	*Staphylococcus* (MRSA, MSSA), *Burkholderia* *Stenotrophomonas, Alcaligenes*
Doxycycline	2-4	Max 200 mg/day	Q 12-24 H	*Stenotrophomonas, Staphylococcus*
Intravenous				
Amikacin	30	15 mg/kg/day	Q 8 H	*Pseudomonas*
Aztreonam	200-300	2 g	Q 6-8 H	*Pseudomonas*
Cefepime	150-200	2 g	Q 8 H	*Pseudomonas*
Ceftazidime	150-200	2 g	Q 8 H	*Pseudomonas, Burkholderia, Alcaligenes*
Ciprofloxacin	30	400 mg	Q 8 H	*Pseudomonas, Alcaligenes*
Colistimethate	5-8	5-8 mg/kg/day	Q 8 H	*Pseudomonas*
Doxycycline	4	Max 200 mg/day	Q 12-24 H	*Stenotrophomonas, Staphylococcus*
Gentamicin	10-12	7.5-10 mg/kg/day	Q 6-8 H	*Pseudomonas*
Imipenem	60-100	2-4 g	Q 6 H	*Pseudomonas, Burkholderia, Alcaligenes*
Meropenem	120	1-2 g	Q 8 H	*Pseudomonas, Burkholderia, Alcaligenes*
Piperacillin–Tazobactam	300-400 (piperacillin component)	4.5 g	Q 4-6 H	*Pseudomonas, Alcaligenes, Staphylococcus MSSA*
Ticarcillin–Clavulanate	300-400 (ticarcillin component)	3.1 g	Q 4 H	*Pseudomonas, Alcaligenes* *Staphylococcus* (MSSA)
Tobramycin	10-12	7.5-10 mg/kg/day	Q 6-8H	*Pseudomonas*
Vancomycin	60	15 mg/kg	Q 6-12 H	*Staphylococcus* (MRSA, MSSA)
Inhalation				
Tobramycin (Tobi®, Bethkis®)	60-600 mg/day	60-600 mg/day	Q 12 H	*Pseudomonas*
Tobramycin (TOBI Podhaler®)	224 mg/day	224 mg/day	Q 12 H	
Colistimethate	75 mg/day	75 mg/day	Q 12 H	*Pseudomonas*
Aztreonam (Cayston®)	225 mg/day	225 mg/day	Q 8 H	*Pseudomonas*

Early in life, patients are routinely colonized with *Staphylococcus aureus* and then later with *P. aeruginosa*. A 5- to 7-year study of cephalexin prophylaxis in young CF children showed decreased *S. aureus* colonization; however, there was an increase in frequency of *P. aeruginosa* infections. Ultimately, this study showed no significant improvement in health outcomes; therefore, prophylaxis

for *S. aureus* colonization is not recommended.[15]

The finding of *P. aeruginosa* on sputum culture is a predictor of morbidity and mortality. There are relatively few antibiotics available for the treatment of *P. aeruginosa*. Antibiotics available include extended-spectrum penicillins, select cephalosporins, select carbapenems, aztreonam, quinolones, colistimethate, and aminoglycosides. The only two mechanisms of action represented in this group are cell wall destruction and inhibited cell wall synthesis by ribosomal attachment. Standard practice is to combine these two mechanisms for the best bactericidal results. It is not unusual for patients to have multiple organisms growing in their sputum. The clinician can review the quantitative sputum culture for both the organisms present and the amount or colony forming units grown. By targeting the organisms with the most numerous organisms present and reviewing the susceptibility panels, the clinician can choose the most appropriate regimen. After years of drug exposure, older CF patients will exhibit multidrug-resistant *P. aeruginosa*. At this point, sputum cultures can be sent to specialized laboratories that will test combinations of antibiotics and report out any synergy results. The CF Foundation recommends inhaled tobramycin (TOBI®) to CF patients 6 years or older, with mild-to-severe lung disease with persistent *Pseudomonas* present in sputum cultures. Aerosolized antibiotics deliver drug locally to the lung, providing concentrations that may overcome the standard measures of resistance while decreasing the risk of systemic side effects. Routine monitoring of serum aminoglycoside levels is unnecessary in patients with normal renal function while receiving inhaled tobramycin. It is recommended that CF patients use a preservative-free formulation of aerosolized antibiotics to prevent occurrence of bronchospasm.[11]

One study examined the pharmacokinetics of inhaled TOBI® specifically looking at sputum concentrations in CF patients receiving three cycles of routine TOBI® (28 days on, 28 days off), 300 mg twice daily. The study followed 258 patients for 24 weeks, and showed that approximately 95% of patients achieved sputum concentrations of more than 25 times the minimum inhibitory concentration (MIC) of *Pseudomonas* isolates. This confirmed at 25 times the MIC, inhaled TOBI® can be efficacious in helping prevent the progression of lung disease. [12]

In 2010, the Food and Drug Administration (FDA) approved an inhaled formulation of aztreonam, known as Cayston®, for the treatment of *Pseudomonas*. Cayston® is approved for CF patients older than 6 years with mild to severe lung disease and persistent *Pseudomonas* present in sputum cultures. This inhaled formulation of aztreonam has demonstrated improvement

in respiratory symptoms and lung function in patients older than 6 years. Cayston® has been compared with TOBI® in a head-to-head trial and met noninferiority and superiority endpoints. It requires an Altera nebulizer that can deliver the medication in 3 minutes. This in itself increases compliance and has a positive impact on the quality of life in CF patients.[19]

Other organisms that may be seen are *Alcaligenes*, *Stenotrophomonas*, *Mycobacteria*, *Aspergillus*, and *Burkholderia*. *Stenotrophomonas* is intrinsically multidrug resistant and pathogenic. A risk factor for acquiring this organism may be broad-spectrum antibiotic use (carbapenems and cephalosporins). Quite often this bacteria is misidentified and confirmatory testing may show *Burkholderia*. Prevalence in American CF patients is reported to be 13.1%. Treatment choice is trimethoprim–sulfamethoxazole or doxycycline. Mycobacteria have been isolated from adults and children with CF. The most common species identified are *M. avium* complex, *M. abscessus* complex, *M. a. bollettii*, and *M. a. massiliense*. Acquisition of nontuberculous mycobacteria (NTM) is highly associated with older individuals with CF. In consideration of the growing concern, the CF Foundation and European CF Society have developed consensus recommendations for management of NTM in CF patients.[18]

Aspergillus species has a prevalence of 10% to 25% in American CF patients. During the TOBI® trials, patients treated with aerosolized tobramycin appeared to be more at risk for colonization with *Aspergillus* than the placebo group. Although *Aspergillus* does not directly inhibit lung function, it may cause allergic bronchopulmonary aspergillosis (ABPA) which is an immunologic-mediated response to the presence of *Aspergillus* in the lungs. ABPA affects 2% to 19% of people with CF.[12] *B. cepacia* is now known to be a bacterial species called “genomovars.” Currently, up to nine species have been identified. The two typical antimicrobial choices to treat *B. cepacia* are ceftazidime and trimethoprim-sulfamethoxazole. It is important to recognize the transmission of *B. cepacia* from patient to patient has been shown via droplet route, and therefore proper infection control precautions should be taken.[20,21]

Although CF patients are not more susceptible to respiratory viral infections, the outcome of such illnesses may be more severe. Decline in pulmonary function can be directly related to the number of annual viral infections. Newborns diagnosed with CF should be evaluated to receive respiratory syncytial virus (RSV) prevention with Synagis® (palivizumab), a monoclonal antibody. Synagis® is usually dosed at 15 mg/kg intramuscularly once a month during the RSV season, and can be administered until 2 years of age. All CF patients who are 6 months of age or older should also receive the annual

influenza vaccine.[17]

4 CF patients are unique in respect to a larger volume of distribution and a faster rate of clearance. With a larger volume of distribution, patients may require larger antibiotic doses. Dosing intervals become shorter because drugs are eliminated faster. Critically ill patients may vary from their baseline function and require closer monitoring. However, as patients age, they tend to approach normal population parameters. Therapeutic drug monitoring and necessary dosage and regimen adjustments are critical to the successful treatment of CF patients. For example, once daily dosing of intravenous aminoglycosides is preferred for ease of home care administration, and may actually work well in this setting. However, given the possibility of a shortened half-life, each patient's unique pharmacokinetic parameters must be calculated to determine if once daily dosing is appropriate.[22,23]

Fertility and Contraception

As people with CF into their reproductive years, discussions about contraception and having children may arise during clinic visits, and these conversations should include genetic counseling and options for contraception. Drug–drug interactions between oral contraceptive pills (OCPs) and antibiotics should be monitored. Studies have shown that OCP use in CF patients is safe and effective in comparison to other contraception methods. Patches may not reliably adhere to the skin as a result of increased sweat on the surface of the skin.

The issues surrounding the use of contraception among CF men are similar to those among the normal population. CF men should not assume they are infertile, and should adhere to using protective measures in order to prevent unwanted pregnancy and the spread of sexually transmitted diseases. Should a CF male with a nonfunctioning vas deferens desire to become a biological parent, microsurgical epididymal aspiration of spermatozoa with intracytoplasmic sperm injection into the oocyte can be performed.[11]

Diabetes

As CF patients live longer, glucose intolerance and cystic fibrosis-related diabetes (CFRD) are common complications. Even though it shares features of type 1 and type 2 diabetes, CFRD is unique because it is influenced by factors specific to CF, including insulin deficiency (due to a scarred pancreas), undernutrition, chronic and acute infection, elevated energy expenditure, glucagon deficiency, malabsorption, abnormal intestinal transit time, and liver

dysfunction. In comparison to the general CF population, patients with CFRD show a higher mortality rate in those greater than 30 years of age. The average onset of CFRD is between 18 and 21 years, with a slight female predominance and is more commonly seen in severe *CFTR* gene mutations.[23,24]

It is recommended that at age 10 years and every year thereafter, CF patients be screened for CFRD. The OGTT should be used as the A1C is not a reliable indicator of diabetes in this population. In stable outpatients, fasting glucose levels of more than or equal to 126 mg/dL (7.0 mmol/L) are diagnostic of CFRD. A 2-hour OGTT plasma glucose level of more than or equal to 200 mg/dL (11.1 mmol/L) repeated on two separate days may also be diagnostic of CFRD.[23]

A desired goal in this population is to control hyperglycemia and prevent hypoglycemia in order to reduce acute and chronic diabetes complications. Because insulin deficiency is the hallmark of CFRD, insulin is the recommended medical treatment. Insulin regimens are individualized based on the patient's lifestyle and circumstances. Exercise is encouraged because it can improve peripheral insulin sensitivity and have beneficial effects in overall health, pulmonary function, and well-being.[23]

Oral antidiabetic agents have inconsistent results in the literature; therefore, support for their use in therapy for CFRD patients is not recommended. Medications that help improve insulin sensitivity do not address the primary problem of insulin deficiency in CF. Metformin's mechanism of action is to improve hepatic and peripheral insulin sensitivity. However, it is contraindicated in patients with hypoxia due to the risk of fatal lactic acidosis. Additionally, metformin's multiple GI effects include anorexia, diarrhea, flatulence, and abdominal discomfort. Thiazolidinediones help enhance peripheral insulin sensitivity, but there is serious potential for hepatic toxicity due to the underlying liver problems in CF patients. The use of acarbose is also discouraged due to its mechanism of action, which reduces postprandial glucose and insulin excursion by limiting intestinal absorption of glucose. This inhibits the energy absorption in malnourished individuals while causing diarrhea, anorexia, and abdominal discomfort. Sulfonylureas were once considered due to their ability to enhance insulin secretion by acting on a specific islet beta-cell receptor; however, they also cause severe hypoglycemia and acceleration of beta cell loss. Newer antidiabetic agents effective for treatment of type 1 and type 2 diabetes are currently being studied for treatment of CFRD. One current focus is in glucagon-like-peptide (GLP)1, which is an incretin hormone the body releases in response to eating. At least one study has found that CF patients may have a deficiency of this hormone. This deficiency was found in both CF patients with diagnosed

diabetes and those without diabetes. It is not yet known how this plays into the future determination of diabetes in CF patients. There are ongoing studies evaluating the results of supplementation with GLP-1 in CF patients. A disadvantage of utilizing these new agents in CFRD is that these therapies target weight loss as well as glycemic control. Weight loss in CF patients may be detrimental to overall health, as the goal is to optimize nutrition status which contributes to optimal pulmonary health and survival.[25–27]

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulators

An exciting breakthrough in CF treatment focuses on treating the basic defect of the disease: CFTR dysfunction. Treatment has been focused on end organ effects such as pancreatic insufficiency and prevention of lung disease. CFTR modulators are a recent addition to the treatment possibilities of CF. The modulators focus on the root of the disease by partially restoring function of the mutated CFTR. Genetic mutations can be broken down into six classes based on their effect on the CFTR functionality. See **Fig. 46-2** and **Table 46-5**.

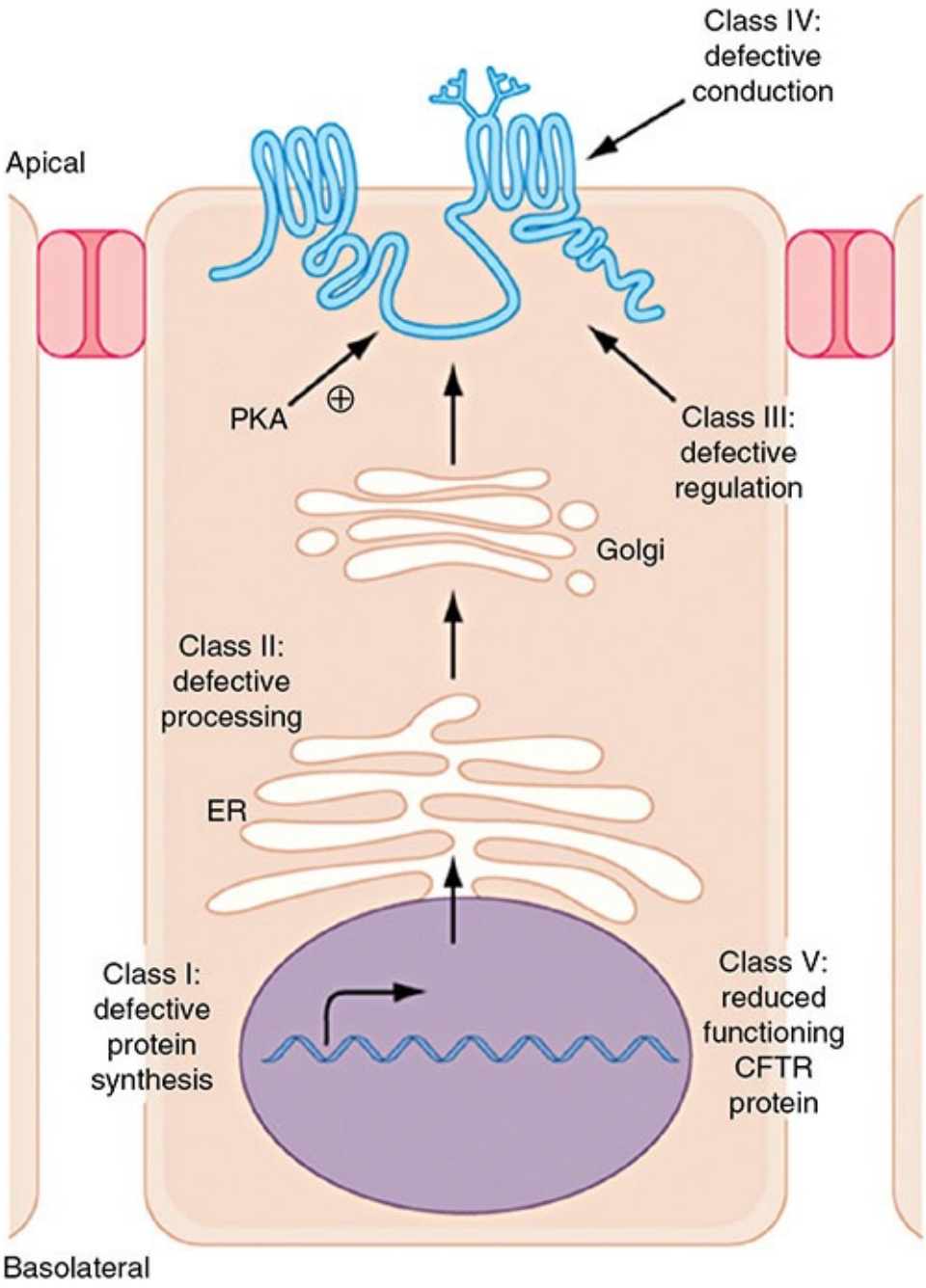


FIGURE 46-2 Schema describing classes of genetic mutations in the *CFTR* gene and effects on CFTR protein/function. Note the ΔF508 mutation is a class II mutation and, like class I mutations, would be predicted to produce no mature CFTR protein in the apical membrane. (CFTR, cystic fibrosis transmembrane conductance regulator.) (*Reproduced with permission from Chapter 259. Cystic Fibrosis. Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson J, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 18th ed. New York: McGraw-Hill; 2012.*)

TABLE 46-5 CFTR Genetic Mutations

Mutation	CFTR Functionality
Class I	No protein produced
Class II	Defect in protein trafficking
Class III	High turnover of protein from surface
Class IV	Abnormal chloride transport
Class V	Not enough protein produced
Class VI	Increased turnover at cell surface

Kalydeco® (ivacaftor) is approved for patients 2 years or older with the Class III mutations with the similar gating defect as the *G551D* mutation. Ivacaftor works by potentiating the activity of the CFTR protein, so that the channels stay open longer on the cell surface. As a result, mucus is thinned by fluid movement into the airways making airway clearance easier for the patient.

In a randomized, double-blind, placebo-controlled trial evaluating ivacaftor in patients 12 years or older, ivacaftor met effectiveness endpoints. Researchers saw significant improvements in lung function, risk of pulmonary exacerbations, respiratory symptoms, and weight and sweat chloride concentrations. The change in baseline FEV_1 was greater than 10.6 percentage points in comparison with placebo (*P* less than 0.001) with an improvement in pulmonary function noted by 2 weeks and sustained through week 48. An average weight increase of 2.7 kg was seen in the ivacaftor group versus placebo at the end of 48 weeks. Common side effects to monitor for are cataracts, myalgia, headache, upper respiratory infections, elevated liver enzymes, and chest pain.

Orkambi® is a combination of ivacaftor and lumacaftor, a CFTR potentiator and CFTR corrector. It is approved for patients 6 years or older with the homozygous *ΔF508* mutation. In two phase 3 placebo controlled, randomized control trials, Orkambi® showed improvement in percentage of predicted FEV_1, as well as reduction in pulmonary exacerbations in comparison to placebo. Side effects are similar to ivacaftor.[28–30]

Special Populations

Pregnancy As patients with CF live longer, more women choose to become pregnant. CF women considering pregnancy and their partners should both undergo genetic counseling. CF women who become pregnant are considered a high-risk pregnancy; therefore, several considerations should be addressed

before and during pregnancy. These patients should be screened and treated accordingly for CFRD. Evaluation of the current medication regimen is crucial to avoid potential harm to the fetus. During the first 3 months of pregnancy, vitamin levels should be monitored to avoid toxicity to the fetus while continuing vitamin D, E, and K supplementation.

Several complications that will arise during CF pregnancy include increases in minute ventilation, oxygen uptake, blood volume, and cardiac output. In a woman with severe lung disease, these changes may lead to right-sided heart failure.

Other pharmacotherapy issues that are seen in this population are altered pharmacokinetics and increased maintenance of nutritional and pulmonary health. The CF woman who chooses to breastfeed must take into account the additional nutritional requirement of approximately 500 kcal/day (2100 kJ/day). The addition of the fetus impacts the CF woman's health by placing a strain on a precariously balanced state of being.[11]

Pediatrics Education of the parents is emphasized in this population. Medication administration techniques and explanation of how medications work and why they are important are key to an engaged family. Parents also have the additional challenge of maintaining a clean home environment, communicating with the education system, and monitoring the child's health status. As the child grows into adolescence, adherence with medications and ACT often becomes an issue. Parents are also counseled to encourage their child to adhere to pulmonary health and nutritional health practices. Peer pressure and social restraints may interfere with CF compliance and may influence the patients to disregard their personal well-being.

Transplant Patients Lung transplantation is an option for those with the most severe lung disease. Short-term survival after transplant has improved with a 1-year survival rate of 80%, 3 years of 60%, and 5 years of 50%. The first year after transplant still remains the most critical as the risk of complications is the highest during this time. Criteria for selection of transplant candidates include not only an FEV_1 of less than 30%, but also gender, nutritional status, diabetic status, sputum microbiology, and the number of pulmonary exacerbations. Factors affecting compliance to CF care and to immunosuppressant therapy may also be taken under consideration for candidacy.[11,31]

EVALUATION OF THERAPEUTIC OUTCOMES

CF patients are often monitored every 1 to 3 months, depending on the acuity of their illness. Clinicians will evaluate the patient's pulmonary function and assess for unusual respiratory symptoms to determine if the current pharmacotherapy regimen is effective. Airway clearance, inflammation, and bacterial colonization must be under control to optimize pulmonary function. Adequate growth (pediatrics) and nutrition (pediatrics and adults) are also evaluated at each visit. The pharmacist is integral for optimization of pharmacotherapy and must also evaluate and encourage patient/family adherence to recommended treatment, both nonpharmacologic and pharmacologic.

Desired Outcomes

Pulmonary and Sinus

The goal of treatment is to prevent and treat sinusitis and acute pulmonary exacerbations. Routine care goals are to increase the FEV1 and promote optimal pulmonary function tests. Effective airway clearance is promoted with counseling on the use of appropriate medications and ACT. Prevention and treatment of bacterial colonization are also keys to maintaining lung function.

Gastrointestinal Optimizing growth and nutrition is done primarily with the use of pancreatic enzyme supplementation. This in turn will promote healthy bowel habits and maintenance of appropriate fat-soluble vitamin levels. Evaluating and supporting needed caloric intake is important to support lung function. It is essential to provide mutation analysis with appropriate genetic counseling at the time of diagnosis and periodically thereafter. As patients and significant others reach reproductive age it is key to offer both possible birth control methods and support couples in family planning with education and resources.

Psychosocial Each patient will need ongoing education and support to encourage adherence to pharmacological and nonpharmacological therapies. Counseling to help cope with a lifelong disease as well as guidance to live a fulfilling life are paramount to successful treatment.

CONCLUSION

Multidisciplinary care for CF patients should involve pulmonologists, gastroenterologists, pharmacists, social workers, respiratory therapists, and dieticians. The complexity of care requires good communication within the CF

team and with the patient/family. Although intravenous (IV) antibiotics have historically been a mainstay of therapy, recent focus has shifted to optimizing nutrition status and promoting effective pulmonary clearance. New treatment modalities such as CFTR modulators necessitate greater involvement by pharmacists. As patients live longer, more social issues arise and medical issues become more complex.

Postclass Engaged Learning Activity

Conduct a literature search and identify a research article that evaluates the tezacaftor/ivacaftor combination drug for the treatment of cystic fibrosis. Write a summary about the study methods, what metrics were used to evaluate efficacy and safety, and how the drug adds to the current armamentarium of drugs for cystic fibrosis care. This activity is meant to develop your literature evaluation skills and practice critical review of new medications.

ABBREVIATIONS

ABPA	allergic bronchopulmonary aspergillosis
ACT	airway clearance therapy
ADEK	fat-soluble vitamins A, D, E, K

BMD	bone mineral density
CF	cystic fibrosis
CFRD	cystic fibrosis related diabetes
CFTR	cystic fibrosis transmembrane conductance regulator
DIOS	distal intestinal obstruction syndrome
ENaC	amiloride-sensitive epithelial sodium channel
FDA	Food and Drug Administration
FEV_1	forced expiratory volume at 1 second
FVC	forced vital capacity
GI	gastrointestinal
IRT	immunoreactive trypsinogen
IV	intravenous
MAI	*Mycobacterium avium-intracellulare*
MIC	minimum inhibitory concentration
NDA	new drug application
NSAIDs	nonsteroidal anti-inflammatory drugs
NTM	nontuberculous mycobacteria
OGTT	oral glucose tolerance test
OCPs	oral contraceptive pills
PEG	percutaneous endoscopic gastrostomy
PERT	pancreatic enzyme replacement therapy
QPIT	quantitative pilocarpine iontophoresis test
RSV	respiratory syncytial virus

REFERENCES

1. Cystic Fibrosis. US National Library of Medicine Genetics Home reference. Available at https://ghr.nlm.nih.gov/condition/cystic-fibrosis. Accessed Februrary 2018.
2. Lynch JP 3rd, Sayah DM, Belperio JA, Weigt SS. Lung transplantation for cystic fibrosis: Results, indications, complications, and controversies. *Semin Respir Crit Care Med*. 2015;36(2):299–320. doi: 10.1055/s-0035-1547347.
3. Cystic Fibrosis Foundation. Cystic Fibrosis Foundation Patient Registry, 2016 Annual Data Report to the Center Directors. Bethesda, MD.
4. Farrell PM, White TB, Ren CL, et al. Diagnosis of cystic fibrosis: Consensus guidelines from the Cystic Fibrosis Foundation. *J Pediatr*.

2017;181S:S4–S15. e1.

5. Ramsey BW, Welsh MJ. AJRCCM: 100-Year Anniversary. Progress along the pathway of discovery leading to treatment and cure of cystic fibrosis. *Am J Respir Crit Care Med*. 2017;195(9):1092–1099.
6. Quinton PM. Cystic fibrosis: Lessons from the sweat gland. *Physiology*. 2007;22:212–225.
7. Rowe SM, Miller S, Sorscher EJ. Cystic fibrosis. *N Engl J Med*. 2005;352(19):1992–2001.
8. Stallings VA, Stark LJ, Robinson KA, et al. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: Results of a systematic review. *J Am Diet Assoc*. 2008;108(5):832–839.
9. Borowitz DS, Grand RJ, Durie PR. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. Consensus Committee. *J Pediatr*. 1995;127:681.
10. Tangpricha V, Kelly A, Stephenson A, et al. An update on the screening, diagnosis, management, and treatment of vitamin D deficiency in individuals with cystic fibrosis: Evidence-based recommendations from the Cystic Fibrosis Foundation. *J Clin Endocrinol Metab*. 2012;97(4):2011–3050.
11. Yankaskas JR, Marshall BC, Sufian B, et al. Cystic fibrosis adult care. *Chest*. 2004;125:1S–39S.
12. Geller DE, Pitlick WH, Nardella PA. “Pharmacokinetics and bioavailability of aerosolized tobramycin in cystic fibrosis.” *Chest*. 2002:22(1):219–226.
13. Targett K, Bourke S, Nash E, Murphy E, Ayres J, Devereux G. Employment in adults with cystic fibrosis. *Occup Med (Lond)*. 2014;64(2):87–94.
14. Flume PA, Robinson KA, O’Sullivan BP, et al. Cystic fibrosis pulmonary guidelines: Airway clearance therapies. *Respir Care*. 2009;54(4):522–537.
15. Mogayzel PJ, Naureckas ET, Robinson KA, et al. Cystic fibrosis pulmonary guidelines: Chronic medications for maintenance of lung health. *Am J Respir Crit Care Med*. 2013;187:680–689.
16. Elkins MR, Robinson M, Rose BR, et al. A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. *N Engl J Med*. 2006;354(3):229–240.

17. Quan JM, Tiddens HA, Sy JP, et al. A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities. *J Pediatr*. 2001;139(6):813–820.
18. Floto RA, Olivier KN, Saiman L, et al. US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis. *Thorax*. 2016;71(Suppl 1):i1–i22.
19. Assael BM, Pressler T, Bilton D, et al. Inhaled aztreonam lysine vs. inhaled tobramycin in cystic fibrosis: A comparative efficacy trial. *J Cyst Fibros*. 2012;12(2):130–140. doi: 10.1016/j.jcf.2012.07.006.
20. Cystic Fibrosis Foundation. Aspergillus and Allergic Bronchopulmonary Aspergillosis. https://www.cff.org/Life-With-CF/Daily-Life/Germs-and-Staying-Healthy/What-Are-Germs/Aspergillus-and-Allergic-Bronchopulmonary-Aspergillosis/. Accessed 3/30/2018.
21. Horsley A, Jones AM, Lord R. Antibiotic treatment for Burkholderia cepacia complex in people with cystic fibrosis experiencing a pulmonary exacerbation. *Cochrane Database Syst Rev*. 2016;(1):CD009529. doi: 10.1002/14651858.CD009529.pub3.26789750.
22. Yaffe S, Gerbracht LM, Mosovich LL, et al. Pharmacokinetics of methicillin in patients with cystic fibrosis. *J Infect Dis*. 1977;135(5):828–831.
23. Powell SH, Thompson WL, Luthe MA, et al. Once-daily vs. continuous aminoglycoside dosing: Efficacy and toxicity in animal and clinical studies of gentamicin, netilmicin and tobramycin. *J Infect Dis*. 1983;5:918–932.
24. Moran A, Brunzell C, Cohen RC, et al. Clinical care guidelines for cystic fibrosis-related diabetes. *Diabetes Care*. 2010;33(12):2697–2708.
25. Lewis C, Blackman SM, Nelson A, et al. Diabetes-related mortality in adults with cystic fibrosis. Role of genotype and sex. *Am J Respir Crit Care Med*. 2015;191(2):194–200.
26. Hillman M, Eriksson L, Mared L, Helgesson K, Landin-olsson M. Reduced levels of active GLP-1 in patients with cystic fibrosis with and without diabetes mellitus. *J Cyst Fibros*. 2012;11(2):144–149.
27. Kelly A, Moran A. Update on cystic fibrosis-related diabetes. *J Cyst Fibros*. 2013;12(4):318–331.
28. Ren CL, Morgan RL, Oermann C, et al. Cystic Fibrosis Foundation pulmonary guidelines. Use of cystic fibrosis transmembrane conductance

regulator modulator therapy in patients with cystic fibrosis. *Ann Am Thorac Soc*. 2018;15(3):271–280.

29. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Eng J Med*. 2011;365:1663–1672.
30. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor-Ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. *N Eng J Med*. 2015;373:220–231.
31. National Heart, Lung, and Blood Institute. Lung Transplantation: What Are the Risk Factors in Lung Transplant? https://www.nhlbi.nih.gov/node/3963. Accessed 4/8/2018.

Drug-Induced Pulmonary Diseases

Hengameh H. Raissy and Michelle S. Harkins

KEY CONCEPTS

1. Specific patient populations are more susceptible to drug-induced pulmonary toxicities.
2. If a drug-induced pulmonary disease is suspected, the probable offending agent should be discontinued and supportive care provided.

INTRODUCTION

The manifestations of drug-induced pulmonary diseases span the spectrum of pathophysiologic conditions of the respiratory tract. As with most drug-induced diseases, the pathological changes are nonspecific. Therefore, the diagnosis is often difficult and, in most cases, is based on the exclusion of all other possible causes. The true incidence of drug-induced pulmonary disease is unknown due to the nonspecific pathology and the interaction between the underlying disease state and the drugs.

Considering the physiologic and metabolic capacity of the lung, it is surprising that drug-induced pulmonary disease is not more common. The lung is the only organ of the body that receives the entire circulation. In addition, the lung contains a heterogeneous population of cells with a variety of metabolic functions, including *N*-alkylation, *N*-dealkylation, *N*-oxidation, reduction of *N*-oxides, and *C*-hydroxylation.

In the United States, more than 2 million cases of adverse drug reactions occur every year with 100,000 reported deaths[1] and 0.3% of in-hospital deaths are drug-related.[2] Epidemiologic studies reveal the importance of drug-induced pulmonary disease. In a 2-year prospective survey of a community-based general practice, 41% of 817 patients experienced at least one adverse drug reactions.[3]

Four patients, or 0.5% of the total respondents, experienced adverse respiratory symptoms. In a recent retrospective analysis of clinical case series in France, 898 patients reported a drug allergy, with bronchospasm reported and subsequently confirmed in nearly 7% of these patients.[4]

Adverse pulmonary reactions are uncommon in the general population but are among the most serious reactions, often requiring intervention. In a study of 270 adverse reactions leading to hospitalization from two populations, 3% were respiratory in nature.[5] Of the reactions considered to be life-threatening, 12.3% were respiratory. An early report on death caused by drug reactions from the Boston Collaborative Drug Surveillance Program indicated that 7 of 27 drug-induced deaths were respiratory in nature.[6] A follow-up study confirmed that 6 of 24 drug-induced deaths were respiratory in nature.[7]

DRUG-INDUCED APNEA

1 Apnea may be induced by central nervous system depression or respiratory neuromuscular blockade (**Table e47-1**). Patients with chronic obstructive airway disease, alveolar hypoventilation, and chronic carbon dioxide retention have an exaggerated respiratory response to narcotic analgesics and sedatives. In addition, the injudicious administration of oxygen in patients with carbon dioxide retention can worsen ventilation-perfusion mismatching, further elevating pCO_2 and thus producing apnea.[8] Although the benzodiazepines are touted to cause less respiratory depression than barbiturates, they may produce a profound additive or synergistic effect when taken in combination with other respiratory depressants. Combining intravenous diazepam with phenobarbital to stop seizures in an emergency department frequently results in admissions to an intensive care unit for assisted mechanical ventilation, regardless of the drug administration rate. Rapid intravenous administration of any of the benzodiazepines, even without coadministration of other respiratory depressants, will result in apnea. The risk appears to be the same for the various available agents (diazepam, lorazepam, and midazolam). Respiratory depression and arrests resulting in death and hypoxic encephalopathy have occurred following rapid intravenous administration of midazolam for conscious sedation prior to medical procedures. Benzodiazepine-associated respiratory depression has been reported more commonly in the elderly and the chronically debilitated as well as in combination with opioid analgesics. Concurrent use of inhibitors of cytochrome P450 3A4 with benzodiazepines is likely to lead to a greater risk of

respiratory depression.

Prolonged apnea may follow the administration of any of the neuromuscular blocking agents used for surgery, particularly in patients with hepatic or renal dysfunction. In addition, persistent neuromuscular blockade and muscle weakness have been reported in critically ill patients who are receiving neuromuscular blockers continuously for more than 2 days to facilitate mechanical ventilation.[9,10] This has resulted in delayed weaning from mechanical ventilation and prolonged intensive care unit stays. This prolonged neuromuscular blockade has been principally observed with pancuronium and vecuronium in patients with renal disease. Both agents have pharmacologic active metabolites that are renally excreted.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

SECTION 6 GASTROINTESTINAL DISORDERS

Evaluation of the Gastrointestinal Tract

Keith M. Olsen and Rachael V. McCaleb

KEY CONCEPTS

1. The patient history is key to evaluating gastrointestinal (GI) tract disorders and should include the problem onset, the setting in which it developed, and its presentation. Patient warning signs and alarm symptoms should be identified quickly and referral for further evaluation should be obtained in a prompt manner.
2. A complete physical examination should be performed, the severity and location of symptoms directing the focus of the examination.
3. Contrast agents, barium sulfate and Gastrografin® (diatrizoate meglumine and diatrizoate sodium solution), have gradually been replaced by endoscopy, but allow evaluation of the hollow organs of the digestive tract for mucosally based lesions as well as narrowing or strictures involving the GI tract.
4. The upper GI series involves radiographic visualization of the esophagus, stomach, and duodenum; whereas, the lower GI series involves visualization of the colon and rectum.
5. Enteroclysis is used to evaluate the small bowel by introducing contrast agents by tube through the nose or mouth directly into the small intestine.
6. Transabdominal ultrasound, computed tomography, and magnetic resonance imaging provide images of the gallbladder, liver, pancreas, and abdominal wall.
7. Radionuclide imaging is sometimes useful to visualize and evaluate the liver, spleen, bile ducts, and gallbladder.
8. The endoscope, an illuminated optical instrument, remains the cornerstone

of GI diagnosis and most importantly therapy. Common examples of endoscopic procedures include esophagogastroduodenoscopy, colonoscopy, enteroscopy, endoscopic retrograde cholangiopancreatography, and endoscopic ultrasound.

9. Capsule endoscopy, a newer less invasive endoscopic technique, takes pictures of the GI tract in the assessment of the small bowel in particular.

10. Ambulatory esophageal pH measurement is an important diagnostic test for gastroesophageal reflux disease and is often performed in conjunction with upper endoscopy. Most systems today are completely wireless and patient friendly. Multichannel intraluminal impedance and pH monitoring combines acid exposure with impedance changes in resistant flow to aid the diagnosis of reflux in patients receiving a proton pump inhibitor and other antisecretory medications.

INTRODUCTION

The gastrointestinal (GI) tract is an organ system responsible for nutrient absorption, waste excretion, and immunity. It is composed of the upper GI tract (oral cavity, esophagus, and duodenum), lower GI tract (small intestine, cecum, colon, rectum, and anus), and associated glandular organs (gallbladder, pancreas, and liver). A variety of symptoms can arise from GI tract dysfunction, including heartburn, dyspepsia, abdominal pain, nausea, vomiting, diarrhea, constipation, and GI bleeding. Signs and symptoms of malabsorption, hepatitis, and GI infection are also commonly seen. All clinicians must recognize warning symptoms that include weight loss, intractable vomiting, anemia, dysphagia, odynophagia, and bleeding; and a patient presenting with any of these symptoms should be immediately referred for further diagnostic interventions.

Despite the rapid proliferation of technology for the diagnosis of digestive diseases, the patient history and physical examination remain important for initial assessment, triage, and guidance of further diagnostic interventions. When combined with a thorough patient history and physical examination, diagnostic procedures are essential in the evaluation of GI disorders. This chapter describes the most commonly used clinical tools to evaluate patients with GI tract-related diseases.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

49

Gastroesophageal Reflux Disease

Dianne May, Michael L. Thiman, and Satish S.C. Rao

KEY CONCEPTS

1. Gastroesophageal reflux disease (GERD) can be described on the basis of either esophageal symptoms or esophageal tissue injury. The common symptoms include heartburn, regurgitation, chest pain, and dysphagia.
2. Endoscopy is commonly used to evaluate mucosal injury from GERD and to assess for the presence of Barrett's esophagus or other complications, such as strictures or adenocarcinoma.
3. Whereas ambulatory reflux monitoring only measures acid reflux, combined impedance–pH monitoring measures both acid and nonacid reflux.
4. The goals of GERD treatment are to alleviate symptoms, decrease the frequency of recurrent disease, promote healing of mucosal injury, and prevent complications.
5. GERD treatment is determined by disease severity and includes: (a) lifestyle changes and patient-directed therapy with antacids, nonprescription H2-receptor antagonists, and/or nonprescription proton pump inhibitors; (b) pharmacologic treatment with prescription-strength acid suppression therapy; (c) surgery; and (d) endoscopic therapies.
6. Patients with typical GERD symptoms should be treated with lifestyle modifications as appropriate and a trial of empiric acid suppression therapy. Those who do not respond to empiric therapy or who present with alarm symptoms such as dysphagia, weight loss, or GI bleeding should undergo endoscopy.
7. Surgical intervention is a viable alternative treatment for select patients when long-term pharmacologic management is undesirable or when patients have complications.

8. Acid suppression is the mainstay of GERD treatment. Proton pump inhibitors provide the greatest symptom relief and the highest healing rates, especially for patients with erosive disease or moderate-to-severe symptoms or with complications.
9. Many patients with GERD will relapse if medication is withdrawn; so long-term maintenance treatment may be required. A proton pump inhibitor is the drug of choice for maintenance of patients with moderate-to-severe GERD.
10. Patient medication profiles should be reviewed for drugs that may aggravate GERD. Patients should be monitored for adverse drug reactions and potential drug–drug interactions.

Preclass Engaged Learning Activity

Watch video entitled, "GERD" in AccessPharmacy by Bryan Love. This ~6-minute video summarizes the normal function of the esophagus and stomach compared to that seen with acid reflux, complications of GERD, process of acid production, and pharmacologic therapy for GERD. Student understanding regarding the COLLECT, ASSESS, and PLAN steps of the Patient Care Process are addressed with this video.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common medical disorder. A consensus definition of GERD is "symptoms or complications resulting from refluxed stomach contents into the esophagus or beyond, into the oral cavity (including the larynx) or lung."[1] The key is that these troublesome symptoms adversely affect the well-being of the patient. Episodic heartburn that is not frequent enough or painful enough to be considered bothersome by the patient is not included in this definition of GERD.

Gastroesophageal reflux disease can be further classified as either symptom-based or tissue injury-based depending on how the patient presents.[1] Symptom-based GERD may exist with or without esophageal injury and most commonly presents as heartburn, regurgitation, or dysphagia. Less commonly, odynophagia (painful swallowing), water brash, belching, bloating, or hypersalivation may

also occur. The absence of tissue injury or erosions is commonly termed nonerosive reflux disease (NERD). Tissue injury-based GERD may exist with or without symptoms. The spectrum of injury includes esophagitis (inflammation of the lining of the esophagus), Barrett's esophagus (when tissue lining the esophagus is replaced by tissue similar to the lining of the intestine), strictures, and esophageal adenocarcinoma.[1] Esophagitis occurs when the esophagus is repeatedly exposed to refluxed gastric contents for prolonged periods of time.[1] This can progress to erosion of the squamous epithelium of the esophagus (erosive esophagitis). Complications of long-term reflux may include the development of strictures, Barrett's esophagus, or possibly adenocarcinoma of the esophagus.

Gastroesophageal reflux symptoms associated with disease processes in organs other than the esophagus are referred to as extraesophageal reflux syndromes. Patients with extraesophageal reflux syndromes may present with chest pain, hoarseness, chronic cough, or asthma. An association between these syndromes and GERD should only be considered when they occur along with esophageal GERD syndrome because these extraesophageal symptoms are nonspecific and have many other causes.[1]

Many patients suffering from mild GERD do not go on to develop erosive esophagitis and are often managed with lifestyle changes, antacids, and nonprescription histamine-2 receptor antagonists (H2RAs) or nonprescription proton pump inhibitors (PPIs). Those with more severe symptoms (with or without tissue injury) predictably follow a course of relapsing disease, requiring more intensive treatment with acid suppression therapy followed by long-term maintenance therapy. Periodic assessment is important to assure the lowest effective medication dose is being used. Antireflux surgery offers an alternative for select patients in whom prolonged medical management is undesirable, those with refractory GERD, or those with complications. Bariatric surgery may be an option in obese patients. Endoscopic therapies continue to be evaluated in an effort to find a less invasive alternative therapy that bridges the gap between pharmacologic management and more invasive surgery.

EPIDEMIOLOGY

GERD occurs most commonly in those older than age 40 years. Although mortality is rare, GERD may have a significant economic impact and impact on quality of life. The true prevalence of GERD is difficult to assess because many patients do not seek medical treatment, symptoms do not always correlate well

with the severity of the disease, and there is no standardized definition or universal gold standard method for diagnosing the disease. However, the prevalence has risen significantly over the last 20 years with approximately 20% of adults in North America suffering from GERD symptoms on a weekly basis.[2,3] The prevalence of GERD varies depending on the geographic region.[2,3]

Two contributing factors for increased prevalence of GERD in females include pregnancy and the presence of nonerosive reflux disease.[4] Whereas the prevalence of erosive esophagitis is higher in men.[4] Gender is an important factor in the development of Barrett's esophagus and esophageal adenocarcinoma, which are both more common in men. Adenocarcinoma of the esophagus is fivefold more common in those with chronic GERD symptoms than those who do not have GERD.[2] The relationship of adenocarcinoma to Barrett's esophagus, or even just long-standing GERD that may also be an independent risk factor for esophageal adenocarcinoma, remains to be clearly defined.

Other risk factors and comorbidities that may contribute to the development or worsening of GERD symptoms include family history, smoking, alcohol consumption, certain medications and foods, respiratory diseases, reflux chest pain syndrome, and obesity. Obese patients are 2.5 times more likely to experience GERD symptoms.[5] Other conditions that may be associated with GERD continue to be reported. In one study, there was an increased incidence of reflux esophagitis noted in Korean patients with nonalcoholic fatty liver disease.[6] An increased prevalence of GERD has also been noted in patients with major depressive disorder. The exact mechanism of this association has not been determined at this time.[7]

PATHOPHYSIOLOGY

The key factor in the development of GERD is the abnormal reflux of gastric contents from the stomach into the esophagus, oral cavity, and/or the lung.[1] In some cases, gastroesophageal reflux is associated with defective lower esophageal sphincter (LES) pressure or function (**Fig. 49-1**). Patients may have decreased gastroesophageal sphincter pressures related to (a) spontaneous transient LES relaxations, (b) transient increases in intra-abdominal pressure, or (c) an atonic LES, all of which may lead to the development of gastroesophageal reflux. Problems with other normal mucosal defense mechanisms, such as abnormal esophageal anatomy, improper esophageal clearance of gastric fluids,

reduced mucosal resistance to acid, delayed or ineffective gastric emptying, inadequate production of epidermal growth factor, and reduced salivary buffering of acid, may also contribute to the development of GERD. Substances that may promote esophageal damage on reflux into the esophagus include gastric acid, pepsin, bile acids, and pancreatic enzymes. Thus, the composition and volume of the refluxate, as well as duration of exposure, are important aggressive factors in determining the consequences of gastroesophageal reflux.

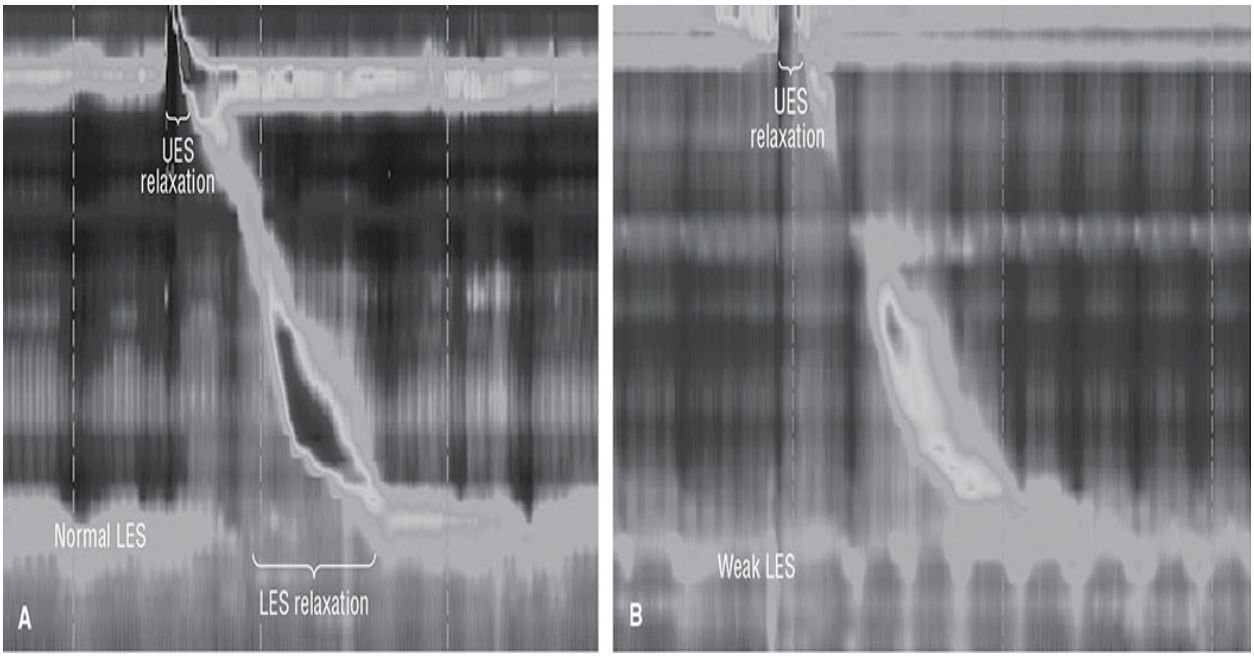


FIGURE 49-1 Comparison of a normal esophageal high-resolution manometry showing normal upper esophageal sphincter and lower esophageal sphincter (LES) resting pressure and relaxations with a water bolus (*A*), compared with that seen in a patient with GERD and a weak resting LES (*B*).

The presence of an “acid pocket” has gained attention as a potential explanation for postprandial reflux symptoms and may represent a target for treatment of reflux disease. While gastric acidity is buffered by food, pH monitoring has shown that this buffering effect may vary in different parts of the stomach and esophagus. The acid pocket is thought to be an area of unbuffered acid in the proximal stomach that accumulates after a meal and may contribute to GERD symptoms postprandially.[8] It occurs due to meal-stimulated acid not mixing well with the chyme in the proximal stomach. Gastric secretions form a distinct layer above the chyme.[8] GERD patients are predisposed to upward migration of acid from the acid pocket. In addition, the acid pocket may also be positioned above the diaphragm in patients, especially in those with hiatal

hernia, which increases the risk for acid reflux.

Lower Esophageal Sphincter Pressure

The LES is a specialized thickening of the smooth muscle lining of the distal esophagus with an elevated basal resting pressure. The sphincter is normally in a tonic, contracted state, preventing the reflux of gastric material from the stomach, but relaxes on swallowing to permit the passage of food into the stomach. There are three mechanisms by which defective LES pressure may cause gastroesophageal reflux. First, and probably most importantly, reflux may occur following spontaneous transient LES relaxations that are not associated with swallowing. Although the exact mechanism is unknown, esophageal distension, vomiting, belching, and retching cause relaxation of the LES. While not thought to contribute significantly to erosive esophagitis, these transient relaxations, which are normal postprandially, may play an important role in symptom-based esophageal reflux syndromes. Transient decreases in sphincter pressure are responsible for more than half of the reflux episodes in patients with GERD. The propensity to develop gastroesophageal reflux secondary to transient decreases in LES pressure is probably dependent on numerous factors, including the degree of sphincter relaxation, efficacy of esophageal clearance, patient position (more common in recumbent position), gastric volume, and intragastric pressure. Second, reflux may occur following transient increases in intra-abdominal pressure (stress reflux). An increase in intra-abdominal pressure such as that occurring during straining, bending over, coughing, eating, or a Valsalva maneuver may overcome a weak LES, and thus may lead to reflux. Third, the LES may be atonic, thus permitting free reflux as seen in patients with scleroderma.

Various foods and medications may aggravate esophageal reflux by decreasing LES pressure or by precipitating symptomatic reflux by direct mucosal irritation (**Table 49-1**). Pregnancy is a condition in which reflux is common. There are many postulated reasons for the increased incidence of heartburn during pregnancy, including hormonal effects on esophageal muscle, LES tone, and physical factors (increased intra-abdominal pressure) resulting from an enlarging uterus. A decrease in LES pressure resulting from any of the previously mentioned causes is not always associated with gastroesophageal reflux. Likewise, individuals who experience decreases in sphincter pressures and subsequently reflux do not always develop GERD. The other natural defense mechanisms (anatomic factors, esophageal clearance, mucosal resistance, and other gastric factors) must be evoked to explain this phenomenon.

TABLE 49-1 Foods and Medications That May Worsen GERD Symptoms

Foods/Beverages	Medications
Decreased Lower Esophageal Sphincter Pressure	
Fatty meal	Anticholinergics
Carminatives (peppermint, spearmint)	Barbiturates
Chocolate	Caffeine
Coffee, cola, tea	Dihydropyridine calcium channel blockers
Garlic	Dopamine
Onions	Estrogen
Chili peppers	Nicotine
Alcohol	Nitrates
	Progesterone
	Tetracycline
	Theophylline
Direct Irritants to the Esophageal Mucosa	
Spicy foods	Aspirin
Orange juice	Bisphosphonates
Tomato juice	Nonsteroidal anti-inflammatory drugs (NSAIDs)
Coffee	Iron
Tobacco	Quinidine
	Potassium chloride

Anatomic Factors

Disruption of the normal anatomic barriers by a hiatal hernia (when a portion of the stomach protrudes through the diaphragm into the chest) was once thought to be a primary etiology of gastroesophageal reflux and esophagitis. Now it appears that a more-important factor related to the presence or absence of symptoms in patients with hiatal hernia is the LES pressure. Patients with hypotensive LES pressures and large hiatal hernias are more likely to experience gastroesophageal reflux following abrupt increases in intra-abdominal pressure compared with patients with a hypotensive LES and no hiatal hernia. Although anatomic factors are still considered significant by some, the diagnosis of hiatal hernia is currently

considered a separate entity with which gastroesophageal reflux may simultaneously occur.

Esophageal Clearance

In many patients with GERD, the problem is not that they produce too much acid but that the acid spends too much time in contact with the esophageal mucosa. Contact time is dependent on the rate at which the esophagus clears the noxious material, as well as the frequency of reflux. Swallowing contributes to esophageal clearance by increasing salivary flow. Saliva contains bicarbonate that buffers the residual gastric material on the surface of the esophagus. The production of saliva decreases with increasing age, making it more difficult to maintain a neutral intraesophageal pH. In addition, swallowing is decreased during sleep, making nocturnal GERD a problem in many patients.

Mucosal Resistance

Within the esophageal mucosa and submucosa there are mucus-secreting glands that may contribute to the protection of the esophagus. Bicarbonate moving from the blood to the lumen can neutralize acidic refluxate in the esophagus. When the mucosa is repeatedly exposed to the refluxate in GERD, or if there is a defect in the normal mucosal defenses, hydrogen ions diffuse into the mucosa, leading to the cellular acidification and necrosis that ultimately cause esophagitis. In theory, mucosal resistance may be related not only to esophageal mucus but also to tight epithelial junctions, epithelial cell turnover, nitrogen balance, mucosal blood flow, tissue prostaglandins, and the acid–base status of the tissue. Saliva is also rich in epidermal growth factor, stimulating cell renewal.

Gastric Emptying/Increased Intra-abdominal Pressure

Delayed gastric emptying can contribute to gastroesophageal reflux. An increase in gastric volume may increase both the frequency of reflux and the amount of gastric fluid available to be refluxed. Gastric volume is related to the volume of material ingested, rate of gastric secretion, rate of gastric emptying, and amount and frequency of duodenal reflux into the stomach. Factors that increase gastric volume and/or decrease gastric emptying, such as smoking and high-fat meals, are often associated with gastroesophageal reflux. This partially explains the

prevalence of postprandial gastroesophageal reflux. Fatty foods may increase postprandial gastroesophageal reflux by increasing gastric volume, delaying the gastric emptying rate, and decreasing the LES pressure. Patients with gastroesophageal reflux, particularly infants, may have a defect in gastric antral motility. The delay in emptying may promote regurgitation of feedings, which might, in turn, contribute to two common complications of GERD in infants (eg, failure to thrive and pulmonary aspiration).[9]

Increased GERD symptoms and complications occur in obese patients. Obesity is considered an independent risk factor for GERD due to increased intra-abdominal pressure and reduced LES pressure.[10] An increased risk for developing both erosive esophagitis and Barrett's esophagus can be attributed to obesity. A gain in BMI of >3.5 kg/m^2 is associated with increased new-onset GERD symptoms, regardless of baseline BMI.[11] Transient LES relaxations, incompetent LES, and impaired esophageal motility have all been attributed to obesity.[12,13]

Composition of Refluxate

The composition, pH, and volume of the refluxate are important aggressive factors in determining the consequences of gastroesophageal reflux. If the pH of the refluxate is less than 2, esophagitis may develop secondary to protein denaturation. In addition, pepsinogen is activated to pepsin at this pH and may also cause esophagitis. Duodenogastric reflux esophagitis, or "alkaline esophagitis," refers to esophagitis induced by the reflux of bilious and pancreatic fluid. The term alkaline esophagitis may be a misnomer in that the refluxate may be either weakly alkaline or acidic in nature. Although bile acids have both a direct irritant effect on the esophageal mucosa and an indirect effect of increasing hydrogen ion permeability of the mucosa, symptoms are more often related to acid reflux than to bile reflux. Specifically, the percentage of time that the esophageal pH is less than 4 is greater for patients with severe disease as compared with that for patients with mild disease. Nevertheless, the combination of acid, pepsin, and/or bile is a potent refluxate in producing esophageal damage.

The pathophysiology of gastroesophageal reflux is a complex cyclic process. It is difficult, if not impossible, to determine which occurs first: gastroesophageal reflux leading to defective peristalsis with delayed clearing or an incompetent LES pressure leading to gastroesophageal reflux. Understanding the factors associated with the development of GERD provides insight into the treatment modalities currently used to manage patients suffering from this

disease.

Complications

Several complications may occur with gastroesophageal reflux, including esophagitis, esophageal strictures, Barrett's esophagus, and esophageal adenocarcinoma. Strictures are common in the distal esophagus and are generally 1 to 2 cm in length. The use of nonsteroidal anti-inflammatory drugs or aspirin is an additional risk factor that may contribute to the development or worsening of GERD complications. In some patients, the reparative process leads to the replacement of the squamous epithelial lining of the esophagus by specialized columnar-type epithelium (Barrett's esophagus), which increases the incidence of esophageal strictures by as much as 30%. Screening for Barrett's esophagus is indicated in men with chronic GERD symptoms (>5 years) and/or heartburn or acid regurgitation occurring at least weekly; and two or more of the following risk factors for Barrett's esophagus or esophageal adenocarcinoma: (1) >50 years old; (2) Caucasian; (3) central obesity (waist circumference greater than 102 cm or waist-hip ratio greater than 0.9); (4) tobacco use (current or previous use); and (5) family history of Barrett's esophagus or esophageal adenocarcinoma.[14] The risk of esophageal adenocarcinoma may be higher for patients with Barrett's esophagus as compared with that for the general population, although not as high as previously thought. The annual risk of esophageal adenocarcinoma was 0.2% to 05% in those with nondysplastic Barrett's esophagus.[14] The annual risk of cancer progression increases to 0.7% in those with low-grade dysplasia and as high as 7% in those with high-grade dysplasia.[14]

CLINICAL PRESENTATION

1 Gastroesophageal reflux disease (GERD) can be described on the basis of either esophageal symptoms or esophageal tissue injury. The common symptoms include heartburn, regurgitation, chest pain, and dysphagia. The severity of the symptoms of gastroesophageal reflux does not always correlate with the degree of esophageal tissue injury, but it does correlate with the duration of reflux. Similar frequency and severity of both heartburn and regurgitation have been found in patients with NERD compared with those with erosive esophagitis with some differences noted based on gender.[15] Reflux hypersensitivity may contribute to the patient's perception of symptom severity despite normal

esophageal reflux exposure.[16] The clinical presentation of GERD overlaps with other conditions such as eosinophilic esophagitis, functional dyspepsia, and gastroparesis leading to challenges in managing GERD patients. It is important to distinguish GERD symptoms from those of other diseases, especially when chest pain or pulmonary symptoms are present.

Diagnostic Tests

The most useful tool in the diagnosis of gastroesophageal reflux is the clinical history, including presenting symptoms and associated risk factors.[1] Patients presenting with typical symptoms of reflux, such as heartburn or regurgitation, do not usually require invasive esophageal evaluation. These patients generally benefit from an initial empiric trial of acid suppression therapy. A clinical diagnosis of GERD can be assumed in patients who respond to appropriate therapy.[1] However, response to an empiric course of PPI was only 71% sensitive and 44% specific as compared to the combination of endoscopy and ambulatory pH monitoring.[17] This is due to the diverse symptom profile seen in GERD with variable responses to PPIs. PPIs are the most effective in patients with erosive esophagitis and less with regurgitation, extraesophageal symptoms, gastroparesis, achalasia, eosinophilic esophagitis, or functional gastrointestinal disorders. A strategy based on symptom domain and assessment of esophageal function testing may better define therapy.[18] The presence of erosive esophagitis or Barrett's esophagus per endoscopy, or abnormal pH testing defines "proven" GERD.[19] In addition having a "proven" diagnosis of GERD helps limit PPI use to those who are most likely to respond and avoid unnecessary adverse effects that have been reported increasingly such as renal failure, enteric infections, vitamin/mineral deficiencies, bone fractures, and hypomagnesemia.[17,18] Proven GERD should be established before long-term acid suppression therapy is considered.

Further diagnostic evaluation is useful to prevent misdiagnosis, identify complications, and assess treatment failures.[13,20] Diagnostic tests should be performed in those patients who do not respond to therapy and in those who present with alarm symptoms (eg, dysphagia, odynophagia, and weight loss), which may be more indicative of complicated disease. Additional diagnostic testing can help stratify patients with GERD into management categories that helps guide clinicians to the most appropriate therapy.[19]

2 Useful tests in diagnosing GERD include upper endoscopy, ambulatory reflux monitoring, combined impedance–pH monitoring, manometry/high-

resolution esophageal pressure topography, and impedance manometry. Endoscopy is commonly used to evaluate mucosal injury and to assess for the presence of Barrett's esophagus or other complications, such as strictures or adenocarcinoma. Biopsies are necessary to diagnose Barrett's esophagus. A camera-containing capsule swallowed by the patient offers the newest technology for visualizing the esophageal mucosa via endoscopy. The PillCam ESO is less invasive than traditional endoscopy and takes less than 15 minutes to perform in the clinician's office but biopsies cannot be obtained. Unfortunately, the presence or absence of mucosal damage does not prove the patient's symptoms are reflux related; for that, ambulatory reflux monitoring is useful.

CLINICAL PRESENTATION

GERD[1,17,22,23]

Symptom-Based GERD Syndromes (With or Without Esophageal Tissue Injury)

Typical symptoms (may be aggravated by activities that worsen gastroesophageal reflux such as recumbent position, bending over, or eating a meal high in fat):

- Heartburn (hallmark symptom described as a substernal sensation of warmth or burning rising up from the abdomen that may radiate to the neck; may be waxing and waning in character)
- Regurgitation/belching
- Reflux chest pain

Alarm symptoms (these symptoms may be indicative of complications of GERD such as Barrett's esophagus, esophageal strictures, or esophageal adenocarcinoma and require further diagnostic evaluation):

- Dysphagia (common)
- Odynophagia
- Bleeding
- Weight loss

Tissue Injury-Based GERD Syndromes (With or Without Esophageal Symptoms)

Symptoms (may present with alarm symptoms such as dysphagia, odynophagia, or unexplained weight loss):

- Esophagitis
- Strictures
- Barrett's esophagus
- Esophageal adenocarcinoma

Extraesophageal GERD Syndromes

- These symptoms have an association with GERD, but causality should only be considered if a concomitant esophageal GERD syndrome is also present):
- Chronic cough
- Laryngitis
- Wheezing
- Asthma (~50% with asthma have GERD)

Diagnostic Tests For GERD

Clinical History

- Generally used to make a clinical diagnose GERD in patients with typical symptoms

Endoscopy

- Preferred for assessing for mucosal injury and complications. Biopsies are needed to identify Barrett's esophagus, adenocarcinoma, and eosinophilic esophagitis (a nonacid-related esophageal disorder that generally does not respond well to PPI therapy).
- Indications for endoscopy: (1) persistent or progressive GERD symptoms despite appropriate therapy; (2) presence of dysphagia or odynophagia; (3) unexplained weight loss of more than 5%; (4) presence of GI bleeding, strictures; (5) screening for Barrett's esophagus in high-risk patients; (6) placement of wireless pH monitoring; (7) prior to endoscopic or surgical antireflux procedures or after procedures in those with recurrent symptoms.[22]
- Note: noninflammatory GERD and major motor disorders may be missed by endoscopy.

Ambulatory Reflux Monitoring With or Without Impedance

- Useful for (a) patients not responding to acid suppression therapy when endoscopy is normal; (b) those with atypical / extrapyramidal symptoms; or (c) those contemplating surgery.
- Assesses the acid exposure time (AET) and frequency of reflux episodes and helps determine if symptoms are acid-related.
  - An AET of less than 4% is considered normal while greater than 6% is considered abnormal.[17]
  - Less than 40 reflux episodes in a 24-hour period is considered normal while more than 80 reflux episodes per 24-hour period is considered abnormal.
- Reflux sensitivity is defined as positive symptom association in the absence of breakthrough acid.[23]
- Monitoring without impedance measures only acid reflux (no nonacid reflux); adding impedance measures both acid and nonacid reflux
  - Testing patients off PPI therapy is recommended (1) to evaluate the AET in patients with normal endoscopy or low-grade esophagitis and no previously positive pH testing; (2) in those considering antireflux surgery.[17]
  - Testing patients on double-dose PPI therapy is recommended in patients with (1) prior Los Angeles grade C or D esophagitis; (2) long segment Barrett's esophagus; or (3) prior abnormal ambulatory pH monitoring. In these cases, pH-impedance monitoring is recommended to correlate refractory symptoms with reflux episodes or to identify inadequate acid suppression.

Manometry/High-Resolution Esophageal Pressure Topography (HREPT)

- Useful in those who have failed twice-daily PPI therapy with normal endoscopic findings to identify motor disorders, to evaluate peristaltic function in those who are candidates for antireflux surgery, and to assure proper placement of pH probes (the recent advancement of the tubeless pH monitoring system using endoscopic landmarks for placement may negate the need for manometry for ensuring proper placement of esophageal pH probes).

Impedance Manometry

- Evaluates bolus transit esophageal clearance/retention.
- Evaluates LES and upper esophageal sphincter pressures and peristalsis.

Empiric Proton Pump Inhibitor as a Diagnostic Test for GERD

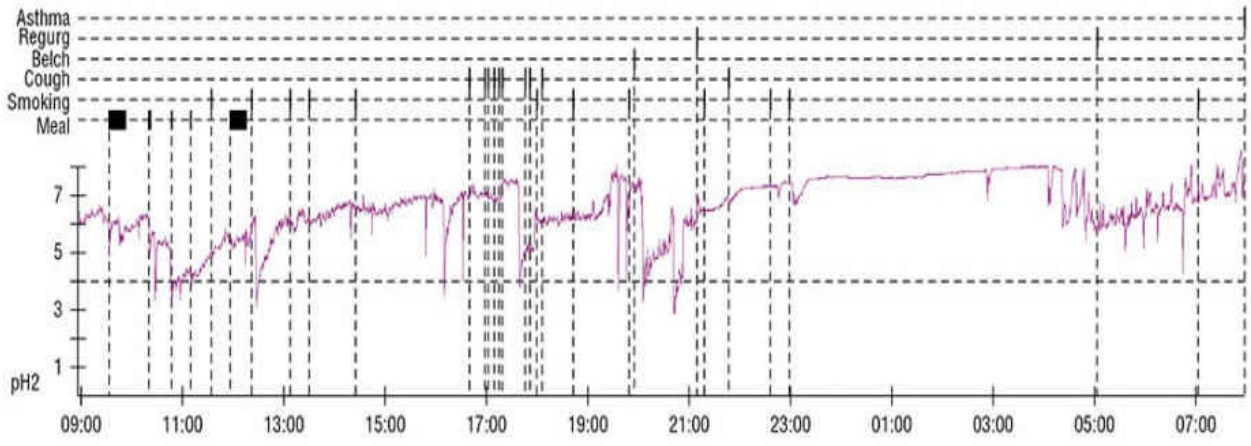
- Less expensive and more convenient than ambulatory reflux monitoring but lacks standardized dosing regimen and duration of the diagnostic trial.

Barium Radiography

- Not routinely used to diagnose GERD because it lacks sensitivity and specificity; cannot identify Barrett's esophagus. Can detect hiatal hernia.

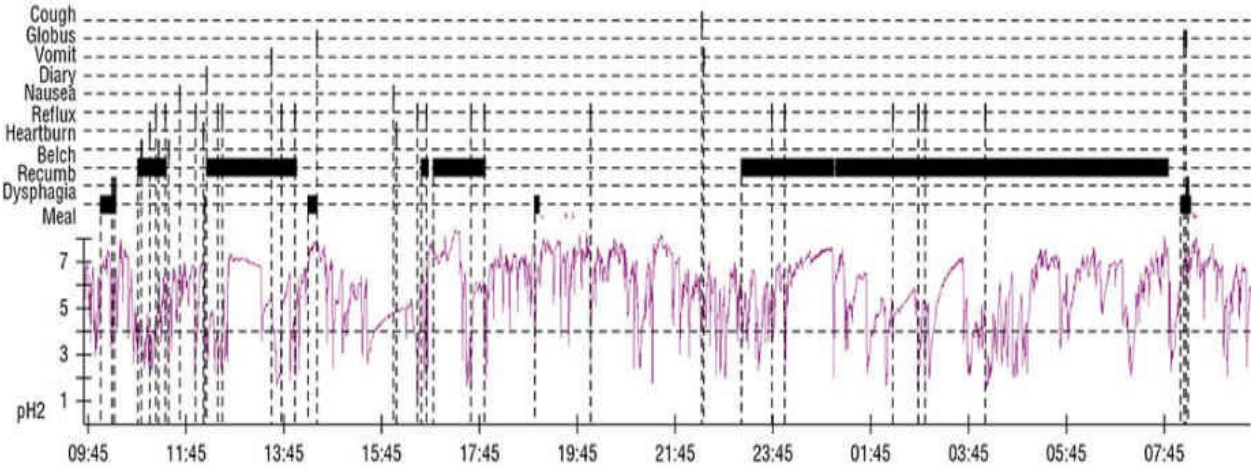
3 Whereas ambulatory reflux monitoring (24-hour pH monitoring) only measures acid reflux, combined impedance-pH monitoring measures both acid and nonacid reflux. Ambulatory reflux monitoring is performed by passing a small pH probe transnasally and placing it approximately 5 cm above the LES. Patients are asked to keep a diary of symptoms that later are correlated with the pH measurement corresponding to the time the symptom was reported (**Fig. 49-2**). Approximately 24 hours of data can be obtained using this method. The wireless pH monitoring involves attaching a radiotelemetry capsule to the esophageal mucosa. The advantages of this method are that a longer period of monitoring is possible (48-96 hours), it may demonstrate superior recording accuracy compared with some catheter designs, and it is more comfortable for the patient because a nasogastric tube is unnecessary.[1,17] Early referral for ambulatory pH monitoring may reduce cost compared to long duration trials of PPIs.[21]

A



Normal 24 hour ambulatory esophageal pH test						
	Total	Normal	Upright	Normal	Supine	Normal
• Fraction time pH <4 (%)	1.9	<4.2	1.9	<6.3	0%	<1.2
• Number of refluxes	81		81		0	
• Number of long refluxes (>5 min)	0		0		0	
• Duration of longest reflux (min)	2.3		2.3		0	
• Time pH <4 (min)	25.9		25.9		0	

B



Abnormal 24-hour ambulatory esophageal pH test						
	Total	Normal	Upright	Normal	Supine	Normal
• Fraction time pH <4 (%)	16	<4.2	10.6	<6.3	20.6	<1.2
• Number of refluxes	332		143		189	
• Number of long refluxes (>5 min)	10		6		4	
• Duration of longest reflux (min)	7.9		7.1		7.9	
• Time pH <4 (min)	220.5		66.8		153.7	

FIGURE 49-2 Graphical representation of a normal 24-hour ambulatory esophageal pH test profile in a healthy subject and a table summarizing key results (*A*) compared with an abnormal 24-hour ambulatory esophageal pH test (*B*) showing significant acid reflux (multiple events of pH drop below 4) and abnormal 24-hour profile in the table.

TREATMENT

Therapeutic modalities used in the treatment of gastroesophageal reflux are targeted at reversing the various pathophysiologic abnormalities.

Desired Outcomes

4 The goals of treatment are to (a) alleviate or eliminate the patient's symptoms, (b) decrease the frequency or recurrence and duration of gastroesophageal reflux, (c) promote healing of the injured mucosa, and (d) prevent complications. Therapy is directed at augmenting defense mechanisms that prevent reflux and/or decrease the aggressive factors that worsen reflux or mucosal damage. Therapy is directed at (a) decreasing the acidity of the refluxate; (b) decreasing the gastric volume available to be refluxed; (c) improving gastric emptying; (d) increasing LES pressure; (e) enhancing esophageal acid clearance; and (f) protecting the esophageal mucosa.

General Approach to Treatment

5 GERD treatment is determined by disease severity and includes: (a) lifestyle changes and patient-directed therapy with antacids, nonprescription H2RAs and/or nonprescription PPIs; (b) pharmacologic treatment with prescription-strength acid suppression therapy; (c) surgery; and (d) endoscopic therapies (**Table 49-2**).[1,24] The initial therapeutic modality used is in part dependent on the patient's condition (frequency of symptoms, degree of esophagitis, and presence of complications) (**Table 49-3**). A step-down approach, starting with a PPI, instead of an H2RA, is most often advocated. Once esophageal healing has occurred or symptoms improved, patients should be stepped down to the lowest effective dose of PPI or switched to an H2RA. The clinician should determine the most appropriate approach for the individual patient. Every attempt should be made to aggressively control symptoms and to prevent relapses early in the

course of the patient’s disease in order to prevent the complications. For patients with moderate-to-severe GERD, especially those with erosive disease, starting with a PPI as initial therapy is advocated because of its superior efficacy over H2RAs.

TABLE 49-2 Evidence-Based Treatment Recommendations for GERD in Adults[1,24]

Recommendation	Level of Evidence and Strength of Evidence[a]
Lifestyle Modifications	
• Weight loss in overweight GERD patients or those who have recently gained weight.	Moderate, Conditional
• Elevation of the head end of the bed and avoidance of food 2-3 hours before bedtime if nocturnal GERD symptoms present.	Low, Conditional
• Routine elimination of foods that can trigger reflux is not recommended in the treatment of GERD.	Low, Conditional
Acid Suppression Therapy	
• Therapy of choice for symptom relief and healing of erosive esophagitis is an 8-week PPI course. There is similar efficacy among all PPIs.	High, Strong
• For maximal pH control, delayed-release PPIs should be administered 30-60 minutes before meals.	Moderate, Strong
• PPIs should be started at once daily dosing prior to the first meal each day.	Moderate, Strong
• Patients with Barrett's esophagus can be treated similarly to those with GERD who do not have Barrett's esophagus.	Moderate, Strong
• Flexibility with meal time administration may be seen with newer PPIs (eg, dexlansoprazole).	Moderate, Conditional
• When clinically indicated, PPIs are considered safe in pregnancy.	Moderate, Conditional
• Adjustments of dose timing and/or twice daily dosing may be beneficial in patients with nighttime symptoms, variable schedules, and/or sleep disturbances who are partial responders to PPI therapy.	Low, Strong
• In patients with typical GERD symptoms who also have extraesophageal symptoms, a PPI trial is recommended.	Low, Strong
• Optimization of proton pump inhibitor therapy should be assessed in anyone with refractory GERD symptoms.	Low, Strong
• Increasing to twice daily dosing or switching PPI may be beneficial in partial responders to PPI therapy.	Low, Conditional
• Further evaluation is recommended for nonresponders to PPI therapy.	Low, Conditional
• If adverse effects occur with PPI, may consider switching to an alternative PPI.	Low, Conditional
• Patients with osteoporosis can use a PPI.	Moderate, Conditional
• Concern for hip fracture with PPI should be considered in those with osteoporosis AND other risk factors for hip fracture.	Moderate, Conditional
• PPIs are a risk factor for development of *Clostridium difficile*.	Moderate, Moderate
• PPIs are a risk factor for development of Community-Acquired Pneumonia with short-term use (but not long-term use).	Moderate, Conditional
• PPIs can be used in patients on clopidogrel and there is not an increased risk for adverse cardiovascular events.	High, Strong
Promotility Therapy and Other Nonacid Suppression Therapies	
• Prokinetic medications and/or baclofen should not be used to manage GERD without diagnostic evaluation.	Moderate, Conditional
• Sulcralfate is not generally recommended in nonpregnant GERD patients.	Moderate, Conditional
Maintenance Therapy	
• Maintenance therapy is recommended for (1) patients with continued symptoms after PPI discontinuation; (2) patients with complications including erosive esophagitis and Barrett's esophagus.	Moderate, Strong
• The lowest effective dose should be used when long-term PPI therapy is indicated for maintenance. Strategies such as on-demand and intermittent therapy may be beneficial.	Low, Conditional
• H2-receptor antagonists may be used as maintenance therapy in patients without erosive disease when the goal is heartburn relief.	Moderate, Conditional
Surgery	
• Surgery is a long-term treatment option in GERD patients.	High, Strong
• Surgery is not generally recommended in PPI nonresponders.	High, Strong
• Surgery is not generally recommended in patients with extraesophageal symptoms not responding to PPI therapy.	Moderate, Strong
• Endoscopic therapy or transoral incisionless fundoplication not recommended as alternative to medical or traditional surgical procedures.	Moderate, Strong
• Bariatric surgery (gastric bypass) should be considered in obese patients contemplating surgical therapy.	Moderate, Conditional

[a]Level of evidence per Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system: High = further research not likely to change authors' confidence in the estimate of effect; Moderate = further research would likely have an impact on the confidence in the estimate of effect; Low = further research would be expected to have an important impact on the confidence in the estimate of the effect and would be likely to change the evidence. Strength of evidence per GRADE system: Strong = desired effects of an intervention clearly outweigh the undesirable effects; Conditional = there is uncertainty about the trade-offs between desirable effects and undesirable effects.[1,24]

TABLE 49-3 Therapeutic Approach to GERD in Adults

Recommended Treatment Regimen	Brand Name	Oral Dose	Comments
Intermittent, mild heartburn (individualized lifestyle modifications + patient-directed therapy with antacids and/or nonprescription H_2RAs *or* nonprescription PPIs)			
Individualized lifestyle modifications			Lifestyle modifications should be individualized for each patient
Patient-directed therapy with antacids (≥12 years old)			
Magnesium hydroxide/aluminum hydroxide with simethicone	Maalox®	10-20 mL as needed or after meals and at bedtime	If symptoms are unrelieved with lifestyle modifications and nonprescription medications after 2 weeks, patient should seek medical attention; do not exceed 16 teaspoonfuls per 24 hours
Antacid/alginic acid	Gaviscon®	2-4 tablets or 10-20 mL after meals and at bedtime	Note: Content of alginic acid varies greatly among products; the higher the alginic acid the better (at least 500 mg)
Calcium carbonate	Tums®	500 mg, 2-4 tablets as needed	
Patient-directed therapy with nonprescription H2-receptor antagonists (up to twice daily) (≥12 years old)			
Cimetidine	Tagamet HB®	200 mg	If symptoms are unrelieved with lifestyle modifications and nonprescription medications after 2 weeks, patient should seek medical attention
Famotidine	Pepcid AC®	10-20 mg	
Nizatidine	Axid AR®	75 mg	
Ranitidine	Zantac®	75-150 mg	
Patient-directed therapy (>18 years old) with nonprescription proton pump inhibitors (taken once daily)			
Esomeprazole	Nexium® 24HR	20 mg	If symptoms are unrelieved with lifestyle modifications and nonprescription medications after 2 weeks, patient should seek medical attention
Lansoprazole	Prevacid® 24HR	15 mg	
Omeprazole	Prilosec OTC®	20 mg	
Omeprazole/sodium bicarbonate	Zegerid OTC®	20 mg/1,100 mg	
Symptomatic relief of GERD (individualized lifestyle modifications + prescription-strength H2-receptor antagonists *or* prescription-strength proton pump inhibitors)			
Individualized lifestyle modifications			Lifestyle modifications should be individualized for each patient
Prescription-strength H2RAs (for 6-12 weeks)			
Cimetidine (off-label use)	Tagamet®	400 mg four times daily or 800 mg twice daily	• For typical symptoms, treat empirically with prescription-strength acid suppression therapy • If symptoms recur, consider maintenance therapy. Note: Most patients will require standard doses for maintenance therapy
Famotidine	Pepcid®	20 mg twice daily	
Nizatidine	Axid®	150 mg twice daily	
Ranitidine	Zantac®	150 mg twice daily	
Prescription-strength PPIs (for 4-8 weeks)			
Dexlansoprazole	Dexilant®	30 mg once daily for 4 weeks	• For typical symptoms, treat empirically with prescription-strength acid suppression therapy • Patients with moderate-to-severe symptoms should receive a PPI as initial therapy • If symptoms recur, consider maintenance therapy
Esomeprazole	Nexium®	20-40 mg once daily	
Lansoprazole	Prevacid®	15 mg once daily	
Omeprazole	Prilosec®	20 mg once daily	
Omeprazole/sodium bicarbonate	Zegerid®	20 mg once daily	
Pantoprazole (Off-label use)	Protonix®	40 mg once daily	
Rabeprazole	Aciphex®	20 mg once daily	
Healing of erosive esophagitis or treatment of patients with moderate-to-severe symptoms or complications (individualized lifestyle modifications + high-dose H2-receptor antagonists *or* proton pump inhibitors *or* antireflux surgery)			
Individualized lifestyle modifications			Lifestyle modifications should be individualized for each patient
PPIs (up to twice daily for up to 8 weeks)			
Dexlansoprazole	Dexilant®	60 mg daily	• For extraesophageal or alarm symptoms, obtain endoscopy with biopsy to evaluate mucosa • If symptoms are relieved, consider maintenance therapy. PPIs are the most effective maintenance therapy for patients with extraesophageal symptoms, complications, and erosive disease. Start with twice-daily PPI therapy if reflux chest syndrome present • Patients not responding to pharmacologic therapy, including those with persistent extraesophageal symptoms, should be evaluated via manometry and/or ambulatory reflux monitoring
Esomeprazole	Nexium®	20-40 mg daily	
Lansoprazole	Prevacid®	30 mg once or twice daily	
Omeprazole	Prilosec®	20 mg once or twice daily	
Rabeprazole	Aciphex®	20 mg once or twice daily	
Pantoprazole	Protonix®	40 mg once or twice daily	

Recommended Treatment Regimen	Brand Name	Oral Dose	Comments
High-dose H2-receptor antagonists (for 8-12 weeks)			
Cimetidine	Tagamet®	400 mg four times daily or 800 mg twice daily	Note: If high-dose H_2RA needed, may consider using proton pump inhibitor to lower cost, increase convenience, and increase tolerability Note: Four times daily H_2RA is considered off-label use for Nizatidine
Famotidine	Pepcid®	20-40 mg twice daily	
Nizatidine	Aciphex®	150 mg two to four times daily	
Ranitidine	Zantac®	150 mg four times daily	
Interventional therapy			
Antireflux surgery Bariatric surgery Endoscopic therapies			

While weight loss in obese patients and elevation of the head end of the bed are beneficial for most GERD patients, recommending all lifestyle modifications to all patients is not recommended.[1] Instead, education on lifestyle modifications should be tailored to the individual needs of the patient. **Table 49-4** lists some of the lifestyle modifications that can be recommended on an individualized basis.

TABLE 49-4 Nonpharmacologic Treatment of GERD with Lifestyle Modifications[13]

- Elevate the head end of the bed (increases esophageal clearance). Use 6- to 8 in. (15-20 cm) blocks under the head side of the bed
- Weight reduction (reduces symptoms) in obese patients
- Avoid foods that may decrease lower esophageal sphincter pressure or increase transient lower esophageal sphincter relaxation (fats, chocolate, alcohol, peppermint, and spearmint)
- Include protein-rich meals in diet (augments lower esophageal sphincter pressure)
- Avoid foods that have a direct irritant effect on the esophageal mucosa (spicy foods, orange juice, tomato juice, and coffee)
- Behaviors that may reduce esophageal acid exposure
  - Eat small meals and avoid sleeping immediately after meals (sleep after 3 hours if possible; decreases gastric volume)
  - Stop smoking (decreases spontaneous esophageal sphincter relaxation)
  - Avoid alcohol (increases amplitude of the lower esophageal sphincter, peristaltic waves, and frequency of contraction)
  - Avoid tight-fitting clothes
  - Always take drugs in the sitting upright or standing position and with plenty of liquid, especially for those that have a direct irritant effect on the esophageal mucosa (eg, bisphosphonates, tetracyclines, quinidine, potassium chloride, iron salts, aspirin, nonsteroidal anti-inflammatory drugs)

6 Patients with typical GERD symptoms should be treated with lifestyle modifications as appropriate and a trial of empiric acid suppression therapy. Those who do not respond to empiric therapy or who present with alarm symptoms such as dysphagia, weight loss, or GI bleeding should undergo endoscopy.[25] Acid suppression therapy with PPIs or H2RAs is the mainstay of GERD treatment. Patients presenting with moderate-to-severe symptoms (with or without esophageal erosions) should be started on a PPI as initial therapy because it provides the most rapid symptomatic relief and healing in the highest percentage of patients.[1] H2-receptor antagonists in divided doses are effective for patients with milder GERD symptoms. However, when standard doses of H2RA therapy are not effective at relieving symptoms, it is considered more cost effective and efficacious to switch to a PPI.

Promotility agents (such as metoclopramide) are not as effective as acid suppression agents. Combining a promotility agent with acid suppression medications offer only modest improvements in symptoms over standard doses of H2RAs and should not be routinely recommended. In addition, the availability of a promotility agent that has an acceptable adverse effect profile is lacking. Mucosal protectants, such as sucralfate, have a limited role in the

treatment of GERD.

Maintenance therapy may be necessary to control symptoms and to prevent complications. For patients with more severe symptoms (with or without esophageal erosions) or for patients with other complications, maintenance therapy with a PPI is most effective. Routine use of combination therapy is not recommended in GERD maintenance therapy. In cases of refractory GERD, the diagnosis should be confirmed through further diagnostic tests before long-term, high-dose acid suppression therapy is considered.[1]

Nonpharmacologic Therapy

Nonpharmacologic treatment of GERD includes lifestyle modifications, antireflux surgery, bariatric surgery (in obese patients), and endoscopic therapies.

Lifestyle Modifications

The most common lifestyle modifications that a patient should be educated about include weight loss in obese patients and elevation of the head end of the bed, especially for those patients who have symptoms while in a recumbent position.[1] Other lifestyle modifications should be individualized based on the patient's specific situation. These include consumption of smaller meals and not sleeping for at least 3 hours after eating, avoidance of foods or medications that exacerbate GERD, smoking cessation, avoidance of tight-fitting clothes, and avoidance of alcohol (see Table 49-4).[13]

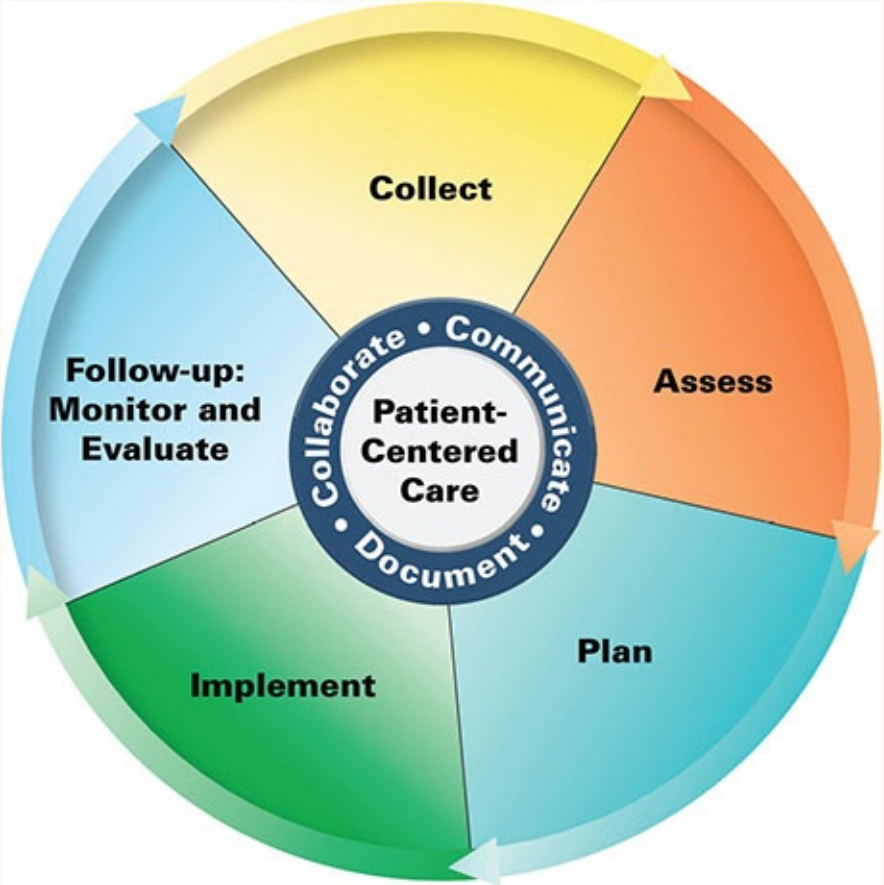
Obesity increases the risk of GERD symptoms and complications including Barrett's esophagus. There is a clear association between body mass index (BMI), waist circumference and weight gain.[1] Surprisingly, weight gain in those considered to have a normal BMI is also associated with new onset GERD symptoms.[1] Even more alarming is the potential association between BMI and cancer in the esophagus and gastric cardia.[1] A high-fat meal will decrease LES pressure for 2 hours or more postprandially. In contrast, a high-protein, low-fat meal will elevate LES pressure. A weight loss goal of at least 10% is recommended to help to improve GERD symptoms.[26]

Elevating the head end of the bed by approximately 6 to 8 in. (15-20 cm) with a foam wedge under the mattress (not just elevating the head with pillows) decreases nocturnal esophageal acid contact time and should be recommended. In general, anything that improves sleep hygiene may reduce GERD symptoms because transient LES relaxations are reduced during sleep.[27] Many foods have

been linked to worsening GERD symptoms; however, the evidence is weak for this association. Some foods decrease LES pressure (eg, fats and chocolates), while other foods can act as direct contact irritants to the esophageal mucosa (citrus juice, tomato juice, coffee, and pepper) (see Table 49-1).

Patient profiles should be evaluated to identify potential medications that may exacerbate GERD symptoms (see Table 49-1). Some medications decrease LES pressure, while other medications can act as direct contact irritants to the esophageal mucosa. Proper patient education can help prevent dysphagia or esophageal ulceration. Patients should be closely monitored for worsening symptoms when any of these medications are started. If symptoms worsen, alternative therapies may be warranted. The clinician must weigh the risks and benefits of continuing a medication known to worsen GERD and esophagitis.

Smoking can cause aerophagia (eg, air swallowing), which leads to increased belching and regurgitation. Smoking cessation has historically been recommended as an important lifestyle modification in the management of GERD patients; however, data are lacking to show that symptoms improve for patients who quit smoking and the current guidelines do not recommend this as an effective nonpharmacologic option for GERD. Nevertheless, patients with GERD should be encouraged to quit smoking because it may be a risk factor for Barrett's esophagus and esophageal adenocarcinoma.[14] Alcohol decreases LES pressure and may exacerbate symptoms such as heartburn.



Patient Care Process for the Management of Gastroesophageal Reflux Disease

Collect

- Patient characteristics (eg, age, race, sex, weight, body mass index, pregnant)
- Patient history (past medical, family, social, dietary habits, tobacco use)
- Health literacy and barriers to medication access
- Thorough history of prescription, nonprescription, and natural medication use
- Medication allergies and intolerances (include actual reaction to medication)
- Laboratory results for major organ function (eg, SCr to calculate CrCL, liver enzymes to assess hepatic function)

Assess

- Assess major organ function (eg, creatinine clearance, hepatic impairment)
- Determine the type, frequency, duration of symptoms, and identify exacerbating factors
- Identify alarm symptoms or extraesophageal symptoms that require further diagnostic evaluation by clinician (see section “Clinical Presentation”)
- Review lifestyle factors, including foods that may be contributing to symptoms (see Table 49-1)
- Review medication profile for medications that may be contributing to symptoms (see Table 49-1) and potential drug–drug interactions
- Assess what has been done so far (including medications and lifestyle modifications)
- Establish goals of therapy and if they are currently being met. (see section “Desired Outcomes”)
- Assess the appropriateness and effectiveness of current GERD regimen

Plan*

- Identify individualized lifestyle modifications that may improve symptoms (see Table 49-4)
- Determine appropriate therapy (may include both nonpharmacologic and pharmacologic) based on patient’s presentation (see Table 49-2)
- For pharmacologic therapy, include medication name, dose, route, frequency, and duration of therapy recommendation (see Table 49-3)
- Establish monitoring parameters for safety (eg, drug–drug, drug–food, drug–disease, and drug–lab interaction checking; short- and long-term adverse effects, and prevention of complications)
- Establish monitoring parameters for efficacy (eg, resolution of symptoms, improvement of symptoms, and healing of injured mucosa) (see Table 49-5)
- Identify patient education that may be needed (eg, purpose of medication, individualized lifestyle modifications, adverse effects, administration clinical pearls, adherence, potential need for long-term maintenance therapy, etc)
- For refractory symptoms, seek potential causes such as medication

adherence, timing of medication, drug interactions, etc

- Screen for symptoms that would require further diagnostic evaluation from clinician (eg, alarm symptoms, atypical symptoms, or complications)

Implement*

- Counsel patient on individualized lifestyle modifications that may improve symptoms (eg elevating head of the bed with a wedge, weight management, etc.) (see Table 49-4)
- Initiate appropriate nonpharmacologic and pharmacologic therapy based on patient presentation. (see Tables 49-2 and 49-3)
- Recommend additions, modifications, or discontinuations to therapy based on patient response
- Provide patient education with regard to disease state, lifestyle modifications, and treatment plan. Counsel patient on (a) what causes GERD and things to avoid; (b) when to take their medication (eg, 30 minutes before meal); (c) what potential adverse effects or drug interactions may occur
- Use motivational interviewing techniques to maximize medication adherence
- Schedule follow-up as appropriate

Follow-up: Monitor and Evaluate

- Follow-up after 8 to 16 weeks to assess effectiveness of acid-suppression therapy. Recommend alternative therapy when necessary
- Monitor patient for safety goals established above
- Evaluate the need for maintenance therapy based on patient presentation and response to therapy
- Assess improvement in quality-of-life measures such as physical, psychological, and social functioning and well-being
- Evaluate patient for the presence of adverse drug reactions, complications or new drug–drug interactions
- Stress the importance of medication adherence to treatment plan to patient as indicated

* *Collaborate with patient, caregivers, and other healthcare professionals.*

Many patients are noncompliant with lifestyle modifications, and even those who do comply generally continue to have symptoms that require acid suppression therapy. Nonetheless, it is important to regularly stress the potential benefits of lifestyle modifications that would benefit each individual patient.

Interventional Approaches

Interventional approaches include antireflux surgery, bariatric surgery, magnetic sphincter augmentation, and endoscopic therapies. These are discussed in more detail below.

Antireflux Surgery 7 The goal of antireflux surgery is to re-establish the antireflux barrier, to position the LES within the abdomen where it is under positive (intra-abdominal) pressure, and to close any associated defect in the diaphragmatic hiatus by reinforcing the crural muscles. Surgical intervention is a viable alternative treatment for select patients when long-term pharmacologic management is undesirable or when patients have complications. It is indicated when (1) long-term pharmacologic management is undesirable, (2) persistent proven GERD symptoms or esophageal mucosal damage despite appropriate pharmacologic therapy, and (3) significant esophagogastric junction disruption (eg, hiatal hernia).[17] The most common antireflux surgery performed is laparoscopic Nissen fundoplication. Patients should undergo ambulatory reflux pH monitoring and high resolution esophageal manometry prior to antireflux surgery.[27] Patients with typical symptoms who are responsive to PPIs and those with abnormal pH monitoring showing positive correlation with GERD symptoms show the most benefit from antireflux surgery while those with atypical or extraesophageal symptoms show a lower response to antireflux surgery. The major complications with antireflux surgery include gas bloat syndrome (inability to belch or vomit), dysphagia, vagal denervation, and splenic trauma. Long-term effectiveness of antireflux surgery is uncertain.[28]

Success of antireflux surgery in patients with PPI-refractory heartburn depends on careful screening and ruling out nonacid related causes of heartburn, such as eosinophilic esophagitis, achalasia, and biliary disease. The number of patients with truly refractory GERD is much smaller and laparoscopic Nissen fundoplication surgery is superior to continuing PPIs. More than two thirds of patients after anti-reflux surgery had more than a 50% improvement in symptoms at one year compared to just 28% with continued PPI use.[29]

Bariatric surgery, specifically Roux-en-Y gastric bypass, should be considered in obese patients (BMI greater than 35 kg/m^2) contemplating

surgery.[1] The consideration of bariatric surgery in obese patients for improvement of GERD symptoms is a result of the proposed difference in pathophysiology in this patient population. Abdominal pressure may play a greater role in the development of GERD in obese patients. Studies evaluating the effect of gastric banding procedures on GERD have shown mixed results, while studies have more consistently demonstrated the benefits of gastric bypass in the management of GERD in obese patients.[30]

Magnetic sphincter augmentation A ring of titanium-encased magnets can be surgically implanted at the esophagogastric junction to improve lower esophageal resistance and reduce symptoms of GERD.[19] Five-year results show long-term reduction in esophageal acid and symptom improvement with minimal complications.[31,32]

Endoscopic Therapies Endoscopic therapies are less invasive than surgical fundoplication and aim for a similar efficacy. Two endoscopic therapies are radiofrequency ablation [Stretta®] of the LES and endoscopic suturing of the LES (transoral incisionless fundoplication [EsophyX®]). Radiofrequency ablation is used for the management of Barrett's esophagus primarily when dysplasia is present and is recommended in patients with Barrett's esophagus with esophageal high-grade dysplasia. Current guidance also acknowledges radiofrequency ablation as a treatment option in low-grade dysplasia.[14] Transoral incisionless fundoplication creates a valve at the esophagogastric junction and is beneficial in patients with chronic GERD with abnormal pH test or low grade erosive esophagitis with either no hiatal hernia or a hiatal hernia less than or equal to 2 cm.[27] However, it was less effective than laparoscopic Nissen fundoplication.[33]

Pharmacologic Therapy

Pharmacologic treatment consists of a) patient-directed therapy with nonprescription antacids, H2RAs, or PPIs and b) prescription-strength acid suppression therapy or c) promotility medications.

Patient-Directed Therapy

Patient-directed therapy, where patients self-treat themselves with nonprescription medications, is appropriate for mild, intermittent symptoms. Patients with continuous symptoms lasting longer than 2 weeks should seek

medical attention.[25]

Antacids and Antacid–Alginic Acid Products Patients should be educated that antacids are an appropriate component of treating milder GERD symptoms, even though documentation of their efficacy in placebo-controlled clinical trials is lacking. Antacids may offer immediate symptomatic relief and help maintain the intragastric pH greater than 4, which decreases the activation of pepsinogen to pepsin, a proteolytic enzyme. The neutralization of gastric fluid may also lead to increased LES pressure. Patients who require frequent use of antacids for chronic symptoms should be treated with prescription strength acid suppression therapy.

Some antacid products are combined with alginic acid, which is not a potent neutralizing agent and does not enhance LES pressure; however, it does form a highly viscous solution or "raft" that floats on the surface of the gastric contents. This viscous solution serves as a protective barrier for the esophagus against reflux of gastric contents and reduces the frequency of the reflux episodes. The combination product may be superior to antacids alone in relieving the symptoms of GERD.[34] The alginic acid "raft" can adapt to the acid pocket, continuously floating above newly secreted acid near the esophagogastric junction. The combination product may be superior to antacids alone in relieving the symptoms of GERD. There was a significant benefit favoring alginate therapy when compared to antacids in GERD; however, with moderate heterogeneity.[35] Alginate may also improve symptoms in patients on once daily PPI still having residual reflux symptoms.[36] Efficacy data indicating endoscopic healing are lacking. There are many Gaviscon® products with varying amounts of alginic acid. Some of the Gaviscon® products contain lower amounts of alginic acid or list alginic acid under inactive ingredients with no amounts specified. Products with a higher alginic acid component (such as Gaviscon Advance® and Gaviscon Double-Action®) are preferred (eg, 500 mg). Patients should be encouraged to check medication labels for ingredients.

Antacid or antacid combination products interact with a variety of medications by altering gastric pH, increasing urinary pH, adsorbing medications to their surfaces, providing a physical barrier to absorption, or forming insoluble complexes with other medications. Antacids have clinically significant drug interactions with tetracycline, ferrous sulfate, isoniazid, sulfonylureas, and quinolone antibiotics. Antacid–drug interactions are influenced by composition, dose, dosage schedule, and formulation of the antacid. They may also cause constipation or diarrhea depending on the

magnesium or aluminum content.

Dosage recommendations for antacids in the management of GERD are somewhat difficult to derive from the literature. Doses range from hourly to an as-needed basis (see Table 49-3). In general, antacids have a short duration of action, which necessitates frequent administration throughout the day to provide continuous neutralization of acid. Taking antacids after meals can increase the duration of action from about 1 to 3 hours; however, nighttime acid suppression cannot be maintained with bedtime doses.

Nonprescription H2-Receptor Antagonists and Proton Pump Inhibitors Nonprescription H2-receptor antagonists (cimetidine, famotidine, nizatidine, and ranitidine) are effective in diminishing gastric acid secretion when taken prior to meals and decrease GERD symptoms associated with exercise. Antacids may have a slightly faster onset of action, while the H2RAs have a much longer duration of action compared with antacids.

The PPIs esomeprazole, omeprazole (alone or combined with sodium bicarbonate) and lansoprazole are available without a prescription for the short-term treatment of heartburn. Patients who do not respond to lifestyle modifications and patient-directed therapy after 2 weeks should be seen by their clinician.[25]

Acid Suppression Therapy

8 Acid suppression is the mainstay of GERD treatment. Proton pump inhibitors provide the greatest symptom relief and the highest healing rates, especially for patients with erosive disease, moderate-to-severe symptoms, or complications.

Proton Pump Inhibitors Proton pump inhibitors (dexlansoprazole, esomeprazole, lansoprazole, omeprazole [with or without sodium bicarbonate], pantoprazole, and rabeprazole) block gastric acid secretion by inhibiting gastric H^+/K^+-adenosine triphosphatase in gastric parietal cells. This produces a profound, long-lasting antisecretory effect capable of maintaining the gastric pH greater than 4, even during postprandial acid surges. A correlation exists between the percentage of time the gastric pH remains greater than 4 during the 24-hour period and healing erosive esophagitis.

The efficacy is similar among all of the PPIs.[27] Symptomatic relief is seen in approximately 83% of patients with endoscopic evidence of injury after 8 weeks treated with a PPI, whereas the endoscopic healing rate at 8 weeks is 78%.[1]

Symptom response to NERD is less robust with approximately 60% of patients experiencing complete relief with PPI therapy.[1] PPIs are superior to H2RAs in treating patients with moderate-to-severe GERD and should be given empirically to those with troublesome symptoms. This includes not only patients with esophageal tissue injury (eg, Barrett's esophagus, strictures, or esophagitis) but also patients with symptom-based GERD syndromes. Patients with uncomplicated GERD who respond well to a short-term course of PPI therapy should attempt to discontinue or to lower to the lowest effective dose.[37] Rebound acid hypersecretion occurred when PPIs were withdrawn after 8 weeks of PPI therapy in healthy volunteers making potential withdrawal of PPI difficult. One suggested strategy to minimize this effect is to taper the PPI over 3 to 8 weeks.[38] While no specific tapering regimen is recognized, strategies could include administering PPI every other day for two weeks then twice weekly for two to three weeks then once weekly; or alternating PPI with an H2RA each month for three months then switch off of the PPI. Others have advocated lowering the dose by going from twice daily to once daily or halving the dose; or stopping the PPI and use more of an "on-demand" regimen.[39] Unfortunately, data are lacking on tapering strategies for PPIs.

Twice-daily PPI use is indicated in those not responding to a standard once daily course of therapy. Before increasing the frequency to twice daily, optimization of PPI therapy should be assessed (eg, taken 30-60 minutes prior to largest meal each day). In patients who are partial responders to initial PPI therapy, a trial of an alternative PPI may also be considered. Either strategy (twice-daily PPI or switching to an alternative PPI) have resulted in about a 20% improvement in symptoms with neither strategy demonstrating a clear advantage.[1] Partial response may also be due to abnormal patient perception, altered motility or impaired LES dynamics where adjunctive therapy addressing the underlying cause may be helpful.[40] Patients with Barrett's esophagus should be treated similarly to patients without Barrett's esophagus.[1] Further diagnostic evaluation is indicated for patients not responding to twice daily PPI therapy.

The most common adverse effects associated with PPIs include headache, diarrhea, nausea, and abdominal pain. Increasing concerns regarding PPI safety have been reported in the literature. Community-acquired pneumonia has been reported with short-term use in GERD patients.[1] Enteric infections, vitamin B_{12} deficiency, hypomagnesemia, and bone fractures are potential long-term adverse effects associated with PPIs (**Table 49-5**).[37,41–43] Gastric acidity plays an important role in the absorption of minerals such as calcium and magnesium, as

well as with vitamin B_{12}. While PPIs have not been shown to have a direct effect on the pH in the colon, they do have a downstream effect on colonic bacteria increasing the risk for *Clostridium difficile* infections.[37] There is no evidence to support the use of probiotics in patients on long-term PPIs to prevent infection.[37] Despite potential concerns, data are lacking to recommend calcium, vitamin B_{12}, or magnesium intake above the recommended daily allowance unless there are other risk factors that warrant additional supplementation. Likewise, routine screening or monitoring of bone mineral density, serum creatinine, magnesium or vitamin B_{12} levels are not recommended just because the patient is on long-term PPI therapy.[37] Other concerns, include chronic kidney disease and end stage renal disease. Proposed mechanisms for kidney injury include repeated bouts of acute interstitial nephritis, concurrent NSAD use, diabetes, and hypomagnesemia. Chronic kidney disease occurred in 3.68% of patients started on a PPI over a 5-year period compared to 2.56% in patients on an H2RA (HR = 1.28). End stage renal disease occurred in 0.04% of PPI users compared with 0.026% of H2RA users over a 5-year period. (HR = 1.96).[44]

TABLE 49-5 Drug Monitoring[37,41–43]

Drug	Adverse Drug Reaction	Monitoring Parameter	Comments
Antacids			
• Magnesium hydroxide/ aluminum hydroxide • Antacid/alginic acid • Calcium carbonate	• Diarrhea or constipation (depending on product) • Alterations in mineral metabolism • Acid–base disturbances	• Periodic calcium and phosphate levels in patients on chronic therapy	• Use caution with aluminum- and calcium-containing antacids in patients with renal impairment • Aluminum-containing antacids may bind to phosphate in the gut and lead to bone demineralization
H2-Receptor Antagonists			
• Cimetidine • Famotidine • Nizatidine • Ranitidine	• Headache, somnolence, fatigue, dizziness, and either constipation or diarrhea	• Monitor for CNS effects, especially in the elderly • Monitor vitamin B_{12} serum concentrations in those on chronic, long-term therapy or in those on higher doses	• May see increased CNS effects (rare) in those over 50 years of age or in those with renal or hepatic dysfunction • May be associated with vitamin B_{12} deficiency with longer duration therapy and in higher doses
Proton Pump Inhibitors			
• Dexlansoprazole • Esomeprazole • Lansoprazole • Omeprazole • Omeprazole/ sodium bicarbonate • Pantoprazole • Rabeprazole	*Most common adverse effects:* • Headache, dizziness, somnolence, diarrhea, constipation, flatulence, abdominal pain, and nausea *Other important adverse effects:* • Enteric infections (*C. difficile* infections) • Increased risk of pneumonia *Long-term adverse effects:* • Hypomagnesemia • Bone fractures • Vitamin B_{12} deficiency	• Number and type of diarrhea episodes • Periodic magnesium levels warranted in those on higher doses or who are on therapy for greater than 1 year • Routine bone density studies or calcium supplementation should only be considered if other risk factors for osteoporosis or bone fractures are present • Respiratory symptoms within first 30 days of therapy • Periodic vitamin B_{12} serum concentration with long-term use	• Acid suppression may result in loss of host defense against ingested spores and bacteria permitting a higher burden of exposure • Hypomagnesemia is uncommon but can be life-threatening; has been seen as soon as 3 months after starting therapy but more likely in those on PPIs greater than 1 year • May increase risk for osteoporosis-related fractures of the hip, wrist or spine; Most common with high-dose (eg, multiple daily doses) and long-term use (eg, ≥1 year) Patients with known osteoporosis can remain on proton pump inhibitor • PPIs may inhibit secretion of intrinsic factor, which potentially can lead to vitamin B_{12} deficiency; this is not common and usually associated with use for >3 years • May increase risk of community-acquired pneumonia, particularly within the first 30 days of therapy

In one study, dysmotility and PPI use were independent risk factors for not only small intestinal bacterial overgrowth, but also small intestinal fungal overgrowth.[45] Significant liver impairment resulted in a sevenfold to ninefold increase in area under the serum concentration versus time curve and increased serum half-life of PPIs. While clear recommendations are not available, it may be prudent to consider a lower dose of PPIs in patients with liver impairment. The risk of dementia or cognitive decline in patients receiving PPIs has raised concerns in the lay press; however, the evidence for this association is weak.

While most of this data on these adverse events are from observational studies and results have been variable, overuse of PPI should still be minimized as the clinical implications of chronic therapy are better elucidated. Best practice advice from the American Gastroenterology Association states there is no convincing evidence to rank PPI formulations on potential risks.[37] More importantly, changing the paradigm to a more individualized approach to diagnosing GERD has been advocated based on careful assessment of anatomy, motor function, reflux burden and symptomatic phenotype as a strategy to reduce the overuse of PPIs.[17]

Drug interactions with the PPIs vary slightly with each agent. All PPIs can decrease the absorption of medications such as ketoconazole or itraconazole, which require an acidic environment to be absorbed. Concerns have been raised regarding the concomitant use of PPIs, particularly omeprazole, with clopidogrel since it is the strongest inhibitor of CYP2C19.[46,47] Clopidogrel, a prodrug, is converted to its active metabolite via the CYP2C19 and CYP3A4 enzymes. Inhibition of CYP2C19 by PPIs, specifically omeprazole, may decrease the effectiveness of clopidogrel. Careful review of the risk-to-benefit profile regarding the use of PPIs for patients on clopidogrel should be considered. Selection of a PPI with less inhibition of CYP2C19 may limit the risk of interaction with clopidogrel.

Another consideration, particularly with omeprazole, are potential polymorphic gene variations seen in the hepatic activity of CYP2C19. This is especially true for patients who are considered “slow metabolizers” of omeprazole, which is more common in the Asian population but also found in approximately 3% of the white population. Unfortunately, it is unclear which patients have the polymorphic gene variation that makes them slow metabolizers. Like omeprazole, the metabolism of esomeprazole may also be altered for patients with this polymorphic gene variation. Despite these concerns, there are certain patients with upper GI bleeding or those with multiple risk factors for GI bleeding who require antiplatelet therapy would benefit from PPI therapy. Risk factors for GI bleeding include advanced age, use of anticoagulants, steroids or nonsteroidal anti-inflammatory drugs, presence of *Helicobacter pylori*, or previous history of bleeding or peptic ulcer disease complications.[48] For patients on clopidogrel, using an alternative acid suppression agent, such as an H2RA or a PPI other than omeprazole and esomeprazole or using an alternative antiplatelet agent may be an acceptable alternative if there are concerns.

The PPIs degrade in acidic environments and are therefore formulated in a

delayed-release capsule or tablet formulation. Dexlansoprazole, esomeprazole, lansoprazole, and omeprazole contain enteric-coated (pH-sensitive) granules in a capsule form. Dexlansoprazole is unique in that the capsule is a dual delayed-release formulation, with the first release occurring 1 to 2 hours after the dose and the second release occurring 4 to 5 hours after the dose. The clinical significance of this dual release is to allow the medication to have a longer lasting benefit, at least 16 to 18 hours. While there is little data on a role in refractory GERD for this unique delayed-release formulation, 88% of patients with well-controlled GERD symptoms on twice daily PPI therapy maintained symptom control upon transition to dexlansoprazole.[49] Patients taking pantoprazole or rabeprazole should be instructed not to crush, chew, or split the delayed-release tablets.

For patients who are unable to swallow the capsule or for pediatric patients, there are several alternative administration methods available. The contents of the delayed-release capsules can be mixed in applesauce or placed in orange juice. If a patient has a nasogastric tube, the contents of an omeprazole capsule can be mixed in 8.4% sodium bicarbonate solution. Esomeprazole granules can be dispersed in water. Esomeprazole, omeprazole, and pantoprazole are also available in a delayed-release oral suspension powder packet, while dexlansoprazole and lansoprazole is available as a delayed-release, orally disintegrating tablet. Two 30 mg dexlansoprazole orally disintegrating tablets is not interchangeable with one 60 mg orally disintegrating tablet. Rabeprazole is available in a capsule sprinkle that can be opened and placed in a small amount of soft food such as applesauce. Esomeprazole and pantoprazole are available in an IV formulation, which offers an alternative route of administration for patients who are unable to take an oral PPI. Importantly, the IV product is not more efficacious than oral PPIs and is significantly more expensive. Careful patient selection is necessary to avoid the increased cost from the use of the IV product.

Omeprazole is also available in a delayed-release tablet and in a combination product with sodium bicarbonate in an immediate-release capsule and oral suspension (Zegerid®). This is the only immediate-release PPI and it should be taken on an empty stomach at least 1 hour before a meal. Zegerid® powder for oral suspension offers an alternative to the delayed-release capsules, or IV formulation in adult patients with a nasogastric tube. The Zegerid® capsule should be swallowed whole and not opened, sprinkled on food, or administered via nasogastric tube. The 20 and 40 mg Zegerid® capsules have the same amount of sodium bicarbonate so two 20 mg capsules cannot be substituted for a 40 mg

capsule.

Patients should be instructed to take their PPI in the morning, 30 to 60 minutes before breakfast or before their biggest meal of the day, to maximize efficacy, because these agents inhibit only actively secreting proton pumps. Dexlansoprazole can be taken without regards to meals. Patients with nocturnal symptoms may benefit from taking their PPI prior to the evening meal. If dosed twice daily, the second dose should be administered approximately 10 to 12 hours after the morning dose and prior to a meal or snack.

H2-Receptor Antagonists H2RAs (cimetidine, famotidine, nizatidine, and ranitidine) in divided doses are effective in treating patients with mild-to-moderate GERD.[1] The majority of the trials assessing the efficacy of standard doses of H2RAs indicate that symptomatic improvement is achieved in an average of 60% of patients after 12 weeks of therapy.[25] However, endoscopic healing rates tend to be lower, an average of 50% of patients at 12 weeks.[25]

The efficacy of H2RAs in the management of GERD is extremely variable and is frequently lower than desired. Response to the H2RAs is dependent on the (a) severity of disease, (b) dosage regimen used, and (c) duration of therapy. These factors are important to keep in mind when comparing clinical trials and/or assessing a patient's response to therapy. The severity of esophagitis at baseline has a profound impact on the patient's response to H2RAs. For symptomatic relief of mild GERD, low-dose, nonprescription H2RAs or standard doses given twice daily may be beneficial. Patients who do not respond to standard doses may be hypersecreters of gastric acid and will require higher doses. Although higher doses of H2RAs may provide higher symptomatic and endoscopic healing rates, limited information exists regarding the safety of these regimens, and they can be less effective and more costly than once-daily PPIs. Unlike duodenal ulcer disease, in which the duration of therapy is relatively short (eg, 4-6 weeks), prolonged courses of H2RAs are frequently required in the treatment of GERD.

Because all of the H2RAs have similar efficacy, selection of the specific agent to use in the management of GERD should be based on factors such as differences in pharmacokinetics, safety profile, and cost. Patients should be monitored for the presence of adverse effects, as well as potential drug interactions, especially when on cimetidine. Cimetidine may inhibit the metabolism of theophylline, warfarin, phenytoin, nifedipine, and propranolol, among others. An alternate H2RA should be selected if the patient is on any of these medications. Headache, fatigue, dizziness, and constipation/diarrhea are the most common adverse effects associated with the use of H2RAs.

Promotility Agents

Promotility agents may be useful as an adjunct to acid suppression therapy for patients with a known motility defect (eg, LES incompetence, decreased esophageal clearance, and delayed gastric emptying). Unfortunately, all available promotility agents are fraught with undesirable adverse effects and are not generally as effective as acid suppression therapy.

Metoclopramide Metoclopramide, a dopamine antagonist, increases LES pressure in a dose-related manner and accelerates gastric emptying in gastroesophageal reflux patients. However, it does not improve esophageal clearance. Metoclopramide provides symptomatic improvement for some patients with GERD; however, substantial data supporting endoscopic healing are lacking. In addition, metoclopramide's adverse effect profile, including extrapyramidal effects, tardive dyskinesia, and other CNS effects, limits its usefulness in treating many patients with GERD. The risk of adverse effects is much greater for elderly patients and for patients with renal dysfunction because the drug is primarily eliminated by the kidneys. Contraindications include Parkinson's disease, mechanical obstruction, concomitant use of other dopamine antagonists or anticholinergic agents, and pheochromocytoma.

Bethanechol Bethanechol, a promotility drug, has limited value in the treatment of GERD because of unwanted adverse effects, such as urinary retention, abdominal discomfort, nausea, and flushing. It is not routinely recommended for the treatment of GERD.

Other Promotility Drugs Under Investigation Other promotility drugs under investigation include domperidone and baclofen. Because domperidone does not cross the blood–brain barrier, it does not cause the CNS effects seen with metoclopramide. However, it is not currently available in the United States. Baclofen, a gamma aminobutyric acid (GABA) receptor type B agonist, may decrease esophageal acid exposure and the number of reflux episodes by decreasing the number of transient relaxations of the LES. This may help limit the extension of the "acid pocket" into the distal esophagus by increasing the postprandial LES pressure.[50] However, this agent has many adverse effects, limiting its usefulness in GERD. Other GABA type B agonists, as well as metabotropic glutamate type 5 (mGluR5) receptor antagonists are under development as potential prokinetic agents; however their effectiveness has not been promising to date.[51]

Mucosal Protectants

Sucralfate, a nonabsorbable aluminum salt of sucrose octasulfate, has limited value in the treatment of GERD. It may not be useful in the routine treatment of acid reflux but may be useful in the management of radiation esophagitis and bile or nonacid reflux GERD.

Combination Therapy

Combination therapy with an acid suppression agent and a promotility agent or a mucosal protectant agent would seem logical given the multifactorial nature of the disease, particularly in light of the disappointing results seen with many monotherapy regimens. However, data to support combination therapy are limited, and this approach should not routinely be recommended unless a patient has GERD plus motor dysfunction occurring. The effectiveness of the addition of an H2RA at bedtime to PPI therapy for the treatment of nocturnal symptoms may decrease over time due to tachyphylaxis with H2RAs. Therefore, “as needed” use of bedtime H2RA may be a more appropriate approach if combination with a PPI is deemed necessary. Using the omeprazole–sodium bicarbonate immediate-release product in addition to once-daily proton pump inhibitors may offer an alternative for nocturnal GERD symptoms.

Maintenance Therapy

9 Many patients with GERD will relapse if medication is withdrawn; so long-term maintenance treatment may be required. A PPI is the drug of choice for maintenance of patients with moderate-to-severe GERD, erosive disease, or other complications such as Barrett’s esophagus. Patients who have symptomatic relapse following discontinuation of therapy or lowering of medication doses, including patients with complications such as Barrett’s esophagus, strictures, or erosive esophagitis, should be considered for long-term maintenance therapy to prevent complications or worsening of esophageal function.[15]

In patients with uncomplicated GERD who respond to short-term PPI therapy, lowering the PPI dose or discontinuing the PPI should be considered. If this is not possible, ambulatory esophageal reflux pH/impedance monitoring should be performed to assure symptoms are GERD-related and not due to a functional syndrome prior to committing to lifelong PPI use.[37] Patients receiving chronic PPI therapy should be periodically evaluated to assure the lowest possible effective dose is used.[52,37] The goal of maintenance therapy is to improve quality of life by controlling the patient’s symptoms and preventing complications.

Patients should be counseled on the importance of complying with lifestyle changes and long-term maintenance therapy in order to prevent recurrence or worsening of disease. H2-receptor antagonists may be effective maintenance therapy for patients with mild disease.[1] Low doses of a PPI or alternate-day dosing may be effective in some patients with mild symptoms, thereby allowing dose reduction in some cases. “On-demand” or intermittent maintenance therapy, by which patients take their PPI only when they have symptoms, may be effective for patients with endoscopy-negative GERD.[1,27] Although not well studied, many patients with only mild-to-moderate symptoms may decide on their own to use “on-demand” for the financial benefit and patient satisfaction.[27] However, patients with persistent symptoms and/or complications generally require standard doses of PPIs.

Metoclopramide is not approved for maintenance therapy, and its use is limited by adverse effect profile. Antireflux surgery may also be considered a viable alternative to long-term drug therapy for maintenance of healing for patients who are candidates.

Maintenance Therapy with H_2-Receptor Antagonist The studies evaluating the efficacy of the H2RAs in maintaining GERD patients in remission have been disappointing. Currently, ranitidine 150 mg twice daily is the only H2RA regimen that is FDA approved for maintenance of healing of erosive esophagitis.

Maintenance Therapy with Proton Pump Inhibitors Long-term use of the PPIs is associated with adverse effects such as hypomagnesemia, enteric infections, and risk for bone fractures; however, there is no evidence of carcinoid tumors directly linked to their use. Prolonged hypergastrinemia leading to the development of colonic polyps, and potentially adenocarcinoma, was also a concern that has proven unfounded with long-term use.

The role of *H. pylori* status for patients with GERD is uncertain. As a consequence of the controversy surrounding *H. pylori* and GERD, specific guidelines on how to handle patients who are *H. pylori* positive are lacking. Most clinicians would probably opt to eradicate *H. pylori* infections once detected. However, routine screening for *H. pylori* is not recommended as part of the diagnosis and management of GERD. Further studies are needed to determine the role of *H. pylori* for patients with GERD.

Special Populations

There are several special populations that should be considered when discussing

GERD, such as patients with extraesophageal symptoms, pediatric patients, elderly patients, and patients with refractory symptoms.

Patients with Extraesophageal GERD

Extraesophageal symptoms (such as asthma, laryngitis, or chest pain) should prompt investigation for other possible causes outside of GERD. Because there are many causes of asthma and laryngeal symptoms, a concomitant esophageal GERD syndrome must also be present to associate these symptoms with GERD. A trial of PPI therapy is recommended for those with extraesophageal symptoms with concurrent typical GERD symptoms. Patients with extraesophageal symptoms without the presence of typical GERD symptoms should undergo ambulatory esophageal reflux monitoring prior to initiation of PPI therapy. If symptoms continue, patients should be evaluated with manometry, ambulatory esophageal reflux monitoring, or impedance–pH monitoring to rule out dysmotility or refractory symptoms.[1] The optimal dose of proton pump inhibition is not well-defined. For patients not responding to empiric therapy, ambulatory reflux monitoring may be beneficial in determining acid exposure as it relates to symptoms and should be performed prior to committing the patient to lifelong PPI use. Maintenance therapy is generally indicated for patients who respond to the therapeutic trial or have endoscopic evidence of reflux. Antireflux surgery may be an option in select patients but is generally not recommended for management of extraesophageal symptoms that persist despite PPI therapy.

In patients with chronic cough suspected to be reflux related, lifestyle modifications are recommended.[53] Acid suppression therapy is unlikely to be beneficial if heartburn or regurgitation is not also present. If the patient does have concomitant heartburn or regurgitation with a chronic cough, PPI therapy may be beneficial but may take up to 3 months before resolution of cough.[53] After 3 months, more diagnostic evaluation is needed.

Pediatric Patients with GERD

Many infants have physiologic reflux with little or no clinical consequence. Uncomplicated gastroesophageal reflux usually manifests as regurgitation or “spitting up” and resolves without incident by about 12 months of life.[9] It usually responds to supportive therapy, including dietary adjustments, postural management, and reassurance for the parents. Thickened feedings may be useful in milder cases. While this does not decrease reflux episodes, it may decrease the incidence of regurgitation.[9] This strategy of thickening feedings may be

appropriate for full-term infants; however, may be associated with necrotizing enterocolitis in preterm infants. Chronic vomiting associated with gastroesophageal reflux must be distinguished from other causes, such as neurologic, metabolic, eating, and rumination disorders. Smaller, more frequent feedings may be beneficial. In formula-fed infants, an extensively hydrolyzed protein may help identify milk protein sensitivity as the cause of unexplained GERD-like symptoms, likewise, exclusion of milk and eggs in the maternal diet for breastfeeding infants may be appropriate.[9]

Developmental immaturity of the LES is one suspected cause of gastroesophageal reflux in infants. Like adults, transient LES relaxations seem to be the most common cause of gastroesophageal reflux in children. Other causes include impaired luminal clearance of gastric acid, neurologic impairment, and type of infant formula. Complications, although rare, include distal esophagitis, failure to thrive, esophageal peptic strictures, Barrett's esophagus, and pulmonary disease. Further diagnostic evaluation is indicated in all who experience apnea or an apparent life-threatening event.

The benefits of using promotility medications, such as metoclopramide, erythromycin, bethanechol, and baclofen, are outweighed by the potential adverse effects that may occur and, therefore, cannot be routinely recommended.[9] Careful consideration should be made before medication is recommended, especially in children younger than 1 year of age. Overprescribing of acid suppression therapy may lead to increased risk of infection and other adverse effects in premature infants.[54,55] When medication is deemed necessary, ranitidine is commonly used at a dose of 5 to 10 mg/kg/d in 2 to 3 divided doses in pediatric patients aged 1 month to 16 years.[9] Tachyphylaxis may develop making the effectiveness of H2-receptor antagonists less than optimal.

Proton pump inhibitor use in children is increasing, especially in those with esophagitis. Most patients will respond to once-daily PPI dosing. **Table 49-6** details indications and dosing of PPIs in pediatric patients. Dexlansoprazole and pantoprazole have not been adequately studied in younger pediatric patients. When examining adverse effect data from currently available trial data the authors noted that overall PPI therapy was well tolerated with mostly mild-to-moderate adverse effects in the short-term. Adverse effects with individual agents included diarrhea, abdominal pain, and vomiting with headache noted in older age groups and upper and lower respiratory tract infections noted in infants. Additional long-term data is needed in this population especially in infants younger than 1 year of age.[56] Long-term use of a PPI without a clear

diagnosis of GERD is not recommended.[9]

TABLE 49-6 Oral Proton Pump Inhibitor Therapy in Pediatric Patients

Drug	Indication	Age	Recommended Oral Dose (daily)	
Dexlansoprazole	GERD, erosive esophagitis	≥12 years		30 mg
		≥12 years		60 mg
		12-17 years		30 mg
Esomeprazole	Erosive esophagitis	1 month–1 year	3-5 kg	2.5 mg
			>5-7.5 kg	5 mg
			>7.5	10 mg
		1-11 years	<20 kg	10 mg
			≥20 kg	10-20 mg
		≥12 year		20-40 mg
	Symptomatic GERD	1-11 years		10 mg
		>12 years		20 mg
Lansoprazole	Symptomatic GERD, erosive esophagitis	1-11 years	≤30 kg	15 mg
			>30 kg	30 mg
	Erosive esophagitis	≥12 year		30 mg
	Symptomatic GERD	≥12 year		15 mg
Omeprazole	GERD, maintenance of healing of erosive esophagitis	≥1 year	5 to <10 kg	5 mg
			10 to <20 kg	10 mg
			≥20 kg	20 mg
Pantoprazole	Erosive esophagitis	≥5 years	≥15 to <40 kg	20 mg
			≥40 kg	40 mg
Rabeprazole	GERD	1-11 years	<15 kg	5-10 mg
			≥15 kg	10 mg
		≥12 years		20 mg

Elderly Patients with GERD

Many elderly patients have decreased host defense mechanisms, such as saliva production. In addition, they have more comorbidities, medications, and physiologic changes that put them at higher risk. Often these patients do not seek medical attention because they feel their symptoms are part of the normal aging process. They may also present with atypical symptoms such as chest pain,

asthma, poor dentition, or jaw pain. Decreased GI motility is a common problem in elderly patients. Unfortunately, there are no good promotility agents available to these patients. Elderly patients are especially sensitive to the CNS effects of metoclopramide. They may also be sensitive to the CNS effects of H2RAs. Proton pump inhibitors appear to be the most useful treatment modality because they have superior efficacy and are dosed once daily, which is beneficial in all patients, but is especially beneficial in the elderly. Long-term risk of bone fractures may be of concern in this population. Patients at risk for bone fractures should be monitored appropriately.

Patients with Refractory GERD

What constitutes refractory GERD is not well-defined. Prior to increasing the dose to twice daily, adherence and proper timing of PPI therapy should be optimized. Refractory GERD should be considered in patients who have not responded to a standard course of twice-daily PPI therapy over a 12 week period. Variations in drug metabolism in certain patients may contribute to refractory GERD. Switching to another PPI or increasing the dose to twice daily may be beneficial; however, the latter may reduce compliance.[27] Re-educating patients regarding lifestyle modifications is recommended.[27] Manometry or ambulatory esophageal reflux monitoring is useful for patients who are not responding to therapy who have normal endoscopic findings.

The majority of patients with refractory symptoms experience nocturnal acid breakthrough. Dexlansoprazole offers greater dosing flexibility since it does not need to be administered with food so may provide effective control of nocturnal symptoms.[57] Likewise, omeprazole-sodium bicarbonate immediate release products can be given without regard to meals and may be useful in controlling nocturnal symptoms.[57] The addition of an H2RA at bedtime for nocturnal symptoms has been suggested; however, the effect may be short-lived due to tachyphylaxis.

Antireflux surgery, magnetic sphincter augmentation, and endoscopic therapies may have a role in refractory GERD, depending on the scenario. If tests are negative, the patient is unlikely to have GERD and PPI therapy should be discontinued and alternative diagnosis should be investigated.[1] Baclofen may be beneficial for patients with residual acid or weakly acidic reflux by decreasing transient LES relaxations although with potential adverse effects seen in some patients.[27] Functional heartburn or reflux hypersensitivity may be treated with tricyclic antidepressants, selective serotonin reuptake inhibitors,

serotonin-norepinephrine reuptake inhibitors, or trazodone.[27] Eosinophilic esophagitis or dysmotility syndromes are causes of nonacid-related esophageal symptoms and require therapies other than a PPI.[27,58]

EVALUATION OF THERAPEUTIC OUTCOMES

The long-term benefits of treatment are difficult to assess because of the limited information known about the epidemiology and natural history of GERD. Consequently, successful outcomes are generally measured in terms of three separate end points: (a) relieving symptoms, (b) healing the injured mucosa, and (c) preventing complications.

10 The short-term goal of therapy is to relieve symptoms such as heartburn and regurgitation to the point at which they do not impair the patient's quality of life. Patients should be educated regarding specific lifestyle modifications that are applicable to their individual situation including weight loss and raising the head end of the bed. Patient medication profiles should be reviewed for medications that may aggravate GERD. Patients should be monitored for adverse drug reactions. Table 49-5 reviews common adverse drug reactions and monitoring of medications used in GERD. Drug-drug interactions should also be assessed and these agents should be avoided if possible. The frequency and severity of symptoms should be monitored, and patients should be counseled on symptoms that suggest the presence of complications requiring immediate medical attention, such as dysphagia. Patients should also be monitored for the presence of extraesophageal symptoms, such as laryngitis asthma or chest pain. These symptoms require further diagnostic evaluation. Long-term maintenance treatment is indicated for patients who have strictures because the strictures commonly recur if reflux esophagitis is not treated.

The second goal is to heal the injured mucosa. Again, individualized lifestyle modifications and the importance of complying with the therapeutic regimen chosen to heal the mucosa should be stressed. Patients should be educated about the risk of relapse and the need for long-term maintenance therapy to prevent recurrence or complications.

The final, long-term goal of therapy is to decrease the risk of complications (esophagitis, strictures, Barrett's esophagus, and esophageal adenocarcinoma). A small subset of patients may continue to fail treatment despite therapy with high doses of H2RAs or a proton pump inhibitor. Patients should be monitored for the presence of continual pain, dysphagia, or odynophagia.

Postclass Engaged Learning Activity

Perform a PubMed search to identify a new primary literature publication concerning GERD management published in the last year. Describe what the current practice is and what this new article adds to our knowledge regarding the management of GERD. Describe the potential impact for GERD patients in terms of safety and/or efficacy. This activity is intended to develop skills in interpretation and application of primary literature in practice.

ABBREVIATIONS

AET	acid exposure time
BMI	body mass index
CYP	cytochrome P450
GABA	gamma aminobutyric acid
GERD	gastroesophageal reflux disease
H2RA	histamine-2 receptor antagonist
HREPT	high-resolution esophageal pressure topography
HRQL	health-related quality of life
LES	lower esophageal sphincter
mGluR5	metabotropic glutamate type 5
NERD	nonerosive reflux disease
PPI	proton pump inhibitor
TLESR	transient lower esophageal sphincter relaxation

REFERENCES

1. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol*. 2013;108:308–328. doi:10.1038/ajg.2012.444.
2. Rubenstein JH, Chen JW. Epidemiology of gastroesophageal reflux disease. *Gastroenterol Clin North Am* 2014;43(1):1–14.
3. El-Serag HB, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: A systematic review. *Gut* 2014;63(6):871–880.
4. Kim YS, Kim N, Kim GH. Sex and gender differences in gastroesophageal reflux disease. *J Neurogastroenterol Motil*.

2016;22(4):575–588. doi: 10.5056/jnm16138.

5. Nwokediuko SC. Current trends in the management of gastroesophageal reflux disease: A review. *ISRN Gastroenterol*. 2012;2012:391631. doi:10.5402/2012/391631.
6. Yang HJ, Chang Y, Park SK, et al. Nonalcoholic fatting liver disease is associated with increased risk of reflux esophagitis. *Dig Dis Sci* 2017;62:3605–3613.
7. Chou PH, Lin CC, Lin CH, et al. Prevalence of gastroesophageal reflux disease in major depressive disorder: A population-based study. *Psychosomatics* 2014;55(2):155–162.
8. Kahrilas PJ, McColl K, Fox M, et al. The acid pocket: A target for treatment in reflux disease? *Am J Gastroenterol*. 2013;108:1058–1064. doi:10.1038/ajg.2013.132.
9. Lightdale JR, Gremse DA; Section on Gastroenterology, Hepatology, and Nutrition. Gastroesophageal reflux: Management guidance for the pediatrician. *Pediatrics*. 2013;131:e1684–e1695. doi: 10.1542/peds.2013-0421.
10. Camilleri M, Malhi H, Acosta A. Gastrointestinal complications of obesity. *Gastroenterology* 2017;152:1656-1670. doi: 10.1053/j.gastro.2016.12.052.
11. Hallan A, Bomme M, Hveem K, et al. Risk factors on the development of new-onset gastroesophageal reflux symptoms. A population-based prospective cohort study: The HUNT study. *Am J Gastroenterol*. 2015;110:393–400. doi: 10.1038/ajg.2015.18.
12. Khan A, Kim A, Sanossian C, et al. Impact of obesity treatment on gastroesophageal reflux disease. *World J Gastroenterol*. 2016;22:1627–38.
13. Pandit S, Boktor M, Alexander JS, et al. Gastroesophageal reflux disease: A clinical overview for primary care physicians. *Pathophysiology*. 2018;25:1–11.
14. Shaheen NJ, Falk GW, Iyer PS, Gerson L. ACG Clinical Guideline: Diagnosis and management of Barrett's esophagus. *Am J Gastroenterol*. 2016;111:30–50. doi:10.1038/ajg.2015.322.
15. Lee SW, Lee TY, Lien HC, Yang SS, Yeh HZ, Chang CS. Characteristics of symptom presentation and risk factors in patients with erosive esophagitis and nonerosive reflux disease. *Med Prin Pract* 2014;23(5):460–464.
16. Tack J, Pandolfino JE. Pathophysiology of gastroesophageal reflux

disease. *Gastroenterology* 2018;154:277-288. doi: 10.1053/j.gastro.2017.09.047.

17. Gyawali CP, Kahrilas PJ, Savarino E, et al. Modern diagnosis of GERD: The Lyon Consensus. *Gut*. 2018;67:1351–1362. doi: 10.1136/gutjnl-2017-314722.
18. Vaezi MF, Pandolfino JE, Vela MF, Shaheen NJ. White Paper AGA: Optimal strategies to define and diagnose gastroesophageal reflux disease. *Clin Gastroenterol Hepatol*. 2017;15:1162–1172. doi: 10.1016/j.cgh.2017.03.021.
19. Gyawali CP, Fass R. Management of gastroesophageal reflux disease. *Gastroenterology* 2018;154:302–318.
20. Harnik IG. In the clinic. Gastroesophageal reflux disease. *Ann Intern Med*. 2015;163(1):ITC1. doi: 10.7326/AITC201507070.
21. Kleiman DA, Beninato T, Bosworth BP, et al. Early referral for esophageal pH monitoring is more cost-effective than prolonged empiric trials of proton-pump inhibitors for suspected gastroesophageal reflux disease. *J Gastrointest Surg* 2014;18(1):26–33.
22. American Society for Gastrointestinal Endoscopy. The role of endoscopy in the management of GERD. *Gastrointestinal Endoscopy*. 2015;81(6):1305–1310. doi: 10.1016/j.gie.2015.02.021.
23. Yadlapati R, Vaezi MF, Vela MF, et al. Management options for patients with GERD and persistent symptoms on proton pump inhibitors: Recommendations from an expert panel. *Am J Gastroenterol*. 2018;1–7. doi: 10.1038/s41395-018-0045-4.
24. GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004;328:1490–1494.
25. DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Am J Gastroenterol* 2005;100:190–200.
26. Garvey WT, Mechanick JI, Brett EM. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocr Pract* 2016;22(7): 842–884.
27. Sandhu DS, Fass R. Current trends in the management of gastroesophageal reflux disease. *Gut and Liver* 2018;12(1):7–16.
28. Katz PO, Katzka DA. Getting into a TIF(F) over fundoplication. *Gastroenterology* 2018;154:1227–1233.

29. Spechler SJ, Lee RH, Smith BR, et al. A VA cooperative randomized trial of medical and surgical treatments for patients with heartburn that is refractory to proton pump inhibitors. Gastroenterology. 2018;154(6):S-129.
30. Nadaleto BF, Herbella FA, Patti MG. Gastroesophageal reflux disease in the obese: Pathophysiology and treatment. *Surgery*. 2015;159:475–486. doi:10.1016/j.surg.2015.04.034.
31. Saino G, Bonavina L, Lipham JC, et al. Magnetic sphincter augmentation for gastroesophageal reflux at 5 years: Final results of a pilot study show long-term acid reduction and symptom improvement. *J Laparoendosc Adv Surg Tech.* 2015;25(10):787–792.
32. Chen M, Huang D, Wu A, et al. Efficacy of magnetic sphincter augmentation versus Nissen fundoplication for gastroesophageal reflux disease in short term: A meta-analysis. *Can J Gastroenterol Hepatol*. 2017;2017:9596342.
33. Richter JE, Kumar A, Lipka S, et al. Efficacy of laparoscopic Nissen fundoplication vs transoral incisionless fundoplication or proton pump inhibitors in patients with gastroesophageal reflux disease: A systematic review and network meta-analysis. *Gastroenterology*. 2018;154:1298–1308. doi: 10.1053/j.gastro.2017.12.021.
34. Sweis R, Kaufman E, Anggiansah A, et al. Post-prandial reflux suppression by a raft-forming alginate (Gaviscon Advance) compared to a simple antacid documented by magnetic resonance imaging and pH-impedance monitoring: Mechanistic assessment in healthy volunteers and randomized, controlled, double-blind study in reflux patients. *Aliment Pharmacol Ther* 2013;37:1093–1102.
35. Leiman DA, Riff BP, Morgan S, et al. Alginate therapy is effective treatment for gastroesophageal reflux disease symptoms: A systematic review and meta-analysis. *Dis Esophagus*. 2017;30:1–8.
36. Reimer C, Lodrup AB, Smith G, et al. Randomised clinical trial: alginate (Gaviscon Advance) vs placebo as add-on therapy in reflux patients with inadequate response to a once daily proton pump inhibitor. *Aliment Pharmacol Ther*. 2016;43:899–909. doi: 10.1111/apt.13567.
37. Freedberg DE, Kim LS, Yang YX. The risks and benefits of long-term use of proton pump inhibitors: Expert review and best practice advice from the American Gastroenterological Association. *Gastrenterology*. 2017;152:706–715. doi: 10.1053/j.gastro.2017.01.031.

38. Reimer C, Sondergaard B, Hilsted L, Bytzer P. Proton-pump inhibitor therapy induces acid-related symptoms in healthy volunteers after withdrawal of therapy. *Gastroenterology* 2009;137:80-87.
39. Farrell B, Pottie K, Thompson W, et al. Deprescribing proton pump inhibitors: Evidence-based clinical practice guideline. *Can Fam Physician* 2017;63:354–364.
40. Triadafilopoulos G, Clarke JO, Hawn M. Precision GERD management for the 21st century. *Dis Esophagus*. 2017;30:1–6. doi: 10.1093/dote/dox079.
41. FDA Drug Safety Communication: Possible Increased Risk of Fractures of the Hip, Wrist, and Spine with the Use of Proton Pump Inhibitors.2010. Available at: www.fda.gov. Accessed June 28, 2018.
42. FDA Drug Safety Communication: Possible Increased Risk of Fractures of the Hip, Wrist, and Spine with the Use of Proton Pump Inhibitors. Update. 2011. Available at: www.fda.gov. Accessed June 2018.
43. Gyawali CP. Proton pump inhibitors in gastroesophageal reflux disease: Friend or foe. *Curr Gastroenterol Rep*. 2017;19:46.
44. Xie Y, Bowe B, Li T, et al. Proton pump inhibitors and risk of incident CKD and progression to ESRD. *J Am Soc Nephrol*. 2016;27:1–11. doi: 10.1681/ASN.2015121377.
45. Jacobs C, Coss Adame E, Attaluri A, et al. Dysmotility and proton pump inhibitor use are independent risk factors for small intestinal bacterial and/or fungal overgrowth. *Aliment Pharmacol Ther* 2013;37:1103–1111.
46. Hariharan S, Southworth MR, Madabushi R. Clopidogrel, CYP2C19 and proton pump inhibitors: What we know and what it means. *J Clin Pharmacol*. 2014;54:884–88.
47. Bouziana SD, Tziomalos K. Clinical relevance of clopidogrel-proton pump inhibitors interaction. *World J Gastrointest Pharmacol Ther* 2015;6:17–21.
48. Abraham NS, Hlatky MA, Antman EM, et al. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: A focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: A report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *Circulation* 2010;122:2619–2633.
49. Fass R, Inadomi J, Han C et al. Maintenance of heartburn relief after step-

down from twice-daily proton pump inhibitor to once-daily dexlansoprazole modified release. *Clin Gastroenterol Hepatol* 2012;10:247–53.

50. Scarpellini E, Boescstaens V, Farre R, et al. Effect of baclofen on the acid pocket at the gastroesophageal junction. *Dis Esophagus*. 2014;28:488–495. doi: 10.1111/dote.12224.
51. Kuo P, Holloway RH. Beyond acid suppression: New pharmacologic approaches for treatment of GERD. *Curr Gastroenterol Rep* 2010;12:175–180.
52. Yadlapati R, Gawron A, Bilimoria K, et al. Development of quality measures for the care of patients with gastroesophageal reflux disease. *Clin Gastroenterol Hepatol*. 2015;13(5):874–883. doi: 10.1016/j.cgh.2014.11.012.
53. Kahrilas PJ, Altman KW, Chang AB, et al. Chronic cough due to gastroesophageal reflux in adults: CHEST Guideline and Expert Panel Report. *Chest* 2016;150(6):1341–1360.
54. Hassall E. Over-prescription of acid-suppressing medications in infants: How it came about, why it's wrong, and what to do about it. *J Pediatr* 2012;160(2):193–198.
55. Terrin G, Passariello A, De Curtis M, et al. Ranitidine is associated with infections, necrotizing enterocolitis, and fatal outcome in newborns. *Pediatrics* 2012;129:e40–e45.
56. Kierkus J, Oracz G, Dorczowski B, et al. Comparative safety and efficacy of proton pump inhibitors in pediatric gastroesophageal reflux disease. *Drug Safety* 2014;37(5):309–316.
57. Kung YM, Hsu WH, Wu MC, et al. Recent advances in the pharmacological management of gastroesophageal reflux disease. *Dig Dis Sci* 2017;62:3298–3316.
58. Subramanian CR, Triadafilopoulos G. Refractory gastroesophageal reflux disease. *Gastroenterol Rep* 2015;3:41–53.

50

Peptic Ulcer Disease and Related Disorders

Bryan L. Love and Phillip L. Mohorn

KEY CONCEPTS

1. Psychological stress, cigarette smoking, nonsteroidal anti-inflammatory drug (NSAID) use, and certain foods/beverages can exacerbate ulcer symptoms and should be avoided.
2. Eradication of *Helicobacter pylori* (*H. pylori*) is recommended in all patients who test positive, especially in those patients with an active ulcer, a documented history of a prior ulcer, or a history of ulcer-related complications.
3. The selection of an *H. pylori* eradication regimen should be based on several factors, including: efficacy, safety, antibiotic resistance, cost, and the likelihood of medication adherence. The recommended initial treatment options with the strongest level of evidence include bismuth quadruple and concomitant therapy, both administered for 10 to 14 days. Clarithromycin-based triple therapy is no longer preferred due to increasing resistance and reduced eradication rates.
4. When first-line therapy fails, salvage treatment for *H. pylori* should contain different antibiotics due to potential resistance. Patients with reported penicillin allergy should be considered for penicillin skin testing after failing first-line therapy since many can safely be treated with amoxicillin containing salvage regimens.
5. PPI co-therapy reduces the risk of NSAID-related gastric and duodenal ulcers and is at least as effective as recommended dosages of misoprostol and superior to the histamine-2 receptor antagonists (H2RAs).
6. Standard PPI dosages and a nonselective NSAID are as effective as a selective cyclooxygenase-2 (COX-2) inhibitor in reducing the risk of

NSAID-induced ulcers and upper gastrointestinal (GI) complications.

7. Patients with peptic ulcer disease (PUD), especially those receiving *H. pylori* eradication or misoprostol co-therapy, require patient education regarding their disease and drug treatment to successfully achieve a positive therapeutic outcome.
8. Treatment for severe peptic ulcer bleeding after appropriate endoscopic treatment includes IV administration of a PPI loading dose followed by a 72-hour continuous infusion.
9. Coagulopathy and respiratory failure requiring mechanical ventilation are two of the highest risk factors for developing stress-related mucosal bleeding (SRMB). Prophylactic drug therapy should be administered to critically ill patients with one of these complications.
10. Since there are limited data to support the selection of a PPI over an IV H2RA for SRMB prophylaxis, agent selection should be based on appropriate individual patient characteristics (eg, nothing by mouth, presence of nasogastric tube, thrombocytopenia, renal failure).

Preclass Engaged Learning Activity

Conduct a brief internet search of the most commonly available nonprescription proton pump inhibitor (PPI) medications. Construct a table including the drug name, brand name(s), dosage, and potential side effects. Then, make a brief list of test results and symptom information you would want to collect if a patient whose care you were managing was taking a PPI. This activity is intended to get you familiar with the types of PPIs available to consumers without a prescription, as patients with peptic ulcer disease (PUD) could already be self-treating with some of these. This exercise also illustrates the potential dangers of treating acid reflux with nonprescription medications when more serious concerns might be present (peptic ulcer disease, ischemic heart disease, etc.).

PEPTIC ULCER DISEASE

Gastric-acid is a critical component of upper gastrointestinal (GI) tract complications including gastritis, erosions, and peptic ulcer.[1–3] Peptic ulcer

disease (PUD) differs from gastritis and erosions in that ulcers are larger (greater than or equal to 5 mm) and extend deeper into the muscularis mucosa.[1] The three common forms of peptic ulcers can be grouped according to their etiology: *Helicobacter pylori*–positive, nonsteroidal anti-inflammatory drug (NSAID)–induced, and stress-related mucosal damage (SRMD) (**Table 50-1**).

TABLE 50-1 Comparison of Common Forms of Peptic Ulcer

Characteristic	*H. pylori*–Induced	NSAID-Induced	SRMD
Condition	Chronic	Chronic	Acute
Site of damage	Duodenum > stomach	Stomach > duodenum	Stomach > duodenum
Intragastric pH	More dependent	Less dependent	Less dependent
Symptoms	Usually epigastric pain	Often asymptomatic	Asymptomatic
Ulcer depth	Superficial	Deep	Most superficial
GI bleeding	Less severe, single vessel	More severe, single vessel	More severe, superficial mucosal capillaries

GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; SRMD, stress-related mucosal damage.

H. pylori–positive and NSAID-induced ulcers are chronic peptic ulcers that differ in etiology, clinical presentation, and tendency to recur (see Table 50-1). These ulcers develop most often in the stomach and duodenum of ambulatory patients (**Fig. 50-1**). Occasionally, ulcers develop in the esophagus, jejunum, ileum, or colon. The natural course of chronic PUD is characterized by frequent ulcer recurrence. The cause of ulcer recurrence is often multifactorial, although *H. pylori* infection and NSAID use are commonly associated. In addition, cigarette smoking, alcohol use, gastric acid hypersecretion, and medication nonadherence are frequently related.

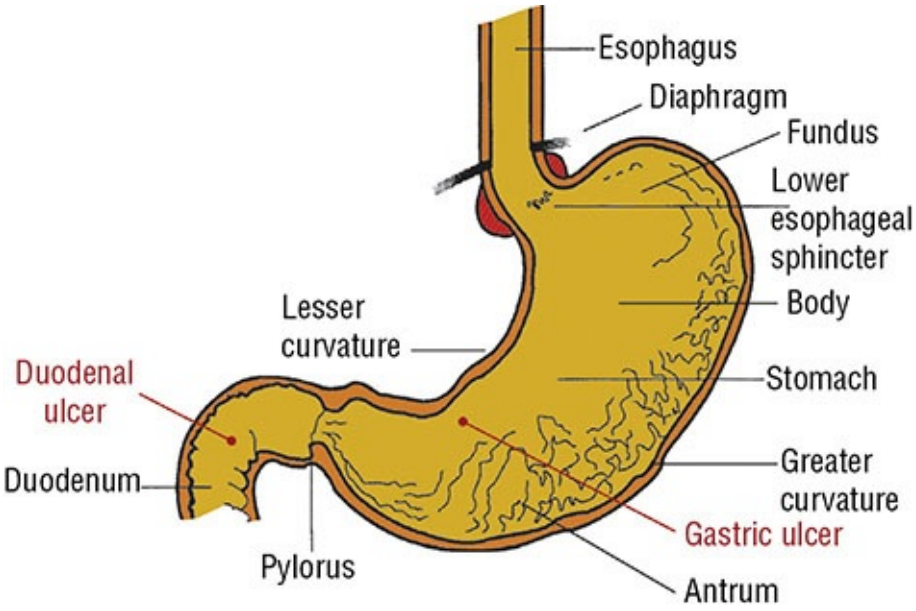


FIGURE 50-1 Anatomic structure of the stomach and duodenum and most common locations of gastric and duodenal ulcers.

Other conditions such as Zollinger-Ellison syndrome (ZES), radiation, chemotherapy, vascular insufficiency, and other chronic diseases (**Table 50-2**) are associated with development and recurrence of peptic ulcers.[1,2] Although a strong association exists between chronic pulmonary diseases, chronic renal failure including hemodialysis, and cirrhosis, the pathophysiologic mechanisms of these associations remain unclear.(1)[1] In contrast, SRMD occurs primarily in the stomach of critically ill patients (see Table 50-1).[1]

TABLE 50-2 Potential Causes of Peptic Ulcer

Common causes
Helicobacter pylori infection
NSAIDs
Critical illness (stress-related mucosal damage)
Uncommon causes of chronic peptic ulcer
Idiopathic (non–*H. pylori*, non-NSAID peptic ulcer)
Hypersecretion of gastric acid (eg, Zollinger-Ellison syndrome)
Viral infections (eg, cytomegalovirus)
Vascular insufficiency (eg, crack cocaine associated)
Radiation therapy
Chemotherapy (eg, hepatic artery infusions)
Infiltrating disease (eg, Crohn's disease)
Diseases and medical conditions associated with chronic peptic ulcer
Cirrhosis
Chronic renal failure
Chronic obstructive pulmonary disease
Cardiovascular disease
Organ transplantation

NSAIDs, nonsteroidal anti-inflammatory drugs.

This chapter focuses on issues surrounding chronic PUD due to *H. pylori* and NSAIDs. A brief discussion of other PUD-related disorders (ZES, upper GI bleeding, and SRMD) is also included.

EPIDEMIOLOGY

4 The epidemiology of PUD is complicated, and the prevalence is difficult to estimate given the variability in *H. pylori* infection, NSAID use, and cigarette smoking. In addition, endoscopy, radiology, symptoms, or other methods have different sensitivity and specificity to detect ulcers.[1,2,4] Despite these limitations, gastroduodenal ulcers occur in 0.1% to 0.3% of the general population annually, and the lifetime prevalence of PUD is between 5% and 10%. The prevalence and incidence of PUD in the United States has decreased in recent years, reflecting improvements in drug therapy, the dramatic shift to ambulatory management, and changes in the criteria and coding system for mortality and hospitalization data. Although mortality, hospitalization, and ambulatory care visits have declined, emergency department visits for GI hemorrhage related to PUD have increased in recent years.[5] Mortality rates are higher among those older than or

65 years and in males compared to females.[5] Despite continued improvements, PUD remains a common GI disease, resulting in impaired quality of life, work loss, and high-cost medical care.

7 The prevalence of *H. pylori* varies by geographic location, socioeconomic conditions, ethnicity, and age. In the United States and other industrialized countries, *H. pylori* prevalence has declined with successive birth cohorts and is thought to correlate with improved hygiene and living conditions compared with developing countries.[5–7] In the United States *H. pylori* prevalence is approximately 30% to 40%, but it is much higher in adults older than 60 years (50%-60%) than in children younger than 12 years (10%-15%). The rate of *H. pylori* acquisition in children is declining due to improved environmental conditions in Western populations, but maternal colonization remains an important transmission factor. Disparities in *H. pylori* prevalence continue to exist among African Americans and Hispanic persons with infection rates approximately two to three times that of non-Hispanic Whites.[7] Adults with some college education have reduced prevalence of *H. pylori*, probably related to improved socioeconomic status and living conditions.[7] Infection rates do not differ with gender or smoking status.

Nonsteroidal Anti-Inflammatory Drugs

Gastroduodenal ulcers develop in up to 15% to 40% of chronic NSAID users, but up to 80% of short-term users may have ulcers detected upon endoscopy.[8] Gastric ulcers are most common, occur primarily in the antrum, and are of greater concern because of their potential to cause ulcer-related upper GI complications, such as bleeding, strictures, and perforations.[8] Between 2% and 4% of patients with an NSAID ulcer will bleed or perforate.[9] In the United States at least 100,000 hospitalizations and between 7,000 and 10,000 deaths are directly attributed to NSAIDs each year. Ulcer-related complications and death among regular NSAID users are 3 to 10 times higher compared with nonusers.[9]

ETIOLOGY

H. pylori infection and NSAID use are the most common risk factors for PUD. Less common factors including ZES with hypersecretion of acid (see Table 50-2) can also be involved.[1] Disruptions in normal mucosal defense and healing mechanisms allow acid and pepsin to reach the gastric epithelium.[1] Benign

gastric ulcers, erosions, and gastritis can occur anywhere in the stomach, although the antrum and lesser curvature represent the most common locations (see Fig. 50-1). Most duodenal ulcers occur in the first part of the duodenum (duodenal bulb).

Helicobacter pylori

H. pylori are spiral, microaerophilic, gram-negative bacteria with flagella that has urease, catalase, and oxidase activity. These factors allow the bacterium to survive in the acidic environment of the stomach. Bacterial urease converts urea to ammonia that neutralizes gastric acid, there by alkalinizing the microenvironment. Catalase activity enables the bacterium to survive reactive oxidation by phagocytes attempting to kill the organism, but the resulting inflammation damages the gastric epithelial lining allowing *H. pylori* to thrive. Bacterial flagella facilitate the initial infection and allows for colonization of the gastric mucosa.[10] *H. pylori* is primarily transmitted via person to person routes by either gastro–oral (vomitus) or fecal–oral (diarrhea) contact. Risk factors for acquiring *H. pylori* include close contact within households, low socioeconomic status, and country of origin.[2]

H. pylori infection can cause both acute and chronic gastritis in infected individuals and is associated with multiple GI complications. PUD, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer (**Fig. 50-2**) have all been linked to *H. pylori* infection.[1,2,6,11,13] Most infected individuals remain asymptomatic, but 10% to 20% will develop PUD during their lifetime and about 1% will develop gastric cancer.[1,2] Environmental factors, host genetics, and *H. pylori* strain virulence factors play an important role in the pathogenesis of PUD and gastric cancer.[2] *H. pylori* infection increases the risk of GI bleeding and peptic ulcers by threefold to sevenfold.[11] No specific link has been established between *H. pylori* and dyspepsia, nonulcer dyspepsia (NUD), or gastroesophageal reflux disease (GERD).[11,12] However, some patients with dyspepsia and NUD may have symptom improvement from *H. pylori* eradication.[11] Conversely, eradication of *H. pylori* may worsen GERD symptoms in some patients, but eradication should be attempted due to the known gastric cancer risk.[11] *H. pylori* is also associated with iron deficiency anemia, although the benefit of eradication remains unknown.[11]

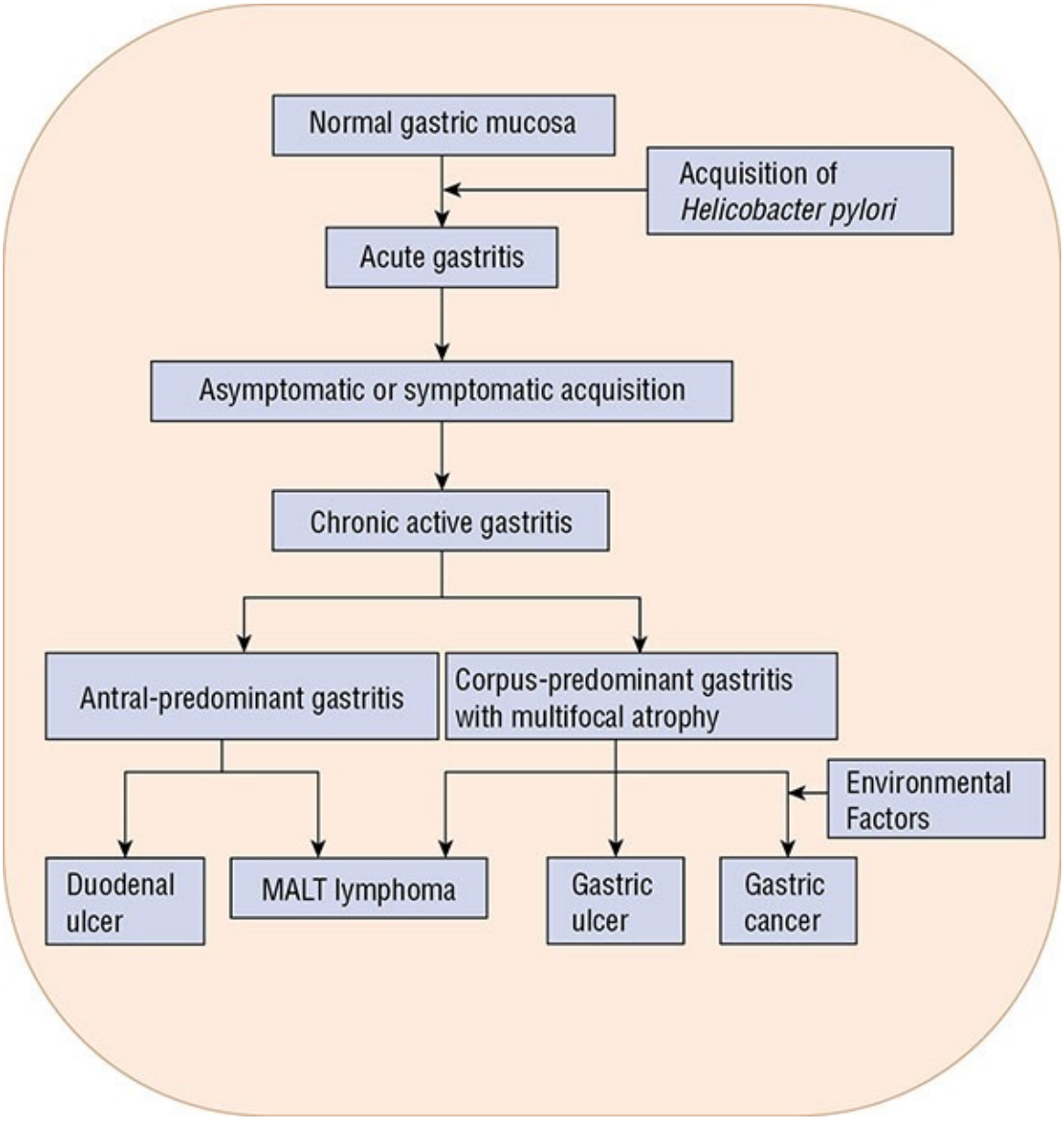


FIGURE 50-2 The natural history of *Helicobacter pylori* infection in the pathogenesis of gastric ulcer and duodenal ulcer, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer.

Nonsteroidal Anti-Inflammatory Drugs

Prescription and nonprescription NSAIDs (**Table 50-3**), are widely used in the United States, and have been linked to PUD. There is overwhelming evidence linking chronic NSAID (including low-dose aspirin) use to upper GI tract injury, PUD, gastritis, and superficial erosion.[1,14,16] In susceptible individuals, NSAIDs cause superficial mucosal damage consisting of petechiae (intramucosal

hemorrhages) within minutes of ingestion, and progress to erosions with continued use.[8] These lesions typically heal within a few days and rarely cause ulcers or acute upper GI bleeding. NSAID-induced ulcers occur less frequently in the esophagus, small bowel, and colon.[8,9] The mechanisms by which NSAIDs damage the lower GI tract is not clear, but the enteropathy is associated with lower GI bleeding.

TABLE 50-3 Selected NSAIDs and COX-2 Inhibitors

Nonsalicylates[a]
Nonselective (traditional) NSAIDs: indomethacin, piroxicam, ibuprofen, naproxen, sulindac, ketoprofen, ketorolac, flurbiprofen, diclofenac
Selective COX-2 inhibitors: etodolac, nabumetone, meloxicam, celecoxib, rofecoxib,[b] valdecoxib[b]
Salicylates
Acetylated: aspirin
Nonacetylated: salsalate, trisalicylate

[a]Based on COX-1-to-COX-2 selectivity ratio.

[b]Withdrawn from US market.

COX-2, cyclooxygenase-2; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 50-4 lists the risk factors associated with NSAID-induced ulcers and upper GI complications. Combinations of factors confer an additive risk.[8,9,17,18] Advanced age is an independent risk factor, and the incidence of NSAID-induced ulcers increases linearly with the age of the patient.[1] The high incidence of ulcer complications in older individuals may be explained by age-related changes in gastric mucosal defense. The relative risk of NSAID complications is increased for patients with a previous peptic ulcer and may be as high as 14-fold in those with a history of an ulcer-related complication.[1,19] Although the risk of ulcer complications is greatest during the first few months after initiating continuous NSAID therapy, it does not vanish with long-term treatment.[4]

TABLE 50-4 Risk Factors Associated with NSAID-Induced Ulcers and Upper GI Complications[a]

Age >65
Previous peptic ulcer
Previous ulcer-related upper GI complication
High-dose NSAIDs
Multiple NSAID use
Selection of NSAID (eg, COX-1 vs COX-2 inhibition)
NSAID-related dyspepsia
Aspirin (including cardioprotective dosages)
Concomitant use of
NSAID plus low-dose aspirin
Oral bisphosphonates (eg, alendronate)
Corticosteroids
Anticoagulant or coagulopathy
Antiplatelet drugs (eg, clopidogrel)
Selective serotonin reuptake inhibitor
Chronic debilitating disorders (eg, cardiovascular disease, rheumatoid arthritis)
Helicobacter pylori infection
Cigarette smoking
Alcohol consumption

[a]Combinations of risk factors are additive.

COX-2, cyclooxygenase-2; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs.

Data from references 1, 9, and 15

NSAID ulcers and related complications are dependent upon the dose, duration of use, and type of NSAID. Although dose is important, low doses of nonprescription NSAIDs and low cardioprotective dosages of aspirin (81-325 mg/day) increase risk of ulcer formation[1,4,9,18] Factors such as NSAID potency, longer duration of effect, and a greater propensity to inhibit cyclooxygenase-1 (COX-1) versus cyclooxygenase-2 (COX-2) isoenzymes are associated with increased risk (see Table 50-3).[1,4,9,20] NSAID-related dyspepsia, in itself, does not correlate directly with mucosal injury or clinical events. However, new-onset dyspepsia, changes in severity, or dyspepsia not relieved by antiulcer medications may suggest an ulcer or ulcer complication.[1] Nonacetylated salicylates (eg, salsalate) may be associated with decreased GI toxicity.[1,9,15] Buffered or enteric-coated aspirin confers no added protection from upper GI events.[9,15] NSAID ulcer and GI complication risk are increased with the use of multiple NSAIDs or the concomitant use of low-dose aspirin, oral bisphosphonates, corticosteroids, anticoagulants, antiplatelet drugs, and selective serotonin reuptake inhibitors.[18,20,23] The risk of an ulcer-related GI complication is greater when an NSAID or COX-2 inhibitor (see Table 50-3) is

coadministered with low-dose aspirin than when either drug is taken alone.[18] The NSAID may also reduce the antiplatelet effects of aspirin, although NSAIDs vary in their effects on platelet function. Corticosteroids, when used alone, do not potentiate the risk of ulcer or complications, but the relative risk is increased twofold in corticosteroid users who are also taking concurrent NSAIDs.[23] The relative risk of GI bleeding increases up to 20-fold when NSAIDs are taken concomitantly with anticoagulants (eg, warfarin) and up to sixfold with the concurrent use of serotonin reuptake inhibitors.[21,23] Coadiministration of clopidogrel in combination with aspirin, an NSAID, or an anticoagulant significantly increases the risk of GI bleeding compared with either agent taken alone.[14] Even when prescribed as monotherapy, clopidogrel increases the risk of rebleeding for patients with a history of a bleeding ulcer.[24] Prasugrel and ticagrelor have greater potent platelet inhibition than clopidogrel and are associated with a greater risk of bleeding.[22,25]

H. pylori and NSAIDs act independently to increase ulcer risk and ulcer-related bleeding and appear to have additive effects.[11] Thus, the incidence of peptic ulcer is higher in *H. pylori*–positive NSAID users. Whether *H. pylori* infection is actually a risk factor for NSAID ulcers remains controversial.[11] However, eradication is reported to reduce the incidence of peptic ulcer if undertaken prior to starting the NSAID but does not reduce the risk for patients who were previously taking an NSAID.[11]

Cigarette Smoking

Cigarette smoking has been linked to PUD, but it is uncertain whether smoking causes peptic ulcers. The prevalence of ulcer disease is nearly double in current and former smokers (11.4% and 11.5%) compared to those who never smoked (6%). The risk of peptic ulcers greatest in smokers with a large daily use, but ulcer risk is modest when fewer than 10 cigarettes are smoked per day.[26] Cigarette smoking impairs ulcer healing, promotes ulcer recurrence, and increases ulcer risk. However, the underlying mechanisms by which cigarette smoking exerts these adverse effects remains unclear. Possible mechanisms include mucosal ischemia, inhibition of pancreatic bicarbonate secretion, and increases in gastric acid and mucous secretion, but these effects are inconsistent.[27]

Psychological Stress

Psychosocial stress may influence the pathogenesis of PUD, but it can be difficult to determine whether the stressful exposure was present before development of ulcer.[28] Clinical observation suggests that ulcer patients are adversely affected by stressful life events. However, results from controlled trials are conflicting and have failed to document a cause-and-effect relationship. Emotional stress may induce behavioral risks such as smoking and the use of NSAIDs or alter the inflammatory response or resistance to *H. pylori* infection.[28,29] The role of stress and how it affects PUD is complex and probably multifactorial.

Dietary Factors

The effects of diet and nutrition on the pathophysiology PUD is uncertain. Carbonated beverages, coffee, tea, beer, milk, and spices often cause dyspepsia, but they do not appear to increase the risk of PUD.[1] Dietary interventions such as bland or restricted diets do not alter the frequency of ulcer recurrence. Although caffeine is a gastric acid stimulant, constituents in decaffeinated coffee or tea, caffeine-free carbonated beverages, beer, and wine may also increase gastric acid secretion. In high concentrations, alcohol ingestion is associated with acute gastric mucosal damage and upper GI bleeding; however, there is insufficient evidence to confirm that alcohol causes ulcers.[1]

PATHOPHYSIOLOGY

The pathophysiology of gastric and duodenal ulcers is determined by the balance between aggressive (gastric acid and pepsin) and protective (mucosal defense and repair) factors.[1] Gastric acid is secreted by the parietal cells, which contain receptors for histamine, gastrin, and acetylcholine.[1] Acid (as well as *H. pylori* infection and NSAID use) is an independent factor that contributes to the disruption of mucosal integrity.[1] Acid secretion is increased in patients with duodenal ulcers and may be a consequence of *H. pylori* infection.[30] In contrast, patients with gastric ulcer usually have normal or reduced rates of acid secretion (hypochlorhydria).

The amount of acid secreted under basal or fasting conditions is referred to as basal acid output (BAO); after maximal stimulation, maximal acid output (MAO).[1] Basal and maximal acid secretion varies with time of day and the individual’s psychological state, age, gender, and health status. The BAO follows

a circadian rhythm, with the highest acid secretion occurring at night and the lowest in the morning. An increase in the BAO:MAO ratio suggests a basal hypersecretory state such as ZES.

Pepsin is an important enzyme cofactor in the proteolytic activity involved in ulcer formation. Pepsinogen, the inactive precursor of pepsin, is secreted by the chief cells in the gastric fundus (see Fig. 50-1). Pepsin activity is determined by pH as it is activated by acid pH (optimal pH of 1.8-3.5), reversibly inactivated at pH 4, and irreversibly destroyed at pH 7.

Mucus and bicarbonate secretion, intrinsic epithelial cell defense, and mucosal blood flow protect the gastroduodenal mucosa from noxious endogenous and exogenous substances.[1] The viscous nature and near-neutral pH of the mucus–bicarbonate barrier protect the stomach from the acidic contents in the gastric lumen. Mucosal repair after injury is related to epithelial cell restitution, growth, and regeneration. Endogenous prostaglandins' (PGs) production facilitate mucosal integrity and repair. The term *cytoprotection* is often used to describe this process, but *mucosal defense* and *mucosal protection* are more accurate terms, as PGs prevent deep mucosal injury and not superficial damage to individual cells.[8,31] Gastric hyperemia and increased PG synthesis characterize adaptive cytoprotection, the short-term adaptation of mucosal cells to mild topical irritants that enables the stomach to initially withstand the damaging effects of irritants. Alterations in mucosal defense that are induced by *H. pylori* or NSAIDs are the most important cofactors in the formation of peptic ulcers.[8,32]

Helicobacter pylori

In infected people, *H. pylori* resides between the gastric mucus layer and surface epithelial cells, or any location where gastric-type epithelium is found. Its spiral shape and flagellum permits it to move from the lumen of the stomach, where the pH is low, to the mucus layer, where the local pH is neutral. *H. pylori* produces large amounts of urease, which hydrolyzes urea in the gastric juice and converts it to ammonia and carbon dioxide. The local buffering effect of ammonia creates a neutral microenvironment within and surrounding the bacterium, protecting it from the lethal effect of gastric acid. *H. pylori* also produces acid-inhibitory proteins, which allow it to adapt to the low-pH environment of the stomach.

H. pylori binds to gastric-type epithelium by adherence pedestals, which prevent the organism from being shed during cell turnover and mucus secretion.

Colonization of the antrum and corpus (body) of the stomach is associated with gastric ulcer and cancer. Antral organisms colonize gastric tissue that develops in the duodenum secondary to changes in gastric acid or bicarbonate secretion leading to duodenal ulcer (see Fig. 50-2). Although *H. pylori* causes chronic gastric mucosal inflammation in all infected individuals, only a minority actually develop an ulcer or gastric cancer.[1] The difference in the diverse clinical outcomes is related to variations in bacterial pathogenicity and host susceptibility.

Bacterial enzymes (urease, lipases, and proteases), bacterial adherence, and *H. pylori* virulence factors produce gastric mucosal injury. Lipases and proteases degrade gastric mucus, ammonia produced by urease may be toxic to gastric epithelial cells, and bacterial adherence enhances the uptake of toxins into gastric epithelial cells. *H. pylori* induces gastric inflammation by altering the host inflammatory response and damaging epithelial cells directly by cell-mediated immune mechanisms or indirectly by activated neutrophils or macrophages attempting to phagocytose bacteria or bacterial products. However, *H. pylori* strains are genetically diverse and account for differences in adaptation within the human host. Two of the most important are cytotoxin-associated gene protein (CagA) and vacuolating cytotoxin (VacA). About 60% of *H. pylori* strains in the United States possess CagA, but CagA-positive strains increase the risk for severe PUD, gastritis, and gastric cancer compared with CagA-negative strains. The VacA gene codes for the VacA cytotoxin, a vacuolating toxin. Although VacA is present in most *H. pylori* strains, strains vary in cytotoxicity and increased risk for peptic ulcer and gastric cancer. Host polymorphisms are important markers of disease susceptibility and may identify high-risk patients.

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs, including aspirin (see Table 50-3), cause gastric mucosal damage by local and systemic mechanisms, but systemic inhibition of endogenous mucosal PG synthesis is believed to be the primary mechanism.[4] The onset of injury is initiated by the acidic properties of many of the NSAIDs while systemic inhibition of the protective PGs limits the ability of the mucosa to defend against injury and thus plays the predominant role in the development of gastric ulcer.[4] Acidic NSAIDs (eg, aspirin) have topical irritant properties and they decrease the hydrophobicity of the mucous gel layer in the gastric mucosa. Most non-aspirin NSAIDs have topical irritant effects, but aspirin is the most damaging. Although NSAID prodrugs, enteric-coated aspirin tablets, salicylate derivatives,

and parenteral or rectal preparations are associated with less acute gastric mucosal injury, they can cause ulcers and related GI complications because of systemic inhibition of endogenous PGs.

COX is the rate-limiting enzyme in the conversion of arachidonic acid to PGs and is inhibited by NSAIDs (**Fig. 50-3**). Two similar COX isoforms have been identified: COX-1 is found in most body tissue, including the stomach, kidney, intestine, and platelets; COX-2 is undetectable in most tissues under normal physiologic conditions, but its expression can be induced during acute inflammation and arthritis (**Fig. 50-4**). COX-1 produces protective PGs that regulate physiologic processes such as GI mucosal integrity, platelet homeostasis, and renal function. COX-2 is induced (unregulated) by inflammatory stimuli such as cytokines and produces PGs involved with inflammation, fever, and pain. It is also constitutionally expressed in organs such as the brain, kidney, and reproductive tract. Adverse effects (eg, GI or renal toxicity) of NSAIDs are primarily associated with the inhibition of COX-1, whereas anti-inflammatory actions result primarily from NSAID inhibition of COX-2.[8]

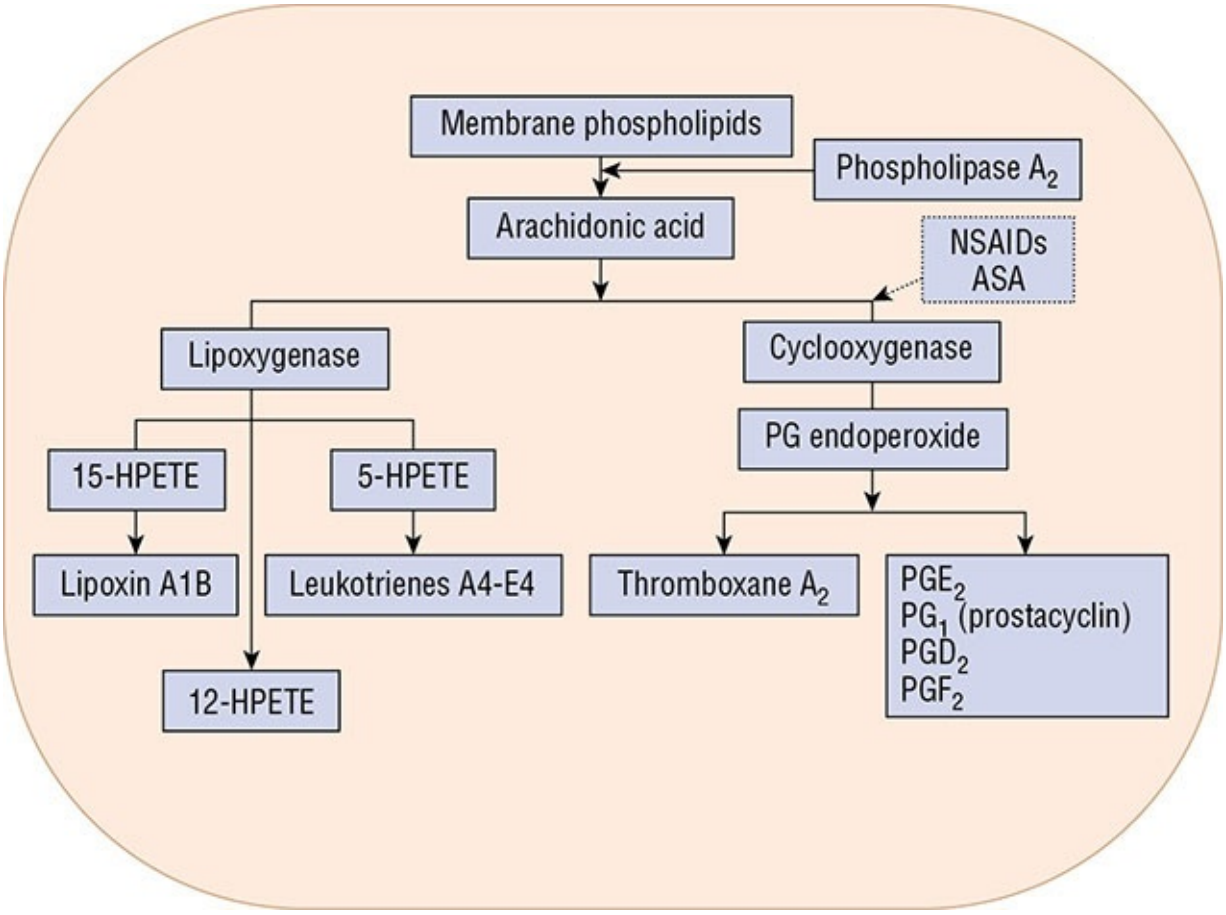


FIGURE 50-3 Metabolism of arachidonic acid after its release from membrane phospholipids. Broken arrow indicates inhibitory effects. (ASA, aspirin; HPETE, hydroperoxyeicosatetraenoic acid; NSAIDs, nonsteroidal antiinflammatory drugs; PG, prostaglandin.)

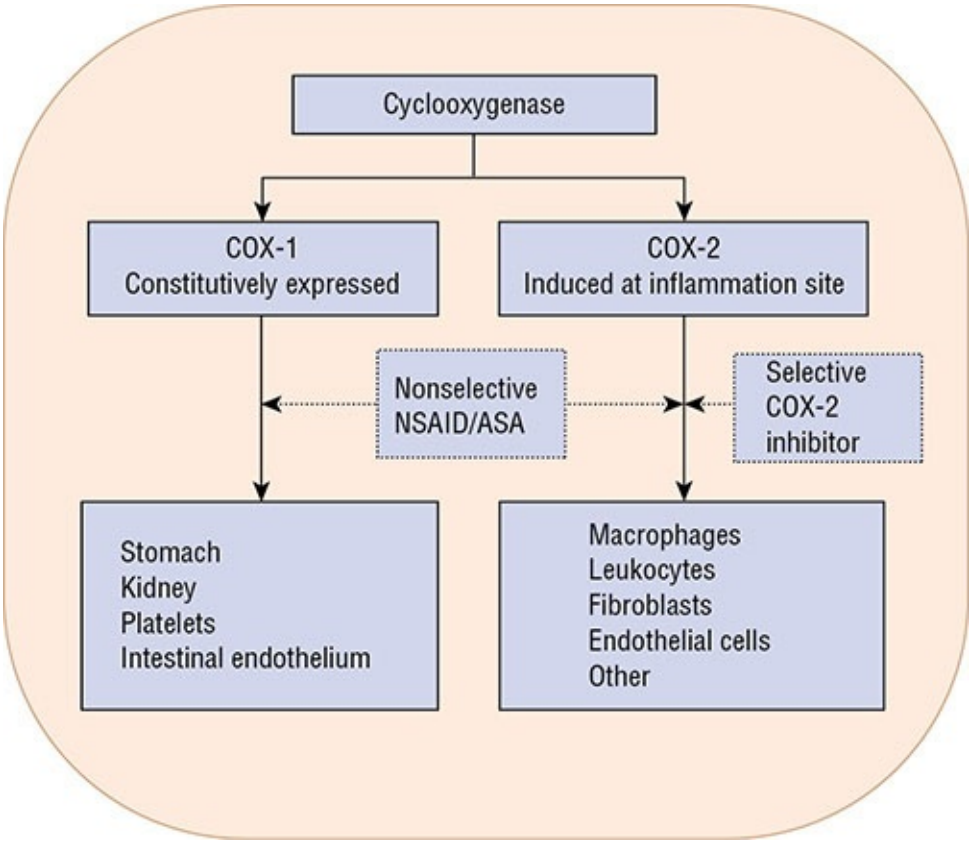


FIGURE 50-4 Tissue distribution and actions of cyclooxygenase (COX) isoenzymes. Nonselective nonsteroidal antiinflammatory drugs (NSAIDs) including aspirin (ASA) inhibit COX-1 and COX-2 to varying degrees; COX-2 inhibitors inhibit only COX-2. Broken arrow indicates inhibitory effects.

The COX-1-to-COX-2 inhibitory ratio determines the relative GI toxicity of a specific NSAID. Nonselective NSAIDs, including aspirin (see Table 50-3), inhibit both COX-1 and COX-2 to varying degrees and are associated with an increased propensity to cause gastric ulcers. In contrast, the selective COX-2 inhibitors preferentially inhibit COX-2 in vitro resulting in a reduced risk of ulcers and related GI complications (see Table 50-3). The selectivity for the COX-2 isoenzyme varies among NSAIDs. Celecoxib, meloxicam, etodolac, and nabumetone are considered only partially selective and have more risk of GI complications compared to rofecoxib and valdecoxib50. The addition of aspirin to a selective COX-2 inhibitor reduces its ulcer-sparing benefit and increases

ulcer risk.[9] Aspirin and non-aspirin NSAIDs irreversibly inhibit platelet COX-1, resulting in decreased platelet aggregation and prolonged bleeding times, thereby increasing the potential for upper and lower GI bleeding. Coadministration of NSAIDs may reduce the antiplatelet effects of aspirin. Clopidogrel, prasugrel, ticagrelor, and related medications that affect platelet aggregation do not cause ulcers, per se, but may impair healing of gastric erosions leading to ulceration and bleeding.[14,22,25,33]

Complications

The most serious, life-threatening complications of chronic PUD are upper GI bleeding, perforation, and obstruction.[34] Bleeding peptic ulcers, caused by the erosion of an ulcer into an artery, are the most common cause of non-variceal upper GI bleeding, occurring in 26% to 59% of patients.[35] It may be occult (hidden) and insidious or may present as melena (black-colored stools) or hematemesis (vomiting of blood). NSAID use (especially in older adults) is the most important risk factor for upper GI bleeding. Mortality is highest in patients with uncontrolled bleeding or who have a rebleeding event after the initial bleeding has stopped (see section “Upper Gastrointestinal Bleeding” below).[35]

Gastric perforation into the peritoneal cavity is the second most common ulcer-related complication, occurring in up to 7% of patients with PUD.[34] Depending on location, the ulcer may penetrate into an adjacent structure (pancreas, biliary tract, or liver) rather than opening freely into a cavity. Although the incidence of perforated peptic ulcers has decreased with the availability of PPIs, the mortality and morbidity remain high. Mortality can range from 1.3% to 20% and morbidity is also elevated (20%-50%) among patients requiring surgical intervention for perforated peptic ulcers. The pain of perforation is usually sudden, sharp, and severe, beginning first in the epigastrium, but quickly spreading over the entire abdomen. Most patients experience ulcer symptoms prior to perforation; however, older patients who experience perforation in association with NSAID use may be asymptomatic. The duodenum can be narrowed as a result of chronic inflammation and scaring from ulcers, resulting in gastric outlet obstruction. Although gastric outlet obstruction is rare, patients often present with severe vomiting and hematemesis.[20] Perforation, penetration, and gastric outlet obstruction occur most often with long-standing PUD.

CLINICAL PRESENTATION

There is significant variability in the clinical presentation of PUD depending on the severity of epigastric pain and the presence of complications (**Table 50-5**). Pain related to duodenal ulcer often occurs 1 to 3 hours after meals and is usually relieved by food, but this is variable. Food may precipitate or accentuate gastric ulcer pain. Antacids usually provide immediate pain relief in most ulcer patients. Pain usually diminishes or disappears during treatment; however, recurrence of epigastric pain after healing often suggests an unhealed or recurrent ulcer.

TABLE 50-5 Clinical Presentation of PUD

General
- Mild epigastric pain or acute life-threatening upper GI complications

Symptoms
- Abdominal pain that is often epigastric and described as burning but may present as vague discomfort, abdominal fullness, or cramping
- A typical nocturnal pain that awakens the patient from sleep (especially between 12 and 3 AM)
- The severity of ulcer pain varies from patient to patient and may be seasonal, occurring more frequently in the spring or fall; episodes of discomfort usually occur in clusters, lasting up to a few weeks and followed by a pain-free period or remission lasting from weeks to years
- Changes in the character of the pain may suggest the presence of complications
- Heartburn, belching, and bloating often accompany the pain
- Nausea, vomiting, and anorexia are more common for patients with gastric ulcer than with duodenal ulcer but may also be signs of an ulcer-related complication

Signs
- Weight loss associated with nausea, vomiting, and anorexia
- Complications including ulcer bleeding, perforation, penetration, or obstruction

Laboratory tests
- Gastric acid secretory studies
- The hematocrit and hemoglobin are low with bleeding, and stool hemoccult tests are positive
- Tests for *Helicobacter pylori* (see Table 50-6)

Diagnostic tests
- Fiber-optic upper endoscopy (esophagogastroduodenoscopy) detects more than 90% of peptic ulcers and permits direct inspection, biopsy, visualization of superficial erosions, and sites of active bleeding
- Upper GI radiography with barium has been replaced with upper endoscopy as the diagnostic procedure of choice for suspected peptic ulcer

GI, gastrointestinal; PUD, peptic ulcer disease.

The presence or absence of epigastric pain does not define an ulcer and ulcer healing does not necessarily render the patient asymptomatic. Symptoms may remain because of sensitization of afferent nerves in response to mucosal injury. Conversely, the absence of pain does not preclude an ulcer diagnosis especially in the elderly who may present with a “silent” ulcer complication possibly related to differences in the way the elderly perceive pain or the analgesic effect of NSAIDs.

Dyspepsia alone is of little clinical value when assessing subsets of patients

who are most likely to have an ulcer. Patients taking NSAIDs often report dyspepsia, but these symptoms do not always correlate with an ulcer. Nonulcer dyspepsia, or NUD, refers to the lack of an ulcer upon endoscopy in a patient with ulcer-like symptoms.[36] *H. pylori* gastritis or duodenitis may cause ulcer-like symptoms in the absence of peptic ulceration. There is no one sign or symptom that differentiates between *H. pylori*–positive and NSAID-induced ulcer.

Diagnosis

Symptoms of PUD are nonspecific and are of limited predictive value for diagnosis. The diagnosis of PUD depends on visualizing the ulcer crater (see Table 50-5).[4,20] Upper endoscopy has replaced radiography as the diagnostic procedure of choice because it provides a more accurate diagnosis and permits direct visualization of the ulcer and implementation of therapeutic maneuvers to control bleeding such as injection of epinephrine or deployment of hemostatic clips.

Tests for *Helicobacter pylori*

The diagnosis of *H. pylori* infection can be made using endoscopic or nonendoscopic tests (**Table 50-6**).[4,11,20,37] All patients with active PUD, past history of PUD without documentation of prior cure, low-grade gastric MALT lymphoma or history of endoscopic resection for early gastric cancer should be tested for *H. pylori*.[11] Testing that requires upper endoscopy is invasive, more expensive, and usually requires a mucosal biopsy for histology, culture, or detection of urease activity. The updated Sydney system recommends taking five tissue samples from different sites within the stomach, as patchy distribution of *H. pylori* infection can lead to false-negative results.[38] Because antibiotics, including bismuth salts, and proton pump inhibitors (PPIs) may decrease the sensitivity of rapid urease test, they should be withheld prior to endoscopic testing for 4 weeks and 2 weeks, respectively.[11,37,39] If the patient has been taking these medications, then a gastric biopsy for histology is preferred.[37]

TABLE 50-6 Tests for Detection of *Helicobacter pylori*

Test	Description	Comments
Endoscopic tests		
Histology	Microbiologic examination using various stains	Gold standard; greater than 95% sensitive and specific; permits classification of gastritis; results are not immediate; not recommended for initial diagnosis; tests for active *H. pylori* infection
Culture	Culture of biopsy	Enables sensitivity testing to determine appropriate treatment or antibiotic resistance; 100% specific; results are not immediate; not recommended for initial diagnosis; used after failure of second-line treatment; tests for active *H. pylori* infection
Biopsy (rapid) urease	*H. pylori* urease generates ammonia, which causes a color change	Test of choice at endoscopy; greater than 90% sensitive and specific; easily performed; rapid results (usually within 24 hours); tests for active *H. pylori* infection
Polymerase chain reaction	*H. pylori* DNA detected in gastric tissue	Test is highly specific and sensitive; high rate of false-positives and false-negatives; positive DNA does not directly equate to presence of the organism; considered a research technique
Nonendoscopic tests		
Antibody detection (laboratory-based)	Detects antibodies to *H. pylori* in serum using laboratory-based ELISA tests and latex agglutination techniques	Quantitative; less sensitive and specific than endoscopic tests; more accurate than in office; unable to determine if antibody is related to active or cured infection; antibody titers vary markedly among individuals and take 6 months to 1 year to return to the uninfected range; not affected by PPIs or bismuth; antibiotics given for unrelated indications may cure the infection, but antibody test will remain positive
Antibody detection (can be performed in office or near patient)	Detects IgG antibodies to *H. pylori* in whole blood or finger stick	Qualitative; quick (within 15 minutes); unable to determine if antibody is related to active or cured infection; most patients remain seropositive for at least 6 months to 1 year after *H. pylori* eradication; not affected by PPIs, bismuth, or antibiotics
Urea breath test	*H. pylori* urease breaks down ingested labeled C-urea, patient exhales labeled CO_2	Tests for active *H. pylori* infection; 95% sensitive and specific; results take about 2 days; antibiotics, bismuth, PPIs, and H2RAs may cause false-negative results; withhold PPIs or H2RAs (1-2 weeks) and bismuth or antibiotics (4 weeks) prior to testing; recommended test to confirm posttreatment eradication of *H. pylori*
Fecal antigen	Identifies *H. pylori* antigen in stool by enzyme immunoassay using polyclonal anti–*H. pylori* antibody	Tests for active *H. pylori* infection; sensitivity and specificity comparable to urea breath test when used for initial diagnosis; antibiotics, bismuth, and PPIs may cause false-negative results, but to a lesser extent than with the urea breath test; may be used posttreatment to confirm eradication, but patients may have a reluctance to obtain stool samples

ELISA, enzyme-linked immunosorbent assay; H2RA, H_2-receptor antagonist; PPIs, proton pump inhibitors.

Data from references 10, 20, and 48.

Nonendoscopic tests (urea breath test [UBT], serologic antibody detection tests, and the fecal antigen test) may identify active infection or detect antibodies (see Table 50-6) and are less invasive, more convenient, and less expensive than the endoscopic tests.[11,20,37] However, antibody tests do not differentiate between active infection and previously eradicated *H. pylori*.

The UBT is the most accurate noninvasive test and is based on *H. pylori* urease activity.[38] The ^{13}Carbon (nonradioactive isotope) and ^{14}Carbon

(radioactive isotope) tests require that the patient ingest radiolabeled urea, which is then hydrolyzed by *H. pylori* (if present in the stomach) to ammonia and radiolabeled bicarbonate. The radiolabeled bicarbonate is absorbed in the blood and excreted in the breath. In addition to being noninvasive, another advantage of UBT over biopsy is that it overcomes the possible sampling error associated with endoscopic biopsy secondary to irregular distribution of *H. pylori*.[38] The fecal antigen test is less expensive and easier to perform than the UBT, and may be useful in children.

Serologic tests are a cost-effective alternative for the initial diagnosis of *H. pylori* infection in the untreated patient. Antibodies to *H. pylori* usually develop about 3 weeks after infection and remain present after successful eradication. Therefore, serology should not be used to confirm *H. pylori* eradication. Office-based tests are less expensive, widely available, and provide rapid results, but the results are less accurate and more variable than the laboratory-based tests. Salivary and urine antibody tests are under investigation.

Testing for *H. pylori* is only recommended if eradication therapy is planned. Serologic antibody testing is a reasonable choice if endoscopy is not planned. The diagnostic accuracy of *H. pylori* tests for patients with an active bleeding ulcer has been questioned because of the potential for false-negative results. However, endoscopic biopsy-based tests such as the rapid urease test have a high degree of specificity in these patients (see section “Peptic Ulcer–Related Bleeding”).[11]

Confirmation of eradication is indicated posttreatment whenever *H. pylori* is identified and treated.[11]Endoscopic biopsy-based tests, UBT and fecal antigen are the recommended tests to confirm *H. pylori* eradication. Testing for eradication should be delayed at least 4 weeks after the completion of antibiotics and after PPI has been discontinued for 2 weeks to avoid confusing bacterial suppression with eradication.[11]

Clinical Course and Prognosis

PUD is characterized by periods of exacerbations and remissions.[1] Ulcer pain is usually recognizable and episodic, but symptoms are varied, especially in older adults and for patients taking NSAIDs. Antiulcer medications, including the histamine-2 receptor antagonists (H2RAs), PPIs, and sucralfate, relieve symptoms, accelerate ulcer healing, and reduce the risk of ulcer recurrence, but they do not cure the disease. Both duodenal and gastric ulcers recur unless the underlying cause (*H. pylori* or NSAID) is addressed. Successful *H. pylori*

eradication markedly decreases ulcer recurrence and complications. Prophylactic co-therapy or a COX-2 inhibitor decreases the risk of upper GI events for patients who are taking NSAIDs. GI bleeding, perforation, and obstruction remain troublesome complications of chronic PUD. Mortality for patients with gastric ulcer is slightly higher than in duodenal ulcer and the general population. The development of gastric cancer in *H. pylori*–infected individuals is a slow process that occurs over 20 to 40 years and is associated with a lifetime risk of less than 1%.[13]

TREATMENT

General Approach to Treatment

The treatment of PUD varies depending on the etiology of the ulcer (*H. pylori* or NSAID), whether the ulcer is initial or recurrent, and whether complications have occurred (**Fig. 50-5**). Treatment is aimed at relieving ulcer pain, healing the ulcer, preventing ulcer recurrence, and reducing ulcer-related complications. Antimicrobials in combination with antisecretory drugs (PPIs or H2RAs) eradicate *H. pylori* infection allowing for ulcer healing and relief of ulcer symptoms. PPIs accelerate ulcer healing and provide more effective relief of symptoms compared to H2RAs or sucralfate, and are preferred for healing *H. pylori*-negative NSAID-induced ulcers. In patients taking NSAIDs for pain, alternative agents such as acetaminophen or nonacetylated salicylate (eg, salsalate) should be used for relief of pain when possible. Patients requiring continuation of NSAID therapy at high risk of developing peptic ulcers should be switched to a selective COX-2 inhibitor NSAID or receive prophylactic co-therapy to reduce ulcer risk and related complications.

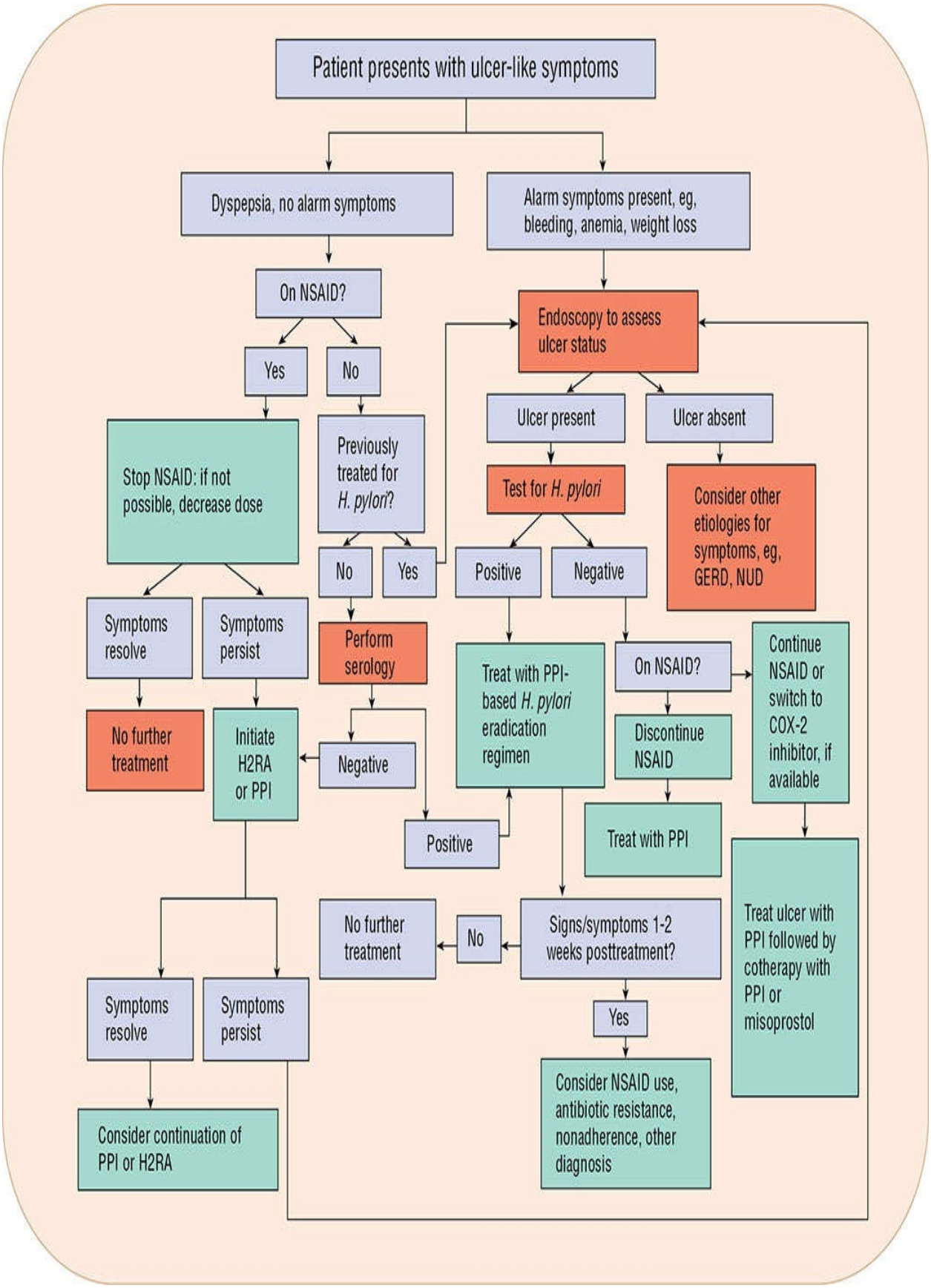

Patient presents with ulcer-like symptoms
Dyspepsia, no alarm symptoms
Alarm symptoms present, eg, bleeding, anemia, weight loss
On NSAID?
Yes
No
Endoscopy to assess ulcer status
Ulcer present
Ulcer absent
Stop NSAID: if not possible, decrease dose
Previously treated for H. pylori?
Test for H. pylori
Consider other etiologies for symptoms, eg, GERD, NUD
No
Yes
Positive
Negative
Symptoms resolve
Symptoms persist
Perform serology
Treat with PPI-based H. pylori eradication regimen
On NSAID?
Continue NSAID or switch to COX-2 inhibitor, if available
No further treatment
Initiate H2RA or PPI
Negative
Discontinue NSAID
Positive
Treat with PPI
Treat ulcer with PPI followed by cotherapy with PPI or misoprostol
No further treatment
No
Signs/symptoms 1-2 weeks posttreatment?
Symptoms resolve
Symptoms persist
Yes
Consider NSAID use, antibiotic resistance, nonadherence, other diagnosis
Consider continuation of PPI or H2RA

FIGURE 50-5 Algorithm. Guidelines for the evaluation and management of a patient who presents with dyspeptic or ulcer-like symptoms. (COX-2, cyclooxygenase-2; GERD, gastroesophageal reflux disease; H2RA, H_2-receptor antagonist; NSAID, nonsteroidal antiinflamatory drug; NUD, nonulcer dyspepsia; PPI, proton pump inhibitor.)

Dietary modifications can be considered for patients unable to tolerate certain foods and beverages. Lifestyle modifications such as reducing stress and smoking cessation are encouraged. Surgery is rarely necessary and is used only for patients with ulcer-related complications.[40]

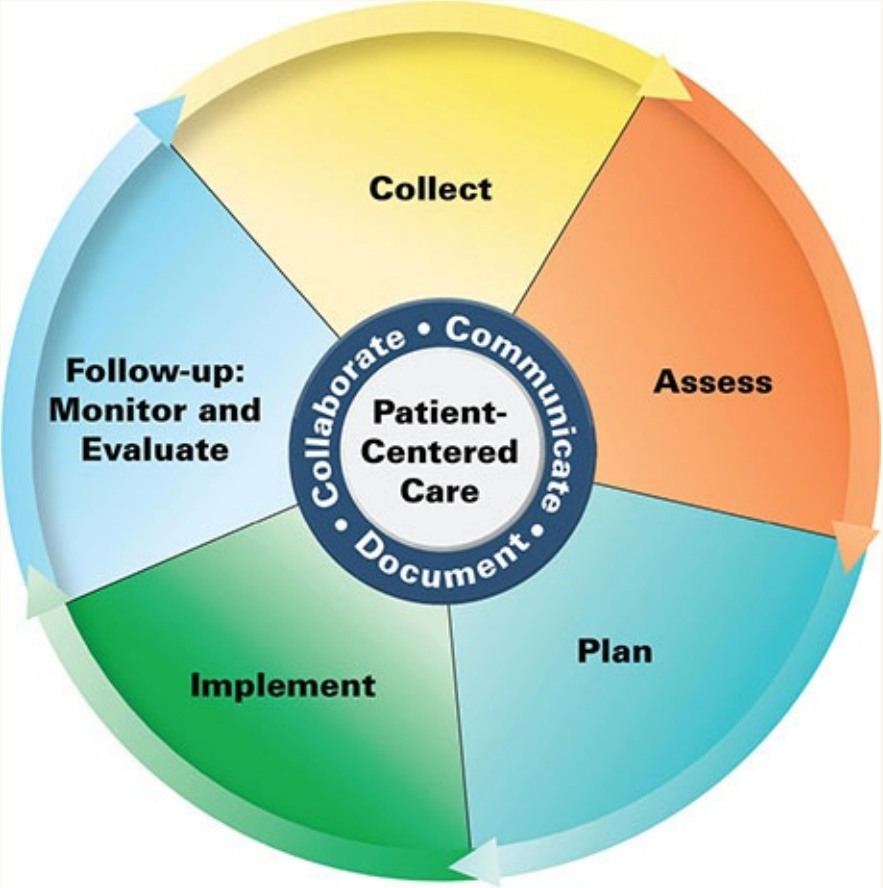
Desired Outcome

The goal of patients with PUD, regardless of the cause, is to relieve ulcer symptoms, heal the ulcer, and prevent recurrence. In patients with NSAID-induced ulcer, withdrawal of the offending agent and careful consideration of the need for continued NSAID therapy can reduce the risk of ulcer recurrence. In *H. pylori*–positive patients with an active ulcer, a previously documented ulcer, or a history of an ulcer-related complication, the goal is to eradicate *H. pylori*, heal the ulcer, and cure the disease. Successful eradication heals ulcers and reduces the risk of recurrence for most patients.

Nonpharmacologic Therapy

1 Lifestyle modifications, including stress reduction and smoking cessation, should be implemented in patients with PUD. There is no specific recommended diet for patients with current or history of PUD; however, patients should avoid foods and beverages (eg, spicy foods, caffeine, and alcohol) that cause dyspepsia or that exacerbate ulcer symptoms. Elective surgery for PUD is rarely performed today because of highly effective medical management. Emergent surgery for patients with ulcer-related complications, including bleeding, perforation, or obstruction, is necessary in about 7% of hospitalized patients.[40] Historically, surgical procedures such as vagotomy with pyloroplasty or vagotomy with antrectomy were performed for cases of medical treatment failure.[1] Vagotomy (truncal, selective, or parietal cell) inhibits vagal stimulation of gastric acid. A truncal or selective vagotomy frequently results in postoperative gastric dysfunction and requires a pyloroplasty or antrectomy to facilitate gastric drainage. When an antrectomy is performed, the remaining stomach is

anastomosed with the duodenum (Billroth I) or with the jejunum (Billroth II). A vagotomy is unnecessary when an antrectomy is performed for gastric ulcer. Postoperative consequences include postvagotomy diarrhea, dumping syndrome, anemia, and recurrent ulceration.



Patient Care Process for Peptic Ulcer Disease (PUD)

Collect

- Patient characteristics (eg, age, sex, pregnant)
- Patient medical history (personal and family) especially prior history of *H. pylori* infection, previous peptic ulcers, or previous upper GI disorders (see Table 50-4)
- Social history (eg, tobacco and ethanol use) as well as recent medical procedures and stress levels (see Table 50-2)
- Current medications, especially NSAIDS (nonprescription and

prescription) use of nonprescription proton pump inhibitors (PPIs), other acid reflux treatments, anticoagulants, and antiplatelet medications. If prior NSAID use, note medication, dosage, and duration of use

- Pain: presence or absence, rating (1-10), quality, and location (see Table 50-5)
- Objective Data
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2-saturation
  - Labs including hemoglobin (Hgb), hematocrit, gastric acid secretory studies, and stool hemoccult
  - Urea breath test (UBT) for detection of *H. pylori*. Follow-up culture with endoscopy recommended (see Table 50-6)
  - Imaging studies: Upper endoscopy

Assess

- Hemodynamic stability (eg, systolic BP >90 mm Hg, Hr >110 bpm, O_2 sat <90% [0.90])
- Presence of active gastric bleeding based on imaging studies
- Presence of GI-bleed provoking factors (low platelets, anticoagulant/antiplatelet use, NSAID use, age >65, recent surgery, severe co-morbidities eg, cardiovascular disease) (see Table 50-4)
- Presence/absence of *H. pylori*
- Emotional status (eg, anxiety, depression, stress levels)
- Ability/willingness to pay for ulcer treatment options
- Ability/willingness to discontinue NSAIDS and switch to another pain reliever, if applicable
- Ability/willingness to obtain laboratory monitoring tests (eg, *H. pylori* status to confirm eradication) (see Table 50-7)
- Ability/willingness to follow a multiple drug regimen for 10 to 14 days, with some doses to be taken at specific times

Plan

- Drug therapy regimen based on ulcer classification and patient's antibiotic tolerance (eg, penicillin allergy) (see)

- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug-specific information, medication administration)
- Self-monitoring for resolution of symptoms such as epigastric pain, dyspepsia, when to seek emergency medical attention

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (endoscopic *H. pylori* culture, lab tests: CBC, serum electrolytes, renal/liver function; see Table 50-10)

Follow-up: Monitor and Evaluate

- Resolution of PUD symptoms such as epigastric pain and dyspepsia
- Presence of adverse effects (eg, N/V/D (PPIs, H2RAs, metronidazole, other antibiotics), headaches (PPIs and H2RAs)
- Patient adherence to treatment plan using multiple sources of information
- Monitor patient for symptoms of PUD recurrence, especially if their risk factors change

** Collaborate with patient, caregivers, and other healthcare professionals.*

Pharmacologic Therapy

Recommendations

2 **Table 50-7** presents guidelines for the eradication of infection in *H. pylori*–positive individuals. **Table 50-8** lists regimens used to eradicate *H. pylori* infection.

TABLE 50-7 Guidelines for the Eradication of *Helicobacter pylori* Infection

Indications for treatment of *H. pylori* infection

- Established indications for the treatment of *H. pylori* include active PUD, past history of PUD (unless eradication previously documented), MALT lymphoma, or after endoscopic resection of gastric cancer
- Controversial indications for the treatment of *H. pylori* infection include individuals with nonulcer dyspepsia, gastroesophageal reflux disease, unexplained iron deficiency anemia, or idiopathic thrombocytopenic purpura; individuals taking long-term low-dose aspirin or initiating chronic treatment with NSAIDs; and individuals at high risk for gastric cancer

Initial treatment of *H. pylori* infection

- Bismuth quadruple therapy and concomitant (non-bismuth quadruple therapy), both administered for 10-14 days, are recommended first-line treatments.
- In penicillin-allergic patients, bismuth quadruple therapy is the preferred initial treatment. Consider referral for allergy testing in patients who fail initial therapy, since many patients who report penicillin allergy are not truly allergic.
- Alternate initial therapies (conditionally recommended) include: Sequential, hybrid, levofloxacin-triple, levofloxacin sequential, and LOAD therapies (see Table 50-8 for a full description).

Eradication of *H. pylori* after initial treatment failure

- Bismuth quadruple therapy or levofloxacin regimens are preferred if the patient received initial treatment with clarithromycin.
- Clarithromycin- or levofloxacin-containing regimens are preferred if patients received initial treatment with bismuth quadruple therapy.
- Selection of the optimal salvage regimen should be based on local antibiotic resistance profile, if available, and the patient's prior antibiotic history.

MALT, mucosa-associated lymphoid tissue; NSAIDs, nonsteroidal anti-inflammatory drugs, PPI, proton pump inhibitor.

Data from references 10, 11, and 48.

TABLE 50-8 Drug Regimens Used to Eradicate *Helicobacter pylori*

Regimen	Duration	Drug #1	Drug #2	Drug #3	Drug #4
Proton Pump Inhibitor–Based Triple Therapy[a]	14 days	PPI once or twice daily[b]	Clarithromycin 500 mg twice daily	Amoxicillin 1 g twice daily *or* metronidazole 500 mg twice daily	
Bismuth Quadruple Therapy[d]	10-14 days	PPI or H2RA once or twice daily[b,c]	Bismuth subsalicylate[d] 525 mg four times daily	Metronidazole 250-500 mg four times daily	Tetracycline 500 mg four times daily
Non-Bismuth Quadruple or "Concomitant" Therapy[e]	10-14 days	PPI once or twice daily on days 1-10[b]	Clarithromycin 250–500 mg twice daily on days 1-10	Amoxicillin 1 g twice daily on days 1-10	Metronidazole 250-500 mg twice daily on days 1-10
Sequential Therapy[e]	10 days	PPI once or twice daily on days 1-10[b]	Amoxicillin 1 g twice daily on days 1-5	Metronidazole 250–500 mg twice daily on days 6-10	Clarithromycin 250-500 mg twice daily on days 6-10
Hybrid Therapy[e]	14 days	PPI once or twice daily on days 1-14[b]	Amoxicillin 1 g twice daily on days 1-14	Metronidazole 250–500 mg twice daily on days 7-14	Clarithromycin 250-500 mg twice daily on days 7-14
Levofloxacin triple	10-14 days	PPI twice daily	Levofloxacin 500 mg daily	Amoxacillin 1 g twice daily	
Levofloxacin Sequential	10 days	PPI twice daily on days 1-10	Amoxicillin 1 g twice daily on days 1-10	Levofloxacin 500 mg once daily on days 6-10	Metronidazole 500 mg twice daily on days 6-10
LOAD	7-10 days	Levofloxacin 250 mg once daily	Omeprazole (or other PPI) at high dose once daily	Nitazoxanide (Alinia) 500 mg twice daily	Doxycycline 100 mg once daily

[a]Although treatment is minimally effective if used for 7 days, 10-14 days is recommended. The antisecretory drug may be continued beyond antimicrobial treatment for patients with a history of a complicated ulcer, for example, bleeding, or in heavy smokers.

[b]Standard PPI peptic ulcer healing dosages given once or twice daily.

[c]Standard H2RA peptic ulcer healing dosages may be used in place of a PPI.

[d]Bismuth subcitrate potassium (biskalcitrate) 140 mg, as the bismuth salt, is contained in a prepackaged capsule (Pylera), along with metronidazole 125 mg and tetracycline 125 mg; three capsules are taken with each meal and at bedtime; a standard PPI dosage is added to the regimen and taken twice daily. All medications are taken for 10 days.

[e]Requires validation as first-line therapy in the United States.

H2RA, H_2>-receptor antagonist; PPI, proton pump inhibitor.

Data from references 3, 10, 11, and 48.

3 The most cost-effective drug regimen should be used whenever feasible. Several first-line therapies are recommended, but bismuth quadruple therapy for 10 to 14 days has the strongest level of recommendation and should be used preferentially. Another recommended first line therapy is concomitant therapy (PPI, clarithromycin, with amoxicillin or metronidazole) for 10 to 14 days. Clarithromycin triple therapy is no longer recommended in areas where *H. pylori* resistance exceeds 15%, which includes all of North America. If a second course of treatment is required, the salvage regimen should contain different antibiotics and patients with reported penicillin allergy should be considered for allergy

testing.

H. pylori testing should be performed in patients with NSAID-induced ulcers to determine their status. If *H. pylori*–positive, treatment should be initiated with a recommended first-line regimen (see Table 50-8). If *H. pylori*-negative, the NSAID should be discontinued, and the patient treated with a PPI, H2RA, or sucralfate (see **Table 50-9**). If the NSAID is continued, co-therapy with a PPI or misoprostol should be implemented. Patients at highest risk of recurrent ulcers or ulcer-related complications should be switched to a selective COX-2 inhibitor.

TABLE 50-9 Drug Dosing Table

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Other
Proton Pump Inhibitors					
Omeprazole, sodium bicarbonate	Prilosec, Zegerid	40 mg daily	20-40 mg/day	Consider adjustment for hepatic disease	Pregnancy Category C
Lansoprazole	Prevacid, various	30 mg daily	15-30 mg/day	Consider adjustment for hepatic disease	Pregnancy Category B
Rabeprazole	Aciphex	20 mg daily	20-40 mg/day	Use with caution in severe hepatic disease	Pregnancy Category B
Pantoprazole	Pantoprazole, various	40 mg daily	40-80 mg/day	Consider adjustment for severe hepatic disease	Pregnancy Category B
Esomeprazole	Nexium	40 mg daily	20-40 mg/day	Limit dose to 20 mg/day in severe hepatic disease	Pregnancy Category B
Dexlansoprazole	Dexilant	30-60 mg daily	30-60 mg/day	Consider dose limit of 30 mg/day in moderate hepatic impairment, dose not established in severe hepatic disease	Pregnancy Category B
H2-Receptor Antagonists					
Cimetidine	Tagamet, various	300 mg four times daily, 400 mg twice daily, or 800 mg at bedtime	800-1,600 mg/day in divided doses	Adjust dose for renal and severe hepatic impairment	Pregnancy Category B
Famotidine	Pepcid, various	20 mg twice daily, or 40 mg at bedtime	20-40 mg/day	Adjust dose for renal impairment	Pregnancy Category B
Nizatidine	Axid, various	150 mg twice daily, or 300 mg at bedtime	150-300 mg/day	Adjust dose for renal impairment	Pregnancy Category B
Ranitidine	Zantac, various	150 mg twice daily, or 300 mg at bedtime	150-300 mg/day	Adjust dose for renal impairment	Pregnancy Category B
Mucosal Protectants					
Sucralfate	Carafate, various	1 g four times daily, or 2 g twice daily	2-4 g/day		Aluminum may accumulate in renal failure, Pregnancy Category B
Misoprostol	Cytotec	100-200 mcg four times daily	400-800 mcg/day		Pregnancy Category X

Data from references 3 and 78.

Maintenance therapy with a PPI or H2RA should be limited to high-risk patients with ulcer complications, patients who fail eradication, and those with *H. pylori*-negative ulcers. Treatment failure is associated with poor medication adherence, antimicrobial resistance, NSAID use, cigarette smoking, acid

hypersecretion, or tolerance to the antisecretory effects of an H2RA.

Treatment of *Helicobacter pylori*–Positive Ulcers

This chapter focuses on the eradication of *H. pylori* in adults. A discussion of the treatment of *H. pylori* infection in children is found elsewhere.[41]

Ideally, treatment of *H. pylori*–positive PUD should be highly-effective, free of significant side effects, easy to adhere to, and cost-effective. Unfortunately, currently available treatments are lacking in one or more of these areas, making it difficult to identify an ideal treatment regimen.[1] The most important predictor of *H. pylori* eradication is antimicrobial resistance.[11] Additional factors that may also be important include duration of therapy, medication adherence, and genetic polymorphism.[42,43] The initial eradication regimen offers the highest likelihood of eradication; therefore, selection of an appropriate first-line regimen is important. No available regimen offers assurance of 100% eradication, and few, if any, currently recommended regimens consistently exceed 90% eradication in studies.[11,44]

Table 50-8 summarizes available first-line drug regimens with antisecretory drug, usually a PPI, in combination with multiple antibiotics and/or bismuth. Two-drug regimens combining a PPI with either amoxicillin or clarithromycin have yielded marginal and variable eradication rates in the United States and are not recommended as first-line therapy.[11] In addition, the use of only one antibiotic is associated with a higher rate of antimicrobial resistance and is therefore not recommended. Clarithromycin, amoxicillin, metronidazole, and tetracycline have in vitro activity against *H. pylori* and have been extensively studied in various combinations and dosing strategies. Because of insufficient data, ampicillin should not be substituted for amoxicillin, doxycycline should not be substituted for tetracycline, and azithromycin or erythromycin should not be substituted for clarithromycin.[45] Bismuth salts have a topical antimicrobial effect.

Antisecretory drugs hastens ulcer healing, relieves pain in patients with an active ulcer, and enhances antibiotic activity by increasing intragastric pH and by decreasing intragastric volume thereby enhancing the topical antibiotic concentration. *PPIs generally produce higher H. pylori eradication rates and are preferred over H2RA.* The PPI is an integral part of the regimen and should be taken 30 to 60 minutes before a meal (see Table 50-8). Prolonged PPI treatment beyond 2 weeks after eradication is usually not necessary for ulcer healing. A single daily dose of a PPI may be less effective than a twice-daily

dose. Substitution of one PPI for another is acceptable and does not enhance or diminish *H. pylori* eradication.[46] An H2RA should not be substituted for a PPI unless there are significant tolerability issues, as H2RA is associated with lower eradication rates. Pretreatment with a PPI does not influence *H. pylori* eradication regardless of the pretreatment duration.[47]

TABLE 50-10 Drug Monitoring Table

Drug	Adverse Drug Reaction	Monitoring Parameter	Comments
PPIs	Headache, N/V/D, flatulence Less common: thrombocytopenia, neutropenia, hypomagnesemia, hypocalcemia, liver function abnormalities, renal impairment	Baseline and periodic CBC, serum electrolytes, renal/liver function	Well tolerated; may be associated with increased risk of fractures, pneumonia, *Clostridium difficile* infection
H2RA	Headache, dizziness, diarrhea, somnolence, gynecomastia (cimetidine) Less common: thrombocytopenia, neutropenia, liver function abnormalities, renal impairment, pancreatitis	Baseline and periodic CBC, serum electrolytes, renal/liver function	
Sucralfate	Constipation		
Misoprostol	Diarrhea, abdominal pain, headache, nausea/vomiting, flatulence, dysmenorrhea, hypophosphatemia	Pregnancy test Serum phosphate	Avoid in pregnancy

CBC, complete blood count; H2RA, H_2-receptor antagonists; PPIs, proton pump inhibitors.

Data from references 78, 87, 88.

Proton Pump Inhibitor–Based Three-Drug Regimens

PPI-based triple therapy (see Table 50-8), once regarded as the preferred initial treatment of choice for eradicating *H. pylori* (see Table 50-7), is no longer recommended as first line-therapy in North America due to the increased rates of clarithromycin resistance (see section "Factors that Predict *Helicobacter pylori* Eradication Outcomes" below).[11,44,48,49] PPI-based triple therapy remains an option in regions where clarithromycin resistance is <15% and no prior macrolide exposure is documented.[11]

If use is indicated, regimens that combine clarithromycin with amoxicillin or metronidazole are more effective than the amoxicillin–metronidazole regimen. The clarithromycin–amoxicillin regimen is preferred initially (see Table 50-7), but metronidazole can be substituted for amoxicillin for penicillin-allergic patients unless alcohol is consumed.[11,48] In most cases, increasing the antibiotic dosage does not improve eradication rates. Since the first treatment regimen offers the highest probability of *H. pylori* eradication, the recommended duration of triple therapy is 14 days.[11] Shorter treatment durations, including 7- to 10-day

courses, should no longer be used because of increased resistance and lower overall eradication rates.[11,50]

Bismuth-Containing Quadruple Therapy

Bismuth-based quadruple therapy (bismuth salicylate, metronidazole, tetracycline, and either a PPI or H2RA) (see Table 50-8) is a recommended first-line option (see Table 50-7), particularly for those patients who are allergic to penicillin.[11] The mean eradication rate for bismuth-based quadruple therapy given for 10 days was 91%, which is considerably higher compared with PPI-based triple therapy.[11] Bismuth quadruple therapy for 10 to 14 days was superior to 7 days of clarithromycin triple therapy (85% vs 73%, RR=1.17).[51] Eradication rates are comparable for different bismuth preparations used (see Table 50-8).[52] All medications except the PPI should be taken with meals and at bedtime. Limitations of this regimen include four times per day dosing, potential for poor medication adherence, and frequent minor side effects.

Sequential Therapy Sequential therapy is a form of eradication therapy in which the antibiotics are administered in a sequence rather than together.[11,53] The basis for sequential therapy is to initially treat with antibiotics that rarely promote resistance (eg, amoxicillin) to reduce the bacterial load and any preexisting resistant organisms that are susceptible. The second sequence follows with different antibiotics (eg, clarithromycin and metronidazole) to kill any remaining organisms. Treatment typically consists of a PPI and amoxicillin for 5 days followed by a PPI, clarithromycin, and tinidazole (or metronidazole) for an additional 5 days (see Table 50-8).[11,53,54] Although this regimen has achieved eradication rates that are superior to the PPI-based three-drug regimens containing clarithromycin,[54] the regimen requires a change in medication mid-treatment, which may contribute to nonadherence. Though promising, the advantages of sequential therapy have yet to be fully validated in the United States, and is only conditionally recommended within the guidelines as a first-line *H. pylori* eradication therapy (see Table 50-7).[11]

Non-Bismuth Quadruple “Concomitant” Therapy and Hybrid Therapy

Non-bismuth quadruple therapy, also called “concomitant” therapy, is a regimen with a PPI, amoxicillin, clarithromycin, and metronidazole taken together at standard doses for 10 to 14 days. Hybrid therapy combines the strategies of

concomitant and sequential therapy. Patients take 7 days of dual therapy (PPI and amoxicillin) followed by 7 days of quadruple therapy (PPI, amoxicillin, clarithromycin, and metronidazole). Although clarithromycin resistance may impact efficacy rates, available evidence suggests that both concomitant and hybrid therapy may be impacted less than clarithromycin triple therapy. Both regimens are first-line alternatives to clarithromycin triple therapy but there is a lack of evidence in North America with these regimens.[11]

Levofloxacin-Based Therapy

Levofloxacin has been studied as first-line and salvage therapy for *H. pylori* eradication, but data are scarce for levofloxacin-based first line treatment regimens. Three regimens using levofloxacin have been suggested: levofloxacin triple therapy with amoxicillin and a PPI; modified sequential therapy with 5 to 7 days of amoxicillin plus a PPI followed by 5 to 7 days of levofloxacin; and quadruple therapy consisting of levofloxacin, nitazoxanide, doxycycline, and a PPI. Eradication was similar with 7 days of clarithromycin-based or levofloxacin triple therapy; however, levofloxacin-based triple therapy for 10 to 14 days was superior to clarithromycin triple therapy for 7 days.[51,55] Levofloxacin sequential therapy had eradication rates higher than pooled clarithromycin-based triple and sequential regimens (87.8% vs 71.1%).[56] A first-line quadruple regimen, termed "LOAD" that contains levofloxacin, omeprazole, nitazoxanide (Alinia), and doxycycline, is not currently recommended within the guidelines due to cost and lack of data.[11,57] However, concerns about using fluoroquinolones to treat *H. pylori* include development of resistance and adverse effects (eg, tendonitis and hepatotoxicity).

Probiotics

Probiotics (eg, strains of *Lactobacillus* and *Bifidobacterium*) limit *H. pylori* colonization and when taken as a supplement to antibiotic therapy, increases eradication rates compared to placebo and may reduce the adverse effects of antibiotic eradication therapy.[58–60] However, the administration of probiotics alone does not eradicate *H. pylori* infection. In the future, the regular intake of probiotics may constitute a low-cost alternative for individuals who are at risk for *H. pylori* infection and, in combination with antibiotics, augment eradication rates. These preliminary data are encouraging and warrant more research in this area.

Eradication of *Helicobacter pylori* After Initial Treatment Failure

H. pylori eradication is often more difficult after initial treatment fails and successful eradication after retreatment is extremely variable.[11] Treatment failures should be referred to a gastroenterologist for further diagnostic evaluation. Second-line (salvage) treatment should (a) use antibiotics that were not used during initial therapy or recently for another infection; (b) be guided by region-specific or individual antibiotic resistance testing, if available; and (c) use an extended duration of treatment up to 10 to 14 days.[11] Ideally, culture and sensitivity or molecular resistance data would be available to guide salvage regimen selection; however, these modalities are infrequently available within the United States and empiric treatment decisions are necessary. European guidelines recommend obtaining antimicrobial sensitivity information following the second failed attempt to eradicate *H. pylori*. Patients failing clarithromycin triple therapy can be treated with either bismuth quadruple therapy or levofloxacin triple regimen for 14 days (see Table 50-7).[61] A 10-day therapy containing PPI, bismuth, tetracycline, and levofloxacin achieved a high eradication rate after failure of first-line treatment with sequential therapy.[62] High-dose dual therapy using amoxicillin plus a PPI with both administered three-to-four times daily for 14 days is an acceptable therapy.[11] Other salvage regimens that include rifabutin and furazolidone are also effective, but these are discussed in more detail elsewhere.[63–65] Penicillin skin testing is now recommended for patients after failing one or two eradication attempts since amoxicillin is an important component of therapy with low prevalence of resistance and many patients reporting penicillin allergy are not truly allergic.[11,66]

Factors that Predict *Helicobacter pylori* Eradication Outcomes

Factors that predict successful *H. pylori* eradication can be divided into host-related and *H. pylori*-related factors. Medication adherence and pharmacogenomic factors are important host-related considerations, and antibiotic resistance is the most important and consistent predictor of *H. pylori* eradication.[48]

Medication adherence decreases with multiple medications, increased

frequency of administration, intolerable adverse effects, and costly drug regimens—all of which can be issues with currently recommended treatment options. Tolerability varies with different regimens, but common adverse effects include nausea, vomiting, abdominal pain, diarrhea, and taste disturbances (metronidazole and clarithromycin). Adverse effects with metronidazole are dose-related (especially when more than 1 g/day) and include a disulfiram-like reaction with alcohol. Tetracycline may cause photosensitivity and should not be used in children because of possible tooth discoloration. Bismuth salts may cause darkening of the stool and tongue. Antibiotic-associated diarrhea and *Clostridium difficile*–associated disease can occur. Oral thrush and vaginal candidiasis may also occur.

An increasingly important predictor of eradication is the presence or absence of resistant *H. pylori* strains.[11] Worldwide resistance rates among *H. pylori* strains (n = 818 isolates) for clarithromycin (30.8%), metronidazole (30.5%), amoxicillin (2%), tetracycline (0%), and levofloxacin (14.2%).[67] While amoxicillin and tetracycline resistance remains low, these data represent notable increases in resistance for metronidazole (25%) and clarithromycin (13%) compared to prior studies.[68] Increasing clarithromycin resistance may explain the decrease in efficacy of triple therapy clarithromycin-containing regimens. Prior antibiotic exposure is likely a factor in the development of resistance as was seen in one study where the proportion of clarithromycin resistance increased from 7% resistance with no prior macrolide exposure to 80% resistance with more than or equal to five courses.[69] Therefore, prior antibiotic use should prompt consideration for possible *H. pylori* resistance. The clinical importance of metronidazole resistance remains uncertain, as resistance can be overcome by using higher dosages and by combining metronidazole with other antibiotics. Resistance to tetracycline and amoxicillin is uncommon. Resistance to bismuth has not been reported.[11] Although the role of antibiotic sensitivity testing prior to initiating *H. pylori* treatment has not been formally established, newly developed molecular-based tests may offer quick and easy determination of *H. pylori* resistance to macrolides and fluoroquinolones allowing optimal regimen selection.[70]

Treatment of Nonsteroidal Anti-Inflammatory Drug–Induced Ulcers

NSAID therapy should be interrupted upon confirmation of an active ulcer. Once stopped, most uncomplicated NSAID ulcers heal with standard 8-week regimens

of an H2RA, PPI, or sucralfate (see Table 50-9).[4] Generally, PPIs are preferred due to more rapid symptom relief and ulcer healing. In patients where the NSAID is continued despite ulceration, treatment with a PPI or misoprostol should be initiated.[71] PPIs are the drugs of choice when the NSAID is continued, as potent acid suppression is required to accelerate ulcer healing. PPI treatment duration should be extended 12 weeks if the NSAID must be continued. In addition, consideration should be given to reducing the NSAID dose, switching to acetaminophen or a nonacetylated salicylate, or using a selective COX-2 inhibitor (see Table 50-3). If the ulcer is *H. pylori*–positive, eradication should be initiated with a regimen that contains a PPI.[4]

Prevention of NSAID-Related Peptic Ulcers

Amongst NSAID users, several therapeutic strategies are available to prevent gastroduodenal ulcers and related upper GI complications. These strategies include co-therapy of an NSAID with a PPI, H2RA, or misoprostol; preferential use of a COX-2 selective NSAID; or combination of a gastroprotective agent with a COX-2 selective NSAID. (see **Table 50-11**). COX-2 selective NSAID in combination with a PPI offers the greatest protection against upper GI complications. This regimen is followed in effectiveness by COX-2 selective NSAIDs alone, nonselective NSAIDs with a PPI, and medical co-therapy with misoprostol.[9,72] Unfortunately, these strategies may not eliminate ulcers and complications for patients at the "highest risk." Nonselective NSAID and co-therapy with a H2RA is effective at preventing duodenal but not gastric ulcers.[9] Selection of a gastroprotective strategy should consider both the GI benefits and the cardiovascular risks associated with NSAIDs.[4] Strategies aimed at reducing the topical irritant effects of nonselective NSAIDs, for example, prodrugs, slow-release formulations, and enteric-coated products, are not effective at preventing ulcers or GI complications.

TABLE 50-11 Prevention of Peptic Ulcer Disease in Patients Receiving Chronic NSAID Therapy

	Low Gastrointestinal Risk[a]	High Gastrointestinal Risk[b,c]
Low Cardiovascular Risk	Nonselective NSAIDs	Nonselective NSAIDs plus PPI; celecoxib plus PPI[d]
High Cardiovascular Risk[e]	Naproxen; add PPI if patient is taking aspirin	No NSAIDs; naproxen plus PPI; low-dose celecoxib plus aspirin plus PPI may be an alternative option[f]

[a]No risk factors.

[b]Presence of risk factors (patients 60 years or older, history of peptic ulcers, receiving concomitant antiplatelet agents, anticoagulants, corticosteroids, or selective serotonin reuptake inhibitors).

[c]In patients with prior history of ulcers, adopt test-and-treat strategy to exclude *H. pylori* infection.

[d]Consider when patients have complicated ulcer history or presence of multiple risk factors.

[e]Use risk calculator (eg, Framingham or ASCVD risk calculators) to estimate cardiovascular risk on the basis of several variables. Patients with a history of cardiovascular events or diabetes are considered high cardiovascular risk.

[f]NSAIDs with increasing selectivity for Cyclooxygenase-2 (COX-2) (ie, celecoxib) have been associated with increased cardiovascular risk, and this risk appears to be increased in patients with established cardiovascular disease. Patients with cardiovascular disease or risk factors, recommendations for pain management (in the order listed) include: acetaminophen, aspirin, tramadol, opioids (short-term), nonacetylated salicylates (eg, diflunisal), NSAIDs with low COX-2 selectivity (eg, naproxen), NSAIDs with some COX-2 selectivity (eg, nabumetone), and COX-2 selective agents (ie, celecoxib).

NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

From Sutton SS, NAPLEX Review, 3rd Edition, McGraw-Hill, Chapter 43: Love, BL.

Misoprostol Co-therapy

Misoprostol, a synthetic analog of prostaglandin E1, has dual gastroprotective effects by improving mucosal blood flow and by stimulating gastric mucous and bicarbonate secretion. It has a short half-life requiring doses to be administered three-to-four times daily. Low-dose misoprostol (400-600 mg/day) was effective at reducing peptic ulcer risk by more than 50%, but high doses were superior to lower doses with risk reduction of over 80%.[73] Misoprostol also limits PUD complications including perforation, gastric outlet obstruction, and bleeding. Misoprostol is associated with high-rates of nausea, diarrhea, and abdominal cramping that increase with the dose limiting its clinical utility.[9]

H2-Receptor Antagonist Co-therapy

Standard doses of H2RA (eg, famotidine 40 mg/day) are effective in reducing NSAID-related duodenal ulcer but not gastric ulcer (the most frequent type of ulcer associated with NSAIDs).[4,14] Higher dosages (eg, famotidine 40 mg twice daily, ranitidine 300 mg twice daily) did not reduce gastric and duodenal ulcers among higher risk patients (ie, age >65 or history of PUD).[74] Famotidine 20 mg twice daily may be an alternative to PPIs for patients taking low cardioprotective dosages of aspirin, but additional studies are required to confirm these findings.[75] H2RAs are not recommended as prophylactic co-therapy because it is likely that they are not as effective as the PPIs or misoprostol in preventing NSAID-induced gastric ulcer and related GI complications.[4] An H2RA, however, may be used to relieve NSAID-related dyspepsia.

Proton Pump Inhibitor Co-therapy

4 PPI co-therapy reduces NSAID-related gastric and duodenal ulcer risk and is better tolerated than misoprostol.[4,9,15,19] In head-to-head comparison, omeprazole demonstrated improved healing and prevention of gastric (RR 0.32; 95%) and duodenal (RR 0.11) ulcers compared with ranitidine.[9] All PPIs are considered equally effective when used in standard dosages (see Table 50-9) for ulcer prevention. PPIs reduce the risk of NSAID-related upper GI bleeding, but do not protect against lower GI bleeding.[19]

Cyclooxygenase-2 Inhibitors

COX-2 inhibitors are a group of drugs that preferentially act on the cyclooxygenase-2 enzyme, exhibiting equivalent anti-inflammatory activity of traditional NSAIDs without the increased risk of gastric or duodenal ulcers. Avoidance of COX-1 isoenzyme inhibition preserves prostaglandin production and its beneficial gastroprotective effects. Celecoxib preferentially inhibits COX-2 and continues to be available but carries the same GI and cardiovascular thrombotic black-box warnings as nonselective NSAIDs. The pooled relative risk for GI events is lower with celecoxib (RR 1.45;) compared to nonselective NSAIDs, but it is not without some risk. Gastroprotective benefits of celecoxib are lessened in aspirin users, thus if low-dose aspirin is needed, co-therapy with PPI is necessary. Similarly, the relative risk of cardiovascular events with celecoxib (RR 1.17;) is lower compared to most nonselective NSAIDs. In comparison to celecoxib, the CV risk with naproxen is thought to be lower and is

preferred in patients with a high cardiovascular risk profile.[4] Increased cardiovascular risk appears to be dependent on several factors including increased COX-2 selectivity, higher dosages, and a longer duration of treatment. Thus, the lowest effective celecoxib dose should be used for the shortest duration of time. Dyspepsia and abdominal pain, fluid retention, hypertension, and renal toxicity are associated with the COX-2 inhibitors and nonselective NSAIDs. Patients taking NSAIDs or COX-2 inhibitors should be counseled about signs and symptoms of adverse events, including upper GI bleeding and cardiovascular risks, and what to do should they occur.

COX-2 Inhibitor Versus NSAID Plus PPI

5 For high GI risk, low CV risk, *H. pylori*-negative patients, a COX-2 selective NSAID alone is at least as beneficial as a nonselective NSAID plus PPI co-therapy in reducing NSAID-related ulcer complications.[4] However, neither the COX-2 selective NSAID nor the NSAID plus a PPI guarantees elimination of upper GI events for high GI risk patients. Combining a COX-2 selective NSAID with a PPI can be considered for very high GI risk patients as it offers the best protection against PUD complications. Patients with complicated peptic ulcer history or presence of multiple risk factors are candidates for COX-2 selective NSAID combined with a PPI.[4]

Treatment of Non–*Helicobacter pylori*, Non-Nonsteroidal Anti-Inflammatory Drug Ulcers

Non–*H. pylori*, non-NSAID (idiopathic) ulcers are not commonly diagnosed compared to NSAID- or *H. pylori*-associated ulcers; however, the incidence of idiopathic ulcers may be increasing, and they may have more morbidity and mortality.[77] Patients should be double-checked to verify that they are *H. pylori*-negative and that they are not taking ulcerogenic medications. Possible explanations for *non–H. pylori*, non-NSAID ulcers include gastric hypersecretion, gastric outlet obstruction, genetic predisposition, concomitant diseases (see Table 50-2), and heavy tobacco use. Treatment should be initiated with conventional ulcer healing therapy (see Table 50-9). Since most patients with idiopathic peptic ulcers have a recurrence within 1 year, maintenance therapy may be required to prevent PUD complications.

Long-Term Maintenance of Ulcer Healing

Long-term maintenance of ulcer healing and the prevention of ulcer-related complications may be necessary in some patients. Because *H. pylori* eradication dramatically decreases ulcer recurrence, continuous maintenance therapy is primarily used to treat high-risk patients who failed *H. pylori* eradication, have a history of ulcer-related complications, have frequent recurrences of *H. pylori*-negative ulcers, and are heavy smokers or NSAID users. For most patients, standard maintenance dosages (see Table 50-9) are effective.[78]

Treatment of Refractory Ulcers

Refractory peptic ulcers are ulcers that persist after 8 to 12 weeks of standard anti-secretory drug treatment. Persistent *H. pylori* infection and use of NSAIDs are the most common causes of refractory ulcers. Additional contributing factors may include Poor patient compliance, cigarette smoking, gastric acid hypersecretion, or tolerance to the antisecretory effects of an H**2**RA (see section "Antiulcer Agents" below). Patients with refractory ulcers should undergo upper endoscopy to confirm a nonhealing ulcer, exclude malignancy, and reassess *H. pylori* status with two or more diagnostic methods to increase sensitivity.[79] *H. pylori*–positive patients should receive eradication therapy (see "Treatment of *H. pylori*–Positive Ulcers" above). Fasting plasma gastrin levels can be checked if Zollinger-Ellison syndrome is suspected. Refractory ulcers despite a complete standard PPI course should be retreated with double-dose of PPI. Consideration can be given to using a different PPI.[79]

Antiulcer Agents

Proton Pump Inhibitors

PPIs (see **Tables 50–9** and **50–12**) dose-dependently inhibit basal and stimulated gastric acid secretion. The duration of acid suppression is a function of binding to the H^+/K^+-adenosine triphosphatase (ATPase) enzyme. When PPI therapy is initiated, the degree of acid suppression increases over the first 3 to 4 days of therapy, as more proton pumps are inhibited. PPIs inhibit only those proton pumps that are actively secreting acid, thus they are most effective when taken 30 to 60 minutes before meals.[78] Symptomatic acid rebound on withdrawal of a PPI has been reported in healthy volunteers after 8 weeks of treatment.[80]

TABLE 50-12 PPI Formulations and Options for Administration

	Omeprazole	Esomeprazole	Lansoprazole	Pantoprazole	Rabeprazole	Dexlansoprazole
Commercially available oral formulations						
Capsule	X[a]	X	X			X[b]
Tablet	X[c]			X	X	
Oral disintegrating tablet			X			
Packet for oral suspension	X[d]	X[e]				
Extemporaneous oral preparations						
Pellets from capsule in water		X				
Pellets from capsule in applesauce	X		X			X
Pellets from capsule in juice	X	X[e]	X			
Extemporaneous preparation of delayed-release PPI in bicarbonate (omeprazole-sodium bicarbonate)	X		X	X		
Parenteral formulations						
IV	Not available in the United States	X		X		

[a]Omeprazole is available as delayed-release enteric-coated pellets in a capsule or as immediate-release capsule that contains 20 or 40 mg of omeprazole with 1,100 mg sodium bicarbonate (equivalent to 304 mg of sodium). Because 20 and 40 mg dosages contain the same amount of bicarbonate, two 20 mg capsules should not be substituted for the 40 mg immediate-release omeprazole-sodium bicarbonate capsule.

[b]Dexlansoprazole is available as a dual delayed-release formulation in capsules for oral administration. The capsule contains dexlansoprazole in a mixture of two types of enteric-coated granules with different pH-dependent dissolution profiles.

[c]Omeprazole oral tablets are available as 20 mg delayed-release nonprescription tablets.

[d]Omeprazole oral suspension is available as 20 or 40 mg omeprazole with 1,680 mg sodium bicarbonate (equivalent to 460 mg of sodium). Because 20 and 40 mg dosages contain the same amount of bicarbonate, two 20 mg packets should not be substituted for the 40 mg immediate-release omeprazole-bicarbonate packet.

[e]No published information; based on omeprazole data.

PPI, proton pump inhibitor; X, product is available.

PPIs are formulated as delayed-release enteric-coated dosage forms that have pH-sensitive granules contained in gelatin capsules (omeprazole, esomeprazole, prescription and nonprescription lansoprazole, and dexlansoprazole), rapidly disintegrating tablets (lansoprazole), and delayed-release enteric-coated tablets (rabeprazole, pantoprazole, and nonprescription omeprazole) (see Table 50-12).[78] The pH-sensitive enteric coating prevents degradation and premature protonation of the drug in stomach allowing the drug to be dissolved then absorbed in the duodenum at a higher pH. Dexlansoprazole is formulated with a dual-release mechanism that provides inhibition of proton pumps that become activated after initial release of the medication while omeprazole is also

available as an immediate-release formulation (oral suspension, oral capsule) containing sodium bicarbonate, which can control intragastric pH in the absence of food.[81] IV products available in the United States include pantoprazole and esomeprazole.

PPIs provide similar rates of ulcer healing (omeprazole, esomeprazole, lansoprazole, rabeprazole, and pantoprazole), symptom relief, and maintenance of ulcer healing when used in recommended dosages (see Table 50-9). Higher than indicated daily doses should be divided to obtain better 24-hour control of intragastric pH. Older adults and patients with renal impairment do not require dosage reductions, but dosage reductions should be considered in patients with severe hepatic disease.[82] Short-term adverse effects of the PPIs are like those observed with the H**2**RAs (headache, nausea, and abdominal pain). Immediate-release formulations contain sodium bicarbonate, and thus are contraindicated for patients with metabolic alkalosis and hypokalemia.

Drug Interactions Since PPIs increase intragastric pH, they may alter the bioavailability of orally administered drugs that are weak bases (eg, ketoconazole), digoxin, or pH-dependent dosage forms. This interaction is especially important with antiretroviral therapies for treatment of HIV, as reduced absorption can lead to therapeutic failure due to development of viral resistance.[83] Omeprazole and esomeprazole selectively inhibit the hepatic CYP2C19 pathway and may decrease the elimination of several drugs (eg, phenytoin, warfarin, diazepam, and carbamazepine).[84] PPIs may increase the metabolic clearance and decrease the GI absorption of levothyroxine resulting in increased thyroid-stimulating hormone levels and a corresponding increase in the levothyroxine dose.[85] Few drug-drug interactions (eg, phenytoin, warfarin, methotrexate) involving PPIs are clinically significant and usually constitute a major clinical risk.[84]

A controversial PPI drug interaction involves the antiplatelet drug clopidogrel. Clopidogrel is converted to its active form through CYP2C19. PPIs may attenuate the antiplatelet effect of clopidogrel by inhibiting or competing for this metabolic pathway. FDA safety guidelines recommend that the coadministration of omeprazole, omeprazole/sodium bicarbonate, or esomeprazole with clopidogrel be avoided because they reduce the effectiveness of clopidogrel. Warnings regarding omeprazole, esomeprazole, and other interacting drugs (eg, cimetidine) are contained in the clopidogrel package insert as well. This interaction is further complicated since genetic polymorphisms of the CYP2C19 pathway leading to decreased biotransformation of clopidogrel to

its active form may also explain reduced effectiveness of clopidogrel. Whether the use of other PPIs such as pantoprazole, lansoprazole, dexlansoprazole, and rabeprazole interacts with clopidogrel remains uncertain as the capacity to inhibit CYP2C19 varies among these PPIs.[86] Although pharmacodynamic studies suggest attenuated anti-platelet effects of clopidogrel with omeprazole, it does not appear to translate to increased cardiovascular risk in observational studies. In the only randomized, double-blind, placebo-controlled study of clopidogrel and omeprazole, there was no increased cardiovascular risk noted; however, the combination reduced the risk of upper GI bleeding. Given the limitations of existing studies, administration of clopidogrel with PPIs should be balanced based upon cardiovascular and gastrointestinal risk.[87]

Potential Long-Term Safety Issues Prolonged hypergastrinemia and chronic hypochlorhydria from long-term PPI use has been associated with numerous potential risks and safety issues (see **Table 50-13**).[88] In most cases, causality is difficult to ascertain because of the study design, confounding variables, and subject selection. All PPIs increase serum gastrin concentrations twofold to fourfold in a dose-dependent manner due to their potent acid-inhibitory effect.[88,89] Fasting gastrin elevations are usually within the normal range and return to baseline within 1 month of discontinuing the drug. In humans, PPIs may lead to enterochromaffin-like (ECL) hyperplasia, but there is no evidence that these changes result in dysplasia, carcinoid tumors, or gastric adenocarcinoma. Long-term PPI therapy in *H. pylori*–positive individuals is associated with progressive atrophic gastritis, but there are insufficient data to link chronic PPI use with gastric cancer in *H. pylori*–positive patients. There is also no evidence to support an association between PPIs and colonic polyps or colorectal cancer. Bacterial overgrowth can occur in the stomach as a consequence of hypochlorhydria, but the full biological significance of this change in quantity and diversity of bacteria in the stomach and small intestine of PPI users remains unclear.[90]

TABLE 50-13 Potential Risks and Safety Issues Associated with the PPIs

Gastric cancers or malignancy
Carcinoid tumors
Atrophic gastritis
Adenocarcinoma
Bacterial overgrowth
Increase in *N*-nitroso compounds from ingested nitrates (carcinogenic)
Enteric infections (*Clostridium difficile, Salmonella typhimurium*, and *Campylobacter jejuni*)
Community-acquired pneumonia
Decreased nutrient absorption:
Iron
Calcium
Cyanocobalamin (vitamin B_{12})
Magnesium
Osteoporosis and related fractures

PPI, proton pump inhibitor.

Data from references 87 and 88.

Chronic PPI therapy may be associated with an increased risk of infection and nutritional deficiences. Gastric acid plays an important role in the defense against bacterial colonization of the stomach and in nutrient absorption. Acid suppression has been implicated as a risk factor for community-acquired pneumonia (CAP) and enteric infections (*C. difficile*, *Salmonella*, *Campylobacter*). There is a higher adjusted relative risk of CAP for patients currently using PPIs compared with controls particularly in patients receiving higher doses or within the first 30 days of therapy.[91–93] The results of these retrospectively designed studies, however, need to be interpreted cautiously because of the variability in the length of therapy for current PPI users and the inclusion of older (older than 60 years) patients with concomitant comorbidities. PPIs are linked with various enteric infections, but the most convincing data were with *C. difficile*. Sustained elevations in intragastric pH may facilitate the survival of *C. difficile* spores. However, the magnitude of risk varies and causality is difficult to establish. The risk of various infections associated with PPI therapy cannot be firmly established until the results of large prospective studies are made available.

The absorption of vitamin B_{12}, dietary iron, and calcium requires an acidic environment and may be adversely affected by long-term use of PPIs (see Table 50-10). The clinical importance of PPIs on absorption has not been established, and routine monitoring of B_{12} and iron levels cannot be routinely recommended. Adequate supplementation and monitoring should be considered in high-risk populations (eg, older patients, vegetarians, alcoholism) who may be already

depleted. Hypomagnesemia, both symptomatic and asymptomatic, has been reported with PPI use with serious adverse events including tetany, arrhythmias, and seizures (see Table 50-10). In most cases it occurs in patients taking PPIs more than 1 year but can occur with as little as 3 months of therapy. The FDA has revised the warnings and precautions of prescription and nonprescription PPIs. High PPI dosage and long-term therapy have been associated with an increased risk of hip, wrist, and spine fractures related to reduction in calcium absorption. The FDA has revised the warnings and precautions of prescription and nonprescription PPIs to reflect this potential risk. Routine bone density tests for osteoporosis screening, calcium supplementation, or other precautions cannot be recommended solely based on chronic PPI therapy. However, it is appropriate to screen and treat older patients for osteoporosis regardless of whether they are receiving long-term PPI therapy.[84]

H2-Receptor Antagonists

Ulcer healing is comparable among H**2**RAs with equipotent multiple daily doses or a single full dose given after dinner or at bedtime (see Table 50-9), but tolerance to their antisecretory effect may occur. Twice-daily administration may be beneficial in patients with daytime ulcer pain while cigarette smokers may require higher doses or a longer duration of treatment. H**2**RAs are renally eliminated thus a dosage reduction is recommended for patients with moderate-to-severe renal failure. The short- and long-term safety of all H**2**RAs is similar. Thrombocytopenia is a common yet likely overestimated hematologic adverse effect that occurs with all H**2**RAs and is reversible (see Table 50-10). The H**2**RAs decrease acid secretion and may alter the bioavailability of orally administered drugs, similar to PPIs. Cimetidine inhibits several CYP450 isoenzymes, resulting in numerous drug interactions (eg, theophylline, lidocaine, phenytoin, warfarin, and clopidogrel). Ranitidine has less potential for hepatic CYP450 drug interactions, while famotidine and nizatidine do not interact with drugs metabolized by the hepatic CYP450 pathway.

Sucralfate

Sucralfate heals peptic ulcers but is not widely used today for this indication. Deterrents to its use include the requirement for multiple doses per day, large tablet size, and the need to separate the drug from meals and potentially interacting medications (eg, fluoroquinolones). Drug interactions can be minimized by giving the interacting drug at least 2 hours before sucralfate, or avoidance as with fluoroquinolones. Constipation may be troublesome especially

in older individuals, and seizures have been observed in dialysis patients taking aluminum-containing antacids. Hypophosphatemia may develop with long-term treatment. Rarely, gastric bezoar formation has been reported (see Table 50-10).

Prostaglandins

Misoprostol, a synthetic PGE_1 analogue, moderately inhibits acid secretion and enhances mucosal defense. Antisecretory effects are dose dependent over the range of 50 to 200 mcg, and cytoprotective effects occur in humans at doses of greater than 200 mcg. The most troublesome adverse effect is diarrhea which is dose-dependent; develops in 10% to 30% of patients; and is accompanied by abdominal cramping, nausea, flatulence, and headache. Taking the drug with or after meals and at bedtime may minimize the diarrhea (see Table 50-10). Misoprostol is contraindicated in pregnant women because it produces uterine contractions that may endanger pregnancy. If misoprostol is prescribed to women in their childbearing years, contraceptive measures must be confirmed, and a negative serum pregnancy test should be documented within 2 weeks of initiating treatment (see Table 50-10).

Bismuth Preparations

Bismuth subsalicylate and bismuth subcitrate potassium are the only available bismuth salts in the United States. Possible ulcer healing mechanisms include an antibacterial effect, a local gastroprotective effect, and stimulation of endogenous PGs. Bismuth salts do not inhibit or neutralize acid. Bismuth subsalicylate is regarded as safe and has few adverse effects when taken in recommended dosages. Bismuth salts should be used with caution in older patients and in renal failure as renal insufficiency may decrease bismuth elimination. Bismuth subsalicylate may cause salicylate sensitivity or bleeding disorders and should be used with caution for patients receiving concurrent salicylate therapy. Bismuth salts impart a black color to stool and possibly the tongue with liquid preparations. Long-term use of bismuth salts is not recommended due to the potential for bismuth toxicity.

Antacids

Antacids neutralize gastric acid, inactivate pepsin, and bind bile salts. Aluminum-containing antacids also suppress *H. pylori* and enhance mucosal defense. The GI adverse effects are most common and are dose dependent: Aluminum-containing antacids cause constipation, and magnesium salts can

cause an osmotic diarrhea. Aluminum-containing antacids (except aluminum phosphate) form insoluble salts with dietary phosphorus and interfere with phosphorus absorption. Hypophosphatemia occurs most often for patients with low dietary phosphate intake (eg, malnutrition or alcoholism). Combined treatment with sucralfate may amplify the hypophosphatemia and aluminum toxicity.

Magnesium excretion is impaired in patients with a creatinine clearance of less than 30 mL/min (0.5 mL/s) that may lead to toxicity; thus, magnesium-containing antacids should be avoided in these patients. Hypercalcemia may occur for patients with normal renal function taking more than 20 g/day of calcium carbonate and for patients with renal failure who are taking more than 4 g/day. The milk-alkali syndrome (ie, hypercalcemia, alkalosis, renal stones, increased blood urea nitrogen, and increased serum creatinine concentration) occurs with high calcium intake for patients with systemic alkalosis produced by either ingestion of absorbable antacids (sodium bicarbonate) or prolonged vomiting. Antacids may alter the absorption and excretion of drugs when administered concomitantly (eg, iron, warfarin, tetracycline, digoxin, quinidine, isoniazid, ketoconazole, or the fluoroquinolones). Most interactions can be avoided by separating the antacid from the oral drug by at least 2 hours.

EVALUATION OF THERAPEUTIC OUTCOMES

6 **Table 50-14** lists the recommendations for treating and monitoring patients with PUD. Relief of epigastric pain should be monitored throughout the course of treatment for patients with either *H. pylori*- or NSAID-related ulcers. Ulcer pain typically resolves in a few days when NSAIDs are discontinued and within 7 days upon initiation of antiulcer therapy. Patients with uncomplicated PUD are usually symptom free after treatment with any of the recommended antiulcer regimens. Persistent or recurrent symptoms within 14 days following treatment completion suggests failure of ulcer healing or *H. pylori* eradication or presence of an alternate diagnosis such as GERD. Eradication should be confirmed after treatment in all patients, particularly among individuals who are at risk for complications (eg, prior bleeding ulcer). The UBT and fecal antigen are the preferred methods to confirm *H. pylori* eradication when endoscopy is not indicated. Medication adherence should be assessed for patients who fail therapy. Many at-risk patients treated with NSAIDs do not receive adequate prophylaxis for GI complications; however, therapeutic outcomes can be improved by advocating preventive strategies. Any signs or symptoms of

bleeding, obstruction, penetration, or perforation require prompt investigation to avoid complications. A follow-up endoscopy is justified for patients with frequent symptomatic recurrence, refractory disease, complications, or suspected hypersecretory states.

TABLE 50-14 Recommendations for Treating and Monitoring Patients with *Helicobacter Pylori*–Associated and NSAID-Induced Ulcers

***H. pylori*–associated ulcer**

1. Recommend drug treatment as presented in the chapter text. See Tables 50–7 and 50–8
2. Assess patient allergies to determine if allergic to penicillin (or other antibiotics) so that drug regimens that contain penicillin (or other antibiotics) can be avoided. Avoid regimens that contain tetracycline in children
3. Assess patient use of alcohol or alcohol-containing products with metronidazole and oral birth control medications with antibiotics and counsel appropriately
4. Assess likelihood of nonadherence to the drug regimen as a cause of treatment failure
5. Recommend a different antibiotic combination if *H. pylori* eradication fails and a second treatment is planned
6. Inform the patient of change in stool color when bismuth salicylate is included in an *H. pylori* eradication regimen
7. Assess and monitor patients for potential adverse effects, especially those associated with metronidazole, clarithromycin, and amoxicillin
8. Assess and monitor patients for potential drug interactions, especially those receiving metronidazole, clarithromycin, or cimetidine
9. Monitor patients for salicylate toxicity, especially patients receiving co-therapy with other salicylates and anticoagulants and patients with renal failure
10. Monitor patients for persistent or recurrent symptoms within 14 days after completion of a course of *H. pylori* eradication therapy
11. Provide patient education to patients who are receiving *H. pylori* eradication therapy and include why antibiotic and antiulcer combinations are used; when and how to take medications; adverse effects; alarm symptoms; the importance of adherence to the entire course of drug treatment; and contact their healthcare provider if alarm symptoms develop (eg, blood in the stools, black tarry stools, vomiting, severe abdominal pain), or if symptoms persist or return after *H. pylori* eradication

NSAID-induced ulcer

1. Recommend drug treatment as presented in the chapter text
2. Assess risk factors for NSAID-induced ulcers and ulcer-related complications and recommend appropriate strategies for reducing ulcer risk (see Table 50-11)
3. Weigh patient risk factors for NSAID-related GI bleeding and cardiovascular events when selecting a strategy to reduce ulcer risk
4. Recommend eradication treatment for *H. pylori*–positive patients taking NSAIDs
5. Monitor patients for signs and symptoms of NSAID-related upper GI complications
6. Assess and monitor patients for potential drug interactions and adverse effects (especially misoprostol)
7. Provide patient education to patients who are at risk of NSAID-induced ulcers or GI-related complications and include why co-therapy is used with nonselective NSAIDs, when and how to take medications, adverse effects, alarm symptoms, when to contact their healthcare provider, and the importance of adherence to drug treatment

RELATED DISORDERS

Upper Gastrointestinal Bleeding

Upper GI bleeding is one of the most common GI emergencies with more than 300,000 hospital admissions annually. There are about 48 to 160 cases of upper GI bleeding per 100,000 adults annually in the United States, and the mortality rate associated with acute hemorrhage remains relatively high between 6% and 14% despite a decreased incidence of PUD and improvements in the management of upper GI bleeding. Upper GI bleeding is categorized as variceal or nonvariceal bleeding. A complete discussion of variceal bleeding is found elsewhere (Chapter 54). Two common types of nonvariceal bleeding are bleeding from chronic peptic ulcers and bleeding from stress-related mucosal damage (SRMD).[94] Upper GI bleeding associated with chronic PUD usually precedes hospital admission. Bleeding associated with SRMD develops in severely ill patients during hospitalization.[94–97] The underlying pathophysiology of bleeding from a peptic ulcer or from SRMD is similar in that impaired mucosal defense in the presence of gastric acid and pepsin leads to mucosal damage. In chronic PUD, *H. pylori* infection and NSAID use are the most important etiologic factors. The primary pathogenic factor of SRMD in critically ill patients is thought to be mucosal ischemia, which is a result of reduced gastric blood flow resulting from splanchnic hypoperfusion.[94–97] Stress-related mucosal lesions are characteristically asymptomatic, numerous, located in the proximal stomach, and unlikely to perforate. Bleeding from SRMD occurs from superficial mucosal capillaries, whereas bleeding associated with chronic PUD usually results from a single vessel.[94–97] The mortality rate associated with clinically important stress-related mucosal bleeding (SRMB) is approximately 50% and is related to disease severity and comorbidities in this patient population. The mortality associated with chronic PUD-related bleeding is approximately 10% but can increase dramatically in select patient populations.[94–97] Initial management of acute upper GI bleeding focuses on aggressive resuscitation and hemodynamic stability.

Peptic Ulcer–Related Bleeding

Clinical Presentation and Diagnosis

Hematemesis (vomiting up blood), melena (dark, tarry stools), or both are most

common presenting signs and symptoms of PUD-related bleeding. Risk for adverse outcomes must be rapidly assessed to determine if the patient's condition constitutes a medical emergency.[98] Two risk stratification tools exist for early assessment and triage. The Blatchford score is used to evaluate the need for urgent endoscopic intervention for patients presenting with PUD-related bleeding. The scale values range from 0 to 23, with higher scores indicating higher risk. The Rockall Score is composed of two assessments: the clinical score, which is performed prior to endoscopy, and the endoscopic score. The use of these risk stratification tools can reduce the requirement of endoscopic procedures and lead to early discharge for low-risk patients while ensuring rapid intervention for patients at higher risk.[98] When considering the risk of death due to PUD bleeding, the following patients generally have poorer prognoses and usually require more aggressive intervention including admission to an intensive care unit (ICU): age older than 65 years, shock, poor overall health, comorbid conditions, low initial hemoglobin/hematocrit, active bleeding (red blood per rectum or hematemesis), sepsis, and elevated serum creatinine or serum transaminases.[95] Diagnostic endoscopy is usually performed within 24 hours of presentation to identify the source of the bleeding, assess the potential risk for rebleeding using the Forrest classification of lesions, and, if appropriate, employ therapeutic interventions to promote hemostasis.[95,99,108,109,112,113]

The appearance of the ulcer at the time of endoscopy is a prognostic indicator for the risk of rebleeding. Clean-based (Forrest type III) and flat spot (pigmented; Forrest type IIc) ulcers are most commonly seen and are associated with a low risk of rebleeding (5% and 10%, respectively). In most cases, patients with clean-based ulcers can be treated as an outpatient after endoscopy on antiulcer therapy, while patients with flat spot ulcers may be admitted to the general hospital ward for brief observation.[94,98] Patients with an adherent clot overlying the ulcer base (Forrest type IIb) are at intermediate risk of rebleeding (22%-33%), and controversy exists as to the appropriate management of these patients. Patients with a visible vessel (Forrest type IIa) or active bleeding (Forrest type Ia or Ib) are at the highest risk of rebleeding (43%-50% and 55%-90%, respectively) and should receive ICU care for at least 24 hours followed by monitoring on a general medical/surgical service for an additional 48 hours as rebleeding significantly increases mortality.[94,98]

Treatment

Initial therapy for patients with defined hemostatic instability should focus on correcting fluid volume loss through appropriate volume resuscitative measures.

This is usually accomplished with a continuous 0.9% sodium chloride infusion or blood products if clinically indicated.[98,100] The use of nasogastric (NG) tubes remains controversial but may aid in early assessment and gastric lavage.[95–100] Several endoscopic treatment approaches (eg, thermocoagulation, argon plasma coagulation therapy, injection sclerotherapy, hemoclipping, and ligation) can be used. To maximize the likelihood of positive outcomes, patients should be treated with a combination of at least two endoscopic modalities, such as thermocoagulation and injection of lesions with epinephrine.[98–100]

Antisecretory agents are often used as adjuvant therapy to endoscopic procedures to prevent PUD rebleeding in high-risk patients because acid impairs clot stability. PPIs reduce the incidence of rebleeding and need for surgery but have no significant impact on overall mortality.[95,98,101] Historically, practice guidelines recommended that high-dose continuous-infusion PPI therapy (equivalent to omeprazole 80 mg given IV as a loading dose, followed by 8 mg/h continuous infusion for 72 hours) be used to reduce the risk of rebleeding in high risk patients who have undergone endoscopy hemostasis. However, there is no benefit in high dose or continuous therapy respectively.[101,102] Thus, intermittent IV dosing of PPIs (at cumulative daily doses of 80-160 mg) may be a therapeutic option that provides a greater ease of administration. PPI therapy is not a replacement for interventional endoscopy in patients with a high risk of rebleeding, as data demonstrate that the combination of a PPI with therapeutic endoscopy is superior to either strategy alone. The risk of rebleeding is greatest within the first 72 hours, and thus antisecretory therapy to prevent rebleeding in high-risk patients should be employed in this time frame. Patients should be transitioned to an oral PPI on completion of IV therapy.[98,100]

Patients with upper GI bleeding should be tested for *H. pylori* at the time of endoscopy (see section “Tests for *H. pylori*” above). However, the tests are associated with an increased rate of false-negatives when obtained during acute bleeding episodes. If the initial results of the rapid urease test and/or histology are negative, a confirmatory test should be performed following the acute bleeding episode.[95] Ulcer treatment, including *H. pylori* eradication, if appropriate, should be initiated after the acute bleeding episode has resolved (see “Treatment of *H. Pylori*–Positive Ulcers” and “Treatment of NSAID-Induced Ulcers” above).

Stress-Related Mucosal Bleeding

Epidemiology and Risk Factors

Clinically important bleeding increases ICU length of stay, results in excessive healthcare costs, and is associated with increased mortality. Thus, attempts to prevent SRMB are warranted in high-risk patients. Prophylactic therapy to prevent bleeding is most effective if initiated early in the patient's course.[97] The majority (75%-100%) of critically ill patients develop SRMD within the first 1 to 3 days of admission to an ICU, but the incidence of clinically important SRMB (defined as overt bleeding with concomitant hemodynamic instability and likely requirement for blood products) is 1% to 8%.[97]

Patients who are at risk for SRMB include those with respiratory failure (need for mechanical ventilation for longer than 48 hours), coagulopathy (INR greater than 1.5, platelet count less than 50,000/mm^3 [50×10^9/L]), hypotension, sepsis, hepatic failure, acute renal failure, high-dose corticosteroid therapy (more than 250 mg/day hydrocortisone or equivalent), multiple trauma, severe burns (more than 35% of body surface area), head injury, traumatic spinal cord injury, major surgery, prolonged ICU admission (more than 7 days), or history of GI bleeding.[103] The relative importance of the various risk factors remains controversial, but most clinicians concur that patients with respiratory failure or coagulopathy should receive prophylaxis, as these two factors are independent risk factors for SRMB.[104]

Prevention and Treatment

Prevention of SRMB includes resuscitative measures that restore mucosal blood and pharmacotherapy that either maintains an intragastric pH of greater than 4 or provides gastric mucosal protection.[97,105] Although the benefits of enteral nutrition to patient outcome (eg, improved nutritional status enhances mucosal integrity) are of overall clinical importance, its precise role as a sole modality to prevent SRMB remains controversial. Patients receiving enteral nutrition may not require medications for SRMB prophylaxis, and such therapies may increase the risk of adverse complications, particularly nosocomial pneumonia, over enteral nutrition alone.[106,107] Therapeutic options for the prevention of SRMB include antacids (which are no longer used because of cumbersome dosage schedules and side effects), antisecretory drugs (H**2**RAs and PPIs), and sucralfate.[97,104]

Sucralfate is an evidence-based option but requires multiple daily dosage administration (up to four times daily), which may occlude nasogastric (NG) tubes, cause constipation, interact with several medications, or increase the potential for aluminum toxicity in patients with renal dysfunction and is thus not

used frequently for SRMB prophylaxis.[103] Antisecretory therapy is generally preferred for SRMB prophylaxis. The PPIs are more potent than H**2**RAs in inhibiting acid secretion and, unlike H**2**RAs, tolerance does not develop. PPIs have become the most widely used therapy despite conflicting evidence of their superiority over H**2**RAs for SRMB prophylaxis.[108–111] In addition, adverse events when the PPIs are used for SRMB prophylaxis include an increased risk of enteric infections, including *C. difficile*–associated diarrhea and nosocomial pneumonia thus potentially increasing hospital-associated costs and providing an argument against their routine use for SRMB prophylaxis.[108,109,111–113] Based on available evidence, several PPI dosing regimens for SRMB prophylaxis exist (see **Table 50-15**).[97]

TABLE 50-15 Pharmacotherapy Options for Prophylaxis of Stress-Related Mucosal Bleeding

Drug and Route	Dosage
Parenteral H2RAs	
Cimetidine	300 mg IV loading dose followed by 50 mg/h as a continuous infusion[a] or 300 mg IV every 6-8 hours
Ranitidine	6.25 mg/h as a continuous infusion or 50 mg IV every 6-8 hours
Famotidine	1.7 mg/h as a continuous infusion or 20 mg IV every 12 hours
Oral/NG Tube PPIs	
Omeprazole	20-40 mg orally/NG tube[b] every 12-24 hours
Omeprazole/ bicarbonate powder for oral suspension	40 mg orally/NG tube to start, then followed by an additional 40 mg in 6-8 hours as a loading dose, and then 40 mg every 24 hours
Lansoprazole	30 mg orally/NG tube[b,c] every 12-24 hours
Pantoprazole	40 mg orally/NG tube[b] every 12-24 hours
Parenteral PPIs	
Pantoprazole	40-80 mg IV every 12-24 hours
Esomeprazole	40 mg IV every 12-24 hours

[a]Product is FDA approved for the prevention of stress-related mucosal bleeding.

[b]Administered as an extemporaneously compounded suspension made with sodium bicarbonate.

[c]Administered as a rapidly disintegrating tablet given orally or by NG tube dissolved in 10 mL of water.

H2RA, histamine-2 receptor antagonist; NG, nasogastric; PPI, proton pump inhibitor.

Even though PPIs have become the most widely used prevention therapy, numerous studies and years of experience support the use of H**2**RAs, and they remain a recommended option for the prevention of SRMB.[97,109,111] Parenteral H**2**RAs may be administered as either continuous infusions or intermittent bolus doses (see Table 50-15). Cimetidine, given as a continuous IV infusion, is the only FDA-labeled H**2**RA for the prevention of SRMB. Drug interactions are more common with cimetidine, thus the other H**2**RAs (famotidine, ranitidine) are used more frequently.[97] Adverse events associated with the use of H**2**RAs for the critically ill patient include thrombocytopenia, mental status changes (more common in older patients or individuals with renal or hepatic compromise), and tachyphylaxis (especially with parenteral or high-dose therapy). Given that the H**2**RAs are renally eliminated, dosage reductions are recommended for patients

with renal dysfunction.[103]

When deciding on the most appropriate pharmacotherapy plan for the prevention of SRMB for a specific patient, the clinical presentation of the patient and medication costs should be used as a guide. Patients who can take oral medication or have a working NG tube in place may be placed on an oral H**2**RA or PPI suspension as a cost-effective measure. For most patients who are not able to utilize one of these routes, an IV H**2**RA is appropriate. However, if the patient has any relative or absolute contraindications to an H**2**RA, then an IV PPI may be the most appropriate prophylaxis option.

Improvement in the patient's overall medical condition (resolution of risk factors, discharge from the ICU, extubation, and oral intake) suggests that prophylactic therapy can be discontinued. Often patients are continued on SRMB prophylaxis on transition to the general medical/surgical unit and are often discharged on oral PPI therapy without an appropriate indication. This results in unnecessary costs for the patient and the healthcare system.[111,112] Patients in whom SRMB prophylaxis is no longer indicated should be identified. If a patient develops clinically important bleeding, endoscopic evaluation of the GI tract is indicated along with aggressive antisecretory therapy (see section "Peptic Ulcer–Related Bleeding" above).

Zollinger-Ellison Syndrome

ZES, characterized by hypersecretion of gastric acid and severe gastroesophageal PUD, is caused by a neuroendocrine tumor (gastrinoma) that is present in the duodenum or pancreas.[114–117] Gastrinoma has a yearly incidence of approximately one to three cases per million in the United States with ZES being the underlying cause of PUD in 0.1% to 1% of patients.[116] ZES occurs spontaneously in 75% to 80% of patients, but 20% to 25% of patients have the familial form associated with multiple endocrine neoplasia type 1 (MEN1), an autosomal-dominant syndrome due to defects in the *MEN1* gene.[115,116] MEN1 patients commonly develop hyperparathyroidism, pituitary adenomas, and neuroendocrine tumors. Half (50%) of patients with MEN1 have ZES making gastrinoma and ZES the most common functional neuroendocrine tumor and syndrome in MEN1.[115,116] Gastrinomas are usually slow growing, but approximately 60% to 90% are malignant with metastases to regional lymph nodes, liver, and other distant sites at time of diagnosis.[116]

Pathophysiology

Gastrinomas are derived from the enteroendocrine cells, form tumors mainly in the pancreas and proximal small intestine and are generally classified under the larger term of neuroendocrine tumors. Most gastrinomas arise in the duodenum. Gastrinomas located in the pancreas carry a greater malignant potential.[117] ZES pathophysiology is related to the trophic action of gastrin on parietal cells of the gastric antrum and the resulting hypersecretion of gastric acid. A majority of patients consequently develop large peptic ulcers frequently in the distal duodenum and even proximal jejunum that is an uncommon location for ulcers resulting from *H. pylori* or the use of NSAIDs.[117]

Clinical Presentation and Diagnosis

Historically, patients with ZES presented with refractory PUD or complications of acid hypersecretion (perforation, penetration, bleeding, and esophageal stricture). Due to the widespread use of PPIs and H2RAs, this form of presentation has decreased drastically.[115] Currently, patients commonly present with severe refractory heartburn, epigastric pain, and profound diarrhea. Diarrhea maybe the only symptom in 10% to 20% of patients and is due to the osmotic load of high gastric acid, inhibition of sodium and water reabsorption by the intestinal brush border of high gastric acid secretion, and a malabsorptive component from inactivation of pancreatic digestive enzymes by gastric acid.[115,117]

ZES diagnosis is established when the serum gastrin is greater than 1,000 pg/mL (ng/L; 481 pmol/L) and the basal acid output (BAO) is more than or equal to 15 mEq/h (mmol/h) for patients with an intact stomach (BAO more than or equal to 5 mEq/h [mmol/h] for patients with previous gastric surgery) or when hypergastrinemia is associated with a gastric pH value of more than or equal to 2.[116,117] In situations in which the serum gastrin is between 100 and 1,000 pg/mL (ng/L; 48 and 481 pmol/L) and gastric pH is less than or equal to 2, a secretin or calcium proactive test is used to aid the diagnosis. Identification of the location of the tumor with imaging techniques is essential, as early surgical resection prior to liver metastases is often curative.[114–117] The widespread use of PPIs, although effective in reducing symptoms, may mask the clinical presentation and PPI-related hypergastrinemia may further complicate the diagnosis.[114,115]

Treatment

Historically, only total gastrectomy was effective at controlling gastric acid hypersecretion. With the development of H2RAs and PPIs, medical management

of ZES is now feasible in almost all patients. Because of their long duration of action and potency, PPIs are now the drugs of choice for treating gastric acid hypersecretion in patients with ZES.[114–116] Many of the PPIs (omeprazole, esomeprazole, lansoprazole, esomeprazole, rabeprazole, and pantoprazole) are effective in ZES. Initial doses of 80 mg/day for pantoprazole (or an equivalent dose of other available PPIs) given every 8 to 12 hours is most effective at controlling gastric acid hypersecretion and reliving symptoms. IV PPIs can be used for those patients who do not tolerate oral therapy. PPIs must be dose adjusted in patients with ZES to normalize BAO levels to less than 15 mEq/h (mmol/h) or less than 5 mEq/h (mmol/h) in patients with reflux esophagitis or prior operations to reduce acid secretion, such as subtotal gastrectomy. PPI therapy can be gradually decreased after adequate control of hypersecretion is achieved.[114–116] Since 60% to 90% of gastrinomas are malignant, management of advanced disease may include surgical resection of primary and metastatic gastrinomas. Nonsurgical therapy may include treatment with chemotherapy, somatostatin analogues such as octreotide, interferon, and targeted-molecular therapies such as a mTor inhibitor (everolimus) or a tyrosine-kinase inhibitor (sunitinib).[114–116]

ACKNOWLEDGMENTS

This chapter is a revision of the chapter on Peptic Ulcer Disease in the 8th edition written by Rosemary R. Berardi and Randolph V. Fugit.

Postclass Engaged Learning Activity

Perform a literature search, preferably of manuscripts within the last 12 months, that focuses on stress-related mucosal damage (SRMD) prevention strategies utilized in intensive and critical care settings. Write a brief summary of one article describing an effective method of prevention (to avoid an overly lengthy summary, limit sources to three to five articles, if possible). Discuss the feasibility and cost-effectiveness of this strategy. This activity is intended to improve your literature evaluation skills and help you consider evidence-based practice in treatment decisions.

Conduct a brief internet search of the most commonly nonprescription proton pump inhibitor (PPI) medications. Construct a table including the drug name, brand name(s), dosage, and potential side effects. Then, make a brief

list of test results and symptom information you would want to collect if a patient whose care you were managing was taking a PPI. What are the potential dangers of taking a PPI without consulting a physician? This activity is intended to get you familiar with the types of PPIs available to consumers without a prescription, as patients with peptic ulcer disease (PUD) could already be self-treating with some of these. This exercise also illustrates the potential dangers of treating acid reflux with nonprescription products when more serious concerns might be present (peptic ulcer disease, ischemic heart disease, etc.)

ABBREVIATIONS

ATPase	adenosine triphosphatase
BAO	basal acid output
CAP	community-acquired pneumonia
CLASS	Celecoxib Long-Term Arthritis Safety Study
COX	cyclooxygenase
COX-1	cyclooxygenase-1
COX-2	cyclooxygenase-2
CYP450	cytochrome P450
ECL	enterochromaffin-like
GERD	gastroesophageal reflux disease
H2RA	histamine-2 receptor antagonist
ICU	intensive care unit
IL	interleukin
INR	international normalized ratio
MALT	mucosa-associated lymphoid tissue
MAO	maximal acid output
MEN 1	multiple endocrine neoplasia type 1
NG	nasogastric
NSAID	nonsteroidal anti-inflammatory drug
NUD	nonulcer dyspepsia
PG	prostaglandin
PPI	proton pump inhibitor
PUD	peptic ulcer disease
SRMB	stress-related mucosal bleeding
SRMD	stress-related mucosal damage
TNF-α	tumor necrosis factor-α
UBT	urea breath test
ZES	Zollinger-Ellison syndrome

REFERENCES

1. Del Valle J. Harrison's Principles of Internal Medicine. 19th ed.2015. [1 online resource (various pagings) illustrations 29 cm.].http://accessmedicine.mhmedical.com/book.aspx?bookid=1130.
2. Lew E. Peptic Ulcer Disease. In: Greenberger NJ, Blumberg RS, Burakoff R, eds. *Current Diagnosis & Treatment: Gastroenterology, Hepatology, & Endoscopy*. 2nd ed. New York, NY: McGraw-Hill Medical; 2012.
3. Love BL, Meade LT. Upper gastrointestinal disorders. In: Sutton SS, ed.

NAPLEX Review Guide. New York, NY: McGraw-Hill Medical; 2015.

4. Lanas A, Chan FKL. Peptic ulcer disease. *Lancet*. 2017;390(10094):613–624. Epub 2017/03/01. doi: 10.1016/S0140-6736(16)32404-7.
5. Peery AF, Crockett SD, Barritt AS, et al. Burden of gastrointestinal, liver, and pancreatic diseases in the United States. *Gastroenterology*. 2015;149(7):1731–1741 e3. Epub 2015/09/04. doi: 10.1053/j.gastro.2015.08.045.
6. Mentis A, Lehours P, Megraud F. Epidemiology and Diagnosis of Helicobacter pylori infection. *Helicobacter*. 2015;20(Suppl 1):1-7. Epub 2015/09/16. doi:10.1111/hel.12250.
7. Nguyen T, Ramsey D, Graham D, et al. The prevalence of Helicobacter pylori remains high in African American and Hispanic veterans. *Helicobacter*. 2015;20(4):305–315. Epub 2015/02/18. doi: 10.1111/hel.12199.
8. Bjarnason I, Scarpignato C, Holmgren E, Olszewski M, Rainsford KD, Lanas A. Mechanisms of damage to the gastrointestinal tract from nonsteroidal anti-inflammatory drugs. *Gastroenterology*. 2018;154(3):500–514. Epub 2017/12/10. doi: 10.1053/j.gastro.2017.10.049.
9. Melcarne L, Garcia-Iglesias P, Calvet X. Management of NSAID-associated peptic ulcer disease. *Expert Rev Gastroenterol Hepatol*. 2016;10(6):723–733. Epub 2016/01/19. doi: 10.1586/17474124.2016.1142872.
10. Kamboj AK, Cotter TG, Oxentenko AS. Helicobacter pylori: The past, present, and future in management. *Mayo Clinic proceedings*. 2017;92(4):599–604. Epub 2017/02/18. doi: 10.1016/j.mayocp.2016.11.017.
11. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG Clinical Guideline: Treatment of Helicobacter pylori Infection. *Am J Gastroenterol*. 2017;112(2):212–239. Epub 2017/01/11. doi: 10.1038/ajg.2016.563.
12. Watari J, Chen N, Amenta PS, et al. Helicobacter pylori associated chronic gastritis, clinical syndromes, precancerous lesions, and pathogenesis of gastric cancer development. *World J Gastroenterol*. 2014;20(18):5461–5473. Epub 2014/05/17. doi: 10.3748/wjg.v20.i18.5461.
13. Amieva M, Peek RM Jr. Pathobiology of Helicobacter pylori-induced gastric cancer. *Gastroenterology*. 2016. Jan;150(1):64-78. doi:

10.1053/j.gastro.2015.09.004. Epub 2015 Sep 16.

14. Lanas A, Gargallo CJ. Management of low-dose aspirin and clopidogrel in clinical practice: A gastrointestinal perspective. *J Gastroenterol*. 2015;50(6):626–637. Epub 2015/01/18. doi: 10.1007/s00535-015-1038-3.
15. Gargallo CJ, Sostres C, Lanas A. Prevention and treatment of NSAID gastropathy. *Curr Treat Options Gastroenterol*. 2014;12(4):398–413. Epub 2014/09/12. doi: 10.1007/s00535-015-1038-3.
16. Mo C, Sun G, Lu ML, et al. Proton pump inhibitors in prevention of low-dose aspirin-associated upper gastrointestinal injuries. *World J Gastroenterol*. 2015;21(17):5382–5392. Epub 2015/05/09. doi: 10.3748/wjg.v21.i17.5382.
17. Lin XH, Young SH, Luo JC, et al. Risk factors for upper gastrointestinal bleeding in patients taking selective COX-2 inhibitors: A Nationwide Population-Based Cohort Study. *Pain medicine (Malden, Mass)*. 2018;19(2):225–231. Epub 2017/05/02. doi: 10.1093/pm/pnx097.
18. Chen WC, Lin KH, Huang YT, et al. The risk of lower gastrointestinal bleeding in low-dose aspirin users. *Aliment Pharmacol Ther*. 2017;45(12):1542–1550. Epub 2017/04/28. doi: 10.1111/apt.14079.
19. Gwee KA, Goh V, Lima G, Setia S. Coprescribing proton-pump inhibitors with nonsteroidal anti-inflammatory drugs: Risks versus benefits. *J Pain Res*. 2018;11:361–374. Epub 2018/03/02. doi: 10.2147/JPR.S156938.
20. Fashner J, Gitu AC. Diagnosis and Treatment of Peptic Ulcer Disease and H. pylori Infection. *Am Fam Physician*. 2015;91(4):236-242. Epub 2015/05/09.
21. Jiang HY, Chen HZ, Hu XJ, et al. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal bleeding: A systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2015;13(1):42–50 e3. doi: 10.1016/j.cgh.2014.06.021.
22. Alfredsson J, Neely B, Neely ML, *et al* Predicting the risk of bleeding during dual antiplatelet therapy after acute coronary syndromes. *Heart (British Cardiac Society)*. 2017;103(15):1168-1176. Epub 2017/04/07. doi:10.1136/heartjnl-2016-310090.
23. Masclee GM, Valkhoff VE, Coloma PM, et al. Risk of upper gastrointestinal bleeding from different drug combinations. Gastroenterology. 2014;147(4):784–792 e9 quiz e13-4. Epub 2014/06/18. doi:10.1053/j.gastro.2014.06.007.
24. Cardoso RN, Benjo AM, DiNicolantonio JJ, et al. Incidence of

cardiovascular events and gastrointestinal bleeding in patients receiving clopidogrel with and without proton pump inhibitors: An updated meta-analysis. *Open Heart*. 2015;2(1):e000248. Epub 2015/07/22. doi: 10.1136/openhrt-2015-000248.

25. Li JJ, Wu XY, Chen JL, et al. Antiplatelet drug ticagrelor delays gastric ulcer healing in rats. *Exp Ther Med*. 2017;14(4):3774–3779. Epub 2017/10/19. doi: 10.3892/etm.2017.4955.
26. Li LF, Chan RL, Lu L, et al. Cigarette smoking and gastrointestinal diseases: The causal relationship and underlying molecular mechanisms (review). *Int J Mol Med*. 2014;34(2):372–380. doi: 10.3892/ijmm.2014.1786.
27. Zhang L, Ren JW, Wong CC, *et al* Effects of cigarette smoke and its active components on ulcer formation and healing in the gastrointestinal mucosa. *Curr Med Chem*. 2012;19(1):63-69.
28. Melinder C, Udumyan R, Hiyoshi A, Brummer RJ, Montgomery S. Decreased stress resilience in young men significantly increases the risk of subsequent peptic ulcer disease: A prospective study of 233 093 men in Sweden. *Aliment Pharmacol Ther*. 2015;41(10):1005–1015. Epub 2015/03/27. doi: 10.1111/apt.13168.
29. Lee YB, Yu J, Choi HH, et al. The association between peptic ulcer diseases and mental health problems—a population-based study: A STROBE compliant article. *Medicine (Baltimore)*. 2017;96(34):e7828. Epub 2017/08/24. doi: 10.1097/MD.0000000000007828.
30. Smolka AJ, Backert S. How Helicobacter pylori infection controls gastric acid secretion. *J Gastroenterol*. 2012;47(6):609-618. Epub 2012/05/09. doi:10.1007/s00535-012-0592-1.
31. Takeuchi K. Pathogenesis of NSAID-induced gastric damage: importance of cyclooxygenase inhibition and gastric hypermotility. *World J Gastroenterol*. 2012;18(18):2147-2160. Epub 2012/05/23. doi:10.3748/wjg.v18.i18.2147.
32. Nejati S, Karkhah A, Darvish H, Validi M, Ebrahimpour S, Nouri HR. Influence of Helicobacter pylori virulence factors CagA and VacA on pathogenesis of gastrointestinal disorders. *Microb Pathog*. 2018;117:43-48. Epub 2018/02/13. doi:10.1016/j.micpath.2018.02.016.
33. Nagata N, Niikura R, Aoki T, et al. Lower GI bleeding risk of nonsteroidal anti-inflammatory drugs and antiplatelet drug use alone and the effect of combined therapy. Gastrointest Endosc. 2014;80(6):1124–1131. Epub

2014/08/05. doi: 10.1016/j.gie.2014.06.039.

34. Hernandez-Diaz S, Martin-Merino E, Garcia Rodriguez LA. Risk of complications after a peptic ulcer diagnosis: Effectiveness of proton pump inhibitors. *Dig Dis Sci*. 2013;58(6):1653–1662. Epub 2013/02/02. doi: 10.1007/s10620-013-2561-9.
35. Samuel R, Bilal M, Tayyem O, Guturu P. Evaluation and management of gastrointestinal bleeding. *Dis Mon*. 2018. Epub 2018/03/12. doi:10.1016/j.disamonth.2018.02.003.
36. Talley NJ. Functional (non-ulcer) dyspepsia and gastroesophageal reflux disease: One not two diseases? *Am J Gastroenterol*. 2013;108(5):775–777. doi: 10.1038/ajg.2013.102.
37. Calvet X. Diagnosis of Helicobacter pylori infection in the proton pump inhibitor era. *Gastroenterol Clin North Am*. 2015;44(3):507–518. Epub 2015/09/01. doi: 10.1016/j.gtc.2015.05.001.
38. Ferwana M, Abdulmajeed I, Alhajiahmed A, et al. Accuracy of urea breath test in Helicobacter pylori infection: Meta-analysis. *World J Gastroenterol*. 2015;21(4):1305–1314. Epub 2015/01/30. doi: 10.3748/wjg.v21.i4.1305.
39. Kilincalp S, Ustun Y, Akinci H, Coban S, Yuksel I. Letter: effect of proton pump inhibitor use on invasive detection of Helicobacter pylori gastritis. *Aliment Pharmacol Ther*. 2015;41(6):599. doi.10.1111/apt.13092.
40. Agaba EA, Klair T, Ikedilo O, Vemulapalli P. A 10-Year review of surgical management of complicated peptic ulcer disease from a single center: Is laparoscopic approach the future? *Surg Laparosc Endosc Percutan Tech*. 2016;26(5):385–390. Epub 2016/10/18. doi: 10.1097/SLE.0000000000000312.
41. Roma E, Miele E. *Helicobacter pylori* infection in pediatrics. *Helicobacter*. 2015;20(Suppl 1):47-53. Epub 2015/09/16. doi:10.1111/hel.12257.
42. Dos Santos AA, Carvalho AA. Pharmacological therapy used in the elimination of Helicobacter pylori infection: A review. *World J Gastroenterol*. 2015;21(1):139–154. Epub 2015/01/13. doi: 10.3748/wjg.v21.i1.139.
43. Heo J, Jeon SW. Optimal treatment strategy for Helicobacter pylori: Era of antibiotic resistance. *World J Gastroenterol*. 2014;20(19):5654–5659. Epub 2014/06/11. doi: 10.3748/wjg.v20.i19.5654.
44. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of

Helicobacter pylori infection-the Maastricht V/Florence Consensus Report. *Gut*. 2017;66(1):6–30. Epub 2016/11/02. doi: 10.1136/gutjnl-2016-312288.

45. Almeida N, Romaozinho JM, Donato MM, *et al* Triple therapy with high-dose proton-pump inhibitor, amoxicillin, and doxycycline is useless for Helicobacter pylori eradication: a proof-of-concept study. *Helicobacter*. 2014;19(2):90-97. doi:10.1111/hel.12106.
46. Nagaraja V, Eslick GD. Evidence-based assessment of proton-pump inhibitors in Helicobacter pylori eradication: A systematic review. *World J Gastroenterol*. 2014;20(40):14527–14536. doi: 10.3748/wjg.v20.i40.14527.
47. Yoon SB, Park JM, Lee JY, *et al* Long-term pretreatment with proton pump inhibitor and Helicobacter pylori eradication rates. *World J Gastroenterol*. 2014;20(4):1061-1066. doi:10.3748/wjg.v20.i4.1061.
48. Siddique O, Ovalle A, Siddique AS, Moss SF. Helicobacter pylori Infection: An Update for the Internist in the Age of Increasing Global Antibiotic Resistance. *Am J Med*. 2018;131(5):473-479. Epub 2018/01/22. doi:10.1016/j.amjmed.2017.12.024.
49. Park JY, Dunbar KB, Mitui M, et al. Helicobacter pylori clarithromycin resistance and treatment failure are common in the USA. *Dig Dis Sci*. 2016;61(8):2373–2380. Epub 2016/03/01. doi: 10.1007/s10620-016-4091-8.
50. Yuan Y, Ford AC, Khan KJ, et al. Optimum duration of regimens for Helicobacter pylori eradication. Cochrane Database Syst Rev. 2013; (12):CD008337. Epub 2013/12/18. doi:10.1002/14651858.CD008337.pub2.
51. Li BZ, Threapleton DE, Wang JY, et al. Comparative effectiveness and tolerance of treatments for Helicobacter pylori: Systematic review and network meta-analysis. *BMJ*. 2015;351:h4052. doi: 10.1136/bmj.h4052.
52. Liang X, Xu X, Zheng Q, et al. Efficacy of bismuth-containing quadruple therapies for clarithromycin-, metronidazole-, and fluoroquinolone-resistant Helicobacter pylori infections in a prospective study. *Clin Gastroenterol Hepatol*. 2013;11(7):802–807 e1. Epub 2013/02/05. doi:10.1016/j.cgh.2013.01.008.
53. Nyssen OP, McNicholl AG, Megraud F, et al. Sequential versus standard triple first-line therapy for Helicobacter pylori eradication. Cochrane Database Syst Rev. 2016;(6):CD009034. Epub 2016/06/29.

doi:10.1002/14651858.CD009034.pub2.

54. He L, Deng T, Luo H. Meta-analysis of sequential, concomitant and hybrid therapy for Helicobacter pylori eradication. *Intern Med*. 2015;54(7):703-710. Epub 2015/04/04. doi:10.2169/internalmedicine.54.3442.
55. Peedikayil MC, Alsohaibani FI, Alkhenizan AH. Levofloxacin-based first-line therapy versus standard first-line therapy for Helicobacter pylori eradication: Meta-analysis of randomized controlled trials. *PloS one*. 2014;9(1):e85620. Epub 2014/01/28. doi: 10.1371/journal.pone.0085620.
56. Kale-Pradhan PB, Mihaescu A, Wilhelm SM. Fluoroquinolone Sequential Therapy for Helicobacter pylori: A Meta-analysis. *Pharmacotherapy*. 2015;35(8):719-730. Epub 2015/07/16. doi:10.1002/phar.1614.
57. Basu PP, Rayapudi K, Pacana T, Shah NJ, Krishnaswamy N, Flynn M. A randomized study comparing levofloxacin, omeprazole, nitazoxanide, and doxycycline versus triple therapy for the eradication of Helicobacter pylori. *Am J Gastroenterol*. 2011;106(11):1970-1975. Epub 2011/10/13. doi:10.1038/ajg.2011.306.
58. Zhu R, Chen K, Zheng YY, et al. Meta-analysis of the efficacy of probiotics in Helicobacter pylori eradication therapy. *World J Gastroenterol*. 2014;20(47):18013–18021. Epub 2014/12/31. doi: 10.3748/wjg.v20.i47.18013.
59. Dang Y, Reinhardt JD, Zhou X, Zhang G. The effect of probiotics supplementation on Helicobacter pylori eradication rates and side effects during eradication therapy: A meta-analysis. *PloS one*. 2014;9(11):e111030. Epub 2014/11/05. doi: 10.1371/journal.pone.0111030.
60. Wang ZH, Gao QY, Fang JY. Meta-analysis of the efficacy and safety of Lactobacillus-containing and Bifidobacterium-containing probiotic compound preparation in Helicobacter pylori eradication therapy. *J Clin Gastroenterol*. 2013;47(1):25-32. Epub 2012/10/24. doi:10.1097/MCG.0b013e318266f6cf.
61. Di Caro S, Fini L, Daoud Y, et al. Levofloxacin/amoxicillin-based schemes vs quadruple therapy for Helicobacter pylori eradication in second-line. *World J Gastroenterol*. 2012;18(40):5669–5678. doi.10.3748/wjg.v18.i40.5669.
62. Hsu PI, Chen WC, Tsay FW, et al. Ten-day Quadruple therapy comprising proton-pump inhibitor, bismuth, tetracycline, and levofloxacin achieves a

high eradication rate for Helicobacter pylori infection after failure of sequential therapy. *Helicobacter*. 2014;19(1):74–79. doi: 10.1111/hel.12085.

63. Molina-Infante J, Shiotani A. Practical Aspects in Choosing a Helicobacter pylori Therapy. *Gastroenterol Clin North Am*. 2015;44(3):519–535. Epub 2015/09/01. doi:10.1016/j.gtc.2015.05.004.
64. Fiorini G, Zullo A, Vakil N, et al. Rifabutin triple therapy Is effective in patients with multidrug-resistant strains of Helicobacter pylori. *J Clin Gastroenterol*. 2018;52(2):137–140. Epub 2016/05/04. doi: 10.1097/MCG.0000000000000540.
65. Zhuge L, Wang Y, Wu S, Zhao RL, Li Z, Xie Y. Furazolidone treatment for Helicobacter Pylori infection: A systematic review and meta-analysis. *Helicobacter*. 2018;23(2):e12468. Epub 2018/02/27. doi:10.1111/hel.12468.
66. Macy E. Penicillin allergy: optimizing diagnostic protocols, public health implications, and future research needs. *Curr Opin Allergy Clin Immunol*. 2015;15(4):308–313. Epub 2015/06/26. doi: 10.1097/ACI.0000000000000173.
67. Ghotaslou R, Leylabadlo HE, Asl YM. Prevalence of antibiotic resistance in Helicobacter pylori: A recent literature review. *World J Methodol*. 2015;5(3):164–174. Epub 2015/09/29. doi: 10.5662/wjm.v5.i3.164.
68. Duck WM, Sobel J, Pruckler JM, et al. Antimicrobial resistance incidence and risk factors among Helicobacter pylori-infected persons, United States. *Emerg Infect Dis*. 2004;10(6):1088–1094. doi: 10.3201/eid1006.030744.
69. McMahon BJ, Hennessy TW, Bensler JM, et al. The relationship among previous antimicrobial use, antimicrobial resistance, and treatment outcomes for Helicobacter pylori infections. *Ann Intern Med*. 2003;139(6):463–469.
70. Megraud F, Benejat L, Ontsira Ngoyi EN, Lehours P. Molecular approaches to identify Helicobacter pylori antimicrobial resistance. *Gastroenterol Clin North Am*. 2015;44(3):577–596. Epub 2015/09/01. doi: 10.1016/j.gtc.2015.05.002.
71. Satoh K, Yoshino J, Akamatsu T, et al. Evidence-based clinical practice guidelines for peptic ulcer disease 2015. *J Gastroenterol*. 2016;51(3):177–194. Epub 2016/02/18. doi: 10.1007/s00535-016-1166-4.
72. Bakhriansyah M, Souverein PC, de Boer A, Klungel OH. Gastrointestinal

toxicity among patients taking selective COX-2 inhibitors or conventional NSAIDs, alone or combined with proton pump inhibitors: A case-control study. *Pharmacoepidemiol Drug Saf*. 2017;26(10):1141–1148. Epub 2017/04/04. doi: 10.1002/pds.4183.

73. Rostom A, Dube C, Wells G, et al. Prevention of NSAID-induced gastroduodenal ulcers. Cochrane Database Syst Rev. 2002;(4):CD002296. Epub 2003/01/10. doi:10.1002/14651858.CD002296.
74. Laine L, Kivitz AJ, Bello AE, Grahn AY, Schiff MH, Taha AS. Double-blind randomized trials of single-tablet ibuprofen/high-dose famotidine vs. ibuprofen alone for reduction of gastric and duodenal ulcers. *Am J Gastroenterol*. 2012;107(3):379-386. Epub 2011/12/22. doi:10.1038/ajg.2011.443.
75. Taha AS, McCloskey C, Prasad R, Bezlyak V. Famotidine for the prevention of peptic ulcers and oesophagitis in patients taking low-dose aspirin (FAMOUS): A phase III, randomised, double-blind, placebo-controlled trial. *Lancet*. 2009;374(9684):119–125. doi: 10.1016/S0140-6736(09)61246-0.
76. Coxib and traditional NSAID Trialists' (CNT) Collaboration, Bhala N, Emberson J, et al. Vascular and uppergastrointestinal e?ects of non-steroidal anti-inflammatory drugs: Meta-analyses of individual participant data fromrandomised trials. *Lancet*. 2013;382(9894):769-779. Epub 2013/06/04. doi:10.1016/S0140-6736(13)60900-9. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)60900-9/fulltext.
77. Wong GL, Wong VW, Chan Y, et al. High incidence of mortality and recurrent bleeding in patients with Helicobacter pylori-negative idiopathic bleeding ulcers. *Gastroenterology*. 2009;137(2):525–531. Epub 2009/05/19. doi: 10.1053/j.gastro.2009.05.006.
78. Boparai V, Rajagopalan J, Triadafilopoulos G. Guide to the use of proton pump inhibitors in adult patients. *Drugs*. 2008;68(7):925-947.
79. Kim HU. Diagnostic and treatment approaches for refractory peptic ulcers. *Clin Endosc*. 2015;48(4):285–290. Epub 2015/08/05. doi: 10.5946/ce.2015.48.4.285.
80. Lodrup AB, Reimer C, Bytzer P. Systematic review: Symptoms of rebound acid hypersecretion following proton pump inhibitor treatment. *Scand J Gastroenterol*. 2013;48(5):515–522. Epub 2013/01/15. doi: 10.3109/00365521.2012.746395.

81. Orbelo DM, Enders FT, Romero Y, et al. Once-daily omeprazole/sodium bicarbonate heals severe refractory reflux esophagitis with morning or nighttime dosing. *Dig Dis Sci*. 2015;60(1):146–162. Epub 2014/01/23. doi: 10.1007/s10620-013-3017-y.
82. Weersink RA, Bouma M, Burger DM, et al. Safe use of proton pump inhibitors in patients with cirrhosis. Brit j Clin Pharmacol. 2018;84(8):1806–1820. Epub 2018/04/25. doi:10.1111/bcp.13615.
83. Lewis JM, Stott KE, Monnery D, et al. Managing potential drug-drug interactions between gastric acid-reducing agents and antiretroviral therapy: Experience from a large HIV-positive cohort. *Int J STD AIDS*. 2016;27(2):105–109. Epub 2015/02/28. doi: 10.1177/0956462415574632.
84. Scarpignato C, Gatta L, Zullo A, et al. Effective and safe proton pump inhibitor therapy in acid-related diseases: A position paper addressing benefits and potential harms of acid suppression. *BMC Med*. 2016;14(1):179. Epub 2016/11/09. doi: 10.1186/s12916-016-0718-z.
85. Skelin M, Lucijanic T, Amidzic Klaric D, *et al* Factors Affecting Gastrointestinal Absorption of Levothyroxine: A Review. *Clinical therapeutics*. 2017;39(2):378-403. Epub 2017/02/06. doi:10.1016/j.clinthera.2017.01.005.
86. Wedemeyer RS, Blume H. Pharmacokinetic drug interaction profiles of proton pump inhibitors: An update. *Drug Saf*. 2014;37(4):201–211. Epub 2014/02/20. doi: 10.1007/s40264-014-0144-0.
87. Bouziana SD, Tziomalos K. Clinical relevance of clopidogrel-proton pump inhibitors interaction. *World J Gastrointest Pharmacol Ther*. 2015;6(2):17-21. Epub 2015/05/08. doi:10.4292/wjgpt.v6.i2.17.
88. Reimer C. Safety of long-term PPI therapy. *Best Pract Res Clin Gastroenterol*. 2013;27(3):443-454. Epub 2013/09/04. doi:10.1016/j.bpg.2013.06.001.
89. Attwood SE, Ell C, Galmiche JP, et al. Long-term safety of proton pump inhibitor therapy assessed under controlled, randomised clinical trial conditions: Data from the SOPRAN and LOTUS studies. *Aliment Pharmacol Ther*. 2015;41(11):1162–1174. Epub 2015/04/11. doi: 10.1111/apt.13194.
90. Tsuda A, Suda W, Morita H, et al. Influence of proton-pump inhibitors on the luminal microbiota in the gastrointestinal tract. *Clin Trans Gastroenterol*. 2015;6:e89. Epub 2015/06/13. doi: 10.1038/ctg.2015.20.
91. Lambert AA, Lam JO, Paik JJ, Ugarte-Gil C, Drummond MB, Crowell

TA. Risk of community-acquired pneumonia with outpatient proton-pump inhibitor therapy: A systematic review and meta-analysis. *PloS one*. 2015;10(6):e0128004. doi: 10.1371/journal.pone.0128004.

92. de Jager CP, Wever PC, Gemen EF, et al. Proton pump inhibitor therapy predisposes to community-acquired Streptococcus pneumoniae pneumonia. *Aliment Pharmacol Ther*. 2012;36(10):941–949. doi.10.1111/apt.12069.
93. Giuliano C, Wilhelm SM, Kale-Pradhan PB. Are proton pump inhibitors associated with the development of community-acquired pneumonia? A meta-analysis. *Expert Rev Clin Pharmacol*. 2012;5(3):337–344. doi:10.1586/ecp.12.20.
94. Rotondano G. Epidemiology and diagnosis of acute nonvariceal upper gastrointestinal bleeding. *Gastroenterol Clin North Am*. 2014;43(4):643–663.doi:10.1016/j.gtc.2014.08.001.
95. Trawick EP, Yachimski PS. Management of non-variceal upper gastrointestinal tract hemorrhage: Controversies and areas of uncertainty. *World J Gastroenterol*. 2012;18(11):1159–1165. doi.10.3748/wjg.v18.11.1159.
96. Wollenman CS, Chason R, Reisch JS, Rockey DC. Impact of ethnicity in upper gastrointestinal hemorrhage. *J Clin Gastroenterol*. 2014;48(4):343–350.doi:10.1097/MCG.0000000000000025.
97. Bardou M, Quenot JP, Barkun A. Stress-related mucosal disease in the critically ill patient. *Nat Rev Gastroenterol Hepatol*. 2015;12(2):98–107.doi:10.1038/nrgastro.2014.235.
98. Klein A, Gralnek IM. Acute, nonvariceal upper gastrointestinal bleeding. *Curr Opin Crit Care*. 2015;21(2):154–162.doi:10.1097/MCC.0000000000000185.
99. Laine L. Upper gastrointestinal bleeding due to a peptic ulcer. *N Engl J Med*. 2016;375(12):1198. Epub 2016/09/23. doi: 10.1056/NEJMc1609017.
100. Khamaysi I, Gralnek IM. Acute upper gastrointestinal bleeding (UGIB): Initial evaluation and management. *Best Pract Res Clin Gastroenterol*. 2013;27(5):633–638. doi: 10.1016/j.bpg.2013.09.002.
101. Neumann I, Letelier LM, Rada G, *et al* Comparison of different regimens of proton pump inhibitors for acute peptic ulcer bleeding. *Cochrane Database Syst Rev*. 2013;6:CD007999.doi:10.1002/14651858.CD007999.pub2.

102. Sachar H, Vaidya K, Laine L. Intermittent vs continuous proton pump inhibitor therapy for high-risk bleeding ulcers: A systematic review and meta-analysis. *JAMA Internal Medicine*. 2014;174(11):1755–1762. Epub 2014/09/10. doi: 10.1001/jamainternmed.2014.4056.
103. ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis. ASHP Commission on Therapeutics and approved by the ASHP Board of Directors on November 14, 1998. *Am J Health Syst Pharm*. 1999;56(4):347–379.
104. Cook D, Guyatt G. Prophylaxis against upper gastrointestinal bleeding in hospitalized patients. *N Engl J Med*. 2018;378(26):2506–2516. Epub 2018/06/28. doi: 10.1056/NEJMra1605507.
105. Barletta JF, Bruno JJ, Buckley MS, Cook DJ. Stress ulcer prophylaxis. *Crit Care Med*. 2016;44(7):1395–1405. Epub 2016/05/11. doi:10.1097/CCM.0000000000001872.
106. El-Kersh K, Jalil B, McClave SA, *et al* Enteral nutrition as stress ulcer prophylaxis in critically ill patients: A randomized controlled exploratory study. *J Crit Care*. 2018;43:108–113. Epub 2017/09/03. doi:10.1016/j.jcrc.2017.08.036.
107. Huang HB, Jiang W, Wang CY, Qin HY, Du B. Stress ulcer prophylaxis in intensive care unit patients receiving enteral nutrition: A systematic review and meta-analysis. *Crit Care*. 2018;22(1):20. Epub 2018/01/29. doi:10.1186/s13054-017-1937-1.
108. Alhazzani W, Alshamsi F, Belley-Cote E, et al. Efficacy and safety of stress ulcer prophylaxis in critically ill patients: A network meta-analysis of randomized trials. *Intensive Care Med*. 2018;44(1):1–11. Epub 2017/12/05. doi: 10.1007/s00134-017-5005-8.
109. Krag M, Perner A, Wetterslev J, Moller MH. Stress ulcer prophylaxis in the intensive care unit: Is it indicated? A topical systematic review *Acta Anaesthesiol Scand*. 2013;57(7):835–847. doi: 10.1111/aas.12099.
110. Alhazzani W, Alenezi F, Jaeschke RZ, Moayyedi P, Cook DJ. Proton pump inhibitors versus histamine 2 receptor antagonists for stress ulcer prophylaxis in critically ill patients: A systematic review and meta-analysis. *Crit Care Med*. 2013;41(3):693–705. Epub 2013/01/16. doi: 10.1097/CCM.0b013e3182758734.
111. Frandah W, Colmer-Hamood J, Nugent K, Raj R. Patterns of use of prophylaxis for stress-related mucosal disease in patients admitted to the intensive care unit. *J Intensive Care Med*. 2014;29(2):96-

103.doi:10.1177/0885066612453542.

112. Barletta JF, Sclar DA. Use of proton pump inhibitors for the provision of stress ulcer prophylaxis: Clinical and economic consequences. *Pharmacoeconomics*. 2014;32(1):5–13. doi: 10.1007/s40273-013-0119-5.
113. Lewis PO, Litchfield JM, Tharp JL, Garcia RM, Pourmorteza M, Reddy CM. Risk and severity of hospital-acquired clostridium difficile infection in patients taking proton pump inhibitors. *Pharmacotherapy*. 2016;36(9):986–993. Epub 2016/07/28. doi: 10.1002/phar.1801.
114. Ito T, Igarashi H, Uehara H, Jensen RT. Pharmacotherapy of Zollinger-Ellison syndrome. *Expert Opin Pharmacother*. 2013;14(3):307–321.doi:10.1517/14656566.2013.767332.
115. Ito T, Igarashi H, Jensen RT. Zollinger-Ellison syndrome: recent advances and controversies. *Curr Opin Gastroenterol*. 2013;29(6):650–661.doi:10.1097/MOG.0b013e328365efb1.
116. Krampitz GW, Norton JA. Current management of the Zollinger-Ellison syndrome. *Adv Surg*. 2013;47:59–79.
117. Epelboym I, Mazeh H. Zollinger-Ellison syndrome: Classical considerations and current controversies. *Oncologist*. 2014;19(1):44–50. doi: 10.1634/theoncologist.2013-0369.

51

Inflammatory Bowel Disease

Brian A. Hemstreet

KEY CONCEPTS

1. The exact cause of inflammatory bowel disease (IBD) is unknown. Proposed causes include infectious, genetic, and environmental factors, as well as immune dysregulation.
2. Ulcerative colitis (UC) is confined to the rectum and colon, causes continuous lesions, and affects primarily the mucosa and the submucosa. Crohn's disease (CD) can involve any part of the GI tract, often causes discontinuous (skip) lesions, and is a transmural process that can result in fistulas, perforations, or strictures.
3. Common GI complications of IBD include rectal fissures, fistulas (CD), perirectal abscess (UC), toxic megacolon (UC), and colon cancer. Extraintestinal manifestations include hepatobiliary complications, arthritis, uveitis, skin lesions (including erythema nodosum and pyoderma gangrenosum), osteoporosis, anemia, and aphthous ulcerations of the mouth.
4. The severity of UC may be assessed by stool frequency, presence of blood in stool, fever, pulse, hemoglobin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), abdominal tenderness, and radiologic or endoscopic findings. The severity of CD can be assessed using similar parameters, in addition to the CD Activity Index, which includes stool frequency, presence of blood in stool, endoscopic appearance, and physician's global assessment.
5. The goals of IBD treatment are resolution of acute inflammation and complications, alleviation of systemic manifestations, maintenance of remission, and improvement in quality of life (QOL).
6. The first line of treatment for mild to moderate extensive UC consists of oral aminosalicylates (ASAs) with oral controlled release budesonide or

prednisone as an alternative. Mesalamine enemas or suppositories are preferred for distal disease. Mesalamine is less effective for CD. Controlled-release budesonide or a tapering course of prednisone with or without azathioprine is preferred as a first-line agent for mild to moderate CD confined to the terminal ileum and/or ascending colon. Patients with more diffuse disease can be managed by a tapering course of prednisone with or with azathioprine.

7. Systemic corticosteroids are often required for acute UC or CD. The duration of steroid use should be minimized and the dose tapered gradually over 3 to 4 weeks if possible.
8. Infliximab, adalimumab, golimumab, and vedolizumab are treatment options for high risk or moderate to severe active UC in outpatients and for those patients with UC who are corticosteroid dependent. Azathioprine or mercaptopurine may be used for maintenance of remission in UC as an alternative to or in combination with tumor necrosis factor-alpha (TNF-α) inhibitors, and in patients failing ASAs or with corticosteroid dependency. Vedolizumab with or without an immunomodulator may also be used as intial therapy or for patients failing TNF-α inhibitors. Tofacitinib is used for patients with moderate to severe UC who have failed TNF-α inhibitors.
9. IV continuous infusion of cyclosporine or infliximab may be effective in treating severe colitis that is refractory to corticosteroids as an option to delay or prevent the need for surgery.
10. Aminosalicylates may prevent recurrence of acute UC in many patients, while corticosteroids are ineffective for this purpose.
11. Treatments for for high risk or moderate to severe CD include infliximab, adalimumab, certolizumab, and vedolizumab. Methotrexate, azathioprine, or mercaptopurine may be used for inadequate response or to reduce steroid dosage and in combination with TNF-α inhibitors; ustekimumab (patients failing other therapies); metronidazole (for perineal or colonic disease); and cyclosporine (for refractory disease) may be used.

INTRODUCTION

There are two forms of idiopathic inflammatory bowel disease (IBD): (a) ulcerative colitis (UC), a mucosal inflammatory condition confined to the rectum and colon, and (b) Crohn’s disease (CD), a transmural inflammation of the GI

tract that can affect any part, from the mouth to the anus.

EPIDEMIOLOGY

Inflammatory bowel disease is most prevalent in Western countries and in areas of northern latitude.[1] Rates of IBD are highest in North America, Northern Europe, and Great Britain.[1,2] The incidence of IBD is increasing worldwide, especially in Westernized and newly industrialized countries.[2–4] CD has an incidence of 6 to 15.5 cases per 100,000 persons per year and a prevalence of 3.6 to 214 per 100,000 people per year.[1,2] The incidence of UC ranges from 1.2 to 20 cases per 100,000 persons per year with a prevalence of 7.6 to 246 per 100,000 persons per year.[1] Although most epidemiologic studies combine ulcerative proctitis with UC, 17% to 49% of cases are classified as proctitis.

Both sexes are affected somewhat equally with IBD, although 20% to 30% more women are affected with CD and slightly more males (60%) are affected with UC.[2] Both UC and CD tend to have bimodal distributions in age of initial presentation. The peak incidence generally occurs in the second (CD) or third (UC) decade of life, with a second peak occurring between 60 and 70 years of age.[1–3] A higher incidence of IBD occurs in the Jewish population, while black and Asian populations have a relatively similar, and possibly lower, incidence of IBD.[2–4]

ETIOLOGY

1 The exact etiology of UC and CD is unknown; however, there are similar factors believed responsible for both conditions. The major theories behind the cause of IBD involve a combination of infectious, genetic, environmental, and immunologic factors. This may involve abnormal regulation of the innate immune response or a reaction to various antigens.[4–7] The microflora of the GI tract may provide an environmental trigger to activate inflammation in genetically susceptible individuals and is highly implicated in the development of IBD.[4,6,7]

Infectious Factors

Microorganisms are proposed to be a major factor in the initiation of inflammation in IBD. In general, there is thought to be shift toward the presence

of more proinflammatory bacteria in the GI tract, often referred to as dysbiosis.[5,7,8] However, no one definitive infectious cause of IBD has been found. Patients with IBD have a decreased diversity of intestinal microbiotica compared with those without IBD as well as increases in aggressive bacterial groups and presence of mucosal and intraepithelial bacteria.[1,5,7] The development and composition of the intestinal microbiotica may be influenced by dietary factors.[6,9] The pathogenesis of IBD may involve a loss of tolerance toward normal GI bacterial flora.[1,7] Other supporting evidence for an infectious etiology are that colitis does not appear to occur in genetically altered germ-free animals, intestinal lesions in IBD predominate in areas of highest bacterial exposure, and differences are observed in the makeup of the resident luminal and mucosal bacterial flora in healthy subjects versus those with IBD.[7,8,10]

Microorganisms may play a key role in the development of IBD. Suspect infectious agents include viruses, protozoans, mycobacteria such as *Mycobacterium paratuberculosis* or *avium*, and other bacteria such as *Ruminococcus gnavus*, *Ruminococcus torques*, *Listeria monocytogenes*, *Chlamydia trachomatis*, and *Escherichia coli*.[4–8,10,11] Patients with CD typically have circulating antibodies to *Saccharomyces cerevisiae*, which demonstrates some immunologic response to intestinal organisms.[5] Bacterial gene products may promote alteration of the intestinal barrier while bacterial antigens or ligands may include and propagate the inflammatory response.[5–7,12] Appendectomy has been associated with an increase in the risk of CD in Caucasian and Middle Eastern patients, while being protective against UC in Caucasian patients.[2]

Genetic Factors

Genetic factors play a significant role in the predisposition to IBD. Studies of monozygotic twins demonstrate a high concordance rate of IBD in both individuals (particularly CD).[1,13] First-degree relatives of patients with IBD may have up to a 20-fold increase in the risk of disease and risk is extended to second and third degree relatives.[5,14] Several genetic markers and loci have been identified that occur more frequently in patients with IBD, however for UC genetics only explain 7.5% of disease variance.[1] Genes may not act independently, but rather function in an integrated manner. This is referred to as the “limited pathway model.”[5] The nucleotide-binding oligomerization domain protein 2 (NOD2), a key component involved in pathogen recognition in the innate immune system, is the major contributor of genetic predisposition to

CD.[4,13,14] Other genes involved in the innate immune system autophagy, such as ATG16L1 and IRGM, as well as genes involved in the interleukin (IL) biologic pathway such as polymorphisms of the IL-23 receptor IL-23R, and IL-12B, STAT3, and CCR6, are strongly associated with CD and possibly UC (IL-23R).[1,12–14] The major genetic region for UC is on chromosome 6p21, in the major histocompatibility region, near human leukocyte antigen (HLA) class II genes.[13] Alterations in the genes encoding for IL-10 and the IL-10 receptor have been implicated in UC.[13,14] Other possible high-risk loci involved in epithelial barrier function, such as ECM1, HNF4A, CDH1, and LAMB1, and Th1 and Th17, involved with helper T-cell types, are implicated in the pathophysiology of UC.[1] Lastly, an emerging area of interest in IBD pathogenesis is in the role of microRNAs, which are small noncoding RNAs that regulate gene expression.[15]

Immunologic Mechanisms

The immune system plays a critical role in the pathogenesis of IBD. Potential immunologic mechanisms include both autoimmune and nonautoimmune phenomena. The innate immune system largely involves the intestinal wall epithelial barrier and its associated secretions in response to contact with organisms.[5] NOD proteins involved in recognition of organisms and toll-like membrane receptors (TLRs) are involved in intestinal surveillance and can lead to release of antibacterial peptides such as defensins, among other functions.[5] Reduction in defensin secretion by Paneth cells is thought to be one contributing factor in the loss of effective barrier function.[5,12,16] Consequently, the bowel wall in CD is infiltrated with lymphocytes, plasma cells, mast cells, macrophages, and neutrophils, often leading to formation of granulomas. Similar infiltration has been observed in the colonic mucosal layer in patients with UC. Given that inflammation is limited to the colon in UC, dysfunction of colonocytes is highly implicated.[1] The colonic mucosal layer in UC may be thinner and less effective in protecting the epithelial cells. This may be due to reduced mucin secretion secondary to defective goblet cell differentiation.[5,12,17] Autoimmune features may be directed against mucosal epithelial cells or against neutrophil cytoplasmic elements. Innate lymphoid cells are also thought to possibly play a role in IBD pathogenesis.[1]

Antineutrophil cytoplasmic antibodies are found in a high percentage of patients with UC (70%) and less frequently in CD.[17] Circulating antibodies to goblet cells and anti-tropomyosin are present in UC, although their contribution

to the disease process is not fully elucidated.[12] Overproduction of circulating IgG1 antibodies in UC may react with epithelium in the eyes, skin, joints, and biliary tract.[1] Dysfunction or reduced expression of the peroxisome proliferator–activated receptor γ in colonocytes may play a role in this process.[1]

Dysregulation of cytokines is a key component of IBD. Specifically, Th1 cytokine activity is excessive in CD and increased expression of interferon-γ in the intestinal mucosa and production of IL-12 production are features of the immune response in CD.[12] In contrast, Th2 cytokine activity is excessive with UC.[1,17,18] This is mediated by excess production of IL-13, which contributes to epithelial cell dysfunction by enhancing natural killer T-cell cytotoxicity, and IL-5, which is involved with eosinophil recruitment and activation.[1,12,17] Upregulation of the IL-13 receptor-2α occurs as well.[1,12,17,18] Activated epithelial cells secrete a variety of substances involved in the recruitment of inflammatory cells. These include IL-1β, epithelial neutrophil-activating peptide 78, IL-8, and monocyte chemoattractant protein 1.[1] Neutrophils produce proteolytic enzymes, such as matrix metalloproteinase-8 and neutrophil elastase, which further contribute to epithelial damage.[17]

Lastly, tumor necrosis factor-alpha (TNF-α) is a pivotal proinflammatory cytokine that is increased in the mucosa and intestinal lumen of patients with CD and UC. TNF-α can recruit inflammatory cells to inflamed tissues, activate coagulation, promote the formation of granulomas in patients with CD, and possibly modify epithelial cell apoptosis.[1,17,18]

Psychological Factors

Mental health changes, particularly stress, appear to possibly correlate with disease flares in IBD, but whether psychological factors are true etiologic factors in the pathophysiologic process is unclear.[19–21] Rates of both pain, anxiety, and depression are higher in patients with IBD compared to the general population, and are reported in up to 19%-21% of patients.[20] Given the complex nature of the disease process and lack of standard measurement processes, documenting the effects of stress in IBD is difficult.[19] Some studies demonstrate that perceived stress and negative mood is significantly different between patients in remission and those experiencing a disease flare.[19,20] Mood-related components, such as anxiety and depression, may contribute to exacerbations of CD.[22] Approximately 50% of patients with IBD reported some type of significant stress during any 3-month period.[23] Additionally, subjects with IBD matched by

sex, age, and geographic region to control subjects reported significantly worse psychological well-being and more distress compared with controls. Stress-related interventions in another study did not appear to alter disease course for patients with IBD, but may result in improved quality of life (QOL).[24] While stress and psychological factors may not be a direct cause of IBD, they may significantly affect QOL. This is compounded by the fact that many patients are young at the time of diagnosis, and may require surgical intervention and temporary or permanent ostomy placement. Patients should be screened for the presence of anxiety and depression as part of their ongoing assessment.

Lifestyle, Dietary, and Drug-Related Causes

Several theories regarding dietary influence on the development of IBD have been proposed. Intake of refined sugars has been associated with development of CD, while increased protein intake has been associated with a higher risk of developing IBD.[25–27] Diet composition and food derivatives may directly influence the makeup of the gut microbiotica, alter intestinal permeability, and affect immune function possibly triggering IBD.[9,26,27] The “hygiene hypothesis” proposes that cleaner conditions in more industrialized countries expose patients to fewer microorganisms at an early age. The immune response to these organisms is altered when encountered later in life.[25,27] Diets low in fruits and vegetables and high in ω-6 polyunsaturated fats may increase the risk of CD.[26] Changes in expression of the aryl hydrocarbon receptor, a transcription factor activated by dietary ligands and involved in the maintenance of the innate immune response, may increase development of IBD.[9,28] Interest has arisen in vitamin D deficiency as a possible cause of IBD given that vitamin D is involved with NOD2 gene induction.[9,29] Diets low in fermentable oligo-, di-, and monosaccharides and polyols, referred to as FODMAPs, improve IBD symptoms in some patients by reducing the osmotic load and fermentation of these sugars.[9] Tea or coffee consumption are protective against development of IBD in Asian patients.[2,9]

Smoking plays an important but contrasting role in UC and CD. It appears to be protective for UC and is associated with fewer disease flare-ups and reduced disease severity.[1,2,13] The risk of developing UC is increased for 2 to 3 years after smoking cessation in patients without IBD. In contrast, smoking is associated with increased frequency and severity of CD, and appears to worsen ileal disease more than colonic.[4,26] Patients with CD who stop smoking have a disease severity that is similar to nonsmokers. Smoking cessation should be

offered to all patients. There are data to support transdermal nicotine replacement as an adjunctive therapy in UC.[30]

Use of nonsteroidal anti-inflammatory drugs (NSAIDs) may trigger disease occurrence or lead to disease flares.[26,31] Inhibition of prostaglandin production through cyclooxygenase inhibition may impair mucosal barrier protective mechanisms. Alteration in platelet function, release of inflammatory mediators, and alteration in the microvascular response to stress are other potential mechanisms of worsening of IBD. Cyclooxygenase-2 inhibitors and cyclooxygenase-1 inhibitors increase risk; however, it is unclear whether cyclooxygenase-2 inhibitors may be safer in select patients with IBD.[2] A large cohort study in U.S. women revealed an increase in risk of developing IBD with NSAID use; however, no association was found with use of aspirin.[31] Use of NSAIDs may be warranted in some patients with IBD, particularly those with arthritic symptoms, if the benefit outweighs the potential risk of disease flare.

Development of IBD in Caucasian patients is associated with antibiotic use in childhood, while risk may be reduced in Asian and Middle Eastern patients.[2,26] Since antibiotics alter the intestinal flora, this appears to be a viable mechanism; however, delineating antibiotics as a causative factor is difficult given that symptoms may not manifest for several weeks to years following a treatment course. Furthermore, antibiotics may induce *Clostridium difficile* infection, which is a cause of colitis. Patients presenting with severe diarrhea for whom a diagnosis of IBD is being entertained should be asked about recent antibiotics, and should be tested for *Clostridioidies difficile* infection. Oral contraceptives may confer increased risk of CD in Caucasian patients, while evidence of association with development of UC is inconclusive.[1,2,26]

PATHOPHYSIOLOGY

UC and CD differ in two general respects: the extent and distribution of inflammation within the GI tract and depth of involvement within the bowel wall. Confusion in the diagnosis can occur, particularly when the inflammation is limited to the colon. For patients in whom it cannot be determined whether they have UC or CD, they are often classified as indeterminate colitis.[1] **Table 51-1** compares pathologic and clinical findings of the two diseases.

TABLE 51-1 Comparison of the Clinical and Pathologic Features of Crohn's Disease and Ulcerative Colitis

Feature	Crohn's Disease	Ulcerative Colitis
Clinical		
Malaise, fever	Common	Uncommon
Rectal bleeding	Common	Common
Abdominal tenderness	Common	May be present
Abdominal mass	Common	Absent
Abdominal pain	Common	Unusual
Abdominal wall and internal fistulas	Common	Absent
Distribution	Discontinuous	Continuous
Aphthous or linear ulcers	Common	Rare
Pathologic		
Rectal involvement	Rare	Common
Ileal involvement	Very common	Rare
Strictures	Common	Rare
Fistulas	Common	Rare
Transmural involvement	Common	Rare
Crypt abscesses	Rare	Very common
Granulomas	Common	Rare
Linear clefts	Common	Rare
Cobblestone appearance	Common	Absent

Ulcerative Colitis

2 Ulcerative colitis is confined to the rectum and colon and affects the mucosal and the submucosal layers. The disease distribution upon initial diagnosis is 30% to 60% proctitis, 16% to 45% left-sided colitis, and 14% to 35% have extensive colitis, also referred to as pancolitis.[1] In some instances, a short segment of terminal ileum may be inflamed; this is referred to as *backwash ileitis*. Unlike CD, the deeper longitudinal muscular layers, serosa, and regional lymph nodes are not usually involved.[1] Fistula, perforation, or obstruction is uncommon because of the more superficial pattern of inflammation.

In UC, abscess formation in the crypts of the mucosa occurs (crypts of Lieberkuhn) secondary to infiltration of lymphocytes, plasma cells, and granulocytes.[1] Crypt abscesses are usually visible only with microscopy but may

be visible when coalescence results in ulceration. Reduced crypt density, distorted crypt architecture and atrophy, and depletion of goblet cells are typical findings.[1,30] Extension and coalescence of ulcers may surround areas of uninvolved mucosa, causing *pseudopolyp* formation. Mucosal damage and friability in UC can result in significant diarrhea and bleeding, although a small percentage of patients experience constipation.

3 Complications of UC may be local, including hemorrhoids, anal fissures, or perirectal abscesses, and are more likely to be present during active colitis. Extraintestinal manifestations (not directly associated with the colon) may occur and are discussed later.

A major complication is toxic megacolon, which is a segmental or total colonic distension of greater than 5.5 to 6 cm with acute colitis and signs of systemic toxicity.[1,32] It occurs in up to 7.9% of UC patients admitted to hospitals and results in death rates of up to 50%. With toxic megacolon, ulceration extends below the submucosa, sometimes reaching the serosa. Vasculitis, swelling of the vascular endothelium, and thrombosis of small arteries occur. Involvement of the muscularis propria causes loss of colonic tone, leading to dilation and potential perforation. Patients typically have a high fever, tachycardia, distended abdomen, elevated white blood cell count, and a dilated colon observed on x-ray.[8,32] Colonic perforation may occur with or without toxic megacolon and is a greater risk with the first episode. Another infrequent major complication is massive colonic hemorrhage. Colonic stricture, sometimes with clinical obstruction, may also complicate long-standing UC.

The risk of colonic dysplasia with transition to colorectal carcinoma (CRC) is fivefold greater for patients with chronic UC with colonic involvement compared with the general population.[33] CRC is responsible for 10% to 15% of deaths in patients with UC.[34] Patients with ulcerative proctitis or proctosigmoiditis are generally not considered to be at increased risk.[33,34] The cumulative risk of developing CRC in patients with chronic UC may be as high as 8% at 20 years.[34] Risk factors for CRC include young age at onset, longer duration of disease, greater extent of colonic involvement, presence of primary sclerosing colangitis (PSC), active histological inflammation, family history of a first degree relative diagnosed with CRC prior to age 50, history of dysplasia, colonic strictures, pseudopolyps, a shortened tubular colon, and male gender.[34] Screening colonoscopy with multiple biopsies should be performed at 8 years after onset of symptoms in patients with left-sided or extensive colitis, with subsequent screenings at 1 to 2 years if negative.[34] Patients with PSC, extensive

colitis with active endoscopic or histologic inflammation, a history of dysplasia, or a family history of a first degree relative diagnosed with CRC prior to age 5 should undergo yearly colonoscopy.[34]

Crohn's Disease

Crohn's disease is characterized as a transmural inflammatory process. The terminal ileum is the most common site of the disorder, but it may occur in any part of the GI tract from mouth to anus.[13,35,36] Patients often have normal bowel separating segments of diseased bowel resulting in discontinuous disease. The mesentery first becomes thickened and edematous, and then fibrotic. Ulcers are typically deep and elongated and extend along the longitudinal axis of the bowel, at least into the submucosa. The "cobblestone" appearance of the bowel wall results from deep mucosal ulceration intermingled with nodular submucosal thickening.

Bowel wall injury is generally extensive, and the intestinal lumen is often narrowed. Small bowel stricture and subsequent obstruction is a complication that may require surgery. Fistula formation is also common, occurring much more frequently than with UC.[13,35] Fistulas often occur in highly inflamed areas, where loops of bowel become matted together by fibrous adhesions. Perianal fistulas may occur in up to 26% of patients within 20 years of diagnosis.[35] Fistulas may connect a segment of the GI tract to skin (enterocutaneous), two segments of the GI tract (enteroenteric), or the intestinal tract with the bladder (enterovesicular) or vagina. Fistulae associated with CD frequently require surgical treatment.

Bleeding with CD is usually not as severe as with UC, although patients with CD may develop hypochromic anemia. The risk of carcinoma is increased but not as greatly as with UC, however patients with CD and a personal history of dysplasia or PSC are at higher risk, and chromoendoscopy should be used during colonscopy.[35]

Nutritional deficiencies are common with CD.[35,37,38] Reported deficiencies include folate, vitamin B_{12}, vitamins A to D, calcium, magnesium, iron, and zinc.[38] Major contributing factors include decreased food intake, intestinal loss, malabsorption, hypermetabolic state, drug-nutrient interactions, and those receiving long-term total parenteral nutrition.[38]

Extraintestinal Manifestations of IBD

Both forms of IBD are associated with development of symptoms and organ involvement outside of the GI tract referred to as extraintestinal manifestations.

Hepatobiliary Complications

Hepatobiliary complications are commonly found in patients with IBD.[1,35,39,40] Hepatic complications include non-alcoholic fatty liver disease, pericholangitis, autoimmune hepatitis, liver abscess, and cirrhosis. Biliary complications include PSC, cholangiocarcinoma, and cholelithiasis.[1,39] Fatty infiltration of the liver may result from malabsorption, protein-losing enteropathy, or corticosteroid use, and may be found in up to 50% of patients with IBD.[39] PSC is associated with progressive fibrosis of intrahepatic and extrahepatic bile ducts in 4% of patients with UC.[39] Cirrhosis may result from cholangitis or chronic active hepatitis. Often the severity of hepatic disease does not correlate with GI disease activity. Gallstones occur in up to 34% of patients with CD (particularly with terminal ileal disease) and are related to bile salt malabsorption.[39]

Joint Complications

Both peripheral and axial arthropathies may be present in patients with IBD. Peripheral arthritis is typically asymmetric, oligoarticular, non-erosive, and occurs in 5% to 20% of patients.[40] Symptoms may present prior to GI symptoms of IBD. Axial arthropathies include sacroiliitis, ankylosing spondylitis, and IBD-associated spondyloarthropathy. The prognosis is not as favorable as peripheral arthritis, as progression is common. Patients with axial involvement should be referred to a rheumatologist in order to assist in the disease management.[40]

Ocular Complications

Ocular complications including dry eye, blepharitis, iritis, uveitis, episcleritis, and conjunctivitis occur in up to 29% of patients with IBD.[1,40] Commonly reported symptoms with iritis and uveitis include blurred vision, eye pain, and photophobia. Episcleritis is associated with scleral injection, burning, and increased secretions. These complications may parallel the severity of intestinal disease, and recurrence after colectomy with UC is uncommon.

Dermatologic and Mucocutaneous Complications

Skin and mucosal lesions associated with IBD include erythema nodosum, pyoderma gangrenosum, aphthous ulceration, and Sweet’s syndrome.[40] Raised,

red, tender nodules on the tibial surfaces of the legs and arms that vary in size from 1 to 5 cm are manifestations of erythema nodosum, and may occur in 4.2% to 7.5% of patients with IBD.[40] These lesions are more commonly observed in CD patients and often correlate with disease severity.

Pyoderma gangrenosum occurs in 0.6% to 2% of patients with IBD and is characterized by skin pustules that progress to a burrowing ulcer with violaceous edges, ranging between 2 and 20 cm.[1,40] They can be seen on any part of the body but commonly occur on the lower extremities.

Oral lesions are found in 4% to 20% of patients with IBD.[35,40] The most common lesion seen with CD is aphthous stomatitis. The severity of these lesions tends to parallel the disease course. Sweet's syndrome, also known as acute febrile neutrophilic dermatosis, is characterized by tender erythematous skin lesions secondary to dermal neutrophil infiltration, and is often associated with fever and a distribution on the upper trunk, face, neck, and arms.[40]

Hematologic, Coagulation, Pulmonary, and Metabolic Abnormalities

Patients with IBD may develop anemia, with a prevalence reported up to 74%.[1,38,40] The anemia may present as iron deficiency related to chronic blood loss, ongoing inflammation, malnutrition, hemolysis, or bone marrow suppression from drug treatment.[38,40] Alternatively, it may be more characteristic of anemia of chronic disease secondary to chronic inflammation and overproduction of cytokines. Patients with IBD are at a 1.5 to 3.6 times higher risk of venous thromboembolism (VTE) compared with the general population.[40] This is secondary to activation of the clotting cascade and platelet activation secondary to inflammation.[40] Occurrence of VTE is higher during disease flares and occurs more often in peripheral veins.[1,40] Patients should be considered for pharmacologic VTE prophylaxis when admitted to the hospital for a disease flare. Patients with IBD may be at increased risk for metabolic bone disease and development of osteoporosis. Osteomalacia is less common in IBD.[40,41] Bone disease may be related to a combination of nutritional deficiencies, especially calcium and vitamin D, chronic cytokine-related inflammatory effects on bone, disease-associated hypogonadism, and use of corticosteroids.[40,41] Pulmonary manifestations occur from the glottis all the way to the small airways, but most commonly involve the large airways and may include interstitial pneumonia, bronchiectasis, and bronchiolitis obliterans.[40]

CLINICAL PRESENTATION

The patterns of clinical presentation of IBD can vary widely. Patients may have a single acute episode that resolves and does not recur, but most patients experience acute flares with alternating periods of remission.

Ulcerative Colitis

There is a wide range of presenting symptoms in UC, ranging from mild abdominal cramping with frequent small-volume bowel movements to profuse diarrhea (Table 51-2). Most patients with UC experience intermittent bouts of illness after varying intervals of remission. A small percentage of patients have continuous unremitting symptoms or a single acute attack with no subsequent symptoms.

TABLE 51-2 Clinical Presentation of Ulcerative Colitis

Signs and symptoms
- Abdominal cramping
- Frequent bowel movements, often with blood in the stool
- Weight loss
- Fever and tachycardia in severe disease
- Blurred vision, eye pain, and photophobia with ocular involvement
- Arthritis
- Raised, red, tender nodules that vary in size from 1 cm to several centimeters

Physical examination
- Hemorrhoids, anal fissures, or perirectal abscesses may be present
- Iritis, uveitis, episcleritis, and conjunctivitis with ocular involvement
- Dermatologic findings with erythema nodosum, pyoderma gangrenosum, or aphthous ulceration

Laboratory tests
- Decreased hematocrit/hemoglobin
- Increased ESR, CRP, and fecal calprotectin
- Leukocytosis and hypoalbuminemia with severe disease
- (+) perinuclear antineutrophil cytoplasmic antibodies

4 While various disease classifications are available for UC, a standard disease severity scoring system is not universally accepted.[1,30] The designations of mild, moderate, severe, and fulminant disease activity are generally used in treatment guideline recommendations, and are determined largely by clinical signs and symptoms:[30]

1. Mild: Fewer than four stools daily, with or without blood, with no systemic disturbance and a normal erythrocyte sedimentation rate (ESR < 30)
2. Moderate: More than four stools per day but with minimal systemic disturbance
3. Severe: More than six stools per day with blood, with evidence of systemic disturbance as shown by fever, tachycardia, anemia, or ESR of greater than 30 mm/h (8.3 μm/s).
4. Fulminant: More than 10 bowel movements per day with continuous bleeding, toxicity, abdominal tenderness, requirement for transfusion, and colonic dilation

With severe disease, the patient typically has profuse bloody diarrhea with a high fever, leukocytosis, and hypoalbuminemia. The patient may be dehydrated with tachycardia and hypotension. This presentation may have a sudden onset with rapid progression.

As an alternative, a clinical care pathway has been developed by the American Gastroenterological Association (AGA). The pathway assesses the severity of UC based on risk for colectomy.[42] Following a diagnosis of UC inflammatory status (based on signs/symptoms, lab markers, and endoscopic findings), comorbidities, and therapy-related complications (if the patient is already receiving treatment) are assessed. Patients are then stratified according to low risk for colectomy (limited anatomic extent and mild endoscopic disease) or high risk for colectomy (extensive colitis, age less than 40 years, deep ulcers, high ESR/CRP, steroid dependence, history of hospitalization, and *Clostrodioidies difficile* or cytomegalovirus infection). Treatment recommendations subsequently based on low versus high risk, and then further based on outpatient or inpatient status.

Determining disease extent, that is, which sections of the colon are involved, is important. This is accomplished via endoscopy. Patients with “distal” disease have inflammation limited to areas distal to the splenic flexure (also referred to as *left-sided* disease), while those with “extensive disease” have inflammation extending proximal to the splenic flexure.[1,30] Inflammation confined to the rectal area is referred to as *proctitis*, while disease involving the rectum and sigmoid colon is referred to as *proctosigmoiditis*. Inflammation of the majority of the colon is called *extensive disease*, sometimes referred to as *pancolitis*. Disease activity may be assessed upon endoscopy using common scoring systems, such as the UCEIS or Mayo Score.[30]

The diagnosis of UC is made on clinical suspicion and confirmed by biopsy, stool examinations, sigmoidoscopy or colonoscopy, or barium radiographic contrast studies.[43] Evaluation of CRP, and fecal calprotectin, a protein released during leukocyte trafficking, may also assist in identifying the presence of intestinal inflammation, and are also helpful in monitoring response to therapy.[43] The presence of extracolonic manifestations may also aid in establishing the diagnosis of UC.[1,30,40]

Crohn's Disease

As with UC, the presentation of CD is highly variable. The time between the onset of complaints and the initial diagnosis may be as long as 3 years. The patient typically presents with diarrhea and abdominal pain. Hematochezia occurs in about one-half of patients with colonic involvement and much less frequently when there is no colonic involvement. A patient may first present with a perirectal or perianal lesions, or extraintestinal manifestations in up to 50% of cases.[13] (Table 51-3). The diagnosis should also be suspected in children with growth retardation, especially with abdominal complaints.

TABLE 51-3 Clinical Presentation of Crohn's Disease

Signs and symptoms
• Malaise and fever
• Abdominal pain
• Frequent bowel movements
• Hematochezia
• Fistula
• Weight loss and malnutrition
• Arthritis
Physical examination
• Abdominal mass and tenderness
• Perianal fissure or fistula
Laboratory tests
• Increased white blood cell count, ESR, CRP, and fecal calprotectin
• (+) anti–*Saccharomyces cerevisiae* antibodies

Much like UC, global classification guidelines for scoring severity of active CD are not available. For patients with luminal nonfistulizing CD, the Crohn's Disease Activity Index (CDAI) is used most often to gauge response to therapy and determine remission and is employed mostly in the research setting. This score system ranges from 0 to 600, with score great than 150 defined as active disease. The Harvey-Bradshaw Index (HBI) is another scoring system that is

also used for CD, and tends to correlate well with the CDAI. A decrease of 3 points in the HBI is defined as a clinical response with complete remission defined as a score of less than 4. Treatment guidelines use the presence of signs and symptoms as their marker for disease activity and severity.[35]

The classification of CD severity is similar to UC.[13,35] Patients with mild to moderate CD are typically ambulatory and have no evidence of dehydration, systemic toxicity, less than 10% loss of body weight, or abdominal tenderness, mass, or obstruction. This correlates to a CDAI of 150 to 220. Moderate to severe disease is considered in patients who fail to respond to treatment for mild to moderate disease or those with fever, weight loss, abdominal pain or tenderness, vomiting, intestinal obstruction, or significant anemia. Severe to fulminant CD is classified as the presence of persistent symptoms or evidence of systemic toxicity despite corticosteroid or biologic treatment or presence of cachexia, rebound tenderness, intestinal obstruction, or abscess with a CDAI more than 450. Disease activity may be assessed and correlated by evaluation of CRP concentrations.

Similar to UC, the AGA has developed a clinical decision support tool for assessing CD severity.[44] Initially, the patient's inflammatory status, comorbidities, and disease- and therapy-related complications are assessed. Patients then stratified as low risk (age at initial diagnosis over 30 years, limited anatomic involvement, no perianal and/or severe rectal disease, superficial ulcers, no prior surgical resection, and no stricturing and/or penetrating disease) or moderate to high risk (age at initial diagnosis less than 30 years, extensive anatomic involvement, perianal and/or severe rectal disease, deep ulcers, prior surgical resection, stricturing and/or penetrating disease).

The course of CD is characterized by periods of remission and exacerbation. Patients may be symptom-free for years, while others experience chronic symptoms in spite of medical therapy. As with UC, the diagnosis of CD involves a thorough evaluation using laboratory, endoscopic, and radiologic testing to detect the extent and characteristic features of the disease.[13,35,43,44] Small bowel involvement, strictures detected on radiographs, and presence of fistulae are characteristic of CD.

TREATMENT

Desired Outcomes

5 The clinician must have a clear concept of realistic therapeutic goals for each patient with IBD. Goals may relate to resolution of acute inflammatory processes, resolution and prevention of complications (eg, fistulae, abscesses, and CRC), alleviation of extraintestinal manifestations, maintenance of remission, or surgical palliation or cure.

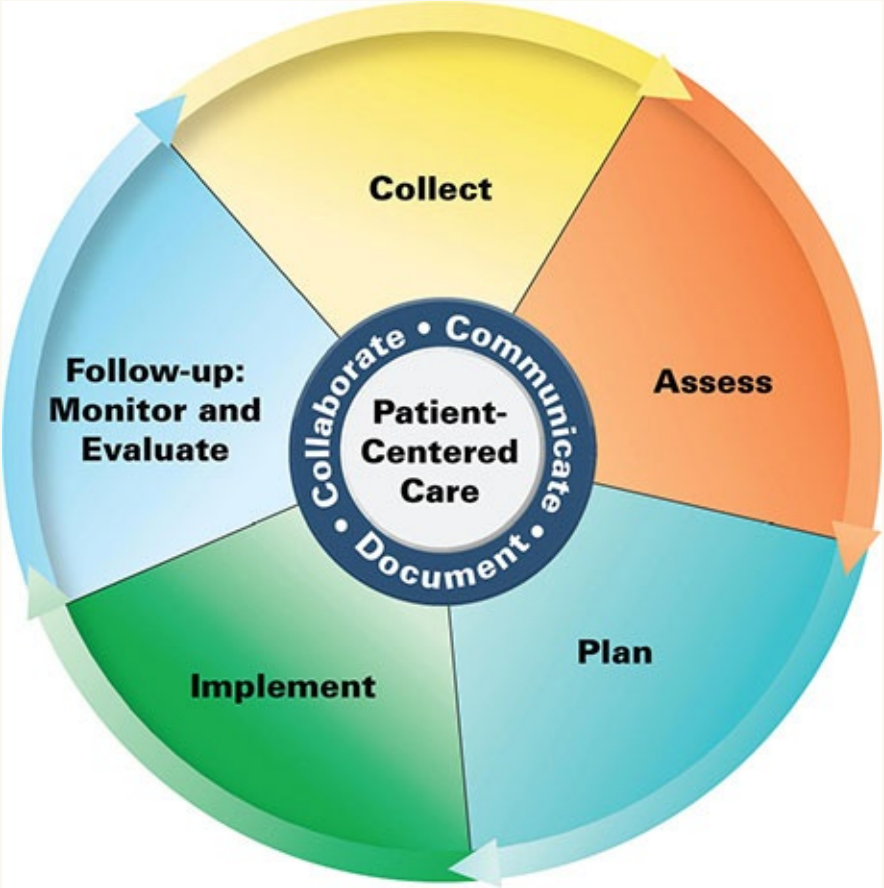
When determining goals of therapy and selecting therapeutic regimens, it is important to understand the natural history of IBD.[1,30,35,45] Some cases of acute UC are self-limited. Following remission, up to 43% of patients may experience relapse in the first year, and almost half may require hospitalization at some point during their disease course.[45] Being young at the time diagnosis, female sex, presence of extra-intestinal manifestations, non-smoking status, and higher levels of education have been associated with higher risk of relapse.[45] With severe colitis, improvement without treatment cannot be expected. The response to medical management of toxic megacolon is variable and emergent colectomy may be required. Crohn's disease tends to be progressive and destructive, with only 20% to 30% having an indolent course.[3,11,35] Patients at risk for progression of CD include young age at diagnosis, extensive bowel involvement, perianal or severe rectal disease or stenosis.[35] Up to 80% of patients will require hospitalization at some point during their disease course, and there are high rates of steroid dependence and the need for surgical intervention.

Much like in other inflammatory diseases, there has been a movement toward use of the "Treat to Target" approach.[13,46] This involves use of specific targets, such as mucosal healing and endoscopic remission, or resolution of symptoms such as abdominal pain and diarrhea, as the main indicators of treatment efficacy. Mucosal healing, defined as the absence of ulceration, has become an important target and is accessed via endoscopy with specific scoring systems used to determine if this outcome has been assessed. Mucosal healing can be used as a monitoring parameter for treatment efficacy, particularly in CD, and if achieved may be predictive of steroid free sustained remission.[35,46] Biomarkers, such as CRP and fecal calprotectin, have also become important adjunctive monitoring parameters to endoscopic approaches.[35,43,44,45,46]

General Approach To Treatment

6 Treatment of IBD centers on agents used to suppress the inflammatory process, induce and then maintain disease remission. Aminosalicylates (ASAs), corticosteroids, antimicrobials, immunosuppressive, and biologic agents are commonly used to treat active disease, with some agents also used to maintain

remission. The severity and extent of the disease should be taken into account, as this will often dictate the dose, route, frequency, and formulation of drug therapies that will be most effective. Patient preference for different drug formulations and cost of therapies should also be taken into account.



Patient Care Process for Treatment of Inflammatory Bowel Disease

Collect

- Patient characteristics (eg, age, sex, weight, vital signs, etc.)
- Patient symptoms, including evidence of abdominal pain, stool frequency, presence of hematochezia, weight loss, or extraintestinal manifestations
- Patient medical, family, and social history (in particular tobacco use)
- Surgical operations (site, date, procedure) and abdominal imaging findings (CT, MRI, ultrasound)

- Thorough medication history at hospital admission (include prescription, non-prescription medications, and other substances), and drug allergies and intolerances.
- Laboratory results for evidence of inflammation (CRP, ESR, WBC), major organ function (particularly kidney and liver), hemoglobin and hematocrit, nutritional status (serum albumin and transferrin), vaccination status, pregnancy status, and pANCA or anti-*Saccharomyces cerevisiae* antibodies if initial diagnostic workup, and pharmacogenomics status for TPMT, if applicable

Assess

- Determine severity of illness based on symptoms, vital signs, stool frequency, and inflammatory markers. Consider use of Crohn's Disease Activity Index to assess disease progress. Include assessment of fluid and electrolyte status
- Determine extent and location of inflammation in the gastrointestinal tract based on endoscopic and imaging procedures
- Assess if extraintestinal disease manifestations and comorbidities are present that may affect section and outcomes of medication regimens.
- Evaluate current medication regimen for potential drug induced exacerbating factors and for efficacy and toxicity of current IBD treatment regimen
- Assess if disease complications are present that may require surgical intervention (abscess or fistulae)
- Estimate creatinine clearance for drug dosing

Plan*

- Determine goals of therapy with monitoring parameters for each goal
- Based on severity and location of Illness, determine the appropriate medications to induce and maintain remission considering severity and site of disease (**Figs. 51-2** and **51-3**)
- Initiate adjunctive medications for pain and diarrhea, if needed
- Check for adverse drug reactions and interactions and dose adjustments based on end-organ function (**Table 51-6**)

Implement

- Initiate medications for short term induction of remission and subsequent maintenance
- Discontinue medications that may be exacerbating symptoms
- Provide patient education on appropriate use of oral, parenteral, or rectally administered medications
- Assure that corticosteroids doses are tapered during discontinuation

Follow-up: Monitor and Evaluate

- Determine if patient shows improvement in the signs and symptoms within 24 to 48 hours for hospitalized patients, and 7 to 14 days for outpatients
- Evaluate laboratory parameters for evidence of drug efficacy and potential toxicity
- Monitor for adverse effects of medications
- Assess adherence to current medication regimen and address barriers to medication use
- Determine the need for dose reduction or tapering of medications intended for short term use, such as corticosteroids

** Collaborate with patient, caregivers, and other healthcare professionals.*

Surgical procedures are sometimes performed when active disease is inadequately controlled with drugs, or when the required drug dosages pose an unacceptable risk of adverse effects. Nutritional considerations are also important because many patients may develop malnutrition. A variety of adjunctive therapies may be used to address complications or symptoms of IBD.

Nonpharmacologic Therapy

Nutritional Support

Proper nutritional support is an important aspect of the treatment of patients with IBD. Malabsorption or maldigestion may occur secondary to the catabolic effects of the disease process. Elevated activity of IL-6 and TNF-α increases protein turnover, resulting in protein loss and muscle wasting.[38] Malabsorption and malnutrition may occur more often in the patient with CD with involvement of the small bowel, as this is where many nutrients are absorbed.[47] Protein–energy malnutrition and suboptimal weight is reported in up to 85% of patients

with CD.[47] Patients who have undergone multiple small bowel resections may have reduction in the absorptive surface of the intestine (ie, “short gut”). Maldigestion with accompanying diarrhea can also occur if there is a bile salt deficiency in the gut.

On an individual patient basis, elimination of specific foods that appear to exacerbate symptoms can be tried; however, exclusion diets are generally not endorsed, even in the setting of severe disease.[48] Increased intake of red meat, protein, sulfur and sulfates, and alcoholic beverages have been associated with disease flares.[9] If attempted, the elimination process must be conducted cautiously, as patients may exclude a wide range of nutritious products without adequate justification. Some patients with IBD may have lactase deficiency as well; therefore, diarrhea may be associated with intake of dairy products. For these patients, avoidance of dairy products or supplementation with lactase generally improves the patient’s symptoms.[48] Patients with small bowel strictures due to CD should avoid excessive high-residue foods, such as citrus fruits and nuts, in order to prevent obstruction. Increases in soluble fiber may induce the production of intestinal short chain fatty acids, which may have intrinsic anti-inflammatory effects.[9]

Many specific diets have been tried to improve nutritional status and symptoms in IBD. As mentioned earlier, use of diets low in FODMAPs may help improve IBD symptoms. The specific carbohydrate diet (SCD) is another option that involves restriction of all carbohydrates except monosaccharides (glucose, fructose, and galactose), as well as restriction of milk, canned fruits and vegetables and processed meats.[9] Some studies have demonstrated improvement in symptoms and inflammation, however patient adherence may by problematic. Exclusive enteral nutrition, which involves use of elemental, semi-elemental, and defined formulas, has shown some benefit in increasing nutritional status and reducing intestinal inflammation and cytokine production.[9,38,47] This may lead to a greater chance of induction and maintenance of remission as well as facilitation of mucosal healing, particularly in patients with CD.[47] Monitoring for efficacy of the enteral feeding is similar to other patient populations receiving enteral nutrition.

Parenteral nutrition has a more limited role in IBD. It is generally reserved for patients with severe malnutrition or those who fail enteral therapy or have a contraindication to receiving enteral therapy, such as perforation, protracted vomiting, short-bowel syndrome, or severe intestinal stenosis.[38,47] Parenteral therapy is not preferred as primary therapy for IBD even in the setting of acute disease flares in hospitalized patients.[48] Home parenteral nutrition may be

necessary for patients requiring long-term therapy, particularly those with short-bowel syndrome. Parenteral nutrition is more costly and is associated with more complications, such as serious infections, compared with enteral nutrition.

Given that the intestinal microbiotica may play a key role in IBD pathogenesis, probiotic administration as an adjunctive treatment of IBD has been explored. Postulated mechanisms for using probiotics in IBD include reestablishment of normal bacterial flora within the gut, reduction in bacterial adhesion and competition for nutrients with pathogenic bacteria, production of antibacterial substances, and promotion of favorable effects on the host immune response.[49,50] Probiotic preparations often contain various organisms such as nonpathogenic *E. coli Nissle*, bifidobacteria, lactobacilli, *Streptococcus thermophilus, or Saccharomyces boulardii*. Probiotics were effective in inducing and maintaining remission in some trials for patients with UC; however, differences in methodology, probiotics used, and underlying treatments for IBD make comparison of trials difficult.[49–52] A formulation of *Bifidobacterium*, lactobacilli, and streptococci (VSL #3) is marketed specifically for use in UC as an adjunctive therapy and for patients who have a surgically constructed ileal pouch anal anastomosis (IPAA) to prevent or treat pouchitis.[30,49,50] Evidence of probiotic use for the induction and maintenance of CD is less compelling and has led to recommendations not supporting widespread use, but rather further investigation.[49–52] While probiotics are considered to be generally safe in patients with IBD, the added cost and requirement to often take multiple doses per day, coupled with the lack of quality data to support their use, should also weigh into the decision to use them in IBD.

Surgery

Despite the availability of medications to treat IBD, many patients will often require surgery. Surgical procedures may involve resection of segments of intestine that are affected, as well as correction of complications (eg, fistulas) or drainage of abscesses.

Rates of colectomy over 20 years UC are reported as 0.55% to 20%.[1,30,45,53,54] Colectomy may be necessary when the patient has disease uncontrolled by maximum medical therapy or when there are complications of the disease such as colonic perforation, toxic megacolon, uncontrolled colonic hemorrhage, or colonic strictures.[1,30,53] Colectomy may be indicated for patients with long-standing disease (greater than 8-10 years), as a prophylactic measure against the development of CRC, and for patients with premalignant changes

(severe dysplasia) on surveillance mucosal biopsies.[33,34,53] Proctocolectomy, after which the patient is left with a permanent ileostomy, is generally considered curative for UC; however, the decision to perform this should take into account the effects on the patient's QOL. Restorative proctocolectomy with construction of an IPAA is the most common surgical procedure performed in UC and is typically well tolerated with a reported failure rate of less than 10%.[53] Patients may develop inflammation of the IPAA, often referred to as pouchitis.

Surgery in patients with CD is usually reserved for patients with intractable hemorrhage, perforation, persistent or recurrent obstruction, abscess, dysplasia, cancer, or medically refractory disease.[13,35] The 10 year cumulative risk of surgical intervention is 40% to 55%, with the 5-year postoperative recurrent rate reported as approximately 50%.[35] The surgical procedures performed most often include resections of the major intestinal areas of involvement. Patients who undergo multiple resections of the small intestine may develop malabsorption related to short-bowel syndrome. For some patients with severe rectal or perianal disease, particularly abscesses, diversion of the fecal stream is performed with a colostomy.

Pharmacologic Therapy

The approach to treatment of IBD should consider all aspects of each individual patient in order to maximize therapy, improve patient symptoms and QOL, and prevent complications. To ensure optimal drug therapy, an assessment of each patient's health literacy and potential barriers to understanding and adherence should be performed. Involving the patient in the care process will help to keep him or her engaged. For the drug classes that are used in the management of IBD, there are several aspects of individualization that may improve efficacy and safety. Since patients with IBD are often seen by GI specialists or surgeons, ensuring that each provider has a current, accurate, and complete medication list will help to prevent potential medication errors. Female patients of childbearing age should discuss with their providers their goals for becoming pregnant, as this may dictate the choice of drugs used.

Drug therapy plays an integral role in the treatment of IBD. None of the drugs used for IBD are curative; therefore, reasonable goals of drug therapy are resolution of acute disease symptoms and induction and maintenance of remission. The major types of drug therapy used in IBD include ASAs, corticosteroids, immunomodulators (azathioprine, mercaptopurine, methotrexate), immunosuppressive agents (cyclosporine and tacrolimus),

antimicrobials (metronidazole and ciprofloxacin), and agents to inhibit TNF-α (anti–TNF-α antibodies), leukocyte adhesion and migration (natalizumab and vedolizumab), interleukin function (ustekinumab), or Janis kinase function (tofacitinib).[1,13,30,35,54]

Sulfasalazine is the prototypical ASA, and is composed of a sulfonamide moiety (sulfapyridine) and mesalamine (5-aminosalicylate acid [5-ASA]) joined by a diazo bond in the same molecule.[55] Sulfasalazine has been used for years to treat IBD but was originally intended to treat arthritis. It is cleaved by gut bacteria in the colon to sulfapyridine (which is mostly absorbed and excreted in the urine) and mesalamine (which mostly remains in the colon and is excreted in stool).[55–58]

The active component of sulfasalazine is mesalamine, which exerts its effects locally in the GI tract; however, the mechanism of action is not completely understood. Beneficial effects of mesalamine may include scavenging of free radicals, inhibition of leukocyte motility, interference with TNF-α, transforming growth factor-β (TGF-β) and nuclear factor κ B (NF-κ β), suppression of IL-1 production, and inhibition of leukotriene and prostaglandin production.[55–58]

Because the effectiveness of sulfasalazine is not related to the sulfapyridine component and since sulfapyridine is believed to be responsible for many of the adverse reactions to sulfasalazine, mesalamine can be administered alone. Given that mesalamine is rapidly and completely absorbed in the small intestine but poorly absorbed in the colon, drug formulations must be designed to deliver mesalamine to the affected areas in the GI while preventing premature absorption.[53,54,55–58] Mesalamine can be used topically as an enema, to treat left-sided disease, or as a suppository for treatment of proctitis (**Fig. 51-1**). In general, the use of topical mesalamine preparations, such as enemas and suppositories, is more effective than oral preparations.[55,56,59,60] Likewise, these therapies may be used concomitantly with the oral mesalamine preparations, which may result in additive efficacy in patients with UC.[60] Oral slow-release formulations will deliver mesalamine to the small intestine and/or colon based on the product design (**Table 51-4**). Slow-release oral formulations of mesalamine, such as Pentasa, release mesalamine from the duodenum to the ileum, with up to 59% of the drug passing into the colon.[55,56] Some dose forms (Asacol, Asacol HD, Delzicol) utilize a pH-dependent coating that releases in response to intestinal pH.[57] Another tablet formulation of mesalamine (Lialda) uses a pH-dependent coating that releases at a pH of 7, in combination with a polymeric matrix core, referred to as the Multi-MatriX (MMX) system, and releases drug evenly throughout the colon also allowing for once-daily dosing.[58]

A capsule formulation of mesalamine (Apriso) utilizes enteric-coated mesalamine granules in a polymer matrix for delayed and extended delivery of mesalamine to the colon and also allows for once-daily dosing.[56,57] Use of once-daily oral mesalamine preparations may enhance adherence, which may help to prevent relapse.[55,57,58] Olsalazine is a dimer of two 5-ASA molecules linked by an azo bond. Mesalamine is released in the colon after colonic bacteria cleave the azo bond.[55] Balsalazide is a mesalamine prodrug that couples mesalamine with the inert carrier molecule 4-aminobenzoyl-*β*-alanine and is also enzymatically cleaved in the colon to release mesalamine.[55] The recommended daily doses of the oral mesalamine derivatives are intended to approximate the molar equivalent of mesalamine present in 4 g of sulfasalazine. Because the oral mesalamine formulations are delayed-release coated tablets or granules, they should not be crushed or chewed. Unlike sulfasalazine, all of these agents are safe to use for patients with sulfonamide allergies.

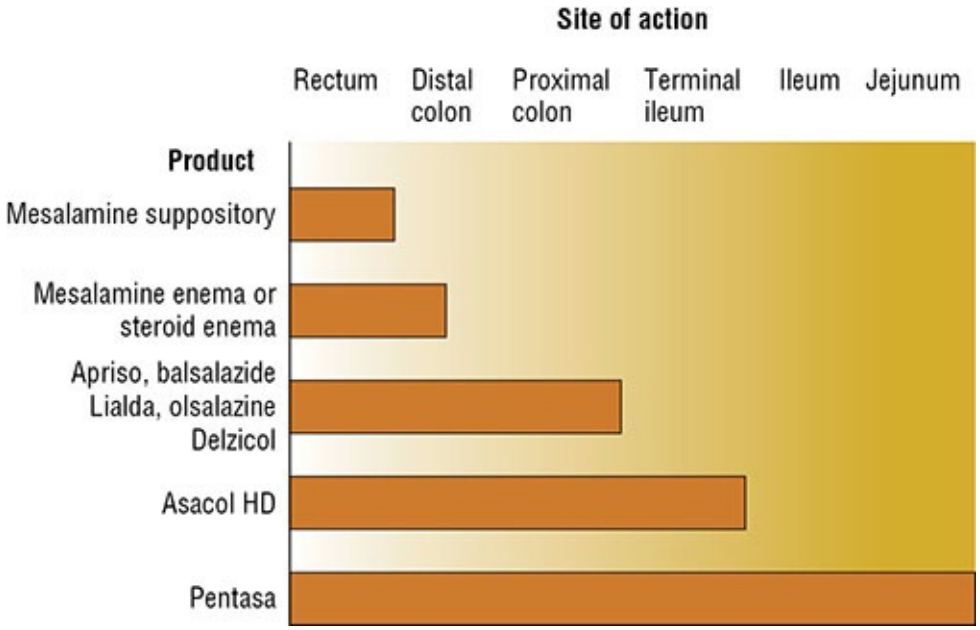


FIGURE 51-1 Site of activity of various agents used to treat inflammatory bowel disease.

TABLE 51-4 Agents for the Treatment of Inflammatory Bowel Disease

Drug	Brand Name	Initial Dose (g)	Usual Range
Sulfasalazine	Azulfidine Azulfidine EN	500 mg-1 g 500 mg-1 g	4-6 g/day 4-6 g/day
Mesalamine suppository	Rowasa	1 g	1 g daily to three times weekly
Mesalamine enema	Canasa	4 g	4 g daily to three times weekly
Mesalamine (oral)	Asacol HD Apriso Lialda Pentasa Delzicol	1.6 g/day 1.5 g/day 1.2-2.4 g/day 2 g/day 1.2 g/day	2.8-4.8 g/day 1.5 g/day once daily 1.2-4.8 g/day once daily 2-4 g/day 2.4-4.8 g/day
Olsalazine	Dipentum	1.5 g/day	1.5-3 g/day
Balsalazide	Colazal	2.25 g/day	2.25-6.75 g/day
Azathioprine	Imuran, Azasan	50-100 mg	1-2.5 mg/kg/day
Cyclosporine	Gengraf Neoral, Sandimmune	2-4 mg/kg/day IV 2-8 mg/kg/day oral	2-4 mg/kg/day IV
Mercaptopurine	Purinethol	50-100 mg	1-2.5 mg/kg/day
Methotrexate	No branded IM injection	15-25 mg IM weekly	15-25 mg IM weekly
Adalimumab	Humira	160 mg SC day 1	80 mg SC 2 (day 15), and then 40 mg every 2 weeks
Adalimumab-atto	Amjevita		
Adalimumab-abdm	Cyltezo		
Certolizumab	Cimzia	400 mg SC	400 mg SC weeks 2 and 4, and then 400 mg SC monthly
Infliximab	Remicade	5 mg/kg IV	5 mg/kg weeks 2 and 6, 5-10 mg/kg every 8 weeks
Infliximab-dyyb	Inflectra		
Infliximab-abda	Renflexis		
Infliximab-qbtx	IXIFI		
Natalizumab	Tysabri	300 mg IV	300 mg IV every 4 weeks
Budesonide	Entocort EC capsule, Uceris tablet	9 mg orally once daily	6-9 mg daily
	Uceris rectal foam	2 mg twice daily	2 mg daily
Vedolizumab	Entyvio	300 mg IV	300 mg IV weeks 2 and 6 and then every 8 weeks
Golimumab	Simponi	200 mg SC	100 mg SC weeks 2 and 4
Ustekinumab	Stelara	Weight based initial IV dose <55 kg (260 mg), 55-85 kg (390 mg), >85 kg (520 mg)	90 mg SC every 8 weeks
Tofacitinib	Xeljanz	10 mg twice daily for 8 weeks; may continue for max of 16 weeks	5 mg twice daily

SC, subcutaneous; IM, intramuscular.

For the ASAs, picking the appropriate formulation and dose of drug for the disease severity and extent is key. Enemas and suppositories, while generally more effective than oral preparations, may not be as acceptable for use, particularly by younger patients. Therefore, individuating the patient's preference for a specific formulation should be taken into account when choosing ASA preparations. Consideration can be given to the use of once-daily products if there is evidence that multiple-daily dosing is affecting patient adherence.[64-66] This must be weighed against the higher cost of these preparations. If expense is an issue, use of generically available agents may be preferred.

7 Corticosteroids are used to suppress acute inflammation in the treatment of IBD, and may be given parenterally, orally, or rectally.[61] They modulate the immune system and inhibit production of cytokines and mediators. It is not clear whether the most important steroid effects are systemic or local (mucosal). Budesonide is a corticosteroid that is administered orally in a controlled-release formulation designed to release in the terminal ileum or the colon depending on the product, or as a rectal foam. The drug undergoes extensive first-pass metabolism; so systemic exposure is thought to be minimized.[57,61]

Immunomodulators such as azathioprine, mercaptopurine, methotrexate, or cyclosporine are also used for the treatment of IBD (see Table 51-4). Azathioprine and mercaptopurine are effectively used in long-term treatment of both CD and UC.[1,30,35,62–64] These agents are generally reserved for patients who fail ASA therapy or are refractory to or dependent on corticosteroids. They may be used in conjunction with mesalamine derivatives, corticosteroids, TNF-α antagonists, and vedolizumab, and must be used for extended periods of time, ranging from a few weeks up to several months, before benefits may be observed.[54,62–64]

Cyclosporine has a short-term benefit in the treatment of acute, severe UC to avoid colectomy in patients failing corticosteroids, but has little efficacy in CD[1,30,35,48,65] It is used initially as a continuous IV infusion of 2 to 4 mg/kg daily.[48,54,66] Cyclosporine poses a risk of nephrotoxicity and neurotoxicity. Studies evaluating tacrolimus for the treatment of IBD suggest a potential role for short-term use in patients with perianal or fistulizing CD; however, results have been variable with few data to support its routine use.[35,67] Methotrexate 15 to 25 mg given intramuscularly or subcutaneously once weekly may useful for maintenance therapy of CD and may result in steroid-sparing effects, while data supporting use in UC are lacking.[35,54,64,68]

Antimicrobial agents may be used as adjunctive therapies in IBD. Metronidazole and ciprofloxacin, often given in combination, have limited value in both induction of remission in luminal CD, but may be used as adjunctive therapy for simple perianal fistulaes.[1,35] Rifamycin antibiotics have demonstrated some efficacy in treatment of both UC and CD but are not routinely recommended.[35,54] Risks of long-term antibiotic use include the development of antibiotic resistance, predisposition to *C. difficile* infection, and adverse effects such as neurotoxicity secondary to metronidazole use.

Biologic agents that target TNF-α have become a key class of agents in the treatment and maintenance of IBD.[54,69–71] Infliximab is an IgG1 chimeric monoclonal antibody that is administered IV and binds TNF-α and inhibits its inflammatory effects. In addition, it lyses activated T cells and macrophages and induces T-cell apoptosis.[54,66,70,71] Infliximab is useful for moderate to severe active CD and UC disease, as well as steroid-dependent or fistulizing disease, as both an induction and a maintenance therapy. Adalimumab is also an IgG1 antibody to TNF-α; however, this agent, unlike infliximab, is fully humanized and contains no murine sequences. Theoretically, the lack of a murine component in adalimumab reduces antibody development seen with use of infliximab. This agent is administered subcutaneously and is a treatment option for patients with moderate to severe active UC and CD and those previously treated with infliximab who have lost response. Certolizumab pegol is a humanized pegylated Fab fragment directed against TNF-α that is also administered subcutaneously. Golimumab is similar in structure to adalimumab and offers similar efficacy to the currently approved agents. Five biosimilar agents are now approved for use in UC and CD: Infliximab-dyyb, infliximab-abda, infliximab-qbtx, adalimumab-abdm, and adalimumab-atto. Biosimilars are highly similar to the FDA-approved biologic agents. There are no clinically meaningful differences in efficacy or adverse effects from the reference products and are considered to be interchangeable with the reference product.[72] However, recent guidelines for UC treatment do not recommended switching patients who have lost response to a TNF-α to the biosilimar to the original brand.[30]

Natalizumab and vedolizumab are biologic agents that inhibits leukocyte adhesion and migration by targeting the α_4 subunit of integrin.[70,71] Vedolizumab works similar to natalizumab but is more specific for the $\alpha_4\beta_7$ subunit of integrin, which targets leukocyte trafficking in the gut.[54,71] Ustekinumab is a biologic agent that blocks IL-21 and IL-23 action by binding to the p40 protein subunit used by these cytokines.[73] It is approved for use in moderate to severe

CD in patients who failed immunomodulators or corticosteroids but have not received anti-TNF therapy. It can also be used for patients who have failed anti-TNF therapy and in combination with immunomodulators. Tofacitinib inhibits the intracellular Janus kinases, which are responsible for the signal transduction of mutiple cytokines involved in the inflammatory cascade.[74] It is approved for patients with moderate to severe UC who are unresponsive to TNF alpha inhibitors.

Treatment of Ulcerative Colitis

Mild to Moderate Active Disease Most patients with mild to moderate active UC can be managed on an outpatient basis with oral and/or topical ASAs. (**Fig. 51-2**; **Table 51-5**). For patients with extensive disease, oral once daily mesalamine is generally preferred at a dose of 2-3 grams/day.[30,78] Topical mesalamine in an enema or suppository formulation is more effective than oral mesalamine or topical steroids for distal disease.[56,59,60] The combination of oral and topical mesalamine is more effective than either alone for patients with left-sided or extensive disease; however, patients may be less willing to use topical formulations.[1,30,56,59,60,78] Sulfasalazine, at doses of 2-4 g/day may be considered in patients already receiving it in remission, or in those with prominent arthritic symptoms.[74]

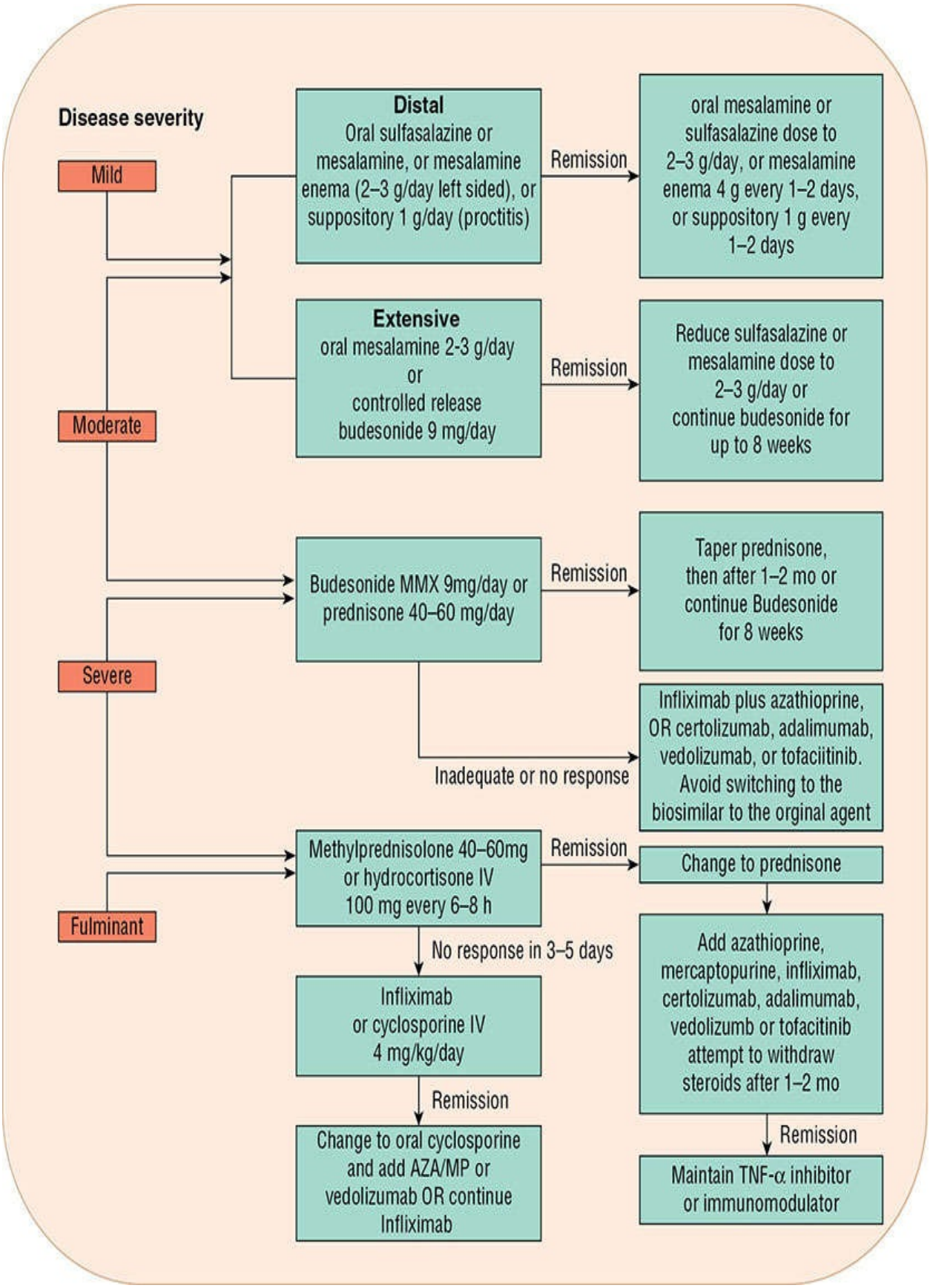

Disease severity
Mild
Moderate
Severe
Fulminant
Distal
Oral sulfasalazine or mesalamine, or mesalamine enema (2–3 g/day left sided), or suppository 1 g/day (proctitis)
Remission
oral mesalamine or sulfasalazine dose to 2–3 g/day, or mesalamine enema 4 g every 1–2 days, or suppository 1 g every 1–2 days
Extensive
oral mesalamine 2-3 g/day or controlled release budesonide 9 mg/day
Remission
Reduce sulfasalazine or mesalamine dose to 2–3 g/day or continue budesonide for up to 8 weeks
Budesonide MMX 9mg/day or prednisone 40–60 mg/day
Remission
Taper prednisone, then after 1–2 mo or continue Budesonide for 8 weeks
Inadequate or no response
Infliximab plus azathioprine, OR certolizumab, adalimumab, vedolizumab, or tofaciitinib. Avoid switching to the biosimilar to the orginal agent
Methylprednisolone 40–60mg or hydrocortisone IV 100 mg every 6–8 h
Remission
Change to prednisone
Add azathioprine, mercaptopurine, infliximab, certolizumab, adalimumab, vedolizumb or tofacitinib attempt to withdraw steroids after 1–2 mo
Remission
Maintain TNF-α inhibitor or immunomodulator
No response in 3–5 days
Infliximab or cyclosporine IV 4 mg/kg/day
Remission
Change to oral cyclosporine and add AZA/MP or vedolizumab OR continue Infliximab

FIGURE 51-2 Treatment approaches for ulcerative colitis.
*Can be considered as an alternative to TNF-alpha inhibitors.

TABLE 51-5 Levels of Evidence for Therapeutic Interventions in Inflammatory Bowel Disease

Interventions	Evidence Grades[a]
Ulcerative Colitis	
Rectal 5-ASA is recommended at a dose of 1g/day for induction of remission in mildly active UC	Strong
5-ASA enemas at a dose of 1 g/day is preferred over rectal steroids for induction of remission in mildly active left-sided colitis	Strong
Rectal 5-ASA at a dose of 1 g/day in combination with oral 5-ASA at a dose of 2 g/day is preferred for induction of remission of mildly active left sided UC	Conditional
Oral budesonide 9 mg/day is preferred in patients who fail or are intolerant of oral or rectal 5-ASA for induction of remission in mildy active UC	Strong
High-dose mesalamine (>3 g/day) is suggested in patients who have suboptimal response to standard dose mesalamine	Conditional
Oral 5-ASA at a dose of at least 2 g/day is recommended for induction of remission in patients with mildly active extensive colitis	Strong
Oral systemic corticosteroids are recommended for induction of remission in patients with UC of any extent who fail to respond to 5-ASA.	Strong
Sulfasalazine, mesalamine, or balsalazide are effective in maintenance of remission of distal disease; combining oral and topical mesalamine is more effective than is either alone	Strong
Sulfasalazine, olsalazine, mesalamine, and balsalazide are effective in preventing relapses in patients with mild to moderate extensive disease	Strong
Corticosteroids are not effective as maintenance treatment	Strong
Oral budesonide is recommended for induction of remission in patients with moderately active UC	Strong
Monotherapy with thiopurines or methotrexate is not recommended for induction therapy in patients with moderate to severe active UC	Strong
Infliximab, adalimumab, and golimumab are effective for induction of remission in moderate to severe active UC.	Strong
Infliximab combined with a thiopurine is effective for induction therapy in moderately severe active UC	Strong
Tofacitinib is effective for induction and maintenance of remission for patients with moderate to severely active UC	Strong
Vedolizumab is effective for induction of remission in moderate to severe active UC	Strong
Tofacitinib is effective for induction of remission in patients with moderate to severe UC	Strong
Crohn's Disease[b]	
Sulfasalazine is effective for treating mild to moderate active colonic CD	Conditional
Mesalamine has not consistently been demonstrated to be effective in active CD	Strong
Ileal release budesonide is effective for mild to moderate ileal or right-sided colonic disease	Strong
Metronidazole is not effective for treatment of luminal CD	Conditional
Ciprofloxacin should not be used for treatment of luminal CD	Conditional
Systemic corticosteroids are effective for short-term treatment of moderate to severely active CD	Strong
Conventional corticosteroids do not consistently achieve mucosal healing	Weak
Thiopurines should be considered for steroid sparing in CD	Strong
Azathioprine and mercaptopurine are not effective to induce short-term remission	Strong
Azathioprine and mercaptopurine are effective for maintenance of remission	Strong
TPMT testing should be considered prior to use of azathioprine or mercaptopurine	Strong
Anti-TNF agents should be given in patients refractory to azathioprine or methrotrexate	Strong
Vedolizumab with or without an immunomodulator should be considered for induction of remission in symptomatic patients	Strong
Natalizumab can be considered for induction of remission	Strong
Infliximab, adalimumab, and certolizumab are effective in lowering or eliminating corticosteroid use in corticosteroid-dependent patients	Strong
Ustekinumab should be given in moderate to severe CD in patients who fail treatment with corticosteroids, thiopurines, methotrexate, or anti-TNF agents or who have no prior exposure to anti-TNF agents	Strong
Cyclosporine, mycophenolate mofetil, and tacrolimus should not be used for CD	Strong
Methotrexate maintenance therapy (15-25 mg IM weekly) is effective for steroid sparing and for maintenance of remission	Conditional
Intravenous corticosteroids should be used for severe to fulminant CD	Conditional
Infliximab, adalimumab, and certolizumab are effective in severely active CD	Strong
Infliximab can be administered for treatment of fulminant CD	Conditional
Infliximab is effective for perianal fistulas	Strong

[a]Strong (desirable effects outweigh undesirable), conditional (uncertainty about trade-offs).

Data from reference 30, 35, 74-78

Oral mesalamine derivatives (see Table 51-2) are alternatives to sulfasalazine for treatment of mild to moderate UC with similar rates of efficacy. Mesalamine preparations are typically better tolerated than sulfasalazine and thus are often chosen preferentially as first-line therapies. Mesalamine suppositories will only reach to approximately 10 to 20 cm within the lower GI tract and thus are reserved for patients with proctitis.[1,56,60,66,74] Enemas will reach to the splenic flexure and are preferred for left-sided disease.[1,30,59,74] The various oral mesalamine products generally have similar rates of efficacy. Doses greater than 3 g/day can be used in patients who are unresponsive to standard doses, and generally should be combined with a rectal mesalamine formulation at a dose of 1 g/day.[30,78] The choice of oral formulations may be dictated by patient-specific factors, such as use of a once-daily formulation to help improve patient adherence and reduce pill burden, or use of a generically available product in patients with limited financial resources.[55–58,78] Controlled release budesonide (Uceris) is an alternative for mild to moderate extensive UC, while the foam may be used for distal disease.[1,57,66,42,74] Budesonide at a dose of 9 mg/day is preferred for patients who are unresponsive to optimized doses of 5-ASA.[30,78] Oral corticosteroids in doses of 40 to 60 mg/day prednisone equivalent can be used as an alternative to budesonide for patients with moderate extensive disease who are refractory to oral ASAs or require more rapid control of symptoms.[30,61] Topical corticosteroids, given as foams, enemas, and suppositories, while effective for patients with distal disease, are generally less effective than mesalamine but can be used for patients with tenesmus or intolerance to meslamine.[30,78]

Moderate to Severe Active Disease Patients with moderate to severe active disease require prompt initiation of therapies to quickly suppress inflammation. Oral 5-ASA products may be effective for moderately severe UC, however budesonide may be used as alternative prior to use of more systemic corticosteroids and is preferred for moderate disease.[30] Systemic corticosteroids are often used in the treatment of moderate to severe active UC regardless of disease location or in those patients who are unresponsive to maximal doses of oral and/or topical mesalamine derivatives.[1,30,42,46,62,66,68,69,70,79] Oral doses of 40 to 60 mg prednisone equivalent daily are recommended.[30,66]

Use of TNF-α inhibitors is the main option for patients with moderate to severe disease who are unresponsive to 5-ASAs or corticosteroids, or are corticosteroid dependent, and are more effective than immunomodulator monotherapy for induction of remission. In general infliximab, adalimumab, and

golimumab and their respective biosimilars have similar rates of efficacy when used as monotherapy in UC.[30] Certolizumab is not approved for use in UC in the United States. Combining infliximab and azathioprine is more effective in inducing corticosteroid-free remission in patients with acute severe colitis and is preferred.[1,30,42,46,64,71,74] Vedolizumab can be used for patients who fail immunomodulators and TNF-*α* inhibitors, or as an alternative first line agent to TNF-*α* inhibitors.[71] Vedolizumab should not be used in combination with TNF-*α* inhibitors but can be combined with immunomodulators, such as azathioprine or methotrexate. Tofacitinib can be used as an alternative to vedolizumab or TNF alpha inhibitors.[30]

Severe or Fulminant Disease Patients with uncontrolled severe colitis or those with incapacitating symptoms require hospitalization for effective management. Under these conditions, patients generally receive nothing by mouth to promote bowel rest. Medications are given by the parenteral route and oral sulfasalazine or mesalamine derivatives are not typically beneficial in this setting because of rapid elimination of these agents from the colon with diarrhea. Patients should be tested for *Clostridoidies difficile* infection and receive VTE prophylaxis.

Systemic corticosteroids are used in the treatment of severe disease and may allow some patients to avoid colectomy. IV hydrocortisone 300 mg daily in three divided doses or methylprednisolone 60 mg once daily is considered a first-line agent.[30,66] Methylprednisolone is typically preferred due to its lesser mineralocorticoid effects. A trial of corticosteroids is warranted in most patients before proceeding to colectomy, unless the condition is grave or rapidly deteriorating. The length of corticosteroid therapy before consideration of surgery is open to debate, with recommendations ranging from 3 to 5 days.[1,30,48,80] Steroids do increase surgical risk, particularly infectious, if an operation is required later.

8 Patients, who are unresponsive to parenteral corticosteroids after 3 to 7 days, have the option of receiving higher-potency agents such as cyclosporine or infliximab.[30] Seventy-six percent to 85% of hospitalized patients who are unresponsive to corticosteroids will typically respond to IV cyclosporine.[65,74] A continuous IV infusion of cyclosporine 2 to 4 mg/kg/day is the typical dose range utilized and may delay the need for colectomy.[1,30,48,65,66] Persistent fever, tachycardia, elevated CRP, hypoalbuminemia, and deep colonic ulcerations may be predictors of failure to respond to cyclosporine.[30,65,81] Patients who are controlled on IV cyclosporine can then be switched to an oral cyclosporine (4-8

mg/kg/day) tapered regimen with transition to azathioprine, mercaptopurine, or vedolizumab.[1,30,48,66] Infliximab is an alternative to cyclosporine at a dose of 5 mg/kg and has demonstrated similar results regarding delaying the need for colectomy for patients with severe disease unresponsive to steroids.[1,48,66,80] Patients who respond to infliximab should be considered for additional doses at 2 and 6 weeks later.[48] The sequential use of cyclosporine and infliximab, or the drugs given in reverse order, is not generally recommended.[48] Tacrolimus may be considered as an alternative to cyclosporine or infliximab.[74] The adverse effects of both cyclosporine and infliximab are potentially serious and should be taken into consideration when using either therapy for patients with severe disease.[65,66]

Maintenance of Remission

9 After remission from active disease is achieved, the goal of therapy is to maintain remission. The major agents used for maintenance of remission are sulfasalazine and the newer mesalamine derivatives, infliximab, adalimumab and its biosimilars, golimumab, and azathioprine or mercaptopurine.

Oral agents, including sulfasalazine, mesalamine, and balsalazide, are all effective options for maintenance therapy. The optimal dose to prevent relapse is 2 to 2.4 g/day of mesalamine equivalent, with rates of relapse over 6 to 12 months reported as 40%.[1,8,30,57,59,60,70,78] The newer mesalamine derivatives are generally better tolerated than sulfasalazine and are associated with fewer adverse effects often making them a preferred choice.[1,30] For patients with left-sided disease or proctitis, mesalamine enemas or suppositories are preferred.[1,59,66] The frequency of administration of topical agents may possibly be lessened to every third night over time.[8,30,59,60,66,78] The combination of topical and oral mesalamine is superior to either regimen alone for maintenance therapy.[60]

Corticosteroids do not have a role in the maintenance of remission with UC because they are ineffective and are associated with serious adverse effects with long-term use.[1,30] Steroids should be gradually withdrawn after 2 to 4 weeks after induction of remission. For patients who require chronic steroid use and are steroid dependent, there is a strong justification for use of alternative therapies. Azathioprine may be effective in preventing relapse of UC for patients who fail ASAs or who are steroid dependent.[30,162–64] Approximately one-third of patients will maintain remission on azathioprine; however, the onset of action is slow and 3 to 6 months may be required before beneficial effects are noted.[54,62,63,82]

Azathioprine is also recommended for patients with severe UC who are transitioned to oral cyclosporine.[1,30,48,63,65]

The TNF-*α* inhibitors or vedolizumab are options for maintenance in patients with moderate to severe UC following induction, and in those who are steroid dependent or have failed azathioprine. Clinically up to one-third of patients may not respond to TNF-α inhibitors and those that do may lose effectiveness over time due to antibody development.[54,71,75] Tofacitinib should be continued in those patients who achieve remission following induction.[30]

Crohn's Disease

Management of CD often proves more difficult than management of UC because of the greater complexity of presentation (**Fig. 51-3**; see Table 51-3). There is a greater potential for reliance on drug therapy with CD because resection of involved areas of the GI tract may not be possible. Recurrence of CD is common following surgery with reported rates of endoscopic recurrence reported as up to 80%.[13]

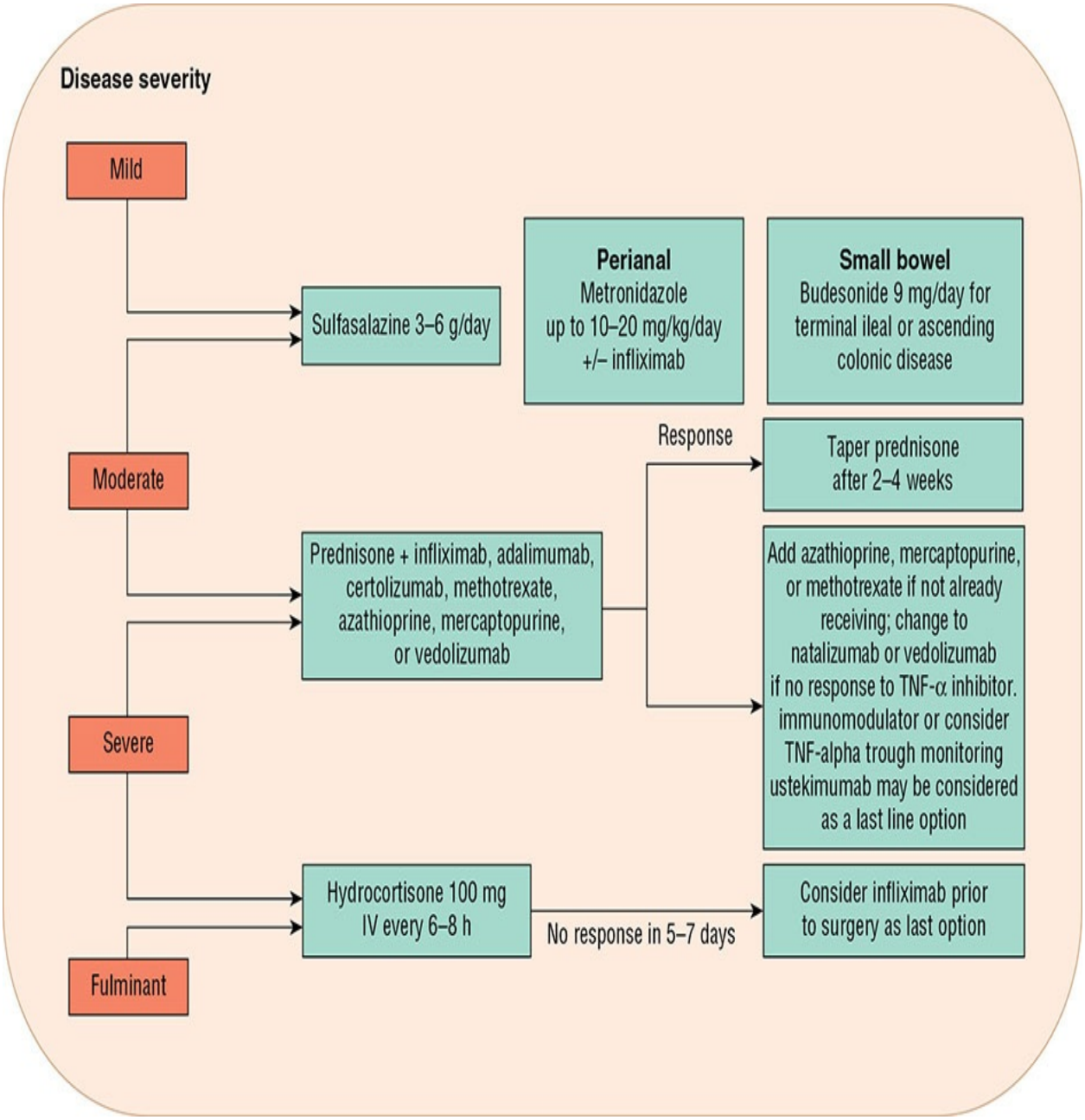


FIGURE 51-3 Treatment approaches for Crohn's disease.

The drug treatment of CD involves many of the same agents used for UC. While the treatment strategy for CD has often followed a similar "step-up" pattern as seen with UC, there has been more interest in the Treat to Target approach in patients with severe disease, which often involves more of a "step-down" approach of using higher potency agents earlier in the disease course.[13,35,36,46]

Mild to Moderate Active Crohn's Disease

While effective in UC, ASAs have not demonstrated significant efficacy in CD. Sulfasalazine is reported to have marginal efficacy when compared with placebo for patients with mild to moderate CD, while the newer mesalamine derivatives are generally considered to have minimal efficacy.[35,70] Despite limited and variable effectiveness, the mesalamine derivatives are often tried as an initial therapy for mild to moderate CD given their more favorable adverse effect profile. Since CD often involves the small intestine, formulations such as Pentasa, which release in the small intestine, may be used.

Systemic corticosteroids are frequently used for the treatment of moderate to severe active CD; however, controlled-release budesonide (Entocort) at a dose of 9 mg daily is a preferred first-line option for patients with mild to moderate ileal or right-sided (ascending colonic) disease.[35,61] This agent is superior to placebo and has demonstrated superiority to mesalamine and is preferred for patients with ileal disease.[35,44,57,83]

While treatment of dysbiosis may seem like a viable option for IBD, antibiotics have little to no efficacy in treating luminal CD and are not recommended.[7,35] Broad spectrum agents may be used for treatment of abscess formation in CD.[35] Metronidazole may have some role in prevention of postoperative recurrence of CD, and is also recommended for use in patients with perianal fistulas, particularly in combination with infliximab.[35]

Moderate to Severe Active Crohn's Disease

Patients with moderate to severe active CD require rapid suppression of inflammation for symptom improvement and prevention of complications. Oral corticosteroids, such as prednisone 40 to 60 mg/day, are generally considered first-line therapies for moderate to severe active CD who are unresponsive to ASAs.[13,35,61] Traditional oral systemic steroids have greater efficacy in inducing remission compared with budesonide in patients with moderate disease; however, the potential for adverse effects is greater, even with short term use.[13,35,61] Hospitalized patients with moderate to severe disease who are unable to tolerate oral therapy are candidates for administration of parenteral steroids, with methylprednisolone or hydrocortisone being first-line options.[13,35] Systemic steroids do not appear to be effective for treatment of perianal fistulas, nor do they induce mucosal healing.[35,36,70]

10 Immunomodulators (azathioprine, mercaptopurine, and methotrexate) are

generally not recommended for induction of remission in moderate to severe CD.[13,35] These agents are largely used for maintenance of remission, and are effective in maintaining steroid-induced remission and reducing steroid dependency, either as monotherapy or in combination with TNF-*α* inhibitors or vedolizumab.[13,35,62,68] Clinical response to azathioprine and mercaptopurine may be related to whole-blood concentrations of the metabolite 6-thioguanine (TGN). Concentrations of TGN between 230 and 450 pmol/8 × 10^8 erythrocytes have beneficial effects when used as monotherapy, but monitoring is not routinely performed or may not be available at some sites.[63,76]

11 Methotrexate given weekly intramuscularly or subcutaneously in doses of 15 to 25 mg is effective in reducing steroid dependency and maintaining remission, and may be considered as an alternative to azathioprine or mercaptopurine.[35]

The TNF-*α* inhibitors, including the biosimilar agents, are the preferred agents in the management of moderate to severe CD.[35,68,84] All agents in this class, with the exception of golimumab, which is not approved for use in CD in the United States, have similar rates of efficacy. The choice of agent depends on patient preference, route of administration, and cost. Adalimumab and certolizumab have the advantage of subcutaneous administration and may be considered alternates to infliximab as initial therapy or in those patients losing response to infliximab. Collectively these agents have demonstrated higher likelihood of induction of remission, reductions in hospitalization and the need for surgery, and lower rates of endoscopic recurrence.[13,35,70,84]

The use of TNF-*α* inhibitors in combination with thiopurines has quickly become the preferred approach to treatment of moderate to severe CD. Combination therapy results in added efficacy and reduction in antibody formation to the TNF-*α* inhibitor, which extends the duration of efficacy. Studies comparing infliximab with azathioprine and the combination of infliximab demonstrate greater rates of remission, steroid free remission, and mucosal healing.[13,35,68] For this reason combination therapy is preferred unless patients have contraindications.

The integrin antagonists are options for patients who do not respond to steroids or TNF-*α* inhibitors, and vedolizumab is also considered a first line alternative to TNF-alpha inhibitors for moderate to severe disease.[35,54,71,85] These agents should not be used in combination with TNF-alpha inhibitors, but may be used with immunomodulators, which will also result in lower rates of antibody development.[35] Vedolizumab is preferred over natalizumab due to the

reduced risk of adverse effects, particularly progressive multifocal leukoencephalopathy (PML). If natalizumab is used, a baseline John Cunningham (JC) virus antibody must be negative prior to initiating therapy, and then should be monitored every 6 months. Therapy should be discontinue if a positive JC virus antibody is detected.[35]

Ustekinumab can be considered for moderate to severe CD in patients who have failed previous treatment with corticosteroids, immunomodulators, or TNF-alpha inhibitors, in patients with no prior exposure to TNF-alpha inhibitors, patients at higher risk for infections, for frail patients, or in patients presenting with extraintestinal manifestations.[35,73]

Severe/Fulminant Active Disease

Patients with severe or fulminant disease require prompt management in the inpatient setting and are often considered for surgical intervention. Parenteral corticosteroids at a dose equivalent of 40 to 60 mg prednisone should be instituted once the presence of abscess has been excluded.[35] TNF-alpha inhibitors may be used in severe disease, and infliximab may be considered in fulminant disease.[35] There are no data to support the use of cyclosporine, tacrolimus, or mycophenolate in patients with severe or fulminant disease.[35] TNF-α inhibitors are also considered first line agents for fistulizing disease, with azathioprine and mercaptopurines as alternatives.[35] Patients may require surgical intervention in the setting of medically refractory disease.

Maintenance of Remission

Maintaining remission is typically more difficult with CD than with UC. There is minimal evidence that sulfasalazine and oral mesalamine derivatives are effective therapies for maintenance of CD following medically induced remission, and therefore these agents are not preferred.[35,86] Mesalamine appears to have limited efficacy in preventing postsurgical relapse following resection, but can be considered in patients with isolated ileal resection who do not qualify for or have a contraindication to immunosuppressive therapy.[35] Metronidazole, 1 to 2 g/day may also be used to prevent postoperative recurrence, but is not recommended for use in medically induced remission.[35]

Systemic corticosteroids have no role in maintenance of remission or prevention of recurrence of CD. These agents do not alter the long-term course of the disease and predispose patients to serious adverse effects with long-term use.[35] Budesonide has been studied at maintenance doses of 6 mg/day for up to

52 weeks with minimal efficacy in maintaining remission.[83,87] As such, use of budesonide as maintenance therapy is recommended for a duration of up to 4 months.[35]

All of the TNF-α inhibitors currently approved for use in CD are viable options for maintenance of remission.[35] Combination therapy with a thiopurine should be highly considered to further improve efficacy and to extend the duration of TNF-α inhibitor efficacy by reducing the immunogencity.[35] If surgical resection is being considered, TNF-α inhibitors should be started within 4 weeks of surgery in high risk patients (smokers, penetrating disease, and prior resection) in order to prevent postoperative recurrence.[35] Methotrexate may be considered as an alternative to thiopurines to maintain corticosteroid induced remission; however, the evidence for its use is weak.[54,68] Vedolizumab, natalizumab, and ustekinumab can be used for maintenance in patients who initially achieve induction of remission with these agents.[35]

Selected Complications

Toxic Megacolon

The treatment required for toxic megacolon includes general supportive, consideration for early surgical intervention, and drug therapy.[32,48] Perforation is reported in up to 36% of patients and can significantly worsen outcomes.[48] Aggressive fluid and electrolyte management is required for dehydration. Transfusion may be necessary if significant blood loss has occurred. Opiates and medications with anticholinergic properties should be discontinued because these agents enhance colonic dilation, thereby increasing the risk of bowel perforation.[48] Broad-spectrum antimicrobials that include coverage for gram-negative bacilli and intestinal anaerobes should be used as preemptive therapy in the event that perforation occurs.[32] If the patient is not receiving corticosteroids, then high-dose IV therapy should be administered to reduce acute inflammation. Emergent surgical intervention, mainly an abdominal colectomy with formation of an ileostomy, is an important consideration for patients with toxic megacolon and prevents death in some patients.[48]

Extraintestinal Manifestations

For some extraintestinal manifestations of IBD, specific therapies can be instituted, whereas for others the treatment that is used for the GI inflammatory

process also addresses the systemic manifestations.

Anemia secondary to blood loss from the GI tract can be treated with oral ferrous sulfate. If the patient is unable to take oral medication and the patient's hematocrit is sufficiently low, blood transfusions or IV iron infusions may be required.[40] Anemia may also be related to malabsorption of vitamin B_{12} or folic acid, particularly for patients who have had ileal resection, so supplementation may be required. Screening for osteoporosis does not differ from the general population, however dual x-ray absorptiometry is recommended for patients using steroids for more than 3 months, in postmenopausal females, patients of age over 60 years, and those who have sustained a low-stress fracture.[41,77] If the patient is deemed high risk for osteoporosis or exhibits a reduced serum vitamin D concentration, vitamin D and calcium should be instituted. If osteoporosis is present, then calcium, vitamin D, and a bisphosphonate or possibly teriparatide are recommended.[40,41] Corticosteroid use should be avoided or limited, and weight-bearing exercise initiated if possible.

There are no consistently recommended therapies for aphthous ulcers; however, topical viscous lidocaine may provide symptom relief while topical corticosteroids may promote healing.[40] Episcleritis or uveitis is often worse during exacerbations of the intestinal disease, and measures improving intestinal disease will improve these systemic manifestations. Cool compresses and topical corticosteroids or NSAIDs may provide symptomatic relief, while immunomodulators and TNF-α inhibitors when in use may also provide benefit.[40] For arthritis associated with IBD, short term NSAID or corticosteroids may be considered. However, NSAID use may exacerbate the underlying IBD and predispose patients to GI bleeding. Intra-articular corticosteroids may be tried to limit the adverse effects of systemically administered agents.[40,88] Skin manifestations often require local wound care and use of topical or systemic corticosteroids.[40] Anti–TNF-α therapies may also improve severe dermatologic manifestations. Although ursodiol may improve liver enzymes in patients with IBD-associated PSC, it has not been demonstrated to have favorable effects on outcomes.[39,40] Liver transplantation is being used more frequently for definitive treatment of PSC.

Special Considerations

Pregnancy and Breastfeeding

The occurrence or consideration of pregnancy may cause significant concerns

for the patient with IBD. Patients with IBD have similar infertility rates as the general female population, and the rate of involuntary childlessness in IBD patients who have not undergone surgery is similar.[89–91] There is a greater risk of adverse pregnancy outcomes such as spontaneous abortion, low birth weight, caesarian section, congenital abnormalities, low Apgar scores, preterm rupture of membranes, and preeclampsia.[97-99] However, most patients can conceive normally and have a normal pregnancy. The impact of IBD disease activity on pregnancy still remains unclear. In patients in remission at the time of conception the rates of reported flares are 20% in CD and 33% in UC, and postpartum rates of relapse are reported as 14%.[89] Preconception counseling in patients with IBD is recommended, in addition to objective assessment of disease activity in order to optimize therapy.[90] Overall patients should optimally achieve at least 3 months of corticosteroid-free remission prior to conceiving.[90] Patients should be managed by a gastroenterologist throughout their pregnancy, and also be referred to an obstetrician who manages high risk patients if they have active or complicated disease.[90]

Diligence should be given to reviewing current medications in patients with IBD who are both contemplating pregnancy or have already conceived. Sulfasalazine is generally well tolerated; however, it does interfere with folate absorption, so supplementation with folic acid 1 mg twice daily should be used during the pregnancy.[75,89,90] Sulfasalazine causes decreased sperm counts and reduced fertility in males and corticosteroids may adversely affect fertility as well.[92] This effect is reversible on discontinuation of the drug, and it is not reported with mesalamine. Other ASAs can be used as well; however, there are concerns regarding the presence of dibutyl phthalate in the coating of Asacol.[89] Mesalamine preparations not containing dibutyl phthalate should be preferentially used.[89,90] Steroids given systemically do not appear to be detrimental to the fetus, and in general can be used in the same manner as in non-pregnant patients.[75,89–91] Due to it lower systemic bioavailability budesonide may be considered safer than other systemic corticosteroids for pregnant patients.[75] While older data suggest an increased risk of preterm birth, azathioprine and mercaptopurine appear to carry an overall minimal risk in pregnant patients, and should be continued in patients receiving these agents as maintenance therapy.[75,90] Given pharmacokinetic changes in azathioprine metabolism occur during pregnancy, monitoring of 6-TGN during and after pregnancy is indicated.[90] Use of TNF-alpha inhibitors in pregnant patients appear to carry an overall low risk, and continuation of therapy is warranted in

most patients. Infliximab, adalimumab, and golimumab do cross the placenta and there are some concerns with increased exposure to the fetus in the third trimester. While the risks is low, consideration can be given to administering the last dose at 22 to 24 weeks of gestation to minimize drug transfer to the fetus in patients considered low risk for relapse.[75,89,90] For newborns of women who were receiving TNF-alpha inhibitors during pregnancy it is recommended that use of live vaccines be avoided.[90] In patients receiving combination therapy with azathioprine and a TNF-alpha inhibitor, consideration of switching to monotherapy can be given, with use of a TNF-alpha inhibitor as prefered therapy.[90] Natalizumab, vedolizumab, and ustekinumab appear to carry low risk when used as monotherapies, however consideration can also be given to administering the last dose at 8 to 10 weeks prior to delivery to minimize fetal exposure.[89] Tofacitinib does not appear to cause birth defects, msicarriage, or adverse fetal outcomes. There is pregnancy registry that women who become pregnant while receiving tofacitinib are encouraged to enroll in. Metronidazole and ciprofloxacin may be used for short courses for treatment of perianal disease, and should be avoided during the first trimester if possible.[75,89,90] Methotrexate should not be used during pregnancy, and should be stopped 3 months prior to conception. It should be stopped immediately in patients who become pregnant while taking it, with referral for obstetric counseling.[90]

Use of agents in breastfeeding women is also a consideration. Sulfasalazine does pose a small risk of kernicterus, as levels of sulfapyridine in breast milk are low or undetectable, and thus monitoring for this symptom should be implemented.[89–91] Other mesalamine derivatives are considered safe in breastfeeding.[89,90] Corticosteroids can be detected in breast milk, with fetal levels approximately 10% to 12% of maternal levels.[90] However, breastfeeding is believed to be safe, however mothers should optimally wait at least 4 hours after an oral dose of systemic corticosteroids before breastfeeding to limit exposure to the child.[90] The anti–TNF-α agents and thiopurines are generally considered safe for use in breastfeeding and carry minimal risk of adverse effects.[75,90] Methotrexate should be avoided in breastfeeding mothers.[90] Metronidazole and cyclosporine should not be given to nursing mothers because these agents are excreted into breast milk and may cause adverse effects.[75,89–91]

Adverse Drug Effects

Drug intolerance often limits the usefulness of agents used to treat IBD. In some cases, adverse effects can be significant and require discontinuation of the

therapy. Knowledge of the common or important adverse reactions will assist in avoiding or minimizing their effects.

Compared with mesalamine, sulfasalazine is more often associated with adverse drug effects, and these effects may be classified as either dose related or idiosyncratic (**Table 51-6**).[30,35,54,55,75] The sulfapyridine portion of the sulfasalazine molecule is believed to be responsible for much of the sulfasalazine toxicity.[30] Dose-related side effects usually include GI disturbances such as nausea, vomiting, diarrhea, or anorexia but may also include headache and arthralgia. These adverse reactions tend to occur more commonly on initiation of therapy and decrease in frequency as therapy is continued. Approaches to the management of these adverse effects include discontinuing the agent for a short period and then reinstituting therapy at a reduced dosage with subsequent slower dose escalation, administration with food, or substituting another enteric-coated 5-ASA product. Folic acid absorption is impaired by sulfasalazine, which may lead to anemia, so oral folic acid supplementation should be administered.

TABLE 51-6 Drug Monitoring Guidelines

Drug(s)	Adverse Drug Reaction	Monitoring Parameters	Comments
Sulfasalazine	Nausea, vomiting, headache Rash, anemia, pneumonitis Hepatotoxicity, nephritis Thrombocytopenia, lymphoma	Folate, complete blood count Liver function tests, Scr, BUN	Increase the dose slowly, over 1-2 weeks
Mesalamine	Nausea, vomiting, headache	GI disturbances	
Corticosteroids	Hyperglycemia, dyslipidemia	Blood pressure, fasting lipid panel	Avoid long-term use if possible or consider budesonide
	Osteoporosis, hypertension, acne	Glucose, vitamin D, bone density	
	Edema, infection, myopathy, psychosis		
Azathioprine/mercaptopurine	Bone marrow suppression, pancreatitis, Lymphoma	Complete blood count	Check TPMT activity
	Liver dysfunction, rash, arthralgia	Scr, BUN, liver function tests, genotype/phenotype	May monitor TGN
Methotrexate	Bone marrow suppression, pancreatitis	Complete blood count, Scr, BUN	Check baseline pregnancy test
	Pneumonitis, pulmonary fibrosis, hepatitis	Liver function tests	Chest x-ray
Infliximab Adalimumab Certolizumab Golimumab	Infusion-related reactions (infliximab), infectionHeart failure, optic neuritis, demyelination, injection site reaction, signs of infection	Blood pressure/heart rate (infliximab)Neurologic exam, mental statusTrough concentrations (infliximab)Antidrug antibodies (all agents)	Need negative PPD and viral serologies
Natalizumab Vedolizumab	Infusion-related reactions	Brain MRI, mental status, progressive multifocal leukoencephalopathy	Vedolizumab not associated with PML
Ustekinumab	Infections, skin cancers	Signs/symptoms of infection, annual skin exam	Rare instances of reversible posterior leukoencephalopathy syndrome (RPLS) Avoid live vaccines
Tofacitinib	Infection, thrombosis, lymphoma, elevated cholesterol, CPK, LFTs, lymphopenia, neutropenia, anemia,	Symptoms of Infection or thrombosis	Avoid live vaccines Screen for baseline TB Do not initiate in patients with lymphocytes < 500/mm^3, ANC <1000/mm^3, or hemoglobin <9g/dl Monitor lipids and LFTs every 4-8 weeks Gastrointestinal perforation has been reported with use of the XR formulation Drug interactions with CYP3A4 and 2C19 inhibitors

Idiosyncratic effects commonly include rash, fever, or hepatotoxicity, as well as relatively uncommon but serious reactions such as bone marrow suppression, thrombocytopenia, pancreatitis, pneumonitis, interstitial nephritis, and hepatitis. For most patients with idiosyncratic reactions, sulfasalazine must be discontinued. In some patients who have experienced allergic reactions to sulfasalazine, a desensitization procedure can be instituted. By gradually increasing sulfasalazine dosage over weeks to months, patient tolerance has been improved.[30] Mesalamine has been associated with development of interstitial nephritis as well, therefore intermittent monitoring of serum creatinine is warranted.[75]

Oral mesalamine derivatives may impose a lower frequency of adverse effects as compared with sulfasalazine.[30] Up to 80% of patients who are intolerant to sulfasalazine will tolerate oral mesalamine derivatives.[30] The most commonly encountered adverse effects are nausea, vomiting, and headache. However, olsalazine may cause watery diarrhea in up to 25% of patients, often requiring drug discontinuation.

There is a greater potential for adverse effects from corticosteroids when used for the treatment of IBD because there is often a requirement for use of high doses for extended periods of time. Adverse effects of corticosteroids include hyperglycemia, hypertension, osteoporosis, acne, fluid retention, electrolyte disturbances, myopathies, muscle wasting, increased appetite, psychosis, infection, and adrenocortical suppression.[30,61,75] To minimize corticosteroid effects, clinicians may use alternate-day steroid therapy; however, some patients do not do well clinically on the days when no steroid is given. For most patients a single daily corticosteroid dose suffices, and divided daily doses are unnecessary. Adrenal insufficiency after abrupt steroid withdrawal often necessitates gradual tapering of steroid therapy for patients using these agents daily for more than 2 to 3 weeks. Due to its lower bioavailability and lower potential for adverse effects, budesonide is preferred in CD involving the ileum or right colon, or in UC, and may also be substituted for prednisone in CD patients who are steroid dependent or require long-term therapy.[35,58,61]

Patients receiving systemic corticosteroids for extended periods of time should be assessed for risk of bone loss and fracture and the need for vitamin D and calcium supplementation. In patients with conventional risk factors for low BMD, screening for osteoporosis and BMD testing should be performed at the time of diagnosis of IBD.[129] In addition, a review of the patient’s medical history should be performed to identify other conditions that may be worsened by

corticosteroids, such as diabetes or hypertension. Adjustment of medications for these types of conditions may need to be made based on the dose and duration of corticosteroid use.

Azathioprine and mercaptopurine may be associated with serious adverse effects such as lymphomas, pancreatitis, or nephrotoxicity.[30,35,62–64,75,93] Adverse events to thiopurines are typically divided into two groups: type A and type B.[63,79,94] Type A reactions are dose related and include malaise, nausea, infectious complications, hepatitis, and myelosuppression. Complete blood counts with differential should be monitored every 2 weeks while doses are being titrated. Type B reactions are considered idiosyncratic and include fever, rash, arthralgia, and pancreatitis (3%-15% of patients).[79,92,94] Predisposition to development of these adverse effects may be related to polymorphisms in the enzyme thiopurine methyltransferase (TPMT), which is partially responsible for activation and metabolism of these drugs. Determination of TPMT activity is recommended prior to initiation of therapy to determine which patients require lower doses of these agents.[63,75,76,94] Alternatively, evaluating TPMT genotype or phenotype can also assist in assessing a patient's risk for toxicity.[62–64,76,94] Doses may need to be reduced by 30% to 70% if low TPMT activity is present.[94] Adjusting azathioprine and mercaptopurine doses by measuring concentrations of metabolites, particularly TGN, may be useful, with target concentrations of 230 to 450 pmol/8 x 10^8 erythrocytes considered optimal.[62–64,76,79,94]

Patients in whom azathioprine or mercaptopurine is being considered should undergo TPMT activity testing or have a genotype or phenotype test performed to determine if dose adjustments are required.[76] Since the initial dosing of these agents is weight based, obtaining a current accurate weight for the patient is necessary as well. As mentioned earlier, monitoring of 6-TGN concentrations may be helpful in the setting of adverse effects or suboptimal response to therapy. Obtaining a family history regarding lymphoproliferative disorders or lymphoma is important for determining if the potential risks outweigh the benefits of long-term use. Women receiving immunosuppressive therapy should undergo annual cervical cancer screening and all patients should be screened annually for melanoma.[77]

With the advent of coadministration of azathioprine with infliximab, development of hepatosplenic T-cell lymphoma (HSTCL) has become a concern. The overall impact of using both drugs together, the contribution of drug classes to the development of lymphoma, and the risk and effects of both drugs are unclear. Those most at risk appear to be younger male patients (<35 years) and most of the risk is thought to be conferred by the thiopurine component.[62,75,95]

Thiopurines are also associated with the develoment of non-melanoma squamous cell carcinoma, with the risk being higher during combination therapy with TNF-α inhibitors.[75,77] Methotrexate is associated with the development of nausea, vomiting, pulmonary fibrosis, pneumonitis, hepatotoxicity, anemia, and renal dysfunction, and is a known abortifacient. Patients should have baseline liver function tests, serum creatinine, BUN, complete blood count, and chest x-ray prior to use. Female patients should have a negative pregnancy test prior to use. Some patients may require supplementation with folic acid. Female patients of childbearing age opting to use methotrexate should have a safe and effective method of birth control available that is based on their preference.

Most patients receiving metronidazole for CD tolerate the agent fairly well; however, mild adverse effects occur frequently. They commonly include nausea, metallic taste, urticaria, and glossitis.[32,35,75] More serious effects that occur with long-term use include development of paresthesias and reversible peripheral neuropathy. Other effects include a disulfiram-like reaction if alcohol is ingested in conjunction.

The TNF-*α* inhibitors may be associated with development of serious adverse effects and carry similar adverse effect profiles for the available agents. Patients who receive infliximab often develop antibodies to infliximab (ATIs), also referred to as antidrug antibodies (ADAs). These ADAs can develop in response to administration of the other TNF-*α* inhibitors as well. Overall up to 50% of patients may lose efficacy after 1 year of treatment due to ADA development.[96] The development of ADAs also results in increases in the occurrence of serious infusion-related reactions and loss of response to the drug. Up to 10% of patients per year require discontinuation of infliximab due to adverse effects and loss of efficacy related to development of ATIs.[68,70,96]

Strategies to reduce ATI formation include administration of a second dose within 8 weeks of the first dose, concurrent administration of steroids (hydrocortisone 200 mg IV on the day of the infusion or oral prednisone the day prior), and use of concomitant immunomodulators agents such as thiopurines.[70,75,96] Loss of efficacy may be managed by a dose escalation to 10 mg/kg, reducing the dosing interval, or switching to another TNF-*α* inhibitor.[35,68,75,76,96,97] Delayed hypersensitivity reactions may also occur up to 14 days after administration, with 5 to 7 days being the most common time frame.[95,97] Autoimmune phenomena, such as lupus and hemolytic anemia, may also occur during infliximab therapy but are uncommon, as are adverse neurologic events such as optic neuritis and demyelinating syndrome.[71,75,83,95] For these reasons patients with a history of demyelinating disease, optic neuritis,

or lymphoma should avoid use of TNF-α antagonists.[95] Infliximab may also cause worsening of heart failure and thus is contraindicated for patients with New York Heart Association Class III or IV heart failure.[98] While the mechanism is unclear, it may relate in part to the cytoprotective effects of TNF on ischemic cardiac tissue, increases in production of nitric oxide and increased peripheral perfusion secondary to TNF, or TNF's role in cardiac remodeling and repair. Due to administration via the subcutaneous route, adalimumab, certolizumab, and golimumab may be more associated with injection site reactions versus infusion-related reactions.

All TNF-α inhibitors predispose patients to development of serious infections, including fungal, bacterial, and viral. Patients with clinically significant active infections should not receive TNF-α inhibitors. While the overall risk of hospitalization for serious infections may be less than previously suspected, development of infection remains a serious concern and increases with age.[75,99] Reactivation of latent mycobacterial infections may occur because of the inhibition of TNF-protective mechanisms; therefore, patients should receive a tuberculin skin test (purified protein derivative [PPD] test) and a chest x-ray prior to initiating therapy to rule out undiagnosed tuberculosis.[99,100] Reactivation of hepatitis B may occur; thus, patients should also be screened for hepatitis B virus infection prior to initiating therapy. Patients should also be screened for hepatitis C infection, although it does not appear that use of TNF-α inhibitors is unsafe or significantly alters the disease course. Natalizumab is associated with development of PML and is only available via the manufacturer's TOUCH prescribing program. Patients receiving natalizumab should be monitored for development of adverse neurologic events and undergo MRI of the brain should development of PML be suspected. Vedolizumab has not been associated with development of PML to date. Usteminumab and tofacitinib carry many of the same adverse effect profile as the TNF-α inhibitors, and baseline screening for TB and hepatitis should be performed. Rare instances of reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Tofacitinib is also associated with development of thrombosis and lymphoma, as well as neutropenia, lymphopenia, and anemia.

For patients receiving TNF-α inhibitors, ustekinumab, and tofacitinib, baseline screening for latent infections should be performed. Obtaining an accurate weight will assist in the dosing of infliximab. Likewise use of infliximab requires administration in an observed infusion center or clinic. If patients are unable to afford to get to their appointment, use of a self-administered agent, such as adalimumab or certolizumab, may be preferred. If

patients appear to be losing response to TNF-α inhibitors, evaluating for ADAs, if assays are available, in addition to evaluating serum trough concentrations may assist the clinician in determining if dose and frequency need to be altered. Recommendation trough concentrations for TNF-α inhibitors include >5 ug/mL (mg/L) for infliximab, >7.5 ug/mL (mg/L) for adalimumab, >20 ug/mL (mg/L) for certolizumab, while optimal concentrations for golimumab are unknown.[76]

Patients should be evaluated for use of recommended vaccines; however, if patients are receiving immunosuppressants or biologic agents, the use of live or attenuated vaccines may be contraindicated.[77] Patients who currently use tobacco should be encouraged to undergo tobacco cessation, as tobacco use will worsen CD. Since nicotine often improves symptoms in UC, it may be more difficult to cease tobacco use in this patient population. Choice of tobacco cessation products should also be based on current amount and patient preference. Nutritional status of patients should also be routinely assessed and patient-specific diets or delivery, such as enteral or parenteral nutrition, should be implemented. Routine screening for depression and anxiety is also recommended in all patients with IBD.[77]

EVALUATION OF THERAPEUTIC OUTCOMES

The success of therapeutic regimens to treat IBD can be measured by patient-reported complaints, signs, and symptoms; by direct clinician examination (including endoscopy); by history and physical examination; by selected laboratory tests; and by QOL measures. Evaluation of IBD severity is difficult because much of the assessment is subjective. Disease rating scales, such as the CDAI or other indices, have been created to make disease assessment more objective. The CDAI is a commonly used scale for patients with nonfistulizing disease and for evaluation of patients during clinical trials.[13,35] The scale incorporates eight elements: (a) number of stools in the past 7 days, (b) sum of abdominal pain ratings from the past 7 days, (c) rating of general well-being in the past 7 days, (d) use of antidiarrheals, (e) body weight, (f) hematocrit, (g) finding of abdominal mass, and (h) a sum of extraintestinal symptoms present in the past week. Elements of this index provide a guide for those measures that may be useful in assessing the effectiveness of treatment regimens. A decrease in CDAI of 100 points is considered a clinically significant response, with a score of less than 150 considered to be disease remission.[13,35] A subsequent scale was developed specifically for perianal CD, known as the *Perianal Crohn's Disease Activity Index* (PDAI). The PDAI includes five items: presence of discharge,

pain, restriction of sexual activity, type of perianal disease, and degree of induration. The HBI may also be used in place of the CDAI.

Standardized assessment tools have also been constructed for UC.[1,30] Elements in these scales vary and include (a) stool frequency, (b) presence of blood in the stool, (c) mucosal appearance (from endoscopy), and (d) physician's global assessment based on physical examination, endoscopy, and laboratory data. While these tools are often used for assessment of patients in clinical trials, they are sometimes used in the clinical setting as well.

Additional studies that are often useful include direct endoscopic examination of affected areas and/or radiocontrast studies. As mentioned earlier, mucosal healing is considered a major end point for patients with luminal disease. For patients with acute disease, assessment of fluid and electrolyte status is important, because these may be lost during diarrheal episodes. Other laboratory tests, such as serum albumin, transferrin, or other markers of visceral protein status as well as markers of inflammation such as ESR or CRP, and fecal calprotectin are used to monitor disease and drug therapy. Lastly assessing for both trough concentrations and presence of ADAs can help guide therapy in patients who are not responding to normal doses of TNF-α inhibitors.

Finally, a patient QOL assessment should be performed regularly.[1,30,35] Inquiry should be made regarding patient's general well-being, emotional function, and social function. Social function may include assessment of the ability to perform routine daily functions and to maintain occupational activities, sexual function, and recreation. The most common tool used to assess QOL is the Inflammatory Bowel Disease Questionnaire (IBDQ), a 32-item questionnaire that covers four disease dimensions: bowel function, emotional status, systemic symptoms, and social function. The IBDQ has shown good correlation with the CDAI.[35] The standard short form 36 (SF-36) is often used as a measure of QOL in IBD intervention trials.

ABBREVIATIONS

ADA	antidrug antibody
ASA	aminosalicylate
ATI	antibody to infliximab
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CRC	colorectal carcinoma
CRP	C-reactive protein
ESR	erythrocyte sedimentation rate
FODMAPS	fermentable oligo-, di-, and monosaccharides and polyols
HBI	Harvey-Bradshaw Index
HLA	human leukocyte antigen
HSTCL	hepatosplenic T-cell lymphoma
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IL	interleukin
IPAA	ileal pouch anal anastomosis
MMX	Multi-MatriX
NF-κ B	nuclear factor κ B
NOD2	nucleotide-binding oligomerization domain protein 2
NSAID	nonsteroidal anti-inflammatory drug
PDAI	Perianal Crohn's Disease Activity Index
PML	progressive multifocal leukoencephalopathy
PPD	purified protein derivative
PSC	primary sclerosing cholangitis
QOL	quality of life
SCD	specific carbohydrate diet
TGF-β	transforming growth factor-β
TGN	thioguanine
TLR	toll-like membrane receptor
TNF-α	tumor necrosis factor-α
TPMT	thiopurine methyltransferase
UC	ulcerative colitis
VTE	venous thromboembolism

REFERENCES

1. Ungaro R, Mehandru S, Allen PB, et al. Ulcerative colitis. *Lancet*. 2017;389(18):1756–1770.

2. Ng SC. Understanding and preventing the global increase of inflammatory bowel diseases. *Gastroenterology*. 2017;152(152):313–321.
3. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology*. 2012;142:46–54.
4. Kaplan GG, Ng SC. Inflammatory bowel disease: innovations and changing paradigms. Gastroenterology. 2017;152:309–312.
5. Gerseman M, Wehkamp J, Strange EF. Innate immune dysfunction in inflammatory bowel disease. *J Intern Med*. 2012;271:421–428.
6. Scharl M, Rogler G. Inflammatory bowel disease pathogenesis: What is new? *Curr Opin Gastroenterol*. 2012;28:301–309.
7. Sartor RB, Wu GD. Role for intestinal bacteria, viruses, and fungi in pathogenesis of inflammatory bowel diseases and therapeutic approaches. 2017;152:327–329.
8. Norman JM, Handley SA, Baldridge MT, et al. Disease specific alterations in the enteric virome in inflammatory bowel disease. *Cell*. 2015;160:447–460.
9. Lewis JD, Abreu MT. Diet as a trigger or therapy for inflammatory bowel disease. Gastroenterology. 2017;152:398–414.
10. Gentschew L, Ferguson LR. Role of nutrition and microbiota in susceptibility to inflammatory bowel diseases. *Mol Nutr Food Res*. 2012;56:524–535.
11. Guo AY, Stevens BW, Wilson RG, et al. Early life environment and natural history of inflammatory bowel disease. *BMC Gastroenterol*. 2014;14:216.
12. Murphy SF, Kwon JH, Boone DL. Novel players in inflammatory bowel disease pathogenesis. *Curr Gastroenterol Rep*. 2012;14:146–152.
13. Torres J, Mehandru S, Colombel JF, et al. Crohn’s disease. *Lancet*. 2017;389:1741–1755.
14. Moller FT, Andersen V, Wohlfahrt J, et al. Familial risk if inflammatory bowel disease: A population-based cohort study 1977-2011. *Am J Gastroenterol* 2015;110:564–571.
15. Chapman CG, Pekow J. The emerging role of miRNAs in inflammatory bowel disease: A review. *Ther Adv Gastroenterol* 2015;8(1):422.
16. Stappenbeck TS, McGovern DP. Paneth cell alterations in the development and phenotype of Crohn’s Disease. Gastroenterology. 2017;152:322–326.

17. Di Sabatino A, Biacnheri P, Rovedatti L, MacDonald TT, Corazza GR. Recent advances in understanding ulcerative colitis. *Intern Emerg Med* 2012;7:103–111.
18. Hamilton MJ, Snapper SB, Blumberg RS. Update on biologic pathways in inflammatory bowel disease and their therapeutic relevance. *J Gastroenterol*. 2012;47:1–8.
19. Rampton DS. The influence of stress on the development and severity of immune mediated diseases. *J Rheumatol*. 2011;38(Suppl 88):43–47.
20. Regueiro M, Greer JB, Szigethy E. Etiology and treatment of pain and pyschosocial issues in patients with inflammatory bowel disease. *Gastroenterology*. 2017;152(152):430–439.
21. Andrews JM, Holtmann G. Stress causes flares of IBD—Much evidence is enough? *Nat Rev Gastroenterol Hepatol* 2011;8:13–14.
22. Camara RJ, Schoepfer AM, Pittet V, Begre S, von Kanel R; Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS) Group. Mood and nonmood components of perceived stress and exacerbation of Crohn's disease. *Inflamm Bowel Dis* 2011;17(11):2358–2365.
23. Singh S, Blanchard A, Walker JR, Graff LA, Miller N, Bernstein CN. Common symptoms and stressors among individuals with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2011;9(9):769–775.
24. Boye B, Lundin KE, Jantschek G, et al. INSPIRE study: Does stress management improve the course of inflammatory bowel disease and disease-specific quality of life in distressed patients with ulcerative colitis or Crohn's disease? A randomized controlled trial. *Inflamm Bowel Dis* 2011;17(9):1863–1873.
25. Neuman MG, Nanau R. Single nucleotide polymorphisms in inflammatory bowel disease. *Transl Res* 2012;160:45–64.
26. Neuman MG, Nanau RM. Inflammatory bowel disease: Role of diet, microbiota, life style. *Transl Res* 2012;160:29–44.
27. Albenberg LG, Lewis JD, Wu GD. Food and gut microbiota in inflammatory bowel disease: A critical connection. *Curr Opin Gastroenterol*. 2012;28:314–320.
28. Monteleone I, MacDonald TT, Pallone F, Monteleone G. The aryl hydrocarbon receptor in inflammatory bowel disease: Linking environment to disease pathogenesis. *Curr Opin Gastroenterol* 2012;28:310–313.
29. Palmer MT, Weaver CT. Linking vitamin D deficiency to inflammatory

bowel disease. *Inflamm Bowel Dis* 2013;19:2245–2256.

30. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG Clinical Guideline: Ulcerative Colitis in Adults. *Am J Gastroenterol* 2019;114:384–413.
31. Ananthakrishnan AN, Higuchi LM, Huang ES, et al. Aspirin, nonsteroidal anti-inflammatory drug use, and risk for Crohn disease and ulcerative colitis. *Ann Intern Med* 2012;156:350–359.
32. Auten DM, Baumgart DC. Toxic Megacolon. *Inflamm Bowel Dis* 2012;18:584–591.
33. Velayos F. Managing risks of neoplasia in inflammatory bowel disease. *Curr Gastroenterol Rep* 2012;14:174–180.
34. Limdi JK, Farraye FA. An Update on Surveillance in Ulcerative Colitis. *Curr Gastroenterol Rep*. 2018;20:1–12.
35. Lichtenstein GR, Loftus EV, Isaacs KI, et al. ACG Clinical Guideline: Management of Crohn's disease in adults. *Am J Gastroenterol*. 2018;113:481–517.
36. Li Na, Shi RH. Updated review on immune factors in pathogenesis of Crohn's disease. *World J Gastroenterol*. 2018;24(1):15–22.
37. Hartman C, Eliakim R, Shamir R. Nutritional status and nutritional therapy in inflammatory bowel diseases. *World J Gastroenterol* 2009;15:2570–2578.
38. Hwang C, Ross V, Mahadevan U. Micronutrient deficiencies in inflammatory bowel disease: From A to zinc. *Inflamm Bowel Dis* 2012;18:1961–1981.
39. Fousekis FS, Thropistos VI, Katsanos KH. Hepatobiliary manifestations and complications in inflammatory bowel disease: A review. *Gastroenterol Res*. 2018;11(2):83–94.
40. Harbord M, Annese V, Vavricka SR, et al. ECCO Guideline/Consensus Paper. The First European Evidence-based Consensus on Extraintestinal manifestations inflammatory bowel disease. *J Crohns Colitis*. 2016;10(3):239–254.
41. American Gastroenterological Association medical position statement: Guidelines on osteoporosis in gastrointestinal diseases. *Gastroenterology* 2003;124:791–794.
42. American Gastroenterological Association. Ulcerative colitis clinical care pathway. http://campaigns.gastro.org/algorithms/UlcerativeColitis/.

Accessed April 27th 2018.

43. Panes J, Jairath V, Levesque BG. Advances in use of endoscopy, radiology, and biomarkers to monitor inflammatory bowel diseases. Gastroenterology. 2017;152:362–373.
44. AGA Institute Guidelines for the identification, assessment and initial medical treatment in Crohn's disease clinical care pathway. http://campaigns.gastro.org/algorithms/IBDCarePathway/. Accessed April 2018.
45. Fumery M, Singh S, Dulai PS, et al. Natural History of Adult Ulcerative Colitis in Population Based Cohorts: A Systematic Review. *Clin Gastroenterol Hepatol*. 2018;16:343–356.
46. Colombel JF, Narula N, Peyrin-Biroulet L. Management strategies to improve outcomes of patients with inflammatory bowel diseases. Gastroenterology. 2017;152:351–361.
47. Forbes A, Goldesgeyme E, Paulon E. Nutrition in inflammatory bowel disease. *J Parenter Enteral Nutr* 2011;35:571–580.
48. Bitton A, Buie D, Enns R, et al. Treatment of hospitalized adult patients with severe ulcerative colitis: Toronto consensus statements. *Am J Gastroenterol* 2012;107:179–194.
49. Derwa Y, Gracie DJ, Hamlin PJ, et al. Systematic review with meta analysis: the efficacy of probiotics in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2017;46:389–400.
50. Jonkers D, Penders J, Masclee A, Pierik M. Probiotics in the management of inflammatory bowel disease: A systematic review of intervention studies in adult patients. *Drugs* 2012;72(6):803–823.
51. Shen J, Zuo Z, Mao A. Effect of Probiotics on Inducing Remission and Maintaining Therapy in Ulcerative Colitis, Crohn's Disease, and Pouchitis: Meta-analysis of Randomized Controlled Trials. *Inflamm Bowel Dis* 2014;20:21–35.
52. Wasilewski A, Zielińska M, Storr M, Fichna J. Beneficial effects of Probiotics, prebiotics, synbiotics, and psychobiotics in inflammatory bowel disease. *Inflamm Bowel Dis*. 2015;21:1674–1682.
53. Biondi A, Zoccali M, Costa S, Troci A, Contessini-Avesani E, Fichera A. Surgical treatment of ulcerative colitis in the biologic therapy era. *World J Gastroenterol* 2012;18(16):1861–1870.
54. Bernstein CN. Treatment of IBD: Where we are and where we are going. *Am J Gastroenterol* 2015;110:114–126.

55. Campregher C, Gasche C. Aminosalicylates. *Best Pract Res Clin Gastroenterol* 2011;25:535–546.
56. Kato S, Ishibashi a, Kani K, et al. Opitmized management of ulcerative proctitis: When and how to use mesalazine suppository. *Digestion*. 2018;97:59–63.
57. Nardelli S, Pisani LF, Tontini GE. MMX technology and its applications in gastrointestinal diseases. *Ther Adv Gastroenterol*. 2017;7:545–552.
58. Yang LPH, McCormack PL. MMX mesalamine: A review of its use in the management of mild to moderate ulcerative colitis. *Drugs*. 2011;71(2):221–235.
59. Cohen RD, Dalal SR. Systematic review: Rectal therapies for the treatment of distal forms of ulcerative colitis. *Inflamm Bowel Dis* 2015;21:1719–1736.
60. Ford AC, Khan KJ, Achkar JP, Moayyedi P. Efficacy of oral vs. topical, or combined oral and topical 5-aminosalicylates, in ulcerative colitis: Systematic review and meta-analysis. *Am J Gastroenterol* 2012;107:167–176.
61. Ford AC, Bernstein CN, Khan KJ, et al. Glucocorticosteroid therapy in inflammatory bowel disease: Systematic review and meta-analysis. *Am J Gastroenterol* 2011;106:590–599.
62. van Gennep S, de Boer NK, d'Haens GR, et al. Thiopurine treatment in ulcerative colitis: A critical review of the evidence for current clinical practice. *Inflamm Bowel Dis*. 2018;24:67–77.
63. Louis E, Irving P, Beaugerie L. Use of azathioprine in IBD: Modern aspects of an old drug. *Gut*. 2014;63(11):1695–1699.
64. Cohen BL, Torres J, Colombel JF. Immunosuppression in inflammatory bowel disease: How much is too much? *Curr Opin Gastroenterol* 2012;28:341–348.
65. Burger DC, Travis S. Colon salvage therapy for acute severe colitis: Cyclosporine or infliximab? *Curr Opin Gastroenterol*. 2011;27:358–362.
66. Teixeira FV, HOsne RS, Sobrado CW. Management of ulcerative colitis: a clinical update. *J Coloproctol*. 2015;35(4):230–237
67. McSharry K, Dalzell AM, Leiper K, El-Matary W. Systematic review: The role of tacrolimus in the management of Crohn's disease. *Aliment Pharmacol Ther*. 2011;34:1282–1294.
68. Terdiman JP, Gruss CB, Heidelbaugh JJ, et al. American

Gastroenterological Association Institute guideline on the use of thiopurines, methotrexate, and anti-TNF-α biologic drugs for the induction and maintenance of remission in Crohn's disease. *Gastroenterology*. 2013;145:1459–1463.

69. Cholapranee A, Hazlewood GS, Kaplan GG. Systematic review and meta-analysis: comparative efficacy of biologics for induction and maintenance of mucosal healing in Crohn's disease and ulcerative colitis. *Alimen Pharmacol Ther*. 2017;45:1291–1302.
70. Mao EJ, Hazlewood GS, Kaplan GG. Systematic review with meta-analysis: comparative efficacy of immunosuppressants and biologics for reducing hospitalization and surgery in Crohn's disease and ulcerative colitis. *Aliment Pharmacol Ther*. 2017;45:3–13.
71. Cote-Daigneault J, Bouin M, Lahaie R, et al. Biologics in inflammatory bowel disease: what are the data? *Un Eur Gastroenterol J* 2015;0(0):110.
72. Radin M, Sciascia S, Roccatello D, et al. Infliximab biosilimars in the treatment of inflammatory bowel disease. BioDrugs. 2017;31:37–49.
73. Armuzzi A, Ardizzone S, Biancone L, et al. Ustekinumab in the management of Crohn's disease: Expert opinion. Dig Liv Dis. 2018;xx:x. https://doi.org/10.1016/j.dld.2018.02.017.
74. Fiorino G, D'amico F, Italia A, et al. JAK Inhibitors: Novel developments in managment of ulcerative colitis. *Best Prac Res Clin Gastroenterol*. 2018;(32-33)89–93.
75. Biancone L, Annese V, Ardizzone S, et al. Safety of treatments for inflammatory bowel disease: Clinical practice guidelines of the Italian Group for the study of Inflammatory Bowel Disease (IG-IBD). Dig and Liver Dis. 2017;49:338–358.
76. Feuerstein JD, Nguyen GC, Kupfer SS, et al. American Gastroenterological Association Institute guideline on therapeutic drug monitoring in Inflammatory Bowel Disease. Gastroenterology. 2017;153:827–834.
77. Farraye FA, Melmed GY, Lichtenstein GR, et al. ACG Clinical Guideline: Preventative Care in Inflammatory bowel disease. Am J Gastroenterol. 2017;112:241–258.
78. Ko CW, Singh S, Feurerstein JD, et al. AGA Clinical Practice Guidelines on the Managment of Mild-Moderate Ulcerative Colitis. 2019;156:748–764.
79. Thomas A, Lohida N. Advanced Therapy for Inflammatory Bowel

Disease: A Guide for the Primary Care Physician. *J Am Board Fam Med*. 2014;27:411–420.

80. Komaki Y, Komaki F, Micic D, et al. Pharmacologic therapies for severe steroid refractory hospitalized ulcerative colitis: A network meta-analysis. J Gastroenterol Hep. 2017;32:1143–1151.
81. Narula N, Fine M, Colombe JF, et al. Systematic review: Sequential rescue therapy in severe ulcerative colitis: Do the benefits outweigh the risks? *Inflamm Bowel Dis* 2015;21:1683–1694.
82. Kennedy NA, Kalla R, Warner B, et al. Thiopurine withdrawal during sustained clinical remission in inflammatory bowel disease: Relapse and recapture rates, with predictive factors in 237 patients. *Aliment Pharmacol Ther* 2014;40:1313–1323.
83. Moja L, Danese S, Fiorino C, et al. Systematic review with network meta-analysis: comparative efficacy and safety of budesonide and mesalazine (mesalamine) for Crohn's disease. *Aliment Pharmacol Ther*. 2015;41:1055–1065.
84. Stidham RW, Lee THC, Higgens PDR, et al. Systematic review with network meta-analysis: The efficacy of anti-TNF agents for the treatment of Crohn's disease. *Aliment Pharmacol Ther* 2014;39:1349–1362.
85. Beniwal-Patel P, Saha S. The role of integrin antagonists in the treatment of inflammatory bowel disease. *Expert Opin Biol Ther* 2014;14:1815–1823.
86. Gordon M. 5-Aminosalicylates to maintain remission in Crohn's Disease: Interpreting conflicting systematic review evidence. *World J Gastrointest Pharmacol Ther*. 2017;8(2):99–102.
87. Peyrin-Biroulet L, Lémann M. Review article: Remission rates achievable by current therapies for inflammatory bowel disease. *Aliment Pharmacol Ther* 2011;33:870–879.
88. Miao XP, Li JS, Ouyang Q, Hu RW, Zhang Y, Li HY. Tolerability of selective cyclooxygenase 2 inhibitors used for the treatment of rheumatological manifestations of inflammatory bowel disease. *Cochrane Database of Syst Rev* 2014;(10):CD007744.doi: 10.1002/14651858.CD007744.pub2.
89. Mahadevan U, McConnell RA, Chambers CD. Drug safety and risk of adverse outcomes for pregnant patients with inflammatory bowel disease. *Gastroenterology*. 2017;152:451–462.
90. Nguyen G, Seow CH, Maxwell C, et al. The Toronto Consensus

Statements for the Management of Inflammatory Bowel Disease in Pregnancy. *Gastroenterology*. 2016;150:734–757.

91. Boyd HA, Basit S, Harpsoe MC, et al. Inflammatory bowel disease and risk of adverse pregnancy outcomes. *PLoS One* 2015;10(6): e0129567.doi:10.1371/journal.pone.0129567.
92. Sands K, Jansen R, Zaslau, et al. Review article: The safety of therapeutic drugs in male inflammatory bowel disease patients wishing to conceive. *Aliment Pharmacol Ther* 2015;41:821–834.
93. Kotlyar DS, Osterman MT, Diamond RH, et al. A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2011;9:3641.e1.
94. Relling MV, Gardner EE, Sandborn WJ, et al. Clinical pharmacogenetics implementation consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing: 2013 update. *Clin Pharmacol Ther*. 2013;93(4):324–325.
95. Andersen NN, Pasternak B, Basit S, et al. Association between tumor necrosis factor-*α* antagonists and risk of cancer in patients with inflammatory bowel disease. *JAMA* 2014;311(23):2406–2413.
96. Yarur AJ, Rubin DT. Therapeutic drug monitoring of anti-tumor necrosis factor agents in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2015;21:1709–1718.
97. Gecse KB, Bemelman W, Kamm MA, et al. A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn’s disease. *Gut* 2014;63:1381–1392.
98. Akobeng AA, Sandborn WJ, Bickston SJ, et al. Tumor necrosis factor-alpha antagonists twenty years later: What do Cochrane reviews tell us? *Inflamm Bowel Dis*. 2014;20:2132–2141.
99. Grijalva CG, Chen L, Delzell E, et al. Initiation of tumor necrosis factor antagonists and the risk of hospitalization for infection in patients with autoimmune diseases. *JAMA* 2011;306(21):2331–2339.
100. Nakase H, Yoshino T, Matsuura M. Role in calcineurin inhibitors for inflammatory bowel disease in the biologics era: When and how to use. *Inflamm Bowel Dis*. 2014;20:2151–2156.

52

Nausea and Vomiting

Leigh Anne Hylton Gravatt, Krista L. Donohoe, and Mandy L. Gatesman

KEY CONCEPTS

1. Nausea and/or vomiting is often a part of the symptom complex for a variety of gastrointestinal (GI), cardiovascular, infectious, neurologic, metabolic, or psychogenic processes.
2. Nausea or vomiting is caused by a variety of medications or other noxious agents.
3. The overall goal of treatment should be to prevent or eliminate nausea and vomiting regardless of etiology.
4. Treatment options for nausea and vomiting include drug and nondrug modalities such as relaxation, biofeedback, and hypnosis.
5. The primary goal with chemotherapy-induced nausea and vomiting (CINV) is to prevent nausea and vomiting throughout the entire risk period; the emetic risk of the chemotherapeutic regimen is a major factor to consider when selecting a prophylactic regimen.
6. Patients undergoing radiation therapy (RT) to the upper abdomen or receiving total body or craniospinal irradiation should receive prophylactic antiemetics for radiation-induced nausea and vomiting (RINV).
7. Patients at high risk of vomiting should receive prophylactic antiemetics for postoperative nausea and vomiting (PONV).
8. Beneficial therapy for patients with balance disorders can most reliably be found among the antihistaminic–anticholinergic agents.

Preclass Engaged Learning Activity

Watch this video that shows a patient's perspective of CINV: https://tinyurl.com/y6nwbr6s. Visit TimeToTalkCINV.com and view the healthcare best practices checklist and other available tools.

INTRODUCTION

Nausea and vomiting are common complaints from individuals of all ages. Management can be simple or detailed and complex, depending on the etiology. This chapter provides an overview of nausea and vomiting, two multifaceted problems. Nausea is defined as the inclination to vomit or as a feeling in the throat or epigastric region alerting an individual that vomiting is imminent. Vomiting is the ejection or expulsion of gastric contents through the mouth and is often a forceful event. Either condition may occur transiently with no other associated signs or symptoms; however, these conditions also may be only part of a more complex clinical presentation.

ETIOLOGY

1 Nausea and vomiting may be associated with a variety of conditions, including gastrointestinal (GI), cardiovascular, infectious, neurologic, or metabolic disease processes. Nausea and vomiting may be a feature of such conditions as pregnancy, or may follow operative procedures or administration of certain medications such as those used in treating cancer. Psychogenic etiologies of these symptoms may be present. Anticipatory etiologies may be involved, such as in patients who have experienced poor nausea and/or vomiting control with previous antineoplastic agents. **Table 52-1** lists specific etiologies associated with nausea and vomiting.[1]

TABLE 52-1 Etiologies of Nausea and Vomiting

Intraperitoneal
- Mechanical obstruction
  - Gastric outlet obstruction
  - Bowel obstruction
- Altered sensorimotor function
  - Gastroparesis
  - Gastroesophageal reflux
  - Intestinal pseudo-obstruction
- Irritable bowel syndrome
- Chronic idiopathic nausea
- Functional vomiting
- Cyclic vomiting syndrome
- Cannabinoid hyperemesis syndrome
- Rumination syndrome
- Inflammatory diseases
- Pancreatitis
- Pyelonephritis
- Cholecystitis
- Appendicitis
- Hepatitis
- Acute gastroenteritis
  - Viral
  - Bacterial
- Biliary colic
- Liver failure

Cardiovascular diseases
- Acute myocardial infarction
- Cardiomyopathy

Neurologic processes
- Increased intracranial pressure
- Migraine headache
- Vestibular disorders
- Intracerebral hemorrhage
- Intracerebral malignancy

Metabolic disorders
- Diabetes mellitus (diabetic ketoacidosis)
- Addison's disease
- Renal disease (uremia)

Psychiatric causes
- Depression
- Anxiety disorders
- Anorexia and bulimia nervosa

Therapy-induced causes
- Antineoplastic agents
- Radiation therapy
- Anticonvulsant preparations
- Digoxin, Cardiac antiarrhythmics
- Opiates
- Oral hypoglycemics
- Oral contraceptives
- Antibiotics
- Volatile general anesthetics

Drug withdrawal
- Opiates
- Benzodiazepines

Miscellaneous causes
- Pregnancy
- Noxious odors
- Postoperative vomiting

Data from Reference 1.

The etiology of nausea and vomiting may vary with the age of the patient. For example, vomiting in the newborn during the first day of life suggests upper digestive tract obstruction or an increase in intracranial pressure.

2 Drug-induced nausea and vomiting is of particular concern, especially with the increasing number of patients receiving antineoplastic agents. A four-level classification system defines the risk for emesis with agents used in oncology (Table 52-2).[2] Although some agents may have greater emetic risk than others, combinations of agents, higher doses, clinical settings, psychological conditions, prior treatment experiences, and unusual stimulus of sight, smell, or taste may alter a patient's response to antiemetic treatment. In this setting, nausea and vomiting may be unavoidable and some patients experience these problems so intensely that chemotherapy is postponed or discontinued.

TABLE 52-2 Emetic Risk of Agents Used in Oncology and Treatment Options

Antiemetic Agent	Antiemetic Dose on Day 1 of Chemotherapy	Antiemetic Dose on Subsequent Days
High Risk (>90%): Anthracycline/Cyclophosphamide combination, Carboplatin AUC >4, Carmustine, Cisplatin, Cyclophosphamide >1,500 mg/m², Dacarbazine, Mechlorethamine, Streptozocin		
NK-1 Antagonist		
Aprepitant	125 mg oral	80 mg oral on days 2-3
Fosaprepitant	150 mg IV	
Netupitant-palonosetron	300 mg / 0.5 mg oral	
Rolapitant	180 mg oral	
5-HT$_3$ Antagonist[a]		
Dolasetron	100 mg oral	
Granisetron	2 mg oral or 1 mg IV or 10 mcg/kg IV or 1 patch or 10 mg SQ	
Ondansetron	8 mg oral twice daily or 24 mg oral or 8 mg IV or 0.15 mg/kg IV	
Palonosetron	0.5 mg oral or 0.25 mg IV	
Ramosetron	0.3 mg IV	
Tropisetron	5 mg oral or 5 mg IV	
Dexamethasone[b]	12 mg or 20 mg oral/IV	8 mg oral/IV daily or twice daily on days 2-4
Olanzapine	10 mg oral	10 mg oral on days 2-4
Moderate Risk (30%-90%): Aldesleukin, Alemtuzumab, Arsenic trioxide, Azacitidine, Bendamustine, Busulfan, Carboplatin AUC <4, Clofarabine, Cyclophosphamide <1,500 mg/m², Cytarabine >1,000 mg/m², Dactinomycin, Daunorubicin, Daunorubicin/cytarabine liposomal, Doxorubicin, Epirubicin, Idarubicin, Ifosfamide, Irinotecan (conventional and liposomal), Melphalan, Oxaliplatin, Romidepsin, Temozolomide, Thiotepa, Trabectedin		
5-HT$_3$ Antagonist		
Dolasetron	100 mg oral	
Granisetron	2 mg oral or 1 mg IV or 10 mcg/kg IV or 1 patch or 10 mg SQ	
Ondansetron	8 mg PO twice daily or 8 mg IV or 0.15 mg/kg IV	
Palonosetron	0.5 mg oral or 0.25 mg IV	
Ramosetron	0.3 mg IV	
Tropisetron	5 mg oral or 5 mg IV	
Dexamethasone	8 mg oral/IV	8 mg oral/IV on days 2-3[c]
Low Risk (10%-30%): Aflibercept, Atezolizumab, Belinostat, Blinatumomab, Bortezomib, Brentuximab, Cabazitaxel, Carfilzomib, Cetuximab, Cytarabine <1,000 mg/m², Docetaxel, Doxorubicin, liposomal (Doxil®), Elotuzumab, Eribulin, Etoposide, Fluorouracil, Gemcitabine, Ipilimumab, Ixabepilone, Methotrexate, Mitomycin, Mitoxantrone, Paclitaxel (conventional and albumin-bound), Necitumumab, Olaratumab, Omacetaxine, Panitumumab, Pemetrexed, Pentostatin, Pertuzumab, Talimogene-laherparepvec, Temsirolimus, Topotecan, Trastuzumab emtansine		
Choose One:		
5-HT$_3$ Antagonist		
Dolasetron	100 mg oral	
Granisetron	2 mg oral or 1 mg IV or 10 mcg/kg IV or 1 patch or 10 mg SQ	

Ondansetron	8 mg oral twice daily or 8 mg IV or 0.15 mg/kg IV
Palonosetron	0.5 mg oral or 0.25 mg IV
Ramosetron	0.3 mg IV
Tropisetron	5 mg oral or 5 mg IV
OR	
Dexamethasone	8 mg oral/IV
Minimal Risk (<10%): Avelumab, Asparaginase (Erwinia and Pegaspargase), Bevacizumab, Bleomycin, Cladribine, Daratumumab, Decitabine, Durvalumab, Fludarabine, Nelerabine, Nivolumab, Obinutuzumab, Ofatumumab, Peginterferon, Pembrolizumab, Pralatrexate, Ramucirumab, Rituximab (IV and SQ), Siltuximab, Trastuzumab, Valrubicin, Vinblastine, Vincristine (conventional and liposomal), Vinorelbine	
No routine prophylactic antiemetics are needed	

[a]No additional 5-HT_3-RA is needed if netupitant/palonosetron is used.

[b]Dexamethasone dose on day 1 should be reduced to 12 mg when given with aprepitant, fosaprepitant, and netupitant/palonosetron due to drug interactions. Dexamethasone dose on days 2-4 should be omitted when used as antiemetic with anthracycline/cyclophosphamide combination regimen or carboplatin AUC ≥4.

[c]Only if regimen is known to cause delayed nausea/vomiting (eg, cyclophosphamide, doxorubicin, oxaliplatin).

Data from Reference 2.

PATHOPHYSIOLOGY

The three consecutive phases of emesis include nausea, retching, and vomiting. Nausea, the subjective feeling of the need to vomit, may be considered a separate and singular symptom. Retching is the labored movement of abdominal and thoracic muscles before vomiting. The final phase of emesis is vomiting, the forceful expulsion of gastric contents caused by GI retroperistalsis. The act of vomiting is coordinated by the brainstem, but requires the contractions of the abdominal muscles, pylorus, and antrum, a raised gastric cardia, diminished lower esophageal sphincter pressure, and esophageal dilation.[1] Vomiting should not be confused with regurgitation, an act in which the gastric or esophageal contents rise to the pharynx but is not usually associated with forceful ejection seen with vomiting. Accompanying autonomic symptoms of pallor, tachycardia,

and diaphoresis account for many of the distressing feelings associated with emesis.

Vomiting is triggered by afferent impulses to the vomiting center (VC), a nucleus of cells in the medulla. Impulses are received from sensory centers, which include the chemoreceptor trigger zone (CTZ), cerebral cortex, and visceral afferents from the pharynx and GI tract. The VC integrates the afferent impulses, resulting in efferent impulses to the salivation center, respiratory center, and the pharyngeal, GI, and abdominal muscles, leading to vomiting.

The CTZ, located in the area postrema of the fourth ventricle of the brain, is a major chemosensory organ for emesis and is usually associated with chemically induced vomiting. Because of its location, blood-borne and cerebrospinal fluid toxins have easy access to the CTZ. Antineoplastic agents primarily stimulate this area rather than the cerebral cortex and visceral afferents. Similarly, pregnancy-associated vomiting probably occurs through stimulation of the CTZ.

Numerous neurotransmitter receptors are located in the VC, CTZ, and GI tract, including cholinergic, histaminic, dopaminergic, opiate, serotonergic, neurokinin (NK), and benzodiazepine receptors. Antineoplastic agents, their metabolites, or other emetic compounds theoretically trigger the process of emesis through stimulation of one or more of these receptors. Antiemetics have been developed to antagonize or block these emetogenic receptors.[3] See **Fig. 52-1**.

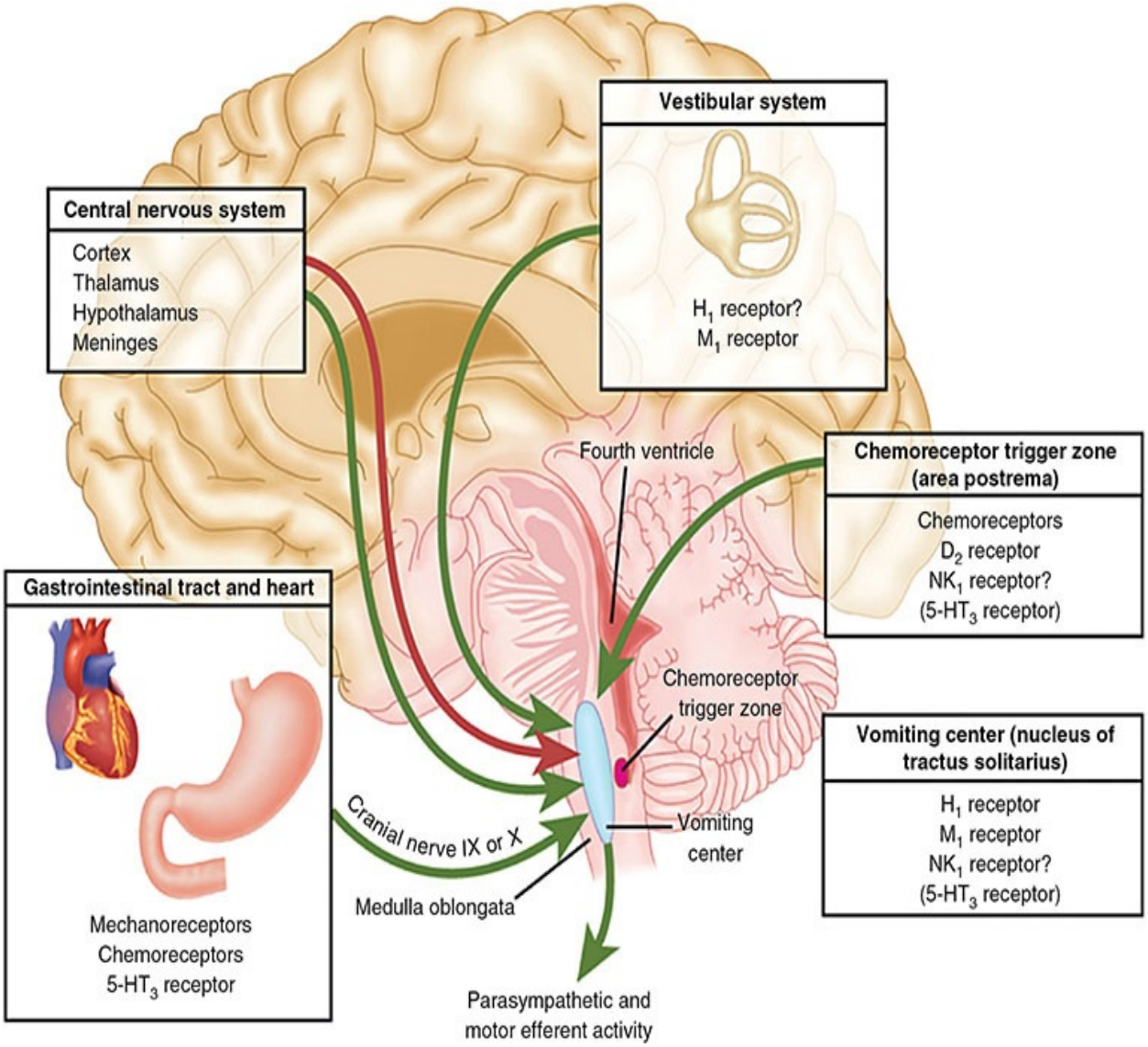


FIGURE 52-1 Pathogenesis of nausea and vomiting: neurologic pathways involved in pathogenesis of nausea and vomiting (see text). (*Reprinted, with permission, from Krakauer EL, et al. Case records of the Massachusetts General Hospital. N Engl J Med. 2005;352:817. © Massachusetts Medical Society...*)

CLINICAL PRESENTATION

Nausea and vomiting is commonly seen in many clinical situations. Patients may present in varying degrees of distress summarized in the Patient Care Process (PCP). See **Table 52-3** for clinical presentation of nausea and vomiting.

TABLE 52-3 Clinical Presentation of Nausea and Vomiting

General
Depending on severity of symptoms, patients may present in mild to severe distress

Symptoms
Simple: Self-limiting, resolves spontaneously, and requires only symptomatic therapy
Complex: Not relieved after administration of antiemetics; progressive deterioration of patient secondary to fluid-electrolyte imbalances; usually associated with noxious agents or pyschogenic events

Signs
Simple: Patient complaint of queasiness or discomfort
Complex: Weight loss; fever; abdominal pain

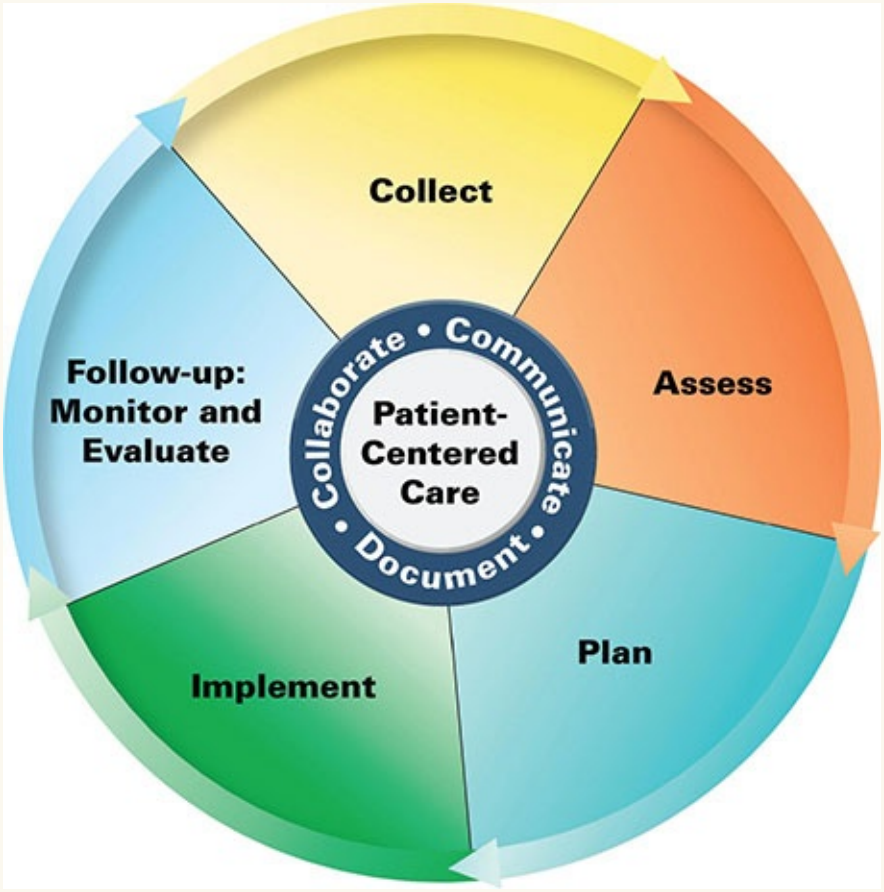
Laboratory tests
Simple: None
Complex: Serum electrolyte concentrations; upper/lower GI evaluation

Other information
Fluid input and output
Medication history
Recent history of behavioral or visual changes, headache, pain, or stress
Family history positive for psychogenic vomiting

TREATMENT

Desired Outcomes

3 The overall goal of antiemetic therapy is to prevent or eliminate nausea and vomiting. This should be accomplished without adverse effects or with clinically acceptable adverse effects. In addition to these clinical goals, appropriate cost issues should be considered, particularly in the management of chemotherapy-induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV).



Patient Care Process for Nausea and Vomiting

Collect

- Patient characteristics (eg, age, sex, pregnancy status, triggers)
- Patient medical history (personal and family), history of NV
- Social history (eg, tobacco/ethanol/cannabis use) and dietary habits
- Current medications including prescription and nonprescription medications, herbal products, dietary supplements
- Objective data (eg, QTc prolongation, BP/pulse, complete metabolic panel, CBC, liver function, weight, skin turgor, urine output)

Assess

- Duration, frequency, severity of nausea and vomiting
- Ability/willingness to pay for treatment options

- Emotional status (eg, presence of anxiety, depression)
- Assess ability of the patient to use oral, rectal, injectable, or transdermal medications
- Success of previous antiemetic regimens
- For CINV: Assess emetic risk of chemotherapy (see Table 52-7)
- For PONV: Assess risk factors for developing PONV (see Table 52-6)

Plan*

- Drug therapy regimen including specific antiemetic(s), dose, route, frequency, and duration (see Table 52-4 and Table 52-7)
- Monitoring parameters including efficacy (eg, reduction in symptoms, resolution of lab abnormalities, resumption of normal oral intake) and safety (eg, QTc prolongation, drug–drug interactions); frequency and timing of follow-up
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, invasive procedures, drug-specific information, medication administration technique)
- Self-monitoring for resolution of symptoms, when to seek emergency medical attention
- Referrals to other providers when appropriate (eg, gastroenterologist, dietitian, OBGYN, oncologist, anesthesiologist)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up, adherence assessment

Follow-up: Monitor and Evaluate

- Resolution of nausea and vomiting symptoms
- Need for rescue antiemetics
- Presence of adverse effects
- Patient adherence to treatment plan

*Collaborate with patient, caregivers, and other healthcare professionals.

General Approach to Treatment

3 Treatment options include drug and nondrug modalities such as relaxation, biofeedback, and hypnosis. Initially patients may choose to not treat or to self-medicate with nonprescription drugs. As symptoms become worse or are associated with more serious medical problems, patients are more likely to utilize prescription antiemetic drugs. When prescribed and used appropriately, these agents can provide relief; however, some patients will never be totally free of symptoms. This lack of relief is most disabling when it is associated with an unresolved medical problem or when the necessary therapy for this condition is the cause of the nausea or vomiting, as in the case of patients who are receiving antineoplastic agents of moderate or high emetic risk.

Nonpharmacologic Management

4 Nonpharmacologic management of nausea and vomiting involves dietary, physical, or psychological strategies that are consistent with the etiology of nausea and vomiting. For patients who are suffering due to excessive or disagreeable food or beverage consumption, avoidance or moderation in dietary intake may lead to symptom resolution. Patients suffering from symptoms of systemic illness may quickly improve as their underlying condition resolves. Finally, patients in whom these symptoms result from labyrinthine changes produced by motion may benefit quickly by assuming a stable physical position.

Nonpharmacologic interventions are classified as behavioral interventions and include relaxation, biofeedback, hypnosis, cognitive distraction, optimism, guided imagery, acupuncture, yoga, transcutaneous electrical stimulation, chewing gum, and systematic desensitization.[4–8] Chewing gum after certain surgical procedures improves bowel function and decreases time to first flatus as well as decreases the incidence of postoperative ileus.[6,7] Some of these modalities, such as with P6 acupuncture bands, are effective at preventing nausea and vomiting in the surgical population.[8] Other therapies, such as ginger and pyridoxine, may be beneficial in specific situations as with nausea and vomiting related to pregnancy.

Changes in diet such as restricting oral intake, eating smaller meals, avoiding spicy or fried foods, and instead eating bland foods such as with the BRAT diet (**B**ananas, **R**ice, **A**pplesauce, and **T**oast) can help alleviate symptoms.

Pharmacologic Therapy

Although many approaches to the treatment of nausea and vomiting have been suggested, antiemetic drugs (nonprescription and prescription) are most often recommended. These agents work in various ways that may be used singularly or in conjunction with each other and represent a number of delivery mechanisms.

Factors that enable the clinician to choose the appropriate regimen include (a) the suspected etiology of the symptoms; (b) the frequency, duration, and severity of the episodes; (c) the ability of the patient to use oral, rectal, injectable, or transdermal medications; and (d) the success of previous antiemetic medications. Please see **Table 52-4** for dosing information of commonly available antiemetic preparations.

TABLE 52-4 Common Antiemetic Preparations and Adult Dosage Regimens[a]

Drug	Adult Dosage Regimen	Dosage Form/Route	Availability
Antacids: Useful with simple nausea/vomiting *Adverse drug reactions: Magnesium products—diarrhea; Aluminum or calcium products—constipation*			
Antacids (various)	15-30 mL every 2-4 hours prn	Liquid/oral	Nonprescription
Antihistaminic–Anticholinergic Agents: Especially problematic in the elderly; increased risk of complications in patients with BPH, narrow angle glaucoma or asthma *Adverse drug reactions: Drowsiness, confusion, blurred vision, dry mouth, urinary retention*			
Dimenhydrinate (Dramamine)	50-100 mg every 4-6 hours prn	Tab, chew tab, cap	Nonprescription
Diphenhydramine (Benadryl)	25-50 mg every 4-6 hours prn 10-50 mg every 2-4 hours prn	Tab, cap, liquid IM, IV	Prescription/Nonprescription
Hydroxyzine (Vistaril, Atarax)	25-100 mg every 4-6 hours prn	Tab, (unlabeled use)	Prescription
Meclizine (Bonine, Antivert)	12.5-25 mg 1 hour before travel; repeat every 12-24 hours prn	Tab, chew tab	Prescription/Nonprescription
Scopolamine (Transderm Scop)	1.5 mg every 72 hours	Transdermal patch	Prescription
Trimethobenzamide (Tigan)	300 mg three to four times daily 200 mg three to four times daily	Cap IM	Prescription
Benzodiazepine: Used for ANV but is contraindicated with olanzapine *Adverse drug reactions: Dizziness, sedation, appetite changes, memory impairment; observe for additive sedation especially if used with narcotic analgesics*			
Lorazepam (Ativan)	0.5-2 mg on night before and morning of chemotherapy	Tab, IV	Prescription (C-IV)
Butyrophenones: Used for breakthrough CINV; Droperidol has limited use *Adverse drug reactions: Haloperidol—sedation, constipation, hypotension, EPS; Droperidol—QTc prolongation and/or torsade de pointes, 12-lead electrocardiogram prior to administration, followed by cardiac monitoring for 2-3 hours after administration*			
Haloperidol (Haldol)	0.5-2 mg every 4-6 hours prn	Tab, liquid, IM, IV	Prescription
Droperidol (Inapsine)[b]	2.5 mg; additional 1.25 mg may be given	IM, IV	Prescription
Cannabinoids: Used for breakthrough CINV *Adverse drug reactions: Eurphoria, somnolence, xerostomia*			
Dronabinol (Marinol)	5-15 mg/m^2 every 2-4 hours prn 4.2-12.6 mg/m^2 every 2-4 hours prn	Cap Oral solution	Prescription (C-III)

Nabilone (Cesamet)	1-2 mg twice daily	Cap	Prescription (C-II)
Corticosteroids: Useful as a single agent or combination therapy for prophylaxis of CINV or PONV *Adverse drug reactions: Insomnia, GI symptoms, agitation, appetite stimulation, hypertension, and hyperglycemia*			
Dexamethasone	See Table 52-7 for CINV dosing and Table 52-6 for PONV dosing	Tab, IV	Prescription
Histamine (H2) Antagonists: Useful with nausea secondary to heartburn or GERD *Adverse drug reactions: Headache, constipation, or diarrhea*			
Cimetidine (Tagamet HB)	200 mg twice daily prn	Tab	Nonprescription
Famotidine (Pepcid AC)	10 mg twice daily prn	Tab	Nonprescription
Nizatidine (Axid AR)	75 mg twice daily prn	Tab	Nonprescription
Ranitidine (Zantac 75)	75 mg twice daily prn	Tab	Nonprescription
5-Hydroxytryptamine-3 Receptor Antagonists: Useful as a single-agent or combination therapy for prophylaxis of CINV or PONV *Adverse drug reactions: Asthenia, constipation, headache*			
	See Table 52-7 for CINV dosing and Table 52-6 for PONV dosing	Tab, IV	Prescription
Miscellaneous Agents • **Metoclopramide:** Prokinetic activity useful in diabetic gastroparesis. *Adverse drug reactions: Asthenia, headache, somnolence, EPS* • **Olanzapine**: Use with caution in elderly; contraindicated with benzodiazepines. *Adverse drug reactions: Sedation, prolonged QTc interval, EPS* • **Pyridoxine:** Used in NVP. May be used alone or in combination with doxylamine 12.5 mg. Combination product available as prescription. *Adverse drug reactions: Drowsiness, headache*			
Metoclopramide (Reglan)	10-20 mg (0.5-2 mg/kg) four times daily	Tab, IV	Prescription
Olanzapine (Zyprexa)	5-10 mg daily	Tab	Prescription
Pyridoxine (Vitamin B_6)	10-25 mg orally three to four times daily	Tab, cap	Nonprescription
Phenothiazines: Useful in simple nausea/vomiting or breakthrough CINV *Adverse drug reactions: Prolonged QTc interval, constipation, dizziness, tachycardia, tardive dyskinesia, drowsiness*			
Chlorpromazine (Thorazine)	10-25 mg every 4-6 hours prn	Tab, liquid	Prescription
	25-50 mg every 4-6 hours prn	IM, IV	
Prochlorperazine (Compazine)	5-10 mg every 4-6 hours prn	Tab, liquid	Prescription
	5-10 mg every 3-4 hours prn	IM	
	2.5-10 mg every 3-4 hours prn	IV	Prescription
	25 mg twice daily prn	Supp	Prescription
Promethazine (Phenergan)	12.5-25 mg every 4-6 hours prn	Tab, liquid, IM, IV, supp	Prescription
Substance P/Neurokinin-1 Receptor Antagonist: Useful in combination therapy for prophylaxis of CINV and PONV *Adverse drug reactions: Constipation, diarrhea, headache, hiccups, dyspepsia, and fatigue*			
Aprepitant	See Table 52-7 for CINV dosing and Table 52-6 for PONV dosing	Cap, IV	Prescription
Fosaprepitant		IV	Prescription
Netupitant/palonosetron		Cap	Prescription
Rolapitant		Cap	Prescription

[a]All regimens should be monitored for resolution or occurrence of nausea and vomiting as well as maintaining an adequate hydration status.

[b]See text for warnings.

ANV, anticipatory nausea and vomiting; C-II, C-III, and C-IV, controlled substance schedule 2, 3, and 4, respectively; cap, capsule; chew tab, chewable tablet; CINV, chemotherapy-induced nausea and vomiting; GERD, gastroesophageal reflux disease; liquid, oral syrup, concentrate, or suspension; PONV, postoperative nausea and vomiting; supp, rectal suppository; tab, tablet.

The treatment of simple nausea and vomiting often involves self-care from a list of nonprescription products. Both nonprescription and prescription drugs are useful in the treatment of simple nausea and vomiting in small, infrequently administered doses and are associated with minimal side effects. As the symptoms persist or become worse, prescription medications may be chosen, either as single-agent therapy or in combination.

The management of complex nausea and vomiting, such as in patients who are receiving antineoplastic agents, may require initial combination therapy. In combination regimens, the goal is to achieve symptomatic control through administration of agents with different pharmacologic mechanisms of action.

Antacids

Patients who are experiencing simple nausea and vomiting may initially use antacids, as many of these products are readily available without a prescription. In this setting, single or combination products, especially those containing magnesium hydroxide, aluminum hydroxide, and/or calcium carbonate, may provide rapid relief, primarily through gastric acid neutralization. These agents are most effective for those with symptoms related to acid reflux or heartburn and must be used with caution in those who experience acute or chronic kidney disease due to the risk of accumulation. These agents may exacerbate other GI complaints that accompany nausea and vomiting, such as diarrhea or constipation, so attention must be paid to which of these agents may worsen these other conditions.

Antihistamine–Anticholinergic Drugs

Antiemetic drugs from the antihistaminic–anticholinergic category work on muscarinic and histamine receptors in the VC and the vestibular system that stimulate nausea and vomiting. As such, these agents are frequently initiated as self-care to prevent nausea and vomiting associated with motion disturbances such as vertigo and motion sickness.

Benzodiazepines

Benzodiazepines are relatively weak antiemetics and are primarily used for their anxiolytic activity to prevent anxiety or anticipatory nausea and vomiting (ANV) that may occur in patients experiencing suboptimal CINV control. Lorazepam may be used as an adjunct to other antiemetics in patients experiencing ANV.

Butyrophenones

Haloperidol and droperidol work by blocking dopaminergic stimulation of the CTZ, which in turn decreases the incidence of nausea and vomiting. Although effective in relieving nausea and vomiting, the use of these agents may be complicated by their propensity to cause extrapyramidal symptoms and QTc prolongation. For these reasons, haloperidol is not considered first-line therapy for uncomplicated nausea and vomiting but has been used in breakthrough CINV and palliative care situations.[9] The current labeling of droperidol recommends that all patients should undergo a 12-lead electrocardiogram prior to administration, followed by cardiac monitoring for 2 to 3 hours after administration because of the possibility of the development of potentially fatal QT prolongation and/or torsade de pointes.[10] Droperidol use is limited to rescue antiemetic for postoperative nausea and vomiting.

Cannabinoids

Cannabinoids have complex effects on the CNS and their effects at cannabinoid receptor 1 (CB1) in neural tissues may explain efficacy in CINV. Medicinal cannabis can be in the use of cannabis or cannabinoids in order to treat various conditions, including nausea and vomiting. Cannabinoids can be administered in a variety of methods including orally, topically, or sublingually. Oral dronabinol and nabilone, FDA-approved synthetic analogs of delta-9-tetrahydrocannabinol (THC), may be therapeutic options when CINV is refractory to other antiemetics. Medicinal marijuana has been approved for use in over half of states in the United States; however, its use remains debatable.[11] There is limited data to support the use of smoked or ingested cannabis for CINV. A meta-analysis of FDA-approved cannabinoids and medicinal cannabis suggested improvement of symptoms in comparison to placebo or active comparators; however, not all trials found statistical significance.[12] The combination of dronabinol and prochlorperazine was significantly more effective when used in combination for the treatment of CINV versus either agent alone.[11] Cannabinoids have the advantage of being effective for other cancer-related side effects such as pain or use as an appetite stimulant.[11–13] Despite these advantages, cannabinoids are not indicated as first-line agents. There is also concern that chronic cannabis use can lead to cyclic nausea and vomiting, which is called cannabinoid hyperemesis syndrome. This syndrome is primarily treated by supportive care, frequent hot showers, and cannabis cessation.[14]

Corticosteroids

Corticosteroids have demonstrated antiemetic efficacy since the initial recognition that patients who received prednisone as part of their Hodgkin's disease protocol appeared to develop less nausea and vomiting than did those patients who were treated with protocols that excluded this agent. The site and mechanism of action of corticosteroids for CINV and PONV are unknown.

Dexamethasone is the most commonly studied and used corticosteroid in the management of CINV and PONV, either as a single agent or in combination with 5-hydroxytryptamine-3 receptor antagonists (5-HT_3-RAs). Dexamethasone is effective in the prevention of both CINV acute emesis and delayed nausea and vomiting when used alone or in combination.[15,16] Given the risk of corticosteroids such as hyperglycemia, fluid retention, and even psychosis, steroids are not indicated for the treatment of simple nausea and vomiting.

H_2-Receptor Antagonists

Histamine-2 receptor antagonists (H_2RA) work by decreasing gastric acid production and are used to manage simple nausea and vomiting associated with heartburn or gastroesophageal reflux. Except for potential drug interactions with a variety of oral chemotherapy agents, these agents cause few side effects when used for episodic relief.

5-Hydroxytryptamine-3 Receptor Antagonists

5-Hydroxytryptamine-3 receptor antagonists (5-HT_3-RAs) block serotonin receptors on sensory vagal fibers in the gut wall; thus, blocking the acute phase of CINV. These agents do not completely block the acute phase of CINV and are less efficacious in preventing the delayed phase, but they are considered the standard of care in the management of CINV, PONV, and radiation-induced nausea and vomiting (RINV).[2,16]

The 5-HT_3-RAs are considered equivalent when used in equipotent doses/schedules so any agent may be used for CINV. Dolasetron should only be used orally for treatment of CINV due to an increased risk of QTc prolongation and other cardiac conduction abnormalities with the IV formulation.[17] Similarly, intravenous doses of ondansetron should not exceed 16 mg due to QTc prolongation.[18] Palonosetron has less effect on QTc and a significantly longer half-life compared to other 5-HT_3-RAs. Granisetron is available in two nonoral formulations: a transdermal patch and an extended-release subcutaneous

injection. The granisetron patch should be applied 24 to 48 hours prior to chemotherapy and may be worn for up to 7 days. The choice of 5-HT_3-RAs for CINV should be based on route of administration, potential side effects, and cost concerns.

Metoclopramide

Metoclopramide works by blocking dopaminergic receptors centrally in the CTZ. It also increases lower esophageal sphincter tone, aids gastric emptying, and accelerates transit through the small bowel, possibly through the release of acetylcholine. The prokinetic activity of metoclopramide makes it useful in patients with nausea and vomiting associated with diabetic gastroparesis. Due to the risk of extrapyramidal symptoms, metoclopramide should be used with caution if used in combination with other dopamine antagonists such as olanzapine or haloperidol.

Neurokinin-1 Receptor Antagonists

Substance P is a peptide neurotransmitter in the NK family whose preferred receptor is the NK_1 receptor. The acute phase of CINV is thought to be mediated by both serotonin and substance P, where substance P is believed to be the primary mediator of the delayed phase. An NK_1 receptor antagonist in combination with other antiemetics is now standard of care for prevention of CINV in both adults and children receiving highly emetogenic chemotherapy.[2] Aprepitant, fosaprepitant, and rolapitant are NK_1 receptor antagonists currently in clinical use, along with one combination NK_1 receptor antagonist/5-HT_3-RA co-formulated product, netupitant/palonosetron (NEPA).

Aprepitant has the potential for numerous drug interactions because it is a substrate and moderate inhibitor of cytochrome isoenzyme CYP3A4 as well as a weak inducer of CYP2C9. It can increase serum concentrations of many drugs, including chemotherapeutic agents metabolized by CYP3A4 such as anthracyclines, bosutinib, cabazitaxel, cyclophosphamide, and ifosfamide.[19] Other significant drug interactions include decreased effectiveness of estrogen-containing contraceptives (oral, patches, vaginal rings), and a decrease in the international normalized ratio when used with warfarin.[20] The dose of oral dexamethasone within the antiemetic regimen should be reduced 50% when coadministered with aprepitant, because of the 2.2-fold increase in observed area under the plasma-concentration-versus-time curve.[21] Conversely, if

dexamethasone is used as part of the chemotherapy regimen, the dexamethasone dose should remain the same.

Fosaprepitant is an injectable form of aprepitant approved by the FDA as an IV substitute for oral aprepitant, given on day 1 only of the CINV prevention regimen.[22] Drug interactions are likely reduced with fosaprepitant compared to oral aprepitant.[19]

Rolapitant has a significantly longer half-life in comparison with aprepitant (7 days vs 9 hours) and therefore should only be administered once in a 2-week period.[23] Although rolapitant has no effects on CYP3A4, it does inhibit p-glycoprotein/ABCB1 and CYP2D6, which may lead to drug interactions with certain antineoplastic agents, including doxorubicin, liposomal vincristine, pazopanib, topotecan, and venetoclax. An intravenous (IV) formulation of rolapitant was approved by the FDA. Postmarketing reports of anaphylaxis, anaphylactic shock, and severe hypersensitivity reactions during or shortly after initiation of IV rolapitant resulted in an FDA warning for this product. Patients with known hypersensitivity to components of IV rolapitant, including soybean oil, may be at an increased risk of reactions. All patients should be screened for cross-reactive allergens including soybeans and other legumes prior to administration.[23]

NEPA, when given in one dose combined with dexamethasone, was noninferior to a combination regimen of aprepitant, granisetron, and dexamethasone regimen in individuals receiving moderate or highly emetogenic chemotherapy.[24] Similar to aprepitant, netupitant is also a moderate inhibitor of CYP3A4, and requires a significant decrease in the dexamethasone dose when used together. Drug interactions with other CYP3A4 substrates would also be expected with NEPA.[25]

Olanzapine

Olanzapine is an antipsychotic that blocks several neurotransmitters including dopamine, serotonin, adrenergic, histamine (H_1), and 5-HT_3-RA. Olanzapine in combination with aprepitant/fosaprepitant, 5-HT_3-RA, and dexamethasone significantly improved nausea control after highly emetogenic chemotherapy.[26] The American Society of Clinical Oncology (ASCO) antiemesis practice guidelines include olanzapine as part of the standard four drug combination antiemetic regimen for highly emetogenic chemotherapy.[2] Sedation is the most common side effects with olanzapine; it should be used with caution in older adults and dose reductions may be necessary in this population.[27,28]

Phenothiazines

Phenothiazines have been the most widely prescribed antiemetic agents and appear to block dopamine receptors, most likely in the CTZ. They are marketed in an array of dosage forms, none of which appears to be more efficacious than the other. These agents may be most practical for long-term treatment and are inexpensive in comparison with newer drugs. Rectal administration is a reasonable alternative in patients in whom oral or parenteral administration is not feasible.

Phenothiazines are most useful in adult patients with simple nausea and vomiting. Intravenously administered prochlorperazine provided faster and more complete relief with less drowsiness than IV promethazine in adult patients treated in an emergency department for nausea and vomiting associated with uncomplicated gastritis or gastroenteritis.[29]

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

There are five categories of CINV: acute, delayed, anticipatory, breakthrough, and refractory. Nausea and vomiting that occurs within 24 hours of chemotherapy administration is defined as acute CINV, whereas when it starts more than 24 hours after chemotherapy administration, it is defined as delayed CINV.[30]

Nausea or vomiting that occurs prior to receiving chemotherapy is termed anticipatory nausea and vomiting (ANV). ANV is believed to be a learned, conditioned, or psychological response that occurs in about 14% of patients by the third cycle of chemotherapy.[4,31,32] ANV triggers include tastes, odors, sights, or thoughts associated with chemotherapy. Risk factors associated with ANV include experiencing CINV with prior chemotherapy cycles and anxiety before receiving chemotherapy.[4] In the setting of optimal antiemetic prophylaxis and no prior history of emesis, reported chemotherapy-induced ANV is rare. Use of newer antiemetic regimens appears to have resulted in a decreased rate of ANV.[31]

Breakthrough nausea and vomiting is defined as emesis occurring despite prophylactic administration of antiemetics and requiring the use of rescue antiemetics. Breakthrough emesis occurs in 10% to 40% of patients treated with antiemetics.[30]

Refractory nausea and vomiting is evident when there is a poor response to antiemetic regimens in prior cycles of chemotherapy. It is also important to rule out other potential causes of nausea and vomiting in the cancer population that are listed in Table 52-5.[2]

TABLE 52-5 Nonchemotherapy Etiologies of Nausea and Vomiting in Cancer Patients

Fluid and electrolyte abnormalities
Hypercalcemia
Volume depletion
Water intoxication
Adrenocortical insufficiency
Drug induced
Opiates
Anti-infectives
GI obstruction
Increased intracranial pressure
Peritonitis
Malignancy (primary tumor or metastases)
Brain
Meninges
Hepatic
Gastrointestinal
Uremia
Infections (septicemia, local)
Radiation therapy

Data from Reference 26.

5 The primary goal with CINV is to prevent nausea and/or vomiting and the emetic risk of the chemotherapeutic regimen is a major factor to consider when selecting a prophylactic regimen.[2]

Clinical practice guidelines for the use of antiemetics in CINV have been published by the National Comprehensive Cancer Network (NCCN), the Multinational Association of Supportive Care in Cancer/European Society of Medical Oncology (MASCC/ESMO), and ASCO.[2,28,32] The NCCN guidelines are updated annually, while the ASCO and ESMO guidelines are updated less frequently. Despite the demonstrated improvement in outcomes with the use of these practice guidelines, they are underutilized by a high percentage of practitioners.[33] Furthermore, product availability and recommended doses are often institution-specific and may vary considerably from the doses listed in Table 52-2.

Principles of Antiemetic Use for CINV

The ASCO, MASCC, and NCCN consensus groups share several of the principles listed below that are important for the effective prevention of CINV in adults.[2,28,32]

1. The primary goal of emesis prevention is no nausea and/or vomiting throughout the period of emetic risk.
2. The duration of emetic risk is 2 days for patients receiving moderately emetogenic chemotherapy and 3 days for highly emetogenic chemotherapy. Emetic prophylaxis should be provided through the entire period of risk.
3. The selection of the antiemetic regimen should be based on the chemotherapy drug with highest emetogenicity (**see** Table 52-2). Prior emetic experience and patient-specific factors should also be considered.
4. When given in equipotent doses, oral and IV 5-HT_3-RAs are equivalent in efficacy.
5. The toxicities of antiemetics should be considered and managed appropriately.

For simplicity, this review will focus on the ASCO guidelines.[2]

Prophylaxis of Acute CINV

Each of the practice guidelines states that the most effective classes of drugs for the prevention of acute emesis are the 5-HT_3-RAs, NK_1 receptor antagonists, olanzapine, and glucocorticoids (especially dexamethasone). Treatment recommendations for the different categories of emesis are outlined in Table 52-2.

High Emetogenic Chemotherapy

Patients receiving high emetogenic chemotherapy (HEC) should receive a four-drug antiemetic regimen that is initiated prior to the administration of chemotherapy on day 1, which includes an NK_1 receptor antagonist, a 5-HT_3-RA, dexamethasone, and olanzapine. Antiemetics administered on the subsequent days following completion of chemotherapy may include aprepitant (if aprepitant was used on day 1), dexamethasone, and olanzapine on days 2 to 4 as outlined in Table 52-2.

The combination of an anthracycline with cyclophosphamide, often used in breast cancer, is considered a highly emetogenic regimen, but dexamethasone on days 2 to 4 may be excluded from the antiemetic plan.

Moderate Emetogenic Chemotherapy

Patients receiving moderate emetogenic chemotherapy (MEC) should receive a two-drug regimen with a 5-HT_3-RA and dexamethasone on day 1. Dexamethasone should be continued on days 2 to 3 only if the chemotherapy agent is known to cause delayed nausea and vomiting (eg, cyclophosphamide, doxorubicin, oxaliplatin). Depending on the dose given, patients receiving carboplatin may receive the three-drug combination of an NK_1 receptor antagonist, a 5-HT_3-RA, plus dexamethasone on day 1 of therapy. If aprepitant was used on day 1, it should be continued on days 2 to 3; otherwise, no additional antiemetics are required in the delayed emetic risk period.[2]

Low or Minimal Emetogenic Chemotherapy

For chemotherapy regimens that are of low emetic risk, either dexamethasone or a 5-HT_3-RA as single agents may be used on day 1 only. For minimal emetic risk, no routine antiemetic prophylaxis is recommended.[2]

High-Dose Chemotherapy with Transplantation

Aprepitant, in combination with a 5-HT_3-RA and dexamethasone given prior to high-dose chemotherapy used as preparative regimens for bone marrow or stem cell transplantation, significantly improved emesis control in the first 1 to 5 days.[34–36] Both ASCO and MASCC/ESMO recommend an NK_1 antagonist, a 5-HT_3-RA, and dexamethasone as prophylaxis for patients receiving high-dose chemotherapy with stem-cell support.[2,32]

Prophylaxis and Treatment of Anticipatory Nausea and Vomiting

Prevention of CINV from the beginning of chemotherapy is essential in preventing ANV.[2,28,32] Nonpharmacologic interventions, such as behavioral therapy with systematic desensitization, hypnosis, acupuncture/acupressure, or

music therapy, may be of benefit for ANV. Benzodiazepine therapy may be used to decrease the occurrence of ANV; however, benzodiazepines may become less effective over time. If ANV occurs, oral lorazepam 0.5 to 2 mg starting the evening prior to chemotherapy and then an additional dose 1 to 2 hours prior to chemotherapy administration may be used.[4]

Treatment of Breakthrough CINV

A general principle in all patients receiving chemotherapy is to prescribe an antiemetic from a different pharmacologic class for rescue of breakthrough nausea and vomiting. Olanzapine should be considered for first-line treatment of breakthrough CINV if it was not part of the original prophylactic antiemetic regimen based on improved response compared with metoclopramide in a phase 3 trial.[37] Other options for rescue medications used in adult patients include prochlorperazine, promethazine, lorazepam, metoclopramide, haloperidol, 5-HT_3-RAs, dexamethasone, or cannabinoids.[2,28] The choice of agent should be based on patient-specific factors, including potential adverse drug reactions, route of administration (oral route may not be appropriate if actively vomiting), and cost. Around-the-clock dosing of rescue antiemetics should be considered rather than as-needed administration.

Considerations and Treatment of Refractory Nausea and Vomiting

Patients should be assessed for effectiveness of the antiemetic regimen prior to each cycle of chemotherapy. If a patient has experienced breakthrough CINV with the previous cycle, consideration should be given to adjusting the antiemetic regimen for the next chemotherapy cycle. The general approach to the management of refractory CINV is to add an additional agent from a different pharmacologic class to the antiemetic regimen.[28] For example, if a patient experienced breakthrough CINV while receiving the standard antiemetic regimen of a $5HT_3$-RA plus dexamethasone for moderately emetogenic chemotherapy, an NK-1 antagonist could be added to the prophylactic antiemetic regimen for the next cycle of chemotherapy. Similarly, olanzapine should be added if it was not previously part of a patient's initial antiemetic regimen.[2] Some patients will experience nausea and vomiting despite optimal acute and delayed prophylaxis. These patients should be assessed for other causes of nausea and vomiting (see Table 52-5).

One potential factor that might explain a less than optimal response is the variability in genetic enzymes responsible for the metabolism, transport, and receptor affinity of antiemetics.[38] The literature on the pharmacogenetics of antiemetic drugs is limited regarding the impact of the polymorphic variability in the drug transport mechanisms such as the ABCB1 or multidrug resistance gene (MDR1), or polymorphisms of metabolism with either CYP2D6 genes, which all may impact the efficacy of the 5-HT_3-RAs. Individuals who are either rapid or ultra-metabolizers of the CYP2D6 enzymes generally respond poorly to 5-HT3-RAs and dopamine D_2 receptor antagonists (prochlorperazine and metoclopramide).[39] Those patients with specific polymorphisms of the ABCB1 transporter, which is found in 5-HT_3-RAs such as ondansetron, and are found to have the 3435T variant had a better response of short-term nausea and vomiting control versus those with the 3435C variant.[40]

There are many limitations given the relatively small number of individuals studied in these trials, typically less than 300 patients, studied in limited ethnic populations and the fact that there are no tests readily available for these genetic polymorphisms. Given that granisetron is the only 5-HT_3-RA available that does not require metabolism via CYP2D6, this agent should be used as an alternative if a patient is less responsive to initial 5-HT_3-RA therapy with other agents.[39] Until there are confirmatory studies of these results, it is premature to utilize genomic analysis for personalized clinical decision-making for use of 5-HT_3-RAs.

Treatment of Multi-day Chemotherapy

Chemotherapy regimens are occasionally administered over multiple days.[2,28] ASCO and NCCN recommendations include using the appropriate antiemetic regimen based on the antineoplastic agent given on each day of chemotherapy and for 2 to 3 days after the last dose of chemotherapy, depending on risk of delayed CINV. When using an NK_1 antagonist for multi-day HEC regimens containing cisplatin, use aprepitant for up to 4 to 5 days.[41] There is limited data for other NK_1 antagonists in the setting of multi-day chemotherapy.

RADIATION-INDUCED NAUSEA AND VOMITING

Nausea and vomiting associated with radiation therapy (RT) is not well

understood and often underestimated by radiation oncologists.[42] RINV is neither as predictable nor as severe as CINV, and many patients receiving RT will not experience nausea or vomiting. Although not as well studied as CINV, RINV occurs in approximately one-third of patients, is site dependent, and can have a substantial impact on a patient's quality of life. Risk factors associated with the development of RINV include combination chemoradiotherapy, prior CINV, upper abdomen RT, and field size.[28]

Four radiotherapy-induced emesis risk groups have been defined by the ASCO and MASCC/ESMO antiemetic practice guidelines:[2,32]

1. Highest risk: Total-body irradiation (TBI)
2. Moderate risk: Upper body or abdomen and craniospinal RT
3. Low risk: Brain, head and neck, thorax, and pelvic RT
4. Minimal risk: Extremity or breast RT

Prophylaxis of RINV

6 Patients undergoing upper abdomen, craniospinal, or total body irradiation should receive prophylactic antiemetics for RINV. The combination of a prophylactic 5-HT_3-RA plus dexamethasone is more effective than placebo.[43] In addition, 5-HT_3-RAs were more effective than placebo or non-5-HT_3-RAs (prochlorperazine or metoclopramide), even in patients undergoing TBI.[43]

The ASCO and MASCC/ESMO guidelines recommend preventive therapy with a 5-HT_3-RA plus dexamethasone in patients who are receiving TBI (high emetic risk).[2,32] ASCO specifies administration of the two-drug regimen on the day of and day after each fraction of TBI. Patients undergoing RT procedures with moderate emetic risk should receive a 5-HT_3-RA prior to each fraction and optional dexamethasone prior to fractions 1 through 5. Those receiving low and minimal emetic risk radiotherapy may be offered rescue therapy with a 5-HT_3-RA, dexamethasone, or dopamine receptor antagonist.[2,32]

POSTOPERATIVE NAUSEA AND VOMITING

Postoperative nausea and vomiting in adults occurs in 30% of patients and usually within 24 hours of undergoing anesthesia.[44] Patients with multiple risk factors are at highest risk for PONV (**Table 52-6**). Patients with zero or one of

the four risk factors present in Table 52-6 are at lowest risk (10%-20%) and those with three to five risk factors are at highest risk for PONV (50%-80%). Moderate risk is defined by this model as the presence of two to three risk factors and high risk is defined as greater than three risk factors. The use of a risk assessment tool can help identify patients most likely to benefit from prophylaxis.[16,45,46]

TABLE 52-6 Risk Factors for Postoperative Nausea and Vomiting (PONV)

Patient-related factors
Age less than 50 years old
Female gender (two to three times greater incidence of PONV vs males)
Nonsmoker
History of PONV or motion sickness (threefold increase in incidence of PONV)
Hydration status
Factors related to anesthesia
Use of general anesthesia
Use of volatile anesthetics
Nitrous oxide
Use of opioids (intraoperative or postoperative)
Factors related to surgery
Type of surgical procedure (laparoscopic, gynecological, cholecystectomy)
Duration of surgery

Data from References 45 and 47.

In addition to using prophylactic antiemetics in moderate- and high-risk patients, other strategies to prevent PONV include using regional rather than systemic anesthesia, propofol, and hydration, as well as avoiding the use of nitrous oxide, volatile anesthetics, or opioids.[16]

Prophylaxis of PONV

7 Patients at highest risk of vomiting should receive two or more prophylactic antiemetics from different pharmacologic classes, while those at moderate risk should receive one or two drugs. Adherence to consensus guidelines for prophylaxis and treatment of PONV decreases emetic episodes.[16] Timing the administration of the antiemetic is vital to the efficacy with PONV and may vary dependent upon the agent. Scopolamine patches must be initiated the evening before the surgery or at least 2 hours prior, whereas NK_1 antagonists should be

given during the induction of anesthesia; all other agents are recommended to be administered at the end of the surgery. Pharmacological options for the prevention of PONV include 5-HT_3-RAs, an NK_1 antagonist, corticosteroids, droperidol, haloperidol, antihistamines, and anticholinergics.

Of the available 5-HT_3-RAs, ondansetron is still considered the "gold standard" agent and has the most data supporting its use at the end of surgical procedures. Ondansetron has greater antivomiting activity versus antinausea activity and is as effective as dexamethasone, droperidol, and IV haloperidol. However, it is less effective than longer acting agents such as aprepitant in decreasing emesis beyond 24 hours and less effective than palonosetron for decreasing the incidence of PONV.[47–50] Granisetron has similar results as ondansetron and is less effective than palonosetron.[47,48,51,52]

Steroids, such as dexamethasone and methylprednisolone, are useful low-cost agents for preventing PONV. Higher doses of dexamethasone (more than 0.1 mg/kg) have been associated with a decrease in nausea and vomiting, and improvement in pain, decreased need for opioids, and improvement in sleep. Dexamethasone should be administered after the induction of anesthesia, and due to its effects on glycemic control, its use should be avoided in patients with uncontrolled diabetes.[16,53,54]

When the different combinations of antiemetics were compared for PONV, no differences were found between 5-HT_3-RA plus droperidol, 5-HT_3-RA plus dexamethasone, and droperidol plus dexamethasone.[55] However, QT prolongation and/or torsade de pointes have been reported with some fatalities in patients receiving droperidol at doses at or below recommended doses. Droperidol should be avoided in patients who have a history of QT prolongation, are over 65 years old, or have a history of alcohol abuse, or when used concomitantly with benzodiazepines, volatile anesthetics, and IV opioids.[10] Low-dose haloperidol is a potential alternative to droperidol therapy and is beneficial in PONV. Haloperidol also carries a risk for potential QTc prolongation and should be used with caution in individuals at high risk for this complication.[16]

Monotherapy with perphenazine, metoclopramide, or scopolamine are as effective as placebo for the prophylaxis of PONV.[16] The guidelines advocate the use of combination therapy versus monotherapy; however, an optimal combination of antiemetics for PONV has not been established. The agents with the most data supporting their use include dexamethasone plus either a 5-HT_3-RA or droperidol or a 5-HT_3-RA plus droperidol.[16] The choice should be based

on use of different mechanisms of action, agents with different adverse effects along with cost considerations. Table 52-7 summarizes the doses for prophylactic antiemetics from the consensus guidelines.[16]

TABLE 52-7 Recommended Prophylactic Doses of Selected Antiemetics for Postoperative Nausea and Vomiting in Adults and Postoperative Vomiting in Children

Drug	Adult Dose	Pediatric Dose (IV)	Timing of Dose[a]
Aprepitant[b]	40 mg orally	Not labeled for use in pediatrics	Within 3 hours prior to induction
Dexamethasone	4-5 mg IV	150 mcg/kg up to 5 mg	At induction
Dimenhydrinate	1 mg/kg IV	0.5 mg/kg up to 25 mg	Not specified
Dolasetron	12.5 mg IV	350 mcg/kg up to 12.5 mg	At end of surgery
Droperidol[c]	0.625-1.25 mg IV	10-15 mcg/kg up to 1.25 mg	At end of surgery
Granisetron	0.35-3 mg IV	40 mcg/kg up to 0.6 mg	At end of surgery
Haloperidol	0.5-2 mg (IM or IV)	*d*	Not specified
Methylprednisolone	40 mg IV	*d*	At induction
Ondansetron	4 mg IV, 8 mg orally disintegrating tablet	50-100 mcg/kg up to 4 mg	At end of surgery
Palonosetron[b]	0.075 mg IV	*d*	At induction
Promethazine[c]	6.25-12.5 mg IV	*d*	At induction
Scopolamine	Transdermal patch	*d*	Prior evening or 4 hours before surgery

[a]Based on recommendations from consensus guidelines.

[b]Labeled for use in PONV but not included in consensus guidelines.

[c]See FDA "black box" warning.

[d]Pediatric dosing not included in consensus guidelines.

Data from Reference 47.

Aprepitant is approved for the prevention of PONV when given orally within 3 hours prior to induction of anesthesia.[20] It is equivalent to ondansetron 4 mg IV in reducing the incidence of nausea and the need for rescue in the 24 hours after surgery, but was significantly better than ondansetron for preventing vomiting in the 24 and 48 hours after surgery.[56] Aprepitant has been studied in combination with dexamethasone in comparison with an ondansetron plus dexamethasone combination and the aprepitant combination was more effective than the ondansetron combination group.[57]

Treatment of PONV

Patients who experience PONV after receiving prophylactic treatment with a combination of a 5-HT_3-RA plus dexamethasone should be given rescue therapy from a different drug class such as a phenothiazine, metoclopramide, or droperidol.[16] Repeating the agent given for PONV prophylaxis within 6 hours of surgery offers no additional benefit. Furthermore, a repeated dose of a 5-HT_3-RA is not effective in treatment of PONV.[58,59] An emetic episode occurring more than 6 hours postoperatively can be treated with any of the drugs used for prophylaxis except dexamethasone and transdermal scopolamine.[16]

If no prophylaxis was given initially, the recommended treatment is low-dose 5-HT_3-RA such as ondansetron 1 mg. Alternative treatments for established PONV include dexamethasone 2 to 4 mg IV, droperidol 0.625 mg IV, or promethazine 6.25 to 12.5 mg IV.[60]

DISORDERS OF BALANCE

Disorders of balance include vertigo, dizziness, and motion sickness. The etiology of these complaints may include diseases that are infectious, postinfectious, demyelinative, vascular, neoplastic, degenerative, traumatic, toxic, psychogenic, or idiopathic. Symptoms of imbalance perceived by the patient present a particular clinical challenge.

8 Beneficial therapy for patients with balance disorders can most reliably be found among the antihistaminic–anticholinergic agents. However, the precise mechanisms of action of these agents are unknown. Oral regimens of antihistaminic–anticholinergic agents given one to several times each day may be effective, especially when the first dose is administered prior to motion.

Motion sickness may be associated with nausea and vomiting. Scopolamine is effective for the prevention of motion sickness and is considered first line for this indication.[61] The usefulness of scopolamine in preventing motion sickness was enhanced with the development of the transdermal system (patch) that increased patient satisfaction and decreased untoward side effects. The patch should be placed several hours before the anticipated motion exposure. First-generation sedating antihistamines are also effective. However, second-generation nonsedating antihistamines, ondansetron, and ginger root are not effective in the prevention and treatment of motion sickness.[62]

ANTIEMETIC USE DURING PREGNANCY

As many as 50% to 80% of pregnant women experience nausea and 50% will have vomiting or retching.[63] The severity of the symptoms varies considerably, from mild nausea to incapacitating nausea and vomiting. The etiology of nausea and vomiting of pregnancy (NVP) is not well understood, but theories proposed include hormonal stimulus, evolutionary adaptation, and psychological predisposition.[63,64] Symptoms are self-limited for a majority of women, although approximately 0.3% to 3% develop hyperemesis gravidarum, a serious condition marked by severe physical symptoms and/or medical complications requiring hospitalization.[65] In its most severe state, hyperemesis gravidarum may result in volume contraction, starvation, and electrolyte abnormalities.

Treatment recommendations for the management of NVP are available from the American College of Obstetricians and Gynecologists (ACOG).[66] Prevention of NVP should be the initial treatment approach. A prenatal vitamin should be started 1 month prior to becoming pregnant, which may help reduce the incidence and severity of NVP.[67] Dietary changes and/or lifestyle modifications such as eating smaller, more frequent meals every 1 to 2 hours, and avoiding foods or odors that trigger symptoms are recommended. Ginger is beneficial in reducing nausea but not vomiting.[66] Persistent nausea and/or vomiting leads to the consideration of drug therapy at a time when teratogenic potential of each agent must be considered. Pyridoxine (vitamin B_6), with or without doxylamine, is recommended as first-line therapy.[66] The US Food and Drug Administration approved a delayed-release formulation of doxylamine and pyridoxine hydrochloride (Diclegis[R]) as a prescription product.[66] Dimenhydrinate, diphenhydramine, prochlorperazine, or promethazine may also be considered in the treatment of NVP.

Patients with persistent NVP or who show signs of dehydration should receive intravenous hydration with thiamine administered before dextrose to prevent Wernicke encephalopathy. Enteral tube feedings should be considered in women with hyperemesis gravidarum not responsive to medical therapy and who cannot maintain weight.[66] Ondansetron, promethazine, and metoclopramide have similar effectiveness for hyperemesis gravidarum, although ondansetron may be better tolerated due to less adverse effects.[68–71] Glucocorticoids, like methylprednisolone, may be used in patients with severe NVP or hyperemesis gravidarum, but should be used only after 10 weeks of gestation due to the increased risk of cleft lip.[62]

ANTIEMETIC USE IN SPECIAL POPULATIONS

Chemotherapy-Induced Nausea and Vomiting in Children

Aprepitant demonstrated improved rates of vomiting versus placebo when combined with ondansetron and dexamethasone in pediatric patients receiving highly emetic chemotherapy.[72] Both ASCO and MASCC/ESMO recommend the three-drug combination of an NK-1 antagonist, a 5-HT_3-RA, and dexamethasone for children receiving HEC.[2,32] If an NK-1 antagonist cannot be used, a 5-HT_3-RA and dexamethasone is recommended. If dexamethasone cannot be used, an NK-1 antagonist with a 5-HT_3-RA should be used.[2,32]

Pediatric patients receiving MEC should receive a 5-HT_3-RA with dexamethasone; if dexamethasone cannot be used, then patients should receive a 5-HT_3-RA with an NK_1 antagonist. Children treated with low emetic risk chemotherapy should receive single agent 5-HT_3-RA prior to chemotherapy, while minimal emetic risk chemotherapy regimens do not require routine antiemetics.[2,32]

Gastroenteritis in Children

Nausea and vomiting associated with pediatric gastroenteritis is usually self-limited and improves with correction of dehydration. The majority of patients can be successfully treated with oral rehydration therapy. Pediatric practitioners may prescribe antiemetics for intractable vomiting due to gastroenteritis. The use of promethazine is contraindicated in patients less than 2 years old and should be used with caution in older children due to the potential risk of fatal respiratory depression.[73] Administration of ondansetron, even given before oral rehydration therapy, is associated with decreased vomiting and a reduced need for intravenous fluid therapy or hospital admissions.[74,75]

Antiemetic Use in Geriatric Patients

Many of the commonly used antiemetics are on the Beers Criteria list, which are medications that may be inappropriate in the older adults due to the risks outweighing the benefits.[76] These include first-generation antihistamines and scopolamine due to their highly anticholinergic side effects. Metoclopramide is also a Beers Criteria medication that may cause extrapyramidal effects including

tardive dyskinesia especially in frail older adults. Ondansetron may be considered a preferred antiemetic in older adults; however, consider drug–drug interactions and potential adverse effects before prescribing.[77]

EVALUATION OF EMETIC OUTCOMES

In assessing emetic outcomes, standardized monitoring criteria should include a subjective assessment and objectives parameters. For patients on chemotherapy, evaluation of emetic outcomes should occur after the administration of each chemotherapy cycle. Adherence to outpatient antiemetic regimens occurs in only about 65% of patients. Patients receiving high-risk regimens are most likely to report symptoms of nausea and vomiting on day 3 after chemotherapy.[2] Documentation of nausea and/or vomiting events will assist the clinician in modifying the antiemetic regimen for the next cycle of chemotherapy.

Postclass Engaged Learning Activity

1. Drug Information Question: What alternative treatment regimens can you use in CINV with a prolonged QTc interval?
2. Drug Information Question: Can you use medical marijuana for nausea and vomiting in your state? Research your state laws and the evidence-based literature for using medical marijuana for nausea and vomiting.

ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
ANV	anticipatory nausea and vomiting
ASCO	American Society of Clinical Oncology
BRAT	Bananas, rice, applesauce, or toast
CINV	chemotherapy-induced nausea and vomiting
CTZ	chemoreceptor trigger zone
GI	gastrointestinal
ESMO	European Society of Medical Oncology
HEC	high emetogenic chemotherapy
5-HT_3-RA	5-hydroxytryptamine-3 receptor antagonist
MASCC	Multinational Association of Supportive Care in Cancer
MDR1	multidrug resistance gene
MEC	moderate emetogenic chemotherapy
NCCN	National Comprehensive Cancer Network
NEPA	netupitant/palonosetron
NK_1	neurokinin-1
NVP	nausea and vomiting of pregnancy
PONV	postoperative nausea and vomiting
RINV	radiation-induced nausea and vomiting
RT	radiation therapy
TBI	total-body irradiation
VC	vomiting center

REFERENCES

1. Hasler WL. Nausea, vomiting, and indigestion. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 19th ed. New York, NY: McGraw-Hill; 2014. http://accessmedicine.mhmedical.com/content.aspx?bookid=1130§ionid=79726154.
2. Hesketh PJ, Kris MG, Bohlke K, et al. Antiemetics: American Society of Clinical Oncology Practice Guideline Update. *J Clin Oncol* 2017;35:3240–3261.
3. Krakauer EL, Zhu AX, Bounds BC, Sahani D, McDonald KR, Brachtel EF. Case records of the Massachusetts General Hospital. *N Engl J Med*. 2005;352:817. Massachusetts Medical Society.

4. Kamen C, Tejani MA, Chandwani K, et al. Anticipatory nausea and vomiting due to chemotherapy. *Eur J Pharmacol* 2014;722:172–179.
5. White PF, Issioui T, Hu J, et al. Comparative efficacy of acustimulation (ReliefBand) versus ondansetron (Zofran) in combination with droperidol for preventing nausea and vomiting. *Anesthesiology*. 2002;97:1075–1081.
6. Craciunas L, Sajid MS, Ahmed AS. Chewing gum in preventing postoperative ileus in women undergoing caesarean section: A systematic review and meta-analysis of randomised controlled trials. *BJOG*. 2014;121:793–799.
7. Purkayastha S, Tilney HS, Darzi AW, Tekkis PP. Meta-analysis of randomized studies evaluating chewing gum to enhance postoperative recovery following colectomy. *Arch Surg*. 2008;143:788–793.
8. Cheong KB, Chang JP, Huang, Y, Zhang ZJ. The effectiveness of acupuncture in the prevention and treatment of postoperative nausea and vomiting—A systematic review and meta-analysis. *PLoS One*. 2013;8(12):e82474.
9. Murray-Brown F, Dorman S. Haloperidol for the treatment of nausea and vomiting in palliative care patients. *Cochrane Database Syst Rev* 2015;11:CD006271.
10. Droperidol [package insert]. Lake Forest, IL: Hospira, Inc.; 2004.
11. Wilkie G, Sakr B, Rizack T. Medical marijuana use in oncology: A review. *JAMA Oncol*. 2016;2(5):670–675.
12. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medicinal use: A systematic review and meta-analysis. *JAMA* 2015;313:2456–2473.
13. Strasser F, Luftner D, Possinger K, et al. Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: A multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-In-Cachexia-Study-Group. *J Clin Oncol*. 2006;24:3394–3400.
14. Sorensen CJ, DeSanto K, Borgelt L, Phillips KT, Monte AA. Cannabinoid hyperemesis syndrome—diagnosis, pathophysiology, and treatment: A systematic review. *J Med Toxicol*. 2017;13:71–87.
15. Italian Group for Antiemetic Research. Double-blind, dose-finding study of four intravenous doses of dexamethasone in the prevention of cisplatin-induced acute emesis. *J Clin Oncol*. 1998;16:2937–2942.
16. Gan TJ, Diemunsch P, Habib AS, et al. Consensus Guidelines for the

management of postoperative nausea and vomiting. *Anesth Analg*. 2014;118:85–113.

17. Dolasetron [package insert]. Bridgewater, NJ: Sanofi-aventis US LLC; 2014.
18. Ondansetron [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2017.
19. Patel P, Leeder JS, Piquette-Miller M, et al. Aprepitant and fosaprepitant drug interactions: A systematic review. *Br J Clin Pharmacol*. 2017;83(10):2148–2162.
20. Emend (aprepitant) [package insert]. Whitehouse Station, NJ: Merck & Co, Inc.; 2017.
21. McCrea JB, Majumdar AK, Goldberg MR, et al. Effects of the neurokinin-1 receptor antagonist aprepitant on the pharmacokinetics of dexamethasone and methylprednisolone. *Clin Pharmacol Ther* 2003;74:17–24.
22. Emend (fosaprepitant) [package insert]. Whitehouse Station, NJ: Merck & Co, Inc.; 2018.
23. Varubi (rolapitant) [package insert]. Waltham, MA: Tesaro, Inc.; 2018.
24. Zhang L, Lu S, Feng J, et al. A randomized phase III study evaluating the efficacy of single-dose NEPA, a fixed antiemetic combination of netupitant and palonosetron, versus an aprepitant regimen for prevention of chemotherapy-induced nausea and vomiting (CINV) in patients receiving highly emetogenic chemotherapy (HEC). *Ann Oncol* 2018;29:452–458.
25. Akynzeo (netupitant and palonosetron) [package insert]. Iselin, NJ: Helsinn Therapeutics, Inc.; 2018.
26. Navari RM, Qin R, Ruddy KJ, et al. Olanzapine for the prevention of chemotherapy-induced nausea and vomiting. *N Engl J Med*. 2016;375:134–142.
27. Yanai T, Iwasa S, Hashimoto H, et al. A double-blind randomized phase II dose-finding study of olanzapine 10 mg or 5 mg for the prophylaxis of emesis induced by highly emetogenic cisplatin-based chemotherapy. *Int J Clin Oncol*. 2018;23:382–388.
28. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology.Antiemesis. Version 1. 2018. Available at: http://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf. Accessed March 21, 2018.

29. Ernst A, Weiss SJ, Park S, et al. Prochlorperazine versus promethazine for uncomplicated nausea and vomiting in the emergency department: A randomized, double-blind clinical trial. *Ann Emerg Med*. 2000;36:89–94.
30. Navari RM, Aapro M. Antiemetic prophylaxis for chemotherapy-induced nausea and vomiting. *N Engl J Med*. 2016;374:1356–1367.
31. Molassiotis A, Lee PH, Burke TA. Anticipatory nausea, risk factors, and its impact on chemotherapy-induced nausea and vomiting: Results from the Pan European Emesis Registry Study. *J Pain Symptom Manage*. 2016;51:987–993.
32. Roila F, Molassiotis A, Herrstedt J, et al. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. *Ann Oncol*. 2016;27(Suppl 5):v119–v133.
33. Jordan K, Gralla R, Jahn F, Molassiotts A. International antiemetic guidelines on chemotherapy induced nausea and vomiting (CINV): Content and implementation in daily practice. *Eur J Pharmacol* 2014;722:197–222
34. Stiff PJ, Fox-Geiman MP, Kiley K, et al. Prevention of nausea and vomiting associated with stem cell transplant: Results of a prospective, randomized trial of aprepitant used with highly emetogenic preparative regimens. *Biol Blood Marrow Transplant*. 2013;19:49–55.
35. Schmitt T, Goldschmidt H, Neben K, et al. Aprepitant, granisetron, and dexamethasone for prevention of chemotherapy-induced nausea and vomiting after high-dose melphalan in autologous transplantation for multiple myeloma: Results of a randomized, placebo-controlled phase III trial. *J Clin Oncol*. 2014;32:3413–3420.
36. Svanberg A, Birgegard G. Addition of aprepitant (Emend) to standard antiemetic regimen continued for 7 days after chemotherapy for stem cell transplantation provides significant reduction of vomiting. *Oncology*. 2015;89:31–36.
37. Navari RM, Nagy CK, Gray SE. The use of olanzapine versus metoclopramide for the treatment of breakthrough chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy. Support Care Cancer. 2003;21:1655–1663.
38. Singh KP, Dhruva AA, Flowers E, Kober KM, Miaskowski. A review of the literature on the relationships between genetic polymorphisms and chemotherapy-induced nausea and vomiting. *Clin Rev Oncol*.

2018;121:51–64.

39. Trammel M, Roedere M, Patel J, McLeod H. Does pharmacogenomics account for variability in the control of acute chemotherapy-induced nausea and vomiting with 5-hydroxytryptamine type 3 antagonist? *Curr Oncol Rep*. 2013;15:276–285.
40. Perwitasari DA, Wessles J, van der Straaten R, et al. Association of ABCB1, 5-HT3B receptor and CYP2D6 genetic polymorphisms with ondansetron and metoclopramide antiemetic response in Indonesian cancer patients treated with highly emetogenic chemotherapy. *Jpn J Clin Oncol*. 2011;41:1168–1176.
41. Albany C, Brames MJ, Fausel C, et al. Randomized, double-blind, placebo-controlled, phase III cross-over study evaluating the oral neurokinin-1 antagonist aprepitant in combination with a 5HT3 receptor antagonist and dexamethasone in patients with germ cell tumors receiving 5-day cisplatin combination chemotherapy regimens: A Hoosier Oncology Group study. *J Clin Oncol*. 2012;30:3998–4003.
42. Enblom A, Bergius Axelsson B, Steineck G, et al. One third of patients with radiotherapy-induced nausea consider their antiemetic treatment insufficient. *Support Care Cancer*. 2009;17:23–32.
43. Salvo N, Doble B, Khan L, et al. Prophylaxis of radiation-induced nausea and vomiting using 5-hydroxytryptamine-3 serotonin receptor antagonists: A systematic review of randomized trials. *Int J Radiat Oncol Biol Phys*. 2012;82:408–417.
44. Wiesmann T, Kranke P, Eberhart L. Postoperative nausea and vomiting—A narrative review of pathophysiology, pharmacotherapy and clinical management strategies. *Expert Opin Pharmacother*. 2015;16:1069–1077.
45. Shaikh SI, Nagarekha D, Hegade G, Marutheesh M. Postoperative nausea and vomiting: A simple yet complex problem. *Anesth Essays Res* 2016; 10:388–396.
46. Apfel CA, Karttila K, Abdalla M, et al. A factorial trial of six intervention for the prevention of postoperative nausea and vomiting. *N Engl J Med*. 2004;350:2441–2451.
47. Diemunsch P, Gan TJ, Philip BK, et al. Single-dose aprepitant vs. ondansetron for the prevention of postoperative nausea and vomiting: A randomized, double-blind phase III trial in patient undergoing open abdominal surgery. *Br J Anaesth*. 2007;99:202–211.
48. Park SK, Cho EJ. A randomized, double-blind trial of palonosetron

compared with ondansetron in preventing postoperative nausea and vomiting after gynaecological laparoscopic surgery. *J Int Med Res*. 2011;39:399–407.

49. Okafor D, Kaye AD, Kaye RJ, Urman RD. The role of neurokinin-1 (substance P) antagonists in the prevention of postoperative nausea and vomiting. *J Anaesthesiol Clin Pharmacol*. 2017;33:441–445.
50. Janicki PK, Schuler HG, Jarzembowski TM, Ross MII. Prevention of postoperative nausea and vomiting with granisetron and dolasetron in relation to CYP2D6 genotype. *Anest Analg*. 2006;102:1127–1133.
51. Gugale AA, Bhalerao PM. Palonosetron and granisetron in postoperative nausea and vomiting. A randomized double-blind prospective study. *Anesth Essays Res* 2016;10:402–407.
52. Gupta P, Sabharwal N, Kale S, Gupta M, Gogia AR. Granisetron versus ondansetron for post-operative nausea and vomiting prophylaxis in elective craniotomies for brain tumors: A randomized, controlled, double-blind study. *Anesth Essays Res*. 2014;8:72–77.
53. Fan Z, Ma J, Ma X, et al. The efficacy of dexamethasone on pain and recovery after total hip arthroplasty: A systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore) 2018.97(13):e0100.
54. Waldron NH, Jones CA, Gan TJ, et al. Impact of perioperative dexamethasone on postoperative analgesia and side-effects: Systematic review and meta-analysis. *Br J Anaesth*. 2013;110:191–200.
55. Habib AS, El-Moalem HE, Gan TJ. The efficacy of the 5-HT3 receptor antagonists combined with droperidol for PONV prophylaxis is similar to their combination with dexamethasone. A meta-analysis of randomized controlled trials. *Can J Anaesth*. 2004;51:311–319.
56. Gan TJ, Apfel C, Kovac A, et al. A randomized, double-blind comparison of the NK1 antagonist, aprepitant versus ondansetron for the prevention of postoperative nausea and vomiting. *Anesth Analg*. 2007;104:1082–1089.
57. Habib AS, Keifer JC, Borel CO, White WD, Gan TJ. A comparison of the combination of aprepitant and dexamethasone versus the combination of ondansetron and dexamethasone for the prevention of postoperative nausea and vomiting in patients undergoing craniotomy. *Anesth Analg*. 2011;112:813–818.
58. Kovac AL, O'Connor TA, Pearman MH, et al. Efficacy of repeat intravenous dosing of ondansetron in controlling postoperative nausea and

vomiting: A randomized, double-blind, placebo-controlled multicenter trial. *J Clin Anesth*. 1999;11:453–459.

59. Candiotti KA, Nhuch F, Kamat A, et al. Granisetron versus ondansetron treatment for breakthrough postoperative nausea and vomiting after prophylactic ondansetron failure: A pilot study. *Anesth Analg*. 2007;104:1370–1373.
60. Habib AS, Gan TJ. The effectiveness of rescue antiemetics after failure of prophylaxis with ondansetron or droperidol: A preliminary report. *J Clin Anesth* 2005;17:62–65.
61. Spinks AB, Wasiak J, Villaneuva EV, Bernath V. Scopolamine (hyoscine) for preventing and treating motion sickness. *Cochrane Database Syst Rev* 2011;(6):CD002851.
62. Brainard A, Gresham C. Prevention and treatment of motion sickness. *Am Fam Physician*. 2014;90:41–46.
63. Flaxman SM, Sherman PW. Morning sickness: A mechanism for protecting mother and embryo. *Q Rev Biol*. 2000;75:113–148.
64. Simpson SW, Goodwin TM, Robins SB, Rizzo AA, Howes RA, Buckwalter DK, et al. Psychological factors and hyperemesis gravidarum. *J Womens Health Gend Based Med*. 2001;10:471–477.
65. Matthews A, Haas DM, O'Mathúna DP, Dowswell T. Interventions for nausea and vomiting in early pregnancy. *Cochrane Database Syst Rev*. 2015;(9):CD007575.
66. Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin No. 189: Nausea and vomiting of pregnancy. *Obstet Gynecol*. 2018;131:e15–e30.
67. Committee on Practice Bulletins-Obstetrics. Practice Bulletin No. 187: Neural tube defects. *Obstet Gynecol*. 2017;130:e279–290.
68. Herrell HE. Nausea and vomiting of pregnancy. *Am Fam Physician* 2014;89(12):965–970.
69. Koren G, Clark S, Hankins GD, et al. Maternal safety of the delayed-release doxylamine and pyridoxine combination for nausea and vomiting of pregnancy: A randomized placebo controlled trial. *BMC Pregnancy Childbirth*. 2015;15:59.
70. Abas MN, Tan PC, Azmi N, Omar SZ. Ondansetron compared with metoclopramide for hyperemesis gravidarum: A randomized controlled trial. *Obstet Gynecol*. 2014;123(6):1272–1279.

71. Tan PC, Khine PP, Vallikkannu N, Omar SZ. Promethazine compared with metoclopramide for hyperemesis gravidarum: A randomized controlled trial. *Obstet Gynecol*. 2010;115(5):975–981.
72. Bakhshi S, Batra A, Biswas B, et al. Aprepitant as an add-on therapy in children receiving highly emetogenic chemotherapy: A randomized, double-blind, placebo-controlled trial. *Support Care Cancer*. 2015;23:3229–3237.
73. Phenergan [package insert]. Philadelphia, PA. Wyeth Pharmaceuticals Inc. 2004.
74. Danewa AS, Shah D, Batra P, et al. Oral ondansetron in management of dehydrating diarrhea and vomiting in children aged 3 months to 5 years: A randomized controlled trial. *J Pediatr*. 2016;169:105–109.
75. Levine DA. Oral ondansetron decreases vomiting, as well as the need for intravenous fluids and hospital admission, in children with acute gastroenteritis. *Evid Based Med*. 2012;17(4):112–113.
76. American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2015;63(11):2227–2246.
77. Reuben DB, Herr KA, Pacala JT, et al. Geriatrics at Your Fingertips 2017. 19th ed. New York, NY: The American Geriatrics Society; 2017.

53

Diarrhea, Constipation, and Irritable Bowel Syndrome

Patricia H. Fabel and Kayce Shealy

KEY CONCEPTS

1. Diarrhea is caused by many viral and bacterial organisms. It is most often a minor discomfort, not life-threatening, and usually self-limited.
2. The four pathophysiologic mechanisms of diarrhea have been linked to the four broad diarrheal groups, which are secretory, osmotic, exudative, and altered intestinal transit. The three mechanisms by which absorption occurs from the intestines are active transport, diffusion, and solvent drag.
3. Management of diarrhea focuses on preventing excessive water and electrolyte losses, dietary care, relieving symptoms, treating curable causes, and treating secondary disorders.
4. Bismuth subsalicylate is marketed for indigestion, relieving abdominal cramps, and controlling diarrhea, including traveler's diarrhea, but may cause interactions with several components if given excessively.
5. Constipation is defined as difficult or infrequent passage of stool, at times associated with straining or a feeling of incomplete defecation.
6. Underlying causes of constipation should be identified when possible and corrective measures taken (eg, alteration of diet or treatment of diseases such as hypothyroidism).
7. The foundation of treatment of constipation is dietary fiber or bulk-forming laxatives that provide 20 to 25 g/day of raw fiber.
8. Irritable bowel syndrome (IBS) is one of the most common GI disorders characterized by lower abdominal pain, disturbed defecation, and bloating. Many non-GI manifestations also exist with IBS. Visceral hypersensitivity is a major culprit in the pathophysiology of the disease.

9. Diarrhea-predominant IBS should be managed by dietary modification and drugs such as loperamide when diet changes alone are insufficient to promote control of symptoms.
10. Several drug classes are involved in the treatment of the pain associated with IBS including tricyclic compounds and the gut-selective calcium channel blockers.

Preclass Engaged Learning Activity

A 5-year-old is prescribed PEG 3350 daily to treat and prevent constipation. The child's mother came across the following articles on social media yesterday:

- https://www.nytimes.com/2015/01/06/science/scrutiny-for-a-childhood-remedy.html?_r=0
- http://6abc.com/news/parents-say-over-the-counter-medicine-sickening-kids-/1753317/

She is very concerned about the safety of using this medication and would like your opinion. How does the information in these news articles compare to the information published in primary literature? How would you respond to the child's mother?

DIARRHEA

Diarrhea is a troublesome discomfort that affects most individuals in the United States at some point in their lives and can be thought of as both a symptom and a sign. Usually diarrheal episodes begin abruptly and subside within 1 or 2 days without treatment. This chapter focuses primarily on noninfectious diarrhea, with only minor reference to infectious diarrhea (see Chapter 131 for a discussion of gastrointestinal infections). Diarrhea is often a symptom of a systemic disease, and not all possible causes of diarrhea are discussed in this chapter. Acute diarrhea is commonly defined as less than 14 days' duration, persistent diarrhea as more than 14 days' duration, and chronic diarrhea as more than 30 days' duration.

To understand diarrhea, one must have a reasonable definition of the

condition; unfortunately, the literature is extremely variable on this. Simply put, diarrhea is an increased frequency and decreased consistency of fecal discharge as compared with an individual's normal bowel pattern. Frequency and consistency are variable within and between individuals. For example, some individuals defecate as often as three times per day, whereas others defecate only two or three times per week. A Western diet usually produces a daily stool weighing between 100 and 300 g, depending on the amount of nonabsorbable materials (mainly carbohydrates) consumed. Patients with serious diarrhea may have a daily stool weight in excess of 300 g; however, a subset of patients experience frequent small, watery passages. Additionally, vegetable fiber-rich diets, such as those consumed in some Eastern cultures (eg, those in Africa), produce stools weighing more than 300 g/day.

Diarrhea may be associated with a specific disease of the intestines or secondary to a disease outside the intestines. For instance, bacillary dysentery directly affects the gut, whereas diabetes mellitus causes neuropathic diarrheal episodes. Furthermore, diarrhea can be considered as acute or chronic disease. Infectious diarrhea is often acute; diabetic diarrhea is chronic. Congenital disorders in GI ion transport mechanisms are another cause of chronic diarrhea.[1] Whether acute or chronic, diarrhea has the same pathophysiologic causes that help in identification of specific treatments.

Epidemiology

The epidemiology of diarrhea varies in developed versus developing countries.[2] In the United States, diarrheal illnesses are usually not reported to the Centers for Disease Control and Prevention (CDC) unless associated with an outbreak or an unusual organism or condition. For example, the acquired immune deficiency syndrome (AIDS) has been identified with protracted diarrheal illness. Diarrhea is a major problem in daycare centers and nursing homes, probably because early childhood and senescence plus environmental conditions are risk factors. Although an exact epidemiologic profile in the United States is not available through the CDC or published literature, chronic diarrhea affects approximately 5% of the adult population and ranges from 3% to 20% in children worldwide.[2–4] In developing countries, diarrhea is a leading cause of illness and death in children, creating a tremendous economic strain on healthcare costs.

1 Most cases of acute diarrhea are caused by infections with viruses, bacteria, or protozoa and are generally self-limited.[5] Although viruses are more commonly associated with acute gastroenteritis, bacteria are responsible for

more cases of acute diarrhea. Evaluation of a noninfectious cause is considered if diarrhea persists and no infectious organism can be identified, or if the patient falls into a high-risk category for metabolic complications with persistent diarrhea. Common causative bacterial organisms include *Shigella*, *Salmonella*, *Campylobacter*, *Staphylococcus*, and *Escherichia coli*. Foodborne bacterial infection is a major concern, as several major food poisoning episodes have occurred that were traced to poor sanitary conditions in meat processing plants. Acute viral infections are attributed mostly to the Norwalk and rotavirus groups.

Physiology

In the fasting state, 9 L of fluid enters the proximal small intestine each day. Of this fluid, 2 L is ingested through diet, while the remainder consists of internal secretions. Because of meal content, duodenal chyme is usually hypertonic. When chyme reaches the ileum, the osmolality adjusts to that of plasma, with most dietary fat, carbohydrate, and protein being absorbed. The volume of ileal chyme decreases to about 1 L/day on entering the colon, which is further reduced by colonic absorption to 100 mL daily. If the small intestine water absorption capacity is exceeded, chyme overloads the colon, resulting in diarrhea. In humans, the colon absorptive capacity is about 5 L daily. Colonic fluid transport is critical to water and electrolyte balance.

Absorption of fluid from the intestines back into the blood occurs by three mechanisms: active transport, diffusion, and solvent drag. Active transport and diffusion are the mechanisms of sodium transport. Because of the high luminal sodium concentration (142 mEq/L [mmol/L]), sodium diffuses from the sodium-rich gut into epithelial cells, where it is actively pumped into the blood and exchanged with chloride to maintain an isoelectric condition across the epithelial membrane. Hydrogen ions are transported by an indirect mechanism in the upper small intestine. As sodium is absorbed, hydrogen ions are secreted into the gut. Hydrogen ions then combine with bicarbonate ions to form carbonic acid, which then dissociates into carbon dioxide and water. Carbon dioxide readily diffuses into the blood for expiration through the lung. The water remains in the chyme.

Paracellular pathways are major routes of ion movement. As ions, monosaccharides, and amino acids are actively transported, an osmotic pressure is created, drawing water and electrolytes across the intestinal wall. This pathway accounts for significant amounts of ion transport, especially sodium. Sodium plays an important role in stimulating glucose absorption. Glucose and amino acids are actively transported into the blood via a sodium-dependent cotransport mechanism. Cotransport absorption mechanisms of glucose–sodium

and amino acid–sodium are extremely important for treating diarrhea.

Gut motility influences absorption and secretion. The amount of time in which luminal content is in contact with the epithelium is under neural and hormonal control. Neurohormonal substances, such as angiotensin, vasopressin, glucocorticoid, aldosterone, and neurotransmitters, also regulate ion transport.

Pathophysiology

2 Four general pathophysiologic mechanisms disrupt water and electrolyte balance, leading to diarrhea, and are the basis of diagnosis and therapy. These are (a) a change in active ion transport by either decreased sodium absorption or increased chloride secretion; (b) change in intestinal motility; (c) increase in luminal osmolarity; and (d) increase in tissue hydrostatic pressure. These mechanisms have been related to four broad clinical diarrheal groups: secretory, osmotic, exudative, and altered intestinal transit.

Secretory diarrhea occurs when a stimulating substance either increases secretion or decreases absorption of large amounts of water and electrolytes. Substances that cause excess secretion include vasoactive intestinal peptide (VIP) from a pancreatic tumor, unabsorbed dietary fat in steatorrhea, laxatives, hormones (such as secretion), bacterial toxins, and excessive bile salts. Many of these agents stimulate intracellular cyclic adenosine monophosphate and inhibit Na^+/K^+-adenosine triphosphatase (ATPase), leading to increased secretion. Also, many of these mediators inhibit ion absorption simultaneously. Secretory diarrhea is recognized by large stool volumes (more than 1 L/day) with normal ionic contents and osmolality approximately equal to plasma. Fasting does not alter the stool volume in these patients.

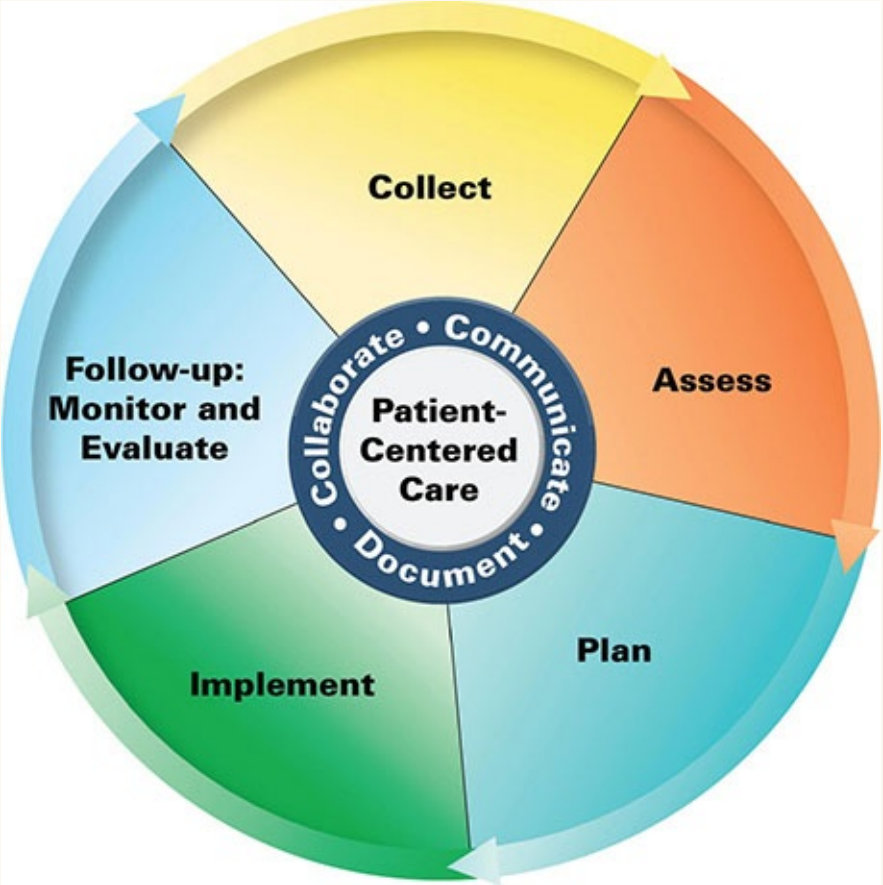
Poorly absorbed substances retain intestinal fluids, resulting in osmotic diarrhea. This process occurs with malabsorption syndromes, lactose intolerance, administration of divalent ions (eg, magnesium-containing antacids), or consumption of poorly soluble carbohydrate (eg, lactulose). As a poorly soluble solute is transported, the gut adjusts the osmolality to that of plasma; in so doing, water and electrolytes flux into the lumen. Clinically, osmotic diarrhea is distinguishable from other types, as it ceases if the patient resorts to a fasting state.

Inflammatory diseases of the GI tract discharge mucus, serum proteins, and blood into the gut. Sometimes bowel movements consist only of mucus, exudate, and blood. Exudative diarrhea affects other absorptive, secretory, or motility functions to account for the large stool volume associated with this disorder.

Altered intestinal motility produces diarrhea by three mechanisms: (1) reduction of contact time in the small intestine, (2) premature emptying of the colon, and (3) bacterial overgrowth. Chyme must be exposed to intestinal epithelium for a sufficient time period to enable normal absorption and secretion processes to occur. If this contact time decreases, diarrhea results. Intestinal resection or bypass surgery and drugs (such as metoclopramide) cause this type of diarrhea. On the other hand, an increased time of exposure allows fecal bacteria overgrowth. A characteristic small intestine diarrheal pattern is rapid, small, coupling bursts of waves. These waves are inefficient, do not allow absorption, and rapidly dump chyme into the colon. Once in the colon, chyme exceeds the colonic capability to absorb water.

Examination of the Stool

Stool characteristics are important in assessing the etiology of diarrhea. A description of the frequency, volume, consistency, and color provides diagnostic clues. For instance, diarrhea starting in the small intestine produces a copious, watery or fatty (greasy), and foul-smelling stool; contains undigested food particles; and is usually free from gross blood. Colonic diarrhea appears as small, pasty, and sometimes bloody or mucoid movements. Rectal tenesmus with flatus accompanies large intestinal diarrhea.



Patient Care Process for Diarrhea

Collect

- Patient characteristics
- Patient medical, family, social history, and dietary habits
- Current medications, including nonprescription
- Vital signs and weight
- Laboratory tests depending upon medical history and other presenting symptoms
  - Thyroid function tests, complete blood count, glucose, serum electrolytes

Assess

- Underlying causes of diarrhea (see **Tables 53-1** and **53-2**)

- Severity and duration of symptoms
- Patient preference for symptom resolution
- Ability/willingness to pay for treatment options

Plan*

- Treat specific cause of diarrhea (ie, diabetes, infectious, etc.)
- Increase fluid intake using oral rehydration solutions (**Table 53-3**)
- Antidiarrheal medication (**Table 53-4**)
- Monitor symptom resolution for efficacy, and pronounced constipation for safety
- Patient education regarding importance of prevention dehydration
- Referral to other providers when appropriate

Implement

- Educate the patient on all aspects of the treatment plan
- Schedule follow-up to monitor safety and efficacy of treatment plan

Follow-up: Monitor and Evaluate

- Determine resolution of diarrhea and related symptoms
- Evaluate for signs and symptoms of dehydration
- Assess for presence of adverse effects (eg, abdominal pain, constipation)
- Assess patient adherence to treatment plan
- Reevaluate periodically until resolution

*Collaborate with patient, caregivers, and other healthcare professionals.

Clinical Presentation

Table 53-1 outlines the clinical presentation of diarrhea, and Table 53-2 shows common drug-induced causes of diarrhea. A medication history is extremely important in identifying drug-induced diarrhea. Many agents, including antibiotics and other drugs, cause diarrhea or, less commonly, pseudomembranous colitis. Self-inflicted laxative abuse for weight loss is popular.

TABLE 53-1 Clinical Presentation of Diarrhea

General

- Usually, acute diarrheal episodes subside within 72 hours of onset, whereas chronic diarrhea involves frequent attacks over extended time periods

Signs and symptoms

- Abrupt onset of nausea, vomiting, abdominal pain, headache, fever, chills, and malaise
- Bowel movements are frequent and never bloody, and diarrhea lasts 12 to 60 hours
- Intermittent periumbilical or lower right quadrant pain with cramps and audible bowel sounds is characteristic of small intestinal disease
- When pain is present in large intestinal diarrhea, it is a gripping, aching sensation with tenesmus (straining, ineffective, and painful stooling). Pain localizes to the hypogastric region, right or left lower quadrant, or sacral region
- In chronic diarrhea, a history of previous bouts, weight loss, anorexia, and chronic weakness are important findings

Physical examination

- Typically demonstrates hyperperistalsis with borborygmi and generalized or local tenderness

Laboratory tests

- Stool analysis studies include examination for microorganisms, blood, mucus, fat, osmolality, pH, electrolyte and mineral concentration, and cultures
- Stool test kits are useful for detecting GI viruses, particularly rotavirus
- Antibody serologic testing shows rising titers over a 3- to 6-day period, but this test is not practical and is nonspecific
- Occasionally, total daily stool volume is also determined
- Direct endoscopic visualization and biopsy of the colon may be undertaken to assess for the presence of conditions such as colitis or cancer
- Radiographic studies are helpful in neoplastic and inflammatory conditions

TABLE 53-2 Drugs Causing Diarrhea

Laxatives
Antacids containing magnesium
Antineoplastics
Auranofin (gold salt)
Antibiotics
Clindamycin
Tetracyclines
Sulfonamides
Any broad-spectrum antibiotic
Antihypertensives
Reserpine
Guanethidine
Methyldopa
Guanabenz
Guanadrel
Angiotensin-converting enzyme inhibitors
Cholinergics
Bethanechol
Neostigmine
Cardiac agents
Quinidine
Digitalis
Digoxin
Nonsteroidal anti-inflammatory drugs
Misoprostol
Colchicine
Proton pump inhibitors
H_2-receptor blockers

Most acute diarrhea is self-limiting, subsiding within 72 hours. However, infants, young children, the elderly, and debilitated persons are at risk for morbid and mortal events in prolonged or voluminous diarrhea. These groups are at risk for water, electrolyte, and acid–base disturbances, and potentially cardiovascular collapse and death. The prognosis for chronic diarrhea depends on the cause; for example, diarrhea secondary to diabetes mellitus waxes and wanes throughout life.

TREATMENT

Diarrhea

Prevention

Acute viral diarrheal illness often occurs in daycare centers and nursing homes. Because person-to-person contact is the mechanism by which viral disease spreads, isolation techniques must be initiated. For bacterial, parasitic, and protozoal infections, strict food handling, sanitation, water, and other environmental hygiene practices can prevent transmission. If diarrhea is secondary to another illness, controlling the primary condition is necessary. Antibiotics and bismuth subsalicylate are advocated to prevent traveler's diarrhea, in conjunction with treatment of drinking water and caution with consumption of fresh vegetables.[6,7]

Desired Outcome

3 If prevention is unsuccessful and diarrhea occurs, therapeutic goals are to (a) manage the diet; (b) prevent excessive water, electrolyte, and acid–base disturbances; (c) provide symptomatic relief; (d) treat curable causes; and (e) manage secondary disorders causing diarrhea (**Figs. 53-1** and **53-2**).

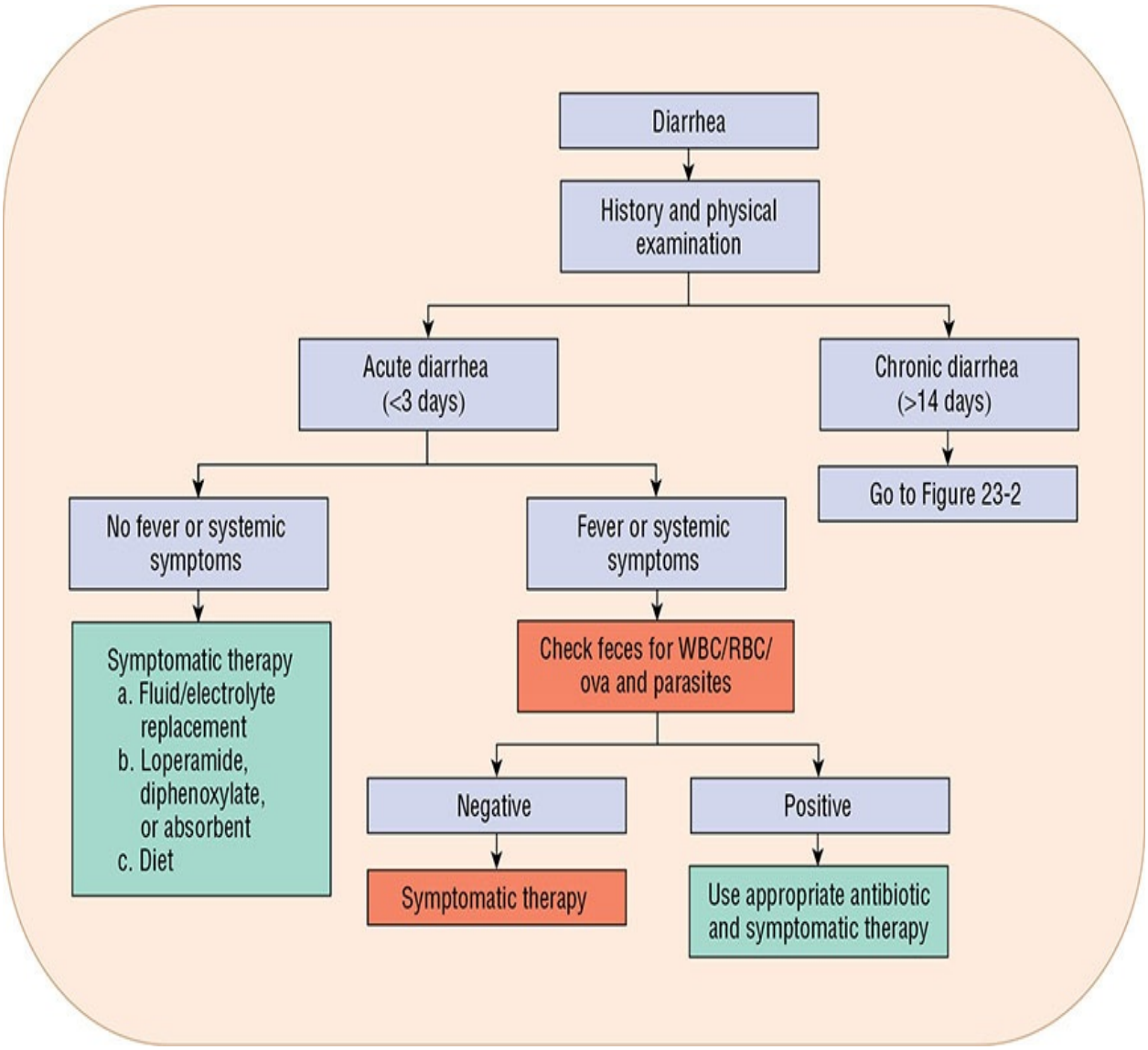


FIGURE 53-1 Recommendations for treating acute diarrhea. Follow the following steps: (a) Perform a complete history and physical examination. (b) Is the diarrhea acute or chronic? If chronic diarrhea, go to Fig. 53-2. (c) If acute diarrhea, check for fever and/or systemic signs and symptoms (ie, toxic patient). If systemic illness (fever, anorexia, or volume depletion), check for an infectious source. If positive for infectious diarrhea, use appropriate antibiotic/anthelmintic drug and symptomatic therapy. If negative for infectious cause, use only symptomatic treatment. (d) If no systemic findings, then use symptomatic therapy based on severity of volume depletion, oral or parenteral fluid/electrolytes, antidiarrheal agents (see Table 53-4), and diet (RBC, red blood cells; WBC, white blood cells).

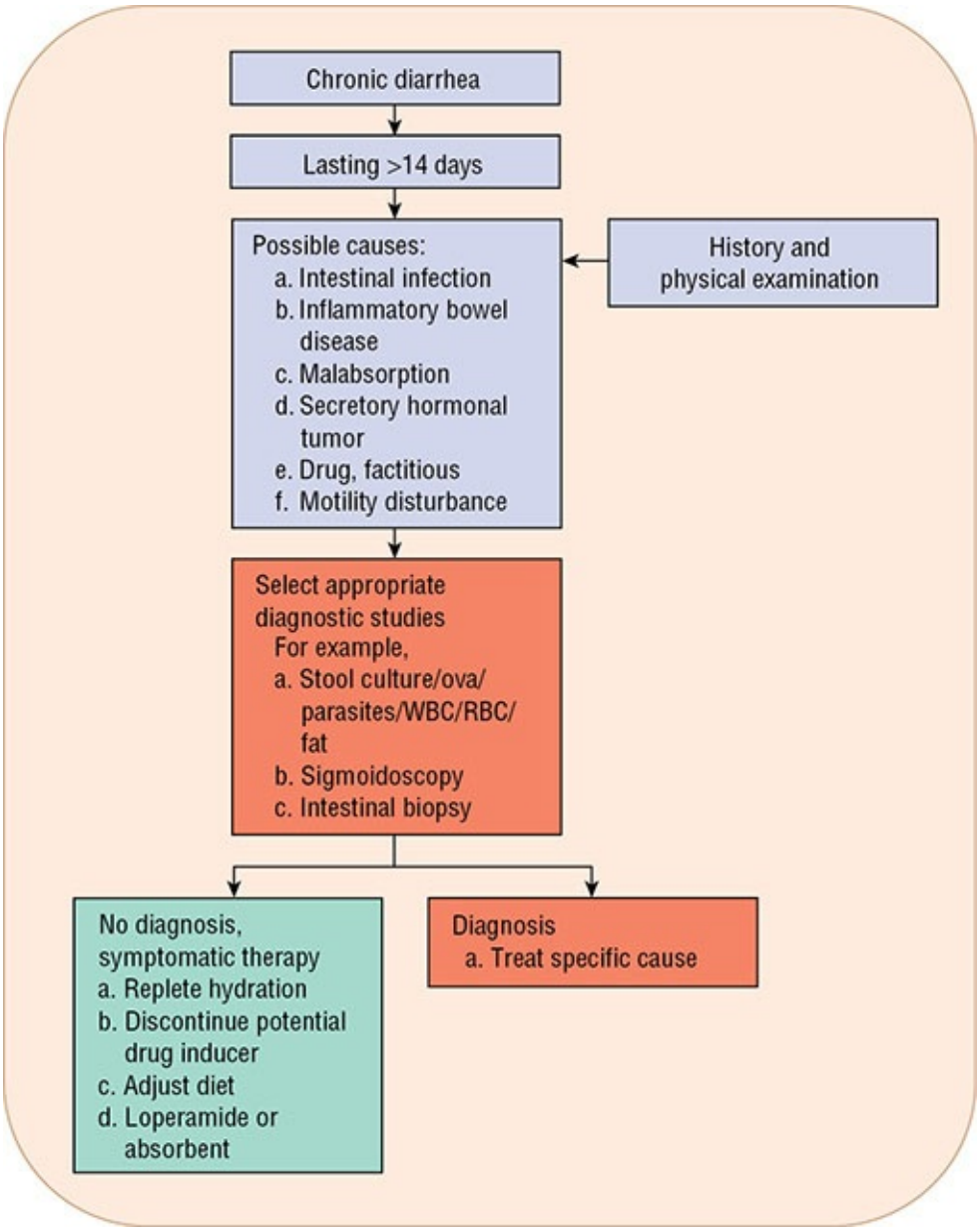


FIGURE 53-2 Recommendations for treating chronic diarrhea. Follow the following steps: (a) Perform a careful history and physical examination. (b) The possible causes of chronic diarrhea are many. These can be classified into intestinal infections (bacterial or protozoal), inflammatory disease (Crohn's disease or ulcerative colitis), malabsorption (lactose intolerance), secretory hormonal tumor (intestinal carcinoid tumor or vasoactive intestinal peptide-secreting tumor [VIPoma]), drug (antacid), factitious (laxative abuse), or motility disturbance (diabetes mellitus, irritable bowel syndrome, or hyperthyroidism). (c) If the diagnosis is uncertain, selected appropriate diagnostic studies should be ordered. (d) Once diagnosed, treatment is planned for the underlying cause with symptomatic antidiarrheal therapy. (e) If no

specific cause can be identified, symptomatic therapy is prescribed (RBC, red blood cells; WBC, white blood cells).

Clinicians must clearly understand that diarrhea, like a cough, may be a body defense mechanism for ridding itself of harmful substances or pathogens. The correct therapeutic response is not necessarily to stop diarrhea at all costs.

Nonpharmacologic Management

Dietary management is a first priority in the treatment of diarrhea. Feeding should continue in children with acute bacterial diarrhea. Fed children have less morbidity and mortality, whether or not they receive oral rehydration fluids. Studies are not available in the elderly or in other high-risk groups to determine the value of continued feeding in bacterial diarrhea.

Water and Electrolytes

Rehydration and maintenance of water and electrolytes are primary treatment goals until the diarrheal episode ends. If the patient is volume depleted, rehydration should be directed at replacing water and electrolytes to normal body composition. Then water and electrolyte composition are maintained by replacing losses. Many patients will not develop volume depletion and therefore will only require maintenance fluid and electrolyte therapy. Parenteral and enteral routes may be used for supplying water and electrolytes. If vomiting and dehydration are not severe, enteral feeding is the less costly and preferred method. In the United States, many commercial oral rehydration preparations are available (Table 53-3).

TABLE 53-3 Oral Rehydration Solutions

	WHO-ORSYT[a]	Pedialyte[b] (Ross)	CeraLyte (Cera Products)	Enfalyte (Mead Johnson)
Osmolality (mOsm/kg or mmol/kg)	245	250	220	167
Carbohydrates[b] (g/L)	13.5	25	40[c]	30[c]
Calories (cal/L [J/L])	65 (272)	100 (418)	160 (670)	126 (527)
Electrolytes (mEq/L; mmol/L)				
Sodium	75	45	50-90	50
Potassium	20	20	20	25
Chloride	65	35	40-80	45
Citrate	—	30	30	34
Bicarbonate	30	—	—	—
Calcium	—	—	—	—
Magnesium	—	—	—	—
Sulfate	—	—	—	—
Phosphate	—	—	—	—

[a]World Health Organization reduced osmolarity oral rehydration solution.

[b]Carbohydrate is glucose.

[c]Rice syrup solids are carbohydrate source.

Because of concerns about hypernatremia, physicians continue to hospitalize patients and use IV fluids to correct fluid and electrolyte deficits in severe dehydration. Oral solutions are strongly recommended.[8–10] In developing countries, the World Health Organization oral rehydration solution (WHO-ORS) saves the lives of millions of children annually.

During diarrhea, the small intestine retains its ability to actively transport monosaccharides such as glucose. Glucose actively carries sodium with water and other electrolytes. The WHO now recommends an ORS with a lower osmolarity, sodium content, and glucose load (see Table 53-3).[11] A separate oral supplement of zinc 20 mg daily for 10 days in addition to ORS significantly reduces the severity and duration of acute diarrhea in developing countries.[2] ORS is a lifesaving treatment for millions afflicted in developing countries. Acceptance in developed countries is less enthusiastic; however, the advantage of this product in reducing hospitalizations may prove its use as a cost-effective alternative, saving millions of dollars in healthcare expenditures.

Pharmacologic Therapy

Various drugs have been used to treat diarrheal attacks (Table 53-4), including antimotility agents, adsorbents, antisecretory compounds, antibiotics, enzymes, and intestinal microflora. Usually these drugs are not curative but palliative.

TABLE 53-4 Selected Antidiarrheal Preparations

	Dose Form	Adult Dose
Antimotility		
Diphenoxylate	2.5 mg/tablet 2.5 mg/5 mL	5 mg four times daily; do not exceed 20 mg/day
Loperamide	2 mg/capsule	Initially 4 mg, and then 2 mg after each loose stool; do not exceed 16 mg/day
Paregoric	2 mg/5 mL (morphine)	5-10 mL one to four times daily
Opium tincture	10 mg/mL (morphine)	0.6 mL four times daily
Difenoxin	1 mg/tablet	Two tablets, and then one tablet after each loose stool; up to eight tablets per day
Adsorbents		
Kaolin-pectin mixture	5.7 g kaolin + 130.2 mg pectin/30 mL	30-120 mL after each loose stool
Polycarbophil	500 mg/tablet	Chew 2 tablets four times daily or after each loose stool; do not exceed 12 tablets per day
Attapulgite	750 mg/15 mL 300 mg/7.5 mL 750 mg/tablet 600 mg/tablet 300 mg/tablet	1,200-1,500 mg after each loose bowel movement or every 2 hours; up to 9,000 mg/day
Antisecretory		
Bismuth subsalicylate	1,050 mg/30 mL 262 mg/15 mL 524 mg/15 mL 262 mg/tablet	Two tablets or 30 mL every 30 minutes to 1 hour as needed up to eight doses per day
Enzymes (lactase)		
	1,250 neutral lactase units/4 drops	Three to four drops taken with milk or dairy product
	3,300 FCC lactase units per tablet	
Bacterial replacement (*Lactobacillus acidophilus*, *Lactobacillus bulgaricus*)		Two tablets or one granule packet three to four times daily; give with milk, juice, or water
Octreotide	0.05 mg/mL 0.1 mg/mL 0.5 mg/mL	Initial: 50 mcg subcutaneously One to two times per day and titrate dose based on indication up to 600 mcg/day in two to four divided doses

Opiates and Their Derivatives

Opiates and opioid derivatives (a) delay the transit of intraluminal contents or (b) increase gut capacity, prolonging contact and absorption. Enkephalins, which are endogenous opioid substances, regulate fluid movement across the mucosa by stimulating absorptive processes. Limitations to the use of opiates include an addiction potential (a real concern with long-term use) and worsening of diarrhea in selected infectious diarrhea.

Most opiates act through peripheral and central mechanisms with the exception of loperamide, which acts only peripherally. Loperamide is antisecretory; it inhibits the calcium-binding protein calmodulin, controlling chloride secretion. Loperamide, available as 2 mg capsules or 1 mg/5 mL solution (both are nonprescription products), is suggested for managing acute and chronic diarrhea. The usual adult dose is initially 4 mg orally, followed by 2 mg after each loose stool, up to 16 mg/day. Used correctly, this agent has rare side effects, such as dizziness and constipation. If the diarrhea is concurrent with a high fever or bloody stool, the patient should be referred to a physician. Also, diarrhea lasting 48 hours beyond initiating loperamide warrants medical attention. Loperamide can also be used in traveler's diarrhea. It is comparable to bismuth subsalicylate for treatment of this disorder.[6] The FDA has released a warning about using high doses of loperamide for euphoria as it can lead to serious side effects including cardiovascular problems.[12] The packaging of loperamide has been reduced to minimize abuse.[13]

Diphenoxylate is available as a 2.5 mg tablet and as a 2.5 mg/5 mL solution. A small amount of atropine (0.025 mg) is included in the product to discourage abuse. In adults, when taken as 2.5 to 5 mg three or four times daily, not to exceed a 20 mg total daily dose, diphenoxylate is rarely toxic. Some patients may complain of atropinism (blurred vision, dry mouth, and urinary hesitancy). Like loperamide, it should not be used in patients who are at risk of bacterial enteritis with *E. coli*, *Shigella,* or *Salmonella*.

Difenoxin, a diphenoxylate derivative also chemically related to meperidine, is also combined with atropine and has the same uses, precautions, and side effects. Marketed as a 1 mg tablet, the adult dosage is 2 mg initially, followed by 1 mg after each loose stool, not to exceed 8 mg/day.

Paregoric, camphorated tincture of opium, is marketed as a 2 mg/5 mL solution and is indicated for managing both acute and chronic diarrhea. It is not widely prescribed today because of its abuse potential.

Adsorbents

Adsorbents are used for symptomatic relief. These products, many not requiring a prescription, are nontoxic, but their effectiveness remains unproven. Adsorbents are nonspecific in their action; they adsorb nutrients, toxins, drugs, and digestive juices. Polycarbophil absorbs 60 times its weight in water and can be used to treat both diarrhea and constipation. It is a nonprescription product and is sold as a 500 mg chewable tablet. This hydrophilic, nonabsorbable product is safe and may be taken four times daily, up to 6 g/day in adults. See Table 53-4 for selected antidiarrheal preparations.

Antisecretory Agents

Bismuth subsalicylate appears to have antisecretory, anti-inflammatory, and antibacterial effects. As a nonprescription product, it is marketed for indigestion, relieving abdominal cramps, and controlling diarrhea, including traveler's diarrhea. Bismuth subsalicylate dosage strengths are a 262 mg chewable tablet, 262 mg/5 mL liquid, and 524 mg/15 mL liquid. The usual adult dose is two tablets or 30 mL every 30 minutes to 1 hour up to eight doses per day.

4 Bismuth subsalicylate contains multiple components that might be toxic if given in excess to prevent or treat diarrhea. For instance, an active ingredient is salicylate, which may interact with anticoagulants or may produce salicylism (tinnitus, nausea, and vomiting). Bismuth reduces tetracycline absorption and may interfere with select GI radiographic studies. Patients may complain of a darkening of the tongue and stools with repeat administration. Salicylate can induce gout attacks in susceptible individuals.

Bismuth subsalicylate suspension is useful in the treatment of secretory diarrhea of infectious etiology as well. With a dose of 30 mL every 30 minutes for eight doses, unformed stools decrease in the first 24 hours. Bismuth subsalicylate may also be effective in preventing traveler's diarrhea.

Octreotide, a synthetic octapeptide analog of endogenous somatostatin, is effective for the symptomatic treatment of carcinoid tumors and other peptide-secreting tumors, dumping syndrome, and chemotherapy-induced diarrhea.[14] It has had limited success in patients with AIDS-associated diarrhea and short-bowel syndrome, does not appear to have an advantage over various opiate derivatives in the treatment of chronic idiopathic diarrhea, and has the disadvantage of being administered by injection.[15] Metastatic intestinal carcinoid tumors secrete excessive amounts of vasoactive substances, including histamine, bradykinin, serotonin (5-hydroxytryptamine, 5-HT), and prostaglandins. Primary

carcinoid tumors occur throughout the GI tract, with most in the ileum. Predominant signs and symptoms experienced by patients with these tumors are attributable to excessive concentrations of 5-hydroxytryptophan and 5-HT. The totality of their clinical effects is termed the carcinoid syndrome. Some patients have a violent, watery diarrhea with abdominal cramping. Initially, diarrhea might be managed with various agents such as codeine, diphenoxylate, cyproheptadine, methysergide, phenoxybenzamine, or methyldopa. But octreotide is now considered first-line therapy for carcinoid syndrome.

Octreotide blocks the release of 5-HT and many other active peptides and has been effective in controlling diarrhea and flushing. It is reported to have direct inhibitory effects on intestinal secretion and stimulatory effects on intestinal absorption. Non–gastrin-secreting adenomas of the pancreas are tumors associated with profuse watery diarrhea. This condition has been referred to as Verner–Morrison syndrome, WDHA (watery diarrhea, hypokalemia, and achlorhydria) syndrome, pancreatic cholera, watery diarrhea syndrome, and vasoactive intestinal peptide-secreting tumor (VIPoma). Excessive secretion of VIP from a retroperitoneal or pancreatic tumor produces most of the clinical features. Surgical tumor dissection is the treatment of choice. In nonsurgical candidates, the profuse watery diarrhea and other symptoms commonly encountered are managed with octreotide.

The dose of octreotide varies with the indication, disease severity, and patient response.[14] For managing diarrhea and flushing associated with carcinoid tumors in adults, the initial dosage range is 100 to 600 mcg/day in two to four divided doses subcutaneously for 2 weeks. For controlling secretory diarrhea of VIPomas, the dosage range is 200 to 300 mcg/day in two to four divided doses for 2 weeks. Some patients may require higher doses for symptomatic control. Patients responding to these initial doses may be switched to Sandostatin LAR Depot, a long-acting octreotide formulation. Initial doses consist of 20 mg given intramuscularly intragluteally at 4-week intervals for 2 months. During the first 2 weeks of therapy the short-acting formulation should be administered subcutaneously. At the end of 2 months, patients with good symptom control may have the dose reduced to 10 mg every 4 weeks, while those without sufficient symptom control may have the dose increased to 30 mg every 4 weeks. For patients experiencing recurrence of symptoms on the 10 mg dose, dosage adjustment to 20 mg should be made. Patients with carcinoid tumors or VIPomas may experience periodic exacerbation of symptoms. Subcutaneous octreotide for several days should be reinstituted in these individuals. In so-called carcinoid crisis, octreotide is given as an IV infusion at 50 mcg/h for 8 to

24 hours.

Because octreotide inhibits many other GI hormones, it has a variety of intestinal side effects. With prolonged use, gallbladder and biliary tract complications such as cholelithiasis may occur. Approximately 5% to 10% of patients complain of nausea, diarrhea, and abdominal pain. Local injection pain occurs with about an 8% incidence. With high doses, octreotide may reduce dietary fat absorption, leading to steatorrhea.

Two other somatostatin analogs, lanreotide and vapreotide, have been studied.[15,16] Lanreotide is approved for use in the United States for acromegaly. The starting dose is 90 mg subcutaneously every 4 weeks for 3 months, and then the dose is adjusted based on growth hormone and insulin-like growth factor levels.[17] Vapreotide is an orphan drug that is indicated for pancreatic and GI fistulas as well as esophageal variceal bleeding.

Miscellaneous Products

Probiotics are microorganisms given to reestablish normal colonic microflora. This supposedly restores normal intestinal function and suppresses the growth of pathogenic microorganisms. *Saccharomyces boulardii*, *Lactobacillus* GG, and *Lactobacillus acidophilus* decrease the duration of infectious and antibiotic-induced diarrhea in adults and children.[18] Probiotics may prevent antibiotic-associated diarrhea (AAD).[19] However, a randomized control trial in hospitalized patients over the age of 65 years found no difference in cases of AAD between a probiotic preparation (two strains of lactobacillus acidophilus and Bifidobacterium) and placebo.[20] The dosage of probiotic preparations varies depending on the brand used. Intestinal flatus is the primary patient complaint experienced with this modality.

Anticholinergic drugs such as atropine block vagal tone and prolong gut transit time. Drugs with anticholinergic properties are present in many nonprescription products. Their value in controlling diarrhea is questionable and limited because of side effects. Angle-closure glaucoma, selected heart diseases, and obstructive uropathies are relative contraindications to the use of anticholinergic agents.

Lactase enzyme products are helpful for patients who are experiencing diarrhea secondary to lactose intolerance. Lactase is required for carbohydrate digestion. When a patient lacks this enzyme, eating dairy products causes an osmotic diarrhea. Several products are available for use each time a dairy product, especially milk or ice cream, is consumed.

Vaccines

Vaccines are a new therapeutic frontier in controlling infectious diarrheas, especially in developing countries.[21] An oral vaccine for cholera (Vaxchora®) is licensed and available in the United States. The Advisory Committee for Immunization Practices (ACIP) recommends the vaccine for adults aged 18-64 years old who are traveling to an endemic area.[22] The vaccine can reduce the risk of severe diarrhea by about 90%.[23]

Oral *Shigella* vaccine, although effective under field conditions, requires five weekly oral doses and repeat booster doses, thereby limiting its practicality for use in developing nations. With about 1,500 serotypes for *Salmonella*, a vaccine is not currently available for humans. There are two newer typhoid vaccine formulations, one a parenteral inactivated whole-cell vaccine and the other an oral live-attenuated (Ty21a) vaccine that is administered in four doses on days 1, 3, 5, and 7, to be completed at least 1 week before exposure. Two rotavirus vaccines prevent gastroenteritis due to rotavirus infection in infants and children.[23] The pentavalent human-bovine reassortant vaccine (RotaTeq from Merck) is administered as a three-oral-dose sequence, and the monovalent human vaccine (Rotarix from GlaxoSmithKline) is administered as a two-oral-dose sequence. A rotavirus vaccine program has been established to reduce child morbidity and mortality from diarrheal disease by accelerating the availability of rotavirus vaccines appropriate for use in developing countries.

Evaluation of Therapeutic Outcomes

Therapeutic outcomes are directed toward key symptoms, signs, and laboratory studies. Constitutional symptoms usually improve within 24 to 72 hours. Monitoring for changes in the frequency and character of bowel movements on a daily basis in conjunction with vital signs and improvement in appetite are of utmost importance. Also, the clinician needs to monitor body weight, serum osmolality, serum electrolytes, complete blood cell counts, urinalysis, and culture results (if appropriate).

Acute Diarrhea

Most patients with acute diarrhea experience mild-to-moderate distress. In the absence of moderate-to-severe dehydration, high fever, and blood or mucus in the stool, this illness is usually self-limiting within 3 to 7 days. Mild-to-moderate acute diarrhea is usually managed on an outpatient basis with oral rehydration,

symptomatic treatment, and diet. Elderly persons with chronic illness as well as infants may require hospitalization for parenteral rehydration and close monitoring.

Severe Diarrhea

In the urgent/emergent situation, restoration of the patient's volume status is the most important outcome. Toxic patients (fever dehydration, hematochezia, or hypotension) require hospitalization, IV fluids and electrolyte administration, and empiric antibiotic therapy while awaiting culture and sensitivity results. With timely management, these patients usually recover within a few days.

CONSTIPATION

5 Constipation is a common complaint among the general population and accounts for many medical visits each year in the United States.[24] It is generally defined by the American Gastroenterology Association (AGA) as difficult or infrequent passage of stool, at times associated with straining or a feeling of incomplete defecation.[25]

Constipation may be further defined by quantitative or qualitative measures. For instance, physicians often use stool frequency to define constipation (most commonly fewer than three bowel movements per week); however, the "normal" frequency of bowel movement is not well established and can vary from person to person. Patients more often describe constipation in terms of symptoms or a combination of quantitative and qualitative descriptors that are difficult to quantify: bowel movement frequency, stool size or consistency (hard or lumpy stools), straining on defecation, inability to defecate at will, and symptoms such as sensation of incomplete evacuation. The condition is considered chronic if symptoms last for at least 3 months. Many people believe that daily bowel movements are required for normal health or that accumulation of toxic substances will occur with infrequent defecation. Inappropriate laxative use by the general public may result from these misconceptions.

Though often considered more of a minor uncomfortable or unpleasant problem, constipation can have serious consequences and be costly to the healthcare system. Costs for medical evaluation of constipation alone have been estimated at more than $2,500 per patient, and patients spend more than $800 million each year on nonprescription laxatives.[24,26]

Epidemiology

The prevalence of constipation depends on the definition used and whether the condition is self-reported or provider-diagnosed. The prevalence of chronic constipation in adults (elder than or equal to 15 years old) worldwide is 14%.[25] The highest incidence was found in South America (16%) and the lowest incidence in Southeast Asia. In North America the prevalence was up to 27%, with most reported estimates ranging from 12% to 19%.[27]

Constipation is more common in women (2.4-fold more likely) and the elderly.[25] Other factors associated with constipation in some reports include inactivity, lower socioeconomic class, lower income, non-white race, symptoms of depression, and history of physical or sexual abuse.

Pathophysiology

Constipation may be primary or secondary. Primary, or idiopathic, constipation occurs without an identifiable underlying cause, whereas secondary constipation may be the result of constipating drugs, lifestyle factors, or medical disorders (**Table 53-5**).[25] Primary constipation can be further divided into three categories —normal transit, slow transit, and pelvic floor dysfunction, or disordered defecation.[28] Normal transit constipation, often referred to as functional, is the most common type. These patients have normal GI motility and stool frequency but may experience difficulty evacuating, passage of hard stools, or bloating and abdominal discomfort. Slow transit constipation represents an abnormality of GI transit time that leads to infrequent defecation. Dysfunction of the pelvic floor muscles and/or anal sphincter is the most frequently encountered reason for disordered defecation. In patients with defecatory disorders, these muscles or sphincter contract during defecation instead of relax and impede evacuation of stool. It is common for patients to have and present with more than one type of constipation.

TABLE 53-5 Possible Causes of Constipation

Conditions	Possible Causes
GI disorders	Irritable bowel syndrome Diverticulitis Upper GI tract diseases Anal and rectal diseases Hemorrhoids Anal fissures Ulcerative proctitis Tumors Hernia Volvulus of the bowel Syphilis Tuberculosis Helminthic infections Lymphogranuloma venereum Hirschsprung's disease
Metabolic and endocrine disorders	Diabetes mellitus with neuropathy Hypothyroidism Panhypopituitarism Pheochromocytoma Hypercalcemia Enteric glucagon excess
Cardiac disorders	Heart failure
Pregnancy	Depressed gut motility Increased fluid absorption from colon Use of iron salts
Lifestyle factors	Dietary changes Inadequate fluid intake Low dietary fiber Decreased physical activity
Neurogenic causes	CNS diseases Trauma to the brain (particularly the medulla) Spinal cord injury CNS tumors Cerebrovascular accidents Parkinson's disease
Psychogenic causes	Ignoring or postponing urge to defecate Psychiatric diseases
Drug induced	See Table 53-6

Factors associated with the increased prevalence of constipation in the elderly include a higher number of daily medications, particularly anticholinergic agents, increased incidence of chronic comorbidities, and changes in mobility status.[26] Changes in diet such as decreased fluid and/or fiber intake, diminished physical activity, and institutionalization can lead to constipation. Physiologic changes such as mesenteric dysfunction and changes in anorectal function, including loss of rectal wall elasticity, are also thought to predispose elderly patients to constipation.

Drug-Induced Constipation

Use of drugs that inhibit the neurologic or muscular function of the GI tract, particularly the colon, may result in secondary constipation.[25] Medications that are commonly associated with causing constipation include opiates, anticholinergic agents, and certain antacids.[26] With most of the agents listed in Table 53-6, the inhibitory effects on bowel function may be dose dependent, with larger doses causing constipation more frequently.

TABLE 53-6 Drugs Causing Constipation

Analgesics
Inhibitors of prostaglandin synthesis
Opiates
Anticholinergics
Antihistamines
Antiparkinsonian agents (eg, benztropine or trihexyphenidyl)
Phenothiazines
Tricyclic antidepressants
Antacids containing calcium carbonate or aluminum hydroxide
Barium sulfate
Calcium channel antagonists
Clonidine
Diuretics (non–potassium-sparing)
Ganglionic blockers
Iron preparations
Muscle blockers (d-tubocurarine, succinylcholine)
Nonsteroidal anti-inflammatory agents
Polystyrene sodium sulfonate

Opiates have effects on all segments of the bowel, but effects are most pronounced on the colon.[23] The major mechanism by which opiates produce constipation has been proposed to be prolongation of intestinal transit time by causing spastic, nonpropulsive contractions. Additionally, anal sphincter tone

may be increased with an accompanying decrease in reflex relaxation leading to difficult rectal evacuation.[29]

While all opiate derivatives are associated with constipation, the degree of intestinal inhibitory effects seems to differ between agents. Orally administered opiates appear to have greater inhibitory effects than parenterally administered products.

Other medications may increase the risk of constipation by a variety of mechanisms. Anticholinergic agents decrease contractility of intestinal muscle while calcium channel blockers are thought to cause rectosigmoid dysfunction, leading to constipation. Nonsteroidal anti-inflammatory drugs (NSAIDs) may lead to constipation due to their inhibition of prostaglandin synthesis.[26]

Clinical Presentation

A symptom-based system for classifying functional constipation (and other functional GI disorders) is often used to define constipation in clinical trials. The Rome criteria encompass both quantitative (frequency) and qualitative (stool consistency, etc.) symptoms associated with constipation.[30]**Table 53-7** outlines general clinical presentation of patients with constipation. According to the Rome IV criteria, patients should have at least two of the signs and symptoms listed in Table 53-7 apply to a minimum of 25% of bowel movements.

TABLE 53-7 Clinical Presentation of Constipation

Signs and symptoms

- Infrequent bowel movements (<3 per week)
- Stools that are hard, small, or dry
- Straining
- Feeling of incomplete evacuation
  - Feeling of anorectal obstruction or blockage
  - Physical tactics needed for defecation
  - Loose stools rarely occur without laxative use

Alarm signs and symptoms

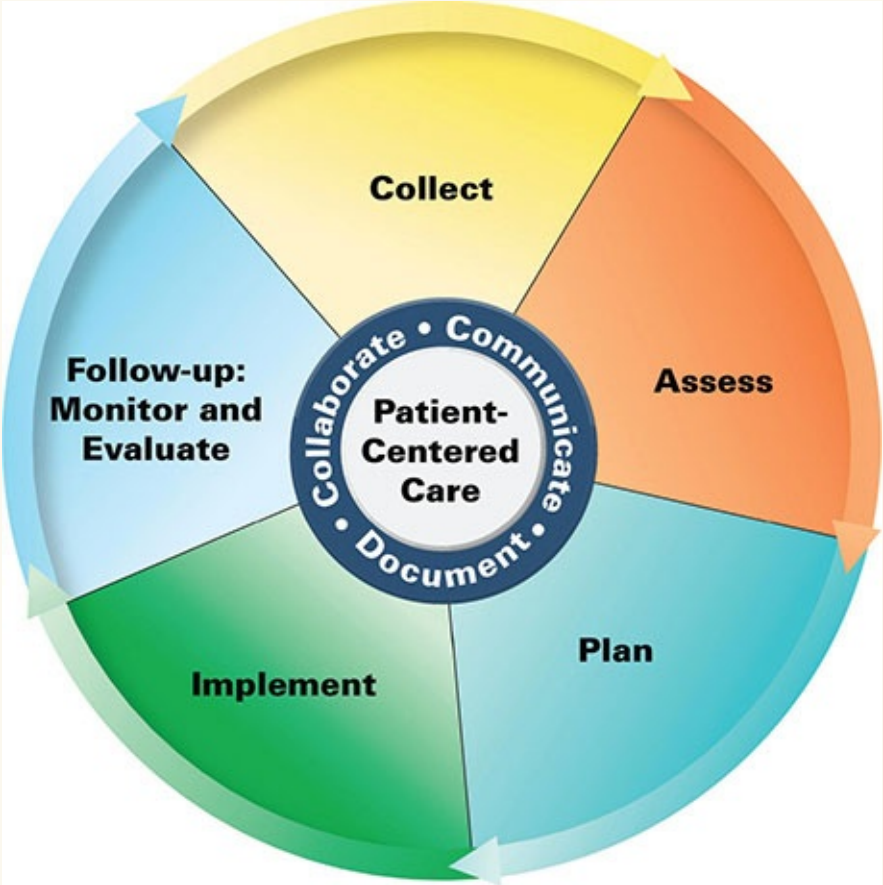
- Hematochezia
- Melena
- Family history of colon cancer
- Family history of inflammatory bowel disease
- Anemia
- Weight loss
- Anorexia
- Nausea and vomiting
- Severe, persistent constipation that is refractory to treatment
- New-onset or worsening constipation in elderly without evidence of primary cause

Physical examination

- Perform rectal exam for presence of anatomical abnormalities (such as fistulas, fissures, hemorrhoids, rectal prolapse) or abnormalities of perianal descent
- Digital examination of rectum to check for fecal impaction, anal stricture, or rectal mass

Laboratory and other diagnostic tests

- No routine recommendations for lab testing—as indicated by clinical discretion
- In patients with signs and symptoms suggestive of organic disorder, specific testing may be performed (ie, thyroid function tests, electrolytes, glucose, complete blood count) based on clinical presentation
- In patients with alarm signs and symptoms or when structural disease is a possibility, select appropriate diagnostic studies:
  1. Protoscopy
  2. Sigmoidoscopy
  3. Colonoscopy
  4. Barium enema



Patient Care Process for Constipation

Collect

- Patient characteristics
- Patient medical, social, and family history including dietary habits
- Current medications, including nonprescription
- Vital signs and weight
- Laboratory tests depending upon medical history and other presenting symptoms
  - Thyroid function tests, complete blood count, glucose, serum electrolytes

Assess

- Underlying causes of constipation (see Tables 53-5 and 53-6)

- Presence of alarm symptoms (Table 53-7)
- Severity of symptoms
- Patient preference for symptom resolution
- Ability/willingness to pay for treatment options

Plan*

- Treat specific cause of constipation (ie, thyroid dysfunction, etc.)
- Dietary modification to increase fiber (Fig. 53-3)
- Laxative or cathartic option if quick resolution desired and no contraindications (Fig. 53-3; Table 53-8)
- Other pharmacologic therapy (Fig. 53-3; Table 53-8)
- Monitor symptom resolution for efficacy, and pronounced diarrhea for safety
- Patient education regarding lifestyle and dietary modifications, drug-specific information, etc.
- Referral to other providers when appropriate (unresolved symptoms or alarm symptoms present)

Implement

- Educate the patient on all aspects of the treatment plan
- Schedule follow-up to monitor safety and efficacy of treatment plan

Follow-up: Monitor and Evaluate

- Determine resolution of constipation and related symptoms
- Assess for presence of adverse effects (eg, abdominal pain, diarrhea)
- Assess patient adherence to treatment plan
- Reevaluate periodically until resolution

*Collaborate with patient, caregivers, and other healthcare professionals.

Evaluation of constipation should attempt to clarify the patient's specific symptoms (ie, exactly what the patient means by constipation).[31] A complete and thorough history should be obtained from the patient, including frequency of bowel movements and duration of symptoms. Constipation occurring abruptly in

an adult may indicate significant colon pathology such as malignancy. Constipation present since early infancy may be indicative of neurologic disorders. The patient should also be carefully questioned about usual diet and laxative regimens. Does the patient have a diet consistently deficient in high-fiber items and containing mainly high refined foods? What laxatives or cathartics has the patient used to attempt relief of constipation? The patient should be questioned about other concurrent medications, with interest focused on agents that might cause constipation.

Evaluation should also include perianal and anal examinations to identify fecal impaction or other anatomical obstructions that may be contributing to or causing constipation. General health status, signs of underlying medical illness (ie, hypothyroidism), and psychological status (eg, depression or other psychological illness) should also be assessed. Laboratory tests may be performed, particularly if the patient is presumed to suffer from secondary causes and is still experiencing symptoms after a trial of fiber supplementation or other nonprescription therapies.[25]

Specific attention should be given to identify any “alarm symptoms” that would warrant further diagnostic workup (see Table 53-7).[25,31,32] Patients with alarm symptoms, a family history of colon cancer, or those more than 50 years old with new symptoms may need further diagnostic evaluation.

TREATMENT

Constipation

Desired Outcome

The major goals of treatment are to (a) relieve symptoms; (b) reestablish normal bowel habits; and (c) improve quality of life by minimizing adverse effects of treatment.

General Approach to Treatment

Figure 53-3 presents a general treatment algorithm for the management of constipation.

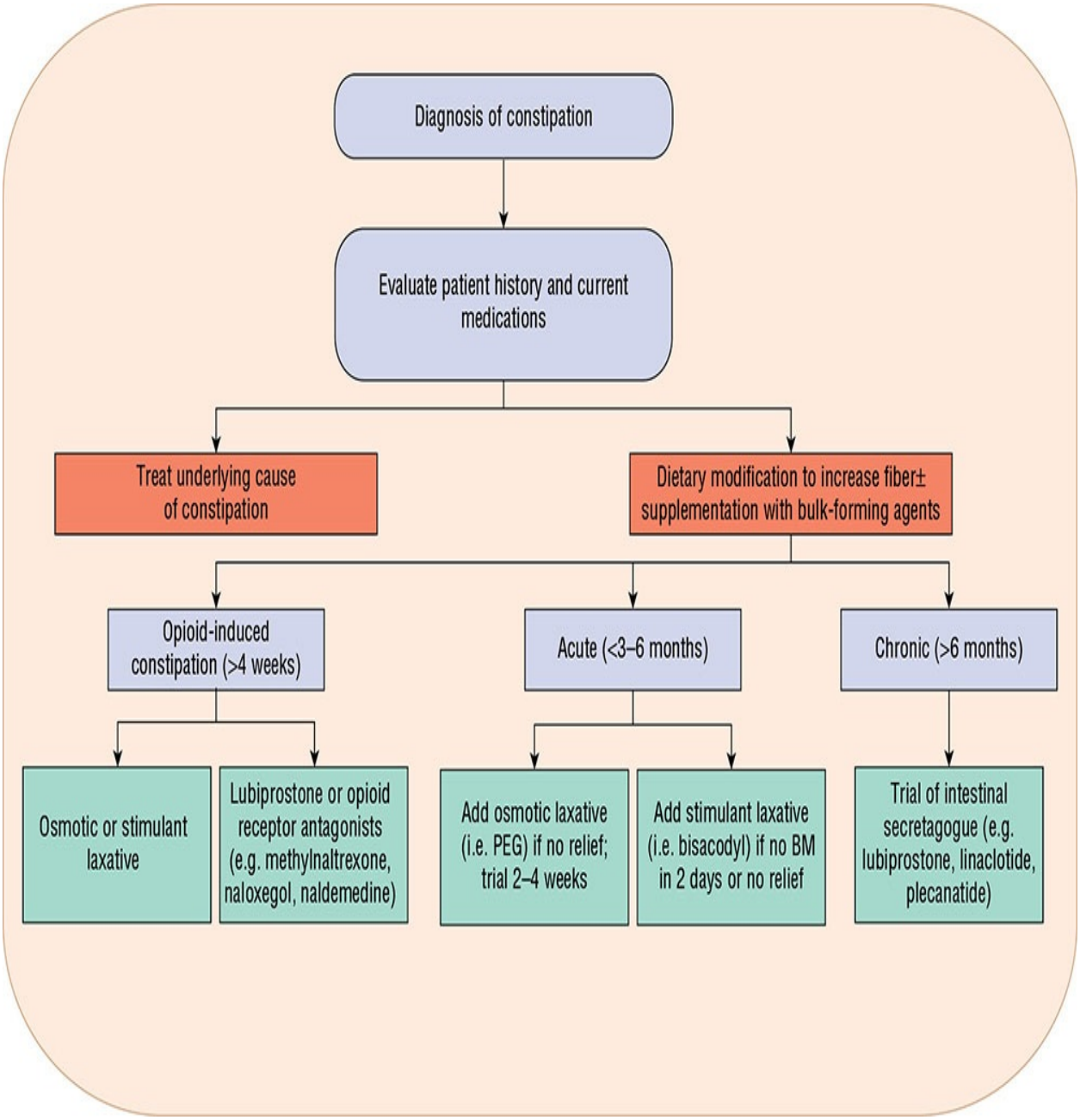


FIGURE 53-3 A general treatment algorithm for constipation.

6 Approaches to the treatment of constipation should begin with attempts to determine its cause. If an underlying disease is recognized as the cause of constipation, attempts should be made to correct it. GI malignancies may be removed via surgical resection. Endocrine and metabolic derangements should be corrected by the appropriate methods. For example, when hypothyroidism is the cause of constipation, cautious institution of thyroid replacement therapy is the most important treatment measure. If a patient is consuming medications

known to cause constipation, consideration should be given to alternative agents. If a patient must remain on constipating medications, then more attention must be given to general measures for prevention of constipation, as discussed in the next section. Also, patients with opioid-induced constipation (OIC) may require the routine use of pharmacologic agents, also discussed below.

The proper management of constipation will require a combination of nonpharmacologic and pharmacologic therapies. Osmotic laxative therapy is considered the preferred first line for the treatment of constipation, in addition to increasing dietary fiber or using fiber supplementation.[30,31] Patients are often encouraged to increase daily fluid intake and physical activity as well dedicate time to respond to the urge to defecate, although efficacy data are conflicting for these measures.[25,33]

Nonpharmacologic Therapy

Dietary Modification

The most important aspect of therapy for constipation for the majority of patients is dietary modification to increase the amount of fiber consumed. Fiber, the portion of vegetable matter not digested in the human GI tract, increases stool bulk, retention of stool water, and rate of transit of stool through the intestine. The result of fiber therapy is an increased frequency of defecation. Also, fiber decreases intraluminal pressures in the colon and rectum, which is thought to be beneficial for diverticular disease and for irritable bowel syndrome (IBS).

7 The specific physiologic effects of fiber are not well understood. Patients should be advised to gradually increase daily fiber intake to 20 to 30 g, through either dietary changes or fiber supplement products (see Bulk-Forming Agents below), a strong recommendation from the American College of Gastroenterology.[34] Fruits, vegetables, and cereals typically have the highest fiber content. Bran, a by-product of milling of wheat, is often added to foods to increase fiber content and contains a high amount of soluble fiber, which may be extremely constipating in larger doses. Raw bran is generally 40% fiber.

A trial of dietary modification with high-fiber content should be continued for at least 1 month before effects on bowel function are determined. Most patients begin to notice effects on bowel function 3 to 5 days after beginning a high-fiber diet, but some patients may require a considerably longer period of time. Patients should be cautioned that abdominal distension and flatulence may be particularly troublesome in the first few weeks of fiber therapy, especially with high bran

consumption. Gradually increasing dietary fiber over a few weeks to the goal of 20 to 30 g may help reduce some of the adverse abdominal effects, as well as ensuring adequate fluid intake. In most cases these problems resolve with continued use.

Surgery

In a small percentage of patients who present with complaints of constipation, surgical procedures are necessary because of the presence of colonic malignancies or GI obstruction from a number of other causes. Patients who have slow-transit-type primary constipation that is refractory to treatment are also surgical candidates.[25,31] Surgery may be required in some endocrine disorders that cause constipation, such as pheochromocytoma, which requires removal of a tumor. In each case, the involved segment of intestine may be resected or revised.

Biofeedback

Patients with constipation due to pelvic floor dysfunction/disordered defecation may have a less favorable response to fiber therapy than other constipation subtypes.[34] Many adult patients with functional defecatory disorders appear to benefit from pelvic floor retraining with biofeedback therapy. The goals of biofeedback are to improve pelvic floor relaxation to facilitate the passage of stool and the procedure is typically performed over 4- to 6-hour-long sessions. Success rates of 65% to 80% have been reported in controlled and uncontrolled studies, and improvement has been sustained for up to 1 year. The value of biofeedback in children with chronic constipation has not been well demonstrated.

Electrical Stimulation

Sacral nerve stimulation is a minimally invasive technique that has been used for treatment of fecal incontinence and there are some reports of its use in severe refractory chronic constipation.[35] However, clinical data supporting the use of electrical stimulation for this purpose are limited and there are currently no recommendations for general practice.

Pharmacologic Therapy

Three general classes of laxatives are discussed in this section: (a) those causing

softening of feces in 1 to 3 days; (b) those that result in soft or semifluid stool in 6 to 12 hours; and (c) those causing watery evacuation in 1 to 6 hours (**Table 53-8**). Other pharmacologic agents available for the treatment of constipation include a calcium channel activator, guanylate cyclase C agonist, and serotonergic agents.

TABLE 53-8 Dosage Recommendations for Pharmacologic Therapy

Agent	Recommended Dose
Agents that Cause Softening of Feces in 1-3 Days	
Bulk-forming agents	
Methylcellulose	4-6 g/day
Polycarbophil	4-6 g/day
Psyllium	Varies with product
Emollients	
Docusate sodium	50-360 mg/day
Docusate calcium	50-360 mg/day
Docusate potassium	100-300 mg/day
Osmotic laxatives Polyethylene glycol 3350	17 g/dose
Lactulose	15-30 mL orally
Sorbitol	30-50 g/day orally
Agents that Result in Soft or Semifluid Stool in 6-12 Hours	
Bisacodyl (oral)	5-15 mg orally
Senna	Dose varies with formulation
Magnesium sulfate (low dose)	<10 g orally
Agents that Cause Watery Evacuation in 1-6 Hours	
Magnesium citrate	18 g 300 mL water
Magnesium hydroxide	2.4-4.8 g orally
Magnesium sulfate (high dose)	10-30 g orally
Sodium phosphates	Varies with salt used
Bisacodyl	10 mg rectally
Polyethylene glycol-electrolyte preparations	4 L
Intestinal Secretagogues	
Lubiprostone	24 mcg orally twice daily
Linaclotide	145 mcg orally daily
Plecanatide	3 mg orally daily
Opioid Antagonists	
Methylnaltrexone	450 mg orally daily or 12 mg subcutaneously daily
Naloxegol	25 mg daily
Naldemedine	0.2 mg daily

Bulk-Forming Agents

Medicinal products, often called “bulk-forming agents,” such as psyllium hydrophilic colloids, methylcellulose, or polycarbophil, have properties similar to those of dietary fiber and may be taken as tablets, powders, or granules.[26] These agents increase the water content of stool to increase stool bulk and weight and relieve the symptoms of constipation within 3 days of initiating therapy.

Bulk-forming laxatives have few adverse effects. The most common effects include flatulence, abdominal bloating, and distention. Rarely, these agents may lead to bowel obstruction. Patients should also be cautioned to consume sufficient fluid while supplementing with bulk-forming agents to avoid obstruction of the esophagus, stomach, small intestine, and colon.

Emollient Laxatives

Emollient laxatives, including docusate in its various salts, are surfactant agents that work by facilitating mixing of aqueous and fatty materials within the intestinal tract; these are commonly referred to as stool softeners.[25] They may increase water and electrolyte secretion in the small and large bowel. Increased stool moisture content should lead to a softer, easier-to-pass stool. These products are generally given orally, although docusate potassium has also been used rectally. With these products, softening of stools occurs within 1 to 3 days of therapy.

Emollient laxatives are ineffective in treating constipation but are used mainly to prevent this condition. They may be helpful in situations in which straining at stool should be avoided, such as after recovery from myocardial infarction (MI), with acute perianal disease, or after rectal surgery. It is unlikely that these agents would be effective in preventing constipation if major causative factors (eg, heavy opiate use, uncorrected pathology, or inadequate dietary fiber) are not concurrently addressed. The use of mineral oil is generally not recommended due to safety concerns.

Although docusates are generally safe, a few adverse effects have been noted. They may increase the intestinal absorption of agents administered concurrently and alter toxic potential.

Hyperosmolar Agents

Lactulose and Sorbitol Lactulose is a nonabsorbable disaccharide that is

metabolized by colonic bacteria to low-molecular-weight acids, resulting in an osmotic effect whereby fluid is retained in the colon.[23] The fluid retained in the colon lowers the pH and increases colonic peristalsis within 2 to 3 days of use. Lactulose increases stool frequency and consistency in patients with chronic constipation (vs placebo) and may be more effective than fiber alone. In comparison to polyethylene glycol (PEG), lactulose is slightly less effective in increasing stool frequency per week and patients are more likely to need additional products for constipation relief. The most common adverse effects include flatulence, nausea, and abdominal discomfort or bloating—although lactulose can be useful in some patients. It may be justified as an alternative for acute constipation or in patients with an inadequate response to increased dietary fiber and bulking agents. In addition to the adverse abdominal effects associated with lactulose, diarrhea and electrolyte imbalances can occasionally occur. Sorbitol, a monosaccharide, also exerts its effect by osmotic action and has been recommended as a cost-effective alternative to lactulose. It is as effective as lactulose but may cause less nausea and is much less expensive.

Polyethylene Glycol PEG is FDA-approved for treatment of constipation at low doses and is expected to produce a bowel movement in 1 to 3 days.[23,36] For this indication, PEG is administered in smaller volumes (10-30 or 17-34 g per 120-240 mL) usually once (or twice) daily. PEG is not absorbed systemically or metabolized by colonic bacteria, and therefore has a lower incidence of adverse effects compared with other osmotic laxatives. Daily use in low dose (17 g) may be safe and effective for up to 6 months, even in children.[38] PEG has a strong recommendation from the American College of Gastroenterology for the treatment of chronic constipation and is available as a nonprescription drug.[30] It is also preferred by the American Gastroenterology Association if fiber supplementation is insufficient due to high efficacy based on high quality of evidence available.[25,31,34] The most common adverse effects are GI-related and include nausea, vomiting, flatulence, and abdominal cramping.[37] PEG solutions with electrolytes are used as bowl cleansing regimens prior to GI-related procedures, and should not be used routinely for treatment of constipation.

Magnesium Salts Magnesium salts, including hydroxide, phosphate, and citrate, and sodium phosphate are categorized as saline cathartics.[25] These agents are frequently used as bowel preparations prior to diagnostic procedures such as colonoscopy. Milk of magnesia (an 8% suspension of magnesium hydroxide), though, may be used occasionally to treat constipation in otherwise healthy adults, but efficacy data are limited. Saline cathartics should not be used on a

routine basis. These agents may cause fluid and electrolyte depletion. Also, magnesium or sodium accumulation may occur in patients with renal dysfunction or congestive heart failure. These risks increase with long-term use.

Glycerin Glycerin is usually administered as a suppository and exerts its effect by osmotic action in the rectum. As with most agents given as suppositories, the onset of action is usually less than 30 minutes. Glycerin is considered a safe laxative, although it may occasionally cause rectal irritation. Its use is acceptable on an intermittent basis for constipation or fecal impaction, particularly in children.[38]

Stimulant Laxatives

Stimulant laxatives such as diphenylmethane (bisacodyl) and anthraquinone (senna and others) derivates primarily affect the colon.[25] These agents stimulate the mucosal nerve plexus of the colon and may also affect intestinal fluid secretion by altering fluid and electrolyte transport, and are expected to cause a bowel movement within 8 to 12 hours of administration. Stimulant laxatives may cause severe abdominal cramping and electrolyte imbalances, particularly with chronic use. Compared with placebo, bisacodyl is effective in treatment of constipation.[25,34] These agents are typically reserved for intermittent use or in patients who fail to respond adequately to bulking and osmotic laxatives. Some patients, though, with severe chronic constipation and nonmodifiable risk factors may use these agents on a more regular basis.[25]

Intestinal Secretagogues

Lubiprostone

Lubiprostone (Amitiza) is a chloride channel activator that acts locally in the gut to open chloride channels on the GI luminal epithelium, which, in turn, stimulates chloride-rich fluid secretion into the intestinal lumen. Increased intraluminal fluid secretion helps to soften stool and accelerate GI transit time.[25] Lubiprostone is FDA-approved for adults with chronic idiopathic constipation as well as treatment of patients with opioid-induced constipation (OIC) at a recommended dose of one 24 mcg capsule twice daily with food.[39] Patients treated with lubiprostone have a significant increase in spontaneous bowel movements versus placebo as well as improvement in straining, stool consistency, and overall constipation severity.[34] Lubiprostone appears safe and

effective for long-term treatment (up to 48 weeks).[40] For most patients, bowel movements occur within 24 to 48 hours of lubiprostone administration. Common adverse effects include nausea, headache, and diarrhea and may be dose dependent.[25] Because of its high cost (especially relative to other available laxative agents) and lack of comparative data with other laxative therapies, lubiprostone is reserved for patients with chronic constipation who fail conventional first-line agents such as osmotic laxatives and fiber supplementation, or for those with OIC.

Linaclotide

Linaclotide (Linzess) is approved for the treatment of constipation and IBS-C.[25] It is a synthetic 14-amino-acid peptide that binds to and activates the guanylate cyclase C receptor found on the intestinal epithelium. This increases intestinal fluid secretion and quickens intestinal motility. Only the 145 mcg dose is approved for treatment of constipation, and patients should be instructed to take linaclotide on an empty stomach at least 30 minutes before the first meal of the day. Diarrhea was the most commonly reported adverse event in clinical trials, followed by flatulence and abdominal pain. Linaclotide should not be used in patients under the age of 18.[41]

Plecanatide

Plecanatide (Trulance) was approved for the treatment of adults with chronic idiopathic constipation.[42] It activates the guanylate cyclase C receptor that increases intestinal fluid secretion and motility similarly to linaclotide. Plecanatide is given once daily without regard to food at a dose of 3 mg. The most common side effect is diarrhea. Plecanatide is contraindicated patients less than six years of age or those with mechanical gastrointestinal obstruction, and should not be used in patients under the age of 18.

Opioid Receptor Antagonists

Alvimopan (Entereg) is an oral GI-specific μ-opioid antagonist approved for short-term use in hospitalized patients to accelerate recovery of bowel function after large or small bowel resection.[43] It antagonizes the GI (peripheral) effects of opioids without affecting analgesia because it does not cross the blood–brain barrier. Alvimopan is only available through a special use program (ENTEREG access support and education [EASE]), which requires hospitals to register and meet all requirements before the drug can be administered. Additionally,

alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than seven consecutive days prior to surgery as they may be more sensitive to the drug's effects. Dosing for alvimopan is as follows: 12 mg capsule administered 30 minutes to 5 hours before surgery and then 12 mg twice daily for up to 7 days or until discharge (maximum of 15 doses).

Methylnaltrexone (Relistor) is μ-receptor antagonist approved for OIC in patients with advanced disease receiving palliative care or when response to laxative therapy has been insufficient for patients with OIC with chronic noncancer pain.[29,43] This agent does not cross the blood–brain barrier or antagonize analgesia; it acts on peripheral μ-receptors to block unwanted opioid side effects such as constipation. It is administered at a weight-based dose as a subcutaneous injection in patients with advanced illness, usually every other day (no more than once daily). For patients with noncancer pain, methlynaltrexone can be given as a 12 mg subcutaneous injection or 450 mg oral dose daily. Laxative use should be discontinued upon initiation of methlnaltrexone, and its use is contraindicated in patients with known or suspected GI obstruction. Patients with reduced creatinine clearance (<60 mL/min [1 mL/s]) or moderate-to-severe hepatic impairment should receive reduced dosing of methlnaltrexone (ie, 150 mg orally or 6 mg subcutaneously).

Naloxegol (Movantik) was approved by the FDA in September 2014 for the treatment of OIC in adult patients with noncancer pain.[44] It is an oral pegylated naloxone molecule and antagonizes the μ-receptor. Pegylation reduces naloxegol's passive permeability of the blood–brain barrier. The recommended dose is 25 mg by mouth once daily, 1 hour before or 2 hours after a meal. The dose should be reduced by half in patients with diminished renal function (CrCl <60 mL/min [1 mL/s]) or in those unable to tolerate 25 mg. The most common side effects are abdominal pain, diarrhea, and nausea. In clinical trials, naloxegol significantly increased the number and frequency of bowel movements compared to placebo at 12 weeks.[43]

Naldemedine (Symproic) is the newest peripherally-acting opioid antagonist approved for treatment of OIC in patients with chronic noncancer pain.[29] The recommended dose is 0.2 mg by mouth once daily, and there are no dose adjustments for renal or hepatic impairment. However, patients with severe hepatic impairment (ie, Child-Pugh class C) should not use naldemedine. The most common adverse effects are abdominal pain and diarrhea. Naldemedine increased the frequency of bowel movements compared to placebo in clinical trials.[29]

Other Agents

Prucalopride is a selective 5-hydroxytryptamine-4 (5-HT_4) receptor agonist approved for treatment of chronic constipation in Europe.[45] It demonstrates proenterokinetic effects (increased colonic motility and transit), specifically in the GI tract. Prucalopride, however, is more selective than the previously available serotonergic agonists cisapride and tegaserod with higher affinity for the 5-HT_4 receptor. Receptor selectivity is thought to improve the safety profile of prucalopride over cisapride and tegaserod, which were removed from the market due to concerns for adverse cardiovascular events. In clinical trials, prucalopride significantly increased the number of complete, spontaneous bowel movements in adults with chronic constipation. Constipation symptoms and quality of life were also improved with prucalopride. This agent has been safely tolerated in clinical trials with no adverse cardiovascular effects versus placebo (although data are limited). Prucalopride has not yet been approved by the FDA.

Probiotics may be useful in the treatment of constipation. Several randomized controlled trials conducted in children and adults revealed that certain strains of probiotics increased weekly stool frequency.[34] However, these trials were small (370 patients total) and only slight improvement was realized (one additional stool per week). More studies are needed to strengthen evidence involving probiotics, but these may be an option for patients seeking alternative treatment.[46]

Prevention

For patients recovering from MI or rectal surgery, straining at defecation should be avoided. The basis of preventive therapy in these patients should be bulk-forming laxatives. Additionally, the use of docusate is popular, although its effectiveness is debated. In pregnant patients, constipation may result because of alterations in hormones or iron supplementation. As described earlier, bulk-forming laxatives and docusates should be the first line of prevention.

Evaluation of Therapeutic Outcomes

The ultimate goal of treatment for constipation is to prevent further episodes of constipation. Short-term goals include alleviation of acute constipation with relief from symptoms. For patients with chronic constipation, the goals include use of proper diet and decreased reliance on laxatives in addition to relief of

symptoms for the patient so that quality of life is not diminished. Effective treatment of constipation requires the patient to become more knowledgeable about the causes of constipation, proper diet, and appropriate use of laxatives.

IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome is the most commonly diagnosed GI condition, a GI syndrome, and is characterized by chronic abdominal pain and altered bowel habits in the absence of any organic cause.

Epidemiology

The prevalence of IBS is approximately 5% to 15% based on North American and European population-based studies; however, there is a wide variation in prevalence by individual country.[47–49] IBS affects men and women, young patients, and the elderly with an overall 2:1 female predominance in North America.[50] However, younger patients and women are more likely to be diagnosed with IBS. Although only 15% of those affected actually seek medical attention, IBS is the cause of between 25% and 50% of all referrals to gastroenterologists.[47]

Pathophysiology

Although the exact pathophysiologic abnormalities with IBS are still being actively investigated, IBS likely results from altered somatovisceral and motor dysfunction of the intestine from a variety of causes. Abnormal CNS processing of afferent signals may lead to visceral hypersensitivity, with the specific nerve pathway affected determining the exact symptomatology expressed. This visceral hypersensitivity is a neuroenteric phenomenon that is independent of motility and psychological disturbances.[49] Factors known to contribute to these alterations include genetics, motility factors, inflammation, colonic infections, mechanical irritation to local nerves, stress, and other psychological factors.

The enteric nervous system contains a significant percentage of the body's 5-HT receptors.[51] Two types of 5-HT receptors exist within the gut: serotonin type 3 (HT_3) and serotonin type 4 (HT_4), which are responsible for secretion, sensitization, and motility. There is an increase in the postprandial levels of 5-HT in the GI tract in those who suffer from diarrhea-predominant IBS when compared with nonsufferers.[51] Therefore, stimulation and antagonism of these 5-

HT receptors have become a focused area for research on new drug therapies for both diarrhea- and constipation-predominant diseases.

Clinical Presentation

8 Irritable bowel syndrome presents as either diarrhea- or constipation-predominant disease and can be defined as lower abdominal pain, disturbed defecation (constipation, diarrhea, or an alternating pattern of both), and bloating in the absence of structural or biochemical factors that might explain these symptoms (Table 53-9). Because IBS can have variable signs and symptoms, two diagnostic criteria "checklists" are commonly used to aid in the workup of a patient suspected of having IBS, the Manning and Rome IV criteria.[52] Table 53-10 shows the symptom criteria for both the Manning[53] and Rome IV[30] symptom-based criteria.

TABLE 53-9 Clinical Presentation of Irritable Bowel Syndrome

Signs and symptoms
- Lower abdominal pain
- Abdominal bloating and distension
- Diarrhea symptoms, >3 stools/day
- Extreme urgency
- Passage of mucus
- Constipation symptoms, <3 stools/week, straining, incomplete evacuation
- Psychological symptoms such as depression and anxiety

Non-GI symptoms
- Urinary symptoms
- Fatigue
- Dyspareunia

Other concurrent conditions
- Fibromyalgia
- Functional dyspepsia
- Chronic fatigue syndrome

Reduced health-related quality of life

TABLE 53-10 Symptom-Based Criteria for Irritable Bowel Syndrome

The Manning criteria[56]

Chronic or recurrent abdominal pain for at least 6 months and two or more of the following:

1. Abdominal pain relieved with defecation
2. Abdominal pain associated with more frequent stools
3. Abdominal pain associated with looser stools
4. Abdominal distension
5. Feeling of incomplete evacuation after defecation
6. Mucus in stools

Rome III diagnostic criteria for irritable bowel syndrome[33]

Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with two or more of the following:

1. Relieved with defecation
2. Onset associated with a change in frequency of stool
3. Onset associated with a change in form (appearance) of stool

Additional diagnostic steps that can be taken include sigmoidoscopy or colonoscopy, examination of the stool for occult blood and ova and parasites, complete blood cell count, erythrocyte sedimentation rate, and serum electrolytes. In some cases, radiographic imaging studies, such as computed tomography scans or barium swallows or enemas, may also be necessary if the findings of the foregoing assessment are not typical for IBS.[47]

TREATMENT

Irritable Bowel Syndrome

General Approach to Treatment

The treatment approach to IBS is based on the predominant symptoms and their severity (**Fig. 53-4**). Milder, less frequent episodes can be managed with lifestyle changes such as dietary restrictions, a higher-fiber diet, physical activity, and relaxation techniques.[54] More persistent disease may require as-needed uses of various antispasmodic or antidiarrheal agents such as loperamide. Lastly, the most severe forms of this disease may call for pharmacologic agents directed specifically at the underlying neurohormonal imbalance, such as the 5-HT_4 agonists (eg, tegaserod), or the 5-HT_3-receptor antagonists (eg, alosetron).

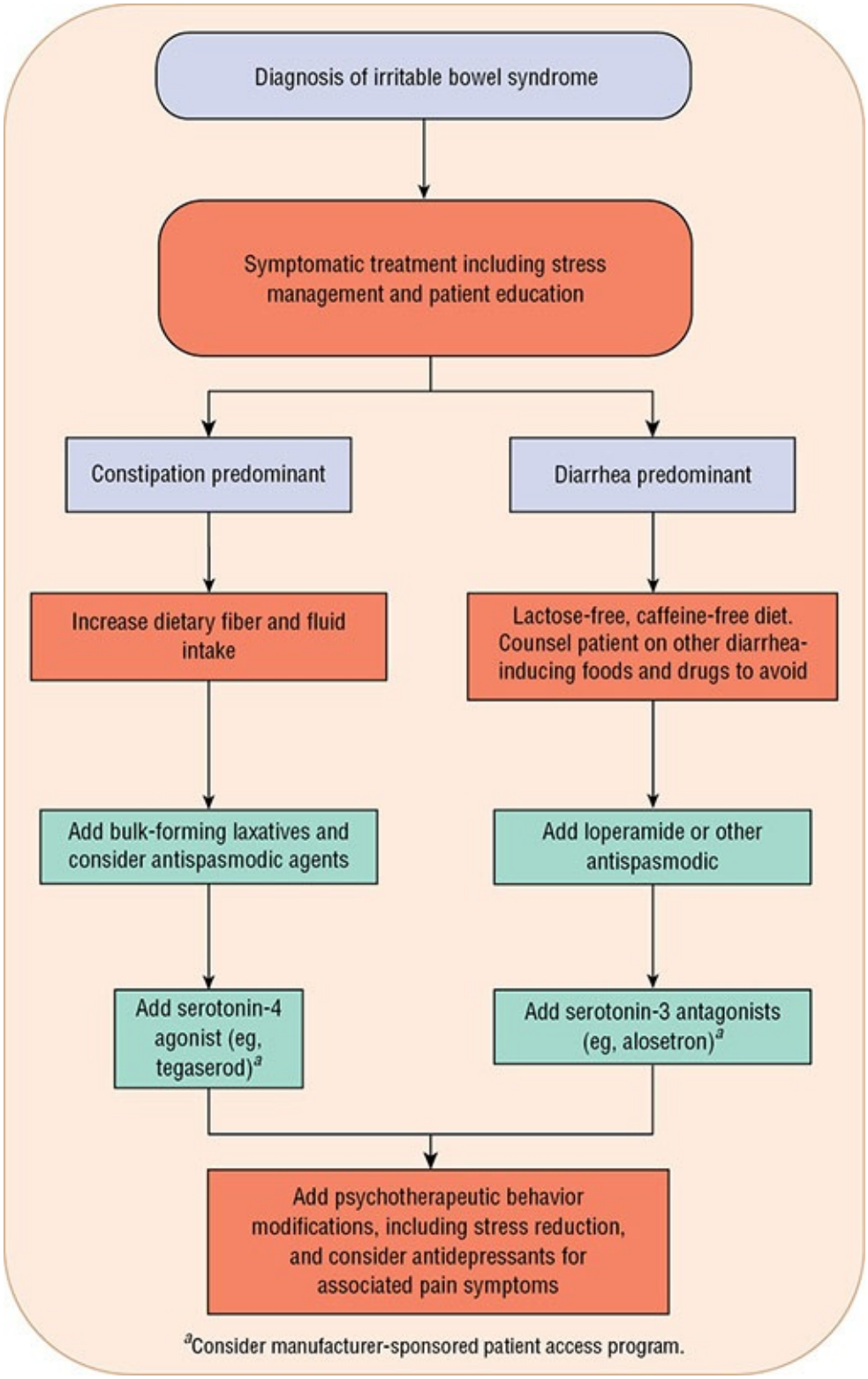


FIGURE 53-4 A general stepwise approach to the management of both constipation- and diarrhea-predominant irritable bowel syndrome.

Alosetron, a 5-HT_3-receptor antagonist, was withdrawn from the US market in 2000 as a result of serious adverse effects, including severe constipation and ischemic colitis that did not appear in the initial clinical trials. It was reintroduced in 2002 and is now limited to an FDA-approved restricted-use program in lower initial doses, and requires extensive postmarketing surveillance. Results of these trials are necessary to definitively determine alosetron's true safety profile, especially with regard to its association with or causation of fatal ischemic colitis.

Constipation-Predominant Disease

In the constipation-predominant patient, dietary fiber may be beneficial. Patients should be instructed to begin with one tablespoonful of fiber with one meal daily and gradually increase the dose to include fiber with two and three meals a day until the desired outcome is achieved. End points that the patient should aim for include bulkier and more easily passed stools. For patients unable to tolerate dietary bran, bulking agents such as psyllium may be substituted.[54] PEG laxatives may be used; however, other laxatives should only be used in the smallest dose for the least amount of time. When lifestyle modifications alone do not control symptoms, linaclotide should be recommended.[50]

The 5-HT_4 partial agonist tegaserod is approved specifically for short-term, intermittent treatment of IBS-C in women.[55–57] Tegaserod is available in the United States through a restricted-access program due to a small, yet significant, increase in ischemia events (MI, cerebrovascular accident [CVA], and unstable angina) in patients with preexisting cardiovascular disease and/or cardiovascular risk factors. It is given as 2 or 6 mg doses given twice daily 30 minutes prior to a meal with water for up to 12 weeks.[56] Stimulation of the 5-HT_4 receptors by tegaserod increases gastric secretions and promotes motility, with improvement in symptoms generally occurring within the first week of therapy. Diarrhea was the most common adverse effect, resulting in drug discontinuation in 1.6% of study subjects.

Diarrhea-Predominant Disease

9 For patients in whom diarrhea is the primary complaint, avoidance of certain food products may be necessary. Caffeine, alcohol, and artificial sweeteners (sorbitol, fructose, and mannitol) are known to irritate the gut and produce a laxative effect. Lactose intolerance should be considered in certain patients;

however, the prevalence of this condition may be exaggerated.

Herbal medicines or teas often contain senna, which may produce diarrhea. In patients with disease persistence following dietary modification, loperamide may be used for episodic management of urgent diarrhea, or in situations in which the patient wishes to avoid the possibility of an acute onset of symptoms.[50] Loperamide decreases intestinal transit, enhances water and electrolyte absorption, and strengthens rectal sphincter tone. Some patients may require continuous therapy, and careful dosage titration can usually be undertaken to prevent the development of constipation.

Diarrhea-predominant IBS caused by excessive stimulation of the 5-HT_3 receptor can be relieved by the drug alosetron which is only available via an FDA-approved restricted-use program due to severe GI adverse effects.[50] Additional information can be found at http://www.lotronex.com. It is indicated for women with diarrhea-predominant symptoms of longer than 6 months' duration that are not relieved by conventional therapy at a dose of 0.5 mg twice daily.

Two agents, eluxadoline and rifaximin, are approved for use in IBS-D.[58,59] Rifaximin is a rifamycin antibacterial indicated for the treatment of travelers' diarrhea that is indicated for the treatment of IBS-D in adults based on several randomized control trials demonstrating improvement in abdominal pain, stool consistency, and bloating.[50,58] The recommended dose is 550 mg orally three times a day for 2 weeks. Recurrences may be retreated up to two times; however, there is no evidence to support repeating the regimen. Eluxadoline is a μ-opioid receptor agonist indicated for adults with IBS-D. The recommended dose is 100 mg orally twice a day with food. A lower dose of 75 mg twice daily is recommended for patients without a gallbladder, who cannot tolerate the 100 mg dose and if they have hepatic impairment.[59] It was approved based on two randomized clinical trials that suggested an improved in abdominal pain and stool consistency. The main side effect observed was constipation.

Use of Antidepressants in Irritable Bowel Syndrome

Tricyclic antidepressants have shown some benefit in treatment of diarrhea-predominant IBS associated with moderate-to-severe abdominal pain, by modulating perception of visceral pain, altering GI transit time, and treating underlying comorbidities.[60,61] Selective 5-HT reuptake inhibitors (SSRI), fluoxetine, citalopram and paroxetine have been studied but the results are conflicting. Large randomized control trials lasting longer than 3 months are

needed to determine SSRIs place in therapy.[62]

Duloxetine, a serotonin-norepinephrine reuptake inhibitor, has been studied in the management of IBS with comorbid generalized anxiety disorder and major depressive disorder. Although the effect was gradual over 12 weeks, both symptom severity and quality of life significantly improved.[63,64]

Figure 53-4 shows a general stepwise approach to the management of both constipation and diarrhea-predominant IBS.

Pain in Irritable Bowel Syndrome

10 Some patients with IBS suffer significant pain associated with their disease. Data supporting the use of antispasmodic agents in these patients are conflicting.[47] A trial of low-dose antidepressant therapy is indicated, especially if pain is associated with eating. Both tricyclic antidepressants and 5-HT reuptake inhibitors produce analgesia and may relieve depressive symptoms if present. Preprandial doses of drugs containing anticholinergic properties may suppress pain (and/or diarrhea) associated with an overactive postprandial gastrocolonic response. Tricyclic antidepressants should be avoided in patients with pain and constipation. In addition, psychotherapy, including cognitive behavioral therapy, relaxation therapy, and hypnotherapy, has been shown to decrease IBS symptoms.[65]

Evaluation of Therapeutic Outcomes

Irritable bowel syndrome is usually classified as constipation-predominant, diarrhea-predominant, or IBS with abdominal pain and bloating. Therapeutic goals in IBS should focus on the patient's primary complaint. Dietary and drug therapy goals should focus on end-organ treatment to relieve abdominal pain (antispasmodic drugs) or disturbed bowel habits (antidiarrheals and bulk-forming agents). Additionally, severe symptoms from CNS dysregulation should be treated with antidepressants, psychotherapy, relaxation/stress management, cognitive behavior treatment, and/or hypnosis aimed at specific affective disorders.[47] Lastly, the 5-HT receptor agonists and antagonists can be used in carefully selected patients whose symptoms are not adequately controlled with other agents. The AGA recommends that patients with severe IBS consider psychological treatments such as psychotherapy, relaxation/stress management, and/or cognitive behavior treatment.

Postclass Engaged Learning Activity

Conduct a literature search and identify a primary research article that has been published in the past 12 months regarding the use of antidepressants to treat IBS. Write a brief summary about the study methods, major findings and how this new information might change current practice. This activity is intended to build your literature evaluation skills and ability to critically appraise research articles.

ABBREVIATIONS

AAD	antibiotic-associated diarrhea
AGA	American Gastroenterology Association
AIDS	acquired immune deficiency syndrome
ATPase	adenosine triphosphatase
CDC	Centers for Disease Control and Prevention
CVA	cerebrovascular accident
EASE	ENTEREG access support and education
5-HT	serotonin
HT_3	serotonin type 3
HT_4	serotonin type 4
$5\text{-}HT_4$	5-hydroxytryptamine-4
IBS	irritable bowel syndrome
IBS-C	constipation-predominant irritable bowel syndrome
MI	myocardial infarction
NSAID	nonsteroidal anti-inflammatory drug
OIC	opioid-induced constipation
ORS	oral rehydration solution
PEG	polyethylene glycol
VIP	vasoactive intestinal peptide

REFERENCES

1. DuPont HL.Persistent Diarrhea A Clinical Review. *JAMA*. 2016;315(24):2712-2723.
2. Farthing M, Salam M, Lindberg G, et al. Acute diarrhea in adults and children: A global perspective. World Gastroenterology Organization

Guidelines. 2012. Available at http://www.worldgastroenterology.org/acute-diarrhea-in-adults.html. Accessed date, May 31, 2018.

3. Scallan E, Majowicz S, Hall G, et al. Prevalence of diarrhoea in the community in Australia, Canada, Ireland, and the United States. *Int J Epidemiol*. 2005;34:454–460.
4. Jones T, McMillian M, Scallan E, et al. A population-based estimate of the substantial burden of diarrhoeal disease in the United States; FoodNet, 1996-2003. *Epidemiol Infect*. 2007;135:293–301.
5. Musher DM, Musher BL. Contagious acute gastrointestinal infections. *N Engl J Med*. 2004;351(23):2417-2427.
6. Lalani T, Maguire JD, Grant EM, et al. Epidemiology and self-treatment of traveler's diarrhea in a larger, prospective cohort of department of defense beneficiaries. *J Travel Med*. 2015;22(3):152–160.
7. Steffen R, Hill DR, Dupont HL. Traveler's diarrhea: A clinical review. *JAMA*. 2015;313(1):71-80.
8. Bhatnagar S, Bhandari N, Mouli U, Bhan M. Consensus statement of IAP National Task Force: Status report on management of acute diarrhea. *Indian Pediatr*. 2004;41:335-348.
9. Atia AN, Buchman AL. Oral rehydration solutions in non-cholera diarrhea: A review. *Am J Gastroenterol*. 2009;104(10):2596-2604.
10. Fine KD, Schiller LR. AGA technical review on the evaluation and management of chronic diarrhea. *Gastroenterology*. 1999;116(6):1464-1486.
11. World Health Organization. WHO/UNICEF Joint Statement: Clinical Management of Acute Diarrhea (WHO/FCH/CAH/04.7). Geneva, Switzerland: World Health Organization; 2004.
12. US Food and Drug Administration. Drug Safety Communication: FDA warns about serious heart problems with high doses of the antidiarrheal medicine loperamide (Imodium), including from abuse and misuse. Available at https://www.fda.gov/Drugs/DrugSafety/ucm504617.htm. Accessed date, May 31, 2018.
13. US Food and Drug Administration. Drug Safety Communication: FDA limits packaging for anti-diarrhea medicine loperamide(Imodium) to encourage safe use. Available at https://www.fda.gov/Drugs/DrugSafety/ucm594232.htm. Accessed date, May 31, 2018.

14. Harris AG, Odorisio TM, Woltering EA, et al. Consensus statement—Octreotide dose titration in secretory diarrhea—Diarrhea Management Consensus Development Panel. *Dig Dis Sci*. 1995;40(7):1464–1473.
15. Schiller LR. Review article: Anti-diarrhoeal pharmacology and therapeutics. *Aliment Pharmacol Ther*. 1995;9(2):87-106.
16. Ruszniewski P, Ducreux M, Chayvialle JA, et al. Treatment of the carcinoid syndrome with the long acting somatostatin analogue lanreotide: A prospective study in 39 patients. *Gut*. 1996;39(2):279–283.
17. Giustina A, Mazziotti G, Cannavo S, et al. High-dose and high-frequency lanreotide autogel in acromegaly: A randomized, multicenter study. *J Clin Endocrinol Metab*. 2017;102(7):2454–2464.
18. Floch MH, Walker WA, Guandalini S, et al. Recommendations for probiotic use—2008. *J Clin Gastroenterol*. 2008;42:S104–S108.
19. Hempel S, Newberry SJ, Maher AR, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea. A systematic review and meta-analysis. *JAMA*. 2012;307(18):1959–1969.
20. Allen SJ, Wareham K, Wang D, et al. A high-dose preparation of lactobacilli and bifidobacteria in the prevention of antibiotic-associated and Clostridium difficile diarrhoea in older people admitted to hospital: A multicentre, randomised, double-blind, placebo-controlled, parallel arm trial (PLACIDE). *Health Technol Assess*. 2013;17(57):1–140.
21. Thompson RF, Bass DM, Hoffman SL. Travel vaccines. *Infect Dis Clin North Am*. 1999;13(1):149-167.
22. CDC. Vaxchora® (lypholized CVD 103-HgR). Available at https://www.cdc.gov/cholera/vaccines.html. Accessed date, 31 May 2018.
23. CDC. Prevention of rotavirus gastroenteritis among infants and children: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR*. 2009;58(RR-2):1–26.
24. Choung RS, Locke GR, Rey E, et al. Factors associated with persistent and nonpersistent chronic constipation, over 20 years. *Clin Gastroenterol Hepatol*. 2012;10:494–500.
25. Bharucha AE, Pemberton JH, Locke GR. American Gastroenterological Association technical review on constipation. *Gastroenterology*. 2013;144:218-238.
26. Gallegos-Orozco JF, Foxx-Orenstein AE, Sterler SM, Stoa JM. Chronic constipation in the elderly. *Am J Gastroenterol*. 2012;107:18-25.

27. Higgins P, Johanson J. Epidemiology of constipation in North America: A systematic review. *Am J Gastroenterol*. 2004;99(4):750-759.
28. Bharucha AE, Pemberton JH, Locke GRIII. American Gastroenterological Association technical review on constipation. *Gastroenterology*. 2013;144:218-238.
29. Murphy JA, Sheriden EA. Evidence based review of pharmacotherapy for opioid-induced constipation in noncancer pain. *Ann Pharmacother*. 2018;52(4):370-379.
30. Lacy BE, Mearin F, Chang L, et al. Bowel disorders. *Gastroenterology*. 2016;150:1393–1407.
31. Barucha AE, Dorn SD, Lembo A, Pressman A. American Gastroenterological Association medical position statement on constipation. *Gastroenterology*. 2013;144:211-217.
32. Brandt L, Prather C, Quigley E, Schiller L, Schoenfeld P, Talley N. Systematic review on the management of chronic constipation in North America. *Am J Gastroenterol*. 2005;100:S5-S21.
33. Ternent CA, Bastawrous AL, Morin NA, et al. Practice parameters for the evaluation and management of constipation. *Dis Colon Rectum*. 2007;50:2013–2022.
34. Ford AC, Moayyedi P, Lacy BE, et al. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. *Am J Gastroenterol*. 2014;109(Suppl 1):S2–S26. quiz S27.
35. Ortiz H, de Miguel M, Rinaldi M, Oteiza F, Altomare DE. Functional outcome of sacral nerve stimulation in patients with severe constipation. *Dis Colon Rectum*. 2012;55:876-880.
36. Lee-Robichaud H, Thomas K, Morgan J, Nelson RL. Lactulose versus polyethylene glycol for chronic constipation. Cochrane Database Syst Rev. 2010;(7):CD007570. doi:10.1002/14651858.CD007570.pub2.
37. DiPalma JA, Cleveland MV, McGowan J, Herrar JL. A randomized, multicenter, placebo-controlled trial of polyethylene glycol laxative for chronic treatment of chronic constipation. *Am J Gastroenterol*. 2007;102:1436-1441.
38. Tabbers MM, DiLorenzo C, Berger MY, et al. Evaluation and treatment of functional constipation in infants and children: Evidence-based recommendations from ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr*. 2014;58(2):258–274.

39. Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: Systematic review and meta-analysis. *Gut*. 2011;60:209-218.
40. Lembo AJ, Johanson JF, Parkman HP, Rao SS, Miner PBJr, Ueno R. Long-term safety and effectiveness of lubiprostone, a calcium channel (ClC-2) activator, in patients with chronic idiopathic constipation. *Dig Dis Sci*. 2011;56:2639–2645.
41. Linzess (linaclotide) [prescribing information]. Irvine, CA: Allergan USA, Inc; January 2017.
42. Trulance (plecanatide) [prescribing information]. New York, NY: Synergy Pharmaceuticals; February 2018.
43. Nee J, Zakari M, Sugarman MA, *et al*. Efficacy of treatments for opioid-induced constipation: Systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2018 ; 16 (10): 1569 – 1584. doi:10.1016/j.cgh.2018.01.021.
44. Leonard J, Baker DE. Naloxegol: Treatment for opioid-induced constipation in chronic non-cancer pain. *Ann Pharmocother*. 2015;49(3):360-365.
45. Shin A, Camilleri M, Kolar G, Erwin P, West CP, Murad MH. Systematic review with meta analysis: Highly selective 5-HT4 agonists (prucalopride, velusetrag, or naronapride) in chronic constipation. *Aliment Pharmacol Ther*. 2014;39:239–253.
46. Chmielewska A, Szajewska H. Systematic review of randomized controlled trials: Probiotics for functional constipation. *World J Gastroenterol*. 2010;16(7):69-75.
47. Brandt L, Chey W, Foxx-Orenstein A, et al. An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol*. 2009;104(S1):S1–S35.
48. Chang FY. Irritable bowel syndrome: The evolution of multi-dimensional looking and multidisciplinary treatments. *World J Gastroenterol*. 2014;20(10):2499-2514.
49. Canavan C, West J, Card T. The epidemiology of irritable bowel syndrome. *Clin Epidemiol*. 2014;6:71-80.
50. Weinberg DS, Smalley W, Heidelbaugh JJ, Sultan S. American Gastroenterological Association Institute Guideline on the pharmacological management of irritable bowel syndrome. *Gastroenterology*. 2014;147(5):1146-1148.

51. Dothel G, Barbaro MR, Raschi E, et al. Advancements in drug development for diarrhea-predominant irritable bowel syndrome. *Expert Opin Investig Drugs*. 2018;27(3):251–263.
52. Dang J, Ardila-hani A, Amichai MM, Chua K, Pimentel M. Systematic review of diagnostic criteria for IBS demonstrates poor validity and utilization of Rome III. *Neurogastroenterol Motil*. 2012;24(9):853-e397.
53. Manning A, Thompson W, Heaton K, Morris A. Towards positive diagnosis of the irritable bowel. *Br Med J*. 1978;2(6138):653-654.
54. National Institute for Health and Care Excellence. Addendum to Guideline CG61. Irritable bowel syndrome in adults: Diagnosis and management of irritable bowel syndrome in primary care. 2015. Available at http://www.nice.org.uk/guidance/cg61/chapter/1-recommendations#clinical-management-of-ibs. Accessed date, July 14, 2016.
55. Camilleri M. Review article: Tegaserod. *Aliment Pharmacol Ther*. 2001;15(3):277-289.
56. Tougas G, Snape WJ, Otten MH, et al. Long-term safety of tegaserod in patients with constipation-predominant irritable bowel syndrome. *Aliment Pharmacol Ther*. 2002;16(10):1701–1708.
57. Muller-Lissner SA, Fumagalli I, Bardhan KD, et al. Tegaserod, a 5-HT4 receptor partial agonist, relieves symptoms in irritable bowel syndrome patients with abdominal pain, bloating and constipation. *Aliment Pharmacol Ther*. 2001;15(10):1655–1666.
58. Xifaxan® [package insert]. Raleigh, NC: Salix Pharmaceuticals Inc; 2015.
59. Viberzi® [package insert]. Cincinnati, OH: Patheon Pharmaceuticals Inc; 2015.
60. Iskandar HN, Cassell B, Kanuri N, et al. Tricyclic antidepressants for management of residual symptoms in inflammatory bowel disease. J Clin Gastroenterol. 2014;48(5):423–429.
61. Xie C, Tang Y, Wang Y. Efficacy and Safety of Antidepressants for the Treatment of Irritable Bowel Syndrome: A Meta-Analysis. PLoS ONE. 2015;10(8):e0127815.
62. Bundeff AW, Woodis CB. Selective serotonin reuptake inhibitors for the treatment of irritable bowel syndrome. *Ann Pharmacother*. 2014;46(6):777-784.
63. Lewis-Fernandex RLam R, Lam P, Lucak S, et al. An open-label pilot study of duloxetine in patients with irritable bowel syndrome and

comorbid major depressive disorder. *J Clin Psychopharmacol*. 2016;36(6):710–715.

64. Kaplan A, Franzen MD, Nickell PV, et al. An open-label trial of duloxetine in patients with irritable bowel syndrome and comorbid generalized anxiety disorder. *Int J Psychiatry Clin Pract*. 2014;18(1):11–15.
65. Heymann-Monnikes I, Arnold R, Florin I, Herda C, Melfsen S, Monnikes H. The combination of medical treatment plus multicomponent behavioral therapy is superior to medical treatment alone in the therapy of irritable bowel syndrome. *Am J Gastroenterol*. 2000;95(4):981–994.

54

Portal Hypertension and Cirrhosis

Julie M. Sease and Alyson G. Wilder

KEY CONCEPTS

1. Cirrhosis is a severe, chronic, potentially irreversible disease associated with significant morbidity and mortality. The progression of cirrhosis secondary to alcohol intake, both in those with alcoholic cirrhosis and cirrhosis due to other causes, can be interrupted by abstinence from alcohol. It is therefore imperative for the clinician to educate and support abstinence from alcohol as part of the overall treatment strategy of the underlying liver disease.
2. Patients with cirrhosis should receive endoscopic screening for varices, and certain patients with varices should receive primary prophylaxis with nonselective β-adrenergic blockade therapy to prevent variceal hemorrhage.
3. When nonselective β-adrenergic blocker therapy is used to prevent re-bleeding, therapy can be titrated to achieve a goal heart rate of 55 to 60 beats/min or the maximal tolerated dose.
4. Octreotide is the preferred vasoactive agent for the medical management of variceal bleeding. Endoscopic band ligation is the primary therapeutic tool for the management of acute variceal bleeding.
5. The combination of spironolactone and furosemide is the recommended initial diuretic therapy for patients with ascites.
6. All patients who have survived an episode of spontaneous bacterial peritonitis (SBP) should receive long-term antibiotic prophylaxis.
7. The mainstay of treatment of hepatic encephalopathy (HE) involves therapy to lower blood ammonia concentrations and includes diet modifications, lactulose, and rifaximin alone or in combination with lactulose.

PRECLASS ACTIVTY

Preclass Engaged Learning Activity

Create a summary table of treatment options for each complication associated with decompensated cirrhosis: ascites, SBP (acute treatment and secondary prophylaxis), HE, variceal bleeding (primary prophylaxis, acute bleeding, and secondary prophylaxis). Use the table below as a guide.

Complication	Treatment/ drug of choice (to include dose, route, and frequency)	Common adverse effects	Monitoring parameters	Patient counseling points/ pharmacy pearls
Portal Hypertension				
Primary prophylaxis against bleed				
Acute bleed				
Secondary prophylaxis of bleed				
Ascites				
SBP				
Acute treatment				
Secondary prophylaxis				
Hepatic encephalopathy				

INTRODUCTION

Chronic liver injury causes damage to normal liver tissue resulting in the development of regenerative nodules surrounded by dense fibrotic material, which are diagnostic hallmarks of cirrhosis.[1] The distorted architecture of the cirrhotic liver impedes portal blood flow, interferes with hepatocyte perfusion, and disrupts hepatic synthetic functions such as the production of albumin.

Clinical consequences of cirrhosis include increased intrahepatic resistance leading to portal hypertension, varices, and variceal bleeding; ascites; infection; encephalopathy; and hepatocellular carcinoma. Additionally, when advanced, cirrhosis can also lead to the development of both renal and pulmonary dysfunction.

1 While cirrhosis has many causes (Table 54-1),[1–3] in more developed countries, primary etiologies include hepatitis C, excessive alcohol intake, and nonalcoholic fatty liver disease.[1,2] Treatment strategies for managing the most commonly encountered clinical complications of cirrhosis are discussed. Fibrosis, even significant enough to have caused cirrhosis, is known to regress when anti-viral therapy for hepatitis B and C is instituted.[1] While this chapter will not focus on anti-viral therapies, this is a facet of medication management that will apply to some patients with cirrhosis.

TABLE 54-1 Etiology of Cirrhosis

Alcoholism
Chronic hepatitis C
Metabolic liver disease
Hemochromatosis
Wilson's disease
Nonalcoholic fatty liver disease
Immunologic disease
Autoimmune hepatitis
Primary biliary cirrhosis
Primary biliary cholangitis
Vascular disease
Budd–Chiari
Drugs
Isoniazid, methyldopa, amiodarone, amoxicillin-clavulanate, nitrofurantoin, diclofenac, methotrexate, nevirapine, propylthiouracil, valproate

Data from References 1, 2, and 3.

EPIDEMIOLOGY

Chronic liver disease and cirrhosis were responsible for nearly 40,326 deaths in America in 2015 making it the 12th leading cause of death.[4] Acute variceal bleeding and spontaneous bacterial peritonitis (SBP) are among the immediately life-threatening complications of cirrhosis. Associated conditions causing significant morbidity include ascites and hepatic encephalopathy (HE). Approximately 50% of patients with cirrhosis develop ascites during 10 years of observation and, within 2 years, nearly half of patients who develop ascites will

die.[5]

PATHOPHYSIOLOGY OF CIRRHOSIS

Any discussion of cirrhosis must be based on a firm understanding of hepatic anatomy and vascular supply. Conceptually, the liver can be thought of as an elaborate blood filtration system receiving blood from the hepatic artery and the portal vein (**Fig. 54-1**), with portal blood originating from the small intestines.[6] Blood enters the liver via the portal triad, which contains branches of the portal vein, hepatic artery, and bile ducts. It then drains through the sinusoidal space (also known as the space of Disse) of the hepatic lobule (**Fig. 54-2**), which is lined by the workhorses of the liver, the hepatocytes. Individual hepatocytes are arranged in plates that are one cell thick and organized around individual central veins. The six or more surfaces of each individual hepatocyte make contact with adjacent hepatocytes, border the bile canaliculi, or are exposed to the sinusoidal space. Filtered blood travels into the terminal hepatic venules, also called central veins, and then empties into larger hepatic veins and eventually into the inferior vena cava. There are functional gradients of hepatocytes based on oxygen saturation. Hepatocytes closest to the portal triad, which contains the hepatic artery, have greater oxygen saturation than those hepatocytes nearer to the terminal hepatic venule. Blood flows past hepatocytes in zone one, then zone two, and finally zone three before entering the central vein. Hepatocytes in zone one are involved in gluconeogenesis, urea synthesis, and oxidative energy metabolism while those in zone three carry out the functions of glycolysis and lipogenesis.

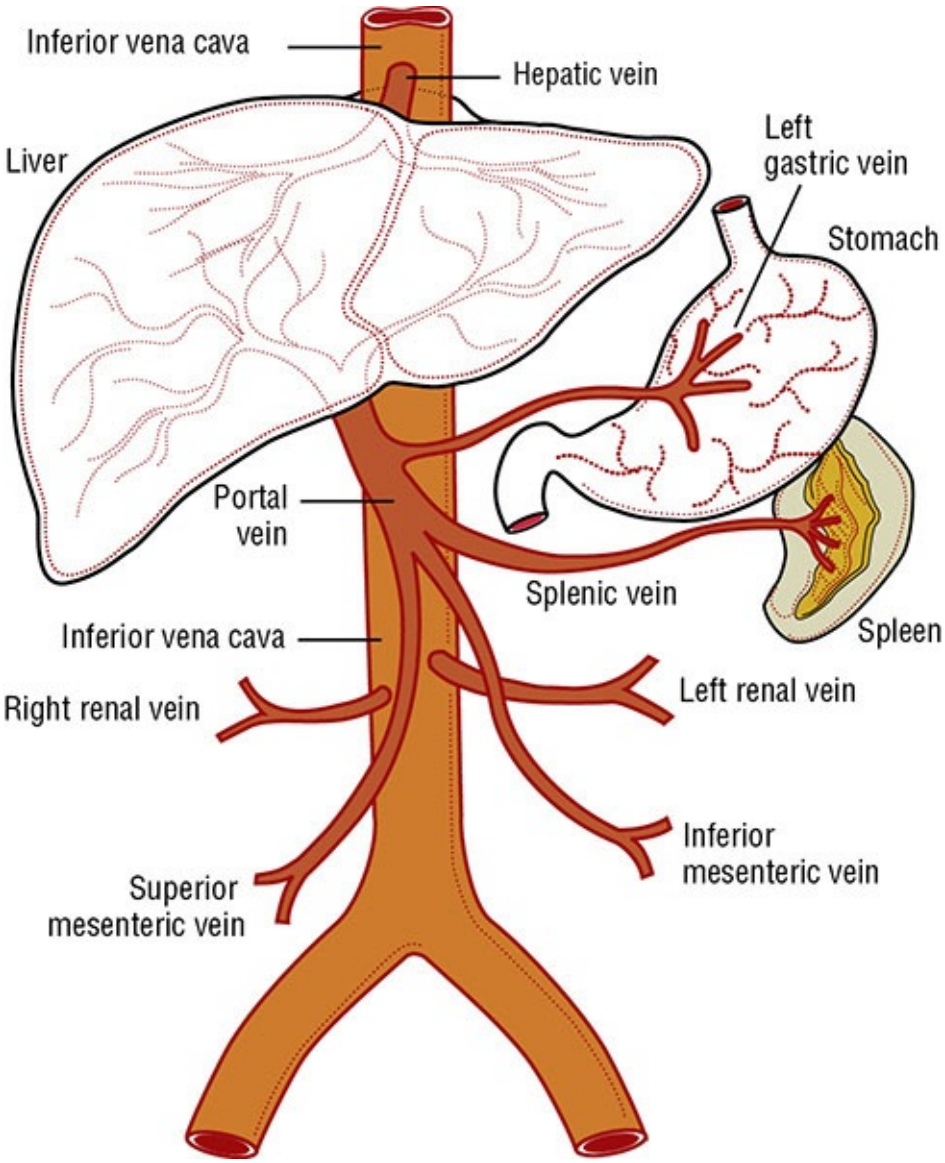


FIGURE 54-1 The portal venous system.

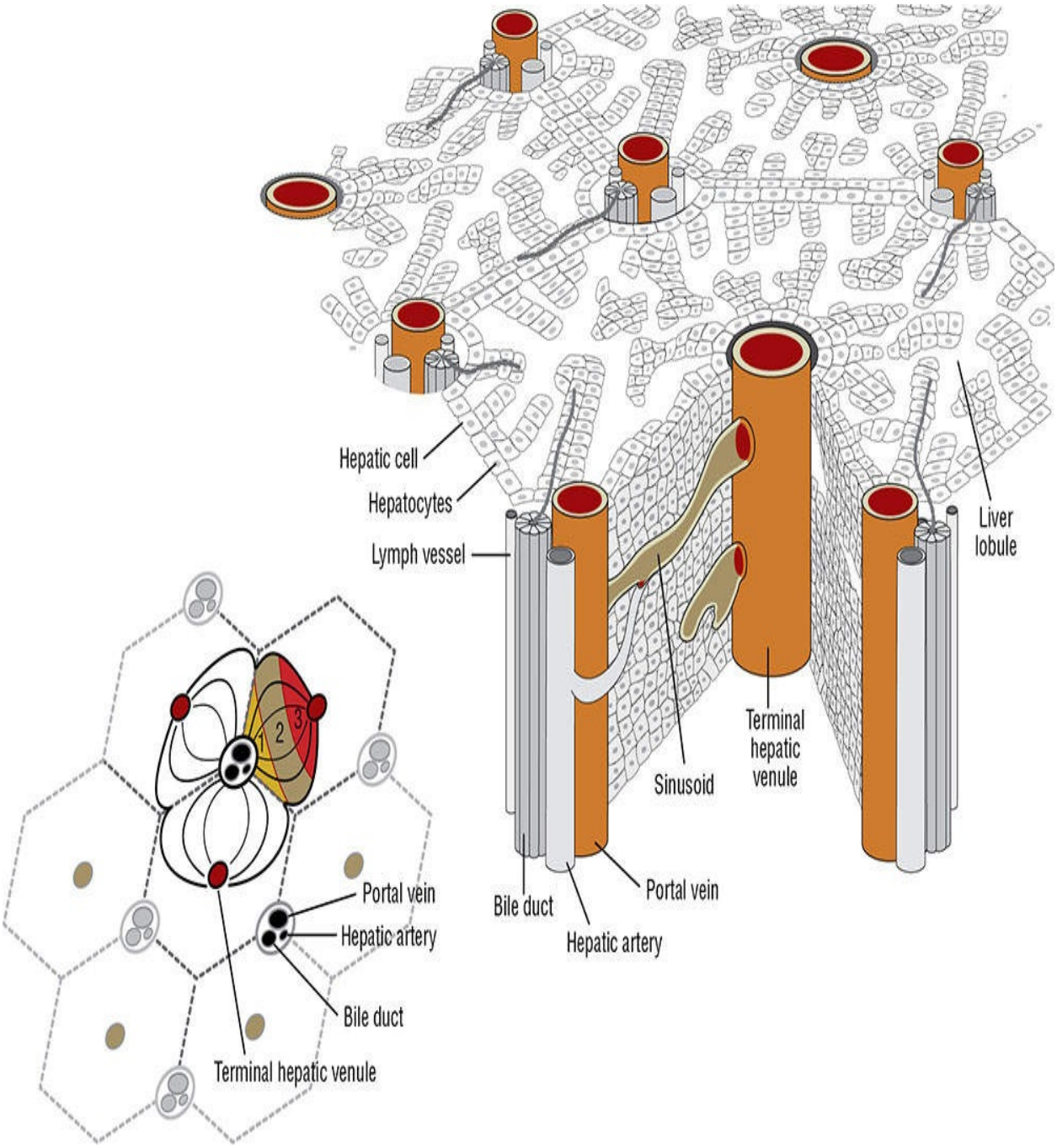


FIGURE 54-2 The hepatic lobule.

Normally, hepatic stellate cells function to store vitamin A and help to maintain the normal matrix in the sinusoidal space.[7] During chronic liver disease, however, hepatic stellate cells undergo an "activation" process, which is the central event in the development of hepatic fibrosis. Activation causes stellate cells to lose vitamin A, become highly proliferative, and synthesize fibrotic scar tissue, which accumulates in the sinusoidal space. Hepatic

sinusoidal endothelial cells lose their fenestrae and become less permeable, decreasing the ability of macromolecules to reach and interact with hepatocytes.[8] When fibrosis continues unsuppressed, cirrhosis develops.[7]

Cirrhosis causes changes to the splanchnic vasculature and circulation.[8] Splanchnic vasodilation and the formation of new blood vessels contribute to an increased splanchnic blood flow, formation of gastroesophageal varices, and variceal bleeding. Additionally, splanchnic vasodilation leads to hypoperfusion of the renal system that causes activation of the renin angiotensin-aldosterone system and, subsequently, significant fluid retention.[9] Therein lies the pathophysiology of ascites and renal dysfunction that often accompany chronic liver disease. Portal-systemic shunting may also occur and is involved in HE and other complications.[8]

ANATOMIC AND PHYSIOLOGIC EFFECTS OF CIRRHOSIS

Cirrhosis and the pathophysiologic abnormalities that cause it result in the commonly encountered problems of ascites, portal hypertension, esophageal varices, HE, and coagulation disorders. Other less common problems in patients with cirrhosis include hepatorenal syndrome, hepatopulmonary syndrome, and endocrine dysfunction. These are discussed under section “Management of Portal Hypertension and Variceal Bleeding.”

Ascites

Ascites is the accumulation of an excessive amount of fluid within the peritoneal cavity.[9] It is the most common major complication of cirrhosis.[5] Approximately half of all cirrhotic patients develop ascites within 10 years of diagnosis. As noted above, portal hypertension activates vasodilatory mechanisms leading to splanchnic vasodilation and a drop in blood pressure.[9] The juxtaglomerular apparatus of the proximal nephrons release renin in response to this drop in blood pressure. Renin converts angiotensinogen to angiotensin I which is then converted to angiotensin II. Angiotensin II causes increased thirst, aldosterone release from the adrenal cortex, with resultant sodium and water retention, and the secretion of vasopressin, also known as antidiuretic hormone. It is through these mechanisms that blood volume is increased. The extra volume is thought to “leak” into the peritoneal cavity from both the mesenteric vessels and diseased

liver itself. Hypoalbuminemia, which results from the decreased synthetic function of the diseased liver, contributes further to mesenteric fluid leakage. The end result of this complex process is the sustained peritoneal ascites of end-stage liver disease (**Fig. 54-3**).

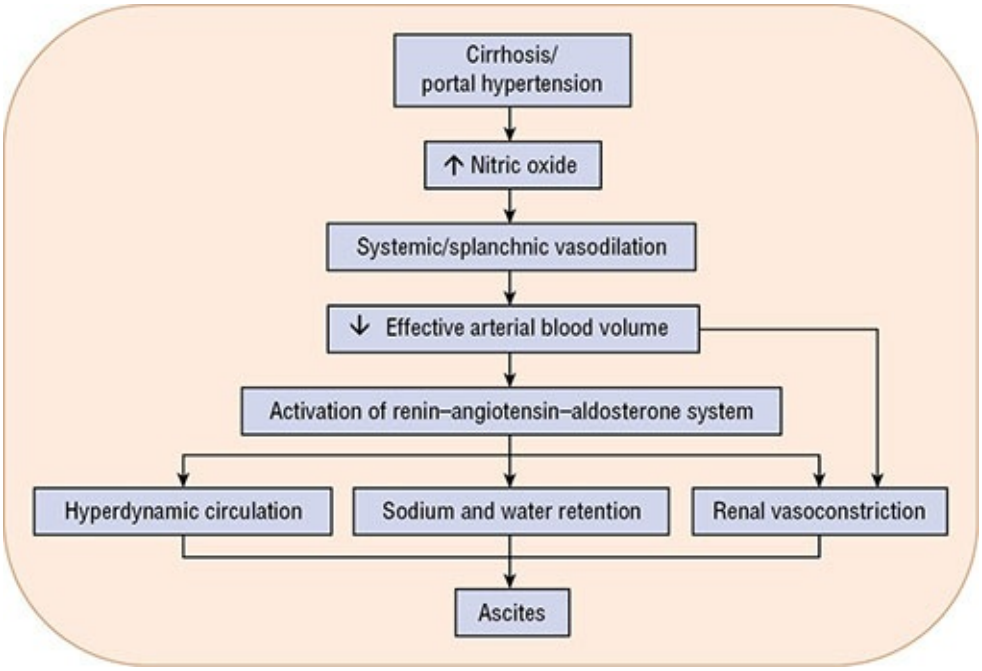


FIGURE 54-3 Pathogenesis of ascites.

Portal Hypertension and Varices

Sinusoidal portal hypertension is most often caused by cirrhosis.[10] It is associated with acute variceal bleeding, a medical emergency that is among the most severe complications of cirrhosis.[11] Portal hypertension is defined by the presence of a gradient of greater than 5 mm Hg (0.7 kPa) between the portal and central venous pressures (see Fig. 54-1).[10] This gradient is called the hepatic venous pressure gradient (HVPG). Esophageal and gastric varices and variceal bleeding may arise after an HVPG pressure gradient of 10 mm Hg (1.3 kPa) is reached.

Progression to bleeding can be predicted by Child-Pugh score, size of varices, and the presence of red wale markings on the varices. First variceal hemorrhage occurs at an annual rate of about 15% and carries a mortality of 7% to 15%. Re-bleeding is common following initial hemorrhage with a median rate of 60% and carries a mortality rate as high as 33%. Prevention of bleeding is a major goal in the therapy of portal hypertension, and strategies include both pharmacologic

and surgical approaches.

Hepatic Encephalopathy

Hepatic encephalopathy is a functional disturbance of the brain caused by liver insufficiency or portal systemic shunting that presents on a wide spectrum of symptom severity ranging from subclinical alterations to coma.[12] Symptoms of HE result from an accumulation of gut-derived nitrogenous substances in the systemic circulation as a consequence of decreased hepatic functioning and shunting through portosystemic collaterals bypassing the liver.[13] Once these substances enter the CNS, they cause alterations of neurotransmission that affect consciousness and behavior. Ammonia is the most commonly cited culprit in the pathogenesis of HE, but glutamine, benzodiazepine receptor agonists, and aromatic amino acids are also potential causes.[12,13] Arterial ammonia levels are commonly increased in both acute and chronic liver diseases, but an established correlation between blood ammonia levels and mental status does not exist.[13] A normal ammonia level finding brings the diagnosis of HE into question.[12] Interventions to lower blood ammonia levels remain the mainstay of treatment for HE.[12,13]

Hepatic encephalopathy is categorized as type A, B, or C.[12] Type A is HE induced by acute liver failure, type B is due to portal-systemic bypass without associated intrinsic liver disease, and type C is HE that occurs in patients with cirrhosis. The severity of HE symptoms, time course (whether episodic, recurrent, or persistent), and whether incited by a precipitating factors (such as infection, GI bleeding, an electrolyte disorder, or constipation) are additional ways in which HE is classified. The majority of episodic cases of HE caused by cirrhosis are associated with a precipitant. For this reason, it is important that precipitating factors be sought and treated when present.

CLINICAL PRESENTATION

Cirrhosis

Signs and Symptoms

- Asymptomatic
- Hepatomegaly and splenomegaly
- Pruritus, jaundice, palmar erythema, spider angiomata, and

hyperpigmentation
- Gynecomastia and reduced libido
- Ascites, edema, pleural effusion, and respiratory difficulties
- Malaise, anorexia, and weight loss
- Encephalopathy

Laboratory Tests

- Hypoalbuminemia
- Elevated prothrombin time (PT)
- Thrombocytopenia
- Elevated alkaline phosphatase
- Elevated aspartate transaminase (AST), alanine transaminase (ALT), and γ-glutamyl transpeptidase (GGT)

Coagulation Defects

End-stage chronic liver disease is associated with decreased synthetic capability of the liver leading to decreased levels of most procoagulant factors as well as the naturally occurring anticoagulants, antithrombin, protein C and protein S.[14] However, two procoagulant factors, factor VIII and von Willebrand factor, are actually elevated in chronic liver disease. Traditionally, it was thought that chronic liver disease induced an acquired bleeding disorder owing to the decrease in most procoagulant factors, but it is now believed that, thanks to the increased levels of factor VIII and von Willebrand factor and the decreased levels of natural anticoagulants (antithrombin, protein C, and protein S), that these patients actually live in a tenuous state of rebalanced hemostasis. The rebalanced homeostasis seen in chronic liver disease can be tipped toward either thrombosis or clinically significant bleeding at any time depending on the circumstances experienced by the patient at the time. The prothrombin time (PT) is a standard component of the Child-Pugh scoring system and the international normalized ratio (INR) is utilized in the model for end-stage liver disease, a prognostic evaluation tool.[15,16] The ability of the PT and INR to accurately measure bleeding risk and assist with estimation of the severity of a patient's liver disease has been called into question.[14]

Both platelet number and function may be affected in cirrhosis.

Thrombocytopenia, a common finding in cirrhosis, could promote bleeding. However, von Willebrand factor, the binding site for platelets, is not decreased by cirrhosis and thrombin generation assays show that platelet procoagulant activity is actually preserved in patients with cirrhosis. Fibrinolysis is another process that is likely rebalanced in cirrhosis. While α 2-antiplasmin and thrombin-activatable fibrinolysis inhibitor levels are reduced, tissue plasminogen activator levels are increased. These changes would be expected to increase the risk for bleeding. However, procoagulant changes, including reduced plasminogen levels and normal to increased platelet activator inhibitor levels, occur concurrently, which provide a homeostasis in the fibrinolysis process.

CLINICAL PRESENTATION

Clinical Presentation: Portal Hypertension

Cirrhotic patients may be asymptomatic; in fact, one-third never develops symptoms.[17] Initial symptoms may be nonspecific including fatigue, loss of appetite, and weight loss. Patients may also present with much more significant symptomatology secondary to decompensation related to cirrhosis complications such as ascites (abdominal distention), SBP (abdominal discomfort with fever), hepatopulmonary syndrome (clubbing), hepatorenal syndrome (fluid overload, oliguria, renal failure), HE (confusion, lethargy), and/or variceal bleeding (secondary to esophageal or gastric varices from portal hypertension).

The approach to a patient with suspected liver disease begins with a thorough history and physical examination. In addition to fatigue, loss of appetite, and weight loss, patients may also experience other nonspecific signs. Muscle wasting, palmar erythema, spider angiomas, parotid gland enlargement, white nails, Dupuytren contracture, peripheral neuropathy and metabolic complications including gynecomastia, testicular atrophy, and axillary hair loss are all possibly related to cirrhosis.

Diagnostics for cirrhosis include liver function tests, coagulation tests, complete blood count, and serologic tests for viral causes including hepatitis B and C. A thorough history is key in determining if alcoholism is the likely cause of a patient’s cirrhosis. A basic history and physical may also uncover the presence of obesity and history of diabetes that are suggestive of nonalcoholic fatty liver disease. Additional testing may include an antinuclear antibody titer to evaluate for the presence of autoimmune hepatitis; serum iron and transferrin saturation, possibly in conjunction with genetic testing, to look for

hemochromatosis; and alpha-1 antitrypsin level and genotyping to test for alpha-1 antitripysin deficiency, a rare disease, but one that can lead to liver disease as well as lung damage. When the underlying cause is still unable to be elucidated, additional testing for antimitochondrial antibodies or a magnetic resonance cholangiopancreatography to look for strictures and dilations of the bile ducts indicating primary biliary cholangitis may be completed. Wilson disease can be screened for using serum ceruloplasmin and copper levels.

Liver Chemistries

Liver chemistries or liver tests are actually markers of liver injury rather than function, though they are commonly referred to as liver function tests.[18] A comprehensive metabolic profile includes AST, ALT, alkaline phosphatase, bilirubin, and albumin. Additionally, the PT and GGT are needed. Liver chemistries are often the first step in the evaluation of patients who present with symptoms or signs suggestive of cirrhosis.[17] The use of liver function tests in the diagnosis and management of cirrhosis is discussed in the following sections. It may be useful to group the tests into two broad categories: (1) markers of liver injury such as AST, ALT and alkaline phosphatase and (2) markers of hepatocellular function such as PT, bilirubin, and albumin.[18]

Aminotransferases

The aminotransferases, AST and ALT, are enzymes involved in the transfer of amino groups of aspartate and alanine to ketoglutaric acid. Also referred to as transaminases, their presence in serum is a marker of hepatocellular injury. While AST is present in the liver, cardiac tissue, skeletal muscle, kidney and brain, ALT is primarily found in the liver. Liver injury, whether acute or chronic, results in increases in the serum concentrations of the aminotransferase enzymes. The degree of elevation, rate of rise, and whether AST > ALT or ALT > AST are helpful in suggesting possible etiologies.

Transaminases will typically be severely elevated as a result of acute insults including conditions like acute viral hepatitis, autoimmune hepatitis, ischemic hepatitis/shock liver, acute Budd-Chiari syndrome, hepatic artery occlusion, diffuse infiltration of cancer into the liver, acute biliary obstruction, liver trauma, eclampsia, and Wilson disease. The highest elevations (>10,000 units per liter [167 μkat/L]) are most apt to occur in shock liver and drug- or toxin-induced hepatitis. Borderline and mild transaminase elevations are seen in a variety of liver and nonliver disease states.

The ratio of AST to ALT with AST>ALT is more likely when cirrhosis of any etiology exists but also occurs in alcoholic and ischemic liver disease. Seventy percent of patients with alcoholic liver disease had ratios greater than two and 92% of patients had ratios greater than one.[19]

Alkaline Phosphatase and γ-Glutamyl Transpeptidase

Elevated serum levels of alkaline phosphatase and GGT occur in cases of liver injury with a cholestatic pattern and therefore often accompany conditions such as primary biliary cirrhosis, primary sclerosing cholangitis, drug-induced cholestasis, and bile duct obstruction.[18] Alkaline phosphatase is not found solely in the liver. When elevations of alkaline phosphatase occur with subsequent elevations of transaminases, confirmation of hepatic origin is not needed. When alkaline phosphatase is elevated without other concurrent liver test abnormalities, the GGT is evaluated since combined elevations of both alkaline phosphatase and GGT levels increase clinical suspicion of hepatic etiology.

A mixed pattern liver injury is evidenced by elevations of both AST/ALT levels and alkaline phosphatase. An R ratio be calculated in these cases which is achieved by utilization of the following formula: R = (ALT value/ALT upper limit of normal)/(alkaline phosphatase value/alkaline phosphatase upper limit of normal). An R ratio above 5 indicates hepatocellular injury. An R ratio below 2 it indicates cholestatic disease. Ratios between 2 and 5 represent a mixed pattern.

Child-Pugh Classification and Model for End-Stage Liver Disease Score

The Child-Pugh classification system has gained widespread acceptance as a means of quantifying the myriad of effects of the cirrhotic process on the laboratory and clinical manifestations of this disease.[15] Recommended drug dosing adjustments for patients in liver failure, when available, are normally based on the Child-Pugh score. The newer MELD-Na scoring system is now the accepted classification scheme used by the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) in the allocation livers for transplantation.[16] The Child-Pugh classification system employs a combination of physical and laboratory findings (**Table 54-2**), whereas the MELD score calculation takes into account a patient's serum creatinine, bilirubin, INR, and etiology of liver disease, omitting the more subjective reports of ascites and encephalopathy used in the Child-Pugh system.

TABLE 54-2 Criteria and Scoring for the Child-Pugh Grading of Chronic Liver Disease

Score	1	2	3
Total bilirubin (mg/dL)	<2 (34.2 µmol/L)	2-3 (34.2-51.3 µmol/L)	>3 (51.3 µmol/L)
Albumin (g/dL)	>3.5 (35 g/L)	2.8-3.5 (28-35 g/L)	<2.8 (28 g/L)
Ascites	None	Mild	Moderate
Encephalopathy (grade)	None	1 and 2	3 and 4
Prothrombin time (seconds prolonged)	<4	4-6	>6

Grade A, <7 points; grade B, 7-9 points; grade C, 10-15 points.

Data from Reference 15.

The MELD scoring calculation is as follows[20]:

$$\begin{aligned}\text{MELD score}^* = {} & 9.57 \times \log_e(\text{creatinine [mg/dL]}) \\ & + 3.78 \times \log_e(\text{bilirubin [mg/dL]}) \\ & + 11.20 \times \log_e(\text{INR}) + 6.43\end{aligned}$$

or using SI units:

$$\begin{aligned}\text{MELD score}^* = {} & 9.57 \times \log_e(\text{creatinine [µmol/L]} \times 0.01131) \\ & + 3.78 \times \log_e(\text{bilirubin [µmol/L]} \times 0.05848) \\ & + 11.20 \times \log_e(\text{INR}) + 6.43\end{aligned}$$

$$\begin{aligned}\text{MELD-Na score} = {} & \text{MELD} - (\text{sodium [mEq/L]}) - (0.025 \times \text{MELD} \\ & \times (140\text{-sodium [mEq/L]})) + 140\end{aligned}$$

or using SI units:

$$\begin{aligned}&\text{MELD-Na score} = \text{MELD} - (\text{sodium [mmol/L]}) - \\ &(0.025 \times \text{MELD} \times (140 - \text{sodium [mmol/L]})) + 140\end{aligned}$$

These classification systems are important because they are used to assess and define the severity of cirrhosis, and predict patient survival, surgical outcome, and risk of variceal bleeding.

Bilirubin

Bilirubin is the product of the breakdown of hemoglobin molecules.[18] Elevations in serum conjugated (or direct) bilirubin indicate hepatocellular dysfunction or cholestasis. When total bilirubin elevation exists, it should be fractionated into direct (conjugated) and indirect (unconjugated) levels. Indirect bilirubin elevations occur due to over-production (as seen with hemolysis), decreased uptake, or decreased hepatic conjugation of bilirubin and can be found in conditions like Gilbert's syndrome. Direct hyperbilirubinemia is the result of liver injury or biliary obstruction and is associated with a number of hepatic diseases including cirrhosis. When cirrhosis has been established, the degree of bilirubin elevation has prognostic significance and is used as a component of the Child-Pugh and MELD scoring systems for quantifying the severity of cirrhosis.[15,20]

Albumin and Coagulation Factors

Albumin and coagulation proteins are markers of hepatic synthetic activity and are therefore used to estimate the level of hepatic functioning in cirrhosis. Albumin and PT are used in the Child-Pugh system for quantifying liver disease, and the INR is used in the MELD scoring system as a marker of coagulation.[15,20] Reduction in albumin usually indicates a disease duration of more than 3 weeks whereas severe liver disease can cause PT elevation in less than 24 hours. These tests are not specific to liver disease as any significant illness can reduce albumin levels and the PT can be elevated for a variety of reasons including anticoagulation with warfarin, vitamin K deficiency, and steatorrhea.

Thrombocytopenia

Thrombocytopenia is a common feature of chronic liver disease.[14] The platelet count is rarely below 30,000/mm^3 to 40,000/mm^3 (30×10^9/L to 40 x 10^9/L) though. When liver abnormality is suspected, a complete blood cell count that includes platelets should be evaluated.

Imaging and Biopsy

Ultrasound technology can be used to detect more advanced cirrhosis as well as to evaluate the presence of portal hypertension and ascites. A liver in the stage of advanced cirrhosis will appear small and nodular on ultrasound.[17] Ultrasound may also be used to evaluate the presence of portal hypertension and ascites.

Elastography via ultrasound or magnetic resonance may be useful in early cirrhosis or when other imaging is not definitive. Sometimes a liver biopsy is required when less invasive testing is inconclusive or when the results of biopsy may dictate the most appropriate management for the patient.

TREATMENT

General Approaches to Treatment

General approaches to therapy in cirrhosis should include the following:

1. Identify and eliminate, where possible, the causes of cirrhosis (eg, alcohol abuse).
2. Assess the risk for variceal bleeding and begin pharmacologic prophylaxis when indicated. Prophylactic endoscopic therapy can be used for patients with high-risk medium and large varices as well as in patients with contraindications or intolerance to nonselective β-adrenergic blockers. Endoscopic therapy is also appropriate for patients suffering acute bleeding episodes. Variceal obliteration with endoscopic techniques in conjunction with pharmacologic intervention is the recommended treatment of choice in patients with acute bleeding.
3. Evaluate the patient for clinical signs of ascites and manage with pharmacologic therapy (eg, diuretics) and paracentesis. Careful monitoring for SBP should be used in patients with ascites who experience acute deterioration of their clinical status.
4. Recognize that HE is a common complication of cirrhosis that requires clinical vigilance and treatment with dietary restriction, elimination of precipitating factors, and therapy to lower ammonia levels.
5. Monitor patients for signs of hepatorenal syndrome, pulmonary insufficiency, and endocrine dysfunction.

Desired Outcomes

The desired therapeutic outcomes can be viewed in two categories: *resolution of acute complications* such as tamponade of bleeding and resolution of hemodynamic instability for an episode of acute variceal hemorrhage and *prevention of complications* through lowering of portal pressure with medical

therapy using nonselective β-adrenergic blocker therapy or supporting abstinence from alcohol. Treatment end points and desired therapeutic outcomes are presented for each of the recommended therapies discussed.

Management of Portal Hypertension and Variceal Bleeding

The management of varices involves three strategies: (a) primary prophylaxis (prevention of the first bleeding episode); (b) treatment of acute variceal hemorrhage; and (c) secondary prophylaxis (prevention of re-bleeding in patients who have previously bled).[10] It is also possible for a patient to have been diagnosed with cirrhosis and portal hypertension but have no varices. These patients would be considered to be in a pre-primary prophylaxis stage. No specific treatment is recommended for pre-primary prophylaxis and, for that reason, the focus of this chapter will be primary prophylaxis, treatment of acute variceal bleeding, and secondary prophylaxis.

Primary Prophylaxis

β-Adrenergic Blockade The mainstay of primary prophylaxis is the use of nonselective β-adrenergic blocking agents such as propranolol, nadolol, or carvedilol.[10,11] These agents reduce portal pressure by reducing portal venous inflow via two mechanisms: a decrease in cardiac output through β_1-adrenergic blockade and a decrease in splanchnic blood flow through β_2-adrenergic blockade that results in unopposed α-1 activity.[10]

Endoscopic Variceal Ligation (EVL) EVL is an endoscopic therapy that consists of placing rubber bands around varices until the varices are obliterated.

Treatment Recommendations: Variceal Bleeding—Primary Prophylaxis

2 All patients with cirrhosis should be screened for varices at the time of diagnosis.[10,11] Transient elastography that shows liver stiffness below 20 kPa in patients with platelets over 150,000/mm^3 (150 × 10^9/L) do not require screening endoscopy.[11] Others should undergo screening endoscopy to identify and evaluate varices. β-adrenergic blocker therapy is not indicated in patients without varices to prevent the formation of varices.[10,11] Patients with small varices plus

risk factors for variceal hemorrhage including red wale marks or Child-Pugh grade C should receive prophylactic therapy with a nonselective β-adrenergic blocker. β-adrenergic blocker therapy is recommended preferentially to EVL in this situation due to the technical difficulty of EVL in the treatment of small varices. β-adrenergic blocker therapy is optional for patients with small varices in the absence of risk factors, but additional studies to confirm benefit in this population are needed. All patients found to have medium to large varices that have not bled should receive primary prophylaxis therapy with a nonselective β-adrenergic blocker or EVL. The choice of treatment should be based on a consideration of resources and expertise as well as patient preferences and characteristics with a particular emphasis on side effects and contraindications.[11] If β-adrenergic blocker therapy is chosen, initiate therapy with oral propranolol 20 mg twice daily or nadolol 20 to 40 mg once daily and titrate every 2 to 3 days to maximal tolerated dose or to a heart rates of 55 to 60 beats/min.[10,21] Or, rather than propranolol or nadolol, carvedilol could be chosen and started at 3.125 mg twice daily with slow titration at intervals of 1 to 2 weeks.[21] In addition to β-adrenergic blockade, carvedilol also provides anti-α-adrenergic activity and enhances the release of nitric oxide.[21,22] Carvedilol reduces portal pressure to a greater degree than propranolol and nadolol and nonresponders to propranolol have good hemodynamic response when switched to carvedilol.[23,24] Once a patient is started on nonselective β-adrenergic blocker therapy, it should generally be continued indefinitely but the patient must be monitored for development of contraindications such as renal impairment and hypotension that may accompany end-stage liver disease.[11] Following initiation and appropriate titration of the β-adrenergic blocker, further endoscopic surveillance is not needed.[10,21] If EVL is chosen, it will be performed every 2 to 4 weeks until the obliteration of varices.[10] Follow-up surveillance will occur at 1 to 3 months and again every 6 to 12 months thereafter.

Approximately 15% of patients have absolute contraindications to nonselective β-adrenergic blockers (ie, those with asthma or those with hypoglycemia unawareness while receiving antihyperglycemic therapy) and another 15% have common side effects such as fatigue, weakness, and shortness of breath that contribute to medication nonadherence.[10] Patients who qualify for β-adrenergic blocker therapy as primary prophylaxis, but who are unable to take or continue it, should be considered for alternative therapy with EVL.[11] Also, EVL may be considered as a possible first option for primary prophylaxis in patients with high-risk medium to large varices.

Acute Variceal Hemorrhage

Variceal hemorrhage is a medical emergency that carries a mortality rate of 7% to 15%, requires admission to an intensive care unit, and is one of the most feared complications of cirrhosis.[10] Treatment of acute variceal bleeding includes general stabilizing and assessment measures as well as specific measures to control the acute hemorrhage and prevent complications.

Initial treatment goals include (a) adequate blood volume resuscitation, (b) protection of airway from aspiration of blood, (c) prophylaxis against SBP and other infections, (d) control of bleeding, (e) prevention of re-bleeding, (f) preservation of liver function/prevention of HE, and (g) prevention of acute kidney injury.[22] Prompt stabilization of blood volume with a goal of maintaining hemodynamic stability and a hemoglobin of 7 g/dL (70 g/L; 4.34 mmol/L) to 8 g/dL (80 g/L; 4.96 mmol/L) should be undertaken.[10,22] Use of recombinant factor VIIa therapy is not recommended in cirrhotic patients with GI hemorrhage at this time.[10] Combination pharmacologic therapy plus endoscopic therapy with EVL (preferred), or sclerotherapy if EVL is not technically feasible, is considered the most rational approach to the treatment of acute variceal bleeding.[10,22] Endoscopy should be performed as soon as possible, but at least within 12 hours of admission.

Vasoactive drug therapy is used to stop or slow bleeding as soon as a diagnosis of variceal bleeding is suspected and is started before endoscopy.[10] The vasoactive drug used to manage acute variceal bleeding in the United States is the somatostatin analogue octreotide. Antibiotic therapy to prevent SBP and other infections, should be implemented upon admission.[11] Intravenous ceftriaxone 1 g/24 hours is recommended. A 250 mg dose of erythromycin intravenously prior to endoscopy may be used to accelerate gastric emptying of clots and improve visibility during the endoscopic procedure.[11,22] Should episodic HE occur secondary to acute GI bleeding, lactulose may be utilized. **Figure 54-4** presents an algorithm for the management of variceal hemorrhage.

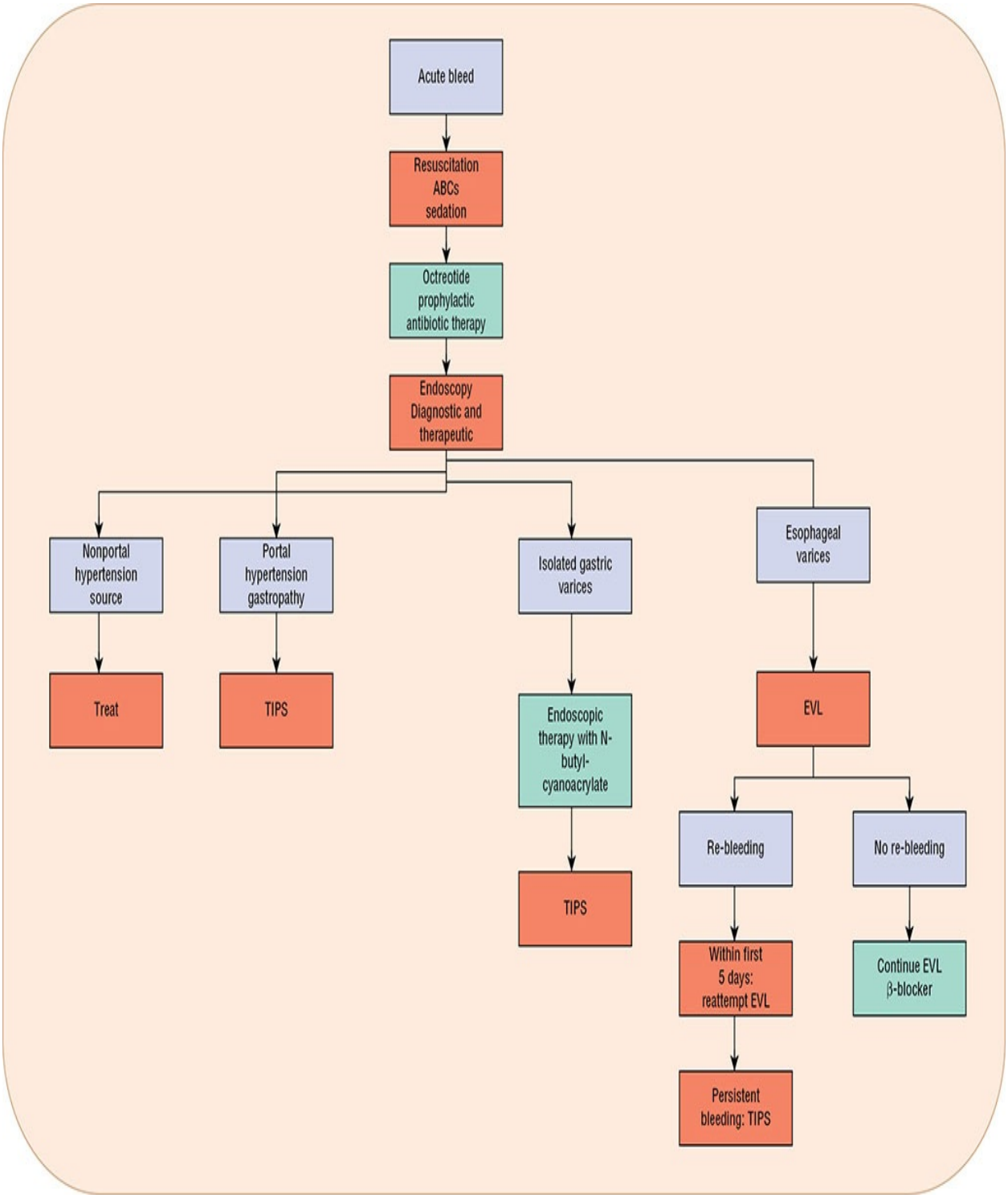
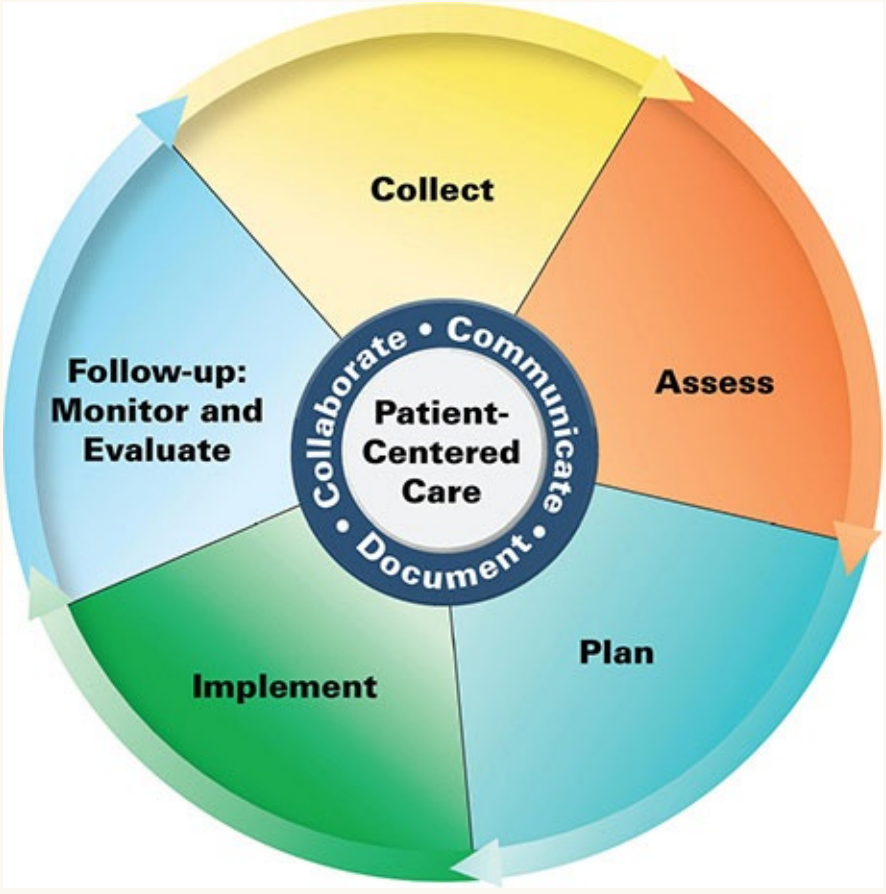


FIGURE 54-4 Management of acute variceal hemorrhage. (ABCs, Airway Breathing Circulation; EVL, endoscopic variceal ligation; TIPS, transjugular intrahepatic portosystemic shunt.)

Octreotide

The splanchnic vasoconstriction from octreotide therapy is due to inhibition of the release of vasodilatory peptides such as glucagon; however, a local vasoconstrictive effect also exists.[25] Somatostatin analogues, including octreotide, are associated with fewer side effects as compared with the most potent splanchnic vasoconstrictor, vasopressin. The primary side effects of octreotide therapy are hyperglycemia, vomiting, bradycardia, hypertension, arrhythmia, and abdominal pain.[10,22] The recommended dosing of octreotide for variceal bleeding consists of an initial IV bolus of 50 mcg followed by a continuous IV infusion of 50 mcg/h.[10] Octreotide can be continued from 2 up to 5 days after acute variceal bleeding in an effort to prevent re-bleeding. Vasoactive therapy discontinuation can be considered once the patient is free of bleeding for at least 24 hours.



Patient Care Process for Cirrhosis

Collect

- Patient medical history
  - Recent history of anorexia or weight loss
  - Risk factors for hepatitis B and C
  - Personal and family history of autoimmune or hepatitic diseases
- Social history (specifically ethanol use—quantity and duration)
- Current medications including nonprescription medications
- Objective data
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2-saturation
  - Labs including albumin, bilirubin, complete blood count (CBC) with platelets, prothrombin time (PT), international normalized ratio (INR), alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transpeptidase (GGT)

Assess

- Presence of jaundice, pruritis, palmar erythema, spider angiomata and hyperpigmentation
- Presence of medications that can cause cirrhosis (see Table 54-1)
- Presence of complications of cirrhosis (ascites, portal hypertension, esophageal varices, hepatic encephalopathy, coagulation disorders)
- Child-Pugh score (see Table 54-2) for need for medication dosage adjustments
- Patient's willingness to stop drinking alcohol

Plan*

- Identify and treat possible causes of cirrhosis (ie, hepatitis C)
- Remove offending medications that may cause or exacerbate cirrhosis or complications of cirrhosis
- Create a plan to treat acute complications of cirrhosis, if present
  - Ascites: sodium restriction and furosemide + spironolactone (see Table 54-4)
  - Portal Hypertension

    Primary prevention of esophageal varices: beta-blocker (nadolol, propranolol, or carvedilol) and/or EVL for prevention

Treatment of acute variceal bleeding: octreotide + EVL, SBP prophylaxis (eg, ceftriaxone, ciprofloxacin or trimethoprim/sulfamethoxazole DS) × 7 days (see Fig. 54-4 and Table 54-3)

Secondary prevention: nadolol or propranolol + EVL

- Spontaneous bacterial peritonitis

  Treatment: empiric antibiotic therapy with appropriate antibiotic (ie, cefotaxime) based on ascitic fluid PMN count and/or symptoms (see Table 54-4)

  Secondary prevention: sulfamethoxazole/trimethoprim DS or ciprofloxacin daily (see Table 54-4)

- Hepatic encephalopathy: dietary protein restriction and lactulose +/− rifaximin

Implement

- Provide patient education and assistance for achieving abstinence from alcohol, if applicable
- Discuss all elements of treatment plan (medications and dietary modifications) with patient
- Provide vaccines as indicated
- Adjust medication doses as needed based on major organ function and patient characteristics.
- Plan to assess progress of treatment including efficacy and adverse effects of treatments (see Table 54-6)

Follow-up: Monitor and Evaluate

- Monitor for long-term efficacy and adverse effects
- Patient's adherence to alcohol abstinence, prescribed medications, and dietary modifications
- Resolution of complications of cirrhosis
- Evaluate for possibility of liver transplant and need for dietitian (ie, sodium and protein restriction)

**Collaborate with patient, caregivers, and other healthcare professionals.*

Prevention of Spontaneous Bacterial Peritonitis

Cirrhotic patients with active bleeding are at high risk of severe bacterial infections such as SBP.[26] Short-term prophylactic antibiotic therapy to reduce the risk of infection during episodes of bleeding not only reduces the likelihood of infections but also reduces the incidence of re-bleeding and increases survival. For these reasons, a short course (7 days maximum) of ceftriaxone 1 g intravenously daily, oral ciprofloxacin 500 mg twice daily (since norfloxacin is no longer available), or trimethoprim-sulfamethoxazole one double-strength tablet twice daily is recommended. In patients with severe cirrhosis in areas with high quinolone resistance, IV ceftriaxone 1 g/day may be preferable.[11]

Endoscopic Interventions: Sclerotherapy and Band Ligation

The Baveno VI Consensus Report recommends that endoscopy be performed within 12 hours of admission in cases of upper GI bleeding. Endoscopy is used to diagnose variceal bleeding, and endoscopic techniques, particularly EVL, are used to stop variceal bleeding. EVL can be repeated if hemorrhage is not controlled or in the event of early recurrence of bleeding (within the first five days). EVL is more effective than sclerotherapy with greater control of hemorrhage, less risk for re-bleeding, lower likelihood of adverse events, and lower mortality.[10] Therefore, consensus recommendation calls for EVL (in conjunction with pharmacologic therapy) as the recommended form of endoscopic therapy for acute variceal bleeding.[11] Endoscopic injection of the tissue adhesive ***N***-butyl cyanoacrylate is recommended to control acute *gastric* variceal bleeding from isolated gastric varices and gastroesophageal varices type 2 that extend beyond the cardia. EVL or tissue adhesive can be used for bleeding from gastroesophageal varices type 1. A pre-endoscopy infusion of erythromycin 250 mg IV, 30 to 120 minutes prior to the procedure, is recommended in the absence of QT interval prolongation.

Interventional and Surgical Treatment Approaches

Child-Pugh class C patients and those in Class B with active hemorrhage at the time of diagnostic endoscopy make up less than 20% of patients admitted with variceal hemorrhage, but these patients do comprise a group who are at high risk for failing standard therapy with EVL plus octreotide.[10] In these cases, early transjugular intrahepatic portosystemic shunt (TIPS) may be considered instead

of standard therapy. The TIPS procedure involves the placement of one or more stents between the hepatic vein and the portal vein (**Fig. 54-5**). TIPS (preferably with polytetrafluoroethylene-covered stents) is also recommended for patients who fail to achieve or maintain hemostasis despite combined endoscopic and pharmacologic therapy.[11]

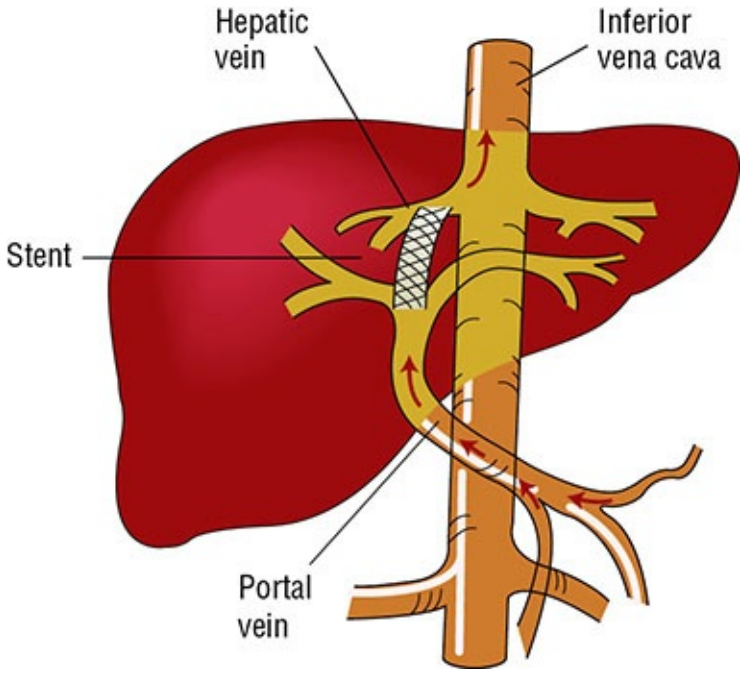


FIGURE 54-5 Transjugular intrahepatic portosystemic shunt (TIPS).

Balloon tamponade may be used as a bridge therapy to control variceal bleeding temporarily (maximum of 24 hours).[11] It should be reserved as a temporizing measure until a more definitive treatment, such as TIPS, can be performed.

Treatment Recommendations: Variceal Hemorrhage

4 Patients require cautious resuscitation with blood products to correct intravascular losses.[10,11,22] Drug therapy with octreotide should be initiated early to control bleeding and facilitate diagnostic and therapeutic endoscopy. Therapy is initiated with an IV bolus of 50 mcg and is followed by a continuous infusion of 50 mcg/h for 2 to 5 days.[10] Patients should be monitored for bradycardia, hypertension, arrhythmia, and abdominal pain. Endoscopy is recommended in any patient with suspected upper GI bleeding due to ruptured varices.[10,11,22] EVL is the recommended form of endoscopic therapy. An additional endoscopic therapy option is injection of the tissue adhesive ***N***-butyl cyanoacrylate for

gastric varices.[11] Short-term antibiotic prophylaxis (maximum 7 days) is recommended.[11,26] Appropriate choices include ceftriaxone 1 g intravenously daily, oral ciprofloxacin 500 mg twice daily (since norfloxacin is no longer available), or trimethoprim-sulfamethoxazole one double-strength tablet twice daily. In patients with advanced cirrhosis in areas of high quinolone resistance, IV ceftriaxone 1 g daily may be preferred.[11] Surgical procedures like TIPS are employed as salvage therapy in patients who have failed repeated endoscopy and vasoactive drug therapy.[11] In patients at highest risk for standard treatment failure, a preemptive decision to utilize early TIPS may occur.

Secondary Prophylaxis

Because re-bleeding after initial control of variceal hemorrhage occurs in a median of 60% of patients and because re-bleeding carries a mortality rate of 33%, it is inappropriate to simply observe patients for evidence of further bleeding.[10] Only patients who undergo shunt surgery or TIPS to control their initial acute bleeding require no further intervention as secondary prophylaxis. Patients who undergo one of these procedures to treat their initial bleeding should be referred for transplantation if they are a candidate. For all others, combination therapy with a β-adrenergic blocker and chronic EVL to eradicate varices is the treatment of choice for secondary prophylaxis of variceal bleeding.[10,11] Nadolol and propranolol are the recommended β-adrenergic blockers for secondary prophylaxis because carvedilol has not been studied for the prevention of re-bleeding.[11] Secondary prophylaxis should be started once vasoactive drug therapy is discontinued and as soon as possible (as early as day 6) following the acute bleeding event.[10]

Drug Therapy

The combination of EVL and a nonselective β-adrenergic blocking agent is recommended since pharmacologic therapy provides protection against re-bleeding until EVL can be repeated a sufficient number of times to obliterate all varices.[10] Patients who refuse EVL should still receive β-adrenergic blocker monotherapy.[11] Likewise, EVL monotherapy is not recommended unless the patient has contraindication or intolerance to β-adrenergic blocker therapy. The addition of isosorbide mononitrate to nonselective β-adrenergic blocker therapy reduces portal pressure more than a β-adrenergic blocker alone, but there is no difference in the overall rate of re-bleeding with this combination and side effects are more likely than with β-adrenergic blocker monotherapy (namely,

headache and light-headedness).[10] Pharmacologic therapy (either isosorbide mononitrate plus nonselective β-adrenergic blocker therapy or β-adrenergic blocker therapy alone) plus EVL is associated with lower re-bleeding rates than either pharmacologic or EVL therapy alone.[10]

The lowest rate of variceal re-bleeding occurs in patients when pharmacologic therapy leads to a reduction in HVPG of at least 10% of baseline or to a measurement less than or equal to 12 mm Hg (1.6 kPa).[11] Ideally, portal pressure monitoring would be used to assess the response to nonselective β-adrenergic blocker therapy and identify responders from nonresponders earlier in the treatment course. Nonselective β-blocker therapy should be utilized regardless of the possibility of HVPG monitoring.

There is ongoing debate regarding the use of β-adrenergic blockers for prophylaxis against variceal bleeding in patients with refractory ascites.[21] The Baveno VI Consensus statement recommends reduction or discontinuation of β-adrenergic blockers in secondary prophylaxis patients with systolic blood pressure <90 mmHg, serum sodium <130 mEq/L (mmol/L), or acute kidney injury.[11] This recommendation assumes that other precipitating drug therapies have already been removed. Re-initiation of β-adrenergic blocker therapy can be considered if the patient's blood pressure, serum sodium and/or kidney function improve, but this should be done carefully and with a slow titration. This may also represent a time when TIPS is considered.

Treatment Recommendations: Variceal Bleeding—Secondary Prophylaxis

3 The combination of EVL plus pharmacologic therapy to prevent re-bleeding is currently considered the most rational therapeutic approach.[10,11] Pharmacologic therapy should be initiated with a nonselective β-blocker such as propranolol 20 mg twice daily or nadolol at a dose of 40 mg once daily.[10] β-Blocker therapy is titrated to achieve a goal heart rate of 55 to 60 beats/min or the maximal tolerated dose. Monitor patients for evidence of bradycardia, bronchospasm, and hypoglycemia, particularly in patients with insulin-dependent diabetes, as well as symptoms of heart failure and excessive sodium and water retention.[10,21] EVL should be conducted every 2 to 4 weeks until variceal obliteration, then the patient should be followed by surveillance endoscopy in 1 to 3 months and every 6 to 12 months thereafter.[10] Patients who cannot tolerate or who fail pharmacologic and endoscopic interventions can be considered for TIPS to prevent bleeding.[11] A summary of evidence-based

treatment recommendations regarding portal hypertension and variceal bleeding is found in **Table 54-3**.

TABLE 54-3 Evidence-Based Table of Selected Treatment Recommendations: Variceal Bleeding in Portal Hypertension

Recommendation	Grade
Prevention of variceal bleeding	
Nonselective β-blocker therapy should be initiated in:	
Patients with small varices and criteria for increased risk of hemorrhage	1b
Patients with medium/large varices	1a
EVL may be recommended for prevention in patients with medium/large varices at high risk of hemorrhage instead of nonselective β-blocker therapy	1a
Treatment of variceal bleeding	
Short-term antibiotic prophylaxis should be instituted on admission	1a
Vasoactive drugs should be started as soon as possible, prior to endoscopy, and maintained for up to 5 days	1a
Endoscopy should be performed to diagnose variceal bleeding and treat bleeding with EVL	1b
Endoscopy should be performed within 12 hours of presentation	5
Unless contraindicated, erythromycin 250 mg IV should be administered 30-120 minutes prior to endoscopy	1b
Secondary prophylaxis of variceal bleeding	
Nonselective β-blocker therapy plus EVL is the best therapeutic option for prevention of recurrent variceal bleeding	1a

Recommendation grading:

1a Systematic review (with homogeneity) of randomized controlled trials

1b Individual randomized controlled trial with narrow confidence interval

1c All or none

2a Systematic review (with homogeneity) of cohort studies

2b Individual cohort study (including low quality randomized controlled trial)

2c Outcomes research; ecological studies

3a Systematic review (with homogeneity) of case-controlled studies

3b Individual case-control study

4 Case-series (and poor quality cohort and case-control studies)

5 Expert opinion

Data from Reference 11.

Management of Ascites and Spontaneous Bacterial Peritonitis

Patients with cirrhosis experience overt fluid retention and ascites as liver disease progresses.[9] The classic physical examination findings of ascites are a bulging abdomen with shifting flank dullness.[5] The development of ascites in patients with cirrhosis is an indication of advanced liver disease and is a poor prognostic sign.[5,9] The principle therapeutic goals for patients with ascites are to control the ascites; to prevent or relieve ascites-related symptoms such as dyspnea, abdominal pain, and abdominal distention; and to prevent life-threatening complications such as SBP and hepatorenal syndrome.[9] Workup includes a history and physical examination, abdominal paracentesis and/or ultrasound, and ascitic fluid analysis.[5]

Spontaneous bacterial peritonitis is an infection of ascitic fluid that occurs in the absence of any evidence of an intraabdominal, surgically treatable source of infection. It is a common complication that develops in 10% to 30% of patients with liver disease and ascites over the course of a year.[26] The key mechanism behind the development of SBP is thought to be bacterial translocation. Most episodes of SBP are caused by *Escherichia coli*, *Klebsiella pneumonia*, and pneumococci.[5] Symptoms and signs of SBP include fever, abdominal pain, abdominal tenderness, encephalopathy, renal failure, acidosis, and leukocytosis.[26] Thirteen percent of patients with SBP present with no symptoms. For this reason, a diagnostic paracentesis with analysis of ascitic fluid should be performed in all patients admitted with ascites.[5,26] SBP is diagnosed when there is positive ascitic fluid bacterial culture and ascitic fluid cell counts show an absolute polymorphonuclear (PMN) leukocyte count of greater than or equal to 250 cells/mm^3 (0.25×10^9/L).

The following treatment guidelines for the management of adult patients with ascites and SBP were updated and approved by the Practice Guidelines Committee of the American Association for the Study of Liver Diseases (AASLD).[5]

Ascites

In adult patients with new-onset ascites as determined by physical examination or radiographic studies, abdominal paracentesis should be performed, and ascitic fluid analysis should include a cell count with differential, ascitic fluid total protein, and a serum-ascites albumin gradient (SAAG). If infection is suspected,

ascitic fluid cultures should be obtained at the time of the paracentesis. The SAAG can accurately determine whether ascites is a result of portal hypertension or another process. If the SAAG is greater than or equal to 1.1 g/dL (11 g/L), the patient almost certainly has portal hypertension. The treatment of ascites secondary to portal hypertension is relatively straightforward and includes abstinence from alcohol, sodium restriction, and diuretics.

1 Abstinence from alcohol is an essential element of the overall treatment strategy. Abstinence from alcohol can result in improvement of the reversible component of alcoholic liver disease, resolution of ascites, or improved responsiveness of ascites to medical therapy. Patients with cirrhosis not caused by alcohol have less reversible liver disease, and, by the time ascites is present, these patients may be best managed with liver transplantation rather than protracted medical therapy.

Beyond avoidance of alcohol, the primary treatment of ascites due to portal hypertension and cirrhosis is salt restriction and oral diuretic therapy. Fluid loss and weight change depend directly on sodium balance in these patients. A goal of therapy is to increase urinary excretion of sodium to greater than 78 mmol/day. Evaluation of urinary sodium excretion, preferably utilizing a 24-hour urine collection, may be helpful, although this collection can be difficult. A random spot urine sodium concentration that is greater than the potassium concentration correlates very well with a 24-hour urinary sodium excretion over 78 mmol/day and is an easier test to complete. Severe hyponatremia, defined as serum sodium less than a threshold of 120 to 125 mEq/L (mmol/L), does warrant fluid restriction. However, hyponatremia of this severity is rare among patients with cirrhosis and ascites and, for this reason, rarely requires specific treatment.

Diuretic Therapy The AASLD practice guidelines recommend that diuretic therapy be initiated with the combination of spironolactone and furosemide or spironolactone alone. Due to the likelihood for development of drug-induced hyperkalemia with spironolactone when used as monotherapy, it is best to use spironolactone as a lone diuretic agent only in patients with minimal fluid overload. Furosemide as lone diuretic therapy is inferior to spironolactone in the treatment of ascites and is not recommended. If tense ascites is present, paracentesis should be performed prior to institution of diuretic therapy and salt restriction. For patients who respond to diuretic therapy, this approach is preferred over the use of serial paracenteses. In patients with refractory ascites, serial paracenteses may be employed. Albumin infusion post-paracentesis is reasonable for extraction volumes exceeding 5 L. Laboratory tests for renal function and electrolytes need to be monitored during therapy. Referral for liver

transplantation should be made in patients with refractory ascites. TIPS is a therapeutic modality for the treatment of refractory ascites that may be considered in appropriately selected patients. Peritoneovenous shunting may be considered in treatment-refractory patients who are not candidates for paracenteses, transplant, or TIPS.

Patients with cirrhosis and ascites should avoid nonsteroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers except under special circumstances. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers should not be used in patients with refractory ascites. While these therapies are not part of the standard therapies of the complications of cirrhosis, nonselective β-adrenergic blocker therapy is indicated for primary and secondary prophylaxis against variceal bleeding in portal hypertension. Unfortunately, nonselective β-adrenergic blocker therapy can cause hypotension in patients with refractory ascites making the condition worse. For this reason, the risks versus benefits of nonselective β-adrenergic blocker therapy in refractory ascites must be carefully weighed and nonselective β-adrenergic blockers avoided or not started in this population unless the benefit of bleeding prophylaxis is considered to outweigh the risk of worsening ascites.

Spontaneous Bacterial Peritonitis

Relatively broad-spectrum antibiotic therapy that adequately covers the three most commonly encountered pathogens (*E. coli, K. pneumoniae*, and pneumococci) is warranted in patients with documented or suspected SBP.[5,26] Empiric therapy should not be delayed while awaiting culture results. In some patients, signs and symptoms of infection are present such as fever, abdominal pain, and unexplained encephalopathy at the bacterascites stage (ie, signs and symptoms are present before the PMN count in the ascitic fluid is elevated).[5] In these patients, signs and symptoms of infection justify empiric antibiotic therapy until culture results are known, regardless of the PMN count in the ascitic fluid.

Cefotaxime IV 2 g every 8 hours, or a similar third-generation cephalosporin, is considered the drug of choice for SBP. A 5-day course of antibiotic therapy is as efficacious as 10 days of therapy. Ofloxacin 400 mg every 12 hours administered orally for an average of 8 days is an alternative for patients without vomiting, shock, significant HE, or serum creatinine over 3 mg/dL (265 μmol/L). IV ciprofloxacin offers another potential treatment alternative. Patients with SBP who previously received quinolone therapy as prophylaxis should be treated with an alternative agent since patients who have received quinolone

therapy may become infected with quinolone-resistant flora.

Secondary bacterial peritonitis, ascitic fluid infection caused by a surgically treatable intraabdominal source, can masquerade as SBP. Free perforation should be considered when multiple or atypical organisms are cultured, a very high ascitic fluid PMN count is seen, or at least two of the following are seen on ascitic fluid analysis: total protein greater than 1 g/dL (10 g/L), lactate dehydrogenase greater than the upper limit of normal for serum, and glucose less than 50 mg/dL (2.8 mmol/L). A 48-hour follow-up PMN count that rises above pretreatment levels despite antibiotic treatment is indicative of secondary nonperforation peritonitis. Patients with free perforation or nonperforation secondary peritonitis should receive a third-generation cephalosporin plus anaerobic coverage in addition to undergoing laparotomy.

Treatment Recommendations: Ascites and Spontaneous Bacterial Peritonitis

15 Adult patients admitted to the hospital with new-onset ascites should have an abdominal paracentesis performed to determine the SAAG, the ascitic fluid cell count and differential, and the ascitic fluid total protein. If ascitic fluid infection is suspected, ascitic fluid should be inoculated into blood culture bottles at the bedside. Patients who drink alcohol should be strongly discouraged from further alcohol use. Sodium restriction to 2,000 mg/day, together with spironolactone and furosemide, is the mainstay of therapy. Diuretic therapy should be initiated with single morning doses of spironolactone 100 mg and furosemide 40 mg administered orally. Diuretic therapy should be titrated every 3 to 5 days using the 100:40 mg dose ratio to attain adequate natriuresis and weight loss (reasonable daily weight loss goal is 0.5 kg). The combination ratio is used because it usually maintains normokalemia. Maximum daily doses of diuretic agents are 400 mg of spironolactone and 160 mg of furosemide. Fluid restriction, unless the serum sodium is less than 120 to 125 mEq/L (mmol/L), and bedrest are not recommended. The random spot urine test should be utilized to confirm a sodium concentration that is greater than the potassium concentration as this correlates well with a 24-hour urinary sodium excretion over the goal of 78 mmol/day. Serum potassium and renal function should be monitored frequently and rapid correction of asymptomatic hyponatremia in patients with cirrhosis should be avoided. If tense ascites is present, paracentesis should be performed prior to institution of diuretic therapy and salt restriction. For patients who respond to diuretic therapy, this approach is preferred over the use of serial paracenteses. Diuretic therapy should be discontinued in patients

who experience uncontrolled or recurrent encephalopathy, severe hyponatremia (serum sodium <120 mEq/L [mmol/L]) despite fluid restriction, or renal insufficiency (serum creatinine >2 mg/dL [177 μmol/L]). Serial paracenteses may be considered for patients with refractory ascites and albumin infusion of 6 to 8 g/L of fluid removed can be considered post-paracentesis when paracentesis volumes exceed 5 L.

Patients with ascitic fluid PMN counts greater than or equal to 250 cells/mm^3 (0.25×10^9/L) should receive empiric antibiotic therapy with IV cefotaxime 2 g every 8 hours or a similar third-generation cephalosporin. Oral ofloxacin 400 mg twice daily may be an alternative option in patients without prior exposure to quinolones, vomiting, shock, severe encephalopathy, or serum creatinine over 3 mg/dL (265 μmol/L). Patients with ascitic fluid PMN counts less than 250 cells/mm^3 (0.25×10^9/L) but with signs and symptoms of infection (symptoms such as abdominal pain, abdominal tenderness, and fever) should also receive empiric antibiotic treatment. Patients with ascitic fluid PMN counts greater than or equal to 250 cells/mm^3 (0.25×10^9/L) and suspicion of SBP should also receive 1.5 g of albumin per kilogram body weight within 6 hours of detection and 1 g of albumin per kilogram body weight on Day 3 if they also have a serum creatinine over 1 mg/dL (88 μmol/L), blood urea nitrogen over 30 mg/dL (10.7 mmol/L), or total bilirubin over 4 mg/dL (68.4 μmol/L).

6 All patients who have survived an episode of SBP should receive long-term antibiotic prophylaxis with daily ciprofloxacin 500 mg daily (since norfloxacin no longer available) or double strength trimethoprim–sulfamethoxazole. Long-term prophylaxis should also be considered for the prevention of SBP in patients with low-protein ascites (<1.5 g/dL [15 g/L]) who also have one of the following: serum creatinine greater than or equal to 1.2 mg/dL (106 μmol/L), blood urea nitrogen greater than or equal to 25 mg/dL (8.9 mmol/L), serum sodium less than or equal to 130 mEq/L (mmol/L), or Child-Pugh score of greater than or equal to 9 with bilirubin greater than or equal to 3 mg/dL (51.3 μmol/L). Short-term prophylaxis (7 days) is indicated in patients with cirrhosis and GI hemorrhage. A summary of evidence-based treatment recommendations regarding ascites and SBP is found in **Table 54-4**.

TABLE 54-4 Evidence-Based Table of Selected Treatment Recommendations: Ascites and Spontaneous Bacterial Peritonitis

Recommendation	Grade
Ascites	
Paracentesis should be performed in patients with apparent new-onset ascites	IC
Sodium restriction of 2,000 mg/day should be instituted as well as oral diuretic therapy with spironolactone and furosemide	IIaA
Diuretic-sensitive patients should be treated with sodium restriction and diuretics rather than serial paracentesis	IIaC
Refractory ascites	
Serial therapeutic paracenteses may be performed	IC
Postparacentesis albumin infusion of 6-8 g/L of fluid removed can be considered if more than 5 L is removed during paracentesis	IIaA
Treatment of SBP	
If ascitic fluid PMN counts are >250 cells/mm^3 (0.25 × 10^9/L), empiric antibiotic therapy should be instituted (cefotaxime 2 g every 8 hours)	IA
If ascitic fluid PMN counts are <250 cells/mm^3 (0.25 × 10^9/L), but signs or symptoms of infection exist, empiric antibiotic therapy should be initiated while awaiting culture results	IB
Ofloxacin 400 mg twice daily may be substituted for cefotaxime in patients without vomiting, shock, grade II or higher encephalopathy, or serum creatinine >3 mg/dL (265 µmol/L) and if there is no prior exposure to quinolones	IIaB
If ascitic fluid polymorphonuclear leukocyte counts are >250 cells/mm^3 (0.25 × 10^9/L), clinical suspicion of SBP is present, and the patient has a serum creatinine >1 mg/dL (88 µmol/L), blood urea nitrogen >30 mg/dL (10.7 mmol/L), or total bilirubin over 4 mg/dL (68.4 µmol/L), 1.5 g/kg albumin should be infused within 6 hours of detection and 1 g/kg albumin infusion should also be given on Day 3	IIaB
Prophylaxis against SBP	
Short-term antibiotic prophylaxis should be used for 7 days to prevent SBP in cirrhosis patients with GI hemorrhage	IA
Patients who survive an episode of SBP should receive long-term prophylaxis with either daily ciprofloxacin or trimethoprim–sulfamethoxazole	IA
Patients with low-protein ascites (<1.5 g/dL [15 g/L]) plus at least one of the following: serum creatinine ≥1.2 mg/dL (106 µmol/L), blood urea nitrogen ≥25 mg/dL (8.9 mmol/L), serum sodium ≤ 130 mEq/L (mmol/L), or Child-Pugh score of ≥9 with bilirubin ≥3 mg/dL (51.3 µmol/L) may also justifiably receive long-term ciprofloxacin or sulfamethoxazole/trimethoprim as prophylaxis	IA

Recommendation grading: Class I—Conditions for which there is evidence and/or general agreement; Class II—Conditions for which there is conflicting evidence and/or a divergence of opinion; Class IIa—Weight of evidence/opinion is in favor of efficacy; Class IIb—Efficacy less well established; Class III—Conditions for which there is evidence and/or general agreement that treatment is not effective and/or potentially harmful; Level A—Data from multiple randomized trials or meta-analyses; Level B—Data derived from single randomized trial or nonrandomized studies; Level C—Only consensus opinion, case studies, or standard of care.

Data from Reference 5.

Management of Hepatic Encephalopathy

Hepatic encephalopathy will occur in 30% to 40% of patients with cirrhosis at some point during the course of their disease.[12] The clinical manifestations of HE vary widely from subclinical alterations to coma. In addition to classification based upon underlying disease, HE is also classified based on severity, time course, and the presence of precipitating factors. To determine the severity of

HE, a grading system that relates neurologic and neuromuscular signs can be used (Table 54-5). The time course of HE is classified as episodic, persistent, or recurrent. Recurrent HE refers to HE episodes that occur in time intervals less than 6 months apart. Persistent HE refers to behavioral symptoms that are always present and periodically interspersed with episodes of overt HE relapses. A precipitating factor or factors such as constipation, infection, diuretic overuse, GI bleeding, or electrolyte abnormalities can be identified in most episodic cases of HE related to cirrhosis, but spontaneous episodic HE can occur as well. The general approach to the management of HE is four pronged and includes the following: care for patients with altered consciousness, identify and treat any other causes besides HE for altered mental status, identify and treat any precipitating factors, and begin empiric HE treatment. Treatment for HE is primarily focused on reducing ammonia blood concentrations through drug therapy aimed at inhibiting ammonia production or enhancing its removal. Additionally, treatment for HE should include avoidance and prevention of precipitating factors in an effort to avoid acute decompensation. In cases where a precipitant of episodic HE has been identified and adequately treated or removed, long-term prophylaxis against another acute HE episode may not be required. Otherwise, chronic therapy to prevent acute decompensation is often required.

TABLE 54-5 Grading System for Hepatic Encephalopathy

Grade	Level of Consciousness	Personality/Intellect	Neurologic Abnormalities
Unimpaired	Normal	Normal	Normal
Minimal	No clinical evidence of change	No clinical evidence of change/alterations identified on psychometric or neuropsychological testing	No clinical evidence of change
I	Trivial lack of awareness; shortened attention span	Euphoria or anxiety; impairment of addition or subtraction	Altered sleep rhythm
II	Lethargic	Obvious personality changes; inappropriate behavior; apathy	Asterixis; dyspraxia; disoriented for time
III	Somnolent but arousable	Bizarre behavior	Responsive to stimuli; confused; gross disorientation to time and space
IV	Coma/unarousable	None	Does not respond to stimuli

Data from Reference 12.

Hyperammonemia

7 Treatment interventions to reduce ammonia blood concentrations are recommended in patients with HE. Decreasing ammonia blood concentrations by

reducing the nitrogenous load from the gut remains a mainstay of therapy for patients with HE. Treatment options most commonly used to decrease ammonia load from the gut include nutritional management, nonabsorbable disaccharides, and antibiotics.

Guidelines for nutritional support of patients with liver disease have been published by the International Society for Hepatic Encephalopathy and Nitrogen Metabolism.[27] Protein withdrawal is a cornerstone of treatment for patients during acute episodes of HE.[12] However, prolonged restriction can lead to malnutrition and poorer prognosis among HE patients. Therefore, once successful reversal of HE symptoms is achieved, protein is added back to the diet in combination with other therapies until a target of 1.2 to 1.5 g/kg/day of protein is reached. Vegetable-source and dairy-source protein may be preferable to meat-source protein because the latter contains a higher calorie-to-nitrogen ratio. Also, the higher fiber content of vegetable protein lowers colonic pH, increasing catharsis. Oral branched-chain amino acid formulations improve symptoms in episodic HE and may be considered as alternative or add-on therapy in patients who do not respond to conventional measures.

The use of lactulose, a nonabsorbable disaccharide, is standard therapy for both acute and chronic HE.[28] Lactulose, when administered orally through ingestion or a nasogastric tube, passes through the GI tract and reaches the colon unchanged. It can also be administered by retention enema. Lactulose is metabolized by gut flora into acetic acid and lactic acid, which lower colonic pH and create a cathartic effect to increase fecal nitrogen waste. Lactulose also decreases survival of urease producing bacteria and promotes conversion of ammonia to ammonium which is not as readily absorbed in the gut.

Neomycin inhibits glutaminase thereby reducing bacterial production of glutamate and ammonia. For this reason, oral neomycin can be used for the treatment of HE. However, this agent is rarely used due to the severity of its potential adverse effects including ototoxicity and nephrotoxicity. Anaerobic bacteria produce urease that hydrolyzes urea to ammonia in the gut. Metronidazole targets these gram-negative anaerobic gut bacteria and, as a result, can be utilized in the management of HE as well. However, neurotoxicity may be problematic so metronidazole is only considered as an alternative agent for HE.

Rifaximin is a synthetic antibiotic structurally similar to rifamycin with a systemic absorption of only 0.4%. Rifaximin 550 mg twice daily is effective in the treatment of HE. It maintains remission better than lactulose alone and reduces the number of hospitalizations for HE as well.[29] Of note, lactulose was

used concomitantly in 90% of patients in this study.

Zinc supplementation may be considered in patients with HE.[12] Zinc is a cofactor for the urea cycle enzymes and important for ammonia detoxification.[28] It is also frequently deficient in patients with cirrhosis. However, supplementation cannot be recommended in the absence of deficiency.

Drugs Affecting Neurotransmission

Flumazenil, a benzodiazepine receptor antagonist, may be considered for short-term therapy in refractory encephalopathic patients with suspected or confirmed benzodiazepine intake.[12]

Treatment Recommendations: Hepatic Encephalopathy

7 The mainstay of therapy of HE involves measures to lower blood ammonia concentrations and includes diet therapy, lactulose, and antibiotics alone or in combination with lactulose.[12,28] Other adjunctive therapies include zinc replacement in patients with zinc deficiency and flumazenil in cases of refractory HE with the possibility of benzodiazepine use.

The target daily protein intake for patients with HE is recommended to be within 1.2 to 1.5 g/kg/day.[12] Consideration may be made to substitute meat-source protein with vegetable or dairy protein. Supplementation with elemental zinc may be considered in patients with cirrhosis who are zinc deficient.

In episodic HE, lactulose is initiated at a dose of 25 ml (16.7 g) orally every 1 to 2 hours (or by retention enema: 300 mL lactulose syrup in 1 L water every 6-8 hours) until catharsis begins and the patient experiences one to two bowel movements.[28] The dose is then decreased to 15 to 45 mL orally every 8 to 12 hours and titrated to produce two to three soft stools per day for chronic therapy. Monitor electrolytes periodically, follow patients for changes in mental status, and titrate to the number of stools as already described.

Rifaximin 550 mg twice daily plus lactulose is superior to lactulose alone in patients with a history of recurrent HE.[29] Rifaximin is usually well tolerated. Because of its more favorable adverse effect profile, rifaximin is now considered the next line of therapy for recurrent HE over either metronidazole or neomycin.[28]

Systemic Complications

In addition to the more common complications of chronic liver disease discussed earlier, other complications can occur, including hepatorenal syndrome, hepatopulmonary syndrome, coagulation disorders, and endocrine dysfunction.

Hepatorenal syndrome, a functional renal failure in the setting of cirrhosis, occurs in the absence of structural kidney damage.[30] Portal hypertension leads to the release of vasodilators that results in blood pooling in the splanchnic vasculature reducing renal blood flow causing renal hypoperfusion. This causes activation of the renin-angiotensin-aldosterone system that results in severe renal vasoconstriction and fluid retention leading to ascites. As liver disease progresses, systemic vasodilation worsens and, subsequently, increased renal vasoconstriction occurs and renal blood flow is further decreased. The result is hepatorenal syndrome that can be separated into two main types. Type 1 occurs rapidly and has a precipitating cause such as SBP. Type 2 occurs more slowly and does not have a precipitating event.

Management of hepatorenal syndrome begins with discontinuing diuretics and any other medication that could potentially decrease effective blood volume and to expanding the intravascular volume with IV albumin at a dose of 1 g/kg up to a maximum of 100 g.[30,31] Precipitating factors, such as infection, fluid loss, and blood loss, should be investigated and treated if found. Liver transplantation is the only definitive treatment for hepatorenal syndrome and the only therapy that will prolong survival. Medications used to bridge patients until transplantation includes arteriolar vasoconstrictor-based treatment with midodrine plus octreotide and IV albumin infusion as already discussed.

Hepatopulmonary syndrome affects somewhere between 5% and 50% of patients with cirrhosis.[32] This abnormality is characterized by a defect in arterial oxygenation, which is caused by the pulmonary vascular dilatation that occurs in the presence of liver disease. These patients present with insidious onset of dyspnea, dyspnea upon standing, clubbing and cyanosis. Cirrhotic patients with these findings should be evaluated for hepatopulmonary syndrome, which is diagnosed based on the presence of arterial hypoxemia. Arterial hypoxemia is defined by measurements of the partial pressure of oxygen, testing for an increased alveolar–arterial oxygen gradient, and contrast-enhanced echocardiography. There is no effective medical management for hepatopulmonary syndrome. Liver transplantation offers the best chance for long-term recovery.

Patients with cirrhosis who are actively bleeding receive resuscitation with packed red blood cells targeting a hemoglobin of 7 to 8 g/dL (70 to 80 g/L; 4.34 to 4.97 mmol/L).[14] Platelet transfusion is used to maintain platelets over

50,000/mm^3 (50 x 10^9/L) during the period of active bleeding. Cryoprecipitate to maintain fibrinogen levels over 100 mg/dL (1 g/L) is also usually recommended.

The presence of cirrhosis can produce abnormal circulating levels of various hormones.[33] Hypogonadism, diabetes mellitus, osteoporosis, and thyroid disorders are among the endocrine disorders that may develop related to advanced liver disease.

Liver Transplantation

The complications seen in patients with chronic liver disease are essentially secondary effects of the circulatory and metabolic changes that accompany liver failure. Unless the underlying etiology of a patient's fibrosis can be cured, cirrhosis generally progresses. Consequently, liver transplantation is often the only treatment that can offer a cure for the most severe complications of end-stage cirrhosis.

ALTERED DRUG PHARMACOKINETICS AND PHARMACODYNAMICS

Cirrhosis modulates the behavior of drugs in the body by inducing kinetic alterations in drug absorption, distribution, and clearance.[34] Additionally, patients with cirrhosis may exhibit pharmacodynamic changes with increased sensitivity to the effects of certain drugs including opiates, benzodiazepines, and nonsteroidal anti-inflammatory drugs. These pharmacodynamic changes are separate and distinct from the enhancement of drug effects seen in cirrhotic patients as a result of pharmacokinetic changes. The pathophysiologic changes that have particular impact on drug handling within the body include reduced liver blood flow, decreased first-pass extraction, systemic shunting, hypoalbuminemia, ascites, portal gastropathy, loss of cytochrome P450 enzymatic metabolic activity, reduced glutathione stores, impaired biliary excretion, and impaired renal excretion. Reduced hepatic blood flow, lower first-pass extraction and portosystemic shunting result in higher bioavailability and serum levels of drugs. Hypoalbuminemia results in higher concentrations of free drug due to less protein binding. Ascites increases the volume of distribution of hydrophilic drugs. Serum levels of various drugs can be higher after normal dosing secondary to impaired biliary and renal excretion that is possible in cirrhosis. Reduced enzymatic clearance by hepatocytes can also lead to reduced first-pass metabolism and reduced hepatic clearance.

Drugs with a high extraction ratio (high-extraction drugs) are dependent on blood flow for metabolism, and the rate of metabolism will be sensitive to changes in blood flow. Drugs with a low extraction ratio (low-extraction drugs) are dependent on intrinsic metabolic activity for metabolism, and the rate of metabolism will reflect changes in intrinsic clearance and protein binding. Furthermore, hepatic biotransformation involves two types of metabolic processes: phase I reactions and phase II reactions. Phase I reactions involve the cytochrome P450 system and include hydrolysis, oxidation, dealkylation, and reduction reactions. Phase II reactions involve conjugation of the drug with an endogenous molecule, such as sulfate or amino acid, rendering it more water soluble and enhancing its elimination. Drug metabolism by phase I reactions, especially oxidation, tend to be significantly impaired in patients with cirrhosis, whereas drugs eliminated by conjugation are relatively unaffected.

The variability and complexity of the interaction between the extent and severity of liver disease and individual characteristics of the drug make it difficult to predict the degree of pharmacokinetic perturbation in an individual patient. Unfortunately, there are no sensitive and specific clinical or biochemical markers that allow us to quantify the extent of liver insufficiency or degree of metabolic activity. In addition, renal insufficiency and alterations that commonly accompany cirrhosis further complicate empiric dosing recommendations in these patients. Dosing recommendations are most commonly nonspecific, with recommendations labeled for patients with mild-to-moderate liver impairment. Dosing information for patients with more severe liver impairment is not available. As a result, when patients with cirrhosis require therapy with drugs that undergo hepatic metabolism (eg, benzodiazepines), monitoring response to therapy and anticipating drug accumulation and enhanced effects is essential. In the case of benzodiazepines, selection of an agent such as lorazepam, an intermediate-acting agent that is metabolized via conjugation and has no active metabolites, is easier to monitor than a drug such as diazepam, a long-acting benzodiazepine that is oxidized in the liver and has an active metabolite with a long half-life of its own.

EVALUATION OF THERAPEUTIC OUTCOMES

Table 54-6 summarizes the management approach for patients with cirrhosis and includes possible adverse drug effects. Cirrhosis is generally a chronic progressive disease that requires aggressive medical management to prevent or delay common complications. Table 54-6 also lists monitoring criteria that need

to be carefully followed in order to achieve the maximum benefit from the medical therapies employed and prevent adverse effects. A therapeutic plan including therapeutic end points for each medical and diet therapy needs to be developed and discussed with the cirrhosis patient.

TABLE 54-6 Drug Monitoring Guidelines

Drug	Adverse Drug Reaction	Monitoring Parameter	Comments
Nonselective β-adrenergic blocker	Heart failure, bronchospasm, glucose intolerance	BP, HR Goal HR: 55-60 beats/min or maximal tolerated dose	Nadolol, propranolol, carvedilol
Octreotide	Bradycardia, hypertension, arrhythmia, abdominal pain	BP, HR, EKG, abdominal pain	
Spironolactone/furosemide	Electrolyte disturbances, dehydration, renal insufficiency, hypotension	Serum electrolytes (especially potassium), SCr, blood urea nitrogen, BP Goal sodium excretion: >78 mmol/day	Spot urine sodium concentration greater than potassium concentration correlates well with daily sodium excretion >78 mmol/day
Lactulose	Electrolyte disturbances	Serum electrolytes Goal number of soft stools per day: 2-3	
Neomycin	Ototoxicity, nephrotoxicity	SCr, annual auditory monitoring	
Metronidazole	Neurotoxicity	Sensory and motor neuropathy	
Rifaximin	Nausea, diarrhea		

BP, blood pressure; HR, heart rate; beats/min, beats per minute; EKG, electrocardiogram; SCr, serum creatinine; mmol, millimole.

Postclass Engaged Learning Activity

Alcohol abuse is a major contributing factor to the development and worsening of cirrhosis. Currently, there are three FDA-approved medication options for the management of alcohol abuse disorder (acamprosate, disulfuram, and naltrexone). Using the following as a guide, create a comparison table for these medications.

Generic name	Brand name	Mechanism of action	Dose, route, and frequency	Common adverse effects	Monitoring parameters	Patient counseling points/pharmacy pearls
Acamprosate						
Disulfuram						
Naltrexone						

ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
ALT	alanine transaminase
AST	aspartate transaminase
EVL	endoscopic variceal ligation
GABA	γ-aminobutyric acid
GGT	γ-glutamyl transpeptidase
HE	hepatic encephalopathy
HVPG	hepatic venous pressure gradient
INR	international normalized ratio
MELD	model for end-stage liver disease
PMN	polymorphonuclear
PT	prothrombin time
SAAG	serum-ascites albumin gradient
SBP	spontaneous bacterial peritonitis
TIPS	transjugular intrahepatic portosystemic shunt

REFERENCES

1. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. *Lancet*. 2014;383(9930):1749–1761.
2. Zhou WC, Zhang QB, Qiao L. Pathogenesis of liver cirrhosis. *World J Gastroenterol*. 2014;20(23):7312–7324.
3. Chalasani NP, Hayashi PH, Bonkovsky HL, Navarro VJ, Lee WM, Fontana RJ; Practice Parameters Committee of the American College of Gastroenterology. ACG clinical guideline: The diagnosis and management of idiosyncratic drug-induced liver injury. *Am J Gastroenterol*. 2014;109(7):950–966.
4. Murphy SL, Xu J, Kochanek KD, Curtin SC, Arias E. Deaths: Final data for 2015. *Natl Vital Stat Rep*. 2017;66(6):1–75.
5. Runyon BA. Management of adult patients with ascites due to cirrhosis: Update 2012. Available at https://www.aasld.org/sites/default/files/guideline_documents/adultascitese Accessed September 22, 2018.
6. Khalili M, Burman B. Liver disease. In: Hammer GD, McPhee SJ,eds.

Pathophysiology of Disease: An Introduction to Clinical Medicine. 7th ed. New York: McGraw-Hill; 2014:385–426.

7. Asahina K. Hepatic stellate cell progenitor cells. *J Gastroenterol Hepatol*. 2012;27(suppl 2):80–84.
8. McConnell M, Iwakiri Y. Biology of portal hypertension. *Hepatol Int*. 2018;12(suppl 1):S11–S23.
9. Moore CM, Van Thiel DH. Cirrhotic ascites review: pathophysiology, diagnosis and management. *World J Hepatol*. 2013;5(5):251–263.
10. Bari K, Garcia-Tsao G. Treatment of portal hypertension. *World J Gastroenterol*. 2012;18(11):1166–1175.
11. de Franchis R; Baveno VI Faculty. Expanding consensus in portal hypertension report of the Baveno VI consensus workshop: Statifying risk and individualizing care for portal hypertension. *J Hepatol*. 2015;63:743–752.
12. Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by AASLD and EASL. *Hepatology*. 2014;60(2):715–735.
13. Blei AT, Cordoba J; Practice Parameters Committee of the American College of Gastroenterology. Hepatic encephalopathy. *Am J Gastroenterol*. 2001;96:1968–1976.
14. Kujovich JL. Coagulopathy in liver disease: A balancing act. *Hematology*. 2015;2015(1):243–249.
15. Pugh RNH, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophagus varices. *Br J Surg*. 1973;60:646–649.
16. About the MELD/PELD Calculator. Available at http://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/. Accessed September 24, 2018.
17. Civan JM. Cirrhosis. *Merck Manual Professional Version*. Kenilworth, NJ: Merck & Co., Inc.; 2018. Available at https://www.merckmanuals.com/professional/hepatic-and-biliary-disorders/fibrosis-and-cirrhosis/cirrhosis. Accessed September 25, 2018.
18. Kwo PY, Cohen SM, Kim JK. ACG practice guideline: Evaluation of abnormal liver chemistries. *Am J Gastroenterol*. 2017;112(1):18–35.
19. Cohen JA, Kaplan MM. The SGOT/SGPT ratio—An indicator of alcoholic disease. *Dig Dis Sci*. 1979;24:835–838.
20. MELD/PELD Calculator Documentation. Available at

https://www.unos.org/wp-content/uploads/unos/MELD_PELD_Calculator_Documentation.pdf. Accessed September 26, 2018.

21. Giannelli V, Lattanzi B, Thalheimer U, Merli M. Beta-blockers in liver cirrhosis. *Ann Gastroenterol*. 2014;27(1):1–7.
22. Brunner F, Berzigotti A, Bosch J. Prevention and treatment of variceal haemorrhage in 2017. *Liver International*. 2017;37(suppl 1):104–115.
23. Sinagra E, Perricone G, D'Amico M, et al. Systematic review with metaanalysis: The haemodynamic effects of carvedilol compared with propranolol for portal hypertension in cirrhosis. *Aliment Pharmacol Ther*. 2014;39:557–568.
24. Reiberger T, Ulbrich G, Ferlitsch A, et al. Carvedilol for primary prophylaxis of variceal bleeding in cirrhotic patients with haemodynamic non-response to propranolol. *Gut*. 2013;62:1634–1641.
25. Well M, Chande N, Adams P, et al. Meta-analysis: Vasoactive medications for the management of acute variceal bleeds. *Aliment Pharmacol Ther*. 2012;35(11):1267–1278.
26. Liou IW, Kim HN. Recognition and management of spontaneous bacterial peritonitis. Hepatitis C Online; 2018. Available at https://www.hepatitisc.uw.edu/go/management-cirrhosis-related-complications/spontaneous-bacterial-peritonitis-recognition-management/core-concept/all. Accessed September 28, 2018.
27. Amodio P, Bemeur C, Butterworth R, et al. The nutritional management of hepatic encephalopathy in patients with cirrhosis: ISHEN practice guidelines. *Hepatology*. 2013;58:325–336.
28. Liou IW, Kim HN. Diagnosis and management of hepatic encephalopathy. Hepatitis C Online; 2018. Available at https://www.hepatitisc.uw.edu/go/management-cirrhosis-related-complications/hepatic-encephalopathy-diagnosis-management/core-concept/all#medical-therapy-overt-hepatic-encephalopathy. Accessed September 29, 2018.
29. Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med*. 2010;362:1071–1081.
30. Erly B, Carey WD, Kapoor B, McKinney JM, Tam M, Wang W. Hepatorenal syndrome: A review of pathophysiology and current treatment options. *Semin Intervent Radiol*. 2015;32(4):445–454.
31. Liou IW, Kim HN. Diagnosis and management of ascites. Hepatitis C

Online; 2018. Available at https://www.hepatitisc.uw.edu/go/management-cirrhosis-related-complications/ascites-diagnosis-management/core-concept/all#management-refractory-ascites. Accessed September 30, 2018.

32. Moller S, Henriksen JH, Bendtsen F. Extrahepatic complications to cirrhosis and portal hypertension: Haemodynamic and homeostatic aspects. *World J Gastroenterol*. 2014;20(42):15499–15517.
33. Eshraghian A, Taghavi SA. Systematic review: Endocrine abnormalities in patients with liver cirrhosis. *Arch Iran Med*. 2014;17(10):713–721.
34. Lewis JH, Stine JG. Review article: Prescribing medications in patients with cirrhosis—a practical guide. *Aliment Pharmacol Ther*. 2013;37:1132–1156.

Drug-Induced Liver Disease

William R. Kirchain and Rondall E. Allen

KEY CONCEPTS

1. Through its normally functioning enzymes and processes the liver often causes a drug to become toxic through a process known as bioactivation.
2. Drug-induced liver disease (DILD) can have many different clinical presentations: idiosyncratic reactions, allergic hepatitis, toxic hepatitis, chronic active toxic hepatitis, toxic cirrhosis, and liver vascular disorders.
3. The mechanisms of DILD are diverse, representing many phases of biotransformation, and are susceptible to genetic polymorphism.
4. The assessment of a possible liver injury caused by drugs should include what is known in the literature, the timing involved, the clinical course, and, always, an exploration for preexisting conditions that may have encouraged the lesion's development.
5. Liver enzyme assays in serum can help to determine if a particular type of liver damage is present.
6. Monitoring for DILD must be tailored to the drug and the patient's potential risk factors.

Preclass Engaged Learning Activity

Consider the following case: A 62-year-old white male presented to the ER with complaints of nausea with one episode of vomiting, generalized abdominal pain and fullness, bright lights, and pruritus. The patient noted that his urine seemed to be very concentrated, frothy, and very dark. The patient was reported to have very pressed, rapid speech, expressing concerns about several businesses that he claimed to own.

PMH: Bipolar I/II disorder—for 32 years

Mixed hyperlipidemia—for 24 years

Type 2 diabetes—for 20 years

Hypertension—for 19 years

FHx: Father (died of alcoholism); mother still alive—has type 2 diabetes mellitus, sibling's health unknown

SHx: Currently works as waiter, smoking 46 pack for years; alcohol—does not drink; cannabis—smokes once a week; other—denied.

From what you have already learned about the liver, diseases in the liver and care of patients in general, consider the following questions: 1. Which symptoms presented above are commonly associated with a dysfunctioning liver? 2. Which are not? 3. What diseases that you have learned so far could cause this type of presentation?

INTRODUCTION

The range of drugs associated with adverse reactions involving the liver is extensive, but in clinical practice is dominated by alcohol, antibiotics, antiseizure medications and acetaminophen.[1] Complementary and herbal medicines also contribute disproportionately to this disease burden. Drug-induced liver disease (DILD) is a potentially fatal, often debilitating outcome of drug treatment. DILD is thought to be responsible for 11% to 13% of all cases of acute liver failure in the United States.[1,2]

Drug-induced liver disease accounts for as much as 20% of acute liver failure in pediatric populations and a similar percentage of adults with acute liver failure.[3] In approximately 75% of these cases, liver transplantation is ultimately required for patient survival.[4] Of patients who required liver transplantation according to the United Network for Organ Sharing, acetaminophen, isoniazid, antiepileptics, and antibiotics collectively account for just over 60% of cases.[5]

The liver's function affects every other organ system in the body; it in turn is exposed to every substance absorbed from the gut and every injected substance that enters the bloodstream.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

56

Pancreatitis

Scott Bolesta and Patricia A. Montgomery

KEY CONCEPTS

ACUTE PANCREATITIS

1. Factors that can contribute to acute pancreatitis should be identified and corrected, including discontinuation of medications that could be potential causes.
2. Patients with acute pancreatitis should receive aggressive fluid replacement to reduce the risks of persistent systemic inflammatory response syndrome (SIRS) and organ failure.
3. Parenteral opioid analgesics are used to control abdominal pain associated with acute pancreatitis despite a lack of high quality evidence to support the practice.
4. Use of prophylactic antibiotics is not recommended in patients with acute pancreatitis without signs or symptoms of infection, including those with predicted severe acute pancreatitis or necrotizing pancreatitis.

CHRONIC PANCREATITIS

5. Chronic pain, malabsorption with resultant steatorrhea, and diabetes mellitus are the hallmark symptoms and complications of chronic pancreatitis.
6. Pain from chronic pancreatitis may initially be treated with nonopioid analgesics, but adjuvant agents may be necessary as the disease progresses.
7. Pancreatic enzyme and fat-soluble vitamin supplementation are the primary treatments for malabsorption due to chronic pancreatitis.
8. Enteric-coated pancreatic enzyme supplements are the preferred dosage form in the treatment of malabsorption and steatorrhea due to chronic pancreatitis.

9 The addition of a histamine-2 receptor antagonist or proton pump inhibitor to pancreatic enzyme supplementation may increase the effectiveness of enzyme therapy for malabsorption and steatorrhea due to chronic pancreatitis.

Preclass Engaged Learning Activity

Identify and review two or three resources that discuss the advantages and disadvantages of using opioids for the treatment of pain associated with both acute and chronic pancreatitis. Some examples of resources include those found on credible internet sites, published review articles, guidelines and other tertiary resources, and primary literature. Make a list of the advantages and disadvantages and rank them in what you feel to be their order of importance when considering the use of opioids for the treatment of pain associated with pancreatitis. This activity is intended to help you develop an understanding of the place of opioids in the treatment of pain from pancreatitis.

INTRODUCTION

Pancreatitis is inflammation of the pancreas with variable involvement of regional tissues or remote organ systems.[1,2] Acute pancreatitis is characterized by severe pain in the upper abdomen and elevations of pancreatic enzymes in the blood.[2] In the majority of patients, acute pancreatitis is a self-limiting disease that resolves spontaneously without complications. Approximately 20% of adults with acute pancreatitis have a severe course.[1,2] While the overall mortality of acute pancreatitis is less than 1%, severe pancreatitis is associated with a mortality as high as 30%.[3] The risk for progression to chronic pancreatitis after an initial episode of acute pancreatitis is related to the etiology. Patients with acute pancreatitis due to gallstone disease have little risk for progression to chronic disease whereas patients with alcohol-related acute pancreatitis have a risk of 14% to 41% based on whether or not they continue to consume alcohol.[4]

Chronic pancreatitis is characterized by long-standing inflammation that eventually leads to a loss of pancreatic exocrine and endocrine functions.[5–7] It is a progressive disease that often goes unnoticed for many years. The usual initial presentation is complaints of chronic abdominal pain. Later in the disease process malabsorption with resultant steatorrhea occurs. This leads to

malnutrition and weight loss. Finally, patients develop diabetes mellitus due to a loss of pancreatic endocrine function.[5,6]

EPIDEMIOLOGY

Acute pancreatitis is the third most common gastrointestinal disorder causing hospitalization in the United States with admission rates of approximately 13 to 45 per 100,000 per year.[3,4] The risk for acute pancreatitis varies widely with geographic, etiologic (eg, alcohol consumption and smoking), environmental, and genetic factors. The incidence of acute pancreatitis has increased in the United States, including in pediatric patients. In adults and children, the increase in acute pancreatitis is often attributed to rising rates of obesity.[4] The annual incidence of chronic pancreatitis in the United States is 5 to 14 per 100,000, and the prevalence is 50 per 100,000.[7] The prevalence increases with age, with an average onset at 62 years, and it is 4.5 times more common in males than females.[7] Also, the prevalence of chronic pancreatitis varies widely based on geographic location.[5,6] There is also racial disparity with the disease, with African Americans having 2 to 3 times the risk than Caucasians, and being more than twice as likely to be hospitalized.[7]

PANCREATIC EXOCRINE PHYSIOLOGY

The pancreas possesses both endocrine and exocrine functions. The islets of Langerhans, which contain the cells of the endocrine pancreas, secrete insulin, glucagon, somatostatin, and other polypeptide hormones. The exocrine pancreas is composed of acini and ductules that secrete about 2.5 L/day of isotonic fluid that contains water, electrolytes, and pancreatic enzymes necessary for digestion. Bicarbonate and other electrolytes are secreted primarily by the centroacinar (ductular) cells in order to neutralize gastric acid. Pancreatic juice is delivered to the duodenum via the pancreatic ducts (**Fig. 56-1**) where the alkaline secretion neutralizes gastric acid and provides an appropriate pH for maintaining the activity of pancreatic enzymes.[8]

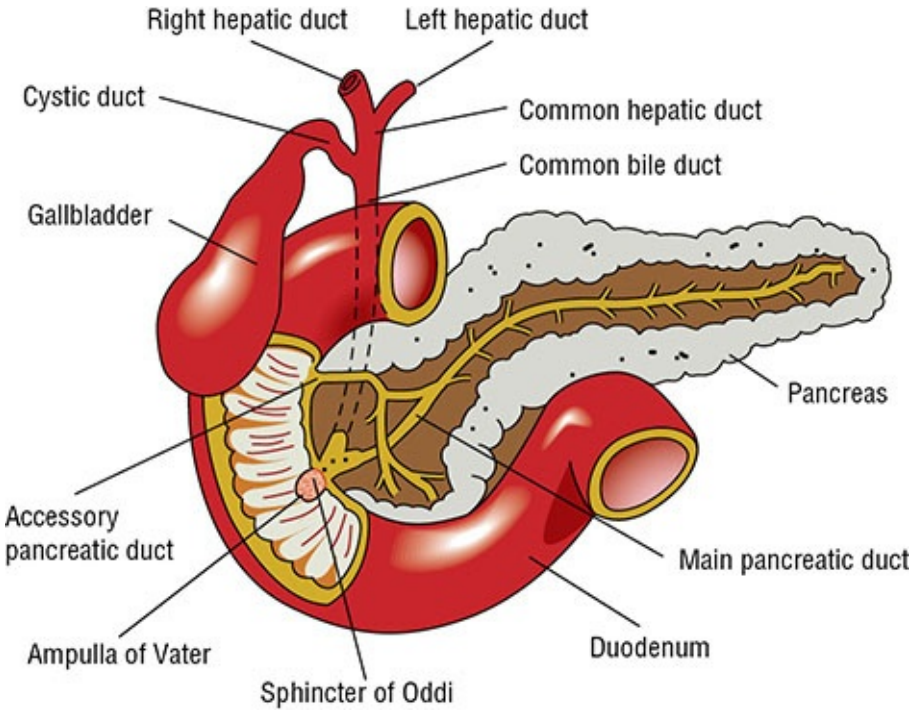


FIGURE 56-1 Anatomic structure of the pancreas and biliary tract.

The major pancreatic exocrine enzyme groups are as follows:

1. Amylolytic: α-amylase
2. Lipolytic: lipase, procolipase, prophospholipase A2, and carboxylesterase
3. Proteolytic: trypsinogens, chymotrypsinogen, procarboxypeptidase A and B, proelastase and mesotrypsin
4. Nucleolytic: ribonuclease and deoxyribonuclease
5. Other: trypsin inhibitor

Amylase is responsible for digestion of starches and glycogen through hydrolysis. The lipolytic enzymes break down triglycerides, cholesterol, and other fats in the digestive tract. Specifically, lipase hydrolyzes triglycerides into fatty acids and monoglycerides. Colipase and bile acids facilitate this process by allowing lipase to act on the hydrophobic surface of fat droplets in the mainly hydrophilic environment. Phospholipase A2 and carboxylesterase continue to break down fatty acids, cholesterol, monoglycerides, and other products of fat digestion. Proteolytic enzymes digest proteins into oligopeptides and free amino acids, while nucleases break down nucleic acids.[8]

The production of proteolytic enzymes in the pancreas occurs in a manner that prevents self-digestion of the pancreas. These enzymes are synthesized

within the acinar cells, stored in vacuoles, and secreted into the duodenum as zymogens (inactive enzymes). Enterokinase secreted by the duodenal mucosa converts trypsinogen to trypsin, which then activates all other proteolytic zymogens along with procolipase and prophospholipase A2. Thus, two important mechanisms protect the pancreas from the potential degradative action of its own digestive enzymes. First, the synthesis of proteolytic enzymes as zymogens requires extrapancreatic activation by trypsin. Second, pancreatic juice contains a low concentration of trypsin inhibitor, which inactivates any autocatalytically formed trypsin within the pancreas. Proteolytic activity of trypsin in the intestinal lumen is not inhibited because the concentration of trypsin inhibitor is minimal. Lipase, amylase, ribonuclease, and deoxyribonuclease are secreted by the acinar cells in their active form.[8]

The regulation of exocrine pancreatic secretion is a complex interplay of neurohormonal feedback with three distinct phases. The first phase is the cephalic phase where the sight, smell, and taste of food produce pancreatic enzyme secretion through stimulus of the vagus nerve. Vasoactive intestinal peptide (VIP) and gastrin-releasing peptide (GRP) released from efferent vagus nerve terminals bind to receptors on the acinar cells stimulating enzyme release.[8] Water and bicarbonate are also released from ductal cells due to VIP stimulation. The gastric phase occurs due to gastric distension from food entering the stomach. This results primarily in secretion of digestive enzymes from the pancreas. Once chyme enters the duodenum, the intestinal phase begins. The chyme causes secretin to be released from the duodenal mucosa when its pH is less than 4.5. Secretin results in water and bicarbonate secretion from the pancreas to increase intestinal pH for stable lipolytic enzyme activity. Digestive enzymes are released from the pancreas due to the presence of fatty acids, peptides, amino acids, and glucose in the duodenum.[8]

The feedback mechanism for continued release of pancreatic enzymes involves the hormone cholecystokinin (CCK). When products of fat, protein, and starch digestion enter the upper small intestine, they stimulate release of CCK from I cells into the blood. Elevated levels of CCK in the serum activate a vasovagal reflex causing further release of VIP and GRP, leading to enhanced pancreatic enzyme secretion. Inhibition of this feedback loop is thought to be due to trypsin. After digestion is complete, unoccupied trypsin is thought to inhibit the release of CCK.[8] A more in-depth discussion of pancreatic physiology can be found elsewhere.[8]

ACUTE PANCREATITIS

Acute pancreatitis may be mild or may be associated with complications including organ failure and pancreatic necrosis. Prognosis and management vary according to the severity of the disease. There are several classification systems for acute pancreatitis that can be used to predict disease severity and outcomes. Some of these systems predict outcomes, but none have demonstrated superiority to the other.[9] In addition, it is not clear how management should change based on classification of severity.

Etiology

Table 56-1 lists the etiologic risk factors associated with acute pancreatitis. Obstruction caused by gallstones is the most common cause of acute pancreatitis in the United States, with alcohol abuse being the second most common. Abdominal obesity increases the risk for both gallstone- and nongallstone-related acute pancreatitis. Moderate elevations in lipid levels are associated with nonalcohol-related pancreatitis.[10] There is also an autoimmune form of pancreatitis.[11] Diabetes mellitus is also associated with an increase in acute pancreatitis as are autoimmune disorders such as inflammatory bowel disease.[4,12] Most remaining cases are classified as idiopathic.[2] Acute pancreatitis can occur as a result from undergoing an endoscopic retrograde cholangiopancreatography (ERCP) procedure and is more common following therapeutic ERCP than diagnostic, with overall rates up to 5.4%. Pregnancy is not considered a cause of acute pancreatitis; however, pregnant women develop pancreatitis as a result of a coincident process, most commonly cholelithiasis.[13] The reported incidence of acute pancreatitis in children has increased in recent years, and the common etiologies are biliary disease, systemic illness, medications, trauma, and idiopathic.[14,15]

TABLE 56-1 Etiologic Risk Factors Associated with Acute Pancreatitis

Structural	Gallstone disease, sphincter of Oddi dysfunction, pancreas divisum, pancreatic tumors
Toxins	Alcohol (ethanol) consumption, scorpion bite, organophosphate insecticides
Infectious	Bacterial, viral (including HIV and H1N1 influenza), parasitic
Metabolic	Hypertriglyceridemia, chronic hypercalcemia
Genetic	Cystic fibrosis, α1-antitrypsin deficiency, hereditary (trypsinogen gene mutations)
Medications	See Table 56-2 for specific drugs
Iatrogenic	Abdominal surgery, ERCP
Kidney disease	Chronic kidney disease, dialysis-related
Trauma	Blunt abdominal trauma
Vascular	Vasculitis, atherosclerosis, cholesterol emboli, coronary artery bypass surgery
Other etiologies	Congenital, Crohn's disease, autoimmune, tropical, solid organ transplantation (eg, liver, kidney, heart), refeeding syndrome
Idiopathic	Undetermined cause

HIV, human immunodeficiency virus; ERCP, endoscopic retrograde cholangiopancreatography.

Data from References 15, 16, 31, 33, and 35.

Medications

1 Factors that can contribute to acute pancreatitis should be identified and corrected, including discontinuation of medications that could be potential causes. Drug-induced acute pancreatitis should be considered when other causes have been excluded and there is a temporal relationship with the initiation of a medication that has been implicated as a cause. Most experts consider drug-induced pancreatitis to be rare, although some reports include higher estimates.[11,16] It is possible that the difficulty in diagnosing drug-induced pancreatitis has led to an underestimation of the rate.[16] Most information on drug-induced acute pancreatitis is obtained from case reports, which do not provide reliable information on incidence. The most convincing case reports involve recurrence on rechallenge; however, rechallenge is rare, occurring only when alternative therapy is not available. Further complicating the evaluation of some reports is use of medications associated with pancreatitis in patient

populations with an increased risk of pancreatitis.[16] Adverse events attributed to newly introduced medications may be reported more frequently.[17] Many medications have been frequently reported to cause acute pancreatitis. Patients with human immunodeficiency virus (HIV) have an increased risk of pancreatitis and there are many reports of pancreatitis attributed to antiretroviral agents.[17,18] Pancreatitis due to azathioprine is reported more frequently in patients with Crohn's disease than patients taking the medication for other indications, suggesting an interaction between the disease and medication. Patients with Crohn's disease often take other medications that can cause pancreatitis, including 5-aminosalycilates, corticosteroids, and sulfasalazine.[19] Patients with type 2 diabetes mellitus have an increased risk of acute pancreatitis. Case reports and some observational studies have linked antihyperglycemic agents, including metformin, sulfonylureas, and incretin mimetics, with pancreatitis. However, a meta-analysis did not find an increase in pancreatitis with incretin mimetics (such as exenatide and sitagliptin) compared to sulfonylureas, metformin, or insulin.[20] Complicating comparisons between agents used to treat diabetes mellitus is that the medications are often used in obese patients and patients with different durations of disease, both of which may also influence disease-associated pancreatitis.[21,22] Polypharmacy is associated with an increased risk of acute pancreatitis.[23]

There are numerous case reports of apparent drug-induced pancreatitis with statins. In contrast, a meta-analysis of lipid-lowering therapies found that statins were associated with a decreased number of acute pancreatitis cases.[24] However, pancreatitis was not a stated end point of any of the trials included and the issue remains controversial.

The onset of drug-induced pancreatitis after initiation of medications ranges from a few months to several years, with a median of 5 weeks; onset after rechallenge can occur within hours. The onset may differ according to the mechanism. Clinicians should be especially suspicious of a drug as a cause of acute pancreatitis in high-risk patients, such as those receiving immunomodulating drugs or who have HIV infection, the elderly, or those with diabetes mellitus.[16]

Mechanisms of drug-induced pancreatitis have been proposed for some medications but remain poorly defined. Possible mechanisms include direct toxic effects of the drug or its metabolites, hypersensitivity, drug-induced hypertriglyceridemia, and alterations of cellular function in the pancreas and pancreatic duct.[25] Ultimately, drug-induced pancreatitis causes damage to the pancreas, which produces a response similar to other causes of pancreatitis. It is

prudent to withdraw a medication when an association is suspected.

Numerous drugs are believed to cause acute pancreatitis, but ethical and practical considerations prevent rechallenge with suspected agents. **Table 56-2** lists specific agents associated with acute pancreatitis. Classification schemes consider rechallenge, the number of case reports, consistency with respect to onset of symptoms following initiation of the suspect medication, and exclusion of other causes.

TABLE 56-2 Medications Associated with Acute Pancreatitis

Well-Supported Association	Probable Association	Possible Association	
5-Aminosalicylic acid	Acetaminophen	Aldesleukin	Indinavir
Asparaginase		Amiodarone	Indomethacin
Azathioprine	Hydrochlorothiazide	Atorvastatin	Infliximab
Bortezomib	Itraconazole		Ketoprofen
	Ifosfamide		
Carbamazepine	Interferon α2b	Calcium	Ketorolac
Cimetidine	Maprotiline	Ceftriaxone	Lipid emulsion
Corticosteroids	Methyldopa	Capecitabine	Liraglutide
Cisplatin	Oxaliplatin	Carboplatin	Lisinopril
Cytarabine		Celecoxib	Mefenamic acid
Didanosine		Clozapine	Metformin
Enalapril		Cholestyramine	Metolazone
Erythromycin		Ciprofloxacin	Metronidazole
Estrogens		Clarithromycin	Nitrofurantoin
Furosemide		Clonidine	Omeprazole
		Cyclosporine	Ondansetron
Mercaptopurine		Danazol	Paclitaxel
Mesalamine		Diazoxide	Pravastatin
Octreotide		Etanercept	Propofol
Olsalazine		Ethacrynic acid	Propoxyphene
Opiates		Exenatide	Rifampin
Pentamidine		Famciclovir	Sertraline
Pentavalent antimonials		Glyburide	Simvastatin Sitagliptin
Sulfasalazine		Gold therapy	Sorafenib
Sulfamethoxazole and trimethoprim		Granisetron	Sulindac
Sulindac		Ibuprofen	Zalcitabine
Tamoxifen		Imatinib	
Tetracyclines			
Valproic acid/salts			

Data from References 17, 18, 24–29.

Pathophysiology

The pathophysiology of acute pancreatitis is based on events that initiate injury and secondary events that establish and perpetuate the injury (**Fig. 56-2**). Gallstones, alcohol abuse, and other causes of pancreatitis produce different initial insults to the pancreas. However, the resulting pathophysiologic process may be similar and include autodigestion, abnormal acinar calcium signaling, and inflammatory response. In acinar cells, the separation of zymogens and lysosomes can be disrupted, resulting in exposure of trypsinogen to lysosomal enzymes such as cathepsin B. The premature activation of trypsinogen to trypsin within the pancreas leads to activation of other digestive enzymes and autodigestion of the gland.[2,11]

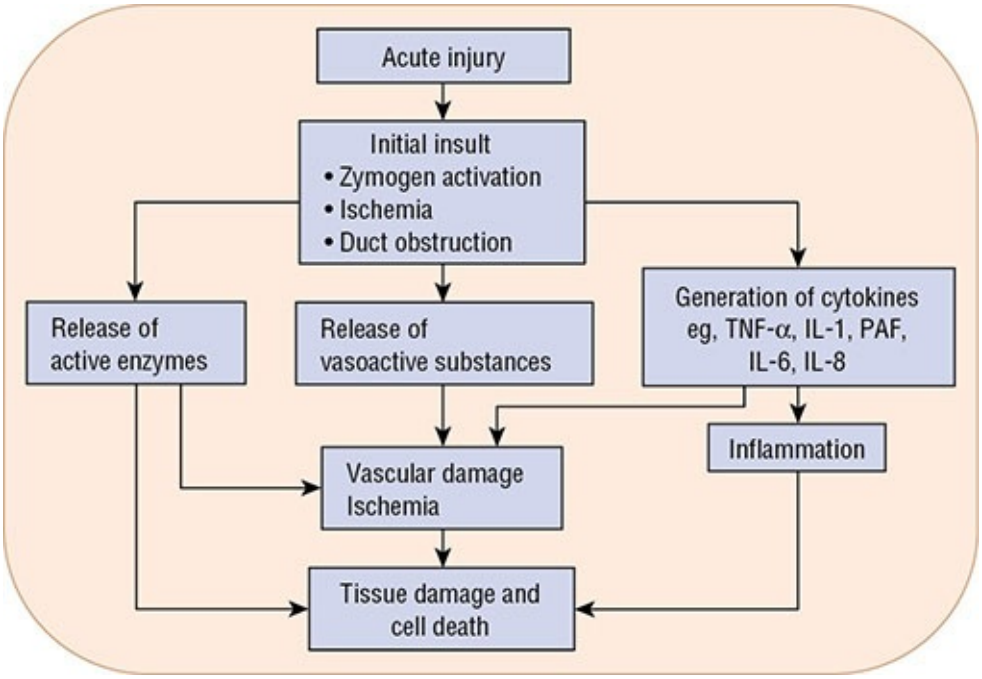


FIGURE 56-2 Pathophysiology of acute pancreatitis: initiating and secondary events. (IL-1β, interleukin-1β; IL-6, interleukin-6; IL-8, interleukin-8; PAF, platelet-activating factor; TNF-*α*, tumor necrosis factor-*α*.).

In addition to activation of digestive enzymes within the pancreas, enzymes are also released into surrounding fat, vascular endothelium, and other surrounding tissues and structures causing further damage and necrosis. Lipase damages fat cells, producing noxious substances that cause further pancreatic and peripancreatic injury. There may be an independent response from intra-acinar activation of inflammatory factors. The release of cytokines by acinar cells directly causes their injury and enhances the inflammatory response.[26] Injured acinar cells liberate chemoattractants that recruit neutrophils,

macrophages, and other cells to the area of inflammation. These immune responses cause a systemic inflammatory response syndrome (SIRS). Vascular damage and ischemia causes the release of kinins, which makes capillary walls permeable and promotes tissue edema. Finally, pancreatic infection may result from increased intestinal permeability and translocation of colonic bacteria.[27]

Clinical Presentation

Signs and Symptoms

The clinical presentation of acute pancreatitis varies depending on the severity of the inflammatory process and whether damage is confined to the pancreas or involves local and systemic complications (Table 56-3).[11]

TABLE 56-3 Presentation and Diagnosis of Acute Pancreatitis

General

- The patient may have acute mild symptoms or present with a severe acute attack with life-threatening complications.

Symptoms

- The patient may present initially with moderate abdominal discomfort to excruciating pain, nausea, shock, and respiratory distress.
- Abdominal pain occurs in 95% of patients. The pain is usually epigastric and radiates to either of the upper quadrants or the back in two-thirds of patients. In gallstone pancreatitis, the pain is typically sudden and quite severe and the intensity is often described as "knife-like" or "boring." The pain usually reaches its maximum intensity within 30 minutes and may persist for hours or days. Repositioning the patient relieves very little of the pain. In alcohol abuse and other cases, the onset of pain may be less abrupt and poorly localized. Pain may not be the dominant symptom if it is masked by multiorgan failure.
- Nausea and vomiting occur in 85% of patients and usually follow the onset of abdominal pain. Vomiting does not provide relief of the abdominal pain.

Signs

- Marked epigastric or diffuse tenderness on palpation with rebound tenderness and guarding in severe cases. The abdomen is often distended and tympanic, with bowel sounds decreased or absent in severe disease.
- Vital signs may be normal, but hypotension, tachycardia, and low-grade fever are often observed, especially with widespread pancreatic inflammation and necrosis.
- Dyspnea and tachypnea are often signs of acute respiratory complications. Jaundice and altered mental status may be present and have multiple causes. Other signs of alcoholic liver disease may be present in patients with alcoholic pancreatitis.

Laboratory tests

- Leukocytosis is frequently present; hyperglycemia or hypoalbuminemia may be present. Liver transaminases, alkaline phosphatase, and bilirubin are usually elevated in gallstone pancreatitis and in patients with intrinsic liver disease. Elevated serum triglycerides may also be a possible etiology.
- The hematocrit may be normal, but hemoconcentration results from multiple factors (eg, vomiting). In patients with third-space fluid loss, hemoconcentration is present and a reasonably accurate marker of severe disease. A hematocrit of greater than 47% (0.47) predicts severe acute pancreatitis and one of less than 44% (0.44) predicts mild disease. Further, failure to reverse hemoconcentration has been associated with pancreatic necrosis.
- Blood urea nitrogen (BUN) that is elevated or rising over the first 24 hours has been associated with increased mortality.
- The total serum calcium is usually normal initially, but hypocalcemia disproportionate to the hypoalbuminemia may develop. Marked hypocalcemia is an indication of severe necrosis and a poor prognostic sign.
- The serum amylase concentration usually rises within 4-8 hours of the initial attack, peaks at 24 hours, and returns to normal over the next 8-14 days. Serum amylase concentrations greater than three times the upper limit of normal are highly suggestive of acute pancreatitis. Persistent elevations suggest extensive pancreatic necrosis and related complications. Normal concentrations may be observed if testing is delayed (ie, amylase may have returned to normal) or in patients with hyperlipidemic pancreatitis (ie, marked triglyceride elevations may interfere with amylase assay). In addition, many nonpancreatic diseases may be associated with hyperamylasemia, including salivary, kidney, hepatobiliary, metabolic, female reproductive tract, and neoplastic diseases.
- Serum lipase is specific to the pancreas and concentrations are elevated and parallel the elevations in serum amylase. Levels remain elevated with pancreatic inflammation and return to normal when the inflammatory process resolves. Because of its longer half-life, elevations of serum lipase can be detected after the serum amylase has returned to normal.
- Additional biomarkers: C-reactive protein (CRP) is a widely available test and levels greater than 150 mg/L at 48-72 hours predict severe acute pancreatitis with accuracy similar to that of APACHE II. Urinary trypsinogen activation peptide is specific for acute pancreatitis but not sensitive and not widely available. Procalcitonin has been studied for severity assessment as well as identification of patients with bacterial infection.
- Thrombocytopenia and an increase in the international normalized ratio are seen in some patients with severe acute pancreatitis and associated liver disease.

Abdominal imaging

- Transabdominal ultrasound should be performed in all patients to detect dilated biliary ducts and stones in the gallbladder.
- CECT is used if the diagnosis cannot be made from clinical and laboratory findings. It is less accurate for evaluating the gallbladder and biliary ducts. The test distinguishes interstitial from necrotizing pancreatitis, but does not distinguish between fat necrosis and acute fluid collection. Tests that are performed in the first few days may miss necrosis. Tests should be performed at least 72-96 hours after symptom onset; tests performed too early may result in unnecessary exposure to risk and increased cost.
- Magnetic resonance imaging is used to grade the severity of acute pancreatitis, identify biliary duct problems that are not seen on CT, or if there are contraindications to CECT. Patients over the age of 40 with pancreatitis of an unknown etiology should be evaluated for pancreatic malignancy with CT or endoscopic ultrasonography.

APACHE, Acute Physiology and Chronic Health Evaluation; CECT, contrast-enhanced computed tomography; CT, computed tomography.

Data from References 11 and 36.

Diagnosis

The diagnosis of acute pancreatitis requires two of the following three: upper abdominal pain, a serum lipase or amylase concentration at least three times greater than the upper limit of normal, or characteristic findings on imaging studies.[28,29] Lipase is more sensitive and specific than amylase and is the preferred laboratory test. Imaging studies are not necessary for diagnosis if the other two findings are positive. Contrast-enhanced computed tomography (CECT) of the abdomen may be used to confirm the diagnosis in patients with amylase or lipase that is not three times the upper limit of normal, or in sedated patients. The diagnosis of acute pancreatitis should also be considered when evaluating patients with SIRS (see Table 56-3).[29] For further information on laboratory tests and abdominal imaging, refer to Table 56-3. Pertinent history includes previous history of pancreatitis, gallstone disease, alcohol use, medication use, recent surgery or ERCP, hyperlipidemia, and family history. Magnetic resonance cholangiopancreatography (MRCP) is useful for detecting retained common bile duct stones. Laboratory tests should include liver enzymes, triglycerides, and calcium. Transabdominal ultrasound of the right upper quadrant is recommended to assess for gallstones.[11,28,29]

Acute pancreatitis is categorized according to the recently revised Atlanta classification. The revised Atlanta Classification defines acute pancreatitis as mild disease (not associated with organ failure, local complications, or systemic complications), moderately severe (transient organ failure, local complications or systemic complications), and severe (persistent organ failure).[30] An alternative classification system was proposed by an international multidisciplinary group using factors that have a causal association with severity (ie, distant organ failure or pancreatic necrosis) rather than events that may be associated with severity.[31] This determinant-based classification includes mild (no organ dysfunction or necrosis), moderate (sterile necrosis or transient organ dysfunction or both), severe (either infected necrosis or persistent organ dysfunction), and critical (infected necrosis and persistent organ dysfunction).

Prediction of severity of acute pancreatitis is useful for decisions involving the need for aggressive treatment, including admission to an intensive care unit.[28,29] Multiple scoring systems have been used to predict which patients with acute pancreatitis are at greatest risk for persistent organ failure.[32] This would be useful in determining aggressiveness of initial therapy as well as in developing clinical trials of interventions. However, development and validation of such

systems remain an ongoing area of research. Scoring systems are developed based on retrospectively identified associations between clinical and laboratory findings and morbidity and mortality.[1,33] Many are too complicated for bedside use or rely on measurements that are not widely available. Some scoring systems have not been validated in prospective trials or have poor predictive ability.[32]

The Acute Physiology and Chronic Health Evaluation II (APACHE II) system is a sensitive predictor of persistent organ failure in patients with acute pancreatitis; however, it is less specific than some scoring systems that were developed for acute pancreatitis.[34] Other tools for assessing the severity of acute pancreatitis include the Bedside Index of Severity in Acute Pancreatitis (BISAP), the Harmless Acute Pancreatitis Score (HAPS), and the Japanese Severity Score (JSS).

The accuracy of several scoring systems was assessed and none had consistent superiority over others.[32] The International Association of Pancreatology/American Pancreatic Association (IAP/APA) guidelines recommend evaluation based on SIRS criteria.[29] Advantages of using SIRS criteria include ease of use and the widespread adoption of processes to ensure that it is routinely assessed. The authors of the American Gastroenterological Association guidelines note a lack of demonstrated clinical benefit from the scoring systems and supports use of a combination of clinical judgment and a variety of scoring tools.[33]

Clinical Course and Prognosis

The clinical course of acute pancreatitis varies from a mild transitory disorder to a severe necrotizing disease. Mild acute pancreatitis is self-limiting and subsides spontaneously within 3 to 5 days. Mortality is influenced by etiology, as idiopathic and postoperative acute pancreatitis have higher rates than gallstone- or alcohol-related disease. First and second occurrences also carry a higher mortality than subsequent episodes. Mortality increases with unfavorable early prognostic signs, local complications, and organ failure. Persistent organ failure is a greater risk than transient organ failure.[35] Severe pancreatitis with either organ failure or infected necrosis is associated with a mortality of approximately 30%, and increases when both are present.[35] Death during the first few days results from SIRS and multiorgan failure. When death occurs after this period, it is usually a result of infected necrosis, pancreatic abscess, and sepsis.[28,29,36]

Complications

Early complications are a result of SIRS and organ failure. The most common systemic complication of acute pancreatitis is respiratory failure.[30] In addition, patients may experience systemic complications due to exacerbation of preexisting renal, lung, or heart disease.[30] A second phase occurs in patients with moderately severe or severe disease. These patients have persistent organ failure and may have local complication including fluid collections that may become necrotic.[30] Long-term complications include glucose intolerance and recurrence of acute pancreatitis.[37,38]

There are also local complications that may occur, including interstitial pancreatitis (acute peripancreatic fluid collection and pancreatic pseudocysts) and collection of necrosis. These develop approximately 3 to 4 weeks after the initial attack. Pancreatic infections occur in 15% to 30% of those with pancreatic necrosis.[28]

TREATMENT

Acute Pancreatitis

Desired Outcome

Treatment of acute pancreatitis is aimed at relieving abdominal pain and nausea, replacing fluids, correcting electrolyte, glucose, and lipid abnormalities, minimizing systemic complications, and managing pancreatic necrosis and infection. Management varies depending on the severity of the attack (**Fig. 56-3**). Patients with mild acute pancreatitis respond very well to the initiation of supportive care. Patients with severe acute pancreatitis should be treated aggressively and monitored closely.

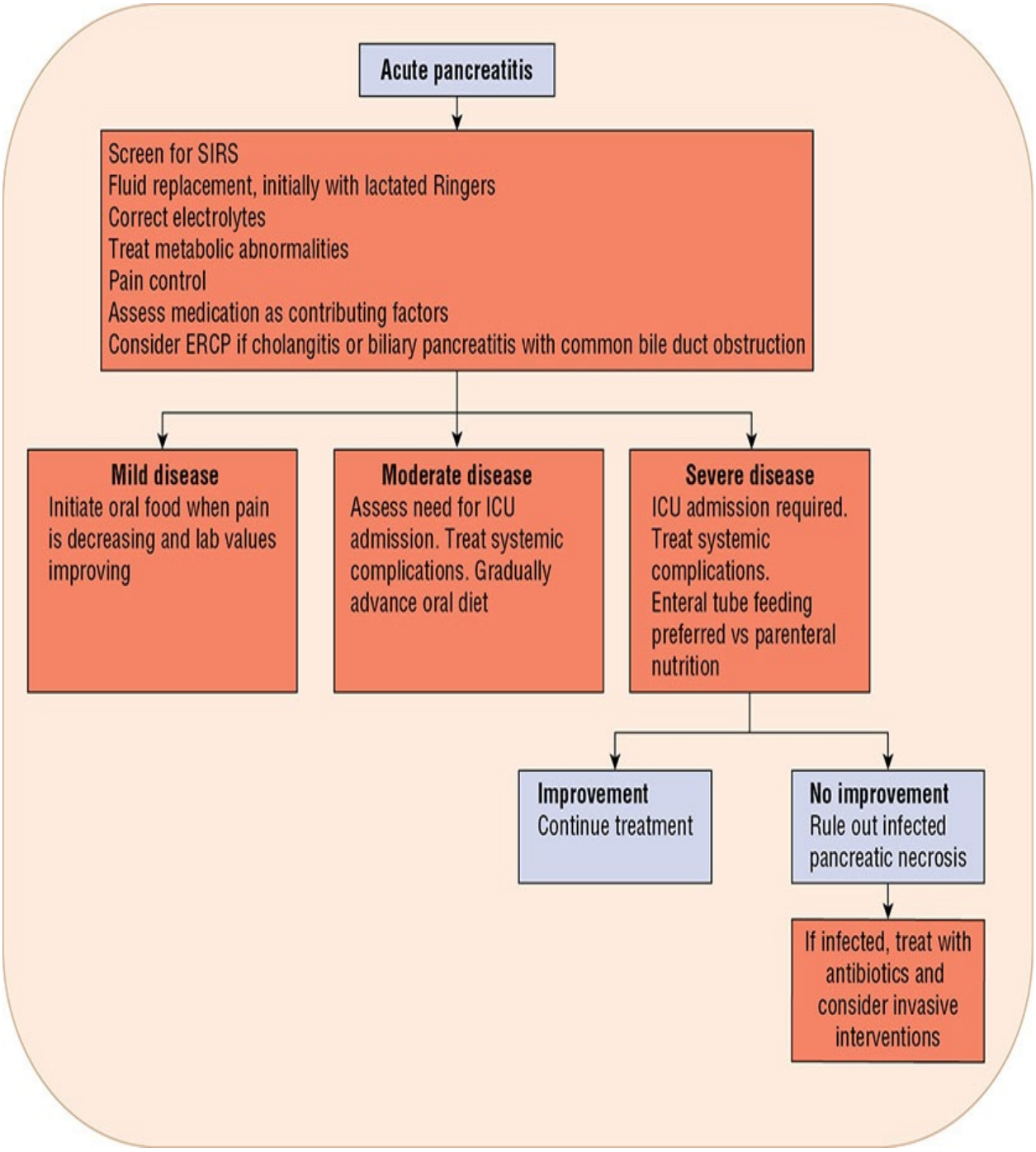


FIGURE 56-3 Algorithm of guidelines for evaluation and treatment of acute pancreatitis. (SIRS, systemic inflammatory response syndrome; ERCP, endoscopic retrograde cholangiopancreatography; ICU, intensive care unit.).

General Approach to Treatment

All patients with acute pancreatitis should receive supportive care, including IV

fluid resuscitation, adequate nutrition, and effective relief of pain and nausea. Patients should be evaluated for admission to the intensive care unit. Patients predicted to follow a severe course may require treatment of systemic complications.[1] Fluid therapy is recommended and may help prevent organ failure.[29,33] Patients with pancreatitis and SIRS should be treated according to SIRS guidelines. IV potassium, calcium, and magnesium are used to correct electrolyte deficiency states. Insulin is used to treat hyperglycemia. Local complications resolve as the inflammatory process subsides. However, patients with necrotizing pancreatitis may require antibiotics and procedural intervention.[29,39] Medications listed in Table 56-2 should be reviewed and discontinued if other etiologies are unlikely.

Nonpharmacologic Therapy

Nonpharmacologic therapy includes ERCP for removal of any underlying biliary tract stones, procedural interventions, and nutritional support. The need for admission to an intensive care unit should be addressed. Advances in minimally invasive surgical techniques are changing practice with respect to timing and approach to managing infected necrotizing pancreatitis, and may help lower the risk of mortality in the most critical patients.[33,39] Patients with alcohol-related pancreatitis should receive abstinence interventions during the inpatient stay.[40]

Nutrition and Probiotics

Nutritional support plays an important role in the management of patients with mild or severe disease as acute pancreatitis creates a catabolic state that promotes nutritional depletion. This can impair recovery, increase the risk of complications, and prolong hospitalization.[41] In the past, there was concern that enteral feeding stimulated pancreatic enzyme secretion and exacerbated the underlying disease. However, enteral nutrition results in decreased multiple organ failure and need for surgical intervention compared with parenteral nutrition.[42] Possible mechanisms for this include protection of the gut barrier and prevention of colonization with pathogenic bacteria, both of which may prevent translocation of bacteria and subsequent infection.[27] Patients with mild acute pancreatitis can begin oral feeding when pain is decreasing and inflammatory markers are improving. It is not necessary to withhold oral nutrition until lipase normalizes.[41] In severe or complicated disease, nutritional deficits develop rapidly and are complicated by tissue necrosis, organ failure,

and surgery. Nutritional support should begin when it is anticipated that oral nutrition will be withheld for more than 1 week.[41] Therefore, enteral nutrition delivered via a nasogastric or nasojejunal tube is preferred over parenteral nutrition in patients with severe acute pancreatitis provided it can be tolerated. If enteral feeding is not possible or if the patient is unable to obtain sufficient nutrients, total parenteral nutrition should be implemented before protein and calorie depletion become advanced.[33] ASPEN guidelines state that IV lipids are considered safe unless the serum triglyceride concentration is greater than 400 mg/dL (4.52 mmol/L) and the patient has a history of hyperlipidemia.[41]

Probiotics may improve outcomes in patients with acute pancreatitis. A meta-analysis, however, did not support the use of probiotics in the treatment of acute pancreatitis, as they have not shown a benefit.[43] Heterogeneity of the included trials due to use of multiple different products complicates interpretation of the results. Overall, use of probiotic agents for acute pancreatitis is not recommended at this time.

Pharmacologic Therapy

Patients with acute pancreatitis often require IV antiemetics for nausea. Those requiring ICU admission should be treated with antisecretory agents (such as famotidine or pantoprazole) if they are at risk of stress-related mucosal bleeding. Patients also require appropriate fluid resuscitation and pain management, but there is controversy surrounding both of these therapies (see Fig. 56-3). Clinical trials have also failed to identify a group of patients that benefit from prophylactic antibiotics.

Fluid Resuscitation

2 Vasodilation from the inflammatory response, vomiting, and nasogastric suction contributes to hypovolemia and fluid and electrolyte abnormalities, thus necessitating replacement. Patients with acute pancreatitis should receive aggressive fluid replacement to reduce the risks of persistent SIRS and organ failure. The IAP/APA guidelines recommend goal directed intravenous fluid with lactated Ringer’s at an initial rate of 5 to 10 mL/kg/hr, while the American College of Gastroenterology guidelines recommend 250 to 500 mL/hr with crystalloids with close monitoring of BUN and adjustment of the rate based on the results.[28,29] Goals for fluid therapy in the management of acute pancreatitis are not well-defined but include one or more of the following: heart rate less

than 120/min, mean arterial pressure 65 to 85 mm Hg, urinary output greater than 0.5 to 1 mL/kg/hr, invasive measures of stroke volume or intrathoracic blood volume, or hematocrit 35% to 44% (0.35-0.44) with transfusion of blood.[28,29]

Studies completed to date have been of low quality and have somewhat conflicting results. Observational studies have identified both benefit (decreased mortality and markers of organ failure) and harm (abdominal compartment syndrome) associated with early aggressive fluid administration.[33] Interpretation of these trials is complicated by the likelihood that sicker patients were given larger volumes of fluid. In a prospective, randomized trial, goal-directed fluid replacement therapy of 3 mL/kg/hr for the first 20 hours did not result in a reduction in SIRS or C-reactive protein (CRP).[44] Studies of fluid resuscitation in acute pancreatitis suggest that some patients may not require aggressive fluid resuscitation, while others may require gradual fluid administration. For example, those with reduced cardiac reserve may do better if fluid is replaced over 72 hours rather than 24 to 48 hours.[45] Patients with sepsis should be resuscitated according to sepsis guidelines.[46]

In addition to questions about the rate and volume of fluid that should be administered to patients with acute pancreatitis, there is also debate regarding which fluid is most appropriate. A small randomized trial found that goal-directed resuscitation with lactated Ringer's produced a reduction in SIRS and CRP at 24 hours compared with normal saline.[44] The study protocol used aggressive replacement with a bolus of 20 mL/kg of lactated Ringer's followed by 150 to 300 mL/hr for the first 24 hours. If patients responded to this therapy as assessed by BUN, the rate could be reduced to 2 mL/kg/hr.

Relief of Abdominal Pain

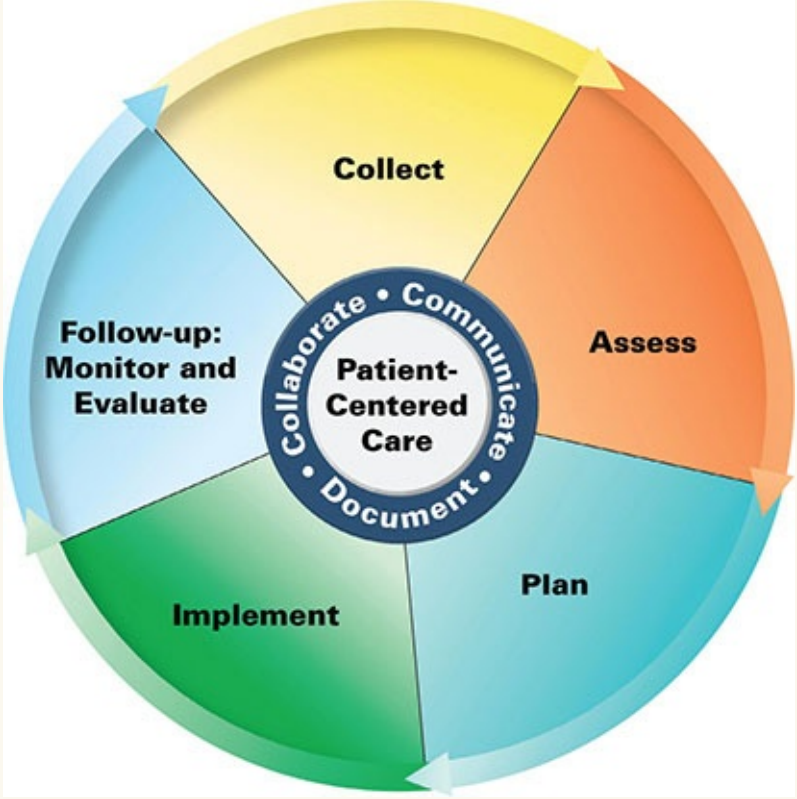
3 Parenteral opioid analgesics are used to control abdominal pain associated with acute pancreatitis despite a lack of high-quality evidence to support the practice. A Cochrane review found a lack of studies to support any specific agent or class of agents for pain management in acute pancreatitis.[47]

Nonsteroidal anti-inflammatory agents may be sufficient in patients with mild or moderate pain due to acute pancreatitis and can be used if not otherwise contraindicated.[48] Parenteral morphine is often recommended for pain control because it provides a longer duration of pain relief than other opioids. Although morphine increases biliary pressure, there is no evidence to indicate that it is contraindicated for use in acute pancreatitis. Patient-controlled analgesia should

be considered in patients who require frequent opioid dosing (eg, every 2-3 hours).

Limitation of Systemic Complications and Prevention of Pancreatic Necrosis

There is currently no specific therapy to prevent the complications and necrosis associated with acute pancreatitis. The use of parenteral histamine-2 receptor antagonists or proton pump inhibitors does not improve the overall outcome of patients with acute pancreatitis.[49] Also, although somatostatin and its synthetic analog octreotide have been used to interrupt the inflammatory process of acute pancreatitis, there are insufficient data to support their routine use, and they are not recommended by guidelines.[28,29,49]



Patient Care Process for Pancreatitis

Collect

- Patient characteristics (eg, age, sex, pregnant)

- Patient history (past medical—hyperlipidemia, recent surgery, gallstone disease or ERCP; social—dietary habits, alcohol use, tobacco use)
- Current and recent (for acute pancreatitis; see Table 56-2) medications
- Medication allergies
- Review of systems for the abdomen and gastrointestinal system (eg, abdominal pain, nausea and vomiting, stool frequency and consistency for chronic pancreatitis; see Tables 56-3 and 56-5)
- Objective data
  - Acute pancreatitis (see Table 56-3)

    Vital signs (eg, BP, heart rate, temperature, respiratory rate)

    Labs (eg, CBC, Chem-7, calcium, albumin, amylase, lipase, transaminases, bilirubin, triglycerides)

    Microbiology results

    Intake/output
  - Chronic Pancreatitis (see Table 56-5)

    Physical exam (eg, weight; assessment for neuropathy, nephropathy, and retinopathy with diabetes)

    Labs (eg, fasting serum glucose, bilirubin, transaminases, pancreatic function tests, calcium, albumin)

Assess

- Acute pancreatitis
  - Causative medications (see Table 56-2)
  - Nutrition and fluid status
  - Abdominal pain: location, radiation, severity, onset
  - Infectious etiologies
  - Continuous hemodynamic monitoring
- Chronic pancreatitis
  - Alcohol and tobacco use
  - Abdominal pain
  - Trends in weight, nutrition status, serum glucose, and stool consistency and frequency (assess for constipation if patient taking opioids)

Plan*

- Acute pancreatitis
  - Fluid support including choice and dose
  - Discontinue suspected causal medications
  - Nutrition support including route and caloric requirements
  - Pain management with specific medication choice, route, and dose
  - Antimicrobial therapy regimen for suspected or identified infection(s)
- Chronic pancreatitis
  - Tailored lifestyle modifications (eg, abstinence from alcohol, smoking cessation; see Fig. 56-4)
  - Nutrition support and dietetic counseling
  - Therapy for abdominal pain (see Fig. 56-4) with analgesics (see Table 56-6) and pancreatic enzymes (see Table 56-7), including the need for treatment of constipation if opioids are utilized
  - Therapy for malabsorption (see Fig. 56-5, and Tables 56-6 and 56-7)
  - Treatment of concomitant diabetes mellitus if present

Implement

- Consultation with additional providers as necessary (eg, dietician, pain management specialist, infectious diseases, gastroenterology, endocrinology) and consider transfer to a specialty center if severe disease
- Pain therapy with clearly identified goals for both the provider and patient
- Fluid and nutrition support as appropriate
- Necessary lifestyle modifications (eg, smoking cessation)
- For patients with acute pancreatitis initiate empiric antimicrobial therapy if necessary and narrow coverage based on cultures and sensitivities
- For patients with malabsorption due to chronic pancreatitis initiate appropriate pancreatic enzyme therapy

Follow-up: Monitor and Evaluate

- Pain control and constipation if opioids utilized
- Acute pancreatitis
  - Fluid and electrolytes along with kidney and liver function (eg, serum

creatinine, BUN, bilirubin, transaminases)
    - Signs and symptoms of infection along with microbiology culture and sensitivity results
    - Hemodynamic parameters for signs of decreased intravascular volume and shock
    - Nutrition status and support (eg, prealbumin, albumin, changes in caloric requirements and delivery route)
    - Discontinuation of causative medication(s) on discharge and identification of necessary therapeutic alternative(s)
    - Brief alcohol cessation intervention prior to discharge for alcohol-related acute pancreatitis
- Chronic pancreatitis
    - Alcohol intake and smoking status utilizing motivational interviewing
    - Weight and effects of diet on abdominal pain and malabsorption symptoms
    - Efficacy of pancreatic enzymes on symptoms of malabsorption (see Fig. 56-5)
    - Serum blood glucose along with signs and symptoms of diabetes mellitus

**Collaborate with patient, caregivers, and other healthcare professionals.*

Antimicrobial Use in Acute Pancreatitis

Antimicrobials have been widely studied in patients with acute pancreatitis, but there are still areas of uncertainty. The IAP/APA guidelines state that selective digestive tract decontamination may be effective in reducing the risk of pancreatic infection, citing one controlled trial.[29] Additional studies are needed before clinicians begin using this strategy in the treatment of acute pancreatitis.

4 Several small, randomized clinical trials have compared antibiotic prophylaxis with no prophylaxis in patients with acute necrotizing pancreatitis with varying results. Recent trials of better quality, including meta-analyses, found that prophylactic antibiotics do not reduce infected necrosis or mortality.[33,50] In addition, overuse of antibiotics increases microbial resistance. Use of prophylactic antibiotics is not recommended in patients with acute

pancreatitis without signs or symptoms of infection, including those with predicted severe acute pancreatitis or necrotizing pancreatitis.[28,29,33] However, empiric antimicrobial therapy may be considered in patients with necrosis who deteriorate or fail to improve within 7 to 10 days.[28]

Because the source of bacterial contamination is most likely the colon, the antibiotic regimen for patients with known or suspected infected pancreatitis should be broad-spectrum, covering the range of enteric aerobic gram-negative bacilli and anaerobic microorganisms. Therapy should be initiated as soon as possible and not delayed in order to obtain cultures.[28,51] Imipenem–cilastatin (500 mg IV every 8 hours) has been widely used because of its good penetration into the pancreas and one positive prophylaxis study.[52] However, it has been replaced on many hospital formularies by one of the newer carbapenems (eg, meropenem). Fluoroquinolones, such as ciprofloxacin or levofloxacin, combined with metronidazole should be considered for penicillin-allergic patients.[53] Patients with infected necrotic pancreatitis are generally treated with a combination of invasive interventions and antibiotics. Antibiotics alone may be sufficient in some cases or at least delay the need for an invasive procedure long enough for the necrotic areas to be walled off.[51,54]

A high mortality associated with candidal infections in severe acute pancreatitis has led investigators to study strategies for identifying patients who might benefit from antifungal prophylaxis.[55] In a series of 479 patients with acute pancreatitis treated at one medical center, the strongest predictor of fungal infection was use of an antibiotic on admission.[56] At this point, prophylactic antifungal therapy is not recommended for patients with acute pancreatitis.[28]

PostERCP Pancreatitis

The clinical characteristics of postERCP pancreatitis are similar to those of acute pancreatitis from other causes. In most cases, the disease course is mild and resolves in several days. The incidence of postERCP pancreatitis has decreased over the past 15 years, most likely due to better patient selection. Several classes of medications have been studied for prevention of postERCP pancreatitis. The best data are with nonsteroidal anti-inflammatory agents (NSAID). When administered prior to the procedure, indomethacin suppositories decreased the incidence of postERCP pancreatitis by 46% in a population at increased risk.[57] This therapy was not associated with an increase in bleeding or renal failure. However, patients at increased risk for adverse effects from NSAIDs were excluded. A post hoc analysis of the data suggested that rectal indomethacin

alone could be more cost-effective than use of a stent or stent plus indomethacin.[58]

CHRONIC PANCREATITIS

Chronic pancreatitis results from long-standing pancreatic inflammation resulting in irreversible destruction of pancreatic tissue with fibrin deposition, leading to a loss of exocrine and endocrine functions.[5–7] It has four different stages beginning with a preclinical inflammatory stage where patients remain asymptomatic or have indistinguishable symptoms.[5] In the second-stage patients present with acute attacks that often resemble those of acute pancreatitis. The third stage consists of episodes of intermittent or constant abdominal pain. Finally, in the burnout stage patients present with diminished or absent pain, but develop malabsorption syndrome due to loss of pancreatic exocrine function and may develop diabetes mellitus from loss of endocrine function.

Etiology

Chronic alcohol consumption, especially heavy drinking, remains the leading cause of chronic pancreatitis in Western society, accounting for up to two-thirds of cases.[7,59,60] A meta-analysis showed that consumption of 40 g/day or more of alcohol poses a significant risk of chronic pancreatitis.[60] Most of the remaining cases can be classified as idiopathic, while a small percentage of cases are due to rare causes, such as autoimmune, hereditary, and tropical pancreatitis.[6,7,61] Various genetic alterations have also been associated with the occurrence of chronic pancreatitis, including mutations of the following genes: protease serine 1 (trypsin 1) (*PRSS1*), serine peptidase inhibitor Kazal type 1 (*SPINK1*), and the cystic fibrosis transmembrane conductance regulator (*CFTR*).[6,7,59,62] There is also a demonstrated risk of chronic pancreatitis with cigarette smoking that appears to be dose-dependent and may contribute to mortality from chronic pancreatitis.[6,59,61,63] There are two classification systems for chronic pancreatitis that take into account the various risk factors associated with the disease (**Table 56-4**).[59]

TABLE 56-4 Classification of Etiology and Risk Factors for Chronic Pancreatitis

M-ANNHEIM	
Multiple	Risk factors
Alcohol	Excessive consumption (>80 g/day), increased consumption (20-80 g/day), moderate consumption (<20 g/day)
Nicotine	Quantitated in pack years for current smokers
Nutritional factors	High-fat and protein diet, hyperlipidemia (especially hypertriglyceridemia)
Hereditary factors	Hereditary pancreatitis, familial pancreatitis, early and late-onset idiopathic pancreatitis, tropical pancreatitis, possible gene mutations (eg, *PRSS1*, *SPINK1*, and *CFTR*)
Efferent duct factors	Pancreas divisum, annular pancreas/congenital abnormalities, pancreatic duct obstruction (eg, tumors), posttraumatic pancreatic duct scars, sphincter of Oddi dysfunction
Immunologic factors	Autoimmune pancreatitis
Miscellaneous and rare factors	Hypercalcemia and hyperparathyroidism, chronic kidney disease, medications, toxins
TIGAR-O	
Toxic-metabolic	Alcohol, tobacco smoking, hypercalcemia, hyperlipidemia, chronic kidney disease, medications, toxins
Idiopathic	Early onset, late-onset, tropical pancreatitis
Genetic mutations	*PRSS1, CFTR, SPINK1*, others
Autoimmune	Isolated, syndromic
Recurrent and severe associated acute pancreatitis	Postnecrotic (severe AP), vascular disease/ischemic, postirradiation
Obstructive	Pancreas divisum, sphincter of Oddi dysfunction, pancreatic duct obstruction (eg, tumor), posttraumatic pancreatic duct scars

AP, acute pancreatitis; PRSS1, cationic trypsinogen; *SPINK1*, serine protease inhibitor Kazal type 1; *CFTR*, cystic fibrosis transmembrane conductance regulator.

Reprinted, with permission, from Conwell DL, Lee LS, Yadav D. American Pancreatic Association Practice Guidelines in Chronic Pancreatitis: Evidence-based report on diagnostic guidelines. Pancreas. 2014;43(8):1162.

Pathophysiology

Although the exact mechanism for the pathogenesis of chronic pancreatitis is unknown, several theories have been proposed. One of the main theories is that repeated episodes of acute pancreatitis lead to the occurrence of chronic pancreatitis.[7,59,64] Repeated episodes of acute pancreatitis initiate inflammation and necrosis that leads to ductal scarring and fibrosis. This leads to ductal obstruction and eventually results in acinar atrophy and fibrin deposition.

Regardless of the pathophysiologic mechanism, several pieces of evidence now point to activation of pancreatic stellate cells as the cause of fibrin deposition in chronic pancreatitis. Various toxins, oxidative stress, and inflammatory mediators activate pancreatic stellate cells.[7,61,64] Activated pancreatic stellate cells then initiate fibrinogenesis. Other mediators generated by the stellate cells themselves perpetuate continued stellate cell activation.

The pathogenesis of pain in chronic pancreatitis has long been thought to be the result of increased pancreatic parenchymal pressure from obstruction, inflammation, and necrosis.[7] However, evidence increasingly points to a neurogenic origin of pain. There is abnormal pain processing in the central nervous system of patients with chronic pancreatitis, with evidence of functional reorganization of the insular cortex.[7,61] Also, visceral nerves in these patients are sensitized. This may explain the hyperalgesia often experienced by these patients, and the need for various methods of pain management. Patients with chronic pancreatitis may also experience pain in areas distant to the pancreas due to impaired inhibition of somatic and visceral pain pathways.

Clinical Presentation

5 Chronic pain, malabsorption with resultant steatorrhea, and diabetes mellitus are the hallmark symptoms and complications of chronic pancreatitis. Although abdominal pain is the most common symptom at any stage, patients may present with various signs and symptoms depending on the stage of the disease. A more comprehensive list of the common signs and symptoms is presented in **Table 56-5**.

TABLE 56-5 Signs, Symptoms, and Diagnosis of Chronic Pancreatitis

Signs

- Malnutrition (especially in chronic alcoholism)
- Abdominal mass (may indicate a pancreatic pseudocyst)
- Jaundice may be seen
- Splenomegaly (rare)

Symptoms

- Abdominal pain
  - Commonly in epigastric area
  - May radiate to the back
  - Described as deep and penetrating
  - May be relieved by bending/leaning forward or bringing knees to the chest
  - Often occurs with meals and at night
  - May be associated with nausea and vomiting
- Steatorrhea
  - Patients describe bulky or foul-smelling stools often with obvious oil droplets
  - Usually have an average of three to four stools per day
  - May be associated with deficiencies in fat-soluble vitamins
  - Watery diarrhea, excess gas, and abdominal cramps are uncommon
- Pancreatic diabetes mellitus
- Diarrhea (associated with steatorrhea)
- Weight loss
  - May be due to severe malabsorption or acute/chronic pain
  - Substantial loss may be due to associated or unrelated malignancy
- Osteoporosis (from vitamin D malabsorption and increased bone resorption)
- Dyspepsia

Laboratory studies

- CBC to rule out infection (ie, infected pseudocyst)
- Serum amylase and lipase
  - Low specificity for chronic pancreatitis
  - May be elevated in acute exacerbations
  - Usually are normal or only slightly elevated
- Total bilirubin, alkaline phosphatase, and hepatic transaminases may be elevated with ductal obstruction
- Fasting serum glucose
- Pancreatic function tests
  - Indirect
    - Serum trypsinogen (<20 ng/mL [mcg/L] is abnormal)
    - Fecal elastase (<200 mcg/g of stool is abnormal)
    - Fecal chymotrypsin (<3 units/g of stool is abnormal)
    - Fecal fat estimation (>7 g/day is abnormal; need to collect 72 hours of stool)
    - ^{13}C-mixed triglyceride breath test (conducted over 6 hours; not available in the United States)
  - Direct
    - Secretin stimulation (evaluates duodenal bicarbonate secretion)
    - Cholecystokinin stimulation (evaluates pancreatic lipase secretion)
  - Serum albumin (may be low with malnutrition)
  - Serum calcium (may be low with malnutrition)

Imaging studies

- Noninvasive
  - Abdominal ultrasound
  - Computed tomography (CT)
  - Magnetic resonance imaging (MRI) with Magnetic resonance cholangiopancreatography (MRCP)
- Invasive
  - Endoscopic ultrasonography (EUS)
  - Endoscopic retrograde cholangiopancreatography (ERCP)

CBC, complete blood count.

Data from References 5, 7, 73, 78, and 79.

Diagnosis

The diagnosis of chronic pancreatitis is based primarily on presenting signs and symptoms in combination with either imaging or pancreatic function studies (see Table 56-5). Although histology would be the best diagnostic test, it is difficult and risky to perform and is generally not recommended.[61] Therefore, testing usually begins with noninvasive or invasive imaging studies. Abdominal ultrasonography and computed tomography (CT) may be used first, but are limited in their ability to produce detailed imaging of pancreatic ductal abnormalities.[65–67] Magnetic resonance imaging (MRI) with MRCP produces more detailed images of the pancreatic ducts.[59,65,66] While ERCP is the gold standard invasive study, it is rarely used due to inter- and intra-observer variability and the risk of postERCP pancreatitis, and endoscopic ultrasonography (EUS) is an equivalent alternative.[59,65,66] In addition to imagining studies, pancreatic function tests are used when imagining is inconclusive, as adjunctive diagnostic study or to quantify the degree of exocrine insufficiency.[65] The most sensitive studies are the secretin and CCK stimulation tests.[59,65,66] However, these are not widely available and are uncomfortable for patients. Indirect studies of pancreatic function are most sensitive during late chronic pancreatitis.[59]

Clinical Course and Prognosis

The clinical course of chronic pancreatitis depends on the etiology. Exocrine insufficiency occurs when lipase secretion is less than 10% of normal.[5,66] Patients with hereditary chronic pancreatitis typically have exocrine insufficiency occur at an early age, while those with alcohol-related disease have exocrine insufficiency occur about 5 years after disease onset, with “burnout” of the pancreas in about 10 years.[66] Patients with early onset idiopathic chronic pancreatitis have delayed progression to exocrine insufficiency compared to those with alcohol-related or late-onset idiopathic disease.[66] Diabetes mellitus occurs later than exocrine insufficiency and has a reported prevalence of 70%.[68]

The life expectancy of patients with chronic pancreatitis is shorter than that of the general population.[4] However, death in patients with chronic pancreatitis most commonly results from other chronic diseases, infection, or malignancy.[4] One of the most significant complications of long-standing disease is pancreatic cancer. A meta-analysis of observational studies of patients with chronic

pancreatitis demonstrated up to a 16-fold increased risk of pancreatic cancer.[69] This risk increases depending on the etiology, with smokers having twice the risk.[66]

TREATMENT

Chronic Pancreatitis

Desired Outcome

The major goals in the treatment of uncomplicated chronic pancreatitis are relief of abdominal pain, treatment of any associated complications such as malabsorption and diabetes mellitus, and improvement in quality of life. Secondary goals include delaying development of complications and treating associated disorders such as depression and malnutrition.

General Approach to Treatment

Treatment of chronic pancreatitis and its complications involves various nonpharmacologic and pharmacologic interventions. Lifestyle modifications should include abstinence from alcohol and smoking cessation.[65–67,70] In addition, patients with steatorrhea may need to eat smaller, more frequent meals and reduce dietary fat intake.[5,66,71] The majority of patients require analgesics and pancreatic enzyme supplementation.[65–67,70] Pain can initially be controlled with medications, but may require more aggressive medical and surgical therapies as the disease progresses. Patients with malabsorption require pancreatic enzymes to reduce steatorrhea and maintain adequate nutrient absorption.[65–67] An antisecretory agent may be added to the regimen when enzymes alone provide an inadequate reduction in steatorrhea.[5,7,66,67]

Nonpharmacologic Therapy

In addition to medical management, the treatment of chronic pancreatitis includes both lifestyle and dietary modifications. Patients should be counseled to abstain from alcohol use, and smoking cessation should be advocated. Cessation of alcohol use may reduce pain in patients with alcoholic chronic pancreatitis, and hastens disease progression and reduces the risk of developing pancreatic cancer.[4,5,65–67,70] Smoking has been associated with more rapid progression of

disease, so cessation should be advocated.[70] Patients with steatorrhea should be counseled to eat small and frequent meals.[66,71] A reduction in dietary fat is not needed routinely, but may be needed in those whose symptoms are uncontrolled with enzyme supplementation.[65,72] Enteral nutrition via a feeding tube is recommended for patients who cannot consume adequate calories, have continued weight loss, experience complications, or require surgery.[71] For patients with chronic pancreatitis requiring tube feeding, use of a jejunal feeding tube is recommended.[71,73]

Invasive procedures and surgery are primarily used to treat uncontrolled pain and the associated complications of chronic pancreatitis. Stents placed via ERCP may be used to treat pancreatic duct strictures in order to relieve parenchymal pressure and reduce pain.[65,74] Extracorporeal shock wave lithotripsy can be used to break up pancreatic stones with ultrasonic vibration prior to removal by ERCP.[67,74,75] Blockade of pain signals through the celiac plexus may be achieved utilizing EUS.[65,67,74] The various complications of chronic pancreatitis that can be treated endoscopically include common bile duct strictures, duodenal obstructions, and pancreatic pseudocysts.[65,74] Various surgical techniques including total pancreatectomy may also be used to relieve pain associated with chronic pancreatitis.[65,67,76] Surgery is more effective at relieving pain than endoscopic procedures, but these trials have a number of limitations.[65,67,76,77] Finally, total pancreatectomy with transplantation of pancreatic islet cells to reduce the need for exogenous insulin is a possible option for the treatment of pain due to chronic pancreatitis.[65,67,78]

Pharmacologic Therapy

General Recommendations

Pharmacologic therapy of chronic pancreatitis is aimed at controlling pain, treating malabsorption and associated steatorrhea, and controlling diabetes mellitus. Once other causes have been excluded, acetaminophen with or without nonsteroidal anti-inflammatory drugs (NSAIDs) should be tried initially for pain management (**Fig. 56-4**).[61,64,73] Patients with inadequate relief from these agents should have adjuvant agents added to their regimen, with opioid analgesics reserved for patients with refractory pain.[64–67,73] The addition of pancreatic enzyme supplements or antioxidants for pain control has been studied, but is not supported by high-quality evidence.[5,61,64–67,70]

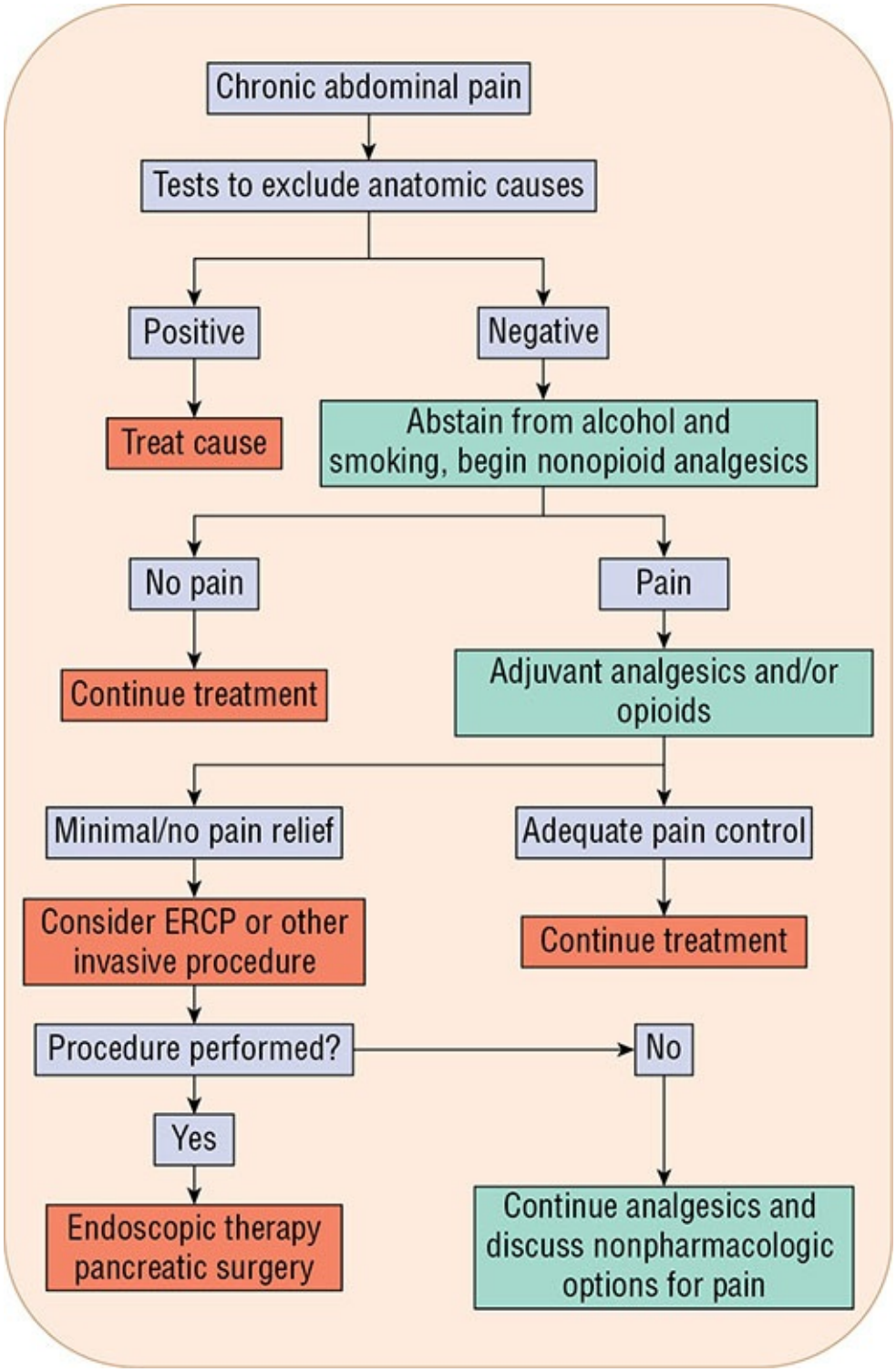


FIGURE 56-4 Algorithm for the treatment of abdominal pain in chronic pancreatitis. (ERCP, endoscopic retrograde cholangiopancreatography.).

Most patients with malabsorption will require pancreatic enzyme supplementation in order to achieve adequate nutritional status and reduction in

steatorrhea (Fig. 56-5). An antisecretory agent (such as ranitidine or omeprazole) should be added to the regimen when there is an inadequate response to enzyme therapy alone.[65–67,72] If these measures are ineffective, documentation of the diagnosis and exclusion of other diseases should be undertaken. Exogenous insulin is the primary pharmacologic agent used in the treatment of diabetes mellitus associated with chronic pancreatitis.[5,61,64,67,68] However, metformin may be initiated in early chronic pancreatitis, and has the added benefit of significantly reducing the risk of pancreatic cancer.[61,64,68]

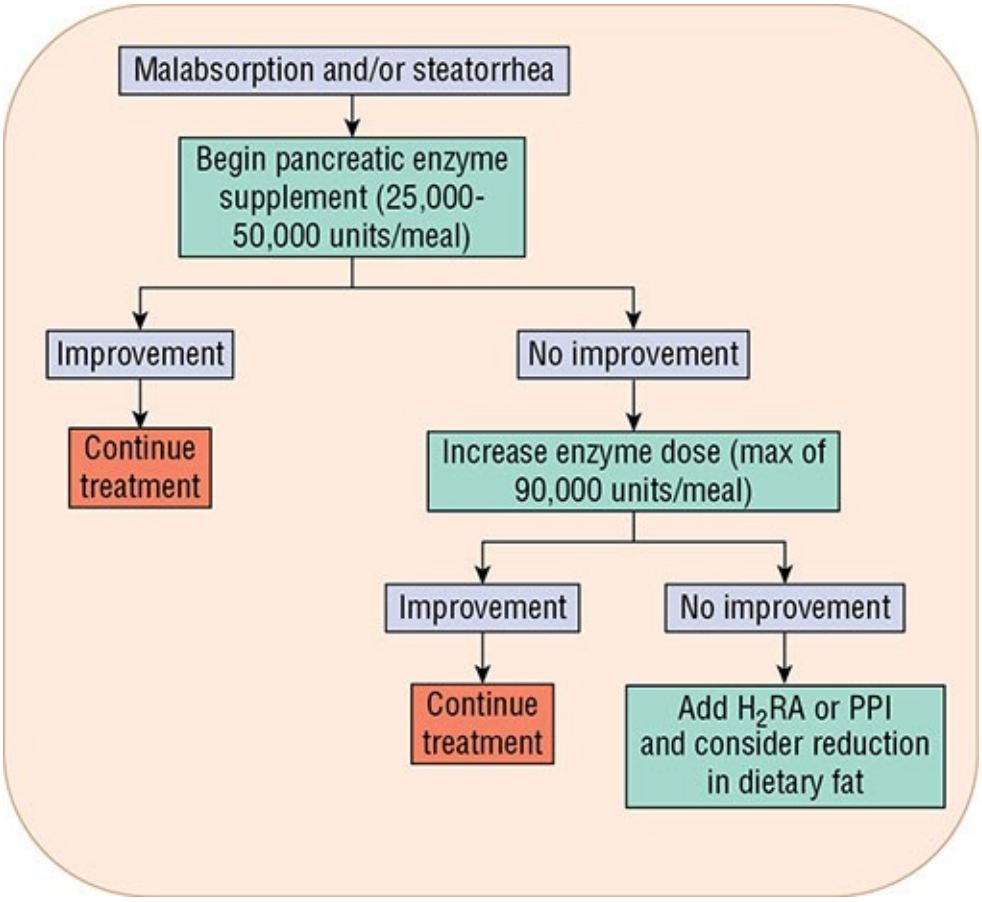


FIGURE 56-5 Algorithm for the treatment of malabsorption and steatorrhea in chronic pancreatitis. (H_2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor.).

Relief of Chronic Abdominal Pain

6 **Analgesics** Pain from chronic pancreatitis may initially be treated with nonopioid analgesics, but adjuvant agents may be necessary as the disease progresses. Regimens should be individualized and should begin with the lowest

effective dose. The dosage regimen should be maximized before adding or substituting agents. Analgesics should be scheduled around the clock rather than as needed in order to maximize efficacy. Scheduling short-acting analgesics prior to meals should help decrease postprandial pain. Acetaminophen or NSAIDs should be used initially.[61,64,73,79] As the response diminishes to adequate doses of nonopioid analgesics, adjuvant agents should be added to the regimen.[61,64,79] Tramadol may also be effective and could be tried before adding opioid analgesics.[79] Opioids are used last as other agents become ineffective or patients have intolerance (**Table 56-6**).[61,64,72,73]

TABLE 56-6 Recommendations for the Pharmacologic Treatment of Chronic Pancreatitis

Treatment of chronic pain (oral drug regimens)

Nonopioid analgesics

- Begin with acetaminophen at doses of 500-650 mg per dose every 4-6 hours following product labeling for maximum daily dose; caution for patients also receiving acetaminophen from other combination analgesics, and in those with liver disease
- Can also start with NSAIDs at low doses (ie, 200-400 mg ibuprofen every 6-8 hours) and titrate to maximum recommended doses as needed; caution in patients with cardiovascular disease or high disease risk, and in patients with kidney impairment or disease

Adjuvant agents

- Pregabalin has the best evidence; begin with 75 mg twice daily; maximum dose of 300 mg twice daily
- Consider use of selective serotonin reuptake inhibitors (eg, paroxetine), serotonin/norepinephrine reuptake inhibitors (eg, duloxetine) and tricyclic antidepressants in patients with difficult-to-manage pain

Opioids

- Tramadol: 50-100 mg every 4-6 hours, not to exceed 400 mg/day; has opioid-like effect; contraindicated in alcohol or hypnotic intoxication; be aware of drug interactions; expensive
- Codeine 30-60 mg every 6 hours; hydrocodone 5-10 mg every 4-6 hours; morphine sulfate (extended-release) 30-60 mg every 8-12 hours; oxycodone 5-10 mg every 6 hours; methadone 2.5-10 mg every 8-12 hours; hydromorphone 0.5-1 mg every 4-6 hours; fentanyl patch 25-100 mcg/hr every 72 hours
- Risk of potentiation with alcohol; impaired respiration; constipation; hypotension; allergy
- Dosing is usually based on providing continuous pain relief; consider combining with acetaminophen; opioid dependence is common; abuse is a concern in alcoholics; tolerance may develop

Treatment of malabsorption and steatorrhea

- Start with pancreatic enzymes containing 25,000-50,000 USP units of lipase with each meal of a preferred product (see Table 56-7); administer dose during meals; administer multiple capsules/tablets throughout the meal; use half the mealtime dose with snacks
- Increase dose to a maximum of 90,000 USP units of lipase per meal
- Products containing enteric-coated microspheres may be more effective than other dose forms

Acid-suppression agents

- May improve efficacy of enzyme therapy for malabsorption and steatorrhea
- Preferred for use with nonenteric-coated dose forms

NSAID, nonsteroidal anti-inflammatory drug; USP, United States Pharmacopeia.

Data from References 5, 61, 65, 66, 70, 72, 73, and 87.

Pancreatic Enzymes Although pancreatic enzymes are primarily used to treat malabsorption associated with chronic pancreatitis, they have also been used to treat pain from the disease. Relief of pain using pancreatic enzymes is thought to be due to their ability to break down CCK.[5,65,73] Release of CCK is normally inhibited by trypsin, but patients with chronic pancreatitis have decreased trypsin production. The proteases in pancreatic enzyme supplements are thought to act as substitutes for endogenous trypsin, leading to a decrease in CCK release. However, mixed results have been found from trials investigating pancreatic enzyme supplements for the treatment of pain from chronic pancreatitis. This may be due to the differences between the various enzyme formulations used in the trials as well as the small number of subjects enrolled.[5,65,66,70] A meta-analysis found no beneficial effect on pain relief.[80] However, trials that used nonenteric-coated enzyme formulations have demonstrated a benefit in the treatment of pain.[64,73,80] Enteric-coated formulations may not release enough proteases in the duodenum to inhibit CCK release. Despite their intuitive mechanism current guidelines do not recommend the use of pancreatic enzyme therapy for the treatment of pain from chronic pancreatitis due to lack of demonstrated beneficial outcomes.[72]

Other Agents Various adjuvant agents are also used in patients experiencing pain from chronic pancreatitis. Selective serotonin reuptake inhibitors and tricyclic antidepressants are used both for treating the concomitant depression that often occurs in patients with chronic pancreatitis and for their potential effects on pain (see Table 56-6).[5,61,64] Gabapentin has been used as an adjunct to opioids.[5,61] Pregabalin was effective for short-term pain control in one prospective trial and meta-analysis.[81,82] Octreotide is not recommended for pain associated with chronic pancreatitis.[5,65,70,72] There is evidence showing that patients with chronic pancreatitis have increased oxidative stress, and the use of antioxidants, such as selenium, vitamins C and E, and β-carotene, has demonstrated some benefit in relieving pain and improving quality of life in these patients.[83–85] However, evidence regarding their benefit remains variable and their widespread use for pain relief in patients with chronic pancreatitis is not generally recommended.[65,66,70,72,85]

Treatment of Malabsorption

7 Pancreatic enzyme and fat-soluble vitamin supplementation are the primary treatments for malabsorption due to chronic pancreatitis. Treatment should begin when steatorrhea is documented and persistent weight loss occurs despite any

dietary modifications. The utilization of pancreatic enzymes enhances the patient's nutritional status and reduces steatorrhea and resultant abdominal symptoms. Malabsorption is minimized if the concentration of lipase delivered to the duodenum with supplementation is about 10% of normal pancreatic output.[5] This requires that 25,000 to 50,000 units of lipase be administered with each meal to start (see Table 56-6).[61,65,67,72,86,87] Half of the necessary mealtime dose is recommended with snacks.[72,87] In many cases the lipase dose will need to be increased due to insufficient lipolytic activity, but doses greater than 90,000 units per meal are not recommended. In addition to enzyme replacement therapy, patients with chronic pancreatitis have deficiencies in fat-soluble vitamins.[88] Thus, they should be assessed for vitamin deficiencies and provided necessary supplementation as required.[5,66,72,87]

8 There is little evidence regarding the optimal dosage form and administration of pancreatic enzyme supplements. Most studies have compared them with placebo rather than other enzyme products, and used quantitation of fat absorption or elimination as a primary measure of efficacy rather than weight gain.[89] While they may not completely eliminate steatorrhea, they improve the quality of life of patients with chronic pancreatitis.[66] Since most exogenous lipase is rapidly and irreversibly destroyed at low intragastric pH, enteric-coated products are preferred for the treatment of malabsorption and steatorrhea. The enteric coating only dissolves at a pH greater than 5.5, which allows a sufficient quantity of enzymes to remain intact until dissolution of the coating in the duodenum.[66] However, enzymes must also be emptied from the stomach into the duodenum at the same rate and time as ingested food. The size of the enteric-coated enzyme preparation influences the rate of enzyme delivery to the duodenum.[5] Likewise, the administration time relevant to a meal influences the timing of enzyme delivery. Products containing enzymes in small enteric-coated microspheres are preferred, and they should be administered with meals.[61,66,72,86] Ideally, patients should eat three to five meals per day, and if patients need to take more than one capsule/tablet per meal the doses should be distributed throughout the meal.[61,72]

Despite enzyme therapy, patients may continue to have steatorrhea and fail to gain sufficient weight. Adherence should be assessed in these patients as the number of capsules required with each meal can lead to reduced adherence. Alternative products with higher lipase content can be tried in order to reduce the number of capsules needed. If this fails, the dose of lipase should be increased. Finally, addition of an antisecretory agent (ie, histamine-2 receptor

antagonist or proton pump inhibitor) may be tried to increase the availability of active enzymes in the duodenum.[66,72,86,87]

Pancreatic Enzyme Supplements Six pancreatic enzyme products have been approved by the FDA since its 2004 mandate that any product marketed would need approval. Only two of these products are specifically approved for exocrine pancreatic insufficiency associated with chronic pancreatitis.[90,91] Dosage forms of approved products include regular-release tablets, enteric-coated beads, bicarbonate-buffered enteric-coated microspheres, and enteric-coated minitablets or microtablets encased in a cellulose or gelatin capsule (**Table 56-7**). Enzymes are easily administered to patients who are able to swallow the capsules or their contents. However, administration to patients with enteral feeding tubes presents a challenge. Products containing microspheres may be administered through feeding tubes in food or solutions with a pH of 4.5 or less.[86] Clinicians must be aware, however, that available products are not equivalent and should consider this before substituting products in patients who require administration through a nonoral route. Careful consideration should also be given to this issue in patient care facilities with limited formularies.

TABLE 56-7 Factors Associated with Hepatitis B Virus Cirrhosis and Risk of HCC

Product	Enzyme Content Per Unit Dose (USP Units)		
	Lipase	Amylase	Protease
Tablets			
ViokaceTM 10,440 lipase units	10,440	39,150	39,150
ViokaceTM 20,880 lipase units	20,880	78,300	78,300
Enteric-coated beads			
Zenpep® 3,000 lipase units	3,000	16,000	10,000
Zenpep® 5,000 lipase units	5,000	27,000	17,000
Zenpep® 10,000 lipase units	10,000	55,000	34,000
Zenpep® 15,000 lipase units	15,000	82,000	51,000
Zenpep® 20,000 lipase units	20,000	109,000	68,000
Zenpep® 25,000 lipase units	25,000	136,000	85,000
Zenpep® 40,000 lipase units	40,000	218,000	136,000
Enteric-coated microspheres with bicarbonate buffer			
Pertzye 4,000 lipase units	4,000	15,125	14,375
Pertzye 8,000 lipase units	8,000	30,250	28,750
Pertzye 16,000 lipase units	16,000	60,500	57,500
Enteric-coated microspheres			
Creon® 3,000 lipase units	3,000	15,000	9,500
Creon® 6,000 lipase units	6,000	30,000	19,000
Creon® 12,000 lipase units	12,000	60,000	38,000
Creon® 24,000 lipase units	24,000	120,000	76,000
Creon® 36,000 lipase units	36,000	180,000	114,000
Enteric-coated minitablets/microtablets			
Pancreaze® 4,200 lipase units	4,200	17,500	10,000
Pancreaze® 10,500 lipase units	10,500	43,750	25,000
Pancreaze® 16,800 lipase units	16,800	70,000	40,000
Pancreaze® 21,000 lipase units	21,000	61,000	37,000
Ultresa 4,000 lipase units	4,000	8,000	8,000
Ultresa 13,800 lipase units	13,800	27,600	27,600
Ultresa 20,700 lipase units	20,700	41,400	41,400
Ultresa 23,000 lipase units	23,000	46,000	46,000

USP, United States Pharmacopeia.

Adverse reactions from pancreatic enzyme supplements are generally benign. High doses can lead to nausea, diarrhea, and intestinal upset.[66] One of the more serious adverse effects of these products is fibrosing colonopathy. It occurs when the enzymes cause deposition of fibrin in the colon leading to colonic stricture. This reaction is uncommon and has been reported mostly in children with cystic fibrosis who received high doses of enzymes for prolonged periods.[66] Another concern with pancreatic enzymes is the risk of possible viral infection due to contamination of these porcine-derived products.[66]

9 **Adjuncts to Enzyme Therapy** The addition of a histamine-2 receptor antagonist or proton pump inhibitor to pancreatic enzyme supplementation may increase the effectiveness of enzyme therapy for malabsorption and steatorrhea. The beneficial effects of these agents result from an increase in gastric and duodenal pH.[66,67,86] This is thought to result in an increase in the amount of active enzymes available in the duodenum. Their use has been mainly recommended with nonenteric-coated enzyme products.[5,65,72,87] In fact, the only nonenteric-coated formulation currently approved by the FDA is indicated for administration with a proton pump inhibitor.[91]

EVALUATION OF THERAPEUTIC OUTCOMES

Acute Pancreatitis

Hydration status, serum electrolytes, pain control, and nutritional status should be assessed periodically in patients with mild acute pancreatitis, depending on the degree of abdominal pain and fluid loss. Patients with severe acute pancreatitis should receive intensive care and close monitoring of vital signs, fluid and electrolyte status, white blood cell count, blood glucose, lactate dehydrogenase, aspartate aminotransferase, serum albumin, hematocrit, BUN, serum creatinine, and international normalized ratio. Continuous hemodynamic and arterial blood gas monitoring is essential. Serum lipase, amylase, and bilirubin require less frequent monitoring. The patient should also be monitored for signs of infection, relief of abdominal pain, and adequate nutritional status. Severity of disease and patient response should be assessed using an evidence-based method.

Chronic Pancreatitis

The severity and frequency of abdominal pain should be assessed periodically in patients with chronic pancreatitis using a standardized scale in order to determine the efficacy of pain therapy. Patients receiving opioids should be prescribed laxatives on an as-needed or scheduled basis and be monitored for constipation. Patients receiving pancreatic enzymes for malabsorption should have their weight and stool frequency and consistency monitored periodically. More objective assessments of fecal fat content, such as the ^{13}C-mixed triglyceride breath test, can be utilized, but are usually unnecessary and impractical in general clinical practice.[5,66] Blood glucose must be closely monitored in patients with diabetes mellitus, and those with long-standing disease should receive appropriate monitoring for nephropathy, retinopathy, and neuropathy.[5]

Postclass Engaged Learning Activity

Using available resources, determine the monthly cash prescription payment for a patient with exocrine pancreatic insufficiency from chronic pancreatitis who requires 30,000 USP units of lipase with each meal; the patient eats four meals a day, along with three snacks. Do this for all FDA-approved pancrelipase products available in the United States. How would this information affect your recommendation of a pancrelipase product for this patient? Now locate the online formulary of a third-party prescription plan in your area. Determine if the plan's coverage of the same pancrelipase products alters your decision in any way.

ABBREVIATIONS

APACHE	Acute Physiology and Chronic Health Evaluation
BISAP	Bedside Index of Severity in Acute Pancreatitis
BUN	blood urea nitrogen
CCK	Cholecystokinin
CECT	contrast-enhanced computed tomography
CFTR	cystic fibrosis transmembrane conductance regulator gene
CRP	C-reactive protein
CT	computed tomography
DPP-4	dipeptidyl peptidase-4
ERCP	endoscopic retrograde cholangiopancreatography
EUS	endoscopic ultrasonography
GLP-1	glucagon-like peptide-1
GRP	gastrin-releasing peptide
HAPS	Harmless Acute Pancreatitis Score
HIV	human immunodeficiency virus
ICU	intensive care unit
JSS	Japanese Severity Score
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
NSAID	nonsteroidal anti-inflammatory drug
PRSS1	protease serine 1 (trypsin 1) gene
SIRS	systemic inflammatory response syndrome
SPINK1	serine peptidase inhibitor Kazal type 1 gene
VIP	vasoactive intestinal peptide

REFERENCES

1. Anand N, Park JH, Wu BU. Modern management of acute pancreatitis. *Gastroenterol Clin North Am*. 2012;41:1–8.
2. Lippi G, Valentino M, Cervellin G. Laboratory diagnosis of acute pancreatitis: In search of the Holy Grail. *Crit Rev Clin Lab Sci*. 2012;49:18–31.
3. Peery AF, Crockett SD, Barritt AS, et al. Burden of Gastrointestinal, Liver, and Pancreatic Diseases in the United States. *Gastroenterology*. 2015;149(7):1731–1741.
4. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology*. 2013;144(6):1252–1261.

5. Forsmark CE. Chronic pancreatitis. In: Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management*. Vol. 10. Philadelphia, PA: Elsevier Saunders; 2016: 994–1026.
6. Brock C, Nielsen LM, Lelic D, Drewes AM. Pathophysiology of chronic pancreatitis. *World J Gastroenterol*. 2013;19(42):7231–7240.
7. Muniraj T, Aslanian HR, Farrell J, Jamidar PA. Chronic pancreatitis, a comprehensive review and update. Part I: epidemiology, etiology, risk factors, genetics, pathophysiology, and clinical features. *Dis Mon*. 2014;60(12):530–550.
8. P SJ. Pancreatic secretion. In: Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management*. Vol. 10. Philadelphia, PA: Elsevier Saunders; 2016: 934–943.
9. Acevedo-Piedra NG, Moya-Hoyo N, Rey-Riveiro M, et al. Validation of the determinant-based classification and revision of the Atlanta classification systems for acute pancreatitis. *Clin Gastroenterol Hepatol*. 2014;12(2):311–316.
10. Lindkvist B, Appelros S, Regner S, Manjer J. A prospective cohort study on risk of acute pancreatitis related to serum triglycerides, cholesterol and fasting glucose. *Pancreatology*. 2012;12(4):317–324.
11. Lankisch PG, Apte M, Banks PA. Acute pancreatitis. *Lancet*. 2015;386(9988):85–96.
12. Shen HN, Chang YH, Chen HF, Lu CL, Li CY. Increased risk of severe acute pancreatitis in patients with diabetes. *Diabet Med*. 2012;29(11):1419–1424.
13. Ducarme G, Maire F, Chatel P, Luton D, Hammel P. Acute pancreatitis during pregnancy: A review. *J Perinatol*. 2014;34(2):87–94.
14. Srinath AI, Lowe ME. Pediatric Pancreatitis. *Pediatr Rev*. 2013;34(2):79–90.
15. Baran B, Karaca C, Soyer OM, *et al* Acute pancreatitis associated with H1N1 influenza during 2009 pandemic: A case report. *Clin Res Hepatol Gastroenterol*. 2012;36:e69–e70.
16. Nitsche C, Maertin S, Scheiber J, Ritter CA, Lerch MM, Mayerle J. Drug-induced pancreatitis. *Curr Gastroenterol Rep*. 2012;14:131–138.
17. Hung WY. Contemporary review of drug-induced pancreatitis: A different perspective. *World J Gastrointest Pathophysiol*. 2014;5(4):405–415.

18. Dragovic G. Acute pancreatitis in HIV/AIDS patients: An issue of concern. *Asian Pac J Trop Biomed*. 2013;3(6):422–425.
19. Jasdanwala S, Babyatsky M. Crohn's disease and acute pancreatitis. A review of literature. *JOP*. 2015;16(2):136–142.
20. Li L, Shen J, Bala MM, et al. Incretin treatment and risk of pancreatitis in patients with type 2 diabetes mellitus: Systematic review and meta-analysis of randomised and non-randomised studies. *BMJ*. 2014;348:g2366.
21. Yang L, He Z, Tang X, Liu J. Type 2 diabetes mellitus and the risk of acute pancreatitis: A meta-analysis. *Eur J Gastroenterol Hepatol*. 2013;25(2):225–231.
22. Faillie JL, Azoulay L, Patenaude V, Hillaire-Buys D, Suissa S. Incretin based drugs and risk of acute pancreatitis in patients with type 2 diabetes: Cohort study. *BMJ*. 2014;348:g2780.
23. Razavi D, Lindblad M, Bexelius T, Oskarsson V, Sadr-Azodi O, Ljung R. Polypharmacy and risk of acute pancreatitis. *Pharmacoepidemiol Drug Saf*. 2016;25(11):1337–1341.
24. Preiss D. Lipid-modifying therapies and risk of pancreatitis: A meta-analysis. *JAMA J Am Med Assoc*. 2012;308(8):804–811.
25. Jones MR, Hall OM, Kaye AM, Kaye AD. Drug-induced acute pancreatitis: A review. *Ochsner J*. 2015;15(1):45–51.
26. Sah RP, Dawra RK, Saluja AK. New insights into the pathogenesis of pancreatitis. *Curr Opin Gastroenterol*. 2013;29(5):523–530.
27. Capurso G, Zerboni G, Signoretti M, et al. Role of the gut barrier in acute pancreatitis. *J Clin Gastroenterol*. 2012;46:S46–S51.
28. Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: Management of acute pancreatitis. *Am J Gastroenterol*. 2013;108(9):1400–1415.
29. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology*. 2013;13(4 Suppl 2):e1–15.
30. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: Revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62(1):102–111.
31. Dellinger EP, Forsmark CE, Layer P, et al. Determinant-based classification of acute pancreatitis severity: An international

multidisciplinary consultation. *Ann Surg*. 2012;256(6):875–880.

32. Mounzer R, Langmead CJ, Wu BU, et al. Comparison of existing clinical scoring systems to predict persistent organ failure in patients with acute pancreatitis. *Gastroenterology*. 2012;142(7):1476–1482.
33. Vege SS, DiMagno MJ, Forsmark CE, Martel M, Barkun AN. Initial Medical Treatment of Acute Pancreatitis: American Gastroenterological Association Institute Technical Review. *Gastroenterology*. 2018;154(4):1103–1139.
34. Yang CJ, Chen J, Phillips AR, Windsor JA, Petrov MS. Predictors of severe and critical acute pancreatitis: A systematic review. *Dig Liver Dis*. 2014;46(5):446–451.
35. Koutroumpakis E, Slivka A, Furlan A, et al. Management and outcomes of acute pancreatitis patients over the last decade: A US tertiary-center experience. *Pancreatology*. 2017;17(1):32–40.
36. Wu BU, Banks PA. Clinical management of patients with acute pancreatitis. *Gastroenterol*. 2013;144(6):1272–1281.
37. Das SL, Singh PP, Phillips AR, Murphy R, Windsor JA, Petrov MS. Newly diagnosed diabetes mellitus after acute pancreatitis: A systematic review and meta-analysis. *Gut*. 2014;63(5):818–831.
38. Yadav D, O'Connell M, Papachristou GI. Natural history following the first attack of acute pancreatitis. *Am J Gastroenterol*. 2012;107(7):1096–1103.
39. Rohan JD, Osman HG, Patel S. Advances in management of pancreatic necrosis. *Curr Probl Surg*. 2014;51(9):374–408.
40. Crockett SD, Wani S, Gardner TB, *et al* American Gastroenterological Association Institute Guideline on Initial Management of Acute Pancreatitis. *Gastroenterol*. 2018;154(4):1096–1101.
41. Mirtallo JM, Forbes A, McClave SA, Jensen GL, Waitzberg DL, Davies AR. International consensus guidelines for nutrition therapy in pancreatitis. *J Parenter Enteral Nutr*. 2012;36(3):284–291.
42. Yi F, Ge L, Zhao J, et al. Meta-analysis: Total Parenteral Nutrition Versus Total Enteral Nutrition in Predicted Severe Acute Pancreatitis. *Intern Med*. 2012;51(6):523–530.
43. Gou S, Yang Z, Liu T, Wu H, Wang C. Use of probiotics in the treatment of severe acute pancreatitis: A systematic review and meta-analysis of randomized controlled trials. *Crit Care*. 2014;18(2):1–10.

44. Wu BU, Hwang JQ, Gardner TH, et al. Lactated Ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis. *Clin Gastroenterol Hepatol*. 2011;9:710–717.
45. Trikudanathan G, Navaneethan U, Vege SS. Current controversies in fluid resuscitation in acute pancreatitis: A systematic review. *Pancreas*. 2012;41:827–834.
46. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock. *Crit Care Med*. 2017;45(3):486–552.
47. Basurto XO, Rigau CD, Urrutia G. Opioids for acute pancreatitis pain. *Cochrane Database Syst Rev*. 2013;7:CD009179.
48. Schorn S, Ceyhan GO, Tieftrunk E, Friess H, Friess, Demir IE. Pain management in acute pancreatitis. *Pancreapedia: Exocrine Pancreas Knowledge Base*. 2015;15. DOI: 10.3998/panc.
49. Moggia E, Koti R, Belgaumkar AP, et al. Pharmacological interventions for acute pancreatitis. *Cochrane Database Syst Rev*. 2017;4:CD011384.
50. Villatoro E, Mulla M, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. *Cochrane Database Syst Rev*. 2010;5:CD002941.
51. Freeman ML, Werner J, van Santvoort HC, et al. Interventions for necrotizing pancreatitis: Summary of a multidisciplinary consensus conference. *Pancreas*. 2012;41(8):1176–1194.
52. Rokke O, Harbitz TB, Liljedal J, et al. Early treatment of severe pancreatitis with imipenem: A prospective randomized clinical trial. *Scand J Gastroenterol*. 2007;42(6):771–776.
53. Schubert S, Dalhoff A. Activity of moxifloxacin, imipenem, and ertapenem against Escherichia coli, Enterobacter cloacae, Enterococcus faecalis, and Bacteroides fragilis in monocultures and mixed cultures in an in vitro pharmacokinetic/pharmacodynamic model simulating concentrations in the human pancreas. *Antimicrob Agents Chemother*. 2012;56(12):6434–6436.
54. Mouli VP, Sreenivas V, Garg PK. Efficacy of conservative treatment, without necrosectomy, for infected pancreatic necrosis: A systematic review and meta-analysis. *Gastroenterol*. 2013;144(2):333–340.
55. Hall AM, Poole LA, Renton B, et al. Prediction of invasive candidal infection in critically ill patients with severe acute pancreatitis. *Crit Care*. 2013;17(2):R49.

56. Schwender BJ, Gordon SR, Gardner TB. Risk factors for the development of intra-abdominal fungal infections in acute pancreatitis. *Pancreas*. 2015;44(5):805–807.
57. Elmunzer BJ, Scheiman JM, Lehman GA, et al. A Randomized Trial of Rectal Indomethacin to Prevent Post-ERCP Pancreatitis. *N Engl J Med*. 2012;366(15):1414–1422.
58. Elmunzer BJ, Higgins PD, Saini SD, et al. Does rectal indomethacin eliminate the need for prophylactic pancreatic stent placement in patients undergoing high-risk ERCP? Post hoc efficacy and cost-benefit analyses using prospective clinical trial data *Am J Gastroenterol*. 2013;108(3):410–415.
59. Conwell DL, Lee LS, Yadav D. American Pancreatic Association Practice Guidelines in Chronic Pancreatitis: Evidence-based report on diagnostic guidelines. Pancreas. 2014; 43 (8): 1162.
60. Samokhvalov AV, Rehm J, Roerecke M. Alcohol consumption as a risk factor for acute and chronic pancreatitis: A systematic review and a series of meta-analyses. *EBioMedicine*. 2015;2(12):1996–2002.
61. Majumder S, Chari ST. Chronic pancreatitis. *Lancet*. 2016;387(10031):1957–1966.
62. Hegyi E, Sahin-Tóth M. Genetic risk in chronic pancreatitis: The trypsin-dependent pathway. *Dig Dis Sci*. 2017;62(7):1692–1701.
63. Sankaran SJ, Xiao AY, Wu LM, Windsor JA, Forsmark CE, Petrov MS. Frequency of progression from acute to chronic pancreatitis and risk factors: A meta-analysis. *Gastroenterol*. 2015;149(6):1490–1500.
64. Lew D, Afghani E, Pandol S. Chronic pancreatitis: Current status and challenges for prevention and treatment. *Dig Dis Sci*. 2017;62(7):1702–1712.
65. Muniraj T, Aslanian HR, Farrell J, Jamidar PA. Chronic pancreatitis, a comprehensive review and update. Part II: Diagnosis, complications, and management. *Disease-a-Month*. 2015;61(1):5–37.
66. Afghani E, Sinha A, Singh VK. An overview of the diagnosis and management of nutrition in chronic pancreatitis. *Nutr Clin Pract*. 2014;29(3):295–311.
67. Forsmark CE. Management of chronic pancreatitis. *Gastroenterology*. 2013;144(6):1282–1291.
68. Ewald N, Hardt PD. Diagnosis and treatment of diabetes mellitus in chronic pancreatitis. *World J Gastroenterol*. 2013;19(42):7276–7281.

69. Kirkegård J, Mortensen FV, Cronin-Fenton D. Chronic pancreatitis and pancreatic cancer risk: A systematic review and meta-analysis. *Am J Gastroenterol*. 2017;112(9):1366–1372.
70. Olesen SS, Juel J, Graversen C, Kolesnikov Y, Wilder-Smith OH, Drewes AM. Pharmacological pain management in chronic pancreatitis. *World J Gastroenterol*. 2013;19(42):7292–7301.
71. Rasmussen HH, Irtun O, Olesen SS, Drewes AM, Holst M. Nutrition in chronic pancreatitis. *World J Gastroenterol*. 2013;19(42):7267–7275.
72. Hoffmeister A, Mayerle J, Beglinger C, et al. English language version of the S3-consensus guidelines on chronic pancreatitis: Definition, aetiology, diagnostic examinations, medical, endoscopic and surgical management of chronic pancreatitis. *Z Gastroenterol*. 2015;53(12):1447–1495.
73. Singh VK, Drewes AM. Medical management of pain in chronic pancreatitis. *Dig Dis Sci*. 2017;62(7):1721–1728.
74. Adler JM, Gardner TB. Endoscopic therapies for chronic pancreatitis. *Dig Dis Sci*. 2017;62(7):1729–1737.
75. Moole H, Jaeger A, Bechtold ML, Forcione D, Taneja D, Puli SR. Success of extracorporeal shock wave lithotripsy in chronic calcific pancreatitis management: A meta-analysis and systematic review. *Pancreas*. 2016;45(5):651–658.
76. Tillou JD, Tatum JA, Jolissaint JS, et al. Operative management of chronic pancreatitis: A review. *Am J Surg*. 2017;214(2):347–357.
77. Ahmed AU, Pahlplatz JM, Nealon WH, van GH, Gooszen HG, Boermeester MA. Endoscopic or surgical intervention for painful obstructive chronic pancreatitis. *Cochrane Database Syst Rev*. 2012;1:CD007884.
78. Bramis K, Gordon-Weeks AN, Friend PJ, et al. Systematic review of total pancreatectomy and islet autotransplantation for chronic pancreatitis. *Br J Surg*. 2012;99:761–766.
79. Anderson MA, Akshintala V, Albers KM, et al. Mechanism, assessment and management of pain in chronic pancreatitis: Recommendations of a multidisciplinary study group. *Pancreatol*. 2016;16(1):83–94.
80. Yaghoobi M, McNabb-Baltar J, Bijarchi R, Cotton PB. Pancreatic enzyme supplements are not effective for relieving abdominal pain in patients with chronic pancreatitis: Meta-analysis and systematic review of randomized controlled trials. *Can J Gastroenterol Hepatol*. 2016;2016:8541839.
81. Gurusamy KS, Lusuku C, Davidson BR. Pregabalin for decreasing

pancreatic pain in chronic pancreatitis. *Cochrane Database Syst Rev*. 2016;2:CD011522.

82. Olesen SS, Bouwense SA, Wilder-Smith OH, van GH, Drewes AM. Pregabalin reduces pain in patients with chronic pancreatitis in a randomized, controlled trial. *Gastroenterol*. 2011;141:536–543.
83. Rustagi T, Njei B. Antioxidant therapy for pain reduction in patients with chronic pancreatitis: A systematic review and meta-analysis. *Pancreas*. 2015;44(5):812–818.
84. Zhou D, Wang W, Cheng X, Wei J, Zheng S. Antioxidant therapy for patients with chronic pancreatitis: A systematic review and meta-analysis. *Clin Nutr*. 2015;34(4):627–634.
85. Ahmed AU, Jens S, Busch OR, et al. Antioxidants for pain in chronic pancreatitis. *Cochrane Database Syst Rev*. 2014;8:CD008945.
86. Trang T, Chan J, Graham DY. Pancreatic enzyme replacement therapy for pancreatic exocrine insufficiency in the 21(st) century. *World J Gastroenterol*. 2014;20(33):11467–11485.
87. Ramsey ML, Conwell DL, Hart PA. Complications of Chronic Pancreatitis. *Dig Dis Sci*. 2017;62(7):1745–1750.
88. Martínez-Moneo E, Stigliano S, Hedström A, et al. Deficiency of fat-soluble vitamins in chronic pancreatitis: A systematic review and meta-analysis. *Pancreatol*. 2016;16(6):988–994.
89. De La Iglesia-García D, Huang W, Szatmary P, et al. Efficacy of pancreatic enzyme replacement therapy in chronic pancreatitis: Systematic review and meta-Analysis. *Gut*. 2017;66(8):1474–1486.
90. *Creon (Pancrelipase)* [package insert]. North Chicago, IL: Abbott Laboratories; 2012.
91. *Viokace (Pancrelipase)* [package insert]. Birmingham, AL: Aptalis Pharma US Inc.; 2012.

57

Viral Hepatitis

Paulina Deming

KEY CONCEPTS

1. Hepatitis A virus (HAV) is transmitted via the fecal–oral route, most often from ingestion of contaminated food or water, or through contact with an infected person.
2. HAV causes an acute, self-limiting illness and does not lead to chronic infection. There are three stages of infection: incubation, acute hepatitis, and convalescence. Rarely, the infection progresses to liver failure.
3. HAV is vaccine preventable. There is no pharmacological treatment specifically for HAV as treatment consists of supportive care.
4. Hepatitis B virus (HBV) causes both acute and chronic infection. Chronic infections are responsible for high rates of liver disease, liver cancer, and death.
5. Vaccination can prevent HBV and is the most effective strategy in preventing complications of HBV infections. Prevention of HBV infections focuses on immunization of all children and at-risk adults.
6. The purpose of anti-HBV drug therapy is for viral suppression and immune control and to prevent progression of liver disease and the complications associated with HBV infections.
7. Initial therapy of chronic HBV is with tenofovir or entecavir because these agents have a high barrier to resistance. Therapy is often long term.
8. Patients undergoing immunosuppressive therapy or chemotherapy should be screened for HBV infections and may require HBV therapy to reduce the risks of reactivating their HBV and developing fulminant liver failure.
9. The hepatitis C virus (HCV) is an insidious, blood-borne infection. Increased screening of all patients born between 1945 and 1965 was implemented to help identify the many people unaware of their infection.

10 Hepatitis C infections can cause significant morbidity (including extrahepatic manifestations) and mortality. Patients with chronic hepatitis C are at risk for end-stage liver disease, cirrhosis, liver transplant, and death as a result of their infection.

11 The goal of anti-hepatitis C virus (HCV) drug treatment is cure. Drug therapy with direct-acting antivirals (DAAs) is highly effective and well tolerated.

Preclass Engaged Learning Activity

Prepare a table to summarize the available HCV-drug therapies. Include the component drug (generic name, strength, and class), expected adverse effects, use in renal insufficiency, use in cirrhosis, the drug's role in therapy, and its duration of use.

Use the https://tinyurl.com/yxz8fgeu Website to clarify the drug's role in therapy.

INTRODUCTION

The major hepatotrophic viruses responsible for viral hepatitis are hepatitis A, hepatitis B, hepatitis C, delta hepatitis, and hepatitis E. All share clinical, biochemical, immunoserologic, and histologic findings. Both hepatitides A and E are spread through fecal–oral contamination, whereas hepatitides B, C, and delta are transmitted parenterally. Infection with delta hepatitis requires coinfection with hepatitis B. Although the rates of acute infection have declined, viral hepatitis remains a major cause of morbidity and mortality with a significant impact on healthcare costs in the United States. Compared with human immunodeficiency virus (HIV), there are three to five times as many people infected with chronic viral hepatitis. In the United States, a national strategy for the elimination of hepatitis B and C was established by the National Academies of Science, Engineering, and Medicine.[1]

Unprecedented therapeutic advances have occurred with the treatment for hepatitis C with the approval of new agents, short duration of therapy, and updated guidelines. For both hepatitides B and C, the challenge remains in increasing awareness of the viral hepatitis epidemic, improving access to curative therapies, and in preventing chronic infection. This chapter focuses on

hepatitides A, B, and C.

HEPATITIS A

Hepatitis A virus (HAV), or infectious hepatitis, is often a self-limiting and acute viral infection of the liver posing a health risk worldwide. The infection is rarely fatal. According to the Centers for Disease Control and Prevention (CDC), rates of reported cases of acute clinical HAV infection in the United States were declining until a multi-state outbreak in 2013.[2] Rates again increased with an estimated 4,000 cases in 2016.[2,3] Outbreaks in 2017 and 2018 were also reported.[3]

Epidemiology

Various patient groups are at increased risk for infection with HAV. Children pose a particular problem with the spread of the disease because they often remain asymptomatic and are infectious for longer periods of time than adults. The most likely patient group affected is household or close personal contacts of an infected person. Infection primarily occurs through the fecal–oral route, by person-to-person, or by ingestion of contaminated food or water. Incidentally, HAV's prevalence is linked to regions with low socioeconomic status and specifically to those with poor sanitary conditions and overcrowding. In general, mortality rates are low but highest among persons 75 years or older.[3]

In the United States, recent HAV outbreaks were identified in persons who use drugs, homeless populations, and among men who have sex with men (MSM).[3] Oral–fecal contact, including contaminated water or food and oral–anal sex can transmit HAV.[4] Foodborne outbreaks occur with local and widespread outbreaks reported annually. Additional patient groups that are at risk include patients with chronic liver disease and persons working with nonhuman primates.

Despite low endemic rates and successful vaccination programs in the United States, travel to HAV endemic areas is a recognized risk for acquiring acute HAV infections. According to the CDC, the majority of travel-related cases correspond to travel to Central and South America and Mexico.[5] Most Americans traveling to Mexico do not consider that country to be a risk in part because of Mexico's proximity to the United States. Moreover, most tourists falsely believe that higher-end resorts imply safety and that short visits to foreign

countries are not associated with a risk for infection.[6] Travel related to international adoptions can also be of risk.

Etiology

1 Hepatitis A is a nonenveloped RNA virus in the *Picornaviridae* family. The virus is stable in the environment, including at low pH and in freezing to moderate temperatures.[5] Inactivation requires disinfecting with a 1:100 dilution of sodium hypochlorite (bleach) in tap water or heating foods to a minimum of 85°C (185°F) for 1 minute.[5] Chlorination of water also effectively kills HAV in water systems. Transmission occurs primarily through the fecal–oral route because HAV is shed in the feces of infected people.[7] Contaminated water or ice are common modes of transmission, as are any foods which may be prepared using contaminated water, including shellfish harvested from contaminated water.

Pathophysiology

HAV infection is usually acute, self-limiting, and confers lifelong immunity. HAV's life cycle in the human host classically begins with ingestion of the virus. Absorption in the stomach or small intestine allows entry into the circulation and uptake by the liver. Replication of the virus occurs within hepatocytes and gastrointestinal (GI) epithelial cells. New virus particles are released into the blood and secreted into bile by the liver. The virus is then either reabsorbed to continue its cycle or excreted in the stool. The enterohepatic cycle will continue until interrupted by antibody neutralization.[7]

Clinical Presentation

2 The incubation period of HAV is approximately 28 days, with a range of 15 to 50 days. **Table 57-1** summarizes the clinical features of acute hepatitis. There are no specific distinguishing features of HAV compared to other types of hepatitis; thus, serological testing for IgM is needed to confirm a diagnosis of acute HAV. Symptoms and severity of HAV vary according to age. Children younger than 6 years typically are asymptomatic and can shed the virus for long periods of time, serving as a reservoir for the spread of HAV. Peak fecal shedding of the virus precedes the onset of clinical symptoms and elevated liver enzymes. Acute hepatitis follows, beginning with the preicteric or prodromal

period. The phase is marked by an abrupt onset of nonspecific symptoms, some very mild.[6] Other, more unusual symptoms include chills, myalgia, arthralgia, cough, constipation, diarrhea, pruritus, and urticaria. The phase generally lasts 2 months. There are no specific symptoms unique to HAV. Liver enzyme levels rise in serum within the first weeks of infection, peaking approximately in the fourth week and normalizing by the eighth week. Conjugated bilirubinemia, clinically evident as dark urine, precedes the onset of the icteric period. GI symptoms may persist or subside during this time and some patients may have hepatomegaly. Duration of the icteric period varies and corresponds to disease duration, averaging between 7 and 30 days.[6]

TABLE 57-1 Clinical Presentation of Acute Hepatitis

	Hepatitis A (HAV)	Hepatitis B (HBV)	Hepatitis C (HCV)
Signs and symptoms	>70% of patients are symptomatic with fever, jaundice, scleral icterus, hepatomegaly. Less common: splenomegaly, skin rash, arthralgia.	Approximately 70% of patients are anicteric or subclinical. Younger patients most likely to be asymptomatic. If symptoms occur, jaundice, dark urine, white stool, abdominal pain, fatigue, fever, chills, loss of appetite, and pruritus are possible.	Approximately 70% of patients are asymptomatic. If symptoms occur, jaundice, dark urine, white stool, abdominal pain, fatigue, fever, chills, loss of appetite, and pruritus are possible.
Laboratory Findings			
Aminotransferase (ALT, AST) Elevations	>1,000 IU/L (16.7 µkat/L) ALT>AST	1,000-2,000 IU/L (16.7 - 33.3 µkat/L) ALT>AST	Highly variable, can be approximately 1,000 IU/L (16.7 µkat/L) ALT>AST
Bilirubin	Elevated and preceded by aminotransferase elevations	Can be within normal or elevated	Elevated and preceded by aminotransferase elevations
Virus Specific Tests	IgM anti-HAV	IgM anti-HBc (+), HBsAg (+)	HCV RNA (+) or quantifiable; HCV antibody reactive within 12 weeks of exposure

IU, international units; L, liter; ALT, alanine transaminase; AST, aspartate transaminase; anti-, antibody; IgM, immunoglobulin; HBc, hepatitis B core; HBsAg, hepatitis B surface antigen; RNA, ribonucleic acid

The diagnosis of acute HAV is made through the immunoglobulin (Ig) M antibody to HAV (anti-HAV). IgM anti-HAV is detectable 5 to 10 days prior to symptomatic HAV infections in the majority of patients. The IgG anti-HAV replaces IgM and indicates host immunity following the acute phase of the infection.[6] Serological testing is available for IgM anti-HAV, IgG anti-HAV, and total anti-HAV (IgM and IgG anti-HAV). Patients who have detectable total anti-HAV with a negative IgM have resolved their infection. Concentrations of antibody often fall to 10 to 100 times lower than what would be expected after a natural course of infection. Detectable antibodies may persist for over 40 years.

Although a positive anti-HAV result confirms protection, undetectable concentration of anti-HAV may not necessarily imply that protective levels were not achieved.[6]

HAV does not lead to chronic infections. Some patients may experience symptoms for up to 9 months. Rarely, patients experience complications from HAV, including relapsing hepatitis, cholestatic hepatitis, and fulminant hepatitis. Fatalities from HAV are generally rare, although more likely in patients older than 50 years and in persons with preexisting liver disease.[6]

A diagnosis of HAV is based on clinical criteria of an acute onset of fatigue, abdominal pain, loss of appetite, intermittent nausea and vomiting, jaundice or elevated serum aminotransferase levels, and serologic testing for IgM anti-HAV. Serologic testing is necessary to differentiate the diagnosis from other types of hepatitis.

TREATMENT

Desired Outcomes

The majority of people infected with HAV can be expected to fully recover without clinical sequelae.[7] Nearly all individuals will have clinical resolution within 6 months of the infection and a majority will have done so by 2 months. Rarely, symptoms persist for longer or patients relapse. The ultimate goal of therapy is complete clinical resolution. Other goals include reducing complications from the infection, normalization of liver function, and reducing infectivity and transmission. Prevention of HAV infection is important because significant costs are accrued during acute HAV infections, including costs of administration and use of immunoglobulin and vaccine, hospitalizations and indirect costs from loss of workdays.

General Approach to Treatment

3 Prevention and prophylaxis are keys to managing this vaccine preventable virus. No specific treatment options exist for HAV infections. Instead, patients should receive general supportive care. The importance of good hand hygiene should be emphasized in preventing disease transmission. Passive immunity with Ig is used for preexposure and postexposure prophylaxis. Active immunity is achieved through vaccination. Vaccines were approved for use in 1995 and

implemented in the routine vaccination of children, as well as at-risk adults, to reduce the overall incidence of HAV.[6]

Prevaccination serologic testing to determine susceptibility is generally not recommended. In some cases, testing may be cost-effective if the cost of the test is less than that of the vaccine and if the person is from a moderate-to-high endemic area and likely to have prior immunity. Similarly, because of high vaccine response, postvaccine serologic testing is not recommended.[6]

Prevention of Hepatitis A

HAV is easily preventable with vaccination. Because children often serve as reservoirs of the disease, vaccine programs have targeted children as the most effective means to control HAV. Two vaccines for HAV are available and are incorporated into the routine childhood vaccination schedule. The Advisory Committee on Immunization Practices (ACIP) recommends expanding vaccine coverage to all children, including catch-up programs for children living in areas without existing vaccination programs. The recommendations were enacted in the attempt to further reduce HAV incidence rates and possibly to eradicate the virus.[6] ACIP guidelines also include HAV vaccination for previously unvaccinated persons anticipating close personal contact with international adoptees from a country of high or intermediate endemicity. Complete HAV vaccination recommendations are available from the CDC (**Table 57-2**).

TABLE 57-2 Recommendations for Hepatitis A Virus Vaccination

- All children at 1 year of age
- Any unvaccinated children ages 2-18 years
- Persons traveling to or working in countries that have high or intermediate endemicity of infection.[a]
- Men who have sex with men
- Users of injection and noninjection drugs
- Persons with occupational risk for infection (eg, persons who work with HAV-infected primates or with HAV in a research laboratory)
- Persons who have clotting factor disorders
- Persons with chronic liver disease
- All previously unvaccinated persons anticipating close personal contact (eg, household contact or regular babysitter) with an international adoptee from a country of high or intermediate endemicity within the first 60 days following the arrival of the adoptee
- Anyone who would like to obtain immunity

[a]Travelers to Canada, Western Europe, Japan, Australia, or New Zealand are at no greater risk for infection than they are in the United States. All other travelers should be assessed for HAV risk.

HAV, hepatitis A virus.

Source: Centers for Disease Control and Prevention.[6]

Routine prevention of HAV transmission includes regular hand washing with soap and water after using the bathroom, changing a diaper, and before food preparation. For travelers to countries with high endemic rates of HAV, even short-term stays in urban and upscale resorts are not risk-free.[6] In particular, contaminated water and ice, fresh produce, and any uncooked foods pose a risk.[7]

Vaccines to Prevent Hepatitis A

The inactivated virus vaccines licensed in the United States are the single-antigen HAVRIX® and VAQTA® and the combination of HAV and HBV antigen vaccine TWINRIX®. Both single-antigen vaccines are available for pediatric (12 months and older) and adult (18 years and older) use, while the TWINRIX® is indicated for adults only (**Table 57-3**). The differences in the vaccines are in the use of a preservative and in expression of antigen content. VAQTA® is formulated without a preservative and uses units of HAV antigen to express potency. HAVRIX® and TWINRIX® use 2-phenoxyphenol as a preservative and antigen content is expressed as enzyme-linked immunosorbent assay (ELISA) units.[6] High seroconversion rates of more than or equal to 94% are achieved with the first dose; however, VAQTA® and HAVRIX® recommend a booster shot to achieve the highest possible antibody titers. Although seroconversion exceeds 90% for HAV after the first dose of TWINRIX®, the

full three-dose series is required for maximal HBV seroconversion. An accelerated dosing schedule of TWINRIX® is available but requires four doses for optimal response. The combined vaccine offers the advantage of immunization against both types of hepatitis in a single vaccine.

TABLE 57-3 Recommended Dosing of Hepatitis A Vaccines

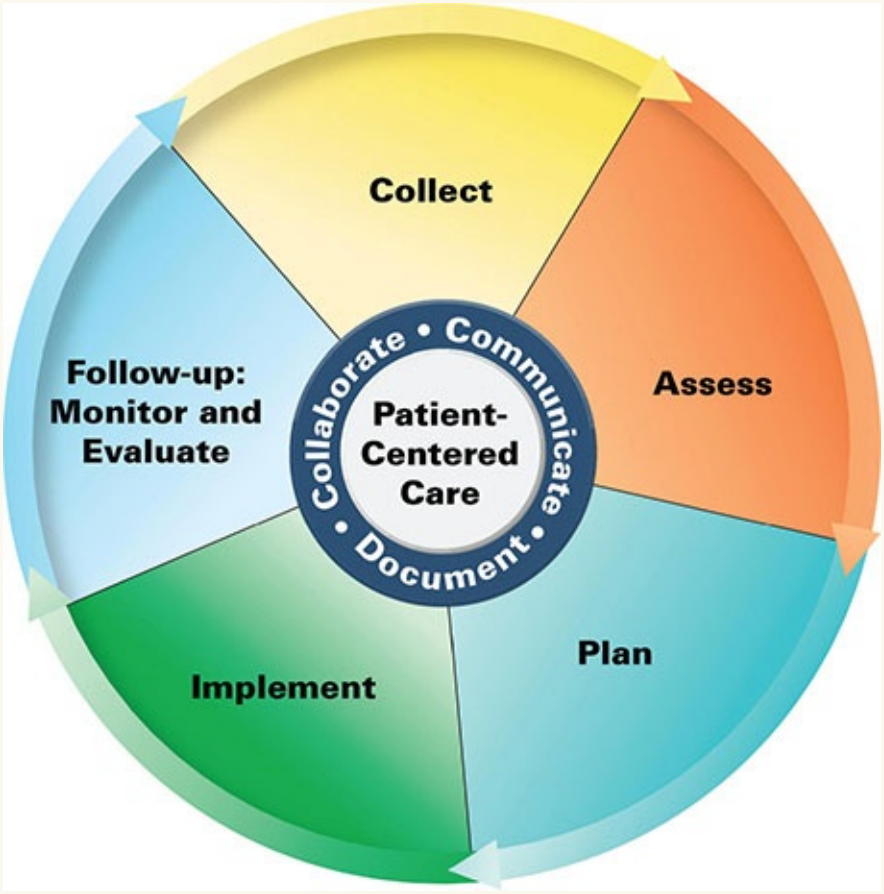
Vaccine	Age (Years)	Dose of Hepatitis A Antigen (Volume)	No. of Doses	Schedule[a]
HAVRIX	1-18	720 ELISA units (0.5 mL)	2	0, 6-12 months
	≥19	1,440 ELISA units (1 mL)	2	0, 6-12 months
VAQTA	1-18	25 units (0.5 mL)	2	0, 6-18 months
	≥19	50 units (1 mL)	2	0, 6-18 months
TWINRIX[b]	≥18	720 ELISA units (1 mL)	3	0, 1, 6 months
	≥18 (accelerated schedule)	720 ELISA units (1 mL)	4	0, 7 days, 21-30 days, +12 months

[a]Zero (0) denotes initial dose, subsequent numbers denote time after initial dose for timing of additional doses.

[b]Combination hepatitis A and B vaccine, also contains 20 mcg of hepatitis B surface antigen and requires a three-dose schedule for adequate HBV response.

ELISA, enzyme-linked immunosorbent assay.

Source: Centers for Disease Control and Prevention.[6]



Patient Care Process for Hepatitis C

Collect

- Patient characteristics (eg, age, sex, weight, vital signs, etc.)
- Patient history (past medical, family, social) and medical record summary including surgical operations (site, date, procedure) and abdominal imaging findings
- Thorough medication history (include prescription, nonprescription medications, and other substances) and drug allergies and intolerances. Previous HCV therapy, if applicable.
- Laboratory results for chronic HCV infection including HCV genotype and viral load (RNA)
- Laboratory results for other viral infections impacting HCV treatment (HBV core antibody, HBV surface antigen, HBV surface antibody, HAV total or IgG antibody, HIV status)

Assess

- Determine severity of underlying liver disease based on laboratory tests, clinical calculators, imaging, and clinical history
- If the patient has cirrhosis, assess the level of liver dysfunction using the Child-Pugh Score to determine options for HCV therapy
- Estimate creatinine clearance to identify which HCV therapies may be used
- Review insurance company formulary preferences for HCV therapy
- Review national guidelines for updated treatment recommendations
- Assess if patient assistance programs may be utilized
- Determine if pretreatment resistance testing is required

Plan*

- Determine goals of therapy with monitoring parameters for each goal
- Based on HCV genotype, severity of underlying liver disease, renal function, and prior treatment experience, determine the appropriate therapy, treatment duration, and monitoring plan
- If ribavirin is part of therapy, review hemoglobin/hematocrit and need for supplemental iron, need for contraception and counseling on avoiding pregnancy
- Establish monitoring goals for efficacy and toxicity
- Identify potential obstacles to treatment success such as insurance requirements regarding refills
- Check for drug interactions with prescribed medications, any over-the-counter medications, herbals, or supplements

Implement

- Initiate HCV anti-viral therapy
- Discontinue or modify adjunct medications if drug interactions anticipated with HCV antivirals
- Assess patient as needed for response to HCV antivirals
- Discuss with patient and patient’s family strategies to address any potential adverse effects
- Discuss with patient and patient’s family strategies to minimize likelihood

for therapy interruptions

Follow-up: Monitor and Evaluate

- Continually reassess patient's use of HCV antivirals, any changes in other medications or herbals and supplements which could compromise HCV therapy, and any adverse effects
- Monitor laboratory tests for response to antiviral therapy and changes in liver enzymes
- Monitor for any interruptions in therapy which could risk the emergence of resistance and treatment failure
- Evaluate patient for cure at least 12 weeks after completion of therapy and discuss implications of cure, HCV antibody positivity, and risks for reinfection
- Reassess patient's risk for reinfection and counsel on harm-reduction strategies

*Collaborate with patient, caregivers, and other healthcare professionals.

In situations of postexposure prophylaxis, either the vaccine or Ig can be used, although vaccine is preferred because it confers the benefit of long-term immunity against HAV. In patients older than 40 years or with underlying medical conditions, vaccine experience is limited, thus vaccine and immunoglobulin may be preferred for optimal protection.[7] Both vaccines may be given concomitantly with Ig and the two brands are interchangeable for booster shots.[6]

Vaccination is recommended for international travel to areas of high or intermediate endemicity and can be given regardless of scheduled dates of departure. For older patients, immunocompromised, or any patients with chronic liver disease or any other chronic medical conditions traveling within 2 weeks, both Ig and vaccine are recommended.[7]

The most common side effects of the vaccines include soreness and warmth at the injection site, headache, malaise, and pain. More than 65 million doses of the vaccine have been administered and despite routine monitoring for adverse events, there are no data to suggest a greater incidence of serious adverse events among vaccinated people compared with nonvaccinated. The vaccine is considered safe.[5–7]

Immunoglobulin

Only one product is available which is a sterile, preservative-free solution used for prophylaxis of hepatitis A, measles, varicella, and rubella viral infections. In 2017, recommendations for increased dose of Ig were established due to concerns for declining HAV antibody from donors. Active immunity is achieved through vaccination, although preexposure prophylaxis is used in situations where protective effects of vaccine may either be inadequate or take too long to develop. Specifically, Ig is recommended with vaccination if travel to an HAV high or intermediate risk country will begin in < 2 weeks and the individual is an older adult, immunocompromised, or has chronic liver disease or other chronic medical condition. Ig is used when preexposure or postexposure prophylaxis against HAV infection is needed in persons for whom vaccination is not an option. Vaccination is preferred for multiple reasons, including that it induces active immunity and, therefore, a longer time of protection against HAV than Ig.

Immunoglobulin (Ig) is a sterile preparation of concentrated antibodies against HAV that provides protection by passive transfer of antibody. Ig is most effective if given in the incubation period of the infection. Receipt of Ig within the first 2 weeks of infection will reduce infectivity and moderate the infection in 85% of patients. Patients who receive at least one dose of the HAV vaccine at least 1 month prior to exposure do not need preexposure or postexposure prophylaxis with Ig.[6] Ig is available as both an intravenous (IV) and intramuscular (IM) injection, but for HAV exposure, only the IM is used.

Serious adverse events from Ig are rare. Anaphylaxis has been reported in patients with IgA deficiency. Patients who had an anaphylaxis reaction to Ig should not receive it. There is no contraindication for use in pregnancy or lactation.

Dosing of Ig is the same for adults and children. For postexposure prophylaxis and for short-term preexposure coverage of less than 3 months, a single dose of 0.02 mL/kg IM is given. For long-term preexposure prophylaxis of less than or equal to 5 months, a single dose of 0.06 mL/kg is used. Either the deltoid or gluteal muscle may be used. In children younger than 24 months, Ig can be given in the anterolateral thigh muscle.[6]

Vaccination is also preferred in most patients who were recently exposed to HAV and who had not been previously vaccinated. In contrast, prophylaxis with Ig may be preferred in patients younger than 12 months or who have an allergy to a vaccine component.[7]

Ig can be given concomitantly with the HAV vaccine. Although the antibody

titer will be lower than with the vaccine administered alone, the response is still protective and coadministration should be considered for the advantages of long-term HAV protection. However, Ig can interfere with the response of other live-attenuated vaccines and should be delayed.

Vaccine efficacy may be reduced in certain patient populations. In HIV-infected patients, greater immunogenic response may correlate with higher baseline CD4-cell counts. Patients with CD4 counts less than 200 cells/mm^3 (0.200×10^9/L) at vaccination have a reduced response rate. Moreover, patients with HIV/HCV coinfection may also have a lowered response.[8]

HEPATITIS B

4 Hepatitis B is highly infectious, approximately 50 to 100 times more so than HIV.[9] In 2015, 3.5% of the population had chronic HBV. The majority of these 257 million people were infected prior to the availability and use of the HBV vaccine in infancy.[9,10] Chronic infection with HBV is a major public health issue as it serves as a reservoir for continued HBV transmission and poses a significant risk of death resulting from liver disease including liver cirrhosis and hepatocellular carcinoma (HCC). According to the World Health Organization (WHO), 650,000 people per year die as a result of complications from HBV.[10] In the United States, there is no national chronic hepatitis surveillance program; however, estimates suggest between 850,000 and 2.2 million people have chronic HBV.[1]

Low public awareness, low perceived risk, and misinformation about HBV can result in discrimination and stigma.[1] In 2013, the Department of Justice recognized patients with chronic HBV infection to be protected under the Americans with Disabilities Act after students with HBV were denied enrollment in health professional schools.

Epidemiology

According to the WHO, chronic HBV infections disproportionately affect low- and middle-income countries.[9,10] Prevalence can vary regionally; however, areas commonly associated with high infectivity rates include sub-Saharan Africa, East Asia, followed by the Amazon and southern parts of Eastern and Central Europe.[10] Most new HBV infections are in children in areas of high HBV prevalence, approximately 45% of the global population. Infections of infants

and children are of special concern because more than 90% of cases lead to chronic infections and serve as ongoing source of infectivity. Major public health initiatives focused on pediatric vaccination have successfully reduced HBV infection in children under 5 from 4.7% to 1.3%.[9] In the United States, 847,000 to 2.2 million patients have chronic HBV infection. Annual rates of acute cases vary but in 2016, the number of new HBV cases was 20,900. Substantial increases in the number of cases of acute HBV reported in 2016 to 2018 in a number of states were attributed to injection drug use and the opioid epidemic. The highest rates of acute HBV were reported among men, White non-Hispanic or Black non-Hispanic, between the ages of 30 to 49 years.[2]

HBV is transmitted sexually, parenterally, and perinatally because concentration of HBV is high in blood, serum, and wound exudates of infected persons. Importantly, the virus can be stable in the environment for at least 7 days and can cause infection during this time. In areas of high HBV prevalence, perinatal transmission from mother to child at birth is most common. Horizontal transmission, such as from an infected child to an uninfected child, is also common. In the United States, perinatal transmission and sexual contact, both homosexual and heterosexual, are key routes of transmission. Lack of infection control practices specifically related to blood glucose monitoring also contributed to HBV outbreaks.[11] Screening recommendations focus on individuals at high risk for HBV including household contacts of an HBV-positive person (**Table 57-4**).[12]

TABLE 57-4 Persons at High Risk for HBV: Recommended Screening

Individuals from the Following Areas	Other Groups
Africa (all countries) Asia (all countries in North, Southeast, East Asia) South Pacific Islands (all countries except Australia and New Zealand) Middle East (all countries except Cyprus and Israel) Malta Spain Arctic (indigenous populations of Alaska, Canada, Greenland) South America (Ecuador, Guyana, Suriname, Venezuela, and Amazonian areas) Central America (Mexico, Guatemala, and Honduras) Eastern Europe (all countries except Hungary) Caribbean (Antigua-Barbuda, Dominica, Granada, Haiti, Jamaica, St. Kitts and Nevis, St. Lucia, Turks and Caicos)	US-born persons not vaccinated as infants whose parents were born in high HBV endemic regions Household, needle-sharing, and sexual contacts of HBsAg-positive patients Infants born to HBsAg-positive mother Persons who have ever injected drugs Persons not in a long-term mutually monogamous relationship (>1 partner in previous 6 months) Persons seeking evaluation or treatment for an STD Men who have sex with men Inmates of correctional facilities Individuals with chronic liver disease Individuals with elevated AST or ALT of unknown etiology Individuals with HIV or HCV Patients with end-stage renal disease including dialysis All pregnant women Persons requiring immunosuppressive therapy (chemotherapy, organ transplantation, rheumatological, or gastroenterologic) Donors of blood, plasma, organs, tissues, or semen Unvaccinated persons with diabetes aged 19-59 years (clinical discretion for persons >60 years) Residents/staff of facilities for developmentally disabled persons Travelers to countries of high or intermediate HBV prevalence Healthcare, public safety workers at risk for occupational exposure to blood or blood-contaminated body fluids Persons who may require postexposure prophylaxis following blood or fluid exposures

HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; STD, sexually transmitted disease; AST, aspartate aminotransferase; ALT, alanine transaminases; HIV, human immunodeficiency virus; HCV, hepatitis C virus.

Data from Reference 12.

Up to half of all children infected before the age of 6 will develop chronic HBV.[9] Children infected in the first year of life have a 90% likelihood of developing chronic HBV infection; thus, prevention of perinatal transmission and pediatric vaccination is critical.

Etiology

The HBV is a DNA virus that infects hepatocytes.[13] There are at least 10 HBV genotypes (GTs) (A-J) with distinct geographic and ethnic distribution. Although particular HBV genotypes can affect the course of HBV infections, testing for HBV GT is not currently recommended for clinical practice.[14]

Pathophysiology

On infection, replication of the virus begins by attachment of the virion to the hepatocyte cell surface receptors. The virion contains an internal capsid shielding a partially double stranded DNA which is released within the hepatocyte nucleus and integrates into the host chromosomal DNA.[13] In the nucleus the DNA is converted into closed, circular DNA (cccDNA) that serves as a template for pregenomic RNA to transcribe various viral proteins and begins the viral life cycle. The viral genome has four reading frames coding for various proteins and enzymes required for viral replication. Several of these proteins are used diagnostically (Table 57-5).

TABLE 57-5 Interpretation of Serologic Tests in Hepatitis B Virus

Tests	Result	Interpretation
HBsAg Anti-HBc Anti-HBs	(–) (–) (–)	Susceptible
HBsAg Anti-HBc Anti-HBs	(–) (+) (+)	Past HBV infection, resolved No further management needed unless undergoing immunosuppressive therapy or chemotherapy
HBsAg Anti-HBc Anti-HBs	(–) (–) (+)	Immune because of vaccination (valid only if test performed 1-2 months after third vaccine dose)
HBsAg Anti-HBc IgM anti-HBc Anti-HBs	(+) (+) (+) (–)	Acute infection
HBsAg Anti-HBc IgM anti-HBc Anti-HBs	(+) (+) (–) (–)	Chronic infection. Further evaluation needed
HBsAg Anti-HBc Anti-HBs	(–) (+) (–)	Possible interpretations: Resolved infection or false positive Requires HBV DNA testing if immunocompromised patient

HBsAg, hepatitis B surface antigen; Anti-, antibody; HBc, hepatitis B core; HBs, hepatitis B surface; IgM, immunoglobulin M.

Note: Anti-HBc includes both IgM anti-HBc and IgG anti-HBc. IgM is present during acute phase of infection.

Source: Data from reference 12 and Hepatitis B Serology, Centers for Disease Control and Prevention. https://www.cdc.gov/hepatitis/hbv/pdfs/serologicchartv8.pdf.

The hepatitis B surface antigen (HBsAg) is the most abundant of the three surface antigens and is detectable at the onset of clinical symptoms. Its persistence past 6 months after initial detection corresponds to chronic infection and indicates an increased risk for cirrhosis, hepatic decompensation, and HCC. The loss of HBsAg indicates that viral replication and protein expression is suppressed and is a goal of therapy. The loss of HBsAg may occur with or without the development of antibody to HBsAg (anti-HBsAg).[14]

The precore polypeptide encodes for the secretory protein hepatitis B e-antigen (HBeAg) and the hepatitis B core antigen (HBcAg) proteins. HBeAg is present in an acute infection and is replaced by antibodies (anti-HBeAg) once an infection is resolved. However, HBeAg is responsible for chronic HBV infection

in children because it promotes immune tolerance to HBV.[13] Due to substantial genetic variability of HBV and propensity for viral mutation, there are viral mutants that are unable to have down-regulated expression of HBeAg without affecting viral replication.[13] HBeAg-negative mutants pose a particular clinical challenge because they are refractory to treatment and have been implicated in acute liver failure.[13] The HBcAg is a nucleocapsid protein that, when expressed on hepatocytes, promotes immune-mediated cell death. It is not readily detectable by current laboratory techniques, instead antibodies to HBcAg are used for diagnostic purposes. High levels of antibodies (IgM anti-HBcAg) are detectable during acute infections. Patients who were infected with HBV at any point will be anti-HBc positive (either as total or IgG anti-HBcAg). Patients who respond to vaccine will have anti-HBsAg only.[11] Only the complete HBV is infectious.[9]

Immune response to HBV affects patient outcomes. In patients who have acute resolving infections, a robust immune response is necessary to quickly neutralize and destroy infected cells before the virus can infect other hepatocytes.[14] Chronic infections are associated with a progressive impairment in immune response. Liver injury is likely caused by secondary, nonspecific inflammation activated by the initial cytotoxic lymphocyte response and as an attempt by the immune system to clear the virus by destroying HBV antigen—presenting hepatocytes. HBV itself is not pathogenic to hepatocytes.[13] Destruction of hepatocytes results in release of circulating, and hence increased alanine aminotransferase (ALT) levels.

Chronic Hepatitis B Virus

4 Chronic HBV is defined as detectable HBsAg for more than 6 months.[12] Chronic infections can be controlled in many cases, but cure is not possible because the HBV template is integrated into the host genome. The most predictive factor for developing a chronic infection is age. Perinatal infections almost always result in chronic infections because of immune tolerance to the virus. The risk of chronicity declines to less than 5% in adult-onset infections. Importantly, chronic HBV infections are differentiated into phases with varied serologic patterns that are dynamic and not necessarily sequential.[14]

Clinical Presentation and Phases of Infection

The clinical symptoms and course of an HBV infection are indistinguishable

from other types of viral hepatitis (Table 57-1). Several phases of an HBV infection exist and are dynamic—progression is not necessarily sequential nor do patient disease characteristics fall clearly within the described parameters (**Table 57-6**).[14] The first phase of the infection is marked by profuse HBV DNA replication resulting in high levels of HBV DNA and HBeAg secretion. The very elevated levels of HBV, typically >1 million IU/mL (kIU/L), make patients highly contagious. This phase is also called "immune tolerant" because hepatic injury is limited.[12] ALT levels remain within normal limits (historically defined as <40 IU/L [0.67 μkat/L]) and no or minimal evidence of fibrosis is seen on liver biopsy.[14] In perinatal or early childhood infections, the phase can persist for years and the likelihood for spontaneous HBeAg seroconversion is low.[14]

TABLE 57-6 Patterns of Chronic Hepatitis B Virus Phases

State	HBeAg Status	ALT Level	HBV DNA IU/mL[a]	Other
Phase 1 ("immune tolerant")	+	WNL[b]	>1 million	
Phase 2 ("immune active")	+	High	>20,000	ALT intermittently or persistently elevated
	-	WNL	>2,000	ALT intermittently or persistently elevated
Phase 3 ("inactive carrier")	-	WNL	<2,000	Anti-HBe +
Phase 5 ("occult infection")	-	WNL	undetectable	Anti-HBc +, HBsAg -, with or without anti-HBs
Reactivation	±	High	>20,000	Associated with immunosuppressive states or therapies

[a]IU/mL is numerically equivalent to the SI unit of kIU/L.

[b]Per AASLD guidelines, ALT normal limits defined as <35 IU/L (0.58 μkat/L)(men); <25 IU/L (0.42 μkat/L)(women).

ALT, alanine transaminase; DNA, deoxyribonucleic acid; HBeAg, hepatitis B e-antigen; HBV, hepatitis B virus; WNL, within normal limits.

Phase 2, or the "immunoactive phase," is marked by the ongoing presence of HBeAg, high levels of HBV DNA, and elevated ALT. Immune activity results in persistent or intermittent elevations of ALT as the immune system responds to HBV-infected hepatocytes and there is evidence of liver injury with progression of fibrosis.[12,14] This phase is more likely and expected more rapidly in adult infections.[14] With the increase in immune activity against HBV-infected hepatocytes, the outcome can include HBeAg seroconversion and HBV DNA suppression. Phase 3, alternatively called the "inactive carrier" or "inactive chronic HBV," is characterized by undetectable or low (<2,000 IU/mL [kIU/L]) HBV DNA, reactive antibody to HBeAg (anti-HBe positive), and normal ALT. Progression of liver disease is unlikely in this phase if ALT remains persistently normal. However, some patients will not see immune control of HBV. Phase 4 is defined as HBeAg negative chronic HBV and is similar to the immune active

phase as seen by elevated ALT levels but is characterized by viral mutation. Mutations within the virus result in loss of HBeAg production but viral replication is not affected and HBV DNA levels range from moderate to high. ALT levels can also fluctuate or be elevated and patients have more advanced liver disease. Phase 5, or the HBsAg-negative phase, is also known at the “occult HBV infection.” Laboratories show a positive antibody to HBcAg (anti-HBc), no HBsAg, and with or without anti-HBs. In most patients the ALT levels are within normal and HBV DNA is usually undetectable. The risks of ongoing liver damage are minimal unless HBV reactivation occurs.

Reactivation of hepatitis B, defined as the recurrence or abrupt rise in HBV replication by an increase in serum HBV DNA of at least 1 $\log^{10}$ and a marked increase in transaminase levels, is well described in the literature in patients receiving cancer chemotherapy, steroids, and other immunosuppressive agents.[15,16] Reactivation is the loss of HBV immune control and can occur in anyone with a prior or current HBV exposure, but patients who are HBsAg positive are at particular risk. Risk of reactivation is especially high among patients undergoing B-cell depleting therapy (eg, rituximab), where reactivation can occur even in the setting of HBsAg negative but anti-HBc positivity,[15] positive undergoing B-cell depleting therapy (eg, rituximab), treatment with anthracycline derivatives (eg, doxorubicin), or moderate-to-high dose steroid therapy (10-20 mg prednisone or equivalent for 4 weeks or longer) are considered high risk for reactivation.[15] Antiviral prophylactic therapy is often indicated to prevent reactivation and continued for at least 6 months, or at least 12 months for B cell–depleting agents, after discontinuation of immunosuppressive therapy.[15]

Cirrhosis

Cirrhosis results as the liver attempts to regenerate while in an environment of persistent inflammation. Most patients with compensated cirrhosis either are asymptomatic or have mild symptoms of epigastric pain and the diagnosis is made by laboratory or imaging findings. The development of cirrhosis is mostly insidious and patients can remain stable for years before disease progression. During cirrhosis, the liver enters a cycle of ongoing liver damage, fibrosis, and attempts at regeneration. On imaging, the classical appearance of a small and knobby liver reflects nodules of regenerating cells integrated with infiltrates of inflammation-induced fibrous tissue. Progression of liver disease is variable and affected by both viral and host factors, in particular the immune response to HBV plays a key role in clinical outcomes (**Table 57-7**). Patients without

cirrhosis have a 5% to 20% risk of progression to cirrhosis over a 5-year period. Subsequently, 20% of all chronic hepatitis B patients develop complications of hepatic insufficiency and portal hypertension as their compensated cirrhosis progresses to decompensated cirrhosis within a 5-year period. Risks for death and decompensation increase with underlying liver disease. All patients with cirrhosis, irrespective of severity or HBV treatment, are at an annual risk of developing HCC and require routine surveillance for HCC as per national guidelines.[12]

TABLE 57-7 Factors Associated with Hepatitis B Virus Cirrhosis and Risk of HCC

Host Factors	Viral Factors
Older age at diagnosis	Persistence of high HBV serum DNA and or HBsAg levels
African origin (greater likelihood for early onset HCC)	Infection with genotype C > B
Asian	Specific HBV mutations
Alcohol abuse	
Chronic coinfection with HCV, delta hepatitis, or HIV	
Diabetes or metabolic syndrome	
Active smoking	
Family history of cirrhosis/HCC	
Presence of cirrhosis (as a risk for HCC)	

HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; DNA, deoxyribonucleic acid.

Data from References 14 and 17.

Hepatocellular Carcinoma

HBV is a known risk factor for the development of HCC and in areas of high HBV endemicity, a major complication of the infection.[9] Although there is a known annual risk of developing HCC in patients with cirrhosis, HCC can occur in patients with HBV who do not have cirrhosis. In most cases, HCC develops after years of inflammatory processes provoked by ongoing HBV infection, however, HBV itself is an oncogenic virus.[10] Several factors influence the development of HCC (Table 57-7), in particular the presence of cirrhosis. In the United States, the majority of cases of HCC are in patients >60 years of age, male, with cirrhosis, and Asian. Patients of African descent are more likely to

develop HCC at a younger age (median 44 years).[17]

Vaccine Prevention of Hepatitis B

5 Vaccination is the most effective strategy to prevent HBV infection and a comprehensive vaccination strategy was implemented in the United States (Table 57-8). Despite substantial declines in HBV, gaps in HBV vaccination persist that contribute to ongoing HBV transmission. Birth dose vaccination of infants born to HBsAg-positive women remains below the 85% target for Healthy People 2020.[18] Similarly, the three-dose vaccine coverage for adults, including patients with chronic liver disease, travelers, diabetics, and healthcare personnel are lower and far below target levels.[19] Vaccination for HBV is less effective than for HAV and requires multiple doses for improved response; however, many patients may start a vaccine series but do not complete it.

TABLE 57-8 Recommendations for Hepatitis B Virus Vaccination

- All Infants
- All previously unvaccinated children <19 years
- All unvaccinated adults aged 19-59 with diabetes; those aged >60 should be vaccinated at the discretion of treating clinician
- Sex partners of persons who are HBsAg positive
- Sexually active persons not in a long-term monogamous relationship (>1 partner/6 months)
- Men who have sex with men
- STD clinic patients
- Persons with HIV
- Current or recent injection drug use
- Household contacts of persons with chronic hepatitis B infection
- Clients and staff of institutions for the developmentally disabled
- Healthcare and public safety workers with anticipated risk for exposure to blood or blood-contaminated fluid in the workplace
- Chronic dialysis/ESRD patients including predialysis, peritoneal dialysis, and home dialysis patients
- Correctional facilities inmates
- International travelers to regions with high or intermediate levels (HBsAg prevalence >2%) of endemic HBV infection
- Persons with chronic HCV infection
- Persons with chronic liver disease (eg, patients with alcoholic liver disease, cirrhosis, fatty liver disease, autoimmune hepatitis, etc.)
- All unvaccinated adults seeking vaccination (specific risk factor not required)

HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; ESRD, end-stage renal disease; MSM, Men who have sex with men; STDs, sexually transmitted diseases.

Data from Reference 19.

The development of the HBV vaccine represented the first vaccine against a major human cancer.[10] Vaccines use HBsAg for the antigen via recombinant DNA technology using yeast to prompt active immunity. Available vaccines include single-antigen products and combination products. The two single-antigen products are Recombivax® HB and Engerix-B®. TWINRIX® is a combination vaccine for HAV and HBV in adults. Comvax® and Pediarix® are used for children and are used for HBV along with other scheduled vaccines. Unlike the HAV vaccine, the HBV vaccine response is generally lower and often

requires at least three doses for optimal protection. In 2017, the FDA approved a new HBV vaccine which uses a novel adjuvant for immunogenicity. Most vaccines use alum whereas the Heplisav-B® vaccine utilizes a toll-like receptor ligand to enhance immunity and allowing for a two-dose vaccine schedule in adult patients (Table 57-9).

TABLE 57-9 Recommended Dosing of Hepatitis B Vaccines (Single Antigen)

Vaccine	Age (Years)	Dose (Volume)	No. of Doses	Schedule[a]
Engerix-B	0-19	10 mcg IM (0.5 mL)	3	0, 1, 6 months
	>20	20 mcg IM (1 mL)	3	0, 1, 6 months
Recombivax	1-19	10 mcg IM (0.5 mL)	3	0, 1, 6 months
	>20	10 mcg IM (1 mL)	3	0, 1, 6 months
Heplisav-B[b]	≥18	0.5 mL	2	0, 1 months

[a]Zero (0) denotes initial dose, subsequent numbers denote time after initial dose for timing of additional doses.

[b]Utilizes different adjuvant; cannot be interchanged with other HBV vaccines.

Source: Centers for Disease Control and Prevention.[6]

The most commonly reported adverse events for single-antigen vaccine are nausea/dizziness, and fever/headache; for combination vaccines, fever, injection site erythema, and vomiting. Similarly, for Heplisav-B, the most common adverse reactions reported within 7 days of vaccination included injection site pain, fatigue, and headache.

Vaccination is the standard for HBV prevention. Passive immunity with hepatitis B Ig offers temporary protection against HBV and is used in conjunction with the hepatitis B vaccine for postexposure prophylaxis in infants born to HBsAg-positive mothers and for select other prophylaxis.[19]

TREATMENT

Desired Outcomes

6 Prevention of HBV, in particular preventing mother to child transmission, is a primary goal with substantial public health benefits. HBV infections are not curable; thus, the goals of therapy are to suppress HBV replication and prevent disease progression to cirrhosis and HCC. Another important goal is preventing

HBV reactivation in patients with inactive HBV infections.

General Approach to Treatment

6 HBV viral suppression is a goal of all therapies.[14] HBe-Ag loss, with or without seroconversion to anti-HBeAg in patients who are HBeAg positive, indicates immune control. Normalization of ALT is another goal associated with viral suppression. An ultimate goal of therapy is the loss of HBsAg with or without anti-HBs seroconversion. This is a goal not often realized but one associated with suppression of HBV replication and viral protein expression and indicates antiviral therapy that can be safely discontinued.

TABLE 57-10 Definitions of Response in Hepatitis B Virus Therapy

Biochemical	Normalization of ALT
Histologic	Decrease in histology activity by at least 2 points as compared with baseline biopsy
Virologic	Undetectable HBV DNA and, in patients previously HBeAg positive, loss of HBeAg

ALT, alanine transaminase; DNA, deoxyribonucleic acid; HBV, hepatitis B virus; HBeAg, hepatitis B e-antigen.

Indications for treatment consider HBV DNA levels, ALT levels, and whether or not the patient has cirrhosis (Table 57-11). All patients with cirrhosis require HBV treatment. In patients without cirrhosis, HBV DNA levels can determine the need for treatment because active viral replication predicts disease progression.[14] Not all chronic HBV patients are candidates for treatment. Some patients may be best managed with periodic monitoring for disease progression because the chances for therapeutic response are unlikely and do not outweigh the risks and costs associated with treatment. The major organizations providing guidelines on the management of HBV infections are the WHO, American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver, and the Asian Pacific Association for the Study of the Liver.

TABLE 57-11 Generally Accepted Criteria for Treatment of HBV

Characteristics:
Anyone with HBeAg (+) or HBeAg (-) active HBV defined as: • HBV DNA >2,000 IU/mL (kIU/L) • ALT 2 × upper limit of normal[a] and/or with evidence of histological disease[b]
Anyone with compensated or decompensated cirrhosis with HBV DNA >2,000 IU/mL (kIU/L)[c]
Anyone not fulfilling above criteria with ALT < 2 × ULN and any detectable HBV DNA (<2,000 IU/mL [kIU/L]), consider: • Patient's age • Family history of HCC • Prior history of HBV treatment • Extrahepatic manifestations of HBV

[a]Per European guidelines, any elevations in ALT.

[b]Moderate or greater fibrosis as determined by biopsy or noninvasive measures.

[c]Per European guidelines, any detectable HBV DNA.

Patient Counseling and Nonpharmacologic Therapy

All chronic HBV patients should be counseled on preventing disease transmission. Sexual and household contacts should be vaccinated against HBV. Barrier protection methods are recommended for casual sex partners or for steady partners who have not completed vaccination series.[12] Concomitant metabolic syndrome and insulin resistance increase hepatic liver disease progression and the development of HCC.[20,21] Other lifestyle factors known to potentiate liver disease include alcohol use and smoking.[12,20] Herbal medicines are an intriguing option to many patients, although no data support their use and some may have harmful effects on liver function.

Pharmacologic Therapy

The long-term goals of therapy include a reduced risk of liver-related complications, reduced progression of liver disease, and reduced rates of HCC. Because hepatic damage is sustained by ongoing viral replication, drug therapy aims to suppress viral replication by either immunomodulating agents or antivirals—the nucleos(t)ide agents (NAs). In the United States, the immune-mediating agents approved for use are pegylated (peg) interferon (IFN)-alfa and IFN-alfa and are injectables. The antiviral agents are all oral therapies and many also have some activity against HIV (entecavir, tenofovir, lamivudine, and

telbivudine); thus, it is important to understand a patient's HIV status before starting therapy. All NAs carry a boxed warning for lactic acidosis. The preferred NAs are those considered to have a high barrier to resistance and include entecavir, tenofovir diprovoxil, and tenofovir alafenamide. Other available NAs which have a low barrier to resistance and are thus not preferred include lamivudine, telbivudine, and adefovir.[12] A major difference in therapy between IFN and the NAs is duration of use: IFN-based therapies are typically administered for a predefined duration, whereas NAs are used until a specific end point is achieved. The key disadvantage and limitation with IFN-based therapy are the side effect profile and laboratory abnormalities associated with its use. In contrast, the NAs are well tolerated and can be safely used even in patients with decompensated cirrhosis.[22]

HBV virological cure, or HBV virus eradication, is not an achievable goal of therapy because of persistence of the cccDNA in hepatocytes and lifelong risk for HBV reactivation. Instead, the goals of therapy include HBeAg loss and sustained virological suppression. For HBeAg-positive patients, treatment is recommended until HBeAg seroconversion and an undetectable HBV viral load are achieved and for 6 months of additional treatment. In HBeAg-negative patients, treatment is recommended indefinitely.[22]

Interferon

IFN-alfa therapy was the first approved therapy for treatment of HBV and improves long-term outcomes and survival. If IFN therapy is used, the peglyated form is preferred. Patients who respond to IFN therapy tend to have a more durable response than that seen with lamivudine, likely as a consequence of IFN's stimulation of the immune response for seroconversion. However, seroconversion with IFN therapy is most likely in patients with HBeAg positivity and who have persistent or intermittently elevated ALT. The recommended duration of therapy is 48 weeks.[22] IFN-based therapies are still limited by multiple adverse effects. The high risk of infection precludes use of IFN in decompensated cirrhotic patients and it is contraindicated in patients with autoimmune disease, uncontrolled psychiatric disease, cytopenias, severe cardiac disease, and uncontrolled seizures.[22] In patients with compensated cirrhosis, IFN can provoke hepatic flares and precipitate hepatic decompensation.[22] The optimal role of IFN-based therapies in HBV treatment is not defined and remain a therapeutic option per guidelines.[14] However, due to the substantial side effects, need for monitoring, and toxicities of IFN-based therapies, IFN is not considered an option in resource-limited countries and not recommended as a

first-line therapy by the WHO.[10]

Entecavir

Entecavir is an oral guanosine NA that acts by inhibiting HBV replication. It has weak activity against HIV.[10] Entecavir is considered to be a first-line agent for HBV therapy because of its efficacy and low rates of resistance.[10,12,14] It is more potent than lamivudine and adefovir in suppressing serum HBV DNA levels, improvement in liver histology, and normalization of ALT levels.[10] Rates of HBeAg seroconversion increase with subsequent years of treatment.[14] The drug is dosed at 0.5 mg orally daily for adults with treatment-naïve or non–lamivudine-resistant infections and at 1 mg daily in lamivudine-experienced patients or patients with decompensated cirrhosis. In treatment-naïve patients, entecavir resistance remains low, demonstrating the high barrier to resistance of the drug.[14] However, resistance to lamivudine is a risk factor for entecavir resistance; thus, guidelines do not recommend to use of entecavir in patients with prior lamivudine experience.[22] Entecavir is safe and well tolerated.

Tenofovir

Due to its high barrier to resistance, tenofovir is considered a first-line therapy in the treatment of HBV.[12,14] For HBV, it is available as a single-agent oral tablet. There are two forms of tenofovir available: tenofovir disoproxil fumarate (tenofovir DF) and tenofovir alafenamide. Tenofovir DF is available as a 300 mg dose for HBV. Tenofovir alafenamide is a prodrug converted to the active tenofovir in the hepatocyte, allowing for a lower dose at 25 mg. Historically, tenofovir diprovoxil was used for HBV where it was highly effective in HBV DNA viral suppression demonstrating regression of fibrosis.[10,23] It is effective even in patients previously treated with other HBV therapies.

Tenofovir alafenamide offers several advantages over tenofovir DF as it allows more efficient delivery of tenofovir directly to the hepatocytes and thus a more direct action against HBV replication. In both HBeAg-positive and HBeAg-negative patients, tenofovir alafenamide was as effective as tenofovir DF and was more likely to result in normalization of ALT.[24] The ability to reduce the systemic exposure to tenofovir allows for an improved safety profile. Compared to tenofovir DF, tenofovir alafenamide demonstrated improved bone safety and smaller changes in estimated glomerular filtration rates.[24,25]

Resistance to tenofovir has not been seen in clinical studies. No resistance was identified to tenofovir DF through a 7-year study period and viral suppression was seen in nearly all patients, regardless of HBeAg status.[23] Similarly, there was no resistance to tenofovir alafenamide with 96 weeks of follow-up.[26]

Lamivudine

Lamivudine, a NA, has antiviral activity against both HIV and HBV but is not recommended as first-line therapy for chronic HBV infections. It is given at a dose of 100 mg by mouth daily.[22] The main limitation to lamivudine use is its likelihood for resistance, which is considered inevitable and can undermine the value of treatment. The emergence of resistant mutants increases with each subsequent year of therapy, with rates approaching 80% after 5 years of therapy, and is associated with returns of serum HBV DNA and elevated ALT levels.[27] Relapse is also associated with reversion of histologic benefits.[14] In HBeAg-negative chronic hepatitis B, where therapy is long-term and the exact duration of therapy unknown, resistance is an especially daunting problem, thus lamivudine is a nonpreferred therapy.[12,14]

Adefovir

Adefovir dipivoxil is an acyclic NA of adenosine monophosphate that inhibits HBV reverse transcriptase and DNA polymerase. Adefovir's role in HBV therapy is unclear. It is no longer recommended as monotherapy by international guidelines because it has a relatively low barrier to resistance and both entecavir and tenofovir are more potent therapies in comparsion.[10]

Telbivudine

Telbivudine acts as a competitive inhibitor of viral reverse transcriptase and DNA polymerase to inhibit HBV DNA synthesis. Compared with lamivudine, telbivudine is a more potent suppressor of HBV DNA.[14] However, similar to lamivudine, telbivudine has a high rate of mutations that limits its efficacy. Due to resistance concerns, telbivudine monotherapy has a limited role in the treatment of HBV and is not a recommended treatment.[10,12]

Alternative Drug Treatments

Combination therapy is not recommended for initial HBV treatment.[14] There

may be a role for combination therapy in select patients with suboptimal HBV DNA viral suppression with entecavir, tenofovir DF, or tenofovir alafenamide, or in patients with multiple underlying HBV resistance mutations.[28] Furthermore, in resource-limited areas where access to monotherapy may be cost-prohibitive, combination therapy may offer a strategy to reduce resistance and provide optimal HBV viral suppression.[27]

Combination therapy is not recommended as initial therapy. Patients who are treatment adherent but have incomplete HBV DNA viral control on entecavir or tenofovir DF/tenofovir alafenamide should be switched to the other drug or combination therapy can be considered.[12,14]

Special Populations

Cirrhosis

All patients with cirrhosis should receive HBV treatment irrespective of HBV DNA, HBeAg status, or ALT elevations. These patients are at risk for worsening complications of end-stage liver disease. Similarly, patients with decompensated cirrhosis should be on HBV therapy and evaluated for liver transplant.[12] Recommended therapies in patients with decompensated cirrhosis include entecavir and tenofovir DF. There are no data using tenofovir alafenamide in patients with decompensated cirrhosis; however, if renal function or bone disease is a concern, it is reasonable to use tenofovir alafenamide. Treatment in these patients is continued indefinitely.[12]

Coinfection with Hepatitis C Virus

Coinfection with HCV increases the progression of liver disease including the risk of HCC; thus, all patients with HBV should be screened for HCV. Moreover, reactivation of HBV can occur in patients undergoing treatment with directly acting antivirals (DAAs) for HCV and may require HBV prophylaxis.[12,14] Patients with both HBV and HCV should be evaluated for HBV treatment according to HBV treatment criteria.

Coinfection with Hepatitis D

Infection with hepatitis D requires infection with hepatitis B. No NAs have demonstrated efficacy against HDV; however, IFN does have some efficacy against HDV and treatment may include either IFN monotherapy or a combination of IFN with an NA.[10,14] There is an overall paucity of data on

HBV–HDV coinfection treatment.

Coinfection with Human Immunodeficiency Virus

In HIV-coinfected patients, initiation of highly active antiretroviral therapy (HAART) is strongly recommended as it may improve overall survival. Therapy should include either tenofovir alafenamide or tenofovir DF since both have efficacy against HIV and HBV.[14]

Pediatric Patients

Most children with chronic HBV are asymptomatic and do not meet currently established criteria for HBV treatment.[14] Treatment is recommended in HBeAg-positive children aged 2 to 18 who have elevated ALT and measurable HBV DNA.[12] A limitation to the recommendations is a lack of clarity regarding the upper limit of normal for ALT in pediatric patients with guidelines using an upper limit of normal of 35 IU/L (0.58 μkat/L) for males and 25 IU/L (0.42 μkat/L)for females.[12] Lamivudine and entecavir are approved for children 2 years and older whereas IFN is approved for use in children 1 year and older. Adefovir and tenofovir DF are approved for children 12 and older, although for HIV, tenofovir DF may be used in children 3 years and older. There are no studies with tenofovir alafenamide in pediatric patients.

Chronic HBV in Pregnancy

Perinatal transmission of HBV is a major cause of chronic HBV. In pregnant females who are HBeAg positive and have an HBV DNA >200,000 IU/mL (kIU/L), tenofovir DF is recommended in the third trimester. Lamivudine and telbivudine are also options; however, due to concerns for resistance these are no longer recommended therapies.[12] Furthermore, to prevent mother-to-child transmission, all infants born to HBsAg-positive women should receive HBV vaccination with or without immunoglobulin within 24 hours of birth.[12,19]

Immunosuppressive or Cytotoxic Therapy

8 Patients who will undergo chemotherapy or immunosuppressive therapy should be assessed for risk of HBV. The American Gastroenterological Association recommends that patients who are at high risk of HBV reaction should receive antiviral prophylaxis, including (1) HBsAg-positive or negative and anti-HBc-positive and undergoing B-cell depleting agents such as rituximab;

(2) HBsAg-positive and anti-HBc-positive treated with anthracycline derivatives such as doxorubicin; (3) HBsAg-positive and anti-HBc-positive undergoing 10 to 20 mg prednisone daily or equivalent therapy or on high-dose (>20 mg prednisone daily or equivalent) corticosteroids for 4 weeks or more.[15,16] Due to moderate risks of reactivation, other immunosuppressive therapies such as tumor necrosis factor alpha inhibitors, cytokine or integrin inhibitors, tyrosine kinase inhibitors, and corticosteroids are also identified as requiring antiviral prophylaxis in patients with specific HBV serological results.[15,16] The CDC recommends testing for hepatitis B for all patients who are to receive chemotherapy or other immunosuppressive agents.

8 Prophylactic therapy is recommended prior to initiation of cancer chemotherapy or immunosuppressive therapy. Patients who have undetectable HBV DNA and who are expected to be on chemotherapy or immunosuppressive treatment for 1 year or less should be treated for HBV for at least 6 months after completion of chemotherapy or immunosuppressive therapy to prevent HBV reactivation.[16]

Resistance Concerns

Current guidelines favor the use of potent agents with a high barrier to resistance. Resistance potential in HBV is evaluated by an antiviral agent's genetic barrier to resistance, or the number of primary mutations needed for antiviral drug resistance to occur. Other factors include cross-resistance and drug potency. Viral suppression is important because the HBV virus requires ongoing viral replication in the setting of antiviral drug pressure to mutate. HBV therapy can be cost-prohibitive for many patients and can favor the use of lamivudine. Unfortunately, lamivudine-based therapies are prone to resistance and may have long-term implications on viral activity, notably the concerns for development of vaccine-resistant mutants.[27]

Hepatitis B Virus Mutations

Although a DNA virus, HBV uses reverse transcriptase, similar to a retrovirus such as HIV. The similarities between HIV reverse transcriptase and HBV polymerase prompted the development of NAs for the treatment of HBV. IFN-based therapies, because they are immune-modulating and not directly antiviral, are not associated with resistance. However, long-term therapy with the NAs is problematic because of the high likelihood of developing HBV viral resistance given HBV's high replication rate and an estimated 10 mutations generated

daily.[10–12] In addition, HBV can archive drug-resistant mutations that allow the virus to quickly select the mutation if the antiviral agent is reintroduced. Cross-resistance among antiviral agents also occurs, further limiting therapeutic options. Lamivudine is most commonly associated with resistance due to (1) its low barrier for developing resistance with a single mutation able to overcome the agent combined with (2) widespread use of lamivudine in some regions.[10]

Resistance to the NA agents occurs by alteration of the active site of the HBV DNA polymerase. Long-term use of lamivudine is associated with resistance mutations of this active site and cross-resistance occurs which also affects telbivudine.[29] Based on clinical studies of NAs with up to 6 years of follow-up, mutations to adefovir and entecavir are possible, although patients on entecavir and tenofovir DF were the least likely to develop resistance.[27] As a result, both entecavir and tenofovir are the preferred first-line agents for HBV. The optimal management of patients with resistant HBV is not clear. In lamivudine-resistant chronic hepatitis B, tenofovir DF showed an earlier and greater suppression of HBV DNA than adefovir. Tenofovir DF can overcome adefovir treatment failure; however, viral suppression by tenofovir DF is reduced, suggesting some cross-resistance with adefovir mutants.[10,27]

Another major factor in resistance is patient adherence to therapy. Studies on adherence suggest suboptimal adherence is common with approximately 40% of patients missing doses.[30]

HEPATITIS C

Approximately 3.2 million people in the United States are chronically infected with HCV.[2] Considering that HCV infection is prevalent in high-risk populations such as prisoners, persons who inject drugs (PWIDs), and the homeless, and that this population is generally excluded from most surveys, the actual number of chronically infected people is not known. HCV is approximately five times as common as HIV and, since 2007, the number of deaths attributable to HCV exceed the number of deaths due to HIV.[2,31] Most acute HCV infections are asymptomatic and the course of the infection is insidious. As a result, many patients are not diagnosed until significant disease progression. Today’s HCV disease burden is associated with the high numbers of patients infected in the 1980s including healthcare associated infections. HCV was not easily identified and testing for the virus was not commonly implemented until the early 1990s. HCV therapies are all-oral, well tolerated with few adverse effects or laboratory

abnormalities, and curative in the overwhelming majority of patients. However, HCV treatment access is variable and may include a number of stipulations which act as barriers to care.

Epidemiology

9 10 HCV is the most common blood-borne pathogen. Since 2010, the number of acute HCV cases increased, due to both improved surveillance and increase in incidence. There were 41,200 new HCV infections in 2016 compared to 16,500 in 2011 and the recent rise in infections is linked to the opioid epidemic.[2] Approximately 45% to 85% of infected people may not be identified with concerns of progressive liver damage due to delay in diagnosis.[1,32] Since 2013, the number of HCV-related deaths among adults between ages 55 and 64 years increased. Targeted testing for HCV of persons born between 1945 and 1965, a recommendation by the CDC and the United States Prevention Services Task Force (USPSTF), attempts to address this rising epidemic.[33]

Transmission of HCV occurs through percutaneous exposure.[34] Injection-drug use is a major factor in the cycle of HCV transmission and the most common reason for the current increase in new infections. In Indiana in 2015, an outbreak of 135 new cases of HIV among PWIDs identified coinfection with HCV in over 84% of patients.[35] Some experts also consider other illicit drug use, for example, intranasal cocaine, as a risk factor because of the possible contamination of drug paraphernalia not limited to syringes and needles. Unsafe injection practices are associated with HCV transmission and include tattoos received in a nonregulated setting and needle stick injuries. Less common routes of transmission include sexual transmission and infants born to HCV-infected women. No specific sexual practices are associated with an increased risk of transmission among monogamous heterosexual partners.[36] Although sexual contact is considered an inefficient means of HCV transmission, multiple sexual partners and coinfection with sexually transmitted diseases, including HIV, increase the risk for HCV sexual transmission. Outbreaks of HCV were demonstrated in MSM with guidelines recommending annual HCV screening for adolescent and adult MSM including HIV-uninfected men seeking HIV preexposure prophylaxis.[34] Historically, blood transfusion posed a major risk for infection. Improved screening of blood in 1992 decreased the risk of transfusion-related HCV.[34] Healthcare-associated transmission is rare; however, unsafe injection practices are often identified as the cause of HCV transmission.

9 Although acute HCV infections are often not recognized and many

progress to chronic infections, routine screening for infection is not recommended. The AASLD, in conjunction with the Infectious Diseases Society of America (IDSA), publish on-line guidelines for testing, managing, and treating HCV (see www.hcvguidelines.org).[34] In 2012, the CDC released recommendations to perform a one-time screening of all patients born between 1945 and 1965.[35] The recommendation was made due to the high rates of HCV in this birth cohort likely attributed to nosocomial or iatrogenic exposure rather than lifestyle factors.[37] Approximately 75% of adults with HCV were born in that age range.[33] Screening is also warranted in patients who are at high risk for infection, especially among PWIDs or who have a history of injection drug use (**Table 57-12**).[34] Any needle-borne exposure in an unregulated setting poses a risk for infection. Given the increase in acute HCV infections among young adults, guidelines recommend testing all pregnant women for HCV.[34]

TABLE 57-12 Recommendations for Hepatitis C Virus Screening

- Anyone born between 1945 and 1965
- Current or past use of injection drug use
- Persons with current or past use of intranasal illicit drug use
- Patients who have ever been on hemodialysis
- Persons with percutaneous/parenteral exposures in an unregulated setting
- Healthcare and public safety workers after a needle-stick or mucosal exposure to HCV-positive blood
- Children born to HCV-positive mothers
- Received blood transfusions or organ transplantations before July 1992
- Received clotting factors before 1987
- Persons who were ever incarcerated
- Coinfection with HIV
- Sexually-active persons about to start preexposure prophylaxis for HIV
- Patients with unexplained elevated ALT levels or evidence of liver disease
- Solid organ donors

ALT, alanine transaminase; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

Data from Reference 34.

The initial test for HCV infection is the anti-HCV or antibody test (**Fig. 57-1**).

Patients who are antibody positive for HCV require confirmatory testing for HCV RNA to verify current HCV infection. Patients who are anti-HCV positive but who do not have a detectable HCV RNA do not have a current HCV infection and no further workup is required in the majority of cases.[38] Furthermore, the presence of antibody does not infer immunity and patients are at risk for HCV infection should they be reexposed.[39]

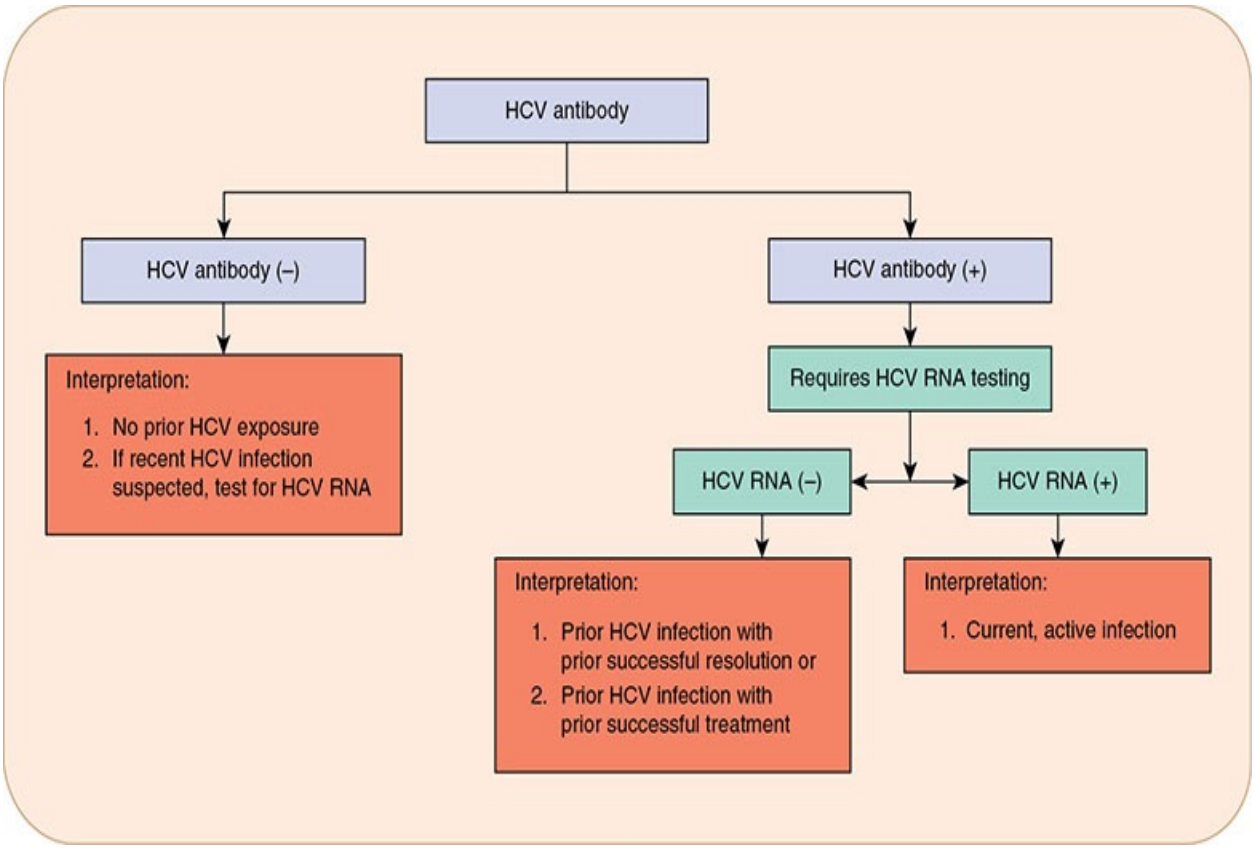


FIGURE 57-1 HCV Testing.

Etiology

HCV is a single-stranded RNA virus notable for lacking a proofreading polymerase and enabling frequent viral mutations.[39] The virus replicates within hepatocytes and, like hepatitis B, is not directly cytopathic. HCV replicates copiously posing an immense challenge for host immune control.[39] Viral mutations can affect direct-acting antiviral (DAA) therapy.

HCV is differentiated into six major GTs, numbered 1 to 6. GTs are further classified into subtypes (a, b, c, etc.). The most widely distributed GTs are 1 and 2, with GT1 the most common. In the United States, GT1a and GT1b, followed

by GT2 and GT3, cause most infections. Chronic HCV infection with any of the GTs can lead to cirrhosis, end-stage liver disease (ESLD), or HCC. Many HCV therapies have pan-genotypic activity; however, therapy may be optimized for a particular genotype as well as level of underlying liver disease.

Pathophysiology

In most cases, an acute HCV infection leads to chronic infection. The immune response in an acute HCV infection is mostly insufficient to eradicate the virus. HCV poses a daunting challenge for immune control because of its rapid viral diversification. HCV genomic mutations are detectable within 1 year of infection. Resolved cases of HCV are defined by a vigorous T-cell response with highly active CD8 and persistent CD4-cell response. CD8 activity mediates protective immunity but requires the aid of CD4 cells to maintain the response during viral mutations.[39]

Clinical Presentation

In an acute HCV infection, most patients are asymptomatic and undiagnosed. HCV RNA is detectable within 1 to 2 weeks of exposure and levels rise quickly during the initial weeks. Approximately one-third of adults will experience some mild and nonspecific symptoms, including fatigue, anorexia, weakness, jaundice, abdominal pain, or dark urine.[40] Acute infections rarely progress to fulminant hepatitis, although the course can be severe and prolonged. If the infection is self-limiting, symptoms last several weeks as ALT and HCV RNA levels subside. In patients who are immunosuppressed or have been infected with HCV for less than 6 months, it is possible that antibody testing is negative and confirmation of HCV RNA requires HCV RNA testing.[34]

Up to 85% of acutely infected patients will go on to develop a chronic HCV infection, defined as persistently detectable HCV RNA for 6 months or more. HCV RNA levels and ALT levels can fluctuate and even have periods of undetectable HCV RNA and normal ALTs. Most patients will have few, if any, symptoms. On physical examination, hepatomegaly is usually present. With advanced disease, stigmata of liver disease are evident, such as spider nevi, splenomegaly, palmar erythema, testicular atrophy, and caput medusae. Chronic inflammation of the liver from chronic HCV infection may result in fibrosis. Fibrosis is defined by altered hepatic perfusion creating a distorted structure and affecting normal function. Fibrosis leads to cirrhosis, although the speed of

fibrosis progression is variable. Understanding whether or not a patient has cirrhosis is necessary for determining optimal HCV therapy and the duration of treatment. Additionally, patients with cirrhosis require follow-up care specifically for management of the complications associated with cirrhosis. Although cirrhosis can be diagnosed by liver biopsy, there are a number of less invasive and more readily available assessments for clinical evaluation.

10 The development of HCV cirrhosis poses a 30% risk over 10 years for the development of end-stage liver disease (ESLD), as well as a 1% to 2% risk per year of developing HCC.[32] Progression to cirrhosis is the primary concern in patients infected with HCV for two decades or longer. Disease progression is not uniform or linear, making it difficult to identify which patients will have progressive liver damage and when. Other concomitant viral infections, comorbidities, and lifestyle factors can contribute to disease progression. Ongoing alcohol use, obesity, and metabolic syndrome can potentiate fibrosis.[34] Viral load is not a factor for disease progression and not associated with degree of fibrosis. Coinfection with HIV or HBV is associated with disease progression as is infection with HCV GT3.[34,41]

10 Although HCV is thought of as a liver disease, chronic HCV is associated with extrahepatic manifestations, or HCV-associated systemic disease. The most common is cryoglobulinemia, a local deposition of immune complexes that cause vasculitis.[34] Typical manifestations involve the skin and internal organ damage, predominantly affecting the kidneys and associated with worsening renal function. Other systemic diseases associated with HCV include cardiovascular disease, diabetes, B-cell non-Hodgkin lymphoma, Sjögren syndrome, glomerulonephritis, arthritis, corneal ulcers, thyroid disease, neuropathies, and skin diseases such as vasculitis, porphyria cutanea tarda, and lichen planus.[42]

9 Despite CDC and USPSTF recommendations for HCV testing of anyone born between 1945 and 1965, screening rates remain low.[43,44] In addition, HCV screening is recommended for all patients with risk factors for transmission. Given the increase in HCV cases and challenges with current screening rates, the AASLD also recommends HCV testing of pregnant women, incarcerated persons, and HIV-infected MSM as well as HIV-uninfected MSM presenting for preexposure prophylaxis.[34] Early diagnosis and treatment can prevent liver damage, cirrhosis, HCC, and death.

TREATMENT

Desired Outcomes

11 The primary goal of therapy is to eradicate HCV infection. Virologic cure, or sustained virologic response (SVR), is defined as a nondetectable HCV RNA at least 12 weeks after completing HCV therapy. Patients who achieve SVR will continue to have detectable HCV antibody, though this does not imply HCV immunity. Resolving the infection prevents the development of chronic HCV infection sequelae including ESLD, HCC, and death. Patients with extrahepatic manifestations of HCV are expected to benefit with reductions in symptoms and disease severity of their extrahepatic disease while experiencing improvements in quality of life measures.[34] As more patients are cured, the risk of transmission is expected to decline and reduce the long-term HCV disease prevalence.[34]

General Approach to Treatment

Treatment for HCV is recommended for all HCV-infected persons. Prior recommendations prioritized patients for treatment (eg, those with cirrhosis or HIV coinfection); however, substantial experience with the DAAs as well as accumulating safety and efficacy data and reduced costs of medications challenge the idea of restricting therapy. Patients with a short-life expectancy (<12 months) who are unlikely to benefit from HC therapy, liver transplantation, or other directed therapy are currently the only populations for whom treatment is not recommended.[34] Importantly, there are no longer any clearly identified contraindications for HCV therapy. In some patients at high risk of transmitting HCV such as PWIDs, HCV treatment may help reduce rates of HCV transmission.[34]

Before therapy is initiated, quantitative HCV testing and genotyping are performed. Quantitative amplification assays for HCV RNA are performed to confirm chronic HCV infection and are used to monitor virologic response once therapy is initiated. Genotyping is also necessary because it may affect the treatment choice and can affect the need for pretreatment resistance testing. An assessment of underlying liver disease is necessary to guide treatment options, need for concomitant ribavirin use, and duration of therapy. Importantly, if patients are identified to have cirrhosis, additional management may be indicated for cirrhosis disease management (eg, need for endoscopy or screening and

surveillance for hepatocellular cancer). Although biopsy was previously recommended, less invasive tests can be used to stage liver disease. The less invasive tests include the use of routine tests and direct serum biomarkers and transient liver elastography. Moreover, the aspartate aminotransferase-to-platelet ratio index (also known as the APRI) or fibrosis-4 index can help identify patients with advanced fibrosis or cirrhosis.[34] Patients with cirrhosis should be staged using the Child-Turcotte Pugh (CTP) score to distinguish compensated or CTP class A cirrhosis, from decompensated or CTP class B or C cirrhosis.

Additionally, all patients should be screened for HBV. There is a risk for potential HBV reactivation in patients with chronic HBV who begin DAA-therapy for HCV, although the mechanism of this reactivation is not understood.

Counseling and Nonpharmacologic Therapy

All patients with chronic HCV should be vaccinated against hepatitis A and B. Lifestyle changes are an important factor in reducing health consequences in hepatitis C. Continued alcohol use is a known risk factor for disease progression and severity. There is no established lower limit of alcohol consumption at which disease progression is not seen. Obesity is also a factor and patients should be encouraged to eat a balanced diet and exercise regularly to maintain a normal weight. Progression of fibrotic changes is associated with obesity. The use of herbal therapy is ineffective and potentially a source of drug interaction with HCV therapies. Patients should be counseled on minimizing HCV transmission risks and harm reduction strategies are recommended by national guidelines.[34]

Pharmacologic Therapy

11 The treatment of chronic HCV was revolutionized with the approval of DAAs. Previously the treatment backbone included the injection of peg-IFN and was associated with a substantial side-effect profile. The current standard of care for all chronic HCV infections, regardless of GT, is an all-oral drug regimen. Despite the change in pharmacological therapy, many patients are aware of the substantial side effects associated with IFN-based therapy and are wary of HCV therapy. It is important to clearly distinguish current therapies from IFN-based ones for patients who are familiar with IFN treatment. **Table 57-13** lists current recommended therapeutic regimens for GT1 treatment-naïve patients. An 8- or 12-week duration of therapy is recommended, depending on whether cirrhosis is present or not.[34] Recommended therapies are ribavirin-free and minimize

treatment duration. Prior treatment experience does not substantially alter retreatment except that there are more limited options for retreatment if patients were previously treated with more recent DAA therapies (Table 57-14). For patients previously treated with an NS5A therapy, the only recommended retreatment is with the combination of sofosbuvir/velpatasvir/voxilaprevir.[34]

TABLE 57-13 AASLD/IDSA Recommended Treatment Regimens for Treatment-Naïve Patients with Hepatitis C Genotypes 1-3 (in alphabetical order)

HCV Genotype	No Cirrhosis	Compensated Cirrhosis (CTP Class A)
1a	Elbasvir/Grazoprevir × 12 weeks[a] Glecaprevir/Pibrentasvir × 8 weeks Ledipasvir/Sofosbuvir × 12 weeks[b] Sofosbuvir/Velpatasvir × 12 weeks	Elbasvir/Grazoprevir × 12 weeks[a] Glecaprevir/Pibrentasvir × 12 weeks Ledipasvir/Sofosbuvir × 12 weeks Sofosbuvir/Velpatasvir × 12 weeks
1b	Elbasvir/Grazoprevir × 12 weeks Glecaprevir/Pibrentasvir × 8 weeks Ledipasvir/Sofosbuvir × 12 weeks[b] Sofosbuvir/Velpatasvir × 12 weeks	Elbasvir/Grazoprevir × 12 weeks Glecaprevir/Pibrentasvir × 12 weeks Ledipasvir/Sofosbuvir × 12 weeks Sofosbuvir/Velpatasvir × 12 weeks
2	Glecaprevir/Pibrentasvir × 8 weeks Sofosbuvir/Velpatasvir × 12 weeks	Glecaprevir/Pibrentasvir × 12 weeks Sofosbuvir/Velpatasvir × 12 weeks
3	Glecaprevir/Pibrentasvir × 8 weeks Sofosbuvir/Velpatasvir × 12 weeks	Glecaprevir/Pibrentasvir × 12 weeks Sofosbuvir/Velpatasvir × 12 weeks[c]

CTP, Child-Turcotte Pugh.

[a]If no NS5A resistance detected.

[b]8-week duration may be considered for patients who are not black, not HIV coinfected, and with an HCV RNA <6 million IU/mL (kIU/L).

[c]Pretreatment resistance testing recommended.

Data from Reference 37.

TABLE 57-14 AASLD/IDSA Recommended Treatment Regimens for Treatment-Experienced Patients with Hepatitis C Genotypes 1-3 (in alphabetical order)

	Peg-Interferon/Ribavirin TE		*NS3 PI + Peg-Interferon TE*	
HCV Genotype	**Non-Cirrhotic**	**Compensated Cirrhosis**	**Non-Cirrhotic**	**Compensated Cirrhosis**
1	Elbasvir/Grazoprevir × 12 weeks[a] Glecaprevir/Pibrentasvir × 8 weeks Ledipasvir/Sofosbuvir × 12 weeksSofosbuvir/Velpatasvir × 12 weeks	Elbasvir/Grazoprevir × 12 weeks[a] Glecaprevir/Pibrentasvir × 12 weeks Sofosbuvir/Velpatasvir × 12 weeks	Ledipasvir/Sofosbuvir × 12 weeks Glecaprevir/Pibrentasvir × 12 weeks Sofosbuvir/Velpatasvir × 12 weeks	Glecaprevir/Pibrentasvir × 12 weeks Sofosbuvir/Velpatasvir × 12 weeks
2	Glecaprevir/Pibrentasvir × 8 weeks Sofosbuvir/Velpatasvir × 12 weeks	Sofosbuvir/Velpatasvir × 12 weeks Glecaprevir/Pibrentasvir × 12 weeks		
3	Sofosbuvir/Velpatasvir × 12 weeks[b]	Elbasvir/Grazoprevir plus Sofosbuvir × 12 weeks Sofosobuvir/Velpatasvir/Voxilaprevir × 12 weeks		

[a]For GT 1a: Recommended treatment if no resistance for NS5A detected.

[b]Resistance testing for Y93 recommended before use; if Y93 present, add ribavirin or use different regimen.

Cirrhosis status also affects the therapeutic options. Patients with decompensated cirrhosis (CTP class B or C) often require concomitant ribavirin and have fewer treatment options due to the underlying level of liver disease and concerns for safety. In general, patients with decompensated cirrhosis should be managed by clinicians with experience of managing end-stage liver disease due to the potential for complications related to cirrhosis developing while on HCV treatment.[34]

The DAAs act on one of three targets on the HCV virion. The DAAs must be used in combination with at least two drugs acting on different targets. The drug nomenclature identifies where the drug is inhibiting viral replication: the N3/4A protease inhibitors end with –previr; NS5A inhibitors end with –asvir; and the NS5B polymerase inhibitors end with –buvir. Early DAAs acted on specific HCV genotypes. Sofosbuvir/velpatasvir, glecaprevir/pibrentasvir, and sofosbuvir/velpatasvir/voxilaprevir are pangenotypic, meaning they are effective in all HCV genotypes. In resource limited areas, the ability to treat without pretreatment genotype testing favors the use of these agents and is an increasingly appealing strategy because it can streamline HCV treatment and reduce costs. As a group, the DAAs are well tolerated and cause few laboratory

abnormalities.

Clinically significant drug–drug interactions are expected with carbamazepine, phenobarbital, phenytoin, oxcarbazepine, rifampin, and St. John's wort and concurrent use of these agents with any of the HCV therapies is expected to result in HCV treatment failure. The use of statins is variable and clinical management can vary from holding statins during HCV therapy to changing or dose reducing the statin. An important resource for timely and updated guidance on HCV-drug interactions is available for free through the University of Liverpool: https://www.hep-druginteractions.org/checker

Sofosbuvir

Sofosbuvir was approved in 2013 for HCV GT1-4 at a dose of 400 mg. Although available as a single product, its use is mostly as the backbone of combination therapies including ledipasvir/sofosbuvir, sofosbuvir/velpatasvir, and sofosbuvir/velpatasvir/voxilaprevir. Sofosbuvir is metabolized to its primary circulating active metabolite GS-331007. Sofosbuvir is well tolerated and has few drug–drug interactions, the majority of drug interactions are related to the agents used in combination with sofosbuvir. Serious symptomatic bradycardia was identified in patients treated with sofosbuvir and taking amiodarone in combination with other DAAs; thus, this combination is not recommended.

Ledipasvir/Sofosbuvir

The fixed dose combination tablet of ledipasvir/sofosbuvir (90 mg/400 mg) is a recommended therapy in patients with HCV GT1 or 4. A 12-week treatment course is highly effective in treatment-naïve patients with or without cirrhosis with an estimated SVR of 95%.[45] Initial studies also demonstrated a high SVR of 94% in patients without cirrhosis, treatment-naïve and with a baseline viral load of less than 6 million IU/mL (kIU/L) treated for 8 weeks. However, due to limited data the level of evidence to support this shorter course of therapy is lower than the 12-week course of treatment and the shorter course is not recommended in patients who have cirrhosis, have a viral load greater than 6 million IU/mL (kIU/L), are Black, or have HIV–HCV coinfection.[34,45] There are no differences in treatment whether patients have GT1a, 1b, or 4; however, there are differences in treatment duration depending on underlying cirrhosis.[46,47] The use of ribavirin did not affect SVR rates and is not routinely recommended. Patients with decompensated cirrhosis are more difficult to treat with lower SVR rates. In these patients, ledipasvir/sofosbuvir plus ribavirin is recommended for

12 weeks of treatment. If patients are unable to tolerated ribavirin due to its hematological effects, ledipasvir/sofosbuvir for 24 weeks is an alternative.[34,48] National guidelines also recommend ledipasvir/sofosbuvir for treatment of HCV GT4 for a 12-week course of therapy.[34]

The combination of ledipasvir/sofosbuvir is well tolerated and can be used in patients with cirrhosis, including CTP Class A, B, and C cirrhosis. Its use in patients with renal insufficiency is limited to patients with an estimated glomerular filtration rate no less than 30 mL/min/1.73 m^2. Headache and fatigue are the most common side effects. Laboratory abnormalities are not frequently encountered. The drug–drug interaction potential is also limited, although amiodarone use is not recommended because of the symptomatic bradycardia observed with the concomitant use of sofosbuvir. Acid suppressive therapy poses a challenge to treatment because ledipasvir requires an acidic environment for absorption. Antacids must be spaced apart by 4 hours whereas histamine blockers should be taken either at the same time or 12 hours apart as ledipasvir/sofosbuvir. The use of proton pump inhibitors is controversial with omeprazole 20 mg once daily recommended by the manufacturer; however, more frequent dosing or higher dosages are expected to compromise the efficacy of ledipasvir.[49] The effect of other proton pump inhibitors is not established and concomitant histamine blockers or antacids must be timed appropriately to avoid a clinically significant drug–drug interaction.

Sofosbuvir/Velpatasvir

Sofosbuvir/velpatasvir as a fixed-dose tablet (400 mg/100 mg) is recommended for use in HCV GT1-6. From the ASTRAL studies 99% SVR was achieved with sofobuvir/velpatasvir in patients with HCV GT1, 2, 4, 5, and 6, irrespective of prior treatment experience or whether patients had cirrhosis or not.[50] In GT3 patients, pretreatment resistance testing is recommended for any patients with cirrhosis or prior treatment experience with pegylated interferon and ribavirin. If the Y93 substitution is detected, ribavirin should be added or an alternative therapy chosen.[34] The need to add ribavirin stems from observations of lower SVR in patients with HCV GT3 and cirrhosis with a detected Y93 substitution as compared to patients without this particular mutation.[51] Subsequent studies showed a numerically higher SVR in patients with HCV GT 3 and cirrhosis who had received concomitant ribavirin, although this did not reach statistical significance.[52]

Sofosbuvir/velpatasvir is well tolerated with few side effects or laboratory

abnormalities. It is recommended for use in patients with all levels of liver disease including decompensated cirrhosis where it is used in combination with ribavirin in order to maximize SVR. Patients with HCV GT1, 2, 3, 4, or 6 and decompensated liver disease treated with sofosbuvir/velpatasvir and ribavirin for 12 weeks achieved an SVR of 94%.[53] Patients with decompensated cirrhosis who cannot tolerate ribavirin may be treated with an extended duration of sofosbuvir/velpatasvir alone for 24 weeks. Most patients with decompensated cirrhosis also demonstrated an improvement in their liver disease (eg, reductions in their Child Pugh score) as a result of treatment. Velpatasvir, like ledipasvir, requires an acidic environment for absorption; thus, it is essential that patients are appropriately counseled to avoid the use of proton pump inhibitors and on timing of other acid suppressive therapy to minimize the drug–drug interaction.

Elbasvir/Grazoprevir

Elbasvir/grazoprevir as a fixed-dose tablet (50 mg/100 mg) is approved for use in patients with HCV GT1 and 4. In the C-EDGE study of treatment-naïve patients with HCV GTs 1, 4, and 6, the overall SVR rate was 95%.[54] Among patients with HCV GT1a, SVR rates were lower than for GT1b and this difference was attributed to the presence of baseline resistance–associated substitutions (RASs). When comparing patients with GT1a versus 1b who did not have any RASs, there was no difference in SVR (99 vs 100% SVR, respectively). However, for patients with baseline RASs and GT1a, the SVR rate dropped to 58%. As a result, in patients with HCV GT1a pretreatment resistance testing is required. If specific mutations are identified, treatment must be modified to include ribavirin and extended to 16 weeks, thus making it an alternative treatment as per guidelines in favor of shorter, ribavirin-free treatments.[34] Elbasvir/grazoprevir is approved for use in patients with HCV GT 1 or 4 and renal insufficiency including hemodialysis.

Glecaprevir/Pibrentasvir

Both glecaprevir and pibrentasvir have pan-genotypic activity against the major HCV GTs and as a combination tablet (100 mg/40 mg) are recommended for use in both treatment-naïve and treatment-experienced patients with HCV GTs 1–6. Moreover, glecaprevir/pibrentasvir is recommended for use in patients with renal insufficiency including patients on hemodialysis. For patients who are treatment naïve and without cirrhosis, the combination is recommended for an 8-week treatment regimen.[34] Patients with compensated cirrhosis or prior treatment

experience must be treated for 12 weeks. The combination was studied in dose finding trials which demonstrated the highest SVR rates ranging from 94% to 100% in patients with HCV GT 1-6 using the currently approved combination tablet. The lowest SVR at 94% was seen in patients with HCV GT3.[55] Baseline mutations for NS3 or NS5A did not affect SVR in clinical trials.[56] However, in patients with prior peginterferon and ribavirin experience with HCV GT3, higher SVR rates were observed with a 16-week course of treatment compared to a 12-week treatment. As a result, glecaprevir/pibrentasvir is considered an alternative treatment for prior interferon experienced patients with HCV GT3.[34]

Although approved for use in patients with prior DAA failure, national guidelines limit the use of glecaprevir/pibrentasvir in this patient population pending further data.[34] Glecaprevir/pibrentasvir is recommended in patients with prior NS3/4A treatment experience (eg, boceprevir or simeprevir). However, glecaprevir/pibrentasvir is an alternative treatment for patients with prior NS5A (eg, ledipasvir) treatment in part due to limited data and the need for an extended 16-week treatment duration in this patient population.[34]

Similar to other DAAs, the combination is not associated with specific laboratory abnormalities and is well tolerated. The most common adverse events include headache and nausea. Glecaprevir/pibrentasvir is contraindicated with ethinyl estradiol products including hormone replacement and oral contraceptives due to a potential for ALT increases.

Sofosbuvir/Velpatasvir/Voxilaprevir

The addition of the pangenotypic protease inhibitor voxilaprevir to sofosbuvir/velpatasvir represents the first triplet regimen against all three targets on the HCV virion. It is available as a combination tablet (100 mg voxilaprevir / 400 mg sofosbuvir/100 mg velpatasvir). Although effective in both treatment-naïve and treatment-experienced patients, the triplet regimen is reserved for patients who have failed prior DAA therapies and represents the last available combination for HCV therapy.[34] Although sofosbuvir/velpatasvir can be safely used in patients with decompensated cirrhosis, due to the presence of the protease inhibitor voxilaprevir, the triplet regimen cannot be used in patients with decompensated cirrhosis.

In patients with HCV GT1-6 who were previously treated with a DAA course including an NS5A agent, a retreatment course of sofosbuvir/velpatasvir/voxilaprevir achieved an SVR of 99%.[57] A lower SVR was seen in patients with cirrhosis at 93%; however, baseline resistance

mutations were not associated with reduced SVR. The combination is also recommended in patients with HCV GT3 who are more difficult to treat including patients with cirrhosis or a known Y93 mutation (ie, patients with prior treatment experience with pegylated interferon and ribavirin tested for GT3 mutations).[34]

Ribavirin

Ribavirin continues to be used in combination with DAAs, although its use has been minimized when alternative treatments are available that are highly effective and ribavirin-free. There are some situations that continue to require ribavirin in order to improve SVR rates, such as in patients with decompensated cirrhosis or those with HCV GT3. The mechanism of action of ribavirin is not well understood. Ribavirin is a synthetic guanosine analog and is ineffective as a monotherapy for HCV. The most common adverse effect of ribavirin is hemolytic anemia, necessitating close monitoring during HCV therapy and contributing to complaints of fatigue during treatment. In addition, ribavirin is a teratogenic agent, Pregnancy Category X, and women of childbearing age as well as female partners of male patients who undergo HCV treatment with ribavirin need to practice two forms of contraception during HCV treatment and for 6 months after to avoid pregnancy.[34]

Special Populations

Clinical trials are conducted with a patient population that generally does not reflect the patient spectrum encountered in clinical practice. HCV infections are associated with patients who may be less likely to be engaged in routine healthcare and underrepresented in clinical trials. Treatment guidelines address some of these higher risk populations and include recommendations for enhanced screening as well as treatment.[34] Published recommendations for treatment in various populations are as follows:

Patients with Decompensated Cirrhosis

Patients with decompensated cirrhosis, defined as CTP class B or C cirrhosis, are at high risk for developing complications of their end-stage liver disease and thus are recommended to be treated by clinicians with expertise in managing decompensated cirrhosis. (AASLD) As a class, the protease inhibitors are not recommended in patients with decompensated cirrhosis due to the risk of further decompensation. The only therapies recommended for use in decompensation

include ledipasvir/sofosbuvir, sofosbuvir/velpatasvir, and daclatasvir with sofosbuvir.

Acute Exposures

Up to 50% of patients will spontaneously clear an HCV infection and the majority will do so within the first 6 months of exposure.[58] However, due to the increase in HCV transmission and the impact on public health, the strategy to wait to treat HCV is under question because HCV transmission may occur during this time and deferring treatment risks losing opportunity to treat if patients become lost to follow up.

Persons Who Inject Drugs

Injection drug use is not a contraindication to therapy and treatment of PWIDs will be necessary to reduce HCV transmission.[59] Treatment of PWIDs is recommended as part of a comprehensive harm-reduction effort, ideally in a multidisciplinary setting.[34,59] Studies in PWIDs suggest treatment outcomes are comparable to rates in those in clinical trials among noninjection drug users and reinfection rates among PWID are low.[60] However, access to HCV therapies is limited as many insurers refuse coverage of HCV therapies in the setting of active drug use.

Alcoholism

Alcohol cessation is recommended for all patients with liver disease. However, due to the short-treatment course, safety profile of the DAAs, and the ability to cure HCV, ongoing alcohol use is not a reason to prevent or defer HCV treatment.

End-Stage Renal Disease

Glecaprevir/pibrentasvir is the only pan-genotypic HCV therapy approved for use in renal insufficiency including hemodialysis. Elbasvir/grazoprevir is also approved but limited to HCV GT1 and 4.

Patients with HCV GT3

In patients with prior TE or underlying cirrhosis and infection with HCV GT3, a more aggressive treatment strategy is recommended due to the observed lower SVR rates as compared to other GTs. For patients who are GT3 and have prior

peginterferon/ribavirin experience, sofosbuvir/velpatasvir is recommended due to the need for longer treatment with glecaprevir/pibrentasvir. Patients who are to be treated using sofosbuvir/velpatasvir who have cirrhosis or have prior TE, pretreatment resistance testing is required. If the Y93 mutation is identified, either ribavirin is added to the treatment course or therapy switched to sofosbuvir/velpatasvir/voxilaprevir.

DAA-Experienced Patients

Patients who failed a course of DAA therapy can be retreated with sofosbuvir/velpatasvir/voxilaprevir if they do not have cirrhosis or have compensated cirrhosis. There are no recommendations for pretreatment resistance testing in this population and given the small number of patients who failed DAA therapy, it is difficult to predict who will fail DAA treatments. Although sofosbuvir/velpatasvir/voxilaprevir is highly effective as a retreatment strategy, given the observations for lower overall SVR in patients with GT3, national guidelines recommend the addition of ribavirin in patients who have GT3, cirrhosis, and prior treatment experience with an NS5A agent.[34,57]

HIV Coinfection

Current guidelines do not distinguish separate treatment recommendations for HIV–HCV coinfection. Potential drug–drug interaction concerns between HCV DAAs and HIV antivirals do merit careful scrutiny and may necessitate antiretroviral drug changes.[34] Sofosbuvir has few clinically significant drug–drug interactions. Daclatasvir has potential for some drug–drug interactions; however, the option to adjust the dose of daclatasvir may mitigate the clinical significance of the interactions. Ledipasvir and velpatasvir increase tenofovir disoproxil levels and may increase the risk of tenofovir-associated renal toxicity; however, this risk appears to be minimized with the availability of tenofovir alafenamide. The combination of ombitasvir/paritaprevir/ritonavir and dasabuvir includes ritonavir as a pharmacokinetic booster; therefore, HIV antiretrovirals which use ritonavir are not recommended or require dosing without ritonavir. Additional drug–drug interactions exist that may require changes in HIV antivirals. Glecaprevir/pibrenasvir exposure can increase when combined with elvitegravir/cobicistat with a concern for potential resultant hepatic toxicity. Pending more data, concomitant use necessitates more frequent monitoring for worsening liver function. HIV treatment poses additional problems because of hepatotoxicity issues associated with HAART, hepatic complications from HIV-associated diseases, as well as flares in hepatitis as CD4 counts recover. In

general, treatment is recommended with coadministration of HIV and HCV therapies. With the exception of didanosine and zidovudine, ribavirin may be used with few drug interactions.

Children

Ledipasvir/sofosbuvir is approved for use in children 3 years of age and older or those weighing 35 kg and above for the treatment of HCV GT1,4,5 or 6.[34] Additional studies are ongoing with younger children at reduced dosages. Children with HCV GT 2 or 3 may be treated with sofosbuvir and ribavirin. The treatment duration is 12 weeks if no cirrhosis or extended to 24 weeks if cirrhosis is present. Glecaprevir/pibrentasvir is also approved children 12 years of age and older.

Post-Organ Transplant

Given the high efficacy of the DAAs and the number of HCV-positive organ donors, some organ transplant centers are offering HCV-positive organs to HCV-negative patients. Both glecaprevir/pibrentasvir and ledipasvir/sofosbuvir with ribavirin can be used in patients post liver transplant for a 12-week treatment course. The use of glecaprevir/pibrentasvir is restricted to patients without cirrhosis whereas ledipasvir/sofosbuvir plus ribavirin can be used in compensated and decompensated cirrhosis. In patients undergoing renal transplant, glecaprevir/pibrentasvir is preferred due to its safety and efficacy in patients with renal impairment.

Prevention

No vaccine is available for HCV. It is unlikely that a vaccine will be developed in the near future because of the mutagenesis of the virus. Patients infected with HCV should be counseled to not donate blood, organ, or semen. Although the likelihood of household transmission is small, patients should minimize risks by avoiding possible blood or mucus exposure, such as not sharing razors or toothbrushes and covering open wounds. Patients who continue to use illegal drugs should avoid sharing all drug paraphernalia, as risk of transmission is not limited to needles and syringes.

Postclass Engaged Learning Activity

Identify a manuscript regarding the use of DAA therapy in patients with chronic HCV infection who are on medication-assisted therapy or have active injection drug use. Write a brief summary about the study's methods, major findings, and how this information might affect current HCV practice.

This activity is intended to build your literature evaluation skills and ability to critically appraise research manuscripts.

ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
ACIP	Advisory Committee on Immunization Practices
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
Anti-HAV	antibody to hepatitis A virus
Anti-HBsAg	antibody to HBsAg
APRI	aminotransferase-to-platelet ratio index
CDC	Centers for Disease Control and Prevention
CTP	Child-Turcotte Pugh
DAA	direct-acting antiviral
ELISA	enzyme-linked immunosorbent assay
ESLD	end-stage liver disease
FDA	Food and Drug Administration
GI	gastrointestinal
GT	genotype
HAART	highly active antiretroviral therapy
HAV	hepatitis A virus
HBcAg	hepatitis B core antigen
HBeAg	hepatitis B e-antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IDSA	Infectious Diseases Society of America
IFN	interferon
Ig	immunoglobulin
IM	intramuscular
IV	intravenous
MSM	men who have sex with men
NAs	nucleos(t)ide analogs
peg-IFN	pegylated interferon
PI	protease inhibitor
PWID	persons who inject drugs
SVR	sustained virologic response
TAF	Tenofovir alafenamide fumarate
TDF	Tenofovir disoproxil fumarate
USPSTF	United States Preventative Services Task Force
WHO	World Health Organization

REFERENCES

1. Department of Health and Human Services. *National Viral Hepatitis Action Plan 2017-2020*. Available at: https://www.hhs.gov/sites/default/files/National%20Viral%20Hepatitis%20 2020.pdf. Accessed September 23, 2018.
2. Centers for Disease Control and Prevention. Surveillance for Viral Hepatitis—United States. 2016 Available at: https://www.cdc.gov/hepatitis/statistics/2016surveillance/index.htm. Accessed September 1, 2018.
3. Centers for Disease Control and Prevention. Emergency Preparedness and Response, Health Alert Network. *Outbreak of hepatitis A virus (HAV) infections among persons who use drugs and persons experiencing homelessness*. June 11, 2018. Available at: https://emergency.cdc.gov/han/han00412.asp. Accessed August 7, 2018.
4. American Sexual Health Association. Hepatitis A. 2018. Available at: http://www.ashasexualhealth.org/stdsstis/hepatitis/hepatitis-a/. Accessed September 23, 2018.
5. Hofmeister MG, Klevens RM, Nelson N. *Hepatitis A*. Centers for Disease Control and Prevention. *Manual for the Surveillance of Vaccine-Preventable Disease*. Atlanta, GA: 2008 (updated May 18, 2018). Available at: https://www.cdc.gov/vaccines/pubs/surv-manual/chpt03-hepa.html. Accessed September 23, 2018.
6. Centers for Disease Control and Prevention. Prevention of hepatitis A through active or passive immunizations: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2006;55(RR07):1–23.
7. Nelson NP. Infectious diseases related to travel: Hepatitis A. In: Centers for Disease Control and Prevention, ed. CDC Yellow Book 2018: Health Information for International Travel. New York: Oxford University Press; 2017. https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/hepatitis-a.
8. Jablonowska E, Kuydowicz J. Durability of response to vaccination against viral hepatitis A in HIV-infected patients: A 5-year observation. *Int J STD AIDS*. 2014;25(10):745–750.
9. World Health Organization. Hepatitis B. July 18, 2018. Available at: http://www.who.int/news-room/fact-sheets/detail/hepatitis-b. Accessed September 14, 2018.
10. World Health Organization. Guidelines for the prevention, care, and

treatment of persons with chronic hepatitis B infection. 2015. Available at: http://apps.who.int/iris/bitstream/10665/154590/1/9789241549059_eng.pdf ua=1&ua=1. Accessed September 25, 2018.

11. Centers for Disease Control and Prevention. In: Hamborsky J, Kroger A, Wolfe S, eds. Epidemiology and Prevention of Vaccine-Preventable Diseases. 13th ed. Washington, DC: Public Health Foundation; 2015. The Pink Book Hepatitis B.
12. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B; AASLD 2018 Hepatitis B Guidance. *Hepatology*. 2018:67;1560–1599.
13. Tong S, Revill P. Overview of hepatitis B viral replication and genetic variability. *J Hepatol*. 2016;64:S41–S48.
14. European Association for the Study of the Liver. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. *J Hepatol*. 2017;67:370–398.
15. Reddy RK, Beavers KL, Hammond SP, et al. American Gastroenterological Association Institute guideline on prevention and treatment of hepatitis B reactivation during immunosuppressive drug therapy. *Gastroenterology*. 2015;148:215–219.
16. Perrillo RP, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology*. 2015;148:221–244.
17. Kennedy K, Graham SM, Arora N, et al. Hepatocellular carcinoma among US and non–US-born patients with chronic hepatitis B: Risk factors and age at diagnosis. *PLoS One*. 2018;13:e0204031.
18. U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion. Healthy People 2020. Washington, DC. Accessed September 15, 2018. Available from: https://www.healthypeople.gov/2020/topics-objectives/topic/immunization-and-infectious-diseases/objectives.
19. Schillie S, Vellozzi C, Reingold A, et al. Centers for Disease Control and Prevention (CDC). Prevention of hepatitis B virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2018; 67:1–31.
20. Yu MW, Lin CL, Yang SH, et al. Influence of metabolic risk factors on risk of hepatocellular carcinoma and liver-related death in men with

chronic hepatitis B: A large cohort study. *Gastroenterology*. 2017;153:1006–1017.

21. Kim JH, Sinn DH, Gwak GY, et al. Insulin resistance and the risk of hepatocellular carcinoma in chronic hepatitis B patients. *J Gastroenterol Hepatol*. 2017;32:1100–1106.
22. Terrault N, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology*. 2016;63:261–283.
23. Buti M, Tsai N, Petersen J, et al. Seven-year efficacy and safety of treatment with tenofovir disoproxil fumarate for chronic hepatitis B virus infection. *Dig Dis Sci*. 2015;60(5):1457–1464.
24. Agarwal K, Brunetto M, Seto WK, et al. 96 weeks treatment of tenofovir alafenamide vs tenofovir disoproxil fumarate for hepatitis B virus infection. *J Hepatol*. 2018;68:672–681.
25. Seto WK, Asahina Y, Brown TT, et al. Improved bone safety of tenofovir alafenamide compared to tenofovir disoproxil fumarate over 2 years in patients with chronic HBV infection. Clin Gastroenterol Hepatol. 2018. doi: 10.1016/j.cgh.2018.06.023.[Epub ahead of print].
26. Cathcart AL, Chan HL, Bhardwaj N, et al. No resistance to tenofovir alafenamide detected through 96 weeks of treatment for chronic hepatitis B infection. *Antimicrob Agents Chemother*. 2018;62: pii: e01064-18. doi: 10.1128/AAC.01064-18.
27. Gish R, Jia J-D, Locarnini S, Zoulim F. Selection of chronic hepatitis B therapy with a high barrier to resistance. *Lancet Infect Dis*. 2012;12:341–354.
28. Lim YS, Yoo BC, Byun KS, et al. Tenofovir monotherapy versus tenofovir and entecavir combination therapy in adefovir-resistant chronic hepatitis B patients with multiple drug failure: results of a randomized trial. *Gut*. 2016;65:1042–1051.
29. Gupta N, Goyal M, Wu CH, Wu GY. The molecular and structural basis of HBV-resistance to nucleos(t)ide analogs. *J Clin Transl Hepatol*. 2014;2:201–211.
30. Giang L, Selinger CP, Lee AU. Evaluation of adherence to oral antiviral hepatitis B treatment using structured questionnaires. *World J Hepatol*. 2012;4:43–49.
31. Ly KN, Xing J, Klevens M, Jiles RB, Ward JW, Holmberg SD. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. *Ann Internal Med*. 2012;156:271–278.

32. Ward J. Perspective: The hidden epidemic of hepatitis c virus in the United States: Occult transmission and burden of disease. *Top Antivir Med*. 2013;21:15–19.
33. Smith BD, Morgan RL, Beckett GA, et al. Centers for Disease Control and Prevention. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. *MMWR Recomm Rep*. 2012;61(RR-4):1–18.
34. AASLD/IDSA. Recommendations for testing, managing, and treating hepatitis C. Available at: http://www.hcvguidelines.org. Accessed October 14, 2018.
35. Conrad C, Bradley HM, Broz D, et al. Community outbreak of HIV infection linked to injection drug use of oxymorphone—Indiana, 2015. *MMWR*. 2016;64(16):443–444.
36. Terrault NA, Dodge JL, Murphy EL, et al. Sexual transmission of HCV among monogamous heterosexual couples: The HCV partners study. *Hepatology*. 2013;57:881–889.
37. Joy JB, McCloskey RM, Nguyen T, et al. The spread of hepatitis C virus genotype 1a in North America: A retrospective phylogenetic study. *Lancet Infect Dis*. 2016;16:698–702.
38. Centers for Disease Control. Testing for HCV infection: An update of guidance for clinicians and laboratorians. *MMWR*. 2013;62(18):362–365.
39. Kanto T, Hayashi N. Immunopathogenesis of hepatitis C virus infection: Multifaceted strategies subverting innate and adaptive immunity. *Intern Med*. 2006;45:183–191.
40. Centers for Disease Control and Prevention. Hepatitis C FAQs for health professionals. Available at: http://www.cdc.gov/hepatitis/hcv/hcvfaq.htm. Accessed September 17, 2018.
41. Kanwal F, Kramer JR, Ilyas J, Duan Z, El-Serag HB. HCV genotype 3 is associated with an increased risk of cirrhosis and hepatocellular cancer in a national sample of U.S. Veterans with HCV. *Hepatology*. 2014;60(1):98–105.
42. Sherman AC, Sherman KE. Extrahepatic manifestations of hepatitis C: Navigating CHASM. *Curr HIV/AIDS Rep*. 2015;12(3):353–361.
43. Kasting ML, Giuliano AR, Reich RR, et al. Hepatitis C virus screening trends: Serial cross-sectional analysis of the national health interview survey population, 2013-2015. *Cancer Epidemiol Biomarkers Prev*. 2018;27:503–513.

44. U.S. Preventive Services Task Force. Final Update Summary: Hepatitis C: Screening. July 2015. Available at: http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSum c-screening. Accessed September 17, 2015.
45. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med*. 2014;370:1879–1888.
46. Afdhal N, Zeuzem S, Kwo P, et al. for the ION-1 Investigators. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med*. 2014;370:1889–1898.
47. Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med*. 2014;370:1483–1493.
48. Charlton M, Everson GT, Flamm SL, et al. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. *Gastroenterology*. 2015;149:649–659.
49. Tapper EB, Bacon BR, Curry MP, et al. Real-world effectiveness for 12 weeks of ledipasvir-sofosbuvir for genotype 1 hepatitis C: the Trio Health Study. *J Viral Hepat*. 2017;24:22–27.
50. Feld JJ, Jacobson IM, Hézode C, et al. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. *N Engl J Med*. 2015;373(27):2599–2607.
51. Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. *N Engl J Med*. 2015.373(27):2608–2617.
52. Esteban R, Pineda JA, Calleja L, et al. Efficacy of sofosbuvir and velpatasvir, with or without ribavirin, in patients with HCV genotype 3 infection and cirrhosis. *Gastroenterology*. 2018. doi:10.1053/j.gastro.2018.06.042.
53. Curry MP, O'Leary JG, Bzowej N, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. *N Engl J Med*. 2015b: 373(27):2618–2628.
54. Zeuzem S, Ghalib R, Reddy KR, et al. Grazoprevir-elbasvir combination therapy for treatment-naive cirrhotic and noncirrhotic patients with chronic hepatitis C virus genotype 1, 4, or 6 infection: A randomized trial. *Ann Intern Med*. 2015;163(1):1–13.
55. Kwo PY, Poordad F, Asatryan A, et al. Glecaprevir and pibrentasvir yield high response rates in patients with HCV genotype 1-6 without cirrhosis. *J*

Hepatol. 2017;67:263–271.

56. Gane E, Poordad F, Wang S, et al. High efficacy of ABT-493 and ABT-530 treatment in patients with HCV genotype 1 or 3 infection and compensated cirrhosis. *Gastroenterology*. 2016b;151:651–659.
57. Bourliere M, Gordon SC, Flamm SL, et al. Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection. *N Engl J Med*. 2017;376:2134–2146.
58. Kamal SM. Acute hepatitis C: A systematic review. *Am J Gastroenterol*. 2008;103(5):1283–1297.
59. Doyle JS, Aspinall EJ, Hutchinson SJ, et al. Global policy and access to new hepatitis C therapies for people who inject drugs. Int J Drug Policy. 2015;26(11):1064–1071.
60. Aspinall EJ, Corson S, Doyle JS, et al. Treatment of hepatitis C virus infection among people who are actively injecting drugs: A systematic review and meta-analysis. *Clin Infect Dis*. 2013;57(suppl 2):S80–S89.

58

Celiac Disease

Priti N. Patel, and Robert A. Mangione

KEY CONCEPTS

1. Celiac disease is a chronic, small intestinal immune-mediated enteropathy caused by intolerance to gluten found in wheat, barley, rye, and other foods when a genetically predisposed person is exposed to the environmental trigger, gluten.
2. The prevalence of celiac disease is 0.7% in America and appears to be increasing in prevalence worldwide.
3. The integrity of the tissue junctions of the intestinal epithelium is compromised in patients with celiac disease; this enables gluten to reach the lamina propria. The presence of gluten in the lamina propria and an inherited combination of genes contribute to the heightened immune sensitivity to gluten that is found in patients with celiac disease.
4. The classic presenting symptom is diarrhea, which may be accompanied by abdominal pain or discomfort; however, it is noteworthy that during the past decade diarrhea has been reported as the main presenting symptom of celiac disease in less than 50% of cases.
5. Dermatitis herpetiformis is a skin manifestation of small intestinal immune-mediated enteropathy caused by exposure to dietary gluten.
6. The frequency of diagnosis of patients with celiac disease has increased; however, the majority of patients with this condition remain undiagnosed.
7. The confirmation of a diagnosis of celiac disease should be based on a combination of findings from the medical history, physical examination, serology, and duodenal biopsy. The recommended serologic marker that is used for screening patients is serum antitissue transglutaminase antibody.
8. Strict, lifelong adherence to a gluten-free diet is the only treatment for celiac disease that is currently available.

9 Clinicians must evaluate the patient with celiac disease for nutritional deficiencies (including folic acid, vitamin B_{12}, fat-soluble vitamins, iron, and calcium) due to malabsorption.

Preclass Engaged Learning Activity

Watch the video "CDF: What is it All About?" at https://tinyurl.com/y4qw5eg4 by Peter HR Green, MD; Celiac Disease Center, Columbia University. This video gives an overview of celiac disease, its burden on patients and caregivers, and gluten.

Watch the video "The Gluten Free Diet: Beyond the Basics" at https://tinyurl.com/y675k8f8 by Janelle Smith, MS, RD; Celiac Disease Foundation. This video discussed the gluten-free diet, the mainstay of treatment of celiac disease.

INTRODUCTION

1 Celiac disease is a small intestinal immune-mediated enteropathy caused by intolerance to ingested gluten, a storage protein found in wheat, barley, and rye. Genetic, environmental, and immune factors all play a role in the development of celiac disease. The mainstay of treatment of the disease is strict, lifelong adherence to a gluten-free diet.[1,2]

A disease resembling celiac disease was first described by a Greek physician in the second century AD.[3] In the mid-1900s, the connection between the ingestion of cereals and celiac disease was made. For many years, celiac disease was considered a disease of childhood with primarily GI symptoms. It is now recognized as a disease of all ages with varied presentation.

Celiac disease has been known as celiac sprue, nontropical sprue, and gluten-sensitive enteropathy; however, these terms are currently not recommended. The nonspecific use of celiac disease–related terminology may lead to misunderstandings. Accepted terms associated with celiac disease should be used and understood when engaging in patient consultations or discussions with other healthcare providers. The publication of the Oslo Definitions has helped to address this concern.[1]

The disease is characterized by both GI and extraintestinal symptoms.

Chronic inflammation caused by exposure to gluten leads to GI discomfort, nutrient malabsorption, and systemic complications. GI symptoms, including diarrhea, cramping, bloating, and flatulence, are the “classic” symptoms; however, a patient with celiac disease may initially present with a variety of extraintestinal symptoms. Patients with subclinical celiac disease have no or minimal symptoms but manifest mucosal damage on biopsy and have positive serologic testing. Patients with celiac disease classified as potential are asymptomatic patients who may show positive serology and have the human leukocyte antigen (HLA)-DQ2 and/or DQ8 haplotype, but have normal mucosa on biopsy.[1,4]

Adherence to a gluten-free diet is essential because it improves symptoms and prevents long-term complications of celiac disease, which include T-cell lymphomas, small bowel adenocarcinoma, and esophageal and oropharyngeal carcinomas.[5]

EPIDEMIOLOGY

2 Originally thought to be a pediatric disease, celiac disease is now being diagnosed in increasing numbers of both adult and pediatric patients due to increased awareness and improved diagnostic techniques.[6] Celiac disease is common in Europe and North America. The prevalence of the disease is 0.71% to 0.79% in the United States, affecting up to 1% of non-Hispanic whites.[7,8] Similar to other autoimmune diseases, the prevalence of celiac disease is higher in females than in males at a rate of 1:2.8.[9] In Finland and the United States, the prevalence of celiac disease has increased fourfold during the past 50 years.[10]

Celiac disease has been less well studied in other parts of the world. Previously believed to rarely occur in nonwhite populations, improved screening and diagnostic techniques now provide evidence that the prevalence of celiac disease in many non-Western nations is similar to that in Europe and North America.[11] The common and increasing use of wheat in diets, coupled with the prevalence of HLA-DQ2, may lead to an increase in the prevalence of celiac disease in the global population in coming years in areas where celiac disease is currently rarely diagnosed.[12,13]

ETIOLOGY

Celiac disease is known to occur when a genetically predisposed person ingests

gluten. Wheat gluten proteins exist in two fractions: gliadins and glutenins. Proteins similar to glutenins, called hordeins and secalins, are found in barley and rye, respectively. **Table 58-1** refers to grains and other foods that do and do not contain gluten and related proteins. Wheat, barley, and rye are all derived from the Triticeae tribe of the grass (Gramineae) family. Ingestion of any of these proteins will lead to an autoimmune response in celiac disease patients. Oats, from the Aveneae tribe, are distantly related and therefore contain fewer disease-activating proteins.[15] One concern with oats is that they may be contaminated with gluten during the manufacturing process.[15]

TABLE 58-1 Grains and Other Foods that Do and Do Not Contain Gluten

Contain Gluten	Do Not Contain Gluten
Wheat	Amaranth
Barley	Buckwheat
Rye	Corn
Bran	Flax
Graham flour	Millet
Spelt	Potato flour
Wheat germ	Quinoa
Triticale	Rice
Oats[a]	Sorghum
	Soybeans
	Tapioca
	Teff

[a]Oats are in a different plant family, but they have also been regarded as problematic, although the ingestion of certified pure gluten-free oats appears to be safe in most patients with celiac disease.[14] Due to the continued difference of opinion regarding the safety of oats, patients are generally advised to discuss the risks and benefits associated with consuming oats with their healthcare provider before they include oats in their diet.

Genetic factors, in combination with exposure to gluten, are necessary for the development of celiac disease. There is a concordance rate of 85% in monozygotic twins indicating that genetics play a large role in the disease, but other factors also are likely to involved.[16,17]

Virtually all patients with celiac disease have variants of HLA-DQ2 or HLA-DQ8 molecules that are expressed on the surface of antigen-presenting cells.[4,5] Other non-HLA genes may also play a role in enhancing genetic susceptibility to

celiac disease.[18]

Various infections and compounds may contribute to the development of celiac disease. Gastrointestinal, upper respiratory, and lower respiratory infections are risk factors for the development of celiac disease. Various drugs, such as olmesartan, azathioprine, methotrexate, as well as others, may play a role in the development of sprue-like bowel disease.[3]

In Sweden, increased rates of diagnosis of celiac disease in the mid-1980s was thought to correspond to a change in infant feeding practices. However, multinational studies show that the timing of gluten introduction or duration of breastfeeding did not avoid the eventual diagnosis of celiac disease, even at children at higher risk due to the presence of one of the high risk HLA haplotypes.[18]

PATHOPHYSIOLOGY

3 During normal digestion, peptides that remain from gastric or pancreatic digestion are broken down into amino acids, dipeptides, or tripeptides by the small intestinal brush-border membrane enzymes.[18] These GI proteases that are found in the intestinal lumen are one of the body's first defenses against potentially toxic dietary proteins.[19,20] The intestinal epithelium, with its intact intercellular tight junctions, functions as the primary barrier to the passage of macromolecules into the lamina propria. Gluten is unusually rich in the amino acids glutamine and proline, which enable part of the molecule to withstand the digestive processes. These peptides are kept within the GI tract and are primarily excreted before they can illicit an immune reaction. Small fractions of gluten do cross this important defense barrier in patients without celiac disease; however, the quantity of gluten that passes across the GI lining is generally insufficient to illicit a significant response from a normally functioning immune system.[19,25]

Pathophysiology of celiac disease is associated with an interaction between gluten and immune, genetic, and environmental factors.[19] In celiac disease, the integrity of the tissue junctions of the intestinal epithelium is compromised, enabling gluten to reach the lamina propria through different routes. The presence of gluten in the lamina propria and an inherited combination of genes contribute to the heightened immune sensitivity to gluten found in patients with celiac disease (**Table 58-2**).[19] The notable immune response to gluten consists of both adaptive and innate immune responses that occur only in individuals who carry the HLA type DQ2 or DQ8.[19] The precise mechanism by which the

immune system leads to damage of the intestinal lining of patients with celiac disease continues to be studied.

TABLE 58-2 Proposed Pathophysiology of Celiac Disease

- Enterocytes release the protein zonulin in response to the presence of indigestible fragments of gluten in the intestine
- Zonulin loosens the intercellular tight junctions
- Abundant quantities of gluten fragments cross the intestinal lining and accumulate under the enterocytes (epithelial cells)
- Gluten induces the enterocytes to secrete interleukin-15 (IL-15)
- IL-15 induces an immune response of intraepithelial lymphocytes against the enterocytes
- The damaged cells release the enzyme tissue transglutaminase (tTG), which modifies the gluten
- Antigen-presenting cells of the immune system join the modified gluten to human leukocyte antigen (HLA) molecules and display the resulting complexes to other immune cells (ie, helper T cells)
- Helper T cells that recognize the complexes secrete molecules that attract other immune cells, which may result in damage to the enterocytes
- Helper T cells spur killer T cells that directly attack the enterocytes
- B cells release antibody molecules that are targeted to gluten and tTG (the role that these antibodies play remains to be further clarified; however, they may cause further damage when they contact their targets on or near the enterocytes)
- Enterocytes are disabled or killed

Data from Reference 19.

Nonceliac gluten sensitivity is a condition in which the ingestion of gluten results in morphological or symptomatic manifestations in the absence of celiac disease.[21] This disorder must therefore be considered in the differential diagnosis of celiac disease. Symptoms alone cannot reliably differentiate celiac disease from nonceliac gluten sensitivity. Therefore, a diagnostic evaluation including celiac serology and small-intestinal biopsy (while the patient is including gluten in their diet) is needed. If these tests are negative, HLA-DQ typing is required to differentiate between the two disorders. Differentiating between these disorders is important as it will impact upon the implications of the level of adherence to the gluten-free diet, approach to continued disease-state monitoring and evaluation, and the counseling of family members (as nonceliac disease sensitivity does not appear to have a strong hereditary basis).[5]

The primary toxic components of wheat gluten are a family of closely related proteins called gliadins.[19] The gliadin peptides induce changes in the epithelium

through innate immunity and in the lamina propria through adaptive immunity.[19]

Tissue transglutaminase (tTG), a ubiquitous enzyme that catalyzes posttranslational modification of proteins and is released during inflammation, may play at least two crucial roles in celiac disease by serving as the main target autoantigen for antiendomysial enzymes and as a deaminating enzyme that raises the immunostimulatory effect of gluten. Expression and activity of tTG are raised in the mucosa of patients with celiac disease.[20] This enzyme, by deaminating glutamine to glutamic acid, makes the gliadin peptides become negatively charged and therefore more capable of fitting into pockets of the HLA-DQ2 (or HLA-DQ8) antigen-binding groove on the antigen-presenting cells.[20,22] Gliadin is presented to gliadin-reactive CD4 T cells through a T-cell receptor, which then results in the production of cytokines that cause tissue damage. This then leads to villous atrophy, crypt hyperplasia, and the expansion of antibody-producing B cells found in celiac disease.[22]

CLINICAL PRESENTATION

4 The recognition of celiac disease may be quite challenging due to the wide range of presenting symptoms, which includes patients who are asymptomatic.[20] Clinical manifestations of celiac disease significantly vary with age group (**Table 58-3**) in that pediatric patients are more likely to experience classic gastrointestinal symptoms while adults are more likely to have atypical symptoms.[24] Infants and young children generally experience diarrhea, abdominal distention, and failure to thrive. Vomiting, irritability, anorexia, and even constipation are also common in these young patients. Extraintestinal manifestations such as short stature, neurologic findings (eg, peripheral neuropathy, ataxia, seizure, migraine, and dementia), or anemia are often found in older children and adolescents.[24] The classic presenting symptom in adults is diarrhea, which may be accompanied by abdominal pain or discomfort; however, during the past decade diarrhea has been reported as the main presenting symptom of celiac disease in less than 50% of cases.[21] Adults may exhibit iron-deficiency anemia or osteoporosis. Less common but important presentations of celiac disease in adults include abdominal pain, constipation, weight loss, neurologic symptoms, dermatitis herpetiformis, hypoproteinemia, hypocalcemia, and elevated liver enzymes. Patients with celiac disease without gastrointestinal symptoms often experience symptoms for a long period of time before celiac disease is diagnosed.[25]

TABLE 58-3 Selected Signs and Symptoms of Celiac Disease

Children	Adults
Symptoms	Symptoms
• Fatigue	• Abdominal pain
• Bloating	• Chronic diarrhea
• Constipation	• Abdominal distension
• Abdominal pain	• Recurrent spontaneous abortion
• Chronic diarrhea	• Peripheral neuropathy
• Irritability	• Depression
• Vomiting	• Fatigue/malaise
Signs	• Ataxia
• Muscle wasting	Signs
• Failure to thrive/weight loss	• Weight loss
• Short stature	• Infertility
• Delayed puberty	• Dermatitis herpetiformis
• Osteopenia/osteoporosis	• Hepatitis
• Hepatitis	• Anemia
• Dental anomalies	• Aphthous ulcers
• Anemia	• Alopecia
	• Malignancy
	• Seizures
	• Osteopenia/osteoporosis
	• Arthritis

Data from Reference 23.

5 Dermatitis herpetiformis is a skin manifestation of small intestinal immune-mediated enteropathy caused by the ingestion of gluten.[1] It occurs more often in males and in patients 30 to 40 years old.[26] This extremely pruritic, bullous skin rash is generally found on the elbows, knees, buttocks, and scalp but can occur anywhere on the body.[26] Although dermatitis herpetiformis was once considered to be a skin disease often found in patients with celiac disease, it may be a cutaneous manifestation of gluten sensitivity.[30] Both celiac disease and dermatitis herpetiformis are mediated by IgA antibodies and are triggered by the ingestion of gluten. Epidermal transglutaminase is an important autoantigen closely linked to dermatitis herpetiformis.[27]

6 The diagnosis of celiac disease is based on clinical suspicion and confirmation with laboratory tests and duodenal biopsy.[5] Although the prevalence of celiac disease has increased, many patients with this condition remain undiagnosed.[5] This is particularly concerning as undiagnosed celiac disease has been associated with a nearly fourfold increased risk of death compared with subjects without serologic evidence of disease.[10]

Healthcare providers should recognize the many and diverse possible symptoms of celiac disease.[21] Only 11% of cases are diagnosed in a timely manner, with an average reported period of 5.8 to 11.7 years from the onset of symptoms to the diagnosis.[28] Clinicians can help reduce the time from the onset of symptoms to the diagnosis of celiac disease by being aware of the common diseases that may also coexist with celiac disease (**Table 58-4**).[28]

TABLE 58-4 Selected Common Misdiagnoses

- Irritable bowel syndrome
- Viral gastroenteritis
- Lactose intolerance
- Amoebic/parasitic infection
- Inflammatory bowel disease
- Psychological dysfunction
- Gallbladder disease
- Chronic fatigue syndrome
- Gastroesophageal reflux disease
- Allergies
- Ulcers
- Cystic fibrosis
- Colitis

Data from Reference 5.

Individuals with certain disorders are more likely to have celiac disease than the general population. Examples include other autoimmune diseases, such as thyroid disease, diabetes mellitus (type 1), multiple sclerosis, myasthenia gravis, Raynaud's disease, rheumatoid arthritis, Addison's disease, chronic active hepatitis, cystic fibrosis, scleroderma, and Sjögren's syndrome; Down's syndrome; neurologic conditions such as ataxia, epilepsy, and cerebral calcifications; and primary biliary cirrhosis. Although patients with these disorders are more frequently found to have celiac disease than the general population, these associated conditions are not believed to cause celiac disease.[20]

7 Diagnostic testing for celiac disease must be performed while the patient continues to consume gluten.[5] A confirmed diagnosis of celiac disease requires both a positive finding on duodenal biopsy and a positive response to a gluten-free diet.[5] The identification of villous atrophy with small bowel endoscopy and biopsy is generally regarded as the diagnostic gold standard (although guidelines from the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition suggest that a small intestinal biopsy may not be required in children with typical symptoms, titers of anti-tTG greater than 10 times the upper normal

limit and predisposing HLA genotype).[29] Although villous atrophy is associated with celiac disease, clinicians must consider that this may also be found in other diseases, including giardiasis, autoimmune enteropathy, tuberculosis, Crohn's disease, intolerance to food other than gluten, intestinal lymphoma, and Zollinger-Ellison syndrome.[5]

Histologic changes seen on biopsy are categorized according to one of several classification systems including the Marsh, Marsh modified, or the Corazza, all of which examine intraepithelial lymphocytes, crypt hyperplasia and villous atrophy.[5] Histologic findings lead to a diagnosis that is followed by placing the patient on a gluten-free diet. Dermatitis herpetiformis is diagnosed by skin biopsy.[30]

Serologic test results provide clinicians with a useful noninvasive tool that helps to determine if symptomatic patients, or patients who are at risk for celiac disease, require a biopsy.[5] Available tests include those for deamidated gliadin peptide (DGP) IgA or IgG antibodies, and antibodies against tTG. The American College of Gastroenterology recommends tTG IgA testing for patients 2 years and older and DGP IgA and IgG combined with IgA tTG for patients younger than 2 years.[5] Although serology is a good method to identify patients who will benefit from endoscopy and biopsy, negative serology should not preclude a biopsy examination in individuals for whom disease is suspected on clinical grounds.[5] Positive serology should be followed with confirmatory testing via biopsy.[5]

Genetic testing can be performed as a means of determining which family members of a diagnosed patient may develop the disease (the prevalence of celiac disease is 10%-12% in first-degree relatives and is also higher than that found in the general population in second-degree relatives).[5] Patients and their family members can be tested for HLA-DQ2 and HLA-DQ8 as HLA-DQ2 is found in up to 95% of celiac disease patients, with most other patients being HLA-DQ8 positive.[5] Although nearly all celiac disease patients carry one of these alleles, they are also found in 30% to 40% of the general population. Therefore, when these alleles are absent, it is extremely unlikely that the individual has celiac disease (ie, the test has a high negative predictive value [NPV]).[5] A patient-administered saliva-based test for HLA-DQ2/DQ8 was released for direct sale to consumers but is not recommended for use in the diagnosis of celiac disease.[5]

In 2017, the US Preventive Services Taskforce stated that the current evidence is "insufficient to assess the balance and harms of screening for celiac

disease in asymptomatic persons."[31]

TREATMENT

Desired Outcomes

Overall goals of treatment include relieving symptoms, healing the intestine, and prevent complications.

General Approach to Treatment

The mainstay of treatment of celiac disease is the strict, lifelong adherence to the gluten-free diet. Supportive care of nutrient deficiencies should be addressed through drug therapy and preventive care, such as vaccines, should be recommended.

Nonpharmacologic

8 **Table 58-5** presents a mnemonic that summarizes the major principles of the treatment of celiac disease. Strict lifelong adherence to a gluten-free diet is the only proven treatment for celiac disease.[20] Patients must recognize that adhering to a gluten-free diet includes not ingesting anything that contains gluten or has been contaminated with gluten. Wheat, barley, and rye must be avoided.[4] Although oats are in a different plant family, they may be problematic; however, the ingestion of certified pure gluten-free oats appears to be safe.[20] Due to the continued difference of opinion regarding the safety of oats, they should be added to the diet cautiously and with monitoring.[5] Patients must also commit to avoiding the ingestion of gluten found in nonfood items such as toothpaste, lip balm, lipstick, etc.[14] A list of gluten-free grains can be found in Table 58-1.

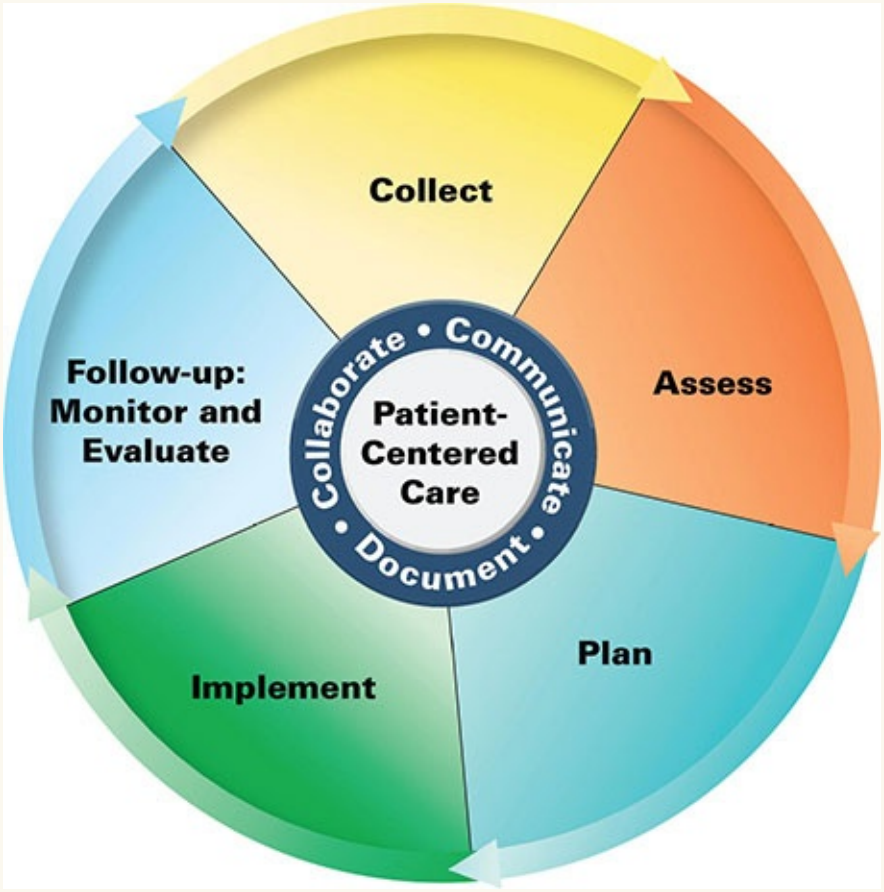
TABLE 58-5 Mnemonic for Celiac Disease

C	Consultation with a skilled dietician
E	Education about the disease
L	Lifelong adherence to a gluten-free diet
I	Identifying and treating nutritional deficiencies
A	Access to an advocacy group
C	Continuous long-term follow-up by a multidisciplinary team

Data from Reference 32.

Oral prescription drugs, nonprescription drugs, vitamin and mineral supplements, and health and beauty aids and cosmetics that have oral ingestion potential must not be overlooked as sources of gluten due to its presence in their formulation or due to contamination or contact.[14] Lack of reliable information can be confusing and although there are published lists of gluten-free drugs, it is often difficult to obtain information about the gluten content of medications.[33,34] Patients with celiac disease are concerned about the possibility of gluten in medications causing disease-related symptoms.[35] Also, the Food and Drug Administration issued draft guidance on "Gluten in Drug Products and Associated labeling Recommendations" in December 2017 have advocated that all medications should be gluten-free.[36] In addition, clinicians should realize that conflicting data regarding drug absorption requires careful selection and use of drugs in patients with celiac disease.[37]

The FDA determined the tolerable daily intake level for gluten in individuals with celiac disease to be 0.4 mg gluten/day for adverse morphologic effects and 0.015 mg gluten/day for adverse clinical effects and ruled that foods labeled on or after August 5, 2014 as gluten free must contain less than 20 ppm gluten.[38,39] Although the ruling pertains to food only, the concerns regarding low-level exposure emphasize why healthcare providers must check to determine whether prescription drugs contain gluten in their formulation or have been contaminated with gluten before these drugs are provided to the patient with celiac disease.



Patient Care Process for Celiac Disease

Collect

- Patient characteristics (eg, age, sex, height, weight)
- Patient medical history (personal and family)
- Social history (eg, tobacco/ethanol use) and dietary habits including intake of gluten-containing grains (see Table 58-1)
- Current medications including nonprescription, herbal products, dietary supplements
- Objective data
  - Results of diagnostic testing (HLA typing, serology, and/or biopsy)
  - Results of testing for nutritional deficiencies (eg, iron, folic acid, vitamin D, vitamin B_{12})
  - Results of other testing (eg, DEXA)

Assess

- Presence of signs and symptoms of malnutrition or nutrient deficiency
- Ability/willingness to follow gluten-free diet
- Ability/willingness to pay for treatment options (gluten-free food, dietary supplements)
- Emotional status (eg, presence of anxiety, depression)
- Family/caregiver support

Plan*

- Patient education (purpose of treatment, dietary and lifestyle modification)
- Self-monitoring for symptoms of celiac disease (intestinal and extra-intestinal)
- Referral to dietician
- Dietary supplement regimen including specific anticoagulant(s), dose, route, frequency, and duration
- Medication regimen including identification of gluten-free oral medications

Implement

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (eg, adherence assessment)

Follow-up: Monitor and Evaluate

- Resolution of celiac disease symptoms (eg, intestinal and extraintestinal)
- Patient adherence to treatment plan
- Resolution of nutritional deficiencies
- Repeat testing as needed (serology, biopsy, labs for nutritional deficiencies, DEXA)

*Collaborate with patient, caregivers, and other healthcare professionals.

9 Newly diagnosed patients should be evaluated for nutritional deficiencies

associated with vitamin and mineral malabsorption, including folic acid, vitamin B_{12}, fat-soluble vitamins, iron, and calcium.[5] Monitoring for potential nutritional deficiencies should also continue during subsequent follow-up visits.

Most adults with celiac disease have some degree of bone loss. Therefore, all patients must be screened for osteoporosis or osteopenia.[40] Supplementing a calcium-rich gluten-free diet with calcium, magnesium, and vitamin D may arrest or reverse celiac decrease–related bone loss. Although their use has not been extensively studied in patients with celiac disease, bisphosphonates and other drugs have been prescribed for patients with bone disease.[37]

Implementing a gluten-free diet presents some challenges. Consultation with a registered dietician is recommended for dietary evaluation and education.[5] Patients are advised to initiate a complete gluten-free lifestyle immediately after diagnosis. Partial adherence to this diet is not adequate. In order to accomplish this objective, patients must be aware of what foods are gluten-free and when in doubt must know how to confirm whether a food contains gluten. Reading labels is extremely important; however, it may be difficult to identify hidden sources of gluten listed among the ingredients. Patients with celiac disease must also determine whether products were processed on equipment shared with wheat, barley, or rye. It may be necessary to call the manufacturers or check their Website to obtain the needed information.[41]

Individuals with celiac disease must also be advised to maintain a gluten-free kitchen. A dedicated toaster, bread maker, waffle iron, and other appliances should be obtained for use in preparing gluten-free meals. Utensils and dishes must be carefully cleaned to avoid gluten contamination. Care must also be taken when dining in restaurants and homes of family and friends. The individuals who prepare and serve the food must be knowledgeable about gluten-free foods and food preparation.[14] The economic burden associated with maintaining a gluten-free diet may present some challenges.[42,43] The relatively low availability and high cost of these foods contribute to the challenges associated with adhering to the required strict diet and may lead to varying degrees of noncompliance.[42,43] Patients also find that the extra cost associated with the special diet is not reimbursed by healthcare plans, and most policies do not pay for consultations with a dietician.[44] These challenges with compliance are particularly concerning as noncompliance with the gluten-free diet is associated with an increased mortality rate and compromised quality of life.[43] Hypervigilance to a strict gluten-free diet may negatively impact upon the patient’s quality of life and clinicians should therefore also promote the social

and emotional well-being of the patient while counseling about the importance of adhering to the gluten-free diet.[45] Patients are also encouraged to investigate their personal circumstances as to whether some of the costs of maintaining a gluten-free diet are eligible for approval as a tax deduction.[44]

Pharmacologic

Dietary avoidance of gluten remains the mainstay of treatment of celiac disease. Novel pharmacologic treatment modalities are under investigation. Most reports related to pharmacotherapy for celiac disease focus on the treatment of refractory disease.

In case reports, corticosteroids, azathioprine, cyclosporine, tacrolimus, infliximab, and alemtuzumab have been reported as effective treatments for refractory celiac disease. Patients characterized to have refractory celiac disease have persistent or recurrent malabsorptive symptoms and signs with villous atrophy despite maintaining a gluten-free diet for more than 12 months.[1] Less than 5% of adult patients have refractory celiac disease.

Based on the pathophysiology of celiac disease, novel targets for the treatment of the disease have been identified: decreasing the antigenic load and modulation of the immune response. Methods of decreasing the antigenic load include blocking the activity of tTG, GI destruction of proline peptides via enzyme therapy, blocking the binding of deaminated proteins to HLA-DQ2 and HLA-DQ8, detoxification of gluten peptides, and decreasing intestinal permeability in patients with celiac disease, in particular through inhibition of zonulin.[3] A zonulin inhibitor, larazotide, was well tolerated and showed variable efficacy in varying doses in three phase-2 studies.[46] A vaccine, Nexvax2, that modulates the immune response has completed phase-1 studies.[47]

Evaluation of Therapeutic Outcomes

Clinical improvement will often be observed within days or weeks of instituting the required diet.[28] Although dermatitis herpetiformis is also treated with the prescribed diet, these cutaneous lesions may not completely resolve for months to years after initiating dietary measures.[30]

Healthcare providers must also be mindful of conditions that are related to celiac disease and that are potential complications of the disease, including certain forms of cancer, neurologic manifestations, osteoporosis, depression, diabetes, infertility, as well as other autoimmune and related illnesses. Cancers

that are of particular concern include thyroid cancer, adenocarcinoma of the small intestine, lymphoma (predominantly non-Hodgkin's lymphoma of any type), esophageal cancer, melanoma, and malignancies found in childhood.[4] Patients with celiac disease have an increased risk of developing certain infectious diseases that includes pneumococcal infection, occurs at a higher rate in celiac disease patients.[48] Therefore, the pneumococcal vaccine should be recommended for all age groups, especially for those patients who did not receive the vaccine as a child.[48] Annual influenza vaccine is advisable as this will reduce the incidence of secondary bacterial infections.[49]

Postclass Engaged Learning Activity

Conduct a literature search and identify a randomized clinical trial published in the past 12 months regarding the treatment of celiac disease. If the manuscript is regarding a dietary intervention, write a brief summary of the study's methods, the major findings, and how this information may be incorporated into current practice. If the manuscript is regarding a new medication, write a brief summary about the medication's mechanisms of action, how it is administered, and a brief summary of the study's findings. This activity is intended to build your literature evaluation skills and ability to critically appraise research manuscripts.

ABBREVIATIONS

HLA	human leukocyte antigen
HR	hazard ratio
IgA	immunoglobulin A
NIH	National Institutes of Health
NPV	negative predictive value
SIgA	serum immunoglobulin A
tTG	tissue transglutaminase

REFERENCES

1. Ludvigsson JF, Leffler DA, Bai JC, et al. The Oslo definitions of celiac disease and related terms. *Gut*. 2013;62:43–52.
2. Fasano A, Catassi C. Celiac disease. *N Engl J Med*. 2012;367(25):2419–

2426.

3. Freeman HJ. Celiac disease: A disorder emerging from antiquity, its evolving classification and risk, and potential new treatment paradigms. *Gut Liver*. 2015;9(1):28–37.
4. Kelly CP, Bai JC, Liu E, et al. Advances in diagnosis and management of celiac disease. *Gastroenterology*. 2015;148(6):1175–1186.
5. Rubio-Tapia A, Hill I, Kelly CP. ACG clinical guidelines: Diagnosis and management of celiac disease. *Am J Gastroenterol*. 2013;108(5):656–676.
6. Catassi C, Gatti S, Fasano A. The new epidemiology of celiac disease. *J Pediatr Gastroenterol Nutr*. 2014;59(Suppl 1):S7–S9.
7. Rubio-Tapia A, Ludvigsson JF, Brantner TL, et al. The prevalence of celiac disease in the United States. *Am J Gastroenterol*. 2012;107:1538–1544.
8. Mardini H, Westgate P. Racial differences in the prevalence of celiac disease in the US population: National Health and Nutrition Examination Survey (NHANES) 2009-2012. *Dig Dis Sci*. 2015;60:1738–1742.
9. Ciccocioppo R, Kruzliak P, Cangemi GC, et al. The spectrum of differences between childhood and adulthood celiac disease. *Nutrients*. 2015;7:8733–8751.
10. Rubio-Tapia A, Kyle RA, Kaplan EL, et al. Increased prevalence and mortality in undiagnosed celiac disease. *Gastroenterology*. 2009;137:88–93.
11. Lionetti E, Gatti S, Puliverenti A, et al. Celiac disease from a global perspective. *Best Pract Res Clin Gastroenterol*. 2015;29:365–379.
12. Kang JY, Kang AHY, Green A, et al. Systematic review: Worldwide variation in the frequency of coeliac disease and changes over time. *Aliment Pharmacol Ther*. 2013;38:226–245.
13. Singh P, Arora S, Singh A, et al. Prevalence of celiac disease in Asia: A systematic review and meta-analysis. *J Gastroenterol Hepatol*. 2016;31(6):1095–1101.
14. See JA, Kaukinen K, Makharia GK, et al. Practical insights into gluten-free diets. *Nat Rev Gastroenterol Hepatol*. 2015;12(10):580–591.
15. Comino I, Moreno Mde L, Sousa C. Role of oats in celiac disease. *World J Gastroenterol*. 2015;21(41):11825–11831.
16. Nistico L, Fagnani C, Coto I, et al. Concordance, disease progression, and heritability of coeliac disease in Italian twins. *Gut*. 2006;55:803–808.

17. Kuja-Halkola R, Lebwohl B, Halfvarson J. Heritability of non-HLA genetics in coeliac disease: A population-based study in 107 000 twins. *Gut*. 2016;65(11):1793–1798.
18. Lebwohl B, Sanders DS, Green PHR. Coeliac disease. *The Lancet*. 2018;391(10115):70–81.
19. Green PHR, Lebwohl B, Greywoode R. Celiac disease. *J Allergy Clin Immunol*. 2015;135(5):1099–1106.
20. DiSabatino A, Corazza GR. Coeliac disease. *Lancet*. 2009;373:1480–1493.
21. Leonard MM, Sapone A, Catassi C, et al. Celiac disease and nonceliac gluten sensitivity: A review. *JAMA*. 2017;318(7):647–656.
22. Green PHR, Cellier C. Celiac disease. *N Engl J Med*. 2007;357:1731–1743.
23. Aronsson CA, Lee H, Liu E, et al. Age at gluten introduction and risk of celiac disease. *Pediatrics*. 2015;135(2):239–245.
24. Vivas S, Vaquero L, Rodríguez-Martín L, et al. Age-related differences in celiac disease: Specific characteristics of adult presentation. *World J Gastrointest Pharmacol Ther*. 2015;6(4):207–212.
25. Paez MA, Gramelspacher AM, Sinacore J. Delay in diagnosis of celiac disease in patients without gastrointestinal complaints. *Am J Med*. 2017;130(11):1318–1323.
26. Bolotin D, Petronic-Rosic V. Dermatitis herpetiformis part I: Epidemiology, pathogenesis, and clinical presentation. *J Am Acad Dermatol*. 2011;64(6):1017–1024.
27. Petronic-Rosic V. Dermatitis herpetiformis and celiac disease. Impact: A Publication of the University of Chicago Celiac Disease Center. Chicago, Il. University of Chicago Celiac Disease Center, Ist Quarter; 2011:1–2.
28. Thom S, Longo BM, Running A, Ashley J. Celiac disease: A guide to successful diagnosis and treatment. *J Nurse Pract*. 2009;5:244–253.
29. Husby S, Koletzko S, Korponay-Szabo IR, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr*. 2012;54(1):136–160.
30. Collin P, Salmi TT, Hervonen K. Dermatitis herpetiformis: A cutaneous manifestation of coeliac disease. *Ann Med*. 2017;49(1):23–31.
31. US Preventive Services Task Force. Screening for Celiac Disease: US

Preventive Services Task Force Recommendation Statement. *JAMA*. 2017;317(12):1252–1257.

32. NIH consensus development conference on celiac disease. *NIH Consens State Sci Statements*. 2004;21:1–23.
33. King AR. The impact of celiac sprue on patients' medication choices. *Hosp Pharm*. 2009;44:105–106.
34. Mangione RA, Patel PN, Shin E, et al. Determining the gluten content of over the counter drugs: Information for patients with celiac disease. *J Am Pharm Assoc*. 2011;51:734–737.
35. Choung RS, Jay L, Al-Lami HS, et al. Concerns regarding gluten presence in medicines is common among individuals with celiac disease, dermatitis herpetiformis, and non-celiac gluten sensitivity. *Gastroenterology*. 2017;152(2):S484–S485.
36. Shah AV, Serajuddin ATM, Mangione RA. Making all medications gluten free. *J Pharmaceut Sci*. 2018;107:1263–1268.
37. Tran T, Smith C, Mangione RA. Drug absorption in celiac disease. *Am J Health-Syst Pharm*. 2013;70:2199–2206.
38. Office of Food Safety Center of Food Safety and Applied Nutrition, Food and Drug Administration. Health Hazard Assessment for Gluten Exposure in Individuals with Celiac Disease: Determination of Tolerable Daily Intake Levels and Levels of Concern for Gluten. 2011. Available at: http://www.fda.gov/downloads/food/scienceresearch/researchaccess/riskass Accessed May 1, 2018.
39. FDA. Questions and Answers: Gluten-Free Food Labeling Final Rule. Available at: https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegul Accessed May 1, 2018.
40. Fouda MA, Khan AA, Sultan M, et al. Evaluation and management of skeletal health in celiac disease: Position statement. *Can J Gastroenterol*. 2012;26(11):819–829.
41. Mangione RA, Patel PN. Caring for patients with celiac disease: The role of the pharmacist. *J Am Pharm Assoc*. 2008;48(4):e125–e135.
42. Krupa-Kozak U. Pathologic bone alterations in celiac disease: Etiology, epidemiology, and treatment. *Nutrition*. 2014;30(1):16–24.
43. Lee A, Ng D, Zivin J, Green H. Economic burden of a gluten-free diet. *J Hum Nutr Diet*. 2007;20:423–430.

44. Stevens L, Rashid M. Gluten-free and regular foods: A cost comparison. *Can J Diet Pract Res*. 2008;69:147–150.
45. Wolf RL, Lebwohl B, Zybert P, et al. Hypervigilance to a gluten-free diet and decreased quality of life in teenagers and adults with celiac disease. Dig Dis Sci. 2018;63(6):1438–1448.
46. Khaleghi S, Ju JM, Lamba A. The potential utility of tight junction regulation in celiac disease: Focus on larazotide acetate. *Therap Adv Gastroenterol*. 2016;9(1):37–49.
47. Goel G, King T, Daveson AJ. Epitope-specific immunotherapy targeting CD4-positive T cells in coeliac disease: Two randomised, double-blind, placebo-controlled phase 1 studies. *Lancet Gastroenterol Hepatol*. 2017;2(7):479–493.
48. Simons M, Scott-Sheldon LAJ, Risech-Neyman Y, et al. Celiac disease and increased risk of pneumococcal infection: A systematic review and meta-analysis. *Am J Med*. 2018;131(1):83–89.
49. Ludvigsson JF, Montgomery SM, Ekbom A, et al. Small-intestinal histopathology and mortality risk in celiac disease. *JAMA*. 2009;302:1171–1178.

SECTION 7 RENAL DISORDERS

Evaluation of Kidney Function

Thomas C. Dowling

KEY CONCEPTS

1. The stage of chronic kidney disease (CKD) should be determined for all individuals based on the level of kidney function, independent of etiology, in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) classification system.
2. Persistent proteinuria indicates the presence of CKD and is associated with mortality and risk of end-stage renal disease (ESRD).
3. Assessment of urine protein excretion, including measurement of a spot urine albumin-to-creatinine ratio, is critical for determining the severity of CKD and monitoring the rate of disease progression.
4. The glomerular filtration rate (GFR) is the single best indicator of kidney function.
5. Measurement of the GFR is most accurate when performed following the exogenous administration of iohexol, iothalamate, or radioisotopes such as technetium-99m diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA).
6. Equations to estimate creatinine clearance (CL_{cr}) or GFR are commonly used in ambulatory and inpatient settings, and incorporate patient laboratory and demographic variables such as serum creatinine concentration (S_{cr}), cystatin C, age, sex, weight, and ethnicity.
7. Longitudinal assessment of GFR and albuminuria is important for monitoring the efficacy of therapeutic interventions, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, which are used to slow or halt the progression of kidney disease.
8. Assessments of kidney structure and function, such as radiography, computed tomography, magnetic resonance imaging, sonography, and biopsy, are predominantly used for determining the diagnosis of a given

condition.

Preclass Engaged Learning Activity

Listen to the ReachMD Podcast on “Drug Dosing Strategies for Renal Patients” (http://tinyurl.com/wdzbwt7). This podcast discusses some important differences between the eGFR that is automatically reported using the MDRD equation, and the Cockcroft–Gault equation which is most often cited in the FDA Drug Product Prescribing Information (formerly called the Package Insert or Product Label). As a companion to this activity, also become familiar with how to locate an FDA-approved drug product label using the Drugs@FDA database, available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

INTRODUCTION

Chronic kidney disease (CKD) continues to be a worldwide health concern, with over 2 million people in the United States estimated to require hemodialysis or kidney transplantation by 2030.[1] In response to this widespread problem, standardized approaches are now used for the identification of individuals with CKD and their subsequent stratification into risk categories for the development of end-stage kidney disease (ESKD or ESRD) (see Chapter 61, “Chronic Kidney Disease”).[1,2] These efforts have heightened the awareness of the need for early identification of patients with CKD and the importance of monitoring the progression of kidney disease.

Comprehensive evaluation of kidney function requires use of qualitative, quantitative, and semi-quantitative methods. Estimation of creatinine clearance (CL_{cr}) has been considered the clinical standard for assessment of kidney function for over 50 years, and it continues to be the preferred method of characterizing kidney function for renal drug dosing purposes in pharmacokinetic studies.[3,4] Newer equations designed to estimate the glomerular filtration rate (GFR) are used in many clinical settings to identify patients with CKD, and in large epidemiology studies to evaluate risks of mortality and progression to stage 5 CKD or ESKD.[5,6] Other tests, such as urinalysis, radiographic procedures, and biopsy, are also valuable tools in the assessment of kidney disease, and these qualitative assessments are useful for determining the

pathology and etiology of kidney disease. Urinalysis, for example, may give clues to the primary location, such as glomerular or tubular, of the kidney disease. Follow-up studies, such as imaging procedures or kidney biopsy, may then further differentiate the specific cause, thereby guiding the selection of the optimal therapeutic intervention.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

60

Acute Kidney Injury

Jenana Halilovic Maker, Lauren Roller, and William Dager

KEY CONCEPTS

1. Three classification systems exist for staging severity of acute kidney injury (AKI): (a) Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease (RIFLE), (b) Acute Kidney Injury Network (AKIN), and (c) Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines. All three classification systems are based on separate criteria for serum creatinine (S_{cr}) and urine output.
2. AKI is a common complication in critically ill patients and is associated with high morbidity and mortality.
3. AKI is typically categorized based on three types of injury: (a) prerenal—decreased renal blood flow, (b) intrinsic—structural damage within the kidney, and (c) postrenal—an obstruction within the urine collection system.
4. Serum creatinine, urea, and urine output are commonly used markers of renal function in clinical practice. However, advances in AKI research have led to the development of multiple novel biomarkers that can be used for risk assessment, early detection, classification, and prognosis in AKI.
5. Conventional formulas used to estimate glomerular filtration rate (eGFR) are not recommended in AKI patients. In addition, drug dose adjustment recommendations are typically based on pharmacokinetic studies conducted in CKD patients and may not be reflective of pharmacokinetic changes seen in AKI patients.
6. The most effective prevention strategies for AKI include limiting exposure to nephrotoxic medications and optimizing the patient's hemodynamic and fluid status. Incorporation of electronic health record alerts may increase early detection and decrease risk of AKI progression.

7. Supportive management remains the primary approach to prevent or reduce complications associated with AKI or comorbid conditions. Supportive therapies include renal replacement therapy (RRT), nutritional support, avoidance of nephrotoxins, and blood pressure and fluid management.
8. For patients with prolonged or severe AKI, RRT is the cornerstone of support along with aggressive fluid and electrolyte management.
9. Drug dosing for AKI patients receiving continuous renal replacement therapy (CRRT) or prolonged RRT is poorly characterized. Dosing requirements of agents primarily eliminated by the kidney may require individualization and adjustment as renal function changes. Therapeutic drug monitoring should be utilized whenever possible for any agent with a narrow therapeutic index.

Preclass Engaged Learning Activity

Consider the following case: A 55-year-old male with past medical history of coronary artery disease, diabetes, and chronic kidney disease presents to the emergency room with weight gain and mental status changes. His serum creatinine (S_{cr}) is 2.8 mg/dL (248 μmol/L) and is significantly increased compared to a S_{cr} value of 1.5 mg/dL (133 μmol/L) from a clinic visit 3 months ago. Briefly describe how you would assess for acute kidney injury in this patient. What questions would you ask the patient? What laboratory values would you order and/or review and why?

INTRODUCTION

Acute kidney injury (AKI) is a clinical syndrome generally defined by an abrupt reduction in kidney function as evidenced by changes in serum creatinine (S_{cr}), blood urea nitrogen (BUN), and urine output. The consequences of AKI can be serious, especially in hospitalized patients. Early recognition along with supportive therapy is the focus of management for those with established AKI, as there is no pharmacologic therapy that directly reverses the injury. Individuals at risk, such as those with history of chronic kidney disease (CKD), need to have their hemodynamic status carefully monitored and their exposure to nephrotoxins minimized. A thorough patient assessment including medical and

surgical history, medication use, physical examination, and multiple laboratory tests is essential. Management goals include maintenance of blood pressure and fluid and electrolyte homeostasis, all of which may be dramatically altered in the presence of AKI. Additional therapies designed to eliminate or minimize the insult that precipitated AKI include discontinuation of any offending agents (ie, nephrotoxins), hydration, maintenance of renal perfusion, and renal replacement therapy (RRT).

In this chapter, the definition, classification, epidemiology, and common etiologies of AKI are presented. Methods to recognize and assess the extent of kidney function loss are also discussed. Finally, preventive strategies for patients at risk and management approaches for those with established AKI are reviewed.

DEFINITION AND CLASSIFICATION OF ACUTE KIDNEY INJURY

1 Three major classification systems have been developed to define and stage AKI in different patient populations. The *R*isk, *I*njury, *F*ailure, *L*oss of Kidney Function, and *E*nd-Stage Kidney Disease (RIFLE) was published in 2004 and the *A*cute *K*idney *I*njury *N*etwork (AKIN) criteria were developed in 2007.[1,2] **Table 60-1** lists an overview of all three classification systems. While generally similar, there are a few noteworthy differences: RIFLE defines AKI as an abrupt (1-7 days) but sustained (more than 24 hours) decrease in kidney function from baseline while AKIN designates a 48-hour period for the decrease to occur. Also, AKIN removed RIFLE's last two classification components (Loss of Kidney Function and End-Stage Kidney Disease [ESKD]) from the staging system and instead places all patients receiving RRT automatically into AKIN stage 3. Finally, AKIN removed all estimated glomerular filtration rate (eGFR) criteria from its staging system and lowered the absolute increase in S_{cr} from 0.5 mg/dL (44 μmol/L) designated for the RIFLE-Risk class to 0.3 mg/dL (27 μmol/L) for AKIN stage 1.[1,2]

TABLE 60-1 RIFLE, AKIN, and KDIGO Classification Schemes for AKI[a]

RIFLE Category	S_{cr} and GFR[b] Criteria	Urine Output Criteria
Risk	S_{cr} increase to 1.5-fold or GFR decrease >25% from baseline	<0.5 mL/kg/hr for ≥6 hours
Injury	S_{cr} increase to twofold or GFR decrease >50% from baseline	<0.5 mL/kg/hr for ≥12 hours
Failure	S_{cr} increase to threefold or GFR decrease >75% from baseline, or S_{cr} ≥4 mg/dL (354 µmol/L) with an acute increase of at least 0.5 mg/dL (44 µmol/L)	Anuria for ≥12 hours
Loss	Complete loss of function (RRT) for >4 weeks	
ESKD	RRT >3 months	
AKIN Criteria	**S_{cr} Criteria**	**Urine Output Criteria**
Stage 1	S_{cr} increase ≥0.3 mg/dL (27 µmol/L) or 1.5- to 2-fold from baseline	<0.5 mL/kg/hr for ≥6 hours
Stage 2	S_{cr} increase >2- to 3-fold from baseline	<0.5 mL/kg/hr for ≥12 hours
Stage 3	S_{cr} increase >3-fold from baseline, or S_{cr} ≥4 mg/dL (354 µmol/L) with an acute increase of at least 0.5 mg/dL (44 µmol/L), or need for RRT	<0.3 mL/kg/hr for ≥24 hours or anuria for ≥12 hours
KDIGO Criteria	**S_{cr} Criteria**	**Urine Output Criteria**
Stage 1	S_{cr} increase ≥0.3 mg/dL (27 µmol/L) or 1.5-1.9 times from baseline	<0.5 mL/kg/hr for 6-12 hours
Stage 2	S_{cr} increase 2-2.9 times from baseline	<0.5 mL/kg/hr for ≥12 hours
Stage 3	S_{cr} increase three times from baseline, or S_{cr} ≥4 mg/dL (354 µmol/L), or need for RRT, or eGFRc <35 mL/min/1.73 m² (0.34 mL/s/m²) in patients <18 years	Anuria for ≥12 hours

AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate; h, hours; KDIGO, Kidney Disease: Improving Global Outcomes; RIFLE, Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease; RRT, renal replacement therapy; S_{cr}, serum creatinine.

[a]For all staging systems, the criterion that leads to worst possible diagnosis should be used.

[b]GFR calculated using the Modification of Diet in Renal Disease (MDRD) equation.

[c]GFR calculated using the Schwartz formula.

The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines working group in 2012 proposed a staging system that shares many similarities with both RIFLE and AKIN.[3] Their staging system, however, is extended in that it includes pediatric patients (younger than 18 years) in KDIGO Stage 3 for those with an eGFR of less than 35 mL/min/1.73 m^2 as determined by the Schwartz formula.[3] More recently, the Acute Disease Quality Initiative (ADQI), a workgroup composed of experts in nephrology and critical care, proposed to further subclassify AKI into those who recover within 48 hours of injury (rapid reversal of AKI) and those whose injury persists beyond 48 hours (persistent AKI). Acute kidney injury becomes acute kidney disease (AKD) if kidney function is impaired beyond 7 days, and can ultimately transition into CKD if the duration exceeds 90 days (**Fig. 60-1**).[4]

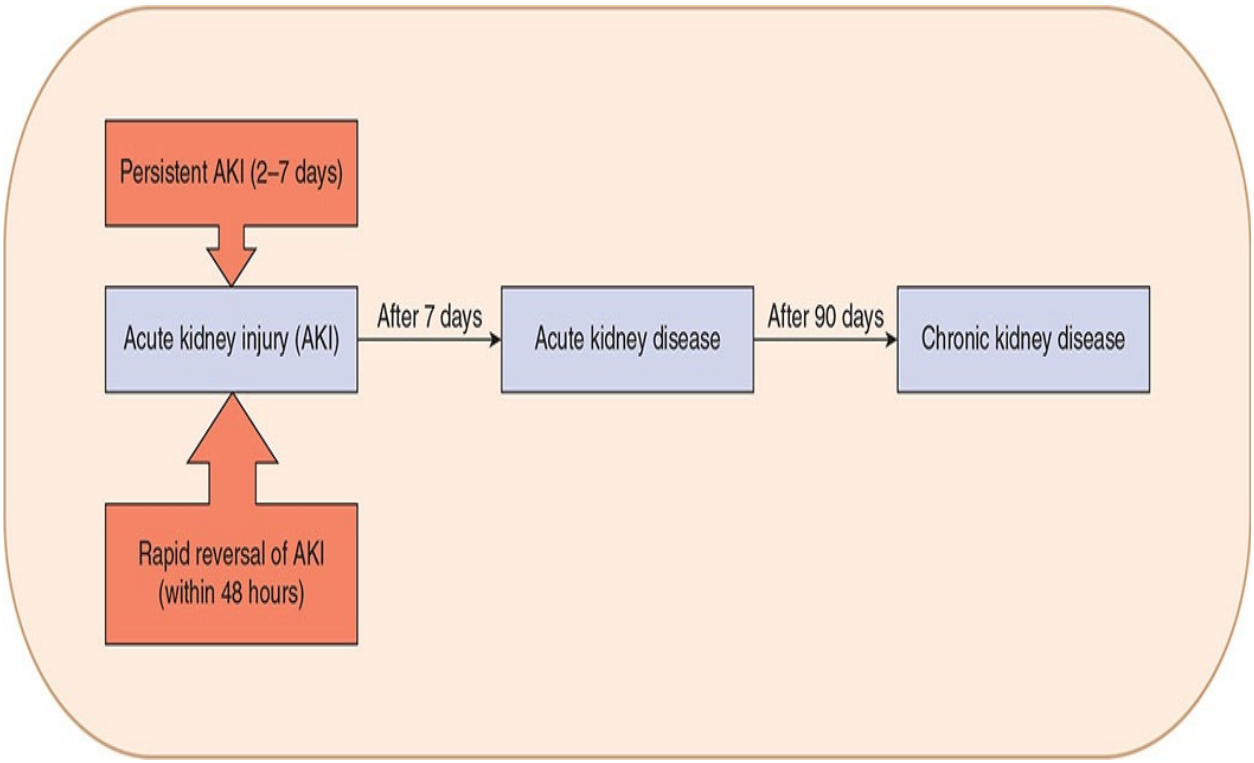


FIGURE 60-1 Continuum of impaired kidney function. Acute kidney injury is an abrupt decrease in kidney function that can either rapidly reverse within the first 48 hours or persist over a period of up to 7 days. Kidney impairment that persists beyond 7 days is termed acute kidney disease and can lead to chronic kidney disease if its duration exceeds 90 days.

All three staging systems have been validated across different patient populations and their staging correlates closely with hospital mortality, cost, and length of hospital stay. The KDIGO criteria seem to identify more patients with AKI and may be slightly more predictive of in-hospital mortality than either RIFLE or AKIN.[5–7]

Since all three staging systems depend on S_{cr} and urine output as the main diagnostic criteria, they are associated with the same inherent weaknesses. An increase in S_{cr} is usually evident roughly 1 or 2 days after development of AKI. This lag time in S_{cr} rise may significantly delay diagnosis of AKI and adversely affect patient outcomes. Urine output decreases earlier and often is the first indicator of AKI but it is a fairly nonspecific marker. Documentation can be challenging, especially with patients able to independently void without ability to document urine output. In fact, patients with AKI can be nonoliguric (urine output greater than 500 mL/day), oliguric (urine output less than 500 mL/day), or anuric (urine output less than 50 mL/day). Urine output will also vary with

volume status, diuretic administration, and the presence of an obstruction. Further, since all criteria are based on detecting an increase in S_{cr} from its baseline, a patient's kidney function prior to the development of AKI needs to be known. If the baseline measure of S_{cr} is not available and the patient has no history of kidney disease, then the baseline S_{cr} value may be estimated using a contemporary eGFR equation with an assumed normal eGFR of 75 mL/min/1.73 m^2.[1] However, this method needs to be interpreted with caution as it has been found to overestimate the incidence of AKI by as much as 40%.[8]

EPIDEMIOLOGY

The epidemiology of AKI varies widely depending on the patient population studied and the criteria used to evaluate the patient. A recent CDC analysis from the National Inpatient Sample and the National Health Interview Surveys noted that the total number of AKI-related hospitalizations increased fourfold over the last two decades (from 953,926 in 2000 to 3,959,560 in 2014). Age-standardized rates of AKI hospitalizations increased 139% (from 23 to 55 per 1,000 persons) among diabetic adults and rose by 230% (from 3.5 to 11.7 per 1,000 persons) among nondiabetic adults.[9]

AKI occurs in 3.0% to 18.3% of hospitalized noncritically ill patients and 30% to 60% of critically ill adults.[10] Risk factors associated with AKI include the presence of CKD, diabetes, heart or liver disease, albuminuria, major surgery (especially cardiac surgery), acute decompensated heart failure, sepsis, hypotension, volume depletion (diarrhea, vomiting, or dehydration), medications (exposure to angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], aminoglycosides, etc.), advanced age, male gender, and African American race.[10–12]

2 Severity, duration, and frequency of AKI appear to be important predictors of poor patient outcomes. Any degree of AKI is associated with an increased risk of death, and the odds increase with the severity of the insult.[10,12] For survivors of AKI, the development of some degree of CKD and need for RRT are other important considerations. In addition, AKI is associated with increased length of hospital stay, cost, readmission, ventilator days, and need for posthospitalization care.[10,12,13]

Early identification of patients at high-risk for AKI could alert healthcare providers to increase surveillance and focus on primary prevention. One AKI-risk prediction model was developed and validated among critically ill patients

that utilizes a scoring system to identify individuals at high risk for AKI.[14] The scoring system (Table 60-2) consists of 10 risk factors. While a patient can score anywhere from 0 to 21 points, a score of 5 points or higher suggests an individual patient is at high-risk for developing AKI. The positive and negative predictive values of the scoring system were found to be 32% and 95%, respectively, indicating that patients with a score of less than 5 are very unlikely to develop AKI.

TABLE 60-2 AKI-Risk Prediction Score

Risk factor	Points
Chronic	
Chronic kidney disease	2
Chronic liver disease	2
Congestive heart failure	2
Hypertension	2
Atherosclerotic coronary vascular disease	2
Acute	
pH ≤7.30	3
Nephrotoxin exposure	3
Severe infection/sepsis	2
Mechanical ventilation	2
Anemia	1

ETIOLOGY

3 The etiology of AKI can be divided into three broad categories based on the anatomic location of the injury associated with the precipitating factor(s). The management of patients presenting with this disorder is largely predicated on identification of the specific etiology responsible for the patient's AKI (Fig. 60-2). Traditionally, the causes of AKI have been categorized as (a) prerenal, which results from decreased renal perfusion in the setting of undamaged parenchymal tissue, (b) intrinsic, the result of structural damage to the kidney, most commonly the tubule from an ischemic or toxic insult, and (c) postrenal, caused by obstruction of urine flow downstream from the kidney.

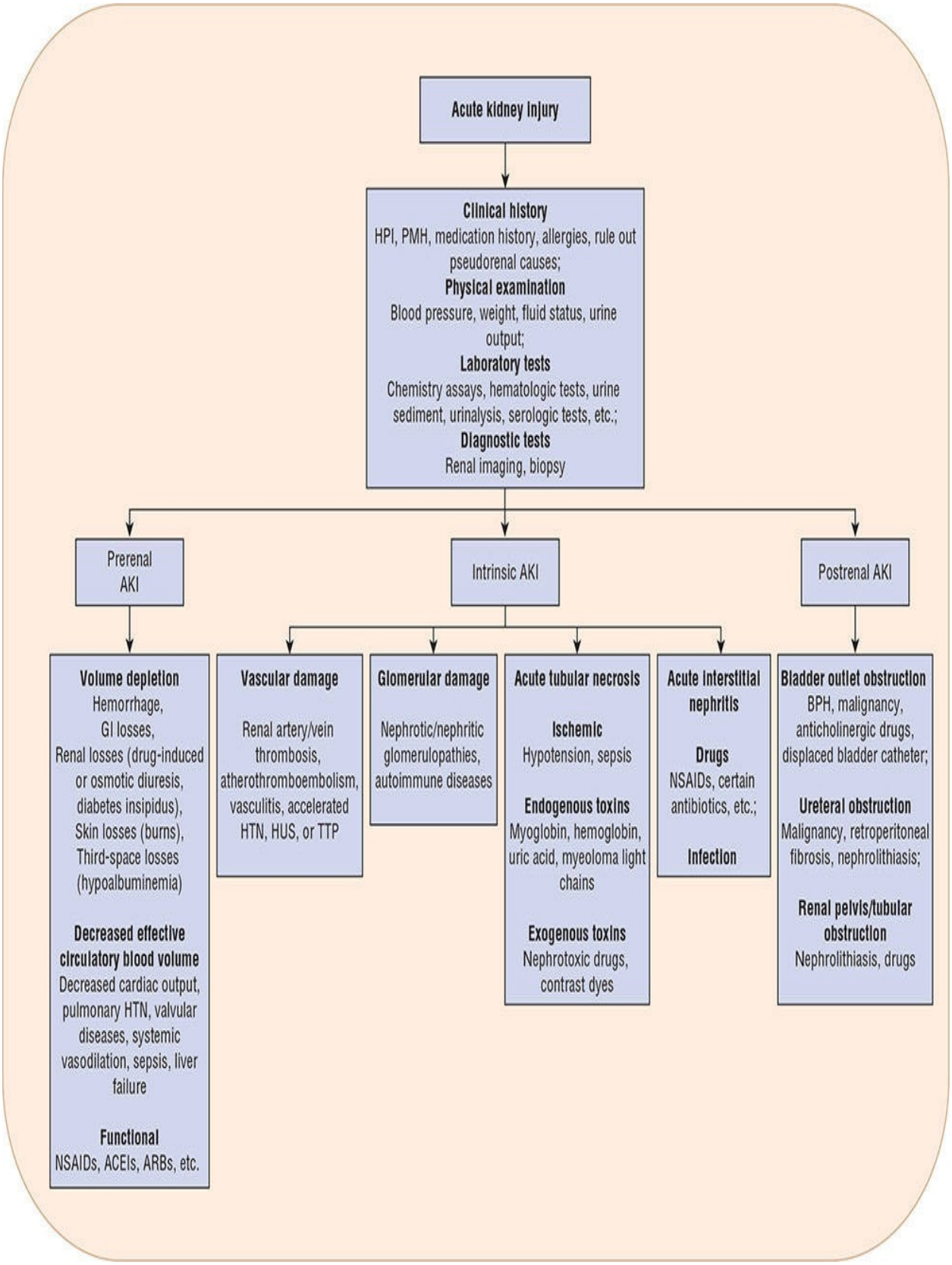


FIGURE 60-2 Classification of acute kidney injury (AKI) based on etiology.

(ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BPH, benign prostatic hyperplasia; HPI, history of present illness; HTN, hypertension; HUS, hemolytic uremic syndrome; NSAIDs, nonsteroidal anti-inflammatory drugs; PMH, past medical history; TTP, thrombotic thrombocytopenic purpura.)

The risk of AKI increases substantially with decreasing glomerular filtration rate (GFR) and presence of albuminuria and underlying CKD. A history of AKI has also been associated with high risk for developing additional episodes of AKI and subsequent complications such as CKD.[10,15]

PATHOPHYSIOLOGY

The pathophysiologic processes involved in the development of the three traditional categories of AKI: prerenal AKI, intrinsic AKI, and postrenal AKI are described below.

Prerenal Acute Kidney Injury

Prerenal AKI or prerenal azotemia results from hypoperfusion of the renal parenchyma, with or without systemic arterial hypotension. Renal hypoperfusion associated with systemic arterial hypotension may be caused by a decline in either the intravascular volume or the effective circulating blood volume. Intravascular volume depletion may result from several conditions, including hemorrhage, excessive gastrointestinal (GI) losses (severe vomiting or diarrhea), dehydration, extensive burns, and diuretic therapy. Effective circulating blood volume may be reduced in conditions associated with a decreased cardiac output and systemic vasodilation. Renal hypoperfusion without systemic hypotension is most commonly associated with bilateral renal artery occlusion or unilateral occlusion in a patient with a single functioning kidney.

Patients with a mild reduction in effective circulating blood volume or volume depletion are generally able to maintain a normal GFR by activating several compensatory mechanisms. Those initial physiologic responses by the body stimulate the sympathetic nervous and the renin–angiotensin–aldosterone system and release antidiuretic hormone if hypotension is present. These responses work together to directly maintain blood pressure via vasoconstriction and stimulation of thirst, which in conscious patients results in increased fluid intake, as well as sodium and water retention. Additionally, GFR may be

maintained by afferent arteriole dilation (mediated by intrarenal production of vasodilatory prostaglandins, kallikrein, kinins, and nitric oxide) and efferent arteriole constriction (mainly mediated by angiotensin II). In concert, these homeostatic mechanisms are often able to maintain arterial pressure and renal perfusion, potentially averting the progression to AKI.[16] If, however, the decreased renal perfusion is severe or prolonged, these compensatory mechanisms may be overwhelmed, and prerenal AKI will be clinically evident.

Patients at risk for prerenal AKI are particularly susceptible to changes in the afferent and efferent arteriolar tone, as they may not be able to compensate as readily. Some drugs interfere with these renal adaptive responses, and the resulting reduction in the glomerular hydrostatic pressure precipitates an abrupt decline in GFR and is sometimes referred to as *functional AKI*. A common cause of this syndrome is a decrease in efferent arteriolar resistance as the result of initiation of an ACE inhibitor or ARB (see Chapter 63). For example, individuals with heart failure are often given an ACE inhibitor or ARB to help improve left ventricular function, but if the dose is titrated too rapidly, they may experience a decline in GFR. If the increase in the S_{cr} is less than 30% from baseline and potassium serum levels are within normal range, the medication can generally be continued. Nonsteroidal anti-inflammatory drugs (NSAIDs) may also precipitate AKI in susceptible individuals due to their impact on renal prostaglandin production and afferent arteriolar vasodilation, which some patients rely on to maintain GFR.[17]

Sepsis is one of the leading clinical conditions associated with AKI. The exact mechanism by which sepsis causes AKI is poorly understood. The traditional presumption that decreased renal hypoperfusion is responsible for reduced GFR has largely been disputed as evidence indicates that there is little association between renal blood flow and GFR. Instead, a complex interplay of different mechanisms may be involved in its pathogenesis, including disturbances in renal microcirculation, inflammation, and metabolic reprogramming.[18,19] Microcirculatory dysfunction is characterized by endothelial dysfunction and shedding of the glycocalyx layer which leads to leukocyte and platelet adhesion, capillary leaking, interstitial edema, and an uneven distribution in blood flow. Tubular epithelial cells develop adaptive metabolic responses that allow them to prioritize energy expenditures to vital functions and minimize risk of replicating damaged DNA. While these responses increase chances of cell survival, they also lead to a reduced GFR.

Intrinsic Acute Kidney Injury

Intrinsic AKI results from direct damage to the kidney and is categorized on the basis of the injured structures within the kidney: vasculature, glomeruli, tubules, and interstitium.

Renal Vasculature Damage

Occlusion of the larger renal vessels resulting in AKI is not common but can occur if large atheroemboli or thromboemboli occlude the bilateral renal arteries or one vessel of the patient with a single kidney. Atheroemboli most commonly develop during vascular procedures that cause atheroma dislodgement, such as angioplasty and aortic manipulations. Thromboemboli may arise from dislodgement of a mural thrombus in the left ventricle of a patient with severe heart failure or from the atria of a patient with atrial fibrillation. Renal artery thrombosis may occur in a similar fashion to coronary thrombosis, in which a thrombus forms in conjunction with an atherosclerotic plaque.

Although smaller vessels can also be obstructed by atheroemboli or thromboemboli, the damage is limited and the development of significant AKI is unlikely. However, these small vessels are susceptible to inflammatory processes that lead to microvascular damage and vessel dysfunction when the renal capillaries are affected. Neutrophils invade the vessel wall, causing damage that can include thrombus formation, tissue infarction, and collagen deposition within the vessel structure. Diffuse renal vasculitis can be severe and promote concomitant ischemic acute tubular necrosis (ATN). Untreated hypertension may also compromise renal microvascular blood flow, causing diffuse renal capillary damage.

Glomerular Damage

Glomerular damage is an uncommon cause of AKI. The glomerulus serves to filter fluid and solute into the tubules while retaining proteins and other large blood components in the intravascular space. Kidney injury may develop when circulating immune complexes deposit in the glomeruli and cause an inflammatory reaction (eg, lupus nephritis, IgA nephropathy).[20] Details on the pathophysiology and specific therapeutic approaches to glomerulonephritis are described in Chapter 64.

Tubular Damage

Most intrinsic AKI cases are due to ATN, which can either result from renal

ischemia or nephrotoxin exposure (eg, aminoglycosides, contrast dyes). The tubules located within the medulla of the kidney are particularly at risk for ischemic injury, as this portion of the kidney is metabolically active and thus has high oxygen requirements, yet, as compared with the cortex, receives relatively low oxygen delivery. Thus, ischemic conditions caused by severe hypotension or exposure to vasoconstrictive drugs preferentially affect the tubules more than any other portion of the kidney.

The clinical evolution of ATN is characterized by four distinct phases: initiation, extension, maintenance, and recovery. Renal tubular epithelial cell injury is the hallmark of the initiation phase that results from vasoconstriction and ischemia, and leads to GFR reduction. Contrary to its name, ATN is not only characterized by necrosis and cell death but by a large spectrum of cellular injury that usually involves sublethal damage to the cells. The extent of injury depends not only on the severity and duration of ischemia but also on the sensitivity of renal cells to the insult which may vary based on the cells' metabolic demands, physical location within the kidney, degree of regional blood perfusion, oxygenation status, and membrane permeability. Further, alterations in cytoskeletal structure lead to a loss of epithelial polarity and barrier function. As a result, the glomerular filtrate starts leaking back into the interstitium and is reabsorbed into the systemic circulation. Additionally, urine flow is obstructed by accumulation of sloughed epithelial cells, cellular debris, and formation of casts.[20,21]

The extension phase is characterized by continued hypoxia following the initial ischemic event and an inflammatory response. Both events are more pronounced in the outer medullary region and the GFR continues to decrease. During the maintenance phase, GFR reaches a nadir during which cellular repair processes are initiated in an attempt to reestablish and maintain cellular and tubular integrity. The surviving cells undergo repair, migration, dedifferentiation, and proliferation. The maintenance phase is eventually followed by a recovery phase, during which new tubule cells are regenerated through redifferentiation and epithelial polarity is reestablished.[20,21]

Interstitial Damage

Acute interstitial nephritis (AIN) is an idiosyncratic delayed hypersensitivity immune reaction that is most commonly caused by drugs (see Chapter 63) and less commonly by infections, autoimmune diseases, or idiopathic causes. AIN is characterized by tubular and interstitial inflammation, and edema with lesions composed of mononuclear cells, with a predominance of lymphocytes (primarily

CD4+ T lymphocytes) and monocytes or macrophages. The specific pathogenic process depends on the cause of AIN. Drug-induced disease is characterized by renal interstitial dendritic and renal tubular epithelial cells recognition of the offending agent as immunogenic and their activation of T lymphocytes which induce proinflammatory molecules. Once acute interstitial inflammation sets in, it can progress very rapidly to a more destructive fibrogenic process marked by increased interstitial matrix, ischemia, tubular atrophy, and interstitial fibrosis.[22,23] The prognosis of AIN varies depending on the specific cause, baseline kidney function, and timely detection of the offending agent; however, it is estimated that almost a quarter of patients may not recover their baseline kidney function.[23]

Postrenal Acute Kidney Injury

Postrenal AKI accounts for less than 5% of all cases of AKI and may develop as the result of obstruction at any level within the urinary collection system (see Fig. 60-2). However, if the obstructing process is above the bladder, it must involve both kidneys (one kidney in a patient with a single functioning kidney) to cause clinically significant AKI, as one functioning kidney can generally maintain a near-normal GFR. Bladder outlet obstruction, the most common cause of obstructive nephropathy, is often the result of a prostatic process (hypertrophy, cancer, or infection), producing a physical impingement on the urethra and thereby preventing the passage of urine. It may also be the result of an improperly placed urinary catheter. Blockage may also occur at the ureter level secondary to nephrolithiasis, blood clots, sloughed renal papillae, or physical compression by an abdominal process. Crystal deposition within the tubules from oxalate and some medications severe enough to cause AKI is uncommon, but it is possible in patients with severe volume contraction and in those receiving large doses of a drug with relatively low urine solubility (see Chapter 63).[20] In these cases, patients have insufficient urine volume to prevent crystal precipitation in the urine. Extremely elevated uric acid concentrations from chemotherapy-induced tumor lysis syndrome can cause obstruction and direct tubular injury as well.[24] Wherever the location of the obstruction, urine will accumulate in the renal structures above the obstruction and cause increased pressure upstream. The ureters, renal pelvis, and calyces all expand, and the net result is a decline in GFR. If renal vasoconstriction ensues, a further decrement in GFR will be observed.

CLINICAL PRESENTATION

The initiating signs or symptoms of AKI are highly variable and largely dependent on the underlying etiology. It may be a change in urinary character (eg, decreased urine output or urine discoloration), edema, electrolyte disturbances, sudden weight gain, or severe abdominal or flank pain. Early recognition and cause identification are critical, as they directly affect the outcome of AKI. One of the first steps in the diagnostic process is to determine if the change in kidney function is acute, chronic, or the result of an acute change in a patient with known CKD (also called acute-on-chronic kidney failure). Patients should also be promptly evaluated for any changes in their fluid and electrolyte status. Patients presenting with AKI in the outpatient environment may have very nonspecific or seemingly unrelated symptoms so that the time of onset of the injury can be difficult to determine. On the other hand, AKI in hospitalized patients is often detected much earlier in its course due to frequent laboratory studies and daily patient assessment.

Patient Assessment

The assessment of a patient with AKI starts with a thorough review of his or her medical records, with a particular focus on chronic conditions, laboratory studies, procedures, and surgeries. An exhaustive review of prescription and nonprescription medicines, herbal products, and recreational drugs may help determine if AKI was potentially precipitated by drug ingestion.

During the initial patient evaluation, presumptive signs and symptoms of AKI need to be differentiated from a potential new diagnosis of CKD. A medical history for kidney disease–related chronic conditions (eg, poorly controlled hypertension or diabetes mellitus), previous laboratory data documenting the presence of proteinuria or an elevated S_{cr}, and the finding of bilateral small kidneys on renal ultrasonography suggest the presence of new onset CKD rather than AKI. However, it is important to note that patients with CKD may develop episodes of AKI as well. In that case, an abrupt rise in the patient's baseline S_{cr} is one of the most useful indicators of the presence of an acute insult to the kidneys. The staging of AKI should also be assessed during the initial insult and decline in kidney function, the stabilization of the decline in function, and the recovery period.

An acute change in urine output is another common and noticeable symptom associated with AKI. The presence of cola-colored urine is indicative of blood in

the urine, a finding commonly associated with acute glomerulonephritis. In hospitalized patients, changes in urine output may be helpful in characterizing the cause of the patient's AKI. Acute anuria is typically caused by either complete urinary obstruction or a catastrophic event (eg, shock or acute cortical necrosis). Oliguria, which often develops over several days, suggests prerenal azotemia, whereas nonoliguric kidney failure usually results from acute intrinsic kidney failure or incomplete urinary obstruction.

Depending on the underlying cause of AKI, patients may present with a variety of symptoms affecting virtually any organ system of the body. Constitutional symptoms such as nausea, vomiting, fatigue, malaise, and weight gain are common but nonspecific. The onset of flank pain is suggestive of a urinary stone; however, if bilateral, it may suggest swelling of the kidneys secondary to acute glomerulonephritis or AIN. Complaints of severe headaches may suggest the presence of severe hypertension and vascular damage. The presence of fever, rash, and arthralgia may be indicative of drug-induced AIN or lupus nephritis.

A thorough physical examination is an important step in evaluating individuals with AKI, as clues regarding the etiology can be evident from the patient's head (eye examination) to toe (evidence of dependent edema) assessment. Evaluation of the patient's volume and hemodynamic status is critical as well, as it will guide management. For example, patients with prerenal AKI can present with either volume depletion or fluid overload. Volume depletion may be evidenced by the presence of postural hypotension, decreased jugular venous pressure (JVP), and dry mucous membranes. Fluid overload, on the other hand, is often reflected by elevated JVP, pitting edema, ascites, and pulmonary crackles.

Conventional Markers of Kidney Function

4 Common laboratory tests used to evaluate the patient with impaired kidney function are described in Chapter e59. Over the past four decades, S_{cr} has been the most widely used laboratory test for estimating creatinine clearance (eCL_{cr}) and eGFR. However, there are several limitations associated with its use since it is affected by factors such as age, gender, race, muscle mass, diet, and hydration status. For example, patients with reduced creatinine production, such as those with low muscle mass, may have very low values (less than 0.6 mg/dL [53 µmol/L]); thus, the presence of a gradual rise to normal values (0.8-1.2 mg/dL [71-106 µmol/L]) may actually suggest the presence of AKI. However, in the

presence of improved nutrition and a large muscle mass, a S_{cr} of 1.2 mg/dL (106 μmol/L) may be a true representation of a person's current renal status. Instead of using only the most current value to determine kidney function, changes in the value from a patient's baseline over the past few days need to be considered. S_{cr} is normally inversely proportional to GFR. However, rapid changes in GFR disrupt this equilibrium and make S_{cr} a very insensitive marker. In fact, changes in S_{cr} will lag behind the GFR's decline by 1 to 2 days due to slow accumulation, increased tubular secretion, and increased extrarenal clearance.[25,26] This can lead to a significant overestimation of the patient's GFR in the early stages of AKI and consequently a potential delay in the diagnosis of the syndrome.

5 Because S_{cr} steady-state values are assumed when one uses several GFR calculation methods, such as the Cockcroft-Gault, MDRD, and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations, they should not be used to estimate GFR in AKI patients with unstable kidney function. These equations will typically overestimate GFR when the AKI is worsening and underestimate it when the AKI is resolving. Instead, it may be useful to evaluate changes in S_{cr} values from the patient's baseline and also consider the S_{cr} sequence values to determine if kidney function is potentially improving or worsening. The most recent S_{cr} reflects the time-averaged kidney function over the preceding time period. Several mathematical approaches to estimate GFR in patients with unstable S_{cr} that incorporate the principles of creatinine accumulation and elimination have been proposed and are discussed in detail in Chapter e59. However, these methods have not been extensively validated in the setting of AKI, and their value for adjusting medication dosing is questionable. Additionally, these equations are complex and are not commonly used in the clinical setting.

Two other widely available markers of kidney function are BUN and urine output. The value of the BUN in AKI is very limited because urea production and renal clearance are heavily influenced by extrarenal factors such as critical illness, volume status, protein intake, and medications. Urine output measured over a specified period of time (eg, 4-24 hours) allows for short-term assessment of kidney function, but its utility is limited to cases in which it is significantly decreased. The presence of anuria suggests complete kidney failure, whereas oliguria indicates some degree of kidney damage. Urine output needs to be interpreted with caution, as it is dependent on several factors, such as hydration status and medications. As mentioned earlier in the chapter, a patient may have

AKI and still maintain a normal urine output; this condition is referred to as *nonoliguric AKI*. Another approach to estimating kidney function is to directly measure CL_{cr} over a short period of time, for example, 4 to 12 hours.[27] Although, potentially precise and simple to do, its accuracy is questionable if the urine output is low or the urine collection is incomplete.

In addition to BUN and S_{cr}, selected blood and urine tests, and urinary sediment are routinely evaluated to differentiate the cause of AKI and guide patient management. For example, a complete blood cell count with differential can help rule out infectious causes of AKI. Serum electrolyte values may be abnormal because of the acute decline of the kidney's ability to regulate electrolyte excretion. Particular attention should be paid to serum potassium, calcium and phosphorus values, which can be markedly elevated and cause life-threatening complications.

Given the limited usefulness of solely using S_{cr} or BUN concentrations to differentiate the etiology of AKI, urinary electrolytes and osmolality should be determined, and both a microscopic and chemical analysis of the urine should be performed (**Table 60-3**). The finding of a high urinary specific gravity, in the absence of glucosuria or mannitol administration, suggests an intact urinary concentrating mechanism and that the cause of the patient's AKI is likely prerenal azotemia. The presence of urinary protein is often difficult to interpret, especially in the setting of acute or chronic kidney failure. A patient with CKD may have a baseline proteinuria, thus clouding the clinical presentation, unless this is known at the time of AKI assessment. Classically, proteinuria is a hallmark of glomerular damage. However, tubular damage can also result in proteinuria, as the tubules are responsible for reabsorbing small proteins that are normally filtered by all glomeruli. The presence of blood also results in a positive urine protein test, so this confounder must always be assessed when a positive urine protein is obtained. Hematuria suggests acute intrinsic AKI secondary to glomerular injury, catheter-related trauma, infection, or a kidney stone. On microscopic examination, the key findings are cells, casts, and crystals, and the presence of one or more of these may suggest specific etiologies of the AKI (**Table 60-4**). The finding of urinary crystals may indicate nephrolithiasis and a postrenal obstruction. If red blood cells or red blood cell casts are present, one should consider the presence of a physical injury to the glomerulus, renal parenchyma, or vascular beds. The finding of white blood cells or white blood cell casts suggests interstitial inflammation (ie, interstitial nephritis), which can be secondary to an allergic, granulomatous, or infectious process.

TABLE 60-3 Diagnostic Parameters for Differentiating Causes of AKI[a]

Laboratory Test	Prerenal AKI	Intrinsic AKI	Postrenal AKI
Urine sediment	Hyaline casts, may be normal	Granular casts, cellular debris	Cellular debris
Urinary RBC	None	2-4 +	Variable
Urinary WBC	None	2-4 +	1 +
Urine Na (mEq/L or mmol/L)	<20	>40	>40
FE_{Na} (%)	<1	>2	Variable
Urine specific gravity	>1.018	<1.012	Variable

AKI, acute kidney injury; FE_{Na}, fractional excretion of sodium; S_{cr}, serum creatinine; RBC, red blood cell; WBC, white blood cell.

[a]Common laboratory tests are used to classify the cause of AKI. Functional AKI, which is not included in this table, would have laboratory values similar to those seen in prerenal AKI. The laboratory results listed under intrinsic AKI are those seen in acute tubular necrosis, the most common cause of intrinsic AKI.

TABLE 60-4 Urinary Findings as a Guide to the Etiology of AKI

Type of Urinary Evaluation	Presence of	Suggestive of
Urinalysis	Leukocyte esterases	Urinary tract infection
	Nitrites	Urinary tract infection
	Protein	
	Mild (<0.5 g/day)	Tubular damage
	Moderate (0.5-3 g/day)	Glomerulonephritis, pyelonephritis, tubular damage
	Large (>3 g/day)	Glomerulonephritis, nephrotic syndrome
	Hemoglobin	Glomerulonephritis, pyelonephritis, renal infarction, renal tumors, kidney stones
	Myoglobin	Rhabdomyolysis-associated tubular necrosis
	Urobilinogen	Hemolysis-associated tubular necrosis
Urine sediment	Microorganisms	Urinary tract infection
Cells	Red blood cells	Glomerulonephritis, urinary tract infection, renal infarction, papillary necrosis, renal tumors, kidney stones
	White blood cells	Urinary tract infection, interstitial nephritis
	Eosinophils	Drug-induced interstitial nephritis, renal transplant rejection
	Epithelial cells	Tubular necrosis
Casts	Granular casts	Tubular necrosis
	Hyaline casts	Prerenal azotemia
	White blood cell casts	Urinary tract infection, interstitial nephritis
	Red blood cell casts	Glomerulonephritis, renal infarct, lupus nephritis, vasculitis
Crystals	Urate	Postrenal obstruction
	Calcium phosphate	Postrenal obstruction

AKI, acute kidney injury.

Simultaneous measurement of urine and serum electrolytes is also helpful in the setting of AKI (see Table 60-2). From these values, a fractional excretion of sodium (FE_{Na}) can be calculated. The equation for the calculation of the FE_{Na} is as follows:

$$FE_{Na} = \frac{\text{Excreted Na}}{\text{Filtered Na}} \times 100 = \frac{U_{vol} \times U_{Na}}{GFR \times S_{Na} \times 100}$$

where

$$GFR = U_{vol} \times U_{Cr}S_{Cr} \times t$$

Thus:

$$FE_{Na} = U_{Na} \times S_{Cr} \times 100 U_{Cr} \times S_{Na}$$

where U_{vol} is urine volume; U_{cr} is urine creatinine concentration; U_{Na} is urine sodium concentration; S_{cr} is serum creatinine concentration; S_{Na} is serum sodium concentration, which usually does not vary much; GFR is the glomerular filtration rate; and *t* is the time period over which the urine is collected.

The FE_{Na} is one of the better diagnostic parameters to differentiate the cause of AKI. A low urinary sodium concentration (less than 20 mEq/L [mmol/L]) and low FE_{Na} (less than 1%) in a patient with oliguria suggest that there is stimulation of the sodium-retentive mechanisms in the kidney and that tubular function is intact. These findings are most characteristic of prerenal azotemia. Unfortunately, diuretic use in the preceding days limits the usefulness of the FE_{Na} calculation by increasing natriuresis, even in hypovolemic patients. The fractional excretion of urea (FE_{Urea}), which can be calculated like FE_{Na}, is sometimes used as an alternative means to assess tubular function in patients receiving diuretics. The inability to concentrate urine results in a high FE_{Na} (greater than 2%), suggesting tubular damage as the primary cause of the intrinsic AKI. However, this is also not an absolute finding, as there are some intrinsic causes that can be associated with a low FE_{Na} (eg, contrast nephropathy, myoglobinuria, and interstitial nephritis). Highly concentrated urine (greater than 500 mOsm/kg [500 mmol/kg]) suggests stimulation of antidiuretic hormone and intact tubular function. These findings are consistent with prerenal azotemia.

Novel Biomarkers of Kidney Damage

A variety of biomarkers have been investigated to detect and predict the clinical outcomes of AKI. While they vary in their origin, function, distribution, and time of release following kidney injury, the large majority are molecules that are released as a result of direct kidney cell damage. The performance of most biomarkers is variable and depends on the patient population, cause of AKI, presence of comorbidities, and timing of biomarker measurements. In general, their ability to detect AKI is significantly better within homogenous patient populations where the time of AKI is known than in heterogeneous populations with multiple comorbidities and unknown AKI time or cause such as critically ill patients. Even though some biomarker tests are now commercially available, these tests are not routinely available at most clinical practice sites. Lastly, there is still a barrier for clinical translation since there are little data available on the impact of the biomarker information on clinical decision making.[28,29]

Two of the most promising biomarkers studied in AKI are tissue inhibitor of metalloproteinases 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7). Both molecules inhibit specific proteins that result in G1 cell-cycle arrest noted to occur during the very early phases of cellular stress or injury. The cell uses cell-cycle arrest as a protective mechanism to avoid cell division when potentially damaged. However, if the cells do not re-initiate the cell cycle and remain arrested, a fibrotic phenotype can develop instead. These findings are of importance as cell-cycle arrest activation and deactivation may prove to be potential targets of therapeutic interventions in the future.[30]

TIMP-2 and IGFBP7 have been validated in critically ill and postoperative surgical patients as a predictor of AKI and of increased risk for mortality or need for RRT.[31] In 2014, the combination of TIMP-2 and IGFBP7 was approved by the Food and Drug Administration (FDA) as the first point-of-care device to detect early AKI. The test (Nephrocheck®) uses a fluorescent immunoassay and reveals test results expressed as an AKI-risk score within 20 minutes. A score over 0.3 $(ng/mL)^2/1,000$ indicates high risk for developing moderate-to-severe AKI within 12 hours of testing. The cutoff value of 0.3 has a sensitivity of 95% and a specificity of only 46%. A second, high-specificity cut-off of 2.0 $(ng/mL)^2/1,000$ was proposed to identify patients at very high risk for AKI who may benefit from active-intervention strategies such as avoidance of contrast dyes, discontinuation of nephrotoxic drugs, and close monitoring of volume and hemodynamic status. The cutoff value of 2.0 has a sensitivity of 37% and a specificity of 95%.[31] Nephrocheck® is not to be used as a standalone test for the

diagnosis of AKI; the test should be used in conjunction with other diagnostic and clinical findings. Further, Nephrocheck® should be avoided in patients experiencing severe albuminuria and hyperbilirubinuria, as they interfere with the test results.[32]

Other biomarkers of kidney damage that have been extensively studied over the last 10 years include neutrophil gelatinase–associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), interleukin 18 (IL-18), liver-type fatty acid binding protein (L-FABP), and *N*-acetyl-beta-D-glucosaminidase (NAG). They have been studied for a variety of uses including risk assessment, early detection, classification, and prognosis of AKI.[29,33] How research advancements in AKI biomarkers are going to be incorporated into routine clinical practice with a patient-centered approach is yet to be determined. Some have advocated for the development of a "biomarker panel" that would allow clinicians to better assess for presence of any changes in kidney function or damage and would guide further patient management. It is important to note that these biomarkers would be used in addition to and not as a replacement for standardized tests for kidney function such as S_{cr} and urine output.[33]

Another opportunity to incorporate biomarkers into clinical practice may be through the development of an "AKI care bundle." A recent study used [TIMP-2][IGFBP7] >0.3 to identify high-risk patients undergoing cardiac surgery.[34] The intervention group received the KDIGO surgery bundle which consisted of avoidance of nephrotoxic agents, discontinuation of ACE-I/ARBs for the first 48 hours of surgery, glycemic control, optimization of volume status, and close hemodynamic monitoring. The occurrence of AKI within 72 hours was significantly lower in the intervention group than in the control group (55.1% vs 71.7%, $p = 0.004$). The severity of AKI was also significantly lower in the intervention group. However, there were no differences in long-term outcomes (such as length of stay, mortality, persistent kidney impairment) measured up to 90 days postsurgery. Further studies are needed to confirm that incorporation of biomarkers can contribute to improved clinical outcomes.

In addition to novel biomarkers, administration of furosemide has emerged as a relatively accurate approach to assessing the likelihood of AKI progression. As a loop diuretic, furosemide is secreted into the proximal tubules where it inhibits the Na-K-Cl cotransporter resulting in increased Na and water excretion. Hence, in order for furosemide to fully exert its effects, tubular function within the nephrons needs to be intact. This approach, called the furosemide stress test or FST, involves administration of 1 mg/kg intravenous furosemide (or 1.5 mg/kg if patient received a loop diuretic in the prior 7 days) to patients with early AKI.

Urine is collected over the next 2 hours and urine output is determined. If the collective urine output is less than 200 mL, then the patient is at an increased risk for progressing to AKI stage 3 and needing RRT.[35] The FST may be an attractive option for select patients with early AKI as it utilizes resources that are readily available in the inpatient setting (furosemide, urinary catheter) and does not require any laboratory testing. Further, when compared to other commonly used biomarkers described earlier, the FST performs significantly better in predicting AKI progression to stage 3.[36] Due to its diuretic and blood pressure lowering properties, the FST should not be used in hemodynamically unstable patients requiring vasopressors and patients that are hypotensive or volume depleted.

The advances in our knowledge of AKI pathophysiology as well as the advent of biomarkers has prompted ADQI to propose the use of two new terms "functional change" and "kidney damage." Functional change refers to changes in glomerular and tubular function and includes markers such as S_{cr}, eGFR, and cystatin C. Kidney damage describes presence of tubular and/or glomerular injury and includes markers such as TIMP-2 and IGFBP7. The rationale behind the proposed changes in terminology stems from the recognition of subclinical kidney injury. According to this, kidney injury may be detected by changes in the plasma or urinary levels of specific biomarkers before overt changes in renal function (decreased eGFR or increased S_{cr}) have occurred. As a result, a patient may have kidney damage without a change in kidney function. Since this patient group is at a greater risk of complications, they may benefit from preventative interventions geared toward minimizing progression and toxicity (ie, avoidance or cessation of nephrotoxic drugs). **Table 60-5** summarizes the relationship between functional change and kidney damage.[37,38]

TABLE 60-5 Classification of AKI Based on Functional and Kidney Damage Biomarkers

		Kidney Damage	
		No	**Yes**
Loss of function	**No**	No loss of function or damage	Kidney damage without loss of function
		Biomarker negative	Biomarker positive
		KDIGO negative	KDIGO negative
	Yes	Loss of function but no kidney damage	Loss of function and presence of kidney damage
		KDIGO positive	KDIGO positive
		Biomarker negative	Biomarker positive

AKI, acute kidney injury; KDIGO, Kidney Disease Improving Renal Outcomes.

Diagnostic Considerations

When the source of kidney injury is unclear after reviewing the patient's history, physical examination, and assessment of laboratory values, imaging techniques such as abdominal radiography, including the kidneys, ureters, and bladder (KUB), computed tomography (CT), and ultrasonography may be helpful. These may reveal small, shrunken kidneys indicative of CKD. Postrenal obstruction can often be identified with a renal ultrasonography and/or CT scan. Renal ultrasonography is also useful in detecting obstruction or hydronephrosis. Nephrolithiasis as small as 5 nm or a narrowing of the ureteral tract can be detected by ultrasonography or more sensitive tests, such as KUB and CT. In cases in which the cause of AKI is not evident, renal biopsies are useful in determining the cause in most patients. Because of the associated risk of bleeding, a renal biopsy is rarely undertaken and should only be performed in those circumstances when a definitive diagnosis is needed to guide therapy, such as the precise etiology of glomerulonephritis (see Chapter 64).

PREVENTION OF ACUTE KIDNEY INJURY

Prevention of AKI is critical since there is no treatment to reverse the insult once it has developed. Several nonpharmacologic and pharmacologic options to reduce the risk of AKI are described below.

Desired Outcomes

The goals of AKI prevention are to (a) screen and identify patients at risk, (b) monitor high-risk patients until the risk has subsided, and (c) implement prevention strategies when appropriate.

General Approach to Prevention

6 The choice of preventive strategy depends on the patient's risk factors for AKI such as comorbidities, planned procedures, and medications, to name a few.

Sometimes, the risk of kidney injury is predictable, such as in the setting of decreased perfusion secondary to compromised cardiac function (eg, postcoronary bypass surgery) or secondary to the administration of a nephrotoxic agent like radiocontrast dye. In these situations, the potential insult to the kidneys cannot be avoided but may be preventable or minimized with intravenous fluids and/or avoidance or removal of any additional insults. In the inpatient setting, volume status optimization, hemodynamic support, and careful assessment of the risk versus benefit of potentially nephrotoxic medications are commonly recommended strategies for the prevention of AKI.

Nonpharmacologic and Pharmacologic Strategies for Prevention of AKI

Electronic Alert Systems

Recent advances in electronic health record (EHR) systems have led to the development of clinical decision support systems and electronic alerts designed to improve and standardize care in certain high-risk patient populations. Electronic alerts have been used for early detection of AKI and increased surveillance of patients on nephrotoxic medications. In general, alerts lead to greater implementation of the intervention, lower loss of kidney function, and decreased exposure to nephrotoxins.[39–41] For example, use of an EHR generated screening tool to identify pediatric patients receiving nephrotoxic medications and to recommend daily S_{cr} monitoring, switching a nephrotoxic drug to a non-nephrotoxic alternative or therapeutic drug monitoring, as appropriate has resulted in a 23% decrease in AKI rates and 42% decrease in AKI intensity.[42] Electronic alerts have the potential to reduce AKI by focusing on more appropriate drug prescribing and monitoring.

Despite favorable outcomes, implementation of electronic alerts is not without risks. One important consideration is alert fatigue, which occurs when providers are exposed to a excessive number of alerts and become desensitized to them as a result. Alert fatigue can be minimized by periodic monitoring of alert effectiveness and by carefully targeting patients who meet certain predefined criteria.[40]

Intravenous Fluids

Intravenous fluids are one of the primary interventions that have consistently shown benefit and are routinely used in the prevention of AKI. Intravenous fluids have largely been studied in association with hemodynamic instability secondary to intravascular volume depletion as well as contrast administration before a radiologic procedure.

Hemodynamic instability and systemic hypotension increase the risk of AKI as they can lead to decreased renal perfusion and subsequent kidney injury. Both isotonic crystalloids and colloid-containing solutions have been used for intravascular volume replacement. Among colloids, synthetic products such as hyperoncotic hydroxyethyl starch (HES) have been associated with impaired kidney function and should generally be avoided.[43] Albumin does not increase the risk of AKI and specific patient populations such as those with cirrhosis and spontaneous bacterial peritonitis may benefit from its therapy.[44] It has been hypothesized that albumin may offer additional advantages to septic patients as it is the main protein responsible for maintaining plasma colloid osmotic pressure, it has antioxidant and anti-inflammatory properties, and acts as a scavenger for reactive oxygen and nitrogen species. However, several studies have found that major patient outcomes such as risk of AKI, need for RRT, and mortality are comparable between albumin replacement therapy and isotonic saline.[45] At this time, the 2012 KDIGO guidelines recommend isotonic crystalloids over colloids for intravascular volume expansion in patients at risk for AKI.[3]

When using crystalloid solutions, options include either balanced solutions or isotonic saline. The main concerns associated with the use of large amounts of saline are hyperchloremic acidosis, interstitial edema, fluid overload, and death.[46–48] The chloride content in isotonic saline is 1.5 times that of plasma (154 mEq/L [mmol/L]) which can lead to hyperchloremic metabolic acidosis. Hyperchloremia in turn can decrease renal artery blood flow and renal tissue perfusion. Further, saline infusions cause a greater increase in interstitial fluid volume than balanced solutions, which may result in increased renal volume and intracapsular pressure, decreased microvascular blood flow, and impaired kidney

function.[48] Some studies have demonstrated more favorable outcomes with balanced fluids, including a significantly lower risk of AKI and reduced need for RRT, while others have not.[48,49] Balanced solutions appear to reduce the incidence of AKI and need for RRT in critically ill patients, but not in noncritically ill patients.[50] Overall, it appears that balanced solutions do not increase risk of AKI or other harmful outcomes and could provide some benefit compared to normal saline solutions.

In addition to correcting hemodynamic instability and hypovolemia, fluids are the mainstay of therapy for the prevention of contrast-induced acute kidney injury (CI-AKI). CI-AKI is a common cause of ATN in the inpatient setting (see Chapter 63 for a detailed discussion of CI-AKI) and is typically characterized by an increase in S_{cr} by at least 0.5 mg/dL (44 μmol/L; or 25% above baseline) within 48 hours of contrast administration. Hydration is thought to counterbalance some of the deleterious effects of radiocontrast dyes by diluting the contrast media, preventing renal vasoconstriction that contributes to hypoxia and ischemia, and minimizing tubular obstruction.[51] Hydration regimens for CI-AKI typically consist of either isotonic saline or sodium bicarbonate infusion and it has been hypothesized that sodium bicarbonate may be more protective as it reduces the formation of oxygen free radicals by alkalinizing renal tubular fluid. However, inconsistent results have been observed, and the recently published PRESERVE trial, a randomized double-blind, placebo-controlled trial conducted in over 5,000 patients undergoing angiography, demonstrated no difference in the risk of CI-AKI or need for RRT between patients who received either isotonic saline or sodium bicarbonate.[52,53] The 2012 KDIGO guidelines currently recommend using either sodium bicarbonate or isotonic saline in high-risk individuals receiving radiocontrast media.[3]

Since there is no consensus on the optimal rate and duration of fluid infusions, CI-AKI hydration protocols may vary across different institutions. A common sodium bicarbonate regimen is 154 mEq/L (mmol/L) infused at 3 mL/kg/hr for 1 hour before the procedure and at 1 mL/kg/hr for 6 hours after the procedure. The rate and duration of normal saline infusion vary, but one frequently cited regimen is 1 mL/kg/hr for 12 hours before and 12 hours after the procedure. The rate of administration may need to be adjusted depending on the patient's cardiopulmonary and volume status.

Another strategy that has been explored for the prevention of CI-AKI is the RenalGuard® system. This closed-loop fluid management system involves administration of a bolus dose of intravenous isotonic saline and 0.25 mg/kg intravenous furosemide, which in turn stimulates diuresis. Once the patient

reaches the target urine flow of at least 300 mL/hr, the urine output is continuously matched with the same amount of intravenous saline administration. This approach allows for a high degree of diuresis but also maintains euvolemia. By allowing for high urinary flow rates while still maintaining fluid balance, the contact time of contrast in the renal tubules can be decreased and risk of developing CI-AKI can be minimized. The RenalGuard® system has been shown to reduce the incidence of CI-AKI in high-risk patients undergoing interventional procedures.[54,55] Currently, RenalGuard® is commercially available in Europe and an investigational device in the United States.

The role of oral hydration (defined as ingestion of a specific amount of water prior and after receiving radiocontrast media) is not as well established as intravenous hydration; however, it has been compared to the intravenous route and found to be as effective in reducing the risk of CI-AKI.[56,57] Oral hydration is best reserved for outpatients with either normal kidney function or mild kidney impairment who are undergoing elective procedures. For inpatients or individuals who require emergent coronary angiography or radiological procedures with contrast exposures, IV hydration is still considered first-line treatment for prevention of CI-AKI.

While administration of intravenous fluids clearly has a critical role in AKI prevention, fluids need to be used judiciously as volume overload can have deleterious effects on the kidneys. The majority of crystalloid solutions redistribute into the interstitial space and can lead to interstitial edema, increased intra-abdominal pressure, decreased renal oxygen delivery, and decreased GFR. In fact, several studies have demonstrated poorer outcomes in patients with fluid overload including increased risk of AKI and decreased recovery of kidney function.[46,58] Hence, fluid administration beyond reestablishing euvolemia is generally not recommended. To prevent excess fluid administration, the patients medication profile should be reviewed, and where feasible, consider minimizing fluids by using intravenous push of medications (eg, diuretics), or other means to provide planned IV medications without compromising therapy.

Remote Ischemic Preconditioning

Remote ischemic preconditioning (RIPC) consists of a transient period of blood supply deprivation to a particular organ or tissue followed by a period of reperfusion. This priming process before a definitive ischemic injury or insult occurs may stimulate release of cytoprotective molecules and attenuate ischemic damage. Even when ischemia is induced at a nontarget site such as limb, it can

confer protection at a more distant site including brain, lung, and kidneys. As a result, RIPC is typically performed using a blood pressure cuff to a remote extremity (eg, upper arm). It consists of three cycles of 5-minute cuff inflation up to 200 mm Hg, or at least 50 mm Hg higher than the patient's systolic blood pressure, followed by a 5-minute cuff deflation period to allow for reperfusion to occur. While the exact mechanism of protection is unknown, it is thought to involve the activation of the humoral, neuronal, and immunomodulatory pathways.[59]

At this time, RIPC for AKI prevention has largely been studied in cardiovascular surgery and after contrast administration with mixed results.[60,61] A recent Cochrane systematic review found RIPC only slightly improved the incidence of AKI and likely had little to no impact on the need for dialysis, length of hospital stay, and mortality.[59] While the 2012 KDIGO guidelines do not comment on RIPC, the European Society for Intensive Care Medicine does not recommend RIPC for AKI prevention due to inconsistent findings.[3,47]

Ascorbic Acid Ascorbic acid has mainly been studied for the prevention of CI-AKI, as its antioxidant properties are thought to alleviate oxidative stress caused by ischemia reperfusion injury. To date, inconsistent results ranging from modest to no benefit have been observed.[62–64] Overall, despite an excellent safety profile and low cost, inadequate evidence exists to support use of ascorbic acid in the treatment or prevention of CI-AKI.

N-acetylcysteine *N*-acetylcysteine (NAC) is another antioxidant that has been widely studied in the prevention of CI-AKI. However, its therapeutic benefit is thought to be quite modest and has not been consistently demonstrated. The PRESERVE trial found that a 5-day course of oral NAC did not reduce risk of CI-AKI, need for RRT, or death in high-risk individuals undergoing angiography when compared to placebo.[53] The 2012 KIDGO guidelines suggest using NAC in combination with IV isotonic saline in patients at risk for CI-AKI; however, these guidelines pre-date the landmark PRESERVE trial, which indicates no benefit of NAC in the prevention of CI-AKI.[47,63,64]

Statins

The 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors, commonly referred to as statins, are one of the first-line therapies for the treatment of hyperlipidemia and prevention of cardiovascular events. Statins also exhibit anti-inflammatory, antioxidant, and endothelium protective effects,

which have led to research on their utility in preventing AKI. So far, statins have largely been studied for prevention of CI-AKI or AKI secondary to major cardiac surgery with mixed results. While statins may reduce the risk of AKI in high-risk patients exposed to contrast agents, they likely have no benefit or lead to higher incidence of AKI in surgery patients.[65–70] Randomized controlled trials are needed to clarify the role of statins in the prevention of AKI.[65,66]

Glycemic Control

In critical illness, both hyper- and hypoglycemia are associated with adverse patient outcomes.[71] Hyperglycemia can occur secondary to stress, inflammation, or drugs (eg, steroids) while hypoglycemia can develop secondary to decreased clearance of insulin, interruptions in nutrition support prior to procedures, or tight insulin protocols. Tight glycemic control with target glucose levels of 80 to 110 mg/dL (4.4 to 6.1 mmol/L) may significantly decrease the risk of AKI and this has been adopted in the ICU setting.[72,73] However, tight glycemic control protocols may also increase risk of hypoglycemia and mortality.[71,74,75] As a result, a more moderate approach to glycemic control is currently favored in the critically ill. Guidelines from the American Diabetes Association and Surviving Sepsis Campaign recommend a glycemic target range of 140 to 180 mg/dL (7.8-10 mmol/L) and less than 180 mg/dL (10 mmol/L), respectively, in critically ill patients.[76,77]

TREATMENT

7 Since there is no specific treatment that can reverse AKI or hasten its recovery, supportive measures that focus on hemodynamics, fluid balance, acid-base balance, and electrolyte homeostasis are the mainstays of therapy.

Desired Outcomes

Short-term goals of AKI management include minimizing the degree of insult to the kidney, reducing extrarenal complications, and expediting the patient's recovery of kidney function. Therapy should focus on maintaining organ functions while sustaining mean arterial pressure. The ultimate goal is to have the patient's kidney function restored to pre-AKI baseline.

General Approach to Treatment

Identification and management of AKI should be prompt. Prerenal sources of AKI should be managed with hemodynamic support and volume replacement, while postrenal AKI therapy should focus on removing the cause of the obstruction.[78] At the same time, patient's comorbidities and baseline kidney function need to be reviewed. Loss of kidney function combined with other clinical conditions, such as cardiac and liver failure, is associated with higher mortality.[79,80] At times, the most effective method for managing AKI may be treatment of the comorbid precipitating event. In patients where CKD is also present, the kidneys have less reserve, and there is a greater likelihood that full recovery may not occur. In more severe AKI, RRT may be necessary to maintain fluid, electrolyte, and acid-base balance while removing accumulating waste products or toxins.[78]

Pharmacologic and Nonpharmacologic Strategies for Treatment of AKI

Currently available pharmacologic and nonpharmacologic therapies are only supportive in nature and focus on managing complications such as fluid overload and acid-base/electrolyte imbalances. Maintaining an adequate fluid status is imperative but also challenging. First-line therapies for volume resuscitation consist of crystalloids such as balanced solutions or isotonic saline. On the other hand, fluid overload may be treated with loop diuretics or RRT.[3,47] Administration of all intravenous fluids should also be evaluated to determine if any notable reduction in daily intake can be accomplished. Patients with severe AKI are more likely to have concomitant acid-base and electrolyte derangements and thus are more likely to receive RRT.

Intravenous Fluids

The principal of fluid therapy is to maintain or restore effective intravascular volume to assure adequate renal perfusion. Similar to preventative hydration strategies, intravenous fluids need to be used judiciously as both volume depletion and fluid overload can adversely affect kidney function and increase mortality. Thus, maintaining adequate fluid balance is a major challenge in AKI patients, particularly those who are critically ill. In addition, the patient should be monitored for fluid intake and urine output, pulmonary and peripheral edema, blood pressure (target mean arterial pressure ≥65 mm Hg), and serum

electrolytes. Urine output ≥0.5 mL/kg/hr is generally targeted during the initial fluid resuscitation phase.[76]

In patients with anuria or oliguria, slower rehydration, such as 250-mL boluses or 100 mL/hr short-term infusions of isotonic saline or a balanced crystalloid solution, should be considered to reduce the risk for pulmonary edema, especially if heart failure or pulmonary insufficiency exists. Isotonic saline has been associated with hyperchloremic metabolic acidosis, especially if the dehydration is accompanied by a severe electrolyte imbalance amenable to large and relatively rapid infusions. For example, if dehydration resulting from severe diarrhea is accompanied by metabolic acidosis as the result of bicarbonate losses, the optimal IV rehydration fluid would be 5% dextrose with 0.45% sodium chloride plus 50 mEq (mmol) of sodium bicarbonate per liter. This fluid will remain mostly in the intravascular space, providing the necessary perfusion pressure to the kidneys, as well as a substantial amount of bicarbonate to correct the acidosis.

If AKI is a result of blood loss or is complicated by symptomatic anemia, red blood cell transfusion to a hemoglobin >7g/dL (70 g/L; 4.34 mmol/L) is the treatment of choice.[76] Once a hemoglobin of >7g/dL (70 g/L; 4.34 mmol/L) is reached, balanced solutions or normal saline can be used to restore intravascular volume. Albumin is typically preferred in individuals with severe hypoalbuminemia secondary to cirrhosis or nephrotic syndrome.[44] In critically ill patients with vasodilatory shock, vasopressors such as norepinephrine, vasopressin, or dopamine may be used in conjunction with fluids in order to maintain adequate hemodynamics and renal perfusion.[3]

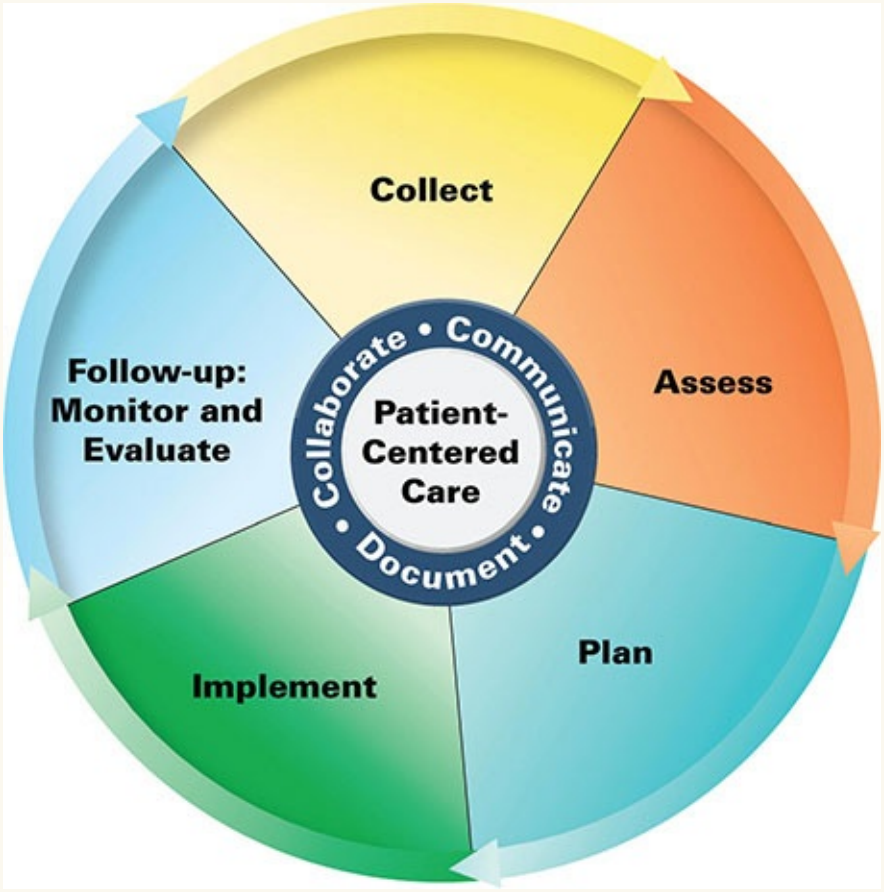
Electrolyte Management

Hypernatremia and fluid retention are frequent complications of AKI. Total daily sodium intake should be monitored as unintended sodium intake from intravenous drugs (ie, antibiotics) or foods can contribute to diuretic therapy failure.

The most common electrolyte disorder encountered in AKI patients is hyperkalemia, as >90% of potassium is renally eliminated. Life-threatening cardiac arrhythmias may occur with serum potassium concentrations greater than 6 mEq/L (mmol/L), so frequent monitoring of potassium is essential. Some foods and medications such as oral phosphorous replacement powders (eg, Neutra-Phos and Neutra-Phos-K) and alkalinizers (Polycitra) contain substantial amounts of potassium (see Chapter 68). Some medications may promote potassium retention by the kidneys and should also be avoided or closely

monitored if used (see Chapters 63 and 68). In general, exogenous potassium supplementation should be avoided in patients with AKI unless warranted by the presence of hypokalemia.

Other electrolytes that require monitoring are phosphorus and magnesium. Both are eliminated by the kidneys and, unlike potassium, are not efficiently removed by dialysis. In the early stages of AKI, hyperphosphatemia may be more common than hypophosphatemia. Patients with significant tissue destruction (eg, trauma, rhabdomyolysis, and tumor lysis syndrome) may have substantial amounts of phosphorus released from the destroyed tissue. Typically, the dietary intake of phosphorus needs to be restricted in advanced stages of AKI. However, patients receiving prolonged RRT can develop deficiency states as a result of reduced body stores. In contrast to the patient with CKD, AKI patients do not usually develop calcium imbalance secondary to the limited duration of the illness. One exception to this is seen in patients who are receiving continuous renal replacement therapy (CRRT) and regional citrate is used as the anticoagulant. Typically, citrate is infused before the dialyzer/hemofilter to bind serum calcium and to prevent the extracorporeal circuit from clotting. To account for the loss of calcium, either calcium chloride or calcium gluconate is administered prior to returning the blood to the patient. Some citrate will reach the systemic circulation, but it is subsequently metabolized by the liver and broken down into calcium and sodium bicarbonate. The goals of citrate anticoagulation are to maintain the circuit ionized calcium between 0.8 and 1.6 mg/dL (0.2 and 0.4 mmol/L), and the patient's systemic ionized calcium between 4.4 and 5.2 mg/dL (1.1-1.3 mmol/L).[3] Since severe hypocalcemia can result in arrhythmias or even death, frequent monitoring of unbound serum calcium concentrations is essential.



Patient Care Process for Acute Kidney Injury

Collect

- Patient characteristics (eg, age, sex, muscle mass)
- Chief complaint/reason for admission
- Patient medical history including other related comorbid conditions (eg, CKD, diabetes, HTN, cirrhosis)
- Current medication list
- Current or recent administration of nephrotoxins (eg, nonsteroidal anti-inflammatory drugs [NSAIDs], ACE-I/ARBs, contrast dyes, aminoglycosides, vancomycin)
- Blood pressure, heart rate, respiratory rate, weight
- Complete blood count and chemistry panel
- Changes in serum creatinine since last visit or admission (if available)

- Volume status (eg, fluid intake, urine output, patient weight)
- Hemodynamic status (eg, BP, MAP)
- Microbiology results (if available)
- Urinalysis results (eg, WBCs, RBCs, protein, granular casts, FE_{Na})
- Acid-base status (eg, arterial or venous blood gases)
- Kidney imaging results (eg, obstruction, hydronephrosis)

Assess

- Stage and severity of AKI using KDIGO criteria (S_{cr} and/or urine output)
- Most likely cause of AKI (eg, medication-induced, sepsis, volume depletion)
- Hemodynamic status / presence of acute hemodynamic changes
- Presence of baseline CKD
- Presence of sepsis, severe sepsis, or septic shock
- Presence of acid-base and/or electrolyte disturbances
- RRT modality and parameters if applicable

Plan

- Review all medications for appropriateness and ensure doses and frequencies are adjusted for patient's current kidney function or RRT
- Approach to symptom relief and need for electrolyte corrections
- Recommend therapeutic drug monitoring when necessary, especially for drugs with a narrow therapeutic index
- Referrals to other providers when appropriate (eg, nephrologist, dietician)

Implement*

- Communicate treatment plant to the patient's primary team and nephrology team (if consulted)
- Document therapy recommendations in the patient's electronic health record or chart
- Modify/enter any dose adjustments or changes in medications in the patient's electronic health record or chart
- Provide patient education regarding all elements of treatment plan (when

possible)

Follow-up: Monitor and Evaluate

- Changes in kidney function (eg, changes in serum creatinine, urine output, continued need for RRT)
- Hemodynamic and volume status
- Electrolytes, acid-base status
- Changes in dialysis type and/or schedule
- Fluid administration
- Serum drug concentration data
- Patient adherence to treatment plan using multiple sources of information
- Status of comorbid conditions
- Overall clinical status and management progression

*Collaborate with patient, caregivers, and other healthcare professionals.

Nutritional Considerations in AKI

Nutritional management of critically ill patients with AKI can be extremely complex, as it needs to account for metabolic derangements resulting from both impaired kidney function and underlying disease processes. Loss of the normal physiologic and metabolic functions of the kidney and the hypercatabolic response to stress and injury will have a significant impact on the metabolism of nutrients. Derangements in glucose, lipid, and protein metabolism result in hyperglycemia and insulin resistance, hypertriglyceridemia, protein catabolism, and negative nitrogen balance. The latter, in particular, is problematic to manage, as increased amino acid turnover and skeletal muscle breakdown lead to muscle wasting and malnutrition that does not respond well to increasing exogenous protein supplementation. The KDIGO guidelines currently recommend a caloric intake goal of 20 to 30 kcal/kg/day (84-126 kJ/kg/day) irrespective of the stage of kidney impairment and preferentially through the enteral route. In the setting of noncatabolic AKI without need for dialysis, 0.8 to 1 g/kg/day of protein is suggested and 1 to 1.5 g/kg/day if patient is receiving RRT.[3] CRRT is associated with an increased removal of small water-soluble molecules such as amino acids and certain nutrients. As a result, hypercatabolic patients receiving CRRT will typically have higher protein requirements up to a maximum of 1.7 g/kg/day.[3]

Renal Replacement Therapy

8 Renal replacement therapy is often utilized to treat fluid overload, electrolyte disturbances (eg, hyperkalemia), acid-base imbalances, uremic complications, and pulmonary edema resulting from severe AKI. Multiple factors influence decisions to initiate dialysis including specific timing and type of modality.[81–85] The most common indications for initiation of RRT are summarized in **Table 60-6**. The choice of continuous versus intermittent RRTs is a matter of considerable debate and usually depends on physician preference and the resources available. No difference in mortality or dialysis dependence has been shown between patients who received continuous or intermittent forms of RRT.[83,86] However, CRRT is generally preferred in hemodynamically unstable patients.[3]

TABLE 60-6 Common Indications for RRT

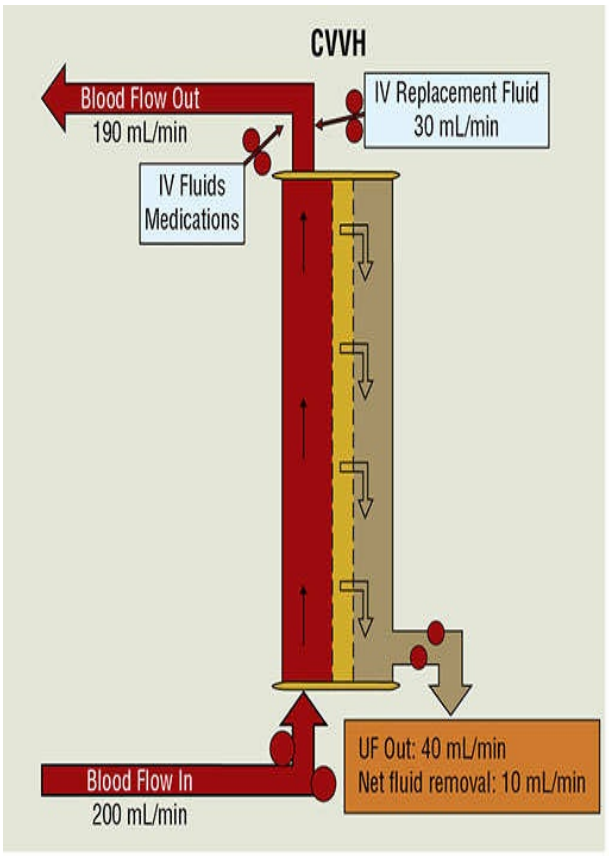
Indication for RRT	Clinical Setting
A: *acid-base abnormalities*	Metabolic acidosis (especially if pH <7.2)
E: *electrolyte imbalance*	Severe hyperkalemia and/or hypermagnesemia
I: *intoxications*	Salicylates, lithium, methanol, ethylene glycol, theophylline, phenobarbital
O: *fluid overload*	Fluid overload (especially pulmonary edema unresponsive to diuretics)
U: *uremia*	Uremia or associated complications (neuropathy, encephalopathy, pericarditis)

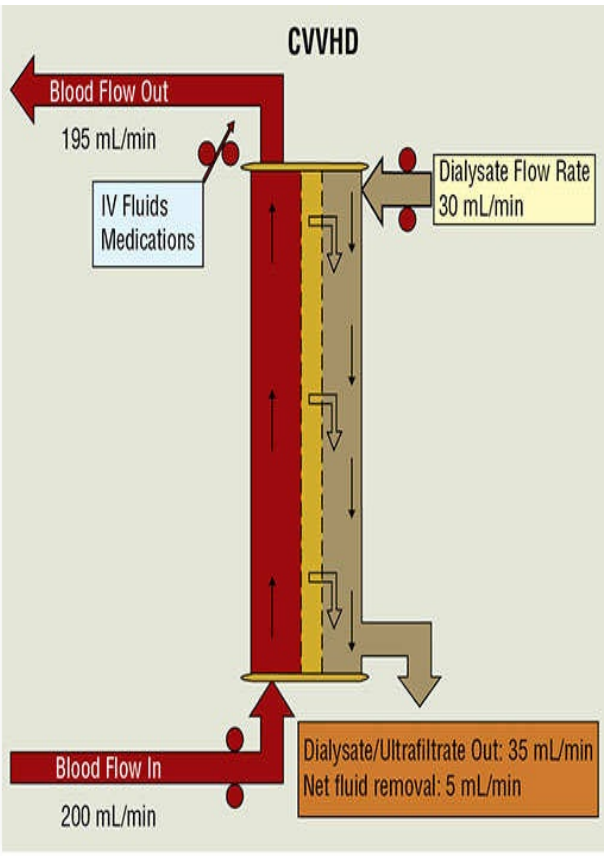
RRT, renal replacement therapy.

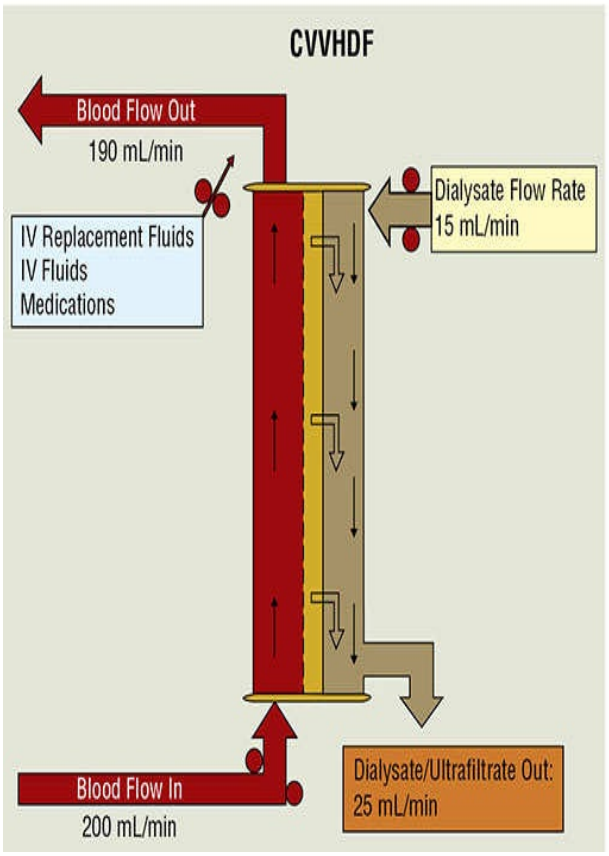
Intermittent Hemodialysis Intermittent hemodialysis (IHD) is the most frequently used RRT. IHD machines are readily available in most acute care facilities, and most healthcare workers are familiar with their use. Hemodialysis treatments usually last 3 to 4 hours, with blood flow rates to the dialyzer typically ranging from 200 to 400 mL/min. Advantages of IHD include rapid removal of volume and solutes and thereby contribute to correction of most of the electrolyte abnormalities associated with AKI. The primary challenge is hypotension, which is typically caused by the rapid removal of intravascular volume over a short period of time. Venous access for dialysis can be difficult in hypotensive patients and can limit the effectiveness of IHD. This can result in ineffective solute clearance, lack of acidosis correction, continued volume overload, and delayed recovery because of further ischemic insults to the

kidneys. Patients with CKD stage 5 generally achieve adequate solute and volume control with three times weekly dialysis, but hypercatabolic, fluid-overloaded patients with AKI may require more frequent hemodialysis treatments. Chapter 62 provides a detailed explanation of the principles and processes of IHD.

Continuous Renal Replacement Therapy Continuous renal replacement therapy is a viable option to manage hemodynamically unstable patients with AKI, especially those who cannot tolerate rapid volume removal. Unlike IHD treatments that last a few hours, CRRT runs continuously 24 hours a day, providing a slower but more consistent removal of solutes and fluid over time. Several CRRT variants have been developed, including continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF) (see Drug dosing considerations in AKI section). These modalities differ in the degree of both their solute removal as well as fluid clearance. The removal of solutes and fluid can be achieved via three different mechanisms: diffusion, convection, and membrane adsorption. CRRT can achieve a greater amount of solute removal and higher mean arterial pressures compared with IHD in critically ill patients with AKI.[86] In CVVH, solute and fluid clearance is primarily a result of convection, in which passive diffusion of the fluid containing solutes is removed, then fluid absent of solutes is replaced (**Fig. 60-3**). CVVHD provides a more extensive solute removal that works primarily by diffusion, where solute molecules at a higher concentration (plasma) pass through the dialysis membrane to an area of lower concentration (dialysate). Also, some fluid is removed as a function of the ultrafiltration coefficient of the dialyzer and the patient's blood pressure. CVVHD potentially has a lower risk of clotting the dialyzer circuit than CVVH because of decreased hemoconcentration, as there is less overall fluid removal during the process. CVVHDF combines both convection and hemodialysis, achieving even higher solute and fluid removal rates (Fig. 60-3).


CVVH
Blood Flow Out
190 mL/min
IV Replacement Fluid
30 mL/min
IV Fluids
Medications
UF Out: 40 mL/min
Net fluid removal: 10 mL/min
Blood Flow In
200 mL/min


CVVHD
Blood Flow Out
195 mL/min
IV Fluids
Medications
Dialysate Flow Rate
30 mL/min
Dialysate/Ultrafiltrate Out: 35 mL/min
Net fluid removal: 5 mL/min
Blood Flow In
200 mL/min


CVVHDF
Blood Flow Out
190 mL/min
IV Replacement Fluids
IV Fluids
Medications
Dialysate Flow Rate
15 mL/min
Dialysate/Ultrafiltrate Out:
25 mL/min
Blood Flow In
200 mL/min

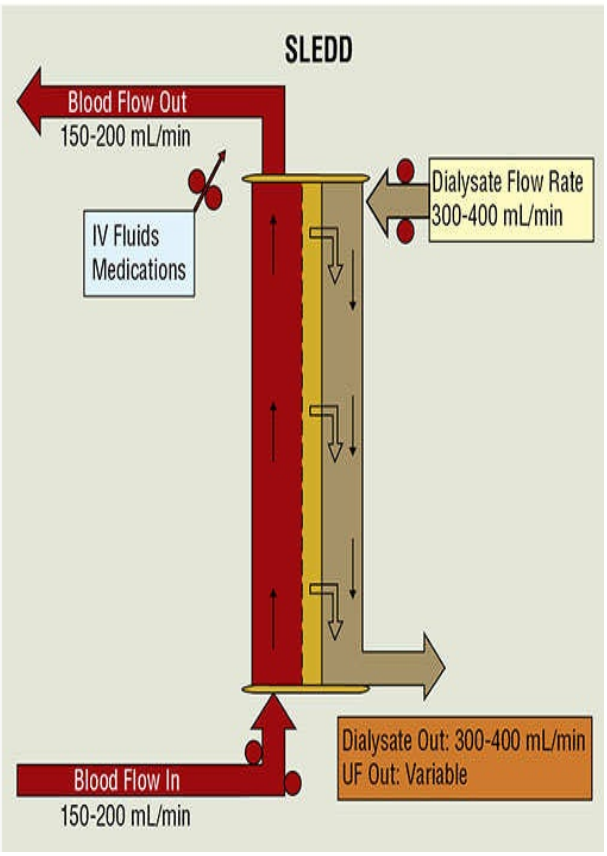

SLEDD
Blood Flow Out
150-200 mL/min
IV Fluids
Medications
Dialysate Flow Rate
300-400 mL/min
Dialysate Out: 300-400 mL/min
UF Out: Variable
Blood Flow In
150-200 mL/min

FIGURE 60-3 Several renal replacement therapies are commonly used in patients with acute kidney injury (AKI), including one of the three primary continuous renal replacement therapy (CRRT) variants: (a) continuous venovenous hemofiltration (CVVH), (b) continuous venovenous hemodialysis (CVVHD), (c) continuous venovenous hemodiafiltration (CVVHDF), and the hybrid intermittent hemodialysis therapy (d) sustained low-efficiency daily dialysis (SLEDD). The blood circuit in each diagram is represented in red, the hemofilter/dialyzer membrane is yellow, and the ultrafiltration/dialysate compartment is brown. Excess body water and accumulated endogenous waste products are removed solely by convection when CVVH is employed. With CVVHD, waste products are predominantly removed as the result of passive diffusion from the blood, where they are in high concentration to the dialysate. The degree of fluid removal that is accomplished by convection is usually minimal. CVVHDF uses convection to a degree similar to that employed during CVVH as well as diffusion, and thus is often associated with the highest clearance of drugs and waste products. Finally, SLEDD employs lower blood and dialysate flow rates than intermittent hemodialysis (IHD), but because of its extended duration, it is a gentler means of achieving adequate waste product and fluid removal.

Studies investigating the optimal CRRT dose in patients with AKI have demonstrated a direct relationship between CRRT dose and patient outcomes. The ultrafiltration rate is an important determinant of the effectiveness of CRRT. Higher ultrafiltration rates ultimately lead to a greater removal of electrolytes, nutrients, and drugs.[86] While early studies favored ultrafiltration rates of 35 to 45 mL/kg/hr, randomized controlled trials found no mortality difference in direct comparisons of ultrafiltration rates of 25 and 40 mL/kg/hr or higher.[86,87] A recent Cochrane review compared an intensive (prescribed dose ≥35 mL/kg/hr) to a less intensive (prescribed dose <35 mL/kg/hr) CRRT regimen and found no difference in mortality, recovery of kidney function, or hospitalization days. However, the risk of hypophosphatemia was higher with the more intensive regimen.[88] Current KDIGO guidelines recommend an ultrafiltration rate of no more than 20 to 25 mL/kg/hr during CRRT.[3] Some clinicians have argued for a slightly higher prescription of 25 to 30 mL/kg/hr to account for various machine interruptions that are common in clinical practice (eg, downtime for procedures, clotting).[85] Currently, CRRT doses between 20 and 30 mL/kg/hr appear to be acceptable and will depend on practice-dependent variables such as timing, patient characteristics, and comorbidities.[86]

Timing of CRRT initiation has not been clearly established to date. In situations when severe and life-threatening complications of AKI are present (eg, refractory acidosis, diuretic-resistant pulmonary edema secondary to fluid overload, uremic complications, overdose from a dialyzable drug), CRRT is clearly indicated. However, in the absence of life-threatening complications, the exact timing of CRRT initiation is uncertain. Clinicians are advised to carefully consider the patient's overall clinical status, severity of kidney impairment and related complications, and trends in the patient's physiologic and laboratory values before deciding whether and when to initiate CRRT.[84]

Anticoagulation is a major consideration for patients receiving CRRT as circuit clotting and filter patency can limit CRRT performance. It is important to note that the drivers for thrombosis and bleeding in severe kidney impairment are unique to this population, creating some limitations in applying approaches utilized in patients with more intact function. Typical anticoagulation is achieved by the administration of parenteral agents such as unfractionated heparin or regional citrate. Unfractionated heparin is widely available and easy to monitor but it also systemically anticoagulates the patient leading to an increased risk of bleeding. Regional citrate chelates ionized calcium in the extracorporeal circuit and impairs progression of the coagulation cascade. To maintain physiologic levels of calcium in the patient's systemic circulation when using regional citrate, most protocols require infusion of parenteral calcium and frequent monitoring of ionized calcium levels. When compared to unfractionated heparin, regional citrate is associated with less circuit clotting and longer filter lifetimes. Also, the risk of bleeding is lower as anticoagulation is limited to the extracorporeal circuit and does not extend to the patient. However, regional citrate increases the production of bicarbonate secondary to dissociation of the calcium-citrate complexes in the liver, which can increase the risk of metabolic alkalosis.[89] At this time, the KDIGO Work Group recommends regional citrate as the preferred anticoagulant of choice for patients receiving CRRT.[3] Regional citrate may not be a feasible option when the supply of parenteral calcium used to neutralize the citrate is limited during periods of short supply.

Other anticoagulants may be used in patients receiving CRRT but their use is less common or only recommended in select circumstances. Low-molecular weight heparins are generally not recommended due to increased cost, limited supporting data, poor removal by CRRT, and generally less data in this patient population (compared to unfractionated heparin or regional citrate). Direct thrombin inhibitors such as argatroban or bivalirudin are typically reserved for

patients with heparin-induced thrombocytopenia, but may be used in settings of heparin resistance or frequent thrombosis of the dialysis circuit.[3,89] Overall, the specific approach to anticoagulation depends on whether there is a need to limit anticoagulation to the circuit alone or extend it to systemically anticoagulate the patient. Many patients on CRRT require systemic anticoagulation for an underlying comorbidity (eg, atrial fibrillation, artificial heart valve) and will not need additional anticoagulation for RRT. As a result, the need for anticoagulation and the specific anticoagulant of choice should be tailored to individual patient requirements and corresponding indications.

Challenges with CRRT may include limited availability of the specialized equipment and other resources necessary to provide the treatments and to individualize the IV replacement, dialysate fluids, and drug therapy adjustments. Also, drug-dosing requirements for patients who are receiving CRRT are complex and not clearly defined.[90] CRRT use is most commonly considered for those patients with higher acuity because of their intolerance of IHD-associated hypotension. Current KDIGO guidelines suggest using CRRT over IHD in hemodynamically unstable patients.[3]

Prolonged Intermittent Renal Replacement Therapies An alternative to CRRT is prolonged intermittent RRT (PIRRT), which has had a variety of names including extended-duration IHD, hybrid IHD, sustained low-efficiency dialysis (SLED), or sustained low efficiency daily dialysis (SLEDD) (see Fig. 60-3). These therapies use lower blood (150-200 mL/min) and dialysate (300-400 mL/min) flow rates with extended treatment periods of 6 to 12 hours. For critically ill patients with AKI, they appear comparable to CRRT for hemodynamic control.[85] Although the use of PIRRT is increasing, our knowledge of its impact on drug removal is limited.[91] Significant differences in the prescribed parameters used in PIRRT, including frequency, duration, and dialysate flow rates, present challenges to healthcare providers responsible for appropriate drug selection and dosing.[92]

Diuretics Loop diuretics are frequently prescribed for the management of fluid overload in patients with established kidney injury. Loop diuretics have several theoretical advantages: increased urine output; decreased risk of ischemic injury by inhibiting the Na-K-Cl cotransporter and thus decreasing oxygen demand; and enhanced renal blood flow due to increased availability of renal prostaglandins. Enhancing urine output from oliguric to nonoliguric may be beneficial in itself, as nonoliguric AKI is associated with better outcomes than oliguric AKI.[93] However, clinical studies have found that even though the loop

diuretics increase urine output, they neither reduce the incidence of AKI nor improve patient outcomes (ie, mortality, need for RRT, kidney recovery) for patients with established AKI.[93] One proposed explanation for this lack of benefit is that loop diuretics may actually decrease renal blood flow by reducing effective circulating arterial volume, which, in turn, may stimulate the adrenergic and the renin–angiotensin systems.[94] Therefore, the KDIGO guidelines recommend limiting the use of loop diuretics to the management of fluid overload and avoiding their use for the sole purpose of prevention or treatment of AKI.[3]

Diuretic resistance is a relatively common problem in patients with AKI for several reasons. Excessive sodium intake may override the ability of the diuretics to eliminate sodium. Patients with ATN have a reduced number of functioning nephrons on which the diuretic may exert its action. Other clinical states, such as glomerulonephritis, are associated with heavy proteinuria. Intraluminal loop diuretics cannot exert their effect in the loop of Henle if they are extensively bound to proteins present in the urine. Still other patients may have greatly reduced bioavailability of oral furosemide because of intestinal edema, often associated with high preload states, which further reduces oral furosemide absorption. Lastly, the breaking phenomenon, which is a progressively decreasing response to natriuresis associated with repeated administration of a loop diuretic, may also lead to diuretic resistance.[93,94] **Table 60-7** includes possible therapeutic options to counteract each form of diuretic resistance.

TABLE 60-7 Common Causes of Diuretic Resistance in Patients with AKI

Causes of Diuretic Resistance	Potential Therapeutic Solutions
Excessive sodium intake (sources may be dietary, IV fluids, and drugs)	Remove sodium from nutritional sources and medications
Inadequate diuretic dose or inappropriate regimen	Increase dose, increase frequency, use continuous infusion or add thiazide
Reduced oral bioavailability (usually furosemide)	Use parenteral therapy, switch to oral torsemide or bumetanide
Nephrotic syndrome (loop diuretic protein binding in tubule lumen)	Increase dose, add thiazide
Reduced renal blood flow	
Drugs (NSAIDs, ACEIs, vasodilators)	Discontinue these drugs if possible
Intravascular depletion	Intravascular volume expansion
Increased sodium resorption	
Distal nephron hyperthrophy	Add thiazide, sodium restriction
Postdiuretic sodium retention	Dietary sodium restriction, use continuous infusion
Heart failure	Assess effective circulatory volume, increase dose, increase frequency, use continuous infusion
Cirrhosis	Assess effective circulatory volume, consider paracentesis
Acute tubular necrosis	Increase diuretic dose, diuretic combination therapy

ACEIs, angiotensin-converting enzyme inhibitors; NSAIDs, nonsteroidal anti-inflammatory drugs.

The most common therapeutic option to overcome diuretic resistance is to use higher doses of loop diuretics. Often, patients with impaired kidney function have lower rates of diuretic secretion into the tubular fluid; consequently, higher doses of loop diuretics are prescribed, or they are used in combination with other classes of diuretic agents. Caution must be taken when increasing intermittent bolus doses as the risk of adverse reactions such as ototoxicity also increases due to higher corresponding peak concentrations. One option to avoid high peak concentrations and postdiuretic sodium retention is to administer loop diuretics as a continuous infusion. Administration via a continuous infusion can achieve

the same degree of diuresis with lower doses and results in no difference in mortality or hospital length of stay. An initial loading dose is recommended prior to the initiation of a continuous infusion of furosemide or its equivalent to decrease the time to the drug's onset of action.[94] One disadvantage of using a continuous infusion is it requires more extensive and frequent monitoring, as infusion rates are usually based on an hourly urine output goal. Typically, increasing intermittent bolus doses or dosing frequency are trialed before implementing the more labor-intensive continuous infusion.

Another approach to overcome diuretic resistance in AKI is to use a loop diuretic in combination with a diuretic from a different pharmacologic class. Diuretics that work at the distal convoluted tubule (chlorothiazide and metolazone) or the collecting duct (amiloride, triamterene, and spironolactone) may have a synergistic effect when administered with loop diuretics by blocking the compensatory increase in sodium and chloride reabsorption (see Chapter 66). Thiazide diuretics are most commonly used in combination with loop diuretics. Oral metolazone is used most often because, unlike other thiazides, it produces effective diuresis at a CL_{cr} less than 20 mL/min (0.33 mL/s). Initiation of metolazone of 2.5 mg daily is a safe and effective starting dose. Oral metolazone is frequently given 30 minutes prior to intravenous loop diuretics to achieve peak effects at the same time to potentially enhance diuresis. The combination of thiazide and thiazide-type diuretics and a loop diuretic has been used successfully in the management of fluid overload. When such combinations are used, there should be a follow-up assessment regarding any improved or enhanced diuresis.[94]

Drug Dosing Considerations in AKI

9 Optimization of drug therapy for patients with AKI is often challenging. The multiple variables influencing responses to the drug regimen include the patient's residual drug clearance, fluid accumulation, and delivery of RRT. In addition, the patient's current kidney function state and corresponding drug elimination influenced by the decline, stabilization or recovery of AKI should be considered. For renally eliminated drugs, particularly for agents with a narrow therapeutic range, serum drug concentration measurements and assessment of pharmacodynamic responses are likely to be necessary. If hepatic function is intact, choosing an agent eliminated primarily by the liver may be preferred. Kidney failure can also independently impair nonrenal drug elimination including metabolism through "organ crosstalk," where the dysfunction of one organ affects another.[95] Unfortunately, pharmacokinetic

studies in patients with established AKI (and CKD) are fairly limited. Further, the use of dosing guidelines based on data derived from patients with stable CKD may not reflect the clearance and volume of distribution in critically ill AKI patients[90] (see Chapter 65). The inability to adequately dose drugs in critically ill patients with AKI requiring RRT may be one factor contributing to the lack of improving outcomes with newer RRT approaches.

Pharmacotherapy regimen decisions should further take into consideration four distinct phases of AKI described earlier, specifically initiation, extension, maintenance, and recovery phase. The initiation and extension phases occur right after the kidney insult. At this point, decisions on drug therapy should include the specific pharmacokinetics of the drug, the potential for increased risk for an adverse drug event, the goals of therapy, and therapeutic drug monitoring (if available). The severity and timing of the decline in kidney function is relatively unpredictable, so frequent monitoring and reevaluation of drug dosing is necessary. S_{cr} measurements lag behind kidney function; that is, today's S_{cr} measurements typically describe yesterday's kidney function, while urine output maybe a more current surrogate marker of function. As kidney function stabilizes, drug therapy regimens typically require fewer alterations. The third phase is recovery, where AKI begins to resolve (increase in urine output may be a signal) and there may be a need to increase the drug dose. It is critically important to follow the patient closely and recognize trends for decreasing or improving kidney function including recovery from the initial insult (eg, recovery of cardiac function in pre-renal failure), along with adjustments or discontinuation of RRT in an effort to achieve and maintain drug therapy management goals.

Edema, which is common in AKI, can significantly increase the volume of distribution of many drugs, particularly water-soluble ones with relatively small volumes of distribution. Increased fluid distribution into the tissues (ie, sepsis and anasarca in heart failure) can also contribute to a larger volume of distribution for many drugs and thereby reduce the proportion of drug in the plasma that is available to be removed by RRT. Because AKI frequently occurs in critically ill patients, multisystem organ failure is often an accompanying problem. In addition to volume overload, reductions in cardiac output or liver function can significantly alter the pharmacokinetic profile of most drugs. For selected renally eliminated drugs or related metabolites with narrow therapeutic windows, close follow-up and dosing adjustments may be necessary.[90,91]

If rapid onset of activity is desired, a loading dose may be necessary to promptly achieve desired serum concentrations because the expanded volume of

distribution and the prolonged elimination half-life extend the time (3.5 times the half-life) needed to reach steady-state concentrations. Maintenance dosing regimens should be reassessed frequently and be based on the patient's most current kidney function. A dose that provides the desired serum concentration on one day may be inappropriate a few days later if the patient's fluid status, RRT prescription, or kidney function has changed dramatically.[90]

Drug therapy individualization for the AKI patient who is receiving any form of RRT is complicated by the fact that patients with AKI may have a higher residual nonrenal clearance than patients with CKD who have a similar CL_{cr}.[90] Alterations in the activity of some, but not all, cytochrome P450 enzymes have been demonstrated in patients with CKD.[95,96] This may be the result of less accumulation of uremic waste products that may alter hepatic function. If a patient with AKI has higher than anticipated nonrenal clearance, this would result in lower than expected, possibly subtherapeutic, drug serum concentrations. For example, to maintain comparable serum concentrations, the imipenem dose requirement in patients with AKI would be 2,000 mg daily as compared with the recommended dosage for patients with ESRD of 1,000 mg daily. As AKI persists, the nonrenal clearance values appear to approach those observed in patients with CKD.[96] Another challenge is that much of the dosing-related data were acquired in patients with CKD, with initial pharmacokinetic assessments done after single-dose administration. The determination of pharmacokinetic parameters using a single-dose model may result in more rapid initial drug removal estimates secondary to distribution from the plasma to the tissue as well. In addition, drug elimination in AKI may be more robust than in CKD. In one analysis involving use of aminoglycosides, elimination in AKI was 30% faster than CKD.[97] Thus, application of dosing regimens derived from studies in patients with CKD and ESRD in addition to the use of more aggressive RRT approaches may result in underdosing of certain drugs and thereby contribute to less than optimal clinical outcomes.

Drug Dosing Considerations in RRT

There are several physicochemical and pharmacokinetic characteristics that can alter drug clearance during RRT, including molecular weight, protein binding, volume of distribution, and degree of renal clearance or fraction eliminated by the kidneys.[98,99] Drug dosage regimen design considerations specific to patients receiving peritoneal dialysis and IHD are presented in Chapter 65. In general, RRT-mediated drug clearance is inversely related to molecular weight, such that

RRT drug clearance decreases as the weight of a drug increases. IHD efficiently clears drugs with a small molecular weight (ie, <500 Da), whereas CRRT therapies can efficiently clear much larger solutes (ie, <15,000 Da). Protein binding can also affect clearance in both IHD and CRRT as the drug-protein complexes increase molecular weight (eg, >50,000 Da), thus making it difficult for the complexes to pass through the pores in the hemofilter.[98,99] Additionally, patients with hypoalbuminemia will have a higher fraction of unbound drug, thus a larger amount of the agent may be removed during RRT. Drugs with a large volume of distribution (V_D) are extensively distributed to extravascular tissues, leaving only a small fraction of the drug in the vascular compartment and limiting drug removal. During CRRT, drugs with a large V_D (>1 L/kg) will exhibit higher clearance due to the extended length of therapy.[98,99] Renal clearance of a drug also plays a role in determining RRT removal. In general, drugs that are predominantly renally cleared are more likely to be cleared via CRRT than drugs that are eliminated primarily by nonrenal mechanisms.

There are marked differences in drug removal between the different RRT modalities. During CVVH, drug removal primarily occurs via convection/ultrafiltration. Convection is the passive transport of drug molecules at the concentration at which they exist in plasma water into the ultrafiltrate. Convective removal is most efficient for smaller molecules, typically less than 15,000 Da (15 kDa) in size, and those that are primarily not protein bound in the plasma. The clearance of a drug by either of these methods is thus a function of the membrane permeability for the drug, which is called the sieving coefficient (SC), and the ultrafiltration rate (UFR). The SC is the ratio of a solute or drug in the ultrafiltrate to that in plasma water. A SC of 1 indicates free transport across the membrane where a SC of 0 indicates no transport across the membrane. In practice, the SC is sometimes estimated by simultaneously measuring the concentration of solute pre-filter or in plasma (Cp) and the concentration of solute in the ultrafiltrate (Cuf), as follows:

$$SC = Cuf/Cp$$

The SC is often approximated by the fraction unbound (f_u), or the fraction of drug unbound to protein in the plasma, because the ratios are often similar and this information may be more readily available than SC. Thus, the clearance of a drug by CVVH, which is largely driven by convection, can be calculated as:

$$Cl_{convection} = UFR \times SC$$

Or, if SC is not available, clearance can be approximated as:

$$Cl_{convection} = UFR \times fu$$

In CVVHD, clearance is a combination of both convection and diffusion, but diffusion is the main mechanism for solute removal. During diffusion, solutes move down a concentration gradient from an area of higher concentration (plasma) to an area of lower concentration (dialysate). Combining convection and diffusion leads to more efficient drug removal. The clearance of a drug via CVVHD, which is largely driven by diffusion, can be approximated as:

$$Cl_{diffusion} = DFR \times fu$$

where DFR is the dialysate flow rate.

In CVVHDF, clearance is a combination of both diffusion and convection. The Cl_{CVVHDF} can be mathematically approximated by combining the clearances from convection and diffusion, as follows:[99]

$$Cl_{CVVHDF} = Cl_{convection} + Cl_{diffusion} \text{ or } (UFR + DFR) \times fu$$

Individualization of pharmacotherapy for a patient receiving CRRT is dependent on the patient's residual kidney function, the clearance of the drug by CRRT, as well as the properties of the drug (ie, molecular weight, V_D, protein binding, and SC). Frequency of CRRT interruptions will also impact drug removal and corresponding dosing requirements. There are differences in the rate of drug removal not only between the three primary modes of CRRT but also within each mode.[90] This is a result of differences in the filter membrane composition, variable degrees of drug binding to the membrane, and permeability characteristics of the membrane.[100,101] Primary factors that influence drug clearance during CRRT are the UFR, blood flow rate, and DFR. For example, clearance in CVVH is directly proportional to the UFR, whereas clearance during CVVHDF, which depends on both the UFR and the DFR, increases as either flow rate increases. Additionally, an increase in the UFR (5-45 mL/min) and DFR (8.3-33.3 mL/min), however, can have dramatic effects on the clearance of many agents during CVVH and CVVHD, respectively, and potentially lead to subtherapeutic effects and loss of efficacy (**Fig. 60-4**).[100] Further, CRRT can rapidly remove excess fluid from edematous patients, thereby changing the V_D of drugs with limited distribution (low V_D suggesting a greater proportion in the plasma or extracellular fluid) fairly rapidly.[101] Drug clearances

attained by IHD, CRRT, and PIRRT all differ from each other and must be added to any endogenous drug clearance that the patient generates.

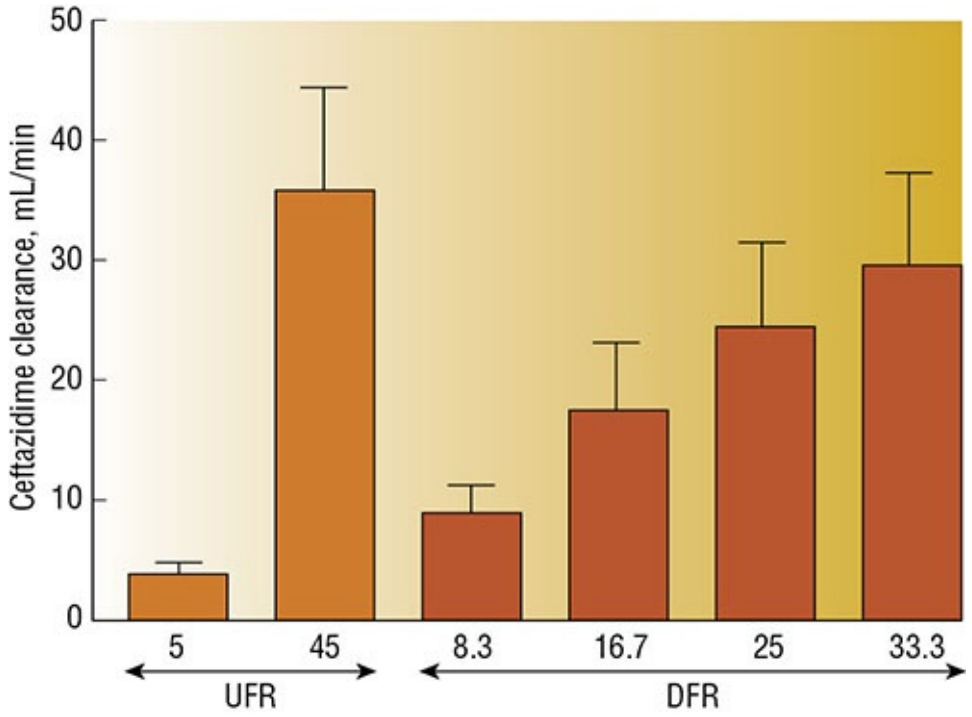


FIGURE 60-4 Effect of increasing ultrafiltration rate (UFR in milliliters per minute) and dialysate flow rate (DFR in milliliters per minute) on the clearance of ceftazidime. (*Data from Reference 100*.)

Limitations of IHD-based dosing charts include variability in the patient's individual pharmacokinetic parameters, differences in the dialysis prescription, such as dialyzer blood flow or duration, unpredictability of dialysis timing based on availability, use of new hemodialyzers, and advances in the technology without knowing how drugs are impacted. Pharmacokinetic and drug dosing assessments in patients with impaired kidney function often are performed after single dose administration to stable CKD subjects. Distribution and clearance estimates in this setting may not reflect those observed at steady state.[102,103] The approach to hemodialysis may also change on a daily basis, especially in hemodynamically unstable individuals with AKI. This could include, for example, the type of dialyzer/filter used, the duration, the degree of hemofiltration compared with convection, and the blood flow rate. Individualization of a dosing regimen may require daily assessment of the clinical status of the patient and any planned or recently administered hemodialysis.

Overall, there are numerous potential pharmacokinetic and pharmacodynamic

alterations to be aware of in the patient with AKI. Unfortunately, there is still a scarcity of data to quantify these changes, and even less evidence demonstrating that if one incorporates these considerations into patient care, the associated outcomes will be improved.

EVALUATION OF THERAPEUTIC OUTCOMES

Vigilant monitoring of patients with AKI is essential, particularly in those who are critically ill. Table 60-8 summarizes the main monitoring parameters for patients with established AKI.

TABLE 60-8 Key Monitoring Parameters for Patients with Established AKI

Parameter	Frequency
Fluid ins & outs	Daily
Patient weight	Daily
Hemodynamics (blood pressure, heart rate, mean arterial pressure, etc.)	Hourly/Every shift
Blood chemistries	
Sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium	Daily
Blood urea nitrogen/serum creatinine	Daily
Drugs and their dosing regimens	Daily
Nutritional regimen	Daily
Blood glucose	Daily (minimum)
Therapeutic drug monitoring of renally cleared drugs (eg, vancomycin aminoglycosides)	Highly variable, about three times weekly
Times of administered doses	Daily
Doses relative to administration of renal replacement therapy	Daily
Urinalysis, Urinary output	
Calculate measured creatinine clearance	Every time measured urine collection performed
Calculate fractional excretion of sodium	Every time measured urine collection performed
Plans for renal replacement therapy	Daily

Once the laboratory-based tests (eg, urinalysis and FE_{Na} calculations) have been conducted to diagnose the cause of AKI, they usually do not have to be repeated. In established AKI, daily measurements of fluid intake and output should be performed. Vital signs should be monitored at least daily or more often if the acuity of illness warrants it. Electrolytes, BUN, S_{cr}, and a complete blood cell count should be considered routine and measured at least daily for hospitalized patients. For medications influenced by RRT, appropriateness of doses should be assessed daily. At times, this may mean measuring a serum drug concentration to determine how to revise the medication regimen. Healthcare providers should be directed to notify the clinical pharmacist when RRT is stopped or discontinued.

Therapeutic drug monitoring should be performed for drugs that have a narrow therapeutic index if results can be obtained in a timely fashion. For patients receiving IHD, measuring a pre-dialysis serum drug concentration has the advantage of allowing time for the result to be reported and the next dose calculated so that it can be administered soon after dialysis. This is especially important if the desired pharmacologic effects are lost during or after hemodialysis because the serum concentration has become subtherapeutic. Serum concentrations drawn right after hemodialysis may reflect plasma concentrations that are transiently depressed until the drug can reequilibrate from the tissues (ie, a redistribution or rebound effect). The advantage of collecting a postdialysis sample is the greater accuracy in determining how much drug was removed during hemodialysis. The down side of this strategy is that it delays dosing calculations and the administration of the next dose, and may ultimately delay the reestablishment of the target concentrations.

CONCLUSION

The unique characteristics of AKI can lead to notable differences in how kidney function is measured and how treatment regimens are developed. Most management approaches involve both prevention and supportive strategies, so as to minimize the potential for additional harm to the kidneys. Understanding the constantly changing status inherent to AKI and how to adjust drug regimens is a key component to optimizing therapy.

Postclass Engaged Learning Activity

Conduct a literature search and identify a primary research manuscript that has been published in the past 12 months regarding use of a medication for the prevention or management of acute kidney injury. Write a brief summary about the medication's intended mechanism of action, the study methods, the major findings, and how this new information might change current practice. This activity is intended to build your experience with accessing and evaluating primary biomedical literature.

ABBREVIATIONS

ACE	angiotensin-converting enzyme
ADQI	Acute Dialysis Quality Initiative
AIN	acute interstitial nephritis
AKD	acute kidney disease
AKI	acute kidney injury
AKIN	Acute Kidney Injury Network
ARB	angiotensin receptor blocker
ATN	acute tubular necrosis
BUN	blood urea nitrogen
CI-AKI	contrast-induced acute kidney injury
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL_{cr}	creatinine clearance
CRRT	continuous renal replacement therapy
CT	computed tomography
CVVH	continuous venovenous hemofiltration
CVVHD	continuous venovenous hemodialysis
CVVHDF	continuous venovenous hemodiafiltration
DFR	dialysate flow rate
eCL_{cr}	estimated creatinine clearance
eGFR	estimated glomerular filtration rate
EHR	electronic health record
ESKD	end-stage kidney disease
FDA	Food and Drug Administration
FE_{Na}	fractional excretion of sodium
FE_{Urea}	fractional excretion of urea
FST	furosemide stress test
GI	gastrointestinal
GFR	glomerular filtration rate
IGFBP7	insulin growth like factor binding protein 7
IHD	intermittent hemodialysis
JVP	jugular venous pressure
KDIGO	Kidney Disease: Improving Global Outcomes
KUB	kidneys, ureters, and bladder
MDRD	Modification of Diet in Renal Disease
NAC	*N*-acetylcysteine
NGAL	neutrophil gelatinase–associated lipocalin
NSAID	nonsteroidal anti-inflammatory drug
PIRRT	Prolonged intermittent renal replacement therapy
RIFLE	Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease
RRT	renal replacement therapy

SC	sieving coefficient
S_{cr}	serum creatinine
SLED	sustained low-efficiency dialysis
TIMP-2	tissue inhibitor of metalloproteinases 2
UFR	ultrafiltration rate

REFERENCES

1. Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure—Definition, outcome measures, animal models, fluid therapy and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004;8:R204–R212.
2. Mehta RL, Kellum JA, Shah SV, et al. Acute kidney injury network: Report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11:R31.
3. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Workgroup. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl*. 2012;2:1–138.
4. Chawla LS, Bellomo R, Bihorac A, et al. Acute kidney disease and renal recovery: Consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. *Nat Rev Nephrol*. 2017;13(4):241–257.
5. Zeng X, McMahon GM, Brunelli SM, et al. Incidence, outcomes, and comparisons across definitions of AKI in hospitalized individuals. *Clin J Am Soc Nephrol*. 2014;9(1):12–20.
6. Pereira M, Rodrigues N, Godinho I, et al. Acute kidney injury in patients with severe sepsis or septic shock: A comparison between the 'Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease' (RIFLE), Acute Kidney Injury Network (AKIN) and Kidney Disease: Improving Global Outcomes (KDIGO) classifications. *Clin Kidney J*. 2017;10(3):332–340.
7. Luo X, Jiang L, Du B, et al. A comparison of different diagnostic criteria of acute kidney injury in critically ill patients. *Crit Care*. 2014;18(4):R144.
8. Lin J, Fernandez H, Shashaty MG, et al. False positive rate of AKI using consensus creatinine-based criteria. *Clin J Am Soc Nephrol*. 2015;10(10):1723–1731.

9. Pavkov ME, Harding JL, Burrows NR. Trends in hospitalizations for acute kidney injury: United States, 2000–2014. *MMWR*. 2018;67:289–293.
10. Hoste EA, Kellum JA, Selby NM, et al. Global epidemiology and outcomes of acute kidney injury. *Nat Rev Nephrol*. 2018. doi:10.1038/s41581-018-0052-0.
11. Grams ME, Sang Y, Ballew SH, et al. A meta-analysis of the association of estimated GFR, albuminuria, age, race, and sex with acute kidney injury. *Am J Kidney Dis*. 2015;66(4):591–601.
12. Hoste EA, Bagshaw SM, Bellomo R, et al. Epidemiology of acute kidney injury in critically ill patients: The multinational AKI-EPI study. *Intensive Care Med*. 2015;41(8):1411–1423.
13. Horkan CM, Purtle SW, Mendu ML, et al. The association of acute kidney injury in the critically ill and postdischarge outcomes: A cohort study. *Crit Care Med*. 2015;43(2):354–364.
14. Malhotra R, Kashani KB, Macedo E, et al. A risk prediction score for acute kidney injury in the intensive care unit. *Nephrol Dial Transplant*. 2017;32(5):814–882.
15. Horne KL, Packington R, Monaghan J, et al. Three-year outcomes after acute kidney injury: Results of a prospective parallel group cohort study. *BMJ Open*. 2017;7(3):e015316.
16. Badr KF, Ichikawa I. Prerenal failure: A deleterious shift from renal compensation to decompensation. *N Engl J Med*. 1988;319:623–629.
17. Ungprasert P, Cheungpasitporn W, Crowson CS, Matteson EL. Individual non-steroidal anti-inflammatory drugs and risk of acute kidney injury: A systematic review and meta-analysis of observational studies. *Eur J Intern Med*. 2015;26(4):285–291.
18. Gomez H, Kellum JA. Sepsis-induced acute kidney injury. *Curr Opin Crit Care*. 2016;22(6):546–553.
19. Bellomo R, Kellum JA, Ronco C, et al. Acute kidney injury in sepsis. *Intensive Care Med*. 2017;43(6):816–828.
20. Ostermann M, Liu K. Pathophysiology of AKI. *Best Pract Res Clin Anaesthesiol*. 2017;31(3):305–314.
21. Bevc S, Ekart R, Hojs R. The assessment of acute kidney injury in critically ill patients. *Eur J Intern Med*. 2017;45:54–58.
22. Krishnan N, Perazella MA. Drug-induced acute interstitial nephritis: Pathology, pathogenesis, and treatment. *Iran J Kidney Dis*. 2015;9(1):3–

13.
23. Joyce E, Glasner P, Ranganathan S, et al. Tubulointerstitial nephritis: Diagnosis, treatment and monitoring. *Pediatr Nephrol*. 2017;32(4):577–587.
24. Lameire N, Vanholder R, Van Biesen W, et al. Acute kidney injury in critically ill cancer patients: An update. *Crit Care*. 2016;20(1):209.
25. Ostermann M. Diagnosis of acute kidney injury: Kidney disease improving global outcomes and beyond. *Curr Opin Crit Care*. 2014;20(6):581–587.
26. Macedo E, Mehta RL. Measuring renal function in critically ill patients: Tools and strategies for assessing glomerular filtration rate. *Curr Opin Crit Care*. 2013;19(6):560–566.
27. Baumann TJ, Staddon JE, Horst HM, Bivins BA. Minimum urine collection periods for accurate determination of creatinine clearance in critically ill patients. *Clin Pharm*. 1987;6:393–398.
28. Wasung ME, Chawla LS, Madero M. Biomarkers of renal function, which and when? *Clin Chim Acta*. 2015;438:350–357.
29. Teo SU, Endre ZH. Biomarkers in acute kidney injury. *Best Prac Res Clin Anesthesiol*. 2017;31:331–344.
30. Kellum JA, Chawla LS. Cell-cycle arrest and acute kidney injury: The light and the dark sides. *Nephrol Dial Transplant*. 2015;0:1–7.
31. Lameire N, Vanmassenhove J, Van Biesen W, et al. The cell cycle biomarkers: Promising research, but do not oversell them. *Clin Kidney J*. 2016;9(3):353–358.
32. Nephrocheck Test Kit package insert. Available at: http://www.astutemedical.com/documents/US-English/NephroCheck-Test-Kit-Package-Insert-US-PN-300152.pdf. Accessed August 24, 2018.
33. Mehta R. Moderator's view: patient-centered approaches for optimizing AKI management: the role of kidney biomarkers. *Nephrol Dial Transplant*. 2017;32:419–422.
34. Meersch M, Schimdt C, Hoffmeier A, et al. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: The PrevAKI randomized controlled trial. *Intensive Care Med*. 2017;43:1551–1561.
35. Chawla LS, Davison DL, Brasha-Mitchell E, et al. Development and standardization of a furosemide stress test to predict the severity of acute

kidney injury. *Crit Care*. 2013;17:R207.

36. Koyner JL, Davison DL, Brasha-Mitchell E, et al. Furosemide stress test and biomarkers for the prediction of AKI severity. *J Am Soc Nephrol*. 2015;26:2023–2031.
37. McCullough PA, Shaw AD, Haase M, et al. Diagnosis of acute kidney injury using functional and injury biomarkers: Workgroup statements from the tenth Acute Dialysis Quality Initiative Consensus Conference. *Contrib Nephrol*. 2013;182:13–29.
38. Kane-Gill SL, Smithburger PL, Kashani K, et al. Clinical relevance and predictive value of damage biomarkers of drug-induced kidney injury. *Drug Saf*. 2017;40:1049–1074.
39. Haase M, Kribben A, Zidek W, et al. Electronic alerts for acute kidney injury. *Dtsch Arztebl Int*. 2017;114:1–8.
40. Martin M, Wilson FP. Utility of electronic medical record alerts to prevent drug nephrotoxicity. *Clin J Am Soc Nephrol*. 2019;14(1):115–123. doi:10.2215/CJN.13841217.
41. Hodgson LE, Roderick PJ, Venn RM, et al. The ICE-AKI study: Impact analysis of a clinical prediction rule and electronic AKI alert in general medical patients. *PLoS One*. 2018;13(8):e0200584.
42. Goldstein SL, Kirkendall E, Nguyen H, et al. Electronic health record identification of nephrotoxin exposure and associated acute kidney injury. *Pediatrics*. 2013;132:756–767.
43. Joannidis M, Druml W, Forni LG, et al. Prevention of acute kidney injury and protection of renal function in the intensive care unit: update 2017: Expert opinion of the Working Group on Prevention, AKI section, European Society of Intensive Care Medicine. *Intensive Care Med*. 2017;43(6):730–749.
44. Caraceni P, Domenicali M, Tovoli A, et al. Clinical indications for the albumin use: Still a controversial issue. *Eur J Intern Med*. 2013;24:721–728.
45. Caironi P, Tognoni G, Masson S, et al. Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med*. 2014;370:1412–1421.
46. Roberts DA, Shaw AD. Impact of volume status and volume therapy on the kidney. *Best Pract Res Clin Anaesthesiol*. 2017;31:345–352.
47. Joannidis M, Druml W, Forni LG, et al. Prevention of acute kidney injury and protection of renal function in the intensive care unit: Update 2017: Expert opinion of the Working Group on Prevention, AKI section,

European Society of Intensive Care Medicine. *Intensive Care Med*. 2017;43(6):730–749.

48. McDermid RC, Raghunathan K, Romanovsky A, et al. Controversies in fluid therapy: Type, dose and toxicity. *World J Crit Care Med*. 2014;3:24–33.
49. Winters ME, Sherwin R, Vilke GM, et al. What is the preferred resuscitation fluid for patients with severe sepsis and septic shock? *J Emerg Med*. 2017;53(6):928–939.
50. Self WH, Semler MW, Wanderer JP, et al. Balanced crystalloids versus saline in noncritically ill adults. *N Engl J Med*. 2018;378:819–828.
51. Scharnweber T, Alhilali L, Fakhran S. Contrast-induced acute kidney injury: Pathophysiology, manifestations, prevention, and management. *Magn Reson Imaging Clin N Am*. 2017;25:743–753.
52. Valette X, Desmeulles I, Savary B, et al. Sodium bicarbonate versus sodium chloride for preventing contrast-associated acute kidney injury in critically ill patients: A randomized controlled trial. *Crit Care Med*. 2017;45:637–644.
53. Weisbord SD, Gallagher M, Jneid H, et al. Outcomes after angiography with sodium bicarbonate and acetylcysteine. *N Engl J Med*. 2018;378:603–614.
54. Barbanti M, Gulino S, Capranzano P, et al. Acute kidney injury with the RenalGuard system in patients undergoing transcatheter aortic valve replacement: The PROTECT-TAVI Trial. *JACC Cardiovasc Interv*. 2015;8:1595–1604.
55. Putzu A, Boscolo Berto M, Belletti A, et al. Prevention of contrast-induced acute kidney injury by furosemide with matched hydration in patients undergoing interventional procedures: A systematic review and meta-analysis of randomized trials. *JACC Cardiovasc Interv*. 2017;10:355–363.
56. Cheungpasitporn W, Thongprayoon C, Brabec BA, et al. Oral hydration for prevention of contrast-induced acute kidney injury in elective radiological procedures: A systematic review and meta-analysis of randomized controlled trials. *N Am J Med Sci*. 2014;6(12):618–624.
57. Akyuz S, Karaca M, Kemaloglu Oz T, et al. Efficacy of oral hydration in the prevention of contrast-induced acute kidney injury in patients undergoing coronary angiography or intervention. *Nephron Clin Pract*. 2014;128(1-2):95–100.

58. Heung M, Wolfgram DF, Kommareddi M, et al. Fluid overload at initiation of renal replacement therapy is associated with lack of renal recovery in patients with acute kidney injury. *Nephrol Dial Transplant*. 2012;27:956–961.
59. Menting TP, Wever KE, Ozdemir—van Brunschot DM, et al. Ischaemic preconditioning for the reduction of renal ischaemia reperfusion injury. *Cochrane Database Syst Rev*. 2017;3. CD010777.
60. Zarbock A, Schmidt C, Van Aken H, et al. Effect of remote ischemic preconditioning on kidney injury among high-risk patients undergoing cardiac surgery: A randomized clinical trial. *JAMA*. 2015;313(21):2133–2141.
61. Hausenloy D, Candilio L, Evans R, et al. Remote ischemic preconditioning and outcomes of cardiac surgery. *N Engl J Med*. 2015;373:1408–1417.
62. Sadat U, Usman A, Gillard JH, et al. Does ascorbic acid protect against contrast-induced acute kidney injury in patients undergoing coronary angiography: A systematic review with meta-analysis of randomized, controlled trials. *J Am Coll Cardiol*. 2013;62(23):2167–2175.
63. Brueck M, Cengiz H, Hoeltgen R, et al. Usefulness of N-acetylcysteine or ascorbic acid versus placebo to prevent contrast-induced acute kidney injury in patients undergoing elective cardiac catheterization: A single-center, prospective, randomized, double-blind, placebo-controlled trial. *J Invasive Cardiol*. 2013;25(6):276–283.
64. Albabtain MA, Almasood A, Alshurafah H, et al. Efficacy of ascorbic acid, N-acetylcysteine, or combination of both on top of saline hydration versus saline hydration alone on prevention of contrast-Induced nephropathy: A prospective randomized study. *J Interv Cardiol*. 2013;26(1):90–96.
65. Vanmassenhove J, Vanholder R, Lameire N. Statins for the prevention of contrast-induced acute kidney injury. *Curr Opin Nephrol Hypertens*. 2016;25:508–517.
66. Verdoodt A, Honore M, Jacobs R, et al. Do statins induce or protect from acute kidney injury and chronic kidney disease: An update review in 2018. *J Transl Int Med*. 2018;28(6):21–25.
67. Fu M, Dai W, Ye Y, et al. High dose of atorvastatin for the treatment of contrast-induced nephropathy after carotid artery stenting. *Am J Ther*. 2017;24:718–722.

68. Marenzi G, Cosentino N, Werba JP, et al. A meta-analysis of randomized controlled trials on statins for the prevention of contrast-induced acute kidney injury in patients with and without acute coronary syndromes. *Int J Cardiol*. 2015;183:47–53.
69. Billings FT, Hendricks PA, Schildcrout JS, et al. High-dose perioperative atorvastatin and acute kidney injury following cardiac surgery: A randomized clinical trial. *JAMA*. 2016;315(9):877–888.
70. He S, Liu Q, Li H, et al. Role of statins in preventing cardiac surgery-associated acute kidney injury: An updated meta-analysis of randomized controlled trials. *Ther Clin Risk Manag*. 2018;14:475–482.
71. Fiaccadori E, Sabatino A, Morabito S, et al. Hyper/hypoglycemia and acute kidney injury in critically ill patients. *Clin Nutr*. 2016;35:317–321.
72. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345:1359–1367.
73. Van den Berghe G, Wilmer A, Hermans G. Intensive insulin therapy in the medical ICU. *New Engl J Med*. 2006;354:449–461.
74. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360:1283–1297.
75. Ling Y, Li X, Gao X. Intensive versus conventional glucose control in critically ill patients: A meta-analysis of randomized controlled trials. *Eur J Intern Med*. 2012;23:564–574.
76. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. *Crit Care Med*. 2017;45:486–552.
77. American Diabetes Association. Standards of medical care in diabetes—2016. *Diabetes Care*. 2016;39(suppl 1):S1–S106.
78. Joslin J, Ostermann M. Care of the critically ill emergency department patient with acute kidney injury. *Emerg Med Int*. 2012;2012:760623.
79. Bielecka-Dabrowa A, Godoy B, Schefold JC, et al. Decompensated heart failure and renal failure: What is the current evidence? *Curr Heart Fail Rep*. 2018;15(4):224–238. doi:10.1007/s11897-018-0397-5.
80. Davenport A, Sheikh MF, Lamb E. Acute kidney injury in acute-on-chronic liver failure: Where does hepatorenal syndrome fit? *Kidney Int*. 2017;92:1058–1070.
81. Zarbock A, Kellum JA, Schmidt C, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients

with acute kidney injury: The ELAIN Randomized Clinical Trial. *JAMA*. 2016;315:2190–2199.

82. Gaudry S, Hajage D, Schortgen F, et al. Initiation strategies for renal-replacement therapy in the intensive care unit. *N Engl J Med*. 2016;375:122–133.
83. Negi S, Koreeda D, Kobayashi S, et al. Acute kidney injury: Epidemiology, outcomes, complications, and therapeutic strategies. *Semin Dial*. 2018. doi:10.1111/sdi.12705.
84. Bagshaw SM, Wald R. Strategies for the optimal timing to start renal replacement therapy in critically ill patients with acute kidney injury. *Kidney Int*. 2017;91:1022–1032.
85. Heung M, Yessayan L. Renal replacement therapy in acute kidney injury: Controversies and consensus. *Crit Care Clin*. 2017;33:365–378.
86. Villa G, Ricci Z, Ronco C. Renal replacement therapy. *Crit Care*. 2015;31:839–848.
87. Bellomo R, Cass A, Cole L, et al. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med*. 2009;361:1627–1638.
88. Fayad AI, Buamscha DG, Ciapponi A. Intensity of continuous renal replacement therapy for acute kidney injury. *Cochrane Database Syst Rev*. 2016;10:CD010613.
89. Brandenburger T, Dimski T, Slowinski T, et al. Renal replacement therapy and anticoagulation. *Best Pract Res Clin Anesthesiol*. 2017;31:387–401.
90. Heintz BH, Matzke GR, Dager WE. Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy*. 2009;29:562–577.
91. Dager WE. Filtering out important considerations for developing drug-dosing regimens in extended daily dialysis. *Crit Care Med*. 2006;34:240–241.
92. Keough LA, Krauss A, Hudson JQ. Inadequate antibiotic dosing in patients receiving sustained low efficiency dialysis. *Int J Clin Pharm*. 2018;40(5):1250–1256. doi:10.1007/s11096-018-0697-6.
93. Nadeau-Fredette AC, Bouchard J. Fluid management and use of diuretics in acute kidney injury. *Adv Chr Kidney Dis*. 2013;20: 45–55.

94. Asare K. Management of loop diuretic resistance in the intensive care unit. *Am J Health-Syst Pharm*. 2009;66:1635–1640.
95. Philips BJ, Lane K, Dixon J, et al. The effects of acute renal failure on drug metabolism. *Expert Opin Drug Metabol Toxicol*. 2014;10:11–23.
96. Vilay AM, Churchwell MD, Mueller BA. Clinical review: Drug metabolism and nonrenal clearance in acute kidney injury. *Crit Care*. 2008;12:235.
97. Dager WE, King JH. Aminoglycosides in intermittent hemodialysis: Pharmacokinetics with individual dosing. *Ann Pharmacother*. 2006;40:9–14.
98. Thompson A, Li F, Gross AK. Considerations for medication management and anticoagulation during continuous renal replacement therapy. *AACN Adv Crit Care*. 2017;28:51–63.
99. Bugge JF. Pharmacokinetics and drug dosing adjustments during continuous venovenous hemofiltration or hemodiafiltration in critically ill patients. *Acta Anaesthesiol Scand*. 2001;45:929–934.
100. Matzke GR, Frye RF, Joy MS, Palevsky PM. Determinants of ceftazidime clearance by continuous venovenous hemofiltration and continuous venovenous hemodialysis. *Antimicrob Agents Chemother*. 2000;44:1639–1644.
101. Churchwell MD, Mueller BA. Drug dosing during continuous renal replacement therapy. *Semin Dial*. 2009;22:185–188.
102. Dager WE. What are the important drug use errors in dialysis patients? Pharmacokinetic and pharmacodynamic principles. *Semin Dial*. 2010;23:466–469.
103. Mavrakanas TA, Samer CF, Nessim SJ, et al. Apixaban pharmacokinetics at steady state in hemodialysis patients. *J Am Soc Nephrol*. 2017;28:2241–2248.

61

Chronic Kidney Disease

Joanna Q. Hudson, Lori D. Wazny, and Paul Komenda

KEY CONCEPTS

1. Chronic kidney disease (CKD) is classified based on the cause of kidney disease, assessment of glomerular filtration rate, and extent of albuminuria over at least a 3-month period.
2. The most common causes of CKD 5D (requiring dialysis or kidney transplantation), often called end-stage renal disease (ESRD), are diabetes mellitus and hypertension.
3. Anemia of CKD is multifactorial with loss of erythropoietin synthesis by the kidney, iron deficiency, and chronic inflammation all implicated.
4. CKD-mineral and bone disorder (CKD-MBD) includes abnormalities in parathyroid hormone (PTH), fibroblast growth factor-23 (FGF-23), phosphorus, calcium, vitamin D, and bone turnover, and contributes to soft-tissue and extravascular calcifications.
5. Guidelines from the Kidney Disease: Improving Global Outcomes (KDIGO) provide information to assist healthcare providers in clinical decision making and the design of appropriate therapy to manage CKD progression and the associated complications.
6. Patient education and shared decision making play a critical role in the appropriate management of patients with CKD and its associated complications. A high functioning multidisciplinary team structure for patients at high risk of progression to ESRD is preferred to effectively design and implement the recommended nonpharmacologic and pharmacologic interventions.
7. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are primary pharmacologic treatments to delay progression of CKD because of their effects on renal hemodynamics to

reduce intraglomerular pressure and proteinuria.

8. Sodium-glucose co-transporter 2 (SGLT-2) inhibitors are emerging as potential agents to prevent progression to later stages of CKD and ESRD and these effects seem to be independent of glucose lowering.
9. Management of anemia includes administration of erythropoiesis-stimulating agents (ESAs) (eg, epoetin alfa, epoetin alfa-epbx, darbepoetin alfa, methoxy polyethylene glycol-epoetin beta) and regular iron supplementation to maintain hemoglobin concentration and prevent the need for blood transfusions. There is a higher risk of cardiovascular events when hemoglobin is targeted to a value of greater than 11 g/dL (110 g/L; 6.83 mmol/L).
10. Management of CKD-MBD includes dietary phosphorus restriction, phosphate-binding agents, activated vitamin D supplementation, and calcimimetic therapy to achieve KDIGO targets.
11. Although statins are not recommended for primary prevention of hyperlipidemia in patients receiving dialysis, they are indicated for primary prevention in those with nondialysis dependent CKD.

Preclass Engaged Learning Activity

Visit the National Institute of Diabetes and Digestive and Kidney Diseases Website. This Website is useful to enhance student understanding of chronic kidney disease, its causes, diagnosis, prevention, and treatment. Review the information under ‘Kidney Disease’. Watch the video titled “How do you check for kidney disease?”. The video provides a brief description of tests to monitor for kidney disease.

INTRODUCTION

1. Chronic kidney disease (CKD) is defined as abnormalities in kidney structure or function, present for 3 months or longer. Lower glomerular filtration rate (GFR) and a higher urinary albumin-to-creatinine ratio (uACR) are both independently associated with adverse events.[1] For decades, kidney disease was primarily considered to be present only when the patient’s estimated or measured creatinine clearance (CLcr) was reduced to less than 50 mL/min (0.83 mL/s). In

2012, a new classification system was proposed that incorporated GFR and uACR. Documentation of the presence of structural changes in those with what previously would have been classified with normal kidney function (ie, CLcr or GFR >90 mL/min [1.50 mL/s]) became the most sensitive indicator of CKD and was designated as stage 1 CKD based on recommendations from the Kidney Disease: Improving Global Outcomes (KDIGO) guideline for evaluation and management of CKD.[1] The KDIGO classification system is referred to as *CGA* staging (*C*ause, *G*FR, *A*lbuminuria). **Figure 61-1** shows the KDIGO GFR and albuminuria categories along with the prognosis based on these factors. A patient is classified with end-stage renal disease (ESRD) when the GFR is below 15 mL/min/1.73 m^2 (0.14 mL/s/m^2) and either chronic dialysis (Chapter 62) or kidney transplantation (Chapter 105) is needed to sustain life. Throughout this chapter CKD stages based on KDIGO classification will be used (eg, CKD 3a or CKD 5). The term CKD 5D indicates a patient with ESRD requiring dialysis as either hemodialysis (CKD 5HD) or peritoneal dialysis (CKD 5PD).

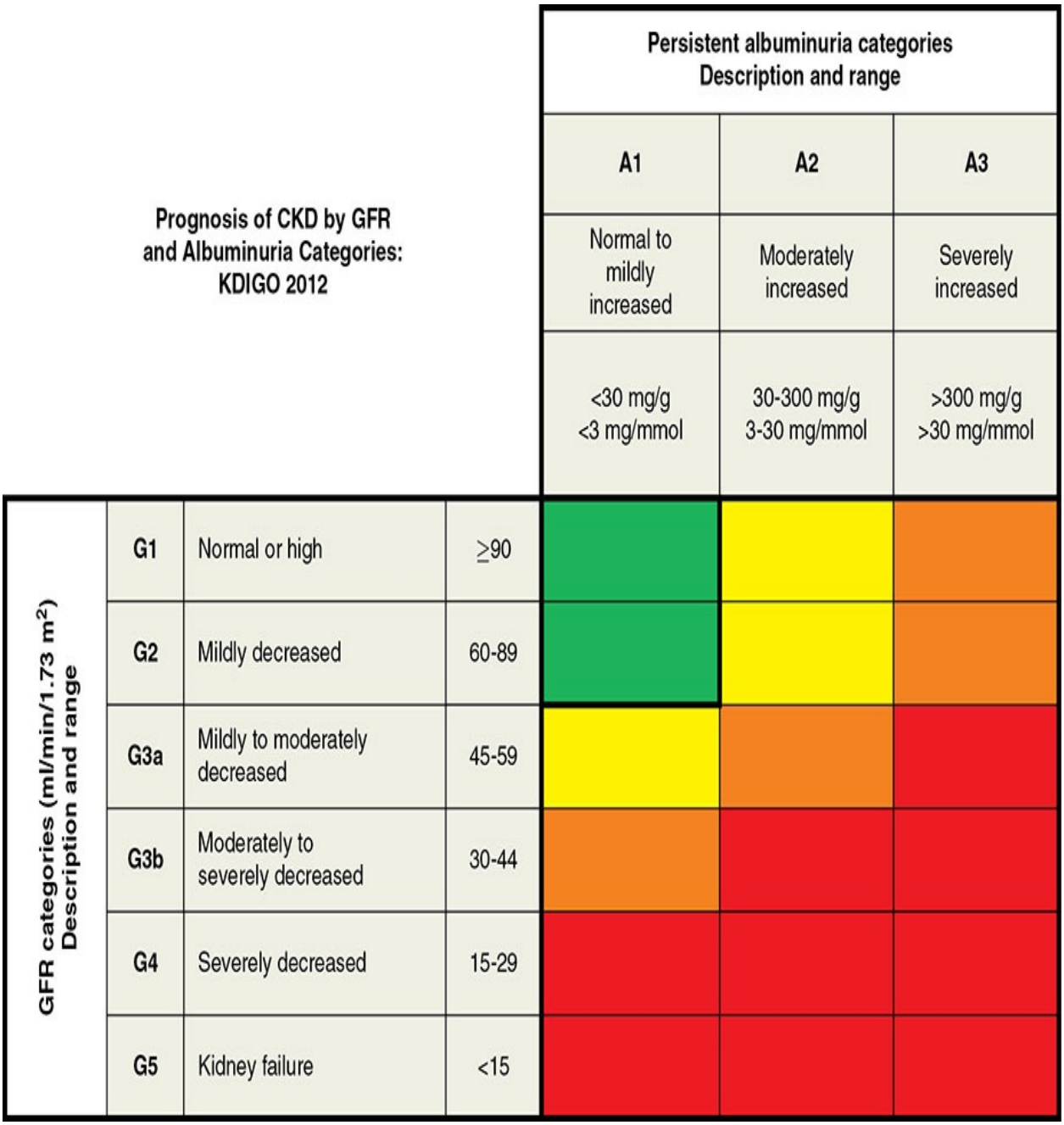
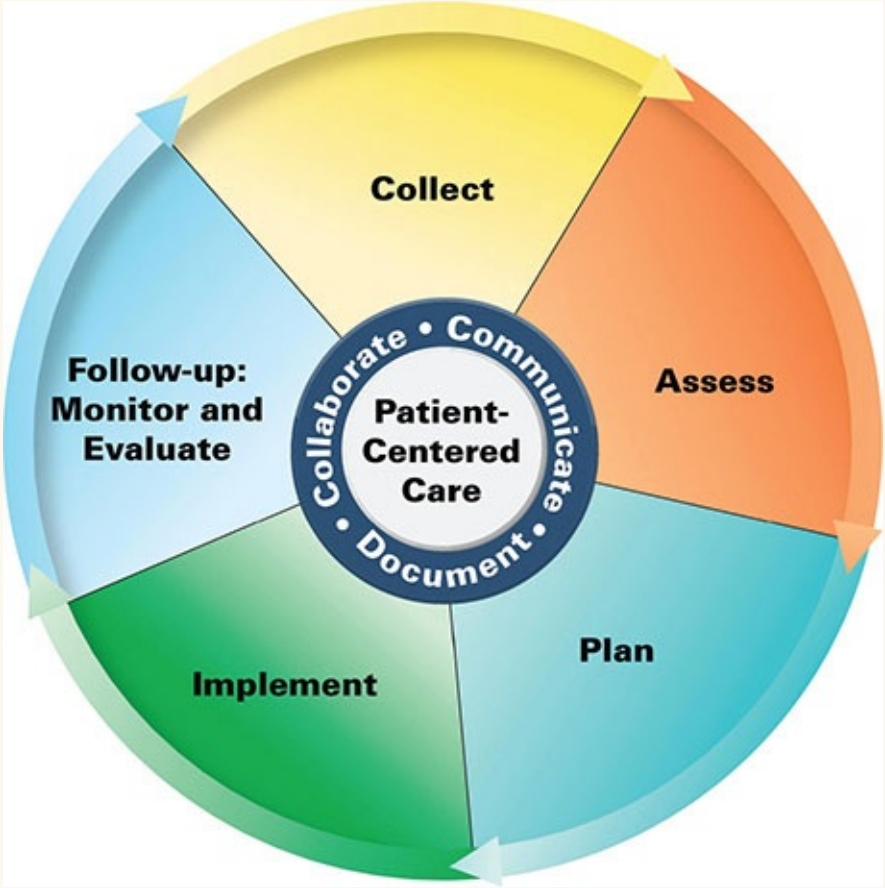


FIGURE 61-1 KDIGO GFR and albuminuria categories and prognosis of CKD by category.[14] To meet criteria for CKD there must be a significant reduction in GFR (categories 3a-5) or there must also be evidence of kidney damage (categories 1 and 2) for 3 months or greater. Prognosis Scale – Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk. (CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.) (*Reprinted with permission from Reference 14.*)

The prognosis of CKD is dependent on the following factors: (a) cause of kidney disease; (b) GFR at time of diagnosis; (c) degree of albuminuria measured by uACR; and (d) presence of other comorbid conditions. Patients with any of the following should be referred to a nephrologist for evaluation and collaborative management: persistent and significant albuminuria (uACR >1000 mg/g or 110 mg/mmol), progression of CKD (eg, a marked but nonacute decline in GFR), presence of a nonsurgical cause of hematuria, hypertension refractory to treatment (eg, ≥4 antihypertensive agents), persistent abnormalities of serum potassium, recurrent or extensive nephrolithiasis, GFR less than 30 mL/min/1.73 m^2 (0.29 mL/s/m^2), or hereditary kidney disease such as polycystic kidney disease even in the presence of normal GFR and uACR.[1]



Patient Care Process for Chronic Kidney Disease (CKD)

Collect

- Patient characteristics (eg, age, sex, CKD stage [see Fig. 61-1] and cause of CKD, medication allergies)
- Past medical history
- Social history (eg, smoking), family/friend supports
- Current medications including OTC (eg, NSAID use), herbals, dietary supplements
- Objective data:
  - Blood pressure, heart rate, weight
  - Labs as outlined in ‘Clinical Presentation’.

Assess

- Serum creatinine, glomerular filtration rate (GFR), or creatinine clearance
- Presence of albuminuria (see Fig 61-1 and Table 61-5)
- Serum potassium concentration—assess frequently in patients with CKD and heart failure requiring adjustment of diuretics and/or ACE inhibitors
- Hemoglobin concentration (see Table 61-6 for ESA initiation)
- Iron indices (transferrin saturation and ferritin)—for patients on an ESA, assess transferrin saturation (TSAT) and ferritin at least every 3 months and assess when clinically indicated (eg, following blood loss)
- Concentrations of calcium, albumin (to calculate corrected calcium), phosphorus, and parathyroid hormone (PTH) (see Table 61-9)
- Blood pressure (see targets in Fig. 61-6)—consider use of home blood pressure monitor
- Insurance coverage of medications, current out-of-pocket cost of medications
- Medication adherence
- Potential drug interactions
- Need for renal dose adjustments
- Other recommendations as outlined in Table 61-3 (eg, vaccines, lifestyle modifications)

Plan

- Drug therapy recommendations, including dose, route, frequency, and duration

- Monitoring parameters, including frequency and timing of follow-up
- Patient education, including purpose of new or changed treatment, lifestyle modifications, medication administration (eg, timing of phosphate binders with meals), injection technique
- Self-monitoring for resolution of symptoms and blood pressure targets, medication to hold on sick days if vomiting or diarrhea occur (eg, ACEI/ARB)
- Referrals to other providers when appropriate (eg, dietitian, occupational therapist, social worker, endocrinologist, CKD nurse)

Implement*

- Provide patient education on all elements of the treatment plan
- Use motivational interviewing strategies to maximize adherence
- Schedule follow-up labs and appointment, adherence assessment

Follow-up: Monitor and Evaluate

- Resolution of CKD symptoms
- Presence of adverse effects (eg, dizziness, constipation, pruritus, hypoglycemia)
- Patient adherence to treatment plan using multiple sources of information

*Collaborate with patient, caregivers, and other healthcare professionals.

Often complications of CKD are unrecognized or are inappropriately managed, and for many patients this contributes to significant morbidity, premature mortality, or a poorer prognosis if and when they require dialysis. Frequent complications of advanced CKD include hypervolemia, hypertension, hyperkalemia, metabolic acidosis, anemia, CKD-related mineral and bone disorder (CKD-MBD), and a disproportionate risk of cardiovascular disease (CVD). This chapter primarily covers the pathophysiology and treatment of progressive CKD, anemia, CKD-MBD, and select cardiovascular (CV) complications. **Table 61-1** lists other complications of advanced CKD not covered in detail. The reader is referred to Chapters 66, 68, and 69 for a more detailed discussion of management and monitoring strategies for CKD patients with hypervolemia, hyperkalemia, and metabolic acidosis, respectively.

TABLE 61-1 Other Complications of Chronic Kidney Disease[a]

Organ System or Complication	Clinical Manifestations
Amyloidosis	Accumulation of β_2-microglobulin Carpal tunnel syndrome
Blood and immune disorders	Bleeding diathesis Impaired cell-mediated immunity Lymphopenia Platelet dysfunction
Endocrine	Hypoglycemic episodes (result of decreased degradation of insulin by the kidney)
GI	Nausea, vomiting, anorexia (from uremia) Delayed gastric emptying Gastroesophageal reflux GI bleeding
Protein–energy wasting	Malnutrition
Neurologic	Peripheral neuropathies Restless leg syndrome Uremic encephalopathy
Uremic pruritus	Generalized itching predominantly of back, face, and extremity used for vascular access, but may affect any area May be more severe during or immediately after hemodialysis

[a]Not all inclusive.

EPIDEMIOLOGY

CKD is recognized as a significant global public health problem.[2] People with CKD experience high morbidity and mortality rates with a resulting economic burden to healthcare systems due to frequent hospitalizations and the high cost of chronic dialysis and kidney transplantation. From 1990 to 2013 the age-adjusted death rates attributable to CKD increased by 37% in 188 countries surveyed and CKD is now the 19th leading cause of life years lost.[3] Worldwide, an estimated 8% to 16% of the general population has CKD and 1.9 million patients are undergoing renal replacement therapy (hemodialysis, peritoneal dialysis, or kidney transplantation).[4,5] As a result, many countries have implemented public health initiatives to reduce the proportion of the population with CKD, increase CKD patient awareness through targeted screening

programs, reduce the rate of new cases of ESRD, and reduce mortality in persons with CKD.[6]

2 In the United States, it is estimated that 15% of the adult population has CKD. In 2016, over 726,000 individuals had ESRD, with 124,000 new cases alone.[7] In the United States and other first-world countries, the leading cause of new ESRD cases is diabetes mellitus followed by hypertension (**Fig. 61-2**).[7,8] It is estimated that diabetes accounts for 50% of cases of ESRD in the developed world.[9] Despite the fact that the incidence rate of ESRD from all major causes has leveled off since 2009, it is projected that the aging population and other changes in the demographics will result in an increased incidence and subsequent increase in prevalence of ESRD by 2030.[10] The prevalence of CKD increases with age, with the highest prevalence in individuals over 60 years mainly attributed to a decrease in estimated GFR (eGFR, less than 60 mL/min/1.73 m^2).[7] While there is some debate as to whether the eGFR decline in older individuals as a consequence of the normal physiological aging process should be considered a *disease* necessitating the label of CKD, the fact remains that patients with reduced eGFR and albuminuria suffer from worse health outcomes regardless of age.[1]

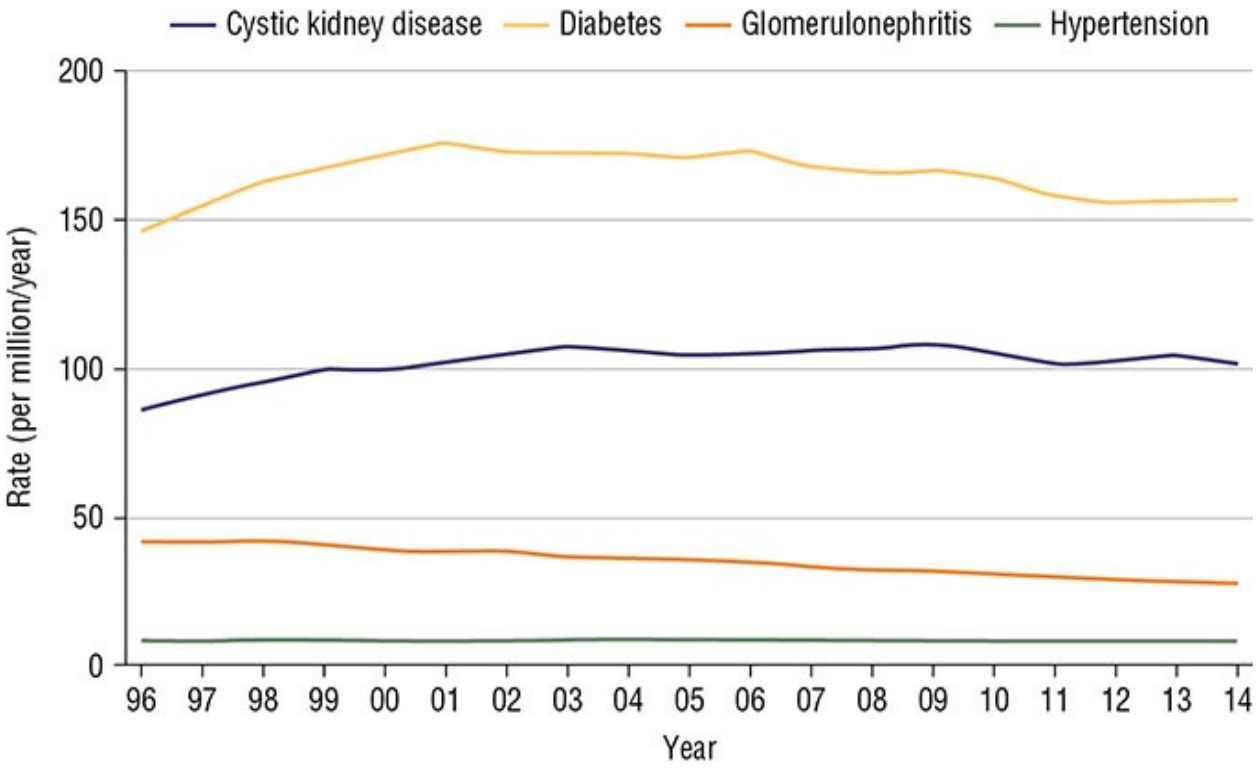


FIGURE 61-2 Trends in adjusted*a* end-stage renal disease (ESRD) incidence rate by primary diagnosis in the US population (1996-2014).[8] *a*Adjusted for age,

sex, and race.

Racial health disparities in CKD also exist and contribute to differing CKD rates. In the United States, the incident rate of ESRD is 2.9 times greater for blacks compared to whites, with hypertension significantly higher among blacks than all other racial groups.[7] Incidence and prevalence of albuminuria are also greater in black than in white individuals. Variants in the APOL1 gene may contribute to this increased risk of nondiabetic kidney disease and albuminuria in individuals of African descent.[11] The incident rate is approximately 31% higher in Hispanics than in non-Hispanics.[7,12] Greater prevalence of obesity, uncontrolled hypertension, and diabetes among non-white individuals are the most common reasons suggested for racial differences in CKD. In terms of socioeconomic factors, the likelihood of ESRD is higher in individuals with low income and less education.[11] A survey in England found that high albuminuria was associated with low socioeconomic status even after adjustment for ethnicity, lifestyle, and clinical variables such as obesity, diabetes, hypertension, and smoking.[13] The specific social and environmental factors are important to consider when evaluating risk of progressive CKD in individual patients.

ETIOLOGY

Susceptibility and Initiation Risk Factors

Clinical and sociodemographic risk factors for susceptibility to and initiation of CKD are listed in **Table 61-2** and are useful for identifying individuals at high risk of developing CKD.[14]

TABLE 61-2 Risk Factors for Susceptibility to and Initiation of Chronic Kidney Disease

Clinical Factors
Diabetes
Hypertension
Obesity
Autoimmune diseases
Systemic infections
Urinary tract infections
Urinary stones
Lower urinary tract obstruction
Neoplasia
Family history of CKD
Recovery from acute kidney injury
Reduction in kidney mass
Exposure to certain drugs
Low birth weight
Sociodemographic Factors
Older age
US ethnic minority status: African American, American Indian, Hispanic, Asian or Pacific Islander
Exposure to certain chemical and environmental conditions
Low income/education

Data from Reference 14.

Predicting Risk of Progression

KDIGO recommends that all patients with CKD be staged according to eGFR and uACR and that their prognosis be considered to help guide further testing and treatment decisions (Fig. 61-1). Estimating equations such as the kidney failure risk equation (KFRE), which incorporates urine data, sex, age, and GFR, have also been used, and these equations provide an accurate 2- and 5-year risk of progression to kidney failure for individuals with stage 3 to 5 CKD.[15] The KFRE has been widely validated in multiple international cohorts and pediatric populations and provides the best current evidence-based approach to assess risk of progression and should be used in combination with expert clinical judgment.[16] Risk equations may also be beneficial to help align resources with risk in assigning priority for referral to nephrologists.

Progression Risk Factors

Progression risk factors are those associated with further decline in kidney function. Persistence of the underlying initiation factors (eg, diabetes mellitus, hypertension, glomerulonephritis) appears to be the most important predictor of

progressive CKD.

Diabetes Mellitus

Achieving a hemoglobin A_{1C} (HbA1c) target of approximately 7% (0.07; 53 mmol/mol Hb) has been shown to prevent the surrogate endpoints of microalbuminuria and macroalbuminuria associated with diabetic chronic kidney disease (DCKD).[17] The evidence to support this recommendation comes from the type 1 diabetes DCCT trial, the long-term follow-up of these participants in the EDIC trial, and subsequent analyses.[18] The evidence for individuals with type 2 diabetes comes from the United Kingdom Prospective Diabetes Study (UKPDS) and the Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type 2 Diabetes Trial.[9,17] While the highest survival rates in individuals with DCKD were associated with HbA1c levels in the range of 7% to 8% (0.07-0.08; 53-64 mmol/mol Hb), the recommendation by the American Diabetes Association and consensus panels is to generally target these levels while being cautious of the limitations of using this marker in patients with CKD and the risk of hypoglycemia.[9,19]

Hypertension

Hypertension is both a cause and result of progressive kidney disease and accounts for just over 31% of cases of ESRD in the United States.[7] KDIGO guidelines for the management of blood pressure in CKD recommend the goal is to control blood pressure at all categories of CKD regardless of the underlying cause since early treatment of hypertension and achievement of target blood pressure have been demonstrated to slow the rate of progression of CKD.[20]

Proteinuria

Proteinuria is a strong independent predictor of accelerated progression of CKD and also a risk factor for CV mortality and morbidity.[1] Albuminuria remains the primary modifiable risk factor associated with CKD progression in most patients.

Smoking

Smoking is associated with kidney damage in the general population as well as in patients with diabetes and hypertension.[21] Acute reductions in GFR and an increase in urinary albumin excretion, heart rate, and blood pressure, likely

secondary to nicotine exposure, have been reported.[22] Smoking is also associated with an increase in CV events in people with CKD.[1]

Obesity

Population data from Kaiser Permanente revealed an increased risk of CKD 5 in overweight and obese subjects.[23] The risk of CKD 5 was directly related to the magnitude of obesity and remained even after adjustment for diabetes and hypertension. A body mass index (BMI) greater than or equal to 25 kg/m^2 at age 20 has been associated with a threefold increase in risk of CKD compared with a BMI lower than 25 kg/m^2.[24] This association has also been shown in metabolically healthy, young, and middle-aged individuals without CKD or proteinuria.[25] Intentional weight loss in individuals with CKD was associated with decreases in proteinuria, systolic blood pressure, and stabilization in GFR during a mean follow-up of 7.4 months.[26] These data suggest that weight reduction be included as part of the treatment of CKD.

PATHOPHYSIOLOGY

Chronic Kidney Disease

Progression of CKD to more advanced stages (stages 4-5) occurs over decades in the majority of people, with the precise mechanism of kidney damage dependent on the etiology of the disease and strongly associated with age, sex, and urine ACR. As evidenced by the variety of initiation and progression factors, kidney damage can result from an array of heterogeneous causes. Diabetic CKD is characterized by glomerular mesangial expansion, while with hypertensive nephrosclerosis, the kidney's arterioles have arteriolar hyalinosis (thickening of the arterial walls). Polycystic kidney disease is characterized by the development and expansion of renal cysts. While the initial structural damage depends on the primary disease affecting the kidney, the key elements of the pathway to ESRD are (a) loss of nephron mass, (b) glomerular capillary hypertension, and (c) proteinuria (**Fig. 61-3**).

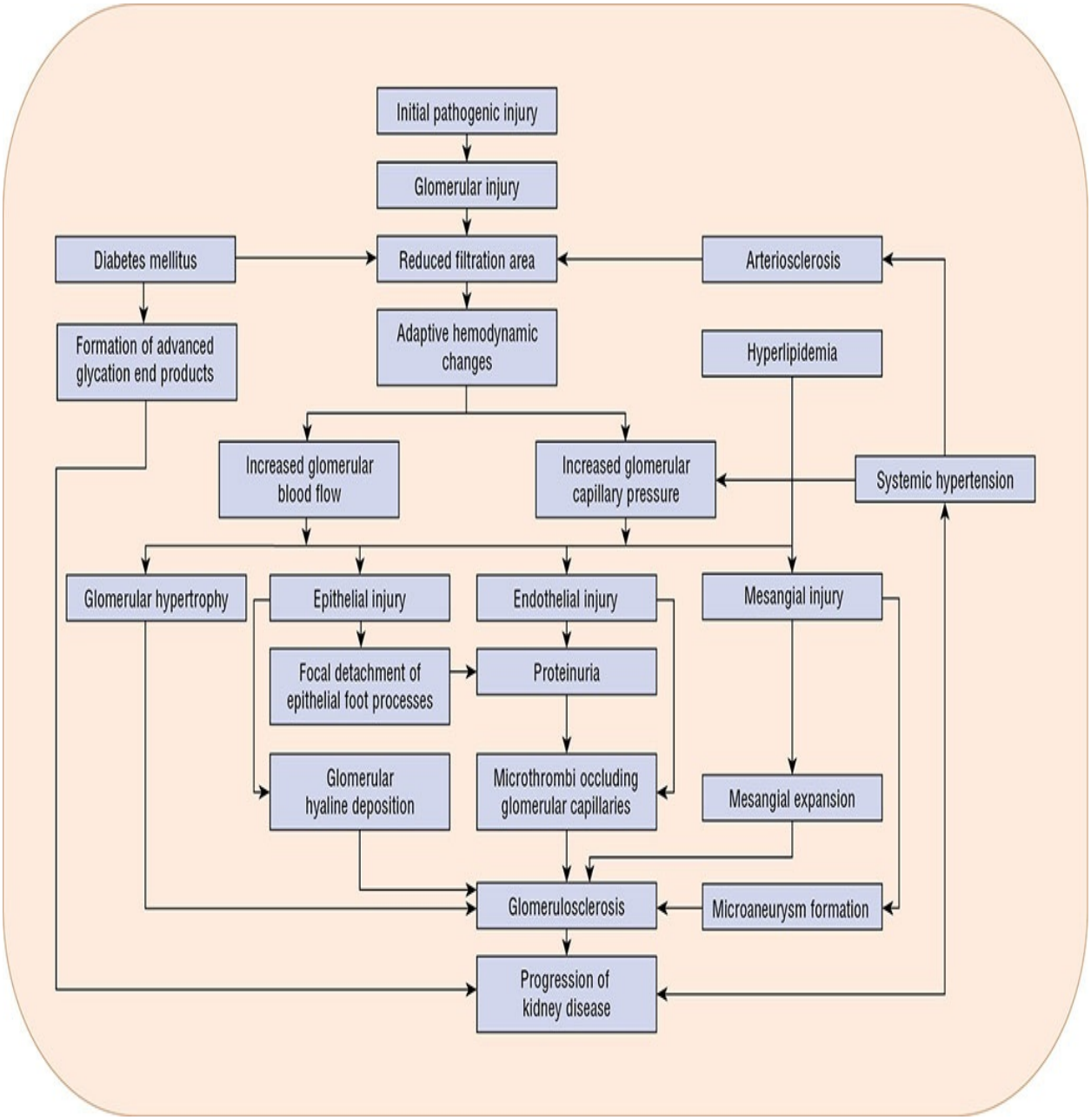


FIGURE 61-3 Proposed mechanisms of progression of kidney disease.

Exposure to any of the initiation risk factors can result in loss of nephron mass. In response to the decrease in nephron function, the remaining nephrons compensate through the process of autoregulation. With nephron loss and the resulting reduction in perfusion pressure and GFR, renin release from the juxtaglomerular apparatus increases and converts angiotensinogen to angiotensin I, which is then converted to angiotensin II (ATII). ATII is a potent vasoconstrictor of both afferent and efferent arterioles, but it preferentially affects the efferent arterioles, leading to increased pressure within the glomerular

capillaries and consequent increased filtration fraction. Initially, this compensatory action may be adaptive and beneficial; however, over time it can lead to the development of intraglomerular hypertension and hypertrophy and a further decline in the number of functioning nephrons. High intraglomerular capillary pressure impairs the size-selective function of the glomerular permeability barrier, resulting in increased urinary excretion of albumin and proteinuria. The development of intraglomerular hypertension usually parallels the development of systemic hypertension. ATII, as well as aldosterone, may also mediate CKD progression through nonhemodynamic effects by increasing growth factors (eg, transforming growth factor beta [TGF-β]) and causing cellular proliferation and hypertrophy of the glomerular endothelial cells, epithelial cells, and fibroblasts ultimately resulting in further inflammation and fibrosis.[27]

Proteinuria alone may promote progressive loss of nephrons as a result of direct cellular damage. Filtered proteins such as albumin, transferrin, complement factors, immunoglobulins, cytokines, and ATII are toxic to kidney tubular cells. Studies have demonstrated that the presence of these proteins in the renal tubule leads to increased production of inflammatory and vasoactive cytokines such as endothelin and monocyte chemoattractant protein-1 (MCP-1).[28] Proteinuria is also associated with the activation of complement components on the apical membrane of proximal tubules. Intratubular complement activation may be the key mechanism of damage in the progressive proteinuric nephropathies.[28] Furthermore, these events ultimately lead to scarring of the interstitium, progressive loss of structural nephron units, and a reduction in GFR.

Anemia of Chronic Kidney Disease

3 The primary cause of anemia of CKD is a decrease in production of erythropoietin, the glycoprotein hormone necessary for erythropoiesis (red blood cell production), by interstitial fibroblasts in the renal cortex of the kidney where approximately 90% of production occurs. In individuals with normal kidney function, plasma concentrations of erythropoietin increase exponentially in response to hypoxia; however, this response is lost as kidney disease progresses to CKD 3 and higher.[29]

Iron deficiency anemia is common in individuals with advanced kidney disease (ie, CKD 4 and 5) due to decreased gastrointestinal (GI) absorption of iron, inflammation, frequent blood testing, blood loss from hemodialysis (HD),

and increased iron demands from erythropoiesis stimulating agent (ESA) therapy. It is the leading cause of resistance to ESAs and the reason frequent iron supplementation is necessary.[29,30] Hepcidin, a hormone produced by the liver, directly inhibits the protein ferroportin that transports iron out of storage cells. When iron stores are high, hepcidin production is increased and results in a decrease in intestinal iron absorption, impairment of iron recycling from macrophages, and decreased mobilization of stored iron from hepatocytes. Hepcidin production is also induced by inflammation or infection. As a result, the increase in hepcidin in inflammatory conditions may lead to a sequestering of iron and ineffective red blood cell production. Conversely, hepcidin production is decreased when iron stores are low. The fact that hepcidin plays such a role in iron regulation has prompted the development of agents to target hepcidin and potentially alter iron transport.[31] At this time there are no commercially available agents.

Additional factors contributing to the development of anemia of CKD are the decreased red cell life span (from the normal of 120 days to approximately 60 days in individuals with CKD 5D), the effects of accumulation of uremic toxins and inflammatory cytokines, and vitamin B_{12} and folate deficiencies.

Chronic Kidney Disease–Related Mineral and Bone Disorder

4 Disorders of mineral and bone metabolism are common in the CKD population and include abnormalities in PTH, calcium, phosphorus, vitamin D, fibroblast growth factor-23 (FGF-23), bone turnover, as well as soft-tissue calcifications. Historically these abnormalities have been described as characteristics of secondary hyperparathyroidism (sHPT) and renal osteodystrophy (ROD). The term CKD-MBD encompasses these abnormalities in mineral and bone metabolism as well as associated calcifications.

The pathophysiology of CKD-MBD is complex (**Fig. 61-4**). Calcium and phosphorus homeostasis is mediated through the effects of PTH, 1,25-dihydroxyvitamin D_3 (calcitriol), and FGF-23 on bone, the GI tract, kidney, and the parathyroid gland. As kidney function declines, there is a decrease in phosphate elimination, which results in hyperphosphatemia and a decrease in serum calcium concentration. Hypocalcemia is the primary stimulus for secretion of PTH by the parathyroid glands. Hyperphosphatemia also increases PTH synthesis and release through its direct effects on the parathyroid gland and

production of prepro-PTH messenger RNA.[32] In an attempt to normalize ionized calcium, PTH increases calcium reabsorption by the distal tubules and decreases phosphate reabsorption in the proximal tubules of the kidney (at least until the GFR falls to approximately 30 mL/min/1.73 m^2 [0.29 mL/s/m^2]) and also increases calcium mobilization from bone. FGF-23 production in bone also increases in response to high phosphate levels and increased PTH and promotes phosphate excretion by the kidney. The result is a relative normalization of calcium and phosphorus, at least in the early stages of CKD; however, this occurs at the expense of an elevated PTH and FGF-23 ("the trade-off hypothesis"). The increase in PTH is most notable when GFR is less than 60 mL/min/1.73 m^2 (0.58 mL/s/m^2) (CKD 3a and higher) and worsens as kidney function further declines.[32] With advanced kidney disease, the kidney fails to respond to PTH or to FGF-23 and abnormalities in calcium and phosphorus worsen. Over time, the negative effects of sustained hyperparathyroidism on bone are realized as calcium resorption from bone persists.

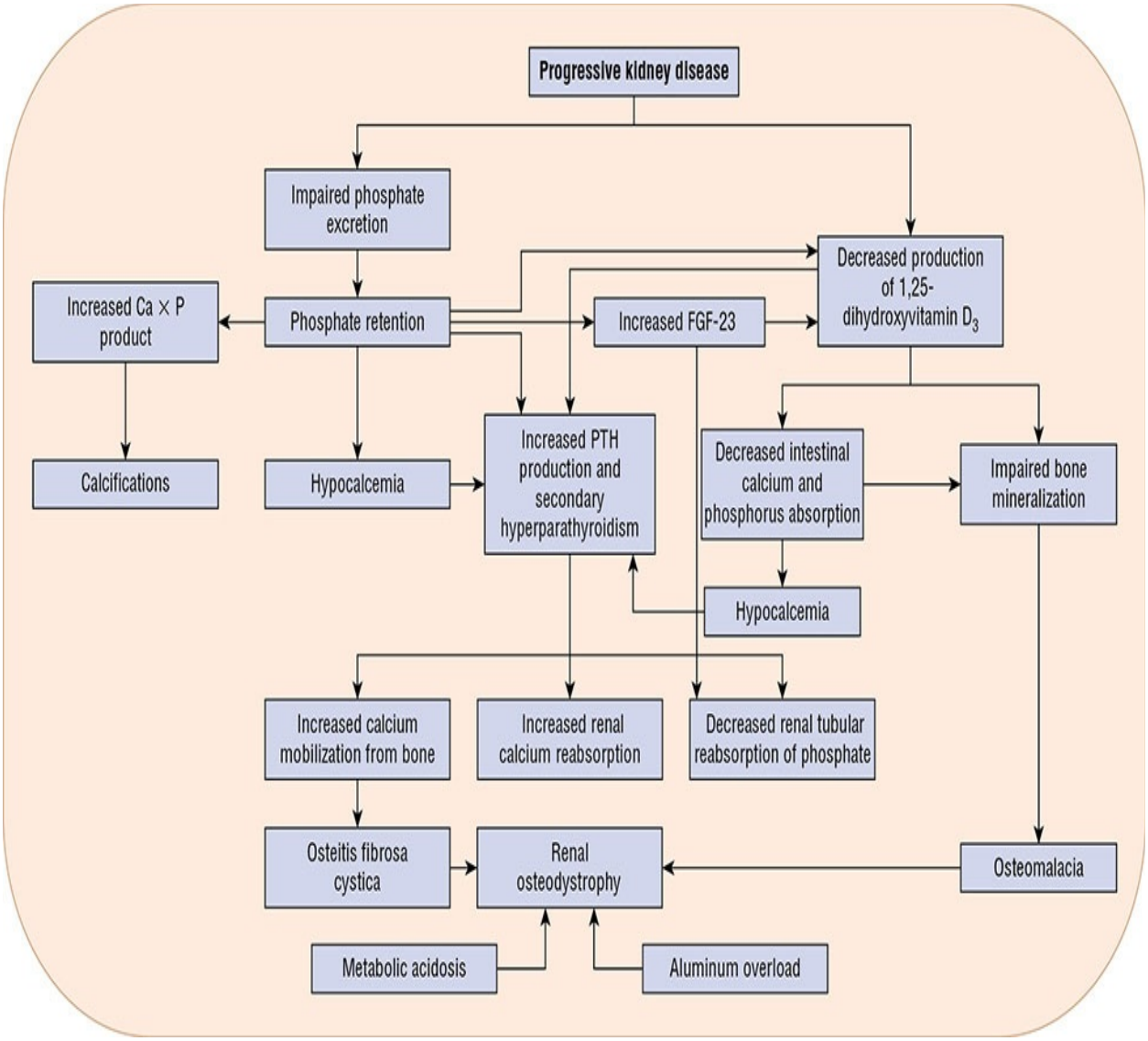


FIGURE 61-4 Pathophysiology of CKD-MBD. (Ca, calcium; FGF-23, fibroblast growth factor-23; PTH, parathyroid hormone.) FGF-23 also increases in response to 1,25-dihydroxyvitamin D_3. These adaptations are lost as kidney disease progresses.

1,25-dihydroxyvitamin D_3 or calcitriol promotes increased intestinal absorption of calcium and phosphorus, which helps normalize ionized calcium. Calcitriol also works directly on the parathyroid gland to suppress PTH production. The enzyme 1-α-hydroxylase is responsible for the final hydroxylation and conversion of the vitamin D precursor, 25-hydroxyvitamin D or 25(OH)D, to calcitriol in the kidney (**Fig. 61-5**). As kidney disease progresses, the concentrations of calcitriol decline due to loss of 1-α-hydroxylase activity. The resultant vitamin D deficiency leads to reduced intestinal calcium

and phosphorus absorption and worsening hyperparathyroidism. Increases in FGF-23 also promote calcitriol deficiency.[32] Calcitriol deficiency is more prevalent in individuals with CKD 4-5. Deficiency in 25(OH)D (levels of <30 ng/mL [75 nmol/L]) is also common in individuals with CKD due to decreased dermal synthesis of vitamin D, decreased exposure to sunlight, and reduced dietary intake of vitamin D.

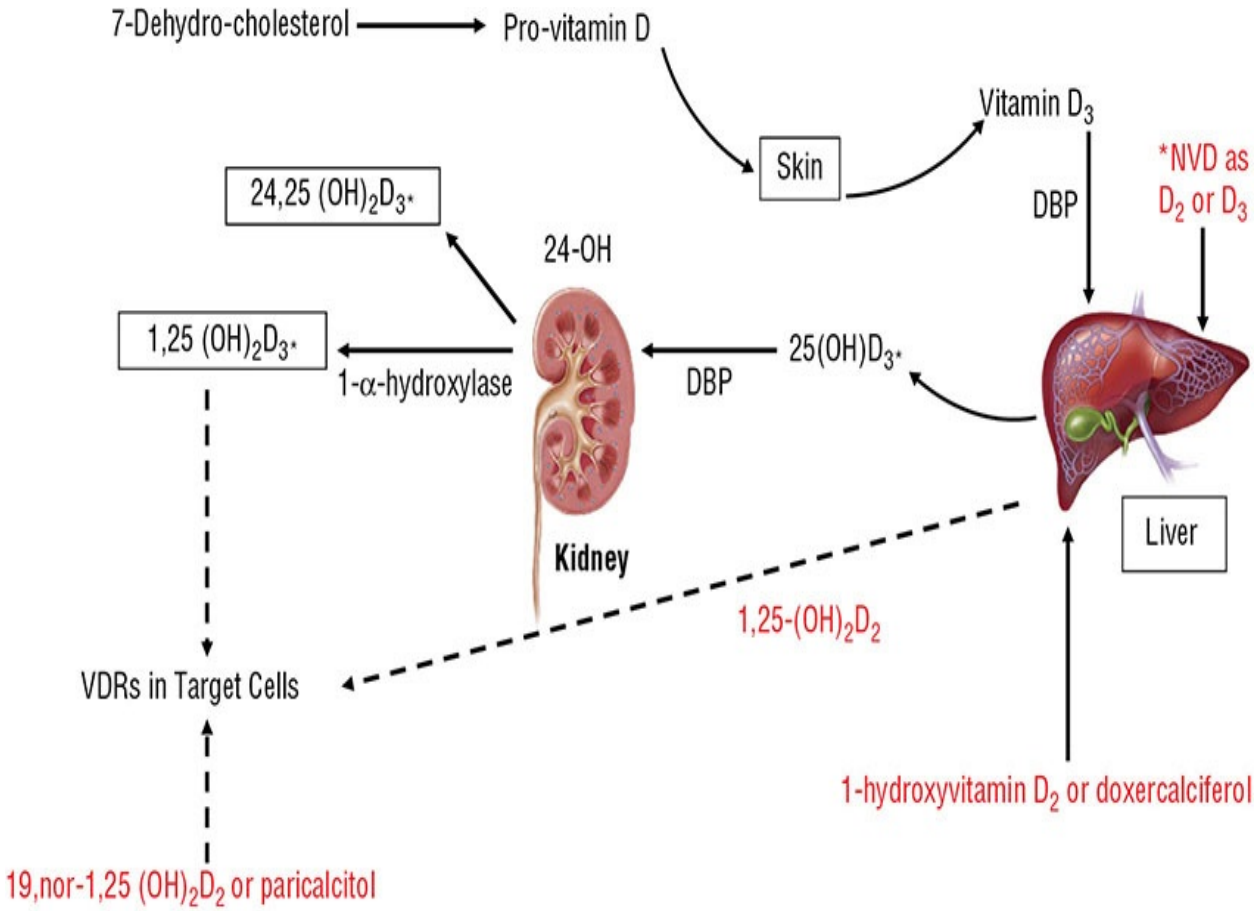


FIGURE 61-5 Vitamin D metabolism. Production of active vitamin D requires conversion of 7-dehydrocholesterol to cholecalciferol (vitamin D_3) by sunlight, followed by the first hydroxylation step in the liver to form 25-hydroxyvitamin D_3 or 25$(OH)D_3$, and the final conversion step in the kidney to form 1,25-dihydroxyvitamin D_3 or calcitriol. Within the kidney vitamin D may also be converted to an inactive form 24,25$(OH)D_3$. *If NVD is administered the resulting compound will be either a D_2 compound (as with ergocalciferol) or a D_3 compound (as with cholecalciferol). Paricalcitol and doxercalciferol are vitamin D analogs. (DBP, vitamin D–binding protein; NVD, nutritional vitamin D; VDRs, vitamin D receptors.)

The abnormalities of CKD-MBD lead to alterations in structural integrity of bone and other associated consequences. The continuous high rate of production of PTH by the parathyroid glands promotes parathyroid hyperplasia. Nodular tissue demonstrates more rapid growth potential and appears to be associated with fewer vitamin D and calcium-sensing receptors, resulting in resistance to exogenous calcitriol therapy. Bone abnormalities are almost universal in dialysis patients and observed in the majority of those with CKD 3-5.[33] The bone abnormalities include osteitis fibrosa cystica (high bone turnover disease), osteomalacia (low bone turnover disease), and adynamic bone disease. Osteitis fibrosa cystica is most common and is characterized by areas of peritrabecular fibrosis. Bone marrow fibrosis and decreased erythropoiesis are also consequences of severe osteitis fibrosa cystica. Osteomalacia was historically noted in HD patients with aluminum toxicity, a finding less common today due to the decreased use of aluminum-containing phosphate binders and changes in the processing of dialysate solutions to decrease aluminum content. Adynamic lesions are characterized by low amounts of fibrosis or osteoid tissue and low bone formation rates. Multiple risk factors for the development of this bone disease include high concentrations of dialysate calcium along with high doses of calcium-containing phosphate binders, aggressive management with vitamin D therapy, diabetes, and aluminum toxicity.[32]

The morbidity and mortality of CKD patients is increased in individuals with both severe hypo- and hyperparathyroidism.[34] Elevations of serum phosphorus, even within the upper limits of the normal range, have been associated with increased risk of CV events and/or mortality (all-cause or CV mortality) in patients with CKD 3-5.[35] FGF-23 has also been associated with increased mortality and cardiovascular events in individuals with CKD. The incidence of calciphylaxis, or rapid calcification of subcutaneous tissue, in patients with advanced kidney disease has increased over the past decade and has been associated with CKD-MBD, an elevated calcium times phosphorus product, and warfarin use.[34,36] Warfarin inhibits the matrix Gla protein, which is a vitamin K–dependent protein that prevents calcium deposition in arteries, and may therefore promote vascular calcification in individuals at risk.[37] Intake of calcium from calcium-based binders may also contribute to coronary artery calcification. These data underscore the need to consider all the consequences of elevated PTH, calcium, and phosphorus, not just their effects on bone.

CLINICAL PRESENTATION OF CHRONIC

KIDNEY DISEASE

CKD is often asymptomatic, which is a reason many patients are not diagnosed with the disease until they reach CKD stage 4 or 5 and are at or near the point of requiring renal replacement therapy. This problem has prompted automated reporting by clinical laboratories of the eGFR as determined by the estimating equations (Modification of Diet in Renal Disease [MDRD] equation or Chronic Kidney Disease Epidemiology Collaboration equations [CKD-EPI equation]) for the purpose of identifying individuals with CKD earlier (see Chapter e59). Comprehensive screening for CKD includes analysis of eGFR and uACR and risk stratification for progression (Fig. 61-1) or estimating equations such as the kidney failure risk equation. Clinicians must understand how to interpret the eGFR and values for urine albumin excretion to appropriately stage individuals with CKD. Chapter e59 provides a detailed discussion of the methods available for detection of urinary albumin and protein.

Diagnostic Considerations for Anemia of Chronic Kidney Disease

Signs and symptoms of anemia of CKD include fatigue, shortness of breath, cold intolerance, chest pain, tingling in the extremities, tachycardia, headaches, and general malaise. Since individuals with anemia of CKD may be asymptomatic, laboratory evaluation is commonly the initial approach to diagnosing anemia of CKD. According to KDIGO guidelines, Hb concentrations should be measured annually in CKD 3, biannually in CKD 4-5, and at least every 3 months in CKD 5D patients.[30] The diagnosis of anemia is made and further workup of anemia is required when the Hb is less than 13 g/dL (130 g/L; 8.07 mmol/L) for adult males and less than 12 g/dL (120 g/L; 7.45 mmol/L) for adult females. As iron deficiency is the primary cause of resistance to treatment of anemia with ESAs, assessment of the iron status is necessary. The TSat provides information on iron immediately available for use in the bone marrow for red blood cell production and the serum ferritin is in indirect measure of storage iron. The TSat is calculated as follows: (serum iron/total iron-binding capacity [TIBC]) × 100). Transferrin is the carrier protein for iron and may be affected by nutritional status. Serum ferritin as an indirect measure of storage iron is an acute-phase reactant, meaning it may be elevated under certain inflammatory conditions and give a false indication of storage iron. Patients may be diagnosed with *absolute iron deficiency* when whole-body iron stores are low (low TSat and ferritin), or

with *functional iron deficiency* when the TSat is low, but the serum ferritin is at or above goal. In this situation, iron is not released rapidly enough to satisfy the demands for erythropoiesis and further evaluation is warranted. If the TSat and serum ferritin values are below the desired thresholds, iron supplementation is necessary.

CLINICAL PRESENTATION

Stage 5 Chronic Kidney Disease (eGFR <15 mL/min/1.73 m^2)

Symptoms

- Fatigue, weakness, shortness of breath, confusion, nausea and vomiting, bleeding, loss of appetite, itching, cold intolerance, and peripheral neuropathies are common.

Signs

- Edema, weight gain (from accumulation of fluid), changes in urine output (volume and consistency), “foaming” of urine (indicative of proteinuria).

Laboratory Tests

- *Decreased*: eGFR, bicarbonate (metabolic acidosis), Hb/hematocrit (Hct) (anemia), transferrin saturation (TSat) and/or ferritin (iron deficiency; note: ferritin may be increased due to inflammatory conditions), vitamin D levels, albumin (malnutrition), glucose (may result from decreased degradation of insulin with impaired kidney function or poor oral intake), and calcium (in early stages of CKD).
- *Increased*: Serum creatinine, blood urea nitrogen, potassium, phosphorus, PTH, FGF-23, uACR, PCR, blood pressure (hypertension is a common cause and result of CKD), glucose (uncontrolled diabetes is a cause of CKD), low-density lipoprotein (LDL) and triglycerides, and calcium (more likely in CKD 5 and CKD 5D).
- *Other*: May be hemoccult-positive if GI bleeding occurs secondary to uremia.

Other Diagnostic Tests

- Urine sediment abnormalities (hematuria, red blood cell and white blood cell casts, renal tubular epithelial cells)
- Pathologic abnormalities indicating glomerular, vascular, tubulointerstitial disease, or cystic and congenital diseases
- Structural abnormalities such as polycystic kidneys, renal masses, renal artery stenosis, cortical scarring due to infarcts and pyelonephritis, or small kidneys (common in more severe CKD) detected by imaging studies (eg, ultrasound, computed tomography, magnetic resonance imaging, angiography)

Additional workup should be done to evaluate other causes of anemia such as blood loss, deficiencies in vitamin B_{12} or folate, or other disease states that contribute to anemia, including human immunodeficiency virus infection and malignancies (see Chapter 118). Red blood cell indices (mean corpuscular volume, mean corpuscular Hb concentration), white blood cell count, differential and platelet count, and absolute reticulocyte count should also be assessed. A stool guaiac test should be performed to rule out GI bleeding. Measurement of serum erythropoietin concentrations is not generally useful since levels may fall into what is considered a “normal” range, but are insufficient relative to the degree of decline in Hb.

Diagnostic Considerations for Chronic Kidney Disease–Related Mineral and Bone Disorder

Symptoms of CKD-MBD are often not evident until significant skeletal damage has developed; consequently, prevention is the key to minimize the risk of long-term complications. When signs and symptoms such as bone pain and skeletal fractures are evident, the disease is not easily amenable to treatment. Thus, the identification of biochemical or imaging abnormalities which typically precede clinical manifestations is an essential component of patient evaluation. The biochemical abnormalities of CKD-MBD that are commonly present in patients with CKD include alterations in serum phosphorus, calcium, PTH, 25(OH)D, $1,25(OH)_2D_3$ or calcitriol, and FGF-23. Because deficiency in the vitamin D precursor, 25(OH)D is common and has been associated with negative outcomes in the CKD population, measurement of 25(OH)D levels in patients with CKD 3-5D is suggested.[34] It should be noted, however, that the assay methods for 25(OH)D are not standardized, which creates a challenge regarding the clinical

implications of abnormal values and limits its value as an indicator of therapeutic response.[38] Current monitoring recommendations and goals of therapy are covered in the section “Treatment of CKD.”

In addition to evaluating biochemical indices that define CKD-MBD, evaluation of bone architecture may be desirable. The gold standard test for diagnosing bone manifestations of CKD-MBD is a bone biopsy for histologic analysis; however, this is a very invasive test that is not easily performed. KDIGO guidelines recommend bone biopsy only in patients in whom the etiology of clinical symptoms and biochemical abnormalities is not clear and the results may lead to changes in therapy.[34] This includes patients experiencing unexplained fractures, persistent hypercalcemia, osteomalacia, an atypical response to standard therapies for elevated PTH, or progressive decreases in bone mineral density despite therapy. Bone biopsy findings are described on the basis of turnover rate, mineralization, and volume. Bone mineral density testing is recommended in patients with CKD 3-5D with evidence of CKD-MBD and/or risk factors for osteoporosis.[34] CKD-MBD is also highly associated with vascular and soft-tissue calcifications, known risk factors for mortality; therefore, diagnostic testing for calcifications should be considered in the evaluation for CKD-MBD.

TREATMENT OF CKD

Desired Outcome of CKD Treatment

The overall goal of therapy in CKD patients is to delay or prevent progression of the disease while minimizing the development or severity of associated complications. Planning for renal replacement therapy (transplantation, HD or PD) should begin for patients deemed high risk for progression to ESRD (eg, at stage 4 CKD). Planning should include patient education about home and facility-based dialysis modalities and options for transplantation. With CKD 5D, the primary goal is to sustain and improve the patient’s quality of life and prevent adverse outcomes by aggressively managing complications of CKD.

General Approach to Treatment of CKD

Individuals with CKD should be evaluated frequently to assess the risk of progression of CKD, to identify the presence and causes of secondary complications and comorbid conditions, and to receive treatment for these

complications prior to development of Stage 5 CKD. Many nonpharmacologic and pharmacologic recommendations can be broadly applied as part of the general approach to care for all CKD patients Table 61-3.

TABLE 61-3 Recommendations for Individuals with Chronic Kidney Disease

Nonpharmacologic
Exercise 30 minutes five times per week [1D]
Weight loss if BMI >25 kg/m^2 [1D]
Smoking cessation [1D]
Alcohol: Two standard drinks per day for men and one standard drink per day for women[a] [2D]
If hypertension: Low-sodium diet (<2 g/day, <90 mmol/day) [1C]
Pharmacologic
Adjust medication doses for kidney function [1A]
Seek pharmacist or medical advice before using over-the-counter medicines or nutritional protein supplements [1B]
Herbal medicines are not recommended [1B]
Temporarily discontinue potentially nephrotoxic/renally excreted drugs if eGFR <60 mL/min/1.73 m^2 in patients who are acutely unwell or hypovolemic (eg, metformin, RAAS blockers, diuretics, NSAIDs/COX II inhibitors, lithium, digoxin) [1C]
Vaccines:
Influenza yearly [1B]
Pneumococcal vaccine if eGFR <30 mL/min/1.73 m^2, nephrotic syndrome, diabetes, or receiving immunosuppression. Single booster dose at year 5 [1B]
Hepatitis B vaccine if eGFR <30 mL/min/1.73 m^2 and risk of progression of CKD [1B]
ASA suggested for patients who have had atherosclerotic events (secondary prevention) unless there is an increased bleeding risk [2B]
Avoid oral phosphate-containing bowel preparations in people with a GFR <60 mL/min/1.73 m^2 (0.58 mL/s/m^2) or in those known to be at risk of phosphate nephropathy [1A]

[a]Standard drink: 30-mL spirits, 100-mL wine, 285-mL full-strength beer, and 425-mL light beer.

BMI, body mass index; CKD, chronic kidney disease; COX; cyclooxygenase; eGFR, estimated glomerular filtration rate; NSAIDs, nonsteroidal anti-inflammatory drugs; RAAS, renin–angiotensin–aldosterone system.

See Table 61-4 for definitions of evidence grading in brackets.

Data from References 1, 17, and 20.

5 Management of CKD should be based on KDIGO consensus guidelines, which are based on evidence and expert recommendations. There are guidelines provided by the Kidney Disease Outcome Quality Initiative Guideline (KDOQI) on CKD and many of the associated complications; however, this chapter emphasizes KDIGO guidelines, which are international guidelines and, in most cases, based on more recent data or opinion. These recommendations should not replace clinical judgment, but rather provide a basis on which treatment decisions can be made in the context of both evidence and opinion. In addition to evaluation and management of CKD, the secondary complications of CKD that are addressed in the currently available KDIGO clinical practice guidelines include blood pressure, CKD-MBD, anemia, lipid management, and hepatitis C. A diabetes guideline is currently under development. **Table 61-4** provides a guide to the grading and strength of recommendations used in these guidelines.

TABLE 61-4 KDIGO Guidelines: Grading and Strength of Recommendations

Grade	Description	Implications for Clinicians
Level 1	"We recommend"	Most patients should receive the recommended course of action.
Level 2	"We suggest"	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.
Grade	**Quality of Evidence**	**Meaning**
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often will be far from the truth.

The strength of recommendation is indicated as Level 1, Level 2, or Not Graded. The quality of the supporting evidence is shown as A, B, C, or D.

Data from Reference 1.

6 Appropriate management of CKD ideally involves a multidisciplinary approach to address the nonpharmacologic and pharmacologic interventions, dietary education, and social/financial concerns. Multidisciplinary CKD team models that have included members such as a nephrologist, nurse, dietitian, pharmacist, and social worker have demonstrated significantly lower risks of starting dialysis and all-cause mortality.[39] Estimates in the pediatric population indicate that the additional salary costs of the multidisciplinary team (pharmacist, nurse, social worker, dietician, data manager) could be recovered in 1 year if dialysis was delayed by 1 year in 2% of patients.[40] The typical team in outpatient dialysis facilities includes physicians (nephrologists), nurses, dietitians, and social workers as mandated by the US government. Although not mandated to be part of the care team, nephrology-trained pharmacists are active members of the care team in some CKD and especially dialysis settings in the

United States and their inclusion has resulted in a reduction of MRPs.[41] In Canada, pharmacists' involvement is more standardized and pharmacists have a more clearly delineated role in the care of the CKD population.[42]

Drug-dosing guidelines based on the degree of kidney function should be followed, and a complete medication history of prescription and nonprescription medications, as well as herbals and nutritional supplements, should be obtained and routinely updated. Appropriate measures should also be taken for patients with CKD to decrease the risk of nephrotoxicity from radiocontrast agents, antibiotics such as aminoglycosides, as well as from nonsteroidal anti-inflammatory drugs and ACEIs (Chapter 63).

Nonpharmacologic Therapy for CKD

Nonpharmacologic therapies for CKD include diet and lifestyle interventions targeted at reducing the risk for CKD progression and are outlined in Table 61-3. With regard to nonpharmacologic strategies to control blood pressure, a low sodium diet in people with CKD has been shown to decrease systolic blood pressure by 6 to 11 mm Hg and diastolic blood pressure by 2 to 5 mm Hg, and is associated with lower antihypertensive dose requirements.[43]

Pharmacologic Therapy for CKD

Pharmacologic therapies used to slow down CKD progression include drugs with demonstrated benefits to reduce proteinuria and to manage the causal factors for CKD; primarily hypertension and diabetes. The next sections focus on pharmacologic therapy targeting these factors. Glomerular disease is the third leading cause of CKD and almost all of the many variants are associated with significant proteinuria. A thorough review of the epidemiology, pathophysiology, and treatment strategies for glomerular diseases is provided in Chapter 64.

Proteinuria

ACEIs and ARBs

7 Evidence from clinical trials has confirmed the beneficial effects of ACEIs and ARBs on kidney function for DCKD. A meta-analysis has shown that the effects of ACEIs or ARBs on key CKD outcomes such as doubling of serum creatinine and prevention of progression of albuminuria are equivalent, and, thus, they can be used interchangeably.[44] An ACEI or an ARB should be used as

first-line therapy if the urine albumin excretion is in category A2 or greater (uACR >30 mg/g; 3.4 mg/mmol) (see **Fig. 61-6** and **Table 61-5**). The antiproteinuric effect of ACEIs and ARBs is a class effect and not specific to any one agent.[20] For patients with hypertension, the primary goal is to achieve the target blood pressure while a secondary goal is to control proteinuria. Specific dosing recommendations for ACEIs and ARBs for the treatment of proteinuria have not been established; consequently, the lowest recommended dose should be initiated. The dose is usually increased until albuminuria is reduced by 30% to 50% or side effects such as a greater than 30% decrease in eGFR or elevation in serum potassium occur (see Fig. 61-6). If patients exhibit a cough with an ACEI, a switch to an ARB is appropriate. A thorough discussion of dose, dose titration, monitoring, and adverse effects of ACEIs and ARBs is presented in Chapter 30.

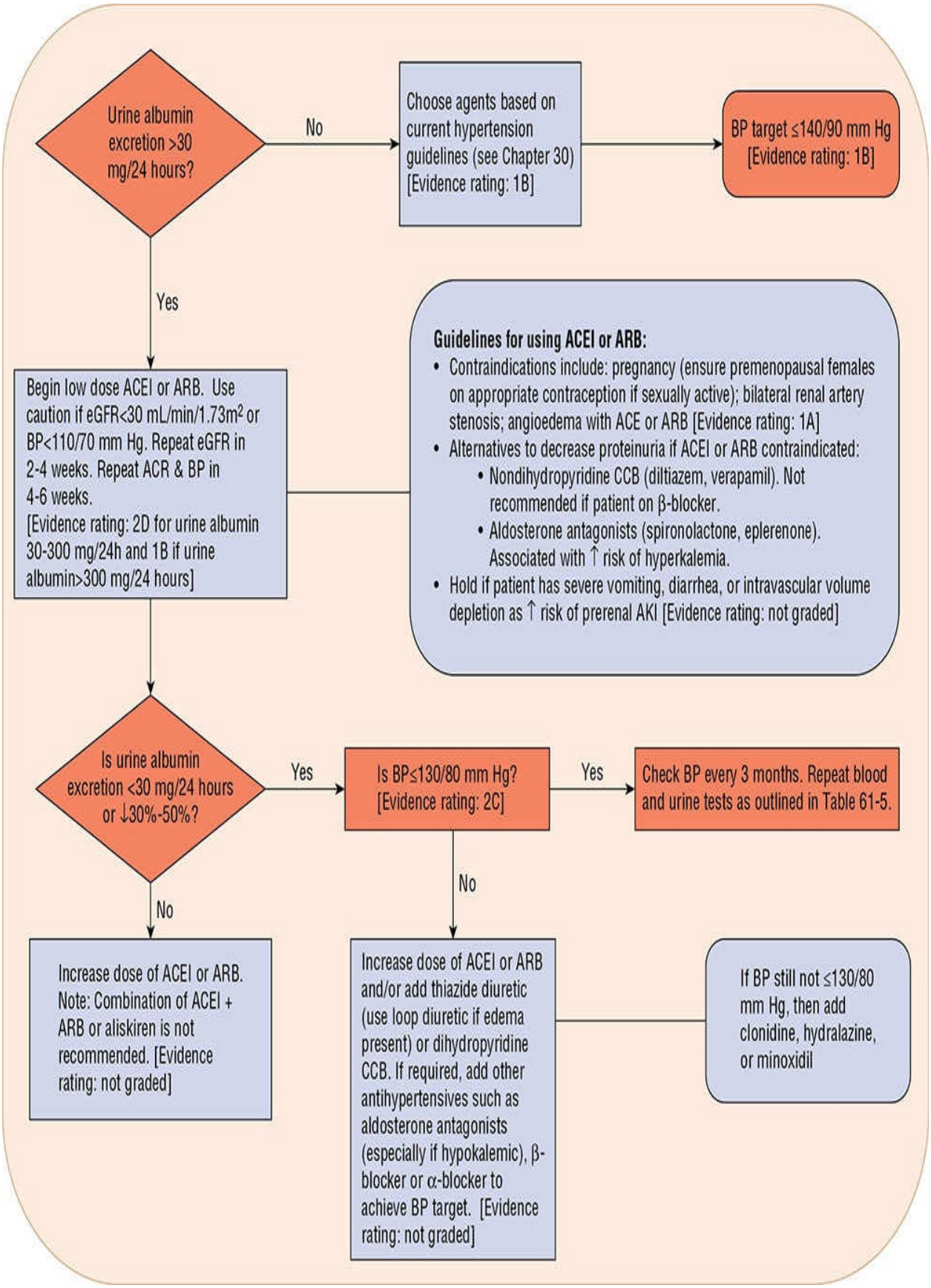

Urine albumin excretion >30 mg/24 hours?
No
Choose agents based on current hypertension guidelines (see Chapter 30) [Evidence rating: 1B]
BP target ≤140/90 mm Hg [Evidence rating: 1B]
Yes
Begin low dose ACEI or ARB. Use caution if eGFR<30 mL/min/1.73m² or BP<110/70 mm Hg. Repeat eGFR in 2-4 weeks. Repeat ACR & BP in 4-6 weeks. [Evidence rating: 2D for urine albumin 30-300 mg/24h and 1B if urine albumin>300 mg/24 hours]
Guidelines for using ACEI or ARB:
• Contraindications include: pregnancy (ensure premenopausal females on appropriate contraception if sexually active); bilateral renal artery stenosis; angioedema with ACE or ARB [Evidence rating: 1A]
• Alternatives to decrease proteinuria if ACEI or ARB contraindicated:
• Nondihydropyridine CCB (diltiazem, verapamil). Not recommended if patient on β-blocker.
• Aldosterone antagonists (spironolactone, eplerenone). Associated with ↑ risk of hyperkalemia.
• Hold if patient has severe vomiting, diarrhea, or intravascular volume depletion as ↑ risk of prerenal AKI [Evidence rating: not graded]
Is urine albumin excretion <30 mg/24 hours or ↓30%-50%?
Yes
Is BP≤130/80 mm Hg? [Evidence rating: 2C]
Yes
Check BP every 3 months. Repeat blood and urine tests as outlined in Table 61-5.
No
No
Increase dose of ACEI or ARB. Note: Combination of ACEI + ARB or aliskiren is not recommended. [Evidence rating: not graded]
Increase dose of ACEI or ARB and/or add thiazide diuretic (use loop diuretic if edema present) or dihydropyridine CCB. If required, add other antihypertensives such as aldosterone antagonists (especially if hypokalemic), β-blocker or α-blocker to achieve BP target. [Evidence rating: not graded]
If BP still not ≤130/80 mm Hg, then add clonidine, hydralazine, or minoxidil

FIGURE 61-6 Treatment of hypertension in chronic kidney disease.[20] (ACEI, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; AKI, acute kidney injury; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate.)

TABLE 61-5 Recommended Monitoring Intervals for Outcome Measure in Patients with Chronic Kidney Disease (Evidence Rating: Not Graded)

		Albuminuria Stage (based on ACR in mg/g)		
KDIGO GFR Category	eGFR (mL/min/1.73 m²)	A1: <30 mg/g (3 mg/mmol)	A2: 30-300 mg/g (3-34 mg/mmol)	A3: >300 mg/g (34 mg/mmol)
1	≥90	12 months	12 months	6 months
2	60-89	12 months	12 months	6 months
3a	45-59	12 months	6 months	4 months
3b	30-44	6 months	4 months	4 months
4	15-29	4 months	4 months	2-3 months
5	<15	1-3 months	1-3 months	1-3 months

Blood tests to monitor: CBC, Na, K, Cl, bicarbonate, urea, creatinine, and eGFR. If DCKD, add HbA1C. Fasting lipid profile at least yearly. At CKD category 3b or later: also add albumin, calcium, phosphorus, parathyroid hormone, serum iron, TIBC, and ferritin.

Urine tests to monitor: uACR (or uPCR if indicated), standard urinalysis, and urine culture and sensitivity only if symptoms suggestive of urinary tract infection.

Data from Reference 1.

The lack of response of some patients to ACEI or ARB therapy may be due to aldosterone escape from renin–angiotensin–aldosterone system (RAAS) blockade. Combination therapy with an ACEI plus an ARB or direct renin inhibitor (aliskiren) produces a more complete blockade of the RAAS and results in a greater reduction in macroalbuminuria.[45] However, several trials have failed to show that dual blockade of the RAAS either slowed progression of CKD or decreased CV events.[46–49] Combination therapy in these trials was also associated with increased risks of hyperkalemia and acute kidney injury. Thus, the combination of an ACEI plus an ARB or aliskiren for the treatment of proteinuria is no longer recommended.

Sodium Glucose Transport-2 Inhibitors

8 Sodium-glucose co-transporter 2 (SGLT-2) inhibitors show considerable promise in slowing progression of DCKD with benefits that seem to be independent of the glucose lowering effect.[50] By reducing glucose and sodium reabsorption in the proximal tubule of the kidney, these agents decrease glomerular hyperfiltration and reduce glomerular hypertension. Post-hoc analysis of the empagliflozin cardiovascular trial (EMPA-REG) showed beneficial kidney effects including reduced albuminuria, slowed eGFR decline, and a 50% reduced risk for progressing to ESRD; these benefits were consistent across patients with eGFR ≥30 mL/min/1.73 m^2.[51] The CREDENCE trial assessed whether canagliflozin 100 mg daily added to renin–angiotensin–aldosterone blockade and baseline diabetic treatments slowed progression of DCKD in participants with Type 2 diabetes mellitus, albuminuria of >300 to 5000 mg/g (34 to 570 mg/mmol), and eGFR of 30 to <90 mL/min/1.73 m^2.[52] The number needed to treat was 22 out of 1,000 patients treated over 2.5 years to prevent the composite outcome of ESRD, doubling of serum creatinine or renal or cardiovascular death. In addition, canagliflozin was shown to prevent 22 hospitalizations for heart failure and 25 events of the composite endpoint of cardiovascular death, myocardial infarction or stroke for every 1,000 subjects treated. The US Food and Drug Administration approved canagliflozin for treatment of DCKD to reduce the risk of renal events, cardiovascular mortality, and hospitalization for heart failure. The Dapa-CKD trial is examining the effects of dapagliflozin on renal outcomes and cardiovascular mortality.[53] A more detailed discussion of SGLT-2 inhibitors may be found in Chapter 91.

Other Agents

The concept of aldosterone escape has led to the search for other drug combinations to further suppress the RAAS in an effort to improve kidney outcomes. A Cochrane systematic review examined the addition of an aldosterone antagonist (spironolactone) to an ACEI or ARB (or both) in patients with CKD 1-4.[54] Aldosterone antagonists significantly reduced proteinuria and blood pressure, but doubled the risk of hyperkalemia and significantly increased the risk of gynecomastia. However, it is unknown whether adding spironolactone to ACEI or ARB (or both) will reduce the risk of major CV events or ESRD. Another meta-analysis of spironolactone in DCKD reported similar results.[55] Dihydropyridine calcium channel blockers (CCBs) do not appear to have any beneficial effects beyond those attributable to reducing blood pressure.

Nondihydropyridine agents (diltiazem and verapamil), however, have yielded beneficial effects on proteinuria, although not as profoundly as ACEIs.[56] The postulated mechanisms for this decrease in kidney injury include suppression of glomerular hypertrophy, inhibition of platelet aggregation, and a decrease in salt accumulation. These agents have been used to reduce proteinuria in combination with an ACEI or ARB despite the fact that there are limited data to support this strategy. In general, nondihydropyridine CCBs should be considered second- or third-line antiproteinuric drugs when an ACEI or ARB is contraindicated or not tolerated (Fig. 61-6).[57]

Hypertension

Figure 61-6 provides an algorithm for recommended blood pressure goals based on the degree of albuminuria present and the choice of antihypertensive agent.

The Systolic Blood Pressure Intervention Trial (SPRINT) assessed whether a lower systolic blood pressure goal of less than 120 mm Hg versus a target of less than 140 mm Hg was desirable.[58] Patients aged 50 years or older with a systolic blood pressure of 130 to 180 mm Hg and an increased risk of CV events were included. CKD 3a to 4 patients (eGFR of 20-59 mL/min/1.73 m^2) were enrolled into this trial as they were considered to be at high CV risk (see Chapter 30 for a discussion of non-CKD results). It is important to note that patients with a history of diabetes, category A3 proteinuria defined as greater than or equal to 1 g/24 hours of protein or albuminuria greater than or equal to 600 mg/24 hours, polycystic kidney disease, or a history of stroke were excluded. In the 2,646 participants with CKD, the composite renal outcome of a decrease in eGFR of 50% or more or the need for chronic dialysis or kidney transplantation was not significant over the 3.3 years duration of this trial. There were also potential harms to all participants (with and without CKD) in the intensive systolic blood pressure group that included significantly increased risks of syncope, hypotension, electrolyte abnormalities, AKI and CKD progression.[58] A target SBP of <120 mm Hg may be appropriate in patients with a Framingham risk score of >15% who do not have comorbidities such as diabetes, stroke, or advanced CKD. It may also be appropriate in patients who achieve SBP in the 120s without requiring a high number of antihypertensives and who are not experiencing adverse effects of therapy. Lastly, patients prescribed ACEI/ARBs or diuretics who are targeting an SBP <120 mm Hg need to be reliable and able to follow instructions to hold these medications when they are unable to maintain adequate fluid intake (eg, vomiting/diarrhea) due to the risk of AKI.

Diabetes

Patients with diabetes should be screened annually for CKD starting at the time of diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes by ordering a serum creatinine, eGFR, and a uACR.[17]

The management of diabetes in patients with CKD includes reduction of proteinuria and achievement of desired blood pressure and HbA1c (Chapter 91). The HbA1c target in this patient population should be 7% (0.07; 53 mmol/mol Hb); however, clinicians may consider a target greater than 7% (0.07; 53 mmol/mol Hb) if there is a risk of hypoglycemia or limited life expectancy (Evidence rating: 1A).[9,17] It should be noted that HbA1C measurements are based on an assumed red blood cell life span of 120 days. In CKD, the red blood cell life span is decreased, so HbA1c values may be falsely low.[9] Hence, in patients with CKD, the HbA1c should be interpreted along with the patient's home blood glucose readings when assessing diabetic control. It is also important to note that patients with CKD 3 and 4 are at higher risk of developing hypoglycemia because of the reduction in metabolism of insulin by the kidney as GFR declines. As a result, these patients may require reduced doses of oral or injectable hypoglycemic agents. Metformin is still considered a first-line agent in individuals with type 2 diabetes and CKD. As previously discussed, SGLT-2 inhibitors are emerging as a potential new treatment of DCKD. These agents may be used in patients with an eGFR above 25 to 30 mL/min/1.73 m^2 (see Chapter 91 for more details). Metformin can be initiated and/or continued in individuals with an eGFR greater than or equal to 45 mL/min/1.73 m^2. It is not recommended to initiate metformin in patients with an eGFR between 30 and 44 mL/min/1.73 m^2, and the decision whether to continue therapy in patients who reach this level of kidney function should be made only after weighing the risks and benefits.[19] Metformin is contraindicated in individuals with an eGFR less than 30 mL/min/1.73 m^2 and should be temporarily discontinued before administering iodinated contrast agents for imaging studies. Dose adjustments or avoidance of other renally eliminated hypoglycemic agents may also be necessary; the dosing, monitoring, and goals of therapies to treat diabetes mellitus are provided in Chapter 91 and an evidence-based approach to drug therapy individualization is presented in Chapter 65.

Evaluation of Therapeutic Outcomes

Frequency of laboratory and urine testing based on CKD category and degree of

albuminuria as defined by KDIGO is shown in Table 61-5. The monitoring necessary for patients with hypertension and diabetes is the same in the CKD population as it is in the non-CKD population, and readers should refer to the appropriate chapters in this textbook for further information.

TREATMENT OF SECONDARY COMPLICATIONS

Anemia of CKD

Treatment of anemia often requires a combination of iron supplementation and ESA therapy to promote and maintain erythropoiesis and to achieve the individual patient goals.

Desired Outcome

The desired outcomes of anemia management are to increase oxygen-carrying capacity, decrease signs and symptoms of anemia, and decrease the need for blood transfusions. Hb is the preferred monitoring parameter for red blood cell production because, unlike Hct, its concentration is not affected by blood storage conditions and instrumentation used for analysis. Initiation of iron or ESA therapy is guided by the patient's Hb, TSat, and ferritin (**Table 61-6**).[30] The risk of mortality and CV events is higher in CKD patients treated to higher Hb target values with an ESA. There are discrepancies, however, in the FDA-approved labeling for ESAs and KDIGO anemia guidelines in terms of when to initiate therapy and the target Hb.[30,59]

TABLE 61-6 KDIGO Recommendations for Initiation of Erythropoiesis Stimulating Agents and Iron in Anemia of Chronic Kidney Disease

	ND-CKD	CKD 5HD and CKD 5PD	Pediatric CKD
ESA initiation	If Hb <10 g/dL (100 g/L; 6.21 mmol/L). Consider rate of fall of Hb, prior response to iron, risk of needing a transfusion, risk of ESA therapy, and presence of anemia symptoms before initiating an ESA. [2C] Do not initiate if Hb ≥10 g/dL (100 g/L; 6.21 mmol/L). [2D]	Use ESAs to avoid drop in Hb to <9 g/dL (90 g/L; 5.59 mmol/L) by starting an ESA when Hb is between 9 and 10 g/dL (90 and 100 g/L; 5.59 and 6.21 mmol/L). [2B]	Selection of Hb concentration at which to initiate ESA therapy should include consideration of potential benefits (eg, improvement in QOL, school attendance, avoidance of blood transfusions) and potential harms. [2D]
Hb level	Do not use ESAs to *intentionally* increase Hb above 13 g/dL (130 g/L, 8.07 mmol/L). [1A] Do not use ESAs to maintain Hb above 11.5 g/dL (115 g/L; 7.14 mmol/L). [2C]	Do not use ESAs to *intentionally* increase Hb above 13 g/dL (130 g/L, 8.07 mmol/L). [1A] Do not use ESAs to maintain Hb above 11.5 g/dL (115 g/L; 7.14 mmol/L). [2C]	Suggest Hb range of 11-12 g/dL (110-120 g/L, 6.83-7.45 mmol/L). [2D]
Iron initiation[a]	If TSat is ≤30% (0.30) and ferritin is ≤500 ng/mL (mcg/L; 1,120 pmol/L). [2C]	If TSat is ≤30% (0.30) and ferritin is ≤500 ng/mL (mcg/L; 1,120 pmol/L). [2C]	If TSat is ≤20% (0.20) and ferritin is ≤100 ng/mL (mcg/L; 225 pmol/L). [1D]

[a]If TSat and serum ferritin are below suggested levels, consider iron supplementation if goal is to increase Hb and/or decrease ESA dose. *Note:* Serum ferritin is an acute-phase reactant-use clinical judgment when above 500 ng/mL (mcg/L; 1120 pmol/L).

CKD, chronic kidney disease; ESA, erythropoiesis stimulating agent; Hb, hemoglobin; ND-CKD, nondialysis CKD patients; QOL, quality of life; TSat, transferrin saturation.

See Table 61-4 for definitions of evidence grading in brackets.

Data from Reference 30.

Despite associations of development of left ventricular hypertrophy (LVH) with worsening anemia, there are no prospective studies demonstrating that early and aggressive treatment improves CV endpoints or reduces LVH in CKD patients. Improvements in quality of life are not universally observed with increases in Hb and such perceived improvements must be weighed against reported risks associated with using ESAs to achieve near-normal Hb levels in the CKD population.[60]

Target Hemoglobin and Use of Erythropoiesis-Stimulating Agents

The target range for Hb in the CKD population has been a topic of much debate. Although the benefits of achieving a normal or near-normal Hb seemed rational when ESAs became available in the late 1980s, the Normal Hematocrit Cardiac Trial (NHCT),[61,62] the Correction of Hb and Outcomes in Renal Insufficiency (CHOIR),[63] and the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE)[64] trials later proved otherwise, and the suggested

target Hb at the time of those trials of 11 to 12 g/dL (110-120 g/L; 6.83-7.45 mmol/L) was subsequently lowered. Several FDA advisories have been released and changes made to the precautions, black box warning, and dosing sections of ESA product labeling promoting more conservative use of ESAs.[65] The current labeling for all ESAs warns that dosing ESAs to target Hb levels greater than 11 g/dL (110 g/L; 6.83 mmol/L) for CKD patients increases the risk for death, serious CV reactions, and stroke. Practitioners are advised to consider ESAs in patients with CKD only when the Hb is below 10 g/dL (100 g/L; 6.21 mmol/L) and to individualize therapy to use the lowest ESA dose necessary to decrease the need for red blood cell transfusions. The goal is not to normalize Hb in patients with CKD treated with an ESA.

Of concern is the fact that CHOIR demonstrated that targeting Hb levels above 11 g/dL (110 g/L; 6.83 mmol/L) with ESA therapy in individuals with CKD not requiring dialysis resulted in increased risk of mortality and CV events compared with patients maintained in a lower Hb range (trial was terminated early).[63] CREATE demonstrated no benefit of targeting a higher Hb target (13-15 g/dL [130-150 g/L; 8.07-9.31 mmol/L]) to reduce CV events in the nondialysis CKD patients.[64] An increased risk of all-cause mortality with ESA treatment was also reported in a meta-analysis of nine randomized controlled trials that included over 5,100 CKD patients treated to Hb targets in the range of 12 to 16 g/dL (120-160 g/L; 7.45-9.93 mmol/L).[66] There was also a higher risk of dialysis access thrombosis and uncontrolled blood pressure in the higher Hb groups. Results from the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) also failed to support a higher Hb.[67] In addition, there was also an almost twofold increase in the risk of stroke (5% in the treatment group vs 2.6% in the placebo group), a finding that was not associated with baseline characteristics of the patients or other potential risk factors. Those patients with a history of cancer in the higher Hb group also had a higher risk of death.

The overall negative CV outcomes observed with higher Hb targets in the randomized trials have prompted much discussion about the potential causes, including not only ESA dose and Hb target, but also the rate of rise in Hb and the variability in Hb over time (eg, degree of fluctuation in Hb). High-dose ESA use has been associated with greater risk of death.[68] Individuals in the CHOIR study who were able to achieve the target Hb did not have worse outcomes. Further analysis of the NHCT data also showed a reduction in mortality by 60% for those individuals who responded to epoetin therapy compared with nonresponders.[62] Such findings have led to discussion of whether hyporesponsiveness to ESAs due to other conditions such as inflammation may

explain the higher event rates in this group of individuals.

Nonpharmacologic Therapy

Nonpharmacologic therapy for anemia of CKD includes maintaining adequate dietary intake of iron as well as folate and B_{12}. A relatively small amount of dietary iron, approximately 1 to 2 mg, is absorbed each day, primarily in the duodenum. Although there is some debate as to whether GI absorption of iron is significantly altered in patients with severe CKD, it is clear that oral intake from dietary sources alone is insufficient to meet the increased iron requirements from initiation of ESA therapy.

Pharmacologic Therapy

9 Pharmacologic therapy for anemia of CKD includes iron supplementation to prevent and correct iron deficiency and ESA therapy to correct erythropoietin deficiency. Iron supplementation is first-line therapy for anemia of CKD if iron deficiency is present, and for some patients the target Hb may be achieved without concomitant ESA therapy. For most individuals with advanced CKD, however, combined therapy with iron and an ESA will be necessary.

Iron Supplementation

Iron supplements provide the elemental iron required for production of Hb and its subsequent incorporation in red blood cells, the net result of which is an increase in the transportation of oxygen to tissues. Iron supplementation is required for *absolute iron deficiency*, but may also be warranted in individuals in whom an increase in Hb or a decrease in ESA dose is desired.[30]

Therapeutic Options Multiple oral and IV products, as well as a newly approved dialysate iron formulation, are marketed in the United States. Oral iron preparations include ferrous salts (ferrous sulfate, ferrous fumarate, and ferrous gluconate), ferric maltol (recently approved for use in the United States), polysaccharide iron complex, and carbonyl iron. These forms of iron differ in terms of the amount of elemental iron: ferrous sulfate (20%), ferrous gluconate (12%), ferrous fumarate (33%), iron polysaccharide (100%), and carbonyl iron (100%). Ferric maltol is a non-salt formulation that contains iron in a stable ferric state as a complex with a trimaltol ligand allowing absorption of ferric iron and maltol across the intestinal wall. A heme iron polypeptide formulation is

also available and contains 12 mg of elemental iron. Numerous nonprescription as well as prescription products that contain these iron formulations are available (see Chapter 118). Approximately 10% of orally administered iron is absorbed in the duodenum and upper jejunum. Absorption of iron is decreased by food and achlorhydria. Some oral iron formulations also include ascorbic acid to enhance iron absorption.

Soluble ferric pyrophosphate citrate (Triferic) is an iron compound added to the dialysate used for HD and crosses from the dialysate to the blood side of the dialyzer by diffusion to allow for continuous iron administration during the procedure. Once in the systemic circulation, ferric pyrophosphate binds directly to transferrin, bypassing the reticuloendothelial system, and is delivered to the bone marrow for use in red blood cell production. Studies to date have shown an increase in Hb concentration and a reduction in ESA dose and IV iron requirements, but no significant increase in ferritin or in nontransferrin bound iron.[69,70] These findings are important when considering the potential adverse effects associated with iron accumulation and free (unbound) iron. The role of this agent in treating anemia of CKD is yet to be determined as this agent is relatively new in the clinical setting.

IV iron preparations are colloids that consist of an iron-containing core that is surrounded by a carbohydrate shell to stabilize the iron complex. Available agents differ in the size of the core and the composition of the surrounding carbohydrate. Such differences affect the rate of dissociation of iron from the complex, the rate of distribution, and the maximum tolerated dose and rate of infusion. Five IV iron products are currently available in the United States (**Table 61-7**).

TABLE 61-7 IV Iron Preparations

Iron Compounds	Brand Names	Half-Life (Hours)	Molecular Weight (Daltons)	FDA-Approved Indications	FDA-Approved Dosing[a]	Dose Ranges (mg)[b,c]
Ferric carboxymaltose	Injectafer	7-12	150,000	Adult patients with intolerance to oral iron or who have had an unsatisfactory response to oral iron and in adult patients with CKD not on dialysis	Give 2 doses separated by at least 7 days of 750 mg per dose (if body weight is ≥50 kg) or 15 mg/kg per dose (if body weight is <50 kg) not to exceed 1,500 mg per course. Give either IV push (100 mg/min) or diluted in not more than 250 mL of 0.9 NaCl as an infusion over at least 15 minutes	750
Ferumoxytol	Feraheme	15	750,000	Adult patients with intolerance to oral iron or who have had an unsatisfactory response to oral iron and in adult patients with CKD	510 mg (17 mL) as a single dose, followed by a second 510 mg dose 3-8 days after the initial dose. Dilute in 50-200 mL of 0.9% NaCl or 5% dextrose and administer as an IV infusion over 15 minutes	510
Iron dextran	INFeD	40-60	96,000	Patients with iron deficiency in whom oral iron is unsatisfactory or impossible	100 mg over 2 minutes (25-mg test dose required) Note: Equation provided by manufacturer to calculate dose based on desired Hb	25-1,000
Iron sucrose	Venofer	6	43,000	Adult and pediatric CKD 5HD patients aged 2 years and older	Adult: 100 mg over 2-5 minutes or 100 mg in maximum of 100 mL of 0.9% NaCl over 15 minutes per consecutive HD session Pediatric: 0.5 mg/kg not to exceed 100 mg per dose over 5 minutes or diluted in 25 mL of 0.9% NaCl administered over 5-60 minutes (give dose every 2 weeks for 12 weeks)	25-1,000
				Adult and pediatric ND-CKD patients aged 2 years and older	Adult: 200 mg over 2-5 minutes on five different occasions within 14-day period. There is limited experience with administration of 500 mg diluted in a maximum of 250 mL of 0.9% NaCl over 3.5 to 4 hours on day 1 and day 14 Pediatric: see pediatric dosing for CKD 5HD (give dose every 4 weeks for 12 weeks)	
				Adult and pediatric CKD 5PD patients aged 2 years and older	Adult: Give 3 divided doses within 28 days as 2 infusions of 300 mg over 1.5 hours 14 days apart followed by one 400-mg infusion over 2.5 hours 14 days later. Dilute in a maximum of 250 mL of 0.9% NaCl Pediatric: see pediatric dosing for CKD 5HD (give dose every 4 weeks for 12 weeks)	
Sodium ferric gluconate	Ferrlecit	1	350,000	Adult and pediatric CKD 5HD patients aged 6 years and older receiving ESA therapy	Adult: 125 mg over 10 minutes or 125 mg in 100 mL of 0.9% NaCl over 60 minutes per HD session Pediatric: 1.5 mg/kg in 25 mL of 0.9% NaCl over 60 minutes per dialysis session; maximum dose 125 mg per dose	62.5-1,000

CKD, chronic kidney disease; ESA, erythropoiesis stimulating agent; ND-CKD, nondialysis CKD patients.

[a]Monitor for 30 minutes following an infusion; KDIGO guidelines recommend monitoring for 60 minutes (1B recommendation for iron dextran, 2C recommendation for non-dextran products).

[b] Dose ranges for iron deficiency in CKD. With the exception of ferric carboxymaltose and ferumoxytol, small doses (eg, 25-150 mg/week) are generally used for maintenance regimens. Larger doses (eg, 1 g) should be administered in divided doses.

[c] Total dose for absolute iron deficiency is approximately 1 g in divided doses (1.5 g for ferric carboxymaltose).

Either oral or IV administration of iron is recommended in non-dialysis patients (eg, CKD stage 3-5). Oral iron supplementation is more convenient since these patients do not have regular IV access; however, at some point they are likely to require IV iron supplementation to correct absolute iron deficiency, especially if they are receiving an ESA. The route of administration should be based on the severity of iron deficiency, availability of IV access, response to prior oral iron therapy, side effects, patient adherence to therapy, and cost. If oral therapy is initiated, a 1- to 3-month trial is recommended to assess response. In patients with CKD 5HD, GI absorption of iron is often inadequate to meet the increase in iron demand from ESA therapy and chronic blood loss. Thus, the IV route is preferred for HD patients.[30] IV administration is also recommended in the PD population, although this often is not practical and the desire to preserve potential future venous access sites for HD (if needed) must be considered. Parenteral iron improves the responsiveness to ESA therapy and, thus, lower ESA doses can be used to maintain the target Hb in HD patients.[30] Iron administration in patients with functional iron deficiency (ie, low TSat, high serum ferritin) is questionable. A trial of IV iron therapy may be warranted if the Hb is less than desired despite high-dose ESA therapy.

Adverse Effects Adverse effects of oral iron are primarily GI in nature and include constipation, nausea, and abdominal cramping (see Chapter 118). These adverse effects are more likely as the dose is escalated and may be present in more than 50% of patients receiving 200 mg of elemental iron per day. These unfavorable effects often discourage patients from taking these medications on a chronic basis. Some of these GI side effects can be minimized if oral iron products are taken with food; however, food may decrease absorption of oral iron.

Adverse effects of IV iron include allergic reactions, hypotension, dizziness, dyspnea, headaches, lower back pain, arthralgia, syncope, and arthritis. Some of these reactions, in particular hypotension, can be minimized by decreasing the dose or rate of infusion of iron. The most concerning potential consequence of IV iron administration is anaphylaxis. Serious reactions to iron dextran including respiratory complications and CV collapse have been reported in approximately 0.6% to 0.7% of patients.[30] Such reactions are believed to be partly a response to antibody formation to the dextran component. Adverse reactions were reported more frequently in those receiving Dexferrum (an iron dextran product now discontinued) compared with INFeD, and these iron dextrans products were not interchangeable.[30] Iron dextran carries a black box warning of the risk of

anaphylactic-type reactions, including fatalities, and a 25-mg test dose is required. A recent analysis of anaphylaxis risk in patients newly exposed to IV iron products (including dextran, gluconate, sucrose, or ferumoxytol) reported the highest risk with iron dextran and the lowest risk with iron sucrose.[71]

The non-dextran IV iron formulations have a better safety record than iron dextran. The labeling for these formulations also includes a warning of the risk of hypersensitivity reactions. Since the approval of ferumoxytol in 2009, there have been 79 cases of anaphylactic reactions, of which 18 were fatal.[72] Almost half of the cases occurred with the first dose and approximately 75% occurred during the infusion or within 5 minutes of completion. In 2015, the FDA required a black box warning for ferumoxytol noting that fatal and serious hypersensitivity reactions including anaphylaxis have occurred and that the risks and benefits should be considered in patients with a history of multiple drug allergies. Ferumoxytol should not be administered IV push (as previously recommended), but should be diluted and administered as an IV infusion (see Table 61-7). As a superparamagnetic oxide, ferumoxytol may alter the diagnostic ability of magnetic resonance imaging studies for up to 3 months after administration; therefore, they should be done prior to administration of ferumoxytol whenever possible.

Long-term administration of IV iron also introduces a risk of iron overload. Deposition of excess iron may affect several organ systems, leading to hepatic, pancreatic, and cardiac dysfunction. Bone marrow biopsy provides the most definitive diagnosis of iron overload, but because it is an extremely invasive procedure, it is not widely employed in most clinical settings. Maintaining target serum ferritin and TSat values is the most reasonable approach to minimize the risk of iron toxicity. The challenge is in defining what should be the upper limit, particularly for serum ferritin, which may be elevated in inflammatory conditions and not reflective of true iron stores in such situations. If symptomatic overload does occur, iron chelating agents such as deferoxamine (Desferal), deferiprone (Ferriprox), deferasirox (Exjade), or phlebotomy may be necessary.

With more restrictions now implemented on use of ESAs, there has been concern regarding the potential detrimental effect of increased iron exposure and higher TSat and ferritin targets on patient outcomes (eg, infection, mortality, hospitalizations) despite the fact that there are no data confirming unequivocally that exposure to IV iron in CKD patients treated with ESA therapy increases patient morbidity or mortality.[73–76] There are opposing conclusions from two studies assessing long-term efficacy and safety of IV iron compared to oral iron:

the FIND-CKD and REVOKE trials.[77,78] In the FIND-CKD trial, 624 nondialysis CKD patients were randomized to IV ferric carboxymaltose administered at high dose (1,000 mg every 4 weeks) to target a ferritin of 400 to 600 ng/mL (mcg/L; 900 to 1350 pmol/L), low-dose (200 mg every 4 weeks) to target a ferritin of 100 to 200 ng/mL (mcg/L; 225 to 450 pmol/L), or oral iron administered as 200 mg/day. After 56 weeks, the high ferritin IV iron group had better outcomes in terms of the increase in mean Hb at 12 months and time to achieve that level, but no differences in adverse events.[77] The REVOKE trial, however, reported a higher risk of cardiovascular adverse events and infection resulting in hospitalization for nondialysis CKD patients receiving 200 mg of IV iron sucrose every 2 weeks (total of 1 g) compared to those receiving approximately 200 mg of elemental oral iron and was terminated early.[78]

Data from an observational study to assess the association between cumulative IV iron dose in a given time frame and mortality in 14,000 HD patients indicated that administration of cumulative IV iron doses below 1,050 mg within 3 months or 2,100 mg within 6 months was not associated with a significant increase in all-cause, CV, or infection-related mortality.[79] In a meta-analysis of seven randomized, controlled trials including 970 dialysis patients, higher-dose IV iron (greater than 400 mg/month) was not associated with greater mortality or infection compared to lower-dose iron, oral iron, or no iron therapy.[76] When observational studies were evaluated, there was also no association between higher-dose IV iron (above 200 mg/month) and mortality, infection, cardiovascular events, or hospitalizations (over 100,000 dialysis patients included for each evaluation).

A recent large randomized controlled trial in the United Kingdom evaluated the safety of high-dose IV iron (400 mg/month) administered proactively (with the upper TSat limit of 40% [0.40] and ferritin of 700 ng/mL [mcg/L; 1,570 pmol/L]) and low-dose IV iron (0-400 mg monthly) administered reactively (with a TSat <20% [0.20] or a ferritin <200 ng/mL [mcg/L; 450 pmol/L] prompting the need for IV iron administration) in 2,141 dialysis patients over a median of 2 years.[80] There were significantly fewer deaths and nonfatal cardiovascular events (nonfatal MI, stroke, hospitalization for heart failure) in the high-dose group compared to the low-dose group and a lower requirement for ESAs and transfusions. This is the most robust evidence to date suggesting that higher iron targets are likely safe.

Drug Interactions Drug interactions with oral iron are common. Iron absorption is decreased by other elements (eg, calcium in calcium-containing phosphate

binders), medications that increase the pH of the GI tract such as proton pump inhibitors and H_2-antagonists, and antibiotics including doxycycline and tetracycline. Iron also decreases absorption of other drugs such as antibiotics (fluoroquinolones, doxycycline) (see Chapter 118).

Dosing and Administration If oral therapy is initiated, the recommended dose is 200 mg of elemental iron per day. With numerous oral agents to choose from, the best option is one that provides adequate elemental iron with the fewest number of dosage units required per day and the lowest incidence of adverse effects. Smaller doses may be better tolerated in some patients. The recommended dose of ferric maltol in ND-CKD patients is 30 mg twice daily. KDIGO guidelines suggest a 1- to 3-month trial of oral therapy in the non-HD CKD population prior to initiating IV therapy.[30] For the HD population, IV therapy is preferred with administration of a 1-g course of IV iron (in divided doses) recommended to initially replete patients with an absolute iron deficiency. The amount per dose and rate at which to administer IV iron depends on the product (see Table 61-7). Typical repletion dosing regimens for IV iron are 100 mg as iron sucrose over 10 dialysis sessions or 125 mg of sodium ferric gluconate over eight dialysis sessions to provide a total of 1 g. The 1-g course of IV iron may be repeated as needed with close monitoring of Hb and iron indices. Iron indices should not be measured within 1 week of receiving an IV iron dose. As a general practice, if IV iron doses higher than those currently approved are needed, they should be infused over a longer period of time (eg, at least 2-4 hours depending on the dose) due to the risk of hypersensitivity reactions, hypotension, dizziness, and nausea. The newer agents, ferumoxytol and ferric carboxymaltose, differ in terms of how rapidly iron is released from the compound, which allows for higher single doses to be administered (Table 61-7).

Without ongoing iron supplementation, many patients quickly become iron-deficient. To prevent iron deficiency and the need for intermittent repletion doses, maintenance doses of IV iron should be administered in HD patients (eg, iron sucrose 25-100 mg/week; sodium ferric gluconate 62.5-125 mg/week).[30] There are many different maintenance dosing protocols in clinical practice for CKD patients and some controversy as to the maximum monthly doses, given safety concerns. The main consideration is to provide enough iron to help achieve and maintain the goal hemoglobin level and to reduce the need for ESAs and transfusions, while minimizing risks of IV iron. Several high-dose and low-dose IV iron dosing strategies were previously discussed (see *Adverse Events*). A recent analysis of the Dialysis Outcome and Practice Patterns Study found that IV iron dosing of less than 300 mg per month may be an effective approach to

maintain hemoglobin compared to the higher doses (300-400 mg/month).[81]

Administration of a 25-mg test dose is required for iron dextran and this test dose should be administered over at least 30 seconds (for InFeD). It is recommended that patients be observed for at least 1 hour before administering the remainder of the dose. Due to the risk of anaphylactic reactions with dextran products, the non-dextran agents are predominantly used in the CKD population. Regardless of which IV iron agent is used, all patients should be monitored for signs and symptoms of hypersensitivity for at least 30 minutes following completion of a dose. KDIGO clinical practice guidelines suggest monitoring patients for at least 60 minutes following administration of IV iron; a 1B recommendation for iron dextran and a 2C recommendation for non-dextran forumulations.[30] These agents should only be administered when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions.

Erythropoiesis-Stimulating Agent Therapy

Since FDA approval of epoetin alfa in 1989, ESA therapy has become an integral part of the care for patients with CKD. ESAs available in the United States are listed in **Table 61-8**. The biosimilar epoetin-alfa epbx was recently approved in the United States. As a biosimilar, this agent has the same indications as the biological drug, epoetin alfa.

TABLE 61-8 Erythropoiesis-Stimulating Agents in Chronic Kidney Disease

Drug Name	Brand Name(s)	Starting Dose	Route of Administration	Half-Life (Hours)
Epoetin alfa	Epogen, Procrit	Adults: 50-100 units/kg three times per week Pediatrics: 50 units/kg three times per week	IV or SC	8.5 (IV) 24 (SC)
Epoetin alfa-epbx	Retacrit	See epoetin alfa information		
Darbepoetin alfa	Aranesp	Adults: ND-CKD: 0.45 mcg/kg once every 4 weeks CKD 5HD or CKD 5PD: 0.45 mcg/kg once per week or 0.75 mcg/kg every 2 weeks Pediatrics: 0.45 mcg/kg once weekly; may give 0.75 mcg/kg once every 2 weeks in ND-CKD patients	IV or SC	25 (IV) 48 (SC)
Methoxy PEG-epoetin beta	Mircera	All adult CKD patients: 0.6 mcg/kg every 2 weeks; Once Hb stabilizes, double the dose and administer monthly (eg, if administering 0.6 mcg/kg every 2 weeks, give 1.2 mcg/kg every month)	IV or SC	134 (IV) 139 (SC)

CKD, chronic kidney disease; ND-CKD, nondialysis CKD patients; PEG, Polyethylene glycol; SC, subcutaneous.

Pharmacology and Mechanism of Action Epoetin alfa is a glycoprotein manufactured by recombinant DNA technology that has the same amino acid sequence as endogenous erythropoietin. Darbepoetin alfa has two additional *N*-linked carbohydrate chains that decrease the affinity for the erythropoietin receptor, but yield a longer duration of activity compared with erythropoietin. Methoxy PEG-epoetin beta was created by integrating an amide bond between methoxy polyethylene glycol-butanoic acid and either the N-terminal or ε-amino group of lysine present in epoetin beta. The compound, which is referred to as a continuous erythropoietin receptor activator, has a much longer half-life than the other ESAs. All ESAs have the same biologic activity as endogenous erythropoietin in that they bind to and activate the erythropoietin receptor to stimulate erythropoiesis.

Pharmacokinetics and Pharmacodynamics All available ESAs may be administered by either the IV or the subcutaneous (SC) route. Although bioavailability is less with SC than with IV administration, the prolonged absorption phase leads to an extended half-life (see Table 61-8). Thus, the same target Hb can be achieved and maintained at SC epoetin doses 15% to 30% lower than IV doses.[30] The prolonged half-lives of darbepoetin alfa and methoxy PEG-epoetin beta offer the advantage of less-frequent dosing. This is of particular benefit for individuals with CKD who are not yet receiving dialysis and those receiving PD since these patients are not in a clinical setting as

frequently as HD patients and do not have regular IV access.

The pharmacodynamic effect of ESAs is important to consider when evaluating response to therapy. With initiation of ESA therapy or a change in dose, the Hb may begin to rise as the result of demargination of reticulocytes; however, it takes approximately 10 days before erythrocyte progenitor cells mature and are released into the circulation. The Hb continues to increase until the life span of the cells stimulated by ESA therapy is reached (mean 2 months; range 1-4 months in patients with ESRD). At this point a new steady state is achieved (ie, the rate at which red blood cells are being produced equals the rate at which they are leaving the circulation). For this reason, it is important to evaluate the Hb response over several weeks and not make dosing changes too soon.

Efficacy Patients will generally respond to ESA therapy in a dose-related fashion. The most common causes of resistance are iron deficiency, acute illness, inflammation, infection, chronic bleeding, aluminum toxicity, malnutrition, hyperparathyroidism, cancer, and chemotherapy.[30] Deficiencies in folate and vitamin B_{12} should also be considered as potential causes of resistance to ESA therapy, as both are essential for optimal erythropoiesis. Use of ACEIs and ARBs has also been associated with hyporesponsiveness to ESA therapy.[30]

Adverse Effects Hypertension is the most common adverse event reported with ESAs and may be associated with the rate of rise in Hb.[29] Hypertensive encephalopathy has also been observed. According to FDA-approved product labeling, ESAs should not be used in those with uncontrolled blood pressure. Protocols established in some clinical settings recommend withholding ESA therapy if blood pressure is above a defined threshold; however, others advocate more judicious use of antihypertensive agents and dialysis to control blood pressure. Seizures have occurred in patients treated with ESAs, particularly within the first 90 days of starting therapy. Thrombosis of the HD vascular access site and other thromboembolic events were reported when ESAs were used to target Hb greater than 13 g/dL (130 g/L; 8.07 mmol/L).[82] The potential for these adverse effects calls for close monitoring of the rate of rise in Hb, changes in blood pressure, and neurologic symptoms following initiation of therapy or a change in ESA dose.

Antibody-associated pure red cell aplasia (PRCA), caused by induction of antibodies directed against the ESA molecule, was reported in the late 1990s and early in 2000 and was primarily associated with subcutaneous administration of Eprex, an epoetin alfa formulation manufactured outside the United States.[83]

This reaction was potentially a result of organic compounds being formed when the stabilizing agent polysorbate was used in combination with uncoated rubber stoppers in the prefilled syringes. There have been very few cases since changes in the packaging of this product were made; however, the cause of PRCA with this formulation has been disputed.[84] Of note, there have been reports of PRCA with methoxy PEG-epoetin beta.[85] An evaluation for PRCA should be considered for patients receiving ESA therapy for more than 8 weeks who develop either a rapid decrease in Hb level (rate of 0.5-1 g/dL/week [5-10 g/L/week; 0.31-0.62 mmol/L/week]) or require one to two blood transfusions per week, and have an absolute reticulocyte count of less than 10,000/μL (10×10^9/L) with a normal platelet and white blood cell count.[30] Discontinuation of ESA therapy is recommended if antibody-mediated PRCA develops because antibodies are cross-reactive and continued exposure may lead to anaphylactic reactions (a grade 1A recommendation).

ESAs have also been associated with a reduction in overall survival and increased risk of progression of certain tumor types among CKD patients (eg, head and neck). ESAs are not indicated in patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure. These are important effects to consider when managing a CKD patient with an oncologic disorder.[86]

Drug–Drug Interactions No significant drug interactions have been reported with the available ESAs.

Dosing and Administration Recommended starting doses of ESA are listed in Table 61-8. Less frequent dosing of epoetin alfa (eg, every 1-2 weeks) is effective and may be preferred for ND-CKD patients since these individuals are seen in the outpatient clinical setting on a relatively infrequent basis. Subcutaneous dosing is also more convenient in this population and in PD patients who do not have regular IV access. Conversion tables for patients who are to be switched from epoetin alfa (units per week) to darbepoetin alfa (micrograms per week) are available in the labeling information for darbepoetin.[87] There is also a conversion chart for patients being converted from epoetin alfa or darbepoetin alfa to methoxy PEG-epoetin beta.[85]

When starting an ESA, Hb levels should be monitored at least monthly (weekly may be preferred) until stable and then monthly thereafter. Dose adjustments should be made based on Hb response with a goal of avoiding an excessively quick rise or the achievement of values above the recommended target values. An acceptable rate of increase in Hb is 1 to 2 g/dL (10-20 g/L; 0.62-1.24 mmol/L) per month. As a general rule, ESA doses should not be

increased more frequently than every 4 weeks, although decreases in dose may occur more frequently in response to a rapid rate of rise in Hb. The dose should be reduced by at least 25% if the Hb increases by more than 1 g/dL (10 g/L; 0.62 mmol/L) in a 2-week period.[29] The dose should be reduced or temporarily discontinued if the Hb level approaches or exceeds 11 g/dL (110 g/L; 6.83 mmol/L) in dialysis patients or 10 g/dL (100 g/L; 6.21 mmol/L) in patients with CKD not requiring dialysis. KDIGO recommendations advocate a decrease in dose as opposed to withholding the ESA when a decrease in Hb concentration is desired (2C grade recommendation).[30] A 25% increase in dose may be considered if the Hb has not increased by 1 g/dL (10 g/L; 0.62 mmol/L) after 4 weeks of ESA treatment and if no causes of hyporesponsiveness to the ESA have been identified. For patients who do not respond adequately over a 12-week escalation period, an increase in ESA dose is unlikely to improve response and may increase risks. Initial hyporesponsiveness to ESAs should be considered when there is no increase in Hb from baseline after the first month of appropriate weight-based dosing. In this situation, escalations in ESA dose beyond double the initial weight-based dose should be avoided (a grade 2D recommendation). Acquired ESA hyporesponsiveness may be suspected when patients previously on a stable ESA dose require two increases in ESA doses up to 50% beyond the previously utilized stable dose.[30] In this situation, repeat escalations in ESA dose beyond double the dose at which they had been stable should be avoided (a grade 2D recommendation). The lowest dose of ESA should be used to maintain an Hb level sufficient to reduce the need for red blood cell transfusions. **Figure 61-7** provides an approach to management of anemia using ESAs and iron therapy in patients with CKD. Of note, this figure does not address functional iron deficiency (eg, TSat <30% and ferritin > 500 ng/mL) where clinical judgment is warranted to determine the need for iron supplementation and/or changes in the ESA regimen.

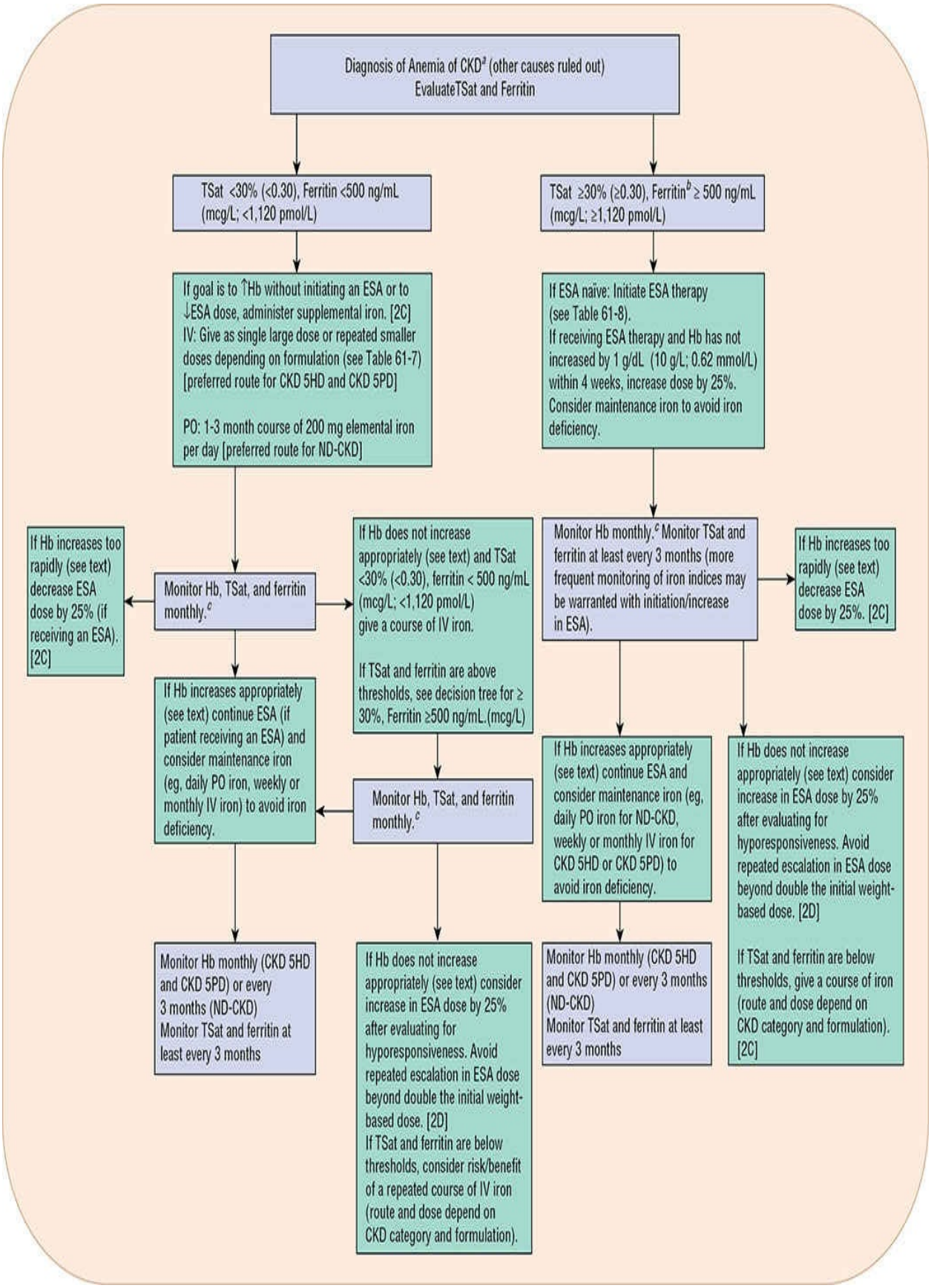

Diagnosis of Anemia of CKD[a] (other causes ruled out)
EvaluateTSat and Ferritin
TSat <30% (<0.30), Ferritin <500 ng/mL (mcg/L; <1,120 pmol/L)
TSat ≥30% (≥0.30), Ferritin[b] ≥ 500 ng/mL (mcg/L; ≥1,120 pmol/L)
If goal is to ↑Hb without initiating an ESA or to ↓ESA dose, administer supplemental iron. [2C]
IV: Give as single large dose or repeated smaller doses depending on formulation (see Table 61-7) [preferred route for CKD 5HD and CKD 5PD]
PO: 1-3 month course of 200 mg elemental iron per day [preferred route for ND-CKD]
If ESA naïve: Initiate ESA therapy (see Table 61-8).
If receiving ESA therapy and Hb has not increased by 1 g/dL (10 g/L; 0.62 mmol/L) within 4 weeks, increase dose by 25%.
Consider maintenance iron to avoid iron deficiency.
If Hb increases too rapidly (see text) decrease ESA dose by 25% (if receiving an ESA). [2C]
Monitor Hb, TSat, and ferritin monthly.[c]
If Hb does not increase appropriately (see text) and TSat <30% (<0.30), ferritin < 500 ng/mL (mcg/L; <1,120 pmol/L) give a course of IV iron.
If TSat and ferritin are above thresholds, see decision tree for ≥ 30%, Ferritin ≥500 ng/mL.(mcg/L)
Monitor Hb monthly.[c] Monitor TSat and ferritin at least every 3 months (more frequent monitoring of iron indices may be warranted with initiation/increase in ESA).
If Hb increases too rapidly (see text) decrease ESA dose by 25%. [2C]
If Hb increases appropriately (see text) continue ESA (if patient receiving an ESA) and consider maintenance iron (eg, daily PO iron, weekly or monthly IV iron) to avoid iron deficiency.
Monitor Hb, TSat, and ferritin monthly.[c]
If Hb increases appropriately (see text) continue ESA and consider maintenance iron (eg, daily PO iron for ND-CKD, weekly or monthly IV iron for CKD 5HD or CKD 5PD) to avoid iron deficiency.
If Hb does not increase appropriately (see text) consider increase in ESA dose by 25% after evaluating for hyporesponsiveness. Avoid repeated escalation in ESA dose beyond double the initial weight-based dose. [2D]
If TSat and ferritin are below thresholds, give a course of iron (route and dose depend on CKD category and formulation). [2C]
Monitor Hb monthly (CKD 5HD and CKD 5PD) or every 3 months (ND-CKD)
Monitor TSat and ferritin at least every 3 months
If Hb does not increase appropriately (see text) consider increase in ESA dose by 25% after evaluating for hyporesponsiveness. Avoid repeated escalation in ESA dose beyond double the initial weight-based dose. [2D]
If TSat and ferritin are below thresholds, consider risk/benefit of a repeated course of IV iron (route and dose depend on CKD category and formulation).
Monitor Hb monthly (CKD 5HD and CKD 5PD) or every 3 months (ND-CKD)
Monitor TSat and ferritin at least every 3 months

FIGURE 61-7 Algorithm for management of anemia of CKD in adults.[30,82] (CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; ND-CKD, nondialysis CKD patients; TSat, transferrin saturation.) See Table 61-4 for definitions of evidence grading in brackets. [a]See Table 61-6 and text for discussion of Hb levels. [b]Clinical judgment should be used to determine if iron supplementation should be continued when ferritin >500 ng/mL (mcg/L; 1,120 pmol/L). [c]Weekly monitoring of Hb may be warranted. Wait at least 1 week after an IV dose of iron to measure TSat and ferritin.

Hypoxia-Inducible Factor Inhibitors

Hypoxia-inducible factor (HIF) is a transcription factor composed of alpha and beta subunits and is a key factor for production of erythropoietin that occurs in response to hypoxia. The beta subunit is present consistently in the HIF complex and binds with one of three isoforms of the alpha subunit to induce expression of target genes depending on the complex formed. It is the HIF-2α subunit that is activated by peritubular fibroblasts of the kidney under hypoxic conditions and is involved in upregulating erythropoietin gene expression and iron transport.[88] When hypoxic conditions exist, the alpha and beta subunits join to form a heterodimer that translocates to the nucleus and binds to the hypoxia response element of erythropoietin to induce erythropoietin production. When hypoxic conditions do not exist, HIF-2α is hydroxylated by prolyl-hydroxylase 2 and subsequently degraded resulting in reduced erythropoietin production. Prolyl-hydroxylase 2 enzymes also target genes involved in promotion of iron absorption and iron transport. A key target for anemia management in CKD is the development of HIF-prolyl-hydroxylase (HIF-PH) 2 inhibitors or HIF stabilizers that mimic the conditions of hypoxia to prevent the hydroxylation process. There are four oral HIF-PH inhibitors in development in phase 3 trials including roxadustat, daprodustat, vadadustat, and molidustat.[88] Demonstrated benefits include improvement in hemoglobin levels and induction of physiologic blood levels of erythropoietin. These agents also decrease hepcidin, increase iron absorption, and improve functional iron deficiency. There is some concern that long-term use of these agents and sustained HIF activation may promote tumor progression due to the effects on vascular endothelial growth factor and angiogenesis. While there remains much to learn about HIF-PH inhibitors, these agents are likely to become an integral therapy for anemia management in CKD.

Transfusions and Adjunct Therapies

Red blood cell transfusions carry many risks and therefore should only be used in select situations, such as acute management of symptomatic anemia, following significant acute blood loss, and prior to surgical procedures that carry a high risk of blood loss, with the goal of preventing inadequate tissue oxygenation or cardiac failure. L-carnitine supplementation and vitamin C were previously suggested as adjunctive treatments of CKD anemia, but are not recommended because of the lack of evidence supporting improved anemia management with these therapies.[30]

Evaluation of Therapeutic Outcomes

Important therapeutic outcomes to monitor in patients with anemia of CKD include Hb, iron status, as well as the need for blood transfusions. Iron status should be assessed at least every 3 months in patients receiving a stable ESA regimen.[30] Iron status should be monitored more frequently (eg, every month) when initiating or increasing the ESA dose, following a course of IV iron, or when other factors put the patient at risk for iron loss (eg, bleeding). Hb levels should be monitored at least every 3 months in patients with CKD not on dialysis or CKD 5PD and at least monthly in CKD 5HD patients. Hb should be monitored at least monthly in patients started on ESA therapy until the Hb is stable. Of note, FDA labeling for ESAs recommends weekly monitoring of Hb with initiation of therapy or a change in dose until the Hb is stable.[82,85,89]

CHRONIC KIDNEY DISEASE–RELATED MINERAL AND BONE DISORDER

Management of PTH, phosphorus, and calcium is important in preventing CKD-MBD and CV and extravascular calcifications. Patients with CKD-MBD usually require a combination of dietary intervention, phosphate-binding medications, vitamin D, and calcimimetic therapy (for ESRD patients) to achieve these goals.

Desired Outcome

10 The desired outcomes for management of CKD-MBD are to “normalize” the biochemical parameters and prevent bone manifestations, CV and extravascular calcifications, and the associated morbidity and mortality with both

nonpharmacologic and pharmacologic interventions. At present there are two guidance documents—KDOQI and KDIGO—that clinicians can use in their patient care decision-making process.[34,90] The 2017 KDIGO clinical practice guidelines for CKD-MBD are emphasized in this chapter.

The KDIGO-recommended targets for calcium, phosphorus, and PTH and frequency of monitoring based on the CKD category are shown in **Table 61-9**. The most appropriate strategy is to evaluate trends in all of these key CKD-MBD parameters to determine a reasonable treatment approach. In contrast to the previous version of the KDIGO CKD-MBD guidelines that recommended a corrected calcium in the normal range, the more recent guidelines emphasize to avoid hypercalcemia and upgraded the level of evidence from a 2D to 2C. This is based on evidence linking higher calcium levels with mortality and nonfatal cardiovascular events.[34] The change in the recommendation for phosphorus from maintaining levels in the normal range to "toward the normal range" is based on evidence linking both high- and low-phosphate concentrations with increased mortality.[34] Despite this association with higher mortality, the effect of phosphorus lowering with therapy (ie, phosphate binders) has not consistently demonstrated improved hard outcomes such as reduced mortality.[91,92]

TABLE 61-9 KDIGO Monitoring and Goals for Calcium, Phosphorus, and Parathyroid Hormone

	Chronic Kidney Disease Stage			
Parameter	**3**	**4**	**5**	**ESRD**
Calcium[a] Monitoring frequency[b] Goal	Every 6-12 months Avoid hypercalcemia [2C]	Every 3-6 months Avoid hypercalcemia [2C]	Every 1-3 months Avoid hypercalcemia [2C]	Every 1-3 months Avoid hypercalcemia [2C]
Phosphorus Monitoring frequency[b] Goal	Every 6-12 months Toward the normal range [2C]	Every 3-6 months Toward the normal range [2C]	Every 1-3 months Toward the normal range [2C]	Every 1-3 months Toward the normal range [2C]
Intact PTH Monitoring frequency[b] Goal	Based on baseline level and CKD progression Avoid progressively rising levels or levels persistently above the upper limit of normal [2C]	Every 6-12 months Avoid progressively rising levels or levels persistently above the upper limit of normal [2C]	Every 3-6 months Avoid progressively rising levels or levels persistently above the upper limit of normal [2C]	Every 3-6 months 2-9 times the upper normal limit [2C]

[a]Usually corrected for albumin.

[b]Not graded.

See Table 61-4 for definitions of evidence grading in brackets.

Data from Reference 34.

Clinicians involved in the care of patients with CKD should know which PTH assays are available in their facilities. PTH is secreted from the parathyroid gland as intact PTH, an 84-amino-acid peptide chain (1-84 PTH) that is biologically active, and as smaller carboxy-terminal PTH fragments.[93] Circulating levels of these fragments (eg, 7-84 PTH) may increase substantially in patients with CKD and actively antagonize the effects of 1 to 84 PTH. The available immunoradiometric assays measure not only the intact PTH molecule but also fragments, which may lead to overestimation of biologically active PTH. While correction factors have been proposed, they cannot be uniformly applied to all commercially available assays and thus inconsistent results are common. Because of the variability in PTH measurement and lack of evidence to support a specific target, it is not surprising KDIGO recommends monitoring trends in serum PTH to guide treatment decisions. The optimal PTH in patients with CKD stages 3a-5, however, is unclear. An increase in PTH is expected in response to declining kidney function and to promote the desired phosphaturic effects; therefore, the guidelines specify that PTH levels *persistently* above the upper limit of normal and *progressively rising* should warrant a treatment decision. KDIGO recommends that PTH values for ESRD patients be within two to nine times the upper limit of the normal range, which corresponds to a PTH of approximately 130 to 600 pg/mL [ng/L; 14-64 pmol/L]).[34] PTH values above 600 pg/mL (ng/L; 64 pmol/L) have been associated with higher CV mortality and hospitalizations.[94]

Monitoring of alkaline phosphatase activity is also recommended as this test may serve as a gauge of a patient's response to therapy and/or bone turnover status. Avoiding the development of vascular calcification and calciphylaxis is also important as treatment options for this complication once it develops are extremely limited.

Nonpharmacologic Therapy

Dietary Phosphorus Restriction

Dietary phosphorus restriction is a first-line intervention for management of hyperphosphatemia and should be initiated for most patients with CKD 3-5.[34] The challenge with dietary restriction of phosphorus is providing enough protein to prevent malnutrition, a common problem in the ESRD population because dialysis patients require a higher protein intake (1.2-1.3 g/kg/day) and foods high in phosphorus are generally high in protein. An additional consideration is the source of phosphorus, organic versus inorganic. Inorganic sources such as from

frozen meals and processed foods include preservatives or additives used during food processing, whereas organic sources such as from meat and plant sources typically do not and may be a better option. Dietary supplements and certain brands of medications also contain phosphate (eg, amlodipine, codeine) and may contribute to phosphate intake.[95] One of the most common obstacles to dietary phosphorus restriction is patient nonadherence because of the poor palatability of the allowed foods. Regular counseling by a dietitian is ideal to design a realistic diet that works with the patient's lifestyle and considers nutritional goals.

Dialysis

HD and PD lower serum phosphorus and calcium, the extent of which is dependent on the concentration of each in the dialysate and the duration of dialysis. It is recommended that the dialysate calcium concentration be between 2.5 and 3 mEq/L (1.25 and 1.5 mmol/L) (a grade 2C recommendation).[34] Removal of phosphorus does occur with dialysis (approximately 2.5-3.5 g/week, dependent on the dialysis prescription); however, conventional dialysis alone does not usually control hyperphosphatemia.[96] Patients on daily HD or nocturnal HD who typically have longer and/or more frequent dialysis sessions have better phosphorus control and require fewer phosphate-binding agents and in some cases may even require phosphate supplementation.

Parathyroidectomy

Parathyroidectomy is a therapeutic option for those patients with persistently elevated PTH associated with hypercalcemia and/or hyperphosphatemia who are refractory to medical therapy (a grade 2B recommendation).[34] Surgical approaches include either subtotal parathyroidectomy or total parathyroidectomy with autotransplantation of parathyroid tissue to an accessible site, such as the forearm. Postoperative hypocalcemia, hypophosphatemia, and hypomagnesemia may occur because of a marked increase in bone production in relation to bone absorption ("hungry bone syndrome"). Following surgery, frequent monitoring of calcium and phosphorus is necessary. Treatment with supplemental calcium and vitamin D may be required for weeks or months.

While a parathyroidectomy is indicated for refractory patients, these patients may experience significant morbidity following the procedure. In a study of over 4,400 ESRD patients who underwent a parathyroidectomy from 2007 to 2009, there was an increase in hospitalizations (particularly for acute myocardial infarction and dysrhythmia) and emergency room visits for treatment of

hypocalcemia in the year following the procedure.[97] For some patients a parathyroidectomy may be ineffective and there is also the risk of oversuppression of PTH and prolonged hypocalcemia.[98]

Pharmacologic Therapy

Patients with CKD-MBD usually require a combination of dietary intervention, phosphate-binding medications, vitamin D, and calcimimetic therapy (for ESRD patients).

Phosphate-Binding Agents

Phosphate-binding agents are used in addition to dietary phosphorus restriction to limit GI absorption. These agents are indicated for CKD patients with progressive or persistent hyperphosphatemia.[34] For many patients the pill burden with phosphate-binding agents contributes to nonadherence and efforts should be made to simplify the regimen when possible. The cost of phosphate binders is also significant, contributing to over 1.5 billion in Medicare costs for US dialysis patients and CKD patients with Medicare Part D.[92]

Pharmacology and Mechanism of Action Drugs that bind dietary phosphorous in the GI tract form insoluble phosphate compounds that are excreted in feces, thus reducing dietary phosphorus absorption. Patients must be instructed to take these agents with meals to maximize the binding of phosphorus from dietary sources. A variety of phosphate-binding agents with varying binding affinities are available, including elemental calcium, iron, and lanthanum-containing compounds, and the nonelemental agent sevelamer (**Table 61-10**). Phosphate binder equivalent doses (compared to 1 g of calcium carbonate) for commonly used phosphate-binder formulations have been estimated as follows: (calcium acetate 667 mg = 0.67; lanthanum 500 mg = 1.0, sevelamer carbonate 800 mg = 0.60, sucroferric oxyhydroxide 500 mg = 1.6, ferric citrate 210 mg = 0.64, aluminum hydroxide 500 mg = 0.75, and aluminum carbonate 500 mg = 0.95).[92,99]

TABLE 61-10 Phosphate-Binding Agents for Treatment of Hyperphosphatemia in Chronic Kidney Disease Patients

Category	Drug	Brand Name	Compound Content	Starting Doses	Dose Titration[a]	Comments[b]
Calcium-based binders	Calcium acetate (25% elemental calcium)	PhosLo	25% elemental calcium (169-mg elemental calcium per 667-mg capsule)	1,334 mg three times a day with meals	Increase or decrease by 667 mg per meal (169-mg elemental calcium)	Comparable efficacy to calcium carbonate with lower dose of elemental calcium Approximately 45-mg phosphorus bound per 1 g calcium acetate Evaluate for drug interactions with calcium
		Phoslyra	667-mg calcium acetate per 5 mL			
	Calcium carbonate[c]	Tums, Os-Cal, Caltrate	40% elemental calcium	0.5-1 g (elemental calcium) three times a day with meals	Increase or decrease by 500 mg per meal (200-mg elemental calcium)	Dissolution characteristics and phosphate binding may vary from product to product Approximately 39-mg phosphorus bound per 1-g calcium carbonate Evaluate for drug interactions with calcium
Iron-based binders	Ferric citrate	Auryxia	210-mg tablets (= 1-g ferric citrate)	420-mg ferric iron three times daily with meals	Increase or decrease dose by 1 or 2 tablets per meal	May increase serum iron, ferritin, and TSat May cause discolored (dark) stools Evaluate for drug interactions with iron
	Sucroferric oxyhydroxide	Velphoro	500-mg chewable tablets	500 mg three times daily with meals	Increase or decrease by 500 mg per day	May cause discolored (dark) stools Evaluate for drug interactions with iron
Resin binders	Sevelamer carbonate	Renvela	800-mg tablet 0.8- and 2.4-g powder for oral suspension	800-1,600 mg three times a day with meals (once-daily dosing also effective)	Increase or decrease by 800 mg per meal	Also lowers low-density lipoprotein cholesterol Consider in patients at risk for extraskeletal calcification Risk of metabolic acidosis with sevelamer hydrochloride (less risk with carbonate formulation) May interact with cipro and mycophenolate mofetil
	Sevelamer hydrochloride	Renagel	400 & 800 mg caplets	800-1,600 mg three times a day with meals	Increase or decrease by 800 mg per meal	
Other elemental binders	Lanthanum carbonate	Fosrenol	500, 750, and 1,000-mg chewable tablets 750 and 1,000-mg oral powder	1,500 mg daily in divided doses with meals	Increase or decrease by 750 mg/day	Potential for accumulation of lanthanum due to some GI absorption (long-term consequences unknown) Evaluate for drug interactions (eg, cationic antacids, quinolone antibiotics)
	Aluminum hydroxide	AlternaGel	Content varies (range 100-600 mg/unit)	300-600 mg three times a day with meals	Not for long-term use requiring titration	Not a first-line agent; risk of aluminum toxicity; do not use concurrently with citrate-containing products Reserve for short-term use (4 weeks) in patients with hyperphosphatemia not responding to other binders Evaluate for drug interactions

TSat, transferrin saturation.

[a]Based on phosphorus levels, titrate every 2 to 3 weeks until phosphorus goal is reached.

[b]GI side effects are possible with all agents (eg, nausea, vomiting, abdominal pain, diarrhea, or constipation).

[c]Multiple preparations available that are not listed.

Efficacy Oral calcium compounds are well established as first-line agents for control of serum phosphorus. Calcium carbonate and calcium acetate are the primary preparations used. Calcium citrate is also available but not used as a binder since the citrate component increases aluminum absorption and may cause more GI side effects. Calcium carbonate is marketed in a variety of dosage forms and is relatively inexpensive. Unfortunately, many calcium carbonate products are considered food supplements and thus do not meet US Pharmacopeia (USP) disintegration and dissolution requirements. In general, nationally advertised brands do meet these requirements, but it is difficult to determine whether private labels or house brands conform to these standards. Variability in gastric pH may also affect disintegration or dissolution, and thus phosphate-binding efficacy. Calcium carbonate is more soluble in an acidic medium and should be administered prior to meals when stomach acidity is highest. In addition, acid-suppressing agents such as ranitidine and proton pump inhibitors may reduce the phosphate-binding activity of calcium carbonate by increasing gastric pH. For patients with hypocalcemia, calcium carbonate or calcium acetate may also be given as a calcium supplement taken between meals to promote calcium absorption. This is a common scenario for patients following a parathyroidectomy.

Sevelamer is a nonabsorbable, nonelemental hydrogel phosphate-binding agent approved for ESRD patients that effectively lowers phosphorus and has also been shown to lower LDL and increase HDL cholesterol. Sevelamer hydrochloride carries the risk of metabolic acidosis, a problem that has been overcome with development of the carbonate formulation. Sevelamer carbonate also comes in a powder formulation, which is a good option for many patients unable to swallow tablets.

Most of the comparative studies to date have focused on calcium-based binders versus sevelamer, which was the first non-calcium– and non-aluminum–based binder made available in the United States. There is evidence that chronic use of calcium-containing phosphate binders promotes progression of vascular calcification; however, not all studies support this finding and recent evidence suggests that this effect may occur with non-calcium–containing binders as well.[92] Available studies have more consistently shown a significant increase in coronary artery calcification with calcium-containing binders compared to sevelamer.[100] The effect of binder choice on mortality, particularly on cardiovascular mortality, is also controversial as studies evaluating this outcome are limited. Results of a recent meta-analysis showed that all-cause mortality and

risk of hypercalcemia were lower in dialysis patients receiving sevelamer when compared with calcium-based binders.[91] KDIGO suggests restricting the dose of calcium-based binders (a grade 2B recommendation); however, a maximum dose was not defined and this is left to clinical judgment.[34]

Lanthanum carbonate is a phosphate binder approved for patients with ESRD and has demonstrated efficacy in controlling phosphorus and maintaining PTH in the target range with less risk of hypercalcemia than calcium-containing binders.[34] The initial daily dose of 1,500 mg (administered in divided doses with meals) is often titrated to a range of 1,500 to 3,000 mg to maintain target phosphorus. The relatively poor GI absorption, which limits systemic effects, and high-binding capacity with phosphorus make this an attractive phosphate-binding agent, particularly when calcium-containing binders are not recommended due to hypercalcemia. Lanthanum is available as a chewable tablet, which may be appealing for some patients.

Ferric citrate and sucroferric oxyhydroxide are the newest iron-based phosphate-binding agents approved for ESRD patients. Sucroferric oxyhydroxide effectively lowers phosphorus over a long-term (1-year) period and may have a lower pill burden compared to other agents.[100] It is also available as a chewable tablet. Ferric citrate effectively lowers phosphorus and also offers the potential advantage of increasing iron indices (TSat and ferritin) while lowering IV iron and ESA use.[100]

Aluminum salts were widely used in the 1980s as phosphate-binding agents because of their high-binding potency. Due to the potential for accumulation and toxicities in patients with CKD, they should no longer be used as first-line agents. KDIGO recommends avoiding the long-term use of aluminum-containing binders in all patients with CKD stage 3a-5D (a 1C recommendation).[34]

Magnesium-containing antacids are also effective phosphate binders and may decrease the amount of calcium-containing binders necessary for control of phosphorus; however, their use is limited by the frequent occurrence of GI side effects (ie, diarrhea) and the potential for magnesium accumulation.

Adverse Effects Adverse effects of all available phosphate binders are generally limited to constipation, diarrhea, nausea, vomiting, and abdominal pain. The risk of hypercalcemia may necessitate restriction of calcium-containing binder use and/or a reduction in dietary intake. Aluminum binders have been associated with CNS toxicity and worsening of anemia, whereas magnesium binder use may lead to hypermagnesemia and hyperkalemia (see Chapter 68); therefore,

aluminum and magnesium are not recommended for regular use in patients with kidney disease. The potential for iron overload should also be considered with ferric citrate, given the effects on increasing iron indices. There is some concern that ferric citrate may contribute to increased aluminum absorption due to the citrate component. There has been a report of lanthanum tablets accumulating in the GI tract and causing severe complications in a patient who swallowed these tablets whole; therefore, it is important to counsel patients to chew these tablets.[101] The same counseling point applies for sucroferric oxyhydroxide.

Drug–Drug and Drug–Food Interactions Calcium-containing phosphate-binding agents interfere with the absorption of several oral medications that are commonly prescribed for CKD patients, including iron, zinc, and quinolone antibiotics. Coadministration of sevelamer with ciprofloxacin and mycophenolate did result in a reduction in bioavailability of these agents and they should be taken at least 2 hours before sevelamer. Coadministration of lanthanum with tetracyclines, fluoroquinolones, levothyroxine, or drugs known to bind with cationic antacids may result in decreased bioavailability of these agents. The iron-containing products, ferric citrate and sucroferric oxyhydroxide also have the potential for drug interactions due to the iron component. In general, it is rational to separate the administration time of oral medications for which a reduction in bioavailability has a clinically significant effect (eg, quinolones) from phosphate binders by at least 1-2 hours before or 3 hours after administration of the phosphate binder. Many phosphate binders are marketed as antacids or calcium supplements, and often CKD patients do not know why they have been prescribed these agents. Regular patient counseling is essential to improve adherence and minimize the potential for drug interactions.

Dosing and Administration Initial dosing regimens for phosphate-binding agents and suggested dose titration schemes are shown in Table 61-10. Doses should be titrated to achieve the recommended serum phosphorus concentrations in conjunction with dietary intervention and dialysis (for ESRD patients).

Vitamin D Therapy

Vitamin D compounds available in the United States include nutritional vitamin D [ergocalciferol (D_2) and cholecalciferol (D_3)], the prohormone calcifediol [25(OH)D_3], active vitamin D [calcitriol (D_3)], and vitamin D analogs [paricalcitol and doxercalciferol (both D_2)] (**Table 61-11**). Nutritional vitamin D (NVD) is derived from dietary plant (D_2) and animal (D_3) sources, or from

supplements. While this chapter focuses on the role of NVD and FDA-approved vitamin D formulations for the management of mineral homeostasis, there are several other therapeutic uses for vitamin D (eg, for CV and immune-related effects) and other analogs available outside the United States which are not discussed (eg, alfacalcidol).

TABLE 61-11 Vitamin D Agents

Generic Name	Brand Name	Form of Vitamin D	Dosage Forms	Initial Dose	Dosage Range	Frequency of Dosing or Dose Titration[a]
Nutritional Vitamin D						
Ergocalciferol	Drisdol	D_2	po	Varies based on 25(OH)D levels	400-50,000 international units	Daily (doses of 400-2,000 international units)
Cholecalciferol[b]	Generic	D_3	po			Weekly or monthly for higher doses (50,000 international units)
Calcifediol	Rayaldee	D_3	po	30 mcg daily	30-60 mcg	Increase after 3 months if PTH above desired range
Vitamin D and Analogs						
Generic Name	**Brand Name**	**Form of Vitamin D**	**Dosage Forms**	**Initial Dose[c,d]**	**Dosage Range**	**Dose Titration[a]**
Calcitriol	Rocaltrol	D_3	po	0.25 mcg daily [*varying doses administered three times per week are also used]	0.25-5 mcg	Increase by 0.25 mcg/day at 4-8 week intervals
	Calcijex		IV	1-2 mcg three times per week	0.5-5 mcg	Increase by 0.5-1 mcg at 2-4 week intervals
Doxercalciferol[e]	Hectorol	D_2	po	ND-CKD: 1 mcg daily ESRD: 10 mcg three times per week	5-20 mcg	Increase by 0.5 mcg at 2-week intervals for daily dosing or by 2.5 mcg at 8-week intervals for three times per week dosing
			IV	ESRD: 4 mcg three times per week	2–8 mcg	Increase by 1-2 mcg at 8-week intervals
Paricalcitol	Zemplar	D_2	po	ND-CKD: 1 mcg daily or 2 mcg three times per week if PTH ≤500 pg/mL(ng/L; 54 pmol/L); 2 mcg daily or 4 mcg three times per week if PTH >500 pg/mL (ng/L; 54 pmol/L)	1-4 mcg	Increase by 1 mcg (for daily dosing) or 2 mcg (for three times per week dosing) at 2-4 week intervals
			IV	ESRD: 0.04-1 mcg three times per week	2.5-15 mcg	Increase by 2-4 mcg at 2-4 week intervals

ESRD, end-stage renal disease; ND-CKD, nondialysis chronic kidney disease; PTH, parathyroid hormone.

[a]Based on PTH, calcium, and phosphorus levels. Decreases in dose are necessary if PTH is oversuppressed and/or if calcium and phosphorus are elevated.

[b]Multiple preparations are available that are not listed.

[c]Dose ratios are as follows: 1:1 for IV paricalcitol to oral doxercalciferol, 1.5:1 for IV paricalcitol to IV doxercalciferol, and 1:1 for IV to oral calcitriol.

[d]Daily orally dosing most common for nonhemodialysis CKD patients, IV or PO dosing three times per week more often used in the hemodialysis population.

[e]Prodrug that requires activation by the liver.

Pharmacology and Mechanism of Action Vitamin D is a cholesterol derivative and is transported in the circulation by vitamin D–binding protein. The process of vitamin D metabolism is shown in Fig. 61-5. Both endogenously synthesized D_3 and NVD compounds (as D_2 or D_3) are converted in the liver to 25(OH)D, by the 25-hydroxylase enzyme. The 25(OH)D form is subsequently converted to the biologically active form 1,25-dihydroxyvitamin D (either D_2 or D_3 depending on the parent compound) by the 1-α-hydroxylase enzyme. This conversion occurs primarily in the kidney, but this enzyme is also present in extrarenal tissues. It is not clear whether active vitamin D produced in extrarenal tissue exerts its effects only locally or contributes to the systemic endocrine functions. It is the concentration of 25(OH)D that is most commonly measured clinically to diagnose vitamin D deficiency. The 25(OH)D form is now available as calcifediol, an extended release oral formulation of the prohormone, indicated for patients with CKD stages 3 or 4 with low 25(OH)D levels.

Calcitriol and the vitamin D analogs bind to the vitamin D receptors (VDRs), which are located in many organ systems including the parathyroid glands, intestine, bone, kidney, heart, nervous, and immune systems. When vitamin D binds to the VDR, there is a conformational change in the VDR that allows for interaction of the receptor with the retinoid X receptor (RXR), a transcriptional factor.[102] The VDR–RXR complex binds to DNA sequences in target genes to either promote or inhibit transcription depending on the organ system. Vitamin D inhibits or suppresses PTH synthesis and also stimulates absorption of serum calcium (and phosphorus) by intestinal cells. As a result, the serum calcium concentration is raised, which decreases PTH secretion by the parathyroid glands. The set point for calcium (ie, the calcium concentration at which PTH secretion is decreased by 50%), which is generally raised in those with CKD-MBD, is lowered when active vitamin D therapy is initiated. This results in a lower ionized calcium concentration becoming effective at suppressing secretion of PTH. Unfortunately, the enhanced GI absorption of calcium and phosphorus associated with calcitriol therapy may lead to hypercalcemia and hyperphosphatemia, which are associated with soft-tissue and vascular calcifications.

The unique interactions of vitamin D with the VDRs have led to the development of vitamin D analogs that vary in their affinity for the VDRs. Paricalcitol and doxercalciferol retain activity with vitamin D receptors on the parathyroid gland to effectively lower PTH, but have less risk of hypercalcemia and hyperphosphatemia due to their lower intestinal activity. Paricalcitol differs

from calcitriol by the absence of the exocyclic carbon 19 and the fact that it is a vitamin D_2 derivative (19-nor-1,25-dihydroxyvitamin D_2). This compound is active as given. Doxercalciferol, however, is a prohormone that does require activation by CYP27 in the liver to form the major active D_2 metabolite 1,25-dihydroxyvitamin D_2 (see Fig. 61-5).

Pharmacokinetics Oral absorption of calcitriol occurs rapidly; therefore, both oral and IV therapies are reasonable options for treatment of CKD-MBD. The half-life of active calcitriol ranges from 15 to 38 hours in patients with ESRD.[103] The half-lives of paricalcitol and doxercalciferol are approximately 15 hours and 32 to 37 hours, respectively.[104,105] These agents are extensively bound to plasma proteins and not removed by dialysis.

Efficacy Calcitriol, paricalcitol, and doxercalciferol are all effective in lowering PTH in patients with CKD; however, the trade-off is the undesired effect of raising calcium and phosphorus concentrations due to increased intestinal absorption. Although these effects are less likely with paricalcitol and doxercalciferol, elevated calcium concentrations have been observed. An all-cause and CV survival benefit has also been reported with these agents in both CKD and ESRD patients in observational studies.[106] These survival benefits, however, have not been substantiated in randomized clinical trials based on meta-analysis of available data.[107] KDIGO does not advocate for routine use of calcitriol and vitamin D analogs in the nondialysis CKD population (a 2C recommendation) and suggests that they be reserved for patients with CKD stages 4-5 (a recommendation that was not graded). These agents may be used in conjunction with calcimimetics when warranted in the dialysis population (a 2B recommendation).[34]

A review and meta-analysis in CKD patients (including ESRD patients) reported that NVD supplementation was associated with an improvement in 25(OH)D levels and decreased PTH without significant hypercalcemia or hyperphosphatemia in nondialysis CKD patients[108]; however, this has not been a consistent finding. In ESRD patients, NVD has resulted in increased levels of 25(OH)D and a decrease in PTH, which suggests a potential role of extrarenal pathways of vitamin D activation; however, these patients typically also require active vitamin D or analog therapy. Calcifediol has been shown to lower PTH with relatively minimal effects on serum calcium and phosphorus in stage 3-4 CKD, which is the reason it has gained approval in nondialysis CKD patients to treat 25(OH)D deficiency.[109] The survival benefit of correcting vitamin D

deficiency with NVD in the CKD population is unknown. The recommendation by KDIGO is that confirmed 25(OH)D deficiency in patients with CKD 3a-5D be corrected using treatment strategies in the general population (a 2C recommendation), which includes NVD therapies.[34,110]

Adverse Effects Although all agents are effective in suppressing PTH, they may cause hypercalcemia and hyperphosphatemia, an effect that is most likely with calcitriol. Oversuppression of PTH and inducement of adynamic bone disease are also distinct possibilities.

Drug–Drug and Drug–Food Interactions Cholestyramine may reduce the absorption of orally administered calcitriol and doxercalciferol. In vitro data suggest that paricalcitol is metabolized by the hepatic enzyme CYP3A4 and thus it has the potential to interact with other agents that are metabolized by this enzyme. Caution is also advised when CYP3A4 inhibitors are given to those receiving doxercalciferol since hydroxylation of this precursor agent may be inhibited.

Dosing and Administration Despite limited evidence, KDIGO guidelines support administering NVD to patients with CKD 3a-5 and ESRD with vitamin D deficiency or insufficiency (a grade 2C recommendation).[34] Calcitriol, doxercalciferol, or paricalcitol should be administered when PTH remains elevated despite the achievement of adequate 25(OH)D levels. ESRD patients typically require calcitriol, doxercalciferol, or paricalcitol.

Calcitriol by either the oral or the IV route may be administered daily (usually 0.25-1 mcg/day) or using a pulse dosing approach (0.5-2 mcg two to three times per week). Recommended doses of available NVD and analogs and suggested dose titration schemes are shown in Table 61-11. Prior to starting therapy, the serum calcium and phosphorus should be within the normal range. This does not mean that vitamin D therapy should be withheld or discontinued in all patients with elevated calcium and phosphorus values, but rather that use of agents with a lower risk of hypercalcemia and hyperphosphatemia and more prudent use of phosphate binders and dietary intervention to lower calcium and phosphorus may be necessary in such patients. Dose adjustments of vitamin D should be made every 2 to 4 weeks based on PTH concentrations and trends in calcium and phosphorus.

Calcimimetics

Cinacalcet hydrochloride (Sensipar) and etelcalcetide (Parsabiv) are

calcimimetic agents approved for treatment of secondary hyperparathyroidism in CKD patients on dialysis. Cinacalcet is available as an oral agent, whereas etelcalcetide is an IV formulation. Both agents are approved for use only in dialysis patients.

Pharmacology and Mechanism of Action Cinacalcet and etelcalcetide work through their interactions on the calcium-sensing receptor (CSR) located on the surface of the chief cells of the parathyroid gland. Cinacalcet works as an allosteric modulator of the CSR through binding to the transmembrane domain of the receptor while etelcalcetide binds directly to the extracellular domain resulting in increased sensitivity of the receptor to extracellular calcium (ie, lowering the threshold for receptor activation by calcium) and subsequently reducing PTH secretion.[111]

Pharmacokinetics Cinacalcet peak concentrations are observed 2 to 6 hours following oral administration. Its elimination half-life is approximately 30 to 40 hours and steady-state plasma concentrations are achieved in approximately 7 days. It has a large volume of distribution (approximately 1,000 L) and is 93% to 97% bound to plasma proteins; thus, removal by dialysis is negligible. Cinacalcet is metabolized by the liver, specifically by the cytochrome P450 isoenzymes CYP3A4, CYP2D6, and CYP1A2.[112] Etelcalcetide has a half-life of 3 to 4 days and plasma levels reach steady state in several weeks.[111] This agent is not metabolized by CYP isoenzymes, but is cleared by renal excretion. Unlike cinacalcet, this agent is avidly cleared by hemodialysis.

Efficacy In clinical trials conducted predominantly in dialysis patients, cinacalcet significantly decreased PTH, calcium, and phosphorus, regardless of the severity of secondary hyperparathyroidism. In nondialysis CKD patients, it reduced PTH, but was associated with a high incidence of hypocalcemia; thus, this agent is not approved for use in nondialysis CKD patients.[113] Cinacalcet may be used as a single agent to control hyperparathyroidism in ESRD patients; however, combined therapy with vitamin D is often necessary to achieve target PTH, calcium, and phosphorus values. In the ADVANCE trial cinacalcet plus low-dose active vitamin D increased coronary artery calcification scores but to a lesser degree than its comparator calcitriol alone.[114] A decrease in all-cause and CV mortality was also suggested by results of an observational study in HD patients prescribed acinacalcet in addition to vitamin D compared with those on vitamin D alone.[115] While these findings were promising, they were not supported by the EVOLVE trial (the Evaluation of Cinacalcet Therapy to Lower

CV Events), a prospective study which revealed that cinacalcet did not significantly reduce the risk of all-cause mortality or major CV events in patients with CKD 5HD.[116] There has been much debate with regard to the design and analysis of the EVOLVE trial and the interpretation of the findings such that many believe this trial to be inconclusive.[113]

Etelcalcetide is effective in lowering PTH in hemodialysis patients.[117] Like cinacalcet, this agent lowers calcium and phosphorus and has also been shown to lower FGF23.[118] When compared to cinacalcet, etelcalcetide was noninferior in terms of reducing PTH levels. In addition, significantly more patients achieved the target reduction in PTH and FGF23 of at least 30%.[119] There was a greater reduction in serum calcium and phosphorus with etelcalcetide compared with cinacalcet. There have not been clinical studies to evaluate the effect of etelcalcetide on mortality or cardiovascular events.

Adverse Effects The most frequent adverse events associated with cinacalcet are nausea and vomiting, which may account for nonadherence. Nausea and vomiting were reported with etelcalcetide in both the placebo-controlled trials and in the comparison trial with cinacalcet at a rate that was not significantly different compared with cinacalcet.[117,119] Since these agents lower serum calcium they should not be started if the corrected serum calcium is less than the lower limit of normal, approximately 8.4 mg/dL (2.10 mmol/L). Serum calcium should be measured within 1 week after initiation or following a dose adjustment. Once the maintenance dose is established, serum calcium should be measured monthly. Potential manifestations of hypocalcemia include paresthesia, myalgia, cramping, tetany, and convulsions. Hypocalcemia may also lead to Q-T interval prolongation and ventricular arrhythmias, which further emphasizes the importance of regular calcium monitoring.

Drug–Drug and Drug–Food Interactions Because cinacalcet is partially metabolized by CYP3A4, there is potential for drug interactions with agents that inhibit this pathway. Coadministration of cinacalcet and ketoconazole, a strong inhibitor of CYP3A4, results in a twofold increase in the area under the curve and maximum concentration. Cinacalcet is also a potent inhibitor of CYP2D6. As a result, dose adjustments of concomitant medications that are predominantly metabolized by this enzyme and have a narrow therapeutic index, such as flecainide, thioridazine, vinblastine, and most tricyclic antidepressants (eg, amitriptyline), may be necessary.[112] Concurrent administration of cinacalcet with amitriptyline increased amitriptyline and nortriptyline (active metabolite) exposure by approximately 20% in CYP2D6-extensive metabolizers. Food has

been shown to increase absorption of cinacalcet by up to 82% compared with fasting; therefore, this medication should be taken with meals to achieve the maximal effect.

There are no drug interactions reported with etelcalcetide. Of note, this agent is not a substrate or inhibitor of CYP isoenzymes or transporter proteins (eg, P-glycoprotein, organic anionic/cationic transporters).

Dosing and Administration The recommended starting dose of cinacalcet is 30 mg orally once daily. Calcium and phosphorus should be measured at 1 week and PTH should be measured within 1 to 4 weeks after starting cinacalcet or adjusting the dose. The dose should be titrated every 2 to 4 weeks to a maximum dose of 180 mg once daily until the desired PTH values are achieved and to maintain goal serum calcium concentrations. Patients with hepatic disease may require lower doses, since the cinacalcet half-life is approximately doubled in those with severe liver disease.[112] Cinacalcet is available as film-coated tablets containing 30, 60, or 90 mg.

Etelcalcetide should be initiated at a dose of 5 mg administered intravenously three times per week at the end of the hemodialysis treatment (during or after rinse back). Calcium and phosphorus should be measured 1 week after initiation and then every 4 weeks for maintenance therapy. PTH levels should be measured 4 weeks after initiation and then per protocol based on the practices of the dialysis center. If PTH levels are above the recommended target range and the corrected serum calcium is within the normal range, the dose of etelcalcetide should be increased in 2.5- or 5-mg increments up to a maximum dose of 15 mg. The dose should be decreased or temporarily discontinued in patients with PTH levels below the target range. In patients with a corrected calcium at or above 7.5 mg/dL (1.9 mmol/L) without symptoms of hypocalcemia a decrease in dose or temporary discontinuation may also be considered. Other interventions to increase calcium may be initiated in this situation if necessary (eg, altering vitamin D therapy, calcium supplementation, etc.). Etelcalcetide may be resumed once the PTH is within the target range and hypocalcemia has resolved, but at a lower dose. If the corrected calcium is below 7.5 mg/dL (1.9 mmol/L), then this agent should be discontinued and reinitiated at a dose 5 mg lower than the last administered dose once hypocalcemia has resolved. Patients who were receiving 2.5 or 5 mg should reinitiate therapy at a dose of 2.5 mg.[120]

Since etelcalcetide is removed by hemodialysis, it should be administered at the end of the hemodialysis treatment and injected into the venous line of the dialysis circuit during or after rinse back. If a dose is missed (eg, due to a missed hemodialysis treatment), then that missed dose should not be administered, but

the patient should resume the regular treatment schedule at the next hemodialysis session. If doses are missed for more than 2 weeks, then etelcalcetide should be restarted at the 5 mg dose.[120] If switching a patient from cinacalcet to etelcalcetide, then cinacalcet should be discontinued for at least 7 days prior to starting etelcalcetide. There are currently no recommendations for switching patients from etelcalcetide to cinacalcet. The fact that etelcalcetide has a longer half-life should be considered if making a transition to cinacalcet.

Pharmacoeconomic Considerations for Anemia and Chronic Kidney Disease–Related Mineral and Bone Disorder

The cost of medications to treat anemia and CKD-MBD is substantial.[7,121] In the United States, insurance requirements for coverage of agents including ESAs, IV iron, and vitamin D analogs can be a major limitation to treatment of the CKD patient with anemia or MBD. The high cost of ESAs is a reason that legislation led to a *bundled* payment system for dialysis patients known as the Prospective Payment System. The Medicare Modernization Act became effective in 2006 and provided for separately billable drugs such as ESAs, IV iron, IV vitamin D to be reimbursed based on the average sales price. The results of CHOIR and perceived overuse of ESAs later prompted Congress to reevaluate the reimbursement system, and in 2009 the bundled reimbursement system for dialysis was established (implemented in 2011), which included a composite rate for services and injectable drugs and oral equivalents. The primary goal of the bundled payment system was to decrease incentives for the overuse of previously separately reimbursable drugs, primarily ESAs because they were the most expensive and due to safety concerns with these agents.

Healthcare providers must consider the reimbursement structure with regard to ESA use and weigh the risks and benefits of ESA and IV iron treatment in individual patients when making decisions about anemia management. Since the introduction of erythropoietin in the late 1980s, the mean Hb rose from an average of 9.7 g/dL (97 g/dL, 6.02 mmol/L) in 1991 to a maximum of 12 g/dL (120 g/L, 7.45 mmol/L) in 2005 as weekly ESA doses increased from an average of approximately 7,300 units to over 19,000 units/week.[7] While doses have decreased since that time (to approximately 9,600 units/week in 2016) due to safety concerns, over 80% of US dialysis patients still receive an ESA.[122] It is clear now, however, that targeting Hb levels above 11 g/dL (110 g/L; 6.83

mmol/L) with ESA therapy increases risk of mortality and CV events. Patients may decide that risk of ESA therapy outweighs the benefits and is one reason a discussion with the patient is necessary. With the availability of biosimilars, the cost of therapy is expected to decrease, although this will depend on how these agents are accepted and adopted in clinical practice.[123]

The US payment system does affect treatment approaches for CKD-MBD. Oral ESRD drugs that do not have an IV equivalent, such as phosphate binders (and previously cinacalcet), are outside the bundle and are reimbursable through Medicare part D, Medicaid, or commercial prescription drug plans. These agents were to be included in the bundle in 2014, but their inclusion has been postponed until 2024. Since Medicare part D plans are administered through various insurance contractors with varying formularies and drug pricing tiers, the covered phosphate binder may be different depending upon the plan. With the recent addition of the intravenous calcimimetic etelcalcetide, calcimimetics will transition into the dialysis bundle over a 2-year period. It is possible that providers may wish to reduce calcimimetic use when this transition period has lapsed.

Cardiovascular Complications of Chronic Kidney Disease

Cardiovascular Disease

Patients with CKD are at increased risk of CVD, independent of the etiology of their kidney disease. This greater burden of CVD in patients with CKD is illustrated in **Fig. 61-8**. The prevalence of any form of CVD is double in elderly CKD patients compared to patients without CKD (65% vs 33%).[7] Twenty six percent of elderly CKD patients had heart failure and 25% had a history of atrial fibrillation. In contrast, the rates in non-CKD patients were 6% and 10%, respectively. This burden of CVD is associated with much higher mortality rates. In general, CKD patients have a lower probability of survival for all of the CVD conditions reported, with late stages of CKD being associated with the worst outcomes. For example, the adjusted two-year survival of myocardial infarction patients without a diagnosis of CKD was 81.7% versus 74.5% for CKD stage 1-2 patients and 58.6% for CKD stage 4-5 patients. The adjusted two-year survival of patients undergoing percutaneous coronary intervention without a diagnosis of CKD was 83.2% versus 76.3% for CKD stage 1-2 patients and 64.3% for CKD stage 4-5 patients.[7]

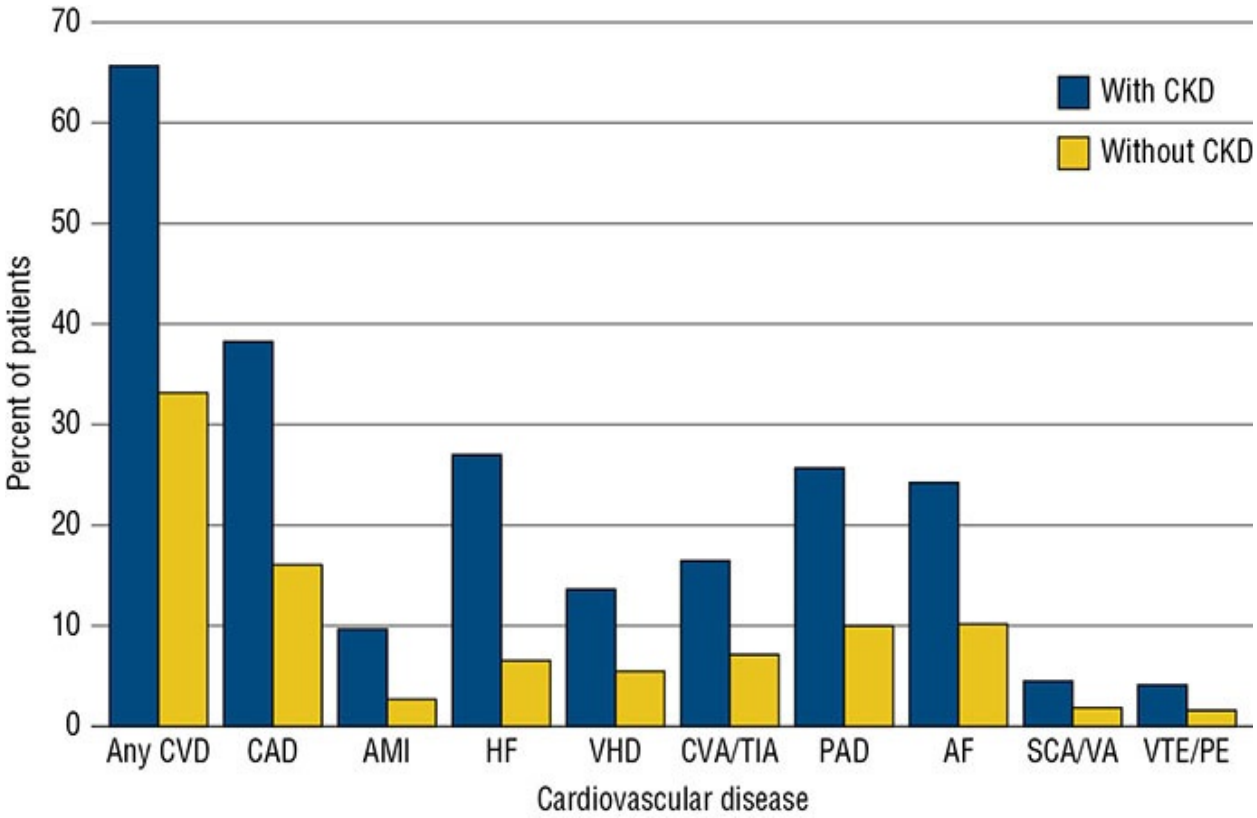


FIGURE 61-8 Cardiovascular disease in elderly patients with or without CKD in 2016.[7] (AF, atrial fibrillation; AMI, acute myocardial infarction; CAD, coronary artery disease; CKD, chronic kidney disease; CVA/TIA, cerebrovascular accident/transient ischemic attack; CVD, cardiovascular disease; HF, heart failure; PAD, peripheral arterial disease; SCA/VA, sudden cardiac arrest and ventricular arrhythmias; VHD, valvular heart disease; VTE/PE, venous thromboembolism and pulmonary embolism.) (Medicare 5% sample of patients aged 66 and older, alive, without end-stage renal disease, and residing in the United States on 12/31/2016, with fee-for-service coverage for the entire calendar year. Note: The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the US government.[7])

Traditional CVD risk factors present in patients with CKD include diabetes mellitus, dyslipidemia, hypertension, LVH, smoking, and obesity. Nontraditional risk factors include proteinuria, hyperhomocysteinemia, anemia, inflammation, and abnormal calcium and phosphate metabolism resulting in vascular calcification oxidative stress.[124] Unfortunately, the lack of randomized trials treating CVD in patients with CKD often leads to treatment decisions that are

based on extrapolation from trials in non-CKD populations and from observational data in CKD.[125] However, the level of care for ischemic heart disease offered to people with CKD should not differ from people without CKD (grade 1A recommendation) as there is evidence indicating that treatment of traditional risk factors in CKD patients is of benefit.[1] These patients should also receive the standard assessments and treatments such as statins for CKD 1-5 (nondialysis), beta-blockers, ACEIs/ARBs, and antiplatelet agents (see Chapter 14). Clinicians should note that in the diagnosis of acute coronary syndrome, elevated serum troponins should be interpreted with caution in individuals with a GFR less than 60 mL/min/1.73 m^2 (0.58 mL/s/m^2) because these markers are often elevated as a result of reduced renal excretion (a grade 1B recommendation).[1]

Patients with CKD should receive standard heart failure therapies (Chapter 17); however, clinicians should be aware that RAAS blockade (eg, ACEI, ARB, spironolactone, eplerenone) and diuretic therapy (eg, furosemide, metolazone) may lead to significant changes in GFR and serum potassium concentrations. Such therapy should not be avoided, but closely monitored and put into the context of individual risks and benefits. With regard to the cardiac biomarkers of B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-pro-BNP) in individuals with a GFR less than 60 mL/min/1.73 m^2 (0.58 mL/s/m^2) (CKD 3a-5), it is recommended that serum concentrations be interpreted with caution with respect to diagnosis of heart failure and assessment of volume status (a grade 1B recommendation).[1]

Aspirin (ASA) is recommended for secondary prevention in all patients with CKD based on decreased mortality in observational studies.[126,127] ASA is generally not recommended for primary prevention as compared to placebo or no treatment as it reduces the risk of myocardial infarction but not all-cause mortality, cardiovascular mortality, or stroke and increases the risk of major and minor bleeding.[128]

Hyperlipidemia

CKD with or without nephrotic syndrome is frequently accompanied by abnormalities in lipoprotein metabolism. Although the concentrations of LDL are not uniformly increased in patients with kidney disease, these patients appear to produce small, dense LDL particles that are more susceptible to oxidation and more atherogenic than larger LDL subfractions. Other lipid abnormalities include low HDL and increased triglycerides.[129] In patients with nephrotic

syndrome, the major lipid abnormalities are elevation of plasma total and LDL cholesterol, with or without low HDL cholesterol, and elevated triglycerides. See Chapter 64 for a detailed discussion of the management of proteinuria in patients with glomerular disease.

The KDIGO lipid guidelines recommend that a complete fasting lipid profile be performed in all adults with newly identified CKD (a grade 1C recommendation).[130] Follow-up lipid levels are not recommended unless the information may alter management (eg, assessing adherence to therapy or assessing CV risk in a patient <50 years and not currently on a statin). Reduction in the risk of CV events in patients with CKD has only been demonstrated with statins or a statin plus ezetimibe combination.[130]

Statins in Chronic Kidney Disease

Statins have been shown to decrease mortality and CV events in CKD 1-5 patients; however, the data are not as compelling in the ESRD population. The Study of Heart and Renal Protection (SHARP) trial was a primary prevention trial that evaluated the effects of combined simvastatin (20 mg) and ezetimibe (10 mg) compared with placebo on time to first major vascular event (nonfatal MI or cardiac death, any stroke, or revascularization) in patients with no history of MI or coronary revascularization and included patients with CKD (6,247) and ESRD (3,023).[131] In all patients receiving combined therapy during the 4.9-year follow-up period, there was a significant 17% reduction in the relative risk (RR) of major vascular events and a 32% reduction in LDL in the patients who were assessed as compliant with therapy (two-thirds were compliant). While overall these results are positive, the study was not powered to evaluate whether the observed effect was significant in ESRD patients as a separate group. A subgroup analysis comparing dialysis versus nondialysis and diabetic versus nondiabetic patients showed no differences in the RR of CV events even after adjustment for the reduction in LDL.

A meta-analysis of statins in dialysis patients indicated that they had no significant beneficial effect on major CV events, all-cause mortality, CV death, or myocardial infarction, and a trend toward increased strokes despite clinically relevant reductions in LDL cholesterol.[132] In contrast, a meta-analysis of statins in nondialysis CKD showed significant reductions in major CV events, CV death, all-cause mortality; myocardial infarction but uncertain effects on stroke.[133]

The KDIGO lipid guidelines[130] make the following recommendations:

1. In adults age 18 to 49 years with CKD but not treated with chronic dialysis or kidney transplantation, we suggest statin treatment in people with one or more of the following [Level 2A]: known coronary disease (myocardial infarction or coronary revascularization); diabetes mellitus; prior ischemic stroke; estimated 10-year incidence of coronary death or nonfatal myocardial infarction greater than 10%.
2. In adults age greater than 50 years with eGFR less than 60 mL/min/1.73 m^2 but not treated with chronic dialysis or kidney transplantation, we recommend treatment with a statin or statin/ezetimibe combination. [Level 1A]
3. In adults with dialysis-dependent CKD, we suggest that statins or statin/ezetimibe combination not be initiated. [Level 2A] However, in patients already receiving statins or statin/ezetimibe combination at the time of dialysis initiation, we suggest that these agents be continued. [Level 2C]

CONCLUSION

The incidence of CKD has recently declined but the prevalence continues to increase especially in high-risk populations. Although efforts to delay progression of CKD including prudent use of ACEIs and ARBs and SGLT-2 inhibitors in diabetic patients are paramount, measures to diagnose and manage the associated secondary complications and comorbid conditions early in the course of the disease are also essential. Common complications of advanced CKD include anemia and CKD-MBD. CV complications are also prevalent in the population with CKD and are the leading cause of mortality in patients with ESRD.

A multidisciplinary team structure is a rational approach to effectively design and implement individual patient care plans often required in the CKD population, given the extensive nonpharmacologic and pharmacologic interventions. Thus, pharmacists are well positioned to actively participate in the chronic disease and medication management of ambulatory CKD and dialysis patients as well as those who are hospitalized.

Postclass Engaged Learning Activity

Conduct a literature search and identify a primary research manuscript that

has been published in the past 12 months regarding a medication to delay CKD progression. If the manuscript is regarding a medication that is discussed in the book chapter, write a brief summary about the study methods, the major findings, and how this new information might change current practice. If the manuscript is regarding a new medication that is not described in the chapter, write a brief summary about the medication's mechanisms of action, how it is administered, and one potential advantage or disadvantage of this new medication compared to the current standard of care. This activity is intended to build your literature evaluation skills and ability to critically evaluate the biomedical literature.

ABBREVIATIONS

ACEI	angiotensin-converting enzyme inhibitor
AKI	acute kidney injury
ARB	angiotensin receptor blocker
ATII	angiotensin II
BMI	body mass index
BNP	B-type natriuretic peptide
CCB	calcium channel blocker
CHOIR	Correction of Hb and Outcomes in Renal Insufficiency
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation
CLcr	Creatinine clearance
CREATE	Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta
CV	cardiovascular
CVD	cardiovascular disease
DCCT	Diabetes Control and Complications Trial
DCKD	Diabetic Chronic Kidney Disease
EDIC	Epidemiology of Diabetes Interventions and Complications
eGFR	estimated glomerular filtration rate
ESA	erythropoiesis-stimulating agent
ESRD	end-stage renal disease
FGF-23	fibroblast growth factor-23
GFR	glomerular filtration rate
GI	gastrointestinal
Hb	hemoglobin
Hct	hematocrit
HbA1c	glycated hemoglobin or hemoglobin A_{1c}
HD	hemodialysis
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
LDL	low-density lipoprotein
LVH	left ventricular hypertrophy
MBD	mineral and bone disorder
MCP-1	monocyte chemoattractant protein-1
MDRD	Modification of Diet in Renal Disease
MRP	medication-related problem
ND-CKD	nondialysis CKD patients (CKD 1-5)
NHCT	Normal Hematocrit Cardiac Trial
NVD	nutritional vitamin D
25(OH)D	25-hydroxyvitamin D
PRCA	pure red cell aplasia
PREVEND	Prevention of Renal and Vascular End-Stage Disease
PTH	parathyroid hormone
RAAS	renin–angiotensin–aldosterone system
REMS	risk evaluation and mitigation strategy
ROD	renal osteodystrophy
RR	relative risk
RXR	retinoid X receptor
SC	subcutaneous
SGLT-2	sodium-glucose co-transporter 2
sHPT	secondary hyperparathyroidism
SPRINT	Systolic Blood Pressure Intervention Trial
TGF-β	transforming growth factor beta
TIBC	total iron-binding capacity
TREAT	Trial to Reduce Cardiovascular Events with Aranesp Therapy
TSat	transferrin saturation
uACR	urinary albumin-to-creatinine ratio
UKPDS	United Kingdom Prospective Diabetes Study
USRDS	United States Renal Data System
VDRs	vitamin D receptors

REFERENCES

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int., Suppl*. 2013;3:1–150.
2. Bruck K, Stel VS, Fraser S, et al. Translational research in nephrology: Chronic kidney disease prevention and public health. *Clin Kidney J*. 2015;8:647–655.
3. Murray CJ, Barber RM, Foreman KJ, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990-2013: Quantifying the epidemiological transition. *Lancet*. 2015;386:2145–2191.
4. Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: Global dimension and perspectives. *Lancet*. 2013;382:260–272.
5. Anand S, Bitton A, Gaziano T. The gap between estimated incidence of end-stage renal disease and use of therapy. *PLoS ONE*. 2013;8:e72860.
6. US Department of Health and Human Services. Healthy People 2020 Objectives for Chronic Kidney Disease. Available at: http://www.healthypeople.gov/2020/topicsobjectives2020/overview.aspx?topicid=6. Last Accessed, January 31, 2019.
7. United States Renal Data System, 2018 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2018.
8. U.S. Renal Data System, USRDS 2016 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD. 2016.
9. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: A report from an ADA Consensus Conference. *Am J Kidney Dis*. 2014;64:510–533.
10. McCullough KP, Morgenstern H, Saran R. Projecting ESRD incidence and prevalence in the United States through 2030. *J Am Soc Nephrol*. 2019;30:127–135.
11. Norton JM, Moxey-Mims MM, Eggers PW, et al. Social determinants of racial disparities in CKD. *J Am Soc Nephrol*. 2016;27:2576–2595.

12. Komenda P, Lavallee B, Ferguson TW, et al. The prevalence of CKD in rural Canadian indigenous peoples: Results from the first nations community based screening to improve kidney health and prevent dialysis (FINISHED) screen, triage, and treat program. *Am J Kidney Dis*. 2016;68:582–590.
13. Fraser SD, Roderick PJ, Aitken G, et al. Chronic kidney disease, albuminuria and socioeconomic status in the Health Surveys for England 2009 and 2010. *J Public Health (Oxf)*. 2014;36:577–586.
14. Inker LA, Astor BC, Fox CH, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis*. 2014;63:713–735.
15. Tangri N, Stevens LA, Griffith J, et al. A predictive model for progression of chronic kidney disease to kidney failure. *JAMA*. 2011;305:1553–1559.
16. Tangri N, Grams ME, Levey AS, et al. Multinational assessment of accuracy of equations for predicting risk of kidney failure: A meta-analysis. *JAMA*. 2016;315:164–174.
17. National Kidney Foundation. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update. *Am J Kidney Dis*. 2012;60:850–886.
18. DCCT/EDIC research group. Effect of intensive diabetes treatment on albuminuria in type 1 diabetes: Long-term follow-up of the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications study. *Lancet Diabetes Endocrinol*. 2014;2:793–800.
19. American Diabetes Association. Microvascular complications and foot care: *Standards of Medical Care in Diabetes-2019. Diabetes Care*. 2019;42:S124–s138.
20. KDIGO Blood Pressure Work Group. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int Suppl*. 2012;2:337–414.
21. Orth SR, Hallan SI. Smoking: A risk factor for progression of chronic kidney disease and for cardiovascular morbidity and mortality in renal patients—absence of evidence or evidence of absence? *Clin J Am Soc Nephrol*. 2008;3:226–236.
22. Hogan SL, Vupputuri S, Guo X, et al. Association of cigarette smoking with albuminuria in the United States: The third National Health and Nutrition Examination Survey. *Ren Fail*. 2007;29:133–142.
23. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass

index and risk for end-stage renal disease. *Ann Intern Med*. 2006;144:21–28.

24. Ejerblad E, Fored CM, Lindblad P, Fryzek J, McLaughlin JK, Nyren O. Obesity and risk for chronic renal failure. *J Am Soc Nephrol*. 2006;17:1695–1702.
25. Chang Y, Ryu S, Choi Y, et al. Metabolically healthy obesity and development of chronic kidney disease: A cohort study. *Ann Intern Med*. 2016;164:305–312.
26. Navaneethan SD, Yehnert H, Moustarah F, Schreiber MJ, Schauer PR, Beddhu S. Weight loss interventions in chronic kidney disease: A systematic review and meta-analysis. *Clin J Am Soc Nephrol*. 2009;4:1565–1574.
27. Gajjala PR, Sanati M, Jankowski J. Cellular and molecular mechanisms of chronic kidney disease with diabetes mellitus and cardiovascular diseases as its comorbidities. *Front Immunol*. 2015;6:340.
28. Abbate M, Zoja C, Remuzzi G. How does proteinuria cause progressive renal damage? *J Am Soc Nephrol*. 2006;17:2974–2984.
29. Fishbane S, Spinowitz B. Update on Anemia in ESRD and earlier stages of CKD: Core curriculum 2018. *Am J Kidney Dis*. 2018;71:423–435.
30. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Inter Suppl*. 2012;2:279–335.
31. Sheetz M, Barrington P, Callies S, et al. Targeting the hepcidin-ferroportin pathway in anemia of chronic kidney disease. *Br J Clin Pharmacol*. 2019.
32. Moorthi RN, Moe SM. CKD-mineral and bone disorder: Core curriculum 2011. *Am J Kidney Dis*. 2011;58:1022–1036.
33. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl*. 2009;S1–130.
34. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int Suppl (2011)*. 2017;7:1–59.
35. Isakova T, Ix JH, Sprague SM, et al. Rationale and approaches to phosphate and fibroblast growth factor 23 reduction in CKD. *J Am Soc*

Nephrol. 2015;26:2328–2339.

36. Nigwekar SU, Thadhani R, Brandenburg VM. Calciphylaxis. *N Engl J Med*. 2018;379:399–400.
37. Portales-Castillo I, Kroshinksy D, Malhotra CK, et al. Calciphylaxis-as a drug induced adverse event. *Expert Opin Drug Saf*. 2018;18(1):29–35.
38. Jones G. Interpreting vitamin D assay results: Proceed with caution. *Clin J Am Soc Nephrol*. 2015;10:331–334.
39. Wang SM, Hsiao LC, Ting IW, et al. Multidisciplinary care in patients with chronic kidney disease: A systematic review and meta-analysis. *Eur J Intern Med*. 2015;26:640–645.
40. Filler G, Lipshultz SE. Why multidisciplinary clinics should be the standard for treating chronic kidney disease. *Pediatr Nephrol*. 2012;27:1831–1834.
41. St Peter WL, Wazny LD, Patel UD. New models of chronic kidney disease care including pharmacists: Improving medication reconciliation and medication management. *Curr Opin Nephrol Hypertens*. 2013;22:656–662.
42. Saxena N, Rizk DV. The interdisciplinary team: The whole is larger than the parts. *Adv Chronic Kidney Dis*. 2014;21:333–337.
43. McMahon EJ, Campbell KL, Bauer JD, Mudge DW. Altered dietary salt intake for people with chronic kidney disease. *Cochrane Database Syst Rev*. 2015:Cd010070.
44. Strippoli GF, Bonifati C, Craig M, Navaneethan SD, Craig JC. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. *Cochrane Database Syst Rev*. 2006;(4):CD006257.
45. Tylicki L, Lizakowski S, Rutkowski B. Renin-angiotensin-aldosterone system blockade for nephroprotection: Current evidence and future directions. *J Nephrol*. 2012;25:900–910.
46. Mann JF, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): A multicentre, randomised, double-blind, controlled trial. *Lancet*. 2008;372:547–553.
47. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med*. 2013;369:1892–1903.

48. Parving HH, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of Aliskiren for type 2 diabetes. *N Engl J Med*. 2012;367:2204–2213.
49. Imai E, Haneda M, Yamasaki T, et al. Effects of dual blockade of the renin-angiotensin system on renal and cardiovascular outcomes in type 2 diabetes with overt nephropathy and hypertension in the ORIENT: A post-hoc analysis (ORIENT-Hypertension). *Hypertens Res*. 2013;36:1051–1059.
50. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcome trials. *Lancet*. 2019;393:31–39.
51. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in Type 2 diabetes. *N Engl J Med*. 2016;375:323–334.
52. Ingelfinger JR, Rosen R. Clinical credence: SGLT2 inhibitors, diabetes, and chronic kidney disease. *N Engl J Med*. 2019;380:2371–2373.
53. AstraZeneca. A study to evaluate the effect of Dapagliflozin on renal outcomes and cardiovascular mortality in patients with chronic kidney disease (Dapa-CKD) (NCT03036150) ClincalTrials.gov 2018.
54. Bolignano D, Palmer SC, Navaneethan SD, Strippoli GF. Aldosterone antagonists for preventing the progression of chronic kidney disease. *Cochrane Database Syst Rev*. 2014;4:Cd007004.
55. Hou J, Xiong W, Cao L, Wen X, Li A. Spironolactone add-on for preventing or slowing the progression of diabetic nephropathy: A meta-analysis. *Clin Ther*. 2015;37:2086–2103. e2010.
56. Hart P, Bakris GL. Calcium antagonists: Do they equally protect against kidney injury? *Kidney Int*. 2008;73:795–796.
57. Stanton RC. Clinical challenges in diagnosis and management of diabetic kidney disease. *Am J Kidney Dis*. 2014;63:S3–21.
58. Wright JT Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103–2116.
59. Kliger AS, Foley RN, Goldfarb DS, et al. KDOQI US commentary on the 2012 KDIGO Clinical Practice Guideline for Anemia in CKD. *Am J Kidney Dis*. 2013;62:849–859.
60. Collister D, Komenda P, Hiebert B, et al. The effect of erythropoietin-stimulating agents on health-related quality of life in anemia of chronic kidney disease: A systematic review and meta-analysis. *Ann Intern Med*.

2016;164:472–478.
61. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med*. 1998;339:584–590.
62. Besarab A, Goodkin DA, Nissenson AR. The normal hematocrit study: Follow-up. *N Engl J Med*. 2008;358:433–434.
63. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med*. 2006;355:2085–2098.
64. Drueke TB, Locatelli F, Clyne N, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med*. 2006;355:2071–2084.
65. FDA Drug Safety Communication: modified dosing recommendations to improve the safe use of erythropoiesis-stimulating agents (ESAs) in chronic kidney disease. Last updated 8/4/2017. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm259639.htm.
66. Phrommintikul A, Haas SJ, Elsik M, Krum H. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: A meta-analysis. *Lancet*. 2007;369:381–388.
67. Pfeffer MA, Burdmann EA, Chen CY, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med*. 2009;361:2019–2032.
68. Koulouridis I, Alfayez M, Trikalinos TA, Balk EM, Jaber BL. Dose of erythropoiesis-stimulating agents and adverse outcomes in CKD: A metaregression analysis. *Am J Kidney Dis*. 2013;61:44–56.
69. Fishbane SN, Singh AK, Cournoyer SH, et al. Ferric pyrophosphate citrate (Triferic) administration via the dialysate maintains hemoglobin and iron balance in chronic hemodialysis patients. *Nephrol Dial Transplant*. 2015;30:2019–2026.
70. Gupta A, Lin V, Guss C, Pratt R, Ikizler TA, Besarab A. Ferric pyrophosphate citrate administered via dialysate reduces erythropoiesis-stimulating agent use and maintains hemoglobin in hemodialysis patients. *Kidney Int*. 2015;88:1187–1194.
71. Wang C, Graham DJ, Kane RC, et al. Comparative risk of anaphylactic reactions associated with intravenous iron products. *JAMA*. 2015;314:2062–2068.
72. FDA drug safety communication: FDA strengthens warnings and changes

prescribing instructions to decrease the risk of serious allergic reactions with anemia drug Feraheme (ferumoxytol). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm440138.htm. Page last updated 3/3/2016. Last accessed January 31, 2019.

73. Macdougall IC. Intravenous iron therapy in patients with chronic kidney disease: Recent evidence and future directions. *Clin Kidney J*. 2017;10:i16–i24.
74. Shepshelovich D, Rozen-Zvi B, Avni T, Gafter U, Gafter-Gvili A. Intravenous versus oral iron supplementation for the treatment of anemia in CKD: An updated systematic review and meta-analysis. *Am J Kidney Dis*. 2016;68:677–690.
75. Avni T, Bieber A, Grossman A, Green H, Leibovici L, Gafter-Gvili A. The safety of intravenous iron preparations: Systematic review and meta-analysis. *Mayo Clin Proc*. 2015;90:12–23.
76. Hougen I, Collister D, Bourrier M, et al. Safety of intravenous iron in dialysis: A systematic review and meta-analysis. *Clin J Am Soc Nephrol*. 2018;13:457–467.
77. Macdougall IC, Bock AH, Carrera F, et al. FIND-CKD: A randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anaemia. *Nephrol Dial Transplant*. 2014;29:2075–2084.
78. Agarwal R, Kusek JW, Pappas MK. A randomized trial of intravenous and oral iron in chronic kidney disease. *Kidney Int*. 2015;88:905–914.
79. Miskulin DC, Tangri N, Bandeen-Roche K, et al. Intravenous iron exposure and mortality in patients on hemodialysis. *Clin J Am Soc Nephrol*. 2014;9:1930–1939.
80. Macdougall IC, White C, Anker SD, et al. Intravenous iron in patients undergoing maintenance hemodialysis. *N Engl J Med*. 2019;380:447–458.
81. Robinson BM, Larkina M, Bieber B, et al. Evaluating the effectiveness of IV iron dosing for anemia management in common clinical practice: Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *BMC Nephrol*. 2017;18:330.
82. Epogen. Package Insert. Amgen. Thousand Oaks, CA. 2018.
83. Macdougall IC, Roger SD, de Francisco A, et al. Antibody-mediated pure red cell aplasia in chronic kidney disease patients receiving erythropoiesis-stimulating agents: New insights. *Kidney Int*. 2012;81:727–732.
84. Macdougall IC, Casadevall N, Locatelli F, et al. Incidence of

erythropoietin antibody-mediated pure red cell aplasia: The Prospective Immunogenicity Surveillance Registry (PRIMS). *Nephrol Dial Transplant*. 2015;30:451–460.

85. Mircera. Package Insert. Hoffmann-La Roche, Inc, South San Francisco, CA. October 2014.
86. Hazzan AD, Shah HH, Hong S, Sakhiya V, Wanchoo R, Fishbane S. Treatment with erythropoiesis-stimulating agents in chronic kidney disease patients with cancer. *Kidney Int*. 2014;86:34–39.
87. Aranesp. Package Insert. Amgen, Thousand Oaks, CA. 2018.
88. Gupta N, Wish JB. Hypoxia-inducible factor prolyl hydroxylase inhibitors: A potential new treatment for anemia in patients with CKD. *Am J Kidney Dis*. 2017;69:815–826.
89. Retacrit. Package Insert. Pfizer, Lake Forest, IL. 2018.
90. Eknoyan G, Levin A, Levin NW. Bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*. 2003;42:1–201.
91. Ruospo M, Palmer SC, Natale P, et al. Phosphate binders for preventing and treating chronic kidney disease-mineral and bone disorder (CKD-MBD). *Cochrane Database Syst Rev*. 2018;8:Cd006023.
92. St Peter WL, Wazny LD, Weinhandl ED. Phosphate-binder use in US dialysis patients: Prevalence, costs, evidence, and policies. *Am J Kidney Dis*. 2018;71:246–253.
93. Soliman M, Hassan W, Yaseen M, Rao M, Sawaya BP, El-Husseini A. PTH assays in dialysis patients: Practical considerations. *Semin Dial*. 2019;32:9–14.
94. Tentori F, Wang M, Bieber BA, et al. Recent changes in therapeutic approaches and association with outcomes among patients with secondary hyperparathyroidism on chronic hemodialysis: The DOPPS study. *Clin J Am Soc Nephrol*. 2015;10:98–109.
95. Nelson SM, Sarabia SR, Christilaw E, et al. Phosphate-containing prescription medications contribute to the daily phosphate intake in a third of hemodialysis patients. *J Ren Nutr*. 2017;27:91–96.
96. Daugirdas JT. Removal of phosphorus by hemodialysis. *Semin Dial*. 2015;28:620–623.
97. Ishani A, Liu J, Wetmore JB, et al. Clinical outcomes after parathyroidectomy in a nationwide cohort of patients on hemodialysis. *Clin J Am Soc Nephrol*. 2015;10:90–97.

98. Wetmore JB, Liu J, Do TP, et al. Changes in secondary hyperparathyroidism-related biochemical parameters and medication use following parathyroidectomy. *Nephrol Dial Transplant*. 2016;31:103–111.
99. Daugirdas JT, Finn WF, Emmett M, Chertow GM. The phosphate binder equivalent dose. *Semin Dial*. 2011;24:41–49.
100. St. Peter WL, Wazny LD, Weinhandl E, Cardone KE, Hudson JQ. A review of phosphate binders in chronic kidney disease: Incremental progress or just higher costs? *Drugs*. 2017;77:1155–1186.
101. Moazzam AA, Boongird S. Ingestion of lanthanum carbonate tablets. *Am J Kidney Dis*. 2013;62:844.
102. Wan LY, Zhang YQ, Chen MD, Liu CB, Wu JF. Relationship of structure and function of DNA-binding domain in vitamin D receptor. *Molecules*. 2015;20:12389–12399.
103. Bailie GR, Johnson CA. Comparative review of the pharmacokinetics of vitamin D analogues. *Semin Dial*. 2002;15:352–357.
104. Zemplar Capsules Package Insert. AbbVie, Inc. North Chicago, IL. 2018.
105. Hectorol Injection. Package Insert. Genzyme Corporation, Cambridge, MA. 2018.
106. Zheng Z, Shi H Fau - Jia J, Jia J Fau - Li D, Li D Fau - Lin S, Lin S. Vitamin D supplementation and mortality risk in chronic kidney disease: A meta-analysis of 20 observational studies. *BMC Nephrol*. 2013;14:199.
107. Lu RJ, Zhu SM, Tang FL, et al. Effects of vitamin D or its analogues on the mortality of patients with chronic kidney disease: An updated systematic review and meta-analysis. *Eur J Clin Nutr*. 2017;71:683–693.
108. Kandula P, Dobre M, Schold JD, Schreiber MJ Jr, Mehrotra R, Navaneethan SD. Vitamin D supplementation in chronic kidney disease: A systematic review and meta-analysis of observational studies and randomized controlled trials. *Clin J Am Soc Nephrol*. 2011;6:50–62.
109. Sprague SM, Strugnell SA, Bishop CW. Extended-release calcifediol for secondary hyperparathyroidism in stage 3-4 chronic kidney disease. *Expert Rev Endocrinol Metab*. 2017;12:289–301.
110. Melamed ML, Chonchol M, Gutierrez OM, et al. The role of vitamin D in CKD stages 3 to 4: Report of a Scientific Workshop Sponsored by the National Kidney Foundation. *Am J Kidney Dis*. 2018;72:834–845.
111. Harada K, Fujioka A, Konno M, Inoue A, Yamada H, Hirota Y. Pharmacology of Parsabiv((R)) (etelcalcetide, ONO-5163/AMG 416), a

novel allosteric modulator of the calcium-sensing receptor, for secondary hyperparathyroidism in hemodialysis patients. *Eur J Pharmacol*. 2019;842:139–145.

112. Sensipar (cinacalcet HCl) Tablets Package Insert. Amgen Inc., Thousand Oaks, CA. 2017.
113. Bover J, Urena P, Ruiz-Garcia C, et al. Clinical and practical use of calcimimetics in dialysis patients with secondary hyperparathyroidism. *Clin J Am Soc Nephrol*. 2016;11:161–174.
114. Raggi P, Chertow GM, Torres PU, et al. The ADVANCE study: A randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. *Nephrol Dial Transplant*. 2011;26:1327–1339.
115. Block GA, Zaun D, Smits G, et al. Cinacalcet hydrochloride treatment significantly improves all-cause and cardiovascular survival in a large cohort of hemodialysis patients. *Kidney Int*. 2010;78:578–589.
116. Chertow GM, Block GA, Correa-Rotter R, et al. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med*. 2012;367:2482–2494.
117. Block GA, Bushinsky DA, Cunningham J, et al. Effect of etelcalcetide vs placebo on serum parathyroid hormone in patients receiving hemodialysis with secondary hyperparathyroidism: Two randomized clinical trials. *JAMA*. 2017;317:146–155.
118. Friedl C, Zitt E. Role of etelcalcetide in the management of secondary hyperparathyroidism in hemodialysis patients: A review on current data and place in therapy. *Drug Des Devel Ther*. 2018;12:1589–1598.
119. Block GA, Bushinsky DA, Cheng S, et al. Effect of etelcalcetide vs cinacalcet on serum parathyroid hormone in patients receiving hemodialysis with secondary hyperparathyroidism: A randomized clinical trial. *JAMA*. 2017;317:156–164.
120. Parsabiv (etelcalcetide) Injection Package Insert. Amgen Inc., Thousand Oaks, CA. 2018.
121. Yusuf AA, Howell BL, Powers CA, St Peter WL. Utilization and costs of medications associated with CKD mineral and bone disorder in dialysis patients enrolled in Medicare Part D. *Am J Kidney Dis*. 2014;64:770–780.
122. The Dialysis Outcomes and Practice Patterns Study: DOPPS Practice Monitor, February 2019. Available at: http://www.dopps.org/DPM. Accessed February 10, 2019.

123. Fishbane S, Shah HH. The emerging role of biosimilar epoetins in nephrology in the United States. *Am J Kidney Dis*. 2015;65:537–542.
124. Ardhanari S, Alpert MA, Aggarwal K. Cardiovascular disease in chronic kidney disease: Risk factors, pathogenesis, and prevention. *Adv Perit Dial*. 2014;30:40–53.
125. Choi HY, Park HC, Ha SK. How do we manage coronary artery disease in patients with CKD and ESRD? *Electrolyte Blood Press*. 2014;12:41–54.
126. Beattie JN, Soman SS, Sandberg KR, et al. Determinants of mortality after myocardial infarction in patients with advanced renal dysfunction. *Am J Kidney Dis*. 2001;37:1191–1200.
127. McCullough PA, Sandberg KR, Borzak S, Hudson MP, Garg M, Manley HJ. Benefits of aspirin and beta-blockade after myocardial infarction in patients with chronic kidney disease. *Am Heart J*. 2002;144:226–232.
128. Palmer SC, Di Micco L, Razavian M, et al. Antiplatelet agents for chronic kidney disease. *Cochrane Database Syst Rev*. 2013;Cd008834.
129. K/DOQI Workgroup. KDOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis*. 2005;45:16–153.
130. K/DOQI Workgroup. KDIGO clinical practice guideline for lipid management in chronic kidney disease. *Kidney Int Suppl*. 2013;3:259–305.
131. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): A randomised placebo-controlled trial. *Lancet*. 2011;377:2181–2192.
132. Palmer SC, Navaneethan SD, Craig JC, et al. HMG CoA reductase inhibitors (statins) for dialysis patients. *Cochrane Database Syst Rev*. 2013;9:CD004289.
133. Palmer SC, Navaneethan SD, Craig JC, et al. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev*. 2014;5:CD007784.

62

Hemodialysis and Peritoneal Dialysis

Kevin M. Sowinski, Mariann D. Churchwell, and Brian S. Decker†

KEY CONCEPTS

1. Hemodialysis (HD) involves the perfusion of blood and dialysate on opposite sides of a semipermeable membrane. Solutes are removed from the blood by diffusion and convection. Excess plasma water is removed by ultrafiltration.
2. Native arteriovenous (AV) fistulas are the preferred access for HD because of fewer complications and a longer survival rate. Venous catheters are plagued by complications such as infection and thrombosis and often deliver low blood flow rates.
3. Adequacy of HD can be assessed by the *Kt*/*V* and urea reduction ratio (URR). The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative minimum goal *Kt*/*V* is greater than 1.2 per treatment and the URR is greater than 65%.
4. During HD, patients commonly experience hypotension and cramps. Other more serious complications include infection and thrombosis of the vascular access.
5. Peritoneal dialysis (PD) involves the instillation of dialysate into the peritoneal cavity via a permanent peritoneal catheter. The peritoneal membrane lines the highly vascularized abdominal viscera and acts as the semipermeable membrane. Solutes are removed from the blood across the peritoneum via diffusion and ultrafiltration. Excess plasma water is removed via ultrafiltration created by osmotic pressure generated by various dextrose or icodextrin concentrations.
6. Patients on PD are required to instill and drain, manually or via automated systems, several liters of fresh dialysate each day. The more exchanges completed each day results in greater solute removal.

7. Peritonitis is a common complication of PD. Initial empiric therapy for peritonitis should include intraperitoneal antibiotics that are effective against both gram-positive and gram-negative organisms.
8. Nasal carriage of *Staphylococcus aureus* is associated with an increased risk of catheter-related infections and peritonitis. Prophylaxis with intranasal mupirocin (twice a day for 5 days every month) or mupirocin (daily) at the exit site can effectively reduce *S. aureus* infections.

Preclass Engaged Learning Activity

Visit the National Institute of Diabetes and Digestive and Kidney Diseases website <https://www.niddk.nih.gov/health-information/kidney-disease/kidney-failure>. This website is useful to enhance student understanding of and potential treatments for end-stage kidney disease (also known as kidney failure). Review the information provided in the "Hemodialysis" and "Peritoneal Dialysis" links. Watch the video titled "What is Dialysis?" <https://www.youtube.com/watch?v=ZOIsJI8NaSA>. The video provides a brief description of hemodialysis and peritoneal dialysis.

INTRODUCTION

The three primary treatment options for patients with end-stage renal disease (ESRD) are hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation. The United States Renal Data System (USRDS) is the national system that "collects, analyzes, and distributes" data relating to patients with ESRD or Stage 5 chronic kidney disease (CKD) in the United States and releases these data yearly.[1] According to the 2017 USRDS, at the end of 2015, there were 703,243 patients in the United States with ESRD. Of these, greater than 70 percent were being treated with HD or PD, and nearly 30% had a functioning kidney transplant. In 2012, 124,114 new patients started therapy for ESRD (dialysis or transplantation) and more than 88,000 patients died. Greater than 90 percent of new dialysis patients are treated with HD. The number of patients treated with PD has decreased steadily since 2000.[1]

Since 1972, the cost of treating ESRD (both dialysis and kidney transplantation) has been covered by Medicare. In 2015, Medicare fee-for-service spending for patients with ESRD was $33.9 billion, which make up

approximately 7% of all Medicare claim costs. ESRD consumes a vastly disproportionate amount of resources as only 1% of Medicare patients have the disease. Although total spending for ESRD treatment continues to climb by 2.4 % each year, per-patient spending (after adjusting for inflation) increased by only 1.1 % in 2015.[1] There are some positive signs as it relates to public health and ESRD. Although the total number of dialysis patients is increasing in the United States, the number of new dialysis patients per total population has stabilized or slightly decreased from the highest value observed in 1997. The prevalence of ESRD continues to climb, reflective of reduced mortality and enhanced patient care. The two primary diagnoses and underlying etiologies of kidney disease for new patients with ESRD are diabetes and hypertension.[1] Chapter 61 provides a thorough discussion on the epidemiology of chronic kidney disease.

This chapter serves as a primer on the principles and practice of dialysis and the complications associated with the delivery of dialysis treatments. The chapter focuses on HD and PD as the modalities most commonly employed for the management of ESRD (see Chapter 60 for a discussion of the role of renal replacement therapies in the management of acute kidney injury). The pertinent factors that should be considered before the initiation of dialysis are described. The morbidity and mortality associated with HD and PD are compared, as these considerations may influence the dialysis method chosen by patients and clinicians. The variants of HD and PD are detailed, and multiple types of vascular and peritoneal access used with each (ie, catheters and surgical techniques) are illustrated. The concept of dialysis adequacy for each modality is briefly reviewed. Finally, the clinical presentation of common complications of both dialytic therapies is presented, along with pertinent nonpharmacologic and pharmacologic therapeutic approaches. Information resources that describe the influence of CKD on patient’s quality of life, as well as the patient perspective on dialysis and dialysis-related therapies, are presented to highlight the human consequences of chronic disease.

Morbidity and Mortality in Dialysis

Morbidity in patients receiving dialysis can be assessed in a number of different ways including the number of hospitalizations per patient-year, the number of days hospitalized per patient-year, or the incidence of certain complications. The number of all-cause hospital admissions, 1.7 hospitalizations per patient-year, has fallen in recent years from greater than 2 hospitalizations per patient-year in

2006. Trends in hospitalization demonstrate an increase in hospitalization as a consequence of infection and cardiovascular disease and a decrease in hospitalizations as a consequence of vascular access problems. Patients with a functioning kidney transplant have a lower rate of hospitalization and shorter length of stay. Hospitalizations are more frequent for whites than for blacks, and the frequency and duration increase with age in both dialysis modality groups.[1]

The life expectancy of U.S. dialysis patients is markedly lower than that of healthy subjects of the same age and sex. In dialysis patients older than 75 years, the risk of dying is nearly fourfold higher compared to Medicare patients not receiving dialysis.[1] Adjusted all-cause mortality is six- to eightfold greater for dialysis patients compared with age-matched individuals. Approximately 40% of deaths in dialysis patients are cardiovascular related. In fact, those with CKD are more likely to die from cardiovascular disease before they reach ESRD. Infections, usually related to the dialysis access, are the second-most common cause of death in dialysis patients. Although mortality remains high in this patient population, the overall patient mortality rate has fallen among dialysis patients since 2001. Since that time, mortality has declined by 28%. The reductions are dependent on treatment type, and are smallest for HD and greatest for transplantation. In the United States, only 57% of HD patients and 68% of PD patients are alive 3 years after ESRD diagnosis and initiation of dialysis treatment.[1]

In addition to high morbidity and mortality, a dialysis patient's quality of life is generally poor. For example, restrictions caused by thrice weekly HD and/or associated treatments have been shown to impact many areas of a patient's life. These include, but are not limited to, physical endurance, sex, employment, social life, and diet. Patients often complain of fatigue and fear of the unknown related to their disease and its progression. The PD patient or the home HD patient may have some freedom from these restrictions, but this freedom comes with its own constraints.

Indications for Dialysis

Since first published in 2002, The National Kidney Foundation's Kidney Disease Outcome Quality Initiative (KDOQI) has been the primary treatment guideline for CKD. Although the Kidney Diseases: Improving Global Outcomes (KDIGO) guidelines[2] published in 2013, the updated 2015 version of the KDOQI guidelines serve as the most up-to-date recommendations.[3] Planning for dialysis initiation should occur when a patient's kidney function declines to CKD stage 4

(estimated glomerular filtration rate [eGFR] below 30 mL/min/1.73 m^2).[3] Beginning the preparation process at this point allows adequate time for proper education of the patient and family and for the creation of a suitable vascular or peritoneal access. For patients choosing HD, a permanent arteriovenous (AV) access (preferably a fistula) should be surgically created when eGFR falls below 25 mL/min/1.73 m^2, serum creatinine is greater than 4 mg/dL (354 μmol/L), or 1 year prior to the anticipated need for dialysis.[4] The KDIGO and KDOQI guidelines provide recommendations for referral to a specialist in kidney care services and for planning for RRT. The recommendation for timely referral is for patients with progressive CKD in whom the risk of kidney failure within 1 year is greater than 10% based on validated risk prediction tools.[2]

The KDIGO guidelines and commentaries addressing them and the KDOQI guidelines agree that the primary criterion for initiation of dialysis is the patient's clinical status, rather than a specific level of kidney function.[2,5] Namely, dialysis should be initiated when one or more of the following are present: signs or symptoms of kidney failure (eg, serositis, acid-base or electrolyte abnormalities, pruritis); inability to control volume status or blood pressure; a progressive deterioration in nutritional status or cognitive impairment. The guidelines suggest that these signs and symptoms are patient specific but tend to be evident once the patient's eGFR is in the range of 5 to 10 mL/min/1.73 m^2. The guidelines specifically indicate that RRT should be initiated to manage signs and symptoms and not to treat an arbitrary kidney function measurement.[2] The advantages and disadvantages of HD and PD are depicted in **Tables 62-1** and **62-2**, respectively. These factors, along with the patients' concomitant diseases, personal preferences, and support environments, are the principal determinants of the dialysis mode they will receive.[6] The timing of dialysis initiation is a compromise between maximizing patient quality of life by extending the dialysis-free period while avoiding complications that will decrease the length and quality of dialysis-assisted life.[3]

TABLE 62-1 Advantages and Disadvantages of Hemodialysis

Advantages

1. Higher solute clearance allows intermittent treatment.
2. Parameters of adequacy of dialysis are better defined and therefore underdialysis can be detected early.
3. Technique failure rate is low.
4. Even though intermittent heparinization is required, hemostasis parameters are better corrected with hemodialysis than peritoneal dialysis.
5. In-center hemodialysis enables closer monitoring of the patient.

Disadvantages

1. In-center hemodialysis requires multiple visits each week to the hemodialysis center, which translates into loss of patient independence.
2. Disequilibrium, dialysis-induced hypotension, and muscle cramps are common. May require months before the patient adjusts to hemodialysis.
3. Infections in hemodialysis patients may be related to the choice of membranes, the complement-activating membranes being more deleterious.
4. Vascular access is frequently associated with infection and thrombosis.
5. Decline of residual kidney function is more rapid compared to peritoneal dialysis.

TABLE 62-2 Advantages and Disadvantages of Peritoneal Dialysis

Advantages

1. Hemodynamic stability due to slow ultrafiltration rate.
2. Higher clearance of larger solutes, which may explain good clinical status in spite of lower urea clearance.
3. Better preservation of residual kidney function.
4. Convenient intraperitoneal route for administration of drugs such as antibiotics and insulin.
5. Suitable for elderly and very young patients who may not tolerate hemodialysis well.
6. Freedom from the "machine" gives the patient a sense of independence (for continuous ambulatory peritoneal dialysis).
7. Less blood loss and iron deficiency, resulting in easier management of anemia or reduced requirements for erythropoietin and parenteral iron.
8. No systemic heparinization required.
9. Subcutaneous vs intravenous erythropoietin or darbepoetin may reduce overall doses and be more physiologic.

Disadvantages

1. Protein and amino acid losses through peritoneum and reduced appetite from continuous glucose load and sense of abdominal fullness predispose patients to malnutrition.
2. Risk of peritonitis.
3. Catheter malfunction, and exit-site and tunnel infection.
4. Inadequate ultrafiltration and solute clearance in patients with a large body size, unless large volumes and frequent exchanges are employed.
5. Patient burnout and high rate of technique failure.
6. Risk of obesity with excessive glucose absorption.
7. Mechanical problems such as hernias, dialysate leaks, hemorrhoids, or back pain are more common than HD.
8. Extensive abdominal surgery may preclude peritoneal dialysis.
9. No convenient access for intravenous iron administration.

While the intent of this chapter is not to exhaustively compare and contrast HD and PD and the relative benefits of each, there is considerable debate in the literature regarding the mortality differences between HD and PD.[7] Most observational trials suggest that PD is associated with a survival advantage early in therapy, which wanes with increased treatment time. Prospective trials have reported conflicting results relative to efficacy of one modality over another. If there is a survival advantage for PD, the consensus is that the advantage is early in therapy and not with continued therapy. Well-designed studies are extremely difficult to conduct in this population, and thus the question of superiority of one modality over the other is controversial. Differences in outcomes may be related to a wide array of confounding factors, such as the dose of dialysis, baseline

patient health status, physician bias in modality selection, patient compliance with dialysis and medication therapy, or other unknown factors. For example, healthier patients tend to be directed toward PD, and factors such as age, duration of dialysis, and comorbidities play an important role in the complex relationship between patient outcomes and mortality.[8] Without clear distinction between modalities in terms of many important outcomes, the selection of the optimal therapy for a given patient is challenging. The selection of one modality over the other should be based upon patient motivation, desire, geographic distance from an HD unit, healthcare team preference, and patient education rather than survival advantages alone.

HEMODIALYSIS

Although HD was first successfully used in 1940, the procedure was not used widely until the Korean War in 1952. Permanent dialysis access was developed in the 1960s,[9] which allowed routine use of HD in patients with ESRD. Subsequent decades brought advances in dialysis technology, including the introduction of more efficient and biocompatible dialyzer membranes and safer techniques. HD is now the most common type of renal replacement therapy for patients with ESRD.

Principles of Hemodialysis

1 Hemodialysis consists of the perfusion of blood and a physiologic solution on opposite sides of a semipermeable membrane. Multiple substances, such as water, urea, creatinine, potassium, uremic toxins, and drugs, move from the blood into the dialysate, by either passive diffusion or convection as the result of ultrafiltration. Diffusion is the movement of substances down a concentration gradient. The rate of diffusion depends on the difference between the concentration of the solute in blood and dialysate, solute characteristics, ie, size, water solubility, and charge, the dialyzer membrane composition, and blood and dialysate flow rates. Diffusive transport is rapid for small solutes, but decreases with increasing molecular size. Other important diffusive solute transport factors include the membrane thickness, porosity, and the steric hindrance between the membrane pores and solute. Ultrafiltration is the movement of water across the dialyzer membrane as a consequence of hydrostatic or osmotic pressure and is the primary means for removal of excess fluid. Convection occurs when dissolved solutes are “dragged” across a membrane with water transport. This

occurs only if the pores in the dialyzer are large enough to allow them to pass along with water. Convection can be maximized by increasing the hydrostatic pressure gradient across the dialysis membrane, or by changing to a dialyzer that is more permeable to water transport. Diffusion and convection can be controlled independently, and thus a patient's HD prescription can be individualized to attain the desired degree of solute and fluid removal.

Hemodialysis Access

2 Obtaining and maintaining access to the circulation has been a challenge for long-term use and success of HD. Permanent access to the circulation may be accomplished by several techniques, including the creation of an AV fistula, an AV graft, or by the use of venous catheters (**Fig. 62-1**).[10] The native AV fistula is created by the anastomosis of a vein and artery (ie, the radial artery to the cephalic vein or the brachial artery to the cephalic vein). The native AV fistula has many advantages including providing the longest survival time of all blood-access devices and the lowest rate of complications such as infection and thrombosis. Patients with fistulas have increased survival and lower hospitalization rates compared to other HD patients. Finally, AV fistulas are the most cost-effective in terms of placement and long-term maintenance. Ideally, the most distal site (the wrist) is used to construct the first fistula; it is the easiest to create, and in the case of access failure, more proximal sites on the arm are preserved for later use. Unfortunately, fistulas require at least 1 to 2 months to mature before they can be routinely utilized for dialysis. Creation of an AV fistula, however, may be difficult in elderly patients and in patients with peripheral vascular disease, which is a particularly common comorbidity in patients with diabetes.

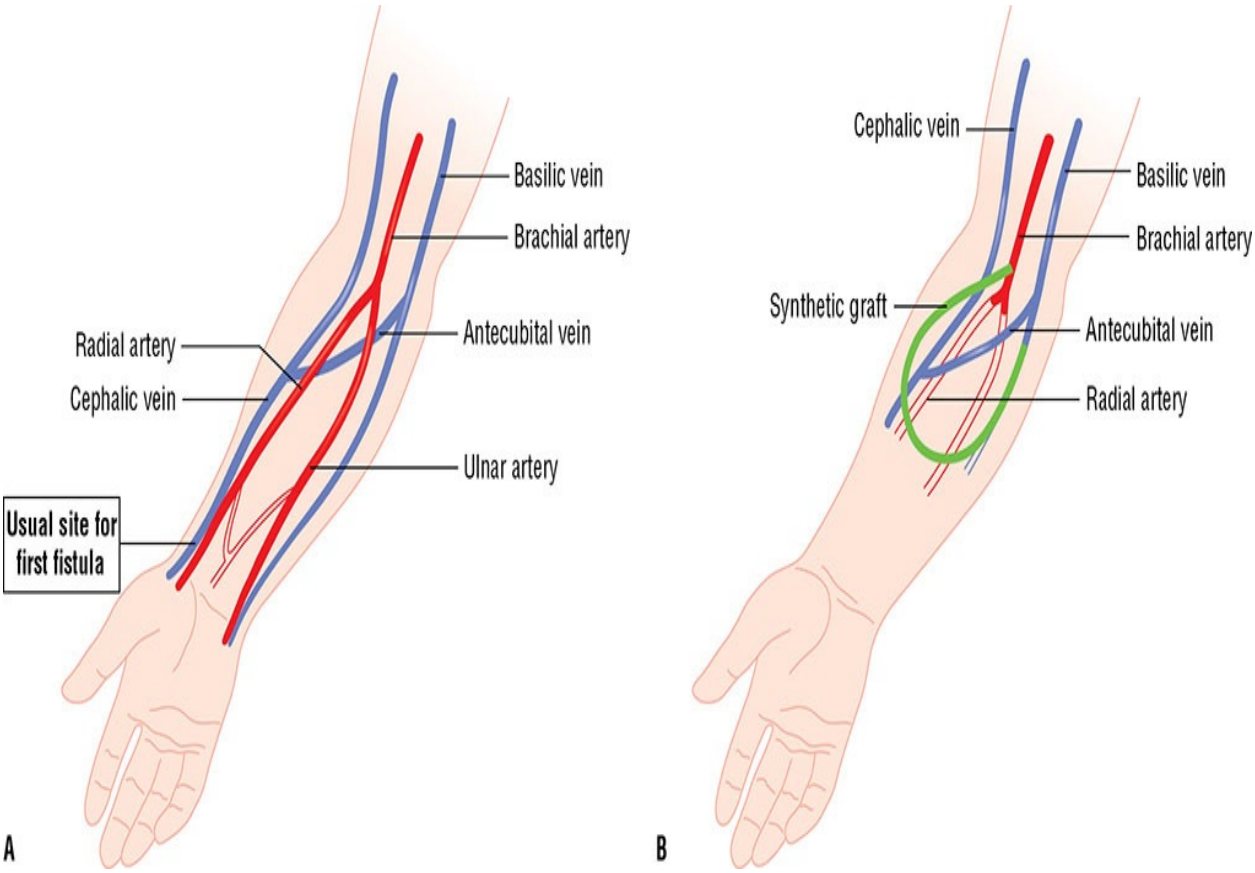


FIGURE 62-1 The predominant types of vascular access for chronic dialysis patients are (*A*) the arteriovenous fistula and (*B*) the synthetic arteriovenous forearm graft. The first primary arteriovenous fistula is usually created by the surgical anastomosis of the cephalic vein with the radial artery. The flow of blood from the higher-pressure arterial system results in hypertrophy of the vein. The most common AV graft (depicted in green) is between the brachial artery and the basilic or cephalic vein. The flow of blood may be diminished in the radial and ulnar arteries since it preferentially flows into the low-pressure graft.

Synthetic AV grafts, usually made of polytetrafluoroethylene, are another permanent AV access option. These grafts require only 2 to 3 weeks before they can be routinely used. Their primary disadvantages are shorter survival of the graft, and higher rates of infection and thrombosis. The least-desirable and least permanent HD access option involves the placement of a central venous catheter. Venous catheters can be placed in the femoral, subclavian, or internal jugular veins. Their main advantage is that they can be used immediately and they are often used in small children, diabetic patients with severe vascular disease, the morbidly obese, and patients who have no viable sites for permanent AV access. Late referrals to a nephrology specialist and delayed placement of a more

appropriate long-term access contribute to the use of venous catheters in chronic HD patients. The major problem with all venous catheters is that they have a short life span and are more prone to infection and thrombosis than either AV grafts or fistulas. Furthermore, some catheters are not able to provide adequate blood flow rates, which can limit the deliverable dose of dialysis.[10–12] Regardless, tunneled dialysis catheters are used frequently because of the ease of insertion, pain-free dialysis needle placement and availability for immediate use. They are, however, associated with increased morbidity, mortality, and cost.[13]

Hemodialysis Procedures

The HD system consists of an external vascular circuit through which the patient's blood is transferred in sterile polyethylene tubing to the dialyzer via a mechanical pump (**Fig. 62-2**).[14] The patient's blood then passes through the dialyzer on one side of the semipermeable membrane and is returned to the patient. The dialysate solution, which consists of purified water and electrolytes, is pumped through the dialyzer countercurrent to the flow of blood on the opposite side of the semipermeable membrane. In most cases, systemic anticoagulation (with heparin) is used to prevent blood clotting in the HD circuit tubing. The process of dialysis results in the removal of metabolic waste products, medications, and water and replenishment of body buffers, such as acetate and bicarbonate.

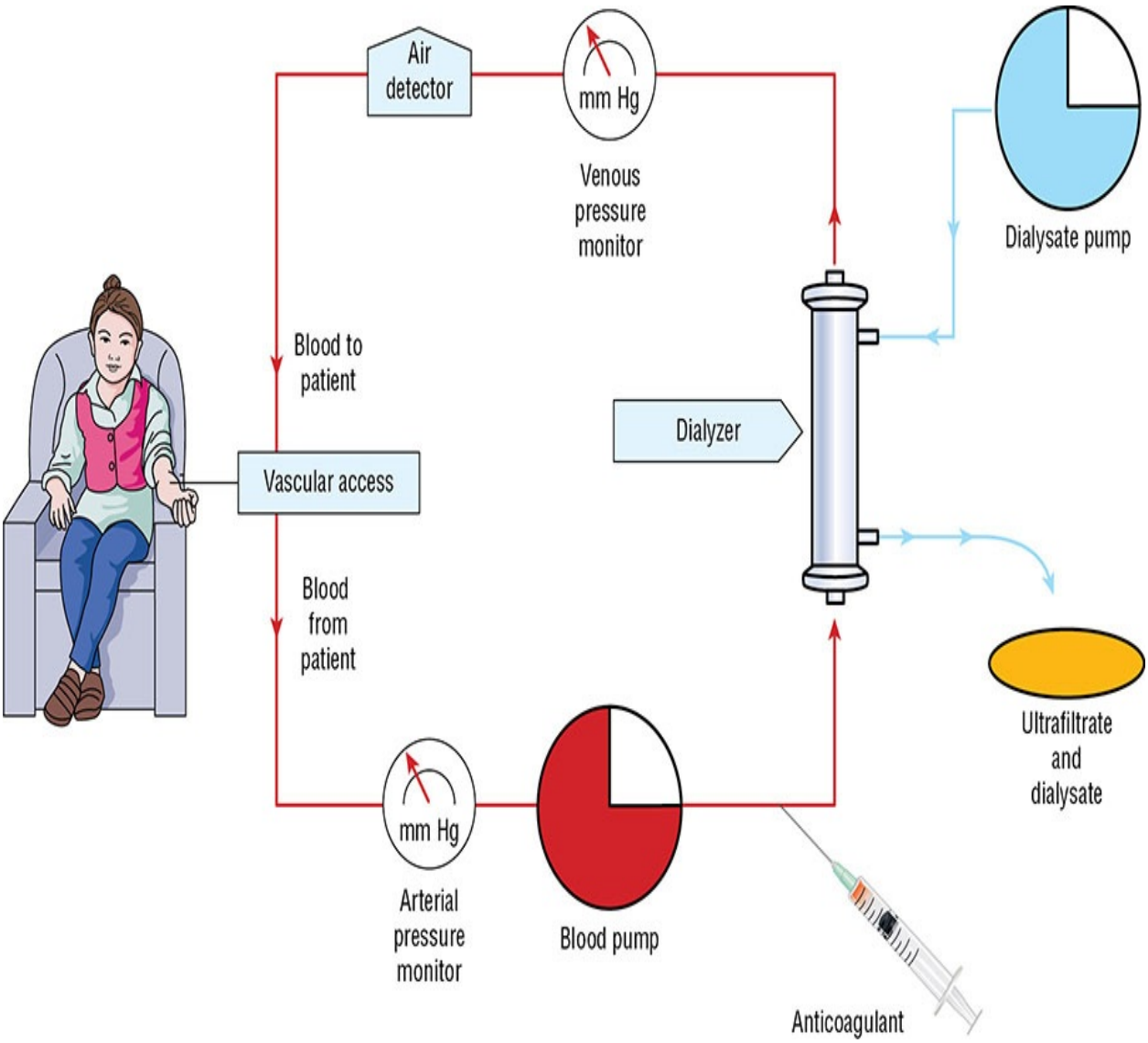


FIGURE 62-2 In hemodialysis, the patient's blood is pumped to the dialyzer at a rate of 300 to 600 mL/min. An anticoagulant (usually heparin) is administered to prevent clotting in the dialyzer. The dialysate is pumped at a rate of 500 to 1000 mL/min through the dialyzer countercurrent to the flow of blood. The rate of fluid removal from the patient is controlled by adjusting the pressure in the dialysate compartment.

Hemodiafiltration (HDF), another variant of traditional HD, enhances convective solute and water transport in addition to diffusive clearance to a much greater extent than high-flux HD.[15–17] When fluid losses exceed those desired for the patient, an IV infusion referred to as replacement fluid may be administered. HDF may improve outcomes due to its ability to remove middle molecular weight uremic solutes more efficiently than the other HD variants.

Recent evidence suggests that HDF improves survival compared to conventional HD.[16,18] Preliminary information suggests that HDF enhances clearance of phosphate, beta-2 microglobulin, and pro-inflammatory solutes. Currently, this procedure is not used extensively in the United States. Barriers to its use are the high cost and logistic issues associated with providing the fluid replacement needs.

Three categories of dialysis membranes have historically been utilized: low flux, high efficiency, and high flux. Low-flux and high-efficiency membranes have small pores that limit clearance to relatively small molecules (size less than or equal to 500 daltons) such as urea and creatinine and are currently utilized for less than 20% of chronic HD procedures.[14] High-flux membranes are now used in the vast majority of patients because they are capable of removing high-molecular-weight endogenous substances, such as β_2-microglobulin, and medications such as vancomycin.[14] The primary reason for using high-flux membranes is that clearance of water as well as low- and high-molecular-weight substances is much greater, allowing for shorter treatment times. To maximize the clearance capacity of high-flux dialyzers, the blood flow rates should be 400 to 600 mL/min, and dialysate flow rates greater than 500 mL/min, which necessitates strict controls and active monitoring of the rate of fluid removal. Typically, these dialyzers are composed of polysulfone, polymethylmethacrylate, polyamide, cellulose triacetate, and polyacrylonitrile.[14]

Hemodialysis is usually prescribed as three sessions weekly for 3 to 5 hours per session. These sessions are usually performed in “in-center” dialysis units. This is a large time commitment for any patient undergoing HD and results in substantial loss of control over their life. Several variants of HD have been explored in an effort to balance dialysis adequacy with patient outcomes and quality of life, including “intensive dialysis” procedures that increase dialysis frequency, enhance dialysis duration, or both.[19–21] Examples of these procedures include: (1) frequent HD (5–7 sessions/week), which can be frequent short (less than 3 hours/session), frequent standard (3-5 hours/session), or frequent long sessions (longer than 5 hours/session); (2) long HD (more than 5 hours/session given 3–7 times/week, which can be long thrice weekly (administered either at night or during the day), long every other night (administered at night) and long frequent (administered at night 5–7 nights/week). Many of these procedures that increase the frequency or duration of dialysis may be associated with improved survival.[19–21] For example, in-center, thrice weekly HD was associated with a higher risk of the composite outcome of death, left-ventricular mass and change in health composite score than in-center six times per week HD.[22] Intensive

dialysis has been associated with reductions in left-ventricular mass and improved blood pressure control, both surrogates for improved cardiovascular outcomes, and improved phosphate removal. Lastly, and perhaps most importantly, these procedures are associated with a reduction in dialysis-related symptoms and improved quality of life.[19–21] Despite the perceived advantages and more frequent use in other countries such as New Zealand and Canada, the use of home HD is uncommon in the United States, with less than 2% of dialysis patients receiving HD care at home at the end of 2015.[1] Potential obstacles to home HD include patient factors (eg, lack of self-efficacy, fear of self-cannulation, fear of catastrophic event, and fear of lack of quality care), and a lack of awareness of the availability of this type of dialysis.[23,24] Finally, there are suggestions that patients receiving intensive dialysis may be at higher risk of access infections and need for vascular access procedures. Further clinical trials are needed to elucidate the role of these types of dialysis therapy. The 2015 KDOQI guidelines have provided new suggestions and/or recommendations that all patients be offered short frequent hemodialysis as an alternative to standard hemodialysis in addition to providing patients with information about the potential risk associated with them.[3]

Adequacy of Hemodialysis

The optimal dose of HD, the patient's dialysis prescription, is that amount of therapy above which there is no cost-effective increment in the patient's quality-adjusted life expectancy. The two primary goals of the dialysis prescription are to achieve the patient's dry weight and the adequate removal of endogenous waste products such as urea. Dry weight is the target postdialysis weight at which the patient is normotensive and free of edema. Measurement of urea removal, while imperfect, is the typical method used to quantify dialysis adequacy. Urea removal reflects the "delivered dose" of dialysis and is utilized as the surrogate for removal of other toxins.

The delivered or desired dose of dialysis in terms of solute removal can be expressed as the urea reduction ratio (URR) or the *Kt/V* (pronounced "K-T-over-V"). The URR is a simple concept and is easily calculated as:

$$\text{URR} = \frac{\text{Predialysis BUN} - \text{Postdialysis BUN}}{\text{Predialysis BUN}} \times 100$$

The URR is frequently used to measure the delivered dialysis dose; however,

it does not account for the contribution of convective removal of urea. The *Kt/V* is a unitless index based on the dialyzer clearance of urea (*K*) in L/h multiplied by the duration of dialysis (*t*) in hours, divided by the urea distribution volume of the patient (*V*) in liters.[25] *Kt/V* is thus the fraction of the patient's total body water that is cleared of urea during a dialysis session. Urea kinetic modeling, using computer software, is the optimal means to calculate the *Kt/V*.[26] An in-depth discussion of the pros and cons of various methods of calculating and interpreting *Kt/V* is beyond the scope of this chapter. The reader is referred to other sources for more in-depth information.[25,26]

3 For patients who receive thrice weekly hemodialysis, KDOQI recommends that the minimally adequate delivered dose of dialysis is a *Kt/V* of 1.2 (equivalent to an average URR of 65%).[3] To achieve this goal, the recommended target prescribed *Kt/V* is 1.4 (equivalent to an average URR of 70%).[3] For patients who receive hemodialysis on a schedule other than thrice weekly, the KDOQI suggests a target standard *Kt/V* of 2.3 volumes /week with a minimum delivered dose of 2.1. Lower doses of dialysis treatment are thought to be associated with increased morbidity and mortality. Many nephrologists believe that even greater doses of dialysis would have positive outcomes in dialysis patients, and so the average dose of dialysis has been increasing in the United States. In 2004, the mean delivered *Kt/V* as reported by the CPM was 1.55.[27] The results of HEMO study, a prospective, randomized trial that assigned patients to either standard (*Kt/V* = 1.25) or high-dose (*Kt/V* = 1.65) dialysis with high-flux or low-flux membranes, revealed that the risk of death was similar in both the standard and high-dose therapy and the low- and high-flux groups. Thus, there does not appear to be any benefit in increasing the dose of dialysis above the current recommendations. The HEMO study only enrolled patients who were on traditional thrice-weekly dialysis, so the applicability of these findings to patients on more intensive regimens such as daily or nocturnal HD regimens remains to be determined. However, intensive HD regimens may result in better control of blood pressure, anemia, phosphate, and sleep apnea.[28] In those relatively few patients who are below the adequacy goal, the deficiency may be related to patient compliance with the dialysis prescription (ie, ending dialysis early) or low blood flow rates caused by access stenosis or thrombosis, or due to the use of catheters. Adequate dialysis may not be achieved in some patients despite compliance and sufficient blood flow. For these patients there are two options to increase urea clearance: use a larger membrane or increase the treatment time.

Complications of Hemodialysis

4 Complications associated with HD therapy are significant and may result in short- and long-term problems that limit therapy effectiveness, and diminish quality of life and life expectancy. These complications that occur during the actual therapy (intradialytic), as well as those associated with vascular access, are discussed in this chapter.[29,30]

Hemodialysis Procedure Complications

The most common complications that occur during the HD procedure include hypotension, hypertension, cramps, nausea and vomiting, headache, chest pain, back pain, and fever or chills.[29,30] **Table 62-3** lists these complications and their etiology and predisposing factors.

TABLE 62-3 Common Complications during Hemodialysis

	Incidence (%)	Etiology/Predisposing Factors
Hypotension	20–30	Hypovolemia and excessive ultrafiltration
		Antihypertensive medications prior to dialysis
		Target dry weight too low
		Diastolic dysfunction
		Autonomic dysfunction
		Low calcium and sodium in dialysate
		High dialysate temperature
		Meal ingestion prior to or during dialysis
Hypertension	5–15	Plasma sodium concentration
		Intravascular volume
		Dialytic removal of antihypertensive medications
		Activation of the Renin Angiotensin Aldosterone system
Cramps	5–20	Muscle hypoperfusion due to ultrafiltration and hypovolemia
		Hypotension
		Electrolyte imbalance
		Acid–base imbalance
Nausea and vomiting	5–15	Hypotension
		Dialyzer reaction
Headache	5	Disequilibrium syndrome
		Caffeine withdrawal due to dialysis removal
Chest and back pain	2–5	Unknown
Pruritus	5	Inadequate dialysis
		Skin dryness
		Secondary hyperparathyroidism
		Abnormal skin concentrations of electrolytes
		Histamine release
		Mast cell proliferation
Fever and chills	<1	Endotoxin release; infection of dialysis catheter

Source: Data from reference 31.

A decrease in blood pressure is often noted during HD, but a symptomatic decline in blood pressure that requires nursing or medical intervention can lead to a reduction in the rate and duration of a treatment session reducing overall treatment efficacy.[30] Intradialytic hypotension (IDH) with a systolic blood pressure <90 mm Hg has been associated with increased mortality.[32] A primary cause of IDH is related to the rate and amount of fluid removed during[29,30] typical HD treatments, although other causes, as listed in **Table 62-4**, may also play a role.[29,30] Symptoms such as nausea and cramping are often present during acute hypotensive episodes. The replacement of acetate with bicarbonate as the dialysate buffer, the use of volumetric ultrafiltration controllers, and individualized or modeled dialysate sodium concentrations have helped reduce the incidence of IDH. Sodium modeling uses a higher initial dialysate sodium concentration (145–155 mmol/L) and tapers sodium concentration down (135–140 mmol/L) over the dialytic session. Dialytic treatment modifications such as sodium individualizing or modeling may decrease post-HD thirst and subsequent intradialytic weight gain. This modification may decrease the need for aggressive dialytic fluid removal and the incidence of IDH.[33–36]

TABLE 62-4 Management of Hypotension

Acute treatment	Place patient in Trendelenburg position
	Decrease ultrafiltration rate
	Give 100–200 mL bolus of normal saline intravenous
	Give 10–20 mL of hypertonic saline (23.4%) intravenous over 3–5 minutes
	Give 12.5 g mannitol
Prevention	
Nonpharmacologic	Accurately set "dry weight"
	Use steady constant ultrafiltration rate
	Keep dialysate sodium >serum sodium
	Lower dialysate temperatures
	Bicarbonate dialysate
	Avoid food before or during hemodialysis
Pharmacologic	Midodrine 2.5–10 mg orally 30 minutes before hemodialysis (start at 2.5 mg and titrate)
	Droxidopa 100–600 mg orally 1 hour before hemodialysis (start at 100 mg and titrate up to 600 mg)
	Other options (limited evidence):
	Levocarnitine 20 mg/kg IV after hemodialysis
	Sertraline 50–100 mg daily
	Fludrocortisone 0.1 mg before hemodialysis
	DDAVP 1–2 intranasal sprays (150 mcg per spray)
Counsel patients	Administer antihypertensive medications in the evening or after hemodialysis
	Minimize intradialytic weight gain by decreasing salt content in their diet

Intradialytic or post-HD hypertension can occur in 5% to 15% of patients receiving HD and may increase post-HD fatigue and the risk of cardiovascular and all-cause mortality.[37] Underlying causes include, not achieving post-HD dry weight goal, over-estimation of dry weight, dialytic removal of antihypertensive medications, or the activation of the renin-angiotensin system secondary to abrupt hypovolemia.[38]

Skeletal muscle cramps complicate 5% to 20% of HD treatments. Although

the pathogenesis of cramps is multifactorial, plasma volume contraction and decreased muscle perfusion caused by excessive ultrafiltration are frequently the initiating events.[31] Pruritus, another complication that may appear to increase in severity during the HD treatment, is a complication of CKD and the management of this condition is discussed in Chapter 61.

Vascular Access Complications

Thrombosis and infection are the most common vascular access complications, with the highest occurrence found in patients with a catheter compared with those with an AV graft or AV fistula.[30,39,40] The maintenance of vascular access patency is critical for patients receiving HD. Predisposing factors are often described using Virchow's triad of blood flow stasis, hypercoagulability, and endothelial injury. Although, aneurysm and stenosis of either an AV fistula graft or surrounding vasculature are resolved primarily through surgical intervention, several pharmacologic therapies have evaluated patency maintenance with conflicting results.[41]. Vascular access stenosis can contribute to decreases in blood flow (blood flow <300 mL/min) through the vascular access increasing the risk of thrombus formation. A decrease in blood flow can occur abruptly, or over days to weeks or intermittently and may require ultrasound, venography, or computed tomography scans for a definitive diagnosis.[40,42] Catheter-related thrombosis can form either inside (intrinsic) or outside (extrinsic) the catheter. An occlusion can form within the lumen at the tip or develop a fibrin sleeve around the catheter where this fibrin sleeve can serve as a nidus for infection and ultimately require catheter removal.[43,44]

Infection is a leading cause of mortality in HD patients.[1] The rate of hospitalizations for bacteremia or septicemia in patients receiving HD was 116 events per 1,000 patient-years in 2010 which is an increase of 51% since 1993.[1]. The risk of sepsis-related death is 100 times greater in patients receiving HD than the general population, and those with an indwelling catheter have the highest risk.[44] The National Healthcare Safety Network (NHSN) dialysis event surveillance report found that 69.8% of access-related blood stream infections (ARBSIs) were in patients with an indwelling central venous catheter (CVC).[45]. The most prevalent pathogens for blood stream infections (BSIs) were Gram-positive (64%) followed by Gram-negative (35%) and Candida species (0.2%). The most frequently isolated micro-organisms in ARBSIs were: *S. aureus* (31.8 %), *S. epidermidis* (15.6%), coagulase-negative staphylococcus (9.7%), *E. faecalis* (4.9%), and *E. coli* (2.9%). The incidence with methicillin-resistant *S.*

aureus (39.5%) and cephalosporin-resistant *E. coli* (17.8%) organisms were highest in patients with a CVC.[45]

Catheter-related infections can develop at the insertion site, hub, or both. The infection source for long-term catheters such as a tunneled cuffed catheter is usually the hub where bacteria can enter the blood leading to a BSI.[40,44] Overall, HD access with a catheter is associated with higher rates of bacteremia, osteomyelitis, septic arthritis, endocarditis, thrombus, and death, as well as increased treatment costs compared with an AV fistula or AV graft.[39,46]

Complications of CKD

Patients receiving HD are likely to have at least one additional comorbid disease such as diabetes, hypertension, cardiovascular disease, or obesity (BMI greater than or equal to 30 kg/m^2 and older age, greater than or equal to 60). The pharmacotherapy management of most CKD complications and comorbid diseases that persist in patients receiving HD are discussed in Chapter 61. The daily medication burden for HD patients is one of the highest for any chronic disease state. The pill burden in HD patients was 16±7 pills/day of which phosphate binder medications accounted for 7.4±4.7 pills/day.[47,48] Adherence to phosphate binder regimens is reported to be 43% in US HD patients. This burden is associated with a lower quality of life in HD patients.[49]

Management of Hemodialysis Complications

The management of HD complications is discussed in this section. The most common causes of HD complications and appropriate management are reviewed.

Hypotension

Acute management of intradialytic hypotension (IDH) includes placing the patient in the Trendelenburg position, decreasing the ultrafiltration rate, lowering the dialysate temperature, modifying dialysate electrolyte concentrations, and/or administering normal or hypertonic saline.[29,34,35,31,50] IDH may not occur during each HD session and a patient's response to therapeutic modifications can be variable, which could necessitate modification of their HD prescription. Patients with IDH will need a careful review of all medications including antihypertensive medications. Evaluation should consider the timing of antihypertensive medication administration and may require adjustments to medications administered the day prior to and the day of HD therapy.[51] Patients

with IDH should be counseled to take their blood pressure medications after HD.

IDH is often due to an insufficient cardiac response to reduced circulating blood volume: often when aggressive ultrafiltration is required to restore dry weight. Most treatments for IDH are directed toward restoring or maintaining adequate blood vessel perfusion in these patients. One approach is to limit interdialytic weight gain (IDWG) that may decrease the rate and volume of fluid removal during HD. Patients are counseled to limit dietary salt intake especially hidden sodium in processed foods. This diet modification can decrease a patient's thirst and subsequent fluid intake.[31] Another approach, decreasing the dialysate temperature to 36.5°C (97.7°F) may help reduce core body temperature, which can decrease vasodilation.[42,50,52] If nonpharmacologic interventions are not adequate to prevent or reduce the incidence of symptomatic IDH, then pharmacologic interventions should be considered (see Table 62-4).

Oral midodrine (5 mg) given two to three times daily can increase blood pressure in patients receiving HD with chronic hypotension on nondialysis days. It is important to note that the effects of midodrine are probably best in patients with hypotension related to autonomic dysfunction. Patients with peripheral vascular disease should be monitored for digital or lower limb ischemia.[53]

Droxidopa is an oral synthetic amino acid analog metabolized by the catecholamine pathway to norepinephrine, resulting in vasoconstriction of peripheral veins and arteries. Droxidopa is FDA approved for neurogenic orthostatic hypotension (NOH), with doses ranging from 100 mg to 600 mg three times daily. Dosing for IDH is not established, but a study randomized patients with a history of IDH to receive droxidopa 400 mg, 600 mg, or placebo 1 hour prior to hemodialysis. It was found that patients receiving droxidopa when compared to placebo had a lower rate of early HD termination due to IDH. Gastrointestinal disorders were the most frequent adverse effect reported in the treatment groups.[54]

Fludrocortisone is a potential agent for symptomatic IDH, including in patients with an inadequate response to midodrine. It increases blood pressure through several mechanisms including enhancing blood vessel sensitivity to circulating catecholamines. Fludrocortisone dosing for orthostatic hypotension generally ranges from 0.1 mg to 1.0 mg per day but IDH dosing has not been determined. A recent case report described a patient receiving HD with a decreased response to midodrine for IDH and an increased number of HD sessions terminated early. The patient received fludrocortisone 0.2 mg in addition to midodrine 10 mg 30 minutes prior to HD. The authors reported early HD termination in 6 out of 45 sessions prior to fludrocortisone initiation but no

occurrences in the 45 sessions post-treatment initiation.[55]

Other potential therapeutic agents for IDH include levocarnitine, sertraline, and intranasal desmopressin acetate (DDAVP). Administration of levocarnitine (20 mg/kg IV at the end of each dialysis session) may reduce hypotensive episodes, particularly with carnitine deficiency.[56] High cost and limited efficacy precludes a strong recommendation for routine levocarnitine use. The administration of sertraline 50 mg daily titrated to 100 mg daily after 1 week improved systolic and diastolic blood pressure in a small trial.[57] An earlier study administered sertraline 50 mg daily and did not report an increase in post-HD blood pressure.[58] The mixed results do not support routine sertraline administration for hypotension. Overall, the use of DDAVP increased post-HD blood pressure and decreased the incidence of IDH.[59] These medications have limited clinical evidence and should be used with caution in patients receiving HD with IDH.

Hypertension

A decline in blood pressure is expected after hemodialysis and improves survival, but a dramatic increase or decrease in blood pressure during or after HD decreases overall survival.[60] An increase in blood pressure either during or post-HD may require a change in the delivery of a HD session, as well as changes in antihypertensive medications or adjustments to the timing of medication administration.[38] Although the underlying mechanism may be multifactorial, antihypertensive medication dialyzability could play a role in HD-related increases in blood pressure.[61] Hemodialysis enhances the clearance of metoprolol, atenolol, and angiotensin-converting enzyme inhibitors (ACE-Is). Recent studies suggest switching to an angiotensin receptor blocker (ARB), carvedilol or amlodipine, in patients experiencing a rise in blood pressure during or post-HD. Antihypertensive medications will require individualization based on patient comorbid conditions and risk of IDH. A retrospective cohort examined patients with heart failure receiving HD and either taking a daily beta-blocker (carvedilol, bisoprolol, or metoprolol CR/XL) or those patients not taking a daily beta-blocker. Patients receiving either carvedilol, bisoprolol, or metoprolol had lower all-cause mortality at 5 years.[62] However, in patients at risk of IDH, a large retrospective study found an increased rate of IDH and risk of all-cause mortality in patients taking carvedilol compared to metoprolol.[63] Initiation of any antihypertensive medication in patients at high-risk should be followed with close monitoring pre- and post-HD in addition to during HD. For

example, one small study found an improvement in patients with intradialytic hypertension when low-dose carvedilol (6.25 mg twice daily) was initiated and titrated as tolerated.

Muscle Cramps

Nonpharmacologic interventions related to dialytic therapy may help alleviate muscle cramps. These measures include adjusting the ultrafiltration rate to avoid hypotension, volume contraction, or hypoosmolality. Other methods to reduce muscle cramps, including compression devices, moist heat, massage, exercise, stretching, or muscle flexing, should be considered first to minimize adverse consequences (Table 62-5).[29,30]

TABLE 62-5 Management of Cramps

Acute treatment	Give 100–200 mL bolus of intravenous normal saline
	Give 10–20 mL of intravenous hypertonic saline (23.4%) over 3–5 minutes
	Give 50 mL of 50% intravenous glucose (nondiabetic patients)
Prevention	
Nonpharmacologic	Accurately set "dry weight"
	Keep dialysate sodium >serum sodium
	Stretching exercises, massage, flexing, or compression devices
Pharmacologic	Vitamin E 400 international units at bedtime.
	Quinine 324 mg daily (second-line therapy)

Both vitamin E and quinine can significantly reduce the incidence of muscle cramps.[64,65] Quinine is well tolerated, but it is associated with temporary sight and hearing disturbances, thrombocytopenia, or gastrointestinal distress. Quinine sulfate is available as 324 mg capsule (Qualaquin, URL Pharma, Philadelphia, PA) and is FDA approved for malaria only. The FDA has warned against the off-label use of quinine for muscle cramps.[66] The dosage for HD-related muscle cramps is one capsule (324 mg) at bedtime or 1 to 2 hours prior to HD.

In a small prospective study of patients receiving HD with at least six episodes of intradialytic muscle cramps in the 30 days prior to enrollment, patients received either placebo or gabapentin 300 mg three times a week

administered 5 minutes prior to HD. After 1 month, patients experienced less episodes of muscle cramps in the treatment arm.[67] Both vitamin E (400 mg) and vitamin C (250 mg) reduce the frequency of cramps in dialysis patients.[68] The combination of these two drugs had an additive effect. Although these data further strengthen the case for vitamin E, it is unclear what role oral vitamin C would play since many patients are on a renal multiple vitamin-containing vitamin C. Furthermore, both vitamin C and vitamin E as long-term therapy must be used with caution since doses of vitamin E greater than 400 U/day have been reported to increase mortality and there is a risk of systemic oxalosis with the accumulation of a vitamin C metabolite, oxalate in HD patients. Pharmacologic interventions to diminish muscle cramps are limited and currently vitamin E has the strongest evidence-based efficacy and safety profile.

Vascular Access Thrombosis

Prevention of vascular access thrombus formation is a key to maintaining therapy for HD patients. Multiple oral and intravenous anticoagulant and antiplatelet agents and intravenous thrombolytic agents have been studied to ascertain their clinical value.

Oral antiplatelet agents' role for the prevention of vascular access thrombosis has been controversial since efficacy is not well established and there is an increased risk of bleeding.[42,69,70] A meta-analysis of randomized controlled trials for the prevention of vascular access failure identified nine trials assessing antiplatelet therapy and dialysis access patency in AV fistula (n=6) and graft (n=3).[71] This analysis found a lower rate of thrombosis or patency failure in patients with an AV fistula taking either aspirin, ticlopidine, or clopidogrel for up to 6 months (RR, 0.49; 95% CI 0.30–0.81). In patients with an AV graft there was no benefit with any of these antiplatelet therapies (RR, 0.94; 95% CI 0.80–1.10). A post-hoc analysis identified that patients receiving aspirin prior to AV graft placement had improved graft patency but not graft survival.[72] Overall, the studies have reported conflicting results, and patients with an AV graft taking aspirin prior to a procedure may have some benefit, but initiating aspirin post-surgery may increase the risk of thrombosis.

The use of warfarin to maintain vascular access patency remains controversial with some trials suggesting an increase in morbidity and mortality.[73–75] HD patients generally require a lower dose and are at a much higher risk of a major hemorrhagic event.[73,75]

The effect of fish oil supplementation, a combination of eicosapentaenoic

acid (EPA) 400 mg and docosahexaenoic acid (DHA) 200 mg, on AV graft patency for 12 months after graft placement revealed that the loss of patency was lower in the fish oil (48%) than the placebo (62%). Fish oil thus may benefit some patients with an AV graft since time to thrombus was longer and thrombus rates were about half that of placebo.[76] Fish oil supplements were also studied in patients scheduled to receive surgery for an AV fistula. Patients were randomized to receive either placebo (olive oil) or fish oil 4 g/day (EPA 46% and DHA 38%) starting the day prior to surgery for 12 weeks. Each study arm had a similar number of patients receiving aspirin 100 mg/day. The rate of AV fistula failure during the first 12 months post-surgery was 47% in both groups with similar rates of thrombus formation in patients receiving fish oil vs placebo (22% vs 23%) including those receiving aspirin or placebo (20% vs 18%).[77]

Catheter-locking solutions with unfractionated heparin (UFH), recombinant tissue plasminogen activator (rt-PA), or sodium citrate instilled in each HD catheter lumen between HD sessions have been associated with a reduction in catheter thrombosis. Sodium citrate 4% is as effective as UFH but may offer a better safety profile at a reduced cost.[78] A systematic review and meta-analysis of randomized controlled trials of HD lock solutions containing UFH and citrate found significantly fewer bleeding episodes.[79] UFH 5,000 units/mL twice weekly and recombinant tissue plasminogen activator (rt-PA) 1 mg per catheter lumen once weekly were instilled in patients receiving HD with a CVC. Alternating the catheter-lock solution regimen with rt-PA significantly decreased catheter malfunction compared to the patients receiving UFH only for catheter patency. The cost of catheter replacement and hospitalization may offset the cost of once weekly administration of rt-PA.

Based on their medical history, Patients at high risk for catheter malfunction or bacteremia (n=373) received post-HD catheter-lock solutions of rt-PA (1 mg/lumen) once weekly plus routine care with either sodium citrate 4% or UFH on the remaining post-HD sessions. Catheter malfunction significantly declined with weekly rt-PA treatment from 18.4 to 10.1 days per 1,000 catheter days and the episodes of bacteremia declined from 0.28 to 0.25 per 1,000 catheter days. Most patients (96%) received routine care with sodium citrate 4%, which may account for the small decline in bacteremia episodes. Overall, the increased cost of weekly rt-PA was not offset by the decline in catheter malfunction or bacteremia.[80] Taurolidine-based catheter solutions were examined in patients with a tunneled catheter (n=177). Patients were randomized to receive either taurolidine citrate with urokinase (Taurolock/U) once weekly plus taurolidine citrate with heparin (Taurolock/Hep) twice a week (n=84) or Taurolock/Hep

(*n*=93) three times a week. During the 6-month study period, no patients in the Taurolock/U group required catheter replacement compared with three patients in the Taurolock/Hep group. The use of rt-PA to restore catheter patency occurred at a lower rate with Taurolol/U (*n*=5) compared to Tauro/Hep (*n*=12). This was a short-term study; therefore, it is difficult to extrapolate long-term benefits until further studies are completed.[81]

The therapeutic alternatives for the management of venous catheter thrombosis are listed in **Table 62-6**. If a catheter-related thrombus is suspected, a forced saline flush should be used to clear the catheter, followed by installation of a thrombolytic. A number of studies have been published using alteplase and reteplase and initial reperfusion rates for both were approximately 90%, respectively.[82] The efficacy, safety, and cost of alteplase, reteplase, and tenecteplase were compared, and venous catheter clearance rates were similar with reteplase (88 ± 4%) and alteplase (81 ± 37%), but markedly lower with tenecteplase (41 ± 5%).[82] The cost analysis favored the use of reteplase, however, to attain these savings, reteplase must be batch prepared. Reteplase is currently not FDA approved for this indication which may limit it use.[82]

TABLE 62-6 Management of Hemodialysis Catheter Thrombosis

Nonpharmacologic therapy
Forced saline flush
Referral to vascular surgeon
Pharmacologic therapy
Alteplase: instill 2 mg/2 mL per catheter lumen port; attempt to aspirate after 30 minutes; may repeat dose if catheter function is not restored in 120 minutes; longer durations of instillation have been used.
Reteplase: instill 0.4 U/0.4 mL in each lumen, attempt to aspirate after 20–30 minutes, may repeat if necessary.

Alteplase is available commercially and is the only agent that is FDA approved, for venous catheter clearance, and is administered as a short dwell for 30 to 60 minutes, as a long dwell, or left in the catheter between treatments. No difference in patency rates between the short or long dwells has been demonstrated. Alteplase has also been given as a short infusion of 2 mg/h over 4 hours for a blocked catheter and 1 mg/h over 4 hours for sluggish blood flow. Infusions may theoretically be more efficacious than the dwell technique because the thrombus is only exposed to the thrombolytic at the very tip of the catheter. Another consideration is dwell versus push techniques for thrombolytic

therapy, with recent data indicating that a push protocol with alteplase is as effective and safe for managing HD catheter dysfunction and might be more practical than a dwell technique.[83]

A retrospective single-center study evaluated the dose of alteplase in patients receiving HD with a catheter requiring a thrombolytic for catheter dysfunction. Patients during the first 3 years of the study received alteplase 1 mg/lumen (*n*=108) and during the last 3 years received alteplase 1 mg/lumen. Dwell time was 30 minutes and independent of dose. Patients receiving alteplase 2 mg dose had a lower rate of catheter removal due to dysfunction (10.2% vs 19.4%). Overall, the instillation of alteplase 2 mg compared to 1 mg resulted in a 89.2% success rate at resolving catheter occlusions versus 80.6% (*p*=0.036).[84]

Infection

Patients who develop a fever during dialysis should immediately be evaluated for infection; blood cultures should be collected prior to the administration of any antibiotics. When an AV fistula infection is suspected, empiric broad-spectrum antibiotic therapy must be initiated usually with vancomycin plus an aminoglycoside. Antibiotic therapy, if the infection is confirmed, should continue for a total of 6 weeks and should be tailored to culture sensitivities. Unfortunately, a suspected infection in an AVG may require more than antibiotic therapy alone, and a surgical procedure to remove the infected graft material may be needed. A suspected infection in a temporary catheter may warrant catheter removal and a culture of the catheter tip should be obtained.[43,85] Since catheter-related infections are more common than infections of an AV fistula or AVG, preventative care approaches are paramount. Preventative care includes minimizing the use and duration of catheters, proper disinfection and sterile technique, and the use of an antimicrobial ointment at the exit site (mupirocin 2%, povidone-iodine). Dialysis unit protocols that employ universal precautions, limit the manipulation of the catheter, utilize an antiseptic wash (tincture of iodine, chlorhexidine, etc.) for skin preparation, and the use of facemasks by the patient and caregiver can significantly reduce the incidence of catheter-related bacteremia.[43,85,86] Topical application of 2% mupirocin ointment to a tunneled HD catheter exit site after each HD session can increase infection-free days. Current recommendations are to apply either povidone-iodine antiseptic ointment or polysporin triple ointment (bacitracin/gramicidin/polymyxin B) to the exit site after each HD session. Long-term monitoring of infection rates of patients receiving HD with a catheter did not reveal an increase in antibiotic resistance with a once-a-week application of a topical polysporin triple ointment

to CVC exit sites.[87]

The Infectious Disease Society of America (IDSA) and KDOQI guidelines address catheter care and the diagnosis and management of catheter-related infections.[43,86] Peripheral blood draws, although recommended by IDSA, are often avoided in HD patients in order to protect potential or future HD vascular access sites. Blood cultures are generally obtained from the blood tubing connecting the catheter to the HD machine. A prospective study examined blood cultures (n=178) obtained from patients receiving HD suspected of a catheter-related blood stream infections (CRBSI). The blood cultures obtained from the HD circuit and venous catheter hub were the most sensitive, specific, and accurate for diagnosing CRBSI compared to blood cultures taken from a peripheral vein and either catheter hub or HD circuit.[88] A full-course of antimicrobial treatment is warranted if blood cultures are found to be positive.[43,86] Empiric therapy with coverage for both gram-positive and gram-negative bacteria should be initiated after the blood cultures are obtained. The incidence of MRSA bacteremia warrants initial treatment with vancomycin for gram-positive coverage and either an aminoglycoside or third-generation cephalosporin for gram-negative coverage.[43,86] Antimicrobial therapy de-escalation should occur once blood cultures identify an organism and antimicrobial susceptibility. For example, if the isolated organism is methicillin-sensitive *S. aureus*, administer IV cefazolin (20 mg/kg, rounded to the nearest 500 mg) after each dialysis session.[85,89] Antibiotic selection should be based on bacterial coverage and the ability to optimize pharmacokinetics by administering a dose either during the last 30 to 60 minutes of HD treatment or during the rinse bath. This method minimizes additional dosages between HD sessions. Examples of antimicrobial agents that meet these objectives are vancomycin, cefazolin, ceftazidime, daptomycin, and aminoglycosides.[86,89]

The IDSA guidelines recommend removal of an infected catheter if *S. aureus*, *Pseudomonas* species, or *Candida* species are the infectious cause. Although removal of the catheter is warranted, this is not always possible in patients receiving HD because of limited vascular access options. Retaining an infected catheter significantly increases a patient's risk of bacteremia recurrence after completing a course of antibiotics; therefore, other options need to be considered. Options such as replacing the catheter over a guidewire or using a catheter-lock solution in conjunction with IV antibiotics are alternatives.[43,86]

The catheter salvage success rate when a catheter-lock solution is used in addition to systemic antibiotics is highly variable and pathogen dependent.[43,86] A catheter-lock solution for a CRBSI with coagulase-negative staphylococcus or a

gram-negative source has had higher success rates when compared with *S. aureus* as the causative pathogen.[90] The IDSA guidelines recommend the use of catheter-lock solutions as adjunctive therapy after each dialysis session for 10 to 14 days in a patient whose catheter was not removed and bacteremia symptoms resolved in 2 to 3 days. The IDSA recommendations for antibiotic therapy are listed in **Table 62-7**.[43,86]

TABLE 62-7 Management of Hemodialysis Access Infection

I. Primary arteriovenous fistula
   A. Treat as subacute bacterial endocarditis for 6 weeks.
   B. Initial antibiotic choice should always cover gram-positive organisms (eg, vancomycin 20 mg/kg IV with serum concentration monitoring or cefazolin 20 mg/kg IV three times per week or after each dialysis session).
   C. Gram-negative coverage is indicated for patients with diabetes, human immunodeficiency virus infection, prosthetic valves, or those receiving immunosuppressive agents, gentamicin 2 mg/kg IV with serum concentration monitoring.

II. Synthetic arteriovenous grafts
   A. Local infection—empiric antibiotic coverage for gram-positive, gram-negative, and *Enterococcus* (eg, gentamicin plus vancomycin then individualized after culture results available). Continue for 2–4 weeks.
   B. Extensive infection—antibiotics as above plus total resection.
   C. If access is less than 1-month-old, antibiotics as above plus remove the graft.

III. Tunneled cuffed catheters (internal jugular, subclavian)
   A. Infection localized to catheter exit site.
      1. No drainage—topical antibiotics (eg, mupirocin ointment).
      2. Drainage present—gram-positive antibiotic coverage, vancomycin 20 mg/kg IV with serum concentration monitoring or cefazolin 20 mg/kg IV three times per week.
   B. Bacteremia with or without systemic signs or symptoms.
      1. Gram-positive antibiotic coverage as in III.A.2.
      2. If symptomatic at 36 hours, remove the catheter.
      3. If stable and asymptomatic, change catheter and provide culture-specific antibiotic coverage for a minimum of 3 weeks.

Source: Data from references 43 and 86.

Microbial colonization of a catheter could affect patency and a patient's access to dialytic treatment. An examination of the catheter-lock solutions, UFH 5,000 U/mL and tetra-sodium EDTA, found an increased rate of microbial colonization with UFH but the tetra-sodium EDTA solution had an increased rate of thrombosis.[91] Alternative solutions to UFH and tetra-sodium EDTA including

catheter-lock solutions containing ethanol 30% combined with sodium citrate 4% or ethanol 70% with UFH 2,000 U/mL have been effective at decreasing CRBSI and improving catheter survival.[92] A commercially available catheter-lock solution containing taurolidine, heparin, and calcium citrate is in clinical trials and may provide an option to maintain catheter patency.

Catheter-locking solutions have been utilized to prevent infection and thrombosis in HD catheters.[93] A meta-analysis of randomized control trials of catheter-related bacteremia and antimicrobial lock solutions identified eight studies with 829 patients and more than 90,100 catheter days. Overall analysis found that the use of an antimicrobial lock solution significantly reduced the risk of a catheter-related infection (relative risk [RR] 0.32; 95% confidence interval [CI] 0.10-0.42).[93] A comparison of UFH 1,000 U/mL to the combination solution of 4% sodium citrate with gentamicin 320 mcg/mL (mg/L; 669 µmol/L) as a catheter-lock solution significantly reduced the incidence of catheter-related bloodstream infections.[94] The value of catheter-lock solutions for treatment and prevention of catheter-related infections is increasingly becoming evident, but the possibility of antibiotic resistance with the wide use of antibiotics in catheter locks remains a concern. Gentamicin resistance to coagulase-negative *Staphylococcus* was reported in a retrospective study using routine post-HD administration of gentamicin (4 mg/mL) combined with UFH (5,000 U/mL) as a catheter-lock solution. Over the 4-year study, there were 80 CRBIs with 21 episodes (26%) of gentamicin resistance identified. The increase in gentamicin resistance led to a discontinuation of the gentamicin-heparin catheter-lock solutions.[95]

PERITONEAL DIALYSIS

Although the concept of peritoneal lavage has been described as far back as the 1700s, it wasn’t until the 1920s that PD was first employed as an acute treatment for uremia. It was used infrequently during subsequent years until the concept of PD as a chronic therapy for ESRD was proposed in the 1960s. Over the ensuing years, the number of patients receiving PD increased slowly until the early 1980s. At that time, several innovations in PD delivery systems were introduced, such as improved catheters and dialysate bags. These innovations led to improved outcomes, decreased morbidity, mortality, and a corresponding increase in the use of PD as a viable alternative to HD for the treatment of ESRD. However, the worldwide use of PD has declined over the past decade.[6] Some patients, such as those with more hemodynamic instability (eg,

hypotension) or significant residual renal function (RRF), and perhaps patients who desire to maintain a significant degree of self-care may be better suited to PD than to HD. Table 62-2 shows the advantages and disadvantages of PD.

Principles of Peritoneal Dialysis

5 The three basic components of HD—namely, a blood-filled compartment separated from a dialysate-filled compartment by a semipermeable membrane—are also present in PD.[96] In PD, the dialysate-filled compartment is the peritoneal cavity, into which dialysate is instilled via a peritoneal catheter that traverses the abdominal wall. The contiguous peritoneal membrane surrounds the peritoneal cavity. The cavity, which normally contains about 100 mL of lipid-rich lubricating fluid, can expand to a capacity of several liters. The peritoneal membrane that lines the cavity functions as the semipermeable membrane, across which diffusion and ultrafiltration occur. The peritoneal dialyzing membrane is comprised of a monocellular layer of peritoneal mesothelial cells, the basement membrane, and underlying connective and interstitial tissue. The peritoneal membrane has a total area that approximates body surface area (approximately 1–2 m^2). Blood vessels supplying and draining the abdominal viscera, musculature, and mesentery constitute the blood-filled compartment.

Unlike HD, the crucial components of PD cannot be manipulated to maximize solute and fluid removal. Because the blood is not in intimate contact with the dialysis membrane as it is in HD, metabolic waste products must travel a considerable distance to the dialysate-filled compartment. In addition, unlike HD, there is no easy method to regulate blood flow to the surface of the peritoneal membrane, nor is there a countercurrent flow of blood and dialysate to increase diffusion and ultrafiltration via changes in hydrostatic pressure. Similarly, there is no easy means available to manipulate the peritoneal membrane. Thus, the available means to enhance PD clearance involve alterations in dialysate volume, dwell time, and the number of exchanges per day. For these reasons, PD is a much-less-efficient process per unit time as compared with HD, and must, therefore, be a virtually continuous procedure to achieve acceptable goals for clearance of metabolic waste products.

Peritoneal Dialysis Access

Access to the peritoneal cavity is via the placement of an indwelling catheter. Many types are available and **Fig. 62-3** shows an example.[96] Most catheters are

manufactured from silastic, which is soft, flexible, and biocompatible. A typical adult catheter is 40 to 45 cm long, 20 to 22 cm of which is inside the peritoneal cavity. Placement of the catheter is such that the distal end lies low in a pelvic gutter. The center section of the catheter has one or two cuffs made of a porous material that is tunneled inside the anterior abdominal wall so that the cuffs provide mechanical support and stability to the catheter, serve as a mechanical barrier to skin organisms, and prevent their migration along the catheter into the peritoneal cavity. The cuffs are placed at different sites surrounding the abdominal rectus muscle. The remainder of the central section of the catheter is tunneled subcutaneously before exiting the abdominal surface, usually a few centimeters below and to one side of the umbilicus.

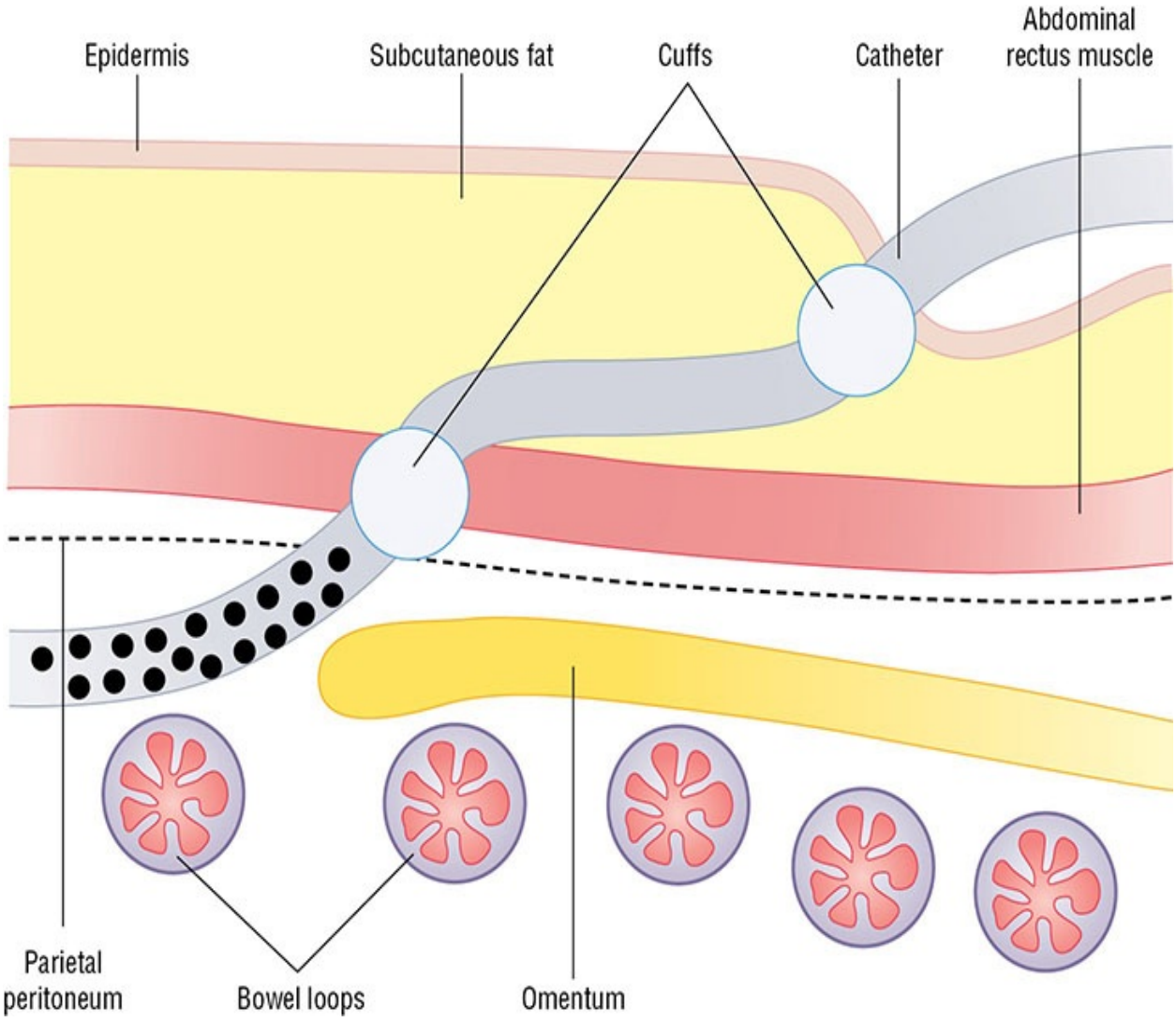


FIGURE 62-3 Diagram of the peritoneal dialysis catheter placement through the abdominal wall into the peritoneal cavity. *(Reprinted with permission from*

Reference 31.)

The placement of the catheter exit site is one of the factors related to the development or prevention of exit-site infections and peritonitis. The external section of most peritoneal catheters ends with a Luer-Lok connector, which can be connected to a variety of administration sets. These catheters can be used immediately if necessary, provided small initial volumes are instilled; however, a maturation period of 2 to 6 weeks is preferred.

Peritoneal Dialysis Procedures

6 Several variants of PD are clinically utilized in the United States. All variants of PD require the placement of a dialysis solution to dwell in the peritoneal cavity for some period, removing the spent dialysate, and then repeating the process. The prescribed dose of PD may be altered by changing the number of exchanges per day, by altering the volume of each exchange, or by altering the strength of dextrose or other osmotic agent in the dialysate for some or all exchanges. Increasing any one of these variables increases the effective osmotic gradient across the peritoneum, leading to increased ultrafiltration and diffusion (solute removal). If the dwell time is extended, equilibrium may be reached, after which time there will be no further water or solute removal. In fact, after a critical period, reverse water movement may occur.[96] In a basic continuous ambulatory peritoneal dialysis (CAPD) system, the patient or caregiver is manually responsible for performing the prescribed number of dialysate exchanges. The patient is connected to a bag of prewarmed peritoneal dialysate via the PD catheter, by a length of tubing called a transfer set. The most common transfer set used is the Y transfer set which consists of a Y-shaped piece of tubing that is attached at its stem to the patient's catheter, leaving the remaining two limbs of the Y attached to dialysate bags, one filled with fresh dialysate and the other empty. The spent dialysate from the previous dwell is drained into the empty bag, and the peritoneum is subsequently refilled from the bag containing fresh dialysate. The Y set is then disconnected and the bag containing the spent fluid and the empty bag that had contained fresh dialysate are detached and discarded. Typically a patient instills 2 to 3 L of dialysate three times during the day with each exchange lasting 4 to 6 hours, and then a single dialysate exchange overnight lasting 8 to 12 hours. At the end of the prescribed dwell period, a new Y set is attached and the process is repeated. The process of outflow, aseptic manipulation of the administration set and catheter, and inflow requires a total time of approximately 30 minutes.

Continuous ambulatory peritoneal dialysis involves performing the dialysate exchanges manually, whereas automated systems collectively termed automated peritoneal dialysis (APD) performs the exchanges with a device referred to as a cycler. APD systems are designed for patients who are unable or unwilling to perform the necessary aseptic manipulations, and for those who require more dialysis. The device is set up in the evening, and the patient attaches the peritoneal catheter to it at bedtime. The machine performs several short-dwell exchanges (usually 1–2 hours) during the night. This permits a long cycle-free daytime dwell of up to 12 to 14 hours. Typical APD regimens involve total 24-hour exchanges of approximately 12 L, which include one or more daytime instillations and dwell periods.[97] This type of regimen is referred to as APD with a "wet" day. The APD variant, nightly intermittent PD, has a similar theme, except that the peritoneal cavity tends to be dialysate-free during the day. This type of regimen is frequently referred to as APD with a "dry" day. A number of variants exist and depend largely on equipment availability, patient and prescriber preference, and whether the patient retains any RRF, which influences the quantity of dialysis prescribed.

The APD systems include continuous cycling PD, tidal PD, and nightly intermittent PD. The prototypic form of APD is usually a hybrid between CAPD and continuous cycling PD, in which some of the daily exchanges (usually the overnight exchanges) are completed using an automated device. Recent advances in PD procedures involve using continuous flow peritoneal dialysate.[98] This technique maintains a fixed intraperitoneal volume and rapid, continuous movement of dialysate into and out of the peritoneal cavity. To accomplish this, two PD catheters (an inlet and outlet catheter) and a means of generating a large volume of sterile dialysate are required. Dialysate is generated via conventional HD equipment or sorbent technology. In continuous flow peritoneal dialysate, clearance of small solutes is three to eight times greater than with APD, and approximates daily HD. Potential applications of continuous flow peritoneal dialysate include daily home dialysis, treatment of acute kidney injury in the intensive care unit, and ultrafiltration of ascites.

Peritoneal Dialysis Solutions

All forms of PD use dialysate solutions, which are commercially available in volumes of 1 to 3 L in flexible polyvinyl chloride plastic bags. It is beyond the scope of this chapter to exhaustively review all the options, but the most commonly used solutions that are commercially available contain glucose or icodextrin with varying concentrations of electrolytes, such as sodium (132

mEq/L [mmol/L]), chloride (96 mEq/L [mmol/L]), calcium (2.5–3.5 mEq/L [1.25–1.75 mmol/L]), magnesium (0.5 mEq/L [0.25 mmol/L]), and lactate (40 mEq/L [mmol/L]). These solutions may contain dextrose (1.5%, 2.5%, 3.86%, or 4.25%) or icodextrin (a glucose polymer) at a concentration of 7.5%. The dextrose solutions are hyperosmolar (osmolarity ranges from 345 to 484 mOsm/L) and induce ultrafiltration (removal of free water) by crystalline osmosis. Dextrose is not the ideal osmotic agent for peritoneal dialysate because these solutions are not biocompatible with peritoneal mesothelial cells or with peritoneal leukocytes. The cytotoxic effects on these cells are mediated by the osmolar load and the low pH of the solutions, as well as the presence of glucose degradation products formed during heat sterilization of these products. Icodextrin PD solution contains icodextrin, a starch-derived glucose polymer. It has an osmolality of 282 to 286 mOsm/kg (mmol/kg), which is isoosmolar with serum. Icodextrin produces prolonged ultrafiltration by a mechanism resembling colloid osmosis resulting in ultrafiltration volumes similar to those with 4.25% dextrose. Icodextrin may have fewer of the metabolic effects associated with dextrose, such as hyperglycemia and weight gain. It is indicated for use during the long (8–16 hours) dwell of a single daily exchange in CAPD and APD patients. Lower glucose degradation product dialysate solutions are also available with similar solute concentrations, but with pH of 7.3.[96,78] These newer, biocompatible dialysate solutions are described as less harmful to the peritoneal membrane and preserve RRF to a greater extent than currently available standard solutions.[99,100] Preservation of RRF in PD and HD patients is important as it has been shown to decrease mortality and increase the time to the first episode of peritonitis. However, the putative benefits of the biocompatible dialysate solutions have not been completely borne out: their use has not consistently slowed the rate of decline in glomerular filtration rate as compared to standard solutions, although the incidence of peritonitis has been lower.[101]

Adequacy of Peritoneal Dialysis

The adequacy of PD is determined by clinical assessment, solute clearance determination, and fluid removal. As in HD, the clearance of urea can be quantified by calculating *Kt/V*. The calculations determine a daily *Kt/V*, which is then converted into a weekly value that is relevant to PD patients.

PD adequacy is a major issue that has received considerable attention. The most recent KDOQI guidelines recommend that patients on PD have a total *Kt/V* of at least 1.7 per week, including both PD *Kt/V and* residual kidney *Kt/V* .[102] It

is important to note that RRF may provide a significant component of the total *Kt/V*. Patients may commence PD with a residual CL_{cr} of approximately 9 to 12 mL/min (0.15–0.200 mL/s), which contributes a renal *Kt/V* of 0.2 to 0.4. Over a period of 1 to 2 years, if RRF progressively deteriorates, the total *Kt/V* will progressively diminish unless PD *Kt/V* is increased (by increasing the prescribed dose of PD) to compensate for the reduced renal *Kt/V*.

For patients producing less than 100 mL urine per day, the weekly *Kt/V* dose of 1.7 must be provided entirely by peritoneal clearance. For patients producing greater than 100 mL urine per day, combined renal and peritoneal urea clearances must exceed the weekly *Kt/V* dose of 1.7.[102] The weekly *Kt/V* dose should be measured within the first month of PD initiation and at least once every 4 months thereafter. It is imperative to detect subtle decreases in RRF along with poor adherence to make necessary alterations to the prescribed PD dose to attain adequate clearance of waste products.

The KDOQI guidelines also stress the importance of preserving RRF in PD patients because it is associated with decreased mortality. Typical measures to preserve RRF include preferential use of ACE-Is or ARBs, regardless of blood pressure, and avoidance of medications or procedures that are associated with insults to the kidney (eg, nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, aminoglycosides, intravenous iodinated radiocontrast dyes, withdrawal of immunosuppressant therapies from a transplanted kidney, hypovolemia, urinary tract obstruction, and hypercalcemia).[102]

Complications of Peritoneal Dialysis

Mechanical, medical, and infectious problems complicate PD therapy. Mechanical complications include kinking of the catheter and inflow and outflow obstruction; excessive catheter motion at the exit site, leading to induration and possible infection and aggravation of tissues; pain from impingement of the catheter tip on the viscera; or inflow pain resulting from a jet effect of too rapid dialysate inflow.

Table 62-8 lists the numerous medical complications of PD. An average PD patient absorbs up to 60% of the dextrose in each exchange. This continuous supply of calories leads to increased adipose tissue deposition, decreased appetite, malnutrition, and altered requirements for insulin in diabetic patients. Fibrin formation in dialysate is common and can lead to obstruction of catheter outflow. Infectious complications of PD are a major cause of morbidity and mortality and are the leading cause of technique failure and transfer from PD to

HD. The two predominant infectious complications are peritonitis and catheter-related infections, which include both exit-site and tunnel infections.

TABLE 62-8 Medical Complications of Peritoneal Dialysis

Cause	Complication	Treatment
Glucose load	Exacerbation of diabetes mellitus	IP insulin
Fluid overload	Exacerbation of heart failure Edema Pulmonary congestion	Increase ultrafiltration Diuretics, if the patient has residual renal function
Electrolyte abnormalities	Hypercalcemia/ Hypocalcemia	Alter dialysate calcium content
PD additives	Chemical peritonitis	Discontinue PD additives
Malnutrition	Albumin loss Loss of amino acids Muscle wasting Increased adipose tissue	Dietary changes Parenteral nutrition Discontinue PD
Unknown	Fibrin formation in dialysate	IP heparin

IP, intraperitoneal; PD, peritoneal dialysis.

Peritonitis

7 The incidence of peritonitis is influenced by connector technology, by the composition of patient populations, and by the use of APD versus CAPD. The incidence of peritonitis reported by most dialysis centers in the United States is about 1 episode every 24 patient-months, although it may be as low as 1 episode every 60 patient-months.[103] Within 1 year of starting CAPD, 40% to 60% of patients develop their first episode of peritonitis (although the incidence is significantly lower in APD patients).

Peritonitis is a major cause of catheter loss in PD patients. The clinical presentation and diagnosis is shown in **Table 62-9**. A statistically significant correlation between infectious complications and death rates has been reported: patients who had more than 1 peritonitis episode per year, 0.5 to 1 episode per year, or less than 0.5 episode per year, 50% died after 3, 4, and 5 years of therapy, respectively. It is important to note that these relationships are not necessarily cause and effect, as many of these patients succumb to cardiovascular events.[104]

TABLE 62-9 Clinical Presentation and Diagnosis of Peritoneal Dialysis-Related Peritonitis

General
- Patients generally present with abdominal pain and cloudy effluent

Symptoms
- The patient may complain of abdominal tenderness, abdominal pain, fever, nausea and vomiting, and chills

Signs
- Cloudy dialysate effluent may be observed
- Temperature may or may not be elevated

Laboratory Tests
- Dialysate white blood cell count >100/mm³ (0.1×10^9/L), of which at least 50% are polymorphonuclear neutrophils
- Gram stain of a centrifuged dialysate specimen

Other Diagnostic Tests
- Culture and sensitivity of dialysate should be obtained

Peritonitis has several imprecise definitions, but guidelines suggest that an elevated dialysate white blood cell count of greater than 100 per microliter (0.1×10^9/L) with at least 50% polymorphonuclear neutrophils indicates the presence of inflammation, of which peritonitis is the most likely cause.[105] A patient who presents with abdominal pain and a cloudy effluent is usually given a provisional diagnosis of peritonitis. Inherent in this definition is a number of false-positive and false-negative diagnoses, because a small percentage of patients with culture-proven peritonitis will have clear dialysate, and some patients, such as menstruating females, may have cloudy PD effluent without clinical infection. Sterile culture peritonitis remains problematic; it is defined as an episode in which there is clinical suspicion of peritonitis, but for which the culture of the dialysate reveals no organism. There are several postulates for the high incidence (up to 20% of episodes) of culture-negative peritonitis. Many peritonitis-producing organisms are slime producers and may adhere to the peritoneal membrane or to the catheter surface and may be protected from exogenous antibiotics. Sufficient numbers of these bacteria may proliferate to cause peritoneal membrane inflammation and clinical peritonitis, but an inadequate number may seed into the peritoneal cavity to be recovered by conventional microbiologic techniques. In addition, free-floating planktonic bacteria may be rapidly phagocytosed by peritoneal white blood cells, thereby rendering them unavailable for culture.[106]

Contemporary methods have increased the recovery rate of organisms and

decreased the culture-negative rate. Centrifugation is currently recommended as the optimum culture method. Centrifugation of a large volume of dialysate (50 mL), resuspension of the sediment in 3 to 5 mL of sterile saline, and subsequent inoculation in culture media produce a culture-negative rate less than 5%. If centrifuge equipment is not available, blood culture bottles can be directly injected with 5 to 10 mL of dialysate effluent. However, this method results in a culture-negative rate of up to 20%.[105]

The majority of infections are caused by gram-positive bacteria, of which *Staphylococcus epidermidis* is the predominant organism. There is no single predominant gram-negative organism. Together, gram-positive and gram-negative organisms account for 80% to 90% of all episodes of peritonitis, and constitute the spectrum against which initial empiric therapy is directed.[107]

Catheter-Related Infections

A catheter-related infection in patients receiving PD includes both exit-site infection (ESI) and tunneled infection. Patients with previous infections tend to have a higher subsequent incidence. A case-controlled study found that 69.8% of patients receiving PD had at least one ESI over a 3-year period and are more likely to develop peritonitis (64%) compared to patients without an ESI.[108] The majority of ESIs are caused by *S. aureus*. In contrast to peritonitis, *S. epidermidis* accounts for less than 20% of ESIs. Although gram-negative organisms, such as *Pseudomonas*, are less common, they can result in significant morbidity. The diagnostic characteristics of these infections are somewhat vague but generally include the presence of purulent drainage, with or without erythema at the catheter exit-site. The risk of ESIs is increased several-fold in patients who are nasal carriers of *S. aureus*.[109]

Management

The management of PD-related complications is discussed in this section.

Peritonitis

The International Society of Peritoneal Dialysis (ISPD) updated the Peritoneal Dialysis-Related Infections recommendations in 2016, which provide guidelines for treatments for peritonitis and tunneled and exit-site infections.[105] These PD-related infections are associated with dialysis modality treatment failures and substantial morbidity and mortality; therefore, appropriate pharmacotherapy

treatment is essential (**Fig. 62-4**). The ISPD guidelines specifically address the importance of peritonitis prevention, dialysis center antibiotic selection, and intraperitoneal (IP) antibiotic dosing and treatment duration for peritonitis.[105] In 2017, ISPD published catheter-related infection recommendations to prevent ESIs and described routine catheter care for PD patients.[107] Both guidelines provide a summary of best practices based on available evidence or consensus in areas where evidence exists.

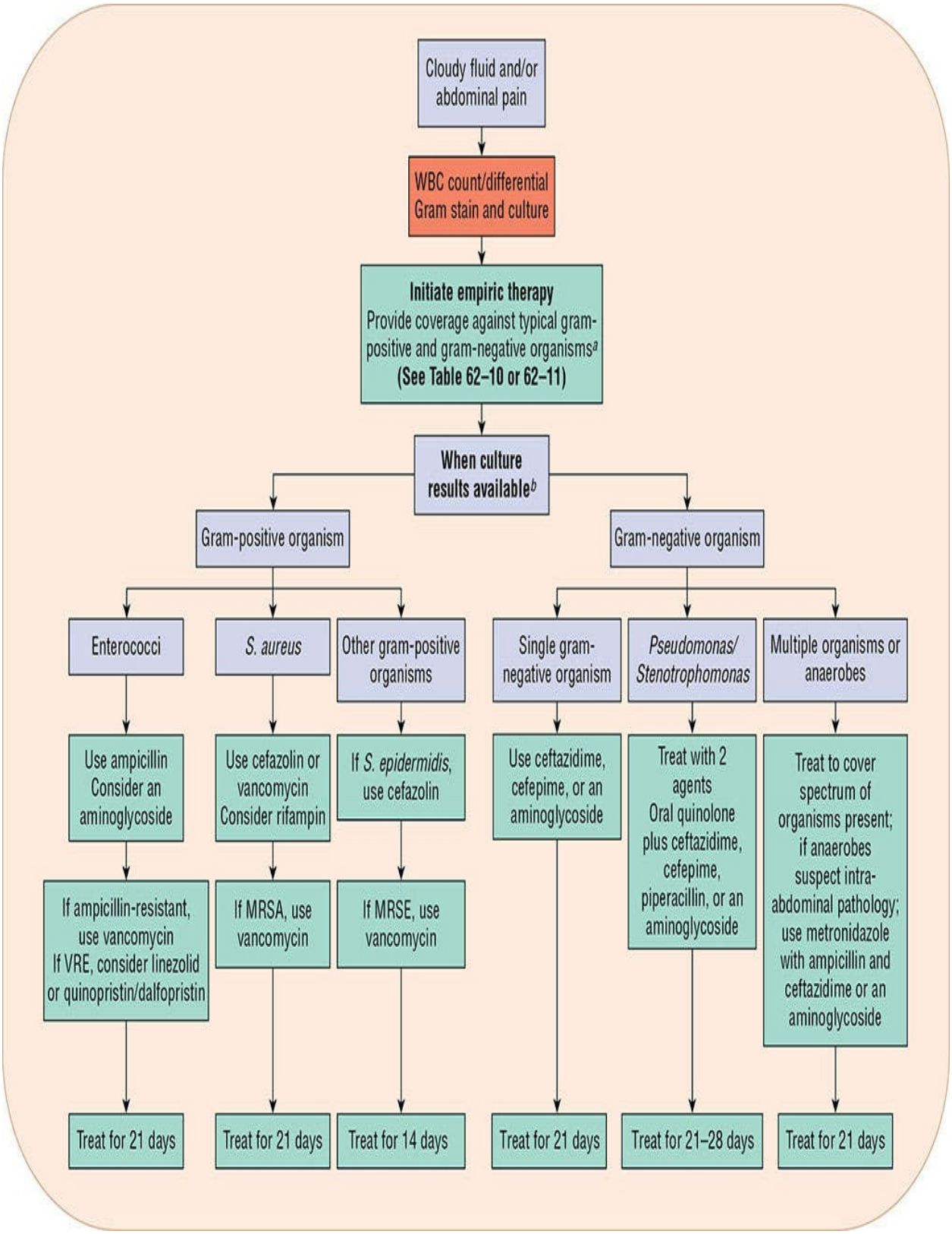


FIGURE 62-4 Pharmacotherapy recommendations for the treatment of bacterial peritonitis in peritoneal dialysis patients.*a* Choice of empiric treatment should be

made based on the dialysis center's and the patient's history of infecting organisms and their sensitivities. [b]Final choice of therapy should always be guided by culture and sensitivity results. (MRSA, methicillin-resistant *Staphylococcus aureus;* MRSE, methicillin-resistant *Staphylococcus epidermidis; S. aureus, Staphylococcus aureus; S. epidermidis, Staphylococcus epidermidis;* VRE, vancomycin-resistant enterococci; WBC, white blood cell.)

The preferred delivery route for antibiotics is IP over IV therapy for the treatment of peritonitis. Antimicrobial dosing recommendations provided in the ISPD guidelines for CAPD dosing distinguish between intermittent (one exchange per day) and continuous therapy (all exchanges). The 2016 guidelines no longer provide APD IP drug dosing recommendations due to a "substantial knowledge gap" within this treatment area. The new guidelines have provided oral and IV dosing recommendations that can be dosed either independent of or in conjunction with IP dosing.[105,107]

Following a single IP antibiotic dose, the drug concentrations achieved in dialysate and serum differ between intermittent and continuous methods. Intermittent IP therapy necessitates that a sufficient amount of drug transfers from the peritoneal cavity to the systemic circulation, thus allowing drug to diffuse back into the peritoneum during drug-free dialysate dwell time(s). Therefore, once daily dosing requires drug(s) be added to the exchange with the longest dwell time (at least 6 hours) to ensure maximum systemic exposure.

Continuous dosing recommendations may require a loading dose with the very first IP dose and a maintenance dose for each subsequent exchange. Vancomycin, aminoglycosides, and cephalosporins generally are administered by either dosing method. It is recommended that a continuous dosing method be used for penicillins and fluoroquinolones. No matter which CAPD drug dosing method is used, the goal is to deliver and maintain adequate peritoneum drug concentrations. Intermittent or continuous dosing is effective for CAPD patients but IP dosing for APD patients may require a different dosing schedule. The rapid overnight dialysate exchanges with APD will increase solute clearance over a short time period. This appears to be particularly important for first-generation cephalosporin agents. The ISPD guidelines recommend continuous dosing of a first-generation cephalosporin because of concerns over inadequate IP drug concentration during the shorter APD dialysate dwells. Another consideration would be to switch a patient to a CAPD regimen until treatment for peritonitis is completed. If a patient is not a good candidate for CAPD, the cycler can be reset to provide a longer dwell period or slower exchange rate to

allow for drug transfer during APD.[105] Intermittent dosing of first-generation cephalosporin for APD does not sustain adequate drug concentrations for most organisms; therefore, continuous dosing may be more effective in providing better drug coverage. Oral ciprofloxacin attains adequate IP drug concentrations in patients receiving APD and is a therapeutic option if the pathogen is susceptible. With regard to RRF, in patients with substantial residual renal function, previous ISPD guidelines recommended dose adjustments for antibiotics with renal elimination. Recent studies suggest these dosing adjustments are not necessary to maintain adequate drug concentrations, resulting in ISPD removing the recommendation for dose adjustments from the 2016 guidelines. The ISPD dosing recommendations for IP antibiotics in CAPD and systemic therapy are shown in **Tables 62-10** and **62-11**, respectively.[105]

TABLE 62-10 Intraperitoneal Antibiotic Dosing Recommendations for Continuous Ambulatory Peritoneal Dialysis Patients

Drug	Intermittent (one exchange daily)	Continuous (all exchanges)
Aminoglycosides		
Amikacin	2 mg/kg	LD 25 mg/L; MD 12 mg/L
Gentamicin	0.6 mg/kg	LD 8 mg/L; MD 4 mg/L
Netilmicin	0.6 mg/kg	MD 10 mg/L
Tobramycin	0.6 mg/kg	LD 3 mg/kg; MD 0.3 mg/kg
Cephalosporins		
Cefazolin	15–20 mg/kg	LD 500 mg/L ; MD 125 mg/L
Cefepime	1,000 mg	LD 250–500 mg/L; MD 100–125 mg/L
Cefoperazone	ND	LD 500 mg/L ; MD 62.5–125 mg/L
Cefotaxime	500–1,000 mg	ND
Ceftazidime	1,000–1,500 mg	LD 500 mg/L; MD 125 mg/L
Ceftriaxone	1,000 mg	ND
Penicillins		
Amoxocillin	ND	MD 150 mg/L
Ampicillin	ND	MD 125 mg/L
Penicillin G	ND	LD 50,000 units/L; MD 25,000 units/L
Quinolones		
Ciprofloxacin	ND	MD 50 mg/L
Others		
Vancomycin	15–30 mg/kg Q5-7d[1]	LD 30 mg/kg; MD 1.5 mg/kg/bag
Daptomycin	ND	LD 100 mg/L; MD 20 mg/L
Aztreonam	2 g	LD 1,000 mg/L; MD 250 mg/L
Teicoplanin	15 mg/kg q 5 days	LD 400 mg/bag; MD 20mg/bag
Linezolid	ND	Oral 200–300 mg daily
Clindamycin	ND	600 mg/bag
Polymixin B	ND	MD 300,000 Unit (30 mg)/bag
Meropenem	1 gram	ND
Antifungals		
Fluconazole	200 mg IP every 24–48 hours	ND
Voriconzaole	2.5 mg/kg IP	ND
Combinations		
Ampicillin/sulbactam	2 gram/1 gram q 12 h	LD 750 mg/L/100 mg/L, MD 100 mg/L
Pipercillin/tazobactam	ND	LD 4 g/0.5 g; MD 1 g/0.125 g
Imipenem/cilastatin	500 mg in alternate exchanges	LD 250 mg/L, MD 50 mg/L
Quinupristin/dalfopristin[2]	25 mg/L in alternate exchanges[2]	ND

[1]Supplemental doses may be required for APD patients.

[2]Given in conjunction with 500 mg intravenous twice daily.

LD, loading dose in mg; MD, maintenance dose in mg; NA, not applicable; ND, no data.

Modified from Reference 105.

TABLE 62-11 Systemic Antibiotic Dosing Recommendations for Treatment of Peritonitis

Drug	Dosing
Ciprofloxacin	Oral 250 mg twice daily
Levofloxacin	Oral 250 mg daily
Moxifloxacin	Oral 400 mg daily
Ertapenem	IV 500 mg daily
Linezolid	IV or oral 600 mg twice daily
Rifampicin	450 mg daily for body weight ≤50 kg, 600 mg daily for body weight ≥50 kg
Trimethoprim/ Sulfamethoxazole	Oral 160 mg/800 mg twice daily
Amphotericin	IV test dose 1 mg; starting dose 0.1 mg/kg/ day over 6 hours increase to target dose 0.75–1.0 mg/kg/day
Caspofungin	IV 70 mg load, then 50 mg daily
Fluconazole	Oral 200 mg loading, then 50 mg daily
Flucytosine	Oral 1 g daily
Posaconazole	IV 400 mg every 12 hours
Voriconazole	Oral 200 mg every 12 hours

Modified from Reference 105.

Initial empiric therapy for peritonitis, regardless of whether a Gram stain was performed or organisms were identified, should include agents effective against both gram-positive and gram-negative organisms. Antibiotic selection should be based on a dialysis center's antibiogram or resistance patterns, a history of the patient's infections, and the organism's antibiotic sensitivity profile. In many cases, a first-generation cephalosporin such as cefazolin in combination with a second drug that provides broader gram-negative coverage, such as ceftazidime, cefepime, or an aminoglycoside, will prove suitable. Patients with documented allergy to cephalosporin antibiotics can be treated with vancomycin and an aminoglycoside. High rates of methicillin resistance have been reported by many dialysis centers, and vancomycin should be used as first-line therapy against gram-positive organisms for patients treated at these centers. Monotherapy with agents providing both gram-positive and gram-negative coverage is an alternative option. Both imipenem-cilastin and cefepime are effective in treating

CAPD-related peritonitis.[110]

After culture and sensitivity results are obtained, antibiotic therapy should be adjusted appropriately (see Fig. 62-4). Tables 62-10 and 62-11 list doses for antibiotics. Treatment should be continued for 14 to 21 days. If the patient does not show signs of clinical improvement within 72 hours after antibiotic treatment is initiated, the culture should be repeated and the patient reevaluated. If the peritoneal dialysate white blood cell count remains high after 4 days of appropriate antibiotic therapy, clinicians should consider removing the peritoneal catheter, starting IV antibiotics, and initiating HD for dialytic maintenance therapy.

Fungal peritonitis is associated with a poor prognosis and high morbidity and mortality. One problem with prospective assessment of antifungal regimens is the infrequency with which these infections occur. This makes it difficult to design and implement comparative studies. Most literature about antifungal treatment is therefore retrospective or limited to reports of local experience. As a result, the ISPD recommendations for treatment of fungal peritonitis are somewhat vague and treatment should be based on culture and sensitivity results. However, one area that has been clarified is the question as to whether the PD catheter should be removed. The ISPD recommendations are to remove the catheter immediately after identifying fungi. If the Gram stain indicates the presence of yeast, treatment may be initiated with IV amphotericin B and oral flucytosine. Once culture and sensitivity results are available, fluconazole, caspofungin, or voriconazole may replace amphotericin B. Guidelines recommend amphotericin B be administered IV and not IP as this agent can cause chemical peritonitis and pain, and has poor peritoneal bioavailability. Treatment with an oral agent continues for an additional 10 days after catheter removal. It remains unclear whether there is any benefit from fungal prophylaxis. Recommendations are also provided for the treatment of mycobacterial, or tuberculous, peritonitis. Although this infection is a rare complication, it can be difficult to diagnose, and treatment requires multiple drugs.

Catheter-Site Infections

Topical antibiotics and disinfectants appear to be effective agents for the prevention of ESIs.[111] Gram-positive organisms should be treated with oral penicillinase-resistant penicillin or a first-generation cephalosporin such as cephalexin (**Fig. 62-5**). Rifampin may be added, if necessary, in slowly resolving or particularly severe *S. aureus* infections. Vancomycin should be avoided in

routine or empiric treatment of gram-positive catheter-related infections, but will be necessary for methicillin-resistant *S. aureus*. Treatment for gram-negative organisms consists of oral quinolones if the organism is susceptible. The effectiveness of oral quinolones may be diminished owing to chelation interactions with drugs containing divalent and trivalent ions, which are commonly taken by dialysis patients. Administration of quinolones should occur at least 2 hours prior to these drugs. In cases where *Pseudomonas aeruginosa* is the pathogen, a quinolone should not be used as monotherapy. Options for a second anti-pseudomonal drug include the IP administration of an aminoglycoside, ceftazidime, cefepime, piperacillin, imipenem-cilastatin, or meropenem. In all cases, antibiotics should be continued until the exit site appears normal; 2 to 3 weeks of therapy may be necessary. A patient with a catheter-related infection that progresses to peritonitis will usually require catheter removal.[105,107]

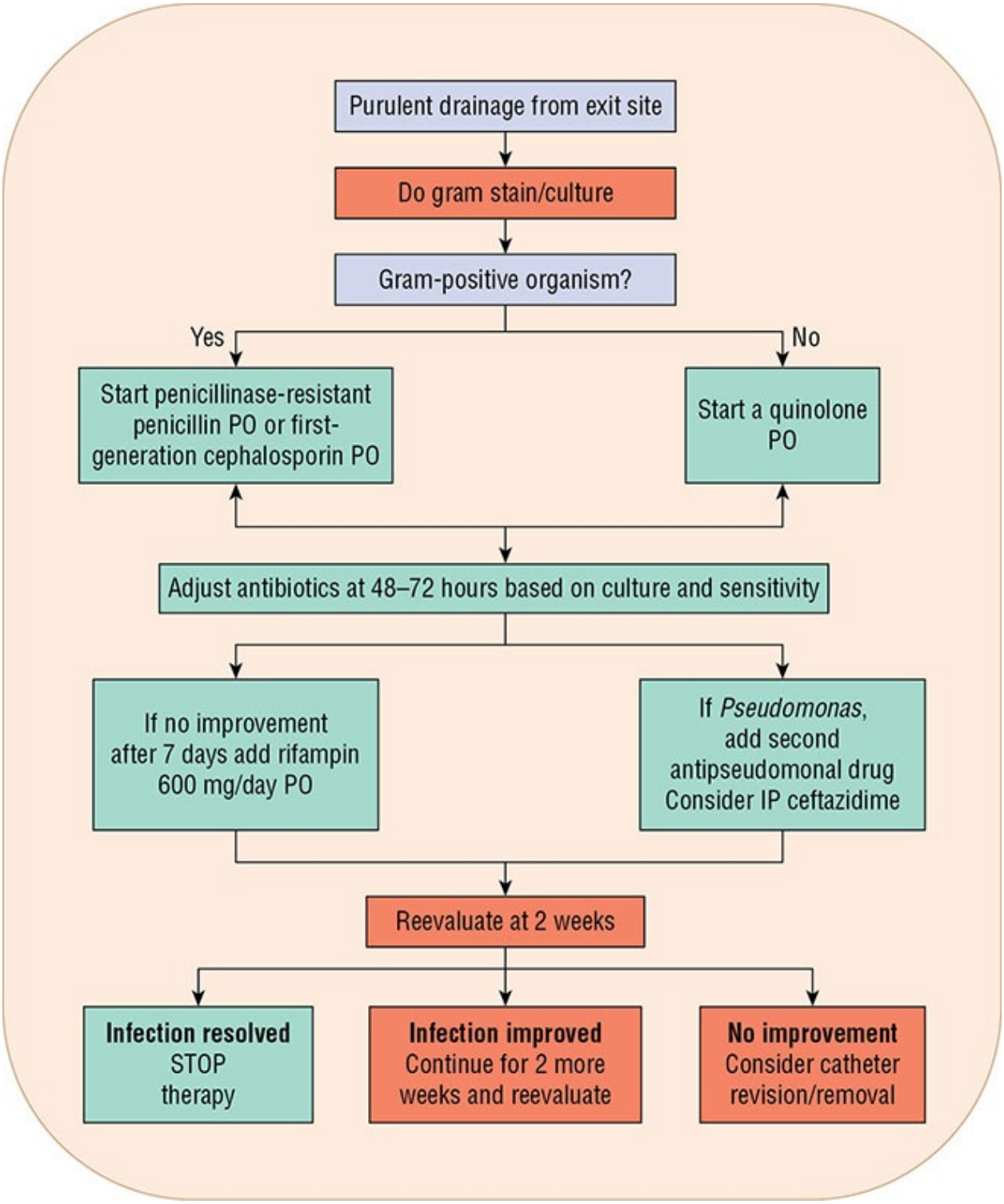


FIGURE 62-5 Management strategy of exit-site infections for peritoneal dialysis patients. (IP, intraperitoneal; PO, orally.) (*Data from Reference 112.*)

Prevention of Peritonitis and Catheter Exit-Site

Infections

8 Attempts to prevent peritonitis and catheter-related infections have included refinement of connector system technology (Luer-Lok connectors), enhanced patient training techniques, and the use of prophylactic antibiotic regimens and vaccines. Several studies have examined the impact of antibacterial agents such as prophylaxis against both peritonitis and tunnel-related infections. Intermittent rifampin 300 mg orally twice a day for 5 days, repeated every 3 months, appears to decrease the number of catheter-related infections, but not the incidence of peritonitis. The efficacy of other antibiotic prophylaxis for peritonitis and catheter-related infections is limited. Long-term, extended-duration prophylaxis with penicillins or cephalosporins is not effective.[105,107]

Nasal carriage of *S. aureus* is associated with an increased risk of catheter-related infections and peritonitis.[105,107] In addition, diabetic patients and those on immunosuppressive therapy are at increased risk for *S. aureus* catheter infections. Prophylaxis with intranasal mupirocin (twice daily for 5–7 days every month), mupirocin (daily) at the exit site, or oral rifampin can effectively reduce *S. aureus* ESIs. Because of the minimal toxicity of mupirocin and the risk of rifampin resistance, mupirocin regimens are preferred.[105,107] However, it is important to note that *S. aureus* isolates with a high degree of resistance to mupirocin have been isolated from PD patients using prophylactic mupirocin at the peritoneal catheter exit-site. A recent study did not observe resistance patterns with the use of mupirocin. Patients in this study applied mupirocin to the exit site either once or thrice weekly. After 3 years, ESIs and peritonitis rates were significantly lower in the thrice-weekly application group.[113] In addition, gentamicin cream applied daily to the exit site has been found to effectively reduce both *S. aureus* and *P. aeruginosa* ESI.[105,107] However, a comparison of mupirocin 2% and gentamicin 0.1% creams for exit-site prophylaxis noted a decrease in gentamicin susceptibility patterns for *Enterobacteriaceae* (12%) and *Pseudomonas* (14%).[114]

A double-blinded, randomized controlled trial compared the use of the topical ointments mupirocin to polysporin triple (P^3; bacitracin, gramicidin and polymixin B) in PD patients ($n = 201$) for the prevention of PD-related infections. Patients applied the ointment to the exit site with each dressing change and were followed for up to 18 months. No significant difference was found between groups for time to first PD-related infections ($P = 0.41$) for either agent but a significant increase in fungal infections was observed in the P^3 versus mupirocin group (7 vs 0; $P = 0.01$). The authors concluded that the use of

P^3 for PD-related infection prophylaxis was not superior to mupirocin and may increase the risk of fungal infections.[115]

The use of polyhexanide was compared to povidone-iodine to prevent ESIs in PD patients in a single-center prospective open label study (n = 46). After 12 months, there was a lower rate of overall infections (P = 0.037) and exit-site infections (P = 0.032) with use of polyhexanide compared to povidone-iodine. The infection source in the polyhexanide group was identified as *P. aeruginosa* (n = 3), but in the povidone-iodine group (n = 9) three sources were identified: *S. aureus* (n = 6), *Corynebacterium jeikeium* (n = 2), *P. aeruginosa* (n = 1). During the study, no infected catheters required removal.[116]

A multicenter open label trial to assess daily application at the exit site of antibacterial honey compared to standard care in PD patients (n = 371). Time to first peritonitis (P = 0.97) and time to first exit-site infection (P = 0.24) were not different between groups but the honey group reported a higher rate of infection in patients with diabetes (*HR* 1.85 [1.05–3.24]; P = 0.03). Also, there was a higher rate of study withdrawal and skin rash in the honey group. The authors concluded that topical use of honey could not be recommended as routine therapy in PD patients.[117] These findings differ from previous smaller studies that examine the use of topical honey to prevent catheter-related infections, which found medical-grade *Leptospermum* honey to be as effective as mupirocin in reducing catheter infections.[118]

CONCLUSION

Because of the limitation of available kidneys for transplantation, HD and PD remain the most widely available and commonly used ESRD treatments. Despite continual advances in dialysis and transplantation, kidney disease is associated with significant morbidity and mortality. Given the lack of a true cure for kidney disease, emphasis has been placed on the prevention and early detection of kidney disease. Goals set by the KDOQI, the Healthy People 2020 initiative, and the Centers for Medicare and Medicaid Services' CPM Project provide guidance and direction for all healthcare practitioners. In fact, there have been significant reductions in the incidence rate of ESRD, enhanced timing and selection of the preferred access placement, and mortality and morbidity.[119,120] For patients with ESRD, a focus on quality of life and rehabilitation is now a valuable and viable goal toward which the nephrology community should direct its research resources. Several links to patient-related videos that discuss CKD patient experiences are presented in **Table 62-12**. Although prevention of ESRD is the

primary goal for clinicians and adequate access to renal transplantation is secondary, dialysis will likely be a part of the treatment paradigm for ESRD for many years to come.

TABLE 62-12 Patient-Related Videos Relative to Dialysis Procedures and Therapies

Source	Web site (accessed 6/18/2018)
Davita Inc.	http://www.davita.com/videos/
NxStage Medical, Inc.	http://www.nxstage.com/homehemodialysis/video-podcasts/patient-training
Fresenius Medical Care	http://www.ultracare-dialysis.com/Header1/LinksResources/VideoLibrary.aspx
National Kidney Foundation	http://www.youtube.com/watch?v=NHS0oyHR4vI&feature=plcp

Postclass Engaged Learning Activity

Conduct a literature search and identify a manuscript that has been published in the past 12 months related to the pharmacotherapy of complications related to hemodialysis. Write a brief summary about the complication that the medication is treating, the medication's intended mechanism of action, the benefits of the medication relative to another treatment or no treatment, and the potential adverse effects related to the medication for treating this condition. This activity is intended to build your experience with accessing the primary biomedical literature and identifying relevant reports of drugs used to treat hemodialysis-related complications.

ABBREVIATIONS

APD	automated peritoneal dialysis
AV	arteriovenous
CAPD	continuous ambulatory peritoneal dialysis
CL_{cr}	creatinine clearance
CPM	clinical performance measures
DHA	docosahexaenoic acid
eGFR	estimated glomerular filtration rate
EPA	eicosapentaenoic acid
ESRD	end-stage renal disease
GFR	glomerular filtration rate
HD	hemodialysis
HDF	hemodiafiltration
IDH	intradialytic hypotension
IDSA	Infectious Disease Society of America
IP	intraperitoneal
ISPD	The International Society of Peritoneal Dialysis
KDIGO	Kidney Diseases: Improving Global Outcomes
NKF-KDOQI	National Kidney Foundation's Kidney Disease/ Dialysis Outcome Quality Initiative
PD	peritoneal dialysis
RRF	residual renal function
UFH	unfractionated heparin
URR	urea reduction ratio
USRDS	United States Renal Data System

REFERENCES

1. U.S. Renal Data System 2017 Annual Data Report: Epidemiology of Kidney Disease in the United States. Bethesda, MD: National Institutes of Health, National Institutes of Diabetes and Digestive and Kidney Diseases; 2017.
2. KDIGO clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Kidney Int Suppl* 2013;3:1–150.
3. National Kidney Foundation KDOQI clinical practice guideline for hemodialysis adequacy. *Am J Kidney Dis* 2015;66:884–930.
4. Yeun JY, Ornt DB, Depner TA. Hemodialysis. In: Skorecki K, Chertow GM, Marsden PA, Taal MW, Yu ASL, eds. *Brenner & Rector's The*

Kidney. 10th ed. Philadelphia: Elsevier; 2016;2294–2346.

5. Andrassy KM. Comments on “KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease”. *Kidney Int*. 2013;84:622–623.
6. Khawar O, Kalantar-Zadeh K, Lo WK, et al. Is the declining use of long-term peritoneal dialysis justified by outcome data? *Clin J Am Soc Nephrol* 2007;2:1317–1328.
7. Sinnakirouchenan R, Holley JL. Peritoneal dialysis versus hemodialysis: Risks, benefits, and access issues. *Adv Chronic Kidney Dis* 2011;18:428–432.
8. Miskulin DC, Meyer KB, Athienites NV, et al. Comorbidity and other factors associated with modality selection in incident dialysis patients: The CHOICE Study. Choices for Healthy Outcomes in Caring for End-Stage Renal Disease. *Am J Kidney Dis* 2002;39:324–336.
9. Himmelfarb J, Ikizler TA. Hemodialysis. *N Engl J Med* 2010;363:1833–1845.
10. Hayashi R, Huang E, Nissenson AR. Vascular access for hemodialysis. *Nat Clin Pract Nephrol* 2006;2:504–513.
11. Allon M, Asif A. Venous catheter access: The basics. In: Daugirdas JT, Blake PG, Ing TS, eds. *Handbook of Dialysis*. 5th ed. Philadelphia: Wolters Kluwer; 2014;121–136.
12. Vachharajani TJ, Wu S, Brouwer-Maier D, Asif A. Arteriovenous fistulas and grafts: The basics. In: Daugirdas JT, Blake PG, Ing TS, eds. *Handbook of Dialysis*. 5th ed. Philadelphia: Wolters Kluwer; 2014;99–120.
13. Chan MR, Yevzlin AS. Tunneled dialysis catheters: Recent trends and future directions. *Adv Chronic Kidney Dis* 2009;16:386–395.
14. Ahmad S, Misra M, Hoenich N, Daugirdas JT. Hemodialysis apparatus. In: Daugirdas JT, Blake PG, Ing TS, eds. *Handbook of Dialysis*. 5th ed. Philadelphia: Wolters Kluwer; 2014;66–88.
15. Tattersall JE, Ward RA, Group E. Online haemodiafiltration: Definition, dose quantification and safety revisited. *Nephrol Dial Transplant* 2013;28:542–550.
16. den Hoedt CH, Mazairac AH, van den Dorpel MA, et al. Effect of hemodiafiltration on mortality, inflammation and quality of life. *Contrib Nephrol* 2011;168:39–52.
17. Canaud B, Bowry S, Stuard S. Hemodiafiltration. In: Daugirdas JT, Blake

PG, Ing TS, eds. *Handbook of Dialysis*. 5th ed. Philadelphia: Wolters Kluwer; 2014;321–332.

18. Mostovaya IM, Blankestijn PJ, Bots ML, et al. Clinical evidence on hemodiafiltration: A systematic review and a meta-analysis. *Semin Dial* 2014;27:119–127.
19. Nesrallah GE, Lindsay RM, Cuerden MS, et al. Intensive hemodialysis associates with improved survival compared with conventional hemodialysis. *J Am Soc Nephrol* 2012;23:696–705.
20. Schachter ME, Chan CT. Current state of intensive hemodialysis: A comparative review of benefits and barriers. *Nephrol Dial Transplant* 2012;27:4307–4313.
21. Hakim RM, Saha S. Dialysis frequency versus dialysis time, that is the question. *Kidney Int* 2014;85:1024–1029.
22. Group FHNT, Chertow GM, Levin NW, et al. In-center hemodialysis six times per week versus three times per week. *N Engl J Med* 2010;363:2287–2300.
23. Pipkin M, Eggers PW, Larive B, et al. Recruitment and training for home hemodialysis: Experience and lessons from the Nocturnal Dialysis Trial. *Clin J Am Soc Nephrol* 2010;5:1614–1620.
24. Cafazzo JA, Leonard K, Easty AC, et al. Patient-perceived barriers to the adoption of nocturnal home hemodialysis. *Clin J Am Soc Nephrol* 2009;4:784–789.
25. Daugirdas JT. Physiologic principles and urea kinetic modeling. In: Daugirdas JT, Blake PG, Ing TS, eds. *Handbook of Dialysis*. 5th ed. Philadelphia: Wolters Kluwer; 2014;25–58.
26. Daugirdas JT. Chronic hemodialysis prescription. In: Daugirdas JT, Blake PG, Ing TS, eds. *Handbook of Dialysis*. 5th ed. Philadelphia: Wolters Kluwer; 2014;192–214.
27. Department of Health and Human Services CMMS, Office of Clinical Standards of Quality (ed). Annual Report: End Stage Renal Disease Clinical Performance Measures Project. Baltimore, MD: National Institutes of Health, National Institutes of Diabetes and Digestive and Kidney Diseases; 2006.
28. Pierratos A, Chan CT, McFarlane PA. Daily (quotidian) hemodialysis. In: Nissenson AR, Fine RN, eds. *Handbook of Dialysis Therapy*. 4th ed. Philadelphia: Saunders/Elsevier; 2008;352–363.
29. Davenport A. Intradialytic complications during hemodialysis. *Hemodial*

Int 2006;10:162–167.

30. Sherman RA, Daugirdas JT, Ing TS. Complications during hemodialysis. In: Daugirdas JT, Blake PG, Ing TS, eds. *Handbook of Dialysis*. 5th ed. Philadelphia: Wolters Kluwer; 2014;215–236.
31. Sherman R, Daugirdas J, Ing T. Complications during hemodialysis. In: Daugirdas J, Blake P, Ing T, eds. *Handbook of Dialysis*. 5th ed. Philadelphia: Wolters Kluwer; 2014;215–236.
32. Flythe JE, Inrig JK, Shafi T, et al. Association of intradialytic blood pressure variability with increased all-cause and cardiovascular mortality in patients treated with long-term hemodialysis. *Am J Kidney Dis* 2013;61:966–974.
33. Thijssen S, Raimann JG, Usvyat LA. The evils of intradialytic sodium loading. *Contrib Nephrol* 2011;171:84–91.
34. Gabutti L, Bianchi G, Soldini D, et al. Haemodynamic consequences of changing bicarbonate and calcium concentrations in haemodialysis fluids. *Nephrol Dial Transplant* 2009;24:973–981.
35. Zhou YL, Liu HL, Duan XF, et al. Impact of sodium and ultrafiltration profiling on haemodialysis-related hypotension. *Nephrol Dial Transplant* 2006;21:3231–3237.
36. Assimon MM, Wenger JB, Wang L, Flythe JE. Ultrafiltration rate and mortality in maintenance hemodialysis patients. *Am J Kidney Dis* 2016;68:911–922.
37. Park J, Rhee CM, Sim JJ, et al. A comparative effectiveness research study of the change in blood pressure during hemodialysis treatment and survival. *Kidney Int* 2013;84:795–802.
38. Denker MG, Cohen DL. Antihypertensive medications in end-stage renal disease. *Semin Dial* 2015;28:330–336.
39. Lok CE. Fistula first initiative: Advantages and pitfalls. *Clin J Am Soc Nephrol* 2007;2:1043–1053.
40. Hicks CW, Canner JK, Arhuidese I, et al. Mortality benefits of different hemodialysis access types are age dependent. *J Vasc Surg* 2015;61:449–456.
41. Allon M. A patient with recurrent arteriovenous graft thrombosis. *Clin J Am Soc Nephrol* 2015;10:2255–2262.
42. Clinical Practice Guidelines for Vascular Access: 2006. *Am J Kidney Dis* 2006;48:S176–S247.

43. O'Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter-related infections. *Am J Infect Control* 2011;39:S1–S34.
44. Bohlke M, Uliano G, Barcellos FC. Hemodialysis catheter-related infection: Prophylaxis, diagnosis and treatment. *J Vasc Access* 2015;16:347–355.
45. Nguyen DB, Shugart A, Lines C, et al. National Healthcare Safety Network (NHSN) Dialysis Event Surveillance Report for 2014. *Clin J Am Soc Nephrol* 2017;12:1139–1146.
46. Xue H, Ix JH, Wang W, et al. Hemodialysis access usage patterns in the incident dialysis year and associated catheter-related complications. *Am J Kidney Dis* 2013;61:123–130.
47. Parker K, Nikam M, Jayanti A, Mitra S. Medication burden in CKD-5D: Impact of dialysis modality and setting. *Clin Kidney J* 2014;7:557–561.
48. Fissell RB, Karaboyas A, Bieber BA, et al. Phosphate binder pill burden, patient-reported non-adherence, and mineral bone disorder markers: Findings from the DOPPS. *Hemodial Int* 2016;20:38–49.
49. Chiu YW, Teitelbaum I, Misra M, et al. Pill burden, adherence, hyperphosphatemia, and quality of life in maintenance dialysis patients. *Clin J Am Soc Nephrol* 2009;4:1089–1096.
50. Chesterton LJ, Selby NM, Burton JO, McIntyre CW. Cool dialysate reduces asymptomatic intradialytic hypotension and increases baroreflex variability. *Hemodial Int* 2009;13:189–196.
51. Assimon MM, Flythe JE. Definitions of intradialytic hypotension. *Semin Dial* 2017;30:464–472.
52. Selby NM, McIntyre CW. A systematic review of the clinical effects of reducing dialysate fluid temperature. *Nephrol Dial Transplant* 2006;21:1883–1898.
53. Rubinstein S, Haimov M, Ross MJ. Midodrine-induced vascular ischemia in a hemodialysis patient: A case report and literature review. *Ren Fail* 2008;30:808–812.
54. Vannorsdall MD, Hariachar S, Hewitt LA. A randomized, placebo-controlled, phase 2 study of the efficacy and safety of droxidopa in patients with intradialytic hypotension. *Postgrad Med* 2015;127:133–143.
55. Seo Y, Jeung S, Kang SM, et al. Use of fludrocortisone for intradialytic hypotension. *Kidney Res Clin Pract* 2018;37:85–88.

56. Higuchi T, Abe M, Yamazaki T, et al. Levocarnitine improves cardiac function in hemodialysis patients with left ventricular hypertrophy: A randomized controlled trial. *Am J Kidney Dis* 2016;67:260–270.
57. Razeghi E, Dashti-Khavidaki S, Nassiri S, et al. A randomized crossover clinical trial of sertraline for intradialytic hypotension. *Iran J Kidney Dis* 2015;9:323–330.
58. Brewster UC, Ciampi MA, Abu-Alfa AK, Perazella MA. Addition of sertraline to other therapies to reduce dialysis-associated hypotension. *Nephrology (Carlton)* 2003;8:296–301.
59. Beladi-Mousavi SS, Beladi-Mousavi M, Hayati F, Talebzadeh M. Effect of intranasal DDAVP in prevention of hypotension during hemodialysis. *Nefrologia* 2012;32:89–93.
60. Assimon MM, Wang L, Flythe JE. Intradialytic hypertension frequency and short-term clinical outcomes among individuals receiving maintenance hemodialysis. *Am J Hypertens* 2018;31:329–339.
61. Weir MA, Dixon SN, Fleet JL, et al. β-Blocker dialyzability and mortality in older patients receiving hemodialysis. *J Am Soc Nephrol* 2015;26:987–996.
62. Tang CH, Wang CC, Chen TH, et al. Prognostic benefits of carvedilol, bisoprolol, and metoprolol controlled release/extended release in hemodialysis patients with heart failure: A 10-year cohort. *J Am Heart Assoc* 2016;5:e002584.
63. Assimon MM, Brookhart MA, Fine JP, et al. A comparative study of Carvedilol Versus Metoprolol initiation and 1-year mortality among individuals receiving maintenance hemodialysis. *Am J Kidney Dis* 2018;72:337–348.
64. El-Hennawy AS, Zaib S. A selected controlled trial of supplementary vitamin E for treatment of muscle cramps in hemodialysis patients. *Am J Ther* 2010;17:455–459.
65. El-Tawil S, Al Musa T, Valli H, et al. Quinine for muscle cramps. *Cochrane Database Syst Rev* 2015;4:CD005044.
66. Houstoun M, Reichman ME, Graham DJ, et al. Use of an active surveillance system by the FDA to observe patterns of quinine sulfate use and adverse hematologic outcomes in CMS Medicare data. *Pharmacoepidemiol Drug Saf* 2014;23:911–917.
67. Beladi Mousavi SS, Zeraati A, Moradi S, Mousavi MB. The effect of gabapentin on muscle cramps during hemodialysis: A double-blind clinical

trial. *Saudi J Kidney Dis Transpl* 2015;26:1142–1148.

68. Khajehdehi P, Mojerlou M, Behzadi S, Rais-Jalali GA. A randomized, double-blind, placebo-controlled trial of supplementary vitamins E, C and their combination for treatment of haemodialysis cramps. *Nephrol Dial Transplant* 2001;16:1448–1451.
69. Dixon BS, Beck GJ, Dember LM, et al. Use of aspirin associates with longer primary patency of hemodialysis grafts. *J Am Soc Nephrol* 2011;22:773–781.
70. Dixon BS, Beck GJ, Vazquez MA, et al. Effect of dipyridamole plus aspirin on hemodialysis graft patency. *N Engl J Med* 2009;360:2191–2201.
71. Palmer SC, Di Micco L, Razavian M, et al. Antiplatelet therapy to prevent hemodialysis vascular access failure: Systematic review and meta-analysis. *Am J Kidney Dis* 2013;61:112–122.
72. Dixon BS, Beck GJ, Dember LM, et al. Use of aspirin associates with longer primary patency of hemodialysis grafts. *J Am Soc Nephrol* 2011;22:773–781.
73. Chan KE, Lazarus JM, Thadhani R, Hakim RM. Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation. *J Am Soc Nephrol* 2009;20:2223–2233.
74. Sood MM, Rigatto C, Bueti J, et al. Thrice weekly warfarin administration in haemodialysis patients. *Nephrol Dial Transplant* 2009;24:3162–3167.
75. Limdi NA, Beasley TM, Baird MF, et al. Kidney function influences warfarin responsiveness and hemorrhagic complications. *J Am Soc Nephrol* 2009;20:912–921.
76. Lok CE, Moist L, Hemmelgarn BR, et al. Effect of fish oil supplementation on graft patency and cardiovascular events among patients with new synthetic arteriovenous hemodialysis grafts: A randomized controlled trial. *JAMA* 2012;307:1809–1816.
77. Irish AB, Viecelli AK, Hawley CM, et al. Effect of fish oil supplementation and aspirin use on arteriovenous fistula failure in patients requiring hemodialysis: A randomized clinical trial. *JAMA Intern Med* 2017;177:184–193.
78. Macrae JM, Dojcinovic I, Djurdjev O, et al. Citrate 4% versus heparin and the reduction of thrombosis study (CHARTS). *Clin J Am Soc Nephrol* 2008;3:369–374.
79. Zhao Y, Li Z, Zhang L, et al. Citrate versus heparin lock for hemodialysis

catheters: A systematic review and meta-analysis of randomized controlled trials. *Am J Kidney Dis* 2014;63:479–490.

80. Hemmelgarn BR, Manns BJ, Soroka SD, et al. Effectiveness and cost of weekly recombinant tissue plasminogen activator hemodialysis catheter locking solution. *Clin J Am Soc Nephrol* 2018;13:429–435.
81. Al-Ali F, Hamdy AF, Hamad A. Safety and efficacy of taurolidine/urokinase versus taurolidine/heparin as a tunneled catheter lock solution in hemodialysis patients: A prospective, randomized, controlled study. *Nephrol Dial Transplant* 2018;33:619–626.
82. Hilleman D, Campbell J. Efficacy, safety, and cost of thrombolytic agents for the management of dysfunctional hemodialysis catheters: A systematic review. *Pharmacotherapy* 2011;31:1031–1040.
83. Vercaigne LM, Zacharias J, Bernstein KN. Alteplase for blood flow restoration in hemodialysis catheters: A multicenter, randomized, prospective study comparing “dwell” versus “push” administration. *Clin Nephrol* 2012;78:287–296.
84. Yaseen O, El-Masri MM, El Nekidy WS, et al. Comparison of alteplase (tissue plasminogen activator) high-dose vs. low-dose protocol in restoring hemodialysis catheter function: The ALTE-DOSE study. *Hemodial Int* 2013;17:434–440.
85. Allon M. Treatment guidelines for dialysis catheter-related bacteremia: An update. *Am J Kidney Dis* 2009;54:13–17.
86. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009;49:1–45.
87. Battistella M, Bhola C, Lok CE. Long-term follow-up of the Hemodialysis Infection Prevention with Polysporin Ointment (HIPPO) study: A quality improvement report. *Am J Kidney Dis* 2011;57:432–441.
88. Quittnat Pelletier F, Joarder M, Poutanen SM, Lok CE. Evaluating approaches for the diagnosis of hemodialysis catheter-related bloodstream infections. *Clin J Am Soc Nephrol* 2016;11:847–854.
89. Fitzgibbons LN, Puls DL, Mackay K, Forrest GN. Management of gram-positive coccal bacteremia and hemodialysis. *Am J Kidney Dis* 2011;57:624–640.
90. Poole CV, Carlton D, Bimbo L, Allon M. Treatment of catheter-related bacteraemia with an antibiotic lock protocol: Effect of bacterial pathogen.

Nephrol Dial Transplant 2004;19:1237–1244.

91. Kanaa M, Wright MJ, Akbani H, et al. Cathasept line lock and microbial colonization of tunneled hemodialysis catheters: A Multicenter Randomized Controlled Trial. *Am J Kidney Dis* 2015;66:1015–1023.
92. Sofroniadou S, Revela I, Kouloubinis A, et al. Ethanol combined with heparin as a locking solution for the prevention of catheter related blood stream infections in hemodialysis patients: A prospective randomized study. *Hemodial Int* 2017;21:498–506.
93. Labriola L, Crott R, Jadoul M. Preventing haemodialysis catheter-related bacteraemia with an antimicrobial lock solution: A meta-analysis of prospective randomized trials. *Nephrol Dial Transplant* 2008;23:1666–1672.
94. Moore CL, Besarab A, Ajluni M, et al. Comparative effectiveness of two catheter locking solutions to reduce catheter-related bloodstream infection in hemodialysis patients. *Clin J Am Soc Nephrol* 2014;9:1232–1239.
95. Landry DL, Braden GL, Gobeille SL, et al. Emergence of gentamicin-resistant bacteremia in hemodialysis patients receiving gentamicin lock catheter prophylaxis. *Clin J Am Soc Nephrol* 2010;5:1799–1804.
96. Correa-Rotter R, Manzano A, Saxena A. Peritoneal dialysis. In: Skorecki K, Chertow GM, Marsden PA, Yu ASL, eds. *Brenner and Rector's The Kidney*. 10th ed. Philadelphia: Elsevier; 2016;2111–2136.
97. Clinical Practice Recommendations For Peritoneal Dialysis Adequacy. *Am J Kidney Dis* 2006;48:S130–S158.
98. Diaz-Buxo JA. Continuous-flow peritoneal dialysis: Update. *Adv Perit Dial* 2004;20:18–22.
99. Thomas J, Teitelbaum I. Preservation of residual renal function in dialysis patients. *Adv Perit Dial* 2011;27:112–117.
100. Garcia-Lopez E, Lindholm B, Davies S. An update on peritoneal dialysis solutions. *Nat Rev Nephrol* 2012;8:224–233.
101. Johnson DW, Brown FG, Clarke M, et al. Effects of biocompatible versus standard fluid on peritoneal dialysis outcomes. *J Am Soc Nephrol* 2012;23:1097–1107.
102. Clinical Practice Guidelines for Peritoneal Dialysis Adequacy. *Am J Kidney Dis* 2006;48:S98–S129.
103. Troidle L, Finkelstein F. Treatment and outcome of CPD-associated peritonitis. *Ann Clin Microbiol Antimicrob* 2006;5:6.

104. Troidle L, Gorban-Brennan N, Finkelstein FO. Outcome of patients on chronic peritoneal dialysis undergoing peritoneal catheter removal because of peritonitis. *Adv Perit Dial* 2005;21:98–101.
105. Li PK, Szeto CC, Piraino B, et al. ISPD Peritonitis Recommendations: 2016 Update on Prevention and Treatment. *Perit Dial Int* 2016;36:481–508.
106. Piraino B, Bernardini J, Bender FH. An analysis of methods to prevent peritoneal dialysis catheter infections. *Perit Dial Int* 2008;28:437–443.
107. Szeto CC, Li PK, Johnson DW, et al. ISPD catheter-related infection recommendations: 2017 update. *Perit Dial Int* 2017;37:141–154.
108. Lloyd A, Tangri N, Shafer LA, et al. The risk of peritonitis after an exit site infection: A time-matched, case-control study. *Nephrol Dial Transplant* 2013;28:1915–1921.
109. Herwaldt LA, Boyken LD, Coffman S, et al. Sources of *Staphylococcus aureus* for patients on continuous ambulatory peritoneal dialysis. *Perit Dial Int* 2003;23:237–241.
110. Wiggins KJ, Johnson DW, Craig JC, Strippoli GFM. Treatment of peritoneal dialysis-associated peritonitis: A systematic review of randomized controlled trials. *Am J Kidney Dis* 2007;50:967–988.
111. Mahaldar A, Weisz M, Kathuria P. Comparison of gentamicin and mupirocin in the prevention of exit-site infection and peritonitis in peritoneal dialysis. *Adv Perit Dial* 2009;25:56–59.
112. Szeto CC, Li PK, Johnson DW, et al. ISPD catheter-related infection recommendations: 2017 update. *Perit Dial Int* 2017;37:141–154.
113. Cavdar C, Saglam F, Sifil A, et al. Effect of once-a-week vs thrice-a-week application of mupirocin on methicillin and mupirocin resistance in peritoneal dialysis patients: Three years of experience. *Ren Fail* 2008;30:417–422.
114. Pierce DA, Williamson JC, Mauck VS. The effect on peritoneal dialysis pathogens of changing topical antibiotic prophylaxis. *Perit Dial Int* 2012;32:525–530.
115. McQuillan RF, Chiu E, Nessim S, et al. A randomized controlled trial comparing mupirocin and polysporin triple ointments in peritoneal dialysis patients: The MP3 study. *Clin J Am Soc Nephrol* 2012;7:297–303.
116. Nunez-Moral M, Sanchez-Alvarez E, Gonzalez-Diaz I, et al. Exit-site infection of peritoneal catheter is reduced by the use of polyhexanide: Results of a prospective randomized trial. *Perit Dial Int* 2014;34:271–277.

117. Johnson DW, Badve SV, Pascoe EM, et al. Antibacterial honey for the prevention of peritoneal-dialysis-related infections (HONEYPOT): A randomised trial. *Lancet Infect Dis* 2014;14:23–30.
118. Johnson DW, van Eps C, Mudge DW, et al. Randomized, controlled trial of topical exit-site application of honey (Medihoney) versus mupirocin for the prevention of catheter-associated infections in hemodialysis patients. *J Am Soc Nephrol* 2005;16:1456–1462.
119. Clinical Practice Guidelines for Vascular Access. *Am J Kidney Dis* 2006;48:S176–S247.
120. Mujais S, Story K. Peritoneal dialysis in the US: Evaluation of outcomes in contemporary cohorts. *Kidney Int Suppl* 2006:S21–S26.

63

Drug-Induced Kidney Disease

Thomas D. Nolin and Mark A. Perazella

KEY CONCEPTS

1. The initial diagnosis of drug-induced kidney disease (DIKD) typically involves detection of elevated serum creatinine (S_{cr}) and blood urea nitrogen, for which there is a temporal relationship between the toxicity and use of a potentially nephrotoxic drug.
2. DIKD is best prevented by avoiding the use of potentially nephrotoxic agents for patients at increased risk for toxicity. However, when exposure to these drugs cannot be avoided, recognition of risk factors and specific techniques, such as hydration, may be used to reduce potential nephrotoxicity.
3. Acute tubular injury/necrosis (ATN) is the most common presentation of DIKD in hospitalized patients. The primary agents implicated are aminoglycosides, radiocontrast media, cisplatin, amphotericin B, and osmotically active agents.
4. Angiotensin-converting enzyme inhibitors (ACEIs) and nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with hemodynamically mediated kidney injury, the pathogenesis of which is a decrease in glomerular capillary hydrostatic pressure.
5. Acute allergic interstitial nephritis (AIN) is observed in up to 27% of kidney biopsies performed for hospitalized patients with unexplained acute kidney injury (AKI). Clinical manifestations of AIN typically (but not always) present approximately 14 days after initiation of therapy and may include fever, maculopapular rash, eosinophilia, arthralgia, as well as pyuria, hematuria, proteinuria, and oliguria.

Preclass Engaged Learning Activity

Visit the National Institute of Diabetes and Digestive and Kidney Diseases website: https://tinyurl.com/y2pnoj26. This website is useful to enhance student understanding of risk factors for and commonly used drugs that are associated with nephrotoxicity. Watch the video titled, "Keeping Kidneys Safe: Know How Medicines Affect the Kidneys,'' https://tinyurl.com/ybjao5qg. The video provides a brief overview of glomerular physiology and hemodynamically mediated nephrotoxic effects of nonsteroidal anti-inflammatory drugs and renin-angiotensin system blockers.

INTRODUCTION

Numerous diagnostic and therapeutic agents have been associated with the development of DIKD or nephrotoxicity. It is a relatively common complication with variable presentations depending on the drug and clinical setting, inpatient or outpatient. Manifestations of DIKD may include acid–base abnormalities, electrolyte imbalances, urine sediment abnormalities, proteinuria, pyuria, and/or hematuria.[1] However, the most common manifestation of nephrotoxicity is a decline in the glomerular filtration rate (GFR) and a corresponding rise in serum creatinine (S_{cr}) concentrations. Initial diagnosis of nephrotoxicity is often delayed because it typically is based on the detection of elevated S_{cr}, for which there is a temporal relationship between the kidney injury (evidenced by the rise in S_{cr}) and exposure to the potentially nephrotoxic drug. This is consistent with contemporary definitions of acute kidney injury (AKI), which rely on either an abrupt increase in S_{cr} or an abrupt decline in urine output (see Chapter e59, "Evaluation of Kidney Function" and Chapter 60, "Acute Kidney Injury").[2]

Nephrotoxicity is often reversible if one discontinues the use of the offending agent, but in some cases it may evolve into AKI and may even progress to stage 5 chronic kidney disease (CKD). Currently, many different mechanisms are responsible for the pathogenesis of DIKD, and the introduction of new drugs with novel mechanisms of action provides the potential for the identification of new presentations of AKI and CKD. This chapter reviews the epidemiology, pathophysiology, risk factors, and basic principles of prevention of DIKD. Detailed discussions of these issues plus management strategies are presented for the most commonly used agents that have been associated with a moderate-to-high likelihood of DIKD.

EPIDEMIOLOGY

The incidence and characteristics of outpatient or community-acquired DIKD are not well understood since mild toxicity is often unrecognized in this setting. However, the acquisition of data regarding the pharmacoepidemiology of these effects has become more important as care increasingly shifts to the outpatient setting. The incidence of community-based AKI requiring dialysis is as high as 29.5 per 100,000 person years and 522.4 per 100,000 person years for patients not requiring dialysis.[3] Although the incidence of drug-induced AKI was not specifically reported, up to 20% of hospital admissions due to AKI have been attributed to nephrotoxicity acquired in the community setting.[4] The incidence of AKI is even higher in hospitalized patients and appears to be increasing over time.[3,5] As many as 22% of adults and 34% of children worldwide experience AKI during a hospital admission.[6] While up to 30% of critically ill patients experience AKI during their hospitalization, and one in four cases is associated with nephrotoxic medication exposure.[7] Indeed, drugs have been implicated in 26% of all cases of in-hospital AKI and as such are a recognized source of significant morbidity and mortality.[1]

1 Because the most common manifestation of DIKD is a decline in GFR leading to a rise in S_{cr} and BUN, the onset of toxicity in hospitalized, acutely ill patients is most often recognized by routine laboratory monitoring. Decreased urine output may also be an early sign of toxicity, particularly with radiographic contrast media, NSAIDs, and ACEIs. In the outpatient setting, nephrotoxicity is often recognized by the development of symptoms such as malaise, anorexia, vomiting, volume overload (shortness of breath or edema), and hypertension. S_{cr} or BUN concentrations and urine collection for creatinine clearance may subsequently be measured to quantify the degree of decline in GFR. Marked intrasubject between-day variability of S_{cr} values has been noted (±20% for values within the normal range; see Chapter e59). Furthermore, they may be altered as the result of dietary changes and initiation of drug therapy, which may interfere with the assay procedure. Nevertheless, changes in S_{cr} or urine output consistent with the diagnostic criteria for AKI (see Chapter e59), when correlated temporally with the initiation of drug therapy, are a common threshold for the identification of DIKD.[1]

CLINICAL PRESENTATION

Drug-Induced Kidney Disease

General

- The most common manifestation is a decline in GFR leading to a rise in S_{cr} and BUN.
- Alterations in renal tubular function without loss of glomerular filtration may be evident.

Symptoms

- Patients may complain of malaise, anorexia, nausea, vomiting, shortness of breath, or edema, particularly in the outpatient setting.

Signs

- Decreased urine output may be an early sign of toxicity, particularly with radiographic contrast media, NSAIDs, and ACEIs, with progression to volume overload and hypertension.
- Proximal tubular injury: Metabolic acidosis with bicarbonaturia; glycosuria in the absence of hyperglycemia; and reductions in serum phosphate, uric acid, potassium, and magnesium due to increased urinary losses.
- Distal tubular injury: Polyuria from failure to maximally concentrate urine, metabolic acidosis from impaired urinary acidification, and hyperkalemia from impaired potassium excretion.

Laboratory Tests

- An abrupt (within 48 hours) reduction in kidney function defined as an absolute increase in S_{cr} of greater than or equal to 0.3 mg/dL (27 μmol/L), a percentage increase in S_{cr} of greater than or equal to 50% (1.5-fold from baseline) within 7 days, or a reduction in urine output (documented oliguria of less than 0.5 mL/kg/hr for more than 6 hours), when correlated temporally with the initiation of drug therapy may indicate drug-induced AKI.[1]

Other Diagnostic Tests

- Urinary excretion of *N*-acetyl-*β*-glucosaminidase, *γ*-glutamyl transpeptidase, glutathione *S*-transferase, and interleukin (IL)-18 are

markers of proximal tubular injury and have been used for the early detection of AKI in critically ill patients.

- Kidney injury molecule-1 (KIM-1) is expressed in the proximal tubule and is upregulated for patients with ischemic acute tubular necrosis (ATN), appearing in the urine within 12 hours after the ischemic insult.
- Neutrophil gelatinase–associated lipocalin (NGAL) protein may be detected in the urine within 3 hours of ischemic injury.
- The urinary cell-cycle arrest biomarkers insulin-like growth factor–binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinase 2 (TIMP-2) can predict AKI in high-risk surgical patients, and clinical outcomes (death and the need for dialysis) in critically ill adults. These biomarkers may have an emerging role in detecting and/or minimizing DIKD.

CLINICAL PRESENTATION

Nephrotoxicity may also be evidenced by primary alterations in renal tubular function without a corresponding loss of glomerular filtration. In this setting, urinary enzymes and low-molecular-weight proteins may be used as earlier and more specific biomarkers of nephrotoxicity compared with S_{cr} and BUN, which are relatively insensitive markers of kidney injury.[8,9] S_{cr} and BUN are used as surrogates of kidney function, not injury per se, and typically significant kidney injury must have occurred days before a rise in either is evident. The emergence of novel biomarkers of kidney injury represents an important opportunity for earlier detection of DIKD. Urinary excretion of KIM-1, *N*-acetyl-β-glucosaminidase, γ-glutamyl transpeptidase, glutathione *S*-transferase, NGAL, and interleukin-18 (markers of proximal tubular injury) have been used for the early detection of acute kidney damage in several patient populations.[8–10] For example, the transmembrane protein KIM-1 is upregulated for patients with ischemic ATN, appearing in the urine within 12 hours after the ischemic insult. Urinary *N*-acetylglucosamine (NAG) concentrations are a highly sensitive indicator of AKI and have been shown to detect AKI in critically ill patients up to 4 days prior to a rise in S_{cr} was observed. Similarly, urinary NGAL is an early marker of AKI, preceding a rise observed in S_{cr} by up to 3 days.[11]

Recently, the urinary cell-cycle arrest biomarkers insulin-like growth factor–binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinase 2 (TIMP-2)

were shown to predict AKI in high-risk surgical patients,[12] and clinical outcomes (death and the need for dialysis) in critically ill adults.[13] To date, no clinical studies demonstrating the utility of IGFBP7 and TIMP-2 in detecting and/or minimizing DIKD have been reported, but several preclinical studies provide proof of principle for the potential clinical role and utility of monitoring TIMP or IGFBP for this purpose. For example, TIMP-1 is an effective biomarker of cisplatin-induced nephrotoxicity in human kidney cells,[14] and is useful in predicting aristolochic acid–induced kidney injury in rats.[15] In the future, urinary biomarkers may facilitate the earlier detection of kidney injury and diagnosis of nephrotoxicity and minimize the long-term consequences of this common drug-induced disorder.

PRINCIPLES FOR PREVENTION OF DRUG-INDUCED NEPHROPATHY

2 The primary principle for prevention of DIKD is to avoid the use of nephrotoxic agents for patients at increased risk for toxicity. Therefore, an awareness of potentially nephrotoxic drugs and knowledge of risk factors that increase renal vulnerability are essential.[16] Exposure to these drugs often cannot be avoided, so several interventions have been proposed to reduce the potential for the development of nephrotoxicity, for example, adjustment of medication dosage regimens based on accurate estimates of kidney function, and careful and adequate hydration to establish high urine flow rates.[17] Other preventative strategies are still theoretical and/or investigational and relate directly to the specific nephrotoxic mechanisms of a given drug.

The several specific drug-induced renal structural-functional alterations that are responsible for the vast majority of cases of DIKD are listed in **Table 63-1**. This chapter discusses the pathophysiologic mechanisms responsible for the development of DIKD with these agents in detail, along with clinical presentation, prevention strategies, therapeutic management approaches, and relevant monitoring plans.

TABLE 63-1 Drug-Induced Kidney Structural-Functional Alterations

Tubular epithelial cell damage

Acute tubular injury/necrosis
- Aminoglycoside antibiotics
- Radiographic contrast media
- Cisplatin, carboplatin
- Ifosfamide
- Amphotericin B
- Cyclosporine, tacrolimus
- Adefovir, cidofovir, tenofovir
- Pentamidine
- Foscarnet
- Zoledronate

Osmotic nephropathy
- Mannitol
- Dextran
- IV immunoglobulin (sucrose)
- Hydroxyethyl starch

Hemodynamically mediated kidney injury

- Angiotensin-converting enzyme inhibitors
- Angiotensin II receptor blockers
- SGLT-2 inhibitors
- NSAIDs
- Cyclosporine, tacrolimus
- OKT3

Obstructive nephropathy

Crystal nephropathy
- Acyclovir
- Sulfonamides
- Indinavir, atazanavir
- Foscarnet
- Methotrexate
- Ascorbic acid, ethylene glycol, orlistat

Nephrolithiasis
- Sulfonamides
- Triamterene
- Indinavir, atazanavir

Nephrocalcinosis
- Oral sodium phosphate solution

Glomerular disease

Minimal change disease
- NSAIDs, COX-2 inhibitors
- Lithium
- Pamidronate
- Interferon-α and β

Membranous disease
- NSAIDs
- Penicillamine
- Captopril

Focal segmental glomerulosclerosis
- Pamidronate
- Interferon-α and β
- Lithium
- Sirolimus
- Anabolic steroids
- Tyrosine kinase inhibitors

Tubulointerstitial disease

Acute allergic interstitial nephritis
- Penicillins
- Ciprofloxacin
- NSAIDs, cyclooxygenase-2 inhibitors
- Proton pump inhibitors
- Loop diuretics

Chronic interstitial nephritis
- Cyclosporine
- Lithium
- Aristolochic acid

Papillary necrosis
- NSAIDs, combined phenacetin, aspirin, and caffeine analgesics

Renal vasculitis, thrombotic microangiopathy, thrombosis, and cholesterol emboli

Vasculitis and thrombosis
- Hydralazine
- Propylthiouracil
- Allopurinol
- Penicillamine
- Gemcitabine
- Mitomycin C

Methamphetamines
- Cyclosporine, tacrolimus
- Adalimumab
- Bevacizumab

Cholesterol emboli
- Warfarin
- Thrombolytic agents

TUBULAR EPITHELIAL CELL DAMAGE

3 Drugs that lead to renal tubular epithelial cell (RTEC) damage typically do so via direct cellular toxicity or ischemia. Damage is most often localized in the proximal and distal tubular epithelia and is termed ATN when cellular degeneration and sloughing from proximal and distal tubular basement membranes are observed. This classically manifests as cellular debris-filled, RTECs and RTEC casts and/or muddy brown granular casts in the urinary sediment.[18] Specific indicators of proximal tubular injury include metabolic acidosis with bicarbonaturia; glycosuria in the absence of hyperglycemia; and reductions in serum phosphate, uric acid, potassium, and magnesium as a result of increased urinary losses.[19] Indicators of distal tubular injury include polyuria from failure to maximally concentrate urine (ie, nephrogenic diabetes insipidus), metabolic acidosis from impaired urinary acidification, and hyperkalemia from impaired potassium excretion.[20]

Acute Tubular Injury/Necrosis

Acute tubular injury/necrosis (ATN) is the most common presentation of DIKD in the inpatient setting. The primary agents associated with this type of injury are aminoglycosides, radiocontrast media, cisplatin, amphotericin B, foscarnet, and osmotically active agents such as immunoglobulins, dextrans, hydroxyethyl starch, and mannitol.[21]

Aminoglycoside Nephrotoxicity

Incidence Aminoglycoside antibiotic–associated nephrotoxicity has been reported to occur in between 10% and 25% of patients receiving a therapeutic course.[22,23] Critically ill patients appear to have a higher risk for nephrotoxicity with reported rates as high as 58%.[24] The large variance is in part a result of the use of different definitions of toxicity, variability between agents in the class, and the risk factors present in the study population.

Clinical Presentation Clinical evidence of aminoglycoside-associated nephrotoxicity is typically seen within 5 to 7 days after initiation of therapy and manifests as a gradual progressive rise in S_{cr} and BUN and decrease in creatinine clearance.[23] Patients usually present with non-oliguria, that is, they maintain

urine volumes greater than 500 mL/day and sometimes have microscopic hematuria and proteinuria.[21] Although renal magnesium wasting can occur (ie, daily excretion of more than 10-30 mg), the risk of symptomatic hypomagnesemia is generally low. Full recovery of kidney function is common if aminoglycoside therapy is discontinued immediately upon discovering signs of toxicity. However, severe AKI may develop occasionally, and for these individuals renal replacement therapy may be required (see Chapter 60). The diagnosis of aminoglycoside-associated nephrotoxicity is often difficult, particularly in critically ill patients with multiple comorbidities and is confounded by other factors that are independently associated with the development of AKI.[24] For instance, concurrent dehydration, sepsis, hypotension, ischemia, and use of other nephrotoxic drugs frequently contribute to AKI in patients who are receiving aminoglycosides.

Pathogenesis Aminoglycoside-associated ATN is primarily due to accumulation of high drug concentrations within proximal tubular epithelial cells, and subsequent generation of reactive oxygen species that produce mitochondrial injury, which leads to cellular apoptosis and necrosis.[22] This results in cell sloughing from proximal tubular basement membranes into the tubular lumen, which can result in tubular obstruction and back leakage of the glomerular filtrate across the damaged tubular epithelium. Toxicity is related to cationic charge of the drugs in this class, which facilitates their binding to negatively charged renal tubular epithelial membrane phospholipids in the proximal tubules, followed by intracellular transport and concentration in lysosomes. The number of cationic groups on the drug molecule appears to correlate with the degree of nephrotoxicity, which is consistent with the observation of higher rates of toxicity with neomycin versus gentamicin, followed by tobramycin, then amikacin.[23]

Risk Factors Multiple risk factors for aminoglycoside-associated nephrotoxicity have been identified: the aggressiveness of aminoglycoside dosing, synergistic toxicity as the result of combination drug therapy, and pre-existing clinical conditions of the patient (**Table 63-2**).[22,24]

TABLE 63-2 Potential Risk Factors for Aminoglycoside Nephrotoxicity

(A) Related to aminoglycoside dosing:
Large total cumulative dose
Prolonged therapy
Trough concentration exceeding 2 mg/L [a]
Recent previous aminoglycoside therapy
(B) Related to synergistic nephrotoxicity. Aminoglycosides in combination with
Cyclosporine
Amphotericin B
Vancomycin
Diuretics
Iodinated radiographic contrast agents
Cisplatin
NSAIDs
(C) Related to predisposing conditions in the patient
Pre-existing kidney disease
Diabetes
Increased age
Poor nutrition
Shock
Gram-negative bacteremia
Liver disease
Hypoalbuminemia
Obstructive jaundice
Dehydration
Hypotension
Potassium or magnesium deficiencies

[a]The equivalent concentration in SI molar units is 4.3 µmol/L for tobramycin and 4.2 µmol/L for gentamicin.

Prevention Aminoglycoside-associated ATN may be prevented by careful and cautious selection of patients and the use of alternative antibiotics whenever possible and as soon as microbial sensitivities are known. Commonly used alternatives include fluoroquinolones (eg, ciprofloxacin or levofloxacin) and third- or fourth-generation cephalosporins (eg, ceftazidime or cefepime). When aminoglycosides are necessary, gentamicin, tobramycin, and amikacin are most commonly used, but therapy should be selected to optimize antimicrobial efficacy. Furthermore, it is imperative to avoid volume depletion, limit the total aminoglycoside dose administered, and avoid concomitant therapy with other nephrotoxic drugs.[22] Future therapeutic alternatives may include new aminoglycoside congeners that retain the desired bactericidal activity and yet are devoid of nephrotoxicity, and may also include concurrent use of antioxidant compounds such as alpha-lipoic acid, vitamin E, and *N*-acetylcysteine.[25,26]

Prospective, individualized pharmacokinetic monitoring has been associated with a decrease in the incidence of aminoglycoside-associated nephrotoxicity.[27] These studies, however, were often small and statistically underpowered. High-dose intermittent dosing of aminoglycosides, termed once daily dosing, used in combination with other antibiotics, has been intensively investigated as a practical cost-effective method to maintain antimicrobial efficacy while reducing the risk of AKI.[27,28] The reduction in incidence may be the result of limited proximal tubular aminoglycoside uptake during the transient, high-peak serum concentrations, and because of the presence of low aminoglycoside concentrations for a greater proportion of the dosing interval, which facilitates excretion of the aminoglycoside.[22] Although greater clinical efficacy and reduced nephrotoxicity may be realized with once daily compared with standard dosing, seriously ill, immunocompromised, and elderly patients, as well as those with pre-existing kidney disease, are not ideal candidates for this approach.

Management Aminoglycoside use should be discontinued or the dosage regimen revised if AKI is evident (ie, there is an S_{cr} increase of 0.5 mg/dL [44 μmol/L] or more that is not attributable to another cause). Other nephrotoxic drugs should be discontinued if possible, and the patient should be maintained adequately hydrated and hemodynamically stable.[28] Short-term renal replacement therapy may be necessary, but end-stage renal disease (ESRD) is rarely the result of aminoglycoside toxicity alone.

Radiographic Contrast Media Nephrotoxicity

Incidence Radiographic contrast media–induced nephrotoxicity (CIN) is the third leading cause of hospital-acquired AKI, accounting for 10% to 13% of cases.[29] Estimates of the incidence varies widely depending on the population studied and presence of risk factors; rising from less than 2% for patients with normal kidney function, to 17% in patients with impaired kidney function, and 23% to 50% of critically ill patients.[21,30,31] However, recent studies indicate that the incidence of AKI in patients receiving radiocontrast is commonly overestimated, with the true incidence approximately 5.5%.[32] As the number of risk factors associated with CIN increases, there is a corresponding increase in the incidence of nephrotoxicity and mortality rates. Approximately fivefold increased risk of death has been reported for patients who develop CIN compared with those who do not, with the highest mortality rates observed for patients who developed AKI and required renal replacement therapy. Specifically, in-hospital mortality for patients who developed CIN was 34%

versus only 7% of patients who received contrast but did not develop AKI.[29] Moreover, a 2-year mortality rate of 81% has been observed for patients who developed CIN and required dialysis.[29]

Clinical Presentation Contrast media–induced nephrotoxicity is usually transient in nature, presenting most commonly as nonoliguria with kidney injury apparent within the first 24 to 48 hours after the administration of contrast. The S_{cr} concentration usually peaks between 3 and 4 days after exposure, with recovery after 7 to 10 days.[23] However, irreversible oliguric (urine volume less than 500 mL/day) AKI requiring dialysis has been reported in high-risk patients.[33] Urinalysis typically reveals tubular enzymuria with hyaline and granular casts but may also be completely void of casts. The urine sodium concentration and fractional excretion of sodium are frequently low, with the latter typically less than 1% (0.01).

Pathogenesis The primary mechanisms by which contrast media induces nephrotoxicity are renal ischemia and direct cellular toxicity.[34] Renal ischemia likely results from systemic hypotension and simultaneous acute vasoconstriction caused by disruption of normal prostaglandin synthesis and the release of adenosine, endothelin, and other renal vasoconstrictors. Subsequently, a sustained reduction in renal blood flow of up to 25% that lasts for several hours immediately following contrast administration may be evident.[34] This reduced renal blood flow leads to a 50% reduction in oxygen partial pressure and renal ischemia, along with increased concentrations of contrast in the renal tubules, which exacerbates the direct cytotoxicity.[34,35] The extent of cellular toxicity is directly related to the duration of tubular cell exposure to contrast. Thus, preservation of high urinary flow rates with adequate hydration before, during, and after contrast administration is vital to keep renal blood flow as high as reasonably possible to minimize tubular cell exposure to the contrast agent.[35] In humans, plasma osmolality is normally between 275 and 290 mOsm/kg (mmol/kg). Since low- and high-osmolar contrast agents are hyperosmolar to plasma (ie, 600-800 mOsm/kg [mmol/kg] and ~2,000 mOsm/kg [mmol/kg], respectively), their use may result in osmotic diuresis, dehydration, renal ischemia, and increased blood viscosity caused by red blood cell aggregation.[36] Oxidative stress has also been implicated in the development of ATN after contrast administration, which may explain the possible benefit of the antioxidants *N*-acetylcysteine and ascorbic acid.[37]

Risk Factors Decreased renal blood flow exacerbates the ischemic and direct

cytotoxic effects of contrast media on the renal tubules. Therefore, pre-existing kidney disease, particularly in those with estimated GFR less than 60 mL/min/1.73 m^2, is the most important risk factor, since lower GFR is associated with increasing levels of risk.[31] Other patient-specific risk factors include conditions associated with decreased renal blood flow (ie, congestive heart failure, dehydration/volume depletion, and hypotension), and patients with atherosclerosis and reduced effective circulating arterial blood volume appear to also have an elevated risk.[38,39] Diabetes is also a significant risk factor, likely due to coexisting kidney disease (diabetic nephropathy). The presence of multiple myeloma has traditionally been considered a relative contraindication for contrast use, but the risk appears to be associated with concomitant dehydration, kidney disease, or hypercalcemia rather than the diagnosis itself. Larger volumes or doses of contrast and the use of low- as well as high-osmolar contrast agents are also independent predictors of CIN.[38,39] Intra-arterial administration of contrast confers greater risk than IV administration.[31] Lastly, concurrent use of nephrotoxins and drugs that alter renal hemodynamics such as NSAIDs and ACEIs also increases risk. Risk factors are additive, and there is a proportional increase in the incidence of CIN and associated mortality as the number of risk factors increases.[39]

Prevention Contrast media–induced nephrotoxicity can be anticipated in the majority of patients who are at risk; so the use of preventative procedures is justified for virtually all patients. **Table 63-3** lists the recommended interventions for prevention of contrast nephrotoxicity. All patients scheduled to receive contrast media should be assessed for risk factors, and the risk-to-benefit ratio should be considered.[29,38,39] High-risk patients can be identified by evaluating medical history and indication for the contrast study, along with their most recent S_{cr} concentrations. Nephrotoxicity is best prevented in high-risk patients by using alternative imaging procedures (eg, ultrasound, noncontrast magnetic resonance imaging, and nuclear medicine scans). However, if contrast media must be used, the smallest adequate volume should be administered.[29] If the ratio of the volume of contrast to be infused relative to the patient's creatinine clearance is greater than or equal to 3.7 (222 if creatinine clearance is expressed in units of mL/s), the likelihood of nephrotoxicity is markedly increased.[39] Therefore, in general, the volume of contrast administered should not be greater than twice the baseline estimated creatinine clearance.

TABLE 63-3 Recommended Interventions for Prevention of Contrast

Nephrotoxicity[37–40]

Intervention	Recommendation	Recommendation Grade[a]
Contrast	• Minimize contrast volume/ dose • Use noniodinated contrast studies • Use low- or iso-osmolar contrast agents	A-1 A-2 A-2
Medications	• Avoid concurrent use of potentially nephrotoxic drugs (eg, NSAIDs, aminoglycosides)	A-2
Isotonic sodium chloride (0.9%)	• Initiate infusion 3-12 hours prior to contrast exposure and continue 6-24 hours postexposure • Infuse at 1-1.5 mL/kg/hr adjusting postexposure as needed to maintain a urine flow rate of 150 mL/hr • Alternatively, in urgent cases, initiate infusion at 3 mL/kg/hr, beginning 1 hour prior to contrast exposure, then continue at 1 mL/kg/hr for 6 hours postexposure	A-1

[a]*Strength of recommendations*: A, B, and C are good, moderate, and poor evidence to support recommendation, respectively. *Quality of evidence*: (1) evidence from more than one properly randomized, controlled trial; (2) evidence from more than one well-designed clinical trial with randomization, from cohort or case-controlled analytic studies or multiple time series, or dramatic results from uncontrolled experiments; and (3) evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.

Low-osmolar (600-800 mOsm/kg [mmol/kg]) nonionic (iohexol and iopamidol) and ionic (ioxaglate) contrast agents may be used to minimize the incidence of nephrotoxicity. Standard hyperosmolar contrast media (eg, low- and high-osmolar agent) are not reabsorbed in the kidney and cause osmotic diuresis, which contributes to the renal toxicity observed with these agents. Low-osmolar contrast agents have less than half the osmolality of high-osmolar (~2,000 mOsm/kg [mmol/kg]) agents and are associated with less toxicity, especially when used for patients with pre-existing kidney disease.[36] However, use of low-osmolar agents does not preclude the development of nephrotoxicity. Even low-

osmolar agents are hyperosmolar relative to plasma, which is likely the reason they have been associated with greater nephrotoxicity than the iso-osmolar nonionic contrast agent iodixanol. Currently, the relative differences in nephrotoxicity between the class of low-osmolar agents and iodixanol are unclear.[39,40]

Volume expansion and correction of dehydration prior to contrast administration is a mainstay of preventive therapy.[35] Parenteral hydration with isotonic saline before and after contrast administration reduces the incidence of toxicity, particularly in high-risk patients, and is currently the most widely accepted preventative intervention.[39] Volume expansion may exert its beneficial effects through dilution of contrast media, prevention of renal vasoconstriction, preservation of high urine flow rates, decreased tubular cell exposure to contrast, and avoidance of tubular obstruction. A recent landmark randomized clinical trial provided no evidence of a benefit of sodium bicarbonate or the thiol-containing antioxidant *N*-acetylcysteine over saline.[41] Current guidelines recommend hydration with isotonic saline for CIN prevention.[39,40] The use of oral hydration is also not currently recommended in lieu of parenteral hydration.[39,40]

Renal replacement therapy, including intermittent hemodialysis and continuous modalities, for example, continuous venovenous hemofiltration (CVVH), effectively removes iodinated contrast, and was considered by some to be a therapeutic option for the prevention of CIN. However, because of the logistical issues (eg, technical difficulty), potential infectious and noninfectious risks, high cost of renal replacement therapy, and lack of consistent clinical efficacy data, renal replacement therapy is not recommended.[31,40]

Management Currently there is no specific therapy available for managing established CIN. Other nephrotoxic drugs should be discontinued if possible, and subsequent contrast studies appropriately timed to minimize cumulative toxicity. Care is supportive as described in Chapter 60. Kidney function (eg, S_{cr} and urine output), electrolytes (eg, sodium and potassium), and volume status should be closely monitored.

Cisplatin Nephrotoxicity

Incidence Cisplatin is one of the most important and widely used antineoplastic drugs for the treatment of solid tumors, often demonstrating exceptional efficacy (ie, cure rates over 90% in testicular cancers).[42] Unfortunately, the primary dose-limiting toxicity of platin-containing compounds is nephrotoxicity. Cisplatin

nephrotoxicity occurs in up to one-third of patients receiving the drug and is a significant cause of morbidity.[42,43] Carboplatin, a second-generation platinum analog, is associated with a lower incidence of nephrotoxicity than cisplatin and thus is the preferred agent in high-risk patients.[44]

Clinical Presentation Cisplatin administration results in impaired tubular reabsorption and decreased urinary concentration ability, leading to increased excretion of salt and water (ie, polyuria) within 24 hours of treatment. Polyuria persists, and a decrease in GFR evidenced by a rise in S_{cr} concentration may be seen within 72 to 96 hours after cisplatin administration.[45] S_{cr} peaks approximately 10 to 14 days after initiation of therapy, with recovery by 21 days.[46] As many as 25% of patients may have reversible elevations in S_{cr} and BUN for 2 weeks after cisplatin treatment. However, kidney damage is dose related and cumulative with subsequent cycles of therapy, so the S_{cr} concentration may continue to rise, and irreversible kidney injury may result.[44] Hypomagnesemia is a hallmark finding of cisplatin nephrotoxicity, due to impaired magnesium reabsorption and thus increased urinary losses.[47] Hypomagnesemia is often accompanied by hypocalcemia and hypokalemia and may be severe, leading to seizures, neuromuscular irritability, or personality changes. Urinalysis typically reveals leukocytes, RTECs, and granular casts.

Pathogenesis The pathogenesis of cisplatin nephrotoxicity is multifactorial in nature and likely begins with cellular uptake and accumulation of the drug in proximal tubular epithelial cells to concentrations that may reach five times the serum concentration.[48] Tubular cell exposure to cisplatin then activates a series of cell signaling pathways, including the mitogen-activated protein kinase (MAPK) pathway, p53, caspase, and the generation of reactive oxygen species, that collectively promote tubular cell injury and death via necrosis and/or apoptosis.[42,43] Simultaneous production of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) within tubular cells activates an inflammatory response, which may worsen the renal insult. Although tubular damage is evident in both the proximal and distal segments, the majority occurs in the proximal tubules and is followed by a progressive loss of glomerular filtration capacity and impaired distal tubular function. Renal biopsies generally reveal necrosis-apoptosis of proximal and distal tubules and collecting ducts, with no obvious morphological changes to the glomeruli.[46]

Risk Factors Risk factors include age more than 65 years, dehydration, pre-

existing kidney disease, renal irradiation, concurrent use of nephrotoxic drugs, large cumulative doses, and alcohol abuse.[49]

Prevention The best renoprotective strategy is a combination of interventions, including prospective dose reduction and decreased frequency of administration, which usually requires using the platin compounds in combination with other chemotherapeutic agents, avoiding concurrent use of other nephrotoxic drugs, and ensuring patients are euvolemic or somewhat hypervolemic prior to initiating treatment.[49,50] Vigorous hydration with isotonic saline should be used for all patients with a goal of maintaining at least 100 to 150 mL/hr of urine output during and after cisplatin treatment. Hydration should be initiated 12 to 24 hours prior to and continued for 2 to 3 days after cisplatin administration at rates of 100 to 250 mL/hr, as tolerated, to maintain a urine flow of 3 to 4 L/day.[45]

Amifostine, an organic thiophosphate that is converted to an active metabolite, chelates cisplatin in normal cells and reduces the nephrotoxicity, neurotoxicity, ototoxicity, and myelosuppression associated with cisplatin and carboplatin therapy. It is also thought to serve as a thiol donor, thereby reducing intracellular reactive oxygen species and corresponding oxidative stress that plays a critical role in the development of cellular injury.[43] Amifostine is FDA approved to reduce nephrotoxicity associated with repeated cisplatin treatment in patients with advanced ovarian cancer. Pretreatment with amifostine should be considered for patients who are at high risk for kidney injury, particularly patients who are elderly, volume depleted, have CKD, or are receiving other nephrotoxic drugs concurrently. The current recommended dose of amifostine is 910 mg/m^2 administered IV over 15 minutes, beginning 30 minutes prior to cisplatin administration. Common toxicities include acute hypotension, nausea, and fatigue.

Other renoprotective strategies include the use of hypertonic saline (eg, administration of each dose in 250 mL of 3% saline) to reduce tubular cisplatin uptake. Classic antioxidants such as ascorbic acid, thiol-based antioxidants such as α-lipoic acid and *N*-acetylcysteine, which reduce oxidative damage by acting as a sulfhydryl donor, and the disulfiram metabolite diethyldithiocarbamate to reduce cytochrome P450 2E1–mediated generation of hydroxyl radicals have also been evaluated.[48,51] Finally, reduced renal exposure can be achieved with the use of localized intraperitoneal administration in conjunction with systemic administration of sodium thiosulfate for those with peritoneal tumors.[45]

Management AKI caused by cisplatin therapy is usually partially reversible

with time and supportive care, including dialysis. Kidney function indices should be closely followed, with S_{cr} and BUN concentrations checked daily. Serum magnesium, potassium, and calcium concentrations should be monitored daily and corrected as needed.[44] Hypocalcemia and hypokalemia may be difficult to reverse until hypomagnesemia is corrected. Progressive kidney disease caused by cumulative nephrotoxicity may be irreversible and in some cases may lead to ESRD and require chronic dialysis support.[44]

Amphotericin B Nephrotoxicity

Incidence Variable rates of amphotericin B nephrotoxicity have been reported that correspond in large part to the cumulative dose administered. Nephrotoxicity may be seen in nearly 30% of patients receiving median cumulative doses as low as 240 mg and reaches an incidence of greater than 80% when cumulative doses approach 5 g.[52–54] Although numerous studies demonstrate lower rates of nephrotoxicity with liposomal formulations compared with conventional amphotericin B, it is difficult to compare rates of toxicity between products and studies because of the variability in the study populations, doses administered, and inconsistent definitions of nephrotoxicity and methods of assessment.[52,53,55]

Clinical Presentation Dose-dependent nephrotoxicity is often evident after administration of cumulative doses of 2 to 3 g as nonoliguria, renal tubular potassium, sodium, and magnesium wasting, impaired urinary concentrating ability, and distal renal tubular acidosis.[23,55] Although the cumulative dose is a significant risk factor, the time to onset of kidney injury varies considerably, ranging from a few days to weeks. Tubular dysfunction usually manifests 1 to 2 weeks after treatment is begun, and potassium and magnesium replacement may be necessary.[52] This is typically followed by a decrease in GFR and a rise in S_{cr} and BUN concentrations. Consequently, kidney function indices should be closely followed, with S_{cr} and BUN concentrations checked daily, and serum magnesium, potassium, and calcium concentrations monitored every other day and corrected as needed.

Pathogenesis Amphotericin B nephrotoxicity occurs predominantly via two mechanisms. The first is direct tubular epithelial cell toxicity resulting from interaction of amphotericin B with ergosterol in the cell membrane, leading to increased tubular cell membrane permeability, lipid peroxidation, and eventual necrosis of proximal tubular cells.[55] The second mechanism is afferent arteriolar vasoconstriction leading to a reduction in renal blood flow and GFR, and

ischemic tubular injury.[23,55]

Risk Factors Risk factors that impact the likelihood of developing amphotericin B nephrotoxicity include pre-existing kidney disease, large individual and cumulative doses, short infusion times, volume depletion, hypokalemia, increased age, and concomitant administration of diuretics and other nephrotoxins, including vancomycin and cyclosporine.[52,55]

Prevention Permanent decrements in GFR are best prevented by incorporating a low threshold (ie, if S_{cr} reaches 2 mg/dL [177 µmol/L] on 2 consecutive days) for stopping amphotericin B or switching to a liposomal formulation. Several lipid formulations of amphotericin B (eg, amphotericin B lipid complex, liposomal amphotericin B) are available and should be used in most high-risk patients as they reduce nephrotoxicity by enhancing drug delivery to sites of infection and reducing interaction with tubular epithelial cell membranes.[53,55] Nephrotoxicity can also be minimized by limiting the cumulative dose, increasing the infusion time, ensuring the patient is well hydrated, and avoiding concomitant administration of other nephrotoxins.[55] Administration of 1 L IV 0.9% sodium chloride daily during the course of therapy appears to reduce toxicity and a single infusion of saline 10 to 15 mL/kg prior to administration of each dose of amphotericin B is generally recommended.[55] A number of other antifungal agents such as itraconazole, voriconazole, and caspofungin are viable alternatives and are now routinely used in lieu of amphotericin B for patients at high risk of developing nephrotoxicity. Administration of the antioxidant *N*-acetylcysteine (600 mg orally twice daily in adults) during amphotericin treatment may be nephroprotective.[56]

Management Amphotericin B nephrotoxicity is best treated by discontinuation of therapy and substitution of alternative antifungal therapy, if possible. Renal tubular dysfunction and glomerular filtration will improve gradually to some degree in most patients, but damage may be irreversible. Kidney function indices should be closely followed, with S_{cr} and BUN concentrations checked daily, and serum magnesium, potassium, and calcium concentrations should be monitored daily and corrected as needed.

Osmotic Nephropathy

Several drugs, including mannitol, low-molecular-weight dextran, hydroxyethyl starch, and radiographic contrast media, or drug vehicles, such as sucrose,

maltose, and propylene glycol, are associated with osmotic nephropathy, which may rarely lead to ATN and AKI.[57] Since osmotic nephropathy does not necessarily negatively affect proximal tubular function, its presence may often go undetected in patients without overt signs of ATN. This likely contributes to the extremely low incidence of osmotic nephropathy reported for causative agents. IV immunoglobulin solutions containing hyperosmolar sucrose may cause osmotic nephropathy and AKI in 1% to 10% of cases, which is usually reversible shortly after discontinuing therapy.[58,59] Maltose-based IV immunoglobulin solutions have also been implicated in the development of osmotic nephropathy. Although IV immunoglobulin-induced AKI is the modern prototype for osmotic nephropathy, it is understood that the vehicle (ie, sucrose or maltose) is the culprit and not the immunoglobulins themselves.[59]

Clinical Presentation

The clinical presentation of osmotic nephropathy is often subtle. While tubular proteinuria or vacuolated tubular cells may be observed on urinalysis for patients with AKI, the definitive diagnosis of osmotic nephropathy is only made via a kidney biopsy.[58] IV immunoglobulin-induced AKI typically presents as oliguria after 2 to 4 days of treatment and may persist for up to 2 weeks. Kidney injury occurs via uptake of the offending agent through pinocytosis into proximal tubular epithelial cells, subsequent formation of vacuoles, and accumulation of lysosomes, which collectively results in an oncotic gradient and thus cellular swelling, tubular luminal occlusion, and compromised cellular integrity.[60] Renal replacement therapy may be necessary for up to 40% of patients developing osmotic nephropathy-associated AKI.[58] However, it is usually reversible, with nearly all patients recovering normal kidney function following withdrawal of the offending drug.

Risk Factors

Risk factors for osmotic nephropathy include excessive doses of offending agents, pre-existing kidney disease, ischemia, older age (greater than 65 years), and concomitant use of other nephrotoxins. Nephrotoxicity may be prevented by limiting the dose, reducing the rate of infusion, and avoiding dehydration and concomitant nephrotoxins.[59,60]

HEMODYNAMICALLY MEDIATED KIDNEY

INJURY

4 Hemodynamically mediated kidney injury generally refers to any cause of AKI resulting from an acute decrease in intraglomerular pressure, including "prerenal" states leading to reduced effective renal blood flow (eg, hypovolemia and congestive heart failure) and medications that affect the renin–angiotensin system (RAS).[23,61] The kidneys receive approximately 25% of resting cardiac output, which renders them particularly susceptible to alterations in renal blood flow and enhances their exposure to circulating drugs.[16,62] Within each nephron, blood flow and pressure are regulated by glomerular afferent and efferent arterioles to maintain intraglomerular capillary hydrostatic pressure, glomerular filtration, and urine output. Afferent and efferent arteriolar vasoconstrictions are primarily mediated by angiotensin II, whereas afferent vasodilation is primarily mediated by prostaglandins (**Fig. 63-1**). This specialized blood flow is precisely regulated by interrelations between arachidonic acid metabolites, natriuretic factors, nitric oxide, the sympathetic nervous system, the RAS, and the macula densa response to distal tubular solute delivery.[62] Drug-induced causes of hemodynamic kidney injury typically stem from constriction of glomerular afferent arterioles and/or dilation of glomerular efferent arterioles. ACEIs, angiotensin II receptor blockers (ARBs), and NSAIDs are the agents that have been most commonly implicated.[23,63]

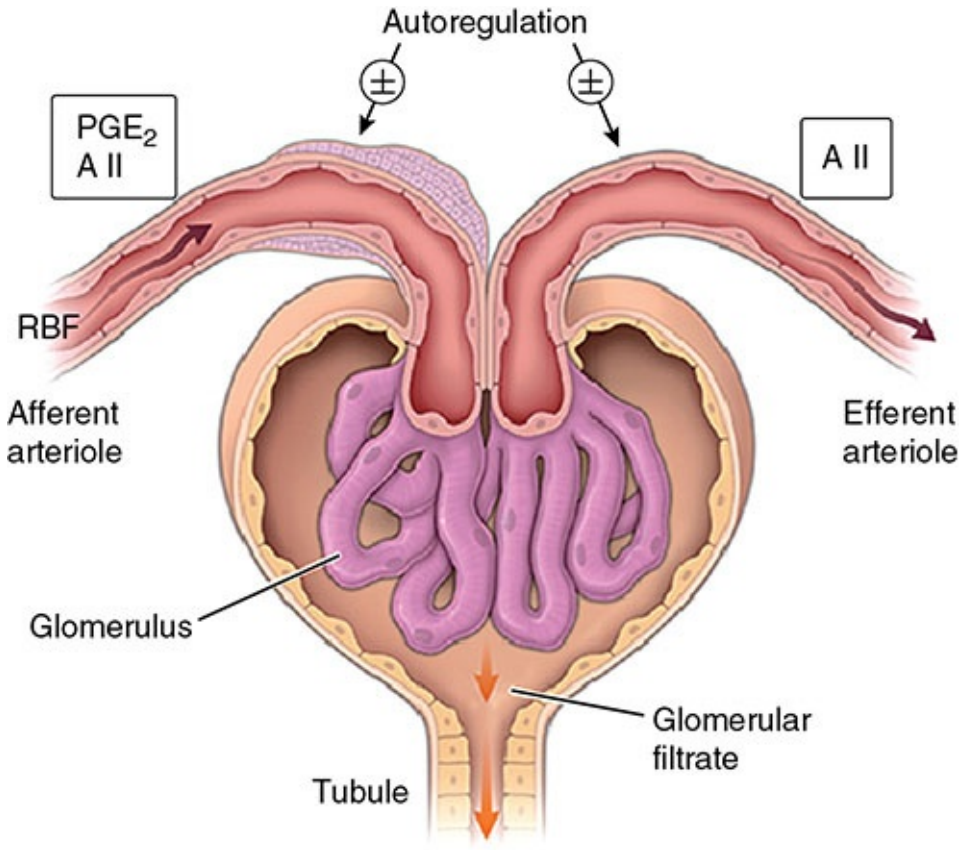


FIGURE 63-1 Normal glomerular autoregulation serves to maintain intraglomerular capillary hydrostatic pressure, glomerular filtration rate, and, ultimately, urine output. (A II, angiotensin II; PGE_2, prostaglandin E_2; RBF, renal blood flow.)

Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers

Angiotensin-converting enzyme inhibitors (ACEIs) and ARBs are extensively utilized for the management of hypertension and prevention of the progression of CKD even though they have been associated with the development of AKI.

Incidence

Patients with renal artery stenosis, volume depletion, and congestive heart failure and those with pre-existing kidney disease, including diabetic nephropathy, are most likely to experience a significant decline in kidney function when therapy with one of these agents is initiated.[23] For example, up to 25% of hospitalized patients with congestive heart failure develop AKI within weeks after beginning

treatment with ACEIs.[64] Moreover, ACEIs and ARBs are among the most commonly implicated medications in emergency hospitalizations, contributing to nearly 3% of emergency room visits for adverse drug events.[65]

Clinical Presentation

Therapy with ACEIs and ARBs will acutely reduce GFR; so a moderate rise in S_{cr} after initiation of therapy should be anticipated.[66] Importantly, a distinction must be made between a potentially detrimental reduction in GFR and a normal, predictable rise in S_{cr}. An increase in S_{cr} of up to 30% is commonly observed within 3 to 5 days of initiating therapy and is an indication that the drug has begun to exert its desired pharmacologic effect.[66] The increase in S_{cr} typically stabilizes within 1 to 2 weeks and is usually reversible upon stopping the drug. Furthermore, an association exists between acute increases in S_{cr} of less than or equal to 30% from baseline that stabilize within the first 2 months of initiating therapy and preservation of kidney function. The S_{cr} threshold for discontinuation of ACEI or ARB therapy is unclear. However, an increase in S_{cr} of more than 30% above baseline in the course of 1 to 2 weeks may necessitate discontinuation of the offending drug.[66]

Pathogenesis

Angiotensin-converting enzyme inhibitors—or ARB-mediated kidney injury—is primarily the result of disruption of normal autoregulation of intraglomerular capillary hydrostatic pressure.[23] Normally, the kidney attempts to maintain GFR by dilating the afferent arteriole and constricting the efferent arteriole in response to a decrease in renal blood flow. During states of reduced blood flow, the juxtaglomerular apparatus increases renin secretion. Plasma renin converts angiotensinogen to angiotensin I, and ultimately angiotensin II by angiotensin-converting enzyme. Angiotensin II constricts the afferent and efferent arterioles, but has a greater effect on the efferent arterioles, resulting in a net increase in intraglomerular pressure.[62] Additionally, renal prostaglandins, prostaglandin E_2 in particular, are released and induce a net dilation of the afferent arteriole, thereby improving blood flow into the glomerulus. Together these processes maintain GFR and urine output (**Fig. 63-2**).

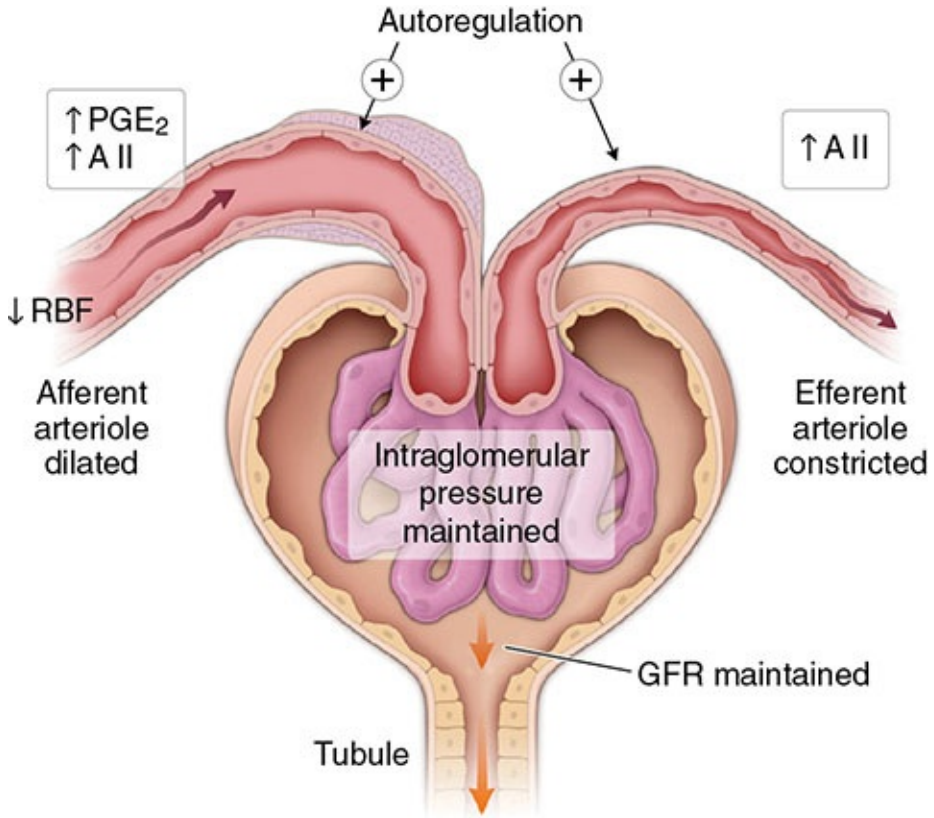


FIGURE 63-2 Glomerular autoregulation during "prerenal" states (ie, reduced blood flow). (A II, angiotensin II; GFR, glomerular filtration rate; PGE_2, prostaglandin E_2; RBF, renal blood flow.)

When ACEI therapy (eg, enalapril or ramipril) is initiated, the synthesis of angiotensin II is decreased, thereby preferentially dilating the efferent arteriole. This reduces outflow resistance from the glomerulus and decreases hydrostatic pressure in the glomerular capillaries, which alters Starling forces across the glomerular capillaries to decrease intraglomerular pressure and GFR. This in turn often leads to nephrotoxicity, particularly in the setting of reduced renal blood flow or effective arterial blood volume (**Fig. 63-3**), that is, prerenal settings (eg, congestive heart failure) in which glomerular afferent arteriolar blood flow is reduced and the efferent arteriole is vasoconstricted to maintain sufficient glomerular capillary hydrostatic pressure for ultrafiltration.[23]

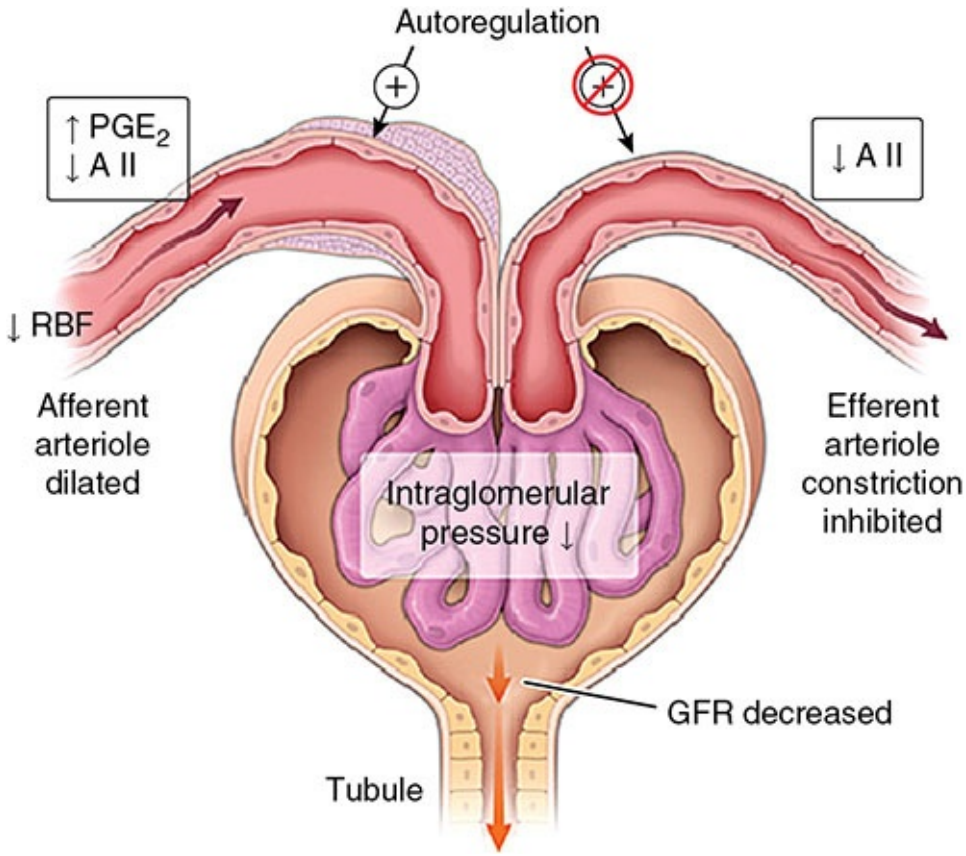


FIGURE 63-3 Pathogenesis of angiotensin-converting enzyme inhibitor (ACEI) nephropathy. (A II, angiotensin II; GFR, glomerular filtration rate; PGE_2, prostaglandin E_2; RBF, renal blood flow.)

Risk Factors

Patients at greatest risk are those dependent on angiotensin II and renal efferent arteriolar constriction to maintain blood pressure and GFR. These include patients with bilateral renal artery stenosis or stenosis in a single kidney (ie, renal transplant); patients with decreased effective arterial blood volume (ie, prerenal states), especially those with decompensated congestive heart failure, volume depletion from excess diuresis or GI fluid loss, hepatic cirrhosis with ascites, and nephrotic syndrome; patients with pre-existing kidney disease; and patients receiving concurrent nephrotoxic drugs, particularly other drugs that affect intraglomerular autoregulation such as NSAIDs.[23,63,67]

Prevention

Hemodynamically mediated AKI caused by ACEIs or ARBs is frequently preventable by recognizing the presence of pre-existing kidney disease or

decreased effective renal blood flow as a result of volume depletion, heart failure, or liver disease. A common strategy for at-risk patients is to initiate therapy with very low doses of a short-acting ACEI (eg, captopril 6.25-12.5 mg), then gradually titrate the dose upward and convert to a longer-acting agent after patient tolerance has been demonstrated. Outpatients may be started on low doses of long-acting ACEIs (eg, enalapril 2.5 mg) with gradual dose titration every 2 to 4 weeks until the maximum dose or desired response is achieved.[66] Kidney function indices and serum potassium concentrations must be monitored carefully, daily for hospitalized patients and every 2 to 3 days for outpatients. Monitoring may need to be more frequent during outpatient initiation of ACEI or ARB therapy for patients with pre-existing kidney disease, congestive heart failure, or suspected renovascular disease. Use of concurrent hypotensive agents and other drugs that affect renal hemodynamics (eg, NSAIDs, diuretics) should be discouraged and dehydration avoided.[66]

Management

Acute decreases in kidney function and the development of hyperkalemia usually resolve over several days after ACEI or ARB therapy is discontinued. Occasionally patients will require management of severe hyperkalemia, as described in detail in Chapter 68, “Potassium and Magnesium Homeostasis.”

Angiotensin-converting enzyme inhibitors or ARB therapy may frequently be reinitiated, particularly for patients with congestive heart failure, after intravascular volume depletion has been corrected or diuretic doses reduced. Slight reductions in kidney function (maintenance of a S_{cr} concentration of 2-3 mg/dL [177-265 µmol/L]) may be an acceptable trade-off for hemodynamic improvement in certain patients with severe congestive heart failure or renovascular disease not amenable to revascularization.

Nonsteroidal Anti-Inflammatory Drugs and Selective Cyclooxygenase-2 Inhibitors

The overall safety of NSAIDs is evidenced by the nonprescription availability in the United States of several drugs in the class (eg, ibuprofen, naproxen, ketoprofen). Although potential adverse renal effects from nonprescription NSAIDs had been a concern, conventional nonselective NSAIDs and selective cyclooxygenase-2 (COX-2) inhibitors are unlikely to acutely affect kidney function in the absence of renal ischemia or excess renal vasoconstrictor activity.

Nevertheless, given their general safety and widespread availability, NSAIDs are among the most commonly used drugs, with approximately 111 million prescriptions worldwide and 30 billion over-the-counter doses of NSAIDs administered annually in the United States.[68]

Incidence

The incidence of NSAID-induced kidney injury is unclear. Historical reports suggest that 500,000 to 2.5 million people develop some degree of NSAID nephrotoxicity in the United States annually.[69]

Clinical Presentation

NSAID- and COX-2-induced AKI usually occurs within 2 to 7 days of initiating therapy,[61,68] particularly with a short-acting agent such as ibuprofen, or within days of some other precipitating event (eg, intravascular volume depletion). Patients typically present with complaints of diminished urine output, weight gain, and/or edema. Urine sodium concentrations (less than 20 mEq/L [mmol/L]) and fractional excretion of sodium (less than 1% [0.01]) are usually low, and BUN, S_{cr}, potassium, and blood pressure are typically elevated. The urine sediment is usually bland and unchanged from baseline but may show occasional RTECs and granular casts.[61,68]

Pathogenesis

The pathogenesis of NSAID- and COX-2-induced AKI lies in the disruption of normal intraglomerular autoregulation.[61] Specifically, NSAIDs inhibit cyclooxygenase (COX)-catalyzed synthesis of vasodilatory prostaglandins, including prostaglandins I_2 (prostacyclin) and E_2, from arachidonic acid.[68] These prostaglandins are synthesized in the renal cortex and medulla by vascular endothelial and glomerular mesangial cells, and their effects are primarily local and result in net afferent arteriolar vasodilation. Vasodilatory prostaglandins have limited activity in states of normal renal blood flow, but in states of decreased renal blood flow, their synthesis is increased and they serve a vital autoregulatory role in the protection against renal ischemia and hypoxia by antagonizing renal arteriolar vasoconstriction due to angiotensin II, norepinephrine, endothelin, and vasopressin. Thus, administration of NSAIDs in the setting of reduced renal blood flow will blunt the usual compensatory increase in prostaglandin activity, altering the normal autoregulatory balance in favor of renal vasoconstrictors, thereby promoting renal ischemia and a

reduction in glomerular filtration.[68]

Risk Factors

Risk factors for NSAID- and COX-2-induced AKI include age more than 60 years, pre-existing kidney disease, hepatic disease with ascites, congestive heart failure, intravascular volume depletion/dehydration, systemic lupus erythematosus, or concurrent treatment with diuretics, ACEIs, or ARBs.[63,67,68] Use of ACEIs, diuretics, and NSAIDs concurrently is associated with a greater than 30% increased risk for AKI, which increases to greater than 60% in patients over age 75 or with pre-existing kidney disease.[63,67] The elderly people are at higher risk because of multiple comorbidities, multiple-drug therapies, and reduced renal hemodynamics. Combined use of NSAIDs or COX-2 inhibitors and concurrent nephrotoxic drugs, particularly other drugs that affect intraglomerular autoregulation, should be avoided in high-risk patients.

Prevention

NSAID- and COX-2 inhibitor–induced AKI can be prevented by recognizing high-risk patients, avoiding potent compounds such as indomethacin and using analgesics with less prostaglandin inhibition, such as acetaminophen, nonacetylated salicylates, aspirin, and possibly nabumetone. Nonnarcotic analgesics (eg, tramadol) may also be useful but do not provide anti-inflammatory activity. When NSAID therapy is essential for high-risk patients, the minimal effective dose should be used for the shortest duration possible, and NSAIDs with short half-lives should be considered (eg, sulindac) along with optimal management of predisposing medical problems and frequent kidney function monitoring. Moreover, use of concurrent hypotensive agents and other drugs that affect renal hemodynamics (eg, ACEIs, ARBs, diuretics) should be discouraged in high-risk patients and dehydration avoided.[68]

Management

NSAID-induced AKI is treated by discontinuation of therapy and supportive care. Use of other nephrotoxic drugs should be avoided. Kidney injury is rarely severe, and kidney function generally recovers within 3 to 5 days.[61] Occasionally, the hemodynamic insult is sufficiently severe to cause ATN, which can prolong injury.

Cyclosporine and Tacrolimus

The calcineurin inhibitors cyclosporine and tacrolimus have dramatically enhanced the success of solid-organ transplantation. As many as 94% of kidney transplant patients are prescribed a calcineurin inhibitor–based immunosuppressive regimen.[70] Nephrotoxicity, however, remains a major dose-limiting adverse effect of both drugs. Although delayed chronic interstitial nephritis has also been reported,[71] acute hemodynamically mediated kidney injury is an important mechanism of calcineurin inhibitor–induced nephrotoxicity.

Incidence

Historically, reversible AKI occurred frequently in transplant recipients during the first 6 months of cyclosporine therapy. The 5-year risk of CKD after transplantation of a nonrenal organ ranges from 7% to 21%, depending on the type of organ transplanted, and the occurrence of CKD in these patients is associated with more than a fourfold increase in the risk of death.[72]

Clinical Presentation

The clinical presentation of acute nephrotoxicity associated with calcineurin inhibitors (ie, hemodynamically mediated AKI) is quite different from the presentation of chronic nephrotoxicity (see “Chronic Interstitial Nephritis” section).[73] AKI may occur within days of initiating therapy, manifesting as a rise in S_{cr} concentration and a corresponding decline in creatinine clearance. Hypertension, hyperkalemia, sodium retention, oliguria, renal tubular acidosis, and hypomagnesemia are frequently observed in the absence of urine sediment abnormalities or morphologic lesions.[70] On the other hand, renal biopsy may reveal thickening of arterioles, mild focal glomerular sclerosis, proximal tubular epithelial cell vacuolization and atrophy, and interstitial fibrosis. Biopsy is most useful to distinguish acute calcineurin inhibitor nephrotoxicity from acute cellular rejection of the transplanted kidney, the latter being evidenced by interstitial infiltrates composed of activated lymphocytes (see Chapter 106, “Osteoarthritis”).[74]

Pathogenesis

The acute hemodynamic changes associated with calcineurin inhibitor nephrotoxicity result from an increase in potent vasoconstrictors including

thromboxane A_2 and endothelin, activation of the renin–angiotensin and sympathetic nervous systems, as well as a reduction in the vasodilators nitric oxide, prostacyclin, and prostaglandin E_2.[70,72,73] The net effect is an imbalance in afferent and efferent tone, resulting in predominantly afferent vasoconstriction with reduced renal plasma flow and GFR. The mechanism of acute nephrotoxicity is generally thought to be dose related, since kidney function improves rapidly following dose reduction.[73]

Risk Factors

Risk factors include age over 65, higher dose, concomitant therapy with nephrotoxic drugs (particularly NSAIDs), and interacting drugs that inhibit calcineurin inhibitor metabolism and transport and thus increase systemic exposure, older kidney allograft age, salt depletion, diuretic use, and polymorphic expression of P-glycoprotein.[70,74]

Prevention

Because acute hemodynamically mediated kidney injury secondary to cyclosporine and tacrolimus appears to be concentration related, pharmacokinetic and pharmacodynamic monitoring is an important means of preventing toxicity.[70] However, the persistent presence of therapeutic or low cyclosporine concentrations does not totally preclude the development of nephrotoxicity. Calcium channel blockers may antagonize the vasoconstrictor effect of cyclosporine by dilating glomerular afferent arterioles and preventing acute decreases in renal blood flow and glomerular filtration.[70] Lastly, decreased doses of cyclosporine or tacrolimus, primarily when used in combination with other nonnephrotoxic immunosuppressants, may minimize the risk of toxicity, but this may increase the risk of chronic rejection.

Management

Acute kidney injury usually improves with dose reduction and treatment of contributing illness or the discontinuation of interacting drugs. CKD is usually irreversible, but progressive toxicity may be limited by discontinuation of cyclosporine (or tacrolimus) therapy or dose reduction, with the continuation of other immunosuppressants.[70,73] S_{cr} and BUN should be closely monitored (daily if possible), as should cyclosporine or tacrolimus concentrations, to ensure that serum concentrations are within the narrow therapeutic range.

SGLT-2 Inhibitors

The sodium-glucose co-transporter-2 (SGLT-2) inhibitors (eg, empagliflozin, canagliflozin, dapagliflozin) are now being employed frequently to enhance serum glucose control in patients with type 2 diabetes mellitus.[75] Clinical trials have demonstrated that these drugs are nephroprotective.[76,77] As such, they are FDA approved and now used in addition to metformin to help with glucose control in patients with type 2 diabetes mellitus. The estimated GFR cutoffs for use of these drugs is <60 mL/min/1.73 m^2 for dapagliflozin and <45 mL/min/1.73 m^2 for empagliflozin and canagliflozin. However, AKI is one complication of canagliflozin and dapagliflozin that has been reported to the FDA Adverse Event Reporting System (FAERS). This led the FDA to issue an FDA Drug Safety Communication, http://www.fda.gov/downloads/Drugs/DrugSafety/UCM506772.pdf, for these two SGLT-2 inhibitors.

Incidence

There is no estimated incidence of AKI available for these drugs. However, over 100 cases of AKI associated with the SGLT-2 inhibitors have been reported to FAERS. This contrasts with the randomized controlled trials that do not note AKI as a complication of these drugs.[76,77] In addition, a propensity-matched analysis also showed no signal for AKI with these drugs.[78]

Pathogenesis

The increase in serum creatinine and development of AKI are likely related to a number of processes. As these drugs induce glucosuria due to inhibition of proximal tubular glucose reabsorption, they induce an osmotic diuresis (natriuresis) that can lead to volume depletion, especially when used along with diuretics. SGLT-2 inhibitor related volume depletion in the setting of RAS blocker therapy (ie, ACEI or ARB therapy) can lead to prominent hemodynamic (prerenal) AKI. When severe, acute tubular injury may develop leading to a classic form of ATN. In addition, the delivery of sodium chloride to the macula densa also induces a phenomenon known as tubuloglomerular feedback, which vasoconstricts glomerular afferent arterioles and reduces GFR, ultimately causing an increase in serum creatinine. The increase in serum creatinine may be interpreted by clinicians as indicative of AKI. However, over the long term, this effect is thought to be one of the major nephroprotective mechanisms of the SGLT-2 inhibitors by reducing hyperfiltration-related injury. It is also possible

that the SGLT-2 inhibitors may cause direct tubular injury. Uricosuria induced by these drugs may cause both crystal-related tubular injury (crystal nephropathy) and crystal-independent mechanisms of injury.[79] Also, increased urinary glucose may promote intratubular oxidative stress by activating aldose reductase and sorbitol and fructose generation.[79]

Risk Factors

According to the FAERS reports, many patients developing AKI with these drugs were older, were also treated with RAS blockers and diuretics, and sometimes were also taking other nephrotoxins such as NSAIDs. Clearly, combining these drugs with the SGLT-2 inhibitors may lead to AKI when volume depletion occurs. Also, concurrent illness that leads to volume depletion (nausea, vomiting, diarrhea) may also increase risk for AKI.

Prevention

Prevention of AKI in patients with type 2 diabetes mellitus taking these drugs requires careful follow-up in patients who are also taking RAS blockers and diuretics. Patients should be counseled to avoid other nephrotoxins, in particular NSAIDs and COX-2 inhibitors, and contact their care provider when a concurrent illness develops. This will allow timely adjustment of the medications.

Management

When AKI develops, stopping the SGLT-2 inhibitor often is enough to allow kidney recovery. However, in patients with volume depletion on exam, holding the SGLT-2 inhibitor (and RAS blocker and diuretic if also prescribed) and giving intravenous fluids typically resolve AKI. In cases where ATN develops, the SGLT-2 inhibitor should be held and usual supportive care, including RRT when required, should be undertaken. The SGLT-2 inhibitor can likely be restarted in patients where kidney function recovers to baseline and eGFR is above the FDA-recommended threshold.

OBSTRUCTIVE NEPHROPATHY

Numerous medications may cause obstructive nephropathy, or kidney injury from deposition or precipitation within the renal tubules and/or collecting system. For example, the precipitation of drug crystals in distal tubular lumens

can lead to intratubular obstruction, interstitial nephritis, and occasionally superimposed ATN, collectively termed crystal nephropathy. Nephrolithiasis, the formation of stones within the kidney, results from abnormal crystal precipitation in the renal collecting system, potentially causing urinary tract obstruction with kidney injury. Several medications that have been associated with development of obstructive nephropathy are listed in Table 63-1.

Crystal Nephropathy

Incidence

The incidence of crystal nephropathy is unclear for most of the implicated agents because histologically confirmed cases are rare, and many drugs cause kidney injury via multiple mechanisms.[80] For example, AKI develops in approximately 2% of patients who receive high-dose methotrexate, likely due to a combination of direct toxic effects and crystal nephropathy.[81,82] Similarly, crystalluria is observed in 20% of patients receiving indinavir, but the number of patients developing crystal nephropathy is unknown.[83]

Pathogenesis

Drugs may induce intratubular obstruction and AKI by direct (precipitation of the drug itself) and indirect means (ie, promoting release and precipitation of tissue-degradation products or cellular casts). For example, antineoplastic drugs may cause acute renal tubular obstruction indirectly by inducing tumor lysis syndrome, hyperuricemia, and intratubular precipitation of uric acid crystals.[49] The diagnosis is supported by a urine uric acid-to-creatinine ratio greater than 1. Uric acid precipitation can be prevented by vigorous hydration with normal saline, beginning at least 48 hours prior to chemotherapy, to maintain urine output 100 mL/hr in adults. Administration of allopurinol 100 mg/m^2 thrice daily (maximum of 800 mg/day) started 2 to 3 days prior to chemotherapy, and urinary alkalinization to pH 7 may also be of value. In patients at high risk of developing tumor lysis syndrome (ie, large tumor burden, pre-existing kidney disease, and older age), a single fixed dose of 3 mg rasburicase may be beneficial.[84]

Drug-induced rhabdomyolysis is another form of indirect toxicity, which can lead to intratubular precipitation of myoglobin and, if severe, AKI.[85] The most common cause of drug-induced rhabdomyolysis is direct myotoxicity from 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors or statins, including lovastatin and simvastatin.[86] The risk of rhabdomyolysis is

increased when these drugs are administered concurrently with gemfibrozil, niacin, or inhibitors of the CYP3A4 metabolic pathway (eg, erythromycin and itraconazole).

Anticoagulant nephropathy, including warfarin-related nephropathy (WRN), is characterized by glomerular hemorrhage with subsequent intratubular obstruction by red blood cell casts. Patients with underlying CKD appear to be at greatest risk. The incidence of WRN may be as high as 33% in CKD versus 16.5% in non-CKD patients. Other risk factors included age, diabetes mellitus, hypertension, and cardiovascular disease.[87]

Intratubular precipitation of drugs or their metabolites can also directly cause AKI. Precipitation of drug crystals is due primarily to supersaturation of a low urine volume with the offending drug or relative insolubility of the drug in either alkaline or acidic urine.[83] Volume depletion is an important risk factor for the development of AKI. Urine pH decreases to approximately 4.5 during maximal stimulation of renal tubular hydrogen ion secretion. Certain solutes can precipitate and obstruct the tubular lumen at this acid pH, particularly when urine is concentrated, such as for patients with volume depletion. For example, several antiviral drugs have been associated with intratubular precipitation and AKI.[88,89] Acyclovir is relatively insoluble at physiologic urine pH and is associated with intratubular precipitation in dehydrated oliguric patients.[83] Foscarnet complexation with ionized calcium may result in precipitation of calcium-foscarnet salt crystals in renal glomeruli, causing primarily a crystalline glomerulonephritis. The salt crystals may then secondarily precipitate in the renal tubules causing tubular necrosis.[23] The protease inhibitors indinavir and atazanavir have been associated with symptomatic crystalluria or nephrolithiasis in 20% to 33% of patients receiving chronic treatment.[83,89] Intratubular indinavir or atazanavir crystal precipitation can be prevented in most patients if the patient consumes adequate hydration to obtain a urinary output of at least 1,500 mL/day.[88] Sulfadiazine, when used at high doses, and methotrexate may also precipitate in acidic urine and can cause oligoanuric kidney injury.[83] Massive administration of ascorbic acid can also result in obstruction of renal tubules with calcium oxalate crystals, leading to “oxalate nephropathy.”[83] Triamterene and the quinolone antibiotic ciprofloxacin may also precipitate in renal tubules and cause kidney injury.[23,80]

Kidney injury caused by intratubular precipitation of most tissue-degradation products or drugs and their metabolites can be largely prevented and possibly treated by administering the drug after vigorously prehydrating the patient,

maintaining a high urine volume, and urinary alkalinization.[88,89]

NEPHROCALCINOSIS

Nephrocalcinosis is a clinical pathologic condition characterized by extensive tubulointerstitial precipitation and deposition of calcium phosphate crystals leading to marked tubular calcification.[90] It is most commonly seen in clinical conditions associated with hypercalcemia and hypercalciuria, such as hyperparathyroidism, malignancy, and less frequently increased intake of calcium or vitamin D. However, nephrocalcinosis can also result from hyperphosphatemia and hyperphosphaturia in the absence of hypercalcemia, as is known to occur for patients who have received oral sodium phosphate solution (OSPS) as a bowel preparation.[91]

Acute Phosphate Nephropathy

The term acute phosphate nephropathy was coined specifically to describe OSPS-induced nephrocalcinosis, as its pathogenesis is the result of increased phosphate intake rather than hypercalcemia.[91] Nephrocalcinosis is associated with use of OSPS for bowel preparation prior to GI procedures, and strong associations have recently been demonstrated between exposure to OSPS and a decline in kidney function, particularly in the elderly and those with pre-existing kidney disease.[91,92]

Incidence

The incidence of acute phosphate nephropathy is between 1 in 1,000 and 1 in 5,000 exposures, translating to roughly 1,400 to 7,000 new cases annually.[93]

Clinical Presentation

Patients usually present with AKI several days to months after exposure to OSPS. Low-grade proteinuria (less than 1 g/day), normocalcemia, and bland urinary sediment are usually observed. Extensive deposition of calcium phosphate in the distal tubules and collecting ducts without glomerular or vascular injury is the hallmark of acute phosphate nephropathy.[83]

Risk Factors

Risk factors include advanced age, pre-existing kidney disease, female sex, hypertension, diabetes, bowel conditions associated with prolonged intestinal transit, high sodium phosphate dosage, volume depletion, and medications that affect renal perfusion or function (eg, diuretics, lithium, NSAIDs, ACEIs, or ARBs).[91]

NEPHROLITHIASIS

Nephrolithiasis (formation of renal calculi or kidney stones) does not present as classic nephrotoxicity since GFR is usually not decreased. Drug-induced nephrolithiasis can be the result of abnormal crystal precipitation in the renal collecting system, potentially causing pain, hematuria, infection, or, occasionally, urinary tract obstruction with kidney injury. The overall prevalence of drug-induced nephrolithiasis is estimated to be 1% to 2% of all cases of nephrolithiasis.[89]

Kidney stone formation, possibly also accompanied by intratubular precipitation of crystalline material, has been a rare complication of drug therapy. Until the development of antiretroviral drugs, triamterene had been the drug most frequently associated with kidney stone formation, with a prevalence of 0.4%.[80] Sulfadiazine is a poorly soluble sulfonamide that may cause symptomatic acetylsulfadiazine crystalluria with stone formation and flank or back pain, hematuria, or kidney injury.[83] A high urine volume and urinary alkalinization to pH greater than 7.15 may be protective. Numerous other drugs have been implicated in the development of nephrolithiasis, including the antibacterial agents ciprofloxacin, amoxicillin, and nitrofurantoin, and various products containing ephedrine, norephedrine, pseudoephedrine, and melamine. Moreover, nephrolithiasis has become a well-known complication of antiretroviral agents, including the protease inhibitors indinavir, atazanavir, nelfinavir, amprenavir, saquinavir, ritonavir, and darunavir.[89]

GLOMERULAR DISEASE

Proteinuria, particularly nephrotic range proteinuria (defined as urine protein excretion greater than 3.5 g/day) with or without a decline in the GFR is a hallmark sign of glomerular injury (see Chapter 64, “Glomerulonephritis”). Glomerular injury associated with drug exposure is broadly classified into either direct cellular toxicity or immune-mediated injury. Glomerular lesions associated

with direct cellular toxicity include thrombotic microangiopathy (see “Renal Vasculitis” section), minimal change glomerular disease, and focal segmental glomerulosclerosis (FSGS). Lesions from immune-mediated injury include vasculitis (see “Renal Vasculitis” section) and membranous nephropathy.[94,95] Although drug-induced glomerular disease is uncommon, a variety of agents have been implicated.

Minimal Change Glomerular Disease

Drug-induced minimal change glomerular disease is frequently accompanied by interstitial nephritis and is most common during NSAID therapy. Lithium, pamidronate, interferon-α, and interferon-β have also been implicated.[94] Patients present abruptly with nephrotic range proteinuria, hypoalbuminemia, and hyperlipidemia and rarely with hematuria and hypertension. The pathogenesis is unknown, but nephrotic range proteinuria as a consequence of NSAID therapy is frequently associated with a T-lymphocytic interstitial infiltrate, suggesting disordered cell-mediated immunity.[68] Proteinuria usually resolves rapidly after discontinuation of the offending drug, and a course of corticosteroids may help resolve the lesion. That said, the majority of adults with NSAID-induced minimal change glomerular disease achieve complete remission over the course of several months, even in the absence of corticosteroid treatment.[94]

Focal Segmental Glomerulosclerosis

Focal segmental glomerulosclerosis is characterized by patchy areas (ie, only some glomeruli are partially affected by the disease) of glomerular sclerosis with interstitial inflammation and fibrosis (see Chapter 64). It represents a pattern of glomerular injury, not a disease per se, and is the final common pathway by which normal glomerular components are replaced by fibrous scar tissue. FSGS has been described in the setting of chronic heroin abuse (known as *heroin nephropathy*).[96] The pathogenesis is unknown but may include direct toxicity by heroin or adulterants and injury from bacterial or viral infections accompanying IV drug use. The bisphosphonates pamidronate and zoledronate, commonly used to treat osteoporosis, malignancy-associated hypercalcemia, and Paget’s disease, are associated with the development of a particularly aggressive variant of FSGS called *collapsing glomerulopathy*.[94] It presents with massive proteinuria (greater than 8 g/day), and it is typically characterized by rising S_{cr} at diagnosis and rapid progression to ESRD. Patients receiving IV formulations, high doses, or

prolonged therapy are at highest risk. Interferon-α, interferon-β, lithium, sirolimus, and anabolic steroids have also been associated with FSGS.

Membranous Nephropathy

Membranous nephropathy is the most common etiology of nephrotic syndrome in Caucasian adults.[95] It is characterized by subepithelial immune complex formation along glomerular capillary loops and, although rarely seen, has classically been associated with gold therapy, penicillamine, captopril, and NSAID use.[95] Patients present with nephrotic range proteinuria and microscopic hematuria, with hypertension and elevated S_{cr} apparent for patients with more advanced disease. The pathogenesis may involve damage to proximal tubule epithelium with antigen release, antibody formation, and glomerular immune complex deposition.[95] Proteinuria usually resolves slowly after discontinuing the offending drug. Patients who remain nephrotic after 6 months should be treated with a 6- to 12-month course of immunosuppressive therapy, which typically consists of prednisone with or without cyclophosphamide.

TUBULOINTERSTITIAL NEPHRITIS

Tubulointerstitial nephritis refers to diseases in which the predominant changes occur in the renal interstitium rather than the tubules. The presentation may be acute and reversible with interstitial edema, rapid loss of kidney function, and systemic symptoms or chronic and irreversible, associated with interstitial fibrosis and minimal to no systemic symptoms.[97]

Acute Allergic Interstitial Nephritis

Incidence

5 The incidence of drug-induced acute allergic interstitial nephritis (AIN) is unclear and likely varies with clinical setting. For example, pathology registries indicate AIN as the histologic lesion in only 2% to 5% of kidney biopsies, but from 10% to 27% of kidney biopsies performed in hospitalized patients with unexplained AKI demonstrate AIN.[61] Multiple drugs have been implicated in the development of AIN (**Table 63-4**). It usually manifests 2 weeks after exposure to a drug but may occur sooner if the patient was previously sensitized.[98]

TABLE 63-4 Drugs Associated with Allergic Interstitial Nephritis

Antimicrobials	
Acyclovir	Indinavir
Aminoglycosides	Rifampin
Amphotericin B	Sulfonamides
β-Lactams	Tetracyclines
Erythromycin	Trimethoprim–sulfamethoxazole
Ethambutol	Vancomycin
Diuretics	
Acetazolamide	Loop diuretics
Amiloride	Triamterene
Chlorthalidone	Thiazide diuretics
Neuropsychiatric	
Carbamazepine	Phenytoin
Lithium	Valproic acid
Phenobarbital	
Nonsteroidal anti-inflammatory drugs	
Aspirin	Ketoprofen
Indomethacin	Phenylbutazone
Naproxen	Diclofenac
Ibuprofen	Zomepirac
Diflunisal	Cyclooxygenase-2 inhibitors
Piroxicam	
Miscellaneous	
Acetaminophen	Immune checkpoint inhibitors
Allopurinol	Lansoprazole
Interferon-α	Methyldopa
Aspirin	Omeprazole
Azathioprine	P-aminosalicylic acid
Captopril	Phenylpropanolamine
Cimetidine	Propylthiouracil
Clofibrate	Radiographic contrast media
Cyclosporine	Ranitidine
Glyburide	Sulfinpyrazone
Gold	Warfarin sodium

Clinical Presentation

Although methicillin-induced AIN is the prototype for AIN, it is now recognized that AIN is associated with all β-lactam antibiotics (including cephalosporins) and numerous other antimicrobials. Clinical signs present approximately 14 days after initiation of therapy and include (with their approximate incidence) fever (27%-80%), maculopapular rash (15%-25%), eosinophilia (23%-80%), arthralgia (45%), and oliguria (50%).[98] Historically, systemic hypersensitivity findings of the classic triad of fever, rash, and arthralgia, often along with eosinophilia and eosinophiluria, were strongly suggestive of the diagnosis of AIN. However, it is now recognized that this constellation of findings is not consistently reliable as one or more are frequently absent. In fact, the triad is seen in only 5% to 10% of patients with AIN, so caution is warranted in basing diagnosis on hypersensitivity findings alone.[99] Eosinophilia alone is insensitive, and eosinophiluria is insensitive and nonspecific, so urinary eosinophils are not considered a useful sign of AIN and are no longer recommended as a diagnostic test.[99] Anemia, leukocytosis, and elevated immunoglobulin E levels may occur. Tubular dysfunction may be manifested by acidosis, hyperkalemia, salt wasting, and concentrating defects.[98]

Nonsteroidal Anti-Inflammatory Drugs NSAID-induced AIN has a different clinical presentation than that seen with most other drugs. Patients are typically over 50 years of age (reflecting NSAID use for degenerative joint disease), the onset is delayed a mean of 6 months from initiation of therapy compared with 2 weeks with β-lactams, and fever, rash, and eosinophilia are typically not observed in patients with NSAID-induced AIN.**91** Concomitant nephrotic syndrome (proteinuria greater than 3.5 g/day) occurs in more than 70% of patients. Prompt diagnosis of AIN is important as discontinuation of the offending drug may prevent irreversible renal damage. Renal biopsy is the most definitive method for diagnosis.

Proton Pump Inhibitors The proton pump inhibitors (PPIs) are widely prescribed to treat acid-related gastrointestinal disease. While they are generally well tolerated and safe, AIN is a complication and it may lead to AKI, and rarely to CKD.[100] In contrast to the classic allergic presentation of AKI seen with the β-lactams, fever, rash, and eosinophilia are rarely seen with PPIs. In addition, the latent period from PPI exposure to AIN is much longer (weeks to months). Kidney biopsy is often required to definitively diagnose PPI-related AIN due to

the lack of diagnostic clinical and laboratory findings.[101]

Immune Checkpoint Inhibitors Immune checkpoint inhibitors are a novel class of cancer immunotherapy noted to be associated with AIN.[102–104] These drugs target immune pathways, including cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death protein-1 (PD-1), that dampen T-cell activation and effector responses to prevent autoimmunity. Cancer cells, however, use these pathways to escape targeting by the immune system. In inhibiting such pathways, immune checkpoint inhibitors stimulate T-cell responses against cancer cells. Off-target organ injury, termed immune-related adverse events (IrAEs), including AIN has been described. AIN has been observed in patients receiving anti-PD-1 agents either as monotherapy or in combination with anti-CTLA-4 drugs.[102–104] The mechanism underlying immune checkpoint inhibitor–associated AIN is unknown, but may be similar to the previously described mechanisms behind AIN from other drugs. Immune checkpoint inhibitors may also favor development of autoantibodies or encourage a pro-inflammatory cytokine milieu.[102] Patients may present with either other IrAEs or no symptoms. Clinical findings such as rash and eosinophilia may not be encountered, while laboratory tests such as pyuria and white blood cell (WBC) casts are present only occasionally. Diagnosis of immune checkpoint inhibitor–associated AIN generally requires kidney biopsy.

Pathogenesis

The pathogenesis of the majority of cases of AIN is considered to be an allergic hypersensitivity response. This is supported by the fact that AIN is characterized as a diffuse or focal interstitial infiltrate of lymphocytes, eosinophils, and occasional polymorphonuclear neutrophils.[97] Granulomas and tubular epithelial cell necrosis are relatively common with drug-induced AIN. Occasionally a humoral antibody-mediated mechanism is implicated by the presence of circulating antibody to a drug hapten–tubular basement membrane complex, low serum complement levels, and deposition of immunoglobulin G and complement in the tubular basement membrane. More commonly, a cell-mediated immune mechanism is suggested by the absence of these findings and the presence of a predominantly T-lymphocyte.[97]

Risk Factors

No specific risk factors have been identified because these are idiosyncratic hypersensitivity reactions. Individuals with other drug allergies may have

increased risk and warrant close monitoring.

Prevention

No specific preventive measures are known because of the idiosyncratic nature of these reactions. Patients must be monitored carefully to recognize the signs and symptoms because promptly discontinuing the offending drug often leads to full recovery.[98]

Management

Corticosteroid therapy may be beneficial and should be initiated immediately or soon after diagnosis of AIN along with discontinuance of the offending drug to avoid the risk of incomplete recovery of kidney function. While various regimens have been used, high-dose oral prednisone 1 mg/kg/day for 4 to 6 weeks with a stepwise taper over the next 4 weeks may be considered. However, if there is no significant improvement in kidney function after 3 to 4 weeks of treatment, then steroids should be discontinued.[97] Typical kidney function indices (eg, S_{cr}, BUN) and signs and symptoms of AIN should be monitored closely for improvement. In PPI-induced AIN, drug discontinuation and corticosteroids are effective in most but not all cases, with CKD occurring in a significant number.[100] Management of immune checkpoint inhibitor–associated AIN generally includes drug discontinuation and corticosteroids, although recommendations on dose and duration are lacking.[102]

Chronic Interstitial Nephritis

Lithium, analgesics, calcineurin inhibitors, aristolochic acid, and only a few other drugs have been reported to cause chronic interstitial nephritis, which is usually a progressive and irreversible lesion.

Lithium

Incidence The prevalence of non-dialysis-dependent CKD stemming from chronic lithium nephrotoxicity in the general population of patients treated with lithium is approximately 1%.[105,106] The prevalence of lithium-induced ESRD among all ESRD patients is between 0.2% and 0.8%.[105] Although several renal tubular lesions are associated with lithium therapy, an impaired ability to concentrate urine (nephrogenic diabetes insipidus) is seen in 20% of all patients receiving lithium therapy.[107]

Clinical Presentation Lithium-induced nephrotoxicity is typically asymptomatic and develops insidiously during years of therapy. Blood pressure is normal and urinary sediment is bland, making detection difficult until the disease progresses significantly.[108] It is usually recognized by rising BUN or S_{cr} concentrations or the onset of hypertension. Polydipsia (excessive thirst) and polyuria (excessive urination) are observed in 40% and 20%, respectively, of patients with nephrogenic diabetes insipidus (see Chapter 66, "Disorders of Sodium and Water Homeostasis"). Although interstitial fibrosis may be observed as early as 5 years after beginning therapy, lithium-induced CKD usually occurs after 10 to 20 years of lithium treatment.[108]

Pathogenesis The precise mechanism of chronic lithium-induced nephrotoxicity is not well characterized. Impaired ability to concentrate urine is a result of a decrease in collecting duct response to antidiuretic hormone, which may be related to downregulation of aquaporin 2 water channel expression during lithium therapy.[108] Chronic tubulointerstitial nephritis attributed to lithium is evidenced most commonly by biopsy findings of interstitial fibrosis, tubular atrophy, and glomerular sclerosis. The pathogenesis may involve cumulative direct lithium toxicity, since duration of therapy correlates with the decline in the GFR.[108]

Risk Factors Historically, the duration of lithium therapy and cumulative dose was considered the major determinants of chronic nephrotoxicity. However, this is now questionable, with some suggesting that long-term lithium therapy in the absence of episodes of acute intoxication is not nephrotoxic.[109] Increased age may also be a risk factor, but daily dose is not.[106,108]

Prevention Prevention of acute and chronic toxicity includes maintaining lithium concentrations as low as therapeutically possible, avoiding dehydration, and monitoring kidney function. It is unknown whether progression to CKD can be prevented by stopping lithium use when mild kidney injury is first recognized. This poses a dilemma as lithium is highly effective for affective disorders and the risks and potential benefits of discontinuing such a beneficial drug need to be carefully considered.[108] However, if lithium therapy is continued, kidney function must be monitored and therapy discontinued if it continues to decline. Amiloride has been used for prevention and treatment of lithium-induced nephrogenic diabetes insipidus, since it blocks epithelial sodium transport of lithium into the cortical collecting duct in the distal nephron.[108]

Management Symptomatic polyuria and polydipsia can be reversed by discontinuation of lithium therapy or ameliorated with amiloride 5 to 10 mg daily during continued lithium therapy (see Chapter 66). If polyuria does not resolve within 7 to 10 days of therapy, then the amiloride dose should be increased to 20 mg daily. Progressive chronic interstitial nephritis is treated by discontinuation of lithium therapy, adequate hydration, and avoidance of other nephrotoxic agents. Lithium serum concentrations, as well as kidney function indices, including urine output, BUN, and S_{cr}, should be monitored closely for resolution of signs and symptoms of toxicity.[108]

Cyclosporine and Tacrolimus

Delayed chronic tubulointerstitial nephritis, considered the Achilles' heel of calcineurin inhibitor–based immunosuppressive regimens, has been reported after several months of therapy and can result in irreversible kidney disease.[70,71] Toxicity is progressive and usually manifests as a slowly rising S_{cr} concentration and decreaseChapter d creatinine clearance that may not reflect the severity of histopathologic changes. All three compartments of the kidney can be affected, evidenced by typical biopsy findings that include arteriolar hyalinosis, glomerular sclerosis, and a striped pattern of tubulointerstitial fibrosis.[71] The pathogenesis appears to involve sustained renal arteriolar endothelial cell injury and increased extracellular matrix synthesis, which ultimately result in chronic ischemia of the tubulointerstitial compartment because of increased release of endothelin-1, decreased production of nitric acid, and upregulation of transforming growth factor-β. Unlike acute nephrotoxicity, chronic toxicity is not dose dependent.[70,71]

Aristolochic Acid

Incidence Although the true incidence of aristolochic acid nephropathy is unknown, approximately 3% to 5% of patients who consume the natural product develop interstitial fibrosis with tubular atrophy.[110]

Clinical Presentation Patients with aristolochic acid nephropathy typically present with mild-to-moderate hypertension, mild proteinuria, glucosuria, and moderately elevated S_{cr} concentrations. Anemia and shrunken kidneys are also common on initial presentation.[111] The overwhelming majority of cases reported to date have been in women. The main pathologic lesions observed in the kidneys are interstitial fibrosis with atrophy and destruction of proximal tubules

throughout the renal cortex; in general, the glomeruli are not affected. Perhaps the most remarkable feature of aristolochic acid nephropathy is the rate at which it progresses. In most individuals, ESRD requiring dialysis or transplantation develops within 6 to 24 months of exposure. An alarming high prevalence (approximately 40%-45%) of urothelial transitional cell carcinoma has been observed in Belgian patients who underwent renal transplantation.[110,111]

Pathogenesis The precise mechanism of aristolochic acid nephropathy and urothelial carcinoma has yet to be characterized. The major components of aristolochic acid are metabolized to mutagenic compounds called *aristolactam I* and *aristolactam II*, respectively, which have been demonstrated to form aristolochic acid–DNA adducts in humans. Recent data indicate that these adducts cause direct DNA damage and may lead to proximal tubular atrophy and apoptosis.[111]

Prevention The primary means of preventing aristolochic acid nephropathy appears to be the limitation of exposure to compounds containing aristolochic acids. Several countries, including the United States, the United Kingdom, Canada, Australia, and Germany, have banned the use of herbs containing *Aristolochia*.[111]

Papillary Necrosis

Papillary necrosis is a form of chronic tubulointerstitial nephritis characterized by necrosis of the renal papillae, the regions of the kidney where the collecting ducts enter the renal pelvis, which leads to progressive kidney disease. Papillary necrosis is associated with diabetes, sickle cell disease, obstruction and infection of the urinary tract, and most commonly analgesic use.[112]

Analgesic Nephropathy

Incidence Prototypical analgesic nephropathy is characterized by chronic tubulointerstitial nephritis with papillary necrosis.[112] Chronic excessive consumption of combination analgesics, particularly those containing phenacetin, was believed to be the major cause and led to the removal of phenacetin and phenacetin mixtures from most world markets. However, contemporary analgesics, particularly aspirin, acetaminophen, and NSAIDs, alone or in combination, are also associated with the development of analgesic nephropathy. The incidence of analgesic nephropathy has declined significantly since removal of phenacetin from many countries, with the prevalence estimated

to now be less than 5% in the US-adult ESRD population.[112]

Clinical Presentation Analgesic nephropathy is a progressive disease that evolves slowly over several years.[112] It is difficult to recognize in the early stages of the disease because patients are often asymptomatic, and it may be underdiagnosed as a cause of ESRD. It is seen more commonly in women than men. Early manifestations are generally nonspecific and may include headache and upper GI symptoms; later manifestations include impaired urinary concentrating ability, dysuria, sterile pyuria, microscopic hematuria, mild proteinuria (less than 1.5 g/day), and lower back pain. As disease progresses, hypertension, atherosclerotic cardiovascular disease, renal calculi, and bladder stones are common, and pyelonephritis is a classic finding in advanced analgesic nephropathy. The most sensitive and specific diagnostic criteria include (a) a history of chronic daily habitual analgesic ingestion (daily use for at least 3 to 5 years); (b) IV pyelography, renal ultrasound, or renal computed tomography imaging, which reveals decreased renal mass and bumpy renal contours; (c) elevated S_{cr}, that is, up to 4 mg/dL (354 μmol/L); and (d) papillary calcifications.[112]

Pathogenesis Analgesic nephropathy originates in the papillary tip as a result of accumulated toxins, drugs and metabolites, decreased blood flow, and impaired cellular energy production. The metabolism of phenacetin to acetaminophen, which is then oxidized to toxic-free radicals that are concentrated in the papilla, appears to be the initiating factor that causes toxicity by mechanisms analogous to acetaminophen hepatotoxicity via glutathione depletion.[113] Cortical interstitial nephritis develops secondary to papillary necrosis. Salicylates potentiate these effects by also depleting renal glutathione, and inhibiting prostaglandin-mediated vasodilation, thus further predisposing the renal medulla to ischemic injury.[113]

Risk Factors The epidemiology of analgesic use and analgesic nephropathy continues to evolve. The classic concept persists that risk for ESRD increases with cumulative consumption of combination analgesics, phenacetin, or acetaminophen and aspirin or NSAIDs. Caffeine contained in combination analgesics may increase risk, but the role is not clear.[112] Chronic use of therapeutic doses of NSAIDs or high-dose acetaminophen, but not aspirin or salicylates alone, can cause analgesic nephropathy.

Prevention Prevention has depended primarily on public health efforts to restrict the sale of phenacetin and combination analgesics. However, risk continues with ongoing availability of nonprescription combination analgesics containing

aspirin, acetaminophen, and caffeine in the United States and throughout the world.

Individuals requiring chronic analgesic therapy may reduce risk by limiting the total dose, avoiding combined use of two or more analgesics, and maintaining good hydration to prevent renal ischemia and decrease the papillary concentration of toxic substances. Acetaminophen remains the preferred nonopiate analgesic for patients with pre-existing kidney disease.

Management Treatment of established nephrotoxicity requires cessation of analgesic consumption.[113] This can prevent progression and may improve kidney function. Kidney function indices, including urine output, BUN, and S_{cr}, should be monitored every several months. Patients should also be monitored for the development of transitional cell carcinoma of the renal pelvis, calyces, ureters, and bladder, which may present years after analgesic nephropathy is diagnosed.

RENAL VASCULITIS, THROMBOSIS, AND CHOLESTEROL EMBOLI

Renal Vasculitis

Drug-induced renal vascular disease commonly presents as vasculitis, thrombotic microangiopathy, or cholesterol emboli.[95,114] Vasculitis implies inflammation of the vessel wall, capillaries, or glomeruli and is typically classified according to vessel size (ie, small, medium, or large vessel vasculitis). Small vessel vasculitides usually affect multiple organ systems, including the kidneys and lungs, and are associated with nonspecific inflammatory symptoms such as fever, malaise, myalgias, arthralgias, and weight loss. Numerous drugs are associated with the development of renal vasculitis, including hydralazine, propylthiouracil, allopurinol, phenytoin, sulfasalazine, penicillamine, and minocycline (see Table 63-1).[95,114] Most drug-induced cases of vasculitis, including hydralazine, propylthiouracil, allopurinol, penicillamine, and the anti-TNF-α drug adalimumab, have been implicated in the development of antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis.[95,114,115] Patients present with hematuria, proteinuria, oliguria, and red cell casts, frequently along with fever, malaise, myalgias, and arthralgias.[114] Treatment typically consists of withdrawing the offending drug and administration of corticosteroids or other immunosuppressive therapy, and usually leads to

resolution of symptoms within weeks to months.

Thrombotic Microangiopathy

Thrombotic microangiopathy is characterized clinically by microangiopathic hemolytic anemia, fragmented red cells, and thrombocytopenia and pathologically by vascular endothelial proliferation, endothelial cell swelling, and intraluminal platelet thrombi in the small vessels, particularly affecting the renal and cerebral capillaries and arterioles.[94,116] The absence of inflammation in vessel walls distinguishes thrombotic microangiopathy from vasculitis. Numerous medications, including oral contraceptive agents, cyclosporine, tacrolimus, muromonab-CD3, many cancer chemotherapeutic agents including antiangiogenesis drugs (eg, bevacizumab, sunitinib, and sorafenib), mitomycin C, cisplatin, and gemcitabine, interferon-α, ticlopidine, clopidogrel, quinine, and several antimicrobial agents (eg, valacyclovir, penicillins, rifampin, and metronidazole) are associated with the development of thrombotic microangiopathy.[94,116] Patients may present with fever, neurological dysfunction, elevated S_{cr} and BUN, and hypertension, along with microangiopathic hemolytic anemia and thrombocytopenia. Kidney injury can be severe and irreversible, although corticosteroids, antiplatelet agents, plasma exchange, plasmapheresis, and high-dose IV immunoglobulin G have each induced clinical improvement.[116] The utility of eculizumab is currently unknown, but case reports suggest potential benefit in gemcitabine-associated thrombotic microangiopathy.

Cholesterol Emboli

Anticoagulants (particularly warfarin) and thrombolytics (eg, urokinase, streptokinase, and tissue-plasminogen activator) are associated with cholesterol embolization of the kidney.[117] These drugs act to remove or prevent thrombus formation over ulcerative plaques or may induce hemorrhage within clots, thereby causing showers of cholesterol crystals that lodge in small-diameter arteries of the kidney (renal arterioles and glomerular capillaries). Cholesterol crystal emboli induce an endothelial inflammatory response, which leads to complete obstruction, ischemia, and necrosis of affected vessels within weeks to months after initiation of therapy.[117] Purple discoloration of the toes and mottled skin over the legs are important clinical clues. Treatment is supportive in nature, since kidney injury is generally irreversible.

PHARMACOECONOMICS

The pharmacoeconomic implications of DIKD are enormous. In general, an episode of AKI leads to higher hospital resource use, with increases in the median direct hospital cost of $2,600 and the hospital length of stay by 5 days.[118] An increase in S_{cr} of greater than or equal to 0.5 mg/dL (44 μmol/L) is independently associated with a 6.5-fold increase in the odds of death, a 3.5-day increase in length of hospital stay, and nearly $7,500 in excess hospital costs even after adjusting for age, sex, and measures of comorbidity.[119] Amphotericin B–induced AKI leads to a mean increased length of hospital stay of 8.2 days and adjusted additional costs of $29,823 per patient.[120] The major driver of the increased costs associated with contrast-induced AKI was the cost of the longer initial hospital stay. The increased availability of automated clinical decision support systems and computer-guided medication dosing for hospital inpatients may improve the safety of potentially harmful drugs and minimize the occurrence of nephrotoxicity in this setting, thereby potentially lowering the corresponding economic consequences.[120]

Postclass Engaged Learning Activity

Conduct a literature search and identify a manuscript that has been published in the past 12 months related to nephrotoxic effects of a specific drug or class of drugs. Write a brief summary about the medication’s intended mechanism of action, the purported pathogenesis of kidney injury, and the corresponding kidney structural-functional alteration it mirrors. This activity is intended to build your experience with accessing the primary biomedical literature and identifying physiologically relevant reports of drug-induced kidney disease.

ABBREVIATIONS

ACEI	angiotensin-converting enzyme inhibitor
AIN	allergic interstitial nephritis
AKI	acute kidney injury
ARB	angiotensin II receptor blocker
ATN	acute tubular necrosis
BUN	blood urea nitrogen
CIN	contrast media–induced nephrotoxicity
CKD	chronic kidney disease
COX	cyclooxygenase
CTLA-4	cytotoxic T-lymphocyte antigen-4
CVVH	continuous venovenous hemofiltration
DIKD	drug-induced kidney disease
ESRD	end-stage renal disease
FSGS	focal segmental glomerulosclerosis
GFR	glomerular filtration rate
IGFBP7	insulin-like growth factor–binding protein 7
IrAE	immune-related adverse event
KIM-1	kidney injury molecule-1
MAPK	mitogen-activated protein kinase
NGAL	neutrophil gelatinase–associated lipocalin
NSAIDs	nonsteroidal anti-inflammatory drugs
OSPS	oral sodium phosphate solution
PD-1	programmed cell death protein-1
PPI	proton pump inhibitor
RAS	renin–angiotensin system
RTEC	renal tubular epithelial cell
S_{α}	serum creatinine
SGLT-2	sodium-glucose co-transporter 2
TIMP-2	inhibitor of metalloproteinase 2
WRN	warfarin-related nephropathy

REFERENCES

1. Mehta RL, Awdishu L, Davenport A, et al. Phenotype standardization for drug-induced kidney disease. *Kidney Int*. 2015;88:226–234.
2. Thomas ME, Blaine C, Dawnay A, et al. The definition of acute kidney injury and its use in practice. *Kidney Int*. 2015;87:62–73.
3. Siew ED, Davenport A. The growth of acute kidney injury: A rising tide or just closer attention to detail? *Kidney Int*. 2015;87:46–61.
4. Elasy TA, Anderson RJ. Changing demography of acute renal failure.

Semin Dial. 1996;9:438–443.

5. Hsu RK, McCulloch CE, Dudley RA, Lo LJ, Hsu CY. Temporal changes in incidence of dialysis-requiring AKI. *J Am Soc Nephrol*. 2013;24:37–42.
6. Susantitaphong P, Cruz DN, Cerda J, et al. World incidence of AKI: A meta-analysis. *Clin J Am Soc Nephrol*. 2013;8:1482–1493.
7. Bentley ML, Corwin HL, Dasta J. Drug-induced acute kidney injury in the critically ill adult: Recognition and prevention strategies. *Crit Care Med*. 2010;38:S169–S174.
8. van Meer L, Moerland M, Cohen AF, Burggraaf J. Urinary kidney biomarkers for early detection of nephrotoxicity in clinical drug development. *Br J Clin Pharmacol*. 2014;77:947–957.
9. Gobe GC, Coombes JS, Fassett RG, Endre ZH. Biomarkers of drug-induced acute kidney injury in the adult. *Expert Opin Drug Metab Toxicol*. 2015;11:1683–1694.
10. Chen LX, Koyner JL. Biomarkers in acute kidney injury. *Crit Care Clin*. 2015;31:633–648.
11. Vaidya VS, Ferguson MA, Bonventre JV. Biomarkers of acute kidney injury. *Annu Rev Pharmacol Toxicol*. 2008;48:463–493.
12. Gocze I, Koch M, Renner P, et al. Urinary biomarkers TIMP-2 and IGFBP7 early predict acute kidney injury after major surgery. *PLoS One*. 2015;10:e0120863.
13. Koyner JL, Shaw AD, Chawla LS, et al. Tissue inhibitor metalloproteinase-2 (TIMP-2)IGF-binding protein-7 (IGFBP7) levels are associated with adverse long-term outcomes in patients with AKI. *J Am Soc Nephrol*. 2015;26:1747–1754.
14. Sohn SJ, Kim SY, Kim HS, et al. In vitro evaluation of biomarkers for cisplatin-induced nephrotoxicity using HK-2 human kidney epithelial cells. *Toxicol Lett*. 2013;217:235–242.
15. Fuchs TC, Mally A, Wool A, Beiman M, Hewitt P. An exploratory evaluation of the utility of transcriptional and urinary kidney injury biomarkers for the prediction of aristolochic acid-induced renal injury in male rats. *Vet Pathol*. 2014;51:680–694.
16. Perazella MA. Renal vulnerability to drug toxicity. *Clin J Am Soc Nephrol*. 2009;4:1275–1283.
17. Ghane Shahrbaf F, Assadi F. Drug-induced renal disorders. *J Renal Inj Prev*. 2015;4:57–60.

18. Perazella MA. The urine sediment as a biomarker of kidney disease. *Am J Kidney Dis*. 2015;66:748–755.
19. Curthoys NP, Moe OW. Proximal tubule function and response to acidosis. *Clin J Am Soc Nephrol*. 2014;9:1627–1638.
20. Subramanya AR, Ellison DH. Distal convoluted tubule. *Clin J Am Soc Nephrol*. 2014;9:2147–2163.
21. Ettore B. Adverse effects of drugs on the kidney. *Eur J Intern Med*. 2015;28:1–8.
22. Wargo KA, Edwards JD. Aminoglycoside-induced nephrotoxicity. *J Pharm Pract*. 2014;27:573–577.
23. Pazhayattil GS, Shirali AC. Drug-induced impairment of renal function. *Int J Nephrol Renovasc Dis*. 2014;7:457–468.
24. Oliveira JF, Silva CA, Barbieri CD, et al. Prevalence and risk factors for aminoglycoside nephrotoxicity in intensive care units. *Antimicrob Agents Chemother*. 2009;53:2887–2891.
25. Balakumar P, Rohilla A, Thangathirupathi A. Gentamicin-induced nephrotoxicity: Do we have a promising therapeutic approach to blunt it? *Pharmacol Res*. 2010;62:179–186.
26. Asci H, Saygin M, Cankara FN, et al. The impact of alpha-lipoic acid on amikacin-induced nephrotoxicity. *Ren Fail*. 2015;37:117–121.
27. Destache CJ. Aminoglycoside-induced nephrotoxicity—a focus on monitoring: A review of literature. *J Pharm Pract*. 2014;27:562–566.
28. Pagkalis S, Mantadakis E, Mavros MN, Ammari C, Falagas ME. Pharmacological considerations for the proper clinical use of aminoglycosides. *Drugs*. 2011;71:2277–2294.
29. Keaney JJ, Hannon CM, Murray PT. Contrast-induced acute kidney injury: How much contrast is safe? *Nephrol Dial Transplant*. 2013;28:1376–1383.
30. Lefel N, Janssen L, le Noble J, Foudraine N. Sodium bicarbonate prophylactic therapy in the prevention of contrast-induced nephropathy in patients admitted to the intensive care unit of a teaching hospital: A retrospective cohort study. *J Intensive Care*. 2016;4:5.
31. Weisbord SD, Palevsky PM. Contrast-associated acute kidney injury. *Crit Care Clin*. 2015;31:725–735.
32. Wilhelm-Leen E, Montez-Rath ME, Chertow G. Estimating the risk of radiocontrast-associated nephropathy. *J Am Soc Nephrol*. 2017;28(2):653–

659.
33. McCullough PA. Contrast-induced nephropathy: Definitions, epidemiology, and implications. *Intervent Cardiol Clin*. 2014;3:357–362.
34. Geenen RWF, Kingma HJ, van der Molen AJ. Pathophysiology of contrast-induced acute kidney injury. *Intervent Cardiol Clin*. 2014;3:363–367.
35. Rojkovskiy I, Solomon R. Intravenous and oral hydration: Approaches, principles, and differing regimens. *Intervent Cardiol Clin*. 2014;3:393–404.
36. Aqeel I, Garcha AS, Rudnick MR. Relative nephrotoxicity of different contrast media. *Intervent Cardiol Clin*. 2014;3:349–356.
37. Toso A, Leoncini M, Maioli M, Tropeano F, Bellandi F. Pharmacologic prophylaxis for contrast-induced acute kidney injury. *Intervent Cardiol Clin*. 2014;3:405–419.
38. Tao SM, Wichmann JL, Schoepf UJ, et al. Contrast-induced nephropathy in CT: Incidence, risk factors and strategies for prevention. *Eur Radiol*. 2016;26(9):3310–3318.
39. Azzalini L, Spagnoli V, Ly HQ. Contrast-induced nephropathy: From pathophysiology to preventive strategies. *Can J Cardiol*. 2016;32(2):247–255.
40. Ohno I, Hayashi H, Aonuma K, et al. JSN, JRS, and JCS Joint Working Group. Guidelines on the use of iodinated contrast media in patients with kidney disease 2012: Digest version. *Circ J*. 2013;77:1883–1914.
41. Weisbord SD, Gallagher M, Jneid H, et al. Outcomes after angiography with sodium bicarbonate and acetylcysteine. *N Engl J Med*. 2018;378(7):603–614.
42. Yang Y, Liu H, Liu F, Dong Z. Mitochondrial dysregulation and protection in cisplatin nephrotoxicity. *Arch Toxicol*. 2014;88:1249–1256.
43. Peres LA, da Cunha AD Jr. Acute nephrotoxicity of cisplatin: Molecular mechanisms. *J Bras Nefrol*. 2013;35:332–340.
44. Perazella MA. Onco-nephrology: Renal toxicities of chemotherapeutic agents. *Clin J Am Soc Nephrol*. 2012;7:1713–1721.
45. Launay-Vacher V, Rey JB, Isnard-Bagnis C, Deray G, Daouphars M. Prevention of cisplatin nephrotoxicity: State of the art and recommendations from the European Society of Clinical Pharmacy Special Interest Group on Cancer Care. *Cancer Chemother Pharmacol*.

2008;61:903–909.

46. Sanchez-Gonzalez PD, Lopez-Hernandez FJ, Lopez-Novoa JM, Morales AI. An integrative view of the pathophysiological events leading to cisplatin nephrotoxicity. *Crit Rev Toxicol*. 2011;41:803–821.
47. Finkel M, Goldstein A, Steinberg Y, Granowetter L, Trachtman H. Cisplatinum nephrotoxicity in oncology therapeutics: Retrospective review of patients treated between 2005 and 2012. *Pediatr Nephrol*. 2014;29:2421–2424.
48. dos Santos NA, Carvalho Rodrigues MA, Martins NM, dos Santos AC. Cisplatin-induced nephrotoxicity and targets of nephroprotection: An update. *Arch Toxicol*. 2012;86:1233–1250.
49. Shirali AC, Perazella MA. Tubulointerstitial injury associated with chemotherapeutic agents. *Adv Chronic Kidney Dis*. 2014;21:56–63.
50. Oh GS, Kim HJ, Shen A, et al. Cisplatin-induced kidney dysfunction and perspectives on improving treatment strategies. *Electrolyte Blood Press*. 2014;12:55–65.
51. Santabarbara G, Maione P, Rossi A, Gridelli C. Pharmacotherapeutic options for treating adverse effects of cisplatin chemotherapy. *Expert Opin Pharmacother*. 2016;17(4):561–570.
52. Rocha PN, Kobayashi CD, de Carvalho Almeida L, et al. Incidence, predictors, and impact on hospital mortality of amphotericin B nephrotoxicity defined using newer acute kidney injury diagnostic criteria. *Antimicrob Agents Chemother*. 2015;59:4759–4769.
53. Hamill RJ. Amphotericin B formulations: A comparative review of efficacy and toxicity. *Drugs*. 2013;73:919–934.
54. Mistro S, Maciel Ide M, de Menezes RG, Maia ZP, et al. Does lipid emulsion reduce amphotericin B nephrotoxicity? A systematic review and meta-analysis *Clin Infect Dis*. 2012;54:1774–1777.
55. Bes DF, Rosanova MT, Sberna N, Arrizurieta E. Deoxycholate amphotericin B and nephrotoxicity in the pediatric setting. *Pediatr Infect Dis J*. 2014;33:e198–e206.
56. Karimzadeh I, Khalili H, Sagheb MM, Farsaei S. A double-blinded, placebo-controlled, multicenter clinical trial of *N*-acetylcysteine for preventing amphotericin B-induced nephrotoxicity. *Expert Opin Drug Metab Toxicol*. 2015;11:1345–1355.
57. Martensson J, Bellomo R. Are all fluids bad for the kidney? *Curr Opin Crit Care*. 2015;21:292–301.

58. Dickenmann M, Oettl T, Mihatsch MJ. Osmotic nephrosis: Acute kidney injury with accumulation of proximal tubular lysosomes due to administration of exogenous solutes. *Am J Kidney Dis*. 2008;51:491–503.
59. Dantal J. Intravenous immunoglobulins: In-depth review of excipients and acute kidney injury risk. *Am J Nephrol*. 2013;38:275–284.
60. Nomani AZ, Nabi Z, Rashid H, et al. Osmotic nephrosis with mannitol: Review article. *Ren Fail*. 2014;36:1169–1176.
61. Perazella MA, Luciano RL. Review of select causes of drug-induced AKI. *Expert Rev Clin Pharmacol*. 2015;8:367–371.
62. Carlstrom M, Wilcox CS, Arendshorst WJ. Renal autoregulation in health and disease. *Physiol Rev*. 2015;95:405–511.
63. Dreischulte T, Morales DR, Bell S, Guthrie B. Combined use of nonsteroidal anti-inflammatory drugs with diuretics and/or renin-angiotensin system inhibitors in the community increases the risk of acute kidney injury. *Kidney Int*. 2015;88:396–403.
64. Cruz CS, Cruz LS, Silva GR, Marcilio de Souza CA. Incidence and predictors of development of acute renal failure related to treatment of congestive heart failure with ACE inhibitors. *Nephron Clin Pract*. 2007;105:c77–c83.
65. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med*. 2011;365:2002–2012.
66. St Peter WL, Odum LE, Whaley-Connell AT. To RAS or not to RAS? The evidence for and cautions with renin-angiotensin system inhibition in patients with diabetic kidney disease *Pharmacotherapy*. 2013;33:496–514.
67. Lapi F, Azoulay L, Yin H, Nessim SJ, Suissa S. Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with nonsteroidal anti-inflammatory drugs and risk of acute kidney injury: Nested case-control study. *BMJ*. 2013;346:e8525.
68. Rahman S, Malcoun A. Nonsteroidal anti-inflammatory drugs, cyclooxygenase-2, and the kidneys. *Prim Care*. 2014;41:803–821.
69. Whelton A. Nephrotoxicity of nonsteroidal anti-inflammatory drugs: Physiologic foundations and clinical implications. *Am J Med*. 1999;106:13S–24S.
70. Naesens M, Kuypers DR, Sarwal M. Calcineurin inhibitor nephrotoxicity. *Clin J Am Soc Nephrol*. 2009;4:481–508.

71. Chapman JR. Chronic calcineurin inhibitor nephrotoxicity lest we forget. *Am J Transplant*. 2011;11:693–697.
72. Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med*. 2003;349:931–940.
73. Issa N, Kukla A, Ibrahim HN. Calcineurin inhibitor nephrotoxicity: A review and perspective of the evidence. *Am J Nephrol*. 2013;37:602–612.
74. Pallet N, Djamali A, Legendre C. Challenges in diagnosing acute calcineurin-inhibitor induced nephrotoxicity: From toxicogenomics to emerging biomarkers. *Pharmacol Res*. 2011;64:25–30.
75. Shyangdan DS, Uthman OA, Waugh N. SGLT-2 receptor inhibitors for treating patients with type 2 diabetes mellitus: A systematic review and network meta-analysis. *BMJ Open*. 2016;6(2):e009417.
76. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375(4):323–334.
77. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644–657.
78. Nadkarni GN, Ferrandino R, Chang A, et al. Acute kidney injury in patients on SGLT2 inhibitors: A propensity-matched analysis. *Diabetes Care*. Nov 2017;40(11):1479–1485.
79. Hahn K, Ejaz AA, Kanbay M, Lanaspa MA, Johnson RJ. Acute kidney injury from SGLT2 inhibitors: Potential mechanisms. *Nat Rev Nephrol*. 2016;12(12):711–712.
80. Nasr SH, Milliner DS, Wooldridge TD, Sethi S. Triamterene crystalline nephropathy. *Am J Kidney Dis*. 2014;63:148–152.
81. Garneau AP, Riopel J, Isenring P. Acute methotrexate-induced crystal nephropathy. *N Engl J Med*. 2015;373:2691–2693.
82. Faught LN, Greff MJ, Rieder MJ, Koren G. Drug-induced acute kidney injury in children. *Br J Clin Pharmacol*. 2015;80:901–909.
83. Herlitz LC, D'Agati VD, Markowitz GS. Crystalline nephropathies. *Arch Pathol Lab Med*. 2012;136:713–720.
84. Jones GL, Will A, Jackson GH, Webb NJ, Rule S; British Committee for Standards in H. Guidelines for the management of tumour lysis syndrome in adults and children with haematological malignancies on behalf of the British Committee for Standards in Haematology. *Br J Haematol*. 2015;169:661–671.
85. Petejova N, Martinek A. Acute kidney injury due to rhabdomyolysis and

renal replacement therapy: A critical review. *Crit Care*. 2014;18:224.
86. Zimmerman JL, Shen MC. Rhabdomyolysis. *Chest*. 2013;144:1058–1065.
87. Brodsky SV, Nadasdy T, Rovin BH, et al. Warfarin-related nephropathy occurs in patients with and without chronic kidney disease and is associated with an increased mortality rate. *Kidney Int*. 2011;80:181–189.
88. Kumar N, Perazella MA. Differentiating HIV-associated nephropathy from antiretroviral drug-induced nephropathy: A clinical challenge. *Curr HIV/AIDS Rep*. 2014;11:202–211.
89. Izzedine H, Lescure FX, Bonnet F. HIV medication-based urolithiasis. *Clin Kidney J*. 2014;7:121–126.
90. Shavit L, Jaeger P, Unwin RJ. What is nephrocalcinosis? *Kidney Int*. 2015;88:35–43.
91. Markowitz GS, Perazella MA. Acute phosphate nephropathy. *Kidney Int*. 2009;76:1027–1034.
92. Choi NK, Lee J, Chang Y, et al. Acute renal failure following oral sodium phosphate bowel preparation: A nationwide case-crossover study. *Endoscopy*. 2014;46:465–470.
93. Markowitz GS, Radhakrishnan J, D'Agati VD. Towards the incidence of acute phosphate nephropathy. *J Am Soc Nephrol*. 2007;18:3020–3022.
94. Markowitz GS, Bomback AS, Perazella MA. Drug-induced glomerular disease: Direct cellular injury. *Clin J Am Soc Nephrol*. 2015;10:1291–1299.
95. Hogan JJ, Markowitz GS, Radhakrishnan J. Drug-induced glomerular disease: Immune-mediated injury. *Clin J Am Soc Nephrol*. 2015;10:1300–1310.
96. Lan X, Rao TK, Chander PN, Skorecki K, Singhal PC. Apolipoprotein L1 (APOL1) Variants (Vs) a possible link between Heroin-associated Nephropathy (HAN) and HIV-associated Nephropathy (HIVAN). *Front Microbiol*. 2015;6:571.
97. Krishnan N, Perazella MA. Drug-induced acute interstitial nephritis: Pathology, pathogenesis, and treatment. *Iran J Kidney Dis*. 2015;9:3–13.
98. Perazella MA, Markowitz GS. Drug-induced acute interstitial nephritis. *Nat Rev Nephrol*. 2010;6:461–470.
99. Perazella MA. Diagnosing drug-induced AIN in the hospitalized patient: A challenge for the clinician. *Clin Nephrol*. 2014;81:381–388.
100. Moledina DG, Perazella MA. PPIs and kidney disease: From AIN to

CKD. *J Nephrol*. 2016;29(5):611–616.

101. Perazella MA. Clinical approach to diagnosing acute and chronic tubulointerstitial disease. *Adv Chronic Kidney Dis*. 2017;24(2):57–63.
102. Perazella MA, Shirali AC. Nephrotoxicity of cancer immunotherapies: Past, present and future. *J Am Soc Nephrol*. 2018;29(8):2039–2052.
103. Shirali AC, Perazella MA, Gettinger S. Association of acute interstitial nephritis with programmed cell death 1 inhibitor therapy in lung cancer patients. *Am J Kidney Dis*. 2016;68(2):287–291.
104. Cortazar FB, Marrone KA, Troxell ML, et al. Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors. *Kidney Int*. 2016;90(3):638–647.
105. Bendz H, Schon S, Attman PO, Aurell M. Renal failure occurs in chronic lithium treatment but is uncommon. *Kidney Int*. 2010;77:219–224.
106. Rej S, Herrmann N, Shulman K. The effects of lithium on renal function in older adults—a systematic review. *J Geriatr Psychiatry Neurol*. 2012;25:51–61.
107. Alsady M, Baumgarten R, Deen PM, de Groot T. Lithium in the Kidney: Friend and Foe? *J Am Soc Nephrol*. 2016;27(6):1587-1595.
108. Grunfeld JP, Rossier BC. Lithium nephrotoxicity revisited. *Nat Rev Nephrol*. 2009;5:270–276.
109. Clos S, Rauchhaus P, Severn A, Cochrane L, Donnan PT. Long-term effect of lithium maintenance therapy on estimated glomerular filtration rate in patients with affective disorders: A population-based cohort study. *Lancet Psychiatry*. 2015;2:1075–1083.
110. Debelle FD, Vanherweghem JL, Nortier JL. Aristolochic acid nephropathy: A worldwide problem. *Kidney Int*. 2008;74:158–169.
111. Luciano RL, Perazella MA. Aristolochic acid nephropathy: Epidemiology, clinical presentation, and treatment. *Drug Saf*. 2015;38:55–64.
112. De Broe ME, Elseviers MM. Over-the-counter analgesic use. *J Am Soc Nephrol*. 2009;20:2098–2103.
113. Braden GL, O'Shea MH, Mulhern JG. Tubulointerstitial diseases. *Am J Kidney Dis*. 2005;46:560–572.
114. Radic M, Martinovic Kaliterna D, Radic J. Drug-induced vasculitis: A clinical and pathological review. *Neth J Med*. 2012;70:12–17.
115. Perez-Alvarez R, Perez-de-Lis M, Ramos-Casals M. Biologics-induced autoimmune diseases. *Curr Opin Rheumatol*. 2013;25:56–64.

116. Izzedine H, Perazella MA. Thrombotic microangiopathy, cancer, and cancer drugs. *Am J Kidney Dis*. 2015;66:857–868.
117. Scolari F, Ravani P. Atheroembolic renal disease. *Lancet*. 2010;375:1650–1660.
118. Lameire NH, Bagga A, Cruz D, et al. Acute kidney injury: An increasing global concern. *Lancet*. 2013;382:170–179.
119. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol*. 2005;16:3365–3370.
120. Hug BL, Witkowski DJ, Sox CM, et al. Occurrence of adverse, often preventable, events in community hospitals involving nephrotoxic drugs or those excreted by the kidney. *Kidney Int*. 2009;76:1192–1198.

64

Glomerular Diseases

Jonathan J. Hogan and Alan H. Lau

KEY CONCEPTS

1. Glomerular diseases are a collection of diseases that affect the filters of the kidney and are mediated by different immunologic pathogenic mechanisms, resulting in varied clinical presentation and therapeutic outcomes.
2. The signs and symptoms associated with glomerular diseases are commonly nephritic (reflecting inflammatory injury) or nephrotic (reflecting noninflammatory injury) in nature, and are characterized by hematuria and proteinuria.
3. Supportive treatments for edema, hypertension, hyperlipidemia, and intravascular thrombosis are important in reducing the complications associated with glomerular diseases. These are especially important since specific and effective therapy for many types of glomerular diseases is not available. Reduction of proteinuria can often improve long-term kidney and patient outcomes.
4. To maximize therapeutic benefits and minimize drug-induced complications, patients have to be monitored closely to assess their therapeutic responses as well as the development of any treatment-induced toxicity.
5. Among all the types of glomerulonephritis, minimal-change nephropathy is most responsive to treatment. Steroids can induce good responses in most patients during initial treatment as well as relapse.
6. Because of the lack of consistently effective treatment for primary focal segmental glomerular sclerosis, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are commonly used for patients with mild disease to control symptoms. Steroids and immunosuppressive agents are reserved for the management of patients with severe disease.

7. The optimal treatment for lupus nephritis depends on the underlying lesion and disease activity, as well as the severity and duration of the patient's condition.
8. The treatment of poststreptococcal glomerulonephritis is mainly supportive and symptomatic. Antibiotic therapy does not prevent subsequent disease development but may reduce the severity.

Preclass Engaged Learning Activity

Visit the National Kidney Foundation website. This website is useful to learn about kidney disease from the perspective of both patients and healthcare providers. Watch the video titled "New Insights Regarding Treatment of Membranous Nephropathy". This video provides an overview of the approach to treating membranous nephropathy, particularly with regards to immunosuppressive therapy.

INTRODUCTION

Glomerular diseases have historically been some of the most difficult kidney disorders to understand and treat. While the precise pathogenetic mechanisms of some glomerular diseases remain unknown, significant advances have been made in the understanding and treatment of these disorders in the past decade. This chapter provides an overview of the primary causes of glomerulonephritis with a focus on their etiology, the pathophysiologic mechanisms responsible for glomerular injury, and the clinical presentation of the eight predominant types of glomerulonephritis. Treatment options and monitoring approaches for each type of glomerulonephritis are also discussed.

NORMAL GLOMERULAR ANATOMY AND FUNCTION

The glomerulus, which is enclosed within the Bowman's capsule, consists of two important components: the capillary wall and the mesangium (**Fig. 64-1**). The capillary wall, which serves as the primary filtration barrier, consists of three well-defined layers: fenestrated endothelium, glomerular basement membrane

(GBM), and visceral epithelial cell layer. The visceral epithelial cells, also known as podocytes, have specialized foot processes embedded in the outer layer of the GBM. It is across this barrier that plasma water flows and ultimately becomes the ultrafiltrate. Under normal conditions, the GBM functions as a compact hydrated gel of matrix proteins with a pore-like structure. The mesangium, which consists of mesangial cells embedded in an extracellular matrix, provides support for the glomerular capillaries and also modulates blood flow through the capillaries.

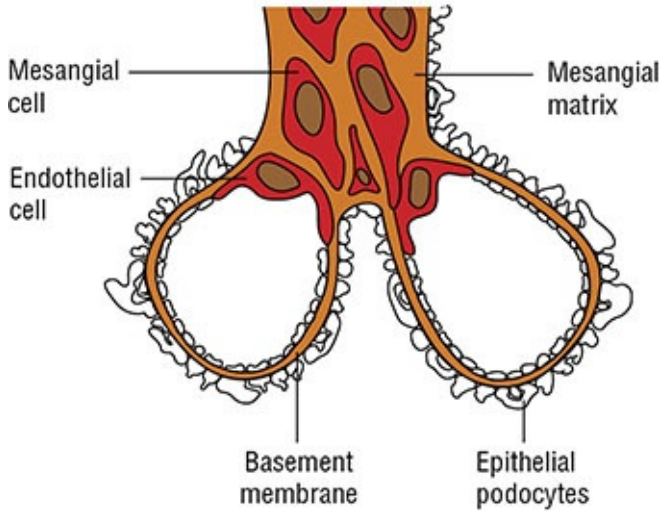


FIGURE 64-1 Microanatomy of the glomerulus.

The unique capillary bed of the glomerulus allows small nonprotein plasma constituents up to the size of inulin, which has a molecular weight of 5.2 kDa, to pass freely while largely excluding macromolecules equal to or larger than albumin, which has a molecular weight of 69 kDa. The ease of solute passage through the glomerular membrane is impacted by both the size and charge of the solute. Fixed, negatively charged sites are found within all three layers of the glomerular capillary wall. The movement of negatively charged molecules is thus restricted more than that of neutral or positively charged molecules. Different glomerular diseases affect this size- and charge-selective barrier to different extents; consequently, glomerulopathies present with varied clinical features and solute-excretion patterns.

Some of the glomerular cells, such as the visceral epithelial cells, have phagocytic function that can remove macromolecules trapped within the filtration barrier. They are also capable of synthesizing the GBM. In contrast, the mesangial cells regulate glomerular hemodynamics in response to angiotensin II and by producing prostaglandins. These cells also synthesize and respond to

various cytokines and thus play a key role in immune-mediated glomerular diseases. Resident phagocytes in the mesangium are responsible for moving macromolecules trapped in the basement membrane into the urinary space. These cells are also involved in the development of both immune and nonimmune glomerular injury.

EPIDEMIOLOGY AND ETIOLOGY

In the United States in 2017 glomerulonephritis was the third most common cause of end-stage kidney disease (ESKD), accounting for approximately 16% of all the living or prevalent ESKD patients. Moreover, nearly 9,000 patients were diagnosed with ESKD because of glomerulonephritis in 2017 alone.[1] The life span of ESKD patients with glomerulonephritis is typically longer than those with other causes, such as diabetes and hypertension.

Humoral and cellular immunologic mechanisms participate in the pathogenesis of many glomerular diseases. Abnormalities in coagulation and metabolism, as well as genetic and vascular diseases, also contribute to glomerular damage. A kidney biopsy, which is required for diagnosis in most cases, may reveal a variety of histopathologic manifestations that vary substantially among the different types of glomerular diseases. An overview of the primary pathogenetic mechanisms is presented in this section, and specific abnormalities for each of the primary types of glomerular diseases are presented in subsequent sections.

GLOMERULAR PATHOPHYSIOLOGY AND HISTOLOGY

1 Classically, the glomerular disorders have been divided into two major categories based on the presence or absence of inflammation on kidney biopsy. This distinction is meant to reflect overall differences in pathobiologies between these two disease groups. Histologically, inflammation is identified by the presence of hypercellularity in the mesangium (ie, mesangial proliferation), inside the glomerular capillary wall (ie, endocapillary proliferation or membranoproliferation), or in Bowman’s space (extracapillary glomerulonephritis, or “crescents”). This inflammation is further described as diffuse (involving more than 50% of glomeruli) or focal (involving less than 50% of glomeruli), and within an individual glomerulus, it may be described as

segmental (involving part of the glomerulus) or global (involving all of the glomerulus). Noninflammatory injury is recognized by damage or alterations in any part of the glomerular parts in the absence of hypercellularity. Fibrosis (also described as sclerosis) is a common final pathway of inflammatory and noninflammatory glomerular injury, and results in focal or global glomerulosclerosis, as well as interstitial fibrosis.

The glomerular capillary wall is particularly susceptible to immune-mediated injury. Antigens and antibodies tend to localize in the glomerulus, probably because of its high blood flow and capillary hydrostatic pressure. Parenchymal damage can be induced as a result of humoral- and cell-mediated immune reactions. Antibodies and sensitized T lymphocytes are the primary mediators of glomerular injury.[2,3] There is an increasing body of evidence to show that infections initiate many forms of glomerulonephritis through different simultaneous and/or sequential pathways that begin with the activation of innate immune response to result in autoimmunity.

Production of antibodies to endogenous or exogenous antigens that are recognized as foreign is the first step in humoral immunologic damage to the glomerulus. Endogenous antigens may be intrinsic glomerular antigens, such as Heymann antigen on the epithelial cell or Goodpasture antigen on the GBM, or previously sequestered antigens, such as DNA or thyroglobulin. Exogenous antigens are most often viral, bacterial, parasitic, or fungal in origin. Circulating antineutrophil cytoplasmic autoantibodies (ANCAs) (ie, autoantibodies that react to cytoplasmic components of neutrophils and monocytes) are found in patients with ANCA-associated glomerulonephritis.

Complexes of antigens and antibodies may be formed in the circulation and then passively entrapped in the glomerular capillary or mesangium. Alternately, experimental antibodies may combine with endogenous glomerular antigens or exogenous antigens entrapped in the glomerulus to form complexes locally, or in situ.[3] The type and extent of glomerular damage depend on the location of the immune complex formation and the rate at which it is removed. Impaired removal facilitates the growth of the complex and thus increases the likelihood of glomerular damage.

Subsequent to antigen–antibody formation, a series of biologic events is triggered that ultimately leads to glomerular injury. Noninflammatory lesions can result from the binding of noncomplement-fixing antibody to the glomerular epithelial cell (mechanism 1) or from the activation of the complement system to form the C5b-9 membrane attack complex (mechanism 2).[3] Both mechanisms can damage the glomerular epithelial cell and result in capillary wall injury and

proteinuria. Inflammatory lesions are induced by glomerular infiltration of circulating inflammatory cells such as neutrophils, monocytes/macrophages, and platelets (mechanism 3) or by proliferation of resident glomerular mesangial cells (mechanism 4), resulting in GBM damage.[3] The migration of neutrophils and monocytes to the glomerular tufts is promoted by chemoattractants such as complement fragments (C3a and C5a), platelet-activating factor, interleukin-8, and monocyte chemotactic protein-1.[4] Various cytokines, chemokines, and growth factors are then released to participate in the inflammatory process.

T cells sensitized to glomerular antigen, macrophages, and resident mesangial cells are important participants in cell-mediated injury. Sensitized T cells can cause glomerular hypercellularity in the absence of antibody deposition.[4] Cytotoxic T cells may bind with the target cells and destroy them. Alternatively, a delayed-type hypersensitivity reaction may be initiated by activated T cells through the release of lymphokines to attract, activate, and transform monocytes into macrophages.[3] These humoral and cellular mediators, in conjunction with a host of toxic molecular entities including reactive oxygen species, proteinases, eicosanoids, and procoagulants, can alter the permeability, blood flow, and function of the glomeruli. Vascular constriction and occlusion follow and result in the eventual destruction of the glomeruli.

Acute forms of glomerular injury frequently lead to chronic kidney disease (CKD), even though the immune factors that induced the initial glomerular injury have resolved. A variety of factors may participate in the progression of kidney injury including systemic and glomerular hypertension, high dietary protein intake, proteinuria, glomerular hypertrophy, hyperlipidemia, activation of the coagulation system, abnormalities of calcium and phosphorus homeostasis, and tubulointerstitial injury. The degree of proteinuria is an index of the severity of glomerular disease and is also associated with the rate of progression of kidney disease. Proteinuria is also accompanied by an increased flux of macromolecules across the mesangium. The mesangial overload may then lead to structural damage. The passage of serum components, such as complement, across the GBM may alter the integrity of the glomerular filtration barrier. The damaging effects of macromolecules other than albumin, such as immunoglobulins, lipoproteins, transferrin, and complement, have not yet been characterized.

CLINICAL PRESENTATION

2 Although patients with glomerular disease may present with an array of signs

and symptoms, they are often categorized into one of two broad clinical phenotypes: nephritic syndrome or nephrotic syndrome (Table 64-1). It should be noted that in clinical practice, some patients have overlapping features of both nephritic and nephrotic syndrome. However, these two phenotypic categories are useful in the initial assessment of disease etiology, prognosis, treatment, and need for kidney biopsy. The unique clinical presentation characteristics of the predominant glomerulopathies are described in the individual disease sections, presented later in the chapter.

TABLE 64-1 Tendencies of Glomerular Diseases to Manifest Nephrotic and Nephritic Features

	Nephrotic Features	Nephritic Features
Minimal-change nephropathy	++++	–
Membranous nephropathy	++++	+
Diabetic glomerulosclerosis	++++	+
Amyloidosis	++++	+
Focal segmental glomerulosclerosis	+++	+
Mesangioproliferative glomerulonephritis	+	++
Membranoproliferative glomerulonephritis	++	+++
Endocapillary Proliferative glomerulonephritis	++	+++
Acute poststreptococcal glomerulonephritis	+	++++
Crescentic glomerulonephritis[a]	+	++++

[a]Can be immune complex-mediated, antiglomerular basement membrane antibody-mediated, or associated with antineutrophil cytoplasmic autoantibodies.

Nephritic syndrome reflects glomerular inflammation and frequently results in microscopic or, occasionally, gross hematuria. Red blood cells are commonly found on urine microscopy as well. In contrast, nephrotic syndrome results in few cells or cellular casts in the urine.

Hematuria occurs when red blood cells leak through the openings of the GBM. The presence of red blood cell casts on urine microscopy is highly indicative of glomerulonephritis or vasculitis. The presence of dysmorphic red

blood cells, those damaged as they pass through the openings in the GBM or as the result of osmotic injury, in the urine is suggestive of inflammatory glomerular disease. The presence of proteinuria indicates a defect of the size- and/or charge-selective barriers within the GBM. Albuminuria, above the normal threshold of 30 mg/day, is associated with increased all-cause mortality, progression to ESKD as well as fatal and nonfatal cardiovascular events.[5] Normal urinary total protein excretion is between 40 and 80 mg/day, with a maximum of 150 mg. Most of the albumin that enters the glomerular filtrate is either reabsorbed or catabolized by the tubular epithelium. The urine dipsticks that are commonly used to detect proteinuria only become positive when albumin excretion is more than 300 to 500 mg/day. They are, therefore, not sensitive enough to detect albumin excretion between 30 and 300 mg/day, which was historically called “microalbuminuria,” and which represents the early stages of kidney injury, as commonly occurs in the setting of diabetes mellitus. The Chemstrip Micral-Test II (Roche Diagnostics, Indianapolis, IN), a simple immunoassay on a dipstick, permits specific and semiquantitative determination of urinary albumin concentrations at five levels: 0, 10, 20, 50, and 100 mg/L. Another qualitative test, Micro-Bumintest (Bayer Diabetes Care, Mishawaka, IN), registers a positive reading when the urine albumin concentration is greater than 40 mg/L.

Hypertension is common among patients with glomerular diseases, as a result of renal sodium retention and the resultant plasma volume expansion. Additionally, increased activity of vasoconstrictors such as angiotensin II is often a contributor to chronic glomerular diseases. Scarring of the glomerulus resulting in regional ischemia is thought to be responsible for the hypertension. Activation of the sympathetic nervous system and the release of vasoconstrictor substances may also contribute.

CLINICAL PRESENTATION

Nephritic and Nephrotic Syndromes

General

- The patients are generally not in acute distress

Symptoms

- The patients may not experience any major symptoms

Nephritic Signs and Laboratory Tests

- Hematuria, dysmorphic red blood cells and red blood cell casts
- Hypertension and edema, particularly as kidney function declines
  - Proteinuria, usually less than 3 g/day
  - Abnormal estimated GFR (elevated serum creatinine)

Nephrotic Signs and Laboratory Tests

- Edema
- Weight gain from fluid retention
- Fatigue
- Proteinuria, greater than 3.5 g/day/1.73 m^2
- Hypoproteinemia (hypoalbuminemia)
- Hypercoagulable state for some patients
- Hyperlipidemia
- Lipiduria

Nephritic Syndrome

Glomerular bleeding resulting in microscopic hematuria is typical in nephritic syndrome. Dysmorphic red cells, especially acanthocytes, are a sensitive and specific marker of glomerular bleeding. The presence of white blood cells, and cellular and granular casts in the urine, is common. The extent of proteinuria is variable. Patients with severe inflammatory glomerular injury tend to have decreased glomerular filtration rate (GFR) because of the reduced glomerular surface area available for filtration, as a result of constriction of the capillary lumen by proliferating mesangial or inflammatory cells.

Nephrotic Syndrome

Nephrotic syndrome is characterized by proteinuria greater than 3.5 g/day/1.73 m^2, hypoproteinemia, edema, and hyperlipidemia. A hypercoagulable state may also be present in some patients. The syndrome may be the result of primary diseases of the glomerulus, or associated with systemic diseases such as diabetes mellitus, lupus, and amyloidosis. Hypoproteinemia, especially hypoalbuminemia, results from increased urinary loss of albumin and an

increased rate of catabolism of filtered albumin by proximal tubular cells.

Edema formation in patients with nephrotic syndrome was traditionally thought to be driven by the reduced plasma oncotic pressure secondary to hypoalbuminemia. If the oncotic pressure was low, the movement of fluid from the vascular space to the interstitial compartment results in a reduction of the plasma volume, which can trigger compensatory renal sodium and water retention by activation of the renin–angiotensin–aldosterone axis, vasopressin, and the sympathetic nervous system (the "underfill" mechanism). However, since experimental data reveal that the plasma volume is actually normal or elevated, hypoalbuminemia may not cause edema until the serum albumin concentration is less than 2 g/dL (20 g/L). In addition, the transcapillary oncotic pressure gradient is not as high as previously thought because increased lymphatic flow reduces the interstitial oncotic pressure by removing protein and fluid from the interstitium, thereby reducing the transcapillary oncotic pressure gradient. Instead, fluid retention is likely mediated by a primary increase in sodium reabsorption at the distal nephron, which is probably caused by tubular resistance to the action of atrial natriuretic peptide (the "overflow" mechanism).[6]

Albuminuria greater than 3 g daily is associated with a significant increase in serum cholesterol concentrations for patients with primary glomerular disease. Hyperlipidemia in nephrotic syndrome is characterized by elevated serum total cholesterol, triglyceride, very-low-density lipoprotein (VLDL), and low-density lipoprotein (LDL) cholesterol concentration.[7] The reduced plasma oncotic pressure as a result of hypoalbuminemia may lead to increased VLDL production and increased liver cholesterol synthesis, along with a decrease in LDL receptor activity, which can then lead to an increase in LDL cholesterol concentration. In addition, reduced serum albumin or the loss of a liporegulatory substance may result in reduced VLDL clearance. Nephrotic patients with hyperlipidemia, especially those with concomitant hypertension, are presumed to have an increased risk for atherosclerotic vascular disease. Hyperlipidemia also promotes the progression of glomerular injury, as evidenced by glomerulosclerosis, mesangial expansion, and hyalinosis.

Many patients with nephrotic syndrome have a hypercoagulable state as the result of defects in the function of several control proteins in the coagulation cascade. The concentration of the coagulation inhibitors antithrombin proteins C and S, along with increased concentrations of factors V, VIII, and fibrinogen as well as abnormal platelet function, may all contribute to the hypercoagulable state. The net result of these alterations in coagulation is an increased risk for arterial and venous thrombosis, especially in the deep leg and renal veins.[8]

Diagnostic Considerations

Patients with suspected glomerular disease should undergo an extensive medical history to identify potential systemic causes (**Table 64-2**). Medication, environmental, and occupational histories may also help identify exposure to potentially nephrotoxic agents. A comprehensive physical examination and laboratory evaluation may reveal the presence of systemic diseases that may contribute to the development of glomerular disease (**Fig. 64-2**). In addition, the patient's age, gender, and ethnic background may be helpful in pinpointing the specific type of glomerular disease. For example, lupus nephritis is more common in young women, whereas the incidence of ANCA-associated vasculitis is dramatically higher in older patients.

TABLE 64-2 Evaluation of Patients Suspected of Having Glomerular Disease

Medical history

To identify symptoms of medical conditions that may cause glomerular disease

- Diabetes mellitus
- Amyloidosis
- Systemic lupus erythematosus
- Other familial conditions associated with kidney disease

To identify symptoms suggestive of nephrotic syndrome

- Reduced appetite
- Fatigue
- Weight gain
- Edema

Medication, environmental, and occupational histories

To identify possible exposure to potentially nephrotoxic drugs, toxins, or chemicals

Physical examination

To identify signs and symptoms associated with systemic diseases

- Hypertension
- Rash
- Arthritis
- Retinopathy
- Neuropathy
- Lymphadenopathy
- Hepatomegaly
- Malignancy

Laboratory evaluation

Urinalysis

- To determine nephrotic nature of glomerular disease
  - Proteinuria, >3.5 g/day/1.73 m^2
  - Lipiduria
- To determine nephritic nature of glomerular disease
  - Hematuria
  - Pyuria
  - Cellular, granular casts

Glomerular filtration rate

- To determine extent of glomerular damage

Other tests

- To identify type and etiology of glomerular disease
  - Serum complement concentration
  - Antinuclear and anti-DNA antibodies
  - Antistreptolysin antibodies
  - Circulating antiglomerular basement membrane antibodies
  - Cryoglobulins

Percutaneous kidney biopsy

- To provide definitive diagnosis of glomerular disease

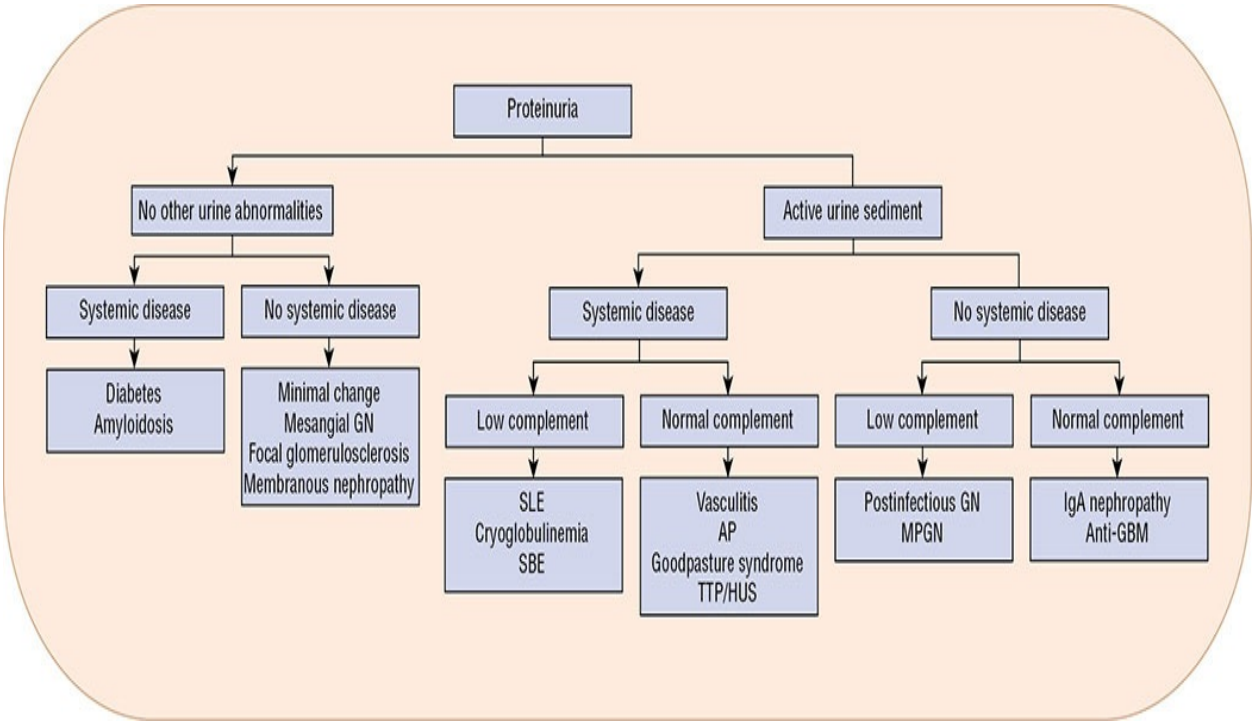


FIGURE 64-2 Clinical presentations of glomerulonephritis. (AP, anaphylactoid purpura; GBM, glomerular basement membrane; GN, glomerulonephritis; HUS, hemolytic uremic syndrome; IgA, immunoglobulin A; MPGN, membranoproliferative glomerulonephritis; SBE, subacute bacterial endocarditis; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura.)

Urinalysis can help differentiate the inflammatory or noninflammatory nature of the disease, as well as to screen for the degree of proteinuria. Estimating the GFR (eGFR) is important to determine the extent of glomerular damage. In the early stages of the disease, the GFR may remain normal. Initial injury to the glomerulus primarily lowers the permeability coefficient (K_f) of the GBM by reducing the surface area available for filtration. The reduced permeability is compensated by an elevation in the glomerular capillary hydrostatic pressure through afferent arteriolar dilation and efferent arteriolar constriction. Extensive glomerular damage may therefore be present before a substantial reduction of total eGFR is evident.

Although the cause of glomerular disease may be established from clinical and laboratory evaluation in some cases, a kidney biopsy is often needed to provide a definitive diagnosis.

TREATMENT

General Approach to Treatment

Because of the variable clinical courses exhibited by the different glomerular diseases, specific treatment approaches have been developed for each disease. The potential therapeutic benefits of treatment regimens should always be weighed against the patient risks. When satisfactory regimens are not available to treat the primary disease, appropriate supportive measures should be employed: optimization of systemic and glomerular blood pressure, reducing proteinuria, and possibly controlling hyperlipidemia may all improve the long-term outcome as well as the quality of life of these patients.

Kidney Disease: Improving Global Outcomes (KDIGO) is a global nonprofit foundation dedicated to improving the care and outcomes of kidney disease patients worldwide, and has promoted coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines for many kidney diseases.[9] The most recent KDIGO clinical practice guidelines for glomerulonephritis were published in 2012, and updated guidelines are expected in the near future. The 2012 clinical practice guidelines, as well as important subsequent advances, are referenced in the ensuing sections that focus on the treatment of individual glomerular diseases.

Nonpharmacologic Therapy

3 For patients with nephrotic syndrome, dietary measures involve restriction of sodium intake to 50 to 100 mEq/day (mmol/day), protein intake of 0.8 to 1 g/day, and a low-fat diet of less than 200-mg cholesterol per day. Total fat should account for less than 30% of daily total calories. Sodium restriction is important not only in the control of edema, but also for the control of hypertension and proteinuria. Similarly, protein restriction not only helps to reduce proteinuria but also has a potential role in decreasing the progression of kidney disease. Smoking cessation is recommended in patients with chronic kidney disease to decrease the risk of cardiovascular events.[10]

Because many immune factors are implicated in the pathogenesis of some glomerular diseases, plasmapheresis or plasma exchange therapy may be used to remove these mediators in select cases.[11] During the procedure, whole blood is removed from the body and centrifugation is used to separate the cellular

elements from the plasma. The cells are then infused back to the patient after resuspension in saline or plasma substitute. The plasma proteins, presumably including the pathogenic immune factors, are thereby removed from the patient.

Pharmacologic Therapy

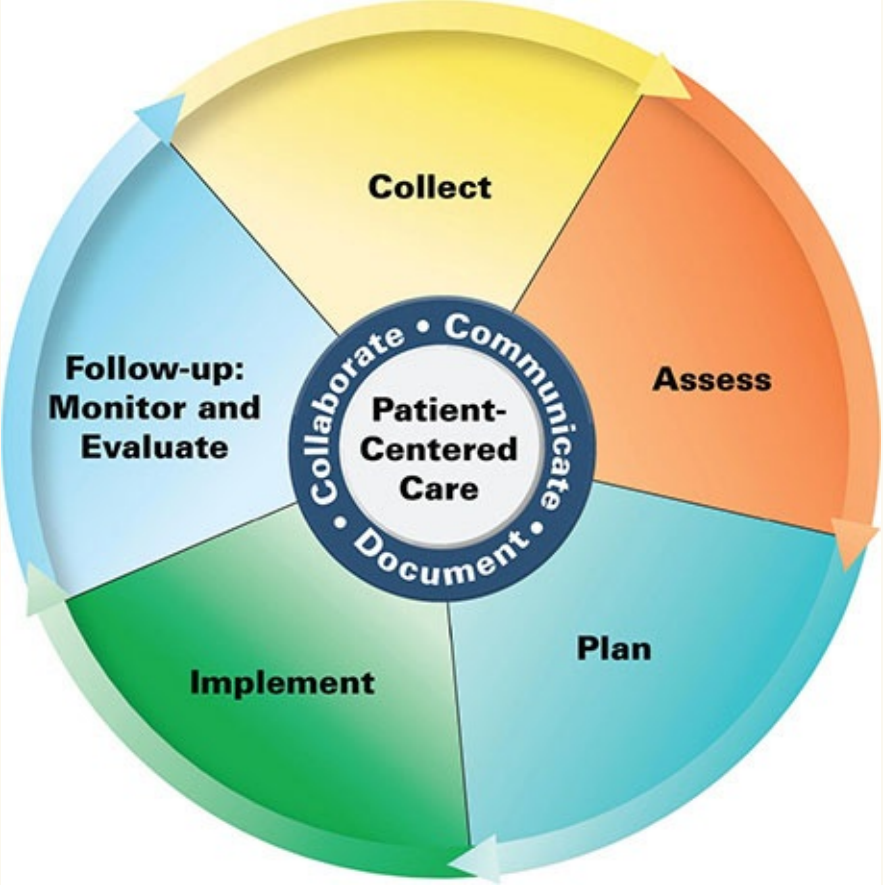
Immunosuppressive Agents

Immunosuppressive agents, alone or in combination, are commonly used to alter the immune processes that are responsible for several of the glomerulonephritis. Corticosteroids as a result of their immunosuppressive and anti-inflammatory activities reduce the production and/or release of many substances that mediate the inflammatory process, such as prostaglandins, leukotrienes, platelet-activating factors, tumor necrosis factors, and interleukin-1 (IL-1). The immunosuppressive effects of corticosteroids are mediated through the inhibition of the release of IL-1 and tumor necrosis factor by activated macrophages, and interleukin-2 by activated T cells. In addition, the actions of migration-inhibiting factor and γ-interferon are inhibited. Cytotoxic agents, such as cyclophosphamide, chlorambucil, or azathioprine, are commonly used to treat glomerular diseases. Cyclosporine and tacrolimus can reduce lymphokine production by activated T lymphocytes, and it may decrease proteinuria by improving the permselectivity of the GBM. Mycophenolate mofetil is useful in some glomerulonephritis because of its effects on T- and B-lymphocytes. Rituximab is used for B-cell depletion and is a useful agent, particularly in antibody-mediated kidney disease.

Diuretics

Management of edema involves sodium restriction, elevation of the lower extremities, and use of support stockings and diuretics. However, severe sodium restriction is difficult to achieve and prolonged bed rest can predispose patients with nephrotic syndrome to thromboembolism. Hence, the use of a loop diuretic such as furosemide is frequently required. Although the delivery of diuretic to the kidney tubules is normal, the presence of large amounts of protein in the urine promotes drug binding, and thereby reduces the availability of the diuretic to the luminal receptor sites. In addition, reduced sodium delivery to the distal tubule secondary to decreased glomerular perfusion may also alter diuretic effectiveness. Large doses of the loop diuretic, such as 160 to 480 mg of furosemide, may be needed for patients with moderate edema (see Chapter 66). Presence of edema fluid in the bowel wall may delay oral drug absorption;

however, clinically relevant changes in pharmacokinetics have not been observed.[12] In some instances, a thiazide diuretic or metolazone may be added to enhance natriuresis.[13] Alternatively, a continuous IV infusion or intermittent IV boluses of a loop diuretic may be employed.[14] For patients with morbid edema, albumin (25%) infusions may be used to expand plasma volume and increase diuretic delivery to the renal tubules, thus enhancing diuretic effect. For patients with significant edema, the goal of treatment should be a daily loss of 1 to 2 lb (0.45-0.9 kg) of fluid until the patient's desired weight has been obtained.



Patient Care Process for Managing Glomerular Disease

Collect

- Patient characteristics (eg, age, sex, ethnicity)
- History of present illness (eg, edema, gross hematuria, extra-renal

symptoms such as hemoptysis and joint pains)

- Patient medical history (personal and family)
- Social history (eg, tobacco use, history of drug use) and dietary habits including sodium intake
- Current medications including OTC NSAID use and blood pressure medications
- Objective data
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2-saturation
  - Labs including serum creatinine (SCr), serum albumin, complete blood count, urinalysis, and random urine protein:creatinine ratio
  - May consider a limited serologic workup (eg, complement component C3 and C4 levels, antinuclear antibody, anti-phospholipase A2 receptor antibody)
  - Renal ultrasound

Assess

- Blood pressure (goal generally <130/80 mmHg)
- Volume status for presence of peripheral edema, pulmonary edema
- Presence of life-threatening, associated complications such as pulmonary hemorrhage and venous thromboembolism
- Ability to monitor weights and blood pressures at home
- Ability to tolerate immunosuppressive therapy such as corticosteroids (eg, hyperglycemia, infection risk, history of depression or psychosis)
- Ability to pay for treatment options

Plan*

- Drug therapy regimens including blood pressure control with angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs)
- Volume control with diuretics
- Home monitoring of blood pressures and weights
- Immunosuppressive therapy, when indicated

- Regular monitoring of relevant labs
- Patient education
- Referral to other providers, when applicable (eg, rheumatologists for patients with ANCA-associated vasculitis)

Implement

- Provide patient education regarding all elements of treatment and follow-up plan
- Schedule follow-up labs and clinic visits

Follow-up: Monitor and Evaluate

- Achievement of remission (definition depends on type of glomerular disease)
- Achievement of blood pressure and volume control
- Taper/discontinue immunosuppressive medications, when applicable
- Monitor for adverse events of treatment

*Collaborate with patient, caregivers, and other healthcare professionals.

Antihypertensive Agents

Optimal control of hypertension for patients with glomerular disease is important in reducing both the progression of kidney disease and the risk for cardiovascular disease (see Chapters 30 and 61). According to JNC 8 guidelines, the target blood pressure for patients with chronic kidney disease defined by GFR less than 60 mL/min/1.73 m^2 (0.58 mL/s/m^2) is less than 140/90 mm Hg.[15] However, the NIH-sponsored SPRINT trial showed that targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause.[16] An analysis of patients in the SPRINT trial with nondiabetic CKD found that the more intensive blood pressure goal (systolic blood pressure <120 mm Hg) was associated with lower rates of cardiovascular outcomes, renal outcomes, and death compared to the <140 mm Hg group.[17]

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) delay the loss of kidney function for patients with diabetic kidney disease, as well as some nondiabetic (primarily glomerulonephritis) kidney diseases. Nondihydropyridine calcium channel

blockers (eg, diltiazem and verapamil) reduce proteinuria and preserve kidney function and could be used as an additional agent. In contrast, the dihydropyridine calcium channel blockers (eg, nifedipine, amlodipine, or nisoldipine) are effective in lowering blood pressure, but without the benefit of proteinuria reduction.[18]

Antiproteinuria Agents

Dietary protein restriction reduces proteinuria and may minimize kidney function deterioration. Secondary analysis of the Modification of Diet in Renal Disease Study for patients with moderate renal insufficiency (GFR of 25-55 mL/min/1.73 m^2 [0.24-0.53 mL/s/m^2]) revealed that reduced protein intake (0.66 g/kg/day) delayed the rate of GFR deterioration for patients with severe renal insufficiency (GFR of 13-24 mL/min/1.73 m^2 [0.13-0.23 mL/s/m^2]).[19] Consequently, modest protein restriction of 0.8 g/kg/day is reasonable for patients with moderate renal insufficiency. Decreasing dietary protein also reduces the intake of phosphorus and potassium. In many instances, the potential benefits of protein restriction have to be balanced against the nutritional deficiencies which may develop. For nondialyzed patients who have GFRs of less than 25 mL/min/1.73 m^2 (0.24 mL/s/m^2), dietary protein intake should be reduced to 0.6 g/kg/day.

Renin–Angiotensin–Aldosterone System Blockade Since proteinuria is recognized to be an independent risk factor for kidney function decline and cardiovascular disease, reducing proteinuria has been shown to be an important surrogate outcome in many glomerular diseases. Disruption of the renin–angiotensin system (RAS) by ACEI, ARB, and the mineralocorticoid receptor blockers (spironolactone and eplerenone) can all decrease proteinuria.[20] The antiproteinuric effect of ACEIs is associated with a fall in filtration fraction, suggesting a reduction in intraglomerular pressure. ACEIs and ARBs may also have direct effects on podocytes, resulting in reduction of proteinuria and glomerular scarring. In addition, angiotensin-converting enzyme (ACE) inhibition may also reduce the effect of angiotensin II on renal cell proliferation, thereby reducing sclerosis. These beneficial effects on proteinuria are beyond what can be attributed by the drug's antihypertensive effects (see Chapters 30 and 61).

Combined use of ACEI and ARB maximizes blockade of RAS by counteracting the effects of angiotensin II produced by non-ACE pathways. In addition, with the blockade of the angiotensin II type 1 receptor, the angiotensin

II produced by the non-ACE pathways may still act on the angiotensin II type 2 receptors, further facilitating vasodilation.[21] An angiotensin II receptor antagonist would provide additional benefit for those patients who do not attain full and persistent remission of proteinuria with an ACEI alone. Such ACEI and ARB combination therapy reduces proteinuria and the rate of kidney function declines more than either treatment alone.[22] However, the ONTARGET trial showed that the combination was not more effective than single-drug therapy in patients with minimal proteinuria.[23] The VA NEPHRON-D trial was terminated early because of increased risk of hyperkalemia and acute kidney injury in patients receiving lisinopril-losartan combination, compared with those receiving losartan monotherapy.[24] In addition, results of the ALTITUDE trial showed that adding the renin inhibitor aliskiren to ACEI or ARB monotherapy increased nonfatal strokes in type 2 diabetes patients with overt nephropathy.[23] In view of these findings, RAS blockage by dual therapy should be avoided because of potential increase in adverse effects; however, there are clinicians recommending the judicious use of combination therapy to take advantage of the powerful proteinuria reduction. It is anticipated that results from ongoing studies may help define the best use of these agents for kidney protection.

A thorough review of the combined use of ACEs and ARBs for diabetic nephropathy and proteinuria reduction can be found in Chapter 61.

Nonsteroidal Anti-inflammatory Agents Nonsteroidal anti-inflammatory drugs (NSAIDs) probably reduce proteinuria through prostaglandin E_2 inhibition, resulting in a reduction in intraglomerular pressure, a decrease in GFR, and restoration of the barrier size selectivity of the GBM.[25] Indomethacin and meclofenamate, the two most evaluated NSAIDs, have similar efficacy to ACEIs, and combined treatment with an ACEI results in additional proteinuria reduction.[26] However, adherence to a low-sodium diet or concurrent use of a diuretic is needed to maximize the antiproteinuric effect. Because of their potential for nephrotoxicity and proteinuria, especially for patients with preexisting CKD, long-term use of an NSAID for renoprotection is not commonly prescribed.[23]

Statins

It is important to manage hyperlipidemia in patients with persistent nephrotic syndrome, especially those with high VLDL and LDL cholesterol levels (see Chapters 31 and 61). Therapy is especially needed for those with concurrent atherosclerotic cardiovascular disease, or with additional risk factors for

atherosclerosis, such as smoking and hypertension.[27] Management of hyperlipidemia may not be required in cases where remission of nephrotic syndrome can be rapidly achieved, such as in children with minimal change disease, since the hyperlipidemia will improve with disease resolution.

β-Hydroxy-β-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, also known as “statins” such as lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, and rosuvastatin, are considered the treatment of choice.[28] They reduce total plasma cholesterol concentration, LDL cholesterol, and total plasma triglyceride concentrations. Aside from the lipid-lowering effects, statins can reduce cardiovascular risk independent of serum lipid concentrations. Such “pleiotropic” effects are mostly mediated through inhibition of protein prenylation, altering signaling pathways that regulate gene expression, membrane trafficking, cell proliferation, migration, and apoptosis. Renoprotection is conferred through the reduction of cell proliferation and mesangial matrix accumulation and their anti-inflammatory and immunomodulatory effects.

Meta-analysis of published studies showed that statins appear to reduce kidney function decline and slow the progression of proteinuria moderately. The beneficial effect may be dose-related and duration-dependent. One analysis revealed that patients with cardiovascular disease were most likely to benefit, compared with those with diabetes or hypertensive nephropathy or glomerulonephritis.[29] In contrast, a large randomized, controlled trial (SHARP) with 9,438 participants showed that simvastatin 20 mg plus ezetimibe 10 mg did not affect the progression of ESKD, although the lipid reduction prevented major cardiovascular events in predialysis CKD patients.[30]

Based on the available data, statins should be used to treat the dyslipidemia in patients with persistent nephrotic syndrome; however, their effect on kidney function preservation is not as clear. The PCSK9 inhibitors, alirocumab and evolocumab, may be especially useful in treating hypercholesterolemia in patients who have nephrotic syndrome and those on peritoneal dialysis, since they tend to have high PCSK9 concentrations.[31] However, the effect of these agents on kidney function needs to be demonstrated in large clinical trials.

Anticoagulants

Renal vein thrombosis, pulmonary emboli, or other thromboembolic events are serious and common complications of nephrotic syndrome, and are frequently seen in those with membranous nephropathy. Although patients who have documented thromboembolic episodes should be anticoagulated with warfarin

until remission of nephrotic syndrome, the use of prophylactic anticoagulation is controversial. A decision analysis study suggested that prophylactic anticoagulation may be beneficial for patients with membranous nephropathy.[32] Also at risk are those who require prolonged bed rest, those receiving high-dose IV steroid therapy, individuals who are volume depleted, as well as postsurgical patients.[25]

Evaluation of Therapeutic Outcomes

The management of patients with glomerular disease involves empiric or targeted pharmacologic therapy in addition to supportive measures to prevent and/or treat the pathophysiologic sequelae, namely, hypertension, edema, and progression of kidney disease. Although the course of the disease and specific treatment regimens may vary, various clinical parameters, such as proteinuria, hematuria, and eGFR changes, are routinely used to assess treatment responses.

4 Patients should be monitored closely for therapeutic response as well as the development of treatment-related toxicities. Although the long-term goal of treatment is to protect kidney function, resolution of nephrotic and nephritic signs and symptoms is an important short-term surrogate target (Table 64-3).

TABLE 64-3 Monitoring Parameters to Assess Response to Glomerular Disease Treatment

Kidney function
- Serum creatinine concentration
- 24-hour urine collection for creatinine clearance determination
- 24-hour urine collection for urinary protein excretion
- Urine protein-to-creatinine ratio

Clinical signs and symptoms
- Nephrotic syndrome
  - Proteinuria
  - Serum lipid concentrations
  - Edema
- Nephritic presentations
  - Hematuria
  - Urinalysis
  - Complete blood count
- Blood pressure
- General well-being: appetite, energy level

Kidney biopsy to assess disease progression and response to therapy

Assessment of drug therapy adverse reactions and toxicities

The frequency of monitoring is dependent on the specific glomerulopathy and severity of the disease.

Serum creatinine concentration as well as creatinine clearance should be evaluated prior to and during treatment; 24-hour urine should be collected to determine the extent of proteinuria. The daily urine protein excretion may be estimated from the urinary total protein-to-creatinine concentration ratio. After establishing the correlation between the 24-hour urinary protein excretion and the protein-to-creatinine ratio, single, random urine specimens may be used in place of a 24-hour urine collection. Home blood pressure monitoring should be performed regularly to assess the need for and/or the adequacy of antihypertensive therapy. The clinical signs and symptoms of edema and fluid overload should be assessed regularly to gauge the need for diuretic initiation or dosage modification. For patients with nephrotic syndrome, serum lipid concentrations should be monitored, at least quarterly. If the patient has hematuria, urinalysis and a complete blood count should be obtained. The clinician should also be aware of the patient's appetite and energy level, because these are indicators of the patient's overall well-being. After initial diagnosis, a repeat kidney biopsy may be needed in some cases to assess response to treatment and disease progression, to determine future treatment strategy, or to confirm the initial diagnosis.

Patients receiving cytotoxic drug treatment should be evaluated to gauge their response and identify the presence of drug-related toxicities every week for a month and then monthly to quarterly thereafter. If a favorable response is

obtained after a course of treatment, the patient may be evaluated every 3 to 4 months. The patient's kidney function, proteinuria, urinalysis, blood pressure, lipid profile, and the overall state of health should be assessed during these regular follow-up visits.

MINIMAL-CHANGE NEPHROPATHY

Epidemiology and Etiology

Minimal-change nephropathy (also termed "nil disease") is the most common cause of nephrotic syndrome in children, accounting for 85% to 90% of nephrotic syndrome for patients between 1 and 4 years of age. The percentage drops to less than 50% after age 10 and it accounts for less than 20% of all cases of idiopathic nephrotic syndrome in adults. Lipoid nephrosis is another term that has been used to describe this type of glomerular disease because lipids, as well as renal tubular cells, are found in the urine. Secondary causes of minimal-change nephropathy include drug exposure (eg, NSAIDs, lithium, and interferons), lupus, and various T-cell–related disorders, such as Hodgkin's disease and leukemia.

Histology

Minimal-change disease is characterized by the absence of definitive pathologic changes with light and immunofluorescence microscopies of a kidney biopsy specimen. The characteristic lesion in patients with minimal-change disease, as visualized under electron microscopy, is the spreading and fusion of the foot processes of epithelial cells (podocytes) over an unchanged GBM.

Pathophysiology

The pathogenesis of minimal-change disease is unknown, although some have proposed that altered cell-mediated immunologic response, specifically T-cell dysfunction or changes in the T-cell subpopulations, may be responsible. The activated lymphocytes are thought to secrete lymphokines that reduce the production of anions in the GBM and alter podocyte integrity. The permeability of the GBM to plasma albumin is increased as the result of the reduction in electrostatic repulsion. The loss of anionic charges also results in fusion of the epithelial cell foot processes.

Clinical Presentation

Most patients present initially with acute onset of nephrotic syndrome. In some cases, this may follow a nonspecific upper respiratory tract infection, allergic reaction, which might have activated T lymphocytes. Massive proteinuria (substantially more than 40 mg/m^2/hr for children and more than 3-3.5 g/day for adults), hypoalbuminemia, and hyperlipidemia are all common. The patient's weight may increase dramatically because of sodium and fluid retention. Nephritic features and gross hematuria are uncommon. Hypertension and decreased kidney function are uncommon in children but are frequently seen in older adults.

Treatment of Minimal-Change Disease

Pharmacologic Therapy

5 **Steroids** Minimal-change disease is most responsive to initial treatment with corticosteroids. In children, steroid therapy is expected to lead to remission in proteinuria in more than 90% of patients and the 10-year renal survival rate exceeds 95%. Because of the excellent response to steroids and the prevalence of this glomerular disease in children, reduction in proteinuria secondary to steroid treatment is considered diagnostic for minimal-change disease without the need for kidney biopsy. Prednisone is commonly administered at 60 mg/m^2/day initially for 4 to 6 weeks. The dose is then reduced to 40 mg/m^2/day every other day for 2 to 5 months, with dose tapering (**Fig. 64-3**).[9] Proteinuria will disappear in 50% of patients after 1 week and in 94% of pediatric patients after 4 weeks of treatment. Commonly, the initial episode is treated with an extended course (months) of therapy, followed by shorter treatment (weeks) for relapses.[33]

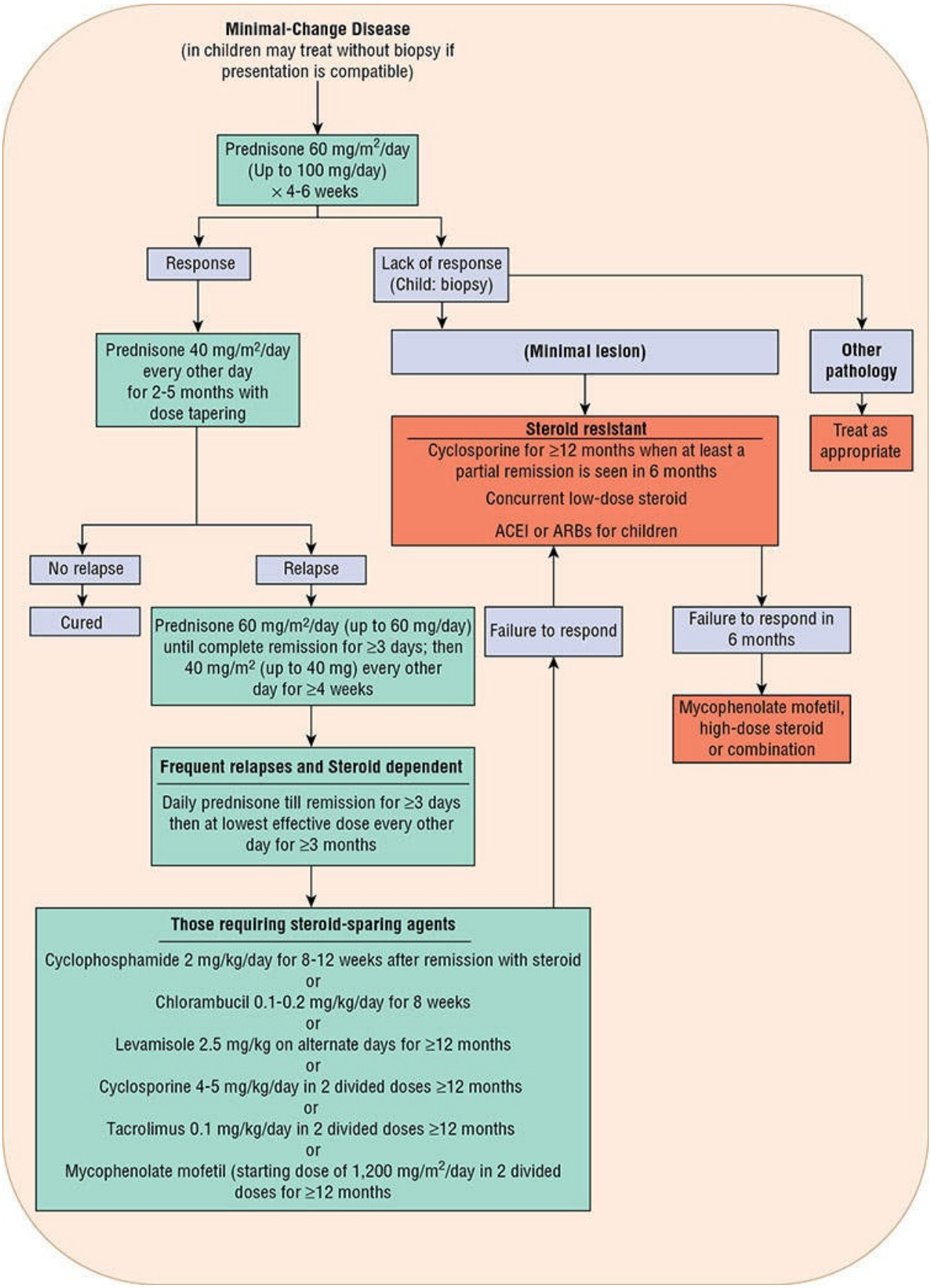

Minimal-Change Disease
(in children may treat without biopsy if presentation is compatible)
Prednisone 60 mg/m²/day (Up to 100 mg/day) × 4-6 weeks
Response
Lack of response (Child: biopsy)
Prednisone 40 mg/m²/day every other day for 2-5 months with dose tapering
(Minimal lesion)
Other pathology
Steroid resistant
Cyclosporine for ≥12 months when at least a partial remission is seen in 6 months
Concurrent low-dose steroid
ACEI or ARBs for children
Treat as appropriate
No relapse
Relapse
Cured
Prednisone 60 mg/m²/day (up to 60 mg/day) until complete remission for ≥3 days; then 40 mg/m² (up to 40 mg) every other day for ≥4 weeks
Failure to respond
Failure to respond in 6 months
Mycophenolate mofetil, high-dose steroid or combination
Frequent relapses and Steroid dependent
Daily prednisone till remission for ≥3 days then at lowest effective dose every other day for ≥3 months
Those requiring steroid-sparing agents
Cyclophosphamide 2 mg/kg/day for 8-12 weeks after remission with steroid
or
Chlorambucil 0.1-0.2 mg/kg/day for 8 weeks
or
Levamisole 2.5 mg/kg on alternate days for ≥12 months
or
Cyclosporine 4-5 mg/kg/day in 2 divided doses ≥12 months
or
Tacrolimus 0.1 mg/kg/day in 2 divided doses ≥12 months
or
Mycophenolate mofetil (starting dose of 1,200 mg/m²/day in 2 divided doses for ≥12 months

FIGURE 64-3 Treatment algorithm for minimal-change disease according to KDIGO guidelines. *(Data from Reference* 9.)

For adults, prednisone 1 mg/kg/day (maximum 80 mg) or alternate-day single-dose therapy of 2 mg/kg (maximum of 120 mg) is given initially for a minimum of 4 weeks to maximum of 16 weeks and then tapered slowly with cessation by 6 months. The remission in proteinuria is slower in adults, with 50% of the patients responding after 8 weeks and an additional 10% to 25% responding after 12 to 16 weeks of treatment.[34]

Relapse As many as 80% to 90% of the patients who respond to initial steroid therapy (steroid sensitive) will experience a relapse of proteinuria, within 6 to 12 months after disease onset. The risk of relapse is affected by the duration of initial steroid therapy. Children who were asymptomatic with proteinuria diagnosed during routine urine screening tend to have less frequent relapses and a more favorable clinical course. In those who relapse, 50% to 65% may have steroid-responsive relapse episodes over the subsequent 3 to 5 years. The dose and duration of steroid treatment for relapse do not appear to influence the subsequent rate of relapse. Commonly, 60 mg/m^2/day of prednisone is given until the urine is free of protein for 3 days, followed by 4 weeks of alternate-day prednisone at 40 mg/m^2 per dose.[33]

Frequent Relapse Approximately 40% of children who are steroid responsive will experience frequent relapses or become steroid dependent, that is, requiring continuous low-dose alternate-day prednisone to maintain an extended relapse-free period.[9] A small number of patients eventually develop resistance to steroids, and a kidney biopsy done at that time often reveals another pathology such as focal segmental glomerulosclerosis (FSGS). It is controversial whether minimal-change disease progresses into FSGS or if FSGS was present at the time of initial clinical presentation.

Cytotoxic Agents Cytotoxic agents are often considered for patients who are steroid resistant, as well as for those who require large doses of steroids to sustain remission (steroid dependent). These agents are also beneficial for pediatric patients who experience growth retardation secondary to chronic use of steroids. Cytotoxic agents are effective in inducing remission and the duration of remission tends to be longer than that induced by steroids. In those who relapse after cytotoxic therapy, they may regain or respond better to steroids than before.

Cyclophosphamide at 2 mg/kg/day for 8 to 12 weeks is very effective in

inducing remission. Alternatively, chlorambucil at 0.1 to 0.2 mg/kg/day may be used. This agent, however, is associated with more adverse effects than cyclophosphamide. Azathioprine is no longer recommended since its effectiveness has not been substantiated in randomized trials.[9]

The immunosuppressive effect of cytotoxic agents can result in serious infections, which are the primary cause of death for patients with minimal-change nephropathy. Other toxicities associated with cyclophosphamide include gonadal fibrosis, which results in sterility, hemorrhagic cystitis, alopecia, and the potential development of malignancy in those on long-term treatment.

Calcineurin Inhibitors Cyclosporine decreases lymphokine production by activated T lymphocytes and thereby reduces proteinuria by reversing the lymphokine-induced alterations in the anionic charge and permeability of the GBM to albumin. For patients with steroid-sensitive or steroid-dependent disease, cyclosporine induces remission in 80% to 85% of patients. However, the disease-free period is not often sustained, and relapse may occur as soon as the drug is tapered or discontinued. The steroid-sparing effect of cyclosporine is useful for steroid-dependent patients, especially those who have experienced significant adverse effects.[9]

Tacrolimus has been used in children and adults with frequent relapse and steroid dependent when preferable, for instance to avoid some of the adverse events associated with cyclosporine. While randomized trials are not available to substantiate its use, it is believed that its efficacy is similar to cyclosporine based on one observational study.[35]

Dosage The usual starting dose of cyclosporine for remission induction is 4 to 5 mg/kg/day in two divided doses with the goal of achieving 12-hour trough serum concentrations of 80 to 150 ng/mL (mcg/L; 67-125 nmol/L). After achieving stable remission for 3 to 6 months, a lower serum concentration, perhaps at 60 to 80 ng/mL (mcg/L; 50-67 nmol/L), can be maintained to minimize cyclosporine-induced nephrotoxicity.[9] Therapy should be maintained for at least 12 months, since most patients experience relapse when treatment is stopped, especially those with a shorter duration of therapy. However, kidney toxicity may become a concern with longer term therapy.

Adverse Events Adverse events such as hypertrichosis and gingival hyperplasia are quite common. Long-term therapy may result in persistent hypertension and progressive kidney failure.

Mycophenolate Mofetil Mycophenolate mofetil is an immunosuppressant that

can suppress T- and B-cell lymphocyte proliferation, B-lymphocyte antibody production, and expression of adhesion molecules. It is reported to have steroid-sparing effects and is useful in frequently relapsing, steroid-dependent, and steroid-resistant patients, as well as in those who fail cytotoxic therapy. KDIGO guidelines recommend a starting dose of 1,200 mg/m^2/day in two divided doses. Therapy should be maintained for at least 12 months since most will relapse when the treatment is stopped.[9] For those who experience relapse, treatment should be continued or another agent started to maintain the remission.

Rituximab Rituximab has been found to reduce relapse rates and the need for prednisone and cyclosporine treatment in steroid dependent patients.[36] As an antiCD20 monoclonal antibody, it may act on the CD20+ B cells or CD17+ B or T cells, or exert a direct effect on the podocyte actin cytoskeleton. Due to the lack of randomized trial data and the potential for serious adverse effects, the 2012 KDIGO guidelines recommended rituximab be considered only for steroid-dependent children who have frequent relapses despite optimal combinations of prednisone and corticosteroid-sparing agents, and/or those who have serious adverse effects from such therapy.[9] Since the 2012 guidelines, multiple case series have been published describing the use of rituximab to decrease both relapses and the need for additional immunosuppression (including steroids) in adults with steroid-dependent minimal change disease.

Levamisole Levamisole, an immunostimulant, has been available for treatment for several decades. The drug is no longer available in the United States; however, it is recommended by KDIGO guidelines as a steroid-sparing agent.[9] Levamisole can promote the maturation of young T cells and restore their function as well as that of phagocytes. It may also inhibit the production of an immunosuppressive lymphokine. Levamisole was found to have a steroid-sparing effect and can enhance maintaining remission in children who had frequent relapse steroid-dependent nephrotic syndrome.[37] The adverse effects of levamisole include mild neutropenia, which is generally reversible, and gastrointestinal upset.

Steroid-Resistant Nephrotic Syndrome While the definition of steroid resistance varies among studies, KDIGO guidelines define it as a minimum exposure to 8 weeks of prednisone 2 mg/kg/day or 4 weeks of 60 mg/m^2/day, followed by 1.5 mg/kg/day or 40 mg/m^2 per dose alternate-day for 4 weeks without clinical response.[9] A kidney biopsy may be needed to identify or confirm the pathology in these patients. Steroids may be continued for an additional 4 weeks for a total

of 12 weeks while awaiting biopsy results.

Calcineurin inhibitors are recommended as initial therapy for steroid-resistant nephrotic syndrome, with a duration of therapy of at least 12 months. ACE inhibitors or ARBs should also be used concurrently to reduce proteinuria. If no response is observed after 6 months, mycophenolate mofetil, high-dose steroid, or a combination of these agents should be considered. Recent analysis of seven case series and one randomized controlled trial shows that rituximab offers promising efficacy and safety for steroid-resistant nephrotic syndrome and should be further investigated by randomized clinical trials.[9,38]

Prognosis

Typically, minimal-change nephropathy follows a course with spontaneous remission (30%-40%) and relapse. However, the long-term prognosis of most patients is good. The majority of pediatric patients will not experience any relapse of the disease 10 years after the initial onset, and most will be free of the proteinuria after puberty. In adults, an 85% to 90% survival rate is seen 10 years after disease onset. Although this condition may spontaneously remit in up to 70% of untreated adults, life-threatening complications may be associated with untreated nephrotic syndrome. Significant deterioration in kidney function is uncommon in both adult and pediatric patients and is observed only in those who are steroid resistant or steroid dependent.

Most children and adults are expected to respond well to steroid therapy. Resistance may be due to undetected FSGS lesion, underlying malignancy, or treatment noncompliance. For those patients with frequent relapses and steroid-dependence, KDIGO guidelines do not indicate a preference for alkylating agents, levamisole, cyclosporine, tacrolimus, or mycophenolate mofetil. Because of the overall favorable outcome of the disease and the relatively uncommon progression into chronic kidney failure, aggressive use of cytotoxic agents is not indicated even for most patients with frequent relapses. Toxicities associated with aggressive therapy do not justify the need to induce remission in those patients who fail to respond to steroids and the nonaggressive use of cytotoxic agents. Symptomatic therapy with diuretics to control edema, in conjunction with a low-salt diet and albumin infusion as needed for acute development of anasarca, is often a more rewarding therapeutic approach. NSAIDs and ACEIs may also be used to reduce the proteinuria, although NSAIDs are commonly avoided since they can induce proteinuria and acute kidney injury.

FOCAL SEGMENTAL GLOMERULOSCLEROSIS

Etiology and Epidemiology

Focal segmental glomerular sclerosis is a clinicopathologic condition that can be idiopathic (ie, primary) or secondary to a variety of conditions such as sickle cell disease, cyanotic congenital heart disease, and morbid obesity which can induce hemodynamic stress on an initially normal nephron population and result in focal scarring of glomeruli. FSGS accounts for less than 20% of the cases of idiopathic nephrotic syndrome in children and approximately 40% in adults; however, it may account for 36% to 80% of the cases in African Americans, potentially due to genetic predisposition with *APOL1* risk alleles.[39,40] The incidence of FSGS has been rapidly increasing, so that it now is the most common glomerular disease that ultimately leads to ESKD. In the United States, FSGS is the most common etiology for proteinuria in African Americans and Hispanics. Severe glomerular injury can also be seen in patients with nephropathy associated with heroin abuse, human immunodeficiency virus (HIV) infection, and genetic mutations involving the podocin and WT1 genes. In addition, heroin, pamidronate, interferon, and anabolic steroid abuse have been associated with FSGS.[39,41]

Pathophysiology

Sclerotic lesions are characteristically found in some of the glomeruli (focal) and usually involve only a portion of the glomeruli (segmental).[39] Similar to minimal-change disease, fusion of foot processes is commonly seen in those glomeruli that are not sclerotic. It is thought that both minimal-change disease and idiopathic FSGS share similar pathogenetic mechanisms, with FSGS resulting in severe injury to the glomerular epithelial cells. During the early stage of FSGS, only a small number of glomeruli may have the segmental sclerotic lesion, and the disease may be confined to the juxtamedullary region. If an inadequate number of glomeruli are sampled during kidney biopsy, the diagnosis of FSGS may be missed, or the patient may be thought to have minimal-change disease. Steroid resistance is much more common in FSGS compared to minimal-change disease and may thus be one of the first clues that the patient, indeed, has FSGS rather than minimal-change disease. Alternatively, a patient may have the steroid-sensitive minimal-change disease initially, which subsequently progresses to steroid-resistant FSGS. The biological basis for this is not known.

Clinical Presentation

Almost all the patients present with proteinuria, and many of them have all the features of nephrotic syndrome, particularly in idiopathic FSGS. The proteinuria is nonselective, containing albumin and other higher-molecular-weight proteins, and is usually less severe when compared to patients who have minimal-change disease. Hypertension, microscopic hematuria, and kidney dysfunction may be seen in up to half of the patients. Reduced kidney function becomes more prevalent as the disease progresses.

The presenting clinical features in nephrotic adults with minimal-change nephropathy can be indistinguishable from that of FSGS, and kidney biopsy is therefore critical in the diagnosis of adults with nephrotic syndrome. African Americans have a fourfold higher risk of developing FSGS than white or Asian patients. They tend to develop the disease earlier and present with nephrotic range proteinuria more often. They are less responsive to steroids and are more likely to experience a rapid decline in kidney function, resulting in ESKD.

Treatment of Focal Segmental Glomerulosclerosis

Pharmacologic Therapy

The treatment of FSGS is controversial because of the lack of data from randomized, prospective, controlled trials, as well as the different pathogeneses that lead to finding FSGS on biopsy.

Steroids For patients with idiopathic FSGS and nephrotic syndrome, KDIGO guidelines recommend daily single dose of prednisone (1 mg/kg/day) or an alternate-day dose regimen (2 mg/kg/day) for at least 4 weeks, up to a maximum of 16 weeks, or until complete remission, with subsequent tapering over 6 months after attaining complete remission.[9] Urinary protein excretion and serum albumin concentration should be monitored to assess efficacy. The median time to induce complete remission is 3 to 4 months, although 5 to 9 months may be needed in some patients. In general, 30% to 50% of all patients are expected to be resistant to steroids (defined by lack of remission in proteinuria after at least 4 months of therapy).

If the patient develops a relapse after an adequate response to the initial treatment, a second course of steroids may be sufficient. In view of the lack of evidence specific for FSGS, the KDIGO recommendations for adults with minimal-change disease can be used to guide treatment of steroid-responsive

primary FSGS. However, if relapse occurs frequently, cytotoxic agents or cyclosporine would be indicated.

Patients who are not nephrotic have a relatively favorable prognosis and thus their need for steroids or other immunosuppressive agents is unlikely. However, close follow-up and good blood pressure control with ACEIs/ARBs may be necessary to minimize disease progression.[39]

Most of the studies conducted predominantly included white patients. In a retrospective review of 72 patients that included 65 African American patients, steroid use was not associated with kidney survival or the induction of proteinuria remission.[42] The initial creatinine level, blood pressure, and severity of renal lesions were significant predictors of kidney survival. About one-third of the patients who received steroids developed complications such as diabetes and significant weight gain.

Cytotoxic Agents When used with steroids during initial therapy, cytotoxic agents were not found to offer any additional beneficial effect.[9] Randomized clinical trials are not available to support their use as first-line therapy.

Calcineurin Inhibitors In patients with uncontrolled diabetes, psychiatric disorder, or severe osteoporosis, calcineurin inhibitors may be used as first-line therapy to avoid the potential steroid side effects on these conditions.[9,39] In steroid-resistant patients, KDIGO guidelines suggest using cyclosporine at 3 to 5 mg/kg/day in divided doses for at least 4 to 6 months. If there is a partial or complete remission, therapy may be continued for at least 12 months, followed by a slow taper.[9] Complete or partial remission was observed in 70% of patients, with a relapse rate of 47%.[43] Tacrolimus may also be used with similar effects.[44] The effect of sirolimus on proteinuria has been found to be conflicting; however, it may cause a rapid decline in GFR, and hence its use for FSGS is not recommended.[45]

Mycophenolate Mofetil A randomized controlled trial compared mycophenolate mofetil with pulse dexamethasone and low-dose prednisone versus cyclosporine in young adult patients with steroid-resistant FSGS, and suggested that the mycophenolate regimen might be beneficial for those who are unable to tolerate prolonged high-dose prednisone.[46]

6 **Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers** Because of the lack of a consistently effective regimen for primary FSGS, many patients with mild disease are treated conservatively. ACEIs and

ARBs are effective in reducing proteinuria and stabilizing kidney function in many patients with primary or secondary FSGS. Control of blood pressure and hyperlipidemia is important as well.[9] For patients who have nephrotic range proteinuria, an elevated serum creatinine concentration, and interstitial scarring on biopsy, corticosteroids with or without immunosuppressive agents are often used as combination therapy.

Steroid-Resistant FSGS About 40% to 60% of patients with primary FSGS with nephrotic syndrome are resistant to steroid treatment. KDIGO guidelines suggest following the guidelines for relapsing minimal-change disease in this population of patients: Cyclosporine 3 to 5 mg/kg/day in divided doses be given for at least 4 to 6 months. Therapy should continue for at least 12 months, followed by slow taper, if there is a partial or complete remission. For those who are unable to tolerate cyclosporine, mycophenolate mofetil and high-dose dexamethasone should be considered.[9] At present, there is insufficient evidence to support the use of alkylating agents, sirolimus, rituximab, and ACTH in steroid-resistant FSGS.

Prognosis

ESKD develops within 10 years in 10% or less of the adults and children who attain complete remission.[39] For patients who are resistant to therapy, the rate of kidney function deterioration to ESKD may be rapid, within 1 year, or slow, over as long as 10 to 20 years; approximately 50% develop ESKD within 10 years. Those patients with severe proteinuria (more than 10-15 g/day), high serum creatinine concentration at diagnosis, initial steroid resistance, or interstitial fibrosis on kidney biopsy are likely to have a more rapid decline in kidney function. Kidney transplantation is often indicated for those patients who develop ESKD; however, FSGS has recurred in 40% of the kidney allografts soon after transplantation.[39] Children, nonblack race, and those with severe disease or rapid progression to ESKD prior to transplantation are more likely to experience a recurrence. The proteinuria may reappear within hours after transplantation, and graft failure may occur in one-third to one-half of the patients. High-dose IV methylprednisolone and cyclosporine may reduce recurrences. ACEIs and plasmapheresis are also used to prolong graft survival, with the hypothesis that pheresis removes a pathogenic (but currently not discovered) circulating factor that injures podocytes. Rituximab may also be helpful in some patients who fail to respond to plasmapheresis.[9,39]

MEMBRANOUS NEPHROPATHY

Etiology and Epidemiology

Membranous nephropathy is one of the most common disorders responsible for nephrotic syndrome in adults. It is also a frequent cause of kidney failure secondary to glomerular disease. The hallmark histologic features of membranous nephropathy are glomerular capillary wall thickening with subepithelial deposits under light and electron microscopy. Autoimmunity is responsible for most cases of membranous nephropathy, and this has been historically termed “primary” membranous nephropathy. Autoantibodies against a podocyte antigen, the M-type phospholipase A2 receptor (PLA2R), have been found in 70% to 80% of patients with membranous nephropathy.[47] In addition, antibodies against thrombospondin type-1 domain-containing 7A have been found in 3% to 5% of cases,[48] and anti-neutral endopeptidase (NEP) antibodies have been discovered in rare cases of neonatal membranous nephropathy. The presence of bovine serum albumin (BSA) and anti-BSA antibodies in certain patients suggests that food antigens may be involved in the pathogenesis. Further, serum anti-PLA2R antibody levels appear to predict disease activity and response to therapy.

About 25% of adults and 80% of children have secondary causes. In the United States, the most common etiologies are autoimmune diseases (eg, lupus), infection (eg, hepatitis B and C), syphilis, neoplasm (eg, carcinoma of the lung, breast, GI tract, or kidney), and medications (eg, gold, penicillamine, or captopril). Malaria and schistosomiasis are common causes in other parts of the world. De novo membranous nephropathy can also occur in the allografts of kidney transplant patients. Because the responses to therapy as well as the prognosis for primary and secondary membranous nephropathy are different, it is important to identify any potential underlying causes for the nephropathy prior to treatment. Although this glomerular disease can occur at any age, the peak incidence is between ages 30 and 50 years and is especially likely in patients older than age 50 years who present with nephrotic syndrome.

Pathophysiology

Examination of kidney tissue under light microscopy reveals normal mesangium and normocellularity. The glomerular capillary wall may be thickened in well-developed lesions. In the advanced stage, the epithelial side of the capillary wall is markedly thickened, and intramembranous deposits are found. Progressive

changes in capillary lumen patency parallel those in the GBM, resulting in glomerulosclerosis with capillary collapse and tubular atrophy in end-stage membranous nephropathy. Immunofluorescence microscopy shows strong capillary wall staining of IgG and C3 on the epithelial side of the basement membrane, and staining can be performed on the kidney biopsy for PLA2R and thrombospondin type-1 domain 7A to confirm their role in disease pathogenesis. Antibody-mediated immune injury appears to be the main pathogenetic mechanism, and activation of the complement system may also play a key role.

Clinical Presentation

Most patients with membranous nephropathy present with heavy proteinuria (exceeding 3.5 g/day). Those patients excreting large amounts of IgG and α_1-microglobulin, indicating more significant tubulointerstitial damage, have a lower remission rate, and are more likely to progress toward kidney failure.

The signs and symptoms are usually insidious in onset and may consist of anorexia, malaise, edema, anasarca, or ascites, and pericardial and pleural effusions may also be present. As a result of a hypercoagulable state, pulmonary embolism may develop but rarely results in death. The incidence of renal vein thrombosis varies from 5% to 62%, and membranous nephropathy should be suspected when there is a sudden onset of hematuria, loin pain, pulmonary embolus, fluctuating or worsening proteinuria or GFR, renal tubular acidosis, or an increase in leg edema. The reasons for the increased incidence of venous thromboembolic disease in membranous nephropathy compared to other glomerular diseases are not well understood. Hypertension is found in approximately 30% of patients and is more common in those with kidney insufficiency.

In addition to heavy proteinuria, urinalysis often reveals lipiduria and oval fat bodies. Microhematuria is seen in fewer than 25% of patients, and gross hematuria and red cell casts are rare. In primary membranous nephropathy, the serum complement concentrations are normal, and as noted previously, antibodies to PLA2R are found in the serum of 70% to 80% of cases. Low levels of complement should alert one to search for secondary causes, such as lupus, hepatitis B infection, or an alternative diagnosis. Similarly, antinuclear antibodies, anti-DNA antibodies, rheumatoid factor, hepatitis B serologies, and serum cryoglobulins are generally negative in primary membranous nephropathy. Occult malignancy has been found in as many as 10% of elderly patients with membranous nephropathy, and recent case reports have shown a

link between cancer and anti-thrombospondin-type-1 domain 7A–associated membranous nephropathy.[49]

Treatment of Membranous Nephropathy

The treatment of primary membranous nephropathy ranges from supportive therapy to immunosuppression. Conservative management of patients with mild disease includes edema control with salt restriction and diuretics and reduction in proteinuria with protein restriction and renin–angiotensin–aldosterone system blockade.[9] The treatment algorithm for membranous nephropathy is presented in **Fig. 64-4**. Management of hypertension and hyperlipidemia is required for most patients. The use of prophylactic anticoagulation is controversial.[50]

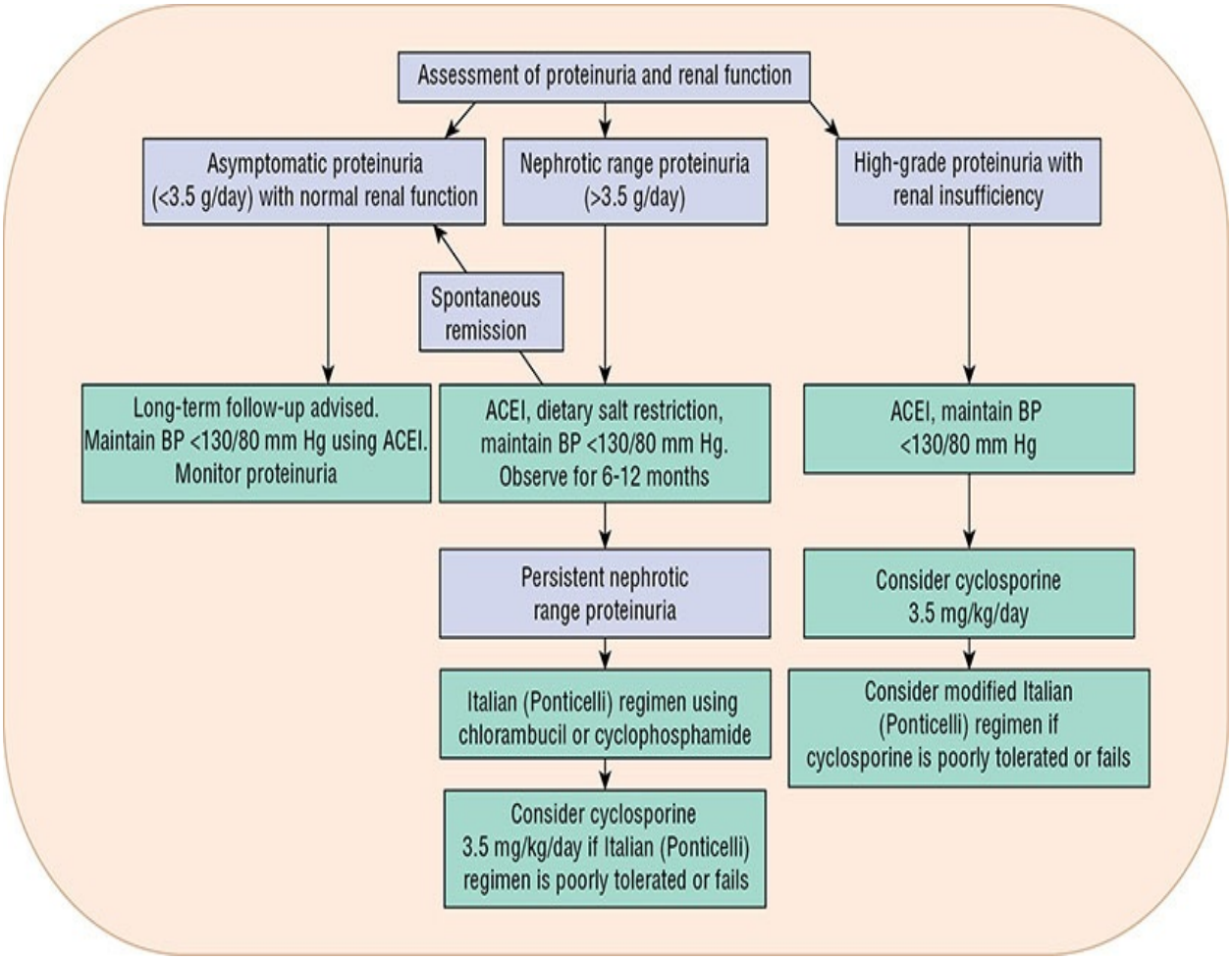


FIGURE 64-4 Treatment algorithm for idiopathic membranous nephropathy. (*Reprinted, with permission, from Geddes CC, Cattran DC. The treatment of idiopathic membranous nephropathy. Semin Nephrol 2000;20:299-308.*)

Immunosuppressive Therapy

Due to the favorable long-term outcomes of patients presenting with mild disease, KDIGO guidelines recommend immunosuppressive therapy only for those with nephrotic syndrome, “severe, disabling or life-threatening symptoms,” or with substantial elevation of serum creatinine within 6 to 12 months from time of diagnosis.[9] Since even partial remission of proteinuria improves long-term kidney and patient survival, inducing a lasting reduction of proteinuria is therefore the primary goal of treatment. Serum anti-PLA2R antibody levels clearly have a role in choosing how to treat patients with membranous nephropathy, but have not yet been incorporated into the KDIGO guidelines.

Steroids Corticosteroids alone were ineffective in improving proteinuria remission rate in all controlled trials and in preventing progression, and the result of a meta-analysis also confirmed the lack of efficacy of steroids when used alone. Therefore, steroid monotherapy is not recommended for the treatment of membranous nephropathy.[9]

Cytotoxic Agents Cytotoxic agents, when used in conjunction with corticosteroids, are effective in increasing the remission rate of proteinuria and preserving kidney function. KDIGO guidelines recommend therapy based on a regimen developed by Ponticelli and colleagues: IV methylprednisolone (1 g) for 3 days followed by oral methylprednisolone (0.5 mg/kg) for the subsequent 27 days of months 1, 3, and 5; oral chlorambucil (0.15-0.2 mg/kg) or cyclophosphamide (2.0 mg/kg/day) daily in months 2, 4, and 6.[51] The 10-year renal survival with this regimen was 92% compared with 60% in the control group receiving only symptomatic therapy. Cyclophosphamide is preferred over chlorambucil for initial therapy, since both agents resulted in similar rates of proteinuria remission and relapse, but with fewer serious side effects in those who received cyclophosphamide.[52] The use of oral cyclophosphamide monotherapy (1.5 mg/kg/day) has also shown efficacy in membranous nephropathy but has also been shown to increase long-term malignancy risk.[53]

Calcineurin Inhibitors Cyclosporine is effective in reducing proteinuria and rate of kidney function decline as well as inducing remission of nephrotic syndrome. KDIGO guidelines recommend using cyclosporine (3.5-5.0 mg/kg/day orally in two equally divided doses 12 hours apart, with prednisone 0.15 mg/kg/day) or tacrolimus (0.05-0.075 mg/kg/day orally in two divided doses 12 hours apart, without prednisone) for at least 6 months for those patients

who have contraindications to receiving the cyclical “Ponticelli” steroid/alkylating agent combination.[9] After attaining a response, the dosage can be reduced at 4- to 8-week intervals to about 50% of the starting dose and this regimen should then be maintained for at least 12 months. Serum drug concentrations should be monitored during initial therapy and when there is an unexplained rise in serum creatinine. Cyclosporine trough concentrations of 125 to 175 ng/mL (mcg/L; 104-146 nmol/L) and 2-hour postdose concentrations of 400 to 600 ng/mL (mcg/L; 333-499 nmol/L) are generally considered nontoxic. Long-term use of calcineurin inhibitors may increase blood pressure and result in nephrotoxicity, especially in patients with preexisting kidney function impairment. Relapses remain common after discontinuing calcineurin inhibitors.

Rituximab Rituximab has been shown to be effective in the treatment of membranous nephropathy in several studies. These include large, uncontrolled case series, a randomized controlled trial compared to conservative therapy, and a retrospective comparison compared with cyclophosphamide-based therapy.[54,55] Treatment decisions should be made in light of the FDA black box warning for potentially fatal infusion reactions as the risk for hepatitis B reactivation. The results of the recently completed Membranous Nephropathy Trial of Rituximab (MENTOR) study will further shed light on the efficacy of using rituximab compared to calcineurin inhibitors for primary membranous nephropathy.[56]

Alternative Therapeutic Options Tetracosactide, a synthetic analog of adrenocorticotropic hormone, as well as a natural highly purified ACTH gel, may offer favorable results. There might be a direct effect of these drugs on podocytes since receptors for endogenous ACTH have been identified on the cells.[57]

Relapse of Nephrotic Syndrome Occurs in 25% to 30% of patients within 5 years after treatment with alkylating agents and 40% to 50% within 1 year after CNIs. The 2012 KDIGO guidelines suggest reinstitution of the same regimen used for inducing the initial remission.[9]

Prognosis

The natural course of idiopathic membranous nephropathy is variable. Up to 30% of the patients experience spontaneous remission, commonly within 2 years of disease onset. Half of the remaining patients have persistent proteinuria with long-term preservation of kidney function, while the other half has gradual loss

of kidney function. Heavy proteinuria (greater than 10 g/day), male gender, elevated serum creatinine concentration at the time of presentation, poorly controlled hypertension, advanced age at onset of disease, non-Asian race, certain human leukocyte antigen phenotypes, and tubulointerstitial fibrosis on initial kidney biopsy are associated with progressive kidney disease. A predictive algorithm, incorporating the level of proteinuria, initial creatinine clearance, as well as the slope of kidney function decline over 6 months, has been developed to determine the risk for disease progression.[58]

In general, patients with idiopathic membranous nephropathy have a relatively benign course with mean 10-year survival of approximately 70%. Those who present with persistent nonnephrotic proteinuria seldom develop kidney insufficiency and have a normal life expectancy. Fewer than 10% of patients develop a remitting and relapsing course. The prognosis for secondary membranous nephropathy depends on the underlying cause. Remission occurs when the infection resolves or when the causative medication is withdrawn. For patients with a transplanted kidney, both de novo and recurrent membranous nephropathy may occur. Patients with positive serum anti-PLA2R antibody titers are at risk for recurrence. Recurrence is typically associated with nephrotic syndrome, and uncontrolled data points to the efficacy of rituximab for treating membranous nephropathy after kidney transplant.[59]

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

Etiology and Epidemiology

Historically, membranoproliferative glomerulonephritis (MPGN) has accounted for 7% to 10% of all cases of biopsy-confirmed glomerulonephritis, and has been the third or fourth leading cause of ESKD among the primary glomerular diseases. MPGN is a “pattern of injury,” rather than a specific disease, caused by many disorders that are distinguished by underlying pathogenesis and/or disease association, often as reflected by different staining on immunofluorescence microscopy on kidney biopsy. Therefore, the field of nephrology is moving away from considering MPGN a glomerular disease category on its own.[50]

Pathophysiology

The several types of MPGN are classified according to the pathologic features.

Immune complex-MPGN, which has historically been included in the group known as type I MPGN, occurs in the setting of infections such as hepatitis C virus (HCV) infection, or can be idiopathic (mostly occurring in children). These patients have evidence of immunoglobulin and complement staining on immunofluorescence microscopy. In the case of HCV-associated glomerulonephritis, the pathogenesis is related to HCV-induced B-cell proliferation with production of pathogenic immune complexes, which may include cryoglobulins.

Patients who have dominant staining for C3 on immunofluorescence microscopy are diagnosed with one of the C3 glomerulopathies: C3 glomerulonephritis or dense deposit disease (formerly called type II MPGN). Dense deposit disease is characterized by the presence of dense deposits of C3 within the GBM, which gives rise to a ribbon-like appearance. The C3 glomerulopathies occur due to dysregulation of the alternative pathway of the complement system.

If there is evidence of monoclonal immunoglobulin deposition on biopsy, then the pathogenesis is linked to an underlying B or plasma-cell clone that is producing the pathogenic monoclonal gammopathy. These disorders have been called Monoclonal Gammopathies of Renal Significance.[60] Finally, in other cases, there is no staining on immunofluorescence microscopy. These cases of MPGN pattern of injury can occur in cases such as thrombotic microangiopathy, which have various pathologies that lead to endothelial injury.

Clinical Presentation

Nephrotic syndrome is the most common presenting condition, although some patients may also have a nephritic component (hematuria), hypertension, and progressive kidney impairment. Hypocomplementemia is commonly seen, particularly in patients with C3 glomerulopathy.

Treatment of Membranoproliferative Glomerulonephritis

Pharmacological Treatment

For patients with idiopathic (immune complex) MPGN, nephrotic syndrome, and progressive decline of kidney function, the 2012 KDIGO guidelines recommend using oral cyclophosphamide or mycophenolate plus low-dose alternate-day or

daily steroids for initial therapy trial of no longer than 6 months.[9]

Treatment of HCV-associated glomerulonephritis involves eradication of the HCV, which now often involves the use of direct acting antiviral therapy. The use of therapies that decrease inflammation (ie, corticosteroids) and deplete B cells (ie, rituximab or cyclophosphamide) is reserved for cases with severe renal involvement, and plasma exchange therapy is considered in case of systemic cryoglobulinemic vasculitis.[61]

Treatment of the C3 glomerulopathies with regimens including rituximab, mycophenolate mofetil, and corticosteroids has been described, as has the use of terminal complement blockade with eculizumab. These approaches have not been evaluated in randomized controlled trials.[62]

Treatments of monoclonal gammopathy-associated kidney disease involves treatment of the underlying B or plasma-cell clone.[60] Treatment of thrombotic microangiopathy is specific to the underlying mechanism of disease. In all cases, ACEIs or ARBs may be used to control blood pressure and reduce proteinuria.

Prognosis

Type I (immune complex) MPGN is a slowly progressive disease that accounts for 80% of all MPGN, but only 5% to 15% of all cases of nephrotic syndrome seen in pediatric and adult patients. It occurs most frequently in patients between 5 and 30 years of age, and because remissions are rare, many patients eventually develop ESKD. The kidney survival is 60% to 65% at 10 years, and the presence of nephrotic syndrome, interstitial disease, and hypertension is a poor prognostic indicator. Progressive kidney disease is also common in patients with C3 glomerulopathy.[63] For those who develop ESKD and undergo kidney transplantation, the recurrence rate may be up to 70% for C3 glomerulonephritis and is approximately 20% to 30% for type I MPGN.

IMMUNOGLOBULIN A NEPHROPATHY

Etiology and Epidemiology

IgA nephropathy, also known as *Berger's disease*, was first described by Jean Berger in France in 1968. It is the most common primary glomerulonephritis in the world and accounts for 10% of patients with ESKD in many countries. The prevalence among patients with glomerular disease who had kidney biopsy varies from 30% to 35% to as high as 45% in Asia and 30% to 40% in Europe.

In the United States, the overall prevalence is approximately 10% to 15% but is as high as 35% among Native Americans living in New Mexico.[64] These differences in prevalence reflect variations in genetic predisposition, as well as the criteria used for urinary screening and kidney biopsy. The high biopsy rate tends to correlate with high frequency of the disease. Since the prevalence of clinically silent IgA nephropathy may be high, 16% in a study from Japan, the actual prevalence of the disease could be much higher than observed.[64]

IgA nephropathy is the most common primary glomerulopathy in young adult Caucasians and is two to six times more common in males than in females. It is uncommon in patients of African ancestry. IgA nephropathy can exist as a benign disease presenting with asymptomatic hematuria; however, it has the ability to present with any clinical syndrome associated with glomerular disease. ESKD occurs in up to half of patients with IgA nephropathy over a 25-year period.

Pathophysiology

Primary IgA nephropathy is an immune-complex-mediated disease in which IgA deposits, either alone or with IgG, IgM, or both, as well as other pathologic lesions, are found in kidney tissues. The pathogenic IgA molecule is abnormal, in that it lacks a galactose residue at the hinge region, and elevated levels of galactose-deficient IgA1 can be found in patients with IgA nephropathy.[65] IgA vasculitis (also known as Henoch–Schönlein purpura) is the systemic form of IgA nephropathy, commonly affecting the joints, skin, and GI tract, and is much more common in children.

The diagnosis of IgA nephropathy is established by the presence of mesangial IgA deposits upon immunofluorescence microscopy examination of the kidney biopsy. The IgA immune complex, composed of IgA antibody bound with an environmental antigen such as a virus, bacteria, or food substances, is presumed to be deposited from the systemic circulation. Alternately, the complex may be formed *in situ*, with the IgA antibody bound with an endogenous antigen in the mesangium. In the mesangium, IgA can bind with receptors on the mesangial cells to induce proliferation and cytokine production. In addition, IgA can activate the alternative complement pathway to induce glomerular damage. The extent of the injury depends on the characteristics of the IgA that favor mesangial deposition, the susceptibility of the mesangium toward deposition, the ability of the patient to mount an inflammatory response to the deposits, and the response of the kidney to the injury in a way that favors progressive kidney

damage.

The Oxford histologic classification system has been developed to provide a uniform approach to biopsy evaluation and disease classification, and its predictive value has been demonstrated in multiple patient cohorts.[66]

Clinical Presentation

IgA nephropathy commonly presents in the second and third decades of life, but it can occur at any age. Many patients have microscopic hematuria and proteinuria for years, persistently or intermittently, during the early stages of the disease. In North America, about 75% of the patients present with gross hematuria concurrent with an infection, commonly in the upper respiratory or gastrointestinal tract.[64] The hematuria may occur 1 to 2 days after the onset of infection symptoms, which is different from the 10- to 14-day delay seen after the pharyngitis in PSGN. Proteinuria is common, and nephrotic range often indicates advanced disease. Hypertension and edema are infrequent but are common in PSGN.

Kidney dysfunction is uncommon at the initial presentation; however, approximately 10% to 20% of the patients develop ESKD within 10 years, and 30% develop it after 20 years. The extent of proteinuria is one of the strongest predictors of poor long-term outcomes.[64] Uncontrolled hypertension, higher amounts of proteinuria, GFR reduction at disease presentation, and obesity are additional risk factors for developing kidney failure.[64]

Treatment of Immunoglobulin A Nephropathy

General Approach to Treatment

Normotensive patients with normal kidney function, isolated microhematuria, and minor proteinuria should be observed closely without specific treatment (**Fig. 64-5**).[9] Patients with proteinuria of 0.5 to 1 g/day should receive optimized supportive therapy, using ACEIs or ARBs to attain BP of less than 130/80 mm Hg and urinary protein excretion of less than 500 mg/day.[9] As of this time, the authors do not have a separate recommendation for patients with CKD. Combined ACEI and ARB may be more effective than monotherapy; however, there is an increase in risk of adverse effects. For patients with persistent proteinuria greater than or equal to 1 g/day, the blood pressure goal would be less than 125/75 mm Hg, steroid therapy for 6 months should be used after 3 to 6

months of optimized supportive care, although recent studies have shown higher rates of serious adverse events in patients treated with steroids. Fish oil may be used if desired. The benefit of immunosuppression for patients with lower GFRs remains controversial.[9]

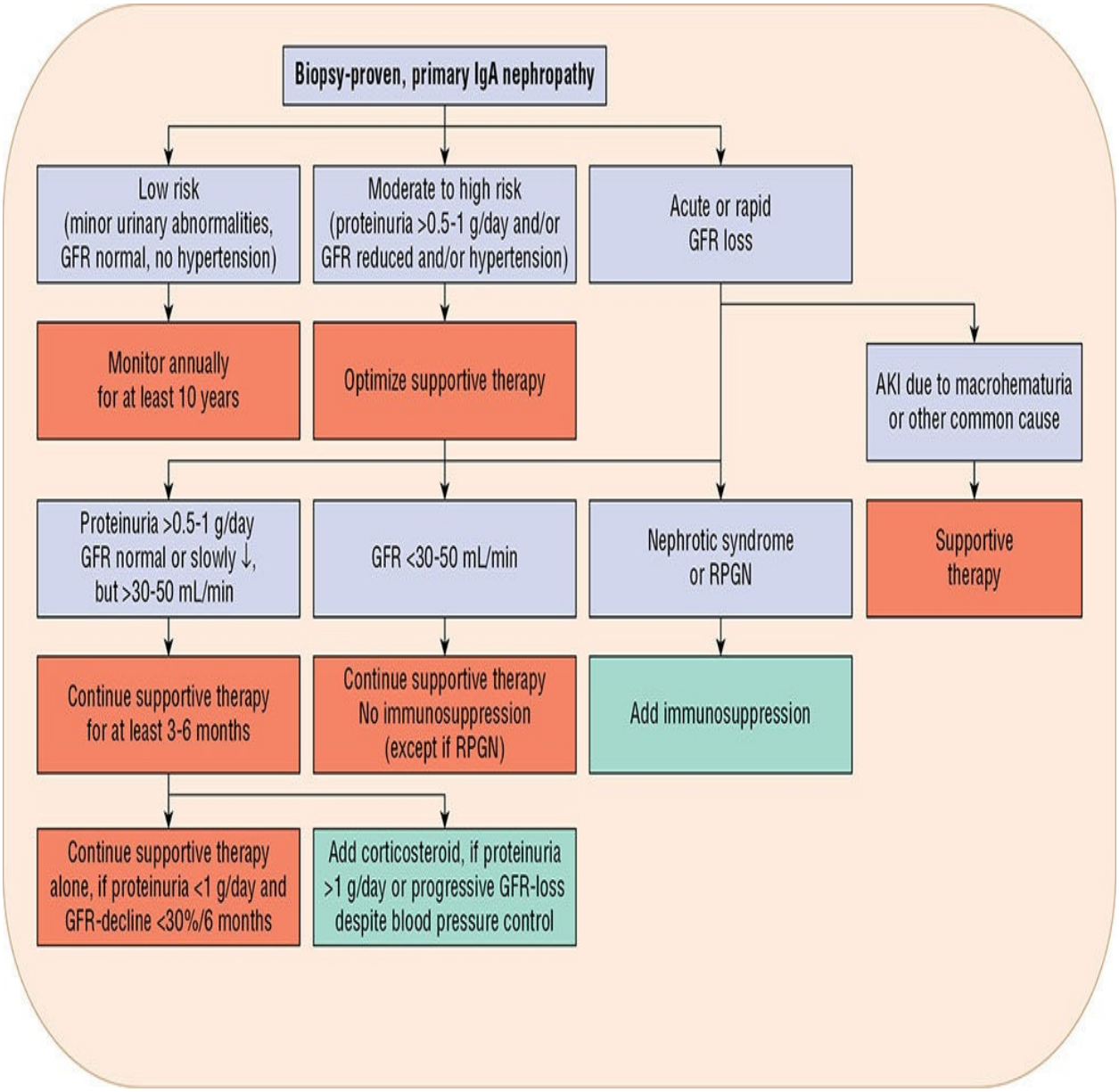


FIGURE 64-5 Treatment algorithm for biopsy-proven IgA nephropathy. Conversion from GFR units of mL/min to mL/s requires multiplication by 0.0167. (*Reprinted, with permission from Floege J, Eitner F. Current therapy for IgA nephropathy. J Am Soc Nephrol 2011;22:1785-1794.*)

Nonpharmacologic Therapy

Low-Gluten Diet and Tonsillectomy Restriction of dietary gluten is effective for patients with celiac disease but not for patients with any identifiable nephritogenic antigens. Removal of the tonsils, which produce IgA_1 and may contribute to IgA nephropathy, may reduce proteinuria and hematuria, as shown in several small, nonrandomized trials in Japan. However, such benefits were not seen in studies in Caucasians. The 2012 KDIGO guidelines did not suggest using tonsillectomy for IgA nephropathy.[9] However, it may be helpful for patients who developed recurrent macroscopic hematuria as provoked by bacterial tonsillitis.

Pharmacological Therapy

Steroids Corticosteroids with or without additional immunosuppressive agents have been used to treat IgA nephropathy for many years. Large doses of steroids (IV methylprednisolone 1 g/day for 3 days at months 1, 3, and 5 and oral prednisone 0.5 mg/kg every other day for 6 months) were able to reduce proteinuria and kidney function deterioration.[67] However, more recent studies have shown higher rates of serious adverse events with corticosteroid therapy, leading to the reevaluation of the risk:benefit ratio for their use in IgA nephropathy.[68] The 2012 KDIGO guidelines suggest a 6-month course of steroid for patients with persistent proteinuria greater than or equal to 1 g/day, despite 3 to 6 months of optimized supportive care and GFR of greater than 50 mL/min/1.73 m^2 (0.48 mL/s/m^2).[9]

Cytotoxic Agents and Mycophenolate Mofetil Several studies have evaluated the efficacy of azathioprine and cyclophosphamide. In some of the studies, cyclophosphamide was used in conjunction with dipyridamole, heparin, and warfarin. It is difficult to assess which of these agents contributed to the limited favorable effects observed. In addition, in many of these studies, blood pressure control and ACE inhibition were not always optimal. At present, there is no clear evidence to support the use of these cytotoxic agents for IgA nephropathy except for those with crescentic IgA nephropathy with rapidly deteriorating kidney function.[9]

Mycophenolate mofetil has been evaluated for treating IgA nephropathy, and favorable results were observed in two studies in China; however, no such beneficial effects were seen in studies from Belgium or the United States. These heterogeneous results, possibly due to differences in ethnicity and achieved drug concentrations, and the potential for adverse effects preclude to the widespread use of mycophenolate for IgA nephropathy.[9]

Fish Oil Anti-inflammatory agents, antiplatelet drugs, and anticoagulants have been tried without success to decrease the production or action of mediators responsible for IgA immune-complex-induced glomerular damage. However, the *n*-3 fatty acids in fish oil reduce the production or action of prostaglandins and leukotrienes, thus limiting the kidney damage caused by inflammation, platelet aggregation, and vasoconstriction. In a controlled trial on patients with heavy proteinuria and mildly impaired kidney function, daily use of fish oil delayed the progression of kidney failure with modest reduction in proteinuria.[69] A meta-analysis of five controlled studies indicated that a minor, but not statistically significant, beneficial effect on kidney function may be observed.[70] Results from several recent studies failed to confirm the beneficial effects reported earlier, and further studies are needed to confirm the role as well as the optimal dose. In many of the studies, 4 to 12 g/day were given for two or more years. Some of the fish oil preparations are rich in cholesterol; thus, it is appropriate to monitor the LDL cholesterol levels for patients receiving therapy. In view of the conflicting study results and the very low-risk profile, KDIGO guidelines suggest using fish oil for patients with persistent proteinuria of greater than or equal to 1 g/day, despite 3 to 6 months of optimized supportive care that includes ACEI or ARB and blood pressure control.[9]

Angiotensin-converting Enzyme Inhibitors and Angiotensin II Receptor Blockers Because hypertension is a negative prognostic indicator of IgA nephropathy outcome and many of these patients already have left ventricular diastolic malfunction despite being normotensive, early antihypertensive intervention with ACEIs or ARBs is important. Indeed, KDIGO guidelines recommend using ACEI or ARBs for reducing proteinuria and controlling blood pressure.[9] Randomized controlled trials have shown that ACEIs and ARBs can reduce proteinuria and improve kidney function. However, the optimal duration of therapy for reducing the risk for ESKD is unknown. There are also no data to support if there is preference of ACEI to ARB, except perhaps a better side-effect profile for ARB when compared with ACEI. There are limited data to suggest that the combined use of ACEI and ARB may offer greater proteinuria reduction than monotherapy. However, further studies are needed to affirm such benefits for the combination therapy.

Alternative Therapeutic Approaches Patients with IgA nephropathy have abnormal production of IgA and several different immunoglobulins. Immunoglobulins, administered IV initially and then intramuscularly, may have beneficial effects through immunomodulation, increased catabolism of

autoantibodies, and blockade of receptors.[71] While favorable results were reported in one trial, large randomized controlled trials are needed to substantiate its efficacy.

Urokinase, danazol, dapsone, sodium cromoglycate, and plasma exchange have also been evaluated, but none is consistently effective or shown to affect kidney function. Cyclosporine, tacrolimus, sirolimus, and mizoribine have been evaluated in a limited number of studies; available results do not support their use for IgA nephropathy. Budesonide is currently being evaluated for the treatment of IgA nephropathy, with one recent study showing positive results compared to placebo.[72]

Antiplatelet agents are commonly used in Japan and rarely outside of Asia for IgA nephropathy. A meta-analysis of seven trials (four in Japan and three in Hong Kong) revealed that these agents reduced proteinuria and stabilized kidney function.[73] In view of the different agents and concurrent immunosuppressive regimens used among the trials, KDIGO guidelines do not currently recommend using these agents.[9]

Prognosis

The majority of the patients with IgA nephropathy have a clinically inconspicuous course and some may experience spontaneous remission. However, others may have an increase in proteinuria and decline in kidney function. It is therefore important to follow the patients over a long period of time since progressive disease may appear in 30% of the patients. Spontaneous remission is seen in only 10% to 25% of children and 5% to 7.5% of adults.[64] Unfortunately, no therapy is known to be consistently effective for the treatment of IgA nephropathy. Because of the slow progression of the disease to ESKD, it is very difficult to conduct trials to evaluate the long-term effectiveness of specific treatments. Since the pathophysiological mechanisms of this disease are not well defined, it has been difficult to design and evaluate results of clinical trials.

Urinary protein excretion and the mean arterial blood pressure at follow-up correlate well with the progression of disease. The risk of developing ESKD is proportional to the amount of proteinuria, under the influence of ACEI and ARB therapy, after 1 year of follow-up. For those patients who develop end-stage kidney failure, transplantation is appropriate, especially for young adults. Recurrence of IgA mesangial deposits in the kidney allograft may occur in up to 50% of patients in 5 years and be universally present at 10 years or more posttransplant, but the recurrence of clinical disease is only approximately 10%

to 15%. There is also no correlation between the aggressiveness of the primary disease and the rate of recurrence. Use of ACEI may improve graft survival while immunosuppression with corticosteroids, azathioprine, and/or cyclosporine is not expected to prevent the recurrent nephropathy. The 2012 KDIGO guidelines do not address the treatment of recurrent IgA nephropathy in patients who have received a kidney transplant. Applying the guidelines for treating native-kidney IgA nephropathy seems to be reasonable.[9]

LUPUS NEPHRITIS

Etiology and Epidemiology

Glomerulonephritis is one of the most serious complications of systemic lupus erythematosus (SLE) and accounts for much of the morbidity and mortality of patients afflicted with the disease. SLE predominantly affects young women between 15 and 40 years of age, with an incidence of 1 in 2,000 women in the United States. African Americans are more susceptible; they develop the disease at a younger age, have nephritis earlier in the course, and are more likely to progress to ESKD.

The kidney manifestations of lupus nephritis (LN) are variable and encompass a wide spectrum of histopathologic lesions.[74] The underlying histopathology is associated with different prognoses and responses to therapy, which cannot be predicted solely based on clinical manifestations. Thus, a kidney biopsy is required to assess the severity of the disease and to predict the short-term and long-term outcomes associated with therapy. Drugs, such as hydralazine and procainamide, are known to precipitate a lupus syndrome; however, they are unlikely to cause disease that affects the kidney.

Pathophysiology

Immune complex deposits, whether formed in the circulation or in situ, can be found in various regions of the glomerulus, as well as the peritubular interstitium and vasculature outside the glomerulus. Based on light, immunofluorescence, and electron microscopy findings, LN can be categorized into six ISN/RPS (International Society of Nephrology/Renal Pathology Society) classifications: I, minimal-mesangial LN; II, mesangial hypercellularity LN; III, focal endocapillary hypercellularity; IV, diffuse endocapillary hypercellularity; V, membranous LN; and VI, advanced sclerosing LN.[74]

The hallmark feature in the pathogenesis of SLE is B-cell hyperactivity and the dysregulated production of autoantibodies against multiple antigens in the body, including DNA and various ribonucleoproteins. The size and location of the immune complexes in the glomerulus correlate with the nature and severity of kidney injury.[74] Deposition of small numbers of stable immune complexes of intermediate size in the mesangium tends to produce less severe inflammation in the glomerulus. The sequestration of the immune complexes in the mesangium prevents them from activating inflammatory mediators. Hence, the lesion is noninflammatory in nature. In contrast, large numbers of intermediate-sized or large immune complexes result in infiltration of inflammatory cells and release of necrotizing enzymes. In addition, the kidney may also sustain damage through mechanisms related to thrombotic microangiopathy.

Clinical Presentation

Females have a higher risk for developing lupus, especially in the adult years. Nephritis is commonly seen within the first 4 years of diagnosis of SLE but may also be the first manifestation of the disease. The clinical presentation ranges from minimal hematuria and proteinuria to severe, rapidly progressive diffuse glomerulonephritis. Proteinuria is very common, and nephrotic syndrome is seen in most patients with membranous lesions. Microscopic hematuria is almost always present, whereas gross hematuria is rare. Active urinary sediments (red cell casts, dysmorphic red cells, and hematuria) are suggestive of the diffuse proliferative lesion.[75] Hypertension is present in 25% to 45% of patients and is associated with a worse prognosis. Poor prognosis and higher risk for kidney involvement were observed among African American, Hispanic, and Asian patients, compared with white and Puerto Rican–Hispanic patients.[76] Other conditions found to be associated with poor prognosis include elevated serum creatinine concentration, heavy proteinuria, anemia (hematocrit less than 26% [less than 0.26]), and disease onset during childhood or in those greater than 60 years of age. Most patients have hypocomplementemia and increased antibody titers for anti-double-stranded DNA, particularly those with focal or diffuse proliferative lesions. Serum creatinine concentration at the time of diagnosis is most predictive of short-term outcome.

Treatment of Lupus Nephritis

General Approach to Treatment

7 The choice of therapy depends on the underlying lesion and the activity, as well as the chronicity indices. Acute life-threatening disease involving multiple organs requires induction treatment that can suppress the disease promptly. In contrast, long-term management of chronic indolent disease requires therapy with more acceptable side-effect profiles. Corticosteroids are the cornerstone of therapy. However, for severe LN, primarily the diffuse hypercellularity types (class III or IV), alkylating agents or mycophenolate mofetil are usually needed in combination with corticosteroids to reduce or prevent the progression to ESKD.

The goal of therapy is to induce a remission in disease. The criteria for remission of kidney disease in the literature has varied between publications, but generally involves the stabilization or improvement in kidney function, improvement or resolution of proteinuria, and improvement or disappearance of hematuria.

Optimal blood pressure control is important. The use of ACEIs or ARBs to slow disease progression through reduction of inflammation and glomerular injury is controversial, but some recent data suggest that this may be helpful in patients with lupus nephritis and antiphospholipid antibody syndrome.[77] Patients with normal kidney function and lower amounts of proteinuria with class I LN and II LN on biopsy typically do not require therapy since they have a benign natural history of their renal disease; in these cases, the use of immunosuppression is focused on treating the extrarenal lupus manifestations.[9] However, close follow-up of kidney function and urinalysis is required.

Induction Treatment

Patients with proteinuria, abnormal kidney function, and/or active urinary sediments require a kidney biopsy to define the underlying lesion and determine the activity and chronicity of disease. For patients with class III, IV, or V LN on kidney biopsy, induction treatment is recommended with corticosteroids and either cyclophosphamide or mycophenolate mofetil.[9] Studies from the 1990s showed that combined use of IV cyclophosphamide and methylprednisolone was shown to be more effective than either agent alone in inducing remission.[78] Alternately, cyclophosphamide may be given orally, but it has been found by some to have more adverse effects because of higher cumulative drug exposure. The risk for adverse events, such as infection, gonadal damage, amenorrhea, and cervical dysplasia, and malignancy is increased with the cytotoxic regimens.

Several trials have found that mycophenolate mofetil with concurrent steroid

therapy is as effective as cyclophosphamide with steroids for inducing remission in severe lupus nephritis, and may also have fewer side effects.[79,80] Some of these studies also included African American and Hispanic patients, who are known to have a poorer prognosis. Based on these data, mycophenolate mofetil is now considered an alternative to cyclophosphamide as initial therapy for patients with class III LN and class IV LN. However, cyclophosphamide may be preferred for severe class III/IV LN since the long-term outcome is not as well established for mycophenolate (**Fig. 64-6**).[9]

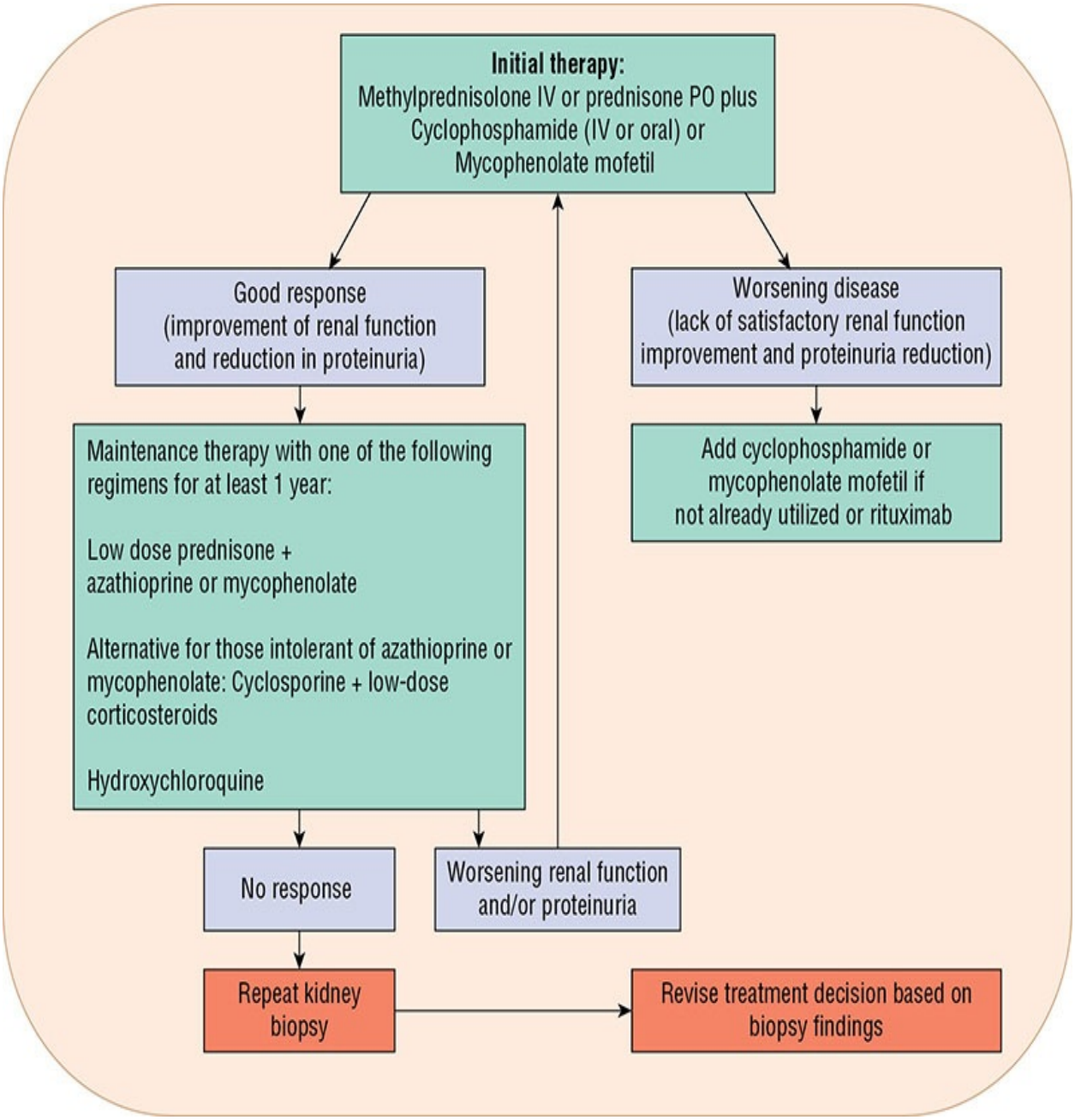


FIGURE 64-6 Treatment algorithm for class III (focal) and class IV (diffuse) lupus nephritis.

Maintenance Treatment

Historically, maintenance therapy has consisted of oral corticosteroids and alkylating agents. However, cyclophosphamide has now been replaced by mycophenolate mofetil and azathioprine as the agents of choice for maintenance therapy in lupus nephritis.[9] The efficacy of mycophenolate or azathioprine as maintenance therapy was evaluated against cyclophosphamide. Patients receiving mycophenolate or azathioprine were found to have better outcome and fewer side effects than cyclophosphamide.[81] Two large, randomized controlled trials have shown that mycophenolate mofetil is either equivalent or better than azathioprine for maintenance therapy.[82,83] Mycophenolate should not be used during pregnancy due to teratogenicity. The duration of maintenance therapy, and whether to continue or stop low-dose corticosteroids, remains unclear.

Calcineurin Inhibitors Cyclosporine may reduce proteinuria, stabilize kidney function, and improve kidney morphology. It has been shown to have comparable efficacy and safety with azathioprine in preventing relapse for patients with diffuse proliferative LN.[84] It is recommended by KDIGO guidelines for those who cannot tolerate the side effects of azathioprine or mycophenolate. Once initiated, therapy is often continued for at least 1 year after complete remission is attained.[9]

Hydroxychloroquine The antimalarial agent hydroxychloroquine can inhibit the toll-like receptors that contribute to autoimmunity. It was reported to be protective against the onset of LN, relapse of the disease, development of ESKD, venous thrombosis, and also a beneficial effect on lipid profiles. Hydroxychloroquine is recommended by KDIGO guidelines for all patients of any class for those receiving the drug should have annual eye examination for possible retinal toxicity, especially after 5 years of continuous use.[9]

Alternative Therapeutic Agents

Many agents have been tested to target the various pathways, costimulatory molecules, and immune mediators responsible for lupus nephritis. The use of rituximab as add-on therapy with standard induction therapy for lupus nephritis is supported by a significant number of uncontrolled studies, but it did not yield significant results in a randomized controlled trial.[85] Belimumab, a monoclonal

antibody that inhibits B-lymphocyte stimulating protein, has been FDA approved for the treatment of SLE, but its use for lupus nephritis is not yet clear.[86] Voclosporin, a calcineurin inhibitor, has also shown improved outcomes when added to mycophenolate and low-dose steroids for induction therapy, although it was also it associated with more adverse events, and thus requires further evaluation.[87]

Prognosis

The prognosis of patients with class I and II disease is generally good, and often no specific treatment is needed. For patients with class V disease, KDIGO guidelines recommend using antiproteinuric and antihypertensive medications. Steroids and immunosuppressive agents are used for extrarenal manifestations of systemic lupus and also for those patients with persistent nephrotic range proteinuria.[9] The survival of patients with classes III and IV disease has improved during the past two to three decades to approximately 74% to 80% at 10 years. Lupus patients with ESKD on dialysis fare as well as those with non-lupus-related kidney disease as do those who receive a kidney transplant. Recurrence of lupus in the kidney allograft is possible but is usually of minor clinical importance.

ANCA-ASSOCIATED VASCULITIS

Etiology and Epidemiology

ANCA-associated vasculitis is a group of systemic diseases that commonly affect the kidneys. Patients are diagnosed based on clinical presentation as having granulomatosis with polyangiitis (GPA, formerly called Wegener's granulomatosis), microscopic polyangiitis (MPA), or eosinophilic granulomatosis with polyangiitis (EGPA, formerly called Churg-Strauss syndrome). The common pathogenesis is linked to pathogenic autoantibodies directed against the neutrophil antigens serine protease-3 (anti-PR3 antibodies) or myeloperoxidase (anti-MPO antibodies) on neutrophils (see below). When kidney involvement occurs, patients commonly present with rapidly progressive glomerulonephritis (RPGN). RPGN describes a clinicopathologic syndrome of rapid loss of kidney function—usually greater than 50% decrement of the GFR within 3 months. The predominant histologic finding of RPGN is extensive extracapillary hypercellularity (crescent) formation, often in more than 50% of

the glomeruli. In ANCA-associated vasculitis, the immunofluorescence microscopy is pauci-immune, that is, there is no significant staining.

Pathophysiology

For patients with ANCA-associated disease, the interaction of anti-PR-3 or anti-MPO antibodies (one of which is present in approximately 90% of patients with pauci-immune crescentic glomerulonephritis) with neutrophils and monocytes, which may have been primed by concurrent infections or inflammatory processes, can lead to activation of these leukocytes and release of toxic oxygen species and lytic enzymes, resulting in vascular injury.[88] These proteinases and reactive oxygen species released by neutrophils and macrophages may result in severe glomerular injury. Platelets and the coagulation system are activated and result in capillary thrombosis. The ruptured capillaries release fibrinogen and procoagulants that may come into contact with thrombogenic tissue debris and lead to fibrinoid changes. Activation of the terminal (C5-9) (membrane-attacking complex) of the complement system also produces severe capillary wall injury. The disruption of the capillary wall allows movement of macrophages and other plasma constituents into Bowman's space and stimulates the formation of crescents, which are composed mainly of parietal epithelial cells, as well as macrophages and fibroblasts. Outside the kidney, a similar pathogenesis may cause small vessel vasculitis in virtually any organ.

Clinical Presentation

ANCA-associated vasculitis can involve virtually any organ system, and patients are classified as having GPA, MPA, or EGPA based on their clinical presentation. As noted above, the classic renal presentation of ANCA-associated vasculitis is an RPGN. Patients can also present with more indolent renal disease. Urinalysis commonly shows nephritic sediments with hematuria, erythrocyte casts, and proteinuria. However, overt nephrotic syndrome is rare, and some patients will have normal amounts of protein in the urine. In addition to the kidney, patients with lung involvement (pulmonary hemorrhage) and central nervous system vasculitis are considered to have severe organ involvement that requires aggressive immunosuppressive therapy.

Laboratory data reveals positive anti-PR-3 or anti-MPO antibodies on ELISA in approximately 90% of patients. Patients also have positive indirect immunofluorescence testing for pANCA and cANCA. Some patients have both antibodies present, which can be observed in the setting of drug-induced

vasculitis. Serum complement levels are often normal.

Treatment of ANCA-Associated Vasculitis

Combined use of high-dose corticosteroids and cyclophosphamide induces remission in the majority of patients with ANCA-associated vasculitis. IV cyclophosphamide, possibly because of the lower cumulative dose administered, is associated with fewer leukopenic complications while being as effective as the oral route in inducing remission; however, the risk of relapse may be higher.[89] Rituximab-based regimens (with corticosteroids) are also recommended by KIDGO guidelines as an alternative initial treatment in patients without severe renal disease or in whom cyclophosphamide is contraindicated.[9,90,91] Plasma exchange therapy has generally been recommended as adjunctive therapy for patients with severe renal failure and pulmonary hemorrhage.[92] The results of the recently completed PEXIVAS study should shed further light onto the role of plasma exchange therapy in patients with ANCA-associated vasculitis.

Maintenance therapy, using azathioprine or rituximab, is recommended in patients who achieve remission, except those who are dialysis-dependent and have no extrarenal manifestation of disease.[93] Trimethoprim-sulfamethoxazole is suggested to be used as an adjunct in patients with upper respiratory disease. The optimum duration of maintenance therapy is not known. The recurrence rate of ANCA-associated vasculitis in the kidney after transplant is 17%, with the average time to relapse from transplantation being 31 months.

ANTI-GLOMERULAR BASEMENT MEMBRANE GLOMERULONEPHRITIS

Etiology and Diagnosis

Anti-glomerular basement membrane (anti-GBM) glomerulonephritis is a rare disease. The direct attack of the anti-GBM antibody on the GBM is responsible for the capillary wall injury. This can result in RPGN and pulmonary hemorrhage. When both lung and kidney injuries are present, it has been historically called Goodpasture’s disease. The diagnosis is made with a kidney biopsy showing a necrotizing and crescentic glomerulonephritis on light microscopy, with linear staining for IgG along the glomerular basement membrane on immunofluorescence microscopy. Anti-GBM antibodies are detectable in the serum of the vast majority of patients.[94]

Treatment and Prognosis

Steroids and cyclophosphamide, in conjunction with plasma exchange, are recommended by the KDIGO guidelines in all patients with anti-GBM glomerulonephritis except those who are dialysis-dependent, have 100% crescent in biopsy sample, and do not have pulmonary hemorrhage. Plasma exchanges remove the pathogenic anti-GBM antibodies in circulation and are conducted for 2 weeks or until the antibodies disappear. Steroids (prednisolone 1 mg/kg/day, tapered over 6 months) and cyclophosphamide (2-3 mg/kg/day for 3 months) are also given to prevent new antibody production and treat inflammation in the kidney. Patients with mild disease may respond well to plasma exchange alone or immunosuppression (steroid and/or cytotoxic agents). For patients with severe disease (poor kidney function and extensive crescent formation), most are not expected to respond to the combination of plasma exchange and steroid/cytotoxic drug therapy. Because of the rapid decline in kidney function, diagnosis should be established early so that therapy can proceed without delay. When the serum creatinine concentration is 6 mg/dL (530 μmol/L) or above or the patient is oliguric or requires dialysis, the response to therapy is usually poor, and the patient may be treated conservatively. Poor response should also be expected when crescents are found in more than 85% of the glomeruli.[9,94]

Clinical recurrence of anti-GBM nephritis after kidney transplant is very rare. Because the frequency of recurrence and its severity are related to the presence of circulating anti-GBM antibody, it is recommended that transplantation should not be performed until the anti-GBM antibody is undetectable for at least 6 to 12 months.

POSTSTREPTOCOCCAL GLOMERULONEPHRITIS

Etiology and Epidemiology

PSGN and glomerulonephritis caused by other infectious agents, such as bacteria, viruses, and parasites, were once common. Improved sanitation, personal hygiene, medical care, and public health measures helped to decrease the incidence of group A streptococcal infection both in the United States and in other developed countries, resulting in a decline of PSGN. In contrast, glomerulonephritis secondary to other infectious agents, such as hepatitis C and

HIV, is seen with increasing frequency.[95]

PSGN is now the most common form of glomerulonephritis in children but is less common than the other types of glomerulonephritis in adults. PSGN is seen mostly in children aged between 5 and 15 years and is uncommon in children younger than 2 years of age and in adults older than 50 years of age. It normally follows pharyngeal or skin infection caused by the nephritogenic strains of group A streptococci; however, other strains of streptococci, such as groups C and G, have also been reported to cause PSGN. Streptococcal pharyngitis is more common in winter and early spring, whereas skin infection is frequently found in summer. The risk for developing acute glomerulonephritis secondary to the nephritogenic strains of bacteria is approximately 10% to 15% for infected patients. However, three to four times more patients may experience a subclinical form of the disease.

Pathophysiology

Streptococcal antigens may induce changes in the glomerular components rendering them immunogenic or autologous IgG may be altered to become antigenic. Alternately, the streptococcal antigens may induce antibodies that react with glomerular antigens. In situ immune complexes are then formed and result in a complement-mediated inflammatory response. The kinin and coagulation cascades are activated, and chemotactic factors are released to recruit neutrophils and monocytes, resulting in acute glomerular lesions.

Examination of the acute PSGN kidneys reveals hypercellular glomeruli with proliferation of mesangial and endothelial cells. Infiltration of neutrophils, monocytes, and eosinophils is apparent within the capillary lumen and also in the mesangial areas. Crescent formation may be seen for patients with severe disease, and if found in more than 30% of the glomeruli, RPGN may be present concurrently.[95] The prognosis is generally poor for these patients, and complete recovery is unlikely. Immunofluorescence examination reveals diffuse granular deposits of IgG and C3 along the GBM and also in the mesangium.

Clinical Presentation

The nephritis is preceded by a latent period following a streptococcal infection. The latent period is commonly 7 to 14 days for pharyngitis and 14 to 28 days for skin infection. An acute nephritic syndrome then develops, commonly with hematuria and edema. Gross hematuria is seen in 70% of patients, and

microscopic hematuria can be found in all patients. Hypertension is usually mild to moderate and results from sodium and water retention. Many patients have signs and symptoms associated with volume overload, which include dyspnea, orthopnea, and cough. Urinalysis of patients with PSGN reveals hematuria, dysmorphic red blood cells, and red cell casts. Proteinuria is common but often not in the nephrotic range. Kidney function is frequently mildly impaired.

Throat or skin culture may be positive for group A streptococci, despite the latent period following the initial infection. However, antibiotic therapy may render the culture result negative. Serologic measurements of antibodies to different streptococcal antigens can confirm recent exposure to the infection. Titers that can be measured include ASO, antistreptokinase, antihyaluronidase (AHase), antideoxyribonuclease B (ADNase B), and antinicotyladenine dinucleotidase (NADase). For most patients with streptococcal pharyngitis, the ASO titers begin to rise about 10 to 14 days later, peak at 3 to 4 weeks, and persist for several months before decreasing. The rise in ASO titers can be reduced by antibiotic treatment and may not be seen for patients with streptococcal skin infection in whom the streptolysin may be bound to skin lipids. ADNase B and AHase titers should be used instead because they are specific and are positive in the majority of patients. The streptozyme test is a combined assay for ASO, ADNase B, NADase, and AHase. Antibodies to other antigens such as zymogen, streptococcal cationic proteinase exotoxin B (SPEB), and plasmin receptor (Plr) have also been evaluated.

Serum complement levels are often decreased for patients with PSGN. If the C3 level is depressed for more than 6 to 8 weeks, MPGN, LN, or glomerulonephritis related to endocarditis or occult visceral abscess should be suspected. Kidney biopsy is not normally indicated unless the patient has prolonged hematuria, proteinuria, or depressed C3 level. Kidney biopsy is needed to detect other types of glomerulonephritis such as lupus, RPGN, or MPGN.[95]

Treatment of Poststreptococcal Glomerulonephritis

General Approach to Treatment

8 The treatment of PSGN is mainly supportive and symptomatic. Early antibiotic therapy does not prevent subsequent PSGN, but it may reduce the severity of the disease. It can, however, prevent the spread of the streptococcal infection to other family members. Antibiotic prophylaxis is not recommended because infected patients will develop long-lasting, often lifelong immunity

against the strain of streptococci. Exposure to another nephritogenic strain of streptococci is possible, but unlikely.

Supportive measures should be used to control fluid volume and blood pressure. Because the hypertension is of the low-renin type, ACEIs and β-blockers are not expected to be useful. If the patient has crescentic disease, use of pulse steroids and/or immunosuppressive agents can be considered; however, the efficacy and safety of these agents have not been established for this condition.[95]

Prognosis

The acute manifestations of PSGN are normally self-limited, and kidney function returns to baseline within 3 to 6 weeks in more than 95% of patients. Diuresis usually begins 7 to 10 days after onset of the acute episode, whereas hypertension and azotemia resolve in 1 to 2 weeks. Gross hematuria lasts for 1 to 2 weeks, and proteinuria usually resolves within 6 months in more than 90% of children. However, microscopic hematuria may persist for up to 2 years. In general, children have more rapid recovery than adults. Prognosis is often better when PSGN occurs during an epidemic than in cases found sporadically. Most of the children will recover fully and be free from chronic complications of PSGN if they have no preexisting kidney disorder, heavy proteinuria, or crescentic glomerular lesions or did not require hospitalization during the acute episode. In contrast, adult patients have a less favorable long-term outcome. As many as 50% of the patients may develop persistent proteinuria, hypertension, and kidney insufficiency, with some resulting in end-stage kidney failure.

CLINICAL BOTTOM LINE

A better understanding of the pathogenic mechanisms leading to glomerular injury has led to marked improvements in the treatment of glomerular diseases. However, glomerulopathies are a heterogeneous group of immune disorders with different clinical courses, prognoses, and responses to current immunologic and nonimmunologic therapies. The optimal treatment strategy for individual patients should therefore be personalized based on the natural history and prognosis of each type of glomerular disease, the efficacy of different immunomodulation regimens in inducing disease remission and preserving kidney function, as well as the characteristics of at-risk patients who warrant aggressive therapy. Judicious use of immunosuppressive agents with careful

monitoring of their adverse effects cannot be overemphasized. In addition, treatment of the disease complications and control of factors that lead to progression of kidney disease are important in reducing the morbidity and mortality of patients with glomerulonephritis. KDIGO guidelines offer clinicians many evidence-based recommendations that are useful in making individual patient treatment decisions.

Postclass Engaged Learning Activity

Conduct a literature search and identify a manuscript that has been published in the past 12 months related to the treatment of membranous nephropathy with immunosuppressive therapy. Write a brief summary about the current approach to immunosuppressive therapies such as cyclophosphamide, rituximab, and cyclosporine, with particular attention to the adverse event profiles of these therapies. This activity is designed to improve your familiarity with using current literature to make evidence-based recommendations for the treatment of glomerular disease.

ABBREVIATIONS

ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitors
ACTH	adrenocorticotropic hormone
ADN	ase Bantideoxyribonuclease
BAH	aseantihyaluronidase
ANCA	antineutrophil cytoplasmic autoantibody
ARB	angiotensin II receptor blocker
ASO	antistreptolysin
BSA	bovine serum albumin
DRIs	direct renin inhibitors
EGPA	eosinophilic granulomatosis with polyangiitis
ESKD	end-stage kidney disease
GBM	glomerular basement membrane
GFR	glomerular filtration rate
GPA	Granulomatosis with polyangiitis
FSGS	focal segmental glomerulosclerosis
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HMG-CoA	β-hydroxy-β-methylglutaryl-coenzyme A
LDL	low-density lipoprotein (cholesterol)
MPA	microscopic polyangiitis
MPGN	membranoproliferative glomerulonephritis
MPO	myeloperoxidase
NAD	aseantinicotyladenine dinucleotidase
NEP	neutral endopeptidase
NSAIDs	nonsteroidal anti-inflammatory drugs
PR-3	serine protease-3
PSGN	poststreptococcal glomerulonephritis
RAS	renin-angiotensin system
RPGN	rapidly progressive glomerulonephritis
SLE	systemic lupus erythematosus
VLDL	very-low-density lipoprotein (cholesterol)

REFERENCES

1. U.S. Renal Data System 2019 Annual Data Report. Minneapolis, MN: USRDS Coordinating Center. 2018. Available at: http://www.usrds.org.
2. Schena FP, Gesualdo L, Grandaliano G, Montinaro V. Progression of renal

damage in human glomerulonephritides: Is there sleight of hand in winning the game? *Kidney Int*. 1997;52(6):1439–1457.

3. Nangaku M, Couser WG. Mechanisms of immune-deposit formation and the mediation of immune renal injury. *Clin Exp Nephrol*. 2005;9(3):183–191.
4. Remuzzi G, Zoja C, Perico N. Proinflammatory mediators of glomerular injury and mechanisms of activation of autoreactive T cells. *Kidney Int Suppl*. 1994;44:S8–S16.
5. Sjoblom P, Nystrom FH, Lanne T, et al. Microalbuminuria, but not reduced eGFR, is associated with cardiovascular subclinical organ damage in type 2 diabetes. *Diabetes Metab*. 2014;40(1):49–55.
6. Schrier RW, Fassett RG. A critique of the overfill hypothesis of sodium and water retention in the nephrotic syndrome. *Kidney Int*. 1998;53(5):1111–1117.
7. Vaziri ND. Molecular mechanisms of lipid disorders in nephrotic syndrome. *Kidney Int*. 2003;63(5):1964–1976.
8. Kerlin BA, Ayoob R, Smoyer WE. Epidemiology and pathophysiology of nephrotic syndrome-associated thromboembolic disease. *Clin J Am Soc Nephrol*. 2012;7(3):513–520.
9. KDIGO. Kidney Disease Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group: KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int*. 2012;2(2):139–274.
10. Staplin N, Haynes R, Herrington WG, et al. Smoking and adverse outcomes in patients with CKD: The Study of Heart and Renal Protection (SHARP). *Am J Kidney Dis*. 2016;68(3):371–380.
11. Clark WF, Huang SS, Walsh MW, et al. Plasmapheresis for the treatment of kidney diseases. *Kidney Int*. 2016;90(5):974–984.
12. Vrhovac B, Sarapa N, Bakran I, et al. Pharmacokinetic changes in patients with oedema. *Clin Pharmacokinet*. 1995;28(5):405–418.
13. Fliser D, Schroter M, Neubeck M, Ritz E. Coadministration of thiazides increases the efficacy of loop diuretics even in patients with advanced renal failure. *Kidney Int*. 1994;46(2):482–488.
14. Rudy DW, Voelker JR, Greene PK, et al. Loop diuretics for chronic renal insufficiency: A continuous infusion is more efficacious than bolus therapy. *Ann Intern Med*. 1991;115(5):360–366.
15. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for

the management of high blood pressure in adults: Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311(5):507–520.

16. Group SR, Wright JT Jr., Williamson JD, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373(22):2103–2116.
17. Cheung AK, Rahman M, Reboussin DM, et al. Effects of intensive BP control in CKD. *J Am Soc Nephrol*. 2017;28(9):2812–2823.
18. Gashti CN, Bakris GL. The role of calcium antagonists in chronic kidney disease. *Curr Opin Nephrol Hypertens*. 2004;13(2):155–161.
19. Levey AS, Adler S, Caggiula AW, et al. Effects of dietary protein restriction on the progression of advanced renal disease in the Modification of Diet in Renal Disease Study. *Am J Kidney Dis*. 1996;27(5):652–663.
20. St Peter WL, Odum LE, Whaley-Connell AT. To RAS or not to RAS? The evidence for and cautions with renin-angiotensin system inhibition in patients with diabetic kidney disease. *Pharmacotherapy*. 2013;33(5):496–514.
21. Ruggenenti P, Cravedi P, Remuzzi G. Mechanisms and treatment of CKD. *J Am Soc Nephrol*. 2012;23(12):1917–1928.
22. Ruggenenti P, Perticucci E, Cravedi P, et al. Role of remission clinics in the longitudinal treatment of CKD. *J Am Soc Nephrol*. 2008;19(6):1213–1224.
23. Gentile G, Remuzzi G, Ruggenenti P. Dual renin-angiotensin system blockade for nephroprotection: still under scrutiny. *Nephron*. 2015;129(1):39–41.
24. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med*. 2013;369(20):1892–1903.
25. Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med*. 1994;330(13):877–884.
26. Perico N, Remuzzi A, Sangalli F, et al. The antiproteinuric effect of angiotensin antagonism in human IgA nephropathy is potentiated by indomethacin. *J Am Soc Nephrol*. 1998;9(12):2308–2317.
27. Warwick GL, Fox JG, Boulton-Jones JM. The relationship between

urinary albumin excretion rate and serum cholesterol in primary glomerular disease. *Clin Nephrol*. 1994;41(3):135–137.

28. Stone NJ, Robinson JG, Lichtenstein AH, et al. ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;129(25 Suppl 2):S1–S45.
29. Turner JM, Bauer C, Abramowitz MK, et al. Treatment of chronic kidney disease. *Kidney Int*. 2012;81(4):351–362.
30. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): A randomised placebo-controlled trial. *Lancet*. 2011;377(9784):2181–2192.
31. Athyros VG, Katsiki N, Karagiannis A, Mikhailidis DP. Statins can improve proteinuria and glomerular filtration rate loss in chronic kidney disease patients, further reducing cardiovascular risk. Fact or fiction? *Expert Opin Pharmacother*. 2015;16(10):1449–1461.
32. Lee T, Biddle AK, Lionaki S, et al. Personalized prophylactic anticoagulation decision analysis in patients with membranous nephropathy. *Kidney Int*. 2014;85(6):1412–1420.
33. Vivarelli M, Massella L, Ruggiero B, Emma F. Minimal change disease. *Clin J Am Soc Nephrol*. 2017;12(2):332–345.
34. Waldman M, Crew RJ, Valeri A, et al. Adult minimal-change disease: Clinical characteristics, treatment, and outcomes. *Clin J Am Soc Nephrol*. 2007;2(3):445–453.
35. Sinha MD, MacLeod R, Rigby E, Clark AG. Treatment of severe steroid-dependent nephrotic syndrome (SDNS) in children with tacrolimus. *Nephrol Dial Transplant*. 2006;21(7):1848–1854.
36. Munyentwali H, Bouachi K, Audard V, et al. Rituximab is an efficient and safe treatment in adults with steroid-dependent minimal change disease. *Kidney Int*. 2013;83(3):511–516.
37. Kiruba Samuel EM, Krishnamurthy S, Bhanudeep S, Muske S. Levamisole in frequently-relapsing and steroid-dependent nephrotic syndrome. *Indian Pediatr*. 2017;54(10):831–834.
38. Jellouli M, Charfi R, Maalej B, et al. Rituximab in the management of pediatric steroid-resistant nephrotic syndrome: A systematic review. *J Pediatr*. 2018;197:191–197.

39. D'Agati VD, Kaskel FJ, Falk RJ. Focal segmental glomerulosclerosis. *N Engl J Med*. 2011;365(25):2398–2411.
40. Kopp JB, Nelson GW, Sampath K, et al. APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. *J Am Soc Nephrol*. 2011;22(11):2129–2137.
41. Herlitz LC, Markowitz GS, Farris AB, et al. Development of focal segmental glomerulosclerosis after anabolic steroid abuse. *J Am Soc Nephrol*. 2010;21(1):163–172.
42. Crook ED, Habeeb D, Gowdy O, et al. Effects of steroids in focal segmental glomerulosclerosis in a predominantly African-American population. *Am J Med Sci*. 2005;330(1):19–24.
43. Frassinetti Castelo Branco Camurca Fernandes P, Bezerra Da Silva G Jr., De Sousa Barros FA, et al. Treatment of steroid-resistant nephrotic syndrome with cyclosporine: Study of 17 cases and a literature review. *J Nephrol*. 2005;18(6):711–720.
44. Roberti I, Vyas S. Long-term outcome of children with steroid-resistant nephrotic syndrome treated with tacrolimus. *Pediatr Nephrol*. 2010;25(6):1117–1124.
45. Cho ME, Hurley JK, Kopp JB. Sirolimus therapy of focal segmental glomerulosclerosis is associated with nephrotoxicity. *Am J Kidney Dis*. 2007;49(2):310–317.
46. Gipson DS, Trachtman H, Kaskel FJ, et al. Clinical trial of focal segmental glomerulosclerosis in children and young adults. *Kidney Int*. 2011;80(8):868–878.
47. Beck LH Jr., Bonegio RG, Lambeau G, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *N Engl J Med*. 2009;361(1):11–21.
48. Tomas NM, Hoxha E, Reinicke AT, et al. Autoantibodies against thrombospondin type 1 domain-containing 7A induce membranous nephropathy. *J Clin Invest*. 2016;126(7):2519–2532.
49. Hoxha E, Wiech T, Stahl PR, et al. A mechanism for cancer-associated membranous nephropathy. *N Engl J Med*. 2016;374(20):1995–1996.
50. Floege J, Barbour SJ, Cattran DC, et al. Management and treatment of glomerular diseases (part 1): Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2019;95(2):268–280.
51. Ponticelli C, Zucchelli P, Passerini P, et al. A 10-year follow-up of a

randomized study with methylprednisolone and chlorambucil in membranous nephropathy. *Kidney Int*. 1995;48(5):1600–1604.

52. Ponticelli C, Altieri P, Scolari F, et al. A randomized study comparing methylprednisolone plus chlorambucil versus methylprednisolone plus cyclophosphamide in idiopathic membranous nephropathy. *J Am Soc Nephrol*. 1998;9(3):444–450.
53. van den Brand JA, van Dijk PR, Hofstra JM, Wetzels JF. Cancer risk after cyclophosphamide treatment in idiopathic membranous nephropathy. *Clin J Am Soc Nephrol*. 2014;9(6):1066–1073.
54. Ruggenenti P, Cravedi P, Chianca A, et al. Rituximab in idiopathic membranous nephropathy. *J Am Soc Nephrol*. 2012;23(8):1416–1425.
55. Dahan K, Debiec H, Plaisier E, et al. Rituximab for severe membranous nephropathy: A 6-month trial with extended follow-up. *J Am Soc Nephrol*. 2017;28(1):348–358.
56. Fervenza FC, Canetta PA, Barbour SJ, et al. A Multicenter Randomized Controlled Trial of Rituximab versus Cyclosporine in the Treatment of Idiopathic Membranous Nephropathy (MENTOR). *Nephron*. 2015;130(3):159–168.
57. Lindskog A, Ebefors K, Johansson ME, et al. Melanocortin 1 receptor agonists reduce proteinuria. *J Am Soc Nephrol*. 2010;21(8):1290–1298.
58. Waldman M, Austin HA 3rd. Treatment of idiopathic membranous nephropathy. *J Am Soc Nephrol*. 2012;23(10):1617–1630.
59. Spinner ML, Bowman LJ, Horwedel TA, et al. Single-dose rituximab for recurrent glomerulonephritis post-renal transplant. *Am J Nephrol*. 2015;41(1):37–47.
60. Fermand JP, Bridoux F, Dispenzieri A, et al. Monoclonal gammopathy of clinical significance: A novel concept with therapeutic implications. *Blood*. 2018;132(14):1478–1485.
61. Jadoul M, Berenguer MC, Doss W, et al. Executive summary of the 2018 KDIGO Hepatitis C in CKD Guideline: Welcoming advances in evaluation and management. *Kidney Int*. 2018;94(4):663–673.
62. Goodship TH, Cook HT, Fakhouri F, et al. Atypical hemolytic uremic syndrome and C3 glomerulopathy—conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) Controversies Conference. *Kidney Int*. 2017;91(3):539–551.
63. Bomback AS, Santoriello D, Avasare RS, et al. C3 glomerulonephritis and dense deposit disease share a similar disease course in a large United

States cohort of patients with C3 glomerulopathy. *Kidney Int*. 2018;93(4):977–985.

64. Wyatt RJ, Julian BA. IgA nephropathy. *N Engl J Med*. 2013;368(25):2402–2414.
65. Tomana M, Novak J, Julian BA, et al. Circulating immune complexes in IgA nephropathy consist of IgA1 with galactose-deficient hinge region and antiglycan antibodies. *J Clin Invest*. 1999;104(1):73–81.
66. Trimarchi H, Barratt J, Cattran DC, et al. Oxford Classification of IgA nephropathy 2016: An update from the IgA Nephropathy Classification Working Group. *Kidney Int*. 2017;91(5):1014–1021.
67. Pozzi C, Andrulli S, Del Vecchio L, et al. Corticosteroid effectiveness in IgA nephropathy: Long-term results of a randomized, controlled trial. *J Am Soc Nephrol*. 2004;15(1):157–163.
68. Lv J, Zhang H, Wong MG, et al. Effect of oral methylprednisolone on clinical outcomes in patients with IgA nephropathy: The TESTING randomized clinical trial. *JAMA*. 2017;318(5):432–442.
69. Donadio JV Jr., Grande JP, Bergstralh EJ, et al. The long-term outcome of patients with IgA nephropathy treated with fish oil in a controlled trial. Mayo Nephrology Collaborative Group. *J Am Soc Nephrol*. 1999;10(8):1772–1777.
70. Dillon JJ. Fish oil therapy for IgA nephropathy: Efficacy and inter-study variability. *J Am Soc Nephrol*. 1997;8(11):1739–1744.
71. Rasche FM, Keller F, Lepper PM, et al. High-dose intravenous immunoglobulin pulse therapy in patients with progressive immunoglobulin A nephropathy: A long-term follow-up. *Clin Exp Immunol*. 2006;146(1):47–53.
72. Fellstrom BC, Barratt J, Cook H, et al. Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): A double-blind, randomised, placebo-controlled phase 2b trial. *Lancet*. 2017;389(10084):2117–2127.
73. Taji Y, Kuwahara T, Shikata S, Morimoto T. Meta-analysis of antiplatelet therapy for IgA nephropathy. *Clin Exp Nephrol*. 2006;10(4):268–273.
74. Bajema IM, Wilhelmus S, Alpers CE, et al. Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: Clarification of definitions, and modified National Institutes of Health activity and chronicity indices. *Kidney Int*. 2018;93(4):789–796.
75. Contreras G, Roth D, Pardo V, et al. Lupus nephritis: A clinical review for

practicing nephrologists. *Clin Nephrol*. 2002;57(2):95–107.
76. Tsokos GC. Systemic lupus erythematosus. *N Engl J Med*. 2011;365(22):2110–2121.
77. Yue C, Li G, Wen Y, Li X, Gao R. Early renin-angiotensin system blockade improved short-term and long-term renal outcomes in systemic lupus erythematosus patients with antiphospholipid-associated nephropathy. *J Rheumatol*. 2018;45(5):655–662.
78. Gourley MF, Austin HA 3rd, Scott D, et al. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. *Ann Intern Med*. 1996;125(7):549–557.
79. Appel GB, Contreras G, Dooley MA, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. *J Am Soc Nephrol*. 2009;20(5):1103–1112.
80. Ginzler EM, Dooley MA, Aranow C, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med*. 2005;353(21):2219–2228.
81. Contreras G, Tozman E, Nahar N, Metz D. Maintenance therapies for proliferative lupus nephritis: Mycophenolate mofetil, azathioprine and intravenous cyclophosphamide. *Lupus*. 2005;14(Suppl 1):s33–s38.
82. Houssiau FA, D'Cruz D, Sangle S, et al. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: Results from the MAINTAIN Nephritis Trial. *Ann Rheum Dis*. 2010;69(12):2083–2089.
83. Dooley MA, Jayne D, Ginzler EM, et al. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. *N Engl J Med*. 2011;365(20):1886–1895.
84. Griffiths B, Emery P, Ryan V, et al. The BILAG multi-centre open randomized controlled trial comparing ciclosporin vs azathioprine in patients with severe SLE. *Rheumatology (Oxford)*. 2010;49(4):723–732.
85. Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: The Lupus Nephritis Assessment with Rituximab study. *Arthritis Rheum*. 2012;64(4):1215–1226.
86. Margiotta DPE, Basta F, Batani V, Afeltra A. Belimumab and low-doses of mycophenolate mofetil as induction therapy of class IV lupus nephritis: Case series and literature review. *BMC Nephrol*. 2018;19(1):54.

87. Rovin BH, Solomons N, Pendergraft WF 3rd, et al. A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis. *Kidney Int*. 2019;95(1):219–231.
88. Xiao H, Hu P, Falk RJ, Jennette JC. Overview of the pathogenesis of ANCA-associated vasculitis. *Kidney Dis (Basel)*. 2016;1(4):205–215.
89. Harper L, Morgan MD, Walsh M, et al. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: Long-term follow-up. *Ann Rheum Dis*. 2012;71(6):955–960.
90. Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med*. 2010;363(3):221–232.
91. Jones RB, Tervaert JW, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med*. 2010;363(3):211–220.
92. Walsh M, Casian A, Flossmann O, et al. Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear. *Kidney Int*. 2013;84(2):397–402.
93. Guillevin L, Pagnoux C, Karras A, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med*. 2014;371(19):1771–1780.
94. Segelmark M, Hellmark T. Anti-glomerular basement membrane disease: An update on subgroups, pathogenesis and therapies. *Nephrol Dial Transplant*. 2019;34(11):1826–1832.
95. Nasr SH, Radhakrishnan J, D'Agati VD. Bacterial infection-related glomerulonephritis in adults. *Kidney Int*. 2013;83(5):792–803.

65

Drug Therapy Individualization for Patients with Chronic Kidney Disease

Marisa Battistella and Thomas D. Nolin

KEY CONCEPTS

1. Chronic kidney disease (CKD) results in minimal alterations in the absorption or bioavailability of most drugs.
2. The volume of distribution (V_D) of many drugs is increased in the presence of acute and CKD as a consequence of volume expansion and/or decreased protein binding.
3. In addition to the expected decrement in renal clearance, nonrenal clearance (ie, gastrointestinal and hepatic drug metabolism and transport) of several drugs is also decreased in CKD patients.
4. Individualization of a drug dosage regimen for a patient with impaired kidney function is based on the pharmacodynamic/pharmacokinetic characteristics of the drug, the patient's degree of residual renal function, and their overall clinical condition.
5. The drug dosing guidelines for CKD patients in many drug information resources are highly variable and many are not optimal for clinical use.
6. The effect of hemodialysis (HD) or peritoneal dialysis on drug elimination is dependent on the characteristics of the drug and the dialysis prescription.
7. HD clearance data can be used to guide the initial drug dosage regimen recommendation for HD patients; however, prospective monitoring of serum concentrations is often warranted especially for narrow therapeutic index drugs.

Preclass Engaged Learning Activity

Visit the US National Library of Medicine website DailyMed. DailyMed is the official provider of US Food and Drug Administration (FDA) approved drug label information (ie, package inserts). Identify a drug approved by the FDA within the last 5 years that requires dose adjustment for impaired kidney function. Review renal drug dosing adjustment recommendations, focusing on the kidney function cutoffs for dose adjustment and the kidney function estimate (eg, creatinine clearance, glomerular filtration rate) upon which the recommendations are based. This website is useful to enhance student understanding of renal drug dosing information.

INTRODUCTION

Chronic kidney disease (CKD) is defined by the presence of abnormalities of kidney function or structure.[1] In its earliest stages, it is characterized by either an estimated glomerular filtration rate (eGFR) less than 89 mL/min/1.73 m^2 or the persistence of one or more markers of kidney damage (eg, albuminuria) for more than 3 months in those with eGFR more than or equal to 90 mL/min/1.73 m^2 (see Chapters e59 “Evaluation of Kidney Function” and 61 “Chronic Kidney Disease”).[1] The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for evaluation and management of CKD eGFR and albuminuria categories are outlined in Table 61-5. It is estimated that 10% to 15% of the global population has CKD and the number of deaths from CKD has risen by more than 80% in the past two decades.[2–4] The prevalence varies widely across the world in part because of true differences in the prevalence of CKD; heterogeneity of the laboratory methods used to detect CKD; environmental factors, public health policies, and genetics.[4] The incidence of CKD has more than doubled in the past 20 years in adults older than 65 years.[5] This is due in part to age-related decreases in kidney function, multiple medical comorbidities, and an increased use of medications that alter kidney function. Many drugs are predominantly eliminated by the kidney and even those that are highly metabolized may require dose adjustment in CKD patients to maximize therapeutic outcomes and to minimize adverse events. Medications which are predominantly renally eliminated unchanged (f_e) may accumulate in CKD patients, which can increase the risk of adverse effects. If 30% or more of a drug is eliminated unchanged in the urine, it will have a high likelihood of requiring dosage regimen adjustment in CKD patients, especially those with stage 3 to 5

disease.[6,7]

The pharmacokinetics of drugs with a fraction of drug eliminated unchanged in the urine less than 30% also may be affected and thus require a dose adjustment. In fact 32% of such drugs approved in the United States from 1998 to 2010 had a dosage-adjustment recommendation for CKD patients in the product labeling.[7] If there is no official dosage regimen recommendation in the product labeling, an adjustment may be calculated on the basis of the drug's f_e and the ratio of the patient's residual renal function relative to an age and gender normal value for estimated creatinine clearance (eCL_{cr}) or eGFR.[7,8] Despite increased conduction of "renal impairment" studies by industry and improvements in approved product labeling language, challenges remain for dose adjustments in CKD patients especially for oncology and anti-retroviral agents.[7] Furthermore, physiologic and biochemical changes such as increased or decreased protein binding, altered cytochrome P450 enzyme activity, and transcellular transport systems that are associated with CKD may also independently impact serum and tissue drug concentrations and necessitate drug dosing adjustments.[6,9] Therefore, in CKD patients, the dosage regimens of many drugs must be altered to prevent toxicity, without compromising the achievement of the desired therapeutic benefit.[6]

For medications that are extensively metabolized or for which dramatic changes in protein binding and/or distribution volume (V_D) have been noted, a complex adjustment strategy may need to be employed.[6,9] Despite extensive published evidence, dosing errors in CKD patients still occur at an alarming rate.[10–13] Studies have shown that the expanded use of electronic medical records has not resolved the need for clinician proactivity to optimize the use of medications in CKD patients; in these studies, up to 85% of the medications ordered had nephrotoxic potential and greater than 20% of the drugs ordered were not dose adjusted for the patient's kidney function.[14–16]

Clinicians thus will often need to design individualized therapeutic regimens to optimize achievement of the desired outcomes. In this chapter, the influence of CKD on absorption, distribution, metabolism, and elimination of medications is characterized. A general approach to individualizing drug therapy for CKD patients is presented along with dosage recommendations for the most commonly used drugs in this patient population. Finally, the impact of chronic renal replacement therapy (ie, peritoneal dialysis and HD) on drug disposition is discussed and dosage recommendations for selected drugs are presented. Drug dosage regimen adjustment strategies for patients with acute kidney injury (AKI)

including those who are receiving continuous renal replacement therapy are presented in Chapter 60, “Acute Kidney Injury.”

PHARMACOKINETIC CHANGES IN CHRONIC KIDNEY DISEASE

The absorption, distribution, metabolism, and renal excretion of many drugs are altered by CKD. An understanding of why and how these processes are impacted by CKD provides a framework to project the influence of CKD on emerging drug therapies. In addition, when known, these effects can be factored into the clinician’s dosage recommendations for individual CKD patients including those who are receiving chronic renal replacement therapy.

Drug Absorption

There is little quantitative information regarding the influence of CKD on drug absorption and bioavailability. The few studies evaluating the absorption of oral medications in CKD patients were not designed to provide an assessment of the drug’s absolute bioavailability (eg, they did not include a comparison of the area under the concentration–time curve [AUC] after oral and intravenous [IV] administration of the drug). Rather, the principal outcomes that were documented were alterations in the peak concentration (C_{max}), time at which the peak concentration was attained (t_{max}), or the fractional amount of drug recovered in the urine in a finite time period.[17]

The absorption and bioavailability of some drugs is highly variable in CKD patients. The mechanisms responsible are multifactorial and include drug interactions, delayed gastric emptying, and decreased gastric acidity. Decreased gastrointestinal (GI) motility secondary to gastroparesis in patients with diabetes may delay the t_{max} and may also reduce the C_{max}. For instance, if a drug undergoes GI metabolism the slower transit time allows for more GI metabolism and thus lower C_{max} of the parent drug. Urea retention in CKD patients results in a high influx of urea into the gut, which in turn results in conversion of urea to ammonia by gastric urease. The subsequent increase in gastric pH may alter the dissolution or ionization properties of weakly basic drugs such as diazepam leading to changes in absorption.[18] A decrease in gastric acidity, that is, an increase in GI pH, associated with the concomitant administration of antacids, H_2-receptor antagonists, proton pump inhibitors, and phosphate binders has been

associated with a lower bioavailability of several antibiotics and digoxin.[18] Finally antacids and vitamin supplements may decrease the bioavailability of some drugs as a result of the formation of insoluble salts or metal ion chelates.[19] Although this is not a disease-specific effect, since CKD patients are frequently taking these medications, the associated drug interactions will impact the absorption of other drugs. Edema of the GI tract, secondary to cirrhosis or congestive heart failure that may be present in CKD patients, can also decrease the absorption of some medications, such as oral furosemide for which a decrease from 50% to 10% has been reported.[19]

The bioavailability of only a few drugs (eg, dihydrocodeine, felodipine, sertraline, and cyclosporine) has been documented to be increased in CKD patients.[20,21] For these drugs, the mechanism is a decrease in metabolism during the drug's first pass through the GI tract and liver. Drug interactions can also independently alter bioavailability. Bioflavonoids in grapefruit juice can inhibit cytochrome P450 3A4 and noncompetitively inhibit the metabolism of drugs metabolized by this enzyme; this interaction can increase the bioavailability of cyclosporine by as much as 20%.[22]

Distribution

2 A drug's volume of distribution reflects the extent of distribution throughout the body. The V_D of many drugs is increased in category G3a, G3b, G4, and G5 CKD patients as well as those with preexisting CKD who develop AKI (**Table 65-1**) and can lead to a decrease in serum drug concentrations.[6,9,23–25] This increase in V_D may be the result of pathophysiologic alterations in body composition, fluid overload secondary to excessive fluid administration or intake, decreased protein binding, or increased tissue binding. Decreased tissue binding of drugs in CKD patients may result in a decrease in V_D, which has been reported for only a few medications (eg, digoxin and pindolol).[23]

TABLE 65-1 Volume of Distribution of Selected Drugs in Patients with ESRD

Drug	Normal (L/kg)	ESRD (L/kg)	Change from Normal
Increased			
Amikacin	0.20	0.29	45%
Cefazolin	0.13	0.17	31%
Cefoxitin	0.16	0.26	63%
Ceftriaxone	0.28	0.48	71%
Cefuroxime	0.20	0.26	30%
Doripenem	0.25	0.47	88%
Dicloxacillin	0.08	0.18	125%
Erythromycin	0.57	1.09	91%
Furosemide	0.11	0.18	64%
Gentamicin	0.20	0.32	60%
Isoniazid	0.60	0.80	33%
Minoxidil	2.60	4.90	88%
Naproxen	0.12	0.17	42%
Phenytoin	0.64	1.40	119%
Trimethoprim	1.36	1.83	35%
Vancomycin	0.64	0.85	33%
Decreased			
Atenolol	1.20	0.90	25%
Chloramphenicol	0.87	0.60	31%
Ciprofloxacin	2.50	1.95	22%
Digoxin	7.30	4.00	45%
Ethambutol	3.70	1.60	57%
Methicillin	0.45	0.30	33%
Metoprolol	5.60	1.00	82%
Pindolol	2.10	1.10	48%
Propranolol	4.40	3.60	18%

ESRD, end-stage renal disease.

Data from References 20, 23, and 34.

Variability in fluid status is a common issue in patients with severe CKD (category G4 and G5), especially those that are critically ill. Many critically ill patients receive large volumes of IV fluids for resuscitation from shock, and can

subsequently develop edema, pleural effusions, or ascites. These therapeutic interventions, in addition to decreased water excretion due to AKI or CKD, often lead to an increase in a drug's V_D and a decrease in its serum concentrations. This is especially problematic with hydrophilic drugs, such as aminoglycosides and cephalosporins for which the V_D may be increased by up to 150%.[26,27]

Effect of Altered Plasma Protein Binding

Protein binding limits drug distribution as only unbound or "free" drug is able to cross cellular membranes and distribute outside the vascular space. Many drugs have been reported to exhibit altered protein binding in CKD patients.[28,29] Protein binding of many acidic drugs such as penicillins, cephalosporins, aminoglycosides, furosemide, and phenytoin is decreased secondary to hypoalbuminemia, qualitative changes in the conformation of the protein binding site, and/or competition for binding sites by other drugs, metabolites, and endogenous substances.[23,29] The result of a decrease in protein binding is an increase in the apparent V_D. A new equilibrium is ultimately established as a result of increased drug elimination/distribution, such that the unbound concentrations remain comparable to those observed in patients with normal kidney function despite the fact that total concentrations are decreased. Thus, the net effect is an alteration in the relationship between total drug concentration and pharmacodynamic effect. For example, protein binding of phenytoin (90% protein-bound, primarily to albumin) is significantly decreased secondary to decreased plasma phenytoin binding affinity for albumin, as well as low serum albumin: these changes alter the relationship between total phenytoin concentration and desired and toxic effects.[28] The resulting increase in unbound fraction, from values of 10% in those with normal kidney function to 20% or more in those with G5 CKD, results in increased hepatic clearance and decreased total concentrations. Thus, in patients with CKD, the therapeutic range based on total phenytoin concentration is shifted downward from normal values of 10 to 20 mg/L (mcg/mL; 40-79 μmol/L) to values as low as 4 to 8 mg/L (mcg/mL; 16-32 μmol/L). Since the unbound concentration therapeutic range is the same for all patients, 1 to 2 mg/L (mcg/mL; 4-8 μmol/L), this measurement provides the best target for individualizing phenytoin therapy in patients with CKD.

One can approximate the total phenytoin concentration that would be observed in category G5 CKD patients if they had normal plasma protein binding ($C_{\text{normal binding}}$). The estimated $C_{\text{normal binding}}$ total phenytoin

concentration can then be interpreted in light of the usual total therapeutic range to assess the patient's response to therapy.[28]

For normal or low albumin (concentration expressed in g/dL) and category G5 CKD:

$$C_{\text{total normal binding}} = C_{\text{total reported}}/[(0.9)(0.48)(\text{albumin}/4.40)] + 0.1$$

where $C_{\text{normal binding}}$ = total phenytoin concentration that would be observed if patient had normal protein binding. C_{reported} = patient's total phenytoin concentration reported by laboratory (represents decreased plasma protein binding).

For albumin expressed in g/L the equation becomes:

$$C_{\text{total normal binding}} = C_{\text{total reported}}/[(0.9)(0.48)(\text{albumin}/44)] + 0.1$$

The principal binding protein for several basic drugs is α1-acid glycoprotein, an acute-phase reactant protein, whose plasma concentrations are increased in CKD patients.[6] As a result of this increase, the unbound fraction of some basic drugs (eg, bepridil, disopyramide) may be significantly decreased and the V_D increased in CKD patients, especially kidney transplant and HD patients.[6]

Effect of Altered Tissue Binding

Distribution also may be affected by altered tissue binding of drugs in CKD patients; this is relatively rare and limited to few drugs, such as pindolol, ethambutol, and most notably digoxin.[23] The V_D of digoxin is decreased by up to 50% in patients with category G5 CKD, leading to elevated serum concentrations.[30] In this case, the absolute amount of digoxin bound to the receptor is decreased and the resultant serum digoxin concentration is higher than anticipated. Thus, in CKD patients, particularly in those with category G5, a "normal" total drug concentration may be associated with either an adverse reaction secondary to elevated unbound drug concentrations, or a subtherapeutic response because of an altered plasma-to-tissue drug concentration ratio. The monitoring of unbound drug concentrations in CKD patients is thus warranted for those drugs that have a narrow therapeutic range, are highly protein bound (unbound fraction of less than 20%), and for which marked variability in the unbound fraction has been reported (eg, phenytoin and disopyramide).

Effect of V_D Calculation Method

Finally, the method used to calculate the volume of distribution may be influenced by impaired kidney function. The three most commonly used volume of distribution terms are: volume of the central compartment (V_c), volume of the terminal phase (V_β and V_{area}), and volume of distribution at steady state (V_{ss}). The V_c for many drugs approximates extracellular fluid volume and thus may be increased or decreased by acute changes. Oliguric AKI is often accompanied by fluid overload and a resultant increased V_c for many drugs. The V_{area} or V_β represents the proportionality constant between plasma concentrations in the terminal elimination phase and the amount of drug remaining in the body. V_β is affected by both distribution characteristics, as well as by the terminal elimination rate constant. V_β and V_{ss} will often be similar in magnitude, with V_β being slightly larger. Because V_{ss} has the advantage of being independent of drug elimination, it is the most appropriate volume term to use when one desires to compare drug distribution volumes between patients with impaired kidney function and those with normal kidney function.[31]

ELIMINATION

Elimination of a drug from the body is characterized in pharmacokinetic terms as total systemic clearance (CL_T), which is the sum of all organ clearances. Typically, CL_T is defined simply as the sum of renal clearance (CL_R) and nonrenal clearance CL_{NR}.[6,9]

Renal Clearance

Kidney function is the most quantifiable determinant of drug clearance. It is important to note that the term “kidney function” includes the combined processes of glomerular filtration, tubular secretion, and reabsorption, as well as endocrine and metabolic functions. Alterations in any or all of these functions secondary to CKD may have a dramatic effect on drug disposition (see Chapter e59). Reduction in kidney mass, the number of functioning nephrons, renal blood flow, GFR, and/or the rate of tubular secretion and reabsorption all contribute to the decreased renal excretory capacity observed in those with CKD.

Renal clearance (CL_R) of a drug is the composite of GFR, tubular secretion,

and reabsorption:

$CL_R = [GFR \times f_u] + [CL_{secretion} - CL_{reabsorption}]$ where f_u is the fraction of the drug unbound to plasma proteins. Drug elimination by filtration occurs by diffusion; while tubular secretion and reabsorption are bidirectional processes that involve carrier-mediated renal transport systems.[32] Renal transport systems have been broadly classified on the basis of substrate selectivity into the anionic and cationic renal transport systems, which are responsible for the transport of a number of organic acidic and basic drugs, respectively.[23,32] Several drugs are actively secreted by one or more of these transporter families, which include organic cationic (eg, famotidine, trimethoprim, and dopamine), organic anionic (eg, ampicillin, cefazolin, and furosemide), nucleoside (eg, zidovudine), and P-glycoprotein (Pgp) transporters (eg, digoxin, vinca alkaloids, and steroids).[32,33] Alterations in filtration, secretion, or reabsorption, secondary to CKD may have a dramatic effect on drug disposition: for drugs that are primarily filtered, a decrease in GFR will result in a proportional decrease in renal drug clearance.

Nonrenal Clearance

3 The effect of CKD on CL_{NR} is less clear than its impact on CL_R, but there has been an increased interest and plethora of new findings in this area in recent years.[23,33–35] CL_{NR} encompasses all routes of drug elimination, excluding renal excretion of unchanged drug, and includes hepatic and extrahepatic metabolism and altered transcellular transport pathways (see **Tables 65-2** and **65-3**). It is mediated largely by kidney disease effects on many cytochrome P450 (CYP) metabolic enzymes, such as CYP3A, and transporters including Pgp, organic anion-transporting polypeptides (OATPs), and multidrug resistance-associated proteins in the GI tract and hepatobiliary system.[33,34]

TABLE 65-2 Impact of ESRD on CL_{NR} of Selected Drugs

Drug Name	Decreased Change in CL_{NR}
Acyclovir	50%
Aztreonam	33%
Bupropion	↓
Captopril	50%
Carvedilol	↓
Cefotaxime	40%
Ceftriaxone	↓
Cimetidine	46%
Ciprofloxacin	33%
Doripenem	↓
Erythromycin	↓
Imipenem	58%
Isoniazid	↓
Ketorolac	↓
Losartan	↓
Lovastatin	↓
Metoclopramide	66%
Minoxidil	46%
Morphine	40%
Nicardipine	37%
Nimodipine	87%
Nortriptyline	↓
Procainamide	60%
Quinapril	↓
Raloxifene	↓
Repaglinide	↓
Rosuvastatin	↓
Simvastatin	↓
Valsartan	↓
Vancomycin	43%
Verapamil	54%
Warfarin	50%

CL_{NR}, nonrenal clearance; ESRD, end-stage renal disease.

↓ a decrease is documented but not quantified.

Data from References 23, 34, and 35.

TABLE 65-3 Major Pathways of Nonrenal Drug CL

CL_{NR} Pathway	Selected Substrates
Oxidative Enzymes	
CYP	
1A2	Polycyclic aromatic hydrocarbons, caffeine, imipramine, theophylline
2A6	Coumarin
2B6	Nicotine, bupropion
2C8	Retinoids, paclitaxel, repaglinide
2C9	Celecoxib, diclofenac, flurbiprofen, indomethacin, ibuprofen, losartan, phenytoin, tolbutamide, *S*-warfarin
2C19	Diazepam, *S*-mephenytoin, omeprazole
2D6	Codeine, debrisoquine, desipramine, dextromethorphan, fluoxetine, paroxetine, duloxetine, nortriptyline, haloperidol, metoprolol, propranolol
2E1	Ethanol, acetaminophen, chlorzoxazone, nitrosamines
3A4/5	Alprazolam, midazolam, cyclosporine, tacrolimus, nifedipine, felodipine, diltiazem, verapamil, fluconazole, ketoconazole, itraconazole, erythromycin, lovastatin, simvastatin, cisapride, terfenadine
Conjugative Enzymes	
UGT	Acetaminophen, morphine, lorazepam, oxazepam, naproxen, ketoprofen, irinotecan, bilirubin
NAT	Dapsone, hydralazine, isoniazid, procainamide
Transporters	
OATP	
1A2	Bile salts, statins, fexofenadine, methotrexate, digoxin, levofloxacin
1B1	Bile salts, statins, fexofenadine, repaglinide, valsartan, olmesartan, irinotecan, bosentan
1B3	Bile salts, statins, fexofenadine, telmisartan, valsartan, olmesartan, digoxin
2B1	Statins, fexofenadine, glyburide
Pgp	Digoxin, fexofenadine, loperamide, irinotecan, doxorubicin, vinblastine, paclitaxel, erythromycin
MRP	
2	Methotrexate, etoposide, mitoxantrone, valsartan, olmesartan
3	Methotrexate, fexofenadine

CL_{NR}, nonrenal clearance; CYP, cytochrome P450; NAT, N-acetyltransferase; MRP, multidrug resistance protein; OATP, organic anion-transporting polypeptides; UGT, uridine diphophate-glucuronlytransferase.

Data from References 23, 33, and 34.

Alterations of CYP Enzyme Activity and Transporters

CKD may lead to alterations in nonrenal clearance of numerous medications as the result of alterations in the activities of uptake and efflux transporters as well as CYP enzymes in the liver and other organs (see Tables 65-2 and 65-3).[23,24,33,35] The effect(s) of kidney disease on nonrenal drug clearance appear to depend partly on whether the decrease in kidney function is acute or chronic in nature. For example, higher residual nonrenal clearance for vancomycin, meropenem, and imipenem has been documented in patients with AKI compared to CKD patients who have comparable CL_{cr}.[36–38] In humans with kidney disease, the activities of CYPs appear to be differentially and only modestly affected. For instance, although it has been reported that CYP3A4 activity is decreased in CKD,[23,34,35,39,40] it is now apparent that OATP uptake activity is decreased and thus the perceived changes in CYP3A4 activity were likely due to altered transporter activity.[41] The decrease in nonrenal clearance of several drugs that are metabolized by a CYP pathway as well as transported in CKD category G4 or G5 patients supports this premise (see Table 65-3). However, these studies must be interpreted with caution, because concurrent drug intake, age, smoking status, and alcohol intake were often not taken into consideration. Furthermore, pharmacogenetic variations in drug-metabolizing enzymes that may have been present in the individual before the onset of AKI or CKD must also be considered.[23,34,35]

Prediction of the effect of kidney disease on the metabolism of a particular drug is difficult and there is no quantitative strategy to predict changes for one drug based on data from another even if they are in the same pharmacologic class. However, some qualitative insight can be gained if one knows what enzyme is involved in the metabolism of the drug of interest and how the enzyme or transporter is affected by the presence of CKD.

Accumulation of Metabolites

Category G4 and G5 CKD patients who are receiving chronic drug therapy may experience significant accumulation of metabolite(s) as well as the parent compound if their ultimate route of elimination is via glomerular filtration. Metabolites of several drugs have significant pharmacologic and/or toxicologic activity. However, the pharmacokinetics and pharmacodynamics of metabolites are not often fully elucidated during the drug development process. In a sense,

the patient with severe CKD is being exposed to a new pharmacologic entity since the sum of the serum concentrations of the metabolite and the parent compound maybe markedly different than those reported in patients with normal kidney function.

The metabolite may have pharmacologic activity similar to that of the parent drug and thus contribute significantly to clinical response; that is true, for example, of oxypurinol, the active metabolite of allopurinol. Another example is morphine; the liver rapidly metabolizes morphine into active metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) which readily cross the blood-brain barrier and bind to opiate receptors, exerting strong analgesic effects. In CKD patients, morphine is metabolized more slowly, and these active metabolites increase, making prolonged narcosis and respiratory depression more likely.[42] Alternatively, the metabolite may have qualitatively dissimilar pharmacologic action; for example, normeperidine has CNS stimulatory activity that reportedly produces seizures, whereas meperidine has CNS depressant actions.[43] Because of the multiplicity of potential interactions of compounds that are primarily metabolized, the practical consequences of metabolite accumulation are difficult to predict and are most often identified in those patients at risk serendipitously.

PHARMACODYNAMICS

CKD can affect multiple organ systems and consequently the response to a given drug may change beyond that predicted upon pharmacokinetic changes alone. For example, several studies have shown that enoxaparin dosage reduction is required in category G4 and G5 CKD patients.[44,45] This appears to be due to the accumulation of uremic toxins which results in complex disturbances of the coagulation system leading to an increase in bleeding. Therefore, it seems that dosage adjustment based on kidney function such as eGFR may not always lead to optimal anticoagulation outcomes in CKD patients.

Successful antibiotic or antiviral treatment of CKD patients requires not only consideration of pharmacokinetic profiles, but also the drugs' pharmacodynamics, which links measures of drug exposure (such as peak and trough serum concentrations, and AUC) to bacteriologic activity.[46] Most antibiotics demonstrate concentration-dependent or time-dependent bacterial killing. In general, for concentration-dependent antibiotics such as fluoroquinolones or aminoglycosides, a high ratio of the peak serum concentration to the minimum inhibitory concentration (MIC, the minimum

concentration required to inhibit bacterial growth) has been associated with increased likelihood of clinical success; whereas for time-dependent antibiotics such as cephalosporins, the percentage of the dosing interval spent above the MIC is the most important pharmacodynamic parameter to maximize clinical success. This has led to the utilization of prolonged infusions or even in some cases to continuous infusions. Thus, it is necessary to administer anti-infective drugs with a time-dependent action more frequently whereas anti-infective drugs with a concentration-dependent action should be administered with a higher maintenance dose and potentially a prolonged dosage interval to increase efficacy while minimizing toxicity. Therefore, both the pharmacodynamics and pharmacokinetics of drugs may need to be considered when initiating antimicrobial therapy in CKD patients. Pharmacodynamic modeling, however, doesn't accurately predict clinical success in some patient settings.[47] Thus large prospective clinical studies are needed to assure that this approach truly enhances patient outcomes.

Estimation of Kidney Function for Drug Dosage Regimen Individualization

Accurate assessment of kidney function is an essential component of determining appropriate drug dosing regimens. Because of the invasive nature and technical difficulties of directly measuring GFR in clinical settings, many equations for estimating GFR have been proposed. A detailed discussion of the pros and cons of estimating equations for GFR and creatinine clearance are presented in Chapter e59. The Cockcroft Gault (CG) equation has been the most commonly used method to estimate kidney function for drug dosing purposes for over 40 years.[48,49] The Modification of Diet in Renal Disease (MDRD) and the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) have been developed primarily for the identification and classification of CKD patients.[50,51]

The automated reporting of eGFR in the clinical setting has led some practitioners to consider substituting eGFR in place of eCL_{cr} for renal dose adjustments. Others argue that use of the MDRD and CKD-EPI equations for drug dosing are not appropriate given that the pharmacokinetic studies were performed using estimated creatinine clearance via the CG equation.[52,53] Furthermore, many studies have highlighted discordance between drug dosing recommendations based on these equations.[53–60] These studies have compared dosing recommendations based on the three different equations for commonly

used drugs in CKD patients. Average discordance rates for the MDRD Study and CG equations were between 20% and 30%.[54–58] Another study that evaluated eight antimicrobial dosing regimens based on CKD-EPI, MDRD, and CG demonstrated overall discordance rates were 15% to 25% between CG and CKD-EPI and 7% to 12% between MDRD and CKD-EPI.[59] Major limitations with these studies include lack of comparison to a gold standard such as measured GFR and the studies did not assess drug concentrations or clinical outcomes.

Serum cystatin C has also been proposed as an alternative marker to estimate GFR, either alone or in combination with serum creatinine. Multiple equations have been proposed to estimate GFR from age, gender, race, and muscle mass based on cystatin C measurements (see Chapter e59)[60–63]; however, their use in drug dosing is limited to a few studies with carboplatin, topotecan, and cefuroxime.[64–66]

Therefore, none of these equations for estimating GFR should be used as the sole determinant for drug dosing decision making. Potential discrepancies in kidney function estimates and corresponding drug dosing regimens necessitate careful consideration of the risk: benefit ratio of each approach within the context of the complete clinical picture of the patient. Since most drug dosage regimen recommendations are based on broad categorical ranges of kidney function, the impact of an eGFR of 40 mL/min/1.73 m^2 versus 50 mL/min/1.73 m^2 is likely of no clinical significance. Furthermore these estimating equations for GFR are based on a standard 1.73 m^2 body surface area (BSA); thus for an individual patient, the BSA must be determined separately so that the eGFR can be expressed in milliliters per minute (mL/min).[52] Nevertheless, regardless of the kidney function estimating equation that was used and published dosing recommendation guidelines that were consulted, clinical judgment will ultimately prevail in the determination of which regimen is best for the patient and feasible to administer given the available dosage forms.

Drug Dosing Information Resources

Prior to 1998, there were no official guidelines regarding when and how to conduct pharmacokinetic and pharmacodynamic studies of a new drug in patients with impaired kidney function. The 1998 FDA guidance on pharmacokinetic studies in patients with impaired kidney function recommended use of renal dosage adjustment categories derived from creatinine clearance (CL_{cr}).[67] This was based on the rationale that CL_{cr} was widely used in patient

care settings as a measure of kidney function, and thus more practical than most other alternatives as a criterion for adjusting drug dosage. Since then both the FDA and the European Medicine Agency (EMA) have issued updated guidance documents on the conduct of pharmacokinetic studies in patients with impaired kidney function.[68,69] The adoption of the 1998 FDA guidance has resulted in improved availability of pharmacokinetic and drug dosing recommendations for drugs which have high (greater than 30%) fraction of the drug eliminated renally unchanged.[7] It appears that there have been significant improvements over the past 15 years in the frequency and rigor with which pharmacokinetic studies have been conducted in the setting of impaired kidney function.

The 2010 proposed revision to the 1998 FDA guidance recommended: (a) conducting studies for nonrenally as well as renally eliminated drugs, (b) conducting studies in patients receiving HD, (c) conducting studies to evaluate pharmacokinetics of therapeutic proteins in patients with impaired kidney function, (d) categorizing kidney function based on eGFR (using the CKD-EPI equation) or CL_{cr} (using the CG equation), and (e) modifications to how the results of renal impairment studies are presented in the official drug label.[69] Furthermore, several recent publications have offered suggestions to pharmaceutical industry and regulatory agencies regarding assessment of kidney function and which populations of patients should be included in the pharmacokinetic studies of new chemical entities during the drug development process.[70,71] These papers present population pharmacokinetics and physiologically based pharmacokinetic models that will assist in providing optimal dosing recommendations for new chemical entities in development in subjects with kidney dysfunction. Finally, the Kidney Disease: Improving Global Outcomes (KDIGO) held a conference to investigate these issues and propose recommendations for practitioners, researchers, and those involved in drug development and regulatory affairs. The conference generated 37 recommendations for clinical practice, 32 recommendations for future research, and 24 recommendations for regulatory agencies to enhance the quality of pharmacokinetic and pharmacodynamic information available to clinicians.[72]

Drug Dosing Regimens for CKD Patients

4 The initial or “loading” dose for CKD patients should be the same as the dose recommended for those with normal kidney function unless the drug’s V_D is known to be altered in the presence of CKD or a concomitant disease then the dose should be increased proportionally (see Table 65-1). Rapid achievement of

therapeutic drug concentrations is important in many patient care situations and thus it is better to start therapy aggressively rather than conservatively. Maintenance dosage regimen guidelines for CKD patients in FDA- or EMA-approved product labeling should be the foundation for ongoing therapy.[72] However, if such information is not available or if there is marked variance between these two agencies' recommendations, the stepwise approach depicted in **Table 65-4** for designing a dosage regimen for a patient with impaired kidney function can be used. In either case, the design of the optimal dosage regimen is dependent on the availability of an accurate characterization of the relationship between the pharmacokinetic parameters of the drug and kidney function and an accurate assessment of the patient's kidney function.

TABLE 65-4 Stepwise Approach to Adjust Drug Dosage Regimens for Patients with Impaired Kidney Function

Step 1	Obtain history and relevant demographic/ clinical information	Ask/obtain patient medical history including:
		Prescription medication
		Over-the-counter medication
		Recreational drugs
		Tobacco and alcohol use
		History of kidney disease
		Height
		Weight
Step 2	Determine kidney function	Measure serum creatinine and/or cystatin C
		Determine eGFR or CL_{cr} for drug dosing based best available methodology
		Order 24-hour urine collection for measured CL_{cr} if necessary
Step 3	Review the medication list	Ensure medications are all indicated
		Evaluate for potential drug interactions
		Identify drugs which need to dosage regimen adjusted
Step 4	Individualize treatment regimen for identified medications	Ascertain best initial dosage regimen from FDA- or EMA-approved product labeling
		For narrow therapeutic range drugs—calculate dosage regimen based on pharmacokinetic characteristics of the drug and the patient's kidney function
		Titrate the dose of drugs to patient effect, if applicable
Step 5	Avoid nephrotoxic drugs	Discontinue or avoid prescription of nephrotoxic medications if possible
Step 6	Monitor	Monitor drug serum concentrations (if available) to guide further therapy
		Monitor parameters of drug response and toxicity
		Monitor kidney function every 3-5 days for acute therapies and monthly or quarterly for chronic medications
Step 7	Reassess	Reassess the patient to evaluate drug efficacy and safety
		Revise regimen based on drug response or change in patient condition (including kidney function)

CL_{cr}, creatinine clearance; eGFR, estimated glomerular filtration rate; EMA, European Medicine Agency; FDA, Food and Drug Administration.

Most dosage adjustment guidelines have proposed the use of a fixed dose or interval for patients with broad ranges of kidney function that are different from those that are the foundation of the CKD staging scheme (see Chapter 61).[9,17,25,52,73–79] Indeed, normal kidney function has often been ascribed to anyone who has a CL_{cr} greater than 80 to 90 mL/min/1.73 m^2 (greater than 0.77-0.87 mL/s/m^2), even though the population normal CL_{cr} values range from 115 to 125 mL/min per 1.73 m^2 (greater than 1.11-1.20 mL/s/m^2) (see Chapter e59). The approved product labeling dosage adjustment recommendations and secondary references often use different ranges to represent mild, moderate, and severe kidney impairment.[52] The ranges for mild, moderate, and severe kidney impairment are typically defined as a CL_{cr} of 60 to 89 mL/min (1-1.48 mL/s), CL_{cr} of 30 to 59 mL/min (0.5-0.99 mL/s), and CL_{cr} of 10 to 29 mL/min (0.17-0.49 mL/s), respectively (**Table 65-5**). ESRD is usually defined as a CL_{cr} of less than 10 mL/min (0.17 mL/s). Each of these categories encompasses a broad range in kidney function, and thus the recommended drug regimen may not be optimal for all patients whose kidney function lies within the given category of kidney function.

TABLE 65-5 GFR Categories Based on KDIGO Classification

GFR Category[a]	GFR (mL/min/1.73 m^2 [mL/s/m^2])	Terms
1	>90 (0.87)	Normal or high
2	60-89 (0.58-0.86)	Mildly decreased
3a	45-59 (0.43-0.57)	Mildly to moderately decreased
3b	30-44 (0.29-0.42)	Moderately to severely decreased
4	15-29 (0.14-0.28)	Severely decreased
5	<15 (0.14)	Kidney failure

GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.

[a]To meet criteria for CKD there must be a significant reduction in GFR (categories 3a-5) or there must also be evidence of kidney damage (categories 1 & 2) for 3 months or greater.

Adapted from Reference 72.

5 FDA-approved drug labels, and commonly used drug information sources

such as *American Hospital Formulary Service Drug Information*,[73] *Goodman and Gilman's The Pharmacological Basis of Therapeutics*,[17,79] *British National Formulary*,[74] and *Drug Prescribing in Renal Failure*[75] are excellent sources of information about a drug's pharmacokinetic characteristics. In some cases, however, they yield marked variation in recommendations and the paucity of details of the methods used to generate the dosing advice has resulted in some clinicians cautioning against their routine clinical use (**Table 65-6**).[80,81] In addition, none of these sources consistently provide the explicit relationships of the kinetic parameters of interest (total body clearance [CL], elimination rate constant [k], and V_D) with a continuous index of kidney function, such as eCL_{cr} or eGFR. To find this information, one may need to identify the original research study that assessed the drug's disposition or a comprehensive review article on the class of drugs of interest. This is a time-consuming process that may be difficult to carry out for each drug and patient combination in real time.

TABLE 65-6 Comparison of Secondary References Used for Drug Dosing in Patients with Impaired Kidney Function

Resource	Pros	Cons
Aronoff's Drug Prescribing in Renal Failure[75]	Exclusive focus on drug dosing in patients with impaired kidney function Information provided for IHD, PD, CRRT Tables include drug PK and dosage adjustment based on CrCl (>50, 10-50, <10 mL/min [>0.83, 0.17-0.83, <0.17 mL/s]) Tables for both adult and pediatric dosing provided Concise, easy to use References to primary literature provided	Updated infrequently; information may not be most current, newer drugs may not be included Some dosage recommendations are not feasible for dialysis patients (ie, q 36 hours dosing interval)
The Renal Drug Handbook[76]	Contains information on clinical use of drugs, drug PK, dose in normal kidney function, dose adjustment in CKD, drug interactions and administration Specific to CKD patients	Updated every few years information may not be most current, newer drugs may not be included References not provided
Lexicomp[77]	Easy to access with a subscription Accessible online and via mobile device Easy to navigate Concise information Dose adjustment in CKD provided (HD and PD)	Difficult to navigate at first No specific focus on CKD patients References to primary literature for dosing not provided
Micromedex[78]	Easy to access with a subscription Accessible via mobile device Comprehensive, detailed information (both "in-depth" and "quick") Dose adjustment in CKD provided (both HD and PD)	Difficult to navigate Can be slow No specific focus on CKD patients References to primary literature for dosing not provided
American Hospital Formulary Service (AHFS)[73]	Detailed drug monographs "Dosage in Renal and Hepatic Impairment/ Special Populations" section for each drug listed Available online with a subscription Online version updated regularly, print version updated yearly	Hard copy version can be difficult to navigate, cumbersome Information on dose adjustment in CKD is minimal No specific focus on CKD patients References to primary literature for dosing not provided

CKD, chronic kidney disease; CrCl, creatinine clearance; CRRT, continuous renal replacement therapy; HD, hemodialysis; IHD, intermittent hemodialysis; PD, peritoneal dialysis; PK, pharmacokinetics.

Data from References 73, 75–78.

Dr Luzius Dettli is often credited for being the first to systematically approach the issue of drug dosing for those with impaired kidney function.[82] The "Dettli Method" is a graphic means to generate drug dosing recommendations based on the linear relationship between the elimination rate constant of a given renally cleared drug and a patient's creatinine clearance:

$$k = k_{NR} + (\alpha \times CL_{cr})$$

where k is the elimination rate constant of the drug based on a first-order one compartment model, k_{NR} is the nonrenal elimination rate constant, and α is a constant relating the renal drug elimination rate constant to the patient's creatinine clearance (CL_{cr}). This approach assumes that the overall elimination rate constant (or clearance) declines linearly with CL_{cr}, and that the nonrenal elimination rate constant (or CL_{NR}) remains constant as kidney function declines. While the first assumption generally holds true for drugs that are mainly renally cleared, the second assumption is flawed, as the functional expression of many drug metabolizing enzymes and drug transporters is decreased in patients with kidney disease.[33,34]

Ideally, one should be able to identify a relationship between CL or k with an estimated GFR or CL_{cr}, such as those depicted in **Table 65-7**. This information, along with the patient's estimated CL_{cr} or GFR, is the foundation upon which one can formulate a therapeutic regimen to attain the desired drug concentration time profile and ultimately the therapeutic outcome when approved product labeling information is not available.

TABLE 65-7 Relationship Between CL_{cr} and CL of Selected Drugs

Drug	Total Body Clearance[a]
Acyclovir	$CL = 3.37 (CL_{cr}) + 0.41$
Amikacin	$CL = 0.6 (CL_{cr}) + 9.6$
Aztreonam	$CL = 0.8 (CL_{cr}) + 26.6$
Cefazolin	$CL = 0.34 (CL_{cr}) + 6.6$
Ceftazidime	$CL = 1.15 (CL_{cr}) + 10.6$
Ciprofloxacin	$CL = 2.83 (CL_{cr}) + 363$
Digoxin	$CL = 0.88 (CL_{cr}) + 23$
Ganciclovir	$CL = 1.24 (CL_{cr}) + 8.57$
Gentamicin	$CL = 0.983 (CL_{cr})$
Imipenem	$CL = 1.42 (CL_{cr}) + 54$
Lithium	$CL = 0.20 (CL_{cr})$
Ofloxacin	$CL = 1.04 (CL_{cr}) + 38.7$
Piperacillin	$CL = 1.36 (CL_{cr}) + 1.50$
Tobramycin	$CL = 0.801 (CL_{cr})$
Vancomycin	$CL = 0.69 (CL_{cr}) + 3.7$

CL, total body clearance; CL_{cr}, creatinine clearance.

[a]Clearance in mL/min can be converted to mL/s through multiplication by 0.0167.

If specific literature recommendations and/or the relationship of kinetic parameters to estimated GFR or CL_{cr} are not available, then one can estimate the CL or *k* of the CKD patient with the method of Rowland and Tozer,[8] provided the fraction of the drug that is eliminated renally unchanged (f_e) in subjects with normal kidney function is known.[83] This approach assumes that the change in CL and *k* are proportional to eCL_{cr}, that the kidney disease does not alter the drug's metabolism, that the metabolites, if formed, are inactive and nontoxic, that the drug obeys first-order (linear) kinetic principles, and that it is adequately described by a one-compartment model. If these assumptions are true, which is rarely the case, then the kinetic parameter/dosage-adjustment factor (*Q*) can be calculated as:

$$Q = 1 - [f_e(1 - \mathrm{KF})]$$

where KF is the ratio of the patient's eCL_{cr} or eGFR to the assumed normal value of 120 mL/min (equivalent to 2 mL/s). Thus, for a drug that is 85% eliminated renally unchanged in a patient who has an eCL_{cr} of 10 mL/min (0.17

mL/s), the *Q* factor would be:

$$\begin{aligned} Q &= 1 - [0.85[1 - (10/120)]] \\ &= 1 - [0.85(0.85(0.92))] \\ &= 1 - 0.78 \\ &= 0.22 \end{aligned}$$

The best method for dosage regimen adjustment must then be selected. Specifically, one must determine whether the desired goal is the maintenance of a similar peak, trough, or average steady-state drug concentration or if there is a clearly defined pharmacodynamic endpoint such as the time above the MIC (eg, cephalosporins) or the ratio of the AUC relative to the MIC (eg, fluoroquinolones).[84] If there is a significant relationship between peak concentration and clinical response (eg, aminoglycosides)[85] or toxicity[83] (eg, phenobarbital and phenytoin), then attainment of the specific target values is critical. If, however, no specific target values for peak or trough concentrations have been reported (eg, antihypertensive agents and benzodiazepines), then a regimen goal of attaining the same average steady-state concentration is likely to be appropriate.

The principle choices to attain the desired average steady-state concentration profile are to decrease the dose or prolong the dosing interval. If the size of the dose is decreased while the dosing interval remains unchanged, the desired average steady-state concentration will be similar; however, the peak will be lower and the trough higher (**Fig. 65-1**). Alternatively, if the dosing interval is increased and the dose size remains unchanged, the peak and trough concentrations in the patient with impaired kidney function will be similar to those in the patient with normal kidney function. This dosage adjustment method is often recommended because it is likely to yield cost savings as a result of a reduction in nursing and pharmacy time, as well as a reduction in the supplies associated with frequent drug administration. Finally, the dose and dosing interval may both need to be changed to allow the administration of a clinically feasible dose (500 mg vs a calculated value of 487 mg) or a practical dosing interval, for example, 12 hours instead of 17 hours.

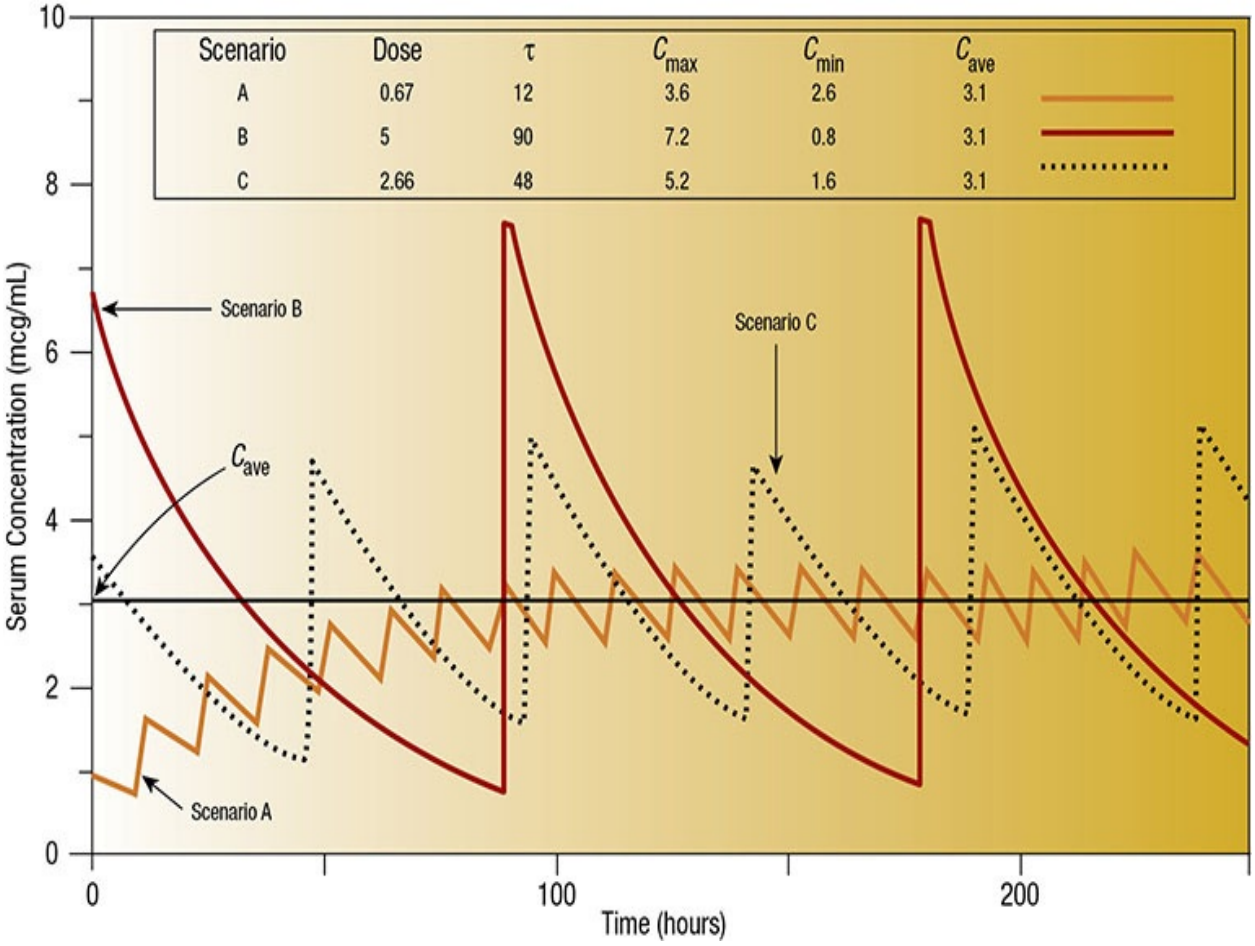


FIGURE 65-1 Although the average steady-state concentrations (C_{ave}) are identical regardless of which dosage-adjustment strategy one decides to implement, the concentration–time profile will be markedly different if one changes the dose and maintains the dosing interval (τ) constant (*Scenario A*), versus changing the dosing interval and maintaining the dose constant (*Scenario B*) or changing both (*Scenario C*).

If the relationship between the pharmacokinetic parameters of the drug and kidney function are known, the first step in the process is to estimate the drug disposition parameters in the patient with kidney disease. The dosage-adjustment factor (*Q*) calculated as the ratio of the estimated *k* or CL of the patient relative to subjects with normal kidney function is then used to determine the dose or dosing interval alterations necessary for the patient.

First, the relationship between drug clearance and CL_{cr} (expressed in conventional units of mL/min) is required; these relationship equations have been reported for several drugs (Table 65-7). How one can apply the relationship between a patient's kidney function and pharmacokinetic characteristics of

ciprofloxacin, a commonly used antibiotic for the treatment of infections in CKD and dialysis patients to develop and individualized dosage recommendation are illustrated in **Table 65-8** and briefly highlighted here. The first step is to calculate the CL of ciprofloxacin for a subject with normal kidney function (CL_{norm}) and CL for the patient with CKD (CL_{CKD}) to obtain the ratio of the predicted clearance values (Q) which can be used to calculate the new dosing regimen.

TABLE 65-8 Stepwise Approach to Calculating a Dosage Regimen Based on a Drug's Pharmacokinetic Characteristics and a Patient's Kidney Function

	Steps	Calculation Examples with Ciprofloxacin
Step 1	Calculate total body clearance of drug in an individual with normal kidney function (CL_{norm}); CL_{cr} = 120 mL/min	$CL_{norm} = [2.83 (CL_{cr})] + 363$ $CL_{norm} = [2.83(120)] + 363$ CL_{norm} = 702.6 mL/min per 1.73 m^2
Step 2	Calculate total body clearance of drug in a patient with impaired kidney function (CL_{fail})	In patient with CL_{cr} = 15 mL/min $CL_{fail} = [2.83(CL_{cr})] + 363$ $CL_{fail} = [2.83(15)] + 363$ CL_{fail} = 405.5 mL/min per 1.73 m^2
Step 3	Calculate the quotient (Q) for a patient with impaired kidney function	$Q = CL_{fail}/CL_{norm}$ $Q = 702.6/405.5$ $Q = 0.58$
Step 4	Calculate the maintenance dose (D_f) or adjusted-dosing interval (τ_f) in a patient with impaired kidney function; D_n = normal dose; τ_n = normal dosing interval	D_n = 500 mg; τ_n = 12 hour $D_f = D_n \times Q$ D_f = 500 mg × 0.58 D_f = 290 mg $\tau_f = \tau_n/Q$ $\tau_f = 12/0.58$ τ_f = 20.7 hour
Step 5	Choose dosing adjustment: 1. Maintain D_n and use τ_f 2. Maintain τ_n and use D_f	Dosing adjustments: 1. 500 mg every 21 hour 2. 290 mg every 12 hour
Step 6	Calculate D_f based on practical dosing interval (τ_p), which is selected	D_n = 500 mg; τ_f = 21 hour; τ = 24 hour (selected to limit missed doses) $D_f = (D_n \times Q \times \tau_p)/\tau_n$ D_f = (500 mg × 0.58 × 24)/12 D_f = 580 mg
Step 7	Recommend dosing regimen (dependent on product availability and limited risk of missed doses)	500 mg every 24 hour

CL_{cr}, creatinine clearance.

Creatinine clearance in mL/min can be converted to mL/s through multiplication by 0.0167. Clearance in mL/min per 1.73 m^2 can be converted to mL/s/m^2 through multiplication by 0.00963.

It is also important to consider other characteristics of antibiotics, such as the most relevant MICs and concentrations associated with toxicities and adverse

events, before modifying a dosage regimen.[86] Ciprofloxacin, a concentration-dependent antibiotic has an associated concentration-dependent postantibiotic effect, in which bactericidal action continues for a period of time after the antibiotic concentration falls below the MIC. The peak concentration and AUC determine efficacy of these antibiotics. Therefore, extending the interval but keeping the same dose allows for this pharmacodynamic action. Furthermore, extending the interval without increasing the dose will achieve high concentrations of ciprofloxacin without an accumulation of drug that could cause dose-dependent toxicities such as seizures.[86]

If the V_D of a drug is significantly altered in CKD patients or if one desires to attain a specific maximum or minimum concentration, the estimation of a dosage regimen becomes more complex. If the relationship between V_D and CL_{cr} has been characterized, then V_D may be estimated. If one assumes that a one-compartment linear model can describe the drug, the predicted V_D may then be used with the predicted k of the drug to yield an adjusted-dosing interval and IV dose.

For orally administered drugs, the τ_f can be calculated and the dose can be approximated from the following equations as:

$$\tau_f = [(-1/k_f)[\ln(C_{min}/C_{max})]] + t_{peak}$$

$$\text{Dose}po = [FC_p^t V_D(k_a - k)]/[k_a(e^{-kt}/1 - e^{-k\tau})(e^{-kat}/1 - e^{-ka\tau})]$$

where F equals bioavailability, C_p^t equals the desired plasma concentration at time t, and k_a is the absorption rate constant.

Although, this approach allows for the individualization of an oral dosage regimen for attainment of specific peak and trough serum concentrations it is rarely used in clinical practice. This is in part due to the paucity of data on the absorption rate constant of individual drug formulations. Thus, many assume that the drug is absorbed extremely rapidly, in which case one can approximate the τ_f and the dose using equations originally proposed for IV dosing as:

$$\tau_f = (-1/k_f)[\ln(C_{min}/C_{max})]$$

$$\text{Dose}po = V_D \times (C_{max} - C_{min})$$

These principles have been used by several investigators to derive dosage

recommendations for many commonly used drugs for CKD patients.[75–78] It should be noted, however, that in most dosing guidelines, the “usual” dose or dose for “normal kidney function” represents eGFR greater than 50 mL/min/1.73 m^2. This assumption, however, could lead to dosing errors for patients with eGFRs of 60 mL/min/1.73 m^2 versus 90 mL/min/1.73 m^2 versus 130 mL/min/1.73 m^2. In fact, augmented renal clearance (ARC) defined as CL_{cr} greater than 130 mL/min/1.73 m^2 (1.25 mL/s/m^2)has been associated with subtherapeutic antibiotic concentrations and patient outcomes when standard doses of antibiotics were administered.[87–89] Although more research has been performed in the past 10 years in the critically ill, clinicians need to be aware of the potential to underdose these patients because of their augmented kidney function and thus need to consider the use of higher doses especially for antibiotics and antivirals.

DRUG DOSAGE REGIMEN DESIGN FOR PATIENTS RECEIVING RENAL REPLACEMENT THERAPY

Continuous renal replacement therapies are used for the management of fluid overload and the removal of uremic toxins in patients with AKI and other conditions. Several forms of continuous renal replacement therapy in clinical use today are extensively described in Chapter 60 and several dosage regimen individualization approaches are also presented in that chapter. Which of these therapies will be optimal for a given patient is dependent on several factors, including bleeding risk, degree of hypercatabolism, acid–base balance, and experience of the healthcare provider team. The rationale and approaches for delivery of renal replacement therapy for those with ESRD are described in Chapter 62, “Hemodialysis and Peritoneal Dialysis.”

This next section will describe drug dosing regimens for patients on peritoneal dialysis and HD, including short-daily hemodialysis (SDHD) and nocturnal hemodialysis (NHD).

Peritoneal Dialysis

Peritoneal dialysis, like other dialysis modalities, has the potential to affect drug disposition; however, drug therapy individualization is often less complicated in these patients as a result of the limited drug clearances achieved with the

variants of this procedure (see Chapter 62). In general, HD is more effective in removing drugs than peritoneal dialysis. If a drug is not removed by HD, then it is unlikely to be significantly removed by peritoneal dialysis. Many of the factors that are important in determining drug dialyzability for other treatment modalities pertain to peritoneal dialysis as well.[90,91] Factors that influence drug dialyzability by peritoneal dialysis include drug-specific characteristics such as molecular weight, solubility, degree of ionization, protein binding, and V_D. The intrinsic properties of the peritoneal membrane that affect drug removal include blood flow and peritoneal membrane surface area, which is approximately equal to the body surface area. There is an inverse relationship between peritoneal drug clearance and molecular weight, protein binding, and V_D. In addition, drug compounds that are ionized at physiologic pH will diffuse across the membrane more slowly than unionized compounds. Detailed reviews of the disposition of several drugs in chronic peritoneal dialysis patients are reported elsewhere.[92,93] The treatment priorities for peritoneal dialysis peritonitis and the recommended drug regimens are presented in detail in Chapter 62.

Peritoneal dialysis, in current practice, is often prescribed to attain a urea clearance of approximately 10 mL/min (0.17 mL/s), so it is unlikely to significantly impact the CL of any drug.[72] In addition, since most medications have a larger molecular size than urea, their resultant CL will likely be even lower: probably between 5 and 7.5 mL/min (0.08-0.13 mL/s). Therefore, drug dosing recommendations for the management of conditions other than peritonitis, reported for patients with estimated CL_{cr} or GFR of 10 to 15 mL/min (0.17-0.25 mL/s), are likely suitable for patients receiving peritoneal dialysis.[75]

Hemodialysis

Although many hemodialyzers have been introduced in the past 20 years and more than 100 different ones were available in North America in 2015, the effect of HD on drug disposition is rarely reevaluated after it is initially reported. Thus, most of the literature, especially for older medications, probably represents an underestimation of the impact of HD on a drug's disposition.[95]

6 The impact of HD on a patient's drug therapy is dependent on several factors, including the physicochemical characteristics of the drug, the dialysis conditions, and the clinical situation for which dialysis is performed. Drug-related factors that affect dialyzability include the molecular weight or size, degree of protein binding, and V_D.[6] The vast majority of dialysis filters in use in

North America up until the mid-1990s were composed of cellulose, cellulose acetate, or regenerated cellulose (cuprophane), and they were generally impermeable to drugs with a molecular weight greater than 1,000 Da.[95] Dialysis membranes in the 21st century are predominantly composed of semisynthetic or synthetic materials (eg, polysulfone, polymethylmethacrylate, or polyacrylonitrile). These high-flux dialysis membranes have larger pore sizes and more closely mimic the filtration characteristics of the human kidney. This allows the passage of most solutes, including drugs (eg, vancomycin) that have a molecular weight of 20,000 Da or less.[95] Therefore, drugs such as vancomycin (1,450 Da) will be more easily removed with high-flux dialyzers. An increase in removal has also been reported with several other drugs that have lower molecular weights such as ceftzadine.[95] Some drugs that are cleared in high-flux dialysis but not through conventional dialysis include: carbamazepine, cisplatin, enoxaparin, ranitidine, valproic acid, sorafenib, and tramadol.[72] Therefore, it is likely that many dosing recommendations for HD patients made prior to this change underestimate the impact of HD on drug removal. If this is the case some have suggested that the dosage of many of these older drugs may need to be increased by as much as 25% to 50% due to enhanced dialytic clearance.[96] Therefore, therapeutic drug monitoring for drugs such as aminoglycosides and vancomycin should be performed to ensure adequate dosing for patients on HD.

Drugs that are small but highly protein bound (ie, greater than 90%) are not well dialyzed because both of the principal binding proteins, α_1-acid glycoprotein and albumin, have a very high molecular weight. For example, the molecular weight of albumin is 60,000 Da; thus, a drug such as apixaban which is 90% bound to plasma proteins would not be removed by HD. Finally, those drugs that are widely distributed, with V_D greater than 2 L/kg such as ciprofloxacin, are poorly removed by HD.

The HD procedure, be it acute for the management of AKI, intermittent three times a week or daily for an extended period or some combination thereof for the management of category G5 CKD patients can dramatically affect the total body clearance of a medication.[95] The primary factors that vary between patients are the composition of the dialysis filter, the filter surface area, the blood, dialysate and ultrafiltration flow rates, and whether or not the dialysis unit reuses the dialysis filter.

Overall, the impact of HD on drug therapy is highly variable and thus one cannot assume that a certain percentage of a drug is removed with each dialysis session; neither should a “yes” or “no” answer regarding the dialyzability of a drug be considered sufficient information to make therapeutic decisions, since

this provides no quantification of the impact of HD. Characteristics of the dialysis procedure that was utilized in the drug study, such as membrane composition and surface area and blood and dialysis flow rates, are thus critical data that should be known before one uses the published HD clearance data to prospectively design a drug dosing regimen for a HD patient.

If drug concentrations can be measured in the clinical setting, the quantitative impact of HD on drug disposition can be calculated in one of several ways.[6] The most commonly utilized means for assessing the effect of HD is to calculate the dialyzer clearance (CL_D) of the drug. The CL_D^p from blood can be calculated as

$$CL_D^p = Q_p[(A_p - V_p)/A_p]$$

where Q_b is the blood flow through the dialyzer and Q_p is the plasma flow, which equals Q_b (1 − hematocrit), A_p is the plasma concentration of drug entering the dialyzer, and V_p is the plasma concentration of the drug leaving the dialyzer. This clearance calculation most accurately reflects dialysis drug clearance as most drugs do not significantly penetrate red blood cells or bind to formed blood elements. However, for drugs that readily partition into and out of erythrocytes, this equation would likely underestimate HD clearance. Furthermore, one must keep in mind that venous plasma concentrations may be artificially high and CL_D^p will be low if plasma water is removed from the blood at a faster rate than the drug. This tends to occur when extensive ultrafiltration is performed simultaneously with diffusion during dialysis.[72]

The following principles may be used to generate a drug dosage regimen recommendation for HD patients, if none is available in FDA or EMA product labeling, by using a value of CL_D that is reported in the literature.[6,17,95] Because clearance terms are additive, the total clearance during dialysis can be calculated as the sum of the patient's residual renal and nonrenal clearance during the interdialytic period (CL_{RES}) and dialyzer clearance (CL_D):

$$CL_T = CL_{RES} + CL_D$$

The half-life during the period between dialysis treatments and during dialysis can then be calculated from the following relationships using an estimate of the drug's V_D, which can be obtained from the literature[6,83]:

CLINICAL PRESENTATION

Dosage Regimen Calculation For a Hemodialysis Patient

A 54-year-old critically ill woman with ESRD was transferred to a medical intensive care unit from the general medical unit, where she was febrile with a temperature of 39°C (102.2°F). Her weight was 64 kg (141 lb) and her height was 65 in. (165 cm). She had a residual CL_{cr} of 5 mL/min (0.083 mL/s), and was receiving high-flux dialysis (F80 polysulfone dialyzer) for 4 hours on Mondays, Wednesdays, and Fridays. She was started on vancomycin for a methicillin-resistant *Staphylococcus aureus* (MRSA) catheter-associated bacteremia and her first dose of 1,000 mg was administered at the end of her HD treatment. The first step is to estimate this patient's pharmacokinetic parameters of vancomycin on the basis of published population data.[96] The V_D in this patient can be estimated to be 54.4 L (0.85 L/kg × 64 kg), and her residual total body clearance (CL_{RES}) estimated from the relationship between CL and CL_{cr} (CL_{RES} = [0.69 × CL_{cr}] +3.7) is 7.15 mL/min (0.12 mL/s) or 0.43 L/hr. The *k* can be approximated as:

$$k = CL_{RES}/V_D$$
$$= 0.43\,L/hr/54.4\,L$$
$$= 0.0079\,hr^{-1}$$

The HD clearance of vancomycin (CL_D) is dependent on the dialyzer and a value of 120 mL/min (2 mL/s; 7.2 L/hr) is a reasonable estimate for this dialyzer.[96,97]

One now can predict what the plasma concentrations of vancomycin will be over the next 24 to 48 hours, assuming the infusion time for the drug (t') was 1 hour. The concentration at the end of the 1-hour infusion (C_{max}) would be:

$$C_{max} = \frac{(Dose/t')}{CL_{RES}}(1 - e^{-kt'})$$
$$= \frac{(1000\,mg/h)}{0.43\,L/h}(1 - e^{-(0.0079)1})$$
$$= (2{,}325.6\,mg/L)(0.0078)$$
$$= 18.1\,mg/L$$

The plasma concentration prior to the next dialysis session (C_{bD}), which is 44 hours away can be calculated as:

$$C_{bD} = C_{max} \times e^{-(CL_{RES}/V_D) \times t}$$
$$= 18.1 \times e^{-0.0079 \times 44}$$
$$= 12.8\ mg/L$$

and the concentration 4 hours later after dialysis (C_{aD}) can be calculated as:

$$C_{aD} = C_{bD} \times e^{-[(CL_{RES}+CL_D)/V_D] \times t}$$
$$= 12.8 \times e^{-[(0.43+7.2)/54.4] \times 4}$$
$$= 12.8 \times e^{-0.14 \times 4}$$
$$= 7.3\ mg/L$$

On the basis of these data, the second dose which should be administered after the second dialysis session should be increased as one generally desires to maintain vancomycin trough concentrations between 15 and 20 mg/L (mcg/mL; 10-14 µmol/L) for a MRSA catheter-associated bacteremia.[98,99] The patient received a vancomycin dose of 1,500 mg 4 hours after the end of the second dialysis session. The increase in serum concentration at the end of this 1-hour infusion (C_{change}) can thus be estimated:

$$C_{change} = \frac{(Dose/t')}{CL_{RES}}(1 - e^{-kt'})$$
$$= \frac{(1500\ mg/h)}{0.43\ L/h}(1 - e^{-(0.0079)1})$$
$$= (3{,}488.4\ mg/L)(0.0078)$$
$$= 27.2\ mg/L$$

Thus, the C_{max} would be approximately 34 mg/L (mcg/mL; 24 µmol/L), the sum of the residual concentration from the first dose of approximately 7 mg/L (mcg/mL; 5 µmol/L) and the C_{change}. The plasma concentration prior to the third dialysis session (C_{bD}), which is 40 hours away can be estimated as:

$$C_{bD} = C_{max} \times e^{-(CL_{RES}/V_D) \times t}$$
$$= 34\,mg/L \times e^{-0.0079 \times 40}$$
$$= 24.8\,mg/L$$

and the concentration 4 hours later after the third dialysis (C_{aD}) can be estimated as:

$$C_{aD} = C_{bD} \times e^{-[(CL_{RES}+CL_D)/V_D] \times t}$$
$$= 24.8 \times e^{-[(0.43+7.2)/54.4] \times 4}$$
$$= 24.8 \times e^{-0.14 \times 4}$$
$$= 14.2\,mg/L$$

This higher dose would be considered by many to have achieved too high of concentrations since the lowest value during the majority of the dosing interval exceeded 24.8 mg/L (mcg/mL; 17.1 µmol/L).

$$t1/2,\ \text{off HD} = 0.693(V_D/CL_{RES})$$
$$t1/2,\ \text{on HD} = 0.693\ (V_D/CL_{RES} + CL_D)$$

Once the key pharmacokinetic parameters have been estimated/calculated, they may be used to simulate the plasma concentration–time profile of the drug for the individual patient and then one can ascertain how much drug to administer and when. This approach to drug therapy individualization can be accomplished in a stepwise fashion assuming first-order elimination of the drug and a one-compartment model.

For medications with a narrow therapeutic index (eg, vancomycin, phenytoin, and gentamicin), therapeutic drug monitoring (eg, plasma concentration measurements and dialyzer clearance estimation) should be utilized to guide drug dosing.[6] The ultimate reason for measuring the plasma concentrations of antibacterial agents is to individualize the patient's dosage regimen to achieve a bacteriologic cure while preventing adverse effects and preserving residual renal function. Thus, there remains one important step in the case above: the calculation of the dose the patient should receive after the second dialysis session. Vancomycin dosing is primarily based on attaining desired trough concentrations, usually between 15 and 20 mg/L (mcg/mL; 10-14 µmol/L). Peak concentrations are rarely used and not recommended to derive dosing recommendations and adjustments; however, for this patient example, a desired

peak concentration of 30 mg/L (mcg/mL; 21 μmol/L), the midpoint of the recommended range of 20 to 40 mg/L (mcg/mL; 14-28 μmol/L) could be utilized to calculate a dose.[98]

Assuming the desired peak concentration of 30 mg/L (mcg/mL; 21 μmol/L) and trough concentration was 15 mg/L (mcg/mL; 10 μmol/L), the postdialysis dose this patient would need can then be calculated using the simplified approach below, because the $t_{1/2}$ is extremely prolonged relative to the infusion time, and thus minimal drug is eliminated during the post HD infusion period:

$$\begin{aligned}\text{Dose} &= V_D \times (C_{max} - C_{min}) \\ &= 40\,\text{L} \times (30\,\text{mg/L} - 15\,\text{mg/L}) \\ &= 600\,\text{mg}\end{aligned}$$

7 It is common practice in most HD units to administer drugs after the patient has received dialysis on the premise that it is desirable to minimize the loss of drug that would result from the additional clearance during HD. Certainly, administration of antihypertensive agents and vasoactive drugs should be avoided in the hours prior to a HD session to minimize the likelihood of hypotension. In some cases, medications for pain are given on a precise schedule and thus the medication would be given to the patient irrespective of the time on dialysis. The administration of traditional doses of tobramycin (1.5 mg/kg) or vancomycin (1,000 mg) during dialysis has been associated with markedly lower AUCs than those observed when the same dose was administered postdialysis; consequently, higher dosage regimens are usually necessary to compensate for the additional loss of drug during the dialysis procedure. Furthermore, emerging pharmacokinetic and pharmacodynamic considerations suggest that it may be optimal approach to administer some drugs, such as aminoglycosides[100,101] and vancomycin during or immediately prior to the start of a dialysis treatment.[102,103] Two evaluations of predialysis and one of intradialytic dosing of aminoglycosides indicate that similar peak concentrations, a prime indicator of efficacy, can be obtained in these scenarios relative to those observed with postdialysis dosing.[100] The AUC during the dosing interval and the subsequent predialysis concentrations were noted to be significantly decreased and thus the risk of ototoxicity and further kidney injury may be minimized. The best dosing schedule, a dose roughly twice that traditionally employed for postdialysis administration, in the 26 patients evaluated by Teigen et al, resulted in the achievement of the desired peak and AUC in approximately 90% of patients.[100]

Performing HD immediately after dosing might also be a good option for

several anticancer drugs. The predialysis administration of a normal dose makes sense when the patient undergoes HD 2 to 12 hours later. This strategy delivers the desired maximum plasma concentration effect while minimizing patient exposure to the toxic drug or metabolite effects.[104–107]

Alternative Hemodialysis Modalities

Short-daily and nocturnal HD are two alternative HD techniques. Both modalities are administered 6 to 7 days a week but differ primarily in the duration of the treatment and blood-flow rate. SDHD is typically for 2 hours per session; nocturnal HD occurs overnight for 6 to 8 hours but at lower blood and dialysate flow rates.[108]

Nocturnal Hemodialysis

NHD use is increasing since there is increased evidence of benefits over conventional thrice-weekly HD (Chapter 62).[109–111] NHD has demonstrated improvements in hypertension, left ventricular hypertrophy, quality-of-life related to burden and effects of kidney disease, and malnutrition compared to conventional HD.[109,110] In addition, North American studies suggest that survival is significantly better in NHD than conventional HD and possibly similar to survival after kidney transplantation.[112,113]

NHD is performed over 5 to 8 hours on 3 to 7 nights per week, thus receive between 24 and 45 hours of dialysis per week, versus 12 hours with conventional HD.[108] The longer dialysis duration removes a higher quantity of solute and fluid, more closely mimicking the human physiological state when compared with conventional HD.[108] There is a paucity of data when it comes to drug dosing with this modality; however, the principles of drug dosing discussed above with intermittent HD can also be applied here. Although there is an increase in dialysis hours, which would suggest an increase in drug removal, the blood and dialysate flow rates are slower and thus drug clearance per unit of time will be less. This has been shown in a study with cefazolin where the cefazolin clearance during NHD was slightly lower (CL = 1.65 L/hr) than during high-flux intermittent HD (CL = 1.85 L/hr)[113]; however, a greater percentage of cefazolin was removed in 8 hours of NHD (80%) than conventional 4-hour high-flux HD (60%). The investigators concluded that a dosing regimen of a 2-g loading dose followed by 1g IV after each NHD was sufficient to achieve concentrations 6 × MIC for *Staphylococcus* species for at least 70% of the dosing interval.[113]

Short-Daily Hemodialysis

SDHD involves 2 hours of dialysis, 6 days of the week, and has been associated with improved control of blood pressure and phosphorus, decreased medication requirements, decrease in left ventricular mass, and improved quality of life.[114,115] It has also shown a trend toward prolonged survival because of these improvements in clinical outcomes. As in the case with NHD, there is also limited data on drug dosing with this modality; however, the general principles of drug dosing for HD also apply here. In SDHD, the number of dialysis sessions per week and blood and dialysate flow rates are similar to intermittent HD, which may suggest similar drug removal. However, for certain medications (smaller size and decreased V_D, and protein binding) drug removal may be increased.

This has been shown in a study with cefazolin where the cefazolin clearance rate in SDHD was slightly higher than the value observed during high-flux intermittent HD; in fact the amount of cefazolin removed in 2 hours of SDHD was similar to that after 4 hours of high-flux HD. The investigators concluded that a dosing regimen of 1 g after each SDHD was sufficient to achieve concentrations 8 × MIC for *Staphylococcus* species for at least 90% of the dosing interval.[116] Therefore, it appears that the same amount of medication given over the entire week for patients on intermittent HD could also be given to patients on SDHD but in smaller amounts administered more frequently. For instance, in intermittent HD, the cefazolin dose is typically 2 g IV after each HD for a total of 6 g/week; whereas in SDHD, the dose would be 1 g IV daily (ie, for 6 days) after each HD.

Overall small solute removal is more efficient if the frequency of HD is increased. Therefore, SDHD and NHD therapies yield different clearance values compared to intermittent three times per week HD. Furthermore, prolonged HD such as in the case of NHD results in less rebound of drug concentrations after the termination of dialysis. This likely occurs because the rate of transfer from the peripheral to central compartment relative to the rate of diffusive removal is lower. Therefore, careful monitoring of drug therapy is necessary when these newer modalities are used to avoid potential errors in designing drug dosing regimens.

CONCLUSION

Subtherapeutic responses to drugs in patients with impaired kidney function are

often misinterpreted and not recognized. The adverse outcomes associated with inappropriate drug dosing have rarely been quantified but warrant future investigations. The utilization of FDA or EMA drug dosage recommendations in official prescribing information should be used for the initiation of therapy in most clinical situations. However, critically ill individuals especially those with preexisting CKD likely have marked pharmacokinetic variability and may require the use of pharmacokinetic principles in conjunction with reliable population pharmacokinetic estimates to determine the optimal drug dosage regimen design. Individualization of all drugs with a narrow therapeutic index for AKI and CKD patients should be undertaken whenever clinical therapeutic monitoring tools are available. The key action step is to use the knowledge we have to improve patient outcomes. The lack of dosage adjustment for CKD patients in ambulatory and hospital environments is an unfortunate reminder of how far we still have to go to optimize the therapy of CKD patients.[10–14,117]

Clinicians should therefore be aware of all the possible alternations in pharmacokinetics of drug, what processes are likely to be altered in the setting of kidney disease and tailor pharmacotherapy accordingly to ensure that CKD patients receive maximal benefits from their drug therapy while minimizing potential adverse outcomes.

Postclass Engaged Learning Activity

Conduct a literature search and identify a manuscript that has been published in the past 5 years related to the assessment of pharmacokinetics and dosing of a new drug (ie, a drug that is now approved by the FDA) in patients with impaired kidney function. Write a brief summary of the pharmacokinetic findings, and of the corresponding dosing recommendations, noting method of assessing kidney function and the kidney function cutoff values for adjusting drug dosing. Next, compare and contrast these recommendations with the FDA-approved drug label information. This activity is intended to build your experience with accessing the primary biomedical literature and identifying renal drug dosing information.

ABBREVIATIONS

A_b	concentration of drug in blood going into the dialyzer (arterial side)
AKI	acute kidney injury
A_p	concentration of drug in plasma going into the dialyzer (arterial side)
$AUC_{0\text{-}t}$	the area under the predialyzer plasma concentration–time curve during hemodialysis
ARC	augmented renal clearance
BSA	body surface area
C_{aD}	plasma concentration after dialysis
C_{bD}	plasma concentration prior to the next dialysis session
CG	Cockcroft–Gault
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration Equation
CL	total body clearance
CL_D^b	dialyzer clearance from blood
CL_{cr}	creatinine clearance
CL_D	dialyzer clearance
CL_{fail}	clearance of a drug in patients with impaired kidney function
CL_{norm}	clearance of a drug in patients with normal kidney function
CL_{NR}	clearance nonrenal

CL_D^p	dialyzer clearance from plasma
CL_R	net renal excretion
CL_D^r	recovery clearance of dialyzer
$CL_{reabsorption}$	tubular reabsorption
CL_{RES}	residual drug clearance in a dialysis patient
$CL_{secretion}$	tubular secretion
CL_T	total clearance during dialysis
C_{max}	peak drug concentration
C_{min}	trough drug concentration
C_{ss}	average steady-state plasma concentration
CYP	cytochrome P450
D_f	maintenance dose for a patient with impaired kidney function
D_n	dose for a patient with normal kidney function
EBT	erythromycin breath test
eCL_{cr}	estimated creatinine clearance
eGFR	estimated glomerular filtration rate
EMA	European Medicine Agency
ESRD	end-stage renal disease
f_e	fraction of drug eliminated unchanged in the urine
f_u	fraction of drug unbound to plasma proteins
GFR	glomerular filtration rate
HD	hemodialysis
INR	international normalized ratio
k	elimination rate constant
k_{DD}	elimination rate constant during dialysis
KDIGO	Kidney Disease: Improving Global Outcomes
KF	ratio of the patient's CL_{cr} to the assumed normal value of 120 mL/min (2 mL/s)
k_{ID}	elimination rate constant between dialysis sessions (interdialytic)
MDRD	Modification of Diet in Renal Disease Study equation
MIC	minimum inhibitory concentration
MRSA	methicillin-resistant *Staphylococcus aureus*
NHD	nocturnal hemodialysis
Q	kinetic parameter/dosage-adjustment factor
Q_b	blood flow through the dialyzer
Q_p	plasma flow through the dialyzer = Q_b (1 − hematocrit)
R	the total amount of drug recovered unchanged in the dialysate
SSRIs	selective serotonin reuptake inhibitors
t'	infusion time of drug
Δt	time in hours between two measured concentrations
$t_{1/2}$	half-life
$t_{1/2,on\ HD}$	half-life during dialysis
$t_{1/2,off\ HD}$	half-life off dialysis
τ_f	dosing interval in a patient with kidney failure
τ_p	practical dosing interval for a patient with kidney failure
τ_n	dosing interval in a patient with normal kidney function
t_{max}	time-to-peak drug concentration
TTR	time in therapeutic range
V_{area}	volume of distribution area
V_b	blood concentration of drug leaving the dialyzer
V_β	volume of terminal phase (serum protein)
V_c	volume of the central compartment
V_D	volume of distribution
V_{ss}	volume of distribution at steady state

REFERENCES

1. Stevens PE, Levin A. Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and Management of Chronic Kidney Disease: Synopsis of the Kidney Disease: Improving Global Outcomes 2012 clinical practice guideline. *Ann Intern Med*. 2013;158:825–830.
2. Mills KT, Xu Y, Zhang W, et al. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. *Kidney Int*. 2015;88:950–957.
3. Radhakrishnan J, Remuzzi G, Saran R, et al. Taming the chronic kidney disease epidemic: A global view of surveillance efforts. *Kidney Int*. 2014;86:246–250.
4. Brück K, Stel VS, Gambaro G, et al. CKD prevalence varies across the European general population. *J Am Soc Nephrol*. 2016;27:2135–2147.
5. National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC). Kidney Disease Statistics for the United States. U.S. Department of Health and Human Services. Available at: http://kidney.niddk.nih.gov/kudiseases/pubs/kustats/ November 2012. Accessed November 2, 2018.
6. Matzke GR, Comstock TJ. Influence of renal disease and dialysis on pharmacokinetics. In: Evans WE, Schentag JJ, Burton ME, eds. *Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring*. 4th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2005:187–212.
7. Matzke GR, Dowling TC, Marks SA, et al. Influence of kidney disease on drug disposition: An assessment of industry studies submitted to the FDA for new chemical entities 1999–2010. *J Clin Pharmacol*. 2016;56:390–398.
8. Rowland M, Tozer TN. *Clinical Pharmacokinetics: Concepts and Applications*. 3rd ed. Philadelphia, PA: Lea & Febiger; 1995:156–183.
9. Matzke GR, Dowling TD. Dosing concepts in renal dysfunction. In: Murphy JE, ed. *Clinical Pharmacokinetics Pocket Reference*. 5th ed. Bethesda, MD: American Society of Health-System Pharmacists; 2011:427–443.
10. Farag A, Garg AX, Li L, et al. Dosing errors in prescribed antibiotics for older persons with CKD: A retrospective time series analysis. *Am J Kidney*

Dis. 2014;63:422–428.

11. Chang F, O'Hare AM, Miao Y, et al. Use of renally inappropriate medications in older veterans: A National Study. *J Am Geriatr Soc*. 2015;63:2290–2297.
12. Muller C, Mimitrov Y, Imhoff O, et al. Oral antidiabetics use among diabetic type 2 patients with chronic kidney disease. Do nephrologists take account of recommendations? *J Diabetes Complications*. 2016;30:675–680.
13. Via-Sosa MA, Lopes N, March M. Effectiveness of a drug dosing service provided by community pharmacists in polymedicated elderly patients with renal impairment: A comparative study. *BMC Fam Pract*. 2013;14:96.
14. Chertow GM, Lee J, Kuperman GJ, et al. Guided medication dosing for inpatients with renal insufficiency. *JAMA*. 2001;286:2839–2844.
15. Salomon L, Deray G, Jaudon MC, et al. Medication misuse in hospitalized patients with renal impairment. *Int J Qual Health Care*. 2003;15:331–335.
16. Aronoff GR, Aronoff JR. Drug prescribing in kidney disease: Can't we do better? *Am J Kidney Dis*. 2014;3:382–383.
17. Thummel KE, Shen DD, Isoherranen N. Appendix II. Design and optimization of dosage regimens: Pharmacokinetic data. In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York, NY: McGraw-Hill; 2011.
18. Ramezani A, Raj DS. The gut microbiome, kidney disease, and targeted interventions. *J Am Soc Nephrol*. 2014;25:657–670.
19. Etemad B. Gastrointestinal complications of renal failure. *Gastroenterol Clin North Am*. 1998;27:875–892.
20. Matzke GR, Frye RF. Drug administration in patients with renal insufficiency. *Drug Saf*. 1997;16:205–231.
21. Barnes JN, Williams AJ, et al. Dihydrocodeine in renal failure: Further evidence for an important role of the kidney in the handling of opioid drugs. *BMJ*. 1985;290:740–742.
22. Min DI, Ku YM, Perry PJ, et al. Effect of grapefruit juice on cyclosporine pharmacokinetics in renal transplant patients. *Transplantation*. 1996;62:123–125.
23. Verbeeck RK, Musuamba FT. Pharmacokinetics and dosage adjustment in

patients with renal dysfunction. *Eur J Clin Pharmacol*. 2009;65:757–773.
24. Olyaei AJ, Steffl JL. A quantitative approach to drug dosing in chronic kidney disease. *Blood Purif*. 2011;31:138–145.
25. Olyaei AJ, Bennett WM. Drug dosing in the elderly patients with chronic kidney disease. *Clin Geriatr Med*. 2009;25:459–527.
26. Brunner M, Pernerstorfer T, Mayer BX, et al. Surgery and intensive care procedures affect the target site distribution of piperacillin. *Crit Care Med*. 2000;28:1754–1759.
27. Álvarez-Lerma F, Grau S. Management of antimicrobial use in the intensive care unit. *Drugs*. 2012;72:447–470.
28. Winter ME. Phenytoin and fosphenytoin. In: Murphy J, ed. *Clinical Pharmacokinetics*. 5th ed. Bethesda MD: American Society of Health System Pharmacists; 2012.
29. Meijers BKI, Bemmers B, Verbeke B, et al. A review of albumin binding in CKD. *Am J Kidney Dis*. 2008;51:839–850.
30. Job ML. Digoxin. In: Murphy JE, ed. *Clinical Pharmacokinetics Pocket Reference*. 5th ed. Bethesda, MD: American Society of Health-System Pharmacists; 2012:139–147.
31. Koup JR. Disease states and drug pharmacokinetics. *J Clin Pharmacol*. 1989;29:674–679.
32. Masereeuw R, Russel FGM. Therapeutic implications of renal anionic drug transporters. *Pharmacol Ther*. 2010;126:200–216.
33. Yeung CK, Shen DD, Thummel KE, et al. Effects of chronic kidney disease and uremia on hepatic drug metabolism and transport. *Kidney Int*. 2014;85:522–528.
34. Naud J, Nolin TD, Leblond FA, et al. Current understanding of drug disposition in kidney disease. *J Clin Pharmacol*. 2012;52:10S–22S.
35. Nolin TD, Unruh ML. Clinical relevance of impaired nonrenal drug clearance in ESRD. *Sem Dialysis*. 2010;23:482–485.
36. Macias WL, Mueller BA, Scarim SK. Vancomycin pharmacokinetics in acute renal failure: Preservation of nonrenal clearance. *Clin Pharmacol Ther*. 1991;50:688–694.
37. Mueller BA, Scarim SK, Macias WL. Comparison of imipenem pharmacokinetics in patients with acute or chronic renal failure treated with continuous hemofiltration. *Am J Kidney Dis*. 1993;21:172–179.
38. Vilay AM, Churchwell MD, Mueller BA. Drug metabolism and clearance

in acute kidney injury. *Crit Care*. 2008;12:235.

39. Nolin TD, Appiah K, Kendrick SA, et al. Hemodialysis acutely improves hepatic CYP3A4 metabolic activity. *J Am Soc Nephrol*. 2006;17:2363–2367.
40. Dowling TC, Briglia AE, Fink JC, et al. Characterization of hepatic cytochrome P4503A activity in patients with end-stage renal disease. *Clin Pharmacol Ther*. 2003;73:427–434.
41. Nolin TD, Frye RF, Le P, et al. ESRD impairs nonrenal clearance of fexofenadine but not midazolam. *J Am Soc Nephrol*. 2009;20:2269–2276.
42. Osborne R, Joel S, Grebenik K, et al. The pharmacokinetics of morphine and morphine glucuronides in kidney failure. *Clin Pharmacol Ther*. 1993;54:158–167.
43. Szeto HH, Inturrisi CE, Houde R, et al. Accumulation of normeperidine, an active metabolite of meperidine, in patients with renal failure of cancer. *Ann Intern Med*. 1977;86:738–741.
44. Bazinet A, Almanric K, Brunet C, et al. Dosage of enoxaparin among obese and renal impairment patients. *Thromb Res*. 2005;116:41–50.
45. Hulot JS, Vantelon C, Urien S, et al. Effect of renal function on the pharmacokinetics of enoxaparin and consequences on dose adjustment. *Ther Drug Monit*. 2004;26:305–310.
46. Ambrose PG, Bhavnani SM, Rubino CM, et al. Pharmacokinetics-pharmacodynamics of antimicrobial therapy: It's not just for mice anymore. *Clin Infect Dis*. 2007;44:79–86.
47. Fish DN, Kiser TH. Correlation of pharmacokinetic/pharmacodynamic-derived predictions of antibiotic efficacy with clinical outcomes in severely ill patients with Pseudomonas aeruginosa pneumonia. *Pharmacotherapy*. 2013;33:1022–1034.
48. Nyman HA, Dowling TC, Hudson JQ, et al. Comparative Evaluation of the Cockcroft-Gault Equation and the Modification of Diet in Renal Disease (MDRD) Study Equation for Drug Dosing: An Opinion of the Nephrology Practice and Research Network of the American College of Clinical Pharmacy. *Pharmacotherapy*. 2011;31:1130–1144.
49. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31–41.
50. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. *Ann Intern Med*. 1999;130:461–470.

51. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
52. Dowling TC, Matzke GR, Murphy JE, Burckart GJ. Evaluation of renal drug dosing: Prescribing information and clinical pharmacist approaches. *Pharmacotherapy*. 2010;30:776–786.
53. Steffl JL, Bennett W, Olyaei AJ. The old and new methods of assessing kidney function. *J Clin Pharmacol*. 2012;52:63S–71S.
54. Wargo KA, Eiland EH, Hamm W, et al. Comparison of the modification of diet in renal disease and Cockcroft-Gault equations for antimicrobial dosage adjustments. *Ann Pharmacother*. 2006;40:1248–1253.
55. Gill J, Malyuk R, Djurdjev O, et al. Use of GFR equations to adjust drug doses in an elderly multi-ethnic group: A cautionary tale. *Nephrol Dial Transpl*. 2007;22:2894–2899.
56. Golik MV, Lawrence KR. Comparison of dosing recommendations for antimicrobial drugs based on two methods for assessing kidney function: Cockcroft–Gault and modification of diet in renal disease. *Pharmacotherapy*. 2008;28:1125–1132.
57. Melloni C, Peterson ED, Chen AY, et al. Cockcroft-Gault versus modification of diet in renal disease: Importance of glomerular filtration rate formula for classification of chronic kidney disease in patients with non–ST-segment elevation acute coronary syndromes. *J Am Coll Cardiol*. 2008;51:991–996.
58. Hermsen ED, Maiefski M, Florescu MC, et al. Comparison of the modification of diet in renal disease and Cockcroft–Gault equations for dosing antimicrobials. *Pharmacotherapy*. 2009;29:649–655.
59. Wargo KA, English TM. Evaluation of the chronic kidney disease epidemiology collaboration equation for dosing antimicrobials. *Ann Pharmacother*. 2010;44:439–446.
60. Stevens LA, Nolin TD, Richardson MM, et al. Comparison of drug dosing recommendations based on measured GFR and kidney function estimating equations. *Am J Kidney Dis*. 2009;54:33–42.
61. Rule AD, Bailey KR, Lieske JC, et al. Estimating the glomerular filtration rate from serum creatinine is better than from cystatin C for evaluating risk factors associated with chronic kidney disease. *Kidney Int*. 2013;83:1169–1176.
62. Shlipak MG, Matsushita K, Ärnlöv J, et al. Cystatin C versus creatinine in determining risk based on kidney function. *N Engl J Med*. 2013;369:932–

943.

63. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med*. 2012;367:20–29.
64. Schmitt A, Gladieff L, Lansiaux A, et al. A universal formula based on cystatin C to perform individual dosing of carboplatin in normal weight, underweight, and obese patients. *Clin Cancer Res*. 2009;15:3633–3639.
65. Viberg A, Lannergård A, Larsson A, et al. A population pharmacokinetic model for cefuroxime using cystatin C as a marker of renal function. *Br J Clin Pharmacol*. 2006;62:297–303.
66. Hoppe A, Séronie-Vivien S, Thomas F, et al. Serum cystatin C is a better marker of topotecan clearance than serum creatinine. *Clin Cancer Res*. 2005;11:3038–3044.
67. US Food Drug Administration. Guidance for industry: Pharmacokinetics in patients with impaired renal function—study design, data analysis and impact on dosing and labelling 1998. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInfc Accessed November 2, 2018.
68. European Medicines Agency. 2014 Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function. Available at: https://www.ema.europa.eu/documents/scientific-guideline/guideline-evaluation-pharmacokinetics-medicinal-products-patients-decreased-renal-function_en.pdf. Accessed November 2, 2018.
69. US Food Drug Administration. Guidance for industry: Pharmacokinetics in patients with impaired renal function—study design, data analysis and impact on dosing and labelling 2010. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInfc Accessed November 2, 2018.
70. Tortorici MA, Cutler D, Zhang L, et al. Design, conduct, analysis, and interpretation of clinical studies in patients with impaired kidney function. *J Clin Pharmacol*. 2012;52:109S–118S.
71. Tortorici MA, Cutler DL, Hazra A, et al. Emerging areas of research in the assessment of pharmacokinetics in patients with chronic kidney disease. *J Clin Pharmacol*. 2015;55:241–250.
72. Matzke GR, Aronoff GR, Atkinson AJ Jr, et al. Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2011;80:1122–1137.

73. AHFS Clinical Drug Information. Bethesda, MD: American Society of Health-System Pharmacists, Inc. Available at: http://www.ahfsdruginformation.com. Accessed April 29, 2019.
74. Joint Formulary Committee. *British National Formulary*. 64th ed. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2004.
75. Aronoff GR, Bennett WM, Berns JS, et al. *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children*. 5th ed. Philadelphia, PA: American College of Physicians-American Society of Internal Medicine; 2007.
76. The Renal Drug Handbook. 4th ed. CRC Press [Internet]. Available at: http://renaldrugdatabase.com. Accessed April 29, 2019.
77. Lexicomp Online. Wolters Kluwer Clinical Drug Information, Inc [Internet]. Available at: https://www.wolterskluwercdi.com/lexicomp-online/. Accessed April 29, 2019.
78. IBM Micromedex. Truven Health Analytics, Inc [Internet]. Available at: https://www.micromedexsolutions.com/. Accessed April 29, 2019.
79. Hilal-Dandan R, Brunton L. *Goodman and Gilman Manual of Pharmacology and Therapeutics*. 2nd ed. New York, NY: McGraw Hill Medical; 2014.
80. Mountford CM, Lee T, de Lemos J, et al. Quality and usability of common drug information databases. *Can J Hosp Pharm*. 2010;63:130.
81. Vidal L, Shavit M, Fraser A, et al. Systematic comparison of four sources of drug information regarding adjustment of dose for renal function. *BMJ*. 2005;331:263–266.
82. Dettli LC. Drug dosage in patients with renal disease. *Clin Pharmacol Ther*. 1974;16:274–280.
83. Matzke GR, Clermont G. Clinical pharmacology and therapeutics. In: Murray PT, Brady HR, Hall JB, eds. *Intensive Care in Nephrology*. Boca Raton, FL: Taylor & Francis,. 2006:245–265.
84. Eyler RF, Mueller BA. Antibiotic pharmacokinetic and pharmacodynamic considerations in patients with kidney disease. *Adv Chronic Kidney Dis*. 2010;17:392–403.
85. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis*. 1998:1–10.
86. Kushner JM, Peckman HJ, Snyder CR. Seizures associated with

fluoroquinolones. *Ann Pharmacother*. 2001;35:1194–1198.

87. Udy AA, Varghese JM, Altukroni M, et al. Subtherapeutic initial β-lactam concentrations in select critically ill patients: Association between augmented renal clearance and low trough drug concentrations. *CHEST Journal*. 2012;142:30–39.
88. Claus BOM, Hoste EA, Colpaert K, et al. Augmented renal clearance is a common finding with worse clinical outcome in critically ill patients receiving antimicrobial therapy. *J Crit Care*. 2013;28:695–700.
89. Hobbs AL, Shea KM, Roberts KM, et al. Implications of augmented renal clearance on drug dosing in critically ill patients: A focus on antibiotics. *Pharmacotherapy*. 2015;35:1063–1075.
90. Janknegt R, Nube MJ. A simple method for predicting drug clearances during CAPD. *Perit Dial Int*. 1985;5:254–255.
91. Maher JF. Influence of continuous ambulatory peritoneal dialysis on elimination of drugs. *Perit Dial Int*. 1987;7:159–165.
92. Manley HJ, Bailie GR. Automated peritoneal dialysis symposium—treatment of peritonitis in APD: Pharmacokinetic principles. *Sem Dialysis*. 2002;15:418–421.
93. Taylor CA III, Abdel-Rahman E, Zimmerman SW, et al. Clinical pharmacokinetics during continuous ambulatory peritoneal dialysis. *Clin Pharmacokinet*. 1996;31:293–308.
94. Li PK, Szeto CC, Piraino B, et al. Peritoneal dialysis-related infections recommendations: 2010 Update. *Perit Dial Int*. 2010;30:393–423.
95. Matzke GR. Status of hemodialysis of drugs in 2002. *J Pharm Pract*. 2002;15:405–418.
96. Matzke GR. Buby J. Vancomycin. In: Murphy JE, ed. *Clinical Pharmacokinetics Pocket Reference*. 5th ed. Bethesda, MD: American Society of Hospital Pharmacists; 2011.
97. Launay-Vacher V, Izzedine H, Mercadal L, et al. Clinical review: Use of vancomycin in haemodialysis patients. *Crit Care*. 2002;6:313.
98. Rybak MJ, Lomaestro BM, Rotschafer JC, et al. Vancomycin therapeutic guidelines: A summary of consensus recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. *Clin Infect Dis*. 2009;49:325–327.
99. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the

Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. *Clin Infect Dis*. 2011;52:1–38.

100. Teigen MM, Duffull S, Dang L, et al. Dosing of gentamicin in patients with end-stage renal disease receiving hemodialysis. *J Clin Pharmacol*. 2006;46:1259–1267.
101. Mohamed OHK, Wahba IM, Watnick S, et al. Administration of tobramycin in the beginning of the hemodialysis session: A novel intradialytic dosing regimen. *Clin J Am Soc Nephrol*. 2007;2:694–699.
102. Zelenitsky SA, Ariano RE, McCrae ML, et al. Initial vancomycin dosing protocol to achieve therapeutic serum concentrations in patients undergoing hemodialysis. *Clin Infect Dis*. 2012;55:527–533.
103. Ariano RE, Fine A, Sitar DS, et al. Adequacy of a vancomycin dosing regimen in patients receiving high-flux hemodialysis. *Am J Kidney Dis*. 2005;46:681–687.
104. Kamata H, Asano K, Soejima K, et al. Appropriate hemodialysis scheduling based on therapeutic drug monitoring of carboplatin in a patient with lung cancer and chronic renal failure. *Gan To Kagaku Ryoho*. 2009;36:1529–1532.
105. Oguri T, Shimokata T, Inada M, et al. Pharmacokinetic analysis of carboplatin in patients with cancer who are undergoing hemodialysis. *Cancer Chemother Pharmacol*. 2010;66:813–817.
106. Haubitz M, Bohnenstengel F, Brunkhorst R, et al. Cyclophosphamide pharmacokinetics and dose requirements in patients with renal insufficiency. *Kidney Int*. 2002;61:1495–1501.
107. Koolen SL, Huitema AD, Jansen RS, et al. Pharmacokinetics of gemcitabine and metabolites in a patient with double-sided nephrectomy: A case report and review of the literature. *Oncologist*. 2009;14:944–998.
108. Kooistra MP. Frequent prolonged home haemodialysis: Three old concepts, one modern solution. *Nephrol Dial Transpl*. 2003;18:16–18.
109. Culleton BF, Walsh M, Klarenbach SW, et al. Effect of frequent nocturnal hemodialysis vs conventional hemodialysis on left ventricular mass and quality of life: A randomized controlled trial. *JAMA*. 2007;298:1291–1299.
110. Jefferies HJ, Virk B, Schiller B, et al. Frequent hemodialysis schedules are associated with reduced levels of dialysis-induced cardiac injury (myocardial stunning). *Clin J Am Soc Nephrol*. 2011;6:1326–1332.

111. Johansen KL, Zhang R, Huang Y, et al. Survival and hospitalization among patients using nocturnal and short daily compared to conventional hemodialysis: A USRDS study. *Kidney Int*. 2009;76:984–990.
112. Pauly RP, Gill JS, Rose CL, et al. Survival among nocturnal home haemodialysis patients compared to kidney transplant recipients. *Nephrol Dial Transpl*. 2009;24:2915–2919.
113. Law V, Walker S, Dresser L, et al. Optimized dosing of cefazolin in patients treated with nocturnal home hemodialysis. *Am J Kidney Dis*. 2014;64:479–480.
114. FHN. Trial Group. In-center hemodialysis six times per week versus three times per week. *N Engl J Med*. 2010;363:2287–2300.
115. Culleton BF, Asola MR. The impact of short daily and nocturnal hemodialysis on quality of life, cardiovascular risk and survival. *J Nephrol*. 2011;24:405.
116. Palmer K, Walker S, Jassal V, et al. Pharmacokinetic study of cefazolin in short daily hemodialysis. *Ann Pharmacother*. 2019;53:348–356.
117. van Dijk EA, Drabbe NRG, Kruijtbosch M, et al. Drug dosage adjustments according to renal function at hospital discharge. *Ann Pharmacother*. 2006;40:1254–1260.

66

Disorders of Sodium and Water Homeostasis

Katherine H. Chessman and Jason S. Haney

KEY CONCEPTS

1. Blood volume and serum osmolality are essential for normal cellular function and are tightly regulated in the human body. Simply put, water balance determines serum sodium concentration, and sodium balance determines volume status.
2. Total body water (TBW) ranges from 45% to 60% of body weight depending on sex and age and is distributed primarily into two compartments: the intracellular compartment or intracellular fluid (ICF; two-thirds [67%] of TBW) and the extracellular compartment or extracellular fluid (ECF; one-third [33%] of TBW).
3. Arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), is synthesized in the hypothalamus and secreted by the posterior pituitary in response to both osmotic and nonosmotic regulators.
4. Hyponatremia, defined as a serum sodium concentration less than 135 mEq/L (mmol/L), is the most common electrolyte abnormality encountered in clinical practice in both adults and children affecting 3 to 6 million persons and 1 million hospitalized patients yearly.
5. Hyponatremia is predominantly the result of an excess of extracellular water relative to sodium because of impaired water excretion.
6. Hypovolemic hypotonic hyponatremia is common in patients taking thiazide diuretics.
7. Euvolemic (isovolemic) hypotonic hyponatremia is associated with a normal or slightly decreased ECF sodium content and increased TBW and ECF volume. Euvolemic hyponatremia is most often caused by the

syndrome of inappropriate ADH secretion (SIADH).

8. Hyponatremia with ECF volume expansion (hypervolemia) occurs in conditions in which sodium and water excretion is impaired. Patients with heart failure (HF), cirrhosis, or nephrotic syndrome have an expanded ECF volume and edema but a decreased effective arterial blood volume.
9. The brain's adaptation to chronic serum hypoosmolality or hyperosmolality leads to neurologic symptoms when either hyponatremia (hypoosmolality) or hypernatremia (hyperosmolality) is corrected too rapidly.
10. Hypernatremia, defined as a serum sodium concentration greater than 145 mEq/L (mmol/L), is always associated with hypertonicity and intracellular dehydration, resulting from a water deficit relative to ECF sodium content.
11. Edema, defined as a clinically detectable increase in interstitial fluid volume, is usually due to heart, kidney, or liver failure, or a combination of these conditions, although it can develop with a rapid decrease in serum albumin concentration along with excess fluid intake such as seen in the setting of burns or trauma.

Preclass Engaged Learning Activity

Visit the National Institute of Diabetes and Digestive and Kidney Diseases website and review the information provided under the topic Diabetes Insipidus at https://www.niddk.nih.gov/health-information/kidney-disease/diabetes-insipidus. In particular, review the information in the section titled "How is fluid regulated in the body?" This website is useful to enhance student understanding of water regulation with application to diabetes insipidus (DI).

INTRODUCTION

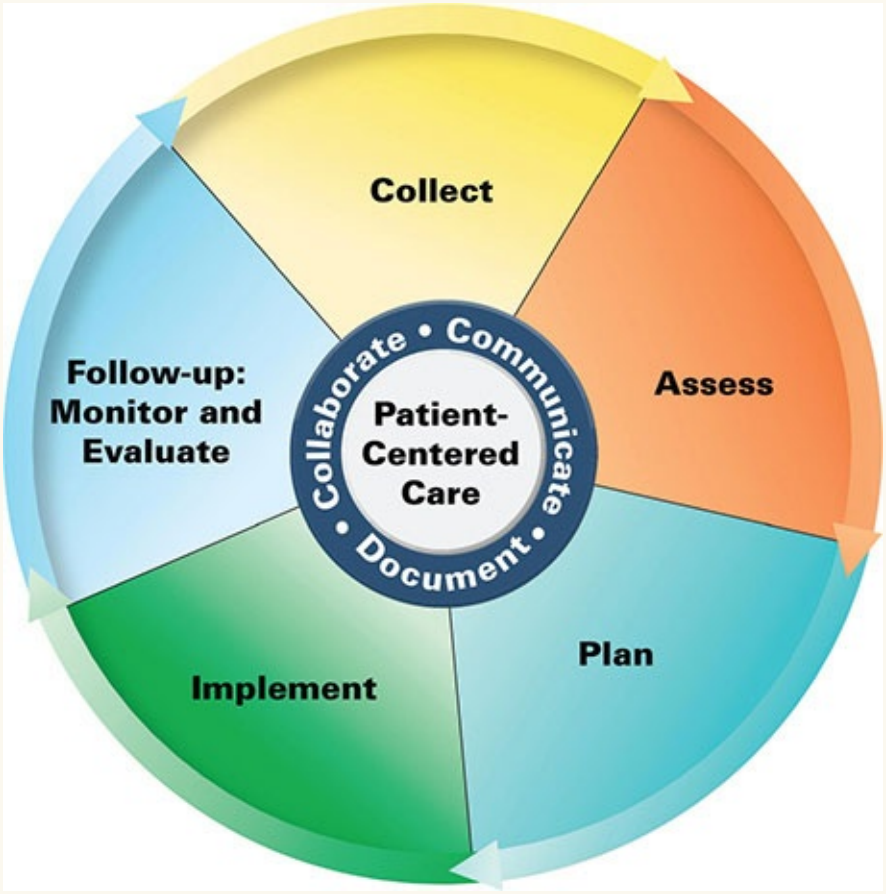
1. Blood volume and serum osmolality are essential for normal cellular function and are tightly regulated in the human body. Simply put, water balance determines serum sodium concentration, and sodium balance determines volume status. Adequate blood volume is required for effective tissue perfusion which is required to deliver oxygen and nutrients to and remove metabolic waste products from tissues. Serum osmolality, determined primarily by the serum sodium

concentration, is an important determinant of intracellular fluid (ICF) volume. Maintaining normal ICF volume in the brain is particularly critical, which is 80% water, and where alterations, especially rapid changes, can result in significant dysfunction, and even death.

Homeostatic mechanisms for controlling blood volume focus on controlling sodium balance, and, in contrast, homeostatic mechanisms for controlling serum osmolality (serum sodium concentration) focus on controlling water balance. Disorders of sodium and water balance are common, caused by a variety of diseases, conditions, and drugs, and potentially serious. This chapter reviews the etiology, pathophysiology, clinical presentation, and treatment options for disorders of sodium and water homeostasis.

SODIUM AND WATER HOMEOSTASIS

The average daily sodium intake of Americans consuming a typical western diet usually exceeds the tolerable upper limit established by the US Department of Agriculture: adults and children older than 13 years, 2.3 g; 9 to 13 years, 2.2 g; 4 to 8 years, 1.9 g; 1 to 3 years, 1.5 g; and infants and young children, 0.12 to 1.2 g.[1] Excessive sodium intake is a major risk factor for hypertension as blood pressure rises with increased sodium intake. Appropriately functioning kidneys excrete excess sodium to maintain the serum sodium concentration and osmolality within a very tight range. The kidney can also conserve sodium during periods of low-sodium intake or in the presence of excessive losses. Both hypo- and hypernatremia are conditions of altered serum tonicity and cell volume that reflect a change in the ratio of total exchangeable body sodium to total body water (TBW).



Patient Care Process for the Management of Disorders of Sodium and Water Homeostasis

Collect

- Patient characteristics (eg, age, sex, pregnant
- Patient history (past medical, diet, recent GI losses, see Tables 66-2 and 66-7)
- Current medications (eg, diuretics, IV fluids, Na-containing treatments; see Tables 66-3 and 66-8)
- Objective data
  - Body weight (current and historical) and recent intake/output
  - ECF volume status (eg, BP, mucous membranes, skin turgor, cardiopulmonary examination, and level of consciousness; see Figs. 66-1 and 66-3)

- Labs (eg, serum Osm, electrolytes, glucose, protein, lipids; urine Osm, Na, and K; and thyroid function tests)

Assess

- Chronicity and severity of the disorder
- Potential causative underlying disorders (eg, diarrhea, CNS disorders, pulmonary disease, cirrhosis, nephrotic syndrome, polydipsia, diabetes insipidus; see Tables 66-2 and 66-7)
- Dysregulated Na- or fluid-related complications (eg, BP variations, CNS changes, edema; see Clinical Presentation boxes and Tables 66-2 and 66-7)
- Current medications that may affect or worsen the disorder (see Tables 66-2, 66-3, 66-7, and 66-8)
- Goals for Na and/or volume status and achievement of the goals

Plan*

- Treat the underlying cause of the disorder, if possible
- Develop a drug therapy regimen including specific drug(s), dose, route, frequency, and duration (see Tables 66-4 to 66-6, 66-9 to 66-12; Figs. 66-4 to 66-6)
- Balance the risks of the underlying disorder versus the risk of rapid overcorrection (see Table 66-4)
- Specify the continuation and discontinuation of existing therapies
- Tailor dietary modifications (eg, water and solute intake) and weight management
- Create monitoring parameters including efficacy (eg, Na, volume status, urine output), safety (rate of Na correction, medication-specific adverse effects), and time frame
- Determine the need for renal replacement therapy based on severity of disorder and kidney function
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug therapy)
- Self-monitoring of volume status and weight
- Referrals to other providers when appropriate (eg, physician, dietician)

Implement*

- Provide patient education regarding all elements of treatment plan
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Attainment of Na and/or volume status goals
- Presence of adverse effects
- Need for long-term management (ie, underlying disorder cannot be corrected)
- Patient adherence to treatment plan using multiple sources of information

* *Collaborate with patient, caregivers, and other healthcare professionals.*

2 TBW ranges from 45% to 60% of body weight depending on sex and age and is distributed primarily into two compartments: the intracellular compartment or intracellular fluid (ICF; two-thirds [67%] of TBW) and the extracellular compartment or extracellular fluid (ECF; one-third [33%] of TBW). The serum (plasma) volume is approximately 17% of the ECF volume. Sodium contributes more than 90% of the ECF osmolality; whereas ICF osmolality is primarily determined by the ICF potassium concentration. The intra- and extracellular sodium and potassium concentrations are maintained by the sodium–potassium–adenosine triphosphatase (Na^+-K^+-ATPase) pump. Because most cell membranes are freely permeable to water, the free flow of water between compartments ensures that the ICF and ECF osmolalities remain equal.

Effective osmoles are solutes that cannot freely cross cell membranes, such as sodium and potassium, which are kept in their respective compartments by the Na^+-K^+-ATPase pump. The ECF concentration of effective osmoles determines its tonicity, which directly affects water distribution between the ECF and ICF. Addition of an isotonic solution (eg, 0.9% NaCl) to the ECF will result in no change in ICF volume because there will be no change in the effective ECF osmolality. However, addition of a hypertonic solution (eg, 3% NaCl) to the ECF will result in a decrease in ICF (cell) volume. Conversely, addition of a hypotonic solution (eg, 0.45% NaCl) to the ECF will result in an increase in ICF (cell) volume. Thus, administration of both hypertonic and hypotonic solutions can result in cell crenation or hemolysis, respectively. **Table 66-1** summarizes the composition and osmolality of commonly used intravenous (IV) solutions

and their expected distribution into the ICF and ECF compartments following administration.

TABLE 66-1 Composition of Common IV Solutions

Solution	Dextrose g/dL (kcal/L)	[Na^+] (mEq/L or mmol/L)	[K^+] (mEq/L or mmol/L)	[Cl^-] (mEq/L or mmol/L)	Other (mEq/L or mmol/L)	Osmolality (mOsm/kg or mmol/kg)	Tonicity	Distribution		
								% ECF	% ICF	Free water (mL/L)
Dextrose 5% in water	5 (170)	0	0	0	—	253	Hypotonic	33	67	1,000 mL
0.2% NaCl[a]	0	34	0	34	—	68	Hypotonic	50	50	750 mL
0.45% NaCl[b]	0	77	0	77	—	154	Hypotonic	67	33	500 mL
0.9% NaCl[c]	0	154	0	154	—	308	Isotonic	100	0	0 mL
Lactated Ringer's[d]	0	130	4	105	Lactate 28 Ca 4.8	273	Isotonic	97	3	0 mL
Plasma-Lyte A[e] Plasma-Lyte 148[e]	0.44 (21)	140	5	98	Acetate 27 Mg 3	294	Isotonic	100	0	0 mL
Normosol-R (pH 6.6) Normosol-R (pH 7.4)	0	140	5	98	Acetate 27 Mg 3	294	Isotonic	100	0	0 mL
3% NaCl[f]	0	513	0	513	—	1,026	Hypertonic	100	0	−2,331 mL

[a]Also referred to as *quarter normal saline.*

[b]Also referred to as *half normal saline.*

[c]Also referred to as *normal saline.*

[d]Also referred to as LR; also available commercially as Dextrose 5% LR.

[e]Plasma-Lyte A pH 7.4; Plasma-Lyte 148 pH 5.5.

[f]Hypertonic solution; results in osmotic removal of water from the ICF.

One g/dL is equivalent to 0.1 g/L; One kcal/L is equivalent to 4.18 kJ/L; Ca, calcium; Cl^-, chloride; ECF, extracellular fluid; ICF, intracellular fluid; IV, intravenous; K^+, potassium; Mg, magnesium; NA, not applicable; Na^+, sodium; NaCl, sodium chloride.

Edelman's equation (simplified) defines serum sodium (Na_S) as a function of the total exchangeable sodium and potassium in the body and the TBW:

$$Na_S = Na_{\text{total body}} + K_{\text{total body}} / TBW,$$

where $Na_{\text{total body}}$ is the total body sodium content; $K_{\text{total body}}$ is the total body potassium content; and TBW is the total body water in liters.[2,3] The serum

sodium concentration (135-145 mEq/L [mmol/L]) is tightly regulated and thus usually varies by no more than 3%. Serum sodium regulation occurs via mechanisms that control serum osmolality and blood volume. The kidney regulates water excretion through a hypothalamic feedback mechanism, such that the serum osmolality remains relatively constant (275-290 mOsm/kg [mmol/kg]) despite day-to-day variations in water intake. While serum osmolality is primarily determined by the sodium concentration, abnormally high glucose and blood urea nitrogen (BUN) concentrations may contribute significantly. Glucose is an effective osmole, but BUN is not; thus, the results of elevated osmolality due to these two substances will have differing effects. Serum osmolality can be estimated as:

$$\text{Osm}_s = (2 \times \text{Na}_s) + (\text{glucose}_s/18) + (\text{BUN}/2.8),$$

where Osm_S is the serum osmolality in mOsm/kg; Na_S is the serum sodium concentration in mEq/L; glucose_S is the serum glucose concentration in mg/dL; BUN is the blood urea nitrogen concentration in mg/dL; and 18 and 2.8 are the factors needed to convert from a weight measurement (mg/dL) to a concentration (mmol/L) for glucose and BUN, respectively. Thus, when using SI units, the equation becomes:

$$\text{Osm}_s = (2 \times \text{Na}_s) + \text{glucose}_s + \text{BUN},$$

where Osm_S is the serum osmolality in mmol/kg; and Na_S, glucose_S, and BUN are the respective concentrations in mmol/L.

3 Arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), is synthesized in the hypothalamus and secreted by the posterior pituitary in response to both osmotic and nonosmotic regulators to maintain water balance. When the serum osmolality increases by as little as 1% to 2%, AVP is released and binds to the arginine vasopressin 2 (V_2) receptor, a G protein-coupled receptor, on the basolateral surface of renal collecting duct cells, resulting in the insertion of water channels (aquaporin 2, AQP2) into both the apical cell membrane of the collecting duct principal cells and intracellular vesicles below the apical membrane increasing permeability.[3,4] Water can then pass through the cell into the peritubular capillary space where it is reabsorbed into the systemic circulation. AVP release also stimulates thirst as an additional means to return serum osmolality toward normal. The combined effect of increased water intake (response to thirst) and decreased water excretion (kidney's response to AVP)

results in a decrease in the serum osmolality. Once the serum osmolality is restored to normal, AVP secretion is inhibited, AQP2 water channels are retrieved, and water permeability returns to the usual low state.[4] Once serum osmolality decreases, AVP secretion is inhibited, and renal excretion of solute-free water (aquaresis) occurs.

While AVP secretion is regulated primarily by osmolality, nonosmotic AVP release occurs when the brain's osmoreceptors detect as little as a 6% to 10% reduction in the effective circulating volume or arterial blood pressure. The effective circulating volume is the portion of the ECF responsible for organ perfusion. A decrease in the effective circulating volume (more accurately, the arterial blood pressure associated with that volume) activates arterial baroreceptors in the carotid sinus and glomerular afferent arterioles, resulting in stimulation of the renin–angiotensin system and increased angiotensin II synthesis. Angiotensin II stimulates both nonosmotic AVP release and thirst. This nonosmotic volume stimulus can override osmotic AVP inhibition. Water conservation then restores the effective circulating volume and blood pressure at the expense of producing a decreased serum osmolality and hyponatremia.[3] Both hypo- and hypernatremia can be associated with either high, low, or normal ECF sodium or volume. To understand treatment options, differentiating between *dehydration* and *hypovolemia* is important. Dehydration refers to a loss of TBW producing hypertonicity while hypovolemia (volume depletion) is a symptomatic deficit in ECF volume. Often these terms are used interchangeably, but they are different processes requiring different types and rates of fluid replacement.[5]

HYPONATREMIA

Epidemiology and Etiology

4 Hyponatremia, defined as a serum sodium concentration less than 135 mEq/L (mmol/L), is the most common electrolyte abnormality encountered in clinical practice in both adults and children, affecting 3 to 6 million persons and 1 million hospitalized patients yearly.[6,7] Although the prevalence is not well established and varies with the patient population studied, it has been estimated to be 15% to 30% of hospitalized patients.[6,7] In one study, the prevalence of mild hyponatremia (serum sodium concentration less than 136 mEq/L [mmol/L]) in hospitalized patients was 42% (28% on admission, 14% during admission); 6.2% of patients evaluated (2.5% on admission, 3.7% during admission) had values less than 126 mEq/L (mmol/L); and 1.2% (0.5% on admission, 0.7% during

admission) had a serum sodium concentration less than 116 mEq/L (mmol/L).[8] The prevalence of hyponatremia in the intensive care unit (ICU) has been reported to be 30% to 40% with a sodium less than 130 mEq/L (mmol/L) seen on admission in approximately 14%.[9] In hospital-based ambulatory care clinics and community clinics, the prevalence of hyponatremia (serum sodium concentration less than 136 mEq/L [mmol/L]) was reported to be 21% and 1.7% to 9.2%, respectively.[8,10] Drug-induced hyponatremia, especially that associated with thiazide diuretics[11,12] and psychotropic medications,[13,14] is common.

Advancing age is a risk factor for hyponatremia, independent of sex.[10,15,16] Residents in nursing homes have a twofold higher incidence of hyponatremia than that observed in age-matched, community-dwelling individuals. More than 75% of these hyponatremic episodes were precipitated by increased intake of hypotonic fluids either orally or through tube feedings or IV fluids.[17] Similarly, ingestion of excessive volumes of hypotonic fluids (water, sports drinks) has been identified as a key risk factor in the development of exercise-associated hyponatremia.[18] In one study, women runners had a threefold higher rate of hyponatremia; however, smaller body size and longer racing time, not sex, were the principal factors accounting for the increased incidence.[19]

Recognition of the high prevalence of hyponatremia is essential because this condition is associated with significant morbidity and mortality.[4,7,9,20–22] Even in asymptomatic patients, chronic hyponatremia has been associated with decreased cognitive function and an increased risk of falls, fractures, and bone loss, particularly in the elderly.[11,20,23–25] In patients with hyponatremia, transient or permanent brain dysfunction can result from either acute effects of hypoosmolality or too rapid correction of hypoosmolality.

5 Hyponatremia is predominantly the result of an excess of extracellular water relative to sodium because of impaired water excretion. The kidney normally has the capacity to excrete large volumes of dilute urine after ingestion of a water load. Nonosmotic AVP release, however, can lead to water retention and a decrease in the serum sodium concentration, despite a decrease in ECF and ICF osmolality. Causes of nonosmotic AVP release include hypovolemia and a decreased effective circulating volume (eg, chronic heart failure [HF], nephrotic syndrome, cirrhosis). The syndrome of inappropriate antidiuretic hormone secretion (SIADH), a common cause of hyponatremia, is associated with some cancers, especially small cell lung cancer and brain tumors, central nervous system (CNS) damage (eg, traumatic brain injury, meningitis), and certain lung conditions (eg, acute respiratory distress syndrome [ARDS], pneumonia,

tuberculosis).

Pathophysiology

Hyponatremia can be associated with normal, increased, or decreased serum osmolality, depending on its cause. **Figure 66-1** provides an algorithm for the assessment and treatment of patients with hyponatremia.[2,6]

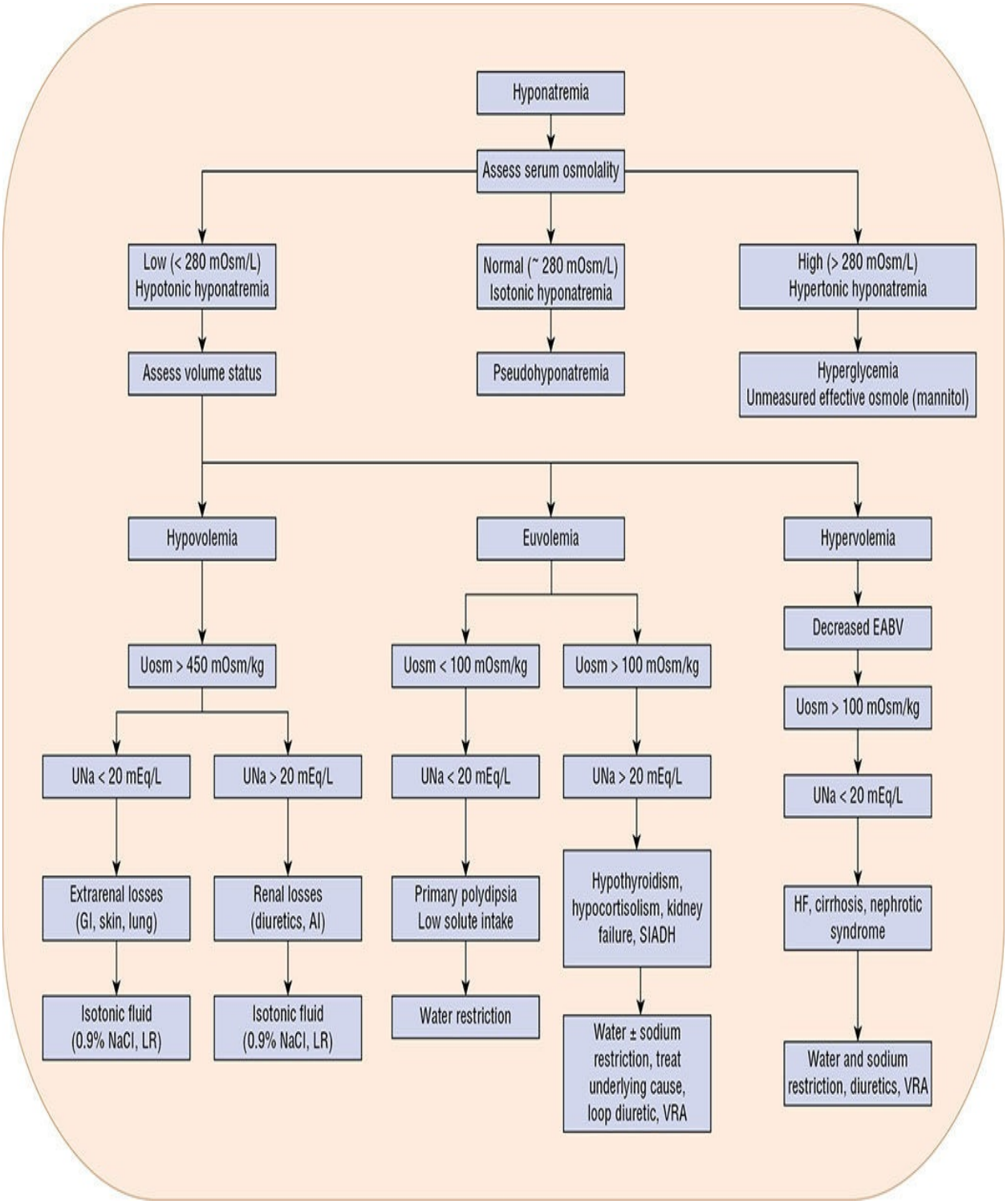


FIGURE 66-1 Algorithm for the assessment and treatment of hyponatremia. (AI, adrenal insufficiency; EABV, effective arterial blood volume; GI, gastrointestinal; HF, heart failure; LR, Lactated Ringers; NaCl, sodium chloride; SIADH, syndrome of inappropriate secretion of antidiuretic hormone; UNa, urine sodium concentration [values in mEq/L are numerically equivalent to

mmol/L]; UOsm, urine osmolality [values in mOsm/kg are numerically equivalent to mmol/kg]; VRA, vasopressin receptor antagonist.)

Isotonic Hyponatremia

Hyponatremia with a normal measured serum osmolality (Fig. 66-1) can be seen in the setting of markedly elevated serum lipids or proteins (eg, hyperproteinemia, multiple myeloma) when flame photometry is used to measure the sodium concentration. This *pseudohyponatremia* is an artifact because elevated lipids or proteins account for a larger than usual proportion of the total sample volume, reducing the percentage of water in the serum (**Fig. 66-2**). Because sodium is distributed in the water component only, the measured serum sodium concentration is falsely decreased. The measurement of serum osmolality is not affected, leading to a discrepancy between the calculated and measured serum osmolality. Pseudohyponatremia is not seen when the sodium concentration is measured via ion-selective electrodes as is most often done in current practice, because all serum samples are diluted and a constant distribution between water and the solid phase of serum is assumed when the serum sodium concentration is calculated. If the measurement of serum osmolality is not available, direct potentiometry using a blood gas analyzer will yield the true sodium concentration.[6]

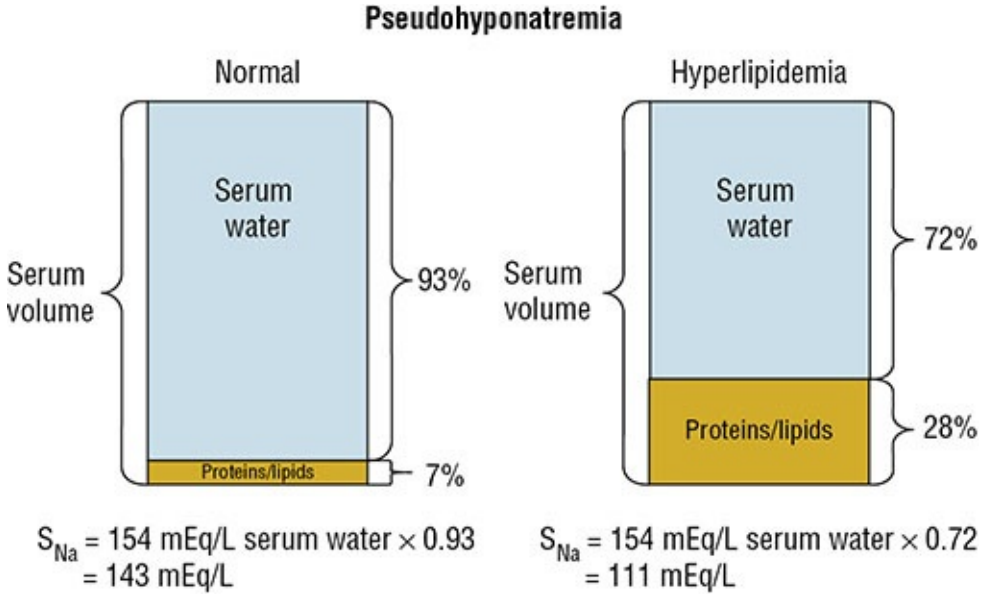


FIGURE 66-2 Elevated serum lipids or proteins result in a larger discrepancy between the volume of the sample and serum water, which leads to a falsely low measurement of the serum sodium concentration when using flame photometry. (S_{Na}, serum sodium concentration [values in mEq/L are numerically equivalent

to mmol/L].)

Hypertonic Hyponatremia

Hypertonic (increased serum osmolality) hyponatremia is due to the presence of excess effective osmoles (other than sodium) in the ECF (Fig. 66-1). Significant hyperglycemia is the most frequent cause. An elevated serum glucose concentration initially causes water diffusion from cells (ICF) into the ECF, thereby decreasing the ICF volume, expanding the ECF volume, and diluting the existing sodium resulting in hyponatremia. The increased ECF volume results in increased urine output (polyuria) which triggers the thirst mechanism (polydipsia). If the hyperglycemia is not corrected and/or extra fluid is not ingested, hypovolemia develops.

The volume of distribution (V_d) of glucose is a complex function of insulin activity, glucose distribution time, ECF volume, and glucose concentration. Using a clinically relevant glucose V_d of 0.3 to 0.5 L/kg, one would predict a 1.5 to 1.9 mEq/L (mmol/L; mean, 1.7 mEq/L [mmol/L]) decrease in the serum sodium concentration for every 100 mg/dL increase in the serum glucose concentration above 100 mg/dL (5.6 mmol/L) or 0.29 mmol/L decrease for every 1 mmol/L increase, and the serum osmolality will increase by 2 mOsm/kg (mmol/kg).[5,26] This correction is only a rough estimate because of the variability in the V_d of glucose. The presence of other effective osmoles (eg, mannitol) can also cause hypertonic hyponatremia. The presence of an unmeasured osmole should be suspected in patients with a normal glucose concentration and hypertonic hyponatremia when there is a significant osmolal gap, defined as the difference between the measured and calculated serum osmolalities.

Hypotonic Hyponatremia

Hypotonic (decreased osmolality) hyponatremia is the most common form of hyponatremia and has many potential causes (Table 66-1). Assessment of ECF volume status is important in the evaluation of a patient with hypotonic hyponatremia. Categorization into one of three groups (decreased, increased, or clinically normal ECF volume) is the essential first step in identifying the pathophysiologic mechanism(s) responsible for the hyponatremia and developing an appropriate treatment plan.

Hypovolemic Hypotonic Hyponatremia

Most patients with ECF volume contraction have lost fluids that are hypotonic

relative to the serum and thus may become transiently hypernatremic. This situation includes patients with fluid losses caused by diarrhea, excessive sweating, and diuretics. This transient hypernatremic hyperosmolality results in osmotic AVP release and thirst. If sodium and water losses continue, the resultant hypovolemia results in more AVP release. Patients who then drink water (a hypotonic fluid) or who are given hypotonic IV fluids retain water, and hyponatremia develops. These patients will typically have a concentrated urine (urine osmolality greater than 450 mOsm/kg [mmol/kg]), reflecting AVP action. The urine sodium concentration will be less than 20 to 30 mEq/L (mmol/L) when sodium losses are extrarenal (eg, diarrhea, vomiting), and greater than 20 to 30 mEq/L (mmol/L) with renal sodium losses (eg, thiazide diuretics, adrenal insufficiency).[20]

6 Hypovolemic hypotonic hyponatremia is common in patients taking thiazide diuretics.[6,11,12] Thiazide diuretic-induced hyponatremia is usually mild and relatively asymptomatic but can be severe. Hyponatremia typically develops within 2 weeks of diuretic initiation but can occur at any time during therapy, particularly after dosage increases or if other causes of hyponatremia are present.[6,27] Elderly women are at the greatest risk for thiazide diuretic–induced hyponatremia.[6,12,27]

Thiazide diuretic–induced hyponatremia is likely related to a balance of direct and indirect effects. These agents block sodium reabsorption in the distal tubules of the renal cortex, thereby increasing sodium and water removal from the body. The resultant decrease in effective circulating volume stimulates AVP release, resulting in increased free water reabsorption in the collecting duct, as well as increased water intake because of thirst stimulation. Hyponatremia develops when the net result of these effects is the loss of more sodium than water.

Conversely, hyponatremia occurs infrequently with loop diuretics due to their different site of action. Loop diuretics block sodium reabsorption in the ascending limb of the loop of Henle. This action decreases medullary osmolality; thus, when loop diuretic use decreases the effective circulating volume and stimulates AVP release, less water reabsorption occurs in the collecting ducts than would occur with normal medullary osmolality. Thiazide diuretics do not alter medullary osmolality because they act in the renal cortex. Additionally, most loop diuretics have a shorter half-life than thiazides, and patients usually replete the urinary sodium and water losses prior to taking the next dose, thereby minimizing AVP stimulation.[27]

Cerebral (renal) salt wasting syndrome is a condition observed most often in patients with intracranial disorders such as subarachnoid hemorrhage or

traumatic brain injury or after neurosurgical procedures, but it can occur in patients without CNS pathology. It results in decreased ECF volume due to a profound natriuresis (urinary sodium loss). A very high urine sodium, osmolality, and volume; high serum BUN; orthostatic hypotension; and low central venous pressure suggest cerebral salt wasting rather than SIADH.[6,20,28] Treatment consists of IV volume repletion with 0.9% NaCl or oral administration of salt supplements and fludrocortisone until resolution of this typically transient condition. If serum sodium concentration is less than 120 mEq/L (mmol/L), 3% NaCl may be needed to correct the serum sodium concentration.[28]

Euvolemic Hypotonic Hyponatremia

7 Euvolemic (isovolemic) hypotonic hyponatremia is associated with a normal or slightly decreased ECF sodium content and increased TBW and ECF volume. Euvolemic hyponatremia is most often caused by SIADH. The increase in ECF volume is not sufficient to cause peripheral or pulmonary edema or other signs of volume overload, and thus patients will appear euvolemic upon physical examination.

In SIADH, water intake exceeds the kidney's capacity to excrete water, either because of increased AVP release via nonosmotic and/or nonphysiologic processes or enhanced sensitivity of the kidney to AVP. In most patients with SIADH, the urine osmolality and sodium concentrations will be greater than 100 mOsm/kg (mmol/kg) and 20 to 30 mEq/L (mmol/L), respectively, due to ECF volume expansion (see **Table 66-2**).[5]

TABLE 66-2 Characteristics of Hypotonic Hyponatremic States

Characteristics	Hypovolemic Hyponatremia	Euvolemic (Isovolemic) Hyponatremia	Hypervolemic Hyponatremia
Water and sodium	Sodium loss >> water loss	Water gain only	Water gain > sodium gain
Causes	Renal: thiazide diuretics	SIADH	Heart failure
	Nonrenal: diarrhea, cerebral salt-wasting		Liver cirrhosis
			Kidney failure
Effect on TBW	↓↓	↑	↑↑
Effect on TBNa	↓	↔	↑↑
Additional laboratory findings	Renal: UOsm high, UNa high	Renal: UOsm low, UNa variable	Renal: UOsm high, UNa high
	Nonrenal: UOsm high, UNa low	Nonrenal: UOsm high, UNa variable	
Clinical presentation	Orthostasis, hypotension, tachycardia, dry mucous membranes, CNS changes	Depends on severity of hyponatremia: seizures, lethargy	Peripheral and pulmonary edema, variable blood pressure
Treatment	0.9% NaCl until vital signs stable; *maintenance* fluids to continue fluid deficit replacement; sodium replacement if cerebral salt wasting; VRA contraindicated	Water restriction, demeclocycline, loop diuretics, VRA	Sodium and water restriction, loop diuretic, VRA

CNS, central nervous system; NaCl, sodium chloride; SIADH, syndrome of inappropriate antidiuretic hormone secretion; TBW, total body water; UNa, urine sodium; UOsm, urine osmolality; VRA, vasopressin receptor antagonist.

The most common causes of SIADH are certain cancers (eg, small cell lung, pancreatic, brain), CNS disorders (eg, head trauma, stroke, meningitis, pituitary surgery), and lung disease (eg, tuberculosis, pneumonia, abscess, acute respiratory distress syndrome).[6] Patients with kidney and adrenal insufficiency or hypothyroidism can also present with euvolemic hyponatremia. A number of drugs can cause SIADH by enhancing AVP release or its action on the kidney or by other mechanisms[14,15,29] (**Table 66-3**). The evaluation of a patient with suspected SIADH should include consideration of these disorders or drugs.

TABLE 66-3 Potential Causes of SIADH

Drug-Induced		Nondrug-Induced
Barbiturates	Nicotine	Malignancy (lung, pancreatic, duodenal)
Bromocriptine	Opioids	CNS (trauma, tumor, meningitis, hemorrhage, stroke)
Carboplatin	Phenothiazines	Pulmonary (pneumonia, ARDS, TB)
Cisplatin	Thioridazine	Postoperative state
Clofibrate	Thiothixene	Nausea
Haloperidol	Tricyclic antidepressants	Anxiety
Monoamine oxidase inhibitors		
Increased sensitivity to ADH		
Acetaminophen	NSAIDs	
AVP analogs (desmopressin)	Oxytocin	
Lamotrigine	Tolbutamide	
Mixed or uncertain mechanism		
ACE inhibitors	Moxifloxacin	
Carbamazepine	Omeprazole	
Chlorpropamide	SSRIs	
Cyclophosphamide	Vinca alkaloids	
Ecstasy		

ACE, angiotensin-converting enzyme; ARDS, acute respiratory distress syndrome; AVP, arginine vasopressin; CNS, central nervous system; NSAIDs, nonsteroidal anti-inflammatory drugs; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SSRIs, selective serotonin receptor inhibitors; TB, tuberculosis.

Euvolemic hypotonic hyponatremia may also be caused by primary or psychogenic polydipsia where more water (usually more than 20 L/day) is ingested than the kidneys can excrete as solute-free water. Unlike in SIADH, AVP secretion is suppressed, resulting in a urine osmolality less than 100 mOsm/kg (mmol/kg). The urine sodium is typically low (less than 15 mEq/L [mmol/L]) due to dilution.[4,14] Hyponatremia may develop even with more modest water intake in individuals who ingest very low-solute diets.

Hypervolemic Hypotonic Hyponatremia

8 Hyponatremia with ECF volume expansion (hypervolemia) occurs in conditions in which sodium and water excretion is impaired. Patients with HF,

cirrhosis, or nephrotic syndrome have an expanded ECF volume and edema but a decreased effective arterial blood volume. The decrease in the effective circulating blood volume results in renal sodium retention and eventual ECF volume expansion and edema. There is concomitant nonosmotic AVP stimulation and water retention in excess of sodium retention, which perpetuates hyponatremia.

CLINICAL PRESENTATION

Patients with chronic (lasting longer than 48 hours) mild hyponatremia (serum sodium concentration 125-134 mEq/L [mmol/L]) are usually asymptomatic, with hyponatremia often being discovered incidentally when serum electrolytes are measured for other reasons. Mild symptoms of hyponatremia frequently go unnoticed by both clinicians and patients.[30] Chronic, mild hyponatremia, however, has been associated with impairment of attention, posture, and gait, all of which contribute to a substantially increased fall risk.[23–25,31,32] Even "asymptomatic" patients, when formally tested, have impaired attention and gait to a degree that is comparable to symptoms seen with a blood alcohol level of 0.06% (13 mmol/L).[30]

Patients with moderate (serum sodium concentration 115-124 mEq/L [mmol/L]), severe (serum sodium concentration 110-114 mEq/L [mmol/L]), or rapidly developing hypotonic hyponatremia may present with a range of CNS symptoms resulting from hypoosmolality-induced brain cell swelling. Classic neurologic symptoms include nausea, malaise, headache, lethargy, restlessness, and disorientation. In severe cases, seizures, coma, respiratory arrest, brainstem herniation, and death can occur.

The presence and severity of symptoms depend on both the degree of the hyponatremia and the rate at which it develops. The degree of hyponatremia is important because serum osmolality decreases in direct proportion to the serum sodium concentration, and water movement into cells, including brain cells, increases as serum osmolality decreases. The rate of change of the serum osmolality is important because brain cells are not able to rapidly adjust intracellular osmolality to minimize cellular volume changes.[3,33,34] When decreased serum osmolality causes water movement into brain cells, inorganic Cl^- and K^+ and organic osmolytes (eg, taurine, glutamate, myoinositol) move out of the cells to decrease intracellular osmolality and minimize the intracellular water shift.[34] The components of this adaptive mechanism occur over different

time frames, with Cl^- and K^+ efflux occurring within minutes to hours and organic osmolyte efflux occurring within hours to days.[33,34] Thus, maximal compensation for decreased serum osmolality typically requires up to 48 hours, and acute changes in serum osmolality are more likely to cause symptoms. Concurrent respiratory failure and hypoxemia increase the risk of adverse neurologic outcomes because hypoxemia diminishes the brain's capacity to actively transport solute out of cells, leading to a higher incidence of cerebral edema.[33,34] Children and women tend to have poorer clinical outcomes. Older women (postmenopausal) with acute hypervolemic hypotonic hyponatremia were reported to have a 25-fold higher risk of death or permanent neurological damage than men.[35] Hyponatremia is an important risk factor for morbidity and mortality in patients with HF and cirrhosis.[4,20]

In addition to CNS symptoms, patients with hypovolemic hyponatremia present with signs and symptoms of hypovolemia, including dry mucous membranes, decreased skin turgor, tachycardia, decreased jugular venous pressure, hypotension, and orthostatic hypotension. The presence of these findings is often helpful in identifying hypovolemic hyponatremia.

CLINICAL PRESENTATION

Hyponatremia

General

- Severity of symptoms depends on the magnitude and rapidity of onset
- Too rapid correction can lead to severe neurologic symptoms

Symptoms

- Symptoms are primarily neurologic in nature
- Mild: may be asymptomatic; nausea, malaise, gait or cognitive disturbance
- Moderate: headache, lethargy, restlessness, disorientation
- Severe: seizures, coma, respiratory arrest, brainstem herniation, death
- Other symptoms depend on etiology: dry mucous membranes, tachycardia, hypotension, reduced or increased urine output

Laboratory tests

- Serum sodium concentration less than 135 mEq/L (mmol/L)
- Serum osmolality and urine sodium concentration variable depending on etiology
- Altered serum glucose or lipids or thyroid function in certain patients

9 The brain's adaptation to chronic serum hypoosmolality or hyperosmolality leads to neurologic symptoms when either hyponatremia (hypoosmolality) or hypernatremia (hypertonicity) is corrected too rapidly. The combination of the adaptive decrease in ICF osmolality and a rapid increase in ECF osmolality results in rapid and excessive water movement out of cells, including brain cells, and ICF volume depletion. Thus, too rapid correction of the serum sodium concentration can lead to an acute decrease in brain cell volume, which contributes to the pathogenesis of *osmotic demyelination syndrome* (ODS) or central pontine myelinolysis.[4,36] While demyelinated lesions identified on magnetic resonance imaging most often occur in the central pons, ODS can extend to extrapontine structures. Patients with ODS may develop hyperreflexia, para- or quadriparesis, parkinsonism, pseudobulbar palsy, *locked-in syndrome* (a condition in which a patient is aware and awake but cannot move or communicate verbally due to complete paralysis of nearly all voluntary muscles except for the eyes), or death in 1 to 7 days.[2,36] Patients with significant cerebral adaptation (eg, chronic serum sodium concentration less than 110 mEq/L [mmol/L]) are at highest risk of developing ODS because these patients have lower intracellular osmolalities at the initiation of therapy, and there is a greater decrease in brain cell volume when the serum osmolality is raised too rapidly.[36] Other conditions that increase the risk of ODS include alcoholism, liver failure, orthotopic liver transplantation, potassium depletion, and malnutrition. Thus, if the duration of hyponatremia is unknown, then it is generally safer to treat as if it is chronic rather than acute when developing an initial therapy plan.

TREATMENT: HYPONATREMIA

General guidelines for the treatment of patients with hyponatremia are shown in Table 66-4. Application of these principles to the treatment of various forms of hyponatremia is discussed in the following sections.

TABLE 66-4 General Guidelines for Treatment of Hyponatremia

- For both short- and long-term management, treat the underlying cause of hyponatremia.
- Appropriate treatment of hypotonic hyponatremia requires balancing the risks of hyponatremia vs the risk of ODS.
- Patients who acutely develop moderate-to-severe hyponatremia and/or patients who have severe symptoms are at greatest risk and potentially benefit most from more rapid correction of hyponatremia.
- Correction of hypovolemic hypotonic hyponatremia is usually best accomplished with 0.9% NaCl, as these patients have both sodium and water deficits.
- Active correction of euvolemic and hypervolemic hypotonic hyponatremia in patients who do not require rapid correction is usually best accomplished by water restriction. Demeclocycline, VRA, or 0.9% NaCl plus a loop diuretic can be used if the initial response to water restriction is not adequate.
- In patients with severe symptoms or severe hyponatremia, 3% NaCl (possibly combined with a loop diuretic) should initially be used to more rapidly correct the hyponatremia. A loop diuretic can be administered concurrently with 3% NaCl to enhance the serum sodium correction by increasing free water excretion.
- Long-term management will be required for patients in whom the underlying cause of hyponatremia cannot be corrected. Depending on the cause, water restriction, increasing sodium intake, and/or a VRA may be used.

NaCl, sodium chloride; ODS, osmotic demyelination syndrome; VRA, vasopressin receptor antagonist.

Desired Outcomes

Regardless of the type or cause of hyponatremia, treatment goals for all patients are to resolve the underlying cause of the sodium and ECF volume imbalance, if possible, and to safely correct the sodium and water derangements. The treatment plan depends on the underlying cause and symptom severity. Patients with acute onset hyponatremia with severe symptoms require more aggressive therapy to correct the hypotonicity. The initial treatment goal is to increase serum tonicity just enough to control severe symptoms which typically requires only a small increase (5%) in serum sodium concentration. Once severe symptoms have abated, then continued serum sodium correction should be achieved at a more controlled rate. Patients who are asymptomatic or who have only mild-to-moderate symptoms do not require rapid correction of the serum sodium concentration. While treatment is dictated by the underlying cause, in all cases the goal is to avoid an increase in the serum sodium concentration of more than 6 to 12 mEq/L (mmol/L) in 24 hours (0.5 mEq/L [mmol/L] per hour) or 18

mEq/L (mmol/L) in any 48-hour period.[2,4,6,20] When the duration of hyponatremia is unknown, a sodium correction rate of no more than 6 to 8 mEq/L (mmol/L) in 24 hours is prudent to avoid ODS.[2]

ACUTE OR SEVERELY SYMPTOMATIC HYPOTONIC HYPONATREMIA

A patient who has or is at high risk of experiencing severe symptoms caused by hyponatremia (serum sodium less than 110-115 mEq/L [mmol/L]) should receive a small amount of 3% NaCl (513 mEq/L [mmol/L]) until severe symptoms resolve.[2,3] While resolution of severe symptoms generally requires approximately a 5% increase in serum sodium concentration, some clinicians suggest that the initial safe target should be a serum sodium concentration of approximately 120 mEq/L (mmol/L).[17] The relative concentrations of urine sodium and potassium (osmotically effective urine cations) should be compared with those of the infusate in planning a treatment regimen for patients with hypotonic hyponatremia.

For the serum sodium concentration to increase after a NaCl infusion, the sodium concentration of the infusate must exceed the sum of the urinary sodium and potassium concentrations so that an effective net free-water excretion is produced.[6] In SIADH, the urinary concentration of osmotically effective cations often exceeds 154 mEq/L (sodium concentration of 0.9% NaCl); thus, 0.9% NaCl administration could worsen hyponatremia. These patients should be preferentially treated with 3% NaCl.[30] The relatively high urinary sodium concentration in patient with SIADH is due to ECF expansion, which minimizes sodium reabsorption along the nephron. When the urine osmolality exceeds 300 mOsm/kg (mmol/kg), it is advisable to administer an IV loop diuretic to increase solute-free water excretion and to prevent volume overload which can result from 3% NaCl administration. Intravenous furosemide 20 to 40 mg given every 6 hours or bumetanide 0.5 to 1 mg given every 2 to 3 hours for several doses is generally sufficient to prevent volume overload and to decrease the urinary concentration of osmotically active cations to less than 150 mEq/L (mmol/L). If intermittent loop diuretic doses are not sufficient to manage volume overload, then either IV furosemide 20 to 40 mg followed by a 10 to 40 mg/hr infusion or IV bumetanide 1 mg followed by a 0.5 to 2 mg/hr infusion can be used.

Patients with hypovolemic hypotonic hyponatremia should be treated initially with 0.9% NaCl. In contrast to SIADH, in these patients avid reabsorption of

sodium throughout the nephron occurs because the effective circulating blood volume is decreased. Thus, the urine sodium concentration usually will be less than 20 mEq/L (mmol/L), substantially less than the sodium content of 0.9% NaCl. While administration of 3% NaCl will correct hyponatremia, it will not correct the hypovolemia and should be reserved for patients with severe symptoms requiring rapid serum sodium correction.

Acute hypervolemic hypotonic hyponatremia is particularly problematic to manage because the sodium and volume needed to minimize the risk of cerebral edema or seizures can worsen already compromised liver, heart, or kidney function. These patients generally should be treated initially with 3% NaCl and fluid (water) restriction. Loop diuretic or arginine vasopressin receptor antagonist (VRA) therapy is often required to facilitate urinary free water excretion.

Determination of a NaCl Infusion Regimen

Multiple approaches can be used for determining an empiric NaCl infusion regimen for a patient with hyponatremia.[2,4,7] While several complex equations have been derived, improved outcomes have not been demonstrated using these equations. Pragmatically, 150 mL or 1 to 2 mL/kg of 3% NaCl can be infused over 20 minutes.[3,6] If symptoms do not resolve, then 100 mL or 1 mL/kg of 3% NaCl can be administered over 10 to 20 minutes every 30 minutes until symptoms resolve and/or the target serum sodium concentration is reached (usually 5-8 mEq/L [mmol/L] from baseline). Within the first hour, the serum sodium should not increase by more than 5 mEq/L (mmol/L). After relief of symptoms, 0.9% NaCl can be used to continue the sodium correction.

Another method is to calculate the sodium deficit, then replace one-third of the deficit in the first 6 hours and the remaining two-thirds over the following 24 to 48 hours or longer depending on the acuity of the serum sodium decrease. Sodium deficit can be calculated using the following equation:

$$\text{Na deficit (mEq or mmol)} = [(Na_D - Na_S) \times TBW],$$

where Na_D is the goal or desired serum sodium (usually no higher than 120 mEq/L [mmol/L] to avoid too rapid correction); Na_S is the patient's current serum sodium concentration; and TBW is the patient's current TBW calculated as shown in **Table 66-5**. Another approach is to estimate the change in serum sodium concentration resulting from the infusion of 1 L of 3% NaCl or 0.9%

NaCl. An example of this approach is shown in Table 66-5.

TABLE 66-5 Assessment and Treatment of Euvolemic Hyponatremia

Change in serum sodium concentration after an IV fluid bolus

$\Delta Na_s = (Na_{IV} - Na_s)/(TBW + volume_{IV})$

ΔNa_s, change in serum sodium concentration; Na_{IV}, sodium concentration of infusate (eg, 154 mEq/L [mmol/L] for 0.9% NaCl; 513 mEq/L [mmol/L] for 3% NaCl); Na_s, initial serum sodium concentration; TBW, total body water (L); and $volume_{IV}$, volume of infused fluid (L)

TBW can be estimated as:
- Term newborn infants: 0.7 L/kg × wt (kg); higher in premature infants depending on degree of prematurity
- Children and men younger than 70 years: 0.6 L/kg × wt (kg)
- Men older than 70 years and women younger than 70 years: 0.5 L/kg × wt (kg)
- Women older than 70 years: 0.45 L/kg × wt (kg)
- Dehydrated, older patients: 0.4 L/kg × wt (kg)
- where wt is the current body weight

Clinical Example

A 66-year-old man (weight, 70 kg [154 lb]; height, 178 cm [5 ft 10 in]) presents with nausea, headache, and confusion which developed over the past 3 days. Ten days ago, he began taking carbamazepine for trigeminal neuralgia. His serum sodium concentration on admission to the emergency department was 109 mEq/L (mmol/L). He is diagnosed with drug-induced SIADH.

Plan of Care

1. Discontinue carbamazepine (the likely etiology of his SIADH).
2. Admit to the hospital for correction of hyponatremia.
3. Increase the serum sodium concentration by no more than 6 to 12 mEq/L (mmol/L) during first 24 hours and no higher than 120 mEq/L (mmol/L); thus, the goal is to increase the sodium concentration by 11 mEq/L (mmol/L).
4. Due to degree of hyponatremia (less than 110 mEq/L [mmol/L]) and the presence of moderate-to-severe symptoms, give 3% NaCl.

Calculate the change in serum sodium after 1 L infusion of 3% NaCl

$$\Delta Na_s = (513\ mEq/L - 109\ mEq/L)/[(0.5\ L/kg \times 70\ kg) + 1\ L] = 11.2\ mEq/L \text{ or } 1.12\ mEq/100\ mL$$

(Note: In SI units, the calculation is the same using mmol/L rather than mEq/L.)

Infusion of 1 L of 3% NaCl will result in a 11.2 mEq/L (mmol/L) rise in the serum sodium concentration. An 11 mEq/L (mmol/L) increase is desired; thus, the appropriate infusion volume is 982 mL [(11 mEq/L/11.2 mEq/L) × 1,000 mL] or [(11 mmol/L/11.2 mmol/L) × 1,000 mL].

(Note: The approach to this calculation would be similar if 0.9% NaCl was used, except that for each 1 L infusion, the expected increase in serum sodium concentration would be only 1.25 mEq/L [mmol/L], and an infusion volume of approximately 8.8 L would be required to achieve the targeted serum sodium concentration.)

Treatment Plan

1. Moderate-to-severe symptoms: serum sodium concentration should be increased by approximately 1.5 mEq/L/hr (mmol/L/hr) over the first 2 to 4 hours of treatment for a total of 3 to 6 mEq/L [mmol/L] or until the symptoms have resolved. An initial infusion rate of 114 mL/hr for the first 2 to 4 hours is needed.
2. Check serum sodium concentration every 1 to 4 hours depending on rate of rise of serum sodium.
3. Once symptoms subside, continue infusion rate at approximately 23 to 31 mL/hr for the next 20 to 22 hours, to slowly correct hyponatremia. Monitor serum sodium concentration every 4 hours or more often if serum sodium is rapidly changing.

IV, intravenous; SIADH, syndrome of inappropriate antidiuretic hormone secretion; NaCl, sodium chloride.

Clinicians may disagree whether or not to administer 3% NaCl to patients

with symptomatic hypotonicity. An advantage of 3% NaCl is more rapid correction of serum sodium concentration with a smaller infusion volume. A disadvantage of 3% NaCl is a higher risk of too rapid correction of serum sodium concentration and ODS. Another disadvantage of 3% NaCl is its high osmolality (1026 mOsm/L) which can result in phlebitis and significant tissue damage with extravasation when given via a peripheral IV catheter. In one study, there was only a 7% complication rate with peripheral administration. Central line administration is preferred, but short-term peripheral administration is acceptable if the infusion rate is low and a relatively large peripheral IV catheter is used.[37] The use of 5% NaCl has been replaced by 3% NaCl due to these infusion issues. Some clinicians have suggested the use of 2% NaCl to avoid infusion-related issues, but this practice has not been evaluated in clinical trials. Fluid choice depends on the cause and the rapidity of development of the patient's hyponatremia as well as the relative risk of slower correction of the hyponatremia versus the development of ODS.

The appropriate infusion volume for a given patient can be estimated using the amount of fluid needed to provide the calculated sodium deficit or the desired proportion of the estimated change that would result from a 1-L infusion. The final step is to calculate an appropriate infusion rate for the calculated volume that will increase the serum sodium concentration by no more than 8 mEq/L (mmol/L) in 24 hours in high-risk patients and by 10 to 12 mEq/L (mmol/L) in 24 hours or 18 mEq/L (mmol/L) in 48 hours in others (see Table 66-5).[5] To minimize the risk of too rapid correction of hyponatremia, giving desmopressin (1-4 mcg) and free water replacement along with 3% NaCl may be considered in patients with severe hyponatremia until the serum sodium concentration reaches 128 mEq/L (mmol/L).[2,20]

Evaluation of Therapeutic Outcomes

Patients with severely symptomatic hypotonic hyponatremia should be admitted to the ICU or other setting that will allow frequent monitoring of CNS symptoms and volume status. Examination of the heart, lungs, and neurologic status should be performed frequently during the first 12 to 24 hours of therapy. The serum sodium concentration should be measured at least every 2 to 4 hours, and the urine sodium, potassium, and osmolality should be measured every 4 to 6 hours during the first 24 to 48 hours of therapy to allow timely infusion rate adjustment to avoid too rapid correction of the serum sodium concentration.[2]

NONEMERGENT HYPOVOLEMIC HYPOTONIC HYPONATREMIA

Most patients with hypovolemic hypotonic hyponatremia are either asymptomatic or have only mild-to-moderate symptoms and do not require rapid sodium correction. Many of these patients are at high risk of developing ODS if serum sodium correction occurs too rapidly because they have chronic hyponatremia and maximum compensation by the brain's osmotic adaptive mechanisms. Treatment should include correction of the underlying condition, if possible, and administration of 0.9% NaCl or other isotonic solution (eg, Lactated Ringers, Plasma-Lyte®, Normosol-R®) to correct the hypovolemia. These solutions will replace the existing sodium and water deficits while conveying a lower risk of too rapid sodium correction than 3% NaCl.

The ECF deficit can be estimated based on the patient's sex, age, and change in body weight. One method and an example of its use is shown in **Table 66-6**. If the patient's previous weight is not known, the ECF deficit can be roughly estimated based on clinical signs and symptoms. The presence of hyponatremia suggests an ECF deficit of 5% or more, whereas the presence of orthostatic hypotension suggests an ECF deficit of at least 10% to 15%. Administration of an isotonic solution would be optimal to correct the patient's ECF volume deficit because essentially 100% of it will remain in the ECF space (see Table 66-1). The overriding initial treatment goal is to restore effective circulating volume; thus, it may be necessary to administer an IV bolus (500-1000 mL in adults; 10-20 mL/kg in children) over a period of 1 hour or less or begin an IV infusion of the isotonic solution at 200 to 400 mL/hr (10-20 mL/kg/hr in children) until symptoms of hypovolemia improve. The infusion rate can then be decreased to 100 to 150 mL/hr (4-6 mL/kg/hr in children) so that the serum sodium concentration does not increase too rapidly. Fluids should be given rapidly enough and in sufficient quantity to restore and maintain adequate tissue perfusion without overloading the cardiovascular or pulmonary system.

TABLE 66-6 Assessment and Treatment of Hypotonic Hypovolemic Hyponatremia

Calculating ECF Deficit

$$\text{ECF deficit (mL)} = \text{ECF}_{\text{normal}} - \text{ECF}_{\text{current}}$$

where ECF volume = 0.33 × TBW

Clinical Example

A 75-year-old woman (usual weight, 50 kg [110 lb]; height, 168 cm [5 ft 6 in]) was started on hydrochlorothiazide 25 mg once daily 10 days ago for hypertension. She presents with complaints of mild nausea and dizziness when she stands up. Her current weight is 45 kg (99 lb). Upon physical examination she has dry mucous membranes and orthostatic hypotension. Her serum sodium concentration is 126 mEq/L (mmol/L).

Calculate the ECF deficit

$$\text{ECF deficit} = (50\,\text{kg} \times 0.4\,\text{L/kg} \times 0.33) - (45\,\text{kg} \times 0.4\,\text{L/kg} \times 0.33) = 660\,\text{mL}$$

(Note: TBW = 0.4 L/kg used because she is a dehydrated older patient; see Table 66-5)

Calculate the expected increase in the serum sodium after infusion of 1 L of 0.9% NaCl (see Table 66-1):

ΔNa_s with 1 L of infusate = [154 mEq/L – 126 mEq/L] / [(0.4 L/kg × 45 kg) + 1 L] = 1.47 mEq/L (mmol/L)

The patient's serum sodium concentration will be 127.5 mEq/L (mmol/L) following the infusion of 1 L 0.9% NaCl

Treatment goals

Restore effective circulating volume and correct serum sodium concentration

Treatment plan

1. Infuse 0.9% NaCl at 200-250 mL/hr until symptoms of hypovolemia improve, then decrease infusion to 150-200 mL/hr so that the serum sodium concentration increases by no more than 6-12 mEq/L (mmol/L) or 0.5-1 mEq/L/hr (mmol/L/hr) over the initial 24 hours. Rate depends on patient status.
2. Hold thiazide diuretic until volume status is restored.
3. Consider restarting diuretic at lower dose, for example, 12.5 mg once daily, if needed.

ECF, extracellular fluid; NaCl, sodium chloride; TBW, total body water.

It is important to recognize that once hypovolemia is corrected, the serum sodium will increase rapidly if the infusion rate is not adjusted appropriately.[2] When the ECF volume is restored, AVP secretion stops, and a rapid water diuresis can ensue, potentially resulting in a rapid increase in serum sodium. Estimating the patient's ECF deficit at the start of therapy may be helpful. If the serum sodium concentration is increasing at a rate greater than 0.5 mEq/L/hr (mmol/L/hr), the infusate can be changed to 0.45% NaCl, and the infusion rate

set to slow the rate of serum sodium increase. In general, 0.45% NaCl should not be infused alone as this hypoosmolar solution (154 mOsm/L) may result in red blood cell hemolysis. Most often, Dextrose 5%/0.45% NaCl is infused to provide a relatively isotonic solution (Dextrose 5% provides 250 mOsm/L to the solution). Potassium depletion or repletion can also affect hyponatremia and its correction. One mEq (mmol) of retained potassium equals 1 mEq (mmol) retained sodium; thus, if hypokalemia is corrected at the same time as hyponatremia, the serum sodium may increase more rapidly.[2]

Evaluation of Therapeutic Outcomes

Patients presenting with evidence of hypovolemia should be reexamined frequently during the initial few hours of therapy. Of note, the urine output will often lag behind during fluid resuscitation, so careful monitoring is critical, especially in patients with underlying heart, lung, or kidney dysfunction. The serum sodium concentration should be measured every 2 to 4 hours to allow timely adjustment of the rate and composition of IV fluids to avoid too rapidly increasing the serum sodium concentration. In patients with a history of HF or kidney insufficiency, 0.9% NaCl should be administered judiciously with frequent cardiopulmonary assessments so that the infusion rate can be adjusted at the earliest sign of pulmonary congestion.

NONEMERGENT EUVOLEMIC HYPOTONIC HYPONATREMIA

The fact that neurological performance is restored to normal with correction of even mild hyponatremia provides a rationale for maintaining the serum sodium concentration at 130 mEq/L (mmol/L) or higher, if possible. Long-term management will be required for patients in whom the underlying cause is not readily correctable.

Treatment of SIADH always involves restricting water and correcting the underlying cause (see Table 66-2). Drugs that could be contributing should be identified and discontinued, if possible. The primary treatment goal is to induce a negative water balance by restricting water intake to less than 1,000 to 1,200 mL/day so that insensible water losses (skin and lung, 900 mL/day) plus obligate urine (500 mL/day) and stool (200 mL/day) losses exceed water intake. Because approximately 850 mL of water per day is ingested in food, and an additional 350 mL are generated from oxidative processes, this degree of water restriction

should result in a negative water balance of several hundred milliliters per day. Further water restriction may be needed but adherence is difficult. An additional goal is to maintain the serum sodium concentration close to 130 mEq/L (mmol/L) to reduce CNS symptoms and avoid iatrogenic hypovolemia.

Patients with chronic SIADH who are unable to restrict water intake sufficiently to maintain an acceptable serum sodium concentration can be treated by increasing solute intake with NaCl supplementation and/or loop diuretic administration. NaCl supplements increase the obligatory daily solute excretion, which augments the kidney's capacity for water excretion. The goal is to increase the daily solute intake and excretion to approximately 900 mOsm (mmol) per day. Because an average diet contains approximately 600 mOsm (mmol), 9 g of NaCl would be required to increase the osmolar excretion to 900 mOsm/day (mmol/day). Each 1 g NaCl tablet contains 17 mmol of sodium and 17 mmol of chloride. Because ECF volume expansion is an expected adverse effect, a loop diuretic should be administered concurrently to avoid volume overload and edema. Loop diuretics will also enhance water excretion by limiting the formation of the medullary concentration gradient.

Demeclocycline

Demeclocycline, a semisynthetic tetracycline antibiotic, is a treatment option for some patients with SIADH whose serum sodium concentration is not adequately controlled by water restriction alone. Demeclocycline essentially causes nephrogenic diabetes insipidus by inhibiting tubular AVP activity, which increases free water excretion. Demeclocycline use in SIADH is largely based on clinical experience rather than data from clinical trials.[38] The usual demeclocycline dosage is 300 mg given orally two to four times daily. Because of the delayed onset of action (3-6 days), this agent has no role in the acute management of severe hyponatremia, and dosage adjustments should be made no more frequently than every 3 to 4 days. Demeclocycline should not be used in patients with liver disease or compromised fluid intake, who are at high risk for demeclocycline-induced renal tubular toxicity and acute kidney failure,[39] who are pregnant, or who are younger than 8 years unless no other options are available because long-term use may interfere with tooth and bone development.

Vasopressin Receptor Antagonists

Therapeutic options for SIADH were expanded with the introduction of the VRAs, also known as vaptans, which are high-affinity non-peptide antagonists

of arginine vasopressin V_2 and V_{1a} receptors.[40] VRAs have dramatic effects on water excretion and were the first significant breakthrough in hyponatremia treatment since loop diuretics. These agents also may be used to treat euvolemic and hypervolemic hypotonic hyponatremia.

Blockade of AVP binding can occur at any of its three distinct receptors: V_{1a}, predominantly in the liver, CNS, and cardiomyocytes; V_2, in the distal nephron; and V_{1b} (formerly V_3), in the anterior pituitary and pancreas.[40] Selective V_2 receptor antagonism prevents AQP2 water channel transport to the apical surface, thereby decreasing AVP-dependent water reabsorption in the collecting duct. AVP inhibition leads to excretion of large volumes of water, decreased urine osmolality, and an increase in the serum sodium concentration.[4] These outcomes are achieved without significantly increasing electrolyte excretion; thus, these agents have been called *aquaretics*. Only two VRAs are currently marketed in the United States, conivaptan and tolvaptan.

Conivaptan (Vaprisol®, Astellas Pharma US, Inc., Northbrook, IL), a mixed vasopressin V_1 and V_2 receptor antagonist, is FDA-labeled for use in the treatment of acute euvolemic and hypervolemic hyponatremia in hospitalized patients. Its utility in chronic hyponatremia is limited because it is only available as an IV formulation, is FDA-labeled for up to 4 days of use, is a moderate CYP3A4 inhibitor, and is not FDA-labeled for use in patients with HF.

Tolvaptan (Samsca®, Otsuka Pharmaceutical Co, Ltd, Tokyo, Japan) is an oral selective VRA with a greater affinity for the V_2 receptor than endogenous AVP. It is FDA-labeled for the treatment of clinically significant (serum sodium concentration less than 125 mEq/L [mmol/L]) euvolemic or hypervolemic hyponatremia or less marked symptomatic hyponatremia that is unresponsive to other therapeutic interventions in patients with HF, cirrhosis, and SIADH. When given alone, it appears to be safe and modestly effective at promoting aquaresis and raising serum sodium concentration by 3.6 mEq/L (mmol/L) at 4 days and 4.4 mEq/L (mmol/L) at 30 days in both short- and intermediate-term studies (SALT-1 and SALT-2), respectively.[41,42] However, in these studies, the average fluid intake was approximately 2 L/day which may have limited the efficacy of tolvaptan. A recent *real-life experience* with tolvaptan in 61 patients with SIADH and resistant hyponatremia reported an average increase in serum sodium concentration of 9 ± 3.9 mEq/L (mmol/L) after 24 hours.[43] In SALT-1 and SALT-2, the percentage of patients with a normal serum sodium concentration (greater than 135 mEq/L [mmol/L]) after one month of tolvaptan use was 53% and 58%, respectively, versus 25% (both studies) with placebo.[41,42]

When used as monotherapy, tolvaptan appears to be superior to either furosemide or water restriction, and when given in combination with furosemide, synergistic effects have been noted.[44]

In critically ill neurological patients, who often require more aggressive care to prevent long-term morbidity, a single tolvaptan dose (7.5 or 15 mg) can effectively increase serum sodium concentration by 5 to 7.8 mEq/L (mmol/L) with the effect sustained for up to 96 hours.[45,46] Correction of hyponatremia in these patients may require multiple doses. Too rapid correction (increasing serum sodium concentration by more than 6-12 mEq/L [mmol/L] in 24 hours) may occur, particularly when a 15-mg dose is given, thus careful monitoring in these high-risk patients is warranted.[45,46] However, reducing the starting dosage to less than 15 mg/day does not appear to eliminate the risk of too rapid sodium correction.[47]

Approximately 10% to 50% of patients do not significantly respond to VRA therapy.[48,49] Therapeutic resistance or failure to respond with VRA therapy could be due to high circulating AVP concentrations, AVP-independent impaired urinary dilution, excessive water intake, or an activating V_2-receptor mutation causing nephrogenic SIADH.[40] There is currently no pharmacogenomic information available for the G protein–coupled receptor family of AVP receptors or the VRAs that can be used to individualize therapy.[50]

Tolvaptan is primarily metabolized to inactive metabolites by CYP3A4 and less than 1% is eliminated unchanged in the urine; thus, its use should be avoided in patient's receiving potent CYP3A4 inhibitors (eg, ketoconazole, clarithromycin, itraconazole, ritonavir). Concomitant therapy with P-glycoprotein inhibitors and grapefruit juice has also been noted to result in increased serum tolvaptan concentrations. Tolvaptan inhibits P-glycoprotein and coadministration with P-glycoprotein substrates should be avoided, if possible.[51] Conversely, optimal tolvaptan benefits may not be realized on usual dosages, and increased dosages may be needed in patients who are receiving potent CYP3A4 inducers (eg, phenytoin, phenobarbital, St. John's Wort). Dose linearity has been observed within the therapeutic range and based on its terminal half-life (5-12 hours after 7 days or more of therapy), minimal accumulation occurs.[52,53] The usual starting tolvaptan dosage is 15 mg given orally once daily, but 7.5 mg should be considered for patients older than 90 years of age.[54]

Tolvaptan oral bioavailability is about 56%, and activity peaks at 2 to 4 hours after a dose. For patients who cannot take tolvaptan tablets orally, the tablets can be crushed, suspended in water, and administered orally or via a nasogastric

tube, but a 25% average decrease in the tolvaptan area under the concentration-time curve may be seen with this administration method.[55] Fluid restriction should be avoided for the first 24 to 48 hours of starting VRA therapy when active sodium correction is occurring.[20] If after 24 hours a greater increase in serum sodium concentration is needed, the dosage may be increased to 30 mg once daily, and after another 24 hours, to a maximum of 60 mg once daily.

Tolvaptan therapy is contraindicated in patients needing rapid serum sodium correction (due to the 2- to 4-hour delayed onset), those unable to sense or respond appropriately to thirst, patients with hypovolemic hyponatremia, patients taking strong CYP3A4 inhibitors, and patients who are anuric. Tolvaptan has not been studied in patients with severe hyponatremia (severe symptoms or serum sodium less than 120 mEq/L [mmol/L]). Patients with more profound hyponatremia are more likely to experience larger increases in serum sodium concentrations. Tolvaptan should be used cautiously in these patients with serum sodium concentration monitoring every 2 to 4 hours.

Tolvaptan effectively produces aquaresis and increases serum sodium concentrations in patients with chronic kidney disease (CKD stages 3, 4, 5) who are not receiving renal replacement therapy.[56,57] VRA use should be avoided with hypertonic saline (eg, 3% NaCl) due to the risk of too rapid and/or overcorrection of the serum sodium concentration. Thirst, dry mouth, weakness, constipation, hyperglycemia, and urinary frequency are the most common adverse effects, but they rarely necessitate therapy discontinuation.[41,42]

Reversible increases in hepatic transaminases have been reported with tolvaptan use; however, concerns for irreversible liver damage arose in the TEMPO 3:4 trial which studied tolvaptan in patients with autosomal-dominant polycystic kidney disease. Tolvaptan dosages (45-120 mg/day) were much higher than those typically used for hyponatremia, and the duration of therapy was longer than 30 days (up to 3 years in some patients). Increases in hepatic transaminases did not meet Hi's criteria for drug-induced liver injury because the total bilirubin was not elevated to more than twice the upper limit of normal.[58]

The FDA has issued a warning that tolvaptan should not be used for more than 30 days and should not be used in anyone with liver disease, including cirrhosis. Additionally, the warning states that if any sign of liver injury occurs during therapy, tolvaptan should be discontinued. To reduce the ODS risk, the FDA-approved labeling also includes a boxed warning stating that tolvaptan therapy should begin or resume only in a hospital where the serum sodium concentration can be closely monitored. A medication guide is included in the package insert given to all patients with each prescription.

VRAs are more expensive compared to other treatment options. Multiple economic analyses have determined tolvaptan therapy to be cost-effective for SIADH and HF when compared to fluid restriction or no additional therapy as evidenced by reduced hospital stay, avoidance of ICU admission, and avoidance of hospital readmission.[59–61] However, the role and cost-effectiveness of VRAs in the management of patients with SIADH are still unclear when considering all therapeutic modalities. Therapy continuation after acute treatment depends on the etiology of SIADH. While many cases are transient, other etiologies will require indefinite treatment. The inability to discontinue the offending agent in drug-induced SIADH may also necessitate long-term treatment. When considering long-term VRA treatment, cost and potential liver toxicity must be weighed against potential benefits.

Currently, it is not clear whether improving or normalizing the serum sodium concentration improves the morbidity and/or mortality associated with hyponatremia. Additional research is needed to compare VRA use with traditional therapies after fluid restriction in the acute phase of nonemergent euvolemic hyponatremia. Further investigation is also warranted for long-term VRA use in asymptomatic or minimally symptomatic hyponatremia, particularly in the elderly, to reduce morbidity (eg, cognitive deficits, gait disturbance, falls, bone fractures).

Evaluation of Therapeutic Outcomes

The serum sodium concentration should be monitored at least every 4 to 6 hours during the active sodium correction phase with treatment other than fluid restriction until reaching a stable value greater than 125 mEq/L (mmol/L). The serum sodium concentration should be measured every 24 to 48 hours when water restriction is initiated until it stabilizes at a concentration at or above 125 mEq/L (mmol/L).[20] Continued decline in the serum sodium concentration would indicate either nonadherence to the prescribed water restriction or the need for more aggressive restriction. If tolvaptan is initiated, the serum sodium concentration should be monitored every 4 to 8 hours for the first 24 to 48 hours.[20]

When the serum sodium has increased by 6 to 8 mEq/L (mmol/L), oral water or IV Dextrose 5% in water (D_5W) should be given to replace urine output to minimize the risk of overcorrecting the serum sodium concentration and ODS. In a recent Cochrane review, VRA therapy increased the risk of a rapid increase in serum sodium (greater than 8 mEq/L [mmol/L] in 24 hours) by 67%, with an

additional three patients per 100 treated with a VRA experiencing a rapid sodium increase versus placebo.[62] In the SALT trials, only 1.8% of patients exceeded the daily limit for changes in serum sodium; however, most had serum sodium concentrations greater than 130 mEq/L (mmol/L) at the start of treatment and were protected from overcorrection by thirst, so the risk of sodium overcorrection in clinical practice may be greater.[41,42] A recent *real-life* analysis reported excessive sodium correction (greater than 12 mEq/L [mmol/L] within 24 hours or greater than 18 mEq/L [mmol/L] within 48 hours) in 23% of patients with profound hyponatremia (baseline serum sodium 119.9 ± 5.5 mEq/L [mmol/L]), although none developed neurological symptoms or ODS.[43] Since 2011, 25 cases of ODS have been reported through the FDA Adverse Events Reporting System (FAERS).[63] Once the serum sodium concentration is stable at 125 mEq/L (mmol/L) or higher, the patient should be evaluated every 2 to 4 weeks to assess neurologic status and to obtain serum and urine sodium, potassium, and osmolality values. Volume status assessments (eg, blood pressure, mucous membranes, skin turgor, heart, and lung examination) should also be done, particularly in patients who are being treated with NaCl supplements and/or loop diuretics.

NONEMERGENT HYPERVOLEMIC HYPOTONIC HYPONATREMIA

The initial treatment goals for patients with asymptomatic or minimally symptomatic hypervolemic (expanded ECF volume) hypotonic hyponatremia include achieving a negative water balance and minimizing rapid changes in brain cell volume until the serum sodium concentration is at or above 125 mEq/L (mmol/L). Management involves correction of the underlying cause, when possible, as well as water restriction to less than 1,000 to 1,200 mL/day. Additionally, dietary sodium intake should be restricted to 1,000 to 2,000 mg/day, depending on the degree of ECF volume expansion. On average, only modest changes in serum sodium concentration are seen over the first 5 days of treatment with fluid restriction (2 mEq/L [mmol/L; IQR 0-4] at 24 hours[64]; 0.7 ± 2.1 mEq/L [mmol/L] on day 5[65]).

In patients with HF, the severity of hypervolemic hypotonic hyponatremia is directly related to HF severity and is associated with poorer short- and long-term prognoses once the serum sodium concentration falls below 137 mEq/L (mmol/L).[66,67] Patients with hypervolemic hypotonic hyponatremia caused by

HF should be treated with measures that can potentially improve cardiac contractility and effective circulating volume, thereby limiting nonosmotic AVP release. Therapeutic options include digitalis or afterload reduction with angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), or angiotensin receptor-neprilysin inhibitors (ARNIs). Of these, only ACEIs have been shown to be of benefit in partially correcting hyponatremia in patients with HF[68]; however, sodium correction with ACEIs has not been shown to lead to better outcomes.[69] No specific ACEI offers any particular advantage for this indication, and the dosage should be titrated to keep the systolic blood pressure between 100 and 130 mm Hg. Dose-limiting adverse effects of ACEIs include hyperkalemia (serum potassium concentration greater than 5.5 mEq/L [mmol/L]) and impaired kidney function. The benefits and risks of continuing ACEI use must be weighed carefully in each case, but a decrease in glomerular filtration rate (GFR) of less than 30% that stabilizes within 2 months of beginning ACEI therapy generally does not require ACEI dosage reduction or discontinuation.[66]

Other potentially treatable causes of asymptomatic hypervolemic hyponatremia include nephrotic syndrome and cirrhosis. ACEIs can be used to decrease proteinuria in patients with nephrotic syndrome, leading to partial correction of hypoalbuminemia and to a decrease in nonosmotic AVP release. Patients with advanced cirrhosis may benefit from placement of a transjugular intrahepatic portosystemic shunt, which can increase the effective circulating volume and thus reduce nonosmotic AVP release. This procedure can potentially exacerbate or precipitate hepatic encephalopathy and is not recommended in patients with a history of encephalopathy.

VRAs have also been used for the treatment of hypervolemic hypotonic hyponatremia in patients with HF or cirrhosis.[70–76] Conivaptan is not an ideal choice for patients with cirrhosis due to its mixed antagonism of the V_1 and V_2 receptors. V_1 receptor blockade in these patients may worsen hypotension, increase bleeding risk, and compromise kidney function.[71] As previously mentioned, the FDA issued a warning regarding tolvaptan use in patients with impaired liver function due to the potential for further liver injury.[63] However, 25% and 31% of patients in the tolvaptan groups of the SALT-1 and SALT-2 trials, respectively, had underlying liver cirrhosis and no cases of further liver injury were reported.[41,42] Subsequent studies have supported these findings.[72,73] The optimal tolvaptan starting dosage in patients with cirrhosis is unknown; however, given the concern for hepatotoxicity, 3.75 or 7.5 mg daily may be

appropriate.[74] Patients with cirrhosis who receive tolvaptan generally have a more modest increase in serum sodium concentrations compared to patients with euvolemic hyponatremia, and the increase may be more dependent on baseline GFR.[74–76] Tolvaptan may be considered in patients with end-stage liver disease awaiting liver transplantation to normalize serum sodium concentrations.[77] The benefit of avoiding the need for rapid perioperative sodium correction outweighs the likely negligible effect of tolvaptan-related liver damage in these patients. It is also reasonable to continue treatment until liver transplantation even if the duration is longer than 30 days.

Tolvaptan dosing for HF-associated hypervolemic hyponatremia is the same as for euvolemic hypotonic hyponatremia. In the short-term management of patients with HF with hypervolemic hyponatremia, tolvaptan use decreases body weight, increases urine output, decreases left ventricular filling pressures, and decreases urine osmolality; however, evidence for clinical benefits such as improved dyspnea is lacking.[78–84] Long-term beneficial effects, reduction in hospitalization or death or slowed HF progression, have not been observed in several pivotal trials. A post-hoc analysis of the EVEREST trial, however, showed patients with severe hyponatremia (less than 130 mEq/L [mmol/L]), who presumably had greater activation of the arginine-vasopressin axis, had reduced cardiovascular morbidity and mortality after discharge.[85] Prolonged tolvaptan use leads to an increased endogenous AVP concentration, and this overstimulation of V_{1a} receptors can lead to increased afterload and HF progression.[86] However, no worsening of left ventricular dilatation was observed after 52 weeks of tolvaptan therapy (30 mg/day).[87] In contrast to European guidelines, an American expert panel on hyponatremia recommended VRAs in nonsevere hyponatremia when fluid restriction is unsuccessful.[20] The 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines recommend short-term use of VRAs in hospitalized patients who have volume overload and persistent severe hyponatremia and who are at risk for or having cognitive symptoms despite fluid restriction and optimization of guideline-directed medical therapy.[88] It is still unknown if VRAs decrease length of hospitalization, rehospitalization rates, or morbidity or increase quality of life when compared to other treatments.

Various biological markers, such as copeptin, the C-terminal segment of the vasopressin precursor (CT-proAVP), apelin, and midregional proatrial natriuretic peptide (MR-proANP), may have diagnostic utility for hyponatremia in HF and improve the overall management.[89] The association between copeptin peptide

concentrations and tolvaptan response was recently investigated in patients with HF and may help determine the most appropriate patients for VRA use.[90,91] Given the potential vascular and cardiac effects of V_{1a} receptor stimulation and V_{1a} receptor dose-dependent activity (as opposed to maximal V_2 signaling at low-AVP activity levels), an oral V_{1a} or nonselective VRA likely would provide greater benefits in patients with HF.[92]

Evaluation of Therapeutic Outcomes

Patients being treated for hypervolemic hyponatremia should initially be evaluated on a daily basis for lung congestion, ascites, peripheral edema, and signs or symptoms of hyponatremia. If water restriction is started, the serum sodium concentration should be measured daily until it stabilizes at 125 mEq/L (mmol/L) or higher. If VRA therapy is initiated, serum sodium concentrations should be monitored every 4 hours to minimize the risk of sodium overcorrection and ODS. Patients should be assessed 1 week following discharge, and then every 2 to 4 weeks to assess adherence to water restriction and other therapies, volume status, and symptoms.

HYPERNATREMIA

Epidemiology and Etiology

10 Hypernatremia, defined as a serum sodium concentration greater than 145 mEq/L (mmol/L), is always associated with hypertonicity and intracellular dehydration, resulting from a water deficit relative to ECF sodium content. This hypertonic state is a potent stimulus for AVP secretion and thirst. Therefore, hypernatremia is most commonly observed in patients with an impaired thirst response or in those who cannot access water. Young infants and children, mechanically ventilated or comatose patients, the elderly, and disabled patients with an impaired sensorium or functional status are therefore at highest risk for this disorder.[93] Hypernatremia generally occurs in sicker patients and has a higher mortality.[94] The incidence of hypernatremia in general medical–surgical hospitalized patients and patients in ICUs has been estimated to be at least 1% and as high as 26%, respectively.[95–98] In a matched case–control study, 92% of 130 cases of hypernatremia in ICU patients were iatrogenic: the result of too little free water and too much hypertonic solution along with increased renal

water loss.[99]

Clinical outcomes in patients with hypernatremia, as in hyponatremia, depend on the severity of the increase and the rapidity with which it develops. In children, mortality from acute hypernatremia developing in less than 72 hours ranges from 10% to 70%, while chronic hypernatremia which develops over 3 or more days has a mortality rate of only 10%.[100] In adults, an acute increase in serum sodium concentration to greater than 160 mEq/L (mmol/L) is associated with a 75% mortality rate, and hypernatremia that develops at a slower rate also has a high mortality rate of approximately 60%.[101] Hypernatremia is often associated with a serious underlying illness, which likely contributes to the higher mortality rate.

Pathophysiology

Hypernatremia most often results from water loss by either renal or extrarenal mechanisms. Hypernatremia also results from hypertonic or isotonic fluid administration or excess sodium ingestion. Patients can develop hypovolemic, hypervolemic, or euvolemic (isovolemic) hypernatremia depending on the relative magnitude of sodium and water loss or gain caused by the underlying condition (**Table 66-7**).

TABLE 66-7 Characteristics of Hypernatremic States

Characteristics	Hypovolemic Hypernatremia	Euvolemic (Isovolemic) Hypernatremia	Hypervolemic Hypernatremia
Water and sodium	Water loss >> sodium loss	Water loss only	Sodium gain > water gain
Causes	Renal: osmotic diuresis, diuretic use, postoperative diuresis, high-output acute tubular necrosis	Congenital or acquired DI Nephrogenic DI Primary polydipsia	Sodium overload (eg, 3% NaCl, sodium bicarbonate, NaCl tablets, concentrated tube feedings, hypertonic dialysate, sodium-containing medications)
Effect on TBW	↓↓	↓	↑
Effect on TBNa	↓	↔	↑↑
Additional laboratory findings	Renal: UOsm high, UNa high Nonrenal: UOsm high, UNa low	Renal: UOsm low, UNa variable Nonrenal: UOsm high, UNa variable	Renal: UOsm high, UNa high
Clinical presentation	Orthostasis, hypotension, tachycardia, dry mucous membranes	Depends on severity of hypernatremia; seizures, lethargy	Peripheral and pulmonary edema, variable blood pressure
Treatment	0.9% NaCl until vital signs stable, then free water replacement	Free water replacement, AVP, or AVP analogue	Free water replacement with loop diuretic, may require hemodialysis to remove volume

AVP, arginine vasopressin; DI, diabetes insipidus; NaCl, sodium chloride; TBNa, total body sodium; TBW, total body water; UNa, urine sodium concentration; UOsm, urine osmolality.

Water loss commonly occurs as a result of insensible losses (evaporative water loss through the skin and lungs) in patients deprived of water. Hospitalized patients who are febrile or being mechanically ventilated are often treated with IV fluids containing insufficient free water to replace insensible losses. Hypernatremia can develop in patients with hypotonic GI losses (eg, diarrhea, vomiting, gastric suctioning) or in patients who have been exposed to high temperatures who suffer large water losses from both sweat and insensible losses.

A water diuresis can be caused by diabetes insipidus (DI), which can be classified as either central DI (decreased AVP secretion) or nephrogenic DI (decreased kidney response to AVP). Patients with untreated DI excrete large volumes (3-20 L/day) of dilute urine, resulting in hypernatremia. Various causes of DI are listed in **Table 66-8**.

TABLE 66-8 Causes of DI

Central	Nephrogenic	Other
Familial[a]	Familial	Gestational
Unreplaced insensible losses	Inherited aquaporin-2 defect	Primary polydipsia (dipsogenic DI)
Skin	Inherited vasopressin V2 receptor defect	
Lung	Hypercalcemia (chronic)	
Hypodipsia	Hypokalemia	
Neurogenic	Kidney disease	
Neurosurgery	Drug-induced	
Tuberculosis	Lithium (most common)	
Head trauma	Foscarnet	
CNS malignancy/cyst	Clozapine	
Ethanol ingestion (transient)	Amphotericin B	
Hypoxic encephalopathy	Cidofovir	
Lung tumor	Demeclocycline	
Sarcoidosis	Didanosine	
Sheehan syndrome[b]	Ifosfamide	
	Orlistat	
	Vasopressin receptor antagonists	

[a]60 mutations in the AVP gene cause neurohypophyseal DI, from US National Library of Medicine. Genetics Home Reference. AVP. http://ghr.nlm.nih.gov/gene/AVP. Accessed October 2018.

[b]Postpartum hypopituitarism caused by severe bleeding during childbirth.

AVP, arginine vasopressin; CNS, central nervous system; DI, diabetes insipidus.

Hypertonic NaCl administration can result in hypervolemic (expanded ECF volume) hypernatremia. This type of hypernatremia is typically iatrogenic following excess sodium bicarbonate administration, hypertonic NaCl enemas, or intrauterine injection of hypertonic NaCl. Normal ECF osmolality is 275 to 290 mOsm/kg (mmol/kg), whereas osmolality of the isotonic IV solutions, Lactated Ringer's and 0.9% NaCl, is 273 mOsm/kg (mmol/kg) and 308 mOsm/kg (mmol/kg), respectively (see Table 66-1). Excessive 0.9% NaCl infusions may lead to sodium accumulation, particularly when dilute urine is excreted. A common cause of hypernatremia in the ICU is sodium intake from IV and enteral fluids and medications.[94,102] Sodium balance should be monitored carefully in critically ill patients to avoid iatrogenic hypernatremia. Patients with hyperaldosteronism also may present with an expanded ECF and mild hypernatremia.

CLINICAL PRESENTATION

Hypernatremia results in water movement from the ICF to the ECF. Patients with central DI often present with sudden onset of polyuria, whereas patients with nephrogenic DI develop polyuria more gradually. Symptoms are similar to those seen with hyponatremia and are primarily neurological due to decreased brain cell volume. Symptoms of mild-to-moderate hypernatremia (hypertonicity) include weakness, lethargy, restlessness, irritability, twitching, and confusion. More severe or rapidly developing hypernatremia can lead to seizures, coma, and death. As discussed in the hyponatremia section, brain cells adapt to ECF tonicity changes by decreasing or increasing the concentration of inorganic (K^+, Cl^-) and organic (glutamate, taurine, and myoinositol) osmolytes.[3,34] ECF hypertonicity results in intracellular organic osmolyte generation within 24 hours of onset leading to an increase in ICF tonicity that then draws water into brain cells, limiting the decrease in cell volume. Thus, patients with chronic hypernatremia are less likely to be symptomatic than patients with acute hypernatremia.

CLINICAL PRESENTATION

Hypernatremia

General

- Increase in serum sodium concentration and osmolality causes acute water movement from the ICF to the ECF
- Decreased brain cell volume can cause cerebral vein rupture, leading to focal intracerebral and subarachnoid hemorrhages and irreversible CNS damage

Symptoms

- Mild: lethargy, weakness, confusion, restlessness, irritability
- Moderate: twitching
- Severe: seizures, coma, death; usually requires acute increase in serum sodium to ≥160 mEq/L (mmol/L)
- Serum sodium ≥180 mEq/L (mmol/L) is associated with high mortality
- Other symptoms (depend on etiology of hypernatremia): postural

hypotension, tachycardia, dry mucous membranes, diminished skin turgor, reduced or increased urine output.

- Signs and symptoms difficult to detect in patients with underlying neurologic dysfunction

Laboratory tests

- Serum sodium concentration ≥145 mEq/L (mmol/L)
- Serum osmolality is always high
- Urine osmolality may be helpful in diagnosing the cause

Hypernatremia is often associated with serious underlying illness, and signs and symptoms related to the illness are often present. Patients with a history of severe diarrhea or vomiting can present with ECF volume depletion. Elderly patients deprived of water after sustaining a stroke or hip fracture often present with mental status changes and other signs of ECF volume depletion. Clinically detectable ECF volume depletion, however, may not be evident until the serum sodium concentration exceeds 160 mEq/L (mmol/L) because these patients primarily have water loss, two-thirds of which is derived from the ICF. The urine will be concentrated, often exceeding 450 mOsm/kg (mmol/kg), because of osmotic and nonosmotic AVP release. The first step in the evaluation and treatment of hypernatremia is assessment of the ECF and urine volume and the serum and urine osmolality (**Fig. 66-3**).

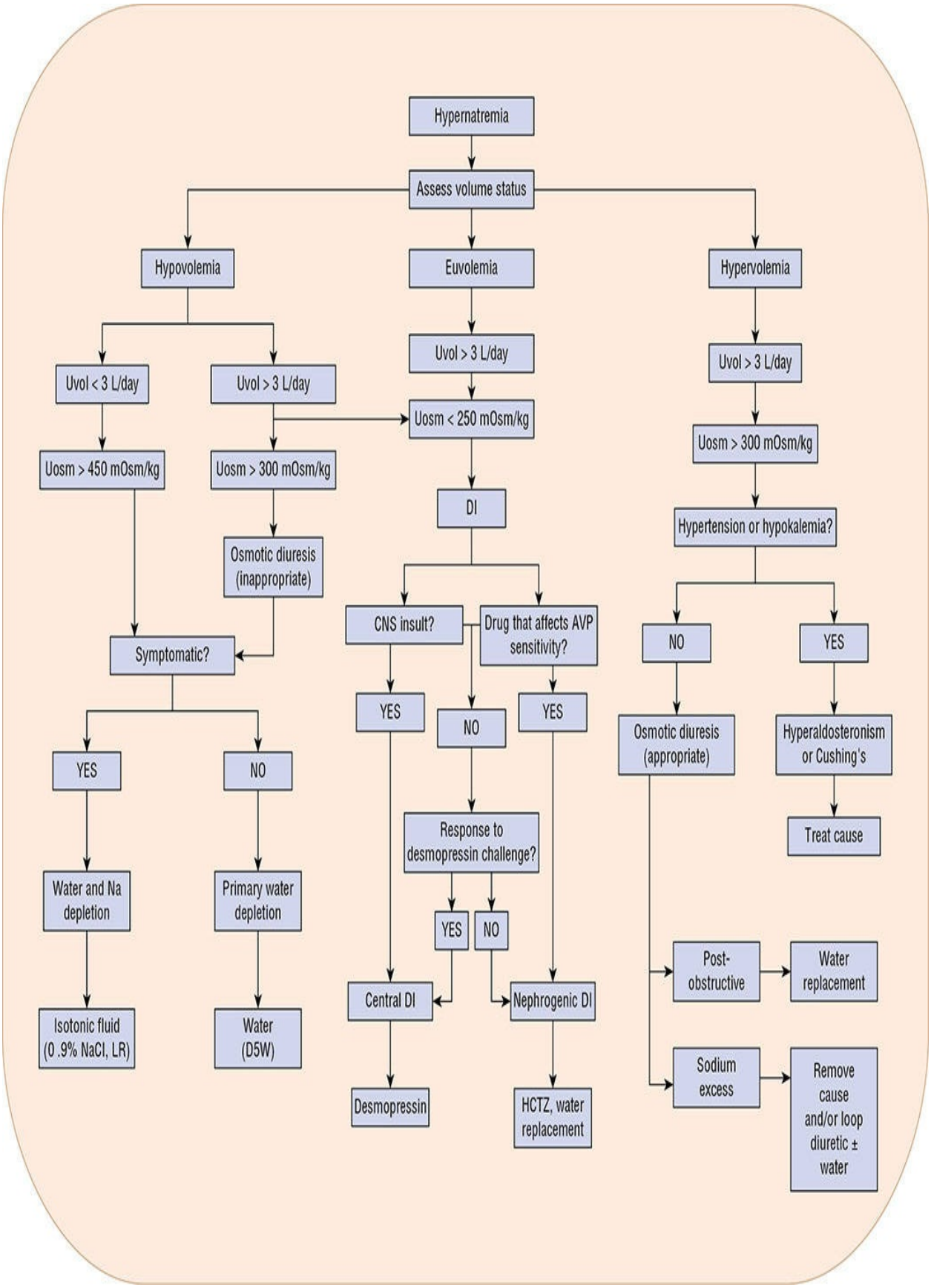

Hypernatremia
Assess volume status
Hypovolemia
Euvolemia
Hypervolemia
Uvol < 3 L/day
Uvol > 3 L/day
Uosm > 450 mOsm/kg
Uosm > 300 mOsm/kg
Osmotic diuresis (inappropriate)
Symptomatic?
YES
NO
Water and Na depletion
Primary water depletion
Isotonic fluid (0 .9% NaCl, LR)
Water (D5W)
Uvol > 3 L/day
Uosm < 250 mOsm/kg
DI
CNS insult?
Drug that affects AVP sensitivity?
YES
NO
YES
Response to desmopressin challenge?
YES
NO
Central DI
Nephrogenic DI
Desmopressin
HCTZ, water replacement
Uvol > 3 L/day
Uosm > 300 mOsm/kg
Hypertension or hypokalemia?
NO
YES
Osmotic diuresis (appropriate)
Hyperaldosteronism or Cushing's
Treat cause
Post-obstructive
Water replacement
Sodium excess
Remove cause and/or loop diuretic ± water

FIGURE 66-3 Algorithm for the assessment and treatment of hypernatremia. (AVP, arginine vasopressin; CNS, central nervous system; D_5W, Dextrose 5% in water; DI, diabetes insipidus; ECF, extracellular fluid; HCTZ, hydrochlorothiazide; LR, Lactated Ringers; Na, sodium; NaCl, sodium chloride; Uosm, urine osmolality [values in mOsm/kg are numerically equivalent to mmol/kg]; Uvol, daily urine volume.)

Patients with a contracted ECF volume and low urine output include those who have sustained insensible water losses that exceed intake, as well as those with extrarenal losses of hypotonic fluids. On physical examination, the patient will have postural hypotension, diminished skin turgor, and delayed capillary refill. Lactic acidosis and low mixed venous oxygen saturation, indicating decreased tissue perfusion, may be present. The daily urine output is typically less than 1 L.

A multicenter, case–control study examined the clinical presentation of hypernatremia in 150 elderly patients in geriatric care facilities. Hypotension, tachycardia, dry oral mucosa, decreased skin turgor, and recent changes in consciousness were all more common in patients with hypernatremia than in controls. In this patient population, the presence of signs of dehydration was variable, with orthostatic hypotension and decreased subclavicular and forearm skin turgor present in at least 60% of patients. Abnormal subclavicular and thigh skin turgor, dry oral mucosa, and recent change in consciousness were significantly and independently associated with hypernatremia.[103]

Osmotic Diuresis

In the presence of an ongoing osmotic diuresis, patients will have a urine volume greater than 3 L/day. Excessive urinary excretion of glucose, sodium, urea, or an exogenously administered solute (eg, mannitol) can be identified either by history or by direct measurement of serum and urinary concentrations of the suspected solute, if possible. Patients with post-obstructive diuresis, such as those with bladder outlet obstruction caused by prostatic hypertrophy, are usually ECF volume expanded because of retained solute because of a reduction in GFR. The osmotic diuresis that follows resolution of the obstruction is appropriate, in that it promotes excretion of the excess solute.

Patients with severe hyperglycemia may have a low measured serum sodium concentration (hyponatremia) but a high corrected sodium concentration (hypernatremia). Patients with severe hyperglycemia present with signs of

volume depletion, and the diuresis is inappropriate as it further exacerbates the ECF volume contraction associated with hyperglycemia. As previously discussed, the estimated (or corrected) serum sodium concentration can be calculated by adding 1.7 mEq/L (mmol/L) for every 100 mg/dL (5.6 mmol/L) increase in the serum glucose concentration before estimating the water deficit.[5,26]

Diabetes Insipidus

Patients with DI tend to maintain a normal ECF volume if they are conscious, can drink, and have free access to water. Patients typically have only a slight increase in the serum sodium concentration (usually 141-145 mEq/L [mmol/L]), and a daily urine volume greater than 3 L.

A water deprivation test has been recommended to aid in the differential diagnosis. This diagnostic test consists of depriving a patient with marked polyuria of water for 8 to 12 hours in a supervised setting to avoid severe hypernatremia and volume depletion. Body weight and urine osmolality and volume are measured before and after administration of desmopressin acetate (4 mcg subcutaneously or intravenously or 10 mcg intranasally).[104] After desmopressin administration, patients with central DI will have a prompt increase in urine osmolality to approximately 600 mOsm/kg (mmol/kg) and decreased urine volume. In patients with nephrogenic DI, the urine osmolality will not increase above 300 mOsm/kg (mmol/kg).

The value of a water deprivation test in patients with polyuria and hypernatremia has been questioned. Because hypernatremia provides a maximal stimulus for AVP secretion, discriminating between nephrogenic and central DI can be based on the serum AVP concentration and urinary response to desmopressin without the need for a water deprivation test. The water deprivation test is likely to be of diagnostic value only in patients with polyuria and a normal serum sodium concentration.[105]

Sodium Overload

Patients who have ingested a large amount of sodium (more than 4 tablespoons table salt [1,400 mEq or mmol sodium]) or who have received more than 5 L of hypertonic fluids are volume expanded, although this volume may not always be clinically evident as edema. Volume expansion results in an osmotic diuresis, polyuria, and a urine osmolality greater than 300 mOsm/kg (mmol/kg). The

excess sodium will be excreted in the urine in patients with normal perfusion and kidney function; with organ dysfunction, volume expansion occurs.

TREATMENT: HYPERNATREMIA

Desired Outcomes

Treatment goals for patients with hypernatremia include correcting the serum sodium concentration to between 145 and 150 mEq/L (mmol/L) at a rate that restores and maintains brain cell volume as close to normal as possible and normalizing ECF volume, if indicated. Hypernatremia is often undertreated; adequate treatment should result in symptom resolution. Although inadvertent overcorrection is more common with hyponatremia, careful titration of fluids and medications should minimize the adverse effects associated with too rapid sodium correction, including cerebral edema, seizures, neurologic damage, and death. However, these complications have almost exclusively been reported in young children with chronic hypernatremia of at least 48 hours duration and serum sodium concentrations greater than 150 mEq/L (mmol/L).[3] Water replacement and dietary sodium restriction can be necessary to prevent recurrence of hypernatremia.

Physical examination with attention to volume status and measurement of the serum and urine sodium and osmolality should be completed every 2 to 3 months during chronic therapy. A 24-hour urine collection to measure urine volume and sodium excretion will help guide diuretic therapy and determine adherence to sodium restriction.

Hypovolemic Hypernatremia

Patients with symptomatic hypovolemic hypernatremia should be treated similarly to those with hypovolemic hyponatremia with 0.9% NaCl or another isotonic fluid until hemodynamic stability is restored (Fig. 66-3). An initial infusion rate of 200 to 300 mL/hr or higher will likely be appropriate for most adults; children generally receive 10 to 20 mL/kg/hr. Once intravascular volume is restored, 0.45% NaCl, D_5W, or another hypotonic fluid may be infused to correct the water deficit. In patients with hypernatremia from water loss, the ECF volume deficit can be estimated as:

$$\text{ECF (water) deficit} = \text{TBW}_{\text{current}} \times [1 - (140/\text{Na}_S)] ,$$

where Na_S is the initial serum sodium concentration (in mEq/L [mmol/L]), and 140 is the normal or goal serum sodium concentration in mEq/L (mmol/L). Although this formula provides an estimate of the water deficit caused by pure free water loss, it underestimates the deficit in patients with hypotonic fluid loss.[3]

The appropriate rate for correcting the water deficit depends on the rapidity with which the hypernatremia developed. Hypernatremia developing in only a few hours can be initially corrected at a rate of approximately 1 mEq/L/hr (mmol/L/h), whereas a rate of 0.5 mEq/L/hr (mmol/L/h) or less should be used when hypernatremia has developed more slowly.[2,3] The sodium should be lowered no more than 10 to 12 mEq/L (mmol/L) per day.[3] Renal replacement therapy may be needed for patients with kidney failure; NaCl will be added to the replacement fluid/dialysate to achieve the same sodium content as the goal serum sodium concentration to avoid too rapid overcorrection and cerebral edema.[94]

The serum sodium concentration and volume status should be monitored every 2 to 3 hours during the first 24 hours of treatment in patients with symptomatic hypernatremia to permit appropriate adjustment of the hypotonic fluid infusion rate. Once symptoms resolve and the serum sodium concentration is less than 148 mEq/L (mmol/L), measuring serum sodium concentrations every 6 to 12 hours and assessing fluid status every 8 to 24 hours is generally adequate.

Recurrent iatrogenic hypernatremia can be prevented by avoiding infusing excessive hypertonic solution, providing adequate *maintenance* fluids, and replacing ongoing abnormal losses. The standard maintenance fluid for adults and children weighing 40 kg or more is Dextrose 5%/0.45% NaCl with 20 mEq (mmol) KCl/L. Children weighing less than 40 kg typically receive Dextrose 5%/0.2% NaCl with 20 mEq (mmol) KCl/L, except infants younger than 3 months who may receive Dextrose 10%/0.2% NaCl with 20 mEq (mmol) KCl/L. These fluids are given to provide a small amount of glucose for CNS function and to replace expected urinary sodium and potassium losses. Estimating daily fluid requirements and calculation of an appropriate maintenance fluid rate is discussed in Chapter 158.

Traditionally, *maintenance* fluids have been administered as dextrose, sodium, and potassium in a hypotonic solution (eg, 0.45% NaCl, 0.2% NaCl). However, concerns related to development of hyponatremia have led to the recommendation that an isotonic fluid be used for *maintenance* fluids in hospitalized patients to reduce the incidence of hyponatremia.[106] Excess administration of 0.9% NaCl can result in ICF dehydration and chloride overload

leading to metabolic acidosis. A *balanced* electrolyte solution (eg, Lactated Ringer's, Plasma-Lyte®) may be preferred in some patients.[107] Excess sodium administration also carries the risk of hypernatremia and volume overload, especially in vulnerable patients. While isotonic fluids may be appropriate for some hospitalized patients, it is important to remember that *maintenance* fluids are appropriate when used as intended, that is, in patients who are euvolemic with no excess ongoing fluid losses and normal kidney function.

Treatment of hyperglycemia-induced osmotic diuresis consists of correcting the hyperglycemia with insulin, as well as administering 0.9% NaCl until signs of ECF volume depletion resolve. Once hemodynamic stability is restored, the free water deficit should be corrected as described above.

Hypernatremia in patients undergoing a post-obstructive diuresis should be treated with a hypotonic fluid (eg, 0.45% NaCl, Pedialyte®) at a rate of approximately half to two-thirds of the urine output over a similar time period. Oral fluid replacement is preferred, if possible. The common practice of administering IV or oral fluids to replace urine output on a 1:1 volume basis tends to perpetuate the diuresis and generally should be avoided.[108]

Euvolemic (Isovolemic) Hypernatremia

Central Diabetes Insipidus Patients with central DI should generally receive AVP replacement therapy with desmopressin, an AVP analog (Fig. 66-3). The intranasal formulation, 1-desamino-8-D-arginine vasopressin (DDAVP), is preferred; however, oral tablets are available and may be useful in some patients. Each insufflation of intranasal DDAVP (100 mcg/mL) delivers 10 mcg of desmopressin acetate. A rhinal tube delivery system is preferred in patients requiring doses that are lower than 10 mcg or not in 10-mcg increments. In infants with congenital DI, preparation of a DDAVP dilution may be required to provide the small dosages needed. The initial intranasal DDAVP dosage for adults is 10 mcg once daily, titrated to 20 mcg twice daily based on the serum sodium concentration.[103] Patients may prefer oral tablets due to the ease of administration, but not all patients will adequately respond to the oral formulation as the bioavailability is only about 5%. Thus, a 0.1-mg tablet is equivalent to 2.5 to 5 mcg of nasal spray, but re-titration is required when transitioning between dosage forms due to the unpredictable absorption. Subcutaneous or IV desmopressin may be administered in cases when the intranasal and oral routes are not feasible.

The desmopressin dosage should be adjusted to achieve adequate urinary concentration during sleep to prevent nocturia, a daily urine volume of

approximately 1.5 to 2 L, and a normal or near normal serum sodium concentration. The mean duration of action of intranasal DDAVP is 7 to 9 hours. The serum sodium concentration should be measured at 24 hours and every 3 to 4 days during the initial dosage titration period, and then every 2 to 4 months. Desmopressin administration results in nonsuppressible AVP activity and presents a risk of water intoxication with excess water retention. Patients must be knowledgeable of the signs and symptoms of both hyponatremia and hypervolemia. Patients who experience water intoxication may minimize the risk of a second episode by delaying one desmopressin dose each week until polyuria and thirst develop, thus demonstrating the continued need for desmopressin therapy.[109]

Nephrogenic Diabetes Insipidus

In patients with nephrogenic DI, concomitant electrolyte disturbances, if present, should be corrected, and any medications that potentially contribute to the pathogenesis should be discontinued, if possible. Because the ongoing urinary losses are essentially free water, patients with nephrogenic DI should receive hypotonic fluids to avoid excess NaCl intake which could worsen hypernatremia (Fig. 66-3). Water or milk can be given enterally or, if necessary, D_5W can be given intravenously at a rate that slightly exceeds the urine output with a goal to normalize the serum sodium concentration at a rate no faster than 0.5 mEq/L/hr (mmol/L/hr).[110] A key goal in treating nephrogenic DI is to induce a mild ECF deficit (1-1.5 L) with a thiazide diuretic and dietary sodium restriction (85 mEq [mmol] Na^+ or 2,000 mg NaCl per day), which can decrease urine volume by as much as 50% (**Table 66-9**). This ECF deficit will increase proximal tubule water reabsorption, decrease the filtrate volume delivered to the distal nephron, and decrease urine volume. In a patient with a maximally dilute urine osmolality (100 mOsm/kg [mmol/kg]), each gram of salt that is avoided will reduce the obligatory urine output by 360 mL because 1 g of table salt provides an osmolar load of approximately 36 mOsm.[110] Indomethacin, 50 mg given orally three times daily, potentiates AVP activity and can be used as adjunctive therapy in patients able to tolerate the gastrointestinal (GI) side effects. The relative benefits of other drug treatments for nephrogenic DI, including thiazide diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs), are not well studied; therefore, the choice of agent is primarily based on clinician preference. It is unclear if there is a significant difference in the risk of a clinically important GFR decrease when these drugs are used to produce a mild ECF volume deficit. Several other medications with antidiuretic properties have been used

successfully in the management of central and nephrogenic DI (Table 66-9). They may be used as adjunctive therapy or rarely as an alternative to DDAVP.

TABLE 66-9 Drugs Used in Central and Nephrogenic DI

Drug	Indication	Dose
Desmopressin acetate	Central and nephrogenic	5-20 mcg intranasally q12-24hr
Chlorpropamide	Central	125-250 mg orally daily
Carbamazepine	Central	100-300 mg orally twice daily
Clofibrate	Central	500 mg orally four times daily
Hydrochlorothiazide	Central and nephrogenic	25 mg orally q12-24hr
Amiloride	Nephrogenic	5-10 mg orally daily
Indomethacin	Central and nephrogenic	50 mg orally q8-12hr

DI, diabetes insipidus.

Hypervolemic Hypernatremia (Sodium and Water Overload)

Treatment of hypervolemic hypernatremia consists of administration of D_5W and a loop diuretic to facilitate excretion of the excess sodium (Fig. 66-3). The volume needed to correct the water deficit and hypernatremia at an appropriate rate can be estimated as described previously. Furosemide, 20 to 40 mg given intravenously every 6 hours, should also be administered.

The serum sodium concentration should initially be measured at least every 2 to 4 hours, and the diuretic continued until signs of ECF volume overload (eg, pulmonary congestion, edema) resolve. The serum sodium concentration can be measured every 6 to 12 hours once the serum sodium concentration is less than 148 mEq/L (mmol/L) and symptoms have resolved.[3]

EDEMA

11 Edema, defined as a clinically detectable increase in interstitial fluid volume,

is usually due to heart, kidney, or liver failure, or a combination of these conditions, although it can develop with a rapid decrease in serum albumin concentration along with excess fluid intake such as seen in the setting of burns or trauma. In an adult, edema formation is indicative of an interstitial volume increase of at least 2.5 to 3 L.

Pathophysiology

Edema develops when excess sodium is retained either as a primary defect in renal sodium excretion or as a response to a decrease in the effective circulating volume (actually the blood pressure resulting from that volume) despite a normal or expanded ECF volume. Under these conditions, the kidneys retain all the water and sodium ingested until the effective circulating volume is restored to near normal. An increase in dietary sodium is accompanied by an increase in water intake caused by the initial increase in serum osmolality and thirst. The resultant ECF volume increase augments kidney perfusion, resulting in a transient GFR increase, which leads to enhanced sodium filtration and excretion. These homeostatic mechanisms are crucial for maintaining sodium balance, as retention of just a few milliequivalents (millimoles) of sodium per day can eventually lead to an expanded ECF volume and edema formation. An increase in the capillary hydrostatic pressure because of ECF volume expansion or an increase in central venous pressure also can lead to edema formation. Edema may also occur when there is an alteration in Starling forces within the capillary. The Starling equation denotes the relationship between factors affecting fluid movement between the capillary and interstitium and is discussed in detail in Chapter 41. Edema may develop rapidly in patients with an acute decompensation in myocardial contractility, which leads to an elevated pulmonary venous pressure that is transmitted back to the pulmonary capillaries, and ultimately results in acute pulmonary edema.

Patients with nephrotic syndrome most often present with edema, frequently periorbital. There are two theories posited to explain edema in nephrotic syndrome: the *underfill* and the *overfill* hypothesis.[111] The underfill hypothesis states that decreased oncotic pressure from hypoalbuminemia (most pronounced with a serum albumin concentration less than 2 g/dL [20 g/L]) leads to excess fluid movement from the intravascular space to the interstitial space (*third spacing*) causing hypovolemia, kidney hypoperfusion, activation of the renin–angiotensin–aldosterone system, and secondary renal sodium retention. The overfill hypothesis is simply that primary renal sodium retention leads to edema. Both mechanisms contribute to edema formation. Distinguishing the

predominant mechanism in individual patients with nephrotic syndrome is clinically important, as patients that are primarily underfilled will likely have worsening hypovolemia and an elevated serum creatinine after initially tolerating diuresis.

Patients with cirrhosis initially develop ascites because of splanchnic vasodilation resulting in an increase in the pressure in the portal circulation (portal hypertension). This combination of portal hypertension and splanchnic vasodilation increases capillary pressure and permeability and facilitates the accumulation of ascites (fluid in the abdominal cavity). Ascites can cause a decrease in effective circulating volume and activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system, leading to secondary hyperaldosteronism. Subsequent renal sodium retention leads to worsened ascites, edema, and hypervolemic hyponatremia.[112]

CLINICAL PRESENTATION: EDEMA

Edema is usually first detected in the feet or periorbital or pretibial area in ambulatory patients and in the presacral area of bed-bound individuals. Edema is described as “pitting” when a depression created by exerting pressure for several seconds over a bony prominence, such as the tibia, does not rapidly refill. Edema severity is rated on a semi-quantitative scale of 1+ to 4+ depending on the depth of the pit: 1+ = 2 mm; 2+ = 4 mm; 3+ = 6 mm; and 4+ = 8 mm.

The extent of edema should be quantified according to the areas involved. Pretibial edema, for example, should be quantified according to how far it extends up the lower leg (eg, one-third up the lower leg). Pulmonary edema, an increase in lung interstitial and alveolar water, is often evidenced by crackles (rales) upon auscultation. Rales should be quantified according to how far the crackles extend from the dependent portion of the lung(s). For example, edema limited to the ankles and feet would indicate less severe edema than edema that extends halfway up the lower legs, and crackles limited to the base of both lungs in an upright person would indicate less severe pulmonary edema than crackles throughout both lung fields. *Anasarca* is a term used to refer to a massive amount of edema generalized throughout the body.

TREATMENT: EDEMA

General Approach

Treatment goals for hypervolemic hypernatremia are to minimize edema and to improve organ function, as well as to relieve symptoms (eg, dyspnea, abdominal distention, extremity pain). The presence of edema does not always dictate the need for diuretic therapy; however, severe pulmonary edema is life-threatening and requires immediate pharmacologic treatment. Other forms of edema may be treated less acutely, with a comprehensive approach that includes not only diuretics but also sodium and water restriction and optimal treatment of the underlying disease. Sodium intake should generally be restricted to 1,000 to 2,000 mg/day. A slow judicious approach in non-life-threatening situations will help minimize complications of diuretic therapy, including excessive diuresis, impaired perfusion, azotemia, impaired cardiac output due to decreased left ventricular end-diastolic filling pressure, and electrolyte abnormalities. Fluid should be removed cautiously in patients with cirrhosis and ascites but no peripheral edema. A maximum of 300 to 500 mL/day can be safely mobilized in patients with isolated ascites before the resultant decreased ECF volume leads to elevated BUN and possibly hepatorenal syndrome.[113]

Diuretic Therapy

Diuretics are the primary pharmacologic therapy for edema when severe or when treatment of the underlying disease and sodium and water restriction are insufficient. Diuretics can be categorized according to the site in the nephron where sodium reabsorption is inhibited. Loop diuretics (furosemide, bumetanide, torsemide, ethacrynic acid) inhibit the sodium–potassium–chloride (Na^+–K^+–$2Cl^-$) carrier in the loop of Henle, while thiazide and thiazide-like diuretics (hydrochlorothiazide, chlorothiazide, chlorthalidone, indapamide, metolazone) inhibit the Na^+–Cl^- carrier in the distal tubule. Potassium-sparing diuretics inhibit the sodium channel in the cortical collecting duct either directly (triamterene, amiloride) or by interfering with aldosterone activity (spironolactone, eplerenone). Acetazolamide, a carbonic anhydrase inhibitor, acts in the proximal convoluted tubule and has been used in patients with diuretic resistance.[27] Diuretic efficacy in patients with edema depends on the amount of filtered sodium normally reabsorbed at its site of action, the amount of sodium reabsorbed distal to its site of action, adequate drug delivery to the site of action, and the amount of sodium reaching the site of action.[27]

All diuretics act by inhibiting sodium reabsorption in the renal tubules, increasing the fractional excretion of sodium (FeNa). Loop diuretics are the most potent diuretics, as evidenced by the fact that they increase peak FeNa from

normal (1% [0.01] or less) to 20% to 25% (0.20-0.25). Thiazide- and potassium-sparing diuretics are less potent and increase peak FeNa only to 3% to 5% (0.03-0.05) and 1% to 2% (0.01-0.02), respectively.[27] Although a large portion of the filtered sodium is reabsorbed in the proximal nephron, the efficacy of proximal-acting diuretics (eg, acetazolamide) is limited by excess fluid and sodium reabsorption in the loop of Henle. Furthermore, sodium reabsorption by the distal tubule can compensate for reduced reabsorption in the loop of Henle when sodium intake is high.

The pharmacogenomics of diuretic therapy, particularly the thiazides, have been studied extensively in the setting of hypertension therapy.[114,115] Multiple genetic polymorphisms possibly affecting diuretic activity at the site of action have been identified, but no clinically significant differences in outcomes have been demonstrated in large randomized studies.[115,116] It is likely that a complex predictive model utilizing pharmacodynamic, pharmacokinetic, and pharmacogenomic parameters will be necessary to predict significantly different diuretic responses and outcomes due to the potential for compensatory mechanisms in other parts of the nephron. While genetic testing for gene variants is now available, it is not yet a practical option to guide diuretic treatment. Additional information regarding genetic testing can be found at www.ncbi.nlm.nih.gov.

The effectiveness of thiazide and loop diuretics is dependent on the drug concentration in the tubular lumen. These diuretics are delivered to the tubular lumen via active transport by the proximal tubular cells. Osmotic diuretics are freely filtered into the tubular lumen in the proximal tubule, whereas spironolactone reaches mineralocorticoid receptors in the cortical collecting duct via diffusion from the systemic circulation.[27]

A threshold concentration of loop or thiazide diuretic must be delivered to the respective site of action to achieve a natriuresis. Once the threshold concentration is achieved, a further diuretic dose increase will not elicit an increased diuretic response. Thus, a *ceiling dose* for these diuretics is recognized. In healthy subjects, administration of IV furosemide 40 mg results in excretion of 200 to 250 mEq (mmol) of sodium in 3 to 4 L of urine over a 3- to 4-hour period.[27]

Loop diuretics, except torsemide, have a rapid onset but short half-life requiring administration every 2 to 3 hours while thiazide diuretics have a longer half-life allowing for less frequent (once daily) dosing (**Table 66-10**). **Table 66-11** lists the maximal effective doses and dosing intervals for loop diuretics in patients with cirrhosis, HF, nephrotic syndrome, and kidney insufficiency.

TABLE 66-10 Characteristics of Thiazide Diuretics

Diuretic	Duration of Action	Initial Daily Dosage	Sequential Nephron Blockade	Maximum Total Daily Dose
Chlorothiazide	6-12 hours	250-500 mg once or twice	500-1,000 mg once plus loop diuretic	1,000 mg
Chlorthalidone	24-72 hours	12.5-25 mg once		100 mg
Hydrochlorothiazide	6-12 hours	25 mg once or twice	25-100 mg once or twice plus loop diuretic	200 mg
Indapamide	36 hours	2.5 mg once		5 mg
Metolazone	12-24 hours	2.5 mg once	2.5-10 mg plus loop diuretic	20 mg

TABLE 66-11 Characteristics of Loop Diuretics

		Recommended Doses				GFR 10-50 mL/min (0.17-0.83 mL/s)	GFR <10 mL/min (<0.17 mL/s)	Maximum Total Daily Dose[a]
Diuretic	Dosing Interval	Normal	Cirrhosis	HF	Nephrotic Syndrome			
Furosemide								
IV	6-8 hours	10-40 mg	40 mg	40-80 mg	120 mg	80 mg	200 mg	200 mg or 160 mg/hr
Oral	6-8 hours	20-80 mg	80 mg	80-160 mg	240 mg	160 mg	320-400 mg	600 mg
Bumetanide								
IV/oral	6-8 hours	1 mg	1 mg	2-3 mg	3 mg	2-3 mg	8-10 mg	10 mg
Torsemide								
IV/oral	24 hours	15-20 mg	10-20 mg	20-50 mg	50 mg	20-50 mg	50-100 mg	200 mg
Ethacrynic acid[b]								
IV	8-12 hours[c]	0.5-1 mg/kg (max 100 mg)						
Oral	12-24 hours	25-100 mg	50-100 mg	50-100 mg				400 mg

[a]Although these doses are generally accepted maximal doses, higher doses may be required due to insufficient quantities in the renal tubular fluid.

[b]Rarely used because of higher rates of ototoxicity and relative insolubility; may be used in a patient with a sulfa allergy.

[c]Repeat doses not routinely recommended.

HF, heart failure; GFR, glomerular filtration rate.

Patients with kidney insufficiency often require larger diuretic doses to achieve adequate drug concentrations at the site of action. The natriuretic response is decreased in patients with kidney insufficiency because the filtered

sodium load falls proportionately as GFR declines. This effect can be partially overcome by administering diuretics more frequently or by using a continuous infusion, a method commonly employed in critically ill patients. Continuous delivery will limit the effect of the post-diuresis sodium retention in the distal nephron. **Table 66-12** lists initial continuous infusion rates based on creatinine clearance and maximum recommended infusion rates.

TABLE 66-12 Continuous Infusion Rates for Loop Diuretics

Drug	Initial Infusion Rate based on Creatinine Clearance (CrCl)			Maximum Infusion Rate	
	CrCl <25 mL/min (0.42 mL/s)	CrCl 25-75 mL/min (0.42-1.25 mL/s)	CrCl >75 mL/min (1.25 mL/s)	Undiluted bolus	Continuous infusion
Bumetanide	1-2 mg/hr	0.5-1 mg/hr	0.5 mg/hr	5 mg/min	0.17 mg/min[a] (up to 5 mg)
Furosemide	20-40 mg/hr	10-20 mg/hr	10 mg/hr	40 mg/min	4 mg/min
Torsemide	10-20 mg/hr	5-10 mg/hr	5 mg/hr	100 mg/min	3.1 mg/hr[b]

[a]Doses of 2-5 mg may be given over 30-60 minutes in a suitable infusion fluid.

[b]Studies used a 100-mg total daily dose as a 25-mg injection over 2 minutes (25% of total daily dose) followed by an infusion of 3.1 mg/hr over 24 hours (75% of total daily dose).

Loop diuretic resistance can be caused by pronounced sodium reabsorption in the distal nephron when sodium absorption in the loop of Henle is blocked. If sodium intake is not restricted, this distal sodium reabsorption can compensate entirely for loop diuretic-induced sodium loss. Patients with diuretic-resistant edema can be treated with a loop diuretic and metolazone. Metolazone should be given first and allowed sufficient time to start blocking distal sodium reabsorption to maximize loop diuretic efficacy.

Impaired diuretic delivery to the site of action is another mechanism of diuretic resistance. Patients with HF and a normal GFR may have impaired oral furosemide absorption. An adequate diuresis is most readily sustained by increasing the frequency of diuretic administration, but a higher dose may also be effective (**Fig. 66-4**). Absorption of orally administered loop diuretics can be compromised by GI edema and delayed gastric emptying, conditions often seen in critically ill patients.

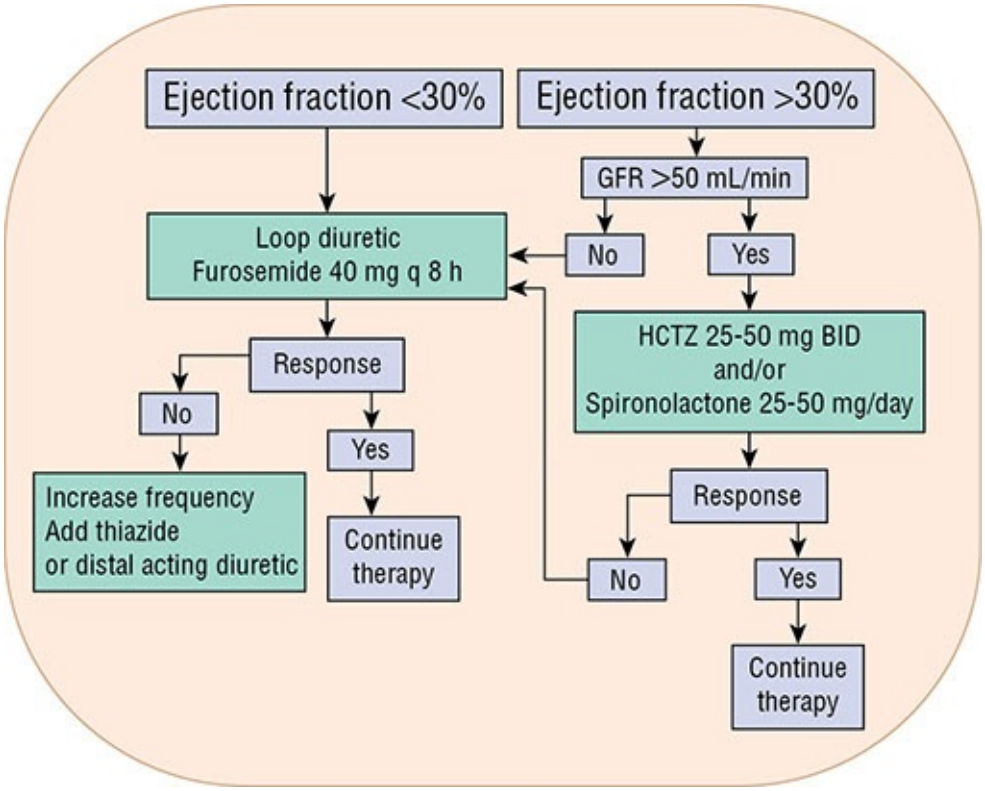


FIGURE 66-4 Algorithm for diuretic use in patients with heart failure. (GFR, glomerular filtration rate [50 mL/min is equivalent to 0.83 mL/s]; HCTZ, hydrochlorothiazide.)

Inadequate drug concentration at the site of action also can be caused by decreased perfusion as might be seen in patients with decompensated HF or those with decreased kidney perfusion. Due to extensive albumin binding (more than 95%), very little of these agents reach the tubule lumen by filtration, and they are almost exclusively transported into the proximal tubule lumen by active secretion via the organic acid secretory pathway.[27] When albumin binding is inhibited by concurrent sulfasoxazole administration, diuretic resistance persists, suggesting a decrease in intrinsic tubular sensitivity to loop diuretics.[117] This impaired natriuretic response can be overcome by using higher diuretic doses to increase unbound drug delivery to the secretory site in the nephron. Decreased intrinsic diuretic activity with repeated dosing may also play a role in diuretic resistance; the mechanism of which is not well understood. A combination of a loop diuretic with a distally acting diuretic is generally necessary to promote a natriuresis that exceeds distal tubular sodium reabsorption in patients with nephrotic syndrome (**Fig. 66-5**).[111]

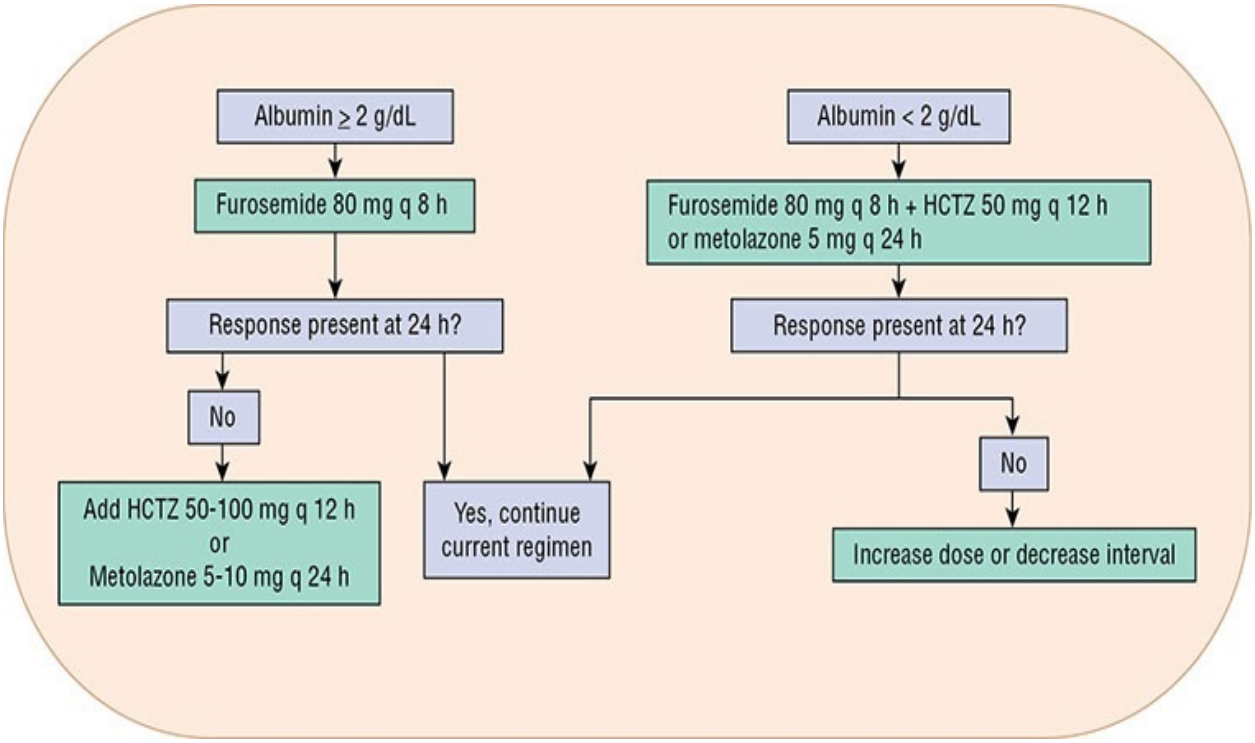


FIGURE 66-5 Algorithm for diuretic therapy in patients with nephrotic syndrome. Albumin concentration of 2 g/dL is equivalent to 20 g/L. (HCTZ, hydrochlorothiazide.)

Secondary hyperaldosteronism from activation of the renin–angiotensin–aldosterone system plays a major role in the pathogenesis of edema in patients with cirrhosis. Therefore, these patients should initially be treated with an aldosterone antagonist (spironolactone) in the absence of impaired GFR and hyperkalemia (**Fig. 66-6**). Thiazides can then be added for patients with a creatinine clearance greater than 50 mL/min (0.83 mL/s). For those with diuretic-resistant edema, a loop diuretic may be used instead of the thiazide. Patients with impaired GFR (creatinine clearance less than 40 mL/min [0.67 mL/s]) will require a loop diuretic, with addition of a thiazide in those who do not achieve adequate diuresis.[112]

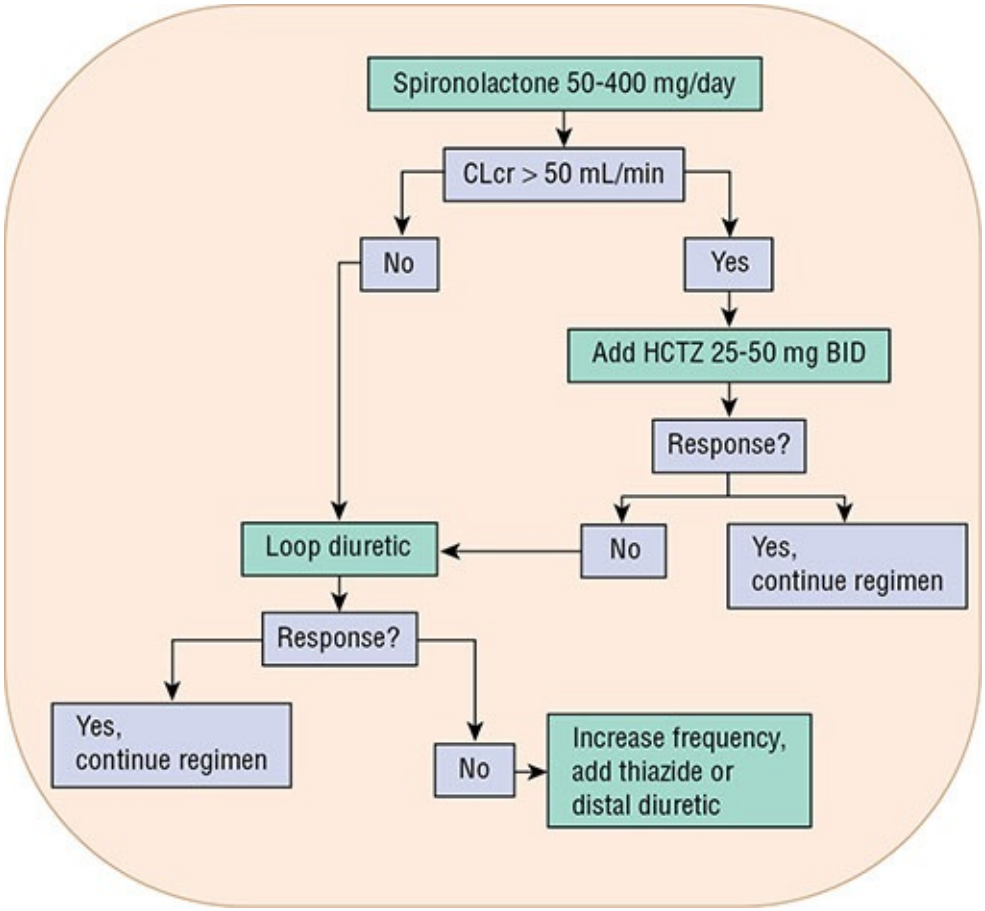


FIGURE 66-6 Algorithm for diuretic use in patients with cirrhosis. (CLcr, creatinine clearance [50 mL/min is equivalent to 0.83 mL/s]; HCTZ, hydrochlorothiazide.)

Adverse effects associated with loop and thiazide diuretics include hypokalemia, excess ECF volume loss (hypovolemia), hypomagnesemia, metabolic alkalosis, and hyperuricemia. Patients with refractory edema treated with high-dose synergistic combinations are at highest risk for developing hypokalemia.[11] As noted earlier, sodium imbalance is a concern with diuretic therapy: hyponatremia with thiazides, hypernatremia with loops. Calcium imbalance also can occur with diuretic use: hypocalcemia with loops, hypercalcemia with thiazides. Thiazide-induced hypercalcemia is more common in patients with mild subclinical hyperparathyroidism. Loop diuretics cause hypercalciuria and can lead to bone disorders (osteopenia, osteoporosis) or kidney stones when used chronically. Chronic use of potassium-sparing diuretics can cause a mild metabolic acidosis and hyperkalemia. Patients with moderate-to-severe kidney dysfunction or those receiving NSAIDs, ACEIs, or ARBs are at highest risk for hyperkalemia. In addition, spironolactone can cause reversible

gynecomastia in about 10% of men receiving it, and in about 50% of men receiving 150 mg/day or more. This side effect has not been associated with eplerenone.[118]

Evaluation of Therapeutic Outcomes

In patients with significant edema, volume status must be monitored carefully to ensure adequate tissue perfusion. Patients should be monitored by careful history and intermittent physical examination to detect signs and symptoms of edema as well as adverse effects. Physical examination should include measurement of blood pressure and pulse in either supine or seated positions and after standing for 2 to 3 minutes to assess for orthostasis. ECF volume can be estimated based on the height of the jugular venous pressure, extent of edema, heart and lung auscultation, and skin turgor. Follow-up monitoring 10 to 14 days after therapy initiation should include measurement of serum sodium, potassium, chloride, bicarbonate, magnesium, calcium, BUN, serum creatinine, and uric acid. A new steady-state balance will have developed over that time period and further fluctuations in ECF volume and electrolyte balance generally do not occur in the absence of a change in clinical status, diuretic dosage, or dietary intake. Repeated blood tests generally are not necessary at every visit unless there is a change in the patient's clinical status.

Postclass Engaged Learning Activity

Conduct a literature search and identify a primary research manuscript that has been published in the past 12 months regarding a medication to treat a disorder of sodium or water homeostasis. If the manuscript is regarding a medication that is discussed in the chapter, then briefly summarize the major findings and how this new information might change current practice. If the manuscript is related to a new medication that is not described in the chapter, then briefly summarize the medication's mechanism(s) of action and the potential advantages or disadvantages of this new medication compared to the current standard of care. This activity is intended to build your literature evaluation skills and ability to critically evaluate the biomedical literature.

ABBREVIATIONS

ACEI	angiotensin-converting enzyme inhibitor
AQP2	aquaporin 2
ARB	angiotensin receptor blocker
AVP	arginine vasopressin, also known as vasopressin and antidiuretic hormone (ADH)
ATPase	adenosine triphosphatase
BUN	blood urea nitrogen
CNS	central nervous system
D_5W	dextrose 5% in water
DDAVP	1-desamino-8-D-arginine vasopressin
DI	diabetes insipidus
ECF	extracellular fluid
FeNa	fractional excretion of sodium
GFR	glomerular filtration rate
GI	gastrointestinal
HF	heart failure
ICF	intracellular fluid
ICU	intensive care unit
IV	intravenous
NSAID	nonsteroidal anti-inflammatory drug
ODS	osmotic demyelination syndrome
SIADH	syndrome of inappropriate antidiuretic hormone secretion
TBW	total body water
VRA	vasopressin receptor antagonist
V_d	volume of distribution

REFERENCES

1. U.S. Department of Health and Human Services and U.S. Department of Agriculture. *2015–2020 Dietary Guidelines for Americans*. 8th ed. December 2015. Available at: http://health.gov/dietaryguidelines/2015/guidelines/. Accessed September 24, 2018.
2. Adrogué HJ, Madias NE. The challenge of hyponatremia. *J Am Soc Nephrol*. 2012;23:1140–1148.
3. Sterns RH. Disorders of plasma sodium: Causes, consequences, and correction. *N Engl J Med*. 2015;372:55–65.

4. Schrier RW. The science behind hyponatremia and its clinical manifestations. *Pharmacotherapy*. 2011;31(5 Pt 2):9S–17S.
5. Bhave G, Neilson EG. Volume depletion versus dehydration: How understanding the difference can guide therapy. *Am J Kidney Dis*. 2011;58:302–309.
6. Spasovski G, Vanholder R, Allolio B, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Nephrol Dial Transplant*. 2014;29(Suppl 2):ii1–ii39.
7. Patterson JH. The impact of hyponatremia. *Pharmacotherapy*. 2011;31(5 Pt 2):5S–8S.
8. Hawkins RC. Age and gender as risk factors for hyponatremia and hypernatremia. *Clin Chim Acta*. 2003;337:169–172.
9. Friedman B, Cirulli J. Hyponatremia in critical care patients: Frequency, outcome, characteristics, and treatment with vasopressin V2-receptor antagonist tolvaptan. *J Crit Care*. 2013;28:219.e1–219.e12.
10. Rondon-Berrios H, Bert T. Mild chronic hyponatremia in the ambulatory setting: Significance and management. *Clin J Am Soc Nephrol*. 2015;10:2268–2278.
11. Sarafidis PA, Georgianos PI, Lasaridis AN. Diuretics in clinical practice. Part II: Electrolyte and acid-base disorders complicating diuretic therapy. *Expert Opin Drug Saf*. 2010;9:259–273.
12. Chow KM, Szeto CC, Wong TY-H, et al. Risk factors for thiazide-induced hyponatraemia. *Q J Med*. 2003;96:911–917.
13. Gandhi S, Shariff SZ, Al-Jaishi A, et al. Second-generation antidepressants and hyponatremia risk: A population-based cohort study of older adults. *Am J Kidney Dis*. 2017;69:87–96.
14. Sahoo S, Grover S. Hyponatremia and psychotropics. *J Geriatri Ment Health*. 2016;3:108–122.
15. Cumming K, Hoyle GE, Hutchison JD, Soiza RL. Prevalence, incidence and etiology of hyponatremia in elderly patients with fragility fractures. *PLoS ONE*. 2014;9(2):e88272.
16. Correia L, Ferreira R, Correia I, et al. Severe hyponatremia in older patients at admission in an internal medicine department. *Arch Gerontol Geriatr*. 2014;54:642–647.
17. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. *Am J Med*. 2006;119(7A):S30–S35.

18. Hew-Butler T, Rosner MH, Fowkes-Godek S, et al. Statement of the third international exercise-associated hyponatremia consensus development conference, Carlsbad, California, 2015. *Clin J Sport Med*. 2015;25:303–320.
19. Almond CSD, Shin AY, Fortescue EB, et al. Hyponatremia among runners in the Boston Marathon. *N Engl J Med*. 2005;352:1550–1556.
20. Verbalis JG, Goldsmith SR, Greenberg A, et al. Diagnosis, evaluation, and treatment of hyponatremia: Expert panel recommendations. *Am J Med*. 2013;126:S1–S42.
21. Koczmara C, Wade AW, Skippen P, et al. Hospital-acquired acute hyponatremia and reports of pediatric deaths. *Dynamics*. 2010;21:21–26.
22. Asadollahi K, Beeching N, Gill G. Hyponatremia as a risk factor for hospital mortality. *Q J Med*. 2006;99:877–880.
23. Tachi T, Yokoi T, Goto C, et al. Hyponatremia and hypokalemia as risk factors for falls. *Eur J Clin Nutr*. 2015;69:205–210.
24. Fehlberg EA, Lucero RJ, Weaver MT, et al. Associations between hyponatraemia, volume depletion and the risk of falls in US hospitalised patients: A case–control study. *BMJ Open*. 2017;7:e017045.
25. Kuo SCH, Kuo PJ, Rau CS, et al. Hyponatremia is associated with worse outcomes from fall injuries in the elderly. *Int J Environ Res Public Health*. 2017;14:E460.
26. Palmer BF, Clegg DJ. Electrolyte and acid-base disturbances in patients with diabetes mellitus. *N Engl J Med*. 2015;373:548–559.
27. Sarafidis PA, Georgianos PI, Lasaridis AN. Diuretics in clinical practice. Part I: Mechanisms of action, pharmacological effects and clinical indications of diuretic compounds. *Expert Opin Drug Saf*. 2010;9:243–257.
28. Oh JY, Shin JI. Syndrome of inappropriate antidiuretic hormone secretion and cerebral/renal salt wasting syndrome: Similarities and differences. *Front Pediatr*. 2015;2:146. doi:10.3389/fped.2014.00146.
29. Liamis G, Milionis H, Elisaf M. A review of drug-induced hyponatremia. *Am J Kidney Dis*. 2008;52:144–153.
30. Decaux G. Is asymptomatic hyponatremia really asymptomatic? *Am J Med*. 2006;119(7A):S79–S82.
31. Kinsella S, Moran S, Sullivan MO, et al. Hyponatremia independent of osteoporosis is associated with fracture occurrence. *Clin J Am Soc*

Nephrol. 2010;5:275–280.

32. Ayus JC, Morits ML. Bone disease as a new complication of hyponatremia: Moving beyond brain injury. *Clin J Am Soc Nephrol*. 2010;5:167–168.
33. Sterns RH, Silver SM. Brain volume regulation in response to hypoosmolality and its correction. *Am J Med*. 2006;119(7A): S12–S16.
34. Fisher SK, Heacock AM, Keep RF, Foster DJ. Receptor regulation of osmolyte homeostasis in neural cells. *J Physiol*. 2010;18:3355–3364.
35. Ayus JC, Arrief AI. Chronic hyponatremic encephalopathy in post-menopausal women—association of therapies with morbidity and mortality. *JAMA*. 1999;281:2299–2304.
36. Murase TM, Sugimura Y, Takefuji S, et al. Mechanisms and therapy of osmotic demyelination. *Am J Med*. 2006;119(7A):S69–S73.
37. Jones GM, Bode L, Riha H, Erdman MJ. Safety of continuous peripheral infusion of 3% sodium chloride solution in neurocritical care patients. *Am J Crit Care*. 2016;26(1):37–42.
38. Miell J, Dhanjal P, Jamookeeah C. Evidence for the use of demeclocycline in the treatment of hyponatremia secondary to SIADH: A systematic review. *Int J Clin Pract*. 2015. doi:10.1111/ijcp.12713.
39. Curtis NJ, van Heyningen C, Turner JJ. Irreversible nephrotoxicity from demeclocycline in the treatment of hyponatremia. *Age Ageing*. 2002;31:151–152.
40. Berl T. Vasopressin antagonists. *N Engl J Med*. 2015;372:2207–2216.
41. Schrier RW, Gross P, Gheorghiade M, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N Engl J Med*. 2006;355:2099–2112.
42. Rozen-Zvi B, Yahav D, Gheorghiade M, et al. Vasopressin receptor antagonists for the treatment of hyponatremia: Systematic review and meta-analysis. *Am J Kidney Dis*. 2010;56:325–337.
43. Tzoulis P, Waung JA, Bagkeris E, et al. Real-life experience of tolvaptan use in the treatment of severe hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion. *Clin Endocrinol (Oxf)*. 2016;84:620–626.
44. Shoaf SE, Bramer SL, Bricmont P, Zimmer CA. Pharmacokinetic and pharmacodynamic interaction between tolvaptan, a non-peptide AVP

antagonist, and furosemide or hydrochlorthiazide. *J Cardiovasc Pharmacol*. 2007;50:213–222.

45. Der-Nigoghossian C, Lesch C, Berger K. Effectiveness and tolerability of conivaptan and tolvaptan for the treatment of hyponatremia in neurocritically ill patients. *Pharmacotherapy*. 2017;37(5):528–534.
46. Llompart-Pou JA, Pérez-Bárcena J, Novo M, Raurich JM. Effect of single-dose of tolvaptan in neurocritical patients with hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion. *Med Intensiva*. 2017;41(8):501–503.
47. Shoaf SE, Bricmont P, Dandurand A. Low-dose tolvaptan PK/PD: Comparison of patients with hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion to healthy adults. *Eur J Clin Pharmacol*. 2017;73(11):1399–1408.
48. Decaux G. V2-antagonists for the treatment of hyponatraemia. *Nephrol Dial Transplant*. 2007;22:1853–1855.
49. Pose A, Almenar L, Gavira JJ, et al. Benefit of tolvaptan in the management of hyponatraemia in patients with diuretic-refractory congestive heart failure: The SEMI-SEC project. *ESC Heart Fail*. 2017;4(2):130–137.
50. Rosskopf D, Michel MC. Pharmacogenomics of G protein-coupled receptor ligands in cardiovascular medicine. *Pharmacol Rev*. 2008;60:513–535.
51. Shoaf SE, Ohzone Y, Ninomiya S, et al. In vitro P-glycoprotein interactions and steady-state pharmacokinetic interactions between tolvaptan and digoxin in healthy subjects. *J Clin Pharmacol*. 2011:51:761–769.
52. Hauptman PJ, Zimmer C, Udelson J, et al. Comparison of two doses and dosing regimens of tolvaptan in congestive heart failure. *J Cardiolvasc Pharmacol*. 2005;46:609–614.
53. Ambrosy A, Goldsmith SR, Gheorghiade M. Tolvaptan for the treatment of heart failure: A review of the literature. *Exp Opin Pharmacother*. 2011;12:961–976.
54. Liu YH, Han XB, Fei YH, Xu HT. Long-term low-dose tolvaptan treatment in hospitalized male patients aged >90 years with hyponatremia: Report on safety and effectiveness. *Medicine (Baltimore)*. 2017;96(52):e9539.
55. McNeely EB, Talameh JA, Adams KFJr, et al. Relative bioavailability of

tolvaptan administered via nasogastric tube and tolvaptan tablets swallowed intact. *Am J Health-Syst Pharm*. 2013;70:1230–1237.

56. Shoaf SE, Bricmont P, Mallikaarjun S. Pharmacokinetics and pharmacodynamics of oral tolvaptan in patients with varying degrees of renal function. *Kidney Int*. 2014;85(4):953–961.
57. Katsumata M, Hirawa N, Sumida K, et al. Effects of tolvaptan in patients with chronic kidney disease and chronic heart failure. *Clin Exp Nephrol*. 2017;21(5):858–865.
58. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med*. 2012;367:2407–2418.
59. Rondon-Berrios H, Berl T. Vasopressin receptor antagonists in hyponatremia: Uses and misuses. *Front Med (Lausanne)*. 2017;4:141.
60. Ramamohan V, Mladsi D, Ronquest N, et al. An economic analysis of tolvaptan compared with fluid restriction among hospitalized patients with hyponatremia. *Hosp Pract (1995)*. 2017;45(3):111–117.
61. Dasta JF, Sundar S, Chase S, et al. Economic impact of tolvaptan treatment vs. fluid restriction based on real-world data among hospitalized patients with heart failure and hyponatremia. *Hosp Pract (1995)*. 2018:2:1–6.
62. Nagler EV, Haller MC, Van Biesen W, et al. Interventions for chronic non-hypovolaemic hypotonic hyponatraemia. *Cochrane Database Syst Rev*. 2018;6:CD010965.
63. FDA Adverse Event Reporting System (FAERS) Public Dashboard. US Food and Drug Administration. Available at: https://fis.fda.gov. as of 6/30/18. Accessed 11/10/18.
64. Gheorghiade M, Gottlieb SS, Udelson JE, et al. Vasopressin V_2 receptor blockade with *tolvaptan* versus fluid restriction in the treatment of hyponatremia. *Am J Cardiol*. 2006;97:1064–1067.
65. Dunlap ME, Hauptman PJ, Amin AN, et al. Current management of hyponatremia in acute heart failure: A report from the Hyponatremia Registry for patients with euvolemic and hypervolemic hyponatremia (HN Registry). *J Am Heart Assoc*. 2017;6:e005261.
66. Lee WH, Packer M. Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure. *Circulation.* 1986;73:257–267.

67. Klein L, O'Connor CM, Leimberger JD, et al. OPTIME-CHF Investigators. Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure: Results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study. *Circulation*. 2005;111:2454–2460.
68. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevation of creatinine: Is this a cause for concern? *Arch Intern Med*. 2000;160:685–693.
69. Baldasseroni S, Urso R, Orso F, et al. Relation between serum sodium levels and prognosis in outpatients with chronic heart failure: Neutral effect of treatment with beta-blockers and angiotensin-converting enzyme inhibitors: Data from the Italian network on congestive heart failure (IN-CHF database). *J Cardiovasc Med*. 2011;12:723–731.
70. Gerbes AL, Gulberg V, Gines P, et al. Therapy of hyponatremia in cirrhosis with a vasopressin receptor antagonist: A randomized double-blind multicenter trial. *Gastroenterology*. 2003;124:933–939.
71. Urso C, Brucculeri S, Caimi G. Employment of vasopressin receptor antagonists in management of hyponatraemia and volume overload in some clinical conditions. *J Clin Pharm Ther*. 2015;40:376–385.
72. Jia JD, Ding HG, Mao H, et al. Utility and safety of tolvaptan in cirrhotic patients with hyponatremia: A prospective cohort study. *Ann Hepatol*. 2017;16(1):123–132.
73. Tahara T, Mori K, Mochizuki M, et al. Tolvaptan is effective in treating patients with refractory ascites due to cirrhosis. *Biomed Rep*. 2017;7(6):558–562.
74. Sakaida I, Terai S, Kurosaki M, et al. Effectiveness and safety of tolvaptan in liver cirrhosis patients with edema: Interim results of post-marketing surveillance of tolvaptan in liver cirrhosis (START study). *Hepatol Res*. 2017;47(11):1137–1146.
75. Jaber BL, Almarzouqi L, Borgi L, et al. Short-term efficacy and safety of vasopressin receptor antagonists for treatment of hyponatremia. *Am J Med*. 2011;124(10):977.e1–977.e9.
76. Pose E, Solà E, Piano S, et al. Limited efficacy of tolvaptan in patients with cirrhosis and severe hyponatremia: Real-life experience. *Am J Med*. 2017;130(3):372–375.
77. Parekh A, Rajaram P, Patel G, Subramanian RM. Utility of tolvaptan in

the perioperative management of severe hyponatremia during liver transplantation: A case report. *Transplant Proc*. 2017;49(10):2399–2401.

78. Felker GM, Mentz RJ, Cole RT, et al. Efficacy and safety of tolvaptan in patients hospitalized with acute heart failure. *J Am Coll Cardiol*. 2017;69(11):1399–1406.
79. Konstam MA, Kiernan M, Chandler A, et al. Short-term effects of tolvaptan in patients with acute heart failure and volume overload. *J Am Coll Cardiol*. 2017;69(11):1409–1419.
80. Ikeda S, Ohshima K, Miyazaki S, et al. Impact of chronic kidney disease on the diuretic response of tolvaptan in acute decompensated heart failure. *ESC Heart Fail*. 2017;4(4):614–622.
81. Gheorghaide M, Niazi I, Quyang J, et al. Vasopressin V2-receptor blockage with tolvaptan in patients with chronic heart failure: Results from a double-blind randomized trial. *Circulation*. 2003;107:2690–2696.
82. Gheorghaide M, Gattis WA, O'Connor CM, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: A randomized controlled trial. *JAMA*. 2004;291:1963–1971.
83. Gheorghiade M, Konstam MA, Burnett JC Jr, et al. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: The EVEREST Clinical Status Trials. *JAMA*. 2007;297:1332–1343.
84. Konstam MA, Gheorghiade M, Burnett JCJr, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: The EVEREST Outcome Trial. *JAMA*. 2007;297:1319–1331.
85. Hauptman PJ, Burnett J, Gheorghiade M, et al. Clinical course of patients with hyponatremia and decompensated systolic heart failure and the effect of vasopressin receptor antagonism with tolvaptan. *J Card Fail*. 2013;19(6):390–397.
86. Costello-Boerrigter LC, Smith WB, Boerrigter G, et al. Vasopressin-2-receptor antagonism augments water excretion without changes in renal hemodynamics or sodium and potassium excretion in human heart failure. *Am J Physiol Renal Physiol*. 2006;290:F273–F278.
87. Udelson JE, McGrew FA, Flores E, et al. Multicenter, randomized, double-blind, placebo-controlled study on the effect of oral tolvaptan on left ventricular dilation and function in patients with heart failure and systolic dysfunction. *J Am Coll Cardiol*. 2005;49:2151–2159.
88. Yancy CW, Jessup M, Bozkurt B, et al. American College of Cardiology

Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128:e240–e327.

89. Hoorn EJ, Zietse R. Diagnosis and treatment of hyponatremia: compilation of the guidelines. *J Am Soc Nephrol*. 2017;28(5):1340–1349.
90. Adams KF, Glotzer J, Lee AK, et al. Pilot study of the relationship of ambient copeptin to the aquaretic effects of tolvaptan in patients with heart failure [ACC.15 abstract 1183-193]. *J Am Coll Cardiol*. 2015;65: (10S):A917.
91. Adams KF. Tolvaptan treatment to reverse worsening outpatient heart failure: Possible role of copeptin in identifying responders (TROUPER). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000. Available at: https://clinicaltrials.gov/ct2/show/NCT02476409. NLM Identifier: NCT02476409. Accessed 11/11/18.
92. Goldsmith SR. Is there a cardiovascular rationale for the use of combined vasopressin V1a/V2 receptor antagonists? *Am J Med*. 2006;119(7 Suppl 1):S93–S96.
93. Al-Absi A, Gosmanova EO, Wall BM. A clinical approach to the treatment of chronic hypernatremia. *Am J Kidney Dis*. 2012;60:1032–1038.
94. Overgaard-Steensen C, Ring T. Clinical review: practical approach to hyponatraemia and hypernatraemia in critically ill patients. *Crit Care*. 2013;17:206.
95. Waite MD, Fuhrman SA, Badawi O, et al. Intensive care unit-acquired hypernatremia is an independent predictor of increased mortality and length of stay. *J Crit Care*. 2013;28:405–412.
96. Palevsky PM, Bhagrath R, Greenberg A. Hypernatremia in hospitalized patients. *Ann Intern Med*. 1996;124:197–203.
97. Aiyagari V, Deibert E, Diringer MN. Hypernatremia in the neurologic intensive care: How high is too high? *J Crit Care*. 2006;21:163–172.
98. Stelfox HT, Ahmed SB, Khandwala F, et al. The epidemiology of intensive care unit-acquired hyponatraemia and hypernatraemia in medical-surgical intensive care units. *Crit Care*. 2008;12:R162.
99. Hoorn EJ, Betjes MG, Weigel J, Zietse R. Hypernatremia in critically ill

patients: Too little water and too much salt. *Nephrol Dial Transplant*. 2008;23:1562–1568.

100. Moritz ML, Ayus JC. The changing pattern of hypernatremia in hospitalized children. *Pediatrics*. 1999;104:435–439.
101. Lindner G, Funk GC. Hypernatremia in critically ill patients. *J Crit Care*. 2013;28:216.e11–216.e20.
102. Buckley MS, Leblanc JM, Cawley MJ. Electrolyte disturbances associated with commonly prescribed medications in the intensive care unit. *Crit Care Med*. 2010;38:S253–S264.
103. Chassagne P, Druesne L, Capet C, et al. Clinical presentation of hypernatremia in elderly patients: A case control study. *J Am Geriatr Soc*. 2006;54:1225–1230.
104. Saifan C, Nasr R, Mehta S, et al. Diabetes insipidus: A challenging diagnosis with new drug therapies. *ISRN Nephrol*. 2013;2013:797620. Available at: http://dx.doi.org/10.5402/2013/797620. Accessed October 2018.
105. Moritz ML. A water deprivation test is not indicated in the evaluation of hypernatremia [letter]. *Am J Kidney Dis*. 2005;46:1150–1151.
106. Feld LG, Neuspiel DR, Foster BA, et al. Clinical practice guideline: Maintenance intravenous fluids in children. *Pediatrics*. 2018;142:e20183083.
107. Semler MW, Self WH, Wanderer JP, et al. Balanced crystalloids versus saline in critically ill adults. *N Engl J Med*. 2018;378:829–839.
108. Shah A, Ellis G, Kucheria R. A guide for the assessment and management of post-obstructive diuresis. *Urology News*. 2015;19. Available at: www.urologynews.uk.com.
109. Reynolds RM, Padfield PL, Seckl JR. Disorders of sodium balance. *BMJ*. 2006;332:702–705.
110. Bockenhauer D, Bichet DG. Pathophysiology, diagnosis and management of nephrogenic diabetes insipidus. *Nat Rev Nephrol*. 2015;11:576–588.
111. Siddall EC, Radhakrishnan J. The pathophysiology of edema formation in the nephrotic syndrome. *Kidney Int*. 2012;82:635–642.
112. Somberg JC, Molnar J. Therapeutic approaches to the treatment of edema and ascites: The use of diuretics. *Am J Ther*. 2009;16:98–101.
113. Pockros PJ, Reynolds TB. Rapid diuresis in patients with ascites from chronic liver disease: The importance of peripheral edema.

Gastroenterology. 1986;90:1827–1833.

114. Thorn CF, Ellison DH, Turner ST, Altman RB, Klein TE. PharmGKB summary: Diuretics pathway, pharmacodynamics. *Pharmacogenet Genomics*. 2013;23:449–453.
115. Peters BJM, Klungel OH, de Boer A, Stricker BHCh, Maitland-vanderZee AH. Pharmacogenetics of cardiovascular drug therapy. *Clin Cases Miner Bone Metab*. 2009;6:55–65.
116. Voora D, Ginsburg GS. Clinical application of cardiovascular pharmacogenetics. *J Am Coll Cardiol*. 2012;60:9–20.
117. Agarwal R, Gorski JC, Sundblad K, Brater DC. Urinary protein binding does not affect response to furosemide in patients with nephrotic syndrome. *J Am Soc Nephrol*. 2000;11:1100–1105.
118. Nappi JM, Sieg A. Aldosterone receptor antagonists in patients with chronic heart failure. *Vasc Heal Risk Manag*. 2011;7:353–363.

67

Disorders of Calcium and Phosphorus Homeostasis

Amy Barton Pai and Angela L. Bingham

KEY CONCEPTS

1. Severe acute hypercalcemia can result in cardiac arrhythmias, whereas chronic hypercalcemia can lead to calcium deposition in soft tissues including blood vessels and the kidney.
2. The correction of hypercalcemia can include multiple pharmacotherapeutic modalities such as hydration, diuretics, bisphosphonates, and steroids, depending on the etiology and acuity of the hypercalcemia.
3. Hypocalcemia is typically associated with an insidious onset; however, some drugs such as cinacalcet are associated with rapid decreases in serum calcium.
4. Acute treatment of hypocalcemia requires calcium supplementation whereas chronic management may require other therapies such as vitamin D to maintain serum calcium concentrations.
5. Hyperphosphatemia occurs most frequently in patients with chronic kidney disease (CKD).
6. Treatment of nonemergent hyperphosphatemia includes the use of phosphate binders to decrease absorption of phosphorus from the gastrointestinal (GI) tract.
7. Hypophosphatemia is a relatively common complication among critically ill patients.
8. Treatment of acute hypophosphatemia usually requires IV phosphorus supplementation.

Preclass Engaged Learning Activity

Visit the Kidney Disease: Improving Global Outcomes (KDIGO) website and review the updated guidelines for CKD-Mineral and Bone Disorder (CKD-MBD). View the CKD-MBD Visual Guidelines related to “Management of Phosphate & Calcium Levels.” Explore the treatment algorithm and the information provided within the decision tree. This website addresses the COLLECT, ASSESS, and PLAN steps of the Patient Care Process and is useful to enhance student understanding of management of calcium and phosphorus in patients with CKD.

INTRODUCTION

Disorders of calcium and phosphorus are common complications of multiple acute and chronic diseases. These disorders are frequently seen in the acute care setting; however, they are also often present in ambulatory patients, usually in a less severe state. The consequences of electrolyte disorders can range from asymptomatic to life-threatening, requiring hospitalization and emergent treatment. The maintenance of fluid and electrolyte homeostasis requires adequate functioning and modulation by multiple hormones on tissues of multiple organ systems.

There are many common drug therapies that can disturb the normal homeostatic mechanisms that maintain calcium and phosphorus balance. In addition, with some drug therapies, toxicity is enhanced when underlying electrolyte disorders are present. Drug-induced disorders typically respond well to discontinuation of the offending agent(s); however, additional therapies are sometimes required to correct the disorder. This chapter reviews the etiology, classification, clinical presentation, and therapy for the most common disorders of calcium and phosphorus homeostasis.

DISORDERS OF CALCIUM HOMEOSTASIS

The maintenance of physiologic calcium concentrations in the intracellular and extracellular spaces is vital for the preservation and function of cell membranes; propagation of neuromuscular activity; regulation of endocrine and exocrine secretory functions; blood coagulation cascade; platelet adhesion process; bone metabolism; muscle cell excitation/contraction coupling; and mediation of the

electrophysiologic slow-channel response in cardiac and smooth-muscle tissue.

The disorders of calcium homeostasis are related to the calcium content of the extracellular fluid (ECF), which is tightly regulated and comprises less than 0.5% of the total body stores of calcium. Skeletal bone contains more than 99% of total body stores of calcium.[1] ECF calcium is moderately bound to plasma proteins (40%), primarily albumin.[2] Ionized or free calcium is the physiologically active form and is the fraction that is homeostatically regulated.[3] Extracellular calcium, however, is most commonly measured as the total serum calcium concentration, which includes both bound and unbound calcium.[2] The normal total calcium serum concentration range is 8.6 to 10.2 mg/dL (2.15-2.55 mmol/L).[3]

Proper assessment of total serum calcium concentrations includes measurement of the patient's serum albumin concentration. Hypoalbuminemia, which can be associated with many chronic disease states, is probably the most common cause of "laboratory hypocalcemia." Patients remain asymptomatic because the unbound or ionized fraction of serum calcium remains normal (normal range, 4.48-5.2 mg/dL [1.12-1.30 mmol/L]).[3] A corrected total serum calcium concentration can be calculated based on the measured total serum calcium and the difference between a patient's measured albumin concentration and the normative value of 4 g/dL (40 g/L) by the following equations:

$$\text{Corrected Serum Calcium (mg/dL)} = \text{Measured Serum Calcium (mg/dL)} + (0.8 \times [4\ \text{g/dL} - \text{measured albumin (g/dL)}])$$

or

$$\text{Corrected Serum Calcium (mmol/L)} = \text{Measured Serum Calcium (mmol/L)} + (0.02 \times [40\ \text{g/L} - \text{measured albumin (g/L)}])$$

The concentration of ionized calcium is closely regulated by the interactions of parathyroid hormone (PTH), phosphorus, vitamin D, and calcitonin (**Fig. 67-1**). PTH increases serum calcium concentrations by stimulating calcium release from bone, increasing renal tubular reabsorption, and enhancing absorption in the gastrointestinal (GI) tract secondary to increased renal production of 1,25-dihydroxy vitamin D3. Vitamin D directly increases serum calcium, as well as phosphorus concentrations, by increasing GI absorption. Indirectly, it can also lead to calcium release from bone and reduced renal excretion. Calcitonin inhibits osteoclastic bone resorption. Calcitonin plasma concentrations are

increased when ionized calcium concentrations are high as the body attempts to return the calcium concentration to the normal range. Disruption of these homeostatic mechanisms results in the clinical manifestations of hypercalcemia or hypocalcemia.

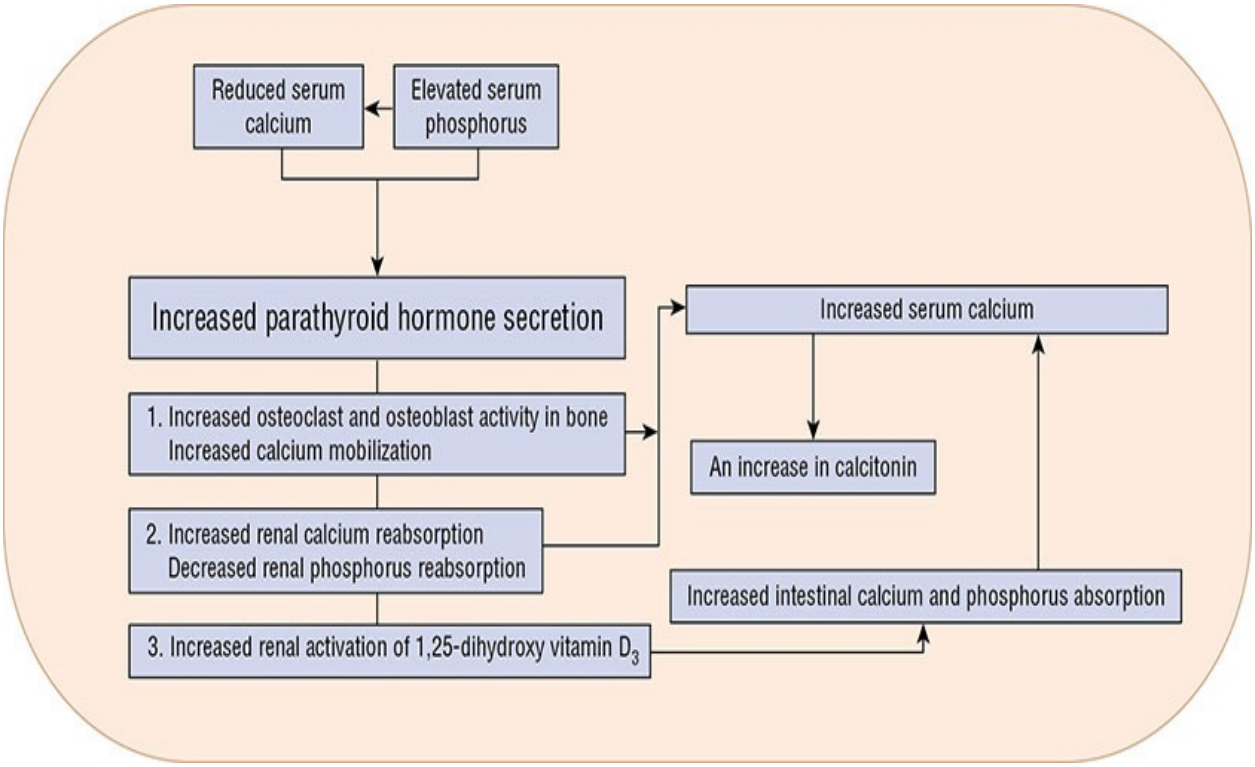


FIGURE 67-1 Homeostatic mechanisms to maintain serum calcium concentrations.

Total serum calcium and ionized calcium are poorly correlated in patients with hypoalbuminemia, critical illness, and acid-base disorders. Alteration of the concentration of albumin or its binding of calcium can be expected to change the unbound fraction of total serum calcium. Each 1 g/dL (10 g/L) drop in the serum albumin concentration below 4 g/dL (40 g/L) will result in a decrease of total serum calcium concentration by 0.8 mg/dL (0.20 mmol/L).[2] This approach to calculating an albumin-adjusted calcium concentration has been found to overestimate the degree of hypercalcemia and usually fails to identify hypocalcemia in critically ill patients, because the ionized calcium concentration may be normal despite a low total serum calcium concentration in the setting of hypoalbuminemia. Therefore, ionized calcium values should be used to assess calcium status in critically ill patients.[3,4] Change in extracellular fluid pH is the most significant cause of changes in calcium binding to albumin. In the presence

of acute metabolic alkalosis the fraction of calcium bound to albumin is increased, thus reducing the plasma concentration of ionized calcium. This can result in symptomatic hypocalcemia with paresthesia, muscle cramping and spasms, memory loss, and seizures.[1] Conversely, metabolic acidosis decreases calcium binding to albumin and results in increased ionized calcium.

HYPERCALCEMIA

There are multiple and diverse causes of hypercalcemia (total serum calcium more than 10.2 mg/dL [2.55 mmol/L]) (Table 67-1). The most common causes of hypercalcemia are cancer and primary hyperparathyroidism.

TABLE 67-1 Etiologies of Hypercalcemia

Neoplasms	**Medications**
Bone metastasis	Thiazides
Breast	Lithium
Multiple myeloma	Vitamin D
Lymphoma	Vitamin A
Leukemia	Calcium
Humoral induced	Aluminum/magnesium antacids
Ovary	Theophylline
Kidney	Tamoxifen
Pheochromocytoma	Ganciclovir
Multiple endocrine neoplasia	**Granulomatous disease**
Lung	Sarcoidosis
Head and neck	Tuberculosis
Esophagus	Cryptococcus
Cervix	Berylliosis
Lymphoproliferative disease	Histoplasmosis
Hyperparathyroidism	Coccidioidomycosis
Primary	Leprosy
Tertiary	**Endocrine disease**
Miscellaneous	Adrenal insufficiency
Immobilization	Hyperthyroidism
Paget's disease	Acromegaly
Familial hypocalciuric hypercalcemia	
Adolescence	
Rhabdomyolysis	

Epidemiology and Etiology

Primary hyperparathyroidism occurs predominantly after age 50 and affects women 3 to 4 times more than men.[5] Hypercalcemia associated with cancer

occurs in approximately 15% to 70% of cancer patients at some time during the course of their disease and is dependent on tumor type.[6] Cancer-associated hypercalcemia is predominantly encountered in hospitalized patients, whereas primary hyperparathyroidism accounts for the vast majority of cases in the outpatient setting.[7,8]

Pathophysiology

Hypercalcemia is the result of one or a combination of three primary mechanisms: increased bone resorption, increased GI absorption, or increased tubular reabsorption by the kidneys (see Fig. 67-1).

Many tumors secrete PTH-related protein (PTHrP), which binds to the PTH receptors in bone and kidney tissue, leading to increased bone resorption and tubular reabsorption.[9] Tumors can also secrete substances such as vitamin D, transforming growth factor, interleukins, prostaglandins, interferon, tumor necrosis factor, and granulocyte-macrophage colony-stimulating factor, which are associated with the development of hypercalcemia.[6] Hypercalcemia of malignancy is generally associated with bone metastases and is a common complication of squamous cell carcinomas of the lung, head, and neck, hematologic malignancies such as multiple myeloma and T-cell lymphomas, and carcinomas of ovary, kidney, bladder, and breast. The most frequent types of malignancy associated with hypercalcemia are carcinomas of the lung and breast.[6] Breast and squamous cell lung carcinomas secrete PTHrP which binds to the type I PTH receptor (PTHR1) and enhances bone resorption.[9,10] In contrast, up to 40% of patients with multiple myeloma develop hypercalcemia principally as the result of osteoclast-mediated bone destruction.[6]

Primary hyperparathyroidism is the most common cause of chronic hypercalcemia in the general population. Benign parathyroid adenomas account for 80% to 85% of these cases of hyperparathyroidism, parathyroid hyperplasia accounts for 15%, and parathyroid carcinoma is the cause in less than 1% of cases.[7]

Other causes of chronic hypercalcemia include medications, endocrine and granulomatous disorders, physical immobilization, high bone-turnover states (adolescence and Paget’s disease), and rhabdomyolysis. Increased GI absorption can be the result of excessive ingestion of vitamin D analogs, calcium supplements, and lithium. Lithium and vitamin A therapy can increase bone resorption, whereas increased renal tubular reabsorption of calcium can occur with thiazide and lithium therapy. The exact mechanism of lithium-induced

hypercalcemia is not known but may include competitive inhibition of calcium influx into cells, increasing the threshold sensitivity of the calcium-sensing receptor (CaSr) and subsequent inhibition of PTH gene transcription.[10] Addison's disease, acromegaly, and thyrotoxicosis are endocrine disorders that can lead to hypercalcemia because of increased renal tubular reabsorption and increased bone resorption. Milk-alkali syndrome is the term applied to those situations where an individual develops hypercalcemia following the ingestion of calcium and absorbable alkali (eg, calcium carbonate) and is a frequent cause of hypercalcemia in patients who are not on dialysis.[11,12] Finally, the granulomatous disorders (sarcoidosis, tuberculosis, histoplasmosis, and leprosy) are associated with hypercalcemia secondary to an increase in GI and renal tubular absorption as the result of granuloma production of 1,25-dihydroxy vitamin D2.[13]

Patients with mild-to-moderate hypercalcemia, that is, total serum calcium concentrations above the upper threshold of normal but less than 13 mg/dL (3.25 mmol/L) or ionized calcium concentrations less than 6 mg/dL (1.50 mmol/L) can often be asymptomatic. This is typically the case for the vast majority of patients who have drug-induced hypercalcemia or primary hyperparathyroidism.[13,14] In fact, one study noted normocalcemia in approximately 20% of patients with a diagnosis of primary hyperparathyroidism, suggesting target tissue resistance to PTH.[14]

Clinical Presentation

1 The presenting signs and symptoms of severe hypercalcemia that occur if the total serum calcium concentration is more than 13 mg/dL (3.25 mmol/L) may differ depending on the acuity of onset.[2] Hypercalcemia of malignancy usually develops quickly and is accompanied by a classic symptom complex of anorexia, nausea and vomiting, constipation, polyuria, polydipsia, and nocturia.[6] Polyuria and nocturia secondary to a urinary-concentrating defect constitute some of the most frequent renal effects of hypercalcemia.[13] Hypercalcemic crisis is characterized by an acute elevation of total serum calcium to a value more than 15 mg/dL (3.75 mmol/L), acute kidney injury, and obtundation (inability to arouse).[14,15] If untreated, hypercalcemic crisis can progress to oliguric acute kidney injury, coma, and life-threatening ventricular arrhythmias.[13] The primary complications associated with chronic hypercalcemia (hyperparathyroidism) include metastatic calcification, hypercalciuria, and chronic kidney disease secondary to interstitial nephrocalcinosis.[13]

Calcium and/or calcium–phosphorus complex deposition in blood vessels and multiple organs is a complication of chronic hypercalcemia and/or concomitant hyperphosphatemia and hyperparathyroidism. Calcium deposits in atherosclerotic lesions contribute to cardiac disease.[16] Intracardiac and arterial calcifications have been found in patients with Paget's disease who have normal kidney function. It is hypothesized that similar calcification processes occur in both bone and vascular tissue, leading to cardiovascular diseases including heart failure, systolic hypertension, and ischemic heart disease.[17]

CLINICAL PRESENTATION

Hypercalcemia

General

- The signs and symptoms of hypercalcemia depend on the severity and on the rapidity of onset.

Symptoms

- Symptoms include fatigue, weakness, anorexia, depression, anxiety, cognitive dysfunction, vague abdominal pain, and constipation. Renal symptoms can include polyuria, polydipsia, and nocturia. Rarely, severe hypercalcemia leads to acute pancreatitis.

Signs

- Renal: Nephrolithiasis; renal tubular dysfunction, particularly decreased concentrating ability; and acute and chronic kidney disease.
- Cardiovascular: Hypercalcemia also directly shortens the myocardial action potential, which is reflected in a shortened QT interval and coving of the ST-T wave. Spontaneous ventricular tachyarrhythmias and elevations in blood pressure have also been reported. Chronic hypercalcemia can lead to cardiac calcification.
- Musculoskeletal: Rheumatologic complaints related to hyperparathyroidism include gout, pseudogout, and chondrocalcinosis.

Laboratory Tests

- Serum calcium concentrations of more than 10.2 mg/dL (2.55 mmol/L) are considered to represent hypercalcemia. Patients with values up to 13

mg/dL (3.25 mmol/L) are generally considered to have mild or moderate hypercalcemia, whereas those with values greater than this indicate the presence of severe hypercalcemia.

The electrocardiographic changes associated with hypercalcemia include shortening of the QT interval and coving of the ST-T wave.[13] Very high-serum calcium concentrations can cause T-wave widening, indicating a repolarization defect that may be associated with spontaneous ventricular tachyarrhythmias.[13] Hypertension and arrhythmias have occurred in the setting of hypercalcemia. The effects of digoxin on cardiac conduction including lowering of the excitation threshold, shortening of the effective refractory period, and increased atrioventricular refractoriness can be potentiated by hypercalcemia.[18]

Nephrolithiasis

Nephrolithiasis (kidney stones) and nephrocalcinosis (calcium deposits in the kidney) are the primary renal complications arising from long-standing hypercalcemia, as the result of primary hyperparathyroidism. Stone formation is dependent on a favorable milieu within the kidney or urinary tract, such as oversaturation of the urine and/or reduced concentrations of endogenous inhibitors of crystal formation (eg, citrate or pyrophosphate). It is estimated 20% to 30% of patients with primary hyperparathyroidism exhibit nephrolithiasis.[19,20] Of note, in those patients with low-glomerular filtration rates (GFRs), the 24-hour urinary calcium will actually diminish secondary to decreased production of 1,25-dihydroxy vitamin D2. However, the fractional excretion of calcium might increase.[20] Sarcoidosis is the other hypercalcemic condition frequently associated with calcium stones.[13] Other causes of nephrolithiasis with calcium-containing stones include hypocitraturia, renal tubular acidosis, hyperoxaluria, and hyperuricosuria, which are conditions that are prevalent among bariatric surgery patients.[21,22] Stone formers who have primary hyperparathyroidism are more likely to be women, older than 50 years, and have a family history of multiple endocrine disorders.[19] High-dietary sodium intake can also raise urinary calcium concentrations, perhaps due to a reduction in calcium reabsorption in the kidney, thus predisposing patients to calcium stones. Although CKD can be the ultimate result of persistent stones, it is the primary cause of kidney disease in less than 2% of the end-stage renal disease population.

TREATMENT

Desired Outcome

The indications for the treatment of acute hypercalcemia are dependent on the severity of hypercalcemia, acuity of its development, and presence or absence of symptoms requiring emergent treatment (eg, necrotizing pancreatitis). The therapeutic intervention plan should be crafted to reverse signs and symptoms, restore normocalcemia within hours to days depending on acuity, and correct or manage the underlying cause of hypercalcemia.

General Approach

Chronic hypercalcemia is usually caused by an underlying medical condition or prescribed pharmacotherapies that can be resolved by successful treatment of the condition or withdrawal of the offending agent resulting in a decrease in serum calcium within days or weeks. Acute hypercalcemic episodes induced by malignancies may be mitigated by chemotherapy and/or radiation treatment. Effective surgical or drug treatment of primary hyperparathyroidism should reduce serum calcium concentrations as well as reduce the development of long-term complications such as vascular complications, CKD, and kidney stones. For treatment of nephrolithiasis the goal in management of serum calcium is prevention of stone formation and diameter. The reduction of serum calcium should be targeted at the underlying disease state causing hypercalcemia (eg, using cinacalcet for primary hyperparathyroidism). Hypercalcemic crisis and acute symptomatic severe hypercalcemia should be considered medical emergencies and treated immediately (**Fig. 67-2**).

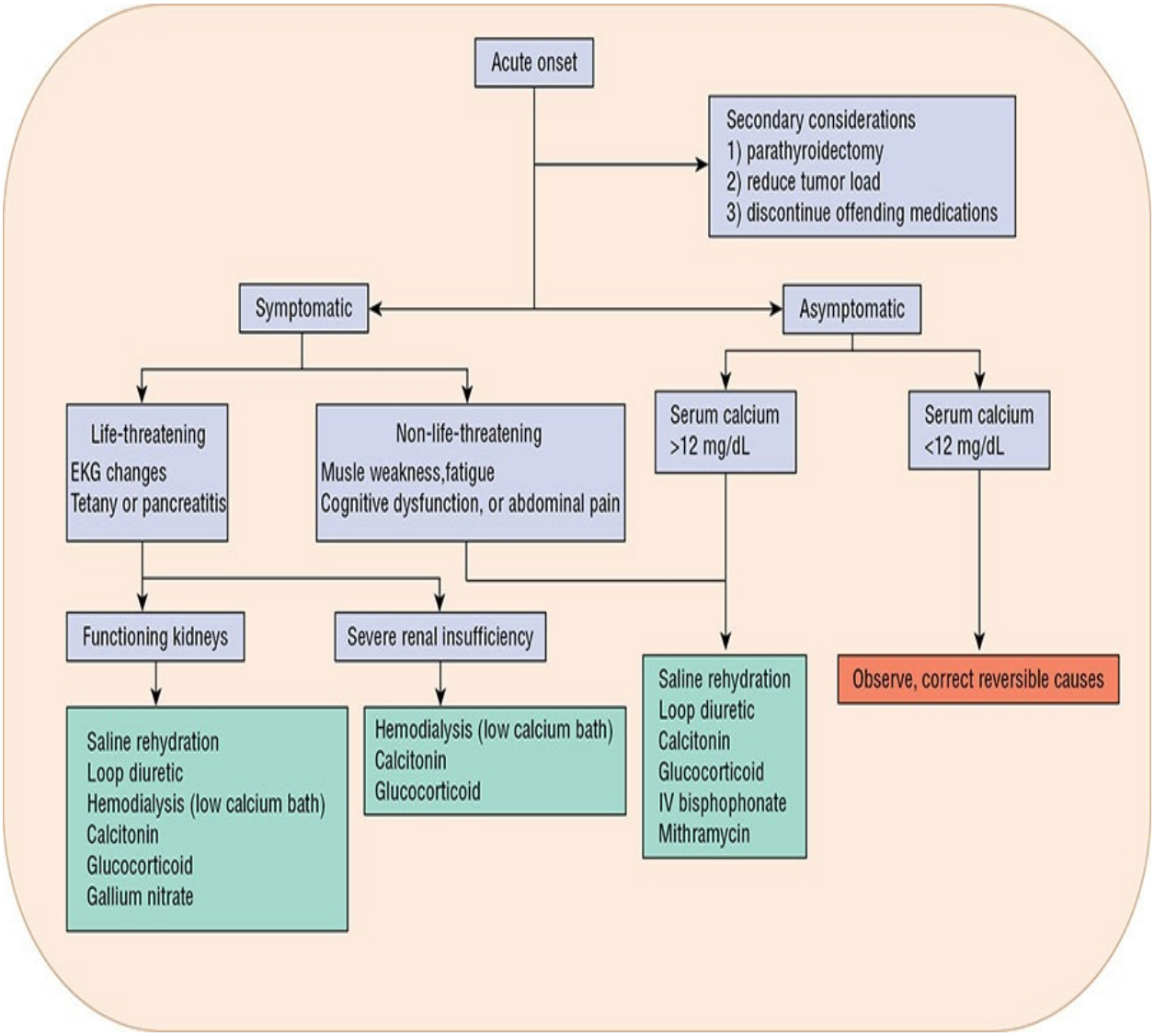
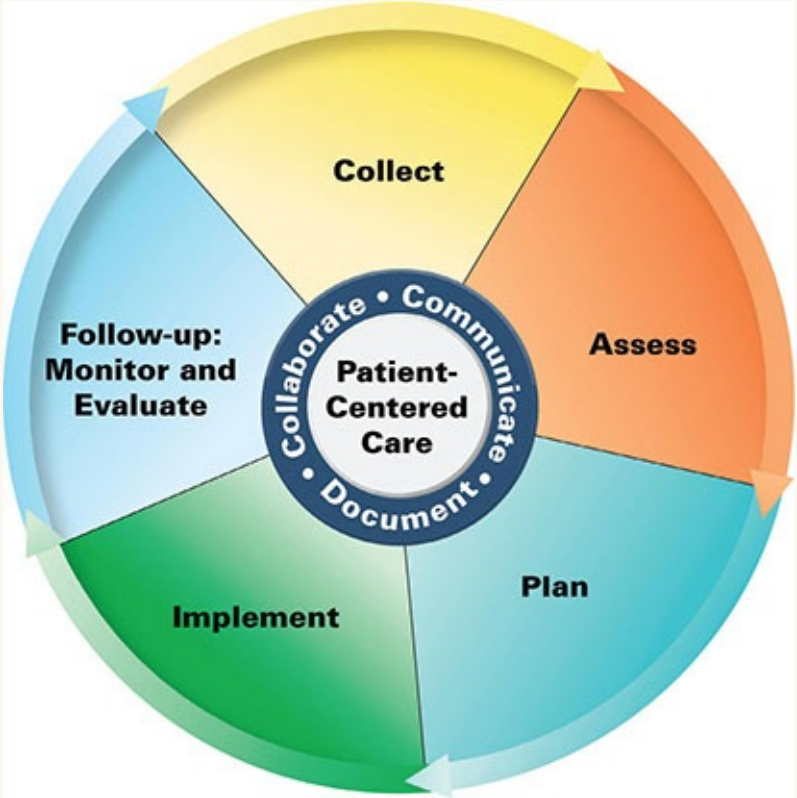


FIGURE 67-2 Pharmacotherapeutic options for the acutely hypercalcemic patient. Serum calcium of 12 mg/dL is equivalent to 3 mmol/L.

These patients may require immediate-acting interventions to promptly reduce the serum calcium concentration if electrocardiographic (ECG) changes, neurologic manifestations, or pancreatitis are present. Pharmacologic therapy consisting of volume expansion and enhancement of urinary calcium excretion with loop diuretics is usually the initial management strategy. Hemodialysis against a zero- or low-calcium dialysate solution should be considered for patients with severely impaired kidney function (CKD stage 4 or 5) who cannot tolerate large fluid loads and in whom diuretics have limited efficacy.[13]



Patient Care Process for the Management of Hypercalcemia

Collect

- Patient characteristics (eg, age, race, sex)
- Patient history (past medical, family, social—dietary habits)
- Evaluate symptoms (see “Clinical Presentation: Hypercalcemia”)
- Current medications, including over-the-counter medications, herbal products, nutritional supplements
- Objective data (see “Clinical Presentation: Hypercalcemia”)
  - Blood pressure, heart rate, height, weight
  - Labs (serum calcium and albumin, ionized calcium when available)
  - Other diagnostic tests when indicated (eg, ECG)

Assess

- Plausible etiology for hypercalcemia (see Table 67-1)

- Acuity of symptoms and urgency for treatment (see Fig. 67-2)
- Current medications and dietary intake that may contribute to or worsen hypercalcemia
- Kidney function (eg, creatinine clearance)
- Serum calcium goal

Plan*

- Pharmacotherapy based on etiology of hypercalcemia including specific dose, route of administration, frequency of administration, and anticipated duration of treatment (see Table 67-2)
- Monitoring parameters including efficacy (eg, reduction in serum calcium, resolution of symptoms), safety (medication-specific adverse effects), and time frame (see Table 67-2)
- Patient education (eg, purpose of treatment, drug therapy, expected time to reduce calcium, need for future medications)

Implement*

- Provide patient education regarding all elements of treatment plan
- Schedule follow-up based on acuity and symptoms

Follow-up: Monitor and Evaluate

- Measure serum calcium to determine response
- Presence of adverse effects
- Consider alternative medication management if desired reduction in calcium is not achieved

* *Collaborate with patient, caregivers, and other healthcare professionals.*

Effective treatment of moderate-to-severe hypercalcemia in the absence of life-threatening symptoms begins with attention to the underlying disorder and correction of associated fluid and electrolyte abnormalities. Patients with primary hyperparathyroidism may require surgery, particularly if they have systemic manifestations.

Patients with malignancy often require surgical or chemotherapeutic reduction of tumor load to control the exogenous supply of cytokines and hormones (eg, PTHrP) that cause hypercalcemia. In contrast, patients with drug-

induced hypercalcemia generally respond to discontinuation of the offending agent.

Pharmacologic Therapy

2 **Symptomatic Patient Management** For those patients with normal-to-moderately impaired kidney function (CKD stages 1-3), the cornerstone of initial first-line treatment of severe, acute hypercalcemia or hypercalcemic crisis is volume expansion with normal saline to increase natriuresis and ultimately urinary calcium excretion (**Table 67-2**). Patients with symptomatic hypercalcemia are often extracellular volume depleted secondary to vomiting and polyuria; thus, rehydration with saline-containing fluids is necessary to interrupt the stimulus for sodium and calcium reabsorption in the renal tubule.[23] Rehydration can be accomplished by the rapid infusion of 1 to 2 L of normal saline followed by a maintenance infusion at 250 to 300 mL/hr, until the patient is fluid resuscitated and serum calcium approaches the upper limit of the normal range.[23] The precise rate depends on concomitant conditions (primarily cardiovascular and renal) and magnitude of hypercalcemia. Patients with advanced kidney disease typically cannot tolerate volume expansion so a saline infusion is contraindicated. The saline infusion rate can be decreased to a rate that approximates the patient's intake of oral or IV fluids. See Chapter 66 for a thorough discussion of how to calculate water deficit and monitor patient's response to saline infusion. Loop diuretics such as furosemide (40-80 mg IV every 1-4 hours) have been used to increase urinary calcium excretion.[23] Loop diuretics block calcium (and sodium) reabsorption in the thick ascending limb of the loop of Henle and augment the calciuric effect of saline alone. Rehydration prior to loop diuretic use is critical because if dehydration persists or becomes worse, the serum calcium can actually increase because of enhanced proximal tubule calcium reabsorption.[24] The primary role for loop diuretics in the setting of hypercalcemia is to minimize the development of volume overload from the administration of saline (Fig. 67-2 and Table 67-2). Furosemide should not be used first line as there is little evidence that supports the efficacy of furosemide in treatment of hypercalcemia.[24] Potassium chloride, 10 to 20 mEq/L (mmol/L), should be considered for addition to the saline infusion after rehydration is accomplished to prevent the development of hypokalemia that is a common adverse effect of aggressive diuretic therapy. Serum magnesium concentrations should also be monitored, and magnesium replacement instituted if magnesium concentrations fall below 1.8 mg/dL (0.74 mmol/L). Rehydration with saline and administration of furosemide may result in normalization of total serum calcium

within 24 to 48 hours; however, patients should be monitored closely for fluid overload.[23,24] Hemodialysis with low or zero calcium dialysate is a treatment option in the case of failure or when calcium concentrations are life threatening.[24] It should be noted that preparing a patient for hemodialysis takes time to achieve vascular access; thus, this approach is best suited for patients already receiving hemodialysis chronically.

TABLE 67-2 Drug Dosing Table for Hypercalcemia

Drug/Brand Name	Starting Dosage	Time Frame to Initial Response	Monitoring and Special Population Considerations
0.9% saline ± electrolytes	200-300 mL/hr	24-48 hours	Electrolyte abnormalities, fluid overload, CI in advanced kidney disease, congestive heart failure
Loop diuretics Furosemide/Lasix® Bumetandide/Bumex® Torsemide/Demadex®	40-80 mg IV q 1-4 hr of furosemide or equivalent	N/A	Electrolyte abnormalities (potassium and magnesium), CI in patients with allergy to sulfas (use ethacrynic acid)
Calcitonin/Miacalcin®	4 units/kg q 12 hr SC/IM 10-12 units/hr IV	1-2 hours	Facial flushing, nausea/vomiting, allergic reaction, CI in patients with allergy to calcitonin
Pamidronate/Aredia®	30-90 mg IV over 2-24 hours	2 days	Fever, fatigue, skeletal pain
Zoledronate/Zometa®	4-8 mg IV over 15 minutes	1-2 days	Fever, fatigue, skeletal pain, CI in advanced kidney disease
Glucocorticoids	40-60 mg oral prednisone equivalents daily	3-5 days	Diabetes, osteoporosis, infection, CI in patients with serious infections, hypersensitivity

CI, contraindicated; SC, subcutaneous.

Asymptomatic Patient Management

Calcitonin In those patients in whom saline hydration therapy is contraindicated (eg, those with severe congestive heart failure [CHF] or moderately-to-severely impaired kidney function), short-term therapy with calcitonin is a viable alternative agent to initiate reduction of serum calcium concentrations within 24 to 48 hours. Calcitonin has a rapid onset of action (within 1-2 hours); however, the degree and extent of serum calcium concentration reduction are often unpredictable.[2]

Subcutaneous or IV administration of salmon calcitonin, 4 to 8 international units/kg every 12 hours, has been used to manage hypercalcemia in patients malignancy.[25] The intranasal formulation of calcitonin has been used in doses of 200 to 400 international units daily; unfortunately, this has resulted in only mild decreases in serum calcium. The lack of significant efficacy of the synthetic

intranasal formulation is the result of the lower potency and shorter duration of action as compared to salmon calcitonin.

Pharmacology Calcitonin decreases serum calcium concentrations, primarily by inhibiting bone resorption. It can also reduce renal tubular reabsorption of calcium, thus promoting calciuresis.[25] Calcitonin from salmon sources is most commonly administered subcutaneously or intramuscularly (for larger volumes), which may rapidly lower calcium concentrations initially, but the effect can be transient.[25]

Adverse Effects The side effects from IV administered calcitonin (facial flushing, nausea, and vomiting) limit patient acceptability. Allergic reactions, although rare, do occur; therefore, a test dose (intradermal injection of 0.1 mL of a 10 units/mL solution) can be given prior to starting therapy.[25] If marked erythema and/or wheal formation does not occur within 15 minutes after administration, then therapy can be initiated. Salmon calcitonin therapy is associated with tachyphylaxis caused by antibody formation to foreign proteins or molecules resembling the calcitonin polypeptide.[26] Tachyphylaxis has been primarily documented in patients receiving therapy for more than 4 months and thus might not be clinically significant in the acute care setting. The addition of corticosteroid therapy or conversion to human calcitonin increases effectiveness.[2]

Bisphosphonates Bisphosphonates block bone resorption very efficiently, render the hydroxyapatite crystal of bone mineral resistant to hydrolysis by phosphatases, and also inhibit osteoclast precursors from attaching to the mineralized matrix, thus blocking their transformation into mature functioning osteoclasts.[13,27] The antiresorptive properties of this class of agents can provide long-term control of serum calcium and are the first-line therapy for cancer-associated hypercalcemia.

Pharmacology The first-line bisphosphonates to treat hypercalcemia are pamidronate and zoledronic acid.[28] The usual dose of pamidronate is 30 to 90 mg as an IV infusion given over no less than 2 hours and up to 24 hours.[28] Pamidronate also has the advantage of single-day therapy.[28] Zoledronic acid is a high-potency bisphosphonate with demonstrated effectiveness in the treatment of hypercalcemia of malignancy. Complete response has been reported in 88.4% to 86.7% of zoledronate- versus 69.7% of pamidronate-treated patients.[29,30] Zoledronic acid IV doses of 4 to 8 mg given over 15 minutes have resulted in

normalization of serum calcium concentrations.[29] IV infusions of 0.02 or 0.04 mg/kg diluted in 5% dextrose (given over 20-50 minutes) have also been effective.[31] The onset of serum calcium concentration decline is slower with bisphosphonate therapy (concentrations begin to decline in 2 days and reach a nadir in 7 days); thus, calcitonin therapy or other interventions may be necessary if more rapid serum calcium reduction is required.[28] Duration of normocalcemia varies, but it usually does not exceed 2 to 3 weeks. Duration of normocalcemia appears to be dependent on the severity and treatment response of the underlying malignancy.[6]

Adverse Effects Fever is a common side effect of IV bisphosphonate therapy. Although oral bisphosphonates are useful for the treatment of bone turnover in Paget's disease, there are insufficient data to suggest their use for the initial treatment of hypercalcemia. The safety of continuous bisphosphonate therapy in treating hypercalcemia of malignancy is currently unknown; however, zoledronic acid has been associated with atrial fibrillation.[32] Kidney function monitoring (serum creatinine) is advised with the use of bisphosphonates, as cases of kidney function decline and acute tubular necrosis have been reported.[33,34] It is advisable to evaluate serum creatinine within a week after the infusion and just prior to the next scheduled dose.[28] Osteonecrosis of the jaw is an area of exposed bone in the maxillofacial or mandibular region that does not heal within 8 weeks after diagnosis.[28] Higher potency bisphosphonates and longer durations of therapy are associated with increased risk.[35]

Denosumab

Pharmacology Denosumab is a monoclonal antibody that inhibits the receptor activator of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) ligand (RANKL), a principal mediator of osteoclast survival. Denosumab is FDA-approved for the treatment of hypercalcemia of malignancy.[36] The drug is effective in treatment of patients with hypercalcemia of malignancy (with or without bone metastases) who are refractory to intravenous bisphosphonate therapy; that is, their corrected serum calcium remains above 12.5 mg/dL (3.13 mmol/L) after more than 7 days of therapy.[36] Denosumab has also been reported to successfully treat hypercalcemia after successful stem cell transplantation and restitution of osteoclast function in patients with osteopetrosis, a heritable disorder associated with defective osteoclast function.[37]

Adverse Effects Denosumab has been associated with osteonecrosis of the jaw.[38] Although advanced kidney disease has not been shown to affect the

pharmacodynamics and pharmacokinetics of denosumab, severe, symptomatic hypocalcemia has been reported in CKD patients receiving the drug.[39] Close monitoring of serum calcium is recommended for patients with creatinine clearance <30 mL/min (0.5 mL/s).[28] This may be due to induction of a hungry bone-like syndrome and warrants careful monitoring.[40]

Corticosteroids Prednisone or an equivalent agent is usually effective in the treatment of hypercalcemia resulting from multiple myeloma, leukemia, lymphoma, sarcoidosis, and hypervitaminoses A and D.[13,27,41] Steroids are effective because they reduce GI calcium absorption.[41] Corticosteroids may also prevent tachyphylaxis to salmon calcitonin.[25] Daily doses of 40 to 60 mg of prednisone or the equivalent have effectively normalized serum calcium values within 3 to 5 days followed by a reduction in urinary calcium excretion within 7 to 10 days. The disadvantages of corticosteroid therapy are its relatively slow onset of action and the potential for diabetes mellitus, osteoporosis, and increased susceptibility to infection.[42]

Cinacalcet The calcimimetic agent cinacalcet is approved for management of parathyroid carcinoma, primary hyperparathyroidism where parathyroidectomy is indicated but cannot be undertaken, and secondary hyperparathyroidism in patients with CKD on dialysis.[43-45] Cinacalcet is an allosteric modulator of the CaSr, and increases the sensitivity for receptor activation by extracellular calcium. This results in reduced PTH and serum calcium concentrations.[43,44] Cinacalcet administered at a starting dose of 30 mg orally twice daily has been used for the treatment of hypercalcemia secondary to parathyroid carcinoma. The dosage is titrated every 2 to 4 weeks in 30-mg increments until the desired serum calcium concentration is achieved. The maximum approved dosage is 90 mg three to four times daily. Hypocalcemia is a common adverse effect and patients with specific CaSR polymorphisms may be particularly susceptible.[43,45] Patients should have serum calcium measured within 1 week after starting or increasing the dose of this agent.[45] The role of cinacalcet in the management of nephrolithiasis is still controversial, but it has shown benefit in patients with primary hyperparathyroidism.[46] Etelcalcetide is the first intravenous calcimimetic that is structurally different from cinacalcet but also acts as an allosteric modulator of the CaSR. Etelcalcetide is only approved to treat secondary hyperparathyroidism in dialysis patients (see Chapter 61).[47]

Pharmacoeconomic Considerations Corticosteroids are inexpensive for treatment of asymptomatic hypercalcemia from a pharmacoeconomic standpoint;

however, the low cost of the drug may be offset by the multitude of long-term side effects and potential need for additional treatment. Calcitonin is only suitable for very short-term therapy and thus the long-term pharmacoeconomic benefits are unknown. The introduction of denosumab and its demonstrated efficacy in preventing and delaying skeletal-related adverse events while reducing hypocalcemia has stimulated cost-effectiveness analyses.[48] Use of bisphosphonates for the management of bone metastases of malignancy is associated with lower morbidity and health gains (quality of life) well below the typical cost-effectiveness threshold.[48] In contrast, although denosumab was associated with additional health gains compared to zoledronic acid, it may not offer economic advantages. Additional considerations for choice of therapy evaluated in a survey of more than 200 physicians included co-pay costs and patient assistance program availability for these agents.[49]

Nephrolithiasis from Chronic Hypercalcemia and Hypercalciuria Patients who develop nephrolithiasis from hypercalciuria are most often treated with sodium citrate to prevent stone formation, thiazide diuretics to decrease urinary calcium excretion, or shock wave lithotripsy (**Table 67-3**). There are multiple approaches to treating and preventing future nephrolithiasis issues which include stone removal or disintegration, using medications to dissolve or prevent stone formation as well as dietary interventions to prevent stone formation.[22] Procedures such as shockwave lithotripsy are effective in disintegrating stones and subsequently allowing for their urinary removal; however, the procedure is painful and expensive. Urinary alkalinizing agents such as potassium or sodium citrate prevent growth of stone diameter, increasing the likelihood of spontaneous passage. These agents can also be used for prevention and are available in liquid form but must be taken consistently multiple times per day to maintain an alkaline urine.[19] Thiazide diuretics decrease urinary calcium excretion and reduce the potential for crystal formation and are commonly used for prevention.[22] Other agents such as calcium-binding resins, natural plant extracts (*Phyllanthus niruri),* and reduction of dietary calcium offer little benefit.

TABLE 67-3 Treatment of Nephrolithiasis Associated with Chronic Hypercalcemia and Hypercalciuria

Intervention	Indications	Comments
Extracorporeal Shock Wave Lithotripsy		
Uses sound waves to break up stones, which then can pass spontaneously	Obstruction of the urinary tract, especially with stones >5 mm	Consider adjunctive use of potassium citrate to inhibit aggregation of residual fragments
Prevention of Stone Formation		
Alkalinizing agents	Treatment for nonemergent active stones. Can also be used for prevention	Potassium citrate preferred over sodium citrate as it decreases urinary calcium, inhibits calcium oxalate precipitation, and increases urinary citrate more
Potassium citrate PO 20 mEq twice daily		
Sodium citrate PO 20-30 mEq twice daily		
Decrease Urinary Calcium Excretion		
Thiazide diuretics	Prevention	Drug of choice in patients with low-bone density
Hydrochlorothiazide (Hydrodiuril®) PO 50 mg every day		
Indapamide (Lozol®) PO 25 mg every day		
Chlorthalidone (Hygroton®) PO 25 mg every day		
Binding Intestinal Calcium		
Cellulose sodium phosphate (Calcibind)	Prevention for those with absorptive hypercalciuria	Alternative to thiazides if intolerant or ineffective, monitor bone density
Calcium-binding ion-exchange resin that decreases GI absorption of calcium: PO 5 g twice daily with oxalate restriction		
Inhibition of Crystal Formation		
Phyllanthus niruri plant extract	Prevention, after shock wave lithotripsy	Commercial preparations with *P. niruri* as the sole ingredient can be difficult to obtain
Inhibits calcium oxalate stone formation by incorporating glycosaminoglycans into the calculi: PO 2 g daily		
Low-Calcium Diet		
Less than 400 mg/day	Prevention	Monitor bone density prior to and periodically during treatment, limit oxalate restriction, can increase hyperoxaluria, data suggest that high-calcium intake may actually be more beneficial

HYPOCALCEMIA

3 Hypocalcemia occurs infrequently in the outpatient setting and is most common in elderly, malnourished patients and those who have received sodium phosphate as a bowel preparation agent.

Epidemiology

Hypocalcemia occurs frequently in adult hospitalized patients. The incidence in critically ill patients ranges from 15% to 50% based on the observation of ionized calcium concentrations less than 4.4 mg/dL (1.10 mmol/L).[4] Emergent treatment of hypocalcemia is rarely warranted unless life-threatening symptoms are present (eg, frank tetany or seizures).

Pathophysiology

Hypocalcemia is the result of alterations in the effect of PTH and vitamin D on the bone, gut, and kidney (see Fig. 67-1). The primary causes of hypocalcemia are vitamin D deficiency and postoperative hypoparathyroidism. Other causes include magnesium deficiency, critical illness, medications, hypoalbuminemia, blood transfusions, peripheral blood progenitor cell harvesting, tumor lysis syndrome, and mutations in the CaSr.[43,50-54] PTH concentrations are elevated in conditions of hypocalcemia, with the exception of hypoparathyroidism and hypomagnesemia.[55]

Vitamin D Deficiency

Vitamin D and its metabolites play an important role in the maintenance of extracellular calcium concentrations and in normal skeletal structure and mineralization. Vitamin D is necessary for the optimal absorption of calcium and phosphorus. On a worldwide basis, the most common cause of chronic hypocalcemia is nutritional vitamin D deficiency. In malnourished populations, manifestations include rickets and osteomalacia. Nutritional vitamin D deficiency is uncommon in Western societies because of the fortification of milk with ergocalciferol. The most common cause of vitamin D deficiency in Western societies is GI disease.[13] Gastric surgery, chronic pancreatitis, small-bowel disease, intestinal resection, and bypass surgery are associated with decreased concentrations of vitamin D and its metabolites.[13] Vitamin D replacement therapy might need to be administered by the IV route if poor oral bioavailability is noted. Decreased production of 1,25-dihydroxyvitamin D3 can occur as a

result of a hereditary defect resulting in vitamin D-dependent rickets.[55] Polymorphisms of the vitamin D receptor have been identified, and these genetic variations can contribute to increased risk of rickets associated with vitamin D- and calcium-deficient diets, especially in certain African and East Asian populations.[56] It also can occur secondary to CKD if there is insufficient production of the 1-α-hydroxylase enzyme for the production of the 1,25-dihydroxy vitamin D3. Treatment of hypocalcemia associated with CKD is reviewed in Chapter 61.

Hypoparathyroidism

Hypoparathyroidism can be caused by autoimmune disease, congenital defects, or iatrogenically by inadvertent removal of some or all of the parathyroid glands during thyroidectomy or from damage with radiation therapy. Surgery is the most common cause of chronic hypoparathyroidism, but only occurs in about 3% of patients who have undergone total thyroidectomy.[55] Chronic hypoparathyroidism that persists for more than 6 months may insidiously lead to hypocalcemia and thus most patients remain asymptomatic.[55] The chronic hypocalcemia may ultimately present as visual impairment secondary to cataracts.[57]

Hungry Bone Syndrome

An acute, symptomatic rapid fall in total serum calcium concentration (to values less than 7 mg/dL [1.75 mmol/L]) is common in patients who have recently had a parathyroidectomy or thyroidectomy. Hypocalcemia in these postsurgical patients is generally transient in nature.[55] The “hungry bone syndrome” is a condition of profound hypocalcemia whereby the bone avidly incorporates calcium and phosphorus from the blood in an attempt to recalcify bone.[58] Serum calcium concentrations should be monitored every 6 hours during the 24 to 48 hours following such surgeries, and pharmacologic doses of calcium can be necessary to prevent or minimize the drop in serum calcium.

Hypomagnesemia

Hypomagnesemia of any cause can be associated with severe symptomatic hypocalcemia that is unresponsive to calcium replacement therapy (see Chapter 68). Reduced serum magnesium concentrations can impair PTH secretion and

induce resistance of target organs to the actions of PTH.[55] Normalization of serum calcium concentrations in these patients is thus dependent on appropriate replacement of magnesium.

Critical Illness

During critical illness or postoperatively, hypocalcemia is common but usually mild. It is hypothesized that cytokines impair PTH secretion, decrease production of 1,25-dihydroxyvitamin D3, and cause PTH end-organ resistance.[55]

Drug-Induced Hypocalcemia

Drug-induced hypocalcemia has been reported due to chelation of calcium (eg, oral sodium phosphate solutions, ethylenediaminetetraacetate, foscarnet), increased enzymatic processing of vitamin D (eg, phenobarbital, phenytoin, ketoconazole), decreased PTH sensitivity (eg, calcitonin), increased sensitivity of the CaSr (eg, cinacalcet), increased excretion of calcium (eg, furosemide), blocked bone resorption (eg, denosumab, bisphosphonates, fluoride), and induction of hypomagnesemia (eg, aminoglycosides).[39,45,55,59]

Chelating agents in blood (citrate) and in radiographic contrast media (ethylenediaminetetraacetate) can cause transient hypocalcemia.[50,51,55] Concentrated citrate is often used in hemodialysis catheter locks and to anticoagulate the dialysis circuit during continuous renal replacement therapy.[60] Symptomatic hypocalcemia has been reported in patients exposed to citrate solutions, which appears to be related to both the concentration of the citrate solution and capacity to metabolize citrate (ie, impaired metabolism with severe liver failure and tissue hypoperfusion).[61] Injection of citrate solutions greater than the volume of the dead space of the catheter lumen or accidental injection of citrate catheter lock solutions that are not intended for systemic administration have been associated with serious cardiovascular problems such as hypotension or cardiac arrest.[62] Oral phosphorus therapy can also result in hypocalcemia by chelation.

The anticonvulsants phenobarbital and phenytoin cause hypocalcemia by increasing catabolism of vitamin D and thereby impairing calcium release from bone and reducing intestinal calcium absorption.[50] By decreasing PTH sensitivity, calcitonin can lead to hypocalcemia.[55] Cinacalcet increases the sensitivity of the CaSr potentially inducing hypocalcemia.[55] Loop diuretics such as furosemide can induce hypocalcemia by increasing calcium excretion.[55]

Denosumab and bisphosphonates block bone resorption and can lead to hypocalcemia, especially in the presence of vitamin D deficiency, insufficient calcium intake, or PTH imbalance.[55] Drugs that cause hypomagnesemia (eg, aminoglycosides, amphotericin B, cyclosporine, diuretics, foscarnet, and cisplatin) are also associated with an increased risk of hypocalcemia.[63]

Clinical Presentation

The clinical manifestations of hypocalcemia are quite variable. The more acute the drop in ionized calcium concentration, the more likely the patient will develop symptoms.[55] Increases in plasma pH enhance the binding of calcium to albumin and thus alkalosis can result in rapid decreases in ionized calcium. Concomitant hypomagnesemia, hypokalemia, hyponatremia, and additive side effects from prescribed medications also increase the likelihood of symptomatic presentation.

CLINICAL PRESENTATION

Hypocalcemia

General

- Acute hypocalcemia may result in rapid decreases in serum ionized calcium. Parathyroidectomy and thyroidectomy are also associated with a rapid reduction in serum calcium. In chronic hypocalcemia, vitamin D deficiency should be considered.

Symptoms

- The symptoms of hypocalcemia include tetany, paresthesia, muscle cramps, and laryngeal spasms. Chronic hypocalcemia is usually associated with depression, anxiety, memory loss, and confusion.

Signs

- Neurologic: The hallmark of acute hypocalcemia is tetany, which is characterized by neuromuscular irritability including seizure potential. Extrapyramidal disorders, mainly parkinsonism but also dystonia, hemiballismus, choreoathetosis, and oculogyric crises occur in 5% to 10% of patients with idiopathic hypoparathyroidism. Chvostek and/or

Trousseau signs can be elicited during physical examination.

- Dermatologic: The skin can be dry, puffy, and coarse. Other dermatologic manifestations can include hyperpigmentation, dermatitis, eczema, and psoriasis. Hair and skin signs including coarse, brittle, and sparse hair with patchy alopecia and brittle nails can also appear.
- Ophthalmologic: Cataract development has been reported to occur with hypocalcemia.
- Dental manifestations: These are usually associated with the presence of chronic hypocalcemia in early development. Signs include dental hypoplasia, failure of tooth eruption, defective enamel and root formation, and abraded carious teeth.
- Cardiovascular: Hypotension, decreased myocardial performance, and CHF have been reported. A prolonged QT interval, arrhythmias, and bradycardia can also occur but are more common with acute or very severe hypocalcemia.
- GI: Steatorrhea can be associated with chronic hypocalcemia.
- Musculoskeletal: Myopathy has been reported.
- Endocrine: Hypocalcemia alone can impair insulin release. In addition, idiopathic hypoparathyroidism can be associated with polyglandular autoimmune syndromes.

Laboratory Tests

- Serum calcium concentrations of less than 8.6 mg/dL (2.15 mmol/L) are considered to represent hypocalcemia if ionized calcium values are also less than 4.4 mg/dL (1.1 mmol/L).

Hypocalcemia can manifest as neuromuscular, central nervous system (CNS), dermatologic, and cardiac sequelae.[3] Acute hypocalcemia is more likely to manifest as neuromuscular (paresthesia, muscle cramps, tetany, and laryngeal spasm) and cardiovascular symptoms, whereas chronic hypocalcemia often presents as CNS (eg, depression, anxiety, memory loss, confusion, hallucinations, and tonic–clonic seizures) and dermatologic symptoms (hair loss, grooved and brittle nails, and eczema).[50] The hallmark sign of acute hypocalcemia is tetany caused by enhanced peripheral neuromuscular irritability.[3] Tetany manifests as paresthesia around the mouth and in the extremities, muscle spasms and cramps, carpopedal (hands and feet) spasms, and

rarely as laryngospasm and bronchospasm.[13] Chvostek and/or Trousseau signs can be elicited during physical examination.[55] Chvostek sign is elicited by tapping the facial nerve anterior to the ear and eliciting twitching of facial muscles. The sensitivity and specificity of Chvostek sign for hypocalcemia are limited; a positive Chvostek sign is observed in 25% of healthy individuals and 29% of patients with hypocalcemia are negative.[55] Trousseau sign is elicited by inflating a blood pressure cuff above systolic blood pressure for 3 minutes and observing whether a carpal spasm is induced. With only 1% of healthy individuals with a positive Trousseau, this sign has greater specificity for hypocalcemia.[55]

The cardiovascular manifestations of hypocalcemia result in ECG changes characterized by a prolonged QT interval and symptoms of decreased myocardial contractility often associated with CHF.[50] Both acute and chronic hypocalcemia can result in a reversible syndrome characterized by acute myocardial failure or refractory CHF. Other cardiovascular manifestations include arrhythmias, bradycardia, and hypotension that are unresponsive to fluid and pressor administration.[50]

TREATMENT

Desired Outcome

4 The goals of therapy for patients with normal kidney function are the resolution of signs and symptoms of hypocalcemia, restoration of normocalcemia, management of associated electrolyte abnormalities, and treatment of the underlying cause of hypocalcemia. The goals for patients with CKD are different and are discussed in Chapter 61. Asymptomatic hypocalcemia associated with hypoalbuminemia requires no treatment because ionized (physiologically active) plasma calcium concentrations are normal. Treatment of hypocalcemia is dependent on identification of the pathogenesis of the underlying disorder, acuteness of onset, and presence and severity of symptoms.

Pharmacologic Therapy

Treatment of hypocalcemia is driven by acuity of onset and how significant the ionized calcium is below the normal range. The first approach to treatment is to evaluate causes that will dictate corrective action. Acute symptomatic hypocalcemia will nearly always require parenteral administration of soluble

calcium salts (**Fig. 67-3**).

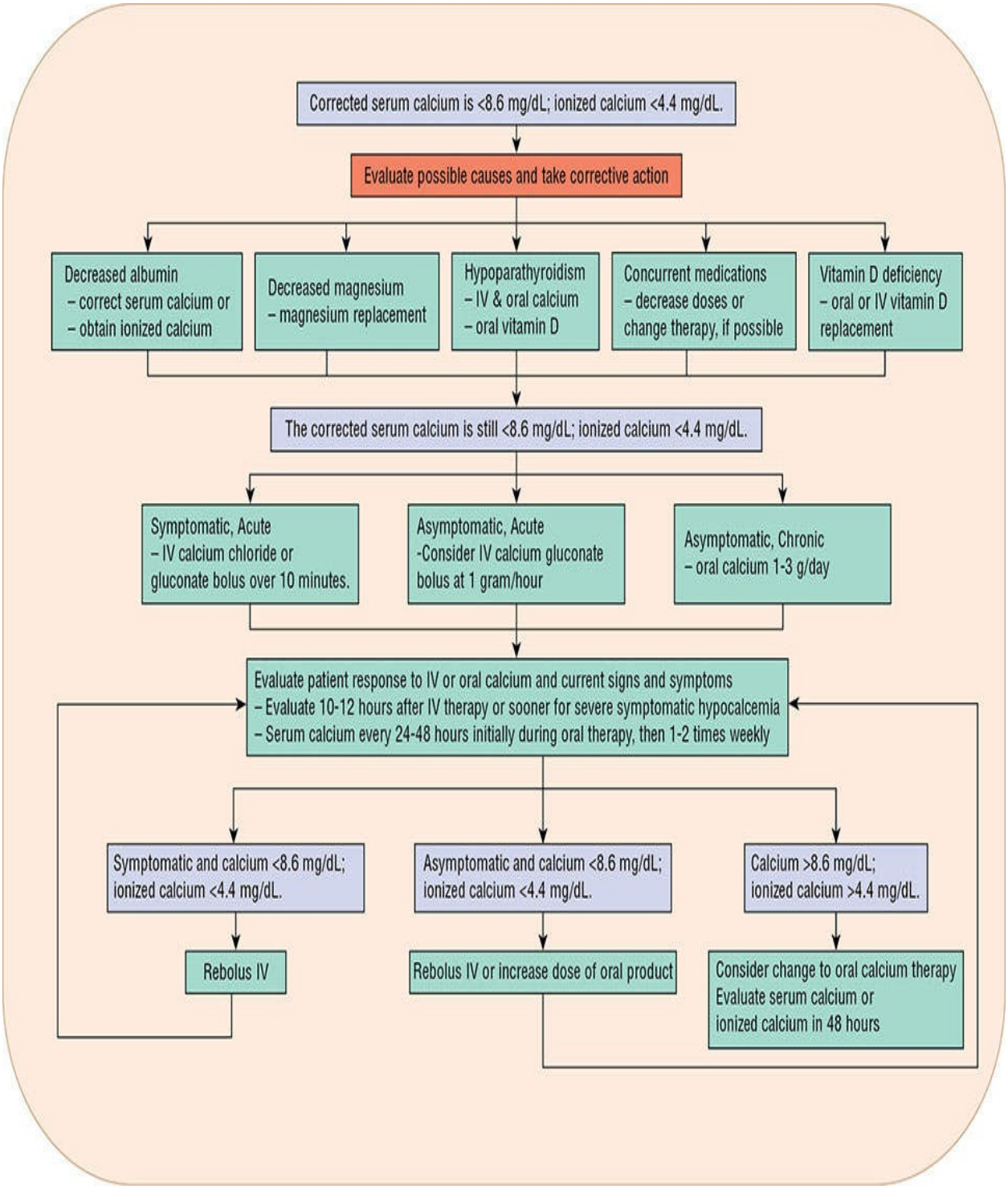


FIGURE 67-3 Hypocalcemia diagnostic and treatment algorithm. Serum calcium of 8.6 mg/dL is equivalent to 2.15 mmol/L. Ionized calcium of 4.4 mg/dL is equivalent to 1.1 mmol/L.

Acute Treatment The initial therapeutic intervention for patients with severe, symptomatic hypocalcemia (ionized calcium <1 mmol/L) is to administer 0.5 to 1 g of calcium chloride (1 g calcium chloride = 13.6 mEq calcium) or up to 3 g of calcium gluconate (1 g calcium gluconate = 4.56 mEq calcium) IV slowly over 10 minutes.[3] The treatment of asymptomatic hypocalcemia is controversial, but many practitioners will supplement calcium to avoid negative consequences of hypocalcemia and progression to clinical manifestations.[3] For mild-to-moderate asymptomatic hypocalcemia (ionized calcium 1-1.12 mmol/L), 1 to 2 g IV calcium gluconate is recommended, and in the case of severe, asymptomatic hypocalcemia, up to 3 g IV calcium gluconate is indicated as in symptomatic patients.[3] For critically ill patients who are asymptomatic with a serum total calcium less than 7 mg/dL (1.75 mmol/L), 1 to 2 g IV calcium gluconate may be administered empirically with follow-up measurement of ionized calcium.[3] In nonemergent, asymptomatic cases, calcium retention and safety are optimized by infusing calcium gluconate at a rate of 1 g/hr.[3] Since calcium chloride delivers three times more elemental calcium than an equivalent amount of calcium gluconate, clinicians must carefully review dosing to ensure medication errors do not occur. Calcium gluconate is generally preferred over calcium chloride for peripheral venous administration because calcium gluconate is less irritating to veins. To prevent tissue necrosis, calcium chloride should be administered via central venous access. Calcium should not be infused at a rate greater than 60-mg elemental calcium per minute because severe cardiac dysfunction, including ventricular fibrillation, can result; thus, electrocardiogram monitoring is recommended.[63] IV calcium administration should be used with caution in patients receiving digitalis glycosides because of the possibility of bradycardia or atrioventricular (A–V) block.[57] In severe hypokalemia, an acute rise in serum calcium from IV calcium administration can result in cardiac arrhythmias. Bolus doses of calcium are only effective for 1 to 2 hours; therefore, repeat doses should be given hourly as needed until severe, symptomatic patients are stabilized.[3,63] Ionized calcium should be reevaluated approximately 10 to 12 hours after supplementation or sooner for severe, symptomatic hypocalcemia.[3] Calcium should not be added to bicarbonate- or phosphate-containing solutions or infused in the same IV line because of the possibility of precipitation.[63]

Chronic Treatment Once acute hypocalcemia is corrected by parenteral administration, further treatment modalities should be individualized according to the cause of hypocalcemia. If hypomagnesemia is present, then magnesium supplementation is indicated until concentrations normalize, which will promote

successful calcium supplementation regardless of route (see Chapter 68). Hypocalcemia secondary to hungry bone syndrome following parathyroidectomy has been attenuated by pretreatment with bisphosphonates, especially with longer duration use and normalization of alkaline phosphatase prior to surgery.[64] Asymptomatic and chronic hypocalcemia associated with hypoparathyroidism and vitamin D-deficient states can be managed by oral calcium and vitamin D supplementation. Therapy is begun with 1 to 3 g/day of elemental calcium.[63] Average maintenance doses range from 2 to 8 g of elemental calcium per day in divided doses. If serum calcium does not normalize, a vitamin D preparation may need to be added. In patients with achlorhydria, a solution of 10% (1-30 mL) calcium chloride orally every 8 hours can raise serum calcium.[63] Treatment of chronic hypoparathyroidism with parathyroid hormone formulations such as teriparatide has been shown to better maintain serum calcium concentrations and normalize urinary calcium.[65]

Treatment of chronic asymptomatic hypocalcemia associated with vitamin D-deficient states should be individualized. The optimal 25-hydroxy vitamin D concentration is controversial, but the Endocrine Society defines vitamin D sufficiency as a concentration of at least 30 ng/mL (75 nmol/L).[66] In patients with malabsorption, vitamin D requirements vary markedly, and large doses can be required. In contrast, vitamin D deficiency associated with anticonvulsant medication can be corrected with smaller doses of vitamin D. The usual oral dose of ergocalciferol is 50,000 international units once weekly for 8 weeks followed by decreased maintenance dosing as needed to achieve the goal 25-hydroxy vitamin D concentration.[66] The treatment of vitamin D deficiency associated with CKD generally requires the administration of 1,25-dihydroxy vitamin D3 or another synthetic vitamin D2 analog such as paricalcitol or doxercalciferol (see Chapter 61). Patients who have reduced 25-hydroxylase activity (eg, hepatic disease) can also require treatment with calcitriol (1,25-dihydroxy vitamin D3). Oral doses of 1,25-dihydroxy vitamin D3 usually range from 0.5 to 2 mcg daily. Some data have shown that animal source vitamin D3 (cholecalciferol) is more efficacious at raising serum 25-hydroxy vitamin D concentrations compared with plant source vitamin D2 (ergocalciferol). However, higher loading and maintenance doses of cholecalciferol may be required to maintain serum 25-hydroxy vitamin D concentrations. In selected cases, increasing calcium ingestion can be required if vitamin D replacement alone is ineffective in returning calcium concentrations to normal.

Adverse Effects

Adverse effects of oral calcium and vitamin D supplementation include hypercalcemia and hypercalciuria, especially in the hypoparathyroid patient, in whom the renal calcium-sparing effect of PTH is absent. Hypercalciuria can increase the risk of calcium stone formation and nephrolithiasis in susceptible patients. One maneuver to help prevent calcium stones is to maintain the urine calcium excretion below 300 mg/day. Intermittently monitoring of 24-hour urine collections for total calcium excretion can help minimize the occurrence of hypercalciuria. The addition of thiazide diuretics for patients at risk for stone formation can result in an increase in tubular calcium reabsorption and reduction of vitamin D requirements (see Table 67-3).[63]

DISORDERS OF PHOSPHORUS HOMEOSTASIS

Inorganic phosphorus in the form of phosphate is an essential element in phospholipid cell membranes, nucleic acids, and phosphoproteins, which are required for mitochondrial function.[1] Phosphorus regulates the intermediary metabolism of carbohydrates, fats, and proteins. Phosphorus also regulates enzymatic reactions including glycolysis, ammoniagenesis, and the 1-hydroxylation of 25-hydroxyvitamin D3.[1,67] In addition, phosphorus is required for the generation of 2,3-diphosphoglycerate (2,3-DPG) in red blood cells, which is required for normal oxygen–hemoglobin dissociation and delivery of oxygen to the tissues.[1] Phosphorus is the source of the high-energy bonds of adenosine triphosphate (ATP), thus fueling a wide variety of physiologic processes, including muscle contractility, electrolyte transport, neurologic function, and other important biochemical reactions.[1] Considering its diverse biologic importance, it is not difficult to appreciate the clinical implications of disorders of phosphorus homeostasis.

Phosphate, the major intracellular anion, is present in living organisms mainly as organic phosphate esters such as 2,3-DPG, adenosine, guanosine triphosphate, and fructose 1,6-diphosphate.[1] Only a small fraction of intracellular phosphorus exists as inorganic phosphate; however, this fraction is critical because it is the source from which ATP is resynthesized.[1] The majority of inorganic phosphate is located in the extracellular space where it is the prime determinant of intracellular phosphate; thus, small increments in the organic phosphate concentrations can profoundly alter both the extracellular and intracellular phosphate concentrations. Metabolic disturbances (acidosis, alkalosis, and ketoacidosis), hydrogen ion shifts, and hormones (PTH, calcitonin, cortisol, and vitamin D) all can cause transcellular shifts in phosphorus concentrations.

Because of these phenomena, the serum phosphorus concentration does not accurately reflect total body stores.[68]

The typical Western diet provides a daily intake of 800 to 1,600 mg of phosphorus. Approximately 60% to 80% of this is absorbed in the GI tract by passive and active transport (vitamin D-mediated). PTH, 1,25-dihydroxy vitamin D3, and low-phosphate diets mediate increased absorption. Decreased absorption occurs under conditions of increased dietary intake of phosphorus and magnesium, glucocorticoid therapy, and hypothyroidism. The normal serum phosphorus concentration in adults is 2.7 to 4.5 mg/dL (0.9-1.45 mmol/L) and for children younger than 12 years it is 4 to 5.6 mg/dL (1.29-1.81 mmol/L). Influx via the GI tract and bone and tubular reabsorption by the kidney are the most important regulators of steady-state serum phosphorus concentrations. Renal excretion of phosphorus is a two-step process: glomerular filtration and proximal tubular reabsorption by passive transport coupled to sodium. Under normal conditions, 85% to 90% of filtered phosphate is reabsorbed, the majority in the early proximal tubule. Renal tubular reabsorption of phosphate is inhibited by PTH and 1,25-dihydroxy vitamin D3.[68] There are increasing data in the literature that indicate fibroblast growth factor 23 (FGF23) is a key regulator of phosphate homeostasis.[69] FGF23 acts principally to decrease tubular reabsorption of phosphate and inhibit 1-α-hydroxylase, thereby reducing the concentration of active vitamin D. FGF23-mediated receptor activation requires klotho, a transmembrane protein. The tissue specificity for FGF23 effects appears to be defined by klotho–FGF23 coexpression. Conversely, phosphate reabsorption in the renal tubule is increased by growth hormone, insulin, and insulin-like growth factor 1.[1] Internal phosphorus balance (transcellular phosphate distribution) is also of importance in the maintenance of normal serum phosphate. The serum phosphate concentration can vary by as much as 2 mg/dL (0.65 mmol/L) throughout the day, primarily as the result of changes in carbohydrate intake, insulin secretion, and diurnal variation.[1]

HYPERPHOSPHATEMIA

Hyperphosphatemia typically results from either CKD, acute kidney injury (AKI), or endogenous intracellular phosphate release. Hyperphosphatemia occurs frequently in patients with AKI and is a nearly universal finding in those with advanced CKD (eg, stages 4 and 5). Tumor lysis syndrome, a complication of chemotherapy associated with massive lysis of cells and release of intracellular contents, is also associated with hyperphosphatemia. The incidence

of tumor lysis syndrome is highest among patients treated for acute lymphoblastic leukemia, acute myeloid leukemia, and Burkitt's lymphoma (see Chapter 151).[53] Other causes of hyperphosphatemia include hemolysis and rhabdomyolysis.

Pathophysiology

5 The most common cause of hyperphosphatemia is a reduction in renal tubular excretion of phosphate despite elevations in PTH and FGF-23 when GFR is markedly impaired (eg, GFR less than 25 mL/min/1.73 m^2 [0.24 mL/s/m^2]).[67,68] Retention of phosphate decreases vitamin D synthesis and induces hypocalcemia, which leads to an increase in PTH, a finding that can be seen in those with stage 2 to 5 CKD. This physiologic response inhibits further tubular reabsorption of phosphorus as the kidney attempts to correct hyperphosphatemia and normalize serum calcium concentrations. Patients with excessive exogenous phosphate administration or who experience massive tissue breakdown or cell lysis in the setting of AKI can rapidly develop moderate-to-severe hyperphosphatemia (serum phosphate more than 6.5 mg/dL [2.10 mmol/L]).[68] Severe hyperphosphatemia (serum phosphate more than 7 mg/dL [2.26 mmol/L]) is commonly encountered in patients with CKD, especially those with GFRs less than 15 mL/min per 1.73 m^2 (0.14 mL/s/m^2) (see Chapter 61).

Hyperphosphatemia caused by an increase in renal tubular reabsorption associated with hypoparathyroidism and decreases in PTH is usually less severe than that observed in patients with advanced kidney disease or excessive exogenous or endogenous introduction of phosphate into the ECF. Acromegaly (mediated by growth hormone) and thyrotoxicosis (mediated by catecholamines) can also cause hyperphosphatemia by increasing tubular phosphate reabsorption.

Exogenous Phosphate Loads

Iatrogenic causes of hyperphosphatemia have been widely reported, and clinicians should be aware of the phosphorus content of IV, oral, and rectally administered products.[70] Although less well-recognized, oral and rectal administration of phosphate-containing solutions such as sodium phosphate (Fleet Phospho-Soda) can also result in severe and life-threatening hyperphosphatemia, especially in patients with moderate-to-severe CKD.[59,70] The risk of mortality is dependent on the amount of phosphorus absorbed from the administered product; however, fatalities have occurred at low-phosphate

concentrations.[70] Acute phosphate nephropathy and kidney failure have also been reported with the use of oral sodium phosphate bowel preparations. The FDA issued a safety warning regarding the use of these products in patients at risk (the elderly, those with CKD) or on medications known to affect renal hemodynamics (eg, diuretics, nonsteroidal anti-inflammatory drugs [NSAIDs], or renin–angiotensin–aldosterone system inhibitors).[71] Acute phosphorus poisoning as a result of ingestion of laundry detergents is a rare and often unrecognized cause of elevated phosphate concentrations.

Rapid Tissue Catabolism

Any disorder that results in necrosis of skeletal muscle (ie, rhabdomyolysis) can generate the release of large amounts of intracellular phosphate into the systemic circulation. This condition is frequently associated with AKI (see Chapter 60) and thus severe hyperphosphatemia can develop because of increased endogenous phosphate release coupled with the impaired renal excretion because phosphaturic hormones (eg, PTH, FGF23) become ineffective. Bowel infarction, malignant hyperthermia, and severe hemolysis are also conditions that can increase endogenous release of phosphate.

Moderate hyperphosphatemia is also commonly observed in patients undergoing treatment for acute leukemia and lymphomas.[53] Chemotherapeutic treatment of acute lymphoblastic leukemia can result in the release of large amounts of phosphate into the systemic circulation secondary to lysis of lymphoblasts. Initiation of chemotherapy for Burkitt's lymphoma results in tumor lysis syndrome, a rapid lysis of malignant cells that results in hyperphosphatemia, hyperuricemia, hyperkalemia, and hypocalcemia.[53]

Acid–Base Disorders

Lactic acidosis and diabetic ketoacidosis can trigger the transcellular shift of endogenous intracellular phosphate into the extracellular space and thereby dramatically increase serum phosphorus concentrations.[72] After the institution of treatment, serum phosphate concentrations should be checked hourly as they can decrease rapidly, and patients can ultimately develop hypophosphatemia.

Clinical Presentation

The severe acute onset of hyperphosphatemia can result in calcium and phosphate complexation and lead to the precipitation of calcium phosphate

crystals in soft tissues, and within the kidney that can result in nephrolithiasis or obstructive uropathy. Extravascular calcification can result in band keratopathy, “red eye,” pruritus, and periarticular calcification, especially in CKD patients. In addition, soft-tissue calcifications in the conjunctiva, skin, heart, cornea, lung, gastric mucosa, and kidney have been observed, primarily in CKD patients with chronic disordered mineral metabolism.[68] Extracellular phosphate can form insoluble nanoparticles with both calcium and fetuin-A which are referred to as calciprotein particles.[1] Calcium-phosphate crystals are likely to form in vivo when the product of the serum calcium and phosphate concentrations exceeds 50 to 60 mg^2/dL^2 (4-4.8 $mmol^2/L^2$). Serum phosphate concentrations greater than 6.5 mg/dL (2.10 mmol/L) have been independently associated with increased morbidity and mortality in patients on maintenance hemodialysis.[73] Other symptoms associated with moderate-to-severe hyperphosphatemia include nausea, vomiting, diarrhea, lethargy, and seizures. The major effects of long-term hyperphosphatemia are related to the development of hypocalcemia (caused by phosphate inhibition of renal 1-α-hydroxylase) and its related consequences, as well as vascular and organ damage resulting from the deposition of calcium-phosphate crystals. Hyperphosphatemia associated with CKD can result in renal osteodystrophy because of overproduction of PTH. This condition is discussed in detail in Chapter 61.

CLINICAL PRESENTATION

Hyperphosphatemia

General

- Serum phosphate concentration is primarily determined by the ability of the kidneys to reabsorb phosphate; therefore, hyperphosphatemia is uncommon in patients with normal kidney function.

Symptoms

- Acute symptoms include GI disturbances, lethargy, obstruction of the urinary tract, and rarely seizures. Symptoms associated with chronic hyperphosphatemia include “red eye” and pruritus.

Signs

- The elevated calcium-phosphate product results in precipitation in arteries,

joints, soft tissues, and the viscera. This can result in tissue necrosis, termed calciphylaxis or calcemic uremic arteriopathy.

Laboratory Tests

- Serum phosphate concentrations more than 4.5 mg/dL (1.45 mmol/L) represent hyperphosphatemia.

TREATMENT

Desired Outcome

Management of patients with acutely elevated serum phosphorus concentrations should be directed at avoiding GI and neurologic symptoms and preventing deposition in the urinary tract to avoid the development of AKI. The treatment of hyperphosphatemia is focused on returning serum phosphorus concentrations to the normal or near normal (for those with CKD) range, with the hope that one can minimize the long-term cardiovascular consequences of calcium-phosphate deposition in the vasculature. The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines suggest that for patients with CKD stages 3 to 5, serum phosphorus should be maintained in the normal range. In dialysis-dependent patients with stage 5 CKD, KDIGO suggests lowering elevated phosphorus concentrations toward the normal range (see Chapter 61).[74]

Pharmacologic Therapy

Severe symptomatic hyperphosphatemia manifesting as hypocalcemia and tetany may be treated by the IV administration of calcium. Although this can seem counterintuitive and many consider it controversial, for a patient with a phosphate of 16 mg/dL (5.17 mmol/L) and a calcium of 7 mg/dL (1.75 mmol/L), for example (the calcium–phosphorus product is 112 mg^2/dL^2 [9 $mmol^2/L^2$]), correction of severe hypocalcemia is of primary importance because of the critical nature of this disorder. If calcium concentrations are not critically low, the initial management strategy should include limitation of all exogenous sources of phosphate and efforts to block further absorption should be initiated. Hemodialysis can be initiated if the patient remains symptomatic despite these interventions.[63]

6 In general, the most effective way to treat nonemergent

hyperphosphatemia is to decrease phosphate absorption from the GI tract by implementing phosphate-binding therapy and altering the dietary content of phosphate.[68] Phosphate-binding agents containing divalent and trivalent cations (calcium, lanthanum, magnesium, iron, and aluminum), or sevelamer are the agents most frequently used in the prevention and treatment of hyperphosphatemia (see Chapter 61).[75] Long-term treatment with aluminum hydroxide and aluminum carbonate should be avoided because the use of these agents has been associated with anemia, CNS disorders, and bone disease.[75] Calcium and magnesium agents are available in oral suspension formulations, which can aid administration in acutely ill patients who are receiving enteral nutrition. The most frequent adverse effect from phosphate-binding agents (especially calcium) is constipation. Typically, calcium salts are the preferred initial phosphate-binding agents except when there is concomitant hypercalcemia or evidence of vascular calcification. For long-term therapy with phosphate binders, it is recommended to avoid hypercalcemia and to limit use of calcium-based phosphate binders, and this may require additional noncalcium agents such as sevelamer.[74] The iron-based binders offer the potential advantage of enhancing iron absorption (ferric citrate coordination complex) or reduced pill burden (sucroferric oxyhydroxide).[76]

HYPOPHOSPHATEMIA

Mild-to-moderate hypophosphatemia is usually asymptomatic and associated with serum phosphate concentrations of 1.5 to 2.7 mg/dL (0.32-0.9 mmol/L), whereas severe hypophosphatemia that is frequently symptomatic is correlated with serum phosphorus concentrations of less than 1.5 mg/dL (0.5 mmol/L).[3]

Incidence

Hypophosphatemia has been observed in approximately 1% to 3% of the laboratory screening panels of patients who have been admitted to a hospital.[77] The incidence in hospitalized critically ill patients is 18% to 28%.[77] Unlike its severe form, mild or moderate hypophosphatemia seldom causes recognizable signs and symptoms.[3]

Pathophysiology

Hypophosphatemia can be the result of decreased GI absorption, reduced

tubular reabsorption, or extracellular to intracellular redistribution.[1] Although mild-to-moderate hypophosphatemia is common and can occur in inpatients and outpatients, severe hypophosphatemia is predominantly encountered in the acute care setting and can be associated with life-threatening symptoms, including seizures, coma, and rhabdomyolysis (**Table 67-4**).

TABLE 67-4 Conditions Associated with the Development of Hypophosphatemia

Decreased GI absorption

Phosphate-binding drugs

- Sucralfate
- Calcium carbonate
- Aluminum/magnesium antacids
- Sevelamer
- Lanthanum carbonate
- Ferric citrate
- Sucroferric oxyhydroxide

Decreased dietary phosphorus intake

Glucocorticoids

Vitamin D deficiency/resistance

Hyperparathyroidism

Chronic diarrhea

Steatorrhea

Reduced tubular reabsorption

Hyperparathyroidism (primary and secondary)

Elevated FGF23

Recovery from burns

Rickets

Malignant neoplasms

Fanconi syndrome

Acute volume expansion

Metabolic acidosis

Renal transplantation

Vitamin D deficiency and/or resistance

Diuretics

- Loop diuretics
- Thiazide diuretics
- Osmotic agents
- Carbonic anhydrase inhibitors (acetazolamide)

Glucocorticoids

Sodium bicarbonate

Internal redistribution

Refeeding syndrome

Nutrition support

Parathyroidectomy (hungry bone syndrome)

Alcoholism

Respiratory alkalosis

Diabetic ketoacidosis (correction)

Dextrose solutions

Insulin

Catecholamines

Anabolic steroids

Glucagon

Calcitonin

Erythropoietin

Decreased GI Absorption

Phosphate-binding substances such as sucralfate, calcium carbonate, sevelamer, lanthanum carbonate, sucroferric oxyhydroxide, ferric citrate coordination complex, and aluminum- or magnesium-containing antacids have the potential to bind large amounts of phosphorus in the gut, thereby preventing absorption. If phosphate-binding agents are ingested on a chronic basis in conjunction with a dietary phosphorus deficiency, hypophosphatemia can result.[3] Patients who are receiving long-term phosphate-binding agents, those with peptic ulcer disease or CKD, and those who may be predisposed to moderate hypophosphatemia (alcoholism) are at highest risk for the development of severe hypophosphatemia. Hyperparathyroidism can cause hypophosphatemia as a result of decreased GI absorption of dietary phosphorus.

Decreased Tubular Reabsorption

Reduced tubular reabsorption of phosphate can occur in hyperparathyroid (primary and secondary) patients with normal kidney function and those with vitamin D deficiency or elevated FGF23 concentrations. Elevated PTH concentrations lead to an increase in serum calcium concentrations and decreased serum phosphate concentrations. Serum phosphorus is decreased as the result of a reduction in renal tubular reabsorption.[72] Recovery from extensive third-degree burns is associated with development of an anabolic state as stress levels decrease and nutritional therapies take effect as well as a marked diuretic phase associated with an impressive renal loss of phosphate.[78] Because phosphate is rapidly incorporated into the new cells, this can contribute to the severity of the hypophosphatemia. Drugs that cause increased renal elimination of phosphate include diuretics (eg, loop diuretics, thiazide diuretics, osmotic diuretics), carbonic anhydrase inhibitors (eg, acetazolamide), glucocorticoids, and sodium bicarbonate.[3] The IV iron formulation ferric carboxymaltose has been associated with the development of hypophosphatemia in 51% of patients treated, and 13% of cases were severe (serum phosphorus less than 1 mg/dL [0.32 mmol/L]) and prolonged.[79] The mechanism is unclear; however, iron deficiency itself is associated with elevated FGF-23.[80]

Internal Redistribution

Rapid refeeding of malnourished patients with high-carbohydrate, high-calorie diets with inadequate amounts of supplemental phosphate can result in severe symptomatic hypophosphatemia. This phenomenon is especially prevalent in patients with other underlying risk factors for the development of hypophosphatemia, such as alcoholism.[78] The etiology of severe hypophosphatemia associated with nutrition support can be separated into two phases: acute, rapid hypophosphatemia secondary to intracellular shifts of phosphate resulting from glucose-induced insulin secretion; and the gradual decrease in serum phosphate concentration over 5 to 10 days secondary to tissue repair in the presence of phosphate deprivation.[81] The development of severe hypophosphatemia secondary to nutrition support can be prevented by appropriate phosphate supplementation. Adult patients with normal kidney function receiving parenteral nutrition require approximately 10 to 15 mmol of phosphorus per 1,000 kcal (or 4,200 kJ) (see Chapter 159).[3] The Recommended Dietary Allowance of phosphorus for healthy adults is provided in 1 L of most enteral nutrition formulations (see Chapter 160).[3] In severely malnourished patients, the phosphorus requirements are higher with the initiation of nutrition support.[3] Phosphorus requirements are also typically increased in patients with critical illness, thermal injury, traumatic brain injury, and liver resection.[3] Transcellular shifts in phosphate also occur after parathyroidectomy, causing severe hypocalcemia and hypophosphatemia because of hungry bone syndrome (deposition of phosphate and calcium in the bone).

Severe and prolonged respiratory alkalosis (a result of hyperventilation, pain, anxiety, and sepsis) can cause hypophosphatemia.[77] Respiratory alkalosis is thought to contribute significantly to the hypophosphatemia observed during alcohol withdrawal.[68] Although patients with diabetic ketoacidosis may present with hyperphosphatemia, the institution of therapy to correct it can cause serum phosphate concentrations to decrease rapidly as phosphate shifts back into the intracellular compartment. In addition, the acidosis associated with the diabetic ketoacidotic state can cause a decomposition of organic compounds inside the cell and a release of inorganic phosphate into the plasma and subsequently into the urine.[82] The combination of intracellular phosphate breakdown and the shift of phosphate into cells on initiation of treatment can lead to severe hypophosphatemia. Drugs associated with transcellular shifts in phosphate include dextrose solutions, glucagon, insulin, catecholamines, calcitonin, erythropoietic agents, and anabolic steroids.

Chronic alcoholism is associated with a variety of serum electrolyte disorders including hypocalcemia, hypomagnesemia, hypokalemia, and

hypophosphatemia. The etiology of hypophosphatemia in patients with alcoholism is multifactorial. Malnutrition, poor dietary intake, diarrhea, vomiting, and the use of phosphate-binding antacids can all contribute to the hypophosphatemia of alcoholism.[83] In addition, serum phosphate concentrations may decrease after hospitalization in patients with alcoholism with the institution of dextrose-containing IV fluids as a result of an intracellular shift of phosphate.[81,83] Hyperventilation associated with the alcohol withdrawal syndrome can also contribute to the development of hypophosphatemia.[81] Patients with alcoholism are particularly susceptible to the complications of hypophosphatemia such as rhabdomyolysis, which is often seen during withdrawal or refeeding.[81] Thus, serum phosphate concentrations should be routinely monitored in patients with alcoholism.

Clinical Presentation

The clinical manifestations of severe hypophosphatemia are diverse and many organ systems can be affected. It is likely that two primary biochemical abnormalities are responsible for most of the clinical manifestations of severe hypophosphatemia.[77] First, intracellular energy stores may be decreased secondary to depletion of intracellular ATP. This can result in disruptions in cellular function. Second, reduced red blood cell 2,3-DPG concentrations are associated with a shift to the left of the oxyhemoglobin saturation curve. This shift is associated with a decrease in the release of oxygen to peripheral tissues (secondary to increased oxygen affinity for hemoglobin) and may result in tissue hypoxia.[77] These metabolic disorders can be seen in a wide variety of organ systems.

Neurologic manifestations of severe hypophosphatemia can result in a metabolic encephalopathy syndrome characterized by irritability, apprehension, weakness, numbness, paresthesia, dysarthria, confusion, obtundation, seizures, and coma.[78,81] Neuropsychiatric disturbances include apathy, delirium, hallucinations, and paranoia. Peripheral neuropathy and symptoms resembling Guillain–Barré syndrome have also been reported.[81]

Severe hypophosphatemia can result in significant dysfunction of skeletal muscle ranging from myalgia, bone pain, and weakness, with chronic hypophosphatemia, to potentially fatal rhabdomyolysis with severe acute hypophosphatemia.[78] Laboratory evaluations can help distinguish between chronic and acute on chronic hypophosphatemia. Elevated alkaline phosphatase, normal creatine phosphokinase, and normal-to-low phosphate and calcium are

present in cases of chronic hypophosphatemia. In contrast, hyperkalemia, hyperuricemia, elevated blood urea nitrogen and creatinine, hypercalcemia, and myoglobinuria are often present in cases in which rhabdomyolysis complicates the acute or chronic hypophosphatemia.[73] Hypophosphatemia can result in acute respiratory failure secondary to respiratory muscle weakness and diaphragmatic contractile dysfunction. Thus, frequent assessment of serum phosphate concentration is indicated in patients at risk for respiratory failure.[77] Likewise, adequate treatment of hypophosphatemia in respiratory failure can aid in successful weaning from the ventilator.[77] Dysphagia and ileus have also been attributed to hypophosphatemia.[77]

Myocardial dysfunction may be impaired in the setting of hypophosphatemia and can result in congestive cardiomyopathy. This has been observed in patients with alcoholism, and postoperative and critically ill patients. Depletion of cardiac ATP stores may be the cause of this syndrome.[84] Arrhythmias have also been reported in patients with hypophosphatemia. Because hypophosphatemia is a potentially reversible cause of heart failure, it should be considered in patients who experience an acute deterioration in ventricular function.

Hematologic manifestations of hypophosphatemia include decreased concentrations of 2,3-DPG, decreased red blood cell ATP, and membrane rigidity.[84] When red blood cell ATP decreases, cells become spherocytic and rigid, and are trapped and destroyed in the spleen.[84] Therefore, hemolysis can be a manifestation of severe hypophosphatemia. Reduction in ATP content of white blood cells can result in mobility, chemotaxis, phagocytosis, and bactericidal dysfunction.[81,84] These changes can contribute to an increased risk of infection in hypophosphatemic patients.

CLINICAL PRESENTATION

Hypophosphatemia

General

- Major conditions associated with symptomatic hypophosphatemia are chronic alcoholism, nutrition support without adequate phosphate supplementation, and the chronic ingestion of antacids. Severe hypophosphatemia can also be seen during treatment of diabetic ketoacidosis and with prolonged hyperventilation.

Symptoms

- Except for the effects on mineral metabolism, the symptoms of hypophosphatemia are caused by two consequences (reduction of red cell 2,3-DPG and reduction of intracellular ATP concentrations), and can impact virtually all organ systems. The symptoms are predominantly neurological and can include irritability, apprehension, weakness, numbness, paresthesia, and confusion. Severe acute development of hypophosphatemia can result in seizures or coma.

Signs

- The initial response of bone to hypophosphatemia contributes to hypercalcemia and hypercalciuria. Prolonged hypophosphatemia can also result in rickets and osteomalacia.
- Neurologic: Severe hypophosphatemia can lead to a metabolic encephalopathy.
- Cardiopulmonary: Impaired myocardial contractility, respiratory failure secondary to ATP depletion, CHF, new onset or worsening of an existing condition.
- Musculoskeletal: Proximal myopathy, dysphagia, and ileus have been reported. Acute hypophosphatemia superimposed on preexisting severe phosphate depletion can lead to rhabdomyolysis.
- Hematologic: Alterations in the hematopoietic system can also occur, resulting in hemolysis, reduction in phagocytotic and granulocyte chemotactic ability, as well as defective clot retraction and thrombocytopenia.

Laboratory Tests

- Serum phosphate concentrations less than 2.7 mg/dL (0.9 mmol/L) are indicative of hypophosphatemia; however, symptomatic hypophosphatemia typically is not evident until serum phosphate less than 1.5 mg/dL (0.5 mmol/L).

Finally, prolonged hypophosphatemia may result in osteopenia and osteomalacia because of enhanced osteoclastic resorption of bone and limited crystallization constituents (phosphate), respectively.[83]

TREATMENT

Desired Outcomes

The goals of therapy are the reversal of signs and symptoms of hypophosphatemia, normalization of serum phosphate concentrations, and management of underlying conditions. Awareness of the clinical situations in which hypophosphatemia is anticipated (eg, alcoholism, diabetic ketoacidosis, initiation of nutrition support in severely malnourished) is of vital importance in preventing and managing hypophosphatemia.

Pharmacologic Therapy

Pharmacologic treatment for hypophosphatemia will typically involve phosphorus salt supplementation. The acuity and other electrolyte conditions dictate the salt, formulation, and route of administration (Table 67-5).

TABLE 67-5 Oral Phosphorus Replacement Therapy with Phosphate, Potassium, and Sodium Content per Packet or Tablet

Product	Phosphate Content	Potassium Content	Sodium Content
Packet			
Phos-NaK®	250 mg (8 mmol)	280 mg (7.1 mEq)	160 mg (6.9 mEq)
Tablet			
Av-Phos 250 Neutral®	250 mg (8 mmol)	45 mg (1.1 mEq)	298 mg (13 mEq)
K-Phos Neutral®	250 mg (8 mmol)	45 mg (1.1 mEq)	298 mg (13 mEq)
K-Phos No. 2®	250 mg (8 mmol)	88 mg (2.3 mEq)	134 mg (5.8 mEq)
Phospha 250 Neutral®	250 mg (8 mmol)	45 mg (1.1 mEq)	298 mg (13 mEq)
Phospho-Trin 250 Neutral®	250 mg (8 mmol)	45 mg (1.1 mEq)	298 mg (13 mEq)
Virt-Phos 250 Neutral®	250 mg (8 mmol)	45 mg (1.1 mEq)	298 mg (13 mEq)

Phosphorus 31 mg = 1 mmol; potassium 39 mg = 1 mEq = 1 mmol; sodium 23 mg = 1 mEq = 1 mmol.

Mild-to-Moderate Hypophosphatemia

Mild-to-moderate (1.5-2.7 mg/dL [0.5-0.9 mmol/L]) or asymptomatic hypophosphatemia can generally be treated by the administration of oral phosphate salts. Fixed-dose and weight-based phosphate supplementation may be used.[3] Oral phosphate salts in divided doses of 1 to 2 g (32-64 mmol) daily

can be provided for mild-to-moderate hypophosphatemia (see Table 67-5). Phosphate concentrations should be monitored daily, with the goal of correcting the reduced phosphate concentration in approximately 7 to 10 days. The primary dose-limiting adverse effect associated with oral phosphate replacement is the development of osmotic diarrhea. For patients who are unable to receive oral supplements, IV phosphorus supplementation may be required. A graduated dosing scheme for IV treatment of hypophosphatemia may be used in patients with normal kidney function.[3] For mild hypophosphatemia (2.3-2.7 mg/dL [0.75-0.9 mmol/L]), an IV phosphate dose of 0.08-0.16 mmol/kg is recommended.[3] In moderate hypophosphatemia (1.5-2.2 mg/dL [0.5-0.75 mmol/L]), an IV phosphate dose of 0.16-0.32 mmol/kg is recommended.[3] Patients with mild-to-moderate hypophosphatemia and impaired kidney function should receive reduced doses, typically ≤50% of the initial empiric dose, with careful monitoring of serum phosphate concentration because they are predisposed to phosphate retention.[3] In the setting of obesity (weight >130% IBW or BMI ≥30 kg/m^2), an adjusted body weight may be used to calculate phosphorus requirements to avoid overdosing. The maximum rate of IV phosphorus infusion is 7.5 mmol/hr.[3] Potassium and sodium are the available salts for IV phosphorus administration. For patients with concomitant hypokalemia, potassium phosphate can be used (1 mmol potassium phosphate = 1.47 mEq K).[3] Patients with hypophosphatemia and normal or elevated serum potassium concentrations should be treated with sodium phosphate (1 mmol sodium phosphate = 1.33 mEq Na).[3] In addition to phosphate supplementation for hypophosphatemia, dipyridamole can decrease renal phosphate leaking and increase serum phosphate. Doses of 75 mg four times daily have resulted in increases in serum 1,25-dihydroxy vitamin D3 and decreases in serum calcium and urolithiasis events.[85]

Severe Hypophosphatemia

8 Patients with severe (less than 1.5 mg/dL [0.5 mmol/L]) or symptomatic hypophosphatemia should be treated with parenteral phosphate replacement. Thus, dosage and infusion recommendations, as well as response to parenteral phosphate replacement, are highly variable.[86] For severe symptomatic hypophosphatemia (<1.5 mg/dL [0.5 mmol/L]), an IV phosphate dose of 0.32 to 0.64 mmol/kg is recommended for patients with normal kidney function.[3] In critically ill trauma patients, doses up to 1 mmol/kg have been used.[87] IV phosphate therapy produces the desired increase in serum phosphate at 24 hours

in 20% to 80% of patients. Response is dependent on the degree of phosphate depletion and replacement dose administered.[83] The initial success is often followed in 48 to 72 hours by recurrent hypophosphatemia, necessitating close monitoring of serum phosphate and repeated administration of phosphate products as warranted.

Adverse Effects of Parenteral Phosphate Parenteral phosphate supplementation is associated with risks of hyperphosphatemia, metastatic soft tissue deposition of calcium-phosphate product, hypomagnesemia, hypocalcemia, hyperkalemia or hypernatremia (dependent on which IV phosphate formulation is administered), and thrombophlebitis from potassium phosphate. Inappropriate administration of large doses of parenteral phosphate over relatively short time periods has resulted in symptomatic hypocalcemia and soft-tissue calcification.[1] The rate of infusion and choice of initial dosage should therefore be based on severity of hypophosphatemia, presence of symptoms, and coexistent medical conditions. Patients should be closely monitored with frequent serum phosphate determinations for 48 to 72 hours after starting IV therapy. Opinions are mixed regarding the optimal time to reevaluate serum phosphorus after supplementation. Several studies have reported monitoring serum phosphorus 12 to 24 hours after supplementation or daily.[3] However, for patients with severe hypophosphatemia, more frequent monitoring may be warranted.[3] It can be necessary to continue administration of IV phosphate for several days in some patients, although other patients may be able to tolerate an oral maintenance regimen. Monitoring should also include assessment of serum potassium, calcium, and magnesium concentrations. Hypomagnesemia secondary to intracellular shifts occurs frequently (27%-80%) in severely hypophosphatemic patients.[75] Therapy with parenteral phosphate should be undertaken with great caution and at reduced dosage for patients with hypercalcemia or impaired kidney function.[81]

CLINICAL BOTTOM LINE

Initial treatment strategy should be based on acuity of onset and severity of symptoms. Because the etiologies of calcium and phosphate disorders are diverse, it is important to integrate the known or anticipated consequences of concomitant diseases into the treatment strategy. The patient’s medication history should be comprehensively assessed to determine whether the electrolyte abnormality may be drug induced. After resolution or treatment of the acute

calcium or phosphate disorder, the medication regimen should be evaluated periodically. This proactive interventional approach will facilitate the management of mild disorders in the community and can reduce the need for hospitalization.

Postclass Engaged Learning Activity

Conduct a literature search and identify an article that has been published within the past 24 months regarding a new medication or patient care process for the management of a calcium or phosphorus disorder. If the article describes a new medication, then write a summary of the drug's mechanism of action, the study methods, the major findings, and how the new medication might change current practice. If the article describes a new patient care process, then compare and contrast it with the existing process outlined in this chapter. This activity is intended to build your literature evaluation skills and increase your ability to assess the place in therapy of a new drug or patient care process.

ABBREVIATIONS

ATP	adenosine triphosphate
CHF	congestive heart failure
CKD	chronic kidney disease
FDA	Food and Drug Administration
FGF23	fibroblast growth factor 23
2,3-DPG	2,3-diphosphoglycerate
NSAID	nonsteroidal anti-inflammatory drug
PTH	parathyroid hormone
PTHrP	PTH-related protein

REFERENCES

1. Brown RB, Razzaque MS. Dysregulation of phosphate metabolism and conditions associated with phosphate toxicity. *Bonekey Rep*. 2015;705.
2. French S, Subauste J, Geraci S. Calcium abnormalities in hospitalized patients. *South Med J*. 2012;4:231–237.
3. Kraft MD. Phosphorus and calcium: A review for the adult nutrition

support clinician. *Nutr Clin Pract*. 2015;1:21–33.

4. Steele T, Kolamunnage-Dona R, Downey C, Toh CH, Welters I. Assessment and clinical course of hypocalcemia in critical illness. *Crit Care*. 2013;3:R106.
5. Khan AA, Hanley DA, Rizzoli R, et al. Primary hyperparathyroidism: Review and recommendations on evaluation, diagnosis, and management. A Canadian and international consensus. *Osteoporos Int*. 2017;1:1–19.
6. Rizzoli R, Body JJ, Brandi ML, et al. Cancer-associated bone disease. *Osteoporos Int*. 2013;12:2929–2953.
7. Silva BC, Cusano NE, Bilezikian JP. Primary hyperparathyroidism. *Best Pract Res Clin Endocrinol Metab*. 2018;5:593–607.
8. Zagzag J, Hu MI, Fisher SB, Perrier ND. Hypercalcemia and cancer: Differential diagnosis and treatment. *CA Cancer J Clin*. 2018;5:377–386.
9. McCauley LK, Martin TJ. Twenty-five years of PTHrP progress: From cancer hormone to multifunctional cytokine. *J Bone Miner Res*. 2012;6:1231–1239.
10. Shapiro HI, Davis KA. Hypercalcemia and “primary” hyperparathyroidism during lithium therapy. *Am J Psychiatry*. 2015;1:12–15.
11. Patel AM, Adeseun GA, Goldfarb S. Calcium-alkali syndrome in the modern era. *Nutrients*. 2013;12:4880–4893.
12. Machado MC, Bruce-Mensah A, Whitmire M, Rizvi AA. Hypercalcemia associated with calcium supplement use: Prevalence and characteristics in hospitalized patients. *J Clin Med*. 2015;3:414–424.
13. Moe SM. Disorders involving calcium, phosphorus, and magnesium. *Prim Care*. 2008;2:215–237,v-vi.
14. Shlapack MA, Rizvi AA, Lopez FA. Normocalcemic primary hyperparathyroidism: Characteristics and clinical significance of an emerging entity. *Am J Med Sci*. 2012;2:163–166.
15. Ahmad S, Kuraganti G, Steenkamp D. Hypercalcemic crisis: A clinical review. *Am J Med*. 2015;3:239–245.
16. Karwowski W, Naumnik B, Szczepanski M, Mysliwiec M. The mechanism of vascular calcification: A systematic review. *Med Sci Monit*. 2012;1:RA1–RA11.
17. McCarty MF, DiNicolantonio JJ. The molecular biology and pathophysiology of vascular calcification. *Postgrad Med*. 2014;2:54–64.

18. Vella A, Gerber TC, Hayes DL, Reeder GS. Digoxin, hypercalcaemia, and cardiac conduction. *Postgrad Med J*. 1999;887:554–556.
19. Cong X, Shen L, Gu X. Current opinions on nephrolithiasis associated with primary hyperparathyroidism. *Urolithiasis*. 2018;5:453–457.
20. Silverberg SJ, Clarke BL, Peacock M, et al. Current issues in the presentation of asymptomatic primary hyperparathyroidism: Proceedings of the Fourth International Workshop. *J Clin Endocrinol Metab*. 2014;10:3580–3594.
21. Ramaswamy K, Killilea DW, Kapahi P, Kahn AJ, Chi T, Stoller ML. The elementome of calcium-based urinary stones and its role in urolithiasis. *Nat Rev Urol*. 2015;10:543–557.
22. Tarplin S, Ganesan V, Monga M. Stone formation and management after bariatric surgery. *Nat Rev Urol*. 2015;5:263–270.
23. Minisola S, Pepe J, Piemonte S, Cipriani C. The diagnosis and management of hypercalcaemia. *BMJ*. 2015;h2723.
24. Carrick AI, Costner HB. Rapid fire: Hypercalcemia. *Emerg Med Clin North Am*. 2018;3:549–555.
25. Lewis MA, Hendrickson AW, Moynihan TJ. Oncologic emergencies: Pathophysiology, presentation, diagnosis, and treatment. *CA Cancer J Clin*. 2011;5:287–314.
26. Grauer A, Ziegler R, Raue F. Clinical significance of antibodies against calcitonin. *Exp Clin Endocrinol Diabetes*. 1995;6:345–351.
27. Stewart AF. Clinical practice. Hypercalcemia associated with cancer. *N Engl J Med*. 2005;4:373–379.
28. Van Poznak C, Somerfield MR, Moy B. Role of bone-modifying agents in metastatic breast cancer: An American society of clinical oncology-cancer care Ontario focused guideline update summary. *J Oncol Pract*. 2017;12:822–824.
29. Wellington K, Goa KL. Zoledronic acid: A review of its use in the management of bone metastases and hypercalcaemia of malignancy. *Drugs*. 2003;4:417–437.
30. Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: A pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol*. 2001;2:558–567.
31. Body JJ, Lortholary A, Romieu G, Vigneron AM, Ford J. A dose-finding

study of zoledronate in hypercalcemic cancer patients. *J Bone Miner Res*. 1999;9:1557–1561.

32. Kim DH, Rogers JR, Fulchino LA, Kim CA, Solomon DH, Kim SC. Bisphosphonates and risk of cardiovascular events: A meta-analysis. *PLoS One*. 2015;4:e0122646.
33. Edwards BJ, Usmani S, Raisch DW, et al. Acute kidney injury and bisphosphonate use in cancer: A report from the research on adverse drug events and reports (RADAR) project. *J Oncol Pract*. 2013;2:101–106.
34. Yachoui R. Early onset acute tubular necrosis following single infusion of zoledronate. *Clin Cases Miner Bone Metab*. 2016;2:154–156.
35. Allen MR. Medication-related osteonecrosis of the jaw: Basic and translational science updates. *Oral Maxillofac Surg Clin North Am*. 2015;4:497–508.
36. Hu MI, Glezerman IG, Leboulleux S, et al. Denosumab for treatment of hypercalcemia of malignancy. *J Clin Endocrinol Metab*. 2014;9:3144–3152.
37. Shroff R, Beringer O, Rao K, Hofbauer LC, Schulz A. Denosumab for post-transplantation hypercalcemia in osteopetrosis. *N Engl J Med*. 2012;18:1766–1767.
38. You T, Lee KH, Lee SH, Park W. Denosumab-related osteonecrosis of the jaw: A case report and management based on pharmacokinetics. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2015;5:548–553.
39. Lambe G, Malvathu R, Thomas HM, Graves A. Hypocalcaemic tetany occurring post a single denosumab dose in a patient with stage 4 chronic kidney disease, followed by calcium- and calcitriol-induced hypercalcaemia. *Nephrology (Carlton)*. 2015;8:583–584.
40. Martin-Baez IM, Blanco-Garcia R, Alonso-Suarez M, Cossio-Aranibar C, Beato-Coo LV, Fernandez-Fleming F. Severe hypocalcaemia post-denosumab. *Nefrologia*. 2013;4:614–615.
41. Malangone S, Campen CJ. Hypercalcemia of malignancy. *J Adv Pract Oncol*. 2015;6:586–592.
42. Wright JD, Tergas AI, Ananth CV, et al. Quality and outcomes of treatment of hypercalcemia of malignancy. *Cancer Invest*. 2015;8:331–339.
43. Filopanti M, Corbetta S, Barbieri AM, Spada A. Pharmacology of the calcium sensing receptor. *Clin Cases Miner Bone Metab*. 2013;3:162–165.

44. Messa P, Alfieri C, Brezzi B. Clinical utilization of cinacalcet in hypercalcemic conditions. *Expert Opin Drug Metab Toxicol*. 2011;4:517–528.
45. Sensipar® (cinacalcet HCl) [package insert]. Thousand Oaks, CA: Amgen, Inc., May 2017.
46. Brardi S, Cevenini G, Verdacchi T, Romano G, Ponchietti R. Use of cinacalcet in nephrolithiasis associated with normocalcemic or hypercalcemic primary hyperparathyroidism: Results of a prospective randomized pilot study. *Arch Ital Urol Androl*. 2015;1:66–71.
47. Harada K, Fujioka A, Konno M, Inoue A, Yamada H, Hirota Y. Pharmacology of Parsabiv((R)) (etelcalcetide, ONO-5163/AMG 416), a novel allosteric modulator of the calcium-sensing receptor, for secondary hyperparathyroidism in hemodialysis patients. *Eur J Pharmacol*. 2019;139–145.
48. Andronis L, Goranitis I, Bayliss S, Duarte R. Cost-effectiveness of treatments for the management of bone metastases: A systematic literature review. *Pharmacoeconomics*. 2018;3:301–322.
49. Arellano J, Hauber AB, Mohamed AF, et al. Physicians' preferences for bone metastases drug therapy in the United States. *Value Health*. 2015;1:78–83.
50. Fong J, Khan A. Hypocalcemia: Updates in diagnosis and management for primary care. *Can Fam Physician*. 2012;2:158–162.
51. Chung HS, Cho SJ, Park CS. Effects of liver function on ionized hypocalcaemia following rapid blood transfusion. *J Int Med Res*. 2012;2:572–582.
52. Kishimoto M, Ohto H, Shikama Y, Kikuta A, Kimijima I, Takenoshita S. Treatment for the decline of ionized calcium levels during peripheral blood progenitor cell harvesting. *Transfusion*. 2002;10:1340–1347.
53. Wilson FP, Berns JS. Tumor lysis syndrome: New challenges and recent advances. *Adv Chronic Kidney Dis*. 2014;1:18–26.
54. Choi KH, Shin CH, Yang SW, Cheong HI. Autosomal dominant hypocalcemia with Bartter syndrome due to a novel activating mutation of calcium sensing receptor, Y829C. *Korean J Pediatr*. 2015;4:148–153.
55. Bove-Fenderson E, Mannstadt M. Hypocalcemic disorders. *Best Pract Res Clin Endocrinol Metab*. 2018;5:639–656.
56. Kitanaka S, Isojima T, Takaki M, Numakura C, Hayasaka K, Igarashi T. Association of vitamin D-related gene polymorphisms with manifestation

of vitamin D deficiency in children. *Endocr J*. 2012;11:1007–1014.

57. De Sanctis V, Soliman A, Fiscina B. Hypoparathyroidism: From diagnosis to treatment. *Curr Opin Endocrinol Diabetes Obes*. 2012;6:435–442.
58. Tachibana S, Sato S, Yokoi T, et al. Severe hypocalcemia complicated by postsurgical hypoparathyroidism and hungry bone syndrome in a patient with primary hyperparathyroidism, Graves' disease, and acromegaly. *Intern Med*. 2012;14:1869–1873.
59. Kan WC, Wang HY, Chien CC, Tan CK, Lin CY, Su SB. Intermediate bioelectrolyte changes after phospho-soda or polyethylene glycol precolonoscopic laxatives in a population undergoing health examinations. *Nephrol Dial Transplant*. 2012;2:752–757.
60. Yon CK, Low CL. Sodium citrate 4% versus heparin as a lock solution in hemodialysis patients with central venous catheters. *Am J Health Syst Pharm*. 2013;2:131–136.
61. Morabito S, Pistolesi V, Tritapepe L, Fiaccadori E. Regional citrate anticoagulation for RRTs in critically ill patients with AKI. *Clin J Am Soc Nephrol*. 2014;12:2173–2188.
62. Polaschegg HD, Sodemann K. Risks related to catheter locking solutions containing concentrated citrate. *Nephrol Dial Transplant*. 2003;12:2688–2690.
63. Kelly A, Levine MA. Hypocalcemia in the critically ill patient. *J Intensive Care Med*. 2013;3:166–177.
64. Witteveen JE, van Thiel S, Romijn JA, Hamdy NA. Hungry bone syndrome. Still a challenge in the post-operative management of primary hyperparathyroidism: a systematic review of the literature. *Eur J Endocrinol*. 2013;3:R45–R53.
65. Cusano NE, Rubin MR, Irani D, Sliney J Jr, Bilezikian JP. Use of parathyroid hormone in hypoparathyroidism. *J Endocrinol Invest*. 2013;11:1121–1127.
66. Holick MF. The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention. *Rev Endocr Metab Disord*. 2017;2:153–165.
67. Blaine J, Chonchol M, Levi M. Renal control of calcium, phosphate, and magnesium homeostasis. *Clin J Am Soc Nephrol*. 2015;7:1257–1272.
68. Felsenfeld AJ, Levine BS, Rodriguez M. Pathophysiology of calcium, phosphorus, and magnesium dysregulation in chronic kidney disease. *Semin Dial*. 2015;6:564–577.

69. Kocelak P, Olszanecka-Glinianowicz M, Chudek J. Fibroblast growth factor 23: Structure, function and role in kidney diseases. *Adv Clin Exp Med*. 2012;3:391–401.
70. Adamcewicz M, Bearelly D, Porat G, Friedenberg FK. Mechanism of action and toxicities of purgatives used for colonoscopy preparation. *Expert Opin Drug Metab Toxicol*. 2011;1:89–101.
71. FDA requires new safety measures for oral sodium phosphate products to reduce risk of acute kidney injury risk associated with both prescription and over-the-counter (OTC) products. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm380757.htm. Accessed December 30, 2018.
72. Kamel KS, Halperin ML. Acid-base problems in diabetic ketoacidosis. *N Engl J Med*. 2015;20:1969–1970.
73. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol*. 2004;8:2208–2218.
74. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD). *Kidney International Supplements*. 2017;1:1–59.
75. Hutchison AJ, Smith CP, Brenchley PE. Pharmacology, efficacy and safety of oral phosphate binders. *Nat Rev Nephrol*. 2011;10:578–589.
76. Pai AB, Jang SM, Wegrzyn N. Iron-based phosphate binders: A new element in management of hyperphosphatemia. *Expert Opin Drug Metab Toxicol*. 2016;1:115–127.
77. Chang WT, Radin B, McCurdy MT. Calcium, magnesium, and phosphate abnormalities in the emergency department. *Emerg Med Clin North Am*. 2014;2:349–366.
78. Subramanian R, Khardori R. Severe hypophosphatemia. Pathophysiologic implications, clinical presentations, and treatment. *Medicine (Baltimore)*. 2000;1:1–8.
79. Hardy S, Vandemergel X. Intravenous iron administration and hypophosphatemia in clinical practice. *Int J Rheumatol*. 2015;468675.
80. Wolf M, White KE. Coupling fibroblast growth factor 23 production and cleavage: Iron deficiency, rickets, and kidney disease. *Curr Opin Nephrol Hypertens*. 2014;4:411–419.
81. Amanzadeh J, Reilly RF Jr. Hypophosphatemia: An evidence-based

approach to its clinical consequences and management. *Nat Clin Pract Nephrol*. 2006;3:136–148.

82. Konstantinov NK, Rohrscheib M, Agaba EI, Dorin RI, Murata GH, Tzamaloukas AH. Respiratory failure in diabetic ketoacidosis. *World J Diabetes*. 2015;8:1009–1023.
83. Felsenfeld AJ, Levine BS. Approach to treatment of hypophosphatemia. *Am J Kidney Dis*. 2012;4:655–661.
84. Gaasbeek A, Meinders AE. Hypophosphatemia: An update on its etiology and treatment. *Am J Med*. 2005;10:1094–1101.
85. Liamis G, Milionis HJ, Elisaf M. Medication-induced hypophosphatemia: A review. *QJM*. 2010;7:449–459.
86. Agarwal B, Walecka A, Shaw S, Davenport A. Is parenteral phosphate replacement in the intensive care unit safe? *Ther Apher Dial*. 2014;1:31–36.
87. Brown KA, Dickerson RN, Morgan LM, Alexander KH, Minard G, Brown RO. A new graduated dosing regimen for phosphorus replacement in patients receiving nutrition support. *JPEN J Parenter Enteral Nutr*. 2006;3:209–214.

68

Disorders of Potassium and Magnesium Homeostasis

Rachel W. Flurie

KEY CONCEPTS

1. Potassium regulates many biochemical processes in the body and is a key cation for electrical action potentials across cellular membranes.
2. The kidney is the primary route of potassium elimination.
3. In patients with concomitant hypokalemia and hypomagnesemia, it is imperative to correct the hypomagnesemia before the hypokalemia.
4. Potassium chloride is the preferred potassium supplement for the most common causes of hypokalemia.
5. Hyperkalemia is a common occurrence in patients with acute kidney injury or chronic kidney disease.
6. Hypomagnesemia is commonly caused by excessive gastrointestinal or renal magnesium wasting.
7. Hypermagnesemia is predominantly observed in patients with acute or chronic kidney disease.
8. Severe hypermagnesemia may affect the neuromuscular and cardiovascular systems.

Preclass Engaged Learning Activity

Watch the video entitled “Hyperkalemia in Primary Care Practice” by the National Kidney Foundation. This 11-minute video provides a brief overview of the risks associated with hyperkalemia, the various causes of hyperkalemia, and prevention and treatment strategies. The video is useful to enhance

student understanding of the COLLECT, ASSESS, and PLAN steps in the patient care process.

INTRODUCTION

Potassium and magnesium are electrolytes that are responsible for numerous metabolic activities. Disorders of these electrolytes are frequently seen in both the acute care and community ambulatory care settings. Therefore, clinicians need a firm understanding of the etiology, pathophysiology, symptoms, pharmacotherapy, and monitoring of these disorders. This chapter describes the homeostatic mechanisms that are responsible for the maintenance of normal potassium and magnesium serum concentrations. The clinical disorders responsible for the development of hyperkalemia, hypermagnesemia, hypokalemia, and hypomagnesemia are also reviewed.

POTASSIUM

Potassium is the most abundant cation in the body, with estimated total-body stores of 3,000 to 4,000 mEq (mmol).[1] Ninety-eight percent of this amount is contained within the intracellular compartment, and the remaining 2% is distributed within the extracellular compartment. The sodium-potassium adenosine triphosphatase (Na^+-K^+-ATPase) pump located in the cell membrane is responsible for the compartmentalization of potassium. This pump is an active transport system that maintains increased intracellular stores of potassium by transporting sodium out of the cell and potassium into the cell at a ratio of 3:2. Consequently, the pump maintains a higher concentration of potassium inside the cell.

The normal serum concentration range for potassium is 3.5 to 5 mEq/L (mmol/L), whereas the intracellular potassium concentration is approximately 150 mEq/L (mmol/L).[2] Approximately 75% of the intracellular potassium is located in skeletal muscle; the remaining 25% is located in the liver and red blood cells. Extracellular potassium is distributed throughout the serum and interstitial space. Potassium is dynamic, in that it is constantly moving between the intracellular and extracellular compartments according to the body's needs. Thus, the serum potassium concentration alone does not accurately reflect the total-body potassium content.

1 Potassium has many physiologic functions within cells, including protein

and glycogen synthesis and cellular metabolism and growth. It is also a determinant of the electrical action potential across the cell membrane.[1] The ratio of the intracellular-to-extracellular potassium concentration is the major determinant of the resting membrane potential across the cell membrane. Serum potassium concentrations outside the normal range can have disastrous effects on neuromuscular activity, in particular cardiac conduction. Hypo- and hyperkalemia are both associated with potentially fatal cardiac arrhythmias, along with other neuromuscular disturbances. Finally, potassium is integral to maintaining blood pressure, prevention of stroke, and potentially other cardiovascular diseases.[3] Both the National High Blood Pressure Education Program and the Institute of Medicine recommend potassium supplementation as a strategy for preventing and treating hypertension.[4,5]

Control of Potassium Homeostasis

Potassium homeostasis, the maintenance of serum potassium within the normal range, is affected by dietary intake, gastrointestinal (GI) and urinary excretion, hepatic and muscular sequestration, hormones, acid–base balance, body fluid tonicity, central and peripheral circadian clocks, and a highly integrated feedback mechanism.[6,7] Together, these mechanisms usually maintain total-body potassium content within a narrow window without appreciable changes in the serum potassium concentration.[6] Deviations in serum potassium concentrations outside of the normal range are a result of nonhomeostatic processes that are not sensitive to changes in potassium balance.[6] The recommended adequate intake of dietary potassium in the United States is 4,700 mg/day; yet the typical American adult only consumes 56% of this recommended amount.[8] Potassium is considered to be a nutrient of concern, because of its beneficial effects on blood pressure, reduction in the risk of kidney stones, and decrease in bone loss.[9] Potassium is abundant in fruits, vegetables, meats, whole grains, and milk products. Most dietary potassium is absorbed, with only 10 to 20 mEq/day (mmol/day) eliminated in feces. The amount eliminated in the feces increases, however, in patients with diarrhea and in those with chronic kidney disease (CKD).[7]

2 The kidney is the primary route of potassium elimination. Potassium is freely filtered, but almost all of it is reabsorbed passively in the proximal tubule and the thick ascending limb of the loop of Henle.[9] Although the amount of potassium filtered by the glomerulus approaches 700 mEq/day (mmol/day), only 10% to 20% is actually excreted in the urine.[9] Potassium excretion is regulated

by its secretion into the distal tubule and collecting duct. Variations in potassium excretion are based on dietary intake, serum potassium concentration, and aldosterone activity. For example, more potassium is renally excreted in conditions that result in high-aldosterone activity (eg, dehydration) when the body is attempting to conserve sodium or when there is an increase in dietary potassium intake. In addition, enteric solute sensors increase kaliuresis in response to high-dietary potassium intake.[1]

Hormones such as insulin, catecholamines, and aldosterone dramatically affect potassium homeostasis. Aldosterone controls renal potassium excretion, which can take several hours to adjust serum potassium concentrations. Rapid buffering of serum potassium concentrations occurs through potassium cellular redistribution, of which insulin and catecholamines play a large role. Insulin is the most important hormonal mediator of potassium balance because it stimulates the cellular Na^+-K^+-ATPase pump to increase transport of potassium into liver, muscle, and adipose tissue.[6] There is a complex negative feedback loop in which insulin secretion tightly regulates serum potassium concentrations: an increase of only a few tenths of a milliequivalent (mmol) of potassium stimulates pancreatic insulin secretion in an attempt to prevent hyperkalemia from developing.[1] If hyperkalemia does occur, glucagon is released from the liver to protect against insulin-induced hypoglycemia. Conversely, hypokalemia inhibits insulin secretion, a finding that explains why some patients receiving diuretics develop hyperglycemia.

An elevation in circulating catecholamines such as epinephrine usually results in the intracellular movement of potassium by two mechanisms.[9] Stimulation of the β-receptor, which directly activates the Na^+-K^+-ATPase pump, and glycogenolysis, which raises blood glucose concentrations, thereby increasing insulin secretion. This dual mechanism is often used therapeutically in patients with hyperkalemia to normalize serum potassium concentrations.

Aldosterone, a mineralocorticoid that is secreted from the adrenal glands in response to high-serum potassium concentrations, promotes urinary potassium excretion. Aldosterone acts on the distal tubule and collecting duct to promote the reabsorption of sodium and water in exchange for potassium. It also increases potassium permeability and transport across the luminal membrane of the nephron by stimulating cellular Na^+-K^+-ATPase pump activity.[7] In patients with impaired kidney function, aldosterone increases potassium excretion in the distal colon.[10]

Changes in acid–base status significantly affect the serum potassium concentration. For example, the infusion of metabolic inorganic acids, such as

hydrochloric acid, results in an increase in serum potassium. The body compensates for excessive hydrogen ions by moving them from the serum into the cell in exchange for intracellular potassium, to maintain electroneutrality. The processes by which this occurs are highly complex and involve cellular H^+-K^+-ATPase pumps and both Na^+-HCO_3^- and K^+-HCO_3^- cotransporters.[11] The efflux of potassium into the serum can result in hyperkalemia. A commonly quoted approximation of the pH effect is that for every 0.1 unit decrease in pH, serum potassium concentration increases by 0.6 to 0.8 mEq/L (mmol/L) (with a wide range of 0.2-1.7).[12] This is often referred to as *false hyperkalemia* because there is not a true excess of total-body potassium. Metabolic acidosis associated with lactic acidosis and ketoacidosis does not result in hyperkalemia, because both cations and anions enter the cell, thus maintaining electroneutrality.[1] Respiratory acidosis also does not significantly affect the serum potassium concentration.

Conversely, metabolic alkalosis has been associated with hypokalemia. As a result of a net loss of hydrogen ion from the serum, intracellular hydrogen ions enter the serum to increase the acidity of the blood. To maintain electroneutrality, extracellular potassium ions are shifted intracellularly. This creates a relative deficiency of potassium in the serum. Serum potassium decreases approximately 0.6 mEq/L (mmol/L) for each 0.1 unit increase in blood pH. This is frequently termed *false hypokalemia* because there is not a true deficiency in total-body potassium.

Finally, hyperosmolality can result in enhanced movement of potassium from the cell into the extracellular fluid. Water movement favors potassium efflux through solvent drag. As cells shrink, intracellular potassium concentrations increase, further promoting potassium efflux.[7] This is seen in conditions such as diabetic ketoacidosis. Conversely, hypoosmolality does not seem to affect potassium distribution.

HYPOKALEMIA

Epidemiology

Hypokalemia (defined as a serum potassium concentration less than 3.5 mEq/L [mmol/L]) is a commonly encountered electrolyte abnormality in clinical practice. Hypokalemia is often categorized as mild (serum potassium 3.1-3.5 mEq/L [mmol/L]), moderate (serum potassium 2.5-3 mEq/L [mmol/L]), or severe (less than 2.5 mEq/L [mmol/L]).[2] When hypokalemia is detected, the

diagnostic workup should evaluate the patient's comorbid disease states and concomitant medications. Hypokalemia is virtually nonexistent in healthy adults. This is due in part to the potassium content in the typical Western diet as well as the body's effective potassium-sparing mechanisms, which tightly regulate the serum potassium concentration. However, as many as 20% of hospitalized patients and up to 40% of patients taking thiazide diuretics will develop hypokalemia.[2]

While transient hypokalemia may be thought of as merely a laboratory abnormality, there are serious potential consequences associated with persistent hypokalemia. Hypokalemia increases mortality in patients with chronic heart failure or CKD, populations typically thought to be more sensitive to the effects of hyperkalemia.[13] Low dietary potassium intake is associated with worsening hypertension and higher risk of stroke.[3]

Etiology and Pathophysiology

Hypokalemia results when there is a total-body potassium deficit, or when serum potassium is shifted into the intracellular compartment. Total-body deficits occur in the setting of poor dietary intake of potassium, or when there are excessive renal and GI losses of potassium. Maintaining a consistent dietary intake of potassium is important because the body has no effective method for storing potassium. At steady state, potassium excretion matches potassium intake; approximately 90% of ingested potassium is renally excreted, whereas 10% is excreted in feces.[9] This underscores the importance of eating a well-balanced diet. Elderly patients with chronic diseases and those undergoing surgery are at increased risk for developing hypokalemia because of insufficient intake or losses resulting from surgery.

Many drugs can cause hypokalemia by a variety of mechanisms including intracellular potassium shifting and increased renal or stool losses (**Table 68-1**). The most common cause of drug-induced hypokalemia is loop and thiazide diuretic administration as these agents inhibit renal sodium reabsorption, which results in increased sodium delivery to the distal tubule. Consequently, hypokalemia develops because the distal tubule selectively reabsorbs sodium, and excretes potassium. Second, because diuretics result in vascular volume contraction, aldosterone is secreted that further promotes the renal excretion of potassium. If concomitant potassium supplements are not provided to patients receiving loop and thiazide diuretics, mild-to-moderate hypokalemia is inevitable.

TABLE 68-1 Mechanism of Drug-Induced Hypokalemia

Transcellular Shift	Enhanced Renal Excretion	Enhanced Fecal Elimination
β_2-Receptor agonists	Diuretics	Laxatives
Epinephrine	Acetazolamide	Sodium polystyrene sulfonate
Albuterol	Thiazides	Phenolphthalein
Terbutaline	Indapamide	Sorbitol
Fomoterol	Metolazone	Patiromer
Salmeterol	Furosemide	Sodium zirconium cyclosilicate
Isoproterenol	Torsemide	
Ephedrine	Bumetanide	
Pseudoephedrine	Ethacrynic acid	
Tocolytic agents	High-dose penicillins	
Ritodrine	Nafcillin	
Nylidrin	Ampicillin	
Theophylline	Penicillin	
Levothyroxine	Mineralocorticoids	
Decongestants	Miscellaneous	
Caffeine	Aminoglycosides	
Insulin overdose	Amphotericin B	
Verapamil overdose	Cisplatin	
Barium overdose		

The second most common etiology of hypokalemia is excessive loss of potassium-rich GI fluid as a result of diarrhea and/or vomiting. The typical potassium loss in feces is approximately 10 mEq/day (mmol/day).[7] In diarrheal states, this amount increases proportionally with the volume of stool output. A case report of a patient with secretory diarrhea reported fecal potassium losses of 130 to 170 mEq/L (mmol/L).[14] Vomiting also accounts for substantial potassium losses, which have been estimated to be as high as 30 to 50 mEq/L (mmol/L) of vomitus.[15] Metabolic alkalosis which often develops in those with severe diarrhea and vomiting as a result of loss of these bicarbonate-rich fluids causes an intracellular shift of potassium, which lowers the serum concentration of potassium even further. Prolonged diarrhea and vomiting tend to affect children and elderly patients profoundly because their kidneys are unable to effectively maintain adequate fluid status.

3 Hypomagnesemia, which is present in more than 50% of cases of clinically significant hypokalemia, contributes to the development of hypokalemia because it reduces the intracellular potassium concentration and promotes renal potassium wasting.[16] While the precise mechanism of the accelerated renal loss is unknown, many believe that the intracellular potassium

concentration may decrease because hypomagnesemia impairs the function of the Na^+-K^+-ATPase pump, thereby promoting potassium wasting. Alternatively, the combination of increased sodium delivery to the distal tubule, elevated aldosterone concentrations, and hypomagnesemia may cause the renal outer medullary potassium channels to excrete more potassium.[16] What is clear is that hypokalemia and hypomagnesemia often coexist as a result of drugs (diuretic administration) or disease states (diarrhea). When concomitant hypokalemia and hypomagnesemia occur, the magnesium deficiency should be corrected first, otherwise full repletion of the potassium deficit is difficult.

TREATMENT

Desired Outcomes

The goals of hypokalemia management are to prevent and/or treat serious life-threatening complications, normalize the serum potassium concentration, identify and correct the underlying cause of hypokalemia, and prevent overcorrection of the serum potassium concentration.

General Approach to Therapy

The general approach to therapy depends on the degree and rapidity with which hypokalemia developed and the presence of signs and symptoms. Serum potassium concentrations between 3.5 and 4 mEq/L (mmol/L) are a sign of early potassium depletion. No pharmacologic therapy is recommended; however, patients should be encouraged to increase their dietary intake of potassium-rich foods. When the serum potassium concentration is between 3 and 3.5 mEq/L (mmol/L), the patient's concomitant conditions and therapies will largely determine whether pharmacologic therapy should be initiated. Most patients will not have signs or symptoms if serum potassium concentrations remain greater than 3 mEq/L (mmol/L). The presence of signs or symptoms with mild hypokalemia warrants the initiation of potassium supplementation. Oral potassium supplementation should be initiated in patients with underlying cardiac conditions that predispose them to cardiac arrhythmias. Patients with serum potassium concentrations less than 3 mEq/L (mmol/L) should always be treated to achieve values between 4 and 4.5 mEq/L (mmol/L). In asymptomatic patients, oral therapy is the preferred route of administration. Intravenous (IV) potassium may be necessary in symptomatic patients with severe depletion, or in

patients who are intolerant to oral supplementation. In patients with concomitant moderate-to-severe hypomagnesemia, the magnesium deficit should be corrected before potassium supplementation is started.[2,9]

CLINICAL PRESENTATION

Hypokalemia

General

- The signs and symptoms of hypokalemia are usually nonspecific and highly variable between patients.

Symptoms

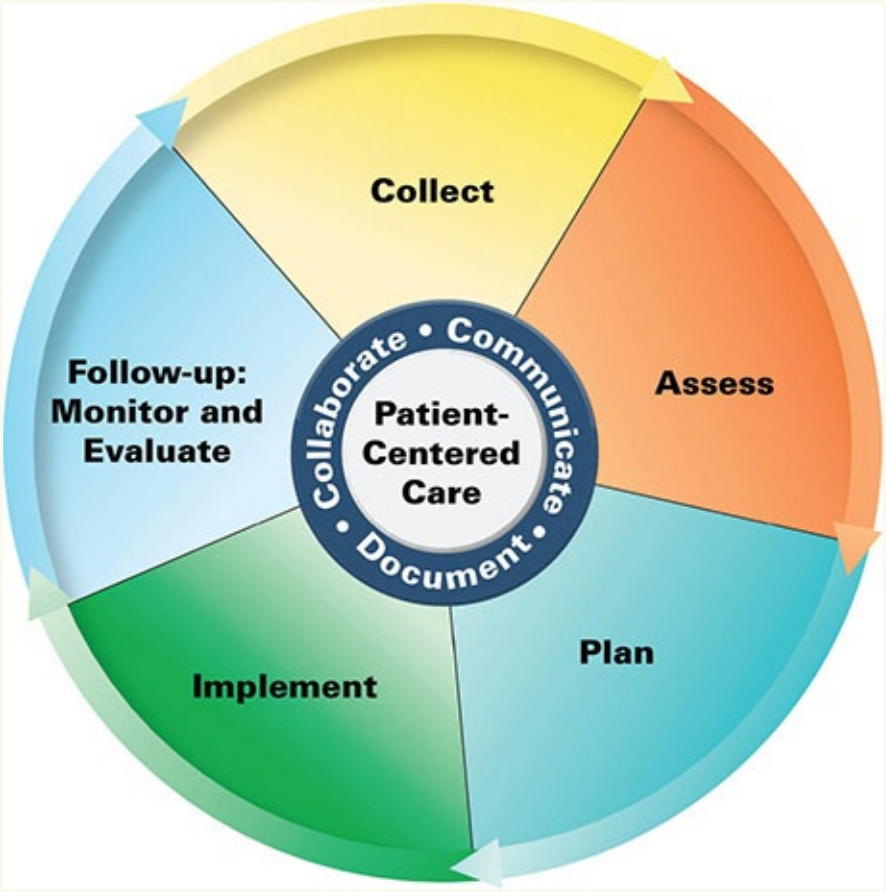
- Symptoms are dependent on the degree of hypokalemia and its rapidity of onset.
- Mild hypokalemia is often asymptomatic.
- Moderate hypokalemia is associated with cramping, weakness, malaise, and myalgias.

Signs

- Cardiovascular: In severe hypokalemia, electrocardiogram (ECG) changes often include ST-segment depression or flattening, T-wave inversion, and U-wave elevation. Clinical arrhythmias include heart block, atrial flutter, paroxysmal atrial tachycardia, ventricular fibrillation, and digitalis-induced arrhythmias.
- Musculoskeletal: Cramping and impaired muscle contraction.

Laboratory Tests

- Serum potassium concentration below 3.5 mEq/L (mmol/L) is diagnostic. Hypomagnesemia (serum magnesium concentration below 1.7 mg/dL [1.4 mEq/L; 0.70 mmol/L]) can also be present.



Patient Care Process for the Management of Potassium and Magnesium Disorders

Collect

- Patient characteristics (eg, age, race, sex)
- Patient history (past medical, family, social—dietary habits)
- Current medications including over-the-counter medications, herbals, dietary supplements
- Subjective data
  - Musculoskeletal and neuromuscular review of systems
  - Intake (food and fluid) and output (urine and stool)
- Objective data
  - BP, heart rate (HR), height, weight
  - Labs (eg, basic metabolic panel, calcium, magnesium, phosphorus)

- Other diagnostic tests when indicated (eg, ECG, urinalysis, urine electrolytes)

Assess

- Presence of symptoms of an electrolyte disorder
- Presence of ECG changes (see Fig. 68-1)
- Severity of electrolyte disorder (eg, change from baseline value, timing of development of electrolyte disorder)
- Kidney function (eg, eGFR, creatinine clearance, presence of chronic kidney disease)
- Current medications that may contribute to electrolyte disorder (see Tables 68-1, 68-6, and 68-8)
- Current diet that may contribute to electrolyte disorder (see Tables 68-2 and 68-9)

Plan*

- Identification of the most likely cause of the electrolyte disorder and discontinuation of offending medication or substance (if applicable)
- Dietary modifications (see Tables 68-2 and 68-9)
- Drug therapy regimen including specific medication, dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Tables 68-4, 68-5, and 68-7)
- Monitoring parameters including efficacy (eg, potassium, magnesium, SCr), safety (medication-specific adverse effects), and need for repeat or additional drug therapy
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug therapy)
- Referrals to other providers when appropriate (eg, physician, dietician)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Resolution of electrolyte disorder and prevention of further episodes
- Presence of adverse effects
- Development/progression of kidney impairment
- Patient adherence to treatment plan using multiple sources of information

* *Collaborate with patient, caregivers, and other healthcare professionals.*

Nonpharmacologic Therapy

The best and most abundant sources of dietary potassium supplementation are fresh fruits and vegetables, fruit juices, and meats (Table 68-2). Increased dietary intake of foods with high-potassium content, however, is not recommended long term because it can add unwanted calories to the patient's diet. Moreover, dietary potassium is almost entirely coupled with phosphate, rather than chloride, so it is not as effective in correcting potassium loss associated with hypochloremic conditions such as vomiting, nasogastric suctioning, and diuretic therapy. Salt substitutes that contain potassium chloride are another effective, inexpensive source of potassium and because they provide chloride as well they are frequently recommended.

TABLE 68-2 Foods That Are High in Potassium

High content (>250 mg)	Very high content (>500 mg)
Kidney beans, cooked	Potato, baked, flesh and skin
Lentils, cooked	Sweet potato, baked in skin
Soybeans, green, cooked	Juice, canned
Lima beans, cooked	Prunes
Soybeans, mature, cooked	Carrot
Pinto beans, cooked	Tomato
Lentils, cooked	Tomato paste
Halibut, cooked	Tomato puree
Rockfish, Pacific, cooked	Beet greens, cooked
Cod, Pacific, cooked	White beans, canned
Tuna, yellowfin, cooked	Plain yogurt, nonfat or low-fat
Rainbow trout, cooked	Clams, canned
Evaporated milk, nonfat	
Low-fat (1%) or reduced fat (2%) chocolate milk	
Skim milk (nonfat)	
Low-fat milk or buttermilk (1%)	
Orange juice, fresh	
Bananas	
Peaches, dried, uncooked	
Prunes, stewed	
Apricots, dried, uncooked	
Plantains, cooked	
Tomato sauce	
Pork loin, center rib, lean, roasted	
Spinach, cooked	

Pharmacologic Therapy

Formal guidelines for potassium supplementation were last published by the National Council on Potassium in Clinical Practice in 2000 (Table 68-3).[17] These guidelines provide a comprehensive framework for potassium administration as a prophylactic and therapeutic replacement for many patient

populations. When deciding how to design the optimal regimen, one must consider: (a) the patient's normal, that is, baseline potassium concentration; (b) underlying medical conditions that can affect potassium balance; (c) concomitant medications that can affect potassium balance; (d) the patient's dietary salt intake; and (e) the patient's ability to comply with the therapeutic regimen.[17]

TABLE 68-3 General Consensus Guidelines for Potassium Replacement

Guideline	Comment
Potassium replacement therapy should accompany dietary consumption of potassium-rich foods.	Potassium-rich foods often cannot completely replace potassium associated with chloride losses (vomiting, diuretics, or nasogastric suction) because it is almost entirely coupled to phosphate. Furthermore, increasing dietary intake of these foods can lead to unwanted weight gain.
Potassium replacement is recommended for sodium-sensitive and hypertensive patients.	A high-sodium diet often results in excessive urinary potassium excretion.
Potassium replacement is recommended in patients who are subject to vomiting, diarrhea, or diuretic/laxative abuse.	These conditions promote excessive renal and GI potassium loss.
Potassium supplementation is best administered orally in divided doses over several days to achieve full repletion.	
Laboratory measurement of serum potassium is convenient, but not always accurate.	Clinicians should be aware of the factors that result in transcellular potassium shifts. Monitoring 24-hour urinary potassium excretion can be necessary in high-risk patients.
Patient adherence to potassium replacement can be increased with compliance-enhancing regimens.	Microencapsulated products have no bitter smell or aftertaste and have much better GI tolerance. Regimens should be made as simple as possible to follow.
A potassium dosage of 20 mEq/day (mmol/day) is usually sufficient to prevent hypokalemia from occurring. Doses of 40-100 mEq (mmol) are usually sufficient to treat hypokalemia.	

A general rule for potassium replacement is that for every 1 mEq/L (mmol/L)

decrease of serum potassium below 3.5 mEq/L (mmol/L), there is a corresponding total-body potassium deficit of 100 to 400 mEq (mmol). Because of the wide variance in projected deficits, each patient's therapy must be individualized and adjustments made on the basis of the patient's signs, symptoms, and frequent measurements of serum potassium. In the acute care setting, the administration of 10 mEq (mmol) of IV or oral potassium should increase the serum potassium concentration by 0.1 mEq/L (mmol/L). This approximation is used as a basis for dose calculations, with frequent measurements of serum potassium to avoid overestimation. In patients receiving chronic loop or thiazide diuretic therapy, 40 to 100 mEq (mmol) of oral potassium supplementation can correct mild-to-moderate potassium deficits. Doses up to 120 mEq (mmol) can be required in more severe deficiencies. When providing oral potassium supplementation, the total daily dose should be divided into three to four doses to minimize the development of GI side effects. Patients receiving diuretics can become chronically hypokalemic and can benefit from combination potassium-sparing diuretic therapy.

4 Whenever possible, potassium supplementation should be administered by mouth. Four salts are available for oral potassium supplementation: chloride, gluconate, phosphate, and bicarbonate. Potassium phosphate should be used when the patient is both hypokalemic and hypophosphatemic; potassium bicarbonate is most commonly used when potassium depletion occurs in the setting of metabolic acidosis. Potassium chloride, however, is the primary salt form used because it is the most effective treatment for the most common causes of potassium depletion (ie, diuretic and diarrhea-induced) as these conditions are associated with potassium and chloride losses.

Potassium chloride can be administered in either tablet or liquid formulations (**Table 68-4**). The liquid forms are generally less expensive; however, patient compliance can be low because of their strong, unpleasant taste. Liquid forms should be used when a rapid response to supplementation is desired. Two sustained-release solid dosage forms are currently available in the United States: a wax-matrix formulation and a microencapsulated formulation. The microencapsulated tablet is generally preferred because it is associated with less GI irritation. IV potassium use should be limited to: (a) severe cases of hypokalemia (serum concentration less than 2.5 mEq/L [mmol/L]); (b) patients exhibiting signs and symptoms such as ECG changes or muscle spasms; or (c) patients unable to tolerate oral therapy. IV supplementation is more dangerous than oral therapy because it is more likely to result in hyperkalemia, phlebitis, and pain at the site of infusion.

TABLE 68-4 Differences Among Oral Potassium Supplements

Supplement	Comment
Controlled-release microencapsulated tablet	Disintegrates better in GI tract; fewer GI erosions as compared to wax-matrix tablets
Encapsulated controlled-release microencapsulated particles	Fewer erosions as compared to wax-matrix tablets
Potassium chloride elixir	Inexpensive, poor taste, poor compliance, immediate effect
Potassium chloride effervescent tablets for solution	More expensive than elixir, convenient
Wax-matrix extended-release tablets	Easier to swallow; more GI erosions as compared to other therapies

The vehicle in which IV potassium is administered is important. Whenever possible, potassium should be prepared in saline-containing solutions (eg, 0.9%-0.45% sodium chloride [NaCl]). Dextrose-containing solutions stimulate insulin secretion, which can cause intracellular shifting of potassium, worsening the patient's hypokalemia, and should be avoided whenever possible. Generally, 10 to 20 mEq (mmol) of potassium is diluted in 100 mL 0.9% NaCl for IV administration. These concentrations are safe when administered through a peripheral vein over an hour. When infusion rates exceed 10 mEq/hr (mmol/hr), ECG monitoring should be performed to detect cardiac changes. The serum potassium concentration should be evaluated following the infusion of each 30 to 40 mEq (mmol) to guide further potassium replacement administration. Multiple doses of potassium can be repeated as needed until the serum potassium concentration normalizes. To allow adequate time for the potassium to equilibrate between the intra- and extracellular spaces, one should wait at least 30 minutes from the end of each infusion and care should be taken to avoid sampling from the same line in which the potassium was infused, as this can result in a spuriously elevated potassium concentration.

In cases of severe potassium depletion, patients can require as much as 300 to 400 mEq/day (mmol/day). In this instance, it is common practice to dilute 40 to 60 mEq (mmol) in 1,000 mL 0.45% NaCl and infuse at a rate not exceeding 40 mEq/hr (mmol/hr). The total 24-hour dose should not exceed 400 mEq (mmol). This should be performed in an intensive care unit under continuous ECG monitoring. Because of the high potassium concentration, and the risk for burning pain and peripheral venous sclerosis, the infusion should be through a

central venous catheter into a large vein (eg, superior vena cava) but care must be taken not to place the tip of the catheter into the right atrium.[18] Directly delivering high potassium concentrations into the heart can result in cardiac arrhythmias. Given the volume required to infuse this dose of potassium, this infusion strategy might be impractical in certain clinical situations (eg, patients requiring fluid restriction). A reasonable approach is to split the potassium dose between the oral and IV routes. For example, if a symptomatic patient requires 120 mEq (mmol) of potassium, the clinician can give 60 mEq (mmol) as the immediate-release potassium liquid, and the other 60 mEq (mmol) can be given through the IV route (20 mEq/100 mL/hr [mmol/100 mL/hr] in three doses). When giving large potassium doses, serum monitoring should be performed following the administration of half the dose to guide the need for additional potassium. This can also help avoid the development of hyperkalemia.

In the rare circumstances when cardiac arrest from hypo-kalemia is imminent, IV bolus dosing of potassium 10 mEq (mmol) over 5 minutes can be initiated and repeated once, if necessary.[18]

Alternative Therapies

Potassium-sparing diuretics are a viable alternative to chronic exogenous potassium supplementation, especially when patients are concomitantly receiving drugs that are known to deplete potassium (eg, diuretics). Spironolactone inhibits the effect of aldosterone in the renal distal convoluted tubule, thereby decreasing potassium elimination in the urine. Spironolactone is especially effective as a potassium-sparing agent in patients with primary or secondary hyperaldosteronism. Amiloride and triamterene are reasonable second-line agents that act by blocking tubular epithelial sodium channels, leading to decreased renal potassium excretion.

Spironolactone is available as 25-, 50-, and 100-mg tablets. The usual starting dose is 25 to 50 mg daily, and can be titrated to a maximum dose of 400 mg/day. The potassium-retaining effects generally take 48 hours to be evident. Principle adverse effects include hyperkalemia, gynecomastia, breast tenderness, and impotence in men. Triamterene is available as 50- and 100-mg capsules. The usual starting dose is 50 mg twice daily, which can be titrated to 100 mg twice daily. Triamterene is also available as a combination product with hydrochlorothiazide (37.5/25 mg, 50/25 mg, or 75/50 mg) and is commonly used for the treatment of hypertension. Common side effects include hyperkalemia, sodium depletion, and metabolic acidosis. The usual starting dose of amiloride is 5 mg daily; however, 10 mg can be given in those with severe hypokalemia. This

is also available as a combination product with hydrochlorothiazide 50 mg. The most common side effects are hyperkalemia and metabolic acidosis.

Concomitant use of potassium supplementation with potassium-sparing diuretics is generally not necessary and when used there is a significant risk of hyperkalemia, especially in patients with CKD or diabetes mellitus.

Evaluation of Therapeutic Outcomes

Serum potassium concentrations should be monitored regularly while the patient is receiving potassium supplementation. For ambulatory patients receiving prophylactic potassium supplementation during diuretic therapy, the serum potassium and magnesium concentrations, as well as kidney function should be monitored every 1 to 2 months. In hospitalized patients receiving oral therapy for mild hypokalemia, the potassium concentration should be monitored every 2 to 3 days. If it does not increase by at least 1 mEq/L (mmol/L) within 96 hours, the clinician should suspect concomitant magnesium depletion. Patients receiving IV potassium supplementation require close ECG monitoring if the infusion rate is greater than 20 mEq/hr (mmol/hr): doses greater than this should be administered only in the presence of continuous ECG monitoring. Additionally, the patient should have potassium concentrations obtained halfway through, and 30 minutes following completion of the total potassium dose to guide further potassium administration. Finally, the patient should be assessed for adverse effects such as pain at the infusion site or phlebitis.

Clinical Bottom Line

Hypokalemia is a frequent medical condition caused by both biological processes and drug therapy. While mild hypokalemia is frequently asymptomatic, severe hypokalemia can cause fatal cardiac dysrhythmias, particularly in patients with underlying cardiac disease. Patients receiving drugs that cause potassium wasting (eg, thiazide or loop diuretics) should be closely followed for the development of hypokalemia and appropriate potassium supplementation should be started when necessary. Generally, oral potassium is sufficient for the management of mild hypokalemia; IV potassium should be reserved for severe deficiency, and its use should be monitored closely.

HYPERKALEMIA

Hyperkalemia, defined as a serum potassium concentration greater than 5 mEq/L (mmol/L), can be further classified according to its severity: mild hyperkalemia (5.1-5.9 mEq/L [mmol/L]), moderate hyperkalemia (6-7 mEq/L [mmol/L]), and severe hyperkalemia (above 7 mEq/L [mmol/L]).[17]

Epidemiology

5 Hyperkalemia is much less common than hypokalemia. In fact, if all patients with AKI and CKD were excluded, the prevalence of hyperkalemia would be less than 1% in the rest of the population. The incidence of hyperkalemia in hospitalized patients is highly variable, and reports have ranged from 1% to 10%.[19] Most cases of hyperkalemia are the result of overcorrection of hypokalemia with IV potassium supplements. Severe hyperkalemia occurs more commonly in elderly patients with impaired kidney function who have been receiving chronic oral potassium supplementation.

CLINICAL PRESENTATION

Hyperkalemia

General

- Related to the effects of excessive potassium on neuromuscular, cardiac, and smooth muscle cell function.

Symptoms

- Frequently asymptomatic.
- The patient might complain of heart palpitations or skipped heartbeats.

Signs

- ECG changes (Fig. 68-1)

Laboratory Tests

- Serum potassium concentration above 5.0 mEq/L (mmol/L) is diagnostic.

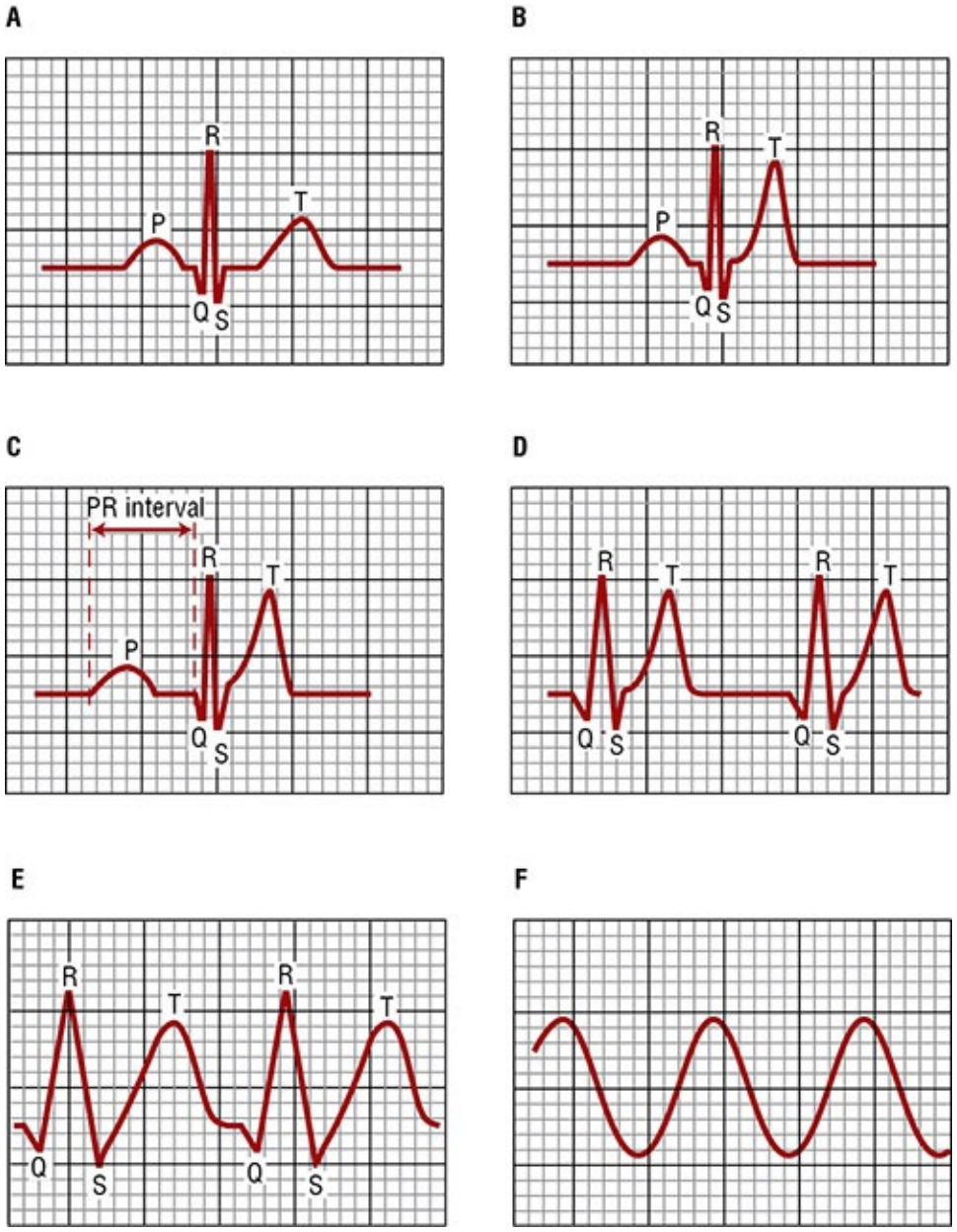


FIGURE 68-1 The earliest electrocardiographic manifestation of hyperkalemia is an increase in the rate of ventricular repolarization, which results in a peaking of the T wave at serum potassium concentrations of ~5.5 to 6 mEq/L (mmol/L) (*B*), relative to the normal ECG presentation (*A*). Further increases in the serum potassium concentration above 6 mEq/L (mmol/L) result in conduction delays through the His-Purkinje system, the atrial myocardium, and the ventricular myocardium. The ECG manifestations of these conduction delays and the sequence in which they occur are a widening of the PR interval (*C*), delay through the His-Purkinje system, a loss of the P wave (*D*), delay through the atrial myocardium, a widening of the QRS complex (*E*), and delay through the ventricular myocardium. Finally, there is a merging of the QRS complex with

the T wave (*F*), which results in a sine-wave appearance.

Etiology and Pathophysiology

Hyperkalemia develops when potassium intake exceeds excretion (true hyperkalemia) (ie, elevated total-body stores), or when the transcellular distribution of potassium is disturbed (ie, normal total-body stores). The four primary causes of hyperkalemia—(1) increased potassium intake, (2) decreased potassium excretion, (3) tubular unresponsiveness to aldosterone, and (4) redistribution of potassium into the extracellular space—are discussed further.

Hyperkalemia Associated with Increased Potassium Intake

Hyperkalemia in this setting is almost always associated with impaired kidney function. Patients with stage 4 or 5 CKD and dialysis patients who are noncompliant with dietary potassium restrictions often present with life-threatening hyperkalemia. Many of these patients do not realize that fresh fruits and vegetables contain large amounts of potassium. Another common dietary source associated with the development of hyperkalemia is potassium chloride salt substitutes. Many dialysis patients are instructed to use salt substitutes to avoid excessive sodium intake in an attempt to control volume overload. These patients unwittingly become hyperkalemic because these products contain approximately 10 to 15 mEq (mmol) potassium per gram, or 200 mEq (mmol) per tablespoon. Finally, some over-the-counter herbal and alternative medicine products may contain significant amounts of potassium. It is thus essential for patients with CKD to receive education regarding dietary sources of potassium as well as information on the potassium content of herbal products when available.

Hyperkalemia Associated with Decreased Renal Potassium Excretion

Normally functioning kidneys excrete 90% of the daily potassium intake. Therefore, when the kidney is unable to excrete potassium appropriately, as in AKI and stage 4 to 5 CKD, potassium is retained and often results in hyperkalemia. Finally, because aldosterone is responsible for potassium excretion via the renal cortical collecting duct, medications and diseases that inhibit this process contribute to hyperkalemia.[20]

Severe hyperkalemia is more common in AKI than in CKD because patients are often hypercatabolic and have underlying disorders, such as rhabdomyolysis or tumor lysis syndrome, which result in release of potassium from injured or lysed cells.[21] Severe hyperkalemia is rare in stable stage 1 to 4 CKD patients, perhaps because of enhanced GI and renal potassium excretion.[22] Additionally, hyperkalemia directly stimulates renal potassium excretion through an effect that is independent of, and additive to, that of aldosterone.[23] Renal excretion of potassium is also inhibited by various endocrine disorders, including adrenal insufficiency, Addison disease, and selective hypoaldosteronism. All of these disorders involve a decreased production of aldosterone, which results in the retention of potassium.

Several drugs have profound effects on the kidney's ability to regulate potassium—five drug classes, in particular: angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-II receptor blockers (ARBs), direct renin inhibitors, potassium-sparing diuretics, and prostaglandin inhibitors such as nonsteroidal anti-inflammatory drugs (NSAIDs). Although hyperkalemia is typically dose-dependent, the rates of hyperkalemia have been reported to range from 2% to 10%.[24–26] Other commonly used drugs that can cause hyperkalemia are β-blockers, digoxin, cyclosporine, tacrolimus, trimethoprim–sulfamethoxazole, and heparin.

Tubular Unresponsiveness to Aldosterone

Sickle cell anemia, systemic lupus erythematosus, and amyloidosis can produce a defect in renal tubular potassium secretion, possibly as the result of an alteration in the aldosterone-binding site.

Redistribution of Potassium into the Extracellular Space

The efflux of potassium from within the cell into the extracellular space, which is associated with no change in total-body potassium stores, is often observed in the presence of metabolic acidosis, diabetes mellitus, CKD, or lactic acidosis. β-Blockers can also result in a transcellular potassium shift.

The serum potassium concentration can also be falsely elevated in some conditions and not reflect the actual in vivo potassium concentration, that is, pseudohyperkalemia. Pseudohyperkalemia occurs most commonly in the setting of extravascular hemolysis of red blood cells. When a blood specimen is not processed promptly and cellular destruction occurs, intracellular potassium is

released into the serum. It can also occur in conditions of thrombocytosis or leukocytosis. If severe hyperkalemia is found in a patient who is asymptomatic with an otherwise normal laboratory report, the hyperkalemia is most likely pseudohyperkalemia, and a repeat blood sample should be collected. Truly elevated potassium concentrations are normally associated with other laboratory abnormalities, such as low carbon dioxide (acidosis) or elevated blood urea nitrogen and creatinine concentrations (indicating impaired kidney function).

TREATMENT

Desired Outcomes

The goals of therapy for the treatment of hyperkalemia are to antagonize adverse cardiac effects, reverse signs and symptoms that are present, and return the serum and total-body stores of potassium to normal. The optimal treatment approach is dependent on the severity of hyperkalemia, the rapidity of its development, and the patient's clinical condition. Cardiac instability and arrhythmias, which can be life-threatening, may be present especially when serum potassium is above 6 mEq/L (mmol/L). Although ECG changes are directly proportional to the plasma potassium concentration and its rate of increase, they may not be present in all patients. Asymptomatic patients with mild hyperkalemia usually require no specific therapy other than dietary education to control intake, and monitoring of serum potassium daily if an inpatient or weekly if an outpatient to assure resolution.

Severe hyperkalemia (above 7 mEq/L [mmol/L]) or moderate hyperkalemia (6-6.9 mEq/L [mmol/L]), when associated with clinical symptoms or ECG changes, requires immediate treatment. Initial treatment should be focused on antagonism of the cardiac membrane actions of hyperkalemia (eg, administration of calcium). Secondarily, one should attempt to decrease extracellular potassium concentration by promoting its intracellular movement (eg, with insulin, β_2-receptor agonists, or sodium bicarbonate) or enhance its removal from the body by hemodialysis: the oral administration of cation-exchange resins, and/or the use of loop diuretics may also be considered in some patients. In any case, the underlying cause of hyperkalemia should be identified and reversed, and exogenous potassium must be withheld.

General Approach to Treatment

A treatment approach for patients with hyperkalemia is outlined in **Fig. 68-2**. In patients who have acute ECG changes, IV calcium should be administered to raise the threshold potential and stabilize the myocardium.[27] At the same time, the serum potassium concentration should be rapidly decreased to below 5 mEq/L (mmol/L) within minutes by administering drugs that cause an intracellular shift of potassium, followed by the initiation of those that increase the elimination of potassium from the body.[27] If the patient is asymptomatic, rapid correction may not be necessary and will likely depend on the clinical context associated with the rise in serum potassium concentration. If one anticipates the need to reduce total-body potassium stores, an ion exchange resin that results in removal of potassium from the body over several hours to days may be initiated shortly after the emergent care has been instituted.

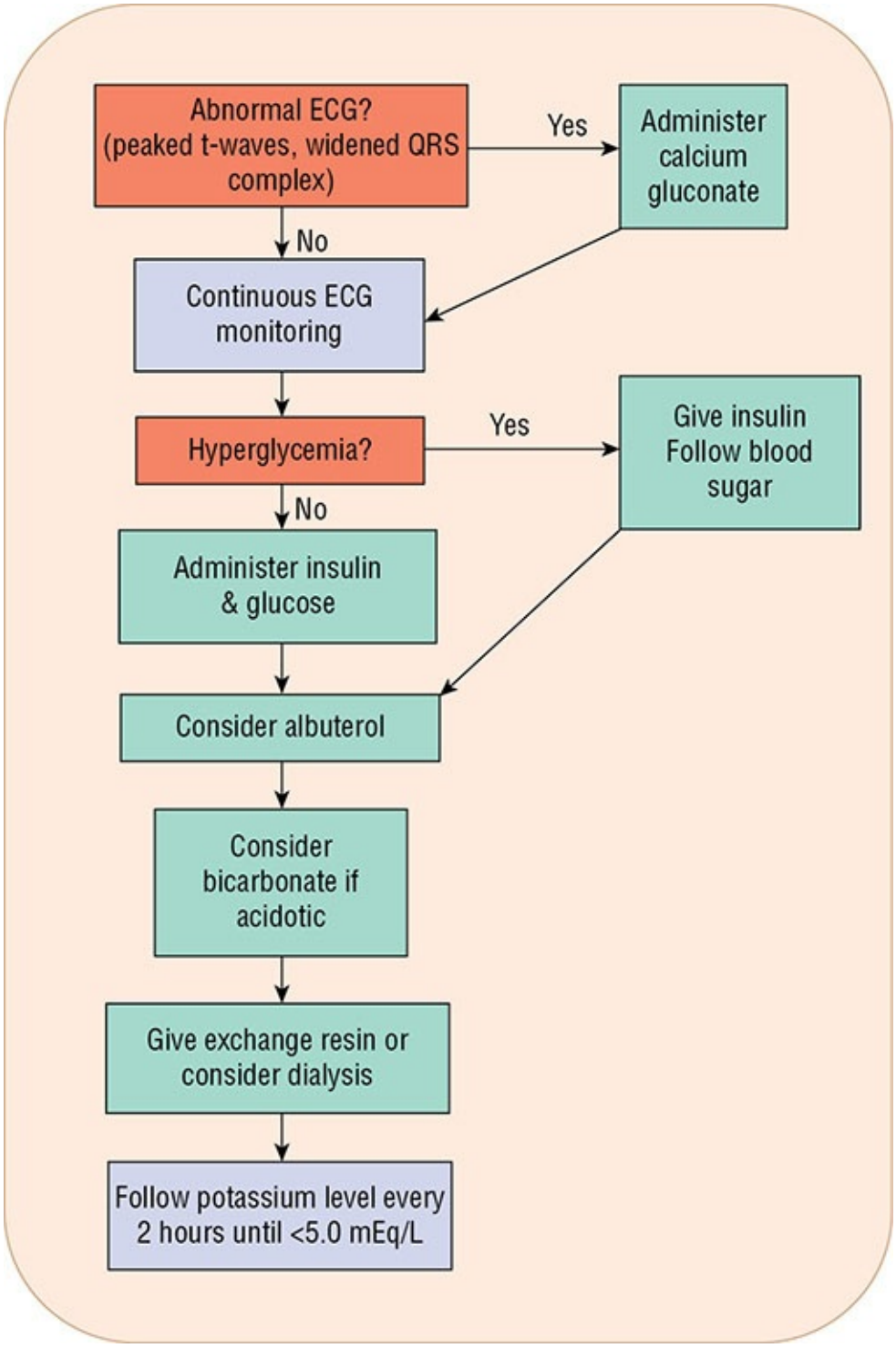


FIGURE 68-2 Treatment approach for hyperkalemia. (Serum potassium of 5.0 mEq/L is equivalent to 5.0 mmol/L.)

Nonpharmacologic Therapy

Hemodialysis patients who ingest foods supplemented with glycyrrhetinic acid, the active ingredient in licorice, may be better able to maintain plasma potassium concentrations within the normal range.[28,29] Glycyrrhetinic acid inhibits the enzyme 11β-hydroxy-steroid dehydrogenase II, thereby increasing cortisol availability in the colon. The net result is enhanced potassium elimination in the feces. Other nonpharmacologic therapies, specifically available for dialysis-dependent patients, are the tailoring of their intermittent dialysis or hemofiltration therapy to include a low potassium dialysate to enhance the removal of potassium (see Chapter 62). Emergency dialysis can be considered in patients with acute kidney injury who have persistent ECG changes or insufficient response to therapies that cause intracellular potassium shifts, although the optimal time to initiate dialysis is not known.[30]

Pharmacologic Therapy

There are several drug therapy options to lower the serum potassium concentration. The optimal regimen for a given patient is dependent on the rapidity and degree of lowering that is necessary. **Table 68-5** provides an overview of the available therapies and their respective onset and duration of action.

TABLE 68-5 Therapeutic Alternatives for the Management of Hyperkalemia

Medication	Dose	Route of Administration	Onset/Duration of Action	Acuity	Mechanism of Action	Expected Result
Calcium	1 g	IV over 5-10 minutes	1-2 minutes/10-30 minutes	Acute	Raises cardiac threshold potential	Reverses electrocardiographic effects
Furosemide	20-40 mg	IV	5-15 minutes/4-6 hours	Acute	Inhibits renal Na^+ reabsorption	Increased urinary K^+ loss
Regular insulin	5-10 units	IV or SC	30 minutes/2-6 hours	Acute	Stimulates intracellular K^+ uptake	Intracellular K^+ redistribution
Dextrose 10%	1,000 mL (100 g)	IV over 1-2 hours	30 minutes/2-6 hours	Acute	Stimulates insulin release	Intracellular K^+ redistribution
Dextrose 50%	50 mL (25 g)	IV over 5 minutes	30 minutes/2-6 hours	Acute	Stimulates insulin release	Intracellular K^+ redistribution
Sodium bicarbonate	50-100 mEq (50-100 mmol)	IV over 2-5 minutes	30 minutes/2-6 hours	Acute	Raises serum pH	Intracellular K^+ redistribution
Albuterol	10-20 mg	Nebulized over 10 minutes	30 minutes/1-2 hours	Acute	Stimulates intracellular K^+ uptake	Intracellular K^+ redistribution
Hemodialysis	4 hours	N/A	Immediate/variable	Acute	Removal from serum	Increased K^+ elimination
Sodium polystyrene sulfonate	15-60 g	Oral or rectal	1 hour/variable	Nonacute	Resin exchanges Na^+ for K^+	Increased K^+ elimination
Patiromer	8.4-25.2 g	Oral	Hours/variable	Nonacute	Resin exchanges Ca^{++} for K^+	Increased K^+ elimination
Sodium zirconium cyclosilicate	5-15 g	Oral	1 hour/variable	Nonacute	Resin exchanges Na^+ for K^+	Increased K^+ elimination

While specific treatment recommendations vary, it is generally accepted that asymptomatic patients with potassium concentrations below 6 mEq/L (mmol/L) can be treated conservatively. In patients with normal kidney function, or those with stage 3 or 4 CKD, this typically involves the administration of furosemide to promote urinary potassium excretion. When given IV at a dosage of 40 to 80 mg, urine flow usually increases within minutes and persists for approximately 4 to 6 hours. Oral furosemide can also be used, keeping in mind the IV:PO dose ratio (1:2) and delayed onset of action compared to IV. Close monitoring of the patient's volume status and other electrolyte concentrations is required while the patient is receiving furosemide. Of note, the effectiveness of diuretics in treating

hyperkalemia has not been studied in a randomized, controlled fashion.

In symptomatic patients, or in those with severe hyperkalemia, emergency care is indicated. Initial therapy in this setting is the administration of IV calcium chloride or gluconate 1 g to treat or prevent life-threatening arrhythmias.[27] Calcium antagonizes the cardiac membrane effect of hyperkalemia by reducing the electrical threshold potential for cardiac myocytes and reverses ECG changes within minutes. IV calcium should not be given to patients receiving digoxin as it can lead to digoxin toxicity. Its duration of action is 30 to 60 minutes, and it can be repeated as needed based on ECG findings. IV calcium can be given as either the chloride or gluconate salt; each is available as a 10% solution by weight. Calcium chloride provides approximately three times more calcium than equal volumes of the gluconate salt; however, it can cause tissue necrosis if extravasation occurs. For this reason, calcium gluconate is more commonly administered, with the standard dose being 10-mL IV bolus over 5 to 10 minutes.

Rapid correction of hyperkalemia may necessitate the administration of drugs that result in an intracellular shift of potassium, such as insulin and dextrose, sodium bicarbonate, and a β_2-adrenergic receptor agonist (eg, albuterol). The treatment of choice depends on the underlying medical disorders accompanying hyperkalemia. For example, in patients with concomitant metabolic acidosis, a sodium bicarbonate bolus or infusion of 50 to 100 mEq (mmol) is the preferred therapy. Sodium bicarbonate helps correct the metabolic acidosis by raising the extracellular pH, in addition to causing a rapid intracellular potassium shift. It should be noted that sodium bicarbonate is much less effective when hyperkalemia is not related to metabolic acidosis.[1] Sodium bicarbonate is also less effective in patients with end-stage renal disease (ESRD), in whom a decrease in serum potassium may not be seen for as long as 4 hours. Use caution in patients sensitive to volume changes as sodium bicarbonate can also lead to hypernatremia and volume overload. Administration of a rapid-acting (eg, insulin lispro 10 units IV) or regular insulin (10 units IV) and dextrose (10% or 50%) is an effective method of reducing potassium. Insulin increases the activity of the Na^+-K^+-ATPase pump, thereby intracellularly shifting potassium. Glucose should be given with insulin because hypoglycemia can develop as a result of the effects of the insulin therapy.[31] Insulin therapy results in a 0.6 to 1 mEq/L (mmol/L) reduction in potassium that is sustained for up to two hours.[32] β_2-Adrenergic agonists have a dual mechanism for lowering serum potassium. First, they stimulate the Na^+-K^+-ATPase pump to promote intracellular potassium uptake. Second, they stimulate pancreatic β-receptors to increase insulin secretion. Albuterol can be administered via IV (0.5 mg given over 15 minutes)

or via nebulizer (10-20 mg nebulized over 10 minutes). It should be noted that injectable albuterol is not available in the United States.

In ESRD patients, decreases in plasma potassium concentration of 0.6 mEq/L (mmol/L) and 1 mEq/L (mmol/L) can be anticipated after inhalation of 10 and 20 mg of albuterol, respectively. Notice that the doses of inhaled albuterol used for hyperkalemia are at least four times higher than those typically used for bronchospasm, so adverse effects are of greater concern. Studies commonly reported tachycardia, tremors, palpitations, mild anxiety, and increase in blood glucose as adverse effects.[32] Furthermore, as many as 40% of patients may be resistant to the hypokalemic effects of albuterol and patients already receiving a nonselective β_2-receptor antagonist may not respond. Inconsistent bioavailability via the inhaled route must also be considered, as it could lead to potential over- or underdosing and an unpredictable response.

While not a fast-acting treatment based on pharmacokinetics, one ion exchange resin, sodium polystyrene sulfonate (SPS), is regularly used in hospitalized patients with acute hyperkalemia. It was approved by the US Food and Drug Administration (FDA) in 1958, and it has been argued that the clinical trials that supported its approval are not up to the current standards of proving a medication's safety and efficacy. SPS (Kayexalate®) is a cation-exchange resin that can be administered orally or rectally by enema. SPS is available in powder form or prepackaged as a 33% sorbitol suspension. The usual oral SPS dose is 15 to 60 g in the 33% sorbitol suspension. The oral route is more effective than the enema and is better tolerated by patients. As the resin passes through the intestines, each gram of SPS exchanges 1 mEq (mmol) of sodium for 1 mEq (mmol) of potassium, which is in a relatively higher concentration in the large intestine. The onset of action of SPS is within 1 hour, and it can be repeated every 4 hours as needed. The medication should be separated from other oral medications by at least 3 hours as it has been shown to bind to and decrease the effectiveness of many oral medications.[33] The sorbitol component of the suspension promotes the excretion of the cationically modified potassium exchange resin by inducing diarrhea. SPS contains a significant amount of sodium (100 mg (4.1 mEq)/g of SPS) and package labeling advices against its use in patients who cannot tolerate even small increases in sodium loads.[34]

There have been several reports of colonic necrosis with the use of SPS.[35,36] In 2009, the FDA mandated a boxed warning for SPS due to reports of colonic necrosis and other serious GI toxicities.[37] The GI toxicities were believed to be associated with the 70% sorbitol; however, there are also reports of GI toxicity when the 33% sorbitol solution was administered. Reports revealed that the

toxicity occurred most commonly in patients who had recently undergone GI surgery or had a current or history of bowel dysfunction. Based on these findings, the 33% sorbitol product is preferred over the 70% sorbitol product, rectal administration should be avoided, and use is contraindicated in patients with bowel dysfunction.

A Cochrane Review evaluated the emergency treatment of hyperkalemia.[38] Many of the reviewed studies were small, and not all intervention groups had sufficient data for meta-analysis to be performed. Most of the data were from nonrandomized, noncontrolled observational studies and case reports. However, given these limitations, inhaled and nebulized β-agonists, and IV insulin and glucose were all deemed effective. The combination of nebulized β-agonists with IV insulin and glucose appeared to be more effective than either agent alone. The meta-analysis results were equivocal for IV bicarbonate, and, notably, SPS was not effective by 4 hours. Given the limitations of this Cochrane Review, clinicians should exercise caution when extrapolating these findings to clinical practice. Nonetheless, the Cochrane database review corroborates the approach detailed in Fig. 68-2. Frequently, management of hyperkalemia will be based on the clinician's personal judgment or institutional protocols. For example, the large majority (95%) of patients being treated for hyperkalemia in academic teaching hospitals receives SPS, with far fewer receiving insulin and IV calcium, and less than 10% of patient receive bicarbonate, albuterol, or hemodialysis.[39]

In nonhospitalized patients who have experienced chronic increases in serum potassium concentration, long-term management of hyperkalemia is focused on dietary restriction of potassium-rich foods and supplements, reducing and avoiding medications that impair renal potassium excretion, and using diuretics or other medications to counteract the effects of medications that increase serum potassium concentrations. Medications used for chronic conditions that are known to cause hyperkalemia include NSAIDs, ACEIs, ARBs, direct renin inhibitors, and aldosterone antagonists. These typically result in asymptomatic hyperkalemia without the need for emergent therapies. To prevent hyperkalemia, clinicians may attempt to lower the dose or switch to another medication without hyperkalemia as a side effect (eg, calcium channel blocker). However, medications that inhibit the renin–angiotensin–aldosterone system (RAAS) have significant beneficial effects on morbidity and mortality in patients with chronic diseases such as diabetes mellitus, congestive heart failure, and CKD. Therefore, reducing or avoiding the use of these medications to prevent hyperkalemia is not often appropriate. The use of a combination of ACEI and ARB is generally avoided due to the increased risk of hyperkalemia.[40] Aldosterone antagonists

have a different mechanism of action and their use in combination with an ACEI or ARB is considered acceptable. The extent of hyperkalemia is greater with a combination ACEI and aldosterone antagonist than a combination ACEI and ARB in patients with diabetic nephropathy, suggesting an extrarenal mechanism of this adverse effect in aldosterone antagonists.[41]

To allow for continued use of RAAS inhibitors, especially in patients prone to hyperkalemia, ion exchange resins may be used. Until recently, SPS was the only option for outpatient providers. A daily dose of SPS in patients with CKD receiving RAAS inhibitors effectively lowers and maintains serum potassium in the normal range.[42,43] Two new cation exchange agents, patiromer and sodium zirconium cyclosilicate, are now available as alternatives to SPS in patients with hyperkalemia. Patiromer (Veltassa™) is a nonabsorbable polymer that exchanges calcium for potassium in the distal colon to increase fecal elimination of potassium. The drug effectively achieves and maintains normokalemia in adults with stage 3 or 4 CKD on stable doses of RAAS inhibitors.[44,45] The most common adverse effects of patiromer include constipation, hypomagnesemia, and diarrhea. The usual dose of patiromer is 8.4 to 25.2 g once daily. Patiromer contains sorbitol to increase drug stability, but at amounts 5- to 10-fold lower than SPS in sorbitol.[22] The package labeling cautions that it should not be used to treat life-threatening hyperkalemia due to its delayed onset of action.[46] Additionally, patiromer can bind to many oral medications, which could lead to decreased absorption of other medications and loss of efficacy. Therefore, it is recommended to administer other oral medications at least 3 hours before or after patiromer.[46]

Sodium zirconium cyclosilicate (ZS-9, Lokelma™) is a nonabsorbable inorganic compound that selectively exchanges sodium for potassium throughout the entire intestinal tract. The drug effectively decreases serum potassium concentrations as soon as one hour after administration of the first dose and for up to 48 hours after administration, with an average decrease of approximately 1 mEq/L (mmol/L) for the 10 g dose.[47,48] ZS-9 exhibits an acute onset of action and has the same label warning as patiromer, that it should not be used to treat life-threatening hyperkalemia. The most common adverse effect of ZS-9 is edema, likely from the exchange of sodium for potassium. The starting dose is 10 g three times daily for 48 hours followed by 5 to 15 g once daily. Like SPS and patiromer, ZS-9 must be separated from other oral medications but the separation time is shorter at 2 hours. This separation is especially important for medications that exhibit pH-dependent solubility.

Evaluation of Therapeutic Outcomes

The frequency and rigor with which one evaluates patients to ascertain if they have achieved the desired therapeutic outcomes depends on the severity and acuity of hyperkalemia. For example, cautious waiting is more common for those with mild or moderate asymptomatic hyperkalemia compared to those with acute symptomatic, severe hyperkalemia. Many drugs such as ACEIs, ARBs, direct renin inhibitors, and spironolactone result in asymptomatic hyperkalemia and changes in dosage or to a different agent may be all that is warranted. In patients with normal kidney function, once these drugs are initiated and the dose titrated, clinicians should check the potassium concentration at least monthly. For those patients with impaired kidney function, monitoring should be biweekly until the dose is stabilized.

In patients who have acute symptomatic hyperkalemia (eg, ECG changes), frequent potassium concentration and ECG monitoring is warranted. The patient should receive continuous ECG telemetry monitoring until the serum potassium concentration decreases below 5 mEq/L (mmol/L), and the ECG abnormalities resolve. Similarly, while the patient is receiving emergent therapy, serial serum potassium concentrations should be obtained hourly until the potassium concentration decreases below 5 mEq/L (mmol/L). For patients who receive insulin and dextrose therapy for hyperkalemia, blood glucose monitoring should be performed hourly or more frequently if patients demonstrate signs and symptoms of hypoglycemia. For patients who receive large doses of sodium bicarbonate therapy for hyperkalemia, an arterial blood gas or serum chemistry profile should be obtained to assess their acid–base status. Furthermore, the patient should be evaluated for signs of fluid overload secondary to the high-sodium load. Patients receiving albuterol therapy should be questioned regularly regarding the development of palpitations and tachycardia. The patient's medication records should be reviewed to assure the patient is not receiving drug therapy that increases the serum potassium concentration. Furthermore, the patient should be questioned regarding the occurrence of diarrheal stool output.

Clinical Bottom Line

Hyperkalemia commonly occurs in patients with reduced kidney function or other metabolic disturbances. It can rapidly evolve into a medical emergency; therefore, prompt identification and appropriate pharmacotherapy is needed. In patients with mild hyperkalemia, potassium binding resins or loop diuretics may be useful, and should be used as first-line therapy. In severe hyperkalemia with

ECG changes, IV calcium should be given to protect against cardiac dysrhythmias. Additionally, rapid-acting therapies such as IV insulin and β_2-adrenergic agonists are indicated to move potassium intracellularly.

DISORDERS OF MAGNESIUM HOMEOSTASIS

Magnesium plays a central role in cellular function and is an important cofactor in more than 300 biochemical reactions in the body, especially those systems that are dependent on adenosine triphosphate. Mitochondrial function, protein synthesis, cell membrane function, parathyroid hormone secretion, and glucose metabolism are just a few important functions affected by magnesium.[49] It is the fourth most abundant extracellular cation and the second most abundant intracellular cation, after potassium. Disorders of magnesium homeostasis are commonly encountered in clinical situations and most frequently are manifested as alterations in cardiovascular and neuromuscular function. Life-threatening conditions such as paralysis and cardiac arrhythmias can occur, making the proper recognition and treatment of these problems of paramount importance. Altered magnesium balance also plays a key role in chronic disease states such as diabetes mellitus, CKD, osteoporosis, development of kidney stones, as well as heart and vascular disease.[50]

Magnesium is principally distributed in bone (67%) and muscle (20%). Because of its predominantly intracellular distribution, measurement of magnesium in the extracellular compartment may not accurately reflect the total-body magnesium content. The majority of magnesium in the extracellular fluid is in the ionized form as only 30% is bound to serum proteins. The normal range for serum magnesium is 1.4 to 1.8 mEq/L (1.7-2.3 mg/dL; 0.70-0.95 mmol/L).

The recommended dietary magnesium intake for adults is approximately 420 mg/day and 320 mg/day for men and women, respectively. The maintenance of magnesium homeostasis depends on the balance between intake and output. Ingested magnesium (30%-40%) is absorbed in the small bowel. The absorption of magnesium decreases as the dietary intake increases. Reductions in absorption have also been noted in the elderly and those with CKD. A small amount is present in intestinal secretions and reabsorbed in the sigmoid colon. The kidneys play a major role in maintaining magnesium balance. Approximately 95% of the filtered magnesium is reabsorbed; thus, in most patients less than 5% is excreted in the urine.[41] Renal magnesium handling is unique, in that approximately 20% of the filtered magnesium is reabsorbed in the proximal tubule; the majority (up to 70%) of reabsorption occurs in the thick ascending limb of the loop of Henle.

This explains why loop diuretics often cause profound urinary magnesium wasting. The remaining 10% is reabsorbed in the distal convoluted tubule.[51] Unlike most other important electrolytes, there is no hormonal regulation of the distribution of magnesium between bone and circulating or intracellular magnesium pools. Because of this, both hypomagnesemia and hypermagnesemia commonly occur.

HYPOMAGNESEMIA

Epidemiology

Hypomagnesemia is a common problem in both ambulatory and hospitalized patients. Although the exact prevalence is difficult to estimate, it has been reported that up to 65% of intensive care unit patients are magnesium-deficient. Although serum magnesium concentrations are not a reliable index of total-body magnesium content, they remain the primary diagnostic tool to evaluate body stores.

Hypomagnesemia is associated with an increase in mortality in critically ill patients. There are limited data regarding the incidence and associated risks of hypomagnesemia in hospitalized general medicine patients, even though they are at an increased risk of hypomagnesemia, given the presence of comorbidities such as congestive heart failure, CKD, and diabetes mellitus. Hypomagnesemia may be observed in as many as 20% of hospitalized general medicine patients and is associated with increased mortality.[52]

Etiology and Pathophysiology

6 Hypomagnesemia is usually associated with disorders of the intestinal tract or kidney.[53] Drugs or conditions that interfere with intestinal absorption or increase renal excretion of magnesium can result in hypomagnesemia (**Table 68-6**). Decreased intestinal absorption as a result of small bowel disease is the most common cause of hypomagnesemia worldwide. These disorders include regional enteritis, radiation enteritis, ulcerative colitis, acute and chronic diarrhea, pancreatic insufficiency and other malabsorptive syndromes, small-bowel bypass surgery, and chronic laxative abuse. Proton pump inhibitors, especially when used chronically, can cause hypomagnesemia through impaired intestinal absorption. Hypomagnesemia is commonly associated with alcoholism, where the etiology is multifactorial, including reduced intake, pancreatic insufficiency,

chronic vomiting and diarrhea, and urinary magnesium wasting.

TABLE 68-6 Causes of Hypomagnesemia

GI

Reduced intake
- Protein-calorie malnutrition
- Prolonged parenteral fluid administration without magnesium
- Alcoholism

Reduced absorption
- Primary hypomagnesemia
- Malabsorption syndromes (eg, tropical sprue, celiac disease, radiation enteritis, or intestinal lymphectasia)
- Short-bowel syndrome (eg, small-bowel resection or ileal bypass)
- Pancreatic insufficiency
- Proton pump inhibitors (long-term use)

Increased loss
- Excessive vomiting
- Prolonged nasogastric suction
- Excessive laxative use
- Intestinal and biliary fistulas
- Prolonged diarrhea (ulcerative colitis, Crohn's disease, or cancer of the colon)

Renal

Primary tubular disorders
- Primary renal magnesium wasting
- Bartter syndrome
- Renal tubular acidosis
- Diuretic phase of acute tubular necrosis
- Postobstructive diuresis
- Postrenal transplant diuresis

Glomerulonephritis

Pyelonephritis

Drug-induced renal losses
- Aminoglycosides
- Amphotericin B
- Cyclosporine
- Tacrolimus
- Diuretics
- Digitalis
- Cisplatin
- Pentamidine
- Foscarnet

Hormone-induced renal losses
- Primary hyperparathyroidism
- Hyperthyroidism
- Aldosteronism
- "Hungry bone syndrome" after parathyroidectomy

Internal redistribution

Diabetic ketoacidosis

Glucose, amino acid, or insulin administration

Massive blood transfusion (citrate)

Pancreatitis with lipedema (magnesium soap)

Other

Excessive sweating and lactation

Hypercalcemia and hypercalciuria

Phosphate depletion

Chronic alcoholism

Extracellular fluid volume expansion

Primary renal magnesium wasting can be caused by a defect in renal tubular magnesium reabsorption, or inhibition of sodium reabsorption in those segments in which magnesium transport follows passively. The former condition is associated with hypercalciuria, nephrolithiasis, and progressive kidney disease, while the latter is associated with Gitelman and Bartter syndromes.[53] Much more common than these is renal magnesium wasting secondary to thiazide and loop diuretics. Other commonly used drugs that can cause renal magnesium wasting include aminoglycosides, amphotericin B, cyclosporine, digoxin, tacrolimus, cisplatin, pentamidine, and foscarnet.[54]

CLINICAL PRESENTATION

TREATMENT

Desired Outcomes

The treatment goals in the management of hypomagnesemia are (a) resolution of the signs and symptoms, (b) restoration of normal magnesium concentrations, (c) correction of concomitant electrolyte abnormalities, and (d) identification and correction of the underlying cause of magnesium depletion.

General Approach to Treatment

Nearly all of the data regarding magnesium replacement therapy have been derived from relatively old data in acutely ill, hospitalized patients. Magnesium supplementation can be given by the oral, intramuscular (IM), or IV route. The severity of the magnesium depletion and the presence of severe signs and symptoms should dictate the route of administration. Because IM administration is painful, it should be reserved for those patients with severe hypomagnesemia and limited venous access. IV bolus administration is associated with flushing, sweating, and a sensation of warmth; thus, bolus administration should be avoided if possible. Additionally, because calcium forms a complex with the sulfate moiety, which is then excreted, large amounts of IV magnesium sulfate should be administered with caution to hypocalcemic patients, as it can further exacerbate calcium deficiency.[50] There have been no clinical trials assessing the

optimal regimen for magnesium replacement; however, it is widely accepted that 8 to 12 g of magnesium sulfate be administered, in divided doses, in the first 24 hours followed by 4 to 6 g/day for 3 to 5 days to adequately replete body stores in those with severe hypomagnesemia.[55] Even if severe magnesium depletion is present, approximately 50% of the administered dose is excreted in the urine. Consequently, magnesium replacement should be performed over 3 to 5 days, and continued supplementation should be provided for patients unable to eat. Table 68-7 lists the commonly used magnesium oral supplements and their respective elemental magnesium content.

TABLE 68-7 Common Magnesium Products and Their Elemental Magnesium Content

Product	Elemental Magnesium Content
Magnesium oxide	242 mg in a 400-mg tablet
Magnesium hydroxide	167 mg in a 400-mg tablet or 5-mL oral suspension
Magnesium chloride	64 mg in each 535-mg tablet
Magnesium citrate	48 mg in each 5 mL of the oral solution
Magnesium gluconate	27 mg in a 500-mg tablet
Magnesium lactate	84 mg in an 84 mg-tablet

Nonpharmacologic Therapy

There are currently no nonpharmacologic options for the management of hypomagnesemia.

Pharmacologic Therapy

It is currently controversial whether all asymptomatic patients require magnesium supplementation when serum magnesium concentration falls below the normal range. In particular, it has been suggested that for patients with type 2 diabetes mellitus, hypomagnesemia contributes to diabetic complications by affecting glucose transport and insulin secretion and utilization. Indeed, it has been shown that oral magnesium supplementation in type 2 diabetic patients with hypomagnesemia improves insulin sensitivity and metabolic control.[56] Others suggest that hypomagnesemia is more likely a consequence of diabetes mellitus. Possible mechanisms of hypomagnesemia in these patients include reduced GI absorption, enhanced renal excretion secondary to an increased

filtered magnesium load and tubular flow, and reduced tubular reabsorption. Metabolic abnormalities such as hypokalemia, hypophosphatemia, and metabolic acidosis may also contribute to its development.[57] While it seems reasonable to provide a supplement for diabetic patients with low serum magnesium concentrations, clinical trials have yet to prove that supplementation leads to improved clinical outcomes.

CLINICAL PRESENTATION

Hypomagnesemia

General

- The dominant organ systems affected by hypomagnesemia are the neuromuscular and cardiovascular systems.

Symptoms

- Neuromuscular symptoms such as tetany, twitching, and generalized convulsions are common.
- Cardiac symptoms include heart palpitations.

Signs

- Neuromuscular: Presence of Chvostek sign, Trousseau sign, tremor, and tetany.
- Cardiovascular: Cardiac arrhythmias (ventricular fibrillation, torsade de pointes, or digoxin-induced arrhythmias), sudden cardiac death, and hypertension can be present. ECG abnormalities include widened QRS complex and peaked T waves with mild hypomagnesemia; and prolonged PR interval, progressive widening of QRS complex, and flattened T waves with moderate-to-severe hypomagnesemia.

Laboratory Tests

- Serum magnesium concentration less than 1.4 mEq/L (1.7 mg/dL ; 0.70 mmol/L). Serum potassium and calcium concentrations can also be low.

Should treatment be warranted, those patients with serum magnesium concentrations greater than 1 mEq/L (1.2 mg/dL; 0.5 mmol/L]) can be treated

with oral supplements. Oral supplementation is preferred because magnesium uptake is a slow process that may require prolonged administration. Several magnesium products are available, including magnesium-containing antacids or laxatives, comprising a variety of magnesium salts in tablet or capsule formulations. Many of the oral products contain very little magnesium, which necessitates three or four doses per day. As expected, diarrhea is the most common dose-limiting side effect of oral therapy, which can greatly reduce patient compliance. Therefore, sustained-release magnesium products are preferred as they not only improve patient compliance, but also reduce the occurrence of GI side effects.

In cases of severe magnesium depletion (serum concentrations less than 1 mEq/L [1.2 mg/dL; 0.5 mmol/L]), or if signs and symptoms are present regardless of the serum concentration, IV magnesium should be administered. A dose of 4 to 6 g in 50 to 100 mL (maximum concentration 1 g/10 mL) should be administered in divided doses over 12 to 24 hours and repeated as necessary in order to maintain magnesium concentrations above 1 mEq/L (1.2 mg/dL; 0.5 mmol/L). Doses of 2 to 4 g in 50 mL infused over 1 hour are frequently used clinically; however, these result in transient benefit because of the extensive renal excretion, and usually have to be repeated daily over 3 to 5 days for adequate repletion. Therapy should be continued until the signs and symptoms have completely resolved. In patients with impaired kidney function, some have reduced the does by 25% to 50%.

Evaluation of Therapeutic Outcomes

In patients with acute, asymptomatic mild-to-moderate hypomagnesemia, serum magnesium concentrations should be obtained at least daily during their hospitalization. Patients receiving oral magnesium therapy should be questioned regarding GI tolerance and the occurrence of diarrhea. Patients being treated for symptomatic severe hypomagnesemia should have their serum magnesium concentration monitored hourly until the serum concentration reaches 1.5 mEq/L (1.8 mg/dL; 0.75 mmol/L) and the symptoms resolve. At that point, the serum magnesium concentration can be monitored every 6 to 12 hours for the next 24 hours while receiving magnesium supplementation. Once the magnesium concentration is stable in the normal range, a concentration can be obtained daily. It should be reiterated that it typically takes 3 to 5 days to fully replete total-body magnesium stores. Patients receiving oral magnesium-containing antacids or supplements should be asked regularly about the occurrence of diarrhea.

Clinical Bottom Line

Hypomagnesemia is generally associated with kidney or GI tract disorders. In cases of mild, chronic magnesium loss, oral magnesium preparations can be used; however, the dose-limiting side effect is diarrhea. For more severe cases of hypomagnesemia, IV magnesium sulfate can be safely administered. Repeated doses may be needed as IV magnesium is rapidly eliminated in urine. In such cases, close monitoring of serum magnesium concentrations is needed.

HYPERMAGNESEMIA

Epidemiology

7 Hypermagnesemia (serum magnesium greater than 1.8 mEq/L [2.3 mg/dL; 0.9 mmol/L]) is a rare occurrence that is generally seen in patients with stage 4 or 5 CKD when magnesium intake exceeds the excretory capacity of the kidneys. Elderly patients are prone to hypermagnesemia because of their reduced glomerular filtration rate (GFR) and because of their tendency to consume magnesium-containing antacids and vitamins.

Etiology and Pathophysiology

Because magnesium excretion decreases as GFR declines, serum magnesium concentrations tend to increase in patients with moderate-to-severe CKD. Indeed, magnesium concentrations steadily increase as the GFR decreases below 30 mL/min/1.73 m^2. As long as the patient maintains a normal diet, the serum magnesium concentration typically stabilizes at approximately 2.5 mEq/L (3 mg/dL; 1.25 mmol/L). If patients with stage 4 or 5 CKD are taking concomitant magnesium-containing antacids, the serum concentration can approach 6 mEq/L (7.3 mg/dL; 3 mmol/L), a value associated with signs and symptoms of toxicity. Critically ill patients with multiorgan system failure receiving enteral or parenteral nutrition are also prone to develop hypermagnesemia. Finally, the parenteral treatment of eclampsia with magnesium sulfate can lead to hypermagnesemia. **Table 68-8** lists other causes of hypermagnesemia.

TABLE 68-8 Causes of Hypermagnesemia

Decreased renal excretion
Acute kidney injury
CKD with exogenous intake
Excessive intake
Treatment of toxemia of pregnancy
Ureteral irrigants (hemiacidrin)
Cathartics
Other
Lithium therapy
Hypothyroidism
Milk-alkali syndrome
Addison disease
Viral hepatitis
Acute diabetic ketoacidosis

CKD, chronic kidney disease.

CLINICAL PRESENTATION: HYPERMAGNESEMIA

8 The signs and symptoms of hypermagnesemia reflect magnesium's action on the neuromuscular and cardiovascular systems.[55,58] The main symptoms include lethargy, confusion, dysrhythmias, and muscle weakness. Symptoms are rare when the serum concentration is below 4 mEq/L (4.9 mg/dL; 2 mmol/L) (**Fig. 68-3**).

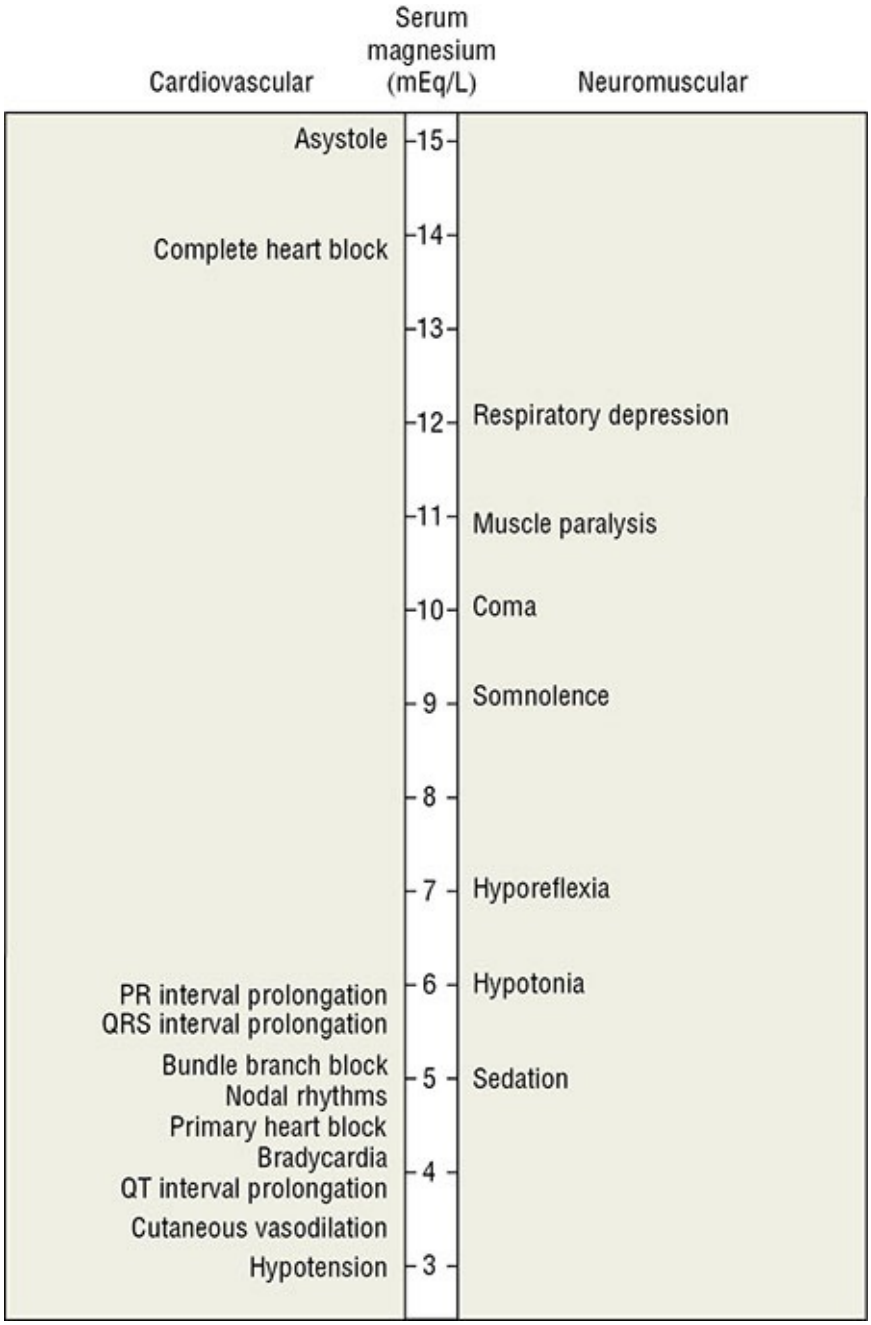


FIGURE 68-3 Clinical findings associated with hypermagnesemia. (Serum magnesium concentrations in mmol/L can be determined by multiplying the serum magnesium value expressed in mEq/L by 0.5.)

TREATMENT

Desired Outcome

The goals of therapy are to (a) reverse the neuromuscular and cardiovascular manifestations of hypermagnesemia, (b) decrease the magnesium concentration toward normal values, and (c) identify and treat the underlying cause of hypermagnesemia.

Nonpharmacologic Therapy

There are currently no nonpharmacologic options for the management of hypermagnesemia.

Pharmacologic Therapy

There are three primary means of treating hypermagnesemia: (1) reduce magnesium intake, (2) enhance elimination of magnesium, and (3) antagonize the physiologic effects of magnesium. The optimal treatment regimen for the management of hypermagnesemia depends on the severity of the patient's signs and symptoms and the degree of serum concentration elevation. IV elemental calcium doses of 100 to 200 mg directly antagonize the neuromuscular and cardiovascular effects of hypermagnesemia. Oral calcium is not effective because of its relatively poor bioavailability and slow onset of action. The clinical effect of calcium is immediate, but the effect is transient; hence, repeated IV doses of 100 to 200 mg of elemental calcium (eg, 2 g of calcium gluconate) might need to be administered hourly until the signs or symptoms abate and the magnesium concentration is normalized. Supportive care with cardiac pacing, vasopressors, and mechanical ventilation can be necessary in life-threatening situations. In patients with normal kidney function, or those with stage 1, 2, or 3 CKD, forced diuresis with 0.45% NaCl and loop diuretics can promote magnesium elimination. An initial IV bolus of furosemide 40 mg or a similar equivalent can be used. Subsequent dosing can be determined based on the patient's clinical response. Patients with CKD can require long-term loop diuretic therapy to maintain adequate fluid and electrolyte balance. In dialysis patients, their hemodialysis prescription should be changed to employ magnesium-free dialysate.

Evaluation of Therapeutic Outcomes

Patients who are receiving IV calcium salts for the treatment of severe,

symptomatic hypermagnesemia should have their serum magnesium concentration evaluated hourly until symptoms abate and the magnesium concentration decreases below 4 mg/dL (3.3 mEq/L; 1.64 mmol/L). Furthermore, the patient should be continuously monitored to detect ECG changes. In CKD patients who can produce urine, forced diuresis with saline and furosemide should reduce the serum magnesium concentration within 6 to 12 hours. Close monitoring of the urine output and physical examination for signs of volume overload are important. Emergency hemodialysis will usually correct the hypermagnesemia within 4 hours and is a reasonable option for those who are currently receiving hemodialysis. To prevent further episodes of hypermagnesemia, the patient should receive dietary education regarding foods and beverages that contain large quantities of magnesium (**Table 68-9**).

TABLE 68-9 Magnesium Content of Selected Foods

Food	Elemental Magnesium Content per Serving (mg)
Halibut, cooked, 3 oz (85g)	90
Almonds, dry roasted, 1 oz (28g)	80
Spinach, boiled, one-half cup (~125mL)	78
Cashews, dry roasted, 1 oz (28g)	74
Peanuts, oil roasted, one-fourth cup (~60 mL)	63
Shredded wheat cereal, two large biscuits	61
Soymilk, plain or vanilla, 1 cup (~250mL)	61
Black beans, cooked, one-half cup (~125mL)	60
Edamame, shelled, cooked, one-half cup (~125mL)	50
Peanuts, dry roasted, 1 oz (28g)	50
Peanut butter, smooth, 2 tablespoons (~30 mL)	49
Bread, whole wheat, 2 slices	46
Avocado, cubed, 1 cup (~250mL)	44
Potato, baked with skin, 3.5 oz (~100g)	43
Yogurt, plain, low fat, 8 oz (~225g)	42
Rice, brown, cooked, one-half cup (~125 mL)	42
Breakfast cereals, fortified with 10% of the daily value for magnesium	40
Instant oatmeal, 1 cup (~250 mL)	36
Kidney beans, canned, one-half cup (~125 mL)	35
Banana, 1 medium	32

Clinical Bottom Line

Hypermagnesemia is generally associated with advanced CKD. Severe cases of hypermagnesemia can result in neurologic symptoms or cardiac dysrhythmias. Should these symptoms occur, IV calcium can counteract these effects. Forced diuresis with saline and loop diuretics is useful in lowering magnesium in patients with mild-to-moderate kidney disease; hemodialysis should be reserved for ESRD patients.

Postclass Engaged Learning Activity

Conduct a literature search and identify a review article that has been published within the past 12 months regarding potassium binders for hyperkalemia. Compare the three available potassium binders (sodium polystyrene sulfonate, patiromer, sodium zirconium cyclosilicate) with regard to their pharmacokinetic and pharmacodynamic effects. Write a brief summary about each medication's mechanism of action, adverse effects, and one potential advantage or disadvantage of the medication compared to the other potassium binders. This activity is intended to build your literature evaluation skills and increase your ability to assess a new drug's place in therapy.

ABBREVIATIONS

ACEI	angiotensin-converting enzyme inhibitor
AKI	acute kidney injury
ARB	angiotensin-II receptor blocker
CKD	chronic kidney disease
ECG	electrocardiogram
ESRD	end-stage renal disease
FDA	Food and Drug Administration
GFR	glomerular filtration rate
GI	gastrointestinal
IM	Intramuscular
IV	Intravenous
NSAID	nonsteroidal anti-inflammatory drug
RAAS	renin–angiotensin–aldosterone system
SPS	sodium polystyrene sulfonate

REFERENCES

1. Palmer BF, Dubose TD. Disorders of potassium metabolism. In: Schrier RW, ed. Schrier RW, ed. *Renal and Electrolyte Disorders*. 8th ed. Philadelphia, PA: Wolters Kluwer; 2018:137–161.
2. Pepin J, Shields C. Advances in diagnosis and management of hypokalemic and hyperkalemic emergencies. *Emerg Med Pract*.

2012;14(2):1–20.

3. Aburto NJ, Hanson S, Gutierrez H, et al. Effect of increased potassium intake on cardiovascular risk factors and disease: Systemic review and meta-analysis. *BMJ*. 2013;346:f1378.
4. Whelton PK, He J, Appel LJ, et al. Primary prevention of hypertension: Clinical and public health advisory from the National High Blood Pressure Education Program. *JAMA*. 2002;288:1882–1888.
5. Food and Nutrition Board, Institute of Medicine. *Panel on Dietary Reference Intakes for Electrolytes and Water. Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate*. Washington, DC: National Academies Press; 2005.
6. Gumz ML, Rabinowitz L, Wingo CS. An integrated view of potassium homeostasis. *N Engl J Med*. 2015;373:60–72.
7. Palmer BF. Regulation of potassium homeostasis. *Clin J Am Soc Nephrol*. 2015;10:1050–1060.
8. U.S. Department of Agriculture and U.S. Department of Health and Human Services. *Dietary guidelines for Americans 2015-2020*. 8th ed. Washington, DC: U.S. Government Printing Office; December 2010.first pub 2015, Skyhorse edition 2017. Skyhorse publishing, Inc New York NY.
9. Malnic G, Giebisch G, Muto S, Wang W, Bailey MA, Satlin LM. Regulation of K^+ excretion. In: Alpern RJ, Moe OW, Alpern RJ, Moe OW, eds. *Seldin and Giebisch's the Kidney*. 5th ed. Amsterdam: Elsevier; 2013:1659–1715.
10. Giebisch G, Krapf R, Wagner C. Renal and extrarenal regulation of potassium. *Kidney Int*. 2007;72:397–410.
11. Aronson PS, Giebisch G. Effects of pH on potassium: New explanations for old observations. *J Am Soc Nephrol*. 2011;22:1981–1989.
12. Adrogue HJ, Madias NE. Sodium and potassium in the pathogenesis of hypertension. *N Engl J Med*. 2007;356:1966–1978.
13. Bowling CB, Pitt B, Ahmed MI, et al. Hypokalemia and outcomes in patients with chronic heart failure and chronic kidney disease. *Circ Heart Fail*. 2010;3:253–260.
14. Van Dinter TG, Fuerst FC, Richardson CT, et al. Stimulated active potassium secretion in a patient with colonic pseudo-obstruction: A new mechanism of secretory diarrhea. *Gastroenterol*. 2005;129:1268–1273.
15. Gennari FJ. Hypokalemia. *N Engl J Med*. 1998;339:451–458.

16. Huang CL, Kuo E. Mechanism of hypokalemia in magnesium deficiency. *J Am Soc Nephrol*. 2007;18:2649–2652.
17. Cohn JN, Kowey PR, Whelton PK, Prisant LM. New guidelines for potassium replacement in clinical practice: A contemporary review by the National Council on Potassium in Clinical Practice. *Arch Intern Med*. 2000;160:2429–2436.
18. 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 10.1. Life threatening emergencies. *Circulation*. 2005;112:IV-121–IV-125.
19. Nyirenda MJ, Tang JI, Padfield PL, Seckl JR. Hyperkalemia. *Br Med J*. 2009;339:b4114.
20. Schaefer TJ, Wolford RW. Disorders of potassium. *Emerg Med Clin N Am*. 2005;23:723–747.
21. Kovesdy CP. Management of hyperkalemia in chronic kidney disease. *Nat Rev Nephrol*. 2014;10:653–662.
22. Li L, Harrison SD, Cope MJ, et al. Mechanism of action and pharmacology of patiromer, a nonabsorbed cross-linked polymer that lowers serum potassium concentration in patients with hyperkalemia. *J Cardiovasc Pharmacol Ther*. 2016;21:456–465.
23. Mount DB. Disorders of potassium balance. In: Skorecki K, ed. *Brenner and Rector's The Kidney*. 10th ed. London, UK: Elsevier; 2016;559–600.
24. Packer M, Poole-Wilson PA, Armstrong PE, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. *Circulation*. 1999;100:2312–2318.
25. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall. *Lancet*. 2003;759–766.
26. Zannad F, McMurray JJV, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364:11–21.
27. Rossignol P, Legrand M, Kosiborod M, et al. Emergency management of severe hyperkalemia: Guideline for best practice and opportunities for the future. *Pharmacol Res*. 2016;113:585–591.
28. Farese S, Jruse A, Pasch A, et al. Glycyrrhetinic acid food supplementation lowers serum potassium concentration in chronic hemodialysis patients. *Kidney Int*. 2009;76:877–884.

29. Ferrari P. Licorice: A sweet alternative to prevent hyperkalemia in dialysis patients? *Kidney Int*. 2009;76:811–812.
30. Bagshaw SM, Lamontagne F, Joannidis M, Wald R. When to start renal replacement therapy in critically ill patients with acute kidney injury: comment on AKIKI and ELAIN. *Critical Care*. 2016;20:245.
31. Schafers S, Naunheim R, Vijayan A, Tobin G. Incidence of hypoglycemia following insulin-based acute stabilization of hyperkalemia treatment. *J Hosp Med*. 2012;7:239–242.
32. Elliott MJ, Ronksley PE, Clase CM, Ahmed SB, Hemmelgarn BR. Management of patients with acute hyperkalemia. *Can Med Assoc J*. 2010;182:1631–1635.
33. FDA recommends separating dosing of potassium-lowering drug sodium polystyrene sulfonate (Kayexalate) from all other oral drugs. FDA Drug Safety Communication. 2017. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm572484.htm.
34. Kayexalate® [package insert]. Bridgewater, NJ: Sanofi-aventis U.S. LLC; 2009.
35. McGowan CE, Saha S, Chu G, et al. Intestinal necrosis due to sodium polystyrene sulfonate (Kayexalate) in sorbitol. *South Med J*. 2009;102:493–497.
36. Sterns RH, Rojas M, Bernstein P, Chennupati S. Ion-exchange resin for the treatment of hyperkalemia: Are they safe and effective? *J Am Soc Nephrol*. 2010;21:733–735.
37. Kayexalate (Sodium Polystyrene Sulfonate) Powder Boxed Warning. 2012. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm186845.htm.
38. Mahoney BA, Smith WAD, Lo DS, et al. Emergency interventions for hyperkalemia. *Cochrane Database Syst Rev*. 2005;18:CD003235.
39. Fordjour KN, Walton T, Doran JJ. Management of hyperkalemia in hospitalized patients. *Am J Med Sci*. 2014;347:93–100.
40. Phillips CO, Kashani A, Ko DK, Francis G, Krumholz HM. Adverse effects of combination angiotensin II receptor blockers plus angiotensin-converting enzyme inhibitors for left ventricular dysfunction. *Arch Intern Med*. 2007;167:1930–1936.
41. Van Buren PN, Adams-Huet B, Nguyen M, Molina C, Toto RD. Potassium handling with dual renin-angiotensin system inhibition in diabetic

nephropathy. *Clin J Am Soc Nephorl*. 2014;9:295–301.
42. Lepage L, Dufour AC, Doiron J, et al. Randomized clinical trial of sodium polystyrene sulfonate for the treatment of mild hyperkalemia in CKD. *Clin J Am Soc Nephrol*. 2015;10:2136–2142.
43. Chernin G, Gal-Oz A, Ben-Assa E, et al. Secondary prevention of hyperkalemia with sodium polystyrene sulfonate in cardiac and kidney patients on renin-angiotensin-aldosterone system inhibition therapy. *Clin Cardiol*. 2012;35:32–36.
44. Weir MR, Bakris GL, Bushinsky DA, et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med*. 2015;372:211–221.
45. Bakris GL, Pitt B, Weir MR, et al. Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease; The AMETHYST-DN randomized clinical trial. *J Am Med Assoc*. 2015;314:151–161.
46. Veltassa™ [package insert]. Redwood City, CA: Relypsa, Inc; 2015.
47. Packham DK, Rasmussen HS, Lavin PT, et al. Sodium zirconium cyclosilicate in hyperkalemia. *N Engl J Med*. 2015;372:222–231.
48. Kosiborod M, Rasmussen HS, Lavin P, et al. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia; The HARMONIZE randomized clinical trial. *J Am Med Assoc*. 2014;12:2223–2233.
49. Chan L. Normal and abnormal magnesium metabolism. In: Schrier RW, ed. *Renal and Electrolyte Disorders*. 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2018;225–252.
50. Musso CG. Magnesium metabolism in health and disease. *Int Urol Nephrol*. 2009;41:357–362.
51. Blaine J, Chonchol M, Levi M. Renal control of calcium, phosphate, and magnesium homeostasis. *Clin J Am Soc Nephrol*. 2015;10:1257–1272.
52. Wolf F, Hilewitz A. Hypomagnesaemia in patients hospitalised in internal medicine is associated with increased mortality. *Int J Clin Pract*. 2014;68:111–116.
53. Martin KJ, Gonzalez EA, Slatopolsky E. Clinical consequences and management of hypomagnesemia. *J Am Soc Nephrol*. 2009;20:2291–2295.
54. Atsmon J, Dolev E. Drug-induced hypomagnesaemia. *Drug Saf*. 2005;28:763–788.

55. Ayuk J, Gittoes NJL. Treatment of hypomagnesemia. *Am J Kidney Dis*. 2014;63(4):691–695.
56. Rodriguez-Moran M Guerrero-Romero F. Oral magnesium supplementation improves insulin sensitivity and metabolic control in type 2 diabetes subjects. *Diabetes Care*. 2003;26:1147–1152.
57. Pham PCT, Pham PMT, Pham SV, Miller JM, Pham PTT. Hypomagnesemia in patients with type 2 diabetes. *Clin J As Soc Nephrol*. 2007;2:366–373.
58. Jahnen-Dechent W, Ketteler M. Magnesium basics. *Clin Kidney J*. 2012;5(suppl 1):i3–i14.

69

Acid–Base Disorders

John W. Devlin and Thomas D. Nolin

KEY CONCEPTS

1. The lung plays a central role in acid–base homeostatic regulation through respiration; an increased respiratory rate eliminates more CO_2, reduces the partial pressure of CO_2 in the blood, and results in a reduced carbonic acid concentration and increased pH.
2. The kidney also plays a central role in the regulation of acid–base homeostasis through the excretion or reabsorption of filtered bicarbonate (HCO_3^-), the excretion of metabolic fixed acids, and the generation of new HCO_3^-.
3. Arterial blood gases (ABGs), along with serum electrolytes, physical findings, medical and medication history, and the clinical condition of the patient, are the primary tools to determine the cause of an acid–base disorder and to design and monitor a course of therapy.
4. Each acid–base disturbance has a compensatory response that attempts to correct the HCO_3^--to-$PaCO_2$ ratio toward normal and mitigate the change in pH. The respiratory compensatory response to metabolic disturbances is initiated rapidly, whereas the metabolic compensatory response to respiratory disturbances occurs more slowly.
5. Metabolic acidosis and metabolic alkalosis are generated by a primary change in the serum bicarbonate concentration. In metabolic acidosis, bicarbonate is lost or a nonvolatile acid is gained, whereas metabolic alkalosis is characterized by a gain in bicarbonate or a loss of nonvolatile acid.
6. Renal tubular acidosis (RTA) refers to a group of disorders characterized by impaired tubular renal acid handling despite normal or near-normal glomerular filtration rates. These patients often present with

hyperchloremic metabolic acidosis.

7. Primary therapy of most acid–base disorders must include treatment or removal of the underlying cause, not just correction of the pH and electrolyte disturbances.
8. Potassium supplementation is always necessary for patients with chronic metabolic acidosis, as the bicarbonaturia resulting from alkali therapy increases renal potassium wasting.
9. Effective treatment of the underlying cause of some organic acidoses (eg, ketoacidosis) can result in bicarbonate regeneration within hours thus mitigating the need for alkali therapy.
10. A patient's response to volume replacement can be predicted by the urine chloride concentration and permits the differential diagnosis of metabolic alkalosis.
11. Loss of gastric acid from vomiting or nasogastric suctioning may lead to hypochloremia and hyperbicarbonatemia and may often lead to a metabolic alkalosis.
12. Aggressive diuretic therapy can produce a metabolic alkalosis, and the accompanying hypokalemia can be serious.
13. Management of metabolic alkalosis due to excessive renal acid excretion usually consists of treatment of the underlying cause of mineralocorticoid excess. In patients in whom the mineralocorticoid excess cannot be corrected, chronic pharmacologic therapy can be required.
14. In most cases of acute respiratory acidosis, such as following cardiopulmonary arrest, sodium bicarbonate therapy is not indicated and can be detrimental. Blood gas analysis should guide therapy.

Preclass Engaged Learning Activity

Watch the video entitled "Acid–Base Balance & Blood Gas Interpretation" in the 2019 National Council Licensure Examination (NCLEX) Review [available at https://youtu.be/kh62SRovgrI]. This 10-minute video provides a brief overview of acid–base balance, disturbances, compensation, and interpretation. This video is useful to enhance student understanding regarding the assessment of acid–base disorders in the patient care process.

INTRODUCTION

Acid–base disorders are common and often serious disturbances that can result in significant morbidity and mortality. This chapter reviews the mechanisms responsible for the maintenance of acid–base balance and the laboratory analyses that aid clinicians in their assessment of acid–base disorders. The pathophysiology of the four primary acid–base disturbances is presented, evidence-based therapeutic options are reviewed, and management guidelines to optimize the outcome of patients with one of these disorders are presented. Given that medications are a frequent cause of acid–base abnormalities and that acid–base abnormalities are often preventable, clinicians must anticipate drug-related problems to avoid or minimize the clinical consequences of acid–base disorders, and when necessary, design appropriate treatment regimens.

ACID–BASE CHEMISTRY

An acid (in this equation, hydrochloric acid) is a substance that can *donate* protons (hydrogen ion [H^+]):

$$\text{(Acid) HCl} \rightarrow H^+ + \text{Chloride ion } (Cl^-)$$

A base (in this equation, ammonia [NH_3]) is a substance that can *accept* protons (hydrogen ion [H^+]):

$$\text{(Ammonia) } NH_3 + H^+ \rightarrow NH^+_4 \text{ (base)}$$

The acid–base pairs commonly encountered in clinical practice are listed in **Table 69-1**.

TABLE 69-1 Acid–Base Pairs

Carbonic acid/bicarbonate	H_2CO_3/HCO_3^-
Monobasic/dibasic phosphate	H_2PO_4/HPO_4^-
Ammonium/ammonia	NH_4^+/NH_3
Lactic acid/lactate	$H_6C_3O_2/H_5C_3O_2^-$

The acidity of body fluids is quantified in terms of the hydrogen ion concentration. By convention, the degree of acidity is expressed as pH, or the

negative logarithm (base 10) of the hydrogen ion concentration. Thus, hydrogen ion concentration and pH are inversely related. Normally, the pH of blood is maintained at 7.40 ($[H^+]$ of 4×10^{-8} M) with a range of 7.35 to 7.45. A pH of less than 6.7 ($[H^+]$ of 2×10^{-7} M), representing a fivefold increase in hydrogen ion concentration, or greater than 7.7 ($[H^+]$ of 2×10^{-8} M), representing a 50% decrease in hydrogen ion concentration, is considered incompatible with life.

The hydrogen ion concentration in blood may not be indicative of that in other body compartments. For example, the pH within cells, within the cerebrospinal fluid, or on the surface of bone can all be altered without causing an alteration in blood pH.[1] Recognizing this caveat, the acid–base status of the body is usually analyzed based on measurement of blood pH. Alterations in blood pH serve as the basis for the diagnosis of acid–base disorders.

The dissociation of acid–base pairs is an equilibrium reaction. This allows the relationship between hydrogen ion concentration or pH and the relative concentrations of the acid and base to be described mathematically in terms of the dissociation constant for the acid–base buffer pair. When expressed as a logarithmic relationship, where p*K* is the negative logarithm of the dissociation constant *K*, this is known as the Henderson–Hasselbalch equation:

$$\text{pH} = \text{p}K + \log([\text{base}]/[\text{acid}])$$

BUFFERS

The ability of a weak acid and its corresponding anion (base) to resist change in the pH of a solution with the addition of a strong acid or base is referred to as *buffering*. An acid–base pair is most efficient in functioning as a buffer at a pH close to its pK. The principal extracellular buffer is the carbonic acid/bicarbonate (H_2CO_3/HCO_3^-) system. Other physiologic buffers include plasma proteins, hemoglobin, and phosphates. The complex buffering of biologic fluids can be analyzed based on a single buffer pair because the isohydric principle requires that all buffer systems remain in chemical equilibrium.

The carbonic acid/bicarbonate buffer system plays a unique role in acid–base homeostasis. In addition to being the most abundant extracellular buffer, the components of this buffer pair exist under dynamic regulation by the body. In the presence of carbonic anhydrase, carbonic acid, $[H_2CO_3]$, is in equilibrium with carbon dioxide (CO_2) gas. Changes in pulmonary ventilation that alter the partial pressure of CO_2 (PCO_2) in the blood regulate the carbonic acid level in the

blood. Conversely, the bicarbonate concentration is independently regulated by the kidney. Because the p*K* for the carbonic acid/bicarbonate system is 6.1, the relationship between pH, carbonic acid, and bicarbonate concentrations can be described by the Henderson–Hasselbalch equation. The concentration of carbonic acid is directly proportional to the amount of CO_2 dissolved in blood, which is equal to the product of PCO_2 and its solubility in physiologic fluids ($PCO_2 \times 0.03$ for PCO_2 expressed in mm Hg or $PCO_2 \times 0.226$ for PCO_2 expressed in kPa). This term can, therefore, be substituted into the equation below in place of $[H_2CO_3]$.

$$pH = 6.1 + \log([HCO_3^-]/[H_2CO_3])$$

$$pH = 6.1 + \log([HCO_3^-]/[PCO_2 \times 0.03]) \text{ for } PCO_2 \text{ in mm Hg}$$

or

$$pH = 6.1 + \log([HCO_3^-]/[PCO_2 \times 0.226]) \text{ for } PCO_2 \text{ in kPa}$$

Thus, hydrogen ion concentration and pH are determined not by the absolute amounts of bicarbonate and PCO_2 present but by their ratio.[1] Under normal physiologic conditions, the kidneys maintain the serum bicarbonate at approximately 24 mEq/L (mmol/L), whereas the lungs maintain the PCO_2 at approximately 40 mm Hg (5.3 kPa). The normal physiologic pH is thus 7.4:

$$pH = 6.1 + \log[24/(0.03 \times 40)] \text{ (or } pH = 6.1 + \log[24/0.226 \times 5.3)])$$

$$pH = 6.1 + 1.3 = 7.4$$

If, in response to an acid load, the serum bicarbonate concentration were to decrease to 12 mEq/L (mmol/L), the predicted pH would be:

$$[HCO_3^-] = 12 \text{ mEq/L (mmol/L)}$$

$$PCO_2 = 40 \text{ mm Hg (5.3 kPa)}$$

$$pH = 6.1 + \log[12/0.03 \times 40] \text{ or}$$

$$pH = 6.1 + \log([12/(0.226 \times 5.3)]$$

$$pH = 6.1 + 1.0 = 7.1$$

However, the normal respiratory response to an acid load is hyperventilation.

As a result, if the PCO_2 decreased to approximately 26 mm Hg (3.5 kPa), the change in pH would be less:

$$[HCO_3^-] = 12 \text{ mEq/L (mmol/L)}$$

$$PCO_2 = 26 \text{ mm Hg (3.5 kPa)}$$

$$pH = 6.1 + \log [12/0.03 \times 26]$$

$$(\text{or } pH = 6.1 + \log [12/0.226 \times 3.5])$$

$$pH = 6.1 + 1.19 = 7.29$$

Thus, the physiologic regulation of both PCO_2 and $[HCO_3^-]$ permits the carbonic acid/bicarbonate system to provide more effective buffering of the extracellular fluids (ECFs) than could be achieved on the basis of chemical buffering alone.

REGULATION OF ACID–BASE HOMEOSTASIS

Cellular metabolism results in the production of large quantities of hydrogen that need to be excreted to maintain acid–base balance. In addition, small amounts of acid and alkali are also presented to the body through the diet. The bulk of acid production is in the form of CO_2, with the average adult producing approximately 15,000 mmol of CO_2 each day from the catabolism of carbohydrate, protein, and fat.[2] When respiratory function is normal, the amount of CO_2 produced metabolically is equal to the amount lost by respiration, and the blood CO_2 concentration remains constant.

Digestion of dietary substances and tissue metabolism also result in the production of nonvolatile acids. These acids are derived primarily from the sulfur-containing amino acids cysteine and methionine, as well as from ingested sulfur. In addition, phosphates are generated from the metabolism of proteins and phospholipids. Neutral substances such as glucose can also be incompletely metabolized to intermediates, such as lactic and pyruvic acid, and fatty acids can be incompletely metabolized to acetoacetic acid and β-hydroxybutyric acid. These dietary and metabolic fixed acids are excreted primarily by the kidney to maintain acid–base homeostasis. On average, daily fixed acid excretion is approximately 0.8 mEq/kg/day (mmol/kg/day).[3]

Three processes, each of which varies in its onset, collectively maintain acid–

base balance: extracellular buffering, ventilatory regulation of carbon dioxide elimination, and renal regulation of hydrogen ion and bicarbonate excretion. Extracellular buffering occurs rapidly and is the body's first defense against a sudden increase in hydrogen ion concentration. Hyperventilation then results in a decrease in PCO_2, returning blood pH toward normal. Finally, over a period of day(s), the kidney will excrete the excess hydrogen ion and acid–base balance will return to normal.

Extracellular Buffering

The body's buffering system can be divided into three components: bicarbonate/carbonic acid, proteins, and phosphates. The bicarbonate buffer is the most important of the body's buffers, because (a) there is more bicarbonate present in the ECF than any other buffer component; (b) the supply of CO_2 is unlimited; and (c) the acidity of ECF can be regulated by controlling either the bicarbonate concentration or the PCO_2.

Carbonic acid represents the respiratory component of the buffer pair because its blood concentration is directly proportional to the PCO_2, which is determined by ventilation. Bicarbonate represents the metabolic component because the kidney may alter its concentration by reabsorption, generating new bicarbonate, or altering elimination.[1] The bicarbonate buffer system easily adapts to changes in acid–base status by alterations in ventilatory elimination of acid (PCO_2) and/or renal elimination of base (HCO_3^-).

The phosphate buffer system consists of serum inorganic phosphate (3.5-5 mg/dL [1.13-1.62 mmol/L]), intracellular organic phosphate, and calcium phosphate in bone. Extracellular phosphate is present only in low concentrations, so its usefulness as a buffer is limited; however, as an intracellular buffer, phosphate is more useful. Calcium phosphate in bone is relatively inaccessible as a buffer, but prolonged metabolic acidosis will result in the release of phosphate from bone.

Intracellular and extracellular proteins also act as buffering systems. The charged side chains of amino acids provide the buffering action. Because the concentration of protein is much greater intracellularly than extracellularly, protein is much more important as an intracellular buffer.

Respiratory Regulation

1 The second process involved in maintenance of acid–base homeostasis is ventilatory regulation of CO_2 elimination. Both the rate and depth of ventilation can be varied to allow for excretion of CO_2 generated by diet and tissue metabolism. Medullary chemoreceptors in the brainstem sense changes in PCO_2 and pH and modulate the control of breathing. Increasing minute ventilation (the total amount of air exhaled over a 1-minute period), by increasing respiratory rate and/or tidal volume (the amount of air exhaled in one breath), will increase CO_2 excretion and decrease the blood PCO_2. Conversely, decreasing minute ventilation decreases CO_2 excretion and increases blood PCO_2. This system rapidly adjusts within minutes to changes in acid–base balance.[1]

Renal Regulation

2 Bicarbonate is freely filtered at the glomerulus because it is a small ion. The bicarbonate load delivered to the nephron is approximately 4,500 mEq/day (mmol/day). To maintain acid–base balance, this entire filtered bicarbonate load must be reabsorbed. Bicarbonate reabsorption occurs primarily in the proximal tubule (**Fig. 69-1**). In the tubular lumen, filtered bicarbonate combines with hydrogen ion, secreted by the apical sodium ion (Na^+)–H^+-exchanger, to form carbonic acid. The carbonic acid is rapidly broken down to CO_2 and water by carbonic anhydrase, an enzyme located on the luminal surface of the brush border membrane. The CO_2 then diffuses into the proximal tubular cell, where it reforms carbonic acid in the presence of intracellular carbonic anhydrase. The carbonic acid dissociates to form hydrogen ions that can again be secreted into the tubular lumen, and bicarbonate that exits the cell across the basolateral membrane and enters the peritubular capillary.

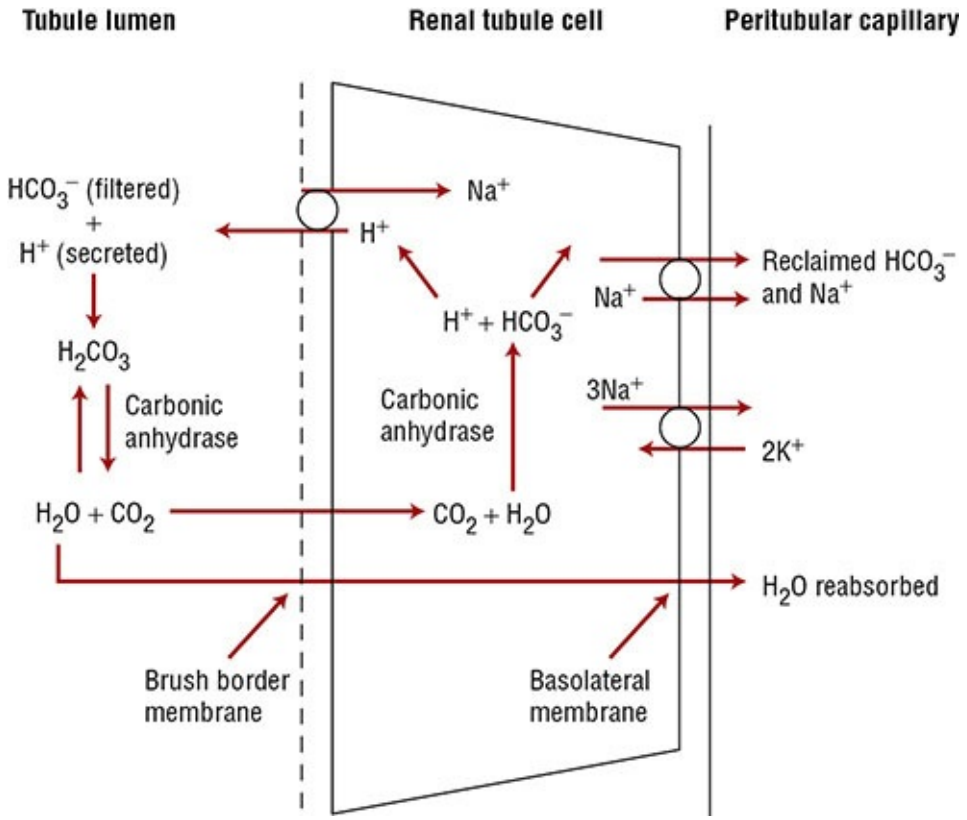


FIGURE 69-1 Proximal tubular bicarbonate reabsorption. In the tubular lumen, filtered bicarbonate (HCO_3^-) combines with hydrogen ion (H^+) secreted by an apical sodium ion (Na^+)–H^+ exchanger to form carbonic acid (H_2CO_3). The carbonic acid is rapidly broken down to carbon dioxide (CO_2) and water by carbonic anhydrase located on the luminal surface of the brush border membrane. The CO_2 then diffuses into the proximal tubular cell, where it reforms carbonic acid in the presence of intracellular carbonic anhydrase. The carbonic acid dissociates the former hydrogen ion that can again be secreted into the tubular lumen, and bicarbonate that exits the cell across the basolateral membrane and enters the peritubular capillary.

Excretion of metabolic fixed acids and generation of new HCO_3^- are achieved in nearly equal parts by renal ammoniagenesis and distal tubular hydrogen ion secretion. Ammoniagenesis plays a critical role in acid–base homeostasis, with ammonium (NH_4^+) excretion comprising approximately 50% of renal net acid excretion. Ammonium is generated from the deamination of glutamine in the proximal tubule. For each ammonium ion excreted in the urine, one bicarbonate ion is regenerated and returned to the circulation.[3]

Distal tubular hydrogen ion secretion accounts for the remaining 50% of net

acid excretion. Although the distal tubule consists of multiple distinct functional segments and cell types, the carbonic anhydrase–containing intercalated cells are primarily responsible for acid–base transport. Specifically, type A intercalated cells function as hydrogen ion secreting cells (**Fig. 69-2**). In these cells, CO_2 combines with water in the presence of intracellular carbonic anhydrase to form carbonic acid, which dissociates to H^+ and HCO_3^-. The H^+ is actively transported into the tubular lumen by a H^+–adenosine triphosphatase (H^+–ATPase). The bicarbonate exits the cell across the basolateral membrane and enters the circulation.[1]

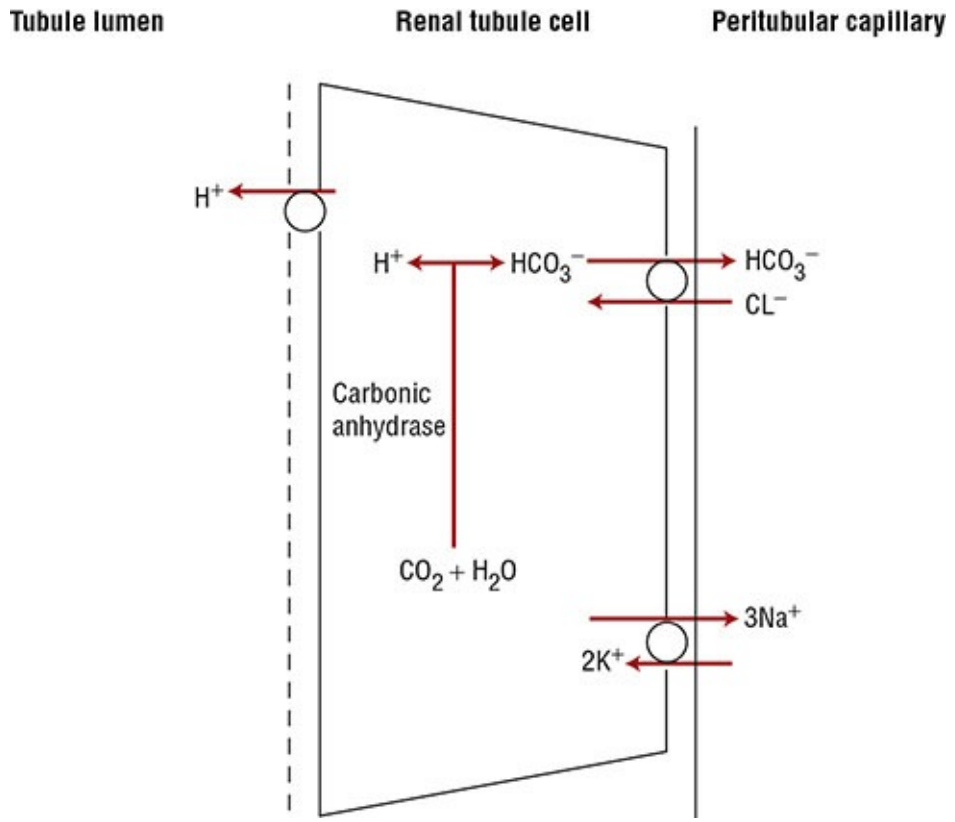


FIGURE 69-2 Collecting duct acid excretion. Hydrogen ion (H^+) and bicarbonate (HCO_3^-) are generated intracellularly from carbon dioxide (CO_2) and water, in the presence of intracellular carbonic anhydrase. The hydrogen ion is actively secreted into the tubular lumen by H^+–ATPase located in the apical (luminal) membrane. Bicarbonate exits the cell across the basolateral membrane and enters the peritubular capillary. (Cl^-, chloride ion; Na^+, sodium ion.)

ACID–BASE DISTURBANCES

3 4 Alterations in blood pH are designated by the suffix “-emia”; *acidemia* is an arterial blood pH less than 7.35 and *alkalemia* is an arterial blood pH more than 7.45. The pathophysiologic processes that result in alterations in blood pH are designated by the suffix “-osis.” These disturbances are classified as either metabolic or respiratory in origin. In metabolic acid–base disorders, the primary disturbance is in the plasma bicarbonate concentration. Metabolic acidosis is characterized by a decrease in the plasma bicarbonate concentration, whereas in metabolic alkalosis the plasma bicarbonate concentration is increased. Respiratory acid–base disorders are caused by alterations in alveolar ventilation that produce corresponding changes in the partial pressure of carbon dioxide from arterial blood ($PaCO_2$). In respiratory acidosis, the $PaCO_2$ is elevated; in respiratory alkalosis, it is decreased. Each disturbance has a compensatory (secondary) response that attempts to correct the HCO_3^--to-$PaCO_2$ ratio toward normal and mitigate the change in pH (Table 69-2). Although the time course of the respiratory compensatory response to metabolic disturbances is rapid, the metabolic compensation for respiratory disturbances is slow. As a result, respiratory disturbances are characterized as acute (minutes to hours in duration), indicating that there has not been sufficient time for metabolic compensation, or chronic (days), indicating that sufficient time for metabolic compensation has elapsed.

TABLE 69-2 Interpretation of Simple Acid–Base Disorders

Acid–Base Disorder	pH	Primary Disturbances	Compensation
Acidosis			
Respiratory	Decrease	Increase $PaCO_2$	Increase HCO_3^-
Metabolic	Decrease	Decrease HCO_3^-	Decrease $PaCO_2$
Alkalosis			
Respiratory	Increase	Decrease $PaCO_2$	Decrease HCO_3^-
Metabolic	Increase	Increase HCO_3^-	Increase $PaCO_2$

HCO_3^-, bicarbonate; $PaCO_2$, partial pressure of carbon dioxide from arterial blood.

CLINICAL ASSESSMENT OF ACID–BASE STATUS

5 A blood gas is measured to determine not only a patient’s acid–base status

but also their oxygenation. Under normal circumstances, the pH difference between arterial and mixed venous blood is not clinically significant. However, the oxygenation difference between arterial and mixed venous blood is always substantial. Arterial samples are designated with the letter "a" (eg, partial pressure of oxygen from arterial blood [PaO_2] and $PaCO_2$), whereas mixed venous samples are labeled with the letter "v" or not labeled (eg, partial pressure of oxygen from venous blood [PvO_2] and partial pressure of carbon dioxide from venous blood [$PvCO_2$]). The normal values for arterial and venous blood gases are shown in **Table 69-3**. Arterial blood reflects how well the blood is being oxygenated by the lungs (an accurate measurement of PaO_2), whereas venous blood reflects how much oxygen tissues are using. Arterial blood rather than venous blood should be used whenever possible because venous blood obtained from an extremity can provide misleading information. If metabolism in the extremity is altered by hypoperfusion, exercise, infection, or some other cause, the difference in the amount of dissolved oxygen between arterial and venous blood can be dramatic. The venous pH and PCO_2 during cardiopulmonary resuscitation might be significantly lower and higher, respectively, than the arterial pH and arterial PCO_2. This indicates a severe tissue acidosis from CO_2 accumulation caused by hypoperfusion.

TABLE 69-3 Normal Blood Gas Values

	Arterial Blood	Mixed Venous Blood
pH	7.40 (7.35-7.45)	7.38 (7.33-7.43)
PO_2	80-100 mm Hg (10.6-13.3 kPa)	35-40 mm Hg (4.7-5.3 kPa)
SaO_2	95% (0.95)	70-75% (0.70-0.75)
PCO_2	35-45 mm Hg (4.7-6.0 kPa)	45-51 mm Hg (6.0-6.8 kPa)
HCO_3^-	22-26 mEq/L (mmol/L)	24-28 mEq/L (mmol/L)

HCO_3^-, bicarbonate; PCO_2, partial pressure of carbon dioxide; PO_2, partial pressure of oxygen; SaO_2, saturation of arterial oxygen.

Analysis of Arterial Blood Gas Data

Arterial blood gases (ABGs) provide an assessment of the patient's acid–base status.[2,3] Low pH values (less than 7.35) indicate an acidemia, whereas high pH values (more than 7.45) indicate an alkalemia (**Fig. 69-3**). In a metabolic acidosis, the pH is decreased in association with a decreased serum bicarbonate concentration and a compensatory decrease in $PaCO_2$. In a respiratory acidosis

while the pH is decreased, the $PaCO_2$ is elevated. The serum bicarbonate concentration is variable, depending on whether it is an acute disturbance (minimal increase in serum bicarbonate) or a chronic respiratory acidosis (substantial increase in serum bicarbonate). In a metabolic alkalosis, the pH is elevated in association with an increased bicarbonate concentration and a compensatory increase in $PaCO_2$. In a respiratory alkalosis, while the pH is also elevated, the $PaCO_2$ is decreased. As with respiratory acidosis, the metabolic compensation is variable: a minimal decrease in serum bicarbonate is often noted in acute respiratory alkalosis, while a larger decrease in $[HCO_3^-]$ is common with chronic respiratory alkalosis. Although each measurement has a normal range (see Table 69-3), it is often easiest to consider the midpoint of each range as the normal value. This would correlate to a pH of 7.4, $PaCO_2$ of 40 mm Hg (5.3 kPa), and HCO_3^- of 24 mEq/L (mmol/L). Steps in acid–base interpretation, using this physiologic approach, are described in **Table 69-4**. While beyond the scope of this chapter, two other approaches to assess acid–base status (ie, the physicochemical [Stewart's] approach and the base excess approach) are sometimes used in clinical practice.[4,5]

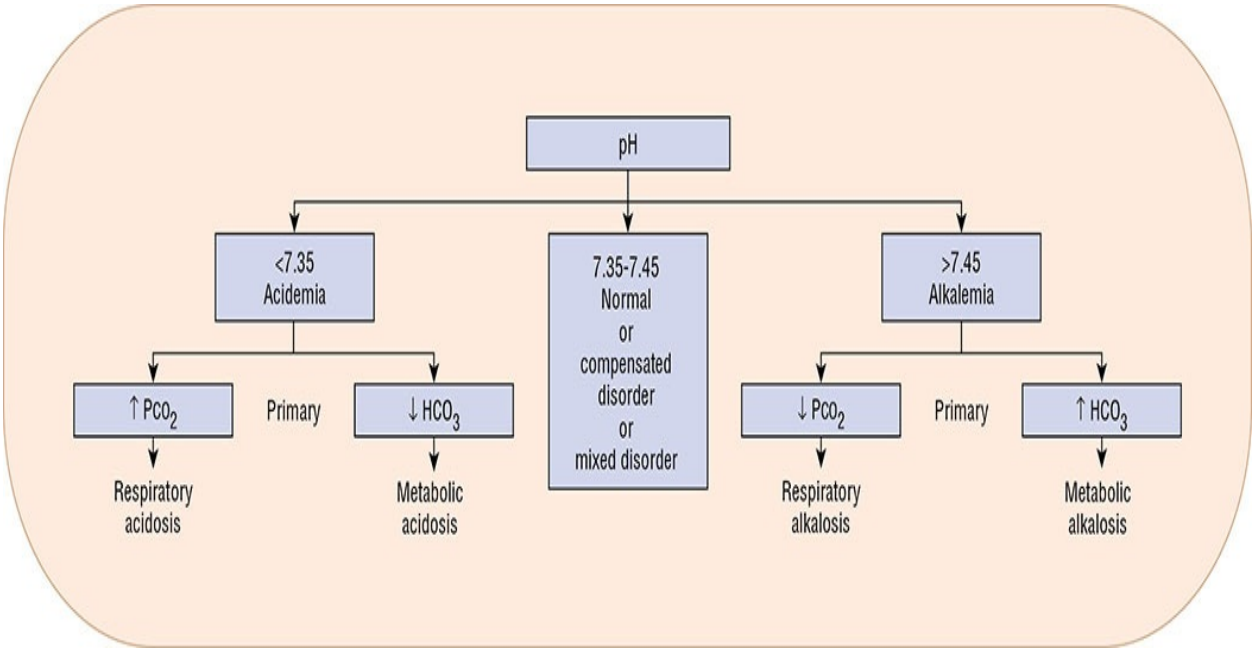


FIGURE 69-3 Analysis of arterial blood gases. (HCO_3^-, bicarbonate; PCO_2, partial pressure of carbon dioxide.)

TABLE 69-4 Steps in Acid–Base Diagnosis

1. Obtain ABGs and electrolytes simultaneously
2. Compare [HCO_3^-] on ABG and electrolytes to verify accuracy
3. Calculate SAG
4. Is acidemia (pH <7.35) or alkalemia (pH >7.45) present?
5. Is the primary abnormality respiratory (alteration in $PaCO_2$) or metabolic (alteration in HCO_3)?
6. Estimate compensatory response (Table 69-7)
7. Compare change in [Cl^-] with change in [Na^+]

[Cl^-], chloride ion; [HCO_3^-], bicarbonate; [Na^+], sodium ion; $PaCO_2$, partial pressure of carbon dioxide from arterial blood; SAG, serum anion gap.

When ABGs differ significantly from those expected on the basis of the patient's clinical condition and previous laboratory determinations, additional venous blood samples should be drawn to assess plasma electrolyte concentrations. The bicarbonate calculated from the patient's $PaCO_2$ and pH of the blood gas should be compared with the measured total CO_2 content (the amount of CO_2 gas extractable from plasma, consisting of HCO_3^-, H_2CO_3, and PCO_2). Ordinarily, the blood gas bicarbonate value is approximately 1 to 2 mEq/L (mmol/L) less than the total CO_2 content.[3] If these values do not correspond, the results should be interpreted with caution because the difference can reflect an error in the blood collection or storage of the sample, or in the calibration of the blood gas analyzer.

METABOLIC ACID–BASE DISORDERS

Metabolic Acidosis

Metabolic acidosis is characterized by a decrease in pH as the result of a primary decrease in serum bicarbonate concentration.

Pathophysiology

Metabolic acidosis can result from the buffering (consumption of HCO_3^-) of an exogenous acid, an organic acid accumulating because of a metabolic disturbance (eg, lactic acid or ketoacids), or the progressive accumulation of endogenous acids secondary to impaired kidney function (eg, phosphates and sulfates).[6,7] The serum HCO_3^- can also be decreased as the result of a loss of bicarbonate-rich body fluids (eg, diarrhea, biliary drainage, or pancreatic fistula) or occur secondary to the rapid administration of non-alkali–containing IV fluids

(dilutional acidosis).[6]

The serum anion gap (SAG), as defined below, can be used to infer whether an organic or mineral acidosis is present.

$$SAG = [Na^+] - [Cl^-] - [HCO_3^-]$$

To maintain electroneutrality, the total concentration of cations in the serum must equal the total concentration of anions.

$$[Na^+] + [UCs] = ([Cl^-] + [HCO_3^-]) + [UAs]$$

The cation concentration is equal to the sodium concentration plus that of "unmeasured" cations (UCs), predominantly magnesium, calcium, and potassium. The anion concentration is equal to the concentrations of chloride, bicarbonate, and "unmeasured" anions (UAs), including proteins, sulfates, phosphates, and organic anions. Therefore, as the result of the combination of the two equations above, the SAG can be expressed as:

$$SAG = [UAs] - [UCs]$$

The normal SAG is approximately 9 mEq/L (mmol/L), with a range of 3 to 11 mEq/L (mmol/L). This value is lower than the value of 12 mEq/L (mmol/L) cited in the literature in the past because of changes in the instrumentation for measurement of serum electrolytes.[3] Increases in the anion gap (AG) to values in excess of 17 to 20 mEq/L (mmol/L) are indicative of the accumulation of unmeasured anions in ECF.[7]

These unmeasured anions are generated as the result of the consumption of HCO_3^- by endogenous organic acids such as lactic acid, acetoacetic acid, or β-hydroxybutyric acid or from the ingestion of toxins such as methanol or ethylene glycol. The degree of elevation in the SAG is dependent on the clearance of the anion, and the multiple factors that influence HCO_3^- concentrations. Thus, the SAG is a relative rather than an absolute indication of the cause of metabolic acidosis. The SAG can also be elevated in the metabolic acidosis because of kidney disease, as a result of the accumulation of various organic anions, phosphates, and sulfates.

In hyperchloremic metabolic acidosis, bicarbonate losses from the ECF are replaced by chloride, and the SAG remains normal. This decrease in bicarbonate may be due to gastrointestinal (GI) tract losses—dilution of bicarbonate in the ECF as a result of the addition of sodium chloride solutions or chloride-

containing acids. Common causes of metabolic acidosis with an increased or a normal SAG are listed in **Table 69-5**.

TABLE 69-5 Common Causes of Metabolic Acidosis

Increased Serum Anion Gap	Normal Serum Anion Gap/Hyperchloremic States
Lactic acidosis (see Table 69-6)	**GI bicarbonate loss**
Kidney disease (acute or chronic)	Diarrhea
Methanol ingestion	External pancreatic or small bowel drainage (fistula)
Ethylene glycol ingestion	Ureterosigmoidostomy, ileostomy
Salicylate overdose	**Drugs**
Starvation	Cholestyramine (bile acid diarrhea)
	Magnesium sulfate (diarrhea)
	Calcium chloride (acidifying agent)
	RTA
	Hypokalemia
	Proximal renal tubular acidosis (type II)
	Distal renal tubular acidosis (type I)
	Carbonic anhydrase inhibitors (eg, acetazolamide)
	Drug-induced hypokalemia
	Amphotericin B
	Furosemide
	Ifosfamide
	Lithium
	Hyperkalemia
	Generalized distal nephron dysfunction (type IV)
	Mineralocorticoid deficiency or resistance
	Tubulointerstitial disease
	Drug-induced hyperkalemia
	Potassium-sparing diuretics (amiloride, spironolactone, triamterene)
	Trimethoprim
	Pentamidine
	Heparin
	ACE inhibitors and receptor blockers
	NSAIDs
	Cyclosporin A
	Others
	Acid ingestion (ammonium chloride, hydrochloric acid, hyperalimentation)
	Expansion acidosis (rapid saline administration)

ACE, angiotensin-converting enzyme; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; RTA, renal tubular acidosis.

Hyperchloremic Metabolic Acidosis

Hyperchloremic metabolic acidosis can result from increased GI bicarbonate loss, renal bicarbonate wasting, impaired renal acid excretion, exogenous acid gain, topiramate, or chloride-containing intravenous fluids.[6] GI disorders such as diarrhea, biliary, or pancreatic drainage through either a surgical drain or fistula can result in the loss of large volumes of bicarbonate-containing fluids. Severe diarrhea, the most common cause of hyperchloremic metabolic acidosis, can lead to a daily loss of 5 to 10 L of fluid containing 100 to 140 mEq/L (mmol/L) of sodium, 20 to 40 mEq/L (mmol/L) of potassium, 80 to 100 mEq/L (mmol/L) of chloride, and 30 to 50 mEq/L (mmol/L) of bicarbonate.[6] Patients who have undergone ureteral diversion into the sigmoid colon or isolated ileal loop can also develop a hyperchloremic metabolic acidosis. This is the result of a net loss of bicarbonate, given that chloride is reabsorbed and bicarbonate is secreted by GI epithelial cells in the presence of the urine that is retained in the colon or bowel loop.

Hyperchloremic metabolic acidosis caused by renal bicarbonate wasting is the defining disturbance in proximal renal tubular acidosis (RTA) and is a complication of therapy with carbonic anhydrase inhibitors, particularly when they are administered for more than 24 to 48 hours.[6–8] Topiramate, an anticonvulsant that inhibits carbonic anhydrase, has been reported to cause hyperchloremic metabolic acidosis, proximal RTA and nephrolithiasis, particularly when administered at higher doses and for prolonged periods.[9] Impaired renal acid excretion that occurs as a result of distal tubular dysfunction in patients with distal RTAs can also occur in patients with moderate to severe kidney disease from other causes. The metabolic acidosis observed in patients with kidney disease is initially hyperchloremic but can progress to an anion-gap acidosis as kidney disease progresses and sulfates, phosphates, and other anions accumulate.[6] Hyperchloremic metabolic acidosis can also result from the exogenous administration of acid (hydrochloric acid, ammonium chloride) or the unbuffered administration of acid salts from the amino acids in total parenteral nutrition fluids.[10]

Renal Tubular Acidosis

6 Renal tubular disorders can involve the proximal tubule, with a resultant failure to reabsorb filtered bicarbonate, or affect acid excretion in the distal tubule. The distal RTAs are the most common, and are all characterized by impaired net acid excretion. The distal RTAs are subdivided into those that are associated with hypokalemia (type I) and those associated with hyperkalemia

(type IV). Type II represents proximal RTA. Type III is extremely rare and will not be discussed. Common causes of RTAs are presented in Table 69-5.

Patients with classic distal (type I) RTA have impaired hydrogen ion secretion and are unable to excrete the daily acid load necessary to maintain acid–base balance.[6,7] These patients are unable to maximally acidify their urine (ie, attain urine pH less than 5.5), even in the face of an acid challenge. Type I RTA may be the result of a primary tubular defect or develop secondary to a wide variety of medications (eg, amphotericin B, ifosfamide, lithium) and disorders including hypercalcemia, multiple myeloma, and systemic lupus erythematosus.[11,12] The primary form of this disorder usually occurs in children and can result in severe acidosis, slowed growth, nephrocalcinosis, and kidney stones. In adults, clinical complications include osteomalacia, nephrocalcinosis, and recurrent kidney stones.

The hyperkalemic distal (type IV) RTAs are a heterogeneous group of disorders characterized by hypoaldosteronism or generalized distal tubule defects. The most common form of type IV RTA is hyporeninemic hypoaldosteronism. This syndrome is most commonly associated with diabetic nephropathy, but can also be seen in a variety of other disorders, including chronic interstitial nephritis, sickle-cell disease, human immunodeficiency virus (HIV) nephropathy, and obstructive uropathy.[11,12] The clinical presentation of this syndrome is often exacerbated by drugs that can interfere with the renin–angiotensin–aldosterone axis, such as β-adrenergic blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and nonsteroidal anti-inflammatory drugs (NSAIDs). Patients with this form of RTA are able to maximally acidify their urine (urine pH less than 5.5).[12] The primary defect in acid excretion is impaired ammoniagenesis caused by decreased kidney function. Treatment to control the hyperkalemia is usually sufficient to reverse the metabolic acidosis, and mineralocorticoid replacement is frequently unnecessary.

Hyperkalemic distal (type IV) RTA resulting from generalized distal tubule defects is less common than hyporeninemic hypoaldosteronism but is more common than classic distal (type I) RTA. Patients with this defect have impaired tubular potassium secretion in addition to impaired urinary acidification (urine pH more than 5.5, despite acidemia or acid loading). Urinary obstruction is the most frequent cause of this disorder, but it can also be associated with sickle-cell nephropathy, systemic lupus erythematosus, HIV nephropathy, analgesic abuse nephropathy, amyloidosis, kidney transplant rejection, and chronic cyclosporine nephrotoxicity.

Proximal (type II) RTA is characterized by defects in proximal tubular reabsorption of bicarbonate. Normally, more than 85% of filtered bicarbonate is reabsorbed in the proximal tubule. Defects in proximal tubular bicarbonate reabsorption result in increased delivery of bicarbonate to the distal nephron, which has a limited capacity for bicarbonate reabsorption. As a result, at a normal serum bicarbonate concentration, the filtered bicarbonate load is incompletely reabsorbed, and is lost in the urine. Thus, patients with proximal RTA present with a chronic, nonprogressive hyperchloremic metabolic acidosis. These patients are able to acidify their urine in response to an acid load, but develop bicarbonaturia at a reduced serum bicarbonate concentration following bicarbonate loading. The impaired bicarbonate reabsorption results in salt wasting and secondary hyperaldosteronism. Hypokalemia, which can be severe, usually develops as a result of the hyperaldosteronism and bicarbonaturia.[6,12] Proximal RTA usually presents as an acquired disorder, secondary to carbonic anhydrase inhibitor therapy, a variety of diseases (eg, amyloidosis, multiple myeloma, or nephrotic syndrome) or exposure to toxins (eg, lead, cadmium, mercury, or outdated tetracyclines).

Elevated Anion Gap Metabolic Acidosis

Metabolic acidosis with an increased SAG commonly results from increased endogenous organic acid production.[13] In lactic acidosis, lactic acid accumulates as a by-product of anaerobic metabolism.[14] Accumulation of the ketoacids β-hydroxybutyric acid and acetoacetic acid defines the ketoacidosis of uncontrolled diabetes mellitus, alcohol intoxication, and starvation (Table 69-5).[15] In advanced kidney disease, accumulation of phosphate, sulfate, and organic anions is responsible for the increased SAG, which is usually less than 24 mEq/L (mmol/L).[2] The severe metabolic acidosis seen in myoglobinuric acute kidney injury caused by rhabdomyolysis may be caused by the metabolism of large amounts of sulfur-containing amino acids released from myoglobin.

The presence of mild elevations in the SAG cannot be automatically attributed to the presence of a high SAG metabolic acidosis. Elevations in the SAG are commonly seen in hospitalized patients, especially those who are critically ill.[16] A variety of factors can contribute to this nonspecific elevation in the SAG, including the presence of alkalemia, which increases the anionic charge of albumin and other plasma proteins. The usefulness of the SAG as a marker of acid–base status is dependent on proper interpretation of a patient's clinical status.[5,12] Despite these limitations, when the SAG exceeds 20 to 25

mEq/L (mmol/L) a significant organic acidosis is likely to be present.[13,14,16]

High anion gap metabolic acidosis can develop in many clinical settings, including uncontrolled diabetes mellitus (see Chapter 91, "Diabetes Mellitus") alcohol intoxication (see Chapter 54, "Portal Hypertension and Cirrhosis," and Chapter 83, "Substance-Related Disorders: Alcohol, Nicotine, and Caffeine"), and starvation (see Chapter 81, "Eating Disorders").[10,11,17] Toxic ingestions of methanol and ethylene glycol are also associated with high anion gap metabolic acidosis and can be differentiated from other causes of SAG because of the presence of an elevated osmolar gap.[17] The mechanisms responsible for the development of acidosis in these settings are diverse.[16]

Lactic Acidosis Lactic acidosis is one of the most common causes of high SAG metabolic acidosis and can impact approximately 1% of hospitalized patients. Lactic acid is the end product of anaerobic metabolism of glucose (glycolysis).[13] In normal individuals, lactic acid derived from pyruvate enters the circulation in small amounts and is promptly removed by the liver. In the liver, and to a lesser extent in the kidney, lactic acid is reoxidized to pyruvic acid, which is then metabolized to CO_2 and H_2O. The normal plasma lactate concentration in healthy subjects is approximately 1 mEq/L (mmol/L).[1,2,14] The diagnosis of lactic acidosis should be considered in all patients with metabolic acidosis associated with an increased SAG. Lactic acidosis is considered to be present when lactate concentrations exceed 4 to 5 mEq/L (mmol/L) in an acidemic patient.

Classically, lactic acidosis has been differentiated into disorders associated with tissue hypoxia (type A lactic acidosis) and disorders associated with deranged oxidative metabolism (type B lactic acidosis), although the distinction between them is blurred (**Table 69-6**).[14] The etiologies of lactic acidosis can also be categorized on the basis of changes in lactate production and/or utilization.[13,15] Metabolic disturbances can result in increased tissue pyruvate production or impaired utilization, with proportional increases in lactate concentrations. Increased lactate production is more commonly associated with alterations in tissue redox state, resulting in preferential conversion of pyruvate to lactate. During anaerobic metabolism, reduced nicotinamide adenine dinucleotide accumulates, driving the conversion of pyruvate to lactate and increasing the lactate-to-pyruvate ratio. States of enhanced metabolic activity (eg, grand mal seizures, strenuous exercise, or hyperthermia), decreased tissue oxygen delivery (eg, severe anemia, hypoxia, circulatory shock, or carbon monoxide poisoning), or impaired oxygen utilization (eg, cyanide toxicity) all

are associated with lactic acidosis. Impaired hepatic clearance of lactate, as seen in hypoperfusion states, liver failure, and alcohol intoxication, can also result in lactic acidosis.

TABLE 69-6 Causes of Lactic Acidosis

Primary decrease in tissue oxygenation
Shock
Severe anemia
Congestive heart failure
Asphyxia
Carbon monoxide poisoning
Deranged oxidative metabolism
Medications
Catecholamines
Linezolid
Metformin
Nalidixic acid
NRTIs (abacavir, lamivudine, tenofovir)
Overdose (iron, isoniazid, salicylates, theophylline)
Propofol infusion syndrome
Propylene glycol toxicity (IV lorazepam, IV pentobarbital, IV phenytoin, IV trimethoprim/sulfamethoxazole)
Sodium nitroprusside (secondary to cyanide toxicity)
Streptozocin
Viekira Pak® (ombitasvir, paritaprevir, ritonavir, dasabuvir)
Diabetes mellitus
Malignancy
Seizures
Methanol, ethanol, or ethylene glycol
Disorders associated with inborn errors of metabolism

Cardiovascular and septic shock, with resultant tissue hypoperfusion, are the most common causes of lactic acidosis.[14] Poor tissue perfusion and hypoxia influence enzymatic pyruvate and lactate metabolism to stimulate anaerobic glycolysis and to decrease lactate utilization. This leads to hyperlactatemia and lactic acidosis. The mortality rate of this type of lactic acidosis can be as high as 80% and correlates with the degree of hyperlactatemia.

Lactic acidosis associated with liver disease, toxins, and congenital enzyme deficiency can be caused by deranged oxidative metabolism or impaired lactate clearance.[2,3,6,14,17] The exact role of diabetes mellitus in the induction of lactic acidosis is not clear.[14,15] It may involve a decrease in pyruvate dehydrogenase activity, the enzyme responsible for pyruvate metabolism. Lactic acidosis in

neoplastic disease is uncommon and reported mostly in patients with myeloproliferative disorders. Leukocytes and neoplastic cells in general have high rates of glycolysis. In the case of a large tumor or tightly packed bone marrow, oxygenation can be decreased, favoring the accumulation of lactate. Lactic acidosis has been reported in patients with massive liver tumors, and it has been postulated that the liver uptake of lactate is decreased in these patients. Lactic acidosis associated with seizures is usually transient and occurs because of excessive muscle activity.[14]

A number of medications have been associated with the development of lactic acidosis.[11,14,18–27] Metformin (0.03 cases per 1,000 person-years) remains the most common medication associated with lactic acidosis.[19] The primary suspected mechanism for metformin-induced lactic acidosis is inhibition of liver gluconeogenesis as the result of its inhibitory effects on pyruvate carboxylase, which is necessary for the conversion of pyruvate to glucose.[15,19] Other possible pathways for metformin-associated lactic acidosis include a decrease in both hepatic intracellular pH and cardiac output, an increase in lactate production in the gut, and increased renal loss of bicarbonate.[19] Risk factors for metformin-induced lactic acidosis include impaired kidney function, liver disease, dehydration, advanced age, alcohol consumption, and supratherapeutic dosing. Metformin should be discontinued during periods of tissue hypoxia (eg, myocardial infarction, sepsis), for 3 days after contrast media has been administered or 2 days before general anesthesia administration. In the latter two cases, metformin should only be reinstituted when the patient's kidney function is stable.

The older nucleoside-analog reverse transcriptase inhibitors (NRTIs), particularly stavudine, have been associated with lactic acidosis (3.9 cases per 1,000 person-years).[20] The proposed mechanism of NRTI-induced lactic acidosis is the inhibition of the enzyme DNA polymerase gamma that is responsible for mitochondrial DNA synthesis.[18] Lactic acidosis has been rarely reported with tenofovir, lamivudine, and abacavir.

Linezolid impairs mitcochondrial function and has been rarely reported to cause lactic acidosis, usually after prolonged (more than or equal to 4 weeks) therapy.[21] The weight loss combination medication phentermine-topiramate (Qysmia®) has been reported to cause lactic acidosis.[22] Use of the Viekira Pak® (ombitasvir, paritaprevir, ritonavir, dasabuvir) was reported to cause lactic acidosis in patients without severe liver dysfunction when used to treat hepatitis C.[23]

Propylene glycol is commonly used as a solubilizing agent in IV drug preparations (eg, lorazepam, pentobarbital, phenytoin, trimethoprim/sulfamethoxazole) and is predominantly metabolized to lactic acid via the hepatic enzyme alcohol dehydrogenase.[24–26] The administration of large doses of propylene glycol, particularly to patients with impaired kidney or liver function, can lead to a lactic acidosis with an osmolar gap. Thus, serial measurement of the osmolar gap can be used to detect propylene glycol accumulation.[24,25]

Reports of the association between propofol and lactic acidosis were initially described in children.[27] This association is now recognized in adults and has come to be known as the propofol-related infusion syndrome. In addition to lactic acidosis, cardiac failure, rhabdomyolysis, and acute kidney injury have been observed primarily because of uncoupling of oxidative phosphorylation and impaired oxidation of free fatty acids. This syndrome is most frequently seen in patients receiving propofol at high doses (more than 5 mg/kg/hr) for more than 2 days.

Clinical Presentation

Chronic metabolic acidosis is usually not associated with severe acidemia and is relatively asymptomatic. The major manifestations are bone demineralization with the development of rickets in children and osteomalacia and osteopenia in adults.[6,28] In infants and children, chronic metabolic acidosis is associated with growth failure and short stature and can be associated with nonspecific symptoms including anorexia, nausea, weight loss, and muscle weakness.

Severe metabolic acidosis is usually associated with acute processes. The manifestations of severe acidemia (pH less than 7.20) involve the cardiovascular, respiratory, and central nervous system (CNS). Hyperventilation is often the first sign of metabolic acidosis. At a pH of 7.2, pulmonary ventilation increases approximately fourfold, and an eightfold increase has been noted at a pH of 7.[3,29] Respiratory compensation can occur as Kussmaul respirations— the deep, rapid respirations seen commonly in patients with diabetic ketoacidosis. In extremely severe acidosis (pH less than 6.8), CNS function is disrupted to such a degree that the respiratory center is depressed.

CNS depression correlates more closely with spinal fluid pH than with blood pH. For this reason, neurologic symptoms tend to occur more frequently and to a greater degree in patients with respiratory acidosis because the CO_2 accumulated in the respiratory form readily crosses the blood–brain barrier to cause acidosis

in the CNS.[4] Because of the slow penetration of administered bicarbonate into the CNS, the CNS pH fails to normalize as rapidly as blood pH. Therefore, patients continue to hyperventilate because of sustained CNS acidity, and severe respiratory alkalosis can occur. Sustained lowering of the $PaCO_2$ within 12 to 36 hours is to be anticipated during the correction of any metabolic acidosis.[4]

Systemic acidosis can cause peripheral arteriolar dilatation, characterized by flushing, a rapid heart rate, and wide pulse pressure. Initially, cardiac output can be increased, but as acidosis becomes more severe, myocardial contractility becomes impaired, and cardiac output decreases. The effects of vagal stimulation are also enhanced at pH levels lower than 7.1, probably as a consequence of inhibition of acetylcholinesterase. This increases the danger of vagally mediated bradycardia and heart block during acidosis.

GI symptoms of metabolic acidosis include loss of appetite, nausea, and vomiting. Severe acidosis (pH less than 7.1) interferes with carbohydrate metabolism and insulin utilization, and results in hyperglycemia. Metabolic acidosis alters potassium homeostasis and contributes to the development of hyperkalemia. The magnitude of the effect on serum potassium depends on the type of acidosis: Acidosis caused by mineral acids (eg, hydrochloric acid) is associated with a greater change in potassium levels than acidosis caused by organic acids (eg, lactic acidosis), in which the increase in potassium attributable to the acidosis per se is minimal.

Compensation

The patient's primary means to compensate for metabolic acidosis is to increase carbon dioxide excretion by increasing the respiratory rate. This results in a decrease in $PaCO_2$. This ventilatory compensation results from stimulation of the respiratory center by changes in cerebral bicarbonate concentration and pH.[1,29] For every 1 mEq/L (mmol/L) decrease in bicarbonate concentration below the average of 24, the $PaCO_2$ decreases by approximately 1 to 1.5 mm Hg (0.13-0.20 kPa) from the normal value of 40 mm Hg (5.3 kPa). General guidelines for the assessment and interpretation of acid–base disorders based on observed compensatory responses are presented in **Table 69-7**.

TABLE 69-7 Guidelines for Interpretation of Acid–Base Disorders Based on Compensatory Responses

Acidosis	Compensation
Metabolic	$PaCO_2$ (in mm Hg) should decrease by 1.3 times the fall in plasma [HCO_3^-] (in mEq/L or mmol/L)
Acute respiratory	The plasma [HCO_3^-] should increase by 0.1 times the increase in $PaCO_2 \pm 3$ (in mm Hg)
Chronic respiratory	The plasma [HCO_3^-] should increase by 0.35 times the increase in $PaCO_2 \pm 4$ (in mm Hg)
Alkalosis	**Compensation**
Metabolic	$PaCO_2$ (in mm Hg) should increase by 0.4-0.6 times the rise in plasma [HCO_3^-] (in mEq/L or mmol/L)
Acute respiratory	The plasma [HCO_3^-] should decrease by 0.2 times the decrease in $PaCO_2$ (in mm Hg), but usually not to <18 mEq/L (mmol/L)
Chronic respiratory	The plasma [HCO_3^-] should fall by 0.35 times the decrease in $PaCO_2$ (in mm Hg), but usually not to <14 mEq/L (mmol/L)

HCO_3^-, bicarbonate; $PaCO_2$, partial pressure of carbon dioxide from arterial blood; multiply values expressed in kPa by 7.519 to convert to mm Hg.

The anticipated $PaCO_2$ associated with a given bicarbonate concentration for patients with uncomplicated metabolic acidosis can be calculated as:[26]

$$PaCO_2 = (1.5 \times [HCO_3^-] + 8) \pm 2 \text{ for } PaCO_2 \text{ in mm Hg}$$

$$(PaCO_2 = (0.2 \times [HCO_3^-] + 1.1) \pm 0.3 \text{ for } PaCO_2 \text{ in kPa})$$

For example, 95% of patients with a plasma bicarbonate of 16 mEq/L (mmol/L) should have an arterial PCO_2 of 30 to 34 mm Hg (4.0-4.5 kPa). An observed arterial PCO_2 within this range is consistent with physiologic respiratory compensation for a metabolic acidosis and suggests that there is no respiratory disturbance. In contrast, if the PCO_2 is less than 30 mm Hg (4.0 kPa), a superimposed respiratory alkalosis can be present, whereas if the PCO_2 is greater than 34 mm Hg (4.5 kPa), a superimposed respiratory acidosis is likely present.

CLINICAL PRESENTATION

Metabolic Acidosis

General

- The patient usually is relatively asymptomatic if the acidosis is acute and mild. In those with severe acidemia (pH less than 7.15-7.20), the cardiovascular, respiratory, and CNS systems can be affected.

Symptoms

- The patient may complain of loss of appetite, nausea, and vomiting.

Signs

- Cardiac: Flushing, a rapid heart rate, wide pulse pressure, and an increase in cardiac output can be seen initially. This can be followed by a reduction in cardiac output, blood pressure, and liver and kidney blood flow.
- Cerebral: Obtundation or coma.
- Metabolic: Insulin resistance; increased protein degradation; increased metabolic demands.
- GI: Nausea, vomiting, loss of appetite.
- Respiratory: Dyspnea, hyperventilation with deep, rapid respirations is seen in those with severe acidosis.
- Chronic acidemia causes bone demineralization with the development of rickets in children and osteomalacia and osteopenia in adults.

Laboratory Tests

- Serum CO_2 is low. Hyperglycemia and hyperkalemia are common. Patients with a pH of less than 7.2 are deemed to have a severe acidosis.

TREATMENT

7 Asymptomatic patients with mild to moderate degrees of acidemia (plasma bicarbonate of 12-20 mEq/L [mmol/L]; pH 7.2-7.4) do not require emergent therapy. They can usually be managed with gradual correction of the acidemia, over a period of days to weeks, using oral sodium bicarbonate or other alkali preparations (**Table 69-8**). In all forms of chronic metabolic acidosis, primary therapy should be directed at treating the underlying disease state. GI pathology should be treated to reduce ongoing bicarbonate losses, and factors that

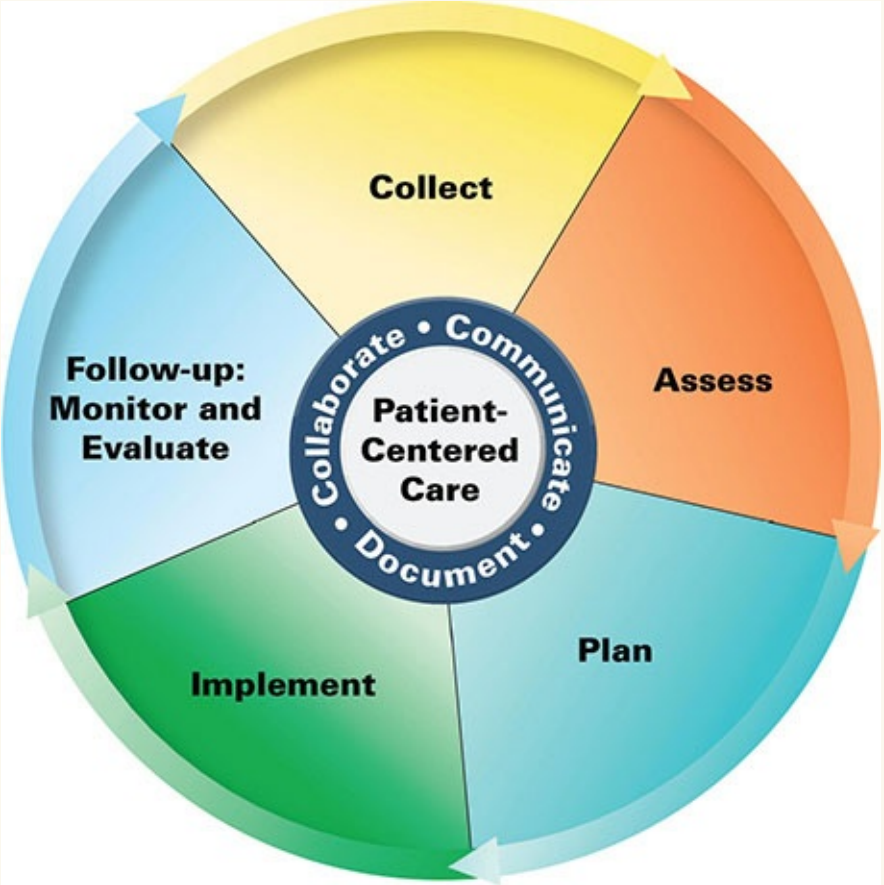
exacerbate RTA should be treated. If acidemia persists, alkali therapy should be instituted with the goal of normalization of blood pH. The loading dose (LD) of alkali to initially correct the acidemia can be calculated as follows:

TABLE 69-8 Therapeutic Alternatives for Oral Alkali Replacement

Generic Name	Trade Name(s)	Milliequivalents of Alkali	Dosage Form(s)	Comment
Shohl's solution (sodium citrate/ citric acid)	Bicitra (Willen)	1 mEq Na/mL; equivalent to 1 mEq bicarbonate	Solution (500 mg Na citrate, 334 mg citric acid/5 mL)	Citrate preparations increase absorption of aluminum
Sodium bicarbonate	Various (eg, Sodamint)	3.9 mEq bicarbonate/ tablet (325 mg)	325 mg tablet	Bicarbonate preparations can cause bloating because of CO_2 production
		7.8 mEq bicarbonate/ tablet (650 mg)	650 mg tablet	
	Baking soda (various)	60 mEq bicarbonate/tsp (5 g/tsp)	Powder	
Potassium citrate	Urocit-K (Mission)	5 mEq citrate/tablet	5 mEq tablet	Citrate preparations increase absorption of aluminum
Potassium bicarbonate/ potassium citrate	K-Lyte (Bristol)	25 mEq bicarbonate/ tablet	25 mEq tablet (effervescent)	Citrate preparations increase absorption of aluminum, while bicarbonate preparations can cause bloating
	K-Lyte DS (Bristol)	50 mEq bicarbonate/ tablet (double strength)	50 mEq tablet (effervescent)	
Potassium citrate/ citric acid	Polycitra-K (Willen)	2 mEq K/mL; equivalent to 2 mEq bicarbonate	Solution (1,100 mg K citrate, 334 mg citric acid/5 mL)	Citrate preparations increase absorption of aluminum
		30 mEq bicarbonate/unit dose packet	Crystals for reconstitution (3,300 mg K citrate, 1,002 mg citric acid/unit dose packet)	
Sodium citrate/ potassium citrate/ citric acid	Polycitra (Willen) Polycitra-LC (Willen)	1 mEq K, 1 mEq Na/mL; equivalent to 2 mEq bicarbonate	Syrup (Polycitra) solution (Polycitra-LC) (both contain 550 mg K citrate, 500 mg Na citrate, 334 mg citric acid/5 mL)	Citrate preparations increase absorption of aluminum

$$\text{LD (mEq or mmol/L)} = (V_D\, HCO_3^- \times \text{body weight [BW]}) \times (\text{desired } [HCO_3^-] - \text{current } [HCO_3^-])$$

where V_D is the volume of distribution of bicarbonate.[6]



Patient Care Process for Acid–Base Disorders

Collect

- Patient characteristics (eg, age, sex, pregnant)
- Patient medical history (eg, prior acid–base disorder, chronic lung or kidney condition, diabetes)
- Current medications, including intravenous fluids (see Tables 69-5, 69-6, 69-10, 69-11, and 69-12)
- Social history (alcohol, potential for toxic ingestion)
- Objective data
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2-saturation
  - Labs including arterial blood gas (ABG), serum electrolytes (including serum CO_2), serum creatinine (SCr), serum osmolality, serum lactate,

blood glucose, urine chloride

- Current fraction of inspired oxygen (FiO_2)

Assess

- [HCO_3^-] on ABG and electrolytes to verify accuracy
- Serum anion gap (SAG)
- Presence of acidemia (pH < 7.35) or alkalemia (pH > 7.45) (see Figure 69-3 and Table 69-4)
- Presence of respiratory disturbance (alteration in $PaCO_2$) or metabolic disturbance (alteration in HCO_3^-)
- Compensatory response (Table 69-7)
- Change in [Cl^-] with change in [Na^+]
- Presence of elevated SAG metabolic acidosis (Table 69-5)
  - Presence of elevated serum osmolar gap and/or serum lactate
- Presence of metabolic alkalosis (Table 69-10)
  - Presence of urine chloride <10 mEq/L (mmol/L) or >20 mEq/L (mmol/L)
- Presence of respiratory acid–base disorder (see Tables 69-11, 69-12, 69-13)

Plan*

- Identification and removal (when possible) of potential cause(s) for the acid–base disorder
- Fluid, electrolyte, or drug therapy (see Tables 69-8 and 69-9, and Figure 69-4)
  - Monitoring parameters may include a repeat RR, O_2-saturation, ABG, and serum electrolytes; repeat serum creatinine (SCr), serum osmolality, serum lactate, blood glucose, and/or urine chloride
- Referals to other providers when appropriate (eg, nephrologist, pulmonologist)

Implement*

- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug-specific information, medication administration

instructions) when the acid–base disorder is chronic
- Schedule follow-up when appropriate

Follow-up: Monitor and Evaluate

- Resolution of acid–base disorder symptoms
- Presence of adverse events (if acid–base disorder treated with medication)
- Patient adherence to treatment plan using multiple sources of information

* *Collaborate with patient, caregivers, and other healthcare professionals.*

For a 60-kg patient with a serum bicarbonate of 15 mEq/L (mmol/L), the LD is calculated thus:

$$\begin{aligned} \text{LD (mEq)} &= (0.5\ \text{L/kg} \times 60\ \text{kg}) \times (24\ \text{mEq/L} - 15\ \text{mEq/L}) \\ &= 30\ \text{L} \times 9\ \text{mEq/L} \\ &= 270\ \text{mEq/L (mmol/L)} \end{aligned}$$

The calculated LD of alkali should be administered over several days to avoid volume overload from the accompanying sodium load. For this scenario, a regimen of 60 to 70 mEq (mmol) three times a day for 3 to 5 days should result in an increase in HCO_3^- levels toward normal. In addition to the calculated LD, supplemental alkali must also be provided to replace ongoing losses, which can be approximated to be 2 mEq/kg (mmol/kg) per day or 40 mEq (mmol) three times a day. In patients with associated volume depletion, bicarbonate replacement can be provided simultaneous with volume resuscitation by substituting bicarbonate for chloride in IV crystalloid solutions.

In patients with chronic metabolic acidosis because of GI bicarbonate losses, maintenance therapy should provide sufficient alkali to replace ongoing bicarbonate losses. The magnitude of this replacement is variable and can be substantial (more than 10 mEq/kg [mmol/kg] per day). In addition, associated losses of other electrolytes, such as potassium and magnesium, may need to be replaced (see Chapter 68, “Potassium and Magnesium Homeostasis”).

Proximal (type II) RTA is a bicarbonate-wasting disorder that requires the administration of large maintenance doses of alkali (10-15 mEq/kg [mmol/kg] per day). As alkali replacement raises the serum bicarbonate concentration toward normal, the proximal tubule’s capacity to reabsorb bicarbonate is

overwhelmed, and renal bicarbonate wasting increases. In children, aggressive therapy of proximal RTA is necessary to avoid growth retardation and osteopenia. Because this is generally a mild, nonprogressive acidosis in adults, the benefit of alkali therapy is frequently outweighed by the risks of increased potassium wasting. In patients with classic distal (type I) RTA, maintenance therapy usually requires only enough alkali to buffer the amount of acid generated from dietary intake and metabolism. This usually approximates 1 to 3 mEq/kg/day (mmol/kg/day).

8 After initial potassium deficits are replaced, ongoing potassium supplementation may not be required, as renal potassium losses decrease following initiation of appropriate alkali therapy. The use of potassium alkali salts can, however, be desirable in patients with associated nephrolithiasis, because sodium salts can increase urinary calcium excretion.

The metabolic acidosis associated with hyperkalemic distal (type IV) RTA with hyporeninemic-hypoaldosteronism that is often seen in patients with diabetes mellitus can be corrected by the treatment of hyperkalemia alone (see Chapter 68). The use of supplemental alkali (1-2 mEq/kg [mmol/kg] per day) to increase sodium intake and stimulate distal tubular potassium secretion can be beneficial. A minority of patients require the administration of pharmacologic amounts of fludrocortisone.[6] Type IV RTA resulting from a generalized distal tubular disorder often responds to low doses of alkali (1.5-2.0 mEq/kg [mmol/kg] per day).[6,12] Corrections of the acidosis along with modest dietary potassium restriction (to 1 mEq/kg [mmol/kg] per day) will often result in the maintenance of serum potassium concentrations of 5 mEq/L (mmol/L) or less.

Acute Severe Metabolic Acidosis

9 The management of life-threatening acute metabolic acidosis (plasma bicarbonate of 8 mEq/L [mmol/L] and pH less than 7.20) is dependent on the underlying cause and the patient's cardiovascular status. In some cases, patients will require emergent hemodialysis therapy (see Chapter 62). Patients with hyperchloremic acidosis (eg, diarrhea-induced) are unable to regenerate bicarbonate, and the generation of new bicarbonate by the kidneys can require several days before one can observe a meaningful change in their status.[6] Thus IV alkali therapy is often required for these patients.

Although conventional wisdom recommends the use of alkali replacement in patients with severe acidemia because of the deleterious effects of acidemia on circulatory function,[2,6,15] studies have not demonstrated that its administration

improves patient outcomes.[30,31] Alkali therapies may either improve or worsen clinically relevant endpoints such as $[H^+]$, $PaCO_2$, lactate concentrations, and cardiac output. The specific patient populations most likely to benefit or be harmed from alkalinizing therapy are presented in **Table 69-9**.

TABLE 69-9 Patient Populations Likely to Benefit or Suffer from Alkalinizing Therapy

Patients with Potential for Benefit	Patients with Potential for Harm
Distal (type I) renal tubular acidosis	Hypernatremia
Severe hypochloremic metabolic acidosis secondary to diarrhea or surgical diversion	Hypervolemia
Specific poisonings and intoxications (eg, salicylate overdose with metabolic acidosis)	Acute kidney injury
	Congestive heart failure
	Pulmonary disease resulting in decreased ventilation
	Acute lung injury where a lung protective ventilation strategy is used
	Diabetic ketoacidosis

There are several therapeutic alternatives available for the acute correction of severe metabolic acidosis. Sodium acetate, sodium citrate, and sodium lactate are unreliable sources of alkali because their alkalinizing effect is dependent on their oxidative conversion to bicarbonate by the liver. This process is often impaired in critically ill patients, especially those with hepatic disease or circulatory failure. Although sodium bicarbonate is the most widely used IV alkalotic agent,[4] several studies suggest that it is frequently ineffective and can actually be deleterious, especially in patients with lactic acidosis.[14,30,31] Among the two remaining alternatives, dichloroacetate (DCA) is investigational and not available in most clinical settings. Tromethamine, or THAM, is a carbon dioxide–consuming, commercially available solution that buffers respiratory as well as metabolic acids but was discontinued by its sole US manufacturer in 2016.

Sodium Bicarbonate

While sodium bicarbonate administration provides fluid and electrolyte replacement and increases arterial pH, neither animal nor clinical studies demonstrate an improvement in cardiac function, organ perfusion, or intracellular pH.[15,30–34] One recent, multicenter, open-label, randomized, controlled trial compared the administration of a 4.2% infusion of sodium bicarbonate (125-250 mL in 30 minutes; up to 1000 mL in 24 hours) to maintain an arterial pH above 7.30 (versus no sodium bicarbonate infusion) in critically ill adults with severe metabolic acidemia (arterial pH ≤7.20, $PaCO_2$ ≤45 mm Hg [6 kPa], and serum bicarbonate ≤20 mEq/L [mmol/L]) and found that sodium bicarbonate administration did not reduce mortality at 28 days.[54] In a pre-specified secondary analysis of the 47% of study patients with baseline acute kidney injury, mortality at 28 days was reduced. However, future research is required to evaluate the role of sodium bicarbonate in patients with severe metabolic acidemia and acute kidney injury given the potential role of renal replacement therapy in this setting. In addition, sodium bicarbonate administration can actually have paradoxical adverse effects on intracellular pH. When bicarbonate is given by IV infusion, the carbon dioxide generated diffuses more readily than bicarbonate across cell membranes and into cerebrospinal fluid. Therefore, the intracellular pH can actually be decreased by administration of bicarbonate.[6,32,35,36]

Excessive sodium bicarbonate administration can result in (a) a shift of the oxyhemoglobin saturation curve to the left, thereby impairing oxygen release from hemoglobin to tissues; (b) sodium and water overload, with subsequent pulmonary congestion and hypernatremia; (c) paradoxical tissue acidosis as a result of the production of CO_2 that freely diffuses into myocardial and cerebral cells;[36] and (d) decreased ionized calcium with a resultant decrease in myocardial contractility. If there is an endogenous source of bicarbonate, such as can occur in the case of ketoacidosis or lactic acidosis, a bicarbonate "overshoot" can develop because the ketoacids (acetoacetic acid and β-hydroxybutyric acid) or lactic acid are converted in the liver to bicarbonate once the underlying cause of acidosis is corrected.[10,11,17] Alkalosis can also result if too much sodium bicarbonate is administered too quickly.

If IV sodium bicarbonate is used, one must be mindful that the goals are to increase, not normalize, pH (to approximately 7.20) and plasma bicarbonate (to 8-10 mEq/L [mmol/L]). There is no calculative method that will assure attainment of these goals with a given dose of sodium bicarbonate because of the multiplicity of competing processes that can affect acid–base status (eg, vomiting, potential increases in endogenous acid production, and kidney disease)

and the marked variability in the volume of distribution of bicarbonate (50% of body weight in patients with mild acidosis to approximately 100% in those with severe acidosis).[6,34,35] The dose of sodium bicarbonate may be calculated using a distribution volume of 50% of body weight for all patients to avoid overtreatment.[34] The total dose calculated as described previously in the RTA section should be administered as an infusion over one-half to several hours. Follow-up monitoring of ABGs, beginning no sooner than 30 minutes after the end of the infusion, should be used to guide further therapeutic decisions.

Bicarbonate therapy is generally not necessary for patients with cardiac arrest, even if the initial arrest was unmonitored. The American Heart Association's Advanced Cardiac Life Support (ACLS) provider manual states that sodium bicarbonate is not useful or effective during resuscitation in hypoxic patients with lactic acidosis.[34] Additionally, sodium bicarbonate is considered to be not useful or effective in those who are undergoing prolonged resuscitation with effective ventilation.[6,30] Furthermore, if sodium bicarbonate is used, it should be used only after defibrillation, cardiac compression, support of ventilation including intubation, and drug therapies such as epinephrine and antiarrhythmic agents have been employed.[34] The initial dose of sodium bicarbonate in this situation is (1 mEq/kg [mmol/kg]) administered by rapid, direct IV injection.[34] Subsequent doses of sodium bicarbonate should be based on measurements of arterial blood pH and $PaCO_2$ given the propensity for it to cause alkalemia.[29,30]

Tromethamine

THAM, no longer available in the United States, is a highly alkaline, sodium-free organic amine that acts as a proton acceptor to prevent or correct acidosis.[6,37] THAM combines with hydrogen ions from carbonic acid to form bicarbonate and a cationic buffer, and also acts as an osmotic diuretic to increase urine flow, urine pH, and the excretion of fixed acids, CO_2, and electrolytes.[35,37] It should be administered via a central line and used with extreme caution in patients with severe liver or kidney failure.

Dichloroacetate

DCA, another investigational agent, facilitates aerobic lactate metabolism by stimulating the activity of lactate dehydrogenase, thus reversing hyperlactatemia and elevating blood pH.[38–40] DCA, when compared to conventional management in controlled studies, however, has not been shown to improve hemodynamic

parameters or clinical outcomes.[38–40] DCA can cause mild drowsiness and peripheral neuropathy that can be ameliorated or prevented with thiamine supplementation.[35] The future role of DCA in the management of metabolic acidosis, particularly lactic acidosis, remains to be clarified.[14]

Metabolic Alkalosis

Pathophysiology

Metabolic alkalosis is a simple acid–base disorder that presents as alkalemia (increased arterial pH) with an increase in plasma bicarbonate.[1,2] It is an extremely common entity in hospitalized patients with acid–base disturbances. Under normal circumstances, the kidney is readily able to excrete an alkali load. Thus, evaluation of patients with metabolic alkalosis must consider two separate issues: (a) the initial process that generates the metabolic alkalosis; and (b) alterations in kidney function that maintain the alkalemic state.[41,42]

Metabolic alkalosis is predominantly maintained because of an abnormality in kidney function. Normally, the kidneys are capable of excreting all of the excess bicarbonate presented to them, even during periods of increased bicarbonate loads.[2] As the serum bicarbonate concentration increases, the filtered bicarbonate load exceeds the maximal rate for bicarbonate reabsorption, and the excess bicarbonate is excreted in the urine. Under normal circumstances, the excess bicarbonate is rapidly excreted, and metabolic alkalosis does not occur or is corrected in a matter of hours.[41]

10 Bicarbonate excretion becomes impaired via several mechanisms, which collectively contribute to the maintenance phase of metabolic alkalosis.[41] The generation of metabolic alkalosis can also result from excessive losses of hydrogen ions from the kidneys or stomach or from a gain secondary to the ingestion or administration of bicarbonate-rich fluids. In general, these mechanisms can be divided into volume-mediated processes (sodium chloride–responsive), volume-independent processes (sodium chloride–resistant), or not classified by either (Table 69-10).[1,3] Patients with a sodium chloride–responsive metabolic alkalosis will have a urinary chloride concentration <10 mEq/L (mmol/L) and patients with a sodium chloride–resistant alkalosis will have a urinary chloride concentration > 20 mEq/L (mmol/L).

TABLE 69-10 Causes of Metabolic Alkalosis Differentiated on the Basis of Their Responsiveness to Sodium Chloride

Sodium chloride–responsive (urinary chloride concentration <10 mEq/L [mmol/L])
GI disorders
Vomiting
Gastric drainage
Villous adenoma of the colon
Chloride diarrhea
Diuretic therapy
Correction of chronic hypercapnia
Cystic fibrosis
Excessive bicarbonate therapy of an organic acidosis
Mild/moderate potassium deficiency
Sodium chloride–resistant (urinary chloride concentration >20 mEq/L [mmol/L])
Excess mineralocorticoid activity
Hyperaldosteronism
Cushing syndrome
Bartter syndrome (sodium transport defect in loop of Henle)
Gitelman syndrome (sodium transport defect in collecting duct)
Excessive black licorice intake
Profound potassium depletion
Magnesium deficiency
Liddle syndrome (enhanced sodium reabsorption in collecting duct)
Estrogen therapy
Unclassified
Alkali administration
Milk-alkali syndrome
Massive blood or plasma protein fraction transfusion
Nonparathyroid hypercalcemia
Carbohydrate refeeding after starvation
Large doses of penicillin

11 **Sodium Chloride–Responsive** Gastric juice, rich in chloride and hydrogen ions, is secreted at a rate of less than 50 mL/hr in the basal state, but can increase up to fivefold with stimulation.[3] In the gastric parietal cells, the hydrogen ion and bicarbonate are generated from CO_2 and water.[3,42,43] The hydrogen ion is secreted into gastric fluid, and the bicarbonate is retained in the ECF. Normally, an amount of bicarbonate equal to the bicarbonate generated in the stomach is eliminated in the alkaline pancreatic and small-bowel secretions, maintaining hydrogen ion balance. With vomiting and nasogastric suctioning, the hydrogen ion is lost externally and metabolic alkalosis results. Diarrhea, as seen with secretory villous adenomas and other secretory diarrheas, often results in excessive GI losses of chloride-rich, bicarbonate-poor fluid, and thus leads to the

generation of metabolic alkalosis.

12 Diuretic agents acting on the thick ascending limb of the loop of Henle (eg, furosemide, bumetanide, and torsemide) and distal convoluted tubule (eg, thiazides) have most commonly been associated with the generation of metabolic alkalosis.[3,44] These agents promote the excretion of sodium and potassium almost exclusively in association with chloride, without a proportionate increase in bicarbonate excretion. Collecting duct hydrogen ion secretion is stimulated directly by the increased luminal flow rate and sodium delivery, and indirectly by intravascular volume contraction, which results in secondary hyperaldosteronism. Renal ammoniagenesis can also be stimulated by concomitant hypokalemia, further augmenting net acid excretion.

Sodium Chloride–Resistant Mineralocorticoid excess plays a significant role in the maintenance of metabolic alkalosis given that it stimulates collecting duct hydrogen ion secretion. Elevated mineralocorticoid levels directly stimulate collecting duct hydrogen ion secretion, indirectly increase ammoniagenesis by causing hypokalemia, and is associated with both acute and chronic causes including profound potassium deficiency, magnesium deficiency, and estrogen therapy.[1,3,40–43,45]

Unclassified Metabolic alkalosis can also be generated by the gain of exogenous alkali. This can be seen as a result of bicarbonate administration or from the infusion of organic anions that are metabolized to bicarbonate, such as acetate, lactate, and citrate. The milk-alkali syndrome was historically a common cause of metabolic alkalosis in patients with peptic ulcer disease secondary to the ingestion of large quantities of milk products and antacids. Administration of high doses of penicillins (eg, ticarcillin) can produce metabolic alkalosis because they act as nonreabsorbable anions, which enhances the secretion of potassium and hydrogen ions and results in hypokalemia and metabolic alkalosis.[11]

Clinical Presentation

There are no unique signs or symptoms associated with mild-to- moderate metabolic alkalosis, but patients may complain of symptoms related to the underlying cause of the disorder (eg, muscle weakness with hypokalemia or postural dizziness with volume depletion).[41,42] They may have a history of vomiting, gastric drainage, or diuretic use, all of which contribute to the development of metabolic alkalosis. Severe alkalemia (blood pH more than 7.60) has been associated with cardiac arrhythmias, particularly in patients with heart

disease, hyperventilation, and hypoxemia.[41] Neuromuscular irritability can be present, with signs of tetany or hyperactive reflexes, possibly caused by the decreased ionized calcium concentration that occurs secondary to the increase in pH. This decrease in ionized calcium may be caused by a conformational change in the albumin molecules to which the calcium is bound, resulting in increased binding, or by decreased competition from hydrogen ions for binding sites on the albumin molecule. Mental confusion, muscle cramping, and paresthesia can also occur. Lastly, patients will be more difficult to liberate from mechanical ventilation.

Compensation

The respiratory response to metabolic alkalosis is hypoventilation, which results in an increased $PaCO_2$. Respiratory compensation is initiated within hours when the central and peripheral chemoreceptors sense an increase in pH. The $PaCO_2$ increases 6 to 7 mm Hg (0.8-0.9 kPa) for each 10 mEq/L (mmol/L) increase in bicarbonate, up to a $PaCO_2$ of approximately 50 to 60 mm Hg (6.7-8.0 kPa) (see Table 69-7) before hypoxia sensors react to prevent further hypoventilation.[1,41] If the $PaCO_2$ is normal or less than normal, one should consider the presence of a superimposed respiratory alkalosis, which can be secondary to fever, gram-negative sepsis, or pain.

TREATMENT

Because the body tolerates alkalemia far less well than acidemia, treatment of metabolic alkalosis is nearly always required and should be aimed at correcting the factor(s) responsible for the maintenance of the alkalosis.[41] For example, vomiting should be treated with antiemetics; gastric losses of hydrogen ions during nasogastric suction can be modulated by giving histamine blockers such as ranitidine or proton pump inhibitors such as omeprazole, and reducing or discontinuing diuretic therapy.[41,46] Metabolic alkalosis will persist until the renal mechanism responsible for maintaining the disorder is corrected, despite the fact that the original cause of the elevated plasma bicarbonate may have resolved. For example, hypovolemia should be treated with sodium chloride to allow excretion of bicarbonate by the kidney. However, patients with severely compromised cardiovascular function may not be able to tolerate this therapeutic approach. In situations such as this and/or the presence of life-threatening

alkalosis, some have advocated reduction in pH by control of ventilation.[41] Although controlled hypoventilation, sometimes using inspired CO_2 with supplemental oxygen to prevent hypoxia, can be lifesaving,[2] this approach is not universally accepted.[41] Therapy for metabolic alkalosis can be conceptualized on the basis of the sodium chloride responsiveness of the disorders (**Fig. 69-4**).

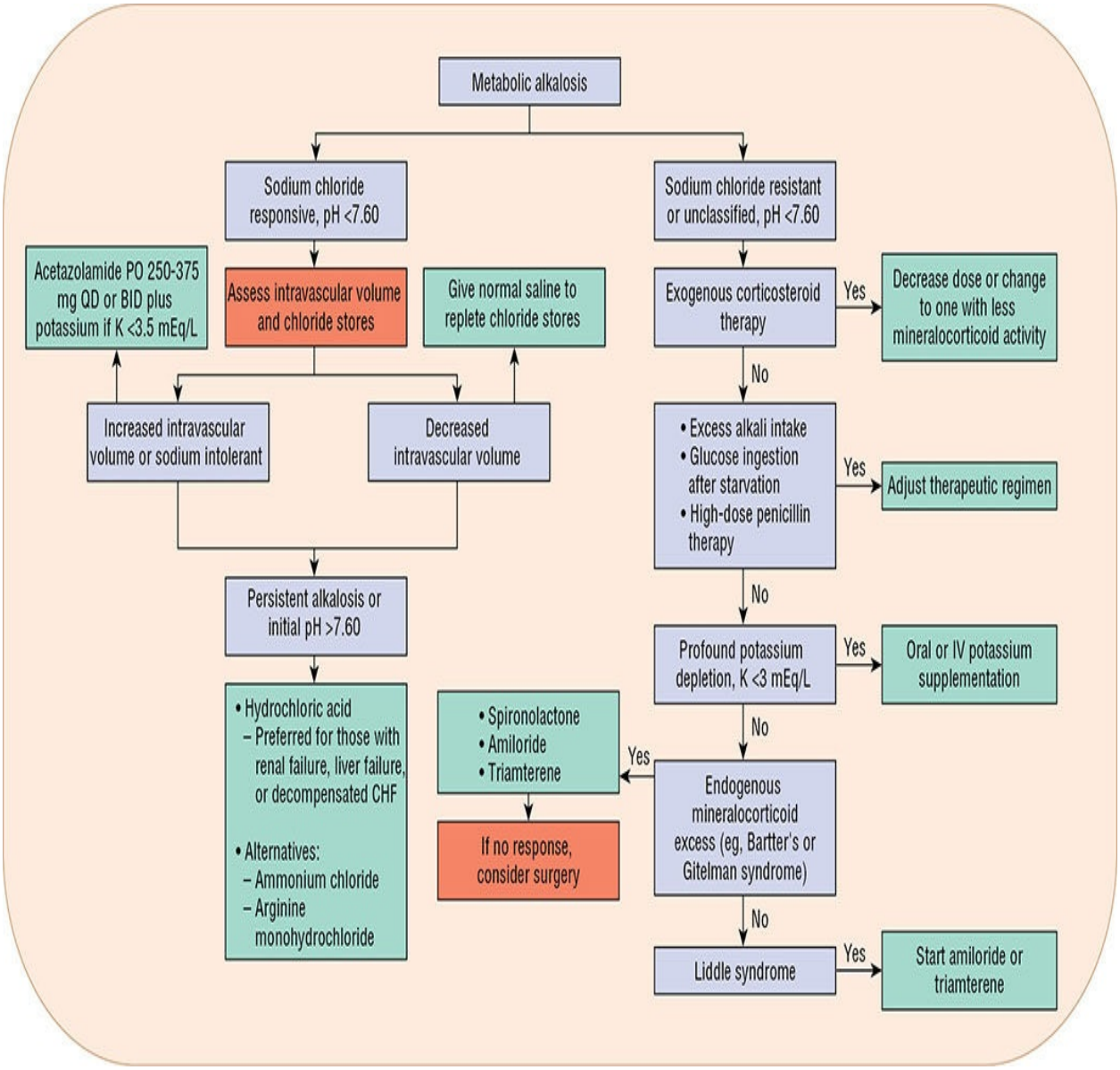


FIGURE 69-4 Treatment algorithm for patients with primary metabolic alkalosis. (BID, twice daily; CHF, chronic heart failure; K, potassium [serum potassium in mEq/L is numerically equivalent to mmol/L]; PO, orally; QD, every day.)

Sodium Chloride–Responsive Metabolic Alkalosis

Sodium chloride–responsive disorders usually result from volume depletion and chloride loss, which can accompany severe vomiting, prolonged nasogastric suction, and diuretic therapy. Initially, therapy is directed at expanding intravascular volume and replenishing chloride stores. Sodium chloride– and potassium chloride–containing solutions should be administered to patients who can tolerate the volume load.[2,41] Patients with metabolic alkalosis who are volume overloaded or intolerant to volume administration because of congestive heart failure can benefit from the carbonic anhydrase inhibitor acetazolamide. This agent inhibits the action of carbonic anhydrase, thereby inhibiting renal bicarbonate reabsorption. Unfortunately, it also increases the renal losses of potassium and phosphate. Administration of acetazolamide (250-375 mg once or twice daily) can promote a sufficient bicarbonate diuresis and return the pH toward normal.[47] However, because the clinical effectiveness of the drug declines as the HCO_3^- concentration decreases, only rarely will this approach fully correct the alkolosis.[41] Among mechanically ventilated chronic obstructive pulmonary disease patients having metabolic alkalosis, administration of acetazolamide 500-1000 mg twice daily (initiated within 48 hours of ICU admission and continued to ICU discharge) appears to reduce the degree of alkalosis while not affecting duration of mechanical ventilation or any other clinically relevant outcome.[48]

Acidifying agents including hydrochloric acid, ammonium chloride, and arginine monohydrochloride can be used to treat severe (pH more than 7.6) symptomatic metabolic alkalosis.[49,50] In general, this management is reserved for patients who are unresponsive to conventional fluid and electrolyte management or who are unable to tolerate the requisite volume load because of decompensated congestive heart failure or advanced kidney disease.[49] Alternatively, hemodialysis using a low-bicarbonate dialysate can be used for the rapid correction of metabolic alkalosis.

Hydrochloric Acid

Hydrochloric acid is usually infused IV via a large central vein as a 0.1 to 0.25 N HCl solution in either 5% dextrose or normal saline, although sterile water has also been used. Extemporaneously prepared solutions can be made by adding 100 to 250 mEq (mmol) of HCl through a 0.22-mm filter into a glass container of saline or dextrose. Hydrochloric acid can also be added to parenteral nutrient solutions and administered via a central line without serious degradation of

proteins.[35] The rate of infusion should be 100 to 125 mL/hr (10-25 mEq/h [mmol/h]), with frequent monitoring of ABGs. To prevent overcorrection, the infusion should be stopped when the arterial pH decreases to 7.50.[49]

The dose of hydrochloric acid can be based on an estimate of the total body chloride deficit:[35]

$$\text{Dose HCl (in mEq or mmol)} = [0.2\ \text{L/kg} \times \text{BW (in kg)}] \times [103 - \text{observed serum chloride}]$$

where the estimated chloride space is 0.2 times the body weight, and the average serum chloride is 103 mEq/L (mmol/L). Alternatively, the dose can be calculated based on the estimated base deficit:[29]

$$\text{Dose HCl (in mEq or mmol)} = [0.5\ \text{L/kg} \times \text{BW (in kg)}] \times (\text{desired } [HCO_3^-] - \text{observed } [HCO_3^-])$$

The dose of hydrochloric acid is usually infused IV over 12 to 24 hours.[35] A severe transient respiratory acidosis can occur if the hydrochloric acid is infused too quickly because of a slower reduction of the elevated bicarbonate concentration in the cerebrospinal fluid than in the ECF. Improvement is usually seen within 24 hours of initiating therapy. ABGs and serum electrolytes should be drawn every 4 to 8 hours to evaluate and adjust therapy.

Ammonium Chloride

Ammonium chloride has a limited role in the treatment of metabolic alkalosis. The liver converts ammonium chloride (NH_4Cl) to urea and free hydrochloric acid:[35]

$$2NH_4Cl + 2HCO_3^- \rightarrow CO(NH_2)_2 + CO_2 + 3H_2O + 2Cl^-$$

The dose of ammonium chloride can be calculated on the basis of the chloride deficit using the same method as for HCl and assuming that 20 g ammonium chloride will provide 374 mEq (mmol) of H^+. However, only one half of the calculated dose of ammonium chloride should be administered so as to avoid ammonia toxicity. Ammonium chloride is available as a 26.75% solution containing 100 mEq (mmol) of H^+ in 20 mL, which should be further diluted prior to administration. A dilute solution can be prepared by adding 20 mL of

ammonium chloride to 500 mL of normal saline and infusing the solution at a rate of no more than 1 mEq/min (mmol/min). Improvement in metabolic status is usually seen within 24 hours. CNS toxicity, marked by confusion, irritability, seizures, and coma, has been associated with more rapid rates of administration. Ammonium chloride must be administered cautiously to patients with impaired kidney or hepatic function. In patients with impaired hepatic function, decreased conversion of ammonia to urea can result in increased ammonia levels and worsened encephalopathy. In patients with kidney disease, the increased urea synthesis can exacerbate uremic symptoms.[35,42]

Arginine Monohydrochloride

Arginine monohydrochloride at a dose of 10 g/hr given IV has been used to treat metabolic alkalosis, although it was never FDA-approved for this purpose.[35] Like ammonium chloride, arginine must undergo metabolism by the liver to produce hydrogen ions, with a conversion of 100 g to 475 mEq (mmol) of H^+. Unlike ammonium chloride, arginine combines with ammonia in the body to synthesize urea; thus it can be used in patients with relative hepatic insufficiency. Patients with kidney disease should not receive arginine monohydrochloride because it can significantly elevate blood urea nitrogen and is associated with severe hyperkalemia.[35,42] The increase in potassium is caused by arginine-induced shifts of potassium from the intracellular to the extracellular space. One recent study of critically ill children with metabolic alkalosis resistant to standard treatment practices found that acetazolamide was more efficacious in resolving the alkalosis than arginine.[50]

Sodium Chloride–Resistant Metabolic Alkalosis

13 Management of these disorders usually consists of treatment of the underlying cause of the mineralocorticoid excess. For patients taking a corticosteroid, a dosage reduction or a switch to a corticosteroid with less mineralocorticoid activity (eg, methylprednisolone) should be considered. Patients with an endogenous source of excess mineralocorticoid activity can require surgery or the administration of spironolactone, amiloride, or triamterene.[2,16,42]

Spironolactone is a competitive antagonist of the mineralocorticoid receptor. Amiloride and triamterene are potassium-sparing diuretics that inhibit the epithelial sodium channel in the distal convoluted tubule and collecting duct. All three agents inhibit aldosterone-stimulated sodium reabsorption in the collecting

duct. In addition, spironolactone directly inhibits aldosterone stimulation of the hydrogen ion secretory pump. Thus, most patients with mineralocorticoid excess, including Bartter and Gitelman syndromes, respond to therapy with these agents.[42] Liddle syndrome, which is a form of pseudohypoaldosteronism caused by overactivity of the epithelial sodium channel, is not responsive to spironolactone but can be treated with either amiloride or triamterene. Although experience is limited, some patients with Bartter and Gitelman syndromes may respond to NSAIDs or ACE inhibitors.[51,52] Finally, aggressive potassium repletion can correct the alkalosis in those who have not responded to the approaches outlined above (see Chapter 68).

RESPIRATORY ACID–BASE DISORDERS

As with the metabolic acid–base disturbances, there are two cardinal respiratory acid–base disturbances: respiratory acidosis and respiratory alkalosis. These disorders are generated by a primary alteration in CO_2 excretion, which changes the concentration of CO_2, and therefore the carbonic acid concentration in body fluids.[1,53] A primary reduction in $PaCO_2$ causes an increase in pH (respiratory alkalosis), and a primary increase in $PaCO_2$ causes a decrease in pH (respiratory acidosis). Unlike the metabolic disturbances, for which respiratory compensation is rapid, metabolic compensation for the respiratory disturbances is slow. Hence, these disturbances can be further divided into acute disorders, with a duration of minutes to hours, and where metabolic compensation has yet to occur, and chronic disorders that have been present long enough for metabolic compensation to be complete.

Respiratory Alkalosis

Respiratory alkalosis is characterized by a primary decrease in $PaCO_2$ that leads to an elevation in pH. The $PaCO_2$ decreases when the excretion of CO_2 by the lungs exceeds the metabolic production of CO_2. It is the most frequently encountered acid–base disorder, occurring physiologically in normal pregnancy and in persons living at high altitudes.[1] Respiratory alkalosis also occurs frequently among hospitalized patients (**Table 69-11**).

TABLE 69-11 Causes of Respiratory Alkalosis

Central stimulation of respiration
Anxiety
Pain
Fever
Brain tumors, vascular accidents
Head trauma
Pregnancy
Progesterone
Catecholamines, theophylline, nicotine
Salicylates
Hypoxemia or tissue hypoxemia
High altitude
Decreased $PaCO_2$
Pneumonia
Pulmonary edema
Severe anemia
Peripheral stimulation of respiration
Pulmonary emboli
Asthma

$PaCO_2$, partial pressure of carbon dioxide from arterial blood.

Pathophysiology

A decrease in $PaCO_2$ occurs when ventilatory excretion exceeds metabolic production. Because endogenous production of CO_2 is relatively constant, negative CO_2 balance is primarily caused by an increase in ventilatory excretion of CO_2 (hyperventilation). The metabolic production of CO_2, however, can be increased during periods of stress or with excess carbohydrate administration (eg, parenteral nutrition). Hyperventilation can develop from an increase in neurochemical stimulation via either central or peripheral mechanisms, or by the result of voluntary or mechanical (iatrogenic) hyperventilation.

A decrease in $PaCO_2$ can occur in patients with cardiogenic, hypovolemic, or septic shock because oxygen delivery to the carotid and aortic chemoreceptors is reduced. This relative deficit in PaO_2 stimulates an increase in ventilation. The hyperventilation in sepsis is also mediated via a central mechanism. Hyperventilation-induced respiratory alkalosis with an elevation in cardiac index and hypotension without peripheral vasoconstriction can therefore be an early sign of sepsis.

Clinical Presentation

Although most patients are asymptomatic, respiratory alkalosis can cause adverse neuromuscular, cardiovascular, and GI effects.[2,3,53] During periods of decreased $PaCO_2$, there is a decrease in cerebral blood flow, which can be responsible for symptoms of light-headedness, confusion, decreased intellectual functioning, syncope, and seizures. Nausea and vomiting can occur, probably as a result of cerebral hypoxia. In severe respiratory alkalosis, cardiac arrhythmias can occur because of sensitization of the myocardium to the arrhythmogenic effects of circulating catecholamines.[2,33] Acute respiratory alkalosis has no effect on blood pressure or cardiac output in awake individuals. Anesthetized patients, however, can experience a decrease in both cardiac output and blood pressure, possibly owing to the lack of a tachycardic response.[33]

The concentration of serum electrolytes can also be altered secondary to the development of respiratory alkalosis. The serum chloride concentration is usually slightly increased, and serum potassium concentration can be slightly decreased. Clinically significant hypokalemia can be a consequence of extreme respiratory alkalosis, although the effect is usually very small or negligible.[2,33] Serum phosphorus concentration can decrease by as much as 1.5 to 2.0 mg/dL (0.48-0.65 mmol/L) because of the shift of inorganic phosphate into cells. Reductions in the blood ionized calcium concentration can be partially responsible for symptoms such as muscle cramps and tetany. Approximately 50% of calcium is bound to albumin, and an increase in pH results in an increase in binding.[33]

Compensation

The initial response of the body to acute respiratory alkalosis is chemical buffering: hydrogen ions are released from the body's buffers—intracellular proteins, phosphates, and hemoglobin—and titrate down the serum bicarbonate concentration. This process occurs within minutes. Acutely, the bicarbonate concentration can be decreased by a maximum of 3 mEq/L (mmol/L) for each 10-mm Hg (1.3 kPa) decrease in $PaCO_2$ (see Table 69-7).[29] When only physicochemical buffering has occurred, the disturbance is referred to as acute respiratory alkalosis.

Metabolic compensation occurs when respiratory alkalosis persists for more than 6 to 12 hours. In response to the alkalemia, proximal tubular bicarbonate reabsorption is inhibited, and the serum bicarbonate concentration decreases. Renal compensation is usually complete within 1 to 2 days. The renal bicarbonaturia as well as decreased NH_4^+ and titratable acid excretion are direct

effects of the reduced $PaCO_2$ and pH on renal reabsorption of chloride and bicarbonate.[2,33] The acuity of the respiratory alkalosis can be assessed on the basis of the degree of renal compensation (see Table 69-7). In fully compensated respiratory alkalosis, the bicarbonate concentration decreases by 4 mEq/L (mmol/L) below 24 for each 10-mm Hg (1.3 kPa) drop in $PaCO_2$. For example, a sustained decrease in $PaCO_2$ of 20 mm Hg (2.7 kPa) will lower serum bicarbonate from 24 to 16 mEq/L (mmol/L) with a resultant pH of 7.46. Bicarbonate concentrations differing from those anticipated using the preceding guidelines suggest a mixed acid–base disorder.

TREATMENT

Because most patients with respiratory alkalosis, especially chronic cases, have few or no symptoms and pH alterations are usually mild (pH not exceeding 7.50), treatment is often not required.[35] The first consideration in the treatment of acute respiratory alkalosis with pH more than 7.50 is the identification and correction of the underlying cause. Relief of pain, correction of hypovolemia with IV fluids, treatment of fever or infection, treatment of salicylate overdose, and other direct measures can prove effective. A rebreathing device, such as a paper bag, can be useful in controlling hyperventilation in patients with the anxiety/hyperventilation syndrome.[53] Oxygen therapy should be initiated in patients with severe hypoxemia. Patients with life-threatening alkalosis (pH more than 7.60), particularly if it is a mixed respiratory and metabolic condition, tend to have complications, such as arrhythmias or seizures, which can require mechanical ventilation with sedation and/or paralysis to control hyperventilation.

Respiratory alkalosis in patients receiving mechanical ventilation is usually iatrogenic. It can often be corrected by decreasing either the set respiratory rate or tidal volume, although other measures can also be employed. The use of a capnograph and spirometer in the breathing circuit enables a more precise adjustment of the ventilator settings. Another method of treating respiratory alkalosis is to increase the amount of dead space in the ventilator circuit by placing a known length of tubing between the artificial airway and the “T” piece of the ventilator. This results in “rebreathing” of expired gas, and therefore an increase in the inspired carbon dioxide concentration, which should increase the carbon dioxide tension of the patient, correcting the respiratory alkalosis. In patients breathing more rapidly than the ventilator settings, sedation with or

without paralysis can be employed.

Respiratory Acidosis

Pathophysiology

Respiratory acidosis occurs when the lungs fail to excrete CO_2 resulting in a lower pH. This can be the result of conditions that centrally inhibit the respiratory center, diseases that interfere with pulmonary perfusion or neuromuscular function, and intrinsic airway or parenchymal pulmonary disease (**Table 69-12**). Acute respiratory acidosis with hypoxemia, hypercarbia, and acidosis is life-threatening. Those disorders that produce an increase in $PaCO_2$ and hypoxemia to a degree compatible with life (eg, chronic obstructive pulmonary disease), with or without oxygen therapy, can result in chronic respiratory acidosis (**Table 69-13**). These patients can function normally without noticeable neurologic defects with $PaCO_2$ concentrations in the range of 90 to 100 mm Hg (12-13.3 kPa) (normal, 40 mm Hg [5.3 kPa]), provided that adequate oxygenation is maintained.[53]

TABLE 69-12 Causes of Acute Respiratory Acidosis

Central
Drugs (anesthetics, opioids, sedatives)
Stroke
Head injury
Infection
Status epilepticus
Perfusion abnormalities
Massive pulmonary embolism
Cardiac arrest
Airway and pulmonary abnormalities
Airway obstruction: Foreign body, laryngeal edema
Aspiration of vomitus
Asthma
COPD
Severe pulmonary edema
Severe pneumonia
ARDS
Smoke inhalation
Pneumothorax
Neuromuscular abnormalities
Brainstem or cervical cord injury
Guillain–Barré syndrome
Myasthenia gravis
Mechanical ventilator
Ventilator malfunction
Inadequate frequency or tidal volume settings
Large dead space
Total parenteral nutrition (increased CO_2 production)

ARDS, adult respiratory distress syndrome; COPD, chronic pulmonary obstructive disease.

TABLE 69-13 Causes of Chronic Respiratory Acidosis

Neuromuscular abnormalities
Brainstem infarct
Obesity-hypoventilation (Pickwickian) syndrome
Tumors
Poliomyelitis
Multiple sclerosis
Diaphragmatic paralysis
Pulmonary abnormalities
Chronic obstructive pulmonary disease
Kyphoscoliosis
Interstitial pulmonary disease
Overzealous parenteral feeding

CLINICAL PRESENTATION

Respiratory Alkalosis

General

- The patient is usually asymptomatic if the condition is chronic and mild.

Symptoms

- The patient may complain of light-headedness, confusion, muscle cramps and tetany, and decreased intellectual functioning.
- Nausea and vomiting can occur, probably as a result of cerebral hypoxia.

Signs

- In severe respiratory alkalosis pH is more than 7.60.

Laboratory Tests

- Serum chloride concentration is usually slightly increased. Serum ionized calcium, potassium, and phosphorus concentration can be decreased.

Clinical Presentation

Respiratory acidosis can produce neurologic symptoms, including altered mental status, abnormal behavior, seizures, stupor, and coma. Hypercapnia can mimic stroke or CNS tumors by producing headache, papilledema, focal paresis, and abnormal reflexes. These CNS symptoms are attributable to the vasodilator effects of CO_2 in the brain that result in an increase in cerebral blood flow.[2] The CNS response to hypercapnia is extremely variable between patients and is most influenced by the acuity of presentation. Given that chronic hypercapnia blunts the usual respiratory stimulus of an elevated $PaCO_2$, hypoxemia rather than hypercapnia provides the primary ventilatory stimulus in patients with severe chronic respiratory acidosis.[53]

The degree to which cardiac contractility and heart rate are altered depends on the severity of the acidosis and the rapidity with which it develops. Modest acute hypercapnia ($PaCO_2$ of 50-55 mm Hg [6.7-7.3 kPa]) stimulates a stress-like response, with elevated catecholamines and corticosteroid hormone levels, and can result in increased cardiac output and pulmonary artery pressure.[27] As

the severity increases, cardiac output declines and vascular resistance decreases leading to refractory hypotension in some patients.[2]

In respiratory acidosis, the serum potassium concentration increases modestly secondary to cellular shifts. The increases are less than those seen with inorganic metabolic acidosis and are difficult to predict for individual patients.

Compensation

The body responds to acute respiratory acidosis with chemical buffering. The increase in $PaCO_2$ results in increased carbonic acid levels. The carbonic acid dissociates, releasing hydrogen ions, which are buffered by nonbicarbonate buffers (ie, proteins, phosphate, and hemoglobin) and bicarbonate. Thus, on the basis of physicochemical factors, increases in $PaCO_2$ raise the serum bicarbonate concentration. In general, in acute respiratory acidosis, the bicarbonate concentration increases by 1 mEq/L (mmol/L) above 24 for each 10 mm Hg (1.3 kPa) increase in $PaCO_2$ above 40 mm Hg (5.3 kPa) (see Table 69-7).

Metabolic compensation occurs when respiratory acidosis is prolonged beyond 12 to 24 hours. In response to hypercapnia and acidemia, proximal tubular bicarbonate reabsorption, ammoniagenesis, and distal tubular hydrogen secretion are enhanced, resulting in an increase in the serum bicarbonate concentration that raises the pH toward normal. Renal compensation for chronic hypercapnia generally results in the plasma bicarbonate concentration increasing by 4 mEq/L (mmol/L) above 24 for each 10 mm Hg (1.3 kPa) increase in $PaCO_2$ above 40 mm Hg (5.3 kPa) (see Table 69-7). The new steady state in acid–base values is generally achieved within 5 days of the onset of hypercapnia in dogs; the time interval necessary for compensation in humans has not been established.

TREATMENT

The treatment of respiratory acidosis is dependent on the chronicity of the patient's condition. Respiratory decompensation in patients with chronic elevations in $PaCO_2$ is frequently seen in those with acute infections and those recently started on narcotic analgesics or oxygen therapy.[33] Aggressive treatment of these conditions can offer considerable benefit and should be initiated. Furthermore, tranquilizers and sedatives should be avoided and supplemental oxygen, if used, should be minimized.

Acute Respiratory Acidosis

When carbon dioxide excretion is severely impaired ($PaCO_2$ more than 80 mm Hg [10.6 kPa]) and/or life-threatening, hypoxia is present (PaO_2 less than 40 mm Hg [5.3 kPa]); the immediate therapeutic goal is to provide adequate oxygenation. Under these circumstances, hypoxia, not acidemia, is the principal threat to life. A patent airway needs to be established, which can necessitate intubation. Excessive secretions must be cleared from the airway and oxygen administered to restore adequate oxygenation. Mechanical ventilation is usually required.

14 The underlying cause of the acidosis should be treated aggressively (ie, bronchodilators for treatment of severe bronchospasm; narcotic or benzodiazepine antagonists to reverse the deleterious effects of these agents on the respiratory center). Bicarbonate administration is rarely necessary in the treatment of respiratory acidosis. Furthermore, rapid correction of acidosis with bicarbonate can eliminate the patient's respiratory drive or precipitate metabolic alkalosis. Cautious use of alkali (bicarbonate) can restore the responsiveness of bronchial muscles to β-adrenergic agonists and thus can be beneficial for those patients with severe bronchospasm.[33] ABGs should be monitored closely to ensure that the respiratory acidosis is resolving without creating a metabolic alkalosis as the result of compensatory elevation in HCO_3^- and decrease in $PaCO_2$. ABGs should be obtained every 2 to 4 hours during the acute phase and less frequently (every 12-24 hours) as the acidosis improves.

CLINICAL PRESENTATION

Respiratory Acidosis

General

- The patient is usually symptomatic.

Symptoms

- The patient may complain of confusion or difficulty thinking and headache.

Signs

- In severe respiratory acidosis.

- Cardiac: Increased cardiac output if moderate that decreases if severe. Refractory hypotension can be present in some patients.
- CNS: Abnormal behavior, seizures, stupor, and coma. Papilledema, focal paresis, and abnormal reflexes can also be present.

Laboratory Tests

- Serum potassium concentration can be modestly increased. Hypercapnia can be moderate ($PaCO_2$ of 50-55 mm Hg [6.7-7.3 kPa]) to severe ($PaCO_2$ of more than 80 mm Hg [10.6 kPa]). Hypoxia (PaO_2 is less than 70 mm Hg [9.3 kPa]) is often present.

Acute Respiratory Acidosis in a Compensated Chronic Respiratory Acidotic Patient

Patients with a history of chronic respiratory acidosis (ie, those with chronic obstructive pulmonary disease) can experience an acute worsening of their respiratory acidosis. This can result in severe life-threatening hypoxemia. As with acute respiratory acidosis, the goals of therapy are maintenance of a patent airway and adequate oxygenation. Individuals with chronic respiratory acidosis are routinely able to tolerate a low PaO_2 and an elevated $PaCO_2$ because of compensation (increased number of red blood cells, hemoglobin content, and 2,3-diphosphoglycerate). The drive to breathe in these patients is dependent on hypoxemia rather than hypercarbia. Administration of oxygen to a patient with chronic respiratory acidosis can eliminate this drive to breathe and result in the syndrome of carbon dioxide narcosis. In this case, if the PaO_2 is 50 mm Hg (6.7 kPa), no oxygen treatment is necessary. If the PaO_2 is less than 50 mm Hg (6.7 kPa), oxygen therapy should be initiated carefully using a controlled flow of oxygen.[2]

ABGs should be checked periodically to ensure adequate oxygenation. If the $PaCO_2$ increases during oxygen therapy, it can be a sign of impending carbon dioxide narcosis and oxygen therapy may need to be discontinued. The underlying cause of the acute exacerbation should be aggressively managed. Pulmonary infections should be treated with the appropriate antibiotics and bronchodilators administered as necessary. Excess secretions should be cleared from the airway to allow proper gas exchange. This can involve increasing oral fluid intake to decrease the viscosity of secretions, deep breathing, and postural

drainage, suction, or bronchoscopy.

MIXED ACID–BASE DISORDERS

Diagnosis

The diagnosis of a mixed disorder depends on an understanding of the appropriate quantitative response of the compensatory mechanisms for each of the simple acid–base disturbances.[2,3,29] To diagnose mixed disorders, one must know how each of the four simple disorders alters pH, $PaCO_2$, and (HCO_3^-) (see Table 69-7). If a given set of blood gases does not decrease within the range of expected responses for a simple acid–base disturbance, a mixed disorder should be suspected. In addition to laboratory information, a thorough history and physical examination of the patient will often lead to the diagnosis, even before the laboratory data are available. Examples of common mixed disturbances follow.

Mixed Respiratory Acidosis and Metabolic Acidosis

A mixed respiratory and metabolic acidosis disturbance is characterized by a failure of compensation. The respiratory disorder prevents the compensatory decrease in $PaCO_2$ expected in the defense against metabolic acidosis. The metabolic disorder prevents the buffering and renal mechanisms from raising the bicarbonate concentration as expected in the defense against respiratory acidosis. In the absence of these compensatory mechanisms, the pH decreases markedly.

Mixed respiratory and metabolic acidosis may develop in patients with cardiorespiratory arrest, in those with chronic lung disease who are in shock, and in metabolic acidosis patients who develop respiratory failure. When treating this mixed disorder, clinicians need to respond to both the respiratory and metabolic acidosis. Improved oxygen delivery must be initiated to improve hypercarbia and hypoxia. Mechanical ventilation may be needed to reduce $PaCO_2$. During the initial stage of therapy, appropriate amounts of alkali should be given to reverse the metabolic acidosis (see section “Treatment,” for “Metabolic Acidosis”).

Mixed Respiratory Alkalosis and Metabolic Alkalosis

The combination of respiratory and metabolic alkalosis is the most common mixed acid–base disorder. This mixed disorder occurs frequently in critically ill

surgical patients with respiratory alkalosis caused by mechanical ventilation, hypoxia, sepsis, hypotension, neurologic damage, pain, or drugs, and with metabolic alkalosis caused by vomiting or nasogastric suctioning and massive blood transfusions. It can also occur in patients with hepatic cirrhosis who hyperventilate, receive diuretics, or vomit, as well as in patients with chronic respiratory acidosis and an elevated plasma bicarbonate concentration who are placed on mechanical ventilation and undergo a rapid decrease in $PaCO_2$.

The renal excretion of bicarbonate that usually occurs as compensation for the respiratory alkalosis is prevented by the complicating metabolic alkalosis. Likewise, the retention of $PaCO_2$ expected to compensate for metabolic alkalosis is prevented by the primary respiratory alkalosis. The failure of compensation that occurs with mixed respiratory and metabolic alkalosis can result in a severe alkalemia.

Administration of sodium chloride and potassium chloride solutions will help correct the metabolic component of a mixed respiratory and metabolic alkalosis, and adjustment of the ventilator and/or treatment of an underlying process that is causing hyperventilation can correct or ameliorate the respiratory component of this mixed disorder.

Mixed Metabolic Acidosis and Respiratory Alkalosis

This mixed disorder is often seen in patients with advanced liver disease, salicylate intoxication, and pulmonary-renal syndromes. The respiratory alkalosis will decrease the $PaCO_2$ beyond the appropriate range for the respiratory compensation usually seen with metabolic acidosis. The plasma bicarbonate concentration also decreases below the level expected in compensation for a simple respiratory alkalosis. In a sense, the defense of pH for either disorder alone is enhanced; thus the pH can be normal or close to normal, with a low $PaCO_2$ and a low (HCO_3^-). Treatment of this disorder should be directed at the underlying cause. Because of the enhanced compensation, the pH is usually closer to normal than in either of the two simple disorders.

Mixed Metabolic Alkalosis and Respiratory Acidosis

This mixed disorder often occurs in patients with chronic obstructive pulmonary disease and chronic respiratory acidosis who are treated with salt restriction, diuretics, and possibly glucocorticoids. When diuretics are initiated, the plasma bicarbonate may increase because of increased renal bicarbonate generation and reabsorption, providing mechanisms for both generating and maintaining

metabolic alkalosis. The elevated pH diminishes respiratory drive and may therefore worsen the respiratory acidosis.

Although the pH may not deviate significantly from normal, treatment may need to be initiated to maintain PaO_2 and $PaCO_2$ at acceptable levels. Because it is often difficult to correctly identify this mixed disorder, it is helpful to observe the patient's response to discontinuation of diuretics and administration of sodium and potassium chloride.[2,29] The $PaCO_2$ will normalize if the patient has a simple metabolic alkalosis, but it will be minimally affected in the setting of a mixed disorder. Treatment should be aimed at decreasing the plasma bicarbonate with sodium and potassium chloride therapy, thereby allowing the renal excretion of retained bicarbonate from the diuretic-induced metabolic alkalosis. This therapy should be used cautiously to avoid exacerbating any underlying congestive heart failure.

CLINICAL BOTTOM LINE

Acid–base disorders are a common and widespread problem, and clinicians can play a key role in identifying, preventing, and properly treating them. Acid–base disorders do not occur only in the intensive care unit setting. Patients in ambulatory and extended care settings have many chronic conditions and drug therapies that commonly affect acid–base balance. Thus clinicians in all practice settings should strive to identify patients at high risk for developing drug-related problems that affect acid–base balance and to undertake appropriate prevention and treatment measures to improve the quality of life of their patients.

Postclass Engaged Learning Activity

Retrieve the following open access study: Kim HJ, Son YK, An WS. Effect of sodium bicarbonate administration on mortality in patients with lactic acidosis: A retrospective analysis. *PLoS One* 2013;8:e65283 [available at PMCID: PMC3673920 and at https://bit.ly/2Gvgvlr]. After reading the study, summarize the study objective, the study population (in both intervention and control groups), and the primary study conclusion. List the other variables known to affect mortality in the ICU that were controlled for in the multivariate, Cox-regression model. Lastly, list two potential reasons why the administration of IV sodium bicarbonate in patient with metabolic acidosis secondary to lactic acidosis may worsen patient outcome, including increased

patient mortality. This activity is intended to strengthen your ability to critically appraise a research manuscript and to better understand the controversy of administering sodium bicarbonate to patients with metabolic acidosis secondary to lactic acidosis.

ABBREVIATIONS

BW	body weight
CNS	central nervous system
DCA	dichloroacetate
ECF	extracellular fluid
H^+	hydrogen ion
HCO_3^-	bicarbonate
H_2CO_3	carbonic acid
HIV	human immunodeficiency virus
NH_4^+	ammonium
$PaCO_2$	partial pressure of carbon dioxide from arterial blood
PaO_2	partial pressure of oxygen from arterial blood
pH	the negative logarithm (base 10) of the hydrogen ion concentration
pK	the negative logarithm of the dissociation constant
$PvCO_2$	partial pressure of carbon dioxide from venous blood
PvO_2	partial pressure of oxygen from venous blood
RTA	renal tubular acidosis
SAG	serum anion gap
THAM	tromethamine (Tris[hydroxymethyl]-aminomethane)
UAs	unmeasured anions
UCs	unmeasured cations

REFERENCES

1. Berend K, de Vries AP, Gans RO. Physiological approach to assessment of acid-base disturbances. *N Engl J Med*. 2014;371(15):1434–1445.
2. Hamm LL, Nakhoul N, Hering-Smith KS. Acid-base homeostasis. *Clin J Am Soc Nephrol*. 2015;10(12):2232–2242.
3. Seifter JL. Integration of acid-base and electrolyte disorders. *N Engl J Med*. 2015;372(4):391–392.

4. Adrogué HJ, Madias NE. Assessing acid-base status: Physiologic versus physicochemical approach. *Am J Kidney Dis*. 2016;68(5):793–802.
5. Berend K. Diagnostic use of base excess in acid-base disorders. *N Engl J Med*. 2018;378(15):1419–1428.
6. Kraut JA, Madias NE. Metabolic acidosis: Pathophysiology, diagnosis and management. *Nat Rev Nephrol*. 2010;6(5):274–285.
7. Albert MS, Dell RB, Winters RW. Quantitative displacement of acid-base equilibrium in metabolic acidosis. *Ann Intern Med*. 1967;66(2):312–322.
8. Leung JC. Inherited renal diseases. *Curr Pediatr Rev*. 2014;10(2):95–100.
9. Gupta S, Gao JJ, Emmett M, Fenves AZ. Topiramate and metabolic acidosis: An evolving story. *Hosp Pract*. 2017;45(5):192–195.
10. Dounousi E, Zikou X, Koulouras V, et al. Metabolic acidosis during parenteral nutrition: Pathophysiological mechanisms. *Indian J Crit Care Med*. 2015;19:270–274.
11. Kitterer D, Schwab M, Alscher MD, et al. Drug-induced acid-base disorders. *Pediatr Nephrol*. 2015;30:1407–1423.
12. Reddy P. Clinical approach to renal tubular acidosis in adult patients. *Int J Clin Pract*. 2011;65:350–360.
13. Kraut JA, Nagami GT. The serum anion gap in the evaluation of acid-base disorders: What are its limitations and can its effectiveness be improved? *Clin J Am Soc Nephrol*. 2013;8:2018–2024.
14. Kraut JA, Madias NE. Lactic acidosis. *N Engl J Med*. 2014;371:2309–2319.
15. Kamel KS, Halperin ML. Acid-base problems in diabetic ketoacidosis. *N Engl J Med*. 2015;372(6):546–554.
16. Al Jaghbeer M, Kellum JA. Acid-base disturbances in intensive care unit patients: Etiology, pathophysiology and treatment. *Nephrol Dial Transplant*. 2015;30:1104–1111.
17. Hamdi H, Hassanian-Moghaddam H, Hamdi A, Zahed NS. Acid-base disturbances in acute poisoning and their association with survival. *J Crit Care*. 2016;35:84–89.
18. Pham AQ, Xu LH, Moe OW. Drug-induced metabolic acidosis. *F1000Res*. 2015;4:1460.
19. Moioli A, Maresca B, Manzione A, et al. Metformin associated lactic acidosis (MALA): Clinical profiling and management. *J Nephrol*. 2016;29(6):783–789.

20. Margolis AM, Heverling H, Pham PA, Stolbach A. A review of the toxicity of HIV medications. *J Med Toxicol*. 2014;10(1):26–39.
21. Kishor K, Dhasmana N, Kamble SS, et al. Linezolid induced adverse drug reactions—an update. *Curr Drug Metab*. 2015;16:553–559.
22. Woloshin S, Schwartz LM. The new weight-loss drugs, lorcaserin and phentermine-topiramate: Slim pickings? *JAMA Intern Med*. 2014;174:615–619.
23. Oberg CL, Hiensch RJ, Poor HD. Ombitasvir-paritaprevir-ritonavir-dasabuvir (Viekira Pak)-induced lactic acidosis. *Crit Care Med*. 2017;45(3):e321–e325.
24. Horinek EL, Kiser TH, Fish DN, et al. Propylene glycol accumulation in critically ill patients receiving intravenous lorazepam infusions. *Ann Pharmacother*. 2009;43:1964–1971.
25. Pillai U, Hothi JC, Bhat ZY. Severe propylene glycol toxicity secondary to use of anti-epileptics. *Am J Ther*. 2014;21:106–109.
26. Bulathsinghala M, Keefer K. Trimethoprim/sulfamethoxazole-induced severe lactic acidosis: A case report and review of the literature. *Medicine (Baltimore)*. 2016;95(17):e3478.
27. Mirrakhimov AE, Voore P, Halytskyy O, et al. Propofol infusion syndrome: A clinical update. *Crit Care Res Pract*. 2015;260:385–393.
28. Chauhan V, Kelepouris E, Chauban N, et al. Current concepts and management strategies in chronic kidney disease: Mineral and bone disorders. *South Med J*. 2012;1045:479–485.
29. Garrubba C, Truscott J. A clinical approach to acid-base conundrums. *JAAPA*. 2016;29(4):1–5.
30. Kim HJ, Son YK, An WS. Effect of sodium bicarbonate administration on mortality in patients with lactic acidosis: A retrospective analysis. *PLoS One* 2013;8:e65283.
31. Velissaris D, Karamouzos V, Ktenopoulos N, et al. The use of sodium bicarbonate in the treatment of acidosis in sepsis: A literature update on a long-term debate. *Crit Care Res Pract*. 2015;2015:605–830.
32. Adrogue HJ, Rashad MN, Gorin AB, et al. Assessing acid–base status in circulatory failure: Differences between arterial and central venous blood. *N Engl J Med*. 1989;320:1312–1316.
33. Gomez H, Kellum JA. Understanding acid-base disorders. *Crit Care Clin*. 2015;31:849–860.

34. Callaway CW, Soar J, Aibiki M, et al. Part 4: Advanced Life Support: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Circulation*. 2015;132(16 Suppl 1):S84–S145.
35. McEvoy GK, Litvak K, Welsh OH, et al. American Hospital Formulary Service, Drug Information. Bethesda, MD: American Society of Health-System Pharmacists; 2015.
36. Geraci MJ, Klipa D, Heckman MG, et al. Prevalence of sodium bicarbonate-induced alkalemia in cardiopulmonary arrest patients. *Ann Pharmacother*. 2009;43:1245–1250.
37. Hoste EA, Colpaert K, Vanholder RC, et al. Sodium bicarbonate versus THAM in ICU patients with mild metabolic acidosis. *J Nephrol*. 2005;18:303–307.
38. Stacpoole PW, Wright EC, Baumgartner TG, et al. A controlled clinical trial of dichloroacetate for treatment of lactic acidosis. *N Engl J Med*. 1992;327:1564–1569.
39. Stacpoole PW, Nagaraja NV, Hutson AD. Efficacy of dichloroacetate as a lactate-lowering drug. *J Clin Pharmacol*. 2003;43:683–691.
40. James MO, Jahn SC, Zhong G, et al. Therapeutic applications of dichloroacetate and the role of glutathione transferase zeta-1. *Pharmacol Ther*. 2017;170:166–180.
41. Kreü S, Jazrawi A, Miller J, Baigi A, Chew M. Alkalosis in critically ill patients with severe sepsis and septic shock. *PLoS One*. 2017;12(1):e0168563.
42. Soifer JT, Kim HT. Approach to metabolic alkalosis. *Emerg Med Clin North Am*. 2014;32:453–463.
43. Gennari FJ. Pathophysiology of metabolic alkalosis: A new classification based on the centrality of stimulated collecting duct ion transport. *Am J Kidney Dis*. 2011;58:626–636.
44. Mikhalidis G, Mikhailidis DP, Elisaf M. Acid–base and electrolyte abnormalities observed in patients receiving cardiovascular drugs. *J Cardiovasc Pharmacol Ther*. 2003;8:267–279.
45. Mustafa QU, Haroon ZH, Ijaz A, et al. Gitelman syndrome. *J Coll Physicians Surg Pak*. 2017;27(3):S30–S32.
46. Barton CH, Vaziri ND, Ness RL, et al. Cimetidine in the management of metabolic alkalosis induced by nasogastric drainage. *Arch Surg*. 1979;1:70–74.

47. Van Berkel MA, Elefritz JL. Evaluating off-label uses of acetazolamide. *Am J Health Syst Pharm*. 2018;75(8):524–531.
48. Faisy C, Meziani F, Planquette B, et al. Effect of acetazolamide vs placebo on duration of invasive mechanical ventilation among patients with chronic obstructive pulmonary disease: A randomized clinical trial. *JAMA*. 2016;315(5):480–488.
49. Guffey JD, Haas CE, Crowley A, et al. Hydrochloric acid infusion for the treatment of metabolic alkalosis in surgical intensive care unit patients. *Ann Pharmacother*. 2018;52(6):522–526.
50. Sierra CM, Hernandez EA, Parbuoni KA. Use of arginine hydrochloride in the treatment of metabolic alkalosis or hypochloremia in pediatric patients. *J Pediatr Pharmacol Ther*. 2018;23(2):111–118.
51. Hene RJ, Koomans HA, Dorhout Mees EJ, et al. Correction of hypokalemia in Bartter's syndrome by enalapril. *Am J Kidney Dis*. 1987;9:200–205.
52. Vinci JM, Gill JR Jr, Bowden RE, et al. The Kallikrein-Kinin system in Bartter's syndrome and its response to prostaglandin synthetase inhibition. *J Clin Invest*. 1987;61:1671–1682.
53. Guerin C, Nesme P, Leray V, et al. Quantitative analysis of acid-base disorders in patients with chronic respiratory failure in stable or unstable respiratory condition. *Respir Care*. 2010;55:1453–1463.
54. Jaber S, Paugam C, Futier E, et al. Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): A multicentre, open-label, randomised controlled, phase 3 trial. *Lancet*. 2018;392(10141):31–40.

SECTION 8 NEUROLOGIC DISORDERS

Evaluation of Neurologic Illness

Melody Ryan and Stephen J. Ryan

KEY CONCEPTS

1. Accurate diagnosis of neurological disorders leads to effective pharmacotherapy.
2. The clinical neurologic history and examination are the cornerstones of neurologic diagnosis and management.
3. History and examination should be modified for the pediatric patient as appropriate.
4. The neurologic history and examination are directed at localization of the disease process so that a differential diagnosis can be formed.
5. After forming the differential diagnosis, appropriate testing helps pinpoint the correct diagnosis.
6. Accurate diagnosis leads to appropriate therapy and management of neurologic conditions.
7. Appropriate history taking and examination techniques are useful for monitoring and evaluating the pharmacotherapeutic plan.
8. Lumbar puncture (LP) should only be performed when it can be done safely. Relative contraindications may include increased intercranial pressure, mass lesions, papilledema, and coagulopathies.

Preclass Engaged Learning Activity

Watch the video entitled “The Neurologic Screening Exam” in AccessPharmacy by Daniel H. Lowenstein. https://accesspharmacy.mhmedical.com/MultimediaPlayer.aspx?MultimediaID=12986884

This 9-minute video provides a brief overview of the neurologic examination including all five components. This visual depiction will aid in student understanding of the examination. The information collected in the neurologic examination is used in the COLLECT and FOLLOW-UP steps in the patient care process.

INTRODUCTION

Accurate diagnosis of neurological disorders leads to effective pharmacotherapy. This diagnosis is built upon history, a detailed neurological examination, and appropriate testing. To contribute most effectively to the care of patients with neurologic illness, one must understand the tools used in the diagnosis and management of these patients. In addition, clinicians must be able to gather their own data through history taking and a targeted neurologic examination to ensure optimal pharmacotherapy in neurologic patients. Despite technologic advances that have led to the development of sensitive diagnostic tests in neuroscience, the clinical neurologic history and examination are still the cornerstones of neurologic diagnosis and management.[1]

SIGNS AND SYMPTOMS OF NEUROLOGIC DISORDERS

As in all of medicine, obtaining an accurate and complete history is of utmost importance in the evaluation of neurologic diseases. In many instances, the diagnosis can be made on the basis of the history, and the neurologic examination can be tailored to optimally evaluate the patient and confirm the diagnosis.[1] Open-ended questions allow the patient to provide the salient history without leading the patient toward preconceived diagnoses. Obtaining an accurate history may be difficult because a number of neurologic diseases potentially affect patients' communication and memory. The details obtained from the family or other observers, support and further expand the data obtained from the patient during history taking; additionally family history can be helpful in diagnosis.[1] Through the patient's history, one can determine the main symptoms, location, onset (acute, subacute, or chronic), progression over time (maximal at onset or steadily gaining intensity), and associated illnesses or risk factors for neurologic disease.[2] The history should also identify factors that

might precipitate or ameliorate the symptoms.[2] Each patient complaint should be thoroughly investigated while taking the history. See **Table e70-1** for questions to assist the clinician in obtaining the neurologic history.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

71

Alzheimer Disease

Emily P. Peron, Kristin M. Zimmerman, Ericka L. Crouse, Patricia W. Slattum, and Sarah E. Hobgood

KEY CONCEPTS

1. Alzheimer disease (AD) is the most common form of dementing illness, and the prevalence of AD increases with each decade of life.
2. The etiology of AD is unknown, and current pharmacotherapy neither cures nor arrests the pathophysiology.
3. Amyloid plaques and neurofibrillary tangles (NFTs) are the pathologic hallmarks of AD; however, the definitive cause of this disease is yet to be determined.
4. Alzheimer disease affects multiple areas of cognition and is characterized by a gradual onset with a slow, progressive decline.
5. A thorough physical examination (including neurologic examination), as well as laboratory and imaging studies, is required to rule out other disorders and diagnose AD before considering drug therapy.
6. Pharmacotherapy for AD focuses on impacting three domains: (1) cognition, (2) neuropsychiatric symptoms, and (3) functional ability.
7. Nondrug therapy and social support for the patient and family are the primary treatment interventions for AD.
8. Cholinesterase inhibitors and memantine are used to treat cognitive symptoms of AD; other medications have been suggested to be beneficial because of their potential preventive or cognitive effects.
9. Appropriate management of vascular disease risk factors may reduce the risk for developing AD and may prevent the worsening of dementia in people with AD.
10. A thorough behavioral assessment and plan with careful examination of

environmental factors should be conducted before initiating drug therapy for behavioral symptoms.

Preclass Engaged Learning Activity

Prior to class, visit the Mini-Cog© Website at http://mini-cog.com. At the top of the screen on the left, select from the "Standardized Mini-Cog©" drop-down menu the "Standardized Mini-Cog© Instrument" tab:

1. Review the three-step process and scoring guidelines on the left-hand side of the page. You do not need to print this document, as you can simply draw a circle on a blank piece of paper for your partner to use while you take notes on a separate piece of paper.
2. Work with a classmate to practice administering the Mini-Cog© to each other and scoring it accordingly.
3. If you get stuck or are not sure how to score an item, return to the "Standardized Mini-Cog©" drop-down menu and select "Administering the Mini-Cog©" and/or "Scoring the Mini-Cog©."
4. You may have questions after working through this exercise, perhaps related to test logistics or next steps. If that is the case, consider returning to the "Standardized Mini-Cog©" drop-down menu and visiting the "FAQs" page.

This activity is intended to increase your familiarity with a brief, freely available dementia screening tool that is often used in clinical settings and as part of the Medicare Annual Wellness Visit. The Mini-Cog© can be administered by any health professional or trained lay health worker.

INTRODUCTION

"I now begin the journey that will lead me into the sunset of my life." Ronald Reagan

Alzheimer disease (AD), first characterized by Alois Alzheimer in 1907, is a gradually progressive dementia affecting cognition, behavior, and functional status. The exact pathophysiologic mechanisms underlying AD are not entirely known, and no cure exists.[1] Although drugs may reduce AD symptoms for a

time, the disease is eventually fatal.

Alzheimer disease profoundly affects the family as well as the patient. The need for supervision and assistance increases until the late stages of the disease, when people with AD become totally dependent on a caregiver for all their basic needs. To address the growing AD crisis facing the United States, the first national strategic plan, the National Alzheimer's Plan, was released in 2012 with the goal of coordinating efforts across the federal government to prevent and treat AD, increase public awareness, and improve the quality of care and support for patients and their caregivers.[2] The US Department of Health and Human Services has since updated this strategic plan to include a timeline for achieving its goal to "develop effective prevention and treatment modalities by 2025."[2]

EPIDEMIOLOGY

1 Alzheimer disease is the most common cause of dementia, accounting for 60% to 80% of cases.[3,4] **Table 71-1** lists the most common types of dementia, as multiple etiologies can result in dementia. This chapter focuses exclusively on dementia of the Alzheimer type; however, the reader is encouraged to use the nonpharmacologic approaches and management of behavioral problems outlined in this chapter as a general treatment approach for other types of dementia that may share similar features with AD.

TABLE 71-1 Common Types of Dementia

Alzheimer disease
Vascular dementia
Dementia with Lewy bodies
Mixed dementia
Other (eg, Parkinson disease dementia, Frontotemporal dementia, Huntington disease, Creutzfeldt–Jakob disease)
Potentially reversible causes of cognitive dysfunction (eg, normal pressure hydrocephalus, thyroid dysfunction, vitamin B_{12} deficiency, delirium, depression, Wernicke–Korsakoff syndrome)

Data from References 2 and 5.

Approximately 5.7 million adults in the United States have AD.[3] By the year 2050, one in five people will be age 65 years or older, and the number of people with AD is projected to double.[3] Most cases present in people age 65 years and older, but approximately 4% of cases occur in people younger than age 65 years. Factors determining age of onset and rate of progression remain largely

undefined. Onset can be as early as age 30 years, resulting in the arbitrary age classifications of early-onset (younger than age 65 years) and late-onset (age 65 years and older).[3] Though increasing age is the greatest risk factor for AD, it is important to note that AD is not a normal part of aging.

Survival following AD diagnosis is typically 4 to 8 years but may be as long as 20 years.[3] Alzheimer disease is the fifth leading cause of death for those age 65 years and older in the United States; however, death among people with AD is often not a direct result of the disease but rather the functional impairments that accompany it.[3] The most common cause of death in people with AD is pneumonia, possibly resulting from swallowing difficulties and immobility in the terminal stage of the disease.[3] Those diagnosed with AD spend, on average, more years in the most severe stage of the disease than any other stage, and much of this time is spent in a nursing home.[3]

ETIOLOGY

Genetics

2 The exact etiology of AD is unknown; however, several genetic and environmental factors have been explored as potential causes. Genetic factors have been linked to both early- and late-onset AD, although dominantly inherited forms of AD account for less than 1% of cases.[6] More than half of early-onset, dominantly inherited cases of AD can be attributed to alterations on chromosomes 1, 14, or 21. These alterations largely impact the processing of a large membrane protein called amyloid precursor protein (APP). Amyloid precursor protein is typically broken down by three major secretase enzymes—α-, β-, and γ-secretase—into nonpathologic fragments as well as potentially pathologic 38 to 43 peptide-long β-amyloid peptide (Aβ) fragments. Of these enzymes, α-secretase is responsible for ensuring that APP is broken down into nonpathologic fragments. Relative alterations in the activity of β- and/or γ-secretase may prove pathologic.[7] As a result, these enzymes may be considered potential therapeutic targets. The majority of early-onset cases are attributed to mutations of a gene located on chromosome 14, which produces a protein called presenilin 1.[8] A structurally similar protein, presenilin 2, is produced by a gene on chromosome 1. Both presenilin 1 and presenilin 2 encode for these secretase enzymes. Scientists have identified more than 160 mutations in presenilin genes, and these mutations appear to result in reduced activity of γ-secretase, which may yield larger and more harmful Aβ fragments.[8,9] The APP is encoded on

chromosome 21. Only a small number of early-onset familial AD cases have been associated with mutations in the APP gene, resulting in overproduction of Aβ or an increase in the proportion of Aβ ending at peptide 42.[8,9] Presence of these mutations, however, is often indicative of development of disease.

Genetic susceptibility to late-onset AD is primarily linked to the apolipoprotein E (*APOE*) genotype. It is hypothesized that *APOE* (a cholesterol transport gene) may be implicated in the pathogenesis of the disease. There are three major subtypes or alleles of *APOE*—**2, *3,* and **4*. Inheritance of the *APOE*4* allele accounts for much of the genetic risk in late-onset AD.[10] The mechanism through which *APOE*4* confers an increased risk is unknown, although *APOE*4* is associated with factors that may contribute to AD pathology, such as abnormalities in mitochondria, cytoskeletal dysfunction, and low glucose usage.[11] The risk for AD is two- to threefold higher in individuals with one *APOE*4* allele and 12-fold higher in individuals with two *APOE*4* alleles compared to those with no *APOE*4* alleles.[11] Moreover, onset of symptoms occurs at a relatively younger age as compared with people having zero or only one copy of *APOE*4* in their genotype.[11] Notably, the prevalence of individuals who carry two copies of the *APOE*4* alleles is only 2%, while the prevalence of those carrying one allele is 25%. Of note, the *APOE*4* allele is not diagnostic of AD, essential for disease presence, or indicative of future disease development. Additional genetic explanatory factors continue to be investigated.

Environmental and Other Factors

A number of factors are associated with an increased risk of AD, including age, decreased reserve capacity of the brain (eg, reduced brain size, low educational level, reduced mental and physical activity), head injury, Down syndrome, depression, mild cognitive impairment (MCI), and risk factors for vascular disease (eg, hypercholesterolemia, hypertension, atherosclerosis, coronary heart disease, smoking, elevated homocysteine, obesity, metabolic syndrome, diabetes).[3,4,12] Whether these vascular risk factors are true causal risk factors for AD contributing to AD pathology, or whether they result in cerebrovascular pathology that, in turn, contributes to the symptoms of AD, remains to be established. The incidence of AD rises with increasing age, and AD may develop in individuals over the course of decades,[3] suggesting that AD is a disease that likely develops throughout adulthood. Of note, more women than men have AD.[3] While this may largely be a factor of women living longer than men, it is also hypothesized that men who live to be older than age 65 years may have

better cardiovascular risk profiles than even women of the same age; this is commonly referred to as “survivor bias.”[3] An analysis of the complex interactions between age, sex, vascular health, and AD is beyond the scope of this chapter.

PATHOPHYSIOLOGY

3 The signature lesions in AD include amyloid plaques and neurofibrillary tangles (NFTs) located in the cortical areas and medial temporal lobe structures of the brain.[1,12,13] Along with these lesions, degeneration of neurons and synapses as well as cortical atrophy occurs. It is unclear if or how these lesions are definitively implicated in the development of AD symptoms. This is particularly true as plaques and NFTs may also be present in other diseases, even in normal aging. Importantly, however, AD-affected subjects appear to have a higher burden of plaques and NFTs in their younger years compared to age-matched controls. Several mechanisms have been proposed to explain changes in the brain that result in symptoms of AD, including misfolding of proteins (Aβ aggregation and deposition leading to the formation of plaques and tangles), synaptic failure and depletion of neurotrophin and neurotransmitters, and mitochondrial dysfunction (oxidative stress, impaired insulin signaling in the brain, vascular injury, inflammatory processes, loss of calcium regulation, and defects in cholesterol metabolism).[1,10,13]

Amyloid Cascade Hypothesis

Amyloid plaques, or protofibrils, are extracellular lesions found in the brain and cerebral vasculature that largely consist of Aβ peptides. These Aβ peptides are comprised of 36 to 43 amino acids and are produced via processing of a larger protein, APP. While less common than other Aβ peptides, $A\beta_{42}$ is prone to aggregation and plaque formation.[1,14] The amyloid cascade hypothesis states that there is an imbalance between the production and clearance of Aβ peptides resulting in their accumulation and aggregation, plaque formation, and ultimately the development of AD.[1,14] Interestingly, however, more recent versions of the amyloid cascade hypothesis assume Aβ that is not sequestered in plaques actually drives the disease.[1,14] Additionally, it is unknown whether the presence of Aβ within or outside of plaques is the primary pathology responsible for AD development, or whether these changes are a marker of an alternate pathology. If treatments that efficiently reduce Aβ production or remove brain

Aβ fail to arrest disease progression in those with early or prodromal disease, it would argue amyloidosis is not the primary pathology in most individuals with AD.

Neurofibrillary Tangles

At the same time Aβ was being identified in plaques, other researchers found that NFTs are common in the cells of the hippocampus and cerebral cortex (regions implicated in AD symptoms) in people with AD. These NFTs are composed of abnormally hyperphosphorylated tau protein. Tau protein provides structural support to microtubules, the cell's transportation and skeletal support system.[4] When tau filaments undergo abnormal phosphorylation at a specific site, they cannot bind effectively to microtubules, and the microtubules collapse. Without an intact system of microtubules, the cell cannot function properly and eventually dies. In general, NFT density correlates with severity of dementia; however, NFTs are found in other dementing illnesses besides AD and may represent a common method by which various inciting factors culminate in cell death.[13]

Inflammatory Mediators

Inflammatory or immunologic paradigms are considered additional hypotheses relevant to AD neurodegeneration.[1] Inflammatory/immunologic hypotheses argue that although Aβ may have direct neurotoxicity, at least some of its toxicity might actually be an indirect consequence of an immune response mediated by Aβ protofibril–induced microglia activation and astrocyte recruitment. This inflammatory response may represent an attempt to clear amyloid deposition; however, it is also associated with release of cytokines, nitric oxide, other radical species, and complement factors that can both injure neurons and promote ongoing inflammation.[1] Indeed, levels of multiple cytokines and chemokines are elevated in AD brains, and certain proinflammatory gene polymorphisms are reported to be associated with AD.[1,15]

Cholinergic Hypothesis

Multiple neuronal pathways are destroyed in AD and neuronal damage can be seen in conjunction with plaque structures.[1,13] Widespread cell dysfunction or degeneration results in a variety of neurotransmitter deficits, with cholinergic

abnormalities being among the most prominent.[1,10] Loss of cholinergic activity correlates with AD severity. In the late stage of AD, the number of cholinergic neurons is reduced, and there is loss of nicotinic receptors in the hippocampus and cortex. Presynaptic nicotinic receptors control the release of acetylcholine as well as other neurotransmitters important for memory and mood, including glutamate, serotonin, and norepinephrine.[1,10]

The discovery of vast cholinergic cell loss led to the development of a cholinergic hypothesis of AD. The cholinergic hypothesis targeted cholinergic cell loss as the source of memory and cognitive impairment in AD. Consequently, it was presumed that increasing cholinergic function would improve symptoms of memory loss. This approach is flawed because cholinergic cell loss appears to be a secondary consequence of AD pathology, not the disease-producing event, and cholinergic neurons are only one of many neuronal pathways destroyed in AD. Simple addition of acetylcholine cannot compensate for the loss of neurons, receptors, and other neurotransmitters lost during the course of the illness. Thus, the goal is to minimize or improve symptoms through augmentation of cholinergic neurotransmission at remaining synapses.

Other Neurotransmitter Abnormalities

Although the cholinergic system has received particular attention in AD pharmaceutical research, deficits also exist in other neuronal pathways. For example, serotonergic neurons of the raphe nuclei and noradrenergic cells of the locus coeruleus are lost, while monoamine oxidase type B activity is increased. Monoamine oxidase type B is found predominantly in the brain and in platelets and is responsible for metabolizing dopamine. In addition, abnormalities appear in glutamate pathways of the cortex and limbic structures, where a loss of neurons leads to a focus on excitotoxicity models as possible contributing factors to AD pathology.

Glutamate is the major excitatory neurotransmitter in the cortex and hippocampus. Many neuronal pathways essential to learning and memory use glutamate as a neurotransmitter, including the pyramidal neurons (a layer of neurons with long axons carrying information out of the cortex), hippocampus, and entorhinal cortex. Glutamate and other excitatory amino acid neurotransmitters have been implicated as potential neurotoxins in AD.[13] Dysregulated glutamate activity is thought to be one of the primary mediators of neuronal injury after stroke or acute brain injury. Although intimately involved in cell injury, the role of excitatory amino acids in AD is yet unclear; however,

blockade of *N*-methyl-D-aspartate (NMDA) receptors decreases activity of glutamate in the synapse and may hypothetically lessen the degree of cellular injury in AD.

Brain Vascular Disease and High Cholesterol

There is growing evidence of a causal association between cardiovascular disease and its risk factors and the incidence of AD. Cardiovascular risk factors that are also risk factors for dementia include hypertension, hypercholesterolemia, and diabetes.[16] For a given amount of AD pathology, vascular disease in the brain may compound the degree of cognitive impairment observed.[14] Vascular disease may accelerate amyloid deposition and reduce clearance of AB from the brain.[17] Presence of cardiovascular risk factors in midlife appears to be most strongly associated with development of AD in late life.[17] Midlife hypertension is adversely associated with AD, while late life hypertension may be inversely associated. Blood pressure appears to decrease in the years leading up to clinical onset of dementia, conceivably because of reductions in physical activity and body weight.[17]

Mechanistically, the increased risk of AD seen among people with prediabetes and diabetes may be a result of microvascular damage or direct neurotoxicity related to increased glucose and insulin levels.[17] Disturbances in insulin-signaling pathways, both in the periphery and the brain, have been linked to AD. Insulin may also regulate the metabolism of Aβ and tau protein.[18]

Research has found multiple links between cholesterol and AD. *APOE* is synthesized in the liver, central nervous system, and cerebrospinal fluid (CSF) and is responsible for transporting cholesterol in the blood through the brain. It is carried by low-density lipoprotein into neurons and binds to NFTs. The *APOE*4* allele is associated with increasing deposition of Aβ and is thought to act as an accelerating modulator in vascular dementia. Elevated cholesterol levels in brain neurons may alter membrane functioning and result in the cascade leading to plaque formation and AD.

Other Mechanisms

Other hypotheses proposed to explain AD pathogenesis include oxidative stress, mitochondrial dysfunction, and loss of estrogen. Each of these mechanisms may contribute to AD pathogenesis, but the extent of the contribution is uncertain. There is a growing body of evidence of a role for oxidative stress and the

accumulation of free radicals in the brains of people with AD.[4] Some epidemiologic studies suggest vitamin E, and possibly the combination of vitamin E and vitamin C, may reduce AD risk, while others do not.[19] Mitochondrial dysfunction may result in disruption of energy metabolism in the neuron.[1,12] The role of estrogen in cognitive aging and dementia continues to be an active area of investigation. Despite convincing evidence that estrogens affect the brain in ways that would be expected to improve cognitive aging and reduce the risk of AD, the results of clinical studies have been largely disappointing.[20]

A single common mechanism for producing AD does not exist. Regardless of the etiology, however, the features remain the same: degeneration of neurons in higher brain areas; accumulation of NFTs and amyloid plaques; profound destruction of cholinergic pathways; and an insidious dementia, slowly progressive until death.

CLINICAL PRESENTATION

4 In the absence of abrupt changes in cognition or function, the onset of AD can be almost imperceptible. There are often pathologic changes related to AD long before symptoms emerge, and further deficits occur progressively over time, affecting multiple areas of cognition and function.[3,12] Early disease may be characterized by changes in learning and memory, planning and organization, and mood. As the disease progresses, patients may experience further declines in these domains, as well as changes in personality, judgment, speech, and spatial orientation. In the late stages, functional decline may be associated with gait changes, swallowing difficulties, and incontinence symptoms; behavioral changes may also result. For treatment and assessment purposes, it is helpful to divide AD symptoms into two basic categories: cognitive symptoms and neuropsychiatric (behavioral) symptoms. Cognitive symptoms are present throughout the illness, whereas behavioral symptoms are less predictable. **Table 71-2** summarizes the stages of AD.

TABLE 71-2 Stages of Alzheimer Disease

Mild (MMSE score 26–21)	Patient has difficulty remembering recent events. Ability to manage finances, prepare food, and carry out other household activities declines. May get lost while driving. Begins to withdraw from difficult tasks and to give up hobbies. May deny memory problems.
Moderate (MMSE score 20–10)	Patient requires assistance with activities of daily living. Frequently disoriented with regard to time (date, year, and season). Recall of recent events is severely impaired. May forget some details of past life events and names of family and friends. Functioning may fluctuate from day to day. Patient generally denies problems. May become suspicious or tearful. Loses ability to drive safely. Agitation, paranoia, and delusions are common.
Severe (MMSE score 9–0)	Patient loses ability to speak, walk, and feed self. Incontinent of urine and feces. Requires care 24 hours a day, 7 days a week.

MMSE, Mini-Mental State Examination.

Data from References 5 and 21.

Diagnosis

Patients or their family and friends may or may not perceive the early decline associated with AD and bring memory complaints to the attention of a primary care clinician. According to the 2018 World Alzheimer Report, dementia is often underdetected, underdiagnosed, and subsequently undertreated.[22] For example, up to 75% of people who meet criteria for dementia are not given a diagnosis in the primary care setting;[23] this may result, at least in part, due to limitations in clinician awareness, training, and/or time.[22] Despite the phenomenon of underdiagnosis, the US Preventive Services Task Force concluded that there are insufficient data to recommend for or against cognitive screening for AD because it could not be determined if the benefits outweigh the risks, as there is no empirical evidence that screening impacts decision-making.[23] That said, an appropriate screening tool may be helpful in aiding diagnosis and leading to earlier treatment.[23] Moreover, the Alzheimer's Association (AA) is currently promoting cognitive screening as part of the Medicare Annual Wellness Visit.[24]

CLINICAL PRESENTATION

Alzheimer Disease

General

- The patient may have vague memory complaints initially, or the patient's significant other may report that the patient is "forgetful." Cognitive decline is gradual over the course of illness. Behavioral disturbances may be present in moderate stages. Loss of daily function is common in advanced stages.

Symptoms

Cognitive

- Memory loss (poor recall and losing items)
- Aphasia (circumlocution and anomia)
- Apraxia
- Agnosia
- Disorientation (impaired perception of time and unable to recognize familiar people)
- Impaired executive function

Neuropsychiatric

- Depression, psychotic symptoms (hallucinations and delusions)
- Behavioral disturbances (physical and verbal aggression, motor hyperactivity, uncooperativeness, wandering, repetitive mannerisms and activities, and combativeness)

Functional

- Inability to care for self (dressing, bathing, toileting, and eating)

Laboratory Tests

- Rule out vitamin B_{12} deficiency with serum vitamin B_{12} testing
- Rule out hypothyroidism and hyperthyroidism with thyroid function tests
- Rules out anemia and infection with complete blood cell count
- Rule out electrolyte and glucose abnormalities and renal and hepatic dysfunction with a comprehensive metabolic panel
- Rule out syphilis with rapid plasma reagin testing

- Rule out human immunodeficiency virus (HIV) with HIV testing

Other Diagnostic Tests

- Computed tomography (CT) or magnetic resonance imaging (MRI) scans may aid diagnosis

The Mini-Mental State Examination (MMSE) is a 30-point assessment tool for AD frequently cited in the literature and employed in practice; because of its copyrighted status, however, the MMSE must either be administered from memory or paid for by the user. Similarly, the Montreal Cognitive Assessment (MoCA) became proprietary in 2019, and users must now be trained and certified. Alternatives include the Mini-Cog and the St Louis University Mental Status Exam (SLUMS).[25] Each of these tools varies in their characteristics, including sensitivity and specificity for identifying an underlying dementia.

Until recently, the only way to confirm a clinical diagnosis of AD was through direct examination of brain tissue at autopsy or biopsy. Several criteria have been used in clinical practice and research for the detection and diagnosis of dementia, including the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) criteria,[26] the Agency for Healthcare Research and Quality (AHRQ) guidelines,[27] the American Academy of Neurology guidelines,[28] the National Institute of Neurological Disorders and Stroke (NINDS) criteria,[29] and the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) criteria.[30] In 2011, revisions to the NINCDS-ADRDA criteria for the clinical diagnosis of AD were recommended by the National Institute on Aging (NIA) and the AA.[31] The new NIA-AA criteria view AD as a spectrum beginning with a preclinical phase progressing to increasingly severe clinical stages of AD. Three workgroups formulated diagnostic criteria for the dementia phase[32]; the symptomatic, predementia phase (MCI)[33]; and the asymptomatic, preclinical phase of AD.[34] The preclinical phase has been further broken down into three stages—stage 1 (asymptomatic cerebral amyloidosis), stage 2 (asymptomatic amyloidosis plus neurodegeneration), and stage 3 (amyloidosis plus neurodegeneration plus subtle cognitive/behavioral decline).[34] Commonalities between guidance documents include the association between impairments in multiple cognitive domains and functional impairment with a clinical diagnosis of AD.

At this time, AD is primarily a clinical diagnosis, but this will likely change

in coming years as brain imaging, CSF testing, and other AD biomarkers supporting definitive diagnosis become increasingly available for routine clinical use. The patient's examination should suggest that cognitive decline from a previously higher baseline has occurred. The history should corroborate this and further indicate that cognitive decline has reached the point where changes in social or occupational functioning are present. It is possible to administer full neuropsychiatric testing—a battery of sophisticated exams that defines cognitive domain strengths and weaknesses and enables a neuroanatomic localization of the observed deficits. When approached in this way, neuropsychiatric testing can indicate a pattern of cognitive decline that is consistent with AD and assist with rendering a diagnosis that is as much a diagnosis of inclusion as it is of exclusion.

Discussing the diagnosis of dementia is potentially distressing for patients and their loved ones, especially at first. Most people, however, prefer to be told about a dementia diagnosis, as it allows them to appropriately plan for the future and access necessary support and treatment services in the meantime.[5]

Objectively defining social or occupational dysfunction can prove tricky in the older patient who may be retired, lead a socially restricted lifestyle, or experience frailty. For such patients, the minimal requirement is to establish a negative impact on day to day life. Early on, this usually involves a change in instrumental activities of daily living (eg, handling finances and organizing medications) rather than basic activities of daily living (eg, hygiene and dressing). Some AD subspecialists use a detailed, standardized, semistructured interview of a nonpatient informant such as a caregiver as the most critical piece of the diagnostic evaluation.[35]

5 For people who meet criteria for dementia (whether the underlying cause is ultimately felt to be AD or not), current recommendations from the American Academy of Neurology include a neuroimaging study (computerized tomography [CT] or magnetic resonance imaging [MRI]), as well as a serologic evaluation that includes blood cell counts, serum electrolytes, liver function tests, a test of thyroid function, and a vitamin B_{12} level to rule out other causes of cognitive decline.[28] When circumstances suggest AD is not the leading entity on the differential diagnosis, other neurologic tests such as CSF analysis or electroencephalogram can occasionally be justified. Neuropsychiatric testing is also considered optional but can prove quite useful for the diagnosis of AD.

Guidelines from the United States, United Kingdom, and Europe currently recommend that structural imaging (noncontrast enhanced CT or, ideally, MRI) be performed in the evaluation of people with suspected dementia.[36] These tests

may identify structural abnormalities consistent with AD or other pathology, such as brain atrophy, vascular damage, or tumors. Efforts to define the role of other AD diagnostic tests are ongoing. Positron emission tomography (PET) scanning may reveal a pattern of hypometabolism typical of AD, but by itself the diagnostic accuracy of PET scanning still lags behind that of the clinical examination and history.[34] Radiologic tracers specific to amyloid plaques, such as florbetapir, may be used to identify individuals with early disease and are often used in research; however, without wide spread access, clinical utility is currently limited. Likewise, *APOE* genotyping is not clinically recommended at this time, as presence of an *APOE*4* allele alone does not cause AD.[37] While *APOE* genotyping by itself is insufficient to make a diagnosis of AD, demonstrating an *APOE*4* allele in a suspected patient increases the specificity of the diagnosis. Unless the person developed dementia before age 60 years and also had a parent who developed AD before age 60 years, presenilin 1, presenilin 2, or APP genotyping is usually not indicated. Unclear benefits, potential harms, and ethical concerns limit testing for genetic causes of dementia; such testing is not part of routine diagnosis and should only be completed with informed consent following genetic counseling.[37]

Mild Cognitive Impairment

It has long been recognized that aging is associated with changes in cognitive function. Importantly, MCI constitutes a syndromic designation that categorizes people with cognitive complaints insufficient to warrant a diagnosis of dementia. The NIA-AA criteria specifically address the diagnosis of MCI.[33] People diagnosed with MCI carry a 10% to 15% chance per year of progressing to an AD diagnosis.[38] While clinicians may be seeing the initial manifestation of a progressive, degenerative dementia that will eventually meet AD diagnostic criteria, it is important to note that not everyone meeting MCI criteria will develop AD.[33,38] When a diagnosis of MCI is made, routine cognitive screening should be done to monitor for further cognitive loss.

TREATMENT

Desired Outcome

6 The primary goal of treatment in AD is to symptomatically treat cognitive

difficulties and preserve patient function for as long as possible. Secondary goals include managing psychiatric and behavioral sequelae. Current AD treatments have not been shown to prolong life, cure AD, or halt or reverse the pathophysiologic processes of the disorder.[35]

General Approach to Treatment

Prior to initiating treatment for AD, a thorough medication review should be completed. Almost any medication can contribute to cognitive impairment in vulnerable individuals, but certain classes of medication are more commonly implicated. Benzodiazepines and other sedative hypnotics, anticholinergics, and antipsychotics have been associated with cognitive impairment.[39] In addition, H_2-receptor antagonists, corticosteroids, and opioids like meperidine have been implicated in cases of delirium or acute cognitive change.[39] Because medications are a reversible cause of cognitive symptoms, medication review and management are essential.

Clinical trials have consistently demonstrated modest benefits of early and continuous treatment with cholinesterase inhibitors.[40] Addition of memantine in moderate-to-severe disease may also provide benefit. Following this approach allows for maximal maintenance of cognition and activities of daily living, with a symptomatic approach being used to address behavioral symptoms as they arise.

Recommendations for patients with renal or hepatic dysfunction or low body weight are detailed in Table 71-6. It is important to consider that most people with AD are older adults and therefore may be taking multiple medications for other acute and chronic health conditions.[41] The benefits of drug therapy for AD and other comorbid medical conditions must be weighed against each drug's time-to-benefit and potential for adverse events.

Provision of education to the patient and family at the time of diagnosis, including discussion of the course of illness, realistic expectations of treatment, and the importance of legal and financial planning are essential to appropriate treatment.

Nonpharmacologic Therapy

7 Alzheimer disease has a profound effect on both the patient and family. Nonpharmacologic interventions are the current primary interventions for management of AD, and medications should be used in the context of

multimodal interventions. Neuropsychiatric symptoms are among the most challenging and distressing symptoms of the disease and may be the determining factor in a family's decision to seek institutional care. Symptoms such as sleep disturbances, wandering, urinary incontinence, agitation, and aggression in patients with dementia are best managed using behavioral interventions rather than medications whenever possible.[40,42]

Upon initial diagnosis, the patient and caregiver should be educated on the course of illness, prognosis, available treatments, legal decisions, and quality of life issues. Caregiving strategies, including stress-management techniques and support group options, should also be discussed. Caregiver education and support programs have been shown to improve caregiver skill, knowledge, confidence, and quality of life, and even delay time to nursing home placement for their loved one.[43] **Table 71-3** lists basic principles of care for people with AD.

TABLE 71-3 Basic Principles of Care for the Person with Alzheimer Disease

1. Consider vision, hearing, or other sensory impairments
2. Find optimal level of autonomy and adjust expectations for patient performance over time
3. Avoid confrontation. Remain calm, firm, and supportive if the patient becomes upset
4. Maintain a consistent, structured environment with stimulation level appropriate to the individual patient
5. Provide frequent reminders, explanations, and orientation cues. Employ guiding, demonstration, and reinforcement
6. Reduce choices, keep requests and demands of the patient simple, and avoid complex tasks that lead to frustration
7. Bring sudden declines in function and the emergence of new symptoms to professional attention

Data from References 2 and 37.

The general approach to nonpharmacologic strategies for behavioral symptoms is to identify the symptom, identify causative factors, and adapt the caregiving environment to remedy the situation.[3] Environmental triggers may include noise, glare, and too much background distraction, including television. Personal discomfort may also trigger behaviors, so it is important to monitor for pain, hunger, thirst, constipation, full bladder, fatigue, infections, skin irritation, personal care, comfortable temperature, fears, and frustrations.[44] Medical comorbidity is a major source of functional and cognitive impairment in people with AD, so general health maintenance is necessary.[3] Interventions should redirect the patient's attention rather than be confrontational and should

specifically address known triggers. Creating a calm environment and removing stressors and triggers is key. Other nonpharmacologic approaches include exercise, light therapy, music therapy, reminiscence therapy, aroma therapy, relaxation techniques, validation therapy, massage and touch therapy, and multisensory stimulation.[45] Caregivers should be referred to support services for assistance in developing nonpharmacologic strategies for managing difficult behaviors.

The caregiver must be prepared to face the changes in life that will occur, and acceptance rarely comes easily. Denial on the part of the patient and rationalization on the part of the family are common. The clinician should encourage the family to address legal and financial matters and designate a durable power of attorney for execution of financial and medical decisions once the patient can no longer make those decisions or is deemed incompetent. The caregiver will need to address issues such as respite services to provide time for rest, relaxation, and conduct of personal business. Eventually, the caregiver will need to face critical and difficult questions with respect to institutionalization. Local and national resources, such as the AA, can provide detailed information regarding support services. **Table 71-4** lists this and other referral sources for caregivers.

TABLE 71-4 Resources for Caregivers of Persons with Alzheimer Disease

The following organizations provide educational literature and information on diagnosis, treatment, social support, and ongoing research in Alzheimer disease:

- US Administration for Community Living, National Family Caregiver Support Program http://acl.gov/programs/support-caregivers/national-family-caregiver-support-program
- National Institute on Aging (NIA) Alzheimer's Disease Education & Referral Center (ADEAR) http://www.nia.nih.gov/health/about-adear-center
- Alzheimer's Association (AA) http://www.alz.org
- Alzforum http://www.alzforum.org
- Caregiver Action Network http://caregiveraction.org
- Family Caregiver Alliance http://www.caregiver.org

Education, communication, and planning are key nonpharmacologic components of caring for a person with AD. Preparation in the early stages of illness may lessen some caregiver stress as the disease progresses.

Pharmacologic Therapy

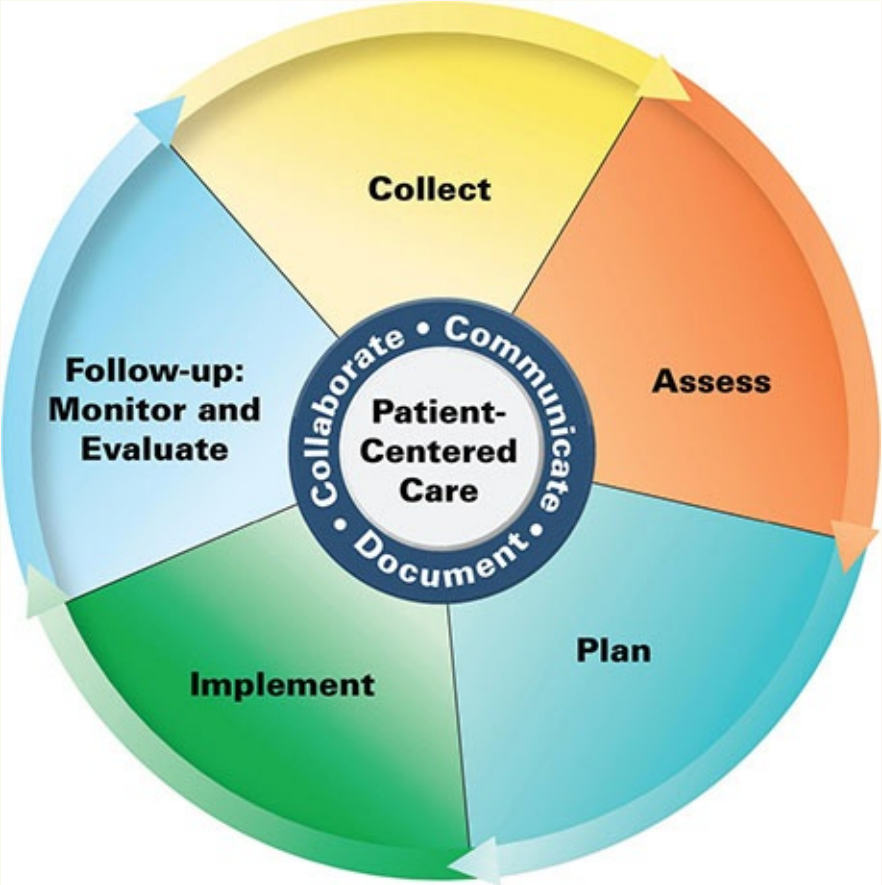
Pharmacotherapy for Cognitive Symptoms

8 **Table 71-5** presents pharmacologic treatment recommendations for managing cognitive symptoms in AD. Cholinesterase inhibitors and NMDA receptor antagonists are indicated for treatment of AD. Current guidelines recommend initiation of cholinesterase inhibitors for AD with no preference for a specific agent.[40] Galantamine and oral rivastigmine are indicated in mild-to-moderate AD. Donepezil and transdermal rivastigmine are indicated in mild, moderate, and severe disease. Despite inconclusive evidence for early intervention, cholinesterase inhibitors are commonly prescribed off-label prior to formal diagnosis of AD. Memantine is indicated for moderate-to-severe AD; current evidence does not support its use in earlier stages of the disease.[40] Additional benefit may be achieved when memantine is added to cholinesterase inhibitor therapy in moderate-to-severe AD.[46] There is no evidence supporting combination therapy of more than one cholinesterase inhibitor. No head-to-head trials comparing memantine monotherapy to cholinesterase inhibitor therapy have been conducted to date.

TABLE 71-5 Pharmacologic Treatment Options for Cognitive Symptoms in Alzheimer Disease

- In mild-to-moderate disease, consider therapy with a cholinesterase inhibitor:
  - Donepezil or
  - Rivastigmine or
  - Galantamine
- Titrate to recommended maintenance dose as tolerated
- In moderate-to-severe disease, consider adding antiglutamatergic therapy:
  - Memantine
- Titrate to recommended maintenance dose as tolerated
- Alternatively, consider memantine or cholinesterase inhibitor therapy alone
- Behavioral symptoms may require additional pharmacologic approaches

Data from Reference 46.



Patient Care Process for Alzheimer Disease

Collect

- Patient characteristics (eg, age, sex)
- Patient history (eg, past medical, family, social history)
- Current medications including medications that may cause or worsen cognitive, neuropsychiatric, and/or functional symptoms (see list of common offending agents, in “Assess”)
- Assessments for cognitive, neuropsychiatric and functional symptoms; for example:
  - Mini-Mental State Examination (cognition)
  - Neuropsychiatric Inventory (behavioral disturbances)
  - Bristol Activities of Daily Living Scale (function)
- Laboratory data

- Comprehensive metabolic panel, including electrolytes, glucose, and liver function tests
- Complete blood cell count, serum B_{12}, and thyroid function tests
- Rapid plasma reagin and human immunodeficiency virus testing

Assess

- Risk factors for Alzheimer disease (eg, age, family history, low education level, smoking)
- Cognitive symptoms (eg, memory loss, aphasia, apraxia, agnosia, disorientation, impaired executive function)
- Neuropsychiatric symptoms (eg, depression, psychotic symptoms, behavioral disturbances)
- Functional symptoms (eg, inability to care for self), including patient's ability to manage and self-administer their own medications
- Medications that may cause or worsen cognitive, neuropsychiatric, and/or functional symptoms; for example:
  - Benzodiazepines and other sedative hypnotics
  - Anticholinergics
  - Opioid analgesics
  - Antipsychotics
  - Anticonvulsants
  - Skeletal muscle relaxants
- Diseases or syndromes that may cause or worsen cognitive, neuropsychiatric, and/or functional symptoms; for example:
  - Alcohol or drug abuse
  - Depression
  - B_{12} or folate deficiency
  - Hypothyroidism
  - Electrolyte disturbances (eg, hypernatremia)
  - Glucose abnormalities (eg, hypoglycemia)
  - Infectious processes (eg, tertiary syphilis)
  - Vision, hearing, or other sensory impairments

- Other common types of dementia in late life (see Table 71-1)
- Stages of Alzheimer disease (see Table 71-2)
- Appropriateness of current living situation (eg, independent living, assisted living, nursing home)
- Appropriateness and effectiveness of current medication regimen

Plan*

- Tailored lifestyle modifications (eg, diet, physical activity) for management of brain vascular health
- Drug therapy regimen for cognitive symptoms (if appropriate) including specific medication(s), dose, route, frequency, and intended duration; specify the continuation and discontinuation of existing therapies (see Tables 71-5 and 71-6)
- Monitoring parameters including efficacy, safety (medication-specific potential adverse drug reactions), and time frame (see Table 71-7)
- Patient, family, and caregiver education (eg, risks vs benefits of treatment, expected outcomes, drug therapy selection)
- Referrals to other health professionals when appropriate (eg, social work, psychology, occupational therapy)

Implement*

- Provide patient, family, and caregiver education regarding all elements of treatment plan
- Provide caregiver access to local and national resources (see Table 71-4)
- Provide family and caregiver education regarding basic principles of care for the patient with Alzheimer disease (see Table 71-3)
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Presence of adverse effects related to medications for cognitive symptoms
- Disease progression, including incidence or worsening of neuropsychiatric symptoms of dementia in accordance with standard assessment tools (see list of commonly used assessments, in “Collect”)
- Patient adherence to treatment plan using multiple sources of information

- Patient, family, and caregiver expectations

* *Collaborate with patient, caregivers, and other health professionals.*

Disagreement exists about how best to determine effectiveness of treatments for AD. Selection of qualitative versus quantitative assessment may bias a clinician's impression of response. Subtle changes are often detected only by psychometric testing. As no standard has been suggested to define the effectiveness of medications for AD, great variation exists between clinicians, and the duration of treatment ranges from months to years. Realistic expectations for treatment success may include slowed decline in behavioral, functional, and cognitive abilities and delayed long-term care placement.[47] An initial dramatic improvement in symptoms is unlikely but may be reported by a minority of patients or their caregivers.[48]

Unfortunately, clinical trials have failed to provide answers to key questions in treating people with AD. Information from clinical trials is insufficient to know if a cholinesterase inhibitor dose–response relationship exists, or if additional cognitive improvement may be gained by increasing to the maximum tolerated dose, rather than continuing with the usual recommended daily dosage. A challenge to interpreting the degree of therapeutic response in clinical trials includes population heterogeneity and difficulties inherent to the diagnosis.[49] For example, individuals given a diagnosis for AD often lack the hallmark pathologies (ie, amyloid plaques and NFTs) on postmortem examination. Additionally, because of overlap between AD and other dementing illness, trials including those diagnosed with AD may in fact include patients with a heterogenous, mixed profile of dementia. Further, as individuals who fail to display the clinical symptoms of the disease may still be developing the underlying pathologies, there may be contamination of control groups. Each of these factors may present a challenge to the internal validity of clinical trials.

Guidance in extrapolating data related to changes in cognition is needed so a reasonable duration of clinical treatment with cholinesterase inhibitors and NMDA antagonists can be determined. One concern is that those who respond to treatment may lose the benefits of that treatment once the medication is stopped.[50] Gaps in treatment have been linked with worse cognitive outcomes in clinical trial extension studies;[51] in a more recent observational study there was no increased risk of institutionalization or death associated with gaps in cholinesterase inhibitor therapy.[52] Regardless, dosing regimens should be simplified and patient and caregiver preferences considered in an effort to

improve medication adherence and persistence.

In natural disease progression studies, scores on the Alzheimer's Disease Assessment Scale—Cognitive Subscale (ADAS-cog) have been shown to worsen (increase) by an average of five or fewer points over 1 year in mild dementia and 7 to 11 points annually in moderate dementia. Based on these findings, the consensus is that a four-point change in the ADAS-cog represents a clinically significant change.[40] Therefore, if a pharmacotherapeutic agent decreases the ADAS-cog score by four points, one could think of this as having delayed progression of disease symptoms by 6 months. The usefulness of the ADAS-cog in clinical practice is limited because of the time required for administration; it is much more practical to assess changes in disease severity using the MMSE or other assessment tool. An untreated person with AD has an average decline of two to four points in MMSE score per year. Successful treatment would reflect a decline of less than two points a year. It is reasonable to change to a different cholinesterase inhibitor if the decline in MMSE score is greater than two to four points after 1 year with the initial agent.[53]

8 **Cholinesterase Inhibitors** In the early 1980s, researchers began to examine means to enhance cholinergic activity in people with AD by inhibiting the hydrolysis of acetylcholine through reversible inhibition of cholinesterase. Tacrine was the first such drug to be examined in a systemaic fashion; however, tacrine was fraught with significant side effects, including hepatotoxicity, which severely limited its usefulness. Tacrine is no longer available in the US market, having been replaced by safer, more tolerable cholinesterase inhibitors. The newer cholinesterase inhibitors donepezil, rivastigmine, and galantamine show similar modest symptomatic improvements in cognitive, global, and functional outcomes in people with mild-to-moderate AD, and duration of benefit varies from 3 to 24 months.[54,55] One open-label extension study of galantamine showed benefit beyond the 24-month mark.[56]

The mechanism of action differs slightly between drugs in this class.[57] Donepezil specifically and reversibly inhibits acetylcholinesterase. Rivastigmine is a pseudo-irreversible inhibitor of both butyrylcholinesterase (an "overflow" enzyme to acetylcholinesterase) and acetylcholinesterase. Galantamine is a selective, competitive, reversible acetylcholinesterase inhibitor that also enhances the action of acetylcholine on nicotinic receptors. The clinical relevance of these differences is unknown.

Choice of cholinesterase inhibitor therapy for an individual patient is based primarily on ease of use, patient preference, cost, and safety issues, such as

potential for drug interactions. Pharmacokinetic properties should also be considered, as rivastigmine and galantamine have short half-lives (1.5 and 7 hours, respectively) compared to donepezil (70 hours). As such, if rivastigmine or galantamine treatment is interrupted for several days or longer, the patient should be restarted at the lowest dose and titrated to the current dose. This is true for all formulations of these drugs, including the rivastigmine transdermal patch.[58–60] Dosing strategies for cholinesterase inhibitors and memantine are summarized in **Table 71-6**.

TABLE 71-6 Dosing of Drugs Used for Cognitive Symptoms

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Other
Cholinesterase Inhibitors					
Donepezil	Aricept, Aricept ODT	5 mg daily in the evening	5-10 mg daily in mild-to-moderate AD 10-23 mg daily in moderate-to-severe AD	No dosage adjustments recommended	Available as: tablet, ODT, oral solution Can be taken with or without food Weight loss associated with 23 mg daily dose
Rivastigmine	Exelon	1.5 mg twice daily (capsule, oral solution) 4.6 mg/day (transdermal patch)	3-6 mg twice a day (capsule, oral solution) 9.5-13.3 mg/day (transdermal patch)	Capsule/oral solution: Renal impairment, hepatic impairment, or low body weight (<50 kg [<110 lb]): Patients may be able to only tolerate lower doses Transdermal patch: Mild-to-moderate hepatic impairment or low body weight: consider maximum daily dose of 4.6 mg every 24 hours	Available as: capsule, oral solution, transdermal patch Take with meals Also indicated for Parkinson disease dementia Application of multiple transdermal patches at same time associated with hospitalization and death
Galantamine	Razadyne, Razadyne ER	4 mg twice daily (tablet, oral solution) 8 mg daily in the morning (extended-release capsule)	8-12 mg twice a day (tablet, oral solution) 16-24 mg (extended-release capsule)	Moderate renal or hepatic impairment: maximum daily dose of 16 mg Severe renal or hepatic impairment: not recommended	Available as: tablet, oral solution, extended-release capsule Take with meals
***N*-methyl-D-aspartate (NMDA) Receptor Antagonist**					
Memantine	Namenda, Namenda XR	5 mg daily (tablet, oral solution) 7 mg daily (extended-release capsule)	10 mg twice daily 28 mg daily (extended-release capsule)	Severe renal impairment: recommended maintenance dose of 5 mg twice daily (tablet, oral solution) or 14 mg daily (extended-release capsule) Severe hepatic impairment: administer with caution	Available as: tablet, oral solution, extended-release capsule Can be taken with or without food Can open capsule and sprinkle contents on applesauce for ease of administration
Cholinesterase Inhibitor + NMDA Receptor Antagonist					
Memantine + Donepezil	Namzaric	7 mg/10 mg (if patient is stabilized on donepezil and not currently on memantine) 28 mg/10 mg (if patient is stabilized on memantine and donepezil)	28 mg/10 mg daily	Severe renal impairment: 14 mg/10 mg daily	Available as: memantine extended-release and donepezil capsule Can be taken with or without food Can open capsule and sprinkle contents on applesauce for ease of administration

ODT, orally disintegrating tablet.

Data from References 58–60.

Adverse drug reactions and corresponding monitoring parameters are described in **Table 71-7**. Cholinesterase inhibitors have similar adverse event profiles, and this class of drugs is generally well-tolerated. The most frequent adverse events associated with these agents are mild-to-moderate gastrointestinal (GI) symptoms (eg, nausea, vomiting, and diarrhea).[61] Gradual dose titration over several weeks to months can improve tolerability.[25] Alternatives to the immediate-release tablet/capsule dosage form are available for patients who have complex dosing regimens, tolerability issues, or difficulty swallowing, though cost may be prohibitive until they are generically available. Bradycardia has been noted to be a potentially dose-limiting side effect for the class. Patients and caregivers should be cautioned against abrupt discontinuation of cholinesterase inhibitor therapy, as this can lead to worsening cognition and behavior in some people with AD.[62] Concurrent use of anticholinergic medications with cholinesterase inhibitors should be avoided and nonpharmacologic interventions employed to manage urinary incontinence, if possible.[63]

TABLE 71-7 Monitoring Drug Therapy for Cognitive Symptoms

Drug	Adverse Drug Reaction	Monitoring Parameter	Comments
Galantamine	Serious skin reactions (Stevens-Johnson syndrome and acute generalized exanthematous pustulosis)	Appearance of skin rash	Discontinue galantamine at first sign of skin rash, unless clearly not drug related If signs/symptoms are suggestive of a serious reaction, consider alternative treatment and do not rechallenge
Rivastigmine	Allergic dermatitis	Application site reaction spread beyond patch size, evidence of a more intense local reaction (increasing erythema, edema, papules, vesicles), and persistence of symptoms for more than 48 hours after patch removal	Discontinue rivastigmine if evidence of disseminated allergic dermatitis appears Patients sensitized by exposure to the transdermal patch may not be able to take rivastigmine by mouth either; allergy testing and close medical supervision recommended
Cholinesterase inhibitors	Dizziness, syncope, bradycardia, atrial arrhythmias, sinoatrial and atrioventricular block, myocardial infarction	Report of dizziness or falls, pulse, blood pressure, and postural blood pressure change	Dizziness is usually mild, transient, and not related to cardiovascular problems Routine pulse checks at baseline, monthly during titration, and every 6 months thereafter
	Nausea, vomiting, diarrhea, anorexia, weight loss	Weight and GI complaints	Take with food to decrease GI upset Usually transient, dose-related GI adverse effects seen with drug initiation, dosage titration, or drug switch Debilitated patients or those weighing <55 kg (<121 lb) may be more likely to experience GI adverse effects and significant weight loss, particularly when rivastigmine is prescribed or when titrating to donepezil 23 mg GI adverse effects less prominent with transdermal versus oral rivastigmine
	Peptic ulcer disease, GI bleeding	Signs or symptoms of active or occult GI bleeding	Of particular concern for patients at increased risk of developing ulcers, such as those with a history of ulcer disease or concurrently taking NSAIDs
	Insomnia, vivid/abnormal dreams, nightmares	Complaints of sleep disturbances, daytime drowsiness	Donepezil can be taken in the morning to decrease risk of sleep disturbances
Memantine	Headache, confusion, dizziness, hallucinations	Report of dizziness or falls, hallucinations	Confusion may be observed during dose titration and is usually transient
	Constipation	GI complaints	Memantine may mitigate GI adverse effects associated with cholinesterase inhibitor therapy

GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs.

Data from References 40, 58–60.

The use of high-dose donepezil 23 mg was approved in 2010.[64] While data reveal an improvement in cognitive measures, many consider this threshold to be clinically insignificant. Additionally, use of this dose is associated with a

threefold increased risk of GI side effects and a near doubling in the rate of treatment withdrawal. This dose is no longer routinely prescribed in clinical practice.

Depending on individual patient response, tolerability, and preference, switching to an alternate dosage form or cholinesterase inhibitor agent may be necessary during the course of AD treatment. Manufacturer recommendations for switching between dosage forms of the same drug are specified in the prescribing information, but the optimal procedure for switching between agents remains uncertain. When switching from one cholinesterase inhibitor to another due to side effect intolerance, a washout period is recommended.[48] Length of the washout period may vary based on drug pharmacokinetics and time to side effect resolution.[48,53] Some patients who fail to respond to donepezil, rivastigmine, or galantamine may respond when switched to a different drug; in the case of lack of initial benefit, an overnight switch is preferred to minimize potential for clinical deterioration.[48,53] To clarify, loss of benefit over time may not be an appropriate reason to switch cholinesterase inhibitors, as the progressive nature of AD is likely to become more noticeable over time.[53] Indeed, initiation of memantine may be a more appropriate next step as patients progress in their disease course.[37]

8 **Antiglutamatergic Therapy** Memantine is the only NMDA antagonist currently available. At concentrations achieved at least under in vitro conditions, memantine blocks glutamatergic neurotransmission by antagonizing NMDA receptors. Glutamate is an excitatory neurotransmitter in the brain implicated in long-term potentiation, a neuronal mechanism important for learning and memory.[37] Blocking NMDA receptors can mitigate excitotoxic neurotoxicity and potentially provide neuroprotection (as has been suggested in animal models); however, there is currently no clinical evidence to indicate that memantine confers neuroprotection in AD.[65]

Memantine is currently indicated for use in moderate-to-severe AD.[66] Its use has been studied in people with moderate and severe AD as monotherapy and in combination with donepezil with favorable results on cognition and function.[46] To date, studies of memantine alone and in combination with cholinesterase inhibitors in mild AD have provided insufficient evidence to support an indication for mild AD.[46]

In its tablet or oral solution form, memantine should be initiated at 5 mg once a day and titrated weekly in 5 mg intervals to the target maintenance dose of 10 mg twice daily. The extended-release capsule form of memantine is to be

initiated at 7 mg daily and titrated up to a maximum of 28 mg daily. Dose titration is achieved in 7 mg intervals with at least 1 week between dose adjustments. Dosing of 5 mg twice daily (tablet and oral solution) or 14 mg daily (extended-release capsule) is recommended in patients with severe renal impairment (creatinine clearance of 5-29 mL/min [0.08-0.49 mL/s]).

Overall, memantine has been well-tolerated in clinical trials. The most common adverse events include headache, constipation, confusion, and dizziness. Memantine has 100% bioavailability regardless of administration with or without food. Protein binding is relatively low (45%). Memantine is not metabolized by the liver and does not inhibit cytochrome P450 activity. It is primarily excreted unchanged in the urine, and the half-life of memantine ranges from 60 to 80 hours.[66,67]

Role of Combination Therapy Combination therapy with memantine added to a cholinesterase inhibitor is generally prescribed for people with moderate-to-severe AD. The rationale for this add-on therapy is that the drug classes have different mechanisms of action.

Combination therapy has been supported in several randomized controlled trials (RCTs) and reviews.[68] Combination therapy has been shown to slow cognitive and functional decline to a statistically significant degree compared to cholinesterase inhibitor monotherapy or no treatment.[68] One trial randomized people with moderate-to-severe AD already receiving stable donepezil treatment to either memantine or placebo. At the end of this 6-month trial, participants randomized to receive memantine (combination therapy) had significantly better outcomes in measures of cognition, function, behavior, and global status than those continued on donepezil monotherapy. The group randomized to receive memantine also had a lower rate of discontinuation due to adverse events versus placebo.[69] Based on data from this study and others, memantine may have a role in mitigating GI adverse events associated with cholinesterase inhibitors.[40]

In 2014, a combination product containing memantine extended-release and donepezil was approved by the US Food and Drug Administration (FDA) for moderate-to-severe AD in patients already stabilized on memantine and donepezil.[70] As drug effectiveness was based on bioequivalence with the two active ingredients, the package insert separately lists the most common side effects of memantine extended-release and donepezil. The fixed-dose combination product comes in four strengths, and dosage reduction is recommended in the case of severe renal impairment. No dosage adjustments are needed in patients with mild or moderate renal or hepatic impairment. The drug

has not been studied in patients with severe hepatic impairment.

Effect of Current Treatments on Neurodegenerative Processes Alzheimer disease is a progressive disorder and affected individuals typically experience some degree of cognitive decline and histologic change years (if not decades) before a diagnosis is made. Therefore, the ideal treatment will be one that not only reverses symptoms by enhancing cognitive function (a symptomatic treatment) but also arrests the neurodegeneration-relevant molecular processes that underlie cognitive decline (a disease-modifying treatment).

Clinical trials for AD prompt consideration of whether positive outcomes suggest either a symptomatic or disease-modifying effect. Any rapid performance improvement in cognitive ability, activities of daily living, or behavioral end points is indicative of a symptomatic effect. All cholinesterase inhibitor agents and memantine demonstrate this pattern. Arrest of decline or a sustained reduction in the slope of decline would argue the presence of a disease-modifying effect; however, it has not been possible to unequivocally demonstrate this in trials of the currently approved treatments. Long-duration, double-blind, placebo-controlled trials to evaluate whether cholinesterase inhibitors, with or without memantine, have disease-modifying effects are difficult to perform, because doing so would require continuing a placebo arm over an extended period, well beyond demonstration of symptomatic benefit. Also, subject attrition over an extended study would complicate both intent-to-treat and observed case analyses.

With the currently approved AD drug treatments, pivotal placebo-controlled trials were followed by open-label extension studies. Published studies have lasted as long as 5 years. As part of these studies, decline in the treatment group was compared with “projected” placebo groups based on the placebo groups followed during the 6-month randomized phase of the efficacy study, as well as natural history cohorts from the pre-cholinesterase inhibitor therapy era. Although analyses of this sort conclude that, for up to at least 5 years, people receiving treatment exceed their projected nontreatment cognitive performance, no convincing evidence of a disease-modifying effect emerges.[71–74]

9 **Management of Brain Vascular Health** Guidelines for the care of people with AD support the management of vascular brain disease and its associated risk factors as part of the treatment of AD.[37] There is a link between AD and cardiovascular disease, including heart failure, atrial fibrillation, and coronary artery disease,[15] and a growing body of evidence that brain vascular disease plays a role in the progression of dementia. Management of brain vascular

disease includes monitoring blood pressure, glucose, and cholesterol, and initiation of appropriate interventions.[75–77]

The World Health Organization and Alzheimer's Disease International encourage primary prevention through public health campaigns targeting smoking, underactivity, midlife obesity, midlife hypertension, and diabetes.[78] Adherence to the Mediterranean Diet (MeDi) or Dietary Approaches to Stop Hypertension (DASH) diet may reduce the risk of cognitive impairment or decline.[17,79] Physical activity is an important component of vascular brain health and has been shown in some short-term studies to be associated with a reduced risk of cognitive impairment as well.[17,80] Of note though is that most positive trial findings have been from cognitively healthy older adults.[17,79]

While appropriate management of vascular disease risk factors may reduce the risk for developing AD,[81] insufficient evidence exists to draw definitive conclusions on the association between risk factor modification and risk of AD.[17,75]

Other Potential Treatment Approaches

Estrogen Estrogen replacement has been studied extensively for the treatment and prevention for AD. Most, but not all, retrospective epidemiologic studies show a lower incidence of AD in women who took estrogen replacement therapy after menopause. Prospective clinical trials have not supported the use of estrogen as a treatment for cognitive decline, and longer trials tend to suggest harm. Overall, the evidence does not support the use of estrogen to treat or prevent dementia.[20] Although phytoestrogens found in soy-containing foods and soy-derived dietary supplements have been suggested for the treatment or prevention of dementia, there are no clinical trials supporting such use.[20]

Anti-inflammatory Agents Retrospective epidemiologic studies suggest a protective effect against AD in patients who have taken nonsteroidal anti-inflammatory drugs (NSAIDs); however, the benefits of anti-inflammatory agents have been less compelling in prospective clinical studies. In fact, no significant cognitive benefit has been demonstrated in persons with AD treated with NSAIDs, aspirin, or steroids.[82] Moreover, because there is a lack of compelling data and also a significant incidence of adverse effects, particularly gastritis and the possibility of GI bleeds, these agents are not recommended for general use in the treatment or prevention of AD.[82]

Lipid-Lowering Agents Randomized controlled trials of statin therapy given in

late life to people at risk for vascular disease indicate that statins do not prevent AD.[83] Four randomized placebo-controlled trials of statin therapy indicated no significant benefit of statin therapy in people with probable or possible AD.[83] Interestingly, cognitive impairment has been recognized as a rare adverse event associated with statin therapy.[84] More research is needed to understand the complex relationship between cholesterol, statin therapy, and cognitive functioning. For now, these agents should be reserved for patients who have other indications for their use.

Dietary Supplements Dietary supplements are widely used for the prevention and treatment of AD, and available evidence has been reviewed.[85–87] A detailed discussion of the many nutraceuticals, herbal products, and medical foods that have been promoted for the prevention and treatment of AD is beyond the scope of this chapter. The more commonly used dietary supplements are described here.

Vitamin E supplementation Based on pathophysiologic theories involving oxidative stress and the accumulation of free radicals in AD, significant interest has evolved regarding the use of antioxidants in the treatment of AD. Two RCTs have evaluated the effects of vitamin E supplementation (1,000 IU twice daily) in people with AD. The first studied people with moderate AD for 2 years and demonstrated a significant delay in the time to institutionalization in the treatment group compared to placebo.[88] The second trial studied the efficacy of α-tocopherol, memantine, or their combination in delaying clinical progression of AD in people with mild-to-moderate AD taking an acetylcholinesterase inhibitor (mean follow-up time of 2.3 years) and showed a reduced annual rate of decline in activities of daily living in those treated with vitamin E, but no cognitive benefits were seen.[89] No significant side effects were reported between treatment groups in either study; however, a meta-analysis found that high-dose vitamin E increases mortality in supplemented subjects.[90] In addition, vitamin E had no benefit in people with MCI in the progression to AD,[91] or in preventing dementia in asymptomatic older men.[92] In light of these findings, there is insufficient evidence to recommend vitamin E supplementation for the treatment or prevention of AD.[93]

Vitamin B supplementation Elevated serum homocysteine is associated with cognitive decline.[94] Supplementation with B vitamins (folic acid along with B_{12} and/or B_6) has been explored to reduce homocysteine levels in older adults with dementia. Clinical trials consistently demonstrate reduced homocysteine levels

in the intervention groups receiving vitamin B supplementation but without significant difference in MMSE scores between control and intervention groups. In other words, reduced homocysteine levels have not translated into improved cognitive outcomes for people with AD thus far.[94]

Ginkgo biloba *Ginkgo biloba* for the prevention and treatment of AD has been extensively studied. Proposed mechanisms for its use in AD include the potential to increase blood flow, decrease blood viscosity, antagonize platelet-activating factor receptors, increase anoxia tolerance, inhibit monoamine oxidase, and serve as an antioxidant. Active ingredients in *Ginkgo biloba* include flavonoids, *Ginkgo* flavone glycosides, and bioflavonoids. Most studies reporting benefit in people with cognitive impairment or dementia have studied a standardized extract, EGb 761, in doses of 240 mg/day for 22 to 26 weeks.[95] The clinical significance of the modest benefits detected is unclear, and direct comparisons to cholinesterase inhibitors or memantine are lacking. A large trial of *Ginkgo biloba* in which the 120 mg twice a day dose was studied did not reduce either the overall incidence rate of dementia or AD in older adults with normal cognition or MCI.[96] Another large trial found that the long-term use of *Ginkgo biloba* extract did not reduce the risk of progression to AD among older adults suffering from memory complaints compared with placebo.[97] Side effects reported from EGb 761 studies were typically mild, including nausea, vomiting, diarrhea, headaches, dizziness, palpitations, restlessness, and weakness. Because EGb also has a potent antiplatelet effect, it should be avoided by individuals taking anticoagulant or antiplatelet therapies and should be used cautiously in patients taking NSAIDs.[95,98]

Medical Foods Several medical foods have been studied for the treatment of MCI or AD, but there is little evidence of benefit to date. Medical foods constitute a unique category that consists of ingestible entities intended for the treatment of diseases that have “specific nutritional requirements” and for which the medical food may manipulate disease-relevant pathophysiology. Medical foods are intended to be used under the supervision of a physician.[99] The medical foods used for people with mild-to-moderate AD are Axona, Souvenaid, and CerefolinNAC.

Axona (caprylidene) is a mixture of medium-chain fatty acids, consisting primarily of the C8 fatty acid caprylic acid.[100] Caprylidene is converted by the liver to a ketone body, β-hydroxybutyrate, which crosses the blood–brain barrier and can be used as an alternative fuel to glucose in the brain. Support for caprylidene efficacy in the treatment of AD comes from a single clinical trial in

which subjects randomized to 40 mg/day of caprylidene for 45 days performed relatively better on the ADAS-cog than did subjects randomized to a placebo.[101] A subanalysis of these data revealed that this benefit was entirely driven by subjects who did not have an *APOE*4* allele. In general, side effects were considered mild, with GI-related effects being the most common. Coconut oil is a source of caprylic acid but may not contain sufficient quantities to meet the needs of a person with AD; however, it continues to be used by some patients as a less expensive alternative to caprylidene.[100]

Souvenaid is a mixture of omega-3 fatty acids (eicosapentaenoic and docosahexaenoic acids), uridine monophosphate, phospholipids, B complex vitamins (B_6, B_{12}, and folate), choline, vitamin E, and selenium.[102] A systematic review and meta-analysis of three RCTs comparing Souvenaid to placebo found no significant differences in cognition, function, or behavior, although one study showed improvement in verbal recall in people with very mild AD in the Souvenaid treatment group.[102] No serious adverse events were reported in the clinical studies.

CerefolinNAC contains vitamin B_{12}, L-methylfolate, and N-acetylcysteine, and its use targets the association of hyperhomocysteinemia with MCI and progression to dementia. In a prospective case-control study of 34 people with AD and hyperhomocysteinemia receiving CerefolinNAC and 82 people with AD without elevated homocysteine levels not receiving CerefolinNAC, longer CerefolinNAC treatment duration, milder baseline severity, and greater magnitude of homocysteine reduction from baseline were all significant predictors of slowed decline in learning and memory.[103] Randomized controlled trials are needed to confirm these findings. To date, there is insufficient evidence to recommend medical foods for the treatment of AD.

Omega-3 Fatty Acids Arguments that omega-3 fatty acids found in fish oil, such as docosahexaenoic acid and eicosapentaenoic acid, could benefit individuals with AD have existed for some years. A recent Cochrane review including three high-quality RCTs ($n = 632$) found no evidence of benefit on cognition, function, dementia severity, or quality of life resulting from supplementation with omega-3 fatty acids in people with AD; no significant adverse events were identified either.[104] There is insufficient evidence at this time to recommend omega-3 fatty acids for the treatment of AD.

Drugs and Treatment Strategies in Development New drug development is focused on disease-modifying and prevention strategies and has fallen broadly

into several categories: treatments designed to reduce levels of brain Aβ or manipulate its configuration, treatments targeting tau protein, anti-inflammatory approaches, and therapies to address insulin resistance in the brain. Although many potential new drugs have advanced to early clinical studies, no new agents have entered the market since 2004. While progress has been made in developing novel biomarkers and improving clinical trial designs, results of clinical trials remain disappointing.[18] Suggestions of efficacy in phase II trials in no way ensure efficacy will be seen in phase III trials. This caveat seems especially pertinent in AD drug development, as phase II trials of flurbiprofen, tramiprosate, rosiglitazone, latrepirdine, bapineuzumab, and solanezumab all reported some evidence of efficacy that did not bear out in phase III studies. Of course, successful development of new AD treatments depends on elucidating AD's true underlying pathophysiology.

One reason for the failure of so many AD therapies may be that current strategies do not target the pathways that ultimately result in AD. Another reason may be that medications are being initiated when the disease has already progressed too far to be reversed.[18] Focus on the amyloid hypothesis of AD and to a lesser extent tau may have led to discounting other approaches to the treatment of AD. Alzheimer disease is likely a multifactorial condition, which suggests that a single approach will not prevent or treat AD in all patients. Some of the potential targets of interest going forward include cerebrovascular disease, dysfunction of neuronal networks, inflammation, infectious agents such as herpes virus or prions, accumulation of neurotoxic proteins related to sleep deprivation and blood–brain barrier dysfunction, mitochondrial dysfunction, environmental factors, and conditions affecting brain vascular health including diabetes, obesity, hypertension, and hypercholesterolemia.[18] There is also a great deal of attention among AD researchers to identify biomarkers for AD, and recommendations are likely to evolve over time as we better understand the underlying pathophysiology of AD and the predictors of patient response. Regardless, at this time there are no specific recommendations regarding the choice of drug, dosing regimen, or treatment duration for cognitive agents (ie, cholinesterase inhibitors and memantine) based on genotype or other biomarkers.

Given the exponentially increasing number of individuals and families facing the diagnosis of AD, government leaders of G7 countries held a summit in 2013 to strategize and drive innovation to improve quality of life for people affected by AD, establishing a goal to find a cure or disease-modifying therapy by 2025.[105] An increase in funding followed, resulting in more research directed

toward achieving this goal. Furthermore, the National Institutes of Health, FDA, pharmaceutical companies, and nonprofit organizations joined together in 2014 to form the “Accelerating Medicines Partnership” to create networks, share data, and manage clinical trials.[106]

Pharmacotherapy of Neuropsychiatric Symptoms

Most patients with AD manifest neuropsychiatric symptoms (also referred to as behavioral and psychological symptoms of dementia [BPSD]) at some point in the illness.[107–109] These symptoms can be roughly divided into four categories: (1) psychotic; (2) hyperactive (eg, inappropriate or disruptive behavior); (3) affective (eg, depression); and (4) apathy.[107,108] Effective management of these problems is important because behavioral symptoms are distressing to both the patient and caregiver, necessitate increased caregiver supervision and patience, and are a leading reason for nursing home placement.

10 Strategies for treatment of BPSD should include nonpharmacologic interventions first, then pharmacologic interventions only when necessary. Behaviors, such as agitation, aggression, delusions, hallucinations, repetitive vocalizations, and wandering, may be caused by medications, medical illness (eg, pain, constipation, dehydration, infection), environmental precipitants, physical/verbal abuse, and unmet physical or psychological needs. Correct possible underlying causes before initiating drug therapy.[109,110] The need for medications may arise when neuropsychiatric symptoms are of sufficient severity to cause significant distress to the patient or caregiver, interfere with function or cause disability, impede delivery of necessary care, or pose a danger to self or others and have not responded to nonpharmacologic interventions.[40,109,111] The balance between potential risks and expected benefits of the intended medication must be acceptable to the patient or surrogate decision maker. Medications should be used cautiously, with adequate monitoring for effectiveness and adverse events.

Despite the high prevalence of neuropsychiatric symptoms in AD, relatively little research has been conducted, and no drug is approved by the FDA for the treatment of BPSD. In light of limited clinical data, treatment is primarily empiric, with side effect profiles used as a guide in selecting the appropriate treatment. For instance, psychotropic medications with anticholinergic effects should be avoided because they may worsen cognition and interfere with cholinesterase inhibitor therapy.

General guidelines governing pharmacologic therapy for BPSD can be

summarized as follows: reserve for situations where nonpharmacologic therapies failed, use reduced doses, monitor closely, titrate dosage slowly, minimize duration of therapy, attempt tapers, and document carefully. Treatment should be considered temporary.[110] Caregivers may have unrealistic expectations regarding the effects of psychotropic medications, and the anticipated benefits and risks of therapy should be clearly explained. Disruptive behaviors and delusions wax and wane with disease progression, and some behaviors (eg, wandering, hoarding, screaming, repetitive behaviors) lack evidence of response to medication.[112] Attempts to slowly taper and discontinue medication should be undertaken regularly in minimally symptomatic patients, as behaviors often fluctuate, changing in character and intensity over time, and the medication may no longer be providing a benefit.[109]

Cholinesterase Inhibitors and Memantine Some evidence supports that cholinesterase inhibitors and memantine may be beneficial in both managing BPSD and reducing their incidence.[108] While cholinesterase inhibitors may improve apathy, depression, tension, and irritability in mild-to-moderate dementia, they do not appear to significantly reduce acute agitation.[108] Memantine shows modest benefit for agitation, aggression, delusions, and hallucinations; however, recent trials of memantine specifically evaluating its effect on treating agitation in people with AD found no benefit.[108] These benefits should be considered along with cognitive benefits in treatment decisions and weighed against the side effects associated with these medications. Long-term effects on behavior have not been demonstrated to date, and further research is needed.

Antidepressants Antidepressants may be prescribed for BPSD to help manage depression, anxiety, apathy, as well as agitation and aggression. Depressive symptoms and anxiety are common in people with AD. Apathy is seen in 48% to 92% of individuals with dementia, and clinically significant depression occurs in approximately 32% with mild dementia, 23% with moderate disease, and 18% in the severe stage of the dementia.[113] Results of trials studying the efficacy of antidepressants in treating depression in people with AD are conflicting,[109] and improvement among participants receiving placebo is also common. In practice, treatment with selective serotonin reuptake inhibitors (SSRIs) is initiated most commonly in people with AD, based on side effect profile, risk of drug interactions, and evidence of efficacy.[109] Among the SSRIs, the best evidence exists for sertraline and citalopram.[109] Serotonergic function may also play a role in some of the other behavioral symptoms of AD, such as agitation, and some

studies support the use of SSRIs in managing these behaviors, even in the absence of depression.[109] Clinical trials are needed to compare the efficacy of SSRIs to atypical antipsychotics. Tricyclic antidepressants should generally be avoided because of their anticholinergic activity.[108] Chapter 85 has a more complete discussion of treatment of depression.

Antipsychotics Antipsychotics are used in the management of neuropsychiatric symptoms in AD despite efforts by the Centers for Medicare and Medicaid Services (CMS) and other groups to reduce their use in nursing homes.[114] Currently, no antipsychotic has gained FDA approval for management of behavioral symptoms in AD. There is modestly convincing evidence that certain atypical antipsychotics provide some benefit for particular neuropsychiatric symptoms. The most studied antipsychotics for BPSD are aripiprazole, risperidone, olanzapine, and quetiapine. More than 20 RCTs have evaluated atypical antipsychotics for BPSD, with more than 5,000 patients participating and treatment durations of 6 to 26 weeks for most trials.[115] A meta-analysis of 16 trials demonstrated the efficacy of these atypical antipsychotics (ie, aripiprazole, risperidone, olanzapine, and quetiapine) over placebo; however, they were associated with a higher risk of adverse effects. The investigators concluded the increased risk of adverse effects and mortality may offset the benefit. A double-blind, placebo-controlled, outpatient trial of 421 people with AD and psychosis, aggression, or agitation randomized to receive olanzapine, quetiapine, risperidone, or placebo for up to 36 weeks found no significant differences among treatments in time to discontinuation of treatment or improvement based on the Clinical Global Impression–Change (CGI-C) response. The investigators concluded that adverse effects may offset the therapeutic advantages of atypical antipsychotics for treatment of psychosis, aggression, or agitation in people with AD.[116]

Adverse events are common with atypical and typical antipsychotics in people with AD and include somnolence, extrapyramidal symptoms, abnormal gait, cerebrovascular events, and increased risk of death.[115] Compared to atypical agents, typical antipsychotics are associated with more severe extrapyramidal effects and hypotension. In 2005, the FDA mandated the addition of a “black box warning” to all atypical antipsychotics due to increased risk of mortality in older adults with dementia-related psychosis; this warning was expanded in 2008 to include all typical antipsychotics as well.[117] Mortality was mostly cardiovascular (eg, sudden death, heart failure) or infectious (eg, pneumonia) in nature. In 2011, the Office of Inspector General released its

"Medicare Atypical Antipsychotic Drug Claims for Elderly Nursing Home Residents" report, which described that the majority (83%) of atypical antipsychotic drug claims were for residents without FDA-approved indications for use.[118] In 2012, CMS launched the National Partnership to Improve Dementia Care in Nursing Homes to improve quality of care for nursing home residents with dementia. The percentage of residents receiving antipsychotic therapy has since decreased, from 23.9% in 2011 to 14.6% in 2018;[114] this still means though that about 1 in 6 people living in nursing homes are receiving antipsychotic medications.

Overall, there is a modest expectation of treatment benefit and potential for significant harm associated with antipsychotic use in people with AD. Individual risk and benefit must be considered and discussed with family and caregivers when initiating therapy. Prescribing of antipsychotics in AD should be restricted to patients with severe symptoms that have not responded to other measures, and treatment should be tapered as early as possible.[110,111] Doses should be initiated at one-third to one-half of the usual adult starting dose (or with smallest available tablet strength), and target doses are much lower than those for other indications.[110] The American Psychiatric Association guidelines recommend tapering and discontinuing the antipsychotic after 4 weeks at an adequate dose if no clinical benefit is seen. If benefit is seen, an attempt to taper should be made 4 months after initiation as need for medication may change and to reduce risk of harm.[110] A meta-analysis of RCTs of antipsychotic discontinuation showed no significant difference in change in severity of BPSD upon discontinuation compared to the continuation group.[119] For patients continued on antipsychotics, monitor for tardive dyskinesia and metabolic adverse effects. Chapter 84 includes a more detailed discussion of antipsychotic adverse events and monitoring.

Miscellaneous Therapies Because antipsychotic and antidepressant therapies have shown only modest efficacy and pose the potential for undesirable side effects, medications traditionally used to treat disruptive behaviors and aggression in other psychiatric and neurologic disorders have been suggested as potential alternatives. These alternatives include benzodiazepines and anticonvulsants.[109]

Benzodiazepines have been used to treat anxiety, agitation, and aggression, but the benefit is unclear especially given the risk of sedation, falls, impaired cognition, respiratory depression, and paradoxical disinhibition.[108] Evidence for their use in BPSD is lacking. Anticonvulsant "mood stabilizers" such as

carbamazepine, lamotrigine, gabapentin, and pregabalin may have some benefit but evidence is limited or conflicting.[120] Adverse effects and drug interactions of carbamazepine often outweigh benefits. Valproic acid is no longer recommended as a result of an association of mood stabilizers with severe side effects in patients with BPSD.[108]

Neuropsychiatric symptoms are often the most difficult aspect of AD for the caregiver. When nonpharmacologic approaches fail, selected antipsychotics and antidepressants may be useful for effective management of behavioral, psychotic, and depressive symptoms, thereby easing caregiver burden and allowing the patient to spend additional time at home. All too often, however, nonpharmacologic measures are not implemented appropriately, and medication overuse is an ongoing problem. Adverse events remain an important concern in this population as well.

EVALUATION OF THERAPEUTIC OUTCOMES

An evaluation of therapeutic outcomes in the person with AD begins with a thorough assessment at baseline and a clear definition of therapeutic goals. Cognitive status, functional performance, mood, and behavior all need to be evaluated before initiation of drug therapy. The clinician should interview both the patient and the caregiver to assess response to drug therapy. In evaluating response to cognitive agents, the clinician should ask questions about the patient's ability to perform daily functional tasks, mood and behavior, and memory and orientation. Objective assessments (eg, MMSE for cognition, Bristol Activities of Daily Living Scale for function, Neuropsychiatric Inventory for behavioral disturbances) can be used to quantify changes over time.[121]

Because target neuropsychiatric symptoms of dementia may manifest differently, a detailed list of symptoms to be treated should be documented in the pharmacotherapy plan to aid in monitoring. These could include, for example, "striking at spouse because patient believes spouse is an impostor" or "verbal threats and refusal to allow clothes to be changed," as opposed to documenting vague symptoms, such as "aggression" or "delusions." To make an accurate assessment of depression, multiple symptoms (eg, sleep, appetite, activity, interest levels) need to be considered in addition to the patient's stated mood. As noted above, the failure of pharmacologic modalities to impact these target symptoms should result in discontinuation. If responses are seen, tapering and subsequent monitoring for recurrence should be undertaken.

The patient should be observed carefully for potential side effects of drug

therapy. The specific side effects to be monitored and the method and frequency of monitoring should be documented. Consensus on frequency of monitoring is lacking, but patients should generally be monitored for adverse events within 2 to 4 weeks of initiation of therapy, for therapeutic effect in 8 to 12 weeks, and at least every 3 to 6 months thereafter.[122] The effects of cognitive agents will not necessarily be obvious, and a treatment period of several months to a year may be necessary before it can be determined whether therapy is beneficial. Cognitive effects of the drug are often noticed only as a plateauing during treatment or as deterioration following drug discontinuation. In general, cognitive agents should be continued if the patient is demonstrating no change in clinical status. If there is doubt, the medication can be slowly tapered and discontinued, and the patient monitored off the drug for 4 to 6 weeks to determine the need for continued therapy. Drug deprescribing for people with AD is aided by the availability of deprescribing guidelines and algorithms for antipsychotics, cholinesterase inhibitors, and memantine.[123] The question of when, if ever, to stop drug therapy for AD remains controversial. Treatment benefits are not always evident, and fear of deterioration can lead to patients being prescribed drug therapy for AD from the time of their diagnosis until death. Some clinicians recommend withdrawing drug therapy if the patient significantly deteriorates in cognition or function, while others wait until the patient has lost all cognitive and functional abilities. As such, side effects, cost, and patient and family preferences factor heavily into drug therapy discontinuation decisions. If cholinesterase inhibitors are discontinued and cognition worsens or behavioral issues emerge, the drugs can be reinitiated.

CONCLUSION

Ultimately, AD, as with other dementias, is a complex condition to evaluate and manage. Clinicians are encouraged to work interprofessionally and collaborate closely with patients and their families to minimize stigma, identify therapeutic goals, and address concerns as they arise.

Postclass Engaged Learning Activity

Visit ClinicalTrials.gov at http://clinicaltrials.gov. Using the “Condition or disease” search field, type “Alzheimer disease”. Consider limiting your search to the United States (or another location of interest). Once completed, click “Search” to see your results.

Note how many studies are listed in your geographic area of interest. Then, identify a study of a medication that is not yet approved for Alzheimer disease by the US Food and Drug Administration and discuss the following questions with a classmate:

1. Is the trial active and still recruiting or has it already been completed?
2. What is the mechanism of action for the medication being studied? Has the medication been previously approved for another indication?
3. What assessment tools are being used to evaluate medication safety and/or efficacy?
4. What are the inclusion and exclusion criteria of the study? Are the investigators recruiting "real world" patients, or are there characteristics of the study population that may skew the results?
5. If you had a patient or family member with Alzheimer disease, would you encourage them to enroll in this study? Why or why not?
6. Do you think the medication in question will continue to be studied? Do you think it will be approved for use during your career as a health professional?

This activity is intended to increase your familiarity with an important resource for people with medical conditions who are seeking answers, weighing treatment options, or simply looking to "pay it forward" by serving as research subjects to help the next generation. Navigating ClinicalTrials.gov is something you may do in your role as clinician, researcher, caregiver, and/or patient in the future. Moreover, critical evaluation of the literature is a necessary part of working as a health professional, so this exercise is intended to help you think through the inclusion and exclusion criteria and study methods of planned, ongoing, or recently closed clinical trials, about which you may read in the future!

ABBREVIATIONS

AA	Alzheimer's Association
Aβ	β-Amyloid peptide
AD	Alzheimer disease
ADAS-cog	Alzheimer's Disease Assessment Scale—Cognitive Subscale
ADRDA	Alzheimer's Disease and Related Disorders Association
AHRQ	Agency for Healthcare Research and Quality
APOE	apolipoprotein E
APP	amyloid precursor protein
CGI-C	Clinical Global Impression–Change
CSF	cerebrospinal fluid
CT	computed tomography
DASH	Dietary Approaches to Stop Hypertension
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
FDA	Food and Drug Administration
HIV	human immunodeficiency virus
MCI	mild cognitive impairment
MeDi	Mediterranean Diet
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
NFT	neurofibrillary tangle
NIA	National Institute on Aging
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
NINDS	National Institute of Neurological Disorders and Stroke
NMDA	*N*-methyl-D-aspartate
NSAID	nonsteroidal anti-inflammatory drug
PET	positron emission tomography
RCT	randomized controlled trial
SLUMS	St Louis University Mental Status Exam
SSRI	selective serotonin reuptake inhibitor

REFERENCES

1. Kumar A, Singh A, Ekavali. A review on Alzheimer's disease

pathophysiology and its management: An update. *Pharmacol Rep*. 2015;67(2):195–203.

2. U.S. Department of Health and Human Services. National Plan to Address Alzheimer's Disease. Available at http://aspe.hhs.gov/system/files/pdf/102526/NatlPlan2012%20with%20No Last accessed, February 9, 2019.
3. Alzheimer's Association. 2018 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2018;14(5):367–429.
4. Jiang T, Yu JT, Tian Y, Tan L. Epidemiology and etiology of Alzheimer's disease: From genetic to non-genetic factors. *Curr Alzheimer Res*. 2013;10(8):852–867.
5. Robinson L, Tang E, Taylor JP. Dementia: Timely diagnosis and early intervention. *BMJ*. 2015;350:h3029.
6. Bertram L, Tanzi RE. The genetics of Alzheimer's disease. *Prog Mol Biol Transl Sci*. 2012;107:79–100.
7. Macleod R, Hillert E-K, Cameron RT, Baillie GS. The role and therapeutic targeting of α-, β- and γ-secretase in Alzheimer's disease. *Futur Sci OA*. 2015;1(3):1–16.
8. Alonso Vilatela ME, López-López M, Yescas-Gómez P. Genetics of Alzheimer's disease. *Arch Med Res*. 2012;43(8):622–631.
9. Kelleher RJ, Shen J. Presenilin-1 mutations and Alzheimer's disease. *Proc Natl Acad Sci*. 2017;114(4):629–631.
10. Hampel H, Mesulam MM, Cuello AC, et al. The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. *Brain*. 2018;141(7):1917–1933.
11. Michaelson DM. APOE ε4: The most prevalent yet understudied risk factor for Alzheimer's disease. *Alzheimers Dement*. 2014;10(6):861–868.
12. Galvin JE, Sadowsky CH. Practical guidelines for the recognition and diagnosis of dementia. *J Am Board Fam Med*. 2012;25(3):367–382.
13. Spires-Jones TL, Hyman BT. The intersection of amyloid beta and tau at synapses in Alzheimer's disease. *Neuron*. 2014;82(4):756–771.
14. Prins ND. Immunotherapy against amyloid-β in Alzheimer's disease: An overview. In: Ingelsson M, Lannfelt L, eds. *Immunotherapy and Biomarkers in Neurodegenerative Disorders Methods in Pharmacology and Toxicology*. New York, NY: Humana Press; 2016;3–17.
15. Tublin JM, Adelstein JM, del Monte F, et al. Getting to the heart of

Alzheimer's disease. *Circ Res*. 2019;124(1):142–149.
16. O'Brien JT, Markus HS. Vascular risk factors and Alzheimer's disease. *BMC Med*. 2014;12:218.
17. de Bruijn RFAG, Ikram MA. Cardiovascular risk factors and future risk of Alzheimer's disease. *BMC Med*. 2014;12:130.
18. Mullane K, Williams M. Alzheimer's disease (AD) therapeutics – 1: Repeated clinical failures continue to question the amyloid hypothesis of AD and the current understanding of AD causality. *Biochem Pharmacol*. 2018;158:359–375.
19. Forbes SC, Holroyd-Leduc JM, Poulin MJ, Hogan DB. Effect nutrients, dietary supplements and vitamins on cognition: A systematic review and meta-analysis of randomized controlled trials. *Can Geriatr J*. 2015;18(4):231–245.
20. Henderson VW. Alzheimer's disease: Review of hormone therapy trials and implications for treatment and prevention after menopause. *J Steroid Biochem Mol Biol*. 2014;142:99–106.
21. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189–198.
22. Alzheimer's Disease International. *World Alzheimer Report 2018*. London, UK: Alzheimer's Disease International. Available at https://www.alz.co.uk/research/WorldAlzheimerReport2018.pdf?2. Last accessed, February 9, 2019.
23. Moyer VA. Screening for cognitive impairment in older adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;160(11):791–797.
24. Cordell CB, Borson S, Boustani M, et al. Alzheimer's Association recommendations for operationalizing the detection of cognitive impairment during the Medicare Annual Wellness Visit in a primary care setting. *Alzheimers Dement*. 2013;9(2):141–150.
25. Rabins PV, Blass DM. In the clinic. Dementia. *Ann Intern Med*. 2014;161(3):ITC1–ITC16.
26. Association AP. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. 5th ed. Washington, DC: American Psychiatric Association; 2013.
27. Agency for Health Care Policy and Research. *Early Identification of Alzheimer's Disease and Related Dementias: Quick Reference Guide for*

Clinicians Number 19. Rockville, MD: Agency for Health Care Policy and Research; 1996.

28. Knopman DS, DeKosky ST, Cummings JL, et al. Practice parameter: Diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2001;56(9):1143–1153.
29. Román GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: Diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology*. 1993;43(2):250–260.
30. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34(7):939–944.
31. Jack CR, Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):257–262.
32. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):263–269.
33. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):270–279.
34. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):280–292.
35. Fillenbaum GG, Peterson B, Morris JC. Estimating the validity of the clinical Dementia Rating Scale: The CERAD experience. Consortium to Establish a Registry for Alzheimer's Disease. *Aging (Milano)*. 1996;8(6):379–385.
36. Harper L, Barkhof F, Scheltens P, et al. An algorithmic approach to

structural imaging in dementia. *J Neurol Neurosurg Psychiatry*. 2014;85(6):692–698.

37. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet*. 2017;390(10113):2673–2734.
38. Geda YE. Mild cognitive impairment in older adults. *Curr Psychiatry Rep*. 2012;14(4):320–327.
39. 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;(4):674–694.
40. Sadowsky CH, Galvin JE. Guidelines for the management of cognitive and behavioral problems in dementia. J Am Board Fam Med. 2012;25(3):350–366. doi: 10.3122/jabfm.2012.03.100183.
41. Parsons C. Polypharmacy and inappropriate medication use in patients with dementia: An under-researched problem. *Ther Adv Drug Saf*. 2017;8(1):31–46.
42. Gitlin LN, Kales HC, Lyketsos CG. Nonpharmacologic management of behavioral symptoms in dementia. *JAMA*. 2012;308(19):2020–2029.
43. Mittelman MS, Bartels SJ. Translating research into practice: Case study of a community-based dementia caregiver intervention. *Health Aff (Millwood)*. 2014;33(4):587–595.
44. Alzheimer's Association. Challenging Behaviors. Available at http://www.alz.org/national/documents/statements_antipsychotics.pdf. Last accessed, February 9, 2019.
45. Catic AG. Nonpharmacologic management of behavioral and psychological symptoms of dementia in long-term care residents. *Ann Long-Term Care*. 2015;23(11):23–30.
46. Rabins PV, Rovner BW, Rummans T, et al. Guideline Watch (October 2014): Practice Guideline for the Treatment of Patients with Alzheimer's Disease and Other Dementias. Available at http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guid Last accessed, February 9, 2019.
47. Howard R, McShane R, Lindesay J, et al. Nursing home placement in the donepezil and memantine in moderate to severe Alzheimer's disease (DOMINO-AD) trial: Secondary and post-hoc analyses. *Lancet Neurol*. 2015;14(12):1171–1181.

48. Stahl SM. *Prescriber's Guide: Stahl's Essential Psychopharmacology*. 5th ed. New York, NY: Cambridge University Press; 2014.
49. Ryan J, Fransquet P, Wrigglesworth J, Lacaze P. Phenotypic heterogeneity in dementia: a challenge for epidemiology and biomarker studies. *Front Public Health*. 2018;6:181.
50. Rainer M, Mucke HA, Krüger-Rainer C, et al. Cognitive relapse after discontinuation of drug therapy in Alzheimer's disease: Cholinesterase inhibitors versus nootropics. *J Neural Transm*. 2001;108(11):1327–1333.
51. Gaudig M, Richarz U, Han J, et al. Effects of galantamine in Alzheimer's disease: Double-blind withdrawal studies evaluating sustained versus interrupted treatment. *Curr Alzheimer Res*. 2011;8(7):771–780.
52. Pariente A, Fourrier-Réglat A, Bazin F, et al. Effect of treatment gaps in elderly patients with dementia treated with cholinesterase inhibitors. *Neurology*. 2012;78(13):957–963.
53. Massoud F, Desmarais JE, Gauthier S. Switching cholinesterase inhibitors in older adults with dementia. *Int Psychogeriatr*. 2011;23(3):372–378.
54. Birks JS, Chong LY, Grimley Evans J. Rivastigmine for Alzheimer's disease. *Cochrane Database Syst Rev*. 2015;9:CD001191.
55. Buckley JS, Salpeter SR. A risk-benefit assessment of dementia medications: Systematic review of the evidence. *Drugs Aging*. 2015;32(6):453–467.
56. Raskind MA, Peskind ER, Truyen L, et al. The cognitive benefits of galantamine are sustained for at least 36 months: A long-term extension trial. *Arch Neurol*. 2004;61(2):252–256.
57. Masters CL, Bateman R, Blennow K, et al. Alzheimer's disease. *Nat Rev*. 2015;1:1–18.
58. *Razadyne (galantamine hydrobromide)*. Beerse, Belgium: Janssen Pharmaceuticals; 2018. Package insert.
59. *Exelon (rivastigmine tartrate)*. East Hanover, NJ: Novartis Pharmaceuticals; 2018. Package insert.
60. *Exelon Patch (rivastigmine transdermal system)*. East Hanover, NJ: Novartis Pharmaceuticals; 2018. Package insert.
61. Lin JS, O'Connor E, Rossom RC, et al. *Screening for Cognitive Impairment in Older Adults: An Evidence Update for the U.S. Preventive Services Task Force*. Rockville, MD: Agency for Healthcare Research and Quality; 2013.

62. Bidzan L, Bidzan M. Withdrawal syndrome after donepezil cessation in a patient with dementia. *Neurol Sci*. 2012;33(6):1459–1461.
63. Triantafylidis LK, Clemons JS, Peron EP, et al. Brain over bladder: A systematic review of dual cholinesterase inhibitor and urinary anticholinergic use. *Drugs and Aging*. 2018;35(1):27–41.
64. Schwartz LM, Woloshin S. How the FDA forgot the evidence: The case of donepezil 23 mg. *BMJ*. 2012;344:e1086.
65. Fonseca-Santos B, Gremião MPD, Chorilli M. Nanotechnology-based drug delivery systems for the treatment of Alzheimer's disease. *Int J Nanomedicine*. 2015;10:4981–5003.
66. *Namenda (memantine hydrochloride)*. Madison, NJ: Allergan, Inc.; 2018. Package insert.
67. *Namenda XR (memantine hydrochloride)*. Dublin, Ireland: Forest Laboratories; 2016. Package insert.
68. Deardorff WJ, Feen E, Grossberg GT. The use of cholinesterase inhibitors across all stages of Alzheimer's disease. *Drugs Aging*. 2015;32(7):537–547.
69. Tariot PN, Farlow MR, Grossberg GT, et al. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: A randomized controlled trial. *JAMA*. 2004;291(3):317–324.
70. *Namzaric capsules (memantine hydrochloride extended release and donepezil hydrochloride)*. Irvine, CA: Allergan, Inc.; 2016. Package insert.
71. Rogers SL, Doody RS, Pratt RD, Ieni JR. Long-term efficacy and safety of donepezil in the treatment of Alzheimer's disease: Final analysis of a US multicentre open-label study. *Eur Neuropsychopharmacol*. 2000;10(3):195–203.
72. Farlow MR, Lilly ML. ENA713 B352 Study Group. Rivastigmine: An open-label, observational study of safety and effectiveness in treating patients with Alzheimer's disease for up to 5 years. *BMC Geriatr*. 2005;5:3.
73. Reisberg B, Doody R, Stöffler A, et al. A 24-week open-label extension study of memantine in moderate to severe Alzheimer disease. *Arch Neurol*. 2006;63(1):49–54.
74. Doody RS, Geldmacher DS, Gordon B, et al. Open-label, multicenter, phase 3 extension study of the safety and efficacy of donepezil in patients with Alzheimer disease. *Arch Neurol*. 2001;58(3):427–433.

75. Dichgans M, Leys D. Vascular cognitive impairment. *Circ Res*. 2017;120(3):573–591.
76. Mongkhon P, Naser AY, Fanning L, et al. Oral anticoagulants and risk of dementia: A systematic review and meta-analysis of observational studies and randomized controlled trials. *Neurosci Biobehav Rev*. 2019;96:1–9.
77. Zonneveld TP, Richard E, Vergouwen MDI, et al. Blood pressure-lowering treatment for preventing recurrent stroke, major vascular events, and dementia in patients with a history of stroke or transient ischaemic attack. *Cochrane Database Syst Rev*. 2018;7:CD007858.
78. World Health Organization and Alzheimer's Disease International. Dementia: A Public Health Priority. Geneva, Switzerland: World Health Organization. Available at.http://apps.who.int/iris/bitstream/10665/75263/1/9789241564458_eng.pd
79. Anstey KJ, Eramudugolla R, Hosking DE, et al. Bridging the translation gap: From dementia risk assessment to advice on risk reduction. *J Prev Alzheimer's Dis*. 2015;2(3):189–198.
80. Jeremy Y, Maaike A, Jennifer R, Naji T. Aerobic exercise to improve cognitive function in older people without known cognitive impairment. *Cochrane Database Syst Rev*. 2015;4:CD005381.
81. Middleton LE, Yaffe K. Promising strategies for the prevention of dementia. *Arch Neurol*. 2009;66(10):1210–1215.
82. Jaturapatporn D, Isaac MG, McCleery J, Tabet N. Aspirin, steroidal and non-steroidal anti-inflammatory drugs for the treatment of Alzheimer's disease. *Cochrane Database Syst Rev*. 2012;2:CD006378.
83. McGuinness B, Craig D, Bullock R, et al. Statins for the treatment of dementia. *Cochrane Database Syst Rev*. 2014;7:CD007514.
84. Schultz BG, Patten DK, Berlau DJ. The role of statins in both cognitive impairment and protection against dementia: A tale of two mechanisms. *Transl Neurodegener*. 2018;7:1–11.
85. Butler M, Nelson VA, Davila H, et al. Over-the-counter supplement interventions to prevent cognitive decline, mild cognitive impairment, and clinical Alzheimer-type dementia. *Ann Intern Med*. 2018;168(1):52–62.
86. Spence J, Chintapenta M, Kwon HI, Blaszczyk AT. A brief review of three common supplements used in Alzheimer's disease. *Consult Pharm*. 2017;32(7):412–414.
87. Libro R, Giacoppo S, Rajan TS, et al. Natural phytochemicals in the treatment and prevention of dementia: An overview. *Molecules*.

2016;21(4):518.

88. Sano M, Ernesto C, Thomas RG, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *N Engl J Med*. 1997;336(17):1216–1222.
89. Dysken MW, Sano M, Asthana S, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: The TEAM-AD VA cooperative randomized trial. *J Am Med Assoc*. 2014;311(1):33–44.
90. Miller ER, Pastor-Barriuso R, Dalal D, et al. Meta-analysis: High-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med*. 2005;142(1):37–46.
91. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med*. 2005;352(23):2379–2388.
92. Kryscio RJ, Abner EL, Caban-Holt A, et al. Association of antioxidant supplement use and dementia in the prevention of Alzheimer's disease by vitamin E and selenium trial (PREADViSE). *JAMA Neurol*. 2017;74(5):567–573.
93. Farina N, Llewellyn D, Isaac MGEKN, Tabet N. Vitamin E for Alzheimer's dementia and mild cognitive impairment. *Cochrane Database Syst Rev*. 2017;4:CD002854.
94. Zhang DM, Ye JX, Mu JS, Cui XP. Efficacy of vitamin B supplementation on cognition in elderly patients with cognitive-related diseases: A systematic review and meta-analysis. *J Geriatr Psychiatry Neurol*. 2017;30(1):50–59.
95. Yuan Q, Wang CW, Shi J, Lin ZX. Effects of Ginkgo biloba on dementia: An overview of systematic reviews. *J Ethnopharmacol*. 2017;195:1–9.
96. DeKosky ST, Williamson JD, Fitzpatrick AL, et al. Ginkgo biloba for prevention of dementia: A randomized controlled trial. *JAMA*. 2008;300(19):2253–2262.
97. Vellas B, Coley N, Ousset PJ, et al. Long-term use of standardised Ginkgo biloba extract for the prevention of Alzheimer's disease (GuidAge): A randomised placebo-controlled trial. *Lancet Neurol*. 2012;11(10):851–859.
98. Stoddard GJ, Archer M, Shane-McWhorter L, et al. Ginkgo and warfarin interaction in a large Veterans Administration population. *AMIA Annu Symp Proc*. 2015;2015:1174–1183.
99. Food and Drug Administration. Frequently Asked Questions About Medical Foods; Second Edition. Available at

http://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocun
Last accessed, February 9, 2019.

100. Chintapenta M, Spence J, Kwon HI, Blaszczyk AT. A brief review of caprylidene (Axona) and coconut oil as alternative fuels in the fight against Alzheimer's disease. *Consult Pharm*. 2017;32(12):748–751.
101. Henderson ST, Vogel JL, Barr LJ, et al. Study of the ketogenic agent AC-1202 in mild to moderate Alzheimer's disease: A randomized, double-blind, placebo-controlled, multicenter trial. *Nutr Metab (Lond)*. 2009;6:31.
102. Onakpoya IJ, Heneghan CJ. The efficacy of supplementation with the novel medical food, Souvenaid, in patients with Alzheimer's disease: A systematic review and meta-analysis of randomized clinical trials. *Nutr Neurosci*. 2017;20(4):119–227.
103. Hara J, Shankle WR, Barrentine LW, Curole MV. Novel therapy of hyperhomocysteinemia in mild cognitive impairment, Alzheimer's disease, and other dementing disorders. *J Nutr Heal Aging*. 2016;20(8):825–834.
104. Phillips P. Omega 3 fatty acids for the treatment of dementia: A Cochrane review summary. *Int J Nurs Stud*. 2017;67:83–84.
105. Pickett J, Bird C, Ballard C, et al. A roadmap to advance dementia research in prevention, diagnosis, intervention, and care by 2025. *Int J Geriatr Psychiatry*. 2018;33(7):900–906.
106. National Institutes of Health. Alzheimer's Disease. Available at http://www.nih.gov/research-training/accelerating-medicines-partnership-amp/alzheimers-disease. Last accessed, February 9, 2019.
107. Masopust J, Protopopová D, Vališ M, et al. Treatment of behavioral and psychological symptoms of dementias with psychopharmaceuticals: A review. *Neuropsychiatr Dis Treat*. 2018;14:1211–1220.
108. Tible OP, Riese F, Savaskan E, von Gunten A. Best practice in the management of behavioural and psychological symptoms of dementia. *Ther Adv Neurol Disord*. 2017;10(8):297–309.
109. Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. *BMJ*. 2015;350:h369.
110. Reus VI, Fochtmann LJ, Eyler AE, et al. The American Psychiatric Association practice guideline on the use of antipsychotics to treat agitation or psychosis in patients with dementia. *Am J Psychiatry*. 2016;173(5):543–546.

111. Ngo J, Holroyd-Leduc JM. Systematic review of recent dementia practice guidelines. *Age Ageing*. 2015;44(1):25–33.
112. Cohen-Mansfield J, Jensen B, Resnick B, Norris M. Knowledge of and attitudes toward nonpharmacological interventions for treatment of behavior symptoms associated with dementia: A comparison of physicians, psychologists, and nurse practitioners. *Gerontologist*. 2012;52(1):34–45.
113. Desai AK, Schwartz L, Grossberg GT. Behavioral disturbance in dementia. *Curr Psychiatry Rep*. 2012;14(4):298–309.
114. National Partnership to Improve Dementia Care in Nursing Homes. National Partnership to Improve Dementia Care in Nursing Homes: Antipsychotic Medication Use Data Report (October 2018). Available at http://www.nhqualitycampaign.org/files/Antipsychotic_Medication_Use_R Last accessed, February 9, 2019.
115. Ma H, Huang Y, Cong Z, et al. The efficacy and safety of atypical antipsychotics for the treatment of dementia: A meta-analysis of randomized placebo-controlled trials. *J Alzheimers Dis*. 2014;42(3):915–937.
116. Schneider LS, Tariot PN, Dagerman KS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med*. 2006;355(15):1525–1538.
117. Food and Drug Administration. Information for Healthcare Professionals: Conventional Antipsychotics. Available at http://www.waughconsulting.info/Portals/29/FDS%20Alert%20on%20Ant Last accessed, February 9, 2019.
118. Levinson DR. Medicare atypical antipsychotic drug claims for elderly nursing home residents. Available at http://oig.hhs.gov/oei/reports/oei-07-08-00150.pdf. Last accessed February 9, 2019.
119. Pan YJ, Wu CS, Gau SS, et al. Antipsychotic discontinuation in patients with dementia: A systematic review and meta-analysis of published randomized controlled studies. *Dement Geriatr Cogn Disord*. 2014;37(3-4):125–140.
120. Supasitthumrong T, Bolea-Alamanac BM, Asmer S, et al. Gabapentin and pregabalin to treat aggressivity in dementia: A systematic review and illustrative case report. Br J Clin Pharmacol. 2019;(4):690–703.
121. Sheehan B. Assessment scales in dementia. *Ther Adv Neurol Disord*. 2012;5(6):349–358.

122. Kim LD, Factora RM. Alzheimer dementia: Starting, stopping drug therapy. *Cleve Clin J Med*. 2018;85(3):209–214.
123. Deprescribing.org. Deprescribing Guidelines and Algorithms. Available at http://deprescribing.org/resources/deprescribing-guidelines-algorithms/. Last accessed, February 9, 2019.
124. *Aricept (donepezil hydrochloride)*. Woodcliff Lake, NJ: Eisai; 2018. Package insert.

72

Multiple Sclerosis

Jacquelyn L. Bainbridge, Augusto Miravalle, Pei Shieen Wong, and Matthew J. Makelky Sr.

KEY CONCEPTS

1. The etiology of multiple sclerosis (MS) is unknown, but it appears to be autoimmune in nature. Currently there is no cure.
2. Multiple sclerosis is characterized by central nervous system (CNS) demyelination and axonal damage.
3. Multiple sclerosis is classified by the nature of progression over time into several categories, which have different clinical presentations and responses to therapy.
4. Studies only support one FDA-approved disease-modifying therapy (DMT), ocrelizumab (Ocrevus), in patients with progressive forms of the illness. Information derived from multiple studies suggests younger patients with progressive illness and those with either superimposed acute relapses or enhancing lesions on magnetic resonance imaging (MRI) scans may benefit from some of the presently used DMTs.
5. The diagnosis of MS is made primarily on the basis of clinical symptoms and examination, but does require evidence of dissemination of lesions over time in multiple parts of the CNS and/or optic nerve. Additional diagnostic criteria include use of MRI, spinal fluid evaluation, and evoked potentials to aid in the diagnosis.
6. Exacerbations or relapses of MS can be disabling. When this is the case, exacerbations and relapses are treated with high-dose glucocorticoids, such as intravenous (IV) methylprednisolone, with onset of clinical response typically within 3 to 5 days.
7. Treatment of relapsing-remitting multiple sclerosis (RRMS) with the DMTs interferon-β (IFN-β) (Avonex, Betaseron, Rebif, Extavia), glatiramer

acetate (Copaxone), natalizumab (Tysabri), ocrelizumab (Ocrevus), mitoxantrone (Novantrone), fingolimod (Gilenya), teriflunomide (Aubagio), dimethyl fumarate (Tecfidera), and alemtuzumab (Lemtrada) can reduce annual relapse rate, lessen relapse severity, slow progression of MRI changes, and slow progression of disability and cognitive decline. In addition, DMTs have been shown to reduce the likelihood of developing a second attack after a first clinically isolated syndrome (CIS) consistent with MS.

8. In most cases, treatment with DMTs should begin promptly after the diagnosis of RRMS, or after a CIS, if the brain MRI is suggestive of high risk of further attacks. Natalizumab, and other choices that have been associated with problematic adverse events, should be reserved for those patients who have failed one or more standard therapies and those with poor prognostic signs.
9. The definition of "treatment inadequacy" for RRMS remains unclear, and therapy changes after "treatment failure" should be individualized.
10. Patients suffering with MS frequently have symptoms such as spasticity, bladder dysfunction, fatigue, neuropathic pain, cognitive dysfunction, and depression that may require treatment. Patients must be counseled that DMTs will not relieve these symptoms. Depression is common in MS and can pose the risk of suicide.

Preclass Engaged Learning Activity

Create a table that lists the current FDA-approved multiple sclerosis (MS) therapies for relapsing-remitting MS (RRMS), primary progressive MS (PPMS), clinically isolated syndrome (CIS), and secondary progressive MS (SPMS). Include the mechanism of action (MOA) and how you believe this helps reduce MS symptoms. This activity is intended to get you familiar with MS drugs, and how they are used in practice for differing forms of the disease.

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) that affects approximately 1 in 200 women, and fewer men, in the United

States.[1] The term “multiple sclerosis” refers to two characteristics of the disease: multiple neurologic symptoms that accrue over time, and characteristic plaques or sclerosed areas seen in numerous areas of the brain and spinal cord.

Although MS was first described more than 140 years ago, the cause remains a mystery, and a cure is still unavailable. Nevertheless, many advances have been made in treating and managing the disease complications and improving the quality of life of affected individuals.

EPIDEMIOLOGY

Epidemiologic aspects of MS have been reviewed in many publications.[1–5] MS affects approximately 2.3 million people worldwide[6] and is usually diagnosed between the ages of 15 and 50 years with a peak incidence occurring in the fourth decade. MS can occur in young children and significantly in older adults as well. While women are afflicted more than men by a ratio of 2:1, men usually develop the first signs of MS at a later age than women and are more likely to develop a progressive form of the disease. The most important factors in determination of disease risk are geography, environmental influences, age, and genetics (discussed under etiology). In general, disease prevalence is higher geographically: the greater the distance from the equator, and within the United States, the higher the disease prevalence in geographic areas above the 37th parallel. Recent studies, however, suggest a waning latitude gradient as demonstrated by a substantial increase in MS incidence in Mediterranean regions. Rising incidence of MS in females appears to be associated with urbanization.[7]

Multiple sclerosis also occurs more frequently in Whites of Scandinavian ancestry compared to other ethnic groups. In addition, an inverse relationship between MS risk and 25-hydroxyvitamin D levels has been proposed.[1,8]

ETIOLOGY

The exact cause of MS is still unknown, but the disease is thought to develop in genetically susceptible individuals exposed to random events and environmental factors that could trigger immune-mediated CNS damage. Genetic variation accounts for approximately 30% of the overall disease risk, and with the advent of genome-wide association studies (GWAS), more than 100 distinct genetic regions have been identified as being associated with MS, collectively

explaining approximately one-third of the genetic component of the condition.

The familial recurrence rate of MS is approximately 5%, with siblings being the most commonly reported relationship,[4] and monozygotic twins displaying a concordance rate of approximately 25%. This is consistent with the idea that an environmental agent is important in the etiology of MS, but also suggests a role for one or more genes. Genes that lie within the major histocompatibility complex (MHC), on the sixth chromosome, have been linked to MS.[1,4] Recent data show genetic variability within the interleukin-2α (IL-2α) and interleukin-7α (IL-7α) receptor genes to be associated with disease risk.[9–11] African Americans are significantly less likely to be diagnosed with MS compared with Whites, although there is emerging evidence that they are more likely to have a severe disease course and respond less to interferon (IFN) therapy.[12,13] A locus on chromosome 1 may be associated with increased susceptibility in African Americans.[14]

While genetics clearly have a role in overall disease risk, nongenetic factors have a proportionately larger contribution, but this is still being studied. To date, the reported environmental factors implicated in MS variably include vitamin D deficiency, smoking, high dietary sodium, circadian disruption, human cytomegalovirus, the Epstein–Barr virus (EBV), and human herpesvirus (HHV)-6.

In general, it is thought that MS risk can be seen in genetically susceptible individuals, who live in a high-risk area for at least 2 years before the age of 15, who were also exposed to a crucial environmental agent. Interestingly, if a genetically susceptible individual migrates from a low- to high-risk area prior to the age of 15 years, their risk of acquiring MS is the same as those who live in a high-risk area all their lives.[2] If the move is made from a high- to a low-risk area, the individual retains the high-risk status if the move is made after the age of 15 years, but acquires the lower risk if the move is made prior to this age.[2] Smoking cigarettes has been associated with both an increased risk of developing MS and with more severe progression of disability.[5,15]

Although no clear association has been identified, certain viruses might participate in the pathogenesis of MS by initiating or activating autoreactive immune cells in genetically susceptible individuals, leading to subsequent demyelination. Evidence to support a viral etiology includes increased immunoglobulin G (IgG) synthesis in the CNS and increased antibody titers to certain viruses. Epidemiologic studies also indicate an exposure to pathogens in childhood, which suggest that “viral” infections may precipitate exacerbations. In addition, data from both humans and experimental animal models suggest that

viral infections with incubation periods have been shown to cause disease with prolonged myelin destruction and a relapsing-remitting course.[1,16]

Although numerous viruses have a hypothetical proposed association with MS, the greatest evidence supports EBV, as autoreactive T cells could be activated by EBV through molecular mimicry due to sequence similarities between EBV and self-peptides. Other potential mechanisms of demyelination include enhanced breakdown and presentation of self-antigens, expression of viral superantigens, or bystander activation.[17] Antibody titers to Epstein–Barr nuclear antigen (EBNA) complex are higher in MS patients versus controls, and have been associated with differences in disease risk depending on time of sample collection.[18] A genetic-environmental interaction has also been reported between the human leukocyte antigen (*HLA) DRB1*1501* variant and antibodies to certain epitopes within EBNA-1 resulting in a 24-fold increased disease risk.[19] In addition, anti-EBNA titers have been associated with RRMS, conversion of CIS to clinically definite multiple sclerosis (CDMS, confirmed diagnosis of MS), and with MRI measures such as gadolinium-enhancing lesions, change in T2-lesion volume, and Expanded Disability Status Scale. Anti-EBNA and anti-vascular cell adhesion (anti-VCA) titers are also associated with gray matter atrophy in MS.[20] Some authors have claimed evidence of active EBV infection, which in time resolves, may lead to EBV-infected B cells being present in postmortem brain tissue of patients diagnosed with MS,[21] while other studies have not replicated these findings.[22] Given all of this, the majority of data suggests that exposure to EBV is associated with developing MS, but does not support the concept of an active or aborting EBV infection directly causing MS.

PATHOPHYSIOLOGY

An important prominent feature of early-stage MS is the concept that immune cell infiltration from the periphery to the CNS can occur as immune cells enter the CNS parenchyma by direct crossing of the blood–brain barrier, the subarachnoid space, or from the choroid plexus across the blood-cerebrospinal fluid (CSF) barrier. Other proposed mechanisms of MS include the “inside out” model where disease progression is an underlying neurodegenerative process that progresses much like primary-progressive multiple sclerosis (PPMS) and secondary-progressive multiple sclerosis (SPMS), with the antigenic constituents being released from the CNS into the periphery causing the inflammatory response.

2 Once in the CNS, immune cells promote neurodegeneration through stripping of the myelin sheath surrounding CNS axons. This activity is associated with an inflammatory, perivenular infiltrate consisting of T and B lymphocytes, macrophages, antibodies, and complement.[16] Demyelination renders axons susceptible to damage, which becomes irreversible when they are severed. Irreversible axonal damage correlates with disability and can be visualized as hypointense lesions, or "black holes," on T1-weighted MRI.[23,24]

Peripheral immune cells, along with activated CNS-resident microglia and astrocytes, promote demyelination as well as oligodendrocyte and neuroaxonal injury. This is mediated through direct cell contact–dependent mechanisms and the action of soluble inflammatory and neurotoxic mediators. The exact trigger for activation of T cells in the periphery remains unclear, but the T cells in MS patients recognize myelin basic protein (MBP), proteolipid protein, myelin oligodendrocyte glycoprotein, and myelin-associated glycoprotein. T-helper subtypes can be either pathogenic or protective in MS. Furthermore, theory holds that certain T-cell subsets are not terminally differentiated, but instead engender a level of plasticity that allows for their conversion from pathogenic to protective and vice versa under certain conditions (**Fig. 72-1**).[25]

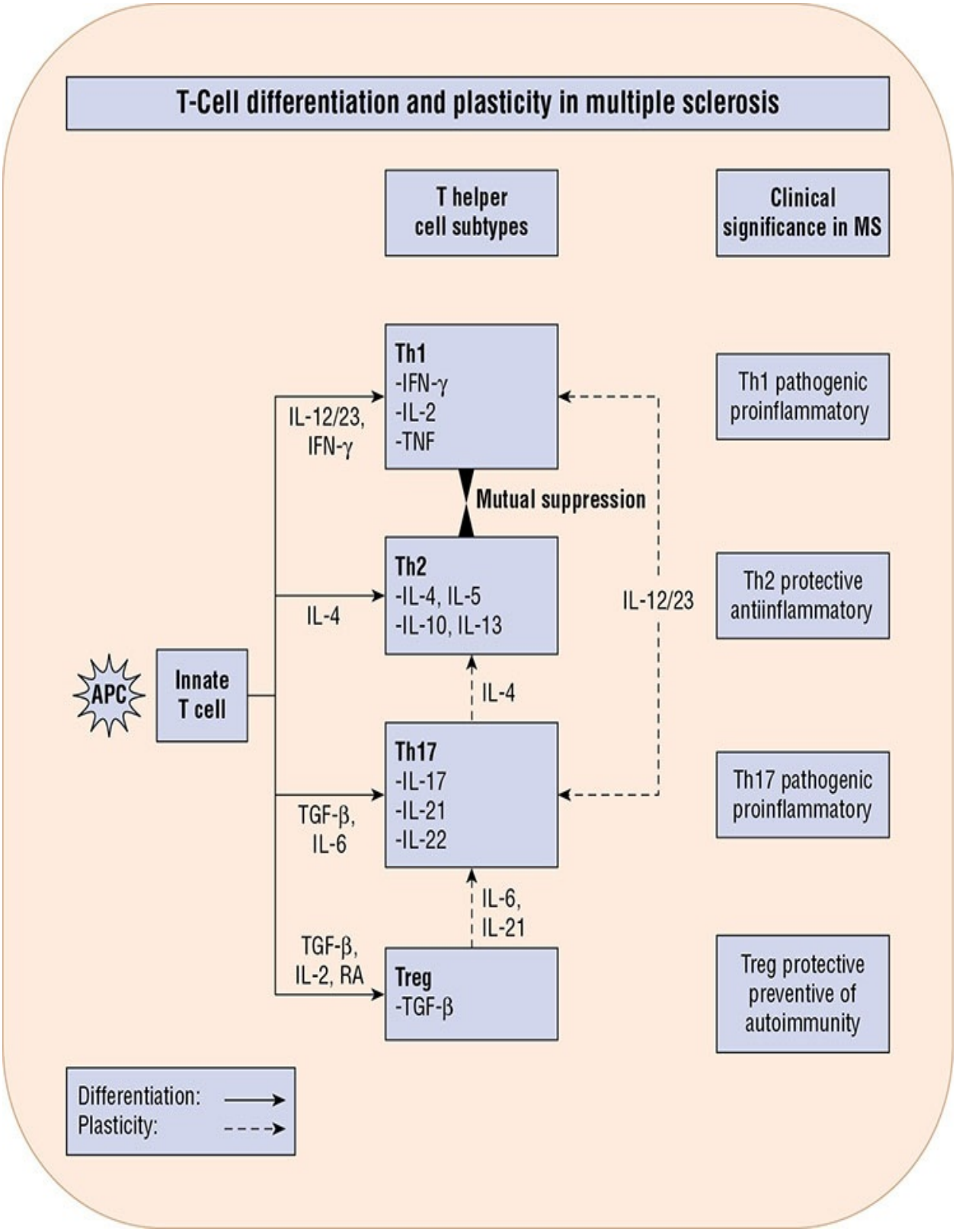


FIGURE 72-1 Upon interaction with an antigen-laden APC and specific cytokines, the innate T cells undergo differentiation into a few lineages

(subtypes). Four subtypes significant for MS pathophysiology are illustrated here (Th1, Th2, Th17, and Treg). Th1 and Th17 are proinflammatory, Th2 is anti-inflammatory, and Treg is regulatory. Th1 and Th2 are mutually suppressive and are relatively stable differentiated subtypes. In contrast, Th17 and Treg subtypes exhibit “plasticity” in that they can undergo phenotypic conversion to another T-cell subtype (Th1 or Th2) in the presence of specific cytokine conditions. This plasticity of Th17 and Treg is the immunologic basis for development of therapeutic agents to favor the production of suitable Th subtypes for combating microbial invasion and also concurrently achieving neurocellular recovery after an infection.[25] (APC, antigen presenting cell; Th, T-helper cell.)

A new concept of T-cell entry into the CNS suggests that the initial lymphocyte invasion in MS may proceed through the ventricles, toward the choroid plexus along a gradient that attracts activated Th17 (T-helper) cells.[26] The actual mediator of myelin and axonal destruction has not been established, but may reflect a combination of macrophages, antibodies, destructive cytokines, and reactive oxygen intermediates. In patients with stable or mild disease, an increase in the number of cells that express messenger RNA (mRNA) for transforming growth factor-β (TGF-β) and interleukin-10 (IL-10) have been found compared with patients with severe disease. Conversely, a reduction in the number of T-regulatory (Treg) cells, which exhibit suppressor activity, is also associated with active MS and can be found in patients with progressive disease. It should be noted, however, that ratios between various T cells (Treg ratios) do not always correlate with disease activity and that experimental evidence associates high 25-hydroxyvitamin D levels with improved Treg function, favoring the Th2 phenotype in the Th1/Th2 balance.[27] Finally, an immunological hallmark of MS is the intrathecal synthesis of multiple clones of immunoglobulins, despite uncertainty regarding the antigen(s) against which these immunoglobulins are directed.[28] Therefore, the complex interplay of a variety of cells, antibodies, and cytokines remains to be elucidated.

It is well accepted that MS lesions are heterogeneous, which may be due to differences in the stage of evolution of the lesions over time, differences in underlying immunopathogenesis, or a combination. Acute lesions show demyelination and axonal destruction with lymphocytic activity consistent with an inflammatory state. In contrast chronic lesions display less inflammatory lymphocytes with active remyelination.[16] As the disease progresses, immune cell infiltration wanes, perhaps due to adaptive immune cell exhaustion from chronic antigen exposure. Chronic CNS-intrinsic inflammation and neurodegeneration

continues independent of peripheral immune activation. As a consequence, meningeal tertiary lymphoid-like structures, which have specifically been documented in secondary progressive disease, may contribute to late-stage inflammation in patients with this form of MS. In general though, the relapsing phases of MS are more inflammatory as[29] opposed to the progressive forms of MS where you see more neurodegeneration leading to long-term disability.

Although traditional descriptions have focused on white matter as the sole location of MS lesions, more recent studies have clearly identified cortical and subcortical gray matter lesions both pathologically[30] and radiographically.[31] In addition, a subset of patients with progressive MS are noted to have abnormalities consistent with B-cell follicles in the meninges.[32]

Just as the full dimensions of the neuropathology are uncertain, so is the pathogenesis of the MS lesion. Substantial evidence suggests it is an autoimmune process directed against myelin and oligodendrocytes, the cells that make myelin[16] (**Fig. 72-2**).

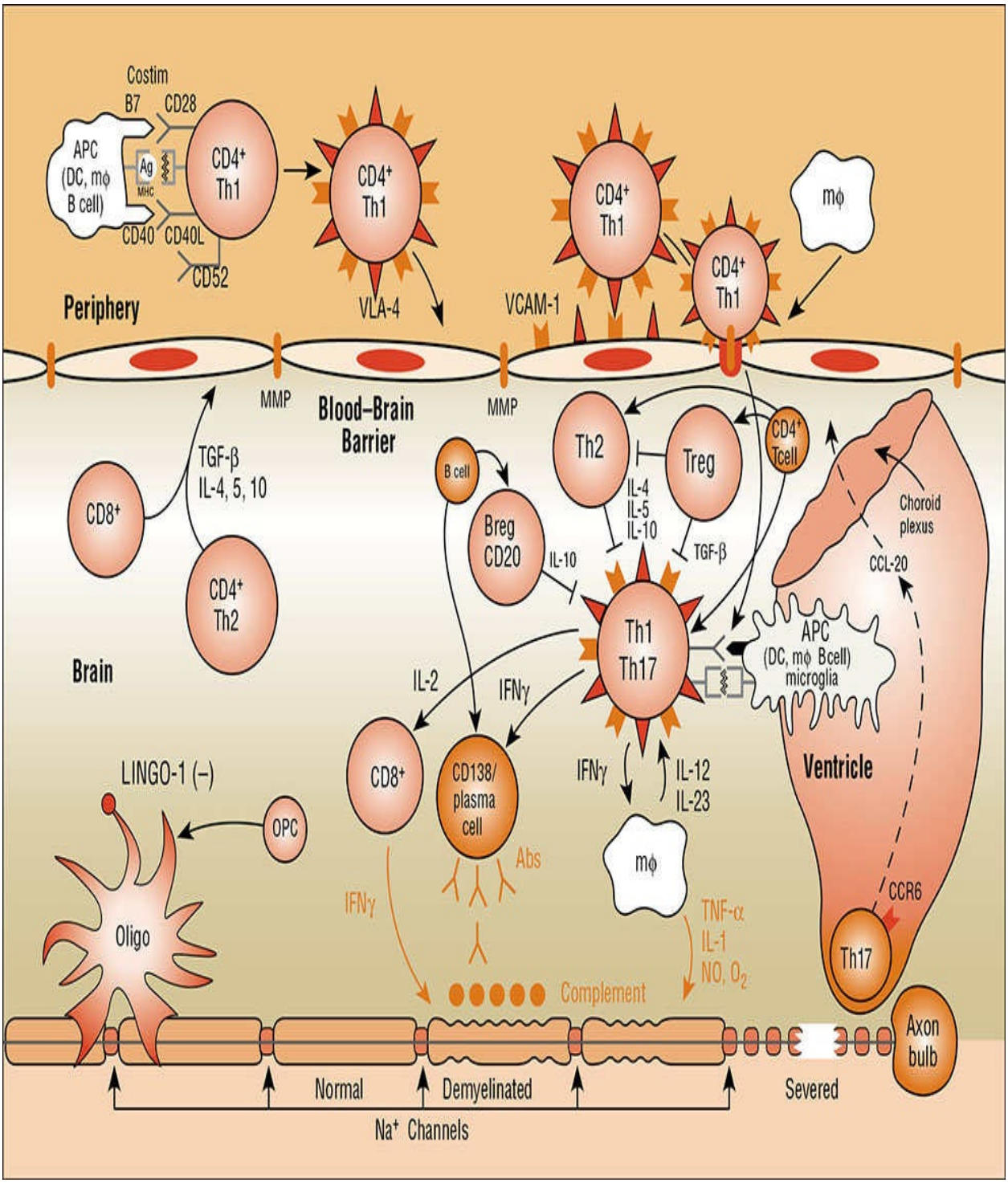


FIGURE 72-2 Autoimmune theory of the pathogenesis of multiple sclerosis (MS). In MS, the immunogenic cells tend to be more myelin-reactive, and these T cells produce cytokines mimicking a Th1-mediated proinflammatory reaction. T-helper cells ($CD4^+$) appear to be key initiators of myelin destruction in MS. These autoreactive $CD4^+$ cells, especially of the T-helper cell type 1 (Th1)

subtype, are activated in the periphery, perhaps following a viral infection. The activation of T- and B-cells requires two signals. The first signal is the interaction between MHC and APC (macrophage, dendritic cell, and B cell). The second signal consists of the binding between B7 on the APC and CD28 on the T cell for T-cell activation. Similarly, CD40 expressed on APCs and CD40L expressed on T cells interact to signal the proliferation of B cells within the blood–brain barrier following the entry to T cells. The T cells in the periphery express adhesion molecules on their surfaces that allow them to attach and roll along the endothelial cells that constitute the blood–brain barrier. The activated T cells also produce MMP that help to create openings in the blood–brain barrier, allowing entry of the activated T cells past the blood–brain barrier and into the CNS. Once inside the CNS, the T cells produce proinflammatory cytokines, especially interleukins (ILs) 1, 2, 12, 17, and 23, tumor necrosis factor-α (TNF-α), and interferon-γ (INF-γ), which further create openings in the blood–brain barrier, allowing entry of B cells, complement, macrophages, and antibodies. The T cells also interact within the CNS with the resident microglia, astrocytes, and macrophages, further enhancing production of proinflammatory cytokines and other potential mediators of CNS damage, including reactive oxygen intermediates and nitric oxide. The role of modulating, or downregulating, cytokines such as IL-4, IL-5, IL-10, and transforming growth factor-β (TGF-β) also has been described. These cytokines are the products of $CD4^+$, $CD8^+$, and Th1 cells.[10] New pathogenic mechanisms involve, but are not limited to, receptor-ligand–mediated T-cell entry via choroid plexus (CCR6-CCL20 axis),[26] coupling of key receptor-ligands for inhibition of myelination/demyelination (LINGO-1/NOGO66/p75 or TROY complex, Jagged-Notch signaling). (Ag, antigens; APC, antigen presenting cell; DC, dendrite cell; IgG, immunoglobulin G; MΦ, macrophage; Na^+, sodium ion; MMP, matrix metalloproteinases; MHC, major histocompatibility complex; OPC, oligodendrocyte precursor cell; VLA, very late antigen; VCAM, vascular cell adhesion molecule.)

Course of Illness

3 The clinical presentation of MS is extremely variable among patients, as well as over time for individuals, and is impacted by multiple external factors. The signs and symptoms of MS can be divided into three categories. Primary symptoms are a direct consequence of conduction disturbances produced by demyelination and axonal damage, and reflect the CNS area that is damaged. Secondary symptoms are complications resulting from primary symptoms; for

example, urinary retention, a primary symptom, can lead to frequent urinary tract infections (UTIs), a secondary symptom. Lastly, tertiary symptoms relate to the effect of the disease on the patient's everyday life.[33]

CLINICAL PRESENTATION

Multiple Sclerosis

General

- Most patients with MS present with nonspecific complaints.

Primary Symptoms/Signs

- Visual complaints/optic neuritis
- Gait problems and falls
- Paresthesias
- Pain
- Spasticity
- Weakness
- Ataxia
- Speech difficulty
- Psychological changes
- Cognitive changes
- Fatigue
- Bowel/bladder dysfunction
- Sexual dysfunction
- Tremor

Laboratory Tests

- MS is a diagnosis of exclusion
- MRI
- CSF studies
- Evoked potentials

Secondary Symptoms

- Recurrent UTIs
- Urinary calculi
- Decubiti and osteomyelitis
- Osteoporosis
- Respiratory infections
- Poor nutrition
- Depression

Tertiary Symptoms

- Financial problems
- Personal/social problems
- Vocational problems
- Emotional problems

The clinical course of CDMS is classified into four categories: (1) RRMS, (2) SPMS, (3) PPMS, and (4) progressive relapsing multiple sclerosis (PRMS).[34] At the onset of symptoms, about 85% of patients have relapses/exacerbations—new symptoms lasting at least 24 hours and separated from other new symptoms by at least 30 days—followed by remissions (complete or incomplete). Exacerbations are frequently referred to as relapses or attacks. This course is called RRMS which is characterized by CNS inflammation; the first clinical presentation is typically CIS, which is not a definite form of MS. During the RRMS phase, there is a correlation between new brain MRI lesions and clinical attacks, but typically, there are many more new MRI lesions than new clinical symptoms. In RRMS patients, attack frequency tends to decrease over time and becomes independent of the development of progressive disabilities.[35] Neurologic recovery following an exacerbation is often quite good early in the disease course, but following repeated relapses, recovery tends to be less complete. In addition, there is a new concept of a radiologically isolated syndrome (RIS), referring to individuals who have clinical scenarios not typical of MS, yet obtain MRI scans for other reasons (eg, headache) and have radiological signs suggestive of MS, which is not a form of definite MS. Some percentage of these patients convert to RRMS over time,[36] although when to start DMT remains unclear and varies by practice.

Approximately 10% to 20% of RRMS patients have a benign course (a

retrospective diagnosis), characterized by few relapses that are often sensory in nature and overall have minimal disability over time. Most RRMS patients (not with benign disease) eventually enter a progressive phase, referred to as SPMS, in which attacks and remissions are difficult to identify, with disability tending to accumulate more significantly during this phase of the illness. Additionally new brain MRI lesions, especially those seen only after the injection of contrast media, are less common, and brain atrophy and T1 holes increase.[37]

4 Approximately 15% of patients never have discrete phases of attacks and remissions but have progressive disease from the outset, known as PPMS. These patients will have symptoms, especially spastic paraparesis that may worsen rapidly or relatively slowly over time, and accrue progressively more disability. Patients with PPMS are often diagnosed at a later age, with the number of males roughly equal to that of females. In general, PPMS patients tend to have a worse prognosis than those who present initially with RRMS, although data suggest progression is variable.[38] Clinical trials have suggested that a significant portion of patients with PPMS do not receive benefit from studied therapies, although ocrelizumab (Ocrevus) is FDA approved for PPMS.[39] Both PPMS and SPMS are characterized as neurodegenerative processes. Finally, a small percentage of patients may have a mixture of both progression and relapses, referred to as progressive-relapsing multiple sclerosis (PRMS). These patients are generally treated as relapsing patients.

Illness progression can be measured in many ways with the most widely used clinical rating scale being the Expanded Disability Status Scale (EDSS), which uses a numerical value ranging from 0 (no disability) to 10 (death) to evaluate neurologic functions.[40] The limitations of this scale are the relative insensitivity to clinical changes not involving impairment of ambulation, such as fatigue, cognition, and affect. Other tools, such as the multiple sclerosis functional composite (MSFC), are being evaluated as a more sensitive measure for changes in MS-related disability over time.[41] Increasingly, MRI is being used as an index of both disease activity and progression[16] with the appearance of new lesions or changes in lesion number, size, and volume being used as outcome measures in research studies. Optical coherence tomography measures the retinal neural fiber layer thickness and may also be a measurable sign of pathological progression over time.[42]

The unpredictable nature of MS makes it impossible to anticipate when an exacerbation will occur. However, certain factors, including infections, heat (including fever), sleep deprivation, stress, malnutrition, anemia, concurrent organ dysfunction, exertion, and childbirth, may aggravate symptoms or lead to

an attack. Interestingly, many patients experience a significant reduction in relapses during the third trimester of pregnancy, followed by a relative increase postpartum.[43]

Between 60% and 80% of individuals diagnosed with MS have been reported to be sensitive to environmental heat. Clinically, increased body temperature might result in worsening of previous neurological deficits, including fatigue and decreased muscular endurance. Blurred vision, known as Uhthoff's phenomenon, is caused by increased body temperature due to physical exercise or physical restraint. Body temperature influences nerve impulses that are blocked or slowed down in a damaged nerve and after normalization of the temperature, signs and symptoms improve or disappear.

Multiple sclerosis usually does not directly diminish life expectancy, although the development of secondary complications such as pneumonia or septicemia (secondary to aspiration in those with swallowing difficulties, decubitus ulcers, or UTIs) or rapid progression of primary lesions affecting respiratory function can lead to a shorter than expected life span. Most of the decrease in life span is seen in patients with rapidly progressive disease and suicide rates in MS patients have been reported to be significantly higher than that seen in the general population.[44] Clinical and demographic factors used to predict prognosis of MS are listed in **Table 72-1**.[5,45]

TABLE 72-1 Prognostic Indicators in Multiple Sclerosis

Indicator	Favorable Prognosis	Unfavorable Prognosis
Age at onset	<40 years	>40 years
Gender	Female	Male
Initial symptoms	Optic neuritis or sensory symptoms	Motor or cerebellar symptoms; polysymptomatic
Disability	Late	Early
Attack frequency in early disease	Low	High
Course of disease	Relapsing/remitting	Progressive
Recovery after first event	Good	Poor
T2 lesions	Low load	High load
T1 black hole lesions	Low rate	High rate
Growth of lesions	Slow	Rapid
Locations of lesions	Single	Multiple

Data from References 46 and 47.

DIAGNOSIS

5 Multiple sclerosis is a diagnosis of exclusion as symptoms can frequently be attributed to other neurologic diseases, just as many syndromes can mimic MS. The diagnosis remains primarily a clinical one that requires demonstration of "lesions separated in space and time." This terminology refers to the occurrence of at least two episodes of neurologic disturbance which reflect distinct sites of CNS damage that cannot be explained by other mechanisms.[48] The McDonald criteria, which was established by an international panel of MS experts,[48] allow for three diagnostic categories for an MS diagnosis which include (1) MS, (2) possible MS (for those individuals at high risk of developing MS), and (3) not MS. With these criteria, an earlier diagnosis of MS can be obtained compared to the older criteria,[49] as they may be somewhat more sensitive and equally specific.[50–52] Key to this diagnosis is the use of MRI which has been endorsed by a consensus panel of the American Association of Neurology.[53] In addition to brain MRI lesions, CSF abnormalities, and visual-evoked potential (VEP) studies may be used as substitutes for clinical lesions in defining "separated in

space and time.” An example of how these criteria may be used can be seen in the fact that several immunotherapies are US FDA approved for use after a single attack (CIS) of demyelination in the context of an appropriately abnormal brain MRI. A proposed set of criteria currently being considered will allow for an earlier diagnosis in patients with CIS to establish “dissemination in space and time” with a single MRI. Therefore, patients will need to have lesions in different areas of their CNS with at least one enhancing lesion that correlates with clinical symptomatology to fulfill these criteria and be diagnosed with CDMS.

Laboratory Studies

To date, there are no tests specific for MS but rather evidence provided by (1) MRI of the brain and spine,[53,54] (2) CSF evaluation examining presence of increased oligoclonal bands and increased IgG, (3) evoked potentials,[48,49] and (4) optic coherence tomography,[55] which all can be used in conjunction with the physical examination and history in establishing the diagnosis. Of these tests, MRI is the most valuable diagnostic tool as it produces images of the brain and spine that reflect damage characteristic of MS plaques in multiple areas of the CNS. Therefore, MRI is the preferred technique for establishing a diagnosis, prognosis, and for following disease progression. Optic neuritis, which is a lesion or lesions on the optic nerve, is a common first symptom of MS and a greater number of T2-weighted lesions (called *T2 burden of disease*) on MRI following optic neuritis or CIS appears to correlate with the development of disability and progression to CDMS.[54] Through the use of the contrast agent gadolinium, new lesions and disruptions of the blood–brain barrier can be determined, and have been associated with early conversion to CDMS in CIS patients.[54,56] It is important to note that these gadolinium enhanced lesions do not correlate well with progression of disability when examined over time, and that brain atrophy, even early in the course of the illness, probably correlates better with progression of disability.[53]

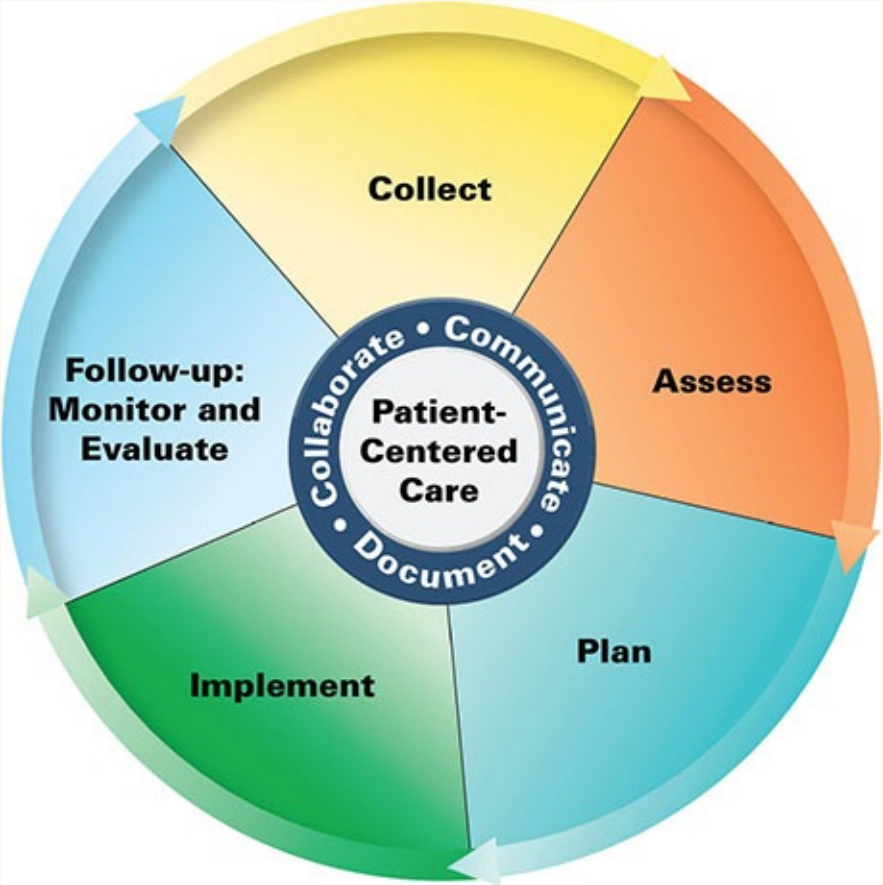
Differential Diagnosis

Because a number of disorders can mimic MS, most patients are first screened with blood tests that test for rheumatologic, collagen-vascular, infectious, and sometimes inherited metabolic diseases. Additionally, electromyography may help in diagnosing amyotrophic lateral sclerosis and neuropathies.

Magnetic resonance imaging, used to rule out tumors and cervical spondylosis, may also lead to MS evaluations for many patients with little or no clinical history of MS. While some of these patients may have MRI scans suggestive of MS (so-called RIS), most have nonspecific scans with identifiable causes for their scan abnormalities, including age greater than 50 years, hypertension, and migraine.[57] The use of established criteria for distinguishing MS lesions from other etiologies enhances diagnostic accuracy.

TREATMENT

Treatment of MS falls into three broad categories: (1) treatment of exacerbations, (2) disease-modifying therapies (DMTs), and (3) symptomatic therapies. While treatment of exacerbations will shorten the duration and possibly decrease the severity of the attack, the DMTs can alter the course of the illness, and diminish progressive disability over time; however, symptomatic management of the disease is of utmost importance to maintain the patient's quality of life. Although different treatment modalities have been studied in the last 30 years, these older trials contained design flaws, and as such, there are no universally accepted treatment algorithms for MS and treatment recommendations often vary among clinicians and centers. Perhaps more importantly, treatment decisions are frequently based on the wishes and goals of individual patients rather than evidence-based algorithms. Recently the American Academy of Neurology (AAN) released practice guidelines for using DMTs for adult MS and one potential algorithm for the immunotherapy of CDMS is shown in Fig. 72-2.



Patient Care Process for Multiple Sclerosis

Collect

- Patient specific demographics such as age, race, gender, geographical places of residence before or after the age of 15, current smoking level and history, family history of MS, and previous infection with certain viruses
- Laboratory values such as vitamin D, liver function tests, complete metabolic panel, and complete blood count
- Magnetic resonance imaging (MRI) of brain and spinal cord with and without contrast
- Lumbar puncture for oligoclonal bands
- Visual-evoked potential results
- Optical coherence tomography (OCT)
- Current diagnosis and date of initial diagnosis and current and past medications

Assess

- Clinical classification of MS (RRMS, SPMS, PPMS, or PRMS)
- Disease progression using the Expanded Disability Status Scale (EDSS), and MRI results
- Total number of disease exacerbations or relapses
- Duration of therapy and dose for current and past medications, side effects experienced during treatment, and medication adherence

Plan*

- Choose a therapy that has the best risk vs. benefit profile for use in the specific form of MS diagnosed, as well as patient specific characterizations and previous treatment history (Table 72-2, Table 72-3, and Table 72-5)
- Choose a therapy with the best adherence profile (twice yearly infusion vs. three times weekly injectable), and more tolerable side effects based on stratified risk factors (JC virus)
- Create a patient-specific monitoring plan based on the therapy chosen (Table 72-3)
- Identify the presence of secondary symptoms requiring pharmacologic management (Table 72-6)

Implement*

- Start primary MS therapy as soon as possible to decrease the chance for disease progression during treatment changes
- Figure 72-3 represents a potential algorithm for MS treatment
- Add pharmacologic treatment for secondary symptoms when appropriate
- Discuss with patients the role of complementary and alternative treatments (Table 72-7)

Follow-up: Monitor and Evaluate

- Safety of current DMT at each visit to ensure the current treatment is best fitted for the specific patient case
- Monitor for common side effects with each specific DMT (Table 72-3), or any side effects that are new once therapy is initiated or changed

- Treatment response (reduction in primary, secondary, and tertiary symptoms of MS) or the occurrence of exacerbations and relapses
- Yearly change in brain lesions via MRI
- Change in daily functioning using the EDSS and other clinical factors used to predict MS prognosis (Table 72-1)

** Collaborate with patient, caregivers, and other healthcare professionals.*

Desired Outcomes

The main goals of treatment are to improve overall quality-of-life, maintain employment, and minimize long-term disability for MS patients. Disease-related treatment goals then include reduction in MS exacerbations or relapses, decreasing the number of white matter lesions and black holes on MRI, averting brain atrophy, and ultimately halting disease progression. With early disease recognition and immediate utilization of FDA-approved DMTs both the main goals of treatment and the disease-related goals can be obtained.

General Approach to Treatment

With the advancement of FDA-approved medications to treat MS, patients are experiencing fewer relapses, slower disease progression, and improved quality of life. The severity of symptoms at initial presentation will determine whether an induction or escalation algorithm will be assigned to an individual patient. When FDA-approved drugs do not alter natural disease progression, investigational agents or non–FDA-approved medications, such as rituximab, may be used. There is some agreement that use of escalation approaches early in the course of the disease, with safer yet partially effective medications, is useful.

As a rule, MS affects patients in their most productive years of life; therefore, practitioners must work with their patients to set realistic expectations over their lifetime and develop a long-term treatment and management plan. Over the course of this illness, patients are likely to acquire secondary and tertiary symptoms of MS. In clinical trials, high nonadherence rates are reported as an important issue for potential treatment failure. The potential reasons identified this nonadherence are lack of perceived benefit, cost, adverse effects, depression, complicated or too frequent dosing, and undesirable routes of administration (eg, subcutaneous, intramuscular injection, intravenous [IV]). **Figure 72-3** represents a clinical algorithm for the treatment of MS.

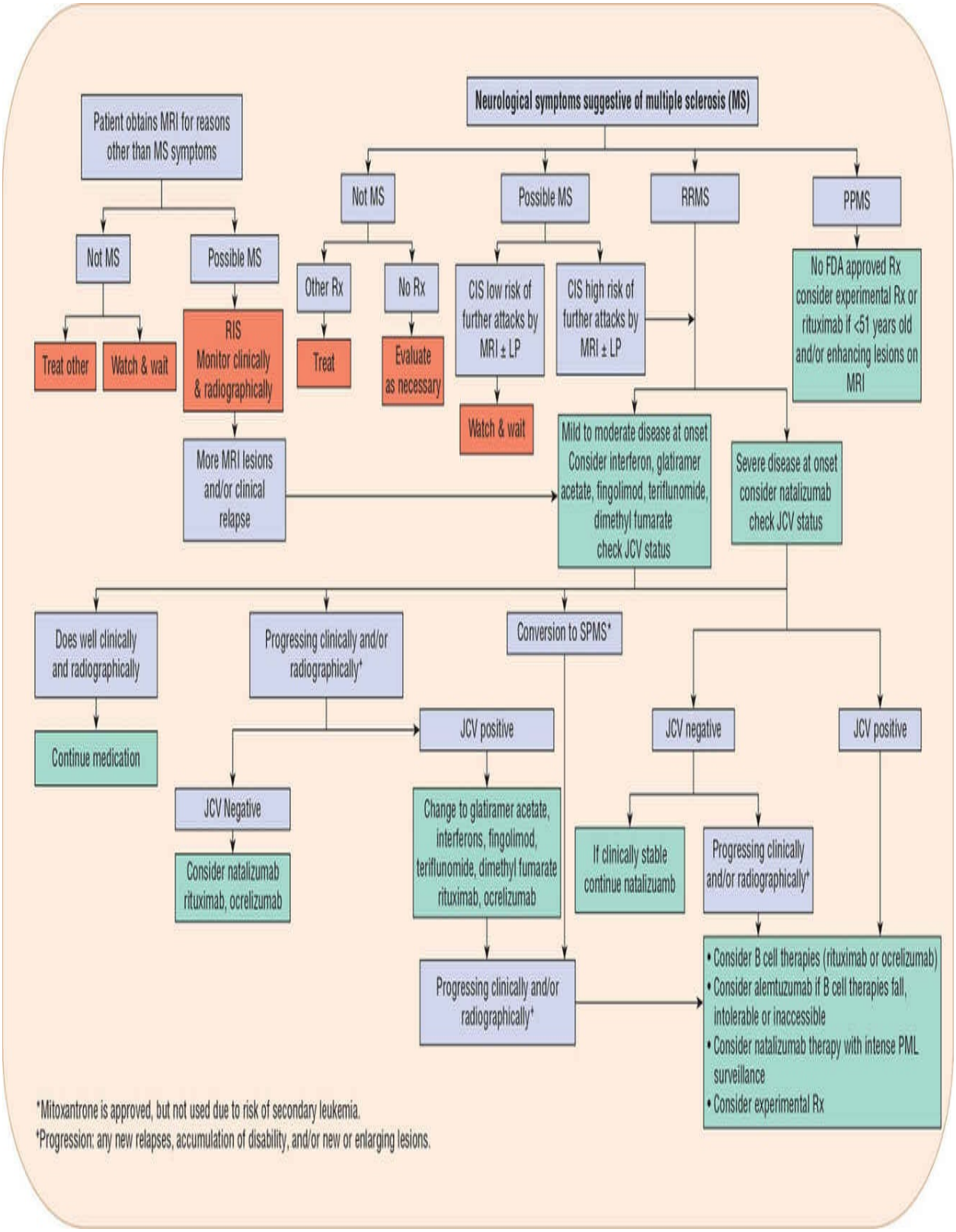


FIGURE 72-3 Algorithm for management of clinically definite multiple sclerosis. (MRI, magnetic resonance imaging; LP, lumbar puncture; MS,

multiple sclerosis; CIS, clinically related syndrome; JCV, John Cunningham virus, PML, Progressive multifocal leukoencephalopathy; RRMS, Relapsing-remitting multiple sclerosis; PPMS, primary progressive multiple sclerosis; SPMS, secondary progressive multiple sclerosis; Rx, prescription medication.)

Nonpharmacologic Therapy

While medications are the primary mainstay of treatment for MS, patients may find that the use of occupational therapy may be useful to keep active. This type of therapy may help improve the ability to complete the activities of daily living or learn new techniques or tools to accomplish these tasks. Furthermore, physical therapy may improve muscle strength to help patients improve their gait and balance. Streching exercises may help reduced muscle spasms or help patients learn how to use mobility aid such as canes, or walkers.

Pharmacologic Therapy

Treatment of Exacerbation

6 Exacerbations are the hallmark of early RRMS. Although recovery after relapses is generally complete, continued relapses over time may be associated with a substantial accumulation of disability. Frequent relapses (more than three relapses per year in the first 2 years after diagnosis) have shown a consistent positive correlation with developing neurological disability later. However, mild exacerbations that do not produce functional decline may not require treatment. Therefore, decisions to treat relapses are usually substantiated by patient expectations, prior experience with corticosteroids, and predicted course of recovery. Generally, accepted indications for treatment include relapses that are mono- or polysymptomatic presentations; relapses that localize to the optic nerve, spinal cord, or brainstem; those with functional limitations that affect activities of daily living; and symptoms that continue to worsen over a period of 2 weeks. When functional ability is affected, the standard intervention is an IV injection of high-dose corticosteroids such as methylprednisolone, which is recommended by the American Academy of Neurology (AAN).[58] While the mechanism of action for corticosteroids in MS is unknown, it is speculated that they improve recovery by decreasing edema in the area of demyelination. Intravenous methylprednisolone in particular has been shown to shorten the duration of exacerbations and also potentially delay repeat attacks for up to 2 years after optic neuritis,[58] although it has not been shown to definitively affect

disease progression.[59]

Methylprednisolone doses range from 500 to 1,000 mg/day, given IV for 3 to (rarely) 10 days, depending on clinical response. Functional recovery after an exacerbation is more rapid if corticosteroids are initiated within 2 weeks of symptom onset, with improvement usually beginning after 3 to 5 days. Short-term steroid use is often accompanied by sleep disturbance, a metallic taste in the mouth, and rarely, gastrointestinal (GI) upset. Patients with diabetes mellitus or a predilection to diabetes mellitus may have significant elevations of blood sugar, requiring the use of insulin. Longer durations of IV methylprednisolone therapy are associated with acne and fungal infections, mood alteration, and rarely, GI hemorrhage (especially in hospitalized patients or in those taking aspirin). In some circumstances, equipotent doses of oral prednisone or dexamethasone can be substituted for IV methylprednisolone, although dexamethasone use is not well supported in the literature. Interestingly, adrenocorticotropic hormone (ACTH) is the only FDA-approved agent for MS exacerbation treatment, although it is rarely used due to cost and availability.

In patients who experience an MS relapse, a small number will have more severe attacks, manifested by hemiplegia, paraplegia, or quadriplegia. If these patients fail to improve with aggressive steroid therapy, plasma exchange (PLEX) every other day for seven treatments can be beneficial for approximately 40% of patients or intravenous immunoglobulin (IVIG) can be given.

A “pseudoexacerbation” is a situation in which patients present with symptoms consistent with an exacerbation for less than 24 hours, or upon further examination it is determined that the exacerbation is precipitated by something other than the natural course of the disease. Potential precipitating events that may contribute to the pseudoexacerbation are heat, infections (eg, UTIs), or stress (emotional or physical). Therefore, these must be ruled out before exacerbation treatment is initiated or DMTs are altered.

Disease-Modifying Therapy

7 Indications and dosing of DMTs are shown in **Table 72-2**. Drugs used to treat MS can be considered either immunomodulatory (able to alter the immune signals without cytotoxic effect or bone marrow suppression) or immunosuppressive (able to alter the immune system through a direct cytotoxic activity or bone marrow suppression); however, these drugs later have a higher risk-to-benefit ratio based on their safety profile.[29] Currently, FDA-approved first-generation therapies (self-injected medications that decrease annualized relapse rate by about 30% and decrease the formation of new white matter

lesion) include four IFN formulations (five brand names), and glatiramer acetate (a non-IFN). The first-generation DMTs are not immediately efficacious for patient symptoms, but rather their efficacy may be seen approximately 1 to 2 years after starting therapy. In addition to first-generation DMTs, the FDA has approved ocrelizumab, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, and alemtuzumab for the treatment of relapsing forms of MS. Ocrelizumab is also FDA-approved for PPMS. Mitoxantrone additionally has an FDA indication for progressive or worsening MS.

TABLE 72-2 Disease-Modifying Therapy

Drug	Brand Name	Indication	Initial Dose	Usual Dose	Comment
First-generation agents					
Self-injectables					
Interferon-β_{1a}	Avonex	Relapsing forms of MS	30 mcg (6 million international units) IM once weekly	30 mcg IM once weekly	Avonex is considered as a low potency interferon Cost per yeara: $75,000-$100,00
Interferon-β_{1a}	Rebif	Relapsing forms of MS	22 mcg SQ three times a week	22 or 44 mcg SQ three times a week	Rebif is considered as a high potency interferon Cost per year*: $100,000-$125,000
Interferon-β_{1b}	Betaseron, Extavia	Relapsing forms of MS	250 mcg (8 million international units) SQ every other day	250 mcg SQ every other day	Betaseron/Extavia is considered as a high potency interferon Pregnancy category C Cost per year*: $75,000-$100,000 (Betaseron/ Extavia)
Pegylated Interferon-β_{1a}	Plegridy	RRMS	6.3 mcg SQ day 1, then 94 mcg SQ on day 15, then 125 mcg SQ on day 29, then 125 mcg SQ every 14 days	125 mg SQ every 14 days	Pregnancy category C Can premedicate or concurrently use an antipyretic/analgesic for flu-like symptoms Cost per year*: $75,000-$100,000
Glatiramer acetate	Copaxone Glatopa	CIS, RRMS	20 mg SQ once daily or 40 mg SQ three times a week	20 mg SQ once daily or 40 mg SQ three times a week	Pregnancy category B Cost per year*: $100,000-$125,000 (Copaxone 20 mg/day), $75,000-$100,000 (Copaxone 40 mg three times a week), $75,000-$100,000 (Glatopa 20 mg/day)
IV infusion					
Mitoxantrone	Novantrone	SPMS, PRMS, and worsening RRMS	12 mg/m^2 IV every 3 months	12 mg/m^2 IV every 3 months	Lifetime dose should not exceed 140 mg/m^2 Pregnancy category D
Second-generation agents					
Oral agents					
Fingolimod	Gilenya	Relapsing forms of MS, Pediatric 10 years and greater	0.5 mg orally once daily, Pediatric: <40 kg 0.25 mg orally once daily, >40 kg 0.5 mg orally once daily	0.5 mg orally once daily, Pediatric: <40 kg 0.25 mg orally once daily, >40 kg 0.5 mg orally once daily	REMS Pregnancy category C Cost per year*: $100,000-$125,000
Teriflunomide	Aubagio	Relapsing forms of MS	7 mg orally once daily	7 or 14 mg orally once daily	Pregnancy category X Cost per year*: $$75,000-$100,000 Cholestyramine and charcoal accelerate teriflunomide elimination
Dimethyl fumarate	Tecfidera	Relapsing forms of MS	120 mg delayed release twice daily for 7 days	240 mg delayed release twice daily	Pregnancy category C Cost per year*: $100,000-$125,000
IV infusion					
Natalizumab	Tysabri	Relapsing forms of MS	300 mg IV every 4 weeks	300 mg IV every 4 weeks	REMS Pregnancy category C Cost per year*: $75,000-$100,000
Alemtuzumab	Lemtrada	RRMS	First treatment course: 12 mg/day IV for 5 consecutive days (60 mg total dose)	Second treatment course: 12 mg/day IV for 3 consecutive days (36 mg total dose) administered 12 months after first treatment course	May premedicate with high-dose corticosteroid (1,000 mg methylprednisolone or equivalent) immediately prior to infusion for first 3 days Also administer herpes viral prophylaxis starting on first day of treatment and continued for at least 2 months after completion of treatment or until CD4$^+$ count is at least 200 cells/μL (0.2 × 10^9/L), whichever occurs last Pregnancy category C REMS Total treatment cost*: $125,000-$150,000 for first year, $75,000-$100,000
Ocrelizumab	Ocrevus	RRMS and PPMS	First treatment course: 300 mg IV followed by 300 mg IV 2 weeks later. Start infusion at 30 mL/hr, then increase by 30 mL/hr every 30 minutes as tolerated to a maximum of 180 mL/hr for a duration of 2.5 hours or longer	Maintenance treatment (given 6 months after the end of first treatment, and every 6 months thereafter): 600 mg IV starting at 40 mL/hr and increased by 40 mL/ hr every 30 minutes as tolerated to a maximum rate of 200 mL/hr for a duration of 3.5 hours or longer	Premedication: antihistamine 30 to 60 min prior to infusion and 100 mg methylprednisolone or equivalent corticosteroid 30 min prior to infusion. Can also consider and antipyretic (acetaminophen) Observe patient for at least 1 hour post infusion for *Pregnancy category: Fetal risk cannot be ruled out* *REMS* Total treatment cost per year*: $75,000-$100,000
Self-injectable					
Daclizumab	Zinbryta	Relapsing forms of MS	150 mg SQ once monthly	150 mg SQ once monthly	Removed from market in 2018 REMS Cost per year: $100,000-$125,000

*Cost: Cost as reported in Red Book. Not all drug companies publish average wholesale price (AWP), and those are calculated in accordance with Truven Health Analytics AWP Policy. It does not include nursing, pharmacy, and technical fees.

CIS, clinically isolated syndrome; IM, intramuscular; PRMS, primary relapsing multiple sclerosis; REMS, Risk Evaluation and Mitigation Strategy; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; SQ, subcutaneous.[46,47]

8 In some patients with poor prognostic factors and poor clinical presentation, ocrelizumab, natalizumab, fingolimod, teriflunomide, and dimethyl fumarate may be prescribed as initial therapy, as opposed to starting a first-generation DMT associated with less serious side-effect risk. This type of algorithm would be considered an induction therapy, where all therapeutic efforts are concentrated in the early phases of disease.

It is important to note that the efficacy of the DMTs may vary considerably between individual patients and for any given patient at different points in time. Moreover, patients with MS may have different tolerance for side effects and risks, as well as preference for different routes of administration. Therefore, access to the full range of options is critical in order for patients with MS and their clinicians to make optimal treatment decisions. Adverse drug reactions and monitoring parameters of DMTs are shown in **Table 72-3**.

TABLE 72-3 Adverse Drug Reactions and Monitoring Parameters

Drug	Adverse Drug Reaction	Monitoring Parameter	Comments
Interferon-β_{1a}	Depression, flu-like symptoms, leukopenia, injection site reactions	Electrolytes, CBC, LFTs, thyroid function, LVEF, depression LFTs at baseline, 1 month, and every 3 months for a year, and every 6 months thereafter	Avoid use in untreated severe depression
Interferon-β_{1b}	Depression, injection site reactions, leukopenia, flu-like symptoms	Electrolytes, CBC, LFTs, thyroid function, depression	Avoid use in untreated severe depression More frequent injection site reactions reported
Glatiramer acetate	Injection site reactions, infection, hypersensitivity, chest tightness, urticaria	MRI, tissue necrosis, postinjection reaction	Chest tightness, urticaria can occur at any dose
Mitoxantrone	Bone marrow suppression, neutropenia, cardiotoxicity, AML, nausea, vomiting, diarrhea, alopecia	CBC, ECG, LVEF, LFTs	Secondary leukemia Lifetime maximum dose due to cardiac toxicity
Natalizumab	PML, depression, fatigue, respiratory infection, arthralgia, hepatotoxicity	JCV antibody, infection, MRI, LFTs	Risk of PML Risk of IRIS when discontinued due to PML
Fingolimod	Lymphocytopenia, macular retinal edema, AV block, infection, headache	CBC, ECG, varicella zoster antibody, blood pressure, ophthalmic examination, LFTs	Requires first dose observation Contraindicated in patients receiving Class I and III antiarrhythmic drugs and those with recent cardiac disease,* second- and third-degree AV block Ketoconazole increases fingolimod serum concentration (3A4 inhibition) Vaccine efficacy may be decreased
Teriflunomide	Steven–Johnson syndrome, liver failure, neutropenia, respiratory infection, activation of TB, alopecia, neuropathy	CBC, LFTs, blood pressure, pregnancy, TB test	Contraindicated in severe hepatic impairment Possibility of TB reactivation Active metabolite of leflunomide
Dimethyl fumarate	Flushing, rash, pruritus, GI discomfort, lymphocytopenia, increased LFTs, albuminuria	CBC, LFTs	Taking with food decreases incidence of flushing
Alemtuzumab	Infusion reactions, infections (nasophyaryngitis, UTI, URI, herpes viral infections), autoimmune disorders, thyroid disorders, immune-mediated thrombocytopenic purpura, Goodpasture syndrome	CBC, thyroid function, antibodies to varicella zoster virus, HPV screening, serum creatinine, TB prior to treatment, infusion reactions, skin exams, urinalysis	May premedicate with high-dose corticosteroid (1,000 mg methylprednisolone or equivalent) immediately prior to infusion for first 3 days. Also administer herpes viral prophylaxis starting on first day of treatment and continued for at least 2 months after completion of treatment or until $CD4^+$ count is at least 200 cells/μL (0.2×10^9/L), whichever occurs last Contraindicated with HIV infection Birth control should be used during treatment and for 4 months after each treatment course Breastfeeding not recommended during treatment and for 4 months following each treatment course
Daclizumab	Upper respiratory tract infection, depression, rash, pharyngitis, increased ALT	LFTs and bilirubin (prior to treatment then monthly during treatment and for 6 months after the last dose) Contraindicated in hepatic disease or hepatic impairment	Live vaccines are not recommended during treatment and up to 4 months after discontinuation Evaluate for tuberculosis prior to treatment
Ocrelizumab	Infusion reactions, nasopharyngitis, upper respiratory tract infection, headache, urinary tract infection, herpes virus–related infections, neoplasms	MRI, active infection before infusion, infusion reactions during and after infusion, skin infections	Live vaccines are not recommended during treatment and after treatment until B-cell repletion, administer all live vaccines 6 weeks before treatment Evaluate for Hepatitis B infection before first dose Avoid pregnancy during treatment and for 6 months after stopping treatment

*Cardiac disease including myocardial infarction, unstable angina, stroke, transient ischemic attack, and heart failure NYHA Class III/IV.

AML, acute myeloid leukemia; CBC, complete blood count; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; IRIS, immune reconstitution inflammatory syndrome; PML, progressive multifocal leukoencephalopathy; LFT, liver function test.

Interferon-β_{1b} and Interferon-β_1a IFN-β_{1b} (Betaseron, Extavia) was the first agent proven to favorably alter the natural course of the illness (**Table 72-4**).[60] Although the exact mechanism of action is unknown, the therapeutic effect of IFN-β_{1b} in MS may be caused by its immunomodulating properties, including the ability to augment suppressor cell function and reduce IFN-γ secretion by activated lymphocytes, its macrophage-activating effect, and its ability to downregulate the expression of IFN-γ–induced class II MHC gene products on antigen-presenting glial cells. IFN suppresses T-cell proliferation and may decrease blood–brain barrier permeability by decreasing matrix metalloproteinases.[60] IFN-β also increases the production of regulatory CD56 (bright) natural killer cells and Treg cells.[61] In general, all IFNs exert these actions in the periphery and at the blood–brain barrier level.

TABLE 72-4 Evidenced-Based Recommendations for Disease-Modifying Treatment of Multiple Sclerosis

Recommendations	Recommendation Grades*
Interferon-β	
• Interferon-β has been shown to reduce attack rates in patients with MS or those with CIS who are at high risk of developing MS	A-I
• It is appropriate to consider IFN-β for any patient with clinically definite MS or who already has RRMS or SPMS and is still experiencing relapses	A-I
• The effectiveness of IFN-β in patients with SPMS but without relapses is uncertain	U-I
• Route of administration of IFN-β products is probably not clinically important with regards to efficacy; however, the side-effect profile does differ	B-II
• Rate of production of neutralizing antibodies is probably less with IFN-β_{1a} than with IFN- β_{1b}	B-I
• Presence of neutralizing antibodies may be associated with a reduction in the clinical effectiveness of IFN-β treatment	C-I
Glatiramer acetate	
• Glatiramer acetate has been shown to reduce the attack rate in patients with RRMS	A-I
• Treatment with glatiramer acetate may slow sustained disability progression in RRMS	C-I
Mitoxantrone	
• Mitoxantrone probably reduces the attack rate in patients with relapsing forms of MS	B-II, III
• Mitoxantrone may have a beneficial effect on disease progression in MS	C-II, III
Natalizumab	
• Natalizumab decreases clinical relapse rate, gadolinium-enhancing lesions, and new T2 lesions	A-I
• Natalizumab in RRMS positively changes measures of disease severity such as EDSS progression rate and changes lesions on MRI in RRMS	A-I
Ocrelizumab	
• Ocrelizumab in PPMS is shown to decrease confirmed disability progression, lessen worsening of timed 25-ft (~7.5 m) walk, decrease T2-weighted MRI lesions volume by 3.5%, and percentage of brain volume loss by 0.90%	A-I
• Ocrelizumab in RRMS positively changes measures of disease severity such as EDSS progression rate and changes lesions on MRI in RRMS	A-I

*Strength of recommendations: A: established; B: probable; C: possible; U: inadequate data to support recommendation.

CIS, clinically isolated syndrome; RCT, randomized controlled trial; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary-progressive multiple sclerosis.

Quality of evidence: Class I, evidence from one or more prospective, randomized, controlled clinical trial; Class II, evidence from cohort or RCT not meeting criteria for class I; Class III, evidence from other controlled trials; Class IV, evidence from uncontrolled studies, case reports, case series, or expert opinion.

Data from References 60 and 62.

IFN-β_{1b} is a nonglycosylated synthetic analog of recombinant IFN-β that is produced in *Escherichia coli*. IFN-β_{1b} is administered subcutaneously every other day at a dose of 250 mcg (8 million international units). Clinical trials have demonstrated that at these doses, IFN-β_{1b} significantly reduces annual relapse rate and MRI burden of disease compared with placebo; however, no significant differences were noted between the IFN and placebo-treated groups with respect to clinical disability.[60] Betaseron is packaged in partially premixed syringes with a new formulation that does not require refrigeration and can be used with an autoinjector. In 2009, an additional IFN product was introduced with the trade name Extavia; however, this is the same medicinal product as Betaseron.

IFN-β_{1a} (Avonex, Rebif) is a natural-sequence glycosylated IFN produced in Chinese hamster ovary cells. Avonex is administered as a 30-mcg dose (6 million international units) intramuscularly once weekly. Rebif is made similarly to Avonex but is given as either 22 or 44 mcg subcutaneously three times weekly. Both are supplied in a 0.5-mL prefilled syringe and should be refrigerated, but remain stable at room temperature for 30 days. Rebif may have lower immunogenicity and a slightly better side-effect profile than Avonex.[63]

Patients receiving IFN-β_{1a} (Avonex), given as a 30-mcg dose administered intramuscularly once weekly for 2 years, demonstrated statistically significant reductions in annual relapse rates (by approximately one-third), as well as disease progression (defined as a confirmed decrease of one point on the EDSS), compared to placebo.[64] When disease progression was assessed by MRI studies, patients receiving active drug had significantly fewer new enhancing lesions compared with placebo-treated patients. Similar results were also seen with a higher dose (44 mcg), more frequent administration (three times weekly), and subcutaneous injection of IFN-β_{1a} (Rebif).[60] Other studies reveal significant effects on slowing brain atrophy[65] and the progression of cognitive decline[64] in patients treated with Avonex. Therefore, taken as a whole these observations show that IFN-β possesses significant disease-modifying activity.

Pegylated IFN-β_{1a} (Plegridy) was FDA approved for treatment of relapsing forms of MS in August 2014. The attachment of polyethylene glycol (PEG) polymer chains to the interferon molecules results in a longer half-life and allows for less frequent dosing. Peg-IFN-β_{1a} is given by subcutaneous injections once every 2 weeks. Results from the pivotal ADVANCE study demonstrated significant reduction in annualized relapse rates (35.6%), reduction of new lesions on MRI scans, and reduction of risk of disability progression when

compared to placebo.[66]

Side effects are similar with all the IFNs, and baseline CBCs, platelet determinations, and LFTs should be documented before and after 1 month of therapy and then repeated every 3 months for 1 year, and every 6 months thereafter. A small percentage of patients develop depressed blood cell counts that usually respond to therapy discontinuation. Additionally, elevation in liver enzymes can be seen that are usually transient in nature and respond to treatment discontinuation. However, rare cases of liver failure that require transplantation have been reported, which have resulted in modifications of the package inserts for IFN-β products to reflect this risk. Other more common adverse effects include injection-site redness and swelling, menstrual irregularities, and rarely injection-site necrosis. Injection-site reactions are probably worse with IFN-β_{1b}, can occur at any time, and can be lessened by using appropriate injection technique including site rotation, topical lidocaine, application of ice before and after the injection, or use of an autoinjector. Additionally, injecting the medications at body temperature (place under armpits to warm) will decrease injection-site pain.

Flu-like symptoms (eg, fever, chills, and myalgias) are seen in most patients and typically occur for up to 24 hours after injection. While these symptoms may be seen with subsequent injections, they typically abate within 1 to 3 months after starting the injections; however, for some patients they may persist. In order to alleviate these flu-like symptoms, patients may try taking the injection at night prior to bedtime in order to sleep through the most bothersome symptoms or use either nonsteroidal anti-inflammatory agents or acetaminophen before and at regular intervals for 24 hours after IFN-β administration. Dosage reduction initiation using one-quarter or one-half the standard dose, with an increase to full dosage over 1 to 2 months, is also beneficial in reducing flu-like side effects.[67] Some authors suggest that because of the transient immune activation that can occur following the introduction of IFN-β, a short burst of oral prednisone can alleviate some adverse effects.[67]

Less commonly reported side effects include transient shortness of breath or tachycardia, thyroid dysfunction, and neutralizing antibodies. Although depression is a common finding in MS patients, all the IFNs, especially IFN-β_{1b}, can produce depressive symptoms and therefore clinicians must monitor all patients carefully for signs of depression and be monitored closely for suicide risk. Most patients will not feel better or have improvement in MS symptoms when taking IFNs, and many will experience side effects; thus, adherence can become a major issue.

Finally, safety data on IFN-β in pregnancy and lactation are lacking. Abortifacient activity in primates has been noted, and until adequate safety data are available, women should be counseled to use appropriate contraception while using these products.

Glatiramer Acetate (Copaxone) Glatiramer acetate (formerly known as copolymer-1) is a synthetic polypeptide consisting of L-alanine, L-glutamic acid, L-lysine, and L-tyrosine. Although the precise mechanism of action is unknown, glatiramer acetate appears to mimic the antigenic properties of myelin basic protein (MBP).[68] This agent also may act by directly binding to MHC class II receptors and inhibiting binding of MBP peptides to T-cell receptor complexes.[68] Glatiramer acetate has demonstrated that it induces Th2 (anti-inflammatory) lymphocytes in experimental allergic encephalomyelitis,[68] which is thought to contribute to "bystander" suppression at the site of the MS lesion resulting in reduced inflammation, demyelination, and axonal damage.[60] Glatiramer acetate may also suppress T-cell activation and recent studies suggest that it may be associated with a neuroprotective effect by inducing brain-derived neurotrophic factor.[69]

Given as a daily 20 mg or three times weekly 40-mg subcutaneous dose, glatiramer acetate, or its generic biosimilar, Glatopa appears to have a relatively mild adverse effect profile with mild pain and pruritus at the injection site being the most common. Approximately 10% of patients experience a one-time transient reaction consisting of chest tightness, flushing, and dyspnea beginning several minutes after injection and lasting usually no longer than 20 minutes. This postinjection reaction can occur with any dose, and is not limited to the first injection. If patients have no history or evidence of coronary artery disease, they may be assured these reactions are almost always self-limited and benign.

Multicenter trials with glatiramer acetate have demonstrated significant reductions in mean annual relapse rate (approximately 29%), comparable with the IFNs.[60] An extension trial, completed after the original pivotal 2-year study, suggests that glatiramer acetate may slow the progression of disability in patients with RRMS.[60] Glatiramer acetate also delays development of T1 holes on brain MRIs[70] and long-term uncontrolled data show that it remains safe and effective for individuals who continue to take it over 10 years.[71] Glatiramer acetate needs to be stored in the refrigerator but can be kept at room temperature for up to 1 week.

On January 28, 2014, the FDA-approved glatiramer acetate (Copaxone) 40 mg/mL administered three times weekly by subcutaneous injection for the

treatment of RRMS based largely on the results of the Glatiramer Acetate Low-frequency Administration (GALA) study.[72] This placebo-controlled trial in treatment-naive patients demonstrated significant reduction in mean annual relapse rate (approximately 34%), reduction of new T2 lesions as well as T1 lesions, and comparable safety profile. Another open-label study entitled GLatiramer Acetate low frequenCy safety and patIent ExpeRience (GLACIER), further demonstrated comparable efficacy with favorable injection-related adverse events and convenience profile when patients were switched from glatiramer acetate 20 mg daily to 40 mg three times weekly.[73]

Natalizumab (Tysabri) Natalizumab is a partially humanized monoclonal antibody directed at the cell surface adhesion molecule $\alpha_4\beta$-integrin (also known as very-late antigen 1, VLA-1). Natalizumab works by attaching to VLA-1 and blocking its interaction with its ligand on CNS endothelium vascular cell adhesion molecule 1 (VCAM-1). Thus, activated lymphocytes are denied entry past the blood–brain barrier. In a phase II study, compared with placebo, natalizumab significantly reduced the number of new gadolinium-enhancing lesions by more than 90%, and diminished relapses.[74] In a 2-year phase III trial (A Randomized, Placebo-Controlled Trial of Natalizumab for Relapsing Multiple Sclerosis [AFFIRM]), natalizumab resulted in a 60% reduction in annual relapse rates, a more than 90% improvement in gadolinium-enhancing lesions, and the progression of disability was significantly delayed, compared to placebo.[75] In a separate 2-year phase III trial (The Safety and Efficacy of Natalizumab in Combination with Interferon Beta-1a in Patients with Relapsing Remitting Multiple Sclerosis [SENTINEL]), natalizumab when added to IFN-β_{1a} (Avonex) reduced relapse rates by more than 50% and gadolinium-enhancing lesions by 84%, compared to patients who continued with IFN-β_{1a} alone.[76] In these trials, natalizumab was infused IV every 4 weeks and was relatively well tolerated, although approximately 1% of patients developed infusion reactions, and 6% developed neutralizing antibodies that diminished the efficacy of the drug.

Natalizumab is FDA approved for use in relapsing forms of MS. However, shortly after natalizumab's initial approval, three patients enrolled in ongoing clinical trials were reported to have contracted progressive multifocal leukoencephalopathy (PML), a rare brain infection most commonly seen in patients with human immunodeficiency virus.[77–79] Based on these reports, the FDA required that natalizumab include a black-box warning about PML and enrollment in a mandatory Risk Evaluation and Mitigation Strategy (REMS)

program called TOUCH. While the estimated risk for developing PML is low, it is high when compared to other MS treatments.[80] As of December 2017, Biogen has reported that natalizumab is correlated to 756 cases of PML with three factors appearing to impact the overall risk. These include, duration of treatment (24 months or longer), prior use of immunosuppressive therapies (mycophenolate mofetil, alemtuzumab, efalizumab, and rituximab), and a history of anti-John Cunningham virus (JCV) antibodies.[81,82] Since the overall predicted seroconversion rate for JCV is 2% to 3% per year, current recommendations are to screen patients at baseline and every 6 months with a JCV test while receiving natalizumab therapy.[83] A two-step enzyme-linked immunosorbent assay (ELISA, STRATIFY TEST) is available for qualitative detection of serum antibodies to the JCV, offering a false-negative rate of 2.5%.[81,82]

For those patients who develop PML, a plasma exchange (PLEX) has been utilized to help clear the drug more rapidly from the blood.[84] An acute syndrome, referred to as immune reconstitution inflammatory syndrome (IRIS), has been associated with acute neurological deterioration after PLEX, requiring the use of high-dose steroids.[85]

Fingolimod (Gilenya) Approved September 21, 2010, fingolimod is the first oral DMT for MS that has a unique mechanism of action as a sphingosine 1-phosphate receptor agonist. Fingolimod exhibits its immunosuppressant properties by sequestering circulating lymphocytes into secondary lymphoid organs. Additionally, fingolimod also reduces the infiltration of T lymphocytes and macrophages into the CNS that may result in neuroprotective effects. In clinical trials, it decreased annualized relapse rates by approximately 52% compared to IFN-β_{1a}. After 7 years of continuous fingolimod therapy, approximately 92% of patients were free of gadolinium-enhancing lesions, although this data was obtained using the 1.25 mg dose, which is different from the recommended dose approved by the FDA of 0.5 mg once daily. Fingolimod is the first DMT to have a pediatric indication of 10 years of age and greater.

A major side effect noted with fingolimod use is pronounced first-dose bradycardia. Other rarer side effects include bradyarrhythmia or atrioventricular block, infections, macular edema, a decrease in forced expiratory volume over 1 second in patients with previously compromised lung function, elevation of liver enzymes, sustained increases of approximately 1 to 2 mm Hg in systolic and diastolic blood pressure, and lymphoma. It is recommended that all patients starting fingolimod treatment be monitored for signs of bradycardia for at least 6 hours after the first dose. The FDA also recommends hourly pulse and blood

pressure monitoring for all patients starting treatment, with electrocardiogram monitoring prior to dosing and at the end of the observation period or continued until all symptoms resolve. The period should extend past 6 hours in patients at higher risk and for some cases continue overnight. Additionally, the package insert requires a new 6-hour observation period in patients who have discontinued and wish to restart therapy. The recommendation varies depending on the time of discontinuation and days of therapy missed. To reduce risks related to bradycardia or atrioventricular block, extended monitoring is now recommended in patients with certain preexisting conditions such as QT prolongation. This is also a concern in patients receiving concomitant drugs that slow the heart rate or atrioventricular conduction, drugs that cause QT interval prolongation, and those who have a known risk for torsades. The following class Ia and class III antiarrhythmic agents are contraindicated with concurrent use of fingolimod: quinidine, procainamide, disopyramide, amiodarone, bretylium, sotalol, ibutilide, azimilide, dofetilide, and dronedarone.[86] Similar to natalizumab, as of March 2018, PML has been reported with fingolimod use in eight patients after 3 years of exposure with this risk being drug specific, and independent of natalizumab treatment.[80] Similar adverse events were found in the pediatric population.

Additional monitoring recommendations for fingolimod use include baseline CBCs, LFTs, ophthalmologic examinations, and ECG in patients with known heart problems. To date, one important drug interaction has been reported as ketoconazole has been shown to increase the area under the curve of fingolimod by 70%. For patients requiring administration of a live vaccine (Zostavax, Flumist, Measles, Mumps, and Rubella [MMR], Yellow Fever [YF-VAX], etc.), consider doing so prior to starting fingolimod or waiting until 2 months after discontinuation.

Teriflunomide (Aubagio) Teriflunomide is an oral immunomodulatory agent, which was FDA approved for the treatment of relapsing forms of MS. The medication works by inhibiting dihydroorotate dehydrogenase to prevent the proliferation of peripheral lymphocytes (T and B cells). The reduction of activated lymphocytes in the CNS reduces the inflammation and demyelination that occurs in patients with MS. Teriflunomide is the active metabolite of leflunomide, an agent approved for the treatment of rheumatoid arthritis; however, teriflunomide is dosed as 7 or 14 mg orally once daily.

In CDMS patients, receiving 7 or 14 mg daily of teriflunomide resulted in a 31% reduction in annualized relapse rates compared with placebo and the risk of disability progression was also reduced by almost 30% for those receiving 14 mg

of teriflunomide daily.[87]

In a 36-week randomized, double-blinded, placebo-controlled study in 179 MS subjects with relapse, the primary outcome was the average number of unique active lesions per MRI scan during treatment. Both the 7 and 14 mg doses resulted in a reduction in the number of unique active lesions per MRI scan compared with placebo (relative risk reductions 0.98 and 1.06, respectively).[88]

Although teriflunomide is not metabolized by CYP450 enzymes, it inhibits CYP2C8 and induces CYP1A2. This medication is also a substrate for the breast cancer–resistant protein (BCRP); therefore, inhibitors of BCRP (eg, cyclosporine) may increase serum concentrations of teriflunomide. Additionally, teriflunomide inhibits other organic anion transporters such as OATP1B1 and OAT3; however, the significance of these drug interactions is unknown at this time. Studies found that concomitant use of warfarin and teriflunomide resulted in a 25% decrease in international normalized ratio (INR), rendering the need for close monitoring. When teriflunomide is coadministered with estradiol and levonorgestrel, the mean maximum serum concentration and area under the curve are increased.

The most common adverse effects seen with teriflunomide are increases in LFTs, alopecia, nausea, diarrhea, influenza, headache, and paresthesia. Recommended monitoring includes obtaining monthly LFTs for the first six months as teriflunomide carries a black-box warning related to the risk of hepatotoxicity. Additionally, teriflunomide also has a black-box warning for teratogenicity as animal studies have associated oral teriflunomide with fetal malformations and embryolethality in female rats, as well as reduced sperm count in male rats. Therefore, teriflunomide is contraindicated in pregnancy and in women of childbearing potential not using reliable contraception. Patients who become pregnant during therapy or within 2 years after discontinuation of therapy should enroll in the Aubagio Pregnancy Registry and consider a cholestyramine washout. Additionally, men taking this medication with partners who wish to become pregnant may consider a cholestyramine washout to reduce serum drug levels, as this drug may remain in the blood for up to 2 years after discontinuation. Teriflunomide may activate tuberculosis, so a negative skin test or treatment of the disease must be documented prior to starting therapy.

Dimethyl Fumarate (Tecfidera) Dimethyl fumarate has an unknown mechanism of action; however, it is an in vitro nicotinic acid receptor agonist and an in vivo activator of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway that is involved in cellular response to oxidative stress. It is approved

by the FDA for relapsing forms of MS.

In the “Efficacy and Safety Study of Oral Dimethyl Fumarate (BG-12) with Active Reference in Relapsing Remitting Multiple Sclerosis (CONFIRM),” dimethyl fumarate decreased the annualized relapse rate by 44% and 51% with twice daily or three times daily dosing, respectively.[89] In “The Determination of the Efficacy and Safety of Oral BG-12 in Relapsing-Remitting MS” study, the annualized relapse rate decreased by 47% and 52% with 240 mg twice daily or three times daily dosing, respectively.[90]

Dimethyl fumarate is metabolized by esterases in the GI tract, blood, and tissues and there are no known drug interactions. It is classified as pregnancy category C and is dosed initially at 120 mg (delayed release) orally twice daily. After 7 days, the dose should be increased to 240 mg (delayed release) orally twice daily. Laboratory monitoring includes a CBC prior to starting therapy, within 6 months of initiating treatment and then annually. Side effects include lymphocytopenia (2%-6%), increased LFTs, and flushing (40%), which should improve over 1 month and is decreased by taking it with food. Four cases of PML have been attributed to patients treated with dimethyl fumarate as of March 2018. Rash, abdominal pain, diarrhea, nausea, and vomiting have also been reported. GI side effects decrease over 1 month and respond to symptomatic treatment. It is also accepted that slowing the dose escalation may decrease the risk of GI side effects.

Alemtuzumab (Lemtrada) Alemtuzumab is a humanized monoclonal antibody against CD52 approved for the therapy of RRMS. CD52 is a glycosylphosphatidylinositol (GPI)–anchored protein consisting of 12 amino acids expressed at high levels on T and B lymphocytes, and to a lesser extent on monocytes, macrophages, and eosinophil granulocytes. Within a few minutes after infusion, alemtuzumab leads to depletion of CD52 positive cells through antibody-dependent cell-mediated cytolysis (ADCC) and complement-dependent cytolysis (CDC).

The two phase III trials, CARE-MS I[91] and II,[92] were randomized, rater-blinded studies with subcutaneous IFN-β_{1a} as active comparator designed to test clinical application of alemtuzumab. CARE-MS I included 581 treatment-naive RRMS patients, whereas CARE-MS II enrolled 637 RRMS patients with breakthrough disease under previous DMTs. Alemtuzumab demonstrated a 50% reduction in relapses compared to IFN-β_{1a} therapy in both CARES-MS I and II. Additionally, a significant reduction in 6-month accumulation of disability was only observed in CARE-MS II but not in CARE-MS I, which might be attributed

to the unexpectedly low rate of disability progression in the IFN-β_{1a} group, indicating a relatively underpowered trial. MRI measures also proved superiority of alemtuzumab with significantly less gadolinium-enhancing lesions, new or enlarging T2 lesions, and brain atrophy. Lastly, significantly more alemtuzumab than IFN-β_{1a}–treated patients were free of any clinical disease and free of any clinical and MRI disease activity as part of these trials. Currently, alemtuzumab therapy is approved for two courses with 12 mg being infused for five consecutive days in the first course and then for 3 days in the second course 1 year later.

Alemtuzumab high efficacy parallels its considerable high risk of infusion-associated reactions (IARs) which affect over 90% of patients. Concomitant corticosteroids, antihistamine, and antipyretic drugs can be utilized with the infusion in order to avoid IARs. Other side effects are most commonly mild to moderate and consist of headache, rash, pyrexia, and nausea. Respiratory tract and urinary tract infections are also common. The accumulation of herpes infections during the CARE-MS studies led to the recommendation that prophylactic acyclovir treatment be implemented 0 to 4 weeks after alemtuzumab infusion to significantly reduce infection rates. Moreover, there are single case reports of spirochetal gingivitis, pyogenic granuloma, esophageal candidiasis, tuberculosis, and listeria meningitis; the latter leading to dietary advice to avoid, for example, unpasteurized cheese.[93] No cases of PML have been reported with alemtuzumab to date.

Additional risks seen with alemtuzumab use include secondary autoimmune disease occurring in approximately 30% to 40% of patients, predominantly impairing thyroid function and manifesting as hyperthyroidism, hypothyroidism, goiter, and thyroiditis. There is also a small but serious risk of immune thrombocytopenia (ITP) that can occur at any time ranging from 1 to 34 months post-alemtuzumab administration. Additionally, glomerulonephritis and single cases of autoimmune neutropenia, hemolytic anemia, and type 1 diabetes have been reported.[93] Extensive monitoring and early intervention allow for an appropriate risk management.

Mitoxantrone (Novantrone) Mitoxantrone, a member of the anthracenedione family, is approved by the FDA for reducing neurologic disability and the frequency of clinical relapses in patients with SPMS (chronic), PRMS, or worsening RRMS.[94] Based on the clinical trials to date, however, the MRI outcomes from mitoxantrone use were not as robust as those seen in the trials of relapsing patients alone.[95] Additionally, although patients with SPMS were

included in the Effect of Mitoxantrone on MRI in progressive MS (MIMS) trial, there was no sub-study documenting its effects on slowing of progression of MS specifically in this subgroup of patients.[94,95] Thus, support for use of mitoxantrone in this context is lacking.[96]

Mitoxantrone is administered as a brief (5- to 15-minute) IV infusion dosed at 12 mg/m^2 every 3 months with a maximum allowable lifetime cumulative dose of 140 mg/m^2. An evaluation of left ventricular ejection fraction and ECG are required prior to administration of each dose. If signs or symptoms of congestive heart failure develop, an evaluation of left ventricular ejection fraction and/or an ECG should be repeated. Other potential side effects noted are nausea, alopecia, menstrual disorder, amenorrhea, upper respiratory tract infection, UTIs, and leukemia. The role that mitoxantrone will ultimately play in the treatment of MS remains unclear, because potential cardiac toxicity limits its long-term use. More recent estimates also suggest the risk of leukemia may be as high as 1 in 145 patients, which has significantly decreased interest in its use for MS patients.[96]

Rituximab (Rituxan) and Ocrelizumab (Ocrevus) Currently rituximab use is not FDA approved for the treatment of RRMS and PPMS, but it is used within this context throughout many MS centers in the United States. Evidence suggests that patients with PPMS who are less than 51 years old and have at least one gadolinium-enhancing lesion may benefit from rituximab therapy when given as an infusion twice yearly.[97] Pharmacologically rituximab is a chimeric monoclonal antibody that targets the CD20 antigen on B cells.

Ocrelizumab is the first drug FDA approved for PPMS, but is also approved for relapsing forms of MS. It is a humanized version of the rituximab monoclonal antibody, and theoretically, should have less autoantibodies and infusion reactions than its chimeric counterpart. Its mechanism of action for MS is unknown, but it is presumed to involve binding to CD20, which is a cell surface antigen present on pre-B and mature B lymphocytes. This blockage of CD20 effectively suppresses immune responses through depletion of CD20-expressing B cells[39].

In two phase III trials, ocrelizumab has been associated with lower rates of disease activity and progression compared to interferon β_{1a} over the period of 96 weeks.[98] The ORATORIO phase III trial was conducted to show the efficacy of ocrelizumab in PPMS patients with ocrelizumab therapy showing approximately a 18% to 25% risk reduction in all study endpoints (confirmed disability progression at 12 and 24 weeks, performance in the timed 25-ft walk test [~7.5 m], total volume of T2-weighted lesion, and decreased change in brain volume)

when compared to placebo.[39]

Common adverse events seen as part of these trials included infusion reactions, which decreased with subsequent dosing, upper respiratory tract infections, and oral herpes activation. Neoplasms were also more common in the ocrelizumab group compared to placebo, with four patients receiving ocrelizumab who developed breast cancer, and three with basal cell carcinoma. Cervical adenocarcinoma in situ and basal cell carcinoma were the two neoplasms seen in the placebo group. This imbalance warrants ongoing evaluation in the context of the epidemiology of neoplasms in the MS population and the long-term experience with this and other CD20 treatments.[39] No cases of PML have been reported with ocrelizumab as of March 2018.

The labeling for dosing and administration states that ocrelizumab is given via peripheral infusion as a two-dose series to begin treatment with 300 mg given on day 1 and another 300 mg given on day 14. Subsequent doses of 600 mg are then given in 6-month intervals. Infusion rates are started at 30 mL/hr (for 300 mg in 250-mL bag starting doses) or 40 mL/hr (for 600 mg in 500-mL bag maintenance dose), which is stepped up based on tolerance of the patient, much like is done with rituximab. There are also maximum infusion rates of 180 mL/hr for 300 mg dosing, and 200 mL/hr with the 600 mg dose. Before the initiation of ocrelizumab, patients should be screened for hepatitis B and before each infusion patients are screened for active infections. Lastly, patients need to be monitored for infusion reactions throughout the infusion and for 1 hour after completion.

Daclizumab (Zinbryta) Daclizumab is a once a month subcutaneous MS DMT reserved for patients who have failed two prior therapies and is thought to modulate IL-2–mediated activation of lymphocytes through binding of CD25. Although daclizumab was approved in May 2016, it was subsequently pulled from the worldwide market in March 2018 due to it causing serious inflammatory brain disorders. Relatively small number of patients (8,000) worldwide were on therapy at the time of discontinuation.

Remaining Questions for Disease-Modifying Therapy

9 Despite encouraging results from well-conducted clinical trials, several relevant treatment issues remain, such as when to begin therapy, which agent to initiate, and when to switch and stop therapies. The MS Coalition has developed an evidence-based paper, which has been endorsed by the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS), to provide

guidance on the use of DMT in MS. Key recommendations regarding treatment and access considerations are summarized in Table 72-5.[99]

TABLE 72-5 Key Recommendations on Treatment and Access Considerations

- Initiation of therapy with an FDA-approved DMT is recommended as soon as possible following a definite diagnosis of relapsing MS, and can also be considered for selected patients with a first clinical attack consistent with MS where other potential causes have been excluded as well as patients with progressive MS with clinical relapses and/or inflammatory activity
- Choice of initial or alternative DMT is complex and should be collaboratively done by the treating clinician and the patient
- Therapy is to be continued indefinitely, unless there is clear lack of benefit, intolerable side effects, inadequate patient compliance, new data that reveal other reasons for cessation, or better therapy becomes available
- Absence of relapses while on treatment should not justify discontinuation of treatment
- When switching DMT due to suboptimal response, an agent with an alternative mechanism of action should be chosen
- Patient and clinician access to all available therapies is necessary due to significant variability in the MS population such as response to therapies, contraindications, risk tolerance, and compliance that may be influenced by route of administration and/or side effects
- Patient access to medication should not be limited by the frequency of relapses, age or other personal characteristics, or level of disability and should not be withheld to allow for determination of coverage by payers, as this puts the patient at increased risk for recurrent disease activity

Data from Reference 99.

Decisions about the use of any medication for MS rests on determining the severity of the illness, the efficacy of the medication, side effect risks, and costs related to the therapy. Clearly, these drugs slow the course of the illness but do not suppress it completely, and in some individuals, there is no apparent benefit. There is now, however, overwhelming evidence that the vast majority of untreated patients will have progressive disease over time. Pathologic data clearly show that even in acute lesions there is significant axonal damage that is essentially irreversible. MRI data show that 80% to 90% of all new enhancing lesions are asymptomatic, suggesting that a “quiet” clinical course does not necessarily mean there is not an ongoing disease activity that ultimately will lead to cognitive deficits and progressive spastic paraparesis.

It is clear that very early therapy is effective. In patients with CIS and two or more T2 lesions on brain MRI (ie, at high risk for developing CDMS), placebo-controlled studies with all three of the IFN agents and glatiramer acetate have shown significant delay in a second attack and positive outcomes on a variety of MRI measures (BENEFIT, Betaseron in Newly Emerging Multiple Sclerosis for Initial Treatment; CHAMPS, Controlled High Risk Subjects Avonex Multiple Sclerosis Prevention Study; and ETOMS, Early Treatment of Multiple Sclerosis).[60,100] Thus, very early therapy is potentially warranted, and IFN-β_{1b}, IFN-β_{1a} (Avonex), and glatiramer acetate are approved by the FDA for use after CIS in those patients with abnormal MRIs consistent with demyelination. The MS Coalition recommends that patients with relapsing disease should be initiated on an FDA-approved DMT as soon as possible following diagnosis.[99]

A second major issue is which drug to use in which patient. There has not been a single, randomized study comparing DMTs in a similar patient population at the same time.[101] In the case of the first-generation self-injectables (see Table 72-3), the pivotal placebo-controlled trials produced results that were more similar than different when comparing across trials, including a nearly identical one-third reduction in relapse rate for all four drugs over 2 years. A small number of studies have suggested that higher dose, more frequent administration of IFN may be more efficacious than lower dose, less frequent administration.[102,103] Other studies argue against this,[104,105] and recent studies note no significant difference in outcomes between standard and double dose IFN-β_{1b} and glatiramer acetate,[104,106] and no difference between IFN-β_{1a} (Rebif) and glatiramer acetate.[107]

A concern with all three IFN products that further complicates our understanding of the clinical differences between IFN products is the development of neutralizing antibodies. In clinical trials, 30% to 40% of patients receiving IFN-β_{1b} developed antibodies directed against the drug.[108] In these patients, the exacerbation rate was similar to that seen in placebo-treated patients. For patients on IFN-β_{1b}, neutralizing antibodies can occur as early as 3 to 6 months into treatment and as late as 18 months, as this product tends to be the most antigenic.[109] With IFN-β_{1a}, neutralizing antibodies were found in 22% of early trials of Avonex, but later studies reported that only 2% to 5% of treated patients developed antibodies which is potentially due to a formulation change making the product less antigenic.[105,109] Percentages of antibody formation for Rebif (approximately 12%) are intermediate, therefore moderate antigenic activity may occur in the first 9 to 15 months of treatment similar to

Avonex.[60,108,109] Approximately 6% of patients treated with natalizumab show neutralizing antibodies that seem to diminish efficacy.[76] The long-term clinical significance of these findings is still not completely clear, although three recent studies have further confirmed the effect of neutralizing antibodies on relapses, MRI lesions, and progression of disability in MS.[109–112] Whether these antibodies are truly cross-reactive between products is unknown, as is the duration of time in which antibodies can be detected. Currently consensus guidelines regarding when to test for neutralizing antibodies, which assay to use, or what titer cutoff to apply to patients in clinical settings exist.[113] Lastly, it is also unknown now that corticosteroid use might impact antibody formation.

8 We now have experience for more than two decades with MS patients taking DMTs, yet clinically we have not seen major improvements as patients continue to have more relapses, more lesions on MRI, more disability, and ongoing slippage into SPMS.[114] There is no accepted definition of treatment inadequacy, although the Canadian Multiple Sclerosis Research Council has suggested a relatively simple approach that incorporates the elements of relapse rate, new MRI lesions, and change on the EDSS.[115] If a patient develops significant and persistent IFN antibodies, movement to a non-IFN antibodies (glatiramer acetate, natalizumab, ocrelizumab, fingolimod, teriflunomide, dimethyl fumarate, mitoxantrone, or possibly rituximab[116]) is reasonable. A second option is addition of an immunosuppressant agent, such as monthly methylprednisolone,[117] azathioprine, methotrexate, or mycophenolate. As noted above, the addition of natalizumab to IFN-β_{1a} was effective, but produced rare cases of PML, and thus this combination should not be used clinically. Interestingly, Birnbaum et al. found the addition of a statin, specifically atorvastatin, into a beta-interferon agent may worsen MS,[118] although these results are not definitive.

Symptomatic Management

10 Many of the symptoms of MS either do not require pharmacologic management or are nonresponsive; therefore, this section addresses the primary symptoms in which pharmacologic management may be of benefit (**Table 72-6**).[33,115,119–122] See the preceding section on the treatment of exacerbations for a discussion of optic neuritis.

TABLE 72-6 Treatment of Selected Primary MS Symptoms

Spasticity	Bladder Symptoms	Sensory Symptoms	Fatigue
Baclofen	Propantheline	Carbamazepine	Amantadine
Dantrolene	Oxybutynin	Phenytoin	Antidepressants
Diazepam	Dicyclomine	Amitriptyline or other TCAs	Modafinil
Clonazepam	DDAVP	Gabapentin	Methylphenidate
Tizanidine	Self-catheterization	Lamotrigine	Dextroamphetamine
Tiagabine	Imipramine or amitriptyline	Pregabalin	Armodafinil
Gabapentin	Prazosin or terazosin	Duloxetine	Fluoxetine
Pregabalin	Botulinum toxin type A		
Botulinum toxin type A	Solifenacin		
Dalfampridine	Darifenacin		
	Trospium		
	Hyoscyamine		
	Mirabegron		
	Tamsulosin		
	Tolerodine		

DDAVP, desmopressin acetate; TCA, tricyclic antidepressant.

Data from References 33, 115, 119–122.

Gait Difficulties and Spasticity Problems with gait can be caused by spasticity, weakness, ataxia, defective proprioception, or a combination of these factors. In general, spasticity is commonly encountered and tends to affect the legs more markedly than the arms, which can result in falls. As spasticity often presents late in disease, the increased muscle tone of a spastic limb often lends pseudo-strength to patients with underlying weakness. While spasticity is amenable to pharmacologic intervention, when using muscle relaxants, one must be careful not to decrease the tone to an extent that ambulation is actually hindered.[33,119] Baclofen (Lioresal), a short-acting γ-aminobutyric acid (GABA) analog, is the preferred agent for spasticity, and is usually started in dosages of 10 mg three times daily which is then titrated upward to achieve the desired response. While most patients achieve a satisfactory response with dosages between 40 and 80 mg/day, dosages higher than the recommended daily maximum of 80 mg may be required by some patients.[33,119] Due to baclofen's relatively short duration of action, wearing-off is common; therefore, continuous intrathecal administration of baclofen (Gablofen) may be an option for patients unable to tolerate or unresponsive to oral therapy. Baclofen should not be discontinued abruptly to avoid the possibility of seizures.[119]

Another agent effective for spasticity is tizanidine (Zanaflex), which is a short-acting, α-adrenergic agonist that acts in the CNS increasing presynaptic inhibition of motor neurons. It appears to have efficacy comparable to baclofen.[119] Dosage must be titrated slowly over 2 to 4 weeks, starting with 4

mg at bedtime, with adjustments based on clinical response. Effective tolerated dosages have ranged from 2 to 36 mg/day. Sedation, dizziness, and dry mouth are the most commonly reported adverse effects, but hypotension also can occur, as well as a rare but severe hepatotoxicity. Tizanidine can be added in small dosages to baclofen, sometimes creating better results and making smaller doses of each drug possible.

In patients who are unable to tolerate baclofen or tizanidine, diazepam (Valium; 2-10 mg/day), clonazepam (Klonopin; 1-3 mg/day), or dantrolene sodium (Dantrium; 100-400 mg/day) may be considered as alternatives, but they generally are less effective than either baclofen or tizanidine. Mild spasticity also may respond to moderately high doses of gabapentin (Neurontin; 1,800-3,600 mg/day) and tiagabine (Gabitril; 8-56 mg/day) may be useful in some patients with spasticity, but side effects can prohibit its use. Pregabalin (Lyrica; 75-300 mg/day) has similar features and mechanism of action as gabapentin, although pregabalin is approximately three times more potent and does not saturate the L-transporter system in the GI tract, so it may prove useful in the treatment of spasticity in MS patients.

Botulinum toxin type A (Botox; dose depending on the muscles injected) has been shown to be effective in alleviating spasticity.[33] The amount of toxin required to exert a pharmacological effect is often too excessive to use safely in the larger muscles; therefore, its use is best limited to smaller areas of focal muscle spasm.

For additional gait disruptions, an alternative approach employs K^+ channel blockers such as 4-aminopyridine (4-AP), which can potentiate synaptic transmission and increase muscle twitch tension. Similar to 4-AP, dalfampridine (Ampyra; 20 mg/day) has been shown to improve walking speed in patients with MS.[120,123] In other countries, dalfampridine is referred to as fampridine.[123] Safety concerns with the use of dalfampridine include the risk of seizures, particularly when patients exceed the maximum dose of 10 mg twice daily. It is also contraindicated in patients with a history of seizures. A REMS program is in place to manage risks associated with dalfampridine use and it is important to educate patients to not take products containing 4-AP with dalfampridine, which is the comparable extended release product. Additionally, the drug should not be chewed, crushed, or cut. If the patient misses a dose, they should take it immediately upon recognition and never double up on the dose, due to the risk of seizures. Commonly reported side effects of dalfampridine include UTIs, insomnia, dizziness, headaches, and balance disorders.

Tremor Cerebellar symptoms such as tremor can be troubling and difficult to

control. Medications that can be helpful include propranolol, primidone, and isoniazid.

Bowel and Bladder Symptoms Patients commonly complain of incontinence, urgency, frequency, and nocturia, which are indications of a hyperreflexic bladder (ie, inability to store urine). A number of anticholinergic agents, including tricyclic antidepressants, are used to treat mild symptoms, but with all anticholinergic agents, great care must be used to avoid falls, decreased cognition, and constipation, which is worsened by the patient's natural instinct to limit fluid intake. Antimuscarinic agents are also used to treat incontinence and in patients with significant sphincter detrusor dyssynergia benefit may be seen from oral use of α-adrenergic blockers or intramuscular use of botulinum toxin type A (Botox; dose depends on the muscles injected) to relax the internal sphincter (see Chapter 101, "Urinary Incontinence").

Intermittent self-catheterization and the Credé maneuver with or without a concomitant anticholinergic agent are recommended in patients with large postvoid residual volumes (more than 100 mL) or when the urinary problem is hyporeflexic in nature (failure to empty). Cholinergic agents (bethanechol) may be useful in patients with a hyporeflexive bladder. Patients with large post-void residual volumes are at risk for developing UTIs and often are prescribed urinary acidifiers such as vitamin C or antiseptics such as methenamine mandelate to prevent infections. Antibiotics used for UTI prophylaxis include sulfamethoxazole/trimethoprim, cephalexin, cinoxacin, and nitrofurantoin.

Constipation is the most common bowel complaint seen in patients with MS, as many medications (eg, narcotics, anticholinergics) as well as voluntary water restriction in those patients with urinary urgency and incontinence may contribute to its risk. Increases in dietary fiber and hydration may alleviate this problem, but in some instances laxatives or enemas may be necessary (see Chapter 35, "Chronic Heart Failure").

Major Depression Major depression is common in patients with MS, and the risk of suicide may be increased markedly compared with healthy subjects.[121] Patients should be monitored closely for the development of major depressive symptomatology and treated accordingly (see Chapter 85, "Depressive Disorders"). IFN products and natalizumab should be used cautiously in patients with significant depression.

Sensory Symptoms Numbness and paresthesia are frequent sensory complaints but usually do not require treatment. Some MS patients may develop acute or

chronic pain syndromes[119] such as trigeminal neuralgia and painful dysesthesias, for which treatment is necessary (see Chapter 77, “Pain Management”).

Sexual Dysfunction Sexual dysfunction in both men and women are common in MS, and counseling should be offered to both partners. Phosphodiesterase inhibitors or Alprostadil, a prostaglandin E1, can be very effective in men with MS who have erectile dysfunction (see Chapter 99, “Erectile Dysfunction”). Sildenafil (Viagra) is currently being studied in females with MS and sexual dysfunction. In patients needing antidepressant therapy for whom sexual dysfunction is a concern, bupropion is preferable to selective serotonin reuptake inhibitors as it has a much lower incidence of sexual side effects.

Fatigue Fatigue, one of the most common complaints in MS patients, can be severely disabling, but treatment is often overlooked. Typically, this secondary symptom presents in the mid-to-late afternoon and can increase with heat exposure, exertion, intercurrent infection, spasticity, weakness, and depression. Amantadine hydrochloride (100 mg twice daily) is used often and may offer significant relief.[33,115] Methylphenidate (Ritalin) and related products, and dextroamphetamine (Dexedrine) are used commonly for fatigue in MS. Modafinil (Provigil), 200 mg daily, up to 400 mg daily may be helpful for MS-related fatigue. The R-enantiomer of modafinil is armodafinil (Nuvigil) dosed at 150 or 250 mg daily, which reaches peak concentrations more quickly with potentially fewer side effects than modafinil. In patients suffering from both depression and fatigue, a more activating antidepressant such as fluoxetine may be employed.

Cognition Cognitive dysfunction is common in MS, affecting up to 50% or more of patients. In general, cognitive dysfunction manifests itself as word-finding difficulties and problems with concentration and short-term memory. A careful review of the patient’s current medications should precede additional pharmacotherapy for cognitive dysfunction, as specifically there are FDA reports for statins and long-term use with proton-pump inhibitors also causing memory concerns. Cognitive dysfunction can be treated with stimulants or cholinesterase inhibitors if appropriate.

Pseudobulbar Palsy Pseudobulbar palsy is a condition caused by progressive degeneration of the corticobulbar tract in patients with MS. Symptoms include dysarthria, dysphonia, dysphagia, and sudden, inappropriate, uncontrollable, emotional outbursts such as crying or laughing. A combination product of dextromethorphan and quinidine 20 mg/10 mg (Nuedexta) is used for the

treatment of this pseudobulbar affect. The mechanism of action is unknown; however, the rationale for utilization of this combination is that dextromethorphan is rapidly metabolized by CYP2D6, and quinidine inhibits the CYP2D6 enzyme to increase the serum concentration of dextromethorphan. Dosing for this combination medication is one capsule daily for 1 week, followed by one capsule twice daily.

Complementary and Alternative Therapies for MS

Approximately 33% to 80% of patients with MS use complementary and alternative medicine (CAM) instead of, or in addition to, disease-modifying and symptomatic therapies.[124] Common CAM therapies include diet and dietary supplements such as vitamins, minerals, and herbs. Antioxidant supplements vitamin A, C, E, α-lipoic acid, coenzyme Q10, grape seed, pine bark extracts, mangosteen, and acai have suggestive evidence of benefiting MS patients. However, for patients with MS, there is a theoretical risk associated with taking antioxidant supplements owing to their ability to stimulate the immune system (T cells and macrophages), which in patients with MS could be counterproductive, possibly worsening or exacerbating their disease, and counteracting the effects of immunomodulators. Other immune-stimulating supplements that should be used with caution are garlic, ginseng (Asian and Siberian), Echinacea, cat's claw, astragalus, alfalfa, and stinging nettle.[125]

The American Academy of Neurology recently updated evidence-based recommendations for the use of CAM in MS[124] (**Table 72-7**). In looking at these, oral cannabis extract is established as an effective treatment for spasticity and pain (Level A), and tetrahydrocannabinol (THC) and Sativex oromucosal spray may also reduce symptoms of spasticity and pain (Level B). However, it is important to note that the safety of these therapies when used in combination with MS disease-modifying therapies (DMTs) has not been studied, along with any potential interactions that may occur from coadministration. While there are limited data to support the effectiveness and safety of most of the CAM therapies for MS, these CAM options may be a consideration in some cases. Overall though, healthcare providers can be a source of objective information regarding the use of CAM for MS and can assist their patients in making the best decision.[125]

TABLE 72-7 American Academy of Neurology Evidence-Based Recommendations on CAM Therapies in MS

CAM Therapy	Type of MS	Symptoms and Reported Use	Effective	Ineffective	Recommendation Level
Oral cannabis extract	RRMS, SPMS, PPMS, MSU	Symptoms of spasticity and pain	x		A
	RRMS, SPMS, PPMS	Signs of Spasticity (short term), tremor (short term)		x	B
	MSU	Signs and symptoms of spasticity (long term)	x		C
	RRMS, SPMS, PPMS, MSU	Bladder symptoms, urge incontinence			U
Synthetic THC	RRMS, SPMS, PPMS	Symptoms of spasticity, pain	x		B
	RRMS, SPMS, PPMS	Signs of spasticity (short term), tremor (short term)		x	B
	MSU	Signs and symptoms of spasticity (long term)	x		C
	RRMS, SPMS, PPMS, MSU	Bladder symptoms, urge incontinence, central neuropathic pain			U
Sativex oromucosal spray	MSU	Symptoms of spasticity, pain, urinary frequency	x		B
		Signs of spasticity, incontinence episodes		x	B
		Tremor		x	C
		Anxiety/sleep, cognition, QOL, fatigue			U
Smoked cannabis	RRMS, SPMS, MSU	Spasticity, pain, balance and posture, cognition			U
Ginkgo biloba	RRMS, SPMS, PPMS	Fatigue	x		C
		Cognitive function		x	A
Lofepramine plus phenylalanine with B_{12} (Cari Loder regimen)	RRMS, SPMS, PPMS	Disability, symptoms, depression, fatigue		x	C
Reflexology	MSU	Paresthesia	x		C
		Pain, HRGOL, disability, spasticity, fatigue, cognition, bowel/bladder function, depression, anxiety, insomnia			U
Bee venom	RRMS, SPMS	MRI lesion number and volume, relapses, disability, fatigue, HRQOL		x	C
Magnetic therapy	RRMS, SPMS, PPMS	Fatigue	x	x	B
		Depression			B
Low-fat diet with omega-3 supplementation	RRMS	Relapses, disability, MRI lesions, fatigue, QOL		x	B

CAM, complementary and alternative medicine; HRQOL, health-related QOL; MS, multiple sclerosis; MSU, MS type unspecified; PCE, oral cannabis extract; PPMS, primary progressive MS; QOL, quality of life; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS; THC, tetrahydrocannabinol; A, established as effective or ineffective; B, probably effective or ineffective; C, possibly effective or ineffective; U, insufficient evidence to determine effectiveness or ineffectiveness.

Data from Reference 124.

Vaccine Recommendations

As a general rule, avoidance of live vaccine administration is recommended in any patients with MS receiving DMTs due to the immunosuppression caused by the DMTs and the potential for the live virus vaccines to cause an increase in MS disease activity. Therefore, a yearly flu shot is recommended for all patients with MS, including patients receiving any DMTs, while use of the intranasal influenza vaccine, FluMist, which is a live-attenuated vaccine, is not. It is also unknown whether there are any direct interactions between DMTs and the intranasal influenza vaccine.[122] An exception to this rule applies to patients opting to take fingolimod who are varicella zoster virus antibody negative as they should receive the varicella zoster virus immunization (even though it is a live-attenuated vaccine) at least 2 months prior to beginning treatment, as this should allow time to mount an antibody response prior to immunosuppression. Shingrix® may or may not be effective or safe in patients taking DMTs.

Personalized Pharmacotherapy

The initial presentation of MS differs between individuals and when a patient is newly diagnosed, modifiable risk factors may be considered prior to selecting therapy. Some of these modifiable risk factors include vitamin D deficiency, excess body weight, and smoking. Vitamin D deficiency has been associated with the risk of developing MS, and higher vitamin D levels may reduce MRI brain activity and thus reduce relapse rates.[8] Excess body weight is also associated with a higher risk of developing MS[126] and smoking is associated with the development of MS, disability, MRI abnormalities, and conversion to CDMS (51%-75% in 3 years).[9,127]

Treatments available for MS need to be individualized based on the initial symptomatology, MRI presentation, and the risk associated with the chosen therapy. Essentially, when patients present, they can be given a modestly effective therapy with a low side-effect profile (eg, IFNs and glatiramer acetate) or a more aggressive therapy with a higher risk profile (natalizumab, fingolimod, or dimethyl fumarate). The weighing of the risks and benefits is ultimately dependent on a patient’s presentation or progression of disease, along with comorbid conditions such as depression.

The importance of adherence cannot be understated in patients taking DMTs as nonadherence has been reported to occur in up to 50% of patients. The reason many patients stop taking their DMTs is multifactorial, and includes perceived lack of efficacy, side effects, undesirable route of administration, and depression.

Patients who remain adherent to their DMTs generally remain employed full-time compared with those who are nonadherent. It is crucial that we establish realistic expectations for our patients on DMTs as overall, as untreated MS patients generally relapse about every 6 months, whereas treated patients relapse about every 2 to 5 years. Therefore, adherence is the key to successful treatment of MS.

EVALUATION OF THERAPEUTIC OUTCOMES

For those with acute exacerbations of MS, response to treatment is commonly seen within days. With respect to DMTs, it is important for the clinician to recognize that over the short term (days to weeks), little or no apparent benefit may be noted by either the patient or the clinician. Therefore, evaluation of therapeutic outcomes, such as decreased MS exacerbations and hospitalizations or perhaps slowed disease progression and disability (as measured using scales such as EDSS), must be conducted over a period of months to years. In an effort to maximize medication adherence and manage disease outcome expectations, patients should be provided with realistic goals and expectations of these treatment options and encouraged to participate in the evaluation of therapeutic response. Initially, it may be important to reevaluate patients at relatively short time intervals to monitor for adverse effects.

Safety monitoring of patients on IFN includes regular laboratory monitoring, patient observation, and questioning for adverse effects or changing disability, and regular neurologic examinations. Laboratory monitoring for individuals on IFN therapy should include a CBC, platelet count, and LFTs that should be completed at baseline, every 3 months for 1 year, and every 6 months thereafter, whereas glatiramer acetate requires no specific laboratory monitoring. Teriflunomide requires a transaminase, bilirubin, CBC, tuberculin skin test, and blood pressure prior to initiating therapy and alanine aminotransferase monthly for 6 months after starting therapy. Teriflunomide is also associated with renal failure and increased serum potassium; therefore, patients should be monitored as needed. Dimethyl fumarate requires a CBC prior to starting therapy, within 6 months of treatment initiation and annually, as well as routine LFTs. Natalizumab, fingolimod, and alemtuzumab have REMS programs to monitor safety and healthcare providers should follow the requirements of these programs.

In addition to counseling patients regarding the adverse effects associated with these drugs, clinicians should actively encourage patients to adhere to their

prescribed regimens.

CONCLUSION

The diagnosis and treatment of MS can be difficult, and until recently medication treatment was very specific depending on the MS center or treating neurologist. The American Academy of Neurology has recently released the most updated guidelines for disease-modifying therapies for adults with multiple sclerosis.[128] The guidelines focus on shared decision making and patient-centered care for MS, where the patient is given general information about dosing schedule, route of administration, and side effects for their specific presentation of disease. The team (including the patient) makes the decision on how to best help the patient manage the disease. More aggressive treatment is called for specifically with alemtuzumab, fingolimod, or natalizumab for people with highly active MS, and ocrelizumab for patients with PPMS who are likely to benefit from therapy unless the risk outweighs the benefits.[128] The most severe adverse effect is PML and the guidelines specifically mention natalizumab, fingolimod, rituximab, ocrelizumab, and dimethyl fumarate as drugs that patients should be counseled on this as an adverse effect. With patient centered MS care, disease outcomes (due to increased adherence) and treatment satisfaction should improve. By treating the disease state with DMTs there is a potential decrease to secondary and tertiary symptoms. It is only through collaboration as a care team that we will be able to combat this debilitating disease.

ACKNOWLEDGMENTS

The authors acknowledge Felecia Hart, Golda Wang, Sarah N. Fischer, and Joan Kaufman, an illustrator, for their contributions to this chapter.

Postclass Engaged Learning Activity

When treating MS there are many different approaches to the intensity of treatment. What are the risks and benefits of starting a patient on self-injected interferon therapy versus infused immunotherapy? Compare and contrast the decrease in MS symptoms and relapses with these therapies in respect to the side effects that are seen with the same therapies, and what side effects are

more common as years on treatment accumulate?

ABBREVIATIONS

AAN	American Academy of Neurology
ACTH	adrenocorticotropic hormone
ADCC	antibody-dependent cell-mediated cytolysis
4-AP	4-aminopyridine
BCRP	breast cancer–resistant protein
CAM	complementary and alternative medicine
CBC	complete blood count
CD	cluster of differentiation
CDC	complement-dependent cytolysis
CDMS	clinically definite multiple sclerosis
CIS	clinically isolated syndrome
CNS	central nervous system
CSF	cerebrospinal fluid

DMT	disease-modifying therapy
EBNA	Epstein–Barr nuclear antigen
EBV	Epstein–Barr virus
ECG	electrocardiogram
EDSS	expanded disability status scale
GI	gastrointestinal
GPI	glycosylphosphatidylinositol
GWAS	genome-wide association study
HHV	human herpesvirus
HLA	human leukocyte antigen
IAR	infusion-associated reaction
IFN	interferon
IgG	immunoglobulin G
IL	interleukin
INR	international normalized ratio
IRIS	immune reconstitution inflammatory syndrome
ITP	immune thrombocytopenia
IV	intravenous
IVIG	intravenous immunoglobulin
JCV	John Cunningham virus
LFT	liver function test
MBP	myelin basic protein
MHC	major histocompatibility complex
MIMS	mitoxantrone in multiple sclerosis
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	multiple sclerosis functional composite
PEG	polyethylene glycol
PLEX	plasma exchange
PML	progressive multifocal leukoencephalopathy
PPMS	primary-progressive multiple sclerosis
PRMS	progressive-relapsing multiple sclerosis
REMS	Risk Evaluation and Mitigation Strategy
RIS	radiologically isolated syndrome
RRMS	relapsing-remitting multiple sclerosis
SPMS	secondary-progressive multiple sclerosis
TGF	transforming growth factor
Th	T-helper cells
THC	tetrahydrocannabinol
Treg	T-regulatory cells
UTI	urinary tract infection
VCA	vascular cell adhesion
VCAM	vascular cell adhesion molecule
VEP	visual-evoked potential
VLA-1	very-late antigen 1

REFERENCES

1. Ascherio A, Munger K. Epidemiology of multiple sclerosis: From risk factors to prevention. *Semin Neurol*. 2008;28:17–28.
2. Goodin DS. The causal cascade to multiple sclerosis: A model for MS pathogenesis. *PLoS One*. 2009;4:e4565.
3. Oksenberg JR, Baranzini SE, Sawcer S, Hauser SL. The genetics of multiple sclerosis: SNPs to pathways to pathogenesis. *Nat Rev Genet*. 2008;9:516–526.
4. Ebers GC. Environmental factors and multiple sclerosis. *Lancet Neurol*. 2008;7:268–277.
5. Healy BC, Ali EN, Guttmann CRG, et al. Smoking and disease progression in multiple sclerosis. *Arch Neurol*. 2009;66:858–864.
6. National MS Society. *Multiple Sclerosis: Just the Facts*. 2018. Available at https://www.nationalmssociety.org/NationalMSSociety/media/MSNational Just-the-Facts.pdf. Accessed April 25, 2018.
7. Kotzamani D, Panou T, Mastorodemos V, et al. Rising incidence of multiple sclerosis in females associated with urbanization. *Neurology*. 2012;78(22):1728–1735.
8. Munger KL, Levin LI, Hollis BW. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA*. 2006;296:2832–2838.
9. Hafler DA, Compston A, Sawcer S, et al. Risk alleles for multiple sclerosis identified by a genomewide study. *N Engl J Med*. 2007;357:851–862.D'Netto MJ, et al. Test. 2009;12:1–2.
10. D'Netto MJ, Ward H, Morrison KM, et al. Risk alleles for multiple sclerosis in multiplex families. *Neurology*. 2009;72:1984–1988.
11. Maier LM, Lowe CE, Cooper J, et al. IL2RA genetic heterogeneity in multiple sclerosis and type 1 diabetes susceptibility and soluble interleukin-2 receptor production. *PLoS Genet*. 2009;5:e1000322.
12. Cree BA, Khan O, Bourdette D, et al. Clinical characteristics of African Americans versus Caucasian Americans with multiple sclerosis. *Neurology*. 2004;63:2039–2045.
13. Cree BA, Al-Sabbagh A, Bennett R, et al. Response to interferon beta-1a treatment in African American multiple sclerosis patients. *Arch Neurol*. 2005;62:1681–1683.

14. Reich D, Patterson N, DeJager PL, et al. A whole-genome admixture scan finds a candidate locus for multiple sclerosis susceptibility. *Nat Genet*. 2005;37:1113–1118.
15. Zivadinov R, Weinstock-Guttman B, Hashmi K, et al. Smoking is associated with increased lesion volumes and brain atrophy in multiple sclerosis. *Neurology*. 2009;73(7):504–510.
16. Frohman EM, Racke MK, Raine CS. Multiple sclerosis—the plaque and its pathogenesis. *N Engl J Med*. 2006;354:942–955.
17. Owens GP, Bennett JL. Trigger, pathogen, or bystander: The complex nexus linking Epstein–Barr virus and multiple sclerosis. *Mult Scler*. 2012;18(9):1204–1248.
18. Levin LI, Munger KL, Rubertone MV, et al. Temporal relationship between elevation of Epstein–Barr virus antibody titers and initial onset of neurological symptoms in multiple sclerosis. *JAMA*. 2005;293:2496–2500.
19. Sundstrom P, Nystrom M, Ruuth K, et al. Antibodies to specific EBNA-1 domains and HLA DRB1*1501 interact as risk factors for multiple sclerosis. *J Neuroimmunol*. 2009;215(1-2):102–107.
20. Zivadinov R, Zorzon M, Weinstock-Guttman B, et al. Epstein–Barr virus is associated with grey matter atrophy in multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2009;80(6):620–625.
21. Serafini B, Rosicarelli B, Franciotta D, et al. Dysregulated Epstein–Barr virus infection in the multiple sclerosis brain. *J Exp Med*. 2007;204:2899–2912.
22. Willis SN, Stadelmann C, Rodig SJ, et al. Epstein–Barr virus infection is not a characteristic feature of multiple sclerosis brain. *Brain*. 2009;132:3318–3328.
23. Trapp BD, Peterson J, Ransohoff RM, et al. Axonal transection in the lesions of multiple sclerosis. *N Engl J Med*. 1998;338:278–285.
24. Truyen L, van Wuesberghe JHTM, Barkof F, et al. Accumulation of hypointense lesions (“black holes”) on T1 spin echo MRI correlates with disease progression in multiple sclerosis. *Neurology*. 1996;47:1469–1476.
25. Zhou L, Chong MM, Littman DR. Plasticity of CD4+ T-cell lineage differentiation. *Immunity*. 2009;30(5):646–655.
26. Reboldi A, Coisne C, Baumjohann D, et al. C-C chemokine receptor 6-regulated entry of TH-17 cells into the CNS through the choroid plexus is required for the initiation of EAE. *Nat Immunol*. 2009;10(5):514–523. doi: 10.1038/ni.1716.19305396.

27. Smolders J, Thewissen M, Peelan E, et al. Vitamin D status is positively correlated with regulatory T cell function in patients with multiple sclerosis. PLoS One. 2009;4:e6635.
28. Owens GP, Bennett JL, Lassmann H, et al. Antibodies produced by clonally expanded plasma cells in multiple sclerosis cerebrospinal fluid. Ann Neurol. 2009;65:639–649.
29. Pirko I, Lucchinetti CF, Sriram S, Bakshi R. Gray matter involvement in multiple sclerosis. Neurology. 2007;68:634–642.
30. Zivadinov R, Minagar A. Evidence for gray matter pathology in multiple sclerosis: A neuroimaging approach. J Neurol Sci. 2009;282:1–4.
31. Magliozzi R, Howell O, Vora A, et al. Meningeal B-cell follicles in secondary progressive multiple sclerosis associate with early onset of disease and severe cortical pathology. Brain. 2007;130:1089–1104.
32. Kinkel PR, Miravalle A. Current guidelines and standard treatments of RR-MS. 2011. Addressing unmet medical needs in relapsing-remitting multiple sclerosis. Available at http://www.futuremedicine.com. Accessed July 27, 2016. doi: 10.2217/ebo.11.111:6-25.
33. Schapiro RT. Managing symptoms of multiple sclerosis. *Neurol Clin*. 2005;23:177–187.
34. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis. *Neurology*. 2014;83:278–286.
35. Confavreux C, Vukusic S. Natural history of multiple sclerosis: A unifying concept. *Brain*. 2006;129(3):606–616.
36. Lebrun C, Bensa C, Debouverie M, et al. Association between clinical conversion to multiple sclerosis in radiologically isolated syndrome and magnetic resonance imaging, cerebrospinal fluid, and visual evoked potential: Follow-up of 70 patients. *Arch Neurol*. 2009;66:841–846.
37. Zivadinov R, Zorzon M. Is gadolinium enhancement predictive of the development of brain atrophy in multiple sclerosis? A review of the literature. *J Neuroimaging*. 2002;12:302–309.
38. Tremlett H, Paty D, Devonshire V. The natural history of primary progressive MS in British Columbia, Canada. *Neurology*. 2005;65:1919–1923.
39. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med*. 2017;376(3):209–220.

40. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology*. 1983;33:1444–1452.
41. Rudick RA, Cutter G, Reingold S. The multiple sclerosis functional composite: A new clinical outcome measure for multiple sclerosis trials. *Mult Scler*. 2002;8:359–365.
42. Gordon-Lipkin E, Chodkowski B, Reich DS, et al. Retinal nerve fiber layer is associated with brain atrophy in multiple sclerosis. *Neurology*. 2007;69:1603–1609.
43. Lee M, O'Brien P. Pregnancy and multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2008;79:1308–1311.
44. Sadovnick AD, Eisen K, Ebers GC, Paty DW. Cause of death in patients attending multiple sclerosis clinics. *Neurology*. 1991;41:1193–1196.
45. Swanson JW. Multiple sclerosis: Update in diagnosis and review of prognostic factors. *Mayo Clin Proc*. 1989;64:577–586.
46. Fisniku LK, Brex PA, Altmann DR, et al. Disability and T2 MRI lesions: A 20-year follow-up of patients with relapse onset of multiple sclerosis. *Brain*. 2008;131(Pt3):808–817.
47. Confavreux C, Vukusic S. Accumulation of irreversible disability in multiple sclerosis from epidemiology to treatment. *Clin Neurol Neurosurg*. 2006;108(3):327–332.
48. McDonald W, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: Guidelines from the International Panel on Diagnosis of Multiple Sclerosis. *Ann Neurol*. 2001;50:121–127.
49. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol*. 2005;58:840–846.
50. Dalton C, Brex P, Miszkiel K, et al. New T2 lesions enable an earlier diagnosis of multiple sclerosis in clinically isolated syndromes. *Ann Neurol*. 2003;53:673–676.
51. Swanton JK, Rovira A, Tintore M, et al. MRI criteria for multiple sclerosis in patients presenting with clinically isolated syndromes: A multicentre retrospective study. *Lancet Neurol*. 2007;6:677–686.
52. Lo CP, Kao HW, Chen SY, et al. Prediction of conversion from clinically isolated syndrome to clinically definite multiple sclerosis according to baseline MRI findings: A comparison of revised McDonald criteria and Swanton modified criteria. *J Neurol Neurosurg Psychiatry*. 2009;80:1107–1109.

53. Fisher E, Rudick R, Simon J, et al. Eight-year follow-up study of brain atrophy in patients with MS. *Neurology*. 2002;59:1412–1420.
54. Frohman EM, Goodin DS, Calabresi PA, et al. The utility of MRI in suspected MS. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2003;61:1332–1338.
55. Galetta KM, Calabresi PA, Frohman EM, Balcer LJ. Optical coherence tomograph (OCT): Imaging the visual pathway as a model for neurodegeneration. *Neurotherapeutics*. 2011;8(1):117–132.
56. Berger T, Rubner P, Schautzer F, et al. Antimyelin antibodies as a predictor of clinically definite multiple sclerosis after a first demyelinating event. *N Engl J Med*. 2003;349:139–145.
57. Zivadinov R, Rudick RA, De Masi R, et al. Effects of IV methylprednisolone on brain atrophy in relapsing-remitting MS. *Neurology*. 2001;57:1239–1247.
58. Goodin DS, Frohman EM, Garmany GP, et al. Disease-modifying therapies in multiple sclerosis: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the Multiple Sclerosis Council for Clinical Practice Guidelines. *Neurology*. 2002;58:169–178.
59. Carmosino MJ, Brousseau KM, Arciniegas DB, et al. Initial evaluations for multiple sclerosis in a university multiple sclerosis center: Outcomes and role of magnetic resonance imaging in referral. *Arch Neurol*. 2005;62:585–590.
60. Kaufman DI, Trobe JD, Eggenberger ER, Whitaker JN. Practice parameter: The role of corticosteroids in the management of acute monosymptomatic optic neuritis. Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2000;54:2039–2044.
61. Vandebark AA, Huan J, Agotsch M, et al. Interferon-beta-1a increases CD56 (bright) natural killer cells and CD4+CD25+ Foxp3 expression in subjects with multiple sclerosis. *J Neuroimmunol*. 2009;215:125–128.
62. Goodin DS, Cohen BA, O'Connor P, et al. Assessment—the use of natalizumab (Tysabri) for the treatment of multiple sclerosis (an evidence-based review): Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2008;71(10):766–773.

63. Giovannoni G, Barbarash O, Casset-Semanaz F, et al. Safety and immunogenicity of a new formulation of interferon beta-1a (Rebif New Formulation) in a Phase IIIb study in patients with relapsing multiple sclerosis: 96-week results. *Mult Scler*. 2009;15:219–228.
64. Fischer JS, Priore RL, Jacobs LD, et al. Neuropsychological effects of interferon-β-la in relapsing multiple sclerosis. *Ann Neurol*. 2000;48:885–892.
65. Simon JH, Jacobs L, Campion M, et al. A longitudinal study of brain atrophy in relapsing MS. *Neurology*. 1999;58:139–145.
66. Calabresi PA, Kieseier BC, Arnold DL, et al. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): A randomized, phase 3 double-blind study. *Lancet Neurol*. 2014;13:657–665.
67. Frohman E, Phillips T, Kokel K, et al. Disease-modifying therapy in multiple sclerosis: Strategies for optimizing management. *Neurology*. 2002;8:227–236.
68. Racke MK, Lovett-Racke AE, Karandikar NJ. The mechanism of action of glatiramer acetate treatment in multiple sclerosis. *Neurology*. 2010;74(suppl 1):S25–S30.
69. Azoulay D, Vachapova V, Shihman B, et al. Lower brain-derived neurotrophic factor in serum of relapsing remitting MS. Reversal by glatiramer acetate. *J Neuroimmunol*. 2005;167:215–218.
70. Fillippi M, Rovaris M, Rocca MA, et al. Glatiramer acetate reduces the proportion of new MS lesions evolving into “black holes”. *Neurology*. 2001;57:731–733.
71. Ford CC, Johnson KP, Lisak RP, et al. A prospective open-label study of glatiramer acetate: Over a decade of continuous use in multiple sclerosis patients. *Mult Scler*. 2006;12:309–320.
72. Khan O, Rieckmann P, Boyko A, et al. Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis. *Ann Neurol*. 2013;73:705–713.
73. Wolinsky JS, Borresen TE, Dietrich DW, et al. GLACIER: An open-label, randomized, multicenter study to assess the safety and tolerability of glatiramer acetate 40 mg three times weekly verus 20 mg daily in patients with relapsing-remitting multiple sclerosis. *Mult Scler Relat Disord*. 2015;4:370–376.
74. Miller DH, Khan OA, Sheremata WA, et al. A controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med*. 2003;348:15–

23.
75. Polman CH, O'Conor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis (AFFIRM). *N Engl J Med*. 2006;354:899–910.
76. Rudick RA, Stuart WH, Calabresi PA, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis (SENTINEL). *N Engl J Med*. 2006;354:911–923.
77. Kleinschmidt-DeMasters BK, Tyler KL. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple-sclerosis. *N Engl J Med*. 2005;353:369–374.
78. Langer-Gould A, Atlas SW, Green AJ, et al. Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. *N Engl J Med*. 2005;353:375–381.
79. Van Assche G, Van Ranst M, Sclot R, et al. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. *N Engl J Med*. 2005;353:362–368.
80. Berger JR. Classifying PML risk with disease modifying therapies. *Mult Scler Relat Disord*. 2017;12:59–63.
81. Gorelik L, Lerner M, Bixler S, et al. Anti-JC virus antibodies: Implications for PML risk stratification. *Ann Neurol*. 2010;68:295–303.
82. Bozic C, Richman S, Plavina T, et al. Anti-John Cunningham virus antibody prevalence in multiple sclerosis patients: Baseline results of STRATIFY-1. *Ann Neurol*. 2011;70(5):742–750.
83. Sadiq SA, Puccio LM, Brydon EW. JCV detection in multiple sclerosis patients treated with natalizumab. *J Neurol*. 2010;257:954–958.
84. Khatri BO, Man S, Giovannoni G, et al. Effect of plasma exchange in accelerating natalizumab clearance and restoring leukocyte function. *Neurology*. 2009;72:402–409.
85. Lindå H, von Heijne A, Major EO, et al. Progressive multifocal leukoencephalopathy after natalizumab monotherapy. *N Engl J Med*. 2009;361:1081–1087.
86. U.S. Food and Drug Administration. FDA Drug Safety Communication: Revised recommendations for cardiovascular monitoring and use of multiple sclerosis drug Gilenya fingolimod. FDA 2013. Available at http://www.fda.gov/Drugs/DrugSafety/ucm303192.htm. Accessed December 17, 2015.

87. O'Connor P, Wolinsky JS, Confavreux C, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med*. 2011;365(14):1293–1303.
88. O'Connor PW, Li D, Freedman MS, et al. A Phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses. *Neurology*. 2006;66(6):894–900.
89. Kita M, Fox RJ, Phillips JT, et al. Effects of BG-12 (dimethyl fumarate) on health-related quality of life in patients with relapsing-remitting multiple sclerosis: Findings from the CONFIRM study. *Mult Scler*. 2014;20(2):253–257.
90. Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med*. 2012;367(12):1098–1107.
91. Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon β 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: A randomised controlled phase 3 trial. *Lancet*. 2012;380:1819–1828. doi: 10.1016/S0140-6736(12)61769-3.
92. Coles AJ, Twyman CL, Arnold DL, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: A randomised controlled phase 3 trial. *Lancet*. 2012;380:1829–1839. doi: 10.1016/S0140-6736(12)61768-1.
93. Havrdova E, Horakova D, Kovarova I. Alemtuzumab in the treatment of multiple sclerosis: Key clinical trial results and considerations for use. *Ther Adv Neurol Disord*. 2015;8:31–45. doi: 10.1177/1756285614563522.
94. Hartung HP, Gonsette R, Konig N, et al. Mitoxantrone in progressive multiple sclerosis, a placebo-controlled, double-blind, randomized, multicentre trial. *Lancet*. 2002;360:2018–2025.
95. Krapf H, Morrissey SP, Zenker O, et al. Effect of mitoxantrone on MRI in progressive MS. Results of the MIMS trial. *Neurology*. 2005;65:690–695.
96. Martinelli V, Bellantonio P, Bergamaschi R, et al. Incidence of acute leukaemia in multiple sclerosis patients treated with mitoxandrone: A multicentre retrospective Italian study. *Neurology*. 2009;73:330–333.
97. Hawker K, O'Connor P, Freedman MS, et al. Rituximab in patients with primary progressive multiple sclerosis: Results of a randomized double-blind placebo-controlled multicenter trial. *Ann Neurol*. 2009;66:460–471.
98. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med*. 2017;376(3):221–234.

99. Costello K, Halper J, Kalb R, et al. The use of disease-modifying therapies in multiple sclerosis. A consensus Paper by the Multiple Sclerosis Coalition. Available at http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed December 17, 2015.
100. Freedman MS, Kappos L, Polman CH, et al. Betaseron in newly emerging multiple sclerosis for initial treatment (BENEFIT): Clinical outcomes. *Neurology*. 2006;(suppl 2):A61.
101. Vartanian T. An examination of the results of the EVIDENCE, INCOMIN, and phase III studies of interferon beta products in the treatment of multiple sclerosis. *Clin Ther*. 2003;1:105–118.
102. Durelli L, Verdun E, Bergui M, et al. Every-other-day interferon-β-1b versus once-weekly interferon-β-1a for multiple sclerosis: Results of a 2-year prospective randomized multicentre study (INCOMIN). *Lancet*. 2002;359:1453–1460.
103. Panitch H, Goodin D, Francis G, et al. Randomized, comparative study of interferon-β-1a treatment regimens in MS. The EVIDENCE Trial. *Neurology*. 2002;59:1496–1506.
104. Koch-Henriksen N, Sorensen PS, Christensen T, et al. A randomized study of two interferon-beta treatments in relapsing-remitting multiple sclerosis. *Neurology*. 2006;66:1056–1060.
105. Clanet M, Radue E, Kappos L, et al. A randomized, double-blind, dose-comparison study of weekly interferon-β-1a in relapsing MS. *Neurology*. 2002;59:1507–1517.
106. O'Connor P, Filippi M, Arnason B, et al. 250 mcg or 500 mcg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: A prospective, randomised, multicentre study. *Lancet Neurol*. 2009;8:889–897.
107. Mikol DD, Barkhof F, Chang P, et al. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the Rebif vs. Glatiramer Acetate in Relapsing MS Disease [REGARD] study): A multicentre, randomised, parallel, open-label trial. *Lancet Neurol*. 2008;7:903–914.
108. Namaka M, Pollitt-Smith M, Gupta A, et al. The clinical importance of neutralizing antibodies in relapsing-remitting multiple sclerosis. *Curr Med Res Opin*. 2006;22:223–239.

109. Bertolotto A. Neutralizing antibodies to interferon beta: Implications for the management of multiple sclerosis. *Curr Opin Neurol*. 2004;17:241–246.
110. Francis GS, Rice GP, Alsop JC, et al. Interferon beta 1a in MS: Results following development of neutralizing antibodies in PRISMS. *Neurology*. 2005;65:48–55.
111. Kappos L, Clanet M, Sandberg-Wollheim M, et al. Neutralizing antibodies and efficacy of interferon beta-1a: A 4-year controlled study. *Neurology*. 2005;65:40–47.
112. Giovannoni G, Goodman A. Neutralizing anti-IFN-beta antibodies: How much more evidence do we need to use them in practice?*Neurology*. 2005;65:6–8.
113. Goodin DS, Frohman EM, Hurwitz B, et al. Neutralizing antibodies to interferon beta: Assessment of their clinical and radiographic impact: An evidence report. *Neurology*. 2007;67:977–984.
114. Kappos L, Polman C, Pozzilli C, et al. Final analysis of the European multicenter trial on IFNβ-1b in secondary-progressive MS. *Neurology*. 2001;57:1969–1975.
115. Freedman MS, Patry DG, Grand'Maison F, et al. Treatment optimization in multiple sclerosis. *Can J Neurol Sci*. 2004;31:157–168.
116. Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Engl J Med*. 2008;358:676–688.
117. Sorensen PS, Mellgren SI, Svenningsson A, et al. NORDIC trial of oral methylprednisolone as add-on therapy to interferon beta-1a for treatment of relapsing-remitting multiple sclerosis (NORMIMS study): A randomised, placebo-controlled trial. *Lancet Neurol*. 2009;8:519–529.
118. Birnbaum G, Cree B, Altafullah I, et al. Combining beta interferon and atorvastatin may increase disease activity in multiple sclerosis. *Neurology*. 2008;71:1390–1395.
119. Mitchell G. Update on multiple sclerosis therapy. *Med Clin North Am*. 1993;77:231–249.
120. Goodman AD, Brown TR, Krupp LB, et al. Sustained-release oral fampridine in multiple sclerosis: A randomised, double-blind, controlled trial. *Lancet*. 2009;373:732–738.
121. Stenager EN, Stenager E, Koch Henriksen N, et al. Suicide and multiple sclerosis: An epidemiological investigation. *J Neurol Neurosurg*

Psychiatry. 1992;55:542–545.

122. National MS Society. News Detail, 2009. Available at http://nationalmssociety.org/news/news-detail/index.aspx?nid=2115. Accessed December 17, 2015.
123. Egeberg M, Oh CY, Bainbridge JL. Clinical overview of dalfampridine: The agent with a novel mechanism of action to help with gait disturbances. *Clinical Therapeutics*. 2012;34:2185–2194.
124. Yadav V, Bever C Jr, Bowen J, et al. Summary of evidence-based guideline—complementary and alternative medicine in multiple sclerosis: Report of the guideline development subcommittee of the American Academy of Neurology. *Neurology*. 2014;82:1083–1092.
125. Bowling AC.*Optimal Health with Multiple Sclerosis: A Guide to Integrating Lifestyle, Alternative, and Conventional Medicine*. New York, NY: Demos; 2014.
126. Munger KL, Chitnis T, Ascherio A. Body size and risk of MS in two cohorts of US women. *Neurology*. 2009;73(19):1543–1550.
127. Hedstrom AK, Baarnhielm M, Olsson T, Alfredsson L. Tobacco smoking, not Swedish snuff use, increases the risk of multiple sclerosis. *Neurology*. 2009;73(9):696–701.
128. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018;90(17):777–788.

73

Epilepsy

Viet-Huong V. Nguyen, Sunita Dergalust, and Edward Chang

KEY CONCEPTS

1. The goal of pharmacotherapy is seizure freedom with minimal side effects, and two-thirds to 80% of patients can achieve this.
2. Accurate classification and diagnosis of seizure type/epilepsy syndrome, including where seizures begin, is critical to selection of appropriate pharmacotherapy.
3. Besides seizure type, antiseizure drug (ASD) selection depends on patient characteristics such as age, gender, ethnicity, susceptibility to side effects, comorbid conditions, ability to adhere with the prescribed regimen, presence or absence of insurance coverage, and need for therapeutic levels to be reached quickly.
4. Pharmacotherapy of epilepsy is highly individualized and requires titration of the dose to optimize ASD therapy (maximal seizure control with minimal or no side effects).
5. If the therapeutic goal is not achieved with monotherapy, a second ASD, preferably with a different mechanism of action, can be added, or the patient's ASD can be switched to an alternative single agent.
6. Patients who do not respond to drug therapy should be referred to a comprehensive epilepsy center to determine if nonpharmacologic treatments such as surgery are potential options.
7. In general, first-generation ASDs are very efficacious but have complex pharmacokinetics, multiple drug–drug interactions, and an increased incidence of adverse effects that in general make them more complicated to manage than either the second- or third-generation ASDs.
8. Second-generation ASDs have unique mechanisms of action and are as efficacious as first- and third-generation ASDs with better tolerability, and

are therefore generally considered first in epilepsy pharmacotherapy.

9. Third-generation ASDs should be reserved for failure of other agents due to cost and limited long-term experience.
10. Despite numerous drug trials, 20% to 35% of patients will have unsatisfactory control with ASDs and will be considered to be drug-resistant.

Preclass Engaged Learning Activity

Create a table of antiseizure drug (ASD) treatment options that groups all available ASDs by mechanism of action and ASD generation.

INTRODUCTION

Epilepsy is a common neurologic condition in which a person is prone to recurrent epileptic seizures. There are many types of epilepsies characterized by different seizure types, ranging in severity and etiologies. While the specific pathophysiologic mechanisms behind different epilepsies are complex, the general pathophysiologic process underlying all epilepsies is disturbed regulation of electrical activity in the brain resulting in synchronized and excessive neuronal discharge.

Beyond seizures, people with epilepsy face many challenges, as they may display neurodevelopmental delay, cognitive impairment, and often suffer from comorbid depression and anxiety. Furthermore, patients with epilepsy may face educational and vocational challenges, have difficulties with independent living, and be victims of stigma and common public misunderstanding. Indeed, the International League Against Epilepsy (ILAE) defines epilepsy not only as "a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures" but also by "the neurobiologic, cognitive, psychological, and social consequences of this condition."[1] Clinicians treating epilepsy must try to address these common psychosocial issues and comorbidities. Therefore, drug therapy should be selected to not only reduce the frequency of seizures as much as possible, but also with the goal of minimizing side effects, addressing coexisting health and social conditions, and overall enhancing quality-of-life (QOL) for patients.

EPIDEMIOLOGY

Epilepsy is the fourth most common neurologic disorder globally and in the United States; only following stroke, migraine, and Alzheimer's disease. In the United States, approximately 3.4 million people suffer from epilepsy with a prevalence of 1.2%. While epilepsy is a chronic disease that can present at all ages, the highest number of new epilepsy cases (incidence) will occur in childhood and in the geriatric population. Among children, epilepsy has the highest incidence in children under 5 years of age with most new cases occurring under 2 years of age. In older populations, the high frequency of epilepsy is now garnering attention as 1.5% of people older than 65 are affected by epilepsy in the United States.[2,3]

The majority of patients with epilepsy has a good prognosis and will be able to attain seizure freedom. However overall, the mortality rate of patients with epilepsy is 2 to 3 times that of the general population and life expectancy in some of these patients is reduced.[4] This increase in mortality has been attributed to a wide variety of reasons including sudden unexplained death in epilepsy (SUDEP).[5] While the exact mechanisms underlying SUDEP are unclear, recent research suggests there may be a cardio-respiratory mechanism involved.[5] Although it is rare in patients with well-controlled epilepsy, SUDEP accounts for up to 15% of all epilepsy-related deaths, with a lifetime risk of 4.6% to 8% in this population.[5]

Although all individuals with epilepsy experience seizures, not all individuals who experience seizures will be diagnosed with epilepsy. Some seizures are provoked and occur as a result of systemic, toxic, or metabolic insults such as drug overdose; alcohol, barbiturate, or benzodiazepine withdrawal; or acute neurologic (eg, brain hemorrhage) or systemic illnesses (eg, hypocalcemia, hypoglycemia, uremia, and eclampsia). Furthermore, some patients will have seizures only associated with fever (eg, febrile seizures). In general, in all of these situations, the occurrence of seizures does not constitute epilepsy, but rather are a symptom of the provoking insult. Therefore, once the provoking insult is removed or treated, there is not "an enduring predisposition to generate epileptic seizures." Each year, 120 per 100,000 people in the United States will be evaluated for a newly recognized seizure whether it be provoked or unprovoked, but only 40 to 70 cases per 100,000 will be diagnosed with epilepsy. Overall at least 10% of the general population will have at least one seizure from *any* cause in their lifetime[2,3]; therefore, showing that it is possible to have a seizure and to not have epilepsy.

ETIOLOGY

Thousands of medical conditions can cause epilepsy, from genetic mutations to acquired injury (eg, stroke or traumatic brain injury). The most common causes vary depending on population. For instance, childhood-onset epilepsy is predominantly caused by genetic and/or developmental structural abnormalities, while epilepsy with an onset at older age is most often caused by acquired structural injury (eg, stroke or traumatic brain injury). Therefore, epilepsy etiologies can be generally classified into six categories reviewed here: (1) genetic; (2) structural; (3) infectious; (4) metabolic; (5) immune; and (6) unknown.[6] It is important to note that these categories are not mutually exclusive as many epilepsies have etiologies that can belong to two or more categories.

Genetic Etiology

Epilepsies with genetic etiology usually present in infancy or childhood with examples being (1) Dravet syndrome associated with mutations in sodium channel, voltage-gated, type I alpha subunit (SCN1A), (2) Childhood Absence Epilepsy (CAE) associated with many different mutations in T-type Ca^{2+} channels and GABA-receptor subunits, and (3) Juvenile Myoclonic Epilepsy (JME) associated with many different mutations including mutations in EF-hand containing protein-1 (EFHC1) and intestinal cell kinase (ICK).[7–11] Prior to 2010, genetic epilepsies have historically been labeled as primary generalized epilepsy or idiopathic generalized epilepsy (IGE), as there were no clear structural brain abnormalities that could be found to be responsible for the epilepsy.[6] However, it is now recognized that most of these disorders have abnormalities at the molecular level and are now also called genetic generalized epilepsies.[6] Genetic etiologies may be passed on from generation to generation or can arise from sporadic mutations, but cannot be acquired after birth.

Structural Etiology

Structural etiologies refer to abnormalities visible on structural neuroimaging and can be acquired or be of genetic origin.[6] Common epilepsies caused by structural abnormalities include cortical dysplasia, mesial temporal lobe epilepsy, and posttraumatic epilepsy. In general, cortical dysplasia is a common cause of childhood onset drug-resistant epilepsy and is a result of disruptions in neuronal migration, proliferation, and differentiation during brain development,

leading to disorganization of the normal structure of the cerebral cortex in certain brain areas. In general, mesial temporal lobe epilepsy is a common type of adult-onset epilepsy that is responsible for many of the drug-resistant epilepsies seen in tertiary care epilepsy clinics. In this structural form of epilepsy, sclerosis occurs in the hippocampus which is the main structure of the mesial temporal lobe, and is characterized by glial scarring, reduced hippocampal volume as seen on magnetic resonance imaging (MRI), and decreased cellular density as seen on biopsy.[12] In contrast, traumatic brain injury epilepsy results from blunt force injury or stroke that causes structural lesions in the brain that may also cause epilepsy.[6]

Infectious Etiology

The most common epilepsy etiology worldwide is infectious.[6] It is important to note that this acquired form of epilepsy occurs when a patient develops epilepsy as the sequelae of an infection, and not when a patient experiences seizures in the setting of acute infection such as meningitis or encephalitis. In developing countries, the most common acquired infectious epilepsy is from neurocysticercosis, a parasitic infection of the brain that results from ingestion of eggs from a pork tapeworm, causing subsequent structural injury that promotes the development of epilepsy.[6]

Metabolic, Immune, and Unknown Etiology

In terms of epilepsy etiology, both the metabolic and immune etiologies are less common, although they are increasingly being recognized and understood.[6] Overall the metabolic etiologies refer to differing metabolic disorders that are associated with epilepsy such as Lafora disease, which is associated with abnormal glycogen metabolism and subsequent development of insoluble glycogen inclusion bodies resulting in epilepsy.[13] Similarly, the immune epilepsies are also being recognized, such as anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis which causes autoimmune-mediated central nervous system (CNS) inflammation and resulting epilepsy.[6] While both of these etiologies carry specific treatment implications, what the field understands about their treatment is currently evolving. It is also important to know that, overall, patients can also present with unprovoked seizures that do not have an identifiable cause, and thus by definition have epilepsy of unknown cause.[6] While standard epilepsy workup procedures need to be followed, it is possible

that these epilepsies may be due to an as-yet-unidentified gene or may be the consequence of an as-yet-unrecognized-structural or -metabolic disorder.

Risk Factors and Seizure Triggers

While certain risk factors may suggest a predisposition to epilepsy, they are not necessarily the causative agent, as known epilepsy risk factors include premature birth with small gestational weight, perinatal injury (eg, anoxia), history of alcohol withdrawal seizures, history of febrile seizures, and family history of seizures.[14] Therefore, while the presence of such risk factors aid in establishing the diagnosis of epilepsy and may help in identifying the underlying epilepsy etiology, they may not explain the mechanistic cause of seizures.

Furthermore, many factors have been shown to trigger seizures in susceptible individuals, with two of the best known seizure triggers being hyperventilation and photostimulation (eg, flashing lights or rapidly changing or alternating images) in certain genetic epilepsies including Juvenile Myoclonic Epilepsy and Childhood Absence Epilepsy. Additional triggers include physical and emotional stress, sleep deprivation, sensory stimuli, and hormonal changes occurring around the time of menses, puberty, or pregnancy, as all of these have been associated with the onset of or an increased frequency of seizures. Lastly, medications such as the use of theophylline, alcohol, high-dose phenothiazines, antidepressants (especially bupropion), and street drug use have all been associated with lowering seizure threshold and provoking seizures in patients with epilepsy.[15]

PATHOPHYSIOLOGY

The underlying general pathophysiologic process at the heart of all epilepsies is neuronal hyperexcitability and hypersynchronization. Initially during a seizure, a small number of hyperexcitable neurons fire abnormally in synchrony resulting in breakdown of normal membrane conductances and inhibitory synaptic currents which allows the excess excitability to spread, either locally to produce a localized focal seizure, or the seizure is propagated by physiologic pathways and networks to involve more remote areas, or more widely to produce a generalized seizure.[16]

In general, neuronal hyperexcitability occurs because there is an enhanced predisposition of a neuron to depolarize and discharge when stimulated. While this may occur as the result of several different mechanisms, it is generally

thought that alterations in the number, type, and biophysical properties of voltage- or ligand-gated K^+, Na^+, Ca^{2+}, and Cl^- ion channels in neuronal membranes play a significant role.[17] In fact, many of the currently available antiseizure drugs (ASDs) have mechanisms of actions that act on these specific ion channels, highlighting the importance of these channels in promoting hyperexcitability. For instance, carbamazepine and phenytoin reduce neuronal excitability by binding sodium channels in their inactive state and slowing channel recovery from inactivation, thereby preventing hyperexcitable neurons from rapidly and repetitively firing; this also blocks firing in a use-dependent fashion.[18,19] Benzodiazepines in contrast bind to the gamma subunit of the $GABA_A$ receptor leading to an increase in chloride ion conductance and inhibition of action potentials.[20] Mutations within these ion channels have been found to be associated with multiple different epilepsies.[9] While the exact nature of these alterations have not been fully elucidated, these genetic alterations may result in differences between the various genetic epilepsies.

Other mechanisms of epileptogenesis, which may play roles in hyperexcitability, are related to alterations in vesicle trafficking and neurotransmitter release. For instance, synaptic vesicle protein 2A (SV2A), a protein responsible for the fusion of vesicles to the membrane, has been found to be upregulated in certain models of epilepsy, and is the target of the second- and third-generation ASDs, levetiracetam and brivaracetam, respectively.[21] Furthermore, alterations in neurotransmitter uptake and metabolism may also play a role in the pathogenesis of epilepsy.[22] An example of this comes from vigabatrin, which is an irreversible inhibitor of γ-aminobutyric acid transaminase (GABA-T).[23] As this enzyme is responsible for the metabolism of the inhibitory neurotransmitter GABA, this medication is felt to exert its efficacy by mechanically increasing GABA and promoting inhibition through GABA-T inhibition.[23]

Additionally, there are many other possible hyperexcitability promoting mechanisms that may be important in the pathophysiology of epilepsy, including possible biochemical modifications of receptors, modulation of second messaging systems and gene expression, and changes in extracellular ion concentrations.[22] It is important to note that hyperexcitability that results simply in increased firing of random individual neurons by itself does not result in epileptic seizures. Epileptic seizures result only when there is also synchronization of excessive neuronal firing.[24] The intrinsic organization of local circuits of certain cerebral structures including the hippocampus, the

neocortex, and the thalamus contributes to synchronization and promotes generation of epileptiform activity and that is why many epileptic networks originate in these brain regions specifically.[24,25] Modifications in the ratio and function of inhibitory circuits in these structures play an important role in promoting epileptogenesis, as a large number of these neurons are interconnected and can become simultaneously inhibited, and then synchronously excited. Although under normal circumstances, these neurons are asynchronous, it is believed that under abnormal circumstances, they become synchronous and act as pacemakers promoting epileptiform activity. Furthermore, sprouting and reorganization of neuronal projections in abnormal tissue or after neuronal injury (eg, head trauma or stroke) may also lead to increased connectivity between neurons and a chronic susceptibility to seizures.[24] Therefore, both excitation and inhibitory connections lie at the heart of the pathophysiologic mechanisms behind epileptogenicity.

CLINICAL PRESENTATION

An epileptic seizure is defined as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.[3] Epileptic seizures can manifest physically in a variety of ways and can range from intense involuntary repetitive muscular contractions (eg, convulsions) to subtle alterations in sensation or consciousness. The new basic seizure classification is based on three key features: (1) where in the brain the seizure originates; (2) the patient's level of awareness during a seizure; and (3) other features of the seizures.[26]

1 Seizures can be classified into an initial three categories depending on how they begin in the brain (eg, onset): (1) focal seizures (previously called partial seizures) that start in a network of cells on only one side of the brain; (2) generalized seizures (previously called primary generalized) that start in a bilaterally distributed network (eg, a network encompassing both sides of the brain); and (3) unknown onset which can later be recategorized when it becomes clear how seizures begin in a particular patient's brain.[26] Understanding seizure onset is important, as it has significant treatment and prognostic implications affecting choice of seizure medication and eligibility for epilepsy surgery. Examples of this include patients with generalized-onset seizures who may have a seizure exacerbation when treated with certain ASDs (eg, treating a patient who has Childhood Absence Epilepsy with carbamazepine)[27] or patients with focal-onset seizures, who are drug resistant, who may be good candidates for

surgical resection, while those with generalized-onset seizures are not.

Focal Seizures

In general, focal seizures may be characterized by whether the patient retains awareness of themselves and their environment including external stimuli (eg, being asked questions) during the seizure, even if immobile and unable to talk or respond. When awareness is retained the seizure is termed a “focal aware seizure” corresponding to what has historically been termed “simple partial seizure.” A focal impaired awareness seizure corresponds to the prior term “complex partial seizure” and is an appropriate classification if the person has impaired awareness at any time during the seizure (eg, they are aware in the beginning but lose awareness at the end, or if they have a vague idea of what is occurring and know that someone is speaking to them but they respond inappropriately).[26]

Additionally, focal seizures can be further subgrouped by earliest most prominent motor sign (eg, automatisms, clonic, myoclonic) or nonmotor sign (eg, autonomic or sensory symptoms) at seizure onset. If motor signs are present, then some type of movement will occur during the seizure such as twitching and jerking (eg, myoclonus), stiffening (tonic contraction), or automatic movements (automatisms) such as smacking lips, rubbing hands, picking at clothes. Nonmotor signs include changes in sensation, emotions, thinking, or experience. The symptoms felt by the individual at the very beginning of a seizure is sometimes called an aura, although this term is now discouraged. Motor or nonmotor symptoms that may appear at onset are listed in **Fig. 73-1**.[26]

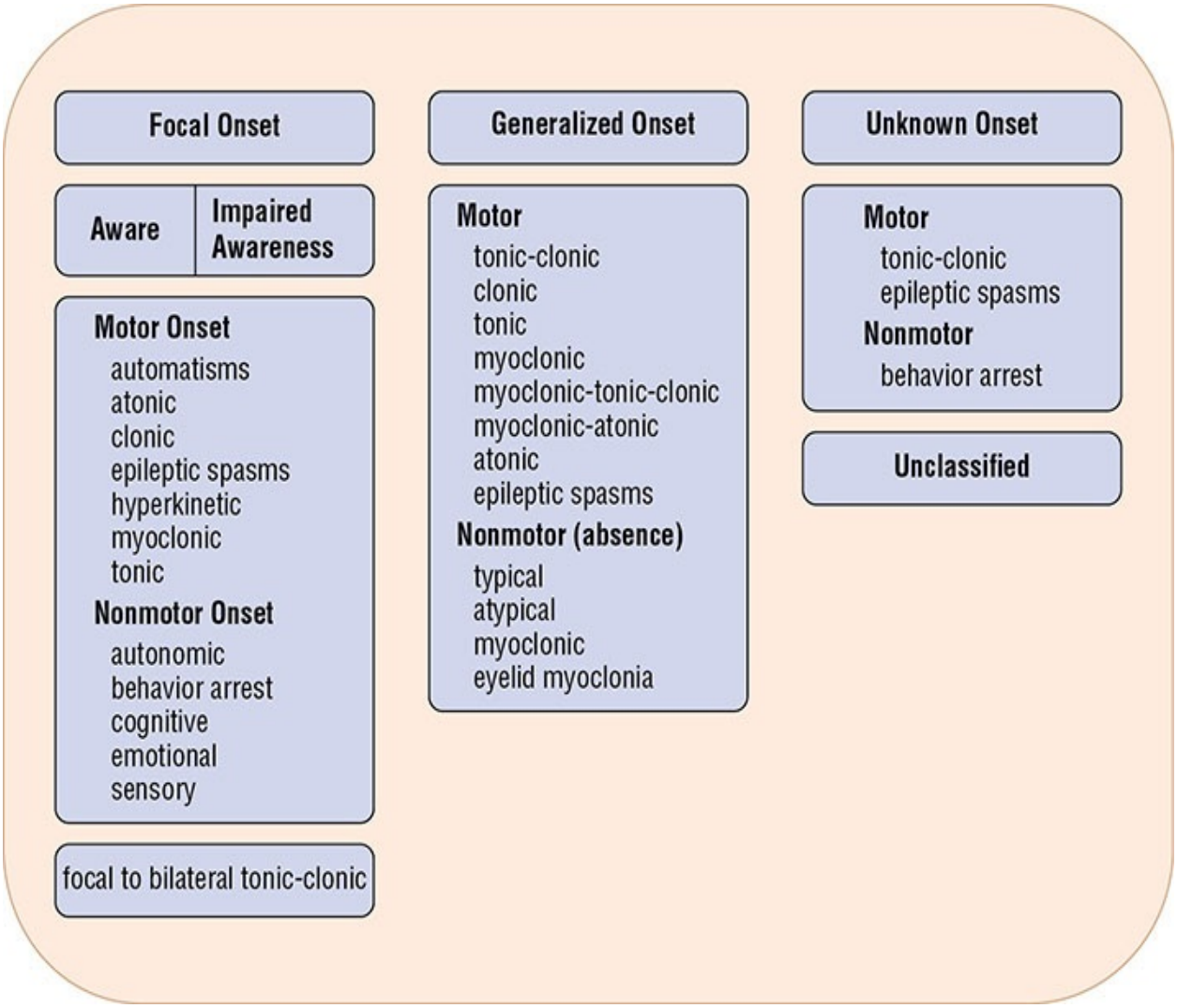


FIGURE 73-1 ILAE 2017 Classification of seizure types—expanded version. (*Adapted from Reference 26.*)

Focal seizures may propagate beyond the brain's one hemisphere to the contralateral hemisphere, resulting in both hemispheres becoming involved. This seizure type is called "focal to bilateral tonic–clonic" and is a special seizure type which previously was called "partial onset with secondary generalization" or "secondarily generalized tonic–clonic (GTC) seizure." The term "to bilateral" is preferred to distinguish this focal-onset seizure from a generalized-onset seizure. During this type of seizure, the person usually becomes unconscious and displays bilateral convulsive features such as tonic–clonic motor features.[26,28]

CLINICAL PRESENTATION

Epilepsy

Focal Aware Seizures

- Patient retains awareness of themselves and their environment including external stimuli

Focal to Bilateral Tonic–Clonic

- Focal seizure with impaired awareness which progresses to bilateral convulsive features such as with tonic–clonic motor features

Focal Impaired Awareness Seizure

- Patient has impaired awareness at any time during the seizure
- May be able to respond to questions during the seizure, but inappropriate response
- May not recall actions after event

Motor signs

- Automatisms: automatic behaviors like lip smacking, chewing, picking at clothing
- Atonic: loss of tone, going limp
- Clonic: rhythmic jerking or twitching of arm, shoulder, face, or leg
- Spasm: trunk flexion
- Hyperkinetic: thrashing/pedaling
- Myoclonic: arrhythmic jerking of arm, shoulder, face, or leg
- Tonic: extension or flexion postures

Nonmotor signs

- Autonomic: flushing, sweating, piloerection, salivation, pallor
- Behavior arrest: pausing, freezing, activity arrest
- Cognitive: language problems, thinking problems, memory phenomenon, and feelings of familiarity (déjà vu) or unfamiliarity (jamais vu)
- Emotion: feelings of fear, depression, joy, anger, extreme aberration of behavior
- Sensory: numbness, tingling, sounds (ringing/buzzing), smells, tastes,

visions (hallucinations), vertigo

Generalized Onset

- Impaired awareness

Motor signs (more common symptoms described below only)

- Tonic–clonic: sudden sharp tonic stiffening of muscles with a subsequent period of clonic movements such as rhythmic jerking of arms and legs (previously called “grand mal”)
- Clonic: rhythmic jerking or twitching of arm, shoulder, face, or leg
- Myoclonic: arrhythmic jerking of arm, shoulder, face, or leg
- Atonic: loss of tone, going limp
- Epileptic spasms: trunk flexion

Nonmotor/absence (more common symptoms described below only)

- Typical: sudden arrest of behavior, blank stare with brief upward rotation of the eyes lasting 2 to 30 seconds
- Eyelid myoclonia: lid jerks

Focal aware seizures may manifest clinically in a variety of ways and can vary depending on where the abnormal firing occurs. For example, seizures manifesting as abnormal movements such as clonic movements (eg, twitching or jerking) of the arm, shoulder, face, or leg indicate seizure activity in motor pathways. Feelings of numbness or tingling indicate sensory or somatosensory involvement and may indicate parietal lobe involvement. Sensory symptoms can also include feelings of fear, depression, joy, anger, or memory phenomena such as feelings of familiarity (déjà vu) or unfamiliarity (jamais vu) that may indicate temporal lobe seizure activity. Visual disturbances or hallucinations may indicate seizure activity involving the occipital lobe, while ringing or buzzing sounds in the ears may indicate seizure activity in auditory areas of the brain. Autonomic symptoms such as sweating, salivation, or pallor indicate seizure activity in autonomic areas of the brain.[28,29]

Focal unaware seizures may manifest with any of the signs and symptoms described for focal aware seizures except that the patient does not retain awareness. The patient may still be able to perform routine tasks such as walking, but such movements are not purposeful or planned and after the event

is over the patient may not recall their actions. The patient may also be able to respond to questions during the seizure, although they may not respond appropriately. The degree of alteration in awareness and responsiveness may be so subtle that witnesses may sometimes not be able to recognize that anything is overtly wrong. For example, during these seizures the patient may simply display behavioral arrest and stare off into space for a minute. They may also display subtle automatisms such as lip smacking, chewing, or picking at their clothing without purpose. On the other hand, some patients may display extreme aberrations of behavior, and some are even mistakenly diagnosed as having psychotic episodes. After the seizure (postictal period), the patient may display altered consciousness, drowsiness, confusion, or even paranoia for a variable period of time and frequently go into a deep sleep.[28,29]

Generalized-Onset Seizures

Generalized-onset seizures start in a network that is bilaterally distributed to both hemispheres of the brain and have previously been referred to as primary generalized seizures. These types of seizures usually always involve impaired awareness and are divided into motor and nonmotor (eg, absence) seizures. It is important to note that generalized “absence” seizures are not synonymous with an “absent stare” which typically accompanies the behavioral arrest that occurs in other seizure types.[26]

Generalized-onset seizures can have a variety of motor symptoms with the major motor category being tonic–clonic. These generalized-onset tonic–clonic seizures were previously called “grand mal” seizures. During these seizures the patient experiences loss of consciousness, followed by a sudden sharp tonic contraction (stiffening) of muscles with a subsequent period of rigidity and clonic movements oftentimes described as jerking of the arms and legs. During the seizure, the patient may cry or moan, due to muscles in the larynx being activated or the patient may lose sphincter control with bladder and/or bowel incontinence or bite their tongue. Postictally, after the patient regains consciousness, the patient may experience confusion, drowsiness, lack of coordination, soreness throughout the body, and amnesia for the event.[28,29]

It is important to remember that bilateral tonic–clonic seizures can also result from focal propagation to contralateral hemispheres and that these seizures must be differentiated from generalized-onset tonic–clonic seizures. Generalized manifestations of seizures can be asymmetrical or symmetrical, rendering difficult the distinction from focal-onset seizures, but certain distinguishing

features such as very early motor or nonmotor signs that may be characteristic of focal-onset seizures, and characteristic findings on EEG aid in distinguishing between the two. Other forms of generalized motor seizures may happen but the generalized tonic–clonic (GTC) seizure is most common and most distinct.[6,28]

Of note, in contrast to other motor seizure categories in which there is a sudden onset of increased tone, a sudden loss of muscle tone occurs in *atonic seizures*. Atonic seizures are not preceded by myoclonic or tonic features and can be very brief. They may present as a head drop, the dropping of a limb, or a slumping to the ground (due to loss of postural tone). These patients often wear protective headware to prevent trauma and atonic seizures are one hallmark of Lennox–Gastaut syndrome.[6,28]

Typical generalized nonmotor seizures, aka “absence” seizures, can manifest as typical absence seizures, atypical absence, absence seizures with myoclonia, or absence seizures with eyelid myoclonia. Most commonly, typical absence seizures manifest as a sudden onset interruption of ongoing activities, a blank stare, and possibly a brief upward rotation of the eyes indicating the abrupt onset and offset of impaired consciousness. The staring and behavioral arrest lasts 2 to 30 seconds during which time the patient is unaware of the environment and unresponsive. The patient has neither a warning that the seizure is going to occur, nor does the patient have postictal confusion or lethargy after the seizures. After cessation of the seizure, the patient will often return to the previous activity as if nothing had happened. These absence seizures generally occur in young children through adolescence. It is important to differentiate these seizures from focal unaware seizures; in general, absence-type seizures are much more brief than the staring spells associated with focal unaware seizures and have minimal postictal manifestations.[6,28,29]

Seizures of Unknown Onset

Seizures of unknown onset are classified based on presence of motor or nonmotor features; however, in some cases it may be impossible to classify a seizure at all. Although this should be a rare occurrence, in such cases this seizure would be an unclassified seizure.[26]

Classification of Epilepsies and Epilepsy Syndromes

A seizure is only a symptom that occurs within epilepsy; therefore, the classification of seizures is distinct from but related to the classification of

epilepsies and epilepsy syndromes. The starting point of epilepsy classification is identification of the seizure type, understanding that some patients may have multiple different seizure types. After seizure types are determined, the epilepsy should be classified into one of four categories: (1) focal epilepsy in which a patient only has focal-onset seizures; (2) generalized epilepsy in which a patient displays evidence of only generalized-onset seizures; (3) combined generalized and focal epilepsy; and (4) unknown in which the epilepsy type is unknown (see **Fig. 73-2**).[6]

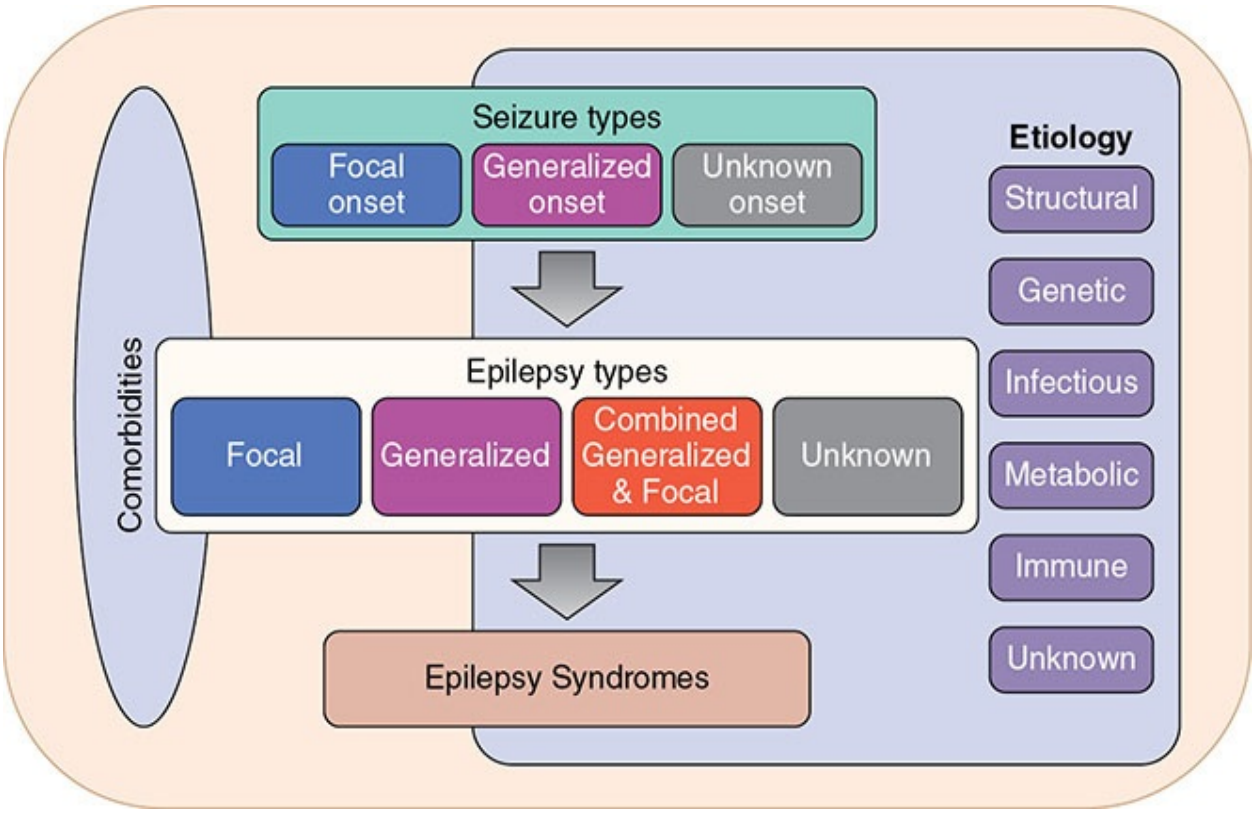


FIGURE 73-2 ILAE Framework for classification of the epilepsies. (*Reprinted with permission from Reference 6.*)

After establishing the epilepsy type, an epilepsy syndrome should be determined if possible. In general, while knowing the etiology and specific comorbid characteristics of an epilepsy patient is important during seizure and epilepsy classification, these parameters can be unknown and are not necessary. However, when determining epilepsy syndromes (the most specific level of epilepsy classification possible), knowing definitive etiology and specific comorbid characteristics is critical (see Fig. 73-2). Epilepsy syndromes are characterized by a known etiology and by a cluster of signs and symptoms including distinctive comorbidities such as intellectual and psychiatric

dysfunction that customarily occur together. Other signs and symptoms include type of seizure, specific electroencephalogram (EEG) findings, specific imaging features, anatomy, precipitating factors, age of onset, severity, chronicity, and diurnal and circadian cycling.[6] Common epilepsy syndromes include childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), and juvenile myoclonic epilepsy (JME).[6] They are often grouped together and called the idiopathic generalized epilepsies (IGEs) or the genetic generalized epilepsies (GGEs). Other well-recognized syndromes are West syndrome, Lennox–Gastaut syndrome (LGS), and Dravet syndrome.[6]

Diagnosis

Epilepsy is a clinical diagnosis, meaning that it is a diagnosis made on the basis of medical signs and patient-reported symptoms, rather than any one diagnostic test. A person is considered to have epilepsy if they meet any of the following conditions: (1) at least two unprovoked (or reflex) seizures occurring greater than 24 hours apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; or (3) diagnosis of an epilepsy syndrome.[30]

Accurate diagnosis also depends on the neurologic examination and diagnostic techniques such as EEG and brain imaging. The neurologic examination is generally nonfocal and focal findings may suggest a nonepilepsy diagnosis or help identify an epilepsy etiology (eg, stroke). The EEG can identify abnormal brain wave patterns that are associated with certain seizure types and epilepsy syndromes and is one of the most common and important diagnostic tests that can be performed for a patient with epilepsy. However, an abnormal epileptiform EEG is found in only approximately 50% of the patients who have epilepsy and sometimes several EEGs must be obtained before convincing epileptiform activity is detected. Video EEG is the gold standard for diagnosing epilepsy and involves hospital admission to facilitate recording video and continuous EEG monitoring until the patient has a typical event. However, this is not the standard for most patients and is generally reserved for cases unresponsive to medication or difficult to characterize.[31,32]

Brain imaging with either a computed tomography scan (CT) or magnetic resonance imaging (MRI) can detect structural lesions that can aid in the diagnosis of seizures and epilepsy types. Initially a CT is commonly performed in a patient who presents after their first seizure, as a way to evaluate for a brain

tumor, cerebral bleeding, or gross anatomical injury. An MRI is preferred for validation of an epilepsy diagnosis as it is the preferred imaging technique to identify more subtle structural abnormalities (eg, sclerosis in the mesial temporal lobes and traumatic brain injury).[32]

There are currently no diagnostic laboratory tests for epilepsy; however, in some cases, particularly following generalized convulsive seizures, serum prolactin levels obtained within 10 to 20 minutes can be transiently elevated.[33] Other laboratory tests can be done to rule out treatable causes of seizures (eg, hypoglycemia, altered electrolyte concentrations, infections, etc.) that do not represent epilepsy.

TREATMENT

Desired Outcomes

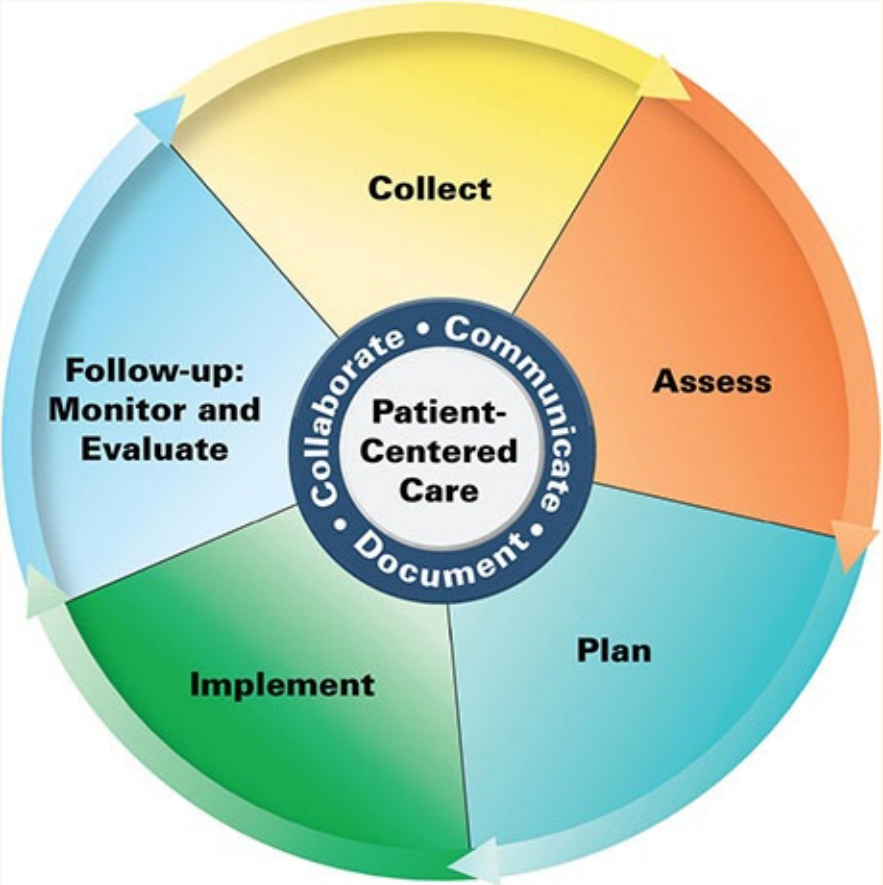
1 Antiseizure drug therapy is the mainstay of epilepsy treatment; however, all currently available ASDs are symptomatic treatments which only prevent seizures from occurring. None have been proven to have any disease modifying or antiepileptogenic properties and no ASDs are curative. Surgery is the only possibly curative therapy and only a select number of patients qualify for surgery (see section “Nonpharmacologic Therapy”). Therefore, the majority of patients with epilepsy will be on life-long ASD therapy. The goal of ASD therapy is eliminating the occurrence of seizures within the shortest possible duration of time and with minimal impact on QOL. In most patients the desired outcome is complete seizure freedom with little to no medication-related side effects. However, in 20% to 35% of patients, complete seizure freedom may not be possible[34] and more obtainable goals that balance seizure control with patient-specific QOL factors and wishes (eg, decrease in the number of seizures with minimized drug adverse effects) should be established.

General Approach to Treatment

When a patient presents after a single isolated seizure, one of three treatment decisions can be made: (1) treat, (2) possibly treat, or (3) do not treat, with the ultimate decision being based on the probability of the patient having a second seizure (ie, propensity for recurrent seizures). The probability of recurrent seizures is higher if certain findings are present, including brain imaging

abnormalities (such as from stroke, trauma, CNS infection, cerebral palsy, and other cognitive developmental disabilities), EEG with epileptiform abnormalities (characterized by spikes or sharp waves), or a nocturnal seizure.[35] For instance, for patients with any of the above findings present, the probability of seizure recurrence may be 2 to 2.5 times that of those without those findings.[35] The decision on whether to start ASD therapy after a single seizure depends on clinician judgment and available clinical evidence. Some clinicians choose to start ASD treatment after one seizure with a definite abnormal MRI or epileptiform EEG while others do not initiate treatment until a second seizure has occurred. In general, however, patients who have had two or more unprovoked seizures should be started on ASDs.[30,35]

2 Once the decision to initiate therapy has been determined, accurate identification of seizure type and epilepsy diagnosis is critical for treatment, as an ASD must be effective for the specific seizure type and epilepsy, or epilepsy syndrome, being treated. For instance, if a patient is diagnosed with the epilepsy syndrome, childhood absence epilepsy (CAE), then an ASD that is effective for that syndrome (eg, ethosuximide) should be selected for that patient, and an ASD that may exacerbate that syndrome (eg, phenytoin or carbamazepine) should be avoided. Only after an accurate diagnosis is obtained, can a care plan, including selection and/or optimization of ASD therapy, be developed.[27]



Patient Care Process for Epilepsy

Collect

- Patient-specific demographics such as age, race, and gender
- A detailed description of seizure semiology from the patient and a witness of the seizure, including the following:
  - Degree of mental status impairment during the event
  - Presence of ictal motor, sensory, autonomic, or other features at onset of the seizure (Fig. 73-1)
  - Tongue biting, cheek biting, and bladder or bowel incontinence during the seizures
  - Seizure time course and any postictal phenomena (eg, fatigue, headaches, confusion, and psychosis)
- Frequency of seizure events and any precipitating factors

- Information on comorbid medical psychiatric, and neurodevelopmental conditions including depression, anxiety, and learning and development
- Family history of epilepsy, risk factors for epilepsy including injury at birth, history of meningitis or encephalitis, history of traumatic brain injury
- Current and past medications including antiseizure drugs (ASDs)
- Duration of past ASD therapy and response to each ASD (eg, decrease or increase in seizure frequency and side effects experienced)
- Allergies to medications including ASDs
- Laboratory values for electrolytes and glucose to rule out provoked seizures, baseline test for renal function, liver function, and complete blood count (CBC)
- Magnetic resonance imaging (MRI) of brain without contrast
- Electroencephalogram (EEG)

Assess

- Seizure, epilepsy, and epilepsy syndrome classification (Figs. 73-1 and 73-2)
- Duration of therapy on current ASD or ASD regimen
- Seizure freedom on current ASDs or current seizure frequency if not seizure-free (Fig. 73-3)
- Side effects experienced on current ASDs (Fig. 73-3)
- Factors for optimal ASD selection including patient-specific factors (Table 73-1)
- Other quality of life factors

Plan*

- Determine need for monotherapy (usually at initiation of therapy) or polytherapy (usually after failure of first or second ASD) (Fig. 73-3)
- Select an ASD that has efficacy for the specific seizure type, epilepsy, or epilepsy syndrome (Table 73-6)
- Considering patient-specific factors, select an ASD with:
  - Most tolerable adverse effect profile (Table 73-5)
  - Least drug–drug interactions with other medications (Tables 73-3 and

73-5)
    - Least complicated ASD pharmacokinetics (Table 73-2)
    - Utility in treating the patients' other comorbid conditions (Table 73-5)
- Create a patient-specific monitoring plan based on the therapy chosen

Implement*

- Identify initial dose and maintenance dose (Table 73-4) along with appropriate formulation (Table 73-5) and dosage size (eg, 25-mg tablets, 100-mg capsules, 250-mg/5-mL oral solution, 1,500 mg/100 mL of diluted solution for intravenous injection) to meet the patients' needs
- Counsel patient on dose, dose formulation, and how to titrate appropriately
- Provide patient with seizure and side effect diary and counsel patient and family on how to record in the diary
- Ensure completion of prior authorizations for insurance coverage as needed
- Ensure prescription is provided on appropriate controlled substance prescription form as needed for any scheduled drugs (Table 73-5)

Follow-up: Monitor and Evaluate

- Treatment response including increase or decrease in seizure frequency and changes in seizure semiology
- Laboratory assessments including complete blood count, chemistries, liver function tests, and ASD serum concentrations if needed
- Monitor for common dose-related side effects, rare idiosyncratic side effects, and long-term side effects
- Monitor for other comorbid conditions such as depression, anxiety, suicidal ideation, and social adjustment
- Monitor for learning and development issues in children
- Monitor seizure triggers
- Monitor adherence

* *Collaborate with patient, caregivers, and other healthcare professionals.*

3 During ASD selection, several possible first-choice drugs are identified based on the type of epilepsy, and then narrowed down to an ideal single agent

based on patient-specific characteristics including age, gender, susceptibility to adverse effects, comorbid medical conditions, interactions with other medications, ability to comply with a prescribed regimen, and cost of therapy/insurance coverage (Table 73-1). Patient-specific characteristics must be taken into consideration as different patient groups may be better suited to receive one ASD over another. For instance, children may be more susceptible to neuropsychiatric adverse effects and ASDs that promote those effects should be avoided, similarly women with child-bearing potential should not be on ASDs with unacceptable teratogenicity, and ASDs that have adverse effects on cognition should be avoided in the elderly as they may be more susceptible to adverse cognitive effects. On the other hand, patients with comorbid conditions, such as migraine headache, bipolar disorder, or neuropathy, may benefit from the use of particular ASDs that can also treat those comorbid conditions and as such specific ASDs would be promoted for use in these patient groups (eg, topiramate for the treatment of epilepsy and migraine, lamotrigine for the treatment of epilepsy and bipolar, pregabalin for the treatment of epilepsy and neuropathy).

TABLE 73-1 Factors to Consider When Making ASD Selection

1. ASD efficacy for the specific seizure type, epilepsy, or epilepsy syndrome
2. Selection of an ASD with the most tolerable adverse effect profile, considering patient-specific factors including age and gender
3. Selection of an ASD that can also treat the patient's other comorbid conditions
4. Drug–drug interactions with other medications
5. Ability to adhere to a prescribed regimen (eg, three or four times daily dosing) and insurance coverage, as this can affect ASD adherence and effectiveness
6. Need for therapeutic levels to be reached quickly

Pharmacokinetic drug interactions are a common complicating factor in ASD selection and an appreciation of pharmacokinetic variability is necessary when selecting an ASD (Table 73-2). In general, ASD drug–drug interactions can occur in any of the pharmacokinetic processes (eg, absorption, distribution, metabolism, or elimination); however, their effects on metabolic pathways are particularly complex and significantly affect management. As such, knowledge of ASD metabolic pathways as well as inducer or inhibitory effects on liver enzymes (Table 73-3) can aid in the optimization of ASD therapy, realizing that caution should be used when ASDs are added to or withdrawn from a drug regimen.

TABLE 73-2 Antiseizure Drug Pharmacokinetic Data

ASD	$t_{1/2}$ (Hours)	Time to Steady State (Days)	Unchanged (%)	V_D (L/kg)	Clinically Important Metabolite	Protein Binding (%)
First Generation						
Carbamazepine	12-17 34 (10,11-epoxide)	21-35 for completion of autoinduction	3	0.8-2	10,11-epoxide	76
Clonazepam	30-40	3-10	2	3.2	No	85
Ethosuximide	17-56	7-10	10-20	0.6-0.7	No	22
Phenobarbital	53-180	12-24	25-50	0.5-1	No	50
Phenytoin	22	7-10	unknown	0.5-1	No	90
Primidone	7-22 10-25 (PEMA) 75-126 (PB)	2-4	<1	0.4-1	Phenylethylmelanomide (PEMA); Phenobarbital (PB)	34
Valproic acid	9-16	2-4	<3	0.14-0.23	No	90
Second Generation						
Felbamate	16-22	3-4	40-50	0.73-0.85	No	25
Gabapentin	5-7	1-2	100	58 L	No	<3
Lamotrigine	12-60	3-15	10	0.9-1.3	No	55
Levetiracetam	6-8	2	66	0.7	No	<10
Oxcarbazepine	2 9 (MHD)	2-3	2	49 L	10-monohydroxy-carbazepine (MHD)	40
Tiagabine	7-9	2	2		No	96
Topiramate	21	4	70	0.6-0.8	No	15-41
Zonisamide	63	14	35	1.45	No	40
Third Generation						
Brivaracetam	9		<10	0.5	No	40
Cannabadiol	56-61	7	Minor	20963-42849 L	7-OH cannabadiol	>94
Clobazam	36-42	7-14	2	100 L	*N*-desmethylclobazam	80-90
Eslicarbazepine	13-20	4-5	67	0.87	S-licarbazepine; oxcarbazepine	<40
Lacosamide	13	3	40	0.6	No	<15
Perampanel	105	14-21	74-80	77 L	No	96
Pregabalin	6	1-2	90	0.5	No	0
Rufinamide	6-10		<2	50 L	No	34
Vigabatrin	5-11		80	1.1	No	0

ASD, antiseizure drug; MHD, monohydroxycarbazepine derivative; PEMA, phenylethylmelanomide; PB, phenobarbital; V_D, volume of distribution.

Data from References 17-20, 23, 36-56.

TABLE 73-3 Antiseizure Drug Elimination Pathways and Major Effects on Hepatic Enzymes

Antiepileptic Drugs	Major Hepatic Enzymes	Renal Elimination (%)	Induces	Inhibits
First Generation				
Carbamazepine	CYP3A4	3	CYP1A2; CYP2B6; CYP2C9/19; CYP3A; GT	None
Clonazepam	CYP3A	2	None	None
Ethosuximide	CYP3A4; CYP2E1	10-20	None	None
Phenobarbital	CYP2C9; CYP2C19	25	CYP 3A4/2C9/2C19/1A2; GT	None
Phenytoin	CYP2C9; CYP2C19	unknown	CYP3A; CYP2C; GT	
Primidone		<1		
Valproate	GT; β-oxidation	<3	None	CYP2C9; GT epoxide hydrolase
Second Generation				
Felbamate	CYP3A4; CYP2E1; other	50	CYP3A4	CYP2C19; β-oxidation
Gabapentin	None	Almost completely	None	None
Lamotrigine	GT	10	GT	None
Levetiracetam	None (undergoes nonhepatic hydrolysis)	66	None	None
Oxcarbazepine (MHD is active oxcarbazepine metabolite)	Cytosolic system	<1 (27 as MHD)	CYP3A4; CYP3A5; GT	CYP2C19
Tiagabine	CYP3A4; CYP1A2; CYP2D6; CYP2C19	2	None	None
Topiramate	Not known	70	CYP3A (dose dependent)	CYP2C19
Zonisamide	CYP3A4	35	None	None
Third Generation				
Brivaracetam	CYP2C19	<10	None	CYP2C19 (weak), GT epoxide hydrolase
Cannabadiol	CYP2C19; CYP3A4; GT	Minor	CYP1A2; CYP2B6; GT	CYP2C8/9/19
Clobazam	CYP3A4; CYP2C19; CYP2B6	2	CYP3A4 (weak)	CYP2C9
Eslicarbazepine	Undergoes hydrolysis	67	GT (mild)	CYP2C19
Lacosamide	CYP2C9/19; CYP3A4	40	None	CYP2C19
Perampanel	CYP3A4/5; CYP1A2; CYP2B6	Undefined	CYP3A4/5; CYP2B6; GT	CYPA3A4/5; CYP2C8; GT
Pregabalin	None	100	None	None
Rufinamide	Hydrolysis	2	CYP3A4 (weak)	CYP2E1 (weak)
Vigabatrin	None	Almost completely	CYP2C9	None

CYP, cytochrome P450 isoenzyme system; GT, glucuronyltransferase.

Data from References 17-20, 23, 36-56.

Finally, when selecting ASD therapy, a patient's ability to adhere to a prescribed regimen and their insurance coverage are also of extreme importance to consider, as these factors can promote poor outcomes. For instance, a prescribed regimen requiring three or four times a day dosing would promote nonadherence in a patient who finds it difficult to remember to take medicines which ultimately would affect that patient's seizure control. Similarly, an ASD that is not covered by insurance or is expensive may also promote nonadherence or adversely affect the patient by causing financial hardship. Ultimately, ASD effectiveness is the result of the interaction of all of specific factors.

Optimizing Dose

4 Once an ASD has been selected, initiate the ASD at an appropriate starting dose, and gradually titrate up to a therapeutic maintenance dose based on individual ASD recommendations (**Table 73-4**). Titration to an adequate therapeutic dose usually occurs over a few weeks and is necessary to allow the patient to slowly adjust to dose-related side effects. Some patients, such as elderly patients who are sensitive to falls, sedation, and other neurocognitive side effects, need to have ASDs started at lower doses and then titrated more slowly. In such cases, a slow titration can last over many weeks or months and may have a lower goal dose. In other patients, such as patients with multiple recent seizures, a therapeutic dose needs to be reached much more quickly, and a more rapid titration over days instead of weeks is appropriate. For such patients, loading doses, either administered orally or intravenously, may be indicated. When considering using a loading regimen, it is important to select ASDs that can be administered safely as loading doses, as medications like lamotrigine and topiramate require slow titration and should not be used in patients who require loading to reach therapeutic levels quickly.

TABLE 73-4 Antiseizure Drug Dosing and Target Serum Concentration Ranges

Drug	Brand Name	Initial or Starting Dose	Usual Range or Maximum Dose	Comments Target Serum Concentration Range
First Generation				
Carbamazepine	Tegretol	400 mg/day	400-1,600 mg	4-12 mcg/mL[a] (17-51 µmol/L)
	Tegretol XR			
Clonazepam	Klonopin	1.5 mg/day	20 mg	20-70 ng/mL (67-233 pmol/L)
Ethosuximide	Zarontin	500 mg/day	500-1,500 mg	40-100 mcg/mL (282-708 µmol/L)
Phenobarbital	Various	1-3 mg/kg/day (10-20 mg/kg LD)	180-300 mg	10-40 mcg/mL[a] (43-172 µmol/L)
Phenytoin	Dilantin	3-5 mg/kg (200-400 mg)	300-600 mg	Total: 10-20 mcg/mL (40-79 µmol/L)
		(15-20 mg/kg LD)		Unbound: 0.5-3 mcg/mL (2-12 µmol/L)
Primidone	Mysoline	100-125 mg/day	750-2,000 mg	5-10 mcg/mL (23-46 µmol/L)
Valproic acid	Depakene	15 mg/kg (500-1,000 mg)	60 mg/kg (3,000-5,000 mg)	50-100 mcg/mL (347-693 µmol/L)
	Depakote DR/ER			
	Depacon			
Second Generation				
Felbamate	Felbatol	1,200 mg/day	3,600 mg	30-60 mcg/mL (126-252 µmol/L)
Gabapentin	Neurontin	300-900 mg/day	4,800 mg	2-20 mcg/mL (12-117 µmol/L)
Lamotrigine	Lamictal	25 mg every other day if on VPA; 25-50 mg/day if not on VPA	100-200 mg if on VPA; 300-500 mg if not on VPA	4-20 mcg/mL (16-78 µmol/L)
	Lamictal XR			
Levetiracetam	Keppra	500-1,000 mg/day	3,000 mg	12-46 mcg/mL (70-270 µmol/L)
	Keppra XR			
Oxcarbazepine	Trileptal	300-600 mg/day	1,200-2,400 mg	3-35 mcg/mL (MHD) (12-139 µmol/L)
	Oxtellar XR			
Tiagabine	Gabitril	4 mg/day	56 mg	0.02-0.2 mcg/mL (0.05-0.5 µmol/L)
Topiramate	Topamax	25-50 mg/day	200-400 mg	5-20 mcg/mL (15-59 µmol/L)
	Trokendi XR			
Zonisamide	Zonegran	100 mg/day	600 mg	10-40 mcg/mL (47-188 µmol/L)
Third Generation				
Brivaracetam	Briviact	100 mg/day	200 mg/day	Not defined
Cannabadiol	Epidiolex	5 mg/kg/day	10-20 mg/kg/day	Not defined
Clobazam	Onfi	≤30 kg 5 mg/day; >30 kg 10 mg/day	≤30 kg up to 20 mg; >30 kg up to 40 mg	0.03-0.3 mcg/mL (0.1-1.0 µmol/L)
Eslicarbazepine	Aptiom	400 mg/day	800-1,600 mg	Not defined
Lacosamide	Vimpat	100 mg/day	400 mg	Not defined
Perampanel	Fycompa	2 mg/day	8-12 mg	Not defined
Pregabalin	Lyrica	150 mg/day	600 mg	Not defined
Rufinamide	Banzel	400-800 mg/day	3,200 mg	Not defined
Vigabatrin	Sabril	1,000 mg/day	3,000 mg	0.8-36 mcg/mL (6-279 µmol/L)

[a]Units mcg/mL and mg/L are numerically equivalent, and units ng/mL and mcg/L are numerically equivalent.

LD, loading dose; MHD, 10-monohydroxycarbazepine derivative.

Data from References 17-20, 23, 36-56.

Determining the optimal therapeutic dose needs to be individualized and takes into account the patient's response to treatment and appearance of side effects. If the patient is seizure free with no adverse effects at a minimal therapeutic dose, then an optimal dose has been achieved and no further increase in dose is necessary. If the patient continues to have seizures at a minimal or moderate-therapeutic dose, further titration to a maximum dose may be needed for optimal seizure control. If the patient continues to have seizures at a maximum dose, or if the patient experiences intolerable adverse effects at any dose, adding a second ASD and then tapering and discontinuing the ineffective or intolerable first ASD is appropriate. Selecting an ASD with a different mechanism of action than the first intolerable or ineffective ASD may increase the likelihood of success with the second ASD, although there is no clear evidence to support this.[57]

5 In general, ASD monotherapy is preferred. However, if the patient continues to have seizures with a second ASD tried as monotherapy at a therapeutic dose, the patient may require dual ASD therapy, and an adjunctive ASD should be gradually added. Selection of an adjunctive ASD with a different or complementary mechanism of action is the basis behind rational polytherapy and is recommended, although again there is no clear evidence in humans to support this.[57] For those patients who continue to have seizures on dual ASD therapy, polytherapy with three or more agents can be considered. A suggested algorithm for a general approach to the treatment of epilepsy is shown in **Fig. 73-3**.

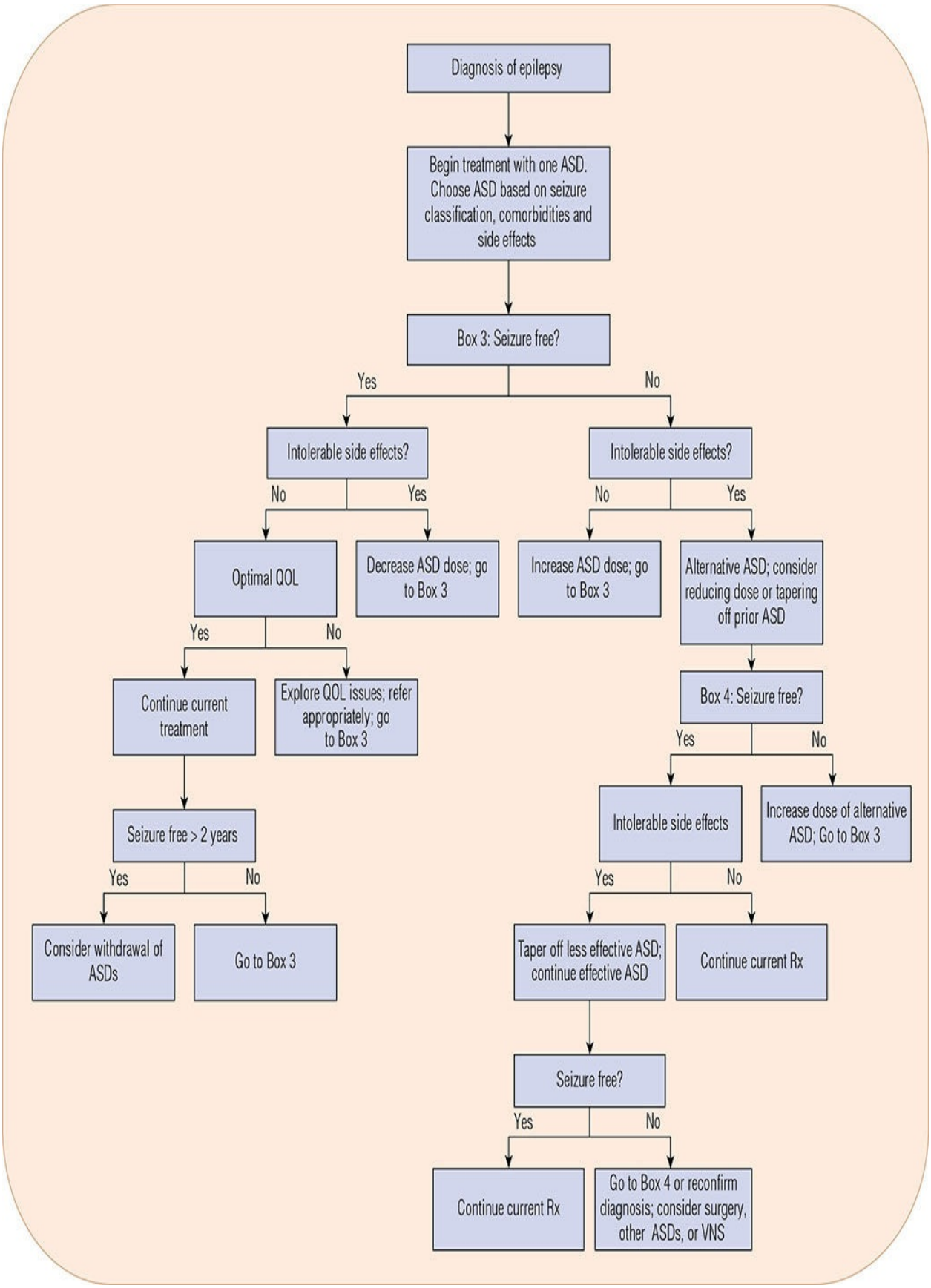

Diagnosis of epilepsy
Begin treatment with one ASD. Choose ASD based on seizure classification, comorbidities and side effects
Box 3: Seizure free?
Yes
No
Intolerable side effects?
Intolerable side effects?
No
Yes
No
Yes
Optimal QOL
Decrease ASD dose; go to Box 3
Increase ASD dose; go to Box 3
Alternative ASD; consider reducing dose or tapering off prior ASD
Yes
No
Continue current treatment
Explore QOL issues; refer appropriately; go to Box 3
Box 4: Seizure free?
Yes
No
Seizure free > 2 years
Intolerable side effects
Increase dose of alternative ASD; Go to Box 3
Yes
No
Yes
No
Consider withdrawal of ASDs
Go to Box 3
Taper off less effective ASD; continue effective ASD
Continue current Rx
Seizure free?
Yes
No
Continue current Rx
Go to Box 4 or reconfirm diagnosis; consider surgery, other ASDs, or VNS

FIGURE 73-3 An algorithm for ASD therapy. (ASD, antiseizure drug; VNS, vagal nerve stimulation.)

Nonpharmacologic Therapy

Pharmacologic therapy with ASDs is the mainstay of treatment for patients with epilepsy. However, approximately 20% to 35% of patients will not be adequately controlled with pharmacologic ASD therapy and may be considered drug-resistant.[34] Nonpharmacologic therapies are available for these drug-resistant patients as well as for those drug-responsive patients in which the benefits of nonpharmacologic therapies outweigh its risk. Nonpharmacologic therapy for epilepsy includes diet, vagus nerve stimulation (VNS), and surgery among other modalities.

The ketogenic diet, devised in the 1920s, is high in fat and low in carbohydrates and protein, which leads to a shift in metabolism resulting in acidosis and ketosis. As protein and calorie intake are set at levels that will meet requirements for growth, most of the calories provided come in the form of heavy cream and butter, although medium-chain triglycerides can be substituted for the dietary fats. Furthermore, no sugar is allowed, the overall fluids are also controlled, and vitamins and minerals are supplemented. Given these restrictions, it requires strict control and parent compliance, as this diet is often used in childhood forms of epilepsy. Although some centers find the diet useful for medically refractory epilepsy patients, particularly those with certain etiologies such as glucose transporter 1 (GLUT1) deficiency, others have found that it is poorly tolerated by patients. Long-term effects include kidney stones, increased bone fractures, and adverse growth effects.[58] An international consensus statement has offered recommendations for employing various forms of the ketogenic diet which may be more tolerable, including the use of the modified Atkins diet and the Low Glycemic Index treatment.[59]

A vagal nerve stimulator is an implanted medical device that is Food and Drug Administration (FDA) approved for use as adjunctive therapy in reducing the frequency of seizures in adults and adolescents older than 12 years of age with partial-onset seizures that are refractory to ASDs. It is also used off-label in the treatment of refractory primary generalized epilepsy. The mechanisms of antiseizure actions of VNS are unknown. Human clinical studies have shown that VNS changes the cerebrospinal fluid (CSF) concentration of inhibitory and stimulatory neurotransmitters and activates specific areas of the brain that generate or regulate cortical seizure activity through increased blood flow. There

is experimental evidence to suggest that the anticonvulsant effect of VNS is mediated by the locus coeruleus.[60]

The VNS device is relatively safe and it may also have a positive effect on mood and behavior, often independent of seizure reduction.[61] The most common side effect associated with stimulation is hoarseness, voice alteration, increased cough, pharyngitis, dyspnea, dyspepsia, and nausea. Serious adverse effects reported include infection, nerve paralysis, hypoesthesia, facial paresis, left vocal cord paralysis, left facial paralysis, left recurrent laryngeal nerve injury, urinary retention, and low-grade fever. In the VNS studies, the percentage of patients who achieved a 50% or greater reduction in their seizure frequency (responders) ranged from 23% to 50% at 3 months.[62,63] It is important to note that VNS effects are not noted immediately and are more long term. Additionally, VNS is also unlikely to lead to seizure freedom but may allow for reduced seizure frequency and reduced medication burden.

6 Surgery is the treatment of choice in selected patients with refractory focal epilepsy, especially those patients with seizures originating from the temporal lobe. A randomized controlled trial, focusing on temporal lobe epilepsy, found that 58% of patients who underwent surgery were seizure free at 1 year compared to 8% of patients who did not undergo surgery.[64] A second randomized controlled study, initiated to evaluate the efficacy of early surgery versus continued medical management in patients who had failed two ASD trials, showed that 11 of 15 patients who had undergone surgery were seizure free at 2-year follow-up, compared to none in the medical therapy group.[65] Certain factors have been found to predict good outcomes in surgical patients including presence of a focal brain lesion on MRI, presence of unilateral mesial temporal sclerosis, presence of a localized temporal lobe positron emission tomography (PET) abnormality (even if brain MRI is normal), concordant EEG data showing location of ictal onset and shorter preoperative seizure duration.[66–68] The last finding is important to emphasize, as it is imperative to identify possibly drug-resistant patients with epilepsy quickly and to refer them to an epilepsy center as soon as possible. Epilepsy surgery is not without risk, as learning and memory can be impaired postoperatively, and general intellectual abilities have also been affected in a small number of patients.[68] Patients may need to continue ASD therapy for a period of time following successful epilepsy surgery, but dosage reduction may be achievable.

Pharmacologic Therapy

ASD Efficacy

There are more than 24 ASDs for the treatment of epilepsy that are FDA approved in the United States. Only a subset of these are approved for monotherapy in epilepsy, and many are approved as add-on treatment only, in large part due to the difficulty in studying ASD monotherapy in randomized clinical trials. As such, despite lack of FDA approval, many clinicians will use most ASDs off-label as monotherapy in clinical practice.

Clinical trials for ASD approval focus on efficacy in either focal-onset epilepsies or specific epilepsy syndromes. Studies to directly compare the efficacy of individual ASDs are not practical and have not been conducted for many ASDs. In general, however, all ASDs appear to have comparable efficacy in focal-onset epilepsies, except for gabapentin, which is considered a weaker ASD and should be used as adjunctive therapy only. In generalized epilepsies and epilepsy syndromes, specific ASDs have been found to have efficacy and are FDA-approved (**Table 73-5**) or have recommendations for use in those epilepsy types (**Tables 73-6** and **73-7**).

TABLE 73-5 Antiseizure Drugs (ASDs)

ASD and Available Formulations	Postulated Mechanism of Action	FDA Indication	Advantages	Disadvantages
First-Generation ASDs				
Carbamazepine Chewable tablet, ER tablet, liquid suspension	Enhances fast inactivation of voltage-gated sodium channels	Monotherapy and adjunctive therapy for focal-onset, TC, and mixed seizure types except for absence seizures	Useful in comorbid bipolar disorder and trigeminal neuralgia	Worsens other seizure types in patients with absence epilepsy; avoid if prior rash with other ASDs due to possible cross-reaction; increased risk of SJS/TEN in HLA-B*1502 and HLA-A*3101 allele in Asians; auto-inducer; active metabolite carbamazepine 10,11 epoxide contributes to idiosyncratic side effects; can cause fetal harm
Clonazepam (Schedule IV) Tablet, ODT	Binds $GABA_A$ receptor and potentiates GABA by modulating chloride conductance	Monotherapy and adjunctive therapy for LGS, akinetic, myoclonic, and absence seizures	Useful in patients with panic disorder, myoclonic seizures, and subcortical myoclonus	May increase TC seizures when used in mixed seizure types; tolerance and dependence may occur; use with other CNS depressant may produce additive CNS effects; may cause respiratory depression; contraindicated in acute narrow angle glaucoma and severe liver impairment; withdrawal symptoms may occur after discontinuation; no adequate data in pregnancy—may cause fetal harm
Ethosuximide Capsule, liquid solution	Inhibition of T-type calcium channels	Monotherapy and adjunctive therapy for absence seizures in patients ≥3 years of age	Drug of choice for absence seizures	Worsens generalized TC seizures and other seizure types; contraindicated in those with allergies to succinimides; may cause fetal harm; use with caution in hepatic/renal dysfunction
Phenobarbital (Schedule III) Tablet, elixir, injectable solution	Binds $GABA_A$ receptor and potentiates GABA by modulating chloride conductance	Not FDA approved (grandfathered); used for focal-onset and generalized seizures		Tolerance and dependence may occur; slow taper needed when discontinuing after prolonged use; use with other CNS depressants may produce additive CNS effects; may cause respiratory depression; can cause fetal harm
Phenytoin ER capsule; liquid suspension; injectable; chewable tablet (Fosphenytoin, a prodrug desterified by esterases in the blood to phenytoin, also available as injectable solution only)	Enhances fast inactivation of voltage-gated sodium channels; inhibits persistent sodium current (I_{NAP}) and increases threshold for action potential firing	Monotherapy and adjunctive therapy for focal-onset and TC seizures; injectable phenytoin and fosphenytoin approved for prevention or treatment of seizures during or after neurosurgical procedures, severe TBI, status epilepticus	Useful in nonadherence as dosed once daily	May aggravate seizures in patients with absence seizures; can increase blood sugar levels in diabetes; HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry; monitoring of free phenytoin levels required in pregnancy, elderly, or low albumin; compromised absorption with concomitant tube feeds
Primidone Tablet	Prodrug converted to active metabolite phenylethylmalonamide (PEMA) and phenobarbital with same mechanism of action	Monotherapy and adjunctive therapy for focal-onset and TC seizures	Useful in essential tremor	Contraindicated in patients with porphyria

DDI: Effect of Drug on Concomitant ASD	DDIs: Effect of Concomitant ASDs on Drug	Common and Dose-Related Adverse Effects	Rare and Serious Adverse Effects[a]	Long-Term Adverse Effects
Potent inducer of CYP3A4, CYP1A2, CYP2B6, CYP2C9/19; decreases levels of brivaracetam, clonazepam, eslicarbazepine, ethosuximide, lamotrigine, oxcarbazepine, perampanel, phenytoin, tiagabine, topiramate, valproate	Phenobarbital, phenytoin, primidone decrease levels; valproate increases carbamazepine-10,11 epoxide	CNS effects including diplopia, dizziness, drowsiness, unsteadiness, lethargy	Boxed warning: Increased risk of SJS/TEN and HLA-B*1502 allele; aplastic anemia and agranulocytosis Other blood dycrasias including thrombocytopenia, leukopenia; DRESS; hyponatremia; increased intraocular pressure; cardiovascular effects including second- and third-degree AV heart block; hepatotoxicity; genitourinary effect; nephrotoxicity	Hyponatremia; metabolic bone disease including osteoporosis, osteopenia, osteomalacia
May affect levels of phenytoin	May be affected by enzyme-inducing or enzyme-inhibiting ASDs	CNS effects including sedation, ataxia; paradoxical reactions such as agitation, irritability, aggression, anxiety, anger, nightmares, hallucinations and psychoses	Boxed warning: Concomitant use with opioids may result in profound sedation, respiratory depression, coma, and death Blood dyscrasias including leukopenia, thrombocytopenia, eosinophilia; rash; cardiovascular or respiratory depression; hepatotoxicity; muscle weakness	Physiologic dependence; loss of effect; hair loss; hirsutism; ankle and facial edema
May affect levels of phenytoin, carbamazepine, phenobarbital, phenytoin, primidone, valproate	Valproate may increase or decrease levels	GI distress including nausea/vomiting, cramps diarrhea; anorexia and weight loss; CNS effects including drowsiness, dizziness, hiccoughs	Blood dyscrasias including leukopenia, agranulocytosis, pancytopenia; rash including SJS; DRESS; hepatic/renal dysfunction; lupus erythematosus	Behavioral changes
May decrease levels of carbamazepine, eslicarbazepine, ethosuximide, lamotrigine, oxcarbazepine, perampanel, phenytoin, rufinamide, tiagabine, topiramate, valproate	Valproate increases levels; phenytoin increases or decreases levels	CNS effects including residual sedation or "hangover," drowsiness, lethargy, confusion, ataxia, vertigo; paroxysmal effects including excitement, irritability and hyperactivity in elderly and children; GI effects including nausea, vomiting	Respiratory depression and apnea; rash (SJS, TEN); cardiac effects including bradycardia, hypotension, syncope; hepatotoxicity	Behavioral changes; connective tissue disorder; intellectual blunting; metabolic bone disease (osteoporosis, osteopenia, osteomalacia); folate deficiency (with megaloblastic anemia)
May decreases levels of brivaracetam, carbamazepine, clonazepam, eslicarbazepine, ethosuximide, felbamate, lamotrigine, oxcarbazepine, perampanel, tiagabine, topiramate, valproate	Ethosuximide, felbamate, oxcarbazepine, methsuximide, topiramate may increase levels; carbamazepine, vigabatrin may decrease levels; phenobarbital, valproate may increase or decrease levels	CNS effects including ataxia, nystagums, slurred speech, decreased coordination, mental confusion, dizziness, insomnia, transient nervousness, headaches	Blood dyscrasias including thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, pancytopenia; rash (SJS/TEN); DRESS; hepatotoxicity, cardiac effects; purple glove syndrome with IV administration	Connective tissue changes including skin thickening, gingival hyperplasia, coarsening of facial features, enlargement of lips; hirsutism; metabolic bone disease (osteoporosis, osteopenia, osteomalacia); peripheral neuropathy; cerebellar atrophy; folate deficiency (with megaloblastic anemia)
May decrease levels of carbamazepine, eslicarbazepine, ethosuximide, lamotrigine, oxcarbazepine, perampanel, phenytoin, rufinamide, tiagabine, topiramate, valproate	Valproate may increase levels; phenytoin may increases or decreases levels	CNS effects including ataxia, vertigo, nystaguma, diplopia, drowsiness, fatigue; GI effect including nausea/vomiting, anorexia, fatigue; emotional disturbances including hyperirritability	Blood dyscrasias including granulocytopenia, agranulocytosis; rash (SJS, TEN); liver dysfunction	Behavioral changes; intellectual blunting; connective tissue disorder; metabolic bone disease (rickets, osteomalacia); folate deficiency (with megaloblastic anemia)

ASD and Available Formulations	Postulated Mechanism of Action	FDA Indication	Advantages	Disadvantages
Valproate Divalproex DR sprinkle capsule, Divalproex DR tablet, Divalproex ER 24-hour tablet, valproic acid IR capsule, valproate sodium injectable solution	Likely potentiates GABAergic transmission among multiple other unknown mechanisms	Monotherapy and adjunctive therapy for focal-onset and multiple seizure types for patients ≥10 years of age; monotherapy and adjunctive therapy for absence seizures in patients ≥10 years of age	Useful in comorbid bipolar disorder and migraine	Contraindicated in significant hepatic dysfunction, mitochondrial disorders caused by DNA polymerase γ (POLG) mutations, urea cycle disorders; use with caution in pancreatitis, bleeding and other hematopoietic disorders; hyperammonemia with and without encephalopathy associated with concomitant topiramate use; pregnancy category D—contraindicated in women of childbearing potential and pregnancy category X for pregnant patients treated for migraine prophylaxis
Second-Generation ASDs				
Felbamate Tablet, liquid suspension	Antagonizes NMDA glutamate receptor; binds to $GABA_A$ receptor and augments GABAergic transmission	Monotherapy and adjunctive therapy for focal-onset seizures with and without TC seizures in patients ≥14 years; adjunctive therapy for focal-onset and generalized seizures associated with LGS in patients aged 2-14	For severe refractory epilepsy ONLY	Contraindicated in patients with hepatic dysfunction, history of blood dyscrasias; use with caution in patients with renal dysfunction; pregnancy category C
Gabapentin Tablet, capsule, oral solution	Binds to presynaptic α2δ subunit of calcium channels with unknown antiseizure effect	Adjunctive therapy for focal-onset seizures with and without TC seizures in patients ≥3 years	Useful in postherpetic neuralgia, chronic pain, and neuropathy; few drug–drug interactions	Considered weakly efficacious; potential abuse when taken with opioids; withdrawal reaction characterized by anxiety, insomnia, nausea, sweating, and increased pain; absorption may be impaired for doses >1,200 mg; no adequate data in pregnancy—may cause fetal harm
Lamotrigine Tablet, chewable tablet[a], ODT[b], XR tablet[a]	Enhances fast inactivation of voltage-gated sodium channels	Adjunctive therapy in focal-onset and TC seizures, generalized seizures of LGS in patients ≥2 years of age; monotherapy in patients with focal-onset seizures ≥16 years of age	Useful in bipolar disease; XR useful in nonadherence as dosed once daily	Slow titration required to avoid rash including SJS; rash more likely to occur if patient with prior rash to other ASD and concomitant use of valproic acid; rash incidence higher in children; may exacerbate myoclonus; dosage adjustment required in patients with moderate and severe liver impairment; no adequate data in pregnancy—may cause fetal harm
Levetiracetam Tablet, XR tablet[a], injectable solution	Binds to and selectively inhibits synaptic vesicle SV2A protein thereby preventing neurotransmitter release	Adjunctive therapy for focal-onset seizures in patients ≥4 years of age, myoclonic seizures in patients with JME ≥12 years of age, and generalized TC seizures in patients ≥6 years of age with generalized epilepsy	Minimal drug–drug interactions; XR useful in nonadherence as dosed once daily	May worsen depression, PTSD, anxiety, thought disorders; dose adjustment in dialysis/renal failure is necessary; pregnancy category C
Oxcarbazepine Tablet, tablet ER[a], liquid suspension[a]	Enhances fast inactivation of voltage-gated sodium channels	Monotherapy and adjunctive therapy for focal-onset seizures in patients ≥4 years of age; adjunctive therapy for focal-onset seizures in patients ≥2 years of age and <4 years of age	Useful in bipolar disorder; ER useful in nonadherence as dosed once daily	Higher incidence of hyponatremia (as high as 25%); must check HLA-B*1502 in Asians to predict SJS or TEN; active MHD metabolite may decrease in pregnancy; no adequate data in pregnant women—may cause fetal harm

DDI: Effect of Drug on Concomitant ASD	DDIs: Effect of Concomitant ASDs on Drug	Common and Dose-Related Adverse Effects	Rare and Serious Adverse Effects[a]	Long-Term Adverse Effects
May increase levels of eslicarbazepine, ethosuximide, felbamate, lamotrigine, oxcarbazepine, phenytoin, phenobarbital, rufinamide, topiramate	Carbamazepine, phenobarbital, phenytoin, primidone decrease levels; felbamate can increase levels; estrogen OCPs may affect levels	GI effects including abdominal pain/GI upset (worse with valproic acid IR), constipation, diarrhea, anorexia, increased appetite, weight gain, nausea/vomiting; CNS effects including blurred vision, ataxia, dizziness, headache, insomnia, nystagmus, somnolence, thinking abnormal, tremor; dose dependent thrombocytopenia (associated with valproate concentrations >100 mg/mL; 693 umol/L).	Boxed warning: hepatotoxicity especially for children <2 years of age and with mitochondrial disorders; fetal risk including neural tube defects, other major malformations, and decreased IQ; pancreatitis including fatal hemorrhagic pancreatitis Hyperammonemia with and without encephalopathy; hypothermia with and without hyperammonemia; DRESS; bleeding and other hematopoietic disorders	Hair and nail changes including alopecia, hirsutism, hair texture and color changes, nail and nail bed disorders; irregular menses and polycystic ovary-like syndrome; weight gain; cerebral pseudoatrophy; osteoporosis and osteopenia
Phenytoin, valproate, carbamazepine-epoxide, phenobarbital levels increased; carbamazepine levels decreased; estrogen OCP levels not affected	Carbamazepine, phenobarbital, phenytoin, primidone decrease levels; valproate does not affect levels to a clinically significant degree	GI effects including anorexia, vomiting, nausea; CNS effects including insomnia, headache, dizziness, somnolence	Boxed warning: Irreversible fatal aplastic anemia with greater risk in women, or history of cytopenia, ASD allergy or significant toxicity, viral infection, and/or immunologic problems; acute liver failure	Aplastic anemia with reported onset between 5-30 weeks; acute liver failure with reported onset occurring in 5 weeks
		CNS effects including somnolence, dizziness, ataxia, fatigue, nystagmus; peripheral edema and weight gain; GI effects including nausea/vomiting	Anaphylaxis, angioedema, DRESS, neuropsychiatric symptoms in children 3 to 12 years of age	Weight gain, peripheral edema
Does not inhibit liver enzymes	Valproate increases lamotrigine levels by 2x; carbamazepine, phenytoin, phenobarbital, primidone decrease levels by 40%; estrogen OCPs decrease lamotrigine by 50%	CNS effects including dizziness, headache, diplopia, ataxia, blurred vision, somnolence, tremor; GI effects including nausea/vomiting, abdominal pain, diarrhea; other effects including rhinitis, pharyngitis, infection, fever; rash	Boxed warning: Rash including SJS, TEN with increased risk if given with valproate, exceeding recommended initial dose or dose escalation DRESS; blood dyscrasias; hemophagocytic lymphohistiocytosis (HLH)	Rash usually appears after 3-4 weeks of therapy and is typically generalized, erythematous, and morbilliform but can progress to SJS
		CNS effects including somnolence, fatigue; behavior effects including aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, irritability	Psychosis, hallucinations	
Inhibitor of CYP2C19 and inducer of CYP3A4/5; increases phenytoin levels; decreases lamotrigine levels through UGT induction; decreases estrogen OCP levels	Carbamazepine, phenytoin and phenobarbital decreases active metabolite levels	CNS effects including dizziness, somnolence, diplopia, fatigue, ataxia, abnormal vision, headache, nystagmus, tremor; GI effects including nausea, vomiting	Hyponatremia; rash (SJS, TEN); DRESS; blood dyscrasias	Hyponatremia

ASD and Available Formulations	Postulated Mechanism of Action	FDA Indication	Advantages	Disadvantages
Tiagabine Tablet	Inhibitor of GABA reuptake transporter GAT1	Adjunctive therapy for focal-onset seizures in patients ≥12 years of age		Has been associated with new-onset seizure, status epilepticus, and exacerbation of EEG abnormalities in those with existing epilepsy; dosage reduction may be necessary in patients with liver disease; pregnancy category C
Topiramate Sprinkle capsule, tablet, XR tablet, capsule, capsule ER	Antagonizes voltage-gated sodium channel; binds to $GABA_A$ receptor and augments GABAergic transmission, antagonizes AMPA/kainate glutamate receptor, weak carbonic anhydrase inhibitor	Monotherapy and adjunctive therapy for focal-onset seizures or primary generalized TC seizures in patients ≥2 years of age; adjunctive therapy for patients with LGS ≥2 years of age	Useful in comorbid migraine and obesity; XR useful in nonadherence as dosed once daily	Avoid in patients with preexisting cognitive issues; renally dose adjust with CrCl <70 mL/min; can cause fetal harm
Zonisamide Capsule	Enhances fast inactivation of voltage-gated sodium channels; inhibits T-type calcium channels; weak carbonic anhydrase inhibitor	Adjunctive therapy for focal-onset seizures in adults	Useful in tremor; useful in nonadherence as dosed once daily	Contraindicated in those with sulfa allergy; dose efficacy may plateau at 400 mg; should not be used in renal failure due to increases in SCr and BUN and possible effects on GFR; pregnancy category C
Third-Generation ASDs				
Brivaracetam (Schedule V) Tablet, oral Solution, injection Solution	Binds to and selectively inhibits synaptic vesicle SV2A protein thereby preventing neurotransmitter release	Monotherapy and adjunctive therapy for focal-onset seizures in patients ≥4 years of age; injection solution approved for ≥16 years of age	Consider converting well-controlled patients from levetiracetam if intolerable psychiatric side effects	Dosage adjustments required in hepatic impairment; no adequate data in pregnancy—may cause fetal harm
Cannabidiol (Schedule V) Oral solution	Unknown—does not act on cannabinoid receptors	Monotherapy or adjunctive therapy for patients with LGS and Dravet syndrome ≥2 years of age	Useful for refractory seizures in LGS and Dravet syndrome	Avoid in patients with hypersensitivity reactions to cannabis, THC; liver function and bilirubin monitoring before and at 1, 3, and 6 months of treatment specially if given with valproate; no adequate data in pregnant woman—may cause fetal harm
Clobazam (Schedule IV) Tablet, oral suspension	Binds $GABA_A$ receptor and potentiates GABA by modulating chloride conductance	Adjunctive therapy for patients with LGS ≥2 years of age		Monitor patients with history of substance abuse; use with other CNS depressant may produce additive CNS effects; may cause respiratory depression, coma, and death; no adequate data in pregnant women—may cause fetal harm
Eslicarbazepine Tablet	Selectively enhances slow inactivation of voltage-gated sodium channels	Monotherapy or adjunctive therapy for focal-onset seizures in patients ≥4 years of age	Useful in nonadherence as dosed once daily	Avoid in severe hepatic impairment; dose adjustment in renal failure; avoid concomitant use with carbamazepine and oxcarbazepine; no adequate data in pregnancy—may cause fetal harm
Lacosamide (Schedule V) Tablet, oral solution, Injectable solution	Selectively enhances slow inactivation of voltage-gated sodium channels	Monotherapy and adjunctive therapy for focal-onset seizures in patients ≥4 years of age; injectable solution approved in patients ≥17 years of age	Minimal drug–drug interactions	Avoid in third-degree heart block; use with caution in patients with underlying proarrhythmic conditions or on concomitant medications that affect cardiac conduction; no adequate data in pregnancy—may cause fetal harm

DDI: Effect of Drug on Concomitant ASD	DDIs: Effect of Concomitant ASDs on Drug	Common and Dose-Related Adverse Effects	Rare and Serious Adverse Effects[a]	Long-Term Adverse Effects
	Carbamazepine, phenytoin, primidone, phenobarbital decreases levels; valproate increases levels by 40%	CNS effects including dizziness, lightheadedness, somnolence, thinking abnormal; behavior effects including asthenia, lack of energy, nervousness, irritability, difficulty with concentration or attention; GI effects including abdominal pain and nausea	Increase in generalized seizures and nonconvulsive SE in patients with refractory epilepsy; occurrence of seizures and SE in patients without epilepsy; moderately severe to incapacitating generalized weakness; exacerbation of EEG abnormalities; rash including SJS	Possibility of long-term ophthalmologic effects
Weak inhibitor of CYP2C19 and inducer of CYP3A4; decreases estrogen OCP levels	Phenytoin carbamazepine decreases levels	CNS effects including fatigue, difficulty concentrating, confusion, language problems, tremor paresthesias; behavioral effects including nervousness, anxiety	Renal stones; glaucoma; oligohidrosis and hyperthermia; metabolic acidosis; rash (SJS, TEN); hypothermia and hyperammonemia with and without encephalopathy when used with valproate	Weight loss, renal stones, metabolic acidosis
	CYP3A4 inhibitors or inducers may alter levels; carbamazepine, phenobarbital, phenytoin, valproate decrease levels	CNS effects including sedation, ataxia, confusion, depression, difficulty concentrating, word-finding difficulties	Oligohidrosis and hyperthermia; renal stones; metabolic acidosis; rash (SJS, TEN); DRESS; fulminant hepatic necrosis; blood dyscrasias	Weight loss, renal stones, metabolic acidosis
Increases carbamazepine metabolite; increases phenytoin levels	CYP2C19 inhibitors may alter levels	CNS effects including sedation, fatigue, ataxia, nystagums; behavioral effects including irritability, aggressive behavior, anxiety; GI effects including nausea, vomiting	Angioedema; bronchospasm; decreased neutrophils; psychosis	
Increases lamotrigine levels; increase levels of clobazam active metabolite by 3 times	CYP3A4 and CYP2C19 inhibitors will increase levels; CYP3A4 and CYP2C19 inducers will decrease levels	CNS effects including somnolence, fatigue, malaise, asthenia; sleep disorders including insomnia, poor quality sleep; GI effects including decreased appetite; diarrhea; transaminase elevations	Hepatotoxicity; hypoxia; respiratory failure	
Inhibitor of CYP2C9 and inducer of CYP3A4; affects levels of CYP2C9, CYP3A4 substrates; decreases estrogen OCP levels	Carbamazepine, felbamate, phenobarbital, phenytoin, primidone decreases levels	CNS effects including somnolence, sedation, lethargy; pyrexia; constipation; drooling	Boxed warning: Concomitant use with opioids increases risk of death Rash (SJS, TEN); anemia; liver enzyme elevations; respiratory depression	
Inhibitor of CYP2C19; affects carbamazepine, phenytoin, phenobarbital, primidone levels; decreases estrogen OCP levels	Carbamazepine, phenobarbital, primidone, and phenytoin decreases levels	CNS effects including dizziness, somnolence, nausea, headache, diplopia, fatigue, vertigo, ataxia, blurred vision, tremor	Hyponatremia; rash (SJS); anaphylaxis, angioedema, DRESS; cardiac effects including prolonged PR interval, AV block; hepatotoxicity; blood dyscrasias	Hyponatremia
Substrate of CYP3A4, CYP2C9, and CYP2C19; carbamazepine, phenytoin, phenobarbital, primdone, decrease levels by 15%-20%	CYP2C19 inhibitor but no clinically significant effects	CNS effects including ataxia, dizziness, diplopia, headache, tremor; GI effects including nausea, vomiting	Cardiac effects including AV conduction abnormalities, prolonged PR interval, atrial arrhythmias, syncope (especially in patients with diabetes)	

ASD and Available Formulations	Postulated Mechanism of Action	FDA Indication	Advantages	Disadvantages
Perampanel (Schedule III) Tablet, oral suspension	Selectively and noncompetitively antagonizes AMPA glutamate receptor on postsynaptic neuron	Monotherapy for focal-onset seizures in patients ≥4 years of age; adjunctive therapy for TC seizures in patients ≥12 years of age	Useful in mixed seizure types; useful in nonadherence as dosed once daily	Avoid in active psychosis or unstable recurrent affective disorders with significant hostility or aggressive behavior; avoid in severe hepatic/renal impairment or hemodialysis; no adequate data in pregnancy—may cause fetal harm
Pregabalin (Schedule V) Capsule, tablet CR, oral solution	Binds to presynaptic α2δ subunit of calcium channels	Adjunctive therapy for focal-onset seizures in patients ≥4 years of age	Useful in patients with diabetic peripheral neuropathy, postherpetic neuralgia, fibromyalgia, neuropathic pain with spinal cord injury; minimal DDIs due to renal excretion	Preexisting cognitive disorders; no adequate data in pregnancy—may cause fetal harm
Rufinamide Tablet, oral suspension	Selectively enhances fast inactivation of voltage-gated sodium channels	Adjunctive therapy for patients with LGS ≥1 year of age		Contraindicated in severe liver impairment or in familial short QT syndrome; use caution with other drugs that shorten QT interval; no adequate data in pregnancy—may cause fetal harm
Vigabatrin Tablet, powder packet	Binds to and irreversibly inhibits GABA transaminase	Adjunctive therapy for refractory focal-onset seizures in patients ≥10 years of age (not indicated as first-line); monotherapy for infantile spasms in patients 1 month to 2 years of age	Useful in infantile spasms for whom potential benefit outweighs risk of vision loss	Permanent vision loss in most patients after a certain duration of exposure requiring eye exams Q3 months; requires REMS program registration; no adequate data in pregnancy—may cause fetal harm

[a]All ASDs may increase the risk of suicidal thoughts or behavior and patients treated with an ASD should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior.

AMPA, A-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid; ASD, antiseizure drug; AV, atrioventricular; BUN, blood urea nitrogen; C_{max}, maximum concentration; CNS, central nervous system; CR, controlled-release; CrCl, creatinine clearance; CYP, cytochrome p450 isoenzyme system; DDI, drug–drug interaction; DR, delayed-release; DRESS, drug rash with eosinophilia and systemic symptoms; EEG, electroencephalogram; FDA, Food and Drug Administration; ER, extended release; GABA, gamma-aminobutyric acid; GAT1, GABA transporter type 1; GI, gastrointestinal; GFR, glomerular filtration rate; HLA, human leukocyte antigen; IQ, intelligence quotient; IR, immediate release; IV, intravenous; LGS, Lennox–Gastaut syndrome; OCP, oral contraceptives; ODT, orally dissolving tablet; PTSD, posttraumatic stress disorder; SJS, Steven–Johnson syndrome; TEN, toxic epidermal necrolysis; TBI, traumatic brain injury; TC, tonic–clonic; UGT, UDP-glucuronosyltransferase; XR, extended-release.

Data from References 17-20, 23, 36-56, 69.

DDI: Effect of Drug on Concomitant ASD	DDIs: Effect of Concomitant ASDs on Drug	Common and Dose-Related Adverse Effects	Rare and Serious Adverse Effects[a]	Long-Term Adverse Effects
Modest enzyme inducer at high doses; carbamazepine, eslicarbazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, topiramate decrease levels; valproate has no effect on levels; decreases estrogen OCP levels		CNS effects including dizziness, somnolence, fatigue, falls, vertigo, ataxia, headache, confusion; GI effects including nausea, weight gain, vomiting, abdominal pain; behavioral effects including irritability anxiety	Boxed warning: Aggression, hostility, irritability, anger, and homicidal ideation	Weight gain
		CNS effects including dizziness, somnolence, blurred vision, difficulty with concentration and attention; dry mouth; edema and weight gain	Potential for abuse when taken with opiates	Weight gain
Weak inhibitor of CYP2E1; weak inducer of CYP3A4; modestly decreases levels of carbamazepine, lamotrigine; increases levels of phenobarbital, phenytoin; decreases estrogen OCP levels	Carbamazepine, phenobarbital, phenytoin decrease levels by 19%-46%; valproate increases levels up to 70%	CNS effects including somnolence, fatigue, coordination abnormalities, dizziness, gait disturbances, ataxia; GI effects including nausea	DRESS; rash (SJS); status epilepticus; leukopenia; QT interval shortening	
Inducer of CYP2C9; decreases levels of phenytoin by 20%; possibly increases levels of carbamazepine by 10%; increases C_{max} of clonazepam		CNS effects including fatigue, somnolence, nystagmus, tremor, blurred vision, memory impairment, abnormal coordination, confusion; weight gain; edema; peripheral neuropathy In pediatric patients: aggression; infection including upper respiratory tract infection, bronchitis, ear infection, and acute otitis media	Boxed warning: Progressive and permanent bilateral peripheral visual constriction including tunnel vision; reduced visual acuity Seizure exacerbation, particularly absence and myoclonic seizures in patients with generalized epilepsies; anemia	Onset of vision loss is unpredictable and can occur after weeks, months, or years with risk increasing in a dose-related and life exposure-related manner; abnormal MRI signal changes in infants treated for infantile spasms strongly suggestive of intramyelinic edema in select brain areas

TABLE 73-6 Evidence for ASD Efficacy, Effectiveness, and Tolerability as Initial Monotherapy in New-Onset or Untreated Epilepsy from AAN and ILAE

	AAN 2004: Focal/Mixed Adult	AAN 2004: Absence Children	AAN 2018: Focal or Unclassified TCS Adult	AAN 2018: GE/ Unclassified GTCS Adults and Children	AAN 2018: Focal, GE, or Unclassified GTCS Adults and Adolescents	AAN 2018: Focal or Unclassified GTCS Children	AAN 2018: Absence Children
First-Generation ASDs							
CBZ	Level A effective		Level U data lacking for GBP, OXC, TPM to be considered over CBZ; Level C VGB less effective/more toxic than CBZ		No recommendation data lacking to compare CBZ-CR, LEV, and VPA-ER		
ETX							Level B ETX should be used before LTG
PB	Level A effective						
PHT	Level A effective		Level U data lacking to consider TPM over PHT				
PRM							
VPA	Level A effective			No recommendation data lacking to compare LTG with VPA	No recommendation data lacking to compare CBZ-CR, LEV, and VPA-ER		Level B VPA should be used before LTG
Second-Generation ASDs							
FBM			Level U data lacking				
GBP	Level A effective		Level C GBP may be possibly effective in ages ≥60 years; Level U Data lacking to consider GBP over CBZ				
LTG	Level A effective	Level B probably effective	Level B probably effective; Level B probably effective in age ≥60 years; Level C PGB 150 mg/day possibly less effective than LTG 100 mg/day	No recommendation data lacking to compare LTG with VPA			Level B ETX and VPA should be considered before LTG
LEV	Level U data lacking	Level U data lacking	Level C Possibly effective		No recommendation data lacking to compare CBZ-ER, LEV, and VPA ER		
OXC	Level A effective	Level U data lacking	Level U data lacking for use of OXC over CBZ				
TGB	Level U data lacking	Level U data lacking					
TPM	Level A effective	Level U data lacking	Level U data lacking for use of TPM over CBZ or PHT	No recommendation data lacking to compare TPM with VPA		No recommendation TPM 400 mg/day more efficacious than 50 mg/day	
ZON	Level U data lacking	Level U data lacking	Level C possibly effective				
Third-Generation ASDs							
CLB			Level U data lacking				

ILAE: Focal Adults	ILAE: Focal Children	ILAE: Focal Elderly	ILAE: GTCS Adults	ILAE: Children GTCS	ILAE: Absence Children	ILAE: BECTS Children	ILAE: JME
Level A established effective	Level C possibly effective	Level C possibly effective	Level C (Class IV evidence CBZ may worsen GTCS)	Level C (Class IV evidence CBZ may worsen GTCS)	Class IV may worsen seizures	Level C possibly effective	Class IV CBZ may worsen AS, MS, GTCS
					Level A established effective		
Level A established effective	Level C possibly effective		Level C possibly effective	Level C possibly effective			
Level A established effective	Level C possibly effective		Level C possibly effective (Class IV PHT may worsen GTCS)	Level C possibly effective (Class IV PHT may worse GTCS)	Class IV may worsen seizures		Class IV PHT may worsen AS, MS, GTCS
Level D potentially effective			Level C possibly effective				
Level B probably effective	Level C possibly effective	Level D potentially effective	Level C possibly effective	Level C possibly effective	Level A established effective	Level C possibly effective	Level D potentially effective
Level C possibly effective		Level A established effective	Level D potentially effective		Level F ineffective	Level D potentially effective	Class IV PHT may worsen AS, MS, GTCS
Level C possibly effective	Level D potentially effective	Level A established effective	Level C possibly effective		Level C possibly effective		Level F LTG worsens seizures
Level A established effective		Level D potentially effective			No conclusion	Level D potentially effective	
Level C possibly effective	Level A established effective		Level C possibly effective	Level D potentially effective	Class IV may worsen seizures	Level D potentially effective	Class IV PHT may worsen AS, MS, GTCS
					Class IV may worsen seizures		Class IV PHT may worsen AS, MS, GTCS
Level C possibly effective	Level C possibly effective	Level D potentially effective	Level C possibly effective	Level C possibly effective			Level D potentially effective
Level A established effective	Level D potentially effective						
	Level D potentially effective						

	AAN 2004: Focal/Mixed Adult	AAN 2004: Absence Children	AAN 2018: Focal or Unclassified TCS Adult	AAN 2018: GE/ Unclassified GTCS Adults and Children	AAN 2018: Focal, GE, or Unclassified GTCS Adults and Adolescents	AAN 2018: Focal or Unclassified GTCS Children	AAN 2018: Absence Children
PGB			Level C PGB 150 mg/day less effective than LTG 100 mg/day				
VGB			Level C VGB less effective than CBZ-IR and more toxic; Level U Data lacking				

AS, absence seizures; ASD, antiseizure drug; AAN, American Academy of Neurology; BECTS, Benign Epilepsy with Centro-Temporal Spikes; CBZ, carbamazepine; CLB, clobazam; CR, controlled release; ER, extended release; ETX, ethosuximide; FBM, felbamate; GBP, gabapentin; GE, generalized epilepsy; GTCS, generalized tonic–clonic seizures; IR, immediate release; JME, Juvenile Myoclonic Epilepsy; LCM, lacosamide; LEV, levetiracetam; LGS, Lennox–Gastaut syndrome; LTG, lamotrigine; MS, myoclonic seizures; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; PRM, primidone; PER, perampanel; RFN, rufinamide; TCS, tonic–clonic seizures; TGB, tiagabine; TPM, topiramate; VGB, vigabatrin; VPA, valproate; VGB, vigabatrin; XR, extended release; ZON, zonisamide.

AAN 2004 and AAN 2018 Levels of Evidence:

Level A: Established as effective, ineffective, or harmful for the given condition in the specified population; Level A rating requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B: Probably effective, ineffective, or harmful for the given condition in the specified population. Level B rating requires at least one convincing class II study or at least three consistent class III studies.

Level C: Possibly effective, ineffective, or harmful for the given condition in the specified population. Level C rating requires at least two convincing and consistent class III studies.

Level U: Data inadequate or conflicting; given current knowledge, treatment is unproven.

ILAE 2013 Levels of Evidence:

Level A: ASD established as efficacious or effective as initial monotherapy. Consists of 1 Class I studies or meta-analysis meeting class I criteria sources OR 2 Class II studies.

Level B: ASD probably efficacious or effective as initial monotherapy. Consists of 1 Class II study or meta-analysis meeting class II criteria.

Level C: ASD possibly efficacious or effective as initial monotherapy. Consists of 2 Class III double-blind or open-label studies.

ILAE: Focal Adults	ILAE: Focal Children	ILAE: Focal Elderly	ILAE: GTCS Adults	ILAE: Children GTCS	ILAE: Absence Children	ILAE: BECTS Children	ILAE: JME
Level C possibly effective	Level C possibly effective		Level D potentially effective		Class IV may worsen seizures		Class IV PHT may worsen AS, MS, GTCS

Level D: ASD potentially efficacious or effective as initial monotherapy. Consists of 1 Class III double-blind or open-label study OR 1 Class IV clinical studies OR data from expert committee reports, opinions from experienced clinicians.

Level E: No data available to assess if ASD is effective as initial monotherapy. Consists of absence of directly applicable clinical evidence upon which to base a recommendation.

Level F: ASD established as ineffective or significant risk of seizure aggravation. Consists of positive evidence of lack of efficacy or effectiveness based on class I to IV studies ORsignificant risk of seizure aggravation based on class I to IV studies.

Class Studies

Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required: (a) primary outcome(s) is/are clearly defined (b) exclusion/inclusion criteria are clearly defined; (c) adequate accounting for drop-outs and cross-overs with numbers sufficiently low to have minimal potential for bias; (d) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above OR a RCT in a representative population that lacks one criterion a–d.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

Data from References 27,70,71.

TABLE 73-7 Evidence for ASD Efficacy and Tolerability in Refractory Epilepsy

	AAN 2004: Adjunct Therapy Focal Adults	AAN 2004: Mono-therapy Focal Adults	AAN 2004: Primary Generalized Adults and Children	AAN 2004: Symptomatic Generalized	AAN 2004: Adjunct Therapy Focal Children	AAN 2004: LGS Drop Attacks in Adults and Children	AAN 2018: Adjunct Focal Adult	AAN 2018: Monotherapy Focal Adults	AAN 2018: Adjunct GE Adults and Children	AAN 2018: Adjunct LGS Adults and Children	2018 AAN: Adjunct Focal Children and Adolescents
Second-Generation ASDs											
FBM								Level U data lacking			
GBP	Level A effective	Level U data lacking	Level U data lacking	Level U data lacking	Level A effective			Level U data lacking			
LTG	Level A effective	Level B probably effective	Level U data lacking	Level A/B probably effective	Level A effective	Level A effective		Level U data lacking	Level B LTG IR and XR probably effective		
LEV	Level A effective	Level U data lacking	Level U data lacking	Level U data lacking	Level U data lacking			Level U data lacking	Level B probably effective in JME		Level B probably effective in 1 month to 16 years
OXC	Level A effective	Level A effective	Level U data lacking	Level U data lacking	Level A effective		Level C XR	Level U data lacking			Level B probably effective in 1 month to 4 years of age
TGB	Level A effective	Level U data lacking	Level U data lacking	Level U data lacking	Level U data lacking			Level U data lacking			Level U data lacking
TPM	Level A effective	Level A effective	Level A effective	Level A/B probably effective	Level A effective	Level A effective	Level B XR probably effective	Level U data lacking			
ZON	Level A effective	Level U data lacking	Level U data lacking	Level U data lacking	Level U data lacking			Level U data lacking			Level B probably effective in 6-17 years of age
Third-Generation ASDs											
CLB							Level C possibly effective	Level U data lacking		Level B probably effective	Level U data lacking
ESL							Level B probably effective	Level C possibly effective			Level U data lacking
LCM							Level B probably effective	Level U data lacking			Level U data lacking
PER							Level A effective	Level U data lacking			Level U data lacking
PGB							Level A effective	Level U data lacking			Level U data lacking
RFN							Level A effective but not first-line	Level U data lacking		Level A effective	Level U data lacking
VGB							Level A effective but not first-line	Level U data lacking	Level C possibly effective		Level U data lacking

AS, absence seizures; ASD, antiseizure drug; AAN, American Academy of Neurology; BECTS, Benign Epilepsy with Centro-Temporal Spikes; CBZ, carbamazepine; CLB, clobazam; CR, controlled release; ER, extended release; ETX, ethosuximide; FBM, felbamate; GBP, gabapentin; GE, generalized epilepsy; GTCS, generalized tonic–clonic seizures; IR, immediate release; JME, Juvenile Myoclonic Epilepsy; LCM, lacosamide; LEV, levetiracetam; LGS, Lennox–Gastaut syndrome; LTG, lamotrigine; MS, myoclonic seizures; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; PRM, primidone; PER, perampanel; RFN, rufinamide; TCS, tonic–clonic seizures; TGB, tiagabine; TPM, topiramate; VPA, valproate; VGB, vigabatrin; ZON, zonisamide.

AAN 2004 and AAN 2018 Levels of Evidence:

Level A: Established as effective, ineffective, or harmful for the given condition in the specified population; Level A rating requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B: Probably effective, ineffective, or harmful for the given condition in the specified population. Level B rating requires at least one convincing class II study or at least three consistent class III studies.

Level C: Possibly effective, ineffective, or harmful for the given condition in the specified population. Level C rating requires at least two convincing and consistent class III studies.

Level U: Data inadequate or conflicting; given current knowledge, treatment is unproven.

Class Studies

Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required: (a) primary outcome(s) is/are clearly defined (b) exclusion/inclusion criteria are clearly defined; (c) adequate accounting for drop-outs and cross-overs with numbers sufficiently low to have minimal potential for bias; (d) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above OR a RCT in a representative population that lacks one criterion a–d.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

Data from References 70, 71.

The limited evidence for long-term efficacy of ASDs as initial monotherapy in new-onset or untreated epilepsy has been recently reviewed by the ILAE, focusing on six age-related seizure types and two epilepsy syndromes. As part of this review, some ASDs were labeled as efficacious, or as probably efficacious as initial monotherapy in certain seizure types, while others could only be labeled as possibly or potentially efficacious based on the evidence in the literature.[27] Furthermore, there is limited evidence that some ASDs may possibly or potentially precipitate or aggravate certain seizure types, and therefore it is suggested that they should be used with caution in those patients (eg, carbamazepine and phenytoin in generalized-onset tonic–clonic seizure types or carbamazepine, gabapentin, oxcarbazepine, phenytoin, tiagabine, and vigabatrin among others in children with absence seizures or in JME).[27] The ILAE findings are summarized in Table 73-6. More recently, in 2018 the American Academy of Neurology also summarized the evidence for ASD efficacy based on best available current evidence in both new-onset epilepsy and refractory epilepsy.[70,71] These are also summarized in Tables 73-6 and 73-7.

ASD Effectiveness

In general, ASD “efficacy” is a measure of the ability of an ASD to prevent seizures or reduce the frequency of seizures in “ideal” circumstances. In contrast, ASD “effectiveness” is a more pragmatic measure of ASD benefit in “real-world” clinical setting and takes into account tolerability and the adverse

effect profile of an ASD. While ASD “efficacy” is generally considered similar in focal-onset epilepsies, ASD “effectiveness” varies and may be dependent on individual patient characteristics and patient-specific factors. Therefore, knowledge of individual ASD side-effect profiles is important in determining ASD effectiveness and plays a significant role in selection and optimization of ASD therapy.

In general, adverse effects can be categorized into two categories, dose-related (eg, concentration dependent) adverse effects and idiosyncratic adverse effects. As ASDs are often used life-long, adverse effects associated with chronic long-term use and related to overall cumulative exposure should also be recognized. A general approach to understanding these different categories of ASD adverse effects is reviewed in the following sections. For specific important adverse effects associated with each individual ASD, please refer to Table 73-5.

Concentration-Dependent Adverse Effects Associated with ASDs

All ASDs have some common dose-related adverse effects that they share as a class, as well as their own unique dose-related adverse effect profile. In general, dose-related adverse effects are related to medication mechanism of action. As all ASDs act on the CNS to exert antiseizure effects, all ASDs commonly cause dose-related CNS side effects including sedation, dizziness, blurred or double vision, difficulty with concentration, ataxia, and impaired cognition which is of particular concern. Barbiturates and sodium channel inhibitors in particular appear to cause more sedation and cognitive impairment than other commonly used ASDs (although in children, barbiturates paradoxically causes hyperactivity). While newer agents have been associated with a lower incidence of neurotoxic side effects, topiramate, in particular, is a newer agent known to cause substantial cognitive impairment.[72]

Concentration-dependent effects are common and troublesome but not usually life-threatening. As they are dose-related, they can be avoided by titrating the dose upward very slowly in many cases or can be alleviated by decreasing the dose.[73] Although they are more likely to occur at higher doses and higher concentration ranges, it is important to note that patients dosed and maintained below or within “therapeutic concentration ranges” may still experience these toxicities.[74] Patients who change from polytherapy with multiple drugs to dual therapy or monotherapy may also demonstrate improvement in neurotoxic

symptoms, especially if principles of rational polytherapy are used.

Idiosyncratic Adverse Effects Associated with ASDs

More uncommon are idiosyncratic side effects, which are generally related to chemical characteristics of the ASD and individual patient susceptibility, rather than the ASD's pharmacology. While most idiosyncratic reactions are mild, they can be serious and even life threatening and can affect virtually any organ, although the skin, liver, and blood cells are the most common targets. The most widely recognized idiosyncratic reactions associated with ASDs are drug rashes, which are more common with particular ASDs (eg, carbamazepine, phenytoin, phenobarbital, and lamotrigine among others) but may occur with any ASD. While these rashes are often mild, some can progress to severe life-threatening rashes including Steven–Johnsons syndrome (SJS) or toxic epidermal necrolysis (TEN). Hepatitis or blood dyscrasias have also occurred with many ASDs and can progress to acute hepatic failure or fatal aplastic anemia such as those rare cases reported with felbamate as well as other ASDs. Additionally, ASD treatment itself may sometimes worsen seizures and can represent a paradoxical toxic effect of the drug.[72,73]

A warning on suicidal behavior and ideation also accompanies all ASDs. This is based on pooled analyses of almost 200 placebo-controlled trials of 11 different ASDs showing that patients randomized to an ASD had approximately twice the risk of suicidal thinking or behavior compared to patients randomized to placebo. While the estimated incidence of suicidal ideation was low, less than 0.5% of patients on ASDs, this was greater than the 0.24% of patients on placebo. While some believed that this risk is nonsignificant, responsible providers must carefully assess this risk when evaluating their patients for ASD therapy, especially as depression and anxiety are common comorbid conditions in epilepsy. Patients and caregivers should be informed that ASDs increase the risk of suicidal thoughts and should be advised to be on the alert for any unusual changes in mood or behavior.[73]

Adverse Effects Associated with Chronic ASD Therapy

Antiseizure drugs are often used life-long and as such adverse effects have been recognized. One such adverse effect of chronic ASD treatment is osteomalacia and osteoporosis.[75,76] The effects on bone can range from asymptomatic high-turnover disease with findings of normal bone mineral density, to markedly

decreased bone mineral density sufficient to warrant the diagnosis of osteoporosis. It has been hypothesized that mechanistically certain drugs, including phenytoin, phenobarbital, carbamazepine, oxcarbazepine, felbamate, and valproate, may interfere with vitamin D metabolism to cause this adverse effect.[77] It is currently unknown whether other ASDs also cause osteomalacia and/or osteoporosis, but patients receiving these drugs should receive supplemental vitamin D and calcium, as well as bone mineral density testing if other risk factors for osteoporosis are present.

Antiseizure Drugs

Of the ASDs currently available, their mechanisms of action fall into four broad categories: (1) modification of ionic conductance (eg, sodium channel inhibition, calcium channel inhibition); (2) enhancement of GABAergic (inhibitory) neurotransmission (eg, $GABA_A$-receptor agonism, inhibition of GABA metabolism/reuptake); (3) suppression of excitatory (usually glutamergic) excitatory neurotransmission (eg, inhibition of kainate/α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid [AMPA] receptor, inhibition of N-methyl D-aspartate [NMDA] receptor, and SV2A binding and modulation of excitatory neurotransmitter release); and lastly (4) other unique or unknown mechanisms.[69] While it is useful to know mechanism of action for rational therapy and polytherapy, it is easiest to organize the ASDs into three generations which are not determined by structure or mechanism of action but by the time period in which they were FDA approved. Each of the three generations of ASDs have specific characteristics that should be considered during selection of initial and subsequent ASD therapy. The following section is meant to highlight these major characteristics. Certain unique characteristics of specific drugs within each class are also highlighted. For more specific information on pharmacokinetics, dosing, FDA-approved indication, preferred use in therapy, drug interactions, and side effects, see Tables 73-2 to 73-5. For additional detailed drug information on each ASD, the reader is referred to the individual FDA-approved ASD package inserts.

First-Generation ASDs

The first-generation ASDs were first approved by the FDA from 1908 to 1978 and include (1) carbamazepine; (2) clonazepam; (3) ethosuximide; (4) phenobarbital; (5) phenytoin (and its esterified prodrug fosphenytoin); (6) primidone; and (7) valproate. It is important to note that valproate is available as

valproic acid and divalproex, which is a specific formulation of valproate composed of sodium valproate and valproic acid in a 1:1 molar relationship. Within the gastrointestinal track, divalproex dissociates to valproate as the active form.[69] The ASDs within this class, while considered to be among the most efficacious in controlling seizures, have complex pharmacokinetics, multiple drug–drug interactions, and an increased incidence of adverse effects that, in general, make them more complicated to manage than either the second- or third-generation ASDs.

Mechanisms of Action With the exception of ethosuximide, all the first-generation ASDs have mechanisms of action that act either to primarily promote GABAergic activity or to inhibit sodium channels. The GABAergic first-generation ASDs include the barbiturate phenobarbital, primidone which is a prodrug metabolized to phenobarbital, and the benzodiazepine clonazepam which is a full $GABA_A$-receptor agonist.[20,37,69] Pharmacologically, these GABAerigic drugs bind to sites at the $GABA_A$ receptor as agonists, increasing chloride channel opening and promoting hyperpolarization, which results in cells that are less susceptible to electrical impuses.[20,37,69] In contrast, phenytoin and carbamazepine bind to voltage-gated sodium channels in their inactive form preventing repetitive and sustained firing of sodium-dependent action potentials and stabilizing the threshold against hyperexcitability.[18,19,69] Because they bind the inactive form of the sodium channel, these agents cause a voltage-dependent and use-dependent block, which may preferentially target hyperexcitable areas that fire frequently.[18,19,69] Lastly, ethosuximide has a unique mechanism of action within this class and inhibits t-type calcium channels in cells of the thalamus and the cortex, preventing the abnormal firing of these cells that occur in absence epilepsies.[38,69]

Pharmacokinetics First-generation ASDs have complex pharmacokinetics, especially phenytoin. In general, phenytoin is highly protein bound with 90% of total phenytoin being bound in individuals with normal protein status and 10% being unbound as free phenytoin. Only unbound free phenytoin is pharmacologically active.[19] Reference ranges for total and free phenytoin levels were created with this ratio in mind, with a total phenytoin level in the therapeutic range of 10 to 20 mg/L (mcg/mL; 40-79 µmol/L) corresponding to a pharmacologically active free phenytoin level of 1 to 2 mg/L (mcg/mL; 4-8 µmol/L). Both total phenytoin and free phenytoin levels are routinely used in practice to guide therapy and it is important to understand what phenytoin level

is being used to accurately interpret the true level of pharmacologically active drug. In patients with low protein status (eg, hypoalbuminemia, end-stage renal disease, critically ill patients), less than 90% of phenytoin is bound and total serum phenytoin levels in the 10 to 20 mg/L (mcg/mL; 40-79 µmol/L) range no longer correspond to an active free phenytoin level of 1 to 2 mg/L (mcg/mL; 4-8 µmol/L) and does not reflect the true level of pharmacologically active phenytoin.[78] Monitoring of free phenytoin levels better reflect the true therapeutic levels in patients with hypoalbuminemia. However, free phenytoin levels, while commonly ordered, are currently not rapidly available through most laboratories (eg, results may take days to weeks). Valproate is also extensively bound to albumin, and due to saturable binding, the valproate free fraction will increase as the total serum concentration increases.[39] Similar to phenytoin therapeutic drug monitoring, the total valproate levels may not represent the amount of free drug available to exert a pharmacologic effect. However, free valproate levels are not commonly ordered, and only total valproate levels are generally easily available. Because only total levels are practically available, it is also important to know the patient's serum albumin level and protein status to aid in interpretation of total phenytoin and valproate serum levels.[39,78] This is especially true with phenytoin as various correction equations can be used to aid in interpreting total serum phenytoin levels in patients with low protein status, including the Winter–Tozer equation.[78] Valproate levels are not routinely corrected for low protein status in clinical practice, although it is still important to be aware of its possible effect. Carbamazepine, ethosuximide, and phenobarbital are also highly protein bound, but this has less of a clinically meaningful impact in practice.[18,37,38]

Phenytoin is metabolized in the liver by CYP450 enzymes and displays Michaelis–Menten pharmacokinetics.[36] The metabolism of phenytoin is generally linear at daily doses of 300 mg and under in most patients. However, at doses greater than 300 mg daily, phenytoin may saturate its metabolizing enzymes and a small change in dose at that point can result in a disproportionally large increase in serum concentrations, potentially leading to toxicity.[19,36] This can also occur at low serum concentrations in some patients. Therefore, at phenytoin doses greater than 300 mg, it is recommended by some to increase by 30-mg increments instead of 100-mg increments.

Carbamazepine, ethosuximide, phenobarbital, and valproate are also hepatically metabolized by CYP450 enzymes but in general display linear pharmacokinetics at clinically relevant doses.[18,37–39] An exception to this is ethosuximide which displays some evidence of nonlinear kinetics at higher

concentrations.[38] Carbamazepine is a particularly strong inducer of CYP metabolism and induces its own metabolism in a process known as autoinduction, where its half-life starts decreasing 3 to 5 days after initiation of therapy with autoinduction being complete within 21 to 28 days.[18,36] Importantly, the reversal of autoinduction is rapid upon carbamazepine discontinuation.

Carbamazepine, ethosuximide, phenobarbital, phenytoin, and valproate all have narrow therapeutic ranges and require monitoring of serum concentrations (see Table 73-3 for target therapeutic ranges of specific ASDs and section "Evaluation of Therapeutic Outcomes" for role of serum concentration monitoring).[36]

Drug–Drug Interactions As all of the first-generation ASDs undergo CYP450 hepatic metabolism, they also have significant drug–drug interactions. In particular, carbamazepine, phenobarbital, and phenytoin are inducers of many CYP proteins. As such, they will affect each other's metabolism if used in combination and may result in decreased levels of one drug or the other drug. They also affect metabolism of all other ASDs and drugs that go through similar CYP450 pathways (Tables 73-2 and 73-4) and vice versa.[18,19,36,37]

Enzyme-inducing ASDs also induce uridine 5′-diphospho-glucuronosyltransferase (UGT) metabolism and have significant interactions with drugs that undergo UGT metabolism, like lamotrigine, a second-generation ASD that undergoes UGT1A4 metabolism.[18,19,36,37]

Valproate on the other hand is an inhibitor of CYP450 and UGT metabolism and inhibits the metabolism of the first-generation ASDs as well as other ASDs and drugs that go through similar CYP450 and UGT pathways. In particular, valproate decreases the clearance of phenobarbital and lamotrigine by 30% to 50% and can lead to phenobarbital and lamotrigine toxicity.[36,39]

Of note, first-generation enzyme-inducing ASDs may cause increased clearance of oral contraceptives (OCs) compromising their efficacy. The enzyme inhibitor, valproate, does not cause OC failure but OCs may cause increased valproate metabolism and subsequent increased risk in seizures. Therefore, in a patient of child bearing age with epilepsy, education around these drug interactions is a must.[18,19,37,39]

Adverse Effects The first-generation ASDs are, in general, associated with a higher incidence of dose-related and idiosyncratic adverse effects including neurotoxic side effects, hepatotoxicity, and SJS/TEN. There are also a number of

unique adverse effects associated with first-generation ASDs that are of particular note such as hyponatremia with carbamazepine, hyperactivity with phenobarbital in children, and gingival hyperplasia and osteoporosis with chronic use of phenytoin.[18,40,49] Valproate especially has a number of unique adverse effects including concentration-dependent thrombocytopenia at serum levels above 100 mg/L (mcg/mL; 693 µmol/L), hyperammonemia related to carnitine deficiency that may or may not lead to encephalopathy, idiosyncratic pancreatitis, and well-known teratogenicity.[39,79] Adverse effects of first-generation ASDs are listed in Table 73-5.

Advantages and Disadvantages First-generation ASDs are very efficacious in epilepsy. Valproate, in particular, is considered a broad-spectrum ASD and is useful in both focal-onset and generalized-onset seizures as well as various epilepsy syndromes.[27,70,71] Phenobarbital has been in use for the longest period of time and is readily available worldwide. Carbamazepine and phenytoin are very efficacious in focal-onset seizures and have known efficacy in controlling tonic–clonic seizures but may exacerbate other generalized seizures and should be used with caution in generalized-onset epilepsy, especially generalized atypical absence.[18,19,27,70,71] Valproate and carbamazepine are also useful in multiple other comorbid conditions including migraine and bipolar disorder.[18,39] Despite their known advantages, however, first-generation ASDs should generally be considered after second-generation ASDs have failed, due to the greater tolerability, fewer drug–drug interactions, and generic availability of the second-generation ASDs. The exception to this rule is ethosuximide, which is the drug of first choice for treatment of absence seizures but has limited use in other epilepsies.[36,80]

Second-Generation ASDs

The second-generation ASDs were developed with knowledge regarding the limitations of the first-generation ASDs and were FDA approved from 1993 to 2000. Included in this class are (1) felbamate; (2) gabapentin; (3) lamotrigine; (4) levetiracetam; (5) oxcarbazepine; (6) tiagabine; (7) topiramate; and (8) zonisamide. In general, these medications are considered to have similar efficacy in controlling seizures as first-generation ASDs, have relatively simple pharmacokinetics with fewer drug–drug interactions, and have an overall lower incidence of adverse effects.

8 **Mechanisms of Action** The second-generation ASDs have mechanisms of

action that include enhancement of GABAergic activity (eg, tiagabine) and sodium channel inhibition (eg, lamotrigine, oxcarbazepine, zonisamide) but also expand beyond that.[69] Notably, ASDs with novel mechanisms of action that were introduced within this generation include felbamate that modulates excitatory neurotransmission via inhibition of the *N*-methyl D-aspartate (NMDA) glutamate receptor, topiramate that inhibits the kainate/α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) glutamate receptor,[40,50] and levetiracetam that modulates excitatory neurotransmission through modulation of presynaptic neurotransmitter release via inhibition of SV2A protein, considered the master regulator molecule of neurotransmitter release.[69,49] For the other medications in this class, their therapeutic effects are seen through novel mechanisms that have not been fully elucidated (eg, gabapentin that binds to presynaptic $\alpha^2\delta$ subunit of calcium channels, possibly resulting in decreased release of the excitatory neurotransmitters glutamate, noradrenaline, substance P, and calcitonin gene-related peptide).[41] Furthermore, topiramate and zonisamide are also carbonic anhydrase inhibitors, although whether or not this impacts antiseizure activity is unknown.[42,50] Additionally, during this time period, a second-generation structurally related derivative of carbamazepine, oxcarbazepine, was also introduced that exhibits a similar mechanism of action as carbamazepine, but with an improved pharmacokinetic and adverse effect profile.[43]

Pharmacokinetics The second-generation ASDs also have pharmacokinetics that are less complex than first-generation ASDs. In general, the second-generation ASDs are not significantly protein bound and are well absorbed with good bioavailability, although of note, gabapentin relies on the L-amino acid carrier protein in the gut and the CNS to be actively transported across those membranes. As binding is saturable, this causes a dose-dependent bioavailability, with decreasing bioavailability with increasing dose, as the transporter is believed to be saturated at doses beyond 1,200 mg per single dose.[41,81]

Unlike the first-generation ASDs which are all hepatically metabolized, two second-generation ASDs, gabapentin and levetiracetam, are primarily renally eliminated and dosage adjustments may be necessary in patients with significantly impaired renal function.[41,49] Additionally, topiramate is approximately 60% renally eliminated and should be dose adjusted in patients with renal impairment, although topiramate also undergoes CYP3A4 metabolism.[50] As for the remaining second-generation ASDs, felbamate,

lamotrigine, oxcarbazepine, tiagabine, and zonisamide are all hepatically metabolized.[40,42–45] In contrast to carbamazepine, oxcarbazepine does not undergo autoinduction and also has an active metabolite (a monohydroxy derivative [MHD}, 10-OH-carbazepine) that is inactivated by glucuronidation and eliminated by the kidneys. As such, oxcarbazepine may also require dosage reduction with significant renal impairment.[43]

Drug–Drug Interactions Since gabapentin and levetiracetam do not undergo any appreciable hepatic metabolism, they therefore display minimal drug–drug interactions.[41,49] Felbamate, oxcarbazepine, tiagabine, zonisamide, and topiramate at higher doses are all hepatically metabolized and while there are some pharmacokinetic effects on the CYP450 pathways,[40,42,43,45,50] these effects are generally much less significant than those of the first-generation ASDs. Specifically, felbamate may induce or inhibit the metabolism of first-generation ASDs (or vice versa).[36,40] Oxcarbazepine inhibits CYP2C19 and induces CYP3A4/5, therefore, causing drug interactions with first-generation ASDs metabolized by these pathways, although to a much lesser extent than its precursor carbamazepine. Additionally, oxcarbazepine may also reduce lamotrigine levels through a suggested induction of UGT enzymes, again to a lesser extent than its precursor carbamazepine.[36,43] Similarly topiramate is a weak inhibitor of CYP2C19 and an inducer of CYP3A4, therefore interacting with the first-generation ASDs as well as other medications that are metabolized by these pathways.[36,50]

Of the second-generation ASDs, lamotrigine has the most substantial drug–drug interactions, which in some cases can be rather significant. Given valproate's enzyme-inhibiting properties, valproate can substantially inhibit the metabolism of lamotrigine, while carbamazepine, phenobarbital, phenytoin can substantially increase the metabolism of lamotrigine due to enzyme induction. As such, detailed dose and titration recommendations are available in the situation for when lamotrigine is used in combination with these ASDs. It is important to follow dose titration recommendations for lamotrigine carefully, as too rapid dose titrations increase the risk for rash including SJS. Of note, lamotrigine itself does not inhibit liver enzymes and, therefore, has a low potential for pharmacokinetic interactions with other drugs.[36,44]

Of note, oxcarbazepine and topiramate both can interact with ethinyl estradiol and cause contraceptive failure, although topiramate doses of less than 200 mg/day are unlikely to alter oral contraceptive pharmacokinetics.[43,50] As with other drugs, the potential of lamotrigine to affect OC metabolism is minimal, but

OCs can affect lamotrigine metabolism[44] as concomitant OCs lead to induction of lamotrigine glucuronidation by ethinyl estradiol. Once the OCs are withdrawn, significant increases in lamotrigine levels can be seen, including during the week of hormone withdrawal as part of various cyclic oral contraceptive treatments.[82]

In contrast to the first-generation ASDs, the second-generation ASDs have wide therapeutic ranges. While serum drug levels of second-generation ASDs are available through most laboratories, they are not routinely monitored, and as such drug levels may take many weeks to come back (see Table 73-3 for target therapeutic ranges of specific ASDs). Of note, one may monitor plasma levels of oxcarbazepine's active metabolite, 10-OH-carbazepine (or MHD), which is more clinically significant than measuring oxcarbazepine levels directly. The therapeutic range for MHD is between 15 and 35 mcg/mL.[36]

Adverse Effects The second-generation ASDs are associated with a lower incidence of dose-related neurotoxic side effects and are considered to be better tolerated than the first-generation ASDs. The exceptions are topiramate, which is associated with word-finding difficulties and cognitive slowing, and zonisamide which is a sodium channel inhibitor and associated with increased sedation and cognitive slowing. These neurotoxic side effects are more common with rapid titration and high doses.[83,84]

Despite being better tolerated overall, there are a number of unique and severe adverse effects associated with individual second-generation ASDs that must be considered when selecting therapy. The most severe of these is associated with felbamate which may potentially cause fatal idiosyncratic reactions including acute liver failure (1 in 10,000 patients), with reported onset between 68 and 354 days of therapy, and aplastic anemia (1 in 3,000 patients), with greater risk being seen in women, those with a history of cytopenia, prior ASD allergy or significant ASD toxicity, viral infection, and/or immunologic problems.[40] Tiagabine has been associated with new-onset seizures and status epilepticus.[45] Lamotrigine can cause rash, usually appearing after 3 to 4 weeks of therapy, and is typically generalized, erythematous, and morbilliform, but can progress to SJS. Rashes are more likely to occur if the patient has had a prior rash to another ASD[85] and risk factors for more serious rashes include concomitant use of valproic acid and situations where high initial doses or rapid dosage escalation is used. When dosed appropriately, the incidence of rash is similar to that of carbamazepine and phenytoin. The incidence of lamotrigine rash is higher in children than in adults.[86]

Of more moderate severity, topiramate and zonisamide are uniquely associated with kidney stones which can occur in 1.5% to 4% of patients, respectively, such that patients should be encouraged to maintain adequate fluid intake for the prevention of this adverse effect. Topiramate and zonisamide can also cause metabolic acidosis especially in patients with renal disease, severe respiratory disorders, diarrhea, surgery, and in patients on the ketogenic diet.[42,50]

Less severely levetiracetam is well recognized for causing irritability in many patients, an effect which may be lessened with dose reduction.[49] Similarly, in patients receiving gabapentin for pain, abrupt discontinuation is associated with a withdrawal reaction characterized by anxiety, insomnia, nausea, sweating, and increased pain.[41]

Oxcarbazepine generally causes fewer side effects than the first-generation carbamazepine, but may have a higher incidence of hyponatremia, which can be as high as 25% of patients.[80] This adverse event occurs more often in elderly patients and in patients receiving concomitant sodium-depleting drugs such as diuretics and is not very common in children. The incidence of rash with oxcarbazepine appears to be less compared to carbamazepine, although approximately 25% to 30% of patients who develop a rash with carbamazepine also experience a similar reaction with oxcarbazepine.[43]

Advantages and Disadvantages As previously stated, the second-generation ASDs are considered to be similar in efficacy to first-generation ASDs, but with better tolerability and fewer drug–drug interactions. Levetiracetam, in particular, is considered a useful broad-spectrum ASD with little, if any, neurotoxic side effects besides irritability. It is routinely used as first-line monotherapy to treat focal-onset epilepsy and to a lesser extent myoclonic seizures of JME and primary generalized seizures, despite being only FDA approved as adjunctive treatment for those seizure types.[36,49] However, increasing recognition of the unusually high prevalence of irritability and its impact on QOL is limiting levetiracetam's more widespread use.

Lamotrigine is also efficacious in many epilepsy types, and besides, rash is generally well tolerated with minimal neurotoxic side effects, especially in elderly patients who may experience less cognitive adverse effects with lamotrigine than with other ASDs.[87] However, its use is mainly limited by the need for slow titration to avoid rash (especially if the patient is on valproate) and it is not a good agent for patients who need to reach therapeutic ASD levels quickly.[44] Both lamotrigine and oxcarbazepine may be a good ASD for patients with comorbid bipolar disorder, with oxcarbazepine not requiring very slow dose

titration.[36,43,44] (See Chapter 86 for more information on the role of these ASDs for bipolar disorder.)

Topiramate and zonisamide are efficacious agents but due to their effects on cognition are sometimes considered after other ASDs. Topiramate additionally requires a very slow titration due to its neurotoxic effects, further limiting its use. On the other hand, topiramate is usually considered earlier in therapy for those patients with epilepsy who also have comorbid migraines or those who have a wish to lose weight as it has efficacy in migraine prevention and can promote significant weight loss. Similarly, zonisamide is considered earlier in therapy for those patients who have issues with medication adherence as it is dosed once daily and has one of the longest half-lives of all the ASDs.[36,42,50]

Gabapentin is oftentimes considered a poorly efficacious ASD that may even exacerbate generalized-onset seizures and should be avoided in generalized-onset epilepsies.[27,70,71] However, it is well tolerated and widely used as adjunctive therapy in focal-onset epilepsy mostly for its benefit in comorbid conditions such as neuropathic pain and not necessarily for its efficacy in controlling seizures.[41] Tiagabine and felbamate have serious adverse effects and are generally reserved for use only after failure of other ASDs, which is unfortunate as felbamate is broad spectrum (eg, can be used in focal-onset epilepsies and generalized-onset epilepsy syndromes like Lennox–Gastaut syndrome [LGS]) and is an effective ASD.[40] Furthermore, because of the risk of fatal aplastic anemia and liver failure, the use of felbamate requires signed written consent.[40]

Third-Generation ASDs

The third-generation ASDs were FDA approved from 2004 to 2018 and include (1) brivaracetam, (2) cannabadiol, (3) clobazam, (4) eslicarbazepine, (5) lacosamide, (6) perampanel, (7) pregabalin, (8) rufinamide, and (9) vigabatrin. Many of the ASDs in this generation were approved for very specific indications only, but are often used off-label in refractory epilepsy after failure of other first-line ASDs.

Mechanisms of Action Similar to the first-generation ASDs, many of the medications within this classification pharmacologically exert their effects through sodium channel inhibition and GABAergic mechanisms, as these continue to be proven to be efficacious in preventing seizures. Of the third-generation ASDs noted above, eslicarbazepine, lacosamide, and rufinamide are third-generation sodium channel inhibitors.[46,53,56] Eslicarbazepine is a derivative

of carbamazepine that has a 5- to 15-fold lower affinity for the resting state of sodium channels than that of carbamazepine or oxcarbazepine, leading to a selectivity for neurons that are firing (typically seen in epilepsy).[46,69] Eslicarbazepine is postulated to inhibit sodium channels, through enhancement of slow inactivation, similar to lacosamide, another third-generation sodium channel inhibitor. Rufinamide, on the other hand, prolongs the inactivation phase of sodium channels similar to phenytoin and carbamazepine.[53,56,69]

Third-generation GABAergic ASDs also include vigabatrin and clobazam. Vigabatrin is an amino acid that is a structural analog of GABA and is a selective, irreversible inhibitor of GABA-transaminase, the enzyme that degrades GABA.[23] Clobazam is a 1, 5-chlorinated benzodiazepine derivative (structurally different from the 1,4 benzodiazepine clonazepam) that binds the $GABA_A$ receptor at the benzodiazepine site as an agonist and enhances inhibitory chloride ion transmission promoting hyperpolarization of the neuron. However, it demonstrates lower affinity for the $GABA_A$ subunits that facilitate sedation, thereby reducing the incidence of this particular side effect.[52] Additionally, unlike traditional benzodiazepines which are nonselective full receptor agonists, clobazam is believed to be only a partial agonist.[52,69]

In addition to these, two other derivatives of second-generation ASDs have also been introduced. The first agent is pregabalin which is a derivative of gabapentin, and pharmacologically works in a similar fashion by binding to presynaptic $\alpha^2\delta$ subunit of calcium channels.[55] The second agent is brivaracetam, which is a more selective derivative of levetiracetam that has a 15- to 30-fold higher affinity for SV2A, and binds SV2A to modulate neurotransmitter release and glutamergic transmission.[51,69] Two new third-generation ASDs with novel mechanisms of action have also been recently introduced. These include perampanel, which is a highly selective noncompetitive AMPA-type glutamate receptor antagonist,[54] and cannabadiol, which is a purified drug derived from marijuana whose exact antiseizure mechanism is unknown.[47]

Pharmacokinetics The third-generation ASDs have variable pharmacokinetic profiles which are unique to the individual agent and while some have simple pharmacokinetics, others have more complex pharmacokinetics almost similar to that of the first-generation ASDs.

The third-generation ASDs with the most simple pharmacokinetics (ie, good absorption, low protein binding, uncomplicated metabolism, linear elimination kinetics) are pregabalin and vigabatrin, and are the only two ASDs in this

generation that are renally cleared.[23,36,55] Rufinamide, while hepatically metabolized, also displays simple pharmacokinetics, undergoing biotransformation via a carboxylesterase-mediated hydrolysis with no involvement of the CYP450 and UGT system.[36,56] Eslicarbazepine, despite being a prodrug that requires hydrolytic first-pass metabolism in the liver to form its active metabolite S-licarbazepine, also has relatively simple pharmacokinetics. After first-pass, eslicarbazepine is subsequently glucuronidated and renally excreted, requiring dosage adjustment in renal impairment but surprisingly not requiring adjustment in hepatic impairment.[36,46] Lacosamide is 40% renally eliminated and 60% hepatically metabolized by CYP3A4, CYP2C9, and CYP2C19, requiring dose adjustment in renal and hepatic impairment, but also otherwise displaying relatively simple pharmacokinetics.[36,53]

The third-generation agents with more complex pharmacokinetic profiles are brivaracetam, clobazam, and perampanel. Brivaracetam is metabolized by CYP2C19, and CYP2C19 poor and fast metabolizers may display altered brivaracetam pharmacokinetics. Brivaracetam dosage adjustment is required in all stages of hepatic impairment.[36,51] Clobazam is metabolized in the liver by CYP3A4 and CYP2C19 to a primary active metabolite *N*-desmethylclobazam that is then metabolized by CYP2C19. As such, its pharmacokinetics is also affected by CYP2C19 polymorphic variants and it also requires dosage adjustment in hepatic impairment.[36,52] Perampanel has complex pharmacokinetics as it is highly protein bound (96%-96%) and eliminated primarily via CYP3A4 metabolism to an inactive metabolite with an elimination half-life of about 100 hours. Its use is not recommended in severe renal or hepatic impairment.[36,54]

Of note, eslicarbazepine and perampanel are the two ASDs in this generation that have long half-lives and are dosed once-a-day. Monitoring of third-generation ASD serum drug is not routinely done and therapeutic ranges have not been clearly identified for some of these ASDs.[36]

Drug–Drug Interactions As previously stated pregabalin undergoes no hepatic metabolism and, similar to its precursor gabapentin, has little to no drug–drug interactions.[36,55] Vigabatrin, while not hepatically metabolized, is an inducer of CYP2C9 and has been noted to have slight effects on CYP2C9 substrates (eg, decreases phenytoin plasma levels by approximately 20% and possibly increases serum carbamazepine by 10%).[23,36]

Third-generation ASDs with lesser drug–drug interactions are lacosamide and

rufinamide. Lacosamide levels may be increased if used in combination with strong inhibitors of CYP3A4, CYP2C9, but most of these interactions are clinically insignificant.[36,53] Lacosamide is also a substrate of CYP2C19 and as such its blood levels can be modestly decreased (~15%-20%) by enzyme-inducing ASDs.[36,53] Rufinamide is a weak inhibitor of CYP2E1 and a weak inducer of CYP3A4 and may modestly affect the clearance of carbamazepine, lamotrigine, phenobarbital, and phenytoin and vice versa.[36,56] Additionally, concurrent use of rufinamide and OCs may result in reduced OCs efficacy while lacosamide does not reduce OC levels.[53,56]

Third-generation ASDs with more significant interactions include brivaracetam, clobazam, eslicarbazepine, and perampanel. Brivaracetam is a CYP2C19 substrate, and carbamazepine, phenobarbital, and phenytoin decrease its levels. Brivaracetam in turn may increase levels of the carbamazepine-epoxide metabolite and phenytoin levels but does not interact with lamotrigine, levetiracetam, oxcarbazepine, topiramate, valproate, or OCs to a significant extent.[51] Clobazam is a CYP3A4 and CYP2C19 substrate and its levels may be affected by CYP3A4- and CYP2C19-inducing and -inhibiting drugs such as felbamate and the first-generation ASDs, respectively.[36,52] Additionally, clobazam inhibits CYP2D6 and may affect the metabolism of other drugs that use this pathway as well as lowering the serum levels of some OCs due to its weak induction effect on CYP3A4.[52] Like carbamazepine, eslicarbazepine is affected by CYP2C19 inducers and can itself inhibit CYP2C19 and affect plasma concentration of drugs metabolized by this enzyme. However, similar to oxcarbazepine, the effects of eslicarbazepine are less significant than carbamazepine. Eslicarbazepine can also induce CYP3A4 affecting drugs that are metabolized by this isoenzyme and may also lower OC levels.[36,46] Of the third-generation ASDs, perampanel has the most potential for drug–drug interactions as its serum levels are decreased by enzyme-inducing ASDs, it displays modest enzyme-inducing properties of its own at the high end of its dose range (12 mg/day), and it may lower OC levels.[36,54]

Adverse Effects Third-generation ASDs have adverse effects which are unique to the individual ASD, with some having minimal side effects, while others are known for specific serious side effects. As the third-generation agents are the most recently FDA-approved ASDs, clinically we have the least long-term experience with their use; therefore, long-term and rare adverse effects may emerge as we gain more experience with these ASDs in a large population.

Among this generation, brivaracetam, lacosamide, and pregabalin are

generally well tolerated, although we have the least experience with brivaracetam (approved in 2016). In general, lacosamide's primary adverse effects are CNS effects; however, these occur at a lower incidence than other ASDs and are more common in patients receiving concomitant treatment with other sodium channel inhibitors. Additionally, lacosamide is also associated with a lengthening of the PR interval which is not clinically significant unless used in combination with another ASD that lengthens the PR interval.[53] Pregabalin has an adverse effect profile that is notable for sedation and weight gain.[55]

Similarly, clobazam also is not commonly associated with any serious adverse effects beyond CNS effects, but as a benzodiazepine, abrupt discontinuation may cause a withdrawal syndrome which could include convulsions, psychosis, hallucinations, behavioral disorder, tremor, and anxiety with milder symptoms presenting as dysphoria, anxiety, and insomnia.[52]

In contrast, eslicarbazepine, rufinamide, and perampanel have more serious adverse effects. Eslicarbazepine as a sodium channel inhibitor is associated with CNS effects and also hyponatremia, although the occurrence of hyponatremia with this agent is less common than with carbamazepine and oxcarbazepine.[46] Eslicarbazepine like its earlier counterparts may still be associated with rash including SJS and TEN, hepatotoxicity, and hematologic adverse reactions. As rufinamide is also a sodium channel inhibitor, it is also associated with increased CNS side effects as well as some rare and serious adverse effects including an increased incidence of convulsions in some patients and precipitation of status epilepticus (SE). Additionally, multiorgan hypersensitivity has occurred within 4 weeks of starting treatment with rufinamide in patients younger than 12 years of age.[56] Aggression is a major common and side effect with perampanel and there is a FDA-boxed warning pertaining to monitoring of psychiatric, behavioral, mood, or personality changes which may be life-threatening.[54]

Vigabatrin has the most serious adverse effects in this generation, as it may cause progressive, irreversible, bilateral concentric visual field constriction in a high percentage of patients. It may also reduce visual acuity in a dose-related and life exposure–related manner. Vigabatrin also may aggravate seizures, particularly absence and myoclonic seizures in patients with generalized epilepsies, and patients with history of depression, psychosis, or behavioral disturbances may be at greater risk to develop psychiatric effects with vigabatrin use.[23,88] Furthermore, in up to 11% of patients (up to age 3 years) treated with high doses of this drug for infantile spasms, MRI findings have been strongly suggestive of intramyelinic edema in select brain areas. While these findings appear to be reversible, their significance is unclear.[23,88]

Advantages and Disadvantages Cannabadiol, rufinamide, and vigabatrin have all been approved for specific epilepsy syndromes (Dravet syndrome and LGS, LGS, and infantile spasms, respectively) and in general should be considered among the first-choice drugs for those indications.[23,47,56]

9 In regards to focal-onset epilepsies, third-generation ASDs have been used in clinical practice for the treatment of these epilepsies and probably have similar efficacy to the first- or second-generation ASDs. However, most third generations are not available in generic form at this time (except for pregabalin) and are less cost-effective than other ASDs. Therefore, third-generation ASDs should be reserved for use after failure of other agents.

Of the third-generation ASDs, lacosamide has become an ASD of choice among many providers, due to its ease of use, including the availability of intravenous loading and lack of drug interactions. However, there is no strong evidence to support this practice and lacosamide is only available as a brand product. Therefore, due to its cost, lacosamide should be reserved as second-line or third-line therapy after failure of other equally efficacious, less expensive ASDs.

Among the third-generation ASDs, clobazam and perampanel may have the most broad use, as clobazam is believed to be efficacious in a wide variety of epilepsies including focal-onset and primary generalized epilepsies (despite having FDA approval only for LGS seizures) and perampanel is approved for focal-onset seizure with or without secondary generalization as well as for primary GTC seizures.[52,54] Perampanel use, however, is somewhat limited by the appearance of aggression in some patients.[54]

Lastly, all ASDs in this generation except for eslicarbazepine, rufinamide, and vigabatrin are controlled substances making prescribing and access much more difficult for these ASDs.[46,47,51,52,53,54,55,56] While vigabatrin is not a controlled substance, access is still restricted as all providers must be certified in the Vigabatrin Risk Evaluation and Mitigation Strategy (REMS) Program in order to prescribe it.[23]

Therapeutic Considerations in the Elderly and Young

The most important aspect of ASD therapy is tailoring the choice of drug to the individual patient using knowledge of an individual ASD’s pharmacodynamic and pharmacokinetic profile and its known advantages and disadvantages combined with knowledge of patient-specific factors including seizure type(s), age, gender, concomitant medical problems (including hepatic function, renal

function), and drug–drug interactions with concurrent medications.

In general, elderly patients are often on many different medications which may contribute to increased sensitivity to neurocognitive effects. Additionally, this population may be more prone to the increased possibility of drug–drug interactions with ASDs that affect the CYP450 system (eg, carbamazepine, phenytoin, and valproate); therefore, a thorough review of all medications is necessary prior to starting or modifying treatment. Hypoalbuminemia is also common in the elderly, and highly albumin-bound ASDs (eg, phenytoin and valproate) can be problematic necessitating close monitoring.[74] As patients age, they can also experience changes in body mass, such as an increase in fat to lean body mass or decrease in body water, which can affect drug volume of distribution and elimination half-life.[74] In addition, the elderly may have compromised renal or hepatic function that require ASD dosage adjustment.[74] Lamotrigine is often considered the medication of choice in elderly patients with focal-onset seizures, as results from a Department of Veterans Affairs cooperative trial found that it had equal efficacy to carbamazepine and gabapentin and was better tolerated than carbamazepine.[87]

For neonates and infants, an increase in the total body water to fat ratio and a decrease in serum albumin and α-acid glycoprotein can result in volume of distribution changes that affect ASD elimination half-life. Additionally, infants up to the age of 3 years have decreased renal elimination of ASDs, with neonates being the most affected. Hepatic activity is also reduced in neonates and infants, but by age 2 to 3 years, hepatic activity then becomes more robust than that seen in adults. Therefore, whereas neonates and infants require lower doses of ASDs, children require higher doses than that seen in adults. As such, therapeutic drug monitoring becomes especially important in the young, even though the definitions of therapeutic blood levels are less certain in these patients than in adults.[74]

Therapeutic Considerations in Women (and Men)

Estrogen and progesterone are among the many hormones that can influence brain electrical excitability, as estrogen has a slight proconvulsant effect, whereas progesterone exerts a mild anticonvulsant effect.[15] In some women, vulnerability to seizures is highest just before and during the menstrual flow (catamenial seizures) and at the time of ovulation, which is believed to be due to a slight increase in estrogen relative to progesterone, or due to progesterone withdrawal and changes in the estrogen-to-progesterone ratio.[15] The risk of

catamenial seizures is estimated be anywhere from 10% to 70% in women with epilepsy.[15] In such women, conventional ASDs should be used as primary agents, but intermittent supplementation with higher dose of ASD or benzodiazepines should be considered. Acetazolamide has also been used during catamenial periods, but with variable and limited success, and hormonal therapy with progestational agents, particularly cyclic natural progesterone therapy, may be effective in certain subsets of patients.[89]

At menopause, seizures often improve in frequency, particularly in women with a catamenial seizure pattern. However, for those women who need hormone replacement therapy, it has been reported that conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate may increase the frequency of epileptic seizures. Therefore, a hormone replacement therapy that consists of just a single estrogenic compound, such as 17-β-estradiol, along with a natural progesterone, may be recommended for women with disruptive menopausal symptoms.[90]

Antiseizure drugs may also have an effect on endogenous and exogenous hormones. As previously stated, enzyme-inducing ASDs increase the metabolism of estrogen, progesterone, and testosterone and increase production of sex hormone-binding globulin, leading to decreases in the free fraction of these hormones endogenously. These alterations lead to disturbances in the regulation of the hypothalamic–pituitary–adrenal axis and contribute to reproductive endocrine disorders including menstrual irregularity, infertility, sexual dysfunction, and in some patients polycystic ovary syndrome (PCOS).[91] Valproate, in particular, may affect sex hormone concentrations causing hyperandrogenism and polycystic changes, especially in women who have gained weight or those who start valproic acid at age less than 20 years.[91] Exogenously, enzyme-inducing ASDs can cause treatment failures in women taking OCs, as discussed in the prior sections, due to increased metabolism of ethinyl estradiol and progestin. Medroxyprogesterone depot injections and hormone-releasing intrauterine systems, on the other hand, are not similarly affected by ASDs, and it is unclear if there is an effect of ASDs on the transdermal contraceptive patch or the emergency contraceptive pill. A supplemental or alternative form of birth control (eg, IUD) is advised if breakthrough bleeding occurs in woman taking certain types of ASDs (eg, enzyme-inducing ASDs) and OCs, and it has been suggested that women use twice the normal dose of emergency contraception.[92]

Antiseizure drugs may also have reproductive endocrine effects in men. Data suggests that men with epilepsy have reduced fertility, and that carbamazepine, oxcarbazepine, and valproic acid are associated with sperm abnormalities. In

addition, valproic acid seems to cause testicular atrophy resulting in reduced testosterone volume, whereas levetiracetam appears to slightly increase serum testosterone. Various ASDs have also been anecdotally reported to affect libido and sexual function in both men and women.[92]

Therapeutic Considerations for Pregnancy and Breastfeeding

Pregnancy and epilepsy is a particularly complex topic. The goal of treatment in pregnant women with epilepsy is to achieve the best possible control of seizure with the minimal adverse effects for both the mother and the child. Epilepsy-related complications during pregnancy include possible changes in seizure frequency, fluctuating ASD plasma levels, and possible teratogenic effects of ASDs.[93,94]

Despite multiple reports of both increased and decreased seizure frequency during pregnancy, a recent practice parameter update issued by the American Academy of Neurology (AAN) found that there was inconclusive evidence to support that pregnancy was associated with changes in seizure frequency. What was concluded, however, was that women with epilepsy who were seizure free for at least 9 months to 1 year prior to pregnancy had a very high probability (84%-92%) of remaining seizure free during pregnancy.[93] It should be noted, however, that if seizures are increasing during pregnancy, it is important to inquire about nonadherence in a normally adherent patient, as women may be concerned about the potential adverse drug effects on the developing fetus.[95]

Fluctuations in ASD concentration may be caused by physiologic changes that occur during pregnancy including reduced gastric motility, nausea and vomiting, increased drug distribution, increased renal elimination, altered hepatic enzyme activity as well as changes in protein binding during pregnancy.[92] Physiologic changes, such as changes in protein binding, can begin as early as the first 10 weeks of pregnancy, and may require up to 4 weeks postpartum to normalize (eg, protein binding in carbamazepine, phenobarbital, and phenytoin). Fluctuations in ASD plasma concentrations due to increased ASD clearance has been found to be true for lamotrigine, carbamazepine, phenytoin, oxcarbazepine, and levetiracetam.[93] Clinical consequences of ASD fluctuations are variable and some women will not experience increased seizure frequency despite fluctuating levels. Women on lamotrigine, however, have been found to undergo a 40% decrease in the ratio of plasma lamotrigine concentration to dose, resulting in deterioration of seizure control in

approximately 75% of pregnant patients.[92] It is therefore recommended that ASD levels, particularly lamotrigine levels, be monitored closely during pregnancy, and that dosage increases occur over the course of the pregnancy if needed. This should be followed up with a rapid decrease in the postpartum period. Of note, fluctuations have also been reported for phenobarbital, valproic acid, primidone, and ethosuximide, although strong evidence for this is lacking.[93]

Adverse pregnancy outcomes associated with ASD use include an increased risk of major congenital malformations (MCMs) compared to nonepileptic women.[94] This risk is believed to be due to ASD exposure and not maternal seizures, as infants born to women with epilepsy who do not take ASDs have the same risk of birth defects as infants born to seizure-free women (2%-3%).[95] The most concerning effects are found with the use of valproic acid which is associated with a risk of MCMs that is 3.5 to 4 times that of offspring from nonepileptic women, especially if taken during the first trimester of pregnancy.[94,96] Furthermore there is an increased risk of neurodevelopmental deficits, including effects on cognition, in children exposed to valproic acid *in utero*.[94,96] These effects are dose-dependent, and the risk of MCM significantly increases at 600 mg/day, with the greatest risk observed at doses that exceed 1,000 mg/day.[96] However, individual susceptibility is genetically determined, and teratogenicity can occur at much lower doses in some persons. Due to these findings, it is recommended that valproate should preferably not be used in pregnant women with epilepsy and that withdrawal of valproate or switching to an alternative treatment should be considered in these patients.

Data on teratogenic risk with the newer agents are limited, although topiramate was recently reclassified from pregnancy category C to D due to an increased association with cleft palate (it may also have a negative effect on birth weight and cause increases in hypospadias).[50] In general, higher ASD doses, higher ASD serum concentrations, polytherapy (especially polytherapy with valproate), and a family history of birth defects appear to increase the teratogenic risk of ASDs.[94] As such, the risk of birth defects is believed to have gone down with decreasing doses and decreasing use of polytherapy.

Deciding on the most effective single-drug treatment prior to conception is vitally important. Teratogenic effects of ASD must always be considered when choosing ASDs for women of reproductive age, even when they do not plan on becoming pregnant, as many unplanned pregnancies occur and MCMs generally occur early in pregnancy before women know that they are pregnant. With proper counseling and management, more than 90% of these pregnancies will

still have satisfactory outcomes. Updated practice parameters are available to aid in the selection of ASDs in pregnancy and the counseling and management of pregnant women with epilepsy.[93,94,96]

Teratogenic effects may possibly be prevented by adequate folate intake, although strong data supporting this practice are lacking. However, as the risk of MCM is possibly decreased by folic acid supplementation, prenatal vitamins with folic acid (0.4-5 mg/day) are recommended for women of child-bearing potential who are taking ASDs. Higher folate doses should be used in women with a history of a previous pregnancy with a neural tube defect or in those taking valproic acid. Additionally, some ASDs may possibly cause neonatal hemorrhagic disorder and there currently is a lack of strong evidence to determine if prenatal vitamin K supplementation can reduce this complication. However, vitamin K 10 mg/day is often administered orally to the mother during the last month of pregnancy and/or administered parenterally to the newborn at delivery.[97]

Some ASDs pass into the breast milk and those with less protein binding will accumulate more. Treatment with ASDs is not necessarily a reason to discourage breastfeeding, although ASD concentrations are measureable in breastfeeding infants. In fact, an argument could be made that since ASDs should rarely be discontinued abruptly, breastfeeding allows for a downward titration of a medication that the baby was exposed to for the past 9 months. Infants born to women taking any ASD (particularly barbiturates or benzodiazepines) should be closely observed for signs of excess sedation, irritability, or poor feeding.[97,98] In general, FDA labeling of ASDs including valproate state that the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for that ASD and any potential adverse effects on the breastfed infant from that ASD or from the underlying maternal condition itself. Additionally, FDA labeling states caution should be exercised when an ASD is administered to a nursing woman.

Therapeutic Considerations in Patients of Asian and South Asian Decent

A common idiosyncratic side effect of ASDs is rash. However, in some cases, the rash can quickly progress to SJS, TEN, or Drug Reactions with Eosinophilia and Systemic Symptoms (DRESS) which are severe and life-threatening conditions. Studies have found that there is a strong association between the presence of an inherited variant of the *HLA-B* gene, *HLA-B*1502*, in these

populations, and the risk of developing SJS/TEN with carbamazepine (and possibly phenytoin, lamotrigine, and oxcarbazepine as well).[18] This *HLA-B* variant is found in up to 15% of individuals from many Asian, Southeast Asian, and South Asian populations including Hong Kong, Thailand, Malaysia, Philippines, Taiwan, North China, India, and to a much lesser extent Japan and Korea. The variant is largely absent in individuals not of Asian origin. Testing for *HLA-B*1502* may be recommended for patients who may need to be initiated on carbamazepine, phenytoin, lamotrigine, or oxcarbazepine therapy in these high-risk populations. If the genetic testing is positive, these ASDs should generally be avoided in these patients. In addition, the *HLA* genotype *HLA-A*3101* has also been found to be associated with multiple carbamazepine-induced cutaneous reactions in Chinese, Japanese, and European populations.[18] It should be noted that many *HLA-B*1502*-positive and *HLA-A*3101*-positive patients treated with ASDs will not develop SJS/TEN or other hypersensitivity reactions, and these reactions can still occur infrequently in *HLA-B*1502*-negative and *HLA-A*3101*-negative patients of any ethnicity. Additionally, of those who do experience SJS/TEN with carbamazepine, 90% will have this reaction within the first few months of treatment.[18]

EVALUATION OF THERAPEUTIC OUTCOMES

The goal of therapy for all ASDs is seizure freedom or reduction in seizure frequency, while minimizing adverse effects. Determining clinical response to treatment involves identifying the number and type of seizures and adverse effects during the monitoring and follow-up phase of treatment. Providing the patient with a seizure and side-effect diary will assist in this effort as the severity and frequency of seizures should be monitored by the patient and the family and recorded in the seizure diary. External factors such as seizure triggers can also influence seizure frequency. Therefore, patients should be educated that seizure triggers should be identified and documented because avoiding them may have a significant impact on seizure control. Additionally, although seizures tend to be stereotyped within an individual, the clinical presentation of the seizure may change over time or with treatment and this should be documented. During all follow-up visits, the seizure diary should be reviewed and both patients and family should be questioned to determine whether patients are truly seizure free.

Additionally, patients should also be monitored for all ASD side effects and assessed for dose-related “neurotoxic” adverse effects (eg, drowsiness, fatigue, dizziness, blurry vision, and incoordination). Such adverse effects are common,

especially when initiating ASD therapy as well as with polytherapy. Neurotoxic adverse effects should be avoided if possible, either by dose reduction of monotherapy, reduction or elimination of polytherapy, or substituting for a better tolerated ASD.

Patients should also be assessed for idiosyncratic adverse effects which usually require withdrawal in an affected patient, including serious rash (ie, SJS, TEN), hematologic dyscrasias, electrolyte abnormalities (eg, hyponatremia), and hepatotoxicity. Laboratory assessment, including complete blood cell (CBC) counts, chemistries, and liver function tests, should be performed at baseline and after initiation of ASDs to monitor for idiosyncratic adverse effects. Other specific laboratory tests can be performed if there is clinical suspicion of adverse effects (eg, measuring ammonia levels in a patient with suspected hyperammonemic encephalopathy from valproic acid). Acute organ failure due to an idiosyncratic reaction, when it occurs, generally occurs within the first 6 months of ASD therapy,[99] although there is a delay between starting the drug and the onset of symptoms. There is also a more rapid onset if a patient who has had an idiosyncratic reaction to a specific drug is rechallenged.[99]

Patients on long-term chronic ASD therapy should be monitored for long-term side effects of ASDs. Specifically for those patients on chronic long-term ASD therapy known to cause osteoporosis (eg, phenytoin and phenobarbital), bone density loss can be measured via bone-density scanning (eg, DEXA) after many years of treatment. Neuropathy can also be monitored via thorough neurologic exam, and gums should be visually inspected for gingival hyperplasia at follow-up. The patient should also be instructed to have regular and thorough dental care.

Medication adherence should also be monitored and when seizures are not controlled, medication nonadherence must always be considered, as it is the single most common reason for treatment failure. It is estimated that up to 60% of patients with epilepsy are nonadherent.[100] The rate of nonadherence is increased by the complexity of the drug regimen and by doses taken three and four times a day.[100] Frequent uncontrolled seizures can also predispose a patient to nonadherence secondary to confusion over whether the drug was taken. Nonadherence is not influenced by age, sex, psychomotor development, or seizure type.[100]

Obtaining serum concentrations of ASDs is a method by which to optimize therapy for an individual patient, but is not a therapeutic end point in itself. A patient’s clinical response is more important than the actual serum drug concentration as seizure control can occur before the “minimum” of the

published therapeutic range is achieved, and side effects can appear before the "maximum" of the range is achieved. Some patients may need and tolerate concentrations beyond the maximum. Clinicians should define a therapeutic range for an individual patient as the concentration below which there are side effects and above which the patient experiences seizures. Then serum levels can be useful to document lack of efficacy, loss of efficacy, and to determine how much room there is to increase a dose based on expected toxicity. Serum levels can also be particularly useful to determine nonadherence and should be checked if adherence is questionable. Depending on the ASD, serum levels can also be useful in patients with significant renal and/or hepatic disease, patients taking multiple drugs, and women who are pregnant or taking OCs.[74,36]

Patients should also be monitored long term for comorbid conditions, social adjustment (including QOL assessments), and drug interactions. Periodic screening for comorbid neuropsychiatric disorders, such as depression, suicidal ideation, and anxiety, is also important. Screening for learning and development issues in children is also imperative as neurodevelopmental comorbidities commonly coexist with epilepsy and may be associated with use of ASDs.[2]

Overall treatment outcomes are increasingly focusing on obtaining an optimal QOL for the patient and the AAN has developed quality performance measures for the clinician that define a high quality of care of these patients. Among those performance measures, it is important to remember to counsel patients about ASD side effects and initiate a discussion about depression. Besides seizure control and ASD side effects, factors that can impact QOL in epilepsy patients and which should be addressed include issues about driving, economic security, forming relationships, epilepsy safety such as precautions when swimming, social isolation, and social stigma.[2,32]

10 After the initiation of treatment, approximately 65% of patients treated for new-onset epilepsy can be expected to be maintained on one ASD and may be seizure free.[34] The percentage of patients who are seizure free on one drug varies by seizure type. After 12 months of treatment, the percentage of who are seizure free is highest for those who have only GTC seizures (48%-55%), lowest for those who have only focal seizures (23%-26%), and intermediate for those with mixed seizure types (25%-32%).[101]

Polytherapy with two or more ASDs is appropriate for those patients who cannot achieve seizure freedom on ASD monotherapy. Of the 35% of patients with unsatisfactory control on monotherapy, 10% will be well controlled with a two-drug treatment. Of the remaining patients, 20% will continue to have unsatisfactory control despite greater than two-drug treatment and are deemed to

be drug resistant.[34] The ILAE consensus definition for drug-resistant epilepsy includes lack of seizure freedom from at least two adequate trials of an ASD as monotherapy or polytherapy, which were appropriately chosen and used.[102] Those who have unsatisfactory control despite multiple drug treatment may be candidates for the ketogenic diet, a vagal nerve stimulator, and/or surgery, which is especially encouraged for those who are good surgical candidates. In fact, the AAN has included assessment about patient knowledge and referral to surgery in their quality performance measures.[32]

For a patient with long-standing epilepsy, adequacy of their current medication regimen, whether they are seizure free or not, should be routinely evaluated. Goals should be reevaluated when necessary, especially in those 20% to 35% of patients where seizure freedom cannot be achieved. In these patients, more obtainable goals which balance seizure control with patient-specific QOL factors[2,32] and wishes (eg, decrease in the number of seizures with minimized drug adverse effects) should be established. Patient education and assurance of patient understanding of the goals is also an essential part of the care plan.

For some patients who have not experienced seizures for many years and who are deemed to have a low risk of recurrence, ASD withdrawal may be considered. The AAN has issued guidelines for discontinuing ASDs in seizure-free patients.[103] After assessing the risks and benefits to both the patient and society, ASD withdrawal can be considered in a patient meeting the following profile: seizure free for 2 to 5 years, a history of a single type of focal seizure or primary generalized seizures, a normal neurologic exam and normal IQ, and an EEG that has normalized with treatment.[104,105] When these factors are present, the relapse rate at 1 year is expected to be 35% and 29% at 2 years.[106] For those patients who relapse after withdrawal, ASDs can be restarted; while seizure freedom can be regained for most patients who restart ASDs, it does not happen for all.[105] Factors associated with a poor prognosis in discontinuing ASDs, despite a seizure-free interval, include a history of a high frequency of seizures, repeated episodes of status epilepticus, a combination of seizure types, and development of abnormal mental functioning.[104,105]

CONCLUSION

Epilepsy is a group of diseases that present with variable signs and symptoms and is a major burden in terms of QOL, morbidity, and risk of premature mortality from SUDEP, especially in those who continue to have seizures.

Pharmacologic management of epilepsy currently consists of symptomatic treatment only. The mainstay of pharmacologic therapy is antiseizure drugs. The goal of ASD therapy is suppression of seizure occurrence in patients. Over the years, over two dozen ASDs with various mechanisms of action, pharmacokinetics, adverse effect profiles, and drug–drug interaction profiles have become available for the treatment of epilepsy. When selecting ASD therapy, ASD efficacy must be balanced with ASD side effects and cost and take into consideration patient-specific factors including age, gender, susceptibility to adverse effects, concomitant medications, and ability to adhere with selected regimen. Suppression of seizures can be achieved with ASD monotherapy or polytherapy in up to two-thirds of all patients with epilepsy but do not alter long-term prognosis. In patients with drug-resistant epilepsy, nonpharmacologic options such as ketogenic diet, vagal nerve stimulation, and epilepsy surgery should be considered. Epilepsy surgery is the most effective way to achieve long-term seizure freedom, but is an option only in few people with drug-resistant epilepsy. With improved understanding of epilepsy pathophysiology and pathogenesis, better, disease modifying, and curative pharmacological treatments may become available.

Postclass Engaged Learning Activity

Selection of an optimal antiseizure drug (ASD) for treatment of epilepsy requires the provider to balance ASD efficacy with ASD adverse effects and ASD cost. Conduct a literature search and identify a primary research manuscript on cost-effectiveness of an ASD or ASDs that has been published in the past 24 months. Write a brief summary about the study methods, the major findings, and how this new information might change current practice. This activity is intended to help you understand how to balance seizure control goals with QOL goals in epilepsy management and also to help build your literature evaluation skills and ability to critically appraise research manuscripts.

ABBREVIATIONS

AAN	American Academy of Neurology
AES	American Epilepsy Society
AMPA	α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid
ASD	antiseizure drug
AUC	area under the drug concentration time curve
CAE	Childhood Absence Epilepsy
C_{max}	maximal blood drug concentration
CT	computed tomography
DEXA	dual energy x-ray absorptiometry
DRESS	Drug Reactions with Eosinophilia and Systemic Symptoms
EEG	electroencephalogram
EFHC1	EF-hand containing protein-1
GABA	γ-aminobutyric acid
GTC	generalized tonic–clonic
IGE	idiopathic generalized epilepsy
ILAE	International League Against Epilepsy
LGS	Lennox–Gastaut syndrome
JME	Juvenile Myoclonic Epilepsy
MCMs	major congenital malformations
MRI	magnetic resonance imaging
NMDA	*N*-methyl-D-aspartate
OC	oral contraceptive
PCOS	polycystic ovary syndrome
PME	Progressive Myoclonic Epilepsy
QOL	quality of life
REMS	Risk Evaluation and Mitigation Strategy
SE	status epilepticus
SJS	Steven–Johnsons syndrome
SP	simple partial
SUDEP	sudden unexplained death in epilepsy
TEN	Toxic Epidermal Necrolysis
T_{max}	time to maximal blood drug concentration
VNS	vagus nerve stimulation
WBC	white blood cell

REFERENCES

1. Fisher RS, van Emde Boas W, Blume W, et al. Epileptic seizures and epilepsy: Definitions proposed by the international league against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia*. 2005;46(4):470–472.
2. England MJ, Liverman CT, Schultz AM, et al. A summary of the Institute of Medicine report: Epilepsy across the spectrum. Promoting health and understanding.. *Epilepsy Behav*. 2012;25(2):266–276.
3. Zack MM, Kobau R. National and State Estimates of the Numbers of Adults and Children with Active Epilepsy—United States, 2015. *MMWR Morb Mortal Wkly Rep*. 2017;66:821–825.
4. Forsgren L, Hauser WA, Olafsson E, et al. Mortality of epilepsy in developed countries: A review. *Epilepsia*. 2005;46(suppl 11):18–27.
5. DiGiorgio CM, Curtis A, Hertling D. Sudden unexpected death in epilepsy: Risk factors, biomarkers, and prevention. *Acta Neurol Scan*. 2018;15:1–11.
6. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017;58(4):512–521.
7. Suzuki T, Delgado-Escueta AV, Aguan K, et al. Mutations in EFHC1 cause juvenile myoclonic epilepsy. *Nat Genet*. 2004;36(8):842–849.
8. Bailey JN, de Nijs L, Bai D, et al. Variant intestinal cell-kinase in juvenile myoclonic epilepsy. *N Engl J Med*. 2018;378:1018–1028.
9. Wei F, Yan L, Su T, et al. Ion channel genes and epilepsy: Functional alteration, pathogenic potential, and mechanism of epilepsy. *Neurosci Bull*. 2017;33(4):455–477.
10. Nieh SE, Sherr EH. Epileptic encephalopathies: New genes and new pathways. *Neurotherapeutics*. 2014;11:796–806.
11. Tanaka M, Olsen RW, Medina MT, et al. Hyperglycosylation and reduced GABA currents of mutated GABRB3 polypeptide in remitting childhood absence epilepsy. *Am J Hum Genet*. 2008;82(6):1249–1261.
12. Malmgren K, Thom M. Hippocampal sclerosis—origins and imaging. *Epilepsia*. 2012;53(S4):19–33.
13. Minassian BA, Lee JR, Herbrick J-A, et al. Mutations in a gene encoding a novel protein tyrosine phosphatase causes progressive myoclonus epilepsy. *Nature Genet*. 1998;20:171–174.
14. Hesdorffer DC. Risk factors. In: Engel J, Pedley TA, eds. *Epilepsy: A*

Comprehensive Text Book. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008;57–63.

15. Jallon P, Zifkin BF. Seizure precipitants. In: Engel J, Pedley TA, eds. *Epilepsy: A Comprehensive Text Book*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008;77–80.
16. Goldberg EM, Coulter DA. Mechanisms of epileptogenesis: A convergence on neural circuit dysfunction. *Nat Rev Neurosci*. 2013;14(5):337–349.
17. Engel J. *Seizures and Epilepsy*. 2nd ed. New York: Oxford University Press; 2013:56–72.
18. Tegretol [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; March 2018.
19. Dilantin [package insert]. New York, NY: Parke-Davis; January 2009.
20. Klonopin [package insert]. South San Francisco, CA: Genentech; October 2013.
21. Rogawski MA, Bazil CW. New molecular targets for antiepileptic drugs: α2δ, SV2A, and Kv7/KCNQ/M potassium channels. *Curr Neurol Neurosci Rep*. 2008;8(4):345–352.
22. Thijs RD, Surges R, Obrien T, Sander JW. Epilepsy in adults. *Lancet*. 2019;393(10172):689–701.
23. Sabril [package insert]. Deerfield, Il: Lundbeck; February 2018.
24. Engel J. Mechanisms of neuronal excitation and synchronization: Neuronal networks. *Seizures and Epilepsy*. 2nd ed. New York, NY: Oxford University Press; 2013;73–81.
25. Huguenard JR, McCormick DA. Thalamic synchrony and dynamic regulation of global forebrain oscillations. *Trends Neurosc*. 2007;30:350–356.
26. Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017;58(4):522–530.
27. Glauser T, Ben-Menachem E, Bourgeois B, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia*. 2013;54(3):551–563.
28. Noachtar S, Peters AS. Semiology of epileptic seizures: A critical review.

Epilepsy Behav. 2009;15(1):2–9.
29. Foldvary-Schaefer N, Unnwongse K. Localizing and lateralizing features of auras and seizures. *Epilepsy Behav*. 2011;20(2):160–166.
30. Fisher RS, Acevedo C, Arzimanoglou A, et al. A practical clinical definition of epilepsy. *Epilepsia*. 2014;55(4):475–482.
31. Bouma HK, Labos C, Gore GC, et al. The diagnostic accuracy of routine electroencephalography after a first unprovoked seizure. *Eur J Neurol*. 2016;23(3):455–463.
32. Fountain NB, Van Ness PC, Swain-Eng R, et al. Quality improvement in neurology: AAN epilepsy quality measures: Report of the Quality Measurement and Reporting Subcommittee of the American Academy of Neurology. *Neurology*. 2011;76(1):94–99.
33. Chen DK, So YT, Fisher RS. Use of serum prolactin in diagnosing epileptic seizures. Report of the Therapeutic and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2005;65:668–675.
34. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med*. 2000;342:314–319.
35. Krumholz A, Wiebe S, Gronseth GS, et al. Evidence-based guideline: Management of an unprovoked first seizure in adults. *Neurology*. 2015;84:1705–1712.
36. Patsalos PN, Spencer EP, Berry DJ. Therapeutic drug monitoring of antiepileptic drugs in epilepsy: A 2018 update. *Ther Drug Monit*. 2018;40(5):526–548.
37. Phenobarbital [package insert]. Boucherville, QC, Canada: Sandoz Canada Inc.; February 2015.
38. Zarontin [package insert]. New York, NY: Parke-Davis; April 2009.
39. Depakote ER [package insert]. Chicago, IL: Abbott Laboratories; October 2011.
40. Felbatol [package insert]. Somerset, NJ: Meda Pharmaceuticals; August 2012.
41. Neurontin [package insert]. New York, NY: Parke-Davis; February 2018.
42. Zonegran [package insert]. Teaneck, NJ: Eisai Inc.; 2006.
43. Trileptal [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Inc.; March 2018.
44. Lamictal [package insert]. Research Triangle Park, NC: GlaxoSmithKline;

July 2018.
45. Gabitril [package insert]. Frazer, PA: Cephalon; April 2009.
46. Aptiom [package insert]. Marlborough, MA: Sunovion Pharmaceuicals Inc.; September 2017.
47. Epidiolex [package insert]. Carlsbad, CA: Greenwich Biosciences; September 2018.
48. Mysoline [package insert]. Aliso Viejo, CA: Valeant Pharmaceuticals; 2009.
49. Keppra [package insert]. Smyrna, GA: UCB Inc.; October 2017.
50. Topamax [package insert]. Titusville, NJ: Jannsen Pharmaceuticals; June 2018.
51. Briviact [package insert]. Smyrna, GA: UCB Inc.; May 2018.
52. Onfi [package insert]. Deerfield, Il: Lundbeck; June 2018.
53. Vimpat [package insert]. Smyrna, GA: UCB Inc.; November 2018.
54. Fycompa [package insert]. Woodcliff Lake, NJ: Eisai Inc.; September 2018.
55. Lyrica [package insert]. New York, NY: Parke-Davis; May 2018.
56. Banzel [package insert]. Woodcliff Lake, NJ: Eisai Inc.; June 2015.
57. Brigo F, Ausserer H, Tezzon F, et al. When one plus one makes three: The quest for rational antiepileptic polytherapy with supraadditive anticonvulsant efficacy. *Epilepsy Behav*. 2013;27(3):439–442.
58. Groesbeck DK, Blum RM, Kossoff EH. Long-term use of the ketogenic diet: Outcomes of 28 children with over 6 years diet duration. *Neurology*. 2006;66(suppl 2):A41.
59. Dossoff EH, Zupec-Kania BA, Amark PE, et al. Optimal clinical management of children receiving the ketogenic diet: Recommendations of the International Ketogenic Diet Study Group. *Epilepsia*. 2009;50:304–317.
60. Krahl SE, Clark KB, Smith DC, et al. Locus coeruleus lesions suppress the seizure-attenuating effects of vagus nerve stimulation. *Epilepsia*. 1998;39:709–714.
61. Shuchman M. Approving the vagus-nerve stimulator for depression. *N Engl J Med*. 2007;356:1604–1607.
62. Salinsky MC, Uthman BM, Ristanovic RK, et al. Vagus nerve stimulation for the treatment of medically intractable seizures: Results of a 1 year open extension trial. *Arch Neurol*. 1996;53:1176–1180.

63. Handforth A, Degiorgio CM, Schachter SC, et al. Vagus nerve stimulation therapy for partial-onset seizures: A randomized active controlled trial. *Neurology*. 1998;51(1):48–55.
64. Wiebe S, Blume WT, Girvin JP, et al. Effectiveness and efficiency of surgery for Temporal Lobe Epilepsy Study Group: A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med*. 2001;345(5):311–318.
65. Engel J, McDermott MP, Wiebe S, et al. Early surgical therapy for drug-resistant temporal lobe epilepsy. *JAMA*. 2012;307:922–930.
66. TI Jeong SW, Lee SK, Hong KS, et al. Prognostic factors for the surgery for mesial temporal lobe epilepsy: Longitudinal analysis. *Epilepsia*. 2005;46(8):1273–1279.
67. Janszky J, Janszky I, Schulz R, et al. Temporal lobe epilepsy with hippocampal sclerosis: Predictors for long-term surgical outcome. *Brain*. 2005;128(Pt 2):395–404.
68. Jeha LE, Najm IM, Bingaman WE, et al. Predictors of outcome after temporal lobectomy for the treatment of intractable epilepsy. *Neurology*. 2006;66(12):1938–1940.
69. Rogawski MA, Loscher W, Rho JM. Mechanism of action of antiseizure drugs and the ketogenic diet. *Cold Spring Harb Perspect Med*. 2016;6:a022780.
70. Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy: Report of the American Epilepsy Society and the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Epilepsy Curr*. 2018;18(4):260–268.
71. Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment-resistant epilepsy: Report of the American Epilepsy Society and the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Epilepsy Curr*. 2018;18(4):269–278.
72. Perucca P, Gilliam FG. Adverse effects of antiepileptic drugs. *Lancet*. 2012;11:792–802.
73. EK St Louis. Minimizing AED adverse effects: Improving quality of life in the interictal state in epilepsy care. *Curr Neuropharmacol*.

2009;7(2):106–114.

74. Patsalos PN, Berry DJ, Bourgeois BFD, et al. Antiepileptic drugs—best practice guidelines for therapeutic drug monitoring: A position paper by the Subcommission on Therapeutic Drug Monitoring, ILAE Commission on Therapeutic Strategies. *Epilepsia*. 2008;49:1239–1276.
75. Pack AM, Morrell MJ, McMahon DJ, et al. Bone health in young women with epilepsy after one year of antiepileptic drug monotherapy. *Neurology*. 2008;70:1586–1593.
76. Lado F, Spiegel R, Masur JH, et al. Value of routine screening for bone demineralization in an urban population of patients with epilepsy. *Epilepsy Res*. 2008;78:155–160.
77. Wang Z, Lin YS, Zheng XE, et al. An inducible cytochrome P4503A4-dependent vit D catabolic pathway. *Mol Pharmacol*. 2012;81:498–509.
78. Anderson GD, Pak C, Doane KW, et al. Revised Winter-Tozer equation for normalized phenytoin concentrations in trauma and elderly patients with hypoalbuminemia. *Ann Pharmacother*. 1997;31:279–284.
79. Jentink J, Loane MA, Dolk H, et al. Valproic acid monotherapy in pregnancy and major congenital malformations. *N Engl J Med*. 2010;362:2185–2193.
80. Berghuis B, van der Palen J, de Haan GJ, et al. Carbamazepine- and oxcarbazepine-induced hyponatremia in people with epilepsy. *Epilepsia*. 2017;58(7):1227–1233.
81. Luer MS, Hamani C, Dujovny M, et al. Saturable transport of gabapentin at the blood-brain barrier. *Neurol Res*. 1999;21:559–562.
82. Christensen J, Petrenaite V, Atterman J, et al. Oral contraceptives induce lamotrigine metabolism: Evidence from a double-blind, placebo-controlled trial. *Epilepsia*. 2007;48:484–489.
83. Shorvon SD. Safety of topiramate: Adverse events and relationship to dosing. *Epilepsia*. 1996;37(S2):S18–S22.
84. Mula M, Trimble M, Thompson P, et al. Topiramate and word-finding difficulties in patients with epilepsy. *Neurology*. 2003;60:1104–1107.
85. Hirsch LJ, Weintraub DB, Buchsbaum R, et al. Predictors of lamotrigine-associated rash. *Epilepsia*. 2006;47:318–322.
86. Messenheimer JA. Rash in adult and pediatric patients treated with lamotrigine. *Can J Neurol Sci*. 1998;25:S14–S18.
87. Rowan AJ, Ramsay ER, Collins JF, et al. New onset geriatric epilepsy: A

randomized study of gabapentin, lamotrigine, and carbamazepine. *Neurology*. 2005;64:1868–1873.

88. Foorozan R. Vigabatrin: Lessons learned from the United States experience. *J Neuroopthalmol*. 2018;38(4):442–450.
89. Herzog AG. Progesterone therapy in women with epilepsy: A 3-year follow-up. *Neurology*. 1999;52(9):1917–1918.
90. Harden CL, Pulver MC, Ravdin L, et al. The effect of menopause and perimenopause on the course of epilepsy. *Epilepsia*. 1999;40(10):1403–1407.
91. Verrotti A, D'Egidio C, Mohn A, et al. Antiepileptic drug, sex hormones, and PCOS. *Epilepsia*. 2011;52:199–211.
92. Savers A, Harden CL. Gender issues for drug treatment. In: Engel J, Pedley TA, eds. *Epilepsy: A Comprehensive Text Book*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008;1263–1269.
93. Harden CL, Hopp J, Ting TY, et al. Practice parameter update: Management issues for women with epilepsy—focus on pregnancy (an evidence-based review): Obstetrical complications and change in seizure frequency. *Neurology*. 2009;73:126–132.
94. Harden CL, Meador KJ, Pennell PB, et al. Management issues for women with epilepsy—Focus on pregnancy (an evidence-based review): II. Teratogenesis and perinatal outcomes. *Neurology*. 2009;50:1237–1246.
95. Williams J, Myson V, Steward S, et al. Self discontinuation of AEDs in pregnancy: Detection by hair analysis. *Epilepsia*. 2002;43(8):824–831.
96. Tomson T, Marson A, Boon P, et al. Valproate in the treatment of epilepsy in girls and women of childbearing potential. *Epilepsia*. 2015;56(7):1006–1019.
97. Harden CL, Pennell PB, Koppel BS, et al. Management issues for women with epilepsy—Focus on pregnancy (an evidence-based review): III. Vitamin K, folic acid, blood levels, and breast-feeding: Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia*. 2009;50:1247–1255.
98. Meador KJ, Baker GA, Browning N, et al. Effects of breastfeeding in children of women taking antiepileptic drugs. *Neurology*. 2010;75:1954–1960.
99. Dreifuss FE, Langer DH, Moline KA, et al. Valproic acid hepatic fatalities-experience since 1984. *Neurology*. 1989;39:201–207.

100. Garnet WR. Antiepileptic drug treatment: Outcomes and adherence. *Pharmacotherapy*. 2000;20:191s–199s.
101. Mattson RH, Cramer JA, Collins JF. Prognosis for total control of complex partial and secondarily generalized tonic-clonic seizures. Department of Veterans Affairs Epilepsy Cooperative Studies No. 118 and No. 264. *Neurology*. 1996;46:68–76.
102. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia*. 2010;51(6):1069–1077.
103. Practice parameter: A guideline for discontinuing antiepileptic drugs in seizure-free patients—summary statement. Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 1996;47(2):600–602.
104. Anderson T, Brathen G, Person A, et al. A comparison between one and three years of treatment in uncomplicated childhood epilepsy: A prospective study. The EEG as a predictor of outcome after withdrawal of treatment. *Epilepsia*. 1997;38:228–232.
105. Chadwick D, Taylor J, Johnson T. Outcomes after seizure recurrence in people with well-controlled epilepsy and the factors that influence it. The MRC antiepileptic drug withdrawal group. *Epilepsia*. 1996;37:1043–1050.
106. Berg AT, Shinnar S. Relapse following discontinuation of antiepileptic drugs: A meta-analysis. *Neurology*. 1994;44:601–608.

74

Status Epilepticus

Stephanie J. Phelps and James W. Wheless

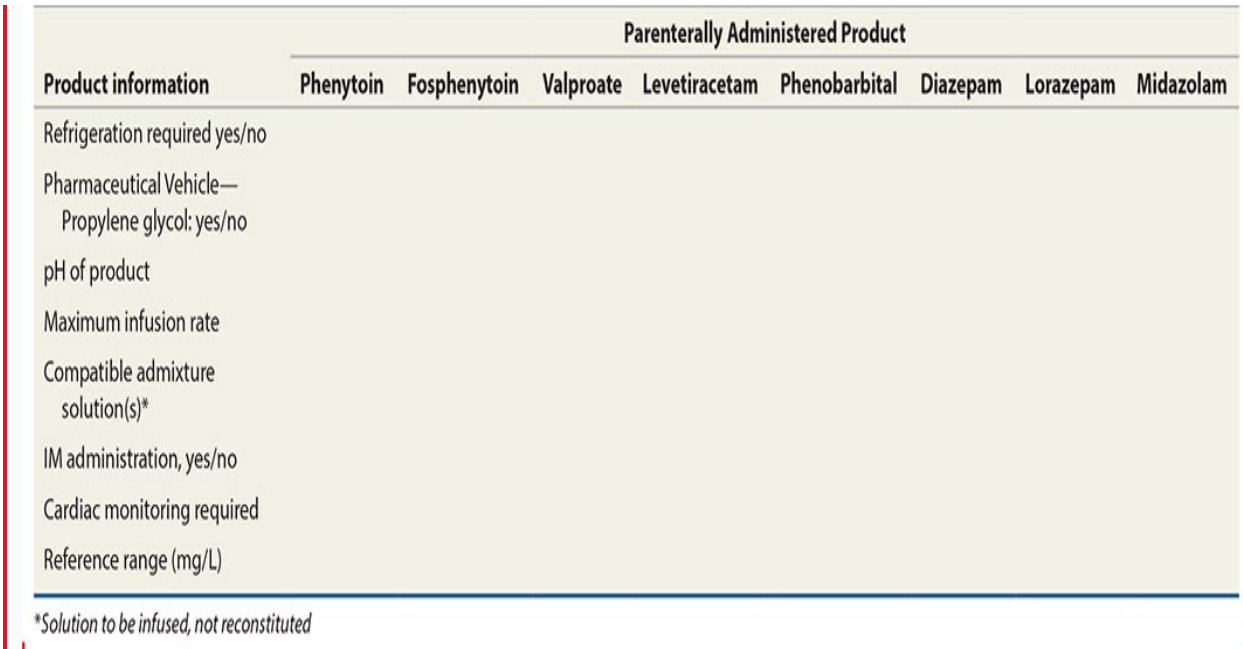
KEY CONCEPTS

1. Status epilepticus (SE) is a neurologic emergency that may be associated with significant morbidity and mortality.
2. Generalized convulsive status epilepticus (GCSE) is defined as any recurrent or continuous seizure activity lasting longer than 30 minutes in which the patient does not regain baseline mental status. Any seizure that does not stop within 5 minutes should be aggressively treated as impending SE.
3. There are two types of SE, GCSE and nonconvulsive status epilepticus (NCSE). GCSE is the most common type and can be divided into four stages: (1) impending, (2) established, (3) refractory, and (4) super-refractory.
4. Although the pathophysiology of GCSE is unknown, experimental models have shown that there is a dramatic decrease in γ-aminobutyric acid (GABA)–mediated inhibitory synaptic transmission and that glutamatergic excitatory synaptic transmission sustains the seizures.
5. During prolonged GCSE, $GABA_A$ receptors move from the synaptic membrane into the cytoplasm where they become functionally inactive. A loss of these receptors on the synaptic surface may result in time-dependent pharmacoresistance to benzodiazepines. The number and activities of glutamatergic N-methyl-D-aspartate (NMDA) receptors also increase, suggesting a role for ketamine.
6. The main purpose of treatment is to prevent or decrease morbidity and mortality of prolonged seizures. Pharmacologic treatment needs to be rapid and aimed at terminating both electrical and clinical seizures. The probability of poorer outcomes increases with an increased length of electroclinical seizure activity.

7. Although IM midazolam, IV lorazepam, IV diazepam, and IV phenobarbital effectively terminate seizures lasting at least 5 minutes, IV lorazepam is the preferred benzodiazepine for initial treatment of GCSE because of its efficacy and long duration of action in the central nervous system (CNS). In patients without an established IV site, midazolam is the preferred benzodiazepine for intramuscular and intranasal administration.
8. Although practice is slowly moving to other anticonvulsants, the hydantoins (ie, phenytoin, fosphenytoin) continue to be the long-acting anticonvulsants used most frequently. Insufficient data exist regarding the comparative efficacy of these two anticonvulsants; however, fosphenytoin is better tolerated and hence preferred. Either should be given concurrently with benzodiazepines.
9. The second anticonvulsant administered is less effective than the first "standard" anticonvulsant in both adults and pediatric patients. The third anticonvulsant may be significantly less effective.
10. If GCSE is not controlled by two anticonvulsants (a benzodiazepine and a standard antiepileptic drug), it is considered to be refractory. In these cases, anesthetic doses of midazolam, pentobarbital, or propofol may be used and assessed with continuous EEG monitoring.

Preclass Engaged Learning Activity

In preparation of the class session, provide missing information (if available) for the following table.



Product information	Parenterally Administered Product							
	Phenytoin	Fosphenytoin	Valproate	Levetiracetam	Phenobarbital	Diazepam	Lorazepam	Midazolam
Refrigeration required yes/no								
Pharmaceutical Vehicle—Propylene glycol: yes/no								
pH of product								
Maximum infusion rate								
Compatible admixture solution(s)*								
IM administration, yes/no								
Cardiac monitoring required								
Reference range (mg/L)								

*Solution to be infused, not reconstituted

Case Question: An order is written for a 15-mg PE/kg fosphenytoin loading dose for a 60-kg patient. The dose is added to 50 mL of an appropriate fluid and is to be given at the maximum rate of administration. The nurse asks what rate the infusion device should be set to (mL/min) and how long it will take to infuse the dose.

INTRODUCTION

1 2 3 Status epilepticus (SE) is a common neurologic emergency that is associated with brain damage and death. The Commission on Classification and Terminology and the Commission on Epidemiology of the International League Against Epilepsy (ILAE) have recently proposed a new definition: Conceptually, SE results from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures. There are two operational dimensions to this new definition. First, the length of the seizure and the time point (5 minutes) beyond which the seizure should be regarded as “continuous seizure activity.” Second, is the time of ongoing seizure activity after which there is a risk of long-term consequences (30 minutes). Both time points are based on animal experiments and clinical research; hence, these time points should be considered the best estimates currently available.[1] The traditional definition defines SE as (a) any seizure lasting longer than 30 minutes whether or not consciousness is impaired or (b)

recurrent seizures without an intervening period of consciousness between seizures.[2] Clinically, this definition has limited use, as the average seizure is less than 2 minutes; and only 40% of seizures lasting 10 to 29 minutes cease without treatment.[3] Pharmacoresistance and mortality significantly increase with prolonged seizure duration. Therefore, aggressive treatment of seizures lasting 5 minutes or more is strongly recommended. It is important to note that SE can present in several forms (**Table 74-1**), including generalized convulsive status epilepticus (GCSE) and nonconvulsive status epilepticus (NCSE).

TABLE 74-1 International Classification of Status Epilepticus

Convulsive		Nonconvulsive	
International	**Traditional Terminology**	**International**	**Traditional Terminology**
Generalized SE • Tonic-Clonic[a,b] • Tonic[c] • Clonic[c] • Myoclonic[b] • *Erratic*[d]	Grand mal, epilepticus convulsivus	Absence[c]	Petit mal, spike-and-wave stupor, spike and-slow-wave or 3/s spike-and-wave, epileptic fugue, epilepsia minora continua, epileptic twilight, minor SE
Secondary generalized SE[a,b] • Tonic • Partial seizures with secondary generalization		Partial SE[a,b] Simple partial Somatomotor Dysphasic Other types Complex partial	Focal motor, focal sensory, epilepsia partialis continua, adversive SE Elementary Temporal lobe, psychomotor, epileptic fugue state, prolonged epileptic stupor, prolonged epileptic confusional state, continuous epileptic twilight state

SE, status epilepticus.

[a]Most common in older children.

[b]Most common in adolescents and adults.

[c]Most common in infants and young children.

[d]Most common in neonates.

Nonconvulsive status epilepticus occurs in 25% of those with SE and is characterized by a fluctuating or continuous “epileptic twilight” state that produces altered consciousness and/or behavior (eg, lethargy and decreased mental function).[4] An electroencephalogram (EEG) is the most important diagnostic and management tool. In most instances, a benzodiazepine and/or valproate remain drugs of choice.[4] Although intravenous (IV) hydantoin, levetiracetam, lacosamide, or phenobarbital can be tried in nonresponders, general anesthesia is usually not appropriate.[4]

3 This chapter will focus on GCSE, which is the most common and severe

form of SE. It is characterized by repeated primary or secondary generalized seizures that involve both hemispheres of the brain, results in a loss of consciousness, and are associated with a persistent postictal state. In general, GCSE can be divided into four phases: (1) stabilization, (2) initial therapy, (3) secondary therapy, and (4) third therapy (Table 74-2).[5]

TABLE 74-2 Generalized Convulsive Status Epilepticus

Phase	Time	Stage	Definition
Stabilization phase	0-5 minutes		An acute condition characterized by convulsive seizures. This may include pre-hospitalization or emergency room care
Initial-therapy phase (5-20 minutes)	0-20 minutes	Impending GCSE	
Second-therapy phase (20-40 minutes)	20-40 minutes	Established GCSE	An acute condition characterized by continuous seizures for at least 20 minutes, or by 20 minutes of intermittent seizures without full recovery of consciousness between events
Third-therapy phase	40-60 minutes	Refractory GCSE	An acute condition characterized by continuous seizures despite initial treatment with 2 AEDs
	>24 hours	Supra-refractory	An acute condition characterized by seizures that continue 24 hours or longer after the administration of anesthesia, including cases in which SE recurs on reduction or withdrawal of anesthesia

AED, antiepileptic drug; GCSE, generalized convulsive status epilepticus; SE, status epilepticus.

EPIDEMIOLOGY

The reported worldwide incidence of GCSE varies considerably and has ranged from 5.1 to 41 per 100,000. A recent meta-analysis involving 11 studies reported a crude annual incidence of 12.6 per 100,000 (95% CI: 10-15.3), with the incidence being highest in developing countries.[6] Although GCSE has no predilection for gender,[6] it does occur more frequently in nonwhites across all ages.[7] The incidence is highest in those younger than 1 year of age[7] and in those older than 60 years of age.[6] Economic income may contribute to a difference in the overall incidence.[6] Most GCSE occurs in individuals with no history of epilepsy; however, approximately 5% of adults and 10% to 25% of children with epilepsy will develop GCSE.

ETIOLOGY

Precipitating events for GCSE vary and generally reflect different populations and referral patterns. Most episodes in individuals with epilepsy occur because

of acute anticonvulsant withdrawal, a metabolic disorder or concurrent illness, or progression of a preexisting neurologic disease. Common etiologies and mortality rates are shown in Table 74-3.[7,8] Precipitating events are divided into those with or without neurologic structural lesions or those with a precipitating injury or insult. Cases with structural lesions or those with a specific neurologic insult are associated with a poor prognosis.

TABLE 74-3 Etiology and Mortality for Pediatric and Adult Cases of Status Epilepticus

Etiology	Mortality Number of Cases (%) $n = 200$ Cases of Pediatric SE	Mortality Number of Cases (%) $n = 512$ Cases of Adult SE
Type I (no Structural Lesion)		
Infection	55 (5)	6 (35)
CNS infection	11 (0)	2 (20)
Metabolic	20 (5)	12 (36)
Low AED levels	16 (0)	24 (7)
Alcohol	0 (0)	13 (8)
Idiopathic	6 (0)	13 (18)
Type II (Structural Lesion)		
Anoxia/hypoxia	27 (13)	14 (65)
CNS tumor	3 (50)	5 (22)
CVA	5 (0)	26 (27)
Drug overdose	5 (0)	3 (23)
Hemorrhage	5 (11)	4 (35)
Trauma	13 (0)	3 (23)
Remote causes[a]	33 (5)	7 (13)

Percentages do not add up to 100% because some patients had multiple etiologies.

AED, antiepileptic drug; CVA, cerebrovascular accident; SE, status epilepticus.

[a]More than half of remote causes were congenital malformations and CVA in pediatric and adult patients, respectively.

Data from References 7 and 8.

There are major differences in etiologies for pediatric and adult patients (see Table 74-3). During their first few weeks of life, infants who are born to mothers addicted to substances of abuse can develop drug withdrawal seizures. Other

neonates can develop GCSE because of pyridoxine deficiency, which should resolve within minutes following IV pyridoxine (100 mg). Acute encephalopathy and metabolic disorders are the major causes of GCSE in those younger than 1 year of age. In young children, the cause is often a nonspecific illness such as fever and/or a viral illness. The most frequent precipitating events in adults are cerebrovascular disease, rapid anticonvulsant withdrawal, and low anticonvulsant serum concentrations. Cerebrovascular disease is the leading cause in those who have their first seizures after age 60. Prescription, over-the-counter, herbal, and recreational drugs should be considered in anyone with new-onset GCSE.

PATHOPHYSIOLOGY

Seizures occur when the excitatory neurotransmission overcomes inhibitory impulses in one or more brain regions. After a single, brief, generalized tonic–clonic seizure (less than 5 minutes), the seizure threshold is significantly elevated. The brain's inhibitory mechanisms restore the balance of normal neurotransmission and prevent runaway excitation. Although it is unknown why the mechanisms that control normal brain homeostasis fails when seizures occur in close succession or the magnitude of the proconvulsant stimulus is severe, compensatory mechanisms can be overwhelmed, and seizures become self-sustaining.

4 While the exact cellular mechanisms are unknown, it appears that seizure initiation is caused by an imbalance between excitatory (eg, glutamate, calcium, sodium, substance P, and neurokinin B) and inhibitory neurotransmission (eg, γ-aminobutyric acid [GABA], adenosine, potassium, neuropeptide Y, opioid peptides, and galanin).[10] More specifically, $GABA_A$-mediated inhibition becomes less effective while glutamate excitatory actions are enhanced. These alterations have implications in understanding how GCSE progresses to refractory disease and impacts decisions related to sequencing antiepileptic medications.

Most of what is known has focused on gated ion channels; however, GCSE is largely caused by glutamate acting on postsynaptic N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-isoxazole-4-propionate (AMPA)/kainate receptors.[10] During GCSE, NMDA subunits are recruited to the synaptic membrane where they form additional receptors that are proconvulsant. Glutamate activation of the NMDA and AMPA receptors causes an opening of the gated calcium and sodium channels, which lead to neuronal depolarization.[11]

Sustained depolarization may maintain GCSE and eventually cause neuronal death through calcium-, free radical–, and kinase-mediated events.[12] Although drugs acting as NMDA and AMPA receptor antagonists seem attractive, it is likely that glutamate is not the sole mechanism for sustaining GCSE and that other mechanisms become increasingly important as the duration of seizures increases.

5 Within minutes of repetitive seizures receptor trafficking (eg, metabotropic GABA and glutamate receptors) occurs, as the $GABA_A$ postsynaptic receptors control chloride channels to produce hyperpolarization (inhibition) of the postsynaptic cell membrane.[11] These receptors have binding sites for GABA and select anticonvulsants (eg, phenobarbital and benzodiazepines) and enhance $GABA_A$-mediated chloride inhibitory currents. It was previously thought that a decrease in presynaptic GABA led to prolonged seizures; however, it is currently held that GABA concentrations increase during the early phases of GCSE and continue to be elevated during late GCSE. During prolonged seizures, postsynaptic $GABA_A$ receptors experience endocytosis which results in a decrease in the number of γ_2 and β_{2-3} subunits as the receptors move from the synaptic membrane into the cytoplasm where they are functionally inactive. These modifications of $GABA_A$ receptors may decrease response to both endogenous GABA and GABA agonists.[10] The γ_2 subunit is associated with benzodiazepine effectiveness; hence, a loss of these on the synaptic surface would result in time-dependent pharmacoresistance to a benzodiazepine. Clinically, the relative potencies of benzodiazepines can be reduced up to 20-fold if seizures persist for more than 30 minutes.[11] For this reason, a benzodiazepine should always be combined with another drug that acts at a different site. A similar phenomenon occurs with sodium channel antagonists (phenytoin); however, the magnitude of resistance is less.

6 As GCSE persists, complex pathophysiologic and biochemical changes lead to systemic alterations, progression of motor phenomena, and development of specific EEG findings.[12] Two distinct and predictable phases have been identified. Phase I occurs during the first 30 minutes of seizure activity, and phase II immediately follows.[12] Although these systemic complications affect the prognosis of GCSE, a prolonged seizure can destroy neurons independent of these events.[11] In fact, the systemic effects of induced seizures in animals can be blocked, but the damage to the neocortex, cerebellum, and hippocampus persists.

During phase I, each seizure markedly increases plasma epinephrine,

norepinephrine, and steroid concentrations, which can cause hypertension, tachycardia, and cardiac arrhythmias. Within minutes, arterial systolic pressures can rise to above 200 mm Hg, and heart rate can increase by 83 beats per minute.[12] Mean arterial pressure does not fall below 60 mm Hg (8.0 kPa); hence, cerebral perfusion pressure is not compromised. In animals, cerebral blood flow is also increased, thereby protecting neurons from hypoxic injury.

In the presence of a hypoxic myocardium, seizure-induced increases in sympathetic and parasympathetic stimulation of the heart can result in ventricular arrhythmias.[12] Autonomic neuron stimulation can cause a release of insulin and glucagon. Concurrently, circulating catecholamines cause an elevation of hepatic cyclic adenosine monophosphate, producing glycogenolysis. Although the patient can be hyperglycemic initially, serum glucose begins to fall.[12]

Seizure-induced muscular contractions and hypoxia cause lactic acid release, which can produce severe acidosis that may be accompanied by hypotension and shock. Muscle contractions can be so severe that rhabdomyolysis with secondary hyperkalemia and acute tubular necrosis can occur. The airway can be obstructed, causing the patient to become cyanotic or hypoxic. Additionally, an increase in salivation and tracheal and pulmonary secretions can cause aspiration pneumonia. Although transient pleocytosis can develop, it should not be attributed to SE until infectious causes have been eliminated. Between seizures, the EEG slows, and blood pressure normalizes and although metabolic demands are increased, the brain is able to adequately compensate.

When seizures exceed 30 minutes (phase II), the EEG ictal discharge and clonic motor activity become continuous, and the patient begins to decompensate.[12] Despite elevated levels of catecholamines, the patient can become hypotensive. During this time, autoregulation of cerebral blood flow becomes dependent on mean arterial pressure and begins to fail. There continues to be excessive consumption of oxygen and glucose; however, compensatory mechanisms are no longer able to meet demands.

During Phase II, the serum glucose concentration may be normal or decreased. Profound hypoglycemia, secondary to hyperinsulinemia, can occur in those with hepatic dysfunction or reduced glycogen stores.[12] Hyperthermia and respiratory deterioration with hypoxia and ventilatory failure can develop, and there may be increased sweating and salivation. Metabolic and biochemical complications, including respiratory and metabolic acidosis, hyperkalemia, hyponatremia, and azotemia, may develop.

Morbidity and Mortality

Generalized convulsive status epilepticus is harmful to the brain and while most contend that the GCSE is responsible for the damage, it is unknown if the morbidity results from the underlying etiology or the GCSE. Regardless of the inducing stimulus, neuronal damage in animal models is evident following 30 to 60 minutes of GCSE, and most progress to develop epilepsy following a prolonged seizure. Interestingly, inhibiting the seizure-induced neuronal damage does not prevent the development of epilepsy, suggesting that the seizures themselves may be harmful. It is hard to establish a relationship between GCSE and long-term outcomes because it is difficult to weigh the effects of seizure type, etiology, duration, concurrent physiologic events, and therapy or lack thereof. It has been shown that patients with a history of prolonged febrile seizures who later developed epilepsy share similar histopathologic changes (ie, hippocampal sclerosis) to those found in animal models of GCSE. In these cases, the period between the initial GCSE and the first epileptic seizure may be months to decades, suggesting a possible link between GCSE and the development of epilepsy. Importantly, studies of GCSE show that the currently available anticonvulsants do not reproducibly prevent the development of epilepsy following prolonged seizures (ie, they are anticonvulsant, not antiepileptogenic).[9]

Patients who develop epilepsy following prolonged GCSE are less likely to experience remission of their seizures and may have decreased cognitive and memory function, mental impairment, or neurologic deficits when compared to those who develop epilepsy and subsequently have GCSE. Most studies have found that younger children, the elderly, and those with preexisting epilepsy have a higher propensity for sequelae. Unless accompanied by an underlying neurologic abnormality, febrile SE is less likely to be associated with sequelae.

Lv et al conducted a meta-analysis of 38 studies and reported an overall worldwide case fatality rate of 14.9%,[6] with the highest rate in those >60 years of age (24.9%) and in those with refractory GCSE (33.3%). Estimated mortality in the United States following GCSE ranges between 22,000 and 42,000 individuals per year, with rates lowest in children. The duration of seizure also impacts mortality, as Kantaene et al reported a one-year mortality rate of 22% for patients with refractory GCSE compared to a rate of 36% for those with supra-refractory GCSE.[13] When compared with other populations, neonates have higher mortality and more neurologic sequelae.

Table 74-3 summarizes the etiology and corresponding mortality rates for

GCSE.[7,8] Interestingly, the mortality associated with many etiologies is significantly greater in adults than in children. Unresponsive patients may die from GCSE, but more frequently they die from the acute illness that precipitated the GCSE. For example, patients with serious central nervous system (CNS) structural changes (eg, hemorrhage and stroke) have a poor prognosis, compared to those with no structural lesion.

Outcome is affected by the time between onset of GCSE and the initiation of treatment and the duration of the seizure. Mortality significantly increases with increased seizure duration (eg, 2.6% for seizures 10-29 minutes, 19% for seizures lasting greater than 30 minutes, and 32% for seizures lasting greater than 60 minutes).[3,8] And while mortality has decreased over the past decade and this probably reflects a recognition of the need to initiate sequenced therapy using large doses of anticonvulsant medication as soon as possible.

CLINICAL PRESENTATION

Accurate diagnosis requires observation, physical examination, laboratory assessment, EEG, and neurologic imaging. The nature and duration of the seizure should be obtained, but a diagnosis of GCSE should not be made until a clinician has observed a seizure. Most patients have an altered consciousness that ranges from obtunded to marked lethargy and somnolence with pronounced eyes-open unresponsiveness and waxy rigidity. Motor features can include muscle contractions, extensor or flexor posturing, and spasms. Over time, the clinical manifestations become less apparent. This has important ramifications, in that seizures appear to have terminated without treatment or when an ineffective therapy is given.

In addition to an assessment of language and cognitive abilities, the physical and neurological examinations should assess motor, sensory, and reflex abnormalities, pupillary response, asymmetry, and posturing. The patient should also be examined for secondary injuries (eg, tongue lacerations, shoulder dislocations, and head and facial trauma).

Laboratory tests are essential to the diagnosis of various etiologies. Hypoglycemia, hyponatremia, hypernatremia, hypomagnesemia, hypocalcemia, and renal failure all can cause seizures. A urine drug screen can help eliminate illicit drug use or drug overdose. Serum drug concentration(s) should be obtained in those on chronic anticonvulsants, as low concentrations can reflect partial adherence or rapid drug withdrawal. Although a baseline serum anticonvulsant concentration would be helpful in determining whether a loading

dose of a specific anticonvulsant is required, the time required to perform the test makes this impractical. Assessment of other laboratory parameters (eg, hematology and chemistries to include albumin, renal function, and hepatic function) that affect anticonvulsant dosing also can be useful. An EEG is a valuable diagnostic tool, particularly in those with prolonged GCSE in whom clinically apparent seizures are not always evident. The initiation of anticonvulsant therapy should not be delayed while awaiting testing or results.

CLINICAL PRESENTATION

Status Epilepticus

Symptoms

- Impaired consciousness (eg, lethargy to coma)
- Disorientation once GCSE is controlled
- Pain associated with injuries (eg, tongue lacerations, shoulder dislocations, back pain, myalgias, headache, and head trauma)

Early Signs

- Generalized convulsions
- Acute injuries or CNS insults that cause extensor or flexor posturing
- Hypothermia or fever suggestive of intercurrent illnesses (eg, sepsis or meningitis)
- Incontinence
- Normal blood pressure or hypotension and respiratory compromise

Late Signs

- Clinical seizures may or may not be apparent
- Pulmonary edema with respiratory failure
- Cardiac failure (dysrhythmias, arrest, and cardiogenic shock)
- Hypotension or hypertension
- Disseminated intravascular coagulation, multisystem organ failure
- Rhabdomyolysis
- Hyperpyrexia

Initial Laboratory Tests

- Complete blood count (CBC) with differential
- Serum chemistry profile (eg, electrolytes, calcium, magnesium, glucose, serum creatinine, alanine aminotransferase [ALT], and aspartate aminotransferase [AST])
- Urine drug/alcohol screen
- Blood cultures
- Arterial blood gas to assess for metabolic and respiratory acidosis, oxygenation
- Serum drug concentration if previous anticonvulsant(s) are suspected or known

Other Diagnostic Tests

- Spinal tap if CNS infection suspected
- EEG should be obtained on presentation and once clinical seizures are controlled
- CT with and without contrast
- MRI
- Radiograph if indicated to diagnose fractures

Once seizures have stopped, it is important to determine if the patient is febrile or has a systemic or CNS infection. Many physiologic consequences of GCSE (eg, leukocytosis, pleocytosis, and hyperthermia) produce symptoms that can be confused with other conditions. If a CNS infection is suspected, a spinal tap should be performed, and empiric antibiotics should be started. If vascular, neoplastic, or infectious etiologies are suspected, computed tomography (CT) or magnetic resonance imaging (MRI) should be obtained once the seizures are controlled.

TREATMENT

Various treatments are available for the management of GCSE. These range from the abortion of impending SE with rescue medications to the use of pharmacologic and nonpharmacologic therapies for GCSE and

refractory/resistant SE.

Desired Outcomes

7 Short-term desired outcomes include (a) immediate termination of all clinical and electrical seizure activity, (b) no clinically significant adverse effects, and (c) lack of recurrent seizure activity. The long-term outcomes involve minimizing or avoiding pharmacoresistant epilepsy and/or the development of neurologic sequelae that significantly impact the quality of life.

Nonpharmacologic Therapy

Stabilization Phase

The time of seizure onset should be noted. Vital signs should be assessed, an adequate and protected airway should be established, ventilation should be maintained, and oxygen should be administered (**Fig. 74-1**). Intravenous access should be established and hyperthermia, if present, should be aggressively treated (eg, rectal or IV acetaminophen and cooling blanket). Febrile GCSE is common in the pediatric patient, and normalization of body temperature helps minimize neurologic morbidity.

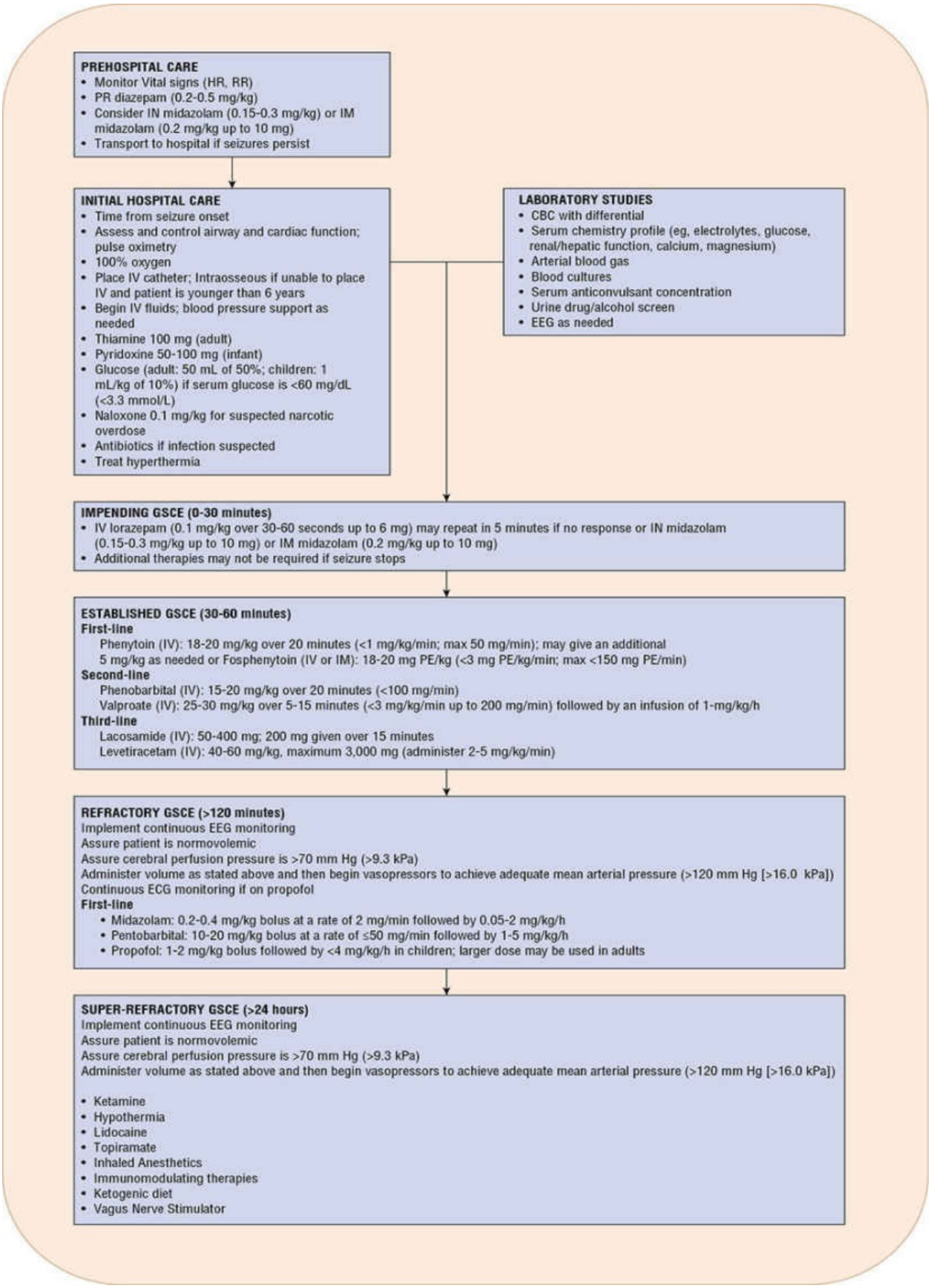
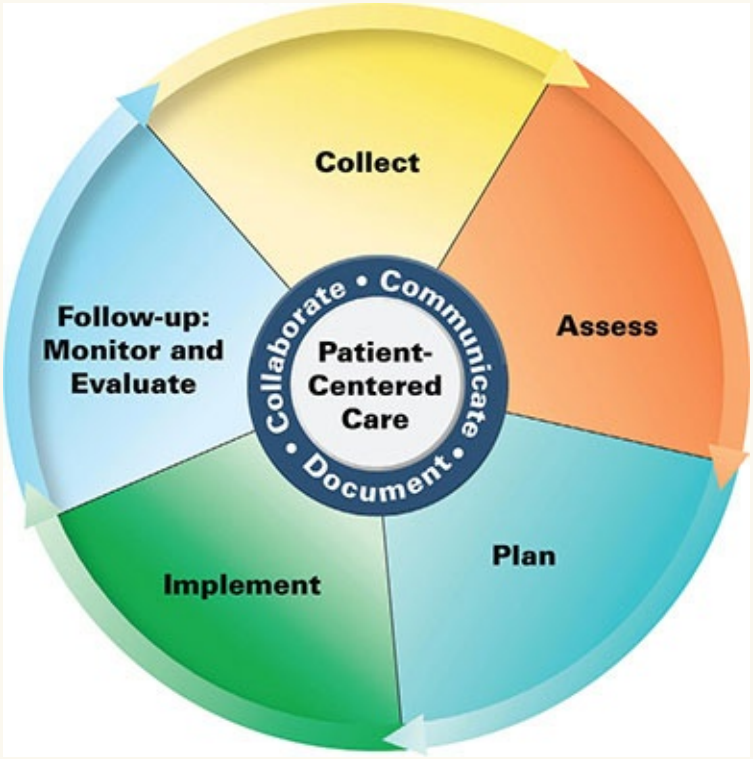

PREHOSPITAL CARE
• Monitor Vital signs (HR, RR)
• PR diazepam (0.2-0.5 mg/kg)
• Consider IN midazolam (0.15-0.3 mg/kg) or IM midazolam (0.2 mg/kg up to 10 mg)
• Transport to hospital if seizures persist
INITIAL HOSPITAL CARE
• Time from seizure onset
• Assess and control airway and cardiac function; pulse oximetry
• 100% oxygen
• Place IV catheter; Intraosseous if unable to place IV and patient is younger than 6 years
• Begin IV fluids; blood pressure support as needed
• Thiamine 100 mg (adult)
• Pyridoxine 50-100 mg (infant)
• Glucose (adult: 50 mL of 50%; children: 1 mL/kg of 10%) if serum glucose is <60 mg/dL (<3.3 mmol/L)
• Naloxone 0.1 mg/kg for suspected narcotic overdose
• Antibiotics if infection suspected
• Treat hyperthermia
LABORATORY STUDIES
• CBC with differential
• Serum chemistry profile (eg, electrolytes, glucose, renal/hepatic function, calcium, magnesium)
• Arterial blood gas
• Blood cultures
• Serum anticonvulsant concentration
• Urine drug/alcohol screen
• EEG as needed
IMPENDING GSCE (0-30 minutes)
• IV lorazepam (0.1 mg/kg over 30-60 seconds up to 6 mg) may repeat in 5 minutes if no response or IN midazolam (0.15-0.3 mg/kg up to 10 mg) or IM midazolam (0.2 mg/kg up to 10 mg)
• Additional therapies may not be required if seizure stops
ESTABLISHED GSCE (30-60 minutes)
First-line
Phenytoin (IV): 18-20 mg/kg over 20 minutes (<1 mg/kg/min; max 50 mg/min); may give an additional 5 mg/kg as needed or Fosphenytoin (IV or IM): 18-20 mg PE/kg (<3 mg PE/kg/min; max <150 mg PE/min)
Second-line
Phenobarbital (IV): 15-20 mg/kg over 20 minutes (<100 mg/min)
Valproate (IV): 25-30 mg/kg over 5-15 minutes (<3 mg/kg/min up to 200 mg/min) followed by an infusion of 1-mg/kg/h
Third-line
Lacosamide (IV): 50-400 mg; 200 mg given over 15 minutes
Levetiracetam (IV): 40-60 mg/kg, maximum 3,000 mg (administer 2-5 mg/kg/min)
REFRACTORY GSCE (>120 minutes)
Implement continuous EEG monitoring
Assure patient is normovolemic
Assure cerebral perfusion pressure is >70 mm Hg (>9.3 kPa)
Administer volume as stated above and then begin vasopressors to achieve adequate mean arterial pressure (>120 mm Hg [>16.0 kPa])
Continuous ECG monitoring if on propofol
First-line
• Midazolam: 0.2-0.4 mg/kg bolus at a rate of 2 mg/min followed by 0.05-2 mg/kg/h
• Pentobarbital: 10-20 mg/kg bolus at a rate of ≤50 mg/min followed by 1-5 mg/kg/h
• Propofol: 1-2 mg/kg bolus followed by <4 mg/kg/h in children; larger dose may be used in adults
SUPER-REFRACTORY GSCE (>24 hours)
Implement continuous EEG monitoring
Assure patient is normovolemic
Assure cerebral perfusion pressure is >70 mm Hg (>9.3 kPa)
Administer volume as stated above and then begin vasopressors to achieve adequate mean arterial pressure (>120 mm Hg [>16.0 kPa])
• Ketamine
• Hypothermia
• Lidocaine
• Topiramate
• Inhaled Anesthetics
• Immunomodulating therapies
• Ketogenic diet
• Vagus Nerve Stimulator

FIGURE 74-1 Algorithm for the treatment of GCSE. (BP, blood pressure; CBC, complete blood count; CI, continuous infusion; D12.5W, 12.5% Dextrose in water; D25W, 25% Dextrose in water; D50W, 50% Dextrose in water; EEG, electroencephalogram; GCSE, generalized convulsive status epilepticus; HR, heart rate; IN, intranasal; PE, phenytoin equivalents; PR, per rectum; RR, respiratory rate.)*a* Because variability exists in dosing, monitor serum concentration.

Laboratory studies including serum glucose and electrolyte levels (including calcium and magnesium), complete blood count, and renal and hepatic function tests should be performed. Anticonvulsant serum concentration should be obtained as needed, and a urine drug screen should be performed if there is suspicion of ingestion.

Although hypoglycemia rarely causes GCSE, adults and children (ages 2 years and older) with a blood glucose less than 60 mg/dL (3.3 mmol/L) should receive 50 mL of a 50% dextrose solution, and 1 mL/kg of a 25% dextrose solution, respectively.[2] Because Wernicke's encephalopathy can develop in alcoholics, adults should receive IV thiamine (100 mg) prior to glucose administration. Serum glucose concentration should be determined to assess the need for further supplementation. Children younger than 12 to 18 months of age should receive pyridoxine (Vitamin B_6) until metabolic causes have been ruled out.

If an infection is suspected, blood cultures, lumbar puncture, and urinalysis may be needed. Antibiotic administration does not need to wait until after the lumbar puncture if the patient is medically unstable. Patients with persistent GCSE should also have frequent arterial blood gas determinations to assess for metabolic acidosis, which should be treated with sodium bicarbonate if the pH is less than 7.2, with assisted ventilation being used to correct respiratory acidosis.



Patient Care Process for Status Epilepticus

Collect *(some items may be deferred to a later time due to time constraints associated with a medical emergency)*

- Patient characteristics (eg, age, weight)
- Time of seizure onset and duration of seizure activity (see Table 74-2)
- Past medical history (eg, known epilepsy and type or prior seizure, drug-allergies) (see Table 74-1)
- Social history (eg, ethanol use, illicit drug use, ketogenic diet)
- Complete a medication history of current prescription, over-the-counter (OTC) medications, herbals products, and dietary supplements including any recently started or stopped medications, (prescription or nonprescription)
- Information (eg, agent, route, dose, response) regarding administration of anticonvulsants immediately prior to emergency department/hospitalization
- Objective data

- Age, weight, height
- Temperature, blood pressure, heart rate, respiratory rate, oxygen (O_2) saturation, arterial blood gases
- Labs including serum chemistries (eg, electrolytes, glucose, magnesium, renal/hepatic function studies; complete blood count (CBC) with differential and blood/urine cultures; urine drug screen (UDS) and serum anticonvulsant concentrations as warranted)
- Electroencephalogram (EEG), computed tomography (CT), magnetic resonance imaging (MRI) as needed

Assess

- If appropriate, assess medication adherence to anticonvulsants prior to admission and correct delivery of anticonvulsants during hospitalization
- Evaluate the appropriateness, effectiveness and safety of all chronic or acute prescription and nonprescription medications. (this should include checking serum drug concentration for an “effective” or “safe” concentration) (see Table 74-4)
- Airway (arterial blood gases, respiratory rate [RR]) and cardiac (blood pressure (BP), heart rate (HR)) stability
- Temperature for the presence of fever
- Possible etiologies for seizure (eg, known epilepsy, febrile, infectious, head trauma/cerebral vascular accident (CVA), drug-associated, low anticonvulsant serum concentrations) (see Table 74-3)
- Presence of seizure provoking factors (eg, ethanol, recreational drugs, adverse drug/herbal effect, drug–drug interaction, low or elevated anticonvulsant serum concentration) (see Table 74-3)
- Duration of seizure activity and characteristics of the seizure (see Table 74-2)
- Available laboratory studies
- Need for adjusted dosing based on organ function (eg, liver, kidney function), serum albumin, weight

Plan*

- Management of nonepilepsy causes for seizure (eg, opioid overdose, electrolytes imbalance) (see Table 74-3 and Fig. 74-1)

- Management of impending seizure activity (initial phase) including agent, dose, route, and method of administration, including the option for alternative agents and need for a second dose (see Table 74-2 and Fig. 74-1)
- Need for concurrent drug therapy including thiamine and glucose, pyridoxine, antipyretic, and empiric antibiotics (see Fig. 74-1)
- First-line anticonvulsant regimens for the second phase (established stage), including agent, dose, method of administration, and frequency including the option for a second dose if needed (see Tables 74-2 and 74-4 and Fig. 74-1)
- Anesthetic drugs for the third phase (refractory GCSE stage) including agent, dosage, method of administration accompanied by a plan to titrate and withdraw therapy (see Tables 74-2, 74-6 and Fig. 74-1)
- Monitor for effectiveness and safety of anticonvulsants including serum anticonvulsant concentration and drug–drug interaction during the management of GCSE (see Table 74-5)
- Drug therapy in transfer to a nonintensive care unit setting or discharge home including the transition to oral therapy and subsequent monitoring of serum anticonvulsant concentrations (see Table 74-4)
- Rescue therapies in the home environment including need, agent, dose, method of administration, and plan should first dose fail. Need for cardiopulmonary resuscitation (CPR) training
- Patient and/or legal guardian medication education at discharge including correct use of rescue therapies

Implement*

- In transition from home to the emergency department (ED), ED to hospitalization, and discharge home, ensure all medications have been ordered, that dosage is appropriate, and discontinued as appropriate (see Tables 74-4 and 74-6)
- Ensure all medications are being dispensed as prescribed (see Tables 74-4 and 74-6)
- Ensure all anticonvulsants are being administered and monitored correctly (see Table 74-5)

Follow-up: Monitor and Evaluate

- Anticonvulsant effectiveness in stopping clinical and electrical seizure activity
- Presence of adverse drug effects or drug–drug interactions (see Table 74-5)
- Therapeutic drug monitoring performed as needed with subsequent interpretation

** Collaborate with patient, caregivers, and other healthcare professionals.*

Because electrical seizures may persist in the absence of overt clinical motor manifestations, an EEG should be performed in patients who continue to have altered consciousness after clinical control of their seizures. Patients with persistent GCSE should also have continuous EEG monitoring.

Ketogenic Diet

A small number of reports have shown that an orally or intravenously administered ketogenic diet in a 4:1 ratio of fat to combined protein and carbohydrate could be tried in severe cases of super-refractory SE.[43,45] Before initiating the diet, metabolic disorders as a possible etiology should be eliminated. Close monitoring of total daily fluid, ketosis, and potential complications is essential. If metabolic acidosis develops, treatment is suggested to maintain serum bicarbonate levels greater than 18 to 20 mEq/L (mmol/L).[43]

Vagus Nerve Stimulation

Acute placement of a vagus nerve stimulator has been used in both pediatric and adult patients with refractory SE.[43] Currently its use for refractory SE is not recommended, as only grade D evidence suggests improvement in generalized refractory SE.[46]

Pharmacologic Therapy

Initial Therapy Phase (5-20 minutes)

When a seizure does not stop within 5 minutes, or when doubt exists regarding the diagnosis, patients should be treated as if they have GCSE (see Fig. 74-1) and initial therapies should be used. The benzodiazepines are the most commonly used classes of anticonvulsants for the initial treatment of GCSE. Only two[14,15] and three[14,16,17] class 1 studies have evaluated the

benzodiazepines in children and adults, respectively.

The benzodiazepines are effective initial therapy in most patients and considered as the initial therapy of choice as the evidence-based guidelines recommend the initial use of IM midazolam, IV lorazepam, or IV diazepam (see Fig. 74-1) in adults and the use of IV lorazepam or IV diazepam in children.[5] Intramuscular midazolam is preferred if IV access is not available; however, generally, one or two IV doses will terminate seizures within 2 to 3 minutes. All benzodiazepines are effective; therefore, preference is determined by differences in pharmacokinetics, route of administration, pharmacoeconomics, adverse-effect profile, and current availability.

Diazepam is extremely lipophilic with a large volume of distribution (1-2 L/kg). Although it initially distributes into the brain within seconds, it rapidly redistributes into fat, causing its CNS half-life to be less than 1 hour and its duration of effect to be less than 30 minutes. The rapid decrease in brain concentration and pharmacoresistance can cause seizure recurrence; hence, a longer-acting anticonvulsant (eg, phenytoin, levetiracetam or phenobarbital) should also be given immediately after diazepam. Dosing can be found in **Table 74-4**.

TABLE 74-4 Dosing of Medications Used in the Initial and Established Treatment of GCSE

Drug (Route)	Brand name	Initial Dose (Maximum Dose)	Maintenance Dose	Comments
Diazepam (IV)	Valium plus generic			
Adult		0.25 mg/kg[a,b,c] (20 mg)	Not used	Given IV at a rate not to exceed 5 mg/min
Pediatric		0.25-0.5 mg/kg[a,c] (20 mg)	Not used	
Fosphenytoin (IV)	Cerebyx plus generic			
Adult		20-25 mg PE/kg	4-5 mg PE/kg/day	Given IV at a rate not to exceed 150 mg PE/min in adults and 3 mg PE/kg/min in pediatric patients
Pediatric		20-25 mg PE/kg	5-10 mg PE/kg/day	
Levetiracetam (IV)	Keppra plus generics			
Adult		2,000-3,000 mg	1,000 mg thrice a day	Given IV over 5-10 minutes
Pediatric		40-60 mg/kg (3,000 mg)	40-60 mg/kg/day, given twice or thrice a day	
Lorazepam (IV)	Ativan plus generic			
Adult		4 mg[b,c] (6 mg)	Not used	Given IV at a rate not to exceed 2 mg/min in adult and pediatric patients
Pediatric		0.1 mg/kg[a,c] (6 mg)	Not used	
Midazolam (IV, IM)	Versed plus generic			
Adult		200 mcg/kg[a,d] (10 mg)	50-500 mcg/kg/hr[e]	Given IV at a rate 0.5-1 mg/min in adults and over 2-3 minutes in pediatric patients
Pediatric		150 mcg/kg[a,d] (10 mg)	60-120 mcg/kg/hr[e]	
Phenobarbital (IV)	Generic			
Adult		10-20 mg/kg[e]	1-4 mg/kg/day[e]	Given IV at a rate not to exceed 100 mg/min in adults and 30 mg/min in pediatric patients
Pediatric		15-20 mg/kg[e]	3-5 mg/kg/day[e]	
Phenytoin (IV)	Dilantin plus generic			
Adult		20-25 mg/kg[f]	4-5 mg/kg/day[e]	Given IV at a rate not to exceed 50 mg/min[g] in adults and 3 mg/kg/min (max 50 mg/min) in pediatric patients
Pediatric		20-25 mg/kg[f]	5-10 mg/kg/day[e]	
Valproate (IV)	Depacon plus generic			
Adult		15-30 mg/kg (3,000 mg)	1-4 mg/kg/hr[e]	Administer at 3 mg/kg/min; and follow by a continuous or intermittent infusion; larger doses may be required in those on hepatic enzyme inducers, monitor serum concentrations
Pediatric		20-25 mg/kg (3,000 mg)	1-4 mg/kg/hr[e], or give every 4-6 hours	

GCSE, generalized convulsive status epilepticus; PE, phenytoin equivalents.

[a]Doses can be repeated every 10 to 15 minutes until the maximum dosage is given.

[b]Initial doses in the elderly are 2 to 5 mg.

[c]Larger doses can be required if patients chronically on a benzodiazepine (eg, clonazepam).

[d]Can be given by the intramuscular, rectal, or buccal routes.

[e]Titrate dose as needed.

[f]Administer additional loading dose based on serum concentration.

[g]The rate should not exceed 25 mg/min in elderly patients and those with known atherosclerotic cardiovascular disease.

8 Most practitioners consider IV-administered lorazepam to be the benzodiazepine of choice for initial therapy of GCSE. A Cochrane Database Review concluded that lorazepam is as effective and safer than diazepam in children.[17] Another Cochrane Database Review that included pediatric and adult data noted no difference in death, requirements for ventilator support, or adverse effects between the two agents; however, when compared to diazepam, there was a significantly lower risk of persistent seizures with lorazepam.[19]

Lorazepam is less lipid soluble than diazepam and takes longer to achieve peak concentrations in the brain; however, its minimal redistribution into fat results in a longer duration of action in the CNS, which can provide seizure protection for up to 24 hours. It also has a higher-affinity binding to the benzodiazepine receptor than diazepam.

Patients chronically on a benzodiazepine (eg, clobazam and clonazepam) might have developed tolerance and could require large doses. Diazepam and lorazepam contain propylene glycol, which can cause dysrhythmia and hypotension if administered too rapidly (**Table 74-5**). They also cause vein irritation; therefore, the parenteral product should be diluted with an equal volume of compatible diluent before administration and because of slow and erratic absorption, standard parenteral formulations should not be given IM.

TABLE 74-5 Adverse Drug Reactions and Monitoring of Patients Receiving Drugs for GCSE

Drug	Adverse Drug Reaction	Monitoring Parameters	Comments
Diazepam	Hypotension and cardiac arrhythmias	Vital signs and ECG during administration	Propylene glycol causes hypotension and cardiac arrhythmias when administered too rapidly; hypotension may occur with large doses
Fosphenytoin	Hypotension and cardiac arrhythmias; paresthesia, pruritus	Vital signs and ECG during administration	Hypotension is less than that noted with phenytoin, as this product does not contain propylene glycol; pruritus generally involves the face and groin areas, is dose and rate related, and subsides 5-10 minutes after infusion
Lidocaine	Fasciculations, visual disturbances, tinnitus, seizures		Occur at serum concentrations between 6 and 8 mg/L (25.6-34.1 μmol/L); seizures >8 mg/L (34.1 μmol/L)
Lorazepam	Apnea, hypotension, bradycardia, cardiac arrest, respiratory depression, metabolic acidosis, and renal toxicity	Vital signs and ECG during administration; HCO_3 and serum creatinine; cumulative dose of propylene glycol	Accumulation of propylene glycol during prolong continuous infusions may cause acidosis
Pentobarbital	Hypotension	Vital signs and ECG during administration	Rate of infusion should be slower or dopamine should be added if hypotension occurs
Phenytoin	Hypotension and cardiac arrhythmia; nystagmus	Vital signs and ECG during administration	Propylene glycol causes hypotension and cardiac arrhythmias when administered too rapidly. Large loading doses are generally not given to elderly individuals with preexisting cardiac disease or in critically ill patients with marginal blood pressure. The infusion rate should be slowed if the QT interval widens or if hypotension or arrhythmias develop; horizontal nystagmus suggests serum concentration above the reference range and toxicity; if a serum phenytoin concentration validates this, the dose should be decreased
Phenobarbital	Hypotension, respiratory, and CNS depression	Vital signs and mental status; EEG if used in anesthesia doses	Contains propylene glycol; if hypotension occurs, slow the rate of administration or begin dopamine; apnea and hypopnea can be more profound in patients treated initially with benzodiazepines
Propofol	Progressive metabolic acidosis, hemodynamic instability, and bradyarrhythmias	Vital signs, ECG, osmolar gap; EEG if used in anesthesia doses	Referred to as propofol-related infusion syndrome, which can be fatal
Topiramate	Metabolic acidosis	Acid base status (serum bicarbonate)	Extremely rare

CNS, central nervous system; ECG, electrocardiogram; EEG, electroencephalogram.

Unfortunately, there are insufficient data comparing IV lorazepam to IV midazolam in GCSE. Midazolam has an extremely short half-life, and maintenance doses must be given by continuous infusion (see Table 74-4). Because of its increased solubility, midazolam has a more reliable IM absorption than either diazepam or lorazepam. A recent Class 1 study showed that when

emergency personnel gives IM midazolam as first-line treatment in the prehospital setting, it was superior to IV lorazepam for cessation of seizures, the requirement for intensive care unit (ICU) admission, and subsequent hospitalization.[14] There was not a difference in recurrent seizures or adverse effects.

Although the evidenced-based guidelines note that intranasal (IN) and buccal midazolam, and per rectum (PR) diazepam are probably effective[5], IN midazolam and PR diazepam are increasingly used in out-of-hospital management and in the emergency department settings. Recent studies have focused on aborting impending SE via transmucosally delivered benzodiazepine (eg, PR, IN, and buccal) when IV and/or IM administration may be difficult or impossible (eg, home setting, extended care, and paramedic) to use.[2,20] Rectal absorption of diazepam is rapid but varies significantly (50%-100%) due to first-pass metabolism and is difficult to administer in the home environment. Buccal and sublingual routes also bypass gastric and hepatic first-pass metabolism, but bioavailability can be incomplete as the drug is often swallowed. Buccal administration is easily accomplished, and the volume of fluid is small enough (eg, 2-5 mL) that aspiration is unlikely. While successful sublingual administration is unlikely due to muscular contractions of the jaw and clenching of teeth, a Cochrane Database Review concluded that buccal midazolam is more effective than PR diazepam in children.[18]

Intranasally administrated midazolam readily crosses the nasal mucosa and the blood-brain barrier to produce a rapid rise in both serum and cerebrospinal fluid concentrations.[2,20] In fact, serum concentrations are comparable to those noted following IV injection. When compared to PR diazepam, all studies have concluded that IN midazolam results in higher serum concentrations, faster onset of action, more effective seizure control, and fewer adverse effects.[2]

Although most reports have used a variety of delivery systems (eg, drops, sprays, and atomization devices), the lack of standardization in delivery and availability of a commercial kit has not impacted efficacy. Because the dose must be administered in a 100 to 200 μL spray or solution, this route can only be used for products that are highly concentrated and have good aqueous solubility. It is imperative to account for medication that will remain in the dead space within the syringe and atomizer tip by overfilling the syringe with 0.1 mL of medication. Medication should be drawn up at the time it is needed and not stored in a plastic syringe, as this may negatively impact efficacy as medication leaches into the plastic.

Effective delivery is best achieved by briskly compressing the syringe plunger

to distribute the drug as a mist rather than as larger droplets that may aggregate and run out of the nose or down the back of the throat, rendering it ineffective.[20] By delivering *half* of the dose into each nostril the surface area available for absorption is doubled. Upper airway infections, the extent of nasal mucosa irritation, and differences in the amount of spray that is swallowed may all impact absorption. However, the variability in the amount absorbed after nasal administration should be comparable to that after oral administration.

The guidelines also recommend the use of IV phenobarbital as an alternative first-line agent in adults.[5] It is an efficacious and well-tolerated initial therapy in adults if benzodiazepines are not an option. Although evidenced-based studies establish IV phenobarbital, its slower rate of administration compared to the benzodiazepines relegates it to alternative initial therapy. Phenobarbital has biphasic distribution into body organs and during phase I, the drug distributes into highly vascular organs but does not distribute into the brain. With the exception of fat, phenobarbital distributes throughout the body during phase II; hence, lean body mass should be used in calculating doses in obese patients. Although the highest brain concentrations occur 12 to 60 minutes after an IV dose, seizures are controlled within minutes of the loading dose.[16]

The loading and maintenance dose for phenobarbital are given in Table 74-4. When necessary, larger loading doses (30 mg/kg) have been used in neonates without adverse effects. Phenobarbital exhibits first-order linear pharmacokinetics, and there is no maximum dose beyond which further doses are likely to be ineffective. For this reason, if the initial loading dose does not stop the seizures within 20 to 30 minutes, an option would be to give an additional dose (10-20 mg/kg) or move to anesthetic agents.[21] Once GCSE is controlled, the maintenance dose should be started within 12 to 24 hours. Although injectable phenobarbital contains propylene glycol, it can be given more rapidly than phenytoin (see Table 74-4). While it can be safely administered IM, its rate of absorption is too slow to be effective.[2]

Although rare, brief cardiorespiratory depression can necessitate assisted ventilation or require intubation (see Table 74-5). This is especially true if a benzodiazepine is used concomitantly with a barbiturate. The rate of respiratory depression in patients with GCSE who received benzodiazepines is lower than that reported in a similar population treated with placebo.[5] Importantly, there was no difference in cardiorespiratory adverse events in adults who are given either a benzodiazepine or phenobarbital.[16] Hypotension secondary to a reduction in vasomotor tone can occur following large doses of either a benzodiazepine or barbturate.[2]

Second-Therapy Phase: Established GSCE (20-40 minutes)

Second-phase anticonvulsants (eg, hydantoin, valproate, phenobarbital, levetiracetam, or lacosamide) may not be needed if seizures stop after administration of initial therapies. The choice of which long-acting, second-line agent to give following the initial therapies is controversial as there is no evidence on which to base a preferred choice. When given, an agent should be administered immediately after a benzodiazepine. Dosing can be found in Table 74-4.

9 A hydantoin is one of three second-line agents that can be used when GCSE is unresponsive to the benzodiazepines or in seizures that recur after successful treatment with a benzodiazepine.[5] However, a meta-analysis concluded that evidence does not support the use of phenytoin as a first- or second-line agent.[22] When used by itself, phenytoin is inferior to lorazepam, phenobarbital, or diazepam plus phenytoin at stopping GCSE within 20 minutes of infusion.[16,23] While the most recent guidelines advocate for a hydantoin[5] and it is frequently used in practice, it is questionable if a hydantoin should be administered alone, in larger doses, or at all when seizures recur following benzodiazepine administration.

Phenytoin has a long half-life (20-36 hours) and causes less respiratory depression and sedation than the benzodiazepines or phenobarbital; however, it cannot be delivered rapidly enough to be considered a first-line single agent.[2] Injectable phenytoin should be diluted to less than or equal to 5 mg/mL in normal saline, otherwise microcrystals will precipitate if it is mixed in a glucose-containing solution. The vehicle (40% propylene glycol) can cause administration-related hypotension and cardiac arrhythmias (see Table 74-5) and for this reason, the maximum rate of infusion is limited (see Table 74-4).

Suggested IV loading doses are provided in Table 74-4. A reduction in the loading dose is recommended for elderly patients, and a larger loading dose is required in obese individuals. If the patient has been on phenytoin prior to admission and the serum concentration is known, this should be considered in determining a loading dose. Although some advocate the administration of an additional 5 mg/kg dose in those with unresponsive GCSE, there is no evidence that this will be beneficial. This practice can cause concentrations to exceed the reference range and produce toxicity. Because phenytoin has poor lipid solubility and enters the brain slowly, it can take up to 60 minutes before the pharmacodynamic effect is apparent. This delay is important when considering

administration of a second loading dose, as therapeutic serum concentrations, 10 to 20 mg/L (40-79 μmol/L), generally do not persist more than 24 hours; hence, maintenance doses (see Table 74-4) should be started within 12 to 24 hours of the loading dose.

Phenytoin has an alkaline pH, which may cause pain and burning during infusion; phlebitis can occur with chronic infusion, and tissue necrosis is likely on infiltration. Intramuscular administration is not recommended because absorption is delayed and erratic, and phenytoin can crystallize in tissue. Although oral loading doses have been used in patients not actively seizing, it may take 4 to 12 hours before adequate serum concentrations are obtained; thus, this practice is not recommended.

Fosphenytoin is considered by many to be the hydantoin of choice[5] as it is a water-soluble phosphate ester that has no known pharmacologic activity and it is converted rapidly (7-15 minutes) and completely (100%) to phenytoin by blood and tissue phosphatases after IV and IM dosing. The conversion delay was a concern initially; however, this time is offset by high protein binding, saturable binding at high concentrations, and the rapid rate of infusion. Since it does not contain propylene glycol, it is compatible with most common IV fluids. It should be dosed using phenytoin equivalents (PE), thereby obviating the need for interconversion between phenytoin and fosphenytoin. The loading dose and rates of administration of fosphenytoin can be found in Table 74-4. Because of delays in achieving adequate phenytoin serum concentrations, a loading dose should not be given IM unless IV access is impossible.

Fosphenytoin serum concentrations have no value, and therefore, serum phenytoin concentrations should be used for therapeutic drug monitoring, and the desired serum concentration range is the same as that for phenytoin. Fosphenytoin cross-reacts with some phenytoin immunoassays causing an overestimation of phenytoin concentration; hence, blood should not be obtained for at least 2 hours after IV and 4 hours after IM administration.

Alternatively, the current guidelines also recommend a single dose of IV valproate or IV levetiracetam as acceptable first-line agents if a benzodiazepine fails to control seizures after 20 minutes, or if seizures recur following a benzodiazepine and/or a hydantoin.[5] Intravenous valproate and continuous infusion diazepam are comparable in GCSE.[24,25] One meta-analysis noted that valproate controlled refractory SE sooner than diazepam. However, there was no difference within 30 minutes of administration.[26] There was also no difference in control of GCSE between valproate and phenytoin.[27] A second meta-analysis noted that there is sufficient evidence to use valproate as first-line therapy in

those with SE refractory to benzodiazepines.

A number of loading and continuous-infusion doses for valproate (see Table 74-4) have been used in both adult and pediatric patients. The current guidelines recommend 40 mg/kg up to 3,000 mg as a single dose.[5] Although the manufacturer originally recommended IV valproate be given no faster than 20 mg/min, much faster rates have been studied (40 mg/min; 2-10 mg/kg/min) and are used for administration of the loading dose. One study suggested the need to consider the effects of enzyme-inducing anticonvulsants when dosing and recommended that the continuous-infusion rate be determined by the presence of concurrent anticonvulsants (no inducers present, 1 mg/kg/hr; one or more inducers [eg, phenytoin and phenobarbital], 2 mg/kg/hr; and inducers and pentobarbital coma, 4 mg/kg/hr).[28] In general, IV valproate has been well tolerated, with no cases of respiratory depression. Hemodynamic instability is extremely rare, but patients' vital signs should be monitored closely during the loading dose for hypotension.

Evidence for the use of IV levetiracetam is limited; however, one meta-analysis noted that sufficient evidence exists to support the use of levetiracetam as first-line therapy in those refractory to benzodiazepines.[22] Historically, it was used in cases of super-refractory SE, but it is being used earlier due to medication shortages that have made traditional drugs unavailable. It has been noted to be as effective as IV lorazepam in aborting seizures and preventing recurrence.[29–31] When compared to phenytoin, levetiracetam was equally effective at terminating seizures and preventing recurrence at 24 hours.[31] Levetiracetam is not hepatically metabolized and is minimally protein bound, which makes drug–drug interactions unlikely. Doses for IV levetiracetam are noted in Table 74-4 and have been infused over about 5 minutes. Although the guidelines recommend a maximum single dose of 4,500 mg,[5] most clinicians use 3,000 mg/day.

Despite phenobarbital being recommended as an alternative first-line agent for initial therapy, the most recent guidelines recommend its use as an alternative agent when a hydantoin, valproic acid, or levetiracetam are not available or has failed. Before moving to third-phase therapies, all agents noted in phase II should be given at maximally tolerated doses. This should be done as a single dose and not as multiple mini-boluses.

Third-Phase Therapies: Refractory GCSE (40-60 minutes)

10 When adequate doses of a benzodiazepine and a single dose of a second anticonvulsant (hydantoin, valproate, levetiracetam and/or barbiturate) has failed, the condition is termed *refractory*.[5] After initial control, seizures have been observed to recur in 6% to 19% of patients and approximately 10% to 15% of patients will develop refractory GCSE, and approximately 30% whose seizures are "clinically" controlled will have persistent electrical manifestations after administration of these anticonvulsants. When a patient develops refractory GCSE, an intense search should be performed for an acute or progressive cause.

While the goal is to stop electrical epileptiform activity, there is no consensus regarding the agent of choice, sequencing of therapy, or treatment of refractory GCSE. Historically, one would recommend a repeat dose of a second-phase therapy be given; however, more practitioners are increasingly using an anesthetic agent and not another traditional anticonvulsant (due to the low probability of an additional traditional anticonvulsant medication interrupting the established GCSE). Without question, there is a clear consensus that if a repeat dose of a traditional anticonvulsant fails, anesthetizing the patient to suppress cerebral ictal discharges should occur[5] (see Table 74-5). An anesthetic dose of midazolam, pentobarbital, or propofol may be indicated and doses for these agents can be found in Table 74-5. Although it is likely that the patient is already being mechanically ventilated, intubation and respiratory support are mandatory during the use of anesthetic agents, along with continuous EEG monitoring.

While HLA-B*1502 has been associated with severe skin reactions in patients receiving phenytoin, this is applicable to chronic and not acute, single dose therapy. Recently, CYP2C variants that included CYP2C9*3, which is known to reduce drug clearance, were identified as important genetic factors associated with phenytoin-related severe cutaneous adverse reactions.[47]

Drug resistance factors have also been identified in human epileptogenic tissue that has been removed surgically. Multidrug resistance proteins (P-glycoprotein) are localized to endothelial cells in brain capillaries and associated astroglia. Since multidrug resistance factors are localized to abnormal tissues, they appear to have little or no effect on systemic pharmacokinetic parameters of a drug but may affect the local distribution of the drug within the target epileptogenic areas. If a role in refractory human epilepsy is confirmed, drugs that inhibit P-glycoprotein (eg, verapamil) may prove useful. However, the role of multidrug-resistant proteins in the treatment of seizure emergencies is not clear.

Benzodiazepines

During prolonged seizures, the number of γ_2 and $\beta_{2\text{-}3}$ subunits on the $GABA_A$ receptors decrease as the receptors move from the synaptic membrane into the cytoplasm where they are functionally inactive. These modifications may decrease the effectiveness of both endogenous GABA and GABA agonists and result in time-dependent pharmacoresistance. Following GCSE that persist for more than 30 minutes, the relative potencies of benzodiazepines can be reduced up to 20-fold. For this reason, some believe that anesthetic doses of midazolam should be the first-line agent in refractory GCSE. If a benzodiazepine is used, it should always be combined with another drug that acts at a different site. **Table 74-6** shows the loading and maintenance doses of midazolam.[24] Most patients respond to these doses within an hour, and although studies used termination of seizures on EEG as the endpoint for success, EEG burst suppression is rarely achieved with the recommended doses of midazolam. Tachyphylaxis rapidly develops within 24 to 48 hours; hence, the dose is often increased to prevent seizure relapse.[2]

TABLE 74-6 Dosing of Medications Used to Treat Refractory or Super-Refractory GCSE

Drug (Brand Name)	Initial Dose (Maximum Dose)	Maintenance Dose	Comments
Ketamine (generics)			
Adult	1-4 mg	1-5 mg/kg/hr	
Pediatric	0.5-2 mg/kg	1-10 mg/kg/hr	
Lacosamide (Vimpat)			
Adult	200-400 mg	200 mg bid	Administer IV over 15 minutes, monitor serum concentrations
Pediatric	6-10 mg/kg (400 mg)	6-12 mg/kg/day, given twice a day	
Lidocaine (generics)			
Adult	50-100 mg	1.5-3.5 mg/kg/hr	Administer IV in ≤2 minutes
Pediatric	1 mg/kg (maximum 3-5 mg/kg in the first hour)	1.2-3 mg/kg/hr	
Midazolam (Versed plus generic)			
Adult pediatric	200 mcg/kg[a] 150 mcg/kg[a]	50-500 mcg/kg/hr[b] 60-120 mcg/kg/hr[b]	Initial dose may be given IM; administer IV over 0.5-1 mg/min; continuous-infusion rate should be increased every 15 minutes in those who do not respond and should be guided by EEG response; development of tachyphylaxis can require frequent increases in dose; decrease dose by 1 mcg/kg/min every 2 hours once GCSE is controlled
Pentobarbital (generics)			
Adult Pediatric	10-20 mg/kg 15-20 mg/kg	1-5 mg/kg/hr[b] 1-5 mg/kg/hr[b]	Over 1-2 hours, the rate of infusion should be slowed or dopamine should be added if hypotension occurs; gradually titrate dose upward until there is evidence of burst suppression on EEG (ie, isoelectric EEG) or prohibitive adverse effects occur. Twelve hours after a burst suppression is obtained, the rate should be titrated downward every 2-4 hours
Propofol (Diprivan plus generic)			
Adult	2 mg/kg	5-10 mg/kg/hr[b]	Over 10 seconds in adults and 20-30 seconds in pediatric patients
Pediatric	3 mg/kg	2-4 mg/kg/hr[c]	
Topiramate (Topamax plus generic)			
Adult Pediatric	300-500 mg 5-15 mg/kg (400 mg)	400-1,600 mg/day 5-10 mg/kg/day, given thrice a day	Given orally in divided dose every 12 hours. Doses as large as 25 mg/kg/day for 2-5 days have been used in children. Monitor serum bicarbonate levels and serum concentrations

EEG, electroencephalogram; GCSE, generalized convulsive status epilepticus; IM, intramuscular; IV, intravenous.

[a]Doses can be repeated twice at 10-15 minute intervals until the maximum dosage is given.

[b]Titrate dose as needed.

[c]Generally recommended not to exceed a dose of 4 mg/kg/hr and a duration of 48 hours.

There is no specific protocol for tapering of midazolam, but some suggest a seizure-free period of 24 to 48 hours followed by decreasing by 1 to 2 mcg/kg/min every 15 minutes.[2] Maintaining the patient's phenytoin and phenobarbital serum concentration(s) above 20 mg/L (79 µmol/L) and 40 mg/L (172 µmol/L), respectively, enhances successful discontinuation.

Because of midazolam's short half-life, patients can return to consciousness more rapidly than those receiving larger doses of more sedating anticonvulsants (eg, phenytoin and phenobarbital). Generally, continuous-infusion midazolam has been well tolerated, with few cases of hypotension and respiratory depression, although hypotension and poikilothermia can occur and can require supportive therapies. When adverse effects do occur, patients recover quickly; however, the use of large doses has caused a "midazolam infusion syndrome" in adults, which is characterized by delayed arousal (ie, hours to days) following discontinuation of midazolam. This has tempered the use of midazolam in adults, but it has continued to be an important agent in pediatrics. The availability of a pharmacological antidote for benzodiazepines, flumazenil, enhances the safe use of midazolam.

Pentobarbital

Another option for anesthesia is the use of a short-acting barbiturate (ie, pentobarbital or thiopental). These agents are preferred because they allow a more rapid reversal of coma. Although barbiturates are frequently used, there are no controlled trials to support this practice. A meta-analysis comparing studies involving midazolam, propofol, and pentobarbital in refractory GCSE found overall response rates were significantly greater in those treated with pentobarbital compared to midazolam or propofol.[32] The recurrence of seizures was also less frequent with pentobarbital and propofol and reported mortality rates were similar for the three drugs, but significant hypotension was more common with pentobarbital.

Several sources note that the initial loading dose of pentobarbital is 5 mg/kg; however, this dose is inadequate to achieve the serum concentrations (40 mg/L; 172 µmoL/L) necessary to induce an isoelectric EEG (see Table 74-6). Although the duration of barbiturate coma in most studies has been 2 to 3 days, it has been used safely for 53 days in an 18-year-old patient.[33] To avoid complications (eg, pneumonia and pulmonary edema), pentobarbital should be discontinued as soon as possible and the risk of seizure recurrence is minimized if other anticonvulsants are at therapeutic concentrations before pentobarbital is

withdrawn. Because pentobarbital is a potent hepatic enzyme inducer, doses of most concurrent anticonvulsants will need to be larger than usual maintenance doses, and the patient will need to be monitored for side effects as de-induction occurs and anticonvulsant concentrations increase. This can take up to 1 month after pentobarbital's discontinuation.

Propofol

Propofol is also a viable alternative as first-line therapy in phase III, as it is extremely lipid soluble, has a large volume of distribution, has a very rapid onset of action and its extremely short half-life promotes easy titration and rapid awakening on drug discontinuation. Although several studies have compared propofol and barbiturates, most studies were underpowered and its efficacy appears to be comparable to midazolam for refractory GCSE.[32,34] Propofol is given as a loading dose that is followed by a continuous infusion; however, the loading dose can be repeated every 3 to 5 minutes until the desired clinical response is obtained. Once EEG burst suppression is achieved, the dose should be reduced.

Adverse drug reactions can be found in Table 74-5 and prolonged infusions greater than 4 mg/kg/hr have been associated with propofol-related infusion syndrome (PRIS).[35,36] Signs and symptoms of PRIS occur primarily in pediatric patients and include progressive metabolic acidosis, hemodynamic instability, and bradyarrhythmias that are refractory to aggressive pharmacological treatments. It may occur with or without the presence of hepatomegaly, rhabdomyolysis, or lipemia. A retrospective case series of 41 patients with refractory GCSE noted that 10% had sudden unexplained cardiorespiratory arrests, and 35% had non-life-threatening features of PRIS.[36] Propofol may be proconvulsant in some patients and involuntary myoclonic movements have been reported. Propofol infusion syndrome is also more common in children, and this limits the use of this agent in the pediatric population.

Vital signs should be carefully monitored, and continuous electrocardiogram (ECG) should assess for dysrhythmias. While no guidelines have been proposed for laboratory monitoring, it would seem advisable to assess serum lactic acid, serum triglycerides, serum creatinine, creatine kinase, and hepatic enzymes in patients receiving doses larger than 4 mg/kg/hr and/or those receiving therapy for more than 48 hours.

The role and position of other anticonvulsants in refractory GCSE remains unclear and the selection of a second-phase anticonvulsant is often complicated by shortages. Although apparently effective in refractory GCSE, literature

supporting the use of lacosamide and topiramate comes from case reports or case series, with two meta-analyses noting there is insufficient evidence to support the routine use of lacosamide in benzodiazepine-resistant GCSE.[22,37,38] Topiramate has been given orally in adults and in children with GCSE and should be implemented at full therapeutic doses and divided three times a day (see Table 74-6).[2,39] To administer nasogastrically, the tablets should be crushed, mixed with water, and administered via syringe into the nasogastric tube. Response tends to be delayed hours to days. Once seizures are controlled, the dose should be tapered to a normal age/weight–appropriate maintenance dosage. Aggressive implementation of large doses of topiramate may cause hyperchloremic, nonanion gap, metabolic acidosis due to inhibition of type II and IV carbonic anhydrase enzymes, which is not dose-related as it has been noted following small doses and after overdoses. If metabolic acidosis occurs, it can be treated with citrates, with a goal of maintaining serum bicarbonate of at least 20 mEq/L (mmol/L).[2]

Super-Refractory GCSE (>24 hours)

Persistent GCSE or recurring seizures after anesthetic drugs have failed are challenging; therefore, agents with a broad range of pharmacologic mechanisms may be tried. Ketamine is a noncompetitive antagonist of glutamatergic N-methyl-D-aspartate (NMDA) receptors that may be tried. During prolonged seizures, the numbers and activities of GABA receptors gradually decrease; thus, the commonly used first-line and second-line antiepileptic drugs gradually fail. Simultaneously, the numbers and activities of glutamatergic NMDA receptors increase, often causing refractory status epilepticus (RSE) and thus providing the possibility of the use of ketamine to treat RSE. A summary of the findings appears in recently published review papers.[2,40] Overall though, ketamine appears to be a reasonable agent to consider in refractory GCSE that has failed general anesthesia, especially in those with cardiac instability and doses can be found in Table 74-6. An advantage of ketamine is its ability to maintain arterial blood pressure, pulse rate, and cardiac output. Adverse events noted with ketamine is its ability to cause hallucinations upon awakening, increased salivation, and increased intraocular and intracranial pressure.

Currently, weak evidence supports the use of lidocaine in supra-refractory GCSE but it has been used when other agents have failed.[41] When administered intravenously (see Table 74-6) it has a rapid onset of action. Although the reference serum concentration range for the antiarrhythmic effects of lidocaine is 2 to 6 mg/L (8.5-25.6 μmol/L), the reference range for GCSE has not been

established. Serum lidocaine concentrations and ECG should be monitored to avoid drug accumulation and toxicity (see Table 74-5).

Today inhaled anesthetics are not used until other approaches fail, and only a few studies have used inhaled anesthetics (particularly isoflurane) for the treatment of refractory SE.[42,43] Halothane, isoflurane, and other inhaled anesthetics can produce EEG suppression; however, these gases are difficult to deliver outside the operating room and require an anesthesiologist. No proven advantages have been shown over traditional anticonvulsants (eg, barbiturate coma or continuous-infusion benzodiazepine), and these gases can increase intracranial pressure. If used, dosing is titrated to obtain EEG burst suppression, and although concentrations required to maintain burst suppression are variable, isoflurane generally stops seizure at concentrations of 0.5% to 3%. It is important to note that these concentrations are not ordinarily associated with hemodynamic effects; however, isoflurane can induce hypotension, so close hemodynamic monitoring is necessary, with the administration of isotonic fluids and vasopressors as needed.

The use of immunomodulating therapies (eg, corticosteroids and IV immune globulin) is based upon animal data that suggest the development of super-refractory GCSE may be due to antibodies directed against the voltage-gated potassium channels and the NMDA receptor.[43] There is also mounting evidence that inflammation plays a role in epileptogenesis, specifically the activation of select inflammatory signaling pathways (eg, interleukin-1 receptor/toll-like receptor [IL-1R/TLR]). Steroids may also decrease blood-brain barrier opening and reverse GABAergic inhibition and affect NMDA and voltage-gated potassium channels. Although little evidence supports the use of steroids, in the absence of contraindications, a trial of large doses of steroids that is followed by IVIG should be considered. Typically, patients are given methylprednisolone 15 mg/kg/day every 6 hours, up to 1 g/day, for 3 days. Patients who respond should continue long-term steroids, IV immunoglobulins, and other immunomodulatory agents such as cyclophosphamide or rituximab.

Controlled mild hypothermia reduces excitatory transmission and epileptic discharges and reduces brain edema, cerebral metabolic rate, oxygen utilization, and ATP consumption. Few studies have assessed the efficacy or safety of hypothermia in refractory GCSE and a meta-analysis suggested that only level D evidence supports the use of hypothermia in refractory SE.[44] Despite an absence of medical evidence, there has been a resurgence in the use of hypothermia, especially in the early use in super-refractory GCSE. When used, a core body temperature of about 32°C to 34°C is targeted for at least 24 to 48 hours. It may

or may not be given in combination with barbiturate anesthetics,[43] but is often used concurrently with ketamine. Cardiovascular and coagulation parameters, biochemistry and acid-base balance, and serum lactate should be monitored. Hypothermia may significantly reduce the clearance of several drugs, including anesthetics and antiepileptics, resulting in a need for monitoring of serum concentrations.[2]

EVALUATION OF THERAPEUTIC OUTCOMES

Initial success is defined as termination of all clinical and electrical seizure activity, but ultimate success is measured by the patient's subsequent quality of life. The morbidity and mortality associated with GCSE are primarily affected by the underlying etiology; however, morbidity and mortality can be minimized by the rapid implementation of a rational therapeutic plan. An EEG is an extremely important tool that not only allows practitioners to determine when abnormal electrical activity has been aborted, but also can assist in determining which anticonvulsant was effective. Because many of the anticonvulsants affect the cardiorespiratory system, it is imperative that vital signs (eg, heart rate, respiratory rate, and blood pressure) be monitored during drug loading and infusion. Finally, it is imperative that the infusion site be assessed for any evidence of infiltration before and during administration of phenytoin. Information regarding the patient's past medical and drug history and imaging studies (eg, MRI) also can help to determine if there is a defined etiology for the original episode of GCSE. This information then can be used to guide future medication therapy, as well as help in determining if the patient is at risk for a poor outcome.

CONCLUSION

GCSE is a medical emergency that requires a healthcare professional to be knowledgeable about the phases of the disorder, therapies that align with each phase, and secondary complications that may need to be addressed. This requires one to have a working knowledge of the Patient Care Process used for status epilepticus and what evidence-based information exists for the selection of therapies. Understanding provoking factors and various etiologies important in prevention and treatment is an integral part of care. It is also essential that those outpatient therapies be aggressively used to abort impending SE.

Postclass Engaged Learning Activity

Review the following paper and write a brief summary of the study methods, the major findings, and how this new information might influence practice. This activity is intended to build your literature evaluation skills and the ability to critically appraise research manuscripts.

Gulati S, Sondhi V, Chakrabarty B, et al. High dose phenobarbitone coma in pediatric refractory status epilepticus; a retrospective case record analysis, a proposed protocol, and review of literature. *Brain Dev*. 2018;40(4):316-324.

ABBREVIATIONS

AMPA	α-amino-3-hydroxy-5-methyl-isoxazole-4-propionate
CNS	central nervous system
CT	computed tomography
ECG	electrocardiogram
EEG	electroencephalogram, electroencephalography
GABA	γ-aminobutyric acid
GCSE	generalized convulsive status epilepticus
ICU	intensive care unit
IL-1R/TLR	interleukin-1 receptor/toll-like receptor
ILAE	International League Against Epilepsy
IM	intramuscular
IN	intranasal
IV	intravenous
MRI	magnetic resonance imaging
NCSE	nonconvulsive status epilepticus
NMDA	N-methyl-D-aspartate
PE	phenytoin equivalents
PRIS	propofol-related infusion syndrome
SE	status epilepticus

REFERENCES

1. Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus—Report of the ILAE Task Force on Classification of

Status Epilepticus. *Epilepsia*. 2015;56(10):1515–1523.

2. Alford EL, Wheless JW, Phelps SJ. Treatment of generalized convulsive status epilepticus in pediatric patients. *J Pediatr Pharmacol Ther*. 2015;20(4):260–289.
3. DeLorenzo RJ, Garnett LK, Towne AR, et al. Comparison of status epilepticus with prolonged seizure episodes lasting from 10 to 29 minutes. *Epilepsia*. 1999;40:164–169.
4. Maganti R, Gerber P, Drees C, Chung S. Nonconvulsive status epilepticus. *Epilepsy Behav*. 2008;12:572–586.
5. Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline—Treatment of convulsive status epilepticus in children and adults: Report of the guideline committee of the American Epilepsy Society. *Epilepsy Curr*. 2016;16(1):48–61.
6. Lv RJ, Wang Q, Cui T, et al. Status epilepticus-related etiology, incidence and mortality: A meta-analysis. *Epilepsy Res*. 2017;136:12–17.
7. DeLorenzo RJ, Pellock JM, Towne AR, Boggs J. Epidemiology of status epilepticus. *J Clin Neurophysiol*. 1995;12:316–325.
8. DeLorenzo RJ, Towne AR, Pellock JM, Ko D. Status epilepticus in children, adults, and the elderly. *Epilepsia*. 1992;33:S15–S25.
9. Temkin NR. Antiepileptogenesis and seizure prevention trials with anti-epileptic drugs: Meta-analysis of controlled trials. *Epilepsia*. 2001;42:515–524.
10. Wasterlain CG, Chen JWY. Mechanistic and pharmacologic aspects of status epilepticus and its treatment with new antiepileptic drugs. *Epilepsia*. 2008;49:63–73.
11. Pitkänen A, Nehlig A, Brooks-Kayal AR, et al. Issues related to development of antiepileptogenic therapies. *Epilepsia*. 2013;54(suppl 4):35–43.
12. Lothman E. The biochemical basis and pathophysiology of status epilepticus. *Neurology*. 1990;40:13–23.
13. Kantanen AM, Reinikainen M, Parviainen I, et al. Incidence and mortality of super-refractory status epilepticus in adults. *Epilepsy Behav*. 2015;49:131–134.
14. Shlbergleit R, Durkalski V, Lowenstein D, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. *N Engl J Med*. 2012;366:591–600.

15. Chamberlain JM, Okada P, Holsti M, et al.; Pediatric Emergency Care Applied Research Network (PECARN). Lorazepam vs diazepam for pediatric status epilepticus: A randomized clinical trial. *JAMA*. 2014;311(16):1652–1660.
16. Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. *N Engl J Med*. 1998;339:792–798.
17. Alldredge BK, Gelb AM, Isaacs SM, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *N Engl J Med*. 2001;345(9):631–637.
18. Appleton R, Macleod S, Martland T. Drug management for acute tonic–clonic convulsions including convulsive status epilepticus in children. *Cochrane Database Syst Rev*. 2008;3:CD001905.
19. Prasad M, Krishnan PR, Sequeira R, Al-Roomi K. Anticonvulsant therapy for status epilepticus. *Cochrane Database Syst Rev*. 2014;9:1–88.
20. Humphries LK, Eiland LS. Treatment of acute seizures: Is intranasal midazolam a viable option? *J Pediatr Pharmacol Ther*. 2013;18:79–87.
21. Crawford TO, Mitchell WG, Fishman LS, Snodgrass SR. Very-high-dose phenobarbital for refractory status epilepticus in children. *Neurology*. 1988;38:1035–1040.
22. Yasiry Z, Shorvon SD. The relative effectiveness of five antiepileptic drugs in treatment of benzodiazepine-resistant convulsive status epilepticus: A meta-analysis of published studies. *Seizure*. 2014;2:167–174.
23. Shaner DM, McCurdy SA, Herring MO, Gabor AJ. Treatment of status epilepticus: A prospective comparison of diazepam and phenytoin versus phenobarbital and optional phenytoin. *Neurology*. 1988;38:202–207.
24. Abend NS, Diugos DJ. Treatment of refractory status epilepticus: Literature review and a proposed protocol. *Pediatr Neurol*. 2008;38:377–390.
25. Chen WB, Gao R, Su Y, et al. Valproate versus diazepam for generalized status epilepticus: A pilot study. *Eur J Neurol*. 2011;18:1391–1396.
26. Mehta V, Singhi P, Singhi S. Intravenous sodium valproate versus diazepam infusion for the control of refractory status epilepticus in children: A randomized controlled trial. *J Child Neurol*. 2007;22:1191–1197.

27. Liu X, Wu Y, Chen Z, et al. A systematic review of randomized controlled trials on the therapeutic effect of intravenous sodium valproate in status epilepticus. *Int J Neurosci*. 2012;12:277–283.
28. Hovinga CA, Chicella MF, Rose DF, et al. Use of IV valproate in three pediatric patients with nonconvulsive or convulsive status epilepticus. *Ann Pharmacother*. 1999;33:579–584.
29. Rossetti AO, Bromfield EB. Determinants of success in the use of oral levetiracetam in status epilepticus. *Epilepsy Behav*. 2006;8:651–654.
30. Misra UK, Kalita J, Maurya PK. Levetiracetam versus lorazepam in status epilepticus: A randomized, open labeled pilot study. *J Neurol*. 2012;25:645–648.
31. Chakravarthi S, Goyal MK, Modi M, et al. Levetiracetam versus phenytoin in management of status epilepticus. *J Clin Neurosci*. 2015;22:959–963.
32. Claassen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: A systematic review. *Epilepsia*. 2002;43:146–153.
33. Mirski MA, Williams MA, Hanlet DF. Prolonged pentobarbital and phenobarbital coma for refractory generalized status epilepticus. *Crit Care Med*. 1995;23:400–404.
34. Brown LA, Levin GM. Role of propofol in refractory status epilepticus. *Ann Pharmacother*. 1998;32:1053–1059.
35. Timpe EM, Eichner SF, Phelps SJ. Propofol-related infusion syndrome in critically ill pediatric patients: Coincidence, association, or causation? *J Pediatr Pharmacol Ther*. 2006;11:17–42.
36. Iyer VN, Hoel R, Rabinstein AA. Propofol infusion syndrome in patients with refractory status epilepticus: An 11-year clinical experience. *Crit Care Med*. 2009;37:3024–3030.
37. Trinka E. What is the evidence to use new intravenous AEDs in status epilepticus? *Epilepsia*. 2011;52(suppl 8):35–38.
38. Paquette V, Culley C, Greanya ED, Ensom MH. Lacosamide as adjunctive therapy in refractory epilepsy in adults: A systematic review. *Seizure*. 2015;25:1–17.
39. Shelton CM, Alford EL, Storgion S, et al. Enteral topiramate in a pediatric patient with refractory status epilepticus: A case report and review of the literature. *J Pediatr Pharmacol Ther*. 2014;19:317–324.

40. Dorandeu F, Dhote F, Barbier L, et al. Treatment of status epilepticus with ketamine, are we there yet? *CNS Neurosci Ther*. 2013;19:411–427.
41. Zeiler FA, Zeiler KJ, Kazina CJ, et al. Lidocaine for status epilepticus in adults. *Seizure*. 2015;31:41–48.
42. Zeiler FA, Zeiler KJ, Teitelbaum J, et al. Modern inhalational anesthetics for refractory status epilepticus. *Can J Neurol Sci*. 2015;42:106–115.
43. Wheless JW. Treatment of refractory convulsive status epilepticus in children: Other therapies. *Semin Pediatr Neurol*. 2010;17:190–194.
44. Bennett AE, Hoesch RE, DeWitt LD, et al. Therapeutic hypothermia for status epilepticus: A report, historical perspective, and review. *Clin Neurol Neurosurg*. 2014;126:103–109.
45. O'Connor SE, Ream MA, Richardson C, et al. The ketogenic diet for the treatment of pediatric status epilepticus. *Pediatr Neurol*. 2014;50:101–103.
46. Zeiler FA, Zeiler KJ, Teitelbaum J, et al. VNS for refractory status epilepticus. *Epilepsy Res*. 2015;112:100–113.
47. Chung WH, Chang WC, Lee YS, et al.; Taiwan Severe Cutaneous Adverse Reaction Consortium; Japan Pharmacogenomics Data Science Consortium. Genetic variants associated with phenytoin-related severe cutaneous adverse reactions. *JAMA*. 2014;312:525–534.

75

Acute Management of the Brain Injury Patient

Bradley A. Boucher and G. Christopher Wood

KEY CONCEPTS

1. Cerebral ischemia is the key pathophysiologic event triggering secondary neuronal injury following severe traumatic brain injury (TBI). Intracellular accumulation of calcium is postulated to be a central pathophysiologic process in amplifying and perpetuating secondary neuronal injury via inhibition of cellular respiration and enzyme activation.
2. *Guidelines for the Management of Severe Brain Injury*, 4th edition, published by the Brain Trauma Foundation (BTF)/American Association of Neurological Surgeons (AANS), serve as the foundation on which clinical decisions in managing adult neurotrauma patients are based; comparable guidelines for infants, children, and adolescents have also been published.
3. Correcting and preventing early hypotension (systolic blood pressure [SBP] less than 100 to 110 mm Hg depending on age) with an SBP goal of 120 to 140 mm Hg and reversal of hypoxemia are primary goals during the initial resuscitative and intensive care of patients with severe TBI.
4. Nonpharmacologic management of intracranial hypertension includes raising the head of the bed 30°, and ventricular drainage if an extraventricular drain (EVD) is present.
5. The principal monitoring parameter for patients with severe TBI within the intensive care environment is increased intracranial pressure (ICP). Cerebral perfusion pressure (CPP) is also a critical monitoring parameter and should be maintained between 60 and 70 mm Hg (8.0 and 9.3 kPa) (greater than 40 mm Hg [5.3 kPa] in pediatric patients) through the use of fluids, vasopressors, and/or ICP normalization therapy.
6. Nonspecific pharmacologic management of intracranial hypertension

should include analgesics, sedatives, and antipyretics; paralytics may be advantageous under selected circumstances.

7. Specific pharmacologic management of intracranial hypertension includes mannitol, hypertonic saline, furosemide, and high-dose pentobarbital. Neither routine use of corticosteroids nor aggressive hyperventilation (ie, $PaCO_2$ less than 25 mm Hg [3.3 kPa]) should be used in the management of intracranial hypertension.
8. Numerous investigational strategies targeted at limiting injury and/or stimulating axonal repair following severe TBI have been employed; however, no proven therapeutic benefits have been identified.
9. Use of phenytoin (alternatively levetiracetam) for the prophylaxis of posttraumatic seizures generally should be discontinued after 7 days if no seizures are observed.

Preclass Engaged Learning Activity

Watch the video entitled "Overview of Traumatic Brain Injury (TBI)" (https://www.youtube.com/watch?v=T0WBMM7WKL4) which is a presentation delivered by Dr. Christopher Wolf and moderated by Brent Ghan at the University of Missouri School of the Health Professions. This 7.5 minute video provides a general overview of human brain anatomy and physiology. Thereafter, TBI pathophysiology is briefly outlined including cerebral contusions, diffuse axonal injury, secondary brain injury, in addition to TBI recovery. This video provides a succinct introduction to the more detailed pathophysiology outlined in the chapter and a context for understanding TBI pharmacologic and nonpharmacologic management.

INTRODUCTION

Traumatic brain injury (TBI) is one of the leading causes of death and disability among children and young adults in the industrialized world and is often referred to as the "silent epidemic."[1] A focus on TBI prevention, improved acute care, and rehabilitation must remain national priorities. This chapter summarizes TBI epidemiology and pathophysiology, and highlights the major guidelines and systematic reviews of the literature pertaining to the management of patients

with severe TBI.

EPIDEMIOLOGY

It is estimated that approximately 2.2 million persons sustain a TBI each year in the United States equating to a TBI nearly every 15 seconds.[1] Among these individuals, over 280,000 require hospital admission, and nearly 50,000 die annually.[1] Importantly, an estimated 5.3 million Americans currently live with disabilities as a result of their TBI, highlighting the enormous physical and emotional toll of this healthcare problem.[2] The economic effects of acute neurotrauma are also enormous, with estimates of direct and indirect spending on patients with TBI requiring hospitalization reaching $76.5 billion in the United States in 2010.[2] Economic costs to society from lost productivity are also massive, especially considering the young age of many patients with TBI.[2] Falls are the leading cause of TBI (47%), while TBI-related hospitalizations and deaths vary based on age.[1,2] For example, death rates from TBI after a fall are highest in patients aged 65 years or older while motor vehicle crashes are the leading cause of death in persons aged 5 to 24 years.[1]

PRIMARY AND SECONDARY BRAIN INJURY PATHOPHYSIOLOGY

The neurologic sequelae of brain trauma can occur instantaneously as a consequence of the primary injury or can result from secondary injuries that follow within minutes, hours, or days after the initial injury.[3] Primary injury involves the external transfer of kinetic energy to various structural components of the brain (eg, neurons, nerve synapses, glial cells, axons, and cerebral blood vessels). The biomechanical forces responsible for primary brain injury can be classified broadly as contact (eg, blunt-object blow, penetrating-missile injuries) and acceleration/deceleration (eg, instantaneous brain movements following motor vehicle accidents).[4] Contact forces to the head commonly result in skull fractures, brain contusions, and/or hemorrhages. Primary brain injuries are categorized further as focal (eg, contusions, hematomas) or diffuse,[4,5] with the latter usually being associated with shearing or stretch forces, which primarily affect axons within the brain (ie, diffuse axonal injury).[4] The type of primary injury (ie, focal vs diffuse) is a major factor as to which of the secondary injury mechanisms discussed below will predominate following a TBI; however, many

patients, especially those involved in high-speed accidents, sustain both types of injury.[4]

1 A complex sequence of pathophysiologic events precipitated by primary brain injury may seriously disrupt the normal central nervous system (CNS) balance between oxygen supply and demand resulting in a metabolic crisis.[6,7] Hypotension in particular during the early posttraumatic period is a major contributor to this imbalance and a primary determinant of outcome. The end result of this imbalance may be cerebral ischemia, the key pathophysiologic event triggering secondary injury.[6] **Figure 75-1** is a simplified schematic of the processes that constitute secondary brain injury and their various interrelationships. The brain is particularly susceptible to ischemia because of its normally high resting energy requirement and its limited capacity to store oxygen, glucose, and adenosine triphosphate (ATP).[3] These phenomena can result in imbalances in cerebral oxygen delivery (CDO_2) and cerebral metabolic rate of oxygen consumption ($CMRO_2$), processes that are closely autoregulated under normal circumstances.[6] Factors that can diminish cerebral oxygen supply following brain injury include cerebral edema, expanding mass lesions (eg, epidural, subdural, and intracerebral hematomas), cerebral vasospasm, and loss of vasoregulatory control. Vasogenic cerebral edema can develop as a consequence of cerebral capillary endothelial damage and disruption of the blood–brain barrier.[7] Cytotoxic cerebral edema is a consequence of loss of cell wall integrity that accompanies ischemia or hypoxia with accumulation of lactic acid secondary to anaerobic metabolism.[7] With cytotoxic and vasogenic edema comes expansion of the intracellular and extracellular fluid spaces, respectively. Increased intracranial pressure (ICP) is the most detrimental consequence of cerebral edema formation and occurs as the brain tissue volume increases within the nondistensible skull. A significant increase in ICP may further compromise cerebral blood flow (CBF) and extend cytotoxic edema. Hence an increase in ICP can be self-perpetuating unless this cycle is reversed. Hypoxemia can further exacerbate local decreases in cerebral oxygen supply following acute respiratory failure and systemic hypotension. Metabolic demand also can increase following neurotrauma secondary to seizures, agitation, and temperature elevation.

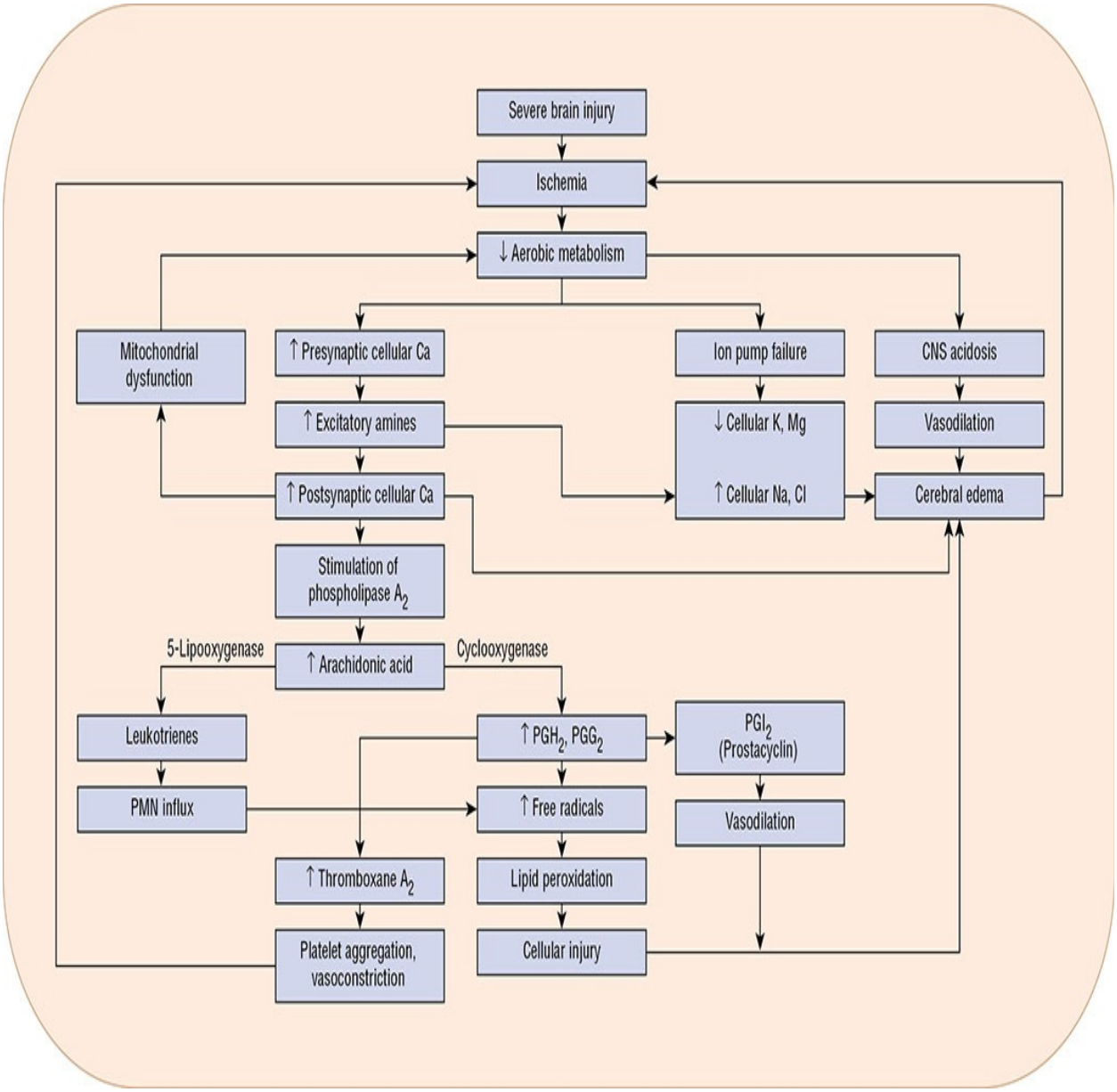


FIGURE 75-1 Schematic illustration of the cascade of biochemical events proposed to occur following severe neurotrauma (secondary brain injury). (Ca, calcium; Cl, chloride; CNS, central nervous system; K, potassium; Mg, magnesium; Na, sodium; PMN, polymorphonucleocyte; PGH_2, prostaglandin H_2; PGG_2, prostaglandin PGG_2; PGI_2, prostaglandin PGI_2.)

The two distinctive end points along the spectrum of secondary neuronal injury are: (a) energy-independent cellular necrosis characterized by membrane cell lysis, edema, and inflammation, and (b) energy-independent apoptosis that leads to cell shrinkage and cell membrane dissolution.[4,8] Apoptosis, which is also known as programmed cell death, requires a cascade of intracellular events

for completion of cell death,[4,8] with the loss of ionic homeostasis being postulated to be a key event in fostering secondary brain injury following cerebral ischemia. As part of this process, cellular influx of sodium, chloride, magnesium, and water occurs with a corresponding efflux of potassium secondary to cytotoxic edema and Na^+-K^+-ATPase pump dysfunction.[3] An influx of calcium into the presynaptic terminal ends of damaged neurons is mediated by N-type voltage-sensitive calcium channels and this influx is postulated to stimulate excessive release of the excitatory amines glutamate and aspartate from the affected neurons. These amines then accumulate in the neuronal synaptic cleft in the presence of cellular energy failure,[3] resulting in ongoing stimulation of postsynaptic cells, which extend neurotoxicity and cell death. The influx of calcium and additional sodium is stimulated by activation of ionophore receptors including the *N*-methyl-D-aspartate (NMDA) receptor.[4,8] Calcium influx and its intracellular accumulation initiate a number of events that amplify and perpetuate secondary neuronal injury as well as mitochondrial dysfunction, which further inhibits cellular respiration, a process already affected by ischemic and/or hypoxic insults.[3,6,8] A second major deleterious effect of calcium is to stimulate activation of autodestructive enzymes, including phospholipases, endonucleases, and proteases, such as the caspase family of enzymes.[4,8] The effect of phospholipase A_2 stimulation includes formation of several arachidonic acid metabolites derived from membrane lipids (eg, thromboxane A_2, prostaglandins, and leukotrienes) that facilitate lipid peroxidation and the formation of reactive oxygen species.[3,6,8] Data suggest that this event occurs very early after injury (eg, before hospitalization), which may limit the effectiveness of exogenously administered antioxidants. Cell-mediated injury involving inflammatory mediators (eg, proinflammatory cytokines) and nitric oxide activation is yet another possible mechanism involved in secondary neuronal injury,[6,7] implicating polymorphonuclear neutrophils, platelets, endothelial cells, and macrophages. Noteworthy is that limited data suggest that activation of some inflammatory mediators may actually be beneficial, such that the relative balance of the mediators rather than absolute concentrations may be the most significant pathophysiologic factor following TBI. Stimulation of platelet aggregation, vasodilation, and vasoconstriction also may occur.[6]

The Glascow Coma Scale (GCS) was designed over 40 years ago and is still the most widely used system to grade the arousal and functional capacity of the cerebral cortex,[9] as it defines the level of consciousness according to eye opening, motor response, and verbal response (**Table 75-1**). A GCS score of 15

corresponds to a normal neurologic examination based on eye, motor, and verbal responses. A GCS score of 3 to 8, 9 to 12, and 13 to 15 is consistent with severe, moderate, and mild or minor brain injury, respectively.[9] The possibility of ethanol or drug intoxication, hypotension, hypoxia, postictal state, hypoglycemia, electrolyte imbalances, or hypothermia altering the neurologic examination always should be considered when administering this scale. Because opiates, sedatives, and neuromuscular blockers affect the neurologic examination, they should not be administered until the initial examination is complete if at all possible. Simple, rapidly attainable clinical variables that are predictive of poor outcomes include extremes of age, presence of hypotension, hypoxia and/or coagulopathy, increased ICP, decreased GCS score (especially the motor score), and pupillary changes.[10]

TABLE 75-1 Glasgow Coma Scale

Response	Score
Eyes	
Open spontaneously	4
To verbal command	3
To pain	2
No response	1
Best motor response	
To verbal command	
Obeys	6
To painful stimulus (pressure to nailbeds)	
Localizes pain	5
Flexion, withdrawal	4
Flexion, abnormal (decorticate rigidity)	3
Extension (decerebrate rigidity)	2
No response	1
Best verbal response	
(Arouse patient with painful stimulus if necessary)	
Oriented and converses	5
Disoriented and converses	4
Inappropriate words	3
Incomprehensible sounds	2
No response	1
Total	3-15

CLINICAL PRESENTATION

Acute Brain Injury

General

- Level of consciousness on admission ranges from completely unresponsive to awake and alert (ie, Glasgow Coma Scale [GCS] 3-15 [Table 75-1]).

Symptoms

- Posttraumatic amnesia (eg, greater than 1 hour), increasing dizziness, a moderate-to-severe headache, nausea/vomiting, limb weakness, or paresthesia may indicate more severe injury.

Signs

- Cerebrospinal fluid (CSF) otorrhea or rhinorrhea, seizures, or unequal or unreactive pupils may indicate more severe injury.
- A rapid deterioration in mental status strongly suggests the presence of an expanding lesion within the skull.
- Severe TBI may be accompanied by significant alterations or instability in vital signs, including abnormal breathing patterns (eg, apnea, Cheyne–Stokes respiration, tachypnea), hypertension, or bradycardia.

Laboratory Tests

- Arterial blood gases (ABGs) indicating hypoxia (ie, decreased PaO_2) or hypercapnia (ie, increased $PaCO_2$) may indicate compromised ventilation.
- A positive blood ethanol concentration and/or positive urine drug screen indicates that drug intoxication may be affecting the patient's mental status in addition to the TBI.
- Electrolyte disturbances can cause alterations in mental status, and their effects may interfere with assessment of the patient's neurological status.

Other Diagnostic Tests

- CT scan of the head is an important diagnostic tool for detecting the presence of mass lesions and structural signs of edema (eg, midline shift, compressed ventricles).

TREATMENT

Desired Outcomes

The overall goal in TBI management is not only reduction in morbidity and mortality, but also optimization of long-term functional outcome for patients. This requires careful attention to the following short-term therapeutic goals: (a) establishment of an adequate airway and maintenance of ventilation and circulation during the initial period of resuscitation and evaluation, (b) maintenance of balance between CDO_2 and $CMRO_2$, (c) prevention or attenuation of secondary neuronal injury, and (d) prevention and/or treatment of associated medical complications.

General Approach to Treatment

2 In July 1995, the Brain Trauma Foundation (BTF) published an extensive document entitled *Guidelines for the Management of Severe Brain Injury* as a joint initiative with the Guidelines Committee of the American Association of Neurological Surgeons (AANS), the Joint Section on Neurotrauma and Critical Care of the AANS, and the Congress of Neurological Surgeons, with subsequent revisions in 2000 and 2007. The fourth revision was released in 2016.[11] Noteworthy is that the BTF is moving to a model of continuous monitoring of the literature, that is, “Living Guidelines,” with no plans to publish a fifth edition of this document.[11] Regardless, this landmark publication presently constitutes the most widely accepted series of evidence-based standards, guidelines, and options for the care of patients with severe TBI in the United States.[12] Recommendations are reported as Level I (high-quality of evidence), Level II (moderate-quality of evidence), or Level III (low-quality of evidence). Data show that compliance with the BTF/AANS guidelines can result in improved patient outcomes relative to mortality rate, functional outcome scores, length of hospitalization, and cost. Additionally, guidelines addressing prehospital TBI management[13] and surgical management[14] have also been published, as have TBI management guidelines for infants, children, and adolescents in 2003 with a second edition published in 2012.[15] The recommendations emanating from these published BTF/AANS guidelines on TBI management and various published systematic reviews will be highlighted throughout the remaining portion of this chapter. Until further clinical studies become available, recommendations from the BTF/AANS guidelines should serve as the foundation on which all clinical decisions in managing severe TBI are based. Nonetheless, it should be noted that the majority of the guidelines are based on Class II evidence (primarily

prospective clinical trials) and Class III evidence (primarily retrospective clinical trials) as few Class I evidence studies (ie, prospective, randomized, controlled trials) are available for treatment of TBI. The pharmacologic management of TBI is summarized in **Table 75-2**. Recommendations provided in this chapter pertain to adults and children unless specifically noted to the contrary.

TABLE 75-2 Pharmacologic Management of TBI

Hyperosmolar therapy
Mannitol effectiveness in lowering ICP is uncertain (No recommendation level due to insufficient evidence).
Hypertonic saline effectiveness in lowering ICP is uncertain (No recommendation level due to insufficient evidence).
Deep venous thrombosis prophylaxis
LMWH or low-dose unfractionated heparin may be used in combination with mechanical prophylaxis. However, there is an increased risk of expansion of intracranial hemorrhage (Recommendation level III).
Anesthetics, analgesics, and sedatives
Prophylactic administration of barbiturates to reduce burst suppression ECG is not recommended (Recommendation level II B).
High-dose barbiturate administration is recommended to control elevated ICP refractory to maximum standard medical and surgical treatment in adults. Hemodynamic stability is essential before and after barbiturate therapy (Recommendation level II B).
Propofol is recommended for the control of ICP, but not for improvement in mortality or 6-month outcomes. High-dose propofol can produce significant morbidity (Recommendation level II B).
Antiseizure prophylaxis
Prophylactic use of phenytoin or valproate is not recommended for preventing late PTS (>7 days) (Recommendation level II A).
Phenytoin is recommended to decrease the incidence of early PTS (within 7 days of injury) (Recommendation level II A).
Levetiracetam cannot be recommended over phenytoin regarding efficacy in preventing early PTS and toxicity. (No recommendation based on insufficient evidence.)
Corticosteroids
The use of steroids is not recommended for improving outcome or reducing ICP in patients with TBI. In patients with moderate or severe TBI, high-dose methylprednisolone is associated with increased mortality and is contraindicated (Recommendation level I).

ECG, electrocardiogram; ICP, intracranial pressure; LMWH, low-molecular-weight heparin; PTS, posttraumatic seizures; TBI, traumatic brain injury. Level I: Recommendation based on a high-quality body of evidence. Level II A: Recommendation based on a moderate-level quality of evidence. Level II B: Recommendation based on a low-quality body of evidence (direct evidence but overall low quality). Level III: Recommendation based on a low-quality body of evidence.

Data from Reference 11.

Pharmacologic Therapy

Initial Resuscitation

3 4 The first priority in the unconscious patient is the establishment of an

airway that facilitates adequate oxygenation and prevents aspiration.[9] Thereafter, restoration and maintenance of systolic blood pressure (SBP) between 120 and 140 mm Hg is desired since having an admission SBP outside this range is associated with increased mortality.[16] More specifically correcting and preventing early hypotension (goal SBP >100 mmHg for patients ages 50-69 years or >110 mmHg for patients ages 15-49 or over 70 years) is critical as it is among the most powerful predictors of outcome.[11] Isotonic saline (0.9% normal saline) and lactated Ringer's solution have been traditionally used as initial resuscitation fluids of choice in patients with TBI. While some clinicians believe that hypertonic saline (eg, 3% or 7.5% saline) is beneficial in this situation, clinical studies have yielded equivocal results relative to their superiority over isotonic solutions.[17] Regardless, no clear consensus exists as to the optimal initial resuscitation fluid. Furthermore, the volume of crystalloids administered requires careful monitoring considering there are data associating lower volumes with improved survival.[18] While albumin therapy may be considered as an alternative to crystalloid fluid resuscitation, a retrospective analysis of 460 patients with TBI revealed an increase in mortality compared with those patients receiving 0.9% normal saline.[19] Vasopressors and inotropic agents may be needed to maintain an adequate mean arterial pressure (MAP) if hypotension persists after adequate restoration of intravascular volume. Nonpharmacologic management of intracranial hypertension includes raising the head of the bed 30°, and ventricular drainage if an extraventricular drain (EVD) is present. **Figure 75-2** is an algorithm summarizing treatment priorities in the initial management of acute TBI.

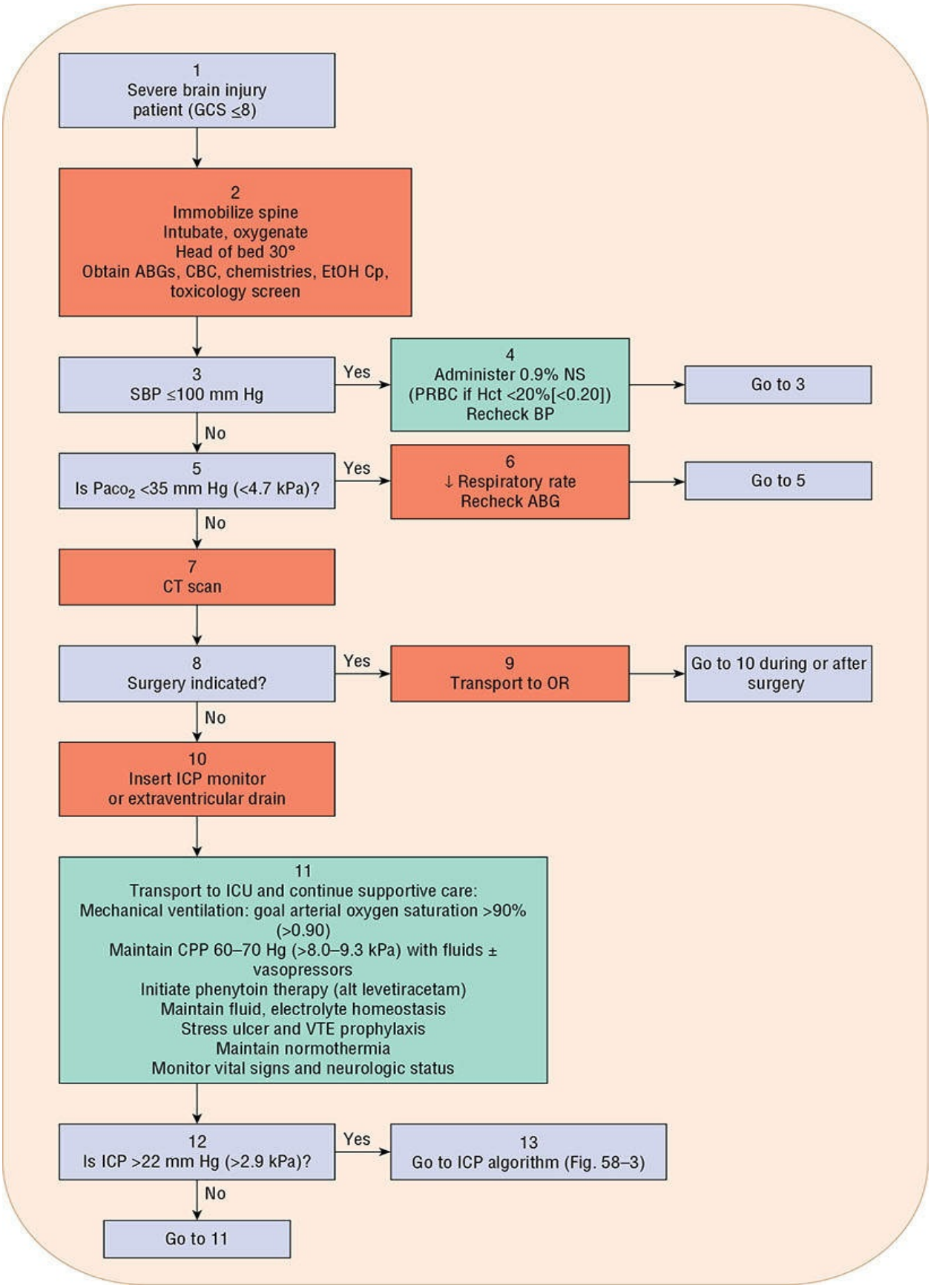
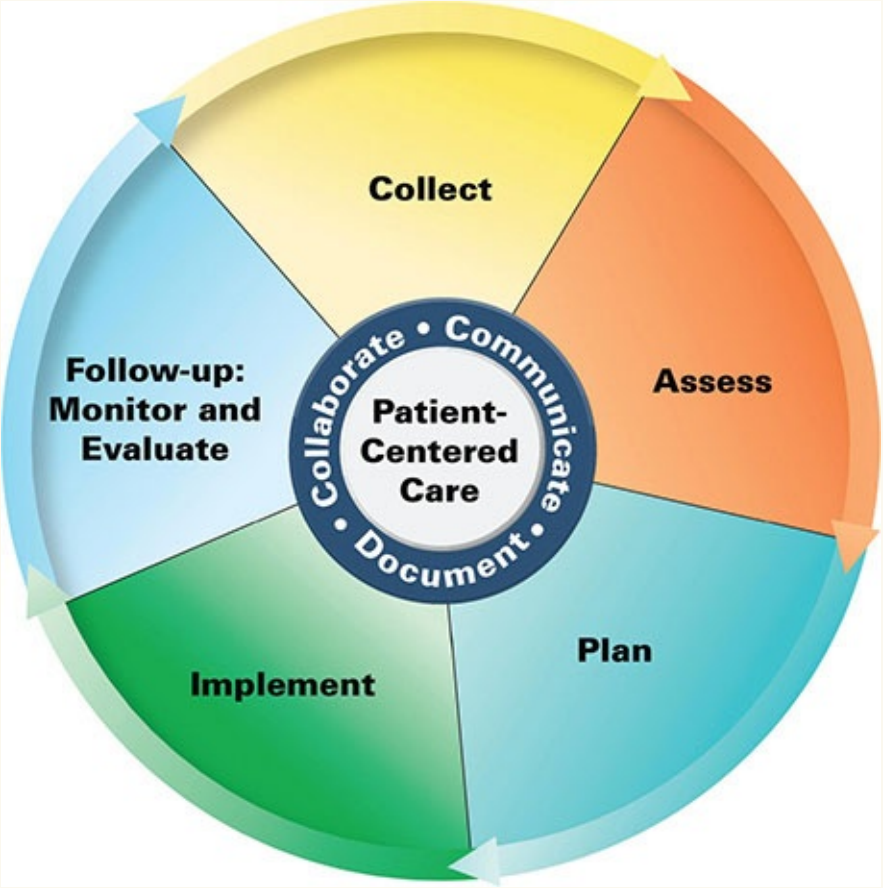

1
Severe brain injury patient (GCS ≤8)
2
Immobilize spine
Intubate, oxygenate
Head of bed 30°
Obtain ABGs, CBC, chemistries, EtOH Cp, toxicology screen
3
SBP ≤100 mm Hg
Yes
4
Administer 0.9% NS
(PRBC if Hct <20%[<0.20])
Recheck BP
Go to 3
No
5
Is $Paco_2$ <35 mm Hg (<4.7 kPa)?
Yes
6
↓ Respiratory rate
Recheck ABG
Go to 5
No
7
CT scan
8
Surgery indicated?
Yes
9
Transport to OR
Go to 10 during or after surgery
No
10
Insert ICP monitor or extraventricular drain
11
Transport to ICU and continue supportive care:
Mechanical ventilation: goal arterial oxygen saturation >90% (>0.90)
Maintain CPP 60–70 Hg (>8.0–9.3 kPa) with fluids ± vasopressors
Initiate phenytoin therapy (alt levetiracetam)
Maintain fluid, electrolyte homeostasis
Stress ulcer and VTE prophylaxis
Maintain normothermia
Monitor vital signs and neurologic status
12
Is ICP >22 mm Hg (>2.9 kPa)?
Yes
13
Go to ICP algorithm (Fig. 58–3)
No
Go to 11

FIGURE 75-2 Algorithm for the acute management of the patient with a TBI. (ABG, arterial blood gas; BP, blood pressure; CBC, complete blood count; CPP, cerebral perfusion pressure; CT, computed tomography; EtOH Cp, ethanol plasma concentration; GCS, Glasgow coma scale; Hct, hematocrit; ICP, intracranial pressure; ICU, intensive care unit; NS, normal saline; OR, operating room; $PaCO_2$, partial pressure of arterial blood carbon dioxide; PRBC, packed red blood cells; SBP, systolic blood pressure.) (*Adapted, with permission, from Management of Acute Traumatic Brain. In: Richardson M, Chant C, Chessman KH, et al., eds.* Pharmacotherapy Self-Assessment Program, *7th ed. Neurology and Psychiatry. Lenexa, KS: American College of Clinical Pharmacy, 2012:143.*)



Patient Care Process for Acute Management of the Brain Injury Patient

Collect

- Glasgow Coma Scale (GCS: Table 75-1), vital signs, physical exam and head computed tomography (CT) scan findings, arterial blood gases, ICP and CPP (if available), laboratory data (see “Clinical Presentation” section)
- Prior and current medications, including alcohol and illicit drugs

Assess

- Consistency between with the GCS/physical exam and injuries on head CT scan (ie, could there be other reasons for the neurologic deficit such as intoxication)
- ICP (goal <22 mmHg [2.9 kPa]) and CPP (goal 60-70 mm Hg [8.0-9.3 kPa]) (Fig. 75-2)
- Need for general ICU supportive care including: mechanical ventilation/appropriate oxygenation, stress ulcer prophylaxis, and sedation/analgesia
- For VTE prophylaxis, it is important to determine if pharmacologic prophylaxis is contraindicated due to intracranial bleeding
- Need for other supportive care measures more specific to TBI including: spine immobilization, seizure prophylaxis, avoiding fever and excessive hyperglycemia, appropriate fluid therapy with a goal of euvolemia, and starting early enteral nutrition

Plan*

- Unless contraindicated, initiate appropriate supportive care measures for the issues outlined above in the Assess section (Fig. 75-2)
- Nonpharmacologic management of increased ICP with first line options (eg, raise head of the bed 30°, open extraventricular drain if ICP >22 mm Hg [2.9 kPa, if present]) (Fig. 75-2)
- Pharmacologic management of increased ICP with first line agents (eg, short-acting sedation and analgesia, and hyperosmolar agents [hypertonic saline, mannitol]) (Fig. 75-3 and Table 75-2)
- Avoid low CPP with IV fluid therapy, possible administration of blood products, or vasopressors (eg, norepinephrine, phenylephrine, dopamine) if SBP <100 mm Hg
- Treat hyperthermia, if present, using antipyretic agents and/or cooling blankets

- If ICP is uncontrolled after optimizing first line options for ICP control, move to second line options (eg, pentobarbital, neuromuscular blocking agents, hyperventilation) (Table 75-3)

Implement*

- Work with the medical team on mutually agreeable and patient-centered implementation of treatments where some differences in opinion and practice may exist (eg, initial choice of sedatives, anticonvulsants, or hyperosmolar agents)
- Work with the medical team and nursing staff to implement an understanding of treatment goals (ie, ICP and CPP), as well as clear priorities in treatment selection and escalation among the many options for treating elevated ICP

Follow-up: Monitor and Evaluate

- Monitor ICP and CPP, especially response to therapies for elevated ICP to determine which modalities work best in each patient (Fig. 75-3)
- Other routine monitoring includes GCS, fluid/electrolyte status, arterial blood gases, and vital signs (Table 75-4)
- Drug-specific monitoring includes issues such as: hypotension from sedatives/opiates, hypertriglyceridemia or PRIS from propofol, risk of bleeding/worsening intracranial hemorrhage from VTE prophylaxis agents, anticonvulsant adverse events such as rash, acute kidney injury from mannitol, or hypernatremia/hyperchloremia from hypertonic saline (Table 75-3)
- Discontinue seizure prophylaxis after 7 days if no seizures occur in the hospital (Table 75-2)

* *Collaborate with patient, caregivers, and other healthcare professionals.*

Postresuscitative Care

Following successful resuscitation, priorities shift toward diagnostic evaluation of intracranial and extracranial injuries, and emergent surgical intervention as needed. In many patients, evacuation of intracranial hematomas (ie, epidural, subdural, and intracerebral hematomas) is essential to control ICP and improve outcome. Elevation of depressed skull fractures and debridement of penetrating

wound tracts are other important emergent surgical procedures in patients with TBI. Decompressive craniectomies (ie, removal of a variable amount of skull bone) with or without temporal or frontal lobectomy may be considered in patients with increases in ICP refractory to more conservative measures.[6] In the largest randomized study to date, patients with TBI and refractory elevated ICPs undergoing decompressive craniectomy had significantly improved survival but higher rates of vegetative state and disability compared with medical therapy.[20] Thus, the role of decompressive surgery in adult patients with TBI and refractory ICP remains controversial in light of these quality of life data outcomes.

Continuous ICP monitoring (eg, EVD and/or intraparenchymal fiberoptic catheter) has been the mainstay of ICP monitoring and treatment for decades in patients with severe TBI. Extraventricular drains have a therapeutic advantage over the alternatives but are associated with a higher complication rate and can be difficult to place in the setting of the swollen brain. Specifically, while CSF can be drained using this device as a means to lower ICP, the most recent BTF/AANS guidelines have softened the indications for ICP monitoring based on data suggesting that invasive monitoring may lack superiority over clinical/radiologic monitoring; challenging the traditional paradigm.[11,21] If continuous ICP monitoring is employed, the goal should be to treat any ICP values above 22 mm Hg (2.9 kPa) since values above this level are associated with increased mortality.[11]

Jugular venous oxygen saturation ($SjvO_2$) monitoring is advocated by some practitioners for the detection of global cerebral hypoxia (ie, adequacy of CBF relative to $CMRO_2$), although it is technically difficult to achieve consistent results.[9] The use of brain tissue oxygen ($PbrO_2$) monitoring is an alternative to $SjvO_2$ to measure oxygen diffusion in patients with TBI[9] and cerebral microdialysis is another technique that has been used successfully as a research tool to measure the cerebral extracellular chemistry of patients with TBI.[9] Lastly transcranial Doppler (TCD)/duplex sonography, a device that can noninvasively measure cerebral blood flow, has been available since 1982 as an advanced cerebral monitoring technique.[22] Nevertheless, each of these advanced monitoring techniques either alone or in combination with conventional ICP monitoring (ie, multimodal monitoring) has limitations and/or potential risks. As such, the only recommendation from BTF/AANS guidelines relates to considering jugular venous oxygen saturation monitoring as a potential advanced monitoring modality to improve outcome in patients with TBI.[11] Biochemical markers (eg, S-100 calcium-binding protein B, neuron-specific enolase, glial

fibrillary acid protein, serum substance P[23]) may have utility in diagnosing and monitoring patients with TBI. However, no clear role has yet to be defined for such markers with each having assorted limitations.[24]

5 Another important monitoring parameter for patients with severe TBI within the intensive care environment is the as cerebral perfusion pressure (CPP), which is the difference between MAP and ICP (ie, CPP = MAP – ICP). Maintenance of an acceptable CPP is postulated to be critical in reducing cerebral ischemia and secondary injury. The BTF/AANS guidelines recommend maintaining a CPP range between 60 and 70 mm Hg (8.0 and 9.3 kPa).[11] Current guidelines also recommend that aggressive attempts to maintain CPP greater than 70 mm Hg (9.3 kPa) in adults should be avoided because of the risk of the acute respiratory distress syndrome.[15] In children, the recommended CPP goal is greater than 40 mm Hg (5.3 kPa).[15] While using a fixed target range is the most common approach for monitoring CPP, the concept of individualizing the CPP target range to restore cerebral vasoreactivity has been advocated.[25]

In order to achieve goal CPP the MAP may need to be increased through the use of fluids and/or vasopressors, and by lowering elevated ICP. In general the goal of volume expansion should be euvolemia as well as avoidance of a hypoosmolar state and negative fluid balance.[9,15,26] If the hemoglobin is below 7 g/dL (70 g/L; 4.34 mmol/L), transfusion of packed red blood cells (PRBCs) is indicated. Nevertheless, liberal transfusions should be avoided since using a hemoglobin target goal of 10 g/dL (100 g/L; 6.21 mmol/L) has been associated with higher incidence of thromboembolic events without an improvement in neurologic outcome based on a recent randomized trial.[27] However, more data are needed before these findings can be applied to all patients with TBI. Furthermore, use of erythropoietin was not associated with an improved neurologic outcome in the same trial.[27] Volume status should be targeted to a central venous pressure of 7 to 12 cm H_2O (0.7-1.2 kPa) if invasive monitoring is employed. After achievement of euvolemia, the patient's head should also be elevated by 30 degrees to promote venous drainage and decrease ICP.[9] If restoration of the intravascular volume is inadequate in elevating MAP to an acceptable level, hypertension should be induced using vasopressors (eg, norepinephrine, phenylephrine, dopamine)[9] and patients should be monitored for renal dysfunction, lactic acidosis, and signs of peripheral ischemia when vasopressors are used, especially in large doses.

TREATMENT

Several general and specific pharmacologic and nonpharmacologic strategies are used in the treatment of intracranial hypertension.

Anesthetics, Analgesics, and Sedatives

6 The use of analgesics and sedatives has an important primary role in the management of intracranial hypertension (**Fig. 75-3** and **Table 75-3**) that are directly related to the association of pain, agitation, excessive muscle movement, and resisting mechanical ventilation with transient increases in ICP. Paralytics are a secondary option in refractory patients or during stimulatory procedures in patients with elevated ICP.[28] Nonetheless, there is no strong evidence that one agent is superior to another in affecting patient outcomes with severe TBI[29] as their effect on ICP, CPP, and MAP are variable.[29] Morphine sulfate is the most commonly used analgesic and sedative in this setting[11,29] and it is important to note that bolus doses of opiates may increase ICP by increasing CBF.[29] However, while continuous infusions of fentanyl and sufentanil are gaining in popularity, their use also may be associated with mild elevations in ICP.[11,29] Propofol has become the sedative of choice in the treatment of patients with TBI among many clinicians because of its ease of titration, rapidly reversible effects on discontinuation, and possible neuroprotective effects.[11] Although it is used for sedation in infants and children who are mechanically ventilated in the intensive care unit (ICU) setting, the Food and Drug Administration (FDA) requires that the manufacturer labeling contains specific information that propofol is not approved for sedation of pediatric patients admitted to an ICU. One of the biggest safety concerns with the use of propofol is the propofol infusion syndrome (PRIS) characterized by hyperkalemia, hepatomegaly, lipemia, metabolic acidosis, myocardial failure, rhabdomyolysis, renal failure, and death in some cases.[11] While initially reported in children, PRIS can also occur in adults; therefore, doses greater than 5 mg/kg/hr and infusion exceeding 48 hours should be used with extreme caution.[11] Triglyceride concentrations also should be monitored in patients receiving prolonged propofol infusions and/or high dosages of propofol considering its lipid emulsion formulation and the potential for inducing hypertriglyceridemia under these conditions. Furthermore, evidence of neurotoxicity associated with propofol in animal studies has raised concerns regarding use of this sedative in patients with TBI.[30,31] Alternative

sedatives include short-acting benzodiazepines (eg, midazolam), especially if there is a reasonable suspicion of alcohol withdrawal as the underlying etiology of the agitation,[32] and intermittent low-dose pentobarbital, ketamine,[33] dexmedetomidine,[34,35] or etomidate (particularly useful in rapid-induction anesthesia). The potential for these agents to decrease MAP and CPP must be monitored closely.[29] Additionally, the cumulative sedative effects of longer-acting drugs, especially benzodiazepines, must be taken into account. The use of any sedative or paralytic agent also must be weighed against its potential to obscure the neurologic examination of the patient.

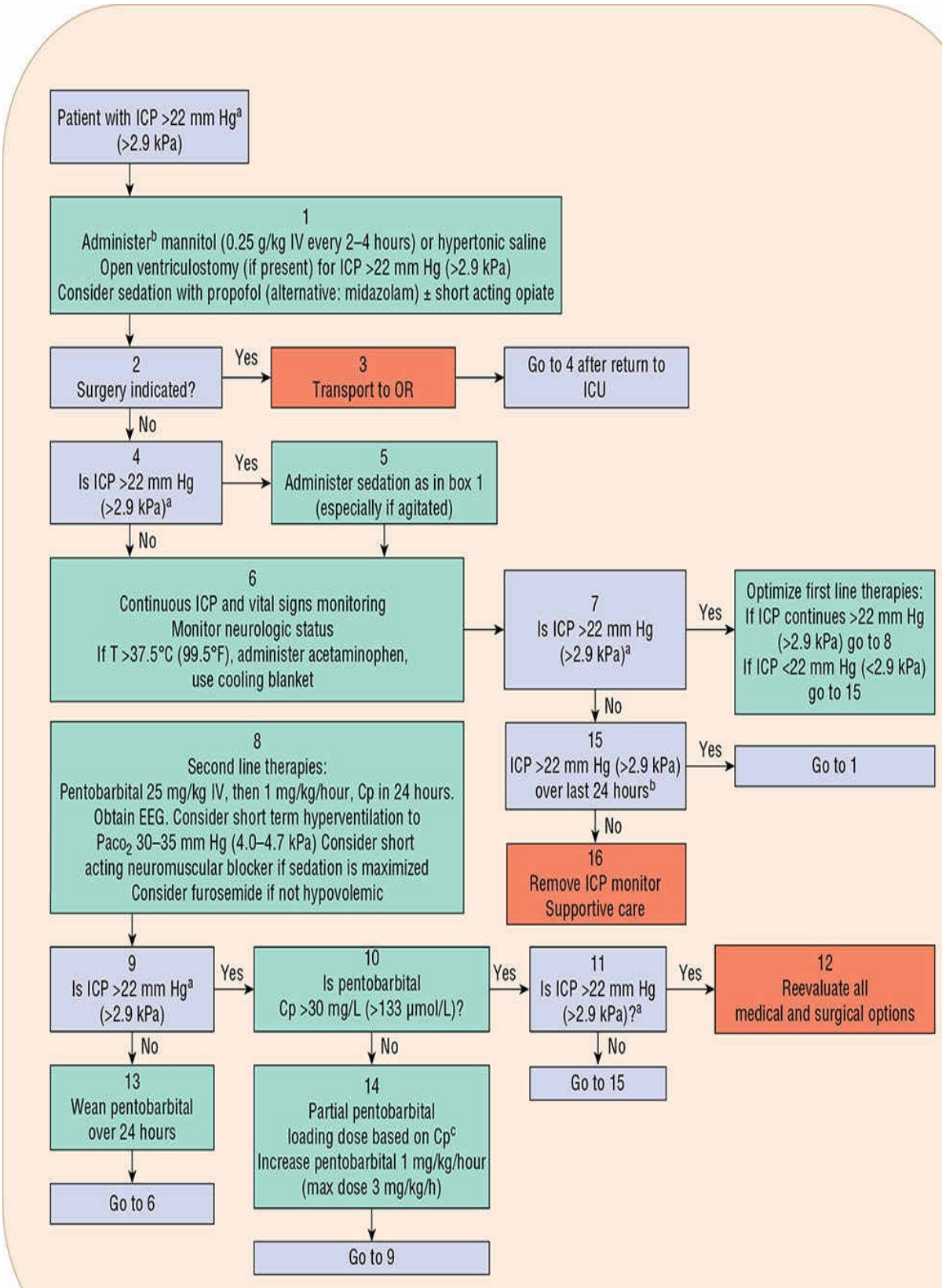

Patient with ICP >22 mm Hg[a] (>2.9 kPa)
1
Administer[b] mannitol (0.25 g/kg IV every 2–4 hours) or hypertonic saline
Open ventriculostomy (if present) for ICP >22 mm Hg (>2.9 kPa)
Consider sedation with propofol (alternative: midazolam) ± short acting opiate
2
Surgery indicated?
Yes
3
Transport to OR
Go to 4 after return to ICU
No
4
Is ICP >22 mm Hg (>2.9 kPa)[a]
Yes
5
Administer sedation as in box 1 (especially if agitated)
No
6
Continuous ICP and vital signs monitoring
Monitor neurologic status
If T >37.5°C (99.5°F), administer acetaminophen, use cooling blanket
7
Is ICP >22 mm Hg (>2.9 kPa)[a]
Yes
Optimize first line therapies:
If ICP continues >22 mm Hg (>2.9 kPa) go to 8
If ICP <22 mm Hg (<2.9 kPa) go to 15
No
15
ICP >22 mm Hg (>2.9 kPa) over last 24 hours[b]
Yes
Go to 1
No
16
Remove ICP monitor
Supportive care
8
Second line therapies:
Pentobarbital 25 mg/kg IV, then 1 mg/kg/hour, Cp in 24 hours.
Obtain EEG. Consider short term hyperventilation to $Paco_2$ 30–35 mm Hg (4.0–4.7 kPa) Consider short acting neuromuscular blocker if sedation is maximized
Consider furosemide if not hypovolemic
9
Is ICP >22 mm Hg[a] (>2.9 kPa)
Yes
10
Is pentobarbital Cp >30 mg/L (>133 µmol/L)?
Yes
11
Is ICP >22 mm Hg (>2.9 kPa)?[a]
Yes
12
Reevaluate all medical and surgical options
No
13
Wean pentobarbital over 24 hours
Go to 6
No
14
Partial pentobarbital loading dose based on Cp[c]
Increase pentobarbital 1 mg/kg/hour (max dose 3 mg/kg/h)
Go to 9
No
Go to 15

FIGURE 75-3 Algorithm for the management of increased ICP. (Cp, plasma concentration; EEG, electroencephalogram; ICP, increased intracranial pressure; ICU, intensive care unit; OR, operating room; PaCO2, partial pressure of arterial blood carbon dioxide.) (*Adapted, with permission, from Management of Acute Traumatic. In: Richardson M, Chant C, Chessman KH, et al., eds. Pharmacotherapy Self-Assessment Program, 7th ed. Neurology and Psychiatry. Lenexa, KS: American College of Clinical Pharmacy, 2012:144.*)

[a]Treatment thresholds: ICP 22 to 29 mm Hg (2.9-3.9 kPa) for >15 minutes; ICP 30 to 39 mm Hg (4.0-5.2 kPa) for >2 minutes; ICP more than or equal to 40 mm Hg (5.3 kPa) for more than 1 minute. Note: Transient increases may occur following respiratory procedures (eg, suctioning, chest physiotherapy, bronchoscopy, and intubation).

[b]Hold if serum osmolality is more than 320 mOsm/kg (mmol/kg).

[c]Partial pentobarbital loading dose (mg) = (30 mg/L – measured Cp) (1 L/kg × wt[kg]) (pentobarbital concentration in µmol/L must first be divided by 4.439 to convert to mg/L).

TABLE 75-3 Drug Dosing and Monitoring in Patients with TBI

Drug (Brand Name)	Adverse Drug Reactions	Monitoring Parameters	Dosage	Comments
Levetiracetam (Keppra)	CNS changes	Seizures, SCr	500 mg IV Q12 hr (during first 14 days)	Caution in patients with renal dysfunction If used for active seizures: increase to 1,000 mg every 12 hours after 14 days, then to 1,500 mg every 12 hours after 28 days
Mannitol (Generic)	Hypotension, renal dysfunction, hyperosmolality	ICP, CPP, BP, serum osmolality, Na, UO, SCr	0.25-1 g/kg IV every 2-4 hours	Avoid in patients with renal failure or CHF
Pentobarbital (Nembutal)	Hypotension, GI hypomotility, induction of hepatic drug metabolism	ICP, CPP, BP, EEG, GI function	10 mg/kg IV over 30 minutes, then 5 mg/kg over 3 hours, then 1 mg/kg/hr	Administer via central line. General dose range for infusion is 1-3 mg/kg/hr
Phenytoin (Dilantin)	Hypotension, dysrhythmias, nystagmus, ataxia, mental status changes, exfoliative dermatitis	Seizures, BP, ECG, phenytoin concentrations, skin	15-20 mg/kg IV over 60 minutes, then 5 mg/kg/day divided every 8 hours or every 12 hours	Administer <50 mg/min; use central line if available Round loading doses up to nearest 250 mg, round maintenance doses up to nearest 25 mg Trauma patients often require higher doses (ie, >6 mg/kg/day) to achieve therapeutic concentrations
Propofol (Diprivan)	Hypotension, hyperkalemia, metabolic, acidosis, rhabdomyolysis, renal failure, hepatomegaly, lipemia	ICP, CPP, BP, SCr, K, arterial pH, triglycerides, lactate	General range: 0.5-3 mg/kg/hr titrated to desired effect	Avoid doses greater than 5 mg/kg/hr or prolonged infusions; not approved for use in children

BP, blood pressure; CHF, congestive heart failure; CPP, cerebral perfusion pressure; ECG, electrocardiogram; EEG, electroencephalography; GI, gastrointestinal; ICP, increased intracranial pressure; K, potassium; Na, sodium; SCr, serum creatinine; UO, urine output.

7 High-dose barbiturate therapy (ie, barbiturate coma) has been used for decades in the management of increased ICP despite a lack of evidence documenting beneficial effects on patient morbidity and mortality.[36] Nonetheless, based largely on beneficial outcomes observed in a randomized clinical trial published in 1988, BTF/AANS and pediatric guidelines recommend that high-dose barbiturate therapy be considered in hemodynamically stable patients with severe TBI refractory to maximal medical ICP-lowering therapy and decompressive surgery.[11,15] Prophylactic use of barbiturates is not advocated in light of insufficient evidence supporting this practice and the potential for adverse events (eg, hypotension).[11,15,36] The mechanism responsible for the cerebral protective effects of barbiturates is generally attributed to suppression of

cerebral metabolism thereby cerebral metabolic demands and CBV.[36] Prior to inducing a barbiturate coma, the patient with severe TBI must be mechanically ventilated with continuous monitoring of arterial blood pressure, electrocardiogram (ECG), and ICP. Pentobarbital is the most commonly used barbiturate for this indication, although thiopental also has been used. Pentobarbital should be administered as an IV loading infusion totaling 25 mg/kg (ie, 10 mg/kg over 30 minutes and then 5 mg/kg/hr for 3 hours), followed by a maintenance infusion of 1 to 2 mg/kg/hr.[11] If the SBP falls during the loading or maintenance infusions, the rate should be slowed temporarily and blood pressure support initiated. The goal of a barbiturate coma is to maintain ICP and CPP at the previously discussed target thresholds in addition to achieving a pentobarbital steady state concentration of between 30 and 40 mg/L (133 and 178 µmol/L) (despite poor correlation between serum concentrations and outcome) and electroencephalography (EEG) burst suppression.[11] Initiation of barbiturate therapy withdrawal can occur when ICP has been controlled satisfactorily for 24 to 48 hours and should be tapered over 24 to 72 hours to prevent ICP spikes.

Side effects associated with high-dose barbiturate therapy involve primarily the cardiovascular system. Hypotension caused by peripheral vasodilation may occur, necessitating decreasing the barbiturate dose or the administration of fluids and vasopressors to maintain blood pressure. A systematic review of the literature suggested that one of every four patients receiving barbiturate therapy will develop hypotension.[36] Gastrointestinal (GI) effects of barbiturates include decreased GI muscular tone and decreased amplitude of contraction; however, on emergence from coma, there may be a period of GI hypermotility. Care should be taken to avoid extravasation of barbiturate solutions because severe tissue damage may occur. Therefore, barbiturates should be administered by continuous infusion through a central line dedicated for this purpose. The potential for barbiturates to induce the hepatic drug metabolism of concurrent medications should be also considered. Lastly, the potential for prolonged interference with the neurologic examination of patients with TBI must be considered prior to the initiation of high-dose barbiturate therapy.

Corticosteroids

7 Although corticosteroids are effective in preventing or reducing cerebral edema in patients with nontraumatic conditions that produce vasogenic edema, studies in patients with TBI have not demonstrated their ability to lower ICP or improve outcomes.[11,15] Specifically, use of corticosteroids following TBI has

been associated with increased mortality and complications including GI bleeding, glucose intolerance, electrolyte abnormalities, and infection. The largest investigation to date was known as the corticosteroid randomization after significant head injury (CRASH) study which indicated a higher risk of death within 2 weeks of enrollment (relative risk 1.18) in those patients receiving corticosteroids compared with patients receiving placebo.[37] Based on this and several other major randomized trials, the BTF/AANS adult and pediatric guidelines recommend that high-dose corticosteroids not be used in patients with moderate-to-severe TBI.[11,15]

Hyperventilation

7 The practice of prolonged aggressive hyperventilation ($PaCO_2$ less than 25 mm Hg [3.3 kPa]) to decrease ICP is no longer recommended[11] as data could not demonstrate improved outcomes using this therapeutic intervention. As such, recommendations for use of this treatment maneuver have been removed from the current BTF/AANS guidelines even as a temporizing measure in managing patients with TBI with elevated ICP.[11]

Hypothermia

Therapeutic hypothermia has been an attractive strategy for attempting to minimize secondary brain injury after TBI for decades. The mechanism underlying a protective effect of hypothermia is likely multifactorial, although a reduction in $CMRO_2$ is offered most frequently as the basis of any therapeutic benefits. Early studies suggested promise for therapeutic hypothermia for patient with TBI, as well as other patient populations with brain ischemia (eg, cardiac arrest patients). Unfortunately, data from large clinical trials of prophylactic therapeutic hypothermia in patients with TBI have not shown improved outcomes.[11,38] In addition, potential side effects of therapeutic hypothermia include coagulation disturbances, infectious complications, and cardiac arrhythmias. Thus, prophylactic therapeutic hypothermia is not recommended as a routine neuroprotective strategy in patients with TBI.[11] While a recent systematic review of therapeutic hypothermia in TBI found some evidence supporting its use was equivocal,[39,40] data from a large prospective trial indicated significantly worse functional outcomes in the hypothermia group compared with controls.[41] Therefore, the role of therapeutic hypothermia, except for perhaps patients with TBI with refractory ICP elevations, is unclear at best.[42]

Osmotic Agents

7 Although a number of osmotic diuretics (eg, urea, glycerol) can be used to decrease ICP, mannitol is unquestionably the most widely employed.[11,43] Despite the common practice of administering mannitol to patients with suspected or actual increases in ICP following brain injury, no clinical trial comparing its effects against placebo have been performed.[44] Based on this lack of evidence, the BTF/AANS guidelines removed the previous recommendation regarding the effectiveness of mannitol for control of increased ICP.[11]

The mechanisms responsible for mannitol's beneficial effects likely relate to (a) an immediate plasma-expanding effect that reduces blood viscosity and increases CBF, and (b) establishment of an osmotic concentration gradient across an intact blood–brain barrier that decreases ICP as water diffuses from the brain into the intravascular compartment.[11] Recommended doses of mannitol typically range from 0.25 to 1 g/kg IV every 2 to 4 hours with higher doses being used in emergency situations and the lower dose for a maintenance regimen.[43] Increased ICP is reduced within minutes following mannitol administration with a maximum effect within 20-60 minutes.[43] In order to maximize benefit and minimize adverse events, it has been suggested that mannitol be administered as a bolus and not as a continuous infusion in this setting.

Several adverse effects are associated with mannitol.[43] In addition to hypotension resulting from its diuretic effect, a reversible acute renal dysfunction may occur in patients with previously normal renal function after long-term, large-dose administration. Patients particularly susceptible are those with advanced age and pre-existing renal dysfunction which is based on data in patients with intracranial hemorrhage.[45] As such, mannitol should be avoided in patients with acute kidney injury or chronic kidney diseases. Acute exacerbation of underlying congestive heart failure and pulmonary edema also may occur following rapid intravascular volume expansion and furosemide is recommended as an alternative diuretic for lowering ICP in these latter patient groups.

While hypertonic saline solutions have been advocated by some as a resuscitative fluid following TBI as previously mentioned, solutions ranging from concentrations of 2% to 23.4% have also been used to acutely lower increased ICP.[46] Doses range from approximately 150 mL of 3% saline solution to 75 mL of 7.5% saline solution to 30 mL of 23.4% saline solution boluses.[43] Saline concentrations greater than 3% should be administered via a central venous catheter.[43] Not only do hypertonic saline solutions create an osmotic gradient in favor of reducing cerebral edema, but evidence suggests that they

may also have beneficial vasoregulatory, immunologic, and neurochemical effects as well.[46] Plasma expansion may also lead to an increase in CBF. It is noteworthy, however, that the 2016 BTF guidelines do not recommend hypertonic saline due to a lack of supporting evidence[11] consistent with a recent systematic review found no mortality benefit or beneficial effect on ICP with the use of hypertonic saline.[47] In contrast, two recent meta-analyses also suggested that hypertonic saline may be modestly more effective than mannitol.[46,48] In most of these studies, the goal of therapy was to treat an elevated ICP, however, for some the goal of therapy was to increase the serum sodium regardless of ICP. If used in this way, hypertonic saline should target serum sodium concentration less than 160 mEq/L (mmol/L) since additional benefit is unlikely at higher concentrations.[43]

Investigational Therapy

8 The steady decrease in morbidity and mortality following severe neurotrauma over the past several decades can be attributed largely to the use of conventional treatment strategies to expeditiously and aggressively manage events resulting in secondary injury (ie, ischemia, hypoxia, increased ICP). Numerous neuroprotective agents targeting specific pathophysiologic processes that are theorized to occur following severe TBI have been investigated over the past three decades in an attempt to further enhance the prospects for a meaningful recovery. Prominent among these strategies have been attempts to modulate calcium influx through the administration of calcium antagonists,[49] glutamate antagonists including magnesium, and the use of antioxidants/free radical scavengers.[50,51] Inhibitors of inflammatory mediators have also been considered as potential neuroprotective agents.[51] Unfortunately, none of these agents to date has demonstrated a significant reduction in morbidity or mortality following severe TBI in clinical trials. More recently there was immense enthusiasm for progesterone as a neuroprotective agent based on two moderately sized clinical studies that demonstrated improved outcome following acute TBI.[52] However, two subsequent large randomized, placebo controlled, prospective trials of progesterone in patients with acute TBI were halted early due to lack of improving functional outcomes dashing hopes for this promising therapy.[53,54] In contrast, interest continues to exist for the pleiotropic cytokine, erythropoietin, as a neuroprotective agent independent of its ability to increase hemoglobin concentrations.[50] Nevertheless, results of clinical investigations of erythropoietin in patients with TBI have produced equivocal results relative to

improved neurologic outcomes and survival benefits.[55,56] Other agents that may have beneficial effects in TBI based on limited clinical or epidemiologic data include 3-hydroxy-3-methylglutaryl (HMG)-coenzyme-A reductase inhibitors and sympatholytics such as β-blockers.[57] While two recent meta-analysis of β-blockers use in patients with TBI demonstrated mortality benefits,[58,59] their usage was associated with increased infection rates as well as overall and ICU length of stay.[59] Thus, evaluation of the benefit to risk ratio for this drug class will require additional prospective, randomized, clinical trials in patients with TBI. Miscellaneous agents and therapies being considered as viable neuroprotective agents based on clinical and/or experimental TBI studies include growth hormone, cyclosporine, nitric oxide synthase inhibitor, minocycline, hyperbaric oxygen, and CNS bone marrow stromal cell transplantation.[57] Others have proposed that stimulation of axonal repair processes versus limiting injury may be the most fruitful neuroprotective pathway for future investigations.[50,60]

The concept of administering commercially available CNS-active agents for nonapproved indications in patients with TBI should presently be considered investigative therapy. Examples include the use of CNS stimulants in the management and rehabilitation of patients with TBI as data supporting this approach are equivocal.[50] Another example is the use of Parkinson's disease medications (eg, amantadine, bromocriptine, carbidopa/levodopa) in patients with severe TBI in an attempt to enhance dopamine release and inhibit reuptake within the injured region of the brain.[61] While intuitively appealing, use of psychoactive agents to improve CNS sequalae in patients with TBI should be administered cautiously since large, well-controlled studies with a wide array of agents are lacking. Additionally, the timing of administration of these drugs is controversial; the potential for cardiovascular side effects in the face of uncertain benefit would suggest that these drugs should be reserved for the postacute phase of treatment (ie, weeks to months postinjury).

Acknowledging the complexities surrounding acute TBI, a broad-based, multidisciplinary approach is undoubtedly needed before breakthrough therapies are identified for this multifaceted, catastrophic condition.[62] Examples of these types of initiatives include the International Mission on Prognosis and Clinical Trial Design (IMPACT) study group,[63] and the BRAIN Initiative—Brain Research Through Advancing Neurotechnologies, which is a Presidential and National Institutes of Health focused program aimed at revolutionizing understanding of the human brain launched in 2014.[64]

Treatment and Prophylaxis of Complications

In addition to specific management of TBI problems such as intracranial hypertension, the potential for secondary complications must also considered in addition to rendering general supportive care. A wide variety of complications occur in more than 20% of patients with TBI and are associated with increased mortality and length of stay.[65] Development and implementation of clinical pathways for consistency of care, and clinical investigation of neuroprotective agents are important in advancing TBI treatment in the future.

Posttraumatic Seizures

9 It is generally agreed that adult patients who have experienced one or more seizures following a moderate-to-severe TBI should receive anticonvulsant therapy to avoid increases in $CMRO_2$ that occur with the onset of subsequent seizures and to prevent the development of (sometimes subclinical) status epilepticus associated with increased mortality.[11] Initial therapy should consist of incremental IV doses of diazepam (5-40 mg adults, 0.1-0.5 mg/kg infants and children) or lorazepam (2-8 mg adults, 0.03-0.1 mg/kg infants and children) to terminate any active seizure activity, followed by IV phenytoin to prevent seizure recurrence. Phenytoin dosing regimens for adults and pediatric patients include an IV loading dose of 15 to 20 mg/kg and 10 to 15 mg/kg, respectively, followed by a maintenance dose of 5 mg/kg/day divided into two or three daily doses. Alternatively, fosphenytoin, a water-soluble phosphate ester of phenytoin, can be administered IV or intramuscularly using the same doses, specified as phenytoin equivalents (PE). The merits of preventive anticonvulsant therapy in patients who have not had a seizure postinjury historically is controversial. Risk factors for early posttraumatic seizures (less than 7 days after injury) include a GCS score of less than 10, a cortical contusion, a depressed skull fracture, a subdural hematoma, an epidural hematoma, an intracerebral hematoma, a penetrating head wound, or a seizure within the first 24 hours of injury.[11] In a landmark randomized, placebo-controlled study, the incidence of early posttraumatic seizures in patients receiving placebo was 14.2% compared with 3.6% in patients receiving phenytoin without a significant increase in drug-related side effects.[66] Thus, it is recommended that phenytoin should be used to prevent seizures in adult and pediatric patients with TBI for the first 7 days after injury.[11,15] Interestingly, recent data suggest that phenytoin may not decrease early posttraumatic seizures and may diminish functional outcome after blunt TBI,[67] fueling debate challenging this longstanding practice.[68] Valproate therapy

is not recommended for patients with TBI, based on a trend for higher mortality compared to short-term phenytoin therapy.[66] Levetiracetam is a potentially attractive option; however, the drug should be used cautiously as large randomized clinical trials of its use has not been conducted in patients with TBI. Furthermore, the cost-effectiveness of levetiracetam versus phenytoin favors phenytoin.[69] Nevertheless, two recent meta-analyses found no difference in the rate of early posttraumatic seizures between the two agents,[70,71] and levetiracetam may have a superior safety profile based on one of these evaluations.[71] In a recent survey of nearly 70 neurotrauma centers in Europe, levetiracetam has become the anticonvulsant drug of choice over phenytoin in patients with TBI.[72] If used in TBI patients, the potential for increased levetiracetam systemic clearance should be considered when dosing this agent.[73] The benefits of prophylactic anticonvulsants beyond 7 days have not been demonstrated, and thus their use for this indication is not recommended.[11,15] Unfortunately, despite reducing the incidence of early seizures following brain injury, no beneficial effects have been documented for anticonvulsants on patient mortality or long-term disability.[11]

Supportive Care

While normalizing ICP and maintaining an adequate CPP are the highest priorities in preventing secondary injury following severe TBI, attention also must be given to preventing and/or treating systemic and extracranial complications. One such complication is systemic hypertension, which can be treated using antihypertensives including IV labetalol, nicardipine, and enaliprilat.[9]

Fluid and electrolyte management is another important area of focus in the critically ill patient with a TBI, as common electrolyte disturbances that should be monitored and treated aggressively include hyponatremia, hypomagnesemia, hypokalemia, and hypophosphatemia.

Furthermore, aggressive nutritional support should be initiated, as evidence suggests that early feeding of patients with TBI (ie, by 7 days) may be associated with a trend toward better outcomes in terms of survival and disability.[9,11,74,75] Early enteral nutrition, in particular, within 48 hours is associated with better survival and better outcome at 1 month postinjury based on a recent retrospective study of patients with severe TBI compared with matched controls not receiving early enteral nutrition.[76]

Hyperglycemia (glucose ≥160 mg/dL [8.9 mmol/L]) is also common in patients with TBI and is associated with worse outcomes.[77] Nevertheless,

intensive insulin therapy versus conventional glucose control should not be used since it is associated with adverse effects on brain glucose metabolism[78] with little to no gain in neurological outcome.[77]

Infectious complications commonly encountered in patients with severe TBI include nosocomial pneumonia, sepsis, urinary tract infections, and meningitis. Treatment of these potentially devastating infections should be aggressive, with careful attention being paid to antibiotic blood–brain barrier penetration for intracranial infections.

Hyperthermia should also be avoided in patients with TBI because patients with elevated temperatures have poorer outcomes than normothermic patients.[79] Hence aggressive maintenance of a core temperature of less than 37.5°C (99.5°F) using acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and cooling blankets is indicated for patients following severe TBI.

Other important therapeutic interventions include acute gastritis prophylaxis, and prevention of decubiti and contractures. Prevention of thromboembolic events is extremely important in the supportive care in TBI patients since they are high risk of developing this complication.[80] This can be accomplished with the use of intermittent pneumatic compression devices (preferred) or graduated compression stockings initially. Thereafter, the decision to start systemic therapy (eg, low-molecular weight heparin or unfractionated heparin) depends on multiple factors. A noteworthy recent study revealed better survival and lower thromboembolic complications in patients with TBI receiving low molecular weight heparin compared with those receiving unfractionated heparin.[81] Generally, patients who had relatively minor bleeding on the initial CT scan and good ICP control can have pharmacological prophylaxis started within 24 to 48 hours postinjury.[82,83] Data suggest that patients with TBI and an intracranial hemorrhage can have systemic anticoagulation prophylaxis safely and effectively (ie, reduced deep venous thromboses) initiated 24 hours after a follow-up CT scan shows no worsening of bleeding in patients with an intracranial hemorrhage.[84] However, a recent evidence-based review recommends waiting 72 hours for patients at moderate-to-high risk of intracranial hemorrhage postinjury.[82] Regardless of initiation time, prophylaxis is continued until patients are ambulatory and systemic anticoagulation must be used with caution in patients with more severe intracerebral hemorrhage, or in patients who may need to undergo craniotomy early in their course.[11] Monitoring for a coagulopathy is important in any patient with a severe TBI, since the incidence is high (greater than 30%), and coagulopathy is associated with a significantly longer ICU length of stay and an almost 10-fold increase in

mortality based on data from a prospective study.[85] A low platelet count was the strongest predictor of intracranial bleeding progression compared with other coagulation tests in patients with TBI based on a recent retrospective study.[86] Reversal of coagulopathy with recombinant factor VIIa in critically ill trauma patients with TBI was popular among some practitioners despite lacking an approved indication or large clinical trials demonstrating its safety and efficacy in patients with TBI.[87] However, tranexamic acid is a less expensive hemostatic alternative to recombinant factor VIIa. Nevertheless, more data are needed to determine the role of this agent in patients with TBI before it is used routinely despite being generally advocated in bleeding trauma patients.[88–90] A study known as CRASH-3 is currently underway investigating the role of early administration tranexamic acid in patients with TBI with intracranial bleeding.[51,91]

There are several opportunities for personalized pharmacotherapy in the supportive care of patients with severe TBI. One of the most common general pharmacokinetic challenges seen in patients with TBI is a larger volume of distribution and more rapid hepatic clearance of drugs than most other patient populations. These pharmacokinetic changes often make the optimizing of phenytoin and, less commonly, pentobarbital concentrations very difficult. As such, recommendations for phenytoin and pentobarbital dosing are weight based, and in the case of phenytoin, usually higher than the 300 mg/day dose that is commonly seen in ambulatory patients. Augmented renal clearance has also been documented in critically ill patients including patients with TBI affecting drugs that are renally eliminated.[92] Furthermore, there can be wide interpatient pharmacodynamic variability in the efficacy of pharmacologic and nonpharmacologic interventions for ICP control. For some patients, there is a high degree of trial and error to find the best combination of interventions that are effective and not contraindicated based on other factors.

CLINICAL PATHWAYS/GUIDELINE IMPLEMENTATION

Use of clinical pathways and formal TBI management guidelines/standardized protocols have been demonstrated to improve TBI patient mortality in studies focused on intracranial hypertension.[93–95] Aggressive ICP monitoring has been associated with improved outcomes in patients with moderate-to-severe TBI as well.[96] Furthermore, a cost–benefit analysis revealed that adoption of the BTF

guidelines resulted in an increase of more than 3,600 lives saved among adult patients with severe TBI admitted annually to US hospitals.[97] In this study, the proportion of patients having a good outcome based on their Glasgow Outcome Scale (GOS) was estimated to increase from 35% to 66% with an overall estimated annual total cost savings exceeding $4 billion.[97] Unfortunately, improved outcomes have not been universally reported with guideline compliance as there is wide compliance variability despite the BTF/AANS guidelines being available for over two decades.[98] Regardless, few practitioners would dispute the overall importance of integrating current evidence-based management guidelines into clinical practice as a means to optimize care and improve the functional outcome of patients with as supported by a recent meta-analysis.[51,99]

EVALUATION OF THERAPEUTIC OUTCOMES

The process for evaluation of therapeutic outcomes is summarized in **Table 75-4**. Patients with severe TBI initially require ICU monitoring with the goals of maintaining or reestablishing neurologic and systemic homeostasis, as well as readily detecting any neurologic deterioration. This requires frequent evaluation of the patient's neurologic status (eg, GCS) and measurement of vital signs, urine output, and arterial oxygen saturation (as well as ICP in patients with an ICP monitor in place). Furthermore, careful attention must be paid to the potential development of a variety of electrolyte, mineral, and acid–base disturbances; coagulopathies; and infections by obtaining various laboratory tests on a daily basis initially. The intensity of monitoring will be a function of the relative degree of neurologic and hemodynamic stability of the patient in the hours and days following the neurologic insult. Lastly, radiologic tests (eg, CT scans) are essential not only for the initial diagnostic evaluation of TBI patients but also as means to evaluate the etiology for any subsequent neurologic deterioration.

TABLE 75-4 Evaluation of Therapeutic Outcomes

General	GCS: Record hourly initially, decrease frequency as neurologic status stabilizes Vital signs (BP, HR, RR, temperature): Record hourly initially, decrease frequency as neurologic status stabilizes UO: Record hourly initially, decrease frequency as neurologic status stabilizes Arterial oxygen saturation: Continuously while in ICU
Risk of increased ICP	ICP: Record hourly, decrease frequency as ICP stabilizes <22 mm Hg (2.9 kPa) (usually not until 48-72 hours postinjury at a minimum) CPP: Record hourly, decrease frequency as CPP stabilizes in the desired range[a]
Laboratory tests	Ethanol concentration and urine drug screen: On admission ABGs: Daily at a minimum while intubated, repeated as needed based on pulmonary instability requiring ventilator setting changes CBC: Daily while in ICU Serum electrolytes (Na, K, Cl): Daily while in ICU. Serum sodium and osmolality may be monitored as frequently as every 6 hours if osmotherapy (mannitol, furosemide, hypertonic saline) is being used Minerals (Mg, Ca, P): Daily initially until concentrations stable
Radiologic procedures	CT scan: Postresuscitation initially with repeat scan(s) as needed based on degree of neurologic instability (eg, decrease in GCS) or initial CT appearance

ABG, arterial blood gas; BP, blood pressure; Ca, calcium; CBC, complete blood count; Cl, chloride; CPP, cerebral perfusion pressure; CT, computed tomography; GCS, Glasgow Coma Scale; HR, heart rate; ICP, increased intracranial pressure; K, potassium; Mg, magnesium; Na, sodium; P, phosphorus; RR, respiratory rate; UO, urine output.

[a]Continuous monitoring mandated initially if technologically feasible.

CONCLUSION

Traumatic brain injuries are exceedingly common and often associated with devastating consequences in terms of both morbidity and mortality. Unraveling the complex pathophysiology of secondary injury following severe TBI has failed to yield major advances to attenuate or reverse these consequences to date. Furthermore, review of several traditional treatment modalities has resulted in recommendations against their use. Nevertheless, adherence to best management practices relative to aggressive treatment of increased ICP, supportive care, and prevention of complications offers victim of severe TBI promise of improved outcomes in the present. Commitment to this condition at the national level may be the turning point to breakthrough therapies of the future.

Postclass Engaged Learning Activity

Conduct a literature search and identify a primary research publication that has been published in the last 24 months relative to the pharmacologic management of TBI including supportive care. If the manuscript is regarding a new treatment modality, write a brief summary about the proposed mechanism

of action for the therapy, study methodology and major findings, advantages of the therapy over current therapy, and feasibility of the therapy being adopted in practice. If the manuscript is focused on an adverse effect of a current therapy discussed in the chapter, summarize the adverse effect in terms of proposed mechanism and magnitude, study methodology, and the implications of the effect relative to altering current pharmacologic management of TBI and/or the Brain Trauma Foundation *Guidelines for the Management of Severe Brain Injury*, 4th ed. This activity is intended to build your literature evaluation skills and ability to critically appraise research manuscripts.

ABBREVIATIONS

AANS	American Association of Neurological Surgeons
ABG	arterial blood gas
ATP	adenosine triphosphate
BTF	Brain Trauma Foundation
CBF	cerebral blood flow
CBV	cerebral blood volume
CDO_2	cerebral oxygen delivery
$CMRO_2$	cerebral oxygen consumption
CPP	cerebral perfusion pressure
CSF	cerebrospinal fluid
CT	computed tomography
ECG	electrocardiogram
EEG	electroencephalography
EVD	extraventricular drain
FDA	Food and Drug Administration
GCS	Glasgow Coma Scale
GI	gastrointestinal
GOS	Glasgow Outcome Scale
HMG	3-hydroxy-3-methylglutaryl
ICP	intracranial pressure
ICU	intensive care unit
MAP	mean arterial pressure
NMDA	*N*-methyl-D-aspartate
NSAID	nonsteroidal anti-inflammatory drug
$PbrO_2$	brain tissue oxygen

PRIS	propofol infusion syndrome
PRBCs	packed red blood cells
SBP	systolic blood pressure
$SjvO_2$	jugular venous oxygen saturation
TBI	traumatic brain injury
TCD	transcranial Doppler

REFERENCES

1. CDC. TBI: Get the Facts. Available at https://www.cdc.gov/traumaticbraininjury/get_the_facts.html2017 [cited February 21, 2018].
2. CDC. CDC grand rounds: Reducing severe traumatic brain injury in the United States. *MMWR Morb Mortal Wkly Rep*. 2013;62(27):549–552.
3. Prins M, Greco T, Alexander D, Giza CC. The pathophysiology of traumatic brain injury at a glance. *Dis Model Mech*. 2013;6(6):1307–1315.
4. Andriessen TM, Jacobs B, Vos PE. Clinical characteristics and pathophysiological mechanisms of focal and diffuse traumatic brain injury. *J Cell Mol Med*. 2010;14(10):2381–2392.
5. McGinn MJ, Povlishock JT. Pathophysiology of traumatic brain injury. *Neurosurg Clin N Am*. 2016;27(4):397–407.
6. Algattas H, Huang JH. Traumatic Brain Injury pathophysiology and treatments: Early, intermediate, and late phases post-injury. *Int J Mol Sci*. 2014;15(1):309–341.
7. Hinson HE, Rowell S, Schreiber M. Clinical evidence of inflammation driving secondary brain injury: A systematic review. *J Trauma Acute Care Surg*. 2015;78(1):184–191.
8. Quillinan N, Herson PS, Traystman RJ. Neuropathophysiology of brain injury. *Anesthesiol Clin*. 2016;34(3):453–464.
9. Frattalone AR, Ling GS. Moderate and severe traumatic brain injury: Pathophysiology and management. *Neurosurg Clin N Am*. 2013;24(3):309–319.
10. Souter MJ, Blissitt PA, Blosser S, et al. Recommendations for the critical care management of devastating brain injury: Prognostication, psychosocial, and ethical management: A position statement for healthcare professionals from the neurocritical care society. *Neurocrit Care*. 2015;23(1):4–13.

11. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurgery*. 2017;80(1):6–15.
12. Alarcon JD, Rubiano AM, Chirinos MS, et al. Clinical practice guidelines for the care of patients with severe traumatic brain injury: A systematic evaluation of their quality. *J Trauma Acute Care Surg*. 2013;75(2):311–319.
13. Gabriel EJ, Ghajar J, Jagoda A, et al. Guidelines for prehospital management of traumatic brain injury. *J Neurotrauma*. 2002;19(1):111–174.
14. Bullock MR, Chesnut R, Ghajar J, et al. Guidelines for the surgical management of traumatic brain injury. *Neurosurgery*. 2006;58(3):S2 1–62.
15. Kochanek PM, Carney N, Adelson PD, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents--second edition. *Pediatr Crit Care Med*. 2012;13(suppl 1):S1–82.
16. Fuller G, Hasler RM, Mealing N, et al. The association between admission systolic blood pressure and mortality in significant traumatic brain injury: A multi-centre cohort study. *Injury*. 2014;45(3):612–617.
17. Gantner D, Moore EM, Cooper DJ. Intravenous fluids in traumatic brain injury: What's the solution? *Curr Opin Crit Care*. 2014;20(4):385–389.
18. Ko A, Harada MY, Barmparas G, et al. Limit crystalloid resuscitation after traumatic brain injury. *Am Surg*. 2017;83(12):1447–1452.
19. Cooper DJ, Myburgh J, Heritier S, et al. Albumin resuscitation for traumatic brain injury: Is intracranial hypertension the cause of increased mortality? *J Neurotrauma*. 2013;30(7):512–518.
20. Hutchinson PJ, Kolias AG, Timofeev IS, et al. Trial of decompressive craniectomy for traumatic intracranial hypertension. *N Engl J Med*. 2016;375(12):1119–1130.
21. Chesnut RM, Temkin N, Carney N, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. *N Engl J Med*. 2012;367(26):2471–2481.
22. Bouzat P, Oddo M, Payen JF. Transcranial Doppler after traumatic brain injury: Is there a role? *Curr Opin Crit Care*. 2014;20(2):153–160.
23. Lorente L, Martin MM, Almeida T, et al. Serum substance P levels are associated with severity and mortality in patients with severe traumatic brain injury. *Crit Care*. 2015;19:192.

24. Neher MD, Keene CN, Rich MC, et al. Serum biomarkers for traumatic brain injury. *South Med J*. 2014;107(4):248–255.
25. Petkus V, Preiksaitis A, Krakauskaite S, et al. Benefit on optimal cerebral perfusion pressure targeted treatment for traumatic brain injury patients. *J Crit Care*. 2017;41:49–55.
26. van der Jagt M. Fluid management of the neurological patient: A concise review. *Crit Care*. 2016;20(1):126.
27. Robertson CS, Hannay HJ, Yamal JM, et al. Effect of erythropoietin and transfusion threshold on neurological recovery after traumatic brain injury: A randomized clinical trial. *JAMA*. 2014;312(1):36–47.
28. Sanfilippo F, Santonocito C, Veenith T, et al. The role of neuromuscular blockade in patients with traumatic brain injury: A systematic review. *Neurocrit Care*. 2015;22(2):325–334.
29. Oddo M, Crippa IA, Mehta S, et al. Optimizing sedation in patients with acute brain injury. *Crit Care*. 2016;20(1):128.
30. Sebastiani A, Granold M, Ditter A, et al. Posttraumatic propofol neurotoxicity is mediated via the pro-brain-derived neurotrophic factor-p75 neurotrophin receptor pathway in adult mice. *Crit Care Med*. 2016;44(2):e70–e82.
31. Thal SC, Timaru-Kast R, Wilde F, et al. Propofol impairs neurogenesis and neurologic recovery and increases mortality rate in adult rats after traumatic brain injury. *Crit Care Med*. 2014;42(1):129–141.
32. Gu JW, Yang T, Kuang YQ, et al. Comparison of the safety and efficacy of propofol with midazolam for sedation of patients with severe traumatic brain injury: A meta-analysis. *J Crit Care*. 2014;29(2):287–290.
33. Zeiler FA, Teitelbaum J, West M, Gillman LM. The ketamine effect on ICP in traumatic brain injury. *Neurocrit Care*. 2014;21(1):163–173.
34. Humble SS, Wilson LD, Leath TC, et al. ICU sedation with dexmedetomidine after severe traumatic brain injury. *Brain Inj*. 2016;30(10):1266–1270.
35. Wang X, Ji J, Fen L, Wang A. Effects of dexmedetomidine on cerebral blood flow in critically ill patients with or without traumatic brain injury: A prospective controlled trial. *Brain Inj*. 2013;27(13-14):1617–1622.
36. Roberts I, Sydenham E. Barbiturates for acute traumatic brain injury. *Cochrane Database Syst Rev*. 2012;12:CD000033.
37. Roberts I, Yates D, Sandercock P, et al. Effect of intravenous

corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): Randomised placebo-controlled trial. *Lancet*. 2004;364(9442):1321–1328.

38. Watson HI, Shepherd AA, Rhodes JKJ, Andrews PJD. Revisited: A systematic review of therapeutic hypothermia for adult patients following traumatic brain injury. *Crit Care Med*. 2018;46(6):972–979.
39. Crompton EM, Lubomirova I, Cotlarciuc I, et al. Meta-analysis of therapeutic hypothermia for traumatic brain injury in adult and pediatric patients. *Crit Care Med*. 2017;45(4):575–583.
40. Lewis SR, Evans DJ, Butler AR, et al. Hypothermia for traumatic brain injury. *Cochrane Database Syst Rev*. 2017;9:CD001048.
41. Andrews PJ, Sinclair HL, Rodriguez A, et al. Hypothermia for intracranial hypertension after traumatic brain injury. *N Engl J Med*. 2015;373(25):2403–2412.
42. Lazaridis C, Robertson CS. Hypothermia for Increased Intracranial Pressure: Is It Dead? *Curr Neurol Neurosci Rep*. 2016;16(9):78.
43. Ropper AH. Hyperosmolar therapy for raised intracranial pressure. *N Engl J Med*. 2012;367(8):746–752.
44. Wakai A, McCabe A, Roberts I, Schierhout G. Mannitol for acute traumatic brain injury. *Cochrane Database Syst Rev*. 2013;8:CD001049.
45. Kim MY, Park JH, Kang NR, et al. Increased risk of acute kidney injury associated with higher infusion rate of mannitol in patients with intracranial hemorrhage. *J Neurosurg*. 2014;120(6):1340–1348.
46. Mortazavi MM, Romeo AK, Deep A, et al. Hypertonic saline for treating raised intracranial pressure: Literature review with meta-analysis. *J Neurosurg*. 2012;116(1):210–221.
47. Berger-Pelleiter E, Emond M, Lauzier F, et al. Hypertonic saline in severe traumatic brain injury: A systematic review and meta-analysis of randomized controlled trials. *CJEM*. 2016;18(2):112–120.
48. Burgess S, Abu-Laban RB, Slavik RS, et al. A systematic review of randomized controlled trials comparing hypertonic sodium solutions and mannitol for traumatic brain injury: Implications for emergency department management. *Ann Pharmacother*. 2016;50(4):291–300.
49. Xu GZ, Wang MD, Liu KG, et al. A meta-analysis of treating acute traumatic brain injury with calcium channel blockers. *Brain Res Bull*. 2013;99:41–47.

50. Diaz-Arrastia R, Kochanek PM, Bergold P, et al. Pharmacotherapy of traumatic brain injury: state of the science and the road forward: Report of the Department of Defense Neurotrauma Pharmacology Workgroup. *J Neurotrauma*. 2014;31(2):135–158.
51. Hawryluk GW, Bullock MR. Past, Present, and Future of traumatic brain injury research. *Neurosurg Clin N Am*. 2016;27(4):375–396.
52. Ma J, Huang S, Qin S, You C. Progesterone for acute traumatic brain injury. *Cochrane Database Syst Rev*. 2012;10:CD008409.
53. Skolnick BE, Maas AI, Narayan RK, et al. A clinical trial of progesterone for severe traumatic brain injury. *N Engl J Med*. 2014;371(26):2467–2476.
54. Wright DW, Yeatts SD, Silbergleit R, et al. Very early administration of progesterone for acute traumatic brain injury. *N Engl J Med*. 2014;371(26):2457–2466.
55. Nichol A, French C, Little L, et al. Erythropoietin in traumatic brain injury (EPO-TBI): A double-blind randomised controlled trial. *Lancet*. 2015;386(10012):2499–2506.
56. Talving P, Lustenberger T, Inaba K, et al. Erythropoiesis-stimulating agent administration and survival after severe traumatic brain injury: A prospective study. *Arch Surg*. 2012;147(3):251–255.
57. Gruenbaum SE, Zlotnik A, Gruenbaum BF, et al. Pharmacologic neuroprotection for functional outcomes after traumatic brain injury: A systematic review of the clinical literature. *CNS Drugs*. 2016;30(9):791–806.
58. Alali AS, Mukherjee K, McCredie VA, et al. Beta-blockers and traumatic brain injury: a systematic review, meta-analysis, and eastern association for the surgery of trauma guideline. *Ann Surg*. 2017;266(6):952–961.
59. Chen Z, Tang L, Xu X, et al. Therapeutic effect of beta-blocker in patients with traumatic brain injury: A systematic review and meta-analysis. *J Crit Care*. 2017;41:240–246.
60. Krieger DW. Therapeutic drug approach to stimulate clinical recovery after brain injury. *Front Neurol Neurosci*. 2013;32:76–87.
61. Bhatnagar S, Iaccarino MA, Zafonte R. Pharmacotherapy in rehabilitation of post-acute traumatic brain injury. *Brain Res*. 2016;1640(Pt A):164–179.
62. Manley GT, Maas AI. Traumatic brain injury: An international knowledge-based approach. *JAMA*. 2013;310(5):473–474.
63. Maas AI, Murray GD, Roozenbeek B, et al. Advancing care for traumatic

brain injury: Findings from the IMPACT studies and perspectives on future research. *Lancet Neurol*. 2013;12(12):1200–1210.

64. BRAIN Initative. Available at http://www.braininitiative.nih.gov: National Institutes of Health; 2014 [cited March 8, 2018].
65. Omar M, Moore L, Lauzier F, et al. Complications following hospital admission for traumatic brain injury: A multicenter cohort study. *J Crit Care*. 2017;41:1–8.
66. Zimmermann LL, Diaz-Arrastia R, Vespa PM. Seizures and the role of anticonvulsants after traumatic brain injury. *Neurosurg Clin N Am*. 2016;27(4):499–508.
67. Bhullar IS, Johnson D, Paul JP, et al. More harm than good: Antiseizure prophylaxis after traumatic brain injury does not decrease seizure rates but may inhibit functional recovery. *J Trauma Acute Care Surg*. 2014;76(1):54–60. discussion 60–51.
68. Verduzco-Gutierrez M, Reddy CC, O'Dell MW. Is there a need for early seizure prophylaxis after traumatic brain injury? *PM R*. 2016;8(2):169–175.
69. Pieracci FM, Moore EE, Beauchamp K, et al. A cost-minimization analysis of phenytoin versus levetiracetam for early seizure pharmacoprophylaxis after traumatic brain injury. *J Trauma Acute Care Surg*. 2012;72(1):276–281.
70. Khan NR, VanLandingham MA, Fierst TM, et al. Should levetiracetam or phenytoin be used for posttraumatic seizure prophylaxis? A systematic review of the literature and meta-analysis. *Neurosurgery*. 2016;79(6):775–782.
71. Xu JC, Shen J, Shao WZ, et al. The safety and efficacy of levetiracetam versus phenytoin for seizure prophylaxis after traumatic brain injury: A systematic review and meta-analysis. *Brain Inj*. 2016;30(9):1054–1061.
72. Huijben JA, Volovici V, Cnossen MC, et al. Variation in general supportive and preventive intensive care management of traumatic brain injury: A survey in 66 neurotrauma centers participating in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study. *Crit Care*. 2018;22(1):90.
73. Spencer DD, Jacobi J, Juenke JM, et al. Steady-state pharmacokinetics of intravenous levetiracetam in neurocritical care patients. *Pharmacotherapy*. 2011;31(10):934–941.
74. Chapple LA, Chapman MJ, Lange K, et al. Nutrition support practices in

critically ill head-injured patients: A global perspective. *Crit Care*. 2016;20:6.

75. Wang X, Dong Y, Han X, et al. Nutritional support for patients sustaining traumatic brain injury: A systematic review and meta-analysis of prospective studies. *PLoS One*. 2013;8(3):e58838.
76. Chiang YH, Chao DP, Chu SF, et al. Early enteral nutrition and clinical outcomes of severe traumatic brain injury patients in acute stage: A multi-center cohort study. *J Neurotrauma*. 2012;29(1):75–80.
77. Hermanides J, Plummer MP, Finnis M, et al. Glycaemic control targets after traumatic brain injury: A systematic review and meta-analysis. *Crit Care*. 2018;22(1):11.
78. Vespa P, McArthur DL, Stein N, et al. Tight glycemic control increases metabolic distress in traumatic brain injury: A randomized controlled within-subjects trial. *Crit Care Med*. 2012;40(6):1923–1929.
79. Bohman LE, Levine JM. Fever and therapeutic normothermia in severe brain injury: An update. *Curr Opin Crit Care*. 2014;20(2):182–188.
80. Skrifvars MB, Bailey M, Presneill J, et al. Venous thromboembolic events in critically ill traumatic brain injury patients. *Intensive Care Med*. 2017;43(3):419–428.
81. Benjamin E, Recinos G, Aiolfi A, et al. Pharmacological thromboembolic prophylaxis in traumatic brain injuries: Low molecular weight heparin is superior to unfractionated heparin. *Ann Surg*. 2017;266(3):463–469.
82. Abdel-Aziz H, Dunham CM, Malik RJ, Hileman BM. Timing for deep vein thrombosis chemoprophylaxis in traumatic brain injury: An evidence-based review. *Crit Care*. 2015;19:96.
83. Phelan HA, Wolf SE, Norwood SH, et al. A randomized, double-blinded, placebo-controlled pilot trial of anticoagulation in low-risk traumatic brain injury: The Delayed Versus Early Enoxaparin Prophylaxis I (DEEP I) study. *J Trauma Acute Care Surg*. 2012;73(6):1434–1441.
84. Farooqui A, Hiser B, Barnes SL, Litofsky NS. Safety and efficacy of early thromboembolism chemoprophylaxis after intracranial hemorrhage from traumatic brain injury. *J Neurosurg*. 2013;119(6):1576–1582.
85. Talving P, Benfield R, Hadjizacharia P, et al. Coagulopathy in severe traumatic brain injury: A prospective study. *J Trauma*. 2009;66(1):55–61. discussion 61–52.
86. Joseph B, Aziz H, Zangbar B, et al. Acquired coagulopathy of traumatic brain injury defined by routine laboratory tests: Which laboratory values

matter? *J Trauma Acute Care Surg*. 2014;76(1):121–125.

87. Yuan Q, Wu X, Du ZY, et al. Low-dose recombinant factor VIIa for reversing coagulopathy in patients with isolated traumatic brain injury. *J Crit Care*. 2015;30(1):116–120.
88. Roberts I, Shakur H, Ker K, et al. Antifibrinolytic drugs for acute traumatic injury. *Cochrane Database Syst Rev*. 2012;12:CD004896.
89. Yutthakasemsunt S, Kittiwatanagul W, Piyavechvirat P, et al. Tranexamic acid for patients with traumatic brain injury: A randomized, double-blinded, placebo-controlled trial. *BMC Emerg Med*. 2013;13:20.
90. Zehtabchi S, Abdel Baki SG, Falzon L, Nishijima DK. Tranexamic acid for traumatic brain injury: A systematic review and meta-analysis. *Am J Emerg Med*. 2014;32(12):1503–1509.
91. Dewan Y, Komolafe EO, Mejia-Mantilla JH, et al. CRASH-3 - tranexamic acid for the treatment of significant traumatic brain injury: Study protocol for an international randomized, double-blind, placebo-controlled trial. *Trials*. 2012;13:87.
92. Udy AA, Jarrett P, Lassig-Smith M, et al. Augmented renal clearance in traumatic brain injury: A single-center observational study of atrial natriuretic peptide, cardiac output, and creatinine clearance. *J Neurotrauma*. 2017;34(1):137–144.
93. Gerber LM, Chiu YL, Carney N, et al. Marked reduction in mortality in patients with severe traumatic brain injury. *J Neurosurg*. 2013;119(6):1583–1590.
94. McCredie VA, Alali AS, Scales DC, et al. Impact of ICU structure and processes of care on outcomes after severe traumatic brain injury: A multicenter cohort study. *Crit Care Med*. 2018;46(7):1139–1149.
95. Talving P, Karamanos E, Teixeira PG, et al. Intracranial pressure monitoring in severe head injury: Compliance with Brain Trauma Foundation guidelines and effect on outcomes: A prospective study. *J Neurosurg*. 2013;119(5):1248–1254.
96. Cnossen MC, Polinder S, Andriessen TM, et al. Causes and consequences of treatment variation in moderate and severe traumatic brain injury: A multicenter study. *Crit Care Med*. 2017;45(4):660–669.
97. Faul M, Wald MM, Rutland-Brown W, et al. Using a cost-benefit analysis to estimate outcomes of a clinical treatment guideline: Testing the Brain Trauma Foundation guidelines for the treatment of severe traumatic brain injury. *J Trauma*. 2007;63(6):1271–1278.

98. Dawes AJ, Sacks GD, Cryer HG, et al. Compliance with evidence-based guidelines and interhospital variation in mortality for patients with severe traumatic brain injury. *JAMA Surg*. 2015;150(10):965–972.
99. Cnossen MC, Lingsma HF, Scholten AC, et al. Adherence to guidelines in adult patients with traumatic brain injury: A living systematic review. *J Neurotrauma*. 2016. doi: 10.1089/neu.2015.4121.

76

Parkinson Disease

Jack J. Chen and Khashayar Dashtipour

KEY CONCEPTS

1. Awareness and continuous surveillance of motor and nonmotor symptoms in combination with thoughtful consideration of initial and adjunctive therapies with adjustment of drug dosing throughout the course of idiopathic Parkinson disease (PD) is required to optimize long-term therapeutic outcomes, minimize adverse effects, and improve quality of life.
2. In general, treatment should be initiated when the disease begins to interfere with activities of daily living, employment, or quality of life.
3. Surgery is an option for patients who require additional symptomatic relief or control of motor complications.
4. Anticholinergic medication can be useful for mild symptoms of PD but, due to anticholinergic side effects, should be used with caution in the elderly and in those with pre-existing cognitive difficulties.
5. Monotherapy, amantadine and the irreversible monoamine oxidase type B (MAO-B) inhibitors provide symptomatic benefit, but less than that of dopamine agonists or carbidopa/levodopa (L-dopa).
6. Carbidopa/L-dopa is the most effective medication for symptomatic treatment.
7. Most carbidopa/L-dopa–treated patients will develop motor complications (eg, fluctuations and dyskinesias).
8. MAO-B inhibitors (irreversible and reversible) and catechol-*O*-methyltransferase (COMT) inhibitors are useful add-on therapies to attenuate motor fluctuations in carbidopa/L-dopa–treated patients.
9. Amantadine is a useful add-on agent to attenuate dyskinesias.
10. Dopamine agonists are effective and, compared to L-dopa, associated with

less risk of developing motor complications but more risk of causing psychiatric symptoms, such as hallucinations and impulse control disorders.

Preclass Engaged Learning Activity

Perform a literature search to identify recent treatment guidelines for motor (eg, treatment of motor symptoms, fluctuations, or dyskinesias) or nonmotor symptoms (eg, treatment of depression, psychosis, orthostatic hypotension, sleep disturbances) of Parkinson disease. Select a guideline and summarize the findings and recommendations. This activity is intended to build your literature search and evaluation skills and ability to summarize evidence-based or guideline recommendations.

INTRODUCTION

The presence of bradykinesia, along with tremor at rest, rigidity, and postural instability (instability of balance) are considered the hallmark motor features of idiopathic Parkinson disease (PD), a disorder of the extrapyramidal system. These clinical features of PD were adeptly described in 1817 by James Parkinson.[1]

EPIDEMIOLOGY

Up to 1 million individuals in the United States have PD. The approximate annual incidence of PD (ie, number of persons diagnosed with PD per year) is age-dependent and ranges from 10 per 100,000 persons in the sixth decade of life (ie, 50-59 years) to 120 per 100,000 persons in the ninth decade of life (ie, 80-89 years).[2] Likewise, the prevalence of PD also increases with age, affecting less than 0.5% of people in their 60s and 2.5% of those older than 80 years.[3] The usual age at time of diagnosis ranges between 55 and 65 years. Overall, a higher preponderance of PD is reported among males.[3]

ETIOLOGY

PD occurs sporadically and the true etiology is unknown. However, the

etiopathogenesis of PD likely involves environmental and genetic factors.[4] At the cellular level, degeneration of dopaminergic neurons (axons and soma) projecting from the substantia nigra pars compacta (SNc) to the striatum (caudate nucleus and putamen) are a hallmark of PD.[5] Additionally, neurons in autonomic ganglia, enteric nervous system, limbic system, olfactory bulb, spinal cord, and neocortex are affected. The underlying mechanisms are interconnected and multifaceted with involvement of toxic biochemical reactions (excitotoxicity, nitric oxide toxicity, oxidative stress), abnormal cellular and cell death signaling pathways (apoptosis, inflammation), dysfunctional organelles (lysosomes, mitochondria), and dysfunctional protein degradation systems (autophagy, ubiquitin proteasomal system) resulting in cytoplasmic protein (α-synuclein) accumulation.[6] Several of these mechanisms result in excessive production of free radicals which exert stress on cells by damaging membranes and organelles. The SNc and the striatum are regions characterized by high levels of oxidative stress due to dopamine degradation and the Fenton reaction (**Fig. 76-1**). Normally, intrinsic antioxidants (eg, glutathione) buffer against oxidant stress, but in PD, this buffer might be impaired or overwhelmed. Pathologic findings reveal a correlation between the extent of nigrostriatal dopamine loss and the severity of certain PD motor features (eg, bradykinesia and rigidity). At the time of PD onset, the estimate losses of SNc neurons and striatal dopamine content are 30% and 50%, respectively.[6] The loss of striatal dopamine exceeds the loss of SNc cell bodies because cellular degeneration begins in the distal presynaptic axon terminals and proceeds over time toward the cell body/soma (ie, “dying back” axonopathy).[7]

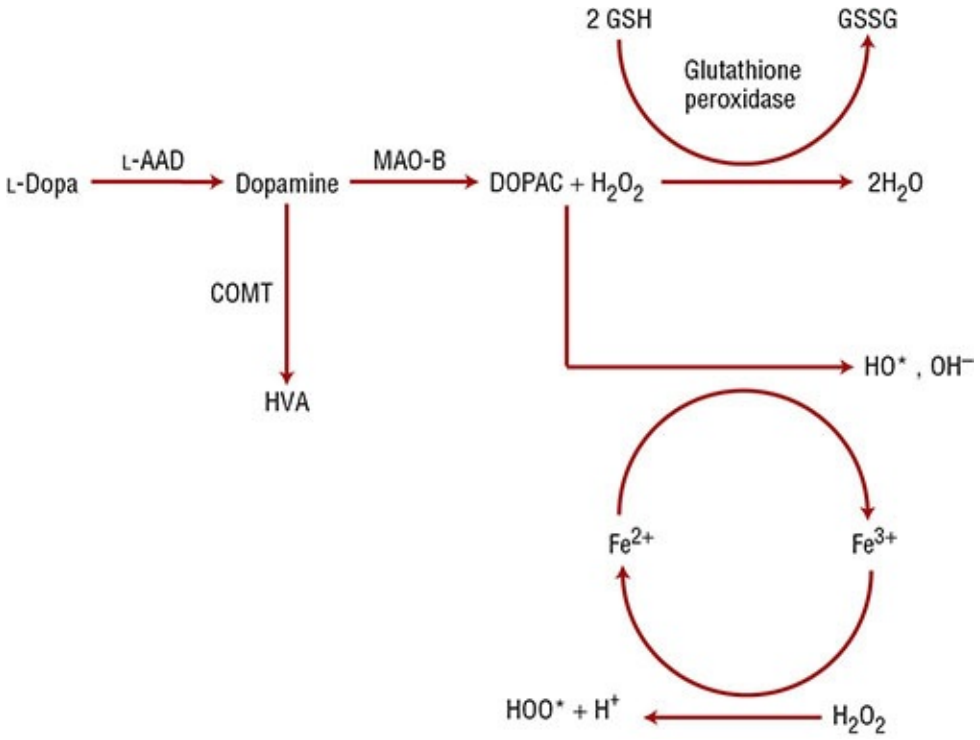


FIGURE 76-1 Dopamine metabolism results in hydrogen peroxide (H_2O_2) formation. In the Fenton reaction, H_2O_2 accepts an electron from ferrous iron (Fe^{2+}) to produce ferric iron (Fe^{3+}) and the hydroxyl radical (HO^*). Fe^{3+} is reduced back to Fe^{2+} by another molecule of H_2O_2, forming a hydroperoxyl radical (HOO^*). The radicals damage cell membranes and organelles (eg, mitochondria) and also induce apoptotic signaling. (COMT, catechol-*O*-methyltransferase; DOPAC, 3,4-dihydroxyphenylacetic acid; GSH, glutathione; GSSG, glutathione disulfide; H^+, proton; H_2O, water; HVA, homovanillic acid; L-AAD, L-aromatic amino acid decarboxylase; OH^-, the hydroxide ion; MAO-B, monoamine oxidase B.).

Aging, genetic constitution, and environmental factors likely increase an individual's risk for PD.[8,9] Epidemiologic research links environmental factors (eg, chronic exposure to pesticides), with an elevated risk. Interestingly, cigarette smoking and caffeine consumption are consistently associated with a lower risk.[9–11] Genetic polymorphisms and epigenetics also modify an individual's risk for PD.[4] It is known that pesticide exposure and genetic forms of parkinsonism (eg, leucine-rich repeat kinase 2 [LRRK2], parkin, PTEN-induced putative kinase 1 [PINK1]) are associated with mitochondrial dysfunction and oxidative stress.

PATHOPHYSIOLOGY

A function of the basal ganglia (composed of subcortical structures including the substantia nigra, striatum, globus pallidus, and subthalamic nucleus) is to regulate voluntary movement. These subcortical structures exist in duplicate, with one structure on each side of the midline. The substantia nigra consists of two parts: the SNc and pars reticulata (SNr). Neuronal projections from the SNc to the striatum are referred to as the *nigrostriatal pathway*. The striatum conveys signals to the SNr, via the dopamine$_1$ (D_1) direct and the dopamine$_2$ (D_2) indirect pathways (**Fig. 76-2A**). The SNr (which is closely linked to the globus pallidus interna [GPi]) receives signals from the striatum and conveys final processed signals to the thalamus, which serves as the "gateway" to the motor cortex. When examining the basal ganglia circuitry, it is important to note that striatal D_1 receptors are coupled to adenylate cyclase and mediate postsynaptic depolarization; thus, D_1 receptor activation results in stimulation of the striatal GABAergic neurons.[12] In contrast, striatal D_2 receptors are coupled to a guanosine triphosphate-binding protein and mediate postsynaptic hyperpolarization; thus, D_2 receptor activation results in inhibition of striatal GABAergic neurons.[12] In PD, reduced dopaminergic activation of D_1 and D_2 receptors and the sequential downstream effect on signaling pathways results in a net inhibitory tone on the thalamus (**Fig. 76-2B**). Dopaminergic therapies help restore functional activity within the D_1 and D_2 pathways with the latter primarily responsible for mediating clinical improvements.

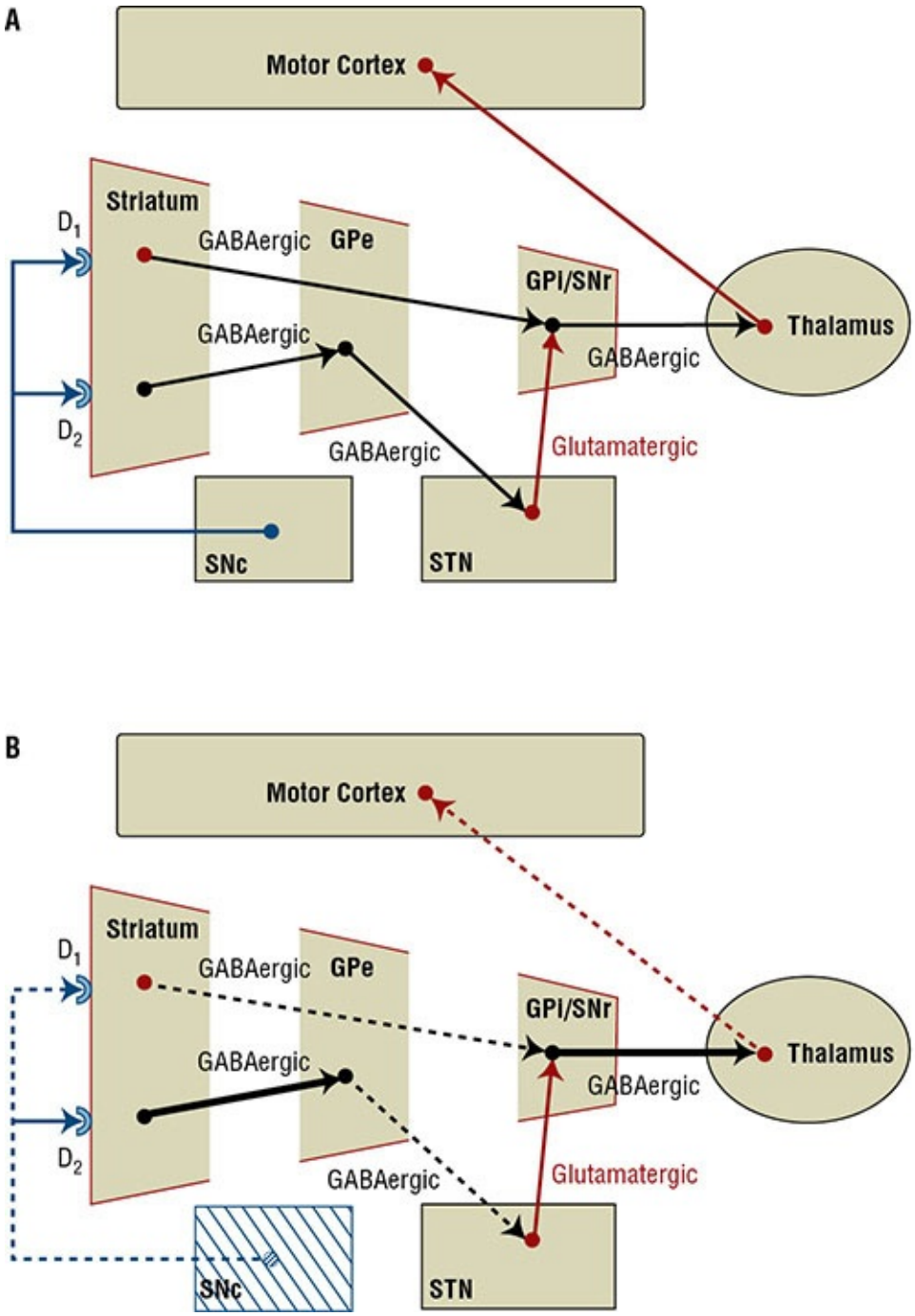


FIGURE 76-2 (*A*) Dopaminergic pathways of the basal ganglia–thalamocortical circuit. Activation of D_1 and D_2 receptors results in depolarization and hyperpolarization, respectively, of postsynaptic neurons. (Red dots and lines represent excitatory input; black dots and lines represent inhibitory input.) (*B*) In Parkinson disease, degeneration of presynaptic nigrostriatal neurons results in inhibition of the thalamocortical circuit and reduced signaling to the motor cortex. (*Dashed lines* represent reduction of neurotransmitter activity; GPe,

globus pallidus externa; GPi, globus pallidus interna; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus.)

Within the SNc, histopathologic features of PD are (1) depigmentation of dopamine-producing neurons (ie, loss of SNc neurons) and (2) presence of Lewy bodies (cytoplasmic filamentous aggregates composed of the protein α-synuclein) in the remaining neurons.[5] Lewy bodies appear in association with adjacent gliosis (ie, a response of glial cells to injury) and the formation and spread of Lewy pathology is proposed to occur in stages. In the premotor stage of PD, Lewy bodies are found in the medulla oblongata, locus coeruleus, raphe nuclei, enteric nervous system, and olfactory bulb. This provides anatomic correlates to observations that mood (eg, anxiety, depression) and peripheral symptoms (eg, constipation, impaired olfaction) are present in premotor stages of PD. Evidence suggests that Lewy pathology develops peripherally in the enteric nervous system and olfactory system and may spread anterogradely or retrogradely to the brain.[13] With the development of Lewy pathology in the midbrain (particularly the SNc), motor features begin to emerge. In advanced stages, Lewy pathology spreads to the cortex, and this may correlate with cognitive and additional behavior changes. Recent investigations have shown that α-synuclein pathology can propagate into adjacent healthy neurons in a nontoxic infectious manner that results in subsequent neuronal toxicity.[14]

CLINICAL PRESENTATION

Idiopathic Parkinson Disease

General Features

- The patient exhibits bradykinesia and at least one of the following: resting tremor, rigidity, or postural instability. Asymmetry of motor features is supportive.

Motor Symptoms

- The patient experiences hypokinetic movements, decreased manual dexterity, difficulty arising from a seated position, diminished arm swing during ambulation, dysarthria (slurred speech), dysphagia (difficulty with swallowing), festinating gait (tendency to pass from a walking to a running pace), flexed posture, “freezing” at initiation of movement, hypomimia (reduced facial animation), hypophonia (reduced voice

volume), and micrographia (Fig. 76-3).

Autonomic and Sensory Symptoms

- The patient experiences bladder dysfunction, constipation, diaphoresis, fatigue, olfactory impairment, orthostatic intolerance, pain, paresthesia, paroxysmal vascular flushing, seborrhea, sexual dysfunction, and sialorrhea (drooling).

Mental Status Changes

- The patient experiences anxiety, apathy, bradyphrenia (slowness of thought processes), cognitive impairment, depression, and hallucinosis/psychosis.

Sleep Disturbances

- The patient experiences excessive daytime sleepiness, insomnia, obstructive sleep apnea, and rapid eye movement (REM) sleep behavior disorder.

Laboratory Tests

- No laboratory tests are available to diagnose PD.

Other Diagnostic Tests

- Genetic testing is not routinely helpful.
- Neuroimaging may be useful for excluding other diagnoses.
- Medication history should be obtained to rule out drug-induced parkinsonism.

The synaptic organization of the basal ganglia also involves a variety of other neurotransmitters and neuromodulators, including acetylcholine, adenosine, enkephalins, γ-aminobutyric acid (GABA), glutamate, serotonin, and substance P. The potential role for drug modulation of these other neurotransmitters and receptor types is an active area of research and novel drug discovery.[15]

Atypical parkinsonian disorders such as multiple system atrophy and progressive supranuclear palsy are characterized by damage to postsynaptic striatal neurons and dopamine receptors. Therefore, dopaminergic therapies are less efficacious in atypical parkinsonism.

The clinical diagnosis of PD is based on the presence of bradykinesia and at

least one of three other features: muscular rigidity, resting tremor, and postural instability (**Table 76-1**).[16] Asymmetry of motor features is a supportive finding. It is important to note that tremor is not always present at the time of diagnosis, and postural instability typically occurs in later stages of PD. Overall, a diagnosis of PD can be made with a high level of confidence in a patient who has bradykinesia (along with rest tremor and/or rigidity), prominent asymmetry, and a good response to dopaminergic therapy. For the diagnosis of PD, other conditions must be reasonably excluded (see Table 76-1). Medication-induced parkinsonism can mimic PD and is the second most common form of parkinsonism.[17] It is important to assess for recent use of medications, especially drugs that block D_2 receptors, such as antipsychotics (eg, haloperidol), metoclopramide, or phenothiazine antiemetics (eg, prochlorperazine).[17] Neurologic conditions that can be mistaken for PD include atypical parkinsonisms and tremor disorders (eg, dystonic tremor, essential tremor). Because the management and prognosis of PD differ from these other conditions, obtaining an accurate diagnosis is important. When the diagnosis is in doubt, referral to a movement disorders specialist is recommended. Currently, efforts are underway to develop and validate diagnostic tools based on personalized clinical, laboratory, imaging, and genomics data.

TABLE 76-1 Diagnostic Criteria and Differential Diagnosis for Parkinson Disease

Parkinson Disease

- Step 1: Presence of bradykinesia and at least one of the following: resting tremor, rigidity, or postural instability
- Step 2: Exclude other types of parkinsonism or tremor disorders (see "Differential Diagnosis")
- Step 3: Presence of at least three supportive positive criteria:
  - Asymmetry of motor signs/symptoms
  - Unilateral onset
  - Progressive disorder
  - Resting tremor
  - Excellent response to carbidopa/L-dopa
  - L-dopa response for 5 years or longer
  - Presence of L-dopa dyskinesias

Differential Diagnosis

- Essential tremor
- Pharmacotoxicity (drug-induced)
  - Antiemetics (eg, metoclopramide, prochlorperazine)
  - Antipsychotics (eg, chlorpromazine, fluphenazine, haloperidol, olanzapine, risperidone, thioridazine)
  - Other drugs (α-methyldopa, cinnarizine, flunarizine, tetrabenazine)
- Environmental toxicity (eg, manganese, organophosphates)
- Infections (eg, human immunodeficiency virus, subacute sclerosing panencephalitis)
- Metabolic disorder (eg, hypothyroidism, parathyroid abnormalities)
- Neoplasms, strokes, traumatic lesions involving the nigrostriatal pathways
- Normal-pressure hydrocephalus
- Parkinsonism with other neuronal system degenerations
  - Corticobasal ganglionic degeneration
- Multiple-system atrophies
- Progressive supranuclear palsy
- Familial (hereditary) parkinsonism
  - Autosomal dominant
  - α-Synuclein gene mutation (*PARK1* and *PARK4*)
  - L-responsive dystonia
  - Leucine-rich repeat kinase 2 (LRRK2) mutation
  - Rapid-onset dystonia parkinsonism (DYT12)
  - Spinocerebellar ataxias (SCA2, SCA3)
- Autosomal recessive
  - Wilson disease
  - Young-onset parkinsonism (DJ-1, parkin, PINK1)
- X-linked recessive
  - Fragile X tremor/ataxia syndrome (FXTAS)
  - Lubag (DYT3 or Filipino dystonia parkinsonism)

PD develops insidiously and progressively worsens over many years. Tremor

of an upper extremity occurring at rest (and occasionally an action or postural tremor) is often the sole presenting complaint. However, only two-thirds of patients with PD have tremor on diagnosis, and some never develop this sign. Tremor in PD is present most commonly in the hands, sometimes with a characteristic pill-rolling motion. Less commonly, tremor may involve the jaw or legs. Like other motor features of PD, resting tremor often begins unilaterally and becomes bilateral with disease progression. Stressful or emotional (either negative or positive) situations often increase the tremor amplitude and severity. Usually, tremor is absent during sleep. Although resting tremor is visibly noticeable in PD and may cause social embarrassment for the patient, it often is the least physically disabling of the motor features.

Rigidity is the increased muscular resistance to passive range of motion and most commonly affects the upper and lower extremities, and occasionally the neck. If tremor is present in the affected extremity, the rigidity is associated with a cogwheel or ratchet-like quality upon examination. Facial muscles also are affected, resulting in hypomimia that may be erroneously interpreted as apathy, depression, or unfriendliness.

Hypokinesia is decreased movement and often described as either bradykinesia (slowness of movement) or akinesia (absence of movement). Movement in PD is often slow throughout an intended action, and difficulty with the initiation of movement also occurs. A progressive slowing and decline in dexterity may impair tasks such as hand clapping, finger tapping, and handwriting (**Fig. 76-3**). Intermittent immobility or akinesia (freezing) is another common characteristic. Freezing is especially likely to occur in situations such as when walking through a narrow doorway or initiating a turn.

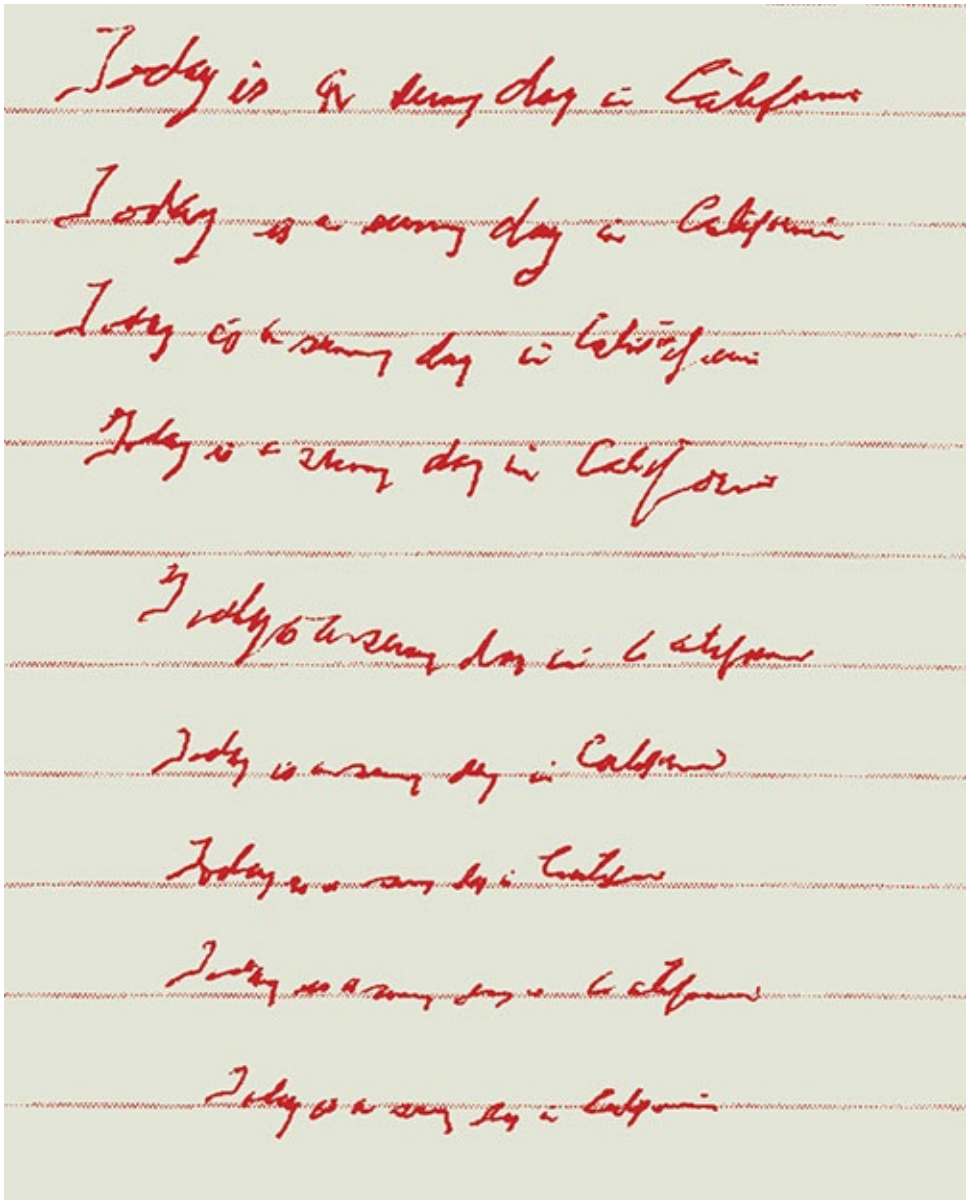


FIGURE 76-3 Example of micrographia in a patient with Parkinson disease. As the sentence “Today is a sunny day in California” is repeatedly handwritten, progressive diminution of letter size occurs (micrographia). The height of each lined row is approximately 5/16 in. (8 mm). (*Used with permission from Jack J. Chen, PharmD.*)

Currently, the clinical diagnosis of PD relies on motor findings; however, neuroimaging along with nonmotor markers (eg, REM sleep behavior disorder, olfactory impairment) may someday aid in detection of PD in premotor or prodromal stages (ie, before onset of motor impairment).[18]

Postural instability, most common in advanced stages of PD, is one of the

most disabling problems of PD because it increases the fall risk and is least amenable to pharmacotherapy. Testing for impaired postural responses by means of the pull test (in which a patient is unable to recover balance after sudden backward displacement at the shoulders) can help identify the risk for falling. Many patients with impaired postural responses also have tendencies for propulsive gait with difficulty halting their steps while in motion (festination) and freezing, which also increases the risk of falling.

Nonmotor symptoms are common in PD and must be identified, assessed, managed, and monitored (**Table 76-2**). These include anxiety, cognitive impairment, constipation, daytime sleepiness, depression, drooling, dysphagia, falling, fatigue, impulsivity, insomnia, orthostatic hypotension, overactive bladder, pain, hallucinations/psychosis, REM sleep behavior disorder, and restless legs syndrome.[19] As a component of managing these nonmotor symptoms, it is important to maintain continuous surveillance of prescription and nonprescription medications for potential side effects that can exacerbate, mimic, or precipitate nonmotor symptoms. If feasible, any identified offending medication should be deprescribed.

TABLE 76-2 Nonmotor Symptoms and Possible Treatments

Symptoms	Possible Treatments
Anxiety	Cognitive behavioral therapy, selective serotonin reuptake inhibitors, venlafaxine, minimize "off" times.
Cognitive impairment	Eliminate anticholinergic agents. Add cholinesterase inhibitor.
Constipation	Fiber, hydration, exercise, laxatives, stool softeners.
Daytime sleepiness	Proper nighttime sleep hygiene, reduce dose of dopamine agonist, referral to sleep specialist to rule out apnea and sleep disorders.
Depression	Selective serotonin reuptake inhibitor, newer-generation serotonin norepinephrine reuptake inhibitor, cognitive behavioral therapy.
Drooling	Local injection of botulinum toxin, atropine sublingual drop, glycopyrrolate, ipratropium sublingual spray.
Dysphagia	Referral to speech therapist, dysphagia diet, avoid anticholinergic medications, manage dry mouth.
Fatigue	Caffeine, armodafinil, modafinil, proper nighttime sleep hygiene, referral to sleep specialist to rule out sleep disorder.
Falling	Referral to physical therapy, assistance with ambulation, minimize risk for bone fractures, treat osteoporosis.
Hallucinations/ psychosis	Dose reduction and/or elimination of adjunctive medications, especially anticholinergic agents. Consider addition of pimavanserin. Note: pimavanserin is FDA-approved for psychosis in PD.
Impulse control disorder	Discontinue dopamine agonist or add clozapine, quetiapine, or naltrexone.
Insomnia	Nonbenzodiazepine $GABA_A$ agonists, trazodone.
Orthostatic hypotension	Reduce dose of alpha-blockers, dopamine agonist, diuretics, vasodilators. Abdominal compression, add salt and water to diet, water boluses, fludrocortisone, midodrine, droxidopa, pyridostigmine.
Overactive bladder	Behavioral therapies (eg, bladder training, fluid management, pelvic floor muscle exercises), antimuscarinic agents, mirabegron, intradetrusor injections of botulinum toxin.
Pain	Treatment as per type of pain (eg, dystonic, musculoskeletal, neuropathic), minimize "off" times, appropriate referral to orthopedics, physical therapy, pain specialist, rheumatology.
REM sleep behavior disorder	Clonazepam, melatonin.
Restless legs syndrome	Dopamine agonist at bedtime; gabapentin.

FDA, Food and Drug Administration; GABA, γ-aminobutyric acid; PD, Parkinson disease; REM, rapid eye movement.

TREATMENT

Desired Outcomes

To date, no treatments have been shown to effectively change the course of PD by slowing or halting its progression (disease modification).[20] Therefore, the goal in the management of PD is to improve motor and nonmotor symptoms so that patients are able to maintain the best possible quality of life.[21] Specific objectives to consider when selecting an intervention include preservation of the ability to perform activities of daily living, employment, improvement of mobility, minimization of adverse effects, treatment complications, putative disease modification, and improvement of nonmotor features. To accomplish some of these objectives, consultation with a team of specialists is helpful (eg, movement disorders, pharmacotherapy, physical therapy, psychiatry, and sleep medicine).

General Approach to Treatment

1 2 Awareness and surveillance of motor and nonmotor symptoms in combination with thoughtful selection of initial and adjunctive therapies with adjustment of drug dosing throughout the course of PD is required to optimize long-term therapeutic outcomes, minimize adverse effects, and improve quality of life. In general, treatment should be initiated when the disease begins to interfere with activities of daily living, employment, or quality of life. **Figure 76-4** illustrates a general treatment approach for early and advanced PD. **Table 76-3** summarizes antiparkinsonian medications and dosing, and **Table 76-4** summarizes monitoring parameters for potential adverse reactions. Treatment guidelines and monographs are updated frequently to keep up with new information and changes in treatment paradigms.[19,22–24] Additionally, general guidelines and recommendations for geriatric health maintenance and disease prevention (eg, bone health, routine vaccinations, vitamin and mineral supplementations) should also be observed.

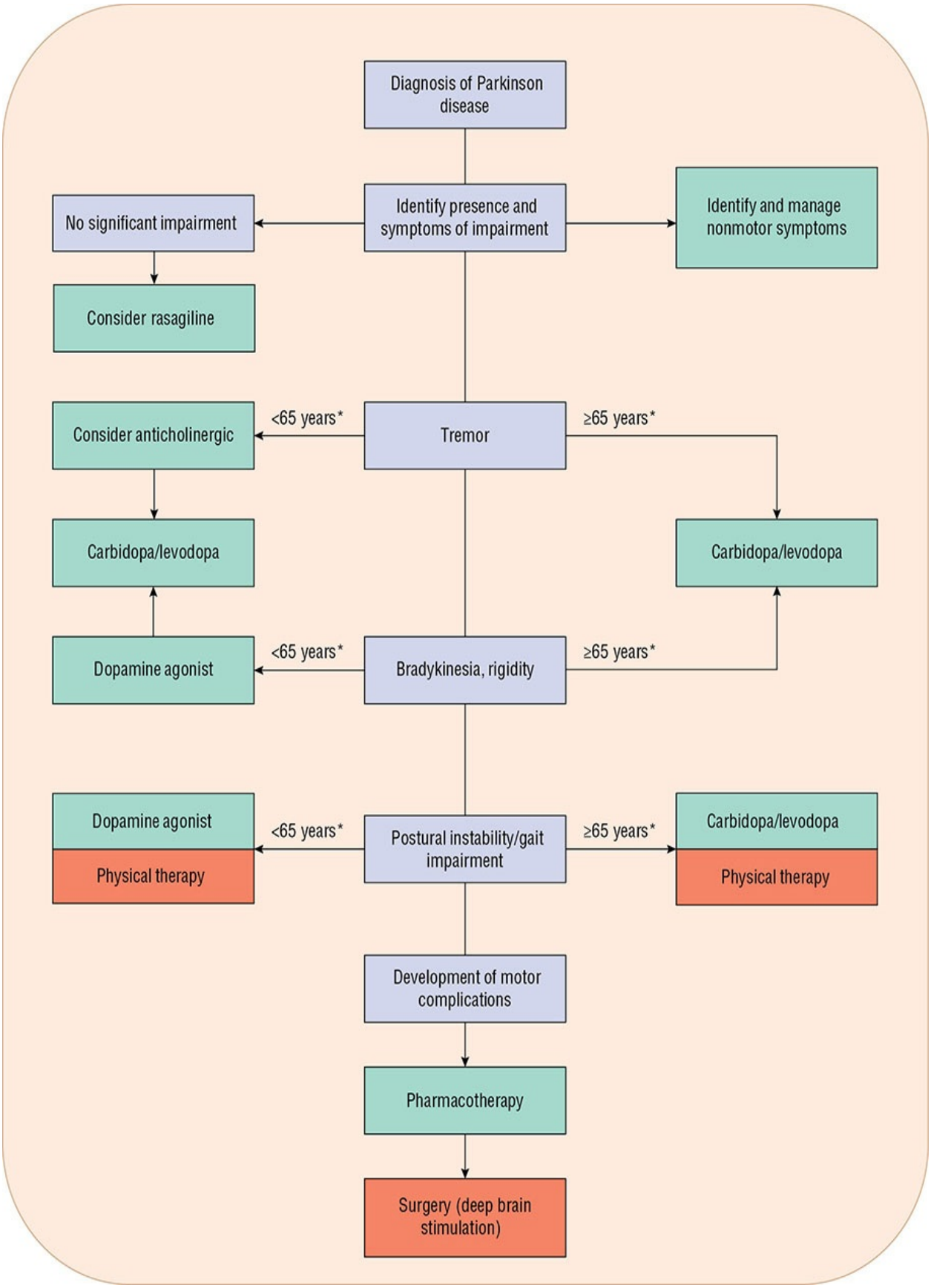

Diagnosis of Parkinson disease
Identify presence and symptoms of impairment
No significant impairment
Identify and manage nonmotor symptoms
Consider rasagiline
Tremor
<65 years*
≥65 years*
Consider anticholinergic
Carbidopa/levodopa
Carbidopa/levodopa
Bradykinesia, rigidity
<65 years*
≥65 years*
Dopamine agonist
Postural instability/gait impairment
<65 years*
≥65 years*
Dopamine agonist
Physical therapy
Carbidopa/levodopa
Physical therapy
Development of motor complications
Pharmacotherapy
Surgery (deep brain stimulation)

FIGURE 76-4 General approach to the management of early to advanced Parkinson disease. (*Age is not the sole determinant for drug choice. Other factors such as cognitive function and overall tolerability of drug (especially in the elderly) should be considered.).

TABLE 76-3 Dosing of Drugs Used in Parkinson Disease[a]

Generic Name	Trade Name	Starting Dose[b] (mg/day)	Maintenance Dose[b] (mg/day)	Dosage Forms (mg)
Anticholinergic Drugs				
Benztropine	Cogentin	0.5-1	1-6	0.5, 1, 2
Trihexyphenidyl	Artane	1-2	6-15	2, 5, 2/5 mL
Carbidopa/Levodopa Products				
Carbidopa/L-dopa	Sinemet	300[c]	300-2,000[c]	10/100, 25/100, 25/250
Carbidopa/L-dopa ODT	Parcopa	300[c]	300-2,000[c]	10/100, 25/100, 25/250
Carbidopa/L-dopa CR	Sinemet CR	400[c]	400-2,000[c]	25/100, 50/200
Carbidopa/L-dopa IR/ER	Rytary	435[c]	435-2,450[c]	23.75/95, 36.25/145, 48.75/195, 61.25/245[d]
Carbidopa/L-dopa enteral suspension	Duopa	1,000[c]	1,000-2,000[c]	4.63/20 per mL
Carbidopa/L-dopa/entacapone	Stalevo	600[e]	600-1,600[e]	12.5/50/200, 18.75/75/200, 25/100/200, 31.25/125/200, 37.5/150/200, 50/200/200
Carbidopa	Lodosyn	25	25-75	25
Levodopa	Inbrija	84	84-420	42[f]
Dopamine Agonists				
Apomorphine	Apokyn	1-3	3-12	30/3 mL[g]
Bromocriptine	Parlodel	2.5-5	15-40	2.5, 5
Pramipexole	Mirapex	0.125	1.5-4.5	0.125, 0.25, 0.5, 1, 1.5
Pramipexole ER	Mirapex ER	0.375	1.5-4.5	0.375, 0.75, 1.5, 3, 4.5
Ropinirole	Requip	0.75	9-24	0.25, 0.5, 1, 2, 3, 4, 5
Ropinirole XL	Requip XL	2	8-24	2, 4, 6, 8, 12
Rotigotine	Neupro	2	2-8	1, 2, 3, 4, 6, 8
COMT Inhibitors				
Entacapone	Comtan	200-600	200-1,600	200
Tolcapone	Tasmar	300	300-600	100, 200
MAO-B Inhibitors				
Rasagiline	Azilect	0.5-1	0.5-1	0.5, 1
Safinamide	Xadago	50	50-100	50, 100
Selegiline	Eldepryl	5-10	5-10	5
Selegiline ODT	Zelapar	1.25	1.25-2.5	1.25, 2.5
Miscellaneous				
Amantadine	Symmetrel	100	200-300	100, 50/5 mL
Amantadine ER	Gocovri	137	274	68.5, 137
Amantadine ER	Osmolex	129	129-258	129, 193, 258

COMT, catechol-*O*-methyltransferase; CR, controlled-release; IR, immediate-release; ER, extended-release; MAO, monoamine oxidase; ODT, orally disintegrating tablet.

[a]Marketed in the United States for Parkinson disease.

[b]Dosages may vary.

[c]Dosages expressed as L-dopa component.

[d]Dosages of Rytary were developed to avoid confusion with other oral carbidopa/L-dopa products that contain L-dopa in multiples of 50 mg.

[e]Dosages expressed as entacapone component.

[f]Capsule containing levodopa dry powder for inhalation

[g]Sterile solution of subcutaneous injection with supplied pen injector.

TABLE 76-4 Monitoring of Potential Adverse Reactions to Drug Therapy for Parkinson Disease

Generic Name	Adverse Drug Reaction	Monitoring Parameter	Comments
Amantadine	Confusion	Mental status; renal function	Reduce dosage; adjust dose for renal impairment
	Livedo reticularis	Lower extremity examination; ankle edema	Reversible upon drug discontinuation
Benztropine and Trihexyphenidyl	Anticholinergic effects, confusion, drowsiness	Dry mouth, mental status, constipation, urinary retention, vision	Reduce dosage; avoid in elderly and in those with a history of constipation, memory impairment, urinary retention
Carbidopa/L-dopa	Drowsiness	Mental status	Reduce dose
	Dyskinesias	Abnormal involuntary movements	Reduce dose; add amantadine
	Nausea	Nausea	Take with food (eg, nonprotein snack)
COMT Inhibitors			
Entacapone	Augmentation of L-dopa side effects; also diarrhea	See carbidopa/L-dopa; also bowel movements	Reduce dose of L-dopa; antidiarrheal agents
Tolcapone	See entacapone; also liver toxicity	See carbidopa/L-dopa; also ALT/AST	See carbidopa/L-dopa; also at start of therapy and for every dose increase, ALT and AST levels at baseline and every 2-4 weeks for the first 6 months of therapy; afterward monitor based on clinical judgment.
Dopamine Agonists			
Apomorphine	Drowsiness	Mental status	Reduce dose
	Nausea	Nausea	Premedicate with trimethobenzamide
	Orthostatic hypotension	Blood pressure, dizziness upon standing	Reduce dose
Bromocriptine	See pramipexole; also pulmonary fibrosis	Mental status; also chest radiograph	Reduce dose; chest radiograph at baseline and once yearly
Pramipexole and Ropinirole	Confusion	Mental status	Reduce dose
	Drowsiness	Mental status	Reduce dose
	Edema	Lower extremity swelling	Reduce dose or discontinue medication
	Hallucinations/delusions	Behavior, mental status	Reduce dose or discontinue medication
	Impulsivity	Behavior	Discontinue medication
	Nausea	Nausea	Titrate dose upward slowly; take with food
	Orthostatic hypotension	Blood pressure, dizziness upon standing	Reduce dose
Rotigotine	See pramipexole; also skin irritation at site of patch application	See pramipexole; also skin examination	See pramipexole; rotate patch application site
MAO-B Inhibitors			
Rasagiline	Nausea	Nausea	Take with food
Selegiline	Agitation/confusion	Mental status	Reduce dose
	Insomnia	Sleep	Administer dose earlier in day
	Hallucinations	Behavior, mental status	Reduce dose
	Orthostatic hypotension	Blood pressure, dizziness upon standing	Reduce dose

ALT, alanine aminotransferase; AST, aspartate aminotransferase; COMT, catechol-*O*-methyltransferase; MAO, monoamine oxidase.

When deciding on therapy for a patient the following patient-specific factors should be taken into account, including age; comorbidities; severity of functional impairment; nonmotor symptoms; patient preferences, therapeutic goals, and outcomes; employment status; drug tolerability; presence of cognitive impairment or motor complications; need for skilled assistance; and health-related economics. The lowest dose of antiparkinson medication that provides satisfactory symptomatic results should be used, and for patients already on carbidopa/L-dopa, optimization of the regimen should be attempted before adding adjunctive agents. With the increasing motor disability, emergence of medication side effects, and changes in severity of nonmotor symptoms, therapy adjustments (eg, dose reductions, medication addition, or discontinuation) are expected, and desired therapeutic endpoints should be routinely reassessed. Currently, there are no pharmacogenomic parameters used to guide PD pharmacotherapy.

For mild functional impairment, initial monotherapy may be initiated with an MAO-B inhibitor, such as rasagiline, with the addition of other therapeutic agents as PD motor symptoms progressively worsen. Dopamine agonist monotherapy provides greater symptomatic benefit for patients with mild-to-moderate impairment. However, dopamine agonists are less well tolerated, especially in older patients and for those who are cognitively impaired, intolerant of dopamine agonists, or experiencing moderate or severe functional impairment, carbidopa/L-dopa is preferred. Ultimately, all patients will require the use of carbidopa/L-dopa either as monotherapy or in combination with other agents. With the development of motor fluctuations, patients should administer carbiopa/L-dopa more frequently or addition of a COMT inhibitor, MAO-B inhibitor, or dopamine agonist to the carbidopa/L-dopa regimen should be considered. For management of carbodopa/L-dopa–induced peak-dose dyskinesias, a reduction in L-dopa dose and/or addition of amantadine should be considered. Surgery is considered only in patients who need more symptomatic control or who are experiencing severe motor complications despite pharmacologically optimized therapy.

Ultimately the treatment plan must evolve as the disease progresses and must include consideration of short-term symptomatic relief as well as long-term effects. Patient education should be communicated with realistic optimism. For example, it should be explained that although there is no cure for PD, modern medicine has many medications that can provide relief of symptoms. Nonpharmacologic interventions such as exercise should be encouraged, and problematic nonmotor features of PD should always be addressed.

Nonpharmacologic Therapy

Surgical Therapy

3 Currently, surgery should be considered an adjunct to pharmacotherapy when patients are experiencing frequent motor fluctuations or disabling dyskinesia or tremor despite an optimized medical regimen. There are several patient-selection criteria for surgery, including a diagnosis of L-dopa–responsive PD and absence of cognitive impairment. Anatomic targets include the thalamus, GPi, and the subthalamic nucleus (STN). Bilateral, chronic, high-frequency electrical stimulation, also known as deep-brain stimulation (DBS), is the preferred surgical modality.[25]

In DBS surgery, a battery-powered neurostimulator is implanted subcutaneously below the clavicle and provides constant electrical stimulation, via electrode wires, to the targeted brain structure. Thalamic DBS is very effective for suppressing tremor (specifically arm tremor), but it does not significantly improve the other parkinsonian features (bradykinesia, rigidity, motor fluctuations, or dyskinesias). Both STN and GPi DBS are associated with improvements in tremor, rigidity, bradykinesia, motor fluctuations, dyskinesia, and activities of daily living; however, STN DBS allows for greater reduction in medications.[26] As with pharmacotherapy, DBS uncommonly improves gait or postural instability.

DBS procedures require routine adjustment of the electrical stimulation parameters (eg, voltage, frequency, and pulse width) to achieve optimal control while minimizing side effects. The electrical stimulation parameters (or “electrical dosage”) are adjusted via a programmable handheld device to meet each patient’s needs and are performed by physicians as well as other trained individuals, including nurse practitioners and clinical pharmacists.

Cell-based restorative procedures such as implantation of dopamine-producing cells (ie, human fetal mesencephalon tissue or retinal pigmented epithelial cells) into the striatum have yielded disappointing clinical results.[27] However, other biotherapies, such as stem cell and gene-based approaches, are currently under investigation and remain highly experimental. Of note, gene delivery of neurotrophic factor directly into the putamen and substantia nigra in patients with advanced PD has not demonstrated benefit.[28]

Pharmacologic Therapy

Anticholinergic Medications

4 Because dopamine provides negative feedback to acetylcholine neurons in the striatum, the degeneration of nigrostriatal dopamine neurons also results in a relative increase of striatal cholinergic interneuron activity. This increased cholinergic activity is believed to contribute to the tremor of PD. The anticholinergic drugs (eg, benztropine and trihexyphenidyl) are considered effective against tremor, but no more so than dopaminergic agents.[21] Sometimes dystonic symptoms associated with PD are also improved by anticholinergic agents. Use of anticholinergic agents is limited due to the development of intolerable side effects (eg, anticholinergic effects), necessitating drug discontinuation. Common adverse effects include blurred vision, confusion, constipation, dry mouth, memory difficulty, sleepiness, and urinary retention (see Table 76-4). Younger patients are better able to tolerate anticholinergic side effects, whereas this drug class is avoided in patients with advanced age, pre-existing cognitive deficits, and dysphagia.

Amantadine

5 Although amantadine can be used for managing symptoms of tremor, rigidity, and bradykinesia, it is most often used for management of L-dopa–induced dyskinesia.[24] Amantadine immediate-release is typically administered 300 mg/day in divided doses and extended-release formulations are also available (see Table 76-3). The precise mechanism of action of amantadine for management of PD is unknown, but enhancement of dopamine release from presynaptic terminals and inhibition of glutamatergic *N*-methyl-D-aspartate (NMDA) receptors are implicated. The antidyskinetic properties of amantadine are presumed to be mediated by antiglutamate properties which, in the setting of dyskinesias, appears to dominate over dopaminergic properties. Amantadine is eliminated renally, and a reduced dose should be administered when renal dysfunction is present (eg, amantadine immediate-release 100 mg/day with creatinine clearances of 30-50 mL/min [0.50-0.84 mL/s], 100 mg every other day for creatinine clearances of 15-29 mL/min [0.25-0.49 mL/s], and 200 mg every 7 days for creatinine clearances of less than 15 mL/min [0.25 mL/s], and patients on hemodialysis).

Side effects of amantadine include confusion, dizziness, dry mouth, and hallucinations with elderly patients being particularly prone to develop confusion. Not uncommonly, amantadine may cause livedo reticularis, a reversible condition characterized by diffuse mottling of the skin affecting the

upper or lower extremities and often accompanied by lower-extremity edema (see Table 76-4).

Carbidopa/L-Dopa

6 L-Dopa is the immediate precursor of dopamine and, in combination with a peripherally acting L-amino acid decarboxylase inhibitor (carbidopa or benserazide), remains the most effective drug for the symptomatic treatment of PD.[24] In the United States, L-Dopa is combined with carbidopa as L-Dopa crosses the blood–brain barrier, whereas carbidopa does not, and the carbidopa then reduces the unwanted peripheral conversion of L-dopa to dopamine. As a result, increased amounts of L-dopa are transported into the brain, and the peripheral adverse effects of dopamine, such as nausea, are reduced. In the SNc, L-dopa is converted to dopamine by the enzyme L-amino acid decarboxylase and inactivated by the enzymes MAO and COMT (**Figs. 76-1** and 76-5).

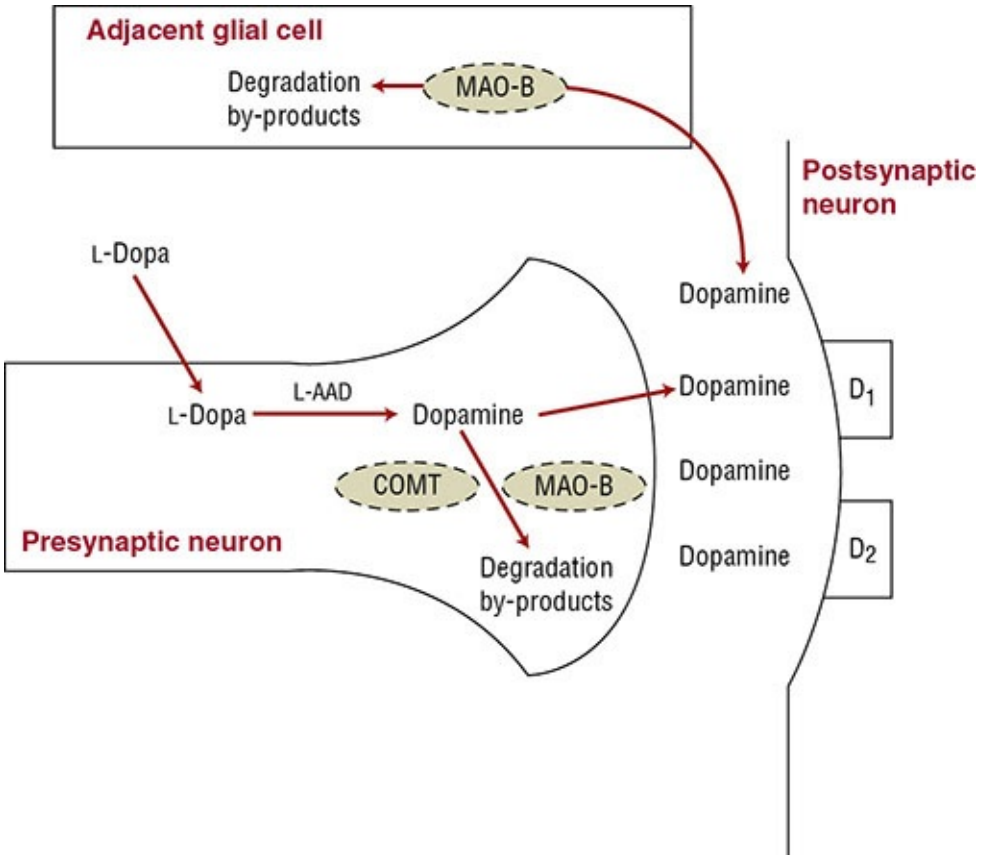


FIGURE 76-5 Dopamine synthesis and metabolism within the striatal neurons. See also Fig. 76-1 for additional details. (COMT, catechol-*O*-methyltransferase; D_1-D_2, dopamine receptors; L-AAD, L-aromatic amino acid decarboxylase; L-Dopa, levodopa; MAO-B, monoamine oxidase B.)

6 Regardless of what the initial therapeutic agent is, ultimately all patients with PD will require L-dopa. With regard to carbidopa, about 75 mg/day is required to sufficiently inhibit the peripheral activity of L-amino acid decarboxylase, but some patients require more. Therefore, the usual initial maintenance carbidopa/L-dopa regimen is 25/100 mg three times daily. As the motor features of PD become progressively more severe, use of higher dosages is required. There is no maximum allowable total daily L-dopa dose; however, in patients with severe PD, the usual maximal dose tolerated is approximately 1,000 to 1,500 mg/day. Slow buildup of dose (eg, increments of 100 mg L-dopa per week) can help minimize treatment-emergent side effects, such as drowsiness and nausea (see Table 76-4).

Various formulations of carbidopa/L-dopa are available (see Table 76-3). For patients with difficulty swallowing intact tablets, an orally disintegrating tablet (ODT) preparation of carbidopa/L-dopa is available, and while this formulation rapidly dissolves on contact with saliva, the carbidopa/L-dopa does not undergo transmucosal absorption and the dissolved drug in saliva must be swallowed for absorption in the proximal duodenum. Additionally, carbidopa/L-dopa is available in an oral capsule formulation containing immediate-release (IR) and extended-release (ER) beads (ie, Rytary) which can be sprinkled on food (eg, apple sauce).

Pharmacokinetics There is marked intra- and intersubject variability in the time to peak plasma concentrations after oral carbidopa/L-dopa, and this may in part be attributed to differences in gastric emptying as L-Dopa is absorbed in the proximal duodenum by a saturable large neutral amino acid transport system. Therefore, competition for this transporter by large dietary (or pharmaceutical) neutral amino acids (eg, leucine, phenylalanine) may result in reduced L-dopa bioavailability. However, for patients with early PD, this interaction is generally not significant.

L-Dopa is not bound to plasma proteins and is actively transported across the blood–brain barrier by the large neutral amino acid transporter system. In advanced PD, special diets involving protein restriction may improve L-dopa responsiveness and are sometimes implemented. A metabolite of L-dopa, 3-*O*-methyldopa, also competes for transport, but it is not clear how this affects L-dopa clinical response.

When peripheral decarboxylation of L-dopa is inhibited by carbidopa, 3-*O*-methylation (via COMT) becomes the predominant catabolic pathway. The elimination half-life of L-dopa is about 1 hour, and this is extended to about 1.5 hours with the addition of carbidopa. With the addition of a COMT inhibitor

such as entacapone to carbidopa/L-dopa, the elimination half-life is extended to about 2 to 2.5 hours.

It is important to note that the controlled-release (ie, Sinemet CR) and IR/ER carbidopa/L-dopa formulations (ie, Rytary) are 70% and 75% bioavailable, respectively, compared to standard IR carbidopa/L-dopa. Manufacturer-provided dosage conversion recommendations are available to guide dosing conversions between carbidopa/L-dopa formulations.

7 **Motor Complications of L-Dopa** Long-term L-dopa therapy is associated with a variety of motor complications, of which end-of-dose "wearing off" (motor fluctuations) and L-dopa peak-dose dyskinesias are the two most commonly encountered.[29] These motor complications can become disabling and a challenge to manage. The approximate risk of developing either motor fluctuations or dyskinesia is 10% per year of L-dopa therapy.[30,31] However, motor complications can occur as early as 6 months after starting L-dopa therapy, especially if excessive doses are used initially.[32] **Table 76-5** lists the common motor complications associated with long-term treatment with L-dopa and suggested initial management strategies. Initiating therapy with the CR form of carbidopa/L-dopa (ie, Sinemet CR) does not reduce the development of motor complications compared with IR carbidopa/L-dopa.[22]

TABLE 76-5 Common Motor Complications and Possible Initial Treatments

Effects	Possible Treatments
End-of-dose "wearing off" (motor fluctuation)	Increase frequency of carbidopa/L-dopa doses; add either COMT inhibitor or MAO-B inhibitor or dopamine agonist; add or switch to extended-release carbidopa/L-dopa (ie, Rytary); use L-dopa inhalation
"Delayed on" or "no on" response	Give carbidopa/L-dopa on empty stomach; use carbidopa/L-dopa ODT; avoid carbidopa/L-dopa SR; use apomorphine subcutaneous or L-dopa inhalation
Start hesitation ("freezing")	Increase carbidopa/L-dopa dose; add a dopamine agonist or MAO-B inhibitor; utilize physical therapy along with assistive walking devices or sensory cues (eg, rhythmic commands, stepping over objects)
Peak-dose dyskinesia	Provide smaller doses of carbidopa/L-dopa; reduce dose of adjunctive dopamine agonist; add amantadine

COMT, catechol-*O*-methyltransferase; MAO, monoamine oxidase; ODT, orally disintegrating tablet; SR, sustained release.

7 **End-of-Dose "Wearing off"** The terms "off" and "on" refer to periods of poor movement (ie, return of tremor, rigidity, or slowness) and good movement, respectively. End-of-dose "wearing off" prior to the next dose of medication is a common type of response fluctuation. This phenomenon is related to the increasing loss of neuronal storage capability for dopamine as well as the short half-life of L-dopa. Initially, exogenous L-dopa is taken up by the remaining SNc neurons, converted to dopamine, and stored in synaptic vesicles. With progressive loss of SNc neurons and storage capacity, patients become more dependent on exogenous carbidopa/L-dopa. Hence, the peripheral pharmacokinetic properties of L-dopa increasingly become the determinant of central dopamine synthesis. With advancing PD, the duration of action of a single carbidopa/L-dopa dose progressively shortens, and in some cases may produce benefits for as little as 1 hour. As a result, carbidopa/L-dopa needs to be given more frequently, although other options are also available (see Table 76-5). In particular, the addition of the COMT inhibitor entacapone or an MAO-B inhibitor (ie, rasagiline, safinamide) extends the action of L-dopa, and either should be considered.[22] A dopamine agonist (eg, pramipexole, ropinirole, or rotigotine) also can be added to a carbidopa/L-dopa regimen for management of "wearing off." The older CR L-dopa product (ie, Sinemet CR) has been

investigated for management of motor fluctuations, but the evidence is not compelling.[22] A newer IR/ER carbidopa/L-dopa formulation (ie, Rytary) contains beads that dissolve at different rates. Following administration, therapeutic L-dopa levels are rapidly achieved and are maintained for 4 to 5 hours providing efficacy for management of motor fluctuations.[33] Also in development is a novel controlled-release, biodegradable, gastroretentive dosage form consisting of a carbidopa/L-dopa-polymer matrix strip folded like an accordion within a capsule. After administration, the "accordion" strip unfolds and is retained in the stomach due to its larger unfolded dimension that prevents passage through the pyloric sphincter.

Carbidopa/L-dopa enteral suspension is effective and safe for patients with advanced PD experiencing persistent, on/off fluctuations.[34] This carbidopa/L-dopa enteral suspension is contained within a medication cassette reservoir and infusion into the small intestine is achieved by a portable pump device. This treatment is semi-invasive as it requires placement of a percutaneous endoscopic gastrostomy tube along with a jejunal extension, through the abdominal wall. The drug infusion typically runs for 16 continuous hours per day and is turned off at night.

For rapid relief of acute off episodes, apomorphine (a subcutaneously administered short-acting dopamine agonist) or a L-dopa dry powder for inhalation may be administered as needed.[35,36] Although not commonly performed, sipping small amounts of carbidopa/L-dopa solution very frequently throughout the day is also a method for managing on/off fluctuations. A solution that is stable for 72 hours at room temperature can be prepared by adding 10 crushed tablets of carbidopa/L-dopa 10/100 (or 25/100) mg and 2 g crystalline ascorbic acid to 1 L of water.[37]

Often though, off episodes occur during the night, and patients will awaken in an off state as a consequence of an overnight decline of drug levels. Therefore, bedtime administration of a dopamine agonist or a drug formulation that provides sustained drug levels overnight (eg, carbidopa/L-dopa CR or IR/ER, ropinirole XL, pramipexole ER, rotigotine transdermal patch) can help reduce nocturnal off episodes and improve functioning upon awakening.

Nonadherence to medications also contributes to the frequency of off episodes. Therefore, engaging and supporting patients and caregivers in overcoming barriers to medication adherence is important.

"Delayed-on" or "no-on" Response "Delayed-on" or "no-on" responses describe a delayed or absent onset of drug effect to individual doses of

carbidopa/L-dopa which can be a result of delayed gastric emptying or decreased absorption in the duodenum. To overcome this effect, chewing a tablet or crushing it and then drinking a full glass of water or using the ODT formulation on an empty stomach can help mitigate effects of delayed gastric emptying. Additionally, subcutaneously administered apomorphine may be used as rescue therapy for delayed-on or no-on periods. Alternatively, a drug-free period ("drug holiday") may be initiated in an attempt to modify postsynaptic dopamine receptors and thus decrease unpredictable off states. Although not commonly performed because of discomfort (to the patient) and medical risks, when drug holidays are performed, it should be under close medical supervision.

Freezing "Freezing," or a sudden, episodic akinesia of the lower extremities, is event described by patients as a feeling where their "feet suddenly feel stuck to the floor" during ambulation or they have difficulty initiating steps (start hesitation) or turns (turn hesitation). As freezing often is exacerbated by anxiety or when perceived obstacles (eg, doorways, turnstiles) are encountered, this event may interfere with ambulation and increase the risk of falls. Management consists of physical therapy along with use of assistive walking devices and sensory cues.

9 **Dykinesias** Another complication of L-dopa therapy is "on" period dyskinesias that are involuntary choreiform movements involving usually the neck, trunk, and lower/upper extremities. Among all the antiparkinson medications, dyskinesias are specific to L-dopa therapy and if patients report "shakiness," it is important to clarify if they are referring to tremor or dyskinesias. To help differentiate the two, it is important to note that dyskinesias are usually associated with peak striatal dopamine levels (peak-dose dyskinesia) and, simplistically, can be thought of as too much movement secondary to extension of the L-dopa pharmacologic effect. Lowering the dose of carbidopa/L-dopa to counteract dyskinesias should be attempted. However, the use of a lower dose may result in suboptimal control of parkinsonian features; thus, necessitating addition of another antiparkinson agent (eg, dopamine agonist). Glutamate overactivity may also be involved, as suggested by the dyskinesia improvement observed with amantadine (NMDA-receptor antagonist) and other antiglutamate ligands.[38] Less commonly, dyskinesias also can develop during the rise and fall of L-dopa effects (the dyskinesia–improvement–dyskinesia or diphasic pattern of response). For severe dyskinesias (despite pharmacologically optimized therapy), surgery should be considered.

"Off-Period" Dystonia In PD, dystonias are sustained muscle contractions that

can occur and more commonly affect a distal lower extremity (eg, clenching of toes or involuntary turning of a foot). Dystonias often occur in the early morning hours, due to waning drug levels, and improve with the first carbidopa/L-dopa dose of the day. Remedies for early morning dystonia include bedtime administration of a long-acting dopamine agonist, long-acting carbidopa/L-dopa, or baclofen. Additionally, focal injections of botulinum toxin type A or B are effective for persistent focal dystonias, which can also occur as L-dopa peak dose effect; therefore, additional management of this specific adverse event is similar to that of dyskinesias.

Monoamine Oxidase B Inhibitors

5 Three selective MAO-B inhibitors (rasagiline, safinamide, selegiline) are available for management of PD (see Table 76-3). The selective inhibition of MAO-B in the brain interferes with the degradation of dopamine and results in prolonged dopaminergic activity. Rasagiline and selegiline contain a propargylamine moiety, which is essential for conferring irreversible ("suicide") inhibition of MAO-B, in contrast to safinamide, which is a reversible MAO-B inhibitor. At therapeutic doses, all three agents preferentially inhibit MAO-B over MAO-A.

A common concern with use of these agents is the potential for interactions with drugs that possess serotonergic activity. Concomitant use of MAO-B inhibitors with meperidine and other selected opioid analgesics is contraindicated because of a small risk of serotonin syndrome. However, concomitant use of serotonergic antidepressants is not contraindicated, and these drugs can be used concomitantly when clinically warranted.[39]

MAO-B inhibitors have also been investigated for neuroprotective properties (clinically referred to as *disease modification*). MAO-B inhibitors possess antiapoptotic properties, and MAO-B inhibition diverts dopamine degradation to an alternate route (ie, COMT) that does not generate free radicals (see Figs. 76-1 and 76-5). To date, clinical studies to demonstrate disease modification with MAO-B inhibitors have yielded inconclusive results.

5 8 Selegiline, also known as L-deprenyl, is marketed for extending L-dopa effects and is typically administered 5 mg twice daily. Selegiline is also available as an ODT formulation administered 1.25 to 2.5 mg once daily, as well as a transdermal formulation which is not indicated for PD. As monotherapy in early PD, selegiline provides modest improvements in motor function.[2] In advanced PD, adjunctive use of selegiline can provide up to 1 hour of extra "on"

time for patients with “wearing off,” although the data are inconsistent,[22] which may be explained, in part, by the poor and erratic bioavailability of selegiline.

As an amphetamine pharmacophore, selegiline undergoes first-pass hepatic metabolism, predominantly via cytochrome P450 (CYP450) 2B6 and 2C19, to end products of L-methamphetamine and L-amphetamine. Adverse effects of selegiline are minimal but can include agitation, insomnia (especially if administered at bedtime), hallucinations, and orthostatic hypotension (see Table 76-4). Selegiline also increases the peak effects of L-dopa and can worsen pre-existing dyskinesias or psychiatric symptoms such as delusions. With the selegiline ODT formulation, first-pass hepatic metabolism is bypassed as a consequence of transmucosal absorption of the drug; hence, bioavailability is improved and formation of amphetamine metabolites is reduced.

58 Rasagiline is a second-generation, irreversible, selective MAO-B inhibitor administered at 0.5 or 1 mg once daily,[39] which is effective as monotherapy in early PD. Additionally, rasagiline is also effective as add-on therapy for managing motor fluctuations in advanced PD with efficacy similar to that of entacapone, offering approximately 1 hour of extra “on” time during the day.[22] In terms of adverse events, rasagiline is well tolerated with minimal gastrointestinal (GI) or neuropsychiatric side effects. Rasagiline is metabolized by hepatic CYP1A2 to aminoindan, which is inactive and devoid of amphetamine-like properties.[40]

58 Safinamide is a reversible, selective MAO-B inhibitor administered at 50 or 100 mg once daily indicated as add-on therapy to carbidopa/L-dopa for managing motor fluctuations and provides up to 1 hour of extra “on” time during the day.[22] Nondopaminergic effects include state-dependent inhibition of voltage-gated sodium channels and modulation of release of glutamate.[41] However, the extent to which these properties of safinamide contribute to the overall action of the drug is unclear. Safinamide is well tolerated with minimal GI or neuropsychiatric side effects and is predominantly metabolized by nonmicrosomal enzymes (cytosolic amidases) to inactive metabolites which are excreted renally.[41]

Catechol-*O*-Methyltransferase Inhibitors

8 Two COMT inhibitors, entacapone and tolcapone, have been developed to extend the effects of L-dopa and are indicated for managing “wearing off”. Mechanistically both reduce the peripheral conversion of L-dopa to dopamine, thus enhancing central L-dopa bioavailability, consequently, in the absence of L-

dopa, they have no effect on PD symptoms. COMT inhibitors increase L-dopa area under the curve by approximately 35% and, for patients with “wearing off,” can increase “on” time by about 1 to 2 hours.[22]

Tolcapone inhibits both peripheral and central COMT, but its use is limited by reports of fatal hepatotoxicity, such that strict monitoring of hepatic function, especially during the first 6 months of therapy, is required (see Table 76-4). Because of the hepatotoxicity risk, tolcapone is reserved for patients with fluctuations that are not responding to other therapies.

Entacapone has a shorter half-life than tolcapone, and 200 mg needs to be given with each dose of carbidopa/L-dopa up to a maximum of eight times per day. A triple-combination product of carbidopa/L-dopa/entacapone offers convenience for some patients (ie, fewer tablets to administer). Unlike tolcapone, entacapone is not associated with hepatotoxicity; therefore, entacapone is considered efficacious and clinically useful as adjunctive therapy to manage motor fluctuations.[22]

With both agents, augmentation of dopaminergic adverse effects may occur and generally are manageable by reduction of the carbidopa/L-dopa dosage. Patients should be advised that other adverse effects include brownish-orange urinary discoloration and delayed onset of diarrhea (weeks to months later).

Dopamine Agonists

Dopamine agonists fall into two pharmacologic subtypes: ergot-derived agonists (bromocriptine) and the nonergot agonists (apomorphine, pramipexole, ropinirole, and rotigotine).[42] Nonergot agonists have a better safety profile and are more commonly used than the ergot-derived agonists. Pharmacologically dopamine agonists stimulate dopamine receptors (eg, D_1, D_2, D_3) and are useful as monotherapy in mild-to-moderate PD, and also as adjuncts to carbidopa/L-dopa therapy to reduce “off” time in patients with motor fluctuations.[22]

10 Compared with long-term carbidopa/L-dopa therapy, dopamine agonist significantly reduce the risk of developing motor complications.[43,44] For younger patients, who are more likely to develop motor complications, dopamine agonists are preferred over carbidopa/L-dopa. For older patients, dopamine agonists should be used conservatively due to greater likelihood for development of intolerable side effects and for patients with cognitive problems or dementia, dopamine agonists should be avoided.

Common adverse effects of dopamine agonists include nausea, confusion, drowsiness, hallucinations, lower-extremity edema, and orthostatic hypotension

(see Table 76-4). When initiating therapy, a slow dose titration is required to minimize development of adverse effects, particularly nausea. The addition of a dopamine agonist to carbidopa/L-dopa therapy also can induce dyskinesias, especially in patients with pre-existing dyskinesias. Less common but serious adverse effects include impulsive and compulsive behaviors (eg, pathologic gambling or shopping; paraphilia), delusions/psychosis, and sleep attacks (sudden, unexpected episodes of sleep). Hallucinations and delusion should be managed using a systematic approach that starts with dose reduction or discontinuation of the dopamine agonist, and if needed, addition of an atypical antipsychotic medication such as clozapine, pimavanserin, or quetiapine.[19,23] Of the atypical antipsychotics, only pimavanserin is FDA-approved for psychosis in PD. Involvement of caregivers in surveillance for potential adverse effects of dopamine agonists, particularly development of delusions, hallucinations, and impulsive behaviors, facilitates earlier detection and management.

Apomorphine is an aporphine alkaloid originally derived from morphine, but lacks narcotic properties.[35] Because of poor oral bioavailability due to extensive hepatic first-pass metabolism, apomorphine is administered subcutaneously. Apomorphine is indicated for patients with advanced PD who are experiencing intermittent “off” episodes despite optimized therapy. Upon subcutaneous administration, apomorphine produces an “on” response within 20 minutes. The effective dose ranges from 2 to 6 mg per injection. Sites of injection (abdomen, upper arm, and upper thigh) should be rotated to avoid development of subcutaneous nodules. Apomorphine elimination half-life is approximately 40 minutes, and the duration of benefit can be up to 100 minutes. Nausea and vomiting are common side effects, and prior to the initiation of apomorphine, patients should be premedicated with the antiemetic trimethobenzamide.

Pramipexole is initiated at a dose of 0.125 mg three times a day and increased every 5 to 7 days, as tolerated, to a maximum of 1.5 mg three times a day. An extended-release pramipexole formulation is also available. Immediate-release ropinirole is initiated at 0.25 mg three times a day and increased by 0.25 mg three times a day on a weekly basis to a maximum of 24 mg/day. An extended-release ropinirole formulation also is available. Pramipexole is renally excreted with an 8- to 12-hour half-life. The initial dosage must be adjusted in renal insufficiency (0.125 mg twice daily for creatinine clearances of 35-59 mL/min [0.58-0.99 mL/s], 0.125 mg once daily for creatinine clearances of 15-34 mL/min [0.25-0.57 mL/s]).

Ropinirole has a 6-hour half-life and is metabolized by CYP1A2; therefore, potent inhibitors (eg, fluoroquinolone antibiotics) and inducers (eg, cigarette

smoking) of this enzyme likely will lead to alterations in ropinirole clearance.

Rotigotine transdermal patch is initiated at 2 mg once daily and increased weekly by 2 mg increments to achieve desired therapeutic effect. The rotigotine transdermal patch provides continuous release of drug over a 24-hour period.[45] The patch application sites should be rotated to minimize skin irritation and rash. Rotigotine disposition is not affected by hepatic or renal impairment, and CYP-mediated drug interactions are not significant.

EVALUATION OF THERAPEUTIC OUTCOMES

1 Comprehensive medication management with optimization of medications related to PD improves patient outcomes.[46] Routine evaluation and monitoring of motor and nonmotor symptoms should occur every 3 to 6 months for patients on a stable treatment regimen. With the changes in pharmacotherapy (eg, drug addition, discontinuation, dose change), follow-up monitoring for efficacy and side effects should occur within 1 or 2 weeks and may occur via telephone. **Table 76-6** lists the monitoring parameters for PD therapy. Patient and caregiver satisfaction is an important component of evaluating therapeutic outcomes. Toward this end, establishing appropriate treatment expectations is important. Patients and caregivers should be educated that symptoms of PD often progresses with time, and adjustments to the medication regimen will be required to manage motor and nonmotor features. Additionally, some symptoms do not respond to pharmacotherapy (eg, freezing, gait, and postural instability). Assessment of the patient's general level of functioning, including activities of daily living and mobility, is important to determine when medication adjustments or physical therapy interventions are needed. It is also important to be aware of and adhere to the general guidelines and recommendations for geriatric health maintenance and disease prevention (eg, bone health, routine vaccinations, and vitamin and mineral supplementations).

TABLE 76-6 Monitoring Parkinson Disease Therapy

1. Monitor medication administration times. Educate the patient that immediate-release carbidopa/L-dopa is absorbed best on an empty stomach but is commonly taken with food (preferably nonprotein snack) to minimize nausea. Avoid administration of conventional selegiline in the late afternoon or evening to minimize insomnia.
2. Monitor to ensure that the patient and/or caregivers understand the prescribed medication regimen. For example, they should understand that catechol-*O*-methyltransferase inhibitors work by enhancing the effect of L-dopa and that the patient should not discontinue medication without notifying the clinician.
3. Monitor and inquire specifically about dose-by-dose effects of medication, including response to doses of medication and the presence of dyskinesias, "wearing-off" effects, dizziness, nausea, orthostasis, or visual hallucinations. Offer suggestions to help alleviate these, or encourage the patient to discuss them with the clinician.
4. Monitor caregiver involvement and facilitation for early detection of abnormal behaviors, dyskinesias, falls, hallucinations, impulsivity, memory problems, mood changes, and sleep disorders.
5. Monitor for nonadherence and, if present, inquire for possible reasons (eg, dosing convenience, financial issues, and adverse effects) and offer suggestions.
6. Monitor for presence of drugs that can exacerbate idiopathic Parkinson disease motor features (eg, D_2-receptor blockers).
7. Monitor for presence of drugs that can exacerbate nonmotor symptoms. Evaluate whether the presence of an anticholinergic agent is causing confusion or cognitive impairment.

Patients and caregivers can participate in treatment by recording medication administration times as well as the duration of on and off times that can be reviewed at each visit. Periodic review of all prescription and nonprescription medications that the patient is taking should be performed to identify use of medications with side effects that can exacerbate PD motor and nonmotor features. For example, D_2 blockers (such as metoclopramide and typical antipsychotics) can worsen motor features and should be avoided. If the patient reports memory problems, medications with anticholinergic properties should be avoided.

Nonmotor symptoms must be identified, assessed, managed, and monitored. These include anxiety, cognitive impairment, constipation, daytime sleepiness, depression, drooling, dysphagia, fatigue, falls, hallucinations/psychosis, impulsivity, insomnia, orthostatic hypotension, overactive bladder, pain, REM sleep behavior disorder, and restless legs syndrome. Screening for anxiety or depressive disorders will help determine if antidepressant or antianxiety therapy is needed. If falling is a problem, it is important to investigate whether falls are

secondary to insufficient motor control, orthostatic hypotension, or drug side effects, such as dizziness. The former may necessitate an increase in dose of antiparkinson agents, and the latter two conditions, a reduction in drug dosage. Physical therapy is also helpful for strengthening ambulation and balance skills to minimize falls. The patient should be questioned about any difficulties with their antiparkinson medications, including presence of adverse effects. Recommendations always should be made in view of the patient's perception of the severity of symptoms and effect on quality of life.

CONCLUSION

Despite many advances in neuroscience, a definitive cause of PD remains unknown. Each of the available therapies provide various degrees of symptomatic benefit, and the choice of agent is patient specific. The appropriate pharmacotherapy can significantly improve a patient's quality of life and functional status. The goal of management remains maintaining acceptable functional control with minimal treatment emergent motor and nonmotor complications. Thoughtful consideration for choice of initial and adjunctive therapy is critical for optimizing short- and long-term outcomes.

Postclass Engaged Learning Activity

Conduct a literature search and identify a primary research manuscript that has been published in the past 12 months regarding the treatment of Parkinson disease. If the manuscript is regarding a new patient care process, write a brief summary about the process, how feasible you believe the process would be to implement in practice, and what setting(s) the process would be best suited (eg, community pharmacy, ambulatory clinic, long-term care facility, hospital). If the manuscript is regarding a medication discussed in this chapter, write a brief summary about the study methods, the major findings, and how this new information might change current practice. If the manuscript is regarding a new medication not described in this chapter, write a brief summary about the medication's mechanisms of action, how it is administered, and one potential advantage or disadvantage of this new medication compared to the current standard of care. This activity is intended to build your literature evaluation skills and ability to critically appraise research manuscripts.

ABBREVIATIONS

COMT	catechol-*O*-methyltransferase
CR	controlled release
CYP450	cytochrome P450
D_1	dopamine receptor subtype 1
D_2	dopamine receptor subtype 2
DBS	deep-brain stimulation
ER	extended release
GABA	γ-aminobutyric acid
GI	gastrointestinal
GPi	globus pallidus interna
IR	immediate release
L-dopa	levodopa
MAO	monoamine oxidase
NMDA	*N*-methyl-D-aspartate
ODT	orally disintegrating tablet
PD	Parkinson disease
REM	rapid eye movement
SNc	substantia nigra pars compacta
SNr	substantia nigra pars reticulate
STN	subthalamic nucleus

REFERENCES

1. Parkinson J. *An Essay on the Shaking Palsy*. London: Sherwood, Neely, and Jones; 1817:1–66.
2. Kasten M, Chade A, Tanner CM. Epidemiology of Parkinson's disease. *Handb Clin Neurol*. 2007;83:129–151.
3. Pringsheim T, Jette N, Frolkis A, et al. The prevalence of Parkinson's disease: A systematic review and meta-analysis. *Mov Disord*. 2014;29:1583–1590.
4. Dashtipour K. Do genetic factors protect against Parkinson's disease? What I can learn from my healthy grandma. *Med Hypotheses*. 2014;83:637–639.
5. Jellinger KA. The pathomechanisms underlying Parkinson's disease. *Expert Rev Neurother*. 2014;14:199–215.
6. Dias V, Junn E, Mouradian MM. The role of oxidative stress in

Parkinson’s disease. *J Parkinsons Dis*. 2013;3:461–491.

7. Burke RE, O’Malley K. Axon degeneration in Parkinson’s disease. *Exp Neurol*. 2013;246:72–83.
8. Coppedè F. Genetics and epigenetics of Parkinson’s disease. *Scientific World J*. 2012;2012:489830.
9. Dick FD, De Palma G, Ahmadi A, et al. Geoparkinson study group. Environmental risk factors for Parkinson’s disease and parkinsonism: The Geoparkinson study. *Occup Environ Med*. 2007;64:666–672.
10. Costa J, Lunet N, Santos C, et al. Caffeine exposure and the risk of Parkinson’s disease: A systematic review and meta-analysis of observational studies. *J Alzheimers Dis*. 2010;20(Suppl 1):S221–S238.
11. Chen H, Huang X, Guo X, et al. Smoking duration, intensity, and risk of Parkinson disease. *Neurology*. 2010;74:878–884.
12. Smith Y, Bevan MD, Shink E, Bolam JP. Microcircuitry of the direct and indirect pathways of the basal ganglia. *Neuroscience*. 1998;86:353–387.
13. Hansen C, Li JY. Beyond α-synuclein transfer: Pathology propagation in Parkinson’s disease. *Trends Mol Med*. 2012;18:248–255.
14. McCann H, Cartwright H, Halliday GM. Neuropathology of α-synuclein propagation and braak hypothesis. *Mov Disord*. 2016;31:152–160.
15. Stayte S, Vissel B. Advances in non-dopaminergic treatments for Parkinson’s disease. *Front Neurosci*. 2014;8:113.
16. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson’s disease. *Mov Disord*. 2015;30:1591–1601.
17. López-Sendón JL, Mena MA, de Yébenes JG. Drug-induced parkinsonism in the elderly: Incidence, management and prevention. *Drugs Aging*. 2012;29:105–118.
18. Jennings D, Siderowf A, Stern M, et al. Conversion to Parkinson disease in the PARS Hyposmic and Dopamine Transporter-Deficit Prodromal Cohort. *JAMA Neurol*. 2017;74:933–940.
19. Seppi K, Chaudhuri KR, Coelho M, et al. Update on treatments for nonmotor symptoms of Parkinson’s disease: An evidence-based medicine review. *Mov Disord*. 2019;34(2):180–198. doi: 10.1002/mds.27602.
20. Lang AE, Espay AJ. Disease modification in Parkinson’s disease: Current approaches, challenges, and future considerations. *Mov Disord*. 2018;33:660–677.
21. Chen JJ, Swope DM. Pharmacotherapy for Parkinson’s disease.

Pharmacotherapy. 2007;27(12 Pt 2):161S–173S.

22. Fox SH, Katzenschlager R, Lim SY SY, et al. International Parkinson and Movement Disorder Society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease. *Mov Disord*. 2018;33(8):1248–1266.
23. National Institute for Health and Care Excellence. Parkinson's disease in adults. NICE Guideline [NG71]. July 2017. Available at https://www.nice.org.uk/guidance/ng71. Accessed August 26, 2019.
24. Fox SH, Katzenschlager R, Lim SY, et al. The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the motor symptoms of Parkinson's disease. *Mov Disord*. 2011;26(Suppl 3):S2–S41.
25. Larson PS. Deep brain stimulation for movement disorders. *Neurotherapeutics*. 2014;11:465–474.
26. Rughani A, Schwalb JM, Sidiropoulos C, et al. Congress of Neurological Surgeons systematic review and evidence-based guideline on subthalamic nucleus and globus pallidus internus deep brain stimulation for the treatment of patients with Parkinson's disease: Executive summary. *Neurosurgery*. 2018;82(6):753–756.
27. Drouin-Ouellet J, Barker RA. The challenges of administering cell-based therapies to patients with Parkinson's disease. *Neuroreport*. 2013;24:1000–1004.
28. Bartus RT, Kordower JH, Johnson EM Jr, et al. Post-mortem assessment of the short and long-term effects of the trophic factor neurturin in patients with α-synucleinopathies. *Neurobiol Dis*. 2015;78:162–171.
29. Khan TS. Off spells and dyskinesias: Pharmacologic management of motor complications. *Cleve Clin J Med*. 2012;79(Suppl 2):S8–S13.
30. Stocchi F. Prevention and treatment of motor complications. *Parkinsonism Relat Disord*. 2003;9(Suppl 2):S73–S81.
31. Pahwa R, Lyons KE. Options in the treatment of motor fluctuations and dyskinesias in Parkinson's disease: A brief review. *Neurol Clin*. 2004;22(Suppl 3):S35–S52.
32. Parkinson Study Group. Levodopa and the progression of Parkinson's disease. *N Engl J Med*. 2004;351:2498–2508.
33. Hauser RA, Hsu A, Kell S, et al. IPX066 ADVANCE-PD investigators. Extended-release carbidopa-levodopa (IPX066) compared with immediate-release carbidopa-levodopa in patients with Parkinson's disease

and motor fluctuations: A phase 3 randomised, double-blind trial. *Lancet Neurol*. 2013;12:346–356.

34. Olanow CW, Kieburtz K, Odin P, et al. The LCIG Horizon Study Group. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: A randomised, controlled, double-blind, double-dummy study. *Lancet Neurol*. 2014;13:141–149.
35. Chen JJ, Obering C. Apomorphine in the management of motor fluctuations associated with Parkinson's disease. *Clin Ther*. 2005;27:1710–1724.
36. LeWitt PA, Hauser RA, Pahwa R, et al. Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: A randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Neurol*. 2019;18(2):145–154. doi: 10.1016/S1474-4422(18)30405-8.
37. Pappert EJ, Buhrfiend C, Lipton JW, et al. Levodopa stability in solution: Time course, environmental effects, and practical recommendations for clinical use. *Mov Disord*. 1996;11:24–26.
38. Johnson KA, Conn PJ, Niswender CM. Glutamate receptors as therapeutic targets for Parkinson's disease. *CNS Neurol Disord Drug Targets*. 2009;8:475–491.
39. Panissett M, Chen JJ, Rhyee SH, et al. Serotonin toxicity association with concomitant antidepressants and rasagiline treatment: Retrospective study (STACCATO). *Pharmacotherapy*. 2014;34:1250–1258.
40. Chen JJ, Swope DM, Dashtipour K. Comprehensive review of rasagiline, a second-generation monoamine oxidase inhibitor, for the treatment of Parkinson's disease. *Clin Ther*. 2007;29:1825–1849.
41. deSouza RM, Schapira A. Safinamide for the treatment of Parkinson's disease. *Expert Opin Pharmacother*. 2017;18:937–943.
42. Blandini F, Armentero MT. Dopamine receptor agonists for Parkinson's disease. *Expert Opin Investig Drugs*. 2014;23:387–410.
43. Rascol O, Brooks DJ, Korczyn AD, et al. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. *N Engl J Med*. 2000;342:1484–1491.
44. Parkinson Study Group. Pramipexole vs levodopa as initial treatment for Parkinson's disease: A 4-year randomized controlled trial. *Arch Neurol*. 2004;61:1044–1053.

45. Chen JJ, Swope DM, Dashtipour K, Lyons KE. Transdermal rotigotine: A clinically innovative dopamine receptor agonist for the management of Parkinson's disease. *Pharmacotherapy*. 2009;29:1452–1467.
46. Schröder S, Martus P, Odin P, Schaefer M. Impact of community pharmaceutical care on patient health and quality of drug treatment in Parkinson's disease. *Int J Clin Pharm*. 2012;34:746–756.

77

Pain Management

Chris M. Herndon, James B. Ray, and Courtney M. Kominek

KEY CONCEPTS

1. Understanding the pathogenesis of pain, helps to guide treatment and patient education.
2. It is important, whenever possible, to ask patients if they have pain, to identify the source of pain, and to assess the characteristics of the pain.
3. The etiology of pain may not always be identifiable.
4. Whenever possible, a multidisciplinary approach and nonpharmacologic strategies should be incorporated.
5. Chronic pain treatment should focus on self-management strategies and focus on active, rather than passive approaches.
6. Selection of nonopioids and opioids should be based on the characteristics and type of pain as well as individual patient factors.
7. Oral or topical analgesics are preferred over other dosage forms whenever feasible, but it is important to adjust the route of administration to the needs of the patient.
8. Patients taking analgesics should be monitored for response (analgesia, functionality, quality-of-life) and side effects.
9. Doses must be individualized for each patient and administered for an adequate duration of time. Around-the-clock regimens should be considered for acute and chronic pain. As-needed regimens should be used for breakthrough pain or when acute pain displays wide variability and/or has subsided greatly.
10. Consider a trial of opioids in those with severe pain that have failed nonpharmacologic and nonopioid treatment when the anticipated benefits are expected to outweigh the risks.

11 Use risk mitigation strategies (informed consent/patient agreements, urine drug monitoring [UDM], opioid overdose education and naloxone distribution, prescription drug monitoring program [PDMP] checks) prior to and periodically during opioid therapy, with frequency determined on the basis of patient risk and presence of aberrant drug-taking behaviors.

Preclass Engaged Learning Activity

Students are requested to watch the following videos on YouTube:

Understanding pain and what to do about it in less than 5 minutes—presented by Painaustralia

URL: https://tinyurl.com/yxjyltp6

Tame the beast: It's time to rethink persistent pain — Lorimer Moseley, David Moen, Sam Chisholm

URL: https://tinyurl.com/y2nbtbb2

INTRODUCTION

If we know that pain and suffering can be alleviated, and do nothing about it, then we ourselves, become the tormentors.

—Primo Levi[1]

Humans have always known and sought relief from pain.[2] Today, pain's impact on society is still great, and pain remains a primary reason patients seek medical advice.[3] In general, pain is defined as: "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[4] However, as pain is subjective, many clinicians define pain as "whatever the patient says it is."

Regrettably, many healthcare providers do not receive adequate training in the treatment of pain. Therefore, understanding the pathophysiology of pain and maintaining a thorough understanding of both nonpharmacologic and pharmacologic treatment modalities are important factors in addressing pain control.

EPIDEMIOLOGY

Data presented in the Institute of Medicine report, “Relieving Pain in America” suggests that greater than 100 million persons in the United States live with chronic pain.[5] Given that greater than 50% of persons reporting low back pain in the previous 3 months also reported interference with basic and complex activities, it is not surprising that the estimated economic burden of chronic pain alone exceeds 500 billion dollars (US) annually.[5] In one year, an estimated 25 million Americans will experience acute pain due to injury or surgery, and one-third will experience severe chronic pain at some point in their lives.[3] Unfortunately, despite much public attention, pain often remains inadequately or inappropriately treated.[6,7]

PATHOPHYSIOLOGY

The pathophysiology of pain involves complex interactions between neural and immune networks within the peripheral and central nervous system in response to afferent sensory stimuli that produces the conscious experience we know as pain. It can be physiologic and protective (adaptive) or pathophysiologic and harmful (maladaptive).[8] Pain is a complex interaction between biological processes (nociception) impacted by individual psychological and social determinates.

Adaptive Pain

The pain experienced from noxious stimuli involving temperature extremes, mechanical trauma, or chemical irritation is called nociceptive pain which is a primitive evolutionary mechanism to protect our body from actual or potential tissue injury. Pain that occurs as a result of unavoidable tissue damage (trauma or surgery) creates sensitization at and adjacent to the site of tissue injury. This process also engages the immune system, and is called inflammatory pain. Nociceptive and inflammatory pains are both adaptive and protective. The physiological processing of pain occurs within a neurotransmission circuit via a number of steps known as transduction, conduction, transmission, modulation, and perception.[8]

Transduction

The first step leading to the sensation of pain is stimulation of specialized nerve

fiber receptors known as *nociceptors*. These high-threshold receptors are found in both somatic and visceral structures and help to discriminate between noxious and innocuous stimuli. Nociceptors are activated and subsequently sensitized by mechanical, thermal, and chemical stimuli.[8] The underlying mechanism of these noxious stimuli (which in and of themselves may sensitize/stimulate the receptor) may be the release/activation of numerous cytokines and chemokines that sensitize and/or activate the nociceptors (**Fig. 77-1**).[8–10]

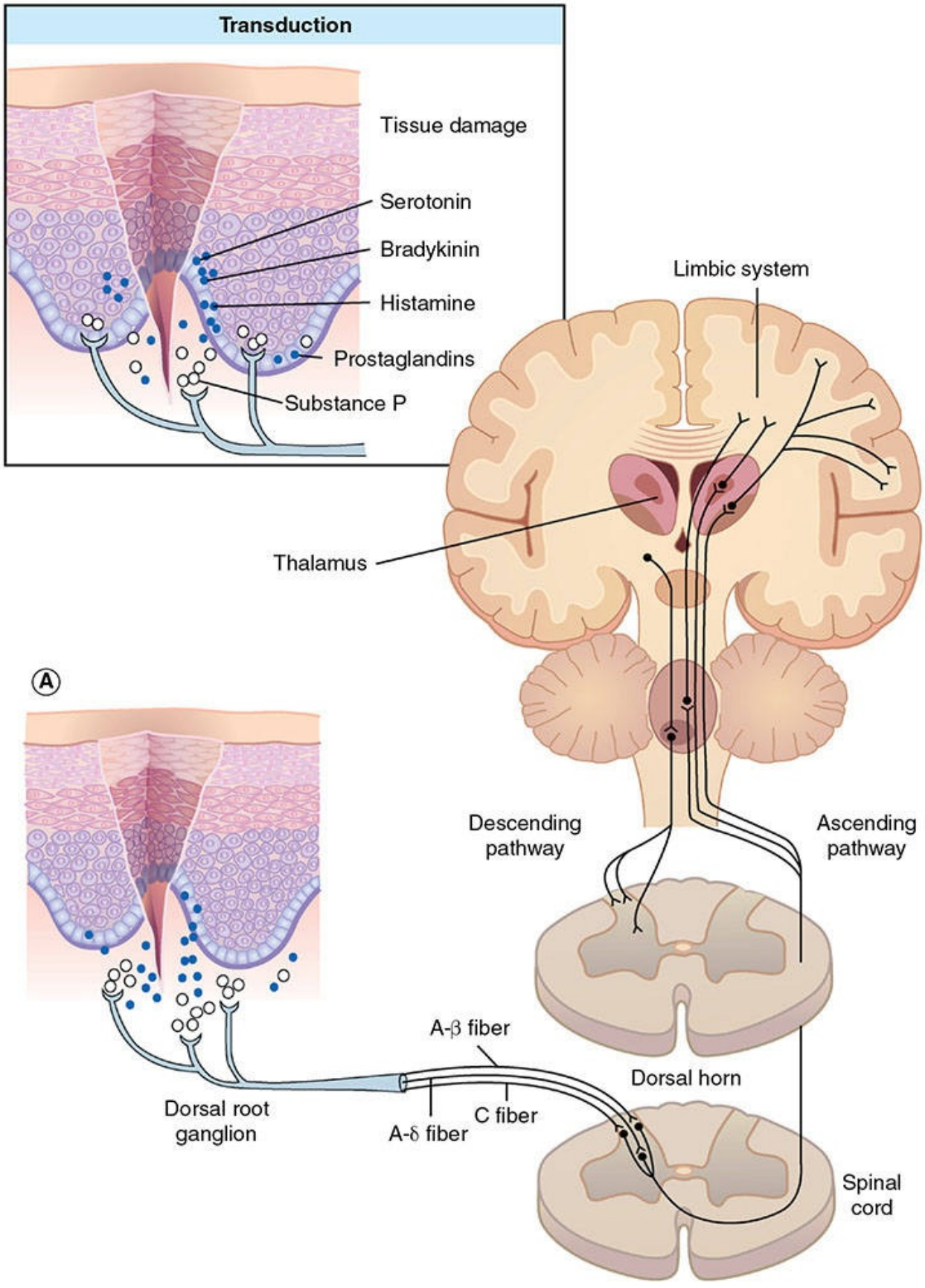

Transduction
Tissue damage
Serotonin
Bradykinin
Histamine
Prostaglandins
Substance P
Limbic system
Thalamus
A
Descending pathway
Ascending pathway
A-β fiber
Dorsal horn
Dorsal root ganglion
C fiber
A-δ fiber
Spinal cord

FIGURE 77-1 Schematic representation of nociceptive pain. (*Used with permission from Pasero C, Portenoy R. Neurophysiology of pain and analgesia and the pathophysiology of neuropathic pain. In: McCaffery M, Pasero C, eds. Pain Assessment and Pharmacologic Management. St. Louis: Mosby, 2011:4–5, Figure 1–2. Copyright © 2011 from Elsevier.*).

Conduction

Nociceptor activation leads to the conversion of a chemical signal into an electrical signal. This requires voltage-gated sodium channels, which produce the generation of action potentials that are conducted along primary afferent A-δ and C-polymodal nerve fibers to the dorsal horn of the spinal cord.[11,12] Stimulation of large-diameter, sparsely myelinated A-δ fibers evokes sharp, well-localized pain, whereas stimulation of unmyelinated, small-diameter C fibers produces aching, poorly localized pain.[13]

Transmission

These afferent, nociceptive pain fibers synapse in various layers (laminae) of the spinal cord's dorsal horn and convert the electrical signal back into a chemical signal by releasing excitatory neurotransmitters, such as glutamate and substance P. The N-type voltage-gated calcium channels regulate the release of these excitatory neurotransmitters. The complex array of events that influence pain can be explained in part by the interactions between neuroreceptors and neurotransmitters that take place in this synapse. Pain signals reach the brain through a host of ascending spinal cord pathways, which include the spinothalamic tract.[13] Other sensory information is also carried along these pathways. Thus, pain is influenced by many factors supplemental to nociception, which prevents simple schematic representation. The thalamus acts as a relay station within the brain, as these pathways ascend and pass the impulses to higher cortical structures where pain can be processed further.[13]

Modulation

The brain and spinal cord modulate pain through a number of intricate processes. Pain transmission may be facilitated by neurotransmitters such as glutamate or substance P to make the signals stronger and the pain more intense. Alternatively, the signal can be attenuated/inhibited by descending pathways that

consist of endogenous opioids (eg, enkephalins and β-endorphins), γ-aminobutyric acid (GABA), norepinephrine, or serotonin.[14,15] Like exogenous opioids, endogenous peptides bind to opioid receptor sites and modulate the transmission of pain impulses.[14] Other receptor types also can influence this system, and blockade of *N*-methyl-D-aspartate (NMDA) receptors may increase the mu (μ)-receptors' responsiveness to opiates.[16]

Perception

The complex interplay between ascending excitatory and descending inhibitory pathways is thought to culminate in a conscious experience that takes place in higher cortical structures. While not well understood, we do know cognitive and behavioral functions can modify pain. Thus, relaxation, distraction, meditation, and guided mental imagery may strongly influence pain perception and decrease pain.[17,18] In contrast, conditions such as depression or anxiety often worsen pain.[19]

Immune System Impact on Pain Signaling

Over the past two decades research has demonstrated that a two-way communication exists between neurons and immune cells within the central nervous system (CNS), especially astrocytes and microglia. Microglia are the equivalent of a macrophage within the CNS.[16,20] Their activation within the CNS in response to nerve injury (both in the periphery and CNS) leads to a complex cascade of events that appears to be responsible for the ongoing pain seen in neuropathic pain conditions. Activated microglia may also play a role in the development of opioid tolerance and opioid-induced hyperalgesia. Evidence is emerging that the interface between immune cells and neurons in the CNS plays a significant role in the maintenance of chronic pain and may offer attractive new potential therapeutic targets.[21]

Maladaptive (Pathologic) Pain

1 Pathophysiologic pain is distinctly different from nociceptive pain, in that it becomes disengaged from noxious stimuli or healing and often is described in terms of chronic pain. This type of pain is a result of damage or abnormal functioning of the peripheral nervous system (PNS) and/or CNS.[16] Maladaptive pain can be neuropathic pain, in which there is ongoing peripheral nerve injury

(eg, postherpetic neuralgia, painful diabetic neuropathy, or chemotherapy-induced neuropathy), or in the CNS (eg, following an ischemic stroke or with multiple sclerosis). Maladaptive pain may also be centralized, where no nerve injury or inflammation exists, but a centrally mediated disturbance in pain processing within the CNS leads to pain hypersensitivity and subsequently spontaneous pain. Classic examples are fibromyalgia, irritable bowel syndrome, temporomandibular joint disorder, and myofascial pain syndrome. Chronic pain states are often mixed with all three mechanisms (nociceptive, neuropathic, and centralized) simultaneously.[22] These pain syndromes are frequently challenging to diagnose and difficult to treat. In addition, the pain reported is often not commensurate with physical exam findings or imaging results, which may result in undertreatment and ultimately inadequate pain relief.

The mechanism responsible for pain of this nature may be the nervous system's dynamic nature. Nerve damage or certain disease states may cause both peripheral (eg, alteration in nociceptive nerve fiber sensitivity, alteration of sodium channels, collateral sprouting of nerve fibers) and central (eg, hyperexcitability of central neurons or central sensitization, NMDA-glutamate receptor activation, central disinhibition) changes in neurotransmission leading to increased pain.[14,16] Pain circuits may rewire themselves both anatomically and biochemically (often referred to as neural plasticity), and this produces a mismatch between pain stimulation and inhibition, potentially resulting in a progressive increase in the discharge of dorsal horn neurons.[23] The end result is chronic pain, where patients may present with episodic or continuous pain transmission (often described as burning, tingling, shock-like, or shooting), exaggerated painful response to normally noxious stimuli (hyperalgesia), and/or painful response to normally non-noxious stimuli (allodynia).[13,24,25] This change over time may help explain why this type of pain often manifests long after the injury or when no actual injury is identified.

CLASSIFICATION OF PAIN

1 2 3 It is helpful in guiding assessment and treatment of pain to classify or subdivide the presenting symptoms into types of pain. There are numerous ways of classifying pain, such as by type of pain (eg, nociceptive, neuropathic, inflammatory), by pain intensity (eg, mild, moderate, or severe), or most commonly by duration of pain (eg, acute, subacute, or chronic pain).

Acute Pain

2 3 Acute pain is a beneficial physiologic process, serving its adaptive purpose by warning individuals of disease states and potentially harmful situations. Unfortunately, severe, unremitting, under-treated acute pain, when it outlives its biologic usefulness, can produce many deleterious effects. Aside from unnecessary suffering, poorly treated acute pain has also been shown to increase one's risk for the development of chronic pain syndromes.[26] Acute pain is typically short in duration, lasting less than 30 days. It is often due to an identifiable cause and is usually nociceptive in nature with common causes including surgery, acute illness, trauma, labor, medical procedures, and cancer or cancer treatment.[27]

Chronic Pain

5 Under normal conditions, acute pain subsides quickly as the healing process decreases the pain-producing stimuli; however, in some instances, pain persists for months to years, leading to a chronic pathologic pain state with features quite different from those of acute pain (**Table 77-1**).[27,28] In many cases the exact etiology of pain may not be identifiable; therefore, chronic pain can be classified as either being associated with cancer (cancer pain) or from noncancer etiologies (chronic noncancer pain). Chronic noncancer pain is often a result of changes to nerve function and transmission, thus making treatment more challenging.[29]

TABLE 77-1 Characteristics of Acute and Chronic Pain

Characteristic	Acute Pain	Chronic Pain
Relief of pain	Highly desirable	Highly desirable
Dependence and tolerance to medication	Unusual	Common
Psychological component	Usually not present	Often a major problem
Organic cause	Common	May not be present
Environmental/family issues	Small	Significant
Insomnia	Unusual	Common component
Treatment goal	Cure	Functionality
Depression	Uncommon	Common

Data from References 27 and 33.

Cancer Pain

1 2 4 Pain associated with potentially life-threatening conditions is often called malignant pain or in the case of cancer, cancer pain.[30] This type of pain includes both chronic and acute (eg, breakthrough pain) components and often has multiple etiologies. This pain may be caused by the disease itself (eg, tumor invasion, organ obstruction), associated with treatment (eg, chemotherapy, radiation, and surgical incisions), or as a result of diagnostic procedures (eg, biopsy).[30] Breakthrough cancer pain may be *idiopathic* (no known precipitating factors), *incident* (due to a predictable cause), or *end of dose failure* (predictable worsening of pain at the end of an analgesic's pharmacodynamic efficacy).[31] Regardless of duration of pain, or suspected underlying etiology, a standardized approach to evaluation of a pain complaint is imperative. Cancer pain crises, frequently considered an acute pain overlaying an ongoing chronic pain, should be considered a medical emergency.

CLINICAL PRESENTATION

2 4 A patient-oriented approach is essential, and symptom assessment methods for pain should not differ from those used in other medical conditions.[32] Therefore, a comprehensive history and physical examination is imperative to evaluate underlying diseases and possible other contributing factors.[27] This

includes asking if the patient has pain and identifying the source of pain when possible; however, the absence of a discreet etiology should not preclude appropriate treatment.[27] A baseline characterization of pain should be obtained using a symptom assessment mnemonic (eg, OLDCARTS or SOCRATES).[33] Ongoing assessment should occur using a consistent and validated method (ie, Wong Baker Faces Scale, Brief Pain Inventory, Numeric Rating Scale, or the Pain-Enjoyment-General Activity Scale).[34]

CLINICAL PRESENTATION

Acute and Chronic Pain

Acute Pain

General

- Look for obvious distress (eg, trauma). In infants, presentation may include changes in feeding habits, increased fussiness, or being inconsolable. Those with dementia may exhibit changes in eating habits, increased agitation, or calling out. Attention also must be given to mental/emotional factors that alter the pain threshold. Anxiety, depression, fatigue, anger, and fear are noted to lower this threshold, whereas rest, mood elevation, sympathy, distraction, and understanding raise the pain threshold symptoms.
- Can be described as sharp, dull, shock-like, tingling, shooting, radiating, fluctuating in intensity, and varying in location (these occur in a timely relationship with an obvious noxious stimuli).

Signs

- Hypertension, tachycardia, diaphoresis, mydriasis, and pallor, but these signs are *not diagnostic*.
- In some cases there are no obvious physical signs.
- Comorbid conditions usually not present.
- Outcome of treatment generally predictable.

Laboratory Tests

- Pain is always subjective.

- There are no specific laboratory tests for pain.
- Pain is best diagnosed based on patient description and history.

Chronic Pain

General

- Can appear to have no noticeable suffering. Attention also must be given to mental/emotional factors that alter the pain threshold. Anxiety, depression, fatigue, anger, and fear are noted to lower this threshold, whereas rest, mood elevation, sympathy, distraction, and understanding raise the pain threshold.

Symptoms

- Can be described as sharp, dull, shock-like, tingling, shooting, radiating, fluctuating in intensity, and varying in location (these often occur *without* a temporal relationship with an obvious noxious stimuli).
- Over time, the pain stimulus may cause symptoms that completely change (eg, sharp to dull, obvious to vague).

Signs

- Hypertension, tachycardia, diaphoresis, mydriasis, and pallor are seldom present.
- In most cases there are *no* obvious signs.
- Comorbid conditions are often present (eg, insomnia, depression, and anxiety).
- Outcome of treatment is often unpredictable.

Laboratory Tests

- Pain is always subjective.
- Pain is best diagnosed based on patient description and history.
- There are *no* specific laboratory tests for pain; however, history and/or diagnostic proof of past trauma (eg, computed tomography) may be helpful in diagnosing etiology. General labs that may be considered include vitamin D, thyroid stimulating hormone (generalized or widespread pain), and B12 (neuropathic pain).

Data from Reference 27.

TREATMENT

Achieving desired pain management outcomes includes both nonpharmacologic and pharmacologic strategies.

Desired Outcomes

4 5 The primary goal of pain treatment depends on the type of pain present and should be tailored to individual patients and circumstances (see “Patient Care Process” section). For example, a desired outcome in the acute postoperative setting may be to achieve a level of pain relief that allows the patient to attain certain functional goals, such as deep breathing or participation in physical therapy. In comparison, the goals in chronic noncancer pain may be to improve or maintain the patient’s level of functioning, decrease pain perception, reduce the use of medications when possible, and improve the patient’s quality of life. Treatment goals for cancer pain or other forms of malignant pain may include adequate pain relief such that a patient can tolerate diagnostic and therapeutic manipulation and permit the patient to function at a level that will allow freedom of movement and choice while minimizing adverse effects of chosen analgesics.[31]

Nonpharmacologic Therapy

2 3 5 The use of nonpharmacologic therapies in the management of pain should always be considered first-line therapy, either alone or in combination with appropriate analgesics. It is important to target all aspects of the biopsychosocial model when treating pain. Collaborating with other professions who are trained to provide nonpharmacologic approaches is essential. In addition, focusing on active therapies over passive therapies is encouraged. The evidence basis for many of the nonpharmacologic approaches is in evolution and the results of these approaches can have varied efficacy based on the skill of the individual applying the modality, as well as the type of pain being treated.

A variety of nonpharmacologic approaches are available. These include physical therapy, manipulation, formal exercise programs, weight loss, and diet

changes (Table 77-2).[35–37] There are a variety of complementary and integrative approaches with evidence in pain treatment and include acupuncture, Tai chi, yoga, mindfulness, meditation, relaxation, and biofeedback.[38]

TABLE 77-2 Nonpharmacologic Approaches to the Treatment of Pain

- Exercise
- Physical therapy
- Diet
  - Anti-inflammatory
  - Elimination
- Weight loss
- Electroanalgesia: application of electrical stimulation to various areas that range from noninvasive to highly invasive
  - Noninvasive: transcutaneous electrical nerve stimulation (TENS)
  - Minimally invasive: percutaneous electrical nerve stimulation (PENS)
  - Highly invasive: spinal cord stimulation (SCS)
- Interventional approaches

Data from Reference 37.

5 Simple interventions (eg, education or introductory information about expected discomfort or pain after certain procedures) reduce patient distress and help reduce post-procedure pain.[39] Psychological techniques (eg, cognitive-behavioral therapy, relaxation training, mindfulness-based stress reduction) have proven effective in reducing pain-related disability and improving global functioning in patients with numerous types of chronic pain.[40]

Electroanalgesia involves the application of electrical stimulation to various locations and range from noninvasive (eg, transcutaneous or percutaneous electrical nerve stimulation) to highly invasive (implanted spinal cord stimulation).[37,41] Transcutaneous electrical nerve stimulation (TENS) may reduce pain by enhancing natural descending inhibitory pathways within the central nervous system. Evidence to date suggests that the frequency of the electrical stimulation delivered, presence or absence of systemic analgesics, and the type of underlying pain may affect the overall efficacy of this treatment.[42] Complementary and integrative approaches to the treatment of chronic pain are outlined in Table 77-3.[43–45]

TABLE 77-3 Complementary and Integrative Approaches for Chronic Pain

Intervention	Description	Evidence	Safety
Tai Chi	Low-impact Mind body exercise Started in China Slow mindful movement with attention to breathing and relaxation	Osteoarthritis Chronic low back pain (CLBP) Fibromyalgia	Minor musculoskeletal aches and pains
Yoga	From India Blend of meditation, breathing, and physical postures	Osteoarthritis Rheumatoid Arthritis Kyphosis Fibromyalgia Low back pain (LBP) Neck pain	Similar to musculoskeletal pain associated with Physical Therapy (PT) Discuss with provider/yoga instructor if glaucoma or osteoporosis
Acupuncture	Stimulation of certain points of the body typically with the insertion of needles into the skin East Asian	*Acute:* Post-surgical pain (reduces opioid dose) Migraine Acute/subacute LBP Ankle sprain *Chronic:* CLBP Osteoarthritis (knee, hip, general) Temporomandibular Disorder (TMD) Headache Migraine Neck pain Shoulder pain Peripheral neuropathy (diabetic, HIV, Bell's palsy, Carpal Tunnel Syndrome (CTS))	Low risk for adverse effects Minor: itching, relaxation, tired Rare: pneumothorax, infections (associated with poor training)
Massage	Soft tissue manipulation	*Acute:* Postoperative pain *Chronic:* CLBP Neck pain Knee osteoarthritis Heel pain Epicondylitis	Low risk for adverse effects
Mindfulness, meditation, and relaxation	A variety of mind-body practices free of judgment Examples: mindfulness-based stress reduction (MBSR), cognitive behavioral therapy (CBT), pain-coping skills training (PCST), diaphragmatic breathing, progressive muscle relaxation, hypnosis, acceptance and commitment therapy, music therapy, guided imagery	*Acute:* Burn patients (music therapy) Acute/procedural pain (music therapy, hypnosis, guided imagery) *Chronic:* LBP (MBSR, CBT, Chronic pain (music therapy, CBT, guided imagery, ACT, progressive relaxation) Headache (mindfulness and relaxation, MBSR) Fibromyalgia (relaxation, guided imagery) Knee pain (PCST) Osteoarthritis (PCST, guided imagery) Rheumatoid arthritis (PCST, guided imagery) Diabetic neuropathy (mindfulness/meditation) TMD (relaxation)	Rare adverse reactions (psychiatric patients, epilepsy, hx of trauma)
Biofeedback	Mind-body practice in which patients are connected to a device that measures their bodily functions (BP, HR, RR) and use the information to alter thoughts and behaviors	Tension/migraine headache CLBP Fibromyalgia Shoulder pain	No to low risk of adverse reactions
Manipulation	Treatment of spine and other joints	Osteoarthritis (hip, knee, ankle, plantar fasciitis, ankle, shoulder, epicondylitis) LBP CTS TMD	Musculoskeletal aches and pains Uncommon serious adverse reactions (cervical artery dissection, stroke, neck injury)

Data from References 37, 38, 43, 44 and 45.

Pharmacologic Therapy

Appropriate Patient Selection

6 7 8 9 Pharmacologic treatment is often considered the cornerstone of pain management. However, proper patient selection using a benefit-to-risk assessment is crucial when determining the optimal therapeutic plan for an individual patient. The potential for benefit with each pharmacologic option, as well as the risk of adverse effects, must be assessed.

Patient Selection Considerations in Acute or Cancer Pain

9 10 11 10 The World Health Organization (WHO) recommends a three-step ladder approach using the nonopioids as initial treatment and escalating treatment to either “weak” or “strong” opioids based on pain intensity ratings (ie, mild, moderate, or severe).[46] However, patient-specific factors, for example, renal or liver dysfunction that would potentially limit treatment with many nonopioid therapies, may lead clinicians to initiate therapy with an opioid to optimize pain relief while minimizing adverse effects. Acute cancer pain crises should be considered a medical emergency. For this we recommend using the approach of the National Comprehensive Cancer Network guidelines on Adult Cancer Pain (**Fig. 77-2**).[31] Inadequate analgesia, opioid-related adverse effects, or loss of an administration route may require rotation to another opioid analgesic. The process for equianalgesic opioid rotation is provided in **Table 77-4**.[47]

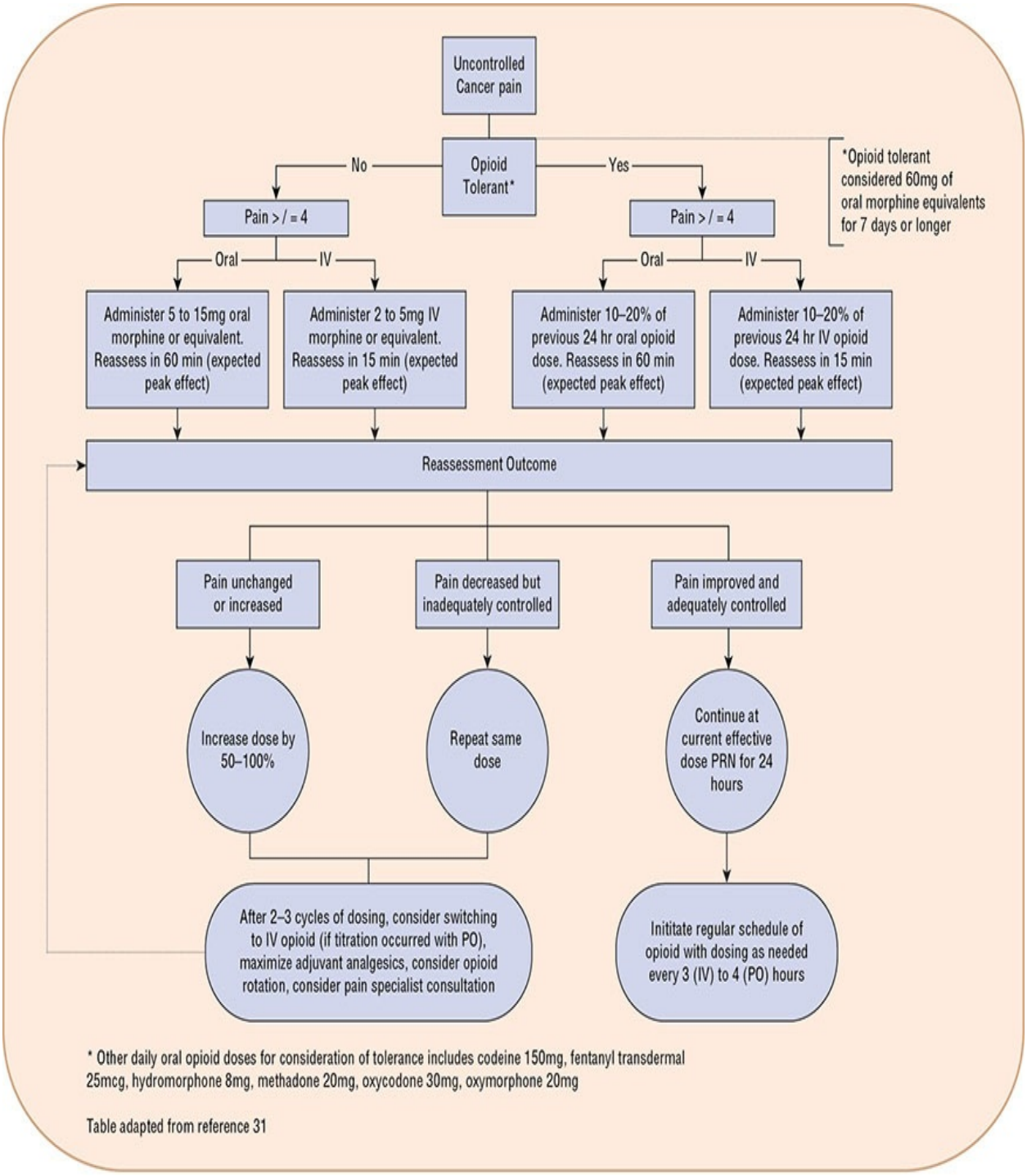


FIGURE 77-2 Algorithm for cancer pain crisis. (*Adapted from National Comprehensive Cancer Center Adult Pain Guidelines.*)

TABLE 77-4 Steps for Equianalgesic Opioid Calculation

Step 1. Use the equianalgesic dose chart in Table 77-11 for a first estimate of the dose of the new drug that is equianalgesic to the old drug.

Step 2. Record the total dose of each opioid given during the past 24 hours. If both parenteral and oral doses of the same opioid were given, calculate a separate total for each.

Step 3. Divide each 24-hour total by the equianalgesic dose in Table 77-11 for that opioid and route, converting the dose into equianalgesic dose units. Add the equianalgesic dose units for all drugs and routes (ie, some clinicians prefer to convert all opioid doses to "oral morphine equivalents" prior to calculating new target dose).

Step 4. Estimate the dose of the new drug by multiplying the sum obtained in Step 3 by the equianalgesic dose for the new drug and route (see example below*).

Step 5. Modify the initial estimate based on the clinical situation and the specific drugs involved. Factors that enter into this process include the following:

a. Effective analgesia, intolerable adverse effects: Calculate the dose of the new opioid as outlined in Steps 1-4. Reduce target dose by 25% to 50% to account for lack of cross-tolerance between various opioids.

b. Ineffective analgesia, no intolerable adverse effects: Calculate the dose of the new opioid as outlined in Steps 1-4. Reduction in target dose outlined in (a) may be disregarded depending on clinical situation and patient-specific variables. Those with severe pain on regularly scheduled opioids for >5 days may have their dose increased by 30% to 50% or an increase equal to the use of supplemental PRN medication per day averaged over the previous 2 to 3 days. Consider more conservative increases (ie, 10% to 20%) in the first few days of therapy in those who have less severe pain or who are frail. Dose increases are safest after steady state has been approached (typically 5 to 6 half-lives).

Step 6. Should PRN dosing of immediate release drug be necessary for break-through pain, provide 10% to 15% of total daily dose of new opioid every 3 to 4 hours depending on individual opioid's duration of analgesia.

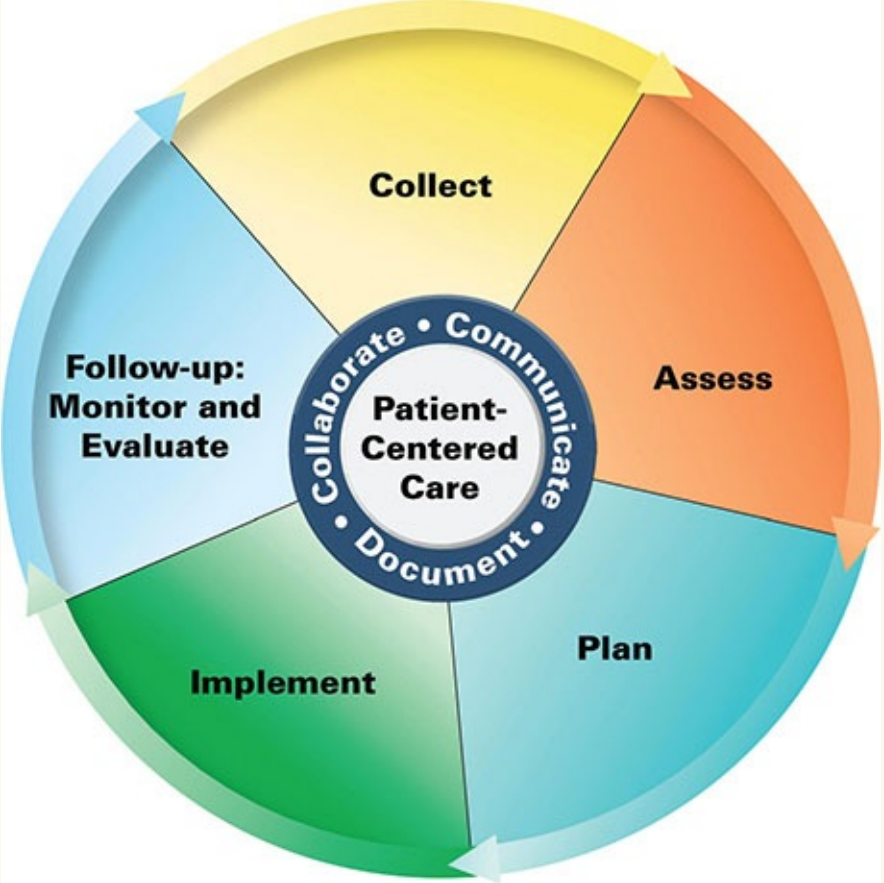
Step 7. Reassess patient frequently following opioid rotation (48 to 72 hours following dose change).

Data from Reference 47.

Patient Selection Considerations in Chronic Noncancer Pain

[3] [4] [5] [7] [8] [9] [10] [11] In all cases of chronic noncancer pain, an integrated systematic approach with a strong emphasis on patient–clinician relationships is essential. Patients and clinicians must realize that optimal

treatment may take months or even years to achieve. Opioids are often a treatment of last resort in chronic noncancer pain and initiated as a time-limited trial to see if there is an improvement in the patient's function while overall tolerability is being assessed. Although long-term opioid therapy can be effective for individual patients in carefully considered situations, limited data exists to support such practice.[36,48] Chronic opioid therapy in this setting requires careful patient selection with judicious attention to risk factors (eg, prior substance abuse disorder history, family history of substance abuse, younger age, male gender, and certain co-occurring mental health conditions) associated with misuse and abuse of these agents to evaluate the balance between potential benefit of therapy and the potential risks in the individual patient.



Patient Care Process for Pain Management

Collect

- Patient-specific characteristics (eg, age, gender, pregnancy, ethnicity)

- Pain and symptom-specific history (eg, onset, location, duration, characteristics, aggravating factors, alleviating factors, timing, and severity)
- Patient history including current and past medications, nonpharmacologic trials, allergies or medication intolerance, and pertinent social history (eg, tobacco, alcohol, or recreational drug use)
- Family history focusing on symptoms (ie, Rheumatoid arthritis) and social behavior (ie, alcoholism, recreational drug use)
- Objective data including vitals, pertinent labs, targeted physical exam, and drug screen results

Assess

- Presence of co-occurring mental health conditions (ie, depression, anxiety, or bipolar) which may confound treatment decisions
- Aberrant drug-taking behaviors as evidenced by prescription drug monitoring programs (PDMP), urine drug screen results, and validated risk screening tools
- Relative or absolute contraindications to the use of opioids, acetaminophen, antidepressants, anticonvulsants, nonsteroidal anti-inflammatory drugs (NSAIDs), or skeletal muscle relaxants
- Chronicity of pain symptom (eg, acute or chronic), likely etiology (eg, neuropathic, musculoskeletal, or visceral), and severity

Plan*

- Patient and symptom-specific lifestyle modification (eg, weight loss, smoking cessation, self-pacing, and pain-trigger avoidance; see Table 77-2)
- Nonpharmacologic treatment modalities (see Table 77-3)
- Drug therapy regimen including dose, route, frequency, and duration (see Table 77-4)
- Monitoring drug therapy regimen including efficacy (analgesic and functional improvement), toxicity, misuse, and ongoing necessity using tools such as urine drug screening, PDMP, and risk assessment tools (see Table 77-14)
- Patient education on safe use, storage, disposal, and risk mitigation following formal Risk Evaluation and Mitigation Strategies when available

(see Table 77-5)

Implement*

- Educate patient and/or caregiver regarding all elements of disease process and treatment plan, ensuring patient and/or caregiver understanding
- Informed consent, including pain or treatment agreements when necessary
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Attainment of treatment goals (eg, improved activity, improved sleep, improved work attendance)
- Presence of adverse effects or aberrant drug-taking behaviors
- Completion of validated risk assessment tools
- Frequent review of PDMP
- Patient adherence to all facets of treatment plan, including nonpharmacologic modalities

**Collaborate with patient, caregivers, and other healthcare professionals.*

Risk Mitigation Strategies

10 11 In addition to identifying and managing risk prior to initiation (eg, misuse, abuse, or respiratory depression), specific strategies should be employed once treatment with an opioid analgesic has been initiated.[36,49] Opioid risk mitigation consists of judicious dose monitoring, regular and random urine drug monitoring, patient informed consent via treatment agreements, pill counts, and frequent review of prescription drug monitoring programs, to name a few.[50] The Centers for Disease Control and Prevention (CDC) have published guidelines to assist clinicians in balancing harms versus benefit of long-term opioid therapy and are summarized in **Table 77-5**.[51] Opioid/pain stewardship refers to opioid risk mitigation on a patient panel or system level and aims to ensure safe and effective use of these agents.[7] Harm reduction, including the co-prescribing of opioid antagonists, is discussed in-depth within Chapter 82 “Substance-Related Disorders: Overview and Depressants, Stimulants, and Hallucinogens.”

TABLE 77-5 Key Recommendations of the Centers for Disease Control and

Prevention Guideline for Prescribing Opioids for Chronic Pain

1. Nonpharmacologic and nonopioid modalities are preferred.
2. If opioid analgesia is warranted, establish realistic treatment goals.
3. Discuss the known risks and realistic benefits of opioid analgesics prior to initiation.
4. Immediate-release opioids are preferred over CR/LA opioid formulations.
5. Use the lowest effective dose of opioid possible. Use caution at any dosage, and carefully reassess evidence of benefit versus risk when exceeding ≥50 MME/day and avoid increasing dose ≥90 MME/day without careful justification.
6. Opioid analgesia should be used for the shortest duration possible. In most cases, 3 days is sufficient for acute pain. More than 7 days will rarely be required for most acute pain indications.
7. Clinicians should regularly evaluate the benefits and harms of ongoing opioid analgesia within 1 to 4 weeks of initiation and at least every 3 months when ongoing opioid therapy is required. Consider taper and discontinuation when harm risk outweighs benefit potential.
8. Careful evaluation of opioid overdose risk should be assessed frequently, and naloxone co-prescribed at opioid doses of ≥50 MME/day or when patients are exposed to concurrent opioid analgesia and benzodiazepines.
9. Prescription drug monitoring programs should be reviewed at opioid initiation and periodically, ranging from every prescription to at least every 3 months.
10. Clinicians should use urine drug screening prior to initiating opioid therapy and periodically when ongoing therapy is warranted.
11. Concurrent prescribing of opioid analgesics and benzodiazepines should be avoided when possible.
12. When Opioid Use Disorder is recognized or suspected, clinicians should offer evidence-based treatment such as medication-assisted therapy (ie, methadone or buprenorphine/naloxone) in combination with behavioral therapies.

MME = morphine milligram equivalent, CR = controlled release, LA = long acting

Data from Reference 36.

Co-Analgesics

5 6 7 Co-analgesics represent a diverse group of pharmacologic agents with individual characteristics that make them useful in the management of pain, but these agents typically are not classified as analgesics. Examples of co-analgesics include antidepressants and anticonvulsants. Chronic pain that has a neuropathic component (eg, diabetic neuropathy) often requires co-analgesic therapy. Anticonvulsants (eg, gabapentin, pregabalin, which may decrease

neuronal excitability), tricyclic antidepressants and serotonin and norepinephrine reuptake inhibitor antidepressants (eg, nortriptyline, duloxetine, venlafaxine—which block the reuptake of serotonin and norepinephrine, thus enhancing pain inhibition), and topically applied local anesthetics (which decrease nerve stimulation) all have demonstrated efficacy in managing various chronic pain conditions.[52]

Nonopioid Analgesics

Acetaminophen and Nonsteroidal Anti-inflammatory Drugs

5 6 7 Analgesics should be initiated with the most effective agent having the fewest potential adverse effects. Acetaminophen and NSAIDs are often preferred first-line therapies in the treatment of mild-to-moderate pain, although the efficacy of acetaminophen has recently been called into question (**Table 77-6**).[53,54] The exact mechanism of acetaminophen is not completely understood but likely involves central prostaglandin modulation.[55] The NSAIDs inhibit formation of varying prostaglandins produced in response to noxious stimuli, thereby decreasing neuronal pain transmission received by the CNS.[38] While acetaminophen is still considered a first-line therapy for some mild pain conditions, in some pain-related disease states, such as osteoarthritis, NSAIDs, either oral or topical, may be preferred.[56,57] In addition, NSAIDs may be useful in the management of cancer-related bone pain and for short-term relief in the management of chronic low back pain.[58,59]

TABLE 77-6 Nonopioid Analgesics

Class and Generic Name (Brand Name)	Approximate Half-Life (h)	Usual Dosage Range (mg)	Maximal Dose (mg/day)
Salicylates			
Acetylsalicylic acid[1] –aspirin (various)	0.25	325-1,000 every 4-6 hours	4,000
Choline and magnesium trisalicylate (various)	9-17	1,000-1,500 every 12 hours 750 every 8 hours (elderly)	3,000
Diflunisal (Dolobid, various)	8-12	500-1,000 initial 250–500 every 8-12 hours	1,500
Salsalate (various)	1	1,000 every 12 hours or 500 every 6 hours	3,000
***Para*-aminophenol**			
Acetaminophen[1] (Oral: Tylenol, various; Parenteral: Ofirmev)	2-3	325-1,000 every 4-6 hours	4,000[2] Dosing for peds lower based on weight
Fenamates			
Meclofenamate (various)	0.8–3.3	50–100 every 4–6 hours	400
Mefenamic acid (Ponstel)	2	Initial 500 250 every 6 hours (max. 7 days)	1,000[3]
Pyranocarboxylic acid			
Etodolac (various) (immediate release)	7.3	200–400 every 6–8 hours	1,000 1,200 with extended-release product
Acetic acid			
Diclofenac potassium (Cataflam, various, Flector [patch] Voltaren Gel, Pennsaid [solution])	1.9	In some patients, initial 100, 50 three times per day Patch available: to be applied twice daily to painful area (intact skin only), Gel and solution dosing joint specific	150[4]
Propionic acids			
Ibuprofen[1] (Motrin, Caldolor, various)	2–2.5	200-400 every 4-6 hours Injectable, 400–800 every 6 hours (infused over 30 min)	3,200[5] 2,400[5] 1,200[6]
Fenoprofen (Nalfon, various)	3	200 every 4-6 hours	3,200
Ketoprofen (various)	2	25-50 every 6-8 hours	300 200 with extended-release product
Naproxen (Naprosyn, Anaprox, various)	12–17	500 initial 500 every 12 hours or 250 every 6-8 hours	1,000[3]
Naproxen sodium[1] (Aleve, various, combined with esomeprazole [Vimovo])	12–17	In some patients, 440 initial[6] 220 every 8-12 hours[6]	660[6]
Pyrrolizine carboxylic acid			
Ketorolac–parenteral (Toradol, various)	5–6	30[7]–60 (single IM dose only) 15[7]–30 (single IV dose only) 10[7]–30 every 6 h (IV dose) (max. 5 days)	30[7]–60 15[7]–30 60[7]–120
Ketorolac—oral, indicated for continuation with parenteral only (various)	5–6	10 every 4-6 h (max. 5 days, which includes parenteral doses)	40
Ketorolac—nasal spray, indicated for acute, moderate to moderately severe pain		In non-elderly patients, initial oral dose of 20 1 spray (15.75 mg) in each nostril every 6-8 hours in adults <65 years and weight ≥50 kg	126
Pyrazols			
Celecoxib (Celebrex)	11	Initial 400 followed by another 200 on first day, then 200 twice daily (note some recommend maintenance doses of 200 mg/day due to cardiovascular concerns)	400

[1]Available both as an over-the-counter preparation and as a prescription drug.

[2]Food and Drug Administration maximum dose. OTC maximum dose 3,000 mg daily. Lower with weight-based dosing in pediatric patients.

[3]Up to 1,250 mg on the first day.

[4]Up to 200 mg on the first day.

[5]Some individuals may respond better to 3,200 mg as opposed to 2,400 mg, although well-controlled trials show no better response; consider risk versus benefits when using 3,200 mg/day.

[6]Over-the-counter dose.

[7]Dose for elderly and those under 50 kg (110 lbs).

FDA, Food and Drug Administration; h, hours; IM, intramuscular; IV, intravenous; ND, no data.

Data from References 47 and 95.

6 7 8 Studies comparing the efficacy of individual NSAIDs have failed to identify greater efficacy of any NSAID compared to another. Therefore, the choice of a particular agent often depends on availability, cost, pharmacokinetics, pharmacologic characteristics, and the side-effect profile. Because of the large interpatient variability in response to individual NSAIDs, it is considered rational therapy to switch to another member of this class if there is inadequate response after a sufficient therapeutic trial of any single agent.[47] The duration of a sufficient trial has not been well defined; however, typically, an NSAID should be continued for a minimum of 1 month prior to evaluating the need to switch agents. Chronic use of NSAIDs may result in serious gastrointestinal (GI), renal, and cardiac toxicity. More recent data lessens the concerns of increased risk of cardiovascular events with celecoxib, a cyclooxygenase (COX)-2 selective NSAID, compared to other nonselective NSAIDs.[60,61] Topical NSAIDs may offer similar efficacy as oral NSAIDs with improved safety and tolerability in the treatment of small or superficial joint arthritis.[62,63] Appropriate patient selection for NSAID therapy is critical to ensure optimal benefit while minimizing potential adverse effects.

Anticonvulsants

6 7 8 The anticonvulsants frequently employed for pain are presented in **Table 77-7**.[64–71] Carbamazepine and oxcarbazepine block voltage-gated sodium channels and potentiate the effects of GABA and is considered the drug of choice for trigeminal neuralgia according to multiple guidelines.[52,65,72,73] The primary metabolic pathway for carbamazepine is CYP3A4. The active metabolite, carbamazepine 10,11-epoxide, auto-induces its own metabolism, making titration difficult. Carbamazepine is associated with many drug–drug interactions through induction of CYP3A4, CYP1A2, CYP2B6, CYP2C9, and CYP2C19. Common side effects during initiation include dizziness, drowsiness, unsteadiness, nausea, and vomiting and can be avoided with low starting doses. Serious dermatologic reactions can occur, including toxic epidermal necrolysis and Stevens–Johnson syndrome (SJS). The risk of dermatological adverse effects is higher in patients who come from Asian descent with an inherited variant, HLA-B*1502, so in at-risk ethnicities, patients should be tested for this allele before initiation of carbamazepine.[74] Rare cases of aplastic anemia and agranulocytosis are also associated with carbamazepine use so a CBC should be monitored during therapy. Hyponatremia is also reported, which requires regular

monitoring of sodium.[75] Cardiovascular effects include hyper/hypotension, congestive heart failure, edema, arrhythmias, atrioventricular block. Elevation in hepatic enzymes should be monitored periodically during treatment.[76]

TABLE 77-7 Co-analgesics: Anticonvulsants

Medication	Mechanism of Action	Role	Dosing	Notes
Carbamazepine and carbamazepine XR	Inhibits voltage-gated sodium channels, potentiate GABA	Trigeminal neuralgia Neuropathic pain	Initial dose: 100 mg PO BID Titrate dose by 100 mg PO BID Target dose: 300–900 mg/day Maximum dose: 1,200 mg/day	Significant drug–drug interactions Monitor CBC, LFTs, sodium level Recommended testing HLA-B†1502 in patients with Asian ancestry Therapeutic drug levels only indicated for high-dose therapy to avoid toxicity. No correlation between analgesia and serum drug concentration
Gabapentin	Inhibition α2δ subunit of the voltage-gated calcium channel leading to decreased release of excitatory neurotransmitters including glutamate, norepinephrine, and substance P	PHN† Neuropathic pain Perioperative pain	100-300 mg steps Increase every 3-5 days as tolerated by 100-300 mg increments	Median dose for response 1,600–2,400 mg/day Risk of misuse/abuse Requires renal dose adjustment
Gabapentin (Gralise)	Refer to gabapentin	PHN†	Take once daily with evening meal Day 1: 300 mg Day 2: 600 mg Day 3-6: 900 mg Days 7-10: 1,200 mg Days 11-14: 1,500 mg Day 15: 1,800 mg Maximum dose: 1,800 mg/day	Refer to gabapentin
Gabapentin enacarbil	Refer to gabapentin	PHN† Restless leg syndrome (RLS)†	Initial dose: 600 mg PO QAM × 3 days Titrate dose: 600 mg PO BID Maximum dose: 1,200 mg/day	Refer to gabapentin
Lamotrigine	Inhibits sodium channels	Neuropathic pain (4th line Canadian NP guidelines, specialist setting NICE guidelines)	Initial 25 mg PO daily Titrate q2weeks to 50 mg/day, 100 mg/day, and 200 mg/day Maximum dose: 400 mg/day	Stevens–Johnson syndrome
Oxcarbazepine	Inhibits sodium channels	Trigeminal neuralgia (EFNS) Neuropathic pain (specialist setting NICE guidelines)	Initial: 150 mg PO BID Titrate by 300 mg q3 days Target dose: 300–600 mg BID Max dose: 1,800 mg/day	Improved tolerability and less drug–drug interactions compared to CBZ
Oxcarbamazepine XR	Refer to oxcarbazepine	(See above under oxcarbamazepine)	Initial dose: 600 mg PO daily Titrate by 600 mg/day weekly Maximum: 2,400 mg/day	Refer to oxcarbazepine
Pregabalin	Refer to gabapentin	DPN† Fibromyalgia† Neuropathic pain associated with spinal cord injury† Neuropathic pain PHN† Perioperative pain	Initial dose: 150 mg/day in 2 or 3 divided doses Titrate dose by 300 mg/day at 1 week Maximum dose: varies by indication. Overall 600 mg/day	Refer to gabapentin
Pregabalin CR	Refer to gabapentin	DPN† PHN†	Initial dose: 165 mg daily Maximum dose: 330 mg/day (DPN) or 330–660 mg/day (PHN)	Refer to gabapentin
Topiramate and Topiramate XR	Inhibits voltage-gated sodium channels, AMPA/kainite subtype of glutamate receptor, and carbonic anhydrase; increases activity of GABA-A receptor	Alcohol use disorder Migraine prophylaxis Neuropathic pain (fourth-line Canadian NP guidelines, specialist setting NICE guidelines)	Initial dose: 25 mg PO daily × 1 week Titrate by 25-50 mg week Target dose: 50 mg PO BID (migraine ppx) or 200-400 mg/day neuropathic pain	Monitor serum bicarbonate and renal function Increase risk for kidney stones Weight loss Decreased sweating/hyperthermia Hyperammonemia

†FDA-approved indication.

All anticonvulsants associated with increased risk for suicidal thoughts and behaviors.

Data from References 95 and 64.

Oxcarbazepine is the keto derivative of carbamazepine and is metabolized to an active metabolite, 10-monohydroxy oxcarbazepine, which does not undergo Phase I metabolism in the liver. This is advantageous for oxcarbazepine with reduced drug–drug interactions and side effects compared to carbamazepine.[76] The most common side effects include dizziness, somnolence, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, headache, nystagmus, tremor, and abnormal gait. Other adverse effects include hyponatremia, angioedema or anaphylactic reactions, pancytopenia, agranulocytosis, and leukopenia.[75] Serious dermatological reactions (SJS, TEN) may also occur and may be associated with HLA-B*1502.[74] It is estimated that about 20% to 30% of those patients who are hypersensitive to carbamazepine will be hypersensitive to oxcarbazepine as well. In addition to its role in trigeminal neuralgia, the National Institute for Health and Care Excellence (NICE) guidelines list oxcarbazepine for the treatment of neuropathic pain in a specialist setting as fourth-line treatment.[52,73,77]

Gabapentinoids, including gabapentin and pregabalin, are common anticonvulsants used in the treatment of neuropathic pain. There are numerous formulations available with varying indications that may include diabetic peripheral neuropathy (DPN), postherpetic neuralgia (PHN), fibromyalgia, neuropathic pain associated with spinal cord injury (SCI), and restless legs syndrome (RLS). Based on several neuropathic pain treatment guidelines, gabapentinoids are considered first-line medications for the treatment of neuropathic pain.[64–66,73] Other roles for gabapentinoids include perioperative pain management as a part of a multimodal approach or “enhanced recovery after surgery” (ERAS) protocols. These agents, however, were not included in the ERAS Society guidelines due to inconclusive evidence.[78–85] In general, evidence has not supported the use of gabapentinoids for the prevention of chronic post-surgical pain.[86] There are negative findings for pregabalin in acute and chronic sciatica as well as gabapentin and pregabalin for nonspecific low back pain.[87,88]

Gabapentinoids do not, as their name may suggest, alter gamma-aminobutyric acid (GABA) binding, uptake, metabolism, or degradation though their pharmacology does lead to GABA-mimetic effects. Primary pharmacodynamic effects are due to inhibition of voltage-gated calcium channels specifically by binding to the presynaptic α2δ subunit. This results in decreased release of excitatory neurotransmitters glutamate, norepinephrine, and substance P.[71]

Common adverse effects, namely dizziness and sedation, can be mitigated with slow dose titration. Gabapentinoids may lead to peripheral edema and

weight gain and may be dose-limiting adverse effects. All anticonvulsants have been associated with increased risk for suicidal thoughts and behavior. Recently, there have been increasing reports of gabapentinoid misuse and abuse, which has resulted in some states classifying them as controlled substances.[89,90] Gabapentionoids are cleared renally and have recommended renal dose adjustments as well as supplemental doses after hemodialysis.[91]

Several neuropathic pain guidelines place lamotrigine as a fourth-line agent or medication for use in a specialist setting.[52,65,73] The mechanism of action of lamotrigine is not entirely known but thought to be related to inhibition of voltage-gated sodium channels. One of the main concerns with the use of lamotrigine is the possibility of life-threatening rash. To minimize the risk of a rash, the dose is titrated slowly (ie, every 2 weeks). If any signs of rash appear, lamotrigine should be discontinued immediately, although other fatal or life-threatening hypersensitivity reactions can occur as lamotrigine is also associated with blood dyscrasias and aseptic meningitis. More common adverse effects include dizziness, nausea, headache, insomnia, somnolence, fatigue, rhinitis, abdominal pain, diplopia, ataxia, blurred vision. Utilizing lamotrigine is further complicated by the potential for multiple drug–drug interactions.

For neuropathic pain, topiramate is listed as a fourth-line agent by the Canadian Pain Society guideline and for use in specialist settings by the NICE guidelines.[65,73] Topiramate is commonly used as a prophylactic medication for migraines and has data supporting its use in radicular low back pain.[92,93] It has four components to its proposed mechanism of action including inhibition of voltage-gated sodium channels, increased effects of $GABA_A$ receptors, blocking AMPA/kainate subtype of glutamate receptors, and inhibiting carbonic anhydrase enzyme. Topiramate has numerous warnings and precautions including secondary angle closure glaucoma, metabolic acidosis, hyperammonemia and encephalopathy, kidney stones, oligohidrosis, hypo/hyperthermia, and cognitive dysfunction. Renal dose adjustments are recommended with a creatinine clearance (CrCl) <70 mL/min (1.17 mL/s) and topiramate is removed via hemodialysis, so supplemental doses are needed. Adverse effects most associated with discontinuation of therapy in studies of migraine patients included paresthesia, fatigue, nausea, difficulty with concentration/attention, insomnia, anorexia, and dizziness. Dose-related side effects include paresthesia, fatigue, nausea, anorexia, dizziness, difficulty with memory, diarrhea, weight loss, concentration/attention problems, and somnolence.

Antidepressants

6 7 8 Select antidepressants have long been used for their anti-nociceptive effects (**Table 77-8**).[94–96] Most tricyclic antidepressants (TCAs) are FDA-approved for major depressive disorder (MDD) aside from clomipramine (obsessive compulsive disorder) and imipramine (MDD and childhood enuresis). In general, however, the TCAs are often used for the treatment of neuropathic pain. The Canadian Pain Society, the Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain, and the European Federation for Neurological Societies (EFNS) list TCAs as first-line options for neuropathic pain.[52,64,65] The NICE guidelines list amitriptyline as a first-line option for neuropathic pain.[73] Interestingly, the American Diabetes Association does not list TCAs as first-line because they are not FDA approved for this indication.[66] Other evidence-based uses of TCAs include low back pain, fibromyalgia, and migraine prophylaxis.[68]

TABLE 77-8 Co-analgesics: Antidepressants

Medication	Mechanism of Action (MOA)	Role	Dosing	Notes
Tricyclic antidepressants (TCA)				
Amitriptyline Desipramine Imipramine Nortriptyline	Inhibits reuptake serotonin and norepinephrine which in turn inhibits descending pain pathway Analgesic effects independent of antidepressant effects and lower doses needed for analgesic effects compared to MDD doses	Fibromyalgia Low back pain Migraine prophylaxis Neuropathic pain	Initial: 10–25 mg PO QHS Titrate by 10-25 mg q3-7 days Maximum: 150 mg	Secondary amines (desipramine, nortriptyline) less anticholinergic activity = less ADE Multiple cardiac ADE (including QTc prolongation, orthostatic hypotension, arrhythmias, tachycardia) Doses > 100 mg/day associated with sudden cardiac death Lowers seizure threshold
Serotonin norepinephrine reuptake inhibitors (SNRI)				
Duloxetine	Inhibits reuptake serotonin and norepinephrine which in turn inhibits descending pain pathway Analgesic effects independent of antidepressant effects	Chronic musculoskeletal pain (low back pain [LBP], osteoarthritis)† Diabetic peripheral neuropathy (DPN)† Fibromyalgia† Chemotherapy-induced neuropathic pain (CINP)	Initial: 30 mg PO daily × 1 week (2 weeks if elderly) Target dose: 60 mg PO daily Maximum dose: 120 mg/day though limited evidence for doses >60 mg providing additional benefit in pain	Avoid CrCl < 30 mL/min (0.50 mL/s) Avoid chronic liver disease or cirrhosis Hypertension Hyponatremia Increased risk of bleeding (GI and CNS)
Milnacipran	Inhibits reuptake serotonin and norepinephrine which in turn inhibits descending pain pathway Analgesic effects independent of antidepressant effects	Fibromyalgia†	Day 1: 12.5 mg PO daily Days 2-3: 12.5 mg PO BID Days 4-7 25 mg PO BID Then increase to 50 mg PO BID Target dose: 100 mg/day Maximum dose: 200 mg/day	Avoid CrCl <30 mL/min (0.50 mL/s) Caution with severe hepatic impairment Increase risk for bleeding
Venlafaxine	Inhibits reuptake serotonin and norepinephrine which in turn inhibits descending pain pathway Analgesic effects independent of antidepressant effects	CINP DPN Fibromyalgia LBP Migraine prophylaxis Painful polyneuropathy Tension-type headache	Initial: venlafaxine SA 37.5 mg PO daily Titrate: by no more than 75 mg/day q4 days Maximum dose: 225 mg/day	Higher doses needed to achieve SNRI effect Dose adjustments with renal/hepatic impairment Hypertension Hyponatremia QTc prolongation Increased bleeding risk

†FDA-approved indication(s).

ADE = adverse drug event.

Data from References 64, 95, and 96.

TCAs exert their effects through inhibition of serotonin and norepinephrine reuptake that enhances the descending inhibitory pain pathway.[68] Regardless of whether a patient has depression or not, TCAs provide analgesic effects.[68] In

addition to activity on serotonin and norepinephrine, TCAs also interact and inhibit acetylcholine muscarinic receptors, alpha-adrenergic receptors, histamine-1 receptors, and voltage-gated sodium channels, all of which contribute to their many side effects.[97,98] Notably, TCAs can be divided into 2 different subgroups — tertiary amines (eg, amitriptyline and imipramine) and secondary amines (eg, nortriptyline and desipramine) with the tertiary amines being metabolized to secondary amines. Secondary amines interact with fewer receptors associated with adverse effects and provide similar analgesic efficacy.[71]

The major downfall with TCAs is their adverse effect profile. There are numerous cardiovascular adverse effects associated with TCAs including slowed cardiac conduction, QTc prolongation, arrhythmias, tachycardia, and orthostatic hypotension. Doses of TCAs in excess of 100 mg/day have been associated with sudden cardiac death.[99] There are varying recommendations regarding electrocardiogram monitoring with TCAs but may be appropriate in patients ≥40–50 years of age prior to starting and periodically during continued use.[71,99] Anticholinergic effects are another major issue with TCAs and often preclude their use in patients with benign prostatic hypertrophy, glaucoma, or cognitive impairment. Sedative effects, owing to their inhibition of histamine receptors, may be unwanted in some patients, though desired in patients with insomnia; thus, TCAs are typically given at bedtime.

Duloxetine, venlafaxine, and milnacipran are serotonin norepinephrine reuptake inhibitors (SNRIs) that are either FDA-approved or have evidence to support their use in various chronic pain syndromes. Similar to TCAs, SNRIs inhibit the reuptake of serotonin and norepinephrine and modulate the descending pain pathway. Though a mental health diagnosis is not needed for analgesic benefit, SNRIs may be particularly useful in those with mental health comorbidities as doses used for pain are frequently similar to those used for mental health conditions. In addition to MDD and generalized anxiety disorder (GAD), duloxetine is FDA-approved for fibromyalgia, chronic musculoskeletal pain (low back pain and osteoarthritis), and diabetic peripheral neuropathic pain. The American College of Physicians' guideline for low back pain recommends duloxetine as a second-line medication for those that fail nonpharmacological approaches and NSAIDs.[100] Venlafaxine is not FDA-approved for any pain diagnoses; however, there is evidence supporting the use of venlafaxine for neuropathic pain, low back pain, fibromyalgia, migraine prophylaxis, and tension-type headache prophylaxis.[101–105] Duloxetine and venlafaxine are considered first-line options for neuropathic pain according to several

neuropathic pain guidelines.[64–66,73] Milnacipran is FDA approved for fibromyalgia syndrome.[106]

More likely side effects of SNRIs include nausea, somnolence, dry mouth, anorexia, erectile dysfunction, and constipation. Seizures, hyponatremia, and worsening of acute angle closure glaucoma may also occur. Because SNRIs impact norepinephrine, hypertension may occur. Therefore, it is important to ensure blood pressure control prior to initiation and monitor it during therapy. In addition, venlafaxine has been associated with QTc prolongation, so caution is advised in those with cardiovascular disease or risk factors for QTc prolongation.[107] There are no agreed upon recommendations for QTc monitoring with venlafaxine. All SNRIs have liver and renal considerations; however, the specific criteria vary amongst the different SNRIs. Furthermore, SNRIs interfere with platelet aggregation and increase risk for bleeding, particularly when combined with NSAIDs, anticoagulants, or corticosteroids. This risk of gastrointestinal bleeding can be reduced with concomitant proton pump inhibitors use.[108,109]

Skeletal Muscle Relaxants

6 7 8 Skeletal Muscle Relaxants (SMRs) are comprised of antispasmodic and antispasticity medications (**Table 77-9**).[110–114] A few medications have properties of both categories (diazepam and tizanidine). Spasticity and spasms have several differences including etiology, symptoms, and causes.[115]

TABLE 77-9 Skeletal Muscle Relaxants

Medication	Role	Mechanism of Action	Dosing	Notes
Baclofen	Antispasticity	Related to GABA, works at spinal cord, inhibits polysynaptic and monosynaptic reflexes	Initial: 5 mg PO TIME Initial: 5 mg PO TID Titrate: q3 days to effect Maximum: 80 mg/day	Withdrawal syndrome (hallucinations, seizures) Respiratory depression Requires renal dose adjustment
Carisoprodol	Antispasmodic/ antispasticity	Centrally acting, changing interneuronal activity in descending reticular formation and spinal cord Meprobamate (primary metabolite) leads to barbiturate effects at $GABA_A$	250-300 mg 4 times daily	Meprobamate (a barbiturate) is primary metabolite and has abuse potential Schedule IV controlled substance Withdrawal syndrome Respiratory depression with opioids, benzodiazepines, or barbituates Metabolized by CYP2C19 which has genetic variabilities
Chlorzoxazone	Antispasmodic	Works in spinal cord and subcortical area of brain by inhibiting multisynaptic reflex arcs	Initial: 250-500 mg 3-4 times daily Maximum dose: 750 mg 3-4 times daily	Rare hepatotoxicity Urine discoloration Respiratory depression when combined with opioids, benzodiazepines, or barbiturates
Cyclobenzaprine	Antispasmodic	Structurally related to TCAs, sedative effects, works at brainstem level, decreases excitability of alpha and gamma motor neurons	Initial: 5 mg PO TID Titrate: increase to 7.5-10 mg TID × 2-3 weeks Elderly: 5 mg dose with less frequent doses	Anticholinergic effects Avoid in elderly Caution in patients with cardiac conduction/arrhythmias Avoid closed angle glaucoma Hepatic dose adjustments
Dantrolene	Antispasticity	Inhibits calcium release from sarcoplasmic reticulum	Initial: 25 mg PO daily × 1 week Titrate dose: 25 mg PO TID × 7 days 50 mg PO TID × 7 days 100 mg PO TIME Maximum dose: 400 mg/day	Black box warning — hepatitis (dose-dependent) Discontinue at 45 days if no benefit
Diazepam	Antispasmodic/ antispasticity	Postsynaptic inhibition of GABA neurons in spinal cord	Adults: 2-10 mg 3-4 times daily	Long half-life Avoid in elderly and renal/hepatic impairment Withdrawal with abrupt discontinuation
Methocarbamol	Antispasmodic	Unknown, sedative properties	Initial: 1,500 mg PO 4 times daily × 2-3 day Then: 750-1,000 mg PO 4 times daily	Urine discoloration Respiratory depression with opioids, benzodiazepines, or barbiturates
Metaxalone	Antispasmodic	Unknown, sedative properties	800 mg PO 3-4 times daily	Respiratory depression when used with opioids, benzodiazepines, or barbiturates Contraindicated in severe liver/renal impairment
Orphenadrine	Antispasmodic	Unknown, suspect analgesic and anticholinergic effects, H_1 receptor antagonist, NMDA receptor antagonist	100 mg PO BID	Anticholinergic effects Rare aplastic anemia
Tizanidine	Antispasmodic/ antispasticity	Centrally acting α-2 agonist, inhibits presynaptic motor neurons, decreases polysynaptic reflex and abnormal contraction of opposing muscle groups	Initial: 4 mg Titrate by 2–4 mg q6–8h Maximum: 36 mg/day	Hypotension Hepatotoxicity Tablets and capsules not bioequivalent Withdrawal syndrome with abrupt discontinuation

Data from References 95 and 115.

Spasticity involves an upper motor neuron disorder.[115] Symptoms include stiffness, hypertonicity, and hyperreflexia.[115] Causes of spasticity include multiple sclerosis, cerebral palsy, spinal cord injury, traumatic brain injury, and post-stroke syndrome.[115] Medications used for spasticity include baclofen, dantrolene, diazepam, and tizanidine.

Baclofen is similar in structure to GABA and binds to $GABA_B$ receptors. These receptors are coupled to Ca^{2+} and K^+ channels located pre- and post-synaptically. Essentially this leads to reduction in the release of excitatory glutamate and increases presynaptic inhibition. Additionally, baclofen may reduce the release of substance P. Sedation, dizziness, weakness, nausea are possible side effects. The most concerning side effect of baclofen is the risk of hallucinations or seizures from withdrawal with abrupt discontinuation. Therefore, baclofen must be tapered slowly if therapy is no longer going to be continued.[115] Baclofen also requires dose adjustment for decreased renal function.[116]

Dantrolene has a limited role in treating spasticity due to its adverse effects as its more typical role is in the treatment of neuroleptic malignant syndrome or malignant hyperthermia. It has a black box warning for fatal or nonfatal hepatitis that has occurred at lower doses but is more likely to occur with higher doses. It is recommended that if no benefit is seen at 45 days the medication be discontinued. Dantrolene works by inhibiting the ryanodine channel that leads to decreased release of Ca^{2+} from the sarcoplasmic reticulum.[115]

Diazepam is not often used for non-cancer pain because of its sedative side effects and potential for abuse. The mechanism of action is binding to $GABA_A$ resulting in increased chloride conductance which subsequently leads to presynaptic inhibition of the spinal cord. Abrupt discontinuation of diazepam can lead to a withdrawal syndrome, most concerning of which is seizures. Diazepam has a long half-life (20–50 hours for parent and up to 100 for active metabolites) which is problematic especially for the elderly. Other groups to avoid the use of diazepam include those with renal or hepatic impairment.[115]

Similar to diazepam, tizanidine has both antispasticity and antispasmodic uses. Tizanidine is an α_2-agonist that works centrally. Pre-synaptically, tizanidine inhibits the release of excitatory neurotransmitters that leads to a reduction in postsynaptic activation of the upper motor neuron. In addition, tizanidine leads to the potentiation of glycine. Not surprisingly, because of its α_2-agonist activity, hypotension can occur. Other significant issues with tizanidine include sedation

and elevation in hepatic enzymes requiring periodic monitoring. Tizanidine is metabolized by CYP1A2 and is contraindicated in combination with ciprofloxacin or fluvoxamine.[115,117]

Spasms are involuntary contractions of the muscle[115,117] and antispasmodics treat musculoskeletal conditions and symptoms like jerks, twitches, and cramps.[115] Associated causes include musculoskeletal pain, fibromyalgia, mechanical low back pain, sciatica, disc herniation, and myofascial pain.[115] According to the American College of Physicians low back pain guideline, NSAIDs or SMRs are recommended as pharmacologic treatment for patients with acute or subacute low back pain.[100] While studies suggest SMRs are associated with a small increase in pain relief, there is no evidence to support improvement in function with SMRs.[100] Importantly, SMRs should be used short-term. If used long-term, SMRs may increase risk for adverse effects and polypharmacy, particularly in the elderly population as many appear on the Beer's List of Potentially Inappropriate Medications for Use in the Elderly from the American Geriatrics Society.[118–120] Antispasmodics include carisoprodol, chlorzoxazone, cyclobenzaprine, diazepam, metaxalone, methocarbamol, orphenadrine, and tizanidine.

Carisoprodol is a Schedule IV controlled substance and is metabolized via CYP2C19 to meprobamate, a barbiturate. Because of its barbiturate activity, carisoprodol has the potential for dependence and abuse. It is centrally acting and changes interneuronal activity in the descending reticular formation and spinal cord. Meprobamate has activity at $GABA_A$ receptors and withdrawal can occur with abrupt discontinuation. Furthermore, respiratory depression can occur when combined with opioids, benzodiazepines, or barbiturates.[115,117]

Chlorzoxazone blocks multisynaptic reflex arcs in the spinal cord and subcortical area of the brain. Sedation is a common side effect of chlorzoxazone and rare adverse effects include hepatotoxicity or GI bleeding. If used chronically, hepatic transaminase monitoring is recommended. Red/orange urine discoloration may occur and respiratory depression may occur when combined with opioids, benzodiazepines, or barbiturates.[115,117]

Structurally, cyclobenzaprine is similar to the TCAs. It is thought to exert its effects through decreasing the excitability of alpha and gamma motor neurons while also leading to CNS depression through the brain stem. Anticholinergic side effects are common and should be used with caution in those with cardiac arrhythmias or conduction disturbances. Cyclobenzaprine should be avoided in those with acute narrow angle glaucoma. With mild hepatic impairment, dose

adjustments are recommended and cyclobenzaprine should be avoided in those with moderate to severe hepatic impairment.[115,117]

The mechanism of action of metaxalone is unclear as it has no activity on skeletal muscle or nerve fibers. Thus, it is suspected that its effects are primarily due to CNS depression. Metaxalone is metabolized through multiple CYP enzymes including CYP1A2, CYP2D6, CYP2E1, and CYP3A4. In those with severe renal or hepatic impairment, metaxalone should not be used. Rare side effects of metaxalone include leukopenia, hemolytic anemia, or hepatic transaminase elevation. Again, respiratory depression can occur when it is used with opioids, benzodiazepines, or barbiturates.[115,117]

Similar to metaxalone, the mechanism of action of methocarbamol is unknown and suspected to be associated with its sedative properties. Respiratory depression can occur when used concomitantly with other medications. Urine discoloration (brown, green, black) is also possible.[115,117]

Orphenadrine is structurally related to diphenhydramine and possesses comparatively higher anticholinergic effects. Yet again, the mechanism of action is not completely elucidated and conjectured due to its sedative and anticholinergic effects. Orphenadrine also inhibits histamine-1 receptors and NMDA receptors. With orphenadrine, GI irritation may occur and there is rare incidence of aplastic anemia. It should be avoided in those with glaucoma, myasthenia gravis, or cardiospasm. Because of the anticholinergic effects, it should be avoided in the elderly. It has a relatively long half-life ranging from 13 to 20 hours. Its CNS depressant effects are magnified when used with other CNS depressants.[115,117]

Topicals

6 7 8 9 The advantages of topicals include addressing local symptoms while minimizing systemic exposure and risk for adverse effects (**Table 77-10**).[121,122] According to the NICE osteoarthritis guidelines, topical NSAIDs should be considered for knee or hand OA before a trial of oral NSAIDs.[123] The American College of Rheumatology (ACR) guidelines for hand, hip, and knee OA also recommend topical NSAIDs including trolamine salicylate as a pharmacologic option. Furthermore, ACR recommends topical NSAIDs over oral NSAIDs in those ≥75 years of age.[57] Additionally, topical capsaicin may be considered as an adjunct to core treatments for hand and knee osteoarthritis according to the NICE guidelines while ACR recommend capsaicin as a pharmacologic option alone or in combination.[57] Capsaicin appears in several

neuropathic pain guidelines though in different places as either second-line, third-line, or fourth-line for peripheral neuropathic pain.[52,64,65,73] Capsaicin activates transient receptor potential vanilloid 1 (TRPV1) channels. There are various over-the-counter (OTC) and prescription strength products available. It is important to note that burning may occur with initial application and that this decreases over time with repeated, scheduled use. Capsaicin is not recommended for as-needed use as repeated application is needed to desensitize C-fibers. The capsaicin 8% patch is FDA-approved for PHN and is to be administered under the direct supervision of a physician. There are specific administration directions in the packaging information including pretreatment of the area with topical anesthetic. Topical medications should not be applied to open skin. The NICE guidelines recommend against the use of rubefacients for osteoarthritis.[123] Lidocaine is also used topically and works by inhibiting voltage-gated sodium channels. For PHN, one guideline places lidocaine as first-line option and may even be preferred over other first-line options in the elderly when CNS adverse effects are a concern.[52] Other guidelines list topical lidocaine as second-line or fourth-line options for neuropathic pain.[64,65]

TABLE 77-10 Topical Analgesics

Medication	Uses	Mechanism of Action	Dosing	Notes
Capsaicin cream (various)	Temporary relief of minor aches and pains of muscles and joints Localized neuropathic pain	Transient receptor potential vanilloid 1 (TRPV1) receptor agonist	Apply 3-4 times daily	Continue scheduled use for 2-4 weeks for best results
Capsaicin 8% patch (Qutenza)	PHN	Transient receptor potential vanilloid 1 (TRPV1) receptor agonist	Apply 1-4 patches to affected area for 60 min Repeat no more frequently than q3 months Max: 4 patches	Administer under supervision of physician Specific administration directions in packaging information Apply topical anesthetic before applying Monitor blood pressure due to transient increase in blood pressure during application
Diclofenac 1% gel (Voltaren)	Pain of osteoarthritis of joints amenable to topical treatment (knees, hands)	Nonsteroid anti-inflammatory drugs (NSAIDs)	Lower extremities: 4 g QID, max 16 g/day Upper extremities: 2 g QID, max 8 g/day Total dose maximum: 32 g/day	Same black box warnings as PO NSAIDs despite low systemic bioavailability (6% of systemic exposure from oral diclofenac) Use dosing card to measure amount
Diclofenac epolamine 1.3% patch (Flector)	Topical treatment of acute pain due to minor strains, sprains, and contusions	NSAIDs	1 patch to most painful area BID	Systemic effects were <1% after 4 days of repeated dosing
Diclofenac topical solution (Pennsaid)	Pain from osteoarthritis of the knee	NSAIDs	1.5%: 40 drops to each affected knee 4 times daily. Apply 10 drops at a time 2%: 2 pumps (40 mg) on each painful knee BID	Same black box warnings as PO NSAIDs
Lidocaine gel/ ointment/patch (various)	Neuropathic pain	Sodium channel blocker	Cream/ointment: Apply to affected area 3 times daily Patch: apply 1 patch to affected area up to 12 h	Apply to intact skin only
Lidocaine 5% patch (Lidoderm)	PHN	Sodium channel blocker	Apply 1-3 patches to site of pain for 12 h Maximum: 3 patches	May cut lidocaine patches Apply to intact skin only Severe hepatic impairment increases risk of side effects
Menthol/methyl salicylate (various)	Minor aches and pains of muscles and joints (simple backache, arthritis, strains, bruises, sprains)	Rubefacient	Apply topically 3-4 times a day to affected area	Do not apply to damaged skin
Trolamine salicylate cream 10% (various)	Aches and pains of muscles and joints (arthritis, simple backache, bruises, sprains, strains)	Rubefacient	Apply topically 3-4 times a day to affected area	Do not apply to damaged skin

Data from Reference 95.

In the management of cancer pain, radiopharmaceuticals (eg, strontium-89 or samarium), corticosteroids, denosumab, and certain bisphosphonates are useful co-analgesics in treating bone pain.[47] Although antihistamines and amphetamines have been used as co-analgesics, they have demonstrated only limited efficacy.

Emerging Agents

Two agents have received widespread attention recently for their potential analgesic benefit, namely cannabis and ketamine. Medical cannabis has been studied primarily in neuropathic pain conditions with equivocal results. Route of administration, dose, and monitoring recommendations are still unclear. More importantly, research on the specific cannabinoids and terpenes present in many of the *cannabis* strains is required considering the widely variable pharmacologic profiles of these substances.[124,125] The non-psychoactive cannabinoid, *cannabidiol* (CBD) may have a significant role in the treatment of chronic pain, although its utility in the absence of delta-9-tetrahydrocannabinol (THC) is unclear.[126]

Ketamine, a non-competitive *N*-methyl-D-aspartate glutamate receptor antagonist, is typically used for procedural sedation and for induction of anesthesia. Given its potent glutamate antagonism, its use has gained popularity among pain specialists for maladaptive pain syndromes, such as Complex Regional Pain Syndrome (CRPS). Guidelines for the use of ketamine as an adjunct analgesic in acute pain are available, but appropriate dose, duration, and patient selection for chronic pain are still unclear.[127] Use of this agent should be supervised by clinicians experienced in its use.

Opioid Agents

1 7 8 9 10 11 Opioids are often the next step in the management of acute pain and cancer-related chronic pain. This medication class may also be an effective treatment option in the management of chronic noncancer pain; however, this continues to be increasingly controversial. When a trial of opioids is warranted, it should follow a complete assessment of the pain complaint, an assessment of the patient's functionality goals, and risk factors for opioid misuse, abuse, diversion, or overdose.[49]

Opioid choice should be based on patient acceptance, analgesic effectiveness,

as well as pharmacokinetic, pharmacodynamic, and side-effect profiles with the attributes provided in **Tables 77-11** and **77-12**.[47,95]

TABLE 77-11 Opioid Analgesics

Class and Generic Name (Brand Name)	Chemical Source	Metabolic Pathway/Metabolites	Route[a]	Equianalgesic Dose in Adults (mg)	Approximate Onset (min)/ Half-Life (h)[b]
Phenanthrenes (morphine-like agonists)					
Morphine (Embeda[i], Arymo ER[i], MorphaBond[i])	Naturally occurring	Phase II via glucuronidation/M3G[j] (inactive) and M6G[j] (active)	IM/IV	10	10-20/2
			PO	25-30	
Hydromorphone (Dilaudid, Exalgo, various)	Semisynthetic	Phase II via glucuronidation/H3G (active)[m], H6G[n]	IM/IV	1.5	10-20/2-3
			PO	7.5	
Oxymorphone (Numorphan, Opana)	Semisynthetic	Phase II via glucuronidation/O3G (inactive)[o]	IM/IV[a]	1	10-20/2-3
			PO	10	
Levorphanol (various)	Semisynthetic	Phase II via glucuronidation/ levorphanol-3-glucuronide (inactive)	PO	Variable	10-20/12-16
Codeine (various)	Naturally occurring	CYP2D6/morphine (active), Phase II glucuronidation/codeine-6-glucuronide (unknown), CYP3A4/norcodeine (inactive)	PO	15-30[c]	10-30/3
Hydrocodone (available as combination, single entity extended release—Hysingla ER[i], Zohydro ER)	Semisynthetic	CYP3A4/norhydrocodone (inactive); CYP2D6/ hydromorphone (active)	PO	5-10[c]	30-60/4
Oxycodone (OxyContin[i], Xtampza[i], RoxyBond[i] Troxyco ER[i] [oxycodone & acetaminophen])	Semisynthetic	CYP3A4/noroxycodone (active), CYP2D6/oxymorphone (active)	PO	15-30[d]	30-60/2-3
Phenylpiperidines (meperidine-like agonists)					
Meperidine (Demerol, various)	Synthetic	Phase II hydrolysis/meperidinic acid, CYP2B6, CYP3A4, & CYP2C19/normeperidine	IM / IV	75	10-20/3-5
			PO	300[d]; not recommended	
Fentanyl (Sublimaze, Duragesic, Lazanda, Abstral, Fentora, Subsys, OTFC, various)	Synthetic	CYP3A4/norfentanyl (inactive)	IM / IV	0.125[e]	7-15/3-4
			Transdermal, Buccal, transmucosal, sublingual, nasal, nebulized	Variable[f]	
				Variable[f]	
Diphenylheptanes (methadone-like agonists)					
Methadone (Dolophine, various)	Synthetic	CYP3A4, CYP2B6, CYP2C19, CYP2C9, CYP2D6/EDDP (inactive)[p]	IM / IV	Variableg (acute)	
			PO	Variableg (acute)	30-60/12-190
Phenylpropanolamines					
Tramadol (Ultram, Rybix, Ryzolt, ConZip, various)	Synthetic	CYP3A4/nortramadol (inactive), CYP2D6/*O*-desmethyltramadol (active)	PO	50-100[c,h,j]	<60/5-7
Tapentadol (Nucynta)	Synthetic	Phase II glucuronidation/ tapentadol-o-glucuronide (inactive), CYP2C9 and CYP2C19/*N*-desmethyltapentadol (inactive), CYP2D6/ hydroxytapentadol	PO	50-10[c,h,j]	Within 60/4
Agonist–antagonist derivatives					
Pentazocine (Talwin, various)	Synthetic	Liver/Alcoholic and carboxylic acid derivatives (inactive), pentazocine glucuronide (inactive)	IM	Not recommended	
			PO	50[c]	15-30/2-3

Class and Generic Name (Brand Name)	Chemical Source	Metabolic Pathway/Metabolites	Route[a]	Equianalgesic Dose in Adults (mg)	Approximate Onset (min)/ Half-Life (h)[b]
Butorphanol (Stadol, various)	Synthetic	CYP3A4/hydroxybutorphanol (active), norbutorphanol (inactive)	IM/IV	2	10-20/3-4
			Intranasal	1[c] (one spray)	
Nalbuphine (Nubain, various)	Synthetic	CYP3A4 CYP2C19/ nornalbuphine, 6-ketonalbuphine	IM / IV	10	<15/5
Buprenorphine (Buprenex, Butrans, Suboxone, Belbuca, Subutex, various)	Synthetic	CYP3A4/norbuprenorphine (active)	IM/IV	0.3	10-20/2-3
			Transdermal	Variable	
			Sublingual	Variable	

IM, intramuscular; IV, intravenous; PO, oral.

[a]The IM route should be avoided whenever possible — produces significant pain with administration and rate and extent of absorption is highly variable. If IV route is unavailable then administer subcutaneously (SC).

[b]ER/LA formulations may vary greatly in terms of onset and duration of analgesia. The reader should consult individual prescribing labels.

[c]Starting dose only (equianalgesia not shown).

[d]Starting doses lower (oxycodone 5–10 mg, meperidine 50–150 mg).

[e]Equivalent PO morphine dose = variable.

[f]For breakthrough pain only. Equianalgesic dose conversion should be avoided for Transmucosal Immediate Release Fentanyl (TIRF) products.

[g]The equianalgesic dose of methadone when compared with other opioids will decrease progressively the higher the previous opioid dose. Caution should be exercised when initiating in opioid naïve patients.

[h]First day of dosing may administer second dose 1 hour after first dose.

[i]Onset of action may differ for long-acting formulations. Ceiling dose recommendations exist and may differ from immediate release dosing recommendations.

[j]FDA approved as abuse-deterrent formulation.

[k]Morphine-3-glucuronide (accumulates in renal failure).

[l]Morphine-6-glucuronide (accumulates in renal failure).

[m]Hydromorphone-3-glucuronide (accumulates in renal failure).

[n]Hydromorphone-6-glucuronide.

[o]Oxymorphone-3-glucuronide.

[p]2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP).

[q]Oral transmucosal fentanyl citrate (OTFC).

Data from References 95, 47, and individual product package inserts.

TABLE 77-12 Dosing Guidelines

Agent(s)	Doses (Use Lowest Effective Dose, Titrate Up or Down Based on Patient Response, Opioid-Tolerant Patients May Need Dose Modification)	Notes
NSAIDs/acetaminophen/ aspirin	Use lowest effective dose for the shortest duration possible	Used in mild-to-moderate pain
		May use in conjunction with opioid agents to decrease doses of each
		Regular alcohol use and of acetaminophen may result in liver toxicity
		Care must be exercised to avoid overdose when combination products containing these agents are used
		Underlying renal impairment, hypovolemia, and CHF may predispose to nephrotoxicity
Morphine	PO 5-30 mg every 4 h[a]	Drug of choice in severe pain
	IM 5-20 mg every 4 h[a]	Use immediate-release product with SR product to control breakthrough pain in cancer patients
	IV 5-15 mg every 4 h[a]	Typical patient controlled analgesia IV dose is 1 mg with a 10-min lock-out interval
	SR 15-30 mg every 12 h (may need to be every 8 h in some patients)	Every 24-h products available
	Rectal 10-20 mg every 4 h[a]	
Hydromorphone	PO 2-4 mg every 4-6 h[a]	Use in severe pain
	XR 8 mg to 64 mg every 24 h	More potent than morphine; otherwise, no advantages
	IM 1-2 mg every 4-6 h[a]	
	IV 0.5-2 mg every 4 h[a]	Typical patient-controlled analgesia IV dose is 0.2 mg with a 10-min lock-out interval
	Rectal 3 mg every 6-8 h[a]	Every 24-h product (Exalgo) available
Oxymorphone	IM 1–1.5 mg every 4-6 h[a]	Use in severe pain
	IV 0.5 mg every 4-6 h[a]	No advantages over morphine
	PO immediate-release 5-10 mg every 4-6 h[a]	Use immediate-release product with controlled-release product to control breakthrough pain in cancer or chronic pain patients
	PO extended-release 5-10 mg every 12 h[a]	Manufacturer recommends 5 mg every 12 h in opioid-naïve patients
		Take ER on empty stomach
Levorphanol	PO 2-3 mg every 6-8 h[a] (Levo-Dromoran)	Use in severe pain
	PO 2 mg every 3-6 h[a] (Levorphanol Tartrate)	Extended half-life useful in cancer patients
	IM 1-2 mg every 6-8 h[a]	In chronic pain, wait 3 days between dosage adjustments
	IV 1 mg every 3-6 h[a]	
Codeine	PO 15-60 mg every 4-6 h[a]	Use in mild-to-moderate pain
	IM 15-60 mg every 4-6 h[a]	Weak analgesic; analgesic prodrug
Hydrocodone	PO 5-10 mg every 4-6 h[a]	Use in moderate/severe pain
Oxycodone	PO 5-15 mg every 4-6 h[a]	Use in moderate/severe pain
	Controlled release 10-20 mg every 12 h	
		Use immediate-release product with controlled-release product to control breakthrough pain in cancer or chronic pain patients
		CR reformulated to deter abuse
Meperidine	IM 50-150 mg every 3-4 h[a]	Use in severe pain
	IV 5-10 mg every 5 min prn[a]	Oral not recommended
		Do not use in renal failure
		May precipitate tremors, myoclonus, and seizures
		Monoamine oxidase inhibitors can induce hyperpyrexia and/or seizures or opioid overdose symptoms
Fentanyl	IV 25-50 mcg/h	Used in severe pain
	IM 50-100 mcg every 1-2 h[a]	**Do not use transdermal in acute pain**
	Transdermal 25 mcg/h every 72 h	Transmucosal for breakthrough cancer pain in patients already receiving or tolerant to opioids
	Transmucosal (Actiq / OTFC Lozenge and Onsolis buccal film) 200 mcg may repeat × 1, 30 min after first dose is started, then titrate	**Always start with lowest dose despite daily opioid intake; product-specific titration recommendations exist**

Agent(s)	Doses (Use Lowest Effective Dose, Titrate Up or Down Based on Patient Response, Opioid-Tolerant Patients May Need Dose Modification)	Notes
	Transmucosal (Fentora Buccal Tablet) 100 mcg, may repeat × 1, 30 min after first dose is started, then titrate	
	Intranasal (Lazanda Spray) 100 mcg (one spray) in one nostril. Wait 2 h prior to redosing	
	Sublingual (Subsys Spray) 100 mcg (1 spray). Wait 4 h prior to redosing	
	Sublingual (Abstral Tablet) 100 mcg tablets placed sublingually. Must wait 2 h prior to redosing	
Methadone	PO 2.5-10 mg every 8-12 h[a]	Effective in severe chronic pain
	IM 2.5-10 mg every 8-12 h[a]	
		Some chronic pain patients can be dosed every 12 h
		Equianalgesic dose of methadone when compared with other opioids will decrease progressively the higher the previous opioid dose. Avoid dose titrations more frequently than weekly in chronic pain maintenance
Pentazocine	PO 50-100 mg every 3-4 h[b] (max. 600 mg daily, for those 50 mg tablet containing 0.5 mg of naloxone)	Second-line agent for moderate-to-severe pain; may precipitate withdrawal in opiate-dependent patients; parenteral doses not recommended
	PO 25 mg every 4 h[b] (max. 150 mg daily, for those 25 mg tablet containing 325 mg of acetaminophen)	
Butorphanol	IM 1-4 mg every 3-4 h[b]	Second-line agent for moderate-to-severe pain
	IV 0.5-2 mg every 3-4 h[b]	May precipitate withdrawal in opiate-dependent patients
	Intranasal 1 mg (1 spray) every 3-4 h[b]	
	If inadequate relief after initial spray, may repeat in other nostril × 1 in 60–90 min	
	Max. 2 sprays (one per nostril) every 3-4 h[b]	
Nalbuphine	IM/IV 10 mg every 3-6 h[b] (max. 20 mg dose, 160 mg daily)	Second-line agent for moderate-to-severe pain; may precipitate withdrawal in opiate-dependent patients
		Used frequently in low doses to treat / prevent opioid-induced pruritus
Buprenorphine	IM 0.3 mg every 6 h[b]	Second-line agent for moderate-to-severe pain
	Slow IV 0.3 mg every 6 h[b]	May precipitate withdrawal in opiate-dependent patients
		Transdermal delivery systems (5, 7.5, 10, 15, 20 micrograms/hour) available for every 7 day administration. Detailed manufacturer dosing conversion recommendations exist
	May repeat × 1, 30-60 min after initial dose	Naloxone may not be effective in reversing respiratory depression
Naloxone	IV / IM 0.4-2 mg	When reversing opiate side effects in patients needing analgesia, dilute and titrate (0.1-0.2 mg every 2-3 min) so as not to reverse analgesia
Tramadol	PO 50-100 mg every 4-6 h[a]	Maximum dose for nonextended-release, 400 mg/24 h; maximum for extended release, 300 mg/24 h
	If rapid onset not required, start 25 mg/day and titrate over several days	Decrease dose in patient with renal impairment and in the elderly
	Extended release PO 100 mg every 24 h	
Tapentadol	PO 50-100 mg every 4-6 h[a]	First day of therapy may administer second dose after the first within 1 h maximum dose first day 700 mg, max. dose thereafter 600 mg (maximum dose for CR 500 mg)

HCL, hydrochloride; IM, intramuscular; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; PO, oral; prn, as needed; SR, sustained release; OTFC, Oral transmucosal fentanyl citrate; CR, controlled release; XR, extended release; mcg, microgram; mg, milligram.

[a]May start with an around-the-clock regimen and switch to prn if/when the painful signal subsides or is episodic.

[b]May reach a ceiling analgesic effect.

Data from References 47, 95, and 131.

The pharmacologic activity of opioids depends on their affinity for and action at one or more central and peripheral opiate receptors. These g-protein coupled receptors include mu (MOR), kappa (KOR), delta (DOR), and noceptin (OLR-1), which have variable physiologic effects. Therapeutic activities and side effects for this medication class range from those exhibited by the MOR agonists (eg, morphine) to those seen with the nonselective antagonists (eg, naloxone). Partial MOR agonists (eg, buprenorphine) and mixed MOR antagonists / KOR agonists (eg, nalbuphine) compete with agonists for opiate receptor sites and, depending on the inherent agonist and antagonist properties, may precipitate opioid withdrawal and pain crisis if initiated in an MOR agonist tolerant patient.[128] Efficacy and side effects also may further differ among opioid agents because of receptor subtype variability and may explain why some patients respond differently to certain opioids, specifically MOR agonists.[129] Opioid antagonists may act centrally (eg, naloxone or naltrexone) or be limited to peripheral action only (eg, naloxegol, methylnaltrexone, or naldemedine) (**Table 77-13**).[95,130]

TABLE 77-13 Central and Peripheral Opioid Antagonists

Generic Name (Brand Name)	Activity	Role	Route	Dose in Adults (mg)	Special Considerations
Naldemedine (Symproic)	Peripheral	CNMP[a], OIC[b]	PO	0.2 mg qday	Avoid with severe hepatic impairment
Naloxone (Narcan, various) Methylnaltrexone (Relistor) Naltrexone (ReVia, Vivitrol) Alvimopan (Entereg) Naloxegol (Movantik)	Central Peripheral Central Peripheral Peripheral	Opioid reversal Cancer and CNMP[a] OIC[b] AUD,[c] OUD[d] Postoperative ileus CNMP[a], OIC[b]	IV, IM, IN SC (both), PO (CNMP) PO, IM PO PO	0.4-2 mg[e] Variable 12 mg Qday-Q12 (PO) 380 mg q4weeks (IM) 12 mg PO 30 min-5h before surgery then 12 mg PO BID starting day after surgery for maximum of 7 days 12.5-25mg qday 1 hour before, 2 hours after a meal	Onset 1-2 (IV) minutes, 2-5 (IM) minutes Half-life 0.5-1.3 h Renal dose adjustments Opioid free for 7-10 days before initiation Limited to 15 doses Renal dose adjustments Avoid with moderate 3A4 inhibitors

[a]Chronic nonmalignant pain.

[b]Opioid-induced constipation.

[c]Alcohol use disorder.

[d]Opioid use disorder.

[e]Starting doses to be used in cases of opioid overdose.

Data from individual package inserts.

The effects of the opioid analgesics are relatively selective, and at normal therapeutic concentrations, do not affect other sensory modalities.[9,128] While sensations of touch and proprioception are preserved, undesirable side effects may increase as the dose is escalated (**Table 77-14**).[9,128] Frequently, when opioids are administered, pain is not eliminated, but its unpleasantness is decreased. Patients report that although their pain is still present, it no longer bothers them.

TABLE 77-14 Major Adverse Effects of the Opioid Analgesics

Effect	Manifestation
Mood changes	Dysphoria, euphoria
Somnolence	Sedation, inability to concentrate
Stimulation of chemoreceptor trigger zone	Nausea, vomiting
Respiratory depression	Decreased respiratory rate, periodic breathing, oxygen desaturation
Decreased gastrointestinal motility	Constipation
Increase in sphincter tone	Biliary spasm, urinary retention (varies among agents)
Histamine release	Urticaria, pruritus, rarely exacerbation of asthma due to bronchospasm(varies among agents)
Tolerance	Larger doses for same effect
Dependence	Withdrawal symptoms upon abrupt discontinuation
Addiction	Genetic predisposition leads to loss of control of drug use, continued use despite harm, compulsion to use, cravings
Hypogonadism	Fatigue, depression, loss of analgesia, sexual dysfunction, amenorrhea (women)
Sleep	Disrupts sleep–wake cycle, causes dose-dependent rapid eye movement (REM) suppression

Data from References 47 and 95.

8 9 Opioids share related pharmacologic attributes and exert a profound effect on the CNS and GI tract. Mood changes, sedation, nausea, vomiting, decreased GI motility, constipation, respiratory depression, dependence, pruritus, and tolerance are evident in varying degrees with all agents.[128] Tolerance to side effects (except to constipation) often develops over time. Some differences exist between the opioids in regards to incidence of side effects, which may assist in selection of the most appropriate agent.

7 8 9 The route of administration depends on individual patient needs, with the oral route being preferred. However, the onset of analgesic effect for oral medications is approximately 45 minutes, and the peak effect usually occurs

1 to 2 hours after administration.[9,47] This delay must be considered when immediate relief is needed in the management of acute pain (ie, postsurgical or cancer breakthrough). Therefore, in some scenarios, such as acute severe pain (eg, pain crisis) or when the patient is unable to take oral medications, alternative routes of therapy, such as intravenous (IV) administration, may be preferred.[31] The relative potency, defined by the equianalgesic dose, of opioids differs greatly (Table 77-11). Equianalgesic dose tables are often based on single-dose studies without regard for patient variability and should be used only as a guide, with further dose titration frequently required.[47,131]

Although true opioid allergies are rare, Table 77-11 can also be used when treating a patient who has a documented hypersensitivity to opioids. Differing chemical classes of opioids may theoretically provide some reduction in cross reactivity when hypersensitivity is of concern. Most reactions, such as pruritus or rash, are either related to associated histamine release from cutaneous mast cells or activation of central MOR receptors and not a true allergic or immunoglobulin-E (IgE) or T-cell response.[132–134] Although caution is always advised, a decrease in potential cross-sensitivity is thought to exist when moving from one opioid structural class to another.[133] The classes are phenanthrenes (morphine-like agonists), phenylpiperidines (fentanyl-like agonists), and diphenylheptanes (methadone-like agonists). When considering cross-sensitivity, the mixed agonist–antagonist and partial agonist class acts much like the morphine-like agonists.[134]

8 9 In the initial stages of acute pain, analgesics should be given around the clock. This should commence after administering a typical starting dose and titrating up or down, depending on the patient's degree of pain and demonstrated side effects (eg, sedation). As-needed schedules may produce wide swings in analgesic plasma concentrations resulting in alternating states of uncontrolled pain and sedation. This may initiate a vicious cycle where increasing amounts of pain medications are needed for relief. As the pain subsides and the need for medication decreases, as-needed schedules may be appropriate, which may also be useful in patients who present with pain that is intermittent or sporadic in nature. When opioids are used in the management of persistent chronic pain, around-the-clock administration schedules should be utilized. As-needed opioids should be used in conjunction with around-the-clock regimens for times when patients experience breakthrough pain, which is a brief, transitory, exacerbation of moderate-to-severe pain typically occurring in patients with underlying persistent pain that may otherwise be controlled.

7 Continuous IV infusion of opioids should be reserved for opioid-tolerant

patients.[135,136] An alternative method is patient-controlled analgesia (PCA), which is a technique by which patients can self-administer a preset dose of an IV opioid via a pump electronically interfaced with a timing device. Compared with traditional as-needed opioid dosing, PCA yields better pain control, improved patient satisfaction, and relatively few differences in side effects.[135,137]

Administration of opioids directly into the CNS (eg, epidural and intrathecal/subarachnoid routes) may also be used by anesthesiology pain consult services in the control of acute, chronic noncancer, and cancer pain; and is useful in more difficult to control pain states (Table 77-15).[138,139]

TABLE 77-15 Intraspinal Opioids

Agent	Single Dose (mg)	Onset of Pain Relief (min)	Duration of Pain Relief (h)	Continual Infusion Dose (mg/h)
Epidural route				
Morphine	1-6	30	6-24	0.1-1
Hydromorphone	0.8-1.5	5-8	4-8	0.1-0.3
Fentanyl	0.025-0.1	5	2-8	0.025-0.1
Sufentanil	0.01-0.06	5	2-4	0.01-0.05
Subarachnoid route				
Morphine	0.1-0.3	15	8-34	–
Fentanyl	0.005-0.025	5	3-6	–

Doses above should not be interpreted as equianalgesic doses for conversion to or from the specific opioid or route of administration.

Data from References 47, 95, and 139.

8 Due to reports of respiratory depression, pruritus, nausea, vomiting, urinary retention, and hypotension, these methods of analgesia require careful monitoring and are best used by experienced practitioners. Respiratory depression is of concern and can occur within minutes with intrathecal fentanyl or manifest as late as 19 hours after a single dose of intrathecal morphine. Guidelines mandate respiratory monitoring for at least 24 hours after a single dose of intrathecal or epidural morphine with standing orders for naloxone (opioid antagonist) for full or partial reversal.[135,136] Analgesia and side effects are evident at even lower doses when opioids are administered intrathecally instead of epidurally. This form of analgesia is often administered as a

continuous-infusion and/or on a patient-controlled basis. When given simultaneously with intrathecal or epidural local anesthetics such as bupivacaine, opioid analgesics have been proven relatively safe and effective. All agents administered directly into the CNS should be preservative free.

Morphine and Congeners

6 10 Despite the availability of several newer agents, morphine remains the prototype opiate analgesic. As new opioid and nonopioid compounds are developed, their efficacy and side-effect profiles are typically compared against morphine as the standard. Using equianalgesic tables, clinicians often refer to "oral morphine equivalents" when describing efficacy or risk of harms of other opioids.[36,131] Many clinicians consider morphine the first-line agent when treating moderate-to-severe pain due to its relative low cost, broad clinical experience, and abundant dosage forms/strengths.

Side effects can be numerous, particularly when morphine is first initiated or when doses are significantly increased. Morphine causes nausea and vomiting through direct stimulation of the chemoreceptor trigger zone, decreased peristalsis, and a vestibular mechanism.[128] Opioid-induced nausea typically subsides over time with continued dosing, although this side-effect may be incredibly troublesome to patients, especially following surgery.[140] As doses of morphine are increased, the respiratory center becomes less responsive to carbon dioxide, causing progressive respiratory depression.[9] This effect is more pronounced with concurrent administration with other respiratory depressants.[141] Respiratory depression often manifests as a decrease in respiratory rate (although minute volume and tidal exchange also are affected).[128] More recently, end-tidal capnography has become commonplace as a means to monitor opioid-induced respiratory depression, especially in those at increased risk.[142]

10 11 Opioid-induced respiratory depression can be rapidly reversed by the opioid antagonist, naloxone.[128] In patients with underlying pulmonary dysfunction or sleep disordered breathing, caution must be exercised when opioids are used, as these patients are already using compensatory breathing mechanisms and are at risk for further respiratory compromise.[143] Caution is also urged when combining opiate analgesics with alcohol or other CNS depressants (ie, benzodiazepines, SMRs, and sleep hypnotics), because this combination is potentially harmful and possibly lethal.[36]

Therapeutic doses of morphine have minimal effects on blood pressure, cardiac rate, or cardiac rhythm when patients are supine; however, morphine

does produce venous and arteriolar vessel dilation, potentially resulting in orthostatic hypotension, and hypovolemic patients may be more susceptible to morphine-induced cardiovascular changes (eg, decreases in blood pressure).[9] Because morphine prompts a decrease in myocardial oxygen demand in ischemic cardiac patients, it is often used to treat pain associated with myocardial infarction, although this practice has been called into question due to the potential for increased mortality.[144]

Morphine decreases the propulsive contractions of the GI tract resulting in constipation. Morphine-induced spasms of the sphincter of Oddi have also been observed; however, the clinical significance of this is unclear. Urinary retention is another significant side effect of morphine and should be routinely assessed. Morphine-induced histamine release often manifests as pruritus, and may even exacerbate bronchospasm in patients with a history of asthma.[47] Therapeutic doses of morphine are not contraindicated in head injury, but drug-induced respiratory depression can increase intracranial pressure. Thus, caution is advised in head trauma patients who are not mechanically-ventilated because morphine may increase intracranial pressures and cloud the neurologic examination results.[128]

Morphine is metabolized to two major metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Whereas M6G contributes to analgesia, M3G may contribute to unwanted neurologic side effects. The metabolites are renally cleared and can accumulate in patients with renal impairment, contributing to greater side effects.[128] Most clinicians recommend avoiding morphine in renally compromised patients (ie, creatinine clearance ≤30 mL/minute [0.50 mL/s]). Morphine also inhibits the release of gonadotropin-releasing hormone from the hypothalamus, thus decreasing plasma testosterone and cortisol (opioid-induced hypogonadism), whereas male patients may present with symptoms of erectile dysfunction, decreased libido, and decreased analgesic efficacy. Women may experience alopecia, amenorrhea, and depressed mood, as well as decreased analgesic efficacy. Recommendations for clinical replacement of these hormones in patients using chronic opioid therapy are not well defined.[145] While the clinical meaning has not clearly been elucidated, morphine and other opioids, depending on the situation being used, may either enhance or inhibit the immune system.[47,128]

Hydromorphone is more potent than morphine, but its overall pharmacologic profile is similar. Some clinicians believe hydromorphone is associated with fewer side effects, especially pruritus, compared with other opioids. However, the research is limited and does not conclusively demonstrate this difference.

Oxymorphone can be administered orally and by injection. Although extended-release and immediate-release oral products are available, it offers no pharmacologic advantage over morphine. Patients must be counseled to take the extended-release oxymorphone without food as high fat meals may greatly increase absorption, resulting in an increased risk of toxicity. Levorphanol has an extended half-life and purported NMDA glutamate receptor activity, but its overall therapeutic effects are similar to the other agents in this class and cost is frequently a barrier to its use.[146,147]

Codeine is a commonly used opioid for the treatment of mild-to-moderate pain. It often is combined with other analgesic products (eg, acetaminophen). Unfortunately, it has the propensity to produce the same side effects as morphine. Due to the risk of toxicity in patients with rapid metabolizer phenotypes, the FDA recommends against codeine's use in children and breastfeeding mothers.[148] Hydrocodone is perhaps the most commonly prescribed opiate in the United States and is available orally as immediate-release combined with nonopioid analgesics, as well as extended-release formulations. Its pharmacologic properties are similar to those of morphine. Oxycodone is a useful oral analgesic for moderate-to-severe pain. This is especially true when the product is used in combination with nonopioids. Although oxycodone shares basic morphine characteristics, the availability of an immediate-release and controlled-release oral dosage form also makes it very useful in chronic pain as well as cancer pain.

Meperidine and Congeners (Phenylpiperidines)

The prototype phenylpiperidine, meperidine, has a pharmacologic profile comparable with that of morphine; however, it is not as potent and has a shorter analgesic duration. Meperidine offers no analgesic advantage over morphine, has greater toxicity (CNS hyperirritability caused by its renally eliminated metabolite normeperidine), and should be limited in use, especially in elderly patients, those with renal dysfunction, or for prolonged treatment durations.[47,149] In particular, avoid long-term usage and use in patients at greatest risk for toxicity (eg, elderly patients and those with renal dysfunction).[149]

Fentanyl is a synthetic opioid structurally related to meperidine that is used often in anesthesiology as an adjunct to general anesthesia. This agent is significantly more potent and faster acting than meperidine. It can be administered parenterally, transmucosally, sublingually, intranasally, and transdermally.[9,128]

Methadone and Congeners

Methadone is a useful analgesic due to its oral efficacy, extended duration of action, and low cost. Properties unique to methadone, compared with other opioids, include the s-isomer's ability to antagonize NMDA receptors, agonist effects at the kappa and delta opioid receptor, as well as the blockade of serotonin and norepinephrine reuptake.[128,150] These properties may prove useful in the treatment of neuropathic and chronic pain. However, few trials have thoroughly evaluated methadone's risks versus benefits.[150,151] Epidemiologic studies suggest a growing number of methadone-related deaths, and cardiac arrhythmias have been associated with this medication, particularly at higher doses or when used concurrently with other agents that prolong QTc intervals.[141] Recommendations exist for specific echocardiogram monitoring for methadone; however, concerns exist regarding their applicability.[150] The equianalgesic dose of methadone may decrease with higher doses of the comparator opioid, complicating conversions from other opioids to methadone. Methadone should not be titrated more frequently than every 5 to 7 days due to its unpredictable potency and variable half-live.[150]

Opioid Agonist–Antagonist Derivatives

This analgesic class produces analgesia and has the potential for less respiratory depression than opioid agonists as they exert their analgesic activity via the KOR and either block or act as partial agonists at the MOR.[128] Agents in this class are considered to have a lower abuse potential than morphine, but psychotomimetic responses (eg, hallucinations and dysphoria), limited analgesic effect, and a potential to initiate withdrawal in opioid-dependent populations have precluded their widespread clinical use. Both butorphanol and nalbuphine are available parenterally, with butorphanol also available as an intra-nasal spray. Nalbuphine is gaining popularity as a treatment for MOR agonist–associated pruritus.[152]

Buprenorphine is a pharmacologically complex opioid, which exhibits KOR antagonism, and several MOR-related actions, including partial agonism. Buprenorphine also displays agonist properties at the opioid receptor-like 1 (ORL-1) receptor which may have clinical ramifications in prevention of tolerance, euphoria / reward, and hyperalgesia.[153] Buprenorphine is available as a sublingual tablet, a buccal film, a once-weekly transdermal patch, or in combination with naloxone as a sublingual film or sublingual tablet. When buprenorphine, with or without naloxone, is prescribed for opioid use disorder, a special DEA license is required by the prescriber.[154]

Central-Acting Opioids

Tramadol and tapentadol are the only centrally acting analgesics currently available in the United States. Tramadol binds to MOR receptors and inhibits serotonin, and to a lesser extent, norepinephrine reuptake.[155] Tapentadol also binds the MOR receptor, but inhibits largely norepinephrine reuptake. Tramadol is indicated for the relief of moderate to moderately severe pain, while tapentadol is indicated for moderate-to-severe acute pain and diabetic peripheral neuropathy.

Both tramadol and tapentadol have side-effect profiles similar to that of the previously mentioned opioid analgesics (eg, dizziness, nausea, somnolence, and constipation). Tapentadol has not been systematically evaluated in patients with seizures, and it should be used with caution in these patients. Seizure risk, as well as risk of hypoglycemia and hyponatremia, may be elevated in patients taking tramadol.[155,156] Tramadol may have a place in treating patients with chronic pain, especially neuropathic pain, while tapentadol may be useful in the management of acute pain and the controlled release product may have a role in chronic pain treatment (eg, diabetes-related nerve pain).[157,158]

Opioid Antagonists

11 The opioid antagonist naloxone binds competitively to opioid receptors but does not produce an analgesic or opioid side-effect response. Therefore, it is used most often to reverse the toxic effects of agonist- and agonist–antagonist-derived opioids. Other opioid antagonists exist, including naltrexone, naloxegol, naldemedine, and methylnaltrexone. Naltrexone's use is primarily limited to addiction medicine, while naloxegol, naldemedine, and methylnaltrexone are peripherally-acting only and used for opioid-induced constipation.[130]

11 With the growing prevalence of illicit (heroin and fentanyl analogs) opioid abuse–related overdoses, pharmacists are increasingly being called upon to assist in the prevention of these deaths. Many states have legislation in place that allows pharmacists to provide expanded access to naloxone for those themselves or have a family member at risk for an opioid overdose. Naloxone may be administered intranasally, intravenously, or intramuscularly.[159] Further discussion of naloxone education, administration, and monitoring is provided in Chapter 82, "Substance-Related Disorders: Overview and Depressants, Stimulants, and Hallucinogens."

1 2 3 4 11 **Tolerance, Hyperalgesia, Physical Dependence, and**

Opioid Use Disorder A barrier that consistently causes clinicians to misjudge and mistreat pain is the misunderstanding of opioid tolerance, hyperalgesia, physical dependence, and addiction. Tolerance is the reduction of drug effect over time as a result of exposure to the drug.[128] It develops at different rates and with great patient variability. However, with stable disease, opioid doses may stabilize over time. Hyperalgesia is an increased sensitivity to pain. Opioids have been implicated in contributing to this phenomenon and can be seen with rapid opioid escalation or high-dose administration.[160] The mechanism or true clinical impact of this phenomenon is not currently understood.

Opioid physical dependence is characterized by an abstinence syndrome following administration of an antagonist drug or abrupt dose reduction or discontinuation of an opioid.[128,129] Clinicians must understand that physical dependence and tolerance are not equivalent to addiction; and with chronic opioid use, physical dependence is expected.[129]

Many definitions and classifications exist to describe the biopsychosocial phenomenon of addiction. The American Society of Addiction Medicine (ASAM) defines addiction as a “primary, chronic disease of brain reward, motivation, memory and related circuitry” leading to biological, psychological, social, and spiritual manifestations.[161] Addiction is characterized by cravings, resulting in an inability to abstain from continued drug use despite harm and impairment in behavioral control. Individually, these behaviors are often described as aberrant, although patients may display aberrant behaviors (eg, medication-related behaviors that are inconsistent with strict adherence to the prescribed treatment) that are not a result of an underlying addiction.[7] A baseline assessment and ongoing evaluation of these behaviors and an individual’s risk of misuse, abuse, and addiction is critical to mitigate risks of chronic opioid therapy and to balance effective pain management and patient safety.[161,162] Higher risk for opioid misuse or abuse is associated with personal substance abuse, misuse, addiction, or diversion history, a significant family history of substance abuse, and underlying psychiatric diagnoses. Modifications to the treatment plan, which should be stratified based on patient risk, include baseline and random drug screens, patient–provider treatment agreements, pill counts, a smaller prescription supply, and regular assessment of aberrant behaviors. Combining these approaches with regular and ongoing assessments of pain and functionality may result in improved outcomes.

Multimodal Therapy

4 5 6 Commonly, multimodal therapy may be employed to optimize either acute or chronic pain management. Multimodal therapy is the concomitant use of different therapeutic interventions with the intent of obtaining additive therapeutic effects. Multimodal analgesia, one type of multimodal therapy, includes combining medications from different analgesic classes (eg, combination therapy with opioids and nonopioids or co-analgesics).[9,129] This often results in analgesia superior to that produced by either agent alone. Multimodal analgesia may also permit the use of lower doses and provide a more favorable side-effect profile, for example when NSAIDs are prescribed with opioids yielding an “opioid sparing” effect.

Regional Analgesia

7 9 Regional analgesia with properly administered local anesthetics can provide relief of both acute and chronic pain (**Table 77-16**).[139,163,164] These agents can be positioned by injection (eg, in joints, in the epidural or intrathecal space, along nerve roots, or in a nerve plexus) or topically. Lidocaine in the form of a patch has proven effective in treating focal neuropathic pain.[64] Regional nerve blocks with local anesthetics may effectively relieve pain. Although rare, elevated plasma concentrations of local anesthetics can cause CNS excitation and depression, including dizziness, tinnitus, drowsiness, disorientation, muscle twitching, seizures, and respiratory arrest.[163] This syndrome is called LAST (local anesthetic systemic toxicity).[165] Cardiovascular adverse effects include myocardial depression, hypotension, decreased cardiac output, heart block, bradycardia, arrhythmias, and cardiac arrest. Disadvantages of such methods include the need for skillful technical application, need for frequent administration, and highly specialized follow-up procedures.

TABLE 77-16 Local Anesthetics[a]

Agent (Brand Name)	Onset (min)	Duration (h)
Esters		
Procaine (Novocain, various)	2-5	0.25-1
Chloroprocaine (Nesacaine, various)	6-12	0.5
Tetracaine (Pontocaine)	≤15	2-3
Amides		
Mepivacaine (Polocaine, various)	3-5	0.75-1.5
Bupivacaine (Marcaine, various)	5	2-4
Bupivacaine liposomal (Exparel—wound infiltration only)	variable	24 local 96 systemic
Lidocaine (Xylocaine, various)	<2	0.5-1
Prilocaine (Citanest)	<2	1-2
Ropivacaine[b] (Naropin)	10-30	0.5-6

[a]Unless otherwise indicated, values are for infiltrative anesthesia.

[b]Epidural administration.

Data from Reference 95.

SPECIAL POPULATIONS

6 9 The elderly and the young are at a higher risk for under-treatment because of potential inability to communicate or rate their pain. It is in these cases that parent or caregiver input becomes paramount to identify changes in behavior, which might suggest pain (eg, fussy, inconsolable, changes in eating patterns, crying out, or agitation). When patients cannot verbalize their pain (eg, coma), monitoring behaviors (eg, agitation) and physiologic signs and symptoms (eg, heart rate) is appropriate. Validated pain assessment tools are available to assist the clinician in approaching patients who are unable to readily communicate the severity of their pain.

In addition, those living with chronic, debilitating, and life-threatening illnesses need specialized pain control and care that is palliative in nature.[164] Although care must be taken in these populations to ensure that proper individualized treatment plans follow accepted guidelines, the key concepts in pain management as outlined in this chapter are the guiding tenets in maximizing pain control.[166,167]

PERSONALIZED PHARMACOTHERAPY

6 8 9 Recent research has illustrated genetic differences in pain transmission and response inter-individually as well as between genders, ages, and ethnicity. More interesting is the pharmacogenomic variability of analgesic response to both opioid and nonopioid analgesics. Genotyping (eg, CYP2D6, CYP2B6) may be useful when considering the addition of an opioid metabolized via one of these enzymes.

Codeine, oxycodone, hydrocodone, and methadone, as well as several of the Selective serotonin reuptake inhibitors and SNRIs, are all either converted to active or inactive metabolites via one of these enzyme pathways.[168–170] Individuals who possess a variant allele for one or more of these enzymes may have unexpected outcomes, including greater than expected toxicity or side effects or lower than expected efficacy, depending on the individual genotype and phenotype. This may be especially relevant for opioids in which much of the analgesic activity relies on conversion to an active metabolite from a relatively inactive parent (ie, codeine, tramadol). Recent data suggests high rates of variant metabolism in patients evaluated for genetic variation in CYP2C9, CYP2C19, and CYP2D6, with over 50% of patients expressing a variant in two or more genes.[171]

In some cases, genotype results may further help explain cases where patients require higher doses to achieve adequate analgesia. For example, data suggests that variants in opioid-receptor subtypes, specifically MOR-1 (OPRM1 gene), may predict efficacy and dosing requirements for some opioids such as morphine or hydromorphone.[172,173]

Use of pharmacogenomic testing results may be beneficial in the accurate interpretation of drug screens when assessing adherence to chronic opioid therapy. For instance, a urine drug screen and confirmation result that reveals only parent drug and no expected metabolites may be explained by drug–drug interactions, CYP poor metabolizer phenotype, or diversion (pill shaving). For more information regarding specific drug gene pairs related to pharmacogenomics, the Clinical Pharmacogenomics Implementation Consortium (CPIC) provides evidence-based peer-reviewed guidelines on interpretation of these testing results (www.cpicpgx.org).

EVALUATION OF THERAPEUTIC OUTCOMES

8 Consistent monitoring for effectiveness (eg, pain relief, adequate functionality) and adverse effects (eg, sedation) is critical in optimizing therapeutic outcomes. Numerous validated scoring tools exist (eg, numeric rating scale, visual analog scale); however, the tools need to be appropriate for the type of pain being evaluated, used consistently, and with good clinical judgment.[27,32] Pain management efficacy, any change in pain, and medication side effects (eg, opioid-induced sedation or constipation) must be assessed and reassessed on a regular basis. Frequency of reassessment should be dictated by the medication's route of administration, duration of action, various pharmacokinetic factors, or other concomitant therapies. Postoperative pain and acute exacerbation of cancer pain may need to be assessed hourly or even more frequently, whereas chronic noncancer pain may require only daily or less frequent assessment. Pain intensity assessment is vital in acute pain, whereas functionality becomes more of an issue in chronic pain. Quality of life must be assessed on a regular basis in all patients. Many advocate using the five "A's" (analgesia, activity, aberrant drug behavior, adverse effects, affect) as key assessment measures for any patient with chronic pain.

It is important to note that often objective signs are lacking for pain evaluation. Acute pain may result in increased sympathetic tone (eg, hypertension, tachycardia, and tachypnea); however, this response is usually diminished as acute pain progresses to chronic pain. The clinician must rely on the patient's description of their pain.

8 9 All opioids can cause constipation. The best management of constipation is prevention and patients should be counseled on the proper intake of fluids and fiber. A stimulating laxative should be added with chronic opioid use. For constipation that doesn't respond to standard bowel regimens, peripherally acting mu-opioid receptor antagonists (PAMORAs) are available for treating opioid-induced constipation. All CNS depressants (eg, alcohol, benzodiazepines) amplify CNS depression when used with opioid analgesics, and use of these combinations should be discouraged when possible. When the combinations are used, patients should be monitored closely.

CONCLUSION

Pain represents a significant source of disability as well as healthcare resource utilization. A thorough understanding of pain pathogenesis is imperative for clinicians involved in its treatment. Multidisciplinary and multimodal approaches to pain management must be considered with nonpharmacological

and nonopioid modalities preferred as first-line treatments. Opioid analgesics are important analgesic alternatives and should be considered after careful patient selection. Monitoring for risk of misuse and abuse while these agents are employed is essential. Adverse effects of all pharmacologic therapy for pain require judicious anticipation and treatment (**Fig. 77-3**).

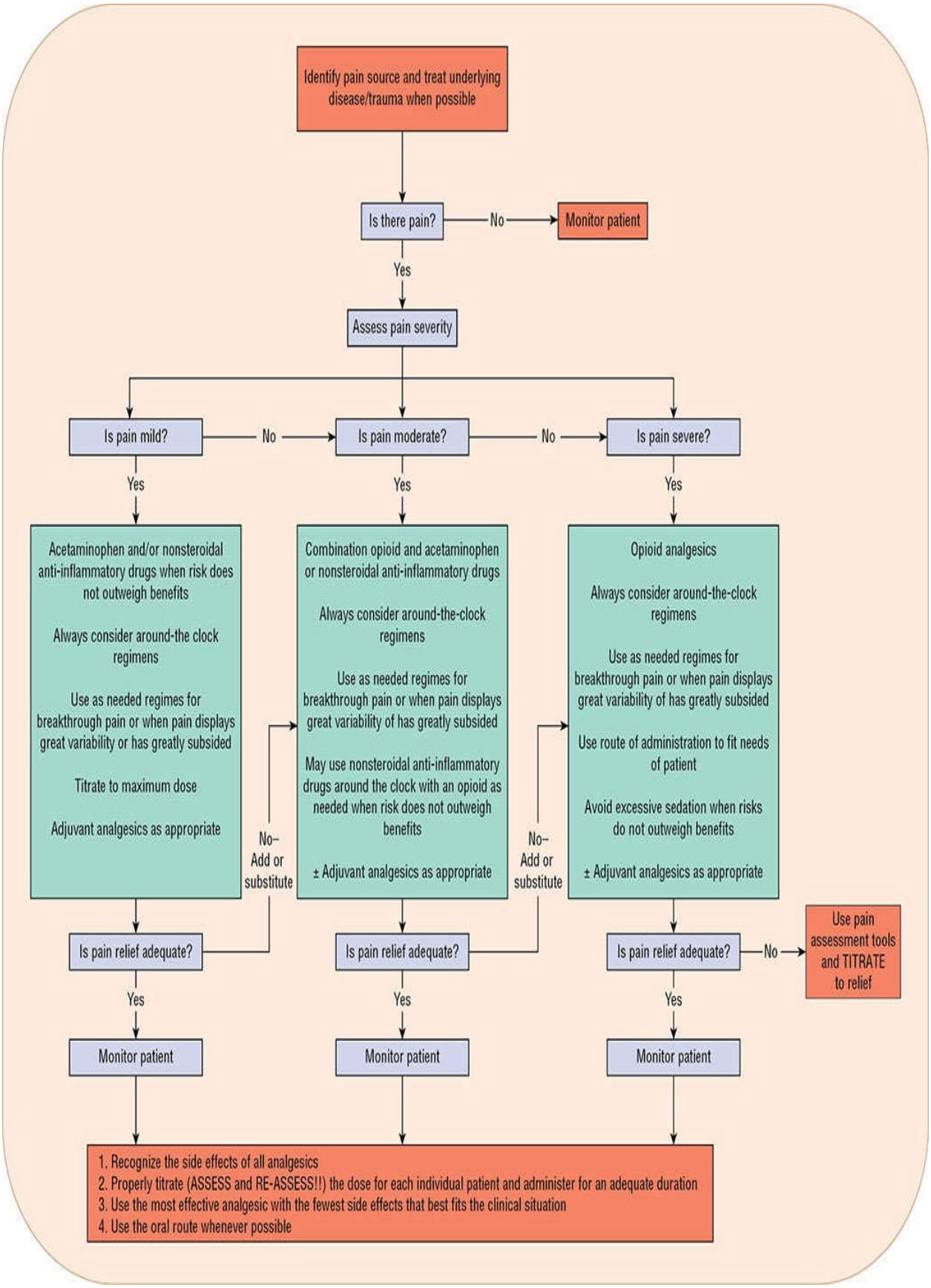

Identify pain source and treat underlying disease/trauma when possible
Is there pain?
No
Monitor patient
Yes
Assess pain severity
Is pain mild?
No
Is pain moderate?
No
Is pain severe?
Yes
Yes
Yes
Acetaminophen and/or nonsteroidal anti-inflammatory drugs when risk does not outweigh benefits
Always consider around-the clock regimens
Use as needed regimes for breakthrough pain or when pain displays great variability or has greatly subsided
Titrate to maximum dose
Adjuvant analgesics as appropriate
Combination opioid and acetaminophen or nonsteroidal anti-inflammatory drugs
Always consider around-the-clock regimens
Use as needed regimes for breakthrough pain or when pain displays great variability of has greatly subsided
May use nonsteroidal anti-inflammatory drugs around the clock with an opioid as needed when risk does not outweigh benefits
± Adjuvant analgesics as appropriate
Opioid analgesics
Always consider around-the-clock regimens
Use as needed regimes for breakthrough pain or when pain displays great variability of has greatly subsided
Use route of administration to fit needs of patient
Avoid excessive sedation when risks do not outweigh benefits
± Adjuvant analgesics as appropriate
No– Add or substitute
No– Add or substitute
Is pain relief adequate?
Is pain relief adequate?
Is pain relief adequate?
No
Use pain assessment tools and TITRATE to relief
Yes
Yes
Yes
Monitor patient
Monitor patient
Monitor patient
1. Recognize the side effects of all analgesics
2. Properly titrate (ASSESS and RE-ASSESS!!) the dose for each individual patient and administer for an adequate duration
3. Use the most effective analgesic with the fewest side effects that best fits the clinical situation
4. Use the oral route whenever possible

FIGURE 77-3 Algorithm for acute pain. (*Data from Omnicare, Inc., Acute Pain Pathway.*).

Postclass Engaged Learning Activity

Use the Pharmacotherapy Casebook: Chapter 70, "Chronic Pain Management: Using Opioid Medication in a Troubled Time Level II" to develop a pain-focused assessment and plan (including rationale) for this case.

ABBREVIATIONS

COX-2	cyclooxygenase-2
GABA	γ-aminobutyric acid
M3G	morphine-3-glucuronide
M6G	morphine-6-glucuronide
NMDA	*N*-methyl-D-aspartate
NSAIDs	nonsteroidal anti-inflammatory drugs
PCA	patient-controlled analgesia
PNS	peripheral nervous system
TENS	transcutaneous electrical nerve stimulation
WHO	World Health Organization
DOR	delta opioid receptor
KOR	kappa opioid receptor
MOR	mu-opioid receptor
CYP	cytochrome P450
CNS	central nervous system
GI	gastrointestinal
IV	intravenous
IM	intramuscular
IgE	immunoglobulin E
ORL-1	opioid receptor-like receptor (noceptin receptor)
ASAM	American Society of Addiction Medicine
OPRM1	opioid receptor, mu-1 gene subtype

REFERENCES

1. Bennett DS, Breakthrough pain: Treatment rationale with opioids. Available at: http://www.medscape.org/viewarticle/461612. Accessed January 6, 2019.
2. Stimmel B. *Pain, Analgesia, and Addiction: The Pharmacology of Pain*. New York, NY: Raven Press; 1983.
3. Blackwell DL, Lucas JW, Clarke TC. Summary health statistics for U.S. adults: National health interview survey, 2012. *Vital Heal Stat 10*. 2014; (260):1–161. Accessed October 4, 2018.http://www.ncbi.nlm.nih.gov/pubmed/24819891.
4. *Classification of Chronic Pain, Second Edition (Revised)*. Washington, DC: IASP; 2012. http://www.iasp-pain.org/PublicationsNews/Content.aspx?ItemNumber=1673&navItemNumber=677. Accessed January 6, 2019.
5. *Institute of Medicine: Relieving Pain in America, A Blueprint for Transforming Prevention, Care, Education, and Research*. Washington, DC: National Academies of Science; 2011. https://iprcc.nih.gov/sites/default/files/IOM_Pain_Report_508C.pdf. Accessed September 25, 2018.
6. Humble SR, Dalton AJ, At the L. A systematic review of therapeutic interventions to reduce acute and chronic post-surgical pain after amputation, thoracotomy or mastectomy. *Eur J Pain*. 2015;19(4):451–465. doi:10.1002 / ejp.567.
7. Webster LR, Fine PG. Approaches to improve pain relief while minimizing opioid abuse liability. *J Pain*. 2010;11(7):602–611. doi:10.1016 / j.jpain.2010.02.008.
8. Woolf CJ. What is this thing called pain? *J Clin Invest*. 2010;120(11):3742–3744. doi:10.1172 / JCI45178.
9. Sparrow C, Quinn TO, Portenoy RD. Physiology and pharmacology of opioids analgesics. In: McCaffery M, Sparrow C, eds. *Pain Assessment and Pharmacologic Management*. St. Louis, MO: Mosby; 2011;283–300.
10. McEntire DM, Kirkpatrick DR, Dueck NP, et al. Pain transduction: A pharmacologic perspective. *Expert Rev Clin Pharmacol*. 2016;9(8):1069–1080. doi.10.1080/17512433.2016.1183481.
11. Dubin AE, Patapoutian A. Nociceptors: The sensors of the pain pathway. *J Clin Invest*. 2010;120(11):3760–3772. doi:10.1172/JCI42843.
12. Cummins TR, Sheets PL, Waxman SG. The roles of sodium channels in nociception: Implications for mechanisms of pain. *Pain*. 2007;131(3):243–

257. doi:10.1016/j.pain.2007.07.026.

13. Fong A, Schug SA. Pathophysiology of pain: A practical primer. *Plast Reconstr Surg*. 2014;134(4 suppl 2):8S–14S. doi.10.1097/PRS.0000000000000682.
14. Sparrow C, Portenoy R. Neurophysiology of pain and analgesia and the pathophysiology of neuropathic pain. In: McCaffery M, Sparrow C, eds. *Pain Assessment and Pharmacologic Management*. St. Louis, MO: Mosby; 2011:1–12.
15. Randich A, Ness T. Modulation of spinal nociceptive processing. In: Fishman SM, Ballantyne JC, Rathmell JP, eds. *Bonica's Pain Management*. Baltimore, MD: Wolters Kluwer Health; 2010.
16. Woolf CJ. Central sensitization: Implications for the diagnosis and treatment of pain. *Pain*. 2011;152(suppl):S2–S15. doi:10.1016/j.pain.2010.09.030.
17. Human LS, Birnie KA, Noel M, et al. Psychological interventions for needle-related procedural pain and distress in children and adolescents. *Cochrane Database Syst Rev*. 2013;10:CD005179. doi:10.1002/14651858.CD005179.pub3.
18. Wetherell JL, Dinner N, Rutledge T, et al. A randomized, controlled trial of acceptance and commitment therapy and cognitive-behavioral therapy for chronic pain. *Pain*. 2011;152(9):2098–2107. doi:10.1016/j.pain.2011.05.016.
19. Tsatali M, Papaliagkas V, Damigos D, Mavreas V, Gouva M, Tsolaki M. Depression and anxiety levels increase chronic musculoskeletal pain in patients with Alzheimer's disease. *Curr Alzheimer Res*. 2014;11(6):574–579. doi:10.2174/1567205011666140618103406.
20. Scholz J, Woolf CJ. The neuropathic pain triad: Neurons, immune cells and glia. *Nat Neurosci*. 2007;10(11):1361–1368. doi.10.1038 / nn1992.
21. Grace PM, Hutchinson MR, Maier SF, Watkins LR. Pathological pain and the neuroimmune interface. *Nat Rev Immunol*. 2014;14(4):217–231. doi:10.1038 / nri3621.
22. Clauw DJ. Fibromyalgia. *J Am Med Assoc*. 2014;311(15):1547. doi:10.1001 / jama.2014.3266.
23. Apkarian OF, Review MN, Farmer MA. Predicting transition to chronic pain. *Curr Opin Neurol*. 2013;26(4):360–367. doi:10.1097 / WCO.0b013e32836336ad.
24. Gold MS, Gebhart GF. Peripheral pain mechanisms and nociceptor

sensitization. In: Fishman SM, Ballantyne JC, Rathmell JP, eds. *Bonica's Pain Management*. Baltimore, MD: Wolters Kluwer Health; 2010;24–34.

25. Apkarian OF. Pain and brain changes. In: Benzon HT, Rathmell JP, Wu CL, eds. *Raj's Practical Management of Pain*. Philadelphia, PA: Mosby; 2008;151–173.
26. Hanley MA, Jensen MP, Smith DG, Ehde DM, Edwards WT, Robinson LR. Preamputation pain and acute pain predict chronic pain after lower extremity amputation. *J Pain*. 2007;8(2):102–109. doi:10.1016 / j.jpain.2006.06.004.
27. McCaffery M, Herr K, Sparrow C. Assessment. In: Sparrow C, McCaffery M, eds. *Pain Assessment and Pharmacologic Management*. St. Louis, MO: Mosby Elsevier; 2011.
28. Twycross RG. Pain and analgesics. *Curr Med Res Opin*. 1978;5(7):497–505. doi:10.1185/03007997809108992.
29. Latremoliere A, Woolf CJ. Central Sensitization: A generator of pain hypersensitivity by central neural plasticity. *J Pain*. 2009;10(9):895–926. doi:10.1016 / J.JPAIN.2009.06.012.
30. Swarm RA, Abernethy AP, Anghelescu DL, et al. Adult cancer pain. *J Natl Compr Canc Netw*. 2013;11(8):992–1022. http://www.ncbi.nlm.nih.gov/pubmed/23946177. Accessed October 9, 2018.
31. Swarm RA, Paice JA, Anghelescu DL, et al. *NCCN Clinical Practice Guidelines in Oncology: Adult Cancer Pain*. 2018. https://www.nccn.org/professionals/physician_gls/PDF/pain.pdf.
32. Breivik H, Borchgrevink PC, Allen SM, et al. Assessment of pain. *Br J Anaesth*. 2008;101(1):17–24. doi:10.1093 / bja / aen103.
33. Clayton HA, Reschak GL, Gaynor HE, Creamer JL. A novel program to assess and manage pain. *Medsurg Nurs*. 2000;9(6):317–321. http://www.ncbi.nlm.nih.gov/pubmed/11904868.
34. Krebs EE, Lorenz KA, Bair MJ, et al. Development and initial validation of the PEG: A three-item scale assessing pain intensity and interference. *J Gen Intern Med*. 2009;24(6):733–738. doi.10.1007/s11606-009-0981-1.
35. Chou R, Qaseem A, Snow V, et al. Diagnosis and treatment of low back pain: A joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med*. 2007;147(7):478–491. http://www.ncbi.nlm.nih.gov/pubmed/17909209.
36. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids

for chronic pain: United States. *JAMA*. 2016;315(15):1624–1645. doi.10.1001 / jama.2016.1464.

37. Bonacre, Clothier AW. *Integrative Pain Management*. Oxford: Oxford University Press; 2016. 10.1093 / with / 9780199315246.001.0001.
38. Tick H, Nielsen A, Pelletier KR, et al. Evidence-based nonpharmacologic strategies for comprehensive pain care. *Explore*. 2018;14(3):177–211. doi.10.1016/j.explore.2018.02.001.
39. O'Donnell KF. Preoperative pain management education: A quality improvement project. *J PeriAnesthesia Nurs*. 2015;30(3):221–227. doi:10.1016/j.jopan.2015.01.013.
40. Darnall BD. Minimize opioids by optimizing pain psychology. *Pain Manag*. 2014;4(4):251–253. doi:10.2217/pmt.14.18.
41. Boldt I, Eriks-Hoogland I, Brinkhof MW, De Bie R, Joggi D, from Elm E. Non-pharmacological interventions for chronic pain in people with spinal cord injury. *Cochrane Database Syst Rev*. 2014;(11):CD009177. doi:10.1002/14651858.CD009177.pub2.
42. Vance CG, Dailey DL, Rachel BA, Devour KA. Using TENS for pain control: The state of the evidence. *Pain Manag*. 2014;4(3):197–209. doi.10.2217/pmt.14.13.
43. Lee C, Crawford C, Hickey A. Active Self-Care Therapies for Pain (PACT) Working Group. Mind–body therapies for the self-management of chronic pain symptoms. *Pain Med*. 2014;15(S1):S21–S39. doi.10.1111 / pme.12383.
44. Kligler B, Teets R, Quick M. Complementary/integrative therapies that work: A review of the evidence. *Am Fam Physician*. 2016;94(5):369–374. http://www.ncbi.nlm.nih.gov/pubmed/27583423. Accessed November 6, 2018.
45. Solloway MR, Taylor SL, Shekelle PG, et al. An evidence map of the effect of Tai Chi on health outcomes. *Syst Rev*. 2016;5(1):126. doi:10.1186 / s13643-016-0300-y.
46. *WHO Guidelines for the Pharmacological and Radiotherapeutic Management of Cancer Pain in Adults and Adolescents*. WHO; 2018. doi: 10.4135/9781446222126.n9.
47. Herndon C, Arnstein P, Darnall B, et al. *Principles of Analgesic Use*. 7th ed. Chicago: American Pain Society; 2016. https://www.amazon.com/Principles-Analgesic-Use-7th-APS/dp/B071WG3PSW. Accessed October 1, 2018.

48. Chou R, Deyo R, Devine B, et al. Evidence Report/Technology Assessment Number 218. *Agency Healthc Res Qual*. 2014. doi:10.23970 / AHRQEPCERTA218.
49. Nuckols TK, Anderson L, Popescu I, et al. Opioid prescribing: A systematic review and critical appraisal of guidelines for chronic pain. *Ann Intern Med*. 2013;160(1):38–47. doi.10.7326/0003-4819-160-1-201401070-00732.
50. Peppin JF, Passik SD, Couto JE, et al. Recommendations for urine drug monitoring as a component of opioid therapy in the treatment of chronic pain. *Pain Med*. 2012;13(7):886–896. doi:10.1111/j.1526-4637.2012.01414.x.
51. CDC guideline for prescribing opioids for chronic pain — United States, 2016. Regulatory Alert FDA Warning/Regulatory Alert Recommendations. *Morb Mortal Wkly Rep*. 2016;65(1).
52. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol*. 2010;17(9):1113–E88. doi:10.1111/j.1468-1331.2010.02999.x.
53. Moore RAA, Derry S, Wiffel PJJ, Straube S, Aldington DJJ. Overview review: Comparative efficacy of oral ibuprofen and paracetamol (acetaminophen) across acute and chronic pain conditions. *Eur J Pain*. 2014;19(9):1213–1223. doi:10.1002 / ejp.649.
54. Machado GC, Maher CG, Ferreira PH, et al. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: Systematic review and meta-analysis of randomised placebo controlled trials. *BMJ*. 2015;350:h1225. Accessed October 9, 2018. http://www.ncbi.nlm.nih.gov/pubmed/25828856.
55. Aronoff D, Oates J, Boutaud O. New insights into the mechanism of action of acetaminophen: Its clinical pharmacologic characteristics reflect its inhibition of the two prostaglandin H2 synthases. *Clin Pharmacol Ther*. 2006;79(1):9–19. doi:10.1016/j.clpt.2005.09.009.
56. McAlindon TO, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthr Cartil*. 2014;22(3):363–388. doi:10.1016 / j.joca.2014.01.003.
57. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res*. 2012;64(4):465–474.

http://www.ncbi.nlm.nih.gov/pubmed/22563589.

58. Roelofs PD, Deyo RA, Koes BW, Scholten RJ, from Tulder MW. Nonsteroidal anti-inflammatory drugs for low back pain: An updated Cochrane review. *Spine (Phila Pa 1976)*. 2008;33(16):1766–1774. doi.10.1097/BRS.0b013e31817e69d3.
59. Yousef AA, Alzeftawy AE. The efficacy of oral piroxicam fast-dissolving tablets versus sublingual fentanyl in incident breakthrough pain due to bone metastases: A double-blinded randomized study. *Support Care Cancer*. October 2018. doi.10.1007/s00520-018-4469-6.
60. Nissen HE, Yeomans ND, Solomon DH, et al. Cardiovascular safety of Celecoxib, Naproxen, or Ibuprofen for arthritis. *N Engl J Med*. 2016;375(26):2519–2529. doi.10.1056 / NEJMoa1611593.
61. Gunter BR, Butler KA, Wallace RL, Smith SM, Harirforoosh S. Non-steroidal anti-inflammatory drug-induced cardiovascular adverse events: A meta-analysis. *J Clin Pharm Ther*. 2017. doi.10.1111/jcpt.12484.
62. Roth SH, Fuller P. Diclofenac topical solution compared with oral diclofenac: A pooled safety analysis. *J Pain Res*. 2011;4:159–167. doi.10.2147/JPR.S20965.
63. Stanos S. Osteoarthritis guidelines: A progressive role for topical NSAIDs. *J Am Osteopat Assoc*. 2013;113(2):123–127. http://www.ncbi.nlm.nih.gov/pubmed/23412673.
64. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis. *Lancet Neurol*. 2015;14(2):162–173. doi.10.1016/S1474-4422(14)70251-0.
65. Moulin D, Boulanger A, Clark AJ, et al. Pharmacological management of chronic neuropathic pain: Revised consensus statement from the Canadian Pain Society. *Pain Res Manag*. 2014;19(6):328–335.
66. Pop-Busui R, Boulton Ajm, Feldman EL, et al. Diabetic neuropathy: A position statement by the American Diabetes Association. *Diabetes Care*. 2016;40(January):136–154. 10.2337/dc16-2042.
67. Waldfogel JM, Nesbit SM, et al. Pharmacotherapy for diabetic peripheral neuropathy pain and quality of life. *Neurology*. 2017;88(29):1958–1967. doi:10.1212 / WNL.0000000000003882.
68. Dharmshaktu P, Tayal V, Kalra BS. Efficacy of antidepressants as analgesics: A review. *J Clin Pharmacol*. 2012;52(1):6–17. doi:10.1177/0091270010394852.
69. Wiffel PJ, Derry S, Moore RA, Kalso EA. Carbamazepine for chronic

neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev*. 2014;(4):CD005451. doi:10.1002/14651858.CD005451.pub3.

70. Wiffel PJ, Derry S, Moore RA. Lamotrigine for acute and chronic pain. *Cochrane database Syst Rev*. 2011. doi:10.1002/14651858.CD006044.pub3.
71. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: Evidence-based recommendations. *Pain*. 2007;132(3):237–251. doi:10.1016/j.pain.2007.08.033.
72. Gronseth G, Cruccu G, Alksne J, et al. Practice parameter: The diagnostic evaluation and treatment of trigeminal neuralgia. *Neurology*. 2008;71:1183–1190.
73. National Institute for Health and Care Excellence. Neuropathic pain – pharmacological management. The pharmacological management of neuropathic pain in adults in non-specialist settings. NICE clinical guideline 173. *Natl Inst Heal Care Excell*. 2013.
74. Kaniwa N, Saito Y. The risk of cutaneous adverse reactions among patients with the *HLA-A* 31:01* allele who are given carbamazepine, oxcarbazepine or eslicarbazepine: A perspective review. *Ther Adv Drug Saf*. 2013;4(6):246–253. doi.10.1177/2042098613499791.
75. Berghuis B, de Haan G-J, van den Broek MPH, Sander JW, Lindhout D, Koeleman BPC. Epidemiology, pathophysiology and putative genetic basis of carbamazepine- and oxcarbazepine-induced hyponatremia. *Eur J Neurol*. 2016;23(9):1393–1399. doi:10.1111/ene.13069.
76. Al-Quliti KW. Update on neuropathic pain treatment for trigeminal neuralgia: The pharmacological and surgical options. *Neurosciences*. 2015. doi:10.17712/nsj.2015.2.20140501.
77. Zhou M, Chen N, He L, Yang M, Zhu C, Wu F. Oxcarbazepine for neuropathic pain. *Cochrane Database Syst Rev*. 2013;12(3):CD007963. doi:10.1002/14651858.CD007963.pub2.
78. Beverly A, Kaye AD, Ljungqvist O, Urman RD. Essential elements of multimodal analgesia in enhanced recovery after surgery (ERAS) guidelines. *Anesthesiol Clin*. 2017;35(2):e115–e143. doi.10.1016/j.anclin.2017.01.018.
79. Arumugam S, Lau CSM, Chamberlain RS. Use of preoperative gabapentin significantly reduces postoperative opioid consumption: A meta-analysis. *J Pain Res*. 2016;9:631–640. doi:10.2147/JPR.S112626.
80. Siddiqui NT, Yousefzadeh A, Yousuf M, Kumar D, Choudhry FK,

Friedman Z. The effect of Gabapentin on delayed discharge from the postanesthesia care unit: A retrospective analysis. *Pain Pract*. 2018;18(1):18–22. doi.10.1111/papr.12575.

81. Jiang H, Huang S, Song J, Wang X, Cao Z. Normal and cohyponormal weighted composition operators on H 2. *Medicine (Baltimore)*. 2010;68(2002):2002. doi:10.1097/MD.0000000000006129.
82. Doleman B, Heinink TP, Read DJ, Faleiro RJ, Lund JN, Williams JP. A systematic review and meta-regression analysis of prophylactic gabapentin for postoperative pain. *Anaesthesia*. 2015;70(10):1186–1204. doi:10.1111/anae.13179.
83. Vyvey M. Steroids as pain relief adjuvants. *Can Fam Physician*. 2010;56(3):1295–1297. doi:56/12/1295.[pii].
84. Yao Z, Shen C, Zhong Y. Perioperative pregabalin for acute pain after gynecological surgery: A meta-analysis. *Clin Ther*. 2015;37(5):1128–1135. doi.10.1016/j.clinthera.2014.04.020.
85. Zhang J, Ho KY, Wang Y. Efficacy of pregabalin in acute postoperative pain: A meta-analysis. *Br J Anaesth*. 2011;106(4):454–462. doi:10.1093/bja/aer027.
86. Martinez V, Pichard X, Fletcher D. Perioperative pregabalin administration does not prevent chronic postoperative pain: Systematic review with a meta-analysis of randomized trials. *Pain*. 2017;158(5):775–783. doi:10.1097/j.pain.0000000000000838.
87. Shanthanna H, Gilron I, Rajarathinam M, et al. Benefits and safety of gabapentinoids in chronic low back pain: A systematic review and meta-analysis of randomized controlled trials. *PLoS Med*. 2017;14(8):e1002369. doi:10.1371/journal.pmed.1002369.
88. Mathieson S, Maher CG, McLachlan AJ, et al. Trial of Pregabalin for acute and chronic sciatica. *N Engl J Med*. 2017;376(12):1111–1120. doi.10.1056/NEJMoa1614292.
89. Schifano F. Misuse and abuse of pregabalin and gabapentin: Cause for concern? *CNS Drugs*. 2014;28(6):491–496. doi:10.1007/s40263-014-0164-4.
90. Evoy KE, Morrison MD, Saklad SR. Abuse and misuse of pregabalin and gabapentin. *Drugs*. 2017;77(4):403–426. doi:10.1007/s40265-017-0700-x.
91. Koncicki HM, Unruh M, Schell JO. Pain management in CKD: A guide for nephrology providers. *Am J Kidney Dis*. 2017;69(3):451–460. doi:10.1053/j.ajkd.2016.08.039.

92. Khoromi S, Patsalides A, Parada S, Salehi V, Meegan JM, Max MB. Topiramate in chronic lumbar radicular pain. *J Pain*. 2005;6(12):829–836. doi:10.1016/j.jpain.2005.08.002.
93. Muehlbacher M, Nickel MK, Kettler C, et al. Topiramate in treatment of patients with chronic low back pain: A randomized, double-blind, placebo-controlled study. *Clin J Pain*. 2006;22(6):526–531. doi.10.1097/.ajp.0000192516.58578.a4.
94. Derry S, Phillips T, Moore RA, Wiffen PJ. Milnacipran for neuropathic pain in adults. *Cochrane Database Syst Rev*. 2015; (7):CD011789.doi:10.1002/14651858.CD011789.
95. Lexicomp. Lexicomp Online; 2018. Available at: online.lexi.com.
96. Macfarlane GJ, Kronisch C, Dean LE, et al. EULAR revised recommendations for the management of fibromyalgia. *Ann Rheum Dis*. 2017;76(2):318–328. doi.10.1136/annrheumdis-2016-209724.
97. DeBattista C. Antidepressant agents. In: Katzung B, ed. *Basic and Clinical Pharmacology*. 14th ed. New York, NY: 2017.
98. Teter C, Kando J, Wells B. Major depressive disorders. In: DiPiro J, Talbert R, Yee G, Matzke G, Wells B, Posey L, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 10th ed. New York, NY: McGraw-Hill; 2016.
99. Gelenberg AJ, Marlene Freeman CP, Markowitz JC, et al. *Practice Guideline for the Treatment of Patients with Major Depressive Disorder Third Edition Work Group On Major Depressive Disorder*. 2010. http://www.psychiatryonline.com/pracGuide/pracGuideTopic_7.aspx.
100. Qaseem A, Wilt TJ, McLean RM, Forciea MA. Noninvasive treatments for acute, subacute, and chronic low back pain: A clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2017;166(7):514–530. doi:10.7326/M16-2367.
101. Kus T, Aktas G, Alpak G, et al. Efficacy of venlafaxine for the relief of taxane and oxaliplatin-induced acute neurotoxicity: a single-center retrospective case–control study. *Support Care Cancer*. 2016;24(5):2085–2091. doi:10.1007/s00520-015-3009-x.
102. Rej S, Dew MA, Karp JF. Treating concurrent chronic low back pain and depression with low-dose venlafaxine: An initial identification of “easy-to-use” clinical predictors of early response. *Pain Med (United States)*. 2014;15(7):1154–1162. doi:10.1111/pme.12456.
103. O’Connor AB, Dworkin RH. Treatment of neuropathic pain: An overview of recent guidelines. *Am J Med*. 2009;122(10 Suppl):S22–S32.

doi:10.1016/j.amjmed.2009.04.007.

104. Bendtsen L, Evers S, Linde M, Mitsikostas DD, Sandrini G, Schoenen J. EFNS guideline on the treatment of tension-type headache: Report of an EFNS task force. *Eur J Neurol*. 2010;17(11):1318–1325. doi.10.1111/j.1468-1331.2010.03070.x.
105. Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults report of the quality standards subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012;78(17):1337–1345. doi:10.1212/WNL.0b013e3182535d20.
106. Sansone RA, Sansone LA. Serotonin norepinephrine reuptake inhibitors: A pharmacological comparison. *Innov Clin Neurosci*. 2014;11(3-4):37–42. Accessed September 25, 2018. http://www.ncbi.nlm.nih.gov/pubmed/24800132.
107. Herndon C, Lider J, Daniels A. Ask the Expert: QT interval and antidepressants. *Pract Pain Manag*. 2015;15(10):1–3. https://www.practicalpainmanagement.com/treatments/pharmacological/no opioids/qt-intervals-antidepressants. Accessed October 20, 2018.
108. De Abajo FJ, Garcia-Rodriguez LA. Risk of upper gastrointestinal tract bleeding associated with selective serotonin reuptake inhibitors and venlafaxine therapy. *Arch Gen Psychiatry*. 2008;65(7):795–803. doi:10.1001/archpsyc.65.7.795.
109. Van Walraven C, Mamdani MM, Wells PS, Williams JI. Inhibition of serotonin reuptake by antidepressants and retrospective cohort study. *BMJ*. 2001;323(7314):655–658. doi:10.1136/BMJ.323.7314.655.
110. Heetla HW, Staal MJ, Proost JH, Van Laar T. Clinical relevance of pharmacological and physiological data in intrathecal baclofen therapy. *Arch Phys Med Rehabil*. 2014;95(11):2199–2206. doi:10.1016/j.apmr.2014.04.030.
111. van Tulder MW, Touray T, Furlan AD, Solway S, Bouter LM. Muscle relaxants for non-specific low back pain. *Cochrane Database Syst Rev*. 2003;(2):Cd004252. doi:10.1002/14651858.cd004252.
112. Beebe FA, Barkin RL, Barkin S. A clinical and pharmacologic review of skeletal muscle relaxants for musculoskeletal conditions. *Am J Ther*. 2005;12(2):151–171. doi:10.1097/01.mjt.0000134786.50087.d8.
113. Witenko C, Moorman-li R, Motycka C, et al. Considerations for muscle

relaxants in low back pain. *Pharm Ther*. 2014;39(6):427–435.

114. Malanga GA, Gwynn MW, Smith R, Miller D. Tizanidine is effective in the treatment of myofascial pain syndrome. *Pain Physician*. 2002;5(4):422–432. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16886022.
115. See S, Ginzburg R. Skeletal muscle relaxants. *Pharmacotherapy*. 2008;28(2):207–213.
116. Vlavonou R, Perreault MM, Barrière O, et al. Pharmacokinetic characterization of baclofen in patients with chronic kidney disease: Dose adjustment recommendations. *J Clin Pharmacol*. 2014;54(5):584–592. doi.10.1002/jcph.247.
117. Fudin J, Raouf M. A review of skeletal muscle relaxants for pain management. *Pract Pain Manag*. 2017;16(5):1–4.
118. Samuel MJ. American Geriatrics Society 2015 updated Beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2015;63(11):2227–2246. doi:10.1111/jgs.13702.
119. Raouf M, Fudin J. A review of skeletal muscle relaxants for pain management. *Pract Pain Manag*. 2016.
120. By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. January 2019. doi.10.1111/jgs.15767.
121. Argoff CE. Topical analgesics in the management of acute and chronic pain. *Mayo Clin Proc*. 2013;88(2):195–205. doi:10.1016/j.mayocp.2012.11.015.
122. Derry S, Wiffen PJ, Kalso EA, et al. Topical analgesics for acute and chronic pain in adults: An overview of Cochrane reviews. *Cochrane Database Syst Rev*. 2017;5:CD008609. doi.10.1002/14651858.CD008609.pub2.
123. Management of osteoarthritis: NICE Pathways. National Institute for Health and Care Excellence; 2015. Available at: https://pathways.nice.org.uk/pathways/osteoarthritis#path=view%3A/pathv of-osteoarthritis.xml&content=view-node%3Anodes-pharmacological-treatments. Accessed November 6, 2018.
124. McCormick M. *The Health Effects of Cannabis and Cannabinoids*; 2017. doi:10.17226/24625.
125. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use:

A systematic review and meta-analysis. *J Am Med Assoc*. 2015;313(24):2456–2473. doi.10.1001/jama.2015.6358.

126. Baron EP. Medicinal properties of cannabinoids, terpenes, and flavonoids in cannabis, and benefits in migraine, headache, and pain: An Update on current evidence and cannabis science. *Headache J Head Face Pain*. 2018;58(7):1139–1186. doi:10.1111/head.13345.
127. Cohen SP, Bhatia A, Buvanendran A, et al. Consensus guidelines on the use of intravenous ketamine infusions for chronic pain from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Reg Anesth Pain Med*. 2018;43(5):521–546. doi.10.1097/AAP.0000000000000808.
128. Yaksh TL, Wallace MS. Opioids, analgesia, and pain management. In: Brunton LL, Chabner BA, Knollman BC, eds. *The Pharmacological Basis of Therapeutics*. 13th ed. New York, NY: McGraw-Hill; 2018;355–386.
129. Pasternak GW. Molecular insights into mu opioid pharmacology: From the clinic to the bench. *Clin J Pain*. 2010;26(suppl 10):S3–S9. doi:10.1097/AJP.0b013e3181c49d2e.
130. Crockett S, Greer K, Heidelbaugh J, Falck-Ytter Y, Hanson B, Sultan S. American Gastroenterological Association Institute guideline on the medical management of opioid-induced constipation. *Gastroenterology*. 2018. [epub ahea:1-9. doi.10.1053/j.gastro.2015.11.008.
131. McPherson ML. *Demystifying Opioid Conversion Calculations*. 2nd ed. Bethesda, MD: American Society of Health-System Pharmacists; 2018.
132. Topaz M, Seger DL, Lai K, et al. High override rate for opioid drug-allergy interaction alerts: Current trends and recommendations for future. *Stud Health Technol Inform*. 2015;216:242–246. http://www.ncbi.nlm.nih.gov/pubmed/26262047. Accessed October 11, 2018.
133. DeDea L. Prescribing opioids safely in patients with an opiate allergy. *JAAPA*. 2012;25(1):17. http://www.ncbi.nlm.nih.gov/pubmed/22384750. Accessed October 11, 2018.
134. Woodall HE, Chiu A, Weissman DE. Opioid Allergic Reactions #175. *J Palliat Med*. 2008;11(10):1340–1342. doi:10.1089/jpm.2008.9817.
135. Chou R, Gordon DB, De Leon-casasola OA, et al. Management of postoperative pain: A clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine,

and the American Society of Anesthesiologists' Committee on Regional Anesthesia. *J Pain*. 2016;17(2):131–157. doi.10.1016/j.jpain.2015.12.008.

136. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: An updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology*. 2012;116(2):248–273. doi.10.1097/ALN.0b013e31823c1030.
137. McNicol ED, Ferguson MC, Hudcova J. Patient controlled opioid analgesia versus non-patient controlled opioid analgesia for postoperative pain. *Cochrane Database Syst Rev*. 2015; (6):CD003348.doi:10.1002/14651858.CD003348.pub3.
138. Bujedo BM, Santos SG, Azpiazu AU, et al. A review of epidural and intrathecal opioids used in the management of postoperative pain. *J Opioid Manag*. 2012;8(3):177–192. doi:10.5055/jom.2012.0114.
139. Ghafoor V, Epshteyn M, Carlson G, Terhaar D, Charry O, Phelps P. Intrathecal drug therapy for long-term pain management. *Am J Health Syst Pharm*. 2007;64:2447–2461. doi:10.2146/ajhp060204.
140. Jokinen J, Smith AF, Roewer N, Eberhart LH, Kranke P. Management of postoperative nausea and vomiting: How to deal with refractory PONV. *Anesth Clin*. 2012;30(3):481–493. doi.10.1016/j.anclin.2012.07.003.
141. Chou R, Weimer MB, Dana T. Methadone overdose and cardiac arrhythmia potential: Findings from a review of the evidence for an American Pain Society and College on Problems of Drug Dependence clinical practice guideline. *J Pain*. 2014;15(4):338–365. doi.10.1016/j.jpain.2014.01.495.
142. Conway A, Douglas C, Sutherland J. Capnography monitoring during procedural sedation and analgesia: A systematic review protocol. *Syst Rev*. 2015;4(1):92. doi.10.1186/s13643-015-0085-4.
143. Zedler B, Xie L, Wang L, et al. Development of a Risk Index for serious prescription opioid-induced respiratory depression or overdose in Veterans' Health Administration patients. *Pain Med*. 2015;16(8):1566–1579. doi.10.1111/pme.12777.
144. Meine TJ, Roe MT, Chen AY, et al. Association of intravenous morphine use and outcomes in acute coronary syndromes: Results from the CRUSADE Quality Improvement Initiative. *Am Heart J*. 2005;149(6):1043–1049. doi.10.1016/j.ahj.2005.02.010.
145. Birthi P, Nagar VR, Nickerson R, et al. Hypogonadism associated with

long-term opioid therapy: A systematic review. *J Opioid Manag*. 2015;11(3):255–278. doi.10.5055/jom.2015.0274.

146. McNulty JP. Chronic pain: Levorphanol, methadone, and the N-methyl-D-aspartate receptor. *J Palliat Med*. 2009;12(9):765–766. doi.10.1089/jpm.2009.0105.
147. Prommer E. Levorphanol: Revisiting an underutilized analgesic. *Palliat Care*. 2014;8:7–10. doi.10.4137/PCRT.S13489.
148. Drug Safety and Availability—FDA Drug Safety Communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm549679.htm. Accessed November 6, 2018.
149. Latta KS, Ginsberg B, Barkin RL. Meperidine: A critical review. *Am J Ther*. 2002;9(1):53–68. Accessed October 11, 2018. http://www.ncbi.nlm.nih.gov/pubmed/11782820.
150. Chou R, Cruciani RA, Fiellin DA, et al. Methadone safety: A clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. *J Pain*. 2014;15(4):321–337. doi.10.1016/j.jpain.2014.01.494.
151. Chou R, Deyo R, Devine B, et al. *The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain*. Agency for Healthcare Research Quality; 2014. http://www.effectivehealthcare.ahrq.gov/.
152. Somrat C, Oranuch K, Ketchada U, Siriprapa S, Thipawan R. Optimal dose of nalbuphine for treatment of intrathecal-morphine induced pruritus after caesarean section. *J Obstet Gynaecol Res*. 1999;25(3):209–213. http://www.ncbi.nlm.nih.gov/pubmed/10467795. Accessed October 11, 2018.
153. Davis MP. Twelve reasons for considering buprenorphine as a frontline analgesic in the management of pain. *J Support Oncol*. 2012;10(6):209–219. doi:10.1016/j.suponc.2012.05.002.
154. Weeks WB, O'Connell MJ. Buprenorphine waivers for physicians. *Health Aff*. 2015;34(8):1428–1428. doi:10.1377/hlthaff.2015.0762.
155. Young JWS, Juurlink DN. Tramadol. *CMAJ*. 2013;185(8):E352.doi:10.1503/cmaj.121592.
156. Nelson LS, Juurlink DN. Tramadol and hypoglycemia: One more thing to worry about. *JAMA Intern Med*. 2015;175(2):194–195.

doi.10.1001/jamainternmed.2014.5260.

157. Elling C, Galic M, Steigerwald I. Tapentadol prolonged release in the treatment of neuropathic pain related to diabetic polyneuropathy. *Lancet Neurol*. 2015;14(7):684–685. doi:10.1016/S1474-4422(15)00059-9.
158. Russell IJ, Kamin M, Bennett RM, Schnitzer TJ, Green JA, Katz WA. Efficacy of tramadol in treatment of pain in fibromyalgia. *J Clin Rheumatol*. 2000;6(5):250–257. http://www.ncbi.nlm.nih.gov/pubmed/19078481. Accessed October 11, 2018.
159. Coe MA, Walsh SL. Distribution of naloxone for overdose prevention to chronic pain patients. *Prev Med*. 2015;80:41–43. doi:10.1016/j.ypmed.2015.05.016.
160. Chen L, Sein M, Vo T, et al. Clinical interpretation of opioid tolerance versus opioid-induced hyperalgesia. *J Opioid Manag*. 2014;10(6):383–393. doi:10.5055/jom.2014.0235.
161. ASAM. Public policy statement: Definition of addiction; 2011. Available at: https://www.asam.org/resources/definition-of-addiction. Accessed September 24, 2015.
162. *Standards of Care for the Addiction Specialist Physician*. Chevy Chase, MD: 2013. http://www.asam.org/docs/default-source/practice-support/quality-improvement/asam-standards-of-care.pdf?sfvrsn=10.
163. Mitra R, Jones S. Adjuvant analgesics in cancer pain: A review. *Am J Hosp Palliat Med*. 2012;29(1):70–79. doi.10.1177/1049909111413256.
164. Melton S, Spencer S. Regional anesthesia techniques for acute pain management. In: Fishman SM, Ballantyne JC, Rathmell JP, eds. *Bonica's Pain Management*. Baltimore, MD: Lippincott, Williams & Wilkins; 2010;723–754.
165. Goyal R, Shukla RN. Local anesthetic systemic toxicity (LAST): Should we not be concerned? *Med J Armed Forces India*. 2012. doi.10.1016/j.mjafi.2012.02.011.
166. Dans M, Smith T, Back A, et al. *NCCN Guidelines Index Table Of Contents Discussion NCCN Guidelines Version 1.2018 Panel Members Palliative Care*. 2018. ;.https://www.nccn.org/professionals/physician_gls/PDF/palliative.pdf.
167. American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons, AGS. Pharmacological management of persistent pain in older persons. *J Am Geriatr Soc*. 2009;57(8):1331–1346.

doi:10.1111/j.1532-5415.2009.02376.x.

168. Argoff CE. Clinical implications of opioid pharmacogenetics. *Clin J Pain*. 2010;26(suppl 10):16-20. doi:10.1097/AJP.0b013e3181c49e11.
169. Xu Y, Johnson A. Opioid therapy pharmacogenomics for noncancer pain: Efficacy, adverse events, and costs. *Pain Res Treat*. 2013;2013:943014. doi.10.1155/2013/943014.
170. Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. *Clin Pharmacol Ther*. 2014;95(4):376–382. doi.10.1038/clpt.2013.254.
171. Sistonen J, Sajantila A, Lao O, Corander J, Barbujani G, Fuselli S. CYP2D6 worldwide genetic variation shows high frequency of altered activity variants and no continental structure. *Pharmacogenet Genomics*. 2007;17(2):93–101. doi:10.1097/01.fpc.0000239974.69464.f2.
172. Verbeurgt P, Mamiya T, Oesterheld J. How common are drug and gene interactions? Prevalence in a sample of 1143 patients with *CYP2C9*, *CYP2C19* and *CYP2D6* genotyping. *Pharmacogenomics*. 2014;15(5):655–665. doi:10.2217/pgs.14.6.
173. Boswell MV, Stauble ME, Loyd GE, et al. The role of hydromorphone and OPRM1 in postoperative pain relief with hydrocodone. *Pain Physician*. 2013;16(3):E227–35. http://www.ncbi.nlm.nih.gov/pubmed/23703421. Accessed October 12, 2018.

78

Headache Disorders

T. Kristopher Harrell and Deborah S. Minor

KEY CONCEPTS

1. Acute migraine therapies should provide consistent, rapid relief and enable the patient to resume normal activities at home, school, or work.
2. A stratified care approach, in which the selection of initial treatment is based on headache-related disability and symptom severity, is the preferred treatment strategy for the patient with migraines.
3. Strict adherence to maximum daily and weekly doses of anti-migraine medications is essential.
4. Preventive therapy should be considered in the setting of recurring migraines that produce significant disability; frequent attacks requiring symptomatic medication more than twice per week; symptomatic therapies that are ineffective, contraindicated, or produce serious side effects; and uncommon migraine variants that cause profound disruption and/or risk of neurologic injury.
5. The selection of an agent for headache prophylaxis should be based on individual patient response, tolerability, convenience of the drug formulation, and coexisting conditions.
6. Each prophylactic medication should be given an adequate therapeutic trial (usually 6 months) to judge its maximal efficacy.
7. A general wellness program and consideration of headache triggers should be included in the management plan.
8. After an effective abortive agent and dose have been identified, subsequent treatments should begin with that same regimen.

Preclass Engaged Learning Activity

Read the following article: Vandenbussche N, Laterza D, Lisicki M, et al. Medication-overuse headache: A widely recognized entity amidst ongoing debate. *J Headache Pain*. 2018;19(1):50. Published July 13, 2018. doi:10.1186/s10194-018-0875-x.

Review other existing literature related to whether medication-overuse headache is a distinct entity. Summarize two key points on both the pro and con sides of the issue. Be prepared to discuss or debate in class. (Note to instructors: It would be a good opportunity to assign teams and have an in-class discussion or formal debate.)

INTRODUCTION

Headache is one of the most common complaints encountered by healthcare practitioners and among the top five principal reasons adults 18 to 44 years of age visit US emergency departments.[1] It can be symptomatic of a distinct pathologic process or can occur without an underlying cause. In 2013, the International Headache Society (IHS) updated its classification system and diagnostic criteria for headache disorders, cranial neuralgias, and facial pain[2] (**Table 78-1**). Designed to facilitate headache diagnosis in clinical practice (as well as to be used for research), the IHS classification provides more precise definitions and standardized nomenclature for both the primary (migraine, tension-type, and cluster headache) and secondary (symptomatic of organic disease) headache disorders. This chapter focuses on the management of the primary headache disorders.

TABLE 78-1 International Headache Society Classification System: Focus on Migraine Headache

Migraine
Migraine without aura
Migraine with aura
Migraine with typical aura (lasting less than 1 hour) with or without headache
Migraine with brainstem aura
Hemiplegic migraine (familial, sporadic)
Retinal migraine (repeated attacks of monocular visual disturbance)
Chronic migraine (occurring on 15 or more days/month for more than 3 months)
Complications of migraine
Status migrainous (debilitating attack lasting for more than 72 hours)
Persistent aura without infarction (symptoms persisting for more than 1 week)
Migrainous infarction (aura symptoms associated with an ischemic brain lesion)
Migraine aura-triggered seizure
Probable migraine with or without aura
Episodic syndromes that may be associated with migraine
Recurrent gastrointestinal disturbance (cyclical vomiting syndrome or abdominal migraine)
Benign paroxysmal vertigo
Benign paroxysmal torticollis
Tension-type headache
Cluster headache and other trigeminal autonomic cephalalgias
Other primary headaches
Headache attributed to head and/or neck trauma
Headache attributed to cranial or cervical vascular disorder
Headache attributed to nonvascular intracranial disorder
Headache attributed to a substance or its withdrawal
Headache attributed to infection
Headache attributed to disorder of homeostasis
Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cervical structure
Headache attributed to psychiatric disorder
Cranial neuropathies and facial pains
Other headache disorders, not elsewhere classified or unspecified

Adapted from Headache Classification Committee of the International Headache Society. The international classification of headache disorders, 3rd ed. Cephalalgia. 2013;33(9):629-808.

Most recurrent headaches are the result of a benign chronic primary headache disorder.[3] Less often, headaches are symptomatic of a serious underlying medical condition, such as an infection, cerebral hemorrhage, or brain mass lesion. The peak prevalence of tension-type and migraine headache, the most common of the primary headache disorders, occurs during the most productive years of life (18-54 years of age).[4] Despite the prevalence of these disorders and their associated disability, studies indicate that most headache sufferers do not obtain appropriate medical care for their headaches.[4,5] An improved understanding of the diagnosis and pathophysiologic mechanisms of the primary headache disorders, particularly migraine, has led to the development of medications capable of providing rapid relief from moderate-to-severe attacks. However, a thorough evaluation of the headache history is essential to establish an accurate headache diagnosis and identify patients who can benefit from these specific therapeutic options.

MIGRAINE HEADACHE

Epidemiology

Results of the American Migraine Prevalence and Prevention Study indicate that 17.1% of women and 5.6% of men in the United States experience one or more migraine headaches per year. While the prevalence of migraine varies considerably by age and gender, the epidemiologic profile has remained stable over the past 8 years. Gender differences in migraine prevalence have been linked to menstruation, but these differences persist beyond menopause. Prevalence is highest in both men and women between the ages of 18 and 44 years and is inversely related to income and educational attainment. In the American Migraine Prevalence and Prevention Study, 93% of those with migraine reported some headache-related disability, and 54% were severely disabled or needed bed rest during an attack.[4,5] A number of neurologic and psychiatric disorders as well as cardiovascular diseases, including stroke, epilepsy, major depression, sleep apnea, obesity, and anxiety and other pain disorders, show increased comorbidity with migraine.[6,7] Whether this relationship is causal or representative of a common pathophysiologic mechanism is unknown. The economic burden of migraine is substantial; however, the indirect costs from work-related disability and losses in productivity are also significant.[8,9]

Etiology

The etiology of migraines is not completely understood. According to earlier theories, the migraine aura was caused by intracerebral arterial vasoconstriction followed by reactive extracranial vasodilation and associated headache. Studies of regional blood flow in the brain do not support this hypothesis, and previous vascular and neural theories of migraine development have merged into a combined theory of neurovascular mechanisms. Most clinicians now believe that the pathogenesis of migraine may be related to complex dysfunctions in neuronal and broad sensory processing.[2,6,7]

The pain and symptoms of migraine may be understood as a combination of altered perceptions resulting from neural suppression and activation of subcortical structures and trigeminal systems. Migraine pain is believed to result from activity within the trigeminovascular system, a network of visceral afferent fibers that arises from the trigeminal ganglia and projects peripherally to innervate the pain-sensitive intracranial extracerebral blood vessels, dura mater, and large venous sinuses[10] (**Fig. 78-1**). These fibers also project centrally, terminating in the trigeminal nucleus caudalis in the brain stem and upper cervical spinal cord, and thus provide a pathway for nociceptive transmission from meningeal blood vessels into higher centers of the central nervous system (CNS). Activation of trigeminal sensory nerves triggers the release of vasoactive neuropeptides, including calcitonin gene-related peptide (CGRP), neurokinin A, and substance P, from perivascular axons. The released neuropeptides interact with dural blood vessels to promote vasodilation and dural plasma extravasation, resulting in neurogenic inflammation. Orthodromic conduction along trigeminovascular fibers transmits pain impulses to the trigeminal nucleus caudalis, where information is relayed further to higher cortical pain centers. Continued afferent input can result in sensitization of these central sensory neurons, producing a hyperalgesic state that responds to previously innocuous stimuli and maintains the headache.[7,10]

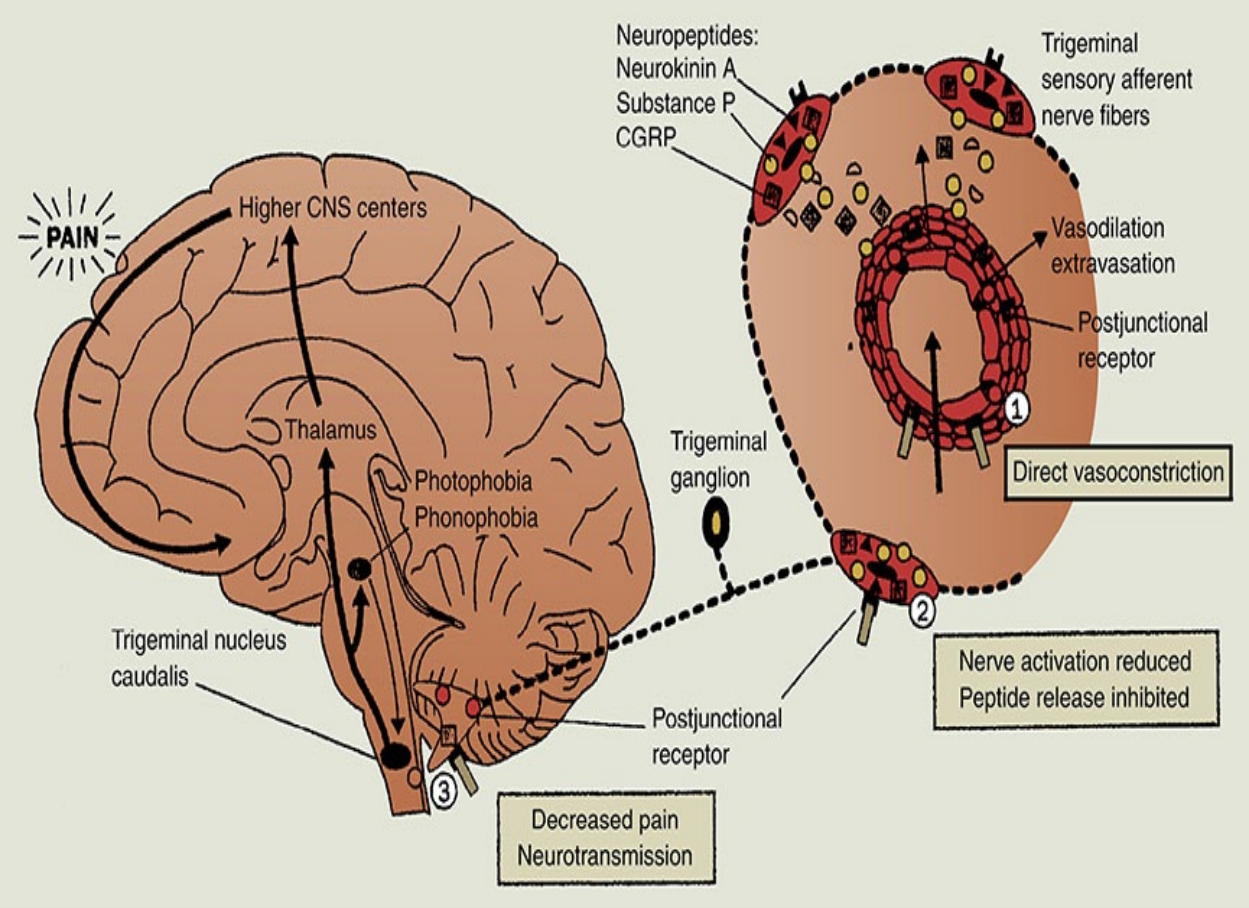


FIGURE 78-1 The pathophysiology of migraine headache. Vasodilation of intracranial extracerebral blood vessels (possibly the result of an imbalance in the brainstem) results in the activation of the perivascular trigeminal nerves that release vasoactive neuropeptides to promote neurogenic inflammation. Central pain transmission may activate other brainstem nuclei, resulting in associated symptoms (nausea, vomiting, photophobia, and phonophobia). The antimigraine effects of the 5-$HT_{1B/ID}$ receptor agonists are highlighted at areas 1, 2, and 3. (CGRP, calcitonin gene-related peptide.) *(Reprinted from the Lancet, Vol. 351, Ferrari MD, Migraine, 1043-1051. Copyright © 1998, with permission from Elsevier.)*

Aura occurs in a subgroup of patients with migraine and also with the other primary headache disorders. The neurologic changes of the aura parallel those that occur during cortical spreading depression, a neuronal event characterized by a wave of depressed electrical activity that advances across the brain cortex at a rate consistent with the spread of aura symptoms.[2,7] Cortical spreading depression can cause inflammation and activation of the trigeminal nucleus caudalis. It is not clear whether this cortical spreading depression and the aura

are the substrate of pain or actually trigger the presentation of migraine.[7,11]

Pathophysiology

Genetic factors seem to play an important role in susceptibility to migraine attacks. Studies in monozygotic twins suggest approximately 50% heritability of migraine with a multifactorial polygenic basis.[11] Although it is possible for any individual to experience a migraine attack, it is the abnormal recurrence that can result in a diagnosis of migraine in a patient. Attack occurrence and frequency are governed by CNS sensitivity to migraine-specific triggers or environmental factors. Patients with migraines appear to have a lowered threshold of response to specific environmental circumstances as a result of genetic factors that govern the balance of CNS excitation and inhibition at various levels. Thus, trigger factors can be viewed as modulators of the genetic set point that predisposes to migraine headache.[7,11] The hyperresponsiveness of the patient's brain may be the result of an inherited abnormality in calcium and/or sodium channels and sodium/potassium pumps that regulate cortical excitability through the release of serotonin (5-hydroxytryptamine [5-HT]) and other neurotransmitters. Increased levels of excitatory amino acids such as glutamate and alterations in levels of extracellular potassium also can affect the migraine threshold and initiate and propagate the phenomenon of cortical spreading depression.[11]

Serotonin (5-HT) has long been implicated as an important mediator of migraine headache and specific populations of 5-HT receptor subfamilies appear to be involved in the pathophysiology and treatment of migraine headache.[7,12] Acute antimigraine drugs such as the ergot alkaloids and triptan derivatives are agonists of vascular and neuronal 5-HT_1 receptor subtypes, resulting in vasoconstriction of meningeal blood vessels and inhibition of vasoactive neuropeptide release and pain signal transmission.[12,13] Drugs used for migraine prophylaxis also modulate neurotransmitter systems.[14] These actions and benefits in migraine management are consistent with the current understanding of migraine pathophysiology and neurovascular disorders.

CLINICAL PRESENTATION

Migraine Headache

General

- Common, recurrent, severe headache
- Interferes with normal functioning
- Divided into two major subtypes
  - Migraine without aura
  - Migraine with aura

Symptoms

- Recurring episodes of throbbing head pain, frequently unilateral, lasting from 4 to 72 hours if left untreated
- Headaches can be severe and associated with nausea, vomiting, and sensitivity to light, sound, and/or movement, but not all symptoms are present in every attack
- Diagnostic alarms from evaluation include
  - Acute onset of the “first” or “worst” headache ever
  - Accelerating pattern of headache following subacute onset
  - Onset of headache after age 50 years
  - Headache associated with systemic illness (eg, fever, nausea, vomiting, stiff neck, and rash)
  - Headache with focal neurologic symptoms or papilledema
  - New-onset headache in a patient with cancer or human immunodeficiency virus (HIV) infection

Signs

- A stable pattern, absence of daily headache
- Positive family history for migraine
- Normal neurologic examination
- Food and menstruation may serve as triggers
- Improvement in headache with sleep
- Aura can signal the migraine headache but is not required for diagnosis

Laboratory Tests

- No one test can diagnose migraine headaches
- Possible tests to consider are:

- Serum chemistries
- Urine toxicology profiles
- Thyroid function tests
- Lyme disease studies
- Complete blood count
- Antinuclear antibody titer
- Erythrocyte sedimentation rate
- Antiphospholipid antibody titer

Diagnostic Tests

- General medical and neurologic physical examination
- Vital signs (fever, hypertension)
- Funduscopy (papilledema, hemorrhage, and exudates)
- Palpation and auscultation of the head and neck (sinus tenderness, hardened or tender temporal arteries, trigger points, temporomandibular joint tenderness, bruits, nuchal rigidity, and cervical spine tenderness)
- Neurologic examination (identify abnormalities or deficits in mental status, cranial nerves, deep tendon reflexes, motor strength, coordination, gait, and cerebellar function)
- Consider neuroimaging studies in patients with abnormal neurologic examination findings of unknown etiology and in those with additional risk factors warranting imaging

Clinical Presentation

The migraine attack has been divided into several phases. *Premonitory symptoms* are experienced by up to 77% of patients with migraines in the hours or days before the onset of headache.[2,7] The previously popular terms *prodrome* and *warning symptoms* should generally be avoided because these are often used mistakenly to include aura.[2] Premonitory symptoms vary widely among patients with migraine, but usually are consistent within an individual. Neurologic symptoms (eg, allodynia, phonophobia, photophobia, hyperosmia, and difficulty concentrating) are common, but psychological (eg, anxiety, depression, euphoria, irritability, drowsiness, fatigue, hyperactivity, and restlessness), autonomic (eg, polyuria, diarrhea, and constipation), and constitutional (eg, stiff neck, yawning,

thirst, food cravings, and anorexia) symptoms also are reported.[2,7]

The migraine *aura*, a complex of positive and negative focal neurologic symptoms that precedes or accompanies an attack, is experienced by approximately 25% of patients with migraines on some occasions.[2,7] The aura typically evolves over 5 minutes or longer and lasts less than 60 minutes, with headache usually occurs within 60 minutes of the end of the aura. Occasionally, aura symptoms begin at the onset of headache or during the attack. The aura is most often visual and frequently affects half the visual field.[2] Visual auras vary in their complexity and can include both positive (scintillations, photopsia, teichopsia, or fortification spectrum) and negative (scotoma and hemianopsia) features. Sensory and motor aura symptoms, such as paresthesias or numbness involving the arms and face, dysphasia or aphasia, weakness, and hemiparesis, also are reported.[2,7]

Migraine *headache* pain is usually gradual in onset, peaking in intensity over a period of minutes to hours and lasting between 4 and 72 hours. Pain can occur anywhere in the face or head but most often involves the frontotemporal region. The headache is typically unilateral and throbbing or pulsating in nature; however, pain can be bilateral at onset or become generalized during the course of an attack.[2,7] Gastrointestinal (GI) symptoms almost invariably accompany the headache. During an attack, patients with migraines frequently experience nausea, and emesis sometimes occurs. Other systemic symptoms associated with the headache phase include anorexia, food cravings, constipation, diarrhea, abdominal cramps, nasal stuffiness, blurred vision, diaphoresis, facial pallor, and localized facial, scalp, or periorbital edema. Sensory hyperacuity, manifested as photophobia, phonophobia, or osmophobia, is reported frequently. Because headache pain usually is aggravated by physical activity, most patients with migraines seek a dark, quiet room for rest and relief. Impaired concentration, depression, irritability, fatigue, or anxiety often accompanies the headache. Once headache pain wanes, patients may experience a postdrome or *resolution phase* characterized by feeling tired, exhausted, irritable, or listless. Impaired concentration may continue, as well as scalp tenderness or mood changes. Some patients experience depression and malaise, whereas others can feel unusually refreshed or euphoric.[2,7,15] The IHS classification and recent reviews provide descriptions of the classic migraine variants and other migraine subtypes[2,7] (see Table 78-1).

Although headaches have many potential causes, most are considered to be primary headache disorders. A comprehensive headache history is the most important element in establishing the clinical diagnosis of migraine.[2,6] A

thorough headache history always should be obtained, and information collected should include age at onset, attack frequency and timing, duration of attacks, precipitating or aggravating factors, ameliorating factors, description of neurologic symptoms, characteristics of the headache pain (quality, intensity, location, and radiation), associated signs and symptoms, treatment history, family and social history, and the impact of headaches on daily life.

Secondary headache can be identified or excluded based on the headache history, as well as the results of general medical and neurologic examinations. Diagnostic and laboratory testing also can be warranted in the setting of suspicious headache features or an abnormal examination. The routine use of neuroimaging (computed tomography or magnetic resonance imaging) generally is not indicated in patients with migraine and a normal neurologic examination, but should be considered in patients with an unexplained abnormal neurologic examination or an atypical headache history. Because migraine headaches usually begin by the second or third decade of life, headaches beginning after age 50 years suggest an organic etiology such as a mass lesion, cerebrovascular disease, or temporal arteritis.[2,3,7] **Table 78-2** lists the IHS diagnostic criteria for migraine with and without aura.[2]

TABLE 78-2 IHS Diagnostic Criteria for Migraine and Cluster Headache

Migraine without aura
At least five attacks
Headache attack lasts 4-72 hours (untreated or unsuccessfully treated)
Headache has at least two of the following characteristics:
- Unilateral location
- Pulsating quality
- Moderate or severe intensity
- Aggravation by or avoidance of routine physical activity (ie, walking or climbing stairs)

During headache at least one of the following:
- Nausea, vomiting, or both
- Photophobia and phonophobia
- Not attributed to another disorder

Migraine with aura (classic migraine)
At least two attacks
Migraine aura fulfills criteria for typical aura, hemiplegic migraine, retinal migraine or brainstem aura
Not attributed to another disorder

Typical aura
Fully reversible visual, sensory, or speech symptoms (or any combination) but no motor weakness
Homonymous or bilateral visual symptoms including positive features (eg, flickering lights, spot, lines) or negative features (eg, loss of vision) or unilateral sensory symptoms including positive features (eg, pins and needles) or negative features (ie, numbness), or any combination
At least two of the following:
- At least one symptom that develops gradually over a minimum of 5 minutes or different symptoms that occur in succession or both
- Each symptom lasts for at least 5 minutes and for no longer than 60 minutes
- Headache that meets criteria for migraine without aura begins during the aura or follows aura within 60 minutes

IHS, International Headache Society.

Adapted from Headache Classification Committee of the International Headache Society. The international classification of headache disorders, 3rd ed. Cephalalgia. 2013;33(9):629-808.

TREATMENT

Desired Outcome

1 Clinicians who care for patients with migraines must appreciate the impact of this painful and debilitating disorder on the life of the patient, the patient's

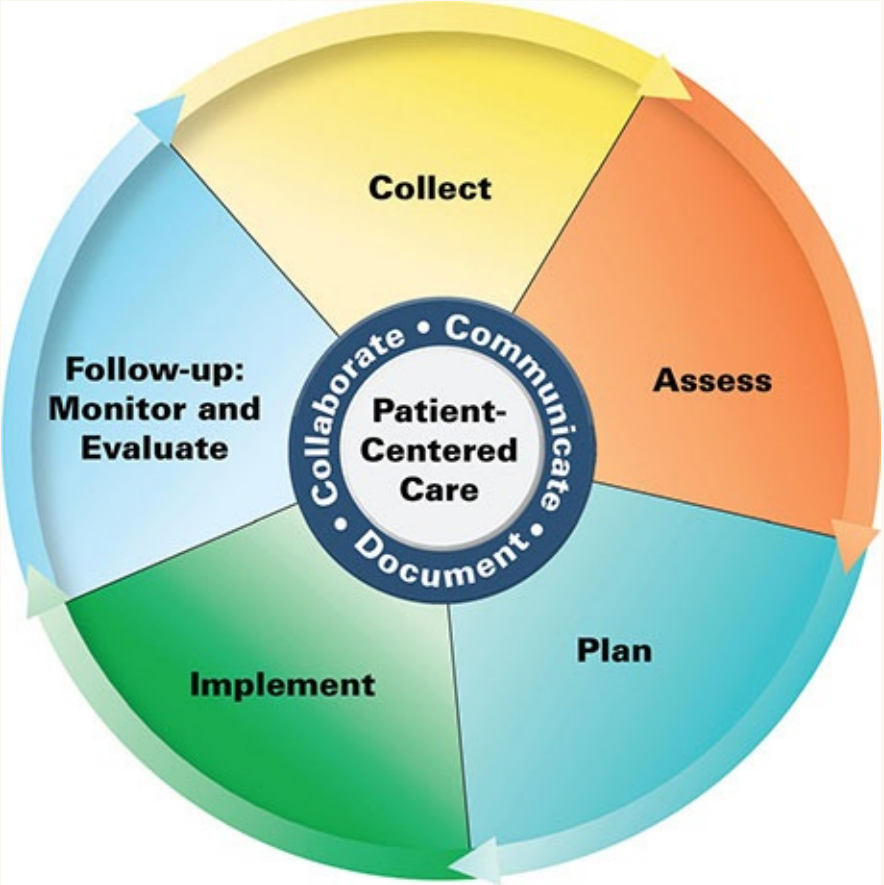
family, and the patient's employer. Treatment strategies must address both immediate and long-term goals. Acute migraine therapies should provide consistent, rapid relief and enable the patient to resume normal activities at home, school, or work. Recurrence of symptoms and treatment-related adverse effects should be minimal. Ideally, patients should be able to manage their own headaches effectively without a medical visit. In addition, patients should take an active role in the creation of a long-term formal management plan. An individualized approach to treatment can result in a reduction in attack frequency and severity, thus minimizing headache-related disability and emotional distress and improving the patient's quality of life. Goals of long-term and acute treatment of migraine are listed in **Table 78-3**.[13,16,17]

TABLE 78-3 Goals of Therapy in Migraine Management

Goals of long-term migraine treatment
Reduce migraine frequency, severity, and disability
Reduce reliance on poorly tolerated, ineffective, or unwanted acute pharmacotherapies
Improve quality of life
Prevent headache
Avoid escalation of headache medication use
Educate and enable patients to manage their disease
Reduce headache-related distress and psychological symptoms
Goals for acute migraine treatment
Treat migraine attacks rapidly and consistently without recurrence
Restore the patient's ability to function
Minimize the use of backup and rescue medications[a]
Optimize self-care for overall management
Be cost-effective in overall management
Cause minimal or no adverse effects

[a]Rescue medications are defined as medications used at home when other treatments fail that permit the patient to get relief without a visit to the physician's office or emergency department.

Data from References 12, 16, and 17.



Patient Care Process for Headache Disorders

Collect

Subjective and Objective data

- Presence of other symptoms
  - Nausea
  - Vomiting
  - Sensitivity to light, sound, and/or movement
- Identification of triggers or aura (Table 78-6)
- Patient characteristics (eg, age, sex, pregnant)
- Patient medical history (personal and family)
- Social history (smoking, diet, physical activity)
- Description of migraine/headache pain (including frequency and location)

- Presence of diagnostic alarms
  - Acute onset of the “first” or “worst” headache ever
  - Accelerating pattern of headache following subacute onset
  - Onset of headache after age 50 years
  - Headache associated with systemic illness (eg, fever, nausea, vomiting, stiff neck, and rash)
  - Headache with focal neurologic symptoms or papilledema
  - New-onset headache in a patient with cancer or human immunodeficiency virus (HIV) infection

Medication History

- Current use, dosage, and frequency of medications (especially over the counter [OTC] aspirin/nonsteroidal anti-inflammatory drug [NSAID] use, herbal products, and dietary supplements) (Tables 78-4 and 78-5)

Diagnostic Tests

- Consider neuroimaging studies in patients with abnormal neurologic examination findings of unknown etiology and in those with additional risk factors warranting imaging
- Physical Exam
- Neurological Exam
- Diagnostic abnormalities (Table 78-2)
  - Vital signs (fever, hypertension)
  - Funduscopy (papilledema, hemorrhage, and exudates)
  - Palpation and auscultation of the head and neck (sinus tenderness, hardened or tender temporal arteries, trigger points, temporomandibular joint tenderness, bruits, nuchal rigidity, and cervical spine tenderness)
  - Deficits in mental status, cranial nerves, deep tendon reflexes, motor strength, coordination, gait, and cerebellar function

Assess

Initial Assessment

- Type of headache, acute or chronic (Table 78-1)
- Other contributing factors (eg, presence of anxiety, depression, or medication over use)

Medication Assessment

- Evaluate need for therapy
- Evaluate current therapy for appropriateness, response, side effects, and medication adherence
- Evaluate other therapy options (compare/contrast based on safety, efficacy, cost/coverage by insurance)

Plan*

- Acute drug therapy regimen if needed (symptomatic or abortive)
- Establish individualized treatment plan for long term
  - Nonspecific agents for mild-to-moderate attacks
  - Reserve migraine-specific agents for more severe attacks
  - Use of prophylactic agents
- Identify goals of treatment and monitoring parameters (Tables 78-3 to 78-5)
- Patient education (avoidance of triggers, headache diary, patient adherence)
- Referrals to other providers when appropriate (eg, secondary headache, psychiatry)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up, sooner if patient is unable to perform daily activities

Follow-up: Monitor and Evaluate*

- Strive for resolution of pain (Table 78-3)
- Aim for absence of adverse effects
- Reduce headache frequency, severity, and associated-disability
- Improve quality of life
- Optimize self-care and management

** Collaborate with patient, caregiver(s), and other healthcare professionals.*

General Approach to Treatment

2 Nonpharmacologic and pharmacologic interventions are available for the management of migraine headache; however, drug therapy remains the mainstay of treatment for most patients. Pharmacotherapeutic management of migraine can be acute (ie, symptomatic or abortive) or preventive (ie, prophylactic). When choosing acute or preventive therapies, the clinician should consider the patient's response to specific medications and their tolerability, as well as coexisting illnesses that can limit treatment choices. Abortive or acute therapies can be migraine-specific (eg, ergots and triptans) or nonspecific (eg, analgesics, antiemetics, nonsteroidal anti-inflammatory drugs [NSAIDs], and corticosteroids) and are most effective at relieving pain and associated symptoms when administered at the onset of migraine[12–14,16–18] (**Table 78-4**). A stratified care approach in which the selection of initial treatment is based on headache-related disability and symptom severity is the preferred treatment strategy for patients.[12,18] Because attack severity varies in individuals, patients may be advised to use nonspecific agents for mild-to-moderate headache not causing disability while reserving migraine-specific medications for more severe attacks. The absorption and efficacy of orally administered drugs can be compromised by gastric stasis or nausea and vomiting that accompany migraine. Pretreatment with antiemetic agents or the use of nonoral treatment (eg, suppositories, nasal sprays, or injections) is advisable when nausea and vomiting are severe.[12,18]

TABLE 78-4 Dosing of Acute Migraine Therapies[a]

Drug	Dose	Usual Range/Comments
Analgesics		
Acetaminophen[a] (Tylenol)	1,000 mg at onset; repeat every 4-6 hours as needed	Maximum daily dose is 4 g
Acetaminophen 250 mg/aspirin 250 mg/caffeine 65 mg[a] (Excedrin Migraine)	2 tablets at onset and every 6 hours	Available over-the-counter as Excedrin Migraine
Nonsteroidal anti-inflammatory drugs		
Aspirin[a]	500-1,000 mg every 4-6 hours	Maximum daily dose is 4 g
Ibuprofen[a] (Motrin)	200-800 mg every 6 hours	Avoid doses >2.4 g/day
Naproxen sodium[a] (Aleve, Anaprox)	550-825 mg at onset; can repeat 220 mg in 3-4 hours	Avoid doses >1.375 g/day
Diclofenac[a] (Cataflam, Voltaren)	50-100 mg at onset; can repeat 50 mg in 8 hours	Avoid doses >150 mg/day
Ergotamine tartrate		
Oral tablet (1 mg) with caffeine 100 mg[b] (Cafergot)	2 mg at onset; then 1-2 mg every 30 minutes as needed	Maximum dose is 6 mg/day or 10 mg/week; consider pretreatment with an antiemetic
Rectal suppository (2 mg) with caffeine 100 mg[b] (Cafergot, Migergot)	Insert 1/2 to 1 suppository at onset; repeat after 1 hour as needed	Maximum dose is 4 mg/day or 10 mg/week; consider pretreatment with an antiemetic
Dihydroergotamine		
Injection 1 mg/mL (D.H.E. 45)[b]	0.25-1 mg at onset IM, IV or subcutaneous; repeat every hour as needed	Maximum dose is 3 mg/day or 6 mg/week
Nasal spray 4 mg/mL[a] (Migranal)	One spray (0.5 mg) in each nostril at onset; repeat sequence 15 minutes later (total dose is 2 mg or 4 sprays)	Maximum dose is 3 mg/day; prime sprayer 4 times before using; do not tilt head back or inhale through nose while spraying; discard open ampules after 8 hours
Serotonin agonists (triptans)		
Sumatriptan[a] (Imitrex)		
Injection	6 mg subcutaneous at onset; can repeat after 1 hour if needed	Maximum daily dose is 12 mg
Oral tablets	25, 50, 85, or 100 mg at onset; can repeat after 2 hours if needed	Optimal dose is 50-100 mg; maximum daily dose is 200 mg; combination product with naproxen, 85/500 mg
Nasal spray	5, 10, or 20 mg at onset; can repeat after 2 hours if needed	Optimal dose is 20 mg; maximum daily dose is 40 mg; single-dose device delivering 5 or 20 mg; administer one spray in one nostril
Zolmitriptan[a] (Zomig, Zomig-ZMT)		
Oral tablets	2.5 or 5 mg at onset as regular or orally disintegrating tablet; can repeat after 2 hours if needed	Optimal dose is 2.5 mg; maximum dose is 10 mg/day Do not divide ODT dosage form
Nasal spray	5 mg (one spray) at onset; can repeat after 2 hours if needed	Maximum daily dose is 10 mg/day
Naratriptan[a] (Amerge)	1 or 2.5 mg at onset; can repeat after 4 hours if needed	Optimal dose is 2.5 mg; maximum daily dose is 5 mg
Rizatriptan[a] (Maxalt, Maxalt-MLT)	5 or 10 mg at onset as regular or orally disintegrating tablet; can repeat after 2 hours if needed	Optimal dose is 10 mg; maximum daily dose is 30 mg; onset of effect is similar with standard and orally disintegrating tablets; use 5-mg dose (15 mg/day maximum) in patients receiving propranolol
Almotriptan[a] (Axert)	6.25 or 12.5 mg at onset; can repeat after 2 hours if needed	Optimal dose is 12.5 mg; maximum daily dose is 25 mg
Frovatriptan[a] (Frova)	2.5 or 5 mg at onset; can repeat in 2 hours if needed	Optimal dose 2.5-5 mg; maximum daily dose is 7.5 mg (3 tablets)
Eletriptan[a] (Relpax)	20 or 40 mg at onset; can repeat after 2 hours if needed	Maximum single dose is 40 mg; maximum daily dose is 80 mg
Miscellaneous		
Metoclopramide[b] (Reglan)	10 mg IV at onset	Useful for acute relief in the office or emergency department setting
Prochlorperazine[b] (Compazine)	10 mg IV or IM, 25 mg rectally at onset	Useful for acute relief in the office or emergency department setting

[a]Limit use of symptomatic medications to fewer than 10 days/month when possible to avoid medication-overuse headache. Level A—established efficacy (≥2 Class I studies).

[b]Level B—probably effective (1 Class I or 2 Class II studies).

ODT, orally disintegrating tablet.

Source: Data from References 12, 16, and 18.

3 The frequent or excessive use of acute migraine medications can also result in a pattern of increasing headache frequency and drug consumption known as *medication-overuse headache* (or *rebound headache*).[2,19] The syndrome itself appears to evolve as a self-sustaining headache-medication cycle in which the headache returns as the medication wears off, leading to the consumption of more drug for relief. The headache history often reflects the gradual onset of an atypical daily or near-daily headache with superimposed episodic migraine attacks. Medication overuse is one of the most common causes of chronic daily headache.[19–21] Agents most commonly implicated in this syndrome include simple and combination analgesics and opiates, with triptans also being implicated.[19–21] Discontinuation of the offending agent leads to a gradual decrease in headache frequency and severity and a return of the original headache characteristics. Although detoxification usually can be accomplished on an outpatient basis, hospitalization can be necessary for the control of refractory rebound headache and other withdrawal symptoms (eg, nausea, vomiting, asthenia, restlessness, and agitation).[19,20] Regulation of nociceptive systems and renewed responsiveness to therapy usually occur within 2 months following medication withdrawal.[2] Most experts recommend limiting use of acute migraine therapies to *fewer than 10 days per month* to avoid the development of medication-overuse headache.[2,6,22]

4 5 6 Preventive migraine therapies are administered on a daily basis to reduce the frequency, severity, and duration of attacks and improve responsiveness to symptomatic migraine therapies[23,24] (**Table 78-5**). Preventive therapy should be considered in the setting of recurring migraines that produce significant disability despite acute therapy; frequent attacks occurring more than twice per week with the risk of developing medication-overuse headache; symptomatic therapies that are ineffective or contraindicated, or produce serious side effects; uncommon migraine variants that cause profound disruption and/or risk of permanent neurologic injury (eg, hemiplegic migraine, basilar migraine, and migraine with prolonged aura); and patient preference to limit the number of attacks.[17,22] Preventive therapy also may be administered preemptively or intermittently when headaches recur in a predictable pattern (eg, exercise-induced migraine or menstrual migraine).[17] The evidence to support the various agents used for migraine prophylaxis has recently been reviewed. Only propranolol, timolol, divalproex sodium, topiramate, erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm are currently approved by the FDA for the indication, although other agents have established or probable

efficacy. Guidelines identify which agents might be effective, but there is insufficient evidence as to how to choose one therapy over another. Thus, the selection of an agent typically is based on its side effect profile and the patient's coexisting/comorbid conditions.[17,23,24] A therapeutic trial of 2 to 3 months is necessary to achieve clinical benefit, but some reduction in attack frequency can be evident by the first month of therapy. Maximal benefits are usually observed by 6 months of treatment.[14,17,23] Drug therapy should typically be initiated with low doses and gradually increased until a therapeutic effect is achieved or side effects become intolerable. Drug doses for migraine prophylaxis are often lower than those necessary for other indications.[17,24] Overuse of acute headache medications will interfere with the effects of preventive treatment.[2,17] Prophylactic treatment usually is continued for at least 6 to 12 months after the frequency and severity of headaches have diminished. After that time, based on discussions with the patient, gradual tapering or discontinuation may be reasonable.[14,22,23] Many patients with migraines experience fewer and less severe attacks for lengthy periods following discontinuation of prophylactic medications or taper to a lower dose. **Figs. 78-2** and **78-3** identify treatment and management algorithms for migraine headache.

TABLE 78-5 Dosing of Prophylactic Migraine Therapies

Drug	Initial Dose	Usual Range	Comments
β-Adrenergic antagonists			
Atenolol[a] (Tenormin)	50 mg/day	50-200 mg/day	
Metoprolol[b] (Toprol, Toprol XL)	100 mg/day in divided doses	100-200 mg/day in divided doses	Dose short-acting 4 times a day and long-acting 2 times a day; available as extended release
Nadolol[a] (Corgard)	40-80 mg/day	80-240 mg/day	
Propranolol[b] (Inderal, Inderal LA)	40 mg/day in divided doses	40-160 mg/day in divided doses	Dose short-acting 2-3 times a day and long-acting 1-2 times a day; available as extended release
Timolol[b] (Blocadren)	20 mg/day in divided doses	20-60 mg/day in divided doses	
Antidepressants			
Amitriptyline[a] (Elavil)	10 mg at bedtime	20-50 mg at bedtime	
Venlafaxine[a] (Effexor, Effexor-XR)	37.5 mg/day	75-150 mg/day	Available as extended release; increase dose after 1 week
Anticonvulsants			
Topiramate[b] (Topamax)	25 mg/day	50-200 mg/day in divided doses	As effective as amitriptyline, propranolol, or valproate; increase by 25 mg/week
Valproic acid/divalproex sodium[b] (Depakene, Depakote, Depakote ER)	250-500 mg/day in divided doses, or daily for extended release	500-1,500 mg/day in divided doses, or daily for extended release	Monitor levels if compliance is an issue
Nonsteroidal anti-inflammatory drugs			
Ibuprofen[a] (Motrin)	400-1,200 mg/day in divided doses	Same as initial dose	Use intermittently, such as for menstrual migraine prevention; daily or prolonged use may lead to medication-overuse headache and is limited by potential toxicity
Ketoprofen[a] (Orudis)	150 mg/day in divided doses	Same as initial dose	
Naproxen sodium[a] (Aleve, Anaprox)	550-1,100 mg/day in divided doses	Same as initial dose	
Serotonin agonists (triptans)			
Frovatriptan[b] (Frova)	2.5 mg/day or 5 mg/day in divided doses	Same as initial dose	Taken in the perimenstrual period to prevent menstrual migraine
Naratriptan[a] (Amerge)	2 mg/day in divided doses	Same as initial dose	
Zolmitriptan[a] (Zomig)	5-7.5 mg/day in divided doses	Same as initial dose	
Miscellaneous			
Histamine[a] (Histatrol)	1-10 ng 2 times/week	Same as initial dose	May cause transient itching and burning at injection site
Magnesium[a]	400 mg/day	800 mg/day in divided doses	May be more helpful in migraine with aura and menstrual migraine
MIG-99[a] (feverfew)	10-100 mg/day in divided doses	Same as initial dose	Withdrawal may be associated with increased headaches
Petasites[b]	100-150 mg/day in divided doses	150 mg/day in divided doses	Use only commercial preparations, plant is carcinogenic
Riboflavin[a]	400 mg/day in divided doses	400 mg/day in divided doses	Benefit only after 3 months

[a]Level B—probably effective (1 Class I or 2 Class II studies).

[b]Level A—established efficacy (≥2 Class I studies).

Source: Data from References 23 and 25.

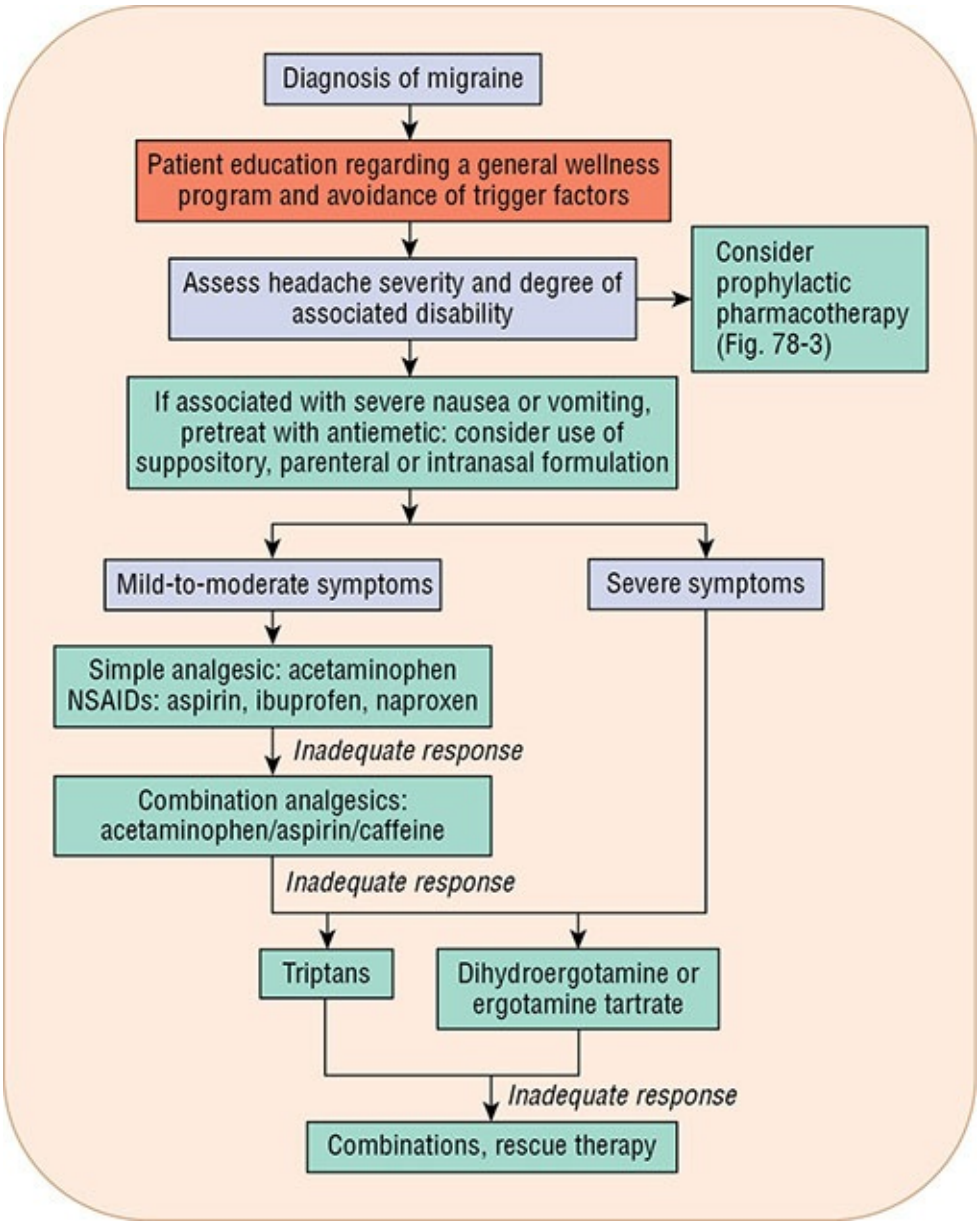


FIGURE 78-2 Treatment algorithm for migraine headaches.

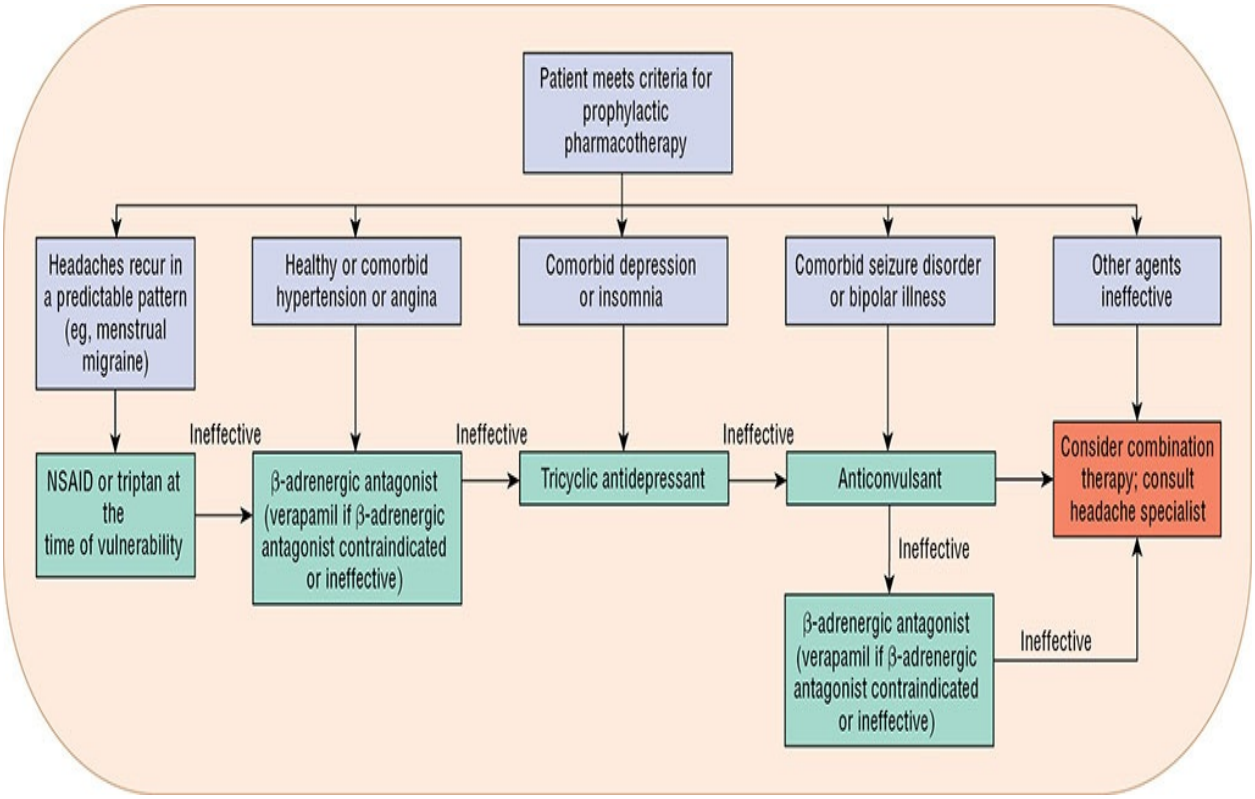


FIGURE 78-3 Treatment algorithm for prophylactic management of migraine headaches. (NSAID, nonsteroidal anti-inflammatory drug.).

Nonpharmacologic Therapy

7 Nonpharmacologic therapy of acute migraine headache is limited but can include application of ice to the head and periods of rest or sleep, usually in a dark, quiet environment. Recommendations for the preventive management of migraine typically suggest that patients identify and avoid individual factors or triggers that consistently provoke migraine attacks[2,3,17,22] (**Table 78-6**). Changes in estrogen levels associated with menarche, menstruation, pregnancy, menopause, oral contraceptive use, and other hormone therapies can trigger, intensify, or alleviate migraine.[3,26] A headache diary that records the frequency, severity, and duration of attacks can facilitate identification of migraine triggers. In appropriate situations, some patients may learn to cope with triggers after a process of controlled exposure and approach/confront strategies.[27] Patients also can benefit from adherence to a wellness program that includes regular sleep, exercise, and eating habits, smoking cessation, and limited caffeine intake. Behavioral interventions, such as relaxation therapy, biofeedback (often used in combination with relaxation therapy), and cognitive therapy, are preventive

treatment options for patients who prefer nondrug therapy or when symptomatic therapies are poorly tolerated, contraindicated, or ineffective.[17]

TABLE 78-6 Commonly Reported Triggers of Migraine

Food triggers
Alcohol
Caffeine/caffeine withdrawal
Chocolate
Fermented and pickled foods
Monosodium glutamate (eg, in Chinese food, seasoned salt, and instant foods)
Nitrate-containing foods (eg, processed meats)
Saccharin/aspartame (eg, diet foods or diet sodas)
Tyramine-containing foods
Environmental triggers
Glare or flickering lights
High altitude
Loud noises
Strong smells and fumes
Tobacco smoke
Weather changes
Behavioral–physiologic triggers
Excess or insufficient sleep
Fatigue
Menstruation, menopause
Sexual activity
Skipped meals
Strenuous physical activity (eg, prolonged overexertion)
Stress or poststress

Data from References 7 and 27.

Pharmacologic Therapy

Abortive Treatments

Analgesics and NSAIDs Simple analgesics and NSAIDs are effective

medications for the management of many migraine attacks (see Table 78-4). They offer a reasonable first-line choice for treatment of mild-to-moderate migraine attacks or severe attacks that have been responsive in the past to similar NSAIDs or nonopiate analgesics. Of the NSAIDs, aspirin, diclofenac, ibuprofen, naproxen sodium, and the combination of acetaminophen plus aspirin and caffeine have established efficacy in controlled clinical trials.[12,16,18] While ketorolac and flurbiprofen are probably effective, evidence for these NSAIDs is either limited or inconsistent. Oral acetaminophen alone also has established efficacy for non-incapacitating migraine.[16] Comparisons with other pharmacotherapeutic classes are limited; however, studies support the comparable efficacy of NSAIDs and triptans in acute migraine. Baseline headache intensity does not predict the success or failure of aspirin or other NSAIDs.[28] There are no studies comparing the relative efficacy of different NSAIDs.[12,18]

Nonsteroidal anti-inflammatory drugs appear to prevent neurogenically mediated inflammation in the trigeminovascular system through the inhibition of prostaglandin synthesis. Metoclopramide can speed the absorption of analgesics and alleviate migraine-related nausea and vomiting.[12,13] Suppository analgesic preparations are an option when nausea and vomiting are severe.[18] Acute NSAID therapy is associated with gastrointestinal (GI) (eg, dyspepsia, nausea, vomiting, and diarrhea) and CNS (eg, somnolence, dizziness) side effects. The NSAIDs should be avoided or used cautiously in patients with previous ulcer disease, renal disease, or hypersensitivity to aspirin.[12,18]

The nonprescription combination of acetaminophen, aspirin, and caffeine was approved for the treatment of migraine in the United States because of its proven efficacy in relieving migraine pain and associated symptoms.[16,18] Aspirin and acetaminophen are also available in prescription combination products containing a short-acting barbiturate (butalbital) or narcotic (codeine). While butalbital or butalbital-containing products are possibly effective for acute migraine based on available evidence, the use of these analgesics or narcotics should be limited because of concerns about overuse, medication-overuse headache, and withdrawal.[16,18,19] Although frequent consumption of aspirin or acetaminophen alone can result in medication-overuse headache, combination analgesics appear to pose a greater risk.[19]

Serotonin Receptor Agonists (Triptans)

Introduction of the 5-HT receptor agonists, or triptans, represented a significant

advance in migraine pharmacotherapy. The first member of this class, sumatriptan, and the second-generation agents zolmitriptan, naratriptan, rizatriptan, almotriptan, frovatriptan, and eletriptan are selective agonists of the 5-HT_{1B} and 5-HT_{1D} receptors. Relief from migraine headache is the result of three key actions: normalization of dilated intracranial arteries through enhanced vasoconstriction, inhibition of vasoactive peptide release from perivascular trigeminal neurons, and inhibition of transmission through second-order neurons ascending to the thalamus.[12,18] The triptans all have established efficacy and are appropriate first-line therapy for patients with mild-to-severe migraine. They are also used for rescue therapy when nonspecific medications are ineffective.[16,18]

Sumatriptan, the most extensively studied acute therapy, is available for subcutaneous, oral, and intranasal administration. Subcutaneous sumatriptan is consistently superior to placebo in alleviating migraine headache and associated symptoms, with relief reported in 70% of patients at 2 hours in a meta-analysis of placebo-controlled studies.[16] In addition to enhanced efficacy, subcutaneous sumatriptan has a more rapid onset of action when compared with the oral formulation. The subcutaneous injection is packaged as an autoinjector device for self-administration by patients. Intranasal sumatriptan provides a faster onset of effect than the oral formulation and produces similar rates of response in placebo-controlled studies.[12,18]

Selection of a triptan is based on characteristics of the headache, convenience of dosing, and the patient's preference. At all marketed doses, the oral triptans are effective and well tolerated.[18] The triptans differ in their pharmacokinetic and pharmacodynamic profiles (**Table 78-7**). In general, triptans can be divided into those with a faster onset and higher efficacy and those with a slower onset and lower efficacy. A recent meta-analysis summarizes the efficacy and tolerability of the oral triptans across published and unpublished studies. Using 100 mg of sumatriptan as the reference dose and based on 2-hour response rates, at doses recommended by the manufacturer, most of the triptans evaluated had similar therapeutic gains; frovatriptan and naratriptan were the exceptions with lower efficacy. Compared with other triptans, frovatriptan and naratriptan have the longest half-lives, the slowest onset of action, and less headache recurrence. This may make them more suitable for patients who have migraine attacks of a slow onset and longer duration. Faster-acting triptans are more efficacious when a rapid onset is necessary. Subcutaneous, intranasal, or orally dissolving tablets may be useful in patients with prominent early nausea or vomiting or those who have difficulty in swallowing tablets. Despite the fact that oral absorption can be delayed during migraine attacks, most patients prefer oral formulations.[12,18]

TABLE 78-6 Pharmacokinetic Characteristics of Triptans

Drug	Half-Life (hours)	Time to Maximal Concentration (t_{max})	Bioavailability (%)	Elimination
Almotriptan	3-4	1.4-3.8 hours	80	MAO-A, CYP3A4, CYP2D6
Eletriptan	4-5	1-2 hours	50	CYP3A4
Frovatriptan	25	2-4 hours	24-30	Mostly unchanged, CYP1A2
Naratriptan	5-6	2-3 hours	63-74	Largely unchanged, CYP450 (various isoenzymes)
Rizatriptan	2-3		45	MAO-A
Oral tablets		1-1.2 hours		
Disintegrating		1.6-2.5 hours		
Sumatriptan	2			MAO-A
SC injection		12-15 minutes	97	
Oral tablets		2.5 hours	14	
Nasal spray		1-2.5 hours	17	
Zolmitriptan	3		40-48	CYP1A2, MAO-A
Oral		2 hours		
Disintegrating		3.3 hours		
Nasal		4 hours		

CYP, cytochrome P450; MAO-A, monoamine oxidase type A.

Data from References 12 and 13.

8 Clinical response to the triptans can vary considerably among individual patients. Individual responses cannot be predicted, and if one triptan fails, a patient can be switched successfully to another triptan.[12,13] After an effective agent and dose have been identified, subsequent treatments should begin with that same regimen. Combination therapy may also improve response rates and diminish migraine recurrence. A proprietary formulation of sumatriptan 85 mg plus naproxen 500 mg in a single tablet was more effective in clinical trials for headache relief and sustained pain-free response than either agent as monotherapy.[16,18]

Side effects to the triptans are common but usually mild to moderate in nature and of short duration. Adverse effects are consistent among the class and include paresthesias, fatigue, dizziness, flushing, warm sensations, and somnolence. Local side effects are reported with the subcutaneous (minor injection site reactions) and intranasal (taste perversion, nasal discomfort) routes. Up to 25% of patients receiving a triptan consistently report “triptan sensations,” including

tightness, pressure, heaviness, or pain in the chest, neck, or throat. The mechanism of these symptoms is unknown, but a cardiac source of pain seems unlikely in most patients. However, all triptans are partial agonists of human 5-HT coronary artery receptors in vitro, resulting in a small but significant vasoconstrictor response. Adverse cardiac events are rare with only isolated cases of myocardial infarction and coronary vasospasm with ischemia reported. The triptans are contraindicated in patients with a history of ischemic heart disease (eg, angina pectoris, Prinzmetal's angina, or previous myocardial infarction), uncontrolled hypertension, and cerebrovascular disease. Patients at risk for unrecognized coronary artery disease should use triptans with caution. Postmenopausal women, men older than 40 years of age, and patients with uncontrolled risk factors should receive a cardiovascular assessment prior to triptan use and have initial doses administered under medical supervision. Triptans are also contraindicated in patients with hemiplegic and basilar migraine and should not be used routinely in pregnancy.[18,21] The triptans should not be given within 24 hours of the ergotamine derivatives. Administration of sumatriptan, rizatriptan, and zolmitriptan within 2 weeks of therapy with monoamine oxidase inhibitors (MAOIs) is not recommended. Eletriptan should not be administered with cytochrome P4503A4 (CYP3A4) inhibitors such as macrolide antibiotics, antifungals, and some antiviral therapies. Concomitant therapy with the selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) (eg, duloxetine, venlafaxine, and mirtazapine) can potentially cause 5-HT syndrome. Regulatory agencies caution against concurrent administration, although it appears the likelihood of CNS adverse events is extremely low. The potential risk of these combinations should be carefully considered and discussed with the patient.[12,13,18] Frequent use of the triptans has been associated with the development of medication-overuse headache.[6,19]

Ergot Alkaloids and Derivatives

Ergotamine tartrate and dihydroergotamine can be considered for the treatment of moderate-to-severe migraine attacks (see Table 78-4). These drugs are nonselective 5-HT_1 receptor agonists that constrict intracranial blood vessels and inhibit the development of neurogenic inflammation in the trigeminovascular system.[12,13] Central inhibition of the trigeminovascular pathway is also reported as well as agonist activity at dopaminergic receptors. Venous and arterial constriction occur with therapeutic doses, but ergotamine tartrate exerts more potent arterial effects than dihydroergotamine.[12,18]

The oral and rectal preparations of ergotamine tartrate that contain caffeine, to enhance absorption and potentiate analgesia, have evidence of being probably effective.[16] Dosage requirements should be titrated strictly to establish an effective but subnauseating dose for future attacks. Despite clinical use since 1926, evidence supporting the efficacy of ergotamine alone in migraine is inconsistent.[12,18]

Dihydroergotamine is available for intranasal and parenteral administration by the IM, subcutaneous, and IV routes.[16,18] Parenteral dihydroergotamine was viewed previously as inpatient or emergency department treatment for moderate-to-severe migraine or intractable headache, but patients can be trained to self-administer dihydroergotamine IM or subcutaneously. Clinical studies support the nasal spray and pulmonary inhaler (still in development) as effective and the IV, IM, and subcutaneous routes of administration as probably effective.[13,16]

Nausea and vomiting (resulting from stimulation of the chemoreceptor trigger zone) are among the most common adverse effects of the ergotamine derivatives. Pretreatment with an antiemetic agent should be considered with ergotamine and IV dihydroergotamine therapy. Other common side effects include abdominal pain, weakness, fatigue, paresthesias, muscle pain, diarrhea, and chest tightness. Rarely, symptoms of severe peripheral ischemia (ergotism), including cold, numb, painful extremities, continuous paresthesias, diminished peripheral pulses, and claudication, can result from the vasoconstrictor effects of the ergot alkaloids. Gangrenous extremities, myocardial infarction, hepatic necrosis, and bowel and brain ischemia have also been reported. Dihydroergotamine is rarely associated with such side effects. Triptans and ergot derivatives should not be used within 24 hours of each other.[12,18] Ergotamine derivatives are contraindicated in patients with renal or hepatic failure; coronary, cerebral, or peripheral vascular disease; uncontrolled hypertension; and sepsis; and in women who are pregnant or nursing. Dihydroergotamine does not appear to cause rebound headache, but dosage restrictions for ergotamine tartrate should be observed strictly to prevent this complication.[18]

Antiemetics

Adjunctive antiemetic therapy is useful for combating the nausea and vomiting that accompany migraine headaches and the medications used to treat attacks (eg, ergotamine tartrate). A single dose of an antiemetic, such as metoclopramide, chlorpromazine, or prochlorperazine, administered 15 to 30 minutes before ingestion of oral abortive migraine medications is often sufficient. Suppository preparations are available when nausea and vomiting are

particularly prominent. Metoclopramide is also useful to reverse gastroparesis and improve absorption from the GI tract during severe attacks.[12]

In addition to antiemetic effects, dopamine antagonist drugs also have been used successfully as monotherapy for the treatment of intractable headache (see Table 78-4). Prochlorperazine administered by the intravenous (IV), IM, or rectal routes and IV metoclopramide provided more effective pain relief than placebo. Chlorpromazine and droperidol also have provided relief from migraine headache when administered parenterally at doses of 0.1 mg/kg and 2.75 to 8.25 mg, respectively. The precise mechanism of action for these agents is unknown; however, these dopamine antagonists offer an alternative to the narcotic analgesics for the treatment of refractory migraine. Drowsiness and dizziness were reported occasionally, and extrapyramidal side effects were reported infrequently in migraine trials. Most of these drugs have a risk for QT prolongation and torsades de pointes.[12,16,18]

Opiate Analgesics

There is inadequate evidence supporting the use of narcotic analgesic drugs (ie, parenteral butorphanol, meperidine, methadone, and tramadol or oral codeine) in the treatment of acute migraine. In contrast, the combinations of either oral codeine or tramadol and acetaminophen are probably effective and butorphanol nasal spray has established efficacy.[16] Opiates have no vasopressor or anti-inflammatory effects and can cause central sensitization, increasing the risk of medication-overuse headache and interfering with the efficacy of other treatments even with intermittent use.[12,16,19] Use of these agents should generally be reserved for patients with moderate-to-severe infrequent headaches in whom conventional therapies are contraindicated, or as “rescue medication” after patients have failed to respond to conventional therapies. Opioid therapy should be supervised closely because of the risk of sedation and the potential for misuse.[12,18]

Miscellaneous Nonspecific Medications

Corticosteroids can be considered as rescue therapy for status migrainous (a severe, continuous migraine that can last up to 1 week) or reducing migraine recurrence. Though there is inadequate evidence for use, IV dexamethasone at a dose of 4 to 16 mg has been used as an adjunct to abortive therapy.[16,18] Limited studies suggest a role for IV valproate 400 to 1,000 mg for headaches of moderate or severe intensity, with the majority of patients reporting

improvement after one dose. Magnesium sulfate 1,000 to 2,000 mg IV (in migraine with aura) and isometheptene combinations are probably effective. Future studies might establish a more defined role for these agents in migraine management.[16]

Prophylactic Pharmacologic Therapy

Antiepileptic drugs

Antiepileptic medications have emerged as important therapeutic options for migraine prophylaxis with valproate, divalproex, and topiramate all having established efficacy.[23] The beneficial effects of these agents are likely caused by multiple mechanisms of action, including enhancement of γ-aminobutyric acid (GABA)-mediated inhibition, modulation of the excitatory neurotransmitter glutamate, and inhibition of sodium and calcium ion channel activity. Antiepiletic drugs are particularly useful in patients with migraines and comorbid seizures, anxiety disorder, or bipolar illness.[17,23,29] The efficacy of sodium valproate and divalproex sodium (a 1:1 molar combination of valproate sodium and valproic acid) has been demonstrated in multiple placebo-controlled studies. In most trials for headache prophylaxis, there were no significant differences in treatment-emergent side effects between these agents and placebo. Nausea and vomiting, the most common early side effects, are self-limited and appear to be less common with divalproex sodium and gradual titration of doses. Alopecia, tremor, asthenia, somnolence, and weight gain are also complaints.[17,23] The extended-release formulation of divalproex sodium is administered once daily and is better tolerated than the enteric-coated formulation. Hepatotoxicity is the most serious side effect of valproate therapy, but the risk appears to be low in patients with migraines (eg, patients older than 10 years of age who are receiving monotherapy and have no underlying metabolic or neurologic disorder). Baseline liver function tests should be obtained, but routine follow-up studies are not necessary in asymptomatic adults on monotherapy. Regular follow-up is necessary, however, for dosage adjustments and monitoring of effects. Valproate when being used for migraine prophylaxis is contraindicated in pregnant women (owing to potential teratogenicity), and in patients with a history of pancreatitis or chronic liver disease.[17,23]

Topiramate is the most extensively studied medication to date for migraine prophylaxis. Efficacy and improvements in health-related quality of life including daily work, home, and social activities have been demonstrated in

several placebo-controlled studies. To minimize adverse effects, topiramate should be initiated at a low dose and slowly titrated upward. The benefits of topiramate are observed as early as 2 weeks after initiation of therapy, with significant reductions in migraine frequency within the first month. Approximately 50% of patients treated to target doses are responders (50% or greater reduction in mean headache frequency). Treatment-emergent adverse events associated with topiramate include paresthesia, fatigue, anorexia, diarrhea, weight loss, hypesthesia, difficulty with memory, language problems, taste perversion, and nausea. Paresthesia is the most common adverse event, occurring in about half of patients at target doses. Weight loss, occurring in 9% to 12% of patients, is a unique adverse effect, as weight gain is a common reason to discontinue other preventive medications. Topiramate should be used with caution or avoided in patients with a history of kidney stones or cognitive impairment.[17,23]

Preliminary studies suggest a role for other antiepileptic drugs for migraine prevention. Carbamazepine is possibly effective, and a recent study evaluated gabapentin, but data are insufficient to determine efficacy. Lamotrigine is classified as possibly or probably ineffective.[23]

Additional information regarding all antiepileptic drugs can be found in Chapter 73.

Antidepressants

The beneficial effects of antidepressants in migraine are independent of their antidepressant activity and may be related to downregulation of central 5-HT_2 receptors, increased levels of synaptic norepinephrine, and enhanced endogenous opioid receptor actions.[7] The tricyclic antidepressant (TCA) amitriptyline and SNRI venlafaxine have demonstrated efficacy in placebo-controlled and comparative studies and are classified as probably effective for migraine prophylaxis (see Table 78-5).[17,23] Use of other antidepressants is based primarily on clinical and anecdotal experience. There are insufficient or conflicting data to support or refute the efficacy of other antidepressants, such as protriptyline, fluoxetine, or fluvoxamine, for migraine prophylaxis.[23]

Anticholinergic side effects are common with the TCAs and limit use of these agents in patients with benign prostatic hyperplasia and glaucoma. Evening doses are preferred because of associated sedation and increased appetite and weight gain can occur. Orthostatic hypotension and cardiac toxicity (slowed atrioventricular conduction) also are reported occasionally.[17,23] The most

common side effects reported with venlafaxine are nausea, vomiting, and drowsiness. Again, the potential risk of 5-HT syndrome should be considered in patients using SSRIs or SNRIs along with a triptan.[18,23] Additional information about the side effects of antidepressants can be found in Chapter 85.

β-Adrenergic Antagonists

β-Adrenergic antagonists are among the most widely used drugs for migraine prophylaxis. Metoprolol, propranolol, and timolol have established efficacy in controlled clinical trials, reducing the frequency of attacks by 50% in greater than 50% of patients.[17,23] Atenolol and nadolol are also probably effective, while nebivolol and pindolol are possibly effective (see Table 78-5).[23] Because the relative efficacy of the individual agents has not been established, selection of a β-blocker can be based on β-selectivity, convenience of the formulation, and tolerability. Although their precise mechanism of antimigraine action is unknown, β-blockers may raise the migraine threshold by modulating adrenergic or serotonergic neurotransmission in cortical or subcortical pathways. Although not first-line treatment for hypertension, β-blockers may be useful along with other therapy in patients with comorbid hypertension or angina. Side effects can include drowsiness, fatigue, sleep disturbances, vivid dreams, memory disturbance, depression, impotence, bradycardia, and hypotension. The β-Blockers should be used with caution in patients with congestive heart failure, peripheral vascular disease, atrioventricular conduction disturbances, asthma, depression, and diabetes.[17,23]

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs are modestly effective for reducing the frequency, severity, and duration of migraine attacks, but potential GI and renal toxicity limit the daily or prolonged use of these agents. Consequently, NSAIDs have been used intermittently to prevent headaches that recur in a predictable pattern, such as menstrual migraine. Administration of NSAIDs in the perimenstrual period can be beneficial in women with true menstrual migraine. NSAIDs should be initiated up to 1 week prior to the expected onset of headache and continued for no more than 10 days.[24] If long-term NSAID therapy is initiated, monitoring of renal function and occult blood loss is necessary. For migraine prevention, the evidence for efficacy is strongest for naproxen and weakest for aspirin.[24,27]

Triptans

Triptans are also useful for the prevention of menstrual migraine. Frovatriptan has established efficacy, while naratriptan and zolmitriptan are probably effective. The triptan is usually started 1 or 2 days before the expected onset of headache and continued during the period of vulnerability.[24,27] A separate indication for pure menstrual migraine is currently being deliberated by regulatory authorities.[23]

Calcitonin Gene-Related Peptide Antagonists

Inhibition of the CGRP receptor is the newest target in the prophylaxis of migraines.[7,17,30] Several anti-CGRP receptor monoclonal antibodies have demonstrated efficacy in the prevention of episodic and chronic migraines (with or without aura).[30] Initial concerns regarding the potential for cardiovascular, pulmonary, and psychiatric adverse effects due to theoretical vasodilatory actions were not substantiated in clinical trials. More data are needed to determine long-term safety and efficacy, particularly in special patient populations (eg, geriatric, pediatric, pregnant women). Access to and cost of these agents may also limit usage.[30]

Miscellaneous Prophylatic Agents

At least two placebo-controlled studies show that petasites, an extract from the butterbur plant *Petasites hybridus*, is an effective preventive treatment for migraine.[17,25] A double-blind, placebo-controlled study demonstrated the probable efficacy of riboflavin (vitamin B_2) 400 mg daily in migraine prophylaxis. Riboflavin was well tolerated and associated with 50% or greater improvement in attack frequency in 54% of patients. However, the benefits of therapy became significant only after 3 months.[17,25] The relatively stable extract of feverfew (*Tanacetum parthenium*), MIG-99, is the most studied herbal preparation for migraine prevention and is classified as probably effective, reducing migraine frequency by 1.9 attacks per month.[17,25] Clinical trials evaluating various formulations of magnesium for migraine prevention have yielded mixed results, but there is probable efficacy.[17,25] As CNS levels of magnesium are known to be significantly low during migraine attacks, magnesium supplementation may be particularly effective for prevention of menstrual migraine.[26] Subcutaneous histamine has been compared with placebo, sodium valproate, and topiramate, with favorable results indicating probable

efficacy in improving headache frequency, duration, and intensity. Transient burning and itching at the injection site were the only reported side effects with histamine administration.[25]

Other agents are possibly effective and may be considered for migraine prevention.[23,25] The angiotensin-converting enzyme inhibitor lisinopril and the angiotensin II receptor blocker candesartan provided effective migraine prophylaxis in recent double-blind, placebo-controlled, crossover studies of these agents.[17,23] Although use is limited by side effects, clonidine and guanfacine have also demonstrated possible efficacy.[23] Coenzyme Q10 was effective for migraine prevention and well tolerated in a small, randomized, double-blind, controlled study.[17,25] In one study, cyproheptadine (4 mg/day) was as effective as propranolol (80 mg/day) in reducing migraine frequency, duration, and severity, while the combination was more effective in attack frequency reduction.[23,25]

The calcium channel blockers, primarily verapamil, have been widely used for preventive treatment, although evidence supporting their use is inadequate or conflicting.[17,23] Extensive clinical experience and verapamil's ease of use suggest a possible role in migraine prevention, with side effects including constipation, hypotension, bradycardia, atrioventricular block, and exacerbation of congestive heart failure.[23]

Localized injections of botulinum toxin type A have been used for various conditions and pain syndromes, including migraine headache. However, no consistent, statistically significant benefits have been found with migraine. The American Academy of Neurology concludes that botulinum toxin is probably ineffective.[17] Further study is needed to confirm the clinical utility and comparative efficacy for many of these miscellaneous agents in the prevention of migraine.

TENSION-TYPE HEADACHE

Epidemiology

Tension-type headache is the most common type of primary headache, with an estimated 1-year prevalence ranging from 38% to 86%,[3,31] which peaks in the fourth decade and is higher among women. The incidence decreases with age.[31] Although most tension-type headache sufferers experience some degree of functional impairment during their attacks, few sufferers seek medical attention,

likely because they have intermittent attacks. Infrequent episodic tension-type headache (defined as fewer than one episode per month) is experienced by 64% of sufferers, while 22% have frequent episodic tension-type headache (episodes on 1-14 days/month). The prevalence of chronic tension-type headache (15 or more days/month, perhaps without recognizable episodes) is estimated at 0.9% to 2.2%.[2,31] Risk factors associated with a poor outcome in tension-type headache include coexisting migraine, depression, anxiety, poor stress management, and the presence of chronic tension-type headache.[32]

Pathophysiology

Although tension-type headache is the most common type of headache, it is the least studied of the primary headache disorders, and there is limited understanding of key pathophysiologic concepts.[2,31] Some evidence supports that migraine and tension-type headaches represent a continuum of headache severity with similarities in mechanisms and pathophysiology. However, more recently, tension-type headache has been recognized as a distinct disorder.[2,31] The mechanism of pain in chronic tension-type headache is thought to originate from myofascial factors and peripheral sensitization of nociceptors. Central mechanisms also are involved, with heightened sensitivity of pain pathways in the CNS.[31] Mental stress, nonphysiologic motor stress, a local myofascial release of irritants, or a combination of these may be the initiating stimulus. Following activation of supraspinal pain perception structures, a self-limiting headache results in most individuals owing to central modulation of the incoming peripheral stimuli. Chronic tension-type headache can evolve from episodic tension-type headache in predisposed individuals due to a change in central circuits and nociceptive processing along the brain stem reflex pathway and subsequent sensitization of the CNS.[31] It is likely that other pathophysiologic mechanisms also contribute to the development of tension-type headache.

Clinical Presentation

Premonitory symptoms and aura are absent with tension-type headache. The pain usually is mild to moderate in intensity and often is described as a dull, nonpulsatile tightness or pressure.[2,31] Bilateral pain is most common, classically described as having a “hatband” pattern. Associated symptoms generally are absent, but mild photophobia or phonophobia may be reported. The disability

associated with tension-type headache typically is minor in comparison with migraine headache, and routine physical activity does not affect headache severity.[2,31] Palpation of the pericranial or cervical muscles can reveal tender spots or localized nodules in some patients.[2] Tension-type headache is classified as either episodic (infrequent or frequent) or chronic based on the frequency and duration of the attacks.[2]

TREATMENT

Desired Outcomes

While pain relieve and prevention of further headaches are the main desired outcomes of treatment, the vast majority of episodic tension-type headache sufferers self-medicate with nonprescription medications and do not consult a healthcare professional. Although pharmacologic and nonpharmacologic treatments are available, simple analgesics and NSAIDs are the mainstay of acute therapy. Most agents used for tension-type headache have not been studied in controlled clinical trials.[32]

Nonpharmacologic Therapy

Psychophysiologic therapy and physical therapy have been used in the management of tension-type headache. Behavioral treatments can consist of cognitive-behavioral therapy (ie, stress management), relaxation training, and biofeedback.[33] These therapies (alone or in combination with pharmacotherapy) can result in a 33% to 64% reduction in headache activity. Relaxation training combined with biofeedback is more effective than other behavioral therapy options.[33] Evidence supporting physical therapeutic options, such as heat or cold packs, ultrasound, electrical nerve stimulation, stretching, exercise, massage, acupuncture, manipulations, ergonomic instruction, and trigger point injections or occipital nerve blocks, is somewhat inconsistent. However, individual patients may benefit from selected modalities in reducing the frequency of tension-type headache or during an acute episode.[32,33]

Pharmacologic Therapy

Simple analgesics (alone or in combination with caffeine) and NSAIDs are

effective for the acute treatment of most mild-to-moderate tension-type headaches. Acetaminophen, aspirin, diclofenac, ibuprofen, naproxen, ketoprofen, and ketorolac have demonstrated efficacy in placebo-controlled and comparative studies.[32] Failure of nonprescription agents can warrant therapy with prescription drugs. The combination of aspirin or acetaminophen with butalbital or, rarely, codeine can be effective options in selected patients; however, use of butalbital and codeine combinations should be avoided when possible owing to the high potential for overuse and misuse.

Acute medications should be taken for episodic tension-type headache not more than 3 days (butalbital-containing), 9 days (combination analgesics), or 15 days (NSAIDs) per month to prevent the development of medication-overuse or chronic tension-type headache.[32] There is no evidence to support the efficacy of muscle relaxants in the management of episodic tension-type headache.[32] Preventive treatment is appropriate for most patients with chronic tension-type headache and should be considered in those with frequent episodic tension-type headache if frequency (more than 2 per week), duration (greater than 3-4 hours), or severity results in medication overuse or substantial disability.[33]

The principles of preventive treatment for tension-type headache are similar to those for migraine headache. The TCAs are prescribed most often for prophylaxis, but other drugs also can be selected after consideration of comorbid medical conditions and respective side effect profiles. In general, the SSRIs are not effective in patients with tension-type headache who do not have depression and limited studies support the use of the SNRIs mirtazapine and venlafaxine in patients with chronic tension-type headache and without depression.[33] Topiramate, gabapentin, and tizanidine may have benefits in chronic tension-type headache; however, confirmation is needed from randomized clinical trials. Data from small randomized studies suggest that trigger point injections of lidocaine may reduce headache frequency with frequent episodic or chronic tension-type headache. Injection of botulinum toxin into pericranial muscles has demonstrated inconsistent efficacy in the prophylaxis of tension-type headache and because of this, it is of uncertain benefit.[33]

CLUSTER HEADACHE

Epidemiology

Cluster headache, the most severe of the primary headache disorders, is characterized by attacks of excruciating, unilateral head pain that occur in series

lasting for weeks or months (ie, cluster periods) separated by remission periods usually lasting months or years.[2,34] Cluster headaches can be episodic or chronic,[2] and is relatively uncommon among the primary headache disorders, but the exact prevalence is uncertain. Estimates from pooled population studies show a lifetime prevalence of 124 per 100,000 or 0.12%.[34,35] The male-to-female ratio for cluster headache is approximately 4:1 with age of onset typically in the second to third decade. Up to 85% of patients with cluster headache are tobacco smokers or have a history of smoking. Tobacco cessation does not, however, seem to improve the course of cluster headaches. Recent genetic epidemiologic surveys support a predisposition for cluster headache can exist in certain families.[34–36]

Pathophysiology

The etiologic and pathophysiologic mechanisms of cluster headache are not completely understood. Neuroimaging studies performed during acute attacks have demonstrated activation of the ipsilateral hypothalamic gray area, implicating the hypothalamus as a modulator of cluster headaches. The hypothalamus secondarily activates trigeminal-autonomic reflexes, leading to the ipsilateral pain and cranial autonomic features characteristic of cluster headache.[34–36] The cyclic and circadian rhythmicity of attacks also implicates a pathogenesis of hypothalamic dysfunction.[35,36] There is some evidence that cluster headache may result from inflammation of the nerves traversing the cavernous sinus resulting in injury to sympathetic fibers of the internal carotid artery.[35]

Clinical Presentation

One hallmark of cluster headaches is the circadian rhythm of painful attacks. Episodic cluster headaches are the most common cluster headache subtype in both men and women, occurring in up to 90% of patients.[35] In episodic cluster headaches, attacks occur daily for a week to several months, followed by long pain-free intervals. Periods of remission average 2 years in length but have been reported to be from 2 months to 20 years in duration. Approximately 15% of patients have chronic symptoms with attacks recurring for over 1 year without remission or with remission periods of less than 1 month.[34,35]

Cluster headache attacks occur commonly at night and more commonly in the spring and fall. Attacks occur suddenly, with pain peaking quickly after onset

and generally lasting 15 to 180 minutes. The pain is excruciating, penetrating, and of a boring (ie, deep, nonpulsating, behind the eye) intensity in orbital, supraorbital, and temporal unilateral locations. The headache is accompanied by cranial autonomic symptoms such as conjunctival injection, lacrimation, nasal stuffiness, rhinorrhea, eyelid edema, facial sweating, and miosis/ptosis, which resolve with resolution of the headache. Most sufferers of cluster headaches also describe restlessness or agitation. Whereas migraine patients retreat to a quiet, dark room, cluster headache patients generally sit and rock or pace about the room clutching their head. Auras are not present with cluster headaches and during the cluster period, attacks occur from once every other day to eight times per day.[34,35] Specific diagnostic criteria for cluster headaches are provided within the IHS classification system.[2]

TREATMENT

Desired Outcomes

As in migraine, therapy for cluster headaches involves both abortive and prophylactic therapy with the overall desired outcomes being resolution or prevention of pain and disability. Abortive therapy is directed at managing the acute attack, whereas prophylactic therapies are started early in the cluster period in an attempt to induce remission. Patients with chronic cluster headache can require prophylactic medications indefinitely.

Abortive Therapy

Oxygen

The standard acute treatment of cluster headache is inhalation of 100% oxygen by nonbreather facial mask at a rate of at least 12 to 15 L/min, with effects usually starting 15 to 20 minutes after treatment.[36–39] Repeat or frequent administration over a short period of time should be avoided, as overuse may increase the frequency or merely delay rather than abort the attack in some patients.[37,38] No side effects have been reported with the use of oxygen, but caution should be used for those who smoke or have chronic obstructive pulmonary disease.

Triptans

The quick onset of subcutaneous and intranasal triptans makes them safe and effective abortive agents for cluster headaches. Subcutaneous sumatriptan (6 mg) is the most effective agent, whereas nasal sprays, which are less effective than subcutaneous administration, may be better tolerated in some patients. Adverse events reported with triptan use in patients with cluster headache are similar to those seen in patients with migraines. Orally administered triptans have limited use in cluster attacks because of their relatively slow onset of action; oral zolmitriptan (10 mg), however, was modestly effective in patients with episodic cluster headache.[36,37]

Ergotamine Derivatives

All forms of ergotamine have been used in cluster headaches, although no controlled clinical trials support their use.[37,39] In clinical use, IV dihydroergotamine may be given as a bolus followed by repeated administration over several days to break the cycle of frequent attacks. Ergotamine tartrate also has provided effective relief from cluster headache attacks when administered sublingually.[37] Dosing guidelines are similar to those for migraine headache therapy.

Prophylactic Therapy

Verapamil

The preferred first-line treatment for prevention of cluster headaches is verapamil, a calcium channel blocker with antianginal and antiarrhythmic properties.[36,38,39] The beneficial effects of verapamil often appear within 2 to 3 weeks of therapy with a typical suggested dosage range from 360 to 960 mg/day, starting with a dose of 240 mg/day. Rarely, patients with refractory cluster headaches are treated with doses as high as 1,200 mg/day. In such patients, an electrocardiogram should be obtained as the dose is increased, due to concerns for bradycardia or heart block.[37,39]

Lithium

Lithium carbonate is effective for episodic and chronic cluster headache attacks and can be used when other drugs are ineffective or contraindicated. A positive response is seen in up to 78% of patients with chronic cluster headache, and in up to 63% of patients with episodic cluster headache. The usual dose is 600 to 1,200 mg/day, with a suggested starting dose of 300 mg twice daily. Lithium

levels should be monitored and maintained between 0.4 and 1.2 mEq/L (mmol/L).[37]

Major side effects include tremor, thyroid and renal dysfunction, and rarely cardiac arrhythmias. Liver, thyroid, and renal function must be carefully monitored during therapy. Lithium should be administered with caution to patients with significant renal or cardiovascular disease, dehydration, pregnancy, or concomitant diuretic or NSAID use.[37,39] Additional details regarding lithium administration can be found in Chapter 86.

Corticosteroids

Although there are few clinical trials evaluating the use of corticosteroids in cluster headache management, they have been used effectively for inducing remission.[37] Therapy is initiated with at least 5 days of 60 to 100 mg/day prednisone and then tapered by a dose reduction of approximately 10 mg/day. To avoid steroid-induced complications, long-term use is generally not recommended and headaches can recur when therapy is tapered or discontinued.[37,39]

Miscellaneous Agents

Other therapies that have been used in the acute management of cluster headache include intranasal lidocaine and subcutaneous octreotide. Limited studies or case reports also support the use of topiramate, divalproex sodium, melatonin, indomethacin, long-acting triptans and intranasal capsaicin for cluster headache prevention.[37–39]

Neurosurgical interventions to relieve chronic cluster headaches in patients refractory to pharmacologic therapy may be considered for some with debilitating headaches.[37] Neurostimulation has gained attention in the last several years. Vagal nerve stimulation and sphenopalatine stimulation studies have shown positive results in small clinical trials.[36,37,40]

EVALUATION OF THERAPEUTIC OUTCOMES

Medications with the highest level of efficacy should be used for treatment. Migraine management should be individualized on the basis of the patient's clinical presentation and medical history. Therapy should usually be initiated with the lowest effective dose and then titrated upward until clinical benefits are achieved, in the absence of adverse events. Medications that increase headache

frequency or severity should be avoided. Many patients try nonpharmacologic or nonprescription treatments for headache management either before or concurrently with other drug therapy. Patients may not know how to take these products optimally and often need instructions and dosing limits.

Analgesics and NSAIDs can be considered the drugs of choice if effective for infrequent mild-to-moderately-severe attacks. The triptans or dihydroergotamine can be used if initial therapies prove ineffective or as first-line therapy in moderate-to-severe migraine headache. Abortive therapy should be instituted early in the course of the attack to optimize efficacy and minimize migraine-related pain and disability. Preventive therapy should be considered in the setting of recurring migraines that produce significant disability; frequent attacks requiring symptomatic medication more than twice per week; symptomatic therapies that are ineffective or contraindicated, or produce serious side effects; and uncommon migraine variants that cause risk of neurologic injury. Efficacy of any prescribed prophylactic regimen should be reassessed periodically. Therapeutic interventions require an adequate trial to achieve clinical benefit and often as long as 6 months for assessment of maximal benefit. A prolonged headache-free interval could allow for gradual dosage reduction and discontinuation of therapy.

Patients should be monitored for frequency, intensity, and duration of headaches, as well as any change in the headache pattern. To this end, patients should be encouraged to keep a headache diary to document the frequency, severity, and duration of attacks, as well as response to medication and potential trigger factors. Careful monitoring is essential to initiate the most appropriate pharmacotherapy, document therapeutic successes and failures, identify medication contraindications, and prevent or minimize adverse events. Patients using acute therapies should be monitored for the frequency of their use of prescription and nonprescription medications to identify potential medication-overuse headache.

Although migraine is widely recognized as a disease that exacts an enormous toll on the sufferer, healthcare providers often do not recognize the degree and scope of functional impairment imposed by migraine on the individual. Approximately 1 out of every 6 healthcare visits for migraine occurs in the emergency department, though management in this setting is often suboptimal. The use of opioids for the acute treatment of migraine in the emergency department is increasing, and the likelihood of unnecessary radiation exposure is greater.[5] Although most episodic migraine sufferers take medications for their headaches, only 2 in 3 patients who have been diagnosed and consulted with a

healthcare provider use migraine-specific treatments. Just 11% of those eligible for use of medications to prevent migraine currently use them, although approximately 38% would benefit from prophylaxis.[14] Patient counseling is necessary to allow for proper medication use (eg, self-injection with sumatriptan), to encourage early use of medications in the headache cycle, and to enhance patient compliance. Strict adherence to dosing guidelines should be stressed to minimize potential toxicity. Patterns of abortive medication use can be documented to establish the need for prophylactic therapy. Prophylactic therapies also should be monitored closely (every 3-6 months until stable) for adverse reactions, abortive therapy needs, adequate dosing, and compliance. Because many patients with migraines who receive inadequate care experience substantial levels of pain and disability, improvement in migraine diagnosis, care, and treatment potentially could result in lower direct and indirect costs of the disease. Consultation with other healthcare practitioners should be encouraged when changes in headache patterns or medication use occur.

CONCLUSION

Even though headache disorders appear to occur as a result of neuronal dysfunction, the precise etiology and nature of the dysfunction are unknown. Serotonergic neurotransmission and the trigeminovascular system appear to play important roles. A careful patient workup, including patient history, physical examination, and appropriate laboratory tests, should identify most headache patients with major disease. A variety of strategies can be helpful for managing migraine, tension-type, and cluster headaches. Management of primary headache disorders is directed at suppressing acute attacks and preventing recurrences. Continuing research in existing and newly identified pathways will better define pathophysiologic mechanisms and aid the search for less toxic and more efficacious pharmacologic agents.

Postclass Engaged Learning Activity

Research the new class of drugs known as calcitonin gene-related peptide receptor inhibitors and answer the following questions:

1) In which headache disorders have these agents demonstrated effectiveness?
2) What is their mechanism of action?
3) Which agents are FDA approved and for what indications?

4) What key patient counseling points should be provided to those taking these medications?
5) What will be the place in therapy for this class of drugs taking into account their advantages and disadvantages?

The purpose of this activity is for you to consider emerging treatment options relevant to headache disorders and future directions in headache pharmacotherapy.

ABBREVIATIONS

CGRP	calcitonin gene-related peptide
CNS	central nervous system
FDA	Food and Drug Administration
GABA	γ-aminobutyric acid
GI	gastrointestinal
5-HT	serotonin, 5-hydroxytryptamine
IHS	International Headache Society
IM	intramuscular
IV	intravenous
MAOI	monoamine oxidase inhibitor
NSAIDs	nonsteroidal anti-inflammatory drugs
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant

REFERENCES

1. Weiss AJ, Wier LM, Stocks C, Blanchard J. Overview of emergency department visits in the United States, 2011. Statistical Brief #174. June 2014. Agency for Health Care Policy and Research, Rockville, MD. Available at: http://www.hcup-us.ahrq.gov/reports/statbriefs/sb174-Emergency-Department-Visits-Overview.pdf. Accessed August 9, 2015.
2. Headache Classification Committee of the International Headache Society. The international classification of headache disorders, 3rd ed. *Cephalalgia*. 2013;33(9):629–808.
3. Bajwa ZH, Wootton RJ. Evaluation of headache in adults. *UpToDate*. 2018;21:1-16. Available at: www.uptodate.com. Accessed July 18, 2018.

4. Smitherman TA, Burch RC, Sheikh H, Loder E. The prevalence, impact, and treatment of migraine and severe headaches in the United States: A review of statistics from national surveillance studies. *Headache*. 2013;53:427–436.
5. Burch RC, Loder S, Loder E, Smitherman TA. The prevalence and burden of migraine and severe headache in the United States: Updated statistics from government health surveillance studies. *Headache*. 2015;55:21–34.
6. Charles A. Migraine. *N Engl J Med*. 2017;377:553–561.
7. Cutrer FM, Bajwa ZH. Pathophysiology, clinical manifestations, and diagnosis of migraine in adults. *UpToDate*. 2018;33:1-31. Available at: www.uptodate.com. Accessed July 18, 2018.
8. Steiner TJ, Birbeck GL, Jensen RH, et al. Headache disorders are third cause of disability worldwide. *J Headache Pain*. 2015;16:58.
9. Messali A, Sanderson J, Blumenfeld AM, et al. Direct and indirect costs of chronic and episodic migraine in the United States: A web-based survey. *Headache*. 2016;56:306–322.
10. Ferrari MD. Migraine. *Lancet*. 1998;351:1043–1051.
11. Silberstein SD, Dodick DW. Migraine genetics: Part II. *Headache*. 2013;53:1218–1229.
12. Ong JJY, De Felice M. Migraine treatment: Current acute medications and their potential mechanisms of action. *Neurotherapeutics*. 2018;15:274–290.
13. Da Silva AN, Tepper SJ. Acute treatment of migraines. *CNS Drugs*. 2012;10:823–839.
14. Lipton RB, Silberstein SD. Episodic and chronic migraine headache: Breaking down barriers to optimal treatment and prevention. *Headache*. 2015;S2:103–122.
15. Bose P, Goadsby PJ. The migraine postdrome. *Curr Opin Neurol*. 2016;29:299–301.
16. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: The American Headache Society evidence assessment of migraine pharmacotherapies. *Headache*. 2015;55:3–20.
17. Bajwa ZH, Smith JH. Preventive treatment of migraine in adults. *UpToDate*. 2018;46:1-11. Available at: www.uptodate.com. Accessed December 13, 2018.
18. Bajwa ZH, Smith JH. Acute treatment of migraine in adults. *UpToDate*.

2018;51:1-27. Available at: www.uptodate.com. Accessed July 18, 2018.

19. Garza I, Schwedt TJ. Medication overuse headache: Etiology, clinical features, and diagnosis. *UpToDate*. 2019;11:1-11. Available at: www.uptodate.com. Accessed July 18, 2018.
20. Garza I, Schwedt TJ. Medication overuse headache: Treatment and prognosis. *UpToDate*. 2018;14:1-15. Available at: www.uptodate.com. Accessed July 18, 2018.
21. Vandenbussche N, Laterza D, Lisicki M, et al. Medication-overuse headache: A widely recognized entity amidst ongoing debate. *J Headache Pain*. 2018;19(1):50.
22. MacGregor EA. Migraine. *Ann Intern Med*. 2013;159:ITC5-1.
23. Silberstein SD, Holland S, Freitag F, et al. Evidence-based guideline update: Pharmacological treatment for episodic migraine prevention in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012;78:1337–1345.
24. Rizzoli P. Preventive pharmacotherapy in migraine. *Headache*. 2014;54:364–369.
25. Holland S, Silberstein SD, Freitag F, et al. Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012;78:1346–1353.
26. Calhoun AH. Estrogen-associated migraine. *UpToDate*. 2018;26:1-18. Available at: www.uptodate.com. Accessed July 18, 2018.
27. Martin PR. Behavioral management of the triggers of recurrent headache: A randomized controlled trial. *Behav Res Ther*. 2014;61:1–11.
28. Lampl C, Voelker M, Steiner TJ. Aspirin is first-line treatment for migraine and episodic tension-type headache regardless of headache intensity. *Headache*. 2012;52:48–56.
29. Minen MT, Begasse De Dhaem O, Kroon Van Diest A, et al. Migraine and its psychiatric comorbidities. *J Neurol Neurosurg Psychiatry*. 2016:87:741–749.
30. Tepper SJ. History and review of anti-calcitonin gene-related peptide (CGRP) therapies: From translational research to treatment. *Headache*. 2018;58:238–275.

31. Taylor FR. Tension-type headache in adults: Pathophysiology, clinical features, and diagnosis. *UpToDate*. 2018;14:1-19. Available at: www.uptodate.com. Accessed July 18, 2018.
32. Taylor FR. Tension-type headache in adults: Acute treatment. *UpToDate*. 2018;14:1-11. Available at: www.uptodate.com. Accessed July 18, 2018.
33. Taylor FR. Tension-type headache in adults: Preventive treatment. *UpToDate*. 2018;15:1-14. Available at: www.uptodate.com. Accessed July 18, 2018.
34. Nesbitt AD, Goadsy PJ. Cluster headache. *BMJ*. 2012;344:e2407.
35. May A. Cluster headache: Epidemiology, clinical features, and diagnosis. *UpToDate*. 2018;11:1-17. Available at: www.uptodate.com. Accessed July 18, 2018.
36. Hoffman J, May A. Diagnosis, pathophysiology, and management of cluster headache. *Lancet Neurol*. 2018;17:75–83.
37. May A. Cluster headache: Treatment and prognosis. *UpToDate*. 2018;31:1-16. Available at: www.uptodate.com. Accessed July 18, 2018.
38. Martelletti P. Cluster headache management and beyond. *Expert Opin Pharmacother*. 2015;16(10)1411–1415.
39. Tfelt-Hansen PC, Jensen RH. Management of cluster headache. *CNS Drugs*. 2012;26(7):571–580.
40. Wolter T, Kaube H. Neurostimulation for chronic cluster headache. *Ther Adv Neurol Disord*. 2012;5(3):175–180.

SECTION 9 PSYCHIATRIC DISORDERS

Evaluation of Psychiatric Disorders

Mark E. Schneiderhan, Leigh Anne Nelson, Jeffrey R. Bishop, and Steven Bauer

KEY CONCEPTS

1. Patients with psychiatric conditions are treated in all healthcare settings. All clinicians can apply the basic skills of the psychiatric assessment to provide the best care for patients.
2. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and the Pocket Guide to the DSM-5 Diagnostic Exam provides clinicians with a standardized approach for the initial assessment and follow-up of patients with psychiatric conditions.
3. The World Health Organization's International Classification of Diseases and Related Health Problems (ICD) is currently used in all patient care settings for billing purposes.
4. Clinicians should be prepared to gather both the psychiatric and physical health history from their patients. Obtaining a release of information (ROI) from patients to communicate with other healthcare providers or significant others is often necessary when sharing protected health information (PHI).
5. Patient interviews should be conducted in an atmosphere that ensures the comfort, privacy, and safety of both the patient and the clinician. Effective listening skills and the application of open-ended questions are essential in the interview process and therapeutic relationship. Motivational interviewing (MI) can empower patients to participate and design achievable treatment goals.
6. If a patient is in crisis, the clinician may feel some apprehension about asking certain assessment questions. Knowing what specific questions to ask can help facilitate inquiry about sensitive areas, such as delusional thinking and suicidality.

7. Current and past medication histories, including allergies, side effects, and clinical response are the cornerstone of effective medication management. The medication history should be assessed for safety (eg, contraindications and drug interactions), tolerability (eg, side effects), efficacy (eg, response of target symptoms and adequate dosage and duration), and adherence (eg, affordability).
8. Baseline mental status examination (MSE), psychiatric rating scales, and psychological/neuropsychological tests are useful tools in diagnosing and monitoring the severity of symptoms and response to treatments of psychiatric disorders.
9. Although there are no diagnostic tests for psychiatric disorders, physical and laboratory assessments can help rule out drug-induced or medical causes that may produce similar or overlapping symptoms.
10. Psychiatric rating scales, cognitive testing (neuropsychiatric rating scales), and psychological testing provide objective measures of psychiatric symptoms, adverse side effects, memory, and intellectual capacity and are often used in research and clinical settings.

Preclass Engaged Learning Activity

Describe the purpose of the Mental Status Examination (MSE).

1. When would you administer a MSE? What type of information do you get from the MSE?
2. How would you use the information obtained from the MSE to care for a patient with psychiatric illness?
3. What is the difference between the MSE and the Mini-Mental Status Examination (MMSE)?

Complete a practice MSE on a simulated patient. The following videos may be helpful in understanding the MSE:

Psychiatric History and Mental Status Examination Tutorial:
http://www.youtube.com/watch?v=U5KwDgWX8L8

(This video describes the MSE.)

Video demonstrating components of the mental status examination (MSE)

Link: http://www.youtube.com/watch?v=1HbgPhq3MzA

(This video gives examples of the MSE and offers the opportunity to complete a practice MSE.)

The activity is intended to build your knowledge of the MSE which is an assessment commonly used in psychiatry. Understanding the MSE can help you identify target symptoms for psychiatric drug therapy.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

80

Attention Deficit/Hyperactivity Disorder

Julie A. Dopheide, Danielle L. Stutzmann, and Steven R. Pliszka

KEY CONCEPTS

1. Untreated or ineffectively treated childhood attention deficit/hyperactivity disorder (ADHD) can lead to poor school performance, poor socialization, and increased risk for traffic accidents, psychiatric comorbidities, unemployment, and incarceration during adolescence and adulthood.
2. ADHD is 74% genetic in origin, and is associated with decreased brain volume, a delay in cortical maturation, and possible dysregulation of the "default mode network," a brain system that regulates attention, prioritization of information, memory, and impulse control.
3. Symptoms of inattention or hyperactivity and impulsivity or all three must be present during childhood and cause functional impairment in two different settings for 6 months to meet DSM-5 diagnostic criteria for ADHD. Adult-onset ADHD requires further study.
4. Prior to initiating pharmacotherapy, overall physical and mental health and psychiatric comorbidities must be assessed, and goals of treatment must be set.
5. Preschoolers, school-age children, adolescents, and adults with ADHD all can benefit from nonpharmacologic interventions that include a healthy diet, education on ADHD, and potentially effective educational, cognitive, and behavioral treatments.
6. The stimulants are the most effective pharmacologic treatment option for all ages with a rapid therapeutic effect, typically within 1 or 2 hours of an effective dose. Methylphenidate is recommended as first-line for children and adolescents while amphetamines are first-line treatment for adults based on efficacy and tolerability.

7. α_2-Adrenergic agonists such as extended-release preparations of guanfacine and clonidine are less effective than stimulants as monotherapy and are used in combination with stimulants or as monotherapy in youth to improve symptom control, particularly oppositional behaviors and insomnia.
8. When ADHD coexists with other neuropsychiatric conditions, such as anxiety disorders, major depression, autism spectrum disorder (ASD) or Tourette disorder, it is optimal to treat the most functionally impairing disorder first (whether it is ADHD or the co-occurring condition) and then treat the second disorder.
9. When ADHD coexists with bipolar disorder, it is necessary to first stabilize the mood with lithium, an anticonvulsant, or an atypical antipsychotic before adding an ADHD-specific medication such as a stimulants.
10. Atomoxetine is a good option to manage ADHD symptoms in adolescents and adults with substance-use disorders or when stimulants are intolerable. It has a delayed onset of effect (2–4 weeks), but it has no abuse potential.

Preclass Engaged Learning Activity

Watch the approximately 7-minute video (Video link) by ADHD researcher and child psychiatrist, Dr. Steven R. Pliszka as he provides an example of a typical interview with a child undergoing evaluation for ADHD and he discusses the clinical assessment of ADHD. An ADHD diagnostic rating tool is used to collect and document information from the child utilized in the diagnostic assessment. Versions of validated diagnostic rating tools for parents and teachers are routinely utilized for diagnostic formulation as well. The video is useful to enhance student understanding regarding the COLLECT and ASSESS steps in the patient care process for managing ADHD.

INTRODUCTION

Once considered primarily a childhood disorder, attention deficit/hyperactivity disorder (ADHD) is now known to persist into adolescence for 75% and into adulthood for approximately 50% of individuals.[1,2] The American Academy of Pediatrics (AAP) considers ADHD a chronic condition that requires ongoing management.[3–5] Functionally impairing inattention, impulsivity, and

hyperactivity in the ADHD brain have been correlated with neuroanatomical and functional brain changes.[6,7] It is unusual for an individual to display signs of the disorder in all settings or even in the same setting at all times; however, there is a persistent pattern of symptoms that continues for 6 months or more.[1,7] Co-occurring anxiety, mood disorders, learning disabilities, medical conditions, and substance use disorders must be considered in assessment and treatment. Behavioral interventions and medications are effective for all ages, but there are special considerations for treatment plan development and monitoring in each age group.[3–5,8]

1 The psychiatric assessment of a child requires obtaining information from the child, parents, caregivers, and teachers.[1,5,9] Treating children with psychotropic medications requires a very different approach than treating adults. Children undergo neurologic, physiologic, and psychosocial changes throughout development. Age-related pharmacodynamic and pharmacokinetic differences can alter drug disposition and response. Psychotropic drug treatment of children is intended to control symptoms or behaviors that impair learning and development.[1,5,9] Children may not be able to articulate symptom response or adverse effects of a medication. Adolescents and adults with ADHD may not have been diagnosed and treated during childhood, putting them at greater risk for the psychosocial consequences of ADHD, including unemployment, unstable relationships, substance abuse, and incarceration.[1,2,5,10,11]

EPIDEMIOLOGY

ADHD is the most well-known and researched neurodevelopmental disorder of childhood. It occurs in approximately 5% to 10% of children and approximately 2.5% to 5% of adults.[12–14] Non-Hispanic Caucasian and African-American children are more likely diagnosed with ADHD compared with children of Hispanic or Asian descent according to CDC and National Children's Health survey data.[12,15] ADHD is more prevalent in males than females with a ratio of 2:1 in children and 1.6:1 in adults.[1] In 2016, 6.1 million children in the United States or 9.4% of those aged 2 to 17 years were diagnosed with ADHD: almost twice the actual rate according to worldwide prevalence studies and the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5).[1,5,16] Methodological inconsistencies in diagnostic assessments likely contribute to increasing diagnosis and differences in prevalence rates internationally. Investigators evaluating 135 ADHD prevalence studies representing seven

regions (North America, South America, Europe, Asia, Africa, Oceania, and the Middle East) found when consistent diagnostic criteria from the DSM-5 are applied, the prevalence of ADHD for children and adolescents is similar among countries globally, at approximately 5.5%.[5,13,14,16] There is increasing concern among healthcare professionals and the public regarding the overdiagnosis of ADHD leading to stigmatization and potentially inappropriate treatment.[5]

Increasing rates of ADHD diagnosis in the United States is likely a factor associated with the observed increased prescribing of ADHD medications. In 2016, the U.S. Centers for Disease control (CDC.gov) reported 2 million of the 6.1 million children with ADHD were first diagnosed at 2 to 5 years of age.[12,16] Of concern is the mode of treatment for these toddlers, as CDC data showed three out of four 2- to 5-year olds with ADHD were prescribed medications and only one out of two were prescribed behavioral interventions. The American Academy of Pediatrics (AAP) recommends a 6-month trial of behavioral interventions and parent training prior to pharmacotherapy in children ages 2- to 4-years old.[12,16] In addition to young children, adolescents and young adults are increasingly being diagnosed with ADHD. A large U.S. pharmacy benefits management company, Express Script's, analysis of pharmacy claims representing 400,000 privately insured individuals younger than 65 years showed that ADHD medication use increased by 35.5% for all age groups between 2008 and 2012. In addition, while the number of adults using ADHD medications was up 53.4% from 2008 to 2012, children still received a higher percentage of ADHD prescriptions compared to adults as 80% of these were stimulants.[17] In 2015, 4% of privately insured women ages 15 to 44 filled a prescription for an ADHD medication, most often a stimulant such as amphetamine salts or methylphenidate. This represents a 344% increase in ADHD medication prescribing in 2015 compared to 2003. Of note, filled prescriptions for nonstimulant ADHD medications did not increase.[18]

Therefore, healthcare professionals and teachers should recommend thorough assessment of ADHD by an experienced clinician using standardized criteria and investigating all possible causes of inattention, impulsivity, and hyperactivity in order to avoid overdiagnosis and potentially inappropriate treatment.

ETIOLOGY AND PATHOPHYSIOLOGY

2 There has been substantial progress in understanding the role of both genetics and the environment, as well as their interaction, in the pathophysiology

of ADHD. An extensive review of twin studies over the past 40 years has shown that the heritability of ADHD (the amount of variance in ADHD symptoms attributable to genetics) averages around 74%.[19] The most extensive genome-wide association study (GWAS) to date was a meta-analysis of 12 studies comparing 20,183 persons with ADHD and 35,191 controls.[20] This study discovered twelve regions that achieved genome-wide significance with *none* of the genes identified in previous candidate gene studies (ie, dopamine transporter) being found to be significant.[19] It remains to be seen exactly how the newly identified genes might be involved in ADHD. Despite the size of the study, all 12 loci identified accounted for only 22% of the genetic variance as the remaining ~50% of the heritability is "missing."[19]

Some of the missing heritability may occur because patients have copies or deletions in the genome that cover multiple genes called copy number variants (CNV). Current CNV studies have implicated a number of systems in ADHD: cholinergic receptors, and genes for central nervous system (CNS) development[21] and on an area of chromosome 15q13.[22] The CNVs affecting the metabotropic glutamatergic receptor 5 gene were found to be enriched in cohorts of patients with ADHD relative to controls.[23] Fasoracetam (NFC) is a metabotropic glutamate receptor activator that recently was administered to 30 adolescents with ADHD in an open trial.[24] All patients had been genotyped for variations in metabotropic glutamatergic genes and after 5 weeks of treatment, there was a statistically significant improvement from baseline to endpoint in ADHD symptoms, with the greatest improvement seen in those with CNVs in the glutamatergic genes. Despite these initial positive results, further double-blind studies are needed.

Increasingly, there is clear evidence that genes involved in ADHD are also involved in other major psychiatric disorders, including schizophrenia, and affective disorders.[25] A significant genetic correlation has been found between ADHD and autism spectrum disorder (ASD) in a large GWAS of individuals with ASD.[26] Thus, genes for neurodevelopmental disorders are not specific to ADHD and may show considerable pleiotropy (one gene influences two or more seemingly unrelated phenotypic traits).[27]

Since gene by environment interaction may also be important, it is critical to examine environmental factors. Twin studies can estimate the amount of variance related to the environment and further subdivide environmental effects into "shared" (an event both twins experience, such as neighborhood) and "non-shared" (one twin has a head injury, the other does not). Surprisingly, shared environmental factors do not appear to have a relationship to ADHD

symptoms.[28] In an Australian population-based control study, over 12,000 children with ADHD were compared to over 30,000 controls on maternal, pregnancy, and birth data.[29] Mothers of children with ADHD were significantly more likely to be younger, single, or to have smoked in pregnancy. Additionally they had a higher level of induced labor, preterm labor, preeclampsia, or early term delivery. Antidepressant use in pregnancy is not related to ADHD,[30] and in an extensive review of prenatal factors in ADHD, Sciberras et al.[31] noted that carefully done prospective studies are needed to determine causality of these factors.

2 Genetics and environment work together to shape the brain and there is an emerging picture of differences in brain structure, function, and connectivity that occur across the life span in individuals with ADHD. Cortical surface area is reduced in ADHD versus controls in both childhood and adulthood; in addition, the age of peak thickness occurs later in ADHD, with the most pronounced delay occurring in the prefrontal cortex.[32] Cortical thickness is also reduced in children with ADHD relative to controls, but when adults with ADHD remit, their cortical thickness is not different from controls.[33] There is evidence that continued use of stimulants for the treatment of ADHD is associated with greater normalization of cortical thickness.[34] Reduced cerebellar volume is the most pronounced difference in ADHD versus controls.[35] The ENIGMA ADHD study obtained structural MRI in 1,713 individuals with ADHD and 1,529 controls, both children and adults.[36] Subcortical structures (accumbens, amygdala, caudate, hippocampus, and putamen) were reduced in those with ADHD relative to controls, with effect sizes of around 0.2. Effects were larger in children than adults. In totality, the structural imaging data suggest ADHD is caused by a wide scale process affecting many regions of the brain.

2 Functional MRI has shown that the brains of children with ADHD fail to activate a network of regions involved in attention and impulse control relative to controls.[37] During inhibitory tasks, children with ADHD fail to activate the right inferior frontal cortex and anterior cingulate cortex. When performing attention tasks, children with ADHD have reduced activation in the basal ganglia, prefrontal cortex, and parietal lobe, while they have increased activation of cuneus. There is increasing interest in the role of the default mode network (DMN) in many psychiatric disorders.[38] The DMN consists of the medial prefrontal cortex, medial parietal lobe, or precuneus, as well as the posterior cingulate. These areas are active during the “resting state” when attention is not engaged; this system is actively suppressed during active attention. A lack of

connectivity between the prefrontal cortex and precuneus is associated with failure of suppression of the DMN, causing lapses in attention and inhibitory control. Multiple studies in ADHD have shown that relative to controls, both children and adults do not have the same degree of anti-correlation of the DMN and attention/control areas.[38–40] Liddle et al.[39] showed that treatment with stimulants can normalize this situation. Functional MRI can be used to assess general connectivity between a very large number of brain regions. A major review showed that children with ADHD have stronger short-range connections (particularly with limbic areas) than controls, but reduced number of long-range connections in the attention and control systems of the brain.[41]

Overall, ADHD is a complex neurodevelopmental disorder involving an array of genetic and environmental risk factors, many of which are shared with other psychiatric disorders. Clinicians can help families to better understand ADHD and minimize its negative impact on outcomes. More background information regarding pharmacogenomics in general can be found in Chapter e6, "Pharmacogenetics."

CLINICAL PRESENTATION

3 The American Academy of Pediatrics (AAP) guideline for the diagnosis, evaluation, and treatment of ADHD in children and adolescents recommends an evaluation for any child between ages 4 and 18 years who presents with academic or behavioral problems and symptoms of inattention, hyperactivity, or impulsivity.[3] At least six symptoms of inattention or hyperactivity and impulsivity causing impairment in more than one major setting (eg, home, school) for 6 months and an onset of symptoms before age 12 are currently required by the DSM-5 for a diagnosis of ADHD in children 4 to 12 years only. Only five symptoms are required for older adolescents and adults (age 17 and over).[1] Validated rating scales, such as the Connors Rating Scales—revised (CRS-revised), and the Vanderbilt ADHD diagnostic scale, are recommended for objective symptom ratings from parents and teachers in different age groups.[3–5] To make a diagnosis of ADHD, the clinician should rule out alternative causes of symptoms (eg, learning disability, situational stressor) and assess for other conditions that may coexist with ADHD including oppositional defiant and conduct disorders, Tourette disorder, ASD, sleep and mood disorders.[1,3,4,5,42]

CLINICAL PRESENTATION

ADHD

General

- Onset of symptoms must be before 12 years of age.

Symptoms

- *Inattention:*
  - Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (eg, overlooks or misses details, or work is inaccurate)
  - Often has difficulty sustaining attention in play activities or tasks (eg, has difficulty remaining focused during lectures, conversations, or lengthy reading)
  - Often has difficulty organizing tasks and activities (eg, poor time management, disorganized work, fails to meet deadlines)
  - Avoids tasks that require sustained mental effort (eg, schoolwork, reviewing lengthy papers, or preparing reports)
  - Often does not seem to listen when spoken to directly (eg, mind seems to wander)
  - Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace
  - Is easily distracted by extraneous stimuli (may include unrelated thoughts)
  - Is often forgetful in daily activities (eg, doing chores, returning calls, paying bills)
  - Loses things necessary for activities (eg, school materials, keys, wallet)
- *Hyperactivity and impulsivity:*
  - Often fidgets with hands or feet or squirms in seat
  - Often leaves seat when remaining seated is expected
  - Often runs about or climbs excessively at inappropriate times (in adolescents or adults may be limited to feeling restless)
  - Often has difficulty playing quietly
  - Often blurts out answers before a question is completed (also finishes the sentences of others; cannot wait for turn in conversation)

- Often interrupts or intrudes on others; may take over what others are doing

- Six or more symptoms must be present for at least 6 months; significant impairment must be seen in two or more settings (eg, home and school); symptoms must be documented by parent, teacher, and clinician. Only five symptoms are required in older adolescents and adults (17 years of age and older).

Data from American Psychiatric Association. Disorders usually first evident in infancy, childhood or adolescence. In: Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013:59-66.*

Preschoolers (3–5 Years)

Preschool-age onset of ADHD may be more likely in children with multiple risk factors including maternal smoking, lead exposure, iron deficiency, developmental delay, ASD, intellectual disability, or genetic loading.[43,44] The DSM-5 diagnostic criteria for ADHD can be applied to preschool-age children, although it may be difficult to document symptoms in multiple settings with different caregivers if the child does not attend preschool.[1,3,12,44] Enrollment in a qualified preschool and a parent training program is often recommended. Both can help parents develop reasonable expectations for their child's development and foster the development of management skills for problem behaviors while diagnostic assessment is underway.

School Age (6–11 Years)

Most cases of ADHD are first realized during ages 6 to 9 years, with the child having difficulty academically and/or socially in school and at home. Most children have combined inattentive and hyperactive or impulsive symptoms that cause functional impairment. This period is crucial to the child's success in school, socialization, and the development of his or her sense of self; therefore, accurate diagnosis and treatment is critical. Comorbid oppositional defiant disorder (ODD), conduct disorder (CD), and aggression are indicators that the child is at greater risk for delinquency and substance abuse in adolescence.[8,10,45] This is the most well-studied age group, with strong data showing benefits of

recognition and treatment with behavioral interventions and medications.[4,5]

Adolescents (12–18 Years)

Hyperactivity decreases in adolescents, and inattention and impulsivity are the more prominent functionally impairing symptoms. There may be fewer numbers of symptoms of ADHD in adolescence, but the symptoms present cause significant functional impairment.[1,8,10] Adolescents with ADHD are increasingly identified as “moody” or having a temper. They are easily overwhelmed by demands and may avoid tasks or approach multiple tasks in a disorganized manner.[8] Decision making is impaired (eg, discontinues ADHD treatment despite functional impairment) and decisions are made based on peer approval.[8] Higher rates of delinquency, drug and alcohol use, and psychiatric comorbidity have been documented in adolescents with ADHD compared with those without ADHD.[3,4,10,11,46] Assessment for substance abuse and risk of diversion must be considered before starting stimulant medication.[8,46] Speeding and increased motor vehicle accidents occur at higher rates in teens with ADHD compared to those without the disorder.[8,47]

Adults

The presence of multiple comorbid conditions, particularly conduct disorder or mood disorder, can increase the likelihood of ADHD chronicity into adulthood. DSM-5 criteria for ADHD in childhood and adolescence also apply to adults. Inattentive symptoms are the most common and functionally impairing in adults, but hyperactive/restless and impulsive symptoms such as being overly talkative, impatient, and intrusive are experienced by many and are associated with higher rates of bipolar disorder and psychosis.[1,2,10,11,48] Cognitive deficits (eg, executive functioning, working memory, task prioritization, lower IQ) have been documented in adults with ADHD in addition to a greater risk for unstable relationships, unemployment, psychiatric hospitalization, and incarceration compared with those without ADHD.[2,10,11,48] In 2017, the World Health Organization published a 6-item questionnaire to update the Adult ADHD Self-Report Scale (ASRS) with DSM-5 diagnostic criteria. This validated screening tool can be used as a first step to a more thorough diagnosis with an experienced clinician.[2,49] Gathering collateral information from family and friends is recommended to either support or refute the diagnosis.

Adult-Onset ADHD

Adult-onset ADHD is increasingly recognized although still controversial. A Brazilian study evaluated 5,249 youth in 1993 at age 11 and found 393 (8.9%) met criteria for ADHD. Evaluation of the group in 2015 at age 18 to 19 years revealed 492 (12.2%) youth with no symptoms in childhood met criteria for ADHD.[50] Interestingly, the childhood-onset group was predominantly male and the young adult-onset group was predominantly female. Both groups had increased levels of impairment (eg, comorbidities, incarceration, suicide attempts) compared to those without ADHD. United Kingdom investigators studied 2,040 twins longitudinally between 1994 and 2015. In adulthood, 166 met criteria for ADHD; 111 of these (67%) had no symptoms during childhood.[51] Adult-onset ADHD raises many questions about potential causes (eg, marijuana use, alcohol use, chronic anxiety), diagnostic categorization, and treatment. Is young adult-onset ADHD a different brain disorder with similar symptoms to childhood-onset ADHD; is the course different? More research is needed.

TREATMENT

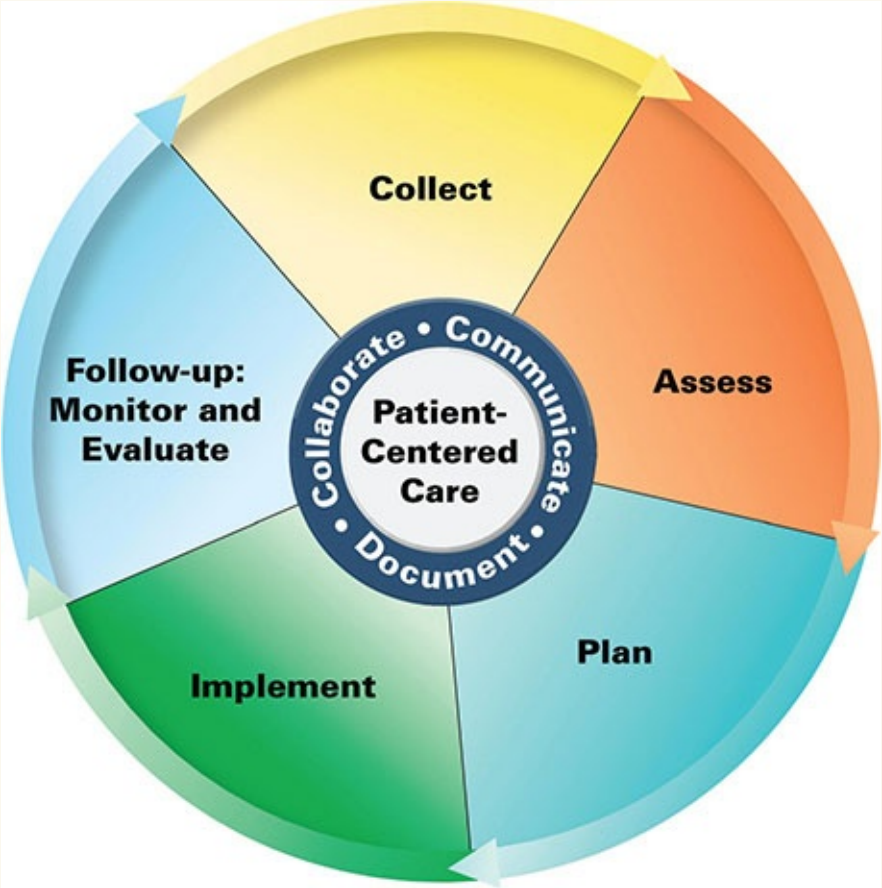
Stimulants are considered first-line therapy in most cases of ADHD; however, age, comorbid conditions, and patient/family preference impact treatment plan development. Pharmacotherapy should be considered whenever a thorough diagnostic assessment results in an ADHD diagnosis. ADHD-specific educational, cognitive, and behavioral interventions are recognized as necessary components of an overall treatment plan aimed at symptom relief and optimal functioning. Several studies show combining medications with behavioral interventions produces the greatest symptom relief and the best outcomes.[2,4,17,52]

Desired Outcomes

4 Specific goals of treatment or desired outcomes must be identified (eg, able to sit in chair for 20 minutes, completes homework assignments, or no longer blurts out comments in class without being called upon).[3,42] For adults, the desired outcome may be to read an entire newspaper before starting another project, improving safety while driving, or successfully completing tasks on time at school or at work.[2,8,48]

Treatment for ADHD may decrease the rate of some serious injuries in youth. Investigators evaluated a large German healthcare database (reflecting 20% of the population) and found that in children with ADHD ages 3 to 17 years, treated with a stimulant or atomoxetine there was no difference in overall injury rates requiring hospital admission compared to untreated children; however, there was a 34% decrease in severe brain injury in the treated group.[53] Similarly, an international review and meta-analysis of about 13,000 youth found that pharmacologic treatment in pediatric patients with ADHD likely has a protective effect, with a 10% reduction in the incidence of any unintentional injury. Of note, traumatic brain injury was excluded as an endpoint, given the potential to increase a patient's likelihood for being diagnosed with ADHD.[54]

Improvement in academic performance and on-task behavior in the classroom has been associated with stimulant treatment of ADHD.[55] A study of 930 young adults with ADHD found treatment with pharmacotherapy (eg, stimulants and atomoxetine) was associated with significantly improved scores on higher education entrance exams compared to never-medicated peers.[56] Review of the Icelandic Medicines Registry and the Database of National Scholastic Examinations revealed that delayed initiation of pharmacologic treatment may be associated with academic decline among youth age 9 to 12 years, particularly in math.[57] Additionally other studies have demonstrated improvement in math productivity, accuracy, and reading speed with methylphenidate treatment, though academic improvements were thought to be small compared to overall symptom improvement.[58]



Patient Care Process for Attention Deficit/Hyperactivity Disorder (ADHD)

Collect

- Patient characteristics (eg, age, gender, sex, pregnancy status)
- Social and family history (eg, foster care, single parent home, extended family involvement; marital status for adults)
- Substance use history (eg, cigarettes, marijuana, alcohol, methamphetamine, hallucinogens, cocaine, opioids)
- Dietary issues (eg, “picky” eater, gluten-sensitive, food allergies)
- Sleep patterns (eg, latency, duration, restless legs)
- Current medications including OTCs, herbal products, dietary supplements, and prior medications for ADHD
- Cardiovascular health history (eg, history of sudden death in family)

- Goals of treatment (eg, finish homework assignments, prevent injury, await turn in lines, positive peer interactions)
- Information on past and current co-occurring neuropsychiatric conditions (eg, Tourette disorder, conduct disorder, bipolar disorder, autism spectrum disorder, epilepsy)
- Objective data
  - Measure symptoms of ADHD with validated rating scales for children or adolescents (eg, Conners, Vanderbilt) and ADHD self-rating questionnaire for adults
  - Gather information on symptoms in multiple settings (eg, school, work, home)
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, body mass index (BMI), growth chart data on percentiles based on general pediatric population
  - Labs including liver function tests (LFTs), electrolytes, renal function, fasting lipid panel and HgA1c, thyroid tests if co-occurring anxiety or mood symptoms, ECG and/or echocardiogram if history reveals significant cardiovascular disease or sudden unexplained death in family member; pregnancy status in female

Assess

- Number and predominance of symptoms (eg, are inattentive symptoms the only significant symptom?)
- Severity of symptoms (eg, hyperactivity, impulsivity, and inattention) and associated functional impairment
- Presence and severity of co-occurring conditions (eg, Tourette disorder, conduct disorder, bipolar disorder, autism spectrum disorder)
- Presence of active substance use disorder in patient and family members
- Presence of side effects from current medications (Tables 80-3 and 80-4)
- Ability/willingness to participate in nonpharmacologic treatment including psychosocial, cognitive, and behavioral interventions
- Identify barriers to adherence to pharmacotherapeutic interventions and participation in ongoing treatment (eg, cost, frequency of medication administration throughout the day, transportation challenges to follow-up appointments)

Plan*

- Drug therapy regimen including specific medication(s), dose, route, frequency, and duration (Tables 80-2 through 80-4 and Fig. 80-1)
- Monitoring parameters including efficacy (eg, decreased symptoms on rating scales) and safety (eg, heart rate, blood pressure, abnormal involuntary movements); frequency and timing of follow-up (Tables 80-3 and 80-4)
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug-specific information, medication administration)
- Referrals to other providers when appropriate (eg, pediatrician, dietician)

Implement*

- Provide patient, parent, caregiver(s), teacher education regarding all elements of treatment plan; education should be delivered in multiple forms (Table 80-1)
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up appointment for monitoring and pharmacotherapy dosage adjustment (Tables 80-1 through 80-3)

Follow-up: Monitor and Evaluate

- Significant improvement in ADHD symptoms (eg, inattention, hyperactivity, impulsivity)
- Presence of adverse effects (eg, insomnia/sedation, appetite change, increased or decreased heart rate)
- Presence of significant drug interactions (eg, fluoxetine and atomoxetine, or paroxetine and amphetamine salts)
- Patient adherence to treatment plan using multiple sources of information
- Re-evaluate dosage and tolerability every 1 to 3 months

* *Collaborate with patient, caregiver(s), and other healthcare professionals.*

Nonpharmacologic Therapy

Educational, Psychosocial, Cognitive, and Behavioral Interventions

5 Education on ADHD as a biologic disorder with brain-derived causes is essential for destigmatizing ADHD and improving treatment acceptance. Parent training and behavioral interventions such as positive rewards for good behavior and structured limit setting are recommended as first-line interventions before medication trials in preschoolers (3- to 5-year-olds) with ADHD. Behavioral interventions for ADHD are described in **Table 80-1**. It is crucial to get parents, teachers, and clinicians involved to coordinate care and provide consistent behavioral management for the child at home and at school. Although methylphenidate has been found safe and effective for ADHD in 4- and 5-year-olds, behavioral interventions are recommended first by most clinicians and guidelines.[3,59] School-age children (6–11 years) also benefit from these behavioral interventions in addition to strategies, such as breaking up homework assignments into shorter, manageable segments. Although it varies by state, children and adolescents with ADHD may qualify for an individualized educational program (IEP) that allows for more time to take an exam, preferred seating, and modified work assignments.[3,4,45] It is noteworthy that most studies comparing behavioral intervention with stimulant therapy in youth found a much stronger effect on ADHD core symptoms from stimulants.[4,5,7,60] Combined behavioral and stimulant therapy resulted in greater improvements on academic and conduct measures in some studies with greater parent and teacher satisfaction ratings. Lower doses of stimulant were effective when behavioral interventions were administered according to several studies.[4,61]

TABLE 80-1 Cognitive, Behavioral, and Psychosocial Interventions for ADHD

Age	Description of Intervention	Typical Outcomes
Preschool and school age	Parent and family education on ADHD	Improved parental understanding and satisfaction
	Training on behavioral modification	Improved compliance with parental commands
	Classroom management instruction for teachers	Improved teacher satisfaction
Adolescent	Break up homework assignments into manageable segments. Structured schedule; organizer	Completion of assignments improves; improved self-esteem and sense of self
Adolescent and adult	ADHD-specific cognitive behavioral therapy	Improved productivity and vocational success
	Metacognitive therapy	Improved relationships

ADHD, attention deficit/hyperactivity disorder.

Data from References 3, 5, 42, 52, 59, 60, and 62.

5 Recommended behavioral interventions for adolescents and adults include keeping an external organizer (eg, smart phone, notebook with “to-do” lists) and breaking up activities into short, manageable tasks. Recognizing triggers for distraction and making a point of thinking before acting are useful interventions and are recommended during cognitive behavioral therapy (CBT) sessions designed to manage adult ADHD.[52,62] Controlled studies have shown that ADHD-specific CBT was more effective than psychoeducation and relaxation in adults with ADHD whose symptoms were only partially responsive to medication.[62] One study in 88 adults compared 12 weekly sessions (1.5-h long) of manualized CBT administered with a long-acting formulation of methylphenidate or amphetamine salts to CBT alone and found greater benefit in ADHD symptoms, organizational skills, and self-esteem in the combination CBT and medication group at the end of 12 weeks. Of note, the CBT alone group continued to improve according to unblinded clinician assessment and self-report after 6 months of treatment.[52] Yoga, meditation, and some dietary supplements have been recommended for ADHD as well, but they should not take the place of more established effective treatments, such as medications and cognitive interventions.[60,63]

Dietary Interventions

Extensive research has evaluated dietary interventions for ADHD, primarily in children with some adolescent data.

When iron and zinc are supplemented in youth with known deficiencies, the therapeutic benefit of stimulant therapy can be enhanced, frequently allowing lower effective doses.[64–66] The role of gingko biloba, vitamin D, Memoemet syrup, and other complementary and alternative products has also been evaluated, with variable efficacy and tolerability.[5] While some evidence is promising, ongoing evaluations are needed before recommending these products, given variability in study design (eg, use of concomitant pharmacotherapy, rating scales to assess symptom improvement, and variability among products used).

Although scientific evidence is lacking, there is a universal belief among families that the avoidance of sugar and artificial sweeteners improves ADHD symptoms. The attention paid to sugar avoidance and healthy diet is the more likely reason for improved behavior. An overall healthy diet with the proper balance of protein, fresh produce, and fiber is recommended.[12,17,60,64]

Pharmacologic Therapy

Figure 80-1 is an algorithm for drug selection in the treatment of ADHD.

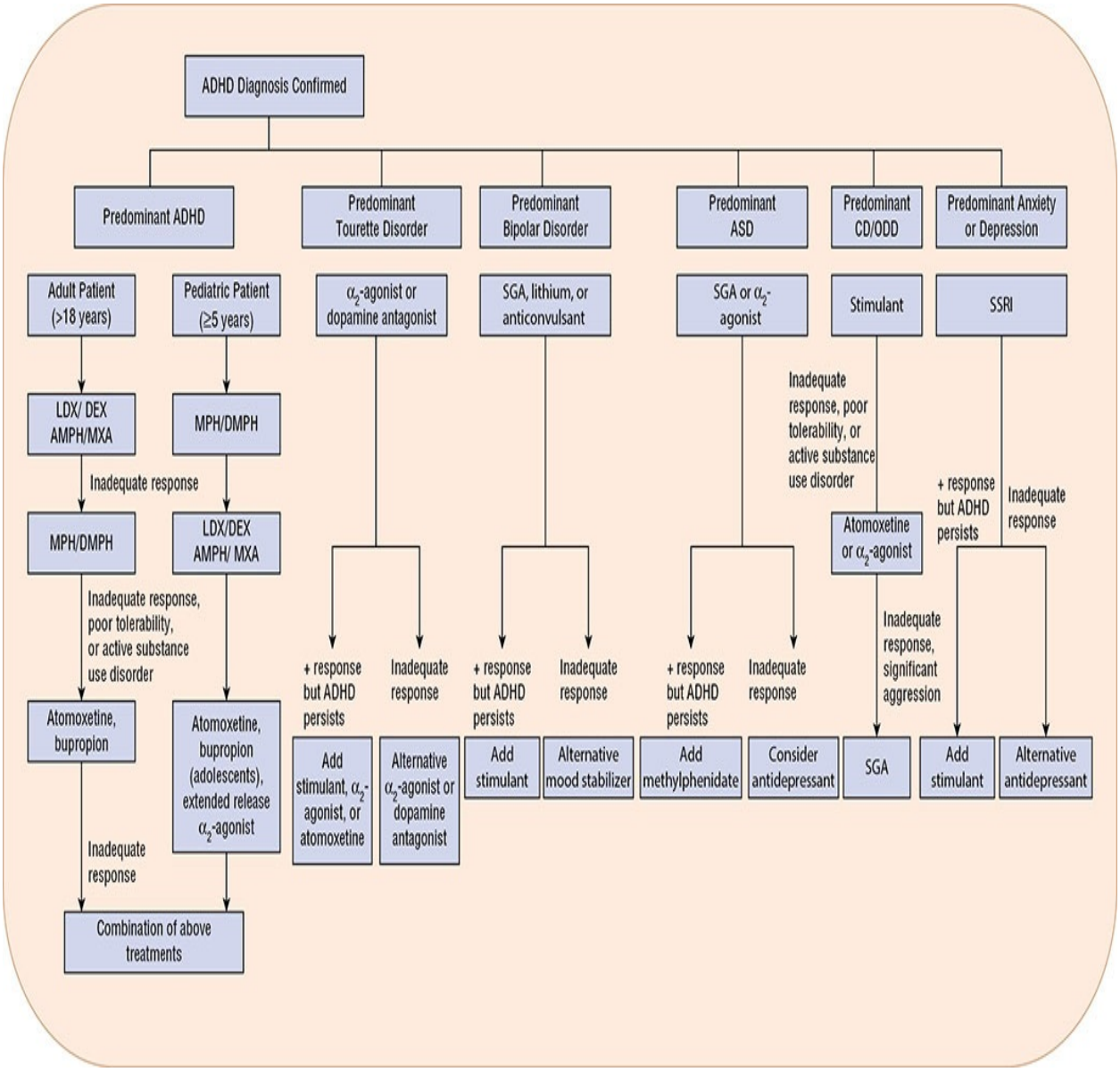


FIGURE 80-1 Algorithm for drug selection in the management of attention deficit/hyperactivity disorder (ADHD). Treat predominant disorder first, reassess, and consider alternative or adjunct medications for optimal symptom control. (AMPH, amphetamine; DEX, dextroamphetamine; DMPH, dexmethylphenidate; LDX, lisdexamfetamine; MPH, methylphenidate; MXA, mixed amphetamine salts; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.).
Data from References 2, 5, 45, 59, and 67–74.

Several studies demonstrate the superiority of stimulants over other pharmacotherapies and behavioral interventions in alleviating core symptoms of ADHD in schoolage children, adolescents, and adults.[5,17,59] Although the United

Kingdom's 2018 National Institute for Health and Care Excellence (NICE) guidelines recommend considering medication as early as 5 years of age, the clinician needs to weigh the risks of starting medication at an early age against the harm of delaying diagnosis and treatment.[3,4,42,44] Clinicians should educate all parents and caregivers regarding realistic expectations of drug therapy, goals of treatment, and the need for adverse effect monitoring in children. Adolescents and adults should be actively engaged in shared decision making regarding drug therapy and monitoring in an attempt to improve treatment persistence. Studies show higher rates of medication non-adherence in adolescents (50%)[8] and adults (30%) compared to children (10–30%). Preventing misuse and diversion of stimulants through frequent communication with patients and family, use of a controlled substance agreement, and by tracking state-wide prescription drug monitoring databases is recommended.[2]

Stimulants

Stimulants are broadly divided into two main chemical classes, methylphenidate (includes dexmethylphenidate) and amphetamines (includes dextroamphetamine and mixed amphetamine salts). Methylphenidate and amphetamines block presynaptic dopamine and norepinephrine reuptake; amphetamines also increase dopamine release.[7,75] Both drugs inhibit monoamine oxidase (MAO), amphetamines more potently than methylphenidate.[75] Because different stimulants work through slightly different mechanisms, the lack of response to one chemical class of stimulant (eg, methylphenidate or dexmethylphenidate) does not preclude response to another class (eg, mixed amphetamine salts, dextroamphetamine, or lisdexamfetamine).[7]

6 Stimulants are the most effective drug treatment options, with a pooled average effect size of 0.7 to 1.0. This is in contrast to nonstimulant drug treatment options such as guanfacine, clonidine, and atomoxetine whose effect sizes range from 0.35 to 0.5 signifying lower efficacy.[4,68,71] A systematic review and meta-analysis of 133 double-blind randomized controlled trials (81 in children and adolescents [*n* = 11,018], 51 in adults [*n* = 5,362], 1 in both) was conducted to assess the efficacy and tolerability of ADHD pharmacotherapy over 12 weeks in different age groups. Overall, the analysis showed stimulants were more effective than nonstimulant medications in all ages; however, stimulants were not as effective in adults compared to children and adolescents.[68]

Among children and adolescents, all approved ADHD medications were

found to be superior to placebo (clinician report), with amphetamines superior to methylphenidate, modafinil, atomoxetine, and guanfacine. Methylphenidate was superior to atomoxetine. Per teacher report, only methylphenidate and modafinil were superior to placebo. Guanfacine and amphetamines were less well tolerated than placebo, with amphetamines demonstrating a significant increase in systolic blood pressure and weight loss among children and adolescents, more than methylphenidate.

Because the largest analysis of clinical trial data showed overall better tolerability with methylphenidate in children and adolescents compared to amphetamine compounds, many clinicians recommend methylphenidate first-line in younger age groups. Nonetheless, amphetamine may be used first-line if patient and clinician prefer it.

In contrast to recommendations in pediatric patients, an amphetamine compound is preferred over methylphenidate as a first-line medication for adults based on the analysis of 12 week trials showing greater efficacy and acceptable tolerability of amphetamine compounds in adults versus pediatric patients.[68] In adults, amphetamines, methylphenidate, bupropion, and atomoxetine were superior to both placebo and modafinil. Modafinil did not demonstrate superiority in adults. With the exception of bupropion, all agents in adults were less well tolerated than placebo.[68]

Stimulant dosing should be titrated for maximum individual efficacy and minimum side effects[4,5,7,42] (**Table 80-2**).

TABLE 80-2 Dosing of Stimulant Drugs Used in the Treatment of ADHD

Stimulant	Duration of Effect	Initial Dose and Available Strengths	Usual Dosing Range; Maximum Dose
Methylphenidate C-II[a]			
Short-acting IR	3–5 hours	5 mg two or three times daily; increase by 5–10 or 20 mg/day at weekly intervals	5–20 mg two or three times a day; maximum dose: 60 mg/day
Ritalin, methylin, generics[b]			
Intermediate-acting	3–8 hours	SR, ER doses; corresponds to the IR dose	20–40 mg every AM or 40 mg every AM and 20 mg in the early afternoon; maximum dose: 60 mg/day
Ritalin SR[b]			
Methylphenidate SR[b]			
Metadate ER[b]			20–40 mg every AM and 20 mg in the early afternoon; maximum dose: 60 mg/day
Methylin ER[b]			
Long-acting		20 mg every AM; available as 10, 20, and 30 mg	20–60 mg/day, given every AM; maximum dose: 60 mg/day
Ritalin LA 50% IR, 50% ER beads[b]	8–10 hours		
Metadate CD 30% IR, 70% ER beads[b]	10–12 hours	20 mg every AM; available as 20, 30, and 40 mg	
Concerta (OROS controlled-release delivery)[b]	10–12 hours	18 mg every AM; available as 18, 27, 36, and 54 mg; 90% bioavailability of IR	27–72 mg/day, given every AM; maximum dose: 72 mg/day
ER inner compartments coated with IR methylphenidate			
Daytrana methylphenidate transdermal system[b]	12 hours when worn for 9 hours	10 mg (12.5 cm^2) applied to clean, dry area on hip each morning and removed after 9 hours	10–30 mg (12.5–37.5 cm^2). Drug active for 3 hours after patch removal
Aptensio XR 40% IR, 60% ER		10 mg; available as 10, 20, 30, 40, 50, and 60 mg capsules	Max: 60 mg daily
Extended-release methylphenidate[b]	10–12 hours		
Cotempla XR-ODT 25% IR, 75% ER[b]	10–12 hours	17.3 mg every AM; available as 8.6, 17.3, 25.9 mg oral disintegrating tablets	17.3–51.8 mg/day; Max: 51.8 mg daily
Quillivant extended-release suspension 20% IR/80% ER[b]	10–12 hours	10–20 mg in AM suspension	Max: 60 mg daily
Must be reconstituted by pharmacist to 25 mg/5 mL concentration		Only studied in 6- to 12-year-olds	Stable for 4 months after reconstituted
Jornay PM[b] delayed-release, extended-release formulation		20 mg in PM; available as 20, 40, 60, 80, and 100 mg capsules	20 mg every evening between 7 and 9 PM; Max: 100 mg daily
(administer at bedtime)			
Adhansia XR 20%IR, 80% ER	12-16 hours	25 mg every AM; available as 23, 35, 45, 55, 70, and 85 mg capsules	Increase by 10-15 mg to max dose;Max: 70 (child) 85 (adult) mg/day
Dexmethylphenidate (Focalin) C-II[b]	3–5 hours	2.5 mg every AM or twice daily; available as 2.5, 5, and 10 mg tablets	5–10 mg/day given twice a day; maximum initial dose: 7.5 mg/day; maximum dose: 20 mg/day
Focalin XR 50% IR, 50% ER beads[b]	10–12 hours	5 mg every AM; available as 5, 10, 15, 25, 30, 35, and 40 mg capsules	5–40 mg/day, given every AM maximum dose: 30 mg/day for children and adolescents; maximum 40 mg/day for adults
Mixed amphetamine salts C-II			
(dextroamphetamine and levoamphetamine 3:1 ratio)			
Short-acting IR (Adderall, mixed amphetamine generics)[c]	4–6 hours	2.5–5 mg every AM to twice daily; available in 5, 10, 7.5, 12.5, 15, 20, 30 mg tablet	5–40 mg; Max: 40 mg/day
Amphetamine C-II (dextroamphetamine and levoamphetamine ratio 1:1)[c]	6–10 hours	2.5–5 mg every AM to twice daily; Available in 5 and 10 mg tablets	5–20 mg; Max: 40 mg/day
Evekeo			
Long-acting XR (Adzenys XR-ODT) dextroamphetamine and levoamphetamine ratio 3:1[d]	10–12 hours	3.1, 6.3, 9.4, 12.5, 15.7, 18.8, extended-release oral disintegrating tablets	3.1–18.8 mg/day; Max: 18.8 mg/day
		3.1 mg Adzenys ODT ~ 5 mg of Adderall XR	
Mydayis (triple bead formulation of mixed amphetamine salts)[e]	12–16 hours	12.5, 25, 37.5, 50, extended-release capsules	12.5–50 mg/day; Max: 50 mg/day (adults), 25 mg/day (pediatrics)
Adzenys ER-oral suspension[d]	10–12 hours	1.25 mg/mL oral suspension	6.3–18.8 mg/day; Max: 18.8 mg/day
Dyanavel XR 2.5 mg/mL	10–12 hours	2.5 mg/1 mL oral suspension	5–20 mg/day; Max: 20 mg/day
Dextroamphetamine and levoamphetamine ratio 3.2:1[d]		2.5 mg of suspension ~ 4 mg of mixed amphetamine salts	
Mixed amphetamine salts C-II	10–12 hours	5–10 mg every AM; available as 5, 10, 20, 30 mg extended-release capsule	5–30 mg; Max: 30 mg/day

Extended-release capsule (Adderall XR) dextroamphetamine and levoamphetamine ratio 3:1[d]			
Dextroamphetamine C-II	4–6 hours	2.5 mg every AM once- or twice-daily dosing	10–40 mg/day (divided in two doses)
Short-acting	3–5 hours		10–40 mg/day given twice daily
Dextroamphetamine generics[c]			
Dexedrine, Zenzedi[c]		2.5 mg every AM to two or three times daily dosing	
Intermediate-acting	5–8 hours	Available as 5, 10, and 15 mg	5–30 mg every day or 5–15 mg twice daily; maximum: 40 mg/day
Dexedrine Spansule[d]		5 mg every AM; available as 5 and 10 mg	
Long-acting			
Lisdexamfetamine (Vyvanse)[d]	10–12 hours	Available as 20, 30, 40, 50, 60, and 70 mg capsules	Start at low end; titrate weekly to response; give in AM
(prodrug converted to dextroamphetamine)			Slower onset compared with other dextroamphetamine products

ER, extended release; IR, immediate release; OROS, osmotically released oral delivery system; ODT, orally disintegrating tablet; SR, sustained release; XR, extended release.

[a]The Drug Enforcement Administration label C-II, schedule II refers to significant abuse potential.

[b]Methylphenidate and dexmethylphenidate products are FDA approved in ≥6 years old.

[c]Immediate-release amphetamine and dextroamphetamine products are FDA approved in ≥3 years old.

[d]Extended-release amphetamine and dextroamphetamine products are FDA approved in ≥6 years old.

[e]Extended-release amphetamine product (immediate-release bead, small intestine dissolution bead, large intestine dissolution bead) FDA approved in ≥13 years old.

Data from References 71, 76–78 and stimulant product package inserts or Daily Med.

Stimulants are available in diverse formulations (immediate release, delayed release, extended release, liquids, orally disintegrating tablets and patches) to allow for individualization of drug selection based on a child's ability to swallow solid formulations and in an attempt to individualize the duration of symptom control. Once-daily stimulant formulations are the preferred treatment for ADHD in most individuals due to convenience and better medication adherence.[5,71,79] Immediate-release formulations have the advantage of lower cost, less insomnia, and potentially fewer growth effects versus extended-release products; however, they also carry a higher risk of diversion and abuse.[2,45,71]

Administration of stimulant medications with food can delay the absorption and subsequently delay the onset of therapeutic effect by 30 minutes to 1 hour for immediate-release preparations, and 1 to 2 hours for extended-release preparations.[7,71,78] Total bioavailability of stimulant can be decreased by 10% to 30% with coadministration of food, more so for beaded formulations of

extended-release stimulant compared with OROS methylphenidate or lisdexamfetamine.[17,71,78]

With immediate-release stimulants, most patients require a two or three times daily dosing schedule because of the short half-lives and duration of action of these drugs (2–4 hours for methylphenidate and dexmethylphenidate and ~4–6 hours for dextroamphetamine or mixed amphetamine salts).[4,7] Drug response is maximal during the absorption phase, is evident in 15 to 30 minutes, and lasts 2 to 6 hours.[4,7]

Drug delivery systems of once-daily products (amphetamine aspartate, amphetamine sulfate, dextroamphetamine sulfate, and dextroamphetamine saccharate [Adderall XR]; methylphenidate [Concerta]; methylphenidate [Daytrana]; dexmethylphenidate [Focalin XR]; methylphenidate [Metadate CD]; and methylphenidate long-acting [Ritalin LA]) provide 8 to 12 hours of symptom control.[71,77] Concerta uses an oral osmotic (OROS) controlled-release delivery system, whereas other oral preparations use combinations of immediate-release and extended-release beads.[7,71,77] Concerta is a nondeformable tablet, and it should not be given to children with gastrointestinal (GI) narrowing because of the risk of obstruction. Mydayis, a long-acting mixed amphetamine salt, provides up to 16 hours of symptom control in adolescents and adults via pH-dependent, triple bead technology.[76,80] Adhansia XR is an extended release methylphenidate capsule with a duration of action up to 16 hours.[77] A novel evening-dosed delayed-release/extended-release methylphenidate product (Jornay PM) has demonstrated improvement in early morning functional impairment among youth with ADHD. DELXIS® technology utilizes a dual-layer (outer delayed-release, inner extended-release layer) microbead delivery system that surrounds an inner methylphenidate loaded core.[78,81,82]

For patients with trouble swallowing pills, several alternative stimulant formulations are available. Methylphenidate transdermal system provides up to 12 hours of symptom control when worn for 9 hours.[71,77] Dyanavel XR, an extended-release amphetamine oral suspension, utilizes ion exchange chemistry (LiquiXR™ technology) to provide continuous release of amphetamine throughout the day.[83] Adzenys ER oral suspension (MXA) is a long-acting mixed amphetamine salt that has demonstrated efficacy in youth 6 to 17 years of age.[84] Cotempla XR-ODT (methylphenidate) and Adzenys XR-ODT MXA should also be considered for youth with trouble swallowing pills. Both products utilize micro-particle technology and have been shown to have effects for 10 to 12 hours.[84,85] Lisdexamfetamine is a prodrug conjugated to an amino acid that

requires cleavage during metabolism to the active dextroamphetamine. It has a longer time to onset of effect (~2 hours) but provides 10 to 12 hour symptom control. As a prodrug, it has lower risk for abuse compared to other long-acting amphetamines where beads may be crushed or snorted. NICE guidelines recommend it as a preferred long-acting amphetamine formulation due to the extent of evidence for efficacy and safety in children, adolescents, and adults, and a lower abuse risk.[71,77]

Adverse Effects The most common adverse effects of stimulants and their management strategies are listed in **Table 80-3**.[45,86] At least 15 cases of priapism (painful prolonged erection), associated with stimulant use, have been reported to the FDA in boys with a mean age of 12.5 years. A few cases of priapism have been reported with atomoxetine, and all cases require immediate medical attention.[45,87] The FDA has received at least 51 reports of skin discoloration associated with the methylphenidate transdermal system, also known as chemical leukoderma, that may not be reversible.[71]

TABLE 80-3 Stimulant Adverse Effects and Their Management

Adverse Effect	Recommendation/Management Strategy
Common	
Reduced appetite, weight loss	Give high-calorie meal when stimulant effects are low (at breakfast or at bedtime), or consider cyproheptadine at bedtime
Stomachache	Administer stimulant on a full stomach; lower dose if possible
Insomnia	Give dose earlier in the day; lower the last dose of the day or give it earlier; consider a sedating medication at bedtime (guanfacine, clonidine, melatonin, or cyproheptadine)
Headache	Divide dose, give with food, or give an analgesic (eg, acetaminophen or ibuprofen)
Rebound symptoms	Consider longer-acting stimulant trial, atomoxetine, or antidepressant
Irritability/jitteriness	Assess for comorbid condition (eg, bipolar disorder); reduce dosage; consider mood stabilizer or atypical antipsychotic
Uncommon to Rare	
Dysphoria	Reduce dosage; reassess diagnosis; consider alternative therapy
Skin discoloration (chemical leukoderma)	Counsel regarding risk before using methylphenidate patch
Zombie-like state	Reduce dosage or change stimulant medication
Tics or abnormal movements	Reduce dosage; consider alternative medication
Priapism (painful erection)	Obtain medical assistance immediately; consider alternative treatment
Hypertension, pulse fluctuations	Reduce dosage; change medication
Hallucinations	Discontinue stimulant; reassess diagnosis; mood stabilizer and/or antipsychotic may be needed
Peripheral vasculopathy, including Raynaud's phenomenon	Obtain medical assistance if severe digital changes observed; consider reducing dosage or alternative medication

Data from References 45, 59, 68, 71, and 87–89.

Psychiatric, cardiac, and growth effects of stimulants have been extensively studied with key data and recommendations in the sections below.

Psychiatric Although considered rare, the FDA has added warnings to the labeling of all ADHD medications (ie, stimulants, atomoxetine, α_2-adrenergic agonists) regarding three broad categories of psychiatric adverse effects: psychosis, mood disturbance (ie, irritability, lability, or depression), and severe anxiety or panic attacks. Treatment-emergent psychosis is estimated to occur in approximately 1.5% of youth with ADHD treated with stimulant medications based on placebo-controlled trials.[45] Hallucinations involving visual or tactile sensations of insects, snakes, or worms were typical in children, with adolescents and adults experiencing hallucinations and delusions.[90] Multimodal Treatment Study of Children with ADHD (MTA), analyzing available data on the emergence of psychosis in 509 youth diagnosed with ADHD at age 7 to 9 years,

showed that 5.1% reported psychosis which was not statistically different than 3.9% of the 276 local normal controls who reported psychosis over the same 10-year follow-up period. Therefore, investigators did not correlate stimulant use or an ADHD diagnosis in either group with the emergence of psychosis, but frequent cannabis use was associated with increased risk of psychosis in both groups.[91]

Sadness from stimulants may in part be genetically mediated, as an association was found between two single nucleotide polymorphisms (SNPS) in the gene encoding for carboxylesterase (CES1), which may impact stimulant metabolism, and the occurrence of sadness in 77 youth taking immediate-release methylphenidate for ADHD.[92] There is also evidence to suggest that preschool-aged youth are more susceptible to sadness, irritability, and mood lability with stimulant treatment compared with adolescents and adults.[45,86]

Literature reviews describe treatment emergent mania, and psychosis with atomoxetine, primarily in those with underlying bipolar disorder or depression. Labeling for atomoxetine includes a warning of increased suicidality largely because of its mechanism of action that is similar to antidepressants. A worldwide analysis of clinical trial and post-marketing data show no increase in suicidality (hazard ratio of 0.96).[93] Both stimulant and atomoxetine have the potential to cause or exacerbate mania, anxiety, panic attacks, or depression. In addition, stimulants and atomoxetine should not be given to manage attention in individuals with a primary psychotic illness such as schizophrenia or schizoaffective disorder due to the high risk of worsening psychosis.[45,93] Clonidine and guanfacine are much less likely than stimulants or atomoxetine to cause psychosis, mania, or anxiety, but treatment-emergent psychosis, irritability, depression, and nightmares have been reported.[94] When psychiatric adverse effects occur, dose reduction or cessation of therapy and supportive treatment is recommended.[45]

Cardiac Stimulants, atomoxetine, and α_2-adrenergic agonists have well-described cardiac and cardiovascular side effects that are not significant for most youth but can be intolerable in some, particularly in those with existing cardiac/cardiovascular disease.[45,95] Clinical trial data show that children who take stimulants for ADHD can have an increased heart rate by 3 to 10 beats/min and/or increased systolic or diastolic blood pressure by 2 to 14 mm Hg.[45,95] To explore the extent of cardiac side effects more thoroughly, investigators used ECG and echocardiography to evaluate cardiac function in 58 children (ages 6–18 years old) with ADHD diagnosed for at least 6 months taking OROS

methylphenidate (mean dose 39.40 mg or 0.93 mg/kg/day) compared to 58 matched control group children diagnosed with ADHD but not yet started on medication. Overall no significant differences were found in terms of blood pressure or ECG findings including QTc measurements; however, youth taking methylphenidate had lower E'septal values on echocardiography.[96] This difference was considered within normal limits and not indicative of cardiac dysfunction.

Clinical trial and post-marketing surveillance data shows atomoxetine treatment has been associated with increased heart rate at an average of approximately 5 beats/min and increased systolic or diastolic blood pressure of approximately 12 mm Hg. An Eli Lilly cardiovascular safety review showed 8% to 10% of patients taking atomoxetine had more significant increases in pulse at ≥20 bpm and increase in systolic and/or diastolic blood pressure of >15 to 20 mmHg.[93] Clonidine and guanfacine may cause dose-related bradycardia and lowered blood pressure in youth that may prevent upward titration in addition to modest widening of the QTc interval (5–7 msec) that warrants monitoring, particularly if the child takes another agent known to prolong QTc such as an antidepressant or antipsychotic.[45,94]

A 9.5-year prospective cohort study of children with ADHD found that, although rare, adverse cardiovascular events were twice as likely to occur in stimulant users as in nonusers.[97] There were 111 cardiovascular events in the 8,300 children with ADHD included in this analysis with hypertension, heart disease not otherwise specified, and cardiovascular disease not otherwise specified comprising 62% of adverse cardiac events, while arrhythmias comprised 23%, and cardiac arrest accounted for less than 1%.[45] The same investigators looked at national rates of stimulant use (n = 714,258) and found 1.8 times greater risk of cardiovascular events in those taking stimulants with greater risk seen with higher doses compared with lower doses.[97]

Overall, stimulant products should be used with caution in pediatrics and in adults with known structural cardiac abnormalities. The American Heart Association recommends careful screening of all children and adolescents prior to initiating pharmacologic therapy for ADHD, including a medical and family history and physical examination.[45] Before starting pharmacotherapy for ADHD in youth or adults, the clinician should consider a baseline electrocardiogram and consultation with a cardiologist if past medical history or family history suggests cardiovascular disease.[2,95,96]

Growth The impact of ADHD medications on growth has been investigated

extensively over the past 40 years as dose-dependent growth deficits of 1 to 1.4 cm/year have been observed with short-term stimulant treatment, mainly in the first 2 years. Weight deficits are more prominent with a mean 3 kg (6.6 lbs) weight decrease in the first year of treatment and 1.2 kg (2.6 lbs) weight decrease in the second year of treatment according to MTA data.[98] Long-term studies on stimulants have reported divergent effects on growth, with many studies showing no clinically significant height deficits by adulthood. MTA study investigators assessed the largest cohort of children with ADHD ranging in age from 7–9 years old to 25 years old (*n*=515), and compared them to classmates without ADHD (*n*=258). These authors reported an overall adult height deficit of 4.7 cm among those consistently taking stimulant medication compared to those not taking a stimulant. Growth deficits were less when stimulants were taken inconsistently. Those taking stimulants consistently were 2.36 cm ± 1.13 cm shorter than those in the "inconsistent" group. Proposed mechanisms of stimulant effects on growth include alterations in growth hormone or growth factor, decreased thyroxine secretion, and suppression of appetite leading to reduced caloric intake.[45,98]

If symptoms can be managed with medication during weekends or summers, a drug-free trial may be considered every year.[45] Time off stimulant appears to lessen stimulant growth suppressant effects, but evidence is lacking to firmly determine the impact of drug holidays on growth.[5,98] Consideration must be given to the risks of untreated ADHD symptoms on learning, socialization, and self-image while off stimulant therapy when determining the frequency and duration of the drug-free trial.[7,99] Drug dosage often varies from year to year, largely because of age-related pharmacokinetic changes. As a child develops, hepatic metabolism slows, and volume of distribution increases.[7]

Other Cases of stimulant-induced peripheral vasculopathy, including Raynaud's phenomenon, have been reported and are related to the peripheral release of catecholamines, resulting in vasoconstriction. Symptoms are typically intermittent and mild, but can include digital ulceration and/or soft tissue breakdown. A retrospective, case–control study demonstrated that among children treated with stimulants, there was a significant association between the development of Raynaud's phenomenon and past or current use of stimulants.[89,100] This risk appears to be dose dependent, with symptoms typically resolving after dose reduction or discontinuation of the medication.[89,101] Additionally, there is a case report of dose-dependent Raynaud's phenomenon with atomoxetine use.[102] Close monitoring for digital

changes is necessary during treatment with stimulants, α-2 agonists, and atomoxetine. Rheumatology consultation may be required for some individuals.

Nonstimulants

Compared to the simulants, nonstimulant medications used for the treatment of ADHD are less effective alternatives than simulants in both children and adolescents. However, for most of these agents, the FDA has approved them both as monotherapy and as adjuncts to stimulants in children and adolescents for improving overall response and for managing behavioral symptoms and insomnia associated with ADHD and some have received FDA for the treatment of ADHD in adults. Potential advantages of non-simulants relative to stimulants include no abuse potential, less potential for growth effects, and less sleep disturbance.[45] See **Table 80-4** for dosing.

TABLE 80-4 Dosing and Adverse Effect Monitoring of Nonstimulant Drugs for ADHD

Drug	Dosing Range and Titration Schedule	Adverse Effect Monitoring
Atomoxetine (Strattera)	≤70 kg (154 lb): start at 0.3–0.5 mg/kg every AM or twice daily, maximum: 1.4 mg/kg/day; ≥70 kg (154 lb): start at 40 mg every AM or divided twice daily, maximum: 100 mg/day	Nausea, anorexia, ↑ blood pressure, ↑ pulse, insomnia, fatigue, sedation, severe liver injury (rare), suicidality
Bupropion (Wellbutrin SR, XL)	50–300 mg/day; 3 mg/kg/day by end of week 1; can increase to 6 mg/kg/day or maximum of 300 mg/day as tolerated	Nausea, insomnia, rash, tics; dose-related risk of seizures
Antipsychotics (for comorbid aggression, mood disorders, tics, or irritability associated with ASD)		
Aripiprazole (Abilify)	2–5 mg daily; can titrate weekly as tolerated to response (usual range: 5–20 mg/day)	Nausea, restlessness, insomnia extrapyramidal symptoms, dizziness, sedation
Haloperidol[a] (Haldol)	0.5–1 mg twice daily; can titrate every 3–4 days as tolerated to response (usual range: 0.5–5 mg/day)	Extrapyramidal symptoms, dizziness, ↑ serum prolactin, sedation
Olanzapine[a] (Zyprexa)	2.5–5 mg every day; can titrate every 3–4 days as tolerated to response (usual range: 7.5–15 mg/day)	Sedation, severe weight gain, restlessness, extrapyramidal symptoms Diabetes, marked hyperlipidemia (never a first-line treatment)
Quetiapine[a] (Seroquel)	25–50 mg twice daily; can titrate every 3–4 days as tolerated to response (usual range: 200–600 mg/day)	Sedation, dizziness, weight gain, diabetes, hyperlipidemia
Risperidone[a] (Risperdal)	0.25–0.5 mg twice daily; can titrate every 3–4 days as tolerated to response (1–4 mg/day)	Extrapyramidal symptoms, dizziness, ↑ serum prolactin, decreased skeletal bone mass, hepatotoxicity, weight gain Diabetes, hyperlipidemia
Ziprasidone[a] (Geodon)	10–20 mg twice daily; can titrate every 3–4 days as tolerated to response (usual range: 40–160 mg/day)	Nausea, restlessness, insomnia extrapyramidal symptoms, sedation, QTc prolongation
Other		
Clonidine (Catapres) or clonidine extended-release XR (Kapvay)	0.05 mg two or four times daily; can increase as tolerated to 0.1–0.4 mg/day. For XR, give 0.1 mg at bedtime; may increase by 0.1 mg weekly; maximum: 0.4 mg/day given twice a day if dose >0.2 mg/day	Sedation, dizziness, heart block (check ECG), constipation, headache, upper abdominal pain
Guanfacine (Tenex) or guanfacine extended-release XR (Intuniv)	0.5 once or twice daily; can increase as tolerated to 1–4 mg/day. Max: 4 mg/day in children/adolescents For XR, give 1 mg in the AM; titrate weekly to response; Max: 4 mg/day in children; 7 mg/day in adolescents	Same as above with potentially lower risk of sedation. Effective dose higher in heavier children

ADHD, attention deficit/hyperactivity disorder; ASD, autism spectrum disorder; ECG, electrocardiogram; SR, sustained release; XL, extended length.

[a]Short-term use (1–4 months) only for severe aggression associated with ADHD; may be longer if comorbidity such as bipolar disorder, Tourette disorder, or autism spectrum disorder.

Data from References 42, 45, 94, and 104.

Atomoxetine Atomoxetine is a selective norepinephrine reuptake inhibitor that should be taken in divided doses in the morning or late afternoon by children for improved tolerability.[106] Adults can take it once daily, usually in the morning.[106]

Placebo-controlled, short-term trials (6–12 weeks) have shown that atomoxetine is effective in reducing ADHD symptoms in children, teens, and adults, and long-term studies show ongoing benefit and safety for children and adolescent responders out to 4 years.[93,106] A controlled trial comparing atomoxetine, OROS methylphenidate, and placebo over 6 weeks in 6- to 16-year-old patients showed that both drugs were significantly better than placebo at improving ADHD symptoms, but OROS methylphenidate was superior to atomoxetine.[106] There was evidence for a preferential response to atomoxetine over stimulants in some individuals.[106]

Atomoxetine has a significantly slower onset of therapeutic effect than stimulants (2–4 weeks vs 1–2 hours with an effective stimulant dose), and full benefit may not be seen for 6 to 12 weeks.[105,106] The practice of combining atomoxetine with a stimulant in partially responsive patients is based on limited data from open trials and case series describing fewer late-day rebound effects and better sleep when atomoxetine is given in the evening; however, the adverse effects are additive.[105,106]

Adverse Effects Possible adverse effects of atomoxetine and their management are similar to those of stimulants, including upset stomach and psychiatric and cardiac adverse effects (see Table 80-4 and "Psychiatric and Cardiac" sections). Although atomoxetine has less potential for growth suppression compared with stimulants, it has a greater risk of fatigue, sedation, and dizziness compared with stimulants or bupropion. Studies show that adults experience overall similar adverse effects as youth but they are less likely to report decreased appetite and are more likely to report urinary hesitation/retention and sexual side effects (decreased libido and erectile disturbances) compared to youth.[105] Unlike stimulants, atomoxetine labeling includes a bolded warning of potential severe liver injury based on 2 cases (1 adult, 1 child) of hepatic injury leading to transplant. A comprehensive safety review over 10 years described 133 cases of liver injury "possibly" related to atomoxetine, with liver functioning returning to normal after atomoxetine discontinuation. Although hepatotoxicity is considered rare, patients and families should be counseled to report signs of liver injury including dark urine, jaundice, or right upper quadrant pain.[93,105]

α_2-Adrenergic Agonists Guanfacine and clonidine are central α_2-adrenergic agonists, acting both presynaptically to inhibit norepinephrine release and postsynaptically to increase blood flow in the prefrontal cortex, which has been shown to enhance working memory and executive functioning. Pharmacologically, both of these medications affect a multitude of

neurotransmitter systems, including catecholamine, indolamine, and α_2-adrenergic receptors on parasympathetic neurons, opioids, imidazole, and amino acid systems.[75,94]

7 Guanfacine has a longer elimination half-life and duration of action (18 hours) compared with clonidine (12 hours), and its greater selectivity for the α_{2a}-adrenergic receptor, compared with clonidine, imparts less sedation and dizziness.[94] Clonidine and guanfacine are not as effective as stimulants for monotherapy treatment (effect size 0.22–0.58 vs 0.8–1.2 for stimulants).[94] In addition to being approved as monotherapy, extended-release clonidine and guanfacine are FDA approved as adjuncts to stimulants in children and adolescents. Therefore, both are prescribed frequently as adjuncts to reduce disruptive behavior, control aggression, or improve sleep in youth.[5,94] Neither have been studied sufficiently for ADHD in adults.

Guanfacine XR can be given once daily during monotherapy while clonidine XR should be given twice daily for optimal symptom coverage. Both are considered acceptable second-line agents for children and adolescents unresponsive to or unable to tolerate stomach upset or insomnia with stimulant medications. Extended-release guanfacine and clonidine are more sedating than stimulants or atomoxetine; therefore, sleepiness during the school day requires careful monitoring.[94] Immediate-release α_2-adrenergic agonists are increasingly used to treat symptoms of ADHD in incarcerated adolescents and adults due to no risk of abuse and potential benefits in controlling aggression and impulsivity, but this practice requires further study.[107]

Adverse Effects The most common side effects of clonidine and guanfacine are dose-dependent sedation, hypotension, and constipation.[4,5,94] The sedation seen with treatment usually subsides after 2 to 3 weeks of therapy.[94] Clinical trials show a mean decrease of 3 to 5 mm Hg in blood pressure with mean heart rate decrease of 3 to 5 beats/min. Both heart block and sudden death have been reported rarely with α_2-adrenergic agonists and further analysis revealed that these events occurred in the context of polypharmacy and/or congenital heart malformation. Regardless, prescreening for existing cardiac problems and increased monitoring when combining medications is warranted.[45,94] Peripheral vasculopathies are well documented with α_2-adrenergic agonists, given their effects on peripheral catecholamine release; however, close monitoring and consideration of a rheumatology referral is warranted should these adverse events occur.[89,101]

Bupropion Bupropion, a monocyclic antidepressant, is a weak dopamine and norepinephrine reuptake inhibitor with no significant direct effect on serotonin or MAO. Its active metabolites augment noradrenergic and dopaminergic function. While not FDA approved for the treatment of ADHD, investigations with bupropion in children and adolescents demonstrated efficacy greater than placebo in two controlled trials and efficacy comparable with methylphenidate in two separate controlled trials (n = 18 and n = 44).[108] Bupropion has been found beneficial for adolescents with depression and ADHD and causes less appetite suppression and weight loss compared with stimulants, but it has a greater risk of seizures.[108] An analysis of data evaluating bupropion for ADHD in adults show it is significantly more effective than placebo and modafinil but less effective than methylphenidate or amphetamine salts.[68]

Adverse Effects Bupropion's adverse effects include nausea, which can resolve over time or with slower dosage titration, and rash, which can require discontinuation of therapy if severe (see Table 80-4). Due to an elevated risk of seizures, bupropion should not be used in patients with a seizure or eating disorder. Additionally, it can cause or exacerbate tics and should be dosed early in the day to minimize the risk of insomnia.[108]

Lithium and Anticonvulsants Lithium and anticonvulsants can be used to control aggression and explosive behavior in patients with a co-diagnosis of oppositional defiant disorder (ODD) or conduct disorder (CD), or those who are not responsive or are only partially responsive to treatment with a stimulant. Given the symptoms heterogeneity and overlap between some mental illnesses, some patients actually have childhood-onset bipolar disorder or combined ADHD–bipolar disorder.[74] Limited data shows lithium is ineffective for ADHD alone but it is more likely effective when bipolar disorder coexists with ADHD.[74] Valproate is the most well-studied anticonvulsant for aggression associated with ADHD. Dosing starts in low divided doses with titration over 1 to 2 weeks to therapeutic response.[109] See Chapter 73, "Epilepsy," for a more extensive discussion regarding adverse events for anticonvulsants and Chapter 86, "Bipolar Disorder," for lithium.

Antipsychotics First-generation antipsychotics such as chlorpromazine and haloperidol can improve symptoms of hyperactivity and impulsivity in children with ADHD, but their negative effects on learning, cognitive functioning, and the significant risk of extrapyramidal side effects (eg, dystonia and tardive dyskinesia) limit their usefulness.[104]

Second-generation antipsychotics such as risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole have been used to control severe aggression in refractory cases of ADHD, particularly if CD or bipolar disorder coexists.[9,109] In general the second-generation antipsychotics pose a lower risk of extrapyramidal side effects compared with conventional agents, but they can cause metabolic side effects such as hyperlipidemia, hyperglycemia, and weight gain in addition to hyperprolactinemia.[104] Ziprasidone has the lowest risk of metabolic side effects among these second-generation antipsychotics. Risperidone is the most well studied for aggression associated with ADHD,[67] but because it has the most potent dopamine antagonism, it poses the highest risk of hyperprolactinemia and associated early puberty, gynecomastia, galactorrhea, amenorrhea, and decreased bone density.[103,104] Aripiprazole is least likely to elevate prolactin due to its dopamine agonist effects.[104] See Chapter 84, "Schizophrenia," for a more thorough discussion regarding the antipsychotics and their adverse effects.

COMORBIDITY AND POLYTHERAPY IN ADHD

8 As previously stated, individuals with ADHD often present with comorbid conditions (Fig. 80-1) which may make polytherapy attractive or necessary. But this can complicate monitoring of therapy, because if multiple drugs are started simultaneously, it is impossible to determine the impact of each drug. In general, the predominance and urgency of symptoms guide the drug selection process. For example, if a child presents as severely anxious or depressed with associated attentional problems, then an antidepressant should be initiated first with monitoring to determine if attentional symptoms improve.[4,73] When a child presents with severe ADHD and associated anxiety or depression, a stimulant should be initiated to treat the more severe ADHD. If ADHD symptoms improve significantly, but anxiety or depression persists, then an antidepressant can be added.[4,73] Studies show that stimulants do not routinely make anxiety disorders worse, but they might not improve symptoms either.[7,73]

Bipolar Disorder

9 Childhood bipolar disorder may be difficult to distinguish from ADHD because inattention, hyperactivity, and impulsivity are common with both conditions. When ADHD is diagnosed in an individual with bipolar disorder, the mood must be stabilized first with lithium, an anticonvulsant, or an atypical

antipsychotic before considering an ADHD-specific treatment.[74,109]

Autism Spectrum Disorders

Autism spectrum disorders (ASD) are estimated to occur in 20% to 50% of youth with ADHD and 30% to 80% of youth with ASD exhibit symptoms of inattention.[110] Impairments can range from mild to severe with poor language development, poor social skills, sensory over-responsivity, emotional dysregulation, inattention, impulsivity, irritability, oppositional behavior, and aggression.[110] There are few studies to guide treatment of ADHD in individuals with ASD. A Cochrane review of 4 U.S. randomized controlled trials involving 113 youth with ASD and ADHD treated with methylphenidate for 4 to 6 weeks demonstrated short-term benefit for hyperactivity and possibly inattention in children who could tolerate methylphenidate. Of note, youth who could not tolerate a test-dose were excluded and there was no evidence that methylphenidate was helpful for social interaction or stereotypical behaviors.[111]

Available evidence shows that stimulants are less effective and less well-tolerated for managing ADHD in youth with more severe forms of ASD.[110,111] If a stimulant trial is initiated, the child with ASD should be monitored carefully for worsening stereotypies, obsessional symptoms, sleep difficulties, poor appetite, irritability, or the emergence of seizures. Atomoxetine was only slightly better than placebo in managing ADHD symptoms in children with ASD according to a 8-week controlled trial that included 97 children between the ages of 6 and 17 years.[69] Clonidine and guanfacine have small, uncontrolled studies only showing benefit in improving attention and decreasing aggressive/impulsive behavior in children with ASD.[110]

Epilepsy

Patients with ADHD are two to three times more likely to experience seizures than age-matched peers, and ADHD is the most common comorbidity in youth with epilepsy.[45,73] While some reviews have demonstrated seizure aggravation and EEG changes related to stimulant treatment,[112,113] most studies show methylphenidate is safe and effective for managing ADHD in youth with epilepsy. A retrospective review of 18,000 Medicaid-enrolled youth with epilepsy and ADHD treated with a stimulant did not demonstrate an increased risk for seizure-related hospitalizations among current or former stimulant users.[114] Given the risk for stimulants to lower the seizure threshold, all

individuals should be stabilized and seizure-free on an anticonvulsant prior to initiation of the stimulant.[73,114,115] If new or worsening seizures are suspected, discontinuation of the stimulant should be considered and cautiously reintroduced once stabilized.[59] The impact of atomoxetine, clonidine, and guanfacine on seizure frequency requires further study.[115] Bupropion use is contraindicated in patients with a seizure disorder.

Substance Use Disorders

Genetics, age (14- to 25-year-olds), psychosocial factors, and comorbidities all influence one's risk for drug and alcohol abuse,[46,116] with ADHD itself being a known risk factor for the development of a substance use disorder. A review of 27 longitudinal studies that followed children with and without ADHD into adolescence or adulthood found that compared with control subjects without ADHD, children with ADHD were (1) nearly three times more likely to report nicotine dependence in adolescence/adulthood, (2) almost two times more likely to meet diagnostic criteria for alcohol abuse or dependence, (3) approximately 1.5 times more likely to meet criteria for marijuana use disorder, (4) twice as likely to develop cocaine abuse or dependence, and (5) more than 2.5 times more likely to develop a substance use disorder overall.[10,116] Observational follow-up of the Multimodal Treatment Study of Children with ADHD (MTA) has provided additional information regarding long-term substance use risk in children with ADHD. As reported on the Substance Use Questionnaire (SUQ), youth with ADHD compared to their peers were more likely to use marijuana weekly (32.8% vs 21.3%) and cigarettes daily (35.9% vs 17.5%) as adults. Additionally, early substance use, specifically the use of alcohol, cigarettes, and marijuana, was more common in the ADHD group compared to peers.[10] This highlights the need for early substance use screening in adolescence, particularly among patients with ADHD.[10]

10 Parents frequently express concern that treating their child with a stimulant, particularly early treatment, may increase the risk of substance abuse. Follow-up studies show that stimulant therapy for ADHD neither increases nor decreases the risk of subsequent drug or alcohol abuse.[10,46] There is evidence that individuals initiating treatment early (before age 8) are less likely to use substances than those who have delayed onset of treatment. Behavioral therapy may also confer some protection against substance use and delinquency.[10,46,116] Atomoxetine, an α_2-adrenergic agonist, or bupropion are preferred agents for individuals with ADHD and active substance use disorders.

Furthermore, other comorbid conditions including depression, anxiety, low self-esteem, conduct disorder, and antisocial personality disorder all increase the risk for developing a substance use disorder in an individual with ADHD.[10,116] These comorbidities also increase the risk for delinquency and incarceration that can prevent treatment and lead to ongoing substance abuse. As youth with ADHD transition to adolescence, parents and clinicians should pay attention to whether the teen could be at risk for substance abuse or inappropriate use of their prescribed medication.[116–118]

Several studies have evaluated protective factors against substance abuse and delinquency for youth both with and without ADHD. These studies found that a quality parent–youth relationship, involving good communication, regular time together, consistent rules, and sharing of information (eg, how the child or adolescent spends free time and who his or her friends are) can be effective in deterring alcohol and substance abuse in youth with or without ADHD.[46,116] Youth support groups at high schools, such as the Gay/Straight Alliance (GSA), are credited with assisting schools with achieving lower rates of illicit drug use and the misuse of prescription ADHD medications compared with schools without GSAs.[117]

Oppositional Defiant and Conduct Disorders

Oppositional defiant disorder (ODD) or conduct disorder (CD) occur in 30% to 60% of youth diagnosed with ADHD and are commonly associated with severe aggression and functional impairment.[119] Causes of ODD, CD, and associated severe aggression in youth with ADHD are multifactorial and include psychosocial adversity factors (eg, maternal mental disorder, paternal criminality, violence in the home), learning disability, disruptive mood dysregulation disorder (DMDD), or bipolar disorder.[119–121] Experts consider psychosocial interventions that include parent training and support for the child's family an essential part of the treatment plan for youth with ADHD, co-occurring with ODD or CD.[42,59,121–125]

Effective treatment of ADHD and CD/ODD is critical in the reduction of a wide range of psychosocial consequences (eg, substance use, violence, unemployment). Evidence-based guidelines recommend stimulants as first-line treatment for oppositional behavior, conduct problems, and aggression in youth with ADHD and comorbid CD/ODD.[122,123,125] Optimization of stimulant monotherapy (particularly methylphenidates) has demonstrated rapid, long-lasting improvements in emotion dysregulation, aggression, and ADHD

symptoms.[126–128] A 2-year follow-up study of youth (*n* = 33,835) with ADHD found that patients with higher rates of adherence to stimulants or atomoxetine were less likely to eventually develop CD/ODD compared to those with poorer adherence, suggesting a possible protective effect of medication treatment.[129]

Studies in adolescents and adults with ADHD show that doses of stimulant above the recommended daily maximum are frequently needed for optimal symptom control prompting the American Academy of Child and Adolescent Psychiatry to publish an "off-label maximum dosage of 100 mg/day for methylphenidate and 60 mg/day for dextroamphetamine and mixed amphetamine salts." These dosage ranges appear in the academy's practice parameter on the treatment of ADHD.[42]

A head-to-head, randomized, 24-week open-label trial among youth treated with atomoxetine (*n* = 80) or OROS-methylphenidate (*n* = 80) demonstrated improvement in emotional/behavioral/externalizing problems in youth, with greater improvement in aggressive behavior and conduct problems in the OROS-methylphenidate group.[130] Treatment guidelines recommend that atomoxetine be considered in individuals who do not respond to or poorly tolerate stimulants.[122–124] Clonidine and guanfacine can be considered as monotherapy or add-on to stimulant treatment, but evidence to support their use is much lower quality.[122,123]

Unfortunately optimizing ADHD-specific medication such as stimulant or atomoxetine is not universally effective for aggression and over half of youth with ADHD and ODD/CD need more than one medication for optimal symptom control.[67] The treatment of severe childhood aggression (TOSCA) study included 168 youth with ADHD and either ODD or CD (mean age of 9 years) and showed that adding risperidone 1 to 3 mg daily to parent training, behavioral therapy, and optimized stimulant resulted in moderate improvement in aggression. A 52-week follow-up of study participants demonstrated an overall benefit for youth who remained on medication, with the risperidone augmented-group demonstrating a small added benefit (improved CGI-S scores). This warrants close evaluation considering the long-term use of risperidone was associated with significant increased risk for weight gain and increased serum prolactin.[131] Overall, guidelines recommend that risperidone should be considered as a short-term treatment for severe aggression and/or explosive anger if not effectively managed by traditional ADHD medications.[122,123]

Tourette Disorder

ADHD occurs in 50% to 60% of youth with chronic tics or Tourette disorder, and 20% of children with ADHD go on to develop chronic tics or Tourette disorder.[69,70,88] Until recently, experts cautioned that stimulants should not be first-line treatments for ADHD in youth with tic disorders due to the stimulant's ability to increase central dopaminergic and noradrenergic activity, potentially exacerbating tics. There is less need for concern according to investigators who conducted a meta-analysis of 22 placebo-controlled trials involving 2,385 children with ADHD and Tourette disorder. The analysis showed that stimulants were not more likely to worsen tics than placebo, and the association between stimulants and new-onset tics was more coincidental than a cause-and-effect relationship.[88] Additionally the timing of tic development in the context of ADHD may have led clinicians to inappropriately attribute new onset tics to stimulant treatment, as epidemiologic studies show that when ADHD and Tourette co-occur, symptoms of ADHD are present 2 to 3 years before tics emerge. Tourette disorder is known for fluctuating symptom severity with tics worsening and remitting in an unpredictable pattern, further diminishing the ability to accurately attribute tic causality.[72,88]

A double-blind, placebo-controlled trial compared monotherapy with methylphenidate or clonidine with the combination of methylphenidate and clonidine in patients with ADHD and Tourette disorder. Overall combination therapy demonstrated the greatest benefit in reducing symptoms of ADHD and tics,[72,88] and clonidine appeared most helpful for impulsivity and hyperactivity, whereas methylphenidate was most helpful for inattention. All treatments were well tolerated, but sedation was common (28%) in those receiving clonidine.[72]

Furthermore, guanfacine was administered to 34 children (mean age 10.4 years), with ADHD and tic disorder during an 8-week, placebo-controlled trial at a dose of 1.5 to 3 mg/day. Tic severity decreased by 31% in the guanfacine group compared with 0% in the placebo group.[72] There was a mean improvement of 37% on the teacher-rated ADHD scale compared with 8% improvement with placebo. Therefore as previously stated, clonidine or guanfacine alone is a less effective alternative to stimulants in the treatment of children with ADHD and this holds true for those with comorbid Tourette disorder.

Atomoxetine appears to be an effective treatment for ADHD and tics in pediatric patients with comorbid Tourette syndrome or chronic motor tic disorder. For this study, 148 children and adolescents were randomized to atomoxetine (0.5–1.5 mg/kg/day) or placebo for up to 18 weeks of treatment. Overall atomoxetine resulted in improvements in the severity of ADHD (effect

size = 0.6) and tics (effect size = 0.3).[105]

Individuals with Tourette disorder and ADHD are more prone to disruptive behaviors including poor frustration tolerance, aggression, and impulsivity, often requiring behavioral interventions and medications that may include second-generation antipsychotics.[72] Second-generation antipsychotics such as risperidone, aripiprazole, and ziprasidone have evidence from controlled trials to support their use in managing motor and vocal tics associated with Tourette disorder; however, aripiprazole is the only agent currently FDA-approved for managing Tourette disorder.[72] See Chapter 84 for more information about antipsychotics.

PERSONALIZED PHARMACOTHERAPY

There are many things to consider when making therapeutic decisions in patients with ADHD such as age, comorbidities, tolerability, potential for drug interactions, and patient preference. In addition, there may be pharmacokinetic and pharmacogenomic factors to consider when personalizing pharmacotherapy. In looking specifically at pharmacogenomics, the functional activity of cytochrome P450 (CYP) 2D6, norepinephrine and dopamine transporters (SLC6A2, SLC6A3), catechol-*o*-methyltransferase (COMT), dopamine receptor (DRD4), carboxylesterases (CES1), and α_2-adrenergic receptor (ADRA2A) has been evaluated as a predictive tool for ADHD medication response and tolerability.[132–136] While formal clinical pharmacogenomic guidelines do not exist for ADHD treatment at this time, medication-specific recommendations exist in some manufacturer labeling (eg, atomoxetine).[137] As the pharmacogenomics of ADHD treatments is a rapidly evolving field, an evidence-based resource available to decipher this work is provided by the Clinical Pharmacogenomics Implementation Consortium (CPIC, www.cpicpgx.org) or the Pharmacogenomics Research Network (PGRN, www.pharmgkb.org).[138] Specifically the CPIC website contains evidence-based expert guidelines for interpretation of specific gene drug pairs, which may be used when testing is completed. It is important to note that CPIC does not recommend testing, but rather aims to serve as a reference for when testing results are available. While routine use of pharmacogenomic testing is not recommended prior to initiation of ADHD medication, consideration should be made in particular clinical scenarios: (a) prior to the initiation of atomoxetine in pediatric patients with previous poor response/tolerability to other substrates of

CYP2D6 and/or who are particularly sensitive to changes in HR/BP; (b) poor tolerability to atomoxetine/stimulants at starting doses; (c) individuals presenting with several psychiatric comorbidities and a history of psychotropic medication poor response/tolerability; (d) family history of poor medication tolerability.

As methylphenidate is de-esterified prior to elimination it is less likely to have metabolic drug interactions compared with mixed amphetamine salts. Gender has been shown to influence the absorption of methylphenidate, with males having increased bioavailability compared with females.[7] Variability in dosage requirements for amphetamine salts, atomoxetine, and bupropion, can be due to inter-individual variability in plasma concentration achieved at a given dose. As all are metabolized via CYP2D6, the bioavailability and half-life of CYP2D6 substrates can be four to eight times greater in those taking a CYP2D6 inhibitor (eg, bupropion, fluoxetine, or paroxetine). Additionally, in CYP2D6 poor metabolizers atomoxetine has a much longer plasma half-life (20 hours compared to 5 hours), resulting in increased total plasma exposure compared to extensive (normal) metabolizers.[139–141] Some studies have shown that CYP2D6 poor metabolizers may experience more insomnia, weight loss, increased heart rate and blood pressure, constipation, and depression associated with atomoxetine treatment compared to extensive metabolizers.[136,137,139,141] Additionally, it has been suggested that poor metabolizers may demonstrate greater therapeutic benefit due to increased exposure to the medication.[136,139] While the manufacturer recommends dose adjustments based on CYP2D6 phenotype and concomitant treatment with potent CYP2D6 inhibitors, routine use of pharmacogenomic testing prior to atomoxetine treatment requires further evaluation.[141]

EVALUATION OF THERAPEUTIC OUTCOMES

Careful documentation of baseline symptoms and complaints over a 1-month predrug period is essential to the evaluation of therapeutic and adverse outcomes. Investigation regarding family history of psychiatric disorders and cardiac disease is essential to determine risk for related adverse drug reactions and to implement appropriate monitoring.[4,45,59] Baseline symptoms can be measured using videotapes, clinician rating scales (eg, ADHD Rating Scale IV, Vanderbilt ADHD Diagnostic Scale), or both. In addition, height, weight, and eating and sleeping patterns should be recorded at baseline and every 3 months.[5,42,45,59]

After the initiation and titration of any drug treatment, it is necessary that parents, teachers, and clinicians assess the overall functioning of the child or adult using standardized rating scales to determine if significant therapeutic benefit justifies continuing medication.[4,42] Therapeutic effects of the stimulants include decreased motor activity and impulsivity and increased attention span.[4,7,42] This suggests that stimulants are indicated for ADHD symptoms and not for primary learning disorders. The benefits of drug therapy must outweigh the potential for adverse effects to justify continued treatment.[4,42]

There is a lack of standardized assessment tools for adults; however, the adult ADHD screening tool can be useful.[49] Short-term studies (1 year or less) in adults with ADHD show that treatment with stimulants improves subjective quality of life. Long-term studies are needed to better assess the risk versus benefit of stimulant therapy on psychosocial and health outcomes.[142]

Atomoxetine, α_2-adrenergic agonists, and bupropion also require monitoring to detect changes in appetite, weight, and sleep patterns, as well as pulse and blood pressure. A therapeutic trial of atomoxetine or bupropion consists of 6 weeks at maximum tolerated doses unless response occurs at a lower dose.[4,42] Atomoxetine's full therapeutic benefit may continue to build over weeks to months, but if there is no significant benefit in the initial 6 weeks, it is unlikely that atomoxetine will be effective; therefore, it can be tapered off.[105]

When guanfacine or clonidine is given, careful clinical monitoring for fatigue, dizziness, and autonomic changes (eg, blood pressure and pulse) is recommended.[45,94] The American Heart Association has stated that ECG monitoring is not required for α_2-adrenergic agonists treatment in children, although many clinicians continue to assess for ECG changes, particularly if there is a family history of cardiac disease, if the patient is taking other agents that impact cardiac function, or if clinical symptoms warrant.[45] When discontinuing treatment, clonidine and guanfacine should be withdrawn slowly (0.05 mg clonidine/0.5 mg guanfacine reductions every 3–7 days) to prevent rebound hypertension or behavioral dyscontrol.[94,143] A therapeutic trial requires 1 to 2 months to assess therapeutic response, although increased sleep usually occurs immediately.[94,143]

Evaluation of therapeutic outcomes is particularly important when antipsychotics are used in youth as the U.S. Office of Inspector general's peer review psychiatrists found quality of care concerns in 67% of 475 medical records of youth receiving antipsychotics through Medicaid.[144] Among the biggest problems were lack of appropriate indications and lack of appropriate

monitoring to ensure safety. Baseline weight, lipids, and fasting glucose should be monitored every 6 months in addition to the need to monitor for extrapyramidal symptoms and hyperprolactinemia.[9,104,144]

CONCLUSION

ADHD is a heritable, well-studied brain disorder that can present at any age, with or without co-occurring conditions. ADHD is best treated with a combination of psychosocial, educational, cognitive-behavioral, and pharmacologic interventions. Treatments should be selected based on age, co-occurring conditions, and patient/family preference.

Postclass Engaged Learning Activity

Conduct a literature search and identify a primary research manuscript that has been published in the past 12 months regarding the treatment of ADHD. If the manuscript is regarding a new nonpharmacologic treatment, write a brief summary about the treatment, how feasible you believe it would be to implement, and describe the role of the patient and the provider in the treatment. If the manuscript is regarding a medication that is discussed in the book chapter, write a brief summary about the study methods, the major findings, and how this new information might change current practice. If the manuscript is regarding a new medication that is not described in the chapter, write a brief summary about the medication's mechanisms of action, how it is administered, and one potential advantage or disadvantage of this new medication compared to the current standard of care. This activity is intended to build your literature evaluation skills and ability to critically appraise research manuscripts.

ABBREVIATIONS

AAP	American Academy of Pediatrics
ADHD	attention deficit/hyperactivity disorder
ASD	autism spectrum disorder
CBT	cognitive behavioral therapy
CD	conduct disorder
CNS	central nervous system
CNV	copy number variants
CRS-revised	Connor's Rating Scales—revised
CYP	cytochrome P450
DMDD	disruptive mood dysregulation with dysphoria
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*)
ECG	electrocardiogram
FDA	Food and Drug Administration
GI	gastrointestinal
IEP	individualized educational program
MAO	monoamine oxidase
MTA	multimodal treatment study of children with ADHD
NICE	National Institute for Health and Care Excellence
NIH	National Institute of Health
NNT	number needed to treat
ODD	oppositional defiant disorder
ODT	orally disintegrating tablet
OROS	osmotically released oral delivery system
SSRI	selective serotonin reuptake inhibitor
SR	sustained release
TOSCA	Treatment of Severe Aggression Study
TCA	tricyclic antidepressant

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fifth Edition (DSM-5). Arlington, VA: American Psychiatric Publishing; 2013.
2. Fields SA, Williams MJ, Hassig MB. Adult ADHD: Addressing a unique set of challenges. *J Fam Pract*. 2017;66(2):68–74.
3. American Academy of Pediatrics, Subcommittee on Attention-

Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management. ADHD: Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*. 2011;128:1007–1022.

4. American Academy of Pediatrics (AAP) Algorithm Pediatrics. Supplemental information: implementing the key action statements: An algorithm and explanation for process of care for the evaluation, diagnosis, treatment, and monitoring ADHD in children and adolescents. *Pediatrics*. 2011;(suppl):S11–S21.
5. Kemper AR, Maslow GR, Hill S, et al. Attention Deficit Hyperactivity Disorder: Diagnosis and Treatment in Children and Adolescents. Comparative Effectiveness Review No. 203. (Prepared by the Duke University Evidence-based Practice Center under Contract No. 290-2015-00004-I.) AHRQ Publication No. 18-EHC005-EF. Rockville, MD: Agency for Healthcare Research and Quality; January 2018. Posted final reports are located on the Effective Health Care Program.
6. Friedman LA, Rapoport JL. Brain development in ADHD. *Curr Opin Neurobiol*. 2015;30:106–111.
7. Pliszka SR. Psychostimulants. In: Rosenberg DR, West GS, eds.*Pharmacotherapy of Child and Adolescent Psychiatric Disorders*. Sussex, UK: Wiley-Blackwell; 2012;65–104.
8. Chan E, Fogler JM, Hammerness PG. Treatment of ADHD in adolescents: A systematic review. *JAMA*. 2016;315(18):1997–2008.
9. Texas Department of Family and Protective Services Web site. 2016. Psychotropic Medications. A Guide to Medical Services at CPS. (Utilization parameters for children and youth in foster care.) Available at: https://www.dfps.state.tx.us/Child_Protection/Medical_Services/documents 03_Psychotropic_Medication_Utilization_Parameters_for_Foster_Children Accessed October 2018.
10. Molina BSG, Howard AL, Swanson JM, et al. Substance use through adolescence into early adulthood after childhood-diagnosed ADHD: Findings from the MTA longitudinal study. *J Child Psychol Psychiatry*. 2018;59(6):692–702.
11. Young S, Moss D, Sedgwick O, *et al*. A meta-analysis of the prevalence of attention deficit hyperactivity disorder in incarcerated populations. *Psychol Med*. 2014;45:247–258.
12. Danielson ML, Bitsko RH, Ghandour RM, Holbrook JR, Kogan MD,

Blumberg SJ. Prevalence of Parent-Reported ADHD Diagnosis and Associated Treatment Among U.S. Children and Adolescents, 2016. *J Clin Child Adolesc Psychol*. 2018;47(2):199–212.

13. Polanczyk G, Willcutt EG, Salum GA, et al. ADHD prevalence estimates across three decades: An updated systematic review and meta-regression analysis. *Int J Epidemiol*. 2014;43(2):434–442.
14. Visser SN, Danielson MLL, Bitsko RH, *et al*. Trends in the parent-report of health care provider-diagnosed and medicated ADHD: United States, 2003-2011. *J Am Acad Child Adolesc Psychiatry*. 2014;53(1):34–46.
15. Bloom B, Jones LI, Freeman G. Summary health statistics for U.S. children: National Health Interview Survey, 2012. National Center for Health Statistics. Vital Health Stat 10 (258). 2013.
16. Centers for Disease Control and Prevention. “Prevalence of ADHD in Young Children” May 2016 posting; Available at: www.cdc.gov/vitalsigns/adhd data. Accessed November 12, 2018.
17. Austerman J, Muzina DJ. US Medication Trends for ADHD: An Express Scripts Report. Available at: http://lab.express-scripts.com/publications/turning-attention-to-adhd-report. March 2014. Accessed August 28, 2015.
18. Anderson KN, Ailes EC, Danielson M, *et al*. Attention-Deficit/Hyperactivity Disorder medication prescription claims among privately insured women aged 15-44 years – United States, 2003-2015. *Morbidity and Mortality Weekly Report*. 2018;67(2):66–70.
19. Faraone SV, Larsson H. Genetics of attention deficit hyperactivity disorder. *Mol Psychiatry*. 2018. doi:10.1038/s41380-018-0070-0. [Epub ahead of print]
20. Demontis D, Walters RK, Martin J, et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nat Genet*. 2018. doi:10.1038/s41588-018-0269-7. [Epub ahead of print]
21. Stergiakouli E, Hamshere M, Holmans P, *et al*. Investigating the contribution of common genetic variants to the risk and pathogenesis of ADHD. *Am J Psychiatry*. 2012;169:186–94.
22. Scerif G, Baker K. Annual research review: Rare genotypes and childhood psychopathology—Uncovering diverse developmental mechanisms of ADHD risk. *J Child Psychol Psychiatry*. 2015;56:251–73.
23. Elia J, Glessner JT, Wang K, *et al*. Genome-wide copy number variation study associates metabotropic glutamate receptor gene networks with

attention deficit hyperactivity disorder. *Nat Genet*. 2012;44:78–84.

24. Elia J, Ungal G, Kao C, *et al*. Fasoracetam in adolescents with ADHD and glutamatergic gene network variants disrupting mGluR neurotransmitter signaling. *Nat Commun*. 2018;9:4.
25. Lee SH, Ripke S, et al. Cross-Disorder Group of the Psychiatric Genomics C. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet*. 2013;45:984–994.
26. Grove J, Ripke S, Als TD, et al. Common risk variants identified in autism spectrum disorder. bioRxiv2017.
27. Thapar A. Discoveries on the genetics of ADHD in the 21st century: New findings and their implications. *Am J Psychiatry*. 2018;175:943–950.
28. Barkley RA. Etiologies of ADHD. In: Barkley RA, ed. Barkley RA, ed. *Attention-Deficit Hyperactivity Disorder: A Handbook for Diagnosis & Treatment*. 4th ed. New York: The Guilford Press; 2014:356–90.
29. Silva D, Colvin L, Hagemann E, Bower C. Environmental risk factors by gender associated with attention-deficit/hyperactivity disorder. *Pediatrics*. 2014;133:e14–22.
30. Laugesen K, Olsen MS, Telen Andersen AB, et al. In utero exposure to antidepressant drugs and risk of attention deficit hyperactivity disorder: A nationwide Danish cohort study. *BMJ Open*. 2013;3:e003507.
31. Sciberras E, Mulraney M, Silva D, Coghill D. Prenatal risk factors and the etiology of ADHD-review of existing evidence. *Current Psychiatry Reports*. 2017;19:1.
32. Shaw P, Malek M, Watson B, Sharp W, Evans A, Greenstein D. Development of cortical surface area and gyrification in attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2012;72:191–7.
33. Shaw P, Malek M, Watson B, Greenstein D, de Rossi P, Sharp W. Trajectories of cerebral cortical development in childhood and adolescence and adult attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2013;74:599–606.
34. Shaw P, Sharp WS, Morrison M, *et al*. Psychostimulant treatment and the developing cortex in attention deficit hyperactivity disorder. *Am J Psychiatry*. 2009;166:58–63.
35. Valera EM, Faraone SV, Murray KE, Seidman LJ. Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder. *Biological Psychiatry.* 2007;61:1361–9.

36. Hoogman M, Bralten J, Hibar DP, et al. Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: A cross-sectional mega-analysis. *Lancet Psychiatry*. 2017;4:310–319.
37. Hart H, Radua J, Nakao T, *et al*. Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: exploring task-specific, stimulant medication, and age effects. *JAMA Psychiatry*. 2013;70:185–198.
38. Castellanos FX, Aoki Y. Intrinsic functional connectivity in attention-deficit/hyperactivity disorder: A science in development. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2016;1:253–261.
39. Liddle EB, Hollis C, Batty MJ, et al. Task-related default mode network modulation and inhibitory control in ADHD: Effects of motivation and methylphenidate. *Journal of Child Psychology & Psychiatry*. 2011;52:761–771.
40. Sripada C, Kessler D, Fang Y, *et al*. Disrupted network architecture of the resting brain in attention-deficit/hyperactivity disorder. *Hum Brain Mapp*. 2014.
41. Tomasi D, Volkow ND. Abnormal functional connectivity in children with attention-deficit/hyperactivity disorder. *Biological Psychiatry*. 2012;71:443–50.
42. Pliszka SR, Bernet W, Bukstein O, *et al*. American Academy of Child and Adolescent Psychiatry Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with ADHD. *J Am Acad Child Adolesc Psychiatry*. 2007;46:894–921.
43. Ghuman JK, Aman MG, Lecavalier L, *et al*. Randomized, placebo-controlled, crossover study methyphenidate for Attention-Deficit/Hyperactivity Disorder symptoms in preschoolers with developmental disorders. *J Child Adolesc Psychopharmacol*. 2009;19(4):329–339.
44. Kaplan A, Adesman A. Clinical diagnosis and management of ADHD in preschool children. *Curr Opin Pediatr*. 2011;23:684–692.
45. Schneider BN, Enenbach M. Managing the risks of ADHD treatments. *Curr Psychiatry Rep*. 2014;16(10):479. doi:10.1007/s11920-014-0479-3.
46. Molina BS, Pelham WEJr. Attention-deficit/hyperactivity disorder and risk of substance use disorder: developmental considerations, potential pathways, and opportunities for research. *Annu Rev Clin Psychol*.

2014;10:607–639.

47. Surman CBH, Fried R, Rhodewalt, Boland H. Do pharmaceuticals improve driving in individuals with ADHD? *CNS Drugs*. 2017;31:857–866.
48. Hechtman L, Swanson J, Sibley MH, *et al*. Functional adult outcomes 16 years after childhood diagnosis of ADHD: MTA results. *J Am Acad Child Adolesc Psych*. 2016;55(11):945–952.
49. Ustun B, Adler LA, Rudin C, *et al*. The World Health Organization Attention-deficit hyperactivity disorder self-report screening scale for DSM-5. *JAMA*. 2017;74(5):520–526.
50. Caye A, Rocha TB, Anselmi L, Murray J, et al. Attention-deficit/hyperactivity disorder trajectories from childhood to young adulthood: Evidence from a birth cohort supporting a late-onset syndrome. *JAMA Psychiatry*. 2016;73(7):705–12. doi:10.1001/jamapsychiatry.2016.0383.
51. Agnew-Blais JC, Polanczyk GV, Danese A, et al. Evaluation of the persistence, remission, and emergence of attention-deficit/hyperactivity disorder in young adulthood.. *JAMA Psychiatry*. 2016;73(7):713–20. doi:10.1001/jamapsychiatry.2016.0465.
52. Cherkasova MV, French LR, Syer CA, et al. Efficacy of cognitive behavioral therapy with and without medication for adults with ADHD: A randomized clinical trial. *J Attent Disorders*. 2016;1–15.
53. Mickolajycyk R, Horn J, Biomath D, et al. Injury prevention by medication among children with ADHD: A case only study. *JAMA Peds*. 2015;169(4):391–395.
54. Ruiz-Goikoetxea M, Cortese S, Aznarez-Sanado M, *et al*. Risk of unintentional injuries in children and adolescents with ADHD and the impact of ADHD medications: A systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2018;84:63–71.
55. Prasad V, Brogan E, Mulvaney C, *et al*. How effective are drug treatments for children with ADHD at improving on-task behaviour and academic achievement in the school classroom? A systematic review and meta-analysis. *Eur Child Adolesc Psychiatry*. 2013;22(4):203–16.
56. Lu Y, Sjölander A, Cederlöf M, *et al*. Association between medication use and performance on higher education entrance tests in individuals with Attention-Deficit/Hyperactivity Disorder. *JAMA Psychiatry*. 2017;74(8):815–822. doi:10.1001/jamapsychiatry.2017.1472.

57. Zoëga H, Rothman KJ, Huybrechts KF, *et al*. A population-based study of stimulant drug treatment of ADHD and academic progress in children. *Pediatrics*. 2012;130(1):e53–62.
58. Kortekaas-Rijlaarsdam AF, Luman M, Sonuga-Barke E, Oosterlaan J. Does methylphenidate improve academic performance? A systematic review and meta-analysis. *Eur Child Adolesc Psychiatry*. 2018. doi:10.1007/s00787-018-1106-3. [Epub ahead of print]
59. ADHD Diagnosis and Management: National Institute for Health and Care Excellence (NICE) Guidelines, published in March 2018. Available at: https://www.nice.org.uk/guidance/ng87. Accessed November 2018.
60. Goode AP, Coeytaux RR, Maslow GR, *et al*. Nonpharmacologic treatments for attention-deficit/hyperactivity disorder: A systematic review. *Pediatrics*. 2018;141(6).
61. Pelham WE, Burrows-MacLean, Gnagy EM, *et al*. A dose-ranging study of behavioral and pharmacological treatment in social settings for children with ADHD. *J Abnorm Child Psychol*. 2014;42:1009–1031.
62. Watson SM, Richels C, Michalek AP, Raymer A. Psychosocial treatments for ADHD: A systemic appraisal of the evidence. *J Atten Disord*. 2015;19(1):3–10.
63. Bader A, Adesman A. Complementary and alternative therapies for children and adolescents with ADHD. *Curr Opin Pediatr*. 2012;24(6):760–769.
64. Millichap JG, Yee MM. The diet factor in attention deficit hyperactivity disorder. *Pediatrics*. 2012;129:330–337.
65. Turner CA, Xie D, Zimmerman BM, Carlarge CA. Iron status in toddlerhood predicts sensitivity to psychostimulants in children. *J Atten Disord*. 2012;16(4):295–303.
66. Tseng PT, Cheng YS, Yen CF, et al. Peripheral iron levels in children with attention-deficit hyperactivity disorder: A systematic review and meta-analysis. *Sci Rep*. 2018;8(1):788. doi:10.1038/s41598-017-19096-x.
67. Aman MG, Bukstein OG, Gadow KD, *et al*. What does risperidone add to parent training and stimulant for severe aggression in child ADHD? *J Am Acad Child Adolesc Psychiatry*. 2014;53(1):47–60.
68. Cortese S, Adamo N, Del Giovane C, et al. Comparative efficacy and tolerability of medications for ADHD in children, adolescents, and adults: A systematic review and network meta-analysis. *Lancet Psych*. 2018;5:727–738.

69. Harfterkamp M, van de Loo-Neus G, Minderaa RB, *et al*. A randomized double-blind study of atomoxetine versus placebo for attention-deficit/hyperactivity disorder symptoms in children with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry*. 2012;51(7):733–741.
70. Hirschtritt ME, Lee PC, Pauls DL, *et al*. Tourette Syndrome Association International Consortium for Genetics. Lifetime prevalence, age of risk, and genetic relationships of comorbid psychiatric disorders in Tourette syndrome. *JAMA Psychiatry*. 2015;72(4):325–33.
71. Mattingly GW, Wilson J, Rostain AL. A clinician's guide to ADHD treatment options. *Postgrad Med*. 2017;129(7):657–666. doi:10.1080/00325481.2017.1354648.
72. Murphy TK, Lewin AB, Storch EA, *et al*. Practice parameter for the assessment and treatment of children and adolescents with tic disorders. *J Am Acad Child Adolesc Psychiatry*. 2013;52(12):1341–1359.
73. Naguy A. Psychopharmacotherapy of attention deficit-hyperactivity disorder in children with comorbid conditions. *Pediatr Neurol*. 2018;82:7–12. doi:10.1016/j.pediatrneurol.2017.09.010.
74. Pataki C, Carlson GA. The comorbidity of ADHD and bipolar disorder: Any less confusion? *Curr Psychiatry Rep*. 2013;15(7):372. doi:10.1007/s11920-013-0372-5.
75. Wilens TE. Mechanism of agents used for ADHD. *J Clin Psychiatry*. 2006;67(suppl 8):32–37.
76. Brams M, Childress AC, Greenbaum M, et al. SHP465 mixed amphetamine salts in the treatment of attention-deficit/hyperactivity disorder in children and adolescents: Results of a randomized, double-blind placebo-controlled study. *J Child Adolesc Psychopharmacol*. 2018;28(1):19–28. doi:10.1089/cap.2017.0053.
77. Steingard R, Taskiren S, Connor DF. New formulations of stimulants: An update for clinicians. *J Child and Adolesc Psychopharmacol*. 2019;29(5):324–339.
78. Pliszka SR, Wilens TE, Bostrom S, et al. Efficacy and safety of HLD200, delayed-release and extended-release methylphenidate, in children with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2017;27(6):474–482. doi:10.1089/cap.2017.0084.
79. Palli SR, Kamble PS, Chen H *et al*. Persistence of stimulants in children and adolescents with ADHD. *J Child and Adolesc Psychopharmacol*. 2012;22(2):139–148.

80. Mydayis package insert. Available at: http://pi.shirecontent.com/PI/PDFs/Mydayis_USA_ENG.pdf, Shire, Lexington MA, U.S. Inc. Accessed November 29, 2018.
81. Childress A, Mehrotra S, Gobburu J, et al. Single-dose pharmacokinetics of HLD200, a delayed-release and extended-release methylphenidate formulation, in healthy adults and in adolescents and children with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2018;28(1):10–18. doi:10.1089/cap.2017.0044.
82. Jornay PM package insert. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209311s000lbl Ironshore Pharmaceuticals, Toronto Canada. Accessed November 29, 2018.
83. Dyanavel XR package insert. Available at: http://dyanavelxr.com/pdfs/pi.pdf, Tris Pharma, Inc, Monomouth Junction, NJ, Accessed November 29. 2018.
84. Adzenys XR-ODT package insert. Available at: http://www.neostxcontent.com/Labeling/Adzenys/Adzenys_PI.pdf, Neos Therapeutics, Grand Prairie TX, U.S. LLC. Accessed November 29, 2018.
85. Cotempla XR-ODT package insert. Available at: http://www.neostxcontent.com/Labeling/Cotempla/Cotempla_PI.pdf, Neos Therapeutics, Grand Prairie TX, U.S. LLC. Accessed November 29, 2018.
86. Clavenna A, Bonati M. Safety of medicines used for ADHD in children. *Arch Dis Child*. 2014;99:866–872.
87. Eiland LS, Bell EA, Erramouspe J. Priapism associated with the use of stimulant medications and atomoxetine for ADHD in children. *Ann Pharmacother*. 2014;48(10):1350–1355. ;.
88. Cohen SC, Mulqueen JM, Ferracioli-Oda E, et al. Meta-analysis: Risk of tics associated with psychostimulant use in randomized placebo-controlled trials. *J Am Acad Child Adolesc Psychiatry*. 2015;54(9):728–736.
89. Khouri C, Blaise S, Carpentier P, et al. Drug-induced Raynaud's phenomenon: Beyond β-adrenoceptor blockers. *Br J Clin Pharmacol*. 2016;82(1):6–16. doi:10.1111/bcp.12912.
90. Kraemer M, Uekerman J, Wiltfang J, *et al*. Methylphenidate-induced psychosis in adult ADHD: Report of 3 new cases and review of the literature. *Clin Neuropharmacol*. 2010;33(4):204–206.
91. Vitiello B, Perez Algorta G, Arnold LE, et al. Psychotic symptoms in attention-deficit/hyperactivity disorder: An analysis of the MTA database.

J Am Acad Child Adolesc Psychiatry. 2017;56(4):336–343. doi:10.1016/j.jaac.2017.01.016.

92. Johnson KA, Barry E, Lambert D, et al. Methylphenidate side effect profile is influenced by genetic variation in the ADHD-Associated CES1 Gene. *J Child Adolesc Psychopharmacol*. 2013;23(10):655–664.
93. Reed VA, Buitelaar JK, Anand E, et al. The safety of atomoxetine for the treatment of children and adolescents with ADHD: A comprehensive review of over a decade of research. *CNS Drugs*. 2016;30:603–628.
94. Hirota T, Schwartz S, Correll CU. Alpha-2 agonists for attention-deficit/hyperactivity disorder in youth: A systematic review and meta-analysis of monotherapy and add-on trials to stimulant therapy. *J Am Acad Child Adolesc Psychiatry*. 2014;53(2):153–173.
95. Berger S. Attention deficit hyperactivity disorder medications in children with heart disease. *Curr Opin Pediatr*. 2016;28(5):607–12.
96. Kara T, Mihcioglu M, Yilmaz S, Akaltun I. Effects of Long-term use of prescription methylphenidate on myocardial performance in children with ADHD: A tissue Doppler imaging study. *J Child Adolesc Psychopharmacol*. 2018 (ahead of print). doi:10.1089/cap.2018.0052.
97. Dalsgaard S, Kvist AP, Leckman JF, *et al*. Cardiovascular safety of stimulants in children with ADHD: A nationwide prospective cohort study. *J Child Adolescent Psychopharmacology*. 2014;24(6):302–310.
98. Richardson E, Seibert T, Uli NK. Growth perturbations from stimulant medications and inhaled corticosteroids. *Transl Pediatr*. 2017;6(4):237–247. doi:10.21037/tp.2017.09.14.
99. Díez-Suárez A, Vallejo-Valdivielso M, Marín-Méndez JJ, et al. Weight, height, and body mass index in patients with attention-deficit/hyperactivity disorder treated with methylphenidate. *J Child Adolesc Psychopharmacol*. 2017;27(8):723–730. doi:10.1089/cap.2016.0150.
100. Goldman W, Seltzer R, Reuman P. Association between treatment with central nervous system stimulants and Raynaud's syndrome in children: A retrospective case-control study of rheumatology patients. *Arthritis Rheum*. 2008;58(2):563–566. doi:10.1002/art.23301.
101. Bayram Ö, Hergüner S. OROS-methylphenidate-induced Raynaud's phenomenon: A dose-related side effect. *J Child Adolesc Psychopharmacol*. 2015;25(6):521–522. doi:10.1089/cap.2015.0033.
102. Gökçen C, Kutuk MO, Coşkun Ş. Dose-dependent Raynaud's

phenomenon developing from use of atomoxetine in a girl. *J Child Adolesc Psychopharmacol*. 2013;23(6):428–430. doi:10.1089/cap.2012.0131.

103. Calarge CA, Burns TL, Schlechte JA, *et al*. Longitudinal examination of the skeletal effects of selective serotonin reuptake inhibitors and risperidone. *J Clin Psychiatry*. 2015;76(5):607–613.
104. Seida JC, Schouten JR, Boylan K, *et al*. Antipsychotics for children and young adults: A comparative effectiveness review. *Pediatrics*. 2012;129:e771–e784.
105. Savill NC, Buitelaar JK, Anand E, *et al*. The efficacy of atomoxetine for the treatment of children and adolescents with attention-deficit/hyperactivity disorder: A comprehensive review of over a decade of clinical research. *CNS Drugs*. 2015;29(2):131–151.
106. Newcorn JH, Kratochvil CJ, Allen RJ, et al. Atomoxetine and osmotically released methylphenidate for the treatment of ADHD: Acute comparison and differential response. *Am J Psych*. 2008;165:721–730. 2008;165:721-730.
107. Mattes JA. Treating ADHD in prison: Focus on alpha-2 agonists (Clonidine and Guanfacine). *J Am Acad Psychiatry Law*. 2016;44(2):151–157.
108. Ng QX. A systematic review of the use of Bupropion for attention-deficit/hyperactivity disorder in children and adolescents. *J Child Adolesc Psychopharmacol*. 2017;27(2):112–116. doi:10.1089/cap.2016.0124.
109. Carlson GA, Klein DN. How to understand divergent views on bipolar disorder in youth. *Annu Rev Clin Psychology*. 2014;10:529–551.
110. Dopheide JA. Autism spectrum disorder. In: Eiland LS, Todd TJ, eds.*Advanced Pediatric Therapeutics: Pediatric Pharmacy Advocacy Group*. Memphis, TN: Allen Press Copyright; 2015;1–8.
111. Sturman N, Deckx L, van Driel ML. Methylphenidate for children and adolescents with autism spectrum disorder. *Cochrane Database Syst Rev*. 2017;11:CD011144. doi:10.1002/14651858.CD011144.pub2.
112. Park J, Choi HW, Yum MS, *et al*. Relationship between aggravation of seizures and methylphenidate treatment in subjects with ADHD and epilepsy. *J Child Adolesc Psychopharmacol*. 2018;28(8):1–10.
113. Ravi M, Ickowicz A. Epilepsy, attention-deficit/hyperactivity disorder and methylphenidate: Critical examination of guiding evidence. *J Can Acad Child Adolesc Psychiatry*. 2016;25:50–58.

114. Liu X, Carney PR, Bussing R, et al. Stimulants do not increase the risk of seizure-related hospitalizations in children with epilepsy. *J Child Adolesc Psychopharmacol*. 2018;28(2):111–116.
115. Verrotti A, Moavero R, Panzarino G, et al. The challenge of pharmacotherapy in children and adolescents with epilepsy-ADHD comorbidity. *Clin Drug Investig*. 2018;38(1):1–8. doi:10.1007/s40261-017-0585-1.
116. Harstad E, Levy S. Committee on substance abuse: Attention-deficit/hyperactivity disorder and substance abuse. *Pediatrics*. 2014;134(1):e293–e301. doi:10.1542/peds.2014-0992.
117. Heck NC, Livingston NA, Flentje A, *et al*. Reducing risk for illicit drug use and prescription drug misuse: High school gay-straight alliances and lesbian, gay, bisexual, and transgender youth. *Addict Behav*. 2014;39(4):824–828.
118. Rabiner DL. Stimulant prescription cautions: Addressing misuse, diversion and malingering. *Curr Psychiatry Rep*. 2013;15(7):375.
119. Findling RL, McBurnett K, White C, Youcha S. Guanfacine extended release adjunctive to a psychostimulant in the treatment of comorbid oppositional symptoms in children and adolescents with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2014;24(5):245–52.
120. Bayard F, Nymberg Thunell C, Abé C, et al. Distinct brain structure and behavior related to ADHD and conduct disorder traits. *Mol Psychiatry*. 2018. doi:10.1038/s41380-018-0202-6. [Epub ahead of print].
121. Blader JC, Pliszka SR, Kafantaris V, *et al*. Prevalence and treatment outcomes of persistent negative mood among children with attention-deficit/hyperactivity disorder and aggressive behavior. *J Child Adolesc Psychopharmacol*. 2016;26(2):164–73. doi:10.1089/cap.2015.0112.
122. Gorman DA, Gardner DM, Murphy AL, *et al*. Canadian guidelines on pharmacotherapy for disruptive and aggressive behaviour in children and adolescents with attention-deficit hyperactivity disorder, oppositional defiant disorder, or conduct disorder. *Can J Psychiatry*. 2015;60(2):62–76.
123. Lillig M. Conduct disorder: Recognition and management. *Am Fam Physician*. 2018;98(10):584–592.
124. Pringsheim T, Hirsch L, Gardner D, Gorman DA. The pharmacological management of oppositional behaviour, conduct problems, and aggression in children and adolescents with attention-deficit hyperactivity disorder,

oppositional defiant disorder, and conduct disorder: A systematic review and meta-analysis. Part 1: psychostimulants, alpha-2 agonists, and atomoxetine. *Can J Psychiatry*. 2015;60(2):42–51.

125. Pappadopulos E, Macintyre Ii JC, Crismon ML, *et al*. Treatment recommendations for the use of antipsychotics for aggressive youth (TRAAY). Part II. *J Am Acad Child Adolesc Psychiatry*. 2003;42(2):145–61.
126. Dougherty DM, Olvera RL, Acheson A, *et al*. Acute effects of methylphenidate on impulsivity and attentional behavior among adolescents comorbid for ADHD and conduct disorder. *J Adolesc*. 2016;53:222–230. doi:10.1016/j.adolescence.2016.10.013.
127. Kutlu A, Akyol Ardic U, Ercan ES. Effect of methylphenidate on emotional dysregulation in children with attention-deficit/hyperactivity disorder + oppositional defiant disorder/conduct disorder. *J Clin Psychopharmacol*. 2017;37(2):220–225. doi:10.1097/JCP.0000000000000668.
128. Masi G, Manfredi A, Nieri G, et al. A naturalistic comparison of methylphenidate and risperidone monotherapy in drug-naive youth with attention-deficit/hyperactivity disorder comorbid with oppositional defiant disorder and aggression. *J Clin Psychopharmacol*. 2017;37(5):590–594. doi:10.1097/JCP.0000000000000747.
129. Wang LJ, Lee SY, Chou MC, et al. Impact of drug adherence on oppositional defiant disorder and conduct disorder among patients with attention-deficit/hyperactivity disorder. *J Clin Psychiatry*. 2018;79(5):. pii: 17m11784.doi:10.4088/JCP.17m11784.
130. Shih HH, Shang CY, Gau SS. Comparative efficacy of methylphenidate and atomoxetine on emotional and behavioral problems in youths with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2018. doi:10.1089/cap.2018.0076. [Epub ahead of print] PubMed PMID: 30457349.
131. Gadow KD, Brown NV, Arnold LE, et al. Severely aggressive children receiving stimulant medication versus stimulant and risperidone: 12-month follow-up of the TOSCA trial. *J Am Acad Child Adolesc Psychiatry*. 2016;55(6):469–78. doi:10.1016/j.jaac.2016.03.014.
132. Bonvicini C, Faraone SV, Scassellati C. Attention-deficit hyperactivity disorder in adults: A systematic review and meta-analysis of genetic, pharmacogenetic and biochemical studies. *Mol Psychiatry*.

2016;21(7):872–84. doi:10.1038/mp.2016.74.

133. Levy F. Applications of pharmacogenetics in children with attention-deficit/hyperactivity disorder. *Pharmgenomics Pers Med*. 2014;7:349–56.
134. Myer NM, Boland JR, Faraone SV. Pharmacogenetics predictors of methylphenidate efficacy in childhood ADHD. *Mol Psychiatry*. 2018;23(9):1–8.
135. Unal D, Unal MF, Alikasifoglu M, Cetinkaya A. Genetic variations in attention deficit hyperactivity disorder subtypes and treatment resistant cases. *Psychiatry Investig*. 2016;13(4):427–33.
136. Wehry AM, Ramsey L, Dulemba SE, *et al*. Pharmacogenomic testing in child and adolescent psychiatry: An evidence-based review. *Curr Probl Pediatr Adolesc Health Care*. 2018;48(2):40–49.
137. Atomoxetine package insert. Available at: https://pi.lilly.com/us/strattera-pi.pdf, Eli Lilly, Indianapolis IN, U.S. Inc. Accessed November 29, 2018.
138. Clinical Pharmacogenetics Implementation Consortium. CPIC guidelines. Available at: https://cpicpgx.org/. Accessed December 29, 2018.
139. Brown JT, Bishop JR. Atomoxetine pharmacogenetics: Associations with pharmacokinetics, treatment response and tolerability. *Pharmacogenomics*. 2015;16(13):1513–1520. doi:10.2217/PGS.15.93.
140. Fijal BA, Guo Y, Li SG, Ahl J, *et al*. CYP2D6 predicted metabolizer status and safety in adult patients with attention-deficit hyperactivity disorder participating in a large placebo-controlled atomoxetine maintenance of response clinical trial. *J Clin Pharmacol*. 2015;55(10):1167–74.
141. Yu G, Li GF, Markowitz JS. Atomoxetine: A review of its pharmacokinetics and pharmacogenomics relative to drug disposition. *J Child Adolesc Psychopharmacol*. 2016;26(4):314–26.
142. Surman CBH, Hammerness PG, Pion K, et al. Do stimulants improve functioning in adults with ADHD: A review of the literature. *European Neuropsychopharmacology*. 2013;23:528–533.
143. Faraone SV, McBurnett K, Sallee FR, *et al*. Guanfacine extended release: A novel treatment for ADHD in children and adolescents. *Clin Therapeutics*. 2013;35(11):1778–1793.
144. Department of Health and Human Services (HHS), Office of Inspector General. *Second-Generation Antipsychotic Drug Use among Medicaid-Enrolled Children: Quality of Care Concerns*. HHS Web site. Available at: https://oig.hhs.gov/oei/reports/oei-07-12-00320.pdf. Accessed November 15, 2018.

81

Eating Disorders

Steven C. Stoner, Valerie L. Ruehter, and Melissa C. Palmer

KEY CONCEPTS

1. Historically, the categorization of eating disorders as a psychiatric illness has faced significant scrutiny, while no longer the case the treatments of these disorders continue to be challenging with limited evidence-based medicine–supported treatments.
2. Despite strong genetic associations for the development of eating disorders as established in monozygotic and dizygotic twin studies, a clear association with a specific genetic linkage or mutation has not been identified.
3. Shifting between eating disorder diagnostic categories is possible, especially when symptom remission is not achieved with treatment.
4. Psychiatric comorbidities are common with all forms of eating disorders, and the differential diagnosis should generally include evaluation for depression, schizophrenia, generalized anxiety, obsessive–compulsive disorder (OCD), and personality disorders.
5. During the process of caloric restoration, calories must be gradually introduced to prevent the potentially fatal complication known as refeeding syndrome. Failure to restore calories quickly enough may result in an unfeeding syndrome.
6. Mortality resulting from suicide in individuals with eating disorders is not uncommon, and clinicians must monitor closely for suicidality and educate appropriately as they would during the treatment of patients with major depressive disorder taking antidepressants.
7. The current preferred treatment approach for anorexia nervosa (AN) includes a minimum of 6 months of psychotherapy, preferably cognitive behavioral therapy (CBT), in adults and family-based therapy in children.

8. Despite limited data, antidepressants are the preferred pharmacologic intervention for the acute and maintenance phases of bulimia nervosa (BN) in combination with nonpharmacologic treatments.
9. A growing body of evidence supports the use of selective serotonin reuptake inhibitors (SSRIs) for the treatment of binge-eating disorder (BED) along with CBT and interpersonal psychotherapy (IPT). Lisdexamfetamine is the sole FDA-approved agent for BED treatment.
10. There is growing sentiment that severe and enduring AN exists and that the focus should be on the impact of the disorder and improving quality of life instead of on treating medical symptoms.

Preclass Engaged Learning Activity

Review the guidelines from the American Psychiatric Association (APA), the National Institute for Health and Care Excellence, and the World Federation of Societies of Biological Psychiatry.[31,104,114] Develop a comparative table by filling in appropriate first- and second-line treatment strategies including both nonpharmacologic and pharmacologic strategies for each of the guidelines.

INTRODUCTION

Eating disorders are widely accepted as serious mental illnesses. The spectrum of eating disorders encompasses several complex diseases, with most sharing the pathologic feature of overevaluation of body shape and weight. Eating disorders arise from the complex interaction between environmental, societal, developmental, psychosocial, genetic, and biologic factors. It is estimated that 5 to 10 million women and 1 million men in the United States alone have an eating disorder. The urbanization of society, social pressure, and obsession with perfection and being thin have led to an increasing prevalence of eating disorders, with a median age of onset between 18 and 21 years, though estimates in adolescent studies suggest median ages of onset between 12 and 13 years.[1,2] Anorexia nervosa (AN), bulimia nervosa (BN), and binge-eating disorder (BED) are the most prevalent forms of eating disorders.[3]

1 Despite an improved understanding of these cognitively and emotionally disabling and potentially fatal disorders, treatment remains difficult. Patients

with eating disorders often demonstrate social difficulties prior to the onset of illness.[4] Pharmacologic intervention is a small part of a comprehensive treatment plan that emphasizes psychotherapy to address some of the social challenges, notably cognitive behavioral therapy (CBT) in adults and family therapy in younger patients.

EPIDEMIOLOGY

Anorexia Nervosa

Anorexia Nervosa (AN) impacts an estimated 0.9% to 2% of women in the United States, occurring predominantly in girls and young women (90%), and usually presenting during adolescent years (median onset 12.3 years of age).[1,2] The estimated 12-month prevalence of the disorder in the general population is 0.4% of females with a smaller percentage in males.[2,3] Longitudinal management of AN is difficult, as patients are often resistant to weight restoration plans, and psychiatric comorbidities exist in over 50% of those with AN.[2] Rates of relapse requiring hospitalization within 1 year exceed 30%, and crude mortality rates are estimated at 5%.[3,5,6]

The promotion of the virtues of being thin is also a potentially negative environmental factor. Many “pro-anorexia” social media outlets inappropriately promote healthy lifestyle aspects of anorexia and being thin as a means of being in control and successful, while also serving as a means of support.[7]

Bulimia Nervosa

Bulimia nervosa (BN) also occurs predominantly in girls and young women (90%) and usually presents in later adolescence or early adult life.[2] Between 1% and 4.6% of adolescent and young adult females meet the diagnostic criteria for BN, with lifetime prevalence estimates of 1.5% in females and 0.5% in men.[1–3,9]

Binge-Eating Disorder

Binge-eating disorder (BED) often presents in adolescence but can also emerge later in life.[3] Overall, BED is more common in females with a lifetime prevalence of 2% to 3.5% in adults and an approximate prevalence of 1% to 5% in adolescent-based studies utilizing the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*, see Chapter e79, “Evaluation of

Psychiatric Illness") criteria.[10,11] The 12-month prevalence rate is an estimated 1.6%.[12]

Other Specified and Unspecified Feeding and Eating Disorders

According to the *DSM-5*, additional diagnostic categories of specified and unspecified feeding and eating disorders exist that apply to cases where symptoms result in distress, but do not meet the full diagnostic criteria of specific feeding or eating disorders.[3] Examples listed within these categories include atypical AN, BN (lower frequency), BED (lower frequency), purging disorder, and night-eating syndrome (NES).[3]

Night-eating syndrome is common in obesity clinic populations and is often accompanied by depressive symptoms. The syndrome is defined by repetitive night eating that includes eating after having been asleep or excessive food consumption following evening meals.[3,13] Night eating affects an estimated 1.5% of the general population with a high prevalence of obesity and psychiatric comorbidities.[14] Patients with NES are reported to benefit from antidepressant therapy, most notably sertraline 50 to 200 mg daily or escitalopram 5 to 20 mg daily.[13,15] Cognitive behavioral therapy may also be of benefit in NES, particularly in promoting weight loss.

Additionally, the *DSM-5* includes Pica, Avoidant/Restrictive Food Intake Disorder, and Rumination Disorder as stand-alone diagnoses within Feeding and Eating Disorders.[3]

ETIOLOGY

The exact etiology of eating disorders remains unknown and is likely multifactorial including a combination of genetic, biologic, developmental, and environmental factors. While it is clear that brain reward mechanisms are altered, the exact biologic basis for eating disorders is difficult to delineate because it is unclear if the biologic changes are caused by or are a result of the aberrant eating behavior.

PATHOPHYSIOLOGY

Structural and functional brain imaging studies utilizing computerized

tomography (CT) and magnetic resonance imaging (MRI) have yielded a number of inconclusive findings. Anorexia nervosa has been linked with the development of enlarged cortical sulci, ventricles, interhemispheric fissure and reductions in grey matter (amygdala, hippocampus, cingulate cortex, and putamen). Dystrophic abnormalities in the cerebrum have also been noted with weight loss, though normalization occurs with weight gain.[16] Abnormalities of the hypothalamic–pituitary–gonadal, hypothalamic–pituitary–adrenal, and hypothalamic–pituitary–thyroid axes are described as potential causes of AN. Amenorrhea is found in the majority of females with anorexia, providing support for the association with gonadotropin.[3,9]

Serotonin, norepinephrine, and dopamine have been studied extensively with well-described roles in controlling eating behaviors. Special emphasis has been placed on the role of serotonin (5-HT), specifically noting reduced cerebrospinal fluid (CSF) basal concentrations of 5-hydroxyindoleacetic acid (5-HIAA), the principal metabolite of 5-HT, as well as increased binding of 5-HT1A receptors and reduced binding of 5-HT2A receptors in different regions within the central nervous system (CNS). Reduced dietary intake of tryptophan-containing foods leads to reduced levels of tryptophan, a requirement for the development of 5-HT.[17,18,19] There is evidence suggesting that 5-HT and dopamine function remain abnormal after weight restoration, with 5-HT activity being abnormally high in patients recovered from AN, while 5-HT2A receptors are reduced and dopamine receptors are increased following recovery.[17,18,19]

Complicating the study of these abnormalities is that their dysfunction is thought to be secondary to weight loss. Ghrelin, an amino-acid peptide produced by the stomach but centrally acting to promote food intake, is a current area of research focus.[20] Another molecular genetic target of study is brain-derived neurotrophic factor (BDNF), which is also an area of study for mood disorders.[19]

2 There are strong genetic influences in AN, and likely associations in both BN and BED as well. In addition, there is a high degree of premorbid anxiety and obsessive tendencies, which are also symptoms of disorders with suspected genetic associations. Twin studies have shown concordance of ~55% and 35% in monozygotic twins and 5% and 30% in dizygotic twins for AN and BN, respectively.

Genetic-based linkage studies have examined multiple single nucleotide peptides to identify predictors for developing AN, offering hope for the future role of personalized medicine in eating disorder treatment. Studies to date have identified possible associations with chromosomes 1, 2, 3, 4, and 13; however, there are no consistent findings to date, and studies are limited by low sample

size.[17,21,22] Genetic mutation studies have focused on polymorphisms of the 5-HT2A receptor.[23] One acquired hereditary abnormality being studied is the presence of low-function alleles associated with the 5-HT transporter (*5-HTTLPR, SLC6A4*) and 5-HT2A receptor gene (*–1438G/A*), with findings suggesting an association with poor treatment response.[24] Additional study has focused on the estrogen receptor I gene (ESRI) with the restrictive form of AN.[25]

Emphasis is also placed on environmental factors such as social stress and psychological and developmental issues related to dysfunctional family relationships that may trigger abnormal eating behaviors. Athletes are at risk for eating disorders, especially female gymnasts, ballet dancers, figure skaters, distance runners, swimmers, male wrestlers, and body builders.[26]

CLINICAL PRESENTATION

Anorexia nervosa and BN occur together in ~30% to 64% of patients with eating disorders, thus appearing as a continuum of symptoms making careful medical and psychiatric assessment at baseline essential.[27] Patients who initially present with either AN or BN may alternate from one to the other, especially in cases where remission is not achieved. **Figure 81-1** demonstrates similar and unique features of both disorders.

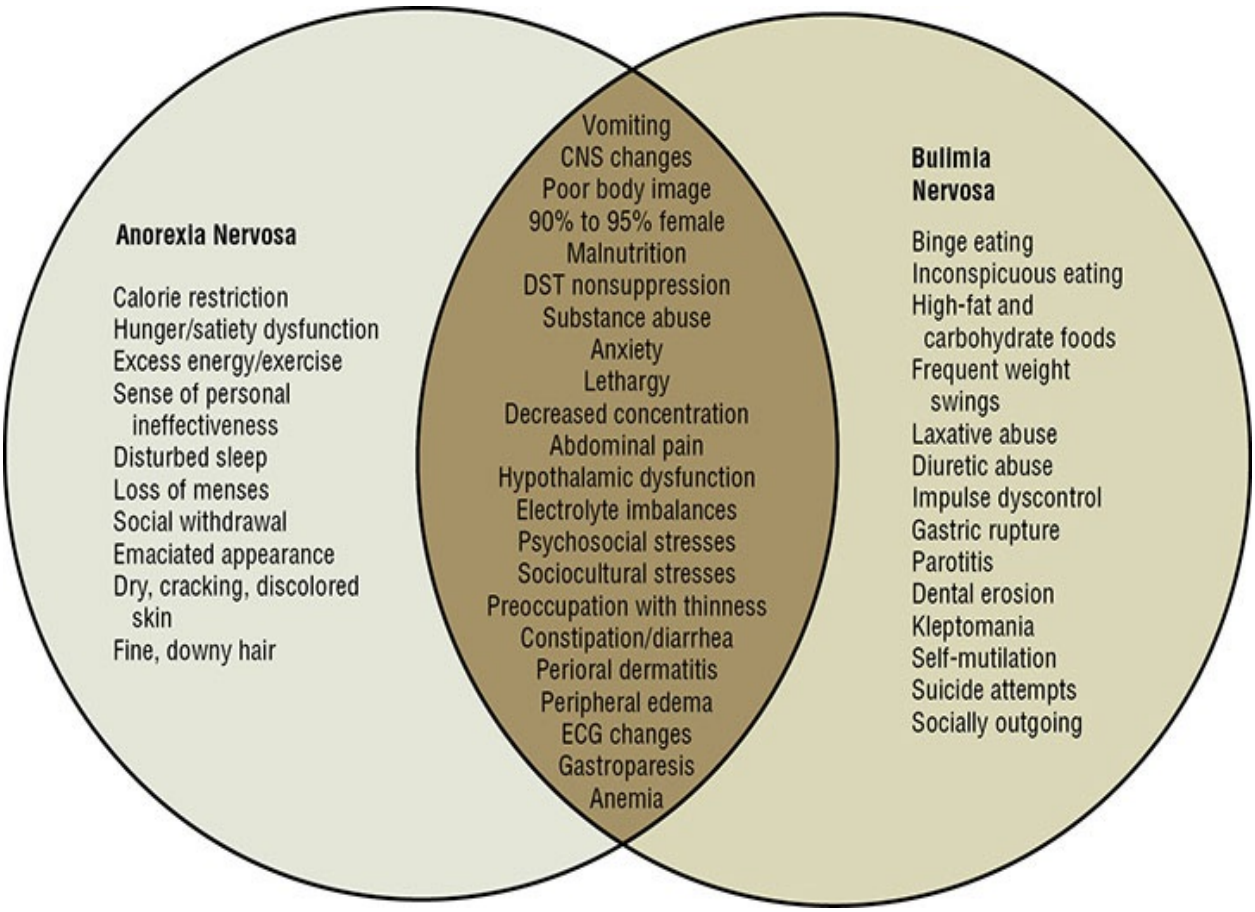


FIGURE 81-1 Signs and symptoms of anorexia nervosa and bulimia nervosa. (DST, dexamethasone suppression test; ECG, electrocardiogram.).

The use of purging methods is not limited to BN. Self-induced vomiting is the most common form of purging behavior.[28] Laxative abuse is another form of purging common in both AN and BN, used by an estimated 3% to 70% of patients.[28,29,30] Although ineffective as a weight-loss strategy, laxative abuse is often used in combination with other behaviors, including exercise, diuretics, enemas, and saunas. Within the diagnostic framework of AN, laxative abuse is most common in those identified with the purging subtype.[28] Psychiatric symptoms of depression, anxiety, and borderline personality disorder are also reported in those who abuse laxatives.[28,29,30]

Depression, schizophrenia, obsessive–compulsive disorder (OCD), and conversion disorders should be included in the differential diagnosis of AN, BN, and BED as eating abnormalities can be a component or share similar symptoms of these illnesses. The salient differences are the overriding drive for thinness, disturbed body image, increased energy directed at losing weight, and binge-eating episodes that are relatively specific for eating disorders. Most patients

with eating disorders experience relief of psychiatric symptoms on refeeding.[31]

Anorexia Nervosa

The presentation of AN includes a recent period of weight loss as well as associated behaviors to promote this, such as vomiting, limiting food intake, and excessive exercise. Current diagnostic criteria for AN include the restriction of energy intake relative to requirements, which leads to low body weight contextually as it relates to age, sex, developmental trajectory, and physical health.[3] The *DSM-5* further classifies AN as restricting type in which patients restrict food intake with no binge-eating or purging behavior over the past 3 months, or binge-eating/purging type, in which patients regularly participate in bingeing or purging over the prior 3 months.[3] The severity of AN is based upon BMI in adults and BMI percentiles in children and adolescents. Comorbid psychiatric conditions, such as major depression, are frequent but should initially be considered secondary to starvation and not a true mood disorder. Specific risk factors for AN include being female, having a sibling with AN, the presence of mood disorders in family members, and comorbid anxiety, personality, or substance use disorders.[32]

CLINICAL PRESENTATION

Anorexia Nervosa

General

- Restriction of energy intake that leads to low body weight and self-evaluation that is influenced by perceptions of weight and body shape.

Symptoms

- Patients have obsessions and fears about eating and gaining weight.
- They complain about feeling full even when they have eaten very little food.
- Denial of symptoms, failure to recognize low body weight, and low self-esteem.
- Patients often feel ineffective and have a lack of self-control.

Signs

- Weakness, lethargy, cachexia, amenorrhea, vomiting, restricted food intake, inappropriate exercise, delayed sexual development, edema, delayed gastric emptying, constipation, abdominal pain, bradycardia, hypotension, osteoporosis, dry cracking skin, lanugo, callus on dorsum of hand, cold intolerance, perioral dermatitis, and erosion of dental enamel.

Laboratory Abnormalities

- Hypokalemia, hypochloremia, hypothyroidism, hypophosphatemia, hypokalemic alkalosis, hypomagnesemia, metabolic acidosis, blood urea nitrogen, hepatic enzymes, leukopenia, thrombocytopenia, anemia, QT interval prolongation, bradycardia, hypercholesterolemia, and bone mineral density.

Other Diagnostic Tests

- Nonspecific electroencephalogram (EEG) changes.

CLINICAL PRESENTATION

Bulimia Nervosa

General

- Patients binge-eat and stop when they have abdominal pain or self-induced vomiting or are interrupted by another person.
- They have a pattern of severe dieting followed by binge-eating episodes.
- They are concerned about their body image but do not have the drive to thinness, which is a characteristic of AN.

Symptoms

- Patients do not eat regular meals and do not feel satiety at the end of a meal.
- They may use purging methods such as laxatives for weight control.
- They have guilt, depression, and self-disparagement after binges.
- Social isolation can result from frequent bingeing.
- Chaotic and troubled personal relationships and substance abuse are common.

Signs

- Bingeing, vomiting, salivary gland inflammation, erosion of dental enamel, callus on dorsum of hand, perioral dermatitis, dental caries, parotid gland enlargement, abdominal pain, upper end of normal body weight or slightly overweight, frequent weight fluctuations, and diminished masticatory ability.

Laboratory Abnormalities

- Hypokalemia, hypochloremic metabolic acidosis, and elevated serum amylase.

Other Diagnostic Tests

- None

4 Psychiatric comorbidity is common, as up to 75% of patients have a primary mood disorder, and there is also an association with personality disorders and anxiety disorders, such as social phobia and OCD.[2,33] The lifetime prevalence of OCD in patients with AN is reported to be as high as 40% compared to 2.5% in the general population.[33,34,35] The impact that psychiatric comorbidity has on treatment outcomes of AN is unknown, but it is important to understand that deprivation of food may contribute to both mood and cognitive fluctuations.

Bulimia Nervosa

The core feature of BN is recurrent episodes of binge-eating (an excessive intake of calorie-laden food over a short period of time). Most patients with BN have normal weight, although they might fluctuate between being underweight and overweight. Patients lack control over their eating and participate in recurrent compensatory behavior to prevent weight gain. These behaviors may include self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications; strict dieting or fasting; or excessive exercise. To meet *DSM-5* criteria, the binges and compensatory behaviors must occur on average at least once weekly for 3 months.[3] Bulimia nervosa can further be differentiated by purging type (regularly engages in self-induced vomiting or the misuse of laxatives, diuretics, or enemas) or non-purging type (uses other inappropriate compensatory behaviors, such as fasting or excessive exercise, but does not

engage in purging activities).[3]

Patients with BN typically binge and vomit at least once daily. Caloric intake varies, but patients can consume between 5,000 and 20,000 cal (20,900 and 83,700 J) during a single binge and they tend to consume foods that are easy to ingest, do not require much chewing or preparation, and are high in carbohydrates or fat. Binge-eating is typically secretive and precipitated by a stressful event, followed by post-binge remorse. In general, binges often last less than 2 hours but can extend to more than 8 hours. To compensate for the excessive caloric intake, many patients fast for prolonged periods, exercise compulsively, purge, or abuse laxatives.

Psychiatric comorbidity for BN includes depression (up to 80%), poor impulse control, and substance use. Approximately 30% to 37% of patients diagnosed with BN have a personal history of substance use.[36] Kleptomania and borderline and avoidant personality disorders are also frequently observed,[33,37] as patients also commonly steal laxatives and comfort items, such as candies and clothes.[9]

Binge-Eating Disorder

Patients with BED present with recurrent episodes of bingeing without the maladaptive compensatory behaviors associated with AN or BN. It is estimated that 5% to 10% of patients seeking treatment for obesity have BED. Comorbid psychiatric disorders are common and reported in greater than 70% of BED patients with depression and low self-esteem seen commonly. The self-deprecating focus on body image possible with BED is less severe than in AN or BN.[35,38] Diagnostic criteria for BED requires recurrent episodes of binge-eating (eating an amount of food in a 2 hour time frame that is larger than what most people would eat in a similar situation and a sense of lack of control over eating during the episode).[3] The binge-eating episodes are required to be associated with at least three of the following: eating more rapidly than normal; eating until feeling uncomfortably full; eating large amounts of food when not physically hungry; eating alone because of embarrassment of how much is being eaten; and feeling disgusted with oneself, depressed, or guilty after the episode. The severity of BED is determined by the number of binge-eating episodes per week (1-3 = mild; 4-7 = moderate; 8-13 = severe; 14 or more = extreme).[3]

Medical Complications of Eating Disorders

5 The potential medical complications of eating disorders involve multiple organ systems. The type of medical complication encountered is dependent on the type and frequency of the eating disorder behavior. Cardiac complications may occur and can include arrhythmias such as sinus bradycardia, cardiac muscle atrophy, orthostatic hypotension, decreased cardiac output, arrhythmia, and QTc interval prolongation.[39,40] During caloric restoration, there is a potential risk for developing refeeding syndrome, which can progress to fatal cardiovascular collapse. This risk is reduced by the gradual versus rapid reintroduction of calories.

CLINICAL PRESENTATION

Binge-Eating Disorder

General

- Repeated episodes of binge-eating that includes a lack of self-control and eating an amount of food that is beyond what most people would eat.
- Episodes of binge-eating may include rapid eating, a sense of fullness to the point of being uncomfortable, eating when not hungry, eating alone secondary to feeling embarrassed, and a sense of self-disgust, depression, or guilt.

Symptoms

- Episodes of binge-eating
- Lack of self-control
- Rapid consumption of food
- Feeling full and eating when not hungry
- Isolation and guilt/depression

Signs

- Obesity
- History of weight loss followed by weight gain
- Binge-eating without compensatory purging
- Psychiatric (eg, depression, anxiety) and medical complications (eg, GERD, hypertension, pain disorders, and asthma) are not uncommon.

Laboratory Abnormalities

- Elevated lipids, glucose, and hemoglobin A1C, abnormal electrolytes, and increased weight.

Other Diagnostic Tests

- None

Metabolic (metabolic acidosis and metabolic alkalosis) and electrolyte disturbances (eg, hypokalemia, hypomagnesemia, and hypocalcemia) and dehydration are often seen. Elevations in bicarbonate levels during periods of hypokalemia can be an indication that the patient is inducing vomiting or using dietary weight-loss medications. Non-anion-gap acidosis has also been reported with the abuse of laxative agents. Additionally, both acute and chronic renal failures have been reported.

Gastrointestinal (GI), oropharyngeal, and dental complications are frequent, as are general complaints of lethargy and fatigue. Evidence of Russell's sign may be present, which is signified by skin lesions on the fingers used to induce vomiting.

Hormonal changes related to the hypothalamic–pituitary–gonadal axis resulting from starvation are often seen. These abnormalities include effects on estradiol, the gonadotropins (eg, luteinizing hormone, follicle-stimulating hormone, and gonadotropin-releasing hormone), thyroid function, adrenal function, and growth hormone.[9,39] Specific to female athletes is the female athlete triad, defined by the development of irregular menses, osteoporosis, and disordered eating.[39,41] An athlete may experience only one or two components of the triad, or all three.[42] Osteopenia and osteoporosis are potential long-term complications of suppressed estrogen. The restoration of weight, specifically in AN, reverses the bone loss, although estrogen supplementation does not appear to be effective.[43] In all cases, the preferred method to address these issues is the normalization of nutrition. The impact on female fertility is not well studied, although the ability to carry a pregnancy to term or to give birth to a child of average birth weight appears reduced.

Chronic starvation can contribute to brain atrophy; however, decreases in white matter and CSF volumes return to normal after a healthy weight is achieved, but gray matter loss can persist.[31,44,45]

Obesity is common in patients with BED and may also be present in patients with BN, placing these patients at an increased risk of medical comorbidities

including type 2 diabetes mellitus and hypertension.[27] Assessment should include measurement of weight, height, pulse rate, blood pressure, and calculation of BMI. Random glucose and ECG should be done as medically indicated.[27]

A thorough physical and laboratory evaluation, as described in Table 81-1, is essential to determine the severity of medical complications.[3,27,31,46]

TABLE 81-1 Physical and Laboratory Assessment of Eating Disorders

Evaluation	Target Symptoms
Pulse	Bradycardia, tachycardia
Blood pressure	Hypotension, orthostasis
Height/weight	Underweight for size and age/body mass index
Respiratory rate	Rapid if heart failure occurs during refeeding
Temperature	Hypothermia, cold intolerance
Electrocardiogram	ST depression, flat T waves, U waves, increased QT interval, atrioventricular block
Gastrointestinal	Hypoactive bowel sounds, gastritis, abdominal distention
Skin	Dryness, scaling, lanugo, hair loss, calluses on fingers and hands
Menses	Amenorrhea
Complete blood count	Leukopenia, anemias, thrombocytopenia
Electrolytes	Hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, or hyperphosphatemia
pH	Metabolic alkalosis (acidosis if laxative abuse)
Amylase	Elevated; pancreatitis rare
Liver	Hypoalbuminemia, elevated γ-glutamyl transferase if alcohol abuse, elevated AST
Thyroid	Low to low normal, but not true thyroid disease
Cortisol	Elevated with lack of suppression on dexamethasone suppression test
Bone density	Osteoporosis, osteopenia
Renal	Reduced eGFR (<60 mL/min [1 mL/s])
Endocrine	Hypoglycemia

Data from References 3, 9, 27, 31, 39, 41–43, and 46.

TREATMENT

Desired Outcomes

The goals for patients with eating disorders are to reduce distorted body image; restore and maintain healthy body weight; establish normal eating patterns; improve psychological, psychosocial, and physical problems; resolve contributory family problems; enhance compliance; and prevent relapse.[31] Specific to BED is the additional goal of weight loss, if applicable.

Anorexia Nervosa

6 The long-term prognosis of patients with AN is not clear, as the majority of studies focus only on patients receiving acute treatment. The course of the disorder most commonly consists of a single episode with subsequent return to normal weight, although patients can still experience issues with disturbed body image, disordered eating, and other psychiatric problems and weight has normalized.[31] Some patients experience an unremitting course leading to death, whereas others suffer episodically. Remission rates appear to be a function of time in treatment, as the lowest rates of remission are reported in shorter-duration follow-up trials, while remission rates near 80% have been reported in longer-term follow-up studies at 8 and 16 years.[47] Despite this, it is estimated that up to 20% remain chronically ill despite weight normalization, return of menses, and improved eating behaviors.[48] The prognosis is more favorable with longer follow-up care and younger age of onset, whereas a poorer prognosis is associated with chronic illness, lower initial weight, poor family relationships, obsessive–compulsive personality symptoms, and the presence of bulimia or purging behavior.[23,48,50] Crude mortality rates appear to be lower than historically projected with the estimated mortality rate being 2.8% to 4%. When death occurs, it is most often the result of cardiac arrest or suicide.[3,47,48]

Bulimia Nervosa

The prognosis of BN appears to be more favorable than that of AN. Patients with milder presenting symptoms who are treated as outpatients tend to do better, whereas those with electrolyte imbalances, esophagitis, dental caries, and salivary gland enlargement have a more complicated course.[9] The presence of psychiatric comorbidity and greater general psychiatric symptom severity has

been determined to be poor prognostic indicators. Longer rates of follow-up tend to have higher rates of remission, reaching 70% or higher with 5 to 20 years of follow-up. However, it is important to note that even in cases in which patients respond, they continue to exhibit symptoms that wax and wane, sometimes meeting full criteria for diagnosis of BN or subthreshold forms of BN on the basis of insufficient frequency and/or duration of disordered eating behavior. Total absence of symptoms is an uncommon outcome, and residual symptoms predispose the patient to relapse.[47] The actual definition of recovery varies, as once-a-month binge–purge episodes are considered by some to be recovery if their episodes were previously more frequent, whereas other clinicians consider a patient recovered only when there is complete absence of these behaviors.[50]

Binge-Eating Disorder

Of all of the eating disorders, BED has the least amount of long-term follow-up data. Studies to date suggest higher remission rates (25%-80%) in 1- and 4-year follow-up studies compared with findings in AN and BN longitudinal studies. These numbers are irrespective of treatment selected and treatment during the follow-up time frame studied. Estimated crude mortality rates range from 0% to 4.7% with a cumulative mortality rate reported at 0.5%.[47,51]

General Approach to Treatment

Treatment plans are individualized based on the severity of specific core features of the eating disorder and comorbid medical and psychiatric conditions. The absence of an adequate support system of family and friends can contribute to failed treatment. A critical first step is to determine the severity of illness, as that drives both the intensity and the setting for delivery of care. Hospitalization is generally reserved for the most severely ill patients. In AN, lower admission BMI and the presence of purging symptoms and austerity predict longer lengths of stay.[52] Some criteria for hospitalization are outlined in **Table 81-2**.[3,23,26,31,53] Medications are part of the comprehensive treatment strategy for eating disorders, but are rarely recommended as the sole treatment.[54,55,56] Comparative, double-blind, placebo-controlled trials are sparse, and most are limited by small sample sizes, ambivalent patient attitudes toward treatment, medical complications, and high dropout rates.[57]

TABLE 81-2 Considerations for Hospitalization of Patients with Eating Disorders

- Rapid weight loss or Body Mass Index (BMI) <12
- Reduced oral intake of food (sudden and persistent)
- Medical complications (eg, edema) and metabolic abnormalities (eg, hypoproteinemia) from bingeing, purging, and starvation (eg, heart rate <40 beats/min, heart rate >120 beats/min, blood pressure <90/60 mm Hg, glucose <60 mg/dL [3.3 mmol/L], potassium <3 mEq/L [mmol/L], or inability to maintain core temperature)
- Co-occurring psychiatric symptoms, notably suicidal ideation, self-harm, psychotic depression, or substance abuse and dependence
- Nonresponsive to outpatient treatment (after 3-4 months) and poor motivation to recover
- Demoralization or nonfunctional family
- Denial of severity of abnormal eating behaviors
- Continuous supervision required to prevent purging (vomiting or laxative abuse)

Data from References 3, 23, 26, 31 and 53.

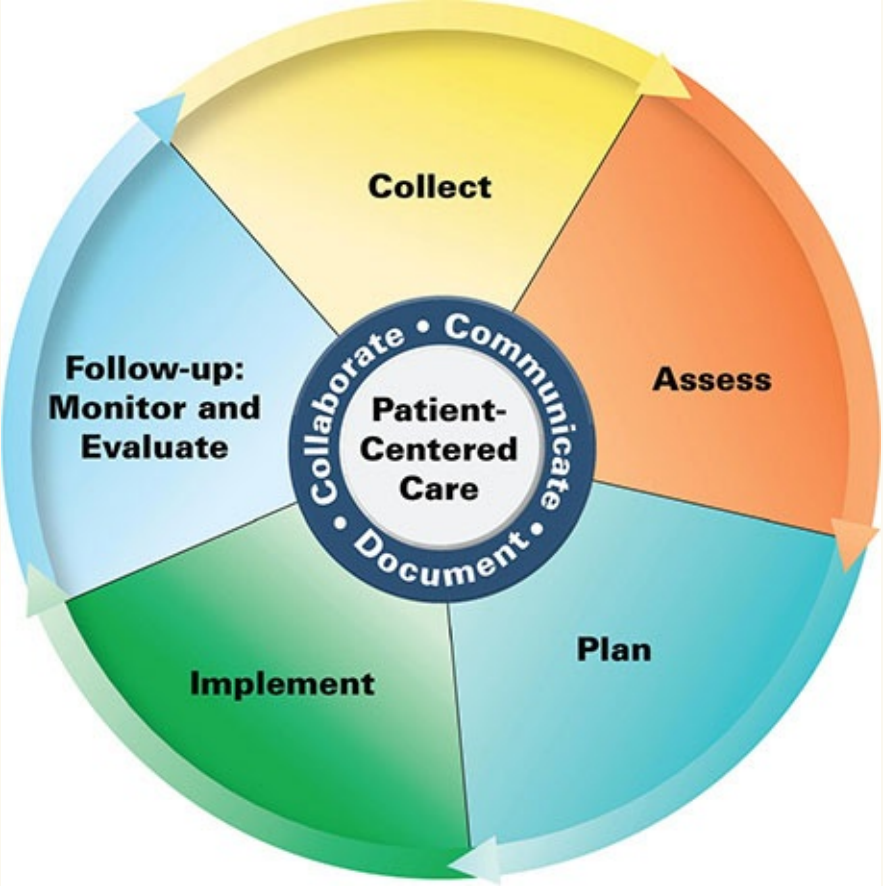
Anorexia Nervosa

Nonpharmacologic Therapy

7 Evidence supports that psychotherapy-based treatments have the greatest likelihood of eliciting a response in AN patients.[27,31,53,58] However, the specific type of psychotherapy that is preferred varies and may include CBT, dialectical behavioral therapy (DBT), focal psychodynamic therapy, behavioral management, specialist supportive clinical management, interpersonal psychotherapy, nutritional counseling, and family therapy.[27,31,33,46,53,58,59] In younger patients, family therapy is the preferred first-line therapy.[60] Patients of lower age, those with shorter duration of illness, with restrictive type AN, who are employed, who are not taking psychotropic medications, and with better social adjustment may have improved outcomes.[59] Current guidelines suggest at least 6 months of psychotherapy is preferred, though studies of at least 1 year in duration have demonstrated favorable outcomes by reducing relapse rates.[27,53,61] Overall, CBT helps the patient overcome distorted thinking, including self-worth as measured by body image, feelings of being fat despite evidence to the contrary, and denial. Additionally CBT teaches patients how to use strategies besides eating to cope.

Interpersonal psychotherapy focuses on interpersonal relationships and functioning, whereas CBT provides positive reinforcement for weight gain.[34] A combined approach of interpersonal psychotherapy and CBT is also a reasonable treatment approach.[58] Many psychiatric symptoms in an acutely ill patient, such

as depression and anxiety, diminish or disappear with weight restoration. Initial treatment is directed toward restoring a healthy weight, especially in inpatient settings where target weights are often more rapidly achieved.[33] After medical stability and appropriate weight are reached, therapy can be redirected toward addressing ongoing interpersonal problems, weight maintenance, cognitive restructuring, and skill development for relapse prevention.[27] Oral refeeding, initially with liquid formulas if necessary, is the most common approach to weight restoration.



Patient Care Process for Eating Disorders

Collect

- Patient characteristics (eg, age, race, sex, pregnant)
- Patient history (past medical, family, social—dietary habits, exercise patterns, laxative use)
- Weight history and body mass index (BMI)

- Current medications and prior eating disorder treatment(s)
- Objective data

  Blood pressure (BP), heart rate (HR), height, weight, and BMI

  Labs (eg, serum electrolytes, serum creatinine [Scr], estimated glomerular filtration rate [eGFR], blood urea nitrogen [BUN], metabolic panel)

  Other diagnostic tests when indicated (eg, ECG, EEG, bone mineral density)

Assess

- Symptoms of eating disorders (eg, anorexia nervosa, bulimia nervosa, and binge-eating disorder) that may include poor body image, weight change, lethargy, binging, purging, GI complaints) (Tables 81-1 and 81-2)
- Presence of mental health conditions (eg, depression, schizophrenia, anxiety disorders)
- Presence of medical conditions (eg, malnourishment, cardiac arrhythmia, refeeding syndrome, metabolic acidosis and alkalosis, dehydration, GI complications, osteopenia, osteoporosis, dental problems) (Fig. 81-1)
- Laboratory abnormalities (eg, hypokalemia, hypothyroidism, hypomagnesemia, hypophosphatemia) (Table 81-1)
- Current medications that may exacerbate eating disorder symptoms (eg, diuretics, laxatives)
- For the type of eating disorder identified, assess the appropriateness of medication therapy (see “Treatment” section)

Plan*

- Nonpharmacologic treatments (eg, nutritional rehab, education, and counseling; cognitive behavioral therapy; interpersonal psychotherapy; dialectical behavior therapy, family, and/or group therapy) (see “Treatment” section)
- Drug therapy dependent upon the eating disorder identified (eg, antidepressants, antipsychotics, anticonvulsants, lisdexamfetamine) (see Fig. 81-2)
- Monitoring parameters including efficacy (eg, BP, cardiovascular events, kidney health), safety (medication-specific adverse effects), and time

frame

- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug therapy)
- Self-monitoring of weight, BMI, BP, and HR—where and how to record results
- Referrals to other providers when appropriate (eg, physician, dietician)

Implement*

- Provide patient education regarding all elements of treatment plan (nonpharmacologic and pharmacologic)
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up assessments of treatment

Follow-up: Monitor and Evaluate

- Changes in eating habits and compensatory behaviors (Fig. 81-1)
- Weight, vital signs, and laboratory values (Table 81-1)
- Psychiatric (mental status examination) and physical condition stability
- Patient adherence to treatment plan using multiple sources of information

* *Collaborate with patient, caregivers, and other healthcare professionals.*

In severe cases when a patient refuses to eat, nasogastric refeeding is preferred over intravenous bolus dosing in part because it can allow for higher initial caloric intake and has been associated with reductions in length of inpatient hospitalizations and increased rate of weight gain without an increase in complications.[62] Total parenteral nutrition is reserved only for the management of severely malnourished patients and if other refeeding methods fail. The decision to administer total parenteral nutrition must be made carefully, because of the potentially devastating psychological effect on patients who do not wish to gain weight.

Current clinical evidence suggests a controlled weight gain of 0.9 to 1.4 kg (2-3 lb) per week in inpatient settings and 0.2 to 0.5 kg (0.5-1 lb) per week in outpatient settings.[3,56,63] Refeeding recommendations vary between younger patients and adults and are considered controversial. An acceptable approach for

younger patients is to begin refeeding at 800 to 1,000 cal/day (3,300-4,200 J/day), while others suggest a more aggressive approach.[64] Adults may be considered for refeeding initiation in the range of 1,000 to 1,600 cal/day (4,200-6,700 J/day) (30-40 cal/kg/day [130-170 J/kg/day]) with slow titration (every other day) upward (100-200 cal/day [420-840 J/day]) until they begin to demonstrate sustained weight gain or achieve target weights.[31,53,65] This can require the intake of an additional 3,500 to 7,000 cal (14,600-29,300 J) per week.[53] Slow refeeding has long been considered important to prevent psychological and medical consequences, including the severe electrolyte disturbance that results from insulin surges known as refeeding syndrome, which can result in death. A criticism is that too conservative of an approach results in further weight loss early in treatment (unfeeding syndrome), contributing to a failure to achieve nutritional recovery goals.[66]

Pharmacologic Therapy

Antidepressants Although many studies examined the role of antidepressants in the treatment of AN, they often have small sample sizes and large confidence intervals.[67] Antidepressants currently have no role in the acute treatment of AN, unless there is another clinical indication present.[23,31,54]

Data suggest that medication is ineffective, especially in cases where the patient is below their expected weight. Thus, antidepressants should be initiated only if depression, anxiety, obsessions, or compulsions persist after the target weight is achieved.[23,63] The duration of treatment when antidepressants are used in this manner is unclear, but one study showed benefit in treated patients for 1 year, and current guidelines suggest 9 to 12 months of therapy.[27,31,53,58,61] Antidepressants, along with psychotherapy, have been used to help maintain weight and prevent relapse, but data supporting this are limited.[67] Most clinicians prefer the selective serotonin reuptake inhibitor (SSRI) antidepressants because they are better tolerated and have greater cardiovascular safety than tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs).[27,31,58,61] Because these patients are sensitive to anticholinergic and cardiovascular effects, if TCAs or MAOIs are used, low starting doses and slow titration toward an effective dose are appropriate. The risk of cardiotoxicity in a malnourished population must not be underestimated, and a baseline electrocardiogram (ECG) should be obtained before initiation of these agents. Chapter 85, “Depressive Disorders,” contains a list of common side effects seen with antidepressant use.

Fluoxetine continues to be the most widely studied SSRI in AN. Most clinicians initiate at low doses, for example, 20 mg/day, and increase to a maximum of 60 mg/day based on response and tolerability.[65,67,68] Some controversy exists regarding when antidepressant therapy should be initiated. During the starvation phases of anorexia, the majority of clinical trials suggest that antidepressants are ineffective, partly due to reduced tryptophan levels, though debate remains as to their effectiveness once weight restoration has occurred. Evidence from a 52-week, randomized, placebo-controlled clinical trial of 93 patients with the treatment arm receiving doses from 20 to 80 mg/day after weight restoration showed no difference between fluoxetine and placebo for time to relapse.[69]

Antipsychotics First- and second-generation antipsychotics have been utilized as a treatment for AN, specifically targeting anxiety and obsessive and paranoid thoughts related to weight gain. First-generation antipsychotics contributed to BMI gains, but provided little benefit overall at reducing other core symptoms, and the associated adverse events were considered to outweigh the benefits. Second-generation antipsychotics have provided an additional alternative for treating AN, with reports of improvement in weight gain and reductions in symptoms such as depression, anxiety, and obsessive–compulsiveness. Most of the data are from case reports or small trials in both adolescents and adults using risperidone 0.5 to 2.5 mg daily, olanzapine 2.5 to 10 mg daily, and quetiapine 50 to 800 mg daily.[69,70,71,72,73,74] Olanzapine in combination with day hospital treatment has been shown to be more effective than day hospital treatment alone in achieving greater weight gain and reducing obsessive symptoms.[73] In addition, an outpatient study examining olanzapine versus placebo, independent of concurrent psychotherapy, demonstrated significant improvement in BMI.[75] Despite these reported benefits, a meta-analytic review of second-generation antipsychotics that included olanzapine, quetiapine, and risperidone did not find significant differences in BMI gains or eating disorder psychometric outcome assessments.[76]

Optimal treatment duration is unknown, as most of the larger studies are less than or equal to 3 months in duration. Chapter 84, “Schizophrenia,” contains a list of common side effects seen with antipsychotic use.

Miscellaneous Agents Metoclopramide can be helpful in reducing bloating, early satiety, and abdominal pain commonly found in AN, but it does not affect weight gain.[31] Low-dose, short-acting benzodiazepines (0.25 mg alprazolam or 0.5 mg lorazepam) given before meals are useful when severe anxiety limits

eating.[31] Estrogen replacement has been used, but restoring menses through refeeding is a preferred approach to minimize bone density loss. Supplementation with zinc is also being studied to assist with weight restoration.[58]

Bulimia Nervosa

Nonpharmacologic Therapy

Outpatient-based treatment is most often recommended except in extreme cases (see Table 81-2). The nondrug strategies used in BN are similar to those used with AN, and they are equally critical to success. Overall, CBT has the strongest evidence supporting its benefit in managing BN.[27,53,58] Current treatment guidelines suggest that CBT should consist of 16 to 20 sessions over a 4- to 5-month period.[27,53] Data suggest that 30% to 50% of individuals who receive CBT for BN are abstinent from binge-eating and purging behaviors by conclusion of the treatment.[76] Interpersonal psychotherapy also plays a role and has a moderate degree of evidence to support its use, but it is considered less effective than CBT.[24,31] A 2014 study demonstrated that CBT was more effective in relieving bingeing and purging than psychoanalytic psychotherapy and was generally faster in alleviating eating disorder features and general psychopathology.[77] Psychodynamic therapy as well as family-based therapy are also viable options for treatment of adolescents with BN.[78,79] Nutritional counseling, planned meals, especially regular consumption of evening meals, and self-monitoring can help interrupt the binge–purge cycle.[80] Programs using motivational teaching and self-help guides based on CBT have shown promise.[34,81,82,83] When such programs have been combined with medication, for example, fluoxetine, enhanced response has been reported. Online delivery of CBT and web-based aftercare may provide an acceptable treatment alternative for patients who have limited access.[84,85] Data support the use of 12-step programs, but they should not be used as monotherapy.[23,31] Additional nonpharmacologic strategies may include the promotion of aerobic exercise, yoga, massage therapy, and body awareness therapy.

Pharmacologic Therapy

8 **Antidepressants** Antidepressants are used in the acute and maintenance phases of BN adjunctively with nonpharmacologic approaches. A wide array of

antidepressants, including TCAs, MAOIs, trazodone, serotonin–norepinephrine reuptake inhibitors (SNRIs), bupropion, and SSRIs, have been studied. Additionally, several reviews analyzing this body of literature have been published, although there continues to be limited placebo-controlled, randomized, double-blind clinical studies.[23,54,86] Antidepressants are reported to reduce depression, anxiety, obsessions, and impulsive behaviors, such as binge-eating and purging, and improve eating habits, although their impact on body dissatisfaction remains unclear. The presence of comorbid mood disorders is not necessary for a response in patients with BN.

The benefit appears to be more robust in the acute phase of the illness, as relapse despite continued antidepressant use is common in patients who are in or near remission.[23,56] Antidepressant response usually occurs in 6 to 8 weeks, and reduction in frequency of binge–purge behavior has been as high as 73% and as low as zero.[54] Abstinence rates (elimination of bingeing and purging behaviors) with short-term use range from 0% to 68%. More data are needed to determine the long-term benefits of antidepressants for preventing relapse of bulimia symptoms. One trial evaluating the impact of fluoxetine versus placebo in the maintenance phase showed a better outcome in patients receiving fluoxetine 60 mg daily, although high dropout rates in both groups blurred the overall benefit.[87]

Selective serotonin reuptake inhibitors are the preferred agents because of their tolerability and because they have been studied in the largest number of patients. Fluoxetine remains the only medication with FDA approval for BN. Efficacy of other SSRI agents is still lacking, but an alternative SSRI may be considered in clinical practice for patients who do not respond to fluoxetine.[86] Tolerability is the primary criterion for selecting an antidepressant in the treatment of BN because of patients' heightened sensitivity to adverse effects and the lack of a clear difference in efficacy between the classes. Even though there is a suggestion that MAOIs produce the most robust effect, the risk of using these medications in impulsive patients limits their use.[56] SNRIs have shown promising results; however, the data supporting their use are limited to case reports. Bupropion, a norepinephrine–dopamine reuptake inhibitor, is contraindicated in patients diagnosed with BN because of the increased risk of seizures seen in patients with an eating disorder.

Before initiating pharmacologic therapy, a careful baseline physical examination, ECG, and laboratory workup are essential. Underlying ECG changes secondary to hypokalemia or bradycardia and atrioventricular block from starvation can be present. There is potential for fatal outcomes secondary to

cardiac arrest or suicide. All antidepressants can cause seizures; thus, a careful risk–benefit assessment is warranted if the patient has predisposing factors such as a personal or family history of seizures, cerebrovascular disease, or alcohol or sedative–hypnotic withdrawal.

Doses in the treatment of BN are similar to those in patients treated for depression, although at the higher end of the range. Readers are referred to Chapter 85 for antidepressant dosing ranges. For fluoxetine, the higher end of the dosing range, 60 mg daily, can be necessary for response.[88] With all agents, most clinicians initially target the bottom to the middle of the dosing range and increase the dose if there is an inadequate response. Slow titration is needed to allow time to develop tolerance to adverse effects. If TCAs are used, serum concentration monitoring is recommended to ensure that absorption is not compromised by purging.

The time for antidepressant onset of effect in BN is unclear. In the absence of data, the definition of a therapeutic trial from the depression literature (4-8 weeks at a therapeutic dose) should be used. A prior study suggested that response (defined as greater than 60% reduction in binge-eating or vomiting frequency) by week 3 is a positive predictor of eventual treatment response.[89] Because the majority of subjects will not experience a complete remission, and there are few data on predictors of response or whether switching to another class will improve response, a clear and specific target should be stated initially.[18]

Optimal duration of treatment after response is poorly defined, although most clinicians treat for 9 months to 1 year and then reevaluate. The evidence is mixed as to whether any early benefit is sustained; hence, the decision to continue treatment should be made based on both initial response and the maintenance of that benefit. If the symptoms return within a few months after antidepressant discontinuation, then the treatment may need to be reinitiated. **Figure 81-2** describes criteria for medication use in BN.

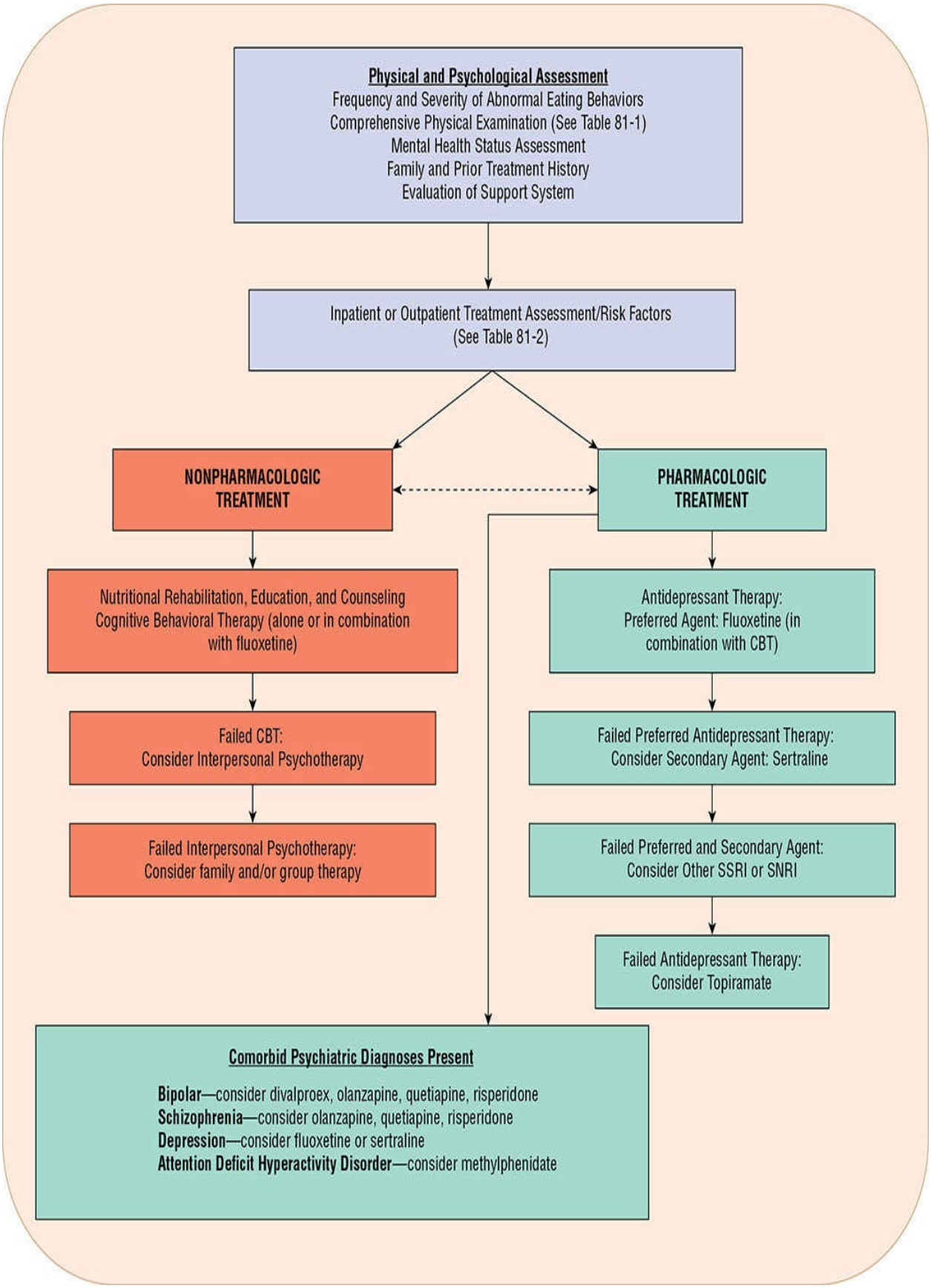

Physical and Psychological Assessment
Frequency and Severity of Abnormal Eating Behaviors
Comprehensive Physical Examination (See Table 81-1)
Mental Health Status Assessment
Family and Prior Treatment History
Evaluation of Support System
Inpatient or Outpatient Treatment Assessment/Risk Factors
(See Table 81-2)
NONPHARMACOLOGIC TREATMENT
PHARMACOLOGIC TREATMENT
Nutritional Rehabilitation, Education, and Counseling
Cognitive Behavioral Therapy (alone or in combination with fluoxetine)
Antidepressant Therapy:
Preferred Agent: Fluoxetine (in combination with CBT)
Failed CBT:
Consider Interpersonal Psychotherapy
Failed Preferred Antidepressant Therapy:
Consider Secondary Agent: Sertraline
Failed Interpersonal Psychotherapy:
Consider family and/or group therapy
Failed Preferred and Secondary Agent:
Consider Other SSRI or SNRI
Failed Antidepressant Therapy:
Consider Topiramate
Comorbid Psychiatric Diagnoses Present
Bipolar—consider divalproex, olanzapine, quetiapine, risperidone
Schizophrenia—consider olanzapine, quetiapine, risperidone
Depression—consider fluoxetine or sertraline
Attention Deficit Hyperactivity Disorder—consider methylphenidate

FIGURE 81-2 Bulimia nervosa treatment algorithm. (CBT, cognitive behavioral therapy; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.).

Miscellaneous Agents Because of the lack of evidence demonstrating their benefit, lithium and traditional anticonvulsants are reserved for patients diagnosed with BN who also have a comorbid bipolar disorder.[31,90] Randomized, placebo-controlled trials with topiramate have demonstrated reduced binge/purge frequency and weight loss versus placebo, although side effects including cognitive impairment and paresthesia may hinder medication adherence.[91,92] Low-dose benzodiazepines before meals can help reduce anxiety associated with refeeding, although long-term use is not warranted because of the risk of abuse and dependence. One double-blind trial with ondansetron has shown benefit, but there are insufficient data to recommend a specific role for this agent.[93] One small, open-label, pilot study of zonisamide showed it to be effective in BN, but due to study limitations, the results should be considered preliminary, and further data are needed to confirm its role in treatment.[94] Data are conflicting on the opiate antagonist naltrexone with only modest improvement seen at high doses, but naltrexone is not recommended due to risk of elevated hepatic transaminases.[70] Antipsychotics and appetite suppressants do not play a role in managing core symptoms of BN.[23]

Combination Therapy

The combination of pharmacologic and nonpharmacologic measures appears to produce the best chance for a positive outcome for patients with BN.[53] Antidepressants, specifically SSRIs, are the drug class of choice in patients diagnosed with BN, whereas other medications are reserved for patients with comorbid psychiatric conditions. Only in unusual circumstances should patients be treated with antidepressants alone. Evidence suggests the greatest benefit is during the acute phase of treatment, whereas data are mixed regarding their role in the prevention of relapse.

Binge-Eating Disorder

Nonpharmacologic Therapy

Individual and group CBT are universally accepted as the nonpharmacologic treatment interventions of choice, specifically aimed at reducing the number

binge-eating episodes with estimated >50% remission rates.[95] In general, IPT has demonstrated comparable efficacy to CBT at 1-, 2-, and 5-year follow-up reviews,[96,97] with DBT and mindfulness also being appropriate psychotherapy treatment interventions, though not considered first-line.[96,97] These interventions have been shown to improve long-term remission rates.[98] Behavioral weight loss programs typically produce only a 5% to 10% weight loss which is often regained in the subsequent 1 to 2 years, although can be considered an alternative treatment to CBT.[93] Sustained weight loss has been more favorably associated with CBT.[95,98,99]

Pharmacologic Therapy

9 The stimulant lisdexamfetamine, antidepressants, and anticonvulsants are the pharmacologic agents that have been most extensively studied in BED. Antidepressants have demonstrated efficacy as monotherapy at reducing binge-eating and improving depressed mood during the acute phases of the illness compared with placebo.[27,70,100,101,102,103] The SSRIs citalopram (20-60 mg in clinical trials; however, doses above 40 mg are not recommended), escitalopram (10-30 mg), fluvoxamine (up to 200 mg), fluoxetine (40-80 mg), and sertraline (100-200 mg) are associated with some level of improvement in BED-related symptoms.[100,101,102,104] This includes a reduction in binge frequency, improved mood symptoms, and reduced obsessive-compulsive symptoms, though not all studies have included each of these outcome measures in their methodology.[104] The majority of the data are with SSRIs given at antidepressant doses,[97] and interestingly, the combination of antidepressants with CBT has not borne out improved outcomes in most studies.[95,98]

Atomoxetine (40-120 mg) and venlafaxine (75-300 mg) have evidence to support improvement in BED symptoms with reduction in binge frequency, reduced BMI, weight loss, and improved mood symptoms.[104] Duloxetine has also been studied in comorbid depression with reductions in binge-eating and depressive symptoms.[105] Although bupropion has not shown improvement in BED outcomes with the exception of two case reports, naltrexone/bupropion did result in Binge Eating Scale score improvement and depressive symptoms with further research warranted.[106,107]

Lisdexamfetamine is a prodrug of dextroamphetamine and is FDA approved for the treatment of moderate to severe BED (30 mg initially and titrated to 50-70 mg daily). Clinical trials demonstrated reductions in numbers of binge days per week, a greater percentage of patients with global clinical improvement, a

higher percentage achieving a 4-week cessation of binge episodes, and improvement in obsessive-compulsive psychometric measures.[108] Such results have been supported out to 52 weeks.[109,110,111]

Topiramate (25-300 mg daily) reduced binge frequency, body weight, and BMI, and remission rates were higher when combined with CBT.[112] Zonisamide (100-600 mg/day) alone and in combination with CBT over the course of 16-week and 1-year studies demonstrated efficacy at reducing binge-eating and weight loss; however, there were high dropout rates due to intolerability.[86]

Orlistat (120 mg given three times daily), along with calorie-restricted diet, produced weight reduction in obese patients with BED.[113] Other medications used to treat obesity, such as liraglutide and the combination of phentermine with topiramate, are being explored as possible treatment options.

Current literature suggests that lisdexamfetamine, SSRIs, topiramate, and dasotraline (dopamine/norepinephrine reuptake inhibitor) hold the most promise in the short term, but long-term data is lacking. As with other eating disorders, nonpharmacologic treatments are a cornerstone of treatment.

EVALUATION OF THERAPEUTIC OUTCOMES

Eating Disorder Guideline Summary

Formalized treatment guidelines are available to assist in the management of eating disorders, specifically for AN, BN, and BED.[27,31,53,104,114] Many of the studies and reports included in this chapter were included in the formation of these treatment guidelines. Although guidelines are an important tool to aid in the decision-making process in developing treatment and management strategies, it is important to note variation in release dates of the various guidelines as this affects the information able to be included at the time of publication.

Anorexia Nervosa

A combination of subjective and objective measures is used to assess response in patients with AN. A reduction in the frequency and severity of abnormal eating habits, normalized exercise patterns and laboratory tests, and a sustained weight close to age-matched non-affected individuals are key indicators of response. A diary recording exercise frequency, menses, food intake, patterns of eating, and associated feelings while eating is a useful tool to track progress, especially in the outpatient setting. Weekly weigh-ins on the same scale, preferably at a

clinician’s office, help monitor progress early in treatment and reduce the focus on weight and anxiety caused by the variability found among different scales. Follow-up laboratory tests and ECGs are not part of routine monitoring unless the patient is restricting food intake, is purging, or continues to lose weight despite treatment. Inpatients require daily assessment of weight and caloric intake, vital signs, and urine output because of the severity of their illness. They also can need monitoring of bathroom privileges early in their care. A healthy weight gain of not more than 0.2 to 0.5 kg (0.4-1.1 lb) per week toward a goal of 90% to 95% of normal weight or a BMI greater than 18.5 kg/m^2 is a critical sign of treatment success. A patient’s use of coping skills and contingencies for dealing with stress, other than manipulating food consumption, also should be assessed. Antidepressants can assist in alleviation of persistent depression, anxiety, and obsessions, after weight restoration. Improvement in mood is expected to occur within 8 weeks. Patients receiving TCAs should be evaluated for dry mouth, constipation, hypotension, and sedation and patients receiving SSRIs should be monitored for agitation, drug-induced anorexia, nausea, weight loss, and insomnia. The decision to use long-term medication must be based on specific and sustained improvement in the target symptoms, balanced against adverse effects.

10 Recent research has focused on quality of life as a primary outcome measure compared to targeting specific symptoms of AN. Quality of life is generally lower in individuals with a history or clinical presence of an eating disorder. The belief behind this change in focus suggests that patients who are otherwise not interested in changing behaviors may be more invested in improving their perceived quality of life. Preliminary findings, however, suggest that improvement in quality of life is in part dependent on symptom improvement and weight gain, thus weight gain and behavioral change should remain the focus of treatment.

Bulimia Nervosa

An individualized treatment and monitoring plan begins with a thorough assessment describing the baseline frequency and severity of treatment-responsive target symptoms and other associated findings. The assessment must be comprehensive, as a patient can hide his or her illness by shifting from one type of behavior to another (eg, exercise to purging).

A comprehensive assessment includes a description of psychiatric symptoms, physical findings, frequency and severity of binge–purge episodes, laxative and

ipecac use, exercise patterns, and laboratory and ECG abnormalities. Interpersonal and relationship problems should also be evaluated. Some findings indicating a more chronic course of illness, such as salivary gland inflammation and erosion of dental enamel, can take months to reverse or might never normalize. Hence, these are not sensitive indicators of early treatment response. Data describing a patient's baseline level of functioning and previous response to treatment should be used to set goals in the current treatment plan.

Response to an antidepressant usually occurs within 4 to 8 weeks after the onset of treatment. If response does not occur, binge–purge behavior should be considered as a factor potentially contributing to the malabsorption of medication. If this behavior is not present, then every attempt should be made to maximize the dose. Serum concentration monitoring, when appropriate as with TCAs, should be done periodically (every 3 to 6 months if a patient is responding and tolerating the medication, or more frequently if clinically indicated). Evaluation of previously described adverse effects also should be part of the monitoring plan. If the patient responds, he or she should be followed for 6 to 12 months, and then reassessed for the need for ongoing medication. If the patient relapses after medication discontinuation, then the medication should be restarted. There is an increased risk of suicidality associated with antidepressant use in major depression, thus suicidality assessments should be included following their initiation, especially early in therapy. Please refer to Chapter 85 for further details and more comprehensive information related to antidepressant use.

Eating disorder patients who are outpatients present a particular challenge to clinicians, as impulsivity associated with BN can increase the risk for suicide. In order to reduce the risk of medication overdoses, prescriptions should be limited to small supplies. In addition, pharmacists should be alert to persons who make large or frequent purchases of laxatives or ipecac syrup, as this is an indicator of possible bulimic behaviors.

Binge-Eating Disorder

Similarly to BN, the frequency and severity of binge episodes should be monitored. In addition, psychiatric symptoms, physical findings, and interpersonal problems should be assessed. There is a suggested association between BED and suicidality and thus close monitoring of mood should be considered an aspect of the treatment plan.[115]

Evaluation of adverse effects should be monitored as indicated during

discussion of AN and BN. If weight loss is being pursued, all appropriate measures such as weight, calculated BMI, and waist circumference are indicated. Please refer to Chapter 161, “Obesity,” for further details and more comprehensive information related to treatment of obesity. Monitoring of metabolic parameters periodically should be assessed. There is a relative paucity of literature to guide length of treatment, although recommendations for BN could be extrapolated to BED.

CONCLUSION

The treatment of AN is complex and involves preferred strategies of psychotherapy that may include CBT, DBT, and nutritional counseling among several others. Pharmacologic strategies are not aimed at core AN symptom reduction, but rather concurrent mental illness that often accompanies AN. This can include the use of both antidepressants and antipsychotics. Antidepressants have not been shown to be clinically meaningful for core AN symptoms, but may be appropriate with co-occurring depression. Antipsychotics have also been shown to aide in managing anxiety, paranoia, and obsessions associated with weight gain, while also helping to improve patient BMIs.

Assessment of BN patients includes frequency and severity of binge–purge episodes, laxative and ipecac use, exercise patterns, physical and laboratory findings, and other psychiatric symptoms. Cognitive behavioral therapy is the nonpharmacologic treatment of choice. Antidepressants, particularly SSRIs, are used in the acute and maintenance phases of BN adjunctively with nonpharmacologic approaches. Antidepressant response usually occurs in 6 to 8 weeks. Monitoring for response as well as adverse effects is a critical part of the plan.

The treatment of BED necessitates a holistic approach including nonpharmacologic therapy such as CBT along with nutritional guidance and weight loss, if applicable. Lisdexamfetamine is the sole FDA-approved agent for treatment of moderate to severe BED, although evidence exists for antidepressants and anticonvulsants, namely topiramate. As with all eating disorders, monitoring for adverse effects and ongoing BED symptoms should be assessed regularly.

Postclass Engaged Learning Activity

Conduct a literature search and identify a primary research manuscript that

has been published in the past 12 months regarding the use of antipsychotics in anorexia nervosa. Write a brief summary about the study methods, the major findings, and how the use of the specific antipsychotic may or may not change current practice. This activity is intended to build your literature evaluation skills and ability to critically appraise research manuscripts.

ABBREVIATIONS

5-HIAA	5-hydroxyindoleacetic acid
5-HT	serotonin
5-HTTLPR, SLC6A4	serotonin transporter
AN	anorexia nervosa
BDNF	brain-derived neurotrophic factor
BED	binge-eating disorder
BMI	body mass index
BN	bulimia nervosa
CBT	cognitive behavioral therapy
CNS	central nervous system
CSF	cerebrospinal fluid
CT	computerized tomography
DBT	dialectical behavior therapy
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
ECG	electrocardiogram
EEG	electroencephalogram
ESRI	estrogen receptor I gene
GI	gastrointestinal
IPT	interpersonal therapy
MAOI	monoamine oxidase inhibitor
MRI	magnetic resonance imaging
NES	night eating syndrome
OCD	obsessive–compulsive disorder
SNRI	serotonin–norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant

REFERENCES

1. Hudson JI, Hiripi E, Pope HG Jr, Kessler RC. The prevalence and correlates of eating disorders in the national comorbidity survey

replication. *Biol Psychiatry*. 2007;61:348–358.

2. Swanson AA, Crow SJ, Le Grange D, et al. Prevalence and correlates of eating disorders in adolescents. *Arch Gen Psychiatry*. 2011;68(7):714–723.
3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Press; 2013;329–360.
4. Cardi V, Tchanturia K, Treasure J. Premorbid and illness related social difficulties in eating disorders: an overview of the literature and treatment developments. *Current Neuropharmacology*. 2018;16(8):1122–1130.
5. Pike KM. Long-term course of anorexia nervosa: response, relapse, remission, and recovery. *Clin Psychol Rev*. 1998;18:447–475.
6. Crow SJ, Peterson CV, Swanson SA, et al. Increased mortality in bulimia nervosa and other eating disorders. *Am J Psychiatry*. 2009;166:1342–1346.
7. Rodgers RF, Skowron S, Chabrol H. Disordered eating and group membership among members of a pro-anorexic online community. *Eur Eat Disorders Rev*. 2012;20:9–12.
8. Hoek H, van Hoeken D. Review of the prevalence and incidence of eating disorders. *Int J Eat Disord*. 2003;34:383–386.
9. Sadock BJ, Sadock VA. *Kaplan and Sadock's Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry*. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003; 739–750. eds.
10. Yilmax Z, Hardaway JA, Bulik CM. Genetics and epigenetics of eating disorders. *Adv Genomics Genet*. 2015;5:131–150.
11. Marzilli E, Cerniglia L, Cimino S. A narrative review of binge eating disorder in adolescence: prevalence, impact, and psychological treatment strategies. *Adolsec Health Med Ther*. 2018;9:17–30.
12. Cossrow N, Pawaskar M, Witt EA, Ming EE, et al. Estimating the prevalence of binge eating disorder in a community sample from the United States: comparing DSM-IV-TR and DSM-5 Criteria. *J Clin Psychiatry*. 2016;77(8):e968–e974.
13. O'Reardon JP, Allison KC, Martino NS, et al. A randomized, placebo-controlled trial of sertraline in the treatment of night eating syndrome. *Am J Psychiatry*. 2006;163:893–898.
14. Fischer S, Meyer AH, Herman E, et al. Night eating syndrome in young

adults: delineation from other eating disorders and clinical significance. *Psychiatry Res*. 2012;200:494–501.

15. Allison KC, Studt SK, Berkowitz RI, et al. An open-label efficacy trial of escitalopram for night eating syndrome. *Eat Behav*. 2013;14:199–203.
16. Phillipou A, Rossell SL, Castle DJ. The neurobiology of anorexia nervosa: a systematic review. *Aust N Z J Psychiatry*. 2014;48(2):128–152.
17. Kaye WH. Neurobiology of anorexia and bulimia nervosa. *Physiol Behav*. 2008;94:121–135.
18. Frank GK, Bailer UF, Henry SE, et al. Increased dopamine D2/D3 receptor binding after recovery from anorexia nervosa measured by positron emission tomography and [11c]raclopride. *Biol Psychiatry*. 2005;58:908–912.
19. Ribases M, Gratacos M, Fernandez-Aranda F, et al. Association of BDNF with anorexia, bulimia, age of onset of weight loss in six European populations. *Hum Mol Genet*. 2004;13(12):1205–1212.
20. Schalla MA. The role of ghrelin in anorexia nervosa. *International Journal of Molecular Sciences*. 2018;19(7):2117.
21. Pinheiro AP, Bulik CM, Thornton LM, et al. Association study of 182 candidate genes in anorexia nervosa. *Am J Med Genet B Neuropsychiatr Genet*. 2010;153B:1070–1080.
22. Grave RD. Eating disorders: Progress and challenges. *Eur J Intern Med*. 2011;22:153–160.
23. Fairburn CG, Harrison PJ. Eating disorders. *Lancet*. 2003;361:407–416.
24. Steiger H, Joober R, Gauvin L, et al. Serotonin-system polymorphisms (5-HTTLPR and –1438G/A) and responses of patients with bulimic syndromes to multimodal treatments. *J Clin Psychiatry*. 2008;69:1565–1571.
25. Versini A, Ramoz N, Le Strat Y, et al. Estrogen receptor I gene is associated with restrictive anorexia nervosa. *Neuropsychopharmacology*. 2010;35:1818–1825.
26. Powers PS. Initial assessment and early treatment options for anorexia nervosa and bulimia nervosa. *Psychiatr Clin North Am*. 1996;19:639–655.
27. Hay P, Chinn D, Forbes D, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of eating disorders. *Aust N Z J Psychiatry*. 2014;48(11):977–1008.
28. Tozzi F, Thornton LM, Mitchell J, et al. Features associated with laxative

abuse in individuals with eating disorders. *Psychosom Med*. 2006;68:470–477.

29. Garner DM, Garner MV, Rosen LW. Anorexia nervosa “restrictors” who purge: implications for subtyping anorexia nervosa. *Int J Eat Disord*. 1993;13:171–185.
30. Shroff H, Reba L, Thornton LM, et al. Features associated with excessive exercise in women with eating disorders. *Int J Eat Disord*. 2006;39:454–461.
31. American Psychiatric Association. Treatment of patients with eating disorders, third edition. *Am J Psychiatry*. 2006;163(7 suppl):4–54.
32. Steinhausen HC, Jakobsen, Helenius D, et al. A nation-wide study of the family aggregation and risk factors in anorexia nervosa over three generations. *Int J Eat Disord*. 2015;48:1–8.
33. Jordan J, Joyce PR, Carter FA, et al. Specific and nonspecific comorbidity in anorexia nervosa. *Int J Eat Disord*. 2008;41:47–56.
34. Halmi KA.Eating disorders: Anorexia nervosa, bulimia nervosa, and obesity. In: Hales RE, Yudofsky SC, eds.*Essentials of Clinical Psychiatry*. 3rd ed. Washington, DC: American Psychiatric Press; 1999;667–685.
35. Braun DL, Sunday SR, Halmi KA. Psychiatric comorbidity in patients with eating disorders. *Psychol Med*. 1994;24:859–867.
36. Herzog DB, Keller MB, Sacks NR, et al. Psychiatric comorbidity in treatment seeking anorexics and bulimics. *J Am Acad Child Adolesc Psychiatry*. 1992;31:810–818.
37. O’Brien KM, Vincent NK. Psychiatric comorbidity in anorexia and bulimia nervosa: nature, prevalence, and causal relationships. *Clin Psychol Rev*. 2003;23:53–74.
38. Grilo CM, White MA, Masheb RM. DSM-IV psychiatric disorder comorbidity and its correlates in binge eating disorder. *Int J Eat Disord*. 2009;42(3):228–234.
39. Rome ES, Ammerman S. Medical complications of eating disorders: an update. *J Adolesc Health*. 2003;33:418–426.
40. Meczekalski B, Podfigurna-Stopa A, Katulski K. Long-term consequences of anorexia nervosa. *Maturitas*. 2013;75:215–220.
41. Birch K. Female athlete triad. *Br Med J*. 2005;330(7485):244–246.
42. Mendelsohn FA, Warren MP. Anorexia, bulimia, and the female athlete triad: evaluation and management. *Endocrinol Metab Clin North Am*.

2010;39:155–167.

43. Mehler PS, MacKenzie TD. Treatment outcomes of osteopenia and osteoporosis in anorexia nervosa: a systematic review of the literature. *Int J Eat Disord*. 2009;42(3):195–201.
44. Kingston K, Szmukler G, Andrews D, et al. Neuropsychological and structural brain changes in anorexia nervosa before and after refeeding. *Psychol Med*. 1996;26:15–28.
45. Lambe EK, Katzman DK, Mikulis DJ, et al. Cerebral gray matter volume deficits after weight recovery from anorexia nervosa. *Arch Gen Psychiatry*. 1997;54:537–542.
46. Le Grange D, Fitzsimmons-Craft EE, Crosby RD, et al. Predictors and moderators of outcome for severe and enduring anorexia nervosa. *Behav Res Ther*. 2014;56:91–98.
47. Keel PK, Brown TA. Update on course and outcome in eating disorders. *Int J Eat Disord*. 2010;43:195–204.
48. Steinhausen HC. The outcome of anorexia nervosa in the 20th century. *Am J Psychiatry*. 2002;159(8):1284–1293.
49. Fichter MM, Quadfleig N. Six year course of bulimia nervosa. *Int J Eat Disord*. 1997;22:361–384.
50. Yu J, Agras WS, Bryson S. Defining recovery in adult bulimia nervosa. *Eat Disord*. 2013;21:379–394.
51. Fichter MM, Quadflieg N. Mortality in eating disorders–results of a large prospective clinical longitudinal study. *Int J Eat Disord*. 2016;49:391–401.
52. Kastner D, Lowe B, Osen B, Voderholzer U, Gumz A. Factors influencing the length of hospital stay of patients with anorexia nervosa-results from a prospective multicenter study. *BMC Health Services Research*. 2018;18(1):22.
53. National Collaborating Centre for Mental Health. *Eating Disorders: Core Interventions in the Treatment and Management of Anorexia Nervosa, Bulimia Nervosa and Related Eating Disorders*. London: British Psychological Society and Royal College of Psychiatrists; 2004:1–36.
54. Mitchell JE, de Zwaan M, Roerig JL. Drug therapy for patients with eating disorders. *Curr Drug Targets CNS Neurol Disord*. 2003;2:17–29.
55. Bacaltchuk J, Hay P. Antidepressants versus placebo for people with bulimia nervosa. *Cochrane Database Syst Rev*. 2003; (4):CD003391[updated November 2005].

56. Nakash-Eisikovits O, Dierberger A, Westen D. A multidimensional meta-analysis of pharmacotherapy for bulimia nervosa: summarizing the range of outcomes in controlled clinical trials. *Harv Rev Psychiatry*. 2002;10:190–211.
57. Halmi KA, Agras WS, Crow S, et al. Predictors of treatment acceptance and completion in anorexia nervosa: implications for future study designs. *Arch Gen Psychiatry*. 2005;62:776–781.
58. Yager J, Devlin MJ, Halmi KA, et al. *Guideline Watch (August 2012): Practice Guideline for the Treatment of Patients with Eating Disorders*. 3rd ed. Available at http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidwatch.pdf.
59. Zipfel S, Wild B, Grob G, et al. Focal psychodynamic therapy, cognitive behavior therapy, and optimised treatment as usual in outpatients with anorexia nervosa (ANTOP study): randomized controlled trial. *Lancet*. 2014;383:127–137.
60. Lock J, La Via MC. Practice parameter for the assessment and treatment of children and adolescents with eating disorders. *J Am Acad Child Adolesc Psychiatry*. 2015;54(5):412–425.
61. Watson HJ, Bulik CM. Update on the treatment of anorexia nervosa: review of clinical trials, practice guidelines, and emerging interventions. *Psychol Med*. 2013;43:2477–2500.
62. Agostino H, Erdstein J, De Meglio G. Shifting paradigms: continuous nasogastric feeding with high caloric intakes in anorexia nervosa. *J Adolesc Health*. 2013;53:590–594.
63. Zerbe KJ. Multimodal treatment of severe eating disorders. *Essent Psychopharmacol*. 2000;3:1–17.
64. Rocks T, Pelly F, Wilkinson P. Nutrition therapy during initiation of refeeding in underweight children and adolescent inpatients with anorexia nervosa: a systematic review of the evidence. *J Acad Nutr Diet*. 2014;114:897–907.
65. Yager J, Anderson AE. Anorexia nervosa. *N Engl J Med*. 2005;353(14):1481–1488.
66. Garber AK, Mauldin K, Michihata N, et al. Higher calorie diets increase rate of weight gain and shorten hospital stay in hospitalized adolescents with anorexia nervosa. *J Adolesc Health*. 2013;53:579–584.
67. Kaye WH, Nagata T, Weltzin TE, et al. Double-blind placebo-controlled

administration of fluoxetine in restricting- and restricting-purging-type anorexia nervosa. *Biol Psychiatry*. 2001;4:644–652.

68. Bulik CM, Berkman ND, Brownley KA, et al. Anorexia nervosa treatment: a systematic review of randomized controlled trials. *Int J Eat Disord*. 2007;40:310–320.
69. Walsh BT, Kaplan AS, Attia E, et al. Fluoxetine after weight restoration in anorexia nervosa: a randomized controlled trial. *JAMA*. 2006;295(22):2605–2612.
70. Flament MF, Bissada H, Spettigue W. Evidence-based pharmacotherapy of eating disorders. *Int J Neuropsychopharmacol*. 2012;15:189–207.
71. Dunican KC, DelDotto D. The role of olanzapine in the treatment of anorexia nervosa. *Ann Pharmacother*. 2007;41:111–115.
72. Mehler-Wex C, Romanos M, Kirchheiner J, Schulze UME. Atypical antipsychotics in severe anorexia nervosa in children and adolescents—review and case reports. *Eur Eat Disord Rev*. 2008;16:100–108.
73. Bissada H, Tasca GA, Barber AM, Bradwejn J. Olanzapine in the treatment of low body weight and obsessive thinking in women with anorexia nervosa: a randomized, double-blind, placebo-controlled trial. *Am J Psychiatry*. 2008;165:1281–1288.
74. Powers PS, Klabunde M, Kaye W. Double-blind placebo-controlled trial of quetiapine in anorexia nervosa. *Eur Eat Disord Rev*. 2012;20:331–334.
75. Attia E, Kaplan AS, Walsh BT, et al. Olanzapine versus placebo for outpatients with anorexia nervosa. *Psychol Med*. 2011;41:2177–2182.
76. Dold M, Aigner M, Klabunde M, Treasure J. Second-generation antipsychotic drugs in anorexia nervosa: a meta-analysis of randomized controlled trials. *Psychotherapy and Psychosomatics*. 2015;84:110–116. doi.10.1159/000369978.
77. Poulsen S, Lunn S, Daniel SIF, et al. A randomized controlled trial of psychoanalytic psychotherapy or cognitive-behavioral therapy for bulimia nervosa. *Am J Psychiatry*. 2014;171(1):109–116.
78. Stefini A, Salzer S, Beich G, et al. Cognitive behavioral and psychodynamic therapy in female adolescents with bulimia nervosa: a randomized controlled trial. *J Am Acad Child Adilesc Psychiatry*. 2017;56(4):329–335.
79. Grange DL, Lock J, Agras WS, Bryson SW, Jo B. Randomized clinical trial of family based treatment and cognitive behavioral therapy for adolescent bulimia nervosa. *J Am Acad Child Adolesc Psychiatry*.

2015;54(11):886–894.

80. Ellison JM, Simonich HK, Wonderlich SA, Crosby RD, et al. Meal patterning in the treatment of bulimia nervosa. *Eating Behaviors*. 2016;20:39–42.
81. Schmidt U, Lee S, Beecham J, et al. A randomized controlled trial of family therapy and cognitive behavior therapy guided self-care for adolescents with bulimia nervosa and related disorders. *Am J Psychiatry*. 2007;164:591–598.
82. Mitchell JE, Agras S, Crow S, et al. Stepped care and cognitive-behavioural therapy for bulimia nervosa: randomized trial. *Br J Psychiatry*. 2011;198:391–397.
83. Wilson GT, Zandberg LJ. Cognitive-behavioral guided self-help for eating disorders: effectiveness and scalability. *Clin Psychol Rev*. 2012;32:343–357.
84. Zerwas SC, Watson HJ, Hofmeier SM, et al. CBT4BN: a randomized controlled trial of online chat and face-to-face group therapy for bulimia nervosa. *Psychother Psychosom*. 2017;86:47–53.
85. Jacobi C, Beintner I, Fitig E, et al. *J Med Internet Res*. 2017; 19(9):e321.
86. Hay PJ, Claudino AM. Clinical psychopharmacology of eating disorders: a research update. *Int J Neuropsychopharmacol*. 2012;15:209–222.
87. Romano SJ, Halmi KA, Sarkar NP, et al. A placebo-controlled study of fluoxetine in continued treatment of bulimia nervosa after successful fluoxetine treatment. *Am J Psychiatry*. 2002;159:96–102.
88. Fluoxetine Bulimia Nervosa Collaborative Study Group. Fluoxetine in the treatment of bulimia nervosa: a multicenter, placebo-controlled, double-blind trial. *Arch Gen Psychiatry*. 1992;49:139–147.
89. Sysko R, Sha N, Wang Y, et al. Early response to antidepressant treatment in bulimia nervosa. *Psychol Med*. 2010;40:999–1005.
90. McElroy SL, Kotwal R, Hudson JI, et al. Zonisamide in the treatment of binge eating disorder: an open-label, prospective trial. *J Clin Psychiatry*. 2004;65(1):50–56.
91. Hoopes SP, Reimherr FW, Hedges DW, et al. Treatment of bulimia nervosa with topiramate in a randomized, double-blind, placebo-controlled trail, part 1: improvement in binge and purge measures. *J Clin Psychiatry*. 2003;64(11):1335–1341.
92. Nickel C, Tritt K, Muehlbacher M, et al. Topiramate treatment in bulimia

nervosa patients: a randomized, double-blind, placebo-controlled trial. *Int J Eat Disord*. 2005;38(4):295–300.

93. Faris PL, Kim SW, Meller WH, et al. Effect of decreasing afferent vagal activity with ondansetron on the symptoms of bulimia nervosa: a randomized double-blind trial. *Lancet*. 2000;355:792–797.
94. Guerdjikova AI, Blom TJ, Martens BE, et al. Zonisamide in the treatment of bulimia nervosa: an open-label, pilot, prospective study. *Int J Eat Disord*. 2013;46(7):747–750.
95. Grilo CM. Psychological and behavioral treatments for binge-eating disorder. *J Clin Psychiatry*. 2017;78(suppl 1):20–24.
96. Hilbert A, Bishop ME, Stein RI, et al. Long-term efficacy of psychological treatments for binge-eating disorder. *Br J Psychiatry*. 2012;200(3):232–237.
97. Kass AE, Kolko RP, Wilfley DE, et al. Psychological treatments for eating disorders. *Curr Opin Psychiatry*. 2013;26(6):549–555.
98. Kober H, Boswell RG. Potential psychological & neural mechanisms in binge eating disorder: implications for treatment. *Clin Psychol Rev*. 2018;60:32–44.
99. Peat CM, Berkman ND, Lohr KN, Brownley KA, et al. Comparative effectiveness of treatments for binge-eating disorder: systematic review and network meta-analysis. *Eur Eat Disorders Rev*. 2017;25:317–328.
100. Devlin MJ, Goldfein JA, Petkova E, et al. Cognitive behavioral therapy and fluoxetine as adjuncts to group behavioral therapy for binge eating disorder. *Obes Res*. 2005;13(6):1077–1088.
101. Kaplan AS. Academy for Eating Disorders International Conference on Eating Disorders. *Expert Opin Investig Drugs*. 2003;12:1441–1443.
102. McElroy SL, Casuto LS, Nelson EB, et al. Placebo-controlled trial of sertraline in the treatment of binge eating disorder. *Am J Psychiatry*. 2000;157:1004–1006.
103. Davis H, Attia E. Pharmacotherapy of eating disorders. *Curr Opin Psychiatry*. 2017;30(6):452–457.
104. Aigner M, Treasure J, Kaye W, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacologic treatment of eating disorders. *World J Biol Psychiatry*. 2011;12:400–443.
105. Guerdjikova AI, McElroy SL, Winstanly EL, et al. Duloxetine in the treatment of binge eating disorder with depressive disorders: a placebo

controlled trial. *Int J Eat Disord*. 2012;45(2):281–289.

106. Ambrogne J. Assessment, diagnosis, and treatment of binge-eating disorder. *J Psychosoc Nurs Ment Health Serv*. 2017;55(8):32–38.
107. Guerdjikova AI, Walsh B, Shan K, Halsbeth AE, et al. Concurrent improvement in both binge eating and depressive symptoms with naltrexone/bupropion therapy in overweight or obese subjects with major depressive disorder in an open-label, uncontrolled study. *Adv Ther*. 2017;34:2307–2315.
108. McElroy SL, Hudson JI, Mitchell JE, et al. Efficacy and safety of lisdexamfetamine for treatment of adults with moderate to severe binge-eating disorder: a randomized clinical trial. *JAMA Psychiatry*. 2015;72(3):235–246.
109. Ward K, Citrome L. Lisdexamfetamine: chemistry, pharmacodynamics, pharmacokinetics, and clinical efficacy, safety, and tolerability in the treatment of binge eating disorder. *Expert Opin Drug Metab Toxicol*. 14(2):229–238.
110. Yung-A H, Duggan ST. Lisdexamfetamine: a review in binge eating disorder. *CNS Drugs*. 2017;31:1015–1022.
111. Hudson JI, McElroy SL, Ferreira-Cornwell MC, Radewonuk J, et al. Efficacy of lisdexamfetamine in adults with moderate to severe binge-eating disorder: a randomized clinical trial. *JAMA Psychiatry*. 2017;74(9):903–910.
112. McElroy S. Pharmacologic treatments for binge-eating disorder. *J Clin Psychiatry*. 2017;78(suppl 1):14–19.
113. Golay A, Laurent-Jaccard A, Habicht F, et al. Effect of orlistat in obese patients with binge-eating disorder. *Obes Res*. 2005;13(10):1701–1708.
114. National Institute for Health and Care Excellence (NICE). Eating disorders: recognition and treatment. May 2017. Available at: https://www.nice.org.uk/guidance/NG69/resources. Accessed March 12, 2018.
115. Conti C, Lanzara R, Scipioni M, Iasenza M, et al. The relationship between binge eating disorder and suicidality: a systematic review. *Front Psychol*. 2017;8:1–11.

82

Substance Use Disorders I: Depressants, Stimulants, and Hallucinogens

Robin Moorman Li, Patrick Leffers, and Paul L. Doering

KEY CONCEPTS

1. Illicit drug use, including the misuse of prescription medications, affects the health and well-being of millions of Americans. Addressing the impact of substance use alone is estimated to cost Americans more than $740 billion each year.
2. Between 1999 and 2016, the number of drug overdose deaths in the United States more than tripled, and the Centers for Disease Control and Prevention (CDC) now estimates that each day at least 115 people in the United States die from an opioid overdose.
3. Opioid overdoses involving prescription opioids, synthetic opioids, and heroin have continued to increase while healthcare professionals, legislators, and the community as a whole continue to work together to focus on prevention, treatment, recovery, and enforcement to reverse this trend.
4. Defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*, substance use disorders (SUD) are diagnosed based on evidence of impaired control, social impairment, risky use, and pharmacological criteria. Severity of disorder can range from mild to moderate to severe.
5. Substance use disorders are chronic illnesses for which there are no cures. The focus of treatment is to develop a holistic treatment plan that provides a recovery that allows the patient to live a full life as they manage the symptoms and decrease risk of relapse.

6. Problems related to abuse of chemical substances can occur acutely (eg, respiratory arrest from using heroin) or after some length of time (eg, dependence or withdrawal from continued use of an opioid). The treatment approach is distinctly different depending on the chronicity of the problem.
7. Deaths attributed to counterfeit opioid or benzodiazepine pills that include illicitly manufactured fentanyl have drastically increased during recent years. Additionally, reports of heroin, cocaine, and other products tainted with fentanyl and related analogues have contributed to the increase in overdoses.
8. Opioid use disorder (OUD) is a chronic often relapsing condition. Viewing OUD as a disorder, providing medication-assisted therapy, patient education, and support has been shown to decrease the risk of accidental overdose or full relapse into opioid use.
9. Behavioral therapy should not be required as a condition for receiving OUD medication unless required through an opioid-treatment program (OTP). The goal is to focus on the patient's individual treatment plan to identify what is best for the patient at the time of therapy and to introduce behavioral therapy if and when the patient is ready.
10. There are currently three Food and Drug Administration (FDA)-approved medications used in OUD including buprenorphine, methadone, and naltrexone. All three medications have demonstrated superiority at reducing illicit opioid use over no treatment. Pharmacotherapy in combination with psychosocial therapy has been found to be more effective than either treatment alone.
11. Naloxone is a mu-opioid receptor antagonist that can be used in the reversal of an opioid overdose. There are multiple routes through which naloxone can be administered, and naloxone is available without a prescription in many states. Pharmacists can play an important role in educating patients on the importance of naloxone use in an opioid overdose situation.
12. Stimulants including cocaine, methamphetamines, and newer derivatives continue to pose a significant issue to the population and healthcare providers. Treatment of acute intoxication from these agents centers on supporting vital functions, while treatment for chronic use or abuse is less well described.
13. Acute intoxication with novel psychoactive substances has a wide variety of psychoactive effects and adverse outcomes, while chronic effects are now

only starting to be recognized with increased investigation.

14. An ever-increasing number of illicit psychoactive substances and drug classes are being used and abused. These classes include synthetic cannabinoids, synthetic amphetamines, and other highly synthetic molecules.

15. Expanded legalization of marijuana by individual states has brought an increase in chronic abuse. Emerging evidence supports the notion that abuse and chronic use is associated with a syndrome of effects now known as cannabinoid use disorder. Treatment of cannabinoid use disorder is in its infancy, but focused efforts may lead to breakthroughs in management in coming years.

Preclass Engaged Learning Activity

Opioids

Watch the video entitled "Opioid Overdose-Administration of Naloxone" by NIH Pain Consortium Centers of Excellence in Pain Education at Saint Louis University Edwardsville. This is a 3-minute video that provides an overview of the three FDA-approved naloxone delivery methods for the treatment of opioid overdose.

https://tinyurl.com/slvh6fx

Marijuana

Complete an Internet search to complete four tasks:

1. Determine which states have approved use of marijuana for medical purposes and which states have legalized the recreational use of marijuana.
2. Choose one state which allows medical marijuana.
3. For that chosen state, determine if that state's Board of Pharmacy has issued a statement or policy about medical marijuana.
4. Search the selected state's pharmacy laws and explain how pharmacists in that state are affected by this legislation.

INTRODUCTION

The book of *Ecclesiastes* wisely reminds us that "[W]hat has been will be again, what has been done will be done again; there is nothing new under the sun."[1] It is doubtful that the author of these sage words was referring to the repeating cycle of substance abuse, but when it comes to this subject there rarely *is* anything new under the sun, and this metaphor aptly applies. Psychoactive drug use dates back to prehistoric times and the Neolithic era (8,500-4,000 BC) where the earliest human use of psychoactive substances consisted almost exclusively of plants and fruits whose mood-altering qualities were accidentally discovered but subsequently deliberately grown.[2] Ancient civilizations (4,000 BC- AD 400) such as the Sumerians, Egyptians, Indians, Chinese, and South Americans used opium, alcohol, cannabis, peyote, psychedelic mushrooms, and coca leaves. The Middle Ages (400-1,400) saw the use of psychoactive plants, such as belladonna and psilocybin mushroom, used by witches and shamans for healing and spiritual purposes.[2] Distilled alcohol, coffee, tea, and opium spread along the trade routes.[2] Almost 5,000 years ago at the Temple of Imhotep, a center for treating mental illness, opium was used in an attempt to cure the mentally ill by inducing visions, performing rituals, and praying to the gods.[2] Evidence of the inhalation of cannabis smoke can be found in the 3rd millennium BC, as indicated by charred cannabis seeds found in a ritual fire at an ancient burial site in present-day Romania.[3]

Thousands of years later, nearly every one of these drugs is still used today in one form or another for their mind-altering effects. For any textbook to remain relevant, it must give emphasis to *current* information in any given content area. This means that space previously budgeted to one subject must give way to more recent trends. For example, if this chapter was written in the late 1960s, great attention would be given to the use and abuse of lysergic acid diethylamide (LSD).[4] In the mid- to late-1970s great attention would be given to the abuse of methaqualone (Quaalude).[5] γ-Hydroxybutyric acid (GHB) made a sudden and dramatic appearance on the scene in the 1990s, but its use has lessened in the past years.[6] The current epidemic of prescription drug abuse has skyrocketed its way into prominence with synthetic opioids, primarily illicitly manufactured fentanyl (IMF), leading to unprecedented overdose deaths across the United States and changing future generations of families forever.[7]

By no means does this suggest that these above-mentioned drugs have disappeared, but instead many have taken a back seat to other, more commonly encountered or abused drugs. For this reason, this rewrite of the present chapter and the one to follow could leave out some of the information from previous editions. The interested reader should consult prior editions of this textbook for

information about these substances.

EPIDEMIOLOGY

Illicit drug use, including the misuse of prescription medications, affects the health and well-being of millions of Americans. Cardiovascular disease, stroke, cancer, lung disease, hepatitis, and infection with the human immunodeficiency virus (HIV) can all be affected by drug use. Some of these effects occur when drugs are used at high doses or after prolonged use. However, other adverse effects can occur after only one or a few occasions of use. Addressing the impact of substance use alone is estimated to cost Americans more than $740 billion each year.[8]

National Survey on Drug Use and Health

The National Survey on Drug Use and Health (NSDUH)[9] is the primary source of statistical information on the recreational use of substances by the US population. Conducted by the federal government since 1971, the survey collects data from a representative sample of the population at their place of residence. The NSDUH obtains information on nine categories of substances: marijuana (including hashish), cocaine (including crack), heroin, hallucinogens, and inhalants, as well as the nonmedical use of prescription-type pain relievers, tranquilizers, stimulants, and sedatives referred to as “psychotherapeutics.”[9]

In 2017, an estimated 30.5 million Americans aged 12 or older were current recreational drug users, meaning that they had used a substance recreationally during the month prior to the survey interview. This corresponds to about one in nine Americans (11.2%). The most commonly used substance in the past month was marijuana, which was reported by 26 million people aged 12 or older. An estimated 3.2 million people endorsed nonmedical use of prescription pain relievers. Sixty-two percent of respondents reported misuse of prescription pain relievers to relieve physical pain and 53.1% of the responders reported obtaining these pain relievers from a friend or a relative.[9] The use of many types of other illicit drugs have not increased in recent years. However, the percentage of people aged 12 or older in 2017 who were current heroin users was higher than the percentages in most years from 2002 to 2015, but noted to be similar to percentages recorded in 2016.[9] Approximately 19.7 million people aged 12 or older in 2017 had a Substance Use Disorder (SUD) in the past year, including 14.5 million people with an alcohol use disorder, 7.5 million with an illicit drug

use disorder (marijuana 4.1 million people; prescription pain relievers 1.7 million people), and 2.3 million who had both an alcohol use and an illicit drug use disorder.[9]

Monitoring the Future Study

Every year the Institute for Social Research at the University of Michigan conducts its Monitoring the Future Study (MTFS), supported under a series of research grants from the National Institute on Drug Abuse.[10] A main purpose of this research is to study changes in the beliefs, attitudes, and behavior of young people in the United States that requires frequent reassessment to identify the rapidly changing patterns. The 2017 MTFS encompassed about 43,000 8th-, 10th-, and 12th-grade students in 360 secondary schools nationwide.[10] In the 2017 report, many illicit drugs have remained fairly stable in regards to annual prevalence of use. A few drugs did demonstrate some decline in use including synthetic marijuana, bath salts, a few specific oral named opioids: Vicodin and OxyContin, and a named stimulant: Ritalin.[10] The data on marijuana demonstrated an increase in use when the data from all three grades were combined. Eighth graders also reported increased use of inhalants which was a change from previous years. In 2017, use of inhalants increased to 4.7%, up 0.9 percentage points after a full decade of declining use. Further monitoring of these usage patterns will need to continue over the next few years.[10]

Economic Impact of Substance Abuse

Substance abuse and addiction have an enormous impact on the American economy. The annual cost of prescription drug abuse alone in 2013 was estimated at 78.5 billion, of which over 30% was attributed to an increase in healthcare and substance abuse treatment costs.[11] Other costs in this estimate include criminal justice and lost productivity costs. Another consequence to consider is the devastating impact on family's quality of life as well as pain and suffering when losing a loved one to an overdose which is immeasurable and cannot be included in this type of estimate.[11]

ETIOLOGY

Overall, the true etiology behind substance use disorders (SUD) is still unknown, as there is no way to predict why some individuals exposed to the substances

develop a SUD, while others may not. In general, it is felt that there needs to be a triad of the right patient, with the right genetic risk factors, being exposed to the right substances in order for a SUD to occur.

PATHOPHYSIOLOGY

Opiates and Opioids

Between 1999 and 2016, the number of drug overdose deaths in the United States more than tripled,[12] and the CDC now estimates each day at least 115 people in the United States die from an opioid overdose.[13] In many drug overdose deaths multiple drugs are involved that leads to difficulty in data collection and reporting. However, the CDC has reported over the years of 1999 to 2016, the United States has seen three different waves of opioid overdose deaths. The first wave started in 1999 that included prescription opioids including natural opioids, semisynthetic opioids, and methadone. This first wave continued to rise as the second wave began in 2010 that demonstrated a substantial increase in heroin overdoses. In 2013, a third wave started in the United States that included a significant rise in overdoses involving synthetic opioids, most of which included illicitly manufactured fentanyl (IMF).[14] Importantly, the CDC data continued to demonstrate the age-adjusted rate of overdose deaths that has increased significantly. It is currently believed overdose death rates have been driven by the synthetic opioids, which were believed to be directly related to IMF, since numbers have doubled between 2015 and 2016. Overdoses from prescription opioids and heroin also continue to increase by 10.6% and 19.5%, respectively.[15]

Opioid prescribing in the United States steadily increased from 2006 through 2012 peaking at 255 million prescriptions dispensed in 2012. This included a prescribing rate of 81.3 prescriptions per 100 persons. Since 2012, the opioid prescribing rate per 100 persons has continued a downward trend with the most recent 2017 data reporting 58.7 prescriptions per 100 persons.[16] Although opioid prescribing has trended downward, the nonmedical use of opioid analgesics has continued to be problematic. The 2017 National Survey on Drug Use and Health rated misuse of prescription pain relievers second in regard to estimates of illicit drug use data.[9] A variety of changes were put into place to improve oversight and education for opioid prescribing and dispensing to raise awareness of the risks associated with opioids and continue to decrease the availability of opioids for nonmedical use. This has progressed over the years

and will continue to expand in hopes of improving the safe use and appropriate prescribing of opioid analgesics.

One such example of oversight has been the newly implemented prescription drug monitoring programs (PDMPs) that are currently fully operational in 49 of 50 states.[17] The PDMPs are electronic systems used for the monitoring of controlled substances and drugs of concern dispensed in the state or dispensed to an address in the state. They require pharmacies to report specified medications to the system on a routine scheduled basis that provides all users with medication data for a specified time period. This is intended to help healthcare practitioners and law enforcement to detect and prevent the diversion and abuse of prescription drugs.[18] Forty-one states currently require prescribers to check the PDMP prior to prescribing controlled substances, although the requirements for checking the PDMP vary and exemptions are allowed in some states.[17]

An additional measure aimed at improving the safe prescribing of opioids, included the CDC's publication of a Guideline for Prescribing Opioids for Chronic Pain in 2016.[19] This document was specifically intended for use by primary care physicians treating patients with chronic nonmalignant pain. The guidelines,[19] were labeled as voluntary; however, many states have utilized them to adopt legislation to guide opioid prescribing limitations. It is important to note these guidelines were not intended for patients being treated for active cancer, palliative care, or end-of-life care issues and are promoted as (1) improving safety and effectiveness of long-term opioid therapy and pain treatment, (2) reducing the risks associated with opioid therapy, and (3) improving communication. The guidelines provide 12 recommendations for prescribing opioids for chronic pain that are broken into three categories including: (1) determining when to initiate or continue opioids for chronic pain, (2) opioid selection, dosage, duration, follow-up, and discontinuation, (3) assessing risk and addressing harms of opioid use (**Table 82-1**).[19]

TABLE 82-1 Center for Disease Control and Prevention (CDC) Guideline for Prescribing Opioids for Chronic Pain: 12 Recommendations

Determine when to Initiate or Continue Opioids

- CDC Recommendation 1
  - Nonpharmacologic and nonopioid therapies are preferred
  - Prior to using opioids:
    - Benefits vs risks should be weighed carefully
    - Nonpharmacological and nonopioid therapy should continue if opioid therapy is part of therapy plan
- CDC Recommendation 2
  - Treatment goals for both pain and function should be established prior to opioid initiation with an exit strategy in place if the treatment option is unsafe or ineffective
- CDC Recommendation 3
  - Opioid risks and realistic benefits should be discussed along with prescriber and patients responsibilities prior to initiating opioid therapy

Opioid Selection, Dosage, Duration, Follow-up, and Discontinuation

- CDC Recommendation 4
  - When initiating opioids, utilize immediate-release opioid formulations for pain management instead of long-acting/extended-release formulations
- CDC Recommendation 5
  - Use lowest effective dose, be cautious, reassess risk vs benefits as patients dose >50 MME per day and avoid exceeding doses of 90 MME per day
  - If a patient exceeds 90 MME per day, justify decision on why patient is on higher dosing of opioid
- CDC Recommendation 6
  - When prescribing for acute pain, use the lowest effective dose of immediate-release opioids for the shortest duration of time; 3 days normally is sufficient, 7 days rarely is needed
- CDC Recommendation 7
  - Reassess within 1-4 weeks after initiating opioid therapy or escalating dose evaluating risk vs benefit.
  - Continual reassessment should occur no less than every 3 months
  - If risks outweigh benefit, initiate taper to lower dose or full discontinuation of opioid therapy

Assessing Risk and Addressing Harms of Opioid use

- CDC Recommendation 8
  - Continue to evaluate risk of opioid therapy initially and throughout treatment
  - Include risk mitigation strategies in practice
  - Offer naloxone when risk factors are identified
- CDC Recommendation 9
  - Review history of state PDMP data prior to starting opioid therapy, periodically during opioid therapy which can range from every prescription to every 3 months
- CDC Recommendation 10
  - Utilize urine drug testing prior to starting opioid therapy and monitor at least annually to screen for prescribed medications, other medications, or illicit substances
- CDC Recommendation 11
  - Avoid concurrent prescribing of opioids and benzodiazepines whenever possible
- CDC Recommendation 12
  - Offer or arrange medication assisted treatment with buprenorphine or methadone along with behavioral therapies to patients identified with opioid use disorder

Data from Reference 19.

Since the release of these guidelines, there has been controversy and implementation inconsistencies surrounding a number of the recommendations as many parties in the healthcare industry adopted these guidelines. Examples of inconsistencies include reports of applying guidelines for patients outside of primary care such as patients with cancer, sickle cell, or recent surgery, imposing inflexible opioid dosage and duration limits, and initiating opioid tapering and discontinuation without patient involvement or proper preparation for the taper.[20] The reader is directed to a summary of these challenges outlined by a consensus panel, authored by Kroenke et al.[20] In response to the concerns, the CDC has issued a clarification of many recommendations in this guideline, authored by Dowell et al. This editorial addresses many of the concerns highlighted by the consensus panel, reiterated the importance of implementing guidelines as they were intended, and stressed clinicians should individualize treatment for each patient. The CDC also highlighted the need for ongoing evaluation and study of the impacts associated with these guidelines, so it is important to check for updates in this rapidly changing area of practice.[21]

The FDA has also increasingly focused on safe opioid prescribing. In 2018, the agency issued its Opioid Analgesic Risk Evaluation and Mitigation strategy (REMS) Education Blueprint for Health Care Providers involved in the Treatment and Monitoring of Patients with Pain. This REMS blueprint now includes the new Opioid Analgesic REMS that has training on both extended-release (ER)/long-acting (LA) opioids and immediate-release (IR) opioids used in the outpatient setting which are not already covered in another REMS program. Additionally, this blueprint provides an outline of core components of acute and chronic pain management and concepts associated with safe prescribing for opioid analgesics that are applicable to all healthcare providers who work with patients that suffer from chronic pain.[22] Medical schools have also been working to expand the training and ongoing professional development needs for medical students and physicians on pain assessment, treatment, and substance use disorders. The Association of American Medical Colleges continue to work on developing new curriculum options for improving training in assessment methods and responsible opioid prescribing.[23]

Another action taken to help with misuse of opioids includes expanded approval of abuse deterrent opioids. Abuse deterrent formulations are designed to deter abuse of certain products, by making it more difficult to administer the product via intravenous injection, nasal snorting, or chewing. Unfortunately, despite preliminary enthusiasm, evidence does not support the conclusion that

abuse deterrent formulations substantially reduce opioid overdose and addiction numbers.[24]

In 2018, the Substance Use Disorder Prevention That Promotes Opioid Recovery and Treatment (SUPPORT) for Patient and Communities Act was signed that focuses on prevention, treatment, recovery, and enforcement to help in the fight against the opioid epidemic. This bill has many policy changes but major policy changes include[25]:

- Lifting restrictions on medications for opioid use disorder, and expanding prescribing rights of these agents to select physician extenders.
- Direct CMS to look for further options in providing telehealth services for substance use disorders for Medicaid and Medicare Patients.
- Expand existing programs allowing more first responders to carry and use naloxone.
- Allow more federal agencies to pursue expanded research projects related to pain and addiction.
- Adjust Medicare and Medicaid processes to limit overprescribing of opioid prescriptions and allow expansion of addiction treatment including adjusting restrictions to improve access to care for addiction treatment.
- Authorize SAMHSA grant programs for “Comprehensive Opioid Recovery Centers” for communities.
- Improve initiatives for education and awareness for healthcare providers on proper pain treatment.
- Improve coordination between federal agencies to test, detect, and stop illicit drugs at the border.
- Increase penalties for drug manufacturers and distributers related to overprescribing of opioids.
- Create an incentive programs for students to pursue a career in the addiction treatment field.

CLINICAL PRESENTATION

The most current *DSM-5*[26] has replaced the previous terminology, substance abuse and substance dependence, with one single term, substance use disorder. Substance use disorder is defined as a “problematic pattern of substance use leading to clinically significant impairment or distress as manifested by at least

two of eleven criteria occurring in the preceding 12-month period." Table 82-2 outlines these criteria.

TABLE 82-2 Eleven Criteria for Substance Use Disorder as Defined by *DSM-5*

Specific Category	Specific Behavior
Impaired Control	1. Substance is often taken in larger amounts or over a longer period of time than intended
Impaired Control	2. Persistent desire or continued unsuccessful efforts to cut down or control substance use
Impaired Control	3. Considerable amount of time is spent obtaining substance, using substance or recovering from use of substance
Impaired Control	4. Craving or strong desire to use substance
Social Impairment	5. Recurrent use of substance is resulting in failure to fulfill major obligations at work, home, or school
Social Impairment	6. Continue to use substance despite persistent social or interpersonal problems
Social Impairment	7. Reducing or missing social, occupation, or recreational events due to substance use
Risky Use	8. Recurrent substance use in situations with increasing risk of physical harm
Risky Use	9. Continued use of substance despite knowledge of persistent or recurrent physical or psychological harm that was caused or worsened by the substance
Pharmacological Indicators	10. Tolerance as experienced by either: a. Need for increased amounts of the substance to achieve intoxication or desired result b. A noticeably decreased effect with continued use of the same amount of substance
Pharmacological Indicators	11. Withdrawal as experienced by either: a. Standard symptoms of withdrawal as defined by specific substance b. Use of a substance or a similar substance to relieve or avoid withdrawal symptoms

Data from Reference 26.

4 The *DSM-5* has established nine types of substance-related disorders including alcohol, cannabis, hallucinogens, inhalants, opioids,

sedatives/hypnotics/anxiolytics, stimulants (ie, cocaine, amphetamine substances), tobacco, and caffeine.[26] Although these substances are addressed individually, the diagnosis is based on a set of behaviors related to that substance which fall into four categories including impaired control, social impairment, risky use, and pharmacological indicators. In Table 82-2, substance use disorders have been found to occur in a broad range of severity from mild (2-3 symptoms) to moderate (4-5 symptoms) to severe (6 or more symptoms).[26]

5 This terminology change removes the negative perception associated with the "abuse" terminology, and focuses on treating patients who are suffering from a disorder. Additionally, it educates clinicians to remember that substance use disorders are chronic illnesses for which there are no cures. The focus of treatment is to develop a holistic treatment plan which provides a recovery that allows the patient to live a full life as they manage the symptoms and decrease risk of relapse.[27] However, a large collection of terms are still commonly used, many without precise meaning. This lack of universal agreement on language hampers effective communication among professionals leading to difficulties in formulating public policy and administering third-party reimbursement programs. At this time, the American Society of Addiction Medicine (ASAM) has both a long and short definition of addiction posted on their website.[28] The short definition reads:

"Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors. Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death."[28]

CLINICAL PRESENTATION

Acute Opioid Withdrawal and Intoxication

General

- Onset of the acute phase of withdrawal ranges from 8 to 24 hours after stopping short-acting opioids to 36 to 72 hours after stopping long-acting opioids. The duration of withdrawal ranges from 7 to 10 days for short-acting opioids, up to 14 days for long-acting opioids, but can last longer depending on the opioid.
- The presence of delirium should raise the question of concurrent withdrawal from another drug, such as alcohol, or another cause of delirium possibly secondary to drug use.

Symptoms

- During withdrawal, patients can experience piloerection, insomnia, muscle aches, restlessness, abdominal cramps, and hot flashes/chills. Some patients experience serious withdrawal reactions. Psychological distress, changes in mood, and suicide are possible during withdrawal.
- Symptoms can be scored on the Clinical Opiate Withdrawal Symptoms (COWS) assessment tool to assess severity of opioid withdrawal.
- While intoxicated, patients can experience euphoria, dysphoria, apathy, sedation, or attention impairment.

Signs

- Tremor, nausea/vomiting, diarrhea, irritability, rhinorrhea, yawning, gooseflesh, perspiration and may be observed during withdrawal.
- Pin-point pupils, decreased breathing, pulmonary edema, loss of consciousness, and death may occur with opioid intoxication.

Laboratory Tests

- Comprehensive metabolic panel to monitor serum electrolyte concentrations in the setting of significant vomiting or diarrhea, liver function tests if using buprenorphine.

Other Diagnostic Tests

- Arterial blood gases, pulse oximetry, and capnography are useful to assess respiratory depression in opioid intoxication.

Data from References 31 and 32.

Additionally, two other definitions continue to be commonly used which were developed in 2003 by the Liaison Committee on Pain and Addiction, a collaborative effort of the American Academy of Pain Medicine (AAPM), the American Pain Society (APS), and the American Society of Addiction Medicine (ASAM).[29] These terms are directly related to the use of medications for the treatment of pain consistent with current understanding of relevant neurobiology, pharmacology, and appropriate clinical practice.[29]

> *Physical dependence* is a state of adaptation that is manifested by a drug class–specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.[29]
>
> *Tolerance* is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.[26,29]

Acute Versus Chronic Problems

6 Misuse of chemical substances causes problems of two types: those that occur acutely and those that arise after continued use of a drug. Acute problems are usually predictable, given the pharmacology of the drug. Chronic abuse of chemical substances can cause a wide array of physical, and psychiatric morbidities. The substance-induced disorders discussed here mainly include intoxication and withdrawal.

The essential feature of substance dependence is the continued use of the substance despite adverse substance-related problems. The criteria for substance dependence are the same for each of the drugs or drug classes, varying only to fit the unique pharmacologic properties of each drug. Patients who take prescribed drugs for appropriate medical indications and in correct doses may still show tolerance, physical dependence, and withdrawal symptoms if the drug is stopped abruptly rather than being tapered. Tolerance and physical dependence are inevitable consequences of chronic treatment with opioids and certain other drugs, but by themselves, tolerance and physical dependence do not imply "addiction." According to *DSM-5*,[26] the overall category of substance-induced disorders includes intoxication, withdrawal, and other substance/medication-induced mental disorders (eg, substance-induced psychotic disorder, substance-induced depressive disorder).

The word *addiction* is not used in this classification scheme, although it is in

common usage in many countries to describe severe problems related to compulsive and habitual use of substances. The more neutral term *SUD* is used to describe the wide range of disorders, from a mild form to a severe state of chronically relapsing, compulsive drug taking. Some clinicians will choose to use the word addiction to describe more extreme presentations, but the word is omitted from the official *DSM-5* SUD diagnostic terminology because of its uncertain definition and its potentially negative connotation.[26]

Intoxication refers to the development of a substance-specific physiological syndrome after exposure, as well as maladaptive behavior caused by the effect of the substance on the central nervous system (CNS). Examples include belligerence, mood lability, impaired judgment, and impaired social or occupational functioning. Evidence for recent intake of the substance can be obtained from the history, physical examination, or laboratory studies. The most common changes involve disturbances in perception, wakefulness, attention, thinking, judgment, motor activity, and interpersonal behavior.[26]

As with most illnesses, the course and prognosis of the disorders of substance use and dependence are variable. Getting patients who are dependent to stop substance abuse can be quite difficult, and many patients return to substance abuse even after treatment. It has been reported that as many as 40% to 60% of treated, substance-dependent patients will relapse within one year.[30] However, many patients can achieve recovery with proper treatment and continued care in counseling programs or 12-step programs such as Alcoholics Anonymous or Narcotics Anonymous. Substance use disorder can be viewed as a chronic illness that can be controlled successfully with treatment but cannot be cured and is associated with a high relapse rate. Without treatment, the course can progress to life-threatening severity, resulting from the effects of the drug, drug contaminants, or medical complications of use.

Opioid Withdrawal

The acute phase of opioid withdrawal syndrome in some cases is similar to a severe case of influenza. Generally, it is not life-threatening, unless there is a concurrent life-threatening medical condition or in extreme cases. However, the severity of the opioid withdrawal varies with each individual and can lead to psychological distress and increased risk of suicide. Opioid withdrawal can result in uncontrolled pain and also miscarriage or premature delivery in pregnant patients.[32] Characteristic signs and symptoms of opioid withdrawal include pupillary dilation, lacrimation, rhinorrhea, piloerection, “gooseflesh,”

yawning, sneezing, anorexia, nausea, vomiting, and diarrhea. Persistent vomiting and diarrhea can lead to dehydration and related complications. Seizures do not occur in most situations. Many validated clinical opiate-withdrawal scales are available to help quantify the withdrawal symptoms including the Clinical Opiate Withdrawal Scale (COWS).[32] The onset and duration of withdrawal symptoms as well as the time of peak occurrence depends on the half-life of the drug involved. Typically, short-acting opioid withdrawal symptoms begin within 8 to 24 hours of the last dose and can last for up to 7 to 10 days. For long-acting opioids such as methadone, symptoms can begin as early as 36 hours following the last dose but takes up to 72 hours to peak with gradual reduction of symptoms over 2 weeks or longer.[31,32] The post-acute phase of withdrawal can last for weeks, months or even longer leading to symptoms such as opioid craving and a negative affect including symptoms such as fear and irritablity.[31,32] It is also important to remember patients who have withdrawn from opioids will have a reduced opioid tolerance that could increase the risk of opioid overdose.[31,32]

Methadone

In 2009, more than 30% of prescription opioid deaths involved methadone, even though only 2% of painkiller prescriptions were for this medication. Six times as many people died of methadone-associated overdoses in 2009 than a decade before.[33] The FDA released warnings regarding methadone in 2006 and over time the numbers of reported deaths gradually decreased. In 2014, data revealed the lowest number of deaths reported since 2003.[34] However, even though the reported number of deaths are decreasing, methadone still accounted for one in four prescription opioid deaths despite only accounting for 1% of all opioids prescribed in 2014.[35]

It is important for prescribers to remember that methadone has pharmacologic properties that are unique among the opioids. A lack of knowledge about methadone among practitioners and patients has been identified as a factor contributing to the deaths associated with methadone. Methadone's elimination half-life (15-60 hours; some reports as long as 120 hours) is longer than its duration of analgesic action (4-8 hours) and its full analgesic effect is usually not achieved for 3 to 5 days.[36] Accordingly, the most recent guidelines suggest that doses should not be increased more frequently than every 5 to 7 days.[36] Additionally, deaths have been reported during conversion from chronic, high-dose treatment with other opioid agonists to methadone, as it has a wide

variability in equianalgesic dosing compared to other opioids. It is critical to understand the pharmacokinetics of methadone when converting patients between other opioids and methadone. Vigilance is necessary during treatment initiation, during conversion between opioids, and during dose adjustments. Additionally, drugs administered concomitantly with methadone should be evaluated for interaction potential. Methadone has also been associated with prolongation of the QTc interval in the most severe cases leading to torsades de pointes. For this reason, methadone guidelines promote electrocardiogram (ECG) monitoring prior to initiation and after significant dose adjustments with methadone.[36]

Heroin

Heroin, also known as diacetylmorphine, is a serious threat to the United States and its use has increased since 2007. Heroin is used by many, and is exceedingly available in large quantities causing a significant number of overdose deaths. In 2017, an estimated 15,958 Americans died from heroin-related overdoses and The National Institutes of Health reports from 2002 to 2017 there was a 7.6-fold increase in the total number of deaths from heroin.[37] The most common first-time users include 18- to 25-year old adults. The National Drug Early Warning System's (NDEWS) Sentinel Community Site Advance Report 2016 reported heroin indicators were climbing throughout the United States, with many sites reaching all-time highs peaks in heroin-related deaths.[38] The main factors associated with the increase in heroin use are increased availability, low cost, and increased purity.[18,39] The DEA expects that high-purity heroin, commonly referred to as white powder heroin, will continue to be available in the United States. Additionally, heroin is now commonly laced or adulterated with fentanyl and related derivatives that are 50 to 100 times more potent than heroin and are increasing overdose deaths. The CDC reported that rates of deaths increased sharply in 2013 in locations where white powder heroin and fentanyl-laced heroin products were found.[7] There are conflicting opinions about whether policy changes implemented to reduce nonmedical prescription opioid abuse had unintended consequences by increasing the use of heroin in the United States.[37] However, there is some evidence suggesting that opioid prescribing policies could help decrease heroin overdose deaths.[40] Harm reduction is an effort focused on educating substance users on safer drug use strategies to possibly reduce the negative consequences associated with drug use. Examples of advice include recommendations on the safest routes of administration of a particular drug, safe injection techniques, specific-drug side effects and management, and

tips for withdrawal and overdose management. An example of an educational handout produced by The Harm Reduction Coalition can be found at: www.harmreduction.org.

Heroin is hydrolyzed to 6-acetyl morphine and subsequently morphine. It acts as an agonist at opioid receptors including the mu, kappa, and delta receptors. Administration can occur via multiple routes including intranasal, intravenous, subcutaneous, intramuscular routes, or smoking. The oral route is not a preferred due to first pass metabolism to morphine leading to less rapid onset of action.[41] A new resurgent method of heroin use known as "chasing the dragon" (CTD) has resurfaced from years ago.[41] Users place heroin on aluminum foil which is then heated with an open flame to create a vapor that is inhaled through a tube. This administration method appeals to users as an easier route, resulting in an intensive "high" compared to "snorting" heroin. While there might be less injection concerns (eg, infections, foreign body reactions, and immediate overdose) with this method of delivery, there are other concerns such as increased risk of stroke, seizures, obstructive hydrocephalus, and leukoencephalopathy.[42]

Heroin is very lipophilic and crosses the blood brain barrier (BBB) quickly. This leads to very rapid absorption and arrival to the site of action; 5 to 10 minutes when administered subcutaneously, 3 to 5 minutes intranasally and intramuscularly, and <1 minute when administered intravenously.[41] The ultimate duration of effect from heroin is dependent on the user's history with the drug with a half-life of approximately 8 hours initially that varies depending on how the drug is administered. As tolerance develops, the half-life decreases leading to earlier symptoms of withdrawal, which include dilated pupils, hostility, sweating, vomiting, diarrhea, yawning, and piloerection. Users increase doses and rates of administration to avoid these withdrawal symptoms, which increases their risk of overdose. Symptoms of heroin use include sedation, decreased respiration, progression to apnea, cardiac arrest and death without medical treatment such as administration of naloxone.[43] Testing for heroin in urine, blood, or other biological samples is difficult due to the very short half-life of intact heroin (2-6 minutes). Unfortunately, the next metabolite, 6-acetylmorphine (6-AM) is only present in urine and blood for approximately 6 to 25 minutes before it is hydrolyzed to morphine and other metabolites. As morphine and other metabolites can be positive on a urine drug screen after heroin use as well as after use of certain prescription opioids, urine drug screens are often misinterpreted and require confirmatory secondary testing and a thorough clinical evaluation.[43,44]

Fentanyl

Fentanyl, a synthetic short-acting opioid analgesic, is 50 to 100 times more potent than morphine and is approved for managing acute or chronic pain, as well as pain associated with advanced cancer. Although pharmaceutical fentanyl can be diverted for misuse, most cases of fentanyl-related morbidity and mortality have been linked to illicitly manufactured fentanyl and fentanyl analogs, collectively referred to as illicitly manufactured fentanyl (IMF). There have been almost yearly CDC public health advisories starting in 2015, regarding fentanyl including a public health advisory regarding increased fentanyl-related overdose deaths, a warning that fentanyl was found in counterfeit pills in the United States in 2016, and a report regarding the rise in fentanyl analogs contributing to opioid overdose deaths in 2018.[7]

7 Generally, the IMF products are sold via illicit drug markets, with individuals seeking them out for their heroin-like effect. Additionally these illegal product are often mixed with heroin and cocaine and marketed as an oral opioid or benzodiazepine.[18] Deaths from counterfeit opioids and benzodiazepine pills laced with fentanyl have been reported and are believed to be contributing to the increased overdose rates. A CDC analysis from 31 states and Washington DC from 2015 to 2016 showed that overdose death rates increased by 21.5%, and the death rates from synthetic opioids (presumed to be IMF) more than doubled. The death rates for heroin, cocaine, and psychostimulants also increased by 19.5%, 52.4%, and 33.3% respectively, and the CDC attributes a portion of rate increases to the presence of IMF in the respective products.[45]

Carfentanil, a Schedule II controlled substance, is the most potent legally marketed fentanyl analog in the United States which is 10,000 times more potent than morphine. It was originally developed as a large animal tranquilizer; however, carfentanil submissions to the National Forensic Laboratory Information System (NFLIS) almost doubled from 2016 to 2017. Other analogues of fentanyl currently include Furanylfentanyl, Acrylfentanyl, 3-methylfentanyl, and U-47700 that are all Schedule I controlled substances. Due to the toxic nature of these IMF products and the high overdose risk with small amounts of these products, the CDC has suggested specific actions be taken, which are delineated on the CDC website: https://emergency.cdc.gov/han/han00413.asp.

Dextromethorphan

Intoxication from the OTC cough suppressant, dextromethorphan[46] occurs from

consuming large doses of liquid cough syrup that is known as “robodosing” or “robotripping” and those who use the cough syrup to get high are sometimes called “syrup heads.”[46] Additionally, “skittles” is a term used to describe abuse of other cough and cold remedies because they look similar to the popular candy. As dextromethorphan is an opioid analog, large doses can create a depressant and sometimes profound hallucinogenic effect, and since it is available OTC it is easily procured by adolescents.[46] The pharmacologic effects of dextromethorphan abuse include hyperexcitability, lethargy, ataxia, slurred speech, diaphoresis, hypertension, nystagmus, and mydriasis. When taken at much higher doses, in addition to its CNS depressant effects,[47] dextromethorphan acts as a dissociative anesthetic, similar to phencyclidine (PCP, “angel dust”) and ketamine (“Special K”). It is these effects, in particular, that are sought by those who use the drug to get high. The recommended treatment for acute overdoses of dextromethorphan is naloxone. Although reports of its efficacy are mixed, it may be helpful in reversing the CNS depressant and neurologic effects.[47]

Loperamide

Loperamide abuse has recently become another alarming and dangerous example of OTC drug abuse. Pharmacologically this drug acts as an intestinal mu-opioid agonist that works locally as a short-term treatment for the symptoms of diarrhea. When used in this fashion, at normal recommended doses, it does not cross the blood brain barrier and will not have any CNS effects.[48] When taken at high doses or if taken with concomitant medications such as corticosteroids, verapamil, or methadone, the serum loperamide levels increase through inhibition of the P-glycoprotein efflux transporter, resulting in CNS effects. Furthermore, loperamide levels can also be increased by taking cytochrome P450 3A4 and 2C8 inhibitors such as cimetidine or drinking grapefruit juice. Some reports indicate abusers are using high-dose loperamide to manage acute opioid withdrawal symptoms or to achieve the euphoric effects; however, side effects associated with supratherapeutic doses include possible cardiac arrhythmias including QTc interval prolongation, torsades de pointes, ventricular dysrhythmias, syncope, and cardiac arrest. Additionally, respiratory depression and central nervous system depression can also occur.[48] In 2018 the FDA released a notice indicating they were working with manufacturers to limit the quantity supplied and also utilizing blister packaging for OTC loperamide, as means to reduce its abuse.[49]

TREATMENT

Desired Outcomes

As with any use disorder the desired treatment options are reduction in dependency on the substance, reduction in withdrawal symptoms, and prevention of death from the substance.

General Approach to Treatment: Opioid Use Disorder

8 In particular, it is important to note that the treatment of opioid use disorder is a chronic, often relapsing condition that needs proper medical treatment and appropriate follow-up. Therefore, viewing OUD as a chronic disorder and providing medication for long term has been shown to decrease the risk of an accidental overdose or full relapse into opioid use. Continued patient education and support is vital to helping patients in continuing their set treatment goals.

Nonpharmacologic Therapy: Opioid Use Disorder

9 In addition to medications, the treatment of OUD may include behavioral therapy. In 2018, the Treatment Improvement Protocol (TIP 63) was issued by the Substance Abuse and Mental Health Services Administration (SAMHSA)[32] entitled “Medications for Opioid Use Disorder.” Discussion of additional information contained in TIP 63 will be provided below but for further details the reader should refer to the website for the full document.[32]

In regards to nonpharmacologic treatment, TIP 63 recommended that behavioral therapy should not be required as a condition for receiving OUD medication (unless required through OTP). Regardless, the main goal is to focus on individual treatment plans to identify what is best for the patient at the time of therapy and to introduce behavioral therapy if and when the patient is ready.[32]

Pharmacologic Therapy: Opioid Use Disorder

A variety of treatment regimens are used for patients during the acute opioid withdrawal phase. Initiating buprenorphine in the emergency room for patients who present with opioid withdrawal symptoms has become a treatment option. The reader is directed to Cisewski et al[50] for a detailed review outlining the

process for establishing this stepwise treatment practice.

Methadone has also been used as a long-acting opioid option to aid in treatment of withdrawal symptoms.[51] The use of clonidine, an alpha-2 agonist, has commonly been used to attenuate withdrawal symptoms such as anxiety, tachycardia, hypertension, chills, and piloerection. Patients must be monitored for side effects including hypotension, dizziness, and sedation following administration of clonidine.[31,51] Lofexidine, also an alpha-2 agonist, has been found to be more effective than placebo in managing withdrawal from methadone or heroin and has demonstrated a better safety profile compared to clonidine.[51,52] Replacement of fluids due to losses from perspiration, vomiting, and diarrhea is crucial during withdrawal and other patient-specific supportive care measures should be provided until the patient stabilizes.[31] Ongoing follow-up is important since post-acute withdrawal can continue for an extended period of time. This can increase risk of relapse and heighten the risk of overdose.[31,51]

10 Although opioid use disorder can range from mild to severe, it often requires continual care including patient centered care involving mental health services, medical services, counseling, and medication assisted therapy (MAT). The three FDA-approved medications used in OUD include methadone, buprenorphine, and naltrexone that work by blunting or blocking the effects of illicit opioids and reducing or eliminating the craving to use opioids. All three agents have demonstrated superiority over no treatment in reducing illicit opioid use,[32,53] and methadone and buprenorphine decrease the risk of overdose deaths.[32,54] All of these medications have unique characteristics that healthcare providers must be aware of, including difference in mechanism of action, routes of administration, and differences in side effects. It is also important to understand what phase of treatment each of these agents are used in, and the regulations associated with their use (**Table 82-3**).

TABLE 82-3 Differences Between Medication Assisted Therapy (MAT) Products

	Methadone	Extended-Release Injectable Naltrexone (XR-NTX)	Buprenorphine
Pharmacology in OUD	Full opioid agonist at mu-opioid receptor with long half-life to allow for once daily dosing for OUD	Antagonist at mu-opioid receptor *(note: does not provide analgesia and is not addictive)*	Partial agonist at mu-opioid receptor with long half-life (up to 36 hours via sublingual administration); blocks intoxicating effects of other opioids
Phase of treatment in OUD; Effect	Medically supervised withdrawal, maintenance; reduces or eliminates withdrawal symptoms and cravings to use opioids, blocks or blunts the effects of illicit opioids	Prevention of relapse to opioid dependence following medically supervised withdrawal; reduces or eliminates cravings to use opioids and blunts or blocks the effects of illicit opioids	Medically supervised withdrawal, maintenance; reduces or eliminates withdrawal symptoms and cravings to use opioids and blocks or blunts the effects of illicit opioids
Route of Administration used in MAT	Provided orally once daily: Commonly given as liquid concentrate in OTPs but current guidelines also allow solid oral-dosage forms as well.	IM extended-release (depot naltrexone) *(note: oral not as effective and use is not common in the treatment of OUD due to insufficient evidence of efficacy and poor medication adherence)*	Sublingual, buccal tablet, buccal film Other routes of administration available after meeting specific criteria: subdermal implant, subcutaneous extended-release injection
Restrictions for prescribing each product	CII; patient must meet Federal Opioid-Treatment Program standards; can be used in hospital settings for OUD treatment	Not a controlled substance but requires a prescription. All naltrexone products can be prescribed by general practitioners and in OUD treatment	CIII; requires waiver to prescribe outside of OTPs. Prescribers will receive separate DEA number with a "X" upon meeting requirements of DATA 2000. To confirm practitioner verification: https//www.samhsa.gov/bupe/lookup-form Implant: Prescribers must be certified in Probuphine REMS program to insert/remove implants Subcutaneous: Healthcare settings and pharmacies must be certified in the Sublocade REMS program and only dispense the medication directly to a provider for administration
Patients that are commonly considered for this type of therapy	Patients with OUD; physiologically dependent on opioids and meet federal OTP admission criteria	Patients with OUD; Patients who are abstinent from short-acting opioids for 7-10 days and long-acting opioids 10-14 days	Patients with OUD; physiologically dependent on opioids
Major side effects	Constipation, vomiting, dizziness, sedation, QTc prolongation, respiratory depression (risk is highest during initiation of methadone or dose titration and concurrent use of benzodiazepines or alcohol)	Injection site pain and tenderness, risk of injection site induration, toothache, LFT elevation, insomnia, nasopharyngitis	Constipation, vomiting, dizziness, sedation, insomnia, blurred vision, respiratory depression (highest risk with concurrent use of CNS depressants including benzodiazepines); sublingual buprenorphine/naloxone sublingual and buccal film: oral hypoesthesia, oral mucosal erythema, glossodynia

Data from References 32.

OUD, Opioid Use Disorder; CII, Schedule II Prescription; CIII, Schedule III Prescription; OTP, Opioid-Treatment Program; IM, Intramuscular; LFT, Liver Function Test; REMS, Risk Evaluation and Mitigation Strategies.

Methadone

Methadone is a mu-opioid agonist that suppresses withdrawal symptoms and controls the craving for opioids in maintenance therapy. Controlled trials have shown that methadone use in patients with OUD is superior to placebo and has demonstrated a reduction of mortality, incidence of HIV infection, and criminality.[32] Recommended once daily dosing of methadone on the first day of treatment for patients tolerant to opioids can range from 10 to 30 mg, depending on the patient's use pattern. The patient should be reassessed in 2 to 4 hours after this initial dose for signs of sedation or symptoms of withdrawal. Additional monitoring and/or treatment can continue if needed during the first day based on the initial response. Although rare, if the dose does exceed 30 mg on the first day of treatment, monitoring for over-sedation should occur for multiple days.[32] In patients who are older than 60 years of age, have identified drug–drug interactions, or have other medical conditions that can lead to increased risk of hypoxia, it is recommended to limit the initial maximum methadone daily dosing to 10 to 20 mg. Dosing ranges for stabilization that eliminate withdrawal and craving, block euphoric effects of illicit opioids, and not normally associated with sedation are commonly between 60 and 120 mg administered once a day for most patients but this can vary considerably.[32,55] Titrating the dose of methadone must be individualized and based on a full assessment of the patient. Due to the long half-life of methadone, which requires an extended time to reach steady state, daily dose adjustments can result in increased risk of over-sedation and possible increased risk of toxicity and should not occur. It is recommended that dose adjustments of 5 to 10 mg should occur gradually, each adjustment should occur no sooner than every 4 to 7 days based on clinical response to allow methadone to reach steady state and account for the other numerous factors that can impact serum levels.[32,36,56] Concerns with methadone include the numerous drug interactions due to the variety of concomitant use of cytochrome P450 (CYP450) inducers that can reduce methadone levels. Concomitant use of alcohol or benzodiazepines can lead to overdose and use should be assessed. Additionally, the risk of QT prolongation is increased with the use of methadone, especially when given with other drugs that also prolong the QT interval. The use of methadone for the treatment of OUD is only approved through the OTP, controlled by the DEA and SAMHSA. However, methadone for the treatment of OUD may be provided to patients during a hospital admission for treatment of other health conditions. Patients who are treated in the OTP most often receive methadone on a daily basis with daily

onsite administration; however, some patients are allowed to take doses at home if they meet a list of criteria set by federal regulations.[57]

Naltrexone

Naltrexone is a mu-opioid antagonist that is available for OUD in both an oral tablet and an extended-release injectable formulation.[58,59] It is important to note that while the oral tablet has not been found to be any more effective than placebo in a meta-analysis of 13 studies,[60] naltrexone reduces illicit opioid use and retained patients in treatment compared to placebo.[61]

To use the oral formulation, patients need to have confirmation of being opioid free for 7 to 10 days by passing a urine drug screen or naloxone challenge. The initial dose given is 25 mg once daily and if the patient does not demonstrate any symptoms of withdrawal, this can be increased to the target dose of 50 mg once daily.[58] Extended-release injectable naltrexone (Vivitrol ®) is FDA-approved for use following opioid detoxification to help prevent relapse.[59] It is important to review all medication-associated side effects with patients, which also needs to include education on the length of time the naltrexone is active and their vulnerability to opioid effects at the end of a dosing interval, after a missed dose, or if the treatment is discontinued. Patients should be informed to contact their provider if any excessive swelling, bruising, or pruritus occurs at the injection site since this could be a sign of improper subcutaneous injection and may require medical treatment.[32] The Risk Evaluation and Mitigation Strategies (REMS) information highlights the risk of severe injection site reactions and provides education for healthcare providers including proper techniques to reduce severe injection site reactions as well as important counseling points to use with patients to identify any signs or symptoms of injection site reactions.[62] Naltrexone is not a controlled substance and is not included in the OTP regulations, but it does require a prescription and a monthly medical office visit. It has been suggested the use of extended-release injectable naltrexone should be part of a comprehensive patient program that includes psychological counseling and support.

Buprenorphine

Buprenorphine is a partial mu receptor agonist that is very lipophilic and is available as buprenorphine alone or buprenorphine/naloxone formulations. These products have been shown in numerous studies and clinical trials to be effective treatment options for OUD both in reducing illicit opioid use, as well as

for retaining patients in treatment.[54] It is now recommended by the TIP 63 expert panel[32] and the Department of Veterans Affairs Guidelines[55] that FDA-approved buprenorphine formulations should be offered to patients with OUD who are appropriate candidates. As buprenorphine is a partial mu receptor agonist, it does provide some intrinsic pain control. Additionally, due to the partial agonist activity, it also has a ceiling effect for respiratory depression, except when combined with CNS depressants such as benzodiazepines or alcohol, where there have been reports of increased risk of respiratory depression. Furthermore, due to the partial agonist activity, any full agonist activity will be blunted, such as that provided from heroin or other opioids. This effect will be prolonged due to the long half-life and prolonged receptor dissociation properties of buprenorphine.[32] At the time of this writing there are currently buprenorphine/naloxone sublingual tablets and films, buprenorphine/naloxone buccal films, buprenorphine implants, buprenorphine tablets, and a buprenorphine extended-release injection.[63–67] Newer products have greater bioavailability compared to previous products making product selection and conversion between buprenorphine products an important consideration for healthcare providers (**Tables 82-4** and **82-5**).[32]

TABLE 82-4 Oral Buprenorphine Products Used in Treatment of Opioid Use Disorder

	Buprenorphine Tablet	Suboxone SL Tablet	Zubsolv SL Tablet	Suboxone SL Film	Bunavail Buccal Film
Strengths of products commercially available/Routes of Administration	Sublingual Tablet: 2 mg 8 mg	Sublingual Tablet: 2/0.5 mg 8/2 mg	Sublingual Tablet: 0.7/0.18 mg 1.4/0.36 mg 2.9/0.71 mg 5.7/1.4 mg 8.6/2.1 mg 11.4/2.9 mg	Sublingual or Buccal Film: 2-0.5 mg 4-1 mg 8-2 mg 12-3 mg	Buccal Film: 2.1-0.3 mg 4.2-0.7 mg 6.3-1 mg
Recommended Once-Daily Target Maintenance Dose and Dosing Ranges	Target Maintenance Dose: 16 mg **Dosing Range:** 4-24 mg*	Target Maintenance Dose: 16/4 mg **Dosing Range:** 4/1 to 24/6 mg*	Target Maintenance Dose: 11.4/2.9 mg **Dosing Range:** 2.9/0.71 to 17.2/4.2 mg†	Target Maintenance Dose: 16/4 mg **Dosing Range:** 4/1 to 24/6 mg*	Target Maintenance Dose: 8.4/1.4 mg **Dosing Range:** 2.1/0.3 to 12.6/2.1 mg

*Doses higher than 24/6 mg have not been shown to offer any further benefit.

†Doses higher than 17.2/4.2 mg have not been shown to offer any added benefit.

Data from References 32, 63, 64, and 115.

SL, sublingual

Note: Refer to individual product dosing information when switching formulations due to possible bioequivalence variability. Monitoring is recommended following a switch in products due to possible variation in response to different formulations.

TABLE 82-5 Extended-Release Products Approved by FDA for Opioid Use Disorder

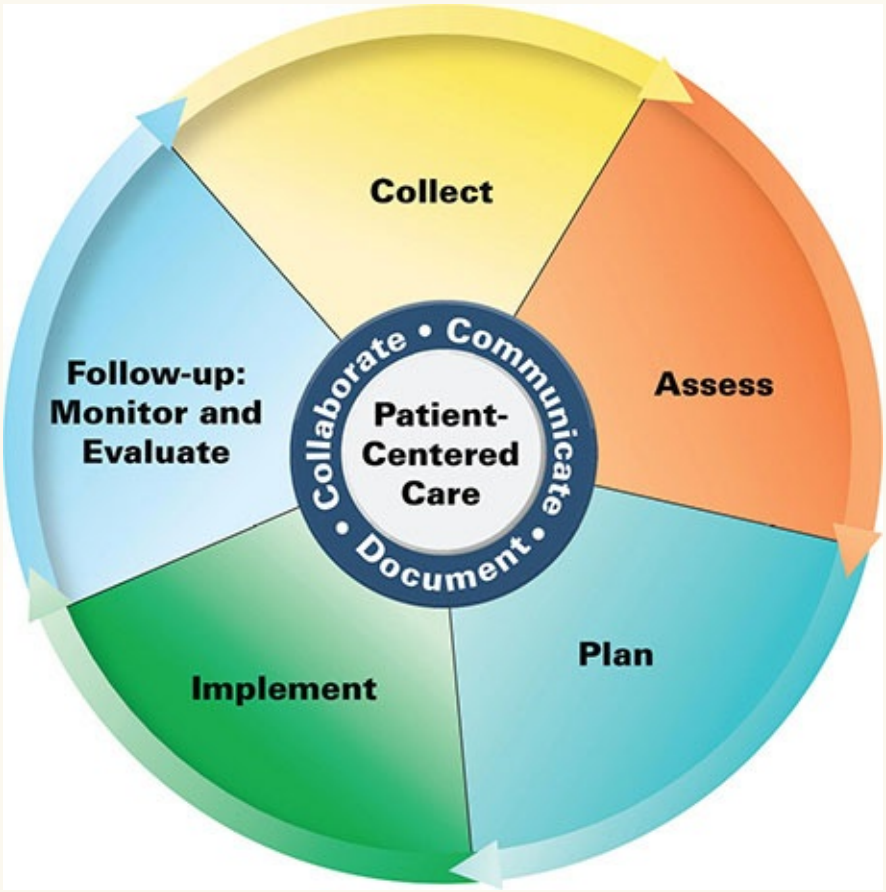
Drug	Trade Name	Dose	Comments
Naltrexone Tablets	Revia	Following 7-10 day opioid-free period opioid for short-acting opioids or 10-14 day opioid-free period for long-acting opioids: begin with dose of 25 mg daily with food. If no signs of withdrawal, increase dose to 50 mg po daily.	• Should be part of a comprehensive treatment plan that includes psychosocial support • Although specific dosage adjustments are not available for patient with hepatic dysfunction, reports of elevated LFTs have been reported; use with caution • Use with caution in patients with renal impairment, although data is limited, naltrexone and active metabolite are renally excreted
Naltrexone XR Injection	Vivitrol	Following 7-10 day opioid-free period for short-acting opioids or 10-14 day opioid-free period for long-acting opioids: 380-mg IM in gluteal area alternating buttocks; every 4 weeks or once a month.	• Must be administered by a healthcare provider • Must use manufacture provided needle and assess body size of patient at each visit so proper needle size is used • Monitor injection site closely for any signs of abnormal pain and contact healthcare provider immediately if this occurs • Dose adjustment is required in mild or moderate hepatic impairment. No data available in severe hepatic impairment • No dose adjustments in mild renal impairment; use caution in patients with moderate to severe renal impairment, naltrexone and active metabolite are renally excreted

Buprenorphine	Probuphine	Four implants are inserted subdermally in the inner side of the upper arm and should remain in place for 6 months.	• Patients must meet specific criteria for use of Probuphine:
			  • Only indicated for patients who are opioid tolerant
			  • Demonstrates clinical stability on transmucosal buprenorphie with Subutex or Suboxone 8 mg/day or less (or transmucosal equivalent) for 3 months or longer without requiring supplemental dose adjustments
			• Probuphine must be inserted or removed within a facility and by a certified provider who has completed the required live training
			• It is recommended to not prescribe prn transmucosal buprenorphine products. If patient is requesting these products, reassessment is indicated
			• Moderate to severe hepatic impairment: use not recommended
			• Limited data in renal impairment, currently no dosage adjustments listed

Buprenorphine	Sublocade	For patients who have achieved clinical stability on equivalent of 8-24 mg of a transmucosal buprenorphine product daily. *Available in two extended-release solutions:* • *100 mg/0.5 mL* • *300 mg/1.5 mL* Directions: Inject 300 mg subcutaneously once a month in abdominal area for 2 months, then decrease dose to 100 mg once monthly in abdominal area.	• Must be administered by a healthcare provider • Steady state occurs after 4-6 months; after discontinuation of detectable buprenorphine levels could occur 12 months or longer; urine and plasma concentration correlations are not known • Injections must occur at least 26 days apart. Follow all manufacturers' direction for preparation and injection • Do not give the injection at the belt or waistband area where pressure will occur • It is important to counsel the patient that there will be a small bump at the injection site that will decrease in size over the next several weeks. It is important not to rub or massage this area • If needed, the most recently injected depot can be removed within the 14 days of injection under local anesthesia • Doses can be adjusted back to 300 mg monthly for patients in which benefits exceed risks • Examine injection site each month for evidence of tampering • Moderate to severe hepatic impairment: use not recommended • Limited data in renal impairment, currently no dosage adjustments listed

mg, milligram; LFTs, Liver Function Tests; IM, Intramuscularly; mL, milliliters.

Data from References 32, 58, 59, and 63–67.



Patient Care Process for Opioid Use Disorder (OUD)

Collect

- Patient characteristics (eg, age, sex, pregnancy status)
- Patient medical history (personal and family)
- Allergy history
- Objective data
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight
  - Prescription drug monitoring program (PDMP) data
  - Labs including urine or oral fluid drug testing, pregnancy test, liver function tests (LFTs), Hepatitis B and C serology, HIV serology

- Social history (eg, tobacco/ethanol use, past substance use, current risk factors for HIV/STIs, current home environment, dependent information, transportation information)
- Family history (family history of substance use disorder (SUD)
- General current physical health
- Current medications including herbal products, dietary supplements, over-the-counter (OTC) medications, nonprescribed medications, prescription medications, illicit substances
- Patient mental health history
- Current family relations/support network
- Educational background
- Current employment
- Living situation (homeless, roommates, safety concerns)
- Opioid use history (eg, age of first use, routes of use, overdose history, drug mixing, withdrawal, tolerance, history of substance abuse treatment), recent alcohol use, recent benzodiazepine use

Assess

- Signs of opioid intoxication or withdrawal
  - Physical findings (drowsy; constricted pupils)
  - Mental status findings (slurred speech, signs of impaired concentration, mood alterations)
  - Scoring using validated tools (eg Clinical Opiate Withdrawal Scale)
- Check Prescription Drug Monitoring Program (PDMP)
- Results of urine drug screen, pill or film counts
- Evaluate opioid overdose risk
  - Evaluate current/past benzodiazepine use
- Evaluate Medication-Assisted Treatment (MAT) products (Tables 82-3 and 82-5)
  - Extended-release injectable naltrexone (XR-NTX)
  - Buprenorphine
  - Methadone
- Ability/willingness to pay for pharmacotherapy for OUD

- Ability/willingness to pay for behavioral treatment for OUD
- Ability/willingness to obtain laboratory monitoring tests (eg, UDS, LFTs)
- Emotional status (eg, presence of anxiety, depression)

Plan*

- Drug therapy regimen including specific drug(s), dose, route, frequency, and duration; (Tables 82-3, 82-4, 82-5, and 82-7)
- Monitoring parameters including efficacy (cravings, relapse, withdrawal reactions) and safety (eg, sedation, other drug-specific side effects); frequency and timing of follow-up
- Patient education (eg, purpose of treatment, possible side effects, importance of proper storage of medication, naloxone education (Tables 82-6 and 82-7)
- Referrals to other providers when appropriate (eg, behavioral health, social worker)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence.
- Provide take home naloxone device and complete proper education
- Schedule follow-up

Follow-up: Monitor and Evaluate

- First week: improve symptoms of withdrawal without causing over-sedation
- Following the first week, maintain dose to limit cravings
- Limit side effects
- Patient adherence to treatment plan using multiple sources of information
- Reevaluate duration of therapy every week until stable

* *Collaborate with patient, caregivers, and other healthcare professionals.*

Patients who achieve clinical stability have longer acting options that may

improve adherence and improve quality of life. These products include a buprenorphine implant that was approved in 2016 and offers 6 months of drug therapy as well as an extended-release buprenorphine monthly injection approved in 2017.[67] Buprenorphine is currently a Schedule III controlled substance with specific prescribing restrictions. As part of the Federal Drug Addiction Treatment Act (DATA 2000)[68] licensed physicians with a valid DEA registration number who meet specific criteria are able to obtain special training and a waiver. Providers will have a special DEA number that begins with a "X" and are allowed to provide buprenorphine for up to 275 patients a year.[69] Additionally, SAMHSA provides a Buprenorphine Practitioner Verification for providers: https://www.samhsa.gov/bupe/lookup-form. Recent legislation has extended regulations to allow physician assistants, nurse practitioners, clinical nurse specialists, certified nurse midwives, and certified registered nurse anesthetists to prescribe buprenorphine. This practice varies by state based on laws and regulations.[25,69]

Prior to prescribing buprenorphine, a full assessment including reviewing the prescription drug monitoring program database and a full medication review should be completed. Care should be taken to screen for drug–drug interactions including HIV medications, benzodiazepines, central nervous system (CNS) depressants, and CYP 450 inducers/inhibitors. Additionally, a urine drug screen, informed consent and treatment agreement should be completed. Comprehensive patient education is very important to help improve adherence to the treatment plan and improve patient safety (**Table 82-6**).[32]

TABLE 82-6 Patient Education Points for Buprenorphine Treatment

Prior to starting buprenorphine therapy and repeat education at induction

- **Communication with prescriber:** Tell your doctors all medications including over-the-counter, herbal, creams, injections, inhalants, street medications, etc. that you are currently taking. This is important so your doctor is aware of what is in your body and if there are any chances of a dangerous drug interactions. Additionally, it is important to tell all of your doctors you are taking buprenorphine. If you are being treated for pain, it is very important to tell your doctor you are currently taking buprenorphine.
- **Goals of therapy:** The goal of your first week of treatment is to improve the symptoms of withdrawal without causing any over-sedation (making you too tired or feeling over medicated). It is important to notify your doctor/prescriber if you are feeling overly tired/sedated or euphoric within 1 to 4 hours of your dose. Dose adjustments might occur initially and it will take a little time for the buprenorphine to become stable in your system. The goals of therapy include finding the right dose to eliminate withdrawal, decrease or even eliminate cravings for opioids, and block the effects of other opioids without severe side effects.
- **Product use:**
  - Buprenorphine products (tablets, sublingual film, and buccal film) are not equivalent. If you have to transition to a new buprenorphine product, a dose adjustment might be required.
  - Take your dose at regular intervals and only as prescribed.
  - If you miss a dose, take the dose as soon as possible. If it is almost time for the next dose, do not double your dose, take only the dose that is prescribed.
  - Leave medication in packaging until you are ready to use.
  - Do not swallow sublingual tablets or film. This can lead to a decreased effect of buprenorphine that can lead to withdrawal symptoms.
    - Sublingual tablets:
      i. Place tablets under tongue and allow the tablet to fully dissolve which can take several minutes
      ii. If your dose requires multiple tablets, all tablets can be placed under the tongue at one time. If this is uncomfortable, only place two tablets under the tongue at a time.
    - Sublingual film:
      i. Drink water prior to placing the film to help the film dissolve easily
      ii. Place film under the tongue, to the left or right of the center of the tongue, and allow to completely dissolve
      iii. If you are prescribed 2 films at a time, place the second film on the opposite side of the tongue. Do not allow the films to touch.
      iv. If you are prescribed more than 2 films at a time, wait until previous films have dissolved and repeat the process.
    - Buccal film:
      i. Wet the inside of your cheek with your tongue or rinse with water prior to placing film
      ii. Hold the film by the edges with two fingers and place on inside of cheek until fully dissolved that can take up to 30 minutes
      iii. If you are prescribed two films, place the second film inside the opposite cheek
      iv. Do not adjust the film placement or touch the film, do not chew or swallow the film
      v. Do not drink or eat until the film has completely dissolved
- **Common side effects:** There are some side effects that can occur when taking buprenorphine. These do not happen all of the time and do not happen to everyone. If you are experiencing any of these side effects please tell your doctor immediately. Do not stop taking buprenorphine without first speaking to your doctor. The most common side effects that have been experienced include headache, nausea, constipation, abdominal pain, insomnia, sweating, and a possible feeling of weakness or lack of energy.
- **Precautions and warnings:**
  - Using alcohol while taking buprenorphine is very dangerous and can lead to increased risk of overdose and possibly death.
  - There is a risk of overdose and possibly death if taking buprenorphine with benzodiazepines or alcohol.
  - Using tobacco products prior to using buprenorphine has been shown to decrease the absorption of buprenorphine decreasing its effectiveness.
  - Long-term buprenorphine maintenance is recommended in many cases. If you stop buprenorphine, there is a high risk of overdose if you return to illicit opioid use.
  - Buprenorphine is an opioid that can cause physical dependence. Do not stop taking buprenorphine without consulting your doctor. If you stop buprenorphine abruptly, you could experience withdrawal symptoms.
  - All medications, including buprenorphine, should be stored in a secure area, preferably in a locked cabinet or safe. It is important to keep medication away from children.
  - It is recommended that you do not drive, operate heavy machinery, or perform any dangerous activities until you are fully aware of how this medication affects you.
  - If you feel you have taken too much buprenorphine, you will need emergency medical attention immediately. Some possible signs include dizziness, confusion, unsteady or faint, slowed reflexes, or breathing slower.
  - Do not inject these products. Serious life-threatening infections could occur. Additionally, serious withdrawal reactions can also occur upon injecting many of these buprenorphine products.
- **Pregnancy:** It is very important to inform your doctors if you become pregnant
- **Counseling options:** Recovery resources and counseling resources are available for you and your family. We can give you further information on this when you are ready.

Maintenance

- **Adherence assessment:** If any discrepancies arise, initiate discussion to identify reasons for discrepancies
  - Complete pill/film count
  - Review PDMP
  - Confirm current buprenorphine dose
  - Review results of urine drug screen
- **Treatment assessment and counseling:**
  - Review treatment goals and assess progress
  - Review and assess benefits and risks of continuing buprenorphine treatment
  - Discuss participation in counseling or encourage counseling if not receiving counseling

Data from References 32, 55, and 64.

When the patient presents to begin buprenorphine, it is important for the clinician to assess the patient carefully for any signs of sedation or intoxication since buprenorphine should not be started under these circumstances. As the patient should present in the beginning stages of withdrawal to start buprenorphine, a validated assessment scale, the Clinical Opiate Withdrawal Scale (COWS), can be used for assessment. It is recommended that treatment start with a COWS score of 12 or higher for the first dose, based on buprenorphine REMS.[32]

Medically supervised withdrawal with buprenorphine consists of an induction phase and a dose-reduction phase, followed by maintenance.[32] Best practice guidelines (eg, TIPs) are periodically issued for treatment of OUDs. The TIP 40[70] (entitled "The Guideline for the Use of Buprenorphine in the Treatment of Opioid Addiction") provides consensus- and evidence-based guidance on the use of buprenorphine and the TIP 63 provides similar guidelines as outlined below for buprenorphine treatment.[32] Induction is the first stage of buprenorphine treatment and involves helping patients begin the process of switching from the opioid of abuse to buprenorphine. The goal of this phase is to find the minimum dose of buprenorphine at which the patient discontinues or markedly diminishes use of other opioids and experiences no withdrawal symptoms, minimal or no side effects, and no craving for the drug of abuse. This phase is commonly initiated in the physician office when the patient is in mild to moderate withdrawal with the last dose of opioid use occurring 6 to 12 hours prior for heroin or short-acting opioids. For longer-acting opioids such as methadone, it is recommended to wait 24 to 72 hours after the last dose. Patients are typically monitored in the office at approximately 2-hour intervals after the first dose of buprenorphine with continued dose titration until the withdrawal symptoms are eliminated. Guidelines recommend weekly follow-up until the patient is stable and then monthly follow-up can be considered.[56] Although office-based induction has traditionally been recommended, home induction is an alternative growing in use.[32] The American Society of Addiction Medicine National Practice Guidelines recommends that both the patient and prescriber have prior experience with MAT to consider this option.[56]

The stabilization phase begins when a patient is experiencing no withdrawal symptoms, is experiencing minimal or no side effects, and no longer has uncontrollable cravings for opioid agonists. Buprenorphine dosage adjustments may be necessary during early stabilization, and frequent contact with the patient increases the likelihood of compliance. Ongoing psychological evaluation for

mental disorders or psychological disorders is recommended so proper medical assistance can be provided immediately if needed.[32]

Maintenance is the longest phase of treatment as this period may be indefinite and longer treatment has been associated with positive treatment outcomes.[71] During the maintenance phase, attention must be focused on the psychosocial and family issues that have been identified during the course of treatment that contribute to a patient's OUD.[71] Other issues related to OUD that need to be addressed during maintenance treatment include, but are not limited to, psychiatric comorbidity, consequences of drug use, family support issues, structuring of time in prosocial activities, employment and financial issues, legal consequences of drug use, and abuse of other substances. Ongoing monitoring will continue including urine drug tests, and patient education regarding this aspect is important so there is understanding that this testing is used more to help them meet treatment goals and not as a tool for punishment.[32]

Naloxone

11 Naloxone is a key strategy in reducing opioid-related deaths,[72] as patients who are currently being treated for OUD, or who are not taking medications for OUD but are at high risk of returning to opioid use, are at substantial risk of overdose. It is imperative that patients and their caregivers are educated on the availability of naloxone and the proper use of this agent. Pharmacologically, naloxone hydrochloride is a competitive mu-opioid receptor antagonist that can be used in the reversal of an opioid overdose. It can be administered through a variety of routes including intravenous (IV), intramuscular (IM), subcutaneous (SQ), intraosseous, (IO), and intranasal (IN).[73] The onset of action when delivered via intravenous route can be as fast as 60 seconds,[73] but is approximately 2 to 5 minutes when delivered IN.[74] The duration of effect is dependent upon the dose and the specific opioid naloxone is reversing. It is important for interested parties to know that if a long-acting opioid such as methadone is involved the patient could show decompensation after initial improvement due to the long half-life of methadone and comparatively short half-life of naloxone.

Since 2014, the FDA has approved two new devices to deliver naloxone that can be administered by nonmedical bystanders: the intramuscular autoinjector Evzio® and an intranasal delivery device, Narcan®. A third option readily available prior to these new devices, the generic injectable naloxone solution used with a mucosal atomization device, is used in the community setting,

although it is not approved by the FDA. For this device, extra education is necessary on how to connect the components and then administer the 1-mg dose per nostril.[75] **Table 82-7** includes more information about naloxone delivery options and counseling information.

TABLE 82-7 Naloxone Delivery Options

	Intramuscular Injection	Auto-Injector (Evzio)	Nasal Spray (Narcan)	Intranasal Spray (Atomizer)
Description of device or what is provided to patient	(2) single use 0.4-mg/mL naloxone vials (2) single use 3-mL syringe 23-25 gauge 1-1.5 in. needles	(1) box 2-mg/0.4-mL prefilled auto injector that include 2 devices and a trainer devices	(1) box that contains two 4-mg/0.1-mL intranasal devices	2-mg/2-mL prefilled naloxone needleless syringe 2 mucosal atomizer devices
Directions for use	Inject 1-mL intramuscularly in shoulder or thigh upon signs of opioid overdose. Call 911 immediately. May repeat once in 2-3 minutes if no response or patient is showing minimal response	Use one auto-injector by injecting in outer thigh by depressing and holding for 5 seconds. The voice automation will direct the patient with this device. Call 911. May repeat ×1 in 2-3 minutes if no response or patient is showing minimal response	Use full contents of nasal spray in one nostril upon signs of opioid overdose. Call 911. May repeat ×1 in 2-3 minutes if no response or patient is showing minimal response, using the other nostril	Spray one-half of contents of syringe into each nostril upon signs of opioid overdose. Call 911. May repeat ×1 in 2-3 minutes if no response or patient is showing minimal response

Naloxone pearls:

- Naloxone has not been shown to cause severe effects or side effects if administered to patients who are currently not taking opioids.
- Naloxone should be given if the patient is intoxicated by a combination of products since the naloxone will still work for the opioid but not for other products such as benzodiazepines or alcohol.

Naloxone counseling topics that should be covered:

- Overdose recognition, response, prevention
- Importance of seeking emergency medical care
- Proper device use and counseling of family members and caregivers
- Proper storage, shelf life. Periodically check expiration date
- Potential side effects associated with naloxone
- Availability of drug treatment program

General opioid safety counseling:

- Take medication only prescribed for you, only take prescribed doses
- Do not mix opioids with alcohol or sleeping pills
- Always store all medications in a locked and secure place
- Dispose of unused medications appropriately
- Do not use opioids/drugs alone. Never buy opioids/drugs from unknown source
- Do not restart opioid at same dose if there is a perioid of abstinence. Overdose is possible due to lower tolerance

Data from References 73-75.

Limitations of take-home naloxone (THN) products continue to be identified including inadequate response to less sensitive opioids such as buprenorphine, fentanyl, or other synthetic opioids.[76] As high doses of naloxone have been needed to treat these overdose patients, it is vital that emergency services are contacted to provide ongoing care.[76] However, the THN products might provide time for arrival of medical professionals and/or transportation to medical facilities for more definitive treatment.

Controversy currently exists regarding concerns that distribution of naloxone may increase drug abuse and misuse, as some authors feel naloxone has contributed by "providing a safety net that encourages riskier use."[76] However, data from communities that have implemented overdose programs prior to this report have documented a decrease in overdose death rates.[74] In fact, overdose education and naloxone distribution (OEND) programs in the community have been occurring since 1996, and the practice was embraced by the World Health Organization (WHO) guidelines which recommend that anyone who might witness an overdose have access to naloxone and proper training.[77]

As the number of opioid overdoses has continued to increase, CDC guidelines recommend increasing use of THN.[19] In fact, improving access has become a goal of many states by expanding those able to distribute naloxone or simplifying the process of obtaining the naloxone, and improved education of healthcare providers and the community as a whole.[78] To further highlight the importance of naloxone for opioid overdose prevention, the US Surgeon General issued a statement emphasizing the importance of learning about naloxone and obtaining a take-home naloxone product. This statement was directed not only at the patients exposed to opioids for various reasons but for any community members who may be in contact with patients at risk for an opioid overdose.[79]

Opioid Use Disorder in Pregnancy

As the rates of opioid use in the United States have increased, the number of pregnant women diagnosed with opioid use disorder has increased substantially.[80] OUD during pregnancy results in an increased risk of preterm labor, neonatal abstinence syndrome, and maternal mortality. The CDC reported the rate of OUDs in women at delivery has more than quadrupled between 1999 and 2014.[80] Current recommendations for a pregnant woman with an OUD requesting treatment includes MAT with methadone or buprenorphine, and behavioral interventions. At this time, the safety of extended-release injectable naltrexone is still under debate. For patients taking naltrexone, it is

recommended that this is converted to buprenorphine or methadone during the pregnancy.[81] More specifics regarding treatment in this population can be obtained from recently released guidance documents for healthcare providers entitled “Clinical Guidance for Treating Pregnant and Parenting Women with Opioid Use Disorder and Their Infants.”[81]

Key to the success of OUD treatments in this population is patient education, which should include topics such as the risks and benefits of the chosen medication. During this discussion, it is important to stress to the patient there are some disagreements on the risks associated with these medications. At this time, research efforts have not linked buprenorphine or methadone use with an increased risk of birth defects and or issues with long-term neurodevelopment.[81] Other important topics to discuss with the patient include risk of neonatal abstinence syndrome and details associated with this syndrome, as well as important strategies for improving her health and the pregnancy. Due to the large number of pregnant women presenting with OUDs, all healthcare providers should look for substance use behaviors in their pregnant patients, and if identified, provide a referral for therapy as quickly as possible to improve the outcome for both the mother and the baby.[81]

General Approach to Treatment: Benzodiazepines and Other Sedative-Hypnotic Withdrawal

Benzodiazepines, while not first-line treatment options, are commonly prescribed for anxiety, muscle spasms, and insomnia in a variety of practices. Pharmacologically, the benzodiazepines increase the affinity of gamma amino butyric acid (GABA) for its receptor and augment GABA-mediated inhibition. This occurs by targeting the $GABA_A$ receptor that has multiple subunits. Activation of these subunits leads to an increase in frequency of ion channel opening that leads to an influx of chloride ions and membrane hyperpolarization.[82] Benzodiazepines vary in pharmacodynamics and pharmacokinetic properties, with additional details being found in Chapter 87, “Anxiety Disorders I: Generalized Anxiety Disorder, Panic, and Social Anxiety Disorders” and Chapter 88, “Anxiety Disorders II: Posttraumatic Stress Disorder and Obsessive-Compulsive Disorder.”

Benzodiazepines have abuse and dependence liability, and patients cannot be switched from one benzodiazepine to another in hopes of decreasing a pattern of drug abuse or dependence behavior. Additionally, long-term use of even therapeutic doses of these agents, can cause physical dependence and withdrawal

symptoms after abrupt discontinuation, including seizures. Gradual tapering of dosage is also associated with less withdrawal and rebound anxiety than abrupt discontinuation.[82]

Benzodiazepine prescribing has increased by over 65% from 1996 to 2013[83] and overdose rates have increased over eightfold from 2002 to 2016.[37] When benzodiazepines are given concomitantly with an opioid, the combination can lead to increased CNS side effects such as dizziness and sedation but also deadly respiratory depression. A cohort study that included over 2 million opioid prescriptions in one year demonstrated 80% of opioids were co-prescribed with a benzodiazepine and the rates of overdose deaths in this group were 10 times higher than opioid analgesics alone.[84] In 2016, the FDA announced a class wide drug labeling change for both opioids and benzodiazepines requiring both classes to include black box warning indicating that concurrent use of opioids and benzodiazepines could cause sedation, respiratory depression, coma, and death.[85] Additionally, the CDC Guidelines for prescribing opioids for chronic pain recommends avoiding concurrent benzodiazepine and opioid prescriptions whenever possible highlighting the dangers of using this combination of medication classes.[19]

A related class of medications includes eszopiclone, zaleplon, and zolpidem, which are prescribed for insomnia, and commonly known as the Z-hypnotics. While pharmacologically they may differ from benzodiazepines, tolerance and withdrawal have been reported with their use and they should be used with caution.[86] Additionally, this class of medication is required by the FDA to include labeling that warns of a variety of psychological and behavioral side effects including sleep driving. Depression and suicidal thoughts have also been linked to these products, although this has been seen mainly in patients taking both sedatives and hypnotics concurrently.[87]

Nonpharmacologic Therapy: Benzodiazepine Withdrawal

Similar to other sedative hypnotic withdrawal, nonpharmacological management as a primary treatment for benzodiazepine withdrawal is not indicated. Rather, the use of supportive care for patients undergoing benzodiazepine withdrawal should be done in combination with pharmacologic therapy.

Pharmacologic Therapy: Benzodiazepine Withdrawal

Treatment of benzodiazepine withdrawal is very similar to the treatment of alcohol withdrawal. The major differences in management is the length of treatment.[82] The duration of withdrawal symptoms in patients physically dependent on benzodiazepines can be variable due to multiple factors including dose of benzodiazepine, duration of use, duration of taper, and pharmacokinetic half-life.[88] Current recommendations suggest a gradual taper extending over 4 to 8 weeks and sometimes longer depending on the duration of use. It is recommended to reduce the daily dose approximately 10% to 25% every 2 weeks to decrease the risk of severe withdrawal reactions and seizures.[82] In some situations an extended tapering schedule could be indicated if withdrawal symptoms continue. Additional recommendations suggest if a patient is taking multiple benzodiazepines, convert to an equivalent single dose of diazepam and begin the taper as directed. There is limited evidence converting a patient taking a single short half-life benzodiazepine to a long half-life benzodiazepine will have better outcomes so this practice is generally not recommended.[82] With all benzodiazepines, protracted minor abstinence symptoms—such as anxiety, insomnia, irritability, sensitivity to light and sound, and muscle spasms—can remain for several weeks or longer in patients with a history of long-term exposure, even after the acute phase of benzodiazepine withdrawal is complete.[89] Additional information on benzodiazepine tapers can be found in Chapter 87.

CLINICAL PRESENTATION

Benzodiazepine Intoxication and Withdrawal

General

- The intoxicated patient may be in acute distress in overdoses or when benzodiazepines are combined with alcohol.
- Patients in withdrawal may be in acute distress and should be treated with a benzodiazepine taper to prevent seizures.

Symptoms

- Symptoms of intoxication may include memory impairment, drowsiness, visual disturbances, confusion, and gastrointestinal disturbances. Patient may appear intoxicated, with slurred speech, poor coordination, swaying, and bloodshot eyes, with or without the odor of alcohol.

- Symptoms of withdrawal can include agitation and restlessness, confusion, anxiety, sleep disturbances, dizziness, flu-like symptoms, impaired memory and concentration, irritability, nausea and vomiting, nightmares, visual disturbances, convulsions, hallucinations, and psychosis.

Signs

- Hypotension or nystagmus may be observed and urinary retention may occur with intoxication.
- Nervousness, sweating, trembling, hypertension, tachycardia, weakness, tremors, and seizures are examples of possible signs in acute withdrawal.

Laboratory Tests

- Qualitative testing to confirm presence of benzodiazepines is useful for diagnostic purposes, but quantitative plasma concentrations are usually not clinically useful.

Data from Reference 82.

Flumazenil

Flumazenil can be used to reverse toxic effects of benzodiazepines and Z-hypnotics. However, caution should be exercised as indiscriminate use can potentiate seizures. The dosing scheme is to give 0.2 mg of flumazenil IV, then 0.3-mg IV if there is an insufficient response, then repeated doses of 0.5-mg IV up to a maximum of 3 mg.[116]

General Approach to Treatment: Stimulants, Hallucinogens, Cannabinoids, and Inhalants

Acute intoxication with stimulants, cannabinoids, cathinones, inhalants and other mind-altering substances continues to be a relevant issue around the world. Improved outcomes are achieved through prompt recognition of symptoms and supportive care. At the time of writing, no antidotes or targeted therapies are available for these agents. Active monitoring and management of vital organ function is often sufficient for a positive outcome. Chronic use disorder and withdrawal from these agents are complex disease states that can require

inpatient monitoring. No medication-assisted therapy is available for the treatment of chronic use involving these agents. Data involving successful treatment of substance use disorders involving stimulants, cannabinoids, cathinones, and inhalants is in its infancy. It likely requires outpatient follow-up and psychosocial intervention for long-term sustained recovery.

Cocaine

According to the 2017 NSDUH survey, approximately 2.2 million people age 12 or greater were current users of cocaine of any form. This figure of 0.8% is similar to estimates for recent years but use of cocaine is higher in comparison to estimates in years 2009 to 2014. Young adults age 18 to 25 account for the largest percentage of current users with all age groups seeing stable rates of use over the past few years.[9]

Cocaine is perhaps the most behaviorally reinforcing of all drugs of abuse. It acts as a local anesthetic when applied topically through inhibition of voltage-gated sodium channels, leading to cardiotoxicity. Cocaine also acts as a sympathetic nervous system stimulator through α- and β-adrenergic stimulation. This can precipitate chest pain and myocardial infarction. In the CNS, the stimulant and euphoric effects occur through inhibition of dopamine and norepinephrine reuptake. The excess dopamine in the ventral tegmental area (VTA) leads to the psychostimulant properties, contributes to psychotic behavior, and portends a high rate of addiction.[90]

CLINICAL PRESENTATION

Cocaine Intoxication and Withdrawal

General

- In overdoses, cocaine is a CNS and cardiac stimulant.
- Cocaine-related deaths are often a result of cardiac arrest or seizures followed by respiratory arrest.

Symptoms

- Symptoms of intoxication include motor agitation, elation, euphoria, hypervigilance, sweating, nausea, and vomiting.
- Symptoms of withdrawal include fatigue, sleep disturbances, nightmares,

depression, and changes in appetite.

- High doses of cocaine and/or prolonged use can trigger paranoia.

Signs

- Tachycardia, mydriasis, and either elevated blood pressure may be observed with overdose.
- Cardiac abnormalities (eg, arrhythmias, infarction) and respiratory depression may be observed with overdose.
- Bradyarrhythmias, myocardial infarction, and tremors may be observed in acute withdrawal.
- Prolonged cocaine snorting can result in ulceration of the mucous membranes of the nose and can damage the nasal septum enough to cause it to collapse.

Laboratory Tests

- Qualitative urine screening tests for drugs of abuse are available; however, they do not change clinical treatment significantly.

Other Diagnostic Tests

- Markers of organ dysfunction may be drawn as clinically indicated.

For many years, cocaine has been administered as the hydrochloride salt form, usually by insufflation, but also by injection. Conversion to the cocaine base, also known as “crack” or “rock,” allows for smoke inhalation which is popular with lower socioeconomic populations, as this form is comparatively inexpensive. The time to peak concentration is rapid for all routes but is fastest by intravenous injection (instantaneous), then smoking (6 minutes), and then finally nasal insufflation (45 minutes).[90] Smoking the drug leads to almost instant absorption and intense euphoria. Peak plasma concentrations of more than 900 ng/mL (mcg/L; 3.0 µmol/L) have been achieved following inhalation of cocaine base vapors, compared with concentrations of only 150 to 200 ng/mL (mcg/L; 0.49-0.66 µmol/L) achieved after insufflation of similar amounts of pure cocaine hydrochloride powder.[91] The high from insufflating is more prolonged lasting 15 to 30 minutes, whereas the high from smoking rapidly dissipates lasting only 5 to 10 minutes. Cocaine is metabolized and eliminated rapidly, with a half-life of approximately 1 hour contributing to its very short duration of

effect.[91] Therefore, the rapid onset and short duration combined provide a powerful incentive for repeated use of the drug. Increased use can reduce the period of stimulation and an appreciable tolerance to the high can develop. Many addicts report failing to achieve as much pleasure as they did from their first exposure with continued use. Many users experience intense drug-use cycling, sometimes lasting days, characterized by rapidly repeating doses of cocaine until their money or supply is exhausted.

Other patterns of use and abuse such as consumption of alcohol along with cocaine use are common and add to the toxicity. Such drug use would seem counterintuitive based on the counteracting effects of the two substances; however, in the presence of alcohol, cocaine is metabolized to cocaethylene, a longer-acting but potent psychoactive compound compared to the parent drug. The risk of death from cocaethylene is greater than from cocaine alone. The cocaine-alcohol combination is one of the most commonly identified combinations among individuals who come to hospital emergency departments with acute substance abuse problems.[92]

Amphetamine, Methamphetamine, and Other Stimulants

According to the 2017 NSDUH survey,[9] 0.3% of the population 12 years or older are current methamphetamine users. The absolute number of users who were older than 26 years of age was highest, but in the 18 to 25 age group, the overall percentage of daily methamphetamine users was higher. This data is echoed by the 2017 MTFS data,[10] which showed that methamphetamine use among 8th, 10th, and 12th graders remained fairly consistent with the previous year. Although no decrease in use was seen in the most recent year, an overall trend of prolonged decreasing rates of use in adolescents continues. It appears that despite the growing problem that methamphetamine poses for society, use appears to start after adolescence.[10]

According to the 2018 National Drug Threat Survey,[18] methamphetamine continues to be readily available in the United States and nearly 62% of DEA field offices categorized the availability of methamphetamine as high in late 2017. Only the Caribbean and Northeast US field offices categorized availability as low; however, the prevalence of use in the Northeast appears to be increasing according to the DEA.

The purity of DEA obtained samples averaged 96.9% and the price per gram has decreased by 13.6% in the previous 5 years.[18] This combination of high

purity and availability in conjunction with low cost means that methamphetamine abuse will likely continue to be a significant contributor to abuse and crime.

The majority of methamphetamine available in the United States is produced in large-scale facilities run by Mexican drug cartels. The bulk of domestic production comes from small laboratories also known as “one-pot,” “shake-and-bake,” or “mom-and-pop” laboratories that produce small amounts of methamphetamine, approximately 1 to 3 g per laboratory, usually for personal use or use among a small group of people. In this process, ephedrine or pseudoephedrine is extracted from OTC cold and allergy tablets and mixed with other household items in a plastic soda bottle, which reduces the ephedrine to produce methamphetamine.[18]

The physiologic and psychologic effects of amphetamines and other stimulants are qualitatively similar to those of cocaine—they diminish fatigue, increase alertness, and suppress appetite. In higher doses stimulants can lead to behavioral changes, perception disturbances, and frank psychosis. Pharmacologically, amphetamines increase the activity of catecholamine neurotransmitters (eg, norepinephrine and dopamine) by stimulating release, decreasing reuptake into the neuron through blocking of vesicular monoamine transporters (VMAT2), and by inhibiting the degradation via monoamine oxidase (MAO).[93] Stimulants improve mood, self-confidence, energy levels, alertness, concentration, and physical performance. Because methamphetamine elevates mood, people who experiment with it tend to use it with increasing frequency and in increasing doses, despite their original intent.[93]

Methamphetamine is used orally, intranasally, rectally, intravenously, and by smoking. Immediately after inhalation or intravenous injection, the methamphetamine user experiences an intense sensation, called a “rush” or “flash,” that lasts only a few minutes and is described as extremely pleasurable. The timing and intensity of the “rush” that accompanies the use of methamphetamine, which is a result of the release of high levels of dopamine in the brain, depend in part on the method of administration. Specifically, the effect is almost instantaneous when smoked or injected, whereas it takes approximately 5 minutes after snorting or 20 minutes after oral ingestion.[94] The duration of effect is about 12 hours per administration but can be altered by route of administration and individual characteristics.[93]

CLINICAL PRESENTATION

Amphetamine Intoxication and Withdrawal

General

- Amphetamine intoxication is an acute condition that may result in death. Pharmacotherapy may be indicated for symptomatic control of agitation, psychosis, and seizures.
- Patients may experience withdrawal symptoms for several days but are usually not in acute distress. Treatment of withdrawal is supportive in nature.

Symptoms

- Amphetamine intoxication may present as increased wakefulness, increased physical activity, decreased appetite, increased respiration, hyperthermia, and euphoria. Other CNS effects include irritability, insomnia, confusion, tremors, convulsions, anxiety, paranoia, chest pain, and aggressiveness. Hyperthermia and convulsions can result in death.
- Depression, altered mental status, drug craving, dyssomnia, and fatigue are all symptoms of withdrawal.

Signs

- Patients with amphetamine intoxication may present with tachycardia, hypertension, seizures, or stroke.

Laboratory Tests

- A qualitative urine screening for drugs of abuse can identify patients who have been exposed to amphetamines. However, false positives are common and the diagnostic benefit is limited.

Negative consequences of stimulant abuse range from headache, palpitations, hypertension, tachycardia, dizziness, anxiety and insomnia to confusion, agitation, paranoia, convulsions, and delirium. Methamphetamine-induced caries, or “meth mouth,” is a characteristic pattern of dental decay commonly observed in patients that smoke methamphetamine.[94] Prolonged use of methamphetamine can result in a tolerance for the drug and increased use at higher dosage levels, creating dependence. Such continual use of the drug with little or no sleep may lead to an extremely irritable and paranoid state.

Discontinuing use of methamphetamine often results in a state of depression, as well as fatigue, anergia, and some types of cognitive impairment that can last from 2 days to several months.[94]

Pharmacists should be wary of persons wishing to purchase large quantities of products containing nonprescription sympathomimetic products such as pseudoephedrine. As a precaution, federal legislation now limits the quantities that can be purchased, along with mandating pseudoephedrine-containing products be kept behind a counter, and suitable identification be shown before purchasing.

Ecstasy and Other Methamphetamine Analogs

Several dozen analogs of amphetamine and methamphetamine are mildly hallucinogenic. Two methamphetamine analogs of most concern are 3,4-methylenedioxyamphetamine and especially 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy or Molly). Ecstasy usually refers to a tablet or pill formulation whereas Molly is most often a powdered form that can be insufflated or smoked. Trends in MDMA use have been declining since its peak in 2001.[10] In recent years the use of MDMA in all grade levels had been on a slow decline; however, the annual prevalence of use has held steady.

Users of MDMA report feelings of trust and empathy with others, decreased inhibition when socializing, and enhanced proprioception in addition to stimulating effects that MDMA shares with amphetamines. These effects are due to the preferential selectivity of MDMA for serotonergic over dopaminergic neurotransmission.[95] In addition to these positively reinforcing effects, MDMA use can result in negative effects such as panic, anxiety, depression, paranoid thinking, and psychosis. Physical symptoms include muscle tension, nausea, blurred vision, faintness, chills, and sweating, as well as vomiting, hyperthermia, dehydration, tremors, insomnia, and convulsions. Furthermore, MDMA also increases heart rate and blood pressure due to its structural similarities with amphetamines.[96]

In general, users perceive MDMA to be a harmless drug, based in part on the fact that the risk of death is low compared with other drugs such as heroin and cocaine. However, mounting evidence points to MDMA’s neurotoxic effects, involving a complex and incompletely understood mechanism. Mechanistically MDMA has been shown to destroy serotonergic neurons in animals, but further research is needed to understand the mechanism behind this loss of serotonin following MDMA exposure.[96] Recent publication of small studies exploring

ecstasy being used therapeutically further complicates the assessment of MDMA's risks and benefits, as preliminary studies have been conducted in posttraumatic stress disorder (PTSD), anxiety disorders, and social anxiety in autism. It should be noted that most of these studies also include psychotherapy as part of the treatment regimen.[97,98]

Pure laboratory grade or FDA-approved MDMA is likely to have fewer adverse events than street forms. Manufacturers of illicit drugs sometimes substitute other potentially more dangerous substances for the one the buyer is expecting, or these products may contain chemical by-products due to incomplete processing of active ingredients. Additionally, combination products are being purposefully or unintentionally produced that contain newer generations of hallucinogenic stimulants to enhance the MDMA experience.[95] Such adulterants include amphetamine analogues such as cathinones as well as synthetic cannabinoids. The effects and adverse effects of these agents can be generally categorized as similar to those of other stimulants; however, experience with these new agents is limited and the agent-specific adverse outcomes with their use continue to appear.[99]

Synthetic Cathinones

Catha edulis (Khat) is a shrub native to the horn of Africa and is cultivated in East Africa and the South West Arabian Peninsula; however, European production has been growing in recent years. The leaves are chewed by inhabitants for their stimulating effects similar to coca leaves in South America. The psychoactive properties are due to several alkaloids in the plants, including cathine and cathinone, thus the name cathinones.[100] Cathinone is moderately potent and rapidly degraded. This led to the synthesis of the more potent methcathinone that was marketed in Russia in the 1930s as an antidepressant; however, reports of abuse surfaced soon after it hit the market, leading to the placement of methcathinone, cathinone and all of its derivatives into Schedule I status in the United States.[100,101] Since the initial manufacture of methcathinone, dozens of derivatives have been synthesized in an attempt to improve the marketability of cathinones and evade law enforcement. These ever changing variations of cathinones have differing activity at dopamine, serotonin, and norepinephrine receptors.[102] Agents that interact more strongly with dopamine pathways lead to psychoactive effects, while those that interact with norepinephrine and serotonin pathways lead to more sympathomimetic and hallucinogenic effects, respectively. Mephedrone, methylone, and methylenedioxypyrovalerone (MDPV) are newer additions to this class.

Synthetic cathinones are referred to by a variety of colorful street names that are also ever evolving. Specific names include “Flakka,” “Meow-Meow,” “Bubbles,” “Bounce,” “Ivory Wave,” and “Vanilla Sky” as examples. More generally, these agents have been referred to as plant food, research chemicals, or most commonly, “bath salts” due to their visual appearance (white crystals) in an attempt to avoid law enforcement.[102]

According to the MTFS, “bath salts” use by school-aged children declined in 2017 to 0.5% over all three grade levels surveyed.[10] This continues a longer trend of declining use that may be due to a decrease in popularity or an increase in use of other stimulants. However, the use of synthetic cathinones appear to be highest in certain groups such as the dance club or dance music party scene. Relatively little is known about the deleterious effects of synthetic cathinones, and these agents are often co-ingested with other stimulants, hallucinogens, depressants, or alcohol. Cathinones are often insufflated or orally ingested, but cases of rectal, intramuscular, and subcutaneous use are reported in the literature. The relatively short duration of effect of these agents (generally 1-2 hours) leads to frequent redosing.

Acute intoxication with cathinones includes a constellation of sympathomimetic symptoms including tachycardia, hypertension, hyperthermia, and diaphoresis and its psychiatric effects include agitation, hallucinations, and delirium. More severe outcomes have included metabolic acidosis, rhabdomyolysis, arrhythmia, serotonin syndrome, acute kidney or liver failure, seizures, and death.[102] The chronic effects from use are not well understood at this time but is likely to be similar to chronic use of other stimulants.

Hallucinogens

The drugs commonly classified as hallucinogens are lysergic acid diethylamide (LSD), psilocybin, dimethyltryptamine (DMT), mescaline, phencyclidine (PCP), ketamine, and other related compounds. Approximately 1.4 million people aged 12 or older are estimated current users of hallucinogens, with the percent of users in each age range varying 0.6%, 1.7% and 0.3% for adolescents, young adults, and adults respectively.[9] These statistics may not include ketamine use as this was recently added to the NSDUH Survey. Pharmacologically, LSD and related drugs stimulate both presynaptic (5-HT_{1A} and 5-HT_{1B}) and postsynaptic (5-HT_2) serotonin receptors in the brain, which functionally can cause either agonist or antagonist effects on serotonin activity. Precisely how the hallucinogens exert their effects remains unclear. Overall, LSD is an

extraordinarily potent compound, producing observable CNS effects at doses as low as 25 mcg. For an in-depth review of the history, current status, and future uses of LSD, the reader is directed to a review by Smith and colleagues.[103]

Novel Psychoactive Substances

13 Recent years have witnessed the emergence or re-popularization of a number of very potent substances from three categories of drugs: the tryptamines, piperazines, and phenethylamines. These drugs, commonly referred to as novel psychoactive substances (NPS), are marketed largely through Internet sales, and are abused by people of all ages. They are illegally manufactured or synthesized in clandestine laboratories, and are often offered as a "research chemical" or marked as "not for human consumption," which is common for many designer drugs. Ascribing specific effects to these compounds is difficult as these substances are often included in unknown mixtures, as well as in conjunction with alcohol, cocaine, opioids, and other substances. In general, all three of these drug types lead to euphoria, hallucinations, and overall feelings of improved energy. The adverse effect profile is similar among the three categories with sympathomimetic toxidrome and psychosis predominating, resulting in several organ systems besides the nervous system being deleteriously affected.[102]

Tryptamines are monoamine compounds originally isolated in plants, animals, and fungi, with synthetic forms including alpha-methyltryptamine (AMT) and 5-Methoxy-N,N-diisopropyltryptamine (5-MeO-DiPT) that is often sold under the name "Foxy." Their chemical structure is similar to serotonin, and in addition to being serotonin reuptake inhibitors, synthetic tryptamines can also be direct agonists at 5-HT_{2A} receptors. Examples of tryptamines found in nature include psilocin and psilocybin in certain varieties of mushrooms. Ayahuasca is an herbal tea brewed from a jungle vine (*Banisteriopsis caapi*), which is now known to contain dimethyltryptamine (DMT), a potent serotonin agonist.[102] Visual hallucinations and euphoria are the main effect reported by users; however, agitation, tachycardia, hyperthermia, and other adverse sequelae have been documented. The onset of effect is usually rapid and can last as long as 6 hours.[102]

Piperazines are another group of chemical compounds with stimulant and hallucinogenic properties, with no natural occurring products, whose desired effects are euphoria and energy. Similar to the other agents discussed in this section, piperazines affect a combination of norepinephrine, dopamine, and serotonin receptors in differing amounts depending on the specific agent. N-

benzylpiperazine (BZP) and 1-(3-trifluoromethyl-phenyl) piperazine (TFMPP) are the two most commonly encountered substances from this class. Piperazines are often used with or as alternatives to ecstasy and are used in similar settings, with that being mainly party and club scenes. After oral ingestion, the onset of action is up to 2 hours and lasts for about 8 hours. Adverse effects are similar to synthetic cathinones, tryptamines, and other stimulant/hallucinogens.[102]

Two carbon phenylethylamines (2C drugs) have structures similar to catecholamines, such as norepinephrine and epinephrine, but they have an additional two carbon atoms between the benzene ring and the terminal amino group. This structural variant appears to result in an increased affinity for the 5-HT_2 receptor and alpha-adrenergic receptors resulting in increased hallucinatory and sympathomimetic effects. These compounds have been schedule I controlled substances since 1994; however, their use and evolution continues. The onset of action for 2C derivatives is fast, approximately 30 minutes when taken orally with users self-reporting positive effects such as changes in proprioception, euphoria, and hallucinations, as well as negative effects are similar to other NPS.[102]

Cannabinoids

Marijuana continues to be the most commonly used illicit drug in the United States, which federally continues to be an illegal substance, despite the multitude of states passing laws allowing medical use and recreational use. In addition, increased media attention surrounding potential medical uses has also contributed to the public's evolving beliefs surrounding its use.[18] In 2017, an estimated 26 million Americans aged 12 or older were current users of marijuana that corresponds to 9.6% of this population. According to the most recent MTFS, the annual prevalence of marijuana use rose, 1.3% to 23.9% with 10%, 26%, and 37% of 8th, 10th, and 12th graders, respectively, reporting use.[10] Interestingly, synthetic marijuana continued its slow decline in use since first being tracked in 2013.[10] Marijuana use is likely to increase for the foreseeable future making abuse and subsequent treatment an increasingly important topic for healthcare providers.

The active compounds within marijuana are known as cannabinoids. One chemical component of marijuana is δ-9-tetrahydrocannabinol (THC) that interacts with the two cannabinoid receptors within the CNS to cause its euphoric and psychoactive effects. Cannabidiol (CBD), the other cannabinoid found in marijuana that does not have psychoactive effects, currently is being

investigated for use in epilepsy and other medical disorders.[104] As a group, cannabinoids interact with two subsets of cannabinoid receptors in the body: cannabinoid receptor 1 (CB_1) and cannabinoid receptor 2 (CB_2). Anandamide and 2-arachidonoylglycerol are the endogenous complements to the CB receptors, although their effects have not been completely described. The CB_1 receptors have been found in presynaptic neurons of the prefrontal cortex and in the hippocampus, and the CB_2 receptors are located in smaller numbers in the prefrontal cortex, hippocampus, and hypothalamus. However, they are thought to play a much larger role in systemic effects of cannabinoids due to their abundance in the immune, peripheral nervous, and gastrointestinal systems.[105] Since THC is a partial agonist at CB_1 and CB_2 receptors, it is thought to create its psychoactive effects through CB_1 receptors. In contrast, CBD binds less tightly with CB receptors and may interact with other receptors within and outside of the CNS.[106] Although the knowledge base surrounding the pharmacology and pharmacodynamics of cannabinoids is rapidly expanding, the current knowledge regarding their therapeutic effects is relatively incomplete compared to other FDA-approved medications.

While marijuana is most commonly smoked, it can be ingested orally with THC and CBD extracts now being incorporated into many other usable forms including edible candies/snacks and vaporizable liquids that can be more palatable for new, young, or inexperienced users. Knowledge of the pharmacokinetic principles for the cannabinoids are not well characterized, but they do show highly variable effects that are greatly affected by route of use. After inhalation of smoke or vapors, peak blood concentrations occurs in about 10 minutes and although bioavailability is higher through inhalation relative to oral ingestion, many factors can affect this. Both THC and CBD are poorly bioavailable due to extensive first-pass metabolism by the liver; therefore, peak concentrations occur at about 2 hours when taken via the oral route. The terminal half-life of THC and CBD after a single use is about 24 hours; however, chronic users have highly altered terminal half-lives due to accumulation and subsequent redistribution from fatty tissues after chronic use.[106]

Synthetic Cannabinoids

14 A growing collection of synthetically derived cannabinoids are being abused for their psychoactive effects. Following identification of THC in 1964, and the endogenous cannabinoid receptors in the 1980s, there was a pharmaceutical effort to synthesize cannabinoid receptor agonists for potential therapeutic

indications like nausea and pain. However, the vast majority of these efforts never reached commercial fruition, and have begun showing up in the illicit market. To increase their attractiveness, they are often brightly packaged and given colorful names such as “K2,” “Spice,” “Aroma,” “Mr. Smiley,” “Zohai,” “Eclipse,” “Black Mamba,” “Red X Dawn,” “Blaze,” and “Dream.” Due to unclear laws regarding their legality, these products had been readily available at gas stations and convenience stores, as recent as a few years ago. Since being listed as a schedule I controlled substance, the overt availability has decreased but they are still readily available.[10] Some synthetic cannabinoids produce a combination of intended effects, as well as unintended adverse effects, that resemble intoxication from THC, the psychoactive component of marijuana. However, synthetic cannabinoids appear to be more potent than natural cannabinoids, and may interact with CB receptors for longer than THC. Symptoms of synthetic cannabinoid toxicity are similar to the euphoric and psychoactive effects of THC. The adverse effects of synthetic cannabinoids include severe agitation, anxiety, nausea, vomiting, tachycardia, elevated blood pressure, tremors, seizures, hallucinations, paranoid behavior, and nonresponsiveness. These effects are likely due to complex CB_1 receptor interactions, direct and indirect, with dopaminergic, serotonergic, and glutaminergic pathways within the parts of the brain linked to psychosis.[105] However, it must not be forgotten that most reported adverse experiences with synthetic cannabinoids are troubled by incomplete knowledge of the specific cannabinoid product used, as well as adulteration with other substances.

Cannabis Use Disorder

15 According to the *DSM-5*, cannabis use disorder (CUD) is a problematic pattern of cannabis use leading to significant social impairment and or psychological distress in spite of negative personal consequences.[26] It is often associated with multiple failed attempts at halting cannabis use, with the rate of occurrence in North America being estimated to be as high as 749 in 100,000.[107] Although CUD has quite a high incidence, its detection and treatment are limited in part by beliefs that marijuana is safe and natural.[104] Abrupt discontinuation of cannabis use can elicit a withdrawal syndrome including anxiety, dysphoria, sleep changes, irritability, and anorexia. Although not life threatening, these withdrawal symptoms can make permanent discontinuation difficult.

Treatment of CUD most often centers around psychosocial interventions such as cognitive behavioral therapy (CBT), motivational enhancement therapy

(MET), or a combination there of. Both CBT and MET have been shown to decrease the number of days of cannabis use, reduce the number of joints used in people with CUD, and improve the severity of CUD. Additionally, CBT has been shown to increase abstinence rates where MET has yet to show this effect in clinical studies. Regardless, the combination of CBT and MET appears to be synergistic.[104] Attempts at using pharmacotherapeutic agents to alleviate CUD have been mostly unsuccessful with escitalopram, fluoxetine, bupropion, nefazodone, venlafaxine, valproate, baclofen, modafinil, atomoxetine, buspirone, and naltrexone all proving ineffective. However, several therapeutic candidates have met with some success. Cannabinoid receptor agonists including dronabinol, nabilone a synthetic THC analogue, and nabiximols (Sativex) a combination THC/CBD product have had varying degrees of success in improving withdrawal symptoms in CUD sufferers. One small study found gabapentin, a voltage-gated calcium channel antagonist, was effective in decreasing cannabis use in addition to abating withdrawal symptoms. N-Acetylcysteine (NAC), a cysteine precursor thought to affect glutamate transmission, decreased rates of cannabis use in adolescents. However, follow-up studies in adults did not confirm these results. These results should be interpreted and extrapolated cautiously due to the low number of patients involved in the studies, with further research being necessary to solidify these promising results.[104]

Cannabinoid Hyperemesis Syndrome

Cannabinoid hyperemesis syndrome (CHS) is a syndrome of cyclical vomiting in habitual users of marijuana that abates after discontinuation of cannabis use and is sometimes alleviated through hot bathing or showering. Although first officially recognized in 2004, the syndrome has likely existed much longer. The pathophysiology underlying CHS is not completely elucidated and several hypotheses are being explored. Since cannabinoids are used therapeutically to treat nausea and vomiting in chemotherapy patients, current hypotheses indicate that signaling in this pathway may be altered in a way that leads to excessive nausea and vomiting. Cannabinoids are also known to alter gastrointestinal hormones, potentially leading to aberrant GI function such as emesis. Other potential explanations include non-THC metabolite interactions, genetic variations in metabolism of cannabinoids, and vasodilation of splanchnic vascular beds.[108] Overall, CHS can be difficult to diagnose as nausea and vomiting are symptoms of many issues, and patients may not be forthcoming with their marijuana use due to its questionable legality. One interesting

symptom, that often sets CHS apart from other causes of severe vomiting, is that CHS sufferers often report relief from hot baths or showers.

A systematic review found that CHS is diagnosed in males with greater frequency. The median age when cannabis use started was 16 years and the median age that CHS symptoms developed was 24 years. The fact there is a long pattern of use before CHS develops makes it harder to diagnose as both user and clinician are likely to consider more recent changes or developments over chronic habits. In the same review, all people diagnosed with CHS self-identified as at least weekly cannabis users and a large majority (~75%) were daily users. There are no consensus diagnostic criteria at this time.[108]

Treatment of CHS is also far from standardized at this time due to an incomplete delineation of causative mechanism. Abstinence from cannabis is the most effective treatment option, but takes several days to weeks for the cyclic vomiting to abate. The use of hot bathing is effective for some people; however, its benefit is short-lived and it is not a sustainable treatment modality.[109] If intravenous fluids and traditional antiemetics are unsuccessful at improving CHS symptoms, other treatment options that are less established have been reported. Dopamine antagonists like haloperidol have been used successfully in small case reports,[110–112] and a growing number of case reports have shown some benefit with topical capsaicin application.[113,114] Capsaicin is thought to interact with the transient receptor potential cation channel subfamily V member 1 or vanilloid receptor 1 (TRVP1 or VR1) to improve nausea and vomiting, although the mechanism by which this affects CHS isn't clearly understood.[108,109] Cannabis hyperemesis syndrome is likely to increase in prevalence as availability of marijuana increases and the potency of marijuana and THC-containing products increases.

Inhalants

Inhalants are a diverse group of substances that include volatile solvents, gases, aerosol sprays, and nitrites that are sniffed, snorted, huffed, or bagged to produce intoxicating effects similar to those of alcohol. These substances are found in common household products such as glues, lighter fluid, cleaning fluids, paint products, nail polish remover, gasoline, rubber glue, waxes, and varnishes. Chemicals found in these products include toluene, benzene, methanol, methylene chloride, acetone, methylethyl ketone, methylbutyl ketone, trichloroethylene, and trichloroethane. The gas used as a propellant in canned whipped cream and in small metallic containers called "whippets" (used to make

whipped cream) is nitrous oxide or “laughing gas.” Most of these products are general anesthetics causing depressive CNS effects. According to the 2017 NSDUH survey, 0.2% of the population greater than 12 years were estimated to be current users of inhalants with the 12- to 17-year-old age group having the highest usage rate.[9] The interested reader is referred to the NIDA website (https://www.drugabuse.gov/drugs-abuse/inhalants) for more information.

Pharmacologic Therapy of Acute Drug Intoxications

Treatment of drug intoxication is mainly supportive with maintenance of vital functions while waiting for the drug to be eliminated. When possible, drug therapy should be avoided because psychotropic drug therapy has the potential for worsening a toxic reaction to another psychoactive agent; however, when patients are agitated, combative, hallucinating, or delusional, drug therapy may be required. Urine drug screens can support clinical evaluation but improper or indiscriminate ordering of these tests can be misleading for a clinician. It must be noted that urine drug screens are facility-specific and only test for around a dozen metabolites of common street drugs. Additionally, knowledge of the metabolism of the suspected drug and its excretion pattern is important for proper interpretation of test results. Since treatment is mainly supportive, more clinical weight should be placed on patient presentation and physiologic parameters, than results of the urine drug screen.

Intoxication with stimulants is treated pharmacologically only if the patient is overtly psychotic, agitated, or posing harm to themselves or staff. Injectable benzodiazepines can be used for agitation, psychosis, tachycardia, and hypertension. Their pharmacology leads to calming of sympathetic and psychological symptoms, and the selection should be based on desired pharmacokinetic characteristics of the available benzodiazepines. Antipsychotic drugs should be avoided when possible as their pharmacology may be additive with psychostimulants already on board. When needed, they should be used at the lowest dose necessary to treat the patient for the shortest duration possible. Other sedatives that can be used in certain situations include ketamine, dexmedetomidine, propofol, and barbiturates. As some of these treatments suppress respiratory drive, they are likely to require intubation for some amount of time and must be given in an environment conducive to such a procedure.

Hallucinogen intoxication is treated in a manner similar to stimulant intoxication with drug therapy often being avoided because patients can respond to careful reassurance, or so-called talk-down therapy. When necessary, short-

term antianxiety and/or antipsychotic drug therapy can be used, as described previously. Hyperthermia should be addressed rapidly with nonpharmacologic measures such as ice baths, cold compresses, and evaporative cooling. Electrolyte abnormalities including hyponatremia can lead to seizures and death and must be monitored closely and corrected accordingly.

Naloxone

Intoxication with CNS depressants can be hard to differentiate. Naloxone can be used to reverse the effects of opioids, and undifferentiated CNS depression can also be treated with naloxone empirically due to its wide safety margin. The usual dosage for naloxone in acute opioid toxicity is 0.04- to 2-mg intravenously that can be repeated as necessary based on response.[115] Recent emergence of highly potent synthetic opioids such as fentanyl, carfentanyl, and other derivatives may require much higher doses than is recommend, as they bind much more tightly to the opioid receptors than traditional opioid derivatives. Other routes of administration for naloxone include intraosseous (IO), intramuscular (IM), intranasal (IN), endotracheal, and via inhalation after nebulization.[115] Time to onset and length of activity can vary drastically based on route of administration. In some instances, a naloxone infusion can be administered when re-sedation occurs after initial naloxone reversal or the half-life of the opioid is expected to be considerably longer than that of naloxone. Although naloxone is effective in reversing opioid overdose, it also can precipitate physical withdrawal in physically dependent opioid patients.[115] Full reversal of the opioid effect is not necessary; instead, achieving adequate ventilation and oxygenation is sufficient for treatment. Monitoring patients closely after naloxone reversal is essential as most opioids will last longer than naloxone reversal and repeat sedation is possible.[115]

EVALUATION OF THERAPEUTIC OUTCOMES

There are a range of situations and substances that patients can present with when considering substance abuse. When considering therapeutic outcomes, each treatment must be evaluated to determine efficacy and safety. When considering efficacy there are a variety of factors that must be considered based on the current stage of therapy and the patient’s specific treatment goals. Each of the medications used in the acute or the chronic setting have unique qualities that must be evaluated for each individual patient. Consistent monitoring for efficacy and appropriateness through treatment is critical. Monitoring for withdrawal

reactions utilizing proper assessment scales (ie, COWS) can aid in evaluating the patient appropriately. The safety of each of these medications has to be considered based on unique side effect profiles and drug-interaction concerns for the selected treatment regimen. Data from urine drug screens and profiles from the PDMP can also help provide critical information on the full clinical picture for each patient. Continual patient education must occur to ensure proper medication administration and safety as the therapy continues. Substance use disorder is a chronic disorder that will need not only pharmacological treatment but ongoing psychosocial and educational support. It is important for health care providers woking in this setting, to work closely with the patient to continue seting appropriate goals in order to achieve favorable treatment outcomes.

CONCLUSION

Substance use disorder is a growing health problem in the United States. The true scope of the problem has only recently been explored. If the opioid epidemic is evidence of the direction of the substance use crisis, the United States will continue to have a growing substance use issue in the coming years. Management of substance use disorders, whether through pharmacotherapy or behavioral therapy, is a rapidly progressing field. Pharmacists are ideally situated in the healthcare system to help in all aspects of tackling this problem, from identifying those with SUD to directing pharmacotherapy to assisting with treatment. All pharmacists, whether substance use treatment specialists or not, will be involved in the patient-centered treatment of SUD.

Postclass Engaged Learning Activity

Opioids

Develop your own case in which naloxone treatment is indicated. Provide the case and explain which naloxone device will be recommended along with the rationale. Upon presenting the case, be prepared to demonstrate how to properly counsel the patient on how to use the naloxone device recommended in the developed case.

Marijuana

Select a partner for this activity. One of you will select one peer-reviewed journal article that supports the **beneficial aspects** or possible uses of marijuana for medical purposes. The second student will find a peer-reviewed

article that identifies **negative aspects** of marijuana use such as adverse effects, sociological issues, or economic impacts. Be able to describe to the class the method that the authors used to arrive at their conclusions. Compare and contrast the information found between the articles and develop a 2- to 3-minute verbal report to present to the class to share your findings. Please make sure to include any dose recommendation and any information on route of administration provided in your articles during your presentation.

ABBREVIATIONS

5-HT	5-Hydroxytryptamine
AMT	alpha-methyltryptamine
ASAM	The American Society of Addiction Medicine
BZP	N-benzylpiperazine
CB1	cannabinoid receptor 1
CB2	cannabinoid receptor 2
CDC	Centers for Disease Control and Prevention
CHS	cannabinoid hyperemesis syndrome
CNS	central nervous system
CMS	Centers for Medicare and Medicaid Services
COWS	Clinical Opiate Withdrawal Scale
CPD	controlled prescription drug
CUD	cannabis use disorder
DATA	Drug Addiction Treatment Act
DAWN	Drug Abuse Warning Network
DEA	Drug Enforcement Administration
DMT	dimethyltryptamine
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
ED	emergency department
FDA	Food and Drug Administration
GHB	γ-Hydroxybutyrate
HIV	human immunodeficiency virus
IMF	illicitly manufactured fentanyl
LAAM	levo-α-acetylmethadol
MDA	3,4-methylenedioxyamphetamine
MDMA	3,4-methylenedioxymethamphetamine
MDPV	methylenedioxypyrovalerone
MTFS	Monitoring the Future Study
NAS	Neonatal Abstinence Syndrome
NFLIS	National Forensic Laboratory Information System
NSDUH	National Survey on Drug Use and Health
NSS	National Seizure System
OTC	over-the-counter
OTP	opioid-treatment programs

OUD	Opioid use disorder
PCP	phencyclidine
PDMP	prescription drug monitoring program
POATS	Prescription Opioid Addiction Treatment Study
REMS	Risk Evaluation and Mitigation Strategy
SAMHSA	Substance Abuse and Mental Health Services Administration
SUD	substance use disorder
TFMPP	1-(3-trifluoromethylphenyl)-piperazine
THC	δ-9-tetrahydrocannabinol
TIPS	Treatment Improvement Protocols
XR-NTX	Extended-release injectable naltrexone

REFERENCES

1. Ecclesiastes 1:9 New International Version. Available at: https://www.biblegateway.com/passage/?search=Ecclesiastes%201:9&version=NIV. Accessed August 8, 2018.
2. Inaba DS, Cohen WE.*Uppers, Downers, All Arounders: Physical and Mental Effects of Psychoactive Drugs*. 8th ed. Medford, OR: CNS Productions, Inc.; 2014.
3. Rudgley R. *The Lost Civilizations of the Stone Age*. New York: Free Press; 2000:138.
4. Frosch WA, Robbins ES, Stern M. Untoward reactions to lysergic acid diethylamide (LSD) resulting in hospitalization. *N Engl J Med*. 1965;273(23):1235–1239.
5. Bridge TP, Ellinwood EHJr. Quaalude alley: A one-way street. *Am J Psychiatry*. 1973;130:217–219.
6. Bechtel LK, Holstege CP. Criminal poisoning: Drug-facilitated sexual assault. *Emerg Med Clin North Am*. 2007;25:499–525.
7. O'Donnell J, Gladden RM, Mattson CL, Kariisa M. Notes from the Field: Overdose Deaths with Carfentanil and Other Fentanyl Analogs Detected—10 States, July 2016–June 2017. *MMWR Morb Mortal Wkly Rep*. 2018;67:767–768.
8. National Institute on Drug Abuse Trends & Statistics. Available at: https://www.drugabuse.gov/related-topics/trends-statistics. Accessed August 15, 2018.

9. Substance Abuse and Mental Health Services Administration. *Key Substance Use and Mental Health Indicators in the United States: Results from the 2017 National Survey on Drug Use and Health (HHS Publication No. SMA 18-5068, NSDUH Series H-53)*. Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration; 2018. Accessed October 28, 2018.https://www.samhsa.gov/data/.
10. Johnston LD, Miech RA, O'Malley PM, Bachman JG, Schulenberg JE, Patrick ME. *Monitoring the Future National Survey Results On Drug Use: 1975–2017: Overview, Key Findings on Adolescent Drug Use*. Ann Arbor, MI: Institute for Social Research, The University of Michigan; 2018. Accessed October 1, 2018.http://monitoringthefuture.org/pubs/monographs/mtf-overview2017.pdf.
11. Florence C, Chao Z, Feijun L. The economic burden of prescription opioid overdose, abuse, and dependence in the United States, 2013. *Medical Care*. 2016;54(10):901–905.
12. Centers for Disease Control and Prevention. 2018 Annual Surveillance Report of Drug-Related Risks and Outcomes—United States. Surveillance Special Report. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. Published August 31, 2018. Available at: https://www.cdc.gov/drugoverdose/pdf/pubs/2018-cdc-drug-surveillance-report.pdf. Accessed September 9, 2018.
13. CDC/NCHS, National Vital Statistics System, Mortality. CDC Wonder, Atlanta, GA: US Department of Health and Human Services, CDC; 2017. Available at: https://wonder.cdc.gov. Accessed September 9, 2018.
14. CDC Understanding the Epidemic. Available at: https://www.cdc.gov/drugoverdose/epidemic/index.html. Accessed September 9, 2018.
15. Seth P, Scholl L, Rudd RA, Bacon S. Overdose deaths involving opioids, cocaine, and psychostimulants—United States, 2015–2016. *MMWR Morb Mortal Wkly Rep*. 2018;67:349–358.
16. US Prescribing Rate Maps July 31, 2017. Available at: https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html. Accessed September 9, 2018.
17. When are prescribers required to use prescription drug monitoring programs? PEW. Available at: http://www.pewtrusts.org/en/research-and-

analysis/data-visualizations/2018/when-are-prescribers-required-to-use-prescription-drug-monitoring-programs. Accessed July 27, 2018.

18. 2018 National Drug Threat Assessment October 2018 DEA-DCT-DIR-032-18. Available at: https://www.dea.gov/sites/default/files/2018-11/DIR-032-18%202018%20NDTA%20final%20low%20resolution.pdf. Accessed November 11, 2018.
19. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *MMWR Recomm Rep*. 2016;65(No. RR-1):1–49.
20. Kroenke K, Alford DP, Argoff C, et al. Challenges with implementing the Centers for Disease Control and Prevention opioid guideline: A consensus panel report. *Pain Medicine*. 2019;20(4):724–735.
21. Dowell D, Haegerich T, Chou R. No shortcuts to safer opioid prescribing. N Engl J Med. 2019;380(24):2285–2287. doi: 10.1056/NEJMp1904190. https://www.nejm.org/doi/full/10.1056/NEJMp1904190. Accessed April 30, 2019.
22. Introduction FDA's Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain. Available at: https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugCla Accessed October 1, 2018.
23. Association of American Medical Colleges Analysis in Brief January. 2018;18(1):1-3. Available at: https://www.aamc.org/download/485934/data/january2018addressingtheop Accessed August 31, 2018.
24. Litman R. Abuse-deterrent opioid formulations. *Anesthesiology*. 2018;128:1015–1025.
25. H.R. 6 SUPPORT for Patients and Communities Act The Substance Use-Disorder Prevention the Promotes Opioid Recovery and Treatment for Patients and Community Act. Available at: https://energycommerce.house.gov/wp-content/uploads/2018/09/HR6_09.26.18-Final-Opioid-Sec-by-Sec_BIPART-BICAM.pdf. Accessed October 25, 2018.
26. American Psychiatric Association. *Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association. Accessed August 10, 2018.http://dx.doi.org/10.1176/appi.books.9780890425596.dsm16.

27. Olsen Y, Sharfstein J. Confronting the stigma of opioid use disorder-and its treatment. *JAMA*. 2014;311(14):1393–1394.
28. American Society of Addiction Medicine Public Policy Statement: Definition of Addiction. Posted August 15, 2011. Available at: https://www.asam.org/docs/default-source/public-policystatments/1definition_of_addiction_long_4-11.pdf?sfvrsn=a8f64512_4. Accessed October 18, 2018.
29. Savage SR, Joranson DE, Covington EC, et al. Definitions related to the medical use of opioids: Evolution towards universal agreement. *J Pain Symptom Manage*. 2003;26:655–667.
30. Substance Abuse and Mental Health Services Administration, Office of Applied Studies. Treatment Episode Data Set (TEDS): 2005. Discharges from Substance Abuse Treatment Services, DASIS Series: S-41, DHHS Publication No. (SMA) 08-4314, Rockville, MD, 2008. Accessed September 27, 2018.
31. Clinical Guidelines for Withdrawal Management and Treatment of Drug Dependence in Closed Settings. Geneva: World Health Organization; 2009. 4, Withdrawal Management. Available at: https://www.ncbi.nlm.nih.gov/books/NBK310652/. Accessed October 1, 2018.
32. Substance Abuse and Mental Health Services Administration. Medications for Opioid Use Disorder. Treatment Improvement Protocol (TIP) Series 63, Full Document. HHS Publication No. (SMA) 18- 5063FULLDOC. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2018. Available at: https://store.samhsa.gov/product/TIP-63-Medications-for-Opioid-Use-Disorder-Full-Document-Including-Executive-Summary-and-Parts-1-5-/SMA18-5063FULLDOC. Accessed September 25, 2018.
33. Vital Signs: Risk for Overdose from Methadone Used for Pain Relief—United States, 1999–2010. Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6126a5.htm. Accessed September 15, 2018.
34. Jones CM, Baldwin GT, Manocchio T, White JO, Mack KA. Trends in methadone distribution for pain treatment, methadone diversion, and overdose deaths—United States, 2002–2014. *MMWR Morb Mortal Wkly Rep*. 2016;65:667–671.

35. Faul M, Bohm M, Alexander C. Methadone prescribing and overdose and the association with Medicaid preferred drug list policies—United States, 2007–2014. *MMWR Morb Mortal Wkly Rep*. 2017;66:320–323. http://dx.doi.org/10.15585/mmwr.mm6612a2.
36. Chou R, Cruciani R, Fiellin D, et al. Methadone safety: A clinical practice guideline from the American pain society and college on problems of drug dependence, in collaboration with the heart rhythm society. *The Journal of Pain*. 2014;15(4):321–337.
37. National Institute on Drug Abuse Overdose Death Rates. Available at: https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates. Accessed September 21, 2018.
38. National Drug Early Warning System Sentinel Community Site Advance Report 2016. Available at: https://ndews.umd.edu/sites/ndews.umd.edu/files/u1424/2016_ndews_scs_ Accessed September 4, 2018.
39. Compton W, Jones C, Baldwin G. Relationship between nonmedical prescription-opioid use and heroin use. *N Engl J Med*. 2016;374:154–163.
40. Dowell D, Zhang K, Noonan RK, et al. Mandatory provider review and pain clinic laws reduce the amounts of opioids prescribed and overdose death rates. *Health Aff (Mill-Wood)*. 2016;35(10):1876–1883.
41. Huecker MR, Marraffa J. Heroin. [Updated 2017 Jun 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2018. Available at: https://www.ncbi.nlm.nih.gov/books/NBK441876/. Accessed October 18, 2018.
42. Alambyan V, Pace J, Miller B. The emerging role of inhaled heroin in the opioid epidemic. *JAMA Neurol*. Published online July 9, 2018. doi:10.1001/jamaneurol.2018.1693. Accessed October 1, 2018.
43. Oelhaf RC, Bhimji SS. Heroin Toxicity. [Updated 2018 Sep 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2018. Available at: https://www.ncbi.nlm.nih.gov/books/NBK430736/. Accessed October 15, 2018.
44. Ellis A, McGwin G, Davis G, et al. Identifying cases of heroin toxicity where 6-acetylmorphine (6-AM) is not detected by toxicological analysis. *Forensic Sci Med Pathol*. 2016;12:243–247.
45. CDC U.S. drug overdose deaths continue to rise, increases fueled by synthetic opioids. Available at: https://www.cdc.gov/media/releases/2018/p0329-drug-overdose-

deaths.html. Press release March 29, 2018. Accessed September 4, 2018.

46. Reissig CJ, Carter LP, Johnson MW, et al. High doses of dextromethorphan, an NMDA antagonist, produce effects similar to classic hallucinogens. *Psychopharmacology (Berl)*. 2012;223(1):1–15.
47. Chyka PA, Erdman AR, Manoguerra AS, et al. American association of poison control centers. Dextromethorphan poisoning: An evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol (Phila)*. 2007;45:662–677.
48. Miller H, Panahi L, Tapia D, et al. Loperamide misuse and abuse. *J Am Pharm Assoc*. 2017;57:S45–S50.
49. FDA drug Safety Communication: FDA limits packaging for anti-diarrhea medicine loperamide (Imodium) to encourage safe use. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm594232.htm. Accessed August 31, 2018.
50. Cisewski DH, Santos C, Koyfman A, Long B. Approach to buprenorphine use for opioid withdrawal treatment in the emergency setting. *Am J Emerg Med*. 2019;37(1):143–150. Accessed November 23, 2018.https://doi.org/10.1016/j.ajem.2018.10.013.
51. Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. Geneva: World Health Organization; 2009. Accessed October 1, 2018. https://www.ncbi.nlm.nih.gov/books/NBK143185.
52. Gowing L, Farrell M, Ali R, White JM. Alpha2-adrenergic agonists for the management of opioid withdrawal. *Cochrane Database Syst Rev*. 2016; (5):CD002024. doi: 10.1002/14651858.CD002024.pub5.
53. Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: A double-blind placebo controlled, multicenter randomised trial. *Lancet*. 2011;377:1506–1513.
54. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2014;(2):CD002207. doi: 10.1002/14651858.CD002207.pub4.
55. VA/DoD clinical practice guideline for the management of substance use disorders. Available at: https://www.healthquality.va.gov/guidelines/MH/sud/VADODSUDCPGRe Accessed September 27, 2018.
56. American Society of Addiction Medicine, The ASAM National Practice

Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. 2015. Available at: https://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf. Accessed September 25, 2018.

57. Federal Guidelines for Opioid Treatment Programs January 2015. Available at: https://store.samhsa.gov/system/files/pep15-fedguideotp.pdf. Accessed September 27, 2018.
58. Revia package insert Duramed Pharmaceuticals last updated October 2013. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/018932s017lbl Accessed October 7, 2018.
59. Vivitrol (extended release naltrexone) prescription drug label. U.S. National Library of Medicine. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=cd11c435-b0f0-4bb9-ae78-60f101f3703f. December 2015. Accessed September 27, 2018.
60. Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment of opioid dependence. *Cochrane Database Syst Rev*. 2011;(4):CD001333.
61. Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: A double-blind placebo controlled, multicenter randomised trial. *Lancet*. 2011;377:1506–1513.
62. Dear Healthcare Provider Letter Important Drug Warning Vivitrol December 8, 2015. Available at: https://www.vivitrolrems.com/content/pdf/patinfo-dhcp-pi-12082015.pdf. Accessed October 11, 2018.
63. Substance Abuse and Mental Health Services Administration. (2016). Sublingual and Transmucosal Buprenorphine for Opioid Use Disorder: Review and Update. Advisory, Volume 15, Issue 1. Available at: https://store.samhsa.gov/system/files/sma16-4938.pdf. Accessed October 11, 2018.
64. Gold Standard, Inc. Buprenorphine. Clinical Pharmacology [database online]. Available at: http://www.clinicalpharmacology.com. Accessed October 11, 2018.
65. Gold Standard, Inc. Naltrexone. Clinical Pharmacology [database online].

Available at: http://www.clinicalpharmacology.com. Accessed October 11, 2018.

66. Sublocade Medication Guide. Last Updated November 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209819s000lbl Accessed October 11, 2018.
67. Probuphine-buprenorphine hydrochloride implant-prescription drug label. U.S. National Library of Medicine. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=10fd7088-cc4a-4bda-a5e3-a82563540a9a. Accessed October 11, 2018.
68. U.S. Department of Justice Drug Enforcement Administration Diversion Control Division. DEA Requirements for DATA Waive Physicians (DWPs). Available at: https://www.deadiversion.usdoj.gov/pubs/docs/dwp_buprenorphine.htm. Accessed September 25, 2018.
69. Implementation of the Provision of the Comprehensive Addiction and Recovery Act of 2016 Relating to the Dispensing of Narcotic Drugs for Opioid Use Disorder. Available at: https://www.federalregister.gov/documents/2018/01/23/2018-01173/implementation-of-the-provision-of-the-comprehensive-addiction-and-recovery-act-of-2016-relating-to. Accessed September 27, 2018.
70. TIP 40 Center for Substance Abuse Treatment. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Treatment Improvement Protocol (TIP) Series 40. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2004. DHHS Publication No. (SMA) 04-3939. Available at: http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=hssamhsatip&part=A72248. Accessed October 25, 2018.
71. Weinsteine Z, Kim H, Chen D, et al. Long-term retention in office based opioid treatment with buprenorphine. *J Subst Abuse Treat*. 2017;74:65–70.
72. National Institute on Drug Abuse Opioid Overdose Crisis. Available at: https://www.drugabuse.gov/drugs-abuse/opioids/opioid-overdose-crisis. Accessed October 12, 2018.
73. Jordan MR, Morrisonponce D. Naloxone. [Updated 2018 Sep 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2018. Available at: https://www.ncbi.nlm.nih.gov/books/NBK441910/. Accessed October 12, 2018.
74. Lim J, Bratberg J, Corey D, et al. Prescribe to prevent: Overdose

prevention and naloxone rescue kits for prescribers and pharmacists. *J Addict Med*. 2016;10(5):300–310.

75. Keck Graduate Institute School of Pharmacy. Opioid Safety: Focus on Furnishing Naloxone. A Guide for California Community Pharmacists. Claremont, CA. August 2018. Available at: http://prescribetoprevent.org/wp2015/wp-content/uploads/OpioidSafetyFocusOnNaloxone-Pharmacists-June2018-links.pdf. Accessed October 23, 2018.
76. Doleac, Jennifer L. and Mukherjee, Anita. The Moral Hazard of Lifesaving Innovations: Naloxone Access, Opioid Abuse, and Crime. Available at: http://dx.doi.org/10.2139/ssrn.3135264. Accessed November 11, 2018.
77. McDonald R, Campbell N, Strang J. Twenty years of take-home naloxone for the prevention of overdose deaths from heroin and other opioids-Conception and maturation. *Drug Alcohol Depend*. 2017;178:176–187.
78. National Alliance for Model State Drug Laws. Naloxone Access Statutes. Available at: http://www.namsdl.org/library/06A653E3-E04E-9112-0CBB0B0FA325DC79/. Accessed October 5, 2018.
79. Surgeon General's Advisory on Naloxone on Opioid Overdose. Available at: https://www.surgeongeneral.gov/priorities/opioid-overdose-prevention/naloxone-advisory.html. Accessed October 5, 2018.
80. Haight SC, Ko JY, Tong VT, Bohm MK, Callaghan WM. Opioid Use Disorder Documented at Delivery Hospitalization—United States, 1999–2014. *MMWR Morb Mortal Wkly Rep*. 2018;67:845–849. doi: http://dx.doi.org/10.15585/mmwr.mm6731a1.
81. Substance Abuse and Mental Health Services Administration. Clinical Guidance for Treating Pregnant and Parenting Women With Opioid Use Disorder and Their Infants. HHS Publication No. (SMA) 18-5054. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2018.
82. Soyka M. Treatment of benzodiazepine dependence. *N Engl J Med*. 2017;376:1147–1157.
83. Bachhuber M, Hennessy S, Cunningham C, et al. Increasing benzodiazepine prescriptions and overdose mortality in the United States, 1996-2013. *Am J Public Health*. 2016;106(4):686–688.
84. Dasgupta N, Funk M, Proescholdbell S, et al. Cohort study of the impact of high-dose opioid analgesics on overdose mortality. *Pain Med*.

2016;17:85–98.

85. FDA Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm518473.htm. Accessed September 25, 2018.
86. Agravat A. 'Z'-hypnotics versus benzodiazepines for the treatment of insomnia. *Prog Neurol Psychiatry*. 2018;22(2):26–29.
87. Wilt T, MacDonald R, Brasure M, et al. Pharmacologic treatment of insomnia disorder: An evidence report for clinical practice guideline by the American College of Physicians. *Ann Intern Med*. 2016;165(2):103–112.
88. Lader M, Kyriacou A. Withdrawing benzodiazepines in patients with anxiety disorders. *Curr Psychiatry Rep*. 2016;18:8.
89. Puening S, Wilson M, Nordstrom K. Psychiatric Emergencies for clinicians: Emergency department management of benzodiazepine withdrawal. *J Emerg Med*. 2017;52(1):66–69.
90. Drake LR, Scott PJ. DARK classics in chemical neuroscience: Cocaine. *ACS Chem Neurosci*. 2018;9(10):2358–2372. doi: 10.1021/acschemneuro.8b00117.
91. Allain F, Minogianis EA, Roberts DCS, Samaha AN. How fast and how often: The pharmacokinetics of drug use are decisive in addiction. *Neurosci Biobehav Rev*. 2015;56:166–179. doi: 10.1016/j.neubiorev.2015.06.012.
92. Graziani M, Nencini P, Nisticò R. Genders and the concurrent use of cocaine and alcohol: Pharmacological aspects. *Pharmacol Res*. 2014;87:60–70. Epub 2014 Jun 24.doi: 10.1016/j.phrs.2014.06.009.
93. Baig AA. DARK side of amphetamine and analogues: Pharmacology, syndromic manifestation, and management of amphetamine addiction. *ACS Chem Neurosci*. 2018;9(10):2299–2303. doi: 10.1021/acschemneuro.8b00137.
94. Radfar SR, Rawson RA. Current research on methamphetamine: Epidemiology, medical and psychiatric effects, treatment, and harm reduction efforts. *Addict Health*. 2014;6(3-4):146–154.
95. Dolan SB, Chen Z, Huang R, Gatch M. "Ecstasy" to addiction: Mechanisms and reinforcing effects of three synthetic cathinone analogs of MDMA. *Neuropharmacology*. 2018;133, 171–180.

96. Parrott AC. MDMA, serotonergic neurotoxicity, and the diverse functional deficits of recreational “Ecstasy” users. *Neurosci Biobehav Rev*. 2013;37(8):1466–1484. doi: 10.1016/j.neubiorev.2013.04.016.
97. Yazar-Klosinski BB, Mithoefer MC. Potential psychiatric uses for MDMA. *Clin Pharm and Ther*. 2017;101:194–196.
98. Feduccia AA, Holland J, Mithoefer MC. Progress and promise for the MDMA drug development program. *Psychopharmacology*. 2018;235:561–571.
99. Kasper AM, Ridpath AD, Gerona RR, et al. Severe illness associated with reported use of synthetic cannabinoids: A public health investigation (Mississippi, 2015). *Clin Toxicol (Phila)*. 2019;57(1):10–18. doi: 10.1080/15563650.2018.1485927.
100. Simmons SJ, Leyrer-Jackson JM, Oliver CF, et al. DARK classics in chemical neuroscience: Cathinone-derived psychostimulants. *ACS Chem Neurosci*. 2018;9(10):2379–2394. doi: 10.1021/acschemneuro.8b00147.
101. Katz DP, Bhattacharya D, Bhattacharya S, et al. Synthetic cathinones: “A khat and mouse game”. *Toxicol Lett*. 2014;229(2):349–356. doi: 10.1016/j.toxlet.2014.06.020.
102. Graddy R, Buresh ME, Rasegar DA. New and emerging illicit psychoactive substances. *Med Clin N Am*. 2018;102:697–714.
103. Smith DE, Raswyck GE, Davidson LD. From Hofmann to the Haight Ashbury, and into the future: The past and potential of lysergic acid diethylamide. *J Psychoactive Drugs*. 2014;46(1):3–10.
104. Levesque A, Le Foll B. When and how to treat possible cannabis use disorder. *Med Clin N Am*. 2018;102:667–681.
105. Fantegrossi WE, Wilson CD, Berquist MD. Propsychotic effects of synthetic cannabinoids: Interactions with central dopamine, serotonin, and glutamate systems. *Drug Metabolism Reviews*. 2018;50(1):65–73. doi: 10.1080/03602532.2018.1428343.
106. Lucas CJ, Galettis P, Schneider J. The pharmacokinetics and the pharmacodynamics of cannabinoids. *Br J Clin Pharmacol*. 2018;84(11):2477–2482. doi: 10.1111/bcp.13710.
107. Peacock A, Leung J, Larney S, et al. Global statistics on alcohol, tobacco and illicit drug use: 2017 Status report. *Addiction*. 2017;113:1905–1926.
108. Sorensen CJ, DeSanto K, Borgelt L, et al. Cannabinoid hyperemesis syndrome: Diagnosis, pathophysiology, and treatment—a systematic review. *J Med Toxicol*. 2017;13:71–87. doi: 10.1007/s13181-016-0595-z.

109. Richards JR, Lapoint JM, Burillo-Putze G. Cannabinoid hyperemesis syndrome: Potential mechanisms for the benefit of capsaicin and hot water hydrotherapy in treatment. *Clinical Toxicology*. 2018;56(1):15–24. doi: 10.1080/15563650.2017.1349910.
110. Inayat F, Virk H, Ullah W, et al. Is haloperidol the wonder drug for cannabinoid hyperemesis syndrome? *BMJ Case Rep*. 2017;2017:pii:bcr2016218239. doi: 10.1136/bcr-2016-218239.
111. Jones JL, Abernathy KE. Successful treatment of suspected cannabinoid hyperemesis syndrome using haloperidol in the outpatient setting. *Case Rep Psychiatry*. 2016;2016:3614053. doi: 10.1155/2016/3614053.
112. Hickey JL, Witsil JC, Mycyk MB. Haloperidol for treatment of cannabinoid hyperemesis syndrome. *Am J Emerg Med*. 2013;31(6):1003.e5–1003.e6. doi: 10.1016/j.ajem.2013.02.021.
113. Dezieck L, Hafez Z, Conicella A, et al. Resolution of cannabis hyperemesis syndrome with topical capsaicin in the emergency department: A case series. *Clinical Toxicol*. 2017;55(8):908–913. doi: 10.1080/15563650.2017.1324166.
114. Graham J, Barberio M, Wang GS. Capsaicin cream for treatment of cannabinoid hyperemesis syndrome in adolescents: A case series. *Pediatrics*. 2017;140(6):pii: e20163795. doi: 10.1542/peds.2016-3795.
115. Naloxone Hydrochloride Injection, USP Package Insert. Vizient, Inc. Last updated April 2018. Available at: http://labeling.pfizer.com/ShowLabeling.aspx?id=4541. Accessed January 13, 2019.
116. Flumazenil Package Insert. Roche Laboratories Inc. Last Updated February 2007. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/020073s016lb Accessed January 15, 2019.

83

Substance-Related Disorders II: Alcohol, Nicotine, and Caffeine

Robin Moorman Li, Lori Dupree, and Paul L. Doering

KEY CONCEPTS

1. Globally, more than 3 million people, predominantly males, died in 2016 from alcohol consumption, which represents 1 in 20 deaths.
2. Studies have identified genotypic and functional phenotypic variants that either serve to protect patients or predispose them toward alcohol dependence.
3. Except at very high and very low blood concentrations, the metabolism of alcohol is considered to follow zero-order pharmacokinetics, and this has important implications for the time course in which alcohol can exert its effects.
4. Disulfiram, naltrexone, and acamprosate are FDA-approved drug therapies for the treatment of alcohol dependence. The clinical utility of these agents to improve sustained abstinence and reduce heavy drinking remains controversial.
5. Tobacco is the number one preventable cause of death in the United States.
6. It is recommended that clinicians ask all adults about tobacco use, advise on how to stop using tobacco products, and provide pharmacotherapy and behavioral treatment options to aid in smoking cessation.
7. All forms of nicotine replacement therapy are effective in reducing the amount smoked and achieving abstinence.
8. Varenicline may be more efficacious than all other single nicotine replacement therapies (NRTs) (except for similar efficacy to the nicotine patch) and is approved by the FDA for up to 6 months of maintenance therapy.

9. Caffeinism is the term coined to describe the clinical syndrome produced by acute or chronic overuse of caffeine. As many as one in five adults consume doses of caffeine generally considered large enough to cause clinical symptoms.
10. Energy drinks continue to be popular particularly among adolescents and emerging adults. Concerns have been raised regarding the safety of these products.

Preclass Engaged Learning Activity

Alcohol Use Disorder

Watch this 5-minute video entitled, "Brief intervention: Steve," which provides an example of an outpatient clinician making an intervention on a patient with an alcohol problem. This video is useful to enhance student understanding of how the AUDIT tool can help collect patient information during a patient interview and how motivational interviewing can effectively help patients realize their problem and develop a plan of action.

https://tinyurl.com/y5xvt3u3

1. The patient in the video scored in Zone 2 of the AUDIT questionnaire. Describe how you would interpret those results.
2. Motivational interviewing is a counseling approach where clinicians use a patient-centered stance in combination with techniques to help patients explore and resolve their own mixed feelings about changing unhealthy behaviors.

The principles of motivational interviewing include:

- Expressing empathy—building rapport and engaging the patient by seeking to understand his/her perspective
- Developing discrepancy—determining the patient's perception of how well current behaviors match desired behaviors
- Rolling with resistance—letting the patient make the arguments for change instead of the clinician arguing for change
- Supporting self-efficacy—using reflective statements to restate the patient's belief which he/she verbalized to be able to change a specific behavior

In the video, which principle(s) of motivational interviewing did the clinician utilize when interviewing the patient?

Smoking Cessation

1. Review the brief case provided
2. Watch the 3-minute video titled, “The 5As in Practice: Role Play of a Brief Intervention” which provides an example of the 5As in smoking cessation used in the clinic setting.

https://tinyurl.com/y437notb

Case:

A 43-year-old woman presented to primary care 2 weeks ago for treatment for a chronic productive cough. During this visit a smoking cessation discussion was captured (see video above) and it was determined she would begin the nicotine patches in 1 week. She is now returning 2 weeks later reporting she had an adverse reaction to the adhesive from the nicotine patches. She has called the quitline once, but would like some other recommendations from you in regards to strategies for smoking cessation as well. What would you recommend?

PMH:

Asthma

Allergies:

PCN

Adhesive (just added today to medical record from experience from nicotine patches)

INTRODUCTION—ALCOHOL

Alcohol, nicotine, and caffeine are considered by most to be socially acceptable drugs, yet they impose an enormous social and economic cost on our society. The World Health Organization (WHO) estimates that in 2016, there were more than 3 million people worldwide who died from alcohol consumption with the majority being males. Long-term alcohol abuse often leads to chronic disease and a causal relationship between alcohol abuse and at least 200 types of chronic disease or injury has been established (eg, esophageal cancer, liver cancer, and cirrhosis of the liver, epileptic seizures, homicide, and motor vehicle

accidents) worldwide.[1] Nationally, between the years of 2010 and 2012, there were approximately 2,200 deaths caused by alcohol poisoning in patients more than 15 years old. During this time period, alcohol poisoning was responsible for an average of 6 deaths predominately in men between the ages of 35 and 64 years.[2]

EPIDEMIOLOGY

According to the National Survey on Drug Use and Health, 140.6 million Americans over the age of 12 reported current alcohol use, with 11.9% reporting heavy alcohol use and 47.4% reporting binge alcohol use in 2017, defined as consuming five drinks or more on the same occasion on at least one day in the past 30 days for males and as consuming four drinks or more on the same occasion on at least one day in the past 30 days for females.[3] Additionally, 12% reported heavy alcohol use, defined as binge drinking on 5 days or more in the past 30 days. In this report, it was estimated that 1 in 10 adolescents between the ages of 12 and 17 years were current alcohol users, while an overall decline in alcohol use has been reported in this age group, this equates to 2.5 million young adults in one month.[3] It is also estimated in this specific age range that there are over 174,000 adolescents who are current heavy alcohol users. In contrast to this age group, the estimates of heavy alcohol users in 2017 rose in older age adults to 3.3 million for those between the ages of 18 and 25 years old, and 13.2 million for those 26 years and older.[3]

2 The disease concept of addiction, using alcoholism as a model, states that individuals who suffer from the disease do not choose to contract the disease any more than someone who suffers from heart disease or diabetes mellitus chooses to contract that illness. Alcohol use disorder (AUD) is a chronic disease characterized by problematic and uncontrolled drinking and is diagnosed based on DSM-5 criteria, which integrates alcohol abuse and alcohol dependence in the diagnosis of AUD, requiring 2 of the 11 criteria to be met during a 12-month period. The DSM-5 criteria asks 11 questions about the amount of alcohol use, the effects of alcohol use both personally and professionally, and any presence of withdrawal symptoms in the past year. Severity is determined based on the number of criteria met and subsequently classified as mild (2-3 symptoms), moderate (4-5 symptoms), or severe (6 or more symptoms)[4,5] It has long been recognized that alcohol dependence is heritable, as 50% of first-degree relatives of people with alcohol use disorder become alcohol-dependent themselves.[6,7] A

recent quantitative meta-analysis evaluated the heritability of AUD using twin and adoption studies and determined similar results.[8] Additional research continues to identify genetic variations leading to not only variations in responses to alcohol, but also the responses to the effects of the pharmacological treatment of AUDs. Prospective data is lacking to determine the effects of genetic polymorphisms on individual responses of medications to treat AUD.[7] Large-scale pharmacoepidemiologic studies have further elucidated the environmental risk factors that are associated with either protective effects or predisposition toward alcoholism (Table 83-1).[9]

TABLE 83-1 Genotypic, Phenotypic, and Environmental Factors That Increase Alcohol-Dependence Risk

Susceptibility Genes	Phenotype	Environment
Regions on chromosomes 1 and 4 that code for the following receptors:	Personality traits that include:	Religious background
$GABA_A$	Novelty seeking	Urban residence (vs rural)
Serotonin 1b	Impulsivity	History of sexual abuse
DRD4	Aggression	Being single
Tryptophan hydroxylase	Depression	Having deceased parents
Neuropeptide Y	Maximum number of alcoholic drinks consumed per day	
Gene that codes for: ALDH2 5HTTLPR		

ALDH2, aldehyde dehydrogenase 2; DRD4, type 4 dopamine receptor gene; GABA, γ-aminobutyric acid; 5HTTLPR, 5 hydroxytryptamine transporter.

Data from References 9, 10, and 12.

ETIOLOGY

Alcohol is a CNS depressant that acts in a dose-dependent fashion, producing sedation that progresses to sleep, unconsciousness, coma, surgical anesthesia, and finally fatal respiratory depression potentially leading to cardiovascular collapse. Alcohol affects endogenous opiates and several neurotransmitter systems in the brain, including γ-aminobutyric acid (GABA), glutamine, and dopamine. Alcohol is available in a variety of concentrations in various alcoholic beverages. There is approximately 14 g of alcohol in a 12-oz (355 mL) can of beer (approximately 5%), in 5 oz (148 mL) of nonfortified wine (approximately 12%), or in one shot (1.5 oz [44 mL]) of 80-proof whiskey (40%).[10] Full

consumption of this amount will cause an increase in blood alcohol level of approximately 20 to 25 mg/dL (4.3 to 5.4 mmol/L) in a healthy 70-kg (154 lb) male, although this varies with the time frame over which the alcohol is consumed, the type of alcoholic beverage, whether food is consumed along with it, and many other patient-specific variables. The lethal dose of alcohol in humans is variable, but deaths generally occur when blood alcohol levels are greater than 400 to 500 mg/dL (87-109 mmol/L).[11]

PATHOPHYSIOLOGY

Absorption of alcohol begins in the stomach within 5 to 10 minutes of oral ingestion with the onset of clinical effects following fairly rapidly. Peak serum concentrations of alcohol usually are achieved 30 to 90 minutes after finishing the last drink, although it is variable depending on the type of alcoholic beverage, type and timing of food consumption, and other factors.[12,13]

More than 90% of alcohol in the plasma is metabolized in the liver by three-enzyme systems that operate within the hepatocyte with the remainder being excreted by the lungs, and in urine and sweat. Alcohol is metabolized to acetaldehyde by alcohol dehydrogenase in the liver cell. In turn, acetaldehyde is metabolized to carbon dioxide and water by the enzyme aldehyde dehydrogenase. A second pathway for oxidation of alcohol uses catalase, an enzyme located in the peroxisomes and microsomes. The third enzyme system, the microsomal alcohol oxidase system, has a role in the oxidation of alcohol to acetaldehyde. These last two mechanisms are of lesser importance than the alcohol dehydrogenase–aldehyde dehydrogenase system.[12,13]

3 The metabolism of alcohol generally is said to follow zero-order pharmacokinetics. This can, in fact, be an oversimplification because at very high or very low concentrations, the metabolism can follow first-order pharmacokinetics. Blood alcohol concentration (BAC) is a measurement of the amount of alcohol present in the blood and as BAC rises, the effects of alcohol can result in different levels of impairment (**Table 83-2**). The specific effects of alcohol on BAC that are reported in the literature are variable. On average, the blood alcohol concentration (BAC) is lowered from 15 to 22.2 mg/dL (3.3–4.8 mmol/L) per hour in the nontolerant individual, assuming that the individual is in the postabsorptive state. In healthy men and women, alcohol has a volume of distribution of 0.6 to 0.8 L/kg, which corresponds closely with total body water.[14]

TABLE 83-2 Specific Effects of Alcohol Related to Blood Alcohol Concentration

BAC (%)* (mmol/L)	Type of Impairment	Effect(s)
0.0–0.05 (0–12)	Mild	Mild speech/memory/attention/ coordination/balance impairment, relaxation, sleepiness
0.06–0.15 (13–34)	Increased	Impaired speech/memory/attention/ coordination/balance, risk of aggression, significantly impaired driving skills, increased risk of injury to self and others, moderate memory impairment
0.16–0.30 (35–65)	Severe	Impaired speech/memory/attention/ coordination/reaction time, balance significantly impaired, driving skills dangerously impaired, judgment and decision making dangerously impaired, blackouts, vomiting and signs of alcohol poisoning common, loss of consciousness
0.31–0.45 (66–98)	Life-threatening	Loss of consciousness, danger of life-threatening alcohol poisoning, significant risk of death

*Grams of ethyl alcohol per 100 mL of whole blood.

BAC, blood alcohol concentration.

Data from Reference 21.

CLINICAL PRESENTATION

Screening for Alcohol Use Disorder

The CAGE questionnaire is a mnemonic for four questions: (a) Have you ever felt the need to *c*ut down on your drinking? (b) Have people *a*nnoyed you by criticizing your drinking? (c) Have you ever felt *g*uilty about your drinking? (d) Have you ever had a drink the first thing in the morning ("*e*ye opener")? This commonly used tool can be used for detecting individuals more likely to be abusing alcohol and therefore at greater risk for alcohol withdrawal. A positive response to two or more of these four questions suggests an increased likelihood of alcohol abuse with an average sensitivity of 0.71 (71%) and an average

specificity of 0.90 (90%).[15]

The Alcohol Use Disorders Identification Test (AUDIT) is a validated 10-question screening tool originally developed to screen for alcohol dependence, problems associated with alcohol use, and the amount and frequency of alcohol consumption in adults in the primary care setting. This screening tool can be completed by the patient or can be completed via an interview with a healthcare provider. Scores greater than 8, out of a possible 40, indicate harmful or hazardous drinking. Scores higher than 13 for women and 15 for men necessitate further evaluation for alcohol dependence.[16] The AUDIT tool, as well as a short version of AUDIT (AUDIT-C), has been used within a broad range of patient population samples and is an appropriate first step in identifying patients struggling with alcohol issues.[17]

Acute Effects of Alcohol

At lower serum concentrations, euphoria and disinhibition may be noted. Additionally slurred speech, altered perception of the environment, impaired judgment, ataxia, incoordination, nystagmus, and hyperreflexia may occur. As plasma levels increase, combative and destructive behavior may occur. With higher levels still, somnolence and respiratory depression may ensue.[18] The typical effects of various BACs are shown in Table 83-2, although effects vary from individual to individual.

Alcohol Poisoning

Acute alcohol poisoning usually occurs with rapid consumption of large quantities of alcoholic beverages. With sustained drinking of moderate amounts of alcohol, the user passes out before a toxic dose of alcohol can be ingested, and/or the person vomits to rid the stomach of its toxic reservoir. With rapid drinking, the person may fall asleep or pass out without vomiting, allowing continued alcohol absorption from the gastrointestinal (GI) tract until fatal BACs are achieved.[18]

Laboratory Studies

In the emergency room, a BAC should be ordered in any patient in whom alcohol ingestion is suspected, regardless of the presenting complaint. For clinical purposes, most laboratories report BAC in units of mg/dL or mmol/L. In

legal cases, results are reported in percentage (grams of ethyl alcohol per 100 mL of whole blood). Along with a BAC, a complete blood count to assess for anemia, serum magnesium, serum glucose, a complete metabolic panel to assess electrolytes, and renal and liver function should be examined. If the diagnosis is unclear, if the intoxication seems atypical, or when there is suspicion of multiple drug ingestions, a complete toxicologic screen to rule out the presence of other substances may be useful.[19]

TREATMENT

Desired Outcomes

While alcohol withdrawal most likely occurs in the face of alcohol use dependence, it is necessary to treat acute withdrawal symptoms (or prevent them from occurring) before other treatments are started for the treatment of primary alcohol dependence. Therefore, the goals for alcohol-dependent persons trying to decrease or discontinue alcohol intake include (a) the prevention and treatment of withdrawal symptoms (including withdrawal seizures and delirium tremens) and medical or psychiatric complications, (b) long-term abstinence after detoxification, and (c) entry into ongoing medical and alcohol-dependence treatment.[20]

Nonpharmacologic Therapy

Due to the severity of signs and symptoms and associated morbidity and mortality with alcohol withdrawal, nonpharmacologic therapy is not recommended. Patients with alcohol withdrawal require a coordinated approach in a monitored setting with the use of inpatient, outpatient, and rehabilitation services.[21]

Pharmacologic Therapy

Following the completion of a baseline assessment by using a validated tool, such as the Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar),[22] symptom-triggered treatment with a benzodiazepine is the current standard of care in alcohol detoxification to assess severity and avoid progression to more severe stages of withdrawal. Trials comparing different

benzodiazepines demonstrated that all appear similarly efficacious in reducing the signs and symptoms of withdrawal. However, there are pharmacokinetic differences (ie, onset of action, duration, metabolism) between benzodiazepines, in addition to route of administration and cost, that guide drug therapy decisions.[21,23]

CLINICAL PRESENTATION

Alcohol Withdrawal

General

- Acute alcohol detoxification and withdrawal after chronic alcohol abuse is a serious condition that can require hospitalization and adjunctive pharmacotherapy.
- At a very high BAC, death is possible.

Symptoms

- The intoxicated patient can present with slurred speech and ataxia. The patient can be sedated or unconscious.
- As BACs decrease rapidly, nausea, vomiting, tremors, and hallucinations can ensue. Delirium tremens (DT) and seizures are the most severe symptoms.
- An evaluation should be completed using the Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar), a 10-item scale to document and score the patient's baseline symptoms (nausea and vomiting, tremors, paroxysmal sweats, anxiety, tactile/auditory/visual disturbances, headache, agitation, orientation and clouding of sensorium).

Signs

- The intoxicated patient can present with nystagmus.
- In withdrawal, the patient can present with tachycardia, diaphoresis, hypertension, and/or hyperthermia.

Laboratory Tests

- In the emergency department, a BAC should be ordered when alcohol ingestion is suspected. Clinical laboratories typically report BAC in units

of milligrams per deciliter or millimoles per liter. A whole blood alcohol level of 150 mg/dL (33 mmol/L) reported in the hospital corresponds to 0.15% BAC obtained by law enforcement.

- A complete blood count to assess for anemia, complete metabolic panel to assess electrolytes, glucose, renal, and liver function, and a serum magnesium level should be ordered.
- A complete toxicologic screen to rule out the presence of other substances can be useful.

Other Diagnostic Tests

- Differentiate acute alcohol intoxication from other medical illnesses (eg, head trauma).
- Order computed tomography (CT) on any patient with focal neurologic findings, failure to improve, new-onset seizures, or mental status out of proportion to degree of intoxication.

Although benzodiazepines are the standard of care, other agents with activity on the GABA system have been evaluated in the treatment of alcohol withdrawal. A Cochrane review[24] of the efficacy and safety of pharmacological options in treating alcohol withdrawal syndrome included a total of 7,333 patients. The medications evaluated included benzodiazepines, baclofen, anticonvulsants (ie, phenobarbital, valproic acid, carbamazepine, gabapentin, topiramate) and psychotropic analgesic nitrous oxide (PAN), along with gamma hydroxybutyrate. Efficacy was determined based on the impact on alcohol withdrawal seizures. Benzodiazepines were more efficacious when compared to both placebo (RR 0.16; 95% CI 0.04–0.69) and antipsychotics (RR 0.24; 95% CI 0.07–0.88). Within the benzodiazepine class comparison, no benzodiazepine was shown statistically to have better efficacy, although there was a trend toward better efficacy with chlordiazepoxide.[24]

Treatment Regimens

Front-Loading Therapy

One initial approach to managing alcohol withdrawal includes using an initial high dose of a long-acting benzodiazepine, such as diazepam 10 to 20 mg or chlordiazepoxide 100 mg, and administering repeated doses every 1 to 2 hours

until the patient is sedated. It is reported that an average of three doses of these long-acting benzodiazepines is commonly utilized to achieve adequate sedation. It is important for providers to monitor the patients carefully for benzodiazepine toxicity, such as excessive sedation, respiratory depression, and delirium. Additionally, this approach should be used with extreme caution in elderly patients or in patients who have liver disease since the elimination rate will be extended, leading to increased risk of toxicity.[19]

Symptom-Triggered Therapy

With symptom-triggered therapy, medication is given only when the patient has symptoms and the CIWA-Ar score is 8 or above. This approach has become the accepted standard for treating alcohol dependence in the hospital setting since it results in a shorter treatment duration, potentially avoiding over-sedation and allowing the clinician to focus on specific therapy for alcohol dependence. Various benzodiazepines have been used in this therapy, including diazepam, chlordiazepoxide, oxazepam, and lorazepam, depending on factors including the patient's age, liver function, available dosage forms, the hospital's formulary, and cost. The patient is then reassessed hourly utilizing the CIWA-Ar score. If the score remains above 8, the patient can continue to receive the dose of selected benzodiazepine. If the score is lower than 8 and the patient appears stable, the time frame for assessment and repeat treatment can extend to 4 to 8 hours (**Table 83-3**).[19,25]

TABLE 83-3 Dosing and Monitoring of Pharmacologic Agents Used in the Treatment of Alcohol Withdrawal

Drug/Route	Dosage Range Per Day (Unless Otherwise Stated)	Indication	Monitoring	Duration of Dosing	Level of Evidence for Efficacy*
Multivitamin oral/IV	1 tablet	Malnutrition	Diet	At least until eating a balanced diet at caloric goal	B3
Thiamine oral/IV	100 mg	Deficiency	CBC, WBC, nystagmus	Empiric × 5 days. More if evidence of deficiency	B2
Crystalloid fluids IV (NS or D5–0.45 NS with 20 mEq [mmol] of KCl per liter)	50-100 mL/hour	Dehydration	Weight, electrolytes urine output, nystagmus if dextrose	Until intake and outputs stabilize and oral intake is adequate	A3
Clonidine oral (Catapres)	0.05-0.3 mg Consider dose reduction in the elderly	Autonomic tone rebound and hyperactivity, hypertensive urgency	Shaking, tremor, sweating, blood pressure	3 days or less	B2
Clonidine transdermal (Catapres-TTS)	TTS-1 to TTS-3 Consider dose reduction in the elderly	Autonomic tone rebound and hyperactivity	Shaking, tremor, sweating, blood pressure	1 week or less. One patch only	B3
Antipsychotics oral/IV haloperidol (Haldol)	2.5 to 5 mg every 2-4 hours	Agitation unresponsive to benzodiazepines, hallucinations (tactile, visual, auditory, or otherwise), or delusions	Subjective response plus rating scale (CIWA-Ar or equivalent), ECG	Individual doses as needed	B1
Antipsychotics, atypical		Agitation unresponsive to benzodiazepines, hallucinations, or delusions in patients intolerant of conventional antipsychotics	Subjective response plus rating scale (CIWA-Ar or equivalent)	Individual doses as needed in addition to scheduled antipsychotic	C3
Quetiapine (Seroquel) oral	25-200 mg; dosage adjustment is necessary in hepatic impairment				
Aripiprazole (Abilify) oral/IV	5–15 mg				
Benzodiazepines (BZD)		Tremor, anxiety, diaphoresis, tachypnea, dysphoria, seizures	Subjective response plus rating scale (CIWA-Ar or equivalent)	Individual doses as needed. Underdosing is more common than overdosing	A2
Lorazepam (Ativan) oral/IV/IM	0.5-8 mg				
Chlordiazepoxide (Librium) oral	25-300 mg				
Diazepam (Valium) oral/IV/IM	5-40 mg				
Oxazepam (Serax) oral	15-30 mg				
Dexmedetomidine (Precedex) IV	0.2 mcg/kg/hr, titrate based on response	Adjunct to BZD for autonomic hyperactivity, sympathetic symptom control	Tremor, blood pressure, heart rate	5 days or less	B2
Phenobarbital (Luminal) oral/IV	30-260 mg	Adjunct to BZD, promotes BZD binding to $GABA_A$ receptor	Sedation, respiratory depression, blood pressure	5 days or less	B2
Alcohol oral		Prevent withdrawal	Subjective signs of withdrawal	Wide variation	C3
Alcohol IV		Prevent withdrawal	Subjective signs of withdrawal	Wide variation	C3

*Strength of recommendations, evidence to support recommendation: A, good; B, moderate; C, poor.

Quality of evidence: (1) evidence from more than one properly randomized controlled trial; (2) evidence from more than one well-designed clinical trial with randomization, from cohort or case–control analytic studies or multiple time series, or dramatic results from uncontrolled experiments; and (3) evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.

CBC, complete blood count; CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol, revised; D5, dextrose 5%; ECG, echocardiogram; KCl, potassium chloride; NS, normal saline; WBC, white blood cell count.

Data from References 30, 32, and 33.

Fixed Dose Therapy

Over the years, benzodiazepines given regularly at a fixed dosing intervals and subsequently tapered off have been highly effective for alcohol withdrawal. However, additional medication may be indicated in the presence of breakthrough withdrawal symptoms. With this approach, monitoring for excessive sedation and respiratory depression is still important. Due to administration of medication regardless of symptoms, fixed dose therapy could be preferred in patients with a history of seizures or DT.[19,23,26]

Treatment of Severe Alcohol Withdrawal

The progression to symptoms to include seizures and/or DT describes severe alcohol withdrawal, where patients are often refractory to benzodiazepines and require aggressive treatment in a closely monitored setting. Alcohol withdrawal seizures do not require treatment with an anticonvulsant drug unless they progress to status epilepticus, because the seizures usually end before another drug can be administered. Phenytoin, which is not cross-tolerant to alcohol, does not prevent or treat withdrawal seizures, and without an IV loading dose, therapeutic blood levels of phenytoin are not reached until the acute withdrawal from alcohol is complete. In general, patients experiencing seizures should be treated supportively and for those requiring escalating doses of benzodiazepines, adjunctive drug therapy options to manage refractory withdrawal symptoms might include phenobarbital, propofol, or dexmedetomidine. These patients should be closely monitored in an intensive care unit in case intubation and mechanical ventilation become necessary.[19,27]

Treatment of Nutritional Deficits and Electrolyte Abnormalities

Fluid status, electrolyte, and vitamin abnormalities should be carefully assessed and corrected in all patients undergoing alcohol withdrawal. Hydration is necessary in patients with vomiting, diarrhea, increased body temperature, or severe agitation. Electrolyte imbalances can often be seen because of inadequate nutrition and fluid volume related to antidiuretic hormone inhibition. Hypokalemia can be corrected with oral potassium supplementation as long as renal function is adequate. Thiamine (vitamin B1) is often depleted and can lead to decreased absorption of glucose. Thiamine deficiency should be addressed prior to glucose administration to prevent the development of Wernicke–

Korsakoff syndrome (eg, mental confusion, eye movement disorders, and ataxia [poor motor coordination]). In practice, thiamine is usually given 100 mg once daily orally, IV, or intramuscularly for 3 to 5 days for prophylaxis; higher doses are utilized for acute treatment of Wernicke's encephalopathy. Additionally, patients also benefit from a daily multivitamin with folate due to poor nutritional status (see Table 83-3).[26,27]

Alcohol hypoglycemia was first described 60 years ago and usually occurs in the absence of overt liver disease. It is more likely to occur if the patient is fasting or exercising or is sensitive to alcohol and it is less likely if the patient is obese. Mechanistically, this can occur as alcohol directly interferes with hepatic gluconeogenesis, but not glycogenolysis. The energy required for metabolism of alcohol is diverted away from the energy needed to take up lactate and pyruvate —substrates for gluconeogenesis. So, patients who drink alcohol can become hypoglycemic once glycogen stores are depleted. Neurologic symptoms of hypoglycemia can be confused with alcohol intoxication, and in the inpatient setting, blood glucose should be monitored regularly.[28] In general, alcohol withdrawal treatment can take place in hospitals, inpatient detoxification units, or outpatient settings. Only patients with mild-to-moderate symptoms should be considered for outpatient treatment, and it is a good idea to have a responsible, sober person available to help the patient monitor symptoms and administer medications. Patients with a strong craving for alcohol, who concurrently use other drugs, who have severe psychiatric problems (ie, suicidal ideations, psychosis), and/or who have a history of seizures or DT are not good candidates for outpatient treatment. Pharmacologic agents used in the treatment of alcohol withdrawal are summarized in Table 83-3.[27,29,30]

Treatment of Alcohol Dependence

Nonpharmacologic Therapy

In alcohol dependence, psychosocial interventions have proved to be beneficial. These interventions include motivational enhancement therapy, family therapies, cognitive behavioral therapy, behavioral approaches, and 12-step programs, such as Alcoholics Anonymous. The combination of a psychosocial intervention and pharmacologic therapy for alcohol dependence can help reduce the frequency of drinking and the risk of binge drinking.[31]

Pharmacologic Therapy

4 In the United States, disulfiram, naltrexone, once-monthly injectable extended-release naltrexone, and acamprosate are the only four drugs that are FDA approved for the treatment of alcohol dependence. Disulfiram acts as a deterrent to the resumption of drinking, and naltrexone is a competitive opioid antagonist that has been shown to reduce cravings for alcohol. Acamprosate is a GABAergic agonist that modulates alcohol cravings (**Table 83-4**). Other drugs, including nalmefene, baclofen, bupropion, various serotonergic agents (including selective serotonin reuptake inhibitors and serotonin-3 [5-HT3] receptor antagonists), topiramate, gabapentin, and varenicline, have also been used either abroad or in the United States off-label for alcohol dependence. A Cochrane review[32] of 25 trials with 2,641 patients evaluated a variety of anticonvulsants, including gabapentin, topiramate, oxcarbazepine, valproate, levetiracetam, pregabalin, zonisamide, and carbamazepine, to determine efficacy in the treatment of alcohol dependence. Overall, these agents did perform better than placebo when comparing the number of drinks per day and average heavy drinking days, but there was insufficient evidence that these agents led to an increased number of patients abstaining from alcohol. The conclusion was there is insufficient evidence of efficacy to support the use of anticonvulsant treatment in alcohol dependence.[32] A recent meta-analysis of seven randomized controlled trials (RCTs) found that topiramate had moderate benefits on the number of abstinence days and frequency of heavy drinking. Of the anticonvulsants, topiramate appears to decrease alcohol consumption and is increasingly prescribed off-label as a treatment of AUD.[33] Further information on FDA-approved and non-FDA-approved pharmacotherapy for the treatment of AUD can be found elsewhere.[31]

TABLE 83-4 Dosing and Monitoring of Pharmacologic Agents Used in the Treatment of Alcohol Dependence

Drug	Dosage Range Per Day	Indication	Monitoring	Duration of Dosing	Level of Evidence for Efficacy*
Disulfiram (Antabuse)	250–500 mg; use with caution in patients with hepatic disease or insufficiency	Deterrence	Facial flushing, liver enzymes	Indefinite	B2
Acamprosate (Campral)	999–1,998 mg and higher (333 mg tablets) Dosage adjustment necessary in renal impairment	Craving	Patient-reported craving, renal function	Indefinite	A1
Naltrexone (ReVia)	50–100 mg; dosage adjustment may be needed in renal and liver impairment	Craving	Patient-reported craving	Indefinite	A1
Naltrexone (Vivitrol)	380 mg intramuscularly once every 4 weeksRisk of hepatotoxicity lower compared to oral formulation due to lack of first pass effect	Craving	Patient-reported craving	Indefinite	B2
Anticonvulsants (eg, lamotrigine [Lamictal], topiramate [Topamax], carbamazepine [Tegretol], valproic acid [Depakote], gabapentin [Neurontin])	Seizure disorder doses	Craving	Patient-reported craving, plasma drug levels	Indefinite	B2
Antidepressants (eg, clomipramine [Anafranil], bupropion [Wellbutrin], doxepin [Sinequan], fluoxetine [Prozac])	Depression doses	Craving, depression, anxiety	Patient-reported craving	Indefinite	B2

*Strength of recommendations: A, B, and C, good, moderate, and poor evidence to support recommendation, respectively.

Quality of evidence: (1) evidence from more than one properly randomized controlled trial; (2) evidence from more than one well-designed clinical trial with randomization, from cohort or case–control analytic studies or multiple time series, or dramatic results from uncontrolled experiments; and (3) evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.

Data from References 23, 33, and 36.

For moderate-to-severe AUD, the American Psychiatric Association (APA) recently published a practice guideline which recommends naltrexone or acamprosate to reduce alcohol consumption or achieve abstinence and disulfiram for patients who have not responded to naltrexone and acamprosate and who understand the potential adverse effects with concurrent alcohol intake. Additionally, the APA also recommends gabapentin or topiramate in moderate-to-severe AUD for patients who prefer one of these drugs or who are intolerant of or who have not responded to the FDA-approved medications.[34]

Disulfiram

Disulfiram deters a patient from drinking by producing an aversive reaction if alcohol is consumed, otherwise it has minimal effects. Pharmacologically, it inhibits aldehyde dehydrogenase in the biochemical pathway for alcohol metabolism, allowing acetaldehyde to accumulate. If a patient consumes alcohol within 12 to 24 hours of taking disulfiram, the resulting increase in acetaldehyde causes severe facial flushing, throbbing headache, nausea and vomiting, chest pain, palpitations, tachycardia, weakness, dizziness, blurred vision, confusion, and hypotension, referred to as a "disulfiram reaction." In severe (rare) cases, the reaction can lead to myocardial infarction, congestive heart failure, cardiac arrhythmia, respiratory depression, convulsions, and death, particularly in vulnerable individuals. When disulfiram is prescribed, abstinence from alcohol is a critically important component of patient education and supervision is recommended to promote adherence.[4,20] Evidence in a meta-analysis of 22 randomized trials found that in 17 open-labeled studies, disulfiram was associated with a higher abstinence benefit compared with controls; blinded studies did not demonstrate a benefit.[35]

Naltrexone

Naltrexone, a potent opiate antagonist, is available for the treatment of opioid dependence, as it blocks the effects of exogenous opioids (for more details, see Chapter 82, "Substance Use Disorders I: Depressants, Stimulants, and Hallucinogens"). It is also FDA approved for the treatment of alcohol dependence, and it is thought to attenuate the reinforcing effects of alcohol. Those who consume alcohol while taking naltrexone report feeling less intoxicated and having fewer alcohol cravings.[4] Evidence suggests that genetics play a role in the clinical response to naltrexone, as the efficacy of naltrexone treatment varies greatly among individuals. In previous preliminary studies, the Asn40Asp (118A>G, A355G, rs1799971) polymorphism in the μ-opioid receptor gene (*OPRM1*) demonstrated an increased response to naltrexone with lower rates of relapse to heavy drinking, however a recent controlled clinical trial disputed these results,[36] therefore further studies are needed.

Administration of naltrexone in alcohol dependence does not induce alcohol withdrawal. However, naltrexone should not be given to patients currently dependent on opiates because it will block the therapeutic effects of opioid analgesics and can precipitate severe opioid withdrawal syndrome. Naltrexone should be used with caution in patients with moderate-to-severe renal

impairment and baseline liver function tests are recommended. Current evidence supports the tolerability of naltrexone in high-risk patients with hepatitis C and HIV. When initiating naltrexone, it is highly suggested that each patient is not in acute alcohol withdrawal and is involved in psychosocial treatment.[7,37] A review of 50 randomized controlled studies,[38] which included 7,793 patients, found that oral naltrexone decreased drinking days by 4% and decreased the risk of heavy drinking by 83% compared to placebo (NNT = 9). The most common side effects were nausea and daytime sedation and the usual starting dose of oral naltrexone is 50 mg/day, but doses of 100 mg/day have been used and studied.[38]

In April 2006, the FDA approved Vivitrol, a once-monthly intramuscular naltrexone formulation, given at a dose of 380 mg IM each month.[37]

Extended-release formulations reduce the likelihood of forgetting or choosing not to take the medication, assuring that once the patient receives an injection, he or she will be "adherent" for the next month. However, the cost is considerably higher than the oral formulation.[39]

The extended release form of naltrexone may be more beneficial in reducing heavy drinking rather than abstinence. This line of thought is supported by a clinical trial where patients receiving 380 mg of the extended-release compound compared with placebo had significantly fewer heavy-drinking days during the study and showed an average reduction of 37.3% in heavy-drinking days compared with 27.4% for placebo-treated patients, which were significantly different. Pettinati et al. contend that their data support the efficacy of extended-release naltrexone 380 mg in relatively higher severity alcohol dependence for both reduction in heavy drinking and maintenance of abstinence.[39]

Acamprosate

Acamprosate is a glutamate modulator at the *N*-methyl-D-aspartate receptor that reduces alcohol craving. Patients treated with acamprosate are more successful in maintaining abstinence from alcohol versus placebo. Acamprosate is well tolerated, with GI adverse effects being the most common. It is not metabolized through the liver, but is excreted through the kidneys and should be used with caution in patients with severe renal dysfunction with appropriate dose adjustment.[4]

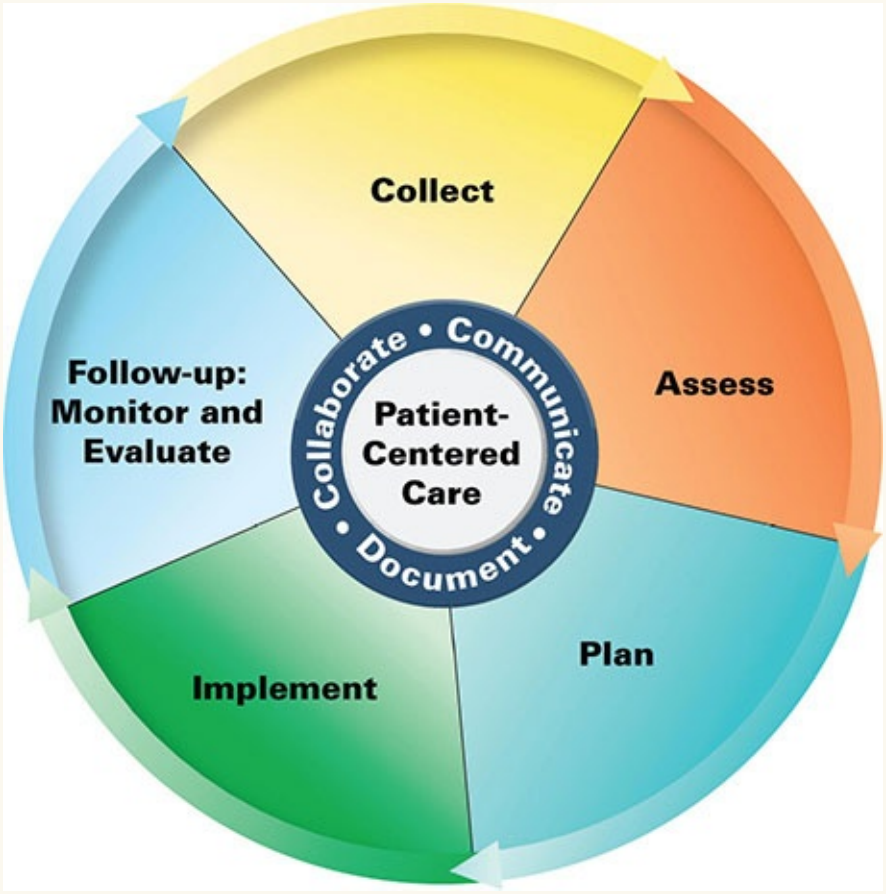
A Cochrane review of 24 RCTs with 6,915 participants[40] found that, compared with placebo, acamprosate significantly reduced the risk of any drinking and significantly increased the cumulative abstinence duration (mean difference 10.94 days). Diarrhea was the only side effect that was more

frequently reported with acamprosate than placebo.

Table 83-4 shows dosing information for acamprosate and other options used in treating alcohol dependence.[20,30,31] When selecting a medication for an individual patient, factors such as ease of administration, available formulations, renal or hepatic disease, pregnancy, adverse effects, or specific symptoms of AUD should guide drug therapy decisions.

EVALUATION OF THERAPEUTIC OUTCOMES

Considering the increasing rates of alcohol use and the variable effects of alcohol from individual to individual, screening tools, such as the CAGE questionnaire and AUDIT, are instrumental in detecting alcohol abuse and identifying the risk of acute alcohol withdrawal. Treating alcohol withdrawal takes precedence over the treatment of alcohol dependence. The assessment of alcohol withdrawal begins with utilizing the CIWA-Ar to assess the severity of withdrawal symptoms before initiating pharmacologic therapy with benzodiazepines. Close monitoring is essential to avoid progression to severe withdrawal, which includes seizures and/or DT.



Patient Care Process for Alcohol Use Disorder

Collect

- Patient characteristics (eg, age, sex, pregnant)
- Patient medical history (personal and family)
- Social history (eg, tobacco/alcohol use) and dietary habits
- Utilize CAGE questionnaire or Alcohol Use Disorders Identification Test (AUDIT) to assess alcohol dependence/abuse
- Current medications including over-the-counter (OTC), herbal products, dietary supplements
- Objective data
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2-saturation
  - Labs including serum creatinine (SCr), liver function tests (LFTs)

Assess

- Hemodynamic instability (eg, systolic BP <90 mm Hg, HR >110 bpm, O_2-sat <90% (0.90), RR >20) to assess for signs of acute alcohol withdrawal
- Utilize motivational interviewing to assess the patient's readiness to quit
- Ability/willingness to pay for pharmacotherapy options for Alcohol Use Disorder (AUD), and abstain from alcohol with disulfiram and avoid opiates with naltrexone
- Ability/willingness to obtain laboratory monitoring tests (eg, SCr [eg, naltrexone, acamprosate], LFTs [ie, disulfiram])
- Emotional status (eg, presence of anxiety, depression)

Plan*

- Drug therapy regimen including specific AUD agent, dose, route, frequency, and duration (see Table 83-4)
- Monitoring parameters including efficacy (eg, decrease in craving, adherence) and safety (eg, adverse effects specific to selected agent, SCr, LFTs); frequency and timing of follow-up
- Patient education (eg, purpose of treatment, drug-specific information, importance of adherence)
- Self-monitoring for adverse effects from pharmacotherapy treatment
- Referrals to other providers when appropriate (eg, behavioral health; highly recommended but not required for pharmacotherapy treatment)

Implement*

- Provide patient education regarding all elements of treatment plan
- Utilize motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (eg, adherence assessment, SCr [eg, naltrexone, acamprosate], LFTs [eg, disulfiram])

Follow-up: Monitor and Evaluate

- Presence of adverse effects (eg, drug specific)
- Patient adherence to treatment plan using multiple sources of information
- Reevaluate duration of therapy initially with frequent follow-up and then

lengthen follow-up to every 1–2 months

** Collaborate with patient, caregivers, and other healthcare professionals.*

For alcohol dependence, both psychosocial interventions and pharmacologic therapy can be beneficial to reduce the frequency of drinking. With four agents approved by the FDA for the treatment of alcohol dependence, careful patient selection must be considered, as each agent works pharmacologically different to reduce cravings (acamprosate and naltrexone) or act as deterrent to the resumption of drinking (disulfiram). Patient counseling on potential adverse effects followed by close monitoring and follow-up are necessary to assess response to therapy and promote adherence.

INTRODUCTION—NICOTINE

5 Approximately 480,000 deaths in the United States each year are attributable to tobacco use, making smoking the number one leading preventable cause of death and disease in the United States.[41] The three leading causes of death attributable to smoking include lung cancer, chronic obstructive pulmonary disease, and ischemic heart disease.[41]

Since 1964, when the first Surgeon General's report on smoking was released, the number of adults who smoke has decreased from 42.4% to 14% in 2017,[42,43] and now there are more former smokers than current smokers.[41] This trend has been supported by the clinical guidelines for tobacco use and dependence such as the 2015 United States Preventative Task Force (USPSTF) Tobacco Smoking Cessation in Adults, Including Pregnant Women: Behavior and Pharmacotherapy Interventions Recommendation Statement (**Fig. 83-1**).[43,44]

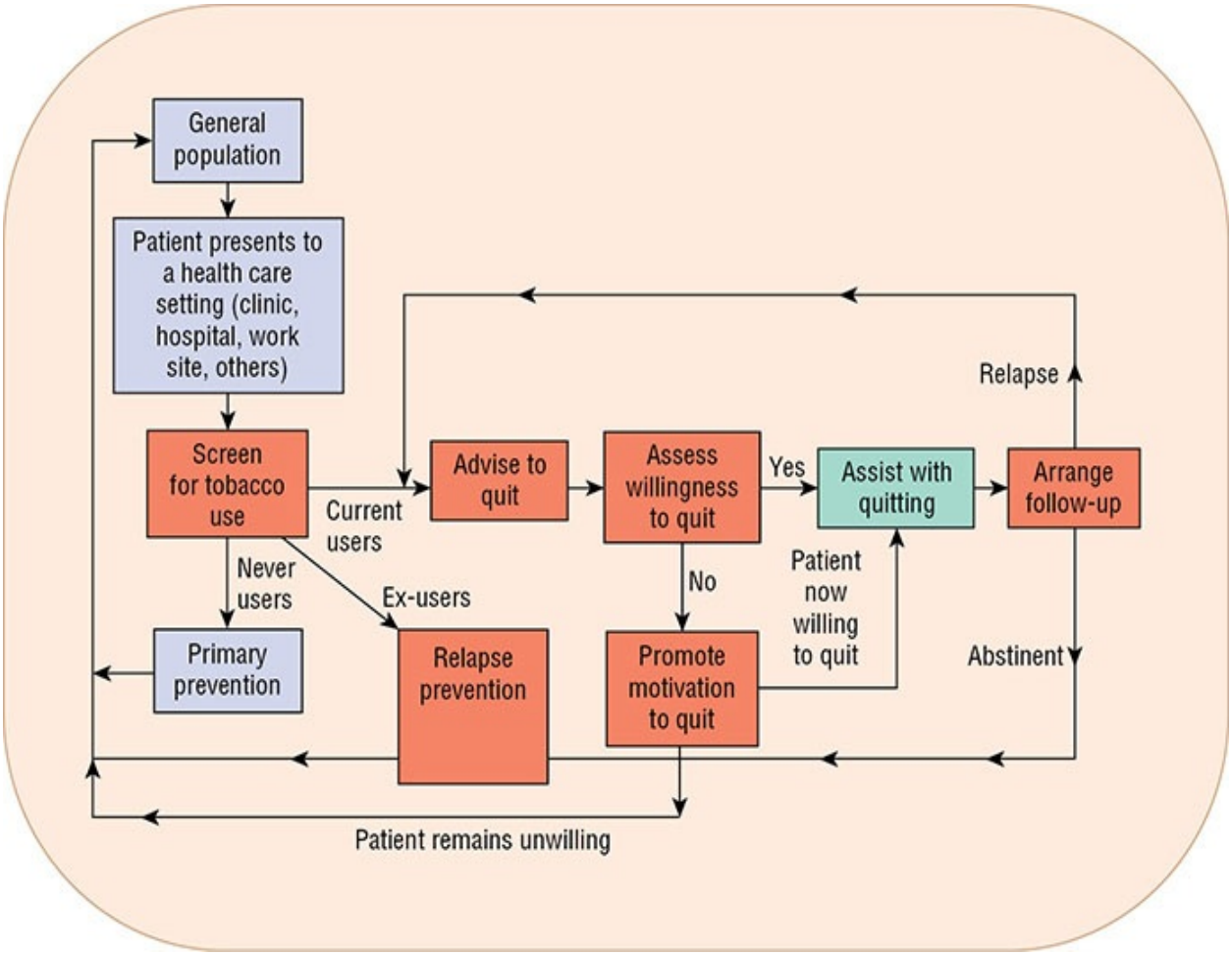


FIGURE 83-1 Model for treatment of tobacco use and dependence.

There have been numerous approaches to smoking cessation including a focus on sales, marketing, and manufacturing of all tobacco products marketed in the United States which are now regulated by the FDA. Federal tobacco excise taxes have increased and states have also added cigarette excise tax rates. Additionally, many states have enacted comprehensive smoke-free laws, and further opportunities for access to smoking cessation pharmacotherapy and counseling are available through the Affordable Care Act passed in 2010.[45]

National telephone quitlines, smoking cessation counseling services, and mass media campaigns have been utilized to improve smoking cessation rates. “Tips from Former Smokers” was a successful federally funded national mass media antismoking campaign,[45] and various internet and mobile phone text messaging programs have been developed over the years. The QuitGuide Mobile App is a free app released by Smokefree.gov, which provides resources to track craving patterns and motivation, and monitors progress as milestones are

achieved.[46] Despite the proved effectiveness of pharmacological and counseling services to aid in sustained smoking cessation, cigarette smoking continues to be the leading cause of preventable morbidity and mortality in the United States.[41]

EPIDEMIOLOGY

The National Survey on Drug Use and Health (NSDUH) reported in 2017 that an estimated 61.1 million people had exposure to a tobacco product at least once in the month prior to being interviewed and 48.7 million of the US population (12 years of age and older) currently smoke cigarettes, defined as smoking at least a part of the cigarette. Of these, 57.1% were daily smokers (27.8 million) and 41.2% (11.4 million) reported smoking a pack or more of cigarettes per day.[3] In addition, 12.5 million smoked cigars, 8.6 million used smokeless tobacco, and 2.3 million smoked pipes.[3] Comparing age groups, data in 2017 demonstrated adults 26 years and older have the highest rate of daily cigarette use (61.5%) with very similar results to data as the previous year. In contrast, adolescents 12 to 17 years of age reported the lowest daily cigarette use in the month previous to the assessment in 2017 (12.2%), which is a decrease from 2016 (15.0%). This is encouraging since this has been a trend reported over multiple years.[3]

Further data has been provided in the Population Assessment of Tobacco and Health (PATH) Study launched in 2011, which is a collaboration between the FDA, NIH, and NIDA. This long-term study is collecting general longitudinal epidemiological data on approximately 45,000 participants 12 years and older, including both current tobacco users and nonusers, to evaluate tobacco use as well as the effects of tobacco use on overall health. The PATH study differs from NSDUH since assessment is completed using biomarkers, detailed assessment of tobacco-use behaviors, and further detailed examination of specific tobacco products to distinguish between products and ensure clarity of usage patterns.[47] The goals of this study are to determine what increases the susceptibility of using tobacco, what products are commonly used including evaluating the use of e-cigarettes; evaluating patterns of use; reviewing the overall health impacts associated with smoking, smoking cessation, and relapse, and identifying any differences associated with racial/ethnic, gender, and age subgroups.[47]

Currently, initial data (from 2013 to 2014 of the PATH Study) indicates that more than 25% of adults were currently using one type of tobacco product during this time period. Approximately 9% of youth had used a tobacco product in the last 30 days, and 1.6% of these were daily users of tobacco. Forty percent

of the respondents indicated they were using multiple tobacco products at the same time, most commonly cigarettes and e-cigarettes together. The PATH Study also found that in adults, tobacco use is higher in males, racial minorities, members of sexual minorities, and individuals who have lower household incomes or lower education levels.[47]

Economic Impact of Smoking

The yearly direct healthcare expenditures associated with smoking for adults is estimated at nearly $170 billion for direct medical care and $156 billion in indirect costs, such as lost productivity.[48] Included in these costs are the estimated $39 billion annually for Medicaid patients. This number is significant, as this small subset of the population has smoking rates higher in comparison to privately insured patients.[49]

Health Risks of Smoking

Cigarette smoking greatly increases the risk of (a) cardiovascular diseases such as stroke, sudden death, and heart attack; (b) nonmalignant respiratory diseases including emphysema, asthma, chronic bronchitis, and chronic obstructive pulmonary disease; (c) lung cancer; and (d) other cancers.[41] Exposure to environmental tobacco smoke (*passive exposure*) has been cited as the cause of lung cancer, stroke, and coronary heart disease in adults.[50] Children who are exposed to environmental smoke have a higher risk of respiratory infection, asthma, and ear infections than those who are not. Sudden infant death syndrome (SIDS) occurs more often in infants whose mothers smoked during pregnancy than in offspring of nonsmoking mothers. Studies continue to determine how environmental smoke can increase the risk of SIDS. Additionally, long-term adverse negative cardiovascular consequences have been identified in children exposed to environmental smoke leading to increased risk of cardiovascular complications later in life.[51]

PATHOPHYSIOLOGY

Nicotine is an agonist at nicotinic acetylcholine receptors (nAchRs) with pharmacologic effects highly dependent on dose. These effects include central and peripheral nervous system stimulation and depression, respiratory stimulation, skeletal muscle relaxation, catecholamine release by the adrenal

medulla, peripheral vasoconstriction, and increased blood pressure, heart rate, cardiac output, and oxygen consumption. Cigarette smoking or low doses of nicotine produce an increased alertness and increased cognitive functioning by stimulating the cerebral cortex. At higher doses, nicotine stimulates dopamine within the “reward” center in the brain’s limbic system.[52] When nicotine is ingested, a feeling of pleasure and relaxation can occur. Repetitive exposure to nicotine leads to neuroadaptation, which builds tolerance to the initial effects. An accumulation of nicotine in the body leads to a more substantial withdrawal reaction if cessation is attempted. Common symptoms experienced during withdrawal can include anxiety, difficulty concentrating, irritability, and strong cravings for tobacco.[53] Onset of these withdrawal symptoms usually occurs within 24 hours and can last for days, weeks, or longer. Additionally, some might experience a state of malaise or inability to experience pleasure during this nicotine withdrawal period. These types of reactions have been termed “hedonic dysregulation” and can be rapidly reversed with nicotine readministration which might be one reason why relapse rates are so high.[54] This powerful force of nicotine addiction is one reason smokers who attempt to achieve smoking cessation have a high rate of relapse, and only 3% remain abstinent 6 months following the quit date.[55]

The genetics associated with nicotine addiction is very complex and continues to be studied with great interest. Progress continues to be made in understanding the human genome and identifying more specific markers for various diseases. Many phenotypes and corresponding genes have been identified as markers, which include the genetic markers, nicotinic cholinergic receptor alpha5 subunit (CHRNA5) and CYP2A6, and the metabolic marker, nicotine metabolism ratio (NMR). All three of these markers have been found to affect smoking behavior, including nicotine dependence and cigarettes per day. Additionally CHRNA5-CHRNA3-CHRNB4 have been found to predict lung cancer, COPD, coronary artery disease, and mortality.[56] Having the ability to identify patients at higher risk can improve chances of diagnosing cancer earlier in the disease process so treatment can begin sooner and improve prognosis.[56]

TREATMENT

Desired Outcomes

Ideally, the desired outcome is that all smokers quit, and that young people never

take up the habit. Unfortunately, this is unlikely to happen. The Healthy People 2020 target has set a goal prevalence of smoking at less than or equal to 12%, which is a realistic and believed to be an achievable goal since current 2017 figures are reported at 13.9% and the trend continues to show a decrease in active smokers.[3,45]

Studies continue to evaluate the effects of polymorphisms in various genes and the effect this has on the efficacy of pharmacotherapy treatment options to offer options for more personalized treatment in the future.[57] Additionally, genetic variability in nicotine metabolism continues to be evaluated since variations in cytochrome P450 2A6 leads to different addiction rates to nicotine and responses to NRT.[56] Further understanding of these variations will continue to prove helpful in creating a personalized pharmacotherapy plan to improve smoking cessation rates.

Nicotine Dependence: Recognition of Behavior

6 The Agency for Healthcare Research and Quality (AHRQ) developed the treatment of tobacco addiction guidelines and in 2015 the United States Preventive Services Task Force (USPSTF) produced the "Tobacco Smoking Cessation in Adults, Including Pregnant Women: Behavior and Pharmacotherapy Interventions Recommendation Statement."[43,44] This recommendation stresses that all healthcare providers should ask each adult about tobacco use, advise any adult who is using tobacco, to stop using tobacco, and provide behavioral inventions and pharmacotherapy options approved by the FDA for smoking cessation to aid in cessation **Figure 83-2**. Recommendations were also included for pregnant women, which are summarized in **Table 83-5**. Additional information regarding the challenges of pharmacotherapy treatment options for smoking cessation in pregnant women is also available.[58]

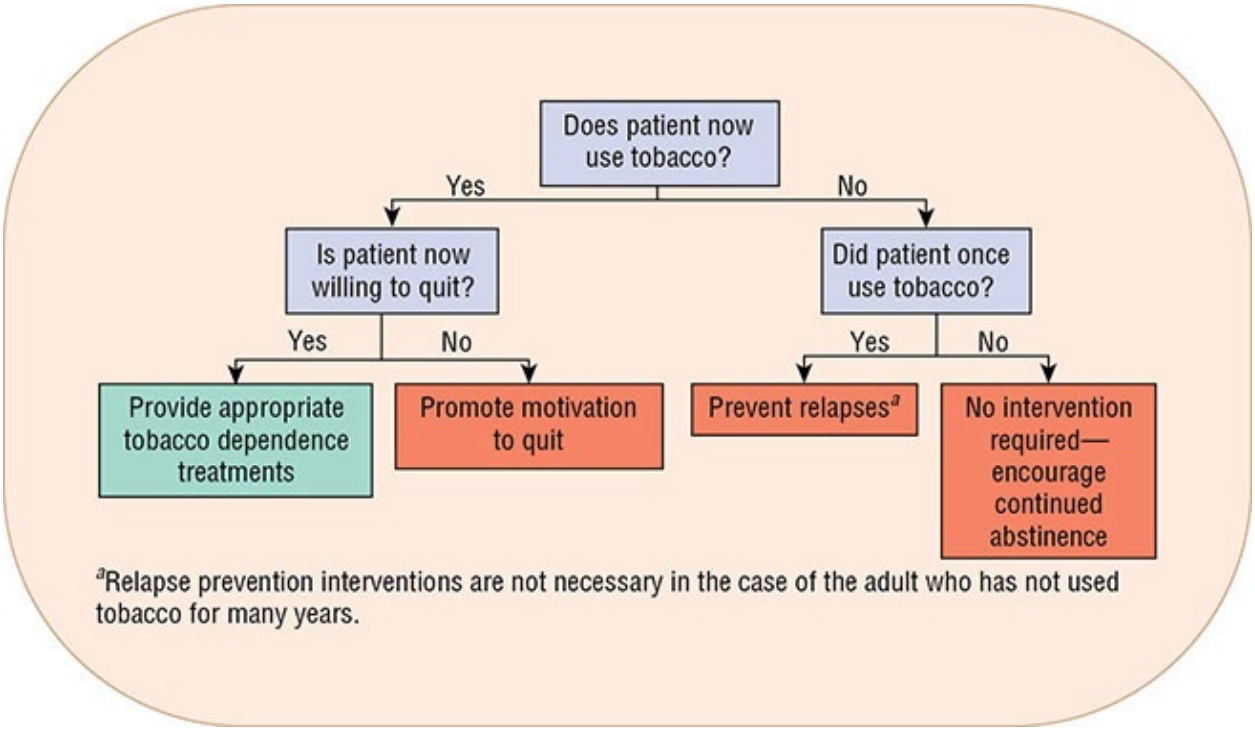


FIGURE 83-2 Algorithm for treating tobacco use.

TABLE 83-5 US Preventive Services Task Force (USPSTF) Tobacco Smoking Cessation in Adults Including Pregnant Women Behavioral and Pharmacotherapy Interventions: Summary Table

Population	Adults>18 Years Old (nonpregnant)	Pregnant Women >18 Years Old

Assessment	• Screen for all tobacco
	  • Consider using 5As or Ask Assist Refer
		• Screen for all tobacco
		  • Consider using 5As or Ask Assist Refer

Behavioral interventions	• In person behavioral support and counseling (group/ individual option) • Printed self-help materials • Telephone counseling (>3 sessions)	• Counseling • Feedback • Health education • Incentives • Social support
Pharmacotherapy	• NRT • Bupropion SR • Varenicline • +/-Behavioral interventions	• Inadequate evidence due to lack of studies to determine benefit vs risk
Comments on benefits and harms	• Conclusion from USPSTF; behavioral interventions and +/- pharmacotherapy interventions with FDA-approved pharmacotherapy agents for smoking cessation demonstrated substantial benefit	• Conclusion from USPSTF; behavioral interventions demonstrated substantial benefit for perinatal outcome and improved smoking abstinence
Electronic nicotine delivery systems	• Evidence on the use of ENDS for tobacco cessation is insufficient, benefit vs risk cannot be determined	• Evidence on the use of ENDS for tobacco cessation is insufficient, benefit vs risk cannot be determined

ENDS, Electronic Nicotine Delivery Systems; FDA, Food and Drug Administration; NRT, Nicotine Replacement Therapy; USPSTF, United States Preventive Services Task Force; vs, versus.

Data from Reference 44.

A well-established method of assessing a patient's smoking status utilizes the 5As which include the following:

1. **A**sk about smoking
2. **A**dvise the person to quit through clear individualized messages
3. **A**ssess the patient's willingness to quit
4. **A**ssist in quitting
5. **A**rrange follow-up and support

The USPSTF statement expanded on the 5As and recommended that for pregnant women a higher comfort level was demonstrated if these questions were asked in a multiple choice format instead of open-ended questions. Additionally, another approach includes the "Ask, Advise, Refer," which can be used to assist patients in obtaining access to smoking cessation services.

Nonpharmacologic Therapy

The USPSTF statement emphasized the importance of counseling sessions and highlighted the goal of reaching at least four in-person sessions, although other data points to cessation rates potentially plateauing after a total of 90 minutes have been completed.[43,44] A Cochrane analysis reviewed 47 trials, which included approximately 18,000 patients, who received a combination of pharmacotherapy treatment and behavioral support either in person, through telephone interaction, or through written information. This review determined that the addition of behavioral support could improve the chances of smoking cessation by 15%.[59] Although comprehensive behavioral interventions have been shown to be more effective in helping people quit smoking and remain abstinent, less intensive treatments may be beneficial as well. Even minimal contacts lasting less than 3 minutes, which include the 5As, are more successful in increasing cessation rates than intervention involving no contact.[43,44]

CLINICAL PRESENTATION

Nicotine Withdrawal

General

- The patient may experience anxiety, but may not be in acute distress. Symptoms can wax and wane over time.

Symptoms

- The patient may complain of cravings, difficulty concentrating, frustration, irritability, and impatience. Hostility, insomnia, and restlessness can also occur.
- Increased skin temperature can be present.

Motivational interviewing is a form of counseling to help patients identify barriers for making a behavior change. A meta-analysis of 28 studies, including over 16,000 smokers who underwent motivational interviewing as part of a smoking cessation program, found that motivational interviewing with standard care or brief cessation advice did improve quit rates modestly.[60] Subgroup analysis found that motivational interviewing was most effective when completed in shorter sessions by general practitioners.[60]

Additionally other forms of interventions have been identified as effective in

improving smoking cessation rates. Telephone-based quitlines, which are operated by the National Cancer Institute and offered in all 50 states, the District of Columbia, Puerto Rico, and Guam via 1–800-QUIT-NOW, provide various options such as recorded messages, counseling services, mailed materials, counselor follow-up services, and access to pharmacotherapy options for smoking cessation.[61] The use of technology to further enhance counseling opportunities has also increased over the years including websites, text messaging, social networking, and smartphone applications. A systematic review and meta-analysis evaluated 20 manuscripts that included over 15,000 smokers who received text messages for smoking cessation and found that patients receiving the text messages were much more likely to achieve smoking cessation by almost 40%.[62]

Furthermore, while counseling alone can be effective, its efficacy is further augmented by the addition of pharmacotherapy, with NRT also being effective independent of counseling services.[63]

Pharmacologic Therapy

All patients attempting to quit should be encouraged to use effective pharmacotherapy agents for smoking cessation except in the presence of special circumstances or contraindications. For pregnant women, the USPSTF statement recommends that the clinicians weigh the benefits and the harms associated with the pharmacotherapy interventions and treat each patient on an individual basis.[43,44] Current recommendations list seven first-line agents including the NRT medications, sustained release bupropion hydrochloride, and varenicline tartrate as treatment options.[43,44] First-line therapy options in smoking cessation are summarized in **Table 83-6**.[64–70]

TABLE 83-6 First-Line Pharmacotherapy Treatment Options for Smoking Cessation

Drug	Dosing	Duration	Comments/Monitoring Parameters
Nicotine Replacement Therapies (NRTs)			

Nicotine patch	Based on cigarettes smoked per day:
	>10 cigs/day:
	Step 1: 21mg/day: Weeks 1-6
	Step 2: 14mg/day: Weeks 7-8
	Step 3: 7mg/day: Weeks 9-10
	<10 cigs/day:
	Step 2: 14mg/day: 6 weeks
	Step 3: 7mg/day: 2 weeks
		10 weeks	• Tapering dosing is considered optional after 6 weeks on a dose
			• Patch can be worn for up to 24 hours per day
			  • If patient has sleep disturbances, remove patch at night and place one patch in morning (~16 hours per day)
			  • If waking up with cravings, patch should be worn for 24 hours
			• Recommended to place patch on determined quit day
			• Place a new patch on each day, hold patch on for 10 seconds to help adherence
			• Rotate patches to avoid skin irritation

Nicotine gum	1st cigarette < 30 minutes after waking: 4 mg
	1st cigarette > 30 minutes after waking: 2 mg
	Weeks 1-6: 1 piece of gum every 1-2 hours prn
	Weeks 7-9: 1 piece every 2-4 hours prn
	Weeks 10-12: 1 piece every 4-8 hours prn
	Then stop
	Do not exceed 24 pieces/day
		12 weeks	• Continuous use can lead to adverse effects (pyrosis, nausea, hiccups)
			• 4 mg strength has shown to be more efficacious in heavy smokers over 6-week time period
			• If patient uses with a cigarette, there is no major risk
			• Counseling on proper use of gum:
			  • Repeat process until peppery sensation does not reoccur
			  • Use alternate sides of mouth when using chew and park method
			  • Park between cheek and gum after a peppery sensation becomes apparent
			  • Do not eat or drink 15 minutes before or during use of gum
			  • Chew each piece slowly

Lozenge available as Nicorette lozenge or Nicorette mini lozenge	1st cigarette < 30 minutes after waking: 4 mg
	1st cigarette > 30 minutes after waking: 2 mg
	Weeks 1-6: 1 lozenge by mouth every 1-2 hours prn
	Weeks 7-9: 1 lozenge by mouth every 2-4 hours prn
	Weeks 10-12: 1 lozenge by mouth every 4-8 hours prn
	Then stop
	Do not exceed 20 lozenges/day
		12 weeks	• Counseling points
			  • Do not eat or drink anything 15 minutes prior to or during lozenge use
			  • Allow the lozenge to dissolve slowly, approximately 20-30 minutes
			  • Nicotine release could create a tingling or warm sensation
			  • Do not chew or swallow the lozenge
			  • Periodically rotate the lozenge to different areas of the mouth

Nicotine oral inhaler + cartridge plus mouthpiece (Nicotrol®)	24-64mg (6-16 cartridges) per day 1. Stop smoking completely before use. 2. Use device by frequent continuous puffing (20 minutes) and use as needed (dosing is very individualized) based on nicotine needed. 3. Recommeded duration of treatment is 3 months 4. Gradual daily dose taper over 6-12 weeks	3-6 months	• Patients should stop smoking prior to starting this product • Most successful patients in trials; use ranged from 6-16 cartridges per day, 20 minutes continuous puffing • Recommended duration of treatment: 3 months with subsequent weaning with gradual reduction over 6-12 weeks • Treatment longer than 6 months has not been studied • Precautions: patients with asthma, chronic pulmonary disease, history of recent myocardial infarction, serious arrhythmias, or worsening angina • Pregnancy Category D

Nicotine metered nasal spray (Nicotrol NS®)	One spray (0.5mg nicotine/spray) into each nostril one to two times each hour when craving cigarette
	Max dose:
	10 sprays per hour
	(max of 80 sprays per day)
		3 months	• Two sprays is considered 1 dose
			• Treatment duration is 3 months; safety beyond 6 months has not been studied
			• Counseling:
			  • Breathe normally while administering spray, do not sniff or inhale deeply while administering spray
			  • For best results, use at least 16 sprays per day which has been found as the minimum effective dose

Non-nicotine Replacement Options			

Bupropion (Zyban)	150 mg by mouth daily × 3 days then 150 mg by mouth bid (dosing interval should be > 8 hours)	3-6 months	• Do not exceed 300mg/day
			• Recommend initiating therapy 1-2 weeks prior to set "quit" day
			• Black box warning for neuropsychiatric warning and suicide warnings removed in 2016; downgraded to warning
			• Pregnancy category: C, excreted into breastmilk
			• Monitor patients with renal/hepatic impairment
			  • Neuropsychiatric adverse events: black box warning removed in December 2016, warning remains
			  • Counseling points: might cause dry mouth, could cause insomnia

Varenicline (Chantix®)	Start with dose titration: Days 1-3: 0.5 mg by mouth once daily Days 3-7: 0.5 mg by mouth twice daily Week 2 until end of treatment: 1 mg by mouth twice daily	3-6 months	• Recommended to begin varenicline 1 week prior to quit day • Maintenance up to 6 months of therapy is approved • Renal impairment dosing for CrCl ≤ 30mL/min (0.5 mL/s) • No dosing adjustment needed in hepatic impairment • If patient has difficulty with cessation, recommend taper smoking by 50% each month with a goal of smoking abstinence in 12 weeks, continue varenicline for another 12 weeks for a full 24 week therapy • Neuropsychiatric adverse events: black box warning removed in December 2016, warning remains • Most common side effects: nausea, sleep problems, constipation, gas, vomiting • Patients with intolerable insomnia might improve with lower doses

Data from References 64–70.

Nicotine Replacement Therapy

7 Nicotine replacement therapy provides lower peak levels and lower levels of nicotine concentrations compared to cigarettes, leading to reductions in the reinforcing effects of smoking. Another benefit of NRT includes the decrease and eventual elimination of exposure to the harmful substances included in cigarettes.[71] Patients have easy access to many of these products since five of these are available over-the-counter, with only the nasal inhaler and the nasal spray currently being prescription products. A recent review showed that all the commercially available forms of NRT (eg, chewing gum, transdermal patches, nasal spray, lozenge, inhalers, and tablets) were effective for smoking cessation and increased quit rates by 10%.[63] Additionally, combinations of these agents have been demonstrated in multiple studies and meta-analyses to improve abstinence rates in comparison to monotherapy.[44,72]

Nicotine Gum

Nicotine gum offers a rapid onset and short duration of effect that can be very beneficial since the amount of nicotine and the timing can be controlled by the patient. The recommended dosing is based on the “time to first cigarette” (TTFC) which indicates the response to the nicotine deprivation. The FDA has approved the nicotine starting doses of 4 mg for patients who experience TTFC less than 30 minutes and 2 mg for patients who experience the TTFC greater than 30 minutes.[73] The gum should be chewed slowly until a peppery or minty taste emerges, and then “parked” between cheek and gums to facilitate nicotine absorption through the oral mucosa. Acidic beverages (eg, coffee, juices, or soft drinks) interfere with the buccal absorption of nicotine, so eating and drinking anything except water should be avoided for 15 minutes before and during chewing. Instructions to chew the gum on a fixed schedule (at least one piece every 1 to 2 hours) for at least 1 to 3 months can be more beneficial than ad libitum use.[43,70] Generally, the gum should be used for up to 12 weeks with no more than 24 pieces chewed per day.

Nicotine Lozenge

The nicotine lozenge is available as a 2-mg or 4-mg dose, with the lower amount recommended for patients who normally smoke their first cigarette later than 30 minutes after awakening, and the higher dose being reserved for smokers who smoke within 30 minutes of waking. It is recommended that no more than 20 lozenges should be used in 1 day,[43,67] for up to 12 weeks. The most common

side effect of the lozenge is nausea. As with the nicotine gum, acidic beverages (eg, coffee, juices, or soft drinks) interfere with the buccal absorption of nicotine, so eating and drinking anything except water should be avoided for 15 minutes before and during use of the lozenge.[43,67]

Nicotine Patch

The nicotine patch is available as a nonprescription medication and is the NRT option which has shown the highest rate of adherence.[74] This nicotine product provides a steady amount of transdermal nicotine for 16 to 24 hours based on the selected product. The patch is available in three strengths and package labeling suggests patients who smoke more than 10 cigarettes per day start with the 21 mg patch and those who smoke less than 10 cigarettes per day start with the 14-mg patch. This initial regimen will be worn for 4 to 6 weeks and then a tapering regimen will begin which includes reducing the patch strength approximately every 2 weeks.[44,69] The patch can be used up to 8 to10 weeks per the labeling guidelines. Patients who experience sleep disruption should remove the 24-hour patch prior to bedtime or use the 16-hour patch.[43,69] The patient should place a new patch on a relatively hairless location, typically between the neck and waist. There are no restrictions on activity while using the patch.[44,69] The most frequent side effect with the nicotine patch is skin irritation related to the adhesive or the medium containing nicotine and not to the nicotine itself. Approximately 50% of patients report skin irritation during the course of treatment and the patch site can be rotated to diminish this problem. Switching to a different brand of patch can also help as different products use different adhesives or media. The gum can be used instead of the patch when the skin irritation is severe; however, less than 5% of patients were forced to discontinue therapy because of skin reactions.[43]

Additionally the patient should be told that using the patch results in less desire to smoke and provides an opportunity for a new nonsmoker to reduce their hand-mouth habit without being burdened by craving. The patient should understand that with smoking, there are naturally peaks and valleys in the amount of nicotine in the bloodstream. However with the patch, there is a steady gradual rise in the blood nicotine concentration that levels off and remains constant for much of the day, and then gradually decreases while the person is asleep.[43] It has also been shown that combining the nicotine patch with an oral formulation, such as the nicotine gum, which allows ad libitum nicotine delivery, can improve the overall cessation without significant increased risk for harm.[44] In fact, various studies have evaluated combination NRTs and based on current

evidence, the use of a nicotine patch can be used with the nicotine gum, lozenge, or nasal spray on an as needed basis. Additionally, it is important to also incorporate the behavioral strategies with the pharmacotherapy as recommended by current guidelines.[72]

Nicotine Nasal Spray

Nicotine nasal spray is available exclusively as a prescription medication and differs from the other short acting NRTs due to the higher peak and trough concentrations, as it is more rapidly absorbed and eliminated than other forms.[72] A dose of nicotine nasal spray consists of one 0.5-mg delivery to each nostril (1 mg total). Initial dosing should be one to two doses per hour, increasing as needed for symptom relief. The minimum recommended treatment is 8 doses per day, with a maximum limit of 40 doses per day (5 doses per hour). Recommended duration of therapy is 3 months. Patients should not sniff, swallow, or inhale through the nose while administering doses because this increases irritating effects.[43,66]

Nicotine Oral Inhaler

The Nicotrol inhaler consists of a mouthpiece and a plastic cartridge which is placed into the inhaler and delivers 4 mg or 10 mg of nicotine, through inhalation via vapor, with absorption mainly occurring in the throat and upper airway.[71] It is suggested the patient actively puff on the inhaler for 5 minutes at a time and adjust use based on effect, as the cartridge can be used for up to 20 minutes of active puffing. The recommended initial dosing is 6 to16 cartridges per day for up to 12 weeks of therapy. It is recommended that the patient start attempting to taper after 6 weeks of initiation.[64] As the inhaler resembles a cigarette, it also provides the sensory stimulation to help decrease some of the cue-induced cravings by alleviating the hand-mouth habit.[72] However, there are some concerns this inhaler may do the opposite and possibly reinforce smoking habits and continue the behavioral dependence on nicotine.[72]

Instructing Patients in the Use of NRT

Compliance with NRT improves when the patient is presented a clear rationale for its use and a realistic expectation about their response. It should be explained nicotine is responsible for addiction and that discontinuation causes craving for cigarettes, tension, irritability, sadness, problems with sleep, and difficulty concentrating. Nicotine-replacement products have relatively few side effects; however, nausea and light-headedness are possible symptoms of nicotine overdose that warrant a reduction of the nicotine dose.

Duration

Those who commit to quitting smoking using NRT should be told that treatment for up to 3 months is common. However, some patients will experience severe withdrawal even beyond this time period; thus, long-term use of NRT might be indicated. Initially, when NRT products were approved by the FDA, they were approved for 8 to 12 weeks of therapy.[73] Long-term use of NRT 6 months or longer has not been linked to any safety concerns[71] and is supported by the 2008 updated US Public Health Service Guidelines.[43]

Electronic Nicotine Delivery Systems

Electronic nicotine delivery systems (ENDS) (also known as e-cigarettes or electronic cigarettes, or vaping devices) are designed to deliver a propylene glycol or glycerin product with a combination of nicotine, flavorings, and/or other chemicals through an aerosol. The device usually includes a battery, a heating coil, an atomizer, a cartridge, which contains the e-liquid (also called “juice”), and a mouthpiece. The range of nicotine delivered to the user can vary according to the product type and brand and is now available in first, second, and third generation models with some products not containing any nicotine at all.[75] It has been suggested that using the ENDS products instead of smoking traditional cigarettes can eliminate the exposure to most of the toxins commonly seen in traditional cigarettes. However, no e-cigarette has been approved by the FDA as a cessation aid. A Cochrane review of two randomized controlled 6-month trials which included over 600 patients demonstrated using e-cigarettes with nicotine might help increase the chances of a successful smoking cessation over placebo. However, it was stressed more studies are needed since the overall evidence is low.[75] Thus, although ENDS may offer a possible benefit during the smoking cessation process, their use is controversial as the potential harms associated with their use are still being evaluated and studied. Additionally use of e-cigarettes among middle school and high school students significantly increased from 2011 to 2015 and it was found by 2015 that e-cigarettes were the most common tobacco product among middle and high school students.[76] To improve regulation of these products, the Deeming Rule was finalized by the FDA, which expanded the FDA’s regulatory authority to include manufacture, import, packaging, labeling, advertising, promotion, sale, and distribution of all tobacco products including ENDS. This prohibited the sale of ENDS products to youth under the age of 18, banning their sale in vending machines, or providing free samples. Manufacturers now have to receive marketing authorization from the FDA, and health warnings on ENDS and other tobacco products are now

required. Furthermore vape shops that mix e-liquid must comply with the same legal requirements as tobacco manufacturers.[77] Despite changes in regulations, these products are still very popular with youth in the United States. The FDA continues to promote education campaigns such as “The Real Cost” Youth E-Cigarette Prevention Campaign which is aimed at youth who have experience with using ENDS or are considering trying these devices. Regardless, work continues in an effort to reduce the toxicity of the tobacco products, find ways to make products less appealing and less addictive and improve the child-resistant packaging.[78]

The level of harm and/or risk associated with secondary passive exposure to ENDS aerosol is an ongoing debate, as passive exposure to the vapor emitted from the ENDS user could be hazardous based on a systematic review of 16 studies.[79] Data show e-cigarette vapor could expose bystanders to chemicals including nicotine, glycine, formaldehyde, acetaldehyde, and propylene glycol leading to an impact on indoor air quality. This risk, however, was noted to be a lower risk than the associated exposure risk from passive exposure from conventional cigarettes.[79] To limit second-hand exposure, many states have extended indoor smoking bans to include ENDS, although the laws for each state vary considerably. The level of carcinogen and toxicant delivered to the user of the ENDS has been raised as a safety concern and due to the large variations in delivery devices, and fluctuations in the amount of product a user will receive, it is difficult to study. While additional concerns have been raised regarding ENDS and toxic substances, the toxic levels of ENDS are estimated to be one fourth to 1/95th the levels of the traditional cigarette.[80] Continued research is needed to evaluate the efficacy of e-cigarette use in regards to where it belongs in helping patients with smoking cessation, as well as the safety concerns with the nicotine addiction, youth exposure, and overall safety of this delivery system in general.

Non-Nicotine Options

Bupropion (Zyban) Pharmacologically, bupropion inhibits neuronal reuptake, and potentiates the effects of norepinephrine and dopamine. Although its precise mechanism in smoking cessation is not well understood, it is felt bupropion’s dopaminergic effects help reduce nicotine craving as the rewarding effects of addictive substances may be due to dopamine neurotransmission.

Bupropion SR is marked under the brand name Zyban and has been shown to be an effective treatment option for smoking cessation, although the brand product Wellbutrin contains the same pharmacological product.[81] A recent meta-analysis involving 65 trials showed that bupropion significantly increased the

incidence of long-term cessation when used as a sole agent in 44 separate trials[82]. Other trials using bupropion as an add-on agent with NRT did not show bupropion had an additional benefit in improving cessation rates.[74] For smoking cessation, the manufacturer recommends a dosage of 150 mg once daily for 3 days and then twice daily (dosing should be at least 8 hours apart) for 7 to 12 weeks or longer, with or without NRT. Patients are instructed to stop smoking during the second week of treatment and are encouraged to use counseling and support services along with the medication. For maintenance therapy, consider bupropion SR 150 mg twice daily for up to 6 months.[43]

Contraindications for bupropion use include current or past seizure disorders, a history of monoamine oxidase inhibitor use over the last 14 days, and a history of anorexia nervosa or bulimia. Along with multiple other precautions listed in the product labeling, current alcohol use and use of medications that lower seizure threshold (eg, antidepressants and antipsychotics) are possible concerns when using this medication.[43] In 2009, the FDA required bupropion manufacturers to add new boxed warnings and to develop a medication guide highlighting the risk of serious neuropsychiatric symptoms in patients using this product. Possible symptoms include depressed mood, agitation, anxiety, hostility, changes in behavior, suicidal thoughts and behavior, and attempted suicide. However, in 2016 following a FDA-requested clinical trial review, the FDA announced the removal of the Black Box Warning and the Risk Evaluation and Mitigation Strategies (REMS) requirement for bupropion although continued to caution that the risk of mental health side effects are still possible, particularly in patients with a past history of mental health disorders or currently being treated for anxiety, depression, or schizophrenia.[83]

8 **Varenicline (Chantix)** Pharmacologically, varenicline is a partial agonist that binds selectively to α_4-β_2-nicotinic acetylcholine receptors (nAChRs) with a greater affinity than nicotine. When bound to the receptor, the drug blocks nicotine binding and also evokes a response, but to a lesser degree than nicotine.[71] Clinically, varenicline acts at sites in the nicotine-affected brain in two ways: by providing nicotine effects to ease withdrawal symptoms and by blocking the effects of nicotine from cigarettes if they resume smoking. Additionally, varenicline has been found to have full agonist, although less potent, activity at α_7 and α_4-β_2 nAChRs and a full agonist at 5-HT_3.[84] A systematic review of 39 trials involving varenicline, results showed an over two- to three-fold increased likelihood of long-term smoking cessation with varenicline compared with no NRT treatment (placebo).[85] Data from the trials

included in this review, also suggested that varenicline could have a role in relapse prevention and that it demonstrated better results compared to bupropion and NRT. These results were also seen in the largest randomized controlled trial for smoking cessation to date, the Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES) trial, which showed that varenicline is more efficacious than all other single NRTs, except for similar efficacy to the nicotine patch.[86]

The recommended dosage for varenicline is 0.5 mg daily for 3 days, increased to 0.5 mg twice daily for 3 days, and then increased to 1 mg twice daily for a standard 12-week treatment. It is suggested the quit date should be set for 1 week after initiating varenicline, but studies have shown allowing a flexible quit date is also efficacious and safe. If abstinence has not been achieved after the 12-week treatment, then a second 12-week treatment may be prescribed.[87] Additionally, continuing varenicline as maintenance therapy for 6 months has been shown to decrease the risk of relapse and is approved by the FDA.[71] Common side effects associated with varenicline are nausea, vomiting, and insomnia, but over the years there have been concerns of neuropsychiatric side effects including suicidal thoughts, depression, and psychosis leading to the black box warning. Therefore ongoing research has been done to examine this risk. Results of the previously mentioned EAGLES trial[86] also included a composite measure of neuropsychiatric symptoms as a primary safety endpoint. Outcomes of this trial indicated there was no evidence of a significant increase in neuropsychiatric adverse effects which could be attributed to varenicline or bupropion. Specifically in the patients with psychiatric histories, moderate-to-severe neuropsychiatric symptoms were reported as 6.5%, 6.7%, 5.2%, and 4.9% of varenicline, bupropion, nicotine patch, and placebo users, respectively. In comparison, for patients without psychiatric histories, moderate-to-severe neuropsychiatric symptoms were reported as 1.3%, 2.2%, 2.5%, and 2.4% of varenicline, bupropion, nicotine patch, and placebo users, respectively. Overall, the risk differences reported for varenicline and bupropion versus placebo or the nicotine patch were nonsignificant. Following review of the trial results, the FDA announced the removal of the black box warning for varenicline as well as bupropion. In addition, a statement was included confirming bupropion, varenicline, and nicotine replacement patches are all more efficacious in smoking cessation compared to placebo regardless of mental illness history.[86,88] The most recent FDA Drug Safety communication indicates that although the risks of direct adverse effects from varenicline are lower than previously thought, the risk is still possible, especially in patients who suffer are under the

care of mental illnesses including schizophrenia, depression, or anxiety.[88] Cardiovascular safety concerns have also been raised regarding varenicline over the years and to date the results of various studies are still conflicting. In 2012, the FDA released a safety review update on the risk of cardiovascular adverse events indicating there is a higher risk of cardiovascular risks associated with varenicline.[89] However, results from the EAGLES extension trial, which was specifically designed to evaluate cardiovascular safety data, concluded there was no evidence of any cardiovascular side effects associated with these medications.[82]

Combination Therapy

While evidence exists for the use of NRT combination therapy, the evidence is not as strong when considering combining a NRT with varenicline. A systematic review and meta-analysis of 3 randomized controlled trials with 904 patients found that combining varenicline with NRT is more effective than varenicline alone. Patients who were treated with both the nicotine patch and varenicline had similar adverse events to monotherapy except for skin reactions from the nicotine patch. Although the results for this study were positive for the combination, there were limited numbers of studies included in this analysis, so larger controlled clinical trials are needed.[90] Utilizing bupropion plus NRT has been shown to be more effective than bupropion monotherapy[91] and is approved by the FDA. Recent studies evaluating the effectiveness of combining varenicline and bupropion have demonstrated that this combination is not any more effective than varenicline as monotherapy.[92]

Second-Line Medications

Second-line medications are therapeutic options for treating tobacco dependence, but have a more limited role than first-line medications because (a) the FDA has not approved them for treatment of tobacco dependence and (b) there are more concerns about potential side effects than with first-line medications.[43] Although these second line medications have shown some efficacy for smoking cessation, they should be considered for use on a case-by-case basis after first-line treatments have been used or considered.

Clonidine

Clonidine is efficacious as a smoking cessation treatment, as evidenced by results from a meta-analysis of six trials which showed it increased smoking

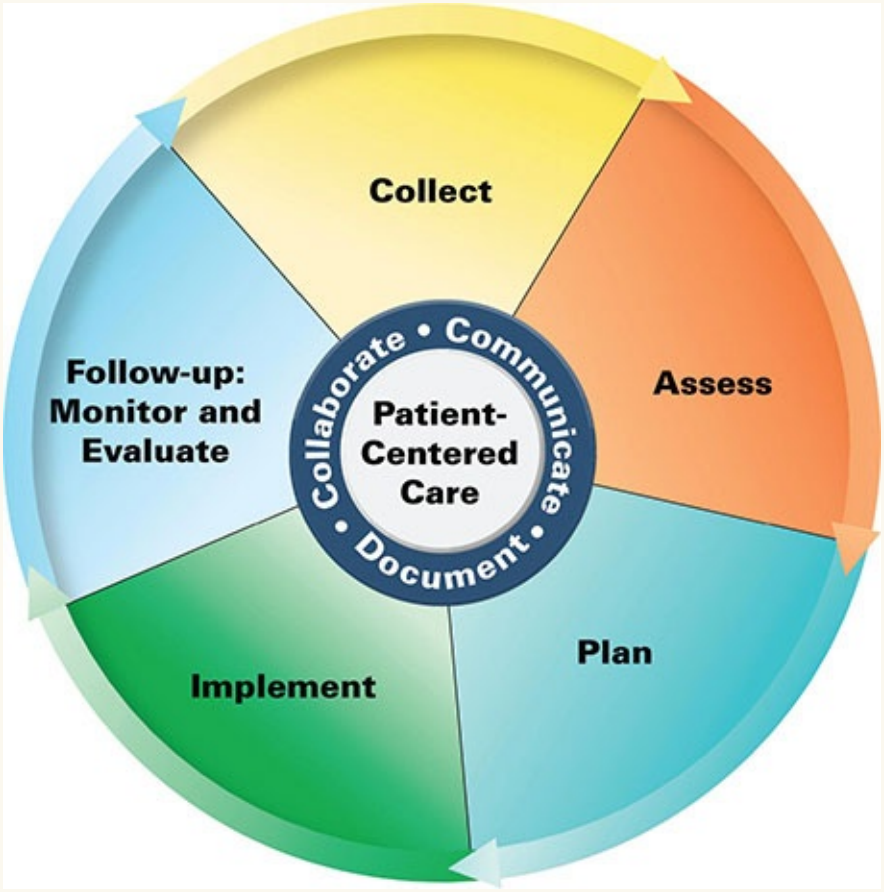
cessation rates by 9%.[93] The main significant side effect seen with clonidine use in most patients is hypotension, particularly postural hypotension; thus, blood pressure should be monitored.[93] Additional side effects include dry mouth, drowsiness, dizziness, and sedation. Overall, clonidine can be considered a second-line, off label, agent to treat tobacco dependence.

Nortriptyline

Nortriptyline is also considered to be efficacious as a second-line agent for tobacco dependence. When used for this indication, therapy is initiated 10 to 28 days before the quit date to allow for steady state to be reached at the target dose. Trials have initiated treatment at a dose of 25 mg/day, increasing gradually to a target dose of 75 to 100 mg/day. Duration of treatment used in smoking cessation trials has been approximately 12 weeks. A meta-analysis of 6 trials with 975 patients showed that nortriptyline as a sole agent does show similar efficacy to NRT and has also been effective in increasing long-term cessation rates.[81] Adding nortriptyline as an adjuvant to NRT did not prove additional benefit in 4 trials which included over 1600 patients.[81] Most commonly reported side effects included sedation, dry mouth, blurred vision, urinary retention, light-headedness, and tremor.[43]

EVALUATION OF THERAPEUTIC OUTCOMES

Assisting a patient with tobacco cessation is a process that could take an extended period of time with extensive education and continual monitoring being vital to this process. It has been shown the most effective treatment strategy for smoking cessation is a combination of behavioral and pharmacological treatment. Frequent monitoring of both treatment strategies early on in the process is recommended. There are seven pharmacological treatment options and patient selection will be determined by a variety of factors. Patient counseling on selected pharmacotherapy options and common adverse effects is vital to ensure proper use and maximum efficacy. Frequent reassessment should occur to monitor overall treatment efficacy and to evaluate breakthrough cravings, withdrawal symptoms, and relapses. Dose adjustments should be made accordingly and patients should be monitored closely and asked to immediately report any adverse effects to ensure proper adherence and prevent relapse.



Patient Care Process for Smoking Cessation

Collect

- Patient characteristics (eg, age, sex, pregnant)
- Patient medical history (personal and family)
- Social history (eg, tobacco/ethanol use) and dietary habits
- Smoking history (eg, current triggers, last cessation attempt, pharmacotherapy trials used in cessation, patient's level of interest for cessation at this time)
- Current medications including OTC use, herbal products, dietary supplements
- Objective data
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2-saturation

- Labs including serum creatinine (SCr), liver function tests (LFTs)

Assess

- Hemodynamic stability (eg, systolic BP >90 mm Hg, HR <110 bpm, O_2-sat >90% (0.90), RR >20)
- Utilize motivational interviewing to assess readiness to quit
- Ability/willingness to pay for pharmacotherapy options and/or behavioral treatment for smoking cessation
- Ability/willingness to obtain laboratory monitoring tests (eg, LFTs [ie, bupropion], SCr [ie, varenicline])
- Emotional status (eg, presence of anxiety, depression)

Plan*

- Drug therapy regimen including specific nicotine replacement therapy (NRT), non-NRT, dose, route, frequency, and duration; (see Tables 83-5 and 83-6)
- Monitoring parameters including efficacy (eg, decreases in craving, smoking) and safety (eg, side effects specific to selected agent); frequency and timing of follow-up
- Patient education (eg, purpose of treatment, lifestyle modification, drug-specific information, medication administration technique; see Table 83-6)
- Self-monitoring for side effects from pharmacotherapy treatment
- Referrals to other providers when appropriate (eg, behavioral health; highly recommended but not required for pharmacotherapy treatment)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Set quit date if appropriate for this patient at this time (if appropriate)
- Schedule follow-up (eg, adherence assessment)

Follow-up: Monitor and Evaluate*

- Quit date set

- Presence of adverse effects (eg, drug specific)
- Patient adherence to treatment plan using multiple sources of information
- Reevaluate duration of therapy initially with frequent follow up and then lengthen follow up to every 1–2 months

* *Collaborate with patient, caregivers, and other healthcare professionals.*

INTRODUCTION—CAFFEINE

9 Caffeine is currently the most widely used psychoactive substance in the world, with 80% to 90% of adults in the United States regularly consuming behaviorally active doses of caffeine,[94] resulting in psychoactive or stimulating responses which can include an increased sense of well-being, concentration, energy, alertness, and sociability.[95] Caffeine is generally recognized as safe by the FDA for use in cola-type beverages as long as levels do not exceed 0.02% (200 parts per million), which is 71 mg of caffeine in a 12-oz (355 mL) serving of cola.[96] A systematic review of data regarding potential adverse effects associated with caffeine found up to 400 mg caffeine per day in health adults was not associated with adverse effects in regards to cardiovascular, behavioral, reproductive, or developmental effects.[97] Additionally, the FDA has cited that 400 mg per day, which is approximately four to five cups of coffee, is generally considered safe for adults. This is different from children and adolescents, as the American Academic of Pediatrics discourages them from consuming stimulants or caffeine, with further study being necessary to determine what the proper levels of consumption would be safe for this patient population.[98] Although in general caffeine consumption in reasonable amounts has been considered fairly safe, there are situations in which problems arise. Caffeinism has been associated with a daily caffeine intake of 1,000 to 1,500mg. This term was coined to describe the clinical syndrome produced by acute or chronic overuse of caffeine which is usually characterized by CNS and peripheral manifestations, most notably anxiety, psychomotor alterations, sleep disturbances, mood changes, and psychophysiological complaints.[95]

Pharmacologically, the risk of developing meaningful clinical manifestations from caffeine becomes high when intake exceeds 500 mg/day. Drinking traditional coffee, it could be assumed this level of caffeine might not be reached, which helps explain why, up until recently, deaths from acute ingestions of caffeine were virtually nonexistent. However, pure caffeine powder has

become available via the internet[99] and one teaspoonful of this bulk powder is estimated to be equivalent to 25 to 30 cups of coffee. As the “recommended dose” is 1/64th to 1/16th of a teaspoonful, which is equivalent to 2 cups of coffee, exceeding this dose has led to toxicity, including life-threatening cardiac arrhythmias and death. Due to this risk, efforts are being made to regulate powdered caffeine, which currently is available for purchase without regulation.[99]

Caffeine in general has been proposed as a “model of drug abuse” despite the facts that its sale is largely unrestricted and that heavy consumption of caffeine-containing beverages is not considered to be drug abuse. The following information represents a broad overview of dependence, withdrawal, and tolerance. The reader interested on more information is urged to consult Juliano et al. and Evatt et al. for further information.[100,101]

EPIDEMIOLOGY

Recently, data from the What We Eat in America/National Health and Nutrition Examination Survey (NHANES) was evaluated regarding caffeine consumption through caffeinated beverages, foods, and energy drinks. This data showed that 89% of men and women in the United States consume caffeine daily, predominantly through caffeinated beverages (98%). The most common caffeinated beverage was coffee (64%), with tea and soft drinks being less popular (16% and 18%, respectively). The intake of caffeine averaged 186 mg/day, and over half of the consumers ingested this amount in one consumption.[102] Caffeine intake among children, adolescents, and young adults is prevalent from foods and beverages based on the 1999 to 2010 NHANES data analyzing ages of participants from 2 years old to 22 years old. It was found that 73% consumed caffeine, and although the caffeine consumption overall remained similar through the years, the choice of beverages has changed from predominately soda in 1999 to 2000 to a combination of soda, sweetened coffee, and energy drinks in 2009 to 2010.[103]

10 A number of energy drinks containing caffeine, taurine, vitamins, and sugar, and sold under brand names such as Red Bull, Monster Energy, Rockstar, and Amp, continue to gain popularity among adolescents and emerging adults. These products are promoted to increase energy, enhance alertness, and promote physical performance. It is reported that approximately 33% of teenagers between the ages of 12 and 17 consume these products and aside from multivitamins, these products are the most popular dietary supplement for young

adults as well.[104] There are two types of products on the market based on volume. One product is similar to a soft drink and will vary on caffeine levels based on the size of the container. For example, the amount of caffeine contained in one can of Red Bull (8.4 oz [250 mL]) is 80 mg of caffeine, although other products can contain higher amounts of caffeine depending on the size of the container. The second product is a smaller volume product referred to as an "energy shot." A 2-oz (60 mL) product claims to contain the "same amount of caffeine as a cup of the leading premium coffee" and also includes a variety of B vitamins and other products claimed to improve energy.[105] Since these products commonly include natural ingredients, they are regulated by the 1994 Dietary Supplement and Education Act and are not required to disclose how much caffeine is in the product.

Over the years, there have been many questions regarding the safety of these products. Emergency room visits attributed to these energy drinks doubled from 2007 to 2011 and upon evaluating the data further, it was identified that patients more than 40 years old had the largest increase in visits.[106] Concerns have been raised in the adolescent population associated with increased blood pressure, insomnia complaints, combining energy drinks with alcohol, and higher risk of alcohol and/or drug abuse.[107]

PATHOPHYSIOLOGY

Caffeine is rapidly and completely absorbed from the GI tract, reaching a peak blood level within 30 to 60 minutes after oral ingestion. It easily crosses the blood–brain barrier, and levels achieved in the brain are proportional to the dose administered.[108] Caffeine is metabolized by cytochrome P450 1A2 (CYP1A2) and has a half-life of approximately 4 to 5 hours in healthy nonsmoking adults. It has been discovered that fast metabolizers of CYP1A2 include heavy caffeine users, children less than 12 years old, and cigarette smokers. Women in later stages of pregnancy are slower metabolizers of caffeine, as are patients with liver dysfunction.[95,108] Overdoses of caffeine are now more common due to the wide availability of energy drinks. Caffeine increases the heart rate and force of cardiac contractions, and also has a strong diuretic effect. Due to the stimulating properties of caffeine, nervousness, agitation, and insomnia may occur with more serious reactions including cardiac arrhythmias, hypotension, and convulsions.[96,98] The key factor promoting caffeine use and dosage increases can be the drug's reinforcing effect on pleasure and reward centers of the brain. Caffeine's pharmacologic actions appear comparable (although less potent) with

those of other stimulants, such as amphetamines and cocaine.[108]

CLINICAL PRESENTATION

The *DSM-5* has four caffeine-related diagnoses, including caffeine intoxication, caffeine withdrawal, other caffeine-induced disorders which include both caffeine-induced sleep and anxiety disorders, and unspecified caffeine-related disorder. Each of these diagnoses could include symptoms which might be attributed to caffeine use, but do not fit in any other category. The *DSM-5* does not currently list a diagnosis of caffeine use disorder, but it has been identified as an area that needs further research to determine if it should become an official diagnosis.[5]

CLINICAL PRESENTATION

Caffeine Intoxication

General

- The patient may not be in acute distress.

Symptoms

- The patient may complain of nausea, vomiting, diarrhea, and psychomotor agitation, and can appear restless, nervous, and excited.

Signs

- The patient can present with facial flushing, diuresis, and muscle twitching.
- Tachycardia or cardiac arrhythmias can also occur.

Laboratory Tests

- Caffeine serum concentrations are rarely used clinically.

CLINICAL PRESENTATION

Caffeine Withdrawal

General

- The patient may not be in acute distress.

Symptoms

- Complaints of headache, nausea, vomiting, drowsiness, poor concentration, and depressed mood may be seen which are adversely affecting overall social/occupational functioning and/or leading to distress.

Laboratory Tests

- Caffeine serum concentrations are rarely used clinically.

The diagnostic criteria for caffeine intoxication includes recent consumption of caffeine normally exceeding 250 mg and five or more symptoms during, or shortly after, consumption of caffeine. The symptoms of caffeine intoxication will usually decrease over 24 hours as the caffeine is eliminated from the body however consumption of very high doses of caffeine could be dangerous and require immediate medical attention.[5]

Caffeine withdrawal is a new diagnosis in the *DSM-5*, which occurs after the abrupt cessation of chronic caffeine use and can occur even with low doses of caffeine in some patients. The diagnosis of caffeine withdrawal requires three of the five listed symptoms, including headache (most common), marked fatigue or drowsiness, altered mood (depressed, irritable, and dysphoric), difficulty in concentrating, or flu-like symptoms, including nausea, vomiting, and muscle pain/stiffness. The extent and severity of withdrawal can vary individually but normally will be more severe with higher chronic doses of caffeine (**Table 83-7**).[5]

TABLE 83-7 ***DSM-5*** **Diagnostic Criteria for Caffeine Withdrawal**

Criteria
Prolonged daily use of caffeine

Abrupt cessation or decrease use in caffeine leading to at least three of the following symptoms after 24 hours of cessation
• Concentration problems
• Mood changes: dysphoric mood, depressed mood, irritability
• Dramatic fatigue or drowsiness
• Headache
• Flu-like symptoms
  • Nausea
  • Vomiting
  • Muscle pain/stiffness

Symptoms negatively impact areas of functioning such as social or occupational aspects of life.
The symptoms experienced cannot be explained by other concurrent medical conditions.

Data from References 5.

Effect on Sleep

Caffeine interferes with sleep in most nontolerant individuals,[100] with tolerant people being much less likely to self-report sleep abnormalities, or they may sense that the insomnia has disappeared altogether. To illustrate, 53% of those consuming less than 250 mg/day agreed that caffeine before bedtime would prevent sleep, compared with 43% of those consuming 250 to 749 mg/day and only 22% of those taking 750 mg/day or more. Even though the higher-level consumers denied that caffeine interferes with their sleep, studies done in the sleep laboratory confirm that caffeine consumers do have greater sleep latency, more frequent awakenings, and altered sleep architecture and that these effects are dose related.

Caffeine During Pregnancy

Over the years, there has been much discussion regarding the safety of caffeine intake during pregnancy and possible risks to the developing fetus. While results of research have been mixed, caffeine has not been shown to be a potent and consistent teratogen. Kuczkowski[109] published an evidence-based review

highlighting the implications of caffeine intake in pregnancy and offering recommendations for practitioners providing peripartum care to expectant mothers who consume caffeine. Kuczkowski concluded that, for the healthy pregnant adult, moderate daily caffeine intake up to 400 mg/day is not associated with adverse effects, such as general toxicity, cardiovascular effects, effects on bone status and calcium balance, changes in adult behavior, increased incidence of cancer, or effects on fertility. The study did not identify any significant positive associations between maternal caffeine consumption and cardiovascular malformations in the developing fetus. The March of Dimes advises women to limit their caffeine intake to less than 200 mg/day, which was prompted by the results of a population-based prospective cohort study, showing that pregnant women consuming 200 mg or more of caffeine a day had double the risk of miscarriage compared with those who had no caffeine.[110] Criticism of this study was swift to follow, and its conclusions have been called into question. A recent systematic review of 380 studies published from 2001 through June 2015 determined that daily consumption of up to 300mg of caffeine per day in a healthy pregnant woman was not associated with any adverse health outcomes or developmental effects.[111]

TREATMENT

Desired Outcomes

Many people drink coffee, tea, and other caffeinated beverages without problems. When adverse health effects occur (eg, insomnia, headaches, anxiety, and palpitations), it may be necessary to cut down on the amount of caffeine ingested or to eliminate it altogether to achieve the goal of elimination of these symptoms.

Nonpharmacologic Therapy

The primary treatment of caffeinism is reducing or discontinuing use of the drug. For some it may be necessary to wean the patient off the drug gradually because going “cold turkey” can produce serious symptoms that compel the user to restart caffeine administration. While decaffeinated beverages can be substituted slowly for the caffeinated type, relapses are less likely to occur when the drug is discontinued all at once, most likely due to the considerable self-discipline required to continue weaning the drug when one knows that an increase in dose

will cause the symptoms to abate. For cases of extreme caffeine toxicity and withdrawal, necessary supportive measures should be instituted to prevent short- and or long-term sequelae.

EVALUATION OF THERAPEUTIC OUTCOMES

Identifying the treatment goals associated with the patient's current caffeine consumption and addressing these goals will be the primary focus in evaluating therapeutic outcomes. When a patient is working to reduce or discontinue caffeine, frequent reassessment should occur to monitor the patient for symptoms of caffeine withdrawal and educate on possible effects of withdrawal. If effects of withdrawal are experienced, appropriate adjustments should be made to improve reaching treatment goals.

CONCLUSION

Alcohol, nicotine, and caffeine are considered by most to be socially acceptable drugs, yet they impose an enormous social and economic cost on our society. It is vital that all healthcare professionals continue to educate patients on the healthcare risks of each of these substances to decrease the negative impact that can occur with chronic use and abuse of these substances.

Postclass Engaged Learning Activity

Alcohol Use Disorder

The case, "Drugs of Abuse," can be found at the following link: https://tinyurl.com/y2tn3bt4

This activity provides a case example of a hospitalized patient admitted for surgery who begins experiencing alcohol withdrawal. Following the case, questions are asked regarding the pharmacokinetics and pharmacodynamics of ethanol associated with acute and chronic use. Further discussion of the case under the ''Approach'' tab includes the pertinent definitions and FDA-approved drugs for alcohol use disorder. ''Pharmacology Pearls'' summarizes key takeaway points from the activity and ''Comprehensive Questions'' assesses the students' knowledge and retention of the activity.

Smoking Cessation

Following review of the case and the video from smoking cessation preclass

activity, use the provided information and follow directions below.

Step 1: Complete Pharmacotherapy Table below to provide your 1st, 2nd, and 3rd recommendations. Include your thought process within the table.

	Recommendation #1	Recommendation #2	Recommendation #3
Medication(s) Name, Dose, Route, etc.			
Mechanism of action(s)			
Rationale for recommendation			
Pros			
Cons			
Possible adverse effects			
Other concerns			

Step 2: Provide any behavioral intervention recommendations you would like to include in your treatment plan. Provide a rationale for this as well.

ABBREVIATIONS

AUD	Alcohol use disorder
AUDIT	Alcohol Use Disorders Identification Test
AUDIT-C	Alcohol Use Disorders Identification Test—Consumption questions
BAC	blood alcohol concentration
CIWA-AR	Clinical Institute Withdrawal Assessment for Alcohol, revised
CT	computed tomography
CUD	Caffeine Use Disorder
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
DT	Delirium tremens
ENDS	Electronic Nicotine Delivery Systems
FDA	Food and Drug Administration
GABA	γ-aminobutyric acid
GI	gastrointestinal
5-HT_3	serotonin-3 receptor
HIV	human immunodeficiency virus
NHANES	National Health and Nutrition Examination Survey
NIH	National Institute of Health
NIDA	National Institute on Drug Abuse

NRT	nicotine replacement therapy
NSDUH	National Survey on Drug Use and Health
PAN	psychotropic analgesic nitrous oxide
RCT	randomized controlled trial
SIDS	sudden infant death syndrome
SR	sustained release
TTFC	time to first cigarette
USPSTF	United States Preventive Services Task Force

REFERENCES

1. World Health Organization Department of Mental Health and Substance Abuse. *Global Status Report on Alcohol and Health 2018*. Geneva: World Health Organization; 2018. License: CC BY-NC-SA 3.0IGO.http://www.who.int/substance_abuse/publications/global_alcohol_
2. Kanny D, Brewer R, Mesnick J, et al. Vital signs: alcohol poisoning deaths —United States 2010–2012. *MMWR*. 2015;63(53):1238-1242. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6353a2.htm?s_cid=mm6353a2_w. Accessed September 28, 2018.
3. Substance Abuse and Mental Health Services Administration. *Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health (HHS Publication No. SMA 18-5068, NSDUH Series H-53)*. Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration; 2018. Accessed September 28, 2018.https://www.samhsa.gov/data. Accessed September 28, 2018
4. Substance Abuse and Mental Health Services Administration and National Institute on Alcohol Abuse and Alcoholism. *Medication for the treatment of alcohol use disorder: a brief guide. HHS Publication No. (SMA) 15-4907*. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2015. https://store.samhsa.gov/system/files/sma15-4907.pdf. Accessed September 28, 2018.
5. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 5th ed, DSM-5*. Arlington, VA: American Psychiatric Association; 2013.
6. Enoch M. Genetic influences on the development of alcoholism. *Curr Psychiatry Resp*. 2013;15(11):412. doi:10.1007/s11920-013-0412-1.
7. Jones J, Comer S, Kranz H. The pharmacogenetics of alcohol use disorder.

Alcoholism Clin Exp Res. 2015;39(3):391-402.

8. Verhulst B, Neale M, Kendler K. The heritability of alcohol use disorders: a meta-analysis of twin and adoption studies. *Psychologic Med*. 2015;54:1061-1072.
9. Agrawal A, Verweij KJ, Gillespie NA, et al. The genetics of addiction—a translational perspective. *Transl Psychiatry*. 2012;2:e140. doi:10.1038/tp.2012.54.
10. Chan L, Anderson G. Pharmacokinetic and pharmacodynamics drug interactions with ethanol (alcohol). *Clin Pharmacokinet*. 2014;53:1115-1136.
11. Perry PJ, Doroudgar S, Van Dyke P. Ethanol forensic toxicology. *J Am Acad Psychiatry Law*. 2017;45:429-38.
12. Cedarbaum AI. Alcohol metabolism. *Clin Liver Dis*. 2012;16:667-685.
13. Nassir F, Ibdah J. Role of mitochondria in alcoholic liver disease. *World J Gastroenterol*. 2014;20(9):2136-2142.
14. Jones AW. Pharmacokinetics of ethanol—Issues of forensic importance. *Forensic. Sci Rev*. 2011;23:91-136.
15. Dhalla S, Kopec JA. The CAGE questionnaire for alcohol misuse: a review of reliability and validity studies. *Clin Invest Med*. 2007;30:33-41.
16. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. *AUDIT: The Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Care*. 2nd ed. Geneva: World Health Organization; 2001.
17. Lundin A, Hallgren M, Balliu N, Forsell Y. The use of alcohol use disorders identification test (AUDIT) in detecting alcohol use disorder and risk drinking in the general population: validation of AUDIT using schedules for clinical assessment in Neuropsychiatry. *Alcohol Clin Exp Res*. 2015;39(1):158-165.
18. National Institute on Alcohol Abuse and Alcoholism. Alcohol overdose: the dangers of drinking too much. Available at http://pubs.niaaa.nih.gov/publications/AlcoholOverdoseFactsheet/Overdos Accessed August 6, 2018.
19. Perry E. Inpatient management of acute alcohol withdrawal syndrome. *CNS Drugs*. 2014;28:401-410.
20. Holt SR, Tobin DG. Pharmacotherapy of alcohol use disorder. *Med Clin N Am*. 2018;102:653-666.
21. Carlson RW, Kumar NN, Wong-McKinstry E, et al. Alcohol withdrawal

syndrome. *Crit Care Clin*. 2012;28:549-585.

22. Sulivan JT, Sykora K, Schneiderman J, et al. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *Br J Addict*. 1989;84:1353-1357.
23. Mayo-Smith MF. Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. *JAMA*. 1997;278:144-151.
24. Amato L, Minozzi S, Davoli M. Efficacy and safety of pharmacological interventions for the treatment of the Alcohol Withdrawal Syndrome. *Cochrane Database Syst Rev*. 2011;(6):CD008537. doi:10.1002/14651858.CD008537.pub2.
25. Mirijello A, D'Angelo C, Ferruli A, et al. Identification and management of alcohol withdrawal syndrome. *Drugs*. 2015;75:353-365.
26. Mayo-Smith MF, Beecher LH, Fischer TL, et al. Working Group on the Management of Alcohol Withdrawal Delirium, Practice Guidelines Committee, American Society of Addiction Medicine. Management of alcohol withdrawal delirium. An evidence-based practice guideline. *Arch Intern Med*. 2004;164:1405-1412[Erratum. Arch Intern Med 2004;164:2068].
27. Schmidt KJ, Doshi MR, Holzhausen JM, et al. Treatment of severe alcohol withdrawal. *Ann Pharmacother*. 2016;50:389-401.
28. Marks V, Teale JD. Drug-induced hypoglycemia. *Endocrinol Metab Clin North Am*. 1999;28:555-577.
29. Muncie HL, Yasinian Y, Oge' L. Outpatient management of alcohol withdrawal syndrome. *Am Fam Physician*. 2013;88(9):589-595.
30. Winslow BT, Onysko M, Hebert M. Medications for alcohol withdrawal disorder. *Am Fam Physician*. 2016;93(6):457-465.
31. Kranzler HR, Soyka M. Diagnosis and pharmacotherapy of alcohol use disorder: A review. *JAMA*. 2018:320:815-824.
32. Pani PP, Trogu E, Pacini M, Maremmani I. Anticonvulsants for alcohol dependence. *Cochrane Database Syst Rev*. 2014;(2):CD008544. doi:10.1002/14651858.CD008544.pub2.
33. Blodgett JC, Del Re AC, Maisel NC, et al. A meta-analysis of topiramate's effects for individuals with alcohol use disorders. *Alcohol Clin Exp Res*. 2014;38:1481-1488.

34. Reus VI, Fochtmann LJ, Bukstein O, et al. The American Psychiatric Association practice guide-line for the pharmacological treatment of patients with alcohol use disorder. *Am J Psychiatry*. 2018;175:86-90.
35. Skinner MD, Lahmek P, Pham H, et al. Disulfiram efficacy in the treatment of alcohol depend-ence: a meta-analysis. *PLoS One*. 2014;9(2):e87366.
36. Oslin D, Leong S, Lynch K, et al. Naltrexone vs. Placebo for the treatment of alcohol depend-ence. *JAMA Psychiatry*. 2015;72(5):430-437.
37. Sudakin D. Naltrexone: not just for opioids anymore. *J Med Toxicol*. 2016;12:71-75.
38. Rosner S, Hackl-Herwerth A, Leucht S, et al. Opioid antagonists for alcohol dependence. *Cochrane Reviews*. 2010;(12):CD001867. doi:10.1002/14651858.
39. Pettinati HM, Silverman BL, Battisti JJ, et al. Efficacy of extended-release naltrexone in patients with relatively higher severity of alcohol dependence. *Alcohol Clin Exp Res*. 2011;35(10):1804-1811. doi:10.1111/j.1530-0277.2011.01524.x[Epub May 16, 2011].
40. Rösner S, Hackl-Herrwerth A, Leucht S, et al. Acamprosate for alcohol dependence. *Cochrane Database Syst Rev*. 2010;(9):CD004332.
41. U.S. Department of Health and Human Services. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General*. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014. https://www.surgeongeneral.gov/library/reports/50-years-of-progress/full-report.pdf.Accessed October 21, 2018.
42. Wang TW, Asman K, Gentzke AS, et al. Tobacco Product Use Among Adults — United States, 2017. *MMWR Morb Mortal Wkly Rep*. 2018;67:1225-1232.
43. Fiore MC, Baily WC. *Treating Tobacco Use and Dependence. Clinical Practice Guidelines*. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service; June 2000[updated May 2008].
44. Siu AL, U.S. Preventive Services Task Force. Behavioral and pharmacotherapy interventions for tobacco smoking cessation in adults, including pregnant women, US Preventive Services Task Force Recommendation Statement. *Annals of Internal Medicine*. 2015; 163:622-634.

45. Murphy-Hoefer R, Davis KC, Beistle D, King BA, Duke J, Rodes R, et al. Impact of the Tips From Former Smokers Campaign on Population-Level Smoking Cessation, 2012–2015. *Prev Chronic Dis*. 2018;15:180051. http://dx.doi.org/10.5888/pcd15.180051.
46. CDC Tips From Former Smokers. FREE QuitGuide Mobile App. Available at: https://www.cdc.gov/tobacco/campaign/tips/quit-smoking/mobile-quit-guide/index.html?s_cid=OSH_tips_D9405. Accessed November 2, 2018.
47. Kasza K, Ambrose B, Conway K, et al. Tobacco-Product use by Adults and Youths in the United States in 2013 and 2014. *NEJM*. 2017;376(4):342-353.
48. Xu X, Bishop EE, Kennedy SM, Simpson SA, Pechacek TF. Annual healthcare spending at-tributable to cigarette smoking: an update. *Am J Prev Med*. 2015;48(3):326-333. Epub 2014/12/17. pmid:25498551; PubMed Central PMCID: PMCPmc4603661.
49. DiGiulio A, Jump Z, Yu A, et al. State Medicaid Coverage for Tobacco Cessation Treatments and Barriers to Accessing Treatments — United States, 2015-2017. *Morbidity and Mortality Weekly Report*. 2018;67(13):390-395.
50. Centers for Disease Control and Prevention. Vital signs: Disparities in Nonsmokers' Exposure to Secondhand Smoke-United States, 1999-2012. *MMWR Morb Mortal Wkly Rep*. 2015;64(4):103-108.
51. Raghuveer G, White D, Hayman L, et al. Cardiovascular Consequences of Childhood Secondhand Tobacco Smoke Exposure: Prevailing Evidence, Burden, and Racial and Socioeconomic Disparities. *Circulation*. 2016;134:e336-e359. doi:10.1161/CIR.0000000000000443.
52. Balfour DJ. Neuroplasticity within the mesoaccumbens dopamine system and its role in tobacco dependence. *Curr Drug Targets CNS Neurol Disord*. 2002;1:413-421.
53. Benowitz N. Nicotine Addiction *NEJM*. 2010;362:2295-2303.
54. Benowitz NL. Clinical pharmacology of nicotine implications for understanding, preventing, and treating tobacco addiction. *Clin Pharmacol Ther*. 2008;83:531-541.
55. Benowitz N. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. *Annu Rev Pharmacol Toxicol*. 2009;49:57-71.
56. Chen LS, Horton A, Bierut L. Pathways to precision medicine in smoking cessation treatments. *Neuroscience Letters*. 2018;669:83-92.

57. Saccone N, Baurley J, Bergen A, et al. The Value of Biosamples in Smoking Cessation Trials: A Review of Genetic, Metabolomic, and Epigenetic Findings. Nicotine & Tobacco. *Nicotine Tob Res*. 2018;20(4):403-413.
58. Scherman A, Tolosa J, McEvoy C. Smoking cessation in pregnancy: A continuing challenge in the United States. *Ther Adv Drug Saf*. 2018; 9(8) 457-474 doi:10.1177/2042098618775366.
59. Stead LF, Koilpillai P, Lancaster T. Additional behavioural support as an adjunct to pharmacotherapy for smoking cessation. *Cochrane Database of Systematic Reviews*. 2015;(10):CD009670. doi:10.1002/14651858.CD009670.pub3.
60. Lindson-Hawley N, Thompson TP, Begh R. Motivational interviewing for smoking cessation. *Cochrane Database Syst Rev*. 2015;(3):CD006936.
61. Centers for Disease Control and Prevention. Frequency Asked Questions about 1-800-QUIT-NOW and National Network of Tobacco Cessation Quitlines. (n.d.). Available at: https://www.cdc.gov/tobacco/quit_smoking/cessation/pdfs/1800quitnow_fa Accessed October 2, 2018.
62. Scott Sheldon L, Lantini R, Jennings E. Text Messaging-Based Interventions for smoking cessation: A systematic review and Meta-Analysis. *JMIR Mhealth Uhealth*. 2016;4(2):e49. Published online May 20, 2016. doi.10.2196/mhealth.5436. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4893152/?report=printable. Accessed September 14, 2018
63. Hartmann-Boyce J, Chepkin SC, Ye W, Bullen C, Lancaster T. Nicotine replacement therapy versus control for smoking cessation. *Cochrane Database of Systematic Reviews*. 2018;(5):CD000146. doi:10.1002/14651858.CD000146.pub5.
64. Nicotrol Inhaler package insert. Pfizer. Last revised December 2008. Available at: https://www.pfizer.com/files/products/uspi_nicotrol_inhaler.pdf. Accessed October 11, 2018.
65. Varenicline Package insert. Pfizer. Last revised June 2018. Available at: http://labeling.pfizer.com/showlabeling.aspx?id=557. Accessed October 11, 2018.
66. Nicotrol Nasal Spray package insert. *Pfizer*. Last revised January 2010. Available at: https://www.pfizer.com/files/products/uspi_nicotrol.pdf.

Accessed October 11, 2018.
67. Nicorette Lozenge labeling information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022360Orig1s Accessed October 11, 2018.
68. Bupropion package insert. Last revised May 2017. GlaxoSmithKline. Available at: https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/PI-MG.PDF. Accessed October 11, 2018.
69. Nicoderm CQ Nicotine patch extended release package insert. Last revised May 2016. GlaxoSmithKline. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=93b2d1b9-83c1-40b5-b6af-90c38c8d6cef. Accessed October 11, 2018.
70. Nicorette Gum labeling information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022360Orig1s Accessed October 11, 2018.
71. Prochaska J, Benowitz N. The Past, Present, and Future of Nicotine Addiction Therapy. *Annu Rev Med*. 2016;67:467-468.
72. Hsia S, Myers M, Chen T Combinations nicotine replacement therapy: strategies for initiation and tapering. *Preventative Medicine*. 2017;97:45-49.
73. Shiffman S, Sembower M, Rohay J, et al. Assigning dose of nicotine gum by time to first cigarette. *Nicotine & Tobacco Research*. 2013; 15(2):407-412.
74. Prochaska J. Nicotine Replacement Therapy as a Maintenance Treatment. *JAMA*. 2015;314(7): 718-719.
75. Hartmann-Boyce J, McRobbie H, Bullen C, Begh R, Stead LF, Hajek P. Electronic cigarettes for smoking cessation. *Cochrane Database of Systematic Reviews*. 2016;(9):CD010216. doi:10.1002/14651858.CD010216.pub3.
76. Singh T, Arrazola RA, Corey CG, et al. Tobacco use among middle and high school students—United States, 2011-2015. *MMWR Morb Mortal Wkly Rep*. 2016;65:361-367.
77. The Facts on the FDA's New Tobacco Rule. Available at: https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm506676.htm. Accessed October 1, 2018.
78. FDA News Release FDA launches new, comprehensive campaign to warn kids about the dangers of e-cigarette sue as a part of agency's Youth

Tobacco Prevention Plan, amid evidence of sharply risking use among kids. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm62 Accessed October 19, 2018.

79. Hess IM, Lachireddy K, Capon A. A systematic review of the health risks from passive exposure to electronic cigarette vapor. *Public Health Res Pract*. 2016;26(2):e2621617. doi:10.17061/phrp2621617.
80. Glasser A, Collins L, Pearson J. Overview of electronic delivery systems: a systematic review. *Am J Prev Med*. 2017;52(2):e33-e66.
81. Hughes JR, Stead LF. Antidepressants for smoking cessation. *Cochrane Database Syst Rev*. 2014;(1):CD000031.
82. Benowitz N, Pipe A, West R, et al. Cardiovascular safety of varenicline, bupropion, and nicotine patch in smokers a randomized clinical trial. *JAMA Intern Med*. 2018;178(5):622-631.
83. FDA Drug Safety Communication: FDA revises description of mental health side effects of the stop-smoking medicines Chantix (varenicline) and Zyban (bupropion) to reflect clinical trial findings. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm532221.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery. Accessed September 13, 2018.
84. Gomez-Coronado N, Walker A, Berk M, et al. Current and emerging pharmacotherapies for cessation of tobacco smoking. *Pharmacotherapy*. 2018;38(2):235-258.
85. Cahill K, Lindson-Hawley N, Thomas KH, Fanshawe TR, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database of Systematic Reviews*. 2016;(5):CD006103. doi:10.1002/14651858.CD006103.pub7.
86. Anthenelli R, Benowitz N, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomized, placebo-controlled clinical trial. *The Lancet.* 2016;387:2507-2520.
87. Rennard S, Hughes J, Cinciripini P, et al. A randomized placebo-controlled trial of varenicline for smoking cessation allowing flexible quite dates. *Nicotine Tob Res*. 2012;14(3):343-350.
88. FDA Drug Safety Communication: FDA revises description of mental health side effects of the stop-smoking medicines Chantix (varenicline) and Zyban (bupropion) to reflect clinical trial findings. Available at:

https://www.fda.gov/Drugs/DrugSafety/ucm532221.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery. Accessed September 13, 2018.

89. FDA Drug Safety Communication: Safety review update of Chantix (varenicline) and risk of cardiovascular adverse events. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm330367.htm #professionals findings https://www.fda.gov/Drugs/DrugSafety/ucm532221.htm. Accessed August 17, 2018.
90. Chang P, Chiang C, Ho W, et al. Combination therapy of varenicline with nicotine replacement therapy is better than varenicline alone: a systematic review and meta-analysis of randomized controlled trials. *BMC Public Health*. 2015;15:689. doi:10.1186/s12889-015-2055-0.
91. Stead LF, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev*. 2012;(11):CD000146.
92. Cinciripini P, Minnix J, Green Ch, et al.; An RCT with the combination of varenicline and bupropion for smoking cessation: clinical implications for front line use. *Addiction*. 2018;113:1673-1682.
93. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database of Systematic Reviews*. 2013;(5):CD009329. doi:10.1002/14651858.CD009329.pub2.
94. Tran N, Barraj L, Bi X, et al. Trends and patterns of caffeine consumption among US teenagers and young adults, NHANES 2003-2012. *Food Chem Toxicol*. 2016;94:227-242.
95. Doepker C, Lieberman H, Smith AP, et al. Caffeine: Friend or Foe? *Annu Rev Food Sci Tech-nol*. 2016;7:117-137.
96. Food and Drug Administration, US Department of Health and Human Services. Multiple Purpose GRAS Food Substances; Caffeine. 21 CFR Sec.182.1180. Available at: http://www.gpo.gov/fdsys/pkg/CFR-2011-title21-vol3/pdf/CFR-2011-title21-vol3-sec182-1180.pdf. 2011. Accessed September 18, 2018.
97. Wikoff D, Welsh B, Henderson R, Brorby G, et al. Systematic review of the potential adverse effects of caffeine consumption in health adults, pregnant women, adolescents, and children. *Food and Chemical Toxicology*. 2017;109:585-648.
98. US Food and Drug Caffeine and Kids: FDA Takes a Closer Look. Available at:

https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm350570.htm. Accessed August 31, 2018.

99. Laskowski L, Henesch J, Nelson L, et al. Start me up! Recurrent ventricular tachydysrhythmias following intentional concentrated caffeine ingestion. *Clinical Toxicology*. 2015;53(8):830-833.
100. Juliano LM, Evatt DP, Richards BD, Griffiths RR. Characterization of individuals seeking treatment for caffeine dependence. *Psychol Addict Behav*. 2012;26:948-954.
101. Evatt D, Juliano L, Giffiths R. A brief manualized treatment for problematic caffeine use: a randomized control trial. *J Consult Clin Psych*. 2016;84(2):113-121.
102. Fulgoni V, Keast D, Lieberman H. Trends in intake and sources of caffeine in the diets of US adults: 2001-2010. *Am J Clin Nutr*. 2015;101(5):1081-1087.
103. Branum A, Rossen L, Schoendorf K. Trends in caffeine intake among US children and adolescents. *Pediatrics*. 2014;133(3):386-393.
104. NIH National Center for Complementary and Integrative Health: Energy Drinks. Available at: https://nccih.nih.gov/health/energy-drinks. Accessed September 23, 2018.
105. 5 hour energy website: http://5hourenergy.com/facts/ingredients/. Accessed September 23, 2018.
106. Mattson ME. Update on Emergency Department Visits Involving Energy Drinks: A Continuing Public Health Concern. January 10, 2013. In: The CBHSQ Report. Rockville (MD): Substance Abuse and Mental Health Services Administration (US). Available at: https://www.ncbi.nlm.nih.gov/books/NBK384664/. Accessed October 2, 20018.
107. Leal W, Jackson D. Energy drinks and escalation in drug use severity: An emergent hazard to adolescent health. *Preventive Medicine*. 2018;111:391-396.
108. Benowitz N. Clinical pharmacology of caffeine. *Ann Rev Med*. 1990;41:277-288.
109. Kuczkowski KM. Caffeine in pregnancy. *Arch Gynecol Obstet*. 2009;280:695-698.
110. Weng X, Odouli R, Li DK. Maternal caffeine consumption during pregnancy and the risk of miscarriage: a prospective cohort study. *Am J Obstet Gynecol*. 2008;198:279.e1-279.e8.

111. Wikoff D, Welsh B, Henderson R, et al. Systematic review of the potential adverse effects of caffeine consumption in health adults, pregnant women, adolescents, and children. *Food and Chemical Toxicology*. 2017;109:585-648.

84

Schizophrenia

M. Lynn Crismon, Tawny Smith, and Peter F. Buckley

KEY CONCEPTS

1. Although multiple neurotransmitter dysfunctions are involved in schizophrenia, the etiology is more likely mediated by multiple subcellular processes that are influenced by different genetic polymorphisms.
2. The clinical presentation of schizophrenia is characterized by positive symptoms, negative symptoms, and impairment in cognitive functioning.
3. Comprehensive care for individuals criteria with schizophrenia must occur in the context of a multidisciplinary mental healthcare environment that offers comprehensive psychosocial services in addition to psychotropic medication management.
4. A thorough patient evaluation (eg, history, mental status examination, physical examination, psychiatric diagnostic interview, and laboratory analysis) should occur to establish a diagnosis of schizophrenia and to identify potential co-occurring disorders, including substance abuse and general medical disorders.
5. Given that it is challenging to differentiate among antipsychotics based on efficacy, side effect profiles become important in choosing an antipsychotic for an individual patient.
6. Pharmacotherapy guidelines should emphasize antipsychotic monotherapies that optimize efficacy-to-side effect ratios before progressing to medications with greater side effect risks. Combination regimens should only be used in the most treatment-resistant patients.
7. Adequate time on a given medication at a therapeutic dose is the most important variable in predicting medication response.
8. Long-term maintenance antipsychotic treatment is necessary for the vast majority of patients with schizophrenia in order to prevent relapse.

9. Thorough patient and family psychoeducation should be implemented, utilizing motivational interviewing methods that focus on patient-driven outcomes in an effort to allow patients to achieve life goals.
10. Pharmacotherapy decisions should be guided by systematic monitoring of patient symptoms, preferably with the use of brief symptom rating scales and systematic assessment of potential adverse effects.

Preclass Engaged Learning Activity

Watch the approximately nine minute video on You Tube, "Four Patients with Schizophrenia." https://tinyurl.com/y5rv6qf7

For each of the patients, list the symptoms that are associated with schizophrenia. Use Table 84-10 as a reference, and for each patient list those symptoms that are present on the Brief Positive and Negative Symptom Scales. The intent of this learning activity is to help you identify symptoms associated with schizophrenia and identify symptoms that can be used to monitor response to pharmacotherapy.

INTRODUCTION

Schizophrenia is one of the most complex and challenging psychiatric disorders as it represents a heterogeneous syndrome of disorganized and bizarre thoughts, delusions, hallucinations, inappropriate affect, and impaired psychosocial functioning. From the time that Kraepelin first described dementia praecox in 1896 until publication of the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) in 2013, the description of this illness has continuously evolved.[1] Scientific advances that increase our knowledge of central nervous system (CNS) physiology, pathophysiology, and genetics will likely improve our understanding of schizophrenia in the future.

EPIDEMIOLOGY

The lifetime prevalence of schizophrenia ranges from 0.28% to 0.6%[2] with the worldwide prevalence being similar among most cultures. Schizophrenia most commonly has its onset in late adolescence or early adulthood and rarely occurs

before adolescence or after the age of 40 years. Although the prevalence of schizophrenia is equal in males and females, the onset of illness tends to be earlier in males as they tend to have their first episode during their early 20s, whereas with females it is usually during their late 20s.[1]

ETIOLOGY

Although the etiology of schizophrenia is unknown, research has demonstrated various abnormalities in brain structure and function.[3] However, these changes are not consistent among all individuals with schizophrenia. Therefore, the cause of schizophrenia is likely multifactorial, that is, multiple pathophysiologic abnormalities can play a role in producing the similar but varying clinical phenotypes we refer to as schizophrenia.

A neurodevelopmental model has been evoked as one possible explanation for the etiology of schizophrenia,[3,4] which comes from studies of brains from people with a diagnosis of schizophrenia. This “schizophrenic lesion” can result in abnormalities in cell shape, position, symmetry, connectivity, and functionality to the development of abnormal brain circuits.[4] The changes seen as part of this research are consistent with a cell migration abnormality during the second trimester of pregnancy, and some studies associate upper respiratory infections during the second trimester of pregnancy with a higher incidence of schizophrenia.[4] Other studies associate low birth weight (LBW; less than 2.5 kg [5.5 lb]), obstetric complications, or neonatal hypoxia with schizophrenia.[4] More recently, theories of maternal stress have been developed which may be related to aberrations in circulating glucocorticoids in utero as a risk factor for schizophrenia.[4] Although imaging studies show decreased cortical thickness and increased ventricular size in the brains of many patients with schizophrenia, this occurs in the absence of widespread changes in the glial cells (or gliosis).[4] One hypothesis for these changes is that obstetric complications and hypoxia, in combination with a genetic predisposition, could activate a glutamatergic cascade resulting in increased neuronal pruning. Genes controlling *N*-methyl-D-aspartate (NMDA) receptor activity are hypothesized to be part of this process, as dendrite pruning, which is part of normal neurodevelopmental process, is higher in individuals with schizophrenia. As synaptic pruning predominantly involves glutamatergic dendrites, hypoxia or other prenatal insults can result in a decreased number of basal neurons overall, and glutamatergic activation can exaggerate the pruning process.[3,4] Furthermore, a relationship has been

documented between autoimmune encephalitis and psychosis, which is based upon glutamate receptor autoantibodies. This is important as studies have shown an increased susceptibility to immune/autoimmune disorders in schizophrenia, as well as abnormalities of autoantibodies and cytokine functioning.[5] Although this etiology is felt to be uncommon, it serves as a model for an emerging immune hypothesis of schizophrenia, which also emphasizes integration of mental and physical well-being.[5]

Numerous studies have shown neuropsychological abnormalities and impairment in reaching normal motor milestones and abnormal movements in young children who later develop schizophrenia.[4] These abnormalities in brain function occur long before the onset of psychotic symptomatology and provide empirical evidence for schizophrenia being a neurodevelopmental disorder.[2] Furthermore, recent brain imaging studies show deteriorative brain changes in patients with frequent relapses,[4,6] with these changes being most pronounced among adolescents with early onset schizophrenia.[4,7] Therefore, continued pathophysiological changes, secondary to the original neurodevelopmental insult, may lead to the first psychotic episode, and brain morphology resembling neurodegeneration.[3,4,7]

Although the risk of developing schizophrenia is estimated as 0.28% to 0.6% worldwide, the risk is approximately 3% if a second-degree relative has the illness and 10% if there is a first-degree relative.[4] If both parents have schizophrenia, the risk of producing an offspring with schizophrenia increases to approximately 40%. Dizygotic twins report a 12% to 14% risk if one twin has the illness, with this increasing to 48% for monozygotic twins.[4] Furthermore, in siblings the onset of illness tends to occur at the same age in each, and adoption studies indicate that environmental changes during the child's developmental stages do not alter their genetic risk, both of which give less credence to the possibility of an environmental precipitant.

1 Numerous approaches have been utilized to study the genetics of neurodevelopment and schizophrenia risk but one single genetic risk factor has not been found.[7] Genome-wide association studies (GWAS) have identified over 120 genetic small-effect loci that account for a small percent of the risk.[3,7] Of major interest is the finding that polymorphisms of the complement component 4 (*C4*) genes on chromosome 6 may be implicated in the abnormal dendritic pruning seen in individuals with schizophrenia.[8] Additionally, increased schizophrenia risk has been linked to about a dozen recurrent copy number variants (CNV) that have high penetrance; however, cumulatively they likely

account for no more than 1% to 2% of all cases.[3,7] Additionally, genetic risk has also been attributed to the synaptic protein neurexin 1 (NRXN1) as well as neuregulin 1 (NRG1) which in particular may increase the risk of developing the first psychotic episode for those who are already at high risk.[3] Furthermore, microRNAs (mRNA), which are small noncoding RNAs critical to neurodevelopment as well as to regulation of adult neuronal processes, have also been linked to schizophrenia risk and are being actively explored.[3]

It is important to appreciate that there is an overlap—both clinically and biologically—between schizophrenia and mood disorders with single nucleotide polymorphisms (SNPs) from chromosomes 3, 10, and 12 being common across schizophrenia, bipolar disorder, and major depression. Two of these SNPs were at loci related to the pathophysiology of calcium-channels.[3,7] Additionally some of the CMVs identified for schizophrenia risk have also been associated with autism spectrum disorder, intellectual disability, and attention-deficit hyperactivity disorder.[7] Thus, several genetic and biological studies now suggest a greater shared genetic—and neurobiological—basis across psychiatric disorders so that the idea of schizophrenia being a distinct “condition” is ever-increasingly being challenged.

PATHOPHYSIOLOGY

Most recent studies have found consistent decreases in gray matter in multiple brain areas, including the frontal lobes, cingulate gyri, and medial temporal regions among others. In fact, a recent longitudinal study of high-risk youth showed a substantially greater decrease in grey matter in high-risk youth who progressed to psychosis than in high-risk youth who did not progress to psychosis and in normal controls.[9] Additionally, increases in ventricular size, as well as decreased white matter in the corpus callosum, have been observed.[9] It is important to note that the changes in hippocampal volume may correspond with impairment in neuropsychological testin g.[4,6] It is felt then, that rather than a decrease in the number of neurons in affected brain areas, a decrease in axonal and dendritic communications between cells can result in a loss of connectivity that can be important with respect to neuronal adaptivity and CNS homeostasis,[4,6] which are likely consistent with the evidence for abnormal neuronal pruning.[2]

1 Historically, schizophrenia has been attributed to dopamine (DA)-receptor defects; however, this is an over simplification. While presynaptic changes in

dopaminergic neurons occur and are consistent with the neurodevelopmental model that has been proposed,[3,6] numerous positron emission tomography (PET) studies have shown brain abnormalities including increased glucose metabolism in the caudate nucleus and decreased blood flow and glucose metabolism in the frontal lobe and left temporal lobe.[4] These findings may indicate dopaminergic hyperactivity in the head of the caudate nucleus and dopaminergic hypofunction in the frontotemporal regions, which may be confirmed by alterations in D_2 receptors densities.[4,6] However, increases in presynaptic DA synthesis and release into the striatum may only translate into a small increase in $D_{2/3}$ receptor availability.[10]

Additionally, PET studies assessing dopamine-1 (D_1) function suggest that subpopulations of patients with schizophrenia may have decreased densities of D_1 receptors in the caudate nucleus and the prefrontal cortex, in addition to the D_2 receptors. Clinically this may lead to hypofrontality within the prefrontal cortex, which can be associated with a lack of volition and cognitive dysfunction, core features of schizophrenia. It is unknown whether these changes represent a primary event or secondary processes related to other pathophysiologic abnormalities in schizophrenia. Because of the heterogeneity in the clinical presentation of schizophrenia, it has been suggested that the DA hypothesis may be more applicable to “neuroleptic-responsive psychosis,” with multiple different etiologies possibly being responsible for causing schizophrenia.[4,6] While attempts have been made to develop relationships between these abnormal findings and behavioral symptoms present in patients with schizophrenia, it is felt that the positive symptoms seen in schizophrenia are possibly more closely associated with DA-receptor hyperactivity in the mesocaudate, whereas negative symptoms and cognitive impairment are most closely related to DA-receptor hypofunction in the prefrontal cortex. As the presynaptic D_1 receptors in the prefrontal cortex are thought to be involved in modulating glutamatergic activity, this hypofunctionality can impact working memory in individuals with schizophrenia.[4,6]

One can examine different neurotransmitter alterations in the context of different schizophrenia phases.[11] In the Predrome Phase, clinically high-risk individuals are thought to exhibit glutamategic synaptic dysfunction that results in a glutamate signaling defect. Partial compensation by gamma-aminobutyric acid (GABA) downregulation and synaptic proliferation are associated with the Prodromal Phase. This deficit in GABA is felt to result in less inhibition of excitatory circuits, producing dopaminergic dysfunction, the onset of psychosis,

and the Syndrome Phase, with the degree of dopamine dysfunction associated with more severe disease.[6] The last phase, the Chronic Phase, is associated with the loss of grey matter compounding the synaptic deficits.[11]

As the glutamatergic system is one of the most widespread excitatory neurotransmitter systems in the brain, hypo- or hyperactive alterations in function can result in toxic neuronal reactions.[11] Dopaminergic innervation from glutamate in the ventral striatum decreases the limbic system's inhibitory activity (perhaps through GABA interneurons) and thus increases arousal. The corticostriatal glutamate pathways have the opposite effect, whereas inhibiting dopaminergic function from the ventral striatum allows increased inhibitory activity in the limbic system. Due to the interaction between glutamatergic and dopaminergic tracts, as well as through GABA interneurons, glutamatergic deficiency produces symptoms similar to those of dopaminergic hyperactivity and possibly those seen in schizophrenia. Therefore, alterations in the interactions between dopamine and glutamate due to NMDA hypofunction have been associated with the latent clinical expression of psychotic symptoms in late adolescence or early adulthood.

Schizophrenia is a complex disorder, and multiple etiologies likely exist. Based on current knowledge, it is naïve to think that any one proposed etiology or one dysfunction in neurotransmission can adequately explain the genesis of this complex disease. Moreover, ongoing research into distinct biomarkers for schizophrenia, as well as the promise of stem cell research to disentangle the pathobiology of this enigmatic disorder, will also help identify phenotypes and help to determine the boundaries between psychosis and mood disorders.[3,7,10,12]

CLINICAL PRESENTATION

Schizophrenia is the most common functional psychosis with great variability occurring in its clinical presentation. Despite numerous attempts to portray a stereotype in movies and on television, the stereotypic person with schizophrenia essentially does not exist, and schizophrenia is not a "split personality." It is a chronic disorder of thought and affect with the individual having a significant disturbance in interpersonal relationships and ability to function in society.

2 The first psychotic episode can be sudden in onset with few premorbid symptoms, or more commonly is preceded by withdrawn, suspicious, peculiar behavior, termed schizoid. During acute psychotic episodes, the patient loses touch with reality, and in a sense, the brain creates a false reality to replace it. Acute psychotic symptoms can include hallucinations (especially hearing

voices), delusions (fixed false beliefs), and ideas of influence (beliefs that one's actions are controlled by external influences). Thought processes are disconnected (loose associations), the patient may not be able to carry on logical conversation (alogia), and can have simultaneous contradictory thoughts (ambivalence). The patient's affect can be flat (no emotional expression), or it can be inappropriate and labile. The patient is often withdrawn and inwardly directed (autism). Uncooperativeness, hostility, and verbal or physical aggression can be seen because of the patient's misperception of reality. Self-care skills are impaired, and the patient is frequently dirty and unkempt, and in general has poor hygiene. Sleep and appetite are often disturbed. When the acute psychotic episode remits, the patient typically has residual features, which is an important point in differentiating schizophrenia from other psychotic disorders. Although residual symptoms and their severity vary, patients can have difficulty with anxiety management, suspiciousness, and lack of volition, motivation, insight, and judgment. Therefore, they often have difficulty living independently and because of poor anxiety management and suspiciousness, they are frequently withdrawn socially, and have difficulty forming close relationships with others. In addition, impaired volition and motivation contribute to poor self-care skills and make it difficult for the patient with schizophrenia to maintain employment.

Patients with schizophrenia frequently experience a lack of historicity, or difficulty in learning from their experiences, resulting in them repeatedly making the same mistakes in social conduct and situations requiring judgment. They have difficulty understanding the importance of treatment, including medications, in maintaining their ability to function in society. Therefore, they tend to discontinue medications and other treatments, and this increases the risk of relapse and rehospitalization.

The co-occurrence of substance abuse (predominantly alcohol or polysubstance—alcohol, cannabis, and cocaine) in patients with schizophrenia is very common and is another frequent reason for relapse and hospitalization.[1] This effect can be caused by direct toxic effects of these drugs on the brain,[20] but is also caused by the medication nonadherence that is associated with substance abuse. Some drugs—most notably heavy cannabis use during adolescence—have been associated with a higher prevalence of schizophrenia, as evidence from multiple sources suggests that cannabis use raises the risk of schizophrenia by about four to six times.[13]

Although the course of schizophrenia is variable, the long-term prognosis for many patients is poor. It is marked by intermittent acute psychotic episodes and impaired psychosocial functioning between acute episodes, with most of the

deterioration in psychosocial functioning occurring within 5 years after the first psychotic episode.[14] By late life, the patient can appear “burned out,” that is, they cease to have acute psychotic episodes, but residual symptoms persist. In a subpopulation of patients, probably 5% to 15%, psychotic symptoms are nearly continuous, and response to antipsychotics is poor.[14]

Schizophrenia is a chronic disorder, and the patient’s history must be carefully assessed for dysfunction that has persisted for longer than six months. After their first episode, patients with schizophrenia rarely have a level of adaptive functioning as high as before the onset of the disorder. *The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5)* should be consulted for the complete criteria for a diagnosis of schizophrenia.[1] The *DSM-5* also asks the clinician to specify the episode severity for schizophrenia after having the diagnosis for at least 1 year and whether the patient is presenting with catatonia.[1]

The *DSM-5* classifies the symptoms of schizophrenia into two categories: positive and negative; however, greater emphasis is now being placed on a third symptom category, cognitive dysfunction.[1,14] The areas of cognition found to be abnormal in schizophrenia include attention, working memory, and executive function. Positive symptoms have traditionally attracted the most attention and are the ones most improved by antipsychotics. However, negative symptoms and impairment in cognition are more closely associated with poor psychosocial function.

CLINICAL PRESENTATION

Schizophrenia

Positive Symptoms

- Suspiciousness
- Unusual thought content (delusions)
- Hallucinations
- Conceptual disorganization

Negative Symptoms

- Affective flattening
- Alogia

- Anhedonia
- Avolition

Cognitive Symptoms

- Impaired attention
- Impaired working memory
- Impaired executive function

Along with these characteristic features of schizophrenia, many patients also have comorbid psychiatric and general medical disorders.[2,14] These include depression, anxiety disorders, substance abuse, and general medical disorders such as respiratory disorders, cardiovascular disorders, and metabolic disturbances. These comorbidities substantially complicate the clinical presentation and course of schizophrenia.

It has been suggested that symptom complexes can correlate with prognosis, cognitive functioning, structural abnormalities in the brain, and response to antipsychotic drugs. Negative symptoms and cognitive impairment can be more closely associated with prefrontal lobe dysfunction and positive symptoms with temporolimbic abnormalities. As many patients demonstrate both positive and negative symptoms, it is those with negative symptoms that frequently have more antecedent cognitive dysfunction, poor premorbid adjustment, low level of educational achievement, and a poorer overall prognosis.[1,14]

TREATMENT

Desired Outcome

3 Pharmacotherapy is a mainstay of treatment in schizophrenia, as it is impossible to effectively implement psychosocial rehabilitation programs without antipsychotic treatment in the majority of patients.[20] A pharmacotherapeutic treatment plan should be developed that delineates drug-related aspects of therapy. Most deterioration in psychosocial functioning occurs during the first 5 years after the initial psychotic episode, and treatment should be particularly assertive during this period.[14] The individualized treatment plan created for each patient should have explicit end points defined, including

realistic goals for the target symptoms most likely to respond, and the relative time course for response.[23] Other desired outcomes include avoiding unwanted side effects (SEs), integrating the patient back into the community, increasing adaptive functioning to the extent possible, and preventing relapse.

Nonpharmacologic Therapy

Psychosocial rehabilitation programs oriented toward improving patients' adaptive functioning are the mainstay of nondrug treatment for schizophrenia. These programs can include case management, psychoeducation, targeted cognitive therapy, basic living skills, social skills training, basic education, work programs, supported housing, and financial support. In particular, programs aimed at supportive employment and housing are effective and considered "best practices." Programs that involve families in the care and life of the patient have been shown to decrease rehospitalization and improve functioning in the community. For particularly low-functioning patients, assertive intervention programs, referred to as *active community treatment* (ACT), are effective in improving patients' functional outcomes. ACT teams are available on a 24-hour basis and work in the patient's home and place of employment to provide comprehensive treatment, including medication, crisis intervention, daily living skills, and supported employment and housing.[16] Medication treatment cannot be successful without proper attention to these other aspects of care, as people with schizophrenia need comprehensive care, with coordination of services across psychiatric, addiction, medical, social, and rehabilitative services. In the United States, this level of coordination is often insufficient, and patients become at risk to "fall through the cracks." Other countries have implemented more robust primary and secondary preventative approaches, highlighting early identification, ease of access to care, and staging of disease management.[15] The National Institute of Mental Health (NIMH) Recovery After Initial Schizophrenia Episode (RAISE) study found that four core interventions ("personalized medication management, family psychoeducation, resilience-focused individual therapy, and supported employment and education") significantly improved the quality of life over a 24-month period for individuals with early schizophrenia as compared to usual community care.[17]

Emphasis is growing on the role that the patient plays in a recovery-based system of care, where the person's lifetime aspirations and goals become the center of care, rather than symptom reduction being the primary focus. This recovery-based approach recognizes the strengths and resilience of people with

schizophrenia, as well as acknowledging how people with schizophrenia can be a support to others who are coping with the illness.[17] It is important to frame clinical decision making in the context of a mutual process involving patient and clinician—rather than a unilateral "here's a prescription … please take these tablets" approach. It is increasingly recognized that psychosocial/cognitive behavioral strategies can help some patients, and computer-based therapies and social media–related approaches are emerging that may be helpful. Cognitive remediation—which uses computer-based cognitive retraining techniques—has been shown to be of benefit.[18] Social media and mobile technology strategies may be harnessed to improve communications, medication adherence, and potentially detect early warning signs of impending relapse in patients with schizophrenia. A list of psychotherapeutic approaches to the treatment of schizophrenia is given in **Table 84-1**.

TABLE 84-1 Psychotherapeutic Approaches to the Treatment of Schizophrenia

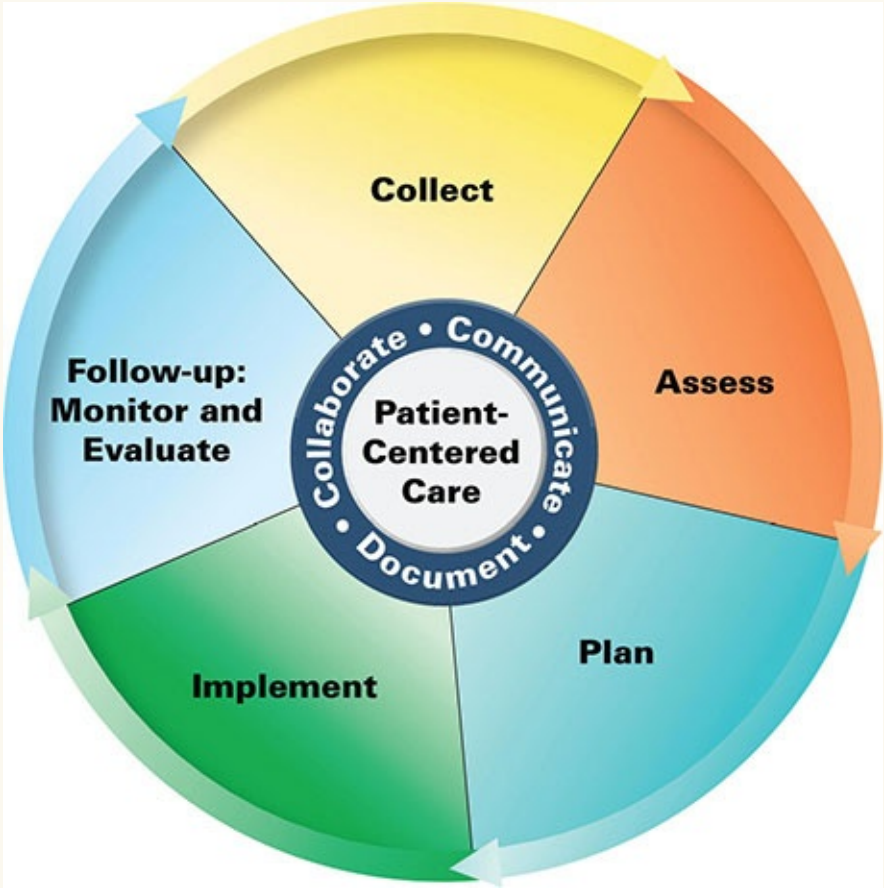
Individual	Group	Cognitive Behavioral
Supportive/counseling	Interactive/ social	Cognitive behavioral therapy
Personal therapy	Family education	Adherence therapy
Social skills & resiliency therapies		
Supported employment and housing		
Rehabilitation therapies		

Data from References 16-18

Pharmacologic Therapy

4 The importance of an initial accurate diagnostic assessment cannot be overemphasized. A thorough mental status examination (MSE), psychiatric diagnostic interview, physical, and neurologic examination, complete family and social history, and laboratory workup must be performed to confirm the diagnosis and exclude general medical or substance-induced causes of psychosis. Laboratory tests, biologic markers, and commonly available brain imaging techniques do not assist in the diagnosis of schizophrenia or selection of medication. A pretreatment patient workup not only is important in excluding other pathology, but also serves as a baseline for monitoring potential medication-related side effects, and should include vital signs, complete blood count, electrolytes, hepatic function, renal function, electrocardiogram (ECG), fasting serum glucose, hemoglobin A1c, serum lipids, thyroid function, and

urine drug screen.



Patient Care Process for Schizophrenia

Collect

- Patient characteristics (eg, age, race, sex, gender identity, pregnant)
- Patient history (past mental and medical, medication adherence, family, social—diet, alcohol and substance use, tobacco use)
- Mental status exam
- Medications (current and past)
- Objective data
- Brief Positive and Negative Symptom Scales (See Table 84-10)
- Blood pressure (BP), heart rate (HR), height, weight, and body mass index (BMI) (See Table 84-11)

- Labs: Hemoglobin A1c (HgA1c), Lipids, other tests if indicated (See Table 84-11)

Assess

- Patient's concerns and attitudes toward treatment, medication adherence (See Table 84-5)
- Symptom severity and the extent that treatment goals have been met
- Do any co-occurring disorders (mental, substance use disorder, medical) need to be addressed?
- Are patient's psychosocial needs being met? (See Table 84-2)
- Medication side effects (See Tables 84-7 and 84-11)
- Appropriateness and effectiveness of current psychotropic regimen

Plan*

- Actively engage patient in care plan
- Drug therapy regimen, specify the continuation and discontinuation of existing therapies (See Figure 84-1 and Tables 84-3, 84-4, and 84-6)
- Monitoring parameters including efficacy and time frame (See Tables 84-10 and 84-11)
- Patient education (eg, medication, life style management)
- Referrals to other providers as appropriate (eg, physician, psychologist, social worker)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Determine symptom attainment (See Table 84-10)
- Presence of adverse effects (See Table 84-11)
- Need for psychosocial interventions
- Patient adherence to treatment plan using multiple sources of information

*Collaborate with patient, caregivers, and other healthcare professionals.

5 Both first-generation antipsychotics (FGAs, also known as traditional) and second-generation antipsychotics (SGAs, also known as atypical) are used in the treatment of schizophrenia,[19,20] with no absolute criterion distinguishing between the two. As compared with the FGAs, the SGAs appear to have the ability to produce antipsychotic response with few or no acutely occurring extrapyramidal side effects (EPS). Other attributes that have been ascribed to some SGAs include enhanced efficacy (particularly for negative symptoms and cognition), near absence of propensity to cause tardive dyskinesia, and lack of effect on serum prolactin.[21] To date, only clozapine truly fulfills all of these criteria, with other SGAs meeting some of them.[21] Therefore, the major factor used in practice when distinguishing among antipsychotics is adverse effects.[19,21,22] While the SGAs have a lower risk of neurologic side effects, particularly effects on movement, this is offset by increased risk of metabolic side effects with some SGAs, including weight gain, hyperlipidemias, and diabetes mellitus. Side effect profiles differ among antipsychotics, and this information in combination with individual patient characteristics should be used in deciding which drug to use in an individual patient.

Results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, primarily in patients with chronic schizophrenia, indicate that olanzapine, compared with quetiapine, risperidone, ziprasidone, and the FGA perphenazine, had modest but not statistically significant superiority in maintenance therapy with treatment persistence as the primary clinical outcome.[23] However, increased metabolic adverse effects occurred with olanzapine, and additional studies of patients early on in their illness highlight the high rate of cardiometabolic disturbances with olanzapine and the need to tailor treatment.[24]

Additionally, previous patient or family history of response to an antipsychotic is helpful in the selection of an agent, and the last consideration in antipsychotic selection is cost. Acquisition cost varies significantly among different antipsychotics and dosage forms, and should be considered in context of any potential advantages of an agent. **Table 84-2** lists antipsychotics and their usual dosage ranges.

TABLE 84-2 Available Antipsychotics and Dosage Ranges

Generic Name	Trade Name	Starting Dose (mg/day)	Usual Dosage Range (mg/day)	Comments
First-Generation Antipsychotics				
Chlorpromazine	Thorazine	50-150	300-1,000	Most weight gain among FGAs
Fluphenazine	Prolixin	5	5-20	
Haloperidol	Haldol	2-5	2-20	Higher dropout rate in first episode
Loxapine	Loxitane	20	50-150	
Loxapine inhaled	Adasuve	10	10	Maximum 10 mg per 24 hours Approved REMS program only
Perphenazine	Trilafon	4-24	16-64	
Thioridazine	Mellaril	50-150	100-800	Significant QTc prolongation
Thiothixene	Navane	4-10	4-50	
Trifluoperazine	Stelazine	2-5	5-40	
Second-Generation Antipsychotics				
Aripiprazole	Abilify	5-15	15-30	
Asenapine	Saphris	5	10-20	Sublingual only, no food or drink for 10 minutes after administration of the dose
Brexpiprazole	Rexulti	1	2-4	
Cariprazine	Vraylar	1.5	1.5-6	Due to long half-life, steady state is not reached for several weeks
Clozapine	Clozaril	25	100-800	Check plasma level before exceeding 600 mg
Iloperidone	Fanapt	1-2	6-24	Care with dosing in CYP2D6 slow metabolizers
Lurasidone	Latuda	20-40	40-120	Take with food; ≥350 calories (1,460 Joules)
Olanzapine	Zyprexa	5-10	10-20	Avoid in first episode because of weight gain
Paliperidone	Invega	3-6	3-12	Bioavailability increased when administered with food
Quetiapine	Seroquel	50	300-800	
Quetiapine XR	Seroquel XR	300 mg	400-800	
Risperidone	Risperdal	1-2	2-8	
Ziprasidone	Geodon	40	80-160	Take with food, ≥500 calories (2,100 Joules)

Note: In first-episode patients, starting dose and target dose should generally be 50% of the usual dose range. See Long-Acting Injectable Antipsychotics in text for dosing of these agents.

REMS: Risk Evaluation and Mitigation Strategy. XR: extended release.

Data from Reference 21, 30, 50-52, 61, 69, and 114.

Published Guidelines and an Algorithm Example

6 **Figure 84-1** outlines a suggested pharmacotherapeutic algorithm for

schizophrenia, based on information from three published guidelines, the Psychopharmacology Algorithm Project at the Harvard Medical School Department of Psychiatry South Shore Program,[19] the Canadian Schizophrenia Guidelines,[22] and the guidelines from the World Federation of Biological Psychiatry.[20,21]

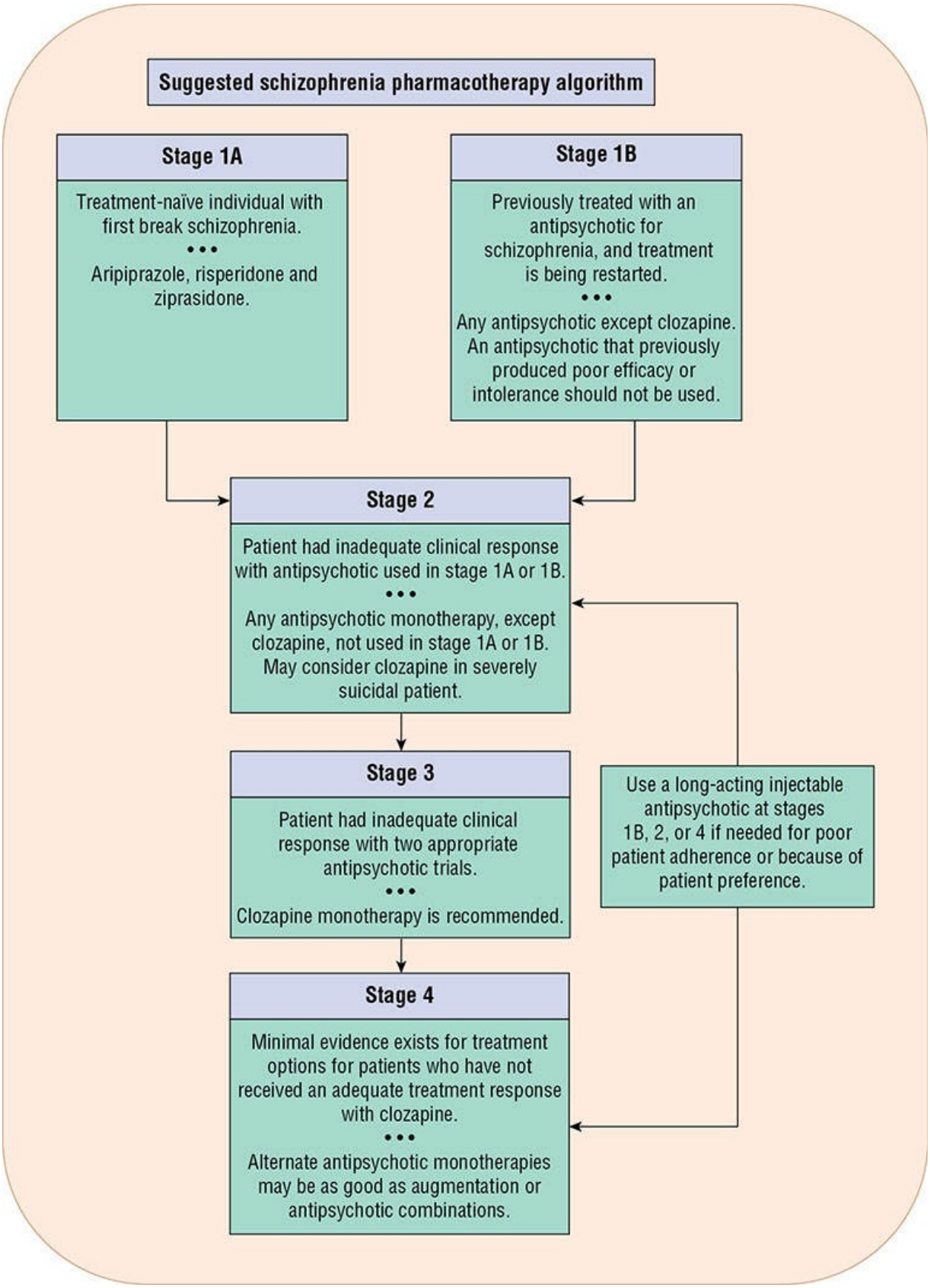

Suggested schizophrenia pharmacotherapy algorithm
Stage 1A
Treatment-naïve individual with first break schizophrenia.
• • •
Aripiprazole, risperidone and ziprasidone.
Stage 1B
Previously treated with an antipsychotic for schizophrenia, and treatment is being restarted.
• • •
Any antipsychotic except clozapine. An antipsychotic that previously produced poor efficacy or intolerance should not be used.
Stage 2
Patient had inadequate clinical response with antipsychotic used in stage 1A or 1B.
• • •
Any antipsychotic monotherapy, except clozapine, not used in stage 1A or 1B. May consider clozapine in severely suicidal patient.
Stage 3
Patient had inadequate clinical response with two appropriate antipsychotic trials.
• • •
Clozapine monotherapy is recommended.
Use a long-acting injectable antipsychotic at stages 1B, 2, or 4 if needed for poor patient adherence or because of patient preference.
Stage 4
Minimal evidence exists for treatment options for patients who have not received an adequate treatment response with clozapine.
• • •
Alternate antipsychotic monotherapies may be as good as augmentation or antipsychotic combinations.

FIGURE 84-1 Suggested pharmacotherapy algorithm for treatment of schizophrenia. Schizophrenia should be treated in the context of an interprofessional model that addresses the psychosocial needs of the patient, necessary psychiatric pharmacotherapy, psychiatric co-occurring mental disorders, treatment adherence, and any medical problems the patient may have. See the text for a description of the algorithm stages. .
Data from References 26–30.

Stage 1A of the treatment algorithm applies to those patients experiencing their first acute episode of schizophrenia. Studies suggest that the use of SGAs during the first acute episode results in greater treatment retention and are more effective in preventing a second psychotic episode compared to FGAs. In addition, SGAs carry a reduced risk of EPS.[21] Among the SGAs, aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone have evidence of efficacy in first-episode patients, with lurasidone showing efficacy in adolescents with schizophrenia, but most were not treatment naive.[19,25] Despite its efficacy, olanzapine is not recommended in first episode because of weight gain and metabolic side effects.[19,21]

Since quetiapine is associated with less time to rehospitalization than other SGAs and causes greater weight gain, some guidelines do not recommend it in stage 1A.[19] This leaves aripiprazole, risperidone, and ziprasidone as the evidence-based options in first-episode patients (stage 1A).[19] Of these, aripiprazole and ziprasidone produce the least weight gain. However, the level of evidence is not sufficiently high to recommend these as the only preferred agents in first episode.[20,22] Because first-episode patients demonstrate greater sensitivity to adverse effects, antipsychotic dosing should be initiated at the lower end of the dose range.[17,19,22]

It is important to note that in first-episode patients, long-acting risperidone injectable was more effective than oral risperidone in preventing relapse over a one-year period.[26] In fact, the relapse rate was six times higher in the oral risperidone group than with the long-acting injectable; therefore, long-acting risperidone can be considered a treatment option for first-episode patients. If this medication is used, patients should first be stabilized on oral risperidone. Most important, it is critical that enriched psychosocial programs be implemented along with appropriate pharmacotherapy.

Stage 1B addresses pharmacotherapy of a patient who was previously treated with an antipsychotic, and treatment is being restarted because the patient stopped taking the medication. If during the initial antipsychotic trial, the patient

experienced a robust improvement in symptoms, good tolerability, and the patient is positive about taking this antipsychotic again, then that medication can be restarted. If a different medication is needed, one from stage 2 should be used. Stage 2 addresses pharmacotherapy in a patient who had inadequate clinical improvement with the antipsychotic used in stage 1A or 1B, or the patient responded but subsequently had a relapse while taking medication. Stage 2 recommends antipsychotic monotherapy with an FGA or SGA not used in stage 1 or stage 1B.[19–22] Because of safety concerns and the need for white blood cell (WBC) monitoring, clozapine is not generally recommended at stage 2.[19,20,22] However, clozapine has superior efficacy in decreasing suicidal behavior, and it should be considered at stage 2 for the suicidal patient.[19,22] Clozapine can also be considered at stage 2 in patients with a history of violence or comorbid substance abuse.[19,27] If a patient has unacceptable side effects with the antipsychotic used during stage 1A, stage 1B, or stage 2, then an alternate antipsychotic for that stage should be chosen.

Long-acting injectable antipsychotics (LAIAs) should be considered as an option at stage 2. The use of LAIAs should be discussed with the patient as a life style choice, and their use should not be reserved for patients with poor medication adherence. In fact, if a patient prefers receiving a LAIA, it should be considered as an option at Stages 1A, 1B, and 2.[19,21,22] If there is good documentation of poor symptom improvement with two different antipsychotic trials at appropriate dose and duration, then pharmacotherapy should be initiated at stage 3. In stage 3, the recommended treatment is clozapine.[19,21,22] In stage 4, only minimal evidence exists for any treatment option for those patients who do not have adequate symptom improvement with clozapine. The Harvard Department of Psychiatry South Shore algorithms present various treatment options for patients who have inadequate improvement with clozapine. However, none of these options have conclusive evidence.[19] It is important to note that the use of antipsychotic combinations is controversial, as limited evidence supports increased efficacy for combination antipsychotic treatment, despite this practice being somewhat common.[19,22]

Predictors of Response

Obtaining a thorough medication history is important, and previous treatment response should help guide antipsychotic selection, in that either a good prior response favors the use of the same agent or a negative prior response suggests the selection of a dissimilar drug. Nonprescription and illicit drug use can

influence psychiatric presentation and needs to be considered when making decisions regarding a patient's diagnosis or antipsychotic response. Amphetamines and other CNS stimulants, cocaine, corticosteroids, digitalis glycosides, indomethacin, marijuana, pentazocine, phencyclidine, and other drugs can induce psychosis in susceptible individuals or exacerbate psychosis in patients with pre-existing psychiatric illness.[1,14,19] Patients with schizophrenia who continue to abuse alcohol or drugs usually have a poor response to medications and a poor overall prognosis. Furthermore, alcohol, caffeine, and nicotine use may potentially result in drug interactions with antipsychotics.

Individual differences in patient response have been either proposed or identified. Acute onset of symptoms and short duration of illness, presence of acute stressors or precipitating factors, later age of onset, family history of affective illness, and good premorbid adjustment as reflected in stable interpersonal relationships or employment are all predictors of good response.[20]

Although controversial, affective symptoms can correlate with an overall good response, while negative symptoms and neuropsychological deficits related to cognition and neurologic soft signs can correlate with poor antipsychotic response.[14,19,20] Additionally, a patient's subjective response within the first 48 hours after being administered an FGA can be associated with drug responsiveness,[28] as an initial dysphoric response, demonstrated by stating a dislike of the medication, or feeling worse or zombie-like, combined with anxiety or akathisia-like symptoms, is associated with poor drug response, adverse effects, and nonadherence.

The importance of developing a therapeutic alliance between the patient and the clinician cannot be underestimated. Patients who form positive therapeutic alliances are more likely to be adherent with all aspects of therapy, experience a better outcome at 2 years, and require smaller antipsychotic doses.[17] However, a certain minority of patients fail to benefit from antipsychotic therapy, and their psychosocial functioning can actually worsen with antipsychotic continuation.

Initial Treatment in an Acute Psychotic Episode

The goals during the first 7 days of treatment should be decreased agitation, hostility, combativeness, anxiety, tension, and aggression, and normalization of sleep and eating patterns. The usual recommendation is to initiate therapy and to titrate the dose over the first few days to an average effective dose, unless the patient's physiologic status or history indicates that this dose can result in unacceptable adverse effects. Because of its strong alpha one (α_1) receptor

antagonism and resulting risk of hypotension, iloperidone and clozapine should be titrated more slowly than other antipsychotics. Rapid titration to high doses is not recommended. Table 84-2[19–22] lists the usual dosage range, with an average dose typically being midrange. Because first-episode psychotic patients have an increased sensitivity to side effects, particularly EPS, typical dosing ranges are approximately 50% of the doses used in chronically ill individuals.[19] If "cheeking" of medication is suspected (where the patient places the medication in their cheek and then spits it out later), liquid formulations and orally disintegrating tablets of different antipsychotics are available. If a patient has shown absolutely no improvement after 2 weeks at a therapeutic dose then later clinical response is unlikely, and moving to the next treatment stage of the algorithm is recommended.[29]

Although some clinicians believe that larger daily doses are necessary in more severely symptomatic patients, data do not support this practice. Some symptoms, such as agitation, tension, aggression, and increased motor activity, may respond more quickly, but side effects can be more common with higher doses. However, interindividual differences in dosage and patient response do occur. In partial but inadequate responders who are tolerating the chosen antipsychotic, it may be reasonable to titrate above the usual dose range. However, this tactic should be time-limited (ie, 2-4 weeks), and if the patient does not achieve further improvement, either the dose should be decreased or an alternative treatment strategy should be tried. As previously stated, rapid titration of antipsychotic dosage is not indicated[19–22]; however, intramuscular (IM) antipsychotic administration (eg, aripiprazole 5.25-9.75 mg IM, haloperidol 2-5 mg IM, olanzapine 2.5-10 mg IM, or ziprasidone 10-20 mg IM) can be used to assist in calming a severely agitated patient. Clinically, agitation can be manifested as loud, physically or verbally threatening behavior, motor hyperactivity, or physical aggression. Although this technique can assist in calming an acutely agitated psychotic patient, it does not improve the extent of remission, time to remission, or the length of hospitalization. Haloperidol (an FGA) given IM for treatment of acute aggression is associated with a higher incidence of EPS than using an injectable SGA. If the patient is receiving an antipsychotic within the usual therapeutic range, the use of lorazepam 2 mg IM as needed in combination with the maintenance antipsychotic is a rational alternative for treatment of aggression. Hypotension, respiratory depression, CNS depression, and death have been reported with injectable lorazepam in combination with either olanzapine or clozapine; thus, parenteral lorazepam is not recommended in combination with either of these medications.[21]

Inhaled loxapine powder is FDA approved with an indication for treatment of acute agitation associated with schizophrenia or bipolar disorder. Because of the risk of bronchospasm, pulmonary distress, and pulmonary arrest, the medication can only be administered in a healthcare facility through the FDA-approved Risk Evaluation and Mitigation Strategy (REMS). Before administration, patients must be screened for a history of asthma, chronic obstructive pulmonary disease, or other lung disease associated with bronchospasm, and use is limited to one 10-mg inhaled dose per 24-hour period.[30] Whether inhaled loxapine offers any therapeutic advantages in acute agitation compared with currently available products is unknown, and patients must be sufficiently cooperative to inhale it appropriately.

Stabilization Therapy

7 Symptom improvement may occur over 6 to 12 weeks. During the first 2 to 3 weeks, goals should include increased socialization and improvement in self-care habits and mood. Improvement in any formal thought disorder should follow and may take an additional 6 to 8 weeks to respond. Patients who are early in the course of their illness tend to experience a more rapid resolution of symptoms than individuals who are more chronically ill. In general, if a patient has shown no improvement after 2 weeks of treatment at therapeutic doses, or has achieved only a partial decrease in positive symptoms within 8 to 12 weeks at adequate doses, then the next algorithm stage should be considered. In more chronically ill patients, symptoms may continue to improve over 3 to 4 months. Quantifying symptom change using a brief symptom rating scale can be helpful in monitoring treatment and making decisions. An optimum target medication dose should be estimated in the initial treatment plan. If the patient begins to show adequate response at a particular dose, then the patient should remain at this dosage as long as symptoms continue to improve. In general, adequate time on a therapeutic antipsychotic dose is the most important factor in predicting medication response. However, if necessary, dose titration can continue within the therapeutic range every 1 or 2 weeks as long as the patient has no side effects.

Before changing medications in a poorly responding patient, the following should be considered: Were the initial target symptoms indicative of schizophrenia or did they represent manifestations of a different diagnosis, a long-standing behavioral problem, a substance abuse disorder, or a general medical condition? Is the patient adherent with pharmacotherapy? Are the persistent symptoms poorly responsive to antipsychotics (eg, impaired insight or

judgment, or fixed delusions)? How does the patient's current status compare with response during previous exacerbations? Would this patient potentially benefit from a change to a different treatment stage (Figure 84-1)? Does this patient have treatment-resistant schizophrenia?

The conclusion that a partially responding patient has achieved as much symptomatic improvement as possible is one that must be made with great care as treatment goals must be realistic. Medications are effective in decreasing many of the symptoms of schizophrenia (and are thus referred to as palliative), but they are not curative, and not all symptoms may abate. Although one should aim to achieve full remission to minimal residual positive symptoms, it is still unclear what a realistic goal is with regard to maximum improvement in negative symptoms.

It is important to screen patients for co-occurring mental disorders, and their presence can become more apparent during the stabilization or maintenance phases of treatment. Examples include substance abuse disorders, depression, obsessive-compulsive disorder, and panic disorder. As co-occurring disorders will limit symptom and functional improvement and increase the risk of relapse, it is critical that treatment for the co-occurring disorder be implemented in combination with evidence-based treatment for schizophrenia.

Maintenance Treatment

Maintenance drug therapy prevents relapse, as shown in numerous double-blind studies, and avoiding relapse is a major goal of treatment.[19–22] The average relapse rate after 1 year is 18% to 32% with active drug (including some nonadherent patients) versus 60% to 80% for placebo.[19–22]

8 After treatment of the first psychotic episode in a patient with schizophrenia, medication should be continued for at least 18 months after remission.[19–22] Many schizophrenia experts recommend that patients with robust medication response be treated for at least 5 years; however, in chronically ill individuals, continuous or lifetime pharmacotherapy is necessary in the majority of patients to prevent relapse. This practice should be approached with the lowest effective dose of the antipsychotic that is likely to be tolerated by the patient.[19–22]

Antipsychotics should be tapered slowly before discontinuation as abrupt discontinuation of antipsychotics, especially clozapine, can result in withdrawal symptoms, felt to be a manifestation of rebound cholinergic outflow. Insomnia, nightmares, headaches, GI symptoms (eg, abdominal cramps, stomach pain,

nausea, vomiting, and diarrhea), restlessness, increased salivation, and sweating are reported. Although available evidence does not indicate a best way to switch from one antipsychotic to another, it is often recommended to taper and discontinue the first antipsychotic over at least 1 to 2 weeks while the second antipsychotic is initiated and the dose titrated.[21] Tapering needs to occur more slowly with clozapine.[29]

Long-Acting Injectable Antipsychotics

Early studies did not consistently demonstrate an advantage of long-acting injectable antipsychotics (LAIAs) over oral agents. In contrast, recent studies, designed to reflect real-world practices, have more consistently demonstrated an advantage in reduced hospitalizations and relapse prevention in patients with schizophrenia.[31] Despite the potential advantages, the use of LAIAs is relatively low compared with oral antipsychotics, and in most Western countries use falls below 20%.[32] Barriers to LAIA use may be clinician or patient driven and include: biases and attitudes, limited insurance coverage, or lack of experience with LAIAs.[33] Traditionally, LAIAs have been primarily used later in the course of treatment and in patients who are unreliable in taking oral medication. More recently, it has been suggested to offer LAIAs to patients as a treatment option earlier in treatment before they develop a pattern of nonadherence.[32,33] For example, they can be presented to a patient as a life style option, in which the patient does not need to address the hassle associated with taking a medication daily.[22] Normalizing the use of LAIAs, providing appropriate education to families and patients on LAIAs, utilizing motivational interview techniques, and offering it as an early treatment option may aid in improving LAIA acceptability with patients.[31]

Treatment nonadherence rates are as high as 60% in patients with schizophrenia that can lead to negative clinical outcomes.[32] Nonadherence can be due to several factors including cognitive impairment, persistent symptoms, substance use, or lack of insight. However, before declaring a patient nonadherent, it should be determined whether the patient's medication nonadherence is because of side effects. If so, an alternative medication with a more favorable side effect profile should be considered before initiating a LAIA. The patient's motivation for treatment is a major factor influencing outcome.

There are currently eight LAIAs available for use in the United States: risperidone (two different formulations), paliperidone palmitate, aripiprazole (monohydrate and lauroxil), olanzapine pamoate, haloperidol decanoate, and

fluphenazine decanoate. Conversion from an oral antipsychotic to a LAIA should start with stabilization on an oral dosage form of the same agent, for a short trial (4-14 days), to determine whether the patient tolerates the medication without significant side effects, especially if the patient has no previous exposure to the oral agent.[31]

With risperidone microspheres (Consta®), measurable serum concentrations are not seen until approximately 3 weeks after single-dose administration. Thus, it is important that the oral antipsychotic be administered for at least 3 weeks after beginning the injections. The recommended starting dose with risperidone microspheres is 25 mg. Clinical experience suggests that titration to doses greater than or equal to 37.5 mg per injection may be necessary for maintenance treatment with demonstrated efficacy seen with an optimal dose range between 25 and 50 mg IM every 2 weeks. Dose adjustments are recommended to be made no more often than once every 4 weeks.[34] Doses above 50 mg every 2 weeks are not recommended, as research indicates no greater clinical efficacy but more EPS.[24] With risperidone extended-release injectable suspension (PERSERIS®), dosing is 90 or 120 mg once monthly, no oral overlap or loading dose is necessary, and it is the only LAIA that is administered subcutaneously in the abdomen.[35]

Paliperidone palmitate (Invega Sustenna®) has the advantage of easy conversion from oral paliperidone to IM treatment, as there is no need for oral overlap, and this formulation offers once-monthly injections with the option to convert to a 3-month formulation.[34] It is initiated with 234 mg on day 1 and 156 mg a week later (+/− 4 days) with deltoid administration for the first two doses as gluteal absorption results in 28% lower C_{max}. The 1-month paliperidone palmitate (1MPP) IM doses are then titrated according to response within a range of 39 to 234 mg and can be injected into either the deltoid or gluteal muscle.[34] If a patient's oral paliperidone is established prior to converting to the 1MPP, the maintenance dose required for similar paliperidone exposure is outlined in Table 84-5.[36]

A 3-month paliperidone palmitate (3MPP, Invega Trinza®) LAIA is approved for the management of schizophrenia and significantly delays time to relapse compared with placebo. The 3MPP provides the longest dosing interval currently available, but requires patients to be treated for at least 4 months with 1MPP prior to its initiation. The first 3MPP dose is based on the previous 1 month injection dose, as shown in **Table 84-3**.[37]

TABLE 84-3 Summary of Available Long-Acting Injectable (LAI) Antipsychotics

Medication Name Parameter	Fluphenazine Decanoate	Haloperidol Decanoate	Risperidone (Risperdal Consta®)	Risperidone (PERSERIS®)	Paliperidone Palmitate (Invega Sustenna®)	Paliperidone Palmitate (Invega Trinza®) (1MPP)	Olanzapine Pamoate (Zyprexa Relprevv®) (3MPP)	Aripiprazole Monohydrate (Abilify Maintena®)	Aripiprazole (Lauroxil Aristada®)
FDA-Approved Indication	Schizophrenia	Schizophrenia	Schizophrenia Bipolar I Disorder maintenance	Schizophrenia	Schizophrenia Schizoaffective Disorder	Schizophrenia	Schizophrenia	Schizophrenia	Schizophrenia
Dose Range (mg)	12.5-100	20-450	12.5-50	90-120	39-234	273-819	150-405	160-400	441-882
PO Overlap	None	4 weeks (none if loading); use PO dose patient was taking prior to injection	3 weeks after first injection: use PO dose patient was taking prior to injection	None	None	None	None	2 weeks PO dose ranges from 10 to 20 mg/day	21 days PO overlap after first injection
Recommended maximum dose	100 mg every 2-3 weeks	450 mg every 4 weeks	50 mg every 2 weeks	120 mg	234 mg every 4 weeks	819 mg every 3 months	300 mg every 2 weeks or 405 mg every 4 weeks	400 mg monthly	882 mg monthly
Initiation or Loading	Can Load	Can Load	None	None	Initiation required	None required, dose used depends on last Invega Sustenna dose as follows: If 78 mg give 273 mg If 117 mg give 410 mg If 156 mg give 546 mg If 234 mg give 819 mg	Initiation required	None	None required, dose depends on PO dose as follows: If 10 mg/day PO give 441 mg/month IM If 15 mg/day PO give 662 mg/month IM If 20 mg PO give 882 mg/month
Time to peak	8-24 hours	4-11 days	4-5 weeks	4-6 hours	13 days	30-33 days	<1 week	5-7 days	5-6 days
T_{ss}	2-3 months	2-3 months	6-8 weeks	60 days	7-11 months	Continues steady-state	3 months	3-4 months	4 months
Half-life	14.2 ± 2.2[a] days	21 days	3-6 days	9-11 days	25-49 days	84-89 days (deltoid) 118-139 days (gluteal)	30 days	29.9-46.5 days	29.2-34.9 days

Injection Site	Gluteal	Yes	Yes	Yes	Abdominal only	Yes after 2nd dose	Yes	Yes	Yes	Yes for all dose strengths
	Deltoid	Yes	Yes	Yes		Yes	Yes	No	No	Yes, but only 441-mg dose
Injection Method/ Technique			Z-Track		Subcutaneous Injection					
Notes				A starting dose of 12.5 mg is recommended in patients with hepatic or renal impairment	90 mg = 3 mg PO Risperidone 120 mg = 4 mg PO Risperidone	Avoid use in patients with moderate-to-severe renal impairment (CrCl <50 mL/min [0.83 mL/s])	Requires at least a 4-month trial with Invega Sustenna. Not recommended in patients with moderate or severe renal impairment (CrCl <50 mL/ min[0.83 mL/s])	Monitor for PDSS Subject to REMS	Maintenance dose reduced to 300 mg if patient experiences adverse events. Dose adjustment needed in CYP2D6 slow metabolizers. Avoid use in patients taking CYP 3A4 inhibitors >14 days	May require up to 2 weeks of PO trial to establish tolerability to aripiprazole before initiating LAIA Avoid use of strong CYP2D6 and 3A4 inhibitors on 662- and 882-mg dose, no adjustment needed for 441-mg dose

CrCl, Creatine Clearance; IM, intramuscular; LAIA, Long-Acting Injectable; PO, Oral; Tss, Time to steady state.

[a]Based on multiple-dose data. Single-dose data indicate a β-half-life of 6-10 days.

Data from References 21, 26, 31, 34, 36-40, and 42.

Olanzapine pamoate monohydrate is a LAIA administered every 2 or 4 weeks and does not require oral overlap. Olanzapine pamoate is recommended for deep gluteal injection, and the initial injectable dose varies from 210 to 405 mg depending on the oral olanzapine daily maintenance dose and the frequency of injectable administration.[34,38] A disadvantage to olanzapine pamoate is its association with postinjection delirium/sedation syndrome (PDSS) occurring in <2% of patients.[38] The symptoms of PDSS are similar to those of an oral olanzapine overdose and include delirium, ataxia, confusion, heavy sedation, or altered levels of consciousness. Although PDSS can occur with any dose and at any time during treatment, most cases have occurred within the first three injections.[39] The most likely explanation for the occurrence of PDSS is an accidental intravascular injection resulting in the drug dissolving more rapidly and sharp increases in plasma levels.[39,40] The product labeling contains an FDA-boxed warning regarding PDSS, and olanzapine pamoate is subject to a REMS with the FDA labeling limiting the availability of olanzapine LAIA to a restricted distribution program. The injection must be administered in a registered

healthcare facility, and the patient must be observed by a health professional for at least 3 hours after administration and must not drive or operate machinery for that day.[38]

Aripiprazole monohydrate LAIA (Abilify Maintena®) is administered as a single intramuscular injection in the gluteal or deltoid muscle once a month at a starting and maintenance dose of 400 mg. If the patient does not tolerate the 400-mg dose, the next injection can be reduced to 300 mg. After the first injection of aripiprazole monohydrate LAIA, a 14-day overlap with oral aripiprazole (10-20 mg/day) or any other antipsychotic is recommended.[34] Aripiprazole lauroxil LAIA (Aristada®) is administered as a single intramuscular injection in the deltoid (441 mg-dose only) or gluteal (441, 662, or 882 mg, once a month). The 882-mg dose can be administered every 6 weeks and the 1,084 mg every 2 months. Aripiprazole lauroxil has the advantage of having initiation dosing available (Aristada Initio®)[41]; however, if Aristada Initio® is not utilized, oral overlap is required for 3 weeks with this LAIA formulation.[40]

For the FGA fluphenazine decanoate, the simplest dosing conversion method recommends 1.25 times the oral fluphenazine daily dose for stabilized patients, rounding to the nearest 12.5-mg interval, which is administered in weekly doses for the first 4 to 6 weeks; or 1.6 times the oral daily dose given weekly for the first 4 weeks for more acutely ill patients.[42] Subsequently, fluphenazine decanoate can be administered once every 2 to 3 weeks. Although oral fluphenazine can be overlapped for 1 week, the dose should be reduced by half with the first injection to reduce the risk of EPS.[42] For haloperidol decanoate, the first dose should be 10 to 20 times the oral haloperidol daily dose and in patients who are at high risk of relapse, require higher doses of haloperidol, and/or are tolerant to oral haloperidol, a loading dose of 20 times the oral dose can be considered.[42] In haloperidol decanoate naïve patients, the initial injection is limited to 100 mg followed by the remaining balance of the first monthly dose given 3 to 7 days later.[34] An oral haloperidol overlap is recommended for the first month if a loading dose strategy is not utilized, but not necessary if the patient receives a loading dose The maintenance dose is typically 10 to 15 times the oral dose once monthly. Table 84-3 provides a summary of the LAIAs.

Methods to Enhance Patient Adherence

Treatment nonadherence rates are as high as 60% in patients with schizophrenia, which can lead to negative clinical outcomes.[32] If nonadherence is suspected, the clinician should ask in a nonjudgmental manner if the patient is having any

difficulty taking their medication and then the reason for nonadherence should be determined. If nonadherence is occurring because of adverse effects, then a medication with a more favorable side effect profile should be considered. Suspected nonadherence can also be assessed by obtaining an antipsychotic serum concentration.[43]

It is often challenging for individuals with chronic illnesses to maintain appropriate medication adherence, and partial adherence is a reality in the treatment of all chronic illnesses.[21] Individuals with serious mental disorders have higher nonadherence rates than those with general medical disorders, with the following explanations provided: denial of illness, lack of insight, grandiosity or paranoia, no perceived need for medication, perceived lack of input into choice of medication or dosage, side effects, misperceived "allergies," too many medications prescribed, or too many doses prescribed daily (see **Table 84-4**). It is estimated that half of patients with schizophrenia or schizoaffective disorder take their medication less than 70% of the time.[21] Clinicians should expect partial medication adherence to be the norm. Discussions regarding this topic should be approached in a positive, nonjudgmental manner, with the clinician actively engaging the patient in care and using motivational interviewing techniques as mechanisms to enhance therapeutic alliance and patient adherence.

TABLE 84-4 Noncompliance with Antipsychotic Medications Is a Multidimensional Dilemma

Patient factors	Medication Factors	Other factors
Lack of insight	Efficacy	Family perspectives
Paranoia	Side effects	Cultural influences
Attitude to medications	Mode of delivery/ ingestion	Physician perspectives and influences
Prior experiences	Cost	Insurance coverage
Perception of efficacy of drug	Availability	Cost of care
Comorbid substance abuse		Medication access and support
		Mental illness stigma

Data from References 44 and 68.

9 Numerous different methods have been used in an attempt to improve treatment adherence of patients with schizophrenia. Interventions that provide continuous focus on adherence and that are of long duration have shown benefit. These should incorporate problem solving techniques and be accompanied by

technical learning aids. As previously noted, programs need to include a focus on patient-driven outcomes, and not just medication adherence, and interventions should include efforts to allow patients to achieve life goals and function. This requires that programs be tailored to the needs of individual patients.[44] Psychoeducation strategies should include motivational interviewing techniques in individual counseling as well as group activities.

Some studies suggest that compliance therapy, targeted cognitive behavioral therapy focusing on medication adherence, can improve patient adherence, but the success seen in early studies has not been consistently replicated.[44]

Groups facilitated by trained individuals who have the illness are alleged to be more effective in enhancing awareness and acceptance of schizophrenia and necessary treatment than groups led only by professionals. Active involvement of family members further increases the likelihood of patient adherence with treatment. In addition to programs provided by community mental health centers, support groups operated by consumer groups such as the National Alliance on Mental Illness (NAMI) are available for patients as well as their families in most urban areas. In the hospital, self-medication administration can reinforce the patient's perception of his or her active role in treatment and when patients miss outpatient appointments, active outreach interventions must be implemented to enhance patient engagement in treatment.[44]

The LAIAs have been a mainstay of treatment for people who are nonadherent with taking their medications orally. However, for various reasons, they are used in only a relatively small subset of patients, and many patients simply do not like getting injections. Recently, a new technology incorporated with the antipsychotic aripiprazole was approved by the FDA. This technology (Abilify MyCite®) includes a biosensor inside the aripiprazole tablet; after the medication is ingested, the coating is degraded which emits a biosensor signal that is picked up by a specific patch worn by the patient.[45] Data are then transferred to a smart phone application and can be shared by the patient with the treating clinician via the internet. It is not known whether this technology will improve patient adherence in a population that is often suspicious and paranoid. Regardless, a great deal of education is necessary to make sure that the patient knows how to use the technology and to assure that the patient wears the patch and uses the smart phone application correctly.

Management of Treatment-Resistant Schizophrenia

In general, "treatment resistant" describes a patient who has had inadequate

symptom response from multiple antipsychotic trials.[19,21,43] The clinical definition of treatment resistance requires persistent symptoms of at least moderate severity, two antipsychotic treatment failures at adequate dosage for at least 6-week duration with each drug with good treatment adherence.[43] Between 10% and 30% of patients receive minimal symptomatic improvement after multiple antipsychotic monotherapy trials.[19,21] An additional 30% to 60% of patients have partial but inadequate improvement in symptoms or unacceptable side effects associated with antipsychotic use. In those patients failing two or more pharmacotherapy trials, a treatment-refractory evaluation should be performed to reexamine diagnosis, substance abuse, medication adherence, and psychosocial stressors. Targeted cognitive behavioral therapy or other psychosocial augmentation strategies should be considered.[19,22]

Clozapine Only clozapine has shown superiority over other antipsychotics in randomized clinical trials for the management of treatment-resistant schizophrenia as most other SGAs have either not been studied in treatment-refractory patients or been evaluated in small open trials. In a seminal study, clozapine was effective in approximately 30% of patients with treatment-resistant schizophrenia, compared with only 4% treated with a combination of chlorpromazine (an FGA) and benztropine (an anticholinergic agent).[46] Other treatment candidates for clozapine include those patients with severe suicidality, aggressive behavior, or those who cannot tolerate neurologic side effects of even conservative doses of other antipsychotics.

Symptomatic improvement with clozapine in the treatment-resistant patient often occurs slowly, and as many as 60% of patients continue to improve if clozapine is used for up to 6 months. This, in combination with clozapine's adverse effect profile, provides sufficient information to conclude that clozapine is not a panacea for schizophrenia. Polydipsia and hyponatremia (psychogenic water drinking) is a frequent problem among treatment-resistant patients, and clozapine reportedly decreases water drinking and increases serum sodium in such patients.[19,21]

Because of the risk of orthostatic hypotension, clozapine is usually titrated more slowly than other antipsychotics, particularly on an outpatient basis. If a 12.5-mg test dose does not produce hypotension, then clozapine 25 mg at bedtime is recommended, increased to 25 mg twice a day after 3 days, and then increased in 25 to 50 mg/day increments every 3 days until a dose of at least 300 mg/day is reached. If tolerated, a minimum trial should be 3 months with a clozapine serum concentration of at least 350 ng/mL (mcg/L; 1.07 μmol/L).

Because high doses are associated with significantly increased side effects, including seizures, a clozapine serum concentration is recommended before exceeding 600 mg/day.[21] If the clozapine serum concentration is greater than 350 ng/mL (mcg/L; 1.07 µmol/L), then further dosage increases are not indicated.[43]

Augmentation and Combination Strategies Little empirical evidence exists to guide treatment decisions for patients who do not respond to clozapine.[19,21,22] Current strategies include augmentation therapy involving the addition of a nonantipsychotic drug to an antipsychotic drug in a poorly or partially responsive patient or combination treatment using two antipsychotics simultaneously.

In a small, single blind, randomized trial, 50% of patients demonstrated clinically significant improvement in symptoms with electroconvulsive therapy (ECT) augmentation of clozapine, compared with no responders in the clozapine monotherapy group. When the patients in the clozapine monotherapy group received ECT, 47% demonstrated clinically significant improvement.[19]

Mood stabilizers are frequently used as an augmentation strategy, and while lithium does not enhance antipsychotic effect, it may improve labile affect and agitated behavior in select patients.[19] Enzyme induction with carbamazepine can cause a decrease in antipsychotic serum concentrations and potentially worsen psychotic symptoms in some patients.[19,47]

Only limited data are available to support antidepressant augmentation of antipsychotics.[19,21,22] However, consistently positive results have been reported when using selective serotonin reuptake inhibitors (SSRIs) to treat obsessive-compulsive symptoms that worsen or arise during clozapine treatment.

Combining an FGA with an SGA and combining different SGAs have been suggested as intervention strategies for treatment-resistant patients. Pharmacodynamically, there is limited rationale to explain how combinations of antipsychotics would produce enhanced efficacy, but increased side effects, particularly increased EPS, metabolic effects, and hyperprolactinemia, are possible results.[22] The evidence to support antipsychotic combinations is scant at best, and recent treatment guidelines state that there is insufficient evidence to support this practice.[22] Regardless, this topic remains highly contentious, and clinicians' practice is often not aligned with available evidence. In general, a series of antipsychotic monotherapies, including clozapine, are preferred over antipsychotic combinations.[22] However, when clozapine fails to produce desired outcomes, a time-limited combination trial is sometimes considered (eg, maximum 12 weeks) and the patient carefully evaluated with rating scales for

changes in symptomatology.[19] If no apparent improvement is observed, then one of the medications should be tapered and discontinued. However, if the patient has a partial response (greater than or equal to 20% improvement in positive symptoms) after 12 weeks with combination treatment, medications should be titrated to doses at the upper end of the therapeutic range, and treatment should continue for an additional 12 weeks before a change in treatment is considered.

Violence in Schizophrenia

Although most people with schizophrenia do not exhibit violent behavior, they are more likely to be violent than the general population. It is estimated that the rate of violence in people with schizophrenia is 9.9% compared with 1.6% in the general population.[27] Risk factors for violence include those associated with violence in the general population (eg, childhood trauma and exposure to violence, alcohol and substance abuse, psychopathy, and access to firearms) and (to some lesser extent) psychotic symptoms.[27] It is estimated that most of the risk of violence is associated with co-occurring substance abuse.[27] Patients are at risk to become violent when they relapse and so keeping patients with schizophrenia clinically stable is a major consideration. Clozapine has been found to be superior to other antipsychotics in decreasing aggressive and violent behavior.[27] Some states have outpatient commitment laws where patients at risk of violence are “forced” to get ongoing care, and if they default, they are sent back to the hospital. Patients who are really dangerous are invariably contained either in the legal system itself or legally as “forensic” patients where they are held by court order in a psychiatric facility.

Antipsychotic Mechanism of Action

The exact mechanism of action of antipsychotics is unknown. It has been suggested that antipsychotics be classified into three different categories: (a) typical (traditional or FGAs) (high D_2 antagonism and low serotonin-2 receptor [5-HT_{2A}] antagonism); (b) atypical (SGAs) (moderate-to-high D_2 antagonism and high 5-HT_{2A} antagonism); and (c) atypical clozapine-like (low D_2 antagonism and high 5-HT_{2A} antagonism).[48] With the exception of aripiprazole and brexipiprazole, all current SGAs have a greater affinity for 5-HT_{2A} receptors than D_2 receptors, and brexipiprazole shows stronger antagonism of the 5-HT_{2A} receptor than aripiprazole.[48,49] Brexipiprazole also demonstrates higher affinity for the serotonin-1A (5-HT_{1A}) receptor compared to aripiprazole but with less

intrinsic D_2 activity than aripiprazole.[49]

Prospective studies of antipsychotic receptor binding in humans have used PET scans to examine neurotransmitter receptor binding at 12 hours postdose in small numbers of individuals at steady-state concentrations. It has been proposed that at least 60% to 65% D_2 receptor occupation is necessary to decrease positive psychotic symptoms, whereas blockade of approximately 77% or more of D_2 receptors is associated with EPS.[48] **Table 84-5** outlines the relative differences in receptor binding for various agents. In general, all FGAs are DA receptor antagonists with high affinity for D_2 receptors, and during chronic treatment, between 70% and 90% of D_2 receptors in the striatum are usually occupied. In contrast, during clozapine treatment only 38% to 47% of D_2 receptors are occupied, even with high doses. Newer SGAs have variable D_2 binding. Low D_2 binding, and thus the atypicality seen with the SGAs, can be directly associated with how rapidly the antipsychotic disassociates from the D_2 receptor.[48] This transient blockade of DA receptors may be adequate to produce antipsychotic effect, but long-term D_2 blockade is required for production of EPS and sustained hyperprolactinemia. Aripiprazole and brexpiprazole are partial agonists at D_2 receptors, and represent a further elaboration of the DA hypothesis of antipsychotic action.[48,49]

TABLE 84-5 Relative Neuroreceptor Binding Affinities of Select Antipsychotics

	Aripiprazole	Asenapine	Chlorpromazine	Clozapine	Haloperidol	Iloperidone	Lurasidone	Olanzapine	Paliperidone	Quetiapine	Risperidone	Ziprasidone
D_1	-	++	+	+	+			++	+	-	+	+
D_2	++++	+++	+++	+	++++	+++	+++	++	+++	+	+++	+++
D_3	++	+++	+++	+	+++	+++		+	++	-	++	++
D_4	+	+++	+++	++	+++	++		++	-	-	-	++
5-HT_{1A}	++	++	-	-	-	++	+	-	-	-	-	+++
5-HT_{1D}	+			-	-			-	+	-	+	+++
5-HT_{2A}	+++	+++	++	+++	+	++++	+++	+++	+++	++	++++	++++
5-HT_{2C}	+	++++	++	++	-	++		++	+	-	++	++++
5-HT_6	+	+++	++	++	-	++		++	-	-	-	+
5-HT_7	++	+++	++	++	-		++++	-	++	-	+++	++
α	+	+++	++++	+++	+++	++++	+	++	+++	+++	+++	++
α	+	++	+	+	-	++	+	+	++	-	++	-
H_1	+	++	++++	+++	-	++	-	+++	-	++	-	-
m_1	++	-		++++	-	-	-	+++	-	++	-	-

Relative neuroreceptor binding affinities of select antipsychotics.

(-) = minimal or none; (+) = low; (++) = moderate; (+++) = high; (++++) = very high

Data from Reference 131, Table 84-1.

Iloperidone's pharmacology is different in that it has high affinity for D_2, dopamine-3 (D_3), and 5-HT_{2A} receptors, and moderate affinity for dopamine-4 (D_4), serotonin-6 (5-HT_6), serotonin-7 (5-HT_7), and α_1-receptors.[50] Asenapine has high affinity for 5-HT_{2A} and D_2 receptors as well as for α_1- and histamine-1 receptors with D_2 occupancy approximating 80% with a sublingual dose of 5 to 10 mg twice daily.[51] Cariprazine has high affinity for D_2 and D_3 receptors as a partial agonist, with the D_3 potency being significantly greater than D_2. It is also a partial agonist at 5-HT_{1A} receptors and an antagonist at serotonin-1B (5-HT_{1B}) receptors.[52] Therefore, given all of these different mechanism of action, it is clear that our understanding of the manner in which they produce an atypical clinical profile is still in its infancy.

With low-dose risperidone (2-5 mg/day), D_2 binding ranges from 60% to 79%, but with doses greater than 6 mg daily, binding commonly exceeds the 77% threshold associated with the development of EPS. Risperidone 2 mg/day

produces 5-HT_{2A} binding greater than 70%, and with 4 mg/day it is nearly 100%.[48] Olanzapine 10 to 20 mg/day produces D_2 binding ranging from 71% to 80%, whereas at 30 to 40 mg/day, it ranges from 83% to 88%. At 5 mg/day, 5-HT_{2A} receptors are near saturation of binding.[48] Ziprasidone has the highest 5-HT_{2A}-to-D_2 affinity ratio of any of the currently available antipsychotics. It is also a potent serotonin-1A (5-HT_{1A}) agonist.[48]

Quetiapine has the lowest D_2 binding. At doses of 300 to 600 mg/day, 12-hour postdose D_2 binding ranges from 0% to 27%. Even at quetiapine 800 mg/day, only 30% of D_2 receptors are occupied. At these same daily doses, 45% to 90% of 5-HT_{2A} receptors are occupied. However, when quetiapine D_2 binding is examined 2 to 3 hours postdose, 58% and 64% of receptors were occupied with 400 and 450 mg, respectively.

The primary therapeutic effects of antipsychotics are thought to occur in the limbic system, including the ventral striatum, whereas EPS are thought to be related to DA blockade in the dorsal striatum. For SGAs, 5-HT_{2A} antagonism in combination with modest D_2 blockade leads to release of DA in the prefrontal cortex, and this is one explanation for the decrease in negative symptoms and improvement in cognition reported with these antipsychotics.[48]

As discussed, antipsychotics vary in their effects on other neurotransmitter receptor systems.[48] Although the significance of these different mechanisms on efficacy is unclear, they do potentially explain differences in side effect profiles. These differences in pharmacodynamics profiles point out that the SGAs are not alike, and patients obtaining an inadequate clinical response (either efficacy or side effects) with one antipsychotic may have a superior response on an alternate drug. Thus, serial SGA monotherapy trials should be tried in patients receiving a suboptimal clinical response (see Fig. 84-1).

Pharmacokinetics

As a class, antipsychotics are highly lipophilic and highly bound to membranes and plasma proteins. They distribute readily into most tissues with a high blood supply and can accumulate in tissues; therefore, they have large volumes of distribution.[53] Most antipsychotics are largely metabolized, primarily through the cytochrome P450 (CYP) pathways in the liver, except for ziprasidone, which is largely metabolized by aldehyde oxidase. Fluphenazine and perphenazine are metabolized through CYP2D6, and thus are susceptible to pharmacogenetically

regulated metabolism.[54] This is also one of the major pathways for the metabolism of aripiprazole, brexpiprazole, haloperidol, iloperidone, and risperidone.[54] Thirty percent to 35% of Africans and Asians are slow to intermediate CYP2D6 metabolizers, and approximately 0% to 5% of African Americans, 1% of Asians, and 5% to 10% of whites are poor metabolizers.[55] In addition, some people of Swedish descent and up to 30% of those from Northern Africa may be ultra-rapid CYP2D6 metabolizers.[56] Genetic variation within CYP1A2 can potentially result in a decrease in the metabolic rate of clozapine, whereas, smoking may increase clozapine metabolism due to the effect of cigarette smoke inducing CYP1A2 linked to a specific genotype.[54,55] Pharmacogenomics should be considered when dosing and monitoring the clinical effects of antipsychotics.[54–56] Additional resources related to specific gene and drug pairs for pharmacogenomics information can be obtained at the Clinical Pharmacogenomics Implementation Consortium (CPIC) Website (www.cipicpgx.org). **Table 84-6** outlines the prominent metabolic pathways of selected antipsychotics.

TABLE 84-6 Pharmacokinetic Parameters of Selected Antipsychotics

Drug	Bioavailability (%)	Half-Life	Major Metabolic Pathways	Active Metabolites
Selected First-Generation Antipsychotics (FGAs)				
Chlorpromazine	10-30	8-35 hours	FMO3, CYP3A4	7-Hydroxy, others
Haloperidol	40-70	12-36 hours	**CYP2D6**, CYP1A2, CYP3A4	Reduced haloperidol
Perphenazine	20-25	8.1-12.3 hours	**CYP2D6**	7-OH-perphenazine
Second-Generation Antipsychotics (SGAs)				
Aripiprazole	87	48-68 hours	**CYP2D6, CYP3A4**	Dehydroaripiprazole
Asenapine	<2 orally 35 SL Nonlinear	13-39 hours	**CYP1A2, UGT1A4**, CYP2D6, CYP3A4	None known
Brexpiprazole	95	91 hours	**CYP2D6, CYP3A4**	DM-3411
Cariprazine		2-4 days, DDCAR 1-3 weeks	**CYP3A4**, CYP2D6	Desmethyl cariprazine (DCAR), Didesmethyl cariprazine (DDCAR)
Clozapine	12-81	11-105 hours	**CYP1A2, CYPD6, CYP3A4**	Desmethylclozapine
Iloperidone	96	18-33 hours	**CYP2D6, CYP3A4**	P88
Lurasidone	10-20	18 hours	**CYP3A4**, CYP1A2	ID-14233 and ID-14326
Olanzapine	80	20-70 hours	CYP1A2, CYP3A4, FMO3	*N*-Glucuronide; 2-OH-methyl; 4-*N*-oxide
Paliperidone ER	28	23 hours	Renal unchanged (59%) CYP3A4 and multiple pathways	None known
Quetiapine	9 ± 4	6.88 hours	**CYP3A4**, CYP3A5	N-desalkylquetiapine
Quetiapine XR		7 hours	**CYP3A4**, CYP3A5	N-desalkylquetiapine
Risperidone	68	3-24 hours	**CYP2D6**, CYP3A4	9-OH-risperidone
Ziprasidone	59	4-10 hours	Aldehyde oxidase, **CYP3A4**, CYP1A2	None

UGT, UDP glucuronosyltransferases genes; FMO3, flavin containing monooxygenase 3 gene; SL, sublingual.

[a]**Bold** print indicates major pathway.

Data from References 49-56, and 129.

Asenapine is unique in that it has less than 2% bioavailability after oral administration, but has a bioavailability of approximately 35% sublingually—the FDA-approved route of administration. Eating and drinking within 10 minutes after sublingual administration will reduce bioavailability, and bioavailability decreases with single doses above 10 mg.[51,56]

Most antipsychotics have fairly long elimination half-lives, generally 24 hours or more, with the exception of quetiapine and ziprasidone, which have short half-lives.[53,56] Among the SGAs, only clozapine has an established

therapeutic serum concentration, with efficacy being associated with a clozapine plasma concentration greater than 350 ng/mL (mcg/L; 1.07 µmol/L).[53] Whether a potential maximum therapeutic clozapine serum concentration exists is unknown. Clozapine serum concentration should be obtained before exceeding 600 mg daily, in patients who develop unusual or severe adverse side effects, in patients who are taking concomitant medications that can cause drug interactions, in patients who have age or pathophysiologic changes suggesting a change in pharmacokinetics, or for assessment of patient adherence.[53,56]

Adverse Effects

Table 84-7 presents the relative risk of common categories of antipsychotic side effects, which are discussed below with respect to organ system affected. A general approach to monitoring and assessing side effects requires prospective monitoring by clinicians, preferably using a thorough review of systems approach. Patient-oriented self-rated side effect scales can be helpful, as many patients with schizophrenia do not readily complain of side effects.

TABLE 84-7 Relative Side Effect Incidence of Commonly Used Antipsychotics[a,b]

	Sedation	EPS	Anticholinergic	Orthostasis	Weight Gain	Prolactin
Aripiprazole	+	+/++[c]	+	+	+	+
Asenapine	+	+/++	±	+	++	+
Brexpiprazole	+	+/++[c]	+	+	+	+
Cariprazine	±	+/++[c]	+	+	+	+
Chlorpromazine	++++	+++	+++	++++	++	+++
Clozapine	++++	+	++++	++++	++++	+
Fluphenazine	+	++++	+	+	+	++++
Haloperidol	+	++++	+	+	+	++++
Iloperidone	+	±	+	+++	++	+
Lurasidone	++	+	+	+	+	+
Olanzapine	++	++	++	++	++++	+
Paliperidone	+	++	+	+	++	++++
Perphenazine	++	++++	++	+	+	++++
Quetiapine	++	+	++	++	++	+
Risperidone	+	++	+	++	++	++++
Thioridazine	++++	+++	++++	++++	+	+++
Thiothixene	+	++++	+	+	+	++++
Ziprasidone	++	++	+	+	+	+

EPS, extrapyramidal side effects—includes dystonias, pseudoparkinsonism, akathisia, and tardive dyskinesia.

Relative side effect risk: ±, negligible; +, low; ++, moderate; +++, moderately high; ++++, high.

[a]Side effects shown are relative risk based on doses within the recommended therapeutic range.

[b]Individual patient risk varies depending on patient-specific factors.

[c]Primarily akathisia

As mentioned previously, medication side effects are one of the primary predictors of patient nonadherence. With the variety of antipsychotics available, using an alternative antipsychotic should be considered in patients who complain of poorly tolerated side effects to improve patient outcomes. As we learn more about relative side effect risks (eg, metabolic, QTc prolongation, and EPS), it will be necessary to regularly reconsider which antipsychotics should be considered first-line treatment alternatives.

Endocrine System Within the hypothalamic tuberoinfundibular tract, DA blockade results in increased prolactin levels with hyperprolactinemia occurring in up to 71% of patients diagnosed with schizophrenia and treated with

antipsychotics.[57] While US-based studies show no gender difference in the incidence of antipsychotic-induced hyperprolactinemia, UK-based studies suggest women are twice as likely to experience antipsychotic-induced hyperprolactinemia than men (52% vs 26% respectively).[57,58] The major side effects associated with hyperprolactinemia are gynecomastia, galactorrhea, menstrual irregularities, infertility, and sexual dysfunction. Although the clinical significance is unclear, chronic hyperprolactinemia has been associated with decreased bone mineral density, which may put patients at higher risk of osteoporosis.[59] Tolerance does not appear to develop to antipsychotic-induced hyperprolactinemia.[60] In general, FGAs are associated with higher rates of hyperprolactinemia than SGAs, the exceptions being risperidone and paliperidone which have reported rates exceeding 70%.[57,58,60] As they have poor penetration of the blood-brain barrier, their greater presence at D_2 receptors in the pituitary gland may be contributing to this side effect.[57,58,60] On the other hand, as a D_2 partial agonist, aripiprazole is more prolactin sparing. Newer antipsychotics including asenapine, iloperidone, lurasidone, brexpiprazole, and cariprazine have not been shown to induce clinically meaningful changes in prolactin levels.[50,51,57,61] If a patient experiences symptomatic hyperprolactinemia, switching to an agent that has minimal sustained effect on prolactin is a reasonable treatment option, as is attempting to lower the antipsychotic dose. However, both interventions run the risk of relapse. A recent meta-analysis suggests that augmentation with aripiprazole 5 to 30 mg daily may help reduce risperidone-induced hyperprolactinemia.[62] However, there have also been case series reporting symptom exacerbation with the addition of aripiprazole and, in general, antipsychotic polypharmacy is not recommended.[57] Dopamine agonists, bromocriptine, cabergoline, and pramipexole have been shown to decrease prolactin but this approach is not recommended due to the lack of controlled trials, as well as reports of psychosis exacerbation.[57] For women with schizophrenia who suffer from amenorrhea due to antipsychotic-induced hyperprolactinemia, metformin 750 to 1,500 mg/day has been shown to restore menstrual function, with improvements being associated with a reduction in prolactin level.[63] While a potentially appealing intervention, especially in patients who are gaining weight and at risk for Type 2 diabetes mellitus (T2DM), additional evidence is needed before recommending metformin as a first-line intervention for women with antipsychotic-induced hyperprolactinemia.[63]

Weight gain is frequently reported in both adults and children receiving antipsychotics,[64,65] and is often seen within the first 12 weeks of antipsychotic

initiation, with the rate of weight gain decreasing over time.[64,65] The risk of cardiovascular-related mortality is higher in individuals with schizophrenia,[66] and this is further aggravated by drug-related weight gain and the high prevalence of smoking. Additionally, obesity is a risk factor for diabetes mellitus.[66,67] Weight gain during treatment is concerning for patients and a reason for poor medication adherence.[68] Clozapine and olanzapine have the highest rates of antipsychotic-induced weight gain (AIWG), with olanzapine being the most studied for this side effect and likely producing the highest risk. Mid-risk antipsychotics include asenapine, iloperidone, paliperidone, quetiapine, and risperidone. Aripiprazole, lurasidone, and ziprasidone are associated with the lowest risk of AIWG.[51,61,64] Newer agents, brexpiprazole and cariprazine, also appear to have low risk of AIWG, similar to aripiprazole.[69]

Although the exact mechanism for AWIG uncertain, it has been associated with antihistaminic effects, antimuscarinic effects, adrenaline alpha-1, and blockade of 5-HT_{2C} receptors.[65] However, dietary factors and activity levels can play a significant role in this population, as well as renourishment after a period of poor self-care. The risk of weight gain may be greater in patients with their first psychotic episode and those who are underweight at baseline.

Several different genetic variations have been associated with predisposition for antipsychotic-associated weight gain. The 5-HT_{2c} gene and its relationship to AIWG is the most extensively studied polymorphism.[54,70] A meta-analysis of all genetic studies looking at the C–759T promoter region polymorphism of the *5-HT_{2C}* receptor gene, confirmed the relationship with AIWG. While the C allele is the major allele in the population, the meta-analysis found that T allele is actually protective against AIWG.[70] In this same meta-analysis, polymorphisms of dopamine receptor D_2 (*D2*), alpha-2 adrenergic receptor (α_2), and melanocortin-4 receptor (*MC4R*) genes were also found to be associated with AIWG. Insulin-induced gene 2 (*INSIG2*) and Guanine Nucleotide Binding Protein (*GNB3*) had smaller effect sizes, but were also found to be associated with AIWG. Polymorphisms in leptin and leptin receptor genes, methylenetetrahydrofolate reductase (*MTHFR*) and brain-derived neurotrophic factor (*BDNF*) gene have been genetic targets; however, results are inconsistent regarding a potential relationship between these polymorphisms and AIWG.[54,70,71] In general, AIWG is most likely polygenic and impacted by environmental factors.

Several approaches have been recommended to address weight gain. Switching the antipsychotic to another agent with less weight gain liability is one

choice, and an American Diabetes Association consensus task force recommends consideration of a change in antipsychotic if a patient gains more than 5% of baseline body weight after starting the drug.[72] Metformin is effective in treating antipsychotic-induced weight gain with a meta-analysis indicating an average of a 3.17 kg (7 lb) weight loss compared with placebo.[73] Dietary restriction, exercise, and behavior modification programs are reported to be successful. Both the Reducing Weight and Diabetes Risk in an Underserved Population (STRIDE) and the Randomized Trial of Achieving Healthy Lifestyles in Psychiatric Rehabilitation (ACHIEVE) clinical trials showed behavioral weight loss interventions resulted in significant weight loss in patients with mental illness receiving antipsychotics. The STRIDE study also showed reductions in fasting glucose over 6- and 12-month periods using such interventions.[70,74,75]

Patients with schizophrenia have a twofold higher prevalence of T2DM compared to the general population.[66] While the illness itself contributes to elevated risk, antipsychotics are a major contributing factor, with individuals exposed to antipsychotics having higher rates of T2DM than those unexposed.[66,67] The exact mechanism by which antipsychotics elevate the risk of T2DM is unknown. While weight gain seen with antipsychotics can lead to insulin resistance and elevated risk of T2DM, a systematic review of antipsychotic-associated diabetic ketoacidosis (DKA) found that weight gain was only associated with roughly half of the included cases, and DKA was often the first indicator of a diabetes diagnosis. SGAs can rapidly and directly influence glucose metabolism independent of AIWG and adiposity.[76] It is possible that antipsychotics also directly cause T2DM through increased insulin resistance or impaired β-cell function or a combination of the two.[67] The greatest increase in glucose impairment typically occurs during the first 14 weeks of treatment,[74] and it is estimated for clozapine, olanzapine, quetiapine, and risperidone that nearly 60% of new-onset diabetes occurred within the first 6 months of treatment initiation.[72,74]

The FDA-approved product labeling for all SGAs reflects the increased risk of diabetes mellitus in patients taking these medications, but risk varies based on the antipsychotic. Clozapine and olanzapine have the highest risk of new-onset diabetes followed by quetiapine and risperidone, while the risk appears lowest with ziprasidone and aripiprazole.[72,74] Although inadequate data are available for asenapine, iloperidone, lurasidone, brexpiprazole, and cariprazine, their risk also appears low.[77] Olanzapine is not recommended as a first-line antipsychotic option due to its metabolic side effect profile[19,20,22]; therefore, designing care

models and standards for managing diabetes in patients with schizophrenia is important in addressing this major health problem.

Cardiovascular System

Orthostatic Hypotension Orthostatic hypotension, thought to be caused by α-adrenergic blockade, is a common side effect of antipsychotics.[78] Clozapine and quetiapine had the highest incidence of orthostatic hypotension in the CATIE study, and iloperidone appears to have the highest risk among newer SGAs.[78] Orthostatic hypotension can occur in any patient, but diabetic patients with pre-existing cardiovascular disease and the elderly are particularly predisposed. Other risk factors may include dehydration, presence of alcoholic neuropathy and antipsychotic combination treatment.[78,79] Patients should be advised to avoid sudden positional changes to allow for adaptation. Tolerance to this effect may occur within 2 to 3 months. If not, lower doses or a change to an antipsychotic with less α-blockade can be attempted. Fluid resuscitation or increasing salt intake may also help minimize orthostatic blood pressure changes.[78,79]

Electrocardiographic Changes The electrocardiographic (ECG) changes seen with antipsychotics include increased heart rate (through sinus tachycardia from anticholinergic effects, or reflex tachycardia from α-adrenergic blockade), flattened T waves, ST segment depression, and prolongation of QT and PR intervals. The most clinically important of these potential changes is prolongation of the QTc interval, which has been associated with ventricular arrhythmias, including torsade de pointes syndrome. This is thought to occur as a result of blockade of the cardiac delayed potassium rectifier channel as well as impairment in autonomic function.[77,79] Among the antipsychotics, thioridazine is most likely to cause these changes and has been shown to prolong the QTc an average of about 30 msec, which is over 20 msec longer than haloperidol, risperidone, olanzapine, or quetiapine, and 15 msec longer than ziprasidone.[80] Thioridazine's effect on QTc prolongation is dose related, and has led to a boxed warning in the FDA-approved product labeling. A recent comprehensive review was not able to stratify the degree of QTc prolongation of nine different SGAs.[81] Iloperidone, however, is subject to pharmacogenomic metabolism and there may be an increased risk of QTc prolongation in CYP2D6 poor metabolizers.[50] High IV doses of haloperidol elevate the risk for QTc prolongation, resulting in a boxed warning in the FDA-approved labeling.[82] Although the precise point at which QTc prolongation becomes clinically dangerous is unclear, the risk for arrhythmia escalates when the QTc interval exceeds 500 msec, or is 60 msec

above the baseline QTc.[81,82] Accordingly, it has been recommended to discontinue a medication associated with QTc prolongation if the interval consistently exceeds 500 msec. A recent comprehensive review suggests that QTc intervals greater than or equal to 450 msec and/or a 30 msec increase in QTc interval from baseline are predictors of a drug's risk to cause torsades.[81]

While QTc prolongation may predict torsade de pointes, it rarely happens in the absence of other risks factors, including patients greater than 60 years, female gender, those with pre-existing cardiac or cerebrovascular disease (including bradycardia, second- or third-degree AV block, and congenital long QTc syndrome), hepatic impairment, hypokalemia, hypomagnesemia, concomitant medications that prolong the QTc interval, metabolic inhibition by another medication, or pre-existing QTc prolongation.[81,82] For patients over the age of 50 years of age, a pretreatment ECG is recommended, as are baseline serum potassium and magnesium levels.

Myocarditis and Cardiomyopathy Myocarditis is an infrequent and dose independent adverse effect that is most likely to occur with clozapine, but has been reported with quetiapine,[78] and possibly with olanzapine.[83] Eighty-seven percent of clozapine-induced myocarditis cases occur within the first 4 weeks of treatment, but cases as late as 22 weeks have been reported.[77,84] Symptoms of clozapine-induced myocarditis can be nonspecific and include: flu-like symptoms (eg, fever, myalgias), respiratory (eg, dyspnea, cough, orthopnea), and cardiac (persistent tachycardia, chest pain, syncope) symptoms. Myocarditis is considered a life-threatening event and therefore early detection is essential. While the incidence of clozapine-induced myocarditis may be as high as 3%, and the mortality rate upwards of 10% to 30%, there are currently no mandatory monitoring parameters.[84] Recommended laboratory monitoring has been proposed with baseline and weekly monitoring of C-Reactive Protein (CRP) for the first 4 weeks, while troponin (I or T) and B-type natriuretic peptide monitoring has also been suggested. A baseline echocardiogram (ECHO) is recommended and repeated if myocarditis is suspected. Both CRP elevations above 100 mg/L and troponin greater than two times the upper limit of normal have been shown to be highly sensitive in detecting clozapine-induced myocarditis. Clozapine rechallenge after the occurrence of myocarditis is debated, and only a few cases have been reported. The decision to rechallenge should only be made in patients where the clinical value greatly outweighs the potential risk, and only after full resolution of the myocarditis and no signs of permanent cardiac damage. A rechallenge should be conducted in a hospital

where close monitoring can occur, as myocarditis recurrence during rechallenge has been reported.[84]

Cardiomyopathy, a potentially life-threatening adverse effect, can also be seen with clozapine, which typically presents later in the course of treatment than myocarditis, with an average time of onset of 14 months.[84,85] The current incidence of cardiomyopathy is estimated to be 0.02% to 0.1%, but this side effect may be under-reported,[85] as shortness of breath, palpitations, and fatigue are the most frequently reported symptoms. The diagnosis of cardiomyopathy is typically made with an ECHO with a reduction in ejection fraction (EF) being the most consistent finding. For patients with an EF less than 25% (0.25), lower recovery and higher mortality rates have been seen, whereas those with an EF greater than 40% (0.40) typically fully recover.[85] In suspected cases of clozapine-induced cardiomyopathy, clozapine should be discontinued, and a rechallenge is not recommended.[86]

Sudden Cardiac Death The risk of sudden cardiac death (SCD) with use of FGAs and SGAs is reported to be twice that of nonusers, with risk increasing with escalated dose.[77,78] It is estimated that 15 cases of SCD occur per 10,000 years of antipsychotic exposure.[77,78] There is insufficient evidence to confer a greater risk with one class of antipsychotics over another.[77,78] A recent case-crossover study involving over 17,000 patients showed that use of antipsychotics was associated with a 1.53-fold increase in ventricular arrhythmia or SCD. The magnitude of effect was greatest among patients who received antipsychotics for a short term (less than 28 days).[87] Nonetheless, prospectively designed studies are needed to confirm dose-dependency with antipsychotic-associated cardiovascular sudden death, and whether risk is different among antipsychotics.

Lipid Changes Treatment with at least some SGAs and phenothiazines is associated with elevated serum triglycerides and cholesterol. Among the SGAs, olanzapine, clozapine, and quetiapine have the highest risk for dyslipidemia, with elevations in serum triglycerides being the most frequently reported abnormality.[51,61] Increased appetite and subsequent weight increase can negatively affect lipids. Independent of weight gain, antipsychotic effects on apolipoprotein B, lipoprotein oxidation, and elevations in sterol regulatory element binding protein-controlled gene expression are among possible mechanisms by which lipid changes may occur with antipsychotics.[88] As previously discussed, olanzapine is associated with greater and significant adverse effects on metabolic parameters, including lipids, blood glucose, and

body weight as compared with other antipsychotics in the CATIE trial.[23]

The occurrence of weight gain, diabetes, and lipid abnormalities during antipsychotic therapy is consistent with the development of metabolic syndrome, and cohorts of patients with schizophrenia have shown elevated prevalence of metabolic syndrome as compared with general population cohorts. Prevalence rates of metabolic syndrome in US populations treated with antipsychotics range from 28% to 60%, with 40.9% reported in the prospectively designed CATIE trial.[89]

Metabolic syndrome consists of raised triglycerides (greater than or equal to 150 mg/dL [1.70 mmol/L]), low HDL cholesterol (less than or equal to 40 mg/dL [1.03 mmol/L] for males, less than or equal to 50 mg/dL [1.29 mmol/L] for females), elevated fasting glucose (greater than or equal to 100 mg/dL [5.6 mmol/L]), blood pressure elevation (greater than or equal to 130/85 mm Hg), and weight gain (abdominal circumference greater than 102 cm [40 in.] for males, greater than 89 cm [35 in.] in females).[90] A diagnosis of metabolic syndrome can be made in individuals who meet at least three of these criteria. Therefore, these abnormalities dictate an important role for general health screening and monitoring in patients with schizophrenia, and prompt intervention when such abnormalities occur. The propensity of individual antipsychotics to produce metabolic disturbances should be considered in the context of individual patient risk factors at the time of drug selection.

Thromboembolism Compared to the general population, the risk of venous thromboembolism (VTE) is twofold higher in individuals with schizophrenia. Sedentary lifestyle, smoking, and metabolic syndrome are all potential explanations for the higher incidence. Increased rates have also been reported in stuporous catatonia and prolonged physical restraints. Additionally, both FGAs and SGAs have been associated with elevating the risk of VTE. The risk may be highest within the first 30 days of antipsychotic exposure and with high dose antipsychotics. Although the mechanism for increased VTE risk is unknown, increased sedative side effects, metabolic side effects, antipsychotic effect on platelet aggregation, and hyperprolactinemia indirectly increasing venous stasis have been proposed.[91] The QThrombosis® is a validated VTE risk calculator that includes antipsychotics in the risk assessment model.[92] This tool may be helpful in identifying patients at elevated risk for VTE and can easily be implemented in clinic practice.

Anticholinergic Effects Patients receiving antipsychotics or antipsychotics in combination with anticholinergics can experience anticholinergic side effects

(eg, dry mouth, constipation, tachycardia, blurred vision, inhibition or impairment of ejaculation, urinary retention, or impaired memory). These side effects are particularly seen with low-potency FGAs, and in elderly patients who are especially sensitive to these effects. Of the SGAs, clozapine and olanzapine have moderately high rates of causing anticholinergic effects. Constipation, caused by slowed peristaltic movement and decreased intestinal fluid content, should be closely monitored and treated, especially in the elderly. Paralytic ileus and necrotizing enterocolitis can also occur.[77,78]

Central Nervous System

Extrapyramidal System Extrapyramidal symptoms is an umbrella term used to describe antipsychotic-induced movement side effects due to excess dopamine blockade in the nigrostriatal pathway. These symptoms include: dystonia, akathisia, pseudoparkinsonism, and tardive dyskinesia, which are explained in detail below.

Dystonia Dystonia is a state of abnormal tonicity, sometimes described simplistically as a severe "muscle spasm.[93] More accurately, dystonias are prolonged tonic contractions, with a rapid onset, usually within 24 to 96 hours of initiating or increasing the dose of an antipsychotic.[94] Types of dystonic reactions include trismus, glossospasm, tongue protrusion, pharyngeal–laryngeal spasms, blepharospasm, oculogyric crisis, torticollis, and retrocollis, but can occur with any skeletal muscle group. They can be life threatening, as in the case of pharyngeal–laryngeal dystonias, and can contribute significantly to patient medication nonadherence. Dystonic reactions occur primarily with high potency FGAs and are greatly reduced with SGAs. Risk factors for dystonia include younger patients (especially males), the use of high-potency agents, rapid titration and high dosage. The overall incidence from the 1960s to the mid-1970s ranged from 2.3% to 10%, but as higher-potency traditional antipsychotics became more widely used, the rate increased to as high as 64%.

Intramuscular or IV anticholinergics (**Table 84-8**) are the treatment of choice for dystonias, with benzodiazepines being a second-line option.[94] Benztropine 2 mg or diphenhydramine 50 mg can be given IM or IV, whereas diazepam 5 to 10 mg by slow IV push or lorazepam 1 to 2 mg intramuscularly are treatment alternatives. Relief from the dystonia is typically seen within 15 to 20 minutes of an intramuscular injection or within 5 minutes of IV administration. The antipsychotic can be continued, with concomitant short-term use of an oral anticholinergic, which is then subsequently tapered and stopped. In general, prophylactic anticholinergic medications are not recommended routinely.

However, prophylaxis is reasonable when using high-potency FGAs (eg, haloperidol or fluphenazine) in young men and in patients with a history of dystonia.[93] Dystonias can also be minimized by the use of lower initial FGA doses or the use of SGAs. Anticholinergics are good choices for prophylaxis, whereas amantadine has not been proven effective for this purpose.

TABLE 84-8 Agents Used to Treat Extrapyramidal Side Effects

Generic Name	Equivalent Dose (mg)	Daily Dosage Range (mg)
Antimuscarinics		
Benztropine[a]	1	1-8[b]
Biperiden[a]	2	2-8
Trihexyphenidyl	2	2-15
Antihistaminic		
Diphenhydramine[a]	50	50-400
Dopamine Agonist		
Amantadine	NA	100-400
Benzodiazepines		
Lorazepam[a]	NA	1-8
Diazepam	NA	2-20
Clonazepam	NA	2-8
β-Blockers		
Propranolol	NA	20-160

NA, Not applicable.

[a]Injectable dosage form can be given intramuscularly for relief of acute dystonia.

[b]In treatment-refractory cases, dosage can be titrated to 12 mg/day with careful monitoring; nonlinear pharmacokinetics have been reported.

Akathisia Akathisia is defined as the inability to sit still and having functional motor restlessness. The most accurate diagnosis of akathisia is made by combining subjective complaints with objective observations (pacing, shifting, shuffling, or tapping feet). Subjectively, patients may describe a feeling of inner restlessness or disquiet or a compulsion to move or remain in constant motion that provides some relief. Akathisia occurs in 20% to 40% of patients treated with high-potency FGAs[93,95] and is frequently accompanied by dysphoria. In severe cases, akathisia may be mistaken for aggression and if left untreated, akathisia has been linked to causing insomnia, increased suicidality, and

development of tardive dyskinesia.[95]

Akathisia generally appears early in antipsychotic treatment, but can be chronic if not appropriately addressed.[95] Risk of akathisia is greater when the antipsychotic dose is increased rapidly or multiple antipsychotics are used, as well as in antipsychotic naïve individuals.[95] Traditionally, a reduction in antipsychotic dosage has been considered the best intervention; however, this might not be a realistic goal in an acutely psychotic patient. A logical alternative is to switch to an antipsychotic with a lower risk of akathisia, or an antipsychotic previously used in the patient without the adverse effect. Akathisia can occasionally occur with SGAs, particularly aripiprazole or risperidone, and quetiapine and clozapine appear to have the lowest risk of producing akathisia.[95]

Unlike acute dystonias, akathisia responds poorly to anticholinergics;[95] therefore, benzodiazepines have been used for treatment of akathisia, but the high prevalence of co-occurring substance abuse in schizophrenia discourages their use.[95] The β-blockers (eg, propranolol in doses up to 160 mg daily) are effective and have the most evidence.[93,95] Additionally, 5-HT_2 receptor antagonists may be protective against akathisia and may be used for its management. Examples of such agents include mirtazapine, trazodone, and cyproheptadine, with mirtazapine having the most data to support its use.[93,95]

Pseudoparkinsonism Pseudoparkinsonism resembles idiopathic Parkinson's disease with an onset of symptoms typically within 1 to 2 weeks after initiation of antipsychotic therapy or a dose increase. However, for some it may be delayed with 50% to 75% of cases occurring within a month and 90% within 3 months.[93,94] A patient with pseudoparkinsonism can present with any of four cardinal symptoms: (a) akinesia, bradykinesia, or decreased motor activity including difficulty initiating movement, as well as extreme slowness, mask-like facial expression, micrographia, slowed speech, and decreased arm swing; (b) tremor that is predominant at rest and decreases with movement, and known as the pill-rolling type, usually involves the fingers and hands, although tremors can also be seen in the arms, legs, neck, head, and chin; (c) cogwheel rigidity, seen as the patient's limbs yielding in jerky, ratchet-like fashion when passively moved by the examiner; and (d) postural abnormalities and instability manifested as stooped posture, difficulty in maintaining stability when changing body position, and a gait that ranges from slow and shuffling to festinating. Fatigue and weakness can be noted, as well as oral abnormalities including dysphagia, dysarthria, and abnormal palmomental and glabellar reflexes. The overall incidence of FGA-induced pseudoparkinsonism ranges from 15.4% to

36%, depending on the drug and dose, and akinesia alone can be seen in 59% of patients on high-potency FGAs. The risk of pseudoparkinsonism with SGAs is low. A secondary data analysis from the CATIE study did not find marked differences in rates of EPS between perphenazine and SGAs, suggesting that a less potent FGA at modest doses may present a similar risk of pseudoparkinsonism as SGAs.[96] Other risk factors for the development of pseudoparkinsonism include increasing age and possibly female gender.

The efficacy of anticholinergic medications in treating symptoms of pseudoparkinsonism is well established,[93,94] although diphenhydramine produces more sedation than the other agents. Table 84-7 outlines the dosing of these medications. Symptoms typically begin to resolve within 3 to 4 days after initiation of treatment, but a minimum of at least 2 weeks of treatment is normally required for full response. Amantadine may be as efficacious for pseudoparkinsonism as anticholinergics, but with significantly less effect on memory function.[93,94] Prophylactic use of these agents against pseudoparkinsonism is less convincing compared with dystonias, and is unnecessary when using SGAs.[93,94] The long-term treatment of pseudoparkinsonism with antiparkinsonism medication is somewhat controversial. An attempt should be made to taper and discontinue these agents in 6 weeks to 3 months after symptom resolution. If symptoms reappear, then switching to an SGA should be considered. Quetiapine, aripiprazole, brexpiprazole, and clozapine are reasonable alternatives in a patient experiencing EPS with other SGAs.[98]

Tardive Dyskinesia (TD) TD is a syndrome characterized by abnormal involuntary hyperkinetic movements occurring late in onset in relation to initiation of antipsychotic therapy. Occurrence of TD is sometimes irreversible and continues to be a controversial issue.

The classic description of tardive dyskinesia is an insidious onset of oral or orofacial movements often associated with lip smacking or tongue thrusting as the disorder progresses, which can interfere with the patient’s ability to chew, speak, or swallow. Other facial movements include frequent blinking, brow arching, grimacing, and upward deviation of the eyes. Involvement of the extremities sometimes occurs, and may involve any skeletal muscle group. Orofacial movements are more common in older patients, whereas the truncal axial movements are classically reported in young adults. Movements can worsen with stress, decrease with sedation, and disappear during sleep. Concentration on motor tasks or attempts to suppress the movements can

actually increase them.[97]

Early signs of tardive dyskinesia can be reversible but if allowed to persist, can become irreversible, even with drug discontinuation. The exact time point in which TD becomes irreversible is unknown, which underscores the importance of early detection.[94] When the antipsychotic dose is decreased or tapered and discontinued, worsening of abnormal movements may occur, followed by possible slow improvement after months or years if the patient remains on lower doses or discontinues treatment. Younger age correlates with a greater chance of reversing TD.[94] No standardized diagnostic criteria for tardive dyskinesia are available. Abnormal involuntary movements can be detected early through physical assessment and the use of rating scales. Available rating scales include the Abnormal Involuntary Movement Scale (AIMS) and the Dyskinesia Identification System: Condensed User Scale (DISCUS).[98] Neither scale is diagnostic in itself.

One of the greatest risk factors for TD is older age, with patients over 65 having a two-to-five fold higher incidence of TD than younger adults.[99] Other risk factors include history of acute EPS, poor antipsychotic drug response, diagnosis of organic mental disorder, diabetes mellitus, mood disorders, female gender, use of anticholinergics, current and cumulative antipsychotic doses, and duration of antipsychotic exposure.[97] Additionally, genetic variation within CYP2D6, vesicular monoamine transporter-2 (VMAT2) gene, and Dopamine D2 receptor (D2) gene have been suggested as being associated with increased risk.[100] A systematic review of 12 studies lasting 1 year or more found the overall risk of TD with SGAs to be approximately 2.9% per year in nonelderly adults as compared with 7.7% for FGAs.[101] These results were confirmed with a recent meta-analysis which indicated that olanzapine and aripiprazole may have a small advantage over non-clozapine SGAs.[102] Tardive dyskinesia is not always permanent, with spontaneous remission of symptoms observed in 25% of patients after 5 years of continued treatment;[21] however, overall morbidity and mortality are greater in tardive dyskinesia patients.

Prevention of TD is important, as treatment of the movements once they occur is difficult. One of the more compelling arguments for the first-line use of SGAs is their lower risk of TD.[21] Therefore, regular neurologic examinations (AIMS or other scales) should be performed at baseline, and American Psychiatric Association guidelines recommend TD monitoring every 6 months for FGAs and annually for SGAs.[97] Patients that are higher risk, such as the elderly, should have more frequent assessments. At the first sign of tardive

dyskinesia, the need for continuing antipsychotic treatment should be assessed, and if the patient is taking an FGA and continuing treatment is indicated, the medication should be switched to an SGA.

In 2017, the VMAT2 inhibitors deutetrabenazine and valbenazine were the first medications to receive FDA approval for the treatment of TD. Both are considered first-line interventions, as they produced clinically significant decreases in AIMS scores in both short- and long-term trials.[103] However, when valbenazine treatment is discontinued, TD symptoms can rapidly return toward pretreatment levels within 4 weeks after discontinuation.[104]

Deutetrabenzine should be initiated at 6 mg twice daily with food, with weekly dose increases of 6 mg up to a maximum dose of 48 mg per day. It is primarily metabolized via CYP2D6 and a maximum daily dose of 36 mg is recommended with concomitant strong CYP2D6 inhibitors or in CYP2D6 poor metabolizers.[103] It is contraindicated in individuals with severe hepatic impairment or those taking a monoamine oxidase inhibitor. The labeling contains warnings about use in patients with untreated depression, suicidality, or at risk for QTc prolongation. Valbenazine is initiated at 40 mg once daily and increased to 80 mg after 1 week. This medication is not recommended for use in combination with strong CYP3A4 inducers, and a maximum daily dose of 40 mg is recommended when used with CYP3A4 strong inhibitors. Both deutetrabenzine and valbenazine labeling includes warnings about suicidality, depression, and QTc prolongation.[103,104]

Numerous other drugs have been used in an attempt to treat tardive dyskinesia. In two controlled trials lasting 22 to 52 weeks, clozapine decreased abnormal involuntary movements.[21] Switching antipsychotic therapy to clozapine has been recommended as a treatment for moderate-to-severe TD.[19–22] A 2013 guideline developed by the American Academy of Neurology (AAN) recommended short-term treatment of TD with either clonazepam (up to 4.5 mg daily) or ginkgo biloba extract 240 mg daily based upon randomized clinical trial data. However, long-term treatment data are lacking.[105] The AAN guideline was developed before the availability of the two VMAT2 inhibitors. However, in patients who do not have access to these agents, or cannot tolerate or fail with their use, clonazepam or ginkgo biloba can be considered.

Seizures An increased risk of drug-induced seizures can occur in patients receiving antipsychotics as these agents decrease the seizure threshold. However, this risk is greater if the following predisposing factors are present: pre-existing seizure disorder, history of drug-induced seizure, abnormal

electroencephalogram (EEG), and pre-existing CNS pathology or head trauma. Seizures are more closely associated with high plasma concentrations, rapid dosage titration, and treatment initiation. The exact mechanism is unknown, but involvement of D_2 and D_s receptors has been proposed.[78] When an isolated seizure occurs, a dosage reduction in the antipsychotic is first recommended, and routine prophylactic use of anticonvulsant therapy is not recommended. Although spontaneously occurring seizures have been reported with most antipsychotics, the highest potential risk for an antipsychotic-related seizure is with clozapine or chlorpromazine. If a change in antipsychotic therapy is required because of a drug-induced seizure, aripiprazole, risperidone, thioridazine, haloperidol, pimozide, trifluoperazine, and fluphenazine are associated with the lowest potential.[78]

Thermoregulation Poikilothermia, the body temperature adjusting to the ambient temperature, can be a serious side effect of antipsychotic therapy in temperature extremes.[106] Hyperpyrexia can be a danger in hot weather or during exercise. Additionally, inhibition of sweating, a result of anticholinergic properties impairing the peripheral mechanisms of heat dissipation can contribute to this problem, which in its severest form can lead to heat stroke. Hypothermia is a risk in cold temperatures, particularly in the elderly. All patients receiving antipsychotics should be educated about these potential problems. Thermoregulatory problems are reportedly more common with the use of low-potency FGAs, but can occur with the more anticholinergic SGAs.

Neuroleptic Malignant Syndrome Neuroleptic malignant syndrome (NMS) occurs in <1% of patients and is reported with both FGAs and SGAs, with the highest incidence occurring with high-potency FGAs.[78] High antipsychotic doses, rapid parenteral administration, use of multiple antipsychotics, previous history of NMS, dehydration, physical restraints, and older age all increase the risk of NMS.[78] Symptoms are most likely to occur within the first week of antipsychotic initiation and develop rapidly over the course of 24 to 72 hours. The mortality rates associated with NMS are high at approximately 10%, with premorbid dehydration elevating the risk of mortality.

Possible mechanisms of NMS include disruption of the central thermoregulatory processes or excess production of heat secondary to skeletal muscle contractions, including the involvement of proinflammatory cytokines. Regardless of the mechanism, the differential diagnoses for NMS includes: heat stroke, lethal catatonia, malignant hyperthermia, anticholinergic toxicity, and serotonin toxicity. The cardinal signs and symptoms of NMS are body

temperature exceeding 38°C (100.4°F) on at least two occasions, mental status changes, autonomic instability (tachycardia, blood pressure, diaphoresis, tachypnea, or urinary or fecal incontinence), and rigidity.[107] Laboratory evaluation, although nonspecific, frequently shows leukocytosis with or without a left shift, and increases in creatine kinase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and myoglobinuria.[106,107] Importantly, NMS treatment should begin with antipsychotic discontinuation and supportive care (eg, IV fluid hydration and benzodiazepines). Dantrolene, bromocriptine, or amantadine may be useful in severe cases as all three agents have reports of reduced time to clinical improvement and reduction in mortality rates.[106]

Many patients with schizophrenia, despite having had NMS, will require future antipsychotic pharmacotherapy. The literature on antipsychotic rechallenge suggests that the risk of rechallenge is acceptable in most patients, provided that the patient is observed for an extended period of time (2 weeks or more is suggested) without antipsychotics, that there is careful monitoring, slow dose titration, and that the patient is maintained on the lowest possible dose.[106,107] A different antipsychotic, an SGA or a low-potency FGA, should be used for rechallenge following an episode of NMS.

Psychiatric Side Effects Aripiprazole has been associated with impulse control disorders, including pathological gambling, uncontrolled sexual urges, uncontrolled spending, binge or compulsive eating and other intense urges. This led to a FDA safety announcement in 2016 and subsequent update to the warnings in the package labeling for all aripiprazole products.[108] Mechanistically the D_2 partial agonist activity and possible D_3 receptor activity seen with aripiprazole have been implicated as potential pathways for this adverse event.[108] Clinicians are encouraged to monitor for changes in impulse control behaviors and reduce the dose or stop aripiprazole should urges develop or worsen.

Ophthalmologic Effects Anticholinergic effects of antipsychotics or concomitant antiparkinson medications can exacerbate narrow-angle (angle-closure) glaucoma. Therefore, antipsychotics with low anticholinergic effects should be used in such individuals, and they should be appropriately monitored.[109]

Opaque deposits in the cornea and lens can occur with chronic phenothiazine treatment, with this adverse event occurring most frequently with chlorpromazine. Although visual acuity is not usually affected, periodic

ophthalmologic examinations are frequently recommended in patients receiving long-term treatment with phenothiazines, as fully formed cataracts are possible.[109]

Because of cataract development and lenticular changes in animals, baseline and periodic eye examinations are recommended in quetiapine's product labeling. However, quetiapine's effects on lens opacity was found to be no different than risperidone in a 2-year comparative trial.[110] Lastly, retinitis pigmentosa can result from use of thioridazine doses greater than 800 mg daily, due to melanin deposits that can result in permanent visual impairment or blindness.

Genitourinary System Urinary hesitancy and retention, secondary to antipsychotic anticholinergic effects are reported with low-potency FGAs and with clozapine; men with benign prostatic hypertrophy are especially prone to this effect.[78] Reducing the antipsychotic dose or switching to an antipsychotic with less anticholinergic activity may help manage this side effects. Alternatively, bethanecol can be used to treat antipsychotic-induced urinary hesitancy and retention.

Urinary incontinence is thought to be caused by α-blockade, and among the SGAs, it appears to be particularly problematic with clozapine.[78] The incidence has been reported to be as high as 44%, and it can be persistent in 25% of patients. Female gender and previous urinary incontinence can be risk factors for developing this side effect.[78]

Although inadequately studied, multiple mechanisms are likely responsible for sexual dysfunction seen with antipsychotic use, including dopaminergic blockade, hyperprolactinemia, histaminergic blockade, anticholinergic effects, and α-adrenergic blockade. However, unmedicated individuals with schizophrenia also report decreased libido. Most, but not all, studies show a relationship between hyperprolactinemia and sexual dysfunction, including decreased libido, erectile dysfunction, difficulty achieving orgasm, and ejaculatory abnormalities. Risperidone and paliperidone produce at least as much sexual dysfunction as FGAs, while other SGAs, with weak effects on prolactin, produce less sexual dysfunction. Patients experiencing sexual dysfunction with FGAs or risperidone or paliperidone should be switched to an SGA with less effect on prolactin.[111]

Priapism, a sustained and painful erection that is unprovoked and persists for longer than an hour, is increasingly reported with antipsychotic medication use. This is believed to occur as a result of α_1-adrenergic receptor blockade, leading

to intracavernosal blood stasis.[112] This can evolve into a urologic emergency, due to the ischemic nature of the priapism, and as such patients experiencing this adverse event require emergency treatment. If left untreated, priapism may lead to permanent impotence.

Hematologic System Transient leukopenia can occur during initial treatment with antipsychotics; however, it typically does not progress to be clinically significant.[113] Agranulocytosis reportedly occurs in 0.01% of patients receiving FGAs, and more frequently with chlorpromazine and thioridazine. The three antipsychotics with the highest relative risk for neutropenia in rank order are clozapine, chlorpromazine, and olanzapine.[113] The onset is usually within the first 8 weeks of therapy. If the absolute neutrophil count (ANC) is less than 500/μL (0.5×10^9/L) the antipsychotic should be discontinued and the ANC monitored closely until it returns to normal and the patient monitored for the development of secondary infections. Agranulocytosis can initially manifest as a local infection, with sore throat, leukoplakia, erythema, and ulcerations of the pharynx. These symptoms in any patient receiving antipsychotics should signal the immediate need for an ANC. Additionally, isolated rare cases of thrombocytopenia and eosinophilia have been reported.

Agranulocytosis with clozapine has significantly inhibited use of this agent, and it is only available through the Clozapine REMS Program.[114] The risk of developing neutropenia or agranulocytosis with clozapine is approximately 3% and 0.8%, respectively,[112] and most cases occur between 6 weeks and 6 months. The baseline ANC must be at least 1,500/μL (1.5×10^9/L) in order to start clozapine, and weekly ANC monitoring for the first 6 months of therapy is mandated in the FDA-approved product labeling. After this time, if the patient's ANC remains greater than 1,500/μL (1.5×10^9/L) the labeling allows ANC monitoring to be decreased to every 2 weeks for the next 6 months. After this, monitoring can be decreased to monthly if all ANCs remain greater than 1,500/μL (1.5×10^9/L). If at any time the ANC drops to less than 500/μL (0.5×10^9/L), clozapine must be discontinued and the ANC monitored daily until it is greater than 1,500/μL (1.5×10^9/L). The FDA-approved product labeling should be consulted for more detailed information regarding ANC monitoring, including monitoring for mild and moderate leukopenia and recommendations for patients with benign ethnic neutropenia.[114]

Dermatologic System Allergic reactions are rare and usually occur within 8 weeks of initiating therapy, manifesting as maculopapular, erythematous, pruritic

rashes that are evident on the face, neck, trunk, or extremities. Contact dermatitis, including the oral mucosa, has been reported in patients and medical personnel exposed to FGA liquid formulations. The risk of oral mucosal reactions can be decreased by mixing the FGA concentrate in a sufficient quantity of a nonacidic liquid and swallowing it quickly. Care should be taken in the handling and preparation of liquid FGAs. Recently, the FDA added a warning for ziprasidone to its labeling regarding the risk for a rare but fatal skin reaction called *Drug Reaction with Eosinophilia and Systemic Symptoms* (DRESS).[115]

Phenothiazines can absorb ultraviolet light, resulting in the formation of free radicals, which can have damaging effects on the skin. All antipsychotics can cause photosensitivity resulting in erythema and sunburn; therefore, exposure to sunlight should be limited, and patients should be educated about the use of a maximally blocking sunscreen, hats, protective clothing, and sunglasses.[113]

Blue-gray or purplish skin coloration in areas exposed to sunlight occurs in patients receiving higher doses of low-potency phenothiazines during long-term administration, especially with chlorpromazine. This adverse event commonly occurs with concurrent corneal or lens pigmentation.

Miscellaneous Adverse Effects A sometimes troubling side effect with clozapine is sialorrhea (drooling), which is typically prominent at night,[113] and affects up to 54% of patients receiving clozapine. The mechanism behind this drooling is unclear; however, two theories exist. The first involves muscarinic receptor activity and clozapine's imbalanced binding affinity to this receptor. The other involves clozapine's alpha antagonist activity at the salivary glands leaving unopposed beta-receptor stimulation and hence hyper-salivation.[113] Anticholinergics such as benztropine and atropine, and α-agonists such as clonidine have been used to treat clozapine-related sialorrhea.[118]

Use in Pregnancy and Lactation

The reproductive health of women with schizophrenia has historically received little attention from clinicians or researchers, partly due to reports of lower fertility rates in women with schizophrenia. However, with the introduction of more prolactin sparing SGAs (exceptions being risperidone and paliperidone), fertility rates in women with schizophrenia are increasing.[116] While data on the safety of antipsychotic medication use during pregnancy and lactation are limited, it is known that greater than 50% of women with schizophrenia who discontinue their medication will experience relapse.[117] Additionally, pregnant

women with untreated schizophrenia are more likely to use alcohol, tobacco and illicit substances and are less likely to engage in prenatal care visits.[118] Therefore, these factors may put women and their offspring at greater risk, outweighing any potential risks associated with antipsychotics use.

Differentiating between the effects of medications in pregnancy and effects of illness itself presents a challenge. Although the risk of teratogenesis with FGAs has not been sufficiently studied, a specific pattern of teratogenicity has not been found.[118] Haloperidol is the best studied FGA with approximately 400 reported exposures.[118] With regard to labor and delivery complications, one small study found a greater than twofold elevated risk of preterm birth in women with schizophrenia taking FGAs as compared with mothers not taking antipsychotics, but did not find an association between FGA exposure and low birth weight or small for gestational age.[119] A major limitation in interpreting this study are the confounding variables such as disease severity, concurrent substance use or other concurrent medications that were not addressed.

Data regarding the safety of SGAs in pregnancy are rapidly increasing but also limited. All SGAs cross the blood-placenta barrier, but to varying degrees. In one study sample, the highest rates of transfer were for olanzapine (72.1%), followed by haloperidol (65.5%) and risperidone (49.2%), with quetiapine being the lowest (24.1%).[117,118] Among the SGAs, safety data are most abundant for olanzapine, quetiapine, and risperidone. Results from the largest database study to date (9,258 pregnant women with SGA exposure in the first trimester) suggest that the SGAs aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone collectively do not increase the risk of congenital malformations or cardiac malformation. This finding held true when evaluating each agent individually, with the exception of a small, but statistically significant increase of congenital (3% vs 5%) and cardiac malformations (1% vs 2%) with risperidone.[120] A meta-analysis of 12 studies (which did not include the previous study) found a greater risk of congenital malformations with SGA exposure in early pregnancy, but no specific abnormality was identified. In this same study, an increased risk of preterm birth was present in the SGA-treated group. However, healthy women composed the control group in these studies, and the underlying disease state being treated with an SGA is an important confounder.[121] Data on pregnancy exposure with the newer SGAs (eg, asenapine, lurasidone, brexpiprazole, and cariprazine) are minimal or absent. While large, well-controlled studies are still needed to determine the safety of all SGAs during pregnancy, the most recent British Association for Psychopharmacology Consensus Guidelines do not currently consider them major teratogens.[118]

The potential for antipsychotic related postnatal and gestational complications are of interest. Weight gain associated with SGAs and the potential risk of gestational diabetes should be considered in drug selection. A recent retrospective cohort study reported an increased risk of gestational patiediabetes in individuals who continued quetiapine or olanzapine during the first 20 weeks of pregnancy versus those who discontinued those agents.[122] An increase risk was not observed for risperidone, aripiprazole, or ziprasidone. However, other population-based studies have not found an increased risk of gestational diabetes with SGAs when controlling for lifestyle and patient-specific confounders.[118] An increased risk of hypertension in women taking antipsychotics during pregnancy as well as venous thromboembolism have also been reported.[116]

Risk of neonatal EPS is increased with in utero exposure to FGAs, with effects in the infant lasting for 3 to 12 months after birth. In 2011, the FDA issued a safety announcement informing healthcare professionals that the pregnancy section of drug labels had been updated for the entire antipsychotic class, highlighting the potential risk for EPS and withdrawal symptoms in newborns whose mothers were treated with antipsychotics during their third trimester.[123] Symptoms of neonatal withdrawal reported to the FDA included agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder.

For many women with schizophrenia, discontinuing the antipsychotic during pregnancy may not be recommended, despite the lack of safety data. The risk of antipsychotic use must be weighed against the benefits of pharmacotherapy in pregnant women experiencing disorganized thoughts, delusions about change in body image or pregnancy, or who are unable to engage in prenatal care.[119] A national pregnancy exposure registry monitors pregnancy outcomes in women exposed to SGAs during pregnancy. Clinicians are encouraged to report SGA use in pregnancy through the registry to assist in gathering safety information. This registry can be accessed at: http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/atypicalantipsychotic. Additionally, a registry supported by the Canadian government may also provide some information regarding the use of antipsychotics in pregnancy (http://motherisk.org/).

Data regarding the use of antipsychotics during breastfeeding are even more limited than their use during pregnancy. Olanzapine is the most studied antipsychotic in breastfeeding (n = 170 exposures), followed by quetiapine (n = 14), risperidone (n = 8), and aripiprazole (n = 4). Overall, olanzapine and quetiapine have reported relative infant doses (RIDs) of less than 4%, meaning

that with continued breastfeeding, infants would only be exposed to 4% of their mothers overall dosage.[124] Risperidone (+ 9-OH-risperidone) and aripiprazole have reports of a slightly higher RID ranges (2.8-9.1 and 0.7-8.3, respectively).[124] Of note, treatment with aripiprazole may lead to reduced milk production as a result of reduced prolactin release.[125] Breast feeding while on clozapine is not recommended due to the risk of severe neutropenia and seizures in the infant.[118] For all of the FGAs, the overall RID is thought to be less than 10%, which is a common threshold indicating that these medications are safe for use in breastfeeding.

Data evaluating long-term outcomes in infants exposed to antipsychotics during breastfeeding is minimal to absent. The co-administration of chlorpromazine and haloperidol is reported to result in developmental delays at 12 to 18 months of age; however, these were not controlled studies.[118] Although most antipsychotics are not contraindicated in breastfeeding, the lowest dosage for antipsychotics should be used in the mother, and the infant carefully monitored for antipsychotic adverse events such as EPS, sedation, seizures, and developmental delays.[118,124,125] Additional studies evaluating short- and long-term side effects, including developmental outcomes, of infants exposed to antipsychotics via breast milk are warranted.

Drug Interactions

Most drug interactions occur because of pharmacodynamic or pharmacokinetic interactions. Common examples of pharmacodynamic interactions resulting in enhanced effect include the excess sedation that can occur when antipsychotics are used concomitantly with other medications that have sedative side effects. Additive antimuscarinic effects can also be seen when antipsychotics are used with other medications possessing antimuscarinic effects, potentially resulting in urinary retention, constipation, blurred vision, or other anticholinergic side effects.[126] Both combined sedative and anticholinergic effects from multiple medications can result in impaired cognition or delirium, particularly in the elderly and other patients predisposed to such problems.[126] Patients are more likely to experience symptomatic orthostatic hypotension when an antipsychotic is used with other medications that cause orthostasis. Metoclopramide, a DA antagonist, is prescribed for treating esophageal reflux or gastroparesis, and patients may be more likely to experience akathisia and other EPS (including TD) if it is used concomitantly with antipsychotics.[127] Although some selective serotonin reuptake inhibitors (SSRIs) can interact with antipsychotics through

enzyme inhibition, they can also interact through pharmacodynamic mechanisms. Since 5-HT_2 receptors are present on the presynaptic dopaminergic neuron, their activation leads to decreased DA release from the presynaptic terminal. Increased availability of 5-HT through the SSRI's effect can activate these receptors, which in turn results in decreased DA release, and adds to the dopaminolytic effects of antipsychotics.[47] In the absence of enzyme inhibition, SSRIs can still precipitate akathisia or EPS when added to a patient stabilized on an antipsychotic. There have also been several cases of serotonin syndrome reported with SGAs used in combination with serotonergic agents, such as SSRIs or tramadol.[47] Another potentially dangerous interaction can occur when medications that slow myocardial conduction, and thus prolong the QTc interval, are used in combination with antipsychotics having the same effect.[47] Careful monitoring should occur with medications that prolong the QTc interval, as well as when antipsychotics with this effect are combined with diuretics.[47]

Food enhances the absorption of both ziprasidone and lurasidone, with the product labels noting a greater than twofold increase in bioavailability when the agents are given with food. Therefore, ziprasidone requires administration with a 500 kcal meal and lurasidone with 350 kcals, as the blood levels obtained when administered with food are not obtainable by simply increasing the dose. The exact mechanism for the impact of food on absorption is not fully understood[61,128] Asenapine, on the other hand, requires that food and drink be avoided for at least 10 minutes after administration to reduce the chance of the patient swallowing the medication instead of allowing for sublingual absorption, which as previously discussed, impacts bioavailability.[51,56]

Asenapine inhibits CYP2D6, and is the only SGA that has been shown to significantly affect the pharmacokinetics of other medications.[51] Table 84-6 lists the known major pathways involved in the metabolism of SGAs. Risperidone is largely metabolized by CYP2D6 to its active metabolite, 9-OH-risperidone (paliperidone), which is thought to have a similar pharmacodynamic profile.[47] Although paliperidone is primarily eliminated renally unchanged, potent inducers of CYP3A4 can cause a potential need for dosage adjustment.[47,56] For asenapine, CYP1A2 is the primary isoenzyme responsible for metabolism with CYP3A4 also being a significant pathway.[47,56]

Based on current information, inhibitors of CYP1A2 have the greatest potential for causing interactions with clozapine and olanzapine, and some concern with asenapine.[47] Examples include cimetidine, fluvoxamine, and fluoroquinolone antibiotics (ie, ciprofloxacin) to varying degrees. To date,

however, no serious inhibition interactions have been reported with olanzapine, which may be a result of olanzapine's wide therapeutic index; however, carbamazepine has been reported to increase olanzapine elimination by as much as 50%.[47] Cigarette smoking is a potent inducer of CYP1A2, and one would expect lower mean olanzapine serum concentrations in smokers compared with those in nonsmokers.

Because of the risk of seizures with higher clozapine tissue concentrations, interactions that inhibit clozapine's metabolism are potentially significant. In particular, fluvoxamine increases clozapine serum concentrations by an average of two- to threefold and up to fivefold.[47] Ciprofloxacin, other fluroquinolones, fluoxetine, and erythromycin can also increase clozapine serum concentrations.[47] As smoking has been associated with a 33% to 55% increase in clozapine clearance,[47] smoking cessation can result in increased clozapine serum concentration that may increase the risk of seizures.[56] Carbamazepine can also induce clozapine metabolism and lead to lower serum concentrations.[47]

A study with the potent CYP3A4 inhibitor ketoconazole showed minimal effects on ziprasidone single-dose pharmacokinetics, with only a 33% mean increase in the ziprasidone area under the time-versus-concentration curve.[47] These results are consistent with data suggesting that aldehyde oxidase is the major metabolic pathway for ziprasidone, with only 30% to 35% being metabolized by CYP3A4.[47]

Modest elevations of aripiprazole serum concentration occur in the presence of ketoconazole or quinidine, which inhibit CYP3A4 and 2D6, respectively. Ketoconazole has a profound effect on decreasing lurasidone metabolism, and it is recommended that they not be used concomitantly.[61,47] Carbamazepine has been reported to decrease aripiprazole serum concentrations.[47]

Since iloperidone is metabolized through CYP2D6 and 3A4, its clearance can be impaired by inhibitors of these pathways. Since iloperidone prolongs the QTc interval, these types of interactions have the potential to be clinically significant. For example, it is recommended that the iloperidone dose be decreased by 50% when used with CYP2D6 inhibitors such as fluoxetine or paroxetine (**Table 84-9**).[47,50]

TABLE 84-9 Common Potential Drug Interactions with Antipsychotic Medications

Mechanism of Interaction	Examples of Interacting Drugs or Other Substances			Clinical Effect
Pharmacodynamic Drug Interactions with Antipsychotics				
Muscarinic receptor blockade	*Anticholinergics* Benztropine Diphenhydramine Trihexyphenidyl			↑ Anticholinergic SE (Blurred vision, constipation, impaired cognition, and urinary retention)
Additive or synergistic sedation	*Sedatives* Benzodiazepines Concomitant AP Diphenhydramine Melatonin and melatonin agonists Mirtazapine Trazodone TCAs Hypnotics Opiates	*Anticholinergics* Benztropine Diphenhydramine Trihexyphenidyl Mirtazapine		↑ sedation Lethargy Impaired cognition Impaired psychomotor activity ↑ Risk of accidents
DA antagonist use for different indication	Metoclopramide			↑ EPS
Cardiovascular interactions				
QTc prolongation	Amitriptyline Clomipramine Imipramine Citalopram Fluorquinolone antibiotics	Procainamide Quinidine		↑ Risk of ECG changes and dysrhythmias
Electrolyte changes	Diuretics			↑ Risk of ECG changes and dysrhythmias
Stimulation of presynaptic 5-HT receptors on DA neuron	SSRIs			↑ EPS
Sympatholytics: α-blockade-↓ NE release	Clonidine Methyldopa Prazosin Nitric oxide containing products			↑ Hypotension
↑ DA receptor binding	Antipsychotics			↑ SEs, particularly EPS
Pharmacokinetic Drug Interactions with Antipsychotics				
Substrate Antipsychotic and Mechanism of Action	**Inhibitor or Inducer**			**Clinical Effect**
Aripiprazole, Brexipiprazole, Cariprazine, and Iloperidone				
Inhibition of AP metabolism (CYP2D6, CYP3A4)	*Antidepressants* Bupropion Clomipramine Doxepin Duloxetine Fluoxetine Fluvoxamine Paroxetine Sertraline *HIV protease inhibitors* Indinavir Nelfinavir Ritonavir	*Anti-infectives* Ciprofloxacin Clarithromycin Erythromycin Fluconazole Ketoconazole Itraconazole *Antipsychotics* Asenapine Chlorpromazine Haloperidol Perphenazine Thioridazine	*Miscellaneous* Ciprofloxacin Chlorpheniramine Cimetidine Cocaine Diltiazem Diphenhydramine Cimetidine Grapefruit juice Haloperidol Hydroxyzine Methadone Quinidine Ticlopidine Verapamil	↑ AP effect ↑ SE
Induction of AP metabolism	*Antiepileptics* Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	*Anti-infectives* Rifampin *Miscellaneous* Glucocorticoids Modafinil	*Herbals* St. John's wort	↓ AP effect
Asenapine				
Eating food or drinking liquids within 10 minutes of asenapine sublingual administration will decrease bioavailability				
Inhibition of AP metabolism (CYP1A2)	*Antidepressants* Fluvoxamine	*Anti-infectives* Ciprofloxacin Fluroquinolones	*Miscellaneous* Amidarone Cimetidine	↑ AP effect ↑ SE

Pharmacokinetic Drug Interactions with Antipsychotics

Substrate Antipsychotic and Mechanism of Action	Inhibitor or Inducer			Clinical Effect
Induction of AP metabolism	*Anti-infectives* Nafcillin	*Miscellaneous* Broccoli Brussels sprouts Chargrilled meat Smoking tobacco	*Miscellaneous* Insulin Modafinil Omeprazole	↓ AP effect
Brexpiprazole (see Aripiprazole above) and *Clozapine*				
Inhibition of AP metabolism (CYP3A4, CYP1A2, CYP2C19)	*Antidepressants* Fluoxetine Fluvoxamine *HIV protease inhibitors* Indinavir Nelfinavir Ritonavir *Anticonvulsants* Felbamate Oxcarbazepine	*Anti-infectives* Ciprofloxacin Clarithromycin Erythromycin Fluconazole Fluroquinolones Ketoconazole Itraconazole Nafcillin	*Miscellaneous* Amidarone Diltiazem Cimetidine Grapefruit juice Haloperidol Modafinil Omeprazole Ticlopidine Topiramate Verapamil Cimetidine	↑ AP effect ↑ SE
Induction of AP metabolism	*Antiepileptics* Carbamazepine Phenobarbital Phenytoin	*Anti-infectives* Rifampin *Miscellaneous* Glucocorticoids Insulin Modafinil Omeprazole Smoking tobacco	*Herbals* St. John's wort	↓ AP effect
Haloperidol				
Inhibition of AP metabolism (CYP2D6, CYP3A4, CYP1A2)	*Antidepressants* Bupropion Doxepin Duloxetine Fluoxetine Fluvoxamine Paroxetine Sertraline *HIV protease inhibitors* Indinavir Nelfinavir Ritonavir Sequinavir	*Anti-infectives* Ciprofloxacin Clarithromycin Erythromycin Fluoconazole Fluoroquinolones Ketoconazole Itraconazole *Antipsychotics* Chlorpromazine Perphenazine	*Miscellaneous* Amiodarone Chlorpheniramine Cimetidine Diltiazem Diphenhydramine Quinidine Diphenhydramine Cimetidine Grapefruit juice Hydroxyzine Methadone Quinidine Verapamil	↑ AP effect ↑ SE
Induction of AP metabolism	*Anticonvulsants* Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	*Anti-infectives* Nafcillin Rifampin *Miscellaneous* Broccoli Brussels sprouts Chargrilled meat Glucocorticoids Insulin Modafinil Omeprazole Modafinil	*Herbals* St. John's wort Tobacco smoking	↓ AP effect
Iloperidone (see Aripiprazole above)				
Olanzapine				
Inhibition of AP metabolism (CYP3A4 and CYP1A2)	*Antidepressants* Fluoxetine (norfluoxetine) Fluvoxamine *HIV protease inhibitors* Indinavir Nelfinavir Ritonavir	*Anti-infectives* Ciprofloxacin Clarithromycin Erythromycin Fluoconazole Fluoroquinolones Ketoconazole Itraconazole	*Miscellaneous* Amiodarone Cimetidine Diltiazem Cimetidine Grapefruit juice Verapamil	↑ AP effect ↑ SE

Pharmacokinetic Drug Interactions with Antipsychotics

Substrate Antipsychotic and Mechanism of Action	Inhibitor or Inducer			Clinical Effect
Induction of AP metabolism	*Antiepileptics* Carbamazepine Oxcarbazepine Phenobarbital Phenytoin *HIV protease inhibitors* Efavirenz Nevirapine	*Anti-infectives* Nafcillin Rifampin *Miscellaneous* Broccoli Brussels sprouts Chargrilled meat Glucocorticoids Insulin Modafinil Omeprazole	*Herbals* St. John's wort Smoking tobacco	↓ AP effect
Paliperidone				
The bioavailability of paliperidone is significantly increased when it is taken with food. Although this could increase paliperidone effect, including adverse effects, the clinical significance is undetermined. Only potent CYP3A4 (eg, carbamazepine, rifampin, St. John's wort) inducers appear to increase paliperidone metabolism and affect dose requirements				
Lurasidone and Quetiapine				
Inhibition of AP metabolism (CYP3A4)	*Antidepressants* Fluoxetine (norfluoxetine) Fluvoxamine Nefazodone *HIV protease inhibitors* Indinavir Nelfinavir Ritonavir Sequinavir	*Anti-infectives* Ciprofloxacin Clarithromycin Erythromycin Fluoconazole Ketoconazole Itraconazole	*Miscellaneous* Amiodarone Cimetidine Diltiazem Grapefruit juice Verapamil	↑ AP effect ↑ SE
Induction of AP metabolism	*Antiepileptics* Carbamazepine Oxcarbazepine Phenobarbital Phenytoin *HIV protease inhibitors* Efavirenz Nevirapine	*Anti-infectives* Rifampin *Miscellaneous* Glucocorticoids Modafinil	*Herbals* St. John's wort	↓ AP effect
Lurasidone AUC and C_{max} increase by two- and threefold when given with at least 350 calories (1460 J) of food regardless of fat content				
Perphenazine and Risperidone				
Note: Because risperidone's metabolite formed through CYP2D6 metabolism is active (paliperidone), the clinical significance of metabolic drug interactions with risperidone is unclear				
Inhibition of AP metabolism (CYP2D6)	*Antidepressants* Bupropion Clomipramine Doxepin Duloxetine Fluoxetine Paroxetine Sertraline *Antipsychotics* Chlorpromazine Haloperidol (reduced haloperidol) Perphenazine	*Miscellaneous* Amiodarone Cimetidine Chlorpheniramine Cocaine Diphenhydramine Cimetidine Haloperidol Hydroxyzine Methadone Quinidine		↑ AP effect ↑ SE
Induction of AP metabolism (via CYP3A34, a minor pathway for risperidone)	Dexamethasone Rifampin			↓ AP effect
Ziprasidone				
The bioavailability of ziprasidone is increased twofold when it is taken with food. Consistent administration with food is recommended				

AP, antipsychotic; AUC, area under the curve; Cmax, maximum plasma concentration; DA, dopamine; EPS, extrapyramidal symptoms; 5-HT, serotonin; NE, norepinephrine; SE, side effect; SSRI, serotonin selective reuptake inhibitor; TCAs, tricyclic antidepressants.

Data from References 21, 25, 34, 37, 38, 47, 48, 50-56, 61, 114, 126-129.

Personalized Pharmacotherapy

Pharmacotherapy must be individualized for each person with schizophrenia. With the possible exception of iloperidone, no laboratory tests are generally available that will predict a patient's response to treatment. Past response to treatment, potential adverse effects, patient personal preference, and medication price are the primary variables that should be used in selecting an antipsychotic that is included in stages 1A, 1B, or 2 of the treatment algorithm. In the CATIE study, the number one reason for drug discontinuation was the patient not wanting to take that medication any more, and the second most common reason was adverse effects.[23] These two factors should be carefully considered in antipsychotic selection and medication dosage must be individualized within the usual dose ranges. Careful consideration must also be given to concomitant medications that may interact with the antipsychotic and necessitate a change in dosage.

Preliminary data suggest a relationship between different genetic markers and clinical improvement as well as QTc prolongation in patients treated with iloperidone.[50,54] Substantial interest exists regarding the potential utility of pharmacogenetic monitoring in the pharmacotherapy of schizophrenia. Increasing relationships are being identified between specific genetic variation in relation to both the pharmacodynamics and pharmacokinetics of different antipsychotics. However, no convincing data have demonstrated that clinical outcomes are superior when using routine pharmacogenetic monitoring in the pharmacotherapy of schizophrenia, nor have cost-effectiveness studies of its use been performed.[54,55] Although promising for the future, routine pharmacogenetic monitoring in all patients with schizophrenia is not currently recommended. However, it may be useful in select patients. For example, if a patient appears particularly sensitive to developing extrapyramidal side effects when treated with antipsychotics metabolized through CYP2D6, it might be useful to perform pharmacogenetic testing to determine whether the patient is a poor CYP2D6 metabolizer. If so, antipsychotics metabolized through CYP2D6 should be used at lower doses, or the patient switched to an antipsychotic not metabolized by CYP2D6.[54] Clinicians should consult accepted guidelines, such as those by the Clinical Pharmacogenetics Implementation Consortium, (https://cpicpgx.org/) before utilizing pharmacogenetic data.[129]

Given that no antipsychotic has proven superiority with regard to efficacy in the treatment of schizophrenia (with the exception of clozapine in treatment

resistance), cost should be a factor in antipsychotic selection. Many antipsychotics have generic equivalents available, and this should be a factor in selecting an antipsychotic.

EVALUATION OF THERAPEUTIC OUTCOMES

10 Assessment of response has traditionally been done subjectively or empirically (a relative sense of how the clinician feels the patient is doing). A formal MSE is used to structure the patient interview and focus on items related to appearance, mood, sensorium, intellectual functioning, and thought processes. However, the MSE is neither specific nor quantitative for the measurement of drug response. Clinicians should be trained to use simple, standardized psychiatric rating scales to assist in objectively rating patient drug responses.[130] The Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Symptom Scale (PANSS) were developed for use in clinical trials as research tools to quantify symptom improvement seen with antipsychotic treatment. Objectively, the use of a numeric indicator (eg, 20%, 30%, or 40% reduction in BPRS score) has been used to quantify overall symptom reduction and classify patients according to different degrees of response. However, these types of rating scales are too long and unwieldy to be routinely used within the time constraints of most clinical practices. Symptom scales used in clinical practice must be sufficiently brief to be used during an ordinary clinic visit (eg, 15-30 minutes) while measuring both positive and negative symptoms, and being sufficiently representative of overall symptomatology. The four-item Positive Symptom Rating Scale (PSRS) and the four item Brief Negative Symptom Assessment (BNSA) are brief scales that meet such criteria (**Table 84-10**).[130] A brief rating scale of positive symptoms, such as the PSRS, should be used at baseline before starting pharmacotherapy, and at each time response to pharmacotherapy is assessed.

TABLE 84-10 Brief Clinical Assessments for Monitoring Antipsychotic Response in Schizophrenia

Four-Item Positive Symptom Rating Scale (PSRS)								
Use each item's anchor points to rate the patient								
1. Suspiciousness	NA[a]	1	2	3	4	5	6	7
2. Unusual thought content	NA	1	2	3	4	5	6	7
3. Hallucinations	NA	1	2	3	4	5	6	7
4. Conceptual disorganization	NA	1	2	3	4	5	6	7
Each item is scored from 1 (not present) to 7 (extremely severe)	SCORE:							
Brief Negative Symptom Assessment (BNSA)								
Use each item's anchor points to rate the patient								
1. Prolonged time to respond	1	2	3	4	5	6		
2. Emotion: Unchanging facial expression, blank, expressionless face	1	2	3	4	5	6		
3. Reduced social drive	1	2	3	4	5	6		
4. Poor grooming and hygiene	1	2	3	4	5	6		
Each item is scored from 1 (normal) to 6 (severe)	SCORE:							

[a]NA, not able to be assessed.

Data from Reference 130.

Similarly, the pharmacotherapeutic plan should include specific monitoring parameters for side effects (**Table 84-11**). The plan should include how the potential side effect will be evaluated, and the frequency of assessment. Given the risk of weight gain, diabetes, and lipid abnormalities associated with many of the SGAs, a consensus task force led by the American Diabetes Association recommends the following baseline parameters before beginning antipsychotics: family history, weight, height, BMI, waist circumference, blood pressure, fasting plasma glucose, and fasting lipid profile.[72] They also recommend follow-up monitoring of these parameters after beginning or changing SGAs. Weight should be monitored monthly for the first 3 months and quarterly thereafter. The other parameters should be assessed at the end of 3 months, and if normal, then at least annually. Self-assessments can be a useful adjunct in treating the patient. Although the patient with schizophrenia may not always be accurate in evaluating symptom severity, the use of patient self-assessments increases patient engagement in care, enhances therapeutic alliance, and gives the clinician an opportunity to identify misconceptions the patient may have regarding symptoms associated with the illness, medication side effects, and the like.[68] Traditionally, clinicians have often accepted partial symptom response in

schizophrenia as success, and have not been aggressive in attempting to achieve greater symptomatic remission. The advent of multiple different SGAs with varying side effect profiles should encourage clinicians to be more assertive in attempting to achieve symptom remission. This is consistent with an increasing focus on remission as a goal of treatment and evolving recovery movements with an emphasis on consumerism in the care of the severely mentally ill.[44]

TABLE 84-11 Antipsychotic Adverse Effects and Monitoring Parameters

Adverse Reaction	Monitoring Parameter	Frequency	Comments
Adverse Effect Monitoring Parameters for all Antipsychotic Medications			
Akathisia	Ask about restlessness or anxiety. Observe patient for restlessness. Barnes Akathisia Scale can also be used	Every visit	
Anticholinergic side effects	Ask patient about constipation, blurry vision, urinary retention, or unusual dry mouth	Every visit	
Glucose intolerance	FBS or HbA1c	At baseline, after 3 months, and if normal, then annually	
Hyperlipidemia	Lipid profile	At baseline, after 3 months, and if normal, then annually	
Orthostatic hypotension	Ask patient about dizziness on standing. If present, check BP and HR in sitting and standing positions	Every visit	The degree of orthostatic change in BP to produce symptoms varies. In general, a BP change of 20 mm Hg or more is significant
Hyperprolactinemia	In women, ask about expression of milk from the breast and menstrual irregularities. In men, ask about breast enlargement or expression of milk from nipples. If symptoms present, check serum prolactin level	Every visit	In the absence of symptoms, there is no need to monitor serum prolactin
Sedation	Ask patient about unusual sedation or sleepiness	Every visit	
Sexual dysfunction	Ask patient about decreased sexual desire, difficulty being aroused, or problems with orgasm	Every visit	Patients with schizophrenia have more sexual dysfunction than the normal population. Compare symptoms with medication-free state
Tardive dyskinesia	Standardized rating scale such as the AIMS or the DISCUS	At baseline, and then every 3 months for FGAs and every 6 months for SGAs	
Weight gain	Measure body weight, BMI, and waist circumference	At baseline, monthly for the first 3 months, and then quarterly	Waist circumference is the single best predictor of cardiac morbidity
Adverse Effect Monitoring Parameters for Specific Antipsychotics			
Agranulocytosis	White blood cell (WBC) and absolute neutrophil counts (ANC)	At baseline, weekly for 6 months, then every 2 weeks for 6 months, and then monthly	Clozapine only
Sialorrhea or excess drooling	Ask patient about problems with excess drooling, waking in the morning with a wet ring on his or her pillow. Visual observation of the patient for drooling	Every visit	Clozapine only
Bronchospasm, respiratory distress, respiratory depression, respiratory arrest	Before administration, patients must be screened for a history of asthma, chronic obstructive pulmonary disease, or other lung disease associated with bronchospasm. Monitor patient every 15 minutes for a minimum of 1 hour after drug administration for signs and symptoms of bronchospasm (ie, vital signs and chest auscultation). Only one 10-mg dose can be given every 24 hours	Every dose administration	Inhaled loxapine only. Can only be administered in approved healthcare facilities registered in REMS program
Postinjection sedation/ delirium syndrome	Observation of the patient for at least 3 hours after drug administration. Monitor for possible sedation, altered level of consciousness, coma, delirium, confusion, disorientation, agitation, anxiety, or other cognitive impairment	Every dose administration	Long-acting olanzapine pamoate monohydrate only. Can only be administered in approved healthcare facilities registered in REMS program

FBS: fasting blood sugar, AIMS: abnormal involuntary movement scale, DISCUS: dyskinesia identification system condensed user scale, FGA: first generation antipsychotic, SGA: second generation antipsychotic.

CONCLUSION

Schizophrenia is a neurodevelopmental disorder whose etiology is currently unknown. A multitude of medications, primarily working through dopamine, serotonin, and glutamatergic antagonism, have been developed to treat symptoms associated with this syndrome. Although there is no cure for schizophrenia, lifelong antipsychotic use combined with comprehensive psychosocial services can allow many of these individuals to function. However, medication adherence can be challenging, and the use of long-acting injectable antipsychotics combined with psychosocial services designed to address engagement with treatment can promote adherence. Antipsychotic medications have a multitude of potential adverse effects, and prudent monitoring is necessary. As the common core symptoms associated with schizophrenia (positive, negative, and cognitive) vary among person to person, continual evaluation of therapeutic outcomes focusing on overall functioning and quality of life is necessary.

Postclass Engaged Learning Activity

Perform a literature review using Pub Med to search and identify an article(s) that discusses a medication for potential use in the treatment of schizophrenia that has a different mechanism of action than currently available antipsychotics. Discuss how this mechanism of action relates to the pathophysiology of schizophrenia and the potential advantages and disadvantages of this medication as compared with currently available antipsychotics. Is its efficacy greater or different than currently available antipsychotics? How does its side effect profile compare with currently available antipsychotics?

ABBREVIATIONS

α_1	alpha one adrenergic receptor
α_2	alpha two adrenergic receptor
AAN	American Academy of Neurology
ACHIEVE	Randomized Trial of Achieving Healthy Lifestyles in Psychiatric Rehabilitation
ACT	active community treatment
ADTA2A	adrenoreceptor alpha-2a
AIMS	Abnormal Involuntary Movement Scale
AIWG	antipsychotic-induced weight gain
ANC	absolute neutrophil count
AP	antipsychotic
APA	American Psychiatric Association
ASP	Autism Spectrum Disorder
AUC	area under the curve
β_2	beta-2 adrenergic receptor
BDNF	brain-derived neurotrophic factor
BLM	buccal–lingual–masticatory
BMI	body mass index
BP	blood pressure
BNSA	Brief Negative Symptom Assessment
BPRS	Brief Psychiatric Rating Scale
C4	complement component 4 genes
CACN1A2	Voltage-Dependent Calcium Channel 1A2
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CK	creatine kinase
CNS	central nervous system
CNV	copy number variant
C_{max}	maximum plasma concentration
CRP	C-Reactive Protein
CYP	cytochrome P450
D_1	dopamine-1 receptor
D_2	dopamine-2 receptor
D_3	dopamine-3 receptor
D_4	dopamine-4 receptor
DA	dopamine
DISCUS	Dyskinesia Identification System: Condensed User Scale
DKA	diabetic ketoacidosis
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
ECG	electrocardiogram or electrocardiographic
ECHO	echocardiogram
ECT	electroconvulsive therapy
EEG	electroencephalogram
EF	ejection fraction
EPS	extrapyramidal side effect
FBS	fasting blood sugar
FDA	Food and Drug Administration
FGA	first-generation antipsychotic

FMO3	flavin containing monooxygenase 3 gene
GABA	gamma-aminobutyric acid
GNB3	Guanine Nucleotide Binding Protein
GWAS	genome-wide association studies
HgA1c	Hemoglobin A1c
5-HT	serotonin or 5-hydroxytryptamine
5-HT_{1A}	serotonin-1A receptor
5-HT_{2}	serotonin-2 receptor
5-HT_{2A}	serotonin-2A receptor
5-HT_{2C}	serotonin-2C receptor
5-HT_{6}	Serotonin-6 receptor
5-HT_{7}	Serotonin-7 receptor
HR	heart rate
ICD	impulse control disorder
IM	intramuscular
INSIG2	insulin-induced gene 2
IV	intravenous
LAIA	long-acting injectable antipsychotic
LBW	low birth weight
MC4R	Melanocortin-4-Receptor
1MPP	1-month paliperidone palmitate (Invega Sustenna®)
3MPP	3-month paliperidone palmitate (Invega Trinza®)
mRNA	microRibonucleic acid
MTHFR	methylenetetrahydrofolate reductase
MSE	mental status examination
NAMI	National Alliance on Mental Illness
NE	norepinephrine
NIMH	National Institute of Mental Health
NMDA	*N*-methyl-D-aspartate
NMS	neuroleptic malignant syndrome
NRG1	neuregulin 1
NRXN1	synaptic protein neurexin 1
PANSS	Positive and Negative Symptom Scale
PDSS	Postinjection delirium/sedation syndrome
PET	positron emission tomography
PORT	Patient Outcomes Research Team
PSRS	Positive Symptom Rating Scale
PSRS	Positive Symptom Rating Scale
RAISE	Recovery After Initial Schizophrenia Episode
REMS	Risk Evaluation and Mitigation Strategy
RID	relative infant dose
RNA	ribonucleic acid
SCD	sudden cardiac death
SEs	side effects
SGA	second-generation antipsychotic
SNP	single nucleotide polymorphism
SSRI	selective serotonin reuptake inhibitor
STRIDE	Reducing Weight and Diabetes Risk in an Underserved Population
T2DM	type 2 diabetes mellitus
TCA	tricyclic antidepressant
TD	tardive dyskinesia
UK	United Kingdom
VMAT2	vesicular monoamine transporter-2
VTE	venous thromboembolism
WBC	white blood cell

REFERENCES

1. American Psychiatric Association. Schizophrenia spectrum and other psychotic disorders. In: *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association; 2013:87–122.
2. Charlson FJ, Ferrari AJ, Santomauro DF, et al. Global epidemiology and burden of schizophrenia: Findings from the global burden of disease study 2016. *Schizophr Bull*. 2018;44:1195–1203.
3. Milan ML, Andrieux A, Bartzokis G, et al. Altering the course of schizophrenia: Progress and perspectives. *Nat Rev Drug Discov*. 2016;15:485–515.
4. Weinberger D, Levitt P. Schizophrenia as a neurodevelopmental disorder. In: Weinberger DR, Harrison P, eds. *Schizophrenia*. 3rd ed. Oxford, UK: Wiley-Blackwell; 2011;326–348.
5. Dalmau J, Graus F. Antibody-mediated encephalitis. *N Engl J Med*. 2018;378:840–851.
6. Howes OD, Murray RM. Schizophrenia: An integrated sociodevelopmental cognitive model. *Lancet*. 2014;383:1677–1687.
7. Birnbaum R, Weinberger DR. Genetic insights into the neurodevelopmental origins of schizophrenia. *Nat Rev Neurosci*. 2017;18:727–740.
8. Sekar A, Bialas AR, de Rivera H, et al. Schizophrenia risk from complex variation of complement component 4. *Nature*. 2016;530:177–183. doi: 10.1038/nature16549.
9. Cannon TD, Chung Y, He G, et al. North American Prodrome Longitudinal Study Consortium. Progressive reduction in cortical thickness as psychosis develops: A multisite longitudinal neuroimaging study of youth at elevated clinical risk. *Biol Psychiatry*. 2015;77(2):147–157.
10. Howes OD, Kambeitz J, Kim E, et al. The nature of dopamine dysfunction in schizophrenia and what this means for treatment. *Arch Gen Psychiatry*. 2012;69:776–786.
11. Krystal JH, Anticevic A. Toward illness phase-specific pharmacotherapy for schizophrenia. *Biol Psychiatry*. 2015;78:738–740.

12. Wright R, Rethelyi JM, Gage FG. Enhancing induced pluripotent stem cell models of schizophrenia. *JAMA Psychiatry*. 2014;71(3):334–335.
13. Evins AE, Green AI, Kane JM, Murray RM. Does using marijuana increase the risk for developing schizophrenia? *J Clin Psychiatry*. 2013;74:e08. doi: 10.4088/JCP.12012tx2c.
14. Lieberman JA, First MB. Psychotic disorders. *New Engl J Med*. 2018;379:270–180.
15. McGorry PD. The next stage for diagnosis: Validity through utility. *World Psychiatry.* 2013;12(3):213–214.
16. Addington D, Anderson E, Kelly M, et al. Canadian practice guidelines for comprehensive community treatment for schizophrenia and schizophrenia spectrum disorder. *Can J Psychiatry*. 2017;62:662–672.
17. Kane JM, Robinson DG, Schooler NR, et al. Comprehensive versus usual community care for first-episode psychosis: 2-Year outcomes from the NIMH RAISE early treatment program. *Am J Psychiatry*. 2015;173:362–372. doi: 10.1176/appi.ajp.2015.15050632.
18. Saperstein AM, Kurtz MM. Current trends in the empirical study of cognitive remediation for schizophrenia. *Can J Psychiatry*. 2013;58(6):311–318.
19. Osser DN, Jalali-Roudsari M, Manschreck T. Schizophrenia. Psychopharmacology algorithms, from the Psychopharmacology Algorithm Project at the Harvard Medical School Dept. of Psychiatry, South Shore Program. Available at http://psychopharm.mobi/algo_live/. Accessed December 26, 2018.
20. Hasan A, Palkai P, Wobrock T, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia—short version for primary care. *Int J Psychiatry Clin Pract*. 2017;21:82–90.
21. Hasan A, Falkai P, Wobrock T, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of schizophrenia, part 1: Update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. *World J Biol Psychiatry*. 2012;13:318–378.
22. Remington G, Addington D, Honer W, et al. Guidelines for the pharmacotherapy of schizophrenia in adults. *Can J Psychiatry*. 2017;62:604–616.
23. Lieberman JA, Stroup S. The NIMH-CATIE schizophrenia study: What

did we learn? *Am J Psychiatry*. 2011;168:770–775.

24. Correll CU, Robinson DG, Schooler NR, et al. Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders: Baseline results from the RAISE-ETP Study. *JAMA Psychiatry*. 2014;71(12):1350–1363.
25. Goldman R, Loebel A, Cuccchiaro J, et al. Efficacy and safety of lurasidone in adolescents with schizophrenia: A 6-week, randomized placebo-controlled study. *J Child Adolesc Psychopharmacol*. 2017;27:516–525.
26. Subotnik KL, Casaus LR, Ventura J, et al. Long-acting injectable risperidone for relapse prevention and control of breakthrough symptoms after a recent first episode of schizophrenia. *JAMA Psychiatry*. 2015;72:822–829.
27. Patchan K, Vyas G, Hackman AL, et al. Clozapine in reducing aggression and violence in forensic populations. *Psychiatr Q*. 2018;89:157–168.
28. Van Putten T, Marder SR. Behavioral toxicity of antipsychotic drugs. *J Clin Psychiatry*. 1987;48(suppl 9):13–19.
29. Samara MT, Leucht C, Leeflang MM, et al. Early improvement as a predictor of later response to antipsychotics in schizophrenia: A diagnostic test review. *Am J Psychiatry*. 2015;172:617–629.
30. de Berardis D, Fornaro M, Orsolini L, et al. The role of inhaled loxapine in the treatment of acute agitation in patients with psychiatric disorders: A clinical review. *Int J Molo Sci*. 2017;18:349. doi: 10.3390/ijms18020349.
31. Sajatovic M, Ross R, Legacy SN, et al. Initiating/maintaining long-acting injectable antipsychotics in schizophrenia/schizoaffective or bipolar disorder—expert consensus survey part 2. *Neuropsychiatr Dis Treat*. 2018;14:1475–1492.
32. Parellada E, Bioque M. Barriers to the use of long-acting injectable antipsychotics in the management of schizophrenia. *CNS Drugs*. 2016;30:689–701.
33. Getzen H, Beasley M, D'Mello DA. Barriers to utilizing long-acting injectable antipsychotic medications. *Ann Clin Psychiatry*. 2014;26:33–38.
34. Citrome L. New second-generation long-acting injectable antipsychotics for the treatment of schizophrenia. *Expert Rev Neurother*. 2013;13:767–783.
35. Prescribing information. *PERSERIS*. North Chesterfield, VA: Indivior Inc.; 2018.

36. Prescribing information. *INVEGA SUSTENNA*. Titusville, NJ: Janssen Pharmaceuticals Inc.; 2017.
37. Prescribing information. *Invega Trinza*. Titusville, NJ: Janssen Pharmaceuticals Inc.; 2018.
38. Prescribing information. *Zyprexa Relprevv*. Indianapolis, IN: Lilly USA; 2018.
39. Samalin L, Garay R, Ameg A, Llorca PM. Olanzapine pamoate for the treatment of schizophrenia: A safety evaluation. *Expert Opin Drug Saf*. 2016;15(3):403–411. doi: 10.1517/14740338.2016.1141893.
40. Jann MW, Penzak SR. Long-acting injectable second-generation antipsychotics: An update and comparison between agents. *CNS Drugs*. 2018;32:241–257. https://doi.org/10.1007/s40263-018-0508-6.
41. Prescribing information. *Aristada Initio*. Waltham, MA: Alkermes, Inc.; 2018.
42. Meyer JM. Understanding the depot antipsychotics: An illustrated guide to kinetics. *CNS Spectrums*. 2013;18:58–68.
43. Howes OD, McCutcheon R, Agid O, de Bartolomeis A, et al. Treatment resistant schizophrenia: Treatment response and resistance in psychosis (TRRIP) working groups consensus guidelines on diagnosis and terminology. *Am J Psychiatry*. 2017;174(3):216–229.
44. Barkhof E, Meijer CJ, de Sonneville LMJ, et al. Interventions to improve adherence to antipsychotic medications in patients with schizophrenia—A review of the past decade. *Eur Psychiatry*. 2012;27:9–18.
45. Prescribing information. *ABILIFT MYCITE*. Rockville, MD: Otsuka America Pharmaceutical Inc.; 2017.
46. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic: A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry*. 1988;45:789–796.
47. Kennedy WK, Jann MW, Kutscher EC. Clinically significant drug interactions with atypical antipsychotics. *CNS Drugs*. 2013;27:1021–1048.
48. Miyamoto S, Miyake N, Jarskog LF, Fleischhacker WW, Lieberman JA. Pharmacological treatment of schizophrenia: A critical review of the pharmacology and clinical effects of current and future therapeutic agents. *Mol Psychiatry*. 2012;17:1206–1227.
49. Maeda K, Sugino H, Akazawa H, et al. Brexpiprazole I: In vitro and in vivo characterization of a novel serotonin-dopamine activity modulator. *J*

Pharmacol Exp Ther. 2014;350:589–604.

50. Citrome L. Iloperidone for schizophrenia: A review of the efficacy and safety profile for this newly commercialized second-generation antipsychotic. *Int J Clin Pract*. 2009;63:1237–1248.
51. Citrome L. Asenapine for schizophrenia and bipolar disorder: A review of the efficacy and safety profile for this newly approved sublingually absorbed second-generation antipsychotic. *Int J Clin Pract*. 2009;63:1762–1784.
52. McCormack PL. Cariprazine: First global approval. *Drugs*. 2015;75:2035–2043.
53. Mauri MC, Volonteri LS, Colasanti A, et al. Clinical pharmacokinetics of atypical antipsychotics: A critical review of the relationship between plasma concentrations and clinical response. *Clin Pharmacokinet*. 2007;46:359–388.
54. Eum S, Lee AM, Bishop JR. Pharmacogenetic tests for antipsychotic medications: clinical implications and considerations. *Dialogues Clin Neurosci*. 2016;18:323–337.
55. Pouget JG, Shams TA, Tiwari AK, Muller DJ. Pharmacogenetics and outcome with antipsychotic drugs. *Dialogues Clin Neurosci*. 2014;16:555–566.
56. Preskorn SH. Clinically important differences in the pharmacokinetics of the ten newer atypical antipsychotics: Part 2. Metabolism and elimination. *J Psychiatr Pract*. 2012;18:361–368.
57. Tewksbury A, Olander A. Management of antipsychotic induced hyperprolactinemia. *Ment Health Clin*. 2016;6(4):185–190. doi: 10.9740/mhc.2016.7.185.
58. Wong-Anuchit C. Clinical management of antipsychotic-induced hyperprolactinemia. *Perspect Psychiatr Care*. 2015;52:145–152. doi: 10.1111/ppc.12111.
59. Kinon BJ, Liu-Seifert H, Stauffer VL, Jacob J. Bone loss associated with hyperprolactinemia in schizophrenia. *Clin Schizophr Relat Psychoses*. 2013;7:114–123.
60. Peuskens J, Pani L, Detraux J, De Hert M. The effects of novel and newly approved antipsychotics on serum prolactin levels: A comprehensive review. *CNS Drugs*. 2014;28:421–453.
61. Citrome L. Lurasidone for schizophrenia: A review of the efficacy and safety profile for this newly approved second-generation antipsychotic. *Int*

J Clin Pract. 2011;65:189–210.

62. Meng M, Li W, Zhang S, et al. Using aripiprazole to reduce antipsychotic-induced hyperprolactinemia: Meta-analysis of currently available randomized controlled trials. *Shanghai Arch Psychiatry*. 2015;27(1):4–17.
63. Bo QJ, Wang ZM, Li XB, Ma X, Wang CY, de Leon J. Adjunctive metformin for antipsychotic-induced hyperprolactinemia: A systematic review. *Psychiatr Res*. 2016;237:257–263.
64. Musil R, Obermeier M, Russ P, Haerle M. Weight gain and antipsychotics: A drug safety review. *Expert Opin Drug Saf*. 2015;14(1):73–96.
65. Jeon SW, Kim YK. Unresolved issues for utilization of atypical antipsychotics in schizophrenia: Antipsychotic polypharmacy and metabolic syndrome. *Int J Mol Sci*. 2017;18(10):E2174. doi: 10.3390/ijms18102174.9e.
66. Reynolds GP, McGowan OO. Mechanism underlying metabolic disturbances associated with psychosis and antipsychotic drug treatment. *J Psychopharmacol*. 2017;31(11):1430–1436. doi: 10.1177/0269881117722987.
67. Whicher CA, Price H, Holt RIG. Mechanisms in endocrinology: Antipsychotic medication and diabetes and impaired glucose regulation. *Eur J Endocrinol*. 2018;178(6):R245–R258. doi: 10.1530/EJE-18-0022.
68. Velligan DI, Weiden PJ, Sajatovic M, et al. The expert consensus guideline series: Adherence problems in patients with serious and persistent mental illness. *J Clin Psychiatry*. 2009;70:1–48.
69. Frankel JS, Schwartz TL. Brexpiprazole and cariprazine: Distinguishing two new antipsychotics from the original dopamine stabilizer aripiprazole. *Ther Adv Psychopharmacol*. 2017;7:29–41. doi: 10.1177/2045125316672136.
70. Shams TA, Muller DJ. Antipsychotic induced weight gain: Genetics, epigenetics and biomarkers reviewed. *Curr Psychiatry Rep*. 2014;16:473–481. doi: 10.1007/s11920-014-0473-9.
71. Zhang JP, Lencz T, Zhang RX, et al. Pharmacogenetic associations of antipsychotic drug-related weight gain: A systematic review and meta-analysis. *Schizophr Bull*. 2016;42(6):1415–1437. doi: 10.1093/schlbulk/sbw058.
72. American Diabetes Association. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004;27:596–601.

73. Mizuno Y, Suzuki T, Nakagawa A, et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: A systematic review and meta-analysis. *Schizophr Bull*. 2014;1385–13403.
74. Wani RA, Dar MA, Margoob MA, Rather YH, Haq I, Shah MS. Diabetes mellitus and impaired glucose tolerance in patients with schizophrenia, before and after antipsychotic treatment. *J Neurosci Rural Pract*. 2015;6(1):17–22.
75. Green CA, Yarborough BJ, Leo MC, Yarborough MT, Stumbo SP, Janoff SL, et al. The STRIDE weight loss and lifestyle intervention for individuals taking antipsychotic medications: A randomized trial. *Am J Psychiatry*. 2015;172(1):71–81.
76. Koalchuk C, Castenllani L, Chintoh A, Remington G, Giacca A, Hahn M. Antipsychotics and glucose metabolism: How brain and body collide. *Am J Physiol Endocrino Metab*. 2018. doi: 10.1152/ajpendo.00164.2018.
77. Orsolini L, Tomasetti C, Valchera A, et al. An update of the safety of clinically used atypical antipsychotics. *Expert Opin Drug Saf*. 2016;15(10):1329–1347. doi: 10.1080/14740338.2016.1201475.
78. Solmi M, Murru A, Pacciarotti I, et al. Safety, tolerability and risks associated with first- and second-generation antipsychotics: A state-of-the-art review. *Ther Clin Risk Manag*. 2017;13:757–777.
79. Leung JY, Barr AM, Procyshyn RM, Honer WG, Pang CC. Cardiovascular side-effects of antipsychotic drugs: The role of the autonomic nervous system. *Pharmacol Ther*. 2012;135(2):113–122.
80. Harrigan EP, Miceli JJ, Anziano R, et al. A randomized evaluation of the effects of six antipsychotic agents on QTc, in the absence and presence of metabolic inhibition. *J Clin Psychopharmacol*. 2004;24:62–69.
81. Hasnain M, Vieweg WVR. QTc interval prolongation and torsades de pointes associated with second generation antipsychotics and antidepressants: A comprehensive review. *CNS Drugs*. 2014;28:887–920.
82. Wenzel-Seifert K, Wittmann M, Haen E. QTc prolongation by psychotropic drugs and the risk of torsade de pointes. *Dtsch Arztebl Int*. 2011;108:687–693.
83. Vang T, Rosenzweig M, Bruhn CH, et al. Eosinophilic myocarditis during treatment with olanzapine: Report of two possible cases. *BMC Psychiatry*. 2016;16:70. doi: 10.1186/s12888-016-0776-y.
84. Curto M, Girardi N, Lionetto L, Ciavarella GM, Ferracuti S, Balderssarini

RJ. Systematic review of clozapine cardiotoxicity. *Curr Psychiatry Rep*. 2016;18:68. doi: 10.1007/s11920-0704-3.

85. Alawani M, Wasywich C, Cicovic A, Kenedi C. A systematic review of clozapine induced cardiomyopathy. *Int J Cardiol*. 2014;176:315–320.
86. Nielsen J, Correll CU, Manu P, Kane JM. Termination of clozapine due to medical reasons: When is it warranted and how can it be avoided? *J Clin Psychiatry*. 2013;74:603–613.
87. Wu CS, Tsai YT, Tsai HJ. Antipsychotic drugs and the risk of ventricular arrhythmia and/or sudden cardiac death: A nationwide case-crossover study. *J Am Heart Assoc*. 2015;4(2). pii: e001568. doi:10.1161/JAHA.114.001568.
88. Ballon JS, Pajvani UB, Mayer LES, et al. Pathophysiology of drug induced weight gain and metabolic effects: Findings from an RCT in healthy volunteers treated with olanzapine, iloperidone, or placebo. *Psychopharmacol*. 2018;32:533–540. doi: 10.1177/0269881118754708.
89. McEvoy JP, Meyer JM, Goff DC, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: Baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. *Schizophr Res*. 2005;80(1):19–32.
90. Monteleone P, Martiadis V, Maj M. Management of schizophrenia with obesity, metabolic and endocrinological disorders. *Psychiatr Clin North Am*. 2009;32:775–794.
91. Hsu WY, Lane HY, Lin CL, Kao CH. A population-based cohort study on deep vein thrombosis and pulmonary embolism among schizophrenia patients. *Schizophr Res*. 2015;162(1-3):248–252. doi: 10.1016/j.schres.2015.01.012.
92. Hippisley-Cox J, Coupland C. Development and validation of risk prediction algorithm (QThrombosis) to estimate future risk of venous thromboembolism: Prospective cohort study. *BMJ*. 2011;343:d4656. doi: https://doi.org/10.1136/bmj.d4656.
93. Burkhard PR. Acute and subacute drug-induced movement disorders. *Parkinsonism Relat Disord*. 2014;20S1:S108–S112.
94. Caroff SN, Campbell EC. Drug-induced extrapyramidal syndromes: Implications for contemporary practice. *Psychiatr Clin North Am*. 2016;39(3):391–411. doi: 10.1016/j.psc.2016.04.003.
95. Pringsheim T, Gardner D, Addington D, et al. Assessment and treatment

of antipsychotic-induced akathisia. *Can J Psychiatry*. 2018. doi: 10.1177/0706743718760288.

96. Peluso M, Lewis S, Barnes T, et al. Extrapyramidal motor side-effects of first and second-generation antipsychotic drugs. *Br J Psychiatry*. 2012;200:387–392.
97. Aquino CCH, Lang AE. Tardive dyskinesia syndromes: Current concepts. *Parkinsonism Relat Disord*. 2014;20S1:S113–S117.
98. Sprague RL, Kalachnik JE. Reliability, validity, and a total score cutoff for the Dyskinesia Identification System Condensed User Scale (DISCUS) with mentally ill and mentally retarded populations. *Psychopharmacol Bull*. 1991;27:51–58.
99. Solmi M, Pigato G, Kane JM, Correll CU. Clinical risk factors for the development of tardive dyskinesia. *J Neurol Sci*. 2018;389:21–27. doi: 10.1016/j.jns.2018.02.012.
100. Zai CC, Maes MS, Tiwari AK, Zai GC, Remington G, Kennedy JL. Genetics of tardive dyskinesia: Promising leads and ways forward. *J Neurol Sci*. 2018;389:28–34. doi: 10.1016/j.jns.2018.02.011.
101. Correll CU, Schenk EM. Tardive dyskinesia and new antipsychotics. *Curr Opin Psychiatry*. 2008;21:151–156.
102. Carbon M, Kane JM, Leucht S, Correll CU. Tardive dyskinesia risk with first-generation and second-generation antipsychotics in comparative randomized controlled trials: a meta-analysis. *World Psychiatry*. 2018;17:330–340. doi:10.1002/wps.20579.
103. Solmi M, Pigato G, Kane JM, Correll CU. Treatment of tardive dyskinesia with VMAT-2 inhibitors: A systematic review and meta-analysis of randomized controlled trials. *Drugs Des Devel Ther*. 2018;12:1215–1238. doi: 10.2147/DDDT.S133205.
104. Correll CU, Josiassen RC, Liang GS, Burke J, O'Brien CF. Efficacy of valbenazine (NBI-98854) in treating subjects with tardive dyskinesia and mood disorder. *Psychopharmacol Bull*. 2017;47:53–60.
105. Bhidayasiri R, Fahn S, Gronseth GS, et al. Evidence-based guideline: Treatment of tardive syndromes— report of the guideline development subcommittee of the American Academy of Neurology. *Neurology*. 2013;81:463–469.
106. Wilson MP, Vilke GM, Hayden SR, Nordstrom K. Psychiatric emergencies for clinicians: Emergency department management of neuroleptic malignant syndrome. *J Emerg Med*. 2016;51:66–69.

107. Gurrera RJ, Caroff SN, Cohen A, et al. An international consensus study of neuroleptic malignant syndrome diagnostic criteria using the Delphi method. *J Clin Psychiatry*. 2011;72:1222–1228.
108. Dhillion R, Bastiampillai T, Cao CZ, Eckert TG, Tibrewal P. Aripiprazole and impulse-control disorders: A recent FDA warning and case report. *Prim Care Companion CNS Disord*. 2017;19. doi: 10.4088/PCC.16102003.
109. Li J, Tripathi RC, Tripathi BJ. Drug-induced ocular disorders. *Drug Saf*. 2008;31:127–141.
110. Laties AM, Flach AJ, Baldycheva I, et al. Cataractogenic potential of quetiapine versus risperidone in long-term treatment of patients with schizophrenia or schizoaffective disorder: A randomized open-label, ophthalmologist-masked, flexible-dose, non-inferiority trial. *J Psychopharmacol*. 2015;29:69–79.
111 Rettenbacher MA, Hofer A, Ebenbichler C, et al. Prolactin levels and sexual adverse effects in patients with schizophrenia during antipsychotic treatment. *J Clin Psychopharmacol*. 2010;30:711–715.
112. Andersohn F, Schmedt N, Weinmann S, et al. Priapism associated with antipsychotics: Role of alpha1 adrenoceptor affinity. *J Clin Psychopharmacol*. 2010;30:68–71.
113. Hasan A, Falkai P, Wobrock T, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 2: Update 2012 on the long-term treatment of schizophrenia and management of antipsychotic induced side effects. *World J Biol Psychiatry*. 2013;14:2–44.
114. Prescribing information. *Clozaril*. Rosemont, PA: HLS Therapeutics (USA), Inc. HLS Therapeutics, Inc.; 2017.
115. FDA Drug Safety Communication: FDA reporting mental health drug ziprasidone (Geodon) associated with rare but potentially fatal skin reactions: 2014. Available at http://www.fda.gov/Drugs/DrugSafety/ucm426391.htm. Accessed June 1, 2015.
116. Vigod SN, Seeman MV, Ray JG, et al. Temporal trends in general and age-specific fertility rates among women with schizophrenia (1996-2009): A population-based study in Ontario, Canada. *Schizophr Res*. 2012;139:169–175.
117. Damkier P, Videnbech P. The safety of second-generation antipsychotics

during pregnancy: A clinically focused review. *CNS Drugs*. 2018;32:351–366.

118. McAllister-Williams RH, Baldwin DS, Cantwell R, et al. British association for psychopharmacology consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum. *J Psychopharmacol*. 2017;31:519–552.
119. Lin HC, Chen IJ, Chen YH, et al. Maternal schizophrenia and pregnancy outcome: Does the use of antipsychotics make a difference? *Schizophr Res*. 2010;116(1):55–60.
120. Huybrechts KF, Hernandez-Diaz S, Patorno E, et al. Antipsychotic use in pregnancy and the risk for congenital malformations. *JAMA Psychiatry*. 2016;73:938–946. doi: 10.1001/jamapsychiatry.2016.1520.
121. Terrana N, Koren G, Pivovarov J, Etwel F, Nulman I. Pregnancy outcomes following in utero exposure to second-generation antipsychotics: A systematic review and meta-analysis. *J Clin Psychopharmacol*. 2015;35:559–565.
122. Park Y, Hernandez-Diaz S, Bateman BT, et al. Continuation of atypical antipsychotic medication during early pregnancy and the risk of gestational diabetes. *Am J Psychiatry*. 2018;175:564–874. doi: 10.1176/appi.ajp.2018.17040393.
123. FDA Drug Safety Communication: Antipsychotic drug labels updated on use during pregnancy and risk of abnormal muscle movements and withdrawal symptoms in newborns. U.S. Food and Drug Administration, February 22, 2011. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm243903.htm. Accessed September 9, 2018.
124. Uguz F. Second generation antipsychotics during the lactation period. A comparative systematic review on infant safety. *J Clin Psychopharmcol*. 2016;36:244–252.
125. Cuomo A, Goracci A, Fagiolini A. Aripiprazole use during pregnancy, peripartum and lactation. A systematic literature search and review to inform clinical practice. *J Affect Disord*. 2018;228:229–237.
126. Ereshefsky L. Drug–drug interactions with the use of psychotropic medications. *CNS Spectr*. 2009;14(suppl 8):1–8.
127. Gaertner J, Ruberg K, Schlesiger G, Frechan S, Voltz R. Drug interactions in palliative care—it's more than cytochrome P450. *Palliat Med*. 2012;26:813–825.

128. Citrome L. Using oral ziprasidone effectively: The food effect and dose-response. *Adv Ther*. 2009;26(8):739–748.
129. Clinical Pharmacogenetics Implementation Consortium. Available at https://cpicpgx.org/. Accessed December 1, 2018.
130. Velligan DI, Lopez L, Castillo DA, et al. Interrater reliability of using brief standardized outcome measures in a community mental health setting. *Psychiatr Serv*. 2011;62:558–560.
131. Nucifora FC, Miohaljevic M, Lee BJ, Sawa A. Clozapine as a model for antipsychotic development. *Neurotherapeutics*. 2017;14:750–761.

85

Major Depressive Disorder

Amy M. VandenBerg

KEY CONCEPTS

1. Multiple guidelines are available to guide the treatment of major depressive disorder (MDD), including medication management. Clinicians treating individuals with MDD should be familiar with key tenets of these guidelines.
2. Other potential causes of symptoms such as medical conditions, medications and other substances must be ruled out first when evaluating a patient for a diagnosis of MDD.
3. The goals of treatment for MDD are the resolution of current symptoms (ie, remission) and the prevention of further episodes of depression (ie, relapse or recurrence).
4. When counseling patients with MDD who are receiving antidepressant medications, the patient should be informed that adverse effects might occur immediately, while symptoms of depression may take 2 to 4 weeks to improve and up to 3 months for full resolution. Adherence to the treatment plan is essential for a successful outcome, and tools to help increase medication adherence should be discussed with each patient.
5. Since available antidepressants are considered equally efficacious for MDD, factors such as comorbid medical conditions, age, side effect profile, and past history of response are used to guide medication selection.
6. When determining if a particular medication is ineffective for a patient, it is essential to evaluate the dose and duration of treatment as well as patient adherence to the medication.
7. Pharmacogenetic tests are now commercially available. However, there are no standard or well-accepted recommendations for the use of pharmacogenetic testing as it relates to antidepressant treatment of MDD.

8 When evaluating response to an antidepressant, in addition to target signs and symptoms, the clinician must consider quality-of-life issues, such as social, and occupational functioning. In addition, the tolerability of the agent should be assessed because the occurrence of side effects may lead to medication nonadherence, especially in cases of recurrent episodes and long-term medication management.

Preclass Engaged Learning Activity

Watch the video entitled "Pharmacology – Antidepressants – SSRIs, SNRIs, TCAs, MAOIs, lithium (Made Easy)" at https://tinyurl.com/uxg4bju. This 19-minute video provides a brief and engaging overview of the pathophysiology of depression and mechanisms of commonly used antidepressant medications.

INTRODUCTION

Major depressive disorder (MDD) is diagnosed when an individual experiences one or more major depressive episodes without a history of mania or hypomania. A major depressive episode and MDD are defined by the criteria listed in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*).[1] Depression is associated with significant functional disability, morbidity, and mortality. Newer generations of antidepressants, such as the selective serotonin reuptake inhibitors (SSRIs), are equally effective and better tolerated than older agents, such as the tricyclic antidepressants (TCAs) and the monoamine oxidase inhibitors (MAOIs). This chapter focuses exclusively on the diagnosis and treatment of MDD.

1 Three key evidence-based guidelines on the assessment and management of MDD are available to assist the clinician. The American Psychiatric Association *Practice Guideline for the Treatment of Patients with Major Depressive Disorder,* Third Edition (2010) (available at www.psych.org) is a practical guide to the management of MDD based on both available data and clinical consensus.[2] The updated British Association of Psychopharmacology (BAP) *evidence-based guidelines for treating depressive disorders with antidepressants* (2015) provide recommendations for antidepressant treatment of MDD.[3] Finally, the Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 *Clinical Guidelines for the management of adults with major*

depressive disorder outlines evidence-based pharmacological treatments for MDD.[4] These three guidelines have many similarities in recommendations.

EPIDEMIOLOGY

While the actual prevalence of depressive disorders, including undiagnosed cases, is unknown, the estimated rate has increased over the past 25 years, but remained consistent over the past decade.[5–7] Overall, the lifetime incidence of depression is estimated at 10% to 15% in men and 20% to 25% in women.[7] Adolescent depression is increasingly common with an annual prevalence (2015) of 19.4% in females and 6.4% in males between 12 and 17 years of age (up from 13.1% and 4.5%, respectively in 2004) with suicide as the second leading cause of death between ages of 10 and 34 years of age.[6,8] Depressive disorders and suicide tend to occur within families. For example, approximately 8% to 18% of patients with major depression have at least one first-degree relative (father, mother, brother, or sister) with a history of depression, compared with 5.6% of those without depression.[9] Furthermore, first-degree relatives of patients with depression are 1.5 to 3 times more likely to develop depression than normal controls.[1,9] A recent meta-analysis found that the heritability of liability for major depression was 37%, whereas the remaining 63% of the variance in liability was due to individual-specific environment (eg, high stress, trauma).[10] Therefore, MDD is relatively common, occurs more frequently in women than in men, and prevalence is influenced by both genetic and environmental factors.

ETIOLOGY

The etiology of depressive disorders is too complex to be totally explained by a single social, developmental, or biologic theory. Several factors appear to work together to cause or precipitate depressive disorders.

PATHOPHYSIOLOGY

The monoamine hypothesis that depression is caused by decreased brain levels of serotonin (5-HT), dopamine (DA), and norepinephrine (NE) has been supported for over 50 years. However, the actual chemical basis for depression remains elusive.[11] This biogenic amine hypothesis evolved as a result of several observations made in the early 1950s. It was noted that the antihypertensive

medication reserpine depleted neuronal storage of NE, 5-HT, and DA and produced clinically significant depression in 15% or more of patients.[12] Subsequently, the hypothesis was supported by the mechanism(s) of antidepressant medications. Additionally, recurrence of depression has been induced by acute depletion of tryptophan (precursor of 5-HT) and 5-HT metabolite levels in cerebrospinal fluid are lower in some patients with MDD.[13] More recent evidence reveals the complexities of the monoamine systems in the brain. These systems are mediated by GABA, neuroactive steroids, endogenous opioids, and nutritional imbalances.[14–20] For the purposes of this chapter, the focus of medication mechanism of action will be the monoamine hypothesis unless otherwise specified (**Fig. 85-1, 85-2**).

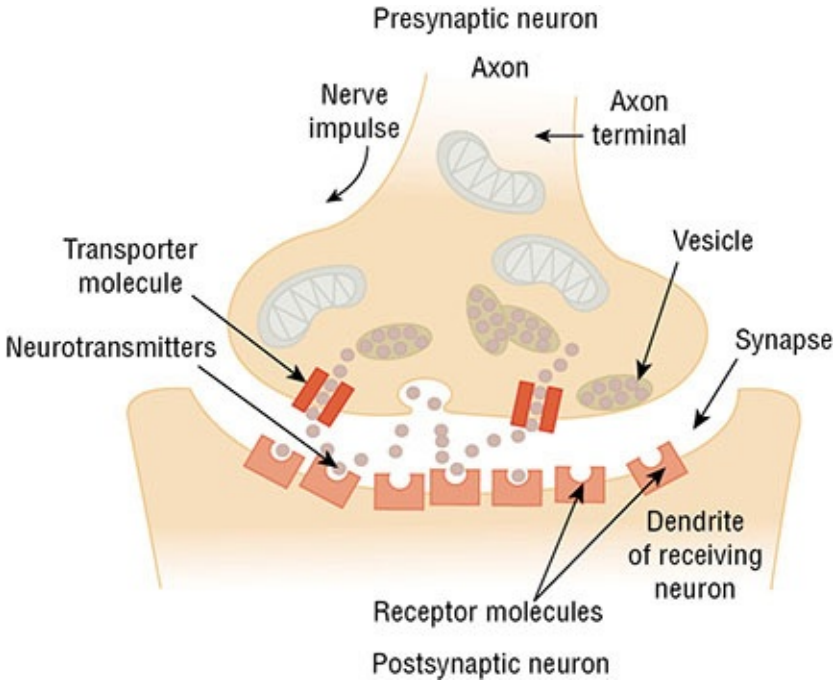


FIGURE 85-1 Monoamine neurotransmitter (NT) regulation at the neuronal level. NTs carry messages between cells. Each NT generally binds to a specific receptor, and this coupling initiates a cascade of events. NTs are reabsorbed back into nerve cells by reuptake pumps (ie, transporter molecules) at which point they may be recycled for later use or broken down by enzymes. For their primary mechanism of action, most antidepressants are thought to inhibit the transporter molecules and allow more NT to remain in the synapse. (*Reprinted from Mind Over Matter: The Brain's Response to Drugs - Teacher's Guide Revision. NIH Publication No. 05-3592. Office of Science Policy and Communications, National Institutes of Health. Revised May 2005. (Located at: https://teens.drugabuse.gov/sites/default/files/moms-combined_0.pdf*)

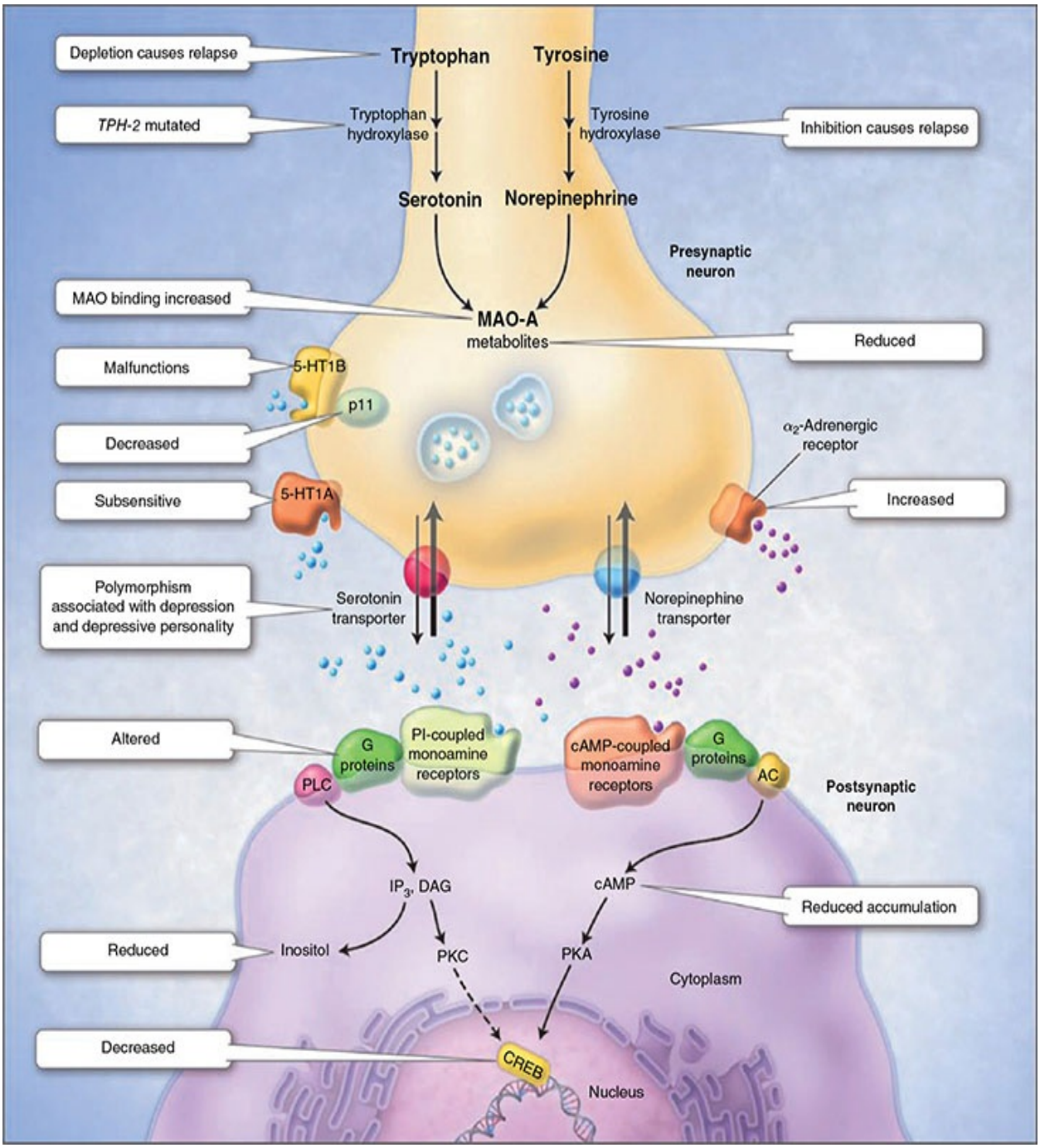


FIGURE 85-2 Perez D, Eldaief M, Epstein J, Silbersweig D, Stern E. Perez D, Eldaief M, Epstein J, Silbersweig D, Stern E Perez, David, et al. The Neurobiology of Depression: An Integrated Systems-Level, Cellular–Molecular and Genetic Overview. In: Barsky AJ, Silbersweig DA, Boland RJ. Barsky A.J., Silbersweig D.A., Boland R.J. Eds. Arthur J. Barsky, et al. eds. *Depression in Medical Illness* New York, NY: McGraw-Hill; http://neurology.mhmedical.com/content.aspx?

bookid=1891&sectionid=138744296. Accessed November 15, 2018.

It must also be noted that these monoamine systems do not function independently, but serve as feedback mechanisms for each other. Therefore, a medication that preferentially enhances NE transmission may secondarily alter both 5-HT and DA activity.[21,22]

Although the increase in monoamines (eg, NE, DA, and 5-HT) occurs rapidly after initiation of an antidepressant, the clinical effects (ie, measurable symptom improvement) are generally delayed by weeks.[13,21] This delay may be the result of a cascade of events from receptor occupancy to gene transcription, downregulation of presynaptic feedback mechanisms, secondary effects on other neurotransmitter symptoms or neuroplasticity,[11,13,23] and has led researchers to focus on the adaptive changes induced by antidepressants. In the mid-1970s, it was recognized that chronic, but not acute, administration of antidepressants to animals caused desensitization of NE-stimulated cyclic adenosine monophosphate synthesis. In fact, for most antidepressants, downregulation of β-adrenergic receptors accompanies this desensitization.[24,25] Studies of many antidepressants have demonstrated that either desensitization or downregulation of NE receptors corresponds to a clinically relevant time course for antidepressant effects.[25] Other studies have revealed desensitization of presynaptic 5-HT_{1A} autoreceptors following chronic administration of antidepressants.[13] Thus, a theory based on changes in receptor sensitivity provides a cogent explanation of the delayed onset of therapeutic response of antidepressant medications. The dysregulation hypothesis incorporates the diversity of antidepressant activity with the adaptive changes occurring in receptor sensitization over several weeks. In this theory, emphasis is placed on a failure of homeostatic regulation of NT systems rather than on absolute increases or decreases in their activities. According to this hypothesis, effective antidepressant agents restore efficient regulation to the dysregulated NT system.[11]

Traditional explanations of the biologic basis of depressive disorders have focused largely on NE and 5-HT. however, most of the evidence that coalesced into the biogenic amine hypothesis of depression does not clearly distinguish between NE and DA. There is an abundance of evidence suggesting that DA transmission is decreased in depression and agents that increase dopaminergic transmission have been found to be effective antidepressants.[21] Specifically, studies suggest that increased DA transmission in the mesolimbic pathway accounts for at least part of the mechanism of action of antidepressant

medications.[21] The mechanisms by which antidepressant medications alter DA transmission remain unclear, but may be mediated either directly by dopaminergic changes or indirectly by primary actions at NE or 5-HT terminals. The complexity of the interaction between 5-HT, NE, and DA is gaining greater appreciation, but a more in-depth understanding of the precise mechanism is needed. Furthermore, the availability of dopaminergic-based first-line and augmentation antidepressant strategies has been slowly growing (eg, bupropion, high-dose venlafaxine, second-generation antipsychotics).

Neuroactive steroids are a growing area of research in depression as a link between the progesterone metabolite, allopregnanolone and depression has been found. Alloprenganolone release is increased in the setting of acute stress and may serve a neuroprotective role. However, chronic stress and MDD have been associated with decreased CNS concentrations of allopregnanolone. Rapid decline in allopregnanolone levels in the postpartum period have been associated with postpartum depression.[26] Furthermore, certain antidepressants have been shown to increase cerebral spinal fluid (CSF) levels of allopregnanolone proportional to depressive symptom response.[16]

Another proposed pathway for depression involves a complex interplay of inflammation and overexcitation resulting in decreased neuroplasticity and neuronal differentiation. Brain-derived neurotrophic factor (BDNF) is a primary mediator of these neuronal changes as well as synaptogenesis. Chronic stress, associated with increased glucocorticoids such as cortisol, may decrease BDNF expression. Evidence suggests this process may be prevented, or possibly even reversed, by antidepressant medications or electroconvulsive therapy (ECT).[27] These treatments have been shown to increase BDNF expression along a timeline similar to antidepressant response.[27]

Chronic stress and inflammation also alter glutamatergic and GABA transmission, changes that have been linked to depression and decreased BDNF. Increased $GABA_A$ receptor activity is associated with decreased transmission of 5-HT and increased NE transmission while increased $GABA_B$ receptor activation is associated with decreased 5-HT and NE transmission.[22] Increased serum and extrasynaptic glutamate has been associated with MDD symptom severity. Many currently available antidepressants decrease serum glutamate concentrations that are thought to increase BDNF activity.[14,27] An example of this is ketamine that inhibits extrasynaptic NMDA receptors, which theoretically results in increased synaptic glutamate activity, triggering BDNF release from synaptic vesicles.[28] Further, BDNF has been shown to decrease expression of

$GABA_A$ receptors possibly resulting in increased 5-HT and NE transmission linking it back to the monoamine hypothesis.[27] The full interaction of all of these related systems is not fully understood. However, the complexities could partially explain differences in response to medications as there are likely distinct subtypes of depression with different pathogenesis.

Biologic Markers

Investigators continue to search for biologic markers to assist in the diagnosis and treatment of depressed patients. Although no gold-standard biologic marker has been discovered, several biologic abnormalities have been variably identified depressed patients. Hypersecretion of cortisol or a lack of cortisol suppression after dexamethasone administration (ie, a positive dexamethasone suppression test) has been positively correlated to depression as well as risk of suicide.[29] Although the widespread use of this test has fallen out of favor in recent decades (due to limited sensitivity and specificity), it has been suggested that the inability of the brain to suppress the hypothalamic–pituitary–adrenal (HPA) axis and the associated stress response could contribute to depression, possibly due to excessive glutamate and decreased BDNF discussed above.[29] According to this theory, there is a disruption somewhere in the normal negative feedback system that controls cortisol levels.

Emerging evidence provides promise for both biologic and genetic markers for MDD. As previously mentioned serum levels of glutamate have correlated with MDD severity and rising concentrations of BDNF in the CNS have correlated to antidepressant response. The genes coding for BDNF production have been identified as well as polymorphisms that result in lower levels of BDNF.[28] Another focus of pharmacogenomics has been on polymorphisms of methylenetetrahydrofolate reductase (*MTHFR*) that may be associated with differences in rates of depression and antidepressant response (inconsistent results to date).[30] Multiple other phenotypes have been identified and are available for testing with commercially available products, but evidence to date does not support routine testing for diagnosis or to predict treatment response.[31] Nor is there enough evidence to support testing CNS concentrations of BDNF or serum concentrations of glutamate.

CLINICAL PRESENTATION

2 When a patient presents with depressive symptoms, it is necessary to investigate the possibility of a contributing medical or drug-induced etiology. All depressed patients should have a complete physical examination, mental status examination, and basic laboratory workup, including a complete blood count (CBC) with differential, thyroid function tests, and electrolytes, to identify any potential medical problems. While a complete discussion of medical conditions associated with depression is beyond the scope of this chapter, multiple common medical conditions are associated with development of depressive symptoms, such as stroke, Parkinson disease, traumatic brain injury, and hypothyroidism. Additionally, other conditions are associated with increased risk for depression including pain, diabetes, seizures, and coronary artery disease.[34] The *DSM-5* describes a diagnostic category for both "Depressive Disorder Due to Another Medical Condition" and "Substance/Medication-Induced Depressive Disorder,"[1] which emphasizes the importance of ruling out alternative causes of symptoms. A complete medication review should include both current and previous medications to assess for both helpful and contributing medications. Additionally, consider the contribution of withdrawal from substances (eg, cocaine, marijuana, or alcohol) to depressive symptoms. **Table 85-1** lists medications commonly associated with causing or exacerbating depressive symptoms.[35–42]

TABLE 85-1 Selected Medications Associated with Depressive Symptoms

Medication class	Individual agents	Comments
Acne treatment	Isotretinoin	• REMS program iPledge recommends monitoring psychiatric symptoms
Anticonvulsants	All FDA-approved anticonvulsants (including clorazepate and clonazepam)	• Specific warning added to labeling under Warnings and Precautions regarding increased risk of suicidal thoughts or behavior • Not all agents with warning have demonstrated increased risk • Controversial
Cardiovascular medications	Reserpine	• Rarely used due to historical reports of depression due to depletion of monoamines
	Angiotensin receptor blockers β-blockers Calcium channel blockers Clonidine Methyldopa	• Conflicting data for most agents • β-blockers classically linked to depression; however, most evidence supports only physical symptoms of fatigue and low energy • Link between cardiovascular disease and depression must be considered
Central nervous system agents	Deutetrabenazine Tetrabenazine Valbenazine	• Deplete synaptic monoamines via decreasing vesicular transport in presynaptic neurons • Deutetrabenazine and tetrabenazine have black box warning for depression and suicidality
Hormonal therapy	Gonadotropin-releasing hormone Oral contraceptives	• Linked to alterations in progesterone and estrogens and possible link to monoamine oxidase activity
	Steroids (eg, prednisone)	• Possible association with inflammation and HPA axis changes in depression
Immunologic agents	Interferons	• Labeled warning, but not black box warning
Smoking cessation medications	Varenicline	• Reports to FDA MedWatch after release • Large postmarketing study does not support increased risk

REMS: Risk Evaluation and Mitigation Strategy, FDA: Food and Drug Administration

Data from References 2, 35–42.

Once other medical or substance related causes of symptoms have been ruled out, the patient should be evaluated for MDD. According to the *DSM-5*, a single major depressive episode is characterized by five (or more) of the symptoms described in **Table 85-2**.[1] At least one of the symptoms is depressed mood (often an irritable mood in children or adolescents) or loss of interest or pleasure in nearly all activities.[1] These symptoms must have been present nearly every day for at least 2 weeks and must represent a change from the patient's previous level of functioning. The *DSM-5 omits* the bereavement exclusion that appeared in earlier DSM editions. Some feel that this omission opens the door to misdiagnosis of normal grief as MDD. The diagnostic code for MDD is

determined by whether this is a single or recurrent depressive episode, current severity, presence of psychotic features, and remission status. The diagnosis can be followed by specifiers that apply to the current episode. The possible specifiers include anxious distress, mixed features (ie, presence of manic/hypomanic features), melancholic features, atypical features, mood-congruent or incongruent psychotic features, catatonia, peripartum onset, and seasonal pattern. The clinician must consider presenting symptoms, their duration, and the patient's current level of social, occupational, or other important areas of functioning. Significant stressors or life events may trigger depression in some individuals but not others, and there may be an important precipitant at the beginning of the disorder.[1]

TABLE 85-2 Diagnostic Criteria for Major Depressive Episode

S	Suicidal ideation with or without plan, suicide attempt; recurrent thoughts of death
I	Interest—loss of interest or pleasure in activities; anhedonia
G	Guilt—inappropriate or excessive in nature; feelings of worthlessness
E	Energy decreased
C	Concentration decreased; difficulty making decisions
A	Appetite changes; typically decreased; resulting in 5% change in weight from baseline
P	Psychomotor agitation or retardation
S	Sleep impairment; typically insomnia but may be hypersomnia

- At least five symptoms must be consistently present over a 2-week period.
- Symptoms must include depressed mood or anhedonia.
- Symptoms must cause substantial distress or impairment in functioning.
- Other medical conditions or substance use do not account for symptoms.

Data from Reference 1.

CLINICAL PRESENTATION Depressive Disorder

Emotional Symptoms

- Diminished ability to experience pleasure
- Loss of interest and pleasure in usual activities, hobbies, or work (anhedonia)

- Pessimism, hopelessness regarding feeling better
- Anxiety
- Voices (auditory hallucinations) saying negative comments or suggesting suicide

Physical Symptoms

- Chronic fatigue resulting in decreased ability to attend to daily tasks (eg, bathing, grooming)
- Fatigue does not improve with rest and is often associated with pain, headache
- Changes in sleep (early morning awakening, difficulty falling asleep, frequent awakening or increased sleep with associated fatigue)[32]
- Appetite changes (most common decreased appetite and unintentional weight loss; some patients may eat more)[32,33]
- Gastrointestinal disturbances, genitourinary issues, cardiovascular complaints (eg, palpitations), loss of libido

Cognitive Symptoms[33]

- Decreased concentration or slowed thinking
- Poor memory for recent events (especially elderly)
- Confused or indecisive

Psychomotor Disturbances

- Slow physical movements, speech and thought processes (psychomotor retardation)
- Restlessness (eg, pacing, wringing of hands), outbursts of anxiety or agitation (eg, crying or yelling); together known as psychomotor agitation

Depression Rating Scales

Instruments to assess the severity of depressive symptoms can be used for both clinical and research purposes. For example, the Montgomery-Åsberg

Depression Rating Scale (MADRS) is a clinician-administered scale that is commonly used in clinical trials given its sensitivity to change.[43] Some depression rating scales are self-administered such as the Beck Depression Inventory (BDI) that takes only 5 to 10 minutes to complete by the respondent.[44] The PHQ-9 is another brief scale that has been validated for use.[45] For a more detailed explanation for both of these instruments, as well as other rating scales and evaluation approaches, refer to Chapter e79.

Emotional Symptoms

A major depressive episode is characterized by a persistent, diminished ability to experience pleasure, and as such a loss of interest and pleasure in usual activities, hobbies, or work is common. Patients appear sad or depressed, and they are often pessimistic and believe that nothing will help them feel better. The occurrence of guilty feelings that are unrealistic is common, and these may reach delusional levels where patients feel that they deserve punishment and may view their present illness as a punishment. A patient suffering from major depression with psychotic features may hear voices (auditory hallucinations) saying that he or she is a bad person and that he or she should commit suicide. Depression with psychotic features may require hospitalization, especially if the patient becomes a danger to self or others. Additionally, anxiety symptoms are present in almost 90% of depressed outpatients, which is important to note as this may have treatment implications.

Additional Symptoms of Depression

Physical symptoms, rather than depressive symptoms, often motivate patients, especially the elderly, to seek medical attention. Chronic fatigue, with a decreased ability to perform normal daily tasks is a common presenting symptom. The fatigue seen in patients with depression often appears worse in the morning, does not improve with rest, and is commonly accompanied by pain, especially headache.

Sleep disturbances generally present as frequent early morning awakening with difficulty returning to sleep. This may coexist with difficulty falling asleep and frequent nighttime awakening. Less frequently, depressed patients complain of increased sleep (hypersomnia), although they experience daytime exhaustion or fatigue. Recognition and management of sleep disturbances among depressed patients is crucial, as it has been estimated that approximately 60% to 90% of

patients experiencing MDD report sleep disturbances.[32]

Appetite disturbances, including complaints of decreased appetite, often result in substantial weight loss, especially in the elderly.[32,33] Some patients lose 2 lb (0.9 kg) or more per week without dieting. Other patients, especially in the ambulatory setting, may overeat and gain weight, although they actually may not enjoy eating.

Patients may present with a variety of other symptoms such as gastrointestinal (GI) issues, genitourinary issues, cardiovascular complaints (eg, palpitations), cognitive impairment (especially elderly), or muscle fatigue. Lastly, patients frequently present with a loss of sexual interest or libido.

In addition to physical symptoms patients with MDD frequently experience cognitive and psychomotor disturbances noted in the Clinical Presentation Box.

Suicide Risk Evaluation and Management

As of 2016, the Centers for Disease Control and Prevention listed suicide as the tenth leading cause of death among Americans and the second leading cause of death among 10- to 34-year-olds.[6] Suicide rates increased between 6% and 58% in 49 of 50 states between 1999 and 2016.[5] All patients diagnosed with MDD should be assessed for suicidal thoughts and factors associated with increased risk for suicide including other psychiatric disorders, substance use disorders, adolescent and younger age adults, physical illness, recent stressful life event, childhood trauma, hopelessness, and male gender.[46] Those with a higher level of risk often have high degree of suicidal intent and describe more specific plans, in particular, plans that are violent and irreversible.[46] It is important to remember that the risk of suicide in those recovering from major depression may increase as they develop the energy and capacity to act on a plan made earlier in a course of illness. Additionally, despite factors to help identify those at greatest risk, it remains very difficult to predict suicidality in any given individual. Therefore, when suicidal intent is suspected, it is important to ask, “Are you thinking about harming or killing yourself?” If the risk is significant, the patient must be referred immediately to an appropriate healthcare professional. Certain depression rating scales, such as the MADRS and PHQ-9 discussed above, include questions that target suicidality, which may help identify those patients at risk. Additionally, the Columbia-Suicide Severity Rating Scale is widely accepted in clinical practice as a validated assessment of suicide risk.[47]

In September 2004, the FDA required manufacturers of antidepressants to add a boxed warning stating that all antidepressants increase the risk of suicidal

thinking and behavior in short-term studies in children and adolescents with depressive disorders. These risks have become a new source of concern among those treating their patients with antidepressants. In order to help deal with the confusion these warnings have caused, experts have recommended the following[48]:

1. It is especially important to closely monitor patients for suicidal ideation and behavior at the beginning of treatment and among younger patients.
2. Discuss the possibility that adverse events may occur, including behavioral agitation or anger, and encourage patients to seek help should this occur.
3. Deal with the subject of suicide directly.

It is important to note that there is little evidence to suggest that withholding antidepressant treatment decreases the risk of eventual suicide and may actually increase the risk. Furthermore, it may be that longer-term medication is needed for any protective effects against suicidality.[48]

In May 2007, the FDA expanded the black box warning regarding suicidality to include young adults 18 to 24 years of age, during the initial stages of treatment. The warning also applies to any medication with either monotherapy or adjunct treatment of depression as an FDA-approved indication even if not classified as an “antidepressant” (eg, aripiprazole, quetiapine).

Assessment of actual suicide risk has proven to be difficult as there are differences in coding of events in clinical trials and complete case data from trials is often not available. Additionally, there appears to be an increased risk of suicidality in the 30 days after antidepressant discontinuation, which is not routinely evaluated in clinical trials.[49] An increased risk of suicidality in children and adolescents has been found in multiple studies and this population should be evaluated carefully upon initiation or discontinuation of antidepressant treatment. The complex relationships between antidepressant use and suicidality will continue to be explored with the hopes of more unequivocal recommendations.

TREATMENT

Desired Outcomes

3 The goal of treating depression is resolution of depressive symptoms and return to previous level functioning. Initial treatment may occur in the hospital or in outpatient treatment settings. Hospitalization is more likely when there is a

high risk of suicide, poor physical health, limited social support or psychotic symptoms. Once a patient has achieved remission of symptoms, the goal of treatment transitions to prevention of further episodes of depression (ie, relapse or recurrence). It should be noted that the standard definition of treatment response in clinical trials is a 50% decrease in symptoms which may mean for patients who started with a high degree of depressive symptomatology, the residual depressive symptoms remain after treatment. This may be compared to depression remission in which few to no depressive symptoms remain.

General Approach to Treatment

There are three phases of treatment for patients with MDD: (a) the *acute* phase lasting approximately 6 to 12 weeks in which the goal is remission (ie, absence of symptoms); (b) the *continuation* phase lasting 4 to 9 months after remission is achieved, in which the goal is to eliminate residual symptoms or prevent relapse (ie, return of symptoms within 6 months of remission); and (c) the *maintenance* phase lasting at least 12 to 36 months in which the goal is to prevent recurrence (ie, a separate episode of depression).[2,50] The duration of antidepressant therapy depends on the risk of recurrence that increases with the number of past depressive episodes. Some guidelines recommend lifelong maintenance therapy for persons at greatest risk for recurrence (persons younger than 40 years of age with two or more prior episodes and persons of any age with three or more prior episodes).[2] An alternative guideline is to treat for at least 2 years in patients considered to be at high risk for relapse.[3] The decision as to “when” and “how” to taper/discontinue an antidepressant regimen is always going to depend on patient- and medication-specific variables. Both SSRIs and SNRIs have an idiosyncratic discontinuation syndrome that may occur; therefore, it is recommended to slowly taper these agents over weeks to months to minimize risk. However, a slow taper is not always effective in preventing discontinuation symptoms.[51]

4 Educating the patient and their support system (eg, family and friends) regarding the delay in antidepressant effects and the importance of adherence should occur before and during the entire course of treatment. The treatment of MDD generally includes nonpharmacologic and pharmacologic strategies, which are discussed in further detail below.

Nonpharmacologic Therapy

In addition to pharmacologic interventions, psychotherapy ("talk therapy") should be employed whenever the patient is able and willing to participate. Traditionally, psychotherapy alone is recommended only for mild to moderately severe cases of MDD. However, recent evidence supports the benefit of cognitive behavioral therapy (CBT) for even severe MDD.[52] Psychotherapy should not be the primary treatment modality for patients with psychotic features. As the effects of psychotherapy and antidepressant medications are considered to be additive, combined treatment may be advantageous for patients with partial responses to either treatment alone and for those with a chronic course of illness. In practice, CBT as primary treatment is limited significantly by cost and logistics (eg, need for more frequent appointments and time off work). Additionally, many insurance plans do not adequately cover the cost of psychotherapy, the availability of providers may be limited in certain areas, and patients may be more reluctant to spend the time in therapy versus taking medication daily. In the landmark Sequenced Treatment Alternatives to Relieve Depression study (STAR*D), evaluation of the psychotherapy arm was limited by low participation rates by patients.[53]

Electroconvulsive therapy (ECT) is a safe and effective treatment for certain severe psychiatric illnesses, including MDD. Patients with MDD are candidates for ECT when a rapid response is needed (eg, severe suicidality, nutritional deficiency, catatonic symptoms), risks of other treatments outweigh potential benefits, a history of symptoms refractory to two antidepressant trials or a history of good response to ECT, and the patient expresses a preference for ECT. A more recent nonpharmacologic approach is repetitive transcranial magnetic stimulation (rTMS), which has demonstrated efficacy in treating MDD without anesthesia required for ECT.[54]

The health benefits of physical activity have long been recognized for many medical conditions, and recent data suggest benefits in depressed patients. The Treatment with Exercise Augmentation for Depression (TREAD) study demonstrated that 16 kcal (67 kJ) per kilogram per week (KKW) exercise was associated with greater MDD remission rates compared with 4 KKW, when both were used as augmentation to an SSRI.[55] The APA task force concluded that integrating exercise into the MDD-treatment plan is medically appropriate and confers many well-accepted health benefits.[56]

Pharmacologic Therapy

Antidepressants are considered first-line treatment for a moderate-to-severe

depressive episode,[2–4] and they can be classified in several ways, including by chemical structure and the presumed mechanism of antidepressant activity. Although the link between the presumed mechanism of action and antidepressant response is tenuous, this classification has the advantage of being based on established pharmacology and clearly explains some of the common, but expected, adverse effects. The knowledgeable clinician can use these antidepressant properties to tailor treatment to individual patient needs and thereby optimize treatment outcome. Currently available antidepressants, including dosing guidance, are provided in **Table 85-3**.[2,3,50,57–60]

TABLE 85-3 Adult Dosing Guidance for Currently Available Antidepressant Medications

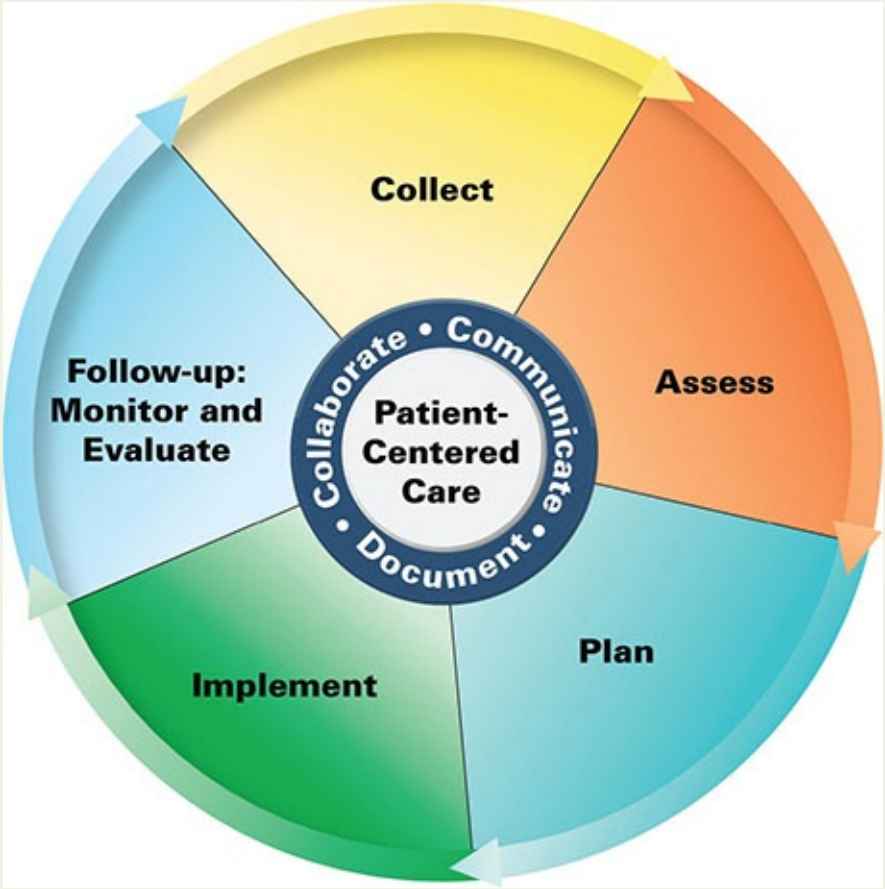
Drug (Brand Name)	Initial Dose (mg/day)	Usual Dosage Range (mg/day)	Comments (eg, Maximum Daily Dosage, Suggested Therapeutic Plasma Concentration)*
Selective Serotonin Reuptake Inhibitors (SSRIs)			
Citalopram (Celexa)	20	20-40	Doses >40 mg/day not recommended due to QT prolongation risk; maximum 20 mg/day for CYP2C19 poor metabolizers or coadministration with CYP2C19 inhibitors; 20 mg/day recommended for patients older than 60 years of age
Escitalopram (Lexapro)	10	10-20	Maximum 20 mg/day; dose may be increased to maximum daily dose after at least 1 week if needed; 5-mg tablet available for unique circumstances
Fluoxetine (Prozac)	20	20-60	Maximum 80 mg/day; dose may be increased in 20-mg increments; doses of 5 or 10 mg/day have been used as initial therapy; doses >20 mg/day may be given in a single daily dose or divided twice daily
Fluvoxamine (Luvox)	50	50-300	Maximum 300 mg/day; daily doses >100-mg total dose should be divided twice daily, with the larger dose given at night Maximum 300 mg/day (ER formulation)
Paroxetine (Paxil)	20	20-50	Maximum 50 mg/day (IR formulation); titrate 10 mg/day increments weekly Maximum 62.5 mg/day (CR formulation); titrate 12.5 mg/day increments weekly
Sertraline (Zoloft)	50	50-200	Maximum 200 mg/day; titrate 25 mg/day increments weekly
Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)			
Newer-generation SNRIs			
Desvenlafaxine (Pristiq)	50	50	Doses up to 400 mg/day have been studied; however, AEs are increased and no additional benefit has been shown at doses exceeding 50 mg/day. Dose reductions or discontinuation may be required if sustained hypertension occurs
Duloxetine (Cymbalta)	30	30-90	Maximum 120 mg/day (given once or twice daily); doses exceeding 60 mg/day not shown to provide increased efficacy for the treatment of MDD
Venlafaxine (Effexor)	37.5-75	75-225	Maximum 375 mg/day (IR); maximum 225 mg/day (ER); may increase in increments up to 75 mg/day at a minimum of every 4 days. Dose reductions or discontinuation may be required if sustained hypertension occurs
Levomilnacipran (Fetzima)	20	40-120	Initial dose (20 mg) for 2 days before dose increases is recommended at intervals of two or more days. Dose adjustment or discontinuation may be required if sustained elevated heart rate or hypertension occurs
Tricyclic antidepressants (TCAs)			
Amitriptyline (Elavil)	25	100-200	Maximum 300 mg/day for MDD; depending on the total dose, it may be given as a single daily dose at bedtime or in divided doses throughout the day; therapeutic serum level 100-250 ng/mL (mcg/L; 370-925 nmol/L); parent drug plus metabolite (nortriptyline)
Desipramine (Norpramin)	25	100-200	Maximum 300 mg/day; suggested therapeutic concentration range for combined imipramine + desipramine: 150-300 ng/mL (mcg/L; 550-1,100 nmol/L)
Doxepin (Sinequan)	25	100-200	Maximum 300 mg/day; may be given in a single daily dose at bedtime (if tolerated) or in divided doses throughout the day; a single dose should not exceed 150 mg
Imipramine (Tofranil)	25	100-200	Maximum 300 mg/day; may be given in a single daily dose at bedtime (if tolerated) or in divided doses throughout the day; suggested therapeutic concentration range for combined imipramine + desipramine: 150-300 ng/mL (mcg/L; 550-1,100 nmol/L)
Nortriptyline (Pamelor)	25	50-150	Maximum 150 mg/day; total daily may be given as a single daily dose (if tolerated) or 25 mg doses given three to four times daily; therapeutic serum level 50-150 ng/mL (mcg/L; 190-570 nmol/L)
Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)			
Bupropion (Wellbutrin)	150 (75 mg given twice daily)	150-450	Maximum 450 mg/day (IR, ER), 400 mg/day (SR); ER dosed once daily; SR dosed once or twice daily; IR may be dosed up to three times daily. Adhering to labeled maximum daily and maximum single doses minimizes effect on seizure threshold.
Mixed Serotonergic Effects (Mixed 5-HT)			
Nefazodone (Serzone)	100	200-400	Maximum 600 mg/day; daily doses should be divided twice daily
Trazodone (Desyrel; Oleptro)	50	150-300	Maximum 600 mg/day; IR daily dose should be divided three times daily and may increase by 50 mg/day increments every 3-7 days; ER dose titration initiated at 150 mg at bedtime and can be increased 75 mg/day every 3 days
Vilazodone (Viibryd)	10	20-40	Target dose 20-40 mg/day unless coadministered with CYP3A4 inhibitor (dose not to exceed 20 mg/day). Dose titration: 10 mg/day for 7 days, 20 mg/day for 7 days, and then may increase to 40 mg/day. Dose must be taken with food to ensure adequate drug absorption and bioavailability.
Vortioxetine (Brintellix)	10	20	Maximum 20 mg/day; minimal difference in efficacy and side effects in clinical trials between 10 and 20 mg
Serotonin and α_2-Adrenergic Antagonist			
Mirtazapine (Remeron)	15	15-45	Maximum 45 mg/day; dose adjustment may be required for renal impairment
Monoamine Oxidase Inhibitors (MAOIs)			
Phenelzine (Nardil)	15	30-90	Divided dosing 2 to 3 times daily; dosing may be increased to 90 mg/day based on tolerance and response
Selegiline (transdermal) (Emsam)	6	6-12	Not to exceed 12 mg/24 hours; dose may be increased by 3 mg/day increments every 2 weeks; site of application should be rotated
Tranylcypromine (Parnate)	10 10-20	20-40 30-60	Maximum 60 mg/day; divided dosing; increase by 10 mg at 1- to 3-week intervals
Isocarboxazid (Marplan)	10-20	30-60	Maximum 60 mg/day; divided dosing

Drug (Brand Name)	Initial Dose (mg/day)	Usual Dosage Range (mg/day)	Comments (eg, Maximum Daily Dosage, Suggested Therapeutic Plasma Concentration)*
Second-generation Antipsychotics (SGA) as Augmentation ($5HT_{2A}$ and D_2 modulators)			
Aripiprazole (Abilify)	2	2-15	FDA approved for augmentation; CANMAT Level 1 evidence, 1st line
Brexpiprazole (Rexulti)	1	1-3	Not FDA approved for augmentation; CANMAT Level 1 evidence, 2nd line
Olanzapine (Zyprexa)	2.5	2.5-10	Not FDA approved for augmentation; CANMAT Level 1 evidence, 2nd line
Quetiapine (Seroquel)	50	150-300	FDA approved for augmentation; CANMAT Level 1 evidence, 1st line
Risperidone (Risperdal)	1	1-3	Not FDA approved for augmentation; CANMAT Level 1 evidence, 1st line
Alternative Augmentation Agents (Not FDA Approved for Antidepressant Augmentation)			
Buspirone (Buspar)	10	10-60	Divided dosing 2 to 3 times daily 5HT1A partial agonist
Lithium	300	600-1200	Dose based on therapeutic levels (target 0.6-1 mEq/L [mmol/L]) Mechanism in depression not fully understood
Triiodothyronine (Cytomel)	0.025	0.025-0.05	Once daily dosing; monitor free T3 levels

*SI conversion for cases where reference ranges are for a mixture of parent drug and active metabolite is calculated based on a 1:1 ratio.

AE, adverse effects; CR, continuous release; ER, extended release; IR, immediate release; MDD, major depressive disorder; SR, sustained release; CANMAT, Canadian Network for Mood and Anxiety Treatments.

Data from References 2, 3, 50, and 57–60.



Patient Care Process for Major Depressive Disorder

Collect

- Patient characteristics (eg, age, sex)
- Current and past medical/psychiatric history (including information on first-degree family members)
- Past medication history, including medications not tolerated and any medication allergies (also collect on first-degree family members)
- Social history (eg, tobacco, ethanol, and other substance use as well as social supports and/or stressors)
- Current medications including over-the-counter (OTC), herbal products, dietary supplements and medical or recreational marijuana
- Objective data
    - Blood pressure, heart rate, weight
    - Labs including thyroid function tests, serum creatinine, complete

blood count (CBC), liver function tests, urine drug screen, blood alcohol level, serum drug levels and pharmacogenomics testing if available

- Reported symptoms of depression or other rating scale assessment (eg, Patient Health Questionnaire 9 [PHQ-9], Beck Depression inventory [BDI]) (Table 85-2 and Chapter e79, "Evaluation of Psychiatric Illness")

Assess

- Suicidality (eg, Columbia-Suicide Severity Scale)
- Severity of illness/need for hospitalization
- Impact of substance use on symptoms and whether substance use disorder is contributing
- Presence of physical conditions that may overlap with depression symptoms (eg, pain resulting in insomnia or limited activity, gastrointestinal symptoms resulting in weight loss) or medications that maybe contributing to depressive symptoms (Table 85-1)
- Past response and adherence (personal or family) to antidepressant medications
- Ability/willingness to follow up with psychiatry services including antidepressant medication management, cognitive behavioral therapy (CBT), outpatient groups
- Barriers to participation in medication management or CBT
- Barriers to adjunctive treatments (eg, exercise, stretching, yoga)
- Pharmacogenomics testing results

Plan*

- Medication therapy regimen including specific agent(s), dose, frequency, and titration plan if applicable (Tables 85-3 and 85-4)
- Monitoring parameters including efficacy (looking for some improvement in 2-4 weeks), safety (change in suicidality), and adverse effects (may be seen in first 1-2 weeks of treatment) (Table 85-4)
- Patient education (eg, purpose of treatment, medication-specific information, medication adherence, and review of laboratory/pharmacogenomics results) (Table 85-5)
- Patient education regarding self-monitoring, when to call the clinic with

questions or concerns, and when to seek emergency medical attention (eg, suicidality)
- Obtain release of information to obtain collateral information (eg, family members, therapists, medical providers)
- Nonpharmacological interventions (eg, diet, exercise, mindfulness)
- Make referrals to other providers when appropriate (eg, neurologist, pain specialist, substance use disorder treatment)
- Potential for drug–drug interactions (Tables 85-7 through 85-9)

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching to maximize adherence
- Schedule follow-up to monitor an assess medication effectiveness (eg, PHQ-9, BDI) and adherence to treatment plan, including therapeutic drug monitoring when appropriate.

Follow-up: Monitor and Evaluate

- Resolution of depressive symptoms using standardized rating scales
- Presence of adverse medication side-effects (Table 85-10)
- Laboratory follow-up when indicated (eg, sodium, liver function tests)
- Patient adherence to treatment plan based in multiple sources of information (eg, medication refill records, caregiver report)
- Consider scheduling early or more frequent (every 1-2 weeks) follow-up visits after initiating therapy to monitor response and behavioral risks such as suicidality. Reevaluate initial response at 2 to 4 weeks and again at 8 to 12 weeks. Reevaluate treatment plan quarterly and reevaluate duration of therapy after patient achieves remission

**Collaborate with patient, caregivers, and other healthcare professionals.*

5 Studies have found that antidepressants are of *equivalent efficacy* in groups of patients when administered in comparable doses. Because one cannot predict which antidepressant will be the most effective in an individual patient, the initial choice is made empirically. Factors that often influence the choice of an antidepressant include the patient's history of response, history of familial antidepressant response, patient's concurrent medical illnesses and medications,

presenting symptoms (eg, insomnia vs. hypersomnia), potential for drug–drug interactions, adverse event profile, patient preference, and medication cost. Although the precise pathophysiology of MDD remains elusive, the clinician can now select from multiple approved medication therapies with different mechanisms of action (Tables 85-3 and 85-4.)[2–4,61] Failure to respond to one antidepressant class or one antidepressant agent within a class does not predict a failed response to another class or another agent within the same class (**Fig. 85-3**). Approximately 50% to 60% of patients with MDD improve with acute medication therapy, compared with about 30% to 40% who improve with placebo.[3,62]

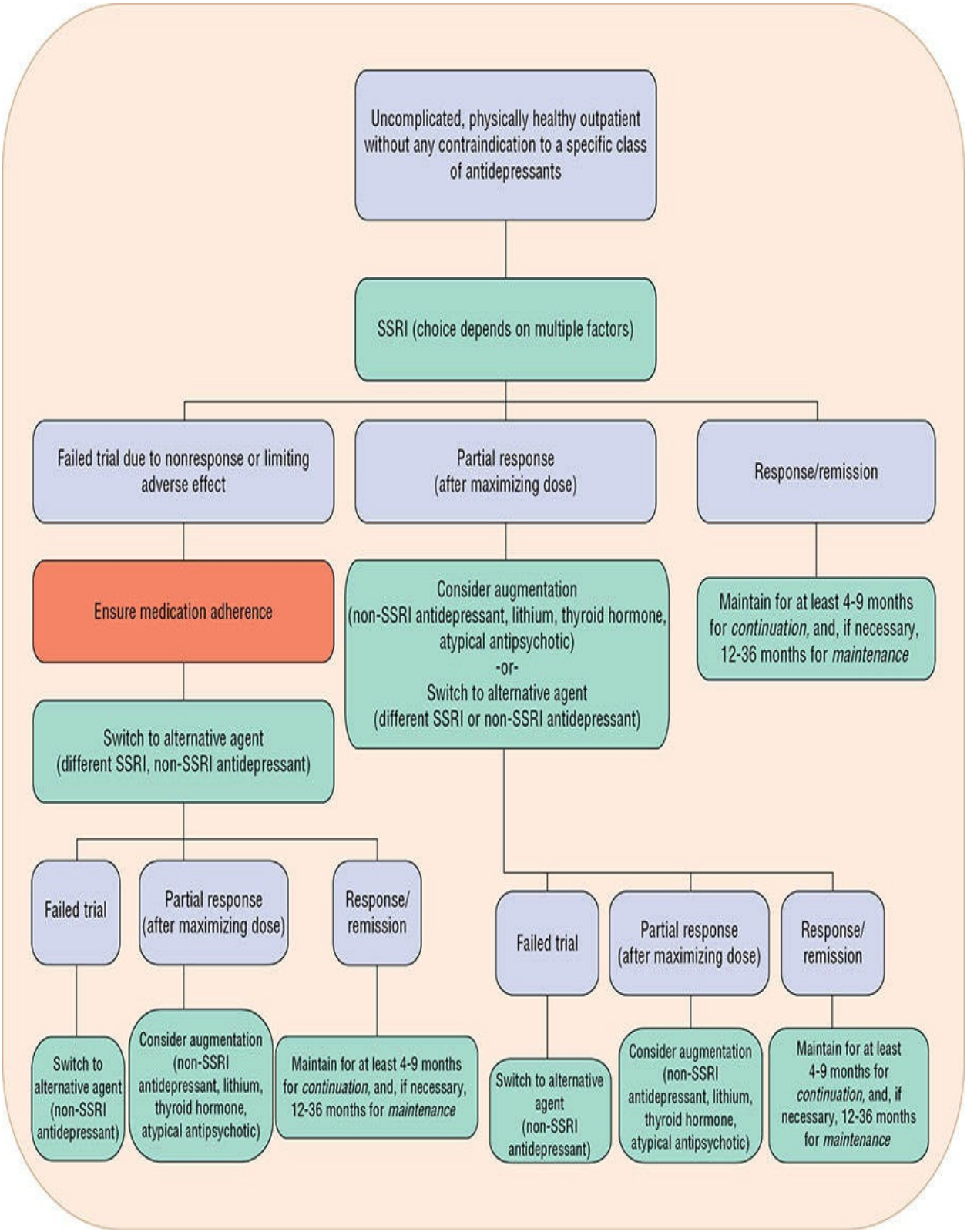


FIGURE 85-3 Suggested algorithm for treatment of uncomplicated MDD. (SSRI, selective serotonin reuptake inhibitor.) Note: both the British Association of Pharmacology (BAP) guidelines and the STAR*D trial suggest that switching

and augmentation strategies are supported by stronger evidence compared to dose increases (among poor antidepressant responders).

Selective Serotonin Reuptake Inhibitors

The efficacy of SSRIs is superior to placebo and comparable to other classes of antidepressants in treating patients with major depression.[2,50] SSRIs are generally chosen as *first-line antidepressants* due to their relative safety in overdose and improved tolerability over traditional TCAs and MAOIs. The decision of which SSRI to use *within* the class is typically based on the nuances of each medication, such as differences in drug interaction profile and pharmacokinetic (PK) parameters (eg, half-life). These concepts will be discussed in greater detail later in this chapter. The STAR-D trial demonstrated that nonresponse to one SSRI does not predict nonresponse to an alternative SSRI and a recent meta-analysis found no differences in efficacy between agents.[53,63]

The SSRIs, as the name implies, have a low affinity for other receptors including α_1-adrenergic, histaminic (H1), and muscarinic (M1) receptors. Given this pharmacology, they are associated with lower rates of orthostatic hypotension, sedation, weight gain, and anticholinergic adverse effects compared to TCAs.[2–4,61] The most common dose-dependent adverse effects seen with SSRI use, which generally are mild and limited to 1 to 2 weeks after initiation or dose increases, are gastrointestinal (GI) symptoms (eg, nausea, vomiting, and diarrhea), anxiety, and headache.[64] Both somnolence and insomnia have been reported with all SSRIs.[65] Additionally the SSRIs may cause clinically relevant impairment in all three stages of the human sexual response (arousal, libido, orgasm)[66]; however it is important to note that depression itself may be associated with sexual dysfunction. A discontinuation or withdrawal syndrome may occur if SSRIs are abruptly discontinued (see details below with SNRIs). In looking at specific agents within this class, there are some notable differences in side effect profiles. Paroxetine has more anticholinergic and antihistaminergic activity that has been linked with increased sedation and weight gain compared to other SSRIs.[2–4,61] In 2011, the FDA released a safety announcement linking citalopram to a dose-dependent increase in QT interval, with recommended, age-dependent dose limits.[67] There has since been controversy regarding this safety warning and potential unintended consequences (eg, underdosing, discontinuation leading to relapse).[67,68] Dose-dependent increase in QT interval may also be associated with escitalopram; however, clinical significance of the

QT increase is questionable with both agents.[68]

Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)

Tricyclic Antidepressants Although TCAs are effective in treating MDD, use has diminished greatly due to the availability of equally effective therapies that are better tolerated and much safer in overdose. All TCAs potentiate the activity of NE and 5-HT by blocking their reuptake. However, the potency and selectivity of TCAs for the inhibition of NE and 5-HT reuptake vary greatly among these agents (see **Table 85-4**). Nortriptyline is most commonly used and may be selected in patients with comorbid migraine headaches, neuropathic pain, or fibromyalgia.

TABLE 85-4 Relative Potencies of Norepinephrine and Serotonin Reuptake Blockade and Selected Receptor Antagonism Profile of Antidepressants

	Reuptake Antagonism				
	NE	5-HT	M1	H1	α1
Selective Serotonin Reuptake Inhibitors (SSRIs)					
Citalopram	0	++++	0	+	0
Escitalopram	0	++++	0	0	0
Fluoxetine	+	++++	0	0	0
Fluvoxamine	0	++++	0	+	0
Paroxetine	++	++++	+	+	0
Sertraline	0	++++	0	0	0
Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)					
Duloxetine	+++	++++	+	0	+
Levomilnacipran	++++	+++	+	0	0
Venlafaxine* and desvenlafaxine	+++	++++	+	+	0
Tricyclic Antidepressants (TCAs)					
Amitriptyline	++	++++	++++	++++	+++
Desipramine	++++	++	++	++	++
Doxepin	++	++	+++	++++	++
Imipramine	++	++++	+++	+++	++++
Nortriptyline	++++	++	++	++	+
Mixed Serotonergic (Mixed 5-HT)					
Nefazodone	0	++	0	+++	+++
Trazodone	0	++	0	++++	+++
Vilazodone	0	++++	0	+	0
Vortioxetine	0	++++	0	+	0
Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)					
Bupropion†	+	0	+	0	0
Serotonin and α_2-Receptor Antagonist					
Mirtazapine	0	0	0	++	++

*Venlafaxine: primarily 5-HT at lower doses, NE at higher doses, and DA at very high doses.

†Bupropion: also blocks dopamine reuptake.

M1, antimuscarinic/anticholinergic side effects; H1, antihistamine, sedation; α1 antiadrenergic, hypotension.

++++, high; +++, moderate; ++, low; +, very low; 0, absent or not adequately studied.

Data from References 2–4, 50, and 61.

The TCAs affect several neurotransmitters and produce a wide range of

pharmacologic actions, including several unwanted, but expected, adverse effects. The most commonly occurring dose-related side effects are associated with blockade of cholinergic receptors (anticholinergic effects) and include dry mouth, constipation, blurred vision, urinary retention, dizziness, and tachycardia. In elderly patients or with very high doses, memory impairment or delirium may occur.[69] Although some tolerance does develop to these adverse effects, they have the potential to impact patient adherence, particularly in the elderly and those receiving long-term maintenance therapy. Additional adverse effects that decrease TCA adherence include weight gain and sexual dysfunction.[69]

Orthostatic hypotension is a common, dose-related, and potentially problematic adverse effect that has been attributed to the affinity of the TCAs for α_1-adrenergic receptors.[61] In patients with history of myocardial infarction, TCAs should be avoided due to risk of severe arrhythmias (QTc prolongation, torsades de pointes) thought to be associated with their class IA antiarrhythmic effects.[70] Additionally, TCAs can cause cardiac conduction delays, may induce heart block in patients with a pre-existing conduction disorder, and overdose is associated with severe arrhythmias.[69] The FDA released a warning in December 2009 that the desipramine prescribing information will be changed to reflect an increased risk of death in patients receiving desipramine who have a *family history* of sudden cardiac death, cardiac dysrhythmias, and cardiac conduction disturbances. More on this reaction can be found at the FDA's MedWatch Website. Therefore, caution should be exercised when prescribing these agents, especially in higher doses, to patients with clinically significant cardiac disease, and to patients with a family history of a cardiac event.

Newer-Generation SNRIs Venlafaxine and its primary active metabolite, desvenlafaxine, inhibit 5-HT reuptake at low doses, and NE reuptake at higher doses, whereas duloxetine equally inhibits both 5-HT and NE reuptake inhibition across all doses. This difference in receptor binding has not been associated with significant differences in efficacy. Some studies suggest that the SNRIs may be associated with higher rates of response and remission than other antidepressants; however, most of these studies involved venlafaxine, and not all studies support this conclusion.[63] The BAP guidelines discuss the possibility of a slight efficacy advantage (ie, lower number needed to treat; NNT) for venlafaxine (as well as escitalopram and sertraline) compared to other antidepressants.[3]

The most recent SNRI to be FDA-approved for MDD is levomilnacipran. This is a single-isomer, extended-release formulation of milnacipran which is

FDA-approved only for the treatment of fibromyalgia. It is too soon to determine its place in therapy for MDD; however, a pharmacological mechanism that makes it relatively unique among the SNRIs is greater potency at inhibiting NE reuptake as compared to 5-HT reuptake.[61,71]

One NE selective reuptake inhibitor, reboxetine, was investigated for MDD and was not FDA approved due to side effects and lack of efficacy.

The most commonly reported adverse effects with SNRIs, similar to those of SSRIs, may be dose-related and include nausea, sexual dysfunction, and activation.[2–4] Hyperhidrosis is a common side effect that appears primarily with SNRIs. Dose-related increases in blood pressure have been reported more with venlafaxine and levomilnacipran but may also occur with duloxetine and desvenlafaxine.[2] Blood pressure should be monitored at baseline and regularly during therapy, especially after dose increases. The discontinuation or withdrawal syndrome that can occur when treatment is stopped, appears to be more severe with SNRIs than SSRIs. Common withdrawal symptoms include headache, fatigue, sweating, musculoskeletal pain, headache, electric shock sensations, and anxiety. While slowly tapering off the medication may help to reduce the risk of the withdrawal syndrome, it may not fully prevent it.[51] Duloxetine has also been associated with idiosyncratic hepatotoxicity (1 per 100,000 case exposures) with enzyme elevations more than three times upper limit of normal in 1% of patients, but does not carry the black box warning associated with nefazodone.[72]

Mixed Serotonergic Medications (Mixed 5-HT)

Trazodone and nefazodone have dual actions on serotonergic neurons, acting as both postsynaptic 5-HT_2 antagonists and presynaptic 5-HT reuptake inhibitors. They may also enhance 5-HT_{1A}-mediated neurotransmission.[61] Trazodone blocks α_1-adrenergic and histaminergic receptors leading to increased side effects (eg, dizziness and sedation) that limit its use as an antidepressant. Recently, a longer-acting extended-release preparation of trazodone was approved by the FDA. However, use remains limited due to high rates of dizziness and somnolence comparable to the immediate release product.[57,73] Use of nefazodone declined after reports of hepatic toxicity began to emerge in the late 1990s. The FDA-approved nefazodone labeling includes a black box warning describing rare cases of liver failure (1 case per 300,000 treatment years) and hepatic impairment (29 cases per 100,000 treatment years).[72] Trazodone and nefazodone are effective agents in treating major depression;

however, both carry risks that limit their usefulness. Generic, immediate-release trazodone is often used adjunctively (in low doses) with other antidepressants to treat insomnia associated with MDD.[65]

Vilazodone and vortioxetine are combination SSRI and 5-HT_{1A} presynaptic receptor partial agonists approved for the treatment of MDD.[71] Presynaptic 5-HT_{1A} partial agonism has previously been investigated as an augmentation mechanism for SSRIs with pindolol, which has preferential antagonism at the presynaptic 5-HT_{1A} receptor.[74] The primary dose-limiting side effect of these two newer agents is nausea. Vortioxetine has additional mechanisms of 5-HT_3 antagonism that is proposed to mitigate some of the nausea. Additionally, vortioxetine is a partial agonist at 5-HT_{1B}, and an antagonist at 5-HT_{1D} and 5-HT_7 receptors.[60] Preliminary data support lack of cognitive side effects and potential for improved cognitive symptoms with vortioxetine in patients with MDD that is linked to the 5-HT_7 receptor antagonism.

Trazodone and nefazodone have minimal anticholinergic effects and comparatively less 5-HT agonist side effects (eg, sexual dysfunction), but they can cause orthostatic hypotension. Sedation, cognitive slowing, and dizziness are the most frequent dose-limiting side effects associated with trazodone, although the dosage used for the treatment of depression is significantly higher than the dosage often used for the treatment of insomnia.[73] Common adverse effects associated with nefazodone include light-headedness, dizziness, orthostatic hypotension, and somnolence. Due to the previously discussed potential for hepatic injury associated with nefazodone use, treatment should not be initiated in individuals with active liver disease or with elevated baseline serum transaminases. A rare but potentially serious adverse effect of trazodone is priapism, which is reported to occur in approximately 1 in 6,000 male patients. Some cases have required surgical intervention (1 in 23,000), and permanent impotence may result.[75] There have been no reports of priapism associated with nefazodone use in men, but there is a published case report of nefazodone-induced clitoral priapism.[75]

Vilazodone and vortioxetine are both associated with significant dose-related GI side effects (eg, diarrhea and nausea), dizziness, insomnia, and decreased libido (particularly among men) when compared to placebo.[71] Rates of sexual dysfunction appear to be lower than with SSRIs; however, in some trials comparator agents known to cause sexual dysfunction (eg, duloxetine) also had lower rates of sexual dysfunction.[60,71]

Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)

Bupropion has no appreciable effect on the 5-HT reuptake, but it inhibits both the NE and DA reuptake that makes it one of the most activating antidepressants.[61] This activation can be particularly helpful for decreased motivation, low energy, and fatigue (common symptoms in elderly patients). It is also FDA-approved for smoking cessation.

Adverse effects associated with bupropion include nausea, vomiting, tremor, insomnia, and dry mouth. The occurrence of seizures in patients taking bupropion appears to be strongly dose-related, and may be increased by predisposing factors such as history of prior seizure activity, severe alcohol withdrawal, head trauma, or CNS tumor. Additionally, bupropion use is contraindicated in patients with eating disorders such as bulimia and anorexia, as these patients are prone to electrolyte abnormalities and are therefore at higher risk for seizure activity. At daily doses of 450 mg (the FDA-approved maximum dose) or less, the incidence of seizures is 0.4%, which is similar to reported rates for clomipramine, desipramine, and citalopram.[76] Bupropion is associated with minimal sexual dysfunction compared with the SSRIs and may actually improve SSRI-induced sexual dysfunction when used as adjunctive treatment.[77]

Serotonin and α_2-Adrenergic Receptor Antagonists

Mirtazapine enhances central noradrenergic and serotonergic activity through the antagonism of central presynaptic α_2-adrenergic autoreceptors and heteroreceptors.[78] Furthermore, it antagonizes postsynaptic 5-HT_2 and 5-HT_3 receptors as well as histamine receptors. The antagonism of 5-HT_2 and 5-HT_3 receptors has been linked to lower anxiety and GI side effects, respectively.

The most common adverse effects of mirtazapine are somnolence, weight gain, dry mouth, and constipation. Certain side effects associated with mirtazapine (eg, somnolence and weight gain in particular) are likely due to mirtazapine's relatively strong antihistaminergic properties.[65] Weight gain associated with mirtazapine after 6 to 8 weeks is in the range of 0.8 to 3 kg.[77] Since mirtazapine causes virtually no nausea, some of the weight gain may be due to improved appetite as loss of appetite is common with depression. Mirtazapine is another agent associated with minimal sexual dysfunction.

Monoamine Oxidase Inhibitors

MAOIs increase the concentrations of NE, 5-HT, and DA within the neuronal synapse through inhibition of the MAO enzymes. Similar to TCAs, chronic therapy causes changes in receptor sensitivity (ie, downregulation of β-adrenergic, α-adrenergic, and serotonergic receptors).[79] The MAOIs isocarboxazid, phenelzine, and tranylcypromine are nonselective inhibitors of MAO-A and MAO-B. A selegiline transdermal patch was approved by the FDA for treatment of MDD that allows inhibition of MAO-A and MAO-B in the brain, yet has reduced effects on MAO-A in the gut.[80]

The most common adverse effect of oral MAOIs is postural hypotension; this is more likely to occur with phenelzine and may be minimized with divided doses. Other common adverse effects include weight gain and sexual side effects (eg, decreased libido and anorgasmia).[2] Phenelzine has mild-to-moderate sedating effects, while tranylcypromine and selegiline may exert a stimulating effect and insomnia due to amphetamine-like metabolites.[59]

Hypertensive crisis, which is a potentially serious and life-threatening but rare adverse reaction, may occur when MAOIs are taken concurrently with certain foods, especially those high in tyramine. Tyramine is usually metabolized by MAO-A in the gut and not absorbed into systemic circulation where it acts as a potent vasoconstrictor. Oral MAOIs block gut MAO-A resulting in absorption of tyramine. In patients on MAOIs, ten milligrams of tyramine can cause marked hypertension and severe headache, and 25 mg can result in hypertensive crisis, whereas the average adult can tolerate over 500 mg of tyramine without a significant impact on blood pressure.[59,81] Symptoms of hypertensive crisis include occipital headache, stiff neck, nausea, vomiting, sweating, and sharply elevated blood pressure which may culminate in cerebrovascular accident and death. For details regarding management of hypertensive emergencies, the reader is referred to Chapter 30, “Hypertension.” Hypertensive crisis or serotonin syndrome may respectively occur when MAOIs are co-ingested with medications that increase norepinephrine (eg, decongestants, SNRIs) or serotonin (eg, antidepressants other than MAOIs). Therefore, education of patients taking MAOIs regarding dietary and medication restrictions is extremely important. Examples of potentially high tyramine foods and medications that should be avoided or used with caution are provided in **Table 85-5**.[59,81]

TABLE 85-5 Dietary and Medication Restrictions for Patients Taking Monoamine Oxidase Inhibitors*

Foods to Avoid Completely	Approximate Tyramine Content (mg) Per Ounce
Aged cheeses (eg, cheddar, blue, Swiss, Camembert)	25-45 60
Chicken liver	2-45
Dry aged meats (eg, mortadella, salami, prosciutto)	Unknown Unknown
Fava beans	Variable
Kim chee	1-3
Red wine	0-80
Sauerkraut	Varies
Smoked or pickled fish (eg, lox, caviar, pickled herring)	20-40 2-60
Soy sauce, fermented soy, miso	
Tap beer	
Yeast extract	
Foods to Eat in Moderation	
American cheese, Parmesan cheese	<2
Canned, filtered beer	<2 per 12 oz (355 mL)
Havarti, brie	Thought to be low
Pepperoni	<2
Pizza (large commercial chains generally safe; avoid gourmet with aged cheeses and meats)	2 slices <1 per 4 oz (120 mL)
White wine	
Foods Without Restrictions	
Fresh dairy products (cottage cheese, cream cheese, fresh milk, ice cream, ricotta, sour cream, yogurt)	
Fresh meats (including fresh sausage)	
Processed meats (eg, lunch meat, hot dogs, ham)	
Spirits (eg, bourbon, gin, rum, vodka)	
Yeast bread products	

Medications to Avoid Completely

Antidepressants*	Dopamine	Methylphenidate
Amphetamines	Ephedrine	Reserpine
Appetite suppressants	Epinephrine	Sympathomimetics
Asthma inhalants	Guanethidine	Tryptophan
Buspirone	Levodopa	
Carbamazepine	Local anesthetics†	
Decongestants	Meperidine	
Dextromethorphan	Methyldopa	

*Tricyclic antidepressants may be used with caution by experienced clinicians in treatment-refractory populations.

†Those containing sympathomimetic vasoconstrictors.

Data from References 59 and 81.

Second-Generation Antipsychotics

The second-generation antipsychotics aripiprazole, brexpiprazole, and quetiapine have been FDA approved for augmentation of antidepressant treatment. Additionally, cariprazine, olanzapine, and risperidone have been studied and are recommended in some treatment guidelines for refractory symptoms.[3,4] The specific mechanisms for these medications in MDD is not fully understood, but is thought to involve modulation of 5-HT and DA activity as they have variable activity at 5-HT_{1A}, 5-HT_{2A}, D_2, and D_3 receptors.[57,58] It is important to note that while these medications may be useful in the treatment of depression they are associated with the risk of metabolic complications and movement disorders. As discussed in detail in Chapter 84, "Schizophrenia," patients taking second-generation antipsychotics must have baseline and follow-up monitoring of metabolic parameters (weight, glucose, lipids, blood pressure) due to the risk of metabolic syndrome. Additionally, patients should be assessed for treatment emergent extrapyramidal symptoms (eg, parkinsonism, akathisia, dystonia). See Chapter 84 for greater detail.

New/Investigational Agents with Novel Mechanisms

In recent years, medications with novel mechanisms have transitioned from proof of concept research to formal clinical trials and, in some cases, FDA approval. As mentioned above, while these agents do not directly alter activity of monoamines, they likely alter activity of monoamines as a secondary effect.

Ketamine is an older anesthetic agent, newly being used for the treatment of depression. Ketamine modulates glutamate activity via extrasynaptic *N*-methyl-*D*-aspartate (NMDA) receptor antagonism that is thought to increase synaptic glutamate activity resulting in increased BDNF activity and synaptogenesis.[28] Though not FDA approved for MDD, ketamine has demonstrated rapid antidepressant effects in sub-anesthetic intravenous doses (0.5 mg/kg) for treatment refractory MDD in multiple studies.[17] Esketamine is the single *s*-isomer of ketamine that has a higher affinity for the NMDA receptor than the *r*-isomer.[82] An intranasal formulation was FDA approved for treatment resistant depression in 2019. The intranasal formulation will overcome some of the barriers associated with intravenous ketamine use, but will have logistical barriers of its own. Intranasal esketamine requires supervised, in-clinic self-administration with two to six intranasal sprays per session and requires 2 hours of in-clinic observation after administration. In trials, patients received doses

twice weekly for 4 weeks and variable dosing thereafter.[83] Overall both ketamine and esketamine appear to be relatively well tolerated at the doses used in clinical trials; however, transient psychotomimetic/dissociative effects and blood pressure elevation (10-20 mm Hg) occurred at higher rates than placebo with both agents.[17,83]

Based on the research involving endogenous allopregnanolone levels and depression, specifically alterations in pregnancy and postpartum, brexanolone (exogenous allopregnanolone) was developed and investigated for the treatment of postpartum depression. This product was FDA approved for the indication of postpartum depression in 2019. Administration involves a 60-hour stepped dose, intravenous infusion. First-pass metabolism precludes oral administration. Brexanolone is thought to exert antidepressant effect by allosteric modulation of $GABA_A$ receptors, which may increase 5HT and NE transmission.[22,84]

The most common adverse effects in brexanolone trials were headache, dizziness, and somnolence. In up to 4% of patients, the infusion was stopped due to excessive sedation or loss of consciousness.[84] It has a mandatory Risk Evaluation and Mitigation Strategies (REMS) program with Elements to Ensure Safe Use (ETASU).

Additional Adverse Events

Serotonin Syndrome (SS) Any antidepressant that increases serotonergic neurotransmission can be associated with SS, especially in situations where a drug interaction increases serotonergic action. The typical triad of symptoms seen in SS includes mental status changes, autonomic instability, and neuromuscular abnormalities (eg, hyperreflexia, myoclonus); however, SS has been identified in cases without all three of these symptoms being present. Therefore, alternative approaches to the well-accepted SS triad have been suggested. For example, it has been proposed that the presence of any of the following symptom clusters is highly diagnostic of SS: (a) tremor + hyperreflexia, (b) spontaneous clonus, (c) muscle rigidity + temperature greater than 38°C (100.4°F) + ocular clonus or inducible clonus, (d) ocular clonus + agitation or diaphoresis, and (e) inducible clonus + agitation or diaphoresis.[85] As serotonin syndrome is primarily a diagnosis of exclusion, other causes of symptoms including neuroleptic malignant syndrome, anticholinergic toxicity, and malignant hyperthermia must be ruled out, with particular attention being paid to the specific medications patients are on, as this too may guide differential diagnosis. Regardless, prompt medical attention is needed for any patient

suspected of having SS syndrome, as the cornerstone to treatment is general medical care (discontinue all potentially causative agents and maintain hydration).

Pharmacokinetics and Pharmacodynamics of Antidepressants

The PK of the antidepressants is summarized in **Table 85-6**.[57,58,71,86] The diversity of SSRIs is evident not only in their chemical structures but also in their PK profiles as the unique PK attributes of each SSRI can be used to guide treatment. For example, the long half-life of fluoxetine and its active metabolite norfluoxetine may be beneficial in instances of partial nonadherence (eg, missed doses). Conversely, caution must be taken to monitor for drug–drug interactions prior to combining another medication with fluoxetine, fluvoxamine, or paroxetine. SSRIs are extensively distributed to the tissues, and all, with the possible exception of citalopram and sertraline, may have a nonlinear pattern of drug accumulation with long-term administration.[87] Therefore, the relationship between the dose and observed effect (eg, side effect) may change over time for the nonlinear SSRIs, and this needs to be considered during treatment.

TABLE 85-6 Pharmacokinetic Properties of Antidepressants

Generic Name	Elimination Half-Life*	Plasma Protein Binding (%)	Clinically Important Metabolites
Selective Serotonin Reuptake Inhibitors (SSRIs)			
Citalopram	33 hours	80	None
Escitalopram	27-32 hours	56	None
Fluoxetine	4-6 days†	94	Norfluoxetine‡
Fluvoxamine	15-26 hours	77	None
Paroxetine	24-31 hours	95	None
Sertraline	27 hours	99§	None
Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)			
Desvenlafaxine	11 hours	30	None
Duloxetine	12 hours	90	None
Levomilnacipran	12 hours	22	None
Venlafaxine	5 hours	27-30	*O*-Desmethyl-venlafaxine
TCAs			
Amitriptyline	9-46 hours	90-97	Nortriptyline
Desipramine	11-46 hours	73-92	2-Hydroxy-desipramine
Doxepin	8-36 hours	68-82	Desmethyl-doxepin
Imipramine	6-34 hours	63-96	Desipramine
Nortriptyline	16-88 hours	87-95	10-Hydroxy-nortriptyline
Mixed Serotonergic (Mixed 5-HT)			
Nefazodone	2-4 hours	99	*meta*-Chlorophenyl-piperazine
Trazodone	6-11 hours	92	*meta*-Chlorophenyl-piperazine
Vilazodone	25 hours	>95	
Vortioxetine	66 hours	98	
Norepinephrine/Dopamine Reuptake Inhibitor (NDRI)			
Bupropion	10-21 hours	82-88	Hydroxy-bupropion Threohydro-bupropion Erythrohydro-bupropion
Serotonin and α_2—Adrenergic Antagonists			
Mirtazapine	20-40 hours	85	None

*Biologic half-life in slowest phase of elimination.

†Four to 6 days with chronic dosing; norfluoxetine, 4-16 days.

‡Take with food to increase area under the curve concentrations by greater than 60%.

§Increases 30%-40% when taken with food.

Data from References 57, 58, 71, and 86.

Bioavailability is low (30%-70%) for most TCAs as a result of first-pass metabolism, which shows great interindividual variation.[88] The TCAs have a large volume of distribution and concentrate in brain and cardiac tissue in laboratory animals. They are bound extensively and strongly to plasma albumin, erythrocytes, α_1-acid glycoprotein, and lipoprotein.[88] The major metabolic pathways are demethylation, aromatic and aliphatic hydroxylation, and glucuronide conjugation, although enterohepatic cycling has been described.[88] Normally, the PK of TCAs is linear within the usual dosage range; however, the elimination half-lives can vary greatly among individual patients, which may be related to pharmacogenomic variability, primarily within CYP2D6 and CYP2C19.[88]

Venlafaxine is metabolized to an active metabolite, *O*-desmethyl-venlafaxine, which contributes to the overall pharmacologic effect,[89] and is also FDA approved as an antidepressant (desvenlafaxine). As might be expected, different formulations of venlafaxine with different PK profiles have variable adverse effect profiles. For example, venlafaxine extended-release formulation has been associated with higher rates of sexual dysfunction among men (37%) compared with the immediate-release formulation (6%); however, this finding has not been replicated.[89] Bupropion is metabolized to multiple active metabolites (Table 85-6) and currently there are three formulations of bupropion hydrochloride (immediate release, sustained release, and extended release), which are equivalent on a total daily dose basis as well as a bupropion hydrobromide formulation that can be converted to equivalent hydrochloride doses.[57,90] The bupropion peak plasma concentrations are lower for the sustained-release formulation of bupropion, and it is believed this may contribute to a lower seizure risk.[90] In 2012, the FDA issued a safety alert noting that some generic bupropion 300-mg extended-release formulations were not bioequivalent to the brand name product. In 2013, they confirmed that all but one manufacturer had proven bioequivalence to the brand name product, which is noted in the FDA Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. It is reasonable to recommend patients fill prescriptions with product from the same manufacturer each time rather than switch between manufacturers.[91] Mirtazapine undergoes biotransformation to several metabolites[92,93]; however, it is primarily eliminated unchanged in the urine (renal elimination). The mirtazapine metabolites are present at such low plasma concentrations they minimally contribute to the overall pharmacologic profile. Levomilnacipran is primarily metabolized via CYPA4 with renal elimination of

over 50% of the dose.[57,58]

Brexanolone undergoes extensive first-pass metabolism is only available in intravenous formulation.[94] Ketamine undergoes extensive first-pass metabolism and has elimination half-life of approximately 2 hours.[57]

An important difference between oral selegiline (FDA approved only for Parkinson's disease) and transdermal selegiline should be noted. Oral selegiline undergoes extensive first-pass metabolism resulting in bioavailability of 4% versus 73% for the transdermal formulation.[80] At low CNS concentrations achieved with the oral formulation, selegiline selectively inhibits MAO-B that results in increased DA levels (hence, the use for Parkinson disease). Nonselective inhibition of both MAO-A (resulting in increased NE and 5HT levels) and MAO-B, which is thought to be important to achieve an antidepressant effect, occurs at higher CNS concentrations only achieved with the transdermal formulation.[80]

Antidepressant Altered Pharmacokinetics Antidepressants may have significantly altered pharmacokinetics (PK) in patients with hepatic or renal disease; however, the data regarding the altered PK parameters are often derived from small, single-dose studies. Changes are variably reported as decreased clearance, increased area under the curve (AUC) or increased half-life.[92] In patients with chronic liver disease, clearance may be decreased 30% (citalopram, mirtazapine) to over 70% (duloxetine, sertraline) and half-life may be increased twofold (citalopram, paroxetine) to threefold (duloxetine, fluoxetine). The AUC of TCAs and bupropion have been reported to increase threefold in cirrhosis.[92] Duloxetine is not recommended in patients with significant hepatic impairment.

Renal impairment and end-stage renal disease (ESRD) do not appear to have the same impact on PK as hepatic impairment with notable exceptions. The half-life of citalopram, escitalopram, and paroxetine may increase 30% to 40%.[93] The AUC of bupropion desvenlafaxine, duloxetine, mirtazapine, and venlafaxine may increase twofold.[93] Duloxetine labeling recommends against use in patients with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2.[93] Bupropion metabolites have also demonstrated accumulation in ESRD. Renal failure does not alter nortriptyline metabolism, but the 10-hydroxy metabolite may accumulate, and protein binding may be diminished, with resulting enhanced sensitivity to the drug.[88]

In patients with significant renal or hepatic impairment, it is reasonable to initiate treatment with 50% lower dose and titrate to 50% to 75% of maximum dose based on tolerability and response. Patients should be monitored for

electrolyte abnormalities and low platelets that can increase risk of arrhythmias and bleeding. Additionally, lower doses and cautious monitoring are prudent when patients are on concomitant medications with overlapping side effect profiles (eg, QTc prolongation).

Plasma Concentration and Clinical Response For the newer antidepressants, a strong correlation has not been established between plasma concentration and clinical response or adverse effects. Studies in acutely depressed patients have demonstrated a correlation between antidepressant effect and plasma concentrations for some TCAs (eg, amitriptyline, nortriptyline, desipramine, and imipramine). However, the best established therapeutic range is for nortriptyline (50-150 ng/mL [mcg/L; 190-570 nmol/L]),[88] which appears to demonstrate a curvilinear plasma concentration–response relationship.

It must be noted that the patient's clinical response, not plasma concentration, should dictate dosage adjustments, as some patients with plasma concentrations outside the suggested therapeutic plasma concentration range respond to treatment, whereas others are nonresponsive regardless of their plasma concentration.

Plasma Concentration Monitoring Because of interindividual variations in plasma concentrations achieved by a given dose, interpretation of plasma concentrations can be very difficult for the TCAs.[88] Although plasma level monitoring is not performed routinely, some indications include inadequate response, relapse, serious or persistent adverse effects, use of higher-than-standard doses, suspected toxicity, elderly patients, pregnant patients, cardiac disease, suspected nonadherence, suspected PK drug interactions, and change in the manufacturer of the product. If plasma concentration monitoring is used to detect nonadherence, a cutoff as low as 30 ng/mL (mcg/L; ~110 nmol/L) for the TCAs has been suggested to avoid confusion with low bioavailability or unusually rapid metabolism. Blood samples for plasma concentration determinations should be obtained at steady state, usually after a minimum of 1 week at constant dosage. Sampling should be performed during the drug elimination phase, usually in the morning, 12 hours after the last dose. Samples collected in this manner are comparable for patients on once-, twice-, or thrice-daily regimens.[88]

Drug Interactions

Drug–drug interactions fall into two broad categories: PK or PD drug interactions. The most common interactions with antidepressants are PK

interactions; however, the clinician must also consider PD interactions. Antidepressants are primarily substrates for cytochrome P450 enzymes and variably act as inhibitors of the enzymes (see Table 85-7).[57,58,86]

TABLE 85-7 Second- and Third-Generation Antidepressants and Cytochrome (CYP) P450 Enzyme Inhibitory Potential

	CYP Enzyme			
Drug	**1A2**	**2C**	**2D6**	**3A4**
Bupropion	0	0	+++	0
Citalopram	0	0	+	NA
Duloxetine	0	0	+++	0
Escitalopram	0	0	+	0
Fluoxetine	0	++	++++	++
Fluvoxamine	++++	++	0	+++
Mirtazapine	0	0	0	0
Nefazodone	0	0	0	++++
Paroxetine	0	0	++++	0
Sertraline	0	++	+	+
(des)-Venlafaxine	0	0	0/+	0

++++, high; +++, moderate; ++, low; +, very low; 0, absent.

Data from References 57, 58, and 86.

Pharmacokinetic Drug Interactions Drug–drug interactions may occur when an antidepressant is coadministered with another medication metabolized through the cytochrome P450 system. Two of the isoenzymes of the cytochrome P450 system, CYP2D6 and CYP3A4, are responsible for the metabolism of most currently marketed medications.[86] The ability of an antidepressant, to inhibit the activity of these enzymes will be a significant contributory factor in determining its capability to cause a PK drug interaction when administered concomitantly. Table 85-7 shows the cytochrome P450 enzyme inhibitory potential of the second- and third-generation antidepressant agents. Patients taking substrates of P450 enzymes should be monitored closely if started on an antidepressant with inhibitory potential. Select examples can be found in Table 85-8.

TABLE 85-8 Select Pharmacokinetic Drug Interactions of NewerGeneration Antidepres

Antidepressant	Interacting Drug / Drug Class	Effect
Selective Serotonin Reuptake Inhibitors		
Citalopram and escitalopram	Omeprazole	Increased serum concentrations of citalopram and escitalopram
Fluoxetine	Alprazolam	Increased plasma concentrations and half-life of alprazolam; increased psychomotor impairment
	Antipsychotics (eg, aripiprazole, haloperidol)	Increased antipsychotic concentrations; increased extrapyramidal side effects
	β-Adrenergic blockers	Increased metoprolol serum concentrations; increased bradycardia; possible heart block
	Carbamazepine	Increased plasma concentrations of carbamazepine; symptoms of carbamazepine toxicity
	Phenytoin	Increased plasma concentrations of phenytoin; symptoms of phenytoin toxicity
	Tamoxifen	Decreased conversion of tamoxifen to active metabolites
	TCAs	Markedly increased TCA plasma concentrations; symptoms of TCA toxicity
	Thioridazine	Thioridazine C_{max} increased; prolonged QTc interval
Fluvoxamine	Alosetron	Increased alosetron AUC (sixfold) and half-life (threefold)
	Alprazolam	Increased AUC of alprazolam by 96%, increased alprazolam half-life by 71%; increased psychomotor impairment
	β-Adrenergic blockers	Fivefold increase in propranolol serum concentration; bradycardia and hypotension
	Carbamazepine	Increased plasma concentrations of carbamazepine; symptoms of carbamazepine toxicity
	Clozapine	Increased clozapine serum concentrations; increased risk for seizures and orthostatic hypotension
	Diltiazem	Bradycardia
	Methadone	Increased methadone plasma concentrations; symptoms of methadone toxicity
	Ramelteon	Increased AUC (190-fold) and C_{max} (70-fold)
	TCAs	Increased TCA plasma concentration; symptoms of TCA toxicity
	Theophylline and caffeine	Increased serum concentrations of theophylline or caffeine; symptoms of theophylline or caffeine toxicity
	Thioridazine	Thioridazine C_{max} increased; prolonged QTc interval
	Warfarin	Increased hypoprothrombinemic response to warfarin
Paroxetine	Antipsychotics (eg, aripiprazole, haloperidol)	Increased antipsychotic concentrations; increased CNS and extrapyramidal side effects
	β-Adrenergic blockers	Increased metoprolol serum concentrations; increased bradycardia; possible heart block
	Tamoxifen	Decreased conversion of tamoxifen to active metabolites
	TCAs	Markedly increased TCA plasma concentrations; symptoms of TCA toxicity
	Thioridazine	Thioridazine C_{max} increased; prolonged QTc interval
Sertraline	Methadone	Increased methadone levels
Serotonin–Norepinephrine Reuptake Inhibitors		
Venlafaxine and desvenlafaxine	CYP3A4 inhibitors	May increase levels of venlafaxine and *O*-desmethylvenlafaxine especially in CYP2D6 poor metabolizers
Duloxetine	Metoprolol	May increase metoprolol levels twofold
	Tamoxifen	Decreased conversion of tamoxifen to active metabolites
	Thioridazine	Thioridazine C_{max} increased; prolonged QTc interval
Levomilnacipran	CYP3A4 inhibitors	Clinically relevant increases in levomilnacipran plasma concentrations may occur
Mixed Serotonergic (mixed 5-HT)		
Vilazodone	CYP3A4 inhibitors	Maximum vilazodone dose 20 mg with coadministration of potent CYP3A4 inhibitor
Vortioxetine	CYP2D6 inhibitors	May need to reduce vortioxetine dose by half with coadministration of potent CYP2D6 inhibitor
Serotonin and α-2-Adrenergic Antagonist		
Mirtazapine	Carbamazepine	Mirtazapine concentration decreased (60%)
Norepinephrine and Dopamine Reuptake Inhibitor		
Bupropion	Tamoxifen	Decreased conversion of tamoxifen to active metabolites

AUC, area under the time concentration curve; C_{max}, maximum concentration; MAOI, monoamine oxidase inhibitor.

NOTE: any medication that augments serotonergic function may impact bleeding risk and should be used with caution in patients receiving NSAIDs or other medications with hematologic effects.

Data from References 2, 57, 58, 71, and 86.

Because the TCAs are metabolized in the liver through the cytochrome P450 system, they may interact with other medications that modify hepatic enzyme activity or hepatic blood flow. TCAs are also extensively protein bound, which can result in drug interactions through displacement from protein-binding sites. Many commonly used medications can interact when given concurrently with TCAs.

As nefazodone use has been severely limited due to its potential to induce liver toxicity, and trazodone is primarily used as a non-FDA-approved hypnotic at low doses, neither of these agents are likely to be involved in clinically significant drug interactions. However, it should be noted that nefazodone is a potent inhibitor of CYP3A4.[86] Vilazodone is primarily metabolized via CYP3A4 and vortioxetine is primarily metabolized via CYP2D6 and both require dose adjustment with inhibitors.[57,58,60]

Pharmacodynamic Drug Interactions Certain PD drug interactions that may occur with antidepressants are concerning and require close monitoring. For example, concurrent use of serotonergic antidepressants with other medications that augment serotonergic function can increase the risk of serotonin syndrome (SS)[85] with some combinations conferring a higher risk than others.

Tramadol presents as an example of a PK interaction increasing the risk of a PD interaction. When tramadol is coadministered with strong CYP2D6 inhibitors, the decrease in metabolism may result in higher levels of the parent drug tramadol, which also exhibits SNRI effects. Therefore, high doses of the combination have been reported to cause serotonin syndrome.[85,95]

See **Table 85-9** for key examples of PD interactions.[57,58,85,95,96,97,98]

TABLE 85-9 Select Pharmacodynamic Drug Interactions of Antidepressants

Medication / Medication Class	Antidepressants / Antidepressant Class	Effect and Management
NSAIDs Aspirin Anticoagulants	SSRIs, SNRIs, TCAs, trazodone, vilazodone, vortioxetine	• FDA warning for increased risk of bleeding • Number needed to harm with NSAIDs = 82 vs. >700 with SSRI alone • Assess for baseline bleeding risk and monitor closely • Educate patient regarding signs of bleeding • Consider histamine-2 (H_2) antagonist in high-risk patients
Triptans	MAOIs, SSRIs, and SNRIs	• FDA warning in labeling • Very low risk • Monitor for signs of serotonin syndrome when frequent high doses are used • Triptan toxicity possible when almotriptan, rizatriptan, sumatriptan, or zolmitriptan are combined with MAO inhibitors
Linezolid	All serotonergic antidepressants	• Linezolid is weak, reversible, nonselective, MAOI • FDA labeling recommends against use with other MAOIs and recommends discontinuing antidepressants if linezolid is started • Actual rate of serotonin syndrome with combination reported at <1% • Abrupt discontinuation of antidepressants can have negative consequences • If linezolid is indicated and patient is already on an antidepressant, monitor for signs of serotonin syndrome upon initiating combination • If patient is on short course of linezolid and in need of treatment for depression, consider postponing antidepressant initiation until course is complete
Tramadol	Bupropion, duloxetine, fluoxetine, paroxetine	• Decreased metabolism results in increased SNRI activity of tramadol • Rare cases of high dose tramadol combined with CYP2D6 inhibitors resulting in serotonin syndrome have been reported • Monitor for increased signs of serotonin syndrome and decreased analgesic response when combination is used

Data from References 57, 58, 85, and 96–98.

There are two types of PD drug interactions that may occur between antidepressant medications and NSAIDs. First, increased risk for abnormal bleeding (eg, upper GI and intracranial hemorrhage) associated with the combined use of antidepressants and NSAIDs is a potentially very serious pharmacodynamic interaction that has been reported in the literature.[95] This first PD interaction is likely mediated by serotonergic mechanisms that occur at the platelet level. Second, recent research suggests that NSAIDs may lessen the efficacy of SSRIs.[97] At this time evidence is insufficient to draw firm conclusions. However, given the volume of prescriptions for both NSAIDs and SSRIs, this is an area of pharmacotherapy that certainly deserves further research and thoughtful prescribing practices.

Lastly, refer to Monoamine Oxidase Inhibitors under Adverse Effects above and Table 85-5 to read more about the hypertensive crisis that may result

following the coadministration of MAOIs and other medications that increase vasopressor response (eg, amphetamines). Notably, MAOIs and TCAs may be coadministered safely in refractory patients with apparent increased efficacy compared with monotherapy; however, severe reactions (eg, hypertensive crisis) and fatalities have occurred.[2,88] Therefore, this combination should be used sparingly by experienced clinicians and monitored extremely carefully.

Alternative Pharmacotherapy

The APA Task Force on Complementary and Alternative Medicine (CAM) as well as CANMAT guidelines include evidence-based and consensus-based recommendations on the use of CAM for the treatment of MDD.[56,99] While these recommendations are not the focus of this chapter, clinicians treating patients with MDD should be cognizant of them.

Omega-3 Fatty Acids Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) omega-3 fatty acids are generally low-risk and demonstrate variable benefit as augmentation in the treatment of MDD. Use of EPA alone or the combination of EPA/DHA is likely more effective than DHA alone. As these agents may increase bleeding risk, their use should be carefully considered in patients taking SSRIs and other concomitant medications associated with bleeding risk (eg, NSAIDs, anticoagulants).

St. John's Wort There is a lack of consensus regarding St. John's wort for the treatment of MDD. Furthermore, St. John's wort induces hepatic metabolic enzymes and is associated with significant drug interactions. The APA Task Force conservatively states that St. John's wort may be reasonable for some individuals with mild-to-moderate MDD while CANMAT considers it to have level 1 evidence as first-line therapy for mild-to-moderate MDD. Further, the BAP guidelines state a "standardized" preparation of St. John's wort "could be considered" in patients with mild-to-moderate MDD, if other first-line medications are not an option.[3]

***S*-Adenosyl-L-Methionine (SAMe)** The use of SAMe received a favorable review by the APA Task Force. However, the final consensus was that more rigorous studies need to confirm the efficacy of SAMe for treating MDD. The CANMAT guidelines consider SAMe as a second-line augmentation strategy while the BAP guidelines state that evidence is developing for use of SAMe as an augmentation strategy in the treatment of MDD.[3]

Folate The three compounds in this category are (a) folic acid, (b) folinic acid, and (c) 5-methyltetrahydrofolate (5-MTHF) as these compounds are involved in the synthesis of key neurotransmitters such as 5-HT. The APA task force states that augmentation with these compounds is reasonable, but more work is needed to clarify which subgroup of patients may achieve the greatest response.[56] For example, in one study, only women responded to folic acid augmentation of fluoxetine treatment. Regardless, CANMAT guidelines consider folate supplementation a third-line augmentation strategy.[4]

Special Populations

Elderly Patients Depression in the elderly is a major public health problem as many elderly depressed patients are inadequately treated, or have their depression missed or mistaken for another disorder, such as dementia. In the elderly, depressed mood, the typical signature symptom of depression, may be less prominent than other depressive symptoms such as loss of appetite, cognitive impairment, sleeplessness, anergia, and anhedonia. Previous research supports that somatic (physical) complaints (eg, pain, fatigue, gastrointestinal symptoms) present more frequently in elderly depressed patients. However, there are many confounders that may account for this (eg, higher rates of physical illness).[32] Appropriate recognition and treatment of depression in the elderly is extremely important. In fact, individuals 65 years of age and older have a high rate of suicidality. Increased suicide attempts in the depressed elderly have been associated with access to firearms, diminished cognitive functioning, sleep disruptions, poor social interactions, and inattention among primary caregivers.[100]

Before initiating antidepressant treatment, a complete physical examination should be performed. When prescribed antidepressants, elderly patients may be either overtreated or under-treated. Overtreatment occurs when age-related PK and PD factors are overlooked and under-treatment results from an overly conservative approach as a result of the patient’s advanced age or concurrent medical problems. In the elderly, SSRIs are usually selected as first-line treatment, and this may enable the clinician to avoid some of the problematic adverse effects commonly associated with TCAs (eg, sedative, anticholinergic, and cardiovascular side effects). Furthermore, there is evidence to suggest that the long-term use of antidepressants such as SSRIs in the elderly, administered with either psychotherapy or clinical management, may prevent a depressive relapse.[32,33] Hyponatremia is more common in elderly women, especially in those taking concomitant diuretics. Mirtazapine has been shown to be an

effective antidepressant in the elderly (at least 65 years of age) and better tolerated than the SSRI paroxetine. Furthermore, secondary measures of anxiety and sleep were improved following mirtazapine administration.[101] In addition to sleep benefits, mirtazapine can be helpful in improving appetite which is commonly diminished in elderly. For those patients whose depressive symptoms include lack of overall energy, use of bupropion may capitalize on the stimulant effect of this medication. Regardless of the specific antidepressant chosen, the effect sizes for antidepressants as a pharmacological class (as compared to placebo) may be smaller in older patients than in younger adult populations.[3]

Pediatric Patients Accumulating evidence indicates that childhood depression occurs quite commonly and symptoms of depression in the young may vary from accepted diagnostic criteria to include several nonspecific symptoms such as boredom, anxiety, somatic complaints (eg, stomach ache), and impulsivity.[102]

Data collected under controlled conditions that support the efficacy of antidepressants in children and adolescents are sparse, and only fluoxetine and escitalopram are FDA-approved for the treatment of depression in patients younger than 18 years of age, although other antidepressants (eg, sertraline) have been studied in this population.[102] The Treatment of Adolescent Depression Study (TADS) found that the combination of fluoxetine and CBT was superior to fluoxetine monotherapy or CBT alone in adolescents 12 to 17 years of age.[103] The Treatment of Resistant Depression in Adolescents (TORDIA) study switched adolescents 12 to 18 years of age with SSRI-resistant depression to venlafaxine or sertraline with or without CBT after nonresponse to antidepressant. Overall this study found no difference in outcomes between the two medications and also found no difference in outcomes when CBT was added to medication.[104] Additionally, the Adolescent Depression Antidepressant and Psychotherapy Trial (ADAPT) did not find a benefit of adding CBT to SSRI therapy in adolescents 11 to 17 years of age.[105]

The use of antidepressants in children and adolescents was complicated when, in March 2004, the FDA issued a black box warning in the product labeling for antidepressant medications warning clinicians and patients of the increased risk for suicidal ideation and behavior when antidepressants are used in this population. Results of subsequent studies attempting to elucidate the risk of antidepressants in young patients have varied. A meta-analysis of published and unpublished clinical trials supported an increased risk; however, the study was impeded by limited access to data. In contrast, several retrospective longitudinal reviews of the use of antidepressants in children refute the increased risk of

suicide attempts or deaths.[106] Furthermore, studies demonstrated a decreased rate of prescribing antidepressants and an increase in suicide rates after the warning appeared in labeling.[107]

The treatment of depression in children remains challenging, as depression can be difficult to diagnose and, once identified, treat. Furthermore, differences in efficacy between medication and placebo may be small and not significant in children below the age of 13 years.[3] However, antidepressants (in particular, the SSRIs) remain viable treatment options when prescribed and monitored appropriately.

Pregnant and Lactating Patients The crucial decision as to whether to use antidepressants during pregnancy continues to be debated and must always include a risk-benefit analysis based upon the available evidence at the time of treatment. Approximately 14% of pregnant women develop clinically significant depression during pregnancy.[108] Furthermore, it has been documented that women who discontinued antidepressant therapy were five times more likely to have a relapse during their pregnancy than were women who continued treatment.[109] While numerous studies, reviews, and meta-analyses have been published over the last decade the absolute risk of antidepressants in pregnancy is still not clear due to methodological issues and confounding factors (eg, prenatal care, continued depressive symptoms during treatment, medical and psychiatric comorbidities, and substance use).[110] An approximate 25% relative increase in congenital heart defects associated with SSRIs is the most consistent finding; however, the increase in risk ranges from 10% to a twofold increase across studies.[110] Other findings have included increased risk of low birth weight and newborn respiratory distress.[108] An oft-cited study reported a sixfold greater likelihood of persistent pulmonary hypertension of newborn infants exposed to an SSRI after the 20th week of gestation; however, the degree of this risk has been debated.[111] These are selected examples of studies assessing both risks and benefits of antidepressants in pregnancy. A full exploration of the conflicting literature on this topic is beyond the scope of this chapter.

Four therapeutic principles have been proposed to guide the clinician in treating women during pregnancy: (a) Pregnancy does not protect against the occurrence of depression, and the likelihood of relapse is very high in untreated women with recurrent illness. (b) Maternal depression adversely affects child development, and prenatal depression may adversely affect the offspring. (c) When attempting to balance benefit and risk, transient postnatal behavioral abnormalities in the offspring of treated mothers must not be assumed to portend

long-term compromise. (d) SSRIs, the most commonly used and best-tolerated treatment for depression, carry a small but significant risk for a serious medical consequence.[112]

In September 2009, the APA and the American College of Obstetricians and Gynecologists released a report discussing the treatment of depression during pregnancy. One of the prominent conclusions of this report was that *both* antidepressant treatment and untreated depression have been associated with potential problems during pregnancy. However, studies to date have not been able to adequately control for all the necessary variables involved in birth outcomes (eg, maternal depressive disorder) and more work needs to be done.[113]

In summary, the risks and benefits of drug therapy during pregnancy must always be weighed, and concerns about the risks of untreated depression during pregnancy should be considered. These include the possibility of low birth weight secondary to poor maternal weight gain, suicidality, potential for hospitalization, potential for marital discord, inability to engage in appropriate obstetric care, and difficulty caring for other children. Several different approaches exist for dealing with pregnancy and antidepressant use. First, discontinuation of an antidepressant before conception is an option for women who are stable and appear likely to remain well while not taking antidepressant medication (eg, no history of recurrence upon discontinuation, no recent history of severe symptoms or suicidality, stable psychosocial supports). Second, continuation of the antidepressant until conception may be reasonable and one with the lowest risk for the fetus (ie, low FDA pregnancy risk class) should be chosen in women of child bearing potential or those trying to conceive. For those who have a history of depressive relapse after medication discontinuation, the antidepressant should be continued throughout pregnancy. There is a great deal of uncertainty regarding long-term antidepressant exposure during breastfeeding due to the lack of data. However, sertraline is recommended and appears in relatively low concentrations in breast milk and in samples taken from infants.[114] Again, the risks of not treating depression in a pregnant or breastfeeding woman should not be underestimated or minimized. Clinicians may consider using the Motherisk program when looking for the most up to date information regarding antidepressant risks in pregnancy and lactation.[115]

Relative Resistance and Treatment-Resistant Depression

The majority of “treatment-resistant” depressed patients are likely the result of

inadequate therapy (relative resistance). This theory is supported by data from the National Institute of Mental Health (NIMH) Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which is generally considered to be one of the premier antidepressant trials among patients with depressive disorders.[53,116] This study showed that one in three depressed patients who previously did not achieve remission with an antidepressant (citalopram) became symptom free with an additional medication (bupropion SR or buspirone) and one in four achieved remission after switching to a different antidepressant (bupropion SR, sertraline, or venlafaxine XR). Furthermore, patients can be switched to another medication within the same class.[117] For example, patients in the STAR*D study not responding to an initial SSRI were shown to be as likely to respond to another SSRI as they were to a medication from a different class.[118] Other key findings of STAR*D include the importance of maximizing dose (higher doses associated with higher remission rates) and adequate trial duration of at least 8 to 12 weeks before deeming a medication ineffective.[53] The BAP guidelines place a higher level of confidence in both augmentation and switching strategies, compared to dose increase approaches.[3]

Although several different definitions for treatment-resistant depression have been proposed, the most widely accepted is depression that has not achieved remission even after two optimal antidepressant trails.[118] More than 40% of patients with MDD being treated with antidepressants meet these criteria.[118] Three pharmacologic approaches that have been used with success for treatment-resistant depression include the following:

1. The current antidepressant may be stopped and another agent initiated (ie, switching). For example, the STAR*D trial compared switching to mirtazapine (up to 60 mg/day) versus nortriptyline (up to 200 mg/day) after two consecutive failed medication treatments.[118] In the mirtazapine group, 12.3% of patients met the remission criterion of a score of 7 or less on the Hamilton Rating Scale for Depression (HAM-D), while 19.8% of nortriptyline patients met this criterion at the end of 14 weeks.
2. The current antidepressant can be augmented by the addition of another agent such as lithium, or another antidepressant can be added (ie, combination antidepressant treatment). For example, the STAR*D trial evaluated the addition of lithium or triiodothyronine (T_3) to current antidepressant treatment. After approximately 10 weeks, T_3 augmentation resulted in higher remission rates (24.7%) compared with lithium (15.9%). However, the differences between these two augmentation strategies were

modest and not statistically significant.[119] Although T3 and lithium demonstrated similar remission rates in this seminal trial, the BAP guidelines provide a stronger recommendation rating for lithium (ie, “A”) compared to T3-based approaches (ie, “B”).[3,119] In contrast, the CANMAT guidelines consider both agents second-line for augmentation with level 2 evidence.[4]

3. The use of atypical antipsychotic agents to augment the antidepressant response is increasing. Aripiprazole, brexpiprazole, and quetiapine are FDA approved for adjunctive treatment for MDD. Aripiprazole and quetiapine have been recommended as first-line agents to augment an antidepressant medication.[4] In a predominantly male population in the Veterans Health Administration, augmentation with aripiprazole was found to be more effective than switching to bupropion but no different from bupropion augmentation.[120]

The APA practice guideline for the treatment of patients with MDD offers direction for managing patients whose symptoms are refractory to medications. These guidelines advise that if patients are still symptomatic after 6 to 8 weeks of medication, a reappraisal of the treatment regimen should be considered.[2] Partial responders should consider changing the dose, augmenting the antidepressant, or adding psychotherapy or ECT. For those with no response, options include changing to a different antidepressant or adding psychotherapy or ECT. Again, the BAP guidelines suggest that stronger evidence exists for switching or augmentation strategies compared to dose increases in patients with inadequate antidepressant response.[3] Comorbid medical or psychiatric conditions should be identified and treated because they may complicate treatment.

6 Before changing a patient’s treatment, the clinician is advised to evaluate the adequacy of the medication dosage and adherence with the prescribed regimen. Issues to be addressed in assessing the patient who has not responded to treatment include the following:

1. Is the diagnosis correct?
2. Does the patient have a psychotic depression?
3. Has the patient received an adequate dose and adequate duration of treatment?
4. Do adverse effects preclude adequate dosing?
5. Has the patient adhered to the prescribed regimen?

6. Was a stepwise approach to treatment used?
7. Was treatment outcome adequately measured?
8. Is there a coexisting or pre-existing medical or psychiatric disorder?
9. Are there other factors that interfere with treatment?

Personalized Pharmacotherapy

7 Pharmacogenetic applications in psychiatry have been explored for some time. Multiple commercially available pharmacogenetic tests are now available; however, there are no standard or well-accepted guidelines for the use of pharmacogenetic testing as it relates to antidepressant treatment. Regardless, in patients who present with the testing already completed, evidence based guidelines produced by the Clinical Pharmacogenomics Implementation Consortium (CPIC) can help determine if medication changes should be made (www.cpic.org). It is important to note that CPIC does not specifically recommend testing in patients, but rather serves as a resource for clinicians who are presented with pharmacogenomics testing results and are looking for assistance in their interpretation. Therefore, while this testing may, one day, be routinely used to guide pharmacotherapy, due to the cost of testing, limitations in currently available research, and uncertainty regarding insurance reimbursement, it is not utilized in many patient populations.[121] In contrast, PK parameters have long been one of the primary considerations when choosing among the antidepressants, particularly within a medication class.[2] For example, PK parameters help the clinician choose a particular SSRI (eg, longer fluoxetine half-life for partial nonadherence).

A clinician can use other aspects of a medication's pharmacological profile to tailor the treatment to a particular patient. For example, antidepressants can generally be classified as either activating or sedating based upon their mechanism of action, and this is often a major consideration in antidepressant choice. Medications that promote noradrenergic activity (eg, bupropion, venlafaxine) or serotonin (eg, SSRIs) may be activating upon initiation and therefore poor choices for a patient suffering from significant insomnia. In contrast, mirtazapine and trazodone have been shown to improve sleep, likely due to antagonism of H_1 and 5-HT_{2A} receptors.[65] Furthermore, doxepin is FDA approved (in lower doses compared to depressive disorders) as pharmacotherapy for primary insomnia.[57,58]

EVALUATION OF THERAPEUTIC OUTCOMES

8 Several monitoring parameters, in addition to plasma concentrations, are useful in managing patients (Table 85-10).[2,57,58] Patients must be monitored for adverse effects, such as sedation and anticholinergic effects, and for remission of previously documented target symptoms. The presence of side effects does not necessarily indicate adequate or excessive dosage. In addition, changes in social and occupational functioning should be assessed. Patients receiving SNRIs should have their blood pressure monitored at regular intervals. Patients older than 40 years of age should receive a pretreatment ECG before starting TCA therapy, and follow-up ECGs should be performed periodically to assess for arrhythmias. Patients should be monitored for the emergence of suicidal ideation after initiation or discontinuation of any antidepressant, especially if other risk factors for suicidality (eg, sleep disturbances) are present. If significant activation or insomnia occurs upon antidepressant initiation, a short-term anxiolytic or hypnotic may be appropriate.[65] Weight gain and sexual dysfunction, common adverse events associated with most antidepressants, may increase nonadherence and should be monitored and discussed with the patient.

TABLE 85-10 Adverse Drug Reactions and Monitoring Parameters Associated with Select Antidepressants

Drug	ADR(s)	Monitoring	Comments
Antidepressants from Each Pharmacologic Class			
Common to all antidepressants			
	Suicidality	Behavioral changes Mental status	(US black box warning) for all antidepressants; caregivers should be alerted to monitor for acute changes in behavior (especially early in treatment)
Selective Serotonin Reuptake Inhibitors (SSRIs)			
Common to all SSRIs			
	Anxiety or nervousness	Assess severity and impact on patient functioning and quality of life	Most prominent on initial treatment; lower initial doses recommended in patients with prominent anxiety
	Hyponatremia	Serum sodium	More likely in elderly females; sodium may decrease within 72 hours of initiating antidepressant
	Nausea	Frequency and severity	May improve with slower dose titration
	Sleep changes (insomnia and somnolence)	Sleep patterns	Among SSRI class: fluoxetine may be more activating; fluvoxamine and paroxetine may be more sedating
	Sexual dysfunction	Assess severity and impact on patient functioning and quality of life	Spontaneous self-reporting may be low; clinician should assess symptoms; reversible on drug discontinuation
SSRI-Specific			
Citalopram (possibly escitalopram)	QTc interval prolongation	Electrocardiogram; electrolytes (eg, potassium, magnesium)	Caution use in "at-risk" patients (eg, electrolyte disturbance); discontinue if QTc persistently >500 ms or increased >5 ms over baseline
Fluoxetine	Anorexia	Weight (over time)	SSRIs are generally considered weight neutral
Paroxetine	Anticholinergic effects	Symptoms: dry mouth, constipation, urinary retention, mental status	Paroxetine possesses relatively more anticholinergic effects than other SSRIs
Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)			
Common to all SNRIs			
	Cardiovascular changes	Increases in blood pressure; heart rate	Possibly less likely with duloxetine; may need to lower/discontinue dose
	Insomnia	Sleep patterns	Possibly less likely with duloxetine
	Nausea	Frequency and severity	May improve with slower dose titration
	Sexual dysfunction	Assess severity and impact on patient functioning and quality of life	Spontaneous self-reporting may be low; clinicians should assess symptoms; reversible on drug discontinuation
	Sweating	Frequency and severity	May require change in therapy
SNRI-Specific			
Desvenlafaxine	Dose-related hyperlipidemia	Lipid profile	Elevations in total cholesterol, low-density lipoproteins, and triglycerides
Duloxetine	Liver toxicity	Liver function tests	May be transient upon initiation or sustained
Mixed Serotonergic Effects (Mixed 5-HT)			
Nefazodone	Liver toxicity	Liver function tests	Nefazodone black box warning in United States for hepatotoxicity
Trazodone	Orthostatic hypotension	Blood pressure, pulse	May be more severe as compared with other antidepressants; rate-limiting side effect
	Priapism	Patient report of sexual side effects, especially painful erection	Patient should seek medical attention for prolonged erection (ie, >4 hours)
Vilazodone and vortioxetine	Nausea	Frequency and severity	Most common dose limiting side effect
Serotonin and α_2–Adrenergic Antagonist			
Mirtazapine	Weight gain	Body weight	Frequently occurring and significant (>7% over baseline) weight gain among adults; diet mediated
Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)			
Bupropion	Seizure activity	Electroencephalogram if indicated	See Table 85-3 for proper dosing, which can help decrease seizure risk; caution use in patients with eating disorders or alcohol use disorders

Data from References 2, 57, 58, 60, 71, 72, and 78.

In addition to the clinical interview, psychometric rating instruments (such as those highlighted earlier in this chapter and in Chapter e79) allow for rapid and reliable measurement of the nature and severity of depressive and associated symptoms. It is helpful to administer the rating scales prior to treatment, 2 to 4 weeks and 8 to 12 weeks after initiation of therapy, and periodically thereafter. It is important to note that lack of robust response at 2 to 4 weeks does not necessarily predict lack of response at 8 to 12 weeks.[53] Interviewing a family member or friend (with the patient's permission) regarding symptoms and daily functioning also can assist in assessment of progress, as they may notice symptom improvements before the patient. Patients should be monitored at more frequent intervals early in treatment, particularly for suicidality. Monitoring is then continued at regular intervals throughout the continuation and maintenance phases of treatment and assessing for reemergence of target symptoms continued for several months after antidepressant therapy is discontinued.

Finally, one useful set of criteria that can be used with a variety of psychometric scales was suggested by Mann.[50] Following these criteria, the following definitions are used: (a) *nonresponse* is less than a 25% decrease in baseline symptoms, (b) *partial response* is a 26% to 49% decrease in baseline symptoms, and (c) *partial remission or response* is greater than a 50% decrease in baseline symptoms. Consistent with other recommendations, *remission* is a return to baseline functioning with no symptoms present.[2]

CONCLUSION

Depression is a highly pervasive and complex disease state that can be impacted by comorbid medical and psychiatric conditions, psychosocial factors, as well as medications. While the precise pathophysiology of MDD is still elusive, and antidepressant medications have directly targeted monoamine systems for the past half-century, our understanding is evolving to include other complementary mechanisms. Additionally, research is revealing more about the complexity of the disease and the impact of genetic polymorphisms (both on pathophysiology and impact on pharmacotherapy outcomes). Individual patient characteristics should be considered when selecting antidepressant therapy and monitoring treatment. The goals of treatment should include remission (complete resolution of symptoms) and improved functioning.

Postclass Engaged Learning Activity

Conduct a literature search and identify a clinical trial of a medication newly FDA approved for treatment of depression that has been published in the past 12 months. Write a brief summary about the study methods, primary and secondary outcomes. Find the package insert for the new product and assess it for risk of pharmacokinetic and pharmacodynamic interactions. Write about one advantage and one disadvantage of the medication compared to previously available options.

ABBREVIATIONS

AHRQ	Agency for Healthcare Research and Quality
APA	American Psychiatric Association
BAP	British Association of Psychopharmacology
BDI	Beck Depression Inventory
BDNF	brain-derived neurotrophic factor
CAM	complementary and alternative medicine
DA	dopamine
DHA	docosahexaenoic acid
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
ECG	electrocardiogram
ECT	electroconvulsive therapy
EPA	eicosapentaenoic acid
5-HT	serotonin
GI	gastrointestinal
HAM-D	Hamilton Rating Scale for Depression
HPA	hypothalamic–pituitary–adrenal
KKW	kilocalories per kilogram per week
5-MTHF	5-methyltetrahydrofolate
MADRS	Montgomery-Åsberg Depression Rating Scale
MAOI	monoamine oxidase inhibitor
MDD	major depressive disorder

NDRI	norepinephrine and dopamine reuptake inhibitor
NE	norepinephrine
NIMH	National Institute of Mental Health
NT	neurotransmitter
PD	pharmacodynamic
PK	pharmacokinetic
rTMS	repetitive transcranial magnetic stimulation
SAMe	*S*-adenosyl-L-methionine
SNRI	serotonin–norepinephrine reuptake inhibitor
SS	serotonin syndrome
SSRI	selective serotonin reuptake inhibitor
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
T_3	triiodothyronine
TADS	Treatment for Adolescents with Depression Study
TCA	tricyclic antidepressant
TORDIA	Treatment of Resistant Depression in Adolescents
TRD	treatment resistant depression
TREAD	Treatment with Exercise Augmentation for Depression

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
2. American Psychiatric Association. *Practice Guideline for the Treatment of Patients With Major Depressive Disorder*. 3rd ed. Arlington, VA: American Psychiatric Association; 2010.
3. Cleare A, Pariante CM, Young AH, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. *J Psychopharmacol*. 2015;29(5):459–525.
4. Kennedy SH, Lam RW, McIntyre RS, et al. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 3. Pharmacological treatments. *Can J Psych*. 2016;61(9):540–560.

5. Centers for Disease Control and Prevention. Vital Signs: Suicide rising across the US. Available at https://www.cdc.gov/vitalsigns/suicide/index.html. Accessed November 27, 2018.
6. Centers for Disease Control and Prevention. National Suicide Statistics. Available at https://www.cdc.gov/violenceprevention/suicide/statistics/index.html. Accessed November 27, 2018.
7. Hasin DS, Sarvet AL, Meyers JL, et al. Epidemiology of adult *DSM-5* major depressive disorder and its specifiers in the united states. *JAMA Psychiatry*. 2018;75(4):336–346.
8. Substance Abuse and Mental Health Services Administration. 2017 National Survey on Drug Use and Health: Major Depressive Episode in the Past Year. Available at: https://www.samhsa.gov/data/report/2017-nsduh-annual-national-report. Accessed Novemeber 27, 2018.
9. Weissman MM, Gershon ES, Kidd KK, et al. Psychiatric disorders in the relatives of probands with affective disorders. The Yale University—National Institute of Mental Health Collaborative Study. *Arch Gen Psychiatry*. 1984;41(1):13–21.
10. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: Review and meta-analysis. *Am J Psychiatry*. 2000;157(10):1552–1562.
11. Belmaker RH, Agam G. Mechanisms of disease major depressive disorder. *N Engl J Med*. 2008;358:55–68
12. Baumeister AA, Hawkins MF, Uzelac SM. The myth of reserpine-induced depression: Role in the historical development of the monoamine hypothesis. *J Hist Neurosci*. 2003;12(2):207–220.
13. Yohn CN, Gergues MM, Samuels BA. The role of 5-HT receptors in depression. *Mol Brain*. 2017;10(1):1–12.
14. Pehrson AL, Sanchez C. Altered γ-aminobutryic acid neurotransmission in major depressive disorder: A critical review of the supporting evidence and the influence of serotonergic antidepressants. *Drug Des Devel Ther*. 2015;9:603–624.
15. Taylor GT, Manzella F. Kappa opioids, salvinorin A and major depressive disorder. *Curr Neuropharmacol*. 2016;14(2):165–176.
16. Schüle C, Nothdurfter C, Rupprecht R. The role of allopregnanolone in depression and anxiety. *Prog Neurobiol*. 2014;113:79–87.

17. Newport DJ, Carpenter LL, McDonald WM. Ketamine and other NMDA antagonists: Early clinical trials and possible mechanisms in depression. *Am J Psychiatry*. 2015;172:950–966.
18. Koopman M, El Aidy S; MIDtrauma consortium. Depressed gut? The microbiota-diet-inflammation trialogue in depression *Curr Opin Psychiatry*. 2017;30(5):369–377.
19. Bender A, Hagan K, Kinston N. The association of folate and depression: A meta-analysis. *J Psychiatr Res*. 2017;95:9–18.
20. Farioli-Vecchioli S, Sacchetti S, di Robilant NV, et al. The role of physical exercise and omega-3 fatty acids in depressive illness in the elderly. *Curr Neuropharmacol*. 2018;16(3):308–326.
21. Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. *Arch Gen Psychiatry*. 2007;64:327–337.
22. Taylor C, Fricker AD, Devi L, et al. Mechanisms of action of antidepressants: From neurotransmitter systems to signaling pathways. *Cell Signal*. 2005;17(5):549–557.
23. Niciu MJ, Ionescu DF, Mathews DC, et al. Second messenger/signal transduction pathways in major mood disorders—moving from membrane to mechanism of action, part I: Major depressive disorder. *CNS Spectrums*. 2013;18:231–241.
24. Feighner JP. Mechanism of action of antidepressant medications. *J Clin Psychiatry*. 1999;60(suppl 4):S4–S11;discussion 12–13.
25. Rivero G, Gabilondo AM, García-Sevilla JA, et al. Increased α2- and β1-adrenoreceptor densities in post-mortem brain of subjects with depression: Differential effect of antidepressant treatment. *J Affective Disorders*. 2014;167:343–350.
26. Kanes S, Colquhoun H, Gunduz-Bruce H, et al. Brexanolone (SAGE-547 injection) in post-partum depression: A randomised controlled trial. *Lancet*. 2017;390:480–489.
27. Björkholm C, Monteggia LM. BDNF: A key transducer of antidepressant effects. *Neuropharmacology*. 2016;102:72–79.
28. Strasburger SE, Bhimani PM, Kaabe JH, et al. What is the mechanism of ketamine's rapid-onset antidepressant effect? A concise overview of the surprisingly large number of possibilities. *J Clin Pharm Ther*. 2017;42(2):147–154.
29. Coryell W, Schlesser M. The dexamethasone suppression test and suicide prediction. *Am J Psychiatry*. 2001;158(5):748–753.

30. Wan L, Yuhong L, Zhang Z, et al. Methylenetetrahydrofolate reductase and psychiatric diseases. *Transl Psychiatry*. 2018;8:242
31. Bousman CA, Dunlop BW. Genotype, phenotype, and medication recommendation agreement among commercial pharmacogenetic-based decision support tools. *Pharmacogenomics J*. 2018;18(5):613–622.
32. Haigh E, Bogucki O, Sigmon S, et al. Depression among older adults: A 20-year update on five common myths and misconceptions. *Am J Geriatr Psychiatry*. 2018;26(1):107–122.
33. Kok RM, Reynolds CF. Management of depression in older adults: A review. *JAMA*. 2017;317(20):2114–2122.
34. Voinov B, Richie WD, Bailey RK. Depression and chronic diseases: It is time for a synergistic mental health and primary care approach. *Prim Care Companion CNS Disord*. 2013;15(2):pii: PCC.
35. Qato DM, Ozenberger K, Olfson M. Prevalence of prescription medications with depression as a potential adverse effect among adults in the United States. *JAMA*. 2018;319(22):2289–2298.
36. Gorton HC, Webb RT, Kapur N, et al. Non-psychotropic medication and risk of suicide or attempted suicide: A systematic review. *BMJ*. 2016;6:e009074.
37. Gibbons RD, Mann JJ. Varenicline, smoking cessation, and neuropsychiatric adverse events. *Am J Psychiatry*. 2013;170(12):1460–1467.
38. Risk evaluation and mitigation strategy (REMS) The iPLEDGE Program. Available at https://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyI Accessed November 20, 2018.
39. Hesdorffer DC, Kanner AM. The FDA alert on suicidality and antiepileptic drugs: Fire or false alarm? *Epilepsia*. 2009;50(5):978–986.
40. Skovlund CW, Mørch LS, Kessing LV, et al. Association of hormonal contraception with depression. *JAMA Psychiatry*. 2016;73(11):1154–1162.
41. Solmi M, Pigato G, Kane JM, et al. Treatment of tardive dyskinesia with VMAT-2 inhibitors: A systematic review and meta-analysis of randomized controlled trials. *Drug Des Devel Ther*. 2018;12:1215–1238.
42. Ranchord AM, Spertus JA, Buchanan DM, et al. Initiation of β-blocker therapy and depression after acute myocardial infarction. *Am Heart J*. 2016;174:37–42.

43. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382–389.
44. Beck AT, Ward CH, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961;4:561–571.
45. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: Validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606–613.
46. Jacobs DG, Baldessarini RJ, Fawcett JA, et al. Practice guidelines for the assessment and treatment of patients with suicidal behaviors. *Am J Psychiatry*. 2003;160(11 suppl):S1–S60.
47. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*. 2011;168(12):1266–1277.
48. Fawcett JA, Baldessarini RJ, Coryell WH, et al. Defining and managing suicidal risk in patients taking psychotropic medications. *J Clin Psychiatry*. 2009;70(6):782–789.
49. Sharma T, Guski LW, Freund N, et al. Suicidality and aggression during antidepressant treatment: Systematic review and meta-analyses based on clinical study reports. *BMJ*. 2016;352:i65.
50. Mann JJ. The medical management of depression. *N Engl J Med*. 2005;353(17):1819–1834.
51. Fava GA, Benasi G, Lucente M. Withdrawal symptoms after serotonin-noradrenalin reuptake inhibitor discontinuation: Systematic review. *Psychother Psychosom*. 2018;87:195–203.
52. Weitz ES, Hollon SD, Twisk J, et al. Baseline depression severity as moderator of depression outcomes between cognigtive behavioral therapy vs pharmacotherapy: An individual patient data meta-analysis. *JAMA Psychiatry*. 2015;72(11):1102–1109.
53. Gaynes BN, Rush AJ, Trivedi MH, et al. The STAR*D study: Treating depression in the real world. *Cleve Clin J Med*. 2008;75(1):57–66.
54. Brunoni AR, Chaimani A, Moffa AH, et al. Repetitive transcranial magnetic stimulation for the acute treatment of major depressive episodes: A systematic review with network meta-analysis. *JAMA Psychiatry*. 2017;74(2):143–153.
55. Trivedi MH. The link between depression and physical symptoms. *Prim Care Companion J Clin Psychiatry*. 2004;6(suppl 1):S12–S16.

56. Freeman MP, Fava M, Lake J, et al. Complementary and alternative medicine in major depressive disorder: The American Psychiatric Association Task Force report. *J Clin Psychiatry*. 2010;71(6):669–681.
57. IBM Micromedex Online (Copyright 2018). Available at https://www.micromedexsolutions.com. Accessed November 15, 2018.
58. Lexicomp Online. Lexi-Comp, Inc (Copyright 1978-2018). Available at http://online.lexi.com. Accessed November 15, 2018.
59. Wimbiscus M, Kostenko O, Malone D. MAO inhibitors: Risks, benefits, and lore. *Cleve Clin J Med*. 2010:77(12):859–882.
60. Al-Sukhni M, Maruschak NA, McIntyre RS. Vortioxetine: A review of efficacy, safety and tolerability with a focus on cognitive symptoms in major depressive disorder. *Expert Opin Drug Saf*. 2015;14(8):1291–1304.
61. O'Donnell JM, Bies RR, Shelton RC. Drug therapy of depression and anxiety disorders. In: Brunton LL, Hilal-Dandan R, Knollmann BC, eds.*Goodman & Gilman: The Pharmacological Basis of Therapeutics*. 13th ed. McGraw-Hill Education; 2018.
62. Walsh BT, Seidman SN, Sysko R, Gould M. Placebo response in studies of major depression: Variable, substantial, and growing. *JAMA*. 2002;287(14):1840–1847.
63. Cipriani A, Forukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: A systematic review and network meta-analysis. *Lancet*. 2018;391:1357–1366.
64. Goldstein BJ, Goodnick PJ. Selective serotonin reuptake inhibitors in the treatment of affective disorders—III. Tolerability, safety and pharmacoeconomics. *J Psychopharmacol*. 1998;12(3 suppl B):S55–S87.
65. Wichniak A, Wierzbicka A, Walecka M, et al. Effect of antidepressants on sleep. *Curr Psychiatry*. 2017;19:63.
66. La Torre A, Giupponi G, Duffy D, Conca A. Sexual dysfunction related to psychotropic drugs: A critical review—part I: Antidepressants. *Pharmacopsychiatry*. 2013;46(5):191–199.
67. Rector TS, Adabag S, Cunningham F, et al. Outcomes of citalopram dosage risk mitigation in a veteran population. *Am J Psychiatry*. 2016;173:896–902.
68. Howland RH. A critical evaluation of the cardiac toxicity of citalopram part 1. *J Psychosocial Nursing*. 2011;49(11):13–16.

69. Settle EC. Antidepressant drugs: Disturbing and potentially dangerous adverse effects. *J Clin Psychiatry*. 1998;59(Suppl 16):S25–S30.
70. Glassman AH, Roose SP, Bigger JT. The safety of tricyclic antidepressants in cardiac patients risk benefit reconsidered. *JAMA*. 1993;269(20):2673–2675.
71. McIntyre RS. The role of new antidepressants in clinical practice in Canada: A brief review of vortioxetine, levomilnacipran ER, and vilazodone. *Neuropsychiatr Dis Treat*. 2017;13:2913–2919.
72. Sedky K, Nazir R, Joshi A. Which psychotropic medications induce hepatotoxicity. *Gen Hosp Psychiatry*. 2012;34:53–61.
73. Zhang L, Xei WW, Li LH. Efficacy and safety of prolonged-release trazodone in major depressive disorder: A multicenter, randomized, double-blind, flexible dose trail. *Pharmacology*. 2014;94:199–206.
74. Rabiner EA, Gunn RN, Castro ME, et al. β-blocker binding to human 5-HT_{1A} receptors *in vivo* and *in vitro*: Implications for antidepressant therapy. *Neuropsychopharmacol*. 2000;23:285–293.
75. Stimmel GL, Gutierrez MA. Counseling patients about sexual issues. *Pharmacotherapy*. 2006;26(11):1608–1615.
76. Steinert T, Fröscher W. Epileptic seizures under antidepressive drug treatment: Systematic review. *Pharmacopsychiatry*. 2018;51:121–135.
77. Gartlehner GHR, Morgan LC, Thaler K, et al. Second-generation antidepressants in the pharmacologic treatment of adult depression: An update of the 2007 comparative effectiveness review. (Prepared by the RTI International–University of North Carolina Evidence-based Practice Center, Contract No. 290-2007-10056-I.) Available at: http://www.effectivehealthcare.ahrq.gov. Accessed November 15, 2018.
78. Gorman JM. Mirtazapine: Clinical overview. *J Clin Psychiatry*. 1999;60(suppl 17):S9–S13.
79. Bryant SG, Brown CS. Current concepts in clinical therapeutics: Major affective disorders, Part 2. *Clin Pharm*. 1986;5(5):385–395.
80. Azzaro AJ, Ziemnia J, Kemper E, et al. Pharmacokinetics and absolute bioavailability of selegiline following treatment of healthy subjects with selegiline transdermal system (6 mg/24 h): A comparison with oral selegiline capsules. *J Clin Pharmacol*. 2007;47:1256–1267.
81. Shulman KI, Walker SE, MacKenzie S, et al. Dietary restriction, tyramine and the use of monoamine oxidase inhibitors. *J Clin Psychopharmacol*.

1989;9:397–402.

82. Daly EJ, Singh JB, Fedgchin M, et al. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: A randomized clinical trial. *JAMA Psychiatry*. 2018;75(2):139–148.
83. Canuso CM, Singh JB, Fedgchin M, et al. Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: Results of a double-blind, randomized, placebo-controlled study. 2018;175(7):620–630.
84. Meltzer-Brody S, Colquhoun H, Riesenberg R, et al. Brexanolone injection in post-partum depression: Two multicentre, double-blind, randomized, placebo-controlled, phase 3 trials. *Lancet*. 2018;392:1058–1070.
85. Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med*. 2005;352(11):1112–1120.
86. Drug interactions Flockhart Table. Available at https://drug-interactions.medicine/iu.edu/main-table.aspx. Accessed November 15, 2018.
87. DeVane CL. Metabolism and pharmacokinetics of selective serotonin reuptake inhibitors. *Cell Mol Neurobiol*. 1999;19(4):443–466.
88. Wells BG. Tricyclic antidepressants. In: Taylor WJ, Caviness MHD, eds.Taylor WJ, Caviness MHD,eds. *A Textbook for the Clinical Application of Therapeutic Drug Monitoring*. Irving, TX: Abbott Laboratories; 1986:449–465.
89. Olver JS, Burrows GD, Norman TR. The treatment of depression with different formulations of venlafaxine: A comparative analysis. *Hum Psychopharmacol*. 2004;19(1):9–16.
90. Jefferson JW, Pradko JF, Muir KT. Bupropion for major depressive disorder: Pharmacokinetic and formulation considerations. *Clin Ther*. 2005;27(11):1685–1695.
91. Update: Bupropion hydrochloride extended-release 300 mg bioequivalence studies. Available at https://www.fda.gov/Drugs/DrugSafety/ucm322161.htm. Released October 10, 2013.
92. Mullish BH, Kabir MS, Thursz MR, et al. Review article: Depression and the use of antidepressants in patients with chronic liver disease or liver transplantation. *Ailment Pharmacol Ther*. 2014;40:880–892.

93. Eyler RF, Unruh ML, Quinn DK, et al. Psychotherapeutic agents in end-stage renal disease. *Semin Dial*. 2015;28(4):417–426.
94. Brexanolone injection, for intravenous use. Sponsor briefing document. FDA Psychoparmacolologic Drug Advisory Committee and Drug Safety and Drug Safety and Risk Management Meeting. November 2, 2018. Available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeeting
95. Bixby AL, VandenBerg A, Bostwick JR. Clinical management of bleeding risk with antidepressants. *Ann Pharmacother*. 2018;[Epub ahead of print].
96. Rickli A, Liakoni E, Hoener MC, et al. Opioid-induced inhibition of the human 5-HT and noradrenaline transporters *in vitro*: Link to clinical reports of serotonin syndrome. *Br J Pharmacol*. 2018;175(3):532–543.
97. Köhler O, Petersen L, Mors O, et al. Inflammation and depression: Combined use of selective serotonin reuptake inhibitors and NSAIDs or paracetamol and psychiatric outcomes. 2015;5(8):e00338.
98. Lorenz RA, VandenBerg AM, Canepa EA. Serotonergic antidepressants and linezolid: A retrospective chart review and presentation of cases. *Int J Psychiatry Med*. 2008;38(1):81–90.
99. Ravindran AV, Balneaves LG, Faulkner G, et al. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder. Section 5. Complementary and alternative medicine treatments. *Can J Psychiatry*. 2016;61(9):576–587.
100. Turvey CL, Conwell Y, Jones MP, et al. Risk factors for late-life suicide: A prospective, community-based study. *Am J Geriatr Psychiatry*. 2002;10(4):398–406.
101. Schatzberg AG, Kremer C, Rodriguez HE, et al. Double-blind, randomized comparison of mirtazapine and paroxetine in elderly depressed patients. *Am J Geriatr Psychiatry*. 2002;10(5):541–550.
102. Mullen S. Major depressive disorder in children and adolescents. *Ment Health Clin*. 2018;8(6):275–283.
103. March J, Silva S, Petrycki S, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for adolescents with depression study (TADS) randomized controlled trial. *JAMA*. 2004;292(7):807–820.
104. Emslie GJ, Mayes T, Porta G, et al. Treatment of resistant depression in adolescents (TORDIA): Week 24 outcomes. *Am J Psychiatry*.

2010;167:782–791.

105. Goodyer I, Dubicka B, Wilkinson P, et al. A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial. *Health Technol Assess*. 2008;12(14):iii–iv,ix-60.
106. Gibbons RD, Brown CH, Hur K, et al. Suicidal thoughts and behavior with antidepressant treatment. *Arch Gen Psychiatry*. 2012;69(6):580–587.
107. Gibbons RD, Brown CH, Hur K, et al. Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. *Am J Psychiatry*. 2007;164:1356–1363.
108. Oberlander TF, Warburton W, Misri S, et al. Neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitor antidepressants and maternal depression using population-based linked health data. *Arch Gen Psychiatry*. 2006;63(8):898–906.
109. Cohen LS, Altshuler LL, Harlow BL, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *JAMA*. 2006;295(5):499–507.
110. Gao SY, Wu QJ, Zhang TN, et al. Selective serotonin reuptake inhibitor use during early pregnancy and congenital malformations: A systematic review and meta-analysis of cohort studies of more than 9 million births. *BMC Medicine*. 2018;16:205.
111. Chambers CD, Hernandez-Diaz S, Van Marter LJ, et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med*. 2006;354(6):579–587.
112. Rubinow DR. Antidepressant treatment during pregnancy: Between Scylla and Charybdis. *Am J Psychiatry*. 2006;163(6):954–956.
113. Yonkers KA, Wisner KL, Stewart DE, et al. The management of depression during pregnancy: A report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. *Gen Hosp Psychiatry*. 2009;31(5):403–413.
114. Freeman MP. Breastfeeding and antidepressants: Clinical dilemmas and expert perspectives. *J Clin Psychiatry*. 2009;70(2):291–292.
115. Motherisk. Available at www.motherisk.org/women/index.jsp. Accessed December 19, 2018.
116. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: Implications for clinical practice. *Am J Psych*. 2006;163:28–40.

117. Rush AJ, Trivedi MH, Wisniewski SR, et al. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med*. 2006;354(12):1231–1242.
118. Fava M, Rush AJ, Wisniewski SR, et al. A comparison of mirtazapine and nortriptyline following two consecutive failed medication treatments for depressed outpatients: A STAR*D report. *Am J Psychiatry*. 2006;163(7):1161–1172.
119. Nierenberg AA, Fava M, Trivedi MH, et al. A comparison of lithium and T(3) augmentation following two failed medication treatments for depression: A STAR*D report. *Am J Psychiatry*. 2006;163(9):1519–1530.
120. Mohamed S, Johnson GR, Chen P, et al. Effect of antidepressant switching vs augmentation on remission among patients with major depressive disorder unresponsive to antidepressant treatment. The VAST-D randomized clinical trial. *JAMA*. 2018;318:132–145.
121. Rosenblat JD, Lee Y, McIntyre RS. Does pharmacogenomics testing improve clinical outcomes for major depressive disorder. A systematic review of clinical trials and cost-effectiveness studies. *J Clin Psychiatry*. 2017;78(6):720–729.

86

Bipolar Disorder

Shannon J. Drayton and Christopher S. Fields

KEY CONCEPTS

1. Bipolar disorder is a cyclic mental illness with recurrent mood episodes that occur over a person's lifetime. The symptoms, course, severity, and response to treatment differ among individuals.
2. Bipolar disorder is likely caused by genetic factors, environmental triggers, and the dysregulation of neurotransmitters, neurohormones, and second messenger systems in the brain.
3. Clinicians should obtain a detailed history, including substance use history and medical history, to expedite the diagnosis and treatment of bipolar disorder.
4. Bipolar disorder is a complex psychiatric illness with significant morbidity and mortality. Suicidal thoughts and behaviors are common in individuals with bipolar disorder and need to be managed with medical and therapeutic interventions.
5. The goal of therapy for bipolar disorder should be to improve patient functioning by reducing mood episodes. This is accomplished by maximizing adherence to therapy and limiting adverse effects.
6. Patients and family members should be educated about bipolar disorder and treatments. Long-term monitoring and adherence to treatment are primary factors in achieving stabilization of the disorder.
7. Lithium, valproate, and second-generation antipsychotics are the mainstays of treatment for different phases of bipolar disorder, acting as primary mood stabilizers. When individuals with bipolar disorder present with an acute mood episode (depressed episode, manic episode or mixed state) despite a primary mood stabilizer, adjunctive medications are considered to target the specific mood state or subtype. These medications can often be

tapered once the acute episode has resolved and the patient is euthymic. Baseline and follow-up laboratory tests are required for most medications for bipolar disorder to monitor for adverse effects.

8 Some patients can be stabilized on one mood stabilizer, but others may require combination therapies or adjunctive agents during an acute mood episode. If possible, adjunctive agents should be tapered and discontinued when the acute mood episode remits and the patient is stabilized. Adjunctive agents may include benzodiazepines, additional mood stabilizers, antipsychotics, and/or antidepressants.

Preclass Engaged Learning Activity

Introductory Video about Bipolar Disorder: Use the link below to view the video titled, "Mental Illness in Stressful Times—An Asian American Family's Story" on the National Institute of Mental Health website. This 6-minute video provides a glimpse into one family's experience with bipolar disorder. The viewing of this video is intended to stimulate deeper thinking about social implications of bipolar disorder and to provoke an appreciation of the hardships and successes that patients with the disorder may face.

Link to video:https://www.nimh.nih.gov/news/media/2016/mental-illness-in-stressful-times-an-asian-american-familys-story.shtml

INTRODUCTION

1 Bipolar disorder is a common, chronic, and often severe cyclic mood disorder characterized by recurrent fluctuations in mood, energy, and behavior.[1–3] It differs from recurrent major depression (or unipolar depression) in that a manic or hypomanic episode occurs during the course of the illness (see section "Clinical Presentation and Diagnosis").[1] Bipolar disorder is a lifelong illness with a variable course and requires both nonpharmacologic and pharmacologic treatments for mood stabilization.[1,2]

EPIDEMIOLOGY

The lifetime prevalence of bipolar disorder in the United States is 4.5% with 1%

of patients meeting criteria for bipolar I, 1.1% for bipolar II, and 2.4% of patients with subthreshold bipolar disorder (ie, cyclothymia, unspecified bipolar disorder).[4,5] Symptom onset for depression, mania, or hypomania in bipolar disorder typically occurs in late adolescence or early adulthood, with greater than two-thirds of those affected developing symptoms before age 18 years.[6,7] Depression and mixed presentations may occur more frequently in women.[8–10]

ETIOLOGY AND PATHOPHYSIOLOGY

2 The exact etiology of bipolar disorder is unknown, but is thought to be a influenced by a complex of developmental, genetic, neurobiologic, and psychological factors.[11] Many theories have been proposed regarding the pathophysiology of mood disorders. Family, twin, and adoption studies report an increased lifetime prevalence risk of having mood disorders among first-degree relatives of patients with bipolar disorder.[12,13] Genetic linkage studies suggest multiple gene loci may be involved in the heredity of mood disorders.[14] Neuroimaging studies indicate that several anatomic regions (primarily the amygdala within the limbic system and the prefrontal cortex) may contribute to functional abnormalities in bipolar patients.[15,16] Many researchers suspect that altered synaptic and circuit functioning account for mood and cognitive changes seen in bipolar disorder, rather than dysfunction of individual neurotransmitters.[17] Environmental or psychological stressors, immunologic factors, and sleep dysregulation all have been associated with bipolar disorder and can negatively influence the course of illness.[18–22]

CLINICAL PRESENTATION AND DIAGNOSIS

1 The essential feature of bipolar spectrum disorders is a history of mania or hypomania that is not caused by any other medical condition, substance, or psychiatric disorder.[1,2] The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) of the American Psychiatric Association (APA) details the present understanding of mood disorders.[1] Bipolar disorder is divided into five subtypes based on the identification of specific mood episodes: bipolar I, bipolar II, cyclothymic disorder, other specified bipolar and related disorder, and unspecified bipolar and related disorder.[1] **Table 86-1** defines the mood disorders by type of episode. Specifiers (ie, hypomanic or major depressive episode) can be added to bipolar I and II to reflect the most recent

mood state. Bipolar disorder is a cyclic mood disorder, and patients may sequentially experience different types of episodes with or without a period of normal mood (euthymia) between episodes. Individuals with bipolar disorder can have mood fluctuations that continue for months, or after one episode they can sometimes go years without recurrence of any type of mood episode. Comorbid conditions associated with bipolar disorder include, but are not limited to, substance abuse, personality disorders, anxiety disorders, eating disorders, and a higher incidence of several medical conditions.[1–3,23–27]

TABLE 86-1 Mood Disorders Defined by Episodes

Disorder Subtype	Episode(s)[a]
Major depressive disorder, single episode	Major depressive episode
Major depressive disorder, recurrent	Two or more major depressive episodes
Bipolar I disorder[b]	Manic episode ± major depressive or hypomanic episode
Bipolar II disorder[c]	Major depressive episode + hypomanic episode
Persistent depressive disorder (Dysthymia)	Depressed mood most days for at least 2 years (1 year in children and adolescents)
Cyclothymic disorder[d]	Chronic fluctuations between subsyndromal depressive and hypomanic episodes (2 years for adults and 1 year for children and adolescents)
Unspecified bipolar and related disorder	Mood states do not meet full criteria for any specific disorder in the bipolar and related disorders class

[a]The length and severity of a mood episode and the interval between episodes vary from patient to patient. Manic episodes are usually shorter and end more abruptly than major depressive episodes. The average length of untreated manic episodes ranges from 4 to 13 months. Episodes can occur regularly (at the same time or season of the year) and often cluster at 12-month intervals. Women have more depressive episodes than manic episodes, whereas men have a more even distribution of episodes.

[b]For bipolar I disorder, 90% of individuals who experience a manic episode later have multiple recurrent major depressive, manic, or hypomanic episodes alternating with a normal mood state.

[c]Approximately 5% to 15% of patients with bipolar II disorder will develop a manic episode over a 5-year period. If a manic episode develops in a patient with bipolar II disorder, the diagnosis is changed to bipolar I disorder.

[d]Patients with cyclothymic disorder have a 15% to 50% risk of later developing a bipolar I or II disorder.

Data from References 1–3.

Diagnostic Difficulty

Episodes of mania or depression may be induced or caused by medical illness, medications, or substance intoxication or withdrawal (refer to **Table 86-2**)[28–36] for causes of mania and Chapter 85 for causes of depression.[1,2] A complete medical, psychiatric, and medication history; physical examination; and laboratory testing are important tools to rule out any organic causes of mania or

depression.[2] An accurate diagnosis is critical because some psychiatric and neurologic disorders present with manic-like or depressive-like symptoms.[2,3] Bipolar disorder commonly co-occurs with substance use disorders and may be difficult to diagnose in the presence of cocaine use or other illicit substances (eg, psychostimulants, bath salts, synthetic marijuana).[37] When making the diagnosis of new-onset bipolar disorder in a geriatric population, clinicians should be particularly aware of secondary causes of mania and depression that may impact treatment.[38]

TABLE 86-2 Secondary Causes of Mania

Medical conditions that induce mania

- CNS disorders (brain tumor, strokes, head injuries, subdural hematoma, multiple sclerosis, systemic lupus erythematosus, temporal lobe seizures, Huntington's disease)
- Infections (encephalitis, neurosyphilis, sepsis, human immunodeficiency virus)
- Electrolyte or metabolic abnormalities (calcium or sodium fluctuations, hyperglycemia or hypoglycemia)
- Endocrine or hormonal dysregulation (Addison's disease, Cushing disease, hyperthyroidism or hypothyroidism, menstruation-related or pregnancy-related or perimenopausal mood disorders)

Medications or drugs that induce mania

- Alcohol intoxication
- Drug withdrawal states (alcohol, α_2-adrenergic agonists, antidepressants, barbiturates, benzodiazepines, opiates)
- Antidepressants (MAOIs, TCAs, 5-HT and/or NE and/or DA reuptake inhibitors, 5-HT antagonists)
- DA-augmenting agents (CNS stimulants: amphetamines, cocaine, sympathomimetics; DA agonists, releasers, and reuptake inhibitors)
- Hallucinogens (LSD, PCP)
- Marijuana intoxication precipitates psychosis, paranoid thoughts, anxiety, and restlessness
- NE-augmenting agents (α_2-adrenergic antagonists, β-agonists, NE reuptake inhibitors)
- Steroids (anabolic, adrenocorticotropic hormone, corticosteroids)
- Thyroid preparations
- Xanthines (caffeine, theophylline)
- Nonprescription weight loss agents and decongestants (ephedra, pseudoephedrine)
- Herbal products (St. John wort)

Somatic therapies that induce mania

- Bright light therapy
- Deep brain stimulation
- Sleep deprivation

CNS, central nervous system; DA, dopamine; 5-HT, serotonin; LSD, lysergic acid diethylamide; MAOI, monoamine oxidase inhibitor; NE, norepinephrine; PCP, phencyclidine; TCA, tricyclic antidepressant.

Data from References 1, 28–36.

Another disease state that presents similarly to bipolar disorder is schizoaffective disorder, which is essentially a mix between schizophrenia and bipolar disorder or unipolar depression. Patients with schizoaffective disorder have mood episodes, but a primary distinguishing factor from bipolar disorder is that these patients experience psychosis between mood episodes during periods

of euthymic mood. Clinicians must rely on the longitudinal history provided by collateral historians who know the patient well to determine if the patient is experiencing psychosis between mood episodes. It can be difficult for clinicians to obtain a full psychiatric history on patients presenting with manic or psychotic symptoms, thus making schizoaffective disorder difficult to differentiate from bipolar disorder. Schizoaffective disorder, bipolar type is best treated with antipsychotics with or without a mood stabilizer as maintenance therapy.

CLINICAL PRESENTATION

Major Depressive Disorder[a]

DSM-5 Criteria[b]

At least 2-week period of either depressed mood or loss of interest or pleasure in normal activities, associated with at least five of the following symptoms:

- Depressed, sad mood (adults); can be irritable mood in children
- Decreased interest and pleasure in normal activities
- Decreased or increased appetite, weight loss or weight gain
- Insomnia or hypersomnia
- Psychomotor retardation or agitation
- Decreased energy or fatigue
- Feelings of excessive guilt or worthlessness
- Impaired concentration or indecisiveness
- Recurrent thoughts of death, suicidal thoughts or attempts

Mania[a]

DSM-5 Criteria[b]

At least 1-week period of abnormally and persistently elevated mood (expansive or irritable) and energy, associated with at least three of the following symptoms (four if the mood is only irritable):

- Inflated self-esteem (grandiosity)
- Decreased need for sleep
- Increased talking (pressure of speech)
- Racing thoughts (flight of ideas)

- Distractibility (poor attention)
- Increased goal-directed activity (socially, at work, or sexually) or psychomotor agitation
- Excessive involvement in activities that are pleasurable but have a high risk for serious consequences (buying sprees, sexual indiscretions, poor judgment in business ventures)

Hypomania[a]

DSM-5 Criteria*b*

At least 4 days of abnormally and persistently elevated mood (expansive or irritable) and energy, associated with at least three of the following symptoms (four if the mood is only irritable):

- Inflated self-esteem (grandiosity)
- Decreased need for sleep
- Increased talking (pressure of speech)
- Racing thoughts (flight of ideas)
- Distractibility (poor attention)
- Increased goal-directed activity (socially, at work, or sexually) or psychomotor agitation
- Excessive involvement in activities that are pleasurable but have a high risk for serious consequences (buying sprees, sexual indiscretions, poor judgment in business ventures)

---

[a]Impairment in social or occupational functioning; may include need for hospitalization because of potential self-harm, harm to others, or psychotic symptoms.

[b]The disorder is not caused by a medical condition (eg, hypothyroidism) or substance-induced disorder (eg, antidepressant treatment, medications, drugs of abuse). Numerous specifiers are available to further characterize episodes (eg, with mixed features, with anxious distress, with rapid cycling, with melancholic features).

Data from Reference 1.

Course of Illness

3 Bipolar disorder is frequently not recognized or treated for many years because of its initial fluctuating course with subsyndromal symptoms of depression, irritability, and hypomania that build up gradually in intensity.[39] Patients typically experience delays averaging 8 years after the onset of the index mood episode until appropriate medication initiation.[40] This delay confers a risk of poor social functioning, increased hospitalizations, and a greater likelihood of lifetime suicide attempts.[41] Onset of illness in early childhood (as opposed to onset in early adulthood) tends to be associated with increased mood episodes, rapid cycling, and comorbid psychiatric conditions as well as a stronger family history of mood disorders.[42] Gender differences may influence a patient's course of illness, tolerability of medication, and response to treatment. Women are more likely to have increased depressive symptoms, older age of onset, better compliance, complex management in pregnancy, and higher association with physical illness such as thyroid abnormalities. In men, there may be increased incidence of mania and substance use.[43]

The kindling theory has been used to explain how bipolar disorder can progress over one's life and why preventive treatment is imperative. Without effective treatment, episodes can become more frequent, severe, and refractory to treatment.[44] Usually there is a period of normal functioning between episodes, but approximately 20% to 30% of patients with bipolar I disorder and 15% with bipolar II disorder have no interepisode period of euthymia because of mood lability, residual subsyndromal mood symptoms, or a direct switch to the opposite polarity.[1]

Rapid cycling (more than four mood episodes per year) is more common in women and occurs in approximately 10% to 20% of bipolar I and II disorder patients.[2,3,45] Frequent and severe episodes of depression appear to be the most common hallmark of rapid cycling. Use of alcohol, stimulants, and antidepressants, as well as sleep deprivation, hypothyroidism, and seasonal changes can play a role in rapid cycling.[3,45,46] Seasonal patterns of mania in the summer and depression during the winter have been observed. Rapid-cycling patients have a poorer long-term prognosis and often require combination therapies.[3]

Fluctuations in hormones and neurotransmitters during the luteal phase of the menstrual cycle, postpartum period, and perimenopause (starting ~10 years before menopause) can precipitate mood changes and increase cycling.[1,47] Women with bipolar I disorder are at greater risk for relapse into mania or

depression during the postpartum period.[2] If a severe mood episode occurs postpartum, there is an increased risk for recurrences during subsequent postpartum periods.[48]

Alcohol and substance abuse is common among patients with bipolar disorder and can have a significant impact on the age of onset, course of the illness, and response to treatment.[3,23,24] Alcohol and drug abuse or dependence has been reported in close to half of bipolar patients.[2,23] Patients with substance use disorders are more likely to have an earlier onset of their illness, mixed states, higher rates of relapse, a poorer response to treatment, comorbid personality disorders, increased suicide risk, and more psychiatric hospitalizations.[3] Bipolar patients often abuse substances such as alcohol, marijuana, or cocaine during episodes, which can result in further impairment of judgment, poor impulse control, treatment nonadherence, and a worsening of the clinical course.[49]

4 More than one-half (55%-65%) of bipolar I patients have some degree of functional disability after the onset of their illness, and approximately 10% to 20% of bipolar patients have severe impairment in their psychosocial and occupational functioning.[2,3,50] In a 1-year longitudinal study in 258 bipolar patients, two-thirds had four or more mood episodes a year despite comprehensive pharmacologic treatment, and approximately 33.2% of the year was spent being depressed compared with 10.8% of the time in a manic phase.[50]

Compared with the general population, individuals with bipolar disorder have a 2.3 times higher mortality rate. Suicide attempts occur in up to 50% of patients with bipolar disorder, and approximately 10% to 19% of individuals with bipolar I disorder commit suicide.[3,51] Studies suggest patients with bipolar II disorder have more suicide attempts than bipolar I patients.[51]

The best predictor for level of functioning during a person's lifetime is adherence with medication treatment. Medication discontinuation occurs in 20% to 60% of patients secondary to multiple factors including intolerance of drug-induced side effects.[52] Failure to recognize the disorder, reluctance to acknowledge it, or poor adherence with treatment are reasons an estimated two-thirds of patients with bipolar disorder do not receive appropriate treatment. Nonadherence with pharmacologic treatment and substance abuse are major factors in relapse and hospitalizations.[2,3]

TREATMENT

Desired Outcomes

5 The desired outcome in treating bipolar disorder is to effectively resolve acute manic, hypomanic, and depressive episodes, as well as prevent further episodes, maintain healthy functioning, promote treatment adherence, and minimize side effects.[2,3] The general principles and goals for the management of bipolar disorder are found in **Table 86-3**.

TABLE 86-3 General Principles for the Management of Bipolar Disorder

Goals of treatment
• Eliminate mood episode with complete remission of symptoms (ie, acute treatment)
• Prevent recurrences or relapses of mood episodes (ie, continuation phase treatment)
• Return to baseline psychosocial functioning
• Maximize adherence with therapy
• Minimize adverse effects
• Use medications with the best tolerability and fewest drug interactions
• Minimize polypharmacy when possible
• Treat comorbid substance use and abuse
• Eliminate alcohol, marijuana, cocaine, amphetamines, and hallucinogens
• Minimize nicotine use and stop caffeine intake at least 8 hours prior to bedtime
• Avoidance of stressors or substances that precipitate an acute episode

Data from References 2, 23, 101.

General Approach to Treatment

6 Treatment of bipolar disorder must be individualized because the clinical presentation, severity, and frequency of episodes vary widely among patients. Treatment approach should include both nonpharmacologic and pharmacologic strategies.[3] Patients and family members should be educated about bipolar disorder (eg, symptoms, causes, and course) and treatment options. Long-term adherence to treatment is the most important factor in achieving stabilization of the disorder.

7 The treatment of bipolar disorder can vary depending on what type of episode the patient is experiencing. Once diagnosed with bipolar disorder, patients should remain on a mood stabilizer (eg, lithium, valproate, or a second-generation antipsychotic) for their lifetime. During acute episodes, medications can be added and then tapered once the patient is stabilized and euthymic. For example, when treating a patient for mania with psychotic features, the patient should be on a mood stabilizer and an antipsychotic. If the antipsychotic is the patient's maintenance therapy, the dose should be increased or perhaps the

medication should be changed altogether if the patient's mood becomes manic. If treating a patient for a severe depressive episode, a clinician may need to maximize the dose of the mood stabilizer or add another medication (eg, quetiapine).

Nonpharmacologic Therapy

The basics of nonpharmacologic approaches should address issues of adequate nutrition, sleep, exercise, and stress reduction.[3] Sleep deprivation, high stress, and deficiencies in dietary essential amino acids, fatty acids, vitamins, and minerals can exacerbate mood episodes and result in worse outcomes.[3] Psychological interventions are aimed at providing individuals with bipolar disorder with self-management skills and tools for mood regulation. Current evidence-based psychological approaches include: cognitive behavioral therapy (CBT), interpersonal and social rhythm therapy, group psychoeducation, family focused therapy, and enhanced relapse prevention/individual psychoeducation. Common features of these psychological interventions are providing education about the condition, identifying prodromal warning signs, developing coping strategies and developing crisis plans.

Pharmacologic Therapy

7 Pharmacotherapy is crucial for the acute and maintenance treatment of bipolar disorder and includes lithium, valproate, carbamazepine, lamotrigine, first-generation antipsychotics (FGAs), second-generation antipsychotics (SGAs), and adjunctive agents such as antidepressants and benzodiazepines. General treatment guidelines for the acute treatment of mood episodes in patients with bipolar I disorder are found in Table 86-4.[2,53,54]

TABLE 86-4 Algorithm and Guidelines for the Acute Treatment of Mood Episodes in Patients with Bipolar I Disorder

Acute Manic or Mixed Episode

General Guidelines

Assess for secondary causes of mania or mixed states (eg, alcohol or drug use)
Discontinue antidepressants
Taper off stimulants and caffeine if possible
Treat substance abuse
Encourage good nutrition (with regular protein and essential fatty acid intake), exercise, adequate sleep, stress reduction, and psychosocial therapy

Hypomania

First, optimize current mood stabilizer if noncompliance is suspected OR initiate mood-stabilizing medication: lithium,[a] valproate,[a] carbamazepine,[a] or SGAs
Consider adding a benzodiazepine (lorazepam or clonazepam) for short-term adjunctive treatment of agitation or insomnia if needed
Alternative medication treatment options: oxcarbazepine
Second, if response is inadequate, consider a two-drug combination:
Lithium[a] **plus** an anticonvulsant or an SGA
Anticonvulsant **plus** an anticonvulsant or SGA

Mania

First, optimize previously prescribed mood stabilizer or medication regimen if noncompliance suspected OR initiate new mood-stabilizing two- or three-drug combinations (lithium,[a] valproate,[a] or SGA) **plus** a benzodiazepine (lorazepam or clonazepam) and/or antipsychotic for short-term adjunctive treatment of agitation or insomnia; lorazepam is recommended for catatonia
Do not combine antipsychotics
Alternative medication treatment options: carbamazepine[a]; if patient does not respond or tolerate, consider oxcarbazepine
Second, if response is inadequate, consider a three-drug combination:
Lithium[a] **plus** an anticonvulsant **plus** an antipsychotic
Anticonvulsant **plus** an anticonvulsant **plus** an antipsychotic
Third, if response is inadequate, consider ECT for mania with psychosis or catatonia,[b] or add clozapine for treatment-refractory illness

Acute Depressive Episode

General Guidelines

Assess for secondary causes of depression (eg, alcohol or drug use)
Taper off antipsychotics, benzodiazepines, or sedative–hypnotic agents if possible
Treat substance abuse
Encourage good nutrition (with regular protein and essential fatty acid intake), exercise, adequate sleep, stress reduction, and psychosocial therapy

Mild-to-Moderate Depressive Episode

First, initiate and/or optimize mood-stabilizing medication: lithium,[a] quetiapine, lurasidone
Alternative anticonvulsants: lamotrigine,[c] valproate[a]; antipsychotics: fluoxetine/olanzapine combination

Severe Depressive Episode

First, optimize current mood stabilizer if noncompliance is suspected OR initiate a new mood-stabilizing medication: lithium[a] or quetiapine or lurasidone
Alternative fluoxetine/olanzapine combination
If psychosis is present, initiate an antipsychotic in combination with above
Do not combine antipsychotics
Alternative anticonvulsants: lamotrigine,[c] valproate[a]
Second, if response is inadequate, consider carbamazepine[a] or adding antidepressant[d]
Third, if response is inadequate, consider a three-drug combination:
Lithium **plus** lamotrigine[c] **plus** an antidepressant[d]
Lithium **plus** quetiapine **plus** antidepressant[d]
Fourth, if response is inadequate, consider ECT for treatment-refractory illness and depression with psychosis or catatonia[b]

[a]Use standard therapeutic serum concentration ranges if clinically indicated; if partial response or breakthrough episode, adjust dose to achieve higher serum concentrations without causing intolerable adverse effects; valproate is preferred over lithium for mixed episodes and rapid cycling; lithium and/or lamotrigine is preferred over valproate for bipolar depression.

[b]ECT is used for severe mania or depression during pregnancy and for mixed episodes; prior to treatment, anticonvulsants, lithium, and benzodiazepines should be tapered off to maximize therapy and minimize adverse effects.

[c]Lamotrigine is not approved for the acute treatment of depression, and the dose must be started low and slowly titrated up to decrease adverse effects if used for maintenance therapy of bipolar I disorder. Lamotrigine may be initiated during acute treatment with plans to transition to this medication for long-term maintenance. A drug interaction and a severe dermatologic rash can occur when lamotrigine is combined with valproate (ie, lamotrigine doses must be halved from standard dosing titration).

[d]Controversy exists concerning the use of antidepressants, and they are often considered third line in treating acute bipolar depression, except in patients with no recent history of severe acute mania or potentially in bipolar II patients.

ECT, electroconvulsive therapy; SGA, second-generation antipsychotic.

Data from References 2, 53.

Product information, dosing, and administration of agents used in the treatment of bipolar disorder are found in **Table 86-5**.

TABLE 86-5 Products, Dosage and Administration, and Clinical Use of Agents Used in the Treatment of Bipolar Disorder

Drug "Brand Name"	Initial Dosing	Usual Dosing; Special Population Dosing	Comments
Lithium salts			
Lithium carbonate "Eskalith[a,b]" "Eskalith CR" "Lithobid" Lithium citrate "Cibalith-S[a,b]"	300 mg twice daily	900-2,400 mg/day in two to four divided doses, preferably with meals Renal impairment: lower doses required with frequent serum monitoring There is wide variation in the dosage needed to achieve therapeutic response and trough serum lithium concentration (ie, 0.6-1.2 mEq/L [mmol/L] for maintenance therapy and 0.8-1.2 mEq/L [mmol/L] for acute mood episodes taken 12 hours after the last dose)	Use alone or in combination with other medications (eg, valproate, carbamazepine, antipsychotics) for the acute treatment of mania and for maintenance treatment
Anticonvulsants			
Divalproex sodium "Depakote[a]" "Depakote ER" Valproic acid[a] "Depakene" Valproate sodium "Depacon"	250-500 mg twice daily A loading dose of divalproex (20-30 mg/kg/day) can be given	750-3,000 mg/day (20-60 mg/kg/day) given once daily or in divided doses Titrate to clinical response Dose adjustment needed with hepatic impairment	Use alone or in combination with other medications (eg, lithium, carbamazepine, antipsychotics) for the acute treatment of mania and for maintenance treatment Use caution when combining with lamotrigine because of potential drug interaction
Lamotrigine "Lamictal[b]"	25 mg daily	50-400 mg/day in divided doses. Dosage should be slowly increased (eg, 25 mg/day for 2 weeks, then 50 mg/day for weeks 3 and 4, and then 50-mg/day increments at weekly intervals up to 200 mg/day) Dose adjustment needed with hepatic impairment	Use alone or in combination with other medications (eg, lithium, carbamazepine) for long-term maintenance treatment for bipolar I disorder
Carbamazepine "Equetro[a]" "Tegretol" "Epitol" "Tegretol-XR" "Carbatrol"	200 mg twice daily	200-1,800 mg/day in two to four divided doses Titrate to clinical response Dose adjustment needed with hepatic impairment	Use alone or in combination with other medications (eg, lithium, valproate, antipsychotics) for the acute and long-term maintenance treatment of mania or mixed episodes for bipolar I disorder. APA guidelines recommend reserving it for patients unable to tolerate or who have inadequate response to lithium or valproate Extended-release tablets should be swallowed whole and not be broken or chewed "Carbatrol" capsules can be opened and contents sprinkled over food
Oxcarbazepine "Trileptal"	300 mg twice daily	300-1,200 mg/day in two divided doses Titrate based on clinical response Dose adjustment required with severe renal impairment	Use after patients have failed treatment with carbamazepine or have intolerable side effects May have fewer adverse effects and be better tolerated than carbamazepine
Atypical antipsychotics			
Aripiprazole "Abilify[a,b]" "Abilify Maintena[b]"	10-15 mg daily	10-30 mg/day once daily	
Asenapine "Saphris[a]"	5-10 mg twice daily sublingually	5-10 mg twice daily sublingually	
Cariprazine "Vraylar[a]"	1.5 mg daily	3-6 mg daily	
Lurasidone "Latuda[c]"	20 mg daily	20-120 mg daily with food	
Olanzapine "Zyprexa[a,b]" "Zyprexa Zydis"	2.5-5 mg twice daily	5-20 mg/day once daily or in divided doses	
Olanzapine and fluoxetine "Symbyax[c]"	6 mg olanzapine and 25 mg fluoxetine daily	6-12 mg olanzapine and 25-50 mg fluoxetine daily	
Quetiapine "Seroquel[a,b]"	50 mg twice daily	50-800 mg/day in divided doses or once daily when stabilized	
Risperidone "Risperdal[a]" "Risperdal M-Tab" "Risperdal Consta[b]"	0.5-1 mg twice daily	0.5-6 mg/day once daily or in divided doses	
Ziprasidone "Geodon[a]"	40-60 mg twice daily	40-160 mg/day in divided doses	

Drug "Brand Name"	Initial Dosing	Usual Dosing; Special Population Dosing	Comments
Benzodiazepines			
Various	Dosage should be slowly adjusted up and down according to response and adverse effects	Use in combination with other medications (eg, antipsychotics, lithium, valproate) for the acute treatment of mania or mixed episodes Use as a short-term adjunctive sedative–hypnotic agent	

[a]FDA-approved for acute mania.

[b]FDA-approved for maintenance.

[c]FDA-approved for acute bipolar depression.

FDA-approved agents may be used as monotherapy in various phases of the illness as noted in table footnotes.[a,b,c]

Data from References 2, 3, 23, 53.

7 The term *mood stabilizer* is often used to describe the class of medications used in the treatment of bipolar disorder for stabilizing the patient's mood and as maintenance therapy for the prevention of mood fluctuations (eg, mania or depression). However, this term may not be accurate, as some medications are more effective for acute mania, some for the depressive episode, and others for the maintenance phase.[55] Lithium, valproate (or divalproex sodium), extended-release carbamazepine, aripiprazole, asenapine, cariprazine, olanzapine, quetiapine, risperidone, and ziprasidone are currently approved by the US Food and Drug Administration (FDA) for the treatment of acute mania in bipolar disorder; only lithium, aripiprazole, olanzapine, IM extended release risperidone, and lamotrigine are approved for the maintenance treatment of bipolar disorder. Quetiapine and lurasidone are the only FDA-approved monotherapy antipsychotics for bipolar depression.

Combination therapies (eg, lithium plus valproate or carbamazepine, lithium or valproate plus an SGA) can provide better acute response and long-term prevention of relapse and recurrence than monotherapy in some bipolar patients.[56] The majority of patients hospitalized for an acute episode will be initiated on combination therapy. After resolution of acute symptoms, the medication regimen should be simplified as much as possible.

Several guidelines and algorithms have been published regarding the treatment of bipolar disorder, and these are generally based on the best available data and clinical consensus of experts. The Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders

(ISBD) published updated treatment guidelines in 2013.[53] In addition, an international task force of the World Federation of Societies of Biological Psychiatry (WFSBP) has published guidelines for the treatment of bipolar disorder. The WFSBP mania, depression, mixed, and maintenance guidelines were updated in 2009, 2010, 2017, and 2013, respectively.[57–60]

Based on the CANMAT, ISBD guidelines and available research, an example treatment algorithm and guidelines for acute mood episodes in adult patients with bipolar I disorder are listed in Table 86-4. Selection of treatment for acute mood episodes (eg, mania or depression) and for maintenance treatment should be individualized. Treatment plans should be based on patient-specific characteristics, comorbid psychiatric and medical conditions, consideration of drug interactions, and avoidance of adverse effects.[2]

Lithium

Lithium was first used in 1949 as a treatment for mania and was approved in 1972 in the United States for the treatment of acute mania and for maintenance therapy. Despite numerous investigations into the biologic and clinical properties of lithium, there is no unified theory for its mechanism of action[61]; however, chronic lithium administration may modulate gene expression and have neuroprotective effects. Lithium is a monovalent cation that is rapidly absorbed, and widely distributed with no protein binding. It is also not metabolized, and is excreted unchanged in the urine and in other body fluids.[61]

Efficacy Lithium is considered a first-line agent for acute mania, acute bipolar depression, and maintenance treatment of bipolar I and II disorders.[53] Early placebo-controlled studies with lithium reported up to a 78% response rate in aborting an acute manic or hypomanic episode, but more recent studies suggest a slower onset of action and more moderate effectiveness when compared with other agents.[62]

In placebo-controlled studies in bipolar depression, lithium has been found to have efficacy, but there can be a 6- to 8-week delay for its antidepressant effects.[62] Lithium's role in the maintenance phase of bipolar disorder in preventing mania and depressive episodes is supported by numerous studies.[62] Lithium also produces a prophylactic response of reducing suicide in patients with bipolar disorder.[63] Relapse can be reduced with the combination of lithium and other medications such as divalproex sodium, carbamazepine, lamotrigine, and antipsychotics.[62] Abrupt discontinuation or noncompliance with lithium

therapy can increase the risk of relapse.[62]

Adverse Effects Adverse effects related to lithium use can be divided into three categories: those that occur early in therapy but are generally innocuous and transient, those that are not dose-related occurring with long-term treatment, and toxic effects that occur with high serum concentrations.[61]

Initial gastrointestinal (GI) and central nervous system (CNS) side effects are often dose-related and are worse at peak serum concentrations (1-2 hours post-dose). Standard approaches for minimizing adverse effects include lowering the dose, taking doses with food, using extended-release products, and trying once-daily dosing at bedtime. Diarrhea can sometimes be managed by switching from tablet or capsule formulation to liquid formulation. Diarrhea produced by lithium is commonly an osmotic diarrhea, and therefore switching to a formulation that clears the gut quickly can ameliorate symptoms.

A benign fine hand tremor can be evident in many patients while a course hand tremor may be a sign of toxicity.[61] Strategies to reduce the fine tremor include standard approaches (eg, switch to long-acting preparation, lower dose if possible) or adding a β-adrenergic antagonist (eg, propranolol 20-120 mg/day).[61]

Polydipsia with polyuria associated with or without nephrogenic diabetes insipidus (DI) can occur in patients treated with lithium. About 30% to 50% of patients will develop nephrogenic DI soon after initiation of lithium treatment.[61] Nephrogenic DI will persist in about 10% to 25% of patients on continued treatment and typically is reversible with discontinuation of lithium.[61] Other nonspecific renal effects may be seen with lithium treatment, but no causality has been established for many of these findings.[61]

Hypothyroidism can occur in patients treated with lithium, occurring more frequently in women than men.[61] Supplemental exogenous thyroid hormone (ie, levothyroxine) can be added to the patients' regimen. If lithium is discontinued, the need for the exogenous thyroid hormone should be reassessed because hypothyroidism can be reversible.

Lithium can cause a variety of benign and reversible cardiac effects, particularly T-wave flattening or inversion (in up to 30% of patients), atrioventricular block, and bradycardia.[61] If a patient has significant preexisting cardiac disease, consultation with a cardiologist and an electrocardiogram (ECG) is recommended at baseline and during lithium therapy.

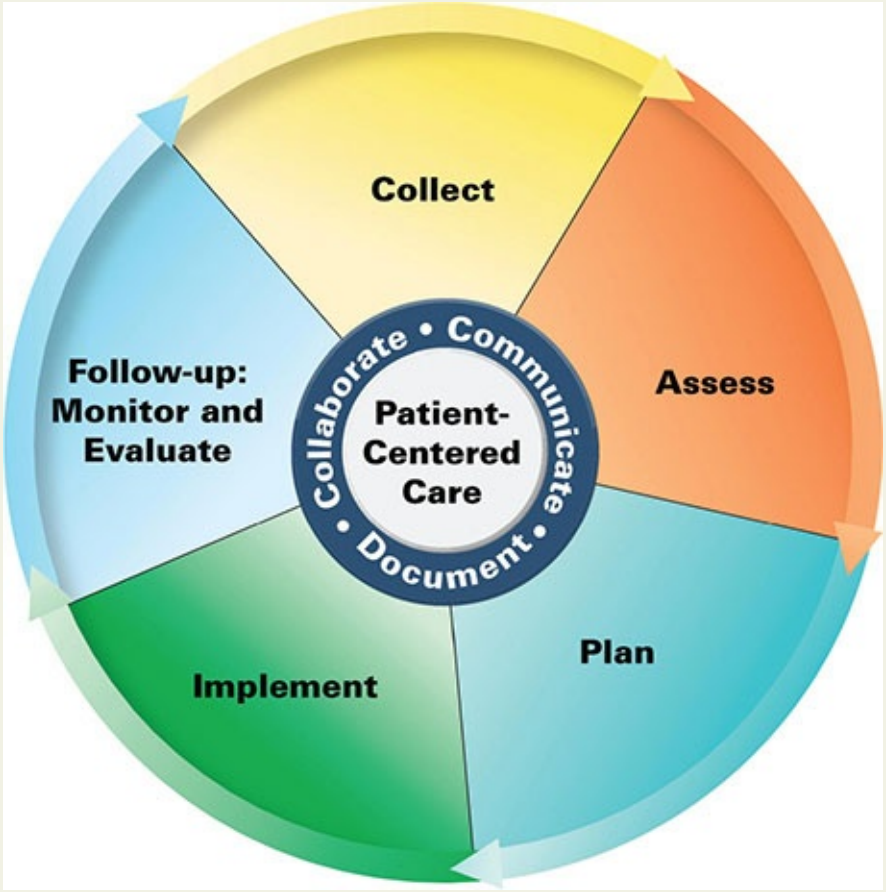
Other adverse effects associated with the use of lithium include: acne and folliculitis (1%), reversible leukocytosis, and weight gain.[61] Weight gain is common (~20% of patients gain greater than 10 kg [22 lbs]) and can be related

to fluid retention, the consumption of high-calorie beverages as a result of polydipsia, or a decreased metabolic rate because of hypothyroidism.[23,64]

Toxicity Lithium is an extremely toxic medication if accidentally or intentionally taken in overdose. Lithium toxicity usually occurs with blood levels greater than 1.5 mEq/L (mmol/L), but elderly patients may experience toxicity at lower levels.[61] Severe lithium intoxication occurs when concentrations are higher than 2 mEq/L (mmol/L), and there is a worsening in several key symptoms: *GI* (eg, vomiting, diarrhea, or incontinence), *coordination* (eg, fine to coarse hand tremor, unstable gait, slurred speech, and muscle twitching), and *cognition* (eg, poor concentration, drowsiness, disorientation, apathy, and coma).[2] There have been several reports of seizures, cardiac dysrhythmias, permanent neurologic impairments with ataxia and memory deficits, and kidney damage with reduced glomerular filtration rate after lithium intoxication.[2]

Situations that predispose patients to lithium toxicity include sodium restriction, dehydration, vomiting, diarrhea, age greater than 50, heart failure, cirrhosis, and drug interactions that decrease lithium clearance. Heavy exercise, sauna baths, hot weather, and fever can promote sodium loss. Patients should be cautioned to maintain adequate sodium and fluid intake (2.5-3 qt [~2.5-3 L] per day of fluids) and to avoid the excessive use of alcohol, coffee, tea, cola, and other caffeine-containing beverages.

If lithium toxicity is suspected, the person should go to an emergency room to be monitored and lithium should be discontinued.[2] Gastric lavage and IV fluids may be needed and the patient should be monitored for fluid balance, renal/electrolyte status, and neurologic changes. Hemodialysis may be considered in lithium-naïve patients who may be presenting in an acute overdose situation when lithium concentrations equal or exceed 4 mEq/L (mmol/L) regardless of clinical status or in patients previously taking lithium when lithium concentrations are 2.5 mEq/L (mmol/L) or greater and moderate-to-severe neurologic toxicity, or as clinically indicated.[61] If hemodialysis is initiated, it should be continued until the lithium concentration is below 1 mEq/L (mmol/L) with levels being taken 8 hours after the last dialysis to account for lithium redistribution.



Patient Care Process for Bipolar Disorder

Collect

- Patient characteristics (eg, age, race, sex, pregnant)
- Patient psychiatric, medical, social, and family history
- Current medications and prior medication use
- Current and past sleep habits/patterns
- Objective data
    - BP, heart rate, height, weight, and BMI
    - Laboratory test (eg, serum electrolytes, Scr, LFTs, TSH)
    - Rating scale scores (YMRS, HAM-D, PHQ-9)

Assess

- Presence of hypomania, mania, or depression

- Adherence to medication regimen
- Appropriateness and effectiveness of current medication regimen
- Serum concentration of medication if appropriate (eg, lithium)
- Current medications that may contribute to or worsen mania or depression
- Suicidality
- Current sleep patterns
- If no response to current medication regimen, reassess diagnosis

Plan*

- If euthymic, continue current regimen if appropriate
- If manic, immediately discontinue antidepressant, optimize regimen, and consider short-term use of benzodiazepine (see Table 86-4)
- If depressed, optimize regimen and consider adding antipsychotic (ie, quetiapine or lurasidone) (see Table 86-4)
- Lifestyle modifications (eg, nutrition, sleep, exercise, stress reduction)
- Monitor for efficacy and safety of medications (see Table 86-6)
- Treat comorbid psychiatric disease states
- Patient education (eg, purpose of treatment, lifestyle modification, drug therapy)
- Self-monitoring for new mood episodes (daily mood chart) and sleep patterns
- Referrals to other providers when appropriate (eg, psychologist, psychiatrist)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Patient’s psychiatric status (rating scale) and safety (suicidality)
- Mood episodes: Document symptoms on a daily mood chart (document life stressors, type of episode, length of episode, and treatment outcome);

monthly and yearly life charts are valuable for documenting patterns of mood cycles

- Suicidal ideation or attempts (suicide completion rates with bipolar I disorder are 10%-15%; suicide attempts are primarily associated with depressive episodes, mixed episodes with severe depression, or presence of psychosis)
- Presence of adverse effects and manage rapidly and vigorously to avoid noncompliance (eg, weight gain, sedation)
- Laboratory tests (see Table 86-6)
- Patient adherence to treatment plan using multiple sources of information and presence of residual symptoms (missing doses of medications is a primary reason for nonresponse and recurrence of episodes)

**Collaborate with patient, caregivers, and other healthcare professionals.*

Drug–Drug Interactions Thiazide diuretics, nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, angiotensin-converting enzyme inhibitors, and salt-restricted diets can elevate lithium levels.[61] Neurotoxicity can occur when lithium is combined with antipsychotics, metronidazole, methyldopa, phenytoin, and verapamil.[2,61] Combining lithium with calcium channel blockers is not recommended because of reports of decreased lithium levels and neurotoxicity.[61] Analgesics such as acetaminophen or aspirin and loop diuretics are less likely to interfere with lithium clearance. Caffeine and theophylline can enhance the renal elimination of lithium. Because lithium has no effect on hepatic metabolizing enzymes, it has fewer drug–drug interactions compared with carbamazepine, oxcarbazepine, and valproate.

Dosing and Administration Lithium dosing depends on the patient's age and weight, tolerance to adverse effects, and the acuity of the illness. Lithium therapy is usually initiated with low-to-moderate doses (600 mg/day) for prophylaxis and higher doses (900-1,200 mg/day) for acute mania, using a two-to-three-times daily dosing regimen.[2,61] The dose should be adjusted based on the steady-state serum concentration and clinical picture of the patient. Immediate-release lithium preparations should be given in two or three divided daily doses, whereas extended-release products can be given once or twice daily. In clinical practice many clinicians dose the immediate-release and extended-release preparations once daily. It is best to initially begin a patient on divided dosing, but once stabilized many patients are able to switch to once-daily dosing

without decompensating.

Lithium levels should be monitored for efficacy and to guide dosing. In general, lithium serum concentrations should be maintained between 0.6 and 1.0 mEq/L (mmol/L).[62] Lithium levels are considered to be at steady state at approximately day 5, and serum samples should be drawn 12 hours post dose. Once a desired serum concentration has been achieved, levels should be drawn in 2 weeks and then if stable every 3 to 6 months or as clinically indicated. Maintenance lithium serum concentrations are usually measured every 3 months, but can be adjusted to every 6 months for stabilized patients, and every 1 to 2 months for patients with frequent mood episodes.[2] Lithium clearance rates increase by 50% to 100% during pregnancy and return to normal postpartum. Thus, lithium levels should be determined monthly during pregnancy and weekly the month before delivery. At delivery, rapid fluid changes can significantly increase lithium levels; thus, a reduction to pre-pregnancy lithium doses and adequate hydration are recommended.[2]

The recommended guidelines for baseline and routine laboratory testing for lithium are listed in **Table 86-6**. A therapeutic trial for outpatients should last a minimum of 4 to 6 weeks with lithium serum concentrations of 0.6 to 1.2 mEq/L (mmol/L). Acutely manic patients can require serum concentrations of 1 to 1.2 mEq/L (mmol/L), and some need up to 1.5 mEq/L (mmol/L) to achieve a therapeutic response. Although serum concentrations less than 0.6 mEq/L (mmol/L) may be associated with higher rates of relapse, some patients can do well at 0.4 to 0.7 mEq/L (mmol/L).[62] For bipolar prophylaxis in elderly patients, serum concentrations of 0.4 to 0.6 mEq/L (mmol/L) are recommended because of increased sensitivity to adverse effects.[61]

TABLE 86-6 Guidelines for Baseline and Routine Laboratory Tests and Monitoring for Patients with Bipolar Disorder Taking Mood Stabilizers

	Baseline: Physical Examination and General Chemistry[a]	Hematologic Tests[b]		Metabolic Tests[c]		Liver Function Tests[d]		Renal Function Tests[e]		Thyroid Function Tests[f]		Serum Electrolytes[g]		Dermatologic[h]		Pharmacogenomic Testing
	Baseline	Baseline	6-12 months	Baseline	6-12 months	Baseline	6-12 months	Baseline	6-12 months	Baseline	6-12 months	Baseline	6-12 months	Baseline	6-12 months	Baseline
SGAs[i]	X			X	X											
Carbamazepine[j]	X	X	X			X	X	X				X	X	X	X	X
Lamotrigine[k]	X													X	X	
Lithium[l]	X	X	X	X	X			X	X	X	X	X	X	X	X	
Oxcarbazepine[m]	X											X	X			X
Valproate[n]	X	X	X	X	X	X	X							X	X	

[a]Screen for drug abuse and serum pregnancy.

[b]Complete blood cell count (CBC) with differential and platelets.

[c]Fasting glucose, serum lipids, and weight.

[d]Lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, and alkaline phosphatase.

[e]Serum creatinine, blood urea nitrogen, urinalysis, urine osmolality, and specific gravity.

[f]Triiodothyronine, total thyroxine, thyroxine uptake, and thyroid-stimulating hormone.

[g]Serum sodium.

[h]Rashes, hair thinning, and alopecia.

[i]Second-generation antipsychotics: Monitor for increased appetite with weight gain (primarily in patients with initial low or normal body mass index); monitor closely if rapid or significant weight gain occurs during early therapy; cases of hyperlipidemia and diabetes reported.

[j]Carbamazepine: Manufacturer recommends CBC and platelets (and possibly reticulocyte counts and serum iron) at baseline, and that subsequent monitoring be individualized by the clinician (eg, CBC, platelet counts, and liver function tests every 2 weeks during the first 2 months of treatment, and then every 3 months if normal). Monitor more closely if patient exhibits hematologic or hepatic abnormalities or if the patient is receiving a myelotoxic drug; discontinue if platelets are<100,000/mm^3 (100 × 10^9/L), if white blood cell (WBC) count is<3,000/mm^3 (3 × 10^9/L), or if there is evidence of bone marrow suppression or liver dysfunction. Serum electrolyte levels should be monitored in the elderly or those at risk for hyponatremia. Carbamazepine interferes with some pregnancy tests.

[k]Lamotrigine: If renal or hepatic impairment, monitor closely and adjust dosage according to manufacturer's guidelines. Serious dermatologic reactions have occurred within 2 to 8 weeks of initiating treatment and are more likely to occur in patients receiving concomitant valproate, with rapid dosage escalation, or using doses exceeding the recommended titration schedule.

[l]Lithium: Obtain baseline electrocardiogram for patients older than 40 years or if preexisting cardiac disease (benign, reversible T-wave depression can occur). Renal function tests should be obtained every 2 to 3 months during the first 6 months, and then every 6 to 12 months; if impaired renal function, monitor 24-hour urine volume and creatinine every 3 months; if urine volume>3 L/day, monitor urinalysis, osmolality, and specific gravity every 3 months. Thyroid function tests should be obtained once or twice during the first 6 months, and then every 6 to 12 months; monitor for signs and symptoms of hypothyroidism; if supplemental thyroid therapy is required, monitor thyroid function tests and adjust thyroid dose every 1 to 2 months until thyroid function indices are within normal range, and then monitor every 3 to 6 months.

[m]Oxcarbazepine: Hyponatremia (serum sodium concentrations<125 mEq/L [mmol/L]) has been reported and occurs more frequently during the first 3 months of therapy; serum sodium concentrations should be monitored in patients receiving drugs that lower serum sodium concentrations (eg, diuretics or drugs that cause inappropriate antidiuretic hormone secretion) or in patients with symptoms of hyponatremia (eg, confusion, headache, lethargy, malaise). Hypersensitivity reactions have occurred in approximately 25% to 30% of patients with a history of carbamazepine hypersensitivity and require immediate discontinuation.

[n]Valproate: Weight gain reported in patients with low or normal body mass index. Monitor platelets and liver function during first 3 to 6 months if evidence of increased bruising or bleeding. Monitor closely if patients exhibit hematologic or hepatic abnormalities or in patients receiving drugs that affect coagulation, such as aspirin or warfarin; discontinue if platelets are<100,000/mm^3/L (100 × 10^9/L) or if prolonged bleeding time. Pancreatitis, hyperammonemic encephalopathy, polycystic ovary syndrome, increased testosterone, and menstrual irregularities have been reported; not recommended during first trimester of pregnancy due to risk of neural tube defects.

SGAs, second-generation antipsychotics.

Data from References 2, 23, 61, 66, 69, 70, 75, 102.

Anticonvulsants

Anticonvulsants are widely prescribed for the treatment of bipolar disorder with varying degrees of evidence. Divalproex sodium (also known as sodium valproate) was marketed in 1995, for the acute treatment of mania in adults and is now the most prescribed mood stabilizer in the United States. It is FDA-approved only for the treatment of acute manic or mixed episodes. However, it is commonly used in clinical practice as maintenance monotherapy for bipolar disorder. Limited data support its use in acute bipolar depression. Carbamazepine is commonly used for both acute and maintenance therapy with the only formulation approved in the United States for bipolar disorder being extended-release carbamazepine, although other formulations can be used. Some data support the use of oxcarbazepine, a 10-keto analogue of carbamazepine, in the treatment of bipolar disorder. However, it is not approved for the treatment of bipolar disorder in the United States. Valproate, carbamazepine, and oxcarbazepine all have a wide range of neurologic, GI, electrolyte, and hematologic adverse effects that require regular assessment and routine blood work. Lamotrigine is FDA-approved for the maintenance treatment of bipolar I disorder. This medication appears to be most effective in the prevention of relapse of depression and does not appear to have efficacy for treatment of acute depression or mania.[65]

Valproate Sodium and Valproic Acid Valproate has antimigraine, mood-stabilizing, and antiaggressive effects.[66] In 1995, the enteric-coated formulation divalproex sodium (sodium valproate) was approved for the acute treatment of mania. Several controlled studies have shown valproate to be as effective as lithium and olanzapine in patients with pure mania, and it can be more effective than lithium in certain subtypes of bipolar disorder (eg, rapid cycling, mixed features, comorbid substance abuse).[2,3,23,45,67] Placebo- and lithium-controlled and open studies report that valproate reduces or prevents recurrent manic, depressive, and mixed episodes.[2,3,23]

Giving lithium, carbamazepine, antipsychotics, or benzodiazepines with valproate can augment its antimanic effects. The addition of valproate to lithium can have synergistic effects in patients who are treatment-refractory and have specifiers of rapid cycling or mixed features, and the combination has demonstrated efficacy in maintenance therapy for bipolar I disorder. Combinations of valproate and carbamazepine can have synergistic effects, but the potential drug interactions make blood level monitoring of both agents essential.[23] Adding adjunctive SGAs to valproate can be effective for

breakthrough mania or if there is incomplete or partial response to monotherapy. Clozapine, olanzapine, and quetiapine can increase the risk of sedation and weight gain when combined with valproate. The combination of valproate and lamotrigine can be effective, but there is an increased risk of rashes, ataxia, tremor, sedation, and fatigue.[66]

Adverse Effects The most frequent dose-related adverse effects with valproate are GI complaints (anorexia, nausea, indigestion, vomiting, mild diarrhea, and flatulence), fine hand tremors, and sedation.[2,23,66] The GI complaints are usually transient, but giving the medication with food, using lower initial doses with gradual increases in doses, or switching to divalproex sodium extended-release tablets can minimize them.[2,23] Reduction of the dose or the addition of a β-blocker can alleviate tremors, and giving the total daily dose at bedtime can minimize daytime sedation.[2,23]

Other adverse effects of valproate include ataxia, lethargy, alopecia, changes in the texture or color of hair, pruritus, prolonged bleeding because of inhibition of platelet aggregation, transient increases in liver enzymes, and hyperammonemia.[23,66] Increased appetite and weight gain occurs in approximately 50% of patients on long-term valproate therapy. Thrombocytopenia can occur at higher doses, and patients should be monitored for bleeding and bruising. Lowering the valproate dose can restore platelet counts to normal levels.[2] Fatal necrotizing hepatitis is a rare idiosyncratic, non–dose-related adverse effect that has occurred in children with epilepsy receiving multiple anticonvulsants.[23,66] A life-threatening hemorrhagic pancreatitis has been reported in both children and adults.[2,23,66] An in-depth discussion of adverse effects can be found in Chapter 73.

Drug–Drug Interactions A summary of drug–drug interactions for valproate can be found in Chapter 73.

Dosing and Administration For healthy inpatient adults with acute mania, the initial starting dosage of valproate is typically 20 mg/kg/day in divided doses over 12 hours. The daily dose is adjusted by 250 to 500 mg every 1 to 3 days based on clinical response and tolerability. Maximum recommended dosing is 60 mg/kg/day (see Table 86-5).[2,23,66] For outpatients who are hypomanic or euthymic, or for elderly patients, the initial starting dose is generally lower (5-10 mg/kg/day in divided doses) and gradually titrated to avoid adverse effects. Once an optimal dose has been achieved, the total daily dose can be divided into two doses or given at bedtime if tolerated.[2,23,66] Extended-release divalproex can be

administered once daily, but bioavailability can be 15% lower than that of immediate-release products, thus requiring slightly higher doses.[2] In clinical practice, patients with bipolar disorder who are stable can be switched between formulations without having to change the dose. This is not the case for patients with seizure disorder.

Recommended baseline and routine laboratory tests for patients taking valproate are listed in Table 86-6. Although therapeutic serum concentrations of valproic acid have not been established in bipolar disorder, most clinicians use the anticonvulsant therapeutic serum range of 50 to 125 mcg/mL (347-866 μmol/L) taken 12 hours after the last dose.[2,23] In one study patients with valproate levels greater than 94.1 mcg/mL (652 μmol/L) had greater efficacy for bipolar mania.[68] Patients with cyclothymia or mild bipolar II disorder can have a therapeutic response to lower doses and blood levels, whereas some patients with a more severe form of bipolar disorder can require up to 150 mcg/mL (1,040 μmol/L). Serum valproic acid levels are most useful when assessing for compliance and toxicity.

Carbamazepine Carbamazepine, a iminostilbene derivative, is structurally related to tricyclic antidepressants (TCAs).[69] Carbamazepine is not a first-line agent for bipolar disorder, and is generally reserved for use after treatment failure with lithium or divalproex sodium. Carbamazepine is effective for the treatment of mania, but its use is generally reserved due to drug interactions.[57] Data supporting the use of carbamazepine for bipolar depression are lacking and are not strong for the use of carbamazepine in maintenance treatment.[58,59] The combination of carbamazepine with lithium, valproate, and antipsychotics is often used for treatment-resistant patients experiencing a manic episode.[23]

Adverse Effects A summary of adverse effects for carbamazepine can be found in Chapter 73. Acute overdoses of carbamazepine are potentially lethal, and serum levels above 15 mcg/mL (63 μmol/L) are associated with ataxia, choreiform movements, diplopia, nystagmus, cardiac conduction changes, seizures, and coma.[2] Gastric lavage, emesis, ECG, and symptomatic treatment are recommended for the management of carbamazepine toxicity.[69] Additionally, the risk of severe dermatologic skin reactions may be greater in patients with specific ancestral backgrounds (see section “Personalized Pharmacotherapy”).

Drug–Drug Interactions There are numerous drug–drug interactions that clinicians must consider when prescribing carbamazepine. Carbamazepine significantly induces the hepatic cytochrome P450 isoenzyme 3A4 and to a

lesser degree 1A2, 2C9/10, and 2D6, which increases the metabolism of many medications (eg, quetiapine, aripiprazole).[2,3,69] Women taking oral contraceptives who receive carbamazepine should be counseled to use a nonhormonal method of birth control.[69]

Carbamazepine is metabolized to an active 10,11-epoxide metabolite; thus, medications that inhibit 3A4 isoenzymes can result in carbamazepine toxicity (eg, diltiazem, fluconazole, ketoconazole, nefazodone, verapamil).[2,3,23,69] When carbamazepine is combined with valproate, the carbamazepine dose should be reduced because valproate displaces carbamazepine from protein-binding sites, thus increasing free levels.[3,23] Combining clozapine and carbamazepine is not recommended because of decreased clozapine concentrations and the possibility of bone marrow suppression with both agents.[69]

Dosing and Administration During an acute manic episode in most hospitalized patients, carbamazepine can be started at 400 to 600 mg/day in divided doses with meals and increased by 200 mg/day every 2 to 4 days up to 10 to 15 mg/kg/day. In outpatients, the initial dose of carbamazepine should be lower and titrated gradually in order to avoid adverse effects. In clinical practice many patients are able to tolerate once-daily dosing of carbamazepine once their mood episode has stabilized. The dose of carbamazepine should be gradually increased until response is achieved or there is evidence of toxicity. During the first month of therapy, serum concentrations of carbamazepine may be affected due to autoinduction of cytochrome P450 3A4 enzymes.[69]

Carbamazepine serum levels are usually obtained every 1 to 2 weeks during the first 2 months, and then every 3 to 6 months during maintenance therapy. Serum levels should be drawn 10 to 12 hours after the dose (trough levels) and at least 4 to 7 days after a dosage change. Although there is no correlation between carbamazepine serum concentration and degree of antimanic or antidepressant response, most clinicians attempt to maintain levels between 6 and 10 mcg/mL (25 and 42 μmol/L) (although some treatment-resistant patients can require serum concentrations of 12-14 mcg/mL [51-59 μmol/L]). Recommended baseline and routine laboratory tests for carbamazepine are listed in Table 86-6.

Oxcarbazepine There are currently less data supporting the use of oxcarbazepine than carbamazepine in the treatment of bipolar disorder. Guidelines typically recommend oxcarbazepine as a third-line treatment option for bipolar mania, as a third- or fourth-line treatment option for maintenance treatment, and it is not recommended for the treatment of bipolar depression.[53]

Adverse Effects Severe dermatologic reactions (eg, Stevens-Johnson syndrome) have been reported at 3 to 10 times the rate of the general population, therefore oxcarbazepine should be discontinued at the first sign of a skin reaction.[70] Risk of this adverse effect may be greater in patients with specific genetic markers (see section "Personalized Pharmacotherapy"). Other adverse effects may include impaired cognitive or psychomotor performance, somnolence or fatigue, and coordination difficulties.[70] In one study, hyponatremia was reported to occur in patients taking oxcarbazepine and carbamazepine at rates of 29.9% and 13.5%, respectively.[71] Severe hyponatremia (sodium ≤128 mEq/L [mmol/L]) was reported by Dong et al. as 12.4% and 2.8% of patients for oxcarbazepine and carbamazepine, respectively.[71] An in-depth discussion of adverse effects can be found in Chapter 73.

Drug–Drug Interactions Oxcarbazepine, a cytochrome P450 2C19 enzyme inhibitor and a 3A3/4 enzyme inducer, has the potential for causing drug interactions.[70] It induces the metabolism of oral contraceptives; thus, alternative contraceptive measures are required.[3,72] Additional drug interactions can be found in Chapter 73.

Dosing and Administration Initial dosing is usually 150 to 300 mg twice daily, and daily doses can be increased by 300 to 600 mg every 3 to 6 days up to 1,200 mg/day in divided doses (with or without food).[70]

Lamotrigine The effectiveness of lamotrigine for the maintenance treatment of bipolar I disorder in adult patients was established in two multicenter, double-blind, placebo-controlled studies.[2] Doses of 200 mg/day were more effective than lower doses, and there were no advantages to using 400 mg/day. Lamotrigine has mood-stabilizing effects; it may have augmenting properties when combined with lithium or valproate, and has low rates of switching patients to mania.[73] Although lamotrigine is not effective for acute mania compared with standard mood stabilizers, it may be beneficial as maintenance therapy of treatment-resistant bipolar I and II disorders.[2,3,59] Lamotrigine seems to be most effective for the prevention of bipolar depression; therefore, clinically it is often used in the treatment of patients with bipolar II. There are case reports of possible lamotrigine-induced mania when added to lithium, carbamazepine, and valproate.[74] In each of the cases reported, the patients had depressive mood symptoms or rapid mood changes requiring additional therapy.[74]

Adverse Effects Common adverse effects include headache, nausea, dizziness,

ataxia, diplopia, drowsiness, tremor, rash, and pruritus.[75] Approximately 10% of patients in premarketing clinical trials developed a maculopapular rash and required discontinuation of therapy.[75] Although most rashes are self-limiting and resolve with continued treatment, some cases progressed to life-threatening conditions such as Stevens-Johnson syndrome. The incidence of rash appears to be greatest with coadministration of valproate, with higher than recommended initial doses, and with rapid dose escalation.[75] Patients should be warned about the rash and the need for discontinuing lamotrigine if the rash is diffuse, involves mucosal membranes, and is accompanied by a fever or sore throat. For an in-depth discussion of the adverse effects of lamotrigine, see Chapter 73.

Drug–Drug Interactions Valproate decreases the clearance of lamotrigine (ie, more than doubles the half-life), and lamotrigine must be administered at a reduced dosage (approximately half the standard dose).[75] For an in-depth discussion of drug–drug interactions with lamotrigine, see Chapter 73.

Dosing and Administration For the maintenance treatment of bipolar disorder, the usual dosage range of lamotrigine is 50 to 300 mg/day. The target dose is generally 200 mg/day (100 mg/day in combination with valproate and 400 mg/day in combination with carbamazepine).[75] For patients not taking medications that affect lamotrigine's clearance, the dose is 25 mg/day for the first 2 weeks of therapy, 50 mg/day for weeks 3 and 4, 100 mg/day for week 5, and 200 mg/day for week 6 and beyond.[2,75] Patients who stop lamotrigine therapy for more than a few days should be restarted on a low dose and titrated every 2 weeks back to their maintenance dose.

Antipsychotics

FGAs and SGAs such as aripiprazole, asenapine, haloperidol, olanzapine, quetiapine, risperidone, and ziprasidone are effective as monotherapy or adjunctive therapy in the treatment of acute mania.[53] Controlled studies in acute mania with lithium or valproate plus an antipsychotic suggest greater efficacy with combination therapies compared to any of these agents alone.[2,53] FGAs (eg, chlorpromazine and haloperidol) are effective in up to 70% of patients with acute mania, particularly those with psychosis and psychomotor agitation. SGAs have demonstrated similar efficacy for the treatment of acute mania associated with agitation, aggression, and psychosis.[2,53]

Treating acute bipolar depression is very challenging, and some antipsychotics may play a useful role. Multiple large randomized controlled

trials support use of quetiapine and lurasidone as a monotherapy and adjunctive treatment options for bipolar depression.[53] Data also support use of combined fluoxetine/olanzapine in treating bipolar depression.[53]

Oral aripiprazole, olanzapine, and long-acting risperidone are effective monotherapy options for maintenance treatment in bipolar disorder.[53] First-generation depot antipsychotics (eg, haloperidol decanoate, fluphenazine decanoate) can have a place in maintenance treatment of bipolar disorder in patients who are noncompliant or treatment-resistant.[2] Clozapine monotherapy has acute and long-term mood-stabilizing effects in refractory bipolar disorder but requires regular white blood cell monitoring for agranulocytosis.[23,76] Long-term safety of antipsychotics as monotherapy or as adjunctive therapy for bipolar maintenance treatment should be evaluated.[2,53,76] Risks versus benefits must be weighed due to the long-term adverse effects (eg, weight gain, type 2 diabetes, hyperlipidemia, hyperprolactinemia, tardive dyskinesia) antipsychotics may cause.[76,77]

Adverse Effects A summary of adverse effects for antipsychotics can be found in Chapter 84.

Drug–Drug Interactions A summary of drug interactions with antipsychotics can be found in Chapter 84.

Dosing and Administration For acute mania, higher initial doses of antipsychotics may be required (eg, olanzapine 20 mg/day in hospitalized patients). Once acute mania is controlled (usually within 7-28 days), the antipsychotic can be gradually tapered and discontinued, and the patient maintained on the mood stabilizer monotherapy.

Monitoring 7 Recommendations for baseline and routine laboratory testing for patients receiving antipsychotics are found in Table 86-6.

Alternative Medication Treatments

8 Some patients can be stabilized on one mood stabilizer, but others may require combination therapies or adjunctive agents during an acute mood episode. If possible, adjunctive agents should be tapered and discontinued when the acute mood episode remits and the patient is stabilized.

Benzodiazepines Weighing the risk-to-benefit ratio, high-potency benzodiazepines such as clonazepam and lorazepam are commonly used as an

alternative to or in combination with antipsychotics when patients are experiencing acute mania, agitation, anxiety, panic, and insomnia, or cannot take mood stabilizers (eg, during the first trimester of pregnancy).[2,3,78,79] Lorazepam is available for intramuscular injection and is useful in the acute management of agitation. Benzodiazepines cause minimal adverse effects compared with antipsychotics, and at higher doses, rapidly sedate agitated patients.[3] They can cause CNS depression, sedation, cognitive and motor impairment, dependence, and withdrawal reactions. When no longer required, benzodiazepines should be gradually tapered and discontinued to avoid withdrawal symptoms.

Antidepressants For many years antidepressants were recommended as adjunctive therapy for acute bipolar depression. Data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) suggest that adjunctive antidepressants may be no better than placebo for acute bipolar depression when combined with mood stabilizers.[80] Controversy exists concerning the use of antidepressants, and many clinicians consider them third line in treating acute bipolar depression, except in patients with no history of severe and/or recent mania or potentially in bipolar II patients.[81] The concern of mood switching (ie, rapidly switching from depression to mania or hypomania) with the use of antidepressants is valid, although not common. Data show that the rate of mood switch with selective serotonin reuptake inhibitors (SSRIs) is around 3.8%, similar to placebo, when combined with mood stabilizers. The rate of mood switch with dual-acting agents (eg, TCAs or venlafaxine) is higher, and thus these agents should be used with caution.[81,82] Before initiating therapy with an antidepressant it is very important to ensure that the patient is on a therapeutic dosage or blood level of a primary mood stabilizer.[2] Patients who have a history of mania after a depressive episode or who have frequent cycling should be treated cautiously with antidepressants.[2,3] In general, the antidepressant should be gradually withdrawn 2 to 6 months after remission, and the patient maintained on a mood-stabilizing agent.[83,84] For more information, see Chapter 85 for comparisons among antidepressants.

Special Populations

The approach for treating bipolar disorder in special populations can vary among clinicians. Patients with comorbid medical conditions or concomitant substance abuse, those older than 65 or younger than 18 years, and pregnant patients can require different treatment approaches.

Comprehensive management during pregnancy is important to decrease the

risk of birth defects, perinatal complications and mortality, preterm birth, low birth weight, and low Apgar scores.[85] Pharmacotherapy during pregnancy is complicated, and the risk-to-benefit ratio must be weighed. Clinicians should always use the lowest effective dose of any medication during pregnancy. Monotherapy should also be considered in order to decrease risk to the mother and child.

When lithium is given during the first trimester the prevalence of Ebstein's anomaly is estimated between 1 and 10.78:1000 and the risk of neural tube defects is 13.4:1000.[85] Lithium freely crosses the placenta and is found in equal concentrations in maternal and fetal blood.[61] When lithium is used during pregnancy, it should be tapered down to the lowest effective dose necessary to decrease the risk of relapse. Lithium can cause perinatal complications in the infant such as hypotonia, jaundice, cyanosis, and lethargy.[85] Milk concentrations of lithium range from 30% to 50% of the mother's serum concentration, and serum concentrations in the nursing infant are 10% to 50% of the mother's; thus, breastfeeding is usually discouraged.[2,86] If using lithium during pregnancy, dose adjustments and close monitoring of serum levels will be needed due to changes in glomerular filtration rates and renal perfusion rates during pregnancy and immediately after delivery.[85]

Neural tube defects cause the most concern for clinicians treating pregnant patients during their first trimester. Data from the North American Antiepileptic Drug Pregnancy Registry show the risk of neural tube defects is about 0.12% for nonexposed babies.[87] Carbamazepine's risk of neural tube defects is estimated to be 3%.[87] Carbamazepine is excreted in breast milk (the milk-to-maternal plasma ratio of carbamazepine is ~0.4).[3] Craniofacial abnormalities, developmental delays, microcephaly, and other abnormalities are also of concern when using anticonvulsants. For pregnant patients treated with lamotrigine, the risk of neural tube defects is estimated to be 2%, but data for lamotrigine are limited compared with those for some older anticonvulsants.[87] Valproate is usually not recommended during the first trimester of pregnancy because the risk of neural tube defects is estimated to be 4%.[87] Australian registry data in patients with epilepsy show dose-related teratogenicity with doses greater than 1,100 mg/day of valproate.[88] Administration of folate can reduce the risk of neural tube defects; therefore, the risks versus benefits of using valproate during pregnancy must be discussed with the patient.[23] Women of childbearing age on valproic acid and pregnant women should receive folic acid supplementation. Valproic acid is excreted into human breast milk in low concentrations and is considered

to be compatible with breastfeeding.[89] One case report of thrombocytopenia and anemia from valproate exposure has been reported in a nursing infant. If the mother receives valproate during breastfeeding, mother and infant should have identical laboratory monitoring.

Caution should be used when prescribing antipsychotics during pregnancy. FGAs have been prescribed for many years in pregnancy and data show little teratogenic risk, but the data are not without question.[90] Data on the SGAs are limited, and clinicians should consider the potential risk of gestational diabetes.[90] Extrapyramidal symptoms, neonatal withdrawal, and sedation should also be considered when prescribing both FGAs and SGAs. There is still a paucity of human data with antipsychotics, and therefore risk-to-benefit ratio must be weighed.

There are few controlled studies in children and adolescents with bipolar disorder. Thus, little is known about the long-term efficacy and safety of specific agents or combination therapies in this population.[91,92] Lithium, valproic acid, and carbamazepine are all used in pediatric bipolar disorder, though data supporting their use are limited. Lithium is the only medication approved as a mood stabilizer for children older than 12 years.[93] Aripiprazole and risperidone are FDA-approved for bipolar mania in patients aged 13 to 17 years.[94] Quetiapine is approved as monotherapy or adjunct to lithium or divalproex in patients aged 10 to 17 years during a manic episode,[94] but it did not show efficacy in a small pilot study of adolescent bipolar depression.[95] Olanzapine is approved for use in patients with manic or mixed episodes aged 13 to 17 years.[94] Ziprasidone has supporting data for its use in pediatric acute mania, but does not have FDA approval.[96] Therefore, long-term data are still needed for all of these agents and recommendations on the treatment of pediatric bipolar depression and maintenance treatment are lacking due to insufficient data.[96] Published guidelines for treatment of bipolar disorder in children and adolescents include the *Practice Parameters for the Assessment and Treatment of Children and Adolescents with Bipolar Disorder* by the American Academy of Child and Adolescent Psychiatry.[91]

Patients with bipolar illness are more likely to have medical comorbidities than the general population (64.3% vs 48.3%),[97] which complicates the management of bipolar disorder in elderly patients. Specific for lithium and aging, reductions in renal clearance nearly doubles the elimination half-life in elderly patients.[98] The half-life of valproate has been reported to also increase with aging,[99] but more importantly, patients with dementia can have increased

sensitivity to the side effects of mood stabilizers as well as antipsychotics, which may be contraindicated in this patient population. No prospective, randomized, placebo-controlled trials have been published examining efficacy of lithium or valproate in elderly patients.[100]

Personalized Pharmacotherapy

New information is quickly evolving in the area of pharmacogenomics that may help clinicians individualize treatment for patients with bipolar disorder. Pharmacogenetic testing is available to determine if patients are poor or rapid metabolizers of cytochrome P450 2D6 and 2C19, as well as other important pharmacogenomic variants, thus predicting an individual's potential to respond to particular therapies as well as help to tailor dosing regimens in an effort to reduce adverse effects. Use of commercially available testing panels is controversial; however, the Clinical Pharmacogenomic Implementation Consortium (CPIC), funded by the National Institutes of Health, has resources to guide clinicians in the use of this information (http://cpicpgx.org/). For carbamazepine and oxcarbazepine in particular, a black box warning is located in the FDA package insert recommending genetic testing for the human leukocyte antigen (HLA) allele, HLA-B 1502, in patients of Asian ancestry to help detect a higher risk of Stevens-Johnson syndrome and toxic epidermal necrolysis.[69]

EVALUATION OF THERAPEUTIC OUTCOMES

The establishment and maintenance of a therapeutic alliance between the patient and clinician is essential in monitoring a patient's psychiatric status and safety; enhancing treatment adherence; promoting good nutrition, sleep, and exercise; identifying stressors; recognizing new mood episodes; and minimizing adverse reactions and drug interactions.[2] Patients who have a partial response or nonresponse to established bipolar therapies should be reassessed for an accurate diagnosis, concomitant medical or psychiatric conditions, compliance with treatment (including blood levels if appropriate), and medications or substances that exacerbate mood symptoms. Nonadherence to medication treatment, delusional symptoms, alcohol or substance abuse, rapid cycling, or mixed states are often associated with poorer treatment outcomes.

CONCLUSION

The diagnosis and treatment of bipolar disorder can be complicated. Once an accurate diagnosis is made clinicians must collaborate with patients to select the best treatment regimen. Clinicians must educate patients to be diligent in self-monitoring of their disease and the reporting of side effects from medications. Compliance with medications is a key component in treatment. Clinicians must realize that there are various options for treating each phase of bipolar disorder and selection of the correct medication is essential to achieve optimal patient outcomes.

Postclass Engaged Learning Activity

Summary Table of Drug Information: Use the information in the chapter and from other drug information resources to create a table of medications used in the treatment of Bipolar Disorder. Separate the top row of the table into the following columns: MOA, Therapeutic Use, Renal Adjustments, Hepatic Adjustments, CYP Metabolism, Supporting Evidence for Use, and Common Adverse Effects. Under the MOA, Therapeutic Use, CYP Metabolism, and Common Adverse Effects columns, write the corresponding information for each medication. For all other columns, simply place a check mark if the column title applies to the drug. For example, if a drug has supporting evidence for use, place an "X" under that column for the drug. The intent of this activity is to help reinforce general fundamental drug information discussed in class.

ABBREVIATIONS

APA	American Psychiatric Association
CANMAT	Canadian Network for Mood and Anxiety Treatments
CNS	central nervous system
DI	diabetes insipidus
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
ECG	electrocardiogram
ECT	electroconvulsive therapy
FDA	Food and Drug Administration
FGAs	first-generation antipsychotics

GI	gastrointestinal
HLA	human leukocyte antigen
ISBD	International Society for Bipolar Disorders
SGAs	second-generation antipsychotics
SSRI	selective serotonin reuptake inhibitor
STEP-BD	Systematic Treatment Enhancement Program for Bipolar Disorder
TCA	tricyclic antidepressant
WFSBP	World Federation of Societies of Biological Psychiatry

REFERENCES

1. American Psychiatric Association. Bipolar and Related Disorders. *Diagnostic and Statistical Manual of Mental Disorders*. American Psychiatric Association; 2013.
2. American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry*. 2002;159(4 Suppl):1–50.
3. Goldberg JF, Harrow M, eds. *Bipolar Disorders: Clinical Course and Outcome*. Washington, DC: American Psychiatric Press; 1999.
4. Merikangas KR, Jin R, He JP, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Arch Gen Psychiatry*. 2011;68(3):241–251.
5. Merikangas KR, Lamers F. The “true” prevalence of bipolar II disorder. *Curr Opin Psychiatry*. 2012;25(1):19–23.
6. Perlis RH, Dennehy EB, Miklowitz DJ, et al. Retrospective age at onset of bipolar disorder and outcome during two-year follow-up: Results from the STEP-BD study. *Bipolar Disord*. 2009;11(4):391–400.
7. Kroon JS, Wohlfarth TD, Dieleman J, et al. Incidence rates and risk factors of bipolar disorder in the general population: A population-based cohort study. *Bipolar Disord*. 2013;15(3):306–313.
8. Nivoli AM, Pacchiarotti I, Rosa AR, et al. Gender differences in a cohort study of 604 bipolar patients: The role of predominant polarity. *J Affect Disord*. 2011;133(3):443–449.
9. Suppes T, Mintz J, McElroy SL, et al. Mixed hypomania in 908 patients with bipolar disorder evaluated prospectively in the Stanley Foundation

Bipolar Treatment Network: A sex-specific phenomenon. *Arch Gen Psychiatry*. 2005;62(10):1089–1096.

10. Sherazi R, McKeon P, McDonough M, Daly I, Kennedy N. What's new? The clinical epidemiology of bipolar I disorder *Harv Rev Psychiatry*. 2006;14(6):273–284.
11. Miklowitz DJ, Cicchetti D. Toward a life span developmental psychopathology perspective on bipolar disorder. *Dev Psychopathol*. 2006;18(4):935–938.
12. Smoller JW, Finn CT. Family, twin, and adoption studies of bipolar disorder. *Am J Med Genet C Semin Med Genet*. 2003;123c(1):48–58.
13. Baldessarini RJ, Tondo L, Vazquez GH, et al. Age at onset versus family history and clinical outcomes in 1,665 international bipolar-I disorder patients. *World Psychiatry*. 2012;11(1):40–46.
14. Craddock N, Sklar P. Genetics of bipolar disorder. *Lancet*. 2013;381(9878):1654–1662.
15. Hales RE, Yudofsky SC, Roberts LW, eds. *American Psychiatric Publishing Textbook of Psychiatry*. 6th ed. American Psychiatric Association Publishing; 2014.
16. Townsend J, Altshuler LL. Emotion processing and regulation in bipolar disorder: A review. *Bipolar Disord*. 2012;14(4):326–339.
17. Martinowich K, Schloesser RJ, Manji HK. Bipolar disorder: From genes to behavior pathways. *J Clin Invest*. 2009;119(4):726–736.
18. Beyer JL, Kuchibhatla M, Cassidy F, Krishnan KR. Stressful life events in older bipolar patients. *Int J Geriatr Psychiatry*. 2008;23(12):1271–1275.
19. Miklowitz DJ, Johnson SL. Social and familial factors in the course of bipolar disorder: Basic processes and relevant Interventions. *Clin Psychol (New York)*. 2009;16(2):281–296.
20. Goldstein BI, Kemp DE, Soczynska JK, McIntyre RS. Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: A systematic review of the literature. *J Clin Psychiatry*. 2009;70(8):1078–1090.
21. Drexhage RC, Knijff EM, Padmos RC, et al. The mononuclear phagocyte system and its cytokine inflammatory networks in schizophrenia and bipolar disorder. *Expert Rev Neurother*. 2010;10(1):59–76.
22. Gruber J, Miklowitz DJ, Harvey AG, et al. Sleep matters: Sleep functioning and course of illness in bipolar disorder. *J Affect Disord*.

2011;134(1-3):416–420.
23. Goodnick PJ. *Mania: Clinical and Research Perspectives*. Washington, DC: American Psychiatric Press; 1998.
24. Ostacher MJ, Perlis RH, Nierenberg AA, et al. Impact of substance use disorders on recovery from episodes of depression in bipolar disorder patients: Prospective data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry*. 2010;167(3):289–297.
25. Sala R, Goldstein BI, Morcillo C, Liu SM, Castellanos M, Blanco C. Course of comorbid anxiety disorders among adults with bipolar disorder in the U.S. population. *J Psychiatr Res*. 2012;46(7):865–872.
26. McElroy SL, Guerdjikova A, Lavanier S, O'Melia A. Bipolar disorder with co-occurring eating disorders: Prevalence and pharmacotherapeutic implications. *Focus (Am Psychiatr Publ)*. 2011;9(4):435–448.
27. Weber NS, Fisher JA, Cowan DN, Niebuhr DW. Psychiatric and general medical conditions comorbid with bipolar disorder in the National Hospital Discharge Survey. *Psychiatr Serv*. 2011;62(10):1152–1158.
28. Ceide ME, Rosenberg PB. Brief manic episode after rituximab treatment of limbic encephalitis. *J Neuropsychiatry Clin Neurosci*. 2011;23(4):E8.
29. Dias RS, Lafer B, Russo C, et al. Longitudinal follow-up of bipolar disorder in women with premenstrual exacerbation: Findings from STEP-BD. *Am J Psychiatry*. 2011;168(4):386–394.
30. Goldsmith M, Singh M, Chang K. Antidepressants and psychostimulants in pediatric populations: Is there an association with mania? *Paediatr Drugs*. 2011;13(4):225–243.
31. Habek M, Brinar M, Brinar VV, Poser CM. Psychiatric manifestations of multiple sclerosis and acute disseminated encephalomyelitis. *Clin Neurol Neurosurg*. 2006;108(3):290–294.
32. Navines R, Castellvi P, Sola R, Martin-Santos R. Peginterferon- and ribavirin-induced bipolar episode successfully treated with lamotrigine without discontinuation of antiviral therapy. *Gen Hosp Psychiatry*. 2008;30(4):387–389.
33. Plante DT, Winkelman JW. Sleep disturbance in bipolar disorder: Therapeutic implications. *Am J Psychiatry*. 2008;165(7):830–843.
34. Santos CO, Caeiro L, Ferro JM, Figueira ML. Mania and stroke: A systematic review. *Cerebrovasc Dis*. 2011;32(1):11–21.

35. Spiegel DR, Weller AL, Pennell K, Turner K. The successful treatment of mania due to acquired immunodeficiency syndrome using ziprasidone: A case series. *J Neuropsychiatry Clin Neurosci*. 2010;22(1):111–114.
36. Valentí M, Pacchiarotti I, Bonnín CM, et al. Risk factors for antidepressant-related switch to mania. *J Clin Psychiatry*. 2012;73(2):e271–e276.
37. Goldberg JF, Garno JL, Callahan AM, Kearns DL, Kerner B, Ackerman SH. Overdiagnosis of bipolar disorder among substance use disorder inpatients with mood instability. *J Clin Psychiatry*. 2008;69(11):1751–1757.
38. Brooks JOIII, Hoblyn JC. Secondary mania in older adults. *Am J Psychiatry*. 2005;162(11):2033–2038.
39. Howes OD, Lim S, Theologos G, Yung AR, Goodwin GM, McGuire P. A comprehensive review and model of putative prodromal features of bipolar affective disorder. *Psychol Med*. 2011;41(8):1567–1577.
40. National Collaborating Centre for Mental H. National Institute for Health and Care Excellence: Clinical Guidelines. *Bipolar Disorder: The NICE Guideline on the Assessment and Management of Bipolar Disorder in Adults, Children and Young People in Primary and Secondary Care*. Leicester (UK): The British Psychological Society & The Royal College of Psychiatrists; 2018.
41. Conus P, Macneil C, McGorry PD. Public health significance of bipolar disorder: Implications for early intervention and prevention. *Bipolar Disord*. 2014;16(5):548–556.
42. Frias A, Palma C, Farriols N. Comorbidity in pediatric bipolar disorder: Prevalence, clinical impact, etiology and treatment. *J Affect Disord*. 2015;174:378–389.
43. Vega P, Barbeito S, Ruiz de Azua S, et al. Bipolar disorder differences between genders: Special considerations for women. *Women's health (London, England)*. 2011;7(6):663–674. quiz 675-666.
44. Bender RE, Alloy LB. Life stress and kindling in bipolar disorder: Review of the evidence and integration with emerging biopsychosocial theories. *Clin Psychol Rev*. 2011;31(3):383–398.
45. Carvalho AF, Dimellis D, Gonda X, Vieta E, McLntyre RS, Fountoulakis KN. Rapid cycling in bipolar disorder: A systematic review. *J Clin Psychiatry*. 2014;75(6):e578–586.
46. Barrios C, Chaudhry TA, Goodnick PJ. Rapid cycling bipolar disorder.

Expert Opin Pharmacother. 2001;2(12):1963–1973.

47. Rasgon N, Bauer M, Glenn T, Elman S, Whybrow PC. Menstrual cycle related mood changes in women with bipolar disorder. *Bipolar Disord*. 2003;5(1):48–52.
48. Blackmore ER, Rubinow DR, O'Connor TG, et al. Reproductive outcomes and risk of subsequent illness in women diagnosed with postpartum psychosis. *Bipolar Disord*. 2013;15(4):394–404.
49. Sherwood Brown E, Suppes T, Adinoff B, Rajan Thomas N. Drug abuse and bipolar disorder: comorbidity or misdiagnosis? *J Affect Disord*. 2001;65(2):105–115.
50. Post RM, Denicoff KD, Leverich GS, et al. Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH life chart method. *J Clin Psychiatry*. 2003;64(6):680–690.
51. Abreu LN, Lafer B, Baca-Garcia E, Oquendo MA. Suicidal ideation and suicide attempts in bipolar disorder type I: An update for the clinician. *Rev Bras Psiquiatr*. 2009;31(3):271–280.
52. Lingam R, Scott J. Treatment non-adherence in affective disorders. *Acta Psychiatr Scand*. 2002;105(3):164–172.
53. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: Update 2013. *Bipolar Disord*. 2013;15(1):1–44.
54. American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry*. 2002;159(4 Suppl):1–50.
55. Bauer MS, Mitchner L. What is a "mood stabilizer"? An evidence-based response *Am J Psychiatry*. 2004;161(1):318.
56. Buoli M, Serati M, Altamura AC. Is the combination of a mood stabilizer plus an antipsychotic more effective than mono-therapies in long-term treatment of bipolar disorder? A systematic review. *J Affect Disord*. 2014;152-154:12–18.
57. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2009 on the treatment of acute mania. *World J Biol Psychiatry*. 2009;10(2):85–116.
58. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies

of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: Update 2010 on the treatment of acute bipolar depression. *World J Biol Psychiatry*. 2010;11(2):81–109.

59. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: Update 2012 on the long-term treatment of bipolar disorder. *World J Biol Psychiatry*. 2013;14(3):154–219.
60. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: Acute and long-term treatment of mixed states in bipolar disorder. *World J Biol Psychiatry*. 2018;19(1):2–58.
61. Lithium. Lexi-comp, Inc. Available at http://online.lexi.com/lco/action/home. Accessed September 2, 2015.
62. Curran G, Ravindran A. Lithium for bipolar disorder: A review of the recent literature. *Expert Rev Neurother*. 2014;14(9):1079–1098.
63. Cipriani A, Hawton K, Stockton S, Geddes JR. Lithium in the prevention of suicide in mood disorders: Updated systematic review and meta-analysis. *BMJ*. 2013;346:f3646.
64. Goodwin FK. Rationale for long-term treatment of bipolar disorder and evidence for long-term lithium treatment. *J Clin Psychiatry*. 2002;63(Suppl 10):5–12.
65. Amann B, Born C, Crespo JM, Pomarol-Clotet E, McKenna P. Lamotrigine: When and where does it act in affective disorders? A systematic review *J Psychopharmacol*. 2011;25(10):1289–1294.
66. Valproate Sodium, Valproic Acid, Divalproex Sodium. Lexi-comp Inc. Available at http://online.lexi.com/lco/action/home. Accessed September 2, 2015.
67. Macritchie K, Geddes JR, Scott J, Haslam D, de Lima M, Goodwin G. Valproate for acute mood episodes in bipolar disorder. *Cochrane Database Syst Rev*. 2003(1):Cd004052.
68. Allen MH, Hirschfeld RM, Wozniak PJ, Baker JD, Bowden CL. Linear relationship of valproate serum concentration to response and optimal serum levels for acute mania. *Am J Psychiatry*. 2006;163(2):272–275.
69. Carbamazepine. Lexi-comp Inc. Available at http://online.lexi.com/lco/action/home. Accessed September 2, 2015.
70. Oxcarbazepine. *Lexicomp Online, AHFS Drug Information 2015*. Hudson, Ohio: Lexi-comp Inc.

71. Dong X, Leppik IE, White J, Rarick J. Hyponatremia from oxcarbazepine and carbamazepine. *Neurology*. 2005;65(12):1976–1978.
72. Perucca E. Clinically relevant drug interactions with antiepileptic drugs. *Br J Clin Pharmacol*. 2006;61(3):246–255.
73. Malhi GS, Mitchell PB, Salim S. Bipolar depression: management options. *CNS Drugs*. 2003;17(1):925.
74. Raskin S, Teitelbaum A, Zislin J, Durst R. Adjunctive lamotrigine as a possible mania inducer in bipolar patients. *Am J Psychiatry*. 2006;163(1):159–160.
75. Lamotrigine. Lexi-comp Inc. Accessed September 2, 2015.
76. Tohen M, Vieta E. Antipsychotic agents in the treatment of bipolar mania. *Bipolar Disord*. 2009;11(Suppl 2):45–54.
77. Marder SR, Essock SM, Miller AL, et al. Physical health monitoring of patients with schizophrenia. *Am J Psychiatry*. 2004;161(8):1334–1349.
78. McEnvoy GK, Miller J, Snow EK, et al. Benzodiazepines. *AHFS Drug Information 2007*. Bethesda, MD: American Society of Health-System Pharmacists; 2007;2508–2518.
79. Alderfer BS, Allen MH. Treatment of agitation in bipolar disorder across the life cycle. *J Clin Psychiatry*. 2003;64(Suppl 4):3–9.
80. Sachs GS, Nierenberg AA, Calabrese JR, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med*. 2007;356(17):1711–1722.
81. Gijsman HJ, Geddes JR, Rendell JM, Nolen WA, Goodwin GM. Antidepressants for bipolar depression: A systematic review of randomized, controlled trials. *Am J Psychiatry*. 2004;161(9):1537–1547.
82. Post RM, Altshuler LL, Leverich GS, et al. Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. *Br J Psychiatry*. 2006;189:124–131.
83. Sachs GS, Koslow CL, Ghaemi SN. The treatment of bipolar depression. *Bipolar Disord*. 2000;2(3 Pt 2):256–260.
84. Sachs GS, Printz DJ, Kahn DA, Carpenter D, Docherty JP. The expert consensus guideline series: medication treatment of bipolar disorder 2000. *Postgrad Med*. 2000;Spec No:1–104.
85. Gentile S. Lithium in pregnancy: the need to treat, the duty to ensure safety. *Expert Opin Drug Saf*. 2012;11(3):425–437.
86. Ernst CL, Goldberg JF. The reproductive safety profile of mood

stabilizers, atypical antipsychotics, and broad-spectrum psychotropics. *J Clin Psychiatry*. 2002;63(Suppl 4):42–55.

87. Hernandez-Diaz S, Smith CR, Shen A, et al. Comparative safety of antiepileptic drugs during pregnancy. *Neurology*. 2012;78(21):1692–1699.
88. Vajda FJ, Hitchcock A, Graham J, O'Brien T, Lander C, Eadie M. The Australian register of antiepileptic drugs in pregnancy: The first 1002 pregnancies. *Aust N Z J Obstet Gynaecol*. 2007;47(6):468–474.
89. Valproic Acid. Lexi-Comp, Inc.; 2017. Accessed August 17, 2018.
90. Galbally M, Snellen M, Power J. Antipsychotic drugs in pregnancy: A review of their maternal and fetal effects. *Ther Adv Drug Saf*. 2014;5(2):100–109.
91. McClellan J, Kowatch R, Findling RL. Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46(1):107–125.
92. Chang KD, Ketter TA. Special issues in the treatment of paediatric bipolar disorder. *Expert Opin Pharmacother*. 2001;2(4):613–622.
93. Madaan V, Chang KD. Pharmacotherapeutic strategies for pediatric bipolar disorder. *Expert Opin Pharmacother*. 2007;8(12):1801–1819.
94. Gentile S. Clinical usefulness of second-generation antipsychotics in treating children and adolescents diagnosed with bipolar or schizophrenic disorders. *Paediatr Drugs*. 2011;13(5):291–302.
95. Zuddas A, Zanni R, Usala T. Second generation antipsychotics (SGAs) for non-psychotic disorders in children and adolescents: A review of the randomized controlled studies. *Eur Neuropsychopharmacol*. 2011;21(8):600–620.
96. Goldstein BI, Sassi R, Diler RS. Pharmacologic treatment of bipolar disorder in children and adolescents. *Child Adolesc Psychiatr Clin N Am*. 2012;21(4):911–939.
97. McIntyre RS, Konarski JZ, Soczynska JK, et al. Medical comorbidity in bipolar disorder: Implications for functional outcomes and health service utilization. *Psychiatr Serv*. 2006;57(8):1140–1144.
98. Hardy BG, Shulman KI, Mackenzie SE, Kutcher SP, Silverberg JD. Pharmacokinetics of lithium in the elderly. *J Clin Psychopharmacol*. 1987;7(3):153–158.
99. Bryson SM, Verma N, Scott PJ, Rubin PC. Pharmacokinetics of valproic acid in young and elderly subjects. *Br J Clin Pharmacol*. 1983;16(1):104–

105.

100. Young RC. Evidence-based pharmacological treatment of geriatric bipolar disorder. *Psychiatr Clin North Am*. 2005;28(4):837–869.
101. Suppes T, Dennehy EB, Hirschfeld RM, et al. The Texas implementation of medication algorithms: Update to the algorithms for treatment of bipolar I disorder. *J Clin Psychiatry*. 2005;66(7):870–886.
102. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004;27(2):596–601.

87

Anxiety Disorders: Generalized Anxiety, Panic, and Social Anxiety Disorders

Sarah T. Melton and Cynthia K. Kirkwood

KEY CONCEPTS

1. Anxiety disorders are among the most common of mental disorders and are underdiagnosed and undertreated.
2. The long-term goal in treatment of generalized anxiety disorder (GAD) is remission with minimal or no anxiety symptoms and no functional impairment.
3. Antidepressants are the agents of choice for the management of GAD.
4. Antidepressants have a lag time of 2 to 4 weeks or longer before antianxiety effects occur in GAD.
5. When monitoring the effectiveness of antidepressants in panic disorder, it is important to allow an adequate amount of time (8–12 weeks) to achieve full therapeutic response.
6. The optimal duration of panic therapy is unknown; 12 to 24 months of pharmacotherapy is recommended before gradual drug discontinuation over 4 to 6 months is attempted.
7. Social anxiety disorder (SAD) is a chronic long-term illness requiring extended therapy. After improvement, at least a 6- to 12-month medication maintenance period is recommended before considering treatment discontinuation.
8. The selective serotonin reuptake inhibitors or venlafaxine are considered first-line pharmacotherapy for social anxiety disorder.
9. An adequate trial of antidepressants in generalized SAD lasts at least 8

weeks, and maximal benefit may not be seen until 12 weeks.

10 The three principal domains in which improvement should be observed in generalized SAD are symptoms, functionality, and well-being.

Preclass Engaged Learning Activity

Visit the National Institute of Mental Health (NIMH) website for Anxiety Disorders (https://www.nimh.nih.gov/health/topics/anxiety-disorders/index.shtml) and review the patient brochures for generalized anxiety disorder and panic disorder. Compare and contrast the signs and symptoms and the available treatment options for these two anxiety disorders. This activity will help you to differentiate the clinical presentation of each disorder and assist you with the ASSESS portion of the "Patient Care Process."

INTRODUCTION

Anxiety is an emotional state commonly caused by the perception of real or perceived danger that threatens the security of an individual. It allows a person to prepare for or react to environmental changes. Everyone experiences a certain amount of nervousness and apprehension when faced with a stressful situation. This is an adaptive response and is transient in nature.

Anxiety can produce uncomfortable and potentially debilitating psychological (eg, worry or feeling of threat) and physiologic arousal (eg, tachycardia or shortness of breath) if it becomes excessive. Some individuals experience persistent, severe anxiety symptoms and possess irrational fears that significantly impair normal daily functioning. These persons often suffer from an anxiety disorder.[1]

1 Anxiety disorders are among the most frequent mental disorders encountered in clinical practice and are often underdiagnosed and undertreated.[2] Healthcare professionals often mistake anxiety disorders for physical illnesses, and less than one-third of patients receive appropriate treatment.[2] Failure to diagnose and manage anxiety disorders results in negative outcomes including overuse of healthcare resources, increased risk for suicide and substance abuse.[3] Individuals with anxiety disorders develop cardiovascular, cerebrovascular,

gastrointestinal (GI), and respiratory disorders at a significantly higher rate than the general population.[3]

To treat anxiety appropriately, the clinician must make a reliable diagnosis. It is essential that the distinction between short-term symptoms of anxiety and anxiety disorders be understood. Common or situational anxiety is a normal response to a stressful circumstance. Although symptoms can be severe, they are temporary and usually last no more than 2 or 3 weeks. In this situation, short-term, “as-needed” treatment with an anxiolytic agent such as a benzodiazepine is common and can provide some symptomatic relief; prolonged drug therapy is not recommended for situational anxiety.[4]

EPIDEMIOLOGY

Anxiety disorders, as a group, are the most commonly occurring psychiatric disorders. According to large population-based surveys, up to 33.7% of the population are affected by an anxiety disorder during their lifetime.[5] According to the National Comorbidity Survey Replication which assessed the prevalence, severity, and comorbidity estimates of mental disorders in the United States, the most recent 1-year prevalence rate for anxiety disorders was 21.3% in persons aged 18 years and older. Specific phobias were the most common anxiety disorder, with a 12-month prevalence of 10.1%. The 1-year prevalence of generalized anxiety disorder (GAD) was 2.9%, panic disorder was 3.1%, and that of social anxiety disorder (SAD) was 8.0%.[5]

In general, anxiety disorders are a group of heterogeneous illnesses that develop before age 30 years and are more common in women, individuals with social issues, and those with a family history of anxiety and depression. Patients often develop another anxiety disorder, major depression, or substance use disorders.[1,2] The clinical picture of mixed anxiety and depression is much more common than an isolated anxiety disorder.[6,7]

ETIOLOGY

The differential diagnosis of anxiety disorders includes medical and psychiatric illnesses and certain drugs.[6,7] Hypotheses on the etiology of anxiety disorders are based on interactions between a combination of factors including vulnerability (eg, genetic predisposition and early childhood adversity) and stress (eg, occupational and traumatic experience). The vulnerability may be

associated with genetic factors and neurobiologic adaptations of the central nervous system (CNS).[8]

Medical Diseases Associated with Anxiety

Anxiety symptoms are an inherent part of the initial clinical presentation of several diseases, which complicates the distinction between anxiety disorders and medical disorders.[4,7] Furthermore, anxiety disorders are associated with chronic medical illness, low levels of physical health-related quality of life (QOL), and physical disability.[2] If anxiety symptoms are secondary to a medical illness, they usually will subside as the medical situation stabilizes. However, the knowledge that one has a physical illness can trigger anxious feelings and further complicate therapy. Persistent anxiety subsequent to a physical illness requires further assessment for an anxiety disorder. Common somatic symptoms of anxiety that frequently present in medical disorders include abdominal pain, palpitations, tachycardia, sweating, flushing, tremor, chest pain or tightness, and shortness of breath. Although less specific, symptoms of muscle tension, headache, and fatigue are also common manifestations of anxiety. Medical disorders most closely associated with anxiety are listed in **Table 87-1**.

TABLE 87-1 Common Medical Illnesses Associated with Anxiety Symptoms

Cardiovascular
- Angina, arrhythmias, cardiomyopathy, congestive heart failure, hypertension, ischemic heart disease, mitral valve prolapse, myocardial infarction

Endocrine and metabolic
- Cushing disease, diabetes, hyperparathyroidism, hyperthyroidism, hypothyroidism, hypoglycemia, hyponatremia, hyperkalemia, pheochromocytoma, vitamin B_{12} or folate deficiencies

Gastrointestinal
- Crohn's disease, irritable bowel syndrome, ulcerative colitis, peptic ulcer disease

Neurologic
- Migraine, seizures, stroke, neoplasms, poor pain control

Respiratory system
- Asthma, chronic obstructive pulmonary disease, pulmonary embolism, pneumonia

Others
- Anemias, cancer, systemic lupus erythematosus, vestibular dysfunction

Data from References 3, 6, and 7.

Psychiatric Diseases Associated with Anxiety

Anxiety can be a presenting feature of several major psychiatric illnesses. Anxiety symptoms are extremely common in patients with mood disorders, schizophrenia, dementia, and substance use disorders. Most psychiatric patients will have two or more concurrent psychiatric disorders (comorbidity) within their lifetime.[5] It is important to diagnose and treat all comorbid psychiatric conditions in patients with anxiety disorders.

Drug-Induced Anxiety

Drugs are a common cause of anxiety symptoms (Table 87-2). Anxiety occurs during the use of CNS-stimulating drugs in a dose-dependent manner, but ingestion of minimal amounts can result in marked anxiety, including panic attacks, in some individuals. The onset of drug-induced anxiety is usually rapid after the initiation of therapy. A thorough medication history evaluating for a recent drug or dosage change is important to rule out a drug-induced etiology for the anxiety.

TABLE 87-2 Drugs Associated with Anxiety Symptoms

Anticonvulsants: Carbamazepine, phenytoin
Antidepressants: Bupropion, selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors
Antihypertensives: Clonidine, felodipine
Antibiotics: Quinolones, isoniazid
Bronchodilators: Albuterol, theophylline
Corticosteroids: Prednisone
Dopamine agonists: Amantadine, levodopa
Herbals: Ma huang, ginseng, ephedra
Illicit substances: Ecstasy, marijuana
Nonsteroidal anti-inflammatory drugs: Ibuprofen, indomethacin
Stimulants: Amphetamines, caffeine, cocaine, methylphenidate, nicotine
Sympathomimetics: Pseudoephedrine, phenylephrine
Thyroid hormones: Levothyroxine
Toxicity: Anticholinergics, antihistamines, digoxin

Data from References 1 and 4.

Anxiety occurs occasionally during the use of CNS depressants, especially in children and the elderly; however, anxiety complaints are more common as complications of drug withdrawal after the abrupt discontinuation of these agents.[6]

PATHOPHYSIOLOGY

Data from biochemical and neuroimaging studies indicate that the modulation of normal and pathologic anxiety states is associated with multiple regions of the brain and abnormal function in several neurotransmitter systems, including norepinephrine (NE), γ-aminobutyric acid (GABA), serotonin (5-HT), dopamine (DA), corticotropin-releasing factor (CRF), and cholecystokinin.[9] Neuroanatomic models of fear (ie, the response to danger) and anxiety (ie, the feeling of fear that is disproportionate to the actual threat) include some key brain areas. The amygdala, a temporal lobe structure, plays a critical role in the assessment of fear stimuli and learned response to fear.[9,10] The locus ceruleus (LC), located in the brain stem, is the primary NE-containing site, with widespread projections to areas responsible for implementing fear responses (eg, vagus, lateral, and paraventricular hypothalamus). The hippocampus is integral in the consolidation of traumatic memory and contextual fear conditioning. The hypothalamus is the principal area for integrating neuroendocrine and autonomic responses to a threat.[9] Recent reviews of potential biomarkers for anxiety disorders in neurochemistry, genetics, and neuroimaging report insufficient evidence of specific biomarkers for diagnosis and treatment response.[11,12]

Neurochemical Theories

Noradrenergic Model

The basic premise of the noradrenergic theory is that the autonomic nervous system of anxious patients is hypersensitive and overreacts to various stimuli. Many anxious patients clearly display symptoms of peripheral autonomic hyperactivity. In response to threat or fearful situations, the LC serves as an alarm center, activating NE release and stimulating the sympathetic and parasympathetic nervous systems. Chronic central noradrenergic overactivity downregulates α_2-adrenoreceptors in patients with GAD. This receptor is hypersensitive in some patients with panic disorder.[9] By administering drugs that have a relatively specific effect on the LC, researchers have further explored the NE theory of anxiety and panic disorder. Drugs with anxiogenic effects (eg, yohimbine [an α_2-adrenergic receptor antagonist]) stimulate LC firing and increase noradrenergic activity. The resultant NE release in turn increases glutamate release (an excitatory neurotransmitter).[9] This produces subjective feelings of anxiety and can precipitate a panic attack in those with panic

disorder, but not in normal volunteers.[9] Drugs with anxiolytic or antipanic effects (eg, benzodiazepines and antidepressants) inhibit LC firing, decrease noradrenergic activity, and block the effects of anxiogenic drugs.[9]

GABA-Receptor Model

There are two superfamilies of GABA-protein receptors: $GABA_A$ and $GABA_B$. Drugs that reduce anxiety and produce sedation target the $GABA_A$ receptor. The $GABA_B$ receptor is a G-protein–coupled receptor postulated to be involved in the presynaptic inhibition of GABA release.[9,13] The $GABA_A$ receptors are ligand-gated ion channels composed of five protein subunits. Several classes of subunits (ie, $\alpha_{1–6}$, $\beta_{1–3}$, $\gamma_{1–3}$, δ, ε, θ, π, $\rho_{1–3}$) surround a central pore, and the receptor is connected to the cytoskeleton.[13] Benzodiazepine ligands enhance the inhibitory effects of GABA.[13] It is important to note that GABA is the major inhibitory neurotransmitter in the CNS, which has a strong regulatory or inhibitory effect on the 5-HT, NE, and dopamine systems. When GABA binds to the $GABA_A$ receptor, neuronal excitability is reduced.

The specific role of the GABA receptors in anxiety disorders has not been established. The number of $GABA_A$ receptors can change with alterations in the environment (eg, chronic stress), and the subunit expression can be altered by hormonal changes.[13] Reductions in benzodiazepine binding and GABA concentrations in the brain are reported in patients with panic disorder.[11]

Serotonin Model

Although there are data suggesting that the 5-HT system is dysregulated in patients with anxiety disorders, definitive evidence that shows a clear abnormality in 5-HT function is lacking. In general, 5-HT is primarily an inhibitory neurotransmitter that is used by neurons originating in the raphe nuclei of the brain stem and projecting diffusely throughout the brain (eg, cortex, amygdala, hippocampus, and limbic system). Abnormalities in serotonergic functioning through release and uptake at the presynaptic autoreceptors (5-$HT_{1A/1D}$), the serotonin-reuptake transporter (SERT) site, or effect of 5-HT at the postsynaptic receptors (eg, 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C}) may play a role in anxiety disorders.[9,11] Preclinical models suggest that greater 5-HT function facilitates avoidance behavior; however, primate studies show that reducing 5-HT increases aggression.[9] It is postulated that greater 5-HT activity reduces NE

activity in the LC, inhibits defense/escape response via the periaqueductal gray (PAG) region, and reduces hypothalamic release of CRF. The selective serotonin reuptake inhibitors (SSRIs) acutely increase 5-HT levels by blocking the SERT to increase the amount of 5-HT available postsynaptically and are efficacious in blocking the manifestations of panic and anxiety.[9]

Low 5-HT activity may lead to a dysregulation of other neurotransmitters. Both the NE and 5-HT systems are closely linked, and interactions between the two are reciprocal and vary. As NE may act at presynaptic 5-HT terminals to decrease 5-HT release, its activity at postsynaptic receptors can cause increased 5-HT release.

Buspirone is a selective 5-HT_{1A} partial agonist that is effective for GAD but not for panic disorder.[14] Because the selective 5-HT_{1A} partial agonists reduce serotonergic activity, GAD symptoms may reflect excessive 5-HT transmission or overactivity of the stimulatory 5-HT pathways. There is circumstantial evidence for the involvement of serotonergic and dopaminergic systems in the pathophysiology of generalized SAD.[15]

Neuroimaging Studies

Functional neuroimaging studies support the crucial role of the amygdala, anterior cingulate cortex (ACC), ventromedial prefrontal cortex, and insula in the pathophysiology of anxiety.[8,11] In GAD there is an abnormal increase in the brain's fear circuitry, as well as decreased activity in the prefrontal cortex, which appears to have a compensatory role in reducing GAD symptoms.[16] Patients with panic have abnormalities of midbrain structures, including the PAG. Neuroimaging studies have shown activation of insula and upper brain stem (including the PAG), as well as deactivation of the ACC during experimental panic attacks.[10] Patients with SAD have greater activity than matched comparison subjects in the amygdala and insula, structures linked to negative emotional responses.[11] Both pharmacotherapy and psychotherapy decreased cerebral blood flow in the amygdala, hippocampus, and surrounding cortical areas in patients with SAD.[8,11]

CLINICAL PRESENTATION

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* classifies anxiety disorders into categories including GAD, panic disorder,

agoraphobia, SAD, specific phobia, and separation anxiety disorder.[1] The characteristic features of these illnesses are anxiety and avoidance behavior. Anxiety symptoms must cause significant distress and impairment in social, occupational, or other areas of functioning, and should not be secondary to a drug or illicit substance or a general medical disorder or occur solely as part of another psychiatric disorder.[1] The anxiety-related syndromes, posttraumatic stress disorder and obsessive-compulsive disorder, are discussed in Chapter 88 "Anxiety Disorders II: Posttraumatic Stress Disorder and Obsessive-Compulsive Disorder."

CLINICAL PRESENTATION Generalized Anxiety Disorder

Psychological and Cognitive Symptoms

- Excessive anxiety
- Worries that are difficult to control
- Feeling keyed up or on edge
- Trouble concentrating or mind going blank

Physical Symptoms

- Restlessness
- Fatigue
- Muscle tension
- Sleep disturbance
- Irritability

Data from References 1, 2, and 3.

CLINICAL PRESENTATION Panic Attack

Psychological Symptoms

- Depersonalization (being detached from oneself)

- Derealization (feelings of being detached from one's environment)
- Fear of losing control, going crazy, or dying

Physical Symptoms

- **Abdominal distress**
- Chest pain or discomfort
- Chills
- Dizziness or light-headedness
- Feeling of choking
- Heat sensations
- Nausea
- Palpitations
- Paresthesias
- Sensations of shortness of breath or smothering
- Sweating
- Tachycardia
- Trembling or shaking

Data from References 1, 2, and 3.

Generalized Anxiety Disorder

The diagnostic criteria for GAD require persistent symptoms for most days for at least 6 months.[1] The essential feature of GAD is unrealistic or excessive anxiety and worry about a number of events or activities.[1] The anxiety or apprehensive expectation is accompanied by at least three psychological or physiologic symptoms. Anxiety and worry are not confined to features of another psychiatric illness (eg, having a panic attack, being embarrassed in public).[1]

The onset, course of illness, and comorbid conditions of GAD are important considerations. GAD has a gradual onset with an average age of 21 years; however, there is a bimodal distribution. Onset occurs earlier when GAD is the primary presentation and later when GAD is secondary. In general, GAD can be

exacerbated or precipitated in later life by severe psychological stressors. Most patients present between the ages of 35 and 45 years, with women twice as likely to have GAD as men. The course of the illness is chronic (ie, episodes can last for a decade or longer) and there is a high percentage of relapse with low overall rates of recovery.[1] Patients report substantial interference with their lives and have a high probability of seeking treatment. Lifetime comorbidity with another psychiatric disorder occurs in 90% of patients with GAD, with depression being found in over 50%.[17]

Panic Disorder

Panic disorder begins as a series of unexpected (spontaneous) panic attacks involving an abrupt surge of intense fear or intense discomfort. The unexpected panic attacks are followed by at least 1 month of persistent concern about having another panic attack, worry about the possible consequences of the panic attack, or a significant maladaptive change in behavior related to the attacks.[1] During an attack, patients describe at least four physiologic and physical symptoms. Panic attacks usually last no more than 20 to 30 minutes, with the peak intensity of symptoms within the first 10 minutes. Often patients seek help at a physician's office or emergency department, only to have their symptoms resolve before or on arrival. Because panic symptoms mimic those present in several medical conditions, patients often are misdiagnosed, and multiple referrals are common.[1]

Secondary to the panic attacks, up to 50% of patients develop agoraphobia.[1] Agoraphobia is marked fear or anxiety about being in at least two situations in which escape might be difficult or where help might not be available in the event of developing panic-like symptoms.[1] As a result, patients often avoid specific situations (eg, using public transportation, being in open or enclosed places, being in a crowd or being outside of the home alone) in which they fear a panic attack might occur.[1]

Complications of panic disorder include depression (10%–65% have major depressive disorder), alcohol use disorder, and high use of health services and emergency rooms.[1] Patients with panic disorder have a high lifetime risk for suicide attempts compared with the general population.[1] The usual course is chronic but waxing and waning.

Social Anxiety Disorder

SAD is characterized by marked fear about one or more social situations in

which the individual is exposed to possible scrutiny by others. Exposure to the feared circumstance usually provokes an immediate situation-related panic attack. Blushing is the principal physical indicator and distinguishes SAD from other anxiety disorders. The fear and anxiety are out of proportion to the actual threat posed by the social situation and is persistent, typically lasting for 6 months or longer.[1] If the fear is restricted to speaking or performing in public, the SAD is specified as performance only.

The mean age of onset of SAD is during the mid-teens with rates slightly higher among women than men and more frequent in younger cohorts. It is a chronic disorder with a mean duration of 20 years.[1] People with SAD can be reluctant to seek professional help despite the existence of beneficial treatments because consultation with a clinician is perceived as a feared social interaction.[18]

Differentiating SAD from other anxiety disorders can be difficult. Panic attacks occur in both SAD and panic disorder, but the distinction between the two is the rationale behind the fear, whereas fear of anxiety symptoms is characteristic of panic disorder and fear of embarrassment from social interaction typifies SAD.[1] A majority of SAD patients eventually develop a concurrent mood, anxiety, or substance use disorder.[18]

Specific Phobia

Specific phobia is marked and persistent fear of a circumscribed object or situation (eg, insects or heights). Apart from contact with the feared object or situation, the patient is usually free of symptoms. Most persons simply avoid the feared object and adjust to certain restrictions on their activities.[1]

CLINICAL PRESENTATION Social Anxiety Disorder

Fears of Being

- Scrutinized by others
- Negatively evaluated (ie, humiliated, embarrassed, or rejected)

Some Feared Situations

- Eating or writing in front of others
- Interacting with authority figures
- Speaking in public

- Talking with strangers
- Use of public toilets

Symptoms of Anxiety

- Blushing
- “Butterflies in the stomach”
- Diarrhea
- Stumbling over words
- Sweating
- Tachycardia
- Trembling

Specifier

Performance; Applies only if the fear is restricted to speaking or performing in public.

Data from References 1 and 18.

TREATMENT

Generalized Anxiety Disorder

Desired Outcomes

2 The goals of therapy in the acute management of GAD are to reduce the severity and duration of the anxiety symptoms and to improve overall functioning. The long-term goal in GAD is remission with minimal or no anxiety symptoms, no functional impairment, and increased QOL.[17] Prevention of recurrence is another long-term consideration.

General Approach

Once GAD is diagnosed, a patient-specific treatment plan, which usually consists of both psychotherapy and drug therapy, is developed. The plan depends on the severity and chronicity of symptoms, age, medication history, and

comorbid medical and psychiatric conditions.[19] Factors such as anticipated adverse effects, history of prior response in the patient or family member, patient preference, and cost should be considered when treatment is initiated. Psychotherapy is the least invasive and safest treatment modality. Antianxiety medication is indicated for patients experiencing symptoms severe enough to produce functional disability. **Table 87-3** lists drug choices for GAD, panic disorder, and SAD.

TABLE 87-3 Drug Choices for Anxiety Disorders

Anxiety Disorder	First-Line Drugs	Second-Line Drugs	Alternatives
Generalized anxiety disorder	Duloxetine Escitalopram Paroxetine Sertraline Venlafaxine XR	Benzodiazepines Buspirone Imipramine Pregabalin	Hydroxyzine Quetiapine
Panic disorder	SSRIs Venlafaxine XR	Alprazolam Citalopram Clomipramine Clonazepam Imipramine	Phenelzine
Social anxiety disorder	Escitalopram Fluvoxamine CR Paroxetine Sertraline Venlafaxine XR	Clonazepam Citalopram	Gabapentin Phenelzine Pregabalin

CR, controlled-release; SSRI, selective serotonin reuptake inhibitor; XR, extended-release.

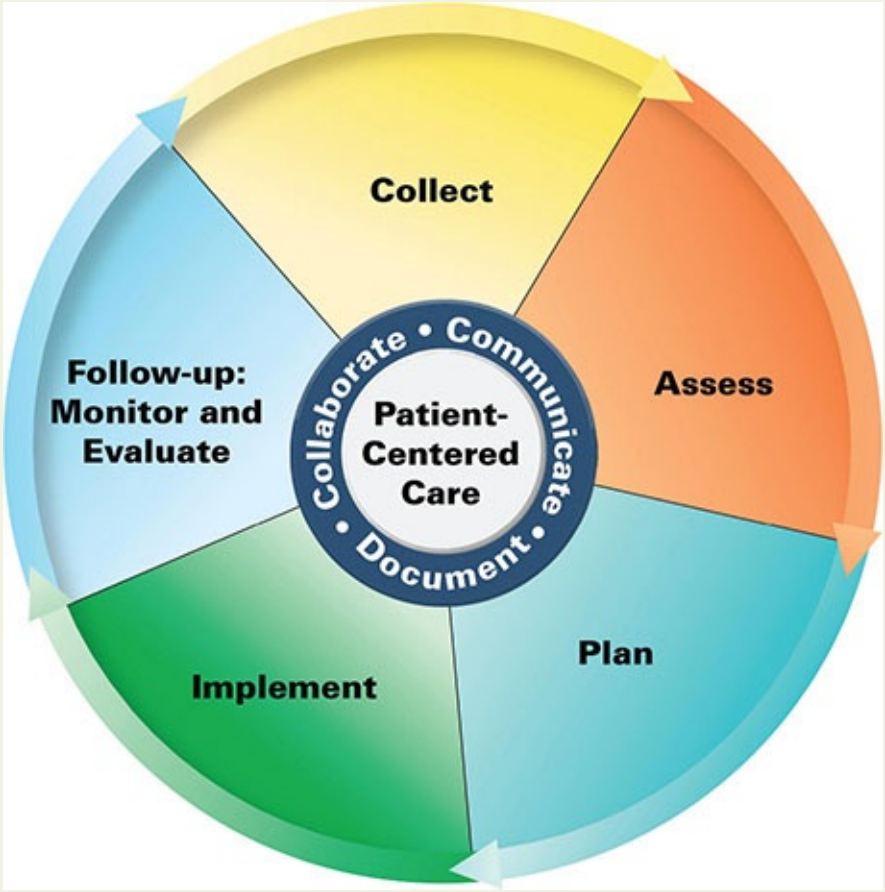
Data from References 2, and 20 to 22.

The need for treatment is determined by patient-specific factors including severity and duration of symptoms, degree of disability, and the presence of coexisting disorders (ie, mood or other anxiety disorders). The patient should be assessed for response to or intolerance of previous treatment approaches. The selection of a specific treatment modality should be based on concurrent medical conditions, contraindications, patient's preference of treatment, and the availability of potential treatment options. The clinician should consider FDA warnings (eg, QTc prolongation for citalopram, teratogenicity with paroxetine) and potential for adverse events with medical disease (eg, anticholinergic effects and weight gain with paroxetine in patients with diabetes, obesity, or benign

prostatic hyperplasia) when selecting an agent. Increased risk of suicidality should be considered in patients taking antidepressants who are younger than 25 years. All patients should receive education that includes information about GAD, treatment choices, and resources for support in the community. The patient should be an integral part of decision making and should be informed about effectiveness, common adverse effects, duration of treatment, cost associated with treatment, and what to expect when treatment is discontinued.[2]

Nonpharmacologic Therapy

Nonpharmacologic treatment modalities in GAD include psychoeducation, short-term counseling, stress management, psychotherapy, mindfulness-based therapy, or exercise. Psychoeducation includes information on the etiology and management of GAD (eg, Anxiety and Depression Association of America, www.adaa.org). Patients with anxiety should be instructed to avoid caffeine, nicotine, nonprescription stimulants, diet pills, and excessive use of alcohol. Most patients with GAD require psychological therapy, alone or in combination with antianxiety drugs, to overcome fears and to learn to manage their anxiety and worry.[21] Cognitive behavioral therapy (CBT) is the most effective psychological therapy in GAD patients. In general, CBT for GAD includes self-monitoring of worry, cognitive restructuring, relaxation training, and rehearsal of coping skills.[21] Psychotherapy or medication alone has comparable efficacy in acute treatment.[22] The relapse rate with CBT is less than with other types of psychological modalities.[22] Controlled trials comparing the efficacy of combining drug and psychotherapy over long-term treatment are lacking.[22] Advantages of CBT over pharmacotherapy include patient preference and lack of troubling adverse effects. However, CBT is not widely available, requires specialized training, and entails weekly sessions for an extended time period (ie, 12–16 weeks).[23] Other options include group therapy (8–12 sessions) and computer-based therapy.[23]



Patient Care Process for Anxiety Disorders

Collect

- Patient characteristics (eg, age, sex, pregnancy)
- Patient medical history (personal and family)
- Patient psychiatric history (personal and family)
- Social history (eg, caffeine, nicotine, ethanol, illicit drug use including route of administration)
- Current medications including over-the-counter (OTC), herbal products, dietary supplements, and prior psychiatric medication use
- Mental status examination
- Objective data

  Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, and weight

  Labs including thyroid stimulating hormone (TSH)

Urinalysis including urine drug testing
Generalized Anxiety Disorder 7-Item Scale, Hamilton Anxiety Disorder Rating Scale, Sheehan Disability Scale, and Patient Health Questionnaire-9 (PHQ-9)

Assess

- Presence of generalized anxiety disorder, panic disorder, or social anxiety disorder
- Presence of comorbid depression or substance use disorder
- Ability/willingness to begin nonpharmacologic treatments, including availability in geographic region
- Ability/willingness to begin pharmacologic treatment
- Ability/willingness to afford nonpharmacologic and/or pharmacologic treatment(s)
- Support of family members/caregivers for treatment

Plan*

- Drug therapy regimen including specific medication(s), dose, route, frequency, and duration (see Figure 87-1, Tables 87-4, 87-5, 87-8, and 87-9)
- Monitoring parameters including efficacy (eg, rating scales, quality of life)
- Patient education (eg, disease, life style changes, medication adherence, when to expect medication to begin working, possible adverse effects, expected duration of therapy, when to contact healthcare professional)
- Self-monitoring for resolution of anxiety symptoms

Implement*

- Provide patient education regarding all aspects of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Resolution of anxiety symptoms
- Presence of adverse effects (eg, sedation, psychomotor impairment,

nausea, headaches, weight gain, sexual dysfunction, etc.)

- Psychiatric rating scale results
- Patient adherence to treatment plan using multiple sources of information
- Re-evaluate in 2 weeks until stable, then every 3 months

**Collaborate with patient, caregivers, and other healthcare professionals.*

Pharmacologic Therapy

The benzodiazepines are the most effective and commonly prescribed drugs for the rapid relief of acute anxiety symptoms (Table 87-4). All benzodiazepines are equally effective anxiolytics, and consideration of pharmacokinetic properties and the patient's clinical situation will assist in the selection of the most appropriate agent.[17]

TABLE 87-4 Benzodiazepine Antianxiety Agents

Drug	Brand Name	Approved Dosage Range (mg/day)	Maximum Dosage for Geriatric Patients (mg/day)	Approximate Equivalent Dose (mg)	Comments
Alprazolam[1]	Xanax	0.75–4	2	0.5	Associated with interdose rebound anxiety
	Xanax XR	1–10[2]			
Chlordiazepoxide[1]	Librium	25–400	40	10	
Clonazepam[1]	Klonopin	1–4[2]	3	0.25–0.5	
	Klonopin Wafer[3]				
Clorazepate[1]	Tranxene	7.5–60	30	7.5	
Diazepam[1]	Valium	2–40	20	5	
Lorazepam[1]	Ativan	0.5–10	3	1	Preferred in elderly
Oxazepam[1]	Serax	30–120	60	30	Preferred in elderly

[1]Available generically.

[2]Panic disorder dose.

[3]Orally disintegrating formulation.

XR, extended-release.

Dosing and equivalence data from References 25–27.

As antidepressants lack the dependency and adverse effect issues seen with benzodiazepines, they have emerged as the treatment of choice for the management of chronic anxiety, especially in the presence of comorbid depressive symptoms. Buspirone is an additional anxiolytic option (Table 87-5)

in patients without comorbid depression or other anxiety disorders. Because of the high risk of adverse effects and toxicity, barbiturates, antipsychotics, antipsychotic–antidepressant combinations, and antihistamines generally are not indicated in the treatment of GAD.[3] It is important to note that the benzodiazepines are more effective in treating the somatic and autonomic symptoms of GAD as opposed to the psychic symptoms (eg, apprehension and worry), which are reduced by antidepressants.[3]

TABLE 87-5 Nonbenzodiazepine Antianxiety Agents for Generalized Anxiety Disorder

Drug	Brand Name	Initial Dose	Usual Range (mg/day)[1]	Comments
Antidepressants				
Duloxetine	Cymbalta	30 or 60 mg/day	60–120	FDA-approved; available generically
Escitalopram	Lexapro	10 mg/day	10–20	FDA-approved; available generically
Imipramine	Tofranil	50 mg/day	75–200	Available generically
Paroxetine	Paxil Pexeva	20 mg/day	20–50	FDA-approved; available generically; avoid in pregnancy
Sertraline	Zoloft	50 mg/day	50–200	Available generically
Venlafaxine XR	Effexor XR	37.5 or 75 mg/day	75–2252	FDA-approved; available generically
Vilazodone	Viibryd	10 mg/day	20–402	During concomitant use of a strong CYP3A4 inhibitor (eg, itraconazole, clarithromycin, voriconazole), dose should not exceed 20 mg once daily
Vortioxetine	Trintellix	5 mg/day	5–20	
Azapirone				
Buspirone	BuSpar	7.5 mg twice daily	15–602	FDA-approved; available generically
Diphenylmethane				
Hydroxyzine	Vistaril	25 or 50 mg four times daily	200–400	FDA-approved; approved in children for anxiety and tension in divided daily doses of 50–100 mg; available generically
Anticonvulsant				
Pregabalin	Lyrica	50 mg three times daily	150–600	Dosage adjustment required in renal impairment; available generically
Atypical antipsychotic				
Quetiapine XR	Seroquel XR	50 mg at bedtime	150–300	Available generically

[1]Elderly patients are usually treated with approximately one half of the dose listed.

[2]No dosage adjustment is required in elderly patients.

XR, extended-release.

Data from References 3 and 28 to 35.

The most recent evidence-based treatment guidelines come from the World Federation of Societies of Biological Psychiatry, the National Institute for Health and Clinical Evidence, and British Association for Psychopharmacology.[3,21,22] A descriptive flowchart with recommendations based on levels of evidence from the International Psychopharmacology Algorithm Project for the psychosocial and pharmacologic management of GAD is shown in **Fig. 87-1**.[36]

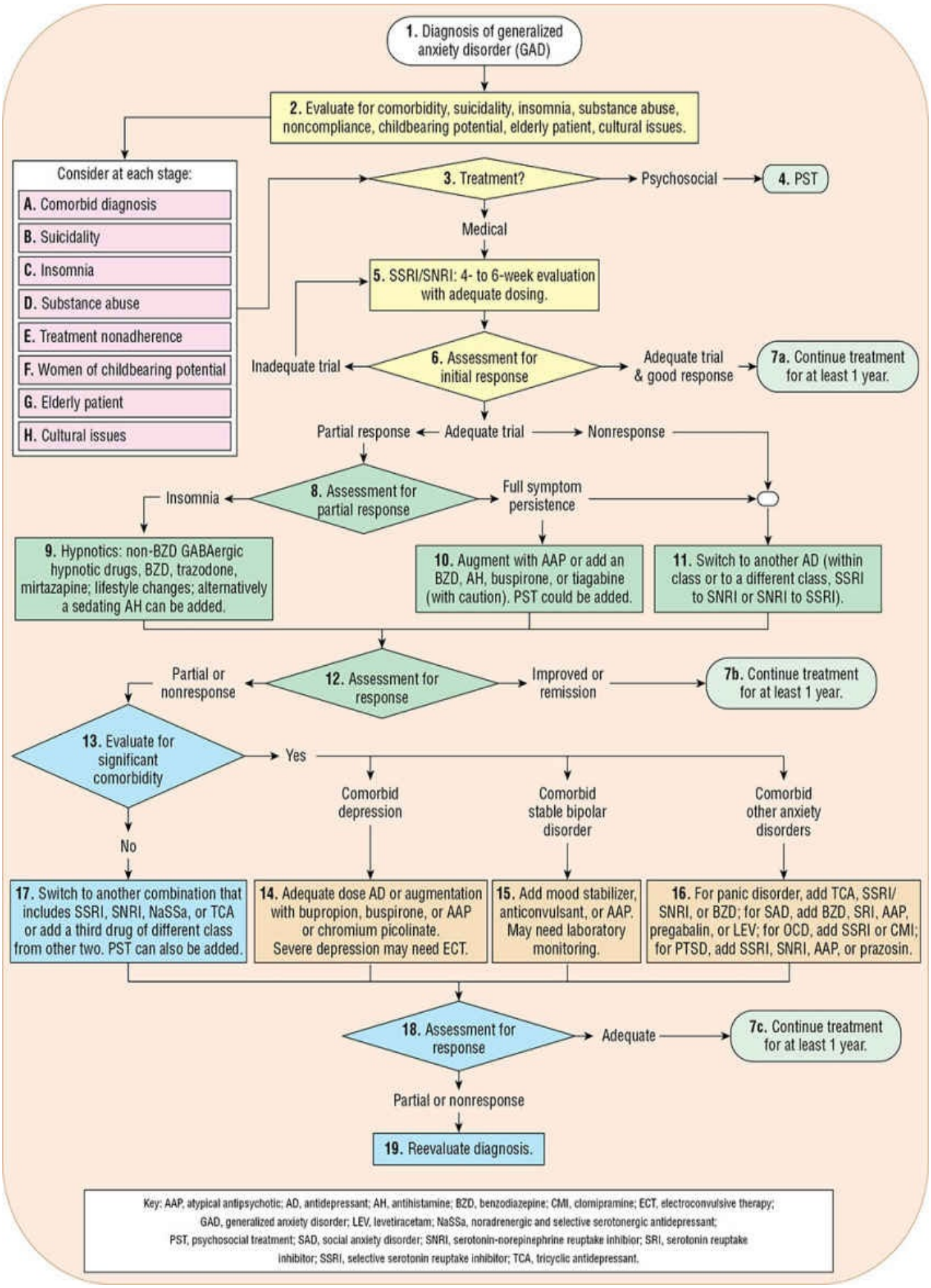

1. Diagnosis of generalized anxiety disorder (GAD)
2. Evaluate for comorbidity, suicidality, insomnia, substance abuse, noncompliance, childbearing potential, elderly patient, cultural issues.
Consider at each stage:
A. Comorbid diagnosis
B. Suicidality
C. Insomnia
D. Substance abuse
E. Treatment nonadherence
F. Women of childbearing potential
G. Elderly patient
H. Cultural issues
3. Treatment?
Psychosocial
4. PST
Medical
5. SSRI/SNRI: 4- to 6-week evaluation with adequate dosing.
6. Assessment for initial response
Inadequate trial
Adequate trial & good response
7a. Continue treatment for at least 1 year.
Partial response
Adequate trial
Nonresponse
8. Assessment for partial response
Insomnia
Full symptom persistence
9. Hypnotics: non-BZD GABAergic hypnotic drugs, BZD, trazodone, mirtazapine; lifestyle changes; alternatively a sedating AH can be added.
10. Augment with AAP or add an BZD, AH, buspirone, or tiagabine (with caution). PST could be added.
11. Switch to another AD (within class or to a different class, SSRI to SNRI or SNRI to SSRI).
12. Assessment for response
Partial or nonresponse
Improved or remission
7b. Continue treatment for at least 1 year.
13. Evaluate for significant comorbidity
Yes
No
Comorbid depression
Comorbid stable bipolar disorder
Comorbid other anxiety disorders
17. Switch to another combination that includes SSRI, SNRI, NaSSa, or TCA or add a third drug of different class from other two. PST can also be added.
14. Adequate dose AD or augmentation with bupropion, buspirone, or AAP or chromium picolinate. Severe depression may need ECT.
15. Add mood stabilizer, anticonvulsant, or AAP. May need laboratory monitoring.
16. For panic disorder, add TCA, SSRI/SNRI, or BZD; for SAD, add BZD, SRI, AAP, pregabalin, or LEV; for OCD, add SSRI or CMI; for PTSD, add SSRI, SNRI, AAP, or prazosin.
18. Assessment for response
Adequate
7c. Continue treatment for at least 1 year.
Partial or nonresponse
19. Reevaluate diagnosis.
Key: AAP, atypical antipsychotic; AD, antidepressant; AH, antihistamine; BZD, benzodiazepine; CMI, clomipramine; ECT, electroconvulsive therapy; GAD, generalized anxiety disorder; LEV, levetiracetam; NaSSa, noradrenergic and selective serotonergic antidepressant; PST, psychosocial treatment; SAD, social anxiety disorder; SNRI, serotonin-norepinephrine reuptake inhibior; SRI, serotonin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

FIGURE 87-1 International Psychopharmacology Algorithm Project (IPAP) generalized anxiety disorder (GAD) algorithm flowchart. Yellow, first-line treatment (nodes 2, 3, 5, 6); green, second-line treatment (nodes 8–12); blue, third-line treatment, no comorbidity (nodes 13,17,18,19); orange, third-line treatment, with comorbidity (nodes 14–16); light green, assessment and evaluation. Levels of evidence used in development of the flowchart were: 1, more than one placebo-controlled trial with sample sizes over 30; 2, one placebo-controlled trial (or active vs active drug comparison) with sample size of 30 or greater; 3, one or small (*n* <30) placebo-controlled trial; 4, case reports or open-label trials; and 5, expert consensus without published evidence. *(Reprinted from The International Psychopharmacology Algorithm Project. IPAP–Generalized Anxiety Disorder Algorithm. http://www.ipap.org/gad/index.php. Accessed December 18, 2018.).*

Antidepressant Therapy

3 Antidepressants are considered first-line agents in the management of GAD. Venlafaxine extended-release, duloxetine, paroxetine, and escitalopram are all FDA-approved antidepressants for GAD (see Table 87-5). Imipramine is considered a second-line agent, despite its efficacy, because of higher toxicity and adverse effect rates.[3]

4 The antianxiety response of antidepressants is delayed by 2 to 4 weeks or longer.[3,17] The pharmacology, pharmacokinetics, and drug interactions of the antidepressants are reviewed in Chapter 85 "Depressive Disorders."

Efficacy Antidepressants are efficacious in the acute and long-term management of GAD. Data support the use of the SSRIs (eg, escitalopram, paroxetine, sertraline), and the serotonin–norepinephrine reuptake inhibitors (SNRIs) (eg, venlafaxine extended-release and duloxetine), for acute therapy (8- to 12-week trials) with response rates between 60% and 68%, and remission rates of approximately 30%.[3,22] A meta-analysis indicated that fluoxetine use was most likely to achieve remission of GAD symptoms; however, sertraline was the best tolerated. In a subanalysis comparing duloxetine, escitalopram, paroxetine, venlafaxine, and pregabalin, duloxetine was most likely to produce a beneficial response, escitalopram was most likely to establish a remission, and pregabalin was the best tolerated.[37]

Mechanism of Action Antidepressant mechanism of action in anxiety disorders is not fully understood. Research indicates that antidepressants modulate

receptor activation of neuronal signal transduction pathways connected to the neurotransmitters 5-HT, DA, and NE. In an animal model of anxiety, a number of candidate genes were identified that were normalized by fluoxetine treatment selectively in the hypothalamus.[38] It is theorized that by activating stress-adapting pathways, SSRIs and SNRIs reduce the somatic anxiety symptoms and the general distress experienced by patients.

Adverse Effects The adverse effects of medications used to treat generalized anxiety are provided in **Table 87-6**. In general, SSRIs and SNRIs are well tolerated, with gastrointestinal (GI) adverse effects and sleep disturbances being the most commonly reported. Headaches and diaphoresis occur early in treatment and are often transient, whereas weight gain and sexual dysfunction may continue in long-term treatment. The use of tricyclic antidepressants (TCAs) in clinical practice is limited by troublesome adverse effects (eg, sedation, anticholinergic effects, and weight gain) in some patients as well as the risk of toxicity in overdose.

TABLE 87-6 Monitoring of Adverse Effects Associated with Medications Used for Anxiety Disorders

Medication Class/Drug	Adverse Drug Reaction	Monitoring Parameter	Comments
SSRIs			
	Jitteriness syndrome	Patient interview	
	Suicidality	Patient interview	Monitor weekly in first few weeks in patients with comorbid depression and patients under age 25
	Nausea, diarrhea	Patient interview	Typically transient
	Headache	Patient interview	Typically transient
	Weight gain	Body weight, BMI, waist circumference	Paroxetine may be more likely to cause weight gain
	Sexual dysfunction	Patient interview	Significant reason for nonadherence
	Hyponatremia	Basic metabolic panel	Monitor at baseline and periodically thereafter. More frequent monitoring required in high-risk groups, especially the elderly (>65 years)
	Thrombocytopenia	Complete blood count	Reported with citalopram
	Teratogenicity	Pregnancy test at baseline	Avoid paroxetine in pregnancy; Pregnancy Category D
	QT prolongation	ECG	Before starting citalopram, consider ECG and measurement of QT interval in patients with cardiac disease
	Discontinuation syndrome	Patient interview	Avoid abrupt discontinuation in all but fluoxetine
SNRIs			
	Jitteriness syndrome	Patient interview	
	Suicidality	Patient interview	Monitor weekly in first few weeks in patients with comorbid depression and patients under age 25
	Nausea, diarrhea	Patient interview	Typically transient
	Headache	Patient interview	Typically transient
	Elevated blood pressure	Blood pressure	Monitor blood pressure on initiation and regularly during treatment
	Sexual dysfunction	Patient interview	Significant reason for nonadherence
	Discontinuation syndrome	Patient interview	Avoid abrupt discontinuation
TCAs			
	Jitteriness syndrome	Patient interview	
	Suicidality	Patient interview	Monitor weekly in first few weeks in patients with comorbid depression and patients under age 25
	Anticholinergic effects	Patient interview	Contraindicated with narrow-angle glaucoma, prostatic hypertrophy, and urinary retention
	Weight gain	Body weight, BMI, waist circumference	
	Sexual dysfunction	Patient interview	Significant reason for nonadherence
	Sedation	Patient interview	Administer dosage at bedtime when feasible
	Arrhythmia	ECG	At baseline and periodically in children and patients >40 years of age
	Orthostatic hypotension	Blood pressure with position changes	
	Cholinergic rebound	Patient interview	Avoid abrupt discontinuation; taper doses
Benzodiazepines			
	Drowsiness, fatigue	Patient interview	Avoid operating large machinery; tolerance to sedation develops after repeated dosing
	Anterograde amnesia and memory impairment	Patient interview	Risk of anterograde amnesia is worsened with concomitant intake of alcohol
	Dependence	Patient interview; Prescription Monitoring Program	Monitor for early refills or escalation of dosage
	Withdrawal symptoms	Physical examination; patient interview	Taper doses on discontinuation
	Respiratory depression	Respiratory rate	Avoid administering with other CNS depressants (ie, opioids, alcohol)
	Psychomotor impairment	Physical examination	Increased risk of falls
	Paradoxical disinhibition	Physical examination; family report	Increase in anxiety, irritability, or agitation may be seen in the elderly or children
Other Drugs			
Buspirone	Nausea, abdominal pain	Patient interview	Typically transient
	Drowsiness, dizziness	Patient interview	Typically transient
Phenelzine	Jitteriness syndrome	Patient interview	

Medication Class/Drug	Adverse Drug Reaction	Monitoring Parameter	Comments
	Suicidality	Patient interview	Monitor weekly in first few weeks in patients with comorbid depression and patients under age 25
	Hypertensive crisis	Blood pressure	Tyramine-free diet and avoidance of drug interactions required
	Orthostatic hypotension	Blood pressure with position changes	Fasting labs at baseline and then periodically
Pregabalin	Dizziness, somnolence	Patient interview	
	Peripheral edema	Physical examination	
	Thrombocytopenia	Complete blood count	
	Weight gain	Body weight	
Quetiapine	Sedation	Patient interview	
	Metabolic syndrome	Body weight, BMI, waist circumference, fasting lipids and glucose	Fasting labs at baseline and then periodically
	Akathisia	Patient interview	
	Tardive dyskinesia	Abnormal Involuntary Movement Scale	
	Orthostatic hypotension	Blood pressure with position changes	

BMI, body mass index; ECG, electrocardiogram; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

Dosing and Administration The antidepressants can be dosed once a day (see Table 87-5). Importantly, some patients require small initial daily doses for the first week or so of therapy to limit the development of transient increased anxiety, also known as jitteriness syndrome. The dose should then be slowly titrated to effect in order to reduce the occurrence of this excess anxiety. Patient education on this particular point in starting medications is critical to assure medication adherence, as this increase in anxiety will dissipate with time and a slow titration regimen.

Benzodiazepine Therapy

Although all benzodiazepines possess anxiolytic properties, only 7 of the 14 currently marketed agents have FDA approval for the treatment of GAD (see Table 87-4) as estazolam, flurazepam, temazepam, quazepam, and triazolam are marketed as sedative–hypnotic agents. Clonazepam is marketed as an antipanic

agent and anticonvulsant,[39] and midazolam is labeled for preoperative sedation. Alprazolam is indicated for the treatment of panic disorder with or without agoraphobia, as well as GAD.[40] Clobazam is indicated for adjunctive treatment of seizures in Lennox–Gastaut syndrome.[27]

Pharmacology and Mechanism of Action The GABA-receptor model of anxiety theorizes that benzodiazepines ameliorate anxiety through potentiation of the inhibitory activity of GABA.[41] Pharmacologically benzodiazepines bind on the $GABA_A$ receptor at the α_1, α_2, α_3, and α_5 subunits in combination with a β subunit and the γ_2 subunit.[42] The anxiolytic effects of benzodiazepines are mediated at the α_2 site, while sedative effects result from binding at the α_1 subunit. The binding sites of GABA and benzodiazepines are at the receptor interfaces of α/β and α/γ_2, respectively. The GABA receptor controls tonic inhibition to reduce neuronal excitability[41]; however other neurotransmitters (eg, 5-HT, NE, and DA) may also be involved in benzodiazepine activity.

Pharmacokinetics Wide differences in milligram potency exist between the benzodiazepine compounds; however, when appropriately dosed, all agents have similar anxiolytic and sedative–hypnotic activity. The variations in lipid solubility between compounds influence the pharmacokinetic properties of benzodiazepines. Knowledge of the different pharmacokinetic and pharmacodynamic properties can assist in choosing an appropriate anxiolytic (**Table 87-7**). After a single dose, the onset, intensity, and duration of pharmacologic effects are important factors to consider when using benzodiazepines for the short-term, intermittent, or as-needed treatment of anxiety. Knowledge of a medication's pharmacokinetic properties, along with specific factors such as metabolic pathways (including active metabolites), lipophilicity, and protein binding can aid in selecting therapy.

TABLE 87-7 Pharmacokinetics of Benzodiazepine Antianxiety Agents

Drug	Time to Peak Plasma Level (Hours)	Elimination Half-Life, Parent (Hours)	Metabolic Pathway	Clinically Significant Metabolites	Protein Binding (%)
Alprazolam	1–2	12–15	Oxidation	—	80
Chlordiazepoxide	1–4	5–30	*N*-Dealkylation	Desmethyl chlordiazepoxide	96
			Oxidation	Demoxepam	
				DMDZ1	
Clonazepam	1–4	30–40	Nitroreduction	—	85
Clorazepate	1–2	Prodrug	Oxidation	DMDZ	97
Diazepam	0.5–2	20–80	Oxidation	DMDZ	98
				Oxazepam	
Lorazepam	2–4	10–20	Conjugation	—	85
Oxazepam	2–4	5–20	Conjugation	—	97

[1]Desmethyldiazepam (DMDZ) half-life 50–100 hours.

Data from References 27 and 42.

The primary determinant of a drug's onset of effect after a single oral dose is the rate of drug absorption. Because of high lipophilicity, diazepam and clorazepate are absorbed rapidly and distributed quickly into the CNS. Therefore, the onset of anxiolytic effect occurs within 30 to 60 minutes, which results in a rapid and intense relief of anxiety. High lipophilicity also increases the extent of drug redistribution into the periphery, particularly adipose tissue, resulting in a shorter duration of effect after a single dose than is suggested by single-dose elimination half-life studies.[42] Clinically, patients can perceive a rapid onset of action, or "rush," which can be euphoric and contribute to misuse, while others may experience an unpleasant feeling of drowsiness or loss of control.

Compared with diazepam, lorazepam and oxazepam are relatively less lipophilic and have a slower absorption and onset of effect. These benzodiazepines have smaller volumes of distribution and a resulting longer duration of action.[42]

Parenteral administration via the intramuscular route should be avoided with diazepam secondary to variability in the rate and extent of drug absorption. Intramuscular lorazepam provides rapid, reliable, and complete absorption.

After multiple dosing, the rate and extent of drug accumulation are functions of the drug's elimination half-life in relation to dosing intervals, clearance, and formation of active metabolites. Differences in clinical effects that occur during and after repeated dosages with the benzodiazepines are related in part to

variability in metabolism and metabolite accumulation.[42]

The benzodiazepines undergo two primary metabolic processes, hepatic oxidation (catalyzed by mainly cytochrome P450 [CYP] 3A4/5, as well as CYP2C19) and glucuronide conjugation. With the exception of lorazepam and oxazepam (which are conjugated only) and clonazepam (which undergoes nitroreduction through N-acetyltransferase-2 [NAT2]), all benzodiazepines are oxidized first and then conjugated and excreted renally.[43] Diazepam's metabolism specifically is also catalyzed by CYP2C19. Oxidation can be impaired in patients with liver disease, in the elderly, and in those who simultaneously use drugs that inhibit oxidation resulting in higher levels of the parent drug and/or an active metabolite.

Many benzodiazepines are converted to desmethyldiazepam (DMDZ), an active metabolite with a long elimination half-life (see Table 87-7) which is further oxidized to oxazepam and then conjugated and excreted. After multiple dosing, accumulation of DMDZ occurs, therapeutically providing a long-lasting antianxiety effect. Furthermore, if oxidation of DMDZ is impaired, its half-life is prolonged, and further drug accumulation can result with repeated dosing.

Clorazepate is a prodrug and possesses no anxiolytic effects until metabolized to DMDZ. Before absorption, clorazepate is metabolized rapidly in the stomach through a pH-dependent process under acidic conditions.

Benzodiazepines with shorter half-lives (eg, alprazolam, lorazepam, and oxazepam) reach steady-state plasma concentrations rapidly, and drug accumulation after repeated dosing is minimal. Oxazepam and lorazepam have no active metabolites.

Benzodiazepine protein binding is extensive, especially for the drugs with a long elimination half-life. After a single dose of a benzodiazepine with a long elimination half-life, the expected duration of clinical activity may not parallel the drug's pharmacokinetic half-life because of drug redistribution.[42] After multiple dosing, drugs with long elimination half-lives and active metabolites require 1 to 2 weeks to reach steady state.

Efficacy Clinical trials of benzodiazepines show that 65% to 75% of patients with GAD have a marked to moderate response, with most of the improvement occurring in the first 2 weeks of therapy.[21,22] Benzodiazepines are more effective on the somatic symptoms of anxiety and fail to obviate the cognitive or psychic symptoms (eg, worry) as mentioned previously.

Adverse Effects The most common adverse events associated with benzodiazepine therapy involve CNS depression (see Table 87-6). This is

manifested clinically as drowsiness, sedation, psychomotor impairment, and ataxia.[44] A transient mild drowsiness is experienced commonly by patients during the first few days of treatment; however, tolerance often develops. Disorientation, depression, confusion, irritability, aggression, and excitement are reported.[43]

Impairment of memory and recall also can occur during benzodiazepine treatment. The memory loss induced by the benzodiazepines typically is limited to events occurring after drug ingestion (anterograde amnesia).[43] Anterograde amnesia is secondary to disordered consolidation processes that store information and is not impairment in the perception or retrieval of information.[3] Benzodiazepines with high affinity for binding to the benzodiazepine receptor (eg, alprazolam) appear to possess a higher potential for amnesia.[43]

Misuse, Dependence, Withdrawal, and Tolerance Two serious complications of benzodiazepine therapy are the potential for misuse and development of physical dependence. Benzodiazepine misuse is rare in the general population of users; however, individuals with a history of misuse of multiple substances (eg, alcohol or sedatives) are at the greatest risk for developing a sedative, hypnotic, or anxiolytic use disorder.[43]

Because of the chronicity of illness, persons with GAD and panic disorder are at high risk of developing benzodiazepine dependence. Benzodiazepine dependence is a physiologic phenomenon demonstrated by the appearance of a predictable abstinence syndrome (withdrawal symptoms) on abrupt discontinuation of therapy.[43,44] Withdrawal symptoms can result because of the sudden dissociation of a benzodiazepine from its receptor site. After abrupt discontinuation, an acute decrease in GABA neurotransmission results, producing a less inhibited CNS.

Benzodiazepine Discontinuation After benzodiazepine therapy is discontinued suddenly, several events can occur. Rebound anxiety represents an immediate, but transient return of original symptoms, at an increased intensity compared with baseline. In contrast, anxiety recurrence or relapse is the return of original symptoms with similar intensity as before treatment.

Withdrawal symptoms are the emergence of new symptoms and a worsening of pre-existing symptoms after benzodiazepine discontinuation. Symptoms can persist for days to weeks and resolve gradually over months. In some patients it may be difficult to distinguish the occurrence of benzodiazepine withdrawal or rebound symptoms from the recurrence, or relapse of the underlying anxiety disorder.

Common symptoms of benzodiazepine withdrawal include anxiety, insomnia, restlessness, muscle tension, and irritability. Less frequently occurring symptoms are nausea, malaise, coryza, blurred vision, diaphoresis, nightmares, depression, hyperreflexia, and ataxia. Tinnitus, confusion, paranoid delusions, hallucinations, and seizures occur rarely. Withdrawal seizures typically occur approximately 1 week after discontinuation for agents with a long elimination half-life. For agents with a short elimination half-life, withdrawal seizures can occur with both therapeutic and high doses of benzodiazepines use and usually sooner, within 3 days of drug discontinuation. Each patient who has abruptly stopped a benzodiazepine or has experienced seizures should be individually approached because high benzodiazepine doses, a long duration of therapy, and concurrent ingestion of drugs that lower the seizure threshold are all risk factors.

Furthermore, similar to withdrawal seizures, the onset of generalized withdrawal symptoms in patients ingesting benzodiazepines with short elimination half-lives occurs much earlier (within 24–48 hours) than in those taking benzodiazepines with long elimination half-lives (within 3–8 days). Other factors associated with an increased incidence and severity of benzodiazepine withdrawal include high doses and long-term benzodiazepine therapy.[43,44]

A strategy to minimize the severity of benzodiazepine withdrawal is a 25% per week reduction in dosage if therapy exceeds 8 weeks.[44] The rate can be decreased to 25% every 2 weeks if withdrawal symptoms emerge near the end of the dosage taper. Long-term use of benzodiazepines (ie, 1 year or longer) requires a 2- to 4-month slow taper. Tapering will not eliminate the emergence of withdrawal symptoms entirely but will prevent severe withdrawal. Slow drug taper is extremely important for the drugs with a short elimination half-life because some individuals have greater difficulty with discontinuation. Withdrawal symptoms with short half-life benzodiazepines were no more severe than with longer half-life agents; therefore, switching from a short- to long-acting benzodiazepine before gradual taper is not supported. Adjunctive use of pregabalin can help reduce withdrawal severity during the benzodiazepine taper.[45] A combination of psychotherapy interventions (including CBT) with tapering protocols resulted in superior discontinuation outcomes.[46] Patients should avoid the intake of alcohol and stimulants during the withdrawal process. Although tolerance develops to the sedative, muscle relaxant, and anticonvulsant activities, the benzodiazepines do not appear to lose anxiolytic or antipanic efficacy. However, the anxiolytic efficacy of benzodiazepines in long-term clinical trials (greater than 6–8 months of chronic use) has not been documented.[3,21,22]

Drug Interactions Drug interactions with the benzodiazepines generally fall into two categories: pharmacodynamic and pharmacokinetic. Simultaneous use of alcohol and a benzodiazepine results in additive CNS depressant effects. In addition, concurrent use of a benzodiazepine and other drugs with CNS depressant properties (eg, opioids, antipsychotics, and antihistamines) can potentiate the adverse sedative effects. When ingested alone in an overdose attempt, benzodiazepines are rarely life-threatening; however, the combination of benzodiazepines with alcohol or other CNS depressant agents is potentially fatal.

Concurrent use of medications that inhibit CYP3A4 (eg, ketoconazole, nefazodone, and ritonavir) can increase the blood levels of alprazolam and diazepam. Drugs that induce cytochrome CYP3A4 (eg, carbamazepine, St. John's wort) can reduce benzodiazepine levels. Drugs that inhibit or induce CYP2C19 (eg, fluoxetine, fluvoxamine, omeprazole) or *N*-acetyltransferase 2 activity can alter diazepam and clonazepam metabolism, respectively. Consult a drug interaction website (http://www.factsandcomparisons.com/facts-comparisons-online.aspx) for further information.

Dosing and Administration Benzodiazepine dosage requirements vary widely among patients and must be individualized. Therapy should be initiated using low doses (eg, alprazolam 0.25 mg three times a day or equivalent doses of other benzodiazepines) and titrated upward to relieve anxiety symptoms and avoid adverse events. After an initial treatment response is achieved, agents with long elimination half-lives can be dosed at bedtime. Dosage adjustments should be made weekly. Three to 4 weeks of a daily dose at the maximum dose constitutes an adequate clinical trial (see Table 87-4).[2,21,22]

The duration of benzodiazepine therapy for the acute management of anxiety should be limited to 2 to 4 weeks. In general, benzodiazepines should be used with a regular dosing regimen and not on an as-needed basis when used for the treatment of an anxiety disorder.[3] Only in the treatment of short-term distress (eg, air travel, dental phobia) as-needed use may be justified.[3] Individuals with persistent symptoms should be managed with antidepressants because of the risk of dependence with continued benzodiazepine therapy.

Patient education should include the anticipated length of drug therapy, potential side effects, and consequences of the ingestion of alcohol and other CNS depressants. Patients should understand that benzodiazepines provide symptomatic relief but do not solve underlying psychological problems. Patients should be instructed not to decrease or discontinue benzodiazepine usage without contacting their prescriber.

Buspirone Therapy

Buspirone is a nonbenzodiazepine anxiolytic that lacks anticonvulsant, muscle relaxant, hypnotic, motor impairment, and dependence properties. It is considered to be a second-line agent for GAD because of inconsistent reports of efficacy (particularly long term), delayed onset of effect (ie, 2 weeks or longer), and lack of efficacy for other potential, concurrent, depressive, and anxiety disorders.[2] Unlike benzodiazepines, buspirone is effective for the psychic symptoms of anxiety.[2]

Pharmacology and Mechanism of Action Buspirone's anxiolytic mechanism of action is unknown. It is thought to exert its anxiolytic effect through partial agonist activity at the 5-HT_{1A} presynaptic receptors, thus reducing the firing of 5-HT neurons.[42]

Pharmacokinetics After an oral dose, buspirone is absorbed rapidly and completely, and undergoes extensive first-pass metabolism. The mean elimination half-life is 2.5 hours, and it must be dosed two to three times daily, which adversely affects adherence to the drug regimen.[42]

Adverse Effects Adverse events include dizziness, nausea, and headaches[42] (see Table 87-6).

Drug Interactions Drugs that inhibit CYP3A4 (eg, verapamil, itraconazole, fluvoxamine) can increase buspirone levels and rifampin caused a 10-fold reduction in buspirone levels. Buspirone reportedly elevates blood pressure in patients taking a monoamine oxidase inhibitor (MAOI).

Dosing and Administration The dose of buspirone can be titrated in increments of 5 mg/day every 2 to 3 days as needed.[42] The onset of improvement in psychic symptoms precedes the relief of somatic symptoms; maximum therapeutic benefit might not be evident for 4 to 6 weeks.

Buspirone is a treatment option for patients with GAD, particularly for those with uncomplicated GAD, in patients who fail other anxiolytic therapies, or in patients with substance use disorders. It is not useful in clinical situations requiring immediate anxiolysis or for situations requiring as-needed anxiolytic therapy.[42] Evidence suggests that buspirone may have less efficacy in patients who have previously used benzodiazepines, as it does not provide the same rapid relief of symptoms.[2]

Alternative Drug Treatments

Hydroxyzine, pregabalin, and atypical antipsychotics are alternative treatments in GAD.[22,28] The effectiveness of hydroxyzine as an antianxiety agent for long-term use (ie, more than 4 months) has not been assessed by systematic clinical studies.[35] Hydroxyzine is commonly used in the primary care setting, but it is considered to be a second-line agent because of adverse effects and lack of efficacy for comorbid disorders.[3] Pregabalin binds to the $\alpha_2\delta$ subunit of voltage-gated calcium channels to reduce nerve terminal calcium influx and acts on "hyperexcited" neurons. The anxiolytic effects produced by pregabalin compare to lorazepam and alprazolam with fewer dropouts in acute efficacy trials.[24] Quetiapine extended-release 150 mg/day monotherapy was superior to placebo in three studies and was as effective as paroxetine 20 mg/day and escitalopram 10 mg/day but with an earlier onset of action.[28] In a 52-week treatment of GAD, quetiapine extended-release was superior to placebo in the prevention of anxiety relapse.[28] Notably, quetiapine is not FDA-approved for GAD, and the long-term risks and benefits of atypical antipsychotics in the treatment of GAD are unclear.[28] Despite some evidence of efficacy, support for the use of kava kava for GAD has been blunted by ongoing safety concerns following numerous reports of liver toxicity.[47] Although valerian, St. John's wort, and passionflower have been used to manage GAD, there is insufficient evidence of their effectiveness and safety.[47]

Special Populations

The management of anxiety in patients with substance use disorders, pregnant women, children, elderly patients, and those patients with adherence problems requires special consideration in the choice of anxiolytic. Patients with GAD may misuse alcohol, cannabis, or other substances to manage anxiety. The symptoms of GAD are similar to those of withdrawal, and it is difficult to confirm the diagnosis of GAD until after abstinence is obtained; therefore, benzodiazepine therapy should be avoided in this population if possible.

Pregnancy There is evidence that maternal anxiety during pregnancy and the postpartum period potentially pose significant risk to the child. Clinical practice guidelines for anxiety disorders recommend use of fluoxetine, sertraline, or citalopram; however, jitteriness, myoclonus, and irritability in the neonate and premature infant have been reported.[48] Paroxetine should be avoided in pregnant women because of risk of cardiovascular malformations.[31]

Cleft lip, cleft palate, and other teratogenic effects are associated with benzodiazepine use, but a causal relationship is inconclusive. Clinicians should avoid benzodiazepine use during the first trimester or using the agent as monotherapy. In addition, efforts should be made to use the lowest dosage for the shortest period of time and divide the total daily dosage into two or three doses to prevent high peak plasma levels.[48] Benzodiazepine risks for the child during the third trimester include sedation, withdrawal symptoms, and "floppy baby syndrome" (eg, hypotonia, low Apgar scores, hypothermia). Alprazolam should be avoided during pregnancy because of neonatal withdrawal. Should benzodiazepines be required during pregnancy, the preferred agents are diazepam and chlordiazepoxide[49]; however the antidepressants are favored for GAD during pregnancy based on safety considerations. Diazepam and clonazepam should not be used in nursing mothers because infants can experience sedation, lethargy, and weight loss.[49]

Children and Adolescents There are few controlled clinical trials of drugs in children and adolescents with GAD. It is known that use of CBT alone or in conjunction with antidepressants can have long-term benefits.[50] Randomized controlled trials of fluvoxamine, fluoxetine, sertraline, duloxetine, and venlafaxine extended-release indicate short-term efficacy[50]; however, irritability and oppositional behavior was reported with clonazepam.[50] No antidepressant is FDA-indicated for GAD in children or adolescents. Increased monitoring for behavioral changes with benzodiazepines and suicide-related adverse effects with antidepressants is necessary if these agents are prescribed.

Hepatic Disease and Elderly Patients Patients with hepatic disease are at risk for drug accumulation and subsequent complications. In particular, duloxetine use should be avoided in patients with hepatic insufficiency.[29] Drug accumulation of benzodiazepines can result in the elderly secondary to a decreased capacity for oxidation and alterations in the volume of distribution. Therefore, intermediate- or short-acting benzodiazepines without active metabolites are preferred for chronic use. Elderly patients are also sensitive to the CNS adverse effects of benzodiazepines (regardless of half-life), and their use is associated with a high frequency of falls and hip fractures. Recent studies of buspirone, duloxetine, escitalopram, sertraline, venlafaxine, and pregabalin showed efficacy in elderly patients with GAD.[2,51,52]

EVALUATION OF THERAPEUTIC OUTCOMES

Initially, anxious patients should be monitored once every 2 weeks for a reduction in the frequency, duration, and severity of anxiety symptoms and improvement in functioning.[2] The clinician should assess the patient for response to treatment by asking about specific target symptoms of anxiety and emergence of adverse events. Ideally, the patient should have no or minimal anxiety or depressive symptoms and no functional impairment. Use of an objective measurement of remission of GAD (eg, Hamilton Rating Scale for Anxiety score less than or equal to 7 and a Sheehan Disability Scale score less than or equal to 1 on each item) can assist in the evaluation of drug response.[2] The Generalized Anxiety Disorder 7-Item Scale is a patient-rated scale that can be used for screening and monitoring improvement of symptoms.[23] The definition of treatment resistance is defined as a poor, partial, or lack of response with at least two antidepressants from different classes. Treatment strategies for patients who do not achieve an appropriate response with a first-line agent include increasing the dose of the SSRI/SNRI, changing to a different agent in the same class, changing to a different agent from a different class, or augmentation of therapy. At any point of nonresponse or loss of previous response, the clinician should assess for (a) symptoms (eg, psychotic symptoms) that may suggest a need for additional medications or (b) reasons for treatment nonadherence (eg, adverse effects, cost of medications, limited understanding of the illness or treatments). Patients should also be assessed for concurrent substance use disorder, concurrent illnesses, and suicidal thoughts. Once a patient has responded to pharmacotherapy, the regimen should be continued for at least 1 year.[21,36] Early discontinuation is associated with a greater risk of relapse.[21]

TREATMENT

Panic Disorder

Desired Outcomes

The goal of therapy in panic disorder is remission. Patients should be free of panic attacks, have no or minimal anticipatory anxiety and agoraphobic avoidance, and have no functional impairment.[20]

General Approach

Therapeutic options include single or combined pharmacologic agents, concurrent psychotherapy, or psychotherapy followed by pharmacotherapy. Most patients without agoraphobic avoidance will improve with pharmacotherapy alone; however, if avoidance is present, CBT typically is initiated concurrently. With all effective drug therapies, resolution of agoraphobic avoidance tends to occur slowly. A meta-analysis comparing the use of SSRIs and venlafaxine in panic disorder showed response to be similar among treatments.[53] Adding psychosocial treatment to pharmacotherapy may improve long-term outcomes by reducing the likelihood of relapse when pharmacotherapy is stopped.[20]

Considerations that guide selection of the treatment modality for panic disorder include patient preference, treatment history, the presence of co-occurring medical or other psychiatric conditions, cost, and treatment availability. Psychosocial treatment in the form of CBT is recommended for patients who prefer nonpharmacologic therapy and who are able to invest the effort and time to attend weekly sessions and between-session homework exercises. Pharmacotherapy with a first-line agent is recommended for patients who prefer medications or who do not have access to or resources to engage in CBT. Combination with psychotherapy and pharmacotherapy is appropriate for patients who have failed monotherapy with medication or CBT.

Providing education about the disorder may relieve some of the symptoms of panic by helping the patient to realize that the symptoms are neither life-threatening nor uncommon. Patients should be informed regarding the lag time before a therapeutic response will occur and any problematic side effects that might affect early adherence (eg, jitteriness syndrome). Many patients are reluctant to take drugs for fear that their illness will worsen or that they will become addicted. Adverse events are often perceived as a worsening of the illness and can contribute to nonadherence or prevent necessary dosage increases. A strong therapeutic alliance between the clinician and the patient is important in supporting the patient through the aspects of the treatment that may provoke anxiety.

Nonpharmacologic Therapy

Patients should be educated to avoid substances that can precipitate panic attacks, including caffeine, nicotine, alcohol, drugs of misuse, and nonprescription stimulants.[1,20] Epidemiologic data suggest that daily smoking increases risk for panic attacks and may be a causal or exacerbating factor in some individuals with panic disorder.[20] Preliminary evidence suggests that

aerobic exercise (eg, walking for 60 minutes or running for 20–30 minutes 4 day/week) may benefit patients with panic disorder.[21] Participation in CBT is associated with short-term improvement in 80% to 90% of patients and 6-month improvement in 75% of patients. A course of CBT for panic disorder is 16 to 20 hours in length conducted over a period of 4 months.[21] Bibliotherapy (the use of self-help books), exercise, and Internet-based CBT are other options.[20]

Pharmacologic Therapy

Panic disorder is treated effectively with several drugs including SSRIs, the SNRI venlafaxine, imipramine, and the benzodiazepines alprazolam and clonazepam[20,21] (**Table 87-8**), with alprazolam, clonazepam, fluoxetine, paroxetine, sertraline, and venlafaxine all approved for this indication. In general, SSRIs are the first-line agents because of their tolerability and efficacy in acute and long-term studies[2,20]; however, the benzodiazepines are the most commonly used drugs for panic disorder.[20] In a meta-analysis of the pharmacotherapy of panic disorder, the following antidepressants were significantly superior to placebo with the following increasing order of effectiveness: citalopram, sertraline, paroxetine, fluoxetine, and venlafaxine for panic symptoms and paroxetine, fluoxetine, fluvoxamine, citalopram, venlafaxine, and mirtazapine for overall anxiety symptoms.[53] Imipramine is effective for panic disorder; however, it is considered to be a second-line agent because of the significant cardiovascular and anticholinergic effects associated with its use. Five practice guidelines are published,[2,3,20–22] and **Fig. 87-2** is an algorithm for the pharmacologic therapy of panic disorder.

TABLE 87-8 Drugs Used in the Treatment of Panic Disorder

Class/Generic Name	Brand Name	Starting Dose	Antipanic Dosage Range (mg)	Comments
SSRIs				
Citalopram	Celexa	10 mg/day	20–40	Dosage used in clinical trials; maximum dose limited by QT prolongation; available generically
Escitalopram	Lexapro	5 mg/day	10–20	Dosage used in clinical trials; available generically
Fluoxetine	Prozac	5 mg/day	10–30	Available generically
Fluvoxamine	Luvox	25 mg/day	100–300	Available generically
Paroxetine	Paxil	10 mg/day	20–60	FDA-approved; available generically
	Pexeva			
	Paxil CR	12.5 mg/day	25–75	
Sertraline	Zoloft	25 mg/day	50–200	FDA-approved; available generically
SNRI				
Venlafaxine XR	Effexor XR	37.5 mg/day	75–225	FDA-approved; available generically
Benzodiazepines				
Alprazolam	Xanax	0.25 mg three times a day	4–10	FDA-approved; available generically
	Xanax XR	0.5–1 mg/day	1–10	
Clonazepam	Klonopin	0.25 mg once or twice per day	1–4	FDA-approved; available generically
Diazepam	Valium	2–5 mg three times a day	5–20	Dosage used in clinical trials; available generically
Lorazepam	Ativan	0.5–1 mg three times a day	2–8	Dosage used in clinical trials; available generically
TCA				
Imipramine	Tofranil	10 mg/day	75–250	Dosage used in clinical trials; available generically
MAOI				
Phenelzine	Nardil	15 mg/day	45–90	Dosage used in clinical trials; available generically

CR, controlled release; MAOI, monoamine oxidase inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRIs, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant; XR, extended release.

Data from References 3, 20, and 54.

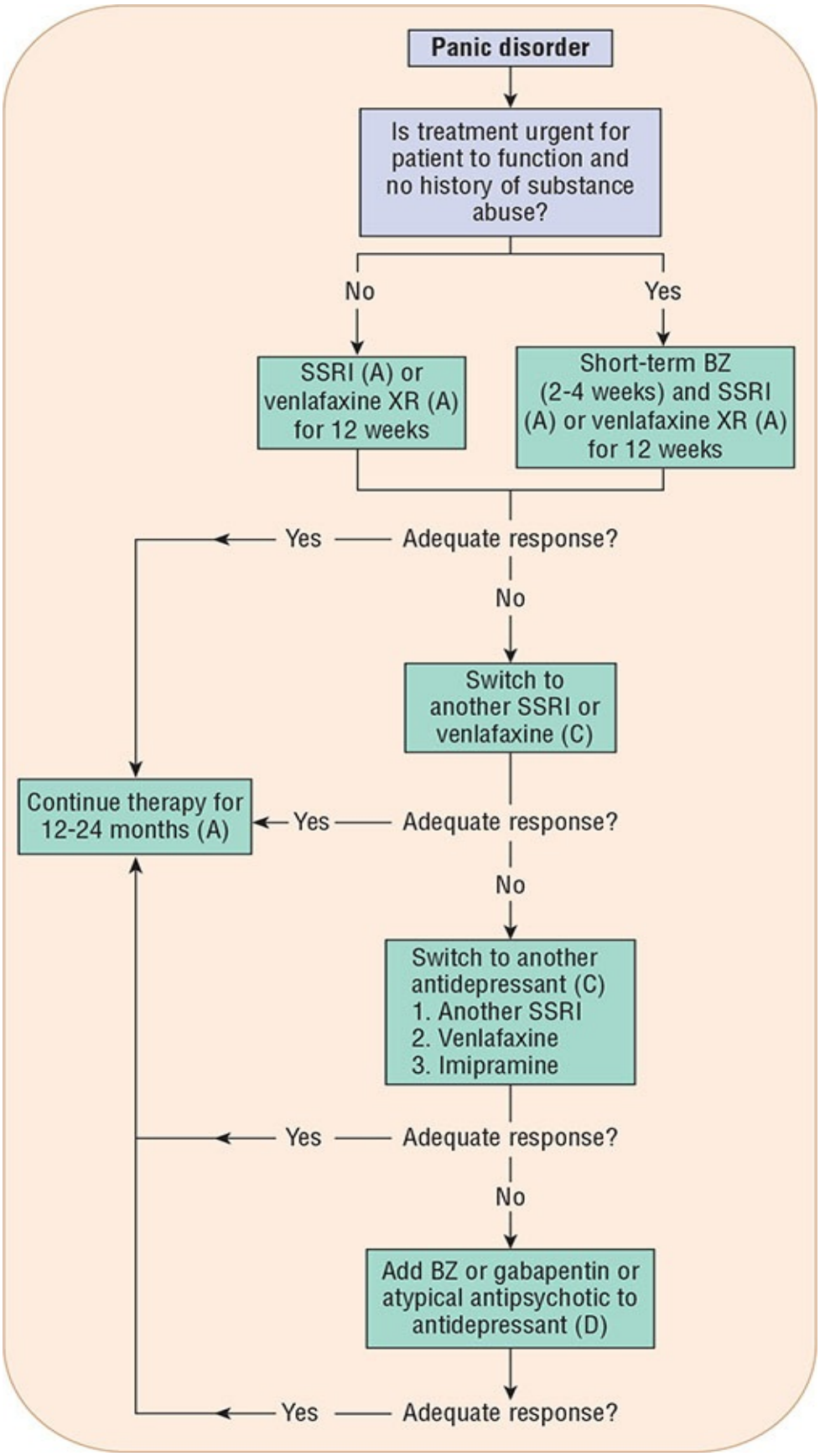

Panic disorder
Is treatment urgent for patient to function and no history of substance abuse?
No
Yes
SSRI (A) or venlafaxine XR (A) for 12 weeks
Short-term BZ (2-4 weeks) and SSRI (A) or venlafaxine XR (A) for 12 weeks
Adequate response?
Yes
No
Switch to another SSRI or venlafaxine (C)
Adequate response?
Yes
Continue therapy for 12-24 months (A)
No
Switch to another antidepressant (C)
1. Another SSRI
2. Venlafaxine
3. Imipramine
Adequate response?
Yes
No
Add BZ or gabapentin or atypical antipsychotic to antidepressant (D)
Adequate response?
Yes

FIGURE 87-2 Algorithm for the pharmacotherapy of panic disorder. Strength of recommendations: A, directly based on category I evidence (ie, meta-analysis of randomized controlled trials [RCT] or at least one RCT); C, directly based on category III evidence (ie, nonexperimental descriptive studies); D, directly based on category IV evidence (ie, expert committee reports or opinions and/or clinical experience of respected authorities). (BZ, benzodiazepine; SSRI, selective serotonin reuptake inhibitor.) (*Adapted from References 20 and 21*.).

Benzodiazepines are considered second-line agents, and because of the risk of dependency should be used only after several trials of antidepressants have failed.[2,20] Additionally because of the potential emergence of depressive symptoms during treatment, benzodiazepines should not be used as monotherapy in a patient who is clinically depressed or has a history of depression. Controlled trials have established that the short-term (4–6 weeks) addition of alprazolam or clonazepam to antidepressants produces a more rapid therapeutic response, with discontinuation of the benzodiazepine by week 7 of therapy.[2] However in patients whose illness is complicated by a history of alcohol or drug misuse, benzodiazepine use should be avoided.[20]

Selective Serotonin Reuptake Inhibitors

Efficacy Clinical studies indicate that all SSRIs are effective in panic disorder.[20] The percentage of patients who become panic-free ranges between 60% and 80%.[20] The antipanic effect of SSRIs is delayed for at least 4 weeks, and some patients do not respond for 8 to 12 weeks.[20]

Adverse Effects Typical antidepressant doses of SSRIs can cause side effects of insomnia, jitteriness, restlessness, and agitation, and lead to drug discontinuation in patients with panic disorder, similar to the effects previously described. Other adverse effects associated with SSRI use in panic disorder are listed in Table 87-6.

Dosing and Administration Low initial doses of SSRIs are recommended (see Table 87-8) to avoid stimulatory side effects (eg, insomnia or nervousness), and should be maintained for the first week of therapy. However, doses at the upper end of the dosing range can be necessary to achieve response after careful titration.[21,54]

Serotonin–Norepinephrine Reuptake Inhibitors

Efficacy Venlafaxine extended-release 75 to 150 mg/day is superior to placebo in the proportion of patients becoming free from full-symptom panic attacks. Other data support the efficacy of venlafaxine in reducing the severity of anticipatory anxiety, fear, and avoidance.[54] Venlafaxine is similar in efficacy to paroxetine in patients with panic disorder and superior to placebo in a relapse prevention study.[54]

Adverse Effects The most common adverse effects of venlafaxine extended-release in clinical trials of panic disorder were nausea, dry mouth, constipation, anorexia, insomnia, somnolence, tremors, sweating, and sexual dysfunction.[20]

Dosing and Administration The dosage of venlafaxine extended-release is 37.5 mg/day for the first 3 to 7 days, and then increased to a minimum of 75 mg/day (Table 87-8). Increasing the dose to 150 mg/day after initial nonresponse or partial response is recommended. A dose–response relationship was not evident in clinical trials.[32]

Tricyclic Antidepressants

Efficacy Imipramine is the most studied TCA, alleviating panic attacks in 75% of patients with panic disorder. Imipramine effectively blocks panic attacks within at least 4 weeks. However, maximal improvement (including antiphobic response) does not occur until 8 to 12 weeks.[20]

Adverse Effects The adverse effects of medications used to treat panic disorder are found in Table 87-6. Up to 40% of patients experience stimulant-like effects, including anxiety, insomnia, and jitteriness.[20] These adverse effects often affect patient adherence, prevent medication dosage increases, and interfere with the overall treatment outcome.

Other problems with TCA use in panic disorder are well documented and include anticholinergic effects, orthostatic hypotension, delayed onset of antipanic effects, and toxicity in overdose.[20] Approximately 25% of patients reportedly discontinue treatment because of side effects, especially weight gain.[20]

Dosing and Administration When using imipramine, treatment should be slowly increased by 10 mg every 2 to 4 days as tolerated (Table 87-8).

Benzodiazepines

Efficacy The high-potency benzodiazepines clonazepam and alprazolam are the

preferred agents for the treatment of panic disorder.[20,21] Alprazolam provides rapid relief for patients in distress, but because of its short half-life, multiple daily dosing is required and often results in profound withdrawal symptoms with missed doses.[20] Additionally diazepam and lorazepam, when taken in sufficiently high doses, are possibly effective in treating panic disorder.[20] Therapeutic response to benzodiazepines occurs in 1 to 2 weeks and relapse rates of 50% or higher are common despite slow drug tapering during discontinuation of therapy.[44]

Adverse Effects Patient acceptance of benzodiazepines is usually not a problem, and except for sedation, side effects are rarely reported (see Table 87-6).

Dosing and Administration Doses of clonazepam can be increased by 0.25 or 0.5 mg every 3 days to 4 mg/day if needed,[40] and alprazolam can be slowly increased over several weeks to reach an ideal dose. The duration of action of immediate-release alprazolam can be as little as 4 to 6 hours which may result in breakthrough symptoms; use of the extended-release alprazolam or clonazepam will avoid this problem. Most patients require 3 to 6 mg/day of alprazolam, and some need higher doses to obtain a full therapeutic (antipanic and antiphobic) response.

Alternative Drug Treatments

Buspirone, trazodone, bupropion, antipsychotics, antihistamines, and β-blockers are ineffective in panic disorder.[2,3,20–22] The majority of studies assessing the efficacy of MAOIs in treating panic disorder were open-labeled and lacked adequate sample sizes. Therefore, MAOIs are reserved for the most refractory or difficult patients.[20]

Phases of Therapy

Acute Phase The main goal of therapy in the acute phase is reduction of symptoms (eg, resolution of panic attacks, reduction in anxiety and phobic fears, resumption of the patient's usual activities).[20,22] The duration of this phase is generally 1 to 3 months depending on the choice of drug. Therapy should be altered if there is no response after 6 to 8 weeks of an adequate dose.

The guiding principle for SSRIs and SNRIs in panic disorder is to start with low doses (approximately one-fourth to one-half of the starting doses for depression), use an adequate dose, and treat for about 12 weeks.[20,22] Adverse effects, often from too high an initial dose, can prevent achievement of an

optimal dosage, compromise treatment response, and contribute to patient nonadherence.

The duration of the acute phase with benzodiazepines is approximately 1 month because response is rapid. A regular dosing schedule rather than an "as-needed" schedule is preferred for patients with panic disorder who are taking benzodiazepines, where the goal is to prevent panic attacks rather than reduce symptoms once an attack has already occurred.[20]

Maintenance Phase and Discontinuation 6 The optimal length of therapy is unknown; however, the total duration of therapy appears to be 12 to 24 months before drug discontinuation over 4 to 6 months is attempted.[20] The dose used in the acute phase is continued into the maintenance phase.[20] When drugs are discontinued too early, a high rate of relapse occurs; thus, longer periods of treatment are associated with a more sustained response. Reinstitution of drug usually results in renewed clinical response.[20] Pharmacotherapy, even of a long duration, might not prevent relapse, and many patients require long-term maintenance therapy.

The most important determinant of adherence with maintenance therapy is the tolerability of adverse events.[20] Some adverse events that are experienced short term become unbearable during long-term management (eg, sexual dysfunction and weight gain). All TCAs, SSRIs (except fluoxetine), and venlafaxine can be associated with discontinuation symptoms.

The primary risk of long-term benzodiazepine use is the development of dependence and withdrawal symptoms upon discontinuation. Abuse of benzodiazepines usually is confined to patients with a personal or family history of substance or alcohol use disorders.[44,45] The approach to benzodiazepine discontinuation involves a slow and gradual tapering of the dose because withdrawal symptoms and rebound anxiety may occur during discontinuation. Benzodiazepines should be tapered very slowly in patients with panic disorder over 2 to 4 months at rates no higher than 10% of the dose per week.[20,44] Patients receiving benzodiazepines and antidepressants should be told not to decrease or discontinue therapy unless authorized by their clinician.[20]

Treatment Resistance

Common reasons for treatment failures are comorbid psychiatric disorders, rapid dosage increases with resulting intolerable side effects, and underdosage.[20] All standard treatments should be tried before using augmentation strategies. In

patients with a partial response to one agent, a low dose of another antipanic agent (eg, a TCA, benzodiazepine, or an SSRI) can be added.[20]

Special Populations

Elderly patients with panic disorder have fewer, less intense symptoms and avoidant behavior than younger patients.[20] Youth often present with fear that they are dying or being smothered, and agoraphobia can be manifested as a fear of leaving home.[1] Overall, CBT is effective in both populations. If pharmacotherapy is used, antidepressants, especially the SSRIs, are preferred for management of panic disorder, and benzodiazepines are second-line agents because of potential problems with disinhibition in these two populations. Limited data suggest that the course of panic disorder is highly variable during pregnancy and the postpartum period. It is unclear whether uncontrolled symptoms of panic disorder affect the course or outcome of pregnancy.[20] Little evidence exists on the use of psychosocial interventions for women with panic disorder who are pregnant, breast-feeding, or planning to become pregnant. Nonpharmacologic interventions should be considered as first-line treatment in these patients. Pharmacotherapy may also be indicated but requires careful evaluation of the potential benefits and risks.[20]

EVALUATION OF THERAPEUTIC OUTCOMES

During the first few weeks of the acute phase of therapy, patients with panic disorder should be seen every 1 to 2 weeks when starting a new medication, and then every 2 to 4 weeks to adjust drug dosages based on improvement in panic symptoms and to monitor for adverse events.[20,21] After the dose is stabilized and symptoms have decreased, visits every 2 months should suffice.[22] The patient should be counseled to maintain a diary to record the date, time, frequency, duration, and intensity of panic episodes, level of anticipatory anxiety or agoraphobic avoidance, and the severity of distress and impairment related to the panic disorder. Treatment outcomes can be assessed objectively by use of the Panic Disorder Severity Scale. Remission is defined as equal to or less than 3 with no or mild agoraphobic avoidance, anxiety, disability, or depressive symptoms. Treatment response is indicated by a 40% or greater reduction in overall score.[2]

At scheduled visits, the clinician can inquire about the level of disability experienced by the patient and have the patient complete the Sheehan Disability

Scale (with a goal of less than or equal to 1 point on each item). During drug discontinuation, the frequency of appointments should be increased to evaluate for emergence of potential withdrawal symptoms and monitor for relapse.

TREATMENT

Social Anxiety Disorder

Desired Outcomes

The goals of therapy in the acute phase of treatment are to reduce physiologic symptoms of anxiety (eg, tachycardia, flushing, and sweating), social anxiety, and phobic avoidance. The duration of this phase is 4 to 12 weeks, depending on the drug therapy.

The goals of therapy in the continuation phase (3–6 months) are to extend the therapeutic benefits, especially the patient's ability to participate in social activities, and improve quality of life (QOL). Although the primary goal of treatment is to reduce anxiety symptoms to manageable levels, even modest reductions in avoidance and discomfort can be highly valued by patients.[18]

7 At least a 6- to 12-month medication maintenance period is recommended to maintain improvement and decrease the rate of relapse.[2,3,22] Situations suggesting a possible need for long-term treatment include the presence of unresolved symptoms or comorbidity, an early onset of disease, and a prior history of relapse.[18] The long-term goal in the treatment of SAD is remission with the disappearance of the core symptoms of social anxiety, little or no anxiety, and no functional impairment or concurrent depressive symptoms.[18,57]

General Approach

Patients with SAD should be identified early and treated aggressively.[19] Obstacles to effective treatment include patient avoidance of therapy secondary to fear and shame, treatment directed toward somatic symptoms or concurrent conditions, and financial barriers.[19] Patients with SAD often respond more slowly and less completely than patients with other anxiety disorders. Therefore, it is important to set reasonable expectations for response to therapy. Consideration of current symptoms, prior treatments, concurrent conditions, and history of substance abuse guides treatment selection.

Both CBT and pharmacotherapy are effective in the treatment of

SAD.[2,18,56,58] Pharmacotherapy is often the most practical choice because CBT might not be available in medically underserved areas. Acute treatment outcomes for CBT and pharmacotherapy are equivalent.[2,3,18] Drug therapy is superior in reducing subjective general anxiety acutely, although CBT has a greater likelihood of maintaining response after termination.[18,57,58]

There are no data to predict which patients will respond best to pharmacotherapy, CBT, or a combination, or maintain gains after discontinuing pharmacotherapy. The only significant indication of treatment response in pharmacotherapy is duration of treatment.[56–59] Some patients elect lifelong therapy, and many are reluctant to attempt drug discontinuation because of fear of relapse.

Despite the availability of effective treatments for social anxiety, most adults in the United States with social anxiety do not receive mental healthcare for their symptoms. Often the symptoms that patients desire to relieve interfere with the ability to seek treatment. Patients often feel embarrassed of what others might think or say about them. It is important to develop an alliance with the patient and offer reassurance throughout the treatment process.

Certain complications may influence the choice of first-line pharmacotherapy. Comorbid depression or suicidal ideation requires careful evaluation and close monitoring. Patients with comorbid substance abuse on presentation may require postponing pharmacotherapy until after detoxification and avoidance of use of benzodiazepines as part of treatment.

Patient-specific education about treatment is important. Patients should be instructed about the gradual onset of effect, when to expect full therapeutic benefit, and that long-term therapy is required. When drug therapy is discontinued, the dosage needs to be gradually decreased over several months, and the patient should be seen more frequently to monitor for signs and symptoms of relapse or withdrawal.

It is important to remember that although pharmacotherapy usually leads to improvement in social and occupational functioning, most patients do not achieve a full remission. Many patients require additional treatment, often in the form of CBT.

Nonpharmacologic Therapy

Patients should be educated about SAD and support groups. Self-help group programs that focus on effective communication can benefit people with anxiety involving public speaking.

In general, CBT consists of exposure therapy, cognitive restructuring, relaxation training techniques, and social skills training.[2,3,18,22,58] Through CBT, patients learn to overcome anxiety in social situations and alter the beliefs and responses that maintain this anxiety, with therapy usually lasting several months and is often conducted in groups.[18,58]

Pharmacologic Therapy

Antidepressant Therapy

8 The SSRIs and venlafaxine are beneficial for patients with concurrent depression and are safe when used in patients with a substance use disorder. Paroxetine, sertraline, fluvoxamine extended-release, and venlafaxine extended-release are approved for the treatment of SAD and are considered first-line agents because of efficacy and tolerability (**Table 87-9**). Controlled trials comparing different SSRIs, or SSRIs and an SNRI, demonstrated equivalent efficacy between agents.[56–58] The TCAs are not effective in SAD.[2,22] Evidence-based guidelines for the treatment of SAD were published by the Canadian Psychiatric Association, World Federation of Societies of Biological Psychiatry, the National Institute for Health and Care Excellence, and the British Association for Psychopharmacology.[2,3,18,22] An algorithm for the pharmacotherapy of SAD appears in **Fig. 87-3**.

TABLE 87-9 Drugs Used in the Treatment of Social Anxiety Disorder

Drug	Brand Name	Initial Dose	Usual Range (mg/day)	Comments
SSRIs				
Citalopram	Celexa	20 mg/day	20–40	Dosage used in clinical trials; maximum dose of 40 mg limited by QT prolongation; available generically
Escitalopram	Lexapro	5 mg/day	10–20	Dosage used in clinical trials; available generically
Fluvoxamine CR	Luvox CR	100 mg	100–300	FDA-approved; available generically
Paroxetine	Paxil	10 mg/day	10–60	FDA-approved; available generically
Paroxetine CR	Paxil CR	12.5 mg/day	12.5–37.5	FDA-approved; available generically
Sertraline	Zoloft	25–50 mg/day	50–200	FDA-approved; available generically
SNRI				
Venlafaxine XR	Effexor XR	75 mg/day	75–225	FDA-approved; available generically
Benzodiazepine				
Clonazepam	Klonopin	0.25 mg/day	1–4	Dosage used in clinical trials; used as augmenting agent; available generically
MAOI				
Phenelzine	Nardil	15 mg at bedtime	60–90	Dosage used in clinical trials; available generically
Alternative Agents				
Buspirone	BuSpar	10 mg twice per day	45–60	Dosage used in clinical trials; used as augmenting agent; available generically
Gabapentin	Neurontin	100 mg three times a day	900–3,600	Dosage used in clinical trials; dosage adjustment required in renal impairment; available generically
Pregabalin	Lyrica	100 mg three times a day	600	Dosage used in clinical trials; dosage adjustment required in renal impairment; available generically
Quetiapine	Seroquel	25 mg at bedtime	25–400	Dosage used in clinical trials; available generically

CR, controlled-release; MAOI, monoamine oxidase inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRIs, selective serotonin reuptake inhibitors; XR, extended-release.

Data from References 2, 3, 22, and 56.

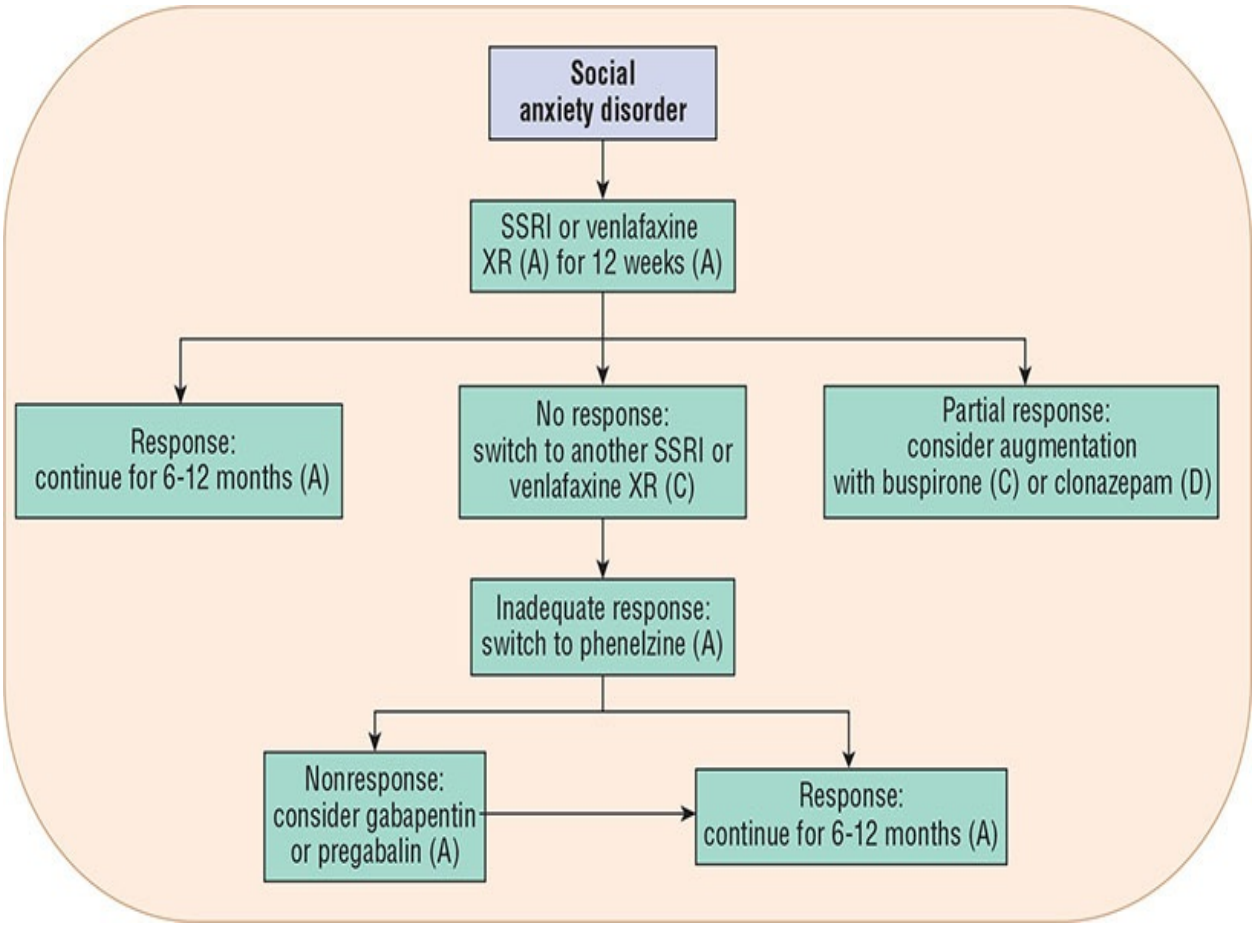


FIGURE 87-3 Algorithm for the pharmacotherapy of social anxiety disorder. Strength of recommendations: A, directly based on category I evidence (ie, meta-analysis of randomized controlled trials [RCT] or at least one RCT); C, directly based on category III evidence (ie, nonexperimental descriptive studies); D, directly based on category IV evidence (ie, expert committee reports or opinions and/or clinical experience of respected authorities). SSRI, selective serotonin reuptake inhibitor. *(Adapted from References 2, 3, 22, and 56.*).

Selective Serotonin Reuptake Inhibitors

Efficacy Large trials of escitalopram, fluvoxamine (immediate- and controlled-release), paroxetine, sertraline, and venlafaxine extended-release have shown efficacy and tolerability. Results of studies with fluoxetine have been inconsistent. The onset of effect with SSRIs is delayed 4 to 8 weeks, and maximum benefit is often not observed until 12 weeks or longer. Large relapse prevention trials with escitalopram, paroxetine, and sertraline demonstrated relapse rates of 4% to 14% with continued drug treatment, compared with 36% to 39% with placebo.[56,58]

Dosing and Administration The SSRIs should be initiated at doses similar to those used for the treatment of depression and administered as a single daily dose (see Table 87-9). If the patient suffers from comorbid panic disorder, the SSRI dose should be started at one-fourth or one-half of the dose. The dose–response curve for SSRIs tends to be relatively flat, but individual patients can require higher doses. Increase the dose as tolerated in patients who have not responded after 4 weeks of therapy.[56–59] When discontinuing an SSRI, the dosage should be tapered monthly (ie, decreasing sertraline by 50 mg or paroxetine by 10 mg) to reduce the risk of relapse and discontinuation symptoms.

Venlafaxine

Efficacy The efficacy of venlafaxine extended-release was established in four double-blind, parallel-group, 12-week, multicenter, placebo-controlled, flexible-dose studies and one double-blind, parallel-group, 6-month, placebo-controlled, fixed/flexible-dose study.[32] Efficacy was assessed with the Liebowitz Social Anxiety Scale (LSAS). In these five trials, venlafaxine extended-release was significantly more effective than placebo on change from baseline to end point on the LSAS total score.[32]

Adverse Effects Adverse effects included anorexia, dry mouth, nausea, insomnia, and sexual dysfunction (see Table 87-6).

Dosing and Administration Additional therapeutic benefits of venlafaxine extended-release above 75 mg/day have not been shown.[32] Venlafaxine should be tapered slowly (ie, decreasing by 37.5 mg/month) to decrease the risk of relapse during discontinuation.

Alternative Agents

Benzodiazepines Benzodiazepines are commonly used in the treatment of patients who cannot tolerate or fail to respond to antidepressants. They are not considered first-line therapy for SAD because of concerns over the adverse effects, potential for dependence, the possibility of rebound anxiety, and ineffectiveness in the treatment of depression. Clonazepam is the most extensively studied benzodiazepine for the treatment of generalized SAD.[56–59]

If clonazepam is prescribed, the acute phase of therapy is about 1 month. Patients should be instructed not to decrease or discontinue clonazepam without consulting their clinician because of the risks of rebound anxiety and withdrawal

symptoms. Clonazepam should be gradually tapered at a rate not to exceed 0.25 mg every 2 weeks.

Anticonvulsants Gabapentin and pregabalin were effective in controlled trials, whereas levetiracetam was ineffective.[56–60]

β-Blockers β-Blockers decrease the perception of anxiety by blunting the peripheral autonomic symptoms of arousal (eg, rapid heart rate, sweating, blushing, and tremor), and they are often used to decrease anxiety in performance-related situations.[56] For patients with performance anxiety, 10 to 80 mg of propranolol or 25 to 100 mg of atenolol can be taken 1 hour before a performance as needed. A test dose should be taken at home before the presentation to assure that β-blockade is sufficient and there are no adverse events. Controlled trials with β-blockers do not support daily use in SAD.[18]

Treatment Resistance

9 An adequate antidepressant trial usually consists of 8 to 12 weeks (at maximum dosages).[56–59] Subsequent options include a trial of a second SSRI or venlafaxine extended-release. Some patients experience clinical benefit during the first 4 weeks of therapy.[56–59] If nonresponsiveness continues, a trial of an alternative agent is warranted.

There are little data on the choice of treatments if there is a partial response to antidepressants therapy in SAD. Published studies offer preliminary support for the combination of an SSRI with a benzodiazepine, gabapentin, or pregabalin.[56–59]

Atypical antipsychotics and MAOIs are options in treatment-resistant SAD. Quetiapine monotherapy showed a large effect size on the Social Phobia Inventory when compared with placebo.[56–59] Although phenelzine is effective in 77% of patients with SAD,[2,18] dietary restrictions, potential drug interactions, and adverse effects (eg, weight gain and hypertensive crisis) have limited its use. If a patient is switched from another antidepressant to phenelzine, an appropriate washout period should be followed. See Chapter 85 for more detail.

Special Populations

SAD can present in children of preschool to elementary school age. If the disorder is not treated, it can persist into adulthood and increase the risk of depression and substance abuse. Both CBT and social skills training are effective nonpharmacologic therapies in children.[56–59] Placebo-controlled and open-label

trials have provided evidence of efficacy of pharmacotherapy with an SSRI or SNRI in children between ages 6 and 17 years.[2,18,56–59] Children and adolescents prescribed an SSRI or SNRI for social anxiety (or for other purposes) should be closely monitored for increased risk of suicidal ideation. Headache, nausea, drowsiness, insomnia, jitteriness, and stomachaches were reported in children receiving antidepressants.[56–59]

Benzodiazepines should be reserved as the last-line agents in children with SAD.[19,52] If prescribed, they should be used for the shortest time period possible. The adverse effects of benzodiazepines in children include drowsiness, oppositional behavior, disinhibition, and fatigue.

Approximately one-fifth of patients with SAD also suffer from an alcohol use disorder as many people with SAD report that they use alcohol to cope with anxiety. Paroxetine significantly reduced social anxiety and the frequency and severity of alcohol use in patients with SAD and an alcohol use disorder.[61] Both MAOIs and benzodiazepines are not appropriate therapy for patients with SAD and alcohol use disorder and SSRIs are the drugs of choice.

EVALUATION OF THERAPEUTIC OUTCOMES

10 The pharmacotherapy of SAD can be monitored in three principal domains: SAD symptoms (eg, fears and physical symptoms), functionality, and well-being or overall improvement.[25,26,59] Response to pharmacotherapy in SAD is defined as a stable, clinically meaningful improvement; where patients no longer have the full range of symptoms but typically continue to experience more than minimal symptoms.[25,26,59]

During the acute phase of treatment, patients should be seen weekly while the drug dosage is titrated. Once the patient responds and the dosage is stabilized, the patient can be seen monthly. Many patients report improvement during the first 4 weeks of therapy, but more than one-quarter of those who do not have a response at week 8 may have a response at 12 weeks. At each visit, the patient should be asked about adverse effects and improvement in symptoms. The patient should be instructed to keep a diary to record fear levels, physical symptoms, cognitions, and anxious behaviors in actual exposures to social situations. The LSAS is a clinician-rated scale of clinical severity and change in SAD for monitoring response.[29] Patients can use the Social Phobia Inventory for self-assessment of SAD symptoms.[29] Full remission is defined as a complete resolution of symptoms across the three SAD domains that is maintained for 3

months or a LSAS score of less than or equal to 30 points.[29]

SPECIFIC PHOBIA

Specific phobia is considered unresponsive to drug therapy, although highly responsive to CBT. The use of benzodiazepines or paroxetine in patients who failed CBT is supported by limited data. Benzodiazepines can be detrimental in patients with specific phobias treated with CBT.[22]

CONCLUSION

Anxiety disorders are common in the population and occur concurrently with other psychiatric disorders. The proper management of anxiety disorders begins with the correct diagnosis as not all patients should receive antianxiety agents. Nonpharmacologic interventions often are effective alone or when combined with drug therapy.

There are several subtypes of anxiety disorders, and the diagnosis determines the type of drug and nonpharmacologic intervention selected. Although benzodiazepines remain the drugs of choice for situational anxiety, antidepressants have emerged as first-line therapy for GAD, panic disorder, and SAD. Benzodiazepines are reserved for use in situations requiring immediate anxiety relief during the first 2 to 4 weeks of therapy with a long-term agent such as an antidepressant. Antidepressants, including the SSRIs and SNRIs, and the benzodiazepines clonazepam and alprazolam are used extensively in patients with GAD, panic disorder, and SAD.

The long-term goal of therapy for GAD, panic disorder, and SAD is remission of core anxiety symptoms with no impairment in functionality, minimal anxiety, and no depressive symptoms. Augmentation with anticonvulsants and atypical antipsychotics shows some promise in treatment-resistant cases.

Postclass Engaged Learning Activity

Read the case “Nervous Neddie” in the *Pharmacotherapy Casebook* located in AccessPharmacy by Sarah Melton and Cynthia Kirkwood. Develop a comprehensive assessment and plan (including monitoring parameters and patient education) that would be used to communicate your recommendations to the interprofessional team. This activity will help you apply the Patient

Care Process to a simulated patient using knowledge gained through preclass and in-class activities. In addition, it will further develop your skillset in conveying nonpharmacologic and pharmacologic recommendations in writing to the interprofessional team.

ABBREVIATIONS

ACC	anterior cingulate cortex
CBT	cognitive behavioral therapy
CNS	central nervous system
CRF	corticotropin-releasing factor
DA	dopamine
DMDZ	desmethyldiazepam
GABA	γ-aminobutyric acid
GAD	generalized anxiety disorder
GI	gastrointestinal
5-HT	serotonin
LC	locus ceruleus
LSAS	Liebowitz Social Anxiety Scale
MAOI	monoamine oxidase inhibitor
NE	norepinephrine
PAG	periaqueductal gray
PHQ-9	Patient Health Questionnaire-9
QOL	quality of life
SAD	social anxiety disorder
SERT	serotonin reuptake transporter
SNRI	serotonin–norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of*

Mental Disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013:189–233.

2. Katzman MA, Bleau P, Blier P, et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry*. 2014;14(suppl 1):S1.
3. Bandelow B, Sher L, Bunevicius R, et al. Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder in primary care. *Int J Psychiatry Clin Pract*. 2012;16:77–84.
4. Roy-Byrne P. Treatment-refractory anxiety; definition, risk factors, and treatment challenges. *Dialogues Clin Neurosci*. 2015;17(2):191–206.
5. Bandelow B, Michaelis S. Epidemiology of anxiety disorders in the 21st century. *Dialogues Clin Neurosci*. 2015;17(3):327–335.
6. Brandish EK, Baldwin DS. Anxiety disorders. *Medicine*. 2012;40(11):599–606.
7. Niles AN, Dour H, Stanton AL, et al. Anxiety and depressive symptoms and medical illness among adults with anxiety disorders. *Psychosom Res*. 2015;78(2):109–115.
8. Craske MG, Stein MB, Elay TC, et al. Anxiety disorders. *Nat Rev Dis Primers*. 2017;3:17024. doi:10.1038/nrdp.2017.24.
9. Martin EI, Ressler KJ, Binder E, et al. The neurobiology of anxiety disorders: Brain imaging, genetics, and psychoneuroendocrinology. *Psychiatr Clin North Am*. 2009;32:549–575.
10. LeDoux JE, Pine DS. Using neuroscience to help understand fear and anxiety: A two-system framework. *Am J Psychiatry*. 2016;173(11):1083–1093.
11. Bandelow B, Baldwin D, Abelli M, et al. Biological markers for anxiety disorders, OCD and PTSD: A consensus statement. Part I: neuroimaging and genetics. *World J Biol Psychiatry*. 2017;17(5):321–365.
12. Bandelow B, Baldwin D, Abelli M, et al. Biological markers for anxiety disorders, OCD and PTSD: A consensus statement. Part II: neurochemistry, neurophysiology and neurocognition. *World J Biol Psychiatry*. 2017;18(3):162–214.
13. Nuss P. Anxiety disorders and GABA neurotransmission: A disturbance of modulation. *Neuropsychiatr Dis Treat*. 2015;11:165–175.
14. Imai H, Tajika A, Chen P, et al. Azapirones versus placebo for panic

disorder in adults. *Cochrane Database Syst Rev*. 2014;(9):CD010828. doi:0.1002/14651858.CD010828.pub2.

15. Warwick JM, Carey PD, Cassimjee N, et al. Dopamine transporter binding in social anxiety disorder: The effect of treatment with escitalopram. *Metab Brain Dis*. 2012;27(2):151–158.
16. Maron E, Nutt D. Biological markers of generalized anxiety disorder. *Dialogues Clin Neurosci*. 2017;19:147–157.
17. Reinhold JA, Rickel K. Pharmacological treatment for generalized anxiety disorder in adults: An update. *Expert Opin Pharmacother*. 2015;16(11):1669–1681.
18. National Institute for Health and Care Excellence: Guidance. Social anxiety disorder: recognition, assessment and treatment. NICE Clinical Guideline 159. May 2013. Available at: http://www.nice.org.uk/guidance/cg159. Accessed December 19, 2018.
19. Abejuela HR, Osser DN. The psychopharmacology algorithm project at the Harvard South Shore Program: An algorithm for generalized anxiety disorder. *Harv Rev Psychiatry*. 2016;24(4):243–256.
20. American Psychiatric Association. *Practice Guideline for the Treatment of Patients with Panic Disorder*. Arlington, VA: American Psychiatric Association; 2009. http://www.psychiatryonline.com/pracGuide/pracGuideTopic_9.aspx. Accessed December 19, 2018.
21. National Institute for Health and Care Excellence. Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. Management in primary, secondary, and community care. NICE Clinical Guideline 113. January 2011. Available at: http://www.nice.org.uk/guidance/cg113. Accessed December 19, 2018.
22. Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: A revision of the 2005 guidelines from the British Association for Pharmacology. *J Psychopharmacol*. 2014;28(5):403–439.
23. Stein MB, Sareen J. Generalized anxiety disorder. *N Engl J Med*. 2015;373:2059–2068.
24. Generoso MB, Trevizol AP, Kasper S, et al. Pregabalin for generalized anxiety disorder: An updated systematic review and meta-analysis. *Int Clin Psychopharmacol*. 2017;32:49–55.

25. Bostwick JR, Cusher MI, Yasugi S. Benzodiazepines: A versatile clinical tool. *Current Psychiatry*. 2012;11(4):55–64.
26. PL Detail-Document, Benzodiazepine Toolbox. Pharmacist's Letter/Prescriber's Letter. August 2014.
27. Benzodiazepines. Facts and Comparisons® eAnswers (Online). Wolters Kluwer Health Inc., 2018. Available at: http://www.wolterskluwercdi.com/facts-comparisons-online/. Accessed July 19, 2018.
28. Hershenberg R, Gros DF, Brawman-Mintzer O. Role of atypical antipsychotics in the treatment of generalized anxiety disorder. *CNS Drugs*. 2014;28(6):519–533.
29. Cymbalta [package insert]. Indianapolis, IN: Eli Lily and Company; December 2017.
30. Lexapro [package insert]. St. Louis, MO: Forest Pharmaceuticals Allergan; January 2017.
31. Paxil [package insert]. Research Triangle Park, NC: GlaxoSmithKline; October 2016.
32. Effexor XR [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc, a subsidiary of Pfizer Inc.; February 2018.
33. Gommoll C, Forero G, Mathews M, et al. Vilazodone in patients with generalized anxiety disorder: A double-blind, randomized, placebo-controlled, flexible-dose study. *Int Clin Psychopharmacol*. 2015;30(6):297–306.
34. Pae CU, Wang SM, Han C, et al. Vortioxetine, a multimodal antidepressant for generalized anxiety disorder: A systematic review and meta-analysis. *J Psychiatr Res*. 2015;64:88–98.
35. Vistaril [package insert]. New York: Pfizer Labs; May 2018.
36. The International Psychopharmacology Algorithm Project. IPAP—Generalized Anxiety Disorder Algorithm. Available at: http://www.ipap.org/gad/index.php. Accessed July 19, 2018.
37. Baldwin D, Woods R, Lawson R, Taylor D. Efficacy of drug treatments for generalized anxiety disorder: Systematic review and meta-analysis. *BMJ*. 2011;342:d1199.
38. David DJ, Samuels BA, Rainer Q, et al. Neurogenesis-dependent and independent effects of fluoxetine in an animal model of anxiety/depression. *Neuron*. 2009;62(4):479–493.

39. Klonopin [package insert]. San Francisco, CA: Genentech Inc; February 2018.
40. Xanax XR [package insert]. New York, NY: Pharmacia and Upjohn Company Inc; April 2017.
41. Chen X, van Gerven J, Cohen A, Jacobs G. Human pharmacology of positive GABA-A subtype-selective receptor modulators for the treatment of anxiety. *Acta Pharmacol Sin*. December 5, 2018. doi:10.1038/s41401-018-0185-5. [Epub ahead of print].
42. Labbate LA, Fava M, Rosenbaum JF, Arana GW. *Handbook of Psychiatric Therapy*. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2010:163–192.
43. Lader M. Benzodiazepine harm: How can it be reduced? *Br J Clin Pharmacol*. 2014;77(2):295–301.
44. Gold J, Ward K. Pharmacist Toolkit: Benzodiazepine Taper. College of Psychiatric and Neurologic Pharmacists 2018. Available at: https://cpnp.org/guideline/benzo. Accessed December 18, 2018.
45. Hadley SJ, Mandel F, Schweitzer E. Switching from long-term benzodiazepine therapy to pregabalin in patients with generalized anxiety disorder: A double-blind, placebo-controlled trial. *J Psychopharmacol*. 2012;26:461–470.
46. Canadian Agency for Drugs and Technologies in Health. Discontinuation strategies for patients with long-term benzodiazepine use: A review of clinical evidence and guidelines. Ottawa (ON); July 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0078914/pdf/PubMedHe Accessed December 18, 2018.
47. Sarris J, Moylan S, Camfield DA, et al. Complementary medicine, exercise, meditation, diet, and lifestyle modification for anxiety disorders: A review of current evidence. *Evid Based Complement Alternat Med*. 2012;2012:809653.
48. Oyebode F, Rastogi A, Berrisford G, et al. Psychotropics in pregnancy: Safety and other considerations. *Pharmacocol Ther*. 2012;135(1):71–77.
49. Bellantuono C, Tofani S, Di Sciascio G, Santone G. Benzodiazepine exposure in pregnancy and risk of major malformations: A critical overview. *Gen Hosp Psychiatry*. 2013;35:3–8.
50. Wehry AW, Beesdo-Baum K, Hennelly MM, et al. Assessment and treatment of anxiety disorders in children and adolescents. *Curr Psychiatry Rep*. 2015;17(7):52. doi:10.1007/s11920-015-0591-z.

51. Andreescu C, Varon D. New research on anxiety disorders in the elderly and an update on evidence-based treatments. *Curr Psychiatry Rep*. 2015;17(7):53. doi: 10.1007/s11920-015-0595-8.
52. Karaiskos D, Pappa D, Tzavellas E, et al. Pregabalin augmentation of antidepressants in older patients with comorbid depression and generalized anxiety disorder: An open-label study. *Int J Geriatr Psychiatry*. 2013;28(1):100–105.
53. Andrisano C, Chiesa A, Serretti A. Newer antidepressants and panic disorder: A meta-analysis. *Int Clin Psychopharmacol*. 2012;28:33–45.
54. Bandelow B, Baldwin DS, Zwanzger P. Pharmacological treatment of panic disorder. *Mod Trends Pharmacopsychiatry*. 2013;29:128–143.
55. PharmGKB: The Pharmacogenomic Database. Available at: http://www.pharmgkb.org/index.jsp. Accessed December 18, 2018.
56. Blanco C, Bragdon LB, Schneier FR, et al. The evidence-based pharmacotherapy of social anxiety disorder. *Int J Neuropsychopharmacol* 2013;16(1):235–249.
57. Leichsenring F, Leweke F. Social anxiety disorder. *N Engl J Med*. 2017;376:2255–2264.
58. Canton J, Scott KM, Glue P. Optimal treatment of social phobia: Review and meta-analysis. *Neuropsychiatr Dis Treat*. 2012;8:203–215.
59. Dalrymple KL. Issues and controversies surrounding the diagnosis and treatment of social anxiety disorder. *Expert Rev Neurother*. 2012;2(8):993–1008.
60. Kawalec P, Cierniak A, Pilc A, et al. Pregabalin for the treatment of social anxiety disorder. *Expert Opin Investig Drugs*. 2015;24(4):585–594.
61. Ipser JC, Wilson D, Akindipe TO, et al. Pharmacotherapy for anxiety and comorbid alcohol use disorders. *Cochrane Database Syst Rev*. 2015;1:CD007505.

88

Posttraumatic Stress Disorder and Obsessive-Compulsive Disorder

Kristen N. Gardner, Jolene R. Bostwick, and Ericka L. Crouse

KEY CONCEPTS

1. Trauma-focused cognitive behavioral therapy (CBT) and eye movement desensitization and reprocessing are the most effective nonpharmacologic methods to reduce symptoms of posttraumatic stress disorder (PTSD).
2. The selective serotonin reuptake inhibitors (SSRIs) and venlafaxine are considered first-line treatments for PTSD.
3. An adequate trial of SSRIs in PTSD requires appropriate dosing and duration of treatment.
4. Patients with PTSD who respond to pharmacotherapy should continue treatment for at least 12 months.
5. CBT with behavioral techniques (eg, exposure and response prevention [ERP]) is the most common initial nonpharmacologic treatment of choice in obsessive-compulsive disorder (OCD).
6. Moderate-to-high dose SSRIs are the drugs of choice for the treatment of OCD.
7. Clomipramine, a tricyclic antidepressant (TCA) with strong serotonin (5HT) reuptake inhibition, is a second-line treatment option for OCD.
8. Eight to 12 weeks is considered an adequate antidepressant trial for OCD treatment.
9. Augmentation of SSRI treatment of OCD with low-to-moderate doses of antipsychotics may be helpful.
10. Medication taper can be considered after 1 to 2 years of treatment in patients with OCD.

Preclass Engaged Learning Activity

PTSD

Prior to class visit the website PTSD: National Center for PTSD on the US Department of Veterans Affairs website at: www.ptsd.va.gov and visit the section “For the Public” to review one or two types of Trauma (eg, war, terrorism, violence and abuse, or disasters)

On the left-hand side menu, visit the section “For Professionals” and complete the following steps:

1. Click on Assessment
2. Click on PTSD Screens
3. Review the following two screening tools: The Primary Care PTSD Screen for DSM-5 (PC-PTSD-5) and the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)
4. Work with a friend or partner to role play and practice administering either the PC-PTSD-5 or the CAPS-5
5. https://tinyurl.com/yykq5vnb

This activity is intended to build your awareness of different types of traumas that patients may experience as well as familiarize yourself with the types of symptoms that patients are screened for when considering a diagnosis of PTSD.

OCD

Identify a mobile-app that may help manage OCD and related symptoms (eg, nOCD, icounselor OCD, headspace). Evaluate the mobile-app from the perspective of a patient with OCD and write a brief review for this application (eg, a single paragraph). Consider the following questions (you do not need to address each item):

- What symptom(s) is this mobile-app intended to help?
- How interactive is the mobile-app in giving feedback to the end user?
- Can the mobile-app be personalized for the end user?
- Do you foresee the mobile-app content and delivery methods accomplishing its purpose?
- Is there scientific research that demonstrates its effectiveness?

- Describe the patient population for which this mobile-app is best suited.

This activity is intended to build your awareness of the growing interest and use of mobile health technology devices to empower patients in self-management of their mental health.

INTRODUCTION

Traumatic or stressful events (eg, wars, terrorist attacks, natural disasters, robbery, physical or sexual assault) can lead to development of PTSD.[1] Initially diagnosed in veterans of war, PTSD is now acknowledged as a significant psychiatric illness in the civilian population and among deployed service personnel of the Afghanistan and Iraq campaigns in whom the suicide rate has escalated.[1,2] PTSD continues to be poorly recognized and diagnosed in clinical practice.[3] Because of its co-occurrence (greater than 50%) with anxiety disorders, depression, substance abuse, and traumatic brain injury, the overlapping symptoms can lead to diagnostic uncertainty.[3] PTSD has been shown to increase the risk of lifetime suicide attempt.[3–6] Advances in the science and treatment of PTSD can assist clinicians in all fields of healthcare to screen patients for a history of trauma and effectively manage PTSD if it is present.

Intrusive obsessive thoughts and compulsive ritualistic behaviors characterize OCD[1] that can be severely debilitating and impair functioning in social, family, and work settings, with an overall decrease in quality of life (QOL). Comorbid depression is common with OCD, with approximately 40% of patients having a history of major depression during their lifetime.[6] OCD is also associated with an increased risk of suicide, with a mean of 13.4% (range 1%-46.3%) of patients reporting a previous history of suicide attempt. Increased understanding of symptom dimensions and treatment response can improve QOL in patients suffering from OCD.

EPIDEMIOLOGY

Within the US population, the estimated lifetime prevalence of PTSD is 8.7%,[1] whereas the lifetime prevalence of OCD has been estimated at 2.3% in the general population.[7]

As PTSD is associated with the incidence of trauma,[1] the most frequently reported traumatic events are assault (physical and sexual) in the United States

with a 52% lifetime prevalence and accidents or fires with a 50% lifetime prevalence of PTSD.[3] The conditional probability of developing PTSD differs between sex and type of trauma. The probability of developing PTSD for men and women after rape is 65% and 46%, after physical assault 2% and 22%, and after an accident are 6% and 9%, respectively.[8] Prevalence of PTSD is consistently higher among women (10.4%-12.3%) than men (5%). As the age of onset and course of PTSD are variable, it is important to note that PTSD can occur at any age, but most cases occur before the age of 40 years. The presentation is also not predictable, because symptoms are related to the duration and intensity of the trauma, the presence of other psychiatric disorders, and how the patient deals with the trauma.[3] Genetic factors can increase vulnerability to PTSD if an individual is exposed to a traumatic event. Lastly, veterans and those whose jobs increase the risk of traumatic exposure (eg, firefighters, first responders, police) have higher rates of PTSD.[1,3]

The epidemiology of OCD is also influenced by age and gender. The age of onset has a bimodal distribution peaking in late childhood/early adolescence and then again in early adulthood.[9,10] In men, the onset of illness is more frequently seen during childhood/adolescence versus early adulthood in women. The annual US prevalence of OCD is greater in females (1.8%) versus males (0.5%).[7] Patients with childhood-onset OCD often have concurrent ADHD and tic disorders whereas affective disorders, other anxiety disorders, and obsessive-compulsive personality disorder are common comorbidities in adult-onset OCD.[1] Greater than 50% of patients with Tourette's Disorder have OCD symptoms, and around 30% will eventually be diagnosed with OCD.[11] Heredity is stronger when there is an early age of onset or comorbidity with tic disorder.[1] The average delay in time to appropriate treatment for OCD following symptom onset is nearly 8 to 10 years[10] as OCD is a disorder that is poorly recognized and patients often do not seek treatment until late during illness.

ETIOLOGY

The exact etiologies of PTSD and OCD are unknown; however, it is likely that abnormalities in several areas of brain functioning interact to cause these chronic disorders. Genetics may also play a role in expression of PTSD and OCD, but environmental factors likely are also involved. A number of genetic markers for PTSD are under evaluation, including genes associated with the hypothalamic-pituitary adrenal (HPA) axis, the amygdala-medial prefrontal cortex (mPFC)-

hippocampus circuit, and the serotonin transporter.[12–14] Given the heterogeneity and individual differences of the PTSD populations, recent studies have focused on gene by environment (G x E).[13] The behaviors in OCD are also heterogeneous, therefore suggesting an underlying genetic heterogeneity, and involvement of more than one gene.[11,15] Potential genes include those affecting 5HT, dopamine (DA), and glutamate.[11] An association with the D_2 receptor gene has been identified in OCD with tics and other potential genes associated with OCD include 5HT transporter and receptors (eg, *5HT1D beta, 5HT2A*, and *5HT2C*). Research on the role of glutamate in OCD has identified genes of interest including glutamate-related synapse (*SAPAP/DLGAP*); glutamate transporter (*SLC1A1*); and NMDA receptor genes (*GRIN* and *GRIK*).[11,15] Further understanding of the role genetics and the environment play in the development of OCD may impact future treatment strategies and are current research areas.

In children between the age of 3 years and puberty, the occurrence of sudden onset OCD and chronic tic disorder following a streptococcal infection has been reported which has been labeled Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS).[16] Controversy currently exists as to whether or not PANDAS should be characterized as a subtype of OCD. Although most patients with OCD do not have a streptococcal etiology, an accurate medical history regarding onset of illness is imperative because specific treatment strategies are indicated. More recently, PANDAS has been broadened to pediatric acute-onset neuropsychiatric syndrome to include OCD symptoms that start after nonstreptococcal infections.

Substance/medication-induced OCD has been described with stimulants including cocaine, amphetamines, and methylphenidate. Furthermore, cases of OCD-like behaviors have been described with dopamine agonists (eg, ropinirole, pramipexole).[11]

PATHOPHYSIOLOGY

Research findings in the areas of neuroendocrinology, neurobiology, and neuroimaging have advanced a number of theories on the pathophysiology of anxiety disorders, OCD, and PTSD. Neuroendocrine changes in the HPA axis are implicated in the pathophysiology of PTSD. The neurobiology of PTSD focuses on alterations in fear learning, threat detection, executive function and emotional regulation, as well as contextual processing.[3] Dysfunction in the cortico-striato-thalamo-cortical circuit is implicated in OCD.[11] As reviewed in Chapter 87, data

from neurochemical and neuroimaging studies indicate that the modulation of normal and pathologic anxiety states is associated with multiple regions of the brain (eg, amygdala, hippocampus, thalamus, and prefrontal cortex).[3] Abnormal function in several neurotransmitter systems, including norepinephrine (NE), γ-aminobutyric acid (GABA), glutamate, dopamine (DA), and serotonin (5-HT), may affect the manifestations of anxiety disorders, OCD and PTSD.[13,17,18]

Neuroendocrine Theories

Neuroendocrine studies provide data that abnormalities occurring pretrauma, during trauma, and posttrauma contribute to PTSD. Trauma exposure is linked to abnormal HPA activity and cortisol patterns.[19] Normally the immediate reaction to stress occurs as an automatic response from the amygdala to the sympathetic and parasympathetic systems and the HPA axis.[17] The release of corticotropin-releasing factor (CRF) stimulates cortisol secretion from the adrenal gland and both catecholamines and cortisol levels rise in tandem. Cortisol then reduces the stress response by tempering the sympathetic reaction through negative feedback on the pituitary and hypothalamus[17] with both systems returning to normal after a few hours.

Data implicate a role for the neuropeptides CRF and neuropeptide Y (NPY) in PTSD, as patients with PTSD have a hypersecretion of CRF but demonstrate subnormal levels of cortisol at the time of trauma and then chronically.[17] Lower plasma cortisol concentrations were associated with greater severity of PTSD symptoms in nonmilitary patients[18] and dysregulation of the HPA axis is postulated to be a risk factor for eventual development of PTSD.[17] The NPY system is a mediator between exposure to stress and development of resilient versus maladaptive responses and the role of NPY in improving resilience is a continued area of research interest.[20]

Neurochemical Theories

Several neurotransmitters may be involved in the pathophysiology of PTSD as 5-HT, NE, and glutamate are associated with the processing of emotional and somatic contents of memories in the amygdala.[18] Alterations in these neurotransmitters are linked to alterations in amygdala activity.[3] The amygdala is involved in processing emotions, acquiring, expressing and regulating fear and traumatic memories, including fear conditioning.[19] The medial prefrontal cortex (mPFC) and hippocampus are involved in contextual processing. The

noradrenergic theory posits that the autonomic nervous system of anxious patients is hypersensitive and overreacts to stimuli. The alarm center, the locus ceruleus, releases NE to stimulate the sympathetic and parasympathetic nervous systems. Hyperactive noradrenergic signaling in patients with PTSD is a consistent research finding and includes increased 24-hour catecholamine excretion.[18] Glutamate signaling abnormalities may result in distortion of amygdala-dependent emotional processing under stress.[17,18] Dysregulation of the processing of sensory input and memories may contribute to the dissociative and hypervigilant symptoms in PTSD. Abnormalities of GABA inhibition may lead to increased awareness or response to stress, as seen in PTSD.[21]

Both 5-HT and DA are implicated in the pathogenesis of OCD as selective and potent serotonergic reuptake inhibitors have consistently been shown effective for symptoms of the illness,[22] especially at higher doses. The most commonly studied serotonin receptors in OCD are 5-HT_{2A}, 5-HT_{1B}, and 5-HT_{2C}.[23] However, DA dysregulation may also contribute to some forms of OCD, as neurologic symptoms (eg, tics) are part of the clinical presentation in some patients with OCD and Tourette's disorder, a disorder of DA function, is often a concurrent disease.[1,11] Additionally use of dopamine agonists can worsen OCD symptoms, whereas augmentation with antipsychotic drugs may improve symptoms in patients with OCD who are partially responsive to SSRIs.[11] More recently glutamate has become another neurotransmitter of interest in OCD, especially in genetic research.[15]

Neuroimaging Studies

Neuroimaging studies suggest that certain areas of the brain are altered by psychological trauma. In PTSD, most functional neuroimaging studies have involved the amygdala, mPFC, dorsal anterior cingulate cortex (dACC), insula, and hippocampus.[3] Findings of increased activation of the amygdala after trauma-related imagery, sounds, or smells indicate that this structure plays a role in the persistence of traumatic memory.[24] Decreased amygdala activation is correlated with resilience to PTSD and response to CBT. Historically, studies have suggested patients with PTSD have reduced amygdala volume; however, a recent study suggested instead that smaller amygdala volume is related to exposure to trauma and not necessarily PTSD.[19] Hypofunctioning of the mPFC is theorized to prevent extinction of fear in patients with PTSD, and is associated with impairments in extinction recall, abnormalities in processing contextual

information and impairments in safety-signal learning.[3] Hyperresponsivity of the dACC, amygdala, and the insula may correlate with impaired response to emotional or salient stimuli or impaired threat detection. Not all magnetic resonance imaging (MRI) studies show reduced hippocampal volume in PTSD; however, reduced hippocampal volume has been linked to reexperiencing symptoms in PTSD.[19] In twin studies, the unaffected twin of patients with PTSD also demonstrated smaller hippocampi compared with twins without PTSD that may suggest that lower hippocampal volumes are likely a precursor associated with vulnerability for subsequent PTSD development.[17]

Neuroimaging studies also suggest that dysfunction in the cortico–striatal–thalamo-cortical circuit, which regulates self-control, is associated with OCD.[11] Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) studies in OCD have shown increased activity in the anterior cingulate cortices, and different patterns of activation in the caudate.[9] Evidence suggests that lower pretreatment activity in the orbitofrontal cortex predicts a better response to SSRIs and improved fluvoxamine response has been correlated with abnormalities in the posterior cingulate cortex.

CLINICAL PRESENTATION

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) made several changes to the classification of anxiety and related disorders[1] with individual chapters for anxiety disorders, trauma- and stressor-related disorders, and obsessive-compulsive and related disorders. The separation of trauma- and stressor-related disorders and obsessive-compulsive and related disorders from the DSM-5 anxiety disorders chapter was based on evidence that anxiety is not a primary component of these disorders but rather a secondary reaction. Generalized anxiety disorder, panic disorder, and social anxiety disorder are discussed in Chapter 87.

Posttraumatic Stress Disorder

Exposure to a traumatic event is required for a diagnosis of PTSD[1] in that the person must have witnessed, experienced, or been confronted with a situation that involved definite or threatened death or serious injury, sexual violence, or possible harm to self or others. Some examples of traumatic events include physical attacks by an intimate partner, severe traffic accidents, military combat, natural disasters, being held hostage, child sexual abuse, witnessing a murder or

injury of another, and learning of a traumatic event that happened to a close family member or friend.

The resulting PTSD symptoms include persistent reexperiencing of the traumatic event, avoidance of stimuli associated with the trauma, numbing of general responsiveness, and persistent symptoms of hyperarousal.[1] Patients must have at least one intrusion symptom, at least one symptom of avoidance of stimuli associated with the trauma, at least two symptoms of negative alterations in cognition and mood, and at least two symptoms of increased arousal. Symptoms from each category need to be present for longer than 1 month and cause significant distress or impairment in functioning. Most persons diagnosed with PTSD also meet criteria for another mental disorder.[1,4]

Anxiety and dissociative symptoms (eg, absence of emotional responsiveness, derealization, inability to recall important features of the trauma) emerging within 1 month after exposure to a traumatic stressor are classified as Acute Stress Disorder (ASD).[1] Symptoms of ASD are experienced during or immediately after the trauma, last for at least 3 days, and resolve within 1 month.

Symptoms most commonly emerge soon after a traumatic event and symptoms may dissipate or chronically persist.[3] Similarly, the severity and course of illness is fluctuating, worsening with life stressors. PTSD co-occurs with mood, anxiety, and substance use disorders.

CLINICAL PRESENTATION Posttramatic Stress Disorder

Intrusion Symptoms

- Recurrent, intrusive distressing memories of the trauma
- Recurrent, disturbing dreams of the event
- Feeling that the traumatic event is recurring (eg, dissociative flashbacks)
- Physiologic reaction to or psychological distress from reminders of the trauma

Avoidance Symptoms

- Avoidance of conversations, thoughts, or feelings about the trauma
- Avoidance of people, places, or activities that are reminders of the event

Persistent Negative Alterations in Thinking and Mood

- Inability to recall an important aspect of the trauma

- Anhedonia
- Estrangement from others
- Restricted affect
- Negative beliefs about oneself
- Distorted beliefs causing one to blame others or themselves for the trauma
- Negative mood state

Hyperarousal Symptoms

- Decreased concentration
- Easily startled
- Self-destructive behavior
- Hypervigilance
- Insomnia
- Irritability or anger outbursts

Specifiers

- Dissociative symptoms: depersonalization or derealization
- With delayed expression: full criteria are not met until at least 6 months posttrauma

Data from References 1 and 4.

Obsessive-Compulsive Disorder

The diagnostic criteria for OCD require the presence of obsessions and/or compulsions that are severe enough to cause marked distress, to be time-consuming (occupy more than 1 hr/day), or cause significant impairment in social or occupational functioning.[1] An obsession is a recurrent, persistent idea, thought, impulse, or image that is experienced as intrusive and inappropriate and produces marked anxiety. A compulsion is defined as a repetitive behavior or mental act generally performed in response to an obsession. While it is most common for patients to have both obsessions and compulsions, some may only

have one or the other. Diagnostically, the compulsive behavior is not pleasurable and is designed to prevent discomfort or the occurrence of a dreaded event that is often unknown and part of the obsession. Therefore, compulsive behaviors are usually performed according to certain rules or in a stereotyped fashion. Common symptom dimensions involve cleaning (eg, contamination obsessions and cleaning compulsions), symmetry (eg, symmetry obsessions and ordering or arranging compulsions), forbidden or taboo thoughts (eg, violent, sexual, or religious obsessions and related compulsions), and harm (eg, fears of causing harm or superstitions and related compulsions).[1,10] For example, patients obsessed with the fear of causing harm (eg, inadvertently hitting a pedestrian), may cause them marked distress and lead to repetitive checking (eg, driving past crosswalks to check for injured pedestrians).[10]

There are two specifiers for OCD related to the degree of insight and the presence of tic-related symptoms.[1] While individuals vary widely in their insight into the irrationality of their obsessive-compulsive symptoms, most will have good or fair insight. The addition of an insight specifier allows the diagnosis to include individuals with poor to absent insight such as those with comorbid psychosis.[10] Individuals with tic-related OCD appear to differ from those with non-tic-related OCD in terms of etiology, illness course, symptom presentation, comorbidities, heredity, and pharmacotherapy response.[1]

CLINICAL PRESENTATION Obsessive-Compulsive Disorder

Obsessions

- Repetitive thoughts (eg, feeling contaminated by germs, fears of harming others)
- Repetitive images (eg, recurrent sexually explicit pictures)
- Repetitive urges (eg, need for symmetry or putting things in specific order)

Compulsions

- Repetitive activities (eg, hand washing, need to ask, need to confess)
- Repetitive mental acts (eg, counting excessively, repeating words silently, praying)

Specifiers

- Insight: good or fair insight, poor insight, or absent insight/delusional beliefs
- Related to a tic disorder

Data from References 1 and 10.

The diversity and oddity of OCD symptoms can obscure an accurate diagnosis as patients often present in a seemingly incongruous manner to nonpsychiatrists for other complaints—dermatologists for eczema or chapped skin, pediatricians for parental concerns over a child's compulsive hand washing, neurologists for tics, or dentists for gum lesions from compulsive teeth brushing.[10] Because patients recognize their compulsive behavior as silly or senseless, they also can become extremely adept at denying symptoms, disguising their rituals, and concealing their illness from friends and family.[1]

It is important to note that OCD is a chronic illness in most patients, with severity of symptoms varying in intensity over time[10] resulting in a significantly impaired QOL, similar to patients diagnosed with schizophrenia.

TREATMENT

Post Traumatic Stress Disorder

Desired Outcomes

The short-term goal of therapy in the management of PTSD is a reduction in core symptoms (eg, intrusive reexperiencing, avoidance, and hyperarousal). Additional goals include improvements in disability, concurrent psychiatric conditions, resilience, and QOL with the long-term goal of PTSD remission.

General Approach to Treatment

In general, patients who seek treatment acutely after a trauma and are in intense distress should receive therapy based on their presenting symptoms (eg, a nonbenzodiazepine hypnotic for difficulty sleeping). Short courses of exposure-based, trauma-focused cognitive behavioral therapy (TFCBT) can be helpful to prevent chronic PTSD in patients with ASD or acute PTSD.[4] If symptoms (eg, hyperarousal, avoidance, dissociation, sleep difficulties, or depressed mood)

persist for 3 to 4 weeks and the patient experiences marked social, occupational, and/or interpersonal impairment, they can be treated with pharmacotherapy, psychotherapy, or both. Many patients with PTSD will improve substantially with pharmacotherapy but retain some symptoms. Treatment regimens usually combine psychoeducation, psychosocial support and/or treatment, and pharmacotherapy; however, newer guidelines specifically emphasize the utility of individual trauma-focused psychotherapies.[3,5]

Nonpharmacologic Therapy

Psychotherapy can be used when a patient suffers from mild symptoms, in patients who prefer not to use medications, or in conjunction with medication in patients with severe symptoms in an effort to improve response.[5] Notably, Veterans Health Administration clinical practice guidelines emphasize the role of trauma-focused psychotherapy as the preferred treatment approach. Patients who have experienced trauma should be educated that they can experience anxiety, depression, nightmares, and even flashbacks as a reaction to the event. Brief courses of individual trauma-focused psychotherapy, focusing on exposure or cognitive restructuring, in close proximity to the traumatic event resulted in lower rates of PTSD 3 and 6 months later. Single-session critical incident stress debriefing has not shown to be effective in preventing development of PTSD and may cause harm.[3,5] Involving the patient in the selection of preferred treatment, especially in those that prefer prolonged exposure therapy, has demonstrated improved health-related quality of life.[25]

1 Psychotherapies for treating PTSD include stress management, TFCBT, cognitive processing therapy (CPT), eye movement desensitization and reprocessing (EMDR), and psychoeducation.[4,5] EMDR involves the process of patients imagining exposure to the traumatic event while simultaneously engaging in bilateral eye movements to assist with processing of this event along with relaxation.[4] The cognitive and behavioral approaches of TFCBT and EMDR are more effective than stress management or group therapy to reduce symptoms of PTSD. Psychoeducation includes information about the disease state, treatment options, and avoidance of excessive use of alcohol and other substances of abuse. CBT for insomnia has been studied in PTSD and may be helpful for sleep disturbances.[5] Novel nonpharmacologic approaches (eg, interpersonal psychotherapy, narrative exposure therapy, written narrative exposure, imagery, transcranial magnetic stimulation [TMS], neurofeedback, acupuncture, yoga, emotional freedom technique, virtual reality exposure,

mindfulness therapies and delivery methods [eg, telemedicine and other technology-based treatments]) are under study.[3,5]

Pharmacologic Therapy

2 Antidepressants are the major pharmacotherapeutic treatment for PTSD. In addition to also being effective for concurrent depression and anxiety disorders. SSRIs and venlafaxine are the first-line pharmacotherapy of PTSD[6,26,27]; however, the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) can also be effective, but they have less favorable side-effect profiles (**Table 88-1**). Both sertraline and paroxetine are approved for the acute treatment of PTSD,[28,29] and sertraline is approved for the long-term (eg, 52 weeks) management of PTSD.[29] A number of drugs can be used as augmentation agents (eg, antiadrenergic drugs, atypical antipsychotics, and anticonvulsants).[4,30] Benzodiazepines are not effective for PTSD.[5,27] A number of treatment guidelines are published,[4,5,30] with **Table 88-2** providing a summary of key points from the treatment guidelines for PTSD. An algorithm for the treatment of PTSD appears in **Fig. 88-1**.

TABLE 88-1 Dosing of Antidepressants in the Treatment of PTSD

Drug	Brand Name	Initial Dose	Usual Range (mg/day)	Comments
SSRIs				
Fluoxetine[a]	Prozac®	10 mg daily	10-80[b]	
Paroxetine[a]	Paxil®, Pexeva®	10-20 mg daily	20-40	Maximum dose is 50 mg daily[c]
Sertraline[a]	Zoloft®	25 mg daily	50-100	Maximum dose is 200 mg daily[c]
Other Agents				
Amitriptyline[a]	Elavil®	25 or 50 mg daily	75-200[b]	
Imipramine[a]	Tofranil®	25 or 50 mg daily	75-200[b]	
Mirtazapine[a]	Remeron®	15 mg every night	30-60[b]	
Nefazodone[a]	n/a	25-100 mg twice daily	150-600[b]	Product has a black box warning for hepatotoxicity
Phenelzine[a]	Nardil®	15 or 30 mg every night	45-90[b]	
Venlafaxine extended-release[a]	Effexor XR®	37.5 mg daily	75-225[b]	

PTSD, posttraumatic stress disorder; SSRIs, selective serotonin reuptake inhibitors; n/a, not applicable.

[a]Available generically.

[b]Dosage used in clinical trials but not FDA-approved.

[c]Dosage is FDA-approved.

Data from References 5, 26, 28, and 29.

TABLE 88-2 Summary of Key Points in Treatment Guidelines for PTSD

Recommendations	Level of Evidence	Comments
First-Line Treatments		
SSRIs: Fluoxetine, paroxetine, sertraline SNRIs: Venlafaxine	I I	At 4 weeks if there is partial response, continue for another 4 weeks. At 8 weeks, if no improvement, increase dose to maximum tolerated or switch to another first-line treatment
Second-Line Treatments		
TCAs: Amitriptyline, imipramine	II	The risk of adverse effects and potential for fatalities in a TCA overdose are higher than with SSRIs or SNRIs
Other: Mirtazapine	II	
Augmentation with prazosin for sleep/nightmares	II	Not recommended in the VA guidelines ***for use in veteran population***
Third-Line treatments		
Augmentation with anticonvulsants or atypical antipsychotics	IV	The VA guidelines recommend against using risperidone as an augmenting agent secondary to metabolic adverse effects. There is insufficient evidence to support routine use of other atypical antipsychotics or anticonvulsants.
MAOIs: Phenelzine	III	Potential adverse effects and dietary restrictions limit use.
Other: Nefazodone	II	Tolerability and risk for hepatotoxicity limit use.

PTSD, posttraumatic stress disorder; SNRIs, serotonin–norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant; VA, Veterans Affairs.

Levels of evidence: I, strong recommendation, full evidence from controlled trials; II, recommended, limited positive evidence from controlled trials; III, may be recommended, evidence from uncontrolled trials or case reports/expert opinion; IV, evidence is insufficient to recommend, inconsistent findings.

Data from References 4, 5, 27, and 31.

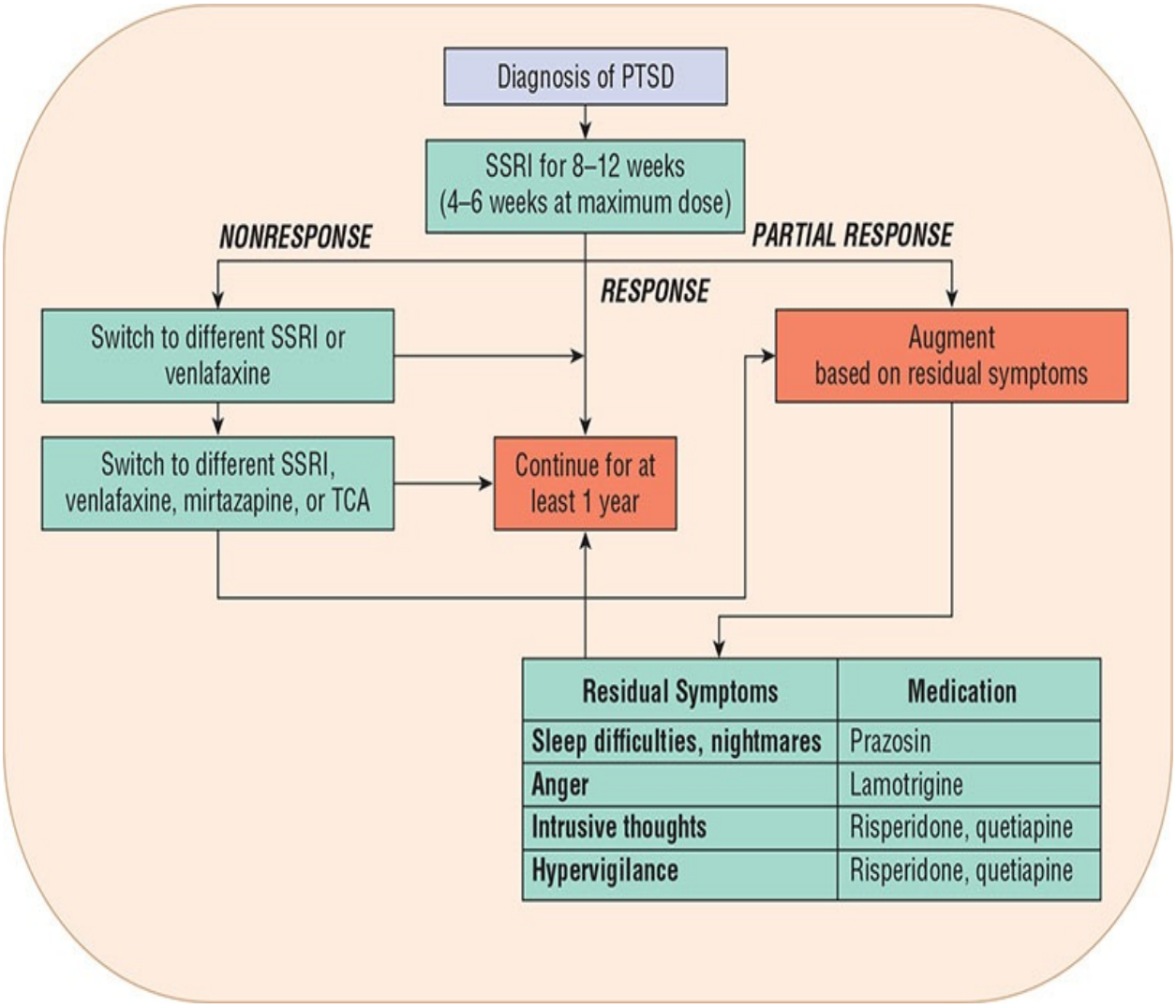
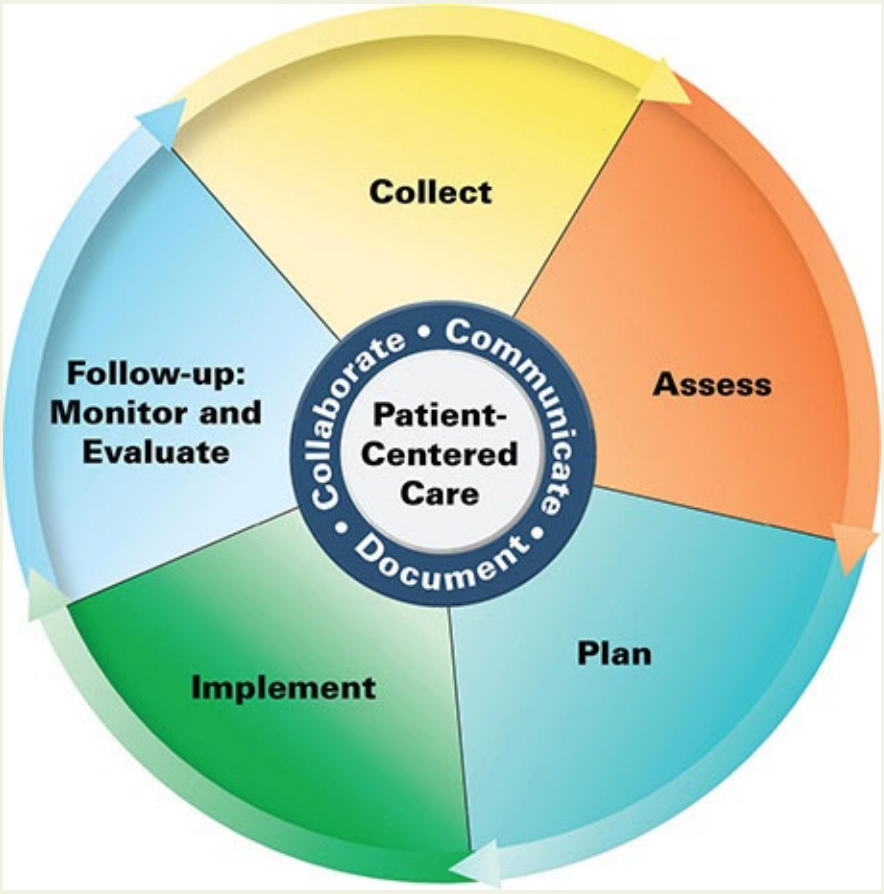


FIGURE 88-1 Algorithm for the pharmacotherapy of posttraumatic stress disorder (PTSD). *(Data from References 26 and 27.)*



Patient Care Process for Posttraumatic Stress Disorder and Obsessive-Compulsive Disorder

Collect

- Patient characteristics (eg, age, sex, pregnant)
- Patient medical history (personal and family, include first-degree relatives' response to medication)
- Social history (eg, tobacco use/ethanol use/substance use/sexual activity)
- Current medications including OTC use, herbal products, dietary supplements, and prior psychiatric medication use
- Patient health preferences, beliefs, and treatment goals
- Objective data
    - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight
    - Lipid panel and A1c or fasting blood sugar if starting antipsychotic

therapy

- Electrocardiogram (ECG) if starting a TCA in a child/adolescent, patient with cardiovascular disease, patient >40 years, or with other risk factors for QT prolongation (eg, electrolyte abnormalities, concomitant medications with the potential to prolong the QT)
- Validated rating scale score (eg, Clinician Administered PTSD Scale [CAPS] or Yale-Brown Obsessive-Compulsive Scale [Y-BOCS])
- Results of any pharmacogenomics testing

Assess

- Target symptoms (eg, intrusion, avoidance, reactivity, mood/cognition for PTSD and obsessions and/or compulsions for OCD) using CAPS, Y-BOCS, or other rating scale assessments
- Functional impairment/quality of life
- Sleep hygiene
- Psychotic symptoms
- Engagement in psychotherapy
- Medication adherence
- Ability/willingness to utilize and pay for pharmacotherapy or engage in psychotherapy
- Ability/willingness to return to clinic for continued regular symptom assessment
- Need to alter treatment plans due to results of pharmacogenomics testing

Plan*

- Drug therapy regimen including specific pharmacotherapy, dose, route, frequency, onset of action, and duration (see Fig. 88-1, Tables 88-1 through 88-4)
- Monitoring parameters including efficacy (eg, rating scale score, sleep, other symptoms such as irritability, functional impairment, symptom diary) and safety (eg, suicidal ideation, adverse effects including insomnia, worsening anxiety or depression, gastrointestinal distress, sexual dysfunction, agitation); frequency and timing of follow-up
- Patient education (eg, purpose of treatment, lifestyle modification, onset of action, treatment duration, drug-specific information, medication

administration technique; see Fig. 88-1 and Tables 88-2, 88-3, and 88-5)

- Self-monitoring for changes in PTSD/OCD symptoms, when to seek emergency medical attention
- Referrals to other providers when appropriate (eg, substance use treatment)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (eg, CAPS/Y-BOCS or other rating scale assessments, adherence assessment, adverse effect assessment)
- Engage caregiver/family in treatment plan, if possible, and with patient permission

Follow-up: Monitor and Evaluate

- Improvement in rating scale scores of PTSD/OCD symptoms
- Presence of adverse effects (eg, sexual dysfunction, insomnia)
- Patient adherence to treatment plan using multiple sources of information
- Reevaluate sleep hygiene
- Reevaluate effectiveness of psychotherapy
- Assess risk for suicidality

*Collaborate with patient, caregivers, and other healthcare professionals.

Antidepressant Therapy

Selective Serotonin Reuptake Inhibitors SSRIs pharmacologically enhance serotonergic functioning and large prospective studies document the efficacy of sertraline and paroxetine in the acute management of PTSD.[25,27,31] While a meta-analysis found that SSRIs were significantly better than placebo for the treatment of PTSD, the overall effect size was small.[32] Adverse reactions reported in patients with PTSD treated with SSRIs include gastrointestinal (GI) symptoms, sexual dysfunction, insomnia, and agitation. Additionally, long-term use of SSRIs (durations of 9-12 months) has been shown to be effective in preventing relapse.[4,30]

Other Antidepressants The serotonin–norepinephrine reuptake inhibitor (SNRI) venlafaxine has shown efficacy in PTSD. In a 12-week, placebo-controlled trial comparing venlafaxine extended-release and sertraline, venlafaxine was effective in reducing the avoidance/numbing and hyperarousal clusters of PTSD, whereas sertraline improved all PTSD symptom clusters.[33] The remission rates for venlafaxine extended-release were 30.2% after 12 weeks[33] and 50.1% after 6 months.[34]

Other antidepressants have been studied in controlled trials with mirtazapine being considered a second-line agent in one guideline,[4] while others highlight insufficient data to recommend use.[5,30] The TCAs amitriptyline and imipramine are also considered second-line agents whereas phenelzine and nefazodone are considered third-line antidepressants if therapeutic trials of SSRIs or venlafaxine have failed. Potential adverse effects or risks associated with these agents (eg, daytime drowsiness and toxicity in overdose with TCAs; dietary restrictions and potential drug interactions with MAOIs; or risk of liver failure with nefazodone) limit their use clinically.[4,30] Bupropion is not recommended in patients with PTSD due to poor quality of evidence, but this agent may be considered as a third-line option.[4,5]

Alternative Drug Treatments Atypical antipsychotics, α_1-adrenergic antagonists, and anticonvulsants can be used as augmenting agents for persistent PTSD symptoms, in cases of partial response to SSRI therapy after 4 to 6 weeks, or for comorbidities.[4,27,30] Data on the efficacy of atypical antipsychotics are conflicting with one study showing quetiapine monotherapy was generally well tolerated and associated with improvements in overall symptomology, reexperiencing, and hyperarousal.[35] Further, guidelines suggest atypical antipsychotic symptoms may be useful in targeting intrusive symptoms[4]; however, any potential benefit must be considered in the context of risks, including metabolic complications. One meta-analysis supports risperidone use among the atypical antipsychotics, while a recent guideline strongly recommends against use of risperidone for PTSD due to limited evidence and adverse effect profile.[5,31]

Prazosin (an alpha-1 receptor antagonist) can be useful in some patients with PTSD, as earlier studies have shown that it may decrease nightmares and symptoms of hyperarousal, as well as improve the core PTSD symptoms, total sleep time, and sleep quality. When used for this purpose the daily doses start at 1 mg and may be increased as tolerated to 25 mg.[36] Its presumed mechanism of action is reduction of noradrenergic transmission. In a more recent study, use of

prazosin among veterans with chronic PTSD did not improve nightmares or sleep quality compared to placebo, though the study population may have selected patients who were less likely to respond to prazosin.[37] In light of this data, newer Veteran's Administration guidelines cite prazosin's effects to be similar to placebo and state there is insufficient evidence to recommend use of this agent in this population.[5] Other pharmacologic options for persistent sleep disturbances are limited. Medications with sedative properties (eg, nefazodone, imipramine, mirtazapine, phenelzine, or atypical antipsychotics) may be considered depending upon individual comorbidities.[5,27] Some evidence supports consideration of eszopiclone for improving PTSD symptoms in addition to sleep latency.

Anticonvulsants can assist in reducing impulsive anger and can also be used in patients with comorbid bipolar disorder; however, the use of an anticonvulsant is not recommended as monotherapy. Some data support efficacy of lamotrigine and topiramate, though overall, data with anticonvulsants are inconsistent.[4,5,27,31]

Dosage and Administration

3 **Acute Phase** PTSD symptoms respond slowly to pharmacotherapy, and some patients never experience full resolution, therefore SSRIs should be started 3 to 4 weeks after exposure to a trauma in patients with no improvement in their acute stress response. The initiation of an SSRI should be at a low dose with gradual titration upward toward antidepressant doses. Eight to 12 weeks is an appropriate duration of antidepressant therapy to determine response.[4,26,30]

Continuation Phase Many patients undergo psychotherapy during the continuation phase of therapy, and medication dosages can vary as patients deal with past traumatic experiences. During this phase, symptoms continue to improve. Six-month relapse prevention trials in patients responsive to fluoxetine or sertraline indicate low rates of relapse with SSRI therapy compared with placebo.[30]

4 **Maintenance and Discontinuation** Patients with PTSD who respond to pharmacotherapy should continue treatment for at least 12 months.[4,26,30,38] If residual symptoms persist, drug therapy should be continued. The decision about when to discontinue therapy is based on response to therapy, relapse prevalence, presence of ongoing stresses, adverse effects, and patient preference. Once the decision is made to discontinue therapy, the medications should be withdrawn and tapered slowly over a period of at least 1 month to reduce the potential for

relapse.

Special Populations

Adults are not the only population susceptible to PTSD, as children who experience stress and trauma (eg, sexual or physical abuse or loss of a parent) are predisposed to develop mood and anxiety disorders. For this patient population, SSRIs are the initial pharmacologic agents of choice[39]; however, psychotherapy (eg, TFCBT) is also a treatment option and studies are ongoing to assess the comparative efficacy and acceptance of psychotherapies for PTSD among children and adolescents.[40,41]

Patients with PTSD and co-occurring substance use disorders also warrant careful consideration given the greater risk for attempted suicide.[42] Guidelines suggest this population may benefit from concurrent treatment of both PTSD and substance use disorder and trauma-focused therapies have demonstrated improvement in PTSD symptoms in this population.

Personalized Pharmacotherapy

The choice of pharmacotherapy should be individualized to the patient's presenting symptoms. Selection of an SSRI or venlafaxine monotherapy is based on the patient's history of prior response, safety, and side-effect tolerability as is largely a trial-and-error process.[43] When selecting an agent, the clinician should consider the potential for adverse consequences in patients with comorbid conditions (eg, anticholinergic effects and weight gain with paroxetine in patients with diabetes, obesity, or benign prostatic hypertrophy) or adverse effects (eg, insomnia with fluoxetine in patients with sleep difficulties). Increased risk of suicidality should be considered in patients taking antidepressants who are 24 years old and younger. If symptoms of insomnia or nightmares continue, prazosin can be added to provide relief. Anticonvulsants or atypical antipsychotics can be added for patients who fail to respond or have a partial response to antidepressant therapy.

Currently there are no guidelines or articles that specifically address the use of pharmacogenomics testing in PTSD.[43] However, there are data that can help guide medication selection based on specific gene drug pairs for many of the antidepressants used in treating PTSD.[43] The Clinical Pharmacogenomics Implementation Consortium (CPIC) is a valuable resource for understanding dosing recommendations for these various drug and gene combinations.[44]

EVALUATION OF THERAPEUTIC OUTCOMES

During the acute phase of therapy, patients should be seen frequently. During months 3 to 6 of therapy, the patient can usually be seen monthly, and in months 6 to 12, visits can usually be extended to every 2 months. On each visit the patient should be asked about previously identified PTSD target symptoms as well as other symptoms including insomnia, suicidal ideation, anger outbursts, irritability, psychosis, ongoing trauma, and disability. The Clinician-Administered PTSD Scale (CAPS) can be used by the clinician to assess symptom severity at each visit.[5] A remission in patients with PTSD is defined as a 70% or greater reduction in symptoms. Patients who have a 50% response or greater reduction in symptoms are considered to have an adequate response, while those with a 25% to 50% reduction in symptoms are considered partial responders. Before deciding that a patient is not responsive to pharmacotherapy, the clinician should ensure patient adherence and that the medication trial has been adequate in both dose and duration.

Many patients with PTSD are sensitive to the adverse effects of drugs and should be monitored carefully for adverse reactions that can delay the escalation of drug dosages or cause the patient distress. See Chapter 85 for details on monitoring antidepressants. Additionally, routine assessment of the metabolic profile is necessary if an atypical antipsychotic is used concurrently (see Chapter 84).[4] When pharmacotherapy is discontinued, patients should be seen more frequently and monitored carefully for signs of relapse or withdrawal.

TREATMENT

Obsessive Compulsive Disorder

Desired Outcomes

Major goals of therapy for OCD include reduction in the frequency and severity of obsessive thoughts and time spent performing compulsive acts.[45] Treatment for OCD generally does not eliminate obsessions or compulsions, but patients can feel remarkably improved with partial resolution of symptoms. Patients typically experience waxing and waning symptoms with only 20% going on to achieve full remission.[1] Optimal treatment increases psychosocial and occupational functioning and improves overall QOL.[45] Efforts should be made to minimize adverse drug events and prevent drug interactions.

General Approach to Treatment

It is important at the outset of therapy to identify and document the specific target symptoms for pharmacotherapy. Rating scales can be used to measure symptom severity at baseline and during treatment to ascertain the degree of improvement. The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) is the most widely used clinician-administered OCD rating scale. A QOL scale can assist the clinician in identifying other areas to target for treatment (eg, depression and reduced physical well-being).[45,46]

The FDA has approved five antidepressants for the management of OCD: clomipramine, fluoxetine, fluvoxamine, paroxetine, and sertraline. CBT and SSRIs are considered effective first-line treatment modalities[45,46] with initial therapy for OCD including CBT alone, SSRI monotherapy, or the combination of CBT and an SSRI. The choice for therapy is based on clinical judgment of symptom severity and patient preferences[45] however, CBT has been largely found to be more effective compared to SSRI monotherapy.[47,48] Patients unable to participate in CBT or with a prior history of medication therapy response should be treated with SSRI monotherapy.[45] Combined CBT and SSRIs is recommended in patients who failed SSRI monotherapy or in those with severe OCD. If a combination of CBT and an SSRI at maximum tolerated dose is unsuccessful, subsequent management options include intensifying CBT, switching to an alternate SSRI, switching to clomipramine, or augmenting with either clomipramine or an antipsychotic.[10,22]

Table 88-3 provides a summary of key points from the treatment guidelines for OCD. Although some OCD symptoms can improve over the first 2 to 6 weeks of therapy, an adequate trial of any medication is considered to be 8 to 12 weeks.[10,21,49]

TABLE 88-3 Summary of Key Points in Treatment Guidelines for OCD

Recommendation	Level of Evidence	Comments
First-Line Treatments		
CBT alone	I	13-20 sessions
SSRI alone	I	8-12 weeks, at least 4-6 weeks at maximum tolerated dose
CBT + SSRI	I	If monotherapy with CBT or SSRI alone does not provide adequate response, combination therapy with CBT + SSRI should be tried before augmentation with another pharmacologic agent
Second-Line Treatments		
Switch to another SSRI or clomipramine	I	
Augmentation with antipsychotic	I	Aripiprazole and risperidone are preferred second-generation antipsychotics for OCD treatment
Switch to venlafaxine	II	
Third-Line Treatments		
Switch to another antipsychotic augmenting agent	I	
Switch to duloxetine or mirtazapine	III	
Augmentation of SSRI with clomipramine	III	Citalopram, escitalopram, and sertraline have less risk to cause clinically significant drug–drug interactions with clomipramine
Maintenance and Discontinuation Phase		
After 1-2 years, gradual taper over several months	I	
Periodic CBT booster sessions for 3-6 months	II	

CBT, cognitive behavioral therapy; OCD, obsessive-compulsive disorder; SSRI, selective serotonin reuptake inhibitor.

Levels of evidence: I, strong recommendation, full evidence from controlled trials; II, recommended, limited positive evidence from controlled trials; III, may be recommended, evidence from uncontrolled trials or case reports/expert opinion.

Data from References 4 and 45.

Nonpharmacologic Therapy

5 CBT with behavioral techniques (eg, exposure and response prevention [ERP]) is the most common initial nonpharmacologic treatment of choice in OCD and is largely considered to be more efficacious than pharmacotherapy.[10,47,48,50] CBT is preferred for motivated patients, particularly children and adolescents, with both mild OCD symptoms and psychiatric comorbidities, and in those with a desire to avoid medications.[9,10,45,50] Additionally, CBT offers flexibility in dosing (eg, weekly or intensively) and format (eg, individual, group, with or without family involvement).[10,50] Furthermore, family psychoeducation to minimize family accommodation (eg, adaptation of family routines that facilitate ritualistic compulsions) should be

integrated into treatment plans to minimize the patient's functional impairment, family conflict/distress, and disruptive behavior to facilitate improved treatment response.[51]

Other nonpharmacologic options include neuromodulatory approaches (eg, deep brain stimulation [DBS], TMS, and electroconvulsive therapy [ECT]) and ablative neurosurgery for severely symptomatic patients who have not achieved sustained response to standard of care interventions.[10,22] While these alternatives may be effective in some patients, uncertainties regarding optimal stimulation site and settings for these neuromodulatory approaches likely contribute to heterogeneity in outcomes.[22] It is important to note that DBS is FDA-approved as a humanitarian device for severe, treatment-resistant OCD,[46] and ablative neurosurgery remains an intervention of last resort.[22] Preliminary data regarding the efficacy of TMS, a noninvasive strategy, and ECT are promising but still inconclusive to support routine use.

Pharmacologic Therapy

6 7 SSRIs are considered to be the drugs of choice for patients with OCD,[45] and while not FDA-approved, citalopram and escitalopram have also shown efficacy in reduction of OCD symptoms.[10,48] Clomipramine, a TCA with strong 5-HT reuptake inhibition, is a second-line treatment option.[54] Benzodiazepines should not be used to treat OCD-related obsessions and compulsions.[22,45]

Antidepressant Therapy

SSRIs and clomipramine are the main antidepressants used in OCD treatment,[45] as current evidence indicates that 5-HT is important for the antiobsessional effects of these medications.[52] Pharmacologically SSRIs and clomipramine inhibit 5-HT reuptake into the presynaptic neuron, making more 5-HT available to postsynaptic receptors and reducing formation of the 5-HT metabolite 5-hydroxyindoleacetic acid. Although other nonclomipramine TCAs (eg, amitriptyline, imipramine, and desipramine) inhibit 5-HT reuptake, they are less potent and selective. Prolonged exposure to increased amounts of 5-HT after chronic antidepressant treatment (2-3 weeks) leads to altered responsiveness of postsynaptic 5-HT receptors or presynaptic autoregulatory receptors that govern 5-HT release in specific brain regions. An improvement in obsessional symptoms may correlate with plasma concentrations of clomipramine but not desmethylclomipramine, the metabolite of clomipramine with less selectivity for

5-HT reuptake inhibition.[53]

Most experts agree that SSRIs are better tolerated than clomipramine.[10] Table 88-5 details the monitoring of SSRI and clomipramine pharmacotherapy in patients with OCD. SSRIs are less likely to cause cardiovascular, sedative, anticholinergic, and weight-gain side effects, and to reduce the seizure threshold. Clomipramine, however, is less likely than SSRIs to cause insomnia, akathisia, nausea, and diarrhea. Regardless of the specific medication used, antidepressant side effects can be more severe when larger doses are used and with faster dose escalation.

SSRIs are effective in the treatment of OCD with almost half (40%-60%) of patients achieving a response.[10] Well-designed trials comparing these medications with placebo in head-to-head comparative trials, and meta-analyses have established that fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and escitalopram are equally effective.[22,48] However, the literature is conflicting in regards to whether clomipramine is more effective than the SSRIs.[10,22,48]

Pharmacokinetics Clomipramine is rapidly absorbed after oral administration[54] with maximum plasma concentrations occurring within 2 to 6 hours. Clomipramine is also highly protein-bound (97%) in the blood and has a half-life of 19 to 37 hours. The drug is metabolized to an active metabolite, desmethylclomipramine, which inhibits NE reuptake. See **Table 88-4** for information on monitoring clomipramine plasma levels. The pharmacokinetics of SSRIs is discussed in Chapter 85. It is important to note that since clomipramine and the SSRIs are extensively metabolized in the liver, patients with significant liver disease should be prescribed these drugs cautiously and in lower doses than those used in healthy subjects. Additionally, increased plasma concentrations of paroxetine occur in subjects with renal impairment necessitating a reduced initial dose.[28] Additionally for elderly patients, little information is available regarding pharmacokinetic changes, therefore the medication selection should be based on history of response and adverse effect profile, with treatment being initiated using a low dose, which is then increased slowly, with vigilance for emergence of adverse effects.[26,45]

TABLE 88-4 Adult Dosing of Serotonin Reuptake Inhibitors in the Treatment of OCD

Drug	Brand Name	Initial Dose	Usual Range	Comments
Citalopram[a,b]	Celexa®	20 mg daily	20-40 mg daily	Maximum dose is 40 mg in adults daily to prevent QTc prolongation; maximum dose of 20 mg daily in elderly patients, CYP2C19 poor metabolizers, or use with concurrent moderate-to-strong CYP2C19 inhibitors (eg, cimetidine, omeprazole)
Clomipramine[a]	Anafranil®	25 mg daily	100-250 mg daily	Doses up to 300 mg daily may be needed in some patients. Steady state trough plasma levels (clomipramine and desmethylclomipramine) should be <500 ng/mL (mcg/L; ~1.7 µmol/L) to minimize risk of conduction delays and seizures
Escitalopram[a,b]	Lexapro®	10 mg daily	10-20 mg daily	Doses up to 40 mg may be needed in some patients
Fluoxetine[a]	Prozac®	20 mg daily	40-60 mg daily	Doses of 80 mg or higher may be needed in some patients
Fluvoxamine[a]	Luvox® Luvox CR®	50 mg daily 100mg bedtime	100-300 mg daily 100-300 mg daily	
Paroxetine[a]	Paxil®, Pexeva®	20 mg daily	40-60 mg daily	Higher doses may be needed in some patients
Sertraline[a]	Zoloft®	50 mg daily	50-200 mg daily	Higher doses may be needed in some patients

OCD, obsessive-compulsive disorder.

[a]Available generically.

[b]Not FDA-approved for treatment of obsessive-compulsive disorder. Optimal dosing guidelines are not well established.

Data from References 10, 26, 28, 29, 54, and 56.

Adverse Effects When selecting pharmacotherapy, the clinician should consider medication specific adverse effects such as QTc prolongation risk with citalopram and escitalopram; anticholinergic effects and weight gain risk (eg, with paroxetine in patients with diabetes, obesity, or benign prostatic hypertrophy); insomnia risk with fluoxetine in patients with sleep difficulties; increased risk of suicidality in patients 24 years old and younger taking antidepressants; and drug–drug interaction risk for which citalopram, escitalopram, and sertraline have the least potential for CYP450 isoenzyme inhibition (see Chapter 85).[22]

Risks to consider with clomipramine include lethality in overdose in patients with suicidal ideation; anticholinergic effects in patients with constipation, narrow-angle glaucoma, or urinary hesitancy; and potential for seizures in patients with epilepsy.[54] Clomipramine use is associated with the risk of QTc prolongation when used alone and in combination with other agents that prolong the QTc interval.[54,55] Clomipramine should also be used with caution in patients with a history of cardiovascular disease or conduction abnormalities. Because of clomipramine's sedative and anticholinergic side effects, it is not usually chosen as first-line therapy for elderly OCD patients.[45] The use of antidepressants in

elderly patients is discussed in Chapter 85.

Other Antidepressants Venlafaxine and duloxetine, 5-HT and NE reuptake inhibitors, as well as mirtazapine may also be effective for OCD.[22] Therefore, these antidepressants can be considered second or third line therapy options.[4] See Table 88-3.

Dosage and Administration

8 Table 88-4 summarizes dosing guidelines for SSRIs and clomipramine. The SSRI dose to achieve response in OCD is often higher than doses used in other indications.[45,46] Data from fixed-dose studies in adults indicate that higher SSRI doses are more efficacious than lower doses, although there is a higher adverse effect burden.[22] However, there are no fixed dose studies to guide clinicians on how high to increase the clomipramine dose. If there is inadequate response to an average antidepressant dose, then it should be incrementally increased to the maximum dose within 5 to 9 weeks from the start of treatment. If there is an inadequate response after 4 to 6 weeks at the maximum dose, then another antidepressant should be tried.[45] Eight to 12 weeks is considered an adequate antidepressant trial for OCD treatment before changing to another agent.

Alternative Drug Treatments

9 **Augmentation with Antipsychotics** Augmentation of SSRI treatment with low-to-moderate doses of antipsychotics may be helpful,[10,22,57] and should be considered for patients with tic-related OCD, comorbid psychosis, and treatment-refractory patients. One-third of treatment-refractory patients with OCD respond to antipsychotic augmentation and perhaps with an earlier response (2-4 weeks) compared to antidepressants.[22] A recent meta-analysis found greater effect sizes for aripiprazole, haloperidol, and risperidone whereas olanzapine, paliperidone, and quetiapine failed to differentiate from placebo; however, quetiapine and olanzapine have been associated with at least one positive result from a randomized controlled trial.[58] First-generation antipsychotics, such as haloperidol, are less preferred given risk of extrapyramidal symptoms. As the long-term use of second-generation antipsychotic augmentation result in higher rates of adverse effects (eg, weight gain, increased blood glucose, lipid abnormalities), treatment should be discontinued if no benefits have been observed after 6 to 10 weeks.[22] Monitoring of antipsychotics can be found in Chapter 84.

Novel Augmentation Strategies While augmentation with antipsychotics have the largest evidence base,[57] recent studies have examined novel augmentation approaches using glutamatergic drugs (eg, *N*-acetylcysteine, riluzole, memantine, lamotrigine, minocycline, and topiramate) and ondansetron with initial promising results.[10,58] D-cycloserine augmentation of ERP in refractory OCD patients have had mixed results; further research is needed to identify patient and treatment characteristics that may differentially moderate response.[59]

Special Populations

Pregnancy Risk–benefit analysis should be made by practitioners when deciding to use pharmacotherapy options during pregnancy.[45,60] The use of antidepressants in pregnancy and lactation is discussed in Chapter 85 and the use of antipsychotics in pregnancy and lactation is discussed in Chapter 84.

Children and Adolescents Younger patients exhibit poorer insight regarding obsessions, have more obsessions involving fear of harm and separation, and possess more rituals involving family members. Similar to adult OCD, CBT including ERP and family members and/or SSRI treatment are considered first-line for pediatric patients depending on illness and patient characteristics.[47,51,55] CBT is superior to pharmacotherapy for mild-to-moderate pediatric OCD.[47]

Both childhood and adult OCD appear to respond similarly to antidepressant therapy with approximately at 50% response rate being seen during the initial SSRI trial in children. Clomipramine, fluvoxamine, sertraline, paroxetine, and fluoxetine are approved by the FDA for the treatment of OCD in children and adolescents.[45] Importantly, in children, the specific side effects of SSRI therapy that are more likely to occur compared to adults include treatment-emergent suicidal ideation, behavioral activation, and mania, and, in fact, all antidepressants now include a black box warning regarding risk for suicide in patients 24 years and younger.[51,57] The risk of suicidality in youth is discussed in Chapter 85. Augmentation of SSRIs with antipsychotics or clomipramine is not well studied in pediatric patients but can be considered for treatment-refractory patients, who failed SSRI augmentation with CBT, based on expert opinion and guideline recommendations.[51,55]

Antidepressant Dosing in Children Pediatric patients often require smaller initial doses of medications (eg, fluoxetine 10 mg daily) compared to adults (eg, fluoxetine 20 mg daily). The starting dose of clomipramine in children is 25 mg daily in divided doses[54] with dose escalations occurring over the first 2 weeks up

to 3 mg/kg or 100 mg, whichever is smaller. Over the next several weeks, the dose can then be increased up to 3 mg/kg with a maximum of 200 mg daily given once daily at bedtime.

Personalized Pharmacotherapy

The choice of an SSRI for the treatment of OCD is based on history of prior response, safety, and side-effect tolerability of the patient (see **Table 88-5**). While all SSRIs are considered equally efficacious, a patient may respond better to one agent over another.[45,48] Therefore, antidepressant treatment decisions should take into account patient specific factors, such as, previous treatment, family history of medication response, patient preference and the patient's ability to pay for medications. Currently, there are no guidelines that specifically address the use of pharmacogenomics testing in OCD. However, there are data that can help guide medication selection based on specific gene drug pairs for many of the antidepressants used in treating OCD. CPIC is a valuable resource for understanding dosing recommendations for these various drug and gene combinations.[44] Use of these guidelines, along with any testing interpretation results, may help reduce the risk of antidepressant specific adverse events, potentially, facilitating successful treatment.

TABLE 88-5 Monitoring of Patients Being Treated for OCD

Drug	Adverse Drug Reaction	Monitoring Consideration
Clomipramine	Dry mouth, constipation, nausea, dyspepsia, anorexia, somnolence, tremors, dizziness, nervousness	Assess at every visit, however, tolerance to these adverse events should occur in 2 weeks after treatment is started or a dosage increase is made. New onset adverse events may occur due to drug–drug interactions
	Seizures	Assess if new onset seizures have occurred at each visit
	Orthostatic hypotension, tachycardia, ECG changes	Obtain baseline ECG and vital signs in pediatric patients, patients >40 years, those with cardiovascular disease, or those with other risk factors for QTc prolongation (eg, electrolyte abnormalities, concomitant QTc prolonging medications)
	Suicidality	Obtain at every visit. Highest risk is in patients ≤24 years
	Agranulocytosis, leukopenia	Obtain CBC with differential if patient complains of sore throat, fever
	Weight gain	Obtain vitals (including height and weight) and assess at each visit
SSRIs	Nausea, vomiting, diarrhea, sexual dysfunction, headache, insomnia	Should be assessed at every visit, but generally these adverse events and mild and short-lived. They may reoccur due to a new drug–drug interaction
	Anxiety and agitation	Assess at each visit. May occur in some patients early in treatment
	Discontinuation syndrome	Slowly taper medication to reduce the occurrence of this adverse event. Patient education is key in recognizing its occurrence
	Suicidality	Assess at every visit. Highest risk is in patients ≤24 years
	QTc prolongation	Obtain baseline ECG and electrolytes. Of most concern with citalopram doses over 40 mg daily in adults and 20 mg daily in elderly patients or in those with risk factors of patients >60 years, female sex, cardiovascular disease, hypokalemia, hypomagnesemia, or concurrent use of drugs that prolong QTc

EVALUATION OF THERAPEUTIC OUTCOMES

Target symptoms of OCD should be monitored closely with the degree of response being used to indicate a need to modify dosage, change drug, or augment therapy. Rating scales can be used to monitor symptom response to therapy for OCD (eg, Y-BOCS) and changes in QOL.[22,45] Response is often defined by an improvement of 25% to 35% in baseline symptoms whereas remission is defined as a total Y-BOCS score less than 16 (out of a total score of 40), both of which still indicates substantial symptomatology.[22] The clinician should inquire about and address problematic adverse effects, including the emergence of suicidal ideation, reported by the patient and the amount of time the patient spends obsessing and performing compulsions (see Table 88-5).[45] Additionally, changes in social and occupational functioning should be assessed.

10 After patients have responded in the acute phase of treatment, treatment gains are maintained with maintenance-phase strategies.[45] Monthly follow-up

visits are recommended for at least 3 to 6 months, and a medication taper can be considered after 1 to 2 years of treatment depending on relapse prevalence, side effects, and patient preferences.[45,51,55] Treatment discontinuation results in higher relapse rates compared with treatment continuation[38] and medication should not be rapidly discontinued. Booster CBT sessions can reduce the risk of relapse when medication is withdrawn.[45] When making the decision to withdraw medication therapy, the drug dosage can be decreased by 10% to 25% every 1 to 2 months with careful observation for symptom relapse. However, most patients require lifelong medication therapy given chronicity of symptoms.[38]

CONCLUSION

Beginning with the DSM-5, both PTSD and OCD related disorders were removed from the anxiety disorder classification. Neurobiological changes in the HPA axis and the cortico-striato-thalamo-cortical circuit are largely implicated in PTSD and OCD, respectively. The age of onset of PTSD is variable since it depends on trauma or stressful event exposure though it typically occurs before age 40 years. OCD has a bimodal age of onset peaking in late childhood/adolescence and in early adulthood. Both conditions have effective nonpharmacological methods to reduce symptoms including trauma focused therapy and EMDR for PTSD and CBT with ERP in OCD. SSRIs are the first-line treatment for both conditions; however, moderate-to-high dose SSRIs are typically needed in OCD treatment. The use of antipsychotics in PTSD is controversial, whereas there is a clear role for antipsychotic augmentation in OCD treatment. Pharmacotherapy should be continued for at least 1 year in PTSD and 1 to 2 years in OCD.

Postclass Engaged Learning Activity

PTSD

Conduct a literature search and identify a primary research manuscript published within the last 12 months regarding the use of 3, 4-Methylenedioxymethamphetamine (MDMA) or ketamine for assistance during psychotherapy for PTSD. Write a list of pros and cons of this treatment approach and develop an opinion as to its place in therapy.

This activity is intended to build your literature evaluation skills and ability to critically appraise research manuscripts.

OPTIONAL ADDITIONAL ACTIVITY

Utilizing http://youtube.com, search for and watch a short video on Eye Movement Desensitization and Reprocessing (EMDR). The goal of this activity is to understand and visualize how EMDR is used in PTSD as well as possibly hear from a patient who has undergone EMDR treatment.

OCD

Conduct a literature search and identify a primary research manuscript that has been published in the past 12 months regarding the treatment of OCD using glutamatergic agents (eg, *N*-acetylcysteine, riluzole, memantine, lamotrigine, glycine partial agonists). Write a brief summary about the medication's mechanisms of action, how it is administered, and one potential advantage or disadvantage of this new medication compared to the current standard of care (eg, CBT with ERP, SSRIs, clomipramine, and antipsychotic augmentation).

This activity is intended to build your literature evaluation skills and ability to critically appraise research manuscripts.

ABBREVIATIONS

ASD	acute stress disorder
CAPS	Clinician-Administered Posttraumatic Stress Disorder Scale
CBT	cognitive behavioral therapy
CPIC	Clinical Pharmacogenomics Implementation Consortium
CRF	corticotropin-releasing factor
DA	dopamine
dACC	dorsal anterior cingulate cortex
DBS	deep brain stimulation
EMDR	eye movement desensitization and reprocessing
ERP	exposure and response prevention
GABA	γ-aminobutyric acid
5-HT	Serotonin (5-hydroxytryptamine)
HPA	hypothalamic–pituitary–adrenal
MAOI	monoamine oxidase inhibitor
NE	norepinephrine

NPY	neuropeptide Y
OCD	obsessive-compulsive disorder
PANDAS	pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection
PTSD	posttraumatic stress disorder
QOL	quality of life
SNP	single nucleotide polymorphism
SNRI	serotonin–norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
TFCBT	trauma-focused cognitive behavioral therapy
TMS	transcranial magnetic stimulation
mPFC	medial prefrontal cortex
Y-BOCS	Yale-Brown Obsessive-Compulsive Scale

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
2. Sher L, Braquehais M, Casas M. Posttraumatic stress disorder, depression, and suicide in veterans. *Cleve Clin J Med*. 2012;79(2):92–97.
3. Shalev A, Liberzon I, Marmar C. Post-traumatic stress disorder. *N Engl J Med*. 2017;376:2459–2469.
4. Katzman MA, Bleau P, Blier P, et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry*. 2014;14(suppl 1):S1.
5. Veterans Health Administration, Department of Defense. VA/DoD clinical practice guideline for the management of post-traumatic stress disorder and acute stress disorder. Washington (DC): Veterans Health Administration, Department of Defense; 2017 June. Available online at https://www.healthquality.va.gov/guidelines/MH/ptsd/VADoDPTSDCPGF Accessibility verified April 9, 2018.
6. De La Vega D, Giner L, Courtet P. Suicidality in subjects with anxiety or obsessive-compulsive and related disorders: Recent advances. *Curr*

Psychiatry Rep. 2018;20(4):26.

7. National Institute of Mental Health. Obsessive-compulsive disorder among adults. Available at https://www.nimh.nih.gov/health/statistics/obsessive-compulsive-disorder-ocd.shtml. Accessed June 20, 2018.
8. Gradus JL. Prevalence and prognosis of stress disorders: A review of the epidemiologic literature. *Clin Epid*. 2017;9:251–260.
9. Richter PMA, Ramos RT. Obsessive-compulsive disorder. *Continuum (Minneap Minn)*. 2018;24(3):828–844.
10. Hirschtritt ME, Bloch MH, Mathews CA. Obsessive-compulsive disorder: advances in diagnosis and treatment. *JAMA*. 2017;317(13):1358–1367.
11. Bokor G, Anderson PD. Obsessive-compulsive disorder. *J Pharm Pract*. 2014;27(2):116–130.
12. Logue MW, Smith AK, Baldwin C, et al. An analysis of gene expression in PTSD implicates genes involved in the glucocorticoid receptor pathway and neural responses to stress. *Psychoneuroendocrinology*. 2015;57:1–13.
13. Guillen-Burgos HF, Gutierrez-Ruiz K. Genetic advances in post-traumatic stress disorder. *Rev Colomb Psiquiat*. 2018;647(2):108–118.
14. Navarro-Mateu F, Escamez T, Koenen KC, et al. Meta-analysis of the 5-HTTLPR polymorphisms in post-traumatic stress disorder. *PLoS One*. 2013;8:e66227.
15. Rajendram R, Kronenberg S, Burton CL, Arnold PD. Glutamate genetics in obsessive-compulsive disorder: A review. *J Can Acad Child Adolesc Psychiatry*. 2017;26(3):205–213.
16. Mullen S. Review of pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections. *Ment Health Clin*. 2015;5(4):184–188.
17. Sherin JE, Nemeroff CB. Posttraumatic stress disorder: The neurobiological impact of psychological trauma. *Dialogues Clin Neurosci*. 2011;13:263–278.
18. Martin EI, Ressler KJ, Binder E, Nemeroff CB. The neurobiology of anxiety disorders: Brain imaging, genetics and psychoneuroendocrinology. *Psychiatr Clin North Am*. 2009;32:549–575.
19. Fragkaki I, Thomaes K, Sijbrandij M. Posttraumatic stress disorder under ongoing threat: A review of neurobiological and neuroendocrine findings. *Eur J Psychotraumatology*. 2016;9:30915.

20. Kautz M, Charney DS, Murrough JW. Neuropeptide Y, resilience, and PTSD therapeutics. *Neurosci Lett*. 2017;649:164–169.
21. Issari Y, Jakubovski E, Bartley CA, et al. Early onset of response with selective serotonin reuptake inhibitors in obsessive-compulsive disorder: A meta-analysis. *J Clin Psychiatry*. 2016;77(5):e605–e611.
22. Fineberg N, Reghuneudanan S, Simpson HB, et al. Obsessive-compulsive disorder (OCD): Practice strategies for pharmacologic and somatic treatment in adults. *Psychiatry Res*. 2015;227:114–125.
23. Sinopoli VM, Burton CL, Kronenberg S, et al. A review of the role of sertotonin system genes in obsessive-compulsive disorder. *Neurosci Biobehav Rev*. 2017;80:372–381.
24. Shin LM, Liberzon I. The neurocircuitry of fear, stress and anxiety disorders. *Neuropsychopharmacology*. 2010;35:169–191.
25. Le QA, Doctor JN, Zoellner LA, Feeny NC. Effects of treatment, choice, and preference on health-related quality-of-life outcomes in patients with posttraumatic stress disorder (PTSD). *Qual Life Res*. 2018;27(6):1555–1562.
26. Bandelow B, Sher L, Bunevicius R, et al. Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder, and post-traumatic stress disorder in primary care. *Int J Psychiatry Clin Pract*. 2012;16:77–84.
27. Ipser JC, Stein DJ. Evidence-based pharmacotherapy of post-traumatic stress disorder. *Int J Neuropsychopharmacol*. 2012;15(6):825–840.
28. Paxil [package insert]. Research Triangle Park, NC: GlaxoSmithKline, October 2016.
29. Zoloft [package insert]. New York, NY: Pfizer Inc, January 2018.
30. Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: A revision of the 2005 guidelines from the British Association of Psychopharmacology. *J Psychopharmacol*. 2014;28(5):403–439.
31. Watts BV, Schnurr PP, Mayo L, Young-Xu Y, Weeks WB, Friedman MJ. Meta-analysis of the efficacy of treatments for posttraumatic stress disorder. *J Clin Psychiatry*. 2013;74(6):e541–e550.
32. Hoskins M, Pearce J, Bethell A, et al. Pharmacotherapy for posttraumatic stress disorder: Systematic review and meta-analysis. *BJP*. 2015;206:93–100.

33. Davidson J, Rothbaum BO, Tucker P, et al. Venlafaxine extended release in posttraumatic stress disorder: A sertraline- and placebo-controlled study. *J Clin Psychopharmacol*. 2006;26:259–267.
34. Davidson J, Baldwin D, Stein DJ, et al. Treatment of posttraumatic stress disorder with venlafaxine extended release: A 6-month randomized controlled trial. *Arch Gen Psychiatry*. 2006;63:1158–1165.
35. Villarreal G, Hamner MB, Cañive JM, et al. Efficacy of quetiapine monotherapy in posttraumatic stress disorder: A randomized, placebo-controlled trial. *Am J Psychiatry*. 2016;173(12):1205–1212.
36. Singh B, Hughes AJ, Mehta G, Erwin PJ, Parsaik AK. Efficacy of prazosin in posttraumatic stress disorder: A systematic review and meta-analysis. *Prim Care Companion CNS Disord*. 2016;18(4):.doi: 10.4088/PCC.16r01943.
37. Raskind MA, Peskind ER, Chow B, et al. Trial of prazosin for post-traumatic stress disorder in military veterans. *N Engl J Med*. 2018;378(6):507–517.
38. Batelaan NM, Bosman RC, Muntingh A, Scholten WD, Huijbregts KM, van Balkom AJLM. Risk of relapse after antidepressant discontinuation in anxiety disorders, obsessive-compulsive disorder, and post-traumatic stress disorder: Systematic review and meta-analysis of relapse prevention trials. *BMJ*. 2017;358:j3927.
39. Ipser JC, Stein DJ, Hawkridge S, Hoppe L. Pharmacotherapy for anxiety disorders in children and adolescents. *Cochrane Database Syst Rev*. 2009;3:CD005170. doi:10.1002/14651858.CD005170.pub2.
40. Keeshin BR, Strawn JR. Psychological and pharmacologic treatment of youth with posttraumatic stress disorder: An evidence-based review. *Child Adolesc Psychiatr Clin N Am*. 2014;23:399–411.
41. Zhang Y, Zhou X, Yang L, et al. Comparative efficacy and acceptability of psychotherapies for post-traumatic stress disorder in children and adolescents: Study protocol for a systematic review and network meta-analysis. *BMJ Open*. 2018;8(3):e020198.
42. Norman SB, Haller M, Hamblen JL, Soutwick SM, Pietrzak RH. The burden of co-occurring alcohol use disorder and PTSD in US Military veterans: Comorbidities, functioning, and suicidality. *Psychol Addict Behav*. 2018;32(2):224–229.
43. Miller MW. Leveraging genetics to enhance the efficacy of PTSD pharmacotherapies. *Neurosci Lett*. 2018 April 22. pii: S0304-

3940(18)30302–1. doi:10.1016/j.neulet.2018.04.039. [Epub ahead of print].

44. Clinical pharmacogenetics implementation consortium. Available at https://cpicpgx.org/. Last accessed, August 10, 2018.
45. American Psychiatric Association. *Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder*. Arlington, VA: American Psychiatric Association; 2007. Available at http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guid Accessed, July 6, 2018.
46. American Psychiatric Association. Guideline Watch (2013): Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder. Available at http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidwatch.pdf. Accessed, July 6, 2018.
47. Öst LG, Riise EN, Wergeland GJ, et al. Cognitive behavioral and pharmacological treatments of OCD in children: A systematic review and meta-analysis. *J Anxiety Disord*. 2016;43:58–69.
48. Skapinakis P, Caldwell DM, Hollingworth W, et al. Pharmacological and psychotherapeutic interventions for management of obsessive-compulsive disorder in adults: A systematic review and network meta-analysis. *Lancet Psychiatry*. 2016;3:730–739.
49. Varigonda AL, Jakubovski E, Bloch MH. Systematic review and meta-analysis: Early treatment response of selective serotonin reuptake inhibitors and clomipramine in pediatric obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry*. 2016;55(10):851–859.
50. Lewin AB, Wu MS, McGuire JF, Storch EA. Cognitive behavior therapy for obsessive-compulsive and related disorder. *Psychiatr Clin N Am*. 2014;37:415–445.
51. Bloch MH, Storch EA. Assessment and management of treatment-refractory obsessive-compulsive disorder in children. *J Am Acad Child Adolesc Psychiatry*. 2015;54(4):251–262.
52. Nestadt G, Grados M, Samuels JF. Genetics of OCD. *Psychiatr Clin North Am*. 2010;33(1):141–158.
53. Marcourakis T, Bernik MA, Lotufo NF, et al. Clomipramine demethylation rate is important on the outcome of obsessive-compulsive disorder treatment. *Int Clin Psychopharmacol*. 2015;30(1):43–48.
54. Anafranil [package insert]. Hazelwood, MO: Mallinckrodt Inc, February

2018.

55. Geller DA, March J. Practice parameter for the assessment and treatment of children and adolescents with obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry*. 2012;51(1):98–113.
56. Balant-Gorgia AE, Gex-Fabry M, Balant LP. Clinical pharmacokinetics of clomipramine. *Clin Pharmacokinet*. 1991;20(6):447–462.
57. Dold M, Aigner M, Lazenberger R, Kasper S. Antipsychotic augmentation of serotonin-reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: An update meta-analysis of double-blind, randomized, placebo-controlled trials. *Int J Neuropsychopharmacol*. 2015;18(9):1–11.
58. Marinova Z, Chuang D, Fineberg N. Glutamate-modulating drugs as a potential therapeutic strategy in obsessive-compulsive disorder. *Current Neuropharmacology*. 2017;15:977–995.
59. Mataix-Cols D, Fernandez de la Cruz L, Monzani B, et al. D-cycloserine augmentation of exposure-based cognitive behavior therapy for anxiety, obsessive-compulsive disorder, and posttraumatic stress disorders: A systematic review and meta-analysis of individual participant data. *JAMA Psychiatry*. 2017;74(5):501–510.
60. Uguz F. Pharmacotherapy of obsessive-compulsive disorder during pregnancy: A clinical approach. *Rev Bras Psiquiatr*. 2015;37(4):334–342.

89

Sleep–Wake Disorders

John M. Dopp and Bradley G. Phillips

KEY CONCEPTS

1. Common causes of insomnia include concomitant psychiatric disorders, significant psychosocial stressors, excessive alcohol use, caffeine intake, and nicotine use.
2. Good sleep hygiene, including relaxing before bedtime, exercising regularly, establishing a regular bedtime and wake-up time, and discontinuing alcohol, caffeine, and nicotine, alone and in combination with drug therapy, should be part of patient education and treatments for insomnia.
3. Long-acting benzodiazepines should be avoided in the elderly.
4. Benzodiazepine receptor agonist tolerance and dependence are avoided by using low-dose therapy for the shortest possible duration.
5. Obstructive sleep apnea may be an independent risk factor for the development of hypertension. When hypertension is present, it is often refractory to drug therapy until sleep-disordered breathing is alleviated.
6. Nasal continuous positive airway pressure is the first-line therapy for obstructive sleep apnea, and weight loss should be encouraged in all obese patients.
7. Pharmacologic management of narcolepsy is focused on two primary areas: treatment of excessive daytime sleepiness and REM sleep abnormalities.
8. Short-acting benzodiazepine receptor agonists, ramelteon, or melatonin taken at appropriate target bedtimes for east or west travel reduce jet lag and shorten sleep latency.
9. Dopamine agonists are standard therapy for restless legs syndrome but have adverse effects that require careful monitoring by patient and providers.

Preclass Engaged Learning Activity

Construct a table of medications used for insomnia, list the half-lives of their parent drug, and whether they are used for difficulty initiating or maintaining sleep.

Medication	Parent Drug Half-Life (hours)	Insomnia Use
Amitriptyline	15	Difficulty maintaining sleep
Zaleplon	1	Difficulty initiating sleep

INTRODUCTION

Approximately 70 million Americans suffer with a sleep-related problem, and as many as 60% of those experience a chronic disorder.[1] In a study by the National Institute on Aging, of 9,000 patients aged 65 years and older, more than 80% report a sleep-related disturbance.[1]

Sleep Cycles

Sleep is divided into two phases: nonrapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. Each night humans typically experience four to six cycles of NREM and REM sleep, with each cycle lasting between 70 and 120 minutes.[2] There are three stages of NREM sleep. Healthy sleep will typically progress through the four stages of NREM sleep prior to the first REM period. From wakefulness, sleep typically progresses quickly through stages 1 and 2. Stage 1 of NREM sleep is the stage between wakefulness and sleep, and individuals describe this experience as being awake, being drowsy, or being asleep. During stage 3 NREM, both metabolic activity and brain waves slow. This slow-wave sleep occurs most frequently early in the sleep period. Stage 3 sleep is called *delta sleep*, as the sleep is characterized by high-amplitude slow activity known as delta waves (0.5–3 Hz) with no eye movements and low tonic muscle activity.

REM sleep involves a dramatic physiologic change from NREM sleep to a state in which the brain becomes electrically and metabolically activated.[2] REM occurs in bursts and is accompanied by a 62% to 173% increase in cerebral blood flow, generalized muscle atonia, bursts of bilateral REMs, poikilothermia,

dreaming, and fluctuations in respiratory and cardiac rate.[2] REM cycles tend to lengthen in the later stages of the sleep cycle.[2]

Circadian Rhythm

At birth human infants spend up to 20 hours a day sleeping with differentiation between REM and NREM sleep occurring at 3 to 6 months of age and the ultradian sleep–wake rhythm changing to a circadian pattern by age 3. Key to this is the suprachiasmatic nucleus of the brain which serves as the biologic clock and paces the circadian rhythm; although the length of a day is 24 hours, in environments devoid of light cues, the sleep–wake cycle lasts about 25 hours.[3] Through development from childhood into adolescence, the amount of nightly delta sleep declines and amount of REM sleep increases. In midlife, however, there is a gradual decline in sleep efficiency and sleep time[2] as elderly persons have lighter and more fragmented sleep, with intermittent arousals, shifts in the sleep stages, and a gradual reduction of slow-wave sleep.

Neurochemistry

The neurochemistry of sleep is complex, as sleep cannot be localized to either a specific area of the brain or a specific neurotransmitter. Overall, NREM sleep appears to be controlled by the basal forebrain, the lower brain stem to the thalamus, and hypothalamus with numerous neurotransmitters mediating NREM sleep, including γ-aminobutyric acid (GABA) and adenosine.[3] In contrast, REM sleep appears to be turned on by cholinergic cells in the mesencephalic, medullary, and pontine gigantocellular regions and turned off by the dorsal raphe nucleus, the locus coeruleus, and the nucleus parabrachialis lateralis, the latter two of which are primarily noradrenergic. The ascending reticular activating system and the posterior hypothalamus also facilitate arousal and wakefulness[4] through neurotransmitters such as dopamine, which has an alerting effect.[5] Additional neurochemicals involved in wakefulness include norepinephrine and acetylcholine in the cortex and histamine and neuropeptides such as substance P and corticotropin-releasing factor in the hypothalamus.[5,6]

Polysomnography

Polysomnography (PSG) is the primary method used to assess and record variables that characterize sleep and aid in diagnosis of sleep disorders. As part

of this assessment, sleep is typically measured and observed in sleep laboratories using an electroencephalogram (EEG), electrooculograms of each eye, electrocardiogram, electromyogram, air thermistors, abdominal and thoracic strain belts, and oxygen saturation monitor. Variables obtained during PSG include sleep onset, arousals, sleep stages, eye movements, leg and jaw movements, arrhythmias, airflow during sleep, respiratory effort, and oxygen desaturations. Additionally, home sleep monitoring that measures variables such as electrocardiogram, oxygen saturation, airflow, and respiratory effort is increasingly used to diagnose sleep apnea.

Classification of Sleep Disorders

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* classifies sleep–wake disorders into 10 categories: (1) insomnia disorder, (2) hypersomnolence disorder, (3) narcolepsy, (4) breathing-related sleep disorders, (5) circadian rhythm sleep disorders, (6) non-REM sleep arousal disorders, (7) nightmare disorder, (8) REM sleep behavior disorder, (9) restless legs syndrome, and (10) substance- or medication-induced sleep disorder.[7]

INSOMNIA

Insomnia is the most common complaint in general medical practice[8] as it frequently causes distress, due to the fear or a feeling of not being able to fall asleep at bedtime, leading to impaired work-related productivity because of daytime fatigue or drowsiness. Therefore, insomnia disorder is subjectively characterized as trouble initiating or maintaining sleep associated with daytime consequences (insomnia not attributed to environment or limited opportunity for sleep).[7–9] Insomnia is classified as chronic when it has a duration of at least three months, occurring at least three times per week.[7,9]

Epidemiology

Primary insomnia usually begins in early or middle adulthood and is rare in childhood or adolescence. Short-term insomnia occurs in 33% to 50% of the adult population,[8] with a 1-year prevalence study of insomnia in the United States reporting that one-third of the individuals surveyed complained of insomnia and 17% reported that the symptoms were serious.[1] Conservative estimates of chronic insomnia range from 9% to 12% in adulthood and up to

20% in the elderly.[1,10] Although young adults are more likely to complain that they have difficulty falling asleep, middle-aged and elderly adults are more likely to complain that they have middle-of-the-night awakening or early morning awakening. Women complain of insomnia twice as frequently as men and individuals who are elderly, unemployed, separated, or widowed, and those with a lower socioeconomic status report a significantly higher incidence of insomnia than the general population. Forty percent of individuals with insomnia also have a concurrent psychiatric disorder (anxiety, depression, or substance abuse)[11] and a significant percentage of those with insomnia use nonprescription drugs or alcohol to self-treat.

TABLE 89-1 Common Etiologies of Insomnia

Situational

- Work or financial stress, major life events, interpersonal conflicts
- Jet lag or shift work

Medical

- Cardiovascular (angina, arrhythmias, heart failure)
- Respiratory (asthma, sleep apnea)
- Chronic pain
- Endocrine disorders (diabetes, hyperthyroidism)
- Gastrointestinal (gastroesophageal reflux disease, ulcers)
- Neurologic (delirium, epilepsy, Parkinson's disease)
- Pregnancy

Psychiatric

- Mood disorders (depression, mania)
- Anxiety disorders (eg, generalized anxiety disorder, obsessive-compulsive disorder)
- Substance abuse (alcohol or sedative-hypnotic withdrawal)

Pharmacologically induced

- Anticonvulsants
- Central adrenergic blockers
- Diuretics
- Selective serotonin reuptake inhibitors
- Steroids
- Stimulants

Differential Diagnosis

Insomnia is considered to be an endogenous disorder caused by either a neurochemical or a structural disorder affecting the sleep–wake cycle. Individuals with primary insomnia can be light sleepers who are easily aroused by noise, temperature, or anxiety. Some studies suggest that primary insomnia is a "hyperarousal state," in that insomnia patients have increased metabolic rates compared with controls and thus take longer to fall asleep.[2] Comorbid or secondary insomnia is frequently a symptom or manifestation of another medical disorder. Evaluation of patients with a complaint of transient or short-term insomnia should focus on recent stressors, such as a separation, a death in the family, a job change, or college exams.

1 Chronic insomnia is frequently comorbid with psychiatric or medical conditions. A complete diagnostic examination should be completed in these individuals and should include routine laboratory tests, physical and mental status examinations, as well as ruling out any medication- or substance-related causes.[12] Other sleep disorders that can have a similar presentation should be ruled out, including restless legs syndrome (RLS), periodic limb movement disorder, and sleep apnea. Common causes of insomnia are listed in **Table 89-1**.

TREATMENT

Desired Outcomes

The goals of treatment of insomnia are to correct the underlying sleep complaint, consolidate sleep, improve daytime functioning and sleepiness, and avoid adverse effects from selected therapies. Drug therapy should be used in the lowest possible dose, for the shortest possible time period.

General Approach to Treatment

Therapeutic management of insomnia is initially based on whether the individual has experienced a short-term or chronic sleep disturbance. Clinical history should assess the onset, duration, and frequency of the symptoms; effect on daytime functioning; sleep hygiene habits; and history of previous symptoms or treatment.[13] Management of all patients with insomnia should include identifying the cause, patient education on sleep hygiene, and stress management. Any unnecessary pharmacotherapy that may worsen insomnia should be eliminated.[10] Short-term insomnia, which generally occurs as a result

of acute stressors, is expected to resolve quickly and should be treated with good sleep hygiene and careful use of sedative-hypnotics.[11,13] Chronic insomnia requires careful assessment for possible underlying medical causes, nonpharmacologic approaches, and careful use of sedative-hypnotics.[12]

Nonpharmacologic Therapy

2 In many cases, insomnia can be treated without sedative-hypnotics. Education about normal sleep and habits for good sleep hygiene are important for all patients with insomnia. Nonpharmacologic interventions for insomnia frequently consist of short-term cognitive behavioral therapies, most commonly stimulus control therapy, sleep restriction, relaxation therapy, cognitive therapy, paradoxical intention, biofeedback, and education on good sleep hygiene (**Table 89-2**).[10,14] In patients aged 55 years and older, research indicates that cognitive behavioral therapy may be more effective than pharmacologic therapy at improving certain measures of insomnia.[15,16]

TABLE 89-2 Nonpharmacologic Recommendations for Management of Insomnia

Stimulus control procedures

1. Establish regular time to wake up and to go to sleep (including weekends).
2. Sleep only as much as necessary to feel rested.
3. Go to bed only when sleepy. Avoid long periods of wakefulness in bed. Use the bed only for sleep or intimacy; do not read or watch television in bed.
4. Avoid trying to force sleep; if you do not fall asleep within 20-30 minutes, leave the bed and perform a relaxing activity (eg, read, listen to music) until drowsy. Repeat this as often as necessary.
5. Avoid blue spectrum light from television, smart phones, tablets, and other mobile devices
6. Avoid daytime naps.
7. Schedule worry time during the day. Do not take your troubles to bed.

Sleep hygiene recommendations

1. Exercise routinely (three to four times weekly) but not close to bedtime because this can increase wakefulness.
2. Create a comfortable sleep environment by avoiding temperature extremes, loud noises, and illuminated clocks in the bedroom.
3. Discontinue or reduce the use of alcohol, caffeine, and nicotine.
4. Avoid drinking large quantities of liquids in the evening to prevent nighttime trips to the restroom.
5. Do something relaxing and enjoyable before bedtime.

Pharmacologic Therapy

Miscellaneous agents

Antihistamines exhibit sedating properties and are included in many nonprescription sleep agents as they are effective in the treatment of mild insomnia and are generally safe.[13] Diphenhydramine and doxylamine are more sedating than pyrilamine. However, patients quickly experience tolerance to sedative effects, and increasing the dose of antihistamines will not produce a linear increase in response. Antihistamines are considered to be less effective than benzodiazepines, and they have the disadvantages of anticholinergic side effects, which are especially troublesome in the elderly.[13,17]

For patients with nonrestorative sleep who should not receive benzodiazepines, antidepressants may be an alternative treatment, especially those who have depression, pain, or a risk of substance abuse. Using antidepressants for insomnia without depression is common but not well studied, and the doses used for treating insomnia are not effective antidepressant

doses.[9,13,14] However, low-dose doxepin (3-6 mg) is FDA-approved for the treatment of sleep maintenance insomnia. Other sedating antidepressants such as amitriptyline, doxepin, and nortriptyline are effective in inducing sleep continuity, although daytime sedation and side effects can be significant.[9,13] Anticholinergic activity, adrenergic blockade, and cardiac conduction prolongation can be problematic, especially in the elderly and in overdose situations.[9] Mirtazapine is a sedating antidepressant that may help patients sleep, but it may also cause daytime sedation and weight gain.

Trazodone is popular for the treatment of insomnia in patients prone to substance abuse or in patients with selective serotonin reuptake inhibitor and bupropion-induced insomnia, as dependence is not a problem with trazodone.[11] Trazodone in doses of 25 to 100 mg at bedtime is sedating and can improve sleep continuity.[11] Side effects associated with trazodone use include carryover sedation and α-adrenergic blockade and orthostasis, which can occur at any age, but it is more dangerous in the elderly. Priapism is a rare but serious side effect.[18]

Suvorexant is a dual orexin A and orexin B receptor antagonist that instead of inducing sleepiness, similar to most treatments for insomina, turns off wake signaling. Suvorexant doses of 10 to 20 mg at bedtime are indicated for difficulty initiating and maintaining sleep. The most commonly reported side effect with suvorexant use is somnolence, and patients should be counseled that sleep paralysis, cataplexy, and other narcolepsy-like symptoms may rarely occur.[19] Caution should be used in patients with depression as suvorexant can worsen depression and trigger suicidal thinking in a dose-dependent manner.

Ramelteon is a melatonin receptor (MT) agonist approved for the treatment of sleep-onset insomnia. It is selective for the MT1 and MT2 melatonin receptors that are thought to regulate the circadian rhythm and sleep onset. The recommended dose is 8 mg taken at bedtime to induce sleep, and although generally well tolerated, the most common adverse events reported are headache, dizziness, and somnolence. Ramelteon is not a controlled substance and can be a viable option for patients with a history of substance abuse; however, patients may not feel that it is as effective, as it does not cause the acute drowsiness associated with other insomnia agents. It does, however, effectively treat sleep-onset difficulties in patients with chronic obstructive pulmonary disease and sleep apnea.[20,21]

Valerian is a herbal sleep remedy that has been studied for its sedative-hypnotic properties in patients with insomnia. The mechanism of action is not fully understood but may involve increasing concentrations of GABA. The

recommended dose for insomnia ranges from 300 to 600 mg. An equivalent dose of dried herbal valerian root is 2 to 3 g soaked in one cup of hot water for 20 to 25 minutes.[22]

Benzodiazepine receptor agonists

The most commonly used treatments for insomnia have been the benzodiazepine receptor agonists (BZDRAs) which are FDA-labeled for the treatment of insomnia (**Table 89-3**). The FDA requires BZDRA labeling to include a caution regarding anaphylaxis, facial angioedema, and complex sleep behaviors (eg, sleep driving, phone calls, sleep eating, etc.). The BZDRAs consist of the newer nonbenzodiazepine GABAA agonists and the traditional benzodiazepines. All BZDRAs bind to GABAA receptors in the brain, resulting in agonist effects on GABAergic transmission and hyperpolarization of neuronal membranes. Traditional benzodiazepines have sedative, anxiolytic, muscle relaxant, and anticonvulsant properties; newer nonbenzodiazepine GABA agonists possess only sedative properties.

TABLE 89-3 Pharmacokinetics of Benzodiazepine Receptor Agonists

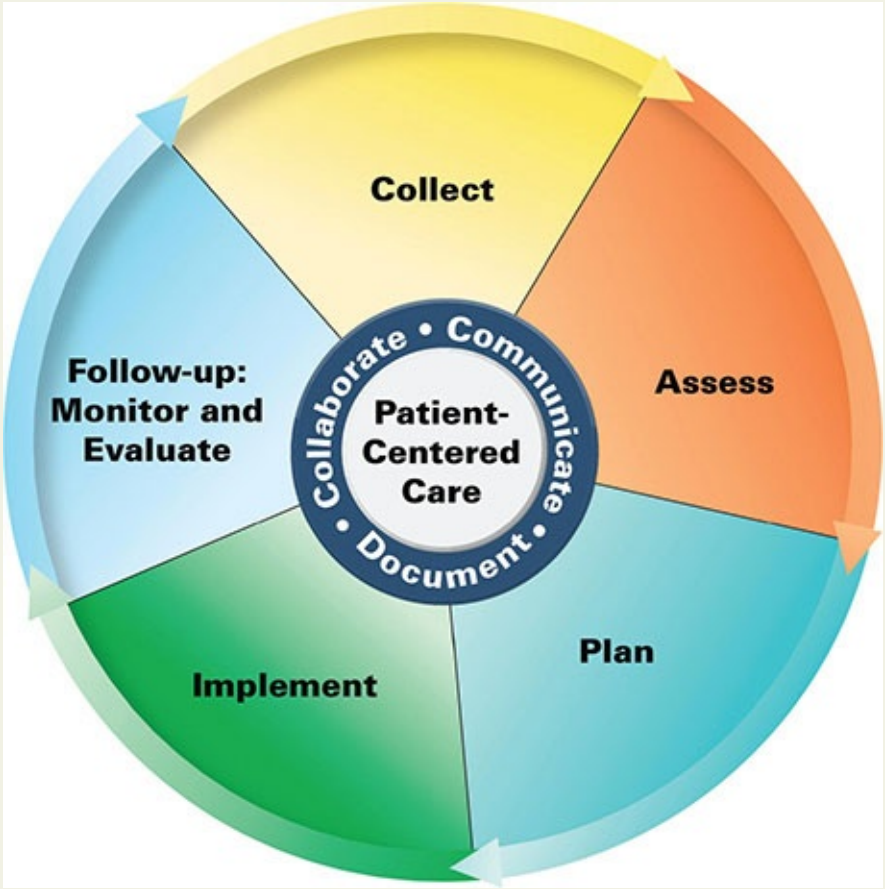
Generic Name (Brand Name)	t_{max} (hours)[a]	Half-Life[b] (hours)	Daily Dose Range (mg)	Metabolic Pathway	Clinically Significant Metabolites
Estazolam (ProSom)	2	12-15	1-2	Oxidation	–
Eszopiclone (Lunesta)	1-1.5	6	2-3	Oxidation	–
				Demethylation	
Flurazepam (Dalmane)	1	8	15-30	Oxidation	Hydroxyethylflurazepam, flurazepam aldehyde
				N-dealkylation	*N*-desalkylflurazepam[c]
Quazepam (Doral)	2	39	7.5-15	Oxidation, *N*-dealkylation	2-Oxo-quazepam, *N*-desalkylflurazepam[c]
Temazepam (Restoril)	1.5	10-15	15-30	Conjugation	–
Triazolam (Halcion)	1	2	0.125-0.25	Oxidation	–
Zaleplon (Sonata)	1	1	5-10	Oxidation	–
Zolpidem (Ambien; Intermezzo)	1.6	2-2.6	1.75-10[d]	Oxidation	–

[a]Time to peak plasma concentration.

[b]Half-life of parent drug.

[c]*N*-desalkylflurazepam, mean half-life 47-100 hours.

[d]Oral and sublingual dosing 5-10 mg; sublingual tablets for middle-of-the night dosing 1.75-3.5 mg (1.75 for women, 3.5 for men).



Patient Care Process for Sleep–Wake Disorders

Collect

- Patient characteristics (eg, age, sex, concomitant medical conditions, environmental or social stressors)
- Information about nighttime sleep complaints and daytime consequences from patient and bedpartner
- Detailed medication history of prescription, OTC, and complementary/alternative medication use
- Subjective and objective data about daytime sleepiness, sleep quality, limb movements, snoring, witnessed apneas, and parasomnias
- Information about sleep routine, sleep hygiene, and social history (caffeine, alcohol, and tobacco use)
- Results from sleep testing (if available)

Assess

- Evaluate if individual environmental or social issues are contributing to sleep difficulties.
- Assess patient medications to determine if any medication may be contributing to sleep and/or daytime complaints.
- Assess any laboratory or sleep study test results that aid in assessment/treatment of sleep complaints (serum ferritin, TSH, etc.).
- Concomitant psychiatric or other medication conditions that should be addressed as part of sleep evaluation (eg, presence of anxiety, depression, chronic pain).

Plan*

- Optimize sleep hygiene and related behaviors (Tables 89-1 and 89-2) that may influence sleep and daytime symptoms.
- For insomnia, if sedative-hypnotic therapy is prescribed, match the duration of action for agent to sleep complaint (eg, short-duration agents for difficulty initiating sleep and moderate duration agents for difficulty maintaining sleep) (Table 89-3).
- Ensure that lowest doses of medication possible are used, but if response is inadequate, consider increasing dose or adding complementary medication.
- For narcolepsy or sleepiness disorders, consider use of long-acting stimulants to increase wakefulness throughout the day with as needed short-acting stimulants for late afternoon or evening periods requiring wakefulness (Table 89-4).

Implement*

- Provide patient education regarding all elements of treatment plan.
- Use motivational interviewing and coaching strategies to maximize adherence.
- Answer patient questions about medications and potential adverse effects.

Follow-up: Monitor and Evaluate

- Evaluate improvement in the specific sleep complaint (eg, how has therapy affected sleep latency or sleep maintenance?).

- Monitor daytime sleepiness, sleep diaries, and diaries of sleep events (PLMS, hallucinations, snoring, apneas, etc.) and monitor cataplexy and other daytime symptoms to determine if therapy is effective.
- Make appropriate changes to therapy to address inadequately controlled symptoms and reported adverse effects (Tables 89-4 and 89-6).

*Collaborate with patient, caregivers, and other healthcare professionals.

Benzodiazepine hypnotics

Benzodiazepines relieve insomnia by reducing sleep latency and increasing total sleep time by increasing stage 2 sleep while decreasing delta sleep.[11] Benzodiazepine hypnotics should not be prescribed for individuals who are pregnant or who have untreated sleep apnea or a history of substance abuse, and patients should be instructed to avoid alcohol and other central nervous system (CNS) depressants.

Adverse effects Side effects are dose dependent and vary according to the pharmacokinetics of the individual benzodiazepine. High doses with long or intermediate elimination half-lives have a greater potential for producing daytime sedation, psychomotor incoordination, and cognitive deficits. Most traditional benzodiazepines maintain hypnotic efficacy for 1 month. However, tolerance can develop with time.

Anterograde amnesia, an impairment of memory and recall of events occurring after the dose is taken, has been reported with most BZDRAs, and is more likely to occur with short-acting agents.[11] Additionally, after abrupt discontinuation of BZDRAs, rebound insomnia, characterized by increased wakefulness beyond baseline amounts, may occur and last for a few nights. Therefore, the lowest effective dosage should be used to minimize rebound insomnia and avoid adverse effects on memory.

3 Benzodiazepine half-lives are prolonged in older patients, increasing the potential for drug accumulation and the incidence of CNS side effects, including prolonged sedation and cognitive and psychomotor impairment. BZDRAs with long elimination half-lives (eg, flurazepam and quazepam) are generally not first-line agents in older patients. Benzodiazepine use is also associated with increased risk of falls and hip fractures in the elderly, but since insomnia itself increases fall and fracture risk, it is unclear if benzodiazepines increase risk

independent of sleep problems.[23]

Nonbenzodiazepine GABAA agonists Zolpidem, zaleplon, and eszopiclone are nonbenzodiazepine hypnotics that selectively bind to GABAA receptors and effectively induce sleepiness. Zolpidem has a duration of action of 6 to 8 hours[24] and is comparable in efficacy to benzodiazepine hypnotics, in that it is effective in reducing sleep latency and nocturnal awakenings, and increasing total sleep time. It does not appear to have significant effects on next-day psychomotor performance. Sustained-release, sublingual, and reduced-strength (1.75 and 3.5 mg) formulations of zolpidem are available and are used to increase total sleep time, to reduce sleep latency, and for middle-of-the night rescue dosing, respectively.

Zolpidem is less disruptive of sleep stages than benzodiazepines and adverse effects include drowsiness, amnesia, dizziness, headache, and GI complaints, which are dose-related.[24] Sleep eating during zolpidem therapy can result in significant weight gain. The recommended daily dose of zolpidem is 10 mg in male patients, or 5 mg in female patients, elderly patients, and those with hepatic impairment. Because food decreases its absorption, zolpidem should be taken on an empty stomach.[25]

Zaleplon has a rapid onset of action with a half-life of 1 hour, and is metabolized to inactive metabolites.[26] It is effective in decreasing time to sleep onset but not for reducing nighttime awakening or for increasing total sleep time.[27] Because of its short half-life, zaleplon has no effect on next-day psychomotor performance and can be used as a sleep aid for middle-of-the-night awakenings.[28] The recommended dose is 10 mg in adults and 5 mg in the elderly.[26] The most common adverse effects with zaleplon are dizziness, headache, and somnolence. There are two-drug interactions of note: zaleplon plasma levels increase when combined with cimetidine and decrease with rifampin.[24]

Eszopiclone is effective in reducing time to sleep onset, wake time after sleep onset, and number of awakenings, and increasing total sleep time and sleep quality. Eszopiclone's duration of action is up to 6 hours,[29] so it can be a good option for treatment of sleep maintenance insomnia or early morning awakenings. The most common adverse effects with eszopiclone are somnolence, unpleasant taste, headache, and dry mouth.[29] Eszopiclone is labeled for long-term use and may be taken nightly for up to 6 months.[29,30]

Other considerations In general, the nonbenzodiazepine hypnotics seem to be

associated with less withdrawal, tolerance, and rebound insomnia than the benzodiazepine hypnotics. None of the nonbenzodiazepine GABAA agonists have significant active metabolites.

Evaluation of Therapeutic Outcomes

An algorithm for the evaluation and treatment of sleep–wake disorders is shown in **Fig. 89-1**. Patients with short-term or chronic insomnia should be evaluated after 1 week of therapy to assess for drug efficacy, adverse effects, and adherence to nonpharmacologic recommendations. For the treatment of insomnia, the choice of a particular BZDRA can be based on its pharmacokinetic profile. When used as a single dose, the extent of distribution and elimination half-life are important in predicting the duration of action. However, after multiple doses, the elimination half-life and formation of active metabolites determine the extent of drug accumulation and resultant clinical effects.[11] Advanced age, liver dysfunction, and drug interactions can prolong drug effects. The pharmacokinetic profiles of BZDRAs are summarized in Table 89-3.

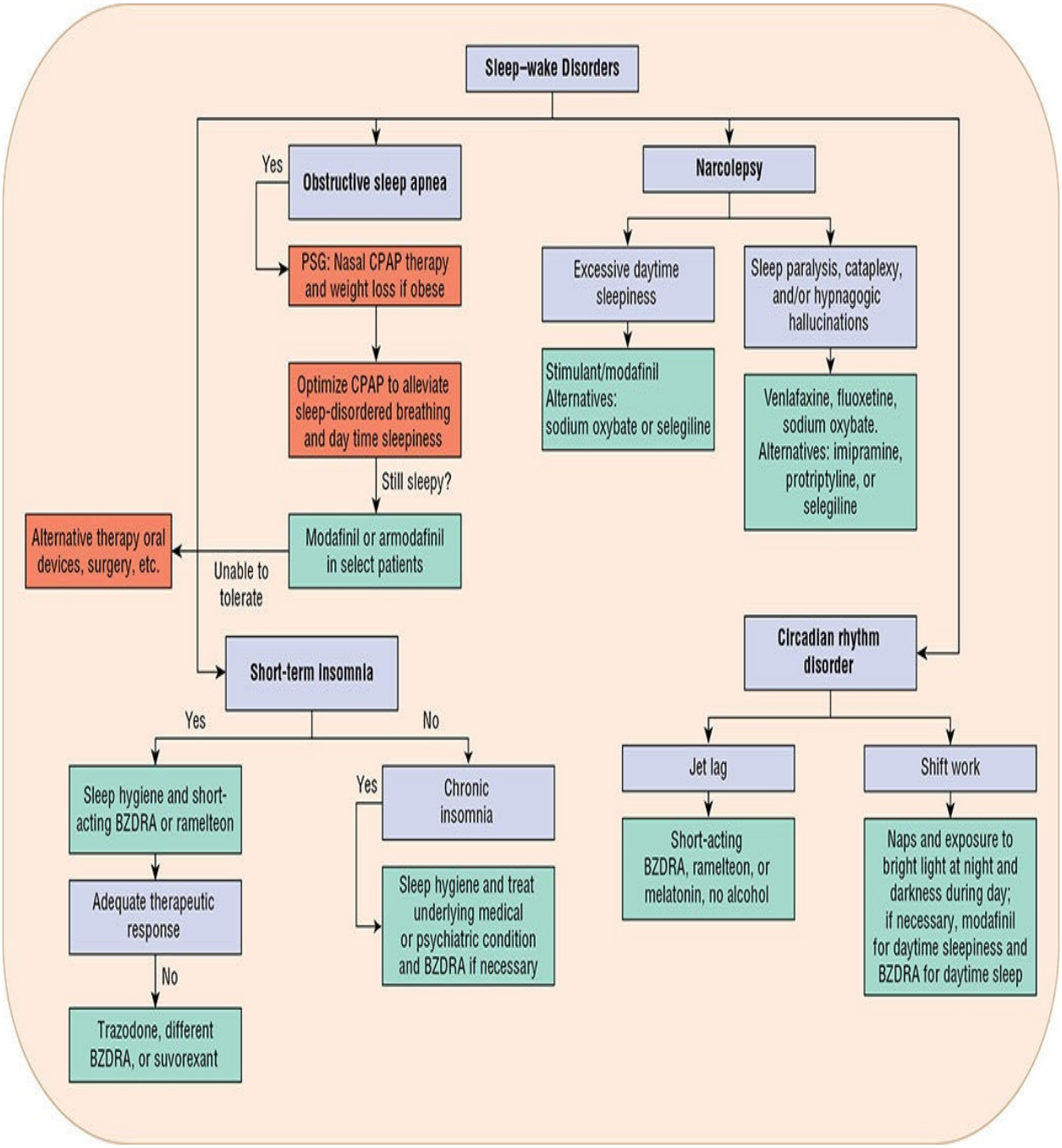


FIGURE 89-1 Algorithm for treatment of dyssomnias. (BZDRA, benzodiazepine receptor agonist; CPAP, continuous positive airway pressure.) *(Adapted, with permission, from Jermaine DM. Sleep disorders. In: Carter BL, et al, eds. Pharmacotherapy Self-Assessment Program. 2nd ed. Kansas City, MO: American College of Clinical Pharmacy; 1995:139–154. Psychiatry Module.)*

Patients should be instructed to keep a sleep diary that include daily recording

of bedtime, wake time, latency of sleep onset, number and duration of awakenings, medication ingestion, naps, and an index of sleep quality. For patients with chronic insomnia, possible medical, psychiatric, and pharmacologic causes should be identified and managed.[11] Patients with insomnia should receive education about possible medication side effects and their management.

4 Clinicians should educate patients about the concepts of tolerance, withdrawal, and rebound insomnia. Tolerance and dependence can be avoided by using hypnotics at the lowest possible dose, intermittently, and for the shortest duration possible. Patients should also receive instruction about frequency of drug use and the expected duration of therapy to help prevent development of dependence. Withdrawal symptoms can be diminished by tapering the dosage gradually.

SLEEP APNEA

Sleep apnea is a common disease, affecting 20 to 25 million Americans. It has a higher prevalence in men, particularly in African American and Hispanic populations[32,33]; however, it also occurs in children and adolescents. It is characterized by repetitive episodes of cessation of breathing during sleep followed by blood oxygen desaturation and brief arousal from sleep to restart breathing. As a result, individuals with sleep apnea experience fragmented sleep, poor sleep architecture, and periods of apnea and hypopnea. PSG is used to diagnose and quantify sleep apnea as central, obstructive, or mixed. Central sleep apnea (CSA) involves impairment of the respiratory drive, whereas obstructive sleep apnea (OSA) is caused by upper airway collapse and obstruction. Patients with mixed sleep apnea experience both CSA and OSA. The overall severity of sleep apnea is determined by the number of apnea (total cessation of airflow) and hypopnea (partial airway closure with blood oxygen desaturation) episodes documented by PSG, which is expressed as the respiratory disturbance index (RDI). Patients with mild sleep apnea have an RDI of between 5 and 15 episodes/hour, and those with moderate apnea have an RDI between 15 and 30 episodes/hour, whereas individuals with severe OSA exhibit more than 30 episodes/hour.

OSA is associated with motor vehicle accidents, depression, increased cancer risk, stroke, and cardiovascular disease.[34–37] Therefore, alleviation of sleep-disordered breathing may improve patient outcomes, particularly those related to cardiovascular disease.[37]

Obstructive Sleep Apnea

OSA is characterized by partial or complete closure of the upper airway, posterior from the nasal septum to the epiglottis, during inspiration. The reason for the loss of upper airway patency is not fully understood and is likely caused by several competing factors. Anatomical factors including neck obesity, narrow airway, and fixed upper airway lesions (eg, polyps, enlarged tonsils) can narrow the upper airway. Intraluminal negative pressure generated during each inspiration also promotes collapse of the upper airway that competes with dilating forces, primarily the pharyngeal dilator muscle. Acromegaly, amyloidosis, and hypothyroidism as well as neurologic conditions that impair upper airway muscle tone may cause OSA. The hallmarks of OSA are witnessed apneas, gasping, or both. Other recognized signs, symptoms, and considerations of sleep apnea include obesity, snoring, daytime sleepiness, family history, and hypertension.

5 OSA is increasingly linked to cardiovascular and cerebrovascular morbidity and mortality, independent of other risk factors.[37] Individuals with OSA are at risk for developing hypertension, and when hypertension is present, it is often resistant to drug therapy.[38] Alleviation of sleep-disordered breathing with nasal positive airway pressure (PAP) can improve blood pressure and attenuate some of the potential hemodynamic and neurohumoral responses that may link OSA to systemic disease.[39,40]

TREATMENT

Desired Outcomes

In the absence of an underlying cause (eg, hypothyroidism, acromegaly), alleviation of sleep-disordered breathing and prevention of associated complications are the primary goals of treatment. Nonpharmacologic measures are the treatments of choice. There is no drug therapy for OSA. However, medications that worsen sleep should be avoided. Practice parameters for the medical treatment of OSA have been published by the American Academy of Sleep Medicine.[41]

Nonpharmacologic Therapy

Positive airway pressure

6 Nasal PAP during sleep is the standard treatment for most patients with OSA. PAP produces a positive pressure column in the upper airway using room air to maintain patency by using a flexible tube that connects the PAP machine to a mask that covers the nose.

PAP delivery may be continuous (CPAP), bi-level (providing a reduced applied pressure during expiration), or auto titrating continuous positive airway pressure therapy (AutoPAP). AutoPAP machines may be programmed to a pressure range allowing the machine to provide individualized pressure based on breath-to-breath analysis of the necessary pressure to keep the airway open. CPAP pressure may be determined during PSG, when the pressure setting is increased (up to 20 cm H_2O [2.0 kPa]) until sleep-disordered breathing is eliminated or by determining which pressure the AutoPAP machine uses 90% to 95% of the time. Barriers to PAP adherence, such as ill-fitted mask and nasal dryness, can be managed; however, PAP nonadherence for one night results in a complete reversal of the gains made in daytime alertness.[42] In the clinical setting, poor PAP adherence may impact blood pressure control and management in patients with OSA and hypertension.

Weight reduction

Obesity can worsen sleep apnea, and weight management should be implemented for all overweight patients with OSA. Additionally, OSA can predispose patients to weight gain, and in obese patients with mild OSA weight loss alone can be effective.[43] Individuals who are morbidly obese and have severe OSA may consider bariatric surgery for weight loss.

Surgery

Surgical therapy (uvulopalatopharyngoplasty) opens the upper airway by removing the tonsils, trimming and reorienting the posterior and anterior tonsillar pillars, and removing the uvula and posterior portion of the palate. Due to the invasive nature of surgical treatment, this is not a first-line option. In very severe cases, a tracheostomy may be necessary. This procedure can be indicated for select individuals who are morbidly obese, have severe facial skeletal deformity, experience severe drops in oxygen saturation (eg, less than 70% [0.70]), or have significant cardiac arrhythmias associated with their OSA.

Other therapies

For individuals who experience OSA only during certain sleep positions (eg,

when lying on their back), positional therapies can be effective alone, but are usually used in conjunction with PAP therapy. Oral appliances can also be used to advance the lower jawbone and to keep the tongue forward to enlarge the upper airway. These therapies should be considered when PAP therapy cannot be tolerated.[44]

Pharmacologic Therapy

The most important pharmacologic intervention for sleep apnea is the avoidance of all CNS depressants (eg, alcohol, hypnotics) and drugs that promote weight gain as both of these worsen OSA. CNS depressant use is potentially lethal, as it reduces the brain's reflex ability to cause a mini-arousal and resume breathing. In addition, certain CNS depressants can relax airway muscles, promoting upper airway collapse. Medications that can cause rhinopharyngeal inflammation and cough as a side effect of therapy (ie, angiotensin-converting enzyme [ACE] inhibitor) may also worsen sleep-disordered breathing.

There is no drug therapy for OSA. In clinical trials, serotonergic agents (eg, fluoxetine, paroxetine), tricyclic antidepressants (TCAs) (ie, imipramine, protriptyline), respiratory stimulants (theophylline), medroxyprogesterone, and clonidine do not clinically improve severity of OSA. The effects of antihypertensive agents on sleep apnea are inconsistent and are likely not clinically significant.

Wake-promoting medications (eg, modafinil, armodafinil) are FDA-approved to improve wakefulness in patients who have residual excessive daytime sleepiness (EDS) while being treated with PAP. Initiation of therapy should be attempted in patients only after PAP therapy has been optimized to alleviate sleep-disordered breathing and EDS. Wake-promoting medications should be avoided in those with concomitant cardiovascular disease. In patients with concurrent rhinitis, nasal steroids are recommended for use along with PAP therapy.[41]

Evaluation of Therapeutic Outcomes

Individuals with sleep apnea should be evaluated after 1 to 3 months of treatment for improvement in alertness and daytime symptoms (eg, sleepiness, impaired memory, and irritability) and weight reduction. Individuals experiencing symptoms (eg, daytime sleepiness, snoring, loss of blood pressure control) despite PAP therapy should have PSG repeated. Symptoms can recur if

patients gain weight, requiring a higher pressure setting. Conversely, PAP pressure settings can be decreased if weight loss is achieved. Patient adherence to PAP therapy can be monitored by assessing the built-in compliance meter that measures the hours used at effective pressure.

Central Sleep Apnea

CSA causes fragmented sleep and consequent daytime somnolence. However, unlike OSA, arousals from sleep are not required to initiate airflow. During PSG, there is an absence of airflow out of the mouth and nose with no activation of the inspiratory muscles. The prevalence of CSA is not well established and is less than OSA. CSA can be idiopathic but more commonly is caused by underlying autonomic nervous system lesions (eg, cervical cordotomy), neurologic diseases (eg, poliomyelitis, encephalitis, and myasthenia gravis), high altitudes, opioid abuse, and congestive heart failure. For these reasons, potential underlying causes for CSA should be evaluated and treated. For example, worsening CSA in heart failure patients can signal the need to optimize heart failure therapies. Practice parameters for the treatment of CSA have been published by the American Academy of Sleep Medicine.[45]

Drug therapy for CSA is limited and is individualized for each patient, based on underlying etiology. Acetazolamide, which induces a metabolic acidosis that stimulates respiratory drive, and theophylline, which improves severity of CSA, have been studied but have minimal effects on clinical variables.[4,46,47]

NARCOLEPSY

Narcolepsy, which is a severely debilitating neurologic disease that affects between 0.03% and 0.06% of adult Americans,[48] often goes undiagnosed or misdiagnosed for years. The prevalence is equal or somewhat higher in men compared to women and it is commonly recognized in the second decade of life and increases in severity through the third and fourth decades.[48] Individuals with narcolepsy complain of EDS, and in the sleep laboratory, exhibit impairment of both the onset and the offset of REM and NREM sleep and have arousals and disturbed sleep during the night.

CLINICAL PRESENTATION Narcolepsy

Symptoms

- Patients may complain of EDS and disrupted nighttime sleep; often they have some accompanying REM sleep abnormality, sleep paralysis, cataplexy, and/or hallucinations.

Laboratory Tests

- Although not routinely tested, there is a high incidence of human leukocyte antigen (HLA) haplotypes DR2 and HLA-DQ6/DQB1 in narcolepsy.
- Cerebrospinal fluid (CSF) concentrations of hypocretin-1 can be measured to confirm a diagnosis. CSF concentrations less than 110 pg/mL (ng/L; 31 pmol/L) positively predict narcolepsy.

Other Diagnostic Tests

- Narcolepsy is diagnosed using the multiple sleep latency test (nap test). The patient takes four to five naps in a day, and narcolepsy is diagnosed if the patient falls asleep quickly (within less than 5 minutes) and goes into REM sleep in two of those nap periods.

Recently, narcolepsy was reclassified as narcolepsy type 1 (narcolepsy with cataplexy) and narcolepsy type 2 (narcolepsy without cataplexy).[9] Four characteristic symptoms differentiate narcolepsy from other sleep disorders and are known as the *narcolepsy tetrad*: EDS, cataplexy, hallucinations, and sleep paralysis. Cataplexy is a sudden bilateral loss of muscle tone of varying severity and duration without the loss of consciousness, which occurs in 70% to 80% of people with narcolepsy.[48] Cataplexy is often precipitated by situations characterized by high emotion (eg, laughter, anger, excitement) and can manifest as subtle changes, such as jaw or head slumping, or severe weakness, such as knee buckling or collapsing to the ground. Cataleptic episodes can be brief, lasting seconds, or can last for several minutes. Sleep paralysis is anepisodic loss of voluntary muscle tone that occurs when the individual is falling asleep or waking where individuals are conscious but not able to move or speak. Hallucinations while falling asleep (ie, hypnagogic) and on awakening (ie, hypnopompic) are brief, dream-like experiences that intrude into wakefulness and are experienced by nearly 70% of patients with narcolepsy. Unfortunately, these symptoms sometimes lead to an incorrect mental illness diagnosis.[48] Mechanistically, cataplexy, sleep paralysis, and hypnagogic hallucinations can be attributed to REM sleep disturbances.[48]

Loss of normal function of the hypocretin-orexin neurotransmitter system appears to play a central role in the pathophysiology of narcolepsy. Neurons containing hypocretin-orexin are found in the lateral hypothalamus and project to various parts of the brain that are thought to regulate sleep. In 75% of patients with narcolepy, hypocretin-orexin is undetectable in cerebrospinal fluid.[49,50] Since patients with narcolepsy and cataplexy have low concentrations of hypocretin-1 (less than 110 pg/mL [ng/L; 31 pmol/L]),[9] an autoimmune process may be responsible for the destruction of hypocretin-producing cells.[51,52] Molecular studies of HLA have found a high prevalence of the HLA-DR2 and HLA-DQ6/DQB1 haplotypes in patients with narcolepsy[53]; however, the HLA-DR2 haplotype is also common in the non-narcolepsy populations and is not diagnostic.[52] As 3% of patients have a first-degree relative with the disorder, there may also be a genetic component associated with this diesease.[49] Lastly, as the onset of this disease occurs in adolescence or adulthood, but not at birth, environmental influences have also been suggested to play a role.

TREATMENT

Desired Outcomes

Nonpharmacologic management of narcolepsy includes counseling the patient and family concerning the illness to alleviate misconceptions around the individual's behavior. Good sleep hygiene should be encouraged, as well as two or more scheduled daytime naps as naps lasting 15 minutes each can help the individual with narcolepsy feel refreshed. The primary objective of pharmacologic treatment of narcolepsy is to reduce symptoms that adversely influence the patient's quality of life and to produce the fullest possible return of normal function for patients within work, school, home, and social settings.

7 Pharmacologic management of narcolepsy is focused on two primary areas: treatment of EDS and REM sleep abnormalities. Drug therapy for narcolepsy is summarized in **Table 89-4**.

TABLE 89-4 Dosing of Drugs Used to Treat Narcolepsy

Generic Name	Brand Name	Initial Dose (mg)	Usual Dose (mg)	Comments
Excessive daytime somnolence				
Dextroamphetamine	Dexedrine	5-10	5-60	Concurrent use of amphetamines and acidic foods may reduce amphetamine absorption
Dextroamphetamine/ Amphetamine salts[a]	Adderall	5-20	5-60	See above
Methamphetamine[b]	Desoxyn	5-15	5-15	See above
Lisdexamfetamine	Vyvanse	20-30	20-70	Prodrug of dextroamphetamine
Methylphenidate	Ritalin	10-40	30-80	May increase risk of bleeding with concomitant warfarin therapy
Modafinil	Provigil	100-200	200-400	May reduce effectiveness of hormonal contraceptives
Armodafinil	Nuvigil	150	150-250	May reduce effectiveness of hormonal contraceptives
Sodium oxybate[c]	Xyrem	4.5 g/night	4.5-9 g/night	Do not use with other CNS depressants
Agents for cataplexy				
Atomoxetine	Strattera	18-100	40-100	Lower doses in CYP2D6 poor metabolizers
Fluoxetine	Prozac	10-20	20-80	Will see cataplexy benefits sooner than antidepressant benefits
Imipramine	Tofranil	50-100	50-250	Anticholinergic side effects
Nortriptyline	Aventyl, Pamelor	50-100	50-200	Anticholinergic side effects
Protriptyline	Vivactil	5-10	5-30	
Venlafaxine	Effexor	37.5	37.5-225	May increase blood pressure
Selegiline	Eldepryl	5-10	20-40	Doses less than 10 mg/day do not require dietary tyramine restrictions

[a]Dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate, and amphetamine sulfate.

[b]Not available in some states.

[c]Also is effective in treating cataplexy.

Data from References 52 and 54.

Pharmacologic Therapy

Modafinil, a racemic compound unrelated to psychostimulants, is a recognized standard treatment for EDS.[54] Armodafinil is the active R-isomer of modafinil and is also FDA-approved for treatment of EDS in narcolepsy. The precise mechanism of action of modafinil and armodafinil is not fully understood. Common adverse effects are usually mild and include headache, nausea,

nervousness, anxiety, and insomnia. The dose of modafinil is between 100 and 400 mg/day, and armodafinil doses are between 150 and 250 mg/day.[55] Although both of these agents are effective in treating EDS, they lack efficacy for the treatment of cataplectic symptoms.[56]

EDS can also be treated with stimulants to improve alertness and to increase daytime performance. Dextroamphetamine and methylphenidate also have FDA approval for the treatment of narcolepsy. Methamphetamine and mixed amphetamine salts have also been used on an off-label basis. Methylphenidate and amphetamines have a fast onset of action and durations of 6 to 10 and 3 to 4 hours, respectively. The doses of methylphenidate and amphetamine formulations can range from 5 to 60 mg daily.

Stimulants improve alertness and daytime performance, and they can elevate mood and prevent sleep. Side effects can include insomnia, hypertension, palpitations, and irritability. Tolerance to long-term stimulant therapy can occur, necessitating dosage increases. Amphetamine use is associated with a greater likelihood of abuse and tolerance, especially when prescribed in high doses. Lisdexamfetamine is an amphetamine prodrug rapidly absorbed and converted in the body to dextroamphetamine, which has a longer duration of action and less risk of abuse since it is active only when taken orally.

To individualize treatment of narcolepsy many clinicians prescribe both immediate-release and sustained-release stimulants to increase alertness throughout the day. Sustained-release stimulants are prescribed with scheduled administration times, and immediate-release stimulants can be taken as needed when the patient requires alertness (eg, driving, etc.). Currently there are no guidelines that recommend pharmacogenomics testing to predict response to simulant medication when being used for the treatment of sleep disorders.

The most commonly used treatments for cataplexy are tricyclic antidepressants (TCAs), selective norepinephrine reuptake inhibitors (SNRIs), and selective serotonin reuptake inhibitors (SSRIs). The mechanism of antidepressants in relieving cataplexy, hypnagogic hallucinations, and sleep paralysis is thought to be mediated through blockade of serotonin and norepinephrine reuptake in the locus coeruleus and raphe which subsequently suppresses REM sleep.[57] Imipramine, protriptyline, clomipramine, fluoxetine, and nortriptyline are effective in approximately 80% of patients. Selegiline improves hypersomnolence and cataplexy through REM suppression and an increase in REM latency. Atomoxetine may improve cataplexy and sleepiness in children, but appears to be less effective than other therapies in adults and older teenagers. In contrast to the antidepressants, methylphenidate and amphetamines

alone are usually ineffective in complete relief from cataplexy.

Sodium oxybate (γ-hydroxybutyrate, Xyrem) improves symptoms of EDS and decreases episodes of sleep paralysis, cataplexy, and hypnagogic hallucinations. Nightly administration of sodium oxybate changes sleep architecture to resemble normal sleep. It increases slow-wave sleep, decreases nighttime awakenings, and increases REM efficiency.[58] Sodium oxybate is available only as a liquid and is taken as two doses; one is taken at bedtime and the second dose is taken 2.5 to 4 hours later. Sodium oxybate is a potent sedative-hypnotic and should not be used concomitantly with any other sedating medications. The most common side effects include nausea, somnolence, confusion, dizziness, and incontinence.

Evaluation of Therapeutic Outcomes

Patients with narcolepsy should keep a diary of the frequency and severity of cataplexy, sleep paralysis, and sleep hallucinations. Patients should be evaluated regularly during medication titrations and then every 6 to 12 months to assess for adverse drug effects (eg, sleep disturbances, hypertension, and cardiovascular abnormalities). The healthcare provider should consider the benefit-to-risk ratio for the individual patient, the cost of medication, the convenience of administration, and the cost of laboratory tests when selecting narcolepsy therapies.[54] One wake-promoting agent may work better than another in an individual patient. Thus, if one agent is not effective at adequate doses, a trial with another agent should be undertaken.

CIRCADIAN RHYTHM DISORDERS

The sleep–wake cycle is under the circadian control of oscillators and can be disrupted by misalignment between an individual's biologic clock and external demands on the sleep cycle. Circadian rhythm sleep disorders usually present with either insomnia or hypersomnia, depending on the individual's performance requirements. Two commonly occurring circadian rhythm sleep disorders are jet lag and shift work sleep problems.

Jet Lag

Jet lag occurs when a person travels across time zones, and the external environmental time is mismatched with the internal circadian clock.

Disturbances in sleep due to jet lag typically last for 2 to 3 days, but can last as long as 7 to 10 days if the time zone changes are greater than 8 hours. Compared with westward travel, eastward travel is associated with a longer duration of jet lag. In addition to decrease in alertness and performance, jet lag can also lead to increased incidence of gastrointestinal (GI) disturbances.

8 Treatment of jet lag includes nonpharmacologic approaches alone or in combination with drug therapy. Jet lag can be minimized in coast-to-coast travel in the United States if the duration is less than 7 days and the normal sleep–wake cycle is observed. For travel lasting longer than 7 days, jet lag severity can be lessened by 1- to 2-hour adjustments in sleep and wake times prior to departure to the destination time zone. Appropriate timing of light exposure along with short-acting BZDRAs, ramelteon, and 0.5 to 5 mg melatonin, taken at appropriate target bedtimes for east or west travel, reduce jet lag and shorten sleep latency.[59]

Shift Work Sleep Disorder

Shift workers comprise approximately 20% of the workforce.[60] Night shift work causes a misalignment in the sleep–wake cycle and circadian rhythm that is associated with a decrease in alertness, performance, and quality of daytime sleep. More than 65% of workers on rotating shifts complain of insomnia, compared with only 20% who work one shift.[61] Shift workers ultimately are at risk of developing shift work sleep disorder (SWSD), which is a complaint of insomnia or excessive sleepiness that occurs because of circadian sleep disruption due to working shifts during normal sleep time.[9,60] Shift workers have a higher injury rate, divorce rate, occurrence of on-the-job sleepiness, and incidence of substance use. They may also be at increased risk of developing peptic ulcers, depression, breast cancer, and sleepiness-related accidents.[60–62] Night shift workers are usually in a state of permanent circadian misalignment because of the tendency to revert to conventional sleep schedules on nonwork days.[61]

Treatment for shift work sleep problems includes optimizing sleep hygiene, extending daytime sleep by sleeping in the afternoon, scheduling a 2- to 3-hour nap on days off from work, or switching to a day shift job. Short-acting BZDRAs, ramelteon, and melatonin can consolidate sleep during day sleep periods and reduce lost sleep time. Modafinil and armodafinil are FDA-approved to improve wakefulness in patients with EDS associated with SWSD. Scheduled exposure to bright lights at night and darkness in the daytime improves

adaptation to night work and daytime sleep.[61]

Restless Legs Syndrome

RLS, or Willis-Ekbom syndrome, is characterized by paresthesias that are usually felt deep in the calf muscles that result the urge to keep limbs in motion. Additionally, these paresthesias can also appear in the thighs and arms. RLS occurs in both males and females, and it occurs more frequently in the elderly. It has been associated with chronic kidney disease, iron deficiency, and pregnancy. Data suggest that RLS can be caused by iron deficiency in the substantia nigra in the CNS[63] and caffeine, stress, alcohol, and fatigue can worsen symptoms. The diagnosis of RLS is based on patient- or partner-reported symptoms and specific diagnostic criteria that include (a) an urge to move the limbs that is usually associated with uncomfortable and unpleasant sensations, (b) symptoms that begin or worsen during rest or inactivity, (c) symptoms that are exclusively present or worse in the evening or night, (d) symptoms that are temporarily relieved by movement, and (e) occurrence of symptoms is not accounted for as symptoms of another medical condition.[64] The discomfort returns when the person tries to sleep, resulting in insomnia. Increasing evidence indicates that RLS adversely affects work performance, quality of life, and increased risk for cardiovascular disease.[65–67] Practice parameter recommendations for treatment of RLS are shown in **Table 89-5**.

TABLE 89-5 Evidence-Based Guidelines for Drug Therapy of RLS

Medication Recommendation[a] (Brand Name)	Strength of Recommendation[b]	Body of Evidence Level[c]
Pramipexole (Mirapex)	Standard	High
Ropinirole (Requip)	Standard	High
Levodopa and dopa decarboxylase inhibitor (Sinemet)	Guideline	High
Opioids (eg, codeine, oxycodone, hydrocodone, methadone)	Guideline	Low
Gabapentin enacarbil (Horizant)	Guideline	High
Gabapentin[d] (Neurontin)	Option	Low
Supplemental iron[e]	Option	Very Low

[a]At the time of publishing, rotigotine was not available in the United States; thus, no recommendations were made for rotigotine in the published practice parameters.

[b]"Standard" indicates recommendations for which there is high or moderate quality of evidence where the benefits clearly outweigh the harms; "Guideline" indicates low quality of evidence where benefits clearly outweigh the harms, or high or moderate quality of evidence when the benefits are closely balanced with harm/burden or there is uncertainty about the benefits/harms/burdens.

[c]Level of evidence: High, very confident in effect estimate of agent; Moderate, moderately confident in effect estimate; Low, limited confidence in effect estimate; Very low, very little confidence in effect estimate.

[d]Pregabalin is recommended similarly to gabapentin.

[e]In patients with low serum ferritin concentrations.

Data from Allen RP, Walters AS, Montplaisir J, et al. Restless legs syndrome prevalence and impact: REST general population study. Arch Intern Med. 2005;165:1286–1292.

TREATMENT

Pharmacologic Therapy

9 Dopamine agonists are standard therapy for RLS but have adverse effects that require careful monitoring by the patient and providers. Dopamine agonists ropinirole, pramipexole, and rotigotine are FDA-approved for RLS treatment.[68] Lower doses of dopamine agonists are used when treating RLS compared with Parkinson's disease. Providers should caution patients that compulsive behaviors (eg, gambling, shopping, eating, etc.) and sudden periods of extreme sleepiness

may emerge during therapy with dopamine agonists. Due to levodopa's short half-life, it may not provide relief over the entire night. Additionally levodopa is associated with a high incidence of symptom augmentation, which is a worsening in symptom severity, increase in symptom distribution, emergence of symptoms earlier in the evening, shortening duration of symptom control, and need for escalating dopaminergic doses to control symptoms. Augmentation can be treated by tapering and discontinuing dopaminergic medications, repleting low body iron stores and switching to alternative medications such as gabapentin. Sedative-hypnotic agents can be effective in patients who have frequent awakenings from their RLS symptoms. Clonazepam at doses ranging from 0.5 to 2 mg has been most frequently studied; however, patients may experience carryover sedation because of its long duration of action. Shorter half-life sedative-hypnotics (eg, zolpidem, zaleplon) can improve sleep and reduce daytime sleepiness without carryover sedation. Opiates such as methadone 5 to 20 mg, codeine 30 to 120 mg, and oxycodone 2.5 mg are effective in patients with painful RLS; however, the potential for tolerance and dependence on opiate therapy should be considered. Gabapentin 300 to 900 mg near bedtime can also be considered for those with paresthetic or painful RLS symptoms.[69] Gabapentin enacarbil (Horizant) is a gabapentin prodrug that is now FDA-approved for the treatment of RLS at a dose of 600 mg taken at 5 pm. Pregabalin recently demonstrated similar or greater efficacy for RLS compared to dopamine agonists. Iron studies should be completed in patients with RLS and iron supplementation initiated in those who are iron deficient. In patients with ferritin concentrations less than 50 to 75 mcg/L (ng/mL), iron supplementation improves RLS symptoms.[70] Patients with RLS or PLMS should be evaluated regularly to monitor for excessive daytime somnolence, tolerance, efficacy, and adverse effects of the medication. Therapy should be monitored for adverse effects found in **Table 89-6**.

TABLE 89-6 Monitoring Patients Taking Medications for RLS and PLMS

Drug or Drug Class	Adverse Drug Reaction	Monitoring Parameter	Comments
Dopamine agonists	Compulsive behaviors	Frequency and quantity of eating, gambling, shopping, other reward behaviors	May occur at any time during therapy but appear to be dose-related
Levodopa/Carbidopa	Symptom augmentation	Location and timing of RLS symptoms	Appearance of symptoms in other areas of body and earlier in day
Gabapentin/Pregabalin	Dizziness	Subjective dizziness, falls	–
Sedative-hypnotics (clonazepam, temazepam, zolpidem, etc.)	Carryover sedation	Morning sleepiness, grogginess	More likely to occur with longer duration agents
Opioids (oxycodone, codeine, hydrocodone, etc.)	Tolerance, constipation	Patient RLS symptoms and response to ongoing therapy	–
Oral iron therapy (ferrous sulfate, etc.)	Gastrointestinal upset, constipation	Monitor for constipation	Prophylactic stool softeners may be necessary to reduce risk of constipation

Periodic Limb Movement Disorder

Periodic limb movements of sleep (PLMS) are stereotypic, repetitive, periodic movements of the legs that occur during sleep every 20 to 40 seconds and last 10 minutes to several hours.[66] The movements usually involve the big toe, but the ankle, knee, and hip can also flex. They can be terminated by a violent kick or other body movement. Often patients will be unaware of these movements and only recognize consequent insufficient sleep and morning leg cramps. A bed partner can describe PLMS. PLMS is diagnosed in the sleep laboratory using electromyogram recordings.

PLMS can occur with RLS or alone because of systemic disease (eg, renal failure) or drug therapy.[71] In fact RLS patients commonly have PLMS, while approximately one-third of patients with PLMS have RLS.[66] TCAs, SSRIs, dopaminergic antagonists, xanthines, nicotine, alcohol, and caffeine can all worsen PLMS. The treatment approach for PLMS is similar to that of RLS in that if the PLMS do not cause disruptions for the patient or bed partner or daytime symptoms, they may not require treatment. Symptomatic or problematic PLMS should be treated with dopaminergic medications to suppress limb movements or sedative-hypnotics to reduce awakenings and consolidate sleep.

PARASOMNIAS

Parasomnias are abnormal behavior or physiologic events that either occur during sleep or are exaggerated by sleep. Many of these disorders are considered

to be disorders of partial arousal from various sleep stages. Parasomnias can be categorized as disorders of arousal (sleepwalking, sleep terrors), sleep–wake transition disorders (sleep-talking), rhythmic movement disorder, REM parasomnias (REM behavior disorder, nightmares), and miscellaneous parasomnias (enuresis, bruxism). Sleepwalking, sleep terrors, and sleep-talking predominantly occur during NREM sleep, whereas others (REM behavior disorder) occur during REM sleep.

Sleepwalking and sleep terrors are found normally in children between the ages of 4 and 12 years and usually resolve in adolescence. These disorders are increasingly recognized to also occur in adulthood, and, contrary to previous beliefs, are not related to psychological or psychiatric pathology.[72] Sleep terrors can begin in adults between the ages of 20 and 30 years. Onset of sleepwalking in adults without a childhood history of sleepwalking should prompt a search for a neurologic or substance use condition.[73] Sleepwalking and sleep terror disorder involve intrusions of wakefulness into NREM sleep during the first third of the night. In sleepwalking, individuals become ambulatory, are difficult to awaken, and are amnestic for the event. Sleep terrors involve intense fear and autonomic arousal. Individuals are difficult to awaken, inconsolable, and amnestic for the event.[73] Patients with REM behavior disorder act out their dreams, often in a violent manner, and are at risk for injury.

Treatment of sleepwalking involves protecting the individual from harm by putting safety latches on doors and windows, removing hazardous objects from bedrooms, and covering glass doors with heavy curtains. In adult patients, benzodiazepines, SSRIs, or TCAs can be beneficial therapies for sleepwalking or other NREM disorders of arousal.[72] Benzodiazepines can also be helpful in curtailing sleep terrors in adults.[73] Nightmares are anxiety-provoking dreams characterized by vivid recall and treatment is directed at reducing stress, anxiety, and sleep deprivation. In extreme cases, low-dose benzodiazepines can be indicated. Clonazepam is the treatment of choice for REM behavior disorder. Melatonin (3-12 mg at bedtime) and pramipexole can also be an effective therapy for REM behavior disorder.[74]

CONCLUSION

Sleep and wake disorders are common but they may be challenging to diagnose since clinical presentation and precise symptoms may be unknown to the individual who is asleep. Practitioners need to perform a sleep history that involves both the patient and his/her bedpartner. Treatments for sleep and wake

disorders are effective, but not curative, and need to be monitored carefully for both safety and efficacy. Practitioners should use the lowest doses of medications for the shortest durations possible, and thoroughly investigate potential underlying causes for sleep and wake disturbances.

Postclass Engaged Learning Activity

Conduct a literature search and identify new potential therapeutic targets for the treatment of narcolepsy. After reading this chapter, an understanding of the pathophysiology of narcolepsy should inform the reader about potential neurotransmitter targets for therapy. Identify obstacles to the development and administration of these potential medications for narcolepsy. What would be advantages regarding how narcolepsy is targeted compared to the current treatment approaches?

ABBREVIATIONS

ACE	angiotensin-converting enzyme
AutoPAP	auto-titrating positive airway pressure
BZDRA	benzodiazepine receptor agonist
CNS	central nervous system
CPAP	continuous positive airway pressure
CSA	central sleep apnea
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
EDS	excessive daytime sleepiness
EEG	electroencephalogram
GABA	γ-aminobutyric acid
GI	gastrointestinal
HLA	human leukocyte antigen
NREM	nonrapid eye movement
OSA	obstructive sleep apnea
PAP	positive airway pressure
PLMS	periodic limb movements of sleep

PSG	polysomnography
RDI	respiratory disturbance index
REM	rapid eye movement
RLS	restless legs syndrome
SWSD	shift work sleep disorder
SNRI	selective norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant

REFERENCES

1. Walsh JK, Engelhardt CL. The direct economic costs of insomnia in the United States for 1995. *Sleep*. 1999;22:S386–S393.
2. Neylan TC, Reynolds CF III, Kupfer DJ. Sleep disorders. In: Yudofsky SC, Hales RE, eds. *American Psychiatric Press Textbook of Neuropsychiatry*. 4th ed. Washington, DC: American Psychiatric Press; 2003:975–1000.
3. Benca RM, Cirelli C, Rattenborg NC, Tononi G. Basic science of sleep. In: Sadock BJ, Sadock VA, eds. *Kaplan and Sadock's Comprehensive Textbook of Psychiatry*. 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:280–294.
4. Dagan Y, Abadi J. Sleep–wake disorder disability: A lifelong untreatable pathology of the circadian time structure. *Chronobiol Int*. 2001;18:1019–1027.
5. Franken P. Long-term versus short-term processes regulating REM sleep. *J Sleep Res*. 2002;11:17–28.
6. Stickgold R, Hobson JA, Fosse R, Fosse M. Sleep, learning and dreams: Off-line memory reprocessing. *Science*. 2001;294:1052–1058.
7. American Psychiatric Association. Sleep-wake disorders. In: *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. 2013. Available at :http://dx.doi.org/10.1176/appi.books.9780890425596.dsm12.
8. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: An American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med*. 2017;13:307–349.
9. American Academy of Sleep Medicine. International Classification of

Sleep Disorders, Third Edition: Diagnostic and Coding Manual. Westchester, IL: American Academy of Sleep Medicine; 2014.

10. Chesson AL, Anderson WM, Littner M, et al. Practice parameters for the nonpharmacologic treatment of chronic insomnia. *Sleep*. 1999;8:1–6.
11. Kirkwood CK. Management of insomnia. *J Am Pharm Assoc*.1999;39:688–696.
12. Sateia MJ, Doghramji K, Hauri PJ, et al. Evaluation of chronic insomnia. *Sleep*. 2000;23:1–39.
13. Lippmann S, Mazour I, Shabab H. Insomnia: Therapeutic approach. *South Med J*. 2001;94:866–874.
14. Vaughn-McCall W. A psychiatric perspective on insomnia. *J Clin Psychiatr*. 2001;62(Suppl 10):27–32.
15. Morgenthaler TI, Kramer M, Alessi C, et al. Practice parameters for the psychological and behavioral treatment of insomnia: An update. An American Academy of Sleep Medicine report. *Sleep*. 2006;29:1415–1419.
16. Sivertsen B, Omvik S, Pallesen S, et al. Cognitive behavioral therapy vs zopiclone for treatment of chronic primary insomnia in older adults: A randomized controlled trial *JAMA*. 2006;295:2851–2858.
17. Hauri PJ. Insomnia. *Clin Chest Med*. 1998;19:157–168.
18. Trazodone [Product Information]. Weston, FL: Apotex Corp, 2014.
19. Belsomra, suvorexant [Product Information]. Whitehouse Station, NJ: Merck and Co., Inc., 2014.
20. Kryger M, Roth T, Wang-Weigand S, et al. The effects of ramelteon on respiration during sleep in subjects with moderate to severe chronic obstructive pulmonary disease. *Sleep Breath*. 2009;13:79–84.
21. Kryger M, Wang-Weigand S, Roth T. Safety of ramelteon in individuals with mild to moderate obstructive sleep apnea. *Sleep Breath*. 2007;11:159–164.
22. Schulz V, Hansel R, Tyler VE.*Rational Phytotherapy: A Physician's Guide to Herbal Medicine*. Berlin:Springer;1998:81.
23. Stone KL, Ensrud KE, Ancoli-Israel S. Sleep, insomnia and falls in elderly patients. *Sleep Med*. 2008;9(Suppl 1):S18–S22.
24. Terzano MG, Rossi M, Palomba V, et al. New drugs for insomnia: Comparative tolerability of zopiclone, zolpidem and zaleplon. *Drug Saf*. 2003;26:261–282.
25. Ambien, zolpidem [product information]. Bridgewater, NJ: Sanofi-

Aventis, 2012.

26. Elie R, Ruteher E, Farr IK, et al. Sleep latency is shortened during 4 weeks of treatment with zaleplon, a novel nonbenzodiazepine hypnotic. *J Clin Psychiatry*. 1999;60:536–544.
27. Walsh JK, Fry J, Erwin CS, et al. Efficacy and tolerability of 14-day administration of zaleplon 5 mg and 10 mg for the treatment of primary insomnia. *Clin Drug Investig*. 1998;16:347–354.
28. Walsh JK, Pollack CP, Shark MMB, et al. Lack of residual sedation following middle-of-the-night zaleplon administration in sleep maintenance insomnia. *Clin Neuropharmacol*. 2000;23:17–21.
29. Lunesta, eszopiclone [product information]. Marlborough, MA: Sunovion, 2010.
30. Krystal AD, Walsh JK, Laska E, et al. Sustained efficacy of eszopiclone over 6 months of nightly treatment: Results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia. *Sleep*. 2003;26:793–797.
31. Jermaine DM. Sleep disorders. In: Carter BL, Angaran DM, Lake KD, Raebel MA, eds. Pharmacotherapy Self-Assessment Program. 2nd ed. Kansas City, MO: American College of Clinical Pharmacy; 1995: 139–154. Psychiatry Module.
32. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: A population health perspective. *Am J Respir Crit Care Med*. 2002;165:1217–1239.
33. Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med*. 1993;328:1230–1235.
34. Peppard PE, Szklo-Coxe M, Hla KM, Young T. Longitudinal association of sleep-related breathing disorder and depression. *Arch Intern Med*. 2006;166:1709–1715.
35. Young T, Finn L, Peppard PE, et al. Sleep disordered breathing and mortality: Eighteen-year follow-up of the Wisconsin sleep cohort. *Sleep*. 2008;31:1071–1078.
36. Terán-Santos J, Jimenez-Gomez A, Cordero-Guevara J. The association between sleep apnea and the risk of traffic accidents. *N Engl J Med*. 1999;340:847–851.
37. Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: An American Heart Association/American College of Cardiology Foundation scientific statement from the American Heart Association

Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. *J Am Coll Cardiol*. 2008;52:686–717.

38. Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: Diagnosis, evaluation, and treatment: A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation*. 2008;117:e510–e526.
39. Marin JM, Agusti A, Villar I, et al. Association between treated and untreated obstructive sleep apnea and risk of hypertension. *JAMA*. 2012;307:2169–2176.
40. Kato M, Roberts-Thomson P, Phillips BG, et al. Impairment of endothelium dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. *Circulation*. 2000;102:2607–2610.
41. Morganthaler TI, Kapen S, Lee-Chiong T, et al. Practice parameters for the medical therapy of obstructive sleep apnea. *Sleep*. 2006;29:1031–1035.
42. Kribbs NB, Pack AJ, Kline LR, et al. Effects of one night without nasal CPAP treatment on sleep and sleepiness in patients with obstructive sleep apnea. *Am Rev Respir Dis*. 2003;147:1162–1168.
43. Peppard PE, Young T, Palta M, et al. Longitudinal study of moderate weight change and sleep-disordered breathing. *JAMA*. 2000;284:3015–3021.
44. Ferguson KA, Cartwright R, Rogers R, et al. Oral appliances for snoring and obstructive sleep apnea: A review. *Sleep*. 2006;29:244–262.
45. Aurora RN, Chowdhuri S, Ramar K, et al. The treatment of central sleep apnea syndromes in adults: Practice parameters with an evidence-based literature review and meta-analyses. *Sleep*. 2012;35:17–40.
46. Javaheri S. Acetazolamide improves central sleep apnea in heart failure: A double-blind, prospective study. *Am J Respir Crit Care Med*. 2006;173:234–237.
47. Javaheri S, Parker TJ, Wexler L, et al. Effect of theophylline on sleep-disordered breathing in heart failure. *N Engl J Med*. 1996;335:562–567.
48. Mitler M, Hayduk R. Benefits and risks of pharmacotherapy for narcolepsy. *Drug Saf*. 2002;25:791–809.
49. Nishino S, Ripley B, Overeem S, et al. Low cerebrospinal fluid hypocretin (orexin) and altered energy homeostasis in human narcolepsy. *Ann Neurol*. 2001;50:381–388.

50. Thannicakal TC, Moore RY, Nienhuis R, et al. Reduced number of hypocretin neurons in human narcolepsy. *Neuron*. 2000;27:469–474.
51. Lin L, Hungs M, Mignot E. Narcolepsy and the HLA region. *J Neuroimmunol*. 2001;117:9–20.
52. Mignot E, Thorsby E. Narcolepsy and the HLA system [letter]. *N Engl J Med*. 2001;344:692.
53. Nakayama J, Miura M, Honda M, et al. Linkage of human narcolepsy with HLA association to chromosome 4p-13-q21. *Genomics*. 2000;65:84–86.
54. Morgenthaler TI, Kapur VK, Brown T, et al. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. *Sleep*. 2007;30:1705–1711.
55. Robertson P, Hellriegel ET. Clinical pharmacokinetic profile of modafinil. *Clin Pharmacokinet*. 2003;42:123–127.
56. Feldman N. Narcolepsy. *South Med J*. 2003;96:277–287.
57. Rosenthal MS. Physiology and neurochemistry of sleep. *Am J Pharm Educ*. 1998;62:204–208.
58. Mamelak M, Black J, Montplaisir J, et al. A pilot study of the effects of sodium oxybate on sleep architecture and daytime alertness in narcolepsy. *Sleep*. 2004;27:1327–1334.
59. Herxheimer A, Petrie KJ. Cochrane Depression, Anxiety and Neurosis Group. Melatonin for the prevention and treatment of jet lag [systematic review].*Cochrane Database Syst Rev*. 2005;2.
60. Drake CL, Roehrs T, Richardson G, et al. Shift work sleep disorder: Prevalence and consequences beyond that of symptomatic day workers. *Sleep*. 2004;27:1453–1462.
61. Garbarino S, Nobili L, Beelke M, et al. Sleep disorders and daytime sleepiness in state police shiftworkers. *Arch Environ Health*. 2002;57:167–175.
62. Knutsson A. Health disorders of shift workers. *Occup Med (Lond)*. 2003;53:103–108.
63. Connor JR, Boyer PJ, Menzies SL,et al. Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. *Neurology*. 2003;61:304–309.
64. Allen RP, Picchietti DL, Garcia-Borreguero D, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: Updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria—

history, rationale, description, and significance. *Sleep Med*. 2014;15:860–873.

65. Allen RP, Bharmal M, Calloway M. Prevalence and disease burden of primary restless legs syndrome: Results of a general population survey in the United States. *Mov Disord*. 2011;26:114–120.
66. Allen RP, Walters AS, Montplaisir J, et al. Restless legs syndrome prevalence and impact: REST general population study. *Arch Intern Med*. 2005;165:1286–1292.
67. Winkelman JW, Finn L, Young T. Prevalence and correlates of restless legs syndrome symptoms in the Wisconsin Sleep Cohort. *Sleep Med*. 2006;7:545–552.
68. Aurora RN, Kristo DA, Bista SR,et al. The treatment of restless legs syndrome and periodic limb movement disorder in adults—An update for 2012: Practice parameters with an evidence-based systematic review and meta-analyses. *Sleep*. 2012;35:1039–1062.
69. Garcia-Borreguero D, Larrosa O, de la Llave Y, et al. Treatment of restless legs syndrome with gabapentin: A double-blind, cross-over study. *Neurology*. 2002;59:1573–1575.
70. Wang J, O'Reilly B, Venkataraman R, et al. Efficacy of oral iron in patients with restless legs syndrome and low-normal ferritin: A randomized, double-blind, placebo-controlled study. *Sleep Med*. 2009;10:973–975.
71. Montplaisir J, Nicolas A, Denesle R, Gomez-Mancilla B. Restless legs syndrome improved by pramipexole: A double-blind randomized trial. *Neurology*. 1999;52:938–943.
72. Mahowald MW, Cramer Bornemann MA.NREM arousal parasomnias. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 5th ed. St. Louis, MO: Elsevier Saunders; 2011:1075–1082.
73. Schenck CH, Mahowald MW. Parasomnias managing bizarre sleep-related behavior disorders. *Postgrad Med*. 2000:107:145–156.
74. Mahowald MW, Schenck CH. REM sleep parasomnias. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 5th ed. St. Louis, MO: Elsevier Saunders; 2011:1083–1097.

90

Intellectual and Developmental Disabilities: Down Syndrome and Autism Spectrum Disorder

Steven R. Erickson

KEY CONCEPTS

1. People with intellectual and developmental disabilities (IDD) have higher incidence of mental illness and challenging behaviors, with dual diagnosis being common.
2. Persons diagnosed with Down syndrome (DS) can be at increased risk for medical and psychiatric comorbidities.
3. People with IDD experience high rates of polypharmacy and polypsychotropic medication use. Assessment should include physical disorders as well as social and environmental factors.
4. People who have DS have higher rates of Alzheimer's-type dementia. A thorough evaluation is needed to differentiate between depression and Alzheimer's disease (AD).
5. Treatment plans for persons with autism focus on increasing social interactions, improving verbal and nonverbal communication, and minimizing the occurrence or impact of ritualistic, repetitive behaviors and other related mood and behavioral problems (eg, overactivity, irritability, and self-injury).
6. Many purported pharmacologic and nonpharmacologic treatments for autism spectrum disorder (ASD) lack objective evidence-based support.
7. A structured teaching approach focusing on increasing social communication and integration with peers is needed when providing services to persons with ASD.

8. Nonpharmacologic interventions for sleep disturbances in children with a diagnosis of ASD should be implemented prior to pharmacotherapy considerations.
9. Psychopharmacologic treatment planning should include monitoring of objective, measurable medication-responsive target behaviors, and assessment of potential adverse effects, which are of critical importance when treating the behavioral symptoms of ASD. Furthermore, the response of individuals to medication therapy is highly variable.
10. The use of FDA-approved medication for off-label indications is an acceptable clinical practice if founded on evidence-based research and informed consent.

Preclass Engaged Learning Activity

Visit the website for "Healthcare for Adults with Intellectual and Developmental Disabilities: Toolkit for Primary Care Providers." https://tinyurl.com/y5dgvnch

Scroll down and click on "Behavioral and Mental Health Issues" link. Read through each section, including the checklists and forms. Then click on the online-training link "For health care professionals," training entitled "Appropriate Use of Psychotropic Medications for People with IDD: Helping Individuals Get the Best Behavioral Health Care."

INTRODUCTION

Developmental disabilities (DD) are chronic disabilities that can be cognitive, physical, or both. The disabilities appear before the age of 22 and are likely to be lifelong.[1] Some developmental disabilities are largely physical issues, such as cerebral palsy or epilepsy, and some individuals may have a condition that includes both a physical and an intellectual disability. Intellectual disability (ID) is a disability characterized by significant limitations in both intellectual functioning and adaptive behavior, which covers many everyday social and practical skills.[2] This chapter will use the term "intellectual or developmental disabilities" (IDD) to refer to people who have conditions associated with DD, ID, or both.

Epidemiology

Down syndrome and autism spectrum disorder are several of the more common diagnoses which make up IDD. It estimated that 1.5% to 2.5% of the US population is living with some form of IDD.[3] The actual frequency and percent of the population of the United States that is characterized as having IDD varies based on the data source and the definition used. For example, the 2010 US Census Bureau found that 1.2 million adults (0.5%) had intellectual disability and 944,000 (0.4%) had developmental disability.[4] Globally, the prevalence of intellectual disability is about one percent of the population.[5] People with IDD primarily live in the community. Living situations include living with family (71%), group homes, or in supported living arrangements of either living by themselves with aid, or with one or two roommates with an aid. Only 13% of adults with IDD live in supervised residential settings.[6]

People with IDD often have some degree of cognitive impairment that may limit their ability to be a collaborative partner in the medication use process, increasing their risk for medication-related problems. Furthermore, those with IDD generally have a high burden of illness which often leads to the person taking multiple medications.[7] Compared to the general population, these multiple medications represent complex regimens that include medications prone to adverse events.[8] Caregivers provide a wide range of support to the person with IDD, depending on the functional ability of the person, including assisting them in navigating the medication use process.[3] In a population health survey conducted in 2013 of people who have IDD, 88.3% of people between the ages of 18 and 39 years and 94.7% of those over age 60 years were taking a chronic medication.[9] The prevalence of polypharmacy, with 5 or more medications, ranged from 30.4% to 45.5% of people who have IDD, with higher rates being seen in older people.

1 Although age-related chronic illness develops in people with IDD similarly to the general population, some conditions may be more prevalent, or occur at an earlier age. The focus of this chapter is on the mental health and behavioral issues that occur in people with IDD. For the purpose of this chapter, the term “dual diagnosis” refers to a person with IDD and who also has a comorbid psychiatric disorder. The prevalence of mental disorders in people with IDD is higher than in the general population. Also, challenging behaviors such as aggression or self-injurious behaviors are seen in some people with IDD and are strongly associated with psychotropic drug prescribing, often with multiple psychotropic medications.[10] Psychiatric and/or behavioral disorders in

persons with an ID, such as depression and anxiety, may result from environmental variables (transitions from family home to group home, change in caregivers), personal variables (age, level of disability, comorbid medical conditions), and the extent to which the individual can cope. The association of life events with depression and anxiety was researched in a community-based population of patients with IDD receiving services from three organizations (mean age 61 years). Assessment variables were age, sex, ID, residential setting, and history of depression or anxiety. Measures of depression and anxiety included the Inventory of Depressive Symptomatology Self Reports and the Glasgow Anxiety Scale of People with an Intellectual Disability. Almost all of the subjects (99.1%) had been exposed to at least one life event during the prior 12-month period, with older subjects experiencing more events.[11] In general, more episodes of major depression, generalized anxiety disorder, and panic disorder were associated with a greater number of negative life events. Therefore, clinicians must be aware of the influence of negative life events on a person with IDD when assessing reasons for challenging behaviors.

The prevalence estimates of mental illness or challenging behaviors in people with IDD range from 30% to 70%.[12] The range of findings can be attributed to a variety of factors including differences in population sampling and methodologies used in identifying psychiatric disorders in persons with IDD. One study of 1,023 people with IDD, which employed a comprehensive individualized clinical assessment, revealed a rate of mental illness of 40.9%.[13] The National Core Indicators project identified a rate for mental illness or psychiatric diagnosis of 66% (*N*=19, 657) for adults who have IDD.[14] The prevalence of challenging behaviors in people with IDD is also high, with percentage of populations varying from over 5% to 17%.[15]

Challenging/Self-Injurious Behaviors

Challenging behaviors may be seen in patients with IDD and include aggression, self-injury, and property destruction that is often lifelong and can result in negative outcomes such as physical injury and social isolation.[16–18] Importantly, challenging behaviors serve different functions and many factors contribute to their occurrence.[19] Mental health disorders in people with IDD may be associated with sensory impairments, negative life events, lack of suitable supports (emotional, social, community, work, and recreational), stress, and limited coping capacity.[20–22] Challenging behaviors may also be associated with early victimization, non-enriched and restrictive environments during childhood

or later on, traumatic brain injury, skill deficiencies in anger management, poor social skills, communication deficits, and psychopathology.

One study found that between 10% and 15% of people with IDD engage in some form of challenging behavior,[23] such as self-injurious behavior (SIB) which is defined as behavior in which a person harms or attempts to harm himself or herself deliberately and physically. Examples include head banging, self-biting, and self-scratching. The prevalence rate of SIB varies from 4% to 23% of people with ID.[24] Results of a recent study using the National Core Indicators database (2015–2016) found that 23.2% of adults surveyed who have IDD needed some or extensive support for SIB.[25] Individuals who required at least some support for SIB were found to have fewer relationships, less inclusion in their communities, and poorer employment outcomes. Notably, SIB, when present, may occur persistently over time and may be associated with a number of causes such as genetic, biological, psychological, environmental, or a combination. It also has been found more commonly in conditions such as Fragile X syndrome, Prader–Willi syndrome, Cri du Chat syndrome, and Lesch Nyhan syndrome.[26] Challenging behavior should not be considered a problem associated with an individual but should be regarded as the result of an interaction between the individual and their environment. The use of positive behavioral supports is gaining acceptance as an alternative form of treatment for SIB.[27] When working with patients who have IDD and mental illness or challenging behaviors, clinicians can screen for sensory impairments, negative social circumstances, stressful life events, and coping capacity. Family and caregivers may be counseled on the value of promoting friendships, social networks, and accommodations for inclusion and participation to decrease isolation and loneliness.[28,29] Diagnostic overshadowing is a potential cause of mis- or under-diagnosis of mental illness in people with ID.[30,31] This refers to clinicians overlooking or minimizing the signs of psychiatric disturbances in a person with an intellectual disability, attributing signs and symptoms of mental illness to the cause of IDD.

DOWN SYNDROME

2 Down syndrome (DS) is associated with common dysmorphic features and a wide range of medical and psychiatric concerns, including a number of developmental abnormalities. Congenital heart defects, seizures, orthopedic abnormalities, sensory defects, leukemia, disorders of the eye (eg, cataracts,

glaucoma), gastrointestinal (GI) tract, immune system, skin, and thyroid gland are all associated with DS. Persons diagnosed with DS also have a high probability (30%) of early onset Alzheimer's disease (AD).[32] Overall, Down syndrome is one of the most common conditions associated with IDD.[33] The live birth prevalence is approximately 1 in 792 live births.[34]

Etiology

Chromosomal analysis has identified the etiology of DS as the presence of an extra chromosome 21. Other names for DS include trisomy 21, which represents one of the most studied abnormal chromosomal conditions. Nondisjunction of chromosome 21 accounts for the majority of the errors. This occurs when chromosomes naturally divide and separate in a process known as disjunction during meiotic division; however, in DS, the chromosomes fail to fully separate and both chromosomes remain in the same cell. The end result is an abnormal number of chromosomes on each strand. For many years, advanced maternal age has been recognized to positively correlate with an increased risk for DS, particularly over age 35 years.[35] More recently though, consideration has also been given to paternal age as data shows that for couples with younger fathers, the odds of having a child with DS were increased almost twofold.[36] Additionally, it has been theorized that two variables, lack of maternal folic acid supplementation and genetic variability that decrease enzymatic processes in folate pathways, may negatively impact meiotic nondisjunction of chromosome 21. However, the National Down Syndrome Project found no association between folate supplementation use and nondisjunction based on younger maternal age (less than 35 year) or ethnicity, but did report an association between older maternal age and a later stage of oocyte meiosis (meiosis II nondisjunction). While these results may explain previously reported finding differences, additional confirmation, controlling for maternal age, is needed.[37]

CLINICAL PRESENTATION Down Syndrome

Diagnostic features

- Facial features can suggest DS, but an additional diagnostic evaluation is necessary.
- Degree of ID ranges from mild to severe.
- Growth delays are common.

Common physical characteristics

- Hypotonia can be evident at birth.
- Facial features include flat nasal bridge and profile, with up-slanted eye folds.
- The palate can be narrow and the neck thick and broad.
- Hands are characteristically short and broad.

Other clinical concerns

- Comorbidity with mental illness, challenging behaviors, and self-injurious behavior.
- An increased risk for congenital heart problems; a cardiac evaluation is generally done shortly after birth with periodic follow-up.
- Congenital cataracts, hearing and sight problems, and hypothyroidism are common.
- Leukemia may occur in early childhood.
- Features of AD can present by the third or fourth decade.

CLINICAL PRESENTATION

The consequences of this chromosomal variance include characteristic facial features, some degree of ID, hypotonia, an increased risk for congenital heart disease, and early onset AD.[38,39] The characteristic facial features make children with DS more readily identifiable at birth with ID ranging from mild to severe.[38] In addition, individuals with DS appear to be at risk to develop depression, anxiety, and obsessive–compulsive disorder (OCD).[40] The differential diagnosis for mood disorders in all patients with DS should include an evaluation of thyroid function, as the clinical signs and symptoms of hypothyroidism and dementia can mimic some of the features of depression, and the risk of a thyroid disorder as a comorbidity in people with DS is estimated at 4% to 18%.[38] In a study of older Medicare beneficiaries with DS in California, 40% were identified as having dementia. Comorbid conditions were more numerous among those with dementia compared to those with DS without dementia, especially among those younger than 65 years. These conditions included hypothyroidism, anemia,

epilepsy, and weight loss.[41]

TREATMENT

Desired Outcomes

Treatment goals in DS are to identify medical and psychiatric comorbidities, set realistic goals, and provide effective social, environmental, nonpharmacologic, and pharmacologic interventions to improve the quality and length of life.

General Approach to Treatment

Medical screenings in patients with DS should assess for hypothyroidism, cardiac problems, sensory impairments (including hearing loss secondary to chronic otitis media with effusion or vision defects due to congenital cataracts or glaucoma), and GI problems (including constipation and celiac disease).[38] Guidelines for health supervision and anticipatory guidance in infants, children, and adolescents with DS are available through the American Academy of Pediatrics (AAP).[39] Guidelines for adults are also available[29] and routine screenings are also recommended throughout the course of life to address psychosocial changes, potential residential or vocational stressors, and the consequences of aging.[38]

Nonpharmacologic Therapy

The use of social supports for both individuals with DS and their family may help develop functional adaptive skills and therefore the fulfillment of the potential of the person with DS. Family education and support network development can assist caregivers by providing tools and resources necessary to more effectively manage persons with DS, allowing these persons to achieve their full potential.

Depressive Symptoms

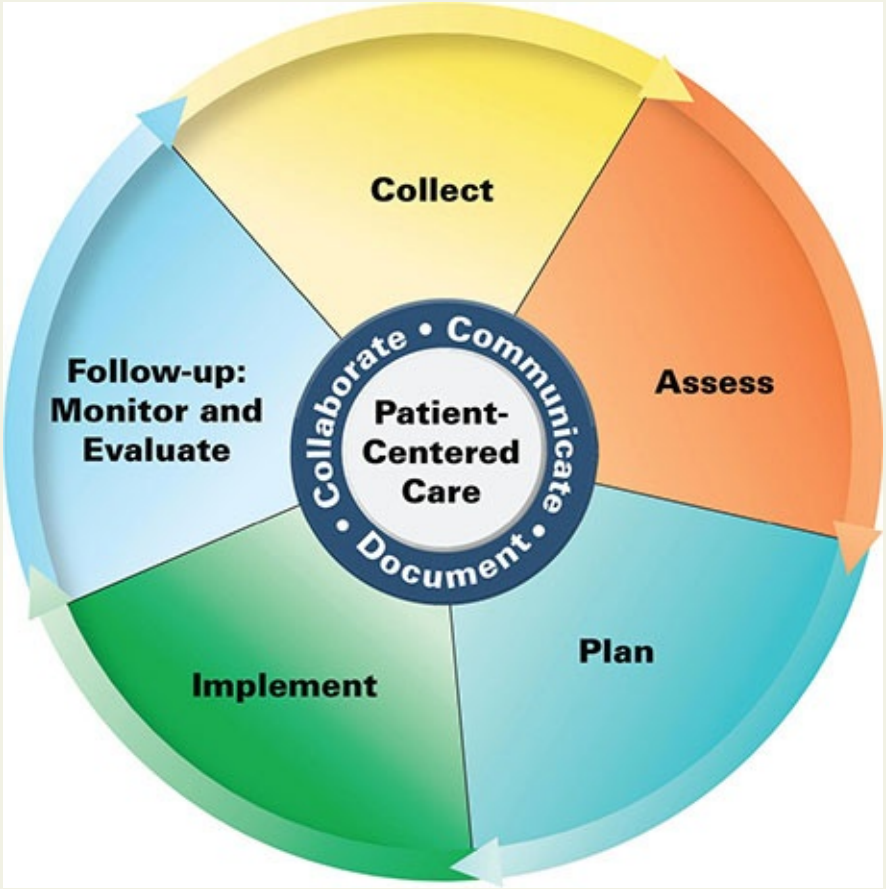
In the treatment of psychiatric disorders, treatment modalities available to the general population also apply to those with DS, with nonpharmacologic options for depression including psychotherapy and electroconvulsive therapy (ECT).[38] Information on the effectiveness of ECT in the DS population is limited to case reports. If communication skills are adequate, psychotherapy may also be an

option with treatment strategies including psychodynamic and cognitive behavior therapy (CBT). While the applicability of psychotherapy can vary with the level of ID, for persons with mild intellectual impairment and depression, this treatment modality may be beneficial. These current behavioral therapy models are more effective in addressing specific problematic behaviors rather than the underlying emotional problems of persons with ID. Furthermore, the extent to which these strategies translate to persons with DS and more severe ID is not known.[38]

Pharmacologic Therapy

Depressive Symptoms

Pharmacotherapy for the treatment of depression in patients with DS follows guidelines used in the general population. For more information on the treatment of depression, see Chapter 85, “Depressive Disorders.” Features of depression commonly seen in persons with DS, in order of frequency, include apathy, disordered sleep, and changes in weight. Difficulty identifying depression in this population is impacted by the level of cognitive impairment, the ability to express abstract concepts (such as helplessness or hopelessness), and the level of adaptive functioning.[38] Clinical trials focused specifically on this population are few, and most information has been based on small studies or case reports. Efficacy with SSRIs and amitriptyline is reported in the DS population. If psychotic features (eg, delusions, hallucinations) are present, low-dose antipsychotic augmentation is recommended. In the studies reviewed, treatment duration was 2 to 3 years.[38]



Patient Care Process for Intellectual and Developmental Disabilities

Collect

- Involve patient as well as one or more caregivers in this process
- Patient characteristics such as age, gender, pregnancy status
- Past medical and psychological history
- Previous life events (eg, changes in living situation)
- Social history (tobacco/ethanol, substance abuse) and dietary habits
- Social and community-based activities
- Current prescription medications, nonprescription medications, and supplements

Assess

- Contraindications to potential medications

- Psychotropic medication already prescribed
- Presence of treatment adverse effects from psychotropic medications
- Physical causes for challenging behaviors such as constipation, gastroesophageal reflux, seizure, aspiration, pain including dental-related pain, sleeping problems (Table 90-1)
- Risk or evidence of harm to self, others, or property
- Frequency of challenging behavior
- Patient's preference for type of therapy if appropriate and identify those involved in the patient's medication use process

Plan*

- Choose medication with strongest evidence and minimal adverse effects (Table 90-2)
- Determine potential drug interactions with other medications
- Education for patient and caregivers
- Develop non-medication intervention based on social and personal factors
- Type of prescription medication insurance and insurance-related regulations in choice of medication

Implement*

- Provide patient education to patient and caregiver
- Work to understand issues related to medication adherence. Choose dosage form that will reduce likelihood of nonadherence

Follow-up: Monitor and Evaluate*

- Reduction in frequency and severity of challenging behaviors
- Presence of adverse effects (Table 90-2)
- Patient adherence to therapy
- Patient's ability to engage in activities in the community
- Caregiver understanding of therapy
- Drug interactions with other medications

**Collaborate with patient, caregivers, and other healthcare professionals.*

As with the treatment of depression in the general population, it is essential to ensure that the medication trial is of appropriate dose and duration before deeming the patient to be a non-responder. Furthermore, ruling out comorbid medical conditions that could contribute to depression is essential.

Challenging Behaviors

3 People with IDD are prescribed psychotropic medications at a rate higher than the general population,[42] which is partly due to an increase in the diagnosis of psychiatric illness within this population, but also because of challenging behaviors not always associated with psychiatric illness. A study of administrative pharmacy claims data of over 52,000 people with IDD found that the most common class of medication dispensed was antipsychotics (21.1% of adults with IDD).[43] The use of psychotropic medication in adults living in group homes in the Netherlands was also found to be high with the primary reason for use being behavioral issues. The authors hypothesize that it is likely that the group home staff found it difficult to deal with people who exhibit socially disruptive behavior.[44] A cross-sectional study conducted in the Netherlands found that of 2,373 adults with ID, 32.2% received antipsychotic drugs. In only 22.5% of cases was the antipsychotic ordered for psychotic disorder or psychotic symptoms. The remainder of people received antipsychotic medication for behavioral problems.[45] The presence of adverse events in patients with IDD taking psychotropic drugs is a challenge, with adverse events reported in 84% of respondents in a small study in the Netherlands. Not only were symptoms reported, but quality of life, as measured by the Intellectual Disability Quality of Life-16 instrument, was found to be lower in patients with adverse events related to medication.[46] Other studies found a high incidence of movement-related adverse events in adults with IDD taking psychotropic medications.[47,48]

Medication management for challenging behaviors or SIB, using risperidone for example, may be effective in both adults and children, with other atypical antipsychotics having limited evidence to support their use.[49] In general, antipsychotic medication has been used to treat aggression; however, the rationale for the use of these medications is generally lacking. Aggression is a component of a challenging behavior, and ranges in prevalence from 11% to 27% of people with IDD. Similar to SIB, risperidone is the only drug with some evidence to support its use for aggressive behaviors.[50] There are no reliable data to support antidepressant, other antipsychotic, or anticonvulsant drugs for the treatment of aggression.[51] Before prescribing medication, clinicians should

complete an in-depth assessment of the behaviors and consider nonmedication-based management options as part of the plan.

Sleep Disorders

Obstructive sleep apnea rates are estimated at 50% to 75% in the DS population.[38] Daytime drowsiness and problematic behaviors may be indicative of both an affective disorder, such as depression, and a medical condition secondary to DS. A comprehensive evaluation, including the impact of obesity on sleep, is needed prior to the addition of pharmacotherapy. If pharmacotherapy is indicated, the medication list for each patient should be carefully reviewed for potential drug–drug interactions and drug–disease contraindications. Parasomnias have been reported with some agents (eg, zolpidem),[52] and the use of medication with this potential effect may require additional monitoring by caregivers, although the frequency of this effect has not been well documented.[53] More information regarding sleep disorders, in general, can be found in Chapter 89, “Sleep Disorders.”

Alzheimer’s Disease in Down Syndrome

4 Persons with DS are at greater risk for AD with increased age, with the proportion of the population affected doubling every 5-year period through 60 years old. Approximately half of people with DS at age 60 have Alzheimer’s associated dementia, and by age 72 years, the prevalence is 67%.[54]

ETIOLOGY

Neuritic plaques and neurofibrillary tangles are the hallmarks of AD. In addition, a gene for amyloid-β precursor protein is located on chromosome 21, which may potentially explain the close relationship between DS and AD regardless of age, gender, and level of ID.[55] While the severity of ID has been theorized to significantly impact the incidence of AD, study results are inconclusive, and the level of ID may limit evaluation. A more extensive discussion of the pathophysiology of AD is beyond the scope of this chapter; more information can be found in Chapter 71, “Alzheimer’s Disease.”

CLINICAL PRESENTATION

In adults with DS, challenging behaviors, such as aggression, loss of previous skills, and disinhibition, may mark a prodromal presentation of AD. Changes in mood and emotional stability may also present.[54] Assessing changes in functionality and cognition is problematic in this population, particularly in those with greater intellectual impairments. Early studies in this population did not specify the diagnostic criteria used for identification of probable or possible AD. It is recommended that baseline neurocognitive and behavioral status be documented once before 35 years of age with reassessment annually up to every 5 years.[56] To meet the diagnostic criteria, the following are needed: baseline functioning data to assess change, functionality changes not explained by general aging, and progressive decline.[57] Accurate diagnosis requires use of an appropriate assessment scale for those with DS, such as the Dementia Scale for Down Syndrome and the Cambridge Examination for Mental Disorders of Older People with Down Syndrome and Others with Intellectual Disabilities.[56] In persons older than 40 with DS, behavior changes are the primary features of the early stages of dementia. Changes may be seen prior to onset with higher frequencies of fear, sadness, and overall behavioral regression. Diagnostic criteria for AD include changes in memory, language skills, and activities of daily living (ADLs). In addition, major functional declines may include behavioral disinhibition, stereotypic or ritualistic behavior, and/or apathy.[57] Risk factors for AD in those with DS include age, genetics, gender, estrogen, multimorbidity, and metabolic syndrome, although information has been limited in some areas. Information on the natural progression of cognitive changes in those with DS and AD continues to emerge.

TREATMENT

Desired Outcomes

The therapeutic goal of treatment is to maintain functioning and quality of life close to baseline for as long as possible. Approaches to therapy for persons with DS combined with AD include nonpharmacologic and pharmacologic interventions. As with the general population with AD, treatment of AD for those with DS is multimodal and includes currently available treatments and supports in order to maintain functionality for as long as possible. Chapter 71 outlines the treatment of AD in the general population, and this chapter specifically discusses AD in a patient with DS.

Nonpharmacologic Treatments

Traditionally, this population receives some level of residential living supports in either the family home, supported living environment, or a residential facility. Including the caregiver along with the patient with DS in assessment and treatment decisions is important to obtain a complete clinical picture.

Pharmacologic Treatments

Pharmacologic treatments neither cure nor stop the pathologic changes associated with AD. The goals of pharmacotherapy in persons with DS and AD, as in the general population of AD patients, are to slow the decline in cognitive function and help preserve ADLs to the greatest extent possible. The use of cholinesterase inhibitors and an *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine in the DS population has been studied. Although limited trial data exist related to the use of memantine in the DS population over age 40 years, results from a smaller prospective randomized double-blind trial did not find treatment or control group improvements for cognition and functional abilities. In fact, both groups declined.[58]

Results on the use of cholinesterase inhibitors to enhance learning and memory in persons with DS have been limited to small sample sizes. Donepezil (3 mg) has been examined in one 24-week, randomized, double-blind, placebo-controlled trial in 21 females with DS and severe ID. At the end of the trial, improvements according to the International Classification of Functioning, Disability and Health (ICF) scaling system were significant and donepezil was well tolerated.[59]

Use of rivastigmine transdermal patches for Alzheimer dementia in adults with DS has also been evaluated in a pilot study that included 10 patients. In this study, for the initial 2 weeks, the patients were given a dose of 1.5 mg orally once daily, which was then increased to twice daily for an additional 4 weeks. After this, the patients received 4.6 mg/24 hours via transdermal patch for the remaining 6-month trial. As this was a case series of rivastigmine use, the findings were compared with previous treatment results, and no significant differences were found. Patch-related adverse effects included erythema, rash, tinnitus, and diarrhea. Problems specific to this population included one participant repeatedly removing the patch which was then followed by marked progression of the disease rendering pharmacotherapy unnecessary.[60]

In patients with DS, who do not meet criteria for AD, but for whom improved cognition is desired, donepezil use has been found to be safe but not

effective.[61,62] Furthermore, small studies using rivastigmine, piracetam, folinic acid, and memantine, all of which target different pathways and receptors, have also failed to show improved cognition in this population.[62] Two drugs that target the GABA system were found to be promising in a mouse model of DS, which did not translate into initial human studies. Furthermore, both pentylenetetrazole and basmisanil have been studied in children, adolescents, and young adults with DS, with no significant impact on cognition or adaptive behavior.[63] A compound found in green tea leaves, Epigallocatechin-3-gallate (EGCG), was found to improve memory recognition, working memory, and quality of life,[64] and when combined with cognitive training for 12 months it was more effective at improving visual recognition memory, inhibitory control, and adaptive behavior than placebo with cognitive training.[65]

While additional information regarding the pharmacotherapy of AD can be found in Chapter 71, pre-existing medical comorbidities, such as congenital heart defects, or concomitant pharmacotherapy may limit use of cholinesterase inhibitors in persons with DS. Clinicians are encouraged to monitor patients receiving cholinesterase inhibitors for commonly reported adverse drug effects and the potential for drug interactions.

A potential neurologic comorbidity of concern in the DS population with AD is seizures. Although seizure activity may increase with age, the distribution of seizure onset is trimodal, with the first peak incidence appearing before 1 year of age (40%) and predominantly consisting of infantile spasms. The second peak occurs between the ages of 20 and 30 years old (40%) and the final peak corresponds to the onset of Alzheimer-related dementia (20%).[56] It is important to note that advancing age and a diagnosis of DS are independent risk factors for seizures.[66] Therefore, monitoring for new-onset seizure activity and medicating with anticonvulsants, as appropriate, are essential. Seizures can impair cognitive functioning, particularly if not well controlled.[67] More information about epilepsy and seizure disorders, in general, can be found in Chapter 73 “Epilepsy.”

Evaluation of Therapeutic Outcomes

Baseline functioning must be established early in adult life prior to the onset of AD, which generally occurs during the third or fourth decade of life. This can be particularly crucial in individuals without expressive language skills. Follow-up evaluations should be performed before age 35 years (at least once) then annually up to every 5 years.[56] If cholinesterase inhibitors are used, evaluations

every 2 to 4 months (after achieving a maintenance dose) are recommended to monitor for effectiveness if the anticipated gains have not been observed. Monitoring for potential medication-related side effects, including diarrhea, nausea, vomiting, insomnia, and headache, is also essential.

Assessment of therapeutic outcomes for those with DS starts with a thorough multidisciplinary evaluation to establish a baseline problem list, identification of clear therapeutic goals, and valid pharmacotherapeutic rationale to guide medication dosing and adverse drug effect monitoring. An in-depth list of treatment targets, both subjective and objective, is important in persons with DS to assist in evaluation of medication response. Careful monitoring for emergence of potential side effects should be regularly conducted and documented as part of ongoing assessment of medication effectiveness and to ensure that side effects are not a contributing factor to behavioral changes.

AUTISM SPECTRUM DISORDER

Autism spectrum disorder (ASD) is a behaviorally defined pervasive developmental disorder (PDD), which includes autistic disorder, Asperger's disorder, or PDD not otherwise specified.[57] These disorders are grouped together and referred to as autism, or autism spectrum disorders, by the Diagnostic and Statistical Manual of Mental Disorders (DSM-V). This section focuses specifically on ASD, which is generally characterized by persistent deficits in social communication and social interaction across multiple contexts as well as restricted, repetitive patterns of behavior, interests, or activities. Symptoms must be present in the early developmental period and cause clinically significant impairment in social, occupational, or other important areas of functioning. The disturbances are not explained by intellectual disability or global developmental delay. Severity of ASD is based on the level of support required for social communication impairments and the degree in which restricted, repetitive patterns of behavior impairs functioning.[57,68] Autism is not a disease but a neurodevelopmental disorder with multiple possible etiologies.[69,70] The onset is typically younger than 3 years of age and is usually, but not always, associated with some degree of ID.[57]

Epidemiology

There has been a recent increase in the reported prevalence of ASD, with the most recent national estimate being 1:68 children identified with ASD.[70,73] It is

suggested that the reported increased prevalence is primarily related to changing and broadening diagnostic criteria, along with an increased index of suspicion, rather than by an actual increased incidence, as ASD is behaviorally identified, and the diagnostic boundaries are not always clear.[71,72] In addition, inclusion of individuals diagnosed with Asperger's disorder and PDD-NOS in newer studies may also be contributing to the increase.[72] Some behaviors (eg, stereotypies) seen in persons with ASD can also be seen in individuals without ASD. One study found children with a history of early institutionalization demonstrated more stereotypical behaviors that markedly decreased following placement in foster care.[73] There is a significant impact of intellectual ability on the expression of ASD symptoms, which results in a lack of homogeneity in clinical expression of the condition.[74] Prevalence estimates vary by sex and race/ethnicity, with autism being four to five times more prevalent in males.[69] When present, ID ranges from mild to severe.

Etiology

The etiology of ASD is attributed to multiple causal factors, including gene mutations, abnormalities in brain development, and genetic–environment interactions.[68] Autism may occur concomitantly with other developmental disorders that have a known genetic basis such as fragile X syndrome[69] and tuberous sclerosis.[75] Current research primarily focuses on genetics and neuropathology. Although a single genetic mutation or variant leading to ASD is yet to be identified, research findings indicate that structural alterations in the genome DNA, known as copy number variations (CNVs), may be involved in ASD as this appears to be a highly heritable disorder.[76] Autism frequently occurs concomitantly with epilepsy[77] and may be associated with microdeletion gene defects that are also risk factors for schizophrenia and attention-deficit/hyperactivity disorder (ADHD). Examples include the association between ASD, intellectual disability, schizophrenia, and seizures with microdeletions on the 15q13.3 and 1q21.1 regions[78]; however, other sites also may be implicated.

Disruptions within critical time periods responsible for the development of excitatory and inhibitory neuron development may also be contributing to the etiology of ASD. Furthermore, a combination of genetic and/or environmental factors, in the absence of any compensatory mechanism, may interfere with brain plasticity[74] or interfere with the excitatory and inhibitory balance expression and/or timing during critical periods.[79] In addition, those diagnosed

with ASD may demonstrate what is termed “unusual sensory processing,” as a diagnosis of ASD has been associated with greater sensory symptoms than other developmental disorders, and for children there is a positive correlation between social impairment and sensory symptoms.[80]

Siblings of affected children have a significantly greater risk of having ASD (3%-18.7%) than those in the general population.[81] Results from a national volunteer registry (2,920 children, 1,235 families, a minimum of 1 child meeting ASD diagnostic criteria, and a minimum of 1 full sibling) found that the sibling concordance rate was 10.9%. Overall, an additional 8.9% of the siblings demonstrated language delay with autistic-like speech quality.[81]

Further support for the high heritability of the disorder was shown by additional research outlining that sibling risk varies based on the gender of the index child: 4% versus 7% for female compared with male. If a second child is diagnosed, the risk for concordance in subsequent siblings increases to between 25% and 30%.[82]

Parental age has been investigated as a potential risk factor for ASD. Results from a case-control study that included a cohort of age- and sex-matched pairs (*n* = 68) found that the unadjusted parental ages were higher for both parents (paternal 4 years higher, maternal 4.8 years higher) in those who had a child with ASD, compared with controls. After adjusting for variables such as educational level and gestational age, the differences widened to 5.9 and 6.5 years, respectively.[83,84] In contrast to this, another research has identified parental age as a risk factor if the mother was less than 30 years old,[84] while other work has found increasing paternal age to be associated with greater risk.[85]

While genetics plays a role in the development of ASD, environmental exposures including toxic chemical exposure, teratogens, perinatal insults, prenatal infections,[69] and copper and zinc levels are all currently under investigation. Immunization with measles/mumps/rubella vaccine has been investigated, and no causal association identified.[86] Well-conducted case-control cross-sectional ecological and cohort studies investigating use of thimerosal, an organomercury compound previously used as a vaccine preservative, found no causal association between thimerosal-containing vaccines and the development of ASD or deficits in neuropsychological function.[87] In a large sample of privately insured children with older siblings, receiving the MMR vaccine (measles-mumps-rubella) was not associated with increased risk of ASD, regardless of whether the older siblings had ASD.[88] Despite the lack of evidence, the neurotoxic effect of mercury exposure continues to be a hotly

debated issue among many advocates for persons with ASD. Clinicians must be well informed on this issue to educate parents and caregivers.

Pathophysiology

The neurodevelopmental foundation of ASD has sparked significant interest in early morphologic changes in brain development, particularly findings of early brain overgrowth. Head circumference at birth ranges from slightly below normal to within normal limits. This finding changes by 2 to 3 months of age when accelerated head growth occurs. The rate of growth may exceed two standard deviations above the average. Approximately 60% of infants diagnosed with ASD compared with 6% of normal infants have this rate of accelerated head growth. The increase positively correlates to the increase in ID severity. Following this period of accelerated head growth, during which time the infant brain may achieve the size of the adult brain, deceleration or a complete cessation of head growth is noted.[69] Mechanistically this accelerated brain growth may predispose the developing brain to increased vulnerability, as development of cortical circuitry is established during critical postnatal periods.

Furthermore, dysfunction of virtually all neural systems in the brain has been proposed at some point as a potential basis of ASD.[89] In contrast to the previously mentioned pathophysiological mechanisms involving head growth, the neuropathologic changes noted in persons with ASD are suggested to be of prenatal origin, primarily in the first 6 months of gestation.[69] These changes suggest that ASD affects a functionally diverse and widely distributed set of neural systems, making the disorder far broader in scope than a simple social interaction disorder.[89] Despite these findings, the pattern of brain abnormality appears somewhat discrete, as autism spares many perceptual and cognitive systems and a localized neural deficit can have more widespread neurofunctional implications through its influence on brain development.[89]

There is also research to support the hypothesis that abnormalities in cholinergic receptors and decreases in the nicotinic receptor binding in the cholinergic system, as well as dysfunction in the GABAergic system,[77] may exist in persons with ASD. Nicotinic receptors enhance cognitive processing (ie, memory and attention) and open the possibility of therapeutic intervention via cholinergic receptor modulation.[90,92] Approximately 25% to 60% of children with ASD have elevated peripheral platelet concentrations of the neurotransmitter serotonin[91] while studies of dopamine and catecholamine metabolites have failed to consistently show abnormalities.

Taken all together these studies outline the many differing and often contradictory hypothesis regarding the pathogenesis of ASD.

CLINICAL PRESENTATION

A multiple-step process has been suggested as a structured approach to differential diagnosis of suspected ASD. As a spectrum disorder, the severity or level of impairment within each of these features may be highly variable. Therefore this structured approach includes a determination of intellectual function and level of language development, followed by assessment of the child's behavior as it relates to chronologic age, mental age, and language age. It is important to identify relevant comorbid medical conditions and the presence of any related contributing psychosocial factors.[92]

CLINICAL PRESENTATION Autism Spectrum Disorder

General

- Individuals typically present with delays or abnormalities in social communication/interaction as well as restricted, repetitive patterns of behavior, interests, or activities.

Diagnostic features

- Significant impairment in nonverbal communications.
- Unable to develop peer relationships.
- Lack of spontaneous interactions with people or the environment.
- Developmental delays in communication.
- Inability to use expressive language appropriate to developmental level.
- Lack of developmentally appropriate play.
- Stereotypical or nonfunctional ritualistic behavior.
- Inability to tolerate change.
- Stereotypic or repetitive, nonfunctional motor movements.
- Limited scope of play or interest.

Data from References 93-95

Oftentimes persons with ASD are normal in physical appearance. Between 2% and 21% of those with ASD also have comorbid seizures, which may increase the risk for greater intellectual impairments.[57,93,96] Other medical comorbidities commonly reported in this population include sleep disturbances, food intolerances, and gastrointestinal dysfunction.[97]

The cardinal features of ASD include sustained impairment of reciprocal social interaction, sustained abnormalities in verbal and nonverbal communication skills, and restricted, repetitive, and stereotypical patterns of behavior, interests, and activities.[57,97] These are primarily manifested as gaze aversion, little/no interest in making friends, preference for solitary activities, repetition of words/phrases, monotone voice, insistence on sameness, and a lack of awareness of other's feelings.[57,98] In most cases (~75%), there is an associated diagnosis of ID, ranging from mild to profound: approximately 30% function in the mild-to-moderate range of ID, whereas 45% to 50% have severe to profound impairment.[92] Epidemiologic data suggest that the risk for development of ASD increases as the IQ decreases.[92] A few individuals with ASD have unusual abilities called splinter functions or islets of precocity. The most significant of these are evidenced in the autistic savant, in which the individuals can have precocity in mathematic calculations, art, music, or rote memory.[57,92]

In many instances, parents note that they were concerned about the child's lack of interest in social interactions since birth, but were sure at least by 3 years of age.[57] In a controlled setting, use of an integrated model for screening was effective in diagnosing children before 36 months of age.[99] Original findings of behaviors suggesting the need for an intellectual evaluation included lack of babbling, pointing, or other gestures by 12 months, no single-word language development by 16 months, no two-word language development by 24 months of age, and loss of previously held language or social skills at any age.[69] Earlier intervention is recommended when the early signs and symptoms of ASD are recognized.

It is difficult to determine if ASD is present in persons with severe to profound ID; therefore, a diagnosis is made in such cases when there are qualitative deficits in social and communicative skills and the specific behaviors characteristic of ASD are present.[57] A key central difference between ID and ASD is that persons with ID alone typically relate to adults in a manner consistent with their mental age, use their language to communicate with others,

and present with a relatively even profile of impairments without splinter functions.[92,94]

Although there are no definitive biologic markers for identifying individuals with ASD, a number of medical evaluations should occur at baseline, to assist in distinguishing the diagnosis as ASD and to rule out other disorders. **Table 90-1** delineates the parameters to be considered in a medical evaluation for persons suspected of having ASD and the rationale for the assessment.

TABLE 90-1 Medical Screening for Individuals with Autism Spectrum Disorder

Parameter	Rationale
Health, medical, behavioral, and developmental history	Perform initial screening or confirm diagnosis; identify underlying cause; assess strengths and weaknesses; identify comorbidities; measure head circumference; identify resources needed
Wood's light exam	Identify depigmented macules associated with tuberous sclerosis
Hearing and vision testing	Profound hearing loss can illicit symptoms mimicking ASD (receptive language deficits); most are normal
Heavy metal testing	Perform if there is a history of malnutrition, recurrent vomiting, early onset seizures, dysmorphic features, presence of ID or developmental delays
Genetic testing for karyotype, fragile X, Rett syndrome	Benefits family for genetic counseling purposes; evaluation of siblings, if applicable; review family history for three generations
Test for inborn errors of metabolism/ metabolic testing	Indicated in those with a history of lethargy, recurrent vomiting, early seizures, dysmorphic or coarse facial features, ID
CBC, thyroid function testing	CBC if anemia suspected; thyroid function tests to rule out baseline thyroid abnormality that can affect mood/activity level
EEG	Evaluate neurologic findings that cannot be explained by the diagnosis of ASD alone or in the presence of developmental regression, particularly language
Neuroimaging	Evaluate neurologic findings that cannot be explained by the diagnosis of ASD alone; identify specific neuropathologic changes associated with ASD, including brain volume

CBC, complete blood count; EEG, electroencephalograph; ID, intellectual disability.

Data from References 59, 72, 100, and 148.

Those individuals with ASD and intelligence quotients (IQs) above 70 who use communicative language by ages 5 to 7 have the best prognoses.[92] Conversely, low IQ scores and failure to develop communicative language by age 5 years correlate with a poorer long-term prognosis.[100] Outcome studies in persons with ASD correlate IQ, particularly verbal IQ, with the ability to be employed and live independently.[89,94] Learning disabilities are an independent

risk factor for development of behavioral problems, and 41% of children with mild, moderate, or severe learning difficulties have a significant emotional behavioral disturbance.[94] Studies indicate that high-IQ children with ASD can make positive changes in communication and social domains more effectively over time. The areas less likely to improve are those related to ritualistic and repetitive behaviors.[98] Up to 80% of children diagnosed with ASD continued to experience marked impairment in social interactions as adults and mild-to-moderate ID was reported for approximately 30%.[101]

In addition to the core symptoms of ASD, many persons with this disorder exhibit other significant maladaptive behaviors, such as aggression to self and others. These behavioral issues can interfere with day-to-day activities and are challenging for the individual, families, and caregivers.[102]

TREATMENT

Desired Outcomes

5 Treatment goals in persons with a diagnosis of ASD are to maximize their ability to lead a full self-directed life through person-centered approaches to care and support. This includes addressing deficits in communication and social interaction using a structured approach and minimizing the impact of restricted behaviors (eg, stereotypies or repetition) appropriate to the level of intellectual ability, language development, and chronologic age. The multimodal treatment plan should address (a) establishing realistic goals for educational efforts, (b) identifying the presence of behavioral target symptoms for intervention, (c) prioritizing target symptoms and comorbid conditions for intervention, (d) using specific methods of outcome monitoring of functional domains (behavioral skills, adaptive skills, academic skills, social interaction skills, communication skills), and (e) monitoring for efficacy and potential adverse effects of medication (if used). The National Institutes of Health (NIH) suggests that evidence-based treatment strategies include the use of both psychoeducational therapies and medications.[103] An effective, well-designed, multimodal treatment plan that is consistently executed has the most potential to positively shape how an individual with ASD interacts with the environment and improve their quality of life and that of their families and caregivers.

6 After a thorough diagnostic evaluation, treatment planning for the individual with ASD is critical to assure consistency and efficacy of interventions. With the often-severe nature of the behavioral and adaptive

problems, it is not surprising that many potential treatment modalities lacking an evidence basis have been proposed for persons with ASD. The two treatment approaches for ASD with evidence-based support and clinical consensus are behavioral/psychoeducational therapies[104] and psychoactive medication intervention[66] as appropriate. All stakeholders (family, educators, caregivers, and clinical professionals) should be involved in the treatment planning process, and decisions should be evidence-based and individualized to the specific identified needs of the individual. The potential for communication deficits often limits self-reporting of psychopathology. A multifaceted approach to information gathering should include direct observation; interviews with patient, parents, family, caregivers, and teachers; and review of the medical record, including any behavioral rating scale information.

Nonpharmacologic Therapy

7 Available evidence suggests that appropriately designed, consistently implemented educational services positively impact the acquisition of social, communicative, self-care, and cognitive skills, each of which facilitates the person's long-term success. Services, such as occupational therapy, physical therapy, and speech pathology, are often integral aspects of an overall educational plan. Because of the pervasive need for sameness in routine, ongoing and consistent year-round educational programming is more effective than intermittent, episodic interventions. Effective language and communication training can lead to generalized improvements in social skills and repetitive behaviors, and thus positively impact other nonspecific maladaptive behavioral problems such as noncompliance, self-injury, and aggression.[105]

Intervention strategies, such as discrete trial training, have demonstrated improvement in challenging behaviors. Educational techniques include structuring the environment, family training, peer role modeling, and sensory integration to optimize environmental interactions.[104] Applied behavior analytic interventions now have evidence and funding to support utilization by people with ASD.[102,106]

Pharmacologic Therapy

6 Many of the studies of psychopharmacologic interventions in persons with ASD have methodologic shortcomings including problems in experimental design and sample size, poorly defined diagnostic criteria, and many clinical

outcomes that were limited in duration or of dubious clinical significance. Among a number of scientifically unsupported treatments for ASD is the use of complementary and alternative medicine (CAM). A study of 540 families of children with ASD found that the child/family had tried an average of seven CAM therapies.[107] Elimination diets in which casein (from dairy products) and/or gluten (from wheat products) are excluded from the diet have demonstrated no benefit. Other such purported therapies include omega-3 fatty acids and selected herbal remedies, specifically ginkgo biloba. However, controlled trials have not demonstrated significant differences between omega-3 and ginkgo biloba supplementation compared to placebo.[108]

8 Current research on the neurobiologic basis of ASD is centered on the serotonergic, peptidergic, dopaminergic, and noradrenergic systems. This research has particular applications for insomnia in children with ASD, as the prevalence of sleep disorders has been reported to range from 44% to 83%.[109] Parents commonly rate sleep disturbance as a significant clinical issue. As with patients without ASD, it is important to determine the underlying etiology of the sleep problem. Behavioral interventions (eg, improved sleep hygiene, eliminating maladaptive sleep habits, and parental education) should be undertaken prior to implementing pharmacotherapy. No medication is approved by the FDA for pediatric insomnia. While controlled trial data are limited, there is support for the use, safety, and effectiveness of melatonin. In a review of the literature for use of melatonin in ASD, 85% (n = 107) reported improved sleep, specifically shorter sleep onset latencies. Doses ranged from 0.75 to 6 mg. Adverse effects were mild (headaches, GI upset, dizziness).[110] Chapter 89 outlines the treatment of sleep disorders in greater detail.

9 Aggression to self and others and severe tantrums are a concern, particularly with adults with ASD. In addition to inclusion of nonpharmacologic interventions, pharmacotherapy is frequently utilized. Despite limited evidence-based support, psychoactive medications have been widely used to minimize the frequency and intensity of these behaviors. It is important that clinicians identify and carefully monitor specific behavioral target symptom response to avoid the practice of overprescribing psychoactive medications.

Antipsychotics

An association between dopamine dysregulation and increased aggression, including self-injury, consistent with animal models, has been proposed.[102] Such findings have led to the use of antipsychotic agents that act as dopaminergic

antagonists to address aggression and self-injurious behavior. The first-generation antipsychotic agent with the most evidence for short- and long-term safety and efficacy is haloperidol. Target behaviors included impaired learning, anger, mood lability, hyperactivity, and social withdrawal. Although results for improvement in the target behaviors were greater in the antipsychotic treatment compared with the placebo group, the risk for the development of dyskinesias and the introduction of new antipsychotic medications have severely limited haloperidol's use.[68,71]

10 As few psychopharmacologic agents have been well studied in this population, and even fewer have received FDA approval, current research is directed primarily toward the atypical antipsychotics. Off-label use of FDA-approved medications (ie, use of an approved drug for an unapproved use) is an acceptable clinical practice when there is evidence-based support for the use of the medication and informed consent is obtained; however, there is a relative lack of robust research in this area at the present time.

Aripiprazole and risperidone are currently FDA approved to treat the behavioral (irritability) symptoms associated with ASD.[111,112] A review of the literature demonstrated that both short- and long-term use of orally administered aripiprazole, dosage range of 2 to 15 mg per day, was effective for irritability in pediatric patients with ASD. Aripiprazole was associated with side effects that resolved with continued use.[113–116] Weight gain was reported during the first 3 to 6 months, plateauing thereafter.[113] Risperidone has the most evidence-based support for treating behavioral problems associated with ASD and is FDA-approved for treatment of SIB, aggression, temper tantrums, and irritability in children and adolescents with ASD.[68] The efficacy of risperidone in the treatment of irritability associated with ASD was established in several short-term studies (6 to 8 weeks), placebo-controlled trials in children and adolescents (aged 5 to 17 years) who met the DSM-IV criteria for ASD. Significant improvements in outcomes measures such as the Aberrant Behavior Checklist (ABC) and the Clinical Global Impression - Change (CGI-C) scale were seen.[117,118] Short-term studies also have shown some success in adults with ASD in reducing repetitive behavior, aggression, irritability, and overall behavioral symptoms.[119] The use of olanzapine is supported by limited trial data in children and adolescents with ASD. Trial durations were generally short (6 to 8 weeks) with small numbers of participants. Positive results are generally reported in global improvement scale assessment; however, the significant weight gain and sedation noted in olanzapine trials are important considerations in weighing risk versus potential benefit.[68] A post-hoc analysis of the health-related quality of life

of pediatric patients receiving aripiprazole found improved scores compared to placebo in three of five subscales, including emotional, social, and cognitive functioning.[120,124]

The atypical antipsychotic agents are less likely to elicit extrapyramidal side effects than first-generation agents due to more potency at serotonin2A (5-HT2A) receptors versus dopamine receptors. However, the newer agents have been implicated in weight gain in some persons with ASD.[68] The potential serum prolactin elevation related to risperidone use is of concern as this may lead to amenorrhea, galactorrhea, and osteoporosis in females and gynecomastia and sexual dysfunction in males. The minimum degree of prolactin elevation that is clinically relevant is uncertain, as are the implications for long-term use in a pediatric population. If detected, strategies include evaluating the risk–benefit with continued use, reducing doses, or changing to another agent with less impact on prolactin. It is recommended that clinicians monitor for the evidence of potential risperidone-mediated prolactin elevations regardless of whether a prolactin level is obtained.[121,125] Additional monitoring recommendations for antipsychotic use and the monitoring of adverse effects can be found in Chapter 84 “Schizophrenia.”

Selective Serotonin Reuptake Inhibitors

Serotonin synthesis differs between children diagnosed with ASD and children without this diagnosis. Compared with adults, 5-hydroxytryptamine (5-HT) synthesis may peak at twice the adult level in developmentally normal children by age 5 years, whereas children with ASD have a more gradual developmental arc with a lower peak.[122] The use of SSRIs is often associated with a decrease in some of the core behavioral symptoms such as stereotypies, social withdrawal, and rigid adherence to routine. A review of the literature for citalopram, escitalopram, fluoxetine, and fluvoxamine found limited support for use of SSRIs to address behaviors of ASD.[122,123] At this time there is no FDA-approved medication for the core symptoms of ASD. Prior to the inclusion of pharmacotherapy for behavior as a component of the plan, utilization of a multifaceted approach is recommended.[124]

Psychostimulants

Psychostimulants have been studied in persons with ASD to address hyperactivity, impulsivity, and inattention. Pharmacologically these agents block the reuptake of dopamine and norepinephrine, which may support their use in

ADHD as their use may correct dysfunction in the regulation of these catecholamines.[125] The largest and most rigorously controlled trial of methylphenidate involved 72 participants, with 74% having a primary diagnosis of ASD. In this placebo-controlled trial, methylphenidate was given in divided doses of 0.125, 0.25, and 0.5 mg/kg (morning and noon doses) with 16 not being able to tolerate the 0.5 mg/kg dose phase. Overall all 3 doses performed better than placebo on improving the core symptoms of ADHD, with the medium dose performing better than the low dose according to the parent and teacher ratings.[126] It is important to note that the doses used in this trial were generally lower since the patients with ASD were unable to tolerate the higher doses commonly used in ADHD patients. In terms of side effects, irritability and stereotypic behaviors, GI complains, and sleep disturbances are seen with the higher doses.[127] Another agent, atomoxetine, has been reported to significantly reduce hyperactivity in small trials with moderate level of adverse effects similar to methylphenidate.[128,129] Overall, findings suggest that treatment response to psychostimulants varies.[130] The α2-agonists, clonidine and guanfacine, have also been used to treat hyperactivity and agitation in persons with ASD because of their effects on inhibition of noradrenergic release and transmission. Both agents have FDA approval for treating symptoms associated with ADHD; however, as with many psychoactive medications used in the ASD population, there is a lack of methodologically sound studies supporting use of these agents. Two trials reported positive outcomes with guanfacine when used for the targeted symptoms of inattentiveness and hyperactivity, with global improvements being noted in one.[130] Therefore, aggressive behavior, sleep disturbances and anxiety may respond to alpha-2 adrenergic receptor agonists with common adverse effects including drowsiness, fatigue, and decreased appetite (**Table 90-2**).[131]

TABLE 90-2 Common Psychotropic Medications Used in Down Syndrome and Austin Spectrum Disorders

Drug	Indications	Target Symptoms	Common Side Effects
Atypical Antipsychotics			
Risperidone	Self-injurious behavior, aggression, temper tantrums, irritability (Risperidone and aripiprazole approved for irritability in ASD)	Irritability, aggression Aberrant social behavior	Sedation, drowsiness, drug-induced extrapyramidal reaction Insomnia, fatigue, parkinsonian-like syndrome, headache Anxiety, dizziness, drooling Hyperprolactinemia, weight gain, Increased appetite Increased serum total and LDL cholesterol, triglycerides, glucose Decreased HDL cholesterol Vomiting, constipation, upper abdominal pain, nausea, urinary incontinence Tremor, nasopharyngitis, cough, rhinorrhea, fever
Aripiprazole			
Cognitive Enhancers			
Memantine Donepezil Rivastigmine	Memory, cognition	Cognition	Hypertension, hypotension Dizziness, insomnia, confusion, headache, anxiety, depression, drowsiness, hallucination, pain, aggressive behavior, fatigue, back pain Weight gain, weight loss (rivastigmine), diarrhea, constipation, vomiting, abdominal pain, urinary incontinence Cough, dyspnea
Miscellaneous			
Oxytocin Vasopressin Balvaptan	Aberrant social behavior Social behavior, communication	Emotion recognition Eye gaze	Nasal discomfort (intranasal oxytocin), tiredness, irritability, diarrhea
Melatonin	Sleep disorder		Dizziness, enuresis, excessive daytime somnolence, headache, nausea, insomnia, nightmares, and transient depression
Methylphenidate Atomoxetine Clonidine Guanfacine	Attention-deficit/ hyperactivity disorder: Treatment of attention-deficit/hyperactivity disorder (ADHD)	Hyperactivity, inattention	Insomnia, headache, irritability Decreased appetite, xerostomia, nausea, early morning awakening Drowsiness and fatigue (clonidine, guanfacine)

Miscellaneous Agents

Limited data are available on the use of cholinesterase inhibitors for disruptive behaviors, such as hyperactivity and irritability, and use of donepezil for these or the core ASD symptoms cannot be supported.[75] Furthermore, no benefit for ADHD or core symptoms was found with galantamine use, and results for rivastigmine are unclear. Use of the NMDA receptor antagonist memantine was associated with hyperactivity as both a side effect and a target behavior. Therefore, additional study is needed for this agent.

Limited support for anticonvulsants for ADHD symptoms in children with ASD was found, despite the high comorbidity of seizures in this population.[130]

Vasopressin, which is thought to influence social behavior, is a closely related hormone to oxytocin. Physiologically the oxytocin and vasopressin receptors are highly expressed in the amygdala, hippocampus, and nucleus accumbens, and play a role in behaviors, bonding, and parental care.[132,133] Short-term studies of intravenous as well as intranasal administration of oxytocin showed decreased repetitive behaviors and enhanced social cognition in patients with ASD[134–137]; however, more recent work on intranasal oxytocin provides inconclusive results.[136,138] The drug balovaptan is an oral agent that inhibits vasopressin V1a from binding to receptors in the brain and was recently designated by the FDA as a breakthrough therapy. Notably, balovaptan has shown the potential to improve social interaction and communication in patients with ASD.[137,138]

The current dearth of evidence-based psychopharmacologic and behavioral research in persons with ASD is being addressed by a network of NIH-funded research centers, including the research units of Pediatric Psychopharmacology, Centers for Programs of Excellence in Autism, and Studies to Advance Autism Research and Treatment. The mission of these units is to foster well-controlled, multicenter, behavioral, and psychopharmacologic intervention studies targeting behavioral symptoms in persons with ASD.

As previously stated, aggression to self and others and severe tantrums are a concern, particularly in adults with ASD. In addition to nonpharmacologic interventions, psychoactive medications have been widely used to minimize the frequency and intensity of these behaviors, despite limited evidence-based support. Although pharmacogenomics to guide rational and targeted pharmacotherapy would be helpful, at present this information is not available.[139,141] This may be in part because of the heterogeneity of the ASD population.

Evaluation of Therapeutic Outcomes

9 Monitoring the safety, efficacy, and tolerability of psychopharmacologic interventions in persons with ASD is imperative to minimize adverse medication-related sequelae and optimize desired therapeutic outcomes. Clinical investigators have used a variety of psychometric assessment instruments in attempts to measure changes in core symptoms such as communication impairment, restricted interests, repetitive, compulsive, ritualistic, or perseverative behaviors, irritability, hyperactivity, and variants of self-injurious behavior. While a comprehensive review of many of these instruments is beyond the scope of this chapter, the Aberrant Behavior Checklist consists of 54 items

divided into 5 domains: irritability, hyperactivity, stereotypic behavior, lethargy, and inappropriate speech. This checklist was designed for assessment of behavioral changes in institutionalized individuals enrolled in pharmacotherapy trials; however, a community-based version is also available.[140,141] In addition, the Children's Yale-Brown Obsessive Compulsive Scale modified for PDDs is a validated scale sensitive to changes in repetitive behavior severity pretreatment and posttreatment.[142]

Intensive medication-related side effects monitoring and assessment is critical in this population, as self-reporting can be unreliable. Therefore, a caregiver-rated instrument, such as the Monitoring of Side Effects Scale can be useful for this purpose as it is a multisystem, quantitative, and qualitative caregiver assessment that rates the presence or absence and severity of a variety of potential medication-related adverse effects for clinician review.[143] Signs and symptoms are written in layperson language and are listed by body area or system. As such, it is a broad-based screening tool that can be enhanced by side effect–specific scales such as those for akathisia (Barnes Akathisia Scale), extrapyramidal effects (Simpson-Angus Scale), or tardive dyskinesia (Dyskinesia Identification System: Condensed User Scale [DISCUS]).[144–146]

9 Use of atypical antipsychotics has been associated with increased risk of developing metabolic syndrome. Children receiving these agents should be monitored for hyperglycemia, dyslipidemia, and weight gain in a manner consistent with the consensus guidelines suggested by the American Diabetes Association and the American Psychiatric Association. For monitoring guidelines, see Chapter 84.

CONCLUSION

Psychotropic medications can be effective for the treatment of mental health conditions for people with IDD. Medication therapy must be coupled with other psychological therapies when a psychiatric disorder is confirmed by comprehensive assessment. Psychotropic medications should be used carefully for people with IDD, as there is increased risk of adverse drug–drug interactions due to a high prevalence of polypharmacy, the patient having atypical responses to psychotropic therapy, and the inability for a person with IDD to describe the harmful or distressing effects of psychotropic therapy other than through changes in behavior.[147] One must remember that when assessing an individual with IDD who is exhibiting mental illness or behavioral issues, physical-related problems may be underlying. For example, a person with minimal verbal

communication may exhibit challenging behavior when experiencing pain from an underlying undetected tumor or broken bone. A complete examination and history taking that includes information from caregivers who work with the person for a long time is necessary in order to make an accurate diagnosis and recommendation for treatment.

Postclass Engaged Learning Activity

Review the "Patient Care Process" section at the beginning of this chapter. Compare and contrast the criteria for each step of the PCP with those of the Toolkit Behavioral and Mental Health Issues "Behavioral Problems and Emotional Concerns: Provider Checklist," the "Risk Assessment Tools for Adults with IDD in Behavioral Crisis," and the "Psychotropic Medication Checklist." This activity will help you envision the important points to assess when consulting on a patient who has an IDD and challenging behavior.

ABBREVIATIONS

AAP	American Academy of Pediatrics
AD	Alzheimer's disease
ADHD	attention-deficit/hyperactivity disorder
ADL	activity of daily living
ASD	autism spectrum disorder
CAM	complementary and alternative medicine
CBT	cognitive behavior therapy
CNV	copy number variation
DISCUS	Dyskinesia Identification System Condensed User Scale
DNA	deoxyribonucleic acid
DS	Down syndrome
ECT	electroconvulsive therapy
GABA	γ -aminobutyric acid
GATA-1	Erythroid transcription factor or GATA-binding factor 1
5-HT	5-hydroxytryptamine
5-HT_{2A}	serotonin$_{2A}$

ICF	International Classification of Functioning, Disability and Health scaling system
ID	intellectual disability
NIH	National Institutes of Health
NMDA	*N*-methyl-D-aspartate
NPI	Neuropsychiatric Inventory
RTT	Rett syndrome
SIB	self-injurious behavior
SIB	Severe Impairment Battery
SSRI	selective serotonin reuptake inhibitor

REFERENCES

1. American Association on Intellectual and Developmental Disabilities. Available at: https://aaidd.org/intellectual-disability/definition/faqs-on-intellectual-disability. Accessed October 30, 2018.
2. American Association on Intellectual and Developmental Disabilities. Available at: https://aaidd.org/intellectual-disability/definition. Accessed October 30, 2018.
3. Bethesda Institute. How Prevalent Are Intellectual and Developmental Disabilities in the United States? Available at: http://flroof.org/publication/view/how-prevalent-are-intellectual-and-developmental-disabilities-in-the-united-states/. Accessed October 30, 2018.
4. Brault MW. Americans with disabilities: 2010. Household Economic Studies. *Current Population Reports*. July 2012;70–131.
5. Maulika PK, Mascarenhasc MN, Mathersc CD, et al. Prevalence of intellectual disability: A meta-analysis of population-based studies. *Res Dev Disabil*. 2011;32:419–436.
6. Braddock D, Hemp R, Tanis ES, et al. *The State of the States in Intellectual and Developmental Disabilities*. Washington, DC: American Association on Intellectual and Developmental Disabilities; 2017.
7. Doan TN, Lennox NG, Taylor-Gomez M, Ware RS. Medication use among Australian adults with intellectual disability in primary healthcare settings: A cross-sectional study. *J Intellect Dev Disabil*. 2013;38:1770–1781.

8. Erickson SR, Nicaj D, Barron S. Complexity of medication regimens of people with intellectual and developmental disabilities. *J Intellect Dev Disabil*. 2018;43:351–361.
9. Victorian population health survey of people with an intellectual disability 2013, State Government of Victoria, Melbourne. Haider SI. Health Intelligence Unit, Systems Intelligence and Analytics, Department of Health and Human Services, 50 Lonsdale Street, Melbourne, Victoria 3000. Department of Health & Human Services 2015.
10. Stolker JJ, Heerdink ER, Leufkens HGHM, et al. Determinants of multiple psychotropic drug use in patients with mild intellectual disabilities or borderline intellectual functioning and psychiatric or behavioral disorders. *General Hospital Psychiatr*. 2001;23:345–349.
11. Hermans H, Evenhuis HM. Life events and their associations with depression and anxiety in older people with intellectual disabilities: results of the HA-ID study. *J Affect Disord*. 2012;138:79–85.
12. Szymanski L, King BH. Summary of the practice parameters for the assessment and treatment of children, adolescents, and adults with mental retardation and comorbid mental disorders. American academy of child and adolescent psychiatry. *J Am Acad Child Adolesc Psychiatry*. 1999;38:1606–1610.
13. Cooper SA, Smiley E, Morrison J, et al. Mental ill-health in adults with intellectual disabilities: prevalence and associated factors. *Br J Psychiatry*. 2007;190:27–35.
14. National Association of State Directors of Developmental Disabilities Services and Human Services Research Institute. Available at: http://www.nationalcoreindicators.org/charts/. Accessed November 28, 2018.
15. Deb S, Kwok H, Bertelli M, et al. International guide to prescribing psychotropic medication for the management of problem behaviors in adults with intellectual disabilities. *World Psychiatry*. 2009;8:181–186.
16. Emerson E, Kiernan C, Alborz A, et al. The prevalence of challenging behaviors: A total population study. *Res Dev Disabil*. 2001;22:77–93.
17. Holden B, Gitlesen JP. A total population study of challenging behavior in the county of Hedmark, Norway: Prevalence and risk markers. *Res Dev Disabil*. 2006;27:456–465.
18. Matson JL, Sipes M, Fodstad JC, Fitzgerald ME. Issues in the management of challenging behaviours of adults with autism spectrum

disorder. *CNS Drugs*. 2011;25:597–606.

19. Cooper SA, Smiley E, Morrison J, et al. Mental ill-health in adults with intellectual disabilities: Prevalence and associated factors. *Br J Psychiatry*. 2007;190:27–35.
20. Hartley SL, MacLean WE Jr. Stressful social interactions experienced by adults with mild intellectual disability. *Am J Intellct Dev Disabil*. 2009;114(2):71–84.
21. Williams L, Hastings R, Owen DM, et al. Exposure to life events as a risk factor for psychological problems in adults with intellectual disabilities: A longitudinal design. *J Intellect Disabil Res*. 2014;58(1):48–60.
22. Scott HM, Havercamp SM. Mental health for people with intellectual disability: The impact of stress and social support. *Am J Intellect Dev Disabil*. 2014;119:552–564.
23. Gemma Unwin G, Deb S. The use of medication to manage behaviour problems in adults with an intellectual disability: A national guideline. *Adv Ment Health Intellect Disabil*. 2010;4:4–11.
24. Cooper SA, Smiley E, Allan LM, et al. Adults with intellectual disabilities: Prevalence, incidence and remission of self-injurious behavior, and related factors. *J Intellect Disabil Res*. 2009;53:200–216.
25. Bradley V, Hiersteiner D, Rotholz D, et al. Personal characteristics and outcomes of individuals with developmental disabilities who need support for self-injurious behaviour. *J Intellect Disabil Res*. 2018. doi.10.1111/jir.12518.
26. Arron K, Oliver C, Moss J, et al. The prevalence and phenomenology of self-injurious and aggressive behavior in genetic syndromes. *J Intellect Disabil Res*. 2011;55:109–120.
27. Rotholz D, Moseley C, Carlson B. State policies and practices in behavior supports for persons with intellectual and developmental disabilities in the United States: a national survey. *Intellect Dev Disabil*. 2013;51:433–445.
28. Gilmore L, Cuskelly M. Vulnerability to loneliness in people with intellectual disability: An explanatory model. *J Policy Pract Intellect Disabil*. 2014;11:192–199.
29. Sullivan WF, Diepstra H, Heng J, et al. Primary care of adults with intellectual and developmental disabilities: 2018 Canadian consensus guidelines. *Can Fam Physician*. 2018;64:245–279.
30. Cooper SA, McLean G, et al. Multiple physical and mental health comorbidity in adults with intellectual disabilities: Population-based cross-

sectional analysis. *BMC Fam Pract*. 2015;16:110.

31. Fletcher R, Barnhill J, Cooper S, eds. *Diagnostic Manual – Intellectual Disability (CM- ID2): A Textbook of Diagnosis of Mental Disorders in Persons with Intellectual Disability*. 2nd ed. Kingston, NY: NADD Press; 2017.
32. Tsao R, Kindelberger C, Freminville B, et al. Variability of the aging process in dementia-free adults with Down syndrome. *Am J Intellect Dev Disabil*. 2015;120:3–15.
33. Sherman SL, Allen EG, Bean LH, Freeman SB. Epidemiology of Down syndrome. *Ment Retard Dev Disabil Res Rev*. 2007;13:221–227.
34. De Graaf G, Buckley F, Skotko BG. Estimates of the live births, natural losses, and elective terminations with Down syndrome in the United States. *Am J Med Genet A*. 2015:165A:756–767.
35. Barca D, Tarta-Arsene O, Dica A, et al. Intellectual disability and epilepsy in Down syndrome. *Maedica*. 2014;9:344–350.
36. Steiner B, Masood R, Rufibach K, et al. An unexpected finding: younger fathers have a higher risk for offspring with chromosomal aneuploidies. *Eur J Hum Genet*. 2015;23:466–472.
37. Hollis ND, Allen EG, Oliver TR, et al. Preconception folic acid supplementation and risk for chromosome 21 nondisjunction: A report from the National Down Syndrome Project. *Am J Med Genet A*. 2013;161A:438–444.
38. Bunt CW, Bunt SK. Role of the family physician in the care of children with Down syndrome. *Am Fam Physician*. 2014;90:851–858.
39. Bull MJ, Committee on Genetics. Health supervision for children with Down syndrome. *Pediatrics*. 2011;128:393–406.
40. Walker JC, Dosen A, Buitelaar JK, Janzing JG. Depression in Down syndrome: A review of the literature. *Res Dev Disabil*. 2011;32:1432–1440.
41. Bayen E, Possin KL, Chen Y, Cleret de Langavant L, Yaffe K. Prevalence of aging, dementia, and multimorbidity in older adults with Down syndrome. *JAMA Neurol*. 2018;75(11):1399–1406. doi.10.1001/jamaneurol.2018.2210.
42. Abbass M, Lunsky Y. Antipsychotic prescription patterns in adults with developmental disability with and without psychotic disorder. *J Dev Disabil*. 2011;17:51–55.

43. Lunsky Y, Klein-Geltink JE, Yates EA, eds. *Atlas on the Primary Care of Adults with Developmental Disabilities in Ontario*. Toronto, Ontario: Institute of Clinical Evaluative Sciences and Centre for Addiction and Mental Health; 2013.
44. Stolker JNJ, Koedoot PJ, Heerdink ER, et al. Psychotropic drug use in intellectually disabled group-home residents with behavioural problems. *Pharmacopsychiatry*. 2002;35:19–23.
45. de Kuiper G, Hoekstra P, Visser F, et al. Use of antipsychotic drugs in individuals with intellectual disability (ID) in the Netherlands: Prevalence and reasons for prescription. *J Intellect Disabil Res*. 2010:54(7):659–667.
46. Scheifes A, Walraven S, Stolker JJ, et al. Adverse events and the relation with quality of life in adults with intellectual disability and challenging behaviour using psychotropic drugs. *Res Dev Disabil*. 2016;49-50:13–21.
47. Mahan S, Holloway J, Bamburg JW, et al. An examination of psychotropic medication side effects: Does taking greater number of psychotropic medications from different classes affect presentation of side effects in adults with ID? *Res Dev Disabil*. 2010;31:1561–1569.
48. Sheehan R, Horsfall L, Strydome A, et al. Movement side effects of antipsychotic drugs in adults with and without intellectual disability: UK population-based cohort study. *BMJ Open*. 2017;7:e017406.
49. Deb S, Sohanpal SK, Soni R, et al. The effectiveness of antipsychotic medication in the management of behaviour problems in adults with intellectual disabilities. *J Intellect Disabil Res*. 2007;51(10):766–777.
50. Felce D, Cohen D, Willner P, et al. Cognitive behavioural anger management intervention for people with intellectual disabilities: Costs of intervention and impact on health and social care resource use. *J Intellect Disabil Res*. 2015;59:68–81.
51. Willner P. The neurobiology of aggression: Implications for the pharmacotherapy of aggressive challenging behaviour by people with intellectual disabilities. *J Intellect Disabil Res*. 2015;59:82–92.
52. Chen CS, Huang MF, et al. Clinical correlates of zolpidem-associated complex sleep-related behaviors: Age effect. *J Clin Psychiatry*. 2014;75:e1314–1318.
53. Stores G, Stores R. Sleep disorders and their clinical significance in children with Down syndrome. *Dev Med Child Neurol*. 2013;55:126–130.
54. Zigman WB. Atypical aging in Down syndrome. *Dev Disabil Res Rev*. 2013;18:51–67.

55. Coppus AMW, Schuur M, Vergeer J, et al. Plasma β-amyloid and the risk of Alzheimer's disease in Down syndrome. *Neurobiol Aging*. 2011;33:1988–1994.
56. Ross WT, Olsen M. Care of the adult patient with Down syndrome. *South Med J*. 2014;107:715–721.
57. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
58. Hanney M, Prasher V, Williams N, et al. Memantine for dementia in adults older than 40 years with Down's syndrome (MEADOWS): A randomized, double-blind, placebo- controlled trial. *Lancet*. 2012;379:528–536.
59. Kondoh T, Kanno A, Itoh H, et al. Donepezil significantly improves abilities in daily lives of female Down syndrome patients with severe cognitive impairment: A 24-week randomized, double-blind, placebo-controlled trial. *Int J Psychiatry Med*. 2011;41:71–89.
60. Prasher VP, Sachdeva N, Adams C, Haque MS. Rivastigmine transdermal patches in the treatment of dementia in Alzheimer's disease in adults with Down syndrome: A pilot study. *Int J Geriatr Psychiatry*. 2013;28:219–220.
61. Kishnani PS, Heller JH, Spiridigliozzi GA, et al. Donepezil for treatment of cognitive dysfunction in children with Down syndrome aged 10-17. *Am J Med Genet A*. 2010;152A: 3028–3035.
62. Livingstone N, Hanratty J, McShane R, Macdonald G. Pharmacological interventions for cognitive decline in people with Down syndrome. *Cochrane Database Syst Rev*. 2015:10:CD011546.
63. Hart SJ, Visootsak J, Tamburri P, et al. Pharmacological interventions to improve cognition and adaptive functioning in Down syndrome: Strides to date. *Am J Med Genet A*. 2017;173A:3029–3041.
64. de la Torre R, DeSola S, Pons M, et al. Epigallocatechin-3-gallate, a DYRK1A inhibitor, reduces cognitive deficits in Down syndrome mouse models and in humans. *Mol Nutr Food Res*. 2014;58:278–288.
65. de la Torre R, de Sola S, Hernandez G, et al. Safety and efficacy of cognitive training plus epigallocatechin-3-gallate in young adults with Downs syndrome (TESDAD): A double- blind, randomized, Placebo-controlled, phase 2 trial. *Lancet Neurol*. 2016;15:801–810.
66. Head E, Powell D, Gold BT, Schmitt FA. Alzheimer's disease in Down syndrome. *Neurodegener Dis*. 2012;1:353–364.

67. Pueschel SM, Louis S, McKnight P. Seizure disorders in Down syndrome. *Arch Neurol*. 1991;48:318–320.
68. Malone RP, Waheed A. The role of antipsychotics in the management of behavioural symptoms in children and adolescents with autism. *Drugs*. 2009;69:535–548.
69. Polsek D, Jagatic T, Cepanec M, et al. Recent developments in neuropathology of autism spectrum disorders. *Transl Neurosci*. 2011;2:256–264.
70. Baio J, Wiggins L, Christensen DL, et al. Prevalence of autism spectrum disorder among children aged 8 years: Autism and Developmental Disabilities Monitoring Network, 11 sites, United States, 2014. *MMWR Surveil Summ*. 2018;67(6):1–23.
71. Muhle R, Trentacoste SV, Rapin I. The genetics of autism. *Pediatrics*. 2004;113:e472–86.
72. Johnson CP, Myers SM, American Academy of Pediatrics Council on Children with Disabilities. Identification and evaluation of children with autism spectrum disorders. *Pediatrics*. 2007;120:1183–1215.
73. Bos KJ, Zeanah CH Jr, Smyke AT, et al. Stereotypies in children with a history of early institutional care. *Arch Pediatr Adolesc Med*. 2010;164:406–411.
74. LeBlanc JJ, Fagiolini M. Autism: A “critical period” disorder? *Neural Plast*. 2011;2011:921680.
75. Dhillon S, Hellings JA, Butler MG. Genetics and mitochondrial abnormalities in autism spectrum disorders: A review. *Curr Genomics*. 2011;12:322–332.
76. Salyakina D, Cukier HN, Lee JM, et al. Copy number variants in extended autism spectrum disorder families reveal candidates potentially involved in autism risk. *PLoS One*. 2011;6:e26049.
77. Sgado P, Dunleavy M, Genovesi S, et al. The role of GABAergic system in neurodevelopmental disorders: A focus on autism and epilepsy. *Int J Physiol Pathophysiol Pharmacol*. 2011;3:223–235.
78. Mefford HC, Batshaw ML, Hoffman EP. Genomics, intellectual disability, and autism. *N Engl J Med*. 2012;366:733–743.
79. Ben-Sasson A, Hen L, Fluss R, et al. A meta-analysis of sensory modulation symptoms in individuals with autism spectrum disorders. *J Autism Dev Disord*. 2009;39:1–11.

80. Simmons DR, Robertson AE, McKay LS, et al. Vision in autism spectrum disorders. *Vision Research*. 2009;49:2705–2739.
81. Ozonoff S, Young GS, Carter A, et al. Recurrence risk for autism spectrum disorders: A Baby Siblings Research Consortium Study. *Pediatrics*. 2011;128:e488–e95.
82. Sandin S, Lichtenstein P, Kuja-Halkola R, et al. The familial risk of autism. *JAMA*. 2014;311:1770–1777.
83. Rahbar MH, Samms-Vaughan M, Loveland KA, et al. Maternal and paternal age are jointly associated with childhood autism in Jamaica. *J Autism Dev Disord*. 2012;42(9):1928–1938.
84. Shelton JF, Tancredi DJ, Hertz-Picciotto I. Independent and dependent contributions of advanced maternal and paternal ages to autism risk. *Autism Res*. 2010;3:30–39.
85. Hultman CM, Sandin S, Levine SZ, et al. Advancing paternal age and risk of autism: New evidence from a population-based study and a meta-analysis of epidemiological studies. *Molecular Psychiatry*. 2011;16:1203–1212.
86. Hensley E, Briars L. Closer look at autism and the measles-mumps-rubella vaccine. *J Am Pharm Assoc*. 2010;50:736–741.
87. Schultz ST. Does thimerosal or other mercury exposure increase the risk for autism? A review of current literature. *Acta Neurobiol Exp (Wars)*. 2010;70:187–195.
88. Jain A, Marshall J, Buikema A, et al. Autism occurrence by MMR vaccine status among US children with older siblings with and without autism. *JAMA*. 2015;313:1534–1540.
89. Costa e Silva JA. Autism, a brain developmental disorder: Some new pathopysiologic and genetics findings. *Metabolism*. 2008;57(suppl 2): S40–S43.
90. Deutsch SI, Urbano MR, Neumann SA, et al. Cholinergic abnormalities in autism: Is there a rationale for selective nicotinic agonist interventions? *Clin Neuropharmacol*. 2010;33:114.
91. Kazek B, Huzarska M, Grzybowska-Chlebowczyk U, et al. Platelet and intestinal 5-HT2A receptor mRNA in autistic spectrum disorders: Results of a pilot study. *Acta Neurobiol Exp (Wars)*. 2010;70:232–238.
92. Sadock BJ, Sadock VA. Pervasive developmental disorders. In: *Synopsis of Psychiatry*. 10th ed. Baltimore, MD: Williams and Wilkins; 2007:1191–205.

93. El Achkar CM, Spence SJ. Clinical characteristics of children and young adults with co-occurring autism spectrum disorder and epilepsy. *Epilepsy Behav*. 2015;47:183–190.
94. Baird G, Cass H, Slonims V. Diagnosis of autism. *BMJ*. 2003;327:488–493.
95. Vannucchi G, Masi G, Toni C, et al. Clinical features, developmental cause, and psychiatric comorbidity of adult autism spectrum disorders. *CNS Spectrums*. 2014;19:157–164.
96. Amiet C, Gourfinkel-An I, Bouzamondo A, et al. Epilepsy in autism is associated with intellectual disability and gender: Evidence from a meta-analysis. *Biol Psychiatry*. 2008;64:577–582.
97. Ming X, Brimacombe M, Chaaban J, et al. Autism spectrum disorders: Concurrent clinical disorders. *J Child Neurol*. 2008;23:6–13.
98. Corsello CM. Early intervention in autism. *Infants & Young Children*. 2005;18:74–85.
99. Oosterling IJ, Wensing M, Swinkels SH, et al. Advancing early detection of autism spectrum disorder by applying an integrated two-stage screening approach. *J Child Psychol Psychiatry*. 2010;51:250–258.
100. Prater CD, Zylstra RG. Autism: A medical primer. *Am Fam Physician*. 2002;66:1667–1674.
101. Vanbergeijk E, Klin A, Volkmar F. Supporting more able students on the autism spectrum: College and beyond. *J Autism Dev Disord*. 2008;38:1359–1370.
102. Parikh MS, Kolevzon A, Hollander E. Psychopharmacology of aggression in children and adolescents with autism: A critical review of efficacy and tolerability. *J Child Adolesc Psychopharmacol*. 2008;18:157–178.
103. National Institute of Neurological Disorders and Stroke. Autism Fact Sheet (NIH Publication No. 15-1877 06-1877). Available at: https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Autism-Spectrum-Disorder-Fact-Sheet#3082_. Accessed June 15, 2015.
104. Beversdorf D. Therapeutic interventions in autism: A review for primary care physicians. *Mo Med*. 2008;105:390–395.
105. Bodfish JW. Treating the core features of autism: Are we there yet? *Ment Retard Dev Disabil Res Rev*. 2004;10:318–326.
106. Granpeesheh D, Tarbox J, Dixon DR. Applied behavior analytic

interventions for children with autism: A description and review of treatment research. *Ann Clin Psychiatry*. 2009;21(3):162–173.

107. Green VA, Pituch KA, Itchon J, et al. Internet survey of treatments used by parents of children with autism. *Res Dev Disabil*. 2006;27:70–84.
108. Brondino N, Fusar-Poli L, Rocchetti M, et al. Complementary and alternative therapies for Autism Spectrum Disorder. *Evid Based Complement Alternat Med*. 2015;2015:258589.
109. Miano S, Ferri R. Epidemiology and management of insomnia in children with autistic spectrum disorders. *Paediatric Drugs*. 2010;12:75–84.
110. Schwichtenberg AJ, Malow BA. Melatonin treatment in children with developmental disabilities. *Sleep Medicine Clinics*. 2015;10:181–187.
111. Baribeau DA, Anagnostou E. An update on medication management of behavioral disorders in autism. *Curr Psychiatry Rep*. 2014;16:437.
112. Politte LC, McDougle CJ. Atypical antipsychotics in the treatment of children and adolescents with pervasive developmental disorders. *Psychopharmacology (Berl)*. 2014;231:1023–1036.
113. Curran MP. Aripiprazole: In the treatment of irritability associated with autistic disorder in pediatric patients. *Paediatric drugs*. 2011;13:197–204.
114. Aman MG, Kasper W, Manos G, et al. Line-item analysis of the Aberrant Behavior Checklist: Results from two studies of aripiprazole in the treatment of irritability associated with autistic disorder. *J Child Adolesc Psychopharmacol*. 2010;20:415–422.
115. Marcus RN, Owen R, Kamen L, et al. A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. *J Am Acad Child Adolesc Psychiatry*. 2009;48:1110–1119.
116. Marcus RN, Owen R, Manos G, et al. Aripiprazole in the treatment of irritability in pediatric patients (aged 6-17 years) with autistic disorder: Results from a 52-week, open-label study. *J Child Adolesc Psychopharmacol*. 2011;21:229–236.
117. McCracken JT, McGough J, Shah B. Risperidone in children with autism and serious behavioral problems. *N Engl J Med*. 2002;347:314–321.
118. Shea S, Turgay A, Carroll A, et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. *Pediatrics*. 2004;114:e634–e641.
119. McDougle CJ, Holmes JP, Carlson DC, et al. A double-blind, placebo-

controlled study of risperidone in adults with autistic disorder and other pervasive developmental disorders. *Arch Gen Psychiatry*. 1998;55:633–651.

120. Varni JW, Handen BL, Corey-Lisle PK et al. Effect of aripiprazole 2 to 15 mg/d on health related quality of life in the treatment of irritability associated with autistic disorder in children: A post hoc analysis of two controlled trials. *Clin Ther*. 2012;34:980–992.
121. Anderson GM, Scahill L, McCracken JT, et al. Effects of short- and long-term risperidone treatment on prolactin levels in children with autism. *Biol Psychiatry*. 2007;61:545–550.
122. West L, Brunssen SH, Waldrop J. Review of the evidence for treatment of children with autism with selective serotonin reuptake inhibitors. *J Spec Pediatr Nurs*. 2009;14:183–191.
123. King BH, Hollander E, Sikich L, et al. Lack of efficacy of citalopram in children with autism spectrum disorders and high levels of repetitive behavior: Citalopram ineffective in children with autism. *Arch Gen Psychiatry*. 2009;66:583–590.
124. Canitano R, Scandurra V. Psychopharmacology in autism: An update. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35:18–28.
125. Handen BL, Taylor J, Tumuluru R. Psychopharmacological treatment of ADHD symptoms in children with autism spectrum disorder. *Int J Adolesc Med Health*. 2011;23:167–173.
126. Posey DJ, Aman MG, McCracken JT, et al. Positive effects of methylphenidate on inattention and hyperactivity in pervasive developmental disorders: an analysis of secondary measures. *Biological Psychiatry*. 2007;61:538–544.
127. Ghuman JK, Aman MG, Lecavalier L, et al. Randomized, placebo-controlled, crossover study of methylphenidate for attention-deficit/hyperactivity disorder symptoms in preschoolers with developmental disorders. *J Child Adolesc Psychopharmacol*. 2009;19:329–339.
128. Arnold LE, Aman MG, Cook AM, et al. Atomoxetine for hyperactivity in autism spectrum disorders: Placebo-controlled crossover pilot trial. *J Am Acad Child Adolesc Psychiatry*. 2006;45:1196–1205.
129. Harfterkamp M, van de Loo-Neus G, Minderaa RB, et al. A randomized double-blind study of atomoxetine versus placebo for attention-deficit/hyperactivity disorder symptoms in children with autism spectrum

disorder. *J Am Acad Child Adolesc Psychiatry*. 2012;51:733–741.

130. Aman MG, Farmer CA, Hollway J, Arnold LE. Treatment of inattention, overactivity, and impulsiveness in autism spectrum disorders. *Child Adolesc Psychiatr Clin N Am*. 2008;17:713–738.
131. Scahill L, McCracken J, King BH, et al. Extended-release guanfacine for hyperactivity in children with autism spectrum disorder. *Am J Psychiatry*. 2015;172:1197–1206.
132. Alvares GA, Quintana DS, Whitehouse AJO. Beyond the hype and hope: critical considerations for intranasal oxytocin research in autism spectrum disorder. *Autism Res*. 2017;10:25–41.
133. Landgraf R, Neumann ID. Vasopressin and oxytocin release within the brain: A dynamic concept of multiple and variable modes of neuropeptide communication. *Front Neuroendocrinol*. 2004;25:150–176.
134. Hollander E, Bartz J, Chaplin W, et al. Oxytocin increases retention of social cognition in autism. *Biol Psychiatry*. 2007;61:498–503.
135. Guastella AJ, Einfeld SL, Gray KM, et al. Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. *Biol Psychiatry*. 2010;67:692–694.
136. Guastella AJ, Gray KM, Rinehart NJ, et al. The effects of a course of intranasal oxytocin on social behaviors in youth diagnosed with autism spectrum disorders: A randomized controlled trial. *J Child Psychol Psychiatry*. 2015;56:444–452.
137. Frye RE. Social skills deficits in autism spectrum disorder: Potential biological origins and progress in developing therapeutic agents. *CNS Drugs*. 2018;32:713–734.
138. Sharma SR, Gonda X, Tarazi FI. Autism spectrum disorder: Classification, diagnosis, and therapy. *Pharmacol Ther*. 2018;190:91–104.
139. Hu VW. A systems approach towards an understanding, diagnosis and personalized treatment of autism spectrum disorders. *Pharmacogenomics*. 2011;12:1235–1238.
140. Aman MG, Singh NN, Turbott SH. Reliability of the Aberrant Behavior Checklist and the effect of variations in instructions. *Am J Ment Defic*. 1987;92:237–240.
141. Aman MG, Singh NN. *Aberrant Behavior Checklist–Community. Supplemental Manual*. East Aurora, NY: Slosson Educational Publications; 1994.

142. Scahill L, McDougle CJ, Williams SK, et al. Children's Yale-Brown Obsessive Compulsive Scale modified for pervasive developmental disorders. *J Am Acad Child Adolesc Psychiatry*. 2006;45:1114–1123.
143. Kalachnik JE.Medication monitoring procedures: Thou shall, here's how. In: Gadow KD, Poling AG, eds. *Pharmacotherapy and Mental Retardation*. Boston, MA: College-Hill; 1985;231–268.
144. Barnes TR. A rating scale for drug-induced akathisia. *Br J Psychiatry*. 1989;154:672–676.
145. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand Suppl*. 1970;212:11–19.
146. Kalachnik JE. Measuring side effects of psychopharmacologic medications in individuals with mental retardation and developmental disabilities. *Ment Retard Dev Disabil Res Rev*. 1999;5:348–359.
147. Sullivan WF, Diepstra H, Heng J, et al. Primary care of adults with intellectual and developmental disabilities. 2018 Canadian consensus guidelines. *Can Fam Physician*. 2018;64:254–279.
148. Russo AJ, Devito R. Analysis of copper and zinc plasma concentration and the efficacy of zinc therapy in individuals with Asperger's syndrome, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) and autism. *Biomarker Insights*. 2011;6:127–133.

SECTION 10 ENDOCRINOLOGIC DISORDERS

91

Diabetes Mellitus

Jennifer Trujillo and Stuart Haines

KEY CONCEPTS

1. Diabetes mellitus (DM) is a metabolic disorder. While there are numerous etiological causes, defects in insulin secretion, insulin action (sensitivity), or both lead to elevations in blood glucose as well as altered fat and protein metabolism.
2. DM is a leading cause of eye and kidney disease. Patients with DM are at high risk for CV events, heart failure, and atherosclerotic disease.
3. The two most common classifications of DM are type 1 (absolute insulin deficiency) and type 2 (relative insulin deficiency due to β-cell dysfunction coupled with insulin resistance). They differ in clinical presentation, pathophysiology, and treatment approach.
4. The prevalence of type 2 DM has doubled worldwide over the last 40 years. This has been attributed to an alarming increase in the prevalence of obesity due to diminished physical activity and increased caloric consumption.
5. The diagnosis of diabetes is made using any of the following criteria: (1) fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L) (2) a hemoglobin A1C (A1C) ≥6.5% (0.065; 48 mmol/mol Hb); (3) a random plasma glucose level ≥ 200 mg/dL (11.1 mmol/L) coupled with classic symptoms of diabetes; or (4) a 2-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during a 75-g oral glucose tolerance test (OGTT). A diagnosis using criteria 1-3 require two abnormal test results from the same sample or in two separate test samples.
6. Goals of therapy in DM are to achieve optimal glycemic control (based on age, comorbid conditions, and patient preferences), reduce the onset and progression of diabetes-related complications, aggressively address CV risk factors, and improve quality of life.

7. Intensive glycemic control prevents the onset and slows the progression of microvascular complications (eg, neuropathy, retinopathy, and nephropathy).
8. Knowledge of the patient's meal patterns and activity levels as well as the pharmacologic properties of antihyperglycemic agents is essential to creating an individualized treatment plan that achieves optimal glycemic control, avoids hypoglycemia, and minimizes adverse effects.
9. Metformin is the drug of choice and, in the absence of contraindications or intolerability, should be included in the treatment regimen for most patients with type 2 DM due to its effectiveness, low risk of hypoglycemia, positive or neutral effects on weight, potential positive impact on CV risk, and low cost.
10. Type 2 DM often requires the use of multiple therapeutic agents (combination therapy) including oral and injected antihyperglycemics to achieve and maintain optimal glycemic control. A persistent decline in β-cell function over time often necessitates periodic adjustment and changes in therapy.
11. Insulin therapy is required in type 1 DM. Intensive basal-bolus insulin therapy or continuous subcutaneous insulin infusion therapy (aka an insulin pump) in motivated individuals is more likely to achieve optimal glycemic control. Basal-bolus therapy includes a long-acting insulin to address fasting glucose and a rapid-acting insulin for mealtime coverage. The use of adjunctive therapy in combination with insulin in patients with uncontrolled or erratic glucose concentrations may be warranted.
12. Aggressive management of CV risk factors in DM is necessary to reduce the incidence of CV events and death. This includes smoking cessation, use of antiplatelet therapy as well as moderate or high potency statins in most patients with DM, and treatment of hypertension.
13. Good blood pressure control in patients with diabetes not only lowers the risk of retinopathy and nephropathy, but also CV events.
14. Strategies to prevent type 1 DM have not yet been successful. For patients at high risk, type 2 DM can be delayed or prevented by engaging in regular aerobic exercise, losing weight, reducing dietary fat, and increasing fiber intake. These lifestyle habits can reduce the risk of type 2 DM by 60%. Although no medication is currently FDA approved to prevent diabetes, several have been shown to delay diabetes onset in high-risk patients.

15 Repeated inaction by practitioners to intensify treatment when patients are not meeting treatment goals is called therapeutic inertia. Several factors contribute to therapeutic inertia. This is a common problem and among the leading contributors of poor outcomes. Diabetes is a chronic condition that requires periodic medication changes to attain and maintain glycemic goals.

16 Patient self-management, therapeutic lifestyle behaviors, and appropriate medication use are equally important components of each patient's treatment plan. Interprofessional teams including physicians (primary care, endocrinologists, ophthalmologists), dentists, dietitians, nurses, pharmacists, podiatrists, social workers, behavioral health specialists, and certified diabetes educators (CDEs) working together can assist persons with DM in achieving optimal health outcomes.

Preclass Engaged Learning Activity

Option 1: Create a table listing all of the **insulin products** currently available on the market. Your table should include insulin analogs and combination products. Organize your table into subsections with the insulin products with the shortest duration of activity appearing first and the products with the longest duration of activity appearing last. For each product, list the generic name, the brand name(s), manufacturer(s), the route of administration, the time to onset of activity, and the duration of activity. Lastly, indicate whether the product is primarily used to control mealtime blood glucose (eg, prandial insulin), fasting blood glucose (eg, basal insulin), or both.

Your table should have the following headers:

Generic Name(s)	Brand Name(s)	Manufacturer(s)	Route	Onset (min)	Duration (hr)	Prandial, Basal, or Both

Option 2: Create a table listing all of the **noninsulin products** currently approved to treat type 2 diabetes. Your table should include combination products. Organize your table into subsections based on drug class (eg, all sulfonylureas should appear in one subsection, all SGLT-2 inhibitors should

appear in another section, etc.). For each product, list the generic name, the brand name(s), manufacturer(s), the route of administration, the anticipated reduction in A1C, and a major side effect to warn patients about. Lastly, indicate whether the product is primarily used to control mealtime blood glucose, fasting blood glucose, or both.

Your table should have the following headers:

Generic Name(s)	Brand Name(s)	Manufacturer(s)	Route	A1C lowering	Most Common Side Effect(s)	Prandial, Basal, or Both

INTRODUCTION

1 2 Diabetes mellitus (DM) is a diverse group of metabolic disorders that all have chronically elevated blood glucose (BG) as their defining feature. In addition to hyperglycemia, DM is associated with abnormal fat and protein metabolism. In the absence of effective treatment, DM can lead to acute complications such as diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic syndrome (HHS). Chronic hyperglycemia can cause vascular and nerve damage, resulting in microvascular, macrovascular, and neuropathic complications. DM is a worldwide problem, significantly impacting people and healthcare systems in low-, middle-, and high-income countries.[1] More than 442 million adults around the globe are now living with DM and its prevalence has nearly doubled over the last 30 years. According to the Centers for Disease Control and Prevention, slightly more than 30 million Americans, including more than 12% of adults, have DM.[2] While 1.5 million new cases of DM are diagnosed in the United States every year, one in four Americans with DM are unaware they have it. While these numbers are startling, the number of adults with prediabetes is far greater—more than 84 million in the United States alone. Prediabetes is a condition of abnormal BG that is not sufficiently high to meet the thresholds that define diabetes but often progresses to the diagnosis. The total direct and indirect medical costs for treating people with DM in the United

States were $245 billion in 2012. The average person with DM spent $13,700 in 2014 on medical care, an amount that was nearly two-and-half times greater than the amount spent by people without DM. DM is the seventh leading cause of death in the United States and among the principal causes of end-stage renal disease, lower extremity amputations, and blindness. Finally, people with DM are at far greater risk for CV disease (eg, myocardial infarction, ischemic stroke).[2] Optimal management of DM substantially lowers the risk of complications, increases life expectancy, and improves the quality of life.

EPIDEMIOLOGY

3 The vast majority of patients with DM are classified into one of two broad categories: type 1 DM and type 2 DM.[3] Patients with type 1 DM have an absolute insulin deficiency. Patients with type 2 DM have varying degrees of β-cell dysfunction often coupled with insulin resistance. Women who develop diabetes during pregnancy are classified as having gestational diabetes (GDM). Less common types of diabetes are caused by genetic defects, pancreatic destruction, endocrine disorders, and medications. See **Table 91-1**.

TABLE 91-1 Classification of Diabetes Mellitus[a]

Type 1 diabetes (β-cell destruction leading to absolute insulin deficiency)
Immune mediated
Idiopathic
Type 2 diabetes (progressive loss of β-cell insulin secretory function and often accompanied by resistance to insulin action)
Gestational diabetes mellitus
Monogenic defects
Maturity-onset diabetes of the young (MODY) caused by a mutation in GCK, HNF1A, HNF1B, or HNF4A gene
Neonatal diabetes caused by a mutation in KCNJ11, ABCC8, INS, GATA6, EIF2AK3, or FOXP3 gene
Genetic syndromes associated with diabetes
Down syndrome
Hemochromatosis
Klinefelter syndrome
Turner syndrome
Diseases Impacting the Pancreas Leading to Diabetes
Cystic fibrosis
Pancreatitis
Pancreatic cancer
Pancreatectomy
Post-transplantation diabetes mellitus
Endocrine diseases frequently associated with diabetes
Acromegaly
Aldosteronoma
Cushing syndrome
Glucagonoma
Hyperthyroidism
Pheochromocytoma
Somatostatinoma
Medication-induced diabetes[a]
Atypical antipsychotics (eg, risperidone, olanzapine)
β-blockers (eg, propranolol, atenolol)
β-adrenergic agonists (eg, albuterol)
Calcineurin inhibitors (eg, cyclosporine, tacrolimus)
Diazoxide
Gatifloxacin
Glucocorticoids (eg, dexamethasone, prednisone)
Growth hormone (rhGH)
HMG-CoA reductase inhibitors (eg, atorvastatin, simvastatin)
Niacin/nicotinic acid
Pentamidine
Protease inhibitors (eg, ritonavir, saquinavir)
Thiazide diuretics (eg, chlorthalidone, hydrochlorothiazide)

[a]Patients with any form of diabetes may require insulin treatment at some stage of their disease. Insulin use does not itself classify the patient.

Data from ADA Classification and Diagnosis 2018.

Type 1 DM accounts for 5% to 10% of all cases of DM and is most often due to autoimmune destruction of the pancreatic β-cells.[5] The prevalence of β-cell autoimmunity in a population is directly related to the incidence of type 1 DM. For example, in Sweden and Finland 3% to 4.5% of the population have circulating islet cell autoantibodies (ICAs) and this is associated with the highest incidence of type 1 DM in the world: 22 to 35 per 100,000 people. The worldwide prevalence of type 1 DM is increasing but the cause is not fully understood.[6]

Markers of β-cell autoimmunity can be found in many adults with diabetes.[5] A variant of type 1 DM is called latent autoimmune diabetes of adults (LADA). These patients often have a poor response to oral agents and require insulin therapy much sooner than most patients with type 2 DM. Idiopathic type 1 DM is a nonautoimmune form of diabetes frequently seen in patients of African and Asian descent. These patients have periods of profound hyperglycemia but only intermittently require insulin therapy.

4 Type 2 DM accounts for 90% to 95% of all cases of DM. The prevalence of type 2 DM in the United States is about 12.1% in adults and is increasing.[2] The risk of developing type 2 DM increases with age and varies widely among racial and ethnic groups.[7] When compared to people of European ancestry, Native Americans, Latino/Hispanic Americans, African Americans, Asian Americans, and Pacific Islanders are more likely to develop type 2 DM. While the prevalence of type 2 DM increases with age, the disorder is increasingly being diagnosed in adolescence and young adulthood. This is likely due to the increasing incidence of obesity and lack of regular physical activity. Genetics play an important role in the development of type 2 DM. Most cases of type 2 DM appear to be polygenic.

The incidence of GDM is increasing and, between 2007 and 2010, it was estimated to occur in 9% of all pregnancies in the United States.[8] Most women become normoglycemic after pregnancy; however, up to 50% of these women develop type 2 DM later in life.[9]

Other less common (1%-2%) forms of DM occur through a variety of mechanisms.[3] Maturity-onset diabetes of the young (MODY) and neonatal diabetes are inheritable forms of DM caused by specific single-gene mutations. Endocrine disorders, particularly acromegaly and Cushing syndrome, commonly induce hyperglycemia. Diseases that injure or destroy the pancreas such as cystic fibrosis, pancreatitis, and pancreatic cancer can damage β-cells and impair insulin secretion. Several medications can also contribute to hyperglycemia by

either impairing insulin secretion, increasing insulin resistance, or both.[4]

ETIOLOGY AND PATHOPHYSIOLOGY

1 Diabetes mellitus is caused by derangements in the secretion of insulin, glucagon, and other hormones and results in abnormal carbohydrate and fat metabolism.[5,7] This is often coupled with insulin resistance, particularly in those with type 2 DM. In many cases, the underlying etiology of the disorder is complex and poorly understood.

After consuming food, carbohydrate ingestion increases the plasma glucose concentration and stimulates the release of incretin hormones from the gut and insulin release from the pancreatic β-cells.[7] The resultant hyperinsulinemia (1) suppresses hepatic glucose production, (2) suppresses glucagon release, and (3) triggers glucose uptake by peripheral tissues. Upwards of 75% of total body glucose disposal occurs in tissues, including the brain and peripheral nerves, which do not require insulin. Brain glucose uptake occurs at the same rate during fed and fasting periods. The remaining 25% of glucose metabolism takes place in the liver and muscle, tissues that require insulin to promote glucose uptake into the cells. During periods of fasting, approximately 85% of glucose is produced by the liver and the remainder by the kidney.

Although fat tissue is responsible for only a small portion of total body glucose disposal, it plays an important role in glucose homeostasis.[7] Insulin exerts a potent antilipolytic effect, reducing plasma-free fatty acid (FFA) levels. Increased levels of FFAs inhibit the uptake of glucose by muscle and stimulate hepatic gluconeogenesis. Lower FFA concentrations result in an increased glucose uptake in muscle and indirectly reduce hepatic glucose production.

Glucagon is produced by pancreatic *α* cells and is secreted in the fasting state.[7] Glucagon stimulates hepatic glucose production and glycogenolysis. Glucagon and insulin secretion are closely linked. Appropriate secretion of both hormones is needed to keep plasma glucose concentrations within a normal range. See **Table 91-2**.

TABLE 91-2 Risk Factors of Type 2 Diabetes

Age ≥45 years old
Family history of type 2 DM (ie, parents or siblings with type 2 diabetes)
High-risk race or ethnicity (ie, African American, Hispanic/Latino, Native American, Asian American, Native Hawaiian, or Pacific Islander)
Overweight or obese (ie, ≥20% over ideal body weight or body mass index [BMI] ≥25 kg/m^2)
Sedentary lifestyle (ie, limited daily physical activity)
History of impaired glucose tolerance, impaired fasting glucose (IFG), or elevated hemoglobin A1C
Hypertension (≥140/90 mm Hg in adults or on therapy for hypertension)
Dyslipidemia (high-density lipoprotein [HDL] cholesterol ≤35 mg/dL (0.91 mmol/L) or a triglyceride level ≥ 250 mg/dL (2.83 mmol/L)
History of GDM or delivery of a baby weighing more than 9 pounds (4 kg)
History of vascular disease (eg, myocardial infarction, ischemic stroke, peripheral arterial disease)
Presence of acanthosis nigricans (ie, dark, thick, and velvety skins around the neck or armpits)
Polycystic ovary disease

Type 1 Diabetes

Formerly called insulin-dependent diabetes, type 1 DM is the result of autoimmune destruction of the β-cells of the pancreas.[5] Type 1 DM is believed to be initiated by exposure to an environmental trigger in a genetically susceptible individual.[10] There is a link between currently known genetic markers for autoimmunity and the development of type 1 DM. However, β-cell autoimmunity develops in less than 10% of the genetically susceptible individuals and progresses to type 1 DM in less than 1%. On the other hand, β-cell autoimmunity, including ICAs, is present at the time of diagnosis in 90% of individuals. Type 1 diabetes most commonly develops in childhood or young adulthood; however, it can occur at any age. Children and adolescents typically have a more rapid rate of β-cell destruction and are more likely to present with DKA. Adults may maintain sufficient insulin secretion to prevent ketoacidosis for many months or years; this slowly progressive form of type 1 DM is sometimes referred to as LADA.

Several genetic polymorphisms have been linked to the development of type 1 DM including certain human leukocyte antigens (HLA) class II alleles on

chromosome 6.[10] Some genetic variants are associated with a higher risk of developing type 1 DM (eg, *DRB1*03-DQB1*0201*, *DRB1*04-DQB1*302*, and *HLA-B*39*) but others appear to be protective (eg, *DRB1*1501-DQA1*0102-DQB1*0602*). Genetic predisposition to the development of type 1 DM has also been associated with certain polymorphisms in the insulin gene region on chromosome 11. Other genes including PTPN22, IL2RA, and CTLA-4 may also play a role in some individuals. However, it should be noted that genetic markers are present in only 30% to 50% of patients with type 1 DM. Moreover, only 50% of monozygotic twins and approximately 10% of dizygotic twins develop type 1 DM. Thus, genetic mutations alone do not predict or explain the etiology of the disease.

In order for type 1 DM to develop, a genetically susceptible individual must be exposed to a trigger that initiates the autoimmune process and destruction of pancreatic β-cells.[10] See **Fig. 91-1**. However, it is unknown precisely what the inciting factors are. Several triggers have been implicated, including early exposure to cow's milk, lack of breastfeeding, gut bacteria (ie, intestinal microbiome), and certain viruses (eg, enterovirus and rotavirus). Although vitamin D deficiency is more prevalent in patients who develop type 1 DM, it is unclear if the relationship is causal or merely an association.

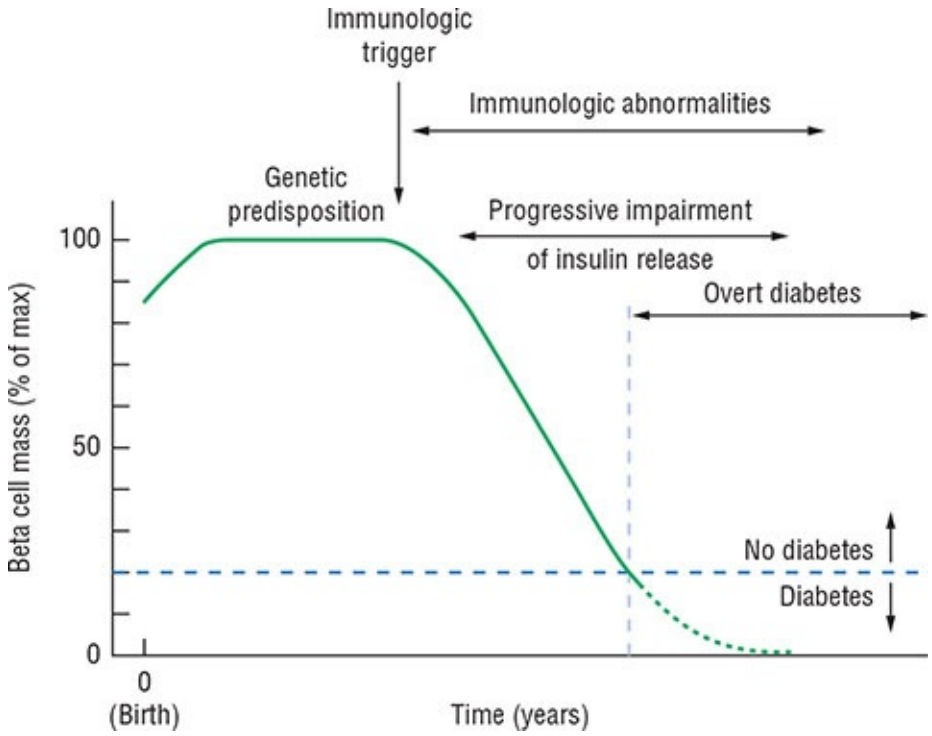


FIGURE 91-1 Clinical course of type 1 diabetes mellitus. (*Adapted from Kaufman ER. Medical Management of Type 1 Diabetes. 6th ed. Alexandria, VA:*

American Diabetes Association; 2012.)

The autoimmune process is mediated by macrophages and T lymphocytes with circulating autoantibodies to various β-cell antigens.[10] The most commonly detected antibody associated with type 1 DM is the islet cell autoantibodies (ICAs). Other antibodies may be formed to insulin, glutamic acid decarboxylase 65 (GAD65), insulinoma-associated antigen-2 (IA-2), and zinc transporter 8 (ZnT8). These antibodies are generally considered markers of disease rather than mediators of β-cell destruction. These markers have been used to identify individuals at risk for type 1 DM and may be useful screening tests to initiate disease prevention strategies. Other autoimmune disorders such as Hashimoto's thyroiditis, Graves' disease, Addison's disease, vitiligo, and celiac sprue are more common in patients with type 1 DM.

In many patients who develop type 1 DM there is a long preclinical period during which markers of autoimmunity can be detected.[10] β-Cell autoimmunity may precede the diagnosis of type 1 DM by up to 13 years. Autoimmunity remits in some individuals or progresses to absolute β-cell failure in others. Hyperglycemia occurs when 60% to 90% of the β-cells have been destroyed. After the initial diagnosis, there is occasionally a period of transient remission called the "honeymoon" phase during which insulin doses can be reduced or withdrawn before continued β-cell destruction requires lifelong insulin replacement therapy.

Amylin is a hormone that is co-secreted from the pancreatic β-cell with insulin. Amylin is also deficient in patients with type 1 DM secondary to the destruction of β-cells. Amylin suppresses inappropriate glucagon secretion, slows gastric emptying, and causes central satiety.

Type 2 Diabetes

Erroneously called noninsulin-dependent diabetes or adult-onset diabetes, type 2 DM is the result of β-cell dysfunction coupled with some degree of insulin resistance.[7] Over time, there is a progressive loss of β-cells. Most individuals with type 2 DM are overweight or obese. Abdominal adiposity is a major contributor to insulin resistance. Genetics play a critical role in the development of type 2 DM as there is a strong inheritance pattern. Hundreds of gene mutations have been linked to the development of type 2 DM. The majority of genetic mutations associated with type 2 DM appear to influence the development and function of β-cells, the sensitivity of cells to insulin action, or

the development of obesity. However, none of these single-gene mutations have demonstrated a strong association with type 2 DM. Thus, type 2 DM is likely polygenetic, with more than one genetic defect contributing to its pathogenesis and a diverse combination of derangements contributing to its development in different populations.

In patients with type 2 DM, high blood pressure and dyslipidemia, characterized by high-serum triglycerides and low HDL-cholesterol levels, are very frequent comorbid conditions. Elevated serum plasminogen activator inhibitor-1 (PAI-1), which contributes to a hypercoagulable state, is also common. There are multiple risk factors for the development of type 2 DM.[11] See Table 91-2.

Most patients who develop type 2 DM have multiple defects that impact the regulation of plasma glucose: (1) impaired insulin secretion; (2) deficiency and resistance to incretin hormones; (3) insulin resistance involving muscle, liver, and adipocytes; (4) excess glucagon secretion; (5) increased hepatic glucose production; (6) upregulation of the sodium-glucose cotransporter in the kidney; (7) systemic inflammation; and (8) diminished satiety.[7] See **Fig. 91-2**.

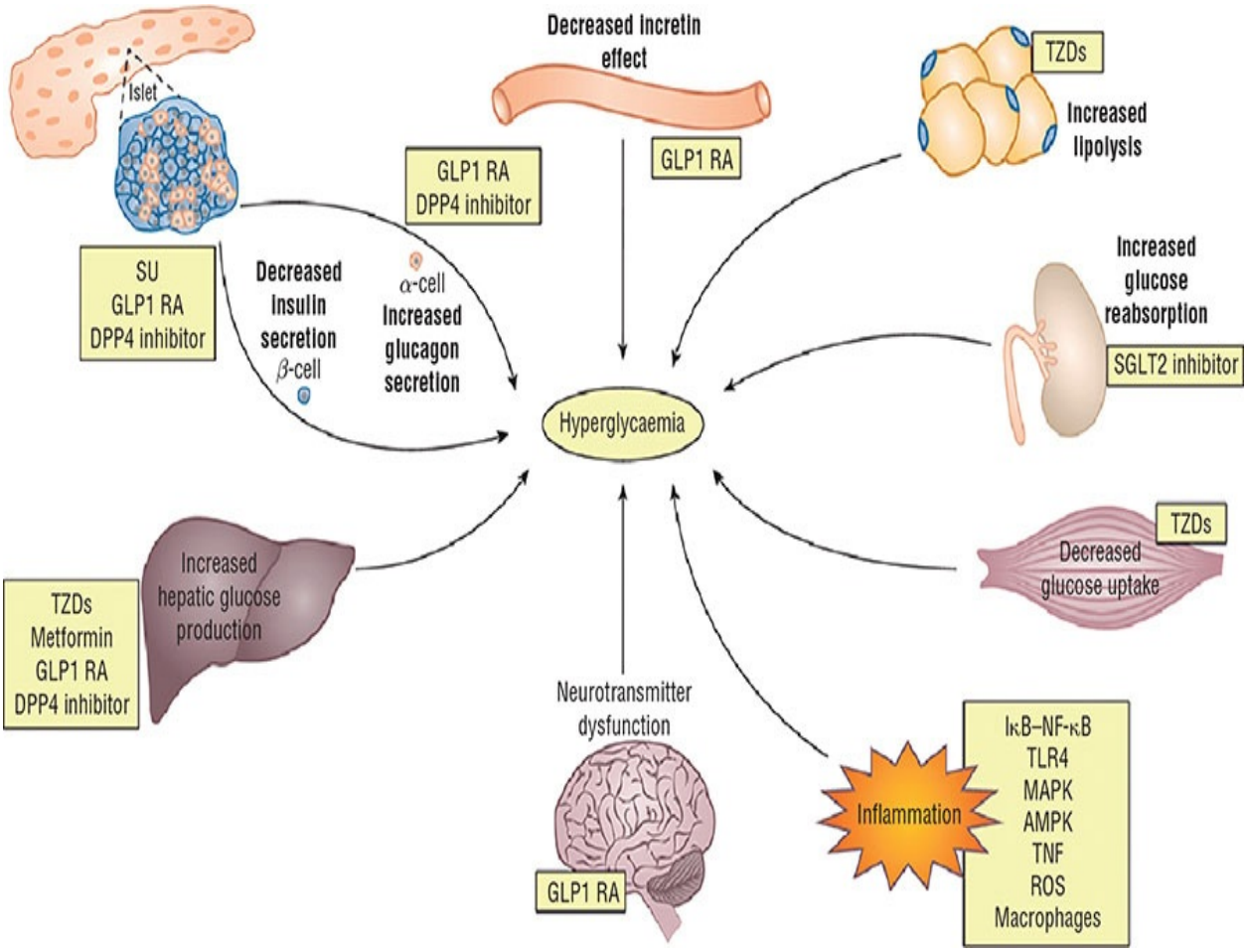


FIGURE 91-2 Pathophysiology of type 2 diabetes mellitus. Multiple defects known as the ominous octet. (*Reproduced, with permission, from Defronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009;58(4):773-95.*)

The pancreas in people with normal-functioning β-cells is able to adjust insulin secretion to maintain normal plasma glucose levels. See **Fig. 91-3**. In nondiabetic, obese individuals, insulin increases in proportion to the severity of the insulin resistance and plasma glucose remains normal. Impaired insulin secretion is therefore requisite for the development of type 2 DM. In the early stages of β-cell dysfunction, first-phase insulin release is deficient, resulting in impaired glucose tolerance (IGT). First-phase insulin involves the release of stored insulin in the β-cell and acts to “prime” the liver for nutrient intake. Without appropriate first-phase insulin release, second-phase insulin must compensate for the subsequent postprandial carbohydrate load in order to normalize glucose levels. When insulin release is no longer sufficient to normalize plasma glucose, dysglycemia, including prediabetes and diabetes,

ensue. In patients with type 2 DM, β-cell mass and function are both reduced. β-cell failure is progressive, starting years prior to the diagnosis of diabetes. People with type 2 DM lose approximately 5% to 7% of β-cell function per year. Progressive β-cell loss is likely the results of several factors, including (1) glucotoxicity; (2) lipotoxicity; (3) insulin resistance; (4) age; (5) genetics; and (6) incretin deficiency. Glucotoxicity occurs when glucose levels chronically exceed 140 mg/dL (7.8 mmol/L). The β-cell is unable to maintain sufficient insulin secretion and, paradoxically, releases less insulin as glucose levels increase.

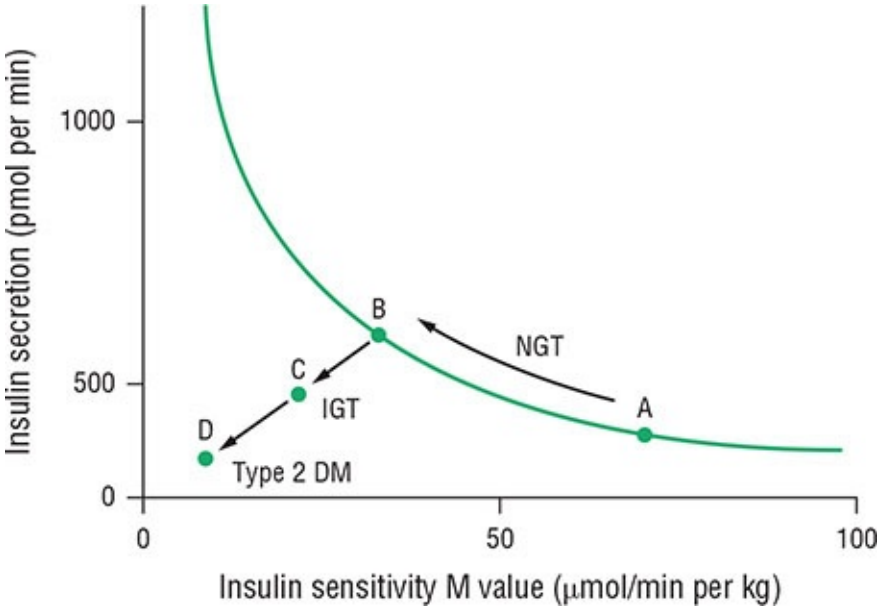


FIGURE 91-3 Metabolic changes over time during the development of type 2 diabetes mellitus. Insulin secretion and insulin sensitivity are related, and as an individual becomes more insulin resistant (by moving from point A to point B), insulin secretion increases. A failure to compensate by increasing the insulin secretion results initially in impaired glucose tolerance (IGT; point C) and ultimately in type 2 DM (point D). NGT, normal glucose tolerance. (*Reproduced, with permission, from Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 19th ed. New York: McGraw-Hill; 2015.*)

In patients with type 2 DM, decreased postprandial insulin secretion is a result of both impaired pancreatic β-cell function and diminished stimulus from gut hormones.[7] The role gut hormones play in insulin secretion is best shown by comparing the response to an oral glucose load versus an intravenous (IV) glucose infusion. In individuals who do not have diabetes, 73% more insulin is

released in response to an oral glucose load compared to IV glucose given to mimic plasma glucose levels achieved during the oral glucose load. The increased insulin secretion in response to an oral glucose stimulus is referred to as “the incretin effect” and is the result of gut hormones, stimulated by oral intake of nutrients (glucose, fat, or protein), that prompt first-phase insulin secretion. In patients with type 2 patients, this “incretin effect” is blunted. Insulin secretion is nearly half of that seen in individuals without diabetes. Two hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are responsible for over 90% of the increased insulin secretion in response to a meal. As patients progress from normoglycemia to type 2 DM, GLP-1 levels decrease as glucose values increase. Patients with type 2 DM remain sensitive to GLP-1 but GIP levels are normal or elevated in type 2 DM, which suggests that some individuals may be resistant to its effect.

GLP-1 is secreted from the L-cells, found in the distal intestinal and colon mucosa, in response to mixed meals.[12] Since GLP-1 concentrations rise within minutes of food ingestion, neural signals and possibly proximal gastrointestinal (GI) tract receptors stimulate GLP-1 secretion. The insulinotropic action of GLP-1 is glucose dependent, enhancing insulin secretion only when glucose concentrations are higher than 90 mg/dL (5.0 mmol/L). In addition to stimulating insulin secretion, GLP-1 suppresses glucagon secretion, slows gastric emptying, and increases satiety thereby reducing food intake. These effects combine to limit PPG excursions. GIP is secreted by K-cells in the intestine and may have a role with insulin secretion when glucose levels are near normal. GIP may also act as an insulin sensitizer in adipocytes. However, GIP has no effect on glucagon secretion, gastric motility, or satiety. While GLP-1 deficiency is common in patients with type 2 DM, it is unlikely to be a primary defect. A small percentage of patients have the transcription factor 7-like 2 (TCF7L2) gene defect, which is associated with decreased β-cell response to GLP-1 and likely contributes to their risk of developing diabetes. GLP-1 and GIP are rapidly inactivated by dipeptidyl peptidase-4 (DPP-4), an enzyme that removes two N-terminal amino acids, and their half-lives are less than 10 minutes.

Resistance to the actions of insulin in the liver contributes significantly to excess hepatic glucose production.[7] In patients with type 2 DM with mild-to-moderate fasting hyperglycemia (140-200 mg/dL, 7.8-11.1 mmol/L), basal hepatic glucose production is increased by approximately 0.5 mg/kg/min. Consequently, the liver of an 80-kg person with diabetes produces an extra 35 g of glucose overnight and causes fasting hyperglycemia. In addition, the liver

inappropriately continues hepatic glucose output after consuming a meal. Therefore, patients with type 2 DM have two sources of glucose in the postprandial state, one from the diet and the other from continued glucose production from the liver.

Peripheral skeletal muscle is a major site for PPG disposal.[7] In response to a physiologic increase in plasma insulin concentration, glucose uptake in to muscle increases linearly, plateauing at 10 mg/kg/min. In patients with type 2 DM, the onset of insulin action in muscle is delayed and glucose uptake in leg muscle is reduced by 50%. Impaired intracellular insulin signaling (eg, the secondary messenger system) is abnormal in patients with type 2 DM with impairments at almost every step of activation due to insulin resistance, lipotoxicity, and glucotoxicity. The compensatory hyperinsulinemia required to overcome impaired insulin signaling can activate an alternative pathway through MAP kinase, which accelerates atherosclerosis. Mitochondrial dysfunction may also play a role in insulin resistance in muscle tissue. Mitochondrial function and density are lower in type 2 DM.

In patients with type 2 DM, fasting plasma FFA levels are elevated and fail to normalize after carbohydrate ingestion.[7] FFAs are stored as triglycerides in adipocytes and serve as an important energy source during fasting. Insulin is a potent inhibitor of lipolysis and restrains the release of FFAs from the adipocyte by inhibiting the lipase enzyme. Chronically elevated plasma FFA concentrations can impair insulin secretion and lead to insulin resistance in muscle and liver. FFA products interfere with multiple steps in the insulin-signaling cascade as well as increase β-cell apoptosis. In addition to elevated FFAs, patients with type 2 DM have increased stores of intracellular fat in the muscle and liver. This increased fat content correlates closely with the presence of insulin resistance in these tissues. Excess lipolysis from fat can contribute to gluconeogenesis indirectly through glycerol and FFA substrate use as well as increase a number of proinflammatory cytokines.

Weight gain leads to insulin resistance in most individuals, but not all. The term *visceral adipose tissue* (VAT) refers to fat cells located within the abdominal cavity and includes omental, mesenteric, retroperitoneal, and perinephric adipose tissue. VAT closely correlates with insulin resistance and fat distribution, rather than obesity per se, and likely explains the variable degree of insulin resistance seen in obese individuals.[7] VAT represents 20% of fat in men and 6% of fat in women. Central obesity can easily be assessed using waist circumference, which is a good surrogate marker for VAT. VAT has a higher rate of lipolysis than subcutaneous fat, resulting in an increase in FFA production.

These fatty acids are released into the portal circulation and drain into the liver, where they stimulate the production of very-low-density lipoproteins. They also increase the risk for developing nonalcoholic fatty liver disease.

VAT also produces a number of adipocytokines, such as tissue necrosis factor-α, interleukin 6, angiotensinogen, PAI-1, and resistin—all of which contribute to insulin resistance, hypertension, and hypercoagulability.[7] Fat cells also produce adiponectin—a adipocytokine that improves insulin sensitivity. Adiponectin decreases hepatic glucose production and increases fatty acid oxidation in muscle. Unfortunately, adiponectin concentrations are inversely related to the amount of VAT.

Type 2 DM patients fail to suppress glucagon in response to a meal and may even have a paradoxical rise in glucagon levels.[7] Several factors contribute: (1) GLP-1 resistance/deficiency, (2) insulin resistance, and (3) insulin deficiency. Ordinarily, postmeal increases in GLP-1 and insulin would suppress glucagon secretion. Thus, hyperglucagonemia further contributes to excessive production of glucose by the liver.

Ninety percent of filtered glucose is reabsorbed in the kidney by sodium glucose cotransporter-2 (SGLT-2), a high-capacity, low-affinity transporter in the proximal renal tubular cells.[13] The remaining 10% is reabsorbed by sodium glucose cotransporter-1 (SGLT-1). In normal healthy people, the renal threshold for glucosuria is at a plasma glucose value of approximately 180 mg/dL (10.0 mmol/L). In patients with diabetes, the renal threshold is increased to 220 to 240 mg/dL (12.2-13.3 mmol/L) before glucosuria occurs. The reason for the more active reabsorption of glucose by proximal renal tubular cells is likely due to an increased expression of SGLT-2 receptors. Increased reabsorption of glucose in the kidneys further contributes to hyperglycemia.

Gestational Diabetes

GDM develops during pregnancy.[14] If DM is diagnosed prior to pregnancy, this is not GDM, but rather pregnancy with pre-existing DM. Hormone changes during pregnancy result in increased insulin resistance, and GDM may ensue if the mother cannot increase insulin secretion to adequately compensate to maintain normoglycemia. Women who develop GDM are predisposed to subsequently developing type 2 DM. GDM and type 2 DM likely share much of the same etiological causes. In most cases, glucose intolerance first appears near the beginning of the third trimester. However, risk assessment and intervention should begin from the first prenatal visit. Detection is important, as therapy will

reduce perinatal morbidity and mortality.

Other Types of Diabetes

Maturity onset diabetes of youth (MODY) is characterized by impaired insulin secretion in response to a glucose stimulus with minimal or no insulin resistance.[3] Patients typically exhibit mild hyperglycemia at an early age and diagnosis is often delayed. The disease is inherited in an autosomal-dominant pattern with at least six different mutations identified to date. MODY 2 and 3 are most common.

CLINICAL PRESENTATION Diabetes Mellitus

Characteristic	Type 1 DM	Type 2 DM
Typical age at diagnosis	<20 years[a]	>30 years[b]
Body habitus	Lean (BMI < 25 kg/m^2)	Overweight or obese (BMI > 25 kg/m^2); abdominal obesity and increased waist:hip ratio
Family history of DM in first-degree relatives	Uncommon (<10%)	Common (>80%)
Insulin resistance	Uncommon (occurs if obese)	Very common
Autoantibodies	Usually present	Rarely present
Onset	Abrupt (days/weeks)	Gradual (years)
Symptoms[c]	Common and may be dramatic	Uncommon and often mild
Ketosis	Prone	Rare
Acute complication	Diabetic ketoacidosis (DKA)	Hyperosmolar hyperglycemic state (HHS)
Need for insulin replacement therapy	Immediate	Years after diagnosis
Long-term complications present at diagnosis	Rare—screening for complications unnecessary	Common—screening for complications recommended

[a]While most patients are diagnosed before age 20, type 1 DM can occur at any age.

[b]While most patients are diagnosed after age 30, type 2 DM is increasingly common in obese adolescents and young adults especially in high-risk populations (eg, African American, Latino/Hispanic Americans, Native Americans)

[c]The classic symptoms of DM include polyuria, polydipsia, polyphagia, weight loss, and fatigue.

The production of mutant insulin molecules has been identified in a few families and also results in abnormal glucose intolerance. Several genetic mutations have been described in the insulin receptor and are associated with insulin resistance. Type A insulin resistance is a clinical syndrome characterized by acanthosis nigricans, virilization in women, polycystic ovaries, and hyperinsulinemia. Anti-insulin receptor antibodies may block the binding of insulin. This has been referred to as type B insulin resistance.

CLINICAL PRESENTATION

The clinical presentation and features of type 1 DM and type 2 DM are different. Although type 1 DM can develop at any age, most patients are diagnosed before the age of 20. Patients with type 1 DM are often lean or thin at the time of diagnosis. In the absence of an adequate supply of insulin, patients with type 1 DM are prone to developing ketoacidosis and many initially present with DKA. Patients with type 1 DM often have symptoms in the days or weeks preceding the diagnosis. These symptoms often include frequent urination (polyuria) due to an osmotic diuresis from glucosuria, excessive thirst (polydipsia) due to dehydration, increased appetite (polyphagia) and weight loss due to caloric loss. Fatigue and lethargy are also common. The onset of symptoms can be triggered by an infection, trauma, or psychological stress.

In contrast, a majority of patients with type 2 DM are asymptomatic or have only mild fatigue at the time of diagnosis. Many patients are incidentally discovered to have type 2 DM based on the results of a routine laboratory test (eg, plasma glucose or A1C) or development of complications (eg, myocardial infarction, stroke, renal impairment). Mild hyperglycemia is likely present for many years prior to the diagnosis and thus explains why both microvascular and macrovascular complications are often present at the time of diagnosis. Most patients with type 2 DM are overweight or obese with an elevated waist:hip ratio. Many will report having first-degree relatives with diabetes.

Diagnosis of Diabetes

5 The diagnosis of diabetes requires the use of glycemic cut points that discriminate patients with normal BG from patients with impaired fasting glucose, impaired glucose tolerance, and diabetes (**Table 91-3** and **Table 91-4**). Current diagnostic criteria are slightly above these cut points. The cut points are meant to reflect the level of glucose above which microvascular complications have been shown to increase.[3] Cross-sectional studies have shown a consistent increase in the risk of developing retinopathy at an FPG level above 99 to 116 mg/dL (5.5-6.4 mmol/L), at a 2-hour PPG level above 125 to 185 mg/dL (6.9-10.3 mmol/L), and an A1C above 5.9 to 6.0% (0.059-0.060; 41-42 mmol/mol Hb).

TABLE 91-3 Definitions of Normal and Abnormal Glycemia

Fasting plasma glucose (FPG)	
Normal fasting glucose	70-99 mg/dL (3.9-5.5 mmol/L)
Impaired fasting glucose (IFG)	100-125 mg/dL (5.6-6.9 mmol/L)
Diabetes mellitus	≥126 mg/dL (7.0 mmol/L)
2-hour post-load plasma glucose (oral glucose tolerance test)	
Normal glucose tolerance	<140 mg/dL (7.8 mmol/L)
Impaired glucose tolerance (IGT)	140-199 mg/dL (7.8-11.0 mmol/L)
Diabetes mellitus[a]	≥200 mg/dL (11.1 mmol/L)
Glycosylated hemoglobin A1C (A1C)	
Normal A1C	4%-5.6% (0.04-0.055; 39-46 mmol/mol Hb)
Increased risk of diabetes mellitus (Prediabetes)	5.7%-6.4% (0.057-0.064; 39-46 mmol/mol Hb)
Diabetes mellitus	≥6.5% (0.065; 48 mmol/mol Hb)

TABLE 91-4 Criteria for the Diagnosis of Diabetes Mellitus[a]

1. A1C ≥6.5% (0.065; 48 mmol/mol Hb). The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the DCCT assay.[a]
2. Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours.[a]
3. Two-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.[a]
4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose concentration ≥200 mg/dL (11.1 mmol/L).

[a]In the absence of unequivocal hyperglycemia, a diagnosis using criteria 1 to 3 requires two abnormal test results from the same sample or in two separate test samples.

If a National Glycohemoglobin Standardization Program method is used, the A1C is the logical test for the diagnosis of diabetes as it measures glycemic exposure over the last 2 to 3 months, in contrast to a single-day, single-point glucose measurement. In addition, patients do not need to fast and the A1C is a

readily available test. An A1C of 6.0% to 6.4% (0.06-0.064; 42-46 mmol/mol Hb) denotes a 10-fold increase in risk of developing diabetes, but does not consistently identify patients with impaired fasting glucose or impaired glucose tolerance. There are slight racial differences in normal A1C levels. One-third fewer individuals with diabetes are identified using the A1C ≥ 6.5% (0.065; 48 mmol/mol Hb) threshold versus an FPG ≥ 126 mg/dL (7.0 mmol/L), yet providers may be more likely to diagnose diabetes from an A1C than from an elevated FPG level. The ADA continues to recommend three other glucose criteria for the diagnosis of diabetes mellitus in nonpregnant adults. See Table 91-4. If the patient has symptomatic hyperglycemia, reconfirming the diagnosis is not required.

Serial measurements, at clinician-defined intervals, can help to identify patients moving toward diabetes and those who are stable. Patients who have even minor increases in glucose or A1C values over time should be followed closely as these are likely the patients who will progress to DM. The A1C measurement can be affected by anemias and several hemoglobinopathies, which would necessitate the use of one of the plasma glucose criteria in these individuals. More information about A1C assay interference can be found at: http://www.ngsp.org/interf.asp.

Screening for Diabetes

Given the long-term complications associated with DM and the potential impact that early interventions can have on worsening hyperglycemia and outcomes, efforts to screen at-risk patients for impaired FPG and the development of diabetes are recommended. Screening begins with identifying patients who are at-risk for developing diabetes and, once identified, encouraging patients to obtain an FPG and A1C measurement to determine if the patient has hyperglycemia.

Type 1 Diabetes

The prevalence of type 1 DM is low in the general population. Due to the acute onset of symptoms in most individuals, screening for type 1 DM in the asymptomatic children or adults is not recommended.[3] Screening for β-cell autoantibody status in high-risk family members may be appropriate. However, such screening is only recommended in the context of clinical research trials for the prevention of type 1 DM.

Type 2 Diabetes

The ADA recommends screening for type 2 DM in asymptomatic adults who are overweight (BMI ≥ 25 kg/m^2 or ≥23 kg/m^2 in Asian-Americans) and have at least one other risk factor for the development of type 2 DM.[3] See Table 91-2. The risk of type 2 DM increases with age, and all adults, even those without risk factors, should be screened every 3 years starting at 45 years old. The recommended screening tests are an FPG, A1C, or 2-hour oral glucose tolerance test (OGTT). The optimal time between screening tests is not known and it may be prudent to screen patients with multiple risk factors every year.

Children and Adolescents

Despite a lack of clinical evidence to support widespread testing of children for type 2 DM, it is clear that more children and adolescents are developing type 2 DM. The ADA recommends screening overweight (defined as BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal) youths who have at least one of the following risk factors: a family history of type 2 DM in first- and second-degree relatives; Native Americans, African Americans, Hispanic Americans, and Asians/South Pacific Islanders; those with signs or conditions associated with insulin resistance (eg, acanthosis nigricans, hypertension, dyslipidemia); or a maternal history of diabetes or GDM during the child's gestation.[3] Screening should be done every 3 years starting at age 10 years or at the onset of puberty if it occurs at a younger age.

Gestational Diabetes

Risk assessment for GDM should occur at the first prenatal visit. Due to the high prevalence of obesity and undiagnosed DM, women with multiple risk factors for type 2 DM should be tested as soon as feasible.[3] All women, even if the initial screen test at the first prenatal visit was negative, should undergo testing at 24 to 28 weeks' gestation. Screening for GDM may be done in one of two ways: (1) a one-step strategy using a fasting 75-g OGTT, or (2) a two-step strategy starting with a nonfasting 50-g glucose load test (GLT). With the standard 75-g OGTT, the diagnosis of GDM is confirmed when fasting, 1-hour, 2-hour, and/or 3-hour glucose values are greater or equal to cut-off values. If a nonfasting 50-g GLT is performed, a fasting 100-g glucose tolerance test must be performed if the 1-hour value is elevated. See **Table 91-5**.

TABLE 91-5 Screening for and Diagnosis of Gestational Diabetes Mellitus

(GDM)

1. One-step method (fasting 75-g OGTT)[a]	
One abnormal value is diagnostic of GDM	
Time	**Plasma Glucose**
Fasting	≥92 mg/dL (5.1 mmol/L)
1 hour	≥180 mg/dL (10.0 mmol/L)
2 hours	≥153 mg/dL (8.5 mmol/L)
2. Two-step method	
Step 1: Perform a 50-g OGTT (nonfasting) at 24-28 weeks of gestation in women not previously diagnosed with diabetes.	
1 hour value ≥140 mg/dL[b]	(7.8 mmol/L)
Step 2: If screening test is positive, perform 100-g OGTT (fasting).	
Two or more abnormal values are diagnostic for GDM	

Carpenter/Coustan		**National Diabetes Data Group**
Time		
Fasting	95 mg/dL (5.3 mmol/L)	105 mg/dL (5.8 mmol/L)
1 hour	180 mg/dL (10.0 mmol/L)	190 mg/dL (10.5 mmol/L)
2 hours	155 mg/dL (8.6 mmol/L)	165 mg/dL (9.2 mmol/L
3 hours	140 mg/dL (7.8 mmol/L)	145 mg/dL (8.0 mmol/L)

[a]Should be performed at 24-28 weeks gestation unless the patient has diabetes. The test should be done in the morning after an 8- to 14-hour fast.

[b]The ACOG recommends a lower threshold of 135 mg/dL (7.5 mmol/L) in high-risk ethnic populations with higher prevalence of GDM; some experts also recommend 130 mg/dL (7.2 mmol/L).

Adapted from American Diabetes Association. Classification and Diagnosis of Diabetes. Diabetes Care. 2015;38(Suppl 1):S8-S16.

GENERAL TREATMENT APPROACH

Initial Evaluation

During an initial visit, a complete medical evaluation should be completed to confirm the diagnosis, classify the type of diabetes, evaluate for any complications or potential comorbid conditions, and review previous treatments and risk factors in established patients. Past medical, family, and social history should be taken as well as medication use, adherence, tolerability, and use of

diabetes technology. Screening for psychosocial conditions, self-management education needs, and hypoglycemia should occur. A thorough physical exam (including height, weight, BMI, blood pressure, thyroid palpitation, and foot exam) and laboratory evaluation (including A1C, lipid profile, liver function tests, serum creatinine, and eGFR) should be performed. A 10-year ASCVD risk score should also be calculated.[15,16]

Goals of Therapy

6 7 The primary goals of therapy for DM are to prevent or delay the progression of long-term micro- and macrovascular complications including retinopathy, neuropathy, diabetic kidney disease, and ASCVD. Additional goals of therapy are to alleviate symptoms of hyperglycemia, minimize hypoglycemia and other adverse effects, minimize treatment burden, and maintain quality of life. This requires glycemic control as well as control of comorbidities and CV risk factors. Glycemic control has demonstrated benefit at reducing long-term complications, but overly intensive control has also led to poor outcomes. Thus, glycemic targets should be individualized for each patient and should be based on balanced considerations of clinical trial evidence and patient-specific factors.[16,17]

Evidence to Support Intensive Glycemic Control

The first trial to evaluate whether good glycemic control could prevent or delay diabetes-related complications was the Diabetes Complications and Control Trial (DCCT) which was performed in patients with type 1 DM.[18] Patients in the study group were treated with intensive therapy—three or more injections of insulin daily or insulin pump, with frequent alterations of insulin therapy based on self-monitoring of blood glucose (SMBG) results plus frequent contact with a health professional; or conventional therapy—one or two insulin injections per day. After 6.5 years, retinopathy, neuropathy, and nephropathy were significantly reduced in the intensive group, but symptomatic and severe hypoglycemia was significantly more frequent. Long-term follow-up of the trial participants demonstrated a reduction in macrovascular complications as well as persistent reductions in microvascular complications, even though the difference in A1C values between treatment groups disappeared over time.[19,20]

The United Kingdom Prospective Diabetes Study (UKPDS) was subsequently performed to evaluate the same question but in patients with type 2 DM. Investigators recruited 5,102 patients between 1977 and 1991. Patients were

followed for an average of 10 years to determine the impact of intensive versus conventional glycemic control on the incidence of long-term complications in patients with newly diagnosed type 2 DM. The results showed that the intensive glycemic control arm (using sulfonylureas and insulin) achieved an A1C of 7.0% (0.070; 53 mmol/mol Hb) compared to 7.9% (63 mmol/mol Hb) in the conventional group. This translated into a modest but significant (12%) reduction in diabetes-related complications, most of which was due to a 25% reduction in microvascular complications. There was also a 16% reduction in ASCVD events in the intensive group, but this did not reach statistical significance.[21] Intensive glucose control using metformin as the initial therapy lowered the risk of diabetes-related complications by 32%, diabetes-related death by 42%, and all-cause mortality by 36% compared to conventional treatment in an overweight cohort of patients.[22] In the long-term UKPDS follow-up study, microvascular benefits of early glucose control persisted 10 years after the end of the original trial and a significant long-term reduction in myocardial infarction (MI) and all-cause mortality emerged in the intensive glucose control arm.[23]

Three additional large-scale studies were performed after the UKPDS to compare the effects of different intensities of glycemic control on the risk of macrovascular complications. These studies were done in patients with advanced type 2 DM who were at high risk for ASCVD. The Action to Control CV Risk in Diabetes (ACCORD) study (*n*=10,251) showed that lower A1C levels (achieved mean A1C 6.4% vs. 7.5% [0.064 vs. 0.075; 46 vs. 58 mmol/mol Hb]) reduced the risk of some microvascular complications but did not reduce the risk of macrovascular complications. The risk of hypoglycemia was significantly higher in the intensive treatment group. Most importantly, this study was stopped early due to an increase in mortality in the intensive treatment arm.[24] The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study (*n*=11,140) similarly showed no significant differences in ASCVD outcomes between two levels of glycemic control (achieved mean A1C 6.3% vs. 7.0% [0.063 vs. 0.070; 45 vs. 53 mmol/mol Hb]) but did show that the more intensive glucose control reduced microvascular complications.[25] The Veterans Affairs Diabetes Trial (VADT; *n*=1,791) also suggested reduced microvascular complications but no significant reduction in ASCVD outcomes with more intensive glycemic control (6.9% vs. 8.5% [0.069 vs. 0.085; 52 vs. 69 mmol/mol Hb).[26] Based on the results of these studies in aggregate, more stringent glucose control requires more intensive treatment and can increase the risk of severe hypoglycemia when insulin therapy

is used. The short-term and long-term benefits and risks must be carefully considered when setting intensive glycemic targets.

Glycemic Targets

Based on the clinical evidence that glycemic control reduces microvascular complications and also has long-term benefits in reducing macrovascular complications, several organizations, including the ADA and AACE, recommend surrogate targets for glycemic control. The ADA Standards of Care indicate that an A1C < 7% (0.07; 53 mmol/mol Hb) is reasonable for most nonpregnant adults. An FPG target range of 80 to 130 mg/dL (4.4 and 7.2 mmol/L) and a PPG target of <180 mg/dL (10.0 mmol/L)(1-2 hours after the beginning of a meal) correspond with an A1C target <7% (0.07; 53 mmol/mol Hb).[17] The AACE guidelines are more aggressive and indicate that an A1C ≤ 6.5% (0.065; 48 mmol/mol Hb) is optimal if it can be achieved in a safe and affordable manner. An FPG target of <110 mg/dL (6.1 mmol/L) and a 2-hour PPG target of <140 mg/dL (7.8 mmol/L) correspond with this recommendation (**Table 91-6**).[27]

TABLE 91-6 Glycemic Target Recommendations in Various Populations

Glycemic targets for most nonpregnant adults with diabetes[a]

	American Diabetes Association (ADA)	American Association of Clinical Endocrinologists (AACE)
Glycosylated hemoglobin (A1C)	<7.0% (0.07; 53 mmol/mol Hb)	≤6.5 (0.065; 48 mmol/mol Hb)
Fasting plasma glucose (FPG)	80-130 mg/dL (4.4-7.2 mmol/L)	<110 mg/dL (6.1 mmol/L)
Postprandial glucose (PPG)	<180 mg/dL (10.0 mmol/L)	<140 mg/dL (7.8 mmol/L)

American Diabetes Association glycemic targets for adolescents and children

A1C	<7.5% (0.075; 58 mmol/mol Hb)
FPG or premeal glucose	90-130 mg/dL (5.0-7.2 mmol/L)
Bedtime or overnight glucose	90-150 mg/dL (5.0-8.3 mmol/L)

American Diabetes Association glycemic targets for pregnant women

A1C	<6.5% (0.065; 48 mmol/mol Hb)
FPG or premeal glucose	<95 mg/dL (5.3 mmol/L)
Postprandial glucose (1 hour)	<140 mg/dL (7.8 mmol/L)
Postprandial glucose (2 hours)	<120 mg/dL (6.7 mmol/L)

American Diabetes Association glycemic targets for older adults

Patient characteristics/health status	A1C	FPG or premeal glucose	Bedtime glucose
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	<7.5% (0.075; 58 mmol/mol Hb)	90-130 mg/dL (5.0-7.2 mmol/L)	90-150 mg/dL (5.0-8.3 mmol/L)
Complex/intermediate (multiple coexisting chronic illnesses or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment)	<8.0% (0.080; 64 mmol/mol Hb)	90-150 mg/dL (5.0-8.3 mmol/L)	100-180 mg/dL (5.6-10.0 mmol/L)
Very complex/poor health (LTC or end-stage chronic illnesses or moderate-to-severe cognitive impairment or 2+ ADL dependencies)	<8.5% (0.085; 69 mmol/mol Hb)	100-180 mg/dL (5.6-10.0 mmol/L)	110-200 mg/dL (6.1-11.1 mmol/L)

[a]Glycemic targets should be individualized. More or less stringent goals may be appropriate for some patients.

ADL, activities of daily living.

Glycemic targets, however, must be individualized based on patient-specific factors and the potential risks and benefits of treatment. Ideally, glycemic targets should be established at the time of diagnosis and should be reviewed and re-evaluated at each visit. When possible, these decisions should be made in collaboration with the patient. Patient or disease factors to consider include: treatment-related risks including hypoglycemia and other adverse effects, disease duration, life expectancy, comorbidities, established vascular complications,

patient attitude and expected treatment effort, resources, and support system. While an A1C < 7% (0.07; 53 mmol/mol Hb) is recommended for most patients, a more stringent goal (such as <6.5% [0.065; 48 mmol/mol Hb]) may be appropriate for some patients if it can be achieved without significant adverse effects, particularly hypoglycemia. Those patients might be younger, with a long life expectancy, with a short duration of diabetes, those treated only with lifestyle modifications or metformin, or those without significant comorbidities. Less stringent goals (such as <8% [0.08; 64 mmol/mol Hb]) may be appropriate for patients who are older or who have a limited life expectancy, a long duration of diabetes, a history of severe hypoglycemia, extensive serious comorbidities or advanced complications. A higher A1C goal may also be appropriate for a patient in whom it remains difficult to achieve the goal despite appropriate education, monitoring, and drug therapy. For those treated with complex medication regimens, especially those that include insulin, the risk of trying to achieve stringent glycemic goals may outweigh the benefit.

Higher A1C goals should be considered in adolescents and children as well as patients >65 years old (Table 91-6).[28] An A1C goal < 7.5% (0.075; 58 mmol/mol Hb) is reasonable for healthy older adults, while an A1C goal < 8.0% (0.080; 64 mmol/mol Hb) or < 8.5% (0.085; 69 mmol/mol Hb) should be considered for those with coexisting chronic diseases, impairments of activities of daily living, cognitive impairment, or who reside in long-term care facilities. Clinicians should consider adjusting the FPG and PPG target ranges to correspond with higher target A1Cs.

NONPHARMACOLOGIC THERAPY

8 Nonpharmacologic therapy such as medical nutrition therapy (MNT), physical activity, and diabetes self-management education (DSME) is a cornerstone of treatment for all patients with diabetes.

Medical Nutrition Therapy

MNT is an evidence-based medical approach to treating diabetes through the use of an individually tailored nutrition plan. There is no standardized “diabetes diet” nor is there a single ideal distribution of macronutrients; therefore, meal planning should be individualized. It is imperative that patients understand the interrelationships between carbohydrate intake, medications, weight, and glucose control. A healthy meal plan that is moderate in calories and carbohydrates and

low in saturated fat (ie, less than 7% of total calories) with all of the essential vitamins and minerals is recommended. Some evidence suggests that a Mediterranean-style diet rich in mono- and poly-unsaturated fats may have glucose and CV benefits and could be considered.[29]

Weight loss or weight maintenance is a crucial element in many patients with type 2 DM. An initial weight loss goal of at least 5% should be targeted in all patients who are overweight or obese through calorie restriction. Strategies to reduce calories include reducing portions and frequency of food intake, decreasing empty calories, added sugars and solid fats, increasing nutrient-dense foods (eg, nonstarchy vegetables), employing low-calorie cooking methods, and tracking calorie intake. Helping the patient adopt healthier eating behaviors that lead to sustained weight loss over time is more important than a specific diet.[29]

Carbohydrate counting is another valuable component of diabetes care. The appropriate amount (grams) and type of carbohydrates is controversial. For individuals with type 1 DM, the focus is more on physiologically regulating insulin administration. For those on fixed doses of mealtime insulin, consistent intake of carbohydrates is recommended to improve glucose control and minimize hypoglycemia. For those on flexible insulin dosing regimens (eg, matching insulin doses to carbohydrate intake amounts), accurate carbohydrate counting to determine mealtime insulin doses is required. For patients with type 2 DM, carbohydrate counting focuses more on a balanced diet with moderate carbohydrate intake at each meal to minimize glucose excursions. Carbohydrate intake from vegetables, fruits, legumes, whole grains, dairy products, and those high in fiber is preferred. Sugar-sweetened beverages and foods with added sugars should be discouraged. Financial and cultural food issues must also be considered. Discourage bedtime and between-meal snacks, set realistic goals, determine what the patient is willing to change, and follow-up to see how and whether those changes occurred.[29]

Physical Activity

Most patients with diabetes benefit from regular physical activity. Aerobic exercise improves insulin sensitivity, modestly improves glycemic control in the majority of individuals, reduces CV risk, contributes to weight loss or maintenance, and improves well-being. Patients should choose activities that they enjoy and are likely to do at regular intervals. Start exercise slowly in previously sedentary patients. It is unclear if asymptomatic patients should be screened for ASCVD prior to beginning an exercise regimen. Screening is

reasonable in patients with long-standing disease (more than or equal to 10 years), multiple CV risk factors, microvascular disease (especially renal disease), or evidence of atherosclerotic disease. If the patient has uncontrolled hypertension, autonomic neuropathy, insensate feet, or proliferative retinopathy, restrictions on recommended activities are recommended. Physical activity goals include at least 150 minutes per week of moderate (50%-70% maximal heart rate) intensity exercise spread over at least 3 days a week with no more than 2 days between activities. In addition, resistance/strength training is recommended at least two times a week as long as the patient does not have proliferative diabetic retinopathy.[29]

Diabetes Self-Management Education and Support (DSME/S)

Consistent, long-term diabetes control requires patients to have a good understanding of their disease and participate in routine self-management strategies to control it. All patients should be offered access to diabetes self-management education and support (DSME/S) programs. There are four critical times to evaluate the need for DSME/S: at diagnosis, annually, when complicating factors arise, and when transitions in care occur.[29] The American Association of Diabetes Educators (AADE) has identified seven self-care behaviors that can be targeted through DSME/S. The behaviors include healthy eating, being active, monitoring, taking medications, problem-solving, reducing risk, and healthy coping.[30] The patient must be involved in the decision-making process and the process must be collaborative. Emphasize that complications can be prevented or minimized with good glycemic control and managing risk factors for ASCVD. Motivational interviewing techniques have been shown to be effective. Briefly, this involves asking open-ended questions that encourage patients to identify and acknowledge barriers that hinder achieving health goals, and then work to address them with the educator’s guidance.

Health professionals with formal training and experience in diabetes education can become certified. Certified diabetes educators (CDEs) must document their experience providing patient education and pass a certification examination. An increasing number of nurses, pharmacists, dietitians, and physicians are becoming CDEs. Formal diabetes education programs often employ several health professionals including CDEs. Accredited diabetes education programs can receive payment through Medicare and private health insurance plans. The AADE and ADA accredit diabetes education programs. It

must be noted, however, that there are not enough CDEs to provide sufficient education to all patients with diabetes. Health care professionals must be well-versed in the educational needs related to diet, physical activity, and other self-care behaviors to provide education and reinforcement of these crucial management strategies. Finally, patients should be advised not to smoke, and smoking cessation counseling should be a routine component of diabetes care.

PHARMACOLOGIC THERAPIES

Insulin

Endogenously produced insulin is cleaved from the larger proinsulin peptide in the β-cell to the active peptide of insulin and inactive C-peptide. All commercially available insulin preparations contain only the active insulin peptide and are produced and manufactured exclusively using recombinant DNA technology. “Human” insulins (NPH, regular) are recombinant DNA–derived human insulin, while insulin analogs have had amino acids substitutions in the insulin molecule that change the onset or duration of action. Most insulin products are administered subcutaneously for the chronic management of diabetes, except for inhaled human insulin which is a dry powder of human recombinant DNA regular insulin which is inhaled and absorbed through pulmonary tissue. The main advantage of insulin over other antihyperglycemic agents is that it can achieve a wide range of glucose targets and the dose can be individualized based on glycemic levels. Disadvantages include the risk of hypoglycemia, the need for injection(s), weight gain, and treatment burden.

Insulin is available in several concentrations containing 100 units/mL (U-100), 200 units/mL (U-200), 300 units/mL (U-300), or 500 units/mL (U-500). The most commonly used insulin concentration is U-100. Concentrated insulins containing more than 100 units/mL may be considered for individuals that require larger doses of insulin to control their diabetes.

The pharmacokinetics and pharmacodynamics of insulin products are characterized by the onset, peak, and duration of appearance and action (see **Table 91-7** and **Fig. 91-4**). Absorption of insulin from a subcutaneous depot is dependent on several factors, including source of insulin, concentration of insulin, additives to the insulin preparations (eg, zinc and protamine), blood flow to the area (rubbing of injection area, increased skin temperature, and exercise in muscles near the injection site may enhance absorption), and injection site. The abdomen provides the most consistent absorption for insulin.

TABLE 91-7 Pharmacodynamics of Insulin Preparations

Preparations (U-100 unless Otherwise Noted)	Onset	Peak[a]	Duration[a]
Ultra-rapid acting			
Insulin aspart (Fiasp)	15-20 min[b]	90-120 min	5-7 hours
Insulin humanis—inhaled (Afrezza)	12 min	35-55 min	1.5-4.5 hours
Rapid-acting			
Insulin aspart (NovoLog)	10-20 min	30-90 min	3-5 hours
Insulin lispro U-100, U-200 (Humalog)			
Insulin glulisine (Apidra)			
Short-acting			
Regular (Humulin R, Novolin R)	30-60 min	2-4 hours	5-8 hours
Intermediate-acting			
NPH (Humulin N, Novolin N)	2-4 hours	4-10 hours	10-24 hours
Regular U-500 (Humulin R 500)	15 min	4-8 hours	13-24 hours
Long-acting			
Insulin detemir (Levemir)	1.5-4 hours	6-14 hours[c]	16-20 hours
Insulin glargine (Lantus, Basaglar)	2-4 hours	No peak	20-24 hours
Insulin glargine U-300 (Toujeo)	6 hours	No peak	36 hours
Insulin degludec U-100, U-200 (Tresiba)	1 hour	No peak	42 hours
Combination Products			
70% NPH/30% Regular (Humulin 70/30, Novolin 70/30)	30-60 min	Dual	10-16 hours
75% NPL, 25% lispro (Humalog 75/25)	5-15 min		10-16 hours
50% NPL, 50% lispro (Humalog 50/50)	5-15 min		10-16 hours
70% insulin aspart protamine, 30% insulin aspart (Novolog 70/30)	5-15 min		15-18 hours

[a]The peak and duration of insulin action are variable, depending on the injection site, duration of diabetes, renal function, smoking status, and other factors.

[b]Onset of appearance is 2.5 minutes compared to 5.2 minutes for insulin aspart (NovoLog).

[c]Long-acting insulins are considered "peakless" although they have exhibited peak effects during comparative testing.

NPH, neutral protamine Hagedorn; NPL, insulin lispro protamine suspension.

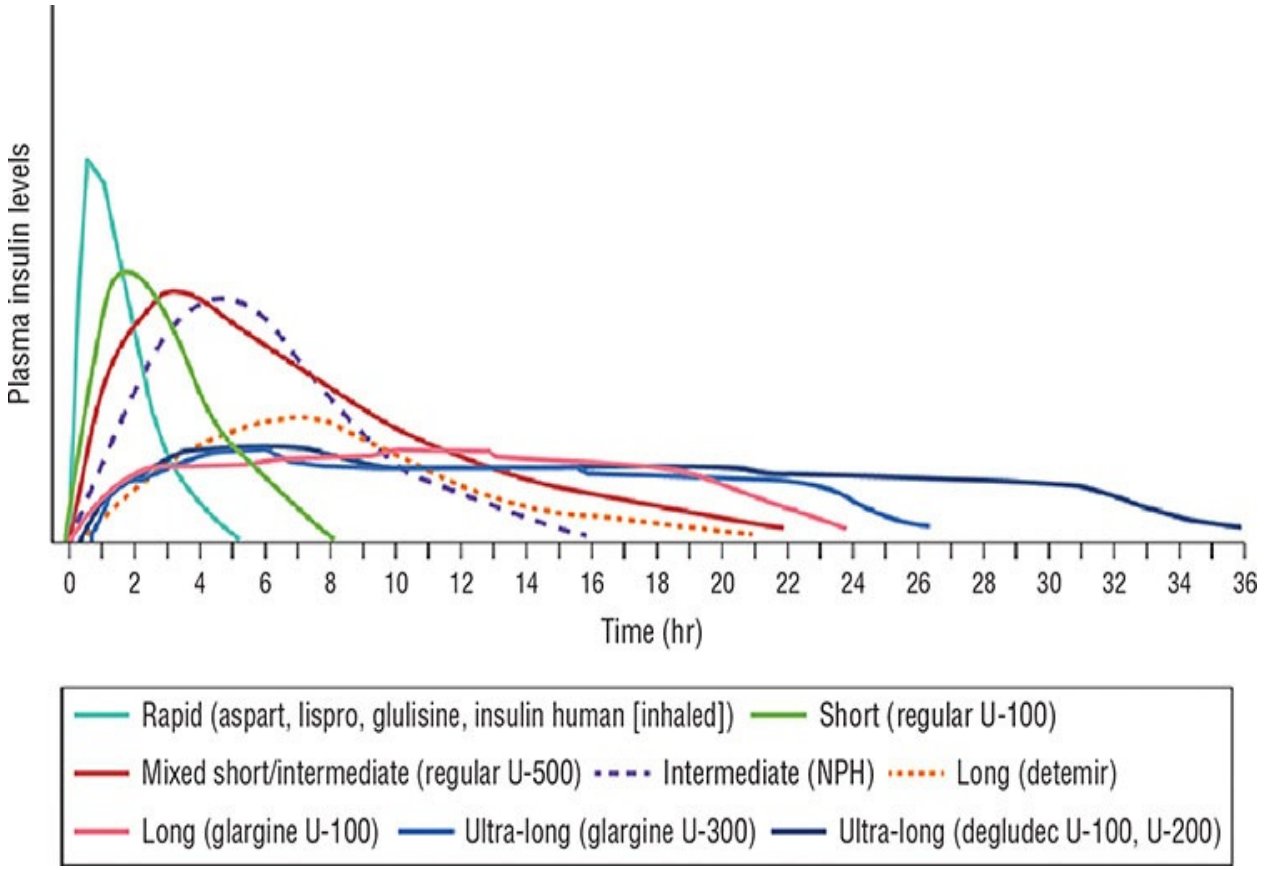


FIGURE 91-4 Pharmacokinetic profiles of currently available insulins.

Basal insulin, also called background insulin, refers to longer acting insulins that regulate BG levels in between meals by suppressing hepatic glucose production and maintaining near-normal glycemic levels in the fasting state. Bolus insulin refers to short or rapid-acting insulins that cover meals (also called prandial insulin) or glycemic excursions (also called correction insulin). Basal insulin is the preferred and most convenient initial insulin formulation in patients with type 2 DM while patients with type 1 DM require a combination of basal and bolus insulin to achieve adequate glycemic control.[31,32]

Basal insulin options include NPH, detemir, glargine U-100, glargine U-300, degludec U-100, or degludec U-200. From a pharmacokinetic/pharmacodynamic (PK/PD) perspective, NPH is the least ideal basal insulin as it has a distinct peak and a duration of action much less than 24 hours (see Fig. 91-4). While it can be given once daily in some patients with type 2 DM, it usually is dosed twice daily. Detemir also has a peak and often lasts less than 24 hours, but has a more ideal profile compared to NPH. It can be given once daily in some patients but should be dosed twice daily at low doses (less than 0.3 units/kg). Insulin glargine

U-100 offers a slightly better profile; it is considered to be peakless and can usually be given once daily. The longer acting agents (glargine U-300 and degludec) have no peak and a longer duration of action compared to glargine U-100 and detemir. They are given once daily (see Fig. 91-4). It is important to consider whether these PK/PD differences translate into clinically meaningful differences in patient outcomes. Clinical trial evidence indicates that all basal insulins can achieve similar A1C reductions if dosed and titrated properly; but the longer acting basal insulins have a lower risk of hypoglycemia, particularly nocturnal hypoglycemia, and may result in less glucose variability. They do however cost more, so the benefits and risks need to be considered on a patient-specific level.

Bolus insulin options include short-acting regular, rapid-acting insulins (aspart, lispro, and glulisine), and ultra-rapid insulins (inhaled human insulin and fast-acting insulin aspart [Fiasp]). Similar to basal insulins, the PK/PD profiles of bolus insulins have improved over time with the rapid-acting insulins offering a faster onset and shorter duration of action compared to regular insulin and the ultra-rapid insulins offering an even faster onset. Rapid and ultra-rapid acting agents may more closely mimic prandial endogenous insulin release. This is likely more relevant to patients with type 1 DM, where therapy is aiming to mimic a functioning pancreas that secretes insulin rapidly after a meal. Rapid-acting insulins have a modestly lower risk of hypoglycemia compared to regular insulin; however, efficacy can be achieved with all prandial insulins and the differences in cost can be substantial. Therefore, when selecting a bolus insulin, a patient-specific evaluation of the benefits and risks should be done.[31,32]

U-500 regular insulin is reserved for use in patients with extreme insulin resistance. It is most often given two or three times a day. To avoid medication errors, it is recommended to prescribe U-500 regular in a pen device or to use U-500 syringes if dispensing U-500 regular in a vial.

Various pre-mixed insulin products, which contain both a basal and a prandial component, are also available and can offer an alternative for patients who require fewer injections or a simpler regimen. However, these products are limited by their fixed mixed formulations which can make tailoring the dosing regimen challenging.

Although endogenous hyperinsulinemia and insulin resistance have been associated with increased CV risk, exogenous insulin therapy has not been associated with increased adverse CV outcomes in several large-scale clinical trials.[18,21,33]

The most common adverse effects reported with insulin is hypoglycemia. It is

more common in patients on intensive insulin therapy regimens. Patients with type 1 DM experience more hypoglycemic events when compared to type 2 DM patients who use insulin. In the UKPDS study, the percentage of type 2 DM patients who needed third-party assistance due to a severe hypoglycemic reaction was 2.3%.[21] In the DCCT study, intensive glycemic control increased the risk of severe hypoglycemia threefold when compared to conventional therapy in patients with type 1 DM.[18] Insulin use is associated with an increased risk of hospitalizations in older adults based on public health surveillance data.[34]

Insulin also causes dose-dependent weight gain, which predominantly occurs in truncal fat. Weight gain can be minimized by using physiologic insulin replacement strategies or combining insulin therapy with other medications that mitigate weight gain or promote weight loss.

Insulin can cause injection site reactions including redness, pain, itching, urticaria, edema, and inflammation. Administration of insulin subcutaneously can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) in some patients. Lipohypertrophy is caused by repeated injections into the same injection site. Due to insulin's anabolic actions, fat accumulates at the injection site and absorption at this site becomes variable. Lipoatrophy, in contrast, is due to insulin antibodies or allergic-type reactions that destroy the fat at the site of injection. Routinely rotating injection sites prevents these problems from developing and, when lipodystrophy is detected, the injection site should be avoided.

Concerns have been raised about a potential risk of cancer with insulin glargine, but trial results have been conflicting. While some studies using administrative data have found an association between insulin glargine and cancer, other meta-analyses and prospective studies have not.[33]

Inhaled human insulin can cause cough and upper respiratory infections and its use in chronic obstructive pulmonary disease and asthma is contraindicated due to bronchospasm risk. Inhaled insulin use has been associated with a small decline in pulmonary function and patients should have spirometry tests performed at baseline, 6 months, and annually thereafter. If a 20% reduction or greater in forced expiratory volume in 1 second is observed, inhaled insulin should be discontinued.

Insulin is degraded in the liver, muscle, and kidney. Liver deactivation is 20% to 50% in a single passage through the liver. Approximately 15% to 20% of insulin metabolism occurs in the kidney. This may explain the lower insulin dosage requirements and longer duration of activity observed in patients with end-stage renal disease.

The dose of insulin must be individualized. In type 1 DM, the average daily requirement for insulin is 0.5 to 0.6 units/kg, with approximately 50% being delivered as basal insulin, and the remaining 50% dedicated to meal coverage. During the honeymoon phase, it may fall to 0.1 to 0.4 units/kg. During acute illness or with ketosis or states of relative insulin resistance, the need for higher dosages is common. In type 2 DM, a higher dosage is required for those patients with significant insulin resistance. Dosages vary widely depending on degree of insulin resistance and concomitant antihyperglycemic medication use. More specific information on insulin dosing is included in the "General Approach to Hyperglycemia Management" section.

The effectiveness of insulin is highly dependent on its appropriate use. Product selection, education and training, and reinforcement is crucial. Counseling must include proper administration (including dose, injection technique, and timing of injection), glycemic targets, SMBG, dose titration or adjustment, storage, and prevention, detection, and treatment of hypoglycemia. Each insulin product is unique in the delivery device used. Some insulin products are available in vials, disposable pen devices, or pen cartridges, but many newer insulins are only available in pen devices. Each pen device product has different quantities, maximum injection doses, storage requirements and expirations. NPH insulin and all suspension-based insulin preparations should be inverted or rolled gently at least 20 times to fully suspend the insulin prior to each use. Improper mixing of the suspension prior to administration can lead to glycemic variability. Pharmacists should review recent guidelines on proper injection technique and prescribing information for specific products prior to counseling patients and utilize reliable, up-to-date patient education resources to ensure product-specific, accurate counseling information.[35,36]

Biguanides

Metformin is the only biguanide available in the United States. It is oral and available as an immediate-release formulation that is dosed twice daily or an extended-release (XR) formulation that is dosed once or twice daily (**Table 91-8**). Its benefits in relation to glucose lowering are complex and not yet fully understood. At the cellular level, metformin activates AMP kinase. Metformin has been shown to decrease hepatic glucose production, yet not all of its effects can be explained by that mechanism and there is increasing evidence of mechanisms in the gut. Additionally, metformin's effects may be partially related to enhanced insulin sensitivity in peripheral (muscle) tissues, which allows for an increased uptake of glucose into muscle cells. Metformin has no direct effect

on the β-cell, but insulin concentrations are reduced due to improved insulin sensitivity.[37]

TABLE 91-8 Dosing Recommendations for Oral Medications Used to Treat Type 2 Diabetes

Generic Name	Starting Dose	Usual Recommended Dose	Maximal dose (mg/day)	Dosing/Use in Renal Insufficiency[a]
Biguanides				
Metformin	500 mg once or twice daily or 850 mg once daily, titrate to target dose as tolerated	1,000 mg twice daily	2,550	Do not initiate if eGFR 30-45; Do not use if eGFR<30
Metformin XR	500 mg to 1,000 mg once daily, titrate to target dose as tolerated	2,000 mg once daily	2,500	Do not initiate if eGFR 30-45; Do not use if eGFR<30
Sulfonylureas (first generation)				
Chlorpropamide	250 mg once daily (100 mg once daily in older adults)	100-500 mg once daily	750	Consider alternative agent or initiate conservatively at 100 mg in renal insufficiency to avoid hypoglycemia
Tolazamide	250 mg once daily (100 mg once daily in older adults or if FPG<200 mg/dL [11.1 mmol/L])	250-500 mg once daily	1,000	Consider alternative agent or initiate conservatively at 100 mg in renal insufficiency to avoid hypoglycemia
Tolbutamide	1,000-2,000 mg once daily (250-500 mg once daily in older adults)	1,000-2,000 mg once daily	3,000	Consider alternative agent or initiate conservatively in renal insufficiency to avoid hypoglycemia
Sulfonylureas (second generation)				
Glimepiride	1-2 mg once daily (1 mg once daily in older adults)	4 mg once daily	8	Initiate conservatively at 1 mg in renal insufficiency to avoid hypoglycemia
Glipizide	5 mg once daily (2.5 mg daily in older adults)	5-10 mg once daily	40	Initiate conservatively at 2.5 mg in renal insufficiency to avoid hypoglycemia
Glipizide XL	5 mg once daily (2.5 mg once daily in older adults)	5-10 mg once daily	20	Initiate conservatively at 2.5 mg in renal insufficiency to avoid hypoglycemia
Glyburide	2.5-5 mg once daily (1.25 mg once daily in older adults)	5-10 mg once daily	20	Consider alternative agent or initiate conservatively at 1.25 mg in renal insufficiency to avoid hypoglycemia
Glyburide micronized	1.5-3 mg once daily (0.75 mg once daily in older adults)	3-6 mg once daily	12	Consider alternative agent or initiate conservatively at 0.75 mg in renal insufficiency to avoid hypoglycemia
Meglitinides				
Nateglinide	120 mg three times daily before meals	120 mg three times daily before meals	360	No adjustment required
Repaglinide	1-2 mg three times daily before meals (0.5 mg before meals if A1C<8% [0.08; 64 mmol/mol Hb])	2-4 mg three times daily before meals	16	Initiate conservatively at 0.5 mg before meals if CrCl 20-40 mL/min (0.33 to 0.67 mL/s)
Thiazolidinediones				
Pioglitazone	15 mg once daily	30 mg once daily	45	No dose adjustment required
Rosiglitazone	4 mg once daily or in two divided doses	4 mg once daily or in two divided doses	8	No dose adjustment required
α-Glucosidase inhibitors				
Acarbose	25 mg once to three times daily with meals	50 mg once to three times daily with meals	300	Avoid if CrCl<25 mL/min (0.42 mL/s)
Miglitol	25 mg once to three times daily with meals	50 mg once to three times daily with meals	300	Avoid if CrCl<25 mL/min (0.42 mL/s)
Sodium-glucose transporter (SGLT)-2 inhibitors				
Canagliflozin	100 mg once daily	100-300 mg once daily	300	100 mg once daily if eGFR 45-60; avoid if eGFR < 30
Dapagliflozin	5 mg once daily	5-10 mg once daily	10	Not recommended if eGFR < 45; avoid if eGFR < 30
Empagliflozin	10 mg once daily	10-25 mg once daily	25	Not recommended if eGFR < 45; avoid if eGFR < 30
Ertugliflozin	5 mg once daily	5-15 mg once daily	15	Avoid if eGFR<60
Dipeptidyl peptidase (DPP)-4 inhibitors				
Alogliptin	25 mg once daily	25 mg once daily	25	12.5 mg once daily if CrCl 30-60 mL/min (0.5-1.0 mL/s); 6.25 mg once daily if CrCl<30 mL/min (0.5 mL/s)
Linagliptin	5 mg once daily	5 mg once daily	5	No dose adjustment needed
Saxagliptin	2.5-5 mg once daily	5 mg once daily	5	2.5 mg once daily if eGFR≤50
Sitagliptin	100 mg once daily	100 mg once daily	100	50 mg once daily if eGFR 30-50 25 mg once daily if eGFR<30
Bile acid sequestrants				
Colesevelam	1.875 g twice daily or 3.75 g once daily	1.875 g twice daily or 3.75 g once daily	3.75 g/day	No dose adjustment needed
Dopamine agonists				
Bromocriptine	0.8 mg once daily	1.6-4.8 mg once daily	4.8	No dose adjustment needed

[a]eGFR units: mL/min/1.73m^2.

Metformin is the drug of choice in patients with type 2 DM due to extensive experience, high efficacy, minimal hypoglycemia risk, positive or neutral effects on weight, potential positive impact on CV risk, manageable side-effect profile, and low cost. Current treatment guidelines recommend initiating metformin as first-line pharmacotherapy unless a contraindication or intolerability exists.[31,32] Metformin consistently reduces A1C levels by 1.5% to 2.0% (0.015 and 0.020; 16 and 22 mmol/mol Hb) and FPG levels by 60 to 80 mg/dL (3.3 to 4.4 mmol/L) in drug naïve patients with A1C values of approximately 9% (0.09; 75 mmol/mol Hb). Metformin does not cause weight gain, and may actually lead to a modest (2-3 kg) weight loss. Since metformin does not directly increase insulin secretion from the pancreas, it has a low risk of hypoglycemia. Metformin also has positive effects on several components of the insulin resistance syndrome. Metformin decreases plasma triglycerides and low-density lipoprotein cholesterol (LDL-C) by approximately 8% to 15% and modestly increases high-density lipoprotein cholesterol (HDL-C) by 2%.

Metformin reduced the composite of all diabetes-related endpoints by 32%, diabetes-related death by 42%, and all-cause mortality by 36% in overweight subjects in the UKPDS compared to conventional treatment. Intensive treatment with metformin was also significantly better than intensive treatment with sulfonylureas or insulin at reducing any diabetes-related endpoint, all-cause mortality, and stroke. However, meta-analyses have not confirmed these benefits.[22,38,39] Metformin frequently causes GI side effects, including diarrhea, abdominal discomfort, and/or stomach upset. These side effects are usually dose-dependent, transient, mild in nature, and can be minimized with slow dose titration. Patients should take metformin with or immediately after meals. When initiating therapy, it is important to use a low dose, typically 500 mg given with the largest meal, to minimize GI adverse effects. The dose is then increased in 500 mg increments over several weeks. Approximately 5% to 10% of patients cannot tolerate metformin despite the slow dose titration. Extended-release metformin may lessen some of the GI side effects, but a recent head-to-head comparison of immediate-release versus extended-release metformin found no significant differences in rates of GI adverse effects.[40]

Metformin may cause a metallic taste, due to metformin in salivary secretions and may lower vitamin B_{12} concentrations. Therefore, B_{12} levels or methylmalonic acid should be measured annually or if a deficiency is suspected. Peripheral neuropathy, a microvascular complication that is common in diabetes, could manifest or worsen with B_{12} deficiency. Vitamin B_{12} supplementation by

sublingual, oral, or injection easily treats this deficiency.

Rare cases of lactic acidosis have been reported with metformin, usually in the setting of severe illness or acute kidney injury. The risk appears to be exceedingly small but may increase in patients with moderate-to-severe renal insufficiency or tissue hypoperfusion states such as acute congestive heart failure, excessive alcohol intake, and hepatic impairment. The clinical presentation of lactic acidosis is often nonspecific flu-like symptoms. The diagnosis is therefore made by laboratory confirmation of high lactic acid levels and acidosis.

Metformin can be used in combination with any other antihyperglycemic therapy and is often continued when insulin therapy is initiated. The target dose for metformin is 1,000 mg twice daily or 2,000 mg daily if the extended-release product is used. The minimal effective dose of metformin is 1,000 mg/day (Table 91-8). Approximately 80% of the glycemic-lowering effect may be seen at 1,500 mg daily.

Metformin is renally excreted and accumulates in patients with renal insufficiency; therefore, metformin is contraindicated in patients with an eGFR < 30 mL/min/1.73 m^2 and should be used with caution in patients with milder renal insufficiency. Initiation of metformin is not recommended in patients with an eGFR 30-45 mL/min/1.73 m^2 but can be continued with increased renal function monitoring; a dose reduction of 50% of maximal dose may be warranted.[41–43] Due to the risk of acute renal failure when IV contrast dye is used during imaging procedures, metformin therapy should be withheld starting the day of the procedure and resumed 2 to 3 days later, if normal renal function has been documented. It need not be withheld for days prior to the procedure.

Sulfonylureas

Sulfonylureas are oral agents, available in either immediate-release or extended-release formulations, typically dosed once or twice daily (Table 91-8). They enhance insulin secretion by binding to a specific sulfonylurea receptor (SUR1) on pancreatic β-cells. Binding closes an adenosine triphosphate-dependent K^+ channel, leading to decreased potassium efflux and subsequent depolarization of the membrane. Voltage-dependent Ca^{+2} channels open and allow an inward flux of Ca^{+2}. Increases in intracellular Ca^{+2} bind to calmodulin on insulin secretory granules, causing translocation of secretory granules of insulin to the cell surface and resultant exocytosis of the granule of insulin. Elevated secretion of insulin from the pancreas travels via the portal vein and subsequently suppresses hepatic

glucose production.

Sulfonylureas are classified as first-generation and second-generation agents. The classification schemes are based on relative potency. First-generation agents (chlorpropamide, tolazamide, and tolbutamide) are lower in potency relative to the second-generation drugs (glyburide, glipizide, and glimepiride), and are rarely used due to a higher risk of adverse effects. When given in equipotent doses, all sulfonylureas are equally effective at lowering BG. On average, glucose-lowering efficacy is considered high with A1C reductions of 1.5% to 2% (0.015 and 0.02; 16 and 22 mmol/mol Hb) and FPG reductions of 60 to 70 mg/dL (3.3 to 3.9 mmol/L) in drug-naïve patients but is dependent on baseline values and duration of diabetes.

Sulfonylureas are the second most prescribed oral drugs for the treatment of type 2 DM. However, their place in therapy is controversial. Based on their extensive track record of safety and effectiveness, their low cost, and their oral route of administration, many clinicians feel comfortable using them. However, many diabetes experts as well as major organizations that publish guidelines for diabetes management either discourage the use of sulfonylureas or suggest using caution due to the risk of hypoglycemia and weight gain. Soon after sulfonylureas are taken, a robust reduction in A1C is seen, but long-term durability is poor in most patients. Sulfonylureas cause a tachyphylaxis to their insulin secretion effect on the β-cell. In vitro testing of β-cells has reported depolarization of the cell, resulting in its inability to secrete insulin. Whether this effect is reversible is unclear. Clinically, this is recognized by the deterioration of A1C.

Sulfonylureas were used extensively in the UKPDS and ADVANCE trials, which both showed a reduction in microvascular complications in patients targeting a more intensive glycemic goal.[21,25] Results from the University Group Diabetes Program raised early concerns about the CV safety of sulfonylureas, with documented higher rates of coronary artery disease in type 2 DM patients given tolbutamide compared to patients given insulin or placebo. Since then, most evidence suggests that sulfonylurea use does not increase macrovascular outcomes or all-cause mortality compared to other active treatments.[21,25,44,45]

The most common side effect of sulfonylureas is hypoglycemia. Due to its active metabolite, glyburide has a higher risk of hypoglycemia compared to other sulfonylureas while glipizide and glimepiride have lower risks.[45,46] Those who skip meals, exercise vigorously, or lose substantial amounts of weight are more prone to experiencing hypoglycemia. A lower dose should initially be used in high-risk patients, in addition, hypoglycemia on low-dose sulfonylureas may

dictate a switch to therapy with a low risk of hypoglycemia. Severe hypoglycemia on sulfonylureas would warrant the same intervention. Because of their risk of hypoglycemia, sulfonylureas should be avoided or used with extreme caution in older adults.[28]

Weight gain is common with sulfonylureas—typically 1 to 2 kg. Whenever possible, clinicians should avoid the use of medications that cause weight gain in patients who are overweight or obese.[47] Many patients report having a sulfa allergy, but cross-reactivity with sulfonylureas is very rare. However, if the patient has a history of anaphylaxis-type reactions to sulfa, it may be best to use a different class of medication.

The starting dose, usual dose, and maximum dose of sulfonylureas are summarized in Table 91-8. Sulfonylureas with long durations of action or those with active metabolites should be avoided in older patients and those with renal insufficiency due to the high risk of hypoglycemia; an alternative agent should be selected. Within the sulfonylurea class, glipizide may be the safest alternative. The dosage can be titrated as soon as every 2 weeks based on FPG values to achieve glycemic goals. Immediate-release glipizide's maximal dose is 40 mg/day, but its maximally effective dose is about 15 to 20 mg/day. Indeed, the maximally effective dose of sulfonylureas is typically 60% to 75% of the stated maximum dose.[31,48]

Thiazolidinediones

Pioglitazone and rosiglitazone are the two currently FDA-approved thiazolidinediones (TZDs) for the treatment of type 2 DM. They are oral agents, dosed once daily (Table 91-8). TZDs work by binding to the peroxisome proliferator activator receptor-γ (PPAR-γ), a nuclear receptor that is predominantly located on fat cells and vascular cells. Activation of PPAR-γ alters the transcription of several genes involved in glucose and lipid metabolism and energy balance. TZDs enhance insulin sensitivity at muscle, liver, and fat tissues. TZDs cause preadipocytes to differentiate into mature fat cells in subcutaneous fat stores. Small fat cells are more sensitive to insulin and more able to store FFAs. This allows a flux of FFAs out of the plasma, visceral fat, and liver into subcutaneous fat, a less insulin-resistant storage tissue. Muscle intracellular fat products, which contribute to insulin resistance, also decline. TZDs also affect adipokines (eg, angiotensinogen, tissue necrosis factor-α, interleukin 6, PAI-1), which can positively affect insulin sensitivity, endothelial function, and inflammation. Of particular note, adiponectin is reduced with

obesity and diabetes, but is increased with TZD therapy, which improves endothelial function, insulin sensitivity, and has a potent anti-inflammatory effect.[49]

TZDs are considered second- or third-line agents and can be used in combination with metformin and other commonly prescribed medications for type 2 DM. TZDs have high glycemic-lowering efficacy and reduce A1C values approximately 1.0% to 1.5% (0.010 to 0.015; 11 to 22 mmol/mol Hb), FPG levels by 60 to 70 mg/dL (3.3 to 3.9 mmol/L) at maximal doses, and they have high durability over time. Glycemic-lowering onset is slow and maximal effects may not be seen until 3 to 4 months of therapy. It is important to inform patients of this fact and that they should not stop therapy even if minimal changes in BG levels are initially seen. Pioglitazone consistently decreases plasma triglyceride levels by 10% to 20%, whereas rosiglitazone tends to have a neutral effect. LDL-C concentrations tend to increase with rosiglitazone 5% to 15%, but do not significantly increase with pioglitazone. Both appear to convert small, dense LDL particles, which have been shown to be more atherogenic, to large, buoyant LDL particles, which may be less atherogenic. Both drugs increase HDL, though pioglitazone may raise it more than rosiglitazone. The ADA algorithm recommends TZDs as a potential second-line treatment choice for type 2 DM, particularly when medication cost is a major concern or for those with a compelling need to avoid hypoglycemia. They can be used in combination with metformin and other second-line options.[31,32]

The effects of TZDs on macrovascular complications are controversial and are not similar between rosiglitazone and pioglitazone. A meta-analysis published in 2007 reported higher rates of myocardial infarction (MI) with rosiglitazone compared to placebo or other diabetes medications.[50] This prompted a safety communication from the FDA and prescribing restrictions for the drug. These restrictions were later removed after re-evaluation of the data determined no increased risk. The prospective, multicenter, open-label trial found that rosiglitazone was noninferior to the metformin/sulfonylurea comparator for all CV outcomes except heart failure.[51,52] Alternatively, pioglitazone has been associated with benefits related to macrovascular outcomes. In the PROactive study, three years of pioglitazone 45 mg resulted in a significant reduction of the composite of all-cause mortality, nonfatal myocardial infarction, or stroke by 16% in patients with type 2 DM who had previous macrovascular events.[53] Pioglitazone has also been shown to decrease the risk of recurrent strokes, but this was not in a diabetes population.

Adverse effects of TZDs include edema, new onset or worsening of pre-

existing heart failure, weight gain, and bone fractures. TZDs cause fluid retention due to peripheral vasodilation and improved insulin sensitization at the kidney with a resultant increase in renal sodium and water retention. Resultant effects include peripheral edema, heart failure, hemodilution of hemoglobin and hematocrit, and weight gain. Peripheral edema is reported in 4% to 5% of patients using TZD monotherapy, but the incidence is significantly increased (more than 15%) when a TZD is used in combination with insulin. TZDs are contraindicated in patients with New York Heart Association Class III and IV heart failure, and great caution should be used in patients with Class I and II heart failure. Edema is dose-related and if not severe, a reduction in the dose may allow the continuation of therapy in the majority of patients. Rarely, TZDs have been reported to worsen macular edema of the eye. Weight gain is also dose-related and is a result of both fluid retention and fat accumulation. Average weight gain varies but a 4-kg weight gain is not uncommon; higher amounts of weight gain may necessitate discontinuation of therapy.

TZDs have also been associated with an increased fracture rate in the upper and lower limbs of postmenopausal women. The risk may relate to TZDs' effect on the pluripotent stem cell and shunting of new cells to fat instead of osteocytes as well as altering osteoblasts/osteoclasts.[54,55] A patient's risk factors for fractures should be considered before selecting a TZD.

TZDs have also been linked to bladder cancer. Bladder tumors have been noted in rodent models using TZDs. Interim analysis of a 10-year observational study with pioglitazone reported an excess of three cases of bladder cancer per 10,000 patient-years of treatment after 5 years of pioglitazone use. Ten-year data using the same database showed no association.[56,57] Other population-based and prospective studies have also reported increased risk with pioglitazone. Excess risk, if present, appears to be mostly in men and smokers, and is dose and duration associated. TZDs should not be used in patients with active bladder cancer and the benefits and risks should be carefully considered before using pioglitazone in patients with a history of bladder cancer.

Premenopausal anovulatory patients may resume ovulation on TZDs due to their insulin-sensitizing effects. Adequate pregnancy and contraception precautions should be explained to all women capable of becoming pregnant.

The recommended starting dosages of pioglitazone is 15 mg once daily and rosiglitazone is 2 mg once daily. Dosages may be increased after 3 to 4 months based on the response to treatment and side effects. The maximum dose and maximum effective dose of pioglitazone is 45 mg and 8 mg once daily for rosiglitazone (Table 91-8). To minimize weight gain and edema, the lowest

effective dose should be used. If side effects occur with a higher dose, the dose should be reduced. Lower doses are recommended when used in combination with insulin, and edema and weight gain should be monitored carefully.

Glucagon-Like Peptide-1 Receptor Agonists

Currently, seven GLP1-RAs are available in the United States. Six of these are delivered subcutaneously with dosing schedules ranging from twice daily to once weekly and one is delivered orally once daily (**Table 91-9**). The class mimics the action of endogenous GLP-1. They stimulate insulin secretion from pancreatic beta-cells in a glucose-dependent manner. In addition, during hyperglycemia, GLP-1 RAs reduce inappropriately elevated levels of glucagon, which results in decreased hepatic glucose output. These agents also have a direct effect on the stomach through the autonomic nervous system to slow gastric emptying, thereby reducing meal-related glucose excursions. Additionally, agents that penetrate the blood–brain barrier increase satiety via the central nervous system. These actions result in a reduction in both glucose and weight. GLP-1 RAs also potentially preserve pancreatic beta-cell function and protect against cytokine-induced apoptosis. All GLP1-RAs result in pharmacologic levels of GLP-1 activity and are resistant to the rapid degradation by the dipeptidyl peptidase 4 (DPP-4) enzyme.

TABLE 91-9 Clinical Comparisons of GLP-1 Receptor Agonists

Generic Name	Primary Glucose Profile Target	Within Class Comparability of A1C and Weight-Lowering Efficacy	Dose/Route	Interval	Renal Dose/Use	Availability, Storage, Preparation
Exenatide	PPG	Low	5-10 mcg SC	Twice daily (30-60 minutes before breakfast and dinner)	Avoid if eGFR<30	• Multidose pens (5 mcg/dose, 10 mcg/dose, 60 doses per pen) • Pen needles not supplied with pen • Keep refrigerated • After first use, store at room temperature. Discard 30 days after first use.
Lixisenatide	PPG	Low	10-20 mcg SC	Once daily (1 hour before breakfast)	Limited experience in severe renal impairment; avoid if eGFR<15	• Multidose pen (10 mcg, 20 mcg, 14 doses per pen) • Pen needles not supplied with pen • Keep refrigerated • After first use, store at room temperature; discard 14 days after first use
Dulaglutide	FPG and PPG	Intermediate	0.75-1.5 mg SC	Once weekly	Limited experience in severe renal impairment	• Single-dose pen (0.75 mg, 1.5 mg) • Pen needle attached • Keep refrigerated • May store at room temperature for 14 days
Exenatide XR	FPG and PPG	Intermediate	2 mg SC	Once weekly	Avoid if eGFR<30	• Single-dose pen (2 mg) • Pen needle supplied with pen • Keep refrigerated; may store at room temperature for 4 weeks • Store flat in original packaging, protected from light • Remove from refrigerator 15 minutes prior to mixing • Requires reconstitution; administer dose immediately once reconstituted
Liraglutide	FPG and PPG	High	0.6-1.8 mg SC	Once daily	Limited experience in severe renal impairment	• Multidose pen (6 mg/mL, 3 mL; each pen delivers doses of 0.6, 1.2, or 1.8 mg) • Pen needles not supplied with pen • Keep refrigerated • After first use, store at room temperature; discard 30 days after first use
Semaglutide	FPG and PPG	Highest	0.25-1 mg SC	Once weekly	No dose adjustment recommended	• Multidose pen (1.34 mg/mL; 1.5 mL, lower dose pen delivers 0.25 mg or 0.5 mg doses; high-dose pen delivers 1 mg dose) • Pen needles supplied with pen • Keep refrigerated. • After first use, store at room temperature; discard 56 days after first use
Semaglutide	FPG and PPG	Highest	3-14 mg orally	Once daily	No dose adjustment recommended	• Store at room temperature • Should be taken 30 minutes before first food, beverage, or other medication of the day with no more than 4 ounces of water

eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; PPG, postprandial glucose; SC, subcutaneous.

GLP-1 RAs are treatment options at multiple points in the type 2 DM disease process and can be used in combination with many other agents including metformin, TZDs, sulfonylureas, SGLT-2 inhibitors, and basal insulin. They are not currently recommended as first-line agents but can be used as monotherapy in patients who cannot tolerate or take first-line therapy. They are recommended as second-line agents for many patient populations including those with established ASCVD or CKD, and those with a compelling need to avoid hypoglycemia or a compelling need to avoid weight gain or induce weight loss. They should not be used in combination with DPP-4 inhibitors due to the similar mechanisms of action. A significant amount of evidence shows the beneficial effect of the combination of GLP-1 RA and a basal insulin. The A1C lowering efficacy with GLP1-RAs is considered high but depends on baseline glycemic control, background therapy, and the specific agent used. GLP-1 RAs can also lead to weight loss. The average weight loss is about 1-3 kg with GLP-1 RAs but is highly dependent on the specific agent used, with clinical trial results varying from an average 0.3 kg weight gain to as much as a 6.5 kg weight loss.

Currently, available GLP-1 RAs include dulaglutide, exenatide, exenatide XR, lixisenatide, liraglutide, and semaglutide (in both an injectable and oral formulation). Multiple differences exist in the characteristics of the individual agents within the class, including molecular structure and size, half-life, duration of action, ability to penetrate different tissue compartments, and homology to native GLP-1, which, in turn, lead to important clinical differences in efficacy, rates of adverse effects, dosing schedules, and impact on glucose profile (Table 91-9). Short-acting agents (exenatide and lixisenatide) predominantly lower PPG levels, likely due to their effect on gastric emptying. Long-acting agents (dulaglutide, liraglutide, exenatide XR, and semaglutide) lower both FPG and PPG, but demonstrate larger effects on FPG levels, due to their longer half-life and resultant suppression of glucagon overnight. Based on several head-to-head trials comparing specific GLP-1 RAs to each other, it appears that liraglutide and semaglutide have the highest A1C and weight-lowering efficacy while exenatide and lixisenatide have the lowest (Table 91-9).[58,59]

Large-scale, CV outcome trials have been completed for exenatide XR, lixisenatide, liraglutide, and semaglutide. Both lixisenatide and exenatide XR demonstrated CV safety, but did not reduce the rate of major adverse CV events (myocardial infarction, stroke, or CV death). Liraglutide, semaglutide, and dulaglutide, however, not only demonstrated CV safety but also demonstrated benefit.[60]

In the Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes (LEADER) trial, liraglutide significantly reduced the risk of CV death, nonfatal myocardial infarction, and nonfatal stroke by 17% compared to placebo in patients with type 2 DM at high CV risk. This result was driven by a significant reduction in CV death. Liraglutide also resulted in a reduction in all-cause mortality and a reduction in the progression of renal disease. Because of these results, liraglutide is also FDA approved to reduce the risk of major adverse CV events in adults with type 2 DM and established CV disease.[61]

In the Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6) trial, semaglutide (SC) significantly reduced the risk of CV death, nonfatal myocardial infarction, and nonfatal stroke by 26% compared to placebo in patients with type 2 DM and high CV risk. There was also a significant reduction in nonfatal stroke with semaglutide compared to placebo and a reduction in the progression of renal disease. No significant differences were seen between groups in CV death or all-cause mortality.[62]

The most common adverse effects associated with GLP1-RAs are GI in nature, including nausea, vomiting, and diarrhea. These adverse effects appear to be dose-related so dose titration is recommended. They usually occur early in the treatment course, are typically mild in nature, and transient. In a small number of patients, the GI side effects are significant enough to require discontinuation. Long-acting preparations tend to have less impact on gastric emptying, and thus a slightly lower risk of nausea, compared to short-acting agents. Patients should be instructed to eat slowly and stop eating when satiated otherwise nausea may worsen or cause vomiting.

GLP1-RAs enhance insulin secretion in a glucose-dependent manner in response to food intake; thus, the risk of hypoglycemia is low when combined with metformin, DPP-4 inhibitors, SGLT-2 inhibitors, or a TZD. However, when combined with a sulfonylurea or insulin, hypoglycemia may occur.

Antibody formation to GLP1-RAs may occur, which could potentially attenuate the glycemic-lowering effects. Antibody formation is more likely to occur with exendin-4 based agents (exenatide, exenatide XR, and lixisenatide) than with other agents. Injection site reactions have also been reported in patients taking injectable GLP-1 RAs. These reactions may be more common in patients with high antibody titers. Exenatide XR can also cause injection site nodules, likely due to its formulation. It is encapsulated in microspheres made of a biodegradable polymer, which release the drug over a sustained time interval. The microspheres can lead to injection site nodules described as pea-sized, hard, subcutaneous, lumps, masses, or induration. Hypersensitivity reactions,

including anaphylaxis and angioedema, have also been reported with most GLP1-RAs.

GLP-1 RAs have been associated with cases of acute pancreatitis, but no causal relationship has been established. While additional study is needed, it should be noted that (1) patients with type 2 DM are at inherently higher risk for developing pancreatitis; (2) GLP1-RAs may mask the initial signs of pancreatitis, including nausea, vomiting, and abdominal pain; and (3) large studies have not linked GLP1-RA use to a higher incidence of acute pancreatitis. In a patient with a history of pancreatitis, the benefits must be weighed against the potential risks. A GLP1-RA should not be used in patients with chronic pancreatitis. If a patient reports abdominal pain, nausea, and repeated vomiting, it is best to discontinue therapy temporarily and confirm that the symptoms are not a sign of a more serious underlying problem. GLP-1 RAs have not been studied in patients with gastroparesis, but since they delay gastric emptying they are not recommended in this patient population.

Long-acting GLP1-RAs are contraindicated in patients with a history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 due to a risk of medullary thyroid carcinoma. This contraindication is based on rodent model data that reported a higher risk of C-cell tumors of the thyroid but has not been seen in humans. Rodents may not be the ideal model to study this effect as they express a high number of GLP-1 receptors on thyroid C-cells. The expression of GLP-1 receptors in the thyroid of humans is minimal. Rodents also have a higher baseline prevalence of C-cell tumors compared to humans. There is no contraindication in patients with a history of other types of thyroid cancers.

The GLP-1 RAs require subcutaneous administration into the abdomen, thigh, or upper arm. Each agent uses a unique injection pen device with unique administration requirements; patients must be instructed on how to use the specific product they have been prescribed. The short-acting agents have specific timing requirements in relation to meals since their mechanisms are more targeted toward slowing gastric emptying postprandially. If the dose of exenatide or lixisenatide is missed, it should not be taken after the meal. The long-acting agents have more flexibility with the timing of doses and can be taken at any time of day, with or without food. Oral semaglutide should be taken 30 minutes before the first food, beverage or other medication of the day with no more than 4 ounces of water. Most of the GLP-1 RAs (except for exenatide XR) have recommended lower doses when initiating the drug, followed by titration to higher doses if needed for glycemic control. This is to minimize GI adverse effects since the GI adverse effects are dose-related and transient. For the once

weekly agents, steady state is attained at 6 to 8 weeks. For GLP1-RAs administered weekly, if a dose is missed it should be taken as soon as possible but not within 3 days of the next dose. Use caution when starting or increasing the dose of GLP-1 RAs in patients with renal insufficiency as there have been case reports of acute kidney injury or worsening renal function. Most occurred in patients who experienced nausea, vomiting, diarrhea, or dehydration. Exenatide and exenatide XR should be avoided in patients with eGFR<30 mL/min/1.73 m^2 and lixisenatide should be avoided in patients with eGFR < 15 mL/min/1.73 m^2.

Dipeptidyl Peptidase-4 Inhibitors

Four DPP-4 inhibitors are approved by the FDA: sitagliptin, saxagliptin, linagliptin, and alogliptin, all of which are oral, once daily products. These agents inhibit the DPP-4 enzyme responsible for the rapid degradation of GLP-1 and GIP, thereby prolonging the half-life of endogenously produced GLP-1 and GIP. Levels of GLP-1 are deficient in patients with type 2 DM. As these agents block nearly 100% of the DPP-4 enzyme activity for at least 12 hours, normal physiologic, GLP-1 levels are achieved. This leads to an increase in glucose-dependent insulin secretion from the pancreas and a reduction in inappropriate postprandial glucagon secretion, resulting in lower glucose levels without an increase in hypoglycemia when used as monotherapy. These drugs do not alter gastric emptying and do not cause nausea or have significant effects on satiety. DPP-4 inhibitors have a neutral impact on weight.

The DPP-4 inhibitors have moderate glucose-lowering efficacy, with an average reduction in A1C of 0.5% to 0.9% (0.005-0.009; 6 to 10 mmol/mol Hb) to when used at maximum doses. DPP-4 inhibitors have a shallow dose–response curve. There are no clear differences in efficacy between medications within the class. DPP-4 inhibitors are considered second- or third-line therapy in the ADA algorithm, particularly when there is a compelling need to minimize hypoglycemia or weight gain, but they have less A1C lowering efficacy compared to other second-line medication classes. Potential advantages of the DPP-4 inhibitors include once daily dose, oral administration, weight neutrality, low risk of hypoglycemia, and good tolerability. They may be used in older adults with moderate-to-severe renal insufficiency or those where drug tolerability is a priority. However, their ability to lower BG is modest and they are expensive.

The DPP-4 inhibitors are extremely well-tolerated. Adverse effects are uncommon but could include stuffy, runny nose; headache; or upper respiratory

tract infections. Safety concerns that have arisen post-market with the DPP-4 inhibitors include heart failure, pancreatitis, and joint pain. The CV outcome trials with saxagliptin, sitagliptin, linagliptin, and alogliptin all demonstrated the overall CV safety of these agents, with no significant differences in major CV outcomes compared with placebo.[60] However, an increased risk of heart failure hospitalizations with saxagliptin compared with placebo in the SAVOR-TIMI trial reached statistical significance, and there was a trend toward increased heart failure hospitalizations with alogliptin compared with placebo in the EXAMINE trial.[60,63] Because of these findings, prescribing information for both saxagliptin and alogliptin includes information about the increased risk of hospitalization for heart failure, particularly in patients with existing heart or kidney disease. Patients taking these medications should contact their health professional if they develop signs and symptoms of heart failure, and providers should consider discontinuing the medication in patients who develop heart failure.

The FDA has also issued a warning on the risk of severe joint pain with DPP-4 inhibitors. This warning was based on 33 cases between 2006 and 2013. The joint pain occurred between 1 day to years after initial use, and symptoms were relieved after discontinuation of the DPP-4 inhibitor. Patients should not stop taking the drug if symptoms occur but should contact their health professional.

Similar to the GLP-1 RA class, there have been reports of increased risk of pancreatitis with DPP-4 inhibitors, but a causal relationship has not been established and individual, large, prospective studies have not shown an increased risk. A meta-analysis did show a small but statistically significant increased risk of pancreatitis with DPP-4 inhibitor use compared with placebo showing one to two cases of acute pancreatitis for every 1,000 patients treated for 2 years. Thus, pancreatitis appears to be an established yet rare safety concern with these agents.[64] Patients should be informed of the risk and appropriate monitoring should occur if a patient develops signs or symptoms of pancreatitis while taking a DPP-4 inhibitor.

DPP-4 plays an important role for T-cell activation. Theoretically, the inhibition of DPP-4 could be associated with adverse immunologic reactions. To date, however, there has been no evidence of clinically relevant changes in immune function.

There is no need to titrate the dose of DPP-4 inhibitors; however, renal dose adjustments are required for alogliptin, saxagliptin, or sitagliptin (Table 91-8).

Sodium-Glucose Cotransporter-2 Inhibitors

Four SGLT-2 inhibitors have been approved by the FDA including canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin, all of which are oral, once daily products. SGLT-2 inhibitors reduce plasma glucose by preventing the kidneys from reabsorbing glucose back into the bloodstream, leading to increased glucose excretion in the urine. By inhibiting SGLT-2, the renal tubular threshold for glucose reabsorption is lowered and glucosuria occurs at lower levels of plasma glucose concentrations. SGLT-2 inhibition lowers BG through an insulin-independent mechanism and exerts its glucose-lowering effect whenever the plasma glucose is elevated. Thus, SGLT-2 inhibitors can lower both FPG and PPG and are effective even in the absolute absence of insulin. Although SGLT-2 inhibitors block the reabsorption of 90% of the filtered glucose load, which could theoretically result in up to 170-g loss of glucose/day in the urine, urinary glucose excretion (UGE) does not exceed 75 to 85 g/day, because SGLT-1 begins to compensate and can reabsorb up to 30% to 40% of the filtered glucose load, when working at maximal capacity. Thus, when SGLT-2 is inhibited, SGLT-1 instantaneously can augment its reabsorption of glucose and blunt the glucosuric effect of the SGLT-2 inhibitor.

The SGLT-2 inhibitors are considered second-line therapies that can be added on to metformin or could be used in combination with other second-line agents. They are not currently recommended as first-line agents but can be used as monotherapy in patients who cannot tolerate or take first-line therapy. They are recommended by the ADA guidelines for many patient populations including those with established ASCVD or CKD, those with a compelling need to avoid hypoglycemia or a compelling need to avoid weight gain or induce weight loss. They are considered to have intermediate A1C lowering efficacy and reduce A1C by 0.5% to 1% (0.005 to 0.01; 6 to 11 mmol/mol Hb). They appear to be more efficacious in patients with higher baseline A1C levels. As eGFR declines, the amount of glucose that reaches the proximal tubule declines; thus, renal impairment decreases the efficacy of SGLT-2 inhibitors. Increased UGE leads to the loss of 200 to 300 kcal/day (840 to 1300 kJ/day), which may contribute to 1 to 5 kg of weight loss. The filtering of more glucose in the urine also causes an osmotic diuresis effect that can result in modest reductions in systolic BP by 3 to 4 mm Hg and diastolic BP by 1 to 2 mm Hg. Because of the insulin-independent mechanism, SGLT-2 inhibitors are unlikely to cause hypoglycemia unless combined with medications such as sulfonylureas, meglitinides, or insulin.

Large-scale, CV outcome trials have been completed for empagliflozin, canagliflozin, and dapagliflozin. Both empagliflozin and canagliflozin demonstrated benefit at reducing major adverse CV events (myocardial

infarction, stroke, or CV death).[60] In the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial, empagliflozin significantly reduced the risk of CV death, nonfatal myocardial infarction, and nonfatal stroke by 14% compared to placebo in patients with type 2 DM at high CV risk. Empagliflozin also reduced all-cause mortality by 32% and death from CV causes by 38%. Because of these results, empagliflozin is also FDA approved to reduce the risk of CV death in adults with type 2 DM and established CV disease. There was also a significant reduction in heart failure hospitalizations with empagliflozin compared to placebo and a reduction in the progression of renal disease.[65]

In the Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes (CANVAS) trial, canagliflozin reduced the risk of CV death, nonfatal myocardial infarction, and nonfatal stroke by 14% compared to placebo in patients with type 2 DM and high CV risk. There was also a significant reduction in heart failure hospitalizations with canagliflozin compared to placebo and a reduction in the progression of renal disease. No significant differences were seen between groups in CV death or all-cause mortality.[66]

In the Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes (DECLARE-TIMI 58) trial, dapagliflozin was noninferior (but not superior) to placebo with regards to the primary outcome of CV death, nonfatal myocardial infarction, and nonfatal stroke in patients with type 2 diabetes who had or were at risk for ASCVD. There was a significant reduction in heart failure hospitalizations with dapagliflozin compared to placebo and a reduction in the progression of renal disease, but no significant differences were seen between groups in CV death or all-cause mortality.[67]

Excess glucose in the urine is responsible for causing genital mycotic infections, the most common side effect of the SGLT-2 inhibitors. There is also a slightly increased risk of urinary tract infections. Genitourinary (GU) infections occur more frequently in women and uncircumcised men. In clinical trials, GU infections led to discontinuation in less than 1% of patients; most GU infections were treated and patients were able to continue the SGLT-2 therapy. Patients should be educated about the signs and symptoms of GU infections and the importance of proper personal hygiene.

SGLT-2 inhibitors can also cause polyuria, dehydration, dizziness, or hypotension due to the osmotic diuresis effects. Symptomatic hypotension may occur more frequently in patients with low baseline BP or an eGFR less than 60 mL/min/1.73 m^2. Concomitant diuretic use may increase the risk of orthostatic hypotension and electrolyte abnormalities. Patients should be monitored

carefully and dose or drug therapy adjustments may be needed. Older adults and patients with stage 4 or 5 chronic kidney disease are not optimal candidates for SGLT-2 inhibitors. Older adults typically have diminished renal function and, because they may have poor thirst response, they are predisposed to dehydration. The mechanism of action and osmotic diuresis with SGLT-2 inhibitors may affect several laboratory tests. LDL-C and HDL-C increase slightly with SGLT-2 inhibitors. Hemoconcentration from diuresis can result in a 2% to 3% increase in hematocrit. Urinalysis will always be positive for glucose due to the mechanism of action.

Other safety concerns that have been raised since SGLT-2 inhibitors have come to market include ketoacidosis, amputations, fractures, and Fournier gangrene. Several cases of ketoacidosis have been reported and meta-analyses have shown a small increased risk, although absolute numbers are small. Unlike the typical presentation of DKA, SGLT-2 inhibitor-related ketoacidosis presents uniquely, in that glucose levels typically do not go over 250 mg/dL (13.9 mmol/L) because of the increased UGE. Most cases have been in patients with type 1 DM, which is not a currently approved use by the FDA. Insulin-deficient patients (those with type 1 DM, LADA, or insulin-requiring type 2 DM) are at the highest risk, especially in the setting of decreased insulin use, increased insulin needs (acute illness or infection, surgery, trauma), or low-carbohydrate intake or dehydration. Patients should be well hydrated prior to treatment initiation, temporarily stop the drug if a serious illness is encountered, and should not decrease the insulin dose prospectively when it is initiated.

Canagliflozin was associated with an increased risk of bone fracture and lower limb amputations in the CANVAS trial. Many of the fractures were distal fractures of the upper extremities after a fall, and thus may be related to dizziness and orthostatic hypotension. Amputations are more common in patients with peripheral neuropathy, peripheral vascular disease, or prior amputations, so caution should be used in this patient population when considering SGLT-2 inhibitor therapy.

Use of SGLT-2 inhibitors has been associated with Fournier gangrene, a rare urological emergency characterized by necrotizing infection of the external genitalia, perineum, and perianal region. To date, 55 cases have been reported and, thus, causality has not been established.[68]

The SGLT-2 inhibitors should be initiated at a low dose. Volume status, adverse effects, and renal function should be assessed. The dose may be titrated in patients who are tolerating the drug well and require additional glucose control. Since the glucose-lowering effect of these medications is dependent on

renal function, it is not recommended to start or continue SGLT-2 therapy for the purpose of glucose lowering when the eGFR is consistently less than 45 mL/min/1.73 m^2. Use and dose recommendations vary between agents for patients with an eGFR between 45 and 60 mL/min/1.73 m^2 (Table 91-8).

α-Glucosidase Inhibitors

Currently, there are two *α*-glucosidase inhibitors approved by the FDA, acarbose, and miglitol, both of which are taken by mouth before meals. *α*-glucosidase inhibitors competitively inhibit maltase, isomaltase, sucrase, and glucoamylase in the small intestine, delaying the breakdown of sucrose and complex carbohydrates. There is no malabsorption of these nutrients, but merely a delay in their absorption. The net effect of this action is to reduce the PPG rise. Distal intestinal degradation of undigested carbohydrate by the gut flora results in gas, CO_2, and methane, as well as the production of short-chain fatty acids, which may stimulate GLP-1 release from intestinal L-cells.

The A1C lowering effects of the *α*-glucosidase inhibitors are modest. PPG concentrations are reduced by 40 to 50 mg/dL (2.2 to 2.8 mmol/L) while FPG levels are relatively unchanged. Patients near target A1C with near-normal FPG levels but high PPG levels are candidates for therapy. Due to their mechanism, GI side effects including flatulence, abdominal pain, and diarrhea are very common and limit their use. Because of the modest A1C effect and the high rates of unpleasant side effects, the ADA does not include the class on their treatment algorithm, but the AACE/ACE algorithm considers them an alternative option that can be used when other medications may be contraindicated or the patient has intolerances. To effectively lower PPG, *α*-glucosidase inhibitors must be taken three times a day with the first bite of each meal.

Meglitinides

Meglitinides are similar to sulfonylureas, except they have a faster onset and shorter duration of action. By binding to a site adjacent to the sulfonylurea receptor, nateglinide and repaglinide stimulate insulin secretion from the β-cells of the pancreas. As monotherapy, both nateglinide and repaglinide significantly reduce PPG excursions and reduce A1C by approximately 0.8% to 1% (0.008 to 0.01; 9 to 11 mmol/mol Hb). Similar to sulfonylureas, the main side effects are hypoglycemia and weight gain. Due to the lack of clinical evidence, their role in therapy is unclear. They are not recommended in the ADA algorithm and are

considered a less favorable choice on the AACE/ACE treatment algorithm. Nateglinide or repaglinide should be taken by mouth with each meal, initiated at a low dose, and titrated over time until glycemic control is achieved. These agents may be used in patients with renal insufficiency and may be a good option for those with erratic meal schedules. Multiple daily dosing may decrease adherence.

Bile Acid Sequestrants

The only bile acid sequestrant approved for the treatment of type 2 DM is colesevelam, an oral once daily medication. Colesevelam acts in the intestinal lumen to bind bile acid, decreasing the bile acid pool for reabsorption. The mechanism for glucose lowering is unclear as is its role in the treatment of type 2 DM. A1C lowering efficacy is modest. Colesevelam reduces LDL-C cholesterol in patients with type 2 DM by 12% to 16%. Colesevelam is weight neutral and has a low risk of hypoglycemia. Although colesevelam lowers plasma glucose and LDL-C, it has not been proven to prevent CV morbidity or mortality. Patients with type 2 DM who need a small reduction in A1C as well as additional LDL-C lowering may be candidates for this agent.

Dopamine Agonists

While bromocriptine has been used to treat Parkinson's disease and other disorders for decades, a new formulation, bromocriptine mesylate, was FDA approved for the treatment of type 2 DM. Bromocriptine used for type 2 DM is a quick release formulation of the dopamine agonist. The exact mechanism by which it improves glycemic control is unknown. Low hypothalamic dopamine levels, especially upon waking are augmented, which may decrease sympathetic tone and output. These effects are speculated to improve hepatic insulin sensitivity and decrease hepatic glucose output. The A1C lowering efficacy is modest and its role in the treatment of type 2 DM is unclear.

Amylin Analogs

Pramlintide is a synthetic analog of amylin, differing from amylin by three amino acids. It is given subcutaneously before meals and is used in patients currently treated with insulin. Pramlintide mimics the action of amylin, a neurohormone co-secreted from the β-cells with insulin and regulates glucose by three key mechanisms; reduces glucagon secretion, slows gastric emptying, and

increases satiety.

Pramlintide was the first noninsulin agent approved for patients with type 1 DM. Pramlintide is effective at lowering PPG levels and A1C and can be an attractive option for some patients as it can also decrease weight and may allow for lower mealtime insulin doses. Pramlintide lowers A1C by approximately 0.6% (0.006; 7 mmol/mol Hb) and produces an average weight loss of 1.5 kg in patients with type 2 DM. In patients with type 1 DM, the average reduction in A1C was 0.4% to 0.5% (0.004 to 0.005; 5 to 6 mmol/mol Hb). Pramlintide is primarily used in patients with type 1 DM as adjunctive therapy in patients who are not achieving PPG goals despite maximizing mealtime insulin doses.

The most common adverse effects associated with pramlintide are GI. Nausea occurs in approximately 20% of patients with type 2 DM and 40% to 50% of patients with type 1 DM. Vomiting or anorexia occurs in approximately 10% of patients. GI adverse effects decrease over time and are dose-related, thus starting with a low dose and slowly titrating as tolerated is recommended. Pramlintide alone does not cause hypoglycemia, but when used in patients on insulin hypoglycemia can occur. To minimize the risk of severe hypoglycemia, the dose of mealtime insulin should be empirically reduced by 30% to 50% when pramlintide is initiated.

Pramlintide dosing is different in patients with type 1 DM and type 2 DM. In type 2 DM, the starting dose is 60 mcg prior to meals and is titrated to the maximally recommended 120-mcg dose as tolerated and warranted based on PPG concentrations. In type 1 DM, dosing starts at 15 mcg prior to meals and can be titrated up in 15-mcg increments to a maximum of 60 mcg prior to each meal, if tolerated.

TREATMENT

Type 2 Diabetes

Hyperglycemia management in patients with type 2 DM should be patient-centered, using shared decision making and a stepwise approach. The treatment approach should place emphasis on compelling evidence, avoidance of unwanted adverse effects, and minimizing hypoglycemia and weight gain. Management decisions should focus on the impact on comorbidities in addition to the impact on glycemia. Upon diagnosis of type 2 DM, the clinician should assess key patient characteristics including current lifestyle, existing comorbidities, clinical characteristics including A1C, age, weight, presence or absence of symptoms, as well as motivation, cultural preferences, health literacy level, and cost

limitations. A patient-specific A1C target should be set and discussed with the patient.

Initial Therapy

Comprehensive lifestyle modifications (medical nutrition therapy [MNT], physical activity, weight loss, smoking cessation, and psychological support) should be implemented at the time of diagnosis and reinforced at every visit since they are the foundational components of diabetes management. To achieve lifestyle modification goals, all patients with type 2 DM should be offered access to ongoing DSME/S programs.

MNT should include improved diet quality and calorie restriction for weight loss or weight maintenance. There is no specific recommended ratio of macronutrients for type 2 DM. Instead, patients should focus on eating patterns that promote foods of demonstrated health benefits and minimize foods of demonstrated harm. All overweight or obese patients should be encouraged to participate in intensive lifestyle management programs to lose weight, with an initial weight loss goal of 5%. Increased physical activity should be encouraged in all patients with type 2 DM to improve glycemic control. Most adults should engage in at least 150 minutes of moderate or vigorous intensity aerobic physical activity spread over the week with no more than 2 consecutive days without activity.[29]

Patients with type 2 DM should consider the quantity, quality, and timing of carbohydrate intake in their diet as a strategy to minimize glucose excursions. Patients should increase carbohydrate intake from vegetables, fruits, legumes, whole grains, and dairy products and should decrease processed foods, refined carbohydrates (ie, foods made with white flour or sugar) or foods/drinks high in added sugar (eg, soda, candy).[29] Quantities of carbohydrates should be considered, although the scientific evidence for specific recommendations is lacking. Education materials often encourage patients to limit carbohydrate intake to no more than 60-75 grams/meal for men, 45-60 grams/meal for women and 15 grams/snack. An easier strategy is to limit the grain/starch of the meal to one-quarter of a 9-inch (23 cm) plate. Carbohydrate intake should be spread out across all meals and snacks.

9 In addition to comprehensive lifestyle modification, metformin should be started as first-line therapy in all patients who do not have contraindications or tolerability issues. This is based on the efficacy, safety, tolerability, cost, clinical evidence, and extensive experience with this medication. Metformin should be

started at a low dose and titrated to the maximum effective dose over time to improve tolerability.[31,32]

If a patient's initial A1C is close to goal (eg, ≤7.5% [0.075; 58 mmol/mol Hb]) and the patient is motivated to initiate lifestyle modifications, the clinician could consider initial treatment with lifestyle alone.[31] Since effectiveness of most oral medications rarely exceeds a 1% (0.01; 11 mmol/mol Hb) reduction in A1C, the clinician may consider starting two medications (metformin plus a second agent) if a patient's initial A1C is more than 1.5% (0.015; 16 mmol/mol Hb) higher than the target A1C.[32] Early introduction of basal insulin should be considered in patients with very high A1C levels (>10% [0.10; 86 mmol/mol Hb), those with symptoms of hyperglycemia, or those with evidence of catabolism (eg, weight loss).[32]

To avoid therapeutic inertia, treatment should be reassessed and modified regularly. Patients not meeting their goals should be seen at least every 3 months. Those that are meeting their goals should be seen at least every 6 months. At these points of reassessment, an A1C level should be drawn, medication adherence should be evaluated, and lifestyle recommendations should be reinforced. If glucose targets have not been met, additional therapy should be added.[31,32]

Stepwise Addition of Medications

10 Type 2 DM is a progressive disease, and the majority of patients will eventually require combination therapy. A stepwise approach is recommended. For patients who have been maximized on metformin therapy and have A1C levels above the target, a second-line antihyperglycemic agent should be added. However, there is no clear-cut second-line agent that should be used. The ADA Standards of Care identify six drug classes to consider in addition to metformin: DPP-4 inhibitors, GLP-1 RAs, SGLT-2 inhibitors, sulfonylureas, thiazolidinediones, and basal insulin.[31] Patient-specific factors to consider when selecting a medication include the individualized A1C target and presence of specific comorbidities (eg, ASCVD, heart failure, CKD, obesity). Drug-specific factors to consider include glucose-lowering efficacy, impact on other comorbidities, impact on weight and hypoglycemia risk, side effect profile, ease of use, and cost (**Table 91-10**).[31,32]

TABLE 91-10 Considerations When Selecting Pharmacotherapy for Type 2 Diabetes

Medication class	Primary Physiologic Action	A1C Reduction Efficacy	Hypoglycemia Risk[a]	Effect on Weight	ASCVD Effects	Cost	Oral/SC	Adverse Effects and Safety
Metformin	↓ hepatic glucose production	High	No	Neutral	Potential benefit	Low	Oral	GI (diarrhea), B12 deficiency
SUs	↑ insulin secretion	High	Yes	Gain	Neutral	Low	Oral	Hypoglycemia, weight gain
TZDs	↑ insulin sensitivity	High	No	Gain	Potential benefit (pioglitazone)	Low	Oral	Edema, weight gain, risk of heart failure, bone fractures, bladder cancer
DPP-4 inhibitors	↑ insulin secretion (glucose dependent); ↓ glucagon secretion (glucose dependent)	Intermediate	No	Neutral	Neutral	High	Oral	Risk of heart failure, pancreatitis, joint pain
SGLT-2 inhibitors	Blocks glucose reabsorption by the kidney, increasing glucosuria	Intermediate	No	Loss	Benefit[b] (empagliflozin, canagliflozin)	High	Oral	GU infections, risk of volume depletion, hypotension, risk of amputations, bone fractures (canagliflozin), risk of DKA
GLP-1 RAs	↑ insulin secretion (glucose dependent); ↓ glucagon secretion (glucose dependent); slows gastric emptying; ↑ satiety	High	No	Loss	Benefit[b] (liraglutide, semaglutide dulaglutide)	High	SC/ Oral	GI (nausea, vomiting), injection site reactions, risk of thyroid C-cell tumors, pancreatitis, cholelithiasis
Basal Insulin	↑ glucose disposal; ↓ hepatic glucose production; suppresses ketogenesis	High	Yes	Gain	Neutral	High	SC	Hypoglycemia, weight gain, injection site reactions

ASCVD, atherosclerotic CV disease; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; DPP, dipeptidyl peptidase; GI, gastrointestinal; GLP, glucagon-like peptide; GU, genitourinary; RA, receptor agonist; SC, subcutaneous; SGLT, sodium-glucose co-transporter; SU, sulfonylurea; TZD, thiazolidinedione.

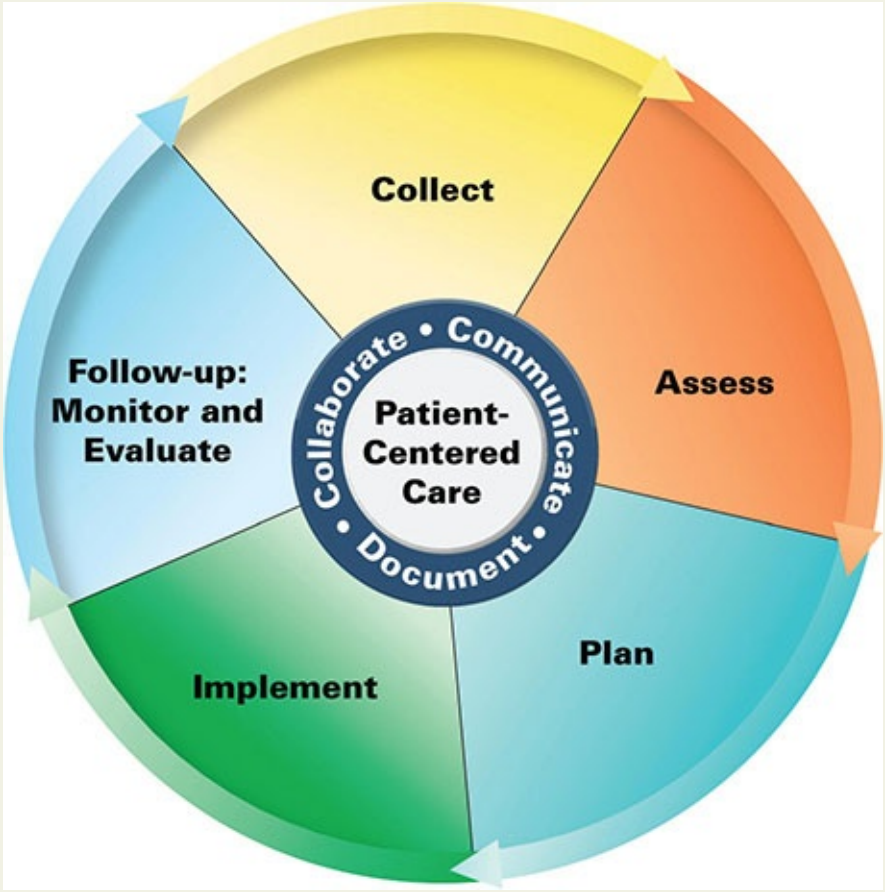
[a]When used as monotherapy.

[b]Specific drugs listed as beneficial are based on current available evidence. It is not clear whether the benefit is a class effect.

Because of evidence from CV outcome trials, SGLT-2 inhibitors or GLP-1

RAs with proven CV benefit are recommended as compelling agents in patients with established ASCVD or CKD. Currently, liraglutide (GLP-1 RA) and empagliflozin (SGLT-2 inhibitor) demonstrated a reduction in major adverse CV events and CV mortality and both have a label indication of reducing CV events. Semaglutide (SC), dulaglutide (GLP-1RAs) and canagliflozin (SGLT-2 inhibitor) demonstrated a reduction in major adverse CV events but did not reduce CV mortality.[31] Among patients with ASCVD, if HF coexists, SGLT-2 inhibitors with a proven benefit of reducing HF progression (empagliflozin, canagliflozin, dapagliflozin) are recommended. In patients with CKD, with or without ASCVD, SGLT-2 inhibitors with a proven benefit of reducing CKD progression (empagliflozin, canagliflozin, dapagliflozin) are recommended. TZDs should be avoided in patients with HF. If the A1C target is not achieved after 3 months of dual therapy or if the patient did not tolerate the selected drug, then triple therapy is warranted and a drug from the other class can then be added.[32]

In those without established ASCVD or CKD, other considerations should be taken into account. If there is a compelling need to minimize weight gain or promote weight loss, GLP-1 RAs or SGLT-2 inhibitors are preferred. GLP-1 RAs have demonstrated varying amounts of weight loss in clinical studies, with the greatest weight loss seen with semaglutide followed by liraglutide, dulaglutide, exenatide, and lixisenatide (Table 91-9). If dual therapy does not achieve glycemic control, a drug from the other class can be added. If a GLP-1 RA or an SGLT-2 inhibitor cannot be used, a weight-neutral medication such as a DPP-4 inhibitor can be selected. Sulfonylureas, insulin, and TZDs are not preferred and should be used cautiously due to weight gain. If there is a compelling need to minimize hypoglycemia, DPP-4 inhibitors, GLP-1 RAs, SGLT-2 inhibitors, or TZDs could be added to metformin. If dual therapy does not achieve glycemic control, a drug from a different recommended class can be added. DPP-4 inhibitors and GLP-1 RAs should not be used together due to similar physiologic actions. Basal insulin and sulfonylureas are not preferred in this setting as they increase the risk of hypoglycemia and should be considered only if necessary and used with caution. If there is a compelling need to minimize cost, sulfonylureas or TZDs can be considered.[32]



Patient Care Process for the Management of Diabetes Mellitus

Collect

- Patient characteristics (eg, age, race, sex, pregnant)
- Characteristics of diabetes (eg, type, age of onset, initial presentation)
- Microvascular and macrovascular complications
- Hypoglycemia episodes, symptoms, frequency, and suspected cause(s)
- History of diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic syndrome (HHS)—frequency, severity, and suspected cause(s)
- Patient history (past medical, family, social—dietary habits, weight history, sleep behaviors, physical activity)
- Current medications (including complementary and alternative therapies) and medication-taking behaviors (eg, adherence, injection technique)
- Past diabetes treatments, response to therapy, reason for discontinuation
- Diabetes and nutritional education (currently enrolled and completed)

- SMBG results and self-management behaviors
- Social and cultural issues—preferences, values, and beliefs; health literacy
- Physical exam: height, weight, BMI, blood pressure, heart rate, comprehensive foot exam
- Labs (eg, glucose, A1C, Scr, BUN, eGFR, fasting lipid panel, urinary albumin/Cr ratio, serum electrolytes)

Assess

- Diagnosis and classification (see Tables 91-1, 91-3, and 91-4)
- Microvascular and macrovascular complications and potential comorbid conditions
- Achievement of A1C and glycemic goals (see Table 91-6)
- Appropriateness, effectiveness, safety/tolerability, treatment burden, cost, and adherence to current antihyperglycemic regimen
- Achievement of weight, lifestyle, and other behavioral goals
- Achievement of goals for comorbidities (eg, blood pressure, lipids, neuropathic pain)
- Screen for depression, anxiety, disordered eating
- Screen for psychosocial problems and barriers to diabetes self-management

Plan*

- Set appropriate A1C and glycemic goals based on age, comorbidities, and other factors (see Table 91-6)
- Tailored lifestyle modifications (eg, diet, exercise, weight management)
- Drug therapy regimen including specific antihyperglycemic agent(s), dose, route, frequency, and duration; specify continuation and discontinuation of existing therapies (see Tables 91-7, 91-8, 91-9, and 91-10)
- Monitoring parameters including efficacy (eg, A1C, SMBG), safety (medication-specific adverse effects, hypoglycemia), and timeframe (see Table 91-10)
- Patient education (eg, purpose of treatment, drug administration, dietary and lifestyle modification)
- Referrals to other providers when appropriate (eg, diabetes educator,

registered dietician, eye care professional, podiatrist, mental health professional)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up including telehealth visits to monitoring and adjust treatment

Follow-up: Monitor and evaluate

- Determine A1C and glycemic goal attainment
- Presence of medication-related adverse effects (see Table 91-10)
- Occurrence/development/progression of diabetes-related complications
- Patient adherence to treatment plan using multiple sources of information

** Collaborate with patient, caregivers, and other healthcare professionals.*

Addition of Injectable Medications

The approach to insulin use in type 2 DM is quite different than in type 1 DM. People with type 1 DM initiate intensive insulin regimens shortly after diagnosis and require basal and prandial insulin to achieve glycemic control. People with type 2 DM can often be managed with oral medications for years before the addition of insulin is needed. Insulin is recommended for patients with extreme (A1C>10% [0.10; 86 mmol/mol Hb]) or symptomatic hyperglycemia. Otherwise, GLP-1 RAs are preferred over insulin by the ADA as the first injectable agent. GLP-1 RAs have demonstrated equal or superior A1C lowering efficacy compared to basal insulin and lead to weight loss instead of weight gain with a low risk of hypoglycemia. Most GLP-1 RAs are started at a low dose and titrated slowly to improve tolerability. If additional glucose lowering is needed after the GLP-1 RA dose has been maximized, basal insulin can be initiated. Switching to a fixed-ratio combination of GLP-1 RA plus basal insulin could be considered as well. Basal insulin is started at a low dose (10 units once daily or 0.1-0.2 units/kg/day) and titrated slowly over time to a target FPG range. Many titration strategies are used in clinical practice. A common method is the 3-0-3 method where the patient checks FPG levels daily for 3 days and calculates the

average of those three readings. If the average is greater than 130 mg/dL (7.2 mmol/L) then the patient increases the dose by 3 units. The patient continues this titration until achieving target FPG levels (ie, 80-130 mg/dL [4.4-7.2 mmol/L] for patients targeting an A1C<7% [0.07; 53 mmol/mol Hb]) or until they've reached a basal insulin dose of 0.7-1.0 units/kg/day. If unexplained hypoglycemia occurs, the dose is decreased by 3 units. If the A1C target is not reached by maximally titrating basal insulin, it indicates that PPG levels are likely elevated. Thus, at that point, a medication that lowers PPG can be considered. GLP-1 RAs or SGLT-2 inhibitors should be considered if the patient is not already taking one. Prandial insulin is also an option. A stepwise approach is recommended when initiating prandial insulin; starting with 4 units or 10% of the basal dose with the largest meal of the day. If the A1C is < 8% (0.08; 64 mmol/mol Hb), the basal dose can be decreased by the same amount to avoid hypoglycemia. The dose should be titrated over time to achieve target PPG levels <180 mg/dL (10.0 mmol/L). A second or third injection can be added to the other meals if needed. The addition of prandial insulin requires more SMBG and patient knowledge and awareness of the relationship between insulin and carbohydrates. It also increases the risk of hypoglycemia and weight gain.[32]

It is important to re-evaluate the appropriateness of oral medications when a patient starts injectable agents. GLP-1 RAs can be used in combination with all oral agents except DPP-4 inhibitors. When insulin is started, metformin should be continued. TZDs should be stopped or the dose should be reduced. Sulfonylureas should be stopped or the dose should be reduced, especially if prandial insulin is initiated. SGLT-2 inhibitors can be continued, although the patient should be educated about the risk of DKA and DPP-4 inhibitors can be continued.[32]

AACE guideline recommendations

Several other organizations such as the AACE also offer guidance for hyperglycemia management. The ADA and AACE guidelines are similar, in that they both recommend a stepwise approach to treatment, with lifestyle modifications and metformin as first-line therapy, followed by the addition of medications from other classes. The AACE guidelines recommend a more aggressive A1C target (<6.5% [0.065; 48 mmol/mol Hb]) for most patients. Dual therapy is recommended initially for any patient with an A1C>7.5% (0.075; 58 mmol/mol Hb) and insulin is recommended for patients with an A1C>9% (0.09; 75 mmol/mol Hb). Finally, the AACE treatment algorithm lists drugs in order of

preference with a focus on minimizing hypoglycemia, weight gain, and other adverse effects.[27]

TREATMENT

Type 1 Diabetes

11 Due to the absolute deficiency of endogenous insulin in people with type 1 DM, exogenous insulin therapy is a requirement. Achieving adequate glycemic control in type 1 DM usually requires intensive insulin therapy. Intensive insulin regimens are designed to provide insulin in a manner that mimics normal physiologic insulin secretion (**Fig. 91-5**), with consistent secretion of basal insulin throughout the day to manage glucose levels overnight and in between meals (ie, basal insulin), and bursts of insulin in response to glucose rises after the ingestion of carbohydrates (ie, prandial insulin).

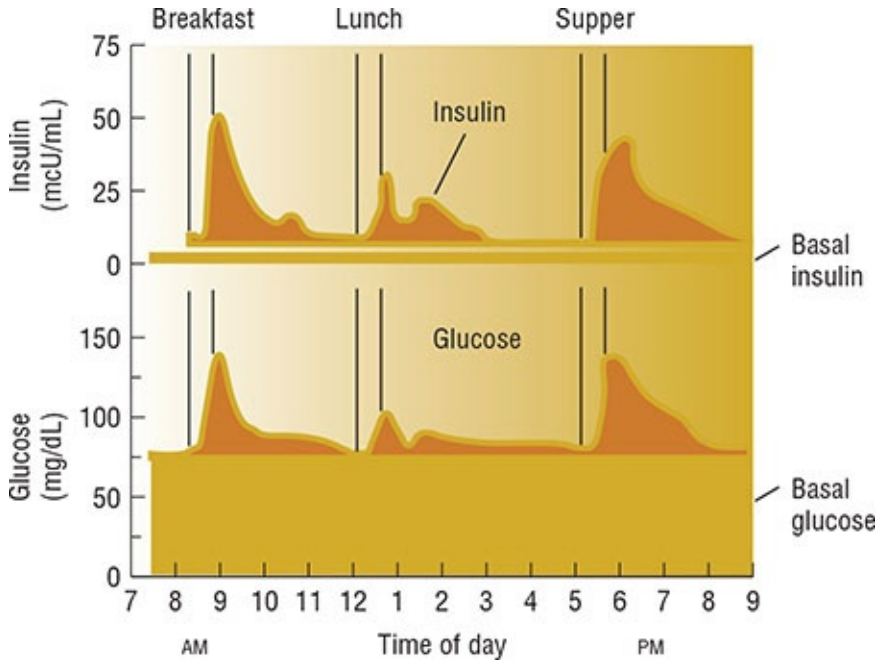


FIGURE 91-5 Relationship between insulin and glucose over the course of a day. Blood glucose values in mg/dL can be expressed in mmol/L by multiplying by 0.0555.

The ADA Standards of Care indicate that most people with type 1 DM should be treated with intensive insulin regimens, either multiple daily injections (MDI) or use of continuous subcutaneous insulin infusion (CSII) via an insulin pump.[31] The choice of which delivery method to use should be tailored to the individualized needs and preferences of the person with type 1 DM. Intensive

insulin therapy is complex because it requires multiple injections or pump boluses per day in addition to basal insulin, routine monitoring, and collaborative decision making. The most successful in therapy is delivered and adjusted based on changes in nutritional intake, glucose levels, stress, and physical activity.

Examples of intensive insulin regimens are portrayed in **Fig. 91-6**. A common MDI approach is one injection of long-acting insulin (eg, insulin glargine U-100) to provide the basal component and three injections of rapid-acting insulin (eg, insulin lispro U-100) to provide the prandial component. This regimen utilizes insulin products with more ideal PK properties, but cost can be prohibitive. A less expensive option consists of two injections of intermediate-acting insulin (eg, NPH insulin) and two injections of short-acting insulin (eg, regular insulin). However, the ADA Standards of Care recommend that most individuals with type 1 DM should use rapid-acting insulins as opposed to regular insulin to reduce the risk of hypoglycemia.[31]

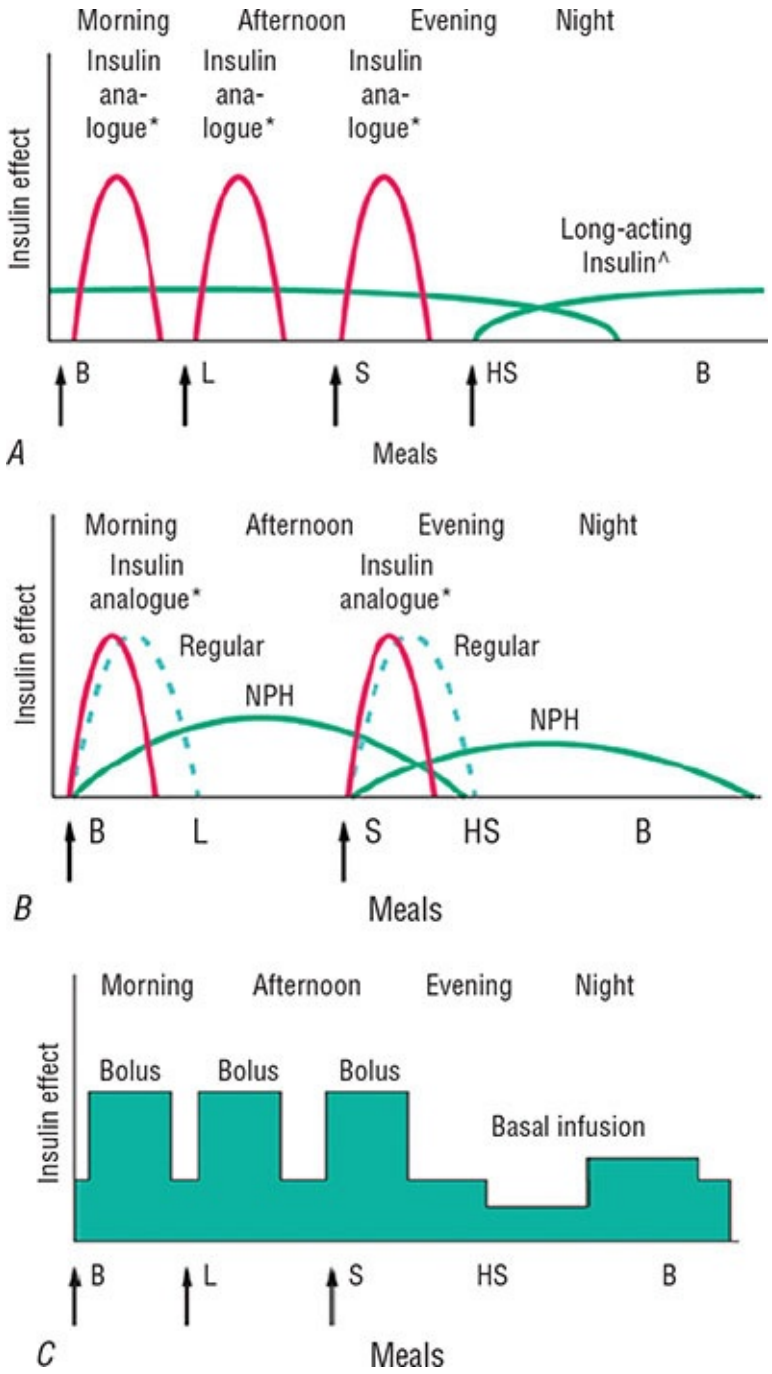


FIGURE 91-6 Common insulin regimens. (A) Multiple-component insulin regimen consisting of one injection of long-acting insulin (^detemir, glargine, degludec) to provide basal glycemic coverage and three injections of rapid-acting insulin (*aspart, lispro, glulisine) to provide glycemic coverage for each meal. (B) Insulin regimen consisting of two injections of intermediate-acting insulin (NPH) and rapid-acting insulin (*aspart, lispro, glulisine [solid red line]), or short-acting regular insulin (green dashed line). Only one formulation of short-acting insulin is used. (C) Insulin administration by insulin infusion device.

The basal insulin rate is decreased during the evening and increased slightly prior to the patient awakening in the morning. Rapid-acting insulin (aspart, lispro, or glulisine) is used in the insulin pump. (*Reproduced, with permission, from Lebovitz HE, ed. Therapy for Diabetes Mellitus and Related Disorders. 4th ed. Alexandria, VA: American Diabetes Association; 2004.*)

Insulin pump therapy or CSII infuses rapid-acting insulin to cover both the basal and prandial insulin needs. The pump infuses a basal rate constantly throughout the day and allows the patient to give bolus doses using a bolus dose calculator based on current glucose levels, carbohydrate intake, and insulin on board. Insulin pump therapy can provide more precise glucose control and allow more flexibility and fine-tune tailoring. However, CSII requires significant patient education and support and both MDI and CSII can achieve good glycemic control. Insulin pump technology is advancing quickly with new generation devices entering the market regularly.

When initiating insulin therapy in someone with newly diagnosed type 1 DM, the starting dose is typically 0.4 to 1.0 units/kg/day of total insulin. The total daily dose of insulin is then divided to give 50% as basal insulin and 50% as prandial insulin (distributed across meals). As an example; an 80 kg patient initiated on 0.5 units/kg/day would start with a total daily dose of 40 units. He could be initially prescribed 20 units of a long-acting insulin such as insulin detemir or glargine and 7 units of rapid-acting insulin, such as insulin aspart, lispro, or glulisine, with breakfast, lunch, and dinner. The insulin doses would then be adjusted based on SMBG data.

The above example provides a starting point, but there is no one gold standard for starting insulin in patients with type 1 DM. Ideally, patients with type 1 DM should learn how to count carbohydrates so they can match their prandial insulin doses to their carbohydrate intake. Patients should also SMBG before each meal or use CGM to evaluate the insulin regimen and make treatment decisions. Bolus insulin doses can be better individualized by using carbohydrate to insulin ratios (C:I ratios) and correction factors (CF). The C:I ratio is used to estimate how many grams of carbohydrate each unit of rapid-acting insulin will cover. A typical C:I ratio for a patient with type 1 DM is 15:1, meaning that 1 unit of rapid-acting insulin will cover 15 grams of ingested carbohydrates. An initial C:I ratio can be estimated by dividing 550 by the total daily dose of insulin the patient is taking. For example, if a patient was taking 40 units of insulin total per day, then his initial C:I ratio would be 550/40 = 14:1.

The CF is used to reduce high glucose levels detected before meals; it is the expected amount that one unit of insulin will decrease the BG under normal

circumstances. The initial CF is estimated by dividing 1650 by the total daily dose. For example, if a patient was taking 40 units of insulin per day, then his CF would be 1650/40 = 41 (which would likely be rounded to 40 for easier use). Once the patient has a C:I and CF established, he can use these before each meal to calculate a specific premeal dose of rapid-acting insulin. For the example above, if the patient expected to eat 60 grams of carbohydrates, had a premeal glucose reading of 200 mg/dL (11.1 mmol/L), and a target glucose of 100 mg/dL (5.6 mmol/L), he would take 7 units of rapid-acting insulin (60/14 = 4.3 units for the carbohydrates and 100/40 = 2.5 units for the correction).

It's important to note that the 550 rule and 1650 rule to calculate the C:I and CF are not well studied and, in clinical practice, some clinicians use 500 instead of 550 and others use 1500 or 1800 instead of 1650. Regardless, these calculations provide an initial C:I and CF values that must be re-evaluated and adjusted over time based on glucose monitoring data.

Lifestyle modifications differ between type 1 DM and type 2 DM. Patients with type 2 DM are often encouraged to "count carbs" as a way to prevent glucose excursions after meals. This involves limiting carbohydrates to 45-75 grams/meal or limiting starches/grains to one-quarter of a 9-inch (23 cm) plate. Patients with type 1 DM count carbs in order to match their prandial insulin dose with their carbohydrate intake using a C:I ratio. To be successful, this requires much more accurate estimations of carbohydrate content than what is needed for type 2 DM management.

Adjunctive Therapy

Pramlintide is an amylin agonist indicated as adjunctive treatment in patients with type 1 DM who are not achieving glycemic targets despite optimization of mealtime insulin. Pramlintide is discussed in more detail earlier in this chapter. In this setting, pramlintide may improve glycemic control and minimize weight gain caused by insulin. However, its use is limited by adverse effects such as nausea and vomiting, modest glucose improvements, increased injections and cost, and increased risk of hypoglycemia. Several other medications have been used off-label and/or are being studied currently as adjunctive therapy in type 1 DM, including the SGLT-2 inhibitors and GLP-1 RAs.

Glucose Monitoring

Similar to patients with type 2 DM, patients should be reassessed every 3 to 6 months (3 months if uncontrolled and 6 months if controlled). An A1C should be

drawn and treatment should be adjusted as needed.[17]

Patients on intensive insulin therapy should SMBG at least four times daily; before meals and at bedtime. Patients should also test before exercise, prior to critical tasks such as driving, and if symptoms of hypoglycemia occur. SMBG is crucial during times of intercurrent illness to detect and prevent DKA. Patients may also benefit from occasionally testing 2 hours after meals.[17]

Continuous glucose monitors report interstitial glucose levels in real time and provide insight into glucose trends. These devices can be used for insulin dosing and some are integrated with insulin pumps. CGM use with intensive insulin therapy can reduce A1C and reduce glucose variability in patients with type 1 DM. Current guidelines recommend CGM in patients with type 1 DM who are not meeting glycemic goals. They are also recommended in patients with hypoglycemia unawareness to better detect and prevent hypoglycemic events.[17]

HYPOGLYCEMIA

Hypoglycemia is a common complication of some diabetes medications including insulin, sulfonylureas, and meglitinides and a major limiting factor to optimal glycemic control. Hypoglycemia can range in severity and is classified as level 1 (hypoglycemia alert value; ≤70 mg/dL [3.9 mmol/L]) which may not cause symptoms but is sufficiently low that it should be treated with a fast-acting carbohydrate and may need a dose adjustment of glucose-lowering therapy, level 2 (clinically significant hypoglycemia; < 54 mg/dL [3.0 mmol/L]) which is sufficiently low to indicate serious, clinically important hypoglycemia, and level 3 (severe hypoglycemia) which is associated with cognitive impairment requiring external assistance for recovery and can be life threatening.[17] Hypoglycemia is associated with falls, injury, motor vehicle accidents, decreased quality of life, and increased risk of CV events, QT prolongation, arrhythmias, and death. Recurrent hypoglycemia increases the risk of developing dementia, and the degree of cognitive impairment has been associated with the frequency and severity of hypoglycemia. All patients taking medications that can cause hypoglycemia should be educated about the prevention, detection, and treatment of hypoglycemia. SMBG is essential to detecting hypoglycemia and taking appropriate action.

Patients can present with a variety of symptoms during an episode of hypoglycemia. Initial autonomic symptoms can include tachycardia, palpitations, sweating, tremors, and hunger. It is important to note that beta-blockers may mask some of these early symptoms. Neuroglycopenic symptoms often occur

when the BG is <60 mg/dL (3.3 mmol/L) and can include cognitive impairment, confusion, behavioral changes, anger, irritability, blurred vision, headaches, seizures, and loss of consciousness. It is important for patients to self-monitor their BG when symptoms occur to confirm that the glucose is <70 mg/dL (3.9 mmol/L).

Some patients may experience hypoglycemia unawareness, defined as the asymptomatic onset of hypoglycemia. These patients are unable to detect the early warning symptoms of hypoglycemia and are thus at increased risk for the serious sequelae associated with severe hypoglycemia. Patients with hypoglycemia unawareness are typically those with longstanding disease, more stringent glycemic control, and frequent hypoglycemia. These patients should check their BG levels prior to any activities that require them to be alert and oriented (e.g., driving). CGM can be particularly helpful to identify hypoglycemic events in patients with hypoglycemia unawareness. Also, temporarily raising glucose targets may reverse hypoglycemia unawareness.

Prevention of hypoglycemic events is a critical component of diabetes management. SMBG can be helpful, but may not be frequent enough to identify hypoglycemia. CGM can be particularly useful in preventing hypoglycemia since it provides the patient with glucose trends which patients can use to adjust their management decisions prior to becoming hypoglycemic. Patients must be educated to understand situations that increase their risk of hypoglycemia, including delaying meals, during or after exercising, or fasting for blood tests or procedures.

Treatment of hypoglycemia dictates ingestion of carbohydrates. Glucose is preferred. Patients should be counseled to carry a source of fast-acting glucose with them at all times. The “rule of 15” is commonly used to teach patients the proper treatment. First, the patient should SMBG to confirm a glucose < 70 mg/dL (3.9 mmol/L) and then ingest 15 grams of fast-acting carbohydrates (1/2 cup [125 mL] of milk, juice, or soda, 1 tablespoon of honey, hard candy, jelly beans, or glucose tablets equivalent to 15 grams of carbohydrates). Foods that include protein or fat should not be used acutely to treat hypoglycemia due to the delayed absorption of glucose. SMBG should be repeated in 15 minutes; if the glucose is <70 mg/dL (3.9 mmol/L), the process should be repeated. Once the BG is normalized, the patient should eat a snack or meal that includes complex carbohydrates and protein to prevent further hypoglycemic episodes.

If the patient is unconscious, IV glucose or glucagon (either via the intramuscular or intranasal route) should be given. Glucagon increases glycogenolysis in the liver and may be given in any situation in which IV

glucose cannot be rapidly administered. A glucagon product should be prescribed and readily available to all patients on insulin who have a history of severe hypoglycemia or at high risk for such events. Family and close friends of the patient should be educated regarding the preparation and administration of glucagon. The traditional glucagon kit requires reconstitution and an intramuscular injection of glucagon. It can take 10 to 15 minutes for the injection to start raising glucose levels and patients often vomit. It is important to position the patient on the side with the head tilted slightly downward to avoid aspiration. Two new glucagon products have been recently approved that may provide an easier option for glucagon administration; a pre-filled syringe that is still administered intramuscularly but does not require reconstitution and a dry powder nasal spray that is administered intranasally.

Finally, clinicians should monitor hypoglycemia at every visit. This involves asking the patient about the frequency, severity, and timing of hypoglycemic events, the need for assistance by a third party, or the need to administer glucagon. Patients experiencing frequent or severe hypoglycemia should have their treatment regimen re-evaluated with a goal of minimizing hypoglycemia.

COMPLICATIONS AND COMORBIDITIES

Achieving good glycemic control is important to reduce the risk of both short-term and long-term complications in patients with type 1 or type 2 DM.[15] Short-term complications include symptoms of excessive urination, fatigue, and weight loss. In patients who are ketosis-prone, sustained elevations of BG above 200 to 300 mg/dL (11.1 to 16.7 mmol/L) can lead to DKA, a potentially life-threatening condition that often requires hospitalization to receive IV fluids and electrolytes. Even in patients who are not prone to ketosis, prolonged periods of poor glycemia can lead to HHS. Poor glycemic control can lead to an increased risk of soft-tissue and urinary tract infections, even in the short-term. Long-term complications are the result of vascular and tissue damage. Long-term complications include atherosclerotic cardiovascular disease (ASCVD) leading to CV events, nephropathy often resulting in renal insufficiency, retinopathy potentially leading to vision loss, and neuropathy that can cause a wide variety of debilitating symptoms. The combination of vascular damage, peripheral nerve dysfunction, and a diminished immune response significantly increase the risk of toe, foot, and leg amputations in patients with diabetes. Males with diabetes are more prone to developing erectile dysfunction. In short, diabetes can negatively impact nearly every organ system throughout the body and therefore a very

comprehensive approach to patient monitoring is required.

Diabetic Ketoacidosis

DKA is a true medical emergency.[69] In patients with type 1 DM, ketoacidosis is usually precipitated by the patient omitting insulin, or acute illness with a subsequent increase in counter-regulatory hormones such as cortisol, catecholamines, glucagon, and growth hormone. Infection is a common cause of DKA and should be thoroughly explored. Patients with DKA may be alert, stuporous, or comatose at presentation. The hallmark diagnostic laboratory values for DKA include hyperglycemia, anion gap acidosis, and large ketonemia or ketonuria.

Patients with DKA have fluid deficits of several liters as well as significant sodium and potassium deficits.[69] Restoration of intravascular volume with normal saline, followed by hypotonic saline to replace free water, potassium supplements, and insulin given by continuous IV infusion to restore the patient's metabolic status are the cornerstones of therapy. Constant infusion of a fixed dose of insulin and the administration of IV glucose when the BG level decreases to less than 250 mg/dL (13.9 mmol/L) is preferable to titration of the insulin infusion based on the glucose level. The latter strategy may delay clearance of the ketosis and prolong treatment. Rapid correction of the glucose, a drop greater than 75 to 100 mg/dL/h (4.2-5.6 mmol/L/h), is not recommended because it has been associated with cerebral edema, especially in children. The insulin infusion should be continued until the urine ketones clear and the anion gap closes. Intramuscular regular insulin or subcutaneous insulin lispro or aspart given every 1 to 2 hours can be used rather than an insulin infusion in patients without hypoperfusion. Long-acting insulin should be given 1 to 3 hours prior to discontinuing the insulin infusion. Hourly bedside monitoring of glucose and frequent monitoring (every 2-4 hours) of potassium is essential.

Treatment with bicarbonate to correct the acidosis is generally not needed and may be harmful, especially in children.[69] Treatment of the inciting medical condition is also vital. Metabolic improvement is manifested by an increase in the serum bicarbonate or pH. Serum phosphorus usually starts high and plummets to lower-than-normal levels. However, replacing phosphorus is of questionable benefit. Fluid administration alone will reduce the glucose concentration, so a decrement in glucose values does not necessarily mean that the patient's metabolic status is improving. Patients may develop hyperchloremic metabolic acidosis with treatment if they have been given large volumes of

normal saline in the course of their treatment. However, this does not require any specific treatment. A flow sheet is helpful for tracking the fluid and insulin therapies and laboratory parameters in these patients.

Hyperosmoslar Hyperglycemia State

HHS is potentially life-threatening acute complication of diabetes associated with very high glucose concentrations, typically greater than 400 mg/dL (22.2 mmol/L).[69] It most often occurs in older patients with type 2 DM or in younger patients with prolonged hyperglycemia and dehydration or significant renal insufficiency. Occasionally, patients with previously undiagnosed type 2 DM present with HHS. Patients with DKA and HHS present quite similarly but typically patients with HHS have much higher plasma glucose, elevated serum osmolality, and little to no ketonuria or ketonemia. HHS typically evolves over several days to weeks, whereas DKA evolves much quicker. Large ketonemia is usually not seen because residual insulin secretion suppresses lipolysis. However, ketones from prolonged fasting may be present. Infection or another medical illness is the usual precipitant. Fluid deficits are often greater and BG concentrations higher—sometimes greater than 1,000 mg/dL (55.5 mmol/L)—in patients with HHS when compared to patients with DKA. BG should be lowered very gradually with hypotonic fluids and low-dose insulin infusions (1-2 units/h). Mortality is high with HHS.

Macrovascular Complications

12 Macrovascular complications are the leading cause of death in people with diabetes. The risk for coronary heart disease (CHD) and ischemic stroke is two to four times greater in patients with diabetes when compared to individuals without diabetes.[70] CV disease is the leading cause of mortality in patients with DM. Addressing CV risk factors—lipids, hypertension, smoking cessation, and antiplatelet therapy—will reduce macrovascular events. The ADA recommends low-dose aspirin therapy (75–162 mg daily) in all patients who have established ASCVD. If the patient is allergic to aspirin, clopidogrel may be used. The role of antiplatelet therapy for the primary prevention of a CV event in patients with diabetes is unclear. While low-dose aspirin reduces the risk of vascular events, in adults who do not have established ASCVD, the benefits are offset by a higher risk of major bleeding.[71] Some clinical practice guidelines recommend aspirin therapy if the 10-year risk of a CV event is greater than 20%.

In patients with diabetes and established ASCVD, the use of a GLP1-RA or an SGLT2 inhibitor should be strongly considered.[72] Several agents in these two classes of medications have been shown in clinical trials to reduce the risk of major cardiovascular adverse events in patients with a history of coronary artery disease, myocardial infarction, ischemic stroke, or peripheral artery disease and those at very high risk of vascular events with multiple ASCVD risk factors in addition to diabetes. The SGLT2 inhibitors, specifically empagliflozin, canagliflozin, and dapagliflozin, significantly reduce the risk of hospitalization due to heart failure. Therefore, this class might be preferred in patients with pre-existing heart failure or those who are at high risk of developing heart failure due to structural heart disease. The GLP1-RA liraglutide and the SGLT2 inhibitor empagliflozin significantly reduced the risk of cardiovascular death and all-cause mortality—many experts consider these agents to be the preferred choices in these two classes based on this compelling data.

Following a myocardial infarction, β-blocker therapy protects patients with diabetes from recurrent CHD events, and the magnitude of benefit is greater than that seen in patients without diabetes.[73] While the adrenergic symptoms produced by hypoglycemia (eg, tachycardia, tremor) can be masked by β-blockers, sweating and neuroglycopenic symptoms are not. Therefore, β-blockers should not be avoided in patients with diabetes if there is a compelling indication to use them.

13 High blood pressure increases the risk of both microvascular and macrovascular complications in patients with DM.[70] The ADA recommends dietary changes, specifically the Dietary Approaches to Stop Hypertension (DASH), and increased physical activity be instituted for all patients whose BP exceeds 120/80 mm Hg. Weight loss is also recommended in those patients who are overweight or obese. Pharmacological therapy, preferably using a class of agents proven to reduce CV event rates, should be instituted if the patient's confirmed office-based BP exceeds 140/90 mm Hg. A combination of two medications should be used if the blood pressure exceeds 160/100 mm Hg. The ADA recommended thresholds and targets for treatment are slightly different than those recommended by the American College of Cardiology/American Heart Association guidelines.[74] While epidemiological data and clinical trials support a blood pressure target less than 130/80, studies that used intensive BP targets often excluded patients with diabetes.[75] The ACCORD-BP study failed to find a significant benefit when patients with diabetes and ASCVD or multiple CV risk factors were treated to a systolic BP target less than 120 mm Hg when compared to patients treated to a 130 to 140 mm Hg target.[76] The ADA

guidelines suggest that a lower target, such as 130/80 mm Hg, may be appropriate in patients at high risk of CV events but does not give this a grade A recommendation due to the lack of high-quality data in patients with diabetes.

ACE inhibitors and ARBs are often used as the initial pharmacological treatment for high blood pressure in patients with diabetes due to their well-documented CV and renal protective effects.[70] However, thiazide diuretics and CCB have also been shown to improve outcomes in patients with diabetes. Most patients require multiple agents, on average three, to attain the BP goals. Thus, diuretics and calcium channel blockers frequently are used in combination with an ACE inhibitor or ARB. For more information regarding the treatment of hypertension in patients with diabetes, see Chapter 30, “Hypertension.”

High-intensity statin therapy is recommended in all patients with diabetes and pre-existing ASCVD.[70] In the absence of ASCVD, a moderate-intensity statin should be prescribed to all patients with type 1 or type 2 DM over the age of 40. In patients younger than 40 years of age, moderate-intensity statin therapy may be appropriate if the patients have multiple CV risk factors.[77] The benefits of statins for the primary prevention of CV events in patients with diabetes were established in the Collaborative Atorvastatin Diabetes Study (CARDS).[78] Patients with diabetes and no documented ASCVD were randomized to atorvastatin 10 mg daily or placebo. The trial was stopped early because major CV events were reduced by 37% in the atorvastatin-treated patients. Data from the Heart Protection Study (HPS) also affirm the benefit of statin therapy. Simvastatin 40 mg daily reduced the risk of a major CV event in patients with diabetes by nearly 25% when compared to placebo-treated patients. Statin therapy is recommended regardless of baseline lipid or LDL-C levels. Because statins may cause birth defects, they should only be used in women of child bearing age who do not wish to become pregnant and are using a reliable form of contraception.

After a statin has been initiated for CV risk reduction, markedly elevated triglycerides (≥500 mg/dL [5.65 mmol/L]) may require additional therapy. Patients with marked hypertriglyceridemia are at risk for pancreatitis. In these circumstances, a fibrate (eg, fenofibrate), omega-3 fatty acid, or niacin can be used to reduce serum triglycerides.[79] The routine use of medications to address hypertriglyceridemia in patients with diabetes with baseline elevations less than 500 mg/dL (5.65 mmol/L) is controversial. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) was conducted in patients with type 2 DM and failed to show a CV benefit from fenofibrate 200 mg daily when compared to placebo. In a subgroup analysis, subjects without ASCVD at baseline

appeared to have a significant reduction in CV events. However, the lipid arm of the ACCORD study also evaluated the use of fenofibrate and it did not significantly lower CV events. Niacin in combination with a statin failed to improve CV outcomes in patients with diabetes as well.

Peripheral arterial disease is another potential macrovascular complication associated with diabetes, which often contributes to foot ulcers and limb amputation.[70] Claudication and nonhealing foot ulcers are common in patients with type 2 DM. Smoking cessation, statin therapy, good glycemic control, and antiplatelet therapy are important strategies in treating peripheral arterial disease. Cilostazol may be useful in select patients to reduce symptoms. Revascularization surgery can be considered; however, small vessel disease that cannot be bypassed is common in diabetes. If a patient develops foot lesions, early detection, debridement, and appropriate footwear are critical to prevent foot or limb loss. For more advanced lesions, skin grafts, topical wound healing, and hyperbaric treatments may be necessary. Foot examinations during each face-to-face encounter with the patient and a yearly Semmes-Weinstein 10 gram-force monofilament test to assess for loss of protective sensation can be used to identify high-risk patients who need further evaluation, routine pediatric care, and closer follow-up.

Microvascular Complications

Microvascular complications are closely related to glycemic control, and efforts to improve glycemia significantly reduce the risk of developing these complications and slow their progression.[80] Microvascular complications take many forms but most commonly manifest as damage to the kidneys, eyes, and peripheral nerves.

Nephropathy

Diabetes mellitus, particularly type 2 DM coupled with hypertension, is among the leading causes of end-stage renal disease in the United States.[80] Albuminuria is a marker of renal damage and a strong predictor of end-stage renal disease in patients with type 1 DM. In type 2 DM, the presence of albuminuria is a strong risk factor for macrovascular disease but a weaker predictor for end-stage kidney disease. The ADA recommends screening for albuminuria at the time of diagnosis in persons with type 2 DM. In type 1 DM, proteinuria rarely occurs before puberty. Screening individuals with type 1 DM should begin with puberty and after 5-year disease duration. There are three methods for assessing

albuminuria: (1) a random spot collection, preferably the first-morning void; (2) a 24-hour timed collection; and (3) a timed (eg, 4- or 10-hour overnight) collection. Modestly elevated albuminuria on a spot urine specimen is defined as a ratio of 30 to 299 mg/g (3.4-33.8 mg/mmol) albumin:creatinine and overt albuminuria is defined as a ratio ≥300 mg/g (33.9 mg/mmol). Timed collections are cumbersome to perform but more accurate than a random spot collection. For timed collections, modest albuminuria is defined as 30 to 300 mg/24 h or an albumin excretion rate of 20 to 200 mcg/min. There is significant day-to-day variability in urinary protein excretion. Therefore, unless the results are unequivocally positive, albuminuria should be confirmed on at least two of three samples over 3 to 6 months. Additionally, when assessing urine protein, conditions that may cause transient elevations in urinary protein or albumin excretion should be excluded. These conditions include intense exercise, recent urinary tract infections, hypertension, short-term hyperglycemia, heart failure, and acute febrile illness.

Glucose and blood pressure control are important for preventing and retarding the progression of nephropathy.[80] ACE inhibitors and ARBs can slow the progression of renal disease in patients with diabetes. However, using a combination of agents to block the renin–angiotensin–aldosterone system—for example using an ACE inhibitor with an ARB, aldosterone receptor blockers, or direct renin inhibitors—has not been shown to improve outcomes and may increase adverse effects. Diuretics frequently are necessary due to the volume-expanded state of the patient and are recommended second-line therapy. The ADA currently recommends a blood pressure goal less than 140/90 mm Hg in patients with nephropathy but a lower blood pressure target (eg, less than 130/80), if it can be achieved without undue burden or side effects, may be desirable. Three or more antihypertensives are often needed to reach goal blood pressure. The SGLT2 inhibitors, specifically empagliflozin, canagliflozin, and dapagliflozin, significantly reduce the progression of CKD. Therefore, this class is preferred in the treatment of type 2 DM in patients with CKD, specifically in those with eGFR 30–60 mL/min/1.73m^2 or a urinary albumin:creatinine > 30 mg/g.

Retinopathy

Diabetic retinopathy is caused by ischemia in the microcirculation in the eye coupled with the inappropriate release of vascular growth factors.[80] Patients with diabetes should have routine dilated eye examinations to fully evaluate the retina. The ADA recommends patients with type 1 DM and patients with

established retinopathy be seen by an ophthalmologist or optometrist trained in diabetic eye disease. Early background retinopathy may reverse with improved glycemic control and optimal blood pressure control. More advanced retinopathy will not fully regress with improved glycemia. Aggressive reductions in BG may acutely worsen retinopathy. Laser photocoagulation has markedly improved sight preservation and is recommended in patients with macular edema and proliferative retinopathy. Intravitreal anti-vascular endothelial growth factor (VEGF) therapy has also been shown to be highly effective for sight preservation. Both bevacizumab, used off-label, and ranibizumab are anti-VEGF monoclonal antibodies. Aflibercept is a VEGF decoy receptor. People with diabetes also have a higher rate of cataracts and open-angle glaucoma.

Neuropathy

Neuropathy in people with diabetes can manifest as: (1) peripheral neuropathy, (2) autonomic neuropathy, and/or (3) focal neuropathies.[80] Distal, symmetrical, peripheral neuropathy is the most common complication seen in type 2 DM patients in outpatient clinics. Paresthesias, perceived hot or cold, numbness, or pain are the predominant symptoms. The feet are involved far more often than the hands as peripheral nerve damage initially affects longer nerve fibers and progresses proximally. Efforts to improve glycemic control is the primary treatment strategy and may alleviate some of the symptoms. If neuropathy is painful, symptomatic treatments can be used, but they will not change the course of the neuropathy. No medication has been shown to be clearly superior to another for the relief of neuropathic pain, and treatment selection should be based on adverse effects, cost, and convenience. Treatment with low-dose tricyclic antidepressants (preferably nortriptyline or desipramine), duloxetine, gabapentin, pregabalin, venlafaxine, topical capsaicin, and tramadol may be considered. If these are unsuccessful, patients should be referred to a pain clinic or neurologist for further evaluation. Duloxetine and pregabalin are FDA approved for the treatment of neuropathic pain associated with diabetic peripheral neuropathy. For those patients with primarily numbness and minimal pain, medications are not effective. None-the-less these patients are at high risk for developing foot ulcerations.

Autonomic neuropathy impacts the autonomic nerves and can lead to resting tachycardia, orthostatic hypotension, chronic constipation, gastroparesis, erectile dysfunction, anhidrosis, heat intolerance, gustatory sweating, dry skin, and hypoglycemic unawareness.[81] Gastroparesis can be a severe and debilitating complication of DM. Improved glycemic control, discontinuation of medications

that slow gastric motility, and the use of metoclopramide or low-dose erythromycin may be helpful. Unfortunately, tachyphylaxis to drug therapies develops within days or weeks. Gastric pacemakers can be considered if symptoms are severe and persistent. Domperidone may also be considered. Although it is not approved for use in the United States, domperidone is available in many other countries and can be requested through the FDA for compassionate use. Diabetic diarrhea most frequently occurs at night. Celiac disease, exocrine insufficiency, and gut bacterial overgrowth should be ruled out. Diabetic diarrhea frequently responds to a 10- to 14-day course of an antibiotic such as doxycycline or metronidazole. In more unresponsive cases, octreotide may be used.

If a patient develops orthostatic hypotension, antihypertensive agents should be discontinued and dietary sodium intake should be liberalized. Some patients may require pharmacologic treatment for orthostatic hypotension with mineralocorticoids (eg, fludocortisone) or adrenergic agonist agents (eg, midodrine). In severe cases, supine hypertension may be extreme, mandating that the patient sleep in a sitting or semi-recumbent position. Patients with cardiac autonomic neuropathy are at a higher risk for silent MI and sudden cardiac death.

Erectile dysfunction is common in diabetes, and initial treatment should include a trial of one of the phosphodiesterase type 5 inhibitors (eg, sildenafil) prior to referral.[80] People with diabetes often require the highest doses of these medications to achieve an adequate response. Sudomotor dysfunction may cause reduced sweating and dry, cracked skin. Use of hydrating creams and ointments is needed. Autonomic neuropathy may also result in gustatory sweating after eating. If sweating is excessive, it may be treated with antiperspirants or anticholinergic drugs. Hypoglycemic unawareness requires the patient to avoid hypoglycemia, as the body will slowly increase the glycemic level at which it will activate the autonomic signals.

Focal neuropathies occur most often in older patients with poorly controlled diabetes. Cranial nerve III, IV, and VI neuropathies, as well as Bell’s palsy, produce quite dramatic symptoms but the course is usually self-limited—partial or full recovery occurs in a few weeks to months. Diabetic amyotrophy, which is characterized by proximal thigh muscle pain and weakness, can be very debilitating. Carpal tunnel syndrome, caused by radial nerve entrapment in the wrist, is also more common in people with diabetes, and tarsal tunnel syndrome may cause foot paresthesias.

SPECIAL POPULATIONS

Prediabetes and Preventing Type 2 DM

Prediabetes, as the name implies, is a condition that frequently precedes the development of diabetes.[3] Patients with prediabetes do not have marked elevated BG but rather impaired fasting glucose (100-125 mg/dL [5.6-6.9 mmol/L]) or abnormal glucose tolerance (140-199 mg/dL [7.8-11.0 mmol/L] 2 hours after ingesting a 75 g carbohydrate load) and often an elevated A1C (5.7%-6.4% [0.057-0.064; 39-46 mmol/mol Hb]). None of these abnormal readings is sufficiently high enough to meet the diagnostic criteria for diabetes. One in three adults in the United States has prediabetes.[2] Most patients with prediabetes are overweight or obese and many concurrently have high blood pressure and dyslipidemia. This is an important patient population to identify because they are at high risk of eventually developing type 2 DM.

14 Given that prediabetes often progresses, there has been significant interest in using both nonpharmacologic and pharmacologic means to prevent or delay the onset of type 2 DM. Weight loss, regular aerobic activity, increased fiber intake, and limiting fat consumption are the four lifestyle pillars for both the treatment and prevention of type 2 DM. The Diabetes Prevention Program (DPP) was a landmark clinical trial which demonstrated that modest weight loss and regular physical activity dramatically reduced the risk of developing type 2 DM in patients with IGT.[82] Patients assigned to the lifestyle intervention group walked 30 minutes per day 5 days per week and lost a mean of 8-pounds (3.6 kg) over the 2.8-year study. These lifestyle changes resulted in a 58% reduction in the risk of developing type 2 DM when compared to a usual care group (5% per year vs. 11% per year). Diet and exercise interventions were effective regardless of age or baseline weight. A third arm of the study randomized patients to receive metformin 850 mg twice daily. The patients in the metformin arm received usual care and did not engage in intensive lifestyle changes. Metformin use leads to, on average, a 4-pound (1.8 kg) weight loss and reduced the risk of developing type 2 DM by 31% when compared to usual care. Younger and overweight individuals who took metformin experienced the greatest reductions. These findings suggest that metformin use may have the greatest impact when prescribed to middle-aged adults who are obese.

Several other medications have also been shown to delay or prevent diabetes. Rosiglitazone and pioglitazone reduce the risk of developing type 2 DM by 60%

to 70% in patients with impaired glucose tolerance.[83,84] Acarbose reduced the risk of developing type 2 DM by 25% in the STOP NIDDM study and may be particularly useful in patients who consume a diet high in starchy carbohydrates such as rice. The GLP1-RA, liraglutide, has also been shown to slow the progression to type 2 DM, reducing the risk by 80% in obese patients taking the medication for weight loss.[85] Insulin glargine reduced the risk of developing type 2 DM by approximately 30% in patients with prediabetes. Angiotensin-converting enzyme inhibitor (ACEi) or angiotensinogen receptor blockers (ARB) have also been shown to lower the risk of developing type 2 DM by 25% in a pooled analysis of several large CV studies.[86] Given that many patients with prediabetes concurrently have high blood pressure, an ACEi or ARB should be preferentially used in this population to treat hypertension.

Unfortunately, pharmacological methods to "prevent" diabetes do not cure but rather delay the onset of diabetes by shifting the curve. No pharmacologic agent is currently FDA approved for the prevention of type 2 DM. Given its relatively low cost and favorable long-term safety profile, metformin, in conjunction with lifestyle changes, is recommended by the ADA to delay the onset of diabetes in patients with prediabetes, particularly those with a BMI > 35 kg/m^2, those aged < 60 years, and women with a history of GDM.[87] Liraglutide is an attractive option for weight loss in obese patients with prediabetes.

Children and Adolescents with Type 2 DM

The incidence and prevalence of type 2 DM are increasing in adolescence.[88] Obesity and physical inactivity are the likely culprits but innate genetic susceptibility is also an underlying factor. Given that children will potentially live with diabetes for many decades and that the timeline for microvascular complications mimics that of adults with diabetes, extraordinary efforts should be made to assist the child and the family adopt lifestyle changes that normalize BG. The only FDA-approved oral agent for the treatment of type 2 DM in children (10-16 years of age) is metformin and, similar to adult guidelines, some experts recommend its routine use in the absence of contraindications. Unfortunately, the durability of the response to metformin monotherapy is relatively poor. Liraglutide has also recently been approved for use in children (10 years of age and older). Sulfonylureas are also commonly used. TZDs improve glycemic control when added to metformin therapy but are not currently FDA approved for use in children. While the DPP-4 inhibitors are an attractive option because they do not cause hypoglycemia this class of

medications has not been adequately studied in children. Insulin therapy continues to be the standard of care when glycemic goals cannot be achieved or maintained with metformin monotherapy. See Table 91-6 for treatment goals in children and adolescents.

Older Adults

Nearly one in four adults over the age of 65 years have diabetes and slightly more than half have prediabetes. Older adults, particularly those with functional disability and cognitive impairments, are less able to adopt healthy lifestyle behaviors and more likely to experience adverse effects from medications.[28] The ADA guidelines recommend a patient-centered approach and there are several factors that should be considered when treating older adults. The number and severity of comorbid conditions, renal dysfunction, ability to engage in self-care, nutritional status, social support, the risk of falls, and life expectancy should all influence glycemic goals and treatment selection. See Table 91-6. The ADA recommends an A1C goal ≤ 7.5% (0.075; 58 mmol/mol Hb) for otherwise healthy older adults who have intact cognitive function but a less stringent goal A1C ≤ 8.0% (0.080; 64 mmol/mol Hb) or ≤8.5% (0.085; 69 mmol/mol Hb) is reasonable in those with multiple chronic diseases or who are functionally dependent. However, glycemic control should not be relaxed so far as to cause symptoms of hyperglycemia or risk the development of DKA or HHS. Other therapeutic goals related to the management of blood pressure and dyslipidemia to prevent the development or progression of kidney disease and CV complications should be likewise tailored to the patient-specific circumstances.[28]

Older adults often have altered perceptions of hypoglycemia and may not experience adrenergic symptoms (eg, tremor, jitteriness, palpitations) due to the age-related loss of autonomic nerve function.[28] Thus neuroglycopenic symptoms (eg, altered mental status, personality changes) may be the first indication the patient's BG is low. For these reasons, over-treatment of DM should be avoided and de-escalation should be strongly considered should severe or frequent hypoglycemia occur. Older adults in long-term care facilities are particularly vulnerable to hypoglycemia.

While a decline in renal function may preclude the use of metformin in some older adults, lower doses may be used if coupled with more frequent monitoring (eg, every 3 months) of renal function when the estimated glomerular filtration rate (eGFR) is consistently above 30 mL/min/1.73 m^2.[28] The efficacy of the SGLT-2 inhibitors decline as renal function declines, thus older adults typically

have a diminished response to this class of agents. SGLT-2 inhibitors may also increase the frequency of urination and cause orthostatic blood pressure changes, increasing the risk of falls.

Sulfonylureas, particularly longer acting agents such as glyburide and chlorpropamide, are more likely to cause hypoglycemia and should be avoided. A higher risk of distal extremity fracture from falls has been documented with canagliflozin as well as the TZDs. The TZDs often cause fluid retention and increase the risk of congestive heart failure. DPP-4 inhibitors are generally well tolerated and do not cause hypoglycemia. Similarly, *α*-glucosidase inhibitors are generally safe and may also be used. The GLP-1 RAs are unlikely to cause hypoglycemia and will likely produce a modest weight loss, which can be advantageous in overweight individuals. However, older patients may be more prone to GI side effects. Simple insulin regimens using a single daily basal insulin dose can be used in older adults, especially if tight glycemic control is not the goal. Both the GLP-1 RAs and insulin therapy require the patient to have adequate motor skills and visual acuity to self-administer doses.

Pregnant Women

The prevalence of DM has increased significantly among women during their reproductive years.[14] In women with type 1 or type 2 DM, discussions about family planning and achieving good glycemic control prior to pregnancy are critical. Organogenesis is largely completed within the first 8 weeks of pregnancy—well before good glycemic control can be achieved in the absence of preconception planning. Unfortunately, major congenital malformations due to poor glucose control in the first trimester of pregnancy remain the leading cause of mortality and serious morbidity in infants of mothers with DM. During preconception planning, all drugs should be reviewed for safety. Known teratogens, such as ACE inhibitors and statins, should be stopped and, if treatment is still needed, an appropriate alternative recommended.

GDM is diagnosed during pregnancy and all women should be screened for GDM between weeks 24 and 28 of the pregnancy. See Table 91-5. The adverse outcomes associated with GDM include birth defects, miscarriage, cesarean section delivery, maternal preeclampsia/eclampsia, preterm delivery, neonatal hypoglycemia, shoulder dystocia, birth injury, and hyperbilirubinemia.[14] Medical nutritional therapy to minimize wide fluctuations in BG is of paramount importance. Intensive educational efforts are usually necessary. Pregnant women without DM maintain plasma glucose concentrations between 50 and 130 mg/dL

(2.8 and 7.2 mmol/L). Normoglycemia is the goal, and failure to maintain this despite dietary interventions will necessitate medication use. Goals during therapy are to keep fasting glucose less than 95 mg/dL (5.3 mmol/L), and either a 1-hour postprandial plasma glucose levels less than 140 mg/dL (7.8 mmol/L) or 2-hour postprandial plasma glucose levels less than 120 mg/dL (6.7 mmol/L). See Table 91-6. Ketosis should also be avoided as much as possible.

Similarly, in patients who have pre-existing type 1 or type 2 DM who become pregnant, premeal, bedtime, and overnight SMBG should be less than 95 mg/dL (5.7 mmol/L) with a peak PPG less than 140 mg/dL (7.8 mmol/L). While the A1C during pregnancy should ideally be between 6% and 6.5% (0.06 and 0.065; 42 and 48 mmol/mol Hb), SMBG must be used to guide therapy because it provides daily information about glycemic control. In women with type 2 DM controlled by lifestyle modification alone, conversion to insulin is often necessary soon after pregnancy is confirmed. Patients previously treated with insulin may need to intensify the regimen to achieve the more stringent therapeutic goals recommended during pregnancy. This may require the use of more complicated regimens coupled with carbohydrate counting and adjustments guided by SMBG. While NPH remains the recommended basal insulin to use during pregnancy, insulin detemir appears to be safe. Insulin pump therapy can be considered. In highly motivated patients, CSII can achieve excellent glycemic control and routinely adjusted throughout the pregnancy.

In women with type 2 DM or GDM, both metformin and glyburide have been studied as alternatives to insulin therapy.[14] Both appear to be effective based on the results of small randomized controlled trials and meta-analyses. However, rare or uncommon adverse fetal events are difficult to discern from these data. Glyburide was not detected in the cord serum of any infant in one study, whereas metformin crosses the placenta. Further study in larger patient populations is needed prior to routinely recommending them, but in patients for whom the complexity of insulin is too difficult or refuses insulin, glyburide or metformin use is justified. Patients with GDM should be evaluated approximately 6 weeks after delivery to ensure that normoglycemia has returned. The lifetime risk for the development of type 2 DM is 30% to 50%, making the periodic screening of women with a history GDM warranted.

Patients with HIV

Patients living with HIV are at higher risk for developing type 2 DM. This risk may be related to HIV infection, concomitant infections such as hepatitis C, and

medications often used to treat HIV and its comorbidities. Pentamidine, commonly used for *Pneumocystis carinii* pneumonia infections, is a β-cell toxin and may cause some patients to develop hypoglycemia from insulin release followed by hyperglycemia. Megestrol, used as an appetite stimulant, can have glucocorticoid-like effects and cause hyperglycemia in some patients. Protease inhibitors, used to manage HIV, can worsen insulin sensitivity, decrease the ability of the β-cell to secrete insulin, and worsen lipotoxicity. Long-term use of stavudine also increases the risk of developing diabetes. Redistribution of fat from subcutaneous to the visceral compartment from medication or HIV infection caused by medications or HIV infection also increases the risk of developing diabetes. Metformin is the drug of choice for HIV patients as weight gain can be minimized. Stavudine, zidovudine, and didanosine may cause lactatemia, especially upon long-term use. It may be advisable to check lactate levels in patients taking these medications prior to metformin use. If lactate levels are greater than two times normal, alternative therapy should be considered. If excess visceral adiposity is noted, a TZD that redistributes fat back to subcutaneous adipose tissue and causes visceral fat apoptosis may be considered. Drugs that promote weight loss should also be considered. Significant drug–drug interactions may also be present.

Hospitalized Patients

Patients with diabetes are frequently admitted to hospitals for an acute illness or surgical procedure. During a hospitalization, patients with diabetes are more likely to experience hyperglycemia, due to physiologic and psychological stress, as well as hypoglycemia, due to unpredictable food intake and medication mismanagement.[89] A structured approach to patient care is recommended and should include standard order sets for insulin and managing hypoglycemia. If a patient with diabetes has not had an A1C performed in the previous 3 months, it should be ordered. Insulin therapy is recommended for patients with type 2 DM if the BG readings are persistently greater than 180 mg/dL (10.0 mmol/L). Most patients who take oral antidiabetic agents will need to transition to insulin therapy to achieve adequate glycemic control during a hospitalization. It is prudent to stop metformin in all patients as contraindications are common in hospitalized patients. The benefits and risks of other antihyperglycemic medications in acutely ill hospitalized patients remain unclear and most experts recommend against their routine use. When insulin is prescribed, patients should receive scheduled doses of a long-acting basal insulin supplemented by short- or rapid-acting insulin for meals and to treat episodes of hyperglycemia. Relying

solely on “sliding-scale” insulin regimens, which withhold insulin when the BG is lower than a predetermined threshold, should be discouraged because they notoriously result in wide fluctuations in BG and do not reduce risk of hypoglycemia. Patient self-management of insulin therapy, including CSII, in the hospital is appropriate for select patients who are proficient at estimating insulin requirements based on carbohydrate intake and have the cognitive and physical skills needed to self-administer insulin and perform SMBG during their hospital stay.

The goal of therapy in most patients who are hospitalized is to maintain the BG between 140 and 180 mg/dL (7.8 to 10.0 mmol/L).[89] More stringent goals may be appropriate in select patients who can be adequately monitored, and adjustments to therapy can be swiftly implemented to reduce the risk of hypoglycemia. One study documented a reduction in mortality following an MI in patients with type 2 DM who received an IV insulin infusion to maintain near-normal glucose concentrations. Similar mortality improvements have been documented in some intensive care unit settings using an IV insulin infusion to maintain tight glucose control. However, the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial failed to find a benefit from tight glycemic control in the ICU setting.[90] Many protocols for IV insulin infusion are currently available and clinicians should use a well-established protocol if an IV insulin infusion is used. The accuracy of point of care (POC) devices to measure plasma glucose has been questioned and large discrepancies between capillary, venous, and arterial plasma samples have been observed in patients with poor peripheral perfusion in ICU settings. The FDA has now established separate criteria with stricter standards for POC glucose meters intended for in-hospital use.

Discharge planning should begin soon after hospital admission using a structured process to create a tailored transition plan from the acute care setting back to home or other settings of care.[89] The plan should clearly communicate medication changes, test results, and follow-up care needs. During the hospitalization, a CDE or a clinician with similar training and experience should assess the patient’s understanding regarding the diagnosis of diabetes, glycemic goals, nutrition, medication administration, disposal of needles and syringes, as well as ability to engage in self-monitoring, and recognize and treat hypoglycemia. Nearly one-third of patients who develop hyperglycemia during a hospitalization have newly diagnosed diabetes and will require follow-up care. Discharge planning should include scheduling follow-up appointments prior to discharge and communicating a discharge summary as soon as possible to the

patient's primary care team.

Patients who require surgery may experience worsening of glycemia similar to those admitted to hospital for a medical illness. Acute stress increases counter-regulatory hormones. Therapy should be individualized based on the type of DM, nature of the surgical procedure, previous therapy, and metabolic control prior to the procedure. Patients on oral agents may need to be transiently switched to insulin to control BG. In patients requiring insulin, scheduled doses of insulin or continuous insulin infusions are preferred. For patients who can eat soon after surgery, basal insulin continuation is warranted. The time-honored approach of giving one-half of the patient's usual morning NPH or basal insulin dose with dextrose 5% in water intravenously is acceptable, with resumption of scheduled insulin, perhaps at reduced doses, within the first day. Patients receiving basal-bolus insulin therapy can continue receiving their usual dose of long-acting insulin while holding the premeal bolus doses until the patient eats. For patients requiring more prolonged periods without oral nutrition following major surgeries, such as coronary artery bypass grafting and major abdominal surgery, continuous IV infusion insulin is preferred. However, "tight" perioperative glucose control has not proven to improve outcomes. Use of IV insulin infusion has been shown to reduce postoperative deep sternal wound infections in patients following coronary artery bypass grafting. Metformin should be discontinued temporarily after any major surgery until it is clear that the patient is hemodynamically stable and normal renal function is documented.

Patients Who Are Acutely Ill

Acute self-limited illness rarely presents a major problem for patients with type 2 DM but instituting a sick day plan can avoid urgent care visits from dehydration. Type 2 DM patients should perform SMBG more often, especially if they take medications that may cause hypoglycemia. Sick day management for patients with type 1 DM is more challenging.[91] While caloric intake generally declines when people feel sick, insulin sensitivity often decreases. Thus patients often require greater amounts of insulin to control BG during periods of acute illness. Patients with type 1 DM should increase the frequency of SMBG, check urine ketones, and consume 120 to 150 g of carbohydrates per day. Patients should continue their usual insulin regimen and use supplemental rapid-acting insulin based on SMBG results. Additional insulin may be needed if ketonuria develops. Ketone testing should be done if two consecutive plasma glucose readings are above 250 mg/dL (13.9 mmol/L) or if vomiting occurs, as this may be a sign of ketosis. Sugar and electrolyte solutions, such as sports drinks, can be

used to maintain hydration and provide electrolytes if there are significant GI or urinary losses. They also provide glucose to keep the patient from developing hypoglycemia. However, if the BG remains consistently elevated, the patient should abstain from sugary drinks and increase intake of sugar-free liquids.

EVALUATION OF PATIENT OUTCOMES

Glycemic control can be measured in several ways.[92] Plasma and BG measurements collected during fasting and postprandial periods can be used to determine the patient's current glycemic status. These tests of glycemia are most useful for detecting hypoglycemia, making adjustments in insulin therapy, and determining the patient's glycemic patterns throughout the day. The A1C is the gold standard for determining overall glycemic control for the previous 2 to 3 months and correlates with the risk of developing many of the long-term complications associated with diabetes. Fructosamine, which measures the amount of glycation on plasma proteins such as albumin, is a test of glycemia that can be useful in patients with altered red blood cell lifespan or a hemoglobinopathy. Fructosamine measures glucose control over the previous 2 to 3 weeks. Unfortunately, fructosamine is not as reliable as the A1C and the correlation between fructosamine measurements and the risk complications from diabetes is unknown. Thus, glycemic goals based on fructosamine have not been established.

While these glycemic goals recommended by the ADA and AACE are useful general targets, treatment goals need to be individualized. Less stringent A1C goals are appropriate in patients with a history of severe hypoglycemia, limited life expectancy, advanced micro/macrovascular complications or comorbidities, and in patients who are frail, have dementia, or have limited social or financial resources. Less stringent goals should also be set for younger children. Conversely, more aggressive glycemic goals are appropriate in patients who are young or middle-aged adults, newly diagnosed, and using treatments that are unlikely to cause hypoglycemia.

Self-monitored blood glucose (SMBG) is an important tool that provides an opportunity to adjust medications, food intake, or physical activity when an SMBG value is obtained. SMBG improves safety by enabling patients to detect hypoglycemia so that it can be treated. In general, SMBG frequency should match how frequently medication changes are needed to achieve glycemic control as well as the risk of hypoglycemia. Frequent SMBG is necessary to achieve near-normal BG concentrations if insulin is used. SMBG empowers

patients to make day-to-day adjustments in prandial insulin doses and is used to determine if corrective doses of insulin are needed. Even in patients who do not use insulin therapy, SMBG can be useful to see how a change in diet or exercise impacts BG. Moreover, SMBG readings are needed to check the accuracy of some CGMs. For patients with type 1 DM, SMBG is typically performed four to six times per day—prior to food intake and physical activity as well as at bedtime. The optimal frequency of SMBG in patients with type 2 DM on oral agents is unknown and its role controversial. Daily SMBG in patients with type 2 DM may be useful in patients who are actively using the information to make changes in their lifestyle behaviors and for a few weeks after medication changes.

Alternate site testing performed on the palm, forearm, or the thigh is less painful than obtaining blood samples from fingertip samples, but only some BG test strips are designed for alternative site testing. Alternative sites tend to have less nerve endings than fingertips and may be more comfortable for a patient. It is important to note that glucose readings obtained from alternative sites will lag behind fingertip capillary blood by 20 to 30 minutes. Therefore, alternate site testing is discouraged in any situation where immediate action will be needed based on the glucose reading, such as testing for hypoglycemia or when the BG is changing rapidly, such as after a meal.

Choosing an appropriate meter depends on the patient's dexterity, vision acuity, cost of the meter and strips, and desired features. Insurance coverage often influences meter choice. When a patient first obtains a new glucometer, it is important to demonstrate the proper methods and have the patient perform the technique. Each meter has specifications for hematocrit, elevation, and temperature tolerances for optimal operation.

The use of CGM has become increasingly common and helpful in patients using intensive insulin therapy or CSII. CGM measures interstitial glucose, which lags behind fingertip capillary SMBG. CGM can be particularly useful in patients with frequent episodes of hypoglycemia, hypoglycemic unawareness, and nocturnal hypoglycemia. CGM can be used to identify glucose patterns and evaluate patients with higher or lower than expected A1C results. Some CGM must be calibrated using SMBG readings after insertion of a new sensor and periodically thereafter. A new sensor must be placed every 7 to 14 days. The ADA currently recommends that CGM be considered in adults with type 1 DM who are at least 25 years of age and those younger than 25 years of age who can demonstrate adherence to its use. CGM data can be transmitted to insulin pumps which can then make recommendations to the patient or automatically adjust the

insulin doses based on the results.

Medication Adherence and Persistence

Despite the armamentarium of treatment options, a large percentage of patients fail to achieve target A1C levels. One major contributing factor to uncontrolled diabetes is poor medication adherence and persistence. Key contributors to adherence include perceived efficacy, hypoglycemia, weight gain, treatment complexity, convenience, cost, patient beliefs about medications, and trust in the health care provider.[93] Therefore, it is crucial to assess adherence and barriers to adherence at every visit and include the patient in the decision-making process. Simplifying the treatment regimen may improve adherence and glycemic control. Fixed-dose combination products may be one way to simplify treatment and has been shown to improve adherence and glycemic control.[94,95] Currently available combination products for the treatment of type 2 DM are listed in **Table 91-11**.

TABLE 91-11 Available Combination Products for Type 2 Diabetes

Drug Classes	Drug Combination		Brand Name
Biguanide and sulfonylurea	Metformin	Glipizide	Metaglip[a]
	Metformin	Glyburide	Glucovance[a]
Biguanide and meglitinide	Metformin	Repaglinide	Prandimet[a]
Biguanide and thiazolidinedione	Metformin	Pioglitazone	Actoplus Met[a], Actoplus Met XR
	Metformin	Rosiglitazone	Avandamet[a]
Biguanide and DPP-4 inhibitor	Metformin	Alogliptin	Kazano
	Metformin	Linagliptin	Jentadueto, Jentadueto XR
	Metformin	Saxagliptin	Kombiglyze XR
	Metformin	Sitagliptin	Janumet, Janumet XR
Biguanide and SGLT-2 inhibitor	Metformin	Canagliflozin	Invokamet, Invokamet XR
	Metformin	Dapagliflozin	Xigduo XR
	Metformin	Empagliflozin	Synjardy, Synjardy XR
	Metformin	Ertugliflozin	Segluromet
Sulfonylurea and thiazolidinedione	Glimepiride	Pioglitazone	Duetact[a]
	Glimepiride	Rosiglitazone	Avandaryl
Thiazolidinedione and DPP-4 inhibitor	Pioglitazone	Alogliptin	Oseni
SGLT-2 inhibitor and DPP-4 inhibitor	Dapagliflozin	Saxagliptin	Qtern
	Empagliflozin	Linagliptin	Glyxambi
	Ertugliflozin	Sitagliptin	Steglujan
Basal insulin and GLP-1 receptor agonist	Insulin glargine U-100	Lixisenatide	Soliqua
	Insulin degludec U-100	Liraglutide	Xultophy

XR, extended release.

[a]Available in generic.

Therapeutic Inertia

15 Another contributing factor to uncontrolled diabetes is therapeutic inertia, which is defined as the failure to initiate or intensify therapy in a timely manner according to evidence-based clinical guidelines. Several studies have shown that it often takes years before treatment is intensified in patients with uncontrolled diabetes. There are multiple reasons for therapeutic inertia including barriers at the patient, provider, and system level. Given the risk of development or progression of diabetes-related complications during treatment delays, it is vital that clinicians combat therapeutic inertia by routinely monitoring patients with

DM and taking action in those who are not achieving therapeutic targets.[96]

CONCLUSION

16 Diabetes mellitus is a heterogeneous group of metabolic disorders which all have elevated BG as their defining diagnostic criteria. Achieving good glycemic control, although important, is but one ingredient to optimal health outcomes in patients with diabetes. A comprehensive plan of care should include not only pharmacological and nonpharmacological strategies to lower BG but also methods to screen, prevent, and manage microvascular and macrovascular complications. Current Health Plan Employer Data and Information Set (HEDIS), performance measures annually reported by the National Committee for Quality Assurance (NCQA), recognizes that quality care to patients with diabetes must address glycemia, blood pressure control, and recommended screening exams.[11] Diabetes is a life-long disease and patients with diabetes need ongoing support through an interprofessional, team-based approach to care. Adjustments to diet, exercise, and pharmacologic therapies are frequently needed. Clinical inertia should be avoided and treatment intensification should be implemented if treatment goals have not been met. Patients should receive follow-up care every 3 months but more frequent follow-up may be necessary if treatment changes have been made. The A1C should be measured every 3 to 6 months, even in patients who are stable on a therapeutic regimen and meeting treatment goals. A fasting lipid profile should be obtained as part of an initial assessment and to determine if statin therapy has adequately reduced LDL cholesterol. Performing foot examinations at each face-to-face visit and obtaining a dilated eye examination at least once a year are also important. People with diabetes should receive the influenza vaccine every year and the pneumococcal vaccines and the hepatitis B vaccine series per Center for Disease Control and Prevention recommendations. Identifying and mitigating CV risks—particularly high blood pressure and tobacco use—is critical. Utilizing an integrated electronic health record, standardized progress notes, and flow sheets can assist the clinician determine whether the patient has met these standards of care. As with many chronic diseases, adherence to dietary recommendation, physical activity, and medications is a challenge for most patients. Frequent follow-up, patient education, and positive family engagement can help patients with diabetes lead healthier, happier lives.

Postclass Engaged Learning Activity

Review and compare the most recent version of the American Diabetes Association (ADA) guideline recommendations in their *Standards of Care* to the most recent version of the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) *Consensus Statement on the Comprehensive Management of Type 2 Diabetes*. Create a table that describes the current recommendations by each of these organizations for each of the following:

1. Preferred, first-line treatments for type 2 diabetes
2. Criteria for initiating treatment with more than one drug for type 2 diabetes
3. Criteria for starting insulin therapy for type 2 diabetes
4. Frequency of blood glucose monitoring for patients with type 2 diabetes
5. Blood pressure goals and preferred antihypertensive treatment
6. Serum cholesterol goals and preferred treatments for dyslipidemia

Your table should have the following columns and headers:

	ADA Guidelines Recommendations	AACE/ACE Guidelines Recommendations
Preferred first-line treatments for type 2 DM		
When to start more than one drug for the initial treatment of type 2 DM		
When to start insulin therapy for type 2 DM		
Blood glucose monitoring recommendations for type 2 DM (frequency)		
Blood pressure goals and preferred antihypertensive treatments		
Blood cholesterol goals and preferred lipid treatments		

ABBREVIATIONS

AACE	American Association of Clinical Endocrinologists
AADE	American Association of Diabetes Educators
ADA	American Diabetes Association
A1C	hemoglobin A1C
ASCVD	atherosclerotic cardiovascular disease
BG	blood glucose

BP	blood pressure
BMI	body mass index
CDE	Certified Diabetes Educator
CF	correction factor
CGM	continuous glucose monitor
CHD	coronary heart disease
C:I	carbohydrate to insulin ratio
CKD	chronic kidney disease
CSII	continuous subcutaneous insulin infusion
CV	cardiovascular
CVD	cardiovascular disease
DKA	diabetic ketoacidosis
DPP-4	dipeptidyl peptidase-4
DM	diabetes mellitus
DSME/S	diabetes self-management education/support
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
FFA	free fatty acid
FPG	fasting plasma glucose
GDM	gestational diabetes
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
GU	genitourinary
HDL-C	high-density lipoprotein cholesterol
HHS	hyperglycemic hyperosmolar syndrome
ICAs	islet cell autoantibodies
ICU	intensive care unit
IGT	impaired glucose tolerance
IV	intravenous
LADA	latent autoimmune disease in adults
LDL-C	low-density lipoprotein cholesterol

MDI	multiple daily injections
MNT	medical nutrition therapy
MODY	mature-onset diabetes in the young
NPH	neutral protamine Hagedorn
OGTT	oral glucose tolerance test
PAI-1	plasminogen activator inhibitor-1
PK/PD	pharmacokinetic/pharmacodynamic
POC	point of care
PPAR-γ	peroxisome proliferator activator receptor-γ
PPG	postprandial glucose
SC	subcutaneous
SGLT2	sodium glucose co-transporter 2
SMBG	self-monitoring of blood glucose
SU	sulfonylurea
TZD	thiazolidinedione
UGE	urinary glucose excretion
VAT	visceral adipose tissue
XR	extended release

REFERENCES

1. World Health Organization. Global report on diabetes. World Health Organization; 2016. Available at: http://www.who.int/iris/handle/10665/204871.
2. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017. Estimates of Diabetes and Its Burden in the United States. Atlanta, GA. Available at: http://www.diabetes.org/assets/pdfs/basics/cdc-statistics-report-2017.pdf. Accessed December 12, 2018.
3. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42(suppl 1):S13–S28.
4. Repaske DR. Medication-induced diabetes mellitus. *Pediatr Diabetes*. Sep 2016;17(6):392–397.
5. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. *Lancet*. 2014;383(9911):69–82.

6. Mayer-Davis EJ, Lawrence JM, Dabelea D, et al. Search for diabetes in youth study: Incidence trends of type 1 and type 2 diabetes among youths, 2002–2012. *New Engl J Med*. 2017;376(15):1419–1429.
7. DeFronzo RA, Ferrannini E, Groop L, et al. Type 2 diabetes mellitus. *Nat Rev Dis Primers*. 2015;1:15019.
8. DeSisto CL, Kim SY, Sharma AJ. Prevalence estimates of gestational diabetes mellitus in the United States, pregnancy risk assessment monitoring system (PRAMS), 2007–2010. *Prev Chronic Dis*. 2014;11:E104.
9. Kampmann U, Madsen LR, Skajaa GO, et al. Gestational diabetes: A clinical update. *World J Diabetes*. 2015;6(8):1065–1072.
10. Van Belle TL, Coppieters KT, Von Herrath MG. Type 1 diabetes: Etiology, immunology, and therapeutic strategies. *Physiol Rev*. 2011;91:79–118.
11. American Diabetes Association. 1. Improving care and promoting health in populations: Standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42(suppl 1):S7–S12.
12. Drucker DJ, Nauck MA. The incretin system: Glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet*. 2006;368(9548):1696–1705.
13. Vallon V. The mechanisms and therapeutic potential of SGLT2 inhibitors in diabetes mellitus. *Annu Rev Med*. 2015;66(1):255–270.
14. American Diabetes Association. 14. Management of diabetes in pregnancy: Standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42(suppl 1):S165–S172.
15. American Diabetes Association. 4. Comprehensive medical evaluation and assessment of comorbidities: Standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42(suppl 1):S34–S45.
16. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American Association of Clinical Endocrinologists and American College of Endocrinology clinical practice guidelines for developing a diabetes mellitus comprehensive care plan-2015. *Endocrine Practice*. 2015;21(suppl 1):1–87.
17. American Diabetes Association. 6. Glycemic targets: Standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42(suppl 1):S61–S70.
18. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J*

Med. 1993;329:977–986.

19. DCCT/EDIC Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005;353:2643–2653.
20. Lachin JM, White NH, Hainsworth DP, et al. Effect of intensive diabetes therapy on the progression of diabetic retinopathy in patients with type 1 diabetes: 18 years of follow-up in the DCCT/EDIC. *Diabetes*. 2015;64:631–642.
21. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837–853.
22. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998;352:854–865.
23. Holman RR, Paul SK, Bethel MA, Mathews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359:1577–1589.
24. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358:2545–2559.
25. The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358:2560–2572.
26. Duckworth W, Abraira C, Mortiz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009;360:1–11.
27. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm: 2018 executive summary. *Endocrine Practice*. 2018;24(1):91–120.
28. American Diabetes Association. 12. Older adults: Standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42(Suppl 1):S139–S147.
29. American Diabetes Association. 5. Lifestyle management: Standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42(suppl 1):S46–S60.
30. Beck J, Greenwood DA, Blanton L, et al. National standards for diabetes

self-management education and support. *Diabetes Educator*. 2017;43(5):448–464.

31. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42(suppl 1):S90–S102.
32. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. Published online Sep; dci180033. Available at: https://doi.org/10.2337/dci18-0033.
33. The ORIGIN trial investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med*. 2012;367 :319–328.
34. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med*. 2011;365:2002–2012.
35. Frid AH, Kreugel G, Grassi G, et al. New insulin delivery recommendations. *Mayo Clin Proc*. 2016;91(9):1231–1255.
36. American Association of Diabetes Educators. Insulin Injection Resources. Available at: https://www.diabeteseducator.org/practice/educator-tools/insulin-injection-resources2. Accessed December 12, 2018.
37. Rena G, Hardie D, Pearson ER. The mechanism of action of metformin. *Diabetologia*. 2017;60(9):1577–1585.
38. Griffin SJ, Leaver JK, Irving GF. Impact of metformin on cardiovascular disease: A meta-analysis of randomized trials among people with type 2 diabetes. *Diabetologia*. 2017;60(9):1620–1629.
39. Maruther NM, Tseng E, Hutfless S, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: A systematic review and meta-analysis. *Ann Intern Med*. 2016;164(11):740–751.
40. Aggarwal N, Singla A, Mattheu C, et al. Metformin extended-release versus immediate-release: An international, randomized, double-blind, head-to-head trial in pharmacotherapy-naïve patients with type 2 diabetes. *Diabetes Obes Metab*. 2018;20(2):463–467.
41. Inzucchi SE, Lipska KJ, Mayo H. Metformin in patients with type 2 diabetes and kidney disease: A systematic review. *JAMA*. 2014;312(24):2668–2675.
42. Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of

mild-to-moderate renal insufficiency. *Diabetes Care*. 2011;34(6):1431–1437.

43. Lalau JD, Kajbaf F, Bennis Y, et al. Metformin treatment in patients with type 2 diabetes and chronic kidney disease stages 3A, 3B, or 4. *Diabetes Care*. 2018;41(3):547–553.
44. Meinert CL, Knatterud GL, Prout TE, Klimt CR. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. *Diabetes*. 1970;19(suppl.):789–830.
45. Khunti K, Chatterjee S, Gerstein HC, et al. Do sulfonylureas still have a place in clinical practice? *Lancet Diabetes Endocrinol*. 2018;6(10):821–832.
46. Gangji AS, Cukierman T, Gerstein HC, et al. A systematic review and meta-analysis of hypoglycemia and cardiovascular events: A comparison of glyburide with other secretagogues and with insulin. *Diabetes Care*. 2007;30(2):389–94.
47. American Diabetes Association. 8. Obesity management for the treatment of type 2 diabetes: Standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42(suppl 1):S81–S89.
48. Neumiller JJ, Alicic RZ, Tuttle KR. Therapeutic considerations for antihyperglycemic agents in diabetic kidney disease. *J Am Soc Nephrol*. 2017;28(8):2263–2274.
49. Hauner H. The mode of action of thiazolidinediones. *Diabetes Metab Res Rev*. 2002;18(Suppl 2):S10–15.
50. Nissen SE, Wolski K. Rosiglitazone revisited: An updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. *Arch Intern Med*. 2010;170:1191–1201.
51. Mahaffey KW, Hafley G, Dickerson S, et al. Results of a reevaluation of cardiovascular outcomes in the RECORD trial. *Am Heart J*. 2013;166:240–249.
52. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): A multicentre, randomised, open-label trial. *Lancet*. 2009;373:2125–2135.
53. Dormandy JA, Charbonnel B, Eckland DJA, et al. Secondary prevention of vascular events in patients with type 2 diabetes in the PROactive study prospective pioglitazone clinical trial in macrovascular events: A randomized controlled trial. *Lancet*. 2005;366:1279–1289.

54. Viscoli CM, Inzucchi SE, Young LH, et al. Pioglitazone and risk for bone fracture: Safety data from a randomized clinical trial. *J Clin Endocrinol Metab*. 2017;102(3):914–922.
55. Kahn SE, Zinman B, Lachin JM, et al. Rosiglitazone-associated fractures in type 2 diabetes: An analysis from a diabetes outcome progression trial (ADOPT). *Diabetes Care*. 2008;31(5):845–851.
56. Lewis JD, Ferrara A, Peng T, et al. Risk of bladder cancer among diabetic patients treated with pioglitazone: Interim report of a longitudinal cohort study. *Diabetes Care*. 2011;34(4):916–922.
57. Lewis JD, Habel LA, Quesenberry CP, et al. Pioglitazone use and risk of bladder cancer and other common cancers in persons with diabetes. *JAMA*. 2015;314(3):265–277.
58. Trujillo JM, Nuffer W, Ellis SL. GLP-1 receptor agonists: A review of head-to-head clinical studies. *Ther Adv Endocrinol Metab*. 2015;6(1):19–28.
59. Lingvay I, Desouza CV, Lalic KS, et al. A 26-week randomized controlled trial of semaglutide once daily versus liraglutide and placebo in patients with type 2 diabetes suboptimally controlled on diet and exercise with or without metformin. *Diabetes Care*. 2018;41(9):1926–1937. https://doi.org/10.2337/dc17-2381.
60. Cefalu WT, Kaul S, Gerstein HC, et al. Cardiovascular outcomes trials in type 2 diabetes: Where do we go from here? Reflections from a Diabetes Care editors' expert forum. *Diabetes Care*. 2018;41:14–31.
61. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375:311–322.
62. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375:1834–1844.
63. Nauck MA, Meier JJ, Cavender MA, et al. Cardiovascular actions and clinical outcomes with glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. *Circulation*. 2017;136(9):849–870.
64. Devries JH, Rosenstock J. DPP-4 inhibitor related pancreatitis: Rare but real! *Diabetes Care*. 2017;40:161–163.
65. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128.

66. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644–657.
67. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347–357.
68. Bersoff-Matcha SJ, Chamberlain C, Cao C, Kortepeter C, Chong WH. Fournier gangrene associated with sodium-glucose cotransporter-2 inhibitors: A review of spontaneous postmarketing cases. *Ann Intern Med*. May 7, 2019. 10.7326/M19-0085.31060053.
69. Umpierrez G, Korytkowski M. Diabetic emergencies: Ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. *Nature Rev Endocrinol*. 2016;12(4):222–232.
70. American Diabetes Association. 10. Cardiovascular disease and risk management: Standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42(suppl 1):S103–S123.
71. The ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med*. 2018;379:1529–1539.
72. Das SR, Everett BM, Birtcher KK, et al. 2018 ACC expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes and atherosclerotic cardiovascular disease: A report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol*. November 2018. doi:10.1016/j.jacc.2018.09.020.
73. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-st-elevation acute coronary sydnromes: Executive summary. *Circulation*. 2014(130):2354–2394.
74. ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA. Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;71:e127–e248.
75. The SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103–2116.
76. The ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1575–1585.
77. ACC/AHA/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/

Guideline on the management of blood cholesterol: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. November 10, 2018 [Epub ahead of print].

78. Naeem F, Mckay G, Fisher M. Cardiovascular outcomes trials with statins in diabetes. *Br J Diabetes*. 2018;18:7–13.
79. Pang J, Chan DC, Watts GF. Origin and therapy for hypertriglyceridaemia in type 2 diabetes. *World J Diabetes*. 2014;5(2):165–175.
80. American Diabetes Association. 11. Microvascular complications and foot care: Standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42(suppl 1):S124–S138.
81. Verrotti A, Prezioso G, Scattoni R, Chiarelli F. Autonomic neuropathy in diabetes mellitus. *Frontier Endocrinol*. 2014;5:205.
82. Diabetes Prevention Program Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2012;346(6):393–403.
83. The DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: A randomized controlled trial. *Lancet*. 2006;368:1096–1105.
84. DeFronzo RA, Tripathy D, Schwenke DC, et al. Pioglitazone for diabetes prevention in impaired glucose tolerance. *N Engl J Med*. 2011;364(12):1104–1115.
85. le Roux CW, Astrup A, Fujioka K, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: A randomised, double-blind trial. *Lancet*. 2017;389(10077):1399–1409.
86. Abuissa H, Jones PG, Marso SP, O'Keefe JH. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for prevention of type 2 diabetes: A meta-analysis of randomized clinical trials. *J Am College Cardiol*. 2005;46(5):821–826.
87. American Diabetes Association. 3. Prevention or delay of type 2 diabetes: Standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42(suppl 1):S29–S33.
88. American Diabetes Association. 13. Children and adolescents: Standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42(suppl 1):S148–

S164.

89. American Diabetes Association. 15. Diabetes care in the hospital: Standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42(suppl 1):S173–S181.
90. The NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360:1283–1297.
91. Brink S, Joel D, Laffel L, et al. Sick day management in children and adolescents with diabetes. *Pediatric Diabetes*. 2014;15(S20):193–202.
92. Goldstein DE, Little RR, Lorenz RA, et al. Tests of glycemia in diabetes. *Diabetes Care*. 2004;27(7):1761–1773.
93. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: Recognizing the scope of the problem and its key contributors. *Patient Prefer Adherence*. 2016;10:1299–1307.
94. Han S, Iglay K, Davies MJ, et al. Glycemic effectiveness and medication adherence with fixed-dose combination or co-administered dual therapy of antihyperglycemic regimens: A meta-analysis. *Curr Med Res Opin*. 2012;28:969–977.
95. Vijayakumar TM, Jayram J, Meghana Cheekireddy V, et al. Safety, efficacy, and bioavailability of fixed-dose combinations in type 2 diabetes mellitus: A systematic updated review. *Curr Ther Res Clin Exp*. 2017:84:4–9.
96. Khunti K, Gomes MB, Pocock S, et al. Therapeutic inertia in the treatment of hyperglycemia in patients with type 2 diabetes: A systematic review. *Diabetes Obes Metab*. 2018;20:427–437.

92

Thyroid Disorders

Michael P. Kane and Gary Bakst

KEY CONCEPTS

1. Thyrotoxicosis is most commonly caused by Graves' disease, which is an autoimmune disorder in which thyroid-stimulating antibody (TSAb) directed against the thyrotropin receptor elicits the same biologic response as thyroid-stimulating hormone (TSH).
2. Hyperthyroidism may be treated with antithyroid drugs such as methimazole (MMI) or propylthiouracil (PTU), radioactive iodine (RAI: sodium iodide-131 [^{131}I]), or surgical removal of the thyroid gland; selection of the initial treatment approach is based on patient characteristics such as age, concurrent physiology (eg, pregnancy), comorbidities (eg, chronic obstructive lung disease), and convenience.
3. MMI and PTU reduce the synthesis of thyroid hormones and are similar in efficacy, although their dosing ranges differ by 20-fold. Overall, PTU has a greater incidence of side effects. Agranulocytosis is a rare but severe adverse effect associated with both medications.
4. Response to MMI and PTU is seen in 4 to 6 weeks and therefore β-blocker therapy may be concurrently initiated to reduce adrenergic symptoms. Maximal response is typically seen in 4 to 6 months; treatment usually continues for 1 to 2 years, and therapy is monitored by clinical signs and symptoms and by measuring the serum concentrations of TSH and free thyroxine (T_4).
5. Adjunctive therapy with β-blockers controls the adrenergic symptoms of thyrotoxicosis but does not correct the underlying disorder; iodine may also be used adjunctively in preparation for surgery and acutely for thyroid storm.
6. Many patients choose to have ablative therapy with ^{131}I rather than undergo

repeated courses of MMI or PTU treatment; most patients receiving RAI eventually become hypothyroid and require thyroid hormone supplementation.

7. Hypothyroidism is most often due to an autoimmune disorder known as *Hashimoto's thyroiditis*.
8. The drug of choice for replacement therapy in hypothyroidism is levothyroxine.
9. Studies of combination therapy with levothyroxine and liothyronine have not shown reproducible benefits. This approach to the treatment of hypothyroidism requires further study.
10. Monitoring of levothyroxine replacement therapy is achieved by observing clinical signs and symptoms and by measuring the serum TSH level. An elevated TSH indicates under-replacement; a suppressed TSH indicates over-replacement.

Preclass Engaged Learning Activity

Using information in this chapter and other sources, fill in the following two tables:

TABLE 1 Treatments for Hyperthyroidism

Therapeutic Option	Onset of Effect	Adverse Effects	Precautions or Contraindications	Drug Interactions	Convenience (ie, dosing schedule, route of admin.)	Cost
Thioamide						
Iodine						
β-Blocker						
Radioactive Iodine (RAI)						
Surgery						

TABLE 2 Treatments for Hypothyroidism

Therapeutic Option	Onset of Effect	Adverse Effects	Precautions or Contraindications	Drug Interactions	Convenience (ie, dosing schedule, route of admin.)	Cost
Levothyroxine						
Liothyronine						
Thyroid—USP						
Liotrix						

INTRODUCTION

Thyroid hormones affect the function of virtually every organ system. In a child, thyroid hormone is critical for normal growth and development. In an adult, the major role of thyroid hormone is to maintain metabolic stability. Substantial reservoirs of thyroid hormone in the thyroid gland and blood provide constant thyroid hormone availability. In addition, the hypothalamic–pituitary– thyroid axis is exquisitely sensitive to small changes in circulating thyroid hormone concentrations, and alterations in thyroid hormone secretion maintain peripheral free thyroid hormone levels within a narrow range. Patients seek medical attention for evaluation of symptoms due to abnormal thyroid hormone levels or because of diffuse or nodular thyroid enlargement.

Thyroid Hormone Synthesis

The thyroid hormones thyroxine (T_4) and triiodothyronine (T_3) (**Fig. 92-1**) are formed within thyroglobulin (TG), a large glycoprotein synthesized in the thyroid cell. Because of the unique tertiary structure of this glycoprotein, iodinated tyrosine residues present in TG are able to bind together to form active thyroid hormones.

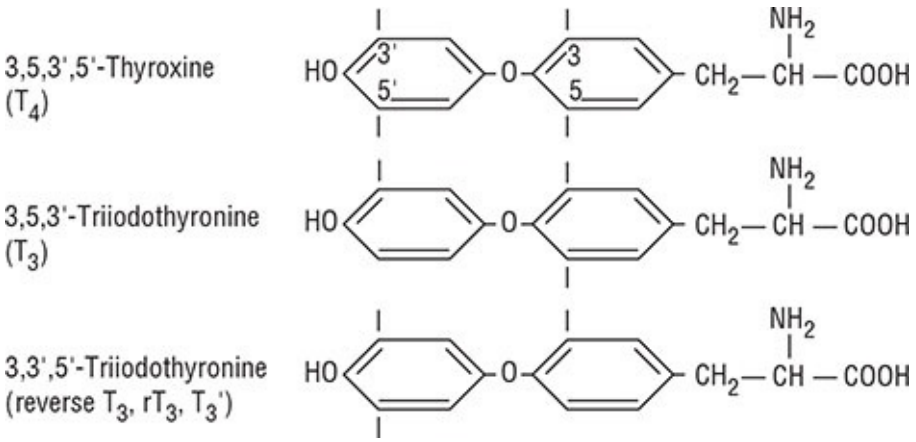


FIGURE 92-1 Structure of thyroid hormones.

Iodide is actively transported through the basolateral membrane via a Na^+/I^- symporter from the extracellular space into the thyroid follicular cell against an electrochemical gradient, driven by the coupled transport of sodium.[1] Structurally related anions such as thiocyanate (SCN^-), perchlorate (ClO_4^-), and pertechnetate (TcO_4^-) are competitive inhibitors of iodine transport.[1] In addition, bromine, fluorine, and, under certain circumstances, lithium block iodide transport into the thyroid (**Table 92-1**). Inorganic iodide that enters the thyroid follicular cell is ushered through the cell to the apical membrane, where it is transported into the follicular lumen by pendrin, and possibly other transport proteins.[1] Located on the luminal side of the apical membrane, thyroid peroxidase oxidizes iodide and covalently binds the organified iodide to tyrosine residues within TG (**Fig. 92-2**). It is interesting that although salivary glands and the gastric mucosa are able to actively transport iodide, they are unable to effectively incorporate iodide into proteins, given the lack of similar oxidizing machinery.

TABLE 92-1 Thyroid Hormone Synthesis and Secretion Inhibitors

Mechanism of Action	Substance
Blocks iodide transport into the thyroid	Bromine Fluorine Lithium
Impairs organification and coupling of thyroid hormones	Thionamides Sulfonamide Salicylamide Antipyrine
Inhibits thyroid hormone secretion	Iodide (large doses) Lithium

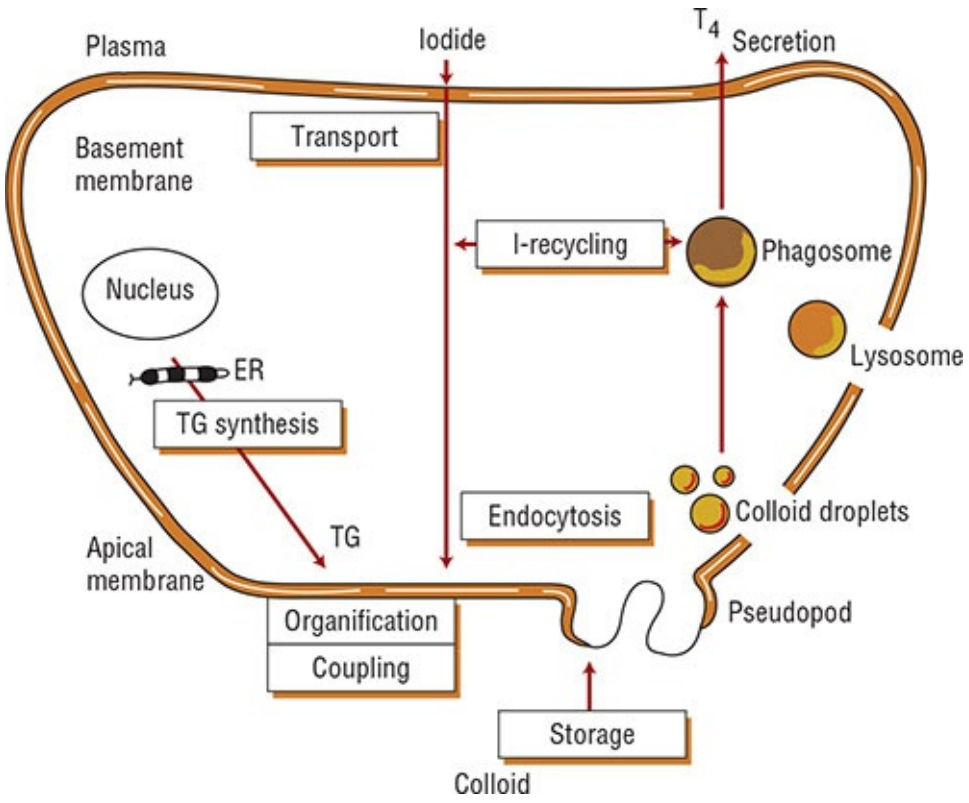


FIGURE 92-2 Thyroid hormone synthesis. Iodide is transported from the plasma, through the cell, to the apical membrane, where it is organified and coupled to the thyroglobulin (TG) synthesized within the thyroid cell. Hormone stored as colloid re-enters the cell through endocytosis and moves back toward the basal membrane, where thyroxine (T_4) is secreted.

The iodinated tyrosine residues monoiodotyrosine (MIT) and diiodotyrosine (DIT) combine to form iodothyronines (**Fig. 92-3**). Thus, two molecules of DIT combine to form T_4, whereas MIT and DIT constitute T_3. In addition to its role in iodine organification, the hemoprotein thyroid peroxidase also catalyzes the

formation of iodothyronines (coupling).

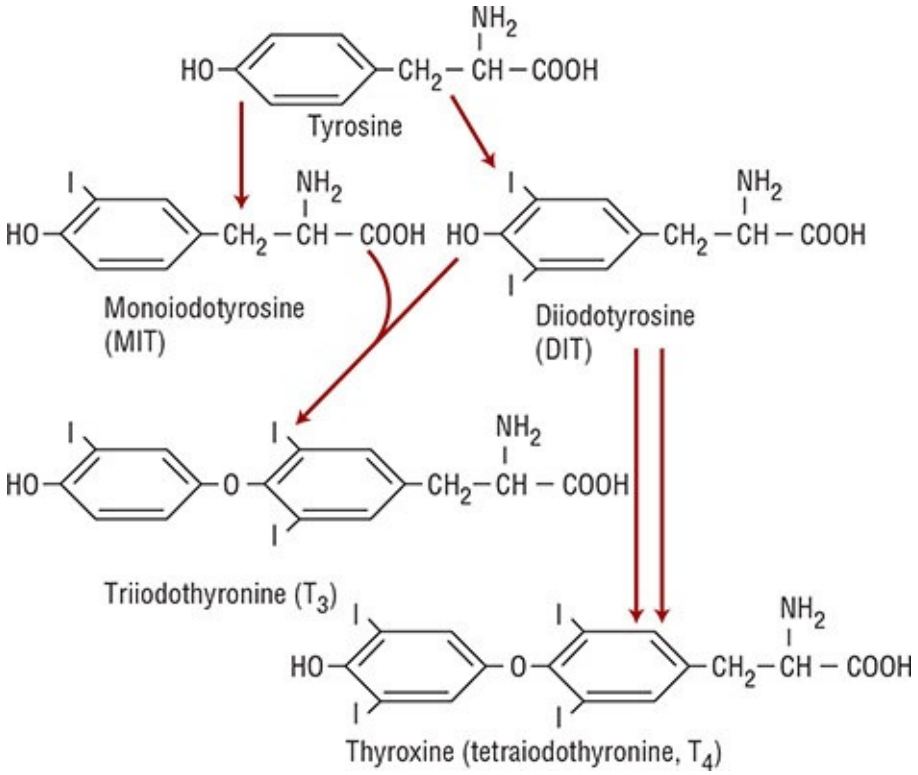


FIGURE 92-3 Scheme of coupling reactions. After tyrosine is iodinated to form monoiodotyrosine (MIT) or diiodotyrosine (DIT) (organification of the iodine), MIT and DIT combine to form triiodothyronine (T_3) or two molecules of DIT combine to form thyroxine T_4 (coupling).

Iodine deficiency causes an increase in the MIT:DIT ratio in TG and leads to a relative increase in the production of T_3.[2] Because T_3 is more potent than T_4, the increase in T_3 production in iodine-deficient areas may be beneficial. The thionamide drugs used to treat hyperthyroidism inhibit thyroid peroxidase and thus block thyroid hormone synthesis.

Thyroglobulin is stored in the follicular lumen and must re-enter the cell, where the process of proteolysis liberates thyroid hormone into the bloodstream. Thyroid follicles active in hormone synthesis are identified histologically by columnar epithelial cells lining a follicular lumen, which is depleted of colloid. Inactive follicles are lined by cuboidal epithelial cells and are replete with colloid. Both iodide and lithium block the release of preformed thyroid hormone, through poorly understood mechanisms.

T_4 and T_3 are transported in the bloodstream primarily by three proteins: (1)

thyroxine-binding globulin (TBG), (2) transthyretin (TTR), and (3) albumin. It is estimated that 99.96% of circulating T_4 and 99.5% of T_3 are bound to these proteins. However, only the unbound (free) thyroid hormone is able to diffuse into the cell, elicit a biologic effect, and regulate thyroid-stimulating hormone (TSH; also known as *thyrotropin*) secretion from the pituitary. Multiple functions have been ascribed to these transport proteins, including (a) assuring minimal urinary loss of iodide, (b) providing a mechanism for uniform tissue distribution of free hormone, and (c) transporting hormone into the central nervous system (CNS).

Whereas T_4 is secreted solely from the thyroid gland, less than 20% of T_3 is produced in the thyroid. The majority of T_3 is formed from the breakdown of T_4 catalyzed by the 5′-monodeiodinase enzymes found in extrathyroidal peripheral tissues. Because the binding affinity of nuclear thyroid hormone receptors (TRs) is 10 to 15 times higher for T_3 than for T_4, the deiodinase enzymes play a pivotal role in determining overall metabolic activity. Three different monodeiodinase enzymes are present in the body. Of the enzymes that catalyze 5′-monodeiodination, type I enzymes are present in peripheral tissues such as the liver and kidney, whereas type II enzymes are found in the CNS, pituitary, and thyroid. Type III enzymes, found in the placenta, skin, and developing brain, inactivate T_4 and T_3 by deiodinating the inner ring at the 5 position. The principal characteristics of these enzymes are listed in **Table 92-2**. T_4 may also be acted on by the enzyme 5′-monodeiodinase to form reverse T_3, but this accounts for a small component of hormone metabolism. Polymorphisms in the deiodinase genes may prove to be of clinical significance. For example, a polymorphism in the type I deiodinase leading to increased activity seems to be associated with an increased circulating ratio of free T_3 to free T_4.[3] Reverse T_3 has no known biologic activity. T_3 is removed from the body by deiodinating degradation and through the action of sulfotransferase enzyme systems converting to T_3 sulfate and 3,3-diiodothyronine sulfates, thus facilitating enterohepatic clearance. Thyronamines are derivatives of thyroid hormone that are present in low concentrations in human serum.[4] The most studied thyronamine, 3-iodothyronamine, can theoretically be made from T_4 by decarboxylation and deiodination. Administration of pharmacologic amounts of 3-iodothyronamine to animals has profound effects on temperature regulation and cardiac function, and shifts fuel metabolism from carbohydrates to lipids. However, a possible physiologic role for thyronamines has yet to be determined,

although altered levels may be associated with some disease states.[4]

TABLE 92-2 Properties of Iodothyronine 5'-Deiodinase Isoforms

Property	Type I	Type II	Type III
Susceptibility to propylthiouracil	High	Low	Low
Tissue localization	Thyroid, liver, kidney	Pituitary, thyroid, CNS, brown adipose tissue	Placenta, developing brain, skin
Preferred substrate	rT_3 and T_3	T_4 and rT_3	T_3 and T_4
Physiologic or pathophysiologic role	Clearance of rT_3 and T_3, the predominant extrathyroidal source of T_3 in hyperthyroidism	Intracellular T_3 production, especially for the brain in hypothyroidism or iodine deficiency, and maintenance of plasma T_3	Clearance of T_3 and T_4
Developmental expression	Expressed latest in development; predominant deiodinase in adult	Expressed second; especially high in brain and brown adipose tissue	Expressed first; high in developing brain; may be important for fetal thyroid hormone metabolism

rT_3, reverse T_3; T_3, triiodothyronine; T_4, thyroxine.

Thyroid Hormone Regulation and Action

The growth and function of the thyroid are stimulated by activation of the thyrotropin receptor by TSH.[5] The receptor belongs to the family of G-protein–coupled receptors. The thyrotropin receptor is coupled to the α subunit of the stimulatory guanine-nucleotide–binding protein ($G_s\alpha$), activating adenylate cyclase and increasing the accumulation of cyclic adenosine monophosphate. Through this mechanism, TSH stimulates the expression of Na^+/I^- symporter, TG, and thyroid peroxidase genes as well as increases apical iodide efflux. Somatic activating mutations in the receptor are commonly seen in autonomously functioning thyroid nodules.[6] Rarely, germline-activating mutations of the TSH receptor have been reported in kindreds with Leclere's syndrome, and thyrotoxicosis can result from germline-activating mutations in G-protein signaling in McCune–Albright syndrome. Conversely, thyrotropin resistance results from point mutations that prevent TSH binding, leading to abnormalities in the thyrotropin receptor–adenylate cyclase system and congenital hypothyroidism.[5] Individuals with this abnormality have high levels of TSH but decreased TG levels and a normal or small thyroid gland.

Thyroid hormone nuclear receptors regulate the transcription of target genes in the presence of physiologic concentrations of T_3.[7] Unlike most other nuclear receptors, TRs also actively regulate gene expression in the absence of hormone, typically resulting in an opposite effect. TRs translocate from the cytoplasm to

the nucleus, interact in the nucleus with T_3, and target genes and other proteins required for basal and T_3-dependent gene transcription. TRs exist in several isoforms, including TRβ1, TRβ2, and TRα1.[7] Thyroid hormone has different actions in different tissues based on tissue-specific expression of the different TR isoforms. There is interest in developing thyroid hormone analogs that selectively activate specific TR isoforms. Such agents could theoretically have targeted desirable effects such as stimulating energy expenditure without having adverse effects on other tissues.[8]

The production of thyroid hormone is regulated in two main ways. First, thyroid hormone is regulated by TSH secreted by the anterior pituitary. The secretion of TSH is itself under negative feedback control by the circulating level of free thyroid hormone and the positive influence of hypothalamic thyrotropin-releasing hormone (TRH). Second, extrathyroidal deiodination of T_4 to T_3 is regulated by a variety of factors including nutrition, nonthyroidal hormones, ambient temperatures, drugs, and illness.

HYPERTHYROIDISM AND THYROTOXICOSIS

Thyrotoxicosis results when tissues are exposed to excessive levels of T_4, T_3, or both.[9] Hyperthyroidism, which is one cause of thyrotoxicosis, refers specifically to overproduction of thyroid hormone by the thyroid gland.

EPIDEMIOLOGY—THYROTOXICOSIS

In the National Health and Nutrition Examination Survey (NHANES) III, 0.7% of those surveyed who were not taking thyroid medications and had no history of thyroid disease had subclinical hyperthyroidism (TSH less than 0.1 mIU/L, and T_4 normal), and 0.5% had “clinically significant” hyperthyroidism (TSH less than 0.1 mIU/L, and T_4 more than 13.2 mcg/dL [170 nmol/L]).[10] The prevalence of suppressed TSH values peaks in people aged 20 to 39, declines in those 40 to 79, and increases again in those 80 or older. Abnormal TSH levels were more common among women than among men.

ETIOLOGY AND PATHOPHYSIOLOGY—THYROTOXICOSIS

If the clinical history and examination do not provide pathognomonic clues to the etiology of the patient's thyrotoxicosis, measurement of the radioactive iodine uptake (RAIU) is critical in the evaluation (**Table 92-3**). The normal 24-hour RAIU ranges from 10% to 30% with some regional variation that is due to differences in iodine intake. An elevated RAIU indicates endogenous hyperthyroidism; that is, the patient's thyroid gland is actively overproducing T_4, T_3, or both. Conversely, a low RAIU in the absence of iodine excess indicates that high levels of thyroid hormone are not a consequence of thyroid gland hyperfunction but are likely due to thyroiditis or hormone ingestion. The importance of differentiating endogenous hyperthyroidism from other causes of thyrotoxicosis lies in the widely different prognosis and treatment of the diseases in these two categories. Therapy of thyrotoxicosis associated with thyroid hyperfunction is mainly directed at decreasing the rate of thyroid hormone synthesis, secretion, or both. Such measures are ineffective in treating thyrotoxicosis that is not the result of endogenous hyperthyroidism, because hormone synthesis and regulated hormone secretion are already at a minimum.

TABLE 92-3 Differential Diagnosis of Thyrotoxicosis

Increased RAIU[a]	Decreased RAIU
TSAb (Graves' disease)	Exogenous sources of thyroid hormone
Multinodular goiter	Medications containing thyroid hormone or iodine
Toxic adenoma	Painless thyroiditis
hCG (trophoblastic diseases)	Subacute thyroiditis
TSH-induced hyperthyroidism	Inflammatory thyroid disease
TSH-secreting tumors	Food sources containing thyroid gland
Selective pituitary resistance to T_4	Ectopic thyroid tissue
Thyroid stimulators other than TSH	Struma ovarii
	Metastatic follicular carcinoma

[a]The RAIU may be decreased if the patient has been recently exposed to excess iodine.

hCG, human chorionic gonadotropin; RAIU, radioactive iodine uptake; TSAb, thyroid-stimulating antibody; TSH, thyroid-stimulating hormone.

CLINICAL PRESENTATION Thyrotoxicosis

General

- Signs and symptoms of thyrotoxicosis affect multiple organ systems. Patients often have symptoms for an extended time period before the diagnosis of hyperthyroidism is made.

Symptoms

- The typical clinical manifestations of thyrotoxicosis include nervousness, anxiety, palpitations, emotional lability, easy fatigability, menstrual disturbances, and heat intolerance. A cardinal sign is weight loss despite an increased appetite.
- Elderly patients are more likely to develop atrial fibrillation with thyrotoxicosis than younger patients. The frequency of bowel movements may increase, but frank diarrhea is unusual. For the elderly patient and for the patient with very severe disease, anorexia may be present as well. Palpitations are a prominent and distressing symptom, particularly in the patient with pre-existing heart disease. Proximal muscle weakness is common and is noted on climbing stairs or in getting up from a sitting position. Women may note their menses are becoming scanty and irregular. Extremely thyrotoxic patients may have tachycardia, heart failure, psychosis, hyperpyrexia, and coma, a presentation described as thyroid storm.[11]

Signs

- A variety of physical signs may be observed including warm, smooth, moist skin, exophthalmos (in Graves' disease only), pretibial myxedema (in Graves' disease only), and unusually fine hair. Separation of the end of the fingernails from the nail beds (onycholysis) may be noted. Ocular signs that result from thyrotoxicosis include retraction of the eyelids and lagging of the upper lid behind the globe when the patient looks downward (lid lag). Physical signs of a hyperdynamic circulatory state are common and include tachycardia at rest, a widened pulse pressure, and a systolic ejection murmur. Gynecomastia is sometimes noted in men. Neuromuscular examination often reveals a fine tremor of the protruded tongue and outstretched hands. Deep tendon reflexes are generally hyperactive. Thyromegaly is usually present.

Diagnosis

- Low TSH serum concentration. Elevated free and total T_4 and T_3 serum concentrations, particularly in more severe disease.
- Elevated radioactive iodine uptake (RAIU) by the thyroid gland when the hormone is being overproduced; suppressed RAIU in thyrotoxicosis due to thyroid inflammation (thyroiditis).

Other Tests

- Thyroid-stimulating antibodies (TSAbs)
- TG
- Thyrotropin receptor antibodies

Causes of Thyrotoxicosis Associated with Elevated RAIU

Graves' Disease

1 Graves' disease is an autoimmune syndrome that usually includes hyperthyroidism, diffuse thyroid enlargement, exophthalmos, and, less commonly, pretibial myxedema and thyroid acropachy (**Fig. 92-4**).[9,12] Graves' disease is the most common cause of hyperthyroidism, with a prevalence estimated to be 3 per 1,000 population in the United States. Hyperthyroidism results from the action of thyroid-stimulating antibodies (TSAbs), which are directed against the thyrotropin receptor on the surface of the thyroid cell. When these immunoglobulins bind to the receptor, they activate downstream G-protein signaling and adenylate cyclase in the same manner as TSH. Autoantibodies that react with orbital muscle and fibroblast tissue in the skin are responsible for the extrathyroidal manifestations of Graves' disease, and these autoantibodies are encoded by the same germline genes that encode for other autoantibodies for striated muscle and thyroid peroxidase. Clinically, the extrathyroidal disorders may not appear at the same time that hyperthyroidism develops.

FIGURE 92-4 Features of Graves' disease. (*A*) Facial appearance in Graves' disease; lid retraction, periorbital edema, and proptosis are marked. (*B*) Thyroid dermopathy over the lateral aspects of the shins. (*C*) Thyroid acropachy. *(Reproduced with permission from Fauci AS, Kasper DL, Longo DL, et al., eds. Harrison's Principles of Internal Medicine. 16th ed. New York: McGraw-Hill; 2005:2114.).*

There is now compelling evidence that heredity predisposes the susceptible individual to the development of clinically overt autoimmune thyroid disease in the setting of appropriate environmental and hormonal triggers. A role for gender in the emergence of Graves' disease is suggested by the fact that

hyperthyroidism is approximately eight times more common in women than in men. Other lines of evidence support a role for heredity. First, there is a well-recognized clustering of Graves' disease within some families. Twin studies in Graves' disease have revealed that a monozygotic twin has a 35% likelihood of ultimately developing the disease compared with a 3% likelihood for a dizygotic twin, resulting in estimation that 79% of the predisposition to Graves' disease is genetic.[13] Second, the occurrence of other autoimmune diseases, including Hashimoto's thyroiditis, is also increased in families of patients with Graves' disease. Third, several studies have demonstrated an increased frequency of certain human leukocyte antigens (HLAs) in patients with Graves' disease. Differing HLA associations have been identified in the various ethnic groups studied. In whites, for example, the relative risk of Graves' disease in carriers of the HLA-DR3 haplotype is between 2.5 and 5, whereas lesser associations have been reported for HLA-B8 and the HLA-DQA*0501 allele.[14] Several gene loci have been associated with autoimmune thyroid diseases such as Graves' disease. It is thought that these susceptibility genes interact with environmental triggers to induce thyroid disease through epigenetic effects.[15]

The thyroid gland is diffusely enlarged in the majority of patients with Graves' disease and is commonly 40 to 60 g (two to three times the normal size). The surface of the gland is either smooth or bosselated, and the consistency varies from soft to firm. For patients with severe disease, a thrill may be felt and a systolic bruit may be heard over the gland, reflecting the increased intraglandular vascularity typical of hyperplasia. Whereas the presence of any of the extrathyroidal manifestations of this syndrome, including exophthalmos, pretibial myxedema, or thyroid acropachy, in a thyrotoxic patient is pathognomonic of Graves' disease, most patients can be diagnosed on the basis of their history and examination of their diffuse goiter (see Fig. 92-4). An important clinical feature of Graves' disease is the occurrence of spontaneous remissions, albeit uncommon. The abnormalities in TSAb production may decrease or disappear over time.

The results of laboratory tests in thyrotoxic Graves' disease include an increase in the overall hormone production rate with a disproportionate increase in T_3 relative to T_4 (**Table 92-4**). In an occasional patient, the disproportionate overproduction of T_3 is exaggerated, with the result that only the serum T_3 concentration is increased (T_3 toxicosis). The saturation of TBG is increased due to the elevated levels of serum T_4 and T_3. As a result, the concentrations of free T_4 and free T_3 are increased to an even greater extent than are the measured

serum total T_4 and T_3 concentrations. The TSH level will be suppressed or undetectable due to negative feedback by elevated levels of thyroid hormone at the pituitary.

TABLE 92-4 Thyroid Function Tests in Different Thyroid Conditions

	Total T_4	Free T_4	Total T_3	TSH
Normal	4.5–10.9 mcg/dL (58-140 nmol/L)	0.8–2.7 ng/dL (10.3-34.7 pmol/L)	60–181 ng/dL (0.92-2.79 nmol/L)	0.5–4.7 mIU/L
Hyperthyroid	↑↑	↑↑	↑↑↑	↓↓[a]
Hypothyroid	↓↓	↓↓	↓	↑↑[a]
Increased TBG	↑	Normal	↑	Normal

[a]Primary thyroid disease.

For the patient with symptomatic disease, measurement of the serum-free T_4 concentration, total T_4, total T_3, and the TSH value will confirm the diagnosis of thyrotoxicosis. For the patient who is not pregnant or lactating, a 24-hour RAIU should be obtained if there is any diagnostic uncertainty, for example, recent onset of symptoms or other factors suggestive of thyroiditis. An increased RAIU indicates that the thyroid gland is inappropriately utilizing the iodine to produce more thyroid hormone at a time when the patient is thyrotoxic.

Thyrotoxic periodic paralysis is a rare complication of hyperthyroidism most commonly observed in Asian and Hispanic populations.[16] It presents as recurrent proximal muscle flaccidity ranging from mild weakness to total paralysis. The paralysis may be asymmetric and usually involves muscle groups that are strenuously exercised before the attack. Cognition and sensory perception are spared, whereas deep tendon reflexes are markedly diminished. The condition is characterized by hypokalemia and low urinary potassium excretion. Hypokalemia results from a sudden shift of potassium from extracellular to intracellular sites rather than reduced total body potassium. High-carbohydrate loads and exercise provoke the attacks. Treatment includes correcting the hyperthyroid state, potassium administration, spironolactone to conserve potassium, and propranolol to minimize intracellular shifts. Some patients with this condition have a mutation in the inwardly rectifying potassium channel Kir2.6.[17]

Toxic Adenoma

An autonomous thyroid nodule is a discrete thyroid mass whose function is independent of pituitary and TSH control. The prevalence of toxic adenoma ranges from about 2% to 9% of thyrotoxic patients and depends on iodine availability and geographic location. Toxic adenomas are benign tumors that produce thyroid hormone. They arise from gain-of-function somatic mutations of the TSH receptor or, less commonly, the $G_s\alpha$ protein; more than a dozen TSH receptor mutations have been described.[6] These nodules may be referred to as *toxic adenomas*, or "hot" nodules, because of their persistent uptake on a radioiodine thyroid scan, despite suppressed uptake in the surrounding non-nodular gland (**Fig. 92-5**). The amount of thyroid hormone produced by an autonomous nodule is mass related. Therefore, hyperthyroidism usually occurs with larger nodules (ie, those more than 3 cm in diameter). Older patients (older than 60 years) are more likely (up to 60%) to be thyrotoxic from autonomous nodules than are younger patients (12%). There are many reports of isolated elevation of serum T_3 in patients with autonomously functioning nodules. Therefore, if the T_4 level is normal, a T_3 level must be measured to rule out T_3 toxicosis. If autonomous function is suspected but the TSH is normal, the diagnosis can be confirmed by a failure of the autonomous nodule to decrease its iodine uptake during exogenous T_3 administration sufficient to suppress TSH. Surgical resection, thionamides, percutaneous ethanol injection, and radioactive iodine (RAI) ablation are treatment options, but since thionamides do not halt the proliferative process in the nodule, definitive therapies are recommended. Ethanol ablation may be associated with pain and damage to surrounding extrathyroidal tissues, limiting its acceptance in the United States. It has been hypothesized that sublethal radiation doses received by the surrounding non-nodular thyroid tissue during RAI therapy of toxic nodules may lead to induction of thyroid cancer. However, thyroid cancer has rarely been associated with RAI therapy, and newer studies suggest hyperthyroidism itself, rather than RAI therapy, as being associated with non-thyroid malignancies.[18] An autonomously functioning nodule, if not large enough to cause thyrotoxicosis, can often be managed conservatively without therapy.

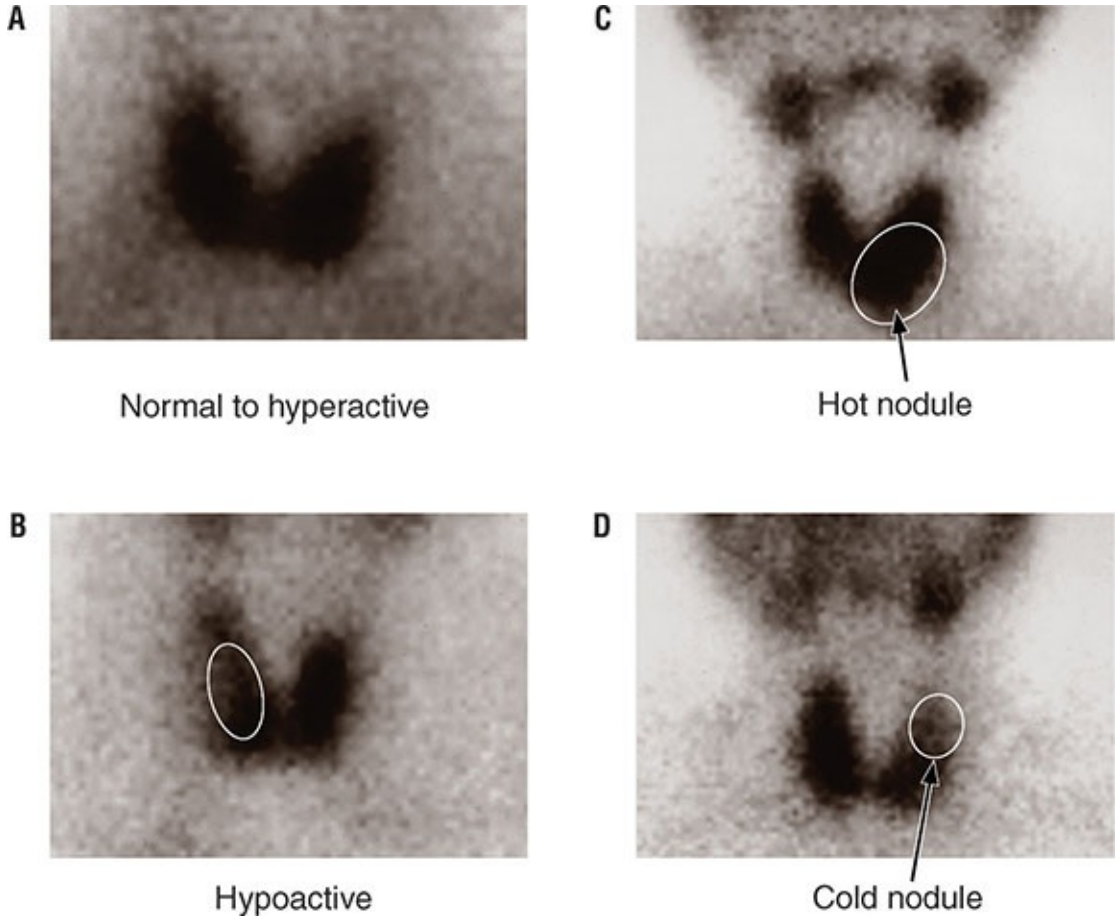


FIGURE 92-5 Radioiodine thyroid scans. (A) Normal or increased thyroid uptake of iodine-125 (^{125}I). (B) Thyroid with marked decrease in ^{125}I uptake in a large palpable mass. (C) Increased ^{125}I uptake isolated to a single nodule, the "hot nodule." (D) Decreased thyroid ^{125}I uptake in an isolated region, the "cold nodule." *(Reproduced with permission from Molina PE. Endocrine Physiology. 2nd ed. New York: McGraw-Hill; 2006:90. Images courtesy of Dr. Luis Linares, Memorial Medical Center, New Orleans, LA.).*

Multinodular Goiters

In multinodular goiters (MNGs), follicles with autonomous function coexist with normal or even nonfunctioning follicles. The pathogenesis of MNG is thought to be similar to that of toxic adenoma: diffuse hyperplasia caused by goitrogenic stimuli, leading to mutations and clonal expansion of benign neoplasms. The functional status of the nodule(s) depends on the nature of the underlying mutations, whether activating such as TSH receptor mutations or inhibitory such as RAS mutations. Thyrotoxicosis in an MNG occurs when a sufficient mass of autonomous follicles generates enough thyroid hormone to exceed the needs of

the patient. It is not surprising that this type of hyperthyroidism develops insidiously over a period of several years and predominantly affects older individuals with long-standing goiters. The patient's complaints of weight loss, depression, anxiety, and insomnia may be attributed to old age. Any unexplained chronic illness in an elderly patient presenting with an MNG calls for the exclusion of hidden (silent) thyrotoxicosis.[19] Current third-generation TSH assays are able to detect subclinical hyperthyroidism.

A thyroid scan will show patchy areas of autonomously functioning thyroid tissue intermixed with hypofunctioning areas. When the patient is euthyroid, therapy is based on the need to reduce goiter size due to mass-related symptoms such as dysphagia. Doses of thyroid hormone sufficient to suppress TSH levels may slow goiter growth or cause some degree of shrinkage, but, in general, suppression therapy for nodular disease is inadequate to address mass effect. The preferred treatment for toxic MNG is RAI or surgery. Surgery is usually selected for younger patients and patients in whom large goiters impinge on vital organs. Alternatively, percutaneous injection of 95% ethanol has also been used to destroy single or multinodular adenomas with a 5-year success rate approaching 80%.

Trophoblastic Diseases Human chorionic gonadotropin is a stimulator of the TSH receptor and may cause hyperthyroidism. The basis for the thyrotropic effect of hCG is the structural similarity of hCG to TSH (similar α subunits and unique β subunits). For patients with hyperthyroidism caused by trophoblastic tumors, serum hCG levels usually exceed 300 U/mL (kU/L) and always exceed 100 U/mL (kU/L). The mean peak hCG level in normal pregnancy is 50 U/mL (kU/L). On a molar basis, hCG has only 1/10,000 the activity of pituitary TSH in mouse bioassays. Nevertheless, this thyrotropic activity may be very substantial for patients with trophoblastic tumors, whose serum hCG concentrations may reach 2,000 U/mL (kU/L).

TSH-Induced Hyperthyroidism To better understand these syndromes, we must first review TSH biosynthesis and secretion. TSH is synthesized in the anterior pituitary as separate α- and β-subunit precursors. The α subunits from luteinizing hormone (LH), follicle-stimulating hormone (FSH), human chorionic gonadotropin (hCG), and TSH are similar, whereas the β subunits are unique and confer immunologic and biologic specificity. Free β subunits are devoid of receptor-binding and biologic activity and require combination with an α subunit to express their activity. Criteria for the diagnosis of TSH-induced hyperthyroidism include (a) evidence of peripheral hypermetabolism, (b) diffuse

thyroid gland enlargement, (c) elevated free thyroid hormone levels, and (d) elevated or inappropriately “normal” serum immunoreactive TSH concentrations. Because the pituitary gland is extremely sensitive to even minimal elevations of free T4, a “normal” or elevated TSH level in any thyrotoxic patient indicates the inappropriate production of TSH.

TSH-Secreting Pituitary Adenomas TSH-secreting pituitary tumors occur sporadically and release a biologically active hormone that is unresponsive to normal feedback control.[20] The mean age at diagnosis is around 40 years, with women being diagnosed more than men (8:7). These tumors may co-secrete prolactin or growth hormone; therefore, the patients may present with amenorrhea/galactorrhea or signs of acromegaly. Most patients present with classic symptoms and signs of thyrotoxicosis. Visual field defects may be present due to impingement of the optic chiasm by the tumor. Tumor growth and worsening visual field defects have been reported following antithyroid therapy because lowering of thyroid hormone levels is associated with loss of feedback inhibition from high thyroid hormone levels.

Diagnosis of a TSH-secreting adenoma should be made by demonstrating lack of TSH response to TRH stimulation, inappropriate TSH levels, elevated α-subunit levels, and radiologic imaging; given the lack of routine availability of TRH, the other three criteria are essential. Note that some small tumors are not identified by MRI. Moreover, 10% of “normal” individuals may have incidental pituitary tumors or other benign focal lesions noted on pituitary imaging.

Transsphenoidal pituitary surgery is the treatment of choice for TSH-secreting adenomas. Pituitary gland irradiation is often given following surgery to prevent tumor recurrence. Dopamine agonists and octreotide have been used to treat tumors, especially those that co-secrete prolactin.

Pituitary Resistance to Thyroid Hormone Resistance to thyroid hormone is a rare condition that can be due to a number of molecular defects, including mutations in the TRβ gene. Pituitary resistance to thyroid hormone (PRTH) refers to selective resistance of the pituitary thyrotrophs to thyroid hormone. As nonpituitary tissues respond normally to thyroid hormone, patients experience the toxic peripheral effects of thyroid hormone excess. About 90% of patients studied have an appropriate increase in TSH in response to TRH; conversely, the TSH will be suppressed by T3 administration.

Patients with PRTH require treatment to reduce their elevated thyroid hormone levels. Determining the appropriate serum T4 level is difficult because TSH cannot be used to evaluate adequacy of therapy. Any reduction in thyroid

hormone carries the risk of inducing thyrotroph hyperplasia. Ideally, agents that suppress TSH secretion could be used to treat these individuals. Glucocorticoids, dopaminergic drugs, somatostatin and its analogs, and thyroid hormone analogs with reduced metabolic activity have all been tried, but with relatively little benefit. β-Blocker therapy can also be used. Triiodothyroacetic acid (TRIAC), an agent that is devoid of thyromimetic properties on peripheral tissues, but blocks the secretion of TSH, has been used to treat this condition. However, it is not available in the United States. Given the ability of retinoid X receptor ligands to inhibit TSH production, drugs such as bexarotene may have therapeutic benefit in PRTH.

Causes of Thyrotoxicosis Associated with Suppressed RAIU

Subacute Thyroiditis

Painful subacute (granulomatous or de Quervain) thyroiditis often develops after a viral syndrome, but rarely has a specific virus been identified in thyroid parenchyma.[21] A genetic predisposition exists, with markedly higher risk for developing subacute thyroiditis for patients with HLA-Bw35. Systemic symptoms often accompany the syndrome, including fever, malaise, and myalgia, in addition to those symptoms due to thyrotoxicosis. Typically, patients complain of severe pain in the thyroid region, which often extends to the ear on the affected side. With time, the pain may migrate from one side of the gland to the other. On physical examination, the thyroid gland is firm and exquisitely tender. Signs of thyrotoxicosis are present.

Thyroid function tests typically run a triphasic course. Initially, serum T_4 levels are elevated due to release of preformed thyroid hormone from disrupted follicles. The 24-hour RAIU during this time is less than 2% due to thyroid inflammation and TSH suppression by the elevated T_4 level. As the disease progresses, intrathyroidal hormone stores are depleted, and the patient may become mildly hypothyroid with an appropriately elevated TSH level. During the recovery phase, thyroid hormone stores are replenished, and serum TSH concentration gradually returns to normal. Recovery is generally complete within 2 to 6 months. Most patients remain euthyroid, and recurrences of painful thyroiditis are extremely rare. The patient with painful thyroiditis should be reassured that the disease is self-limited and is unlikely to recur. Thyrotoxic symptoms may be relieved with β-blockers. NSAIDs will usually relieve the

pain. Occasionally, prednisone (30-40 mg daily) must be used to suppress the inflammatory process. Antithyroid drugs are not indicated because they will not be effective as they do not decrease the release of preformed thyroid hormone.

Painless Thyroiditis

Since its description in 1975, painless (silent and lymphocytic) thyroiditis has been recognized as a common cause of thyrotoxicosis and may represent up to 15% of cases of thyrotoxicosis in North America. In the setting of development of lymphocytic thyroiditis during the first 12 months after the end of pregnancy, the condition is also called *postpartum thyroiditis*. The etiology is not fully understood and may be heterogeneous, but evidence indicates that autoimmunity underlies most cases. There is an increased frequency of HLA-DR3 and DR5 in patients with painless thyroiditis; non-endocrine autoimmune diseases are also more common. Histologically, diffuse lymphocytic infiltration is generally identified. The triphasic course of this illness mimics that of subacute thyroiditis. Most patients present with mild thyrotoxic symptoms. Lid retraction and lid lag are present, but exophthalmos is absent. The thyroid gland may be diffusely enlarged, but thyroid tenderness is absent.

The 24-hour RAIU will typically be suppressed to less than 2% during the thyrotoxic phase of painless thyroiditis. Anti-TG and antithyroid peroxidase antibody (anti-TPOAb) levels are elevated in more than 50% of patients. Patients with mild hyperthyroidism and painless thyroiditis should be reassured that they have a self-limited disease, although patients with postpartum thyroiditis may experience a recurrence of the disease with subsequent pregnancies. As with other thyrotoxic syndromes, adrenergic symptoms may be ameliorated with propranolol or metoprolol. Antithyroid drugs, which inhibit new hormone synthesis, are not indicated because they do not decrease the release of preformed thyroid hormone. A small proportion of patients may have recurrent episodes of thyroiditis, or may develop permanent hypothyroidism.[21]

Exogenous Thyroid Hormone

Thyrotoxicosis factitia is hyperthyroidism due to ingestion of thyroid hormone. This category includes hyperthyroidism produced by the intentional ingestion of exogenous thyroid hormone. Obesity is the most common non-thyroidal disorder for which thyroid hormone is inappropriately used, but thyroid hormone has been used for almost every conceivable problem from menstrual irregularities and infertility to hypercholesterolemia and baldness. There is little evidence to suggest that treatment with thyroid hormone is beneficial for any of these

conditions in euthyroid individuals.[22] Thyrotoxicosis factitia can also occur when too large a dose of thyroid hormone is used to treat conditions in which it is likely to be beneficial, such as differentiated thyroid carcinoma. In addition to this iatrogenic cause, thyrotoxicosis factitia may occur after accidental pediatric ingestion or pharmacy error. Thyrotoxicosis factitia may also be caused by the purposeful and secretive ingestion of thyroid hormone by patients (usually with a medical background) who wish to obtain attention or lose weight.

Thyroid hormone may also be accidentally ingested in food sources. Reports of thyrotoxicosis in Minnesota and Nebraska in the 1980s were attributed to ingestion of ground beef contaminated by bovine thyroid glands. More recently thyrotoxicosis due to porcine thyroid tissue in meat products has been reported in Spain and Uruguay.[23]

Thyrotoxicosis factitia should be suspected in a thyrotoxic patient without evidence of increased hormone production, thyroidal inflammation, or ectopic thyroid tissue. The RAIU is at low levels because the patient's thyroid gland function is suppressed by the exogenous thyroid hormone. Measurement of plasma TG is a valuable laboratory aid in the diagnosis of thyrotoxicosis factitia. TG is normally secreted in small amounts by the thyroid gland; however, when thyroid hormone is taken orally, TG levels tend to be lower than the normal range. In other entities characterized by a low RAIU, such as thyroiditis, leakage of preformed thyroid hormone results in elevated TG levels. If a history of thyroid hormone ingestion is elicited or deduced, exogenous thyroid hormone should be withheld for 4 to 6 weeks, and thyroid function tests should be repeated to ensure a euthyroid state has been restored. Rarely, thyroid hormones may be the drug of abuse and detection is difficult with standard thyroid hormone assays. For example, tiratricol (TRIAC), an endogenous metabolite of T_3 that has been used for weight loss and paradoxically by bodybuilders, will suppress TSH at high doses and may cross-react in many T_3 immunoassays; thus, thyrotoxicosis factitia due to tiratricol abuse may be misinterpreted as T_3 toxicosis, and also lead to serious side effects.[24]

Medications Containing Iodine

Amiodarone may induce thyrotoxicosis (2%–3% of patients), overt hypothyroidism (5% of patients), subclinical hypothyroidism (25% of patients), or euthyroid hyperthyroxinemia, depending on the underlying thyroid function and pathology.[25] Because amiodarone contains 37% iodine by weight, approximately 6 mg/day of iodine is released for each 200 mg of amiodarone,

1,000 times greater than the recommended daily amount of iodine of 150 mcg/day. As a result of this iodine overload, iodine-exacerbated thyroid dysfunction commonly occurs among those patients with pre-existing thyroid disease: thyrotoxicosis in patients with hyperthyroidism or euthyroid nodular autonomy and hypothyroidism in patients with autoimmune thyroid disease. In contrast to hyperthyroidism with increased synthesis of thyroid hormone induced by amiodarone (type I), destructive thyroiditis with leakage of TG and thyroid hormones also occurs (type II), typically among individuals with otherwise normal glands. The two types of amiodarone-induced thyrotoxicosis may be differentiated using color-flow Doppler ultrasonography. Such distinction is critically important, given the therapeutic implications of the two syndromes: type I amiodarone-induced hyperthyroidism responds somewhat to thionamides, whereas type II may respond to glucocorticoids.[25] Obviously, RAI therapy is inappropriate in type I due to the drug-induced iodine excess, and in type II due to lack of increased hormone synthesis. The manifestations of amiodarone-induced thyrotoxicosis may be atypical symptoms such as ventricular tachycardia and exacerbation of the underlying chronic obstructive pulmonary disease, both of which are significant, given the severe underlying cardiac pathology that led to the use of amiodarone in the first place. Amiodarone also directly interferes with type I 5′-deiodinase, leading to reduced conversion of T_4 to T_3 and hyperthyroxinemia without thyrotoxicosis.[25]

High intake of biotin can interfere with thyroid hormone assays, leading to false results of thyroid function tests.[26,27] Excess biotin leads to falsely elevated results of TT4, FT4 and TT3 (competitive immunoassays), and to falsely low TSH levels (immunometric or sandwich immunoassays). This is not an issue of endogenous interference but an interference with the assay itself. Biotin doses of greater than 5,000 mcg/day are associated with major interference on immunoassays; in such circumstances, it is recommended patients hold their biotin doses for 24 to 48 hours before laboratory testing.

Thyroid Cancer

In widely metastatic differentiated papillary or follicular carcinomas with relatively well-preserved function, sufficient thyroid hormones can be synthesized and secreted to produce thyrotoxicosis. In most instances, a previous diagnosis of thyroid malignancy has been made. The diagnosis can be confirmed by whole-body ^{131}I scanning. Treatment with ^{131}I is generally effective at ablating functioning thyroid metastases.

Struma Ovarii

Struma ovarii is a teratoma of the ovary that contains differentiated thyroid follicular cells and is capable of making thyroid hormone. This extremely rare cause of thyrotoxicosis is suggested by the absence of thyroid enlargement in a thyrotoxic patient with a suppressed RAIU in the neck and no findings to suggest thyroiditis. The diagnosis is established by localizing functioning thyroid tissue in the ovary with whole-body RAI (sodium iodide-131 [^{131}I]) scanning. Interestingly, struma ovarii not associated with hyperthyroidism is much more common than struma ovarii associated with hyperthyroidism. Because the tissue is neoplastic and potentially malignant, combined surgical and radioiodine treatment of malignant struma ovarii for both monitoring and therapy of relapse is the recommended treatment.

TREATMENT

Thyrotoxicosis

2 Three common treatment modalities are used in the management of hyperthyroidism: surgery, antithyroid medications, and RAI (Table 92-5).

TABLE 92-5 Treatments for Hyperthyroidism Caused by Graves' Disease

Treatment	Advantages	Disadvantages	Comment
Methimazole (first-line pharmacotherapy) Propylthiouracil (second-line pharmacotherapy)	Noninvasive Low initial cost Low risk of permanent hypothyroidism Possible remissions due to immune effects	Low cure rate (average 40%-50%) Adverse drug reactions Drug compliance	First-line treatment in children, adolescents, and pregnancy Initial treatment in severe cases or preoperative preparation
Radioactive iodine (^{131}I)	Cure of hyperthyroidism Lowest cost, before adjustment for quality of life	Permanent hypothyroidism almost inevitable Might worsen ophthalmopathy Pregnancy must be deferred for 6-12 months; no breast-feeding Small potential risk of exacerbation of hyperthyroidism	Best treatment for toxic nodules and toxic multinodular goiter
Surgery	Rapid, effective treatment, especially in patients with large goiters	Most invasive Least costly in long term after quality-of-life adjustment Permanent hypothyroidism Pain, scar	Potential choice in pregnancy (2nd trimester) if major side effect from antithyroid drugs Potential complications (recurrent laryngeal nerve damage, hypoparathyroidism) Useful when coexisting suspicious nodule present Option for patients who refuse radioiodine

Desired Outcomes

The overall therapeutic objectives are to eliminate the excess thyroid hormone and minimize the symptoms and long-term consequences of hyperthyroidism.

General Approach to Treatment

Therapy must be individualized based on the type and severity of hyperthyroidism, patient age and gender, the existence of nonthyroidal conditions, and response to previous therapy.[28,29] For example, patients with swallowing or breathing difficulties due to impingement of the esophagus or trachea are generally taken for surgical removal of the thyroid. Clinical guidelines for the treatment of hyperthyroidism have been published.[9] Selected recommendations from these guidelines are shown (**Table 92-6**).

TABLE 92-6 Selected Recommendations from the American Thyroid Association Hyperthyroidism Guidelines[9]

Question	Recommendation Strength	Quality of Evidence
How should thyrotoxicosis be evaluated and initially managed?	β-Adrenergic blockade is recommended in all patients with symptomatic thyrotoxicosis, especially elderly patients and thyrotoxic patients with resting heart rates in excess of 90 beats per minute or coexistent cardiovascular disease.	Strong recommendation, moderate quality
If ^{131}I therapy is chosen (*for GD*), how should it be accomplished?	Sufficient radiation should be administered in a single dose (typically 10-15 mCi [370-555 MBq]) to render the patient with GD hypothyroid.	Strong recommendation, moderate quality
If antithyroid drugs are chosen as initial management of GD, how should the therapy be managed?	Methimazole should be used in virtually every patient who chooses antithyroid drug therapy for GD, except during the first trimester of pregnancy when propylthiouracil is preferred, in the treatment of thyroid storm, and in patients with minor reactions to methimazole who refuse radioactive iodine therapy or surgery.	Strong recommendation, moderate quality
If antithyroid drugs are chosen as initial management of GD, how should patients be monitored?	A differential white blood cell (WBC) count should be obtained during febrile illness and at the onset of pharyngitis in all patients taking antithyroid medication.	Strong recommendation, low-quality
If thyroidectomy is chosen for treatment of GD, how should it be accomplished?	If surgery is chosen as the primary therapy for GD, near-total or total thyroidectomy is the procedure of choice.	Strong recommendation, low quality
If thyroidectomy is chosen for treatment of GD, how should it be accomplished?	Patients should be rendered euthyroid prior to the procedure.	Strong recommendation, moderate quality
How should overt hyperthyroidism due to TMNG or TA be managed?	Patients should be treated with RAI therapy or thyroidectomy.	Weak recommendation, moderate quality
How should GD be managed in children and adolescents?	Children with GD should be treated with MMI, RAI therapy, or thyroidectomy. RAI therapy should be avoided in very young children (<5 years). Under age 5, thyroidectomy should be performed.	Strong recommendation, moderate quality
How should hyperthyroidism in pregnancy be managed?	ATD therapy should be used for overt hyperthyroidism due to GD during pregnancy. PTU should be used when ATD therapy is given during the first trimester. MMI should be used when ATD therapy is started after the first trimester.	Strong recommendation, low quality
How should antithyroid treatment be managed during pregnancy?	GD during pregnancy should be treated with the lowest possible dose of antithyroid drugs needed to keep the mother's thyroid hormone levels at or slightly above the reference range for total T4 and T3 values in pregnancy (1.5 times above nonpregnant reference ranges in the second and third trimesters), and the TSH below the reference range for pregnancy. Similarly, free T4 levels should be kept at or slightly above the upper limit of the pregnancy trimester reference range for the assay. Thyroid function should be assessed monthly, and the antithyroid drug dose adjusted as required.	Strong recommendation, low quality
How should other causes of thyrotoxicosis be managed?	Patients taking medications known to cause thyrotoxicosis, including interferon (IFN)-α, interleukin-2, tyrosine kinase inhibitors, and lithium, should be monitored clinically and biochemically at 6-month intervals for the development of thyroid dysfunction.	Strong recommendation, low quality

ATD, antithyroid drug; GD, Graves' disease; ^{131}I, radioactive I-131; TMNG, toxic multinodular goiter; TA, toxic adenoma; SH, subclinical hyperthyroidism.

Nonpharmacologic Therapy

Surgery should be considered for patients with a large thyroid gland (more than 80 g), severe ophthalmopathy, and a lack of remission on antithyroid drug treatment. In case of cosmetic issues or pressure symptoms, the choice in MNG stands between surgery, which is still the first choice, and radioiodine therapy if uptake is adequate. In addition to surgery, the solitary nodule, whether hot or cold, can be treated with percutaneous ethanol injection therapy. For hot nodules, radioiodine is the therapy of choice.[9] Appropriate preparation of the patient for thyroidectomy includes MMI until the patient is biochemically euthyroid (usually 6-8 weeks), followed by the addition of iodides (500 mg/day) for 10 to 14 days before surgery to decrease the vascularity of the gland. Propranolol for several weeks preoperatively and 7 to 10 days after surgery has also been used to maintain a pulse rate of less than 90 beats/min. Combined pretreatment with propranolol and 10 to 14 days of potassium iodide also has been advocated.

The overall complication rate when surgery is performed for MNG by an experienced endocrine surgeon is low. If subtotal thyroidectomy, or an operation that attempts to maintain euthyroidism, is performed for Graves' disease, there is a risk of recurrence of hyperthyroidism that is directly related to remnant thyroid gland size. Near total thyroidectomy is generally recognized as the procedure of choice for patients with Graves' disease.[9] The complication rates of surgery for Graves' disease are low when surgery is performed by a high-volume thyroid surgeon. Surgical complications include hypoparathyroidism (up to 2%) and laryngeal nerve injury (up to 1%). Formal cost-effective analysis indicates that a total thyroidectomy may be the most cost-effective method for managing hyperthyroidism when considering outcomes in quality-adjusted life-years.[30]

Pharmacologic Therapy

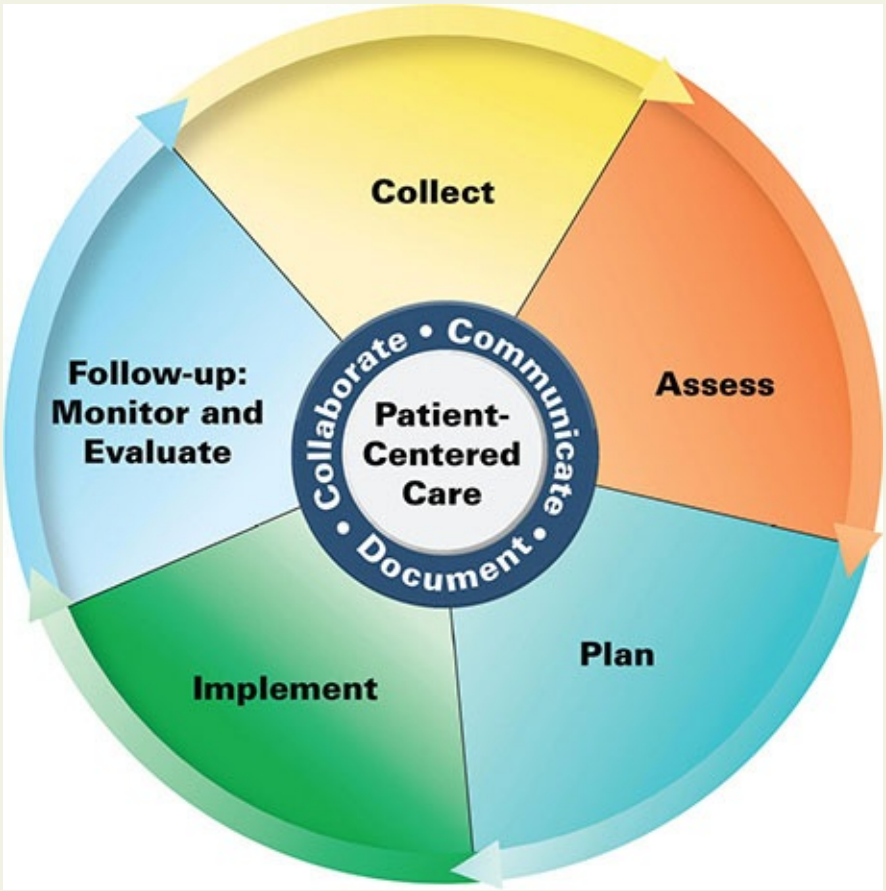
Antithyroid Medications

3 **Thionamide Drugs** Two drugs within this category, MMI and PTU, are approved for the treatment of hyperthyroidism in the United States.[31] They are classified as thioureylenes (thionamides), which incorporate an N–C–S=N group into their ring structures.

Mechanism of Action MMI and PTU share several mechanisms to inhibit the

biosynthesis of thyroid hormone.[32] These drugs serve as preferential substrates for the iodinating intermediate of thyroid peroxidase and divert iodine away from potential iodination sites in TG. This prevents subsequent incorporation of iodine into iodotyrosines and ultimately iodothyronine ("organification"). Second, they inhibit coupling of MIT and DIT to form T_4 and T_3. The coupling reaction may be more sensitive to these drugs than the iodination reaction. Experimentally, these drugs exhibit immunosuppressive effects, although the clinical relevance of this finding is unclear. For patients with Graves' disease, antithyroid drug treatment has been associated with lower TSAb titers and restoration of normal suppressor T-cell function. However, perchlorate (ClO_4^-), which has a different mechanism of action, also decreases TSAbs, suggesting that normalization of the thyroid hormone level may itself improve the abnormal immune function. PTU inhibits the peripheral conversion of T_4 to T_3. This effect is dose related and occurs within hours of PTU administration. MMI does not have this effect. After several weeks of use, depletion of stored hormone and lack of continuing synthesis of thyroid hormone results in the clinical effects of these drugs.

Pharmacokinetics Both antithyroid drugs are well absorbed (80%-95%) from the gastrointestinal tract, with peak serum concentrations about 1 hour after ingestion. The plasma half-life ranges of PTU and MMI are 1 to 2.5 and 6 to 9 hours, respectively, and are not appreciably affected by thyroid status. Urinary excretion is about 35% for PTU and less than 10% for MMI. These drugs are actively concentrated in the thyroid gland, which may account for the disparity between their relatively short plasma half-lives and the effectiveness of once-daily dosing regimens even with PTU. Approximately 60% to 80% of PTU is bound to plasma albumin, whereas MMI is not protein bound. MMI readily crosses the placenta and appears in breast milk. Older studies suggested that PTU crosses the placental membranes only one tenth as well as MMI; however, these studies were done in the course of therapeutic abortion early in pregnancy. Newer studies show little difference between fetal concentrations of PTU and MMI, and both are associated with elevated TSH in about 20% and low T_4 in about 7% of fetuses.[33]



Patient Care Process for the Management of Hyperthyroidism

Collect

- Patient characteristics (eg, age, race, sex, pregnancy status)
- Patient history (past medical, family, social) including patient signs and symptoms: warm, smooth, moist skin, palpitations, exophthalmos, pretibial myxedema, and unusually fine hair; anxiety, tremor, heat intolerance, tachycardia, weight loss, and menstrual disturbances (see Clinical Presentation Box)
- Current medications (including over-the-counter [OTC] and herbal medication use)
- Objective data
    - Heart rate, blood pressure (BP), weight, and body mass index (BMI)
    - Labs (eg, FT4, TT3, TSH, thyroid-stimulating antibodies; serum electrolytes, Scr, ALT)

- Other diagnostic tests when indicated (eg, thyroid ultrasound, RAIU scan)

Assess

- Cause of hyperthyroidism (see Table 92-3)
- Current medications that may contribute to or worsen hyperthyroidism
- Current medications that may interact with antithyroid therapy
- Appropriateness and effectiveness of current antithyroid regimen

Plan*

- Drug therapy regimen including specific antithyroid therapy, dose, and duration (see Table 92-5)
- Monitoring parameters including efficacy (eg, resolution of signs and symptoms) and safety (symptomatic hypothyroidism, adverse effects of medications), laboratory tests (TSH, FT4, TT3, LFTs, and CBC), and time frame
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug therapy)

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Resolution of signs and symptoms
- Presence of adverse effects
- Patient adherence to treatment plan using multiple sources of information

** Collaborate with patient, caregivers, and other healthcare professionals.*

4 ***Dosing and Administration*** MMI is available as 5 and 10 mg tablets and PTU as 50 mg tablets. MMI is approximately 10 to 20 times more potent than PTU. Initial therapy with MMI is given in two or three divided doses totaling 30 to 60 mg/day. PTU is given in dose ranges from 300 to 600 mg daily, usually in

three or four divided doses. Although the traditional recommendation is for divided doses, evidence exists that both drugs can be given as single daily doses. Patients with severe hyperthyroidism may require larger initial doses, and some may respond better at these larger doses if the dose is divided. The maximal blocking doses of MMI and PTU are 120 and 1,200 mg daily, respectively. Once the intrathyroidal pool of thyroid hormone is reduced and new hormone synthesis is sufficiently blocked, clinical improvement should ensue. Usually within 4 to 8 weeks of initiating therapy, symptoms will diminish and circulating thyroid hormone levels will return to normal. At this time the tapering regimen can be started. Changes in dose for each drug should be made on a monthly basis because the endogenously produced T_4 will reach a new steady-state concentration in this interval. Typical ranges of daily maintenance doses for MMI and PTU are 5 to 30 mg and 50 to 300 mg, respectively.

If the objective of therapy is to induce a long-term remission in a patient with Graves' Disease, the patient should remain on continuous antithyroid drug therapy for 12 to 24 months. Antithyroid drug therapy induces permanent remission rates of 10% to 98%, with an overall average of about 40% to 50%.[34] This is much higher than the remission rate seen with propranolol alone (22%–36%). Patient characteristics for a favorable outcome include older patients (older than 40 years), low T_4:T_3 ratio (less than 20), a small goiter (less than 50 g), short duration of disease (less than 6 months), no previous history of relapse with antithyroid drugs, duration of therapy 1 to 2 years or longer, and low TSAb titers at baseline or a reduction with treatment.[32] A 2012 study provides preliminary evidence that a new assay that has better specificity for detection of antibodies that stimulate the TSH receptors, without detecting coexistent blocking antibodies, may be a useful predictor of remission of Graves' disease.[35]

It is important that patients be followed every 6 to 12 months after remission occurs. If a relapse occurs, alternate therapy with RAI is preferred over a second course of antithyroid drugs. Relapses seem to plateau after about 5 years and eventually 5% to 20% of patients will develop spontaneous hypothyroidism. There has been interest in whether concurrent administration of T_4 with thionamide therapy for thyrotoxicosis and subclinical hyperthyroidism can reduce autoantibodies directed toward the thyroid gland and improve remission rate. In a Japanese study, adjunctive treatment with T_4 was associated with a 20-fold reduction in the recurrence rate of Graves' disease compared with the recurrence rate seen for patients treated with antithyroid drugs alone.[36] Attempts to reproduce these results in American and European patients with Graves'

disease have failed to show any delay or reduction in the recurrence of Graves' disease with T_4 administration, and this approach is generally not recommended because of the higher rates of side effects seen with the larger doses of antithyroid drugs needed with this regimen.[9]

Subclinical hyperthyroidism is defined as the finding of a serum TSH below the lower limit of the reference range combined with free T_4 and T_3 concentrations that are normal. Subclinical hyperthyroidism is associated with an increased risk of atrial fibrillation, and may be associated with increased all-cause mortality. Some studies show an increased risk of hip fractures in postmenopausal women with subclinical hyperthyroidism. Most practitioners agree that treatment of older patients (greater than 65 years) with TSH values below 0.1 mIU/L is reasonable. In patients who are younger or have TSH values of 0.1 to 0.4 mIU/L a decision whether to treat the patient for mild hyperthyroidism or to monitor thyroid function depends on the patient's cardiovascular risk factors and bone health.[9,37]

Adverse Effects Minor adverse reactions to MMI and PTU have an overall incidence of 5% to 25% depending on the dose and the drug, whereas major adverse effects occur in 1.5% to 4.6% of patients receiving these drugs.[31] Pruritic maculopapular rashes (sometimes associated with vasculitis based on skin biopsy), arthralgias, and fevers occur in up to 5% of patients and may occur at a greater frequency with higher doses and in children. Rashes often disappear spontaneously but, if persistent, may be managed with antihistamines.

One of the most common side effects is a benign transient leukopenia characterized by a WBC count of less than 4,000/mm^3 (4 x 10^9/L) This condition occurs in up to 12% of adults and 25% of children, and sometimes can be confused with mild leukopenia seen in Graves' disease. This mild leukopenia is not a harbinger of the more serious adverse effect of agranulocytosis, so therapy can usually be continued. If a minor adverse reaction occurs with one antithyroid drug, the alternate thiourea may be tried, but cross-sensitivity occurs for about 50% of patients.[31]

Agranulocytosis is one of the serious adverse effects of thiourea drug therapy and is characterized by fever, malaise, gingivitis, oropharyngeal infection, and a granulocyte count less than 250/mm^3 (0.250 x 10^9/L).[31] These drugs are concentrated in granulocytes, and this reaction may represent a direct toxic effect rather than hypersensitivity. This toxic reaction has occurred with both thioureas, and the incidence varies from 0.5% to 6%. It is higher for patients over age 40 receiving an MMI dose greater than 40 mg/day or the equivalent dose of PTU, is

linked to HLA class II genes containing the DRB1*08032 allele, and is more frequent with initial MMI doses of 30 mg compared with 15 mg.[38] Agranulocytosis usually develops in the first 3 months of therapy. Because the onset is sudden, routine WBC count monitoring has not been recommended. Colony-stimulating factors have been used with some success to restore cell counts to normal, but it is unclear how effective this form of therapy is compared with routine supportive care. Peripheral lymphocytes obtained from patients with PTU-induced agranulocytosis undergo a transformation in the presence of other thionamides, suggesting that these severe reactions are immunologically mediated and patients should not receive other thionamides. Aplastic anemia has been reported with MMI and may be associated with an inhibitor to colony-forming units. Once antithyroid drugs are discontinued, clinical improvement is seen over several days to weeks. Patients should be counseled to discontinue therapy and contact their physician when flu-like symptoms such as fever, malaise, or a sore throat develops. In addition, many clinicians will concomitantly provide an order for a complete blood cell count (with WBC count differential) when prescribing MMI or PTU therapy. If the patient becomes ill and is unable to reach the provider, the patient can still visit the nearest laboratory to have potential agranulocytosis evaluated.

Arthralgias and a lupus-like syndrome (sometimes in the absence of antinuclear antibodies) have been reported in 4% to 5% of patients. This generally occurs after 6 months of therapy. Uncommonly, polymyositis, presenting as proximal muscle weakness and elevated creatine phosphokinase, has been reported with PTU administration. Gastrointestinal intolerance is also reported to occur in 4% to 5% of patients. Hypoprothrombinemia is a rare complication of thionamide therapy. Patients who have experienced a major adverse reaction to one thiourea drug should not be converted to the alternate drug because of cross-sensitivity.[9]

Older reports suggested that congenital skin defects (aplasia cutis) may be caused by MMI and carbimazole, although a registry review from the Netherlands could not find an association between maternal use of these drugs and skin defects. Several serious congenital malformations including tracheoesophageal fistulas and choanal atresia have been observed with MMI and carbimazole but not PTU use during pregnancy.[39,40] PTU has traditionally been considered the drug of choice throughout pregnancy for women with hyperthyroidism, because of concerns about the possible teratogenic effects of MMI. However, currently heightened concerns about the greater risk of hepatotoxicity with PTU when compared to MMI have led to the

recommendation that PTU no longer be considered a first-line drug, except during the first trimester of pregnancy. The issue of choice of antithyroidal agent during pregnancy has been further complicated by two studies that suggest that fetuses exposed to either MMI or PTU during gestation may have increased risk of drug-induced fetal malformations.[41,42] A Danish study revealed that 2% to 3% of children exposed to PTU developed birth defects associated with this therapy.[41] In another study, PTU-associated birth defects, though less severe than MMI-associated birth defects, occurred with similar incidence in a Korean population.[42] The most recent guideline regarding the management of thyroid disease during pregnancy recommends using the lowest effective dose of the antithyroid drug as possible, targeting maternal serum FT4/TT4 at the upper limit or moderately above the reference range.[43]

Hepatotoxicity can be seen with both MMI and PTU, with a prevalence of approximately 1.3%. At moderate doses, some authors have found that initial hepatic enzyme elevations eventually normalize in most patients with continued therapy. PTU-induced subclinical liver injury is common and is usually transient and asymptomatic. Thus, it has generally been thought that therapy with PTU may be continued with caution in the absence of symptoms and hyperbilirubinemia. However, a 1997 literature review documented 49 cases of hepatotoxicity. Twenty-eight cases were associated with PTU use, and 21 cases were associated with MMI use. The hepatotoxicity was associated with seven deaths and three deaths in the PTU and MMI groups, respectively. There did not appear to be a relationship between the dose or duration of thionamide treatment and outcome. During the past 20 years of PTU use in the United States, 22 adults developed severe hepatotoxicity leading to nine deaths and five liver transplants. The risk of this complication was greater in children (1:2,000) than in adults (1:10,000).[44] A recent reanalysis of data reported to the Food and Drug Administration (FDA) from 1982 to 2008 found that toxicity in children was generally related to higher doses of PTU and that toxicity in both children and adults was associated with therapy lasting more than 4 months in duration.[45] In light of such evidence, it has been recommended by the American Thyroid Association (ATA) and the FDA that PTU not be considered as first-line therapy in either adults or children.[9] One of three exceptions includes the first trimester of pregnancy, when the risk of MMI-induced embryopathy may exceed that of PTU-induced hepatotoxicity. Other exceptions include intolerance to MMI and thyroid storm.

Iodides Iodide was the first form of drug therapy for Graves' disease. Its

mechanism of action is to acutely block thyroid hormone release, inhibit thyroid hormone biosynthesis by interfering with intrathyroidal iodide utilization (the Wolff–Chaikoff effect), and decrease the size and vascularity of the gland. This early inhibitory effect provides symptom improvement within 2 to 7 days of initiating therapy, and serum T_4 and T_3 concentrations may be reduced for a few weeks. Despite the reduced release of T_4 and T_3, thyroid hormone synthesis continues at an accelerated rate, resulting in a gland rich in stored hormones. The normal and hyperfunctioning thyroid soon escapes from this inhibitory effect within 1 to 2 weeks by decreasing the active transfer of iodide into the gland. Iodides are often used as adjunctive therapy to prepare a patient with Graves' disease for surgery, to acutely inhibit thyroid hormone release and quickly attain the euthyroid state in severely thyrotoxic patients with cardiac decompensation, or to inhibit thyroid hormone release following RAI therapy. However, large doses of iodine may exacerbate hyperthyroidism or indeed precipitate hyperthyroidism in some previously euthyroid individuals (Jod–Basedow disease). This Jod–Basedow phenomenon is most common in iodine-deficient areas, particularly for patients with pre-existing nontoxic goiter. Iodide is contraindicated in toxic MNG as the autonomous tissue utilizes the iodine for subsequent thyroid hormone synthesis.

Potassium iodide is available either as a saturated solution (SSKI), which contains 38 mg of iodide per drop, or as Lugol's solution, which contains 6.3 mg of iodide per drop. The typical starting dose of SSKI is 3 to 10 drops daily (120-400 mg) in water or juice. There is no documented advantage to using doses in excess of 6 to 8 mg/day. When used to prepare a patient for surgery, it should be administered 7 to 14 days preoperatively. As an adjunct to RAI, SSKI should not be used before, but rather 3 to 7 days after RAI treatment, so that the radioactive iodide can concentrate in the thyroid. The most frequent toxic effects with iodide therapy are hypersensitivity reactions (skin rashes, drug fever, rhinitis, and conjunctivitis), salivary gland swelling, "iodism" (metallic taste, burning mouth and throat, sore teeth and gums, symptoms of a head cold, and sometimes stomach upset and diarrhea), and gynecomastia.

Other compounds containing organic iodide have also been used therapeutically for hyperthyroidism. These include various radiologic contrast media that share a triiodoaminobenzene and monoaminobenzene ring with a propionic acid chain (eg, iopanoic acid and sodium ipodate). The effect of these compounds is a result of the iodine content inhibiting thyroid hormone release as well as competitive inhibition of 5′-monodeiodinase conversion related to their structures, which resemble thyroid analogs. Unfortunately, these extremely

useful agents are no longer available in the United States.

5 **Adrenergic Blockers** Because many of the manifestations of hyperthyroidism are mediated by β-adrenergic receptors, β-blockers (especially propranolol) have been used widely to ameliorate symptoms such as palpitations, anxiety, tremor, and heat intolerance. Although β-blockers are quite effective for symptom control, they have no effect on the urinary excretion of calcium, phosphorus, hydroxyproline, creatinine, or various amino acids, suggesting a lack of effect on peripheral thyrotoxicosis and protein metabolism. Furthermore, β-blockers neither reduce TSAb nor prevent thyroid storm. Propranolol and nadolol partially block the conversion of T_4 to T_3, but this contribution to the overall therapeutic effect is small in magnitude. Inhibition of conversion of T_4 to T_3 is mediated by D-propranolol, which is devoid of β-blocking activity, and L-propranolol, which is responsible for the antiadrenergic effects, has little effect on the conversion.

β-Blockers are usually used as adjunctive therapy with antithyroid drugs, RAI, or iodides when treating Graves' disease or toxic nodules; in preparation for surgery; or in thyroid storm. The only conditions for which β-blockers are primary therapy for thyrotoxicosis are those associated with thyroiditis. The dose of propranolol required to relieve adrenergic symptoms is variable, but an initial dose of 20 to 40 mg four times daily is effective (heart rate less than 90 beats/min) for most patients. Younger or more severely toxic patients may require as much as 240 to 480 mg/day because there seems to be an increased clearance rate for these patients. β-Blockers are contraindicated for patients with decompensated heart failure unless it is caused solely by tachycardia (high output). Nonselective agents and those lacking intrinsic sympathomimetic activity should be used with caution for patients with asthma and bronchospastic chronic obstructive lung disease. β-Blockers that are cardioselective and have intrinsic sympathomimetic activity may have a slight margin of safety in these situations. Other patients in whom contraindications exist are those with sinus bradycardia, those receiving monoamine oxidase inhibitors or tricyclic antidepressants, and those with spontaneous hypoglycemia. β-Blockers may also prolong gestation and labor during pregnancy. Other side effects include nausea, vomiting, anxiety, insomnia, light-headedness, bradycardia, and hematologic disturbances.

Antiadrenergic agents such as centrally acting sympatholytics and calcium channel antagonists may have some role in the symptomatic treatment of hyperthyroidism. These drugs might be useful when contraindications to β-

blockade exist. When compared with nadolol 40 mg twice daily, clonidine 150 mcg twice daily reduced plasma catecholamines, whereas nadolol increased both epinephrine and norepinephrine after 1 week of treatment. Diltiazem 120 mg given every 8 hours reduced heart rate by 17%; fewer ventricular extrasystoles were noted after 10 days of therapy, and diltiazem has been shown to be comparable to propranolol in lowering heart rate and blood pressure.

6 **Radioactive Iodine** Although other radioisotopes have been used to ablate thyroid tissue, ^{131}I is considered to be the agent of choice for Graves' disease, toxic autonomous nodules, and toxic MNGs.[9] RAI is administered as a colorless and tasteless liquid that is well absorbed and concentrates in the thyroid. ^{131}I is a β- and γ-emitter with a tissue penetration of 2 mm and a half-life of 8 days. Other organs take up ^{131}I, but the thyroid gland is the only organ in which organification of the absorbed iodine takes place. Initially, RAI disrupts hormone synthesis by incorporating into thyroid hormones and TG. Over a period of weeks, follicles that have taken up RAI and surrounding follicles develop evidence of cellular necrosis, breakdown of follicles, development of bizarre cell forms, nuclear pyknosis, and destruction of small vessels within the gland, leading to edema and fibrosis of the interstitial tissue. Pregnancy is an absolute contraindication to the use of RAI since radiation will be delivered to the fetal tissue, including the fetal thyroid.

β-Blockers may be given any time without compromising RAI therapy, accounting for their role as a mainstay of adjunctive therapy to RAI treatment. If iodides are administered, they should be given 3 to 7 days after RAI to prevent interference with the uptake of RAI in the thyroid gland. Because thyroid hormone levels will transiently increase following RAI treatment due to release of preformed thyroid hormone, patients with cardiac disease and elderly patients are often treated with thionamides prior to RAI ablation. For patients with underlying cardiac disease, it may be necessary to reinstitute antithyroid drug therapy following RAI ablation. The standard practice is to withdraw the thionamide 4 to 6 days prior to RAI treatment and to reinstitute it 4 days after therapy is concluded. Administering antithyroid drug therapy immediately following RAI treatment may result in a higher rate of posttreatment recurrence or persistent hyperthyroidism. Pretreatment with PTU may lead to higher rates of treatment failure, but this does not appear to be the case with MMI pretreatment. Use of lithium, as adjunctive therapy to RAI therapy, has multiple benefits of increasing the cure rate, shortening the time to cure, and preventing post-therapy increase in thyroid hormone levels.[46] Lithium is likely to achieve these effects

by increasing RAI retention in the thyroid and inhibiting thyroid hormone release from the gland, although it is not commonly used due to its narrow therapeutic index.

Corticosteroid administration will blunt and delay the rise in antibodies to the TSH receptor, TG, and thyroid peroxidase while reducing T_3 and T_4 concentrations following RAI. Bartalena et al. found no progression in ophthalmopathy for patients receiving prednisone after RAI (0% worsened) compared with 3% worsening in those receiving MMI, and 5% worsening in those receiving RAI alone.[47] Theoretically, if shared thyroidal and orbital antigen is involved in the pathogenesis of Graves' ophthalmopathy, antigen released with RAI treatment could aggravate pre-existing eye disease. There is some disagreement as to what degree of ophthalmopathy should be considered a contraindication to RAI. However, in those with moderate or severe orbitopathy it seems reasonable to delay RAI until the patient's eye disease has been stable.

Destruction of the gland attenuates the hyperthyroid state, and hypothyroidism commonly occurs months to years following RAI.[9,32] The goal of therapy is to destroy overactive thyroid cells, and a single dose of 4,000 to 8,000 rad results in a euthyroid state in 60% of patients at 6 months or less. The remaining 40% become euthyroid within 1 year, requiring two or more doses. It is advisable that a second dose of RAI be given 6 months after the first RAI treatment if the patient remains hyperthyroid.[9] Variables that predict an unsuccessful outcome of RAI include gender (men are less likely to develop hypothyroidism), race, the size of the thyroid (euthyroidism is less likely in large glands), severity of disease, and perhaps a higher level of TSAb. In a recent study, predictors of successful treatment with RAI included higher ablative dose, female gender, lower free T_4 levels at diagnosis, and absence of a palpable goiter.[48] The acute, short-term side effects of ^{131}I therapy are minimal and include mild thyroidal tenderness and dysphagia. Concern over increased risk of mutations and congenital defects now appears to be unfounded because long-term follow-up studies have not revealed increased risk for these complications.[49] In some studies examining the risk of malignancies after RAI therapy, there seems to be a small but significant increase in the risk of cancer of the small bowel and thyroid.[49] Although RAI is very effective in the treatment of hyperthyroidism, long-term follow-up from Great Britain suggests that among patients with hyperthyroidism treated with RAI, mortality from all causes and mortality resulting from cardiovascular and cerebrovascular disease and fracture are increased.

A common approach to Graves' hyperthyroidism is to administer a single

dose of 5 to 15 mCi (80–200 μCi/g of tissue). The optimal method for determining ^{131}I treatment doses for Graves' hyperthyroidism is unknown, and techniques have varied from a fixed dose to more elaborate calculations based on gland size, iodine uptake, and iodine turnover.[9] In a trial of 88 patients with Graves' disease, no difference in outcome was seen among high or low, fixed or adjusted doses. Thyroid glands estimated to weigh more than 80 g may require larger doses of RAI. Larger doses are likely to induce hypothyroidism and are seldom given outside the United States due to the imposition of stringent safety restrictions. For example, in the United Kingdom, a nursery school teacher is advised to stay out of school for 3 weeks following a 15 mCi dose of ^{131}I.

Special Populations

Graves' Disease and Pregnancy

Inappropriate increase in the production of hCG is a cause of abnormal thyroid function tests during the first half of pregnancy, and hCG can cause either subclinical (normal T_4 and suppressed TSH) or overt hyperthyroidism. This is because the homology of hCG and TSH leads to hCG-mediated stimulation through the TSH receptor. A recent study showed that at hCG concentrations greater than 400 IU/mL (kIU/L), TSH levels were invariably suppressed and free T_4 levels were generally above the normal range. Most patients with hCG greater than 200 IU/mL (kIU/L) did not have symptoms of hyperthyroidism. The variability of the thyrotropic potency of hCG is believed to depend on its carbohydrate composition.

A very comprehensive guideline has recently been published by the ATA regarding the management of thyroid disease during pregnancy.[43] Hyperthyroidism during pregnancy is almost solely caused by Graves' disease, with approximately 0.1% to 0.4% of pregnancies affected. Although the increased metabolic rate is usually well tolerated in pregnant women, two symptoms suggestive of hyperthyroidism during pregnancy are failure to gain weight despite a good appetite and persistent tachycardia. There is no increase in maternal mortality or morbidity in well-controlled patients. However, postpartum thyroid storm has been reported in about 20% of untreated individuals. Fetal loss is also more common, due to the facts that spontaneous abortion and premature delivery are more common in untreated pregnant women, as are low-birth-weight infants and eclampsia. Transplacental passage of TSAb may occur, causing fetal as well as neonatal hyperthyroidism. An

uncommon cause of hyperthyroidism is molar pregnancy; women present with a large-for-dates uterus and evacuation of the uterus is the preferred management approach.

Because RAI is contraindicated in pregnancy and surgery is usually not recommended (especially during the first trimester), antithyroid drug therapy is usually the treatment of choice for hyperthyroidism. MMI readily crosses the placenta and appears in breast milk.

As previously mentioned, propylthiouracil has been considered the drug of choice during the first trimester of pregnancy, with the lowest possible doses used to maintain the maternal T_4 level in the high-normal range.[43] During this period the risk of MMI-associated embryopathy is believed to outweigh that of PTU-associated hepatotoxicity. To prevent fetal goiter and suppression of fetal thyroid function, PTU is usually prescribed in daily doses of 300 mg or less and tapered to 50 to 150 mg daily after 4 to 6 weeks. PTU doses of less than 200 mg daily are unlikely to produce fetal goiter.[33] During the second and third trimesters, when the critical period of organogenesis is complete, MMI has been thought to be the drug of choice because of the greater risk of hepatotoxicity with PTU.[43] However, a recent study has raised the question of whether this strategy of switching thionamides, and thus exposing the fetus to both drugs, is the optimum approach.[41] Thionamide doses should be adjusted to maintain free T_4 within 10% of the upper normal limit of the nonpregnant reference range. During the last trimester, TSAbs fall spontaneously, and some patients will go into remission so that antithyroid drug doses may be reduced. A rebound in maternal hyperthyroidism occurs in about 10% of women postpartum and may require more intensive treatment than in the last trimester of pregnancy. For example, a study of patients who were euthyroid after thionamide discontinuation and subsequently became pregnant showed a relative risk of 4.26 for relapse of hyperthyroidism occurring 4 to 8 months after delivery.[50]

Neonatal and Pediatric Hyperthyroidism

Following delivery, some babies of hyperthyroid mothers will be hyperthyroid due to placental transfer of TSAbs, which stimulates thyroid hormone production in utero and postpartum. This is likely if the maternal TSAb titers were quite high. The disease is usually expressed 7 to 10 days postpartum and treatment with antithyroid drugs (PTU 5–10 mg/kg/day or MMI 0.5–1 mg/kg/day) may be needed for as long as 8 to 12 weeks until the antibody is cleared (immunoglobulin G half-life is about 2 weeks). Iodide (potassium iodide

one drop per day or Lugol's solution one to three drops per day) and sodium ipodate may be used for the first few days to acutely inhibit hormone release.

Childhood hyperthyroidism has classically been managed with either MMI or PTU. Long-term follow-up studies suggest that this form of therapy is quite acceptable, with 25% of a cohort experiencing remission every 2 years. Again, current recommendations suggest use of MMI as a first-line agent in both adults and children.[9]

Thyroid Storm

Thyroid storm is a life-threatening medical emergency characterized by decompensated thyrotoxicosis, high fever (often more than 39.4°C [103°F]), tachycardia, tachypnea, dehydration, delirium, coma, nausea, vomiting, and diarrhea.[11] Although Graves' disease and less commonly toxic nodular goiter are usually the underlying thyrotoxic pathology,[51] at least two cases of subacute thyroiditis leading to thyroid storm have been reported.

Precipitating factors for thyroid storm include infection, trauma, surgery, RAI treatment, and withdrawal from antithyroid drugs. Although the duration of clinical decompensation lasts for an average duration of 72 hours, symptoms may persist up to 8 days. With aggressive treatment, the mortality rate has been lowered to 20%. The following therapeutic measures should be instituted promptly: (a) suppression of thyroid hormone formation and secretion, (b) antiadrenergic therapy, (c) administration of corticosteroids, and (d) treatment of associated complications or coexisting factors that may have precipitated the storm. Specific agents used in thyroid storm are outlined in **Table 92-7**. PTU in large doses may be the preferred thionamide because, in addition to interfering with the production of thyroid hormones, it also blocks the peripheral conversion of T_4 to T_3. However, β-blockers and corticosteroids will serve the same purpose. A theoretical advantage of MMI is that it has a longer duration of action. If patients are unable to take medications orally, the tablets can be crushed into suspension and instilled by a gastric or rectal tube. Iodides, which rapidly block the release of preformed thyroid hormone, should be administered after thionamide is initiated to inhibit iodide utilization by the overactive gland. If iodide is administered first, it could theoretically provide substrate to produce even higher levels of thyroid hormone.

TABLE 92-7 Drug Dosages Used in the Management of Thyroid Storm

Drug	Regimen
Propylthiouracil	900–1,200 mg/day orally in four or six divided doses
Methimazole	90–120 mg/day orally in four or six divided doses
Sodium iodide	Up to 2 g/day IV in single or divided doses
Lugol's solution	5–10 drops three times a day in water or juice
Saturated solution of potassium iodide (SSKI)	1–2 drops three times a day in water or juice
Propranolol	40–80 mg every 6 hours
Dexamethasone	5–20 mg/day orally or IV in divided doses
Prednisone	25–100 mg/day orally in divided doses
Methylprednisolone	20–80 mg/day IV in divided doses
Hydrocortisone	100–400 mg/day IV in divided doses

Antiadrenergic therapy with the short-acting agent esmolol is preferred, both because it may be used in the patient with pulmonary disease or at risk for cardiac failure and because its effects may be rapidly reversed.[52] Corticosteroids are generally recommended, although there is no convincing evidence of adrenocortical insufficiency in thyroid storm, and the benefits derived from steroids may be caused by their antipyretic action and their effect of stabilizing blood pressure.[11] General supportive measures, including acetaminophen as an antipyretic (do not use aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) because they may displace bound thyroid hormone), fluid and electrolyte replacement, sedatives, digitalis, antiarrhythmics, insulin, and antibiotics, should be given as indicated. Plasmapheresis and peritoneal dialysis have been used to remove excess hormone (and to remove thyroid-stimulating immunoglobulins in Graves' disease) when the patient has not responded to more conservative measures, although these measures do not always work.

An analysis was undertaken to identify cases of thyroid storm occurring in Japan during the period 2004 to 2008.[51] The mortality rate was approximately 10% in the group of 282 patients identified. The most common trigger of the thyrotoxicosis was discontinuation or irregular use of antithyroidal agents. The most common cause of death was either multiorgan failure or congestive heart failure.

EVALUATION OF THERAPEUTIC OUTCOMES—THYROTOXICOSIS

After therapy (surgery, thionamides, or RAI) for hyperthyroidism has been initiated, patients should be evaluated on a monthly basis until they reach a euthyroid condition. Clinical signs of continuing thyrotoxicosis (tachycardia, weight loss, and heat intolerance, among others) or the development of hypothyroidism (bradycardia, weight gain, and lethargy, among others) should be noted. β-Blockers may be used to control symptoms of thyrotoxicosis until the definitive treatment has returned the patient to a euthyroid state. If T_4 replacement is initiated, the goal is to maintain both the free T_4 level and the TSH concentration in the normal range. Once a stable dose of T_4 is identified, the patient may be followed up every 6 to 12 months.

A common, potentially confusing clinical situation should be mentioned. Some patients may have TSH concentrations that continue to be suppressed despite having free T_4 concentrations that become normal or low. For patients with long-standing hyperthyroidism, the pituitary thyrotrophs responsible for making TSH become atrophic. The average amount of time required for these cells to resume normal functioning is 6 to 8 weeks. Therefore, if a thyrotoxic patient has his or her free T_4 concentration lowered rapidly, before the thyrotrophs resume normal function, a period of “transient central hypothyroidism” will be observed. In addition, autoimmune mechanisms may also play a role, with a slower TSH recovery in patients with higher titers of thyroid-binding inhibitory immunoglobulins.

HYPOTHYROIDISM

Hypothyroidism is defined as the clinical and biochemical syndrome resulting from decreased thyroid hormone production.[53] Biochemically, primary hypothyroidism is defined as TSH concentrations above the reference range and free thyroxine and/or triiodothyronine levels below the reference range.

EPIDEMIOLOGY—HYPOTHYROIDISM

Overt hypothyroidism occurs in 1.5% to 2% of women and 0.2% of men, and its incidence increases with age. In the Third National Health and Nutrition

Examination Survey (NHANES III), levels of serum TSH and total T_4 were measured in a representative sample of adolescents and adults (age 12 or older). Among 16,533 people who neither were taking thyroid medication nor reported histories of thyroid disease, 3.9% had subclinical hypothyroidism (serum TSH more than 4.5 mIU/L, and T_4 normal), and 0.2% had "clinically significant" hypothyroidism (TSH more than 4.5 mIU/L, and T_4 less than 4.5 mcg/dL [58 nmol/L]).[10] Subclinical hypothyroidism is commonly regarded as a sign of impending thyroid failure.

ETIOLOGY—HYPOTHYROIDISM

The vast majority of patients have primary hypothyroidism due to thyroid gland failure caused by chronic autoimmune thyroiditis. Special populations with higher risk of developing hypothyroidism include postpartum women, individuals with a family history of autoimmune thyroid disorders and patients with previous head and neck or thyroid irradiation or surgery, other autoimmune endocrine conditions (eg, type 1 diabetes mellitus, adrenal insufficiency, and ovarian failure), some other nonendocrine autoimmune disorders (eg, celiac disease, vitiligo, pernicious anemia, Sjögren's syndrome, and multiple sclerosis), primary pulmonary hypertension, and Down's and Turner's syndromes.

Central hypothyroidism is rare and affects both sexes equally. It is more often associated with pituitary than hypothalamic disorders but frequently involves both.[54] Biochemically, central hypothyroidism is defined by low or low-to-normal TSH concentrations and a disproportionately low concentration of free thyroxine. Secondary hypothyroidism due to pituitary failure is uncommon but should be suspected in a patient with decreased levels of T_4 and inappropriately normal or low TSH levels. Most patients with secondary hypothyroidism due to inadequate TSH production will have clinical signs of more generalized pituitary insufficiency, such as abnormal menses and decreased libido, or evidence of a pituitary adenoma, such as visual field defects, galactorrhea, or acromegaloid features, but isolated TSH deficiency can be congenital or acquired as a result of autoimmune hypophysitis.[55] Generalized (peripheral and central) resistance to thyroid hormone is extremely rare.

PATHOPHYSIOLOGY—HYPOTHYROIDISM

Table 92-8 outlines the causes of hypothyroidism. These causes fall into two

broad categories involving dysfunction of the thyroid gland (primary hypothyroidism) or dysfunction of the pituitary or hypothalamus (secondary hypothyroidism).

TABLE 92-8 Causes of Hypothyroidism

Primary hypothyroidism
Hashimoto's disease
Iatrogenic hypothyroidism
Less common:
• Iodine deficiency
• Enzyme defects
• Thyroid hypoplasia
• Goitrogens
Secondary hypothyroidism
Pituitary disease
Hypothalamic disease

Chronic Autoimmune Thyroiditis

7 Autoimmune thyroiditis (Hashimoto's disease) is the most common cause of spontaneous hypothyroidism in the adult.[53] Patients may present either with goitrous thyroid gland enlargement and mild hypothyroidism or with thyroid gland atrophy and more severe thyroid hormone deficiency. Both forms of autoimmune thyroiditis probably result from cell- and antibody-mediated thyroid injury. The bulk of evidence suggests that the presence of specific defects in suppressor T-lymphocyte function leads to the survival of a randomly mutating clone of helper T lymphocytes, which are directed against normally occurring antigens on the thyroid membrane. Once these T lymphocytes interact with thyroid membrane antigen, B lymphocytes are stimulated to produce thyroid antibodies.[56]

CLINICAL PRESENTATION Hypothyroidism

General

- Hypothyroidism can lead to a variety of end-organ effects with a wide range of disease severity, from entirely asymptomatic to coma with multisystem failure. In the adult, manifestations of hypothyroidism are nonspecific. In the child, thyroid hormone deficiency may manifest as delays in growth or intellectual development.

- Thyroid hormone is essential for normal growth and development during embryonic life. Uncorrected thyroid hormone deficiency during fetal and neonatal development results in mental retardation and/or cretinism. Both in children and adults, there is a slowing of physical and mental activity, as well as of cardiovascular, gastrointestinal, and neuromuscular function.

Symptoms

- Common symptoms of hypothyroidism include dry skin, cold intolerance, weight gain, constipation, and weakness. Complaints of lethargy, depression, fatigue, exercise intolerance, or loss of ambition and energy are also common but are less specific. Muscle cramps, myalgia, and stiffness are frequent complaints of hypothyroid patients. Menorrhagia and infertility may present commonly in women.

Signs

- Objective weakness is common, with proximal muscles being affected more than distal muscles. Slow relaxation of deep tendon reflexes is common. The most common signs of decreased levels of thyroid hormone include coarse skin and hair, cold or dry skin, periorbital puffiness, and bradycardia. Speech is often slow and the voice may be hoarse. Reversible neurologic syndromes such as carpal tunnel syndrome, polyneuropathy, and cerebellar dysfunction may also occur. Galactorrhea may be found in women.

Diagnosis

- A rise in the TSH is the first evidence of hypothyroidism in primary hypothyroidism.
- In secondary hypothyroidism in patients with pituitary disease, serum TSH concentrations are generally low or normal. A serum TSH concentration in the normal range is clearly inappropriate if the patient's T4 is low.
- Many patients will have a free T4 level within the normal range (compensated or subclinical hypothyroidism), with few, if any, symptoms of hypothyroidism. As the disease progresses, the free T4 concentration will drop below the normal level. With increased TSH stimulation, thyroidal production will shift toward greater amounts of

T3, and thus T3 concentrations will often be maintained in the normal range in spite of a low T4. Eventually, free and/or total T_4 and T_3 serum concentrations should be low.

Other Tests

- TPOAbs and anti-TG antibodies are likely to be elevated in autoimmune thyroiditis.

Antithyroid peroxidase (antimicrosomal) antibodies are present in virtually all patients with Hashimoto's thyroiditis and appear to be directed against the enzyme thyroid peroxidase.[57] These antibodies are capable of fixing complement and inducing cytotoxic changes in thyroid cells. Antibodies that are capable of stimulating thyroid growth through interaction with the TSH receptor may occasionally be found particularly in goitrous hypothyroidism; conversely, antibodies that inhibit the trophic effects of TSH may be present in the atrophic type.

Iatrogenic Hypothyroidism

Iatrogenic hypothyroidism follows exposure to destructive amounts of radiation (radioiodine or external radiation) or surgery. Hypothyroidism occurs within 3 months to a year after ^{131}I therapy in most patients treated for Graves' disease. Thereafter, it occurs at a rate of approximately 2.5% each year. External radiation therapy to the region of the thyroid using doses of greater than 2,500 centigray (cGy) for therapy of neck carcinoma also causes hypothyroidism. This effect is dose-dependent and more than 50% of patients who receive more than 4,000 cGy to the thyroid bed develop hypothyroidism. Total thyroidectomy causes hypothyroidism within 1 month. Excessive doses of thionamides used to treat hyperthyroidism can also cause iatrogenic hypothyroidism.

Other Causes of Primary Hypothyroidism

Iodine deficiency, enzymatic defects within the thyroid gland, thyroid hypoplasia, and maternal ingestion of goitrogens during fetal development may cause cretinism. Early recognition and treatment of the resultant thyroid hormone deficiency is essential for optimal mental development.[58] Large-scale neonatal screening programs in North America, Europe, Japan, and Australia are now in place. The frequency of congenital hypothyroidism in North America and

Europe is 1 per 3,500 to 4,000 live births. In the United States, there are racial differences in the incidence of congenital hypothyroidism, with whites being affected seven times as frequently as blacks.

In the adult, hypothyroidism is rarely caused by iodine deficiency and goitrogens. Iodine ingestion in the form of expectorants can lead to hypothyroidism. In sensitive persons (particularly those with autoimmune thyroiditis), the iodide blocks the synthesis of thyroid hormone, leading to an increased secretion of TSH and thyroid enlargement. Thus, both iodine excess and iodine deficiency can cause decreased secretion of thyroid hormone. An example of a goitrogen that can induce hypothyroidism is raw bok choy.[59] Several medications can cause hypothyroidism, including lithium, amiodarone, interferon-α, interleukin-2, tyrosine kinase inhibitors, checkpoint inhibitors,[60] and perchlorate.

Pituitary Disease

Thyroid-stimulating hormone is required for normal thyroid secretion. Thyroid atrophy and decreased thyroid secretion follow pituitary failure. Pituitary insufficiency may be caused by destruction of thyrotrophs by either functioning or nonfunctioning pituitary tumors, surgical therapy, external pituitary radiation, postpartum pituitary necrosis (Sheehan's syndrome), trauma, and infiltrative processes of the pituitary such as metastatic tumors, tuberculosis, histiocytosis, and autoimmune mechanisms.[61] In all these situations, TSH deficiency most often occurs in association with other pituitary hormone deficiencies. The identification of secondary hypothyroidism due to bexarotene use has led to a recognition of the role of rexinoids and retinoids to cause dysregulation of TSH production.[62]

Note that pituitary enlargement in hypothyroidism does not invariably indicate the presence of a primary pituitary tumor. Pituitary enlargement is seen in patients with severe primary hypothyroidism due to compensatory hyperplasia and hypertrophy of the thyrotrophs.[63] With thyroid hormone replacement therapy, serum TSH concentrations decline, indicating that the TSH secretion is not autonomous, and the pituitary resumes a more normal configuration. These patients are easily separated from patients with primary pituitary failure by measuring a TSH level.

Hypothalamic Disease

Thyrotropin-releasing hormone deficiency also causes a rare form of secondary hypothyroidism. In both adults and children, it may occur as a result of cranial irradiation, trauma, infiltrative diseases, or neoplastic diseases.

TREATMENT

Hypothyroidism

Most cases of hypothyroidism result from progressive and permanent damage to the thyroid gland. Replacement of thyroid hormone is the cornerstone of treatment.

Desired Outcomes

The goals of therapy are to restore normal thyroid hormone concentrations in tissue, provide symptomatic relief, prevent neurologic deficits in newborns and children, and reverse the biochemical abnormalities of hypothyroidism.

General Approach to Treatment

8 Levothyroxine (L-thyroxine, T_4) is considered to be drug of choice for treatment of hypothyroidism (Table 92-9).[22] Other commercially available thyroid preparations can be obtained but are not considered preferred therapy. Available thyroid preparations are synthetic (L-thyroxine, liothyronine, and liotrix) or natural in origin (ie, desiccated thyroid). The preparations containing both T_4 and T_3 (liotrix, desiccated thyroid) have relatively high proportions of T_3 and may cause thyrotoxicosis.[22] Liothyronine is a short-acting preparation that requires dosing multiple times a day in order to achieve stable hormone concentrations.[64] The availability of sensitive and specific assays for total and free hormone levels as well as TSH now allows precise dose titration to make adequate replacement without inadvertent overdose. The response of TSH to TRH had been advocated for use by some in order to “fine tune” thyroid replacement, but this is not necessary if the third-generation chemiluminometric assays for TSH, which have detection limits of about 0.01 mIU/L, are used. Clinical guidelines for the management of hypothyroidism have been published by the ATA and provide specific treatment recommendations and critically examine the use of combination therapy with T_4 and T_3[22] (Table 92-10).

TABLE 92-9 Thyroid Preparations Used in the Treatment of

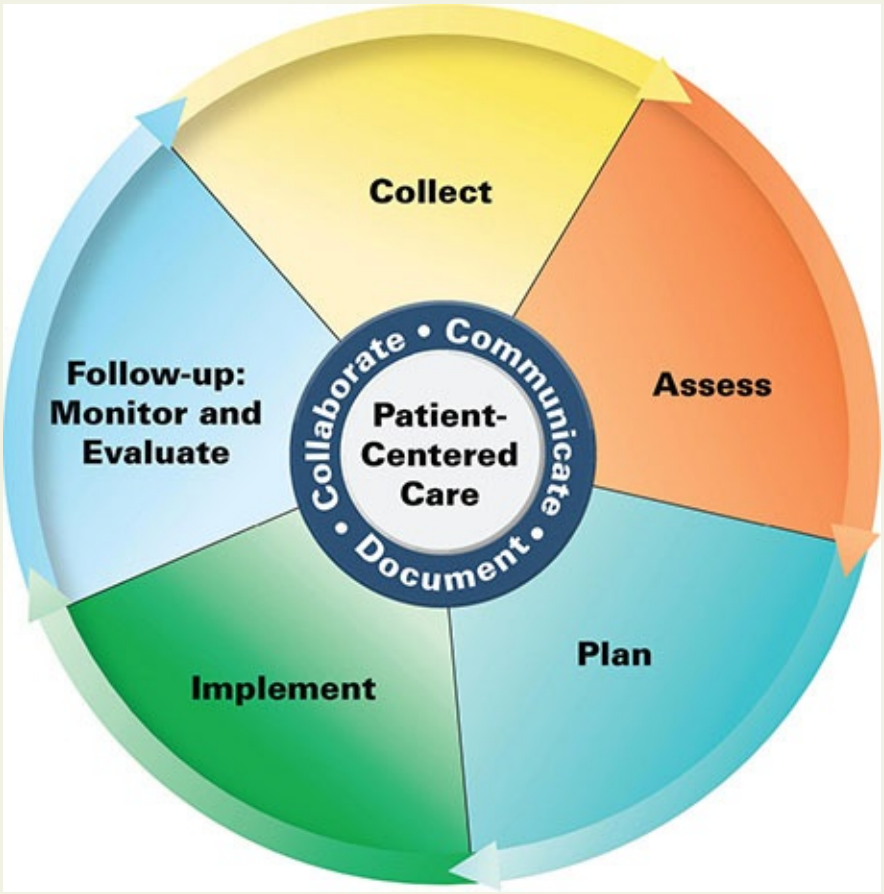
Hypothyroidism

Drug/Dosage Form	Content	Relative Dose	Comments/Equivalency
Thyroid USP Armour Thyroid, Nature-Throid, and Westhroid (T_4:T_3 ratio approximately 4.2:1); Armour, 1 grain = 60 mg; Nature-Throid and Westhroid, 1 grain = 65 mg. Doses include 1/4, 1/2, 1, 2, 3, 4, and 5 grain tablets	Desiccated pork thyroid gland	1 grain (equivalent to 74 mcg of T_4)	High T_3:T_4 ratio; inexpensive
Levothyroxine Synthroid, Levothroid, Levoxyl, Levo-T, Unithroid, and other generics 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, 300 mcg tablets; Tirosint 13–150 mcg liquid in gelatin capsule; Tirosint-Sol liquid solution 13, 25, 50, 75, 88, 100, 112, 137, 150, 175, and 200 mcg in unit-dose ampules; 200 and 500 mcg per vial solution for injection	Synthetic T_4	100 mcg	Stable; predictable potency; generics may be bioequivalent; when switching from natural thyroid to L-thyroxine, lower dose by one-half grain; variable absorption between products; half-life = 7 days, so daily dosing; considered to be drug of choice
Liothyronine Cytomel 5, 25, and 50 mcg tablets	Synthetic T_3	33 mcg (~equivalent to 100 mcg T_4)	Uniform absorption, rapid onset; half-life = 1.5 days, rapid peak and troughs
Liotrix Thyrolar 1/4-, 1/2-, 1-, 2-, and 3-grain tablets	Synthetic T_4:T_3 in 4:1 ratio	Thyrolar 1 = 50 mcg T_4 and 12.5 mcg T_3	Stable; predictable; expensive; risk of T_3 thyrotoxicosis because of high ratio of T_3 relative to T_4

TABLE 92-10 Selected Recommendations from the American Thyroid Association Hypothyroidism Guidelines[22]

Question	Synopsis or Paraphrase of Recommendation	Grading
Is levothyroxine monotherapy considered to be the standard of care for hypothyroidism?	Levothyroxine is recommended as the preparation of choice for the treatment of hypothyroidism due to its efficacy in resolving the symptoms of hypothyroidism.	Strong recommendation, moderate quality
What are the clinical and biochemical goals for levothyroxine replacement in primary hypothyroidism?	Levothyroxine replacement therapy has three main goals. These are (i) to provide resolution of the patients' symptoms and hypothyroid signs, (ii) to achieve normalization of serum thyrotropin, and (iii) to avoid overtreatment.	Strong recommendation, moderate quality
Are there situations in which therapy with levothyroxine dissolved in glycerin and supplied in gelatin capsules may have advantages over standard levothyroxine?	Although there are preliminary small studies suggesting that levothyroxine dissolved in glycerin and supplied in gelatin capsules may be better absorbed than standard levothyroxine, the present lack of controlled long-term outcome studies does not support a recommendation for the use of such preparations in these circumstances.	Weak recommendation, low quality
What factors determine the levothyroxine dose required by a hypothyroid patient for reaching the appropriate serum thyrotropin goal?	When deciding on a starting dose of levothyroxine, the patient's weight, lean body mass, pregnancy status, etiology of hypothyroidism, degree of thyrotropin elevation, age, and general clinical context should all be considered.	Strong recommendation, moderate quality
What is the best approach to initiating and adjusting levothyroxine therapy?	Thyroid hormone therapy should be initiated as an initial full replacement or as partial replacement with gradual increments in the dose titrated upward using serum thyrotropin as the goal. Dose adjustments should be made, with thyrotropin assessment 4–6 weeks after any dosage change.	Strong recommendation, moderate quality
What approach should be taken in patients treated for hypothyroidism who have normal serum thyrotropin values but still have unresolved symptoms?	A minority of patients with hypothyroidism, but normal serum thyrotropin values, may perceive a suboptimal health status of unclear etiology. Acknowledgment of the patients' symptoms and evaluation for alternative causes is recommended in such cases.	Weak recommendation, low quality
In adults requiring thyroid hormone replacement treatment for primary hypothyroidism, is treatment with thyroid extracts superior to treatment with levothyroxine alone?	We recommend that levothyroxine be considered as routine care for patients with primary hypothyroidism, in preference to use of thyroid extracts. High-quality controlled long-term outcome data are lacking to document superiority of this treatment compared to levothyroxine therapy.	Strong recommendation, moderate quality
In adults requiring thyroid hormone replacement treatment for primary hypothyroidism, is combination treatment including levothyroxine and liothyronine superior to the use of levothyroxine alone?	There is no consistently strong evidence of superiority of combination therapy over monotherapy with levothyroxine. Therefore, we recommend against the routine use of combination treatment with levothyroxine and liothyronine as a form of thyroid replacement therapy in patients with primary hypothyroidism.	Weak recommendation, moderate quality
In adults requiring thyroid hormone replacement treatment for primary hypothyroidism who feel unwell while taking levothyroxine, is combination treatment including levothyroxine and liothyronine superior to the use of levothyroxine alone?	For patients with primary hypothyroidism who feel unwell on levothyroxine therapy alone, there is currently insufficient evidence to support the routine use of a trial of a combination of levothyroxine and liothyronine therapy outside a formal clinical trial or N-of-1 trial, due to uncertainty in long-term risk-benefit ratio of the treatment.	Insufficient evidence
Are there data regarding therapy with triiodothyronine alone, either as standard liothyronine or as sustained release triiodothyronine, that support the use of triiodothyronine therapy alone for the treatment of hypothyroidism?	Although short-term outcome data in hypothyroid patients suggest that thrice-daily synthetic liothyronine may be associated with beneficial effects on parameters such as weight and lipids, longer-term controlled clinical trials are needed before considering synthetic liothyronine therapy for routine clinical use.	Strong recommendation, moderate quality

Strong recommendation: Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits. Weak recommendation: Benefits finely balanced with risks and burden. Quality of evidence: High, moderate, or low.



Patient Care Process for the Management of Hypothyroidism

Collect

- Patient characteristics (eg, age, race, sex, pregnancy status)
- Patient history (past medical, family, social) including signs and symptoms: coarse skin and hair, cold or dry skin, periorbital puffiness, and bradycardia; cold intolerance, weight gain, constipation, weakness, muscle cramps, myalgia, and galactorrhea (see Clinical Presentation Box)
- Current medications (including OTC and herbal medication use)
- Objective data
    - Heart rate, blood pressure (BP), weight, and body mass index (BMI)
    - Labs (eg, TSH, FT4, TT3, anti-TG antibodies, TPO antibodies; serum electrolytes, Scr, ALT)
    - Other diagnostic tests when indicated (eg, thyroid ultrasound, RAIU

scan)

Assess

- Cause of hypothyroidism (see Table 92-8)
- Current medications that may contribute to or worsen hypothyroidism
- Current medications that may interact with thyroid hormone replacement therapy
- Appropriateness and effectiveness of current thyroid hormone replacement regimen

Plan*

- Drug therapy regimen including specific thyroid hormone replacement therapy and dose (see Table 92-9)
- Monitoring parameters including efficacy (eg, resolution of signs and symptoms) and safety (arrhythmias, angina, osteoporosis, or symptomatic hyperthyroidism), laboratory data (TSH, FT4, TT3), and follow-up monitoring time frame
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug therapy)

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up visits and laboratory tests

Follow-up: Monitor and Evaluate

- Resolution of signs and symptoms
- Presence of adverse effects
- Patient adherence to treatment plan using multiple sources of information

* Collaborate with patient, caregivers, and other healthcare professionals.

Pharmacologic Therapy

Levothyroxine is the drug of choice for thyroid replacement and suppressive

therapy because it is chemically stable, relatively inexpensive, active when orally administered, free of antigenicity, and has uniform potency. Levothyroxine (T4) administration results in a pool of thyroid hormone that is readily converted to T_3 when needed; in this regard, levothyroxine may be thought of as a prohormone. The ability of levothyroxine to achieve normal T_3 concentrations was illustrated in a study of recently athyreotic patients in whom levothyroxine monotherapy produced similar T_3 levels to those documented prior to the patient's thyroidectomy.[65] Several other studies, however, suggest that athyreotic individuals taking T_4 may have low or low-normal T_3 levels.[66,67]

Liothyronine (T_3) is chemically pure with known potency and has a shorter half-life of 1.5 days. Although it can be used diagnostically in the T_3 suppression test, T_3 has some clinical disadvantages, including a higher incidence of cardiac adverse effects, higher cost, and difficulty in monitoring with conventional laboratory tests. If used, T_3 needs to be administered three times a day and it may take a prolonged period of adjustment to achieve stable euthyroidism.[64] Liotrix is a combination of synthetic T_4 and T_3 in a 4:1 ratio. It is chemically stable and pure and has a predictable potency. The major limitations to this product are high cost and lack of therapeutic rationale, because most T_3 is peripherally converted from T_4. In addition, the T_4:T_3 ratio is much higher than the 14:1 molar ratio produced by the thyroid gland in humans.

9 Trials comparing levothyroxine alone with a combination of levothyroxine plus partial replacement with liothyronine (T_3) have generally shown that combinations of $T_4 + T_3$ are no better than T_4 alone. At least 13 such trials with varying designs have been performed to date.[22] Four of these trials have found that patients expressed a preference for combination therapy. As discussed in recent guidelines,[22] three meta-analyses and a systematic review have also suggested no benefits.[68–71] A secondary analysis, however, suggested that individuals harboring a specific deiodinase polymorphism may have a poorer psychological response to levothyroxine therapy and a better response to combination therapy with both T_4 and T_3. However, no prospective study investigating whether the presence of these polymorphisms affects satisfaction with replacement therapy has yet been reported.[72]

A recent study conducted in rats suggested impairment of type 2 deiodinase activity in the whole body during levothyroxine monotherapy due to deiodinase inactivation, compared with maintenance of deiodinase activity in the

hypothalamus.[73] The lesser activation in the hypothalamus leads to efficient T_3 production in the hypothalamus and normalization of TSH before T_3 normalized in the rest of the body. Accompanying the inactivation of type 2 deiodinase in other tissues, lower serum T_3 and higher T_4/T_3 ratios were seen in rats during monotherapy with L-thyroxine, compared with combination therapy employing a subcutaneous slow release T_3 pellet. Clinical trials of a slow release T_3 preparation, other than a pharmacokinetic study of T_3 sulfate in profoundly hypothyroid individuals,[74] has yet to be conducted.

Desiccated thyroid has historically been derived from pig, beef, or sheep thyroid glands, although pigs are currently the usual source. The United States Pharmacopeia requires thyroid USP to contain 38 mcg (±15%) of L-thyroxine and 9 mcg (±10%) of liothyronine for each 60 to 65 mg (one grain). Thyroid USP, as an animal protein-derived product, may be antigenic in allergic or sensitive patients. Even though desiccated thyroid is inexpensive, its limitations preclude it from being considered as a drug of choice for hypothyroid patients.

Pharmacokinetics

The half-life of levothyroxine is approximately 7 days. This long half-life is responsible for a stable pool of prohormone and the need for only once-daily dosing with levothyroxine. Older studies with levothyroxine suggested that bioavailability was low and erratic; however, this product has been reformulated, and the average bioavailability improved to approximately 80%. Different levothyroxine preparations contain different excipients such as dyes and fillers. The bioavailabilities of Synthroid, Levoxyl, and generic levothyroxine preparations were compared in a blinded, randomized, four-way crossover trial.[75] The study was sponsored by the manufacturers of Synthroid, who have challenged the authors' conclusions that the levothyroxine preparations are bioequivalent and should be interchangeable for the majority of patients. However, because the relationship between T_4 concentration and TSH is not linear, very small changes in T_4 concentration can lead to substantial changes in TSH, which is a more accurate reflection of hormone replacement status. Currently, the FDA mandates that L-thyroxine bioequivalency testing be done using normal volunteers (600 mcg in the fasted state) and three baseline-free T_4 concentrations be used to correct for endogenous T_4 production. Bioequivalency is based on the area under the curve (AUC) and maximum concentration (C_{max}) of T_4 out to 48 hours. Approximately 70% of the AUC is derived from

endogenous production. TSH is not considered, and it is now very clear that T_4 is too insensitive as a measure of bioequivalency.[76] To avoid overtreatment and undertreatment, once a product is selected, switches between levothyroxine products in patients who are stable are not recommended. Currently, several levothyroxine products are available, including AB1, AB2, AB3, and AB4 rated products. This has created several permutations for product interchangeability since no reference drug is mandated in bioequivalency testing.

Adverse Effects

Serious untoward effects are unusual if dosing is appropriate and the patient is carefully monitored during initial treatment. A cross-sectional study showed that of a population of 1,525 individuals taking levothyroxine, 40% actually had abnormal TSH values.[77] Another study showed that 57% of individuals 65 years or older receiving thyroid hormone treatment had abnormal TSH values.[78] Both of these studies suggest that failure to keep a patient's TSH at goal is common. Levothyroxine replacement in athyreotic hypothyroid patients restores systolic and diastolic left ventricular performance within 2 weeks, and the use of levothyroxine may increase the frequency of atrial premature beats but not necessarily ventricular premature beats. Excessive doses of thyroid hormone may lead to heart failure, angina pectoris, and myocardial infarction; rarely, the latter may be caused by coronary artery spasm. Allergic or idiosyncratic reactions can occur with the natural animal-derived products such as desiccated thyroid, but these are extremely rare with the synthetic products used today. The 0.05 mg (50 mcg) Synthroid tablet is the least allergenic (due to a lack of dye and few excipients) and should be tried for the patient suspected to be allergic to thyroid hormone tablets.

Hyperremodeling of cortical and trabecular bone due to hyperthyroidism leads to reduced bone density and may increase the risk of fracture. Compared with normal controls, excess exogenous thyroid hormone results in histomorphometric and biochemical changes similar to those observed in osteoporosis and untreated hyperthyroidism.[79,80] The risk for this complication seems to be related to the dose of levothyroxine, patient age, and gender. Markers for bone turnover include urinary *N*-telopeptides, pyridinoline crosslinks of type I collagen, osteocalcin, and bone-specific alkaline phosphatase. When doses of levothyroxine are used to suppress TSH concentrations to below-normal values (eg, less than 0.3 mIU/L) in postmenopausal women, this adverse effect is more likely to be seen. Cortical bone is affected to a greater degree than trabecular bone at suppressive doses of

L-thyroxine. In contrast, it appears to be much less likely in men and in premenopausal women. Maintaining the TSH between 0.7 and 1.5 mIU/L does not alter bone mineral density in premenopausal women. Although not all studies have shown consistent results, a recent cohort study suggests that treatment with L-thyroxine to achieve a normal TSH has no adverse effect on bone density.[81]

Drug–Drug and Drug–Food Interactions

The time to maximal absorption of levothyroxine is about 2 hours and this should be considered when T_4 concentrations are determined. Ingestion of L-thyroxine with food can impair its absorption.[22] This can potentially affect the TSH concentration achieved if levothyroxine timing with respect to food is varied.[82] Mucosal diseases, such as celiac sprue, diabetic diarrhea, and ileal bypass surgery, can also reduce absorption. Cholestyramine, calcium carbonate, sucralfate, aluminum hydroxide, ferrous sulfate, soybean formula, dietary fiber supplements, and espresso coffee may also impair the absorption of levothyroxine from the gastrointestinal tract (reviewed extensively in recent treatment of hypothyroidism guidelines[22]). Acid suppression with histamine blockers and proton pump inhibitors may also reduce levothyroxine absorption.[83] Drugs that increase nondeiodinative T_4 clearance include rifampin, carbamazepine, and possibly phenytoin. Selenium deficiency and amiodarone may block the conversion of T_4 to T_3.

Several non-randomized studies have suggested that liquid formulations of levothyroxine or formulations in which the levothyroxine is dissolved in glycerin and encased in a gelatin capsule may circumvent the impaired absorption of levothyroxine that may occur with tablet preparations.[84] For patients receiving enteral feeding, liquid levothyroxine added directly to the feeding tube was associated with a similar serum TSH to that seen in another group of patients in whom the feeding was interrupted in order to administer crushed tablets.[85] The former procedure was found to be more convenient by providers. In a study of patients taking proton pump inhibitors, switching to an oral solution was associated with a decrease in serum TSH from a mean of 5.4 to 1.7 mIU/L, suggesting better absorption of the liquid preparation in these patients.[86] A study of patients with gastritis who had a stable serum TSH while taking levothyroxine tablets and were then switched to a lower dose of levothyroxine gel capsules showed that two-thirds of patients had a similar TSH on the lower dose, again suggesting better absorption of the gel capsule formulation.[87] In a double-blind,

randomized, crossover trial of liquid thyroxine in 77 treatment-naive patients with hypothyroidism, no significant differences in thyroid function tests were seen when the liquid preparation was ingested at breakfast or 30 minutes before breakfast.[88] This could provide a solution for patients with difficulties ingesting levothyroxine before breakfast. If the findings of these studies are bolstered by randomized controlled studies in the future, these levothyroxine formulations may prove very convenient for hypothyroid patients.

Dosing and Administration

Recent studies suggest that the average maintenance dose of levothyroxine for most adults is about 125 mcg/day.[53] The replacement dose of levothyroxine is affected by body weight. Estimates of weight-based doses for replacement in hypothyroid patients include 1.6 and 1.7 mcg/kg/day.[22] There is, however, a wide range of replacement doses, necessitating individualized therapy and appropriate TSH monitoring to determine an adequate but not excessive dose.

10 In addition to alleviation of symptoms, the goal of treatment for patients with hypothyroidism is to maintain the patient's TSH within the normal range. Some clinicians are of the opinion that the traditional reference range of approximately 0.5 to 4.5 mIU/L includes at its upper end some individuals who have unrecognized thyroid disease.[89] Thus, some believe that the reference range should be modified downward to 0.5 to 3.5 mIU/L or even 0.5 to 2.5 mIU/L.[90] If this premise is accepted, both the TSH values that trigger L-thyroxine treatment and the TSH treatment goal could potentially be altered. There are cogent arguments on both sides of the issue. Those who suggest maintaining current reference ranges believe that lowering the upper limit of the reference range could result in treating many individuals with thyroid hormone who would not necessarily benefit from such treatment.[91] Those who favor narrowing the reference range suggest that additional patients would, in fact, derive benefit from thyroid hormone treatment.[90] TSH reference ranges also differ for different populations, such as those who are pregnant, specific ethnic groups, and older individuals.[22]

The required dose of levothyroxine is dependent on the patient's age and the presence of associated disorders, as well as the severity and duration of hypothyroidism.[22] Most patients will require approximately 1.7 mcg/kg/day once they reach steady state for full replacement. Dose requirement may be better estimated based on ideal body weight, rather than actual body weight.[92] In patients with long-standing disease and older individuals without known cardiac

disease, therapy should be initiated with 50 mcg daily of levothyroxine and increased after 1 month. The recommended initial daily dose for older patients with known cardiac disease is 25 mcg daily titrated upward in increments of 25 mcg at monthly intervals to prevent stress on the cardiovascular system. Some patients may experience an exacerbation of angina with higher doses of thyroid hormone. Although TSH is an indicator of under-replacement or over-replacement, clinicians often fail to alter the dose based on TSH values clearly outside of the normal range.

Patients with subclinical or mild hypothyroidism (seen more commonly in the elderly and women) have no or few signs or symptoms, normal serum T_3 and T_4 concentrations, and an elevated basal TSH concentration.[37] The prevalence of this disorder in the NHANES III study was found to be 4.3%.[10] Untreated individuals with moderate degrees of subclinical hypothyroidism and negative TPOAb may revert to euthyroidism during follow-up.[93] Increased mortality may be associated with moderate, but not mild subclinical hypothyroidism.[94] Spontaneous recovery of thyroid function and uncertainties about which patient groups may benefit from therapy contribute to the debate about treatment of subclinical hypothyroidism. Although the treatment of subclinical hypothyroidism is controversial, patients presenting with marked elevations in TSH (more than 10 mIU/L) and high titers of TPOAb or prior treatment with ^{131}I may be most likely to benefit from treatment. It should be noted that some studies find that only one of four treated patients experienced improvement. Other patients who may improve with replacement include those with mild symptoms of hypothyroidism and depression. Reduction of events due to ischemic heart disease was only observed in younger patients in one study.[95] If treatment is pursued, reasonable goals in this situation would be to maintain serum T_4 and T_3 levels in the normal range and reduce TSH to a value of 0.5 to 2.5 mIU/L in younger patients and 4 to 6 mIU/L in older patients.[37]

Once euthyroidism is attained, the daily maintenance dose of levothyroxine does not fluctuate greatly. As patients age, the dosing requirement may be reduced.[22] Third-generation TSH assays improved the accuracy with which thyroid hormone replacement can be monitored. The TSH concentration is the most sensitive and specific monitoring parameter for adjustment of levothyroxine dose. Plasma TSH concentrations begin to fall within hours and are usually normalized within 2 weeks, but they may take up to 6 weeks for some patients, depending on the baseline value. Both TSH and T_4 concentrations are used to monitor therapy, and they should be checked every 6 weeks until a

euthyroid state is achieved.[22] Laboratory assessment of thyroid function should be performed approximately 6 weeks after levothyroxine dose initiation or change. This time frame allows achievement of steady state, as the half-life of levothyroxine is approximately 1 week. Serum T_4 concentrations can be useful in detecting noncompliance, malabsorption, or changes in levothyroxine product bioequivalence, among other things.[96] An elevated TSH concentration indicates insufficient replacement. The appropriate dose maintains the TSH concentration in the normal range. T_4 disposal is accelerated by nephrotic syndrome, other severe systemic illnesses, and several antiseizure medications (phenobarbital, phenytoin, and carbamazepine) and rifampin. Pregnancy increases the T_4 dose requirement for 75% of women, probably because of factors such as increased degradation by the placental deiodinase, increased T_4 pool size, and transfer of T_4 to the fetus. The etiology of hypothyroidism also affects the magnitude of the dosage increase. Initiating postmenopausal hormone replacement therapy increases the dose needed in 35% of women, perhaps due to an increased circulating TBG level. Patient noncompliance with prescribed T_4, the most common cause of inadequate treatment, might be suspected for patients with a dose that is higher than expected, variable thyroid function test results that do not correlate well with prescribed doses, and an elevated serum TSH concentration with serum-free T_4 at the upper end of the normal range, which can suggest improved compliance immediately before testing, with a lag in the thyrotropin response.

For patients with central hypothyroidism caused by hypothalamic or pituitary failure, the serum TSH cannot be used to assess adequacy of replacement. Alleviation of the clinical syndrome and restoration of serum T_4 to the normal range are the only criteria available for estimating the appropriate replacement dose of L-thyroxine. Keeping free T_4 values in the upper part of the normal laboratory reference range is a reasonable approach, with modification of this goal to the middle of the normal range in older patients or patients with comorbidities. Concurrent use of dopamine, dopaminergic agents (bromocriptine), somatostatin or somatostatin analogs (octreotide), and corticosteroids suppresses TSH concentrations in individuals with primary hypothyroidism and may confound the interpretation of this monitoring parameter.[22]

TSH-suppressive levothyroxine therapy can be given to patients with nodular thyroid disease and diffuse goiter, and to patients with a history of thyroid irradiation. It is also usually given to patients with papillary or follicular thyroid

cancer. The rationale for suppression therapy is to reduce TSH secretion, which promotes growth and function of abnormal thyroid tissue. However, such management, other than for patients with thyroid cancer or with elevated TSH levels, is quite controversial. Some clinicians rarely recommend or use such therapy; others will recommend a trial of levothyroxine as suppressive therapy in some patients. Three meta-analyses concluded that suppressive therapy for nodules was associated with a small decrease in nodule growth, a statistically nonsignificant reduction in nodule growth, and a significant reduction in nodule growth with longer-term treatment. L-Thyroxine may be given in nontoxic MNG to suppress the TSH to low-normal levels of 0.5 to 1 mIU/L if the baseline TSH is more than 1 mIU/L. Goiter size and thyroid volume may be reduced with suppression therapy. Diffuse goiter associated with autoimmune thyroiditis may also be treated with levothyroxine to reduce goiter size and thyroid volume. If suppressive therapy with levothyroxine is pursued, the age, gender, and menopausal status of the patient need to be considered, along with the risk of cardiac arrhythmias and reduced bone mineral density. Levothyroxine suppression therapy is of benefit to all but the lowest-risk thyroid cancer patients and is generally used in the management of patients with differentiated thyroid cancer, with the TSH goal being influenced by the patient's thyroid cancer stage and other risk factors. Current guidelines from the ATA suggest suppressing the TSH to below 0.1 mIU/L in higher-risk patients, but keeping TSH around the lower limit of normal (0.1–0.5 mIU/L) in low-risk patients.[97]

Special Populations

Myxedema Coma

Myxedema coma is a rare consequence of decompensated hypothyroidism.[11] Clinical features include hypothermia, advanced stages of hypothyroid symptoms, and altered sensorium ranging from delirium to coma. Mortality rates of 60% to 70% necessitate immediate and aggressive therapy. Traditionally, the initial treatment has been IV bolus levothyroxine 300 to 500 mcg.[22] However, as deiodinase activity is markedly reduced, impairing T_4 to T_3 conversion, initial treatment with IV T_3, or a combination of both hormones, has also been advocated.[11] Glucocorticoid therapy with IV hydrocortisone 100 mg every 8 hours should be given until coexisting adrenal suppression is ruled out.[22] All therapies must be administered parenterally as cessation of gastrointestinal peristalsis occurs, preventing absorption of orally administered medications.

Consciousness, lowered TSH concentrations, and improvement in vital signs are expected within 24 hours. Maintenance doses of levothyroxine are typically 75 to 100 mcg given IV until the patient stabilizes and oral therapy is begun. Supportive therapy must be instituted to maintain adequate ventilation, blood pressure, and body temperature, and ensure euglycemia. Any underlying disorder, such as sepsis or myocardial infarction, obviously must be diagnosed and treated.

Congenital Hypothyroidism

In congenital hypothyroidism, full maintenance therapy should be instituted early to improve the prognosis for mental and physical development. The average maintenance dose in infants and children depends on the age and weight of the child. Several studies demonstrate that aggressive therapy with levothyroxine is important for normal development, and current recommendations are for initiation of therapy as soon as possible after birth at a dose of 10 to 15 mcg/kg/day. This dose is used to keep T_4 concentrations at about 10 mcg/dL (130 nmol/L) within 30 days of starting therapy and is associated with improved IQs. The dose is progressively decreased to a typical adult dose as the child ages, with the adult dose given starting in puberty.

Hypothyroidism During Pregnancy

Hypothyroidism during pregnancy leads to an increased rate of stillbirths and possibly lower neuropsychological scores in infants born of women who received inadequate replacement during pregnancy.[43] Thyroid hormone is necessary for fetal growth and must come from the maternal side during the first 2 months of gestation. Although liothyronine may cross the placental membrane slightly better than levothyroxine, the latter is considered the drug of choice. The objective of treatment is to decrease TSH to normal, based on the normal reference range for pregnancy. Current guidelines suggest a TSH below 2.5 mIU/L during the first trimester and a TSH below 3 mIU/L during the remainder of pregnancy.[43] Based on elevated TSH levels during pregnancy, it was found in one study that the mean dose of levothyroxine had to be increased by 48% to decrease TSH into the normal range. However, in individual women the dosage increase needed may vary from approximately 10% to 80%. Increased production of binding proteins, a marginal decrease in free hormone concentration, modification of peripheral thyroid hormone metabolism, and increased T_4 metabolism by the fetal-placental unit all may contribute to

increased thyroid hormone demand. As these changes regress after delivery, the need for increased levothyroxine will decline.[43] Up to 60% of women need to have levothyroxine dose adjustment during pregnancy. Upward adjustment will usually be needed by the eighth week of pregnancy. Current guidelines recommend that hypothyroid patients receiving levothyroxine who become pregnant should increase their levothyroxine dose by 20% to 30% (two additional tablets weekly) as soon as they know they are pregnant.[43] After delivery the levothyroxine dose can be reduced based on T_4 concentrations and measurement of TSH, typically about 6 to 8 weeks after delivery. Many patients can return to their pre-pregnancy dose requirement.

EVALUATION OF THERAPEUTIC OUTCOMES—HYPOTHYROIDISM

Patients with idiopathic hypothyroidism and Hashimoto's thyroiditis on optimal thyroid hormone replacement therapy should have TSH and free T_4 serum concentrations in the normal range.[22] Those who are being treated for thyroid cancer should have TSH suppressed to low levels, with the appropriate TSH concentration being determined based on the patient's risk of recurrence or progression, and TG should be undetectable.[97] Given the half-life of T_4 of 7 days, the appropriate monitoring interval is no more often than 4 weeks. The signs and symptoms of hypothyroidism should be improved or absent (see Clinical Presentation of Hypothyroidism discussed earlier), although it may take several months for the full benefit of therapy to manifest.

CONCLUSION—HYPOTHYROIDISM

Hypothyroidism is a common disorder but if left untreated it can progress into myxedema coma in the absence of an adequate endogenous thyroid reserve. Levothyroxine is a readily available and highly effective treatment that rapidly reverses the biochemical and clinical abnormalities that characterize hypothyroidism. Serum TSH and thyroid hormone levels are useful measures for adjusting the levothyroxine dose.

Postclass Engaged Learning Activity

Case 1

Evelyn is a 27-year-old female who delivered a healthy baby girl 12 weeks ago. During her pregnancy, she had thyroid testing due to a family history of Hashimoto's thyroiditis. Her thyroid hormone levels were normal during pregnancy but her antithyroid antibody (anti-TPO) levels were elevated. She now complains of nervousness, occasional racing heart, and some tremulousness. She has not had any difficulty nursing her baby. She comes in for your evaluation.

On physical exam, her blood pressure is 136/66 and pulse is 94. There are no abnormal eye or skin findings. Her thyroid is minimally enlarged. It is not tender and there is no bruit over it.

Laboratories reveal the following:

FT4=1.8 ng/dL (normal 0.7–1.7 ng/dL) or 23.2 pmol/L (9-21.9 pmol/L)

Total T3=166 ng/dL (normal 70–170 ng/dL) or 2.55 nmol/L (1.01-2.62 nmol/L)

TSH=0.05 mIU/L (normal 0.45–4.5 mIU/L)

Question 1: Which of the following is most likely etiology of this patient's symptoms?

A. Graves' disease

B. Postpartum thyroiditis

C. Toxic multinodular goiter

D. TSH-producing pituitary adenoma

Question 2: Which test would be most appropriate to confirm the diagnosis:

A. Anti-TPO antibody

B. Radioactive iodine uptake scan

C. Thyroid-stimulating antibody (TSAb)

D. Thyroid ultrasound

Question 3: The most appropriate treatment for this patient is:

A. No treatment

B. Radioactive iodine therapy

C. Methimazole

D. Thyroidectomy

Two months later, the patient returns to your office. She is fatigued. She no longer has the tremulousness, nervousness, or racing heart that she previously described. She is otherwise asymptomatic. You repeat thyroid function tests:

FT4=0.8 ng/dL (normal 0.7–1.7 ng/dL) or 10.3 pmol/L (9-21.9 pmol/L)

Total T3=110 ng/dL (normal 70–170 ng/dL) or 1.69 nmol/L (1.01-2.62 nmol/L)

TSH=9.0 mIU/L (normal 0.45–4.5 mIU/L)

Question 4: Based on this new data, which of the following is the most appropriate conclusion?

A. The patient has a new diagnosis of Hashimoto's thyroiditis

B. The patient has a TSH-producing pituitary adenoma

C. The patient has Graves' disease

D. There is no new diagnosis

Case 2

Vinny is a 45-year-old male who had the left lobe of his thyroid gland removed 20 years ago because of a large thyroid nodule. He was well until 5 months ago. At that time, he presented with tachycardia, tremulousness, heat intolerance, and unexplained weight loss. He was seen by his primary care physician and thyroid hormone measurements were obtained:

FT4=5.2 ng/dL (normal 0.7–1.7 ng/dL) or 66.9 pmol/L (9-21.9 pmol/L)

Total T3=580 ng/dL (normal 70–170 ng/dL) or 8.93 nmol/L (1.01-2.62 nmol/L)

TSH=<0.001 mIU/L (normal 0.45–4.5 mIU/L)

An RAIU scan was obtained and the results were as follows:

Thyroid uptake 65% (normal 10%–30%) and scan reported as showing hot nodule in the right lobe entirely suppressing the opposite lobe. It was determined that Vinny had a toxic nodule and a decision was made to treat him with radioactive iodine. Based on the estimated weight of the thyroid gland and iodine uptake, a dose of 15 millicuries of radioactive iodine was

administered.

Question 5: While waiting for radioactive iodine to take effect, Vinny should be treated with which of the following?

A. Methimazole

B. β-blocker

C. Supersaturated potassium iodide (SSKI)

D. Methimazole and a β-blocker

Several weeks later, the patient notes improvement in both symptoms and thyroid hormone levels. He is taken off his antithyroid medications and started on thyroid hormone replacement as the radioactive iodine takes full effect. He begins to complain of increased tearing and a sense of pressure behind his eyes. His conjunctivae are reddened. He is seen by an ophthalmologist and is told he has allergies and is started on antihistamine eye drops. He does not improve and comes to see you. You note excessive tearing, periorbital edema, and proptosis.

Question 6: The cause of these ocular findings is:

A. Nonspecific effects of hyperthyroidism

B. Graves' ophthalmopathy

C. Orbital tumor

D. Allergy

Question 7: Which of the following are risk factors for the development of Graves' ophthalmopathy?

I. Alcohol consumption

II. Smoking

III. Treatment with radioactive iodine

A. I only

B. III only

C. I and II only

D. II and III only

E. I, II, and III are correct

ABBREVIATIONS

AUC	area under the curve
cGy	centigray
C_{max}	maximum concentration
ClO_4^-	perchlorate
DIT	diiodotyrosine
FSH	follicle-stimulating hormone
$G_s\alpha$	the α subunit of the stimulatory guanine-nucleotide–binding protein
hCG	human chorionic gonadotropin
HLA	human leukocyte antigen
^{131}I	sodium iodide-131
L-thyroxine	levothyroxine
LH	luteinizing hormone
MIT	monoiodotyrosine
MMI	methimazole
MNG	multinodular goiter
NHANES III	Third National Health and Nutrition Examination Survey
PRTH	pituitary resistance to thyroid hormone
PTU	propylthiouracil
RAI	radioactive iodine
RAIU	radioactive iodine uptake
SCN^-	thiocyanate
SSKI	saturated solution of potassium iodide
T_3	triiodothyronine
T_4	thyroxine
TBG	thyroxine-binding globulin
TBPA	thyroid-binding prealbumin
TcO_4^-	pertechnetate
TG	thyroglobulin
TPOAb	thyroid peroxidase antibodies
TR	thyroid hormone receptor

TRH	thyrotropin-releasing hormone
TRIAC	triiodothyroacetic acid
TSAb	thyroid-stimulating antibody
TSH	thyroid-stimulating hormone
TTR	transthyretin
WBC	white blood cell

REFERENCES

1. Portulano C, Paroder-Belenitsky M, Carrasco N. The Na^+/I^- symporter (NIS): Mechanism and medical impact. *Endocr Rev*. 2014;35(1):106–149.
2. Obregon MJ, Escobar del Rey F, Morreale de Escobar G. The effects of iodine deficiency on thyroid hormone deiodination. *Thyroid*. 2005;15(8):917–929.
3. Verloop H, Dekkers OM, Peeters RP, Schoones JW, Smit JW. Genetics in endocrinology—Genetic variation in deiodinases: A systematic review of potential clinical effects in humans. *Eur J Endocrinol*. 2014;171(3):R123–R135.
4. Piehl S, Hoefig CS, Scanlan TS, Kohrle J. Thyronamines—Past, present, and future. *Endocr Rev*. 2011;32(1):64–80.
5. Kleinau G, Neumann S, Gruters A, Krude H, Biebermann H. Novel insights on thyroid-stimulating hormone receptor signal transduction. *Endocr Rev*. 2013;34(5):691–724.
6. Kleinau G, Biebermann H. Constitutive activities in the thyrotropin receptor: Regulation and significance. *Adv Pharmacol*. 2014;70: 81–119.
7. Brent GA. Mechanisms of thyroid hormone action. *J Clin Invest*. 2012;122(9):3035–3043.
8. Malm J, Farnegardh M, Grover GJ, Ladenson PW. Thyroid hormone antagonists: Potential medical applications and structure activity relationships. *Curr Med Chem*. 2009;16(25):3258–3266.
9. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association Guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid*. 2016;26(10):1343–421.
10. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin*

Endocrinol Metab. 2002;87(2):489–499.

11. Klubo-Gwiezdzinska J, Wartofsky L. Thyroid emergencies. *Med Clin North Am*. 2012;96(2):385–403.
12. Burch HB, Cooper DS. A young woman with palpitations, goitre and low thyroid-stimulating hormone. *CMAJ*. 2014;186(4):289–291.
13. Brix TH, Kyvik KO, Christensen K, Hegedus L. Evidence for a major role of heredity in Graves' disease: A population-based study of two Danish twin cohorts. *J Clin Endocrinol Metab*. 2001;86(2): 930–934.
14. Ban Y, Concepcion ES, Villanueva R, Greenberg DA, Davies TF, Tomer Y. Analysis of immune regulatory genes in familial and sporadic Graves' disease. *J Clin Endocrinol Metab*. 2004;89(9): 4562–4568.
15. Hasham A, Tomer Y. Genetic and epigenetic mechanisms in thyroid autoimmunity. *Immunol Res*. 2012;54(1-3):204–213.
16. Vijayakumar A, Ashwath G, Thimmappa D. Thyrotoxic periodic paralysis: Clinical challenges. *J Thyroid Res*. 2014;2014:649502.
17. Ryan DP, da Silva MR, Soong TW, et al. Mutations in potassium channel Kir2.6 cause susceptibility to thyrotoxic hypokalemic periodic paralysis. *Cell*. 2010;140(1):88–98.
18. Ryodi E, Metso S, Jaatinen P, et al. Cancer incidence and mortality in patients treated with RAI or thyroidectomy for hyperthyroidism—A nation-wide cohort study with a long-term follow-up. *J Clin Endocrinol Metab*. 2015;100(10):3710–3717.
19. Goichot B, Caron P, Landron F, Bouee S. Clinical presentation of hyperthyroidism in a large representative sample of outpatients in France: Relationships with age, aetiology and hormonal parameters. *Clin Endocrinol (Oxf)*. 2016;84(3):445–451.
20. Beck-Peccoz P, Persani L, Mannavola D, Campi I. Pituitary tumours: TSH-secreting adenomas. *Best Pract Res Clin Endocrinol Metab*. 2009;23(5):597–606.
21. Samuels MH. Subacute, silent, and postpartum thyroiditis. *Med Clinics North Am*. 2012;96(2):223–233.
22. Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: Prepared by the American Thyroid Association task force on thyroid hormone replacement. *Thyroid*. 2014;24(12):1670–1751.
23. Conrey EJ, Lindner C, Estivariz C, et al. Thyrotoxicosis outbreak linked to consumption of minced beef and chorizo: Minas, Uruguay, 2003–2004.

Public Health. 2008;122(11):1264–1274.

24. Cohen-Lehman J, Charitou MM, Klein I. Tiratricol-induced periodic paralysis: A review of nutraceuticals affecting thyroid function. *Endocr Pract*. 2011;17(4):610–615.
25. Basaria S, Cooper DS. Amiodarone and the thyroid. *Am J Med*. 2005;118(7):706–714.
26. Barbesino G. Misdiagnosis of Graves' disease with apparent severe hyperthyroidism in a patient taking biotin megadoses. *Thyroid*. 2016;26:860–863.
27. Elston MS, Sehgal S, Du Toit S, Yarndley T, Conaglen JV. Factitious Graves' disease due to biotin immunoassay interference: A case and review of the literature. *J Clin Endocrinol Metab*. 2016;101(9):3251–3255.
28. Sundaresh V, Brito JP, Wang Z, et al. Comparative effectiveness of therapies for Graves' hyperthyroidism: A systematic review and network meta-analysis. *J Clin Endocrinol Metab*. 2013;98(9): 3671–3677.
29. Abraham P, Avenell A, McGeoch SC, Clark LF, Bevan JS. Antithyroid drug regimen for treating Graves' hyperthyroidism. *Cochrane Database Syst Rev*. 2010;(1):CD003420.
30. In H, Pearce EN, Wong AK, Burgess JF, McAneny DB, Rosen JE. Treatment options for Graves' disease: A cost-effectiveness analysis. *J Am Coll Surg*. 2009;209(2):170–179.
31. Smith TJ, Hegedüs L. Graves' disease. *N Engl J Med*. 2016;375:1552–1565.
32. Burch HB, Cooper DS. Management of Graves' disease: A review. *JAMA*. 2015;314:2544–2554.
33. Momotani N, Noh JY, Ishikawa N, Ito K. Effects of propylthiouracil and methimazole on fetal thyroid status in mothers with Graves' hyperthyroidism. *J Endocrinol Metab*. 1997;82(11):3633–3636.
34. Raber W, Kmen E, Waldhausl W, Vierhapper H. Medical therapy of Graves' disease: Effect on remission rates of methimazole alone and in combination with triiodothyronine. *Eur J Endocrinol*. 2000;142(2):117–124.
35. Giuliani C, Cerrone D, Harii N, et al. A TSHR-LH/CGR chimera that measures functional thyroid-stimulating autoantibodies (TSAb) can predict remission or recurrence in Graves' patients undergoing antithyroid drug (ATD) treatment. *J Clin Endocrinol Metab*. 2012;97(7):E1080–

E1087.

36. Hashizume K, Ichikawa K, Sakurai A, et al. Administration of thyroxine in treated Graves' disease: Effects on the level of antibodies to thyroid-stimulating hormone receptors and on the risk of recurrence of hyperthyroidism. *N Engl J Med*. 1991;324(14):947–953.
37. Cooper DS, Biondi B. Subclinical thyroid disease. *Lancet*. 2012;379(9821):1142–1154.
38. Takata K, Kubota S, Fukata S, et al. Methimazole-induced agranulocytosis in patients with Graves' disease is more frequent with an initial dose of 30 mg daily than with 15 mg daily. *Thyroid*. 2009;19(6):559–563.
39. Foulds N, Walpole I, Elmslie F, Mansour S. Carbimazole embryopathy: An emerging phenotype. *Am J Med Genet Part A*. 2005;132A(2):130–135.
40. Di Gianantonio E, Schaefer C, Mastroiacovo PP, et al. Adverse effects of prenatal methimazole exposure. *Teratology*. 2001;64(5):262–266.
41. Andersen SL, Olsen J, Wu CS, Laurberg P. Birth defects after early pregnancy use of antithyroid drugs: A Danish nationwide study. *J Clin Endocrinol Metab*. 2013;98(11):4373–4381.
42. Seo GH, Kim TH, Chung JH. Antithyroid drugs and congenital malformations: A nationwide Korean cohort study. *Ann Intern Med*. 2018;168:405–413.
43. Alexander EK, Pearce EN, Brent GA, et al. 2017 guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid*. 2017;27(3):315–389.
44. Bahn RS, Burch HS, Cooper DS, et al. The role of propylthiouracil in the management of Graves' disease in adults: Report of a meeting jointly sponsored by the American Thyroid Association and the Food and Drug Administration. *Thyroid*. 2009;19(7):673–674.
45. Glinoer D, Cooper DS. The propylthiouracil dilemma. *Curr Opin Endocrinol Diabetes Obes*. 2012;19(5):402–407.
46. Bogazzi F, Giovannetti C, Fessehatsion R, et al. Impact of lithium on efficacy of radioactive iodine therapy for Graves' disease: A cohort study on cure rate, time to cure, and frequency of increased serum thyroxine after antithyroid drug withdrawal. *J Clin Endocrinol Metab*. 2010;95(1):201–208.
47. Bartalena L, Marcocci C, Bogazzi F, et al. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. *N Engl J of*

Med. 1998;338(2):73–78.

48. Boelaert K, Syed AA, Manji N, et al. Prediction of cure and risk of hypothyroidism in patients receiving 131I for hyperthyroidism. *Clin Endocrinol*. 2009;70(1):129–138.
49. Franklyn JA, Maisonneuve P, Sheppard M, Betteridge J, Boyle P. Cancer incidence and mortality after radioiodine treatment for hyperthyroidism: A population-based cohort study. *Lancet*. 1999;353(9170):2111–2115.
50. Rotondi M, Cappelli C, Pirali B, et al. The effect of pregnancy on subsequent relapse from Graves' disease after a successful course of antithyroid drug therapy. *J Clin Endocrinol Metab*. 2008;93(10):3985–3988.
51. Akamizu T, Satoh T, Isozaki O, et al. Diagnostic criteria, clinical features, and incidence of thyroid storm based on nationwide surveys. *Thyroid*. 2012;22(7):661–679.
52. Duggal J, Singh S, Kuchinic P, Butler P, Arora R. Utility of esmolol in thyroid crisis. *Can J Clin Pharmacol*. 2006;13(3):e292–e295.
53. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. *Lancet*. 2017;390(10101):1550–1562.
54. Persani L. Clinical review: Central hypothyroidism: Pathogenic, diagnostic, and therapeutic challenges. *J Clin Endocrinol Metab*. 2012;97:3068–3078.
55. LaFranchi S. Thyroid hormone in hypopituitarism, Graves' disease, congenital hypothyroidism, and maternal thyroid disease during pregnancy. *Growth Horm IGF Res*. 2006;16(Suppl A):S20–S24.
56. Sinclair D. Clinical and laboratory aspects of thyroid autoantibodies. *Ann Clin Biochem*. 2006;43(Pt 3):173–183.
57. Stassi G, De Maria R. Autoimmune thyroid disease: New models of cell death in autoimmunity. *Nat Rev Immunol*. 2002;2(3):195–204.
58. de Escobar GM, Obregon MJ, del Rey FE. Maternal thyroid hormones early in pregnancy and fetal brain development. *Best Pract Res Clin Endocrinol Metabol*. 2004;18(2):225–248.
59. Chu M, Seltzer TF. Myxedema coma induced by ingestion of raw bok choy. *N Engl J Med*. 2010;362(20):1945–1946.
60. O'Malley G, Lee HJ, Parekh S, et al. Rapid evolution of thyroid dysfunction in patients treated with nivolumab. *Endocr Pract*. 2017;23:1223–1231.

61. Prabhakar VK, Shalet SM. Aetiology, diagnosis, and management of hypopituitarism in adult life. *Postgrad Med J*. 2006;82(966): 259–266.
62. Golden WM, Weber KB, Hernandez TL, Sherman SI, Woodmansee WW, Haugen BR. Single-dose rexinoid rapidly and specifically suppresses serum thyrotropin in normal subjects. *J Clin Endocrinol Metab*. 2007;92(1):124–130.
63. Joshi AS, Woolf PD. Pituitary hyperplasia secondary to primary hypothyroidism: A case report and review of the literature. *Pituitary*. 2005;8(2):99–103.
64. Celi FS, Zemskova M, Linderman JD, et al. The pharmacodynamic equivalence of levothyroxine and liothyronine: A randomized, double blind, cross-over study in thyroidectomized patients. *Clin Endocrinol (Oxf)*. 2010;72(5):709–715.
65. Jonklaas J, Davidson B, Bhagat S, Soldin SJ. Triiodothyronine levels in athyreotic individuals during levothyroxine therapy. *JAMA*. 2008;299(7):769–777.
66. Ito M, Miyauchi A, Morita S, et al. TSH-suppressive doses of levothyroxine are required to achieve preoperative native serum triiodothyronine levels in patients who have undergone total thyroidectomy. *Eur J Endocrinol*. 2012;167(3):373–378.
67. Gullo D, Latina A, Frasca F, Le Moli R, Pellegriti G, Vigneri R. Levothyroxine monotherapy cannot guarantee euthyroidism in all athyreotic patients. *PloS One*. 2011;6(8):e22552.
68. Ma C, Xie J, Huang X, et al. Thyroxine alone or thyroxine plus triiodothyronine replacement therapy for hypothyroidism. *Nucl Med Commun*. 2009;30(8):586–593.
69. Joffe RT, Brimacombe M, Levitt AJ, Stagnaro-Green A. Treatment of clinical hypothyroidism with thyroxine and triiodothyronine: A literature review and metaanalysis. *Psychosomatics*. 2007;48(5): 379–384.
70. Grozinsky-Glasberg S, Fraser A, Nahshoni E, Weizman A, Leibovici L. Thyroxine-triiodothyronine combination therapy versus thyroxine monotherapy for clinical hypothyroidism: Meta-analysis of randomized controlled trials. *J Clin Endocrinol Metab*. 2006;91(7):2592–2599.
71. Escobar-Morreale HF, Botella-Carretero JI, Escobar del Rey F, Morreale de Escobar G. Review: Treatment of hypothyroidism with combinations of levothyroxine plus liothyronine. *J Clin Endocrinol Metabol*. 2005;90(8):4946–4954.

72. Panicker V, Saravanan P, Vaidya B, et al. Common variation in the DIO2 gene predicts baseline psychological well-being and response to combination thyroxine plus triiodothyronine therapy in hypothyroid patients. *J Clin Endocrinol Metab*. 2009;94(5):1623–1629.
73. Werneck de Castro JP, Fonseca TL, Ueta CB, et al. Differences in hypothalamic type 2 deiodinase ubiquitination explain localized sensitivity to thyroxine. *J Clin Invest*. 2015;125(2):769–781.
74. Santini F, Giannetti M, Ricco I et al *et al*, et al. Steady-state serum T3 concentrations for 48 hours following the oral administration of a single dose of 3,5,3′-triiodothyronine sulfate (T3S). *Endocr Pract*. 2014;20(7):680–689.
75. Dong BJ, Hauck WW, Gambertoglio JG, et al. Bioequivalence of generic and brand-name levothyroxine products in the treatment of hypothyroidism. *JAMA*. 1997;277(15):1205–1213.
76. Hennessey JV. Levothyroxine dosage and the limitations of current bioequivalence standards. *Nat Clin Pract Endocrinol Metab*. 2006;2(9):474–475.
77. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Inter Med*. 2000;160(4): 526–534.
78. Somwaru LL, Arnold AM, Joshi N, Fried LP, Cappola AR. High frequency of and factors associated with thyroid hormone over-replacement and under-replacement in men and women aged 65 and over. *J Clin Endocrinol Metab*. 2009;94(4):1342–1345.
79. Vestergaard P, Mosekilde L. Hyperthyroidism, bone mineral, and fracture risk—A meta-analysis. *Thyroid*. 2003;13(6):585–593.
80. Uzzan B, Campos J, Cucherat M, Nony P, Boissel JP, Perret GY. Effects on bone mass of long term treatment with thyroid hormones: A meta-analysis. *J Clin Endocrinol Metab*. 1996;81(12):4278–4289.
81. Schneider R, Schneider M, Reiners C, Schneider P. Effects of levothyroxine on bone mineral density, muscle force, and bone turnover markers: A cohort study. *J Clin Endocrinol Metab*. 2012;97(11):3926–3934.
82. Bach-Huynh TG, Nayak B, Loh J, Soldin S, Jonklaas J. Timing of levothyroxine administration affects serum thyrotropin concentration. *J Clin Endocrinol Metab*. 2009;94(10):3905–3912.
83. Sachmechi I, Reich DM, Aninyei M, Wibowo F, Gupta G, Kim PJ. Effect of proton pump inhibitors on serum thyroid-stimulating hormone level in

euthyroid patients treated with levothyroxine for hypothyroidism. *Endocr Pract*. 2007;13(4):345–349.

84. Virili C, Trimboli P, Romanelli F, Centanni M. Liquid and softgel levothyroxine use in clinical practice: State of the art. *Endocrine*. 2016;54:3–14.
85. Pirola I, Daffini L, Gandossi E, et al. Comparison between liquid and tablet levothyroxine formulations in patients treated through enteral feeding tube. *J Endocrinol Invest*. 2014;37(6):583–587.
86. Vita R, Saraceno G, Trimarchi F, Benvenga S. Switching levothyroxine from the tablet to the oral solution formulation corrects the impaired absorption of levothyroxine induced by proton-pump inhibitors. *J Clin Endocrinol Metab*. 2014;99(12):4481–4486.
87. Santaguida MG, Virili C, Del Duca SC, et al. Thyroxine softgel capsule in patients with gastric-related T4 malabsorption. *Endocrine*. 2015;49(1):51–57.
88. Fallahi P, Ferrari SM, Antonelli A. Oral l-thyroxine liquid versus tablets in patients with hypothyroidism without malabsorption: A prospective study. *Endocrine*. 2016;52:597–601.
89. Spencer CA, Hollowell JG, Kazarosyan M, Braverman LE. National Health and Nutrition Examination Survey III thyroid-stimulating hormone (TSH)-thyroperoxidase antibody relationships demonstrate that TSH upper reference limits may be skewed by occult thyroid dysfunction. *J Clin Endocrinol Metab*. 2007;92(11):4236–4240.
90. Wartofsky L, Dickey RA. The evidence for a narrower thyrotropin reference range is compelling. *J Clin Endocrinol Metab*. 2005;90(9):5483–5488.
91. Surks MI, Goswami G, Daniels GH. The thyrotropin reference range should remain unchanged. *J Clin Endocrinol Metabol*. 2005;90(9):5489–5496.
92. Santini F, Pinchera A, Marsili A, et al. Lean body mass is a major determinant of levothyroxine dosage in the treatment of thyroid diseases. *J Clin Endocrinol Metab*. 2005;90(1):124–127.
93. Somwaru LL, Rariy CM, Arnold AM, Cappola AR. The natural history of subclinical hypothyroidism in the elderly: The cardiovascular health study. *J Clin Endocrinol Metab*. 2012;97(6):1962–1969.
94. McQuade C, Skugor M, Brennan DM, Hoar B, Stevenson C, Hoogwerf BJ. Hypothyroidism and moderate subclinical hypothyroidism are

associated with increased all-cause mortality independent of coronary heart disease risk factors: A PreCIS database study. *Thyroid*. 2011;21(8):837–843.

95. Razvi S, Weaver JU, Butler TJ, Pearce SH. Levothyroxine treatment of subclinical hypothyroidism, fatal and nonfatal cardiovascular events, and mortality. *Arch Intern Med*. 2012;172(10):811–817.
96. Centanni M, Benvenga A, Sachmechi I. Diagnosis and management of treatment-refractory hypothyroidism: An expert consensus report. *J Endocrinol Invest*. 2017;40(12):1289–1301.
97. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2016;26(1):1–133.

93

Adrenal Gland Disorders

Steven M. Smith, Scott G. Garland, and John G. Gums

KEY CONCEPTS

1. Glucocorticoid secretion from the adrenal cortex is stimulated by adrenocorticotropic hormone (ACTH) or corticotropin that is released from the anterior pituitary in response to the hypothalamic-mediated release of corticotropin-releasing hormone (CRH).
2. To ensure the proper treatment of Cushing syndrome, diagnostic procedures should (1) establish the presence of hypercortisolism and (2) discover the underlying etiology of the disease.
3. The rationale for treating Cushing syndrome is to reduce the morbidity and mortality resulting from disorders such as diabetes mellitus, cardiovascular disease, and electrolyte abnormalities.
4. The treatment of choice for both ACTH-dependent and ACTH-independent Cushing syndrome is surgery. Pharmacologic agents are reserved for adjunctive therapy, refractory cases, or inoperable disease.
5. Pharmacologic agents that may be used to manage the patient with Cushing syndrome include steroidogenesis inhibitors, adrenolytic agents, neuromodulators of ACTH release, and glucocorticoid-receptor blocking agents.
6. Spironolactone, a competitive aldosterone-receptor antagonist, is the drug of choice in bilateral adrenal hyperplasia (BAH)–dependent hyperaldosteronism.
7. Addison's disease (primary adrenal insufficiency) is a state of deficiency in cortisol, aldosterone, and various androgens due to the loss of function in all regions of the adrenal cortex.
8. Secondary adrenal insufficiency usually results from exogenous steroid use, leading to hypothalamic–pituitary–adrenal (HPA)–axis suppression

followed by a decrease in ACTH release, and low levels of androgens and cortisol.

9. Virilism results from the excessive secretion of androgens from the adrenal gland and often manifests as hirsutism in females.

Preclass Engaged Learning Activity

Read the Summary of Recommendations of the 2015 Endocrine Society Clinical Practice Guidelines for Treatment of Cushing syndrome published by Nieman et al. in *J Clin Endocrinol Metab*, 2015, 100(8):2807-2831.

Read the Summary of Recommendations of the 2016 Endocrine Society Clinical Practice Guidelines for The Management of Primary Aldosteronism published by Funder et al. in *J Clin Endocrinol Metab*, 2016, 101(5):1889-1916.

Read the Summary of Recommendations of the 2016 Endocrine Society Clinical Practice Guidelines for Diagnosis and Treatment of Primary Adrenal Insufficiency published by Bornstein et al. in *J Clin Endocrinol Metab*, 2016, 101(2):364-389.

All of the above readings can be found at: https://tinyurl.com/y2rg72bk

INTRODUCTION

The adrenal glands were first characterized by Eustachius in 1563. After Addison identified a case of adrenal insufficiency in humans, adrenal anatomy and physiology flourished. Most of the work done in the early and mid-1900s centered on the glucocorticoid cortisol. With the discovery of aldosterone by Simpson and Tait in 1952, adrenal pharmacology turned toward the mineralocorticoid. Conn[1] followed with his classical description of primary aldosteronism (PA) in 1955, and numerous clinicians and investigators have continued to explore the variety of disease processes promoted through the adrenal gland.

PHYSIOLOGY, ANATOMY, AND BIOCHEMISTRY

The adrenal glands are located on the upper poles of each kidney (**Fig. 93-1**). On

average, each adrenal gland weighs 4 g and is 2 to 3 cm in width and 4 to 6 cm in length. The gland is fed by small arteries from the abdominal aorta and renal and phrenic arteries. Drainage of the adrenal gland occurs via the renal vein on the left and the inferior vena cava on the right.

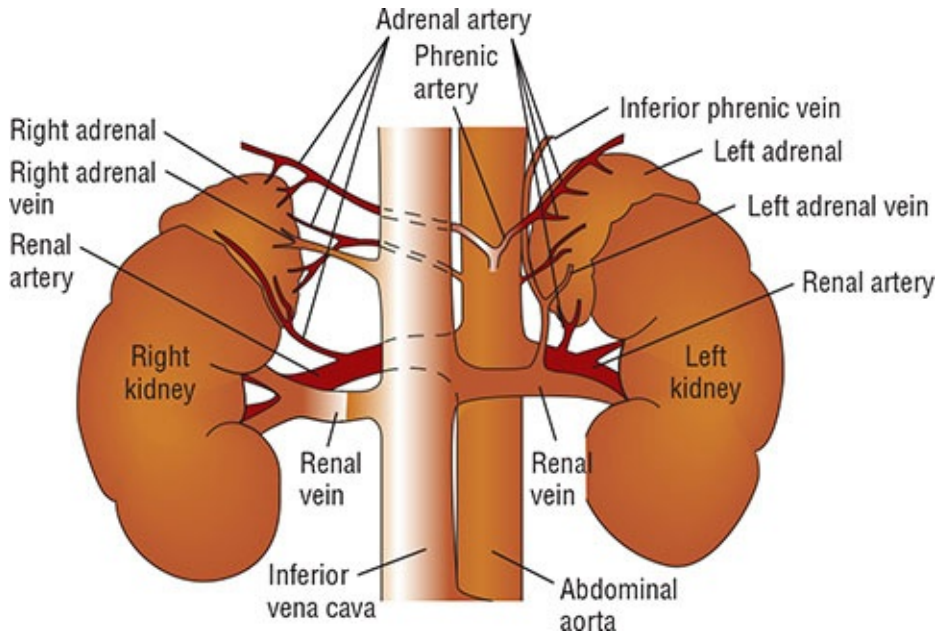


FIGURE 93-1 Anatomy of the adrenal gland.

The adrenal medulla comprises 10% of the total gland and is responsible for the secretion of catecholamines. The adrenal cortex accounts for the remaining 90% and is responsible for the secretion of three types of hormones (**Fig. 93-2**) from three separate zones.

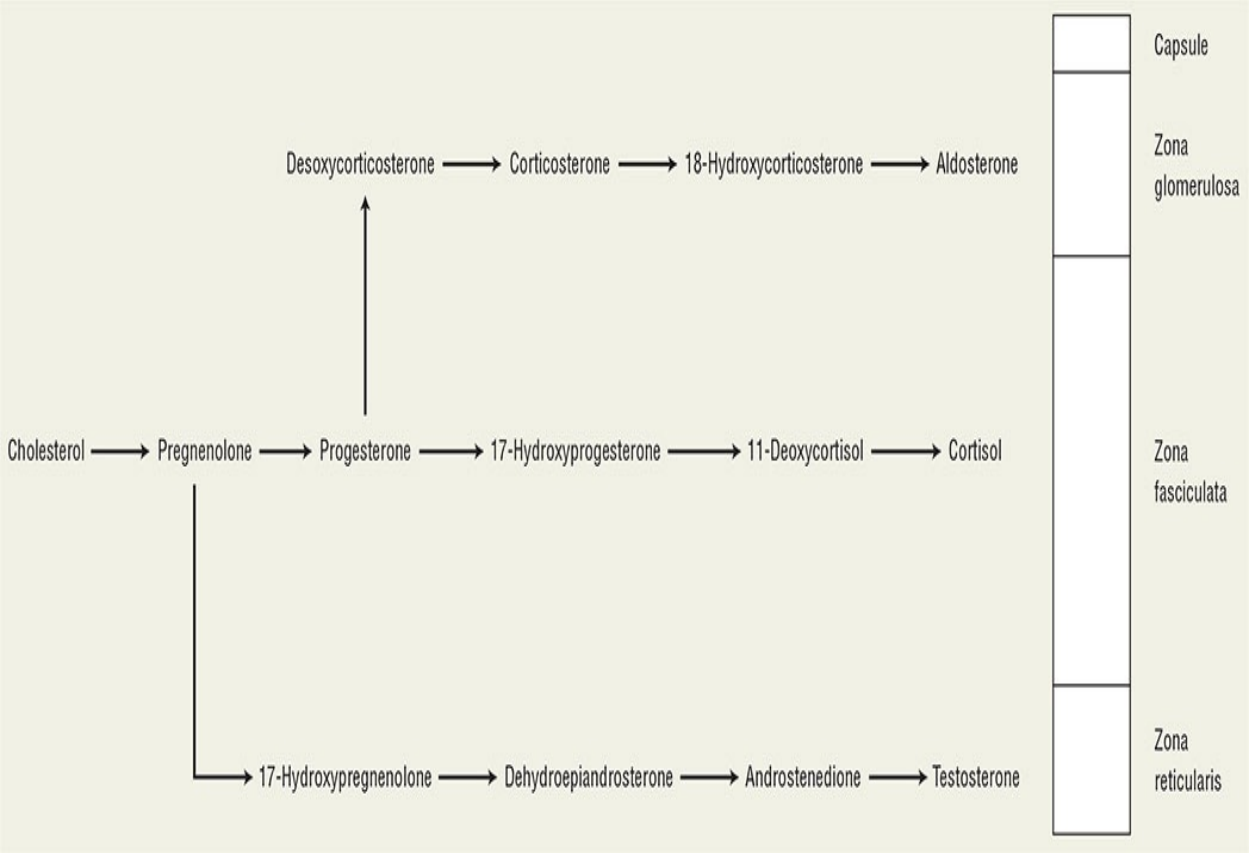


FIGURE 93-2 Hormone synthetic pathways in relation to the zones of the adrenal cortex.

The zona glomerulosa accounts for 15% of the total adrenal cortex and is responsible for mineralocorticoid production, of which aldosterone is the principal end product. Aldosterone maintains electrolyte and volume homeostasis by altering potassium and magnesium secretion and renal tubular sodium reabsorption. The zona fasciculata, the middle zone, makes up 60% of the cortex, is high in cholesterol, and is responsible for basal and stimulated glucocorticoid production. Glucocorticoids, mainly cortisol, are responsible for the regulation of fat, carbohydrate, and protein metabolism. The zona reticularis occupies 25% of the adrenal cortex and is responsible for adrenal androgen production. The androgens, testosterone and estradiol, are the major end products and influence the reproductive system in addition to modulating primary and secondary sex characteristics.

Hormone Production and Metabolism

Adrenal steroid hormone synthesis begins with the conversion of cholesterol to

pregnenolone by cytochrome P450 (CYP) enzymatic side-chain cleavage (Fig. 93-2). Following this rate-limiting step, pregnenolone is converted to various 19- and 21-carbon steroids, depending on the enzymatic capabilities within each zone of the cortex. Androgenic properties predominate in the 19-carbon steroids, whereas mineralocorticoid and glucocorticoid properties manifest in the 21-carbon steroids.

Aldosterone production is initiated by the 21-hydroxylation of progesterone to form deoxycorticosterone. Subsequently, aldosterone synthase converts deoxycorticosterone to aldosterone through the intermediary, corticosterone. The zona glomerulosa preferentially produces aldosterone for three main reasons. First, the zona glomerulosa lacks 17α-hydroxylase activity and therefore can only convert pregnenolone to progesterone. Second, in contrast to the other zones, cells in the zona glomerulosa possess aldosterone synthase activity, which catalyzes the terminal steps in aldosterone synthesis. Lastly, cells of the zona glomerulosa display a greater number of angiotensin II receptors than cells of the other zones. Binding of angiotensin II to these receptors provides the stimulus for initiating the aldosterone biosynthesis cascade. Thus, aldosterone synthesis is a unique feature of the zona glomerulosa, explaining why aldosterone is not affected during disease processes limited to the zona fasciculata or reticularis.

Cortisol is produced from pregnenolone via four successive hydroxylations. These hydroxylations occur primarily in the zona fasciculata, although the zona reticularis is also capable of producing glucocorticoids.

Androgens, produced primarily in the zona reticularis and less commonly in the zona fasciculata, have a 19-carbon structure and serve as precursors to more potent analogs produced in the periphery. The adrenal gland can synthesize estradiol and estrone from testosterone and androstenedione, respectively; however, the quantities synthesized by the adrenal gland are extremely small. The rates of production for the various steroids produced by the adrenal gland are listed in **Table 93-1**.

TABLE 93-1 Rates of Adrenal Production and Plasma Concentrations of Various Steroids

Steroid	24-Hour Secretion (mg)	Plasma Concentration
Aldosterone	0.15 (0.42 µmol)	2-9 ng/dL (55-250 pmol/L; supine, normal-sodium diet)
Androstenedione	2.2-2.5 (7.7-8.7 µmol/L)	50-250 ng/dL (1.7-8.7 nmol/L)
Corticosterone	1-4 (3-12 µmol)	2.4 ± 1.5 ng/dL (69 ± 43 nmol/L; female) 4.2 ± 2.2 ng/dL (121 ± 64 nmol/L; male)
Cortisol	8-25 (22-69 µmol)	0-25 µg/dL (0-690 nmol/L)
11-Deoxycorticosterone	0.60 (1.8 µmol)	2-19 ng/dL (60-575 pmol/L)
11-Deoxycortisol	0.40 (1.2 µmol)	12-158 ng/dL (350-4560 pmol/L)
Progesterone	0	<20 ng/dL (0.6 nmol/L; female)[a] 300-2,000 ng/dL (9.5-64 nmol/L; female)[b] <20-140 ng/dL (0.6-4.5 nmol/L; male)
Testosterone (total)	0.23 (0.8 µmol; female)	6-86 ng/dL (0.2-3.0 nmol/L; female) 270-1,070 ng/dL (9.4-37 nmol/L; male)

[a]Follicular phase of menstrual cycle.

[b]Luteal phase of menstrual cycle.

Data from Kratz A, Ferraro M, Sluss PM, Lewandrowski KB. Laboratory reference values. N Engl J Med. 2004;351(15):1548-1563.

Glucocorticoid metabolism occurs in the liver and is responsible for converting inactive steroids to active metabolites, as well as modifying active steroids to less active or inactive metabolites. Most pharmaceutical steroid products are active; however, in the case of prednisone and cortisone, metabolism is necessary for conversion to the active prednisolone and cortisol, respectively.

Following metabolic conversion, glomerular filtration is primarily responsible for eliminating endogenously produced glucocorticoids. The half-life of cortisol is 70 to 120 minutes, whereas aldosterone exhibits extremely high intrinsic clearance and a corresponding half-life of only 15 minutes.

Metabolism and conversion of the various steroids can be altered by a variety

of disease states and medicinal compounds. Drugs known to enhance steroid clearance include phenytoin, phenobarbital, rifampin, and mitotane. Likewise, diseases such as hyperthyroidism and renal disease can enhance steroid clearance. In contrast, drugs such as estrogens and estrogen-containing oral contraceptives reduce steroid clearance. Similarly, liver disease, age, pregnancy, hypothyroidism, anorexia nervosa, protein-calorie malnutrition, and renal disease are associated with reduced steroid clearance.

Plasma glucocorticoids are bound to one of three plasma proteins in varying degrees. Corticosteroid-binding globulin (CBG), albumin, and α_1-glycoprotein are capable of binding glucocorticoids, with CBG being the principal binding protein. Steroid binding serves as a reservoir for steroids in their inactive state and more than 95% of cortisol is normally bound. Binding to plasma proteins prevents glucocorticoid activity at receptor-activating sites. Therefore, a final but important variable in altered plasma concentration of free (active) steroids is the concentration of plasma proteins.

Regulation of Hormone Secretion

1 Glucocorticoid secretion is regulated by the pituitary hormone, adrenocorticotropic hormone (ACTH [also known as corticotropin]). Under normal conditions, ACTH is released from the anterior pituitary in response to corticotropin-releasing hormone (CRH), which is secreted by the median eminence of the hypothalamus (**Fig. 93-3**). Vasopressin and oxytocin have weak ACTH-releasing activity through binding to the inferior V_3 receptor. CRH, in combination with vasopressin and oxytocin, stimulates greater ACTH secretion than each hormone individually.

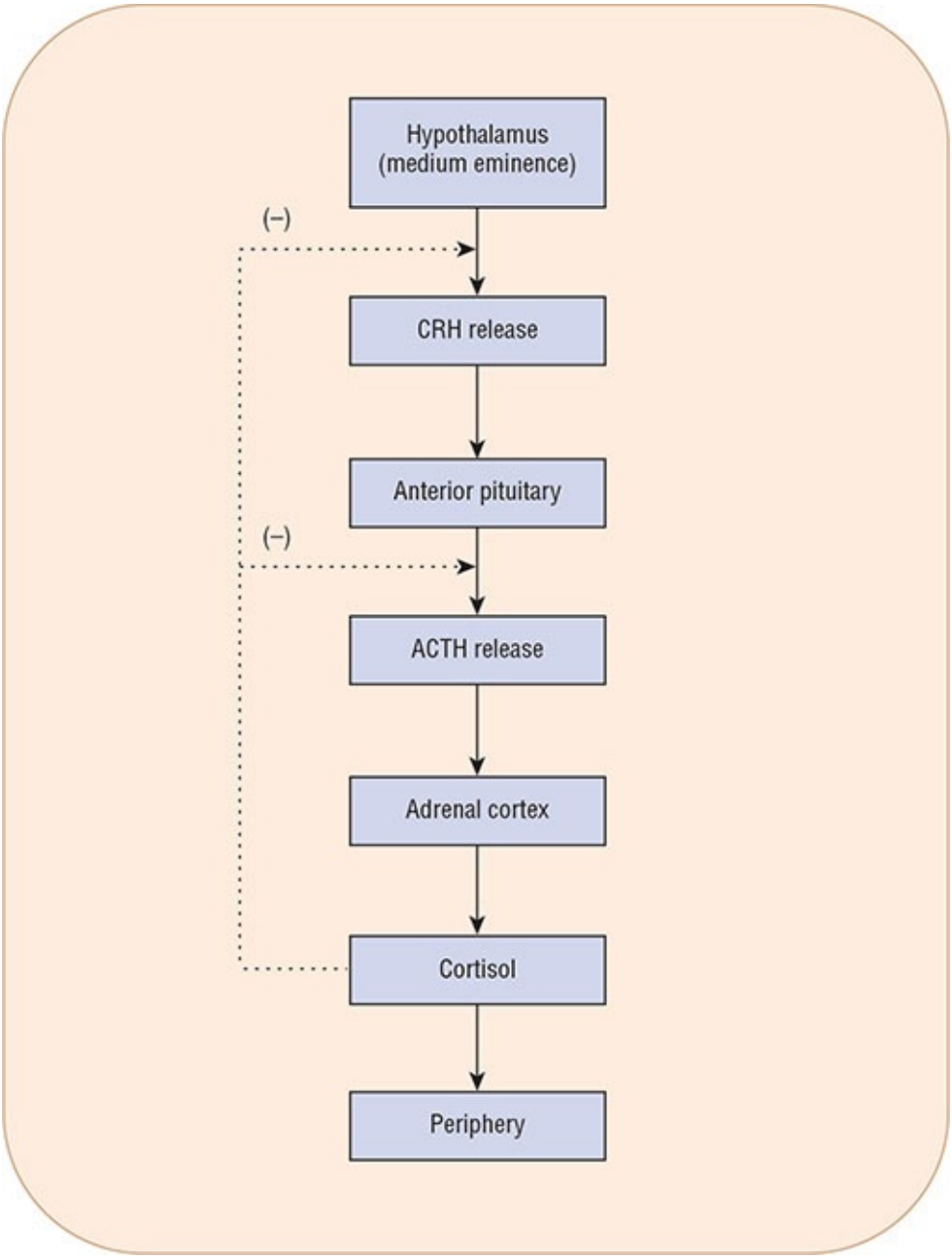


FIGURE 93-3 Negative feedback system involved in the regulation of cortisol secretion under normal conditions. (ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone.).

Additionally, histochemical studies have demonstrated that certain neurotransmitters, such as serotonin and norepinephrine, can stimulate the production of CRH and ACTH. After release, ACTH stimulates the adrenal gland to release cortisol and, to a lesser extent, aldosterone and androgens. The rising cortisol concentration inhibits the secretion of CRH and ACTH through a negative feedback mechanism. In addition, leptin, an adipocyte hormone, has an

inhibitory effect on hypothalamic–pituitary–adrenal (HPA) activity.

Adrenal androgens are regulated in a similar fashion to cortisol. When plasma androgen reaches sufficient concentrations, production is terminated via a negative feedback loop. Androgen release is increased during puberty and in women with hirsutism. Adrenal androgen release decreases with age and in fasting states, including anorexia nervosa.

In contrast to cortisol and adrenal androgens, regulation of aldosterone secretion is considerably more complex. The renin-angiotensin system regulates aldosterone secretion through both intrarenal and extrarenal mechanisms. Renin production and subsequent aldosterone secretion is stimulated by blood pressure lowering (due to volume depletion), erect posture, salt depletion, β-adrenergic stimulation, and CNS excitation (see Chapter 30). Renin production is inhibited by salt loading, angiotensin II, vasopressin, potassium, calcium, blood pressure increases, and a variety of drugs. The renin-mediated production of angiotensin II is the initial stimulus for aldosterone synthesis. Additionally, angiotensin II can be acted on by aminopeptidase and converted to angiotensin III. Both angiotensin II and III are capable of stimulating the zona glomerulosa to secrete aldosterone. Following aldosterone secretion, increases in renal sodium, water retention, and blood pressure occur thereby turning off the stimulus for renin release.

HYPERFUNCTION OF THE ADRENAL GLAND

Adrenal disorders can be categorized as hyperfunction or hypofunction of the adrenal gland. Hyperfunction of the adrenal gland generally involves excess production of adrenal hormones, most notably cortisol, resulting in Cushing syndrome, or aldosterone, resulting in hyperaldosteronism.

Cushing Syndrome

In 1932, Cushing first described a syndrome of pituitary basophilism that attracted national attention. These patients had unexplained central obesity, cutaneous striae, osteoporosis, weakness, hypertension, diabetes mellitus, and congestion. Cushing believed the disease was of a pituitary origin. Ten years later, Albright focused his attention on the “sugar hormone,” which he believed originated from the adrenal cortex.[2] It was not until the development of a method to measure urinary steroids did it become clear that elevated steroids in patients with Cushing syndrome was the result of excess plasma cortisol

(hypercortisolism).

Etiology

Cushing syndrome results from the effects of supraphysiologic concentrations of glucocorticoids originating either from the exogenous administration or, less commonly, endogenous overproduction by the adrenal glands. Excess glucocorticoids are produced in response to overproduction of ACTH (ACTH-dependent) or by abnormal adrenocortical tissues (ACTH-independent). ACTH-dependent Cushing syndrome (≈80% of all Cushing syndrome cases) usually originates from overproduction of ACTH by the pituitary gland. Excessive ACTH chronically stimulates the adrenal glands causing bilateral adrenal hyperplasia (BAH). Approximately 85% of these cases are caused by pituitary adenomas (Cushing disease). Ectopic ACTH-secreting tumors and non-neoplastic corticotropin hypersecretion, possibly secondary to excess CRH production, account for the remainder of ACTH-dependent causes.[3] Ectopic ACTH syndrome refers to excessive ACTH production resulting from an endocrine or nonendocrine tumor, usually of the pancreas, thyroid, or lung. Small-cell carcinoma of the lung will lead to ectopic ACTH secretion in 0.5% to 2% of cases, whereas bronchial carcinoid tumors are usually the most common.[4] Distinguishing between the various etiologies requires a careful history and laboratory work (Table 93-2).

TABLE 93-2 Various Etiologies of Cushing Syndrome and Their Respective Differences

	Pituitary-Dependent	Ectopic ACTH Syndrome	Adrenal Adenoma	Adrenal Carcinoma
Course	Slow	Rapid	Slow	Rapid
Symptoms	Mild to moderate	Atypical	Mild to moderate	Severe
Dominant sex/age	Female/male	Male	None noted	Children
Virilization	+	+	+	+++
Abdominal mass	0	0	0	++
Plasma ACTH concentration	Slightly elevated	High	Low	Low
Dexamethasone suppression test	≥50% suppression	No suppression	No suppression	No suppression
Iodocholesterol scan	Bilateral uptake	Bilateral uptake	Unilateral	None

ACTH, adrenocorticotropic hormone.

The remaining 20% of Cushing syndrome cases are ACTH-independent and divided almost equally between adrenal adenomas and adrenal carcinomas. In

rare cases, macronodular hyperplasia, primary pigmented nodular adrenal disease, and McCune-Albright syndrome is the culprit.[3,5] The majority of adrenal cortex tumors are benign adenomas. Adrenal carcinoma is found more often in children than in adults with Cushing syndrome.

CLINICAL PRESENTATION

Patients with Cushing syndrome commonly present (>90% of patients) with central obesity and facial rounding. Approximately 50% of patients exhibit some peripheral obesity and fat accumulation. Fat accumulation in the dorsocervical area (buffalo hump) is often associated with weight gain, whereas increased supraclavicular fat pads are more specific for Cushing syndrome. Striae are usually present along the lower abdomen and have a red to purple color. Traditionally, complications caused by high blood pressure have been major contributors to the morbidity and mortality of Cushing syndrome. Hypertension is diagnosed in 75% to 85% of patients, with diastolic blood pressures greater than 119 mm Hg noted in over 20% of patients.[6] Glucose intolerance is present in 60% of patients. Thus, many patients meet diagnostic criteria for the metabolic syndrome and have a corresponding increased risk of coronary heart disease (CHD) and stroke. Screening for Cushing syndrome in this population and in patients with uncontrolled diabetes mellitus has been suggested,[7,8] particularly when these conditions surface at an unusually early age.[9] However, screening all patients with type 2 diabetes is likely not cost-effective.[10]

Diagnosis

Iatrogenic (exogenous) Cushing syndrome is the most common etiology. Therefore, all patients exhibiting hypercortisolism should undergo a comprehensive history and evaluation assessing medication use before laboratory testing is performed to identify endogenous causes. Iatrogenic Cushing syndrome can occur from administration of oral, inhaled, intranasal, intra-articular, and topical glucocorticoids, as well as progestins such as medroxyprogesterone acetate and megestrol acetate.[11] Disease severity correlates with exogenous glucocorticoid potency, dose, frequency, route, and treatment duration. Moreover, patients taking CYP3A4 inhibitors concomitantly with a glucocorticoid can be at higher risk of developing iatrogenic Cushing syndrome.[12,13] If exogenous glucocorticoids are being taken, the plasma cortisol concentration can increase, while the corticosterone concentration remains low.[14]

In the absence of any known exogenous causes, the clinician will need to differentiate the syndrome from other syndromes, such as pseudo-Cushing syndrome, that mimic true Cushing syndrome. Patients with obesity, chronic alcoholism, depression, and acute illness of any type can present with certain features of Cushing syndrome. However, these patients may lack true Cushing syndrome. For example, depressed patients, although mimicking the urinary steroid abnormalities of Cushing syndrome, will not resemble a cushingoid patient in appearance. In chronic alcoholism, steroid laboratory panels generally return to baseline after ceasing alcohol intake. And obese patients often will have normal cortisol concentrations for both serum and urinary screening tests. Thus, identifying true cases of Cushing syndrome requires a comprehensive history in combination with laboratory and possibly imaging assessment.

2 The diagnosis of Cushing's syndrome involves two steps: (a) establishing the presence of hypercortisolism, which is relatively easy, and (b) determining the etiology, which can be challenging (**Fig. 93-4**).[5,8,15] The presence of hypercortisolism can be established via one or more of the following tests: 24-hour UFC, midnight plasma cortisol, late-night salivary cortisol, or the low-dose DST (using 1 mg dexamethasone for the overnight test or 0.5 mg/6 h for the classic 2-day study). However, because these tests cannot determine the etiology of Cushing syndrome, other tests and procedures must be subsequently employed. Such tests can include any of the following: plasma ACTH via immunoradiometric assay (IRMA) or radioimmunoassay (RIA); adrenal vein catheterization; metyrapone stimulation test; adrenal, chest, or abdominal computed tomography (CT); CRH stimulation test; inferior petrosal sinus sampling (IPSS); jugular venous sampling (JVS); cavernous sinus sampling; and pituitary magnetic resonance imaging (MRI). High-dose DST has been used in the past but is no longer recommended due to its poor specificity and limited diagnostic value. Other possible tests and procedures include insulin-induced hypoglycemia, somatostatin receptor scintigraphy, the desmopressin stimulation test, the naloxone CRH stimulation test, the loperamide test, the hexarelin stimulation test, and radionuclide imaging.[5,6,8,15-20] **Table 93-3** summarizes the findings from some of the tests used to diagnose Cushing syndrome.

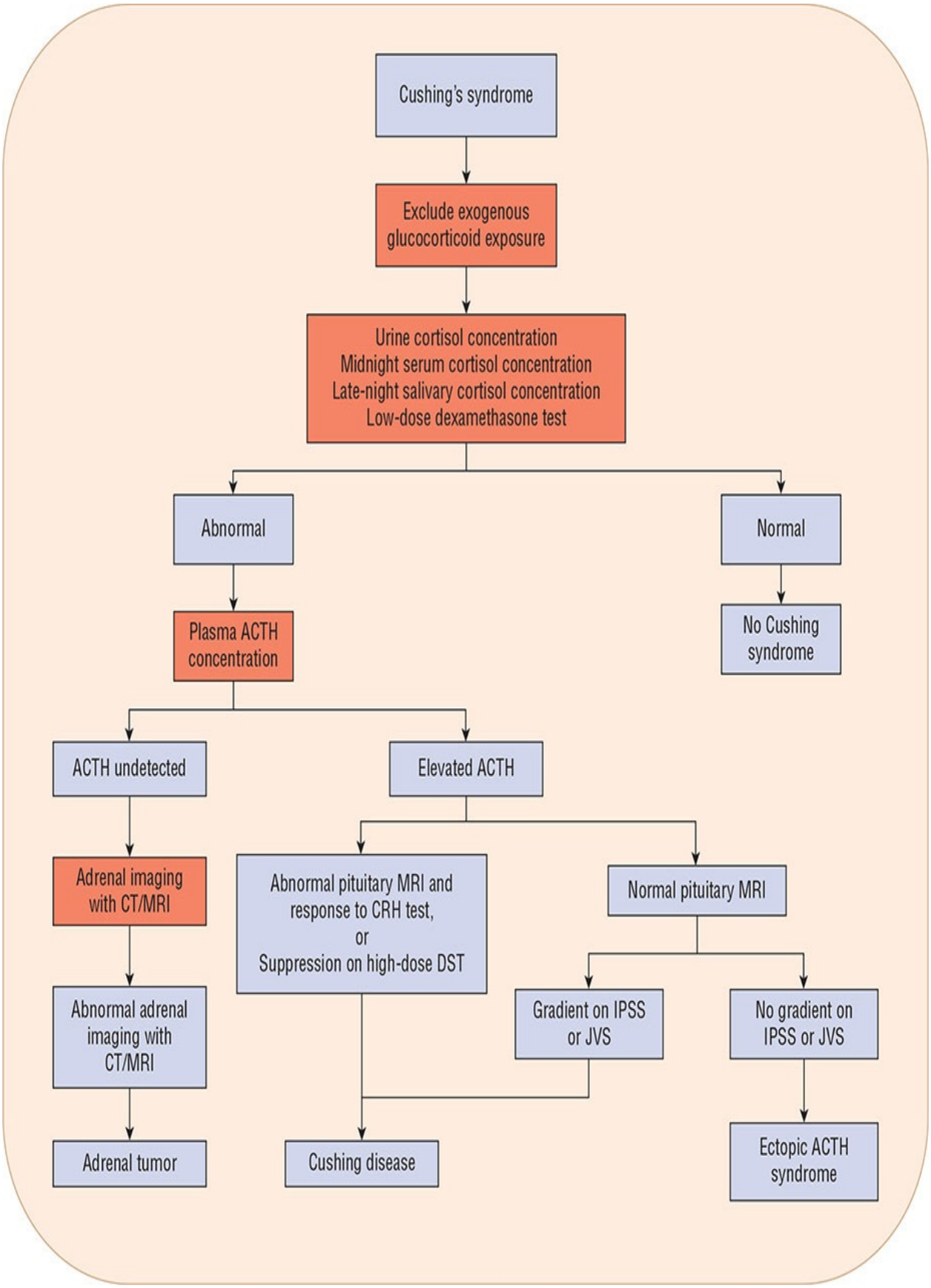

Cushing's syndrome
Exclude exogenous glucocorticoid exposure
Urine cortisol concentration
Midnight serum cortisol concentration
Late-night salivary cortisol concentration
Low-dose dexamethasone test
Abnormal
Normal
No Cushing syndrome
Plasma ACTH concentration
ACTH undetected
Elevated ACTH
Adrenal imaging with CT/MRI
Abnormal adrenal imaging with CT/MRI
Adrenal tumor
Abnormal pituitary MRI and response to CRH test, or Suppression on high-dose DST
Normal pituitary MRI
Gradient on IPSS or JVS
No gradient on IPSS or JVS
Cushing disease
Ectopic ACTH syndrome

FIGURE 93-4 Algorithm for diagnosing Cushing syndrome. (ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; CT, computed tomography; DST, dexamethasone suppression test; IPSS, inferior petrosal sinus sampling; JVS, jugular venous sampling; MRI, magnetic resonance imaging.).

TABLE 93-3 Summary of Tests Used to Diagnose Cushing Syndrome

Test	Normal	Hyperplasia	Adenoma	Carcinoma
Plasma				
Cortisol (µg/dL or nmol/L, in brackets; for am/pm)	5-25/5-15 (140-690/140-415)	↑/↑↑	↑↑/↑↑	↑↑↑/↑↑↑
After low-dose DST	↓	↔	↔	↔
After high-dose DST	↓	↓/↔	↔	↔
ACTH (pg/mL or pmol/L, in brackets)	6-76 (1.3-17)	↑↑	↓	↓
Urine				
Cortisol (µg/24 hours or nmol/day, in brackets)	20-90 (55-250)	↑↑	↑↑	↑↑↑
Saliva				
Cortisol (µg/dL or nmol/L), PM)	Assay-dependent	↑↑	↑↑	↑↑↑

ACTH, adrenocorticotropic hormone; DST, dexamethasone suppression test.

Data from Kratz A, Ferraro M, Sluss PM, Lewandrowski KB. Laboratory reference values. N Engl J Med. 2004;351(15):1548-1563.

Elevated UFC concentrations are highly suggestive of Cushing syndrome, especially values fourfold greater than the upper limit of normal.[3,17] In contrast to plasma measurements of cortisol, UFC measures only unbound cortisol. Consequently, the UFC test is unaffected by conditions and medications that

alter CBG levels. Normal reference values for UFC are 10 to 60 µg per 24-hour period (30-170 nmol/day). A two- to threefold increase in urine cortisol is not uncommon in the patient with hyperfunction of the adrenal gland. Starvation, hydration from water loading (≥5 L/day), alcoholism, and acute stress are all capable of elevating urine cortisol concentrations. Likewise, elevated UFC results can occur during therapy with carbamazepine, fenofibrate, and topical steroids depending on the type of UFC test. Conversely, renal impairment (creatinine clearance [CrCl] of <60 mL/min [1.0 mL/s]) can falsely lower UFC concentrations. Because other pathologic conditions can increase the amount of free cortisol, additional tests may be warranted to confirm the diagnosis, or the diagnostic evaluation should be repeated when the acute stress has resolved. Of all urinary measures, UFC is the most useful assessment for patients with suspected Cushing syndrome.[8,17,19]

In healthy individuals, cortisol release follows a circadian rhythm whereby serum cortisol concentration peaks around 8:00 am and thereafter declines by 60% to 80%, reaching a nadir between 1:00 and 3:00 am. This rhythm is lost in the patient with Cushing syndrome. Although many patients with Cushing syndrome will have serum cortisol values in the high normal range if the serum is assayed in the morning, only 3.4% will have normal values if measured late at night.[14] Thus, a midnight serum cortisol greater than 7.5 µg/dL (210 nmol/L; >1.8 µg/dL [50 nmol/L]if the patient is sleeping) is a highly sensitive assay for Cushing syndrome. However, this test is cumbersome and rarely recommended because it requires that patients be admitted for more than 48 hours to avoid false-positive responses secondary to the stress of hospitalization. An alternative assay is the measurement of late-night salivary cortisol. Salivary cortisol is highly correlated with free serum cortisol and independent of salivary flow rates. Moreover, salivary cortisol concentration reflects changes in serum cortisol within minutes. Salivary cortisol can be considered an acceptable alternative to UFC because of its convenience, stability (1 week), accuracy, and reproducibility. Unfortunately, normal reference ranges are assay-dependent, and cutoff points vary among institutions.[21,22]

CLINICAL PRESENTATION Cushing Syndrome

General

- The most common findings, which are present in 90% of patients, are central obesity and facial rounding.

Symptoms

- A majority of patients complain of myopathies and muscular weakness.

Signs

- Peripheral obesity and fat accumulation are found in 50% of patients.
- Facial plethora is caused by an underlying atrophy of the skin and connective tissue.
- Patients often are described as having moon faces with a buffalo hump.
- Hypertension is seen in 75% to 85% of patients.
- Psychiatric changes can occur in as many as 55% of patients.
- Approximately 50% to 60% of patients will develop Cushing syndrome–induced osteoporosis. Of these, 40% will present with back pain and 20% will have compression fractures of the spine.
- Gonadal dysfunction is common with amenorrhea seen in up to 75% of females.
- Hirsutism is present in 80% of females.

Laboratory Tests

- A midnight plasma cortisol, late-night salivary cortisol, 24-hour urinary free cortisol (UFC), and/or low-dose dexamethasone suppression test (DST) will establish the presence of hypercortisolism.

Other Diagnostic Tests

- The plasma ACTH test, metyrapone stimulation test, CRH stimulation test, or inferior petrosal sinus sampling (IPSS) will help determine the etiology.

In the overnight DST, 1 mg of dexamethasone is administered at 11:00 pm. The following morning at 8:00 am fasting plasma cortisol is obtained for analysis. This supraphysiologic dose of dexamethasone suppresses ACTH stimulation and cortisol production in healthy individuals. In contrast, the negative feedback loop is ineffective in patients with Cushing syndrome who generally exhibit a morning cortisol concentration above 5 µg/dL (140 nmol/L). Some patients with Cushing syndrome administered the overnight DST can

slightly suppress cortisol and using 1.8 μg/dL (50 nmol/L) as a cutoff can increase sensitivity, but at the expense of reduced specificity.[23] Therefore, the overnight DST is useful only as a screening tool for Cushing syndrome. Drugs that induce or inhibit CYP3A4 metabolism can significantly alter dexamethasone concentration, increasing the likelihood of false-positive and false-negative DSTs. Concurrent measurements of dexamethasone concentration with cortisol may improve the accuracy of testing for patients on CYP3A4-modifying drugs, although dexamethasone assays are not widely available. Also noteworthy, pregnancy and estrogen use (including oral contraceptives) increase CBG levels and frequently elicit false-positive results.[17] Consequently, UFC testing is preferred over DST in these patient populations.

The first test used to determine the etiology of Cushing syndrome is the plasma ACTH test. Plasma ACTH concentrations can be measured via RIA or IRMA.[16] In ACTH-dependent Cushing syndrome, ACTH can be normal or elevated. Very high levels of ACTH favor ectopic production. In contrast, ACTH values generally are low (<5 pg/mL [1.1 pmol/L]) in ACTH-independent (adrenal) Cushing syndrome. Furthermore, ACTH levels can appear artificially low in some ectopic ACTH-producing tumors because ACTH can be secreted as an active prohormone that is not detected by the assay.

IPSS offers the highest sensitivity and specificity of any test in differentiating the etiology of Cushing syndrome. This technique requires catheterization of both petrosal sinuses with serial measurements of ACTH in each sinus and a peripheral vein after administration of CRH. A central-to-peripheral ACTH gradient is diagnostic for Cushing disease, whereas no gradient indicates ectopic ACTH production. Complications, such as venous thromboembolism, brain stem vascular damage, high cost, and technical expertise, can limit the use of this test.[16] JVS uses the same concept as IPSS, is less invasive, and produces fewer complications; however, sensitivity is compromised.

Abnormal adrenal anatomy is effectively identified using high-resolution CT scanning and MRI.[24] Nodules as small as 1 to 1.5 cm on the adrenal cortex are easily identified by CT. With the use of thin-section scanning, nodules as small as 3 to 5 mm can be visualized.[25] Importantly, adrenal incidentalomas (masses observed incidentally on imaging) are prevalent in 5% to 10% of the general population. These masses may be functional (secreting), requiring intervention, or nonfunctional (nonsecreting), requiring only periodic observation. For this reason, abnormal imaging results are unable to conclusively diagnose adrenal disease when used alone. Nonadrenal imaging studies may be useful for identifying ectopic sources of ACTH secretion in patients for whom IPSS has

ruled out Cushing disease.

TREATMENT

Desired Outcomes

3 If left untreated, Cushing syndrome is associated with high morbidity and mortality due to hypertension, diabetes mellitus, cardiovascular disease, and electrolyte abnormalities. These disorders limit the survival of the patient with Cushing syndrome to 4 to 5 years following initial diagnosis. The desired outcomes of treatment are to limit such detrimental outcomes and return the patient to a normal functional state by removing the source of hypercortisolism while minimizing pituitary or adrenal deficiencies.

4 The treatment of choice for both ACTH-dependent and ACTH-independent Cushing syndrome is surgical resection of any offending tumors.[3,15] Several secondary pharmacologic treatment options are available that can be used to target the etiology of the disease (Table 93-4).[3,26-29] These pharmacologic options are generally reserved as second-line treatment in patients who are not surgical candidates. They may also be used preoperatively or as adjunctive therapy in the postoperative period awaiting a response. Rarely, monotherapy is used as a palliative treatment when surgery is not indicated.

TABLE 93-4 Possible Treatment Options in Cushing Syndrome Based on Etiology

	Treatment	
Etiology	**Nondrug**	**Drug**
Ectopic ACTH syndrome	Surgery, chemotherapy, irradiation	Metyrapone Ketoconazole
Pituitary-dependent	Surgery, irradiation	Mitotane Metyrapone Mifepristone Cabergoline Pasireotide
Adrenal adenoma	Surgery, postoperative replacement	Ketoconazole
Adrenal carcinoma	Surgery	Mitotane

ACTH, adrenocorticotropic hormone.

Pharmacologic Therapy

5 Pharmacotherapy of Cushing syndrome can be divided into four categories based on the anatomic site of action: (1) steroidogenesis inhibitors, (2) adrenolytic agents, (3) neuromodulators of ACTH release, and (4) glucocorticoid-receptor blocking agents.[26,27] Dosing and monitoring parameters can be found in Tables 93-5 and 93-6, respectively.[3,28,29]

TABLE 93-5 Drug Dosing in the Treatment of Cushing Syndrome

Drug	Brand Name	Initial Dose	Usual Range	Special Populations	Comments
Cabergoline	Dostinex®, 0.5 mg tablets	0.5 mg once weekly	0.5-7 mg once weekly		Maximum: 7 mg/week
Etomidate	Amidate®, 2 mg/mL solution	0.03 mg/kg IV bolus	0.1-0.3 mg/kg/hr infusion		Maximum: 0.3 mg/kg/hr infusion; titrate based on serum cortisol concentration
Ketoconazole	Nizoral®, 200 mg tablets	200 mg once or twice a day	200-1,200 mg/day, divided twice a day	Contraindicated in patients with hepatic disease	Maximum: 1,600 mg/day; CYP3A4 substrate and inhibitor (strong)
Metyrapone	Metopirone®, 250 mg tablets	0.5-1 g/day, divided every 4-6 hours	1-2 g/day, divided every 4-6 hours		Maximum: 6 g/day; CYP3A4 inducer
Mifepristone	Korlym®	300 mg once daily, increased by 300 mg/day every 2-4 weeks	600-1,200 mg/day	Do not exceed 600 mg/day in mild-to-moderate hepatic impairment; avoid in severe hepatic impairment. Do not exceed 600 mg/day in renal impairment	Maximum: 1,200 mg/day not to exceed 20 mg/kg/day
Mitotane	Lysodren®, 500 mg tablets	0.5-1 g/day, increased by 0.5-1 g/day every 1-4 weeks	1-4 g/day		Maximum: 12 g/day (most patients unable to tolerate >8 g/day). Take with food to decrease GI effects
Pasireotide	Signifor®, 0.3, 0.6, 0.9 mg/mL solutions	0.6-0.9 mg twice daily	0.3-0.9 mg twice daily	Reduce dose in hepatic impairment	Maximum: 1.8 mg/day

CYP, cytochrome P450 enzyme; GI, gastrointestinal.

TABLE 93-6 Alternative Steroid Replacement Regimens in the Adrenal Adenoma Patient

Drug	Adverse Drug Reaction	Monitoring Parameters	Comments
Cabergoline	Nausea, dizziness, headache, nasal congestion, constipation, psychiatric symptoms, valvulopathy	Echocardiogram	
Etomidate	Sedation, pain at injection site, hypotension, myoclonus, nausea, vomiting	Frequent sedation scoring initially, serum potassium, serum cortisol	
Ketoconazole	GI upset, dermatologic reactions; elevated hepatic transaminases, hepatotoxicity	Liver function tests, including ALT/AST, total bilirubin, ALP, prothrombin time, and INR testing	Approximately 10% will experience reversible LFT elevations
Metyrapone	Androgenic effects (hirsutism, acne, etc.), blood pressure and electrolyte abnormalities, nausea, vomiting, vertigo, headache, dizziness, abdominal discomfort, allergic rash	Blood pressure, electrolytes	
Mifepristone	Hypokalemia, nausea, fatigue, headache, peripheral edema, dizziness, endometrial hyperplasia	Serum potassium, pregnancy testing, pelvic ultrasound	Abortifacient; rule out pregnancy in women of childbearing potential
Mitotane	GI upset, nausea, diarrhea, lethargy, somnolence, CNS disturbances	UFC and urinary steroid production, serum potassium	GI upset in up to 80%; GI and CNS effects appear to be dose-dependent
Pasireotide	Nausea, diarrhea, cholelithiasis, increased hepatic transaminases, hyperglycemia, sinus bradycardia, QT prolongation	Serum glucose, serum potassium, hemoglobin A1c, liver function tests, UFC, thyroid function, heart rate, ECG	Only available as a subcutaneous injection; expensive

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNS, central nervous system; FDA, Food and Drug Administration; GI, gastrointestinal; INR, international normalized ratio; LFT, liver function tests; UFC, urinary free cortisol.

Several factors may limit the ability to personalize pharmacotherapy in patients with Cushing syndrome. First, few rigorous studies have compared the various pharmacologic options used in Cushing syndrome. Apart from the benefits seen with pasireotide in patients with modestly elevated UFC and the use of mifepristone in patients with concomitant hyperglycemia, data are limited in terms of clinical predictors of disease response to these agents. Second, virtually nothing is known of the pharmacogenomic predictors of individual patient response in these disease states. Finally, because most agents are used off-label, scarce data exist on agent-specific pharmacokinetic parameters in this patient population.

With these limitations in mind, drug selection is determined according to the etiology of Cushing syndrome, individual patient factors, and cost. Once the etiology has been correctly identified, patient sex and gender should be considered since some pharmacologic options (steroidogenesis inhibitors in particular) used in Cushing syndrome affect the sex hormones. Specifically, metyrapone is a clear second choice in women due to a high incidence of hirsutism, whereas ketoconazole may be a secondary choice in men due to drug-

induced gynecomastia and hypogonadism. During pregnancy, metyrapone is commonly used, while mifepristone must be avoided. Additionally, women desiring pregnancy within the next 5 years should avoid mitotane as this agent is stored in adipose tissue for up to several years following discontinuation. Preexisting medication profiles should also be considered since many of the pharmacologic options can inhibit (eg, ketoconazole) or induce (eg, metyrapone) important CYP isoenzymes such as 3A4.

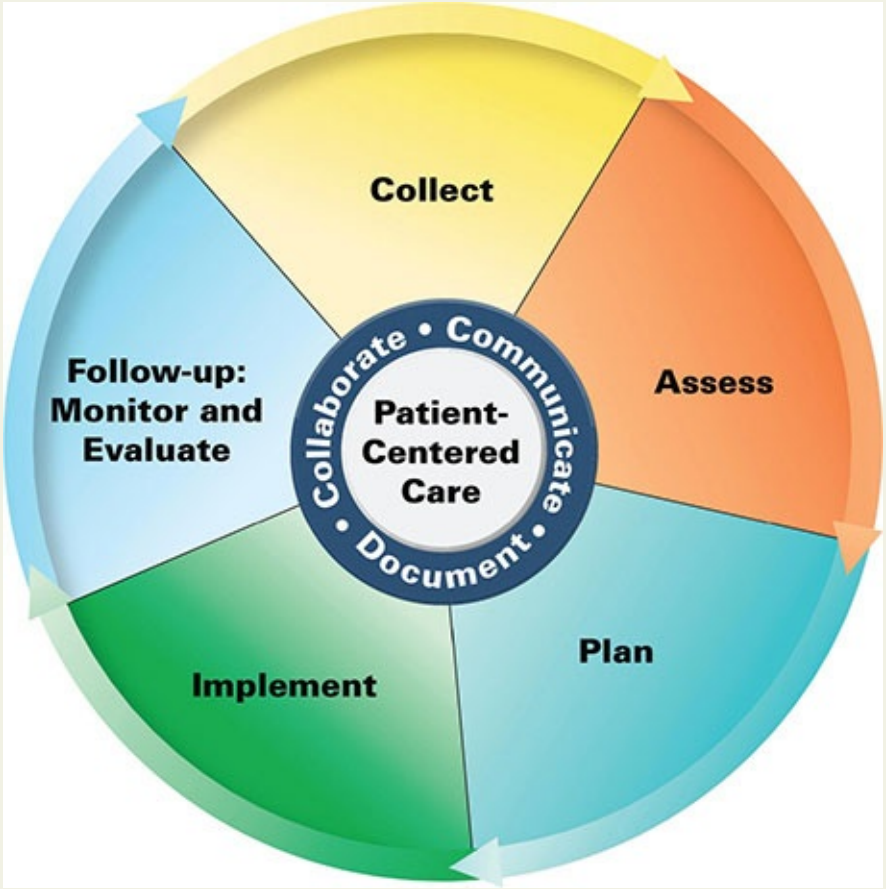
Ultimately, pharmacotherapy is guided by patient response and several agents may need to be tried sequentially to elicit a substantial response. Combination therapy may be more effective and better tolerated than monotherapy in some patients, but studies on what constitutes the most appropriate drug regimens are lacking.

Steroidogenesis Inhibitors

As their name implies, steroidogenesis inhibitors block the production of cortisol. This class includes metyrapone, ketoconazole, and etomidate. Metyrapone inhibits 11β-hydroxylase, the enzyme responsible for converting 11-deoxycortisol to cortisol. Following administration, a sudden decrease in cortisol concentration occurs within hours and prompts a compensatory rise in plasma ACTH concentrations. As ACTH increases and blockage of cortisol synthesis persists, adrenal steroidogenesis efforts are shunted toward androgen production. Consequently, metyrapone is associated with significant androgenic side effects, including hirsutism and increased acne, making it less ideal for women. In addition, metyrapone blocks aldosterone synthesis and causes the accumulation of aldosterone precursors, which exhibit weak mineralocorticoid activity. Blood pressure and electrolyte perturbations can ensue, depending on the level of circulating 11-deoxycortisol and the degree of aldosterone inhibition. Additional adverse effects, including nausea, vomiting, vertigo, headache, dizziness, abdominal discomfort, and allergic rash, have been reported following administration, but are often signs of overtreatment.[26,27,30] Metyrapone is currently available through the manufacturer only for compassionate use.

The imidazole derivative antifungal, ketoconazole, effectively inhibits steroidogenesis via multiple mechanisms when used in large doses. In contrast to the quick onset of metyrapone, the benefits of ketoconazole therapy are achieved only after several weeks of therapy. In addition to lowering serum cortisol levels, ketoconazole exhibits antiandrogenic activity attributable to its inhibition of multiple CYP enzymes as well as 11β-hydroxylase and 17α-hydroxylase.[26] This activity may be beneficial in women with Cushing syndrome but can cause

gynecomastia and hypogonadism in men. Sustained therapy with ketoconazole also imparts beneficial effects on serum cholesterol profiles, including lowering total and low-density lipoprotein (LDL) cholesterol levels. Ketoconazole induces a reversible elevation of hepatic transaminases in approximately 10% of patients.[31] However, concerns have been raised over the risk of severe hepatotoxicity associated with ketoconazole use. In July 2013, the US Food and Drug Administration (FDA) significantly changed the labeling of oral ketoconazole, removing various indications for fungal infections and recommending that oral ketoconazole not be used as first-line therapy for fungal infections. Similarly, the European Medicines Agency has recommended complete removal of oral ketoconazole from European Union markets. These changes were based largely on data in patients with fungal infections, who require lower doses of ketoconazole. However, few data are available on the incidence of severe hepatotoxicity with ketoconazole at the higher doses used in Cushing syndrome. Consequently, monitoring during treatment with ketoconazole should include liver function at baseline, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase (ALP), prothrombin time, and international normalized ratio (INR) testing, according to FDA recommendations. In addition, weekly monitoring of serum ALT should be continued throughout therapy with ketoconazole. In general, ketoconazole should be avoided in patients with preexisting hepatic disease. Additional common adverse effects include gastrointestinal (GI) discomfort and dermatologic reactions.



Patient Care Process for Cushing Syndrome

Collect

- Patient characteristics (eg, age, sex, pregnant)
- Patient medical history (personal and family)
- Social history (eg, tobacco/ethanol use)
- Iatrogenic causes of Cushing syndrome: current medications including corticosteroids (all routes, past and present), medroxyprogesterone acetate, megestrol acetate, gamma-hydroxybutyic acid, CYP3A4 inhibitors and inducers
- Objective data
  - Blood pressure, heart rate, body mass index
  - Test for hypercortisolism: 24-hour UFC, midnight plasma cortisol, late-night salivary cortisol, or low-dose dexamethasone suppression test
  - Follow-up diagnostic tests to differentiate etiologies (see Fig. 93-4)

Assess

- Presence of Cushing syndrome complications:
  - Metabolic: impaired glucose metabolism, dyslipidemia
  - Cardiovascular: hypertension, vascular damage, thrombosis, hypokalemia
  - Immunologic: bacterial, fungal, and viral infections; rebound autoimmunity
  - Musculoskeletal: osteopenia/osteoporosis, myopathy
  - Neuropsychiatric: depression, anxiety, bipolar disorder
  - Reproductive: decreased libido, hypogonadism (men), menstrual irregularity (women)
  - Dermatologic: hirsutism, alopecia, hyperhidrosis
- Physical exam: Peripheral obesity, fat accumulation (Buffalo Hump), rounded face (moon face), striae, ecchymosis, hyperpigmentation, acanthosis nigricans, acne, and thin skin
- Current medications that may contribute to or worsen Cushing syndrome.
- Results of follow-up diagnostic testing for etiology (see Fig. 93-4, and Tables 93-2 and 93-3)
- Ability/willingness to pursue surgical/chemotherapeutic (if indicated) versus medical management

Plan*

- Ensure proper administration of necessary corticosteroid therapy; discontinue unnecessary corticosteroid therapy, with taper if HPA axis integrity is suspect
- Nondrug options for endogenous Cushing syndrome, depending on etiology: surgery, chemotherapy, irradiation, postoperative steroid replacement (see Table 93-4)
- Steroid replacement regimens postoperatively for patients with adrenal adenomas (see Table 93-7)
- Medical management when surgery is not possible or against patient wishes (see Tables 93-5 and 93-6 for specific drugs, dose, route, frequency, adverse effects, and monitoring parameters)
- Patient education (eg, purpose of treatment, dietary and lifestyle

modification, invasive procedures, drug-specific information) and specialist referral when appropriate (eg, endocrinologist)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up for monitoring

Follow-up: Monitor and Evaluate

- Clinical response, including resolution of signs/symptoms
- Treatment-emergent adverse effects (eg, adrenal insufficiency [all], medication-specific adverse effects)
- Monitoring parameters including efficacy (eg, UFC) and safety (eg, ECG, liver function, electrolytes, glycohemoglobin A1c)
- Frequency and timing of follow-up for specific agents (see Table 93-6 and text for agent-specific monitoring)

**Collaborate with patient, caregivers, and other healthcare professionals.*

Ketoconazole may be used concomitantly with metyrapone to achieve synergistic reductions in cortisol levels. Because these drugs differ in their onset of action, coadministration allows for more complete suppression of cortisol synthesis. Moreover, the antiandrogenic actions of ketoconazole therapy may offset the androgenic potential of metyrapone, thus attenuating a major limitation of metyrapone monotherapy.

The anesthetic etomidate is an imidazole derivative similar to ketoconazole that inhibits 11β-hydroxylase.[26] Inhibition of aldosterone synthase and antiproliferative effects on adrenal cortical cells may also play a role.[32] Etomidate is available only in a parenteral formulation and is therefore limited to patients with acute hypercortisolemia requiring emergency treatment or in preparation for surgery. Low doses of etomidate are often sufficient to suppress cortisol synthesis, thus potentially avoiding some of the adverse effects observed with higher doses used in anesthesia. However, close monitoring is recommended to avoid excess sedation with this agent.[32] Frequent monitoring of serum cortisol is also advised to prevent hypocortisolemia. Replacement corticosteroid doses may be necessary if complete blockade of cortisol is

desired.

Adrenolytic Agents

Mitotane is a cytotoxic drug that structurally resembles the insecticide dichlorodiphenyltrichloroethane (DDT). Mitotane inhibits the 11-hydroxylation of 11-desoxycortisol and 11-desoxycorticosterone in the adrenal cortex, resulting in an inhibition of cortisol and corticosterone synthesis. Similar to ketoconazole, mitotane takes weeks to months to exert beneficial effects. Sustained cortisol suppression occurs in most patients (~80%) and may persist following discontinuation of therapy in up to one-third of patients. Because of its cytotoxic nature, mitotane degenerates cells within the zona fasciculata and reticularis, resulting in atrophy of the adrenal cortex. The zona glomerulosa is minimally affected during acute therapy but can be damaged during long-term treatment.[28,29]

Importantly, mitotane can induce significant neurologic and GI side effects and patients should be monitored carefully or hospitalized when initiating therapy. Nausea and diarrhea are common adverse effects that occur at doses greater than 2 g/day and can be avoided by gradually increasing the dose and/or administering the agent with food. Most patients are unable to tolerate doses exceeding 8 g/day. Approximately 80% of patients treated with mitotane develop lethargy and somnolence, and other central nervous system (CNS) adverse drug reactions occur in approximately 40% of patients. Furthermore, significant but reversible hypercholesterolemia and prolongation of bleeding times can result from mitotane use.[26,27] Mitotane increases production of CBG resulting in elevated plasma cortisol measurements; thus, UFC and urinary steroid production should be monitored to assess response to therapy.[26] If necessary, steroid replacement therapy can be given. However, because mitotane also increases extra-adrenal metabolism of exogenously administered corticosteroids (especially hydrocortisone), higher steroid replacement doses may be required. In select patients, supplemental androgen therapy also may be necessary.

Neuromodulatory Agents

Pituitary secretion of ACTH is normally mediated by various neurotransmitters, including serotonin, *γ*-aminobutyric acid (GABA), acetylcholine, and the catecholamines. Although ACTH-secreting pituitary tumors (Cushing disease) self-regulate ACTH production to some degree, these neurotransmitters are still capable of promoting pituitary ACTH production. Consequently, agents that

target these neurotransmitters have been proposed for the treatment of Cushing disease. Such agents include cyproheptadine, ritanserin, ketanserin, bromocriptine, cabergoline, valproic acid, octreotide, lanreotide, pasireotide, rosiglitazone, and tretinoin. However, with the exception of pasireotide, none of these drugs have demonstrated consistent clinical efficacy in the treatment of Cushing disease.

Cyproheptadine, a nonselective serotonin-receptor antagonist and anticholinergic drug, can decrease ACTH secretion in some patients with Cushing disease. However, side effects, including sedation and weight gain, significantly limit the use of this drug. Likewise, selective serotonin type 2-receptor antagonists, including ritanserin and ketanserin, have demonstrated limited efficacy. Owing to their poor efficacy and high relapse rates, these drugs should be avoided except in nonsurgical candidates refractory to more conventional treatments.

Dopamine D_2-receptor agonists, including bromocriptine and cabergoline, initially reduce ACTH secretion in as many as half of all patients with Cushing disease. This action occurs through activation of inhibitory D_2 receptors that are expressed in approximately 80% of pituitary adenomas.[33] Reductions in ACTH levels are often minor and rarely sustained with long-term bromocriptine therapy. Cabergoline exhibits a higher specificity and affinity for D_2 receptors as well as a prolonged half-life compared with bromocriptine. These differences may explain the greater response rates observed with cabergoline monotherapy; however, a sustained response occurs in only 30% to 40% of patients.[34,35] Although generally well-tolerated, side effects associated with cabergoline include nausea, orthostasis, headache, nasal congestion, constipation, nightmares, vivid dreams, and psychosis. The risk of cabergoline-associated cardiac valvulopathy (observed with higher doses used to treat Parkinson disease) has not been well-studied in lower doses typically used for the treatment of Cushing disease.[36]

The somatostatin analogs octreotide and lanreotide generally are ineffective in reducing ACTH secretion in Cushing disease. These two agents primarily target somatostatin receptor subtype 2 (sst_2), whereas pituitary adenomas predominantly express sst_5. Pasireotide, a somatostatin analog, exhibits a high affinity for sst_1, sst_2, sst_3, and, especially, sst_5 receptor subtypes. In a phase 3 study of 162 adults with Cushing disease and an elevated UFC, pasireotide administered at 600 or 900 μg injected subcutaneously twice daily reduced the median UFC by 50% by month 2; levels remained stable for the duration of the

12-month study.[37] Pasireotide is especially effective at normalizing UFC concentrations in patients whose baseline UFC is less than five times the upper limit of normal. Clinical signs and symptoms of Cushing disease are also improved as are blood pressure, weight, LDL cholesterol, and quality of life. Side effects are mostly GI in nature, although 50% to 70% of subjects experience an adverse event related to hyperglycemia; preexisting diabetes mellitus or impaired glucose tolerance increases the risk for these events. Notably, pasireotide increases glycated hemoglobin A1c by an average of 1.4% at 6 months and this effect may be sustained with long-term therapy,[38] likely due to impaired insulin secretion.[39]

Since coexpression of D_2 and sst_5 receptors is common in adrenocorticotropin-secreting adenomas, the combination of pasireotide and cabergoline may produce synergistic effects in reducing cortisol levels.[3] Limited data suggest that step-wise addition of cabergoline and ketoconazole in patients unresponsive to pasireotide may achieve normalization of UFC in the majority of patients; however, additional studies are needed to confirm the efficacy of this combination therapy. Potential drug-drug interactions exist with the combination of pasireotide and ketoconazole, and thus, the combination should be used with caution.[38,40,41]

Glucocorticoid-Receptor Blocking Agents

Mifepristone is a potent progesterone- and glucocorticoid-receptor antagonist that inhibits dexamethasone suppression and increases endogenous cortisol and ACTH levels in normal subjects.[26,30] Clinical experience and trial data in Cushing syndrome suggest that mifepristone is highly effective in reversing the manifestation of hypercortisolism, including hyperglycemia, hypertension, and weight gain.[42] Consequently, mifepristone has an FDA-approved indication for treatment of endogenous Cushing syndrome in patients who have type 2 diabetes or glucose intolerance, and who are not eligible for or have had poor response to surgery. However, because of its novel site of action, mifepristone induces a compensatory rise in ACTH and cortisol. Consequently, efficacy and toxicity monitoring must rely on clinical signs rather than laboratory assessments. Common adverse effects of mifepristone include fatigue, nausea, headache, arthralgia, peripheral edema, endometrial thickening (with or without vaginal bleeding), and significant reductions in serum potassium. Oral potassium supplementation or spironolactone can be effective in mitigating the latter adverse effect, although high doses may be required.[42]

Close monitoring of 24-hour UFC and serum cortisol is essential to detect treatment-induced adrenal insufficiency. Steroid secretion should be monitored with all of these drugs except mifepristone and steroid replacement given as needed. Whatever the choice, pharmacologic therapy in pituitary-dependent disease is mainly centered around patient stabilization prior to surgery or in patients waiting for potential response to other therapies.

Nonpharmacologic Therapy

Pituitary Adenoma

The treatment of choice for Cushing disease is transsphenoidal resection of the pituitary tumor.[3,15,29,30,43] The advantages of this procedure include preservation of pituitary function, low complication rate, and high clinical improvement rate. The overall cure rate of histologically proven microadenomas (tumor diameter <10 mm) approaches 90%, whereas remission rates for macroadenomas (tumor diameter ≥10 mm) generally do not exceed 65%.

For persistent disease following transsphenoidal surgery or when tumor-specific surgery is not possible, several second-line treatment options are available and should be tailored toward the individual patient.[29] In the case of persistent disease following transsphenoidal surgery, repeat surgery may be performed, particularly in patients with evidence of incomplete resection or pituitary lesion on imaging.[29] Although overall remission rates are lower with subsequent procedures, remission can be achieved rapidly when compared to alternative second-line treatments.[29] Alternatively, radiotherapy may be preferred for tumors invading the dura or cavernous sinus because these tumors respond poorly to surgical intervention.[44] Radiotherapy provides clinical improvement in approximately 50% of patients within 3 to 5 years, but increases the risk for pituitary-dependent hormone deficiencies (hypopituitarism).

Adrenal Adenoma

Laparoscopic adrenalectomy is often preferred in patients with unilateral adrenal adenomas for whom transsphenoidal surgery and pituitary radiotherapy have failed or cannot be used.[3,15,30] Bilateral adrenalectomy rapidly reverses hypercortisolism. However, patients can develop Nelson syndrome, an aggressive pituitary tumor that secretes high quantities of ACTH, which causes hyperpigmentation. Because Nelson syndrome occurs in as many as 30% of bilateral adrenalectomy cases, patients should undergo regular MRI scans and

ACTH level assessments. Additionally, these patients require lifelong glucocorticoid and mineralocorticoid supplementation.

Surgical resection of benign adrenal adenoma is associated with relatively few side effects and a high cure rate (95%). The contralateral gland in the patient with adrenal adenoma is usually atrophic; therefore, steroid replacement is needed both perioperatively and postoperatively. **Table 93-7** outlines an approach to steroid replacement for three separate routes of hydrocortisone. Therapy should be continued for 6 to 12 months following surgery. Before replacement therapy is discontinued, recovery of the adrenal axis can be assessed by measuring the morning (8:00 am) cortisol concentration. The cortisol concentration should exceed 20 µg/dL (550 nmol/L) before discontinuing exogenous steroids.[11]

TABLE 93-7 Alternative Steroid Replacement Regimens in the Adrenal Adenoma Patient

	Hydrocortisone Dose (mg)		
Time	**IV**	**IM**	**po**
Operation day	300	50 before surgery and 50 after surgery	
Postoperative day 1	200	50 every 12 hours	
Postoperative day 2	150	50 every 12 hours	
Postoperative day 3	100	50 every 12 hours	
Postoperative day 4		50 every 12 hours	25 every 6 hours
Postoperative day 5		25 every 12 hours	25 every 6 hours[a]
Postoperative day 7			25 every 6 hours
Postoperative days 8-10			25 every 8 hours
Postoperative days 11-20			25 every 12 hours
Postoperative days 21+			20:00 at 8:00 am 10:00 at 4:00 pm

po, orally.

[a]Add fludrocortisone 0.05-2 mg orally once daily starting on postoperative day 5. Adjust dose based on blood pressure, body weight, and serum electrolytes.

Adrenal Carcinoma

Unlike the benign adenoma patient, those with adrenal carcinoma generally have an unfavorable outcome with surgical resection.[15] Often the complete tumor cannot be excised, leaving the patient with some degree of symptoms and extra-adrenal involvement. Radiotherapy can be used if metastases are discovered. In the patient with adrenal carcinoma who is not a surgical candidate, the focus of treatment is on palliative pharmacologic intervention.

Mitotane may be used in inoperable functional and nonfunctional adrenal carcinoma or as adjuvant therapy in surgical patients with a high risk of relapse and may prolong survival by 2 to 3 years.[45] However, mitotane induces tumor regression in fewer than 20% of patients.[46] Metyrapone and ketoconazole can be given as adjunctive treatment to attempt control of steroid hypersecretion. 5-Fluorouracil also has been used in combination therapy.

Ectopic Adrenocorticotropic Hormone Syndrome

In ectopic ACTH syndrome, ACTH-secreting tumors may exist in a variety of sites, including thymic, pulmonary, appendiceal, pancreatic, and thyroid tissues. Locating these sites is often difficult, but essential for determining an appropriate treatment strategy. Surgical resection is the most effective treatment option for these patients, but only approximately 10% to 30% of patients are cured following surgery due to high rates of metastatic disease or occult tumors. The remaining 70% to 90% receive postoperative medication.

Pharmacologic management with steroidogenesis inhibitors is effective in patients with ectopic ACTH syndrome and may be used as primary treatment in patients with occult or metastatic ectopic ACTH syndrome.[29] Mitotane has been used in this setting; however, its side-effect profile generally limits its use. Mifepristone and somatostatin analogues also have been reported to reduce the clinical signs of ectopic ACTH syndrome.[47]

Additional tumor-directed therapy can include systemic chemotherapy, interferon α, chemoembolization, radiofrequency ablation, and radiation therapy.[44] If all else fails, bilateral adrenalectomy can prevent the downstream effects (eg, steroidogenesis) of high levels of tumor ACTH secretion.

Hyperaldosteronism

Excess aldosterone secretion, hyperaldoteronism, can be the result of either primary or secondary causes.[48–51] In primary hyperaldosteronism (PA), the

stimulation for aldosterone secretion arises from within the adrenal gland. Conversely, extra-adrenal stimulation is classified as secondary aldosteronism.

Primary Aldosteronism

Etiology The most common causes of PA include bilateral adrenal hyperplasia (BAH) (65%) and aldosterone-producing adenoma (APA; otherwise known as Conn syndrome) (30%). Rare causes include unilateral (primary) adrenal hyperplasia, adrenal cortex carcinoma, renin-responsive adrenocortical adenoma, and three forms of familial hyperaldosteronism (FH): FH type I, also known as glucocorticoid-remediable aldosteronism (GRA); FH type II, also known as familial occurrence of adenoma or hyperplasia type II; and FH type III.[48,50,51]

CLINICAL PRESENTATION Primary Aldosteronism

Symptoms

- Patients may complain of muscle weakness, fatigue, paresthesias, and headache.

Signs

- Hypertension
- Tetany/paralysis
- Polydipsia/nocturnal polyuria

Laboratory Tests

- A plasma-aldosterone-concentration–to– plasma-renin-activity (PAC–to–PRA) ratio or aldosterone-to-renin ratio (ARR) greater than 30 ng/dL per ng/(mL·h) (830 pmol/L per mcg/(L·h) and a PAC greater than 15 ng/dL (420 pmol/L) is suggestive of PA.
- Common laboratory findings include suppressed PRA, elevated PAC, hypernatremia (>142 mEq/L [mmol/L]), hypokalemia, hypomagnesemia, elevated bicarbonate concentration (>31 mEq/L [mmol/L]), and glucose intolerance.

Confirmatory Tests

- Oral or IV saline loading, fludrocortisone suppression test (FST), and genetic testing

CLINICAL PRESENTATION

PA is present in approximately 10% in patients with hypertension and is a leading cause of secondary hypertension and resistant hypertension. The disease is more common in women than in men, and diagnosis usually occurs between the third and sixth decades of life. Signs and symptoms can include arterial hypertension, which is often moderate to severe and resistant to pharmacologic intervention. Many patients also have hypokalemia (10%-40%), muscle weakness, fatigue, and headache. These features are nonspecific and many patients are asymptomatic. Historically, hypokalemia was considered a requisite feature for PA diagnosis; however, normokalemia exists frequently in patients and does not rule out PA.

Diagnosis

Early diagnosis and treatment of PA are essential as patients with PA are at increased risk of adverse cardiovascular outcomes compared to patients with essential hypertension alone.[52] Diagnostic confirmation of PA is obtainable through screening, confirmatory tests, and subtype differentiation (**Fig. 93-5**). The discovery of the underlying etiology ensures proper treatment. **Table 93-8** lists the various abnormalities that must be ruled out when hyperaldosteronism is suspected.

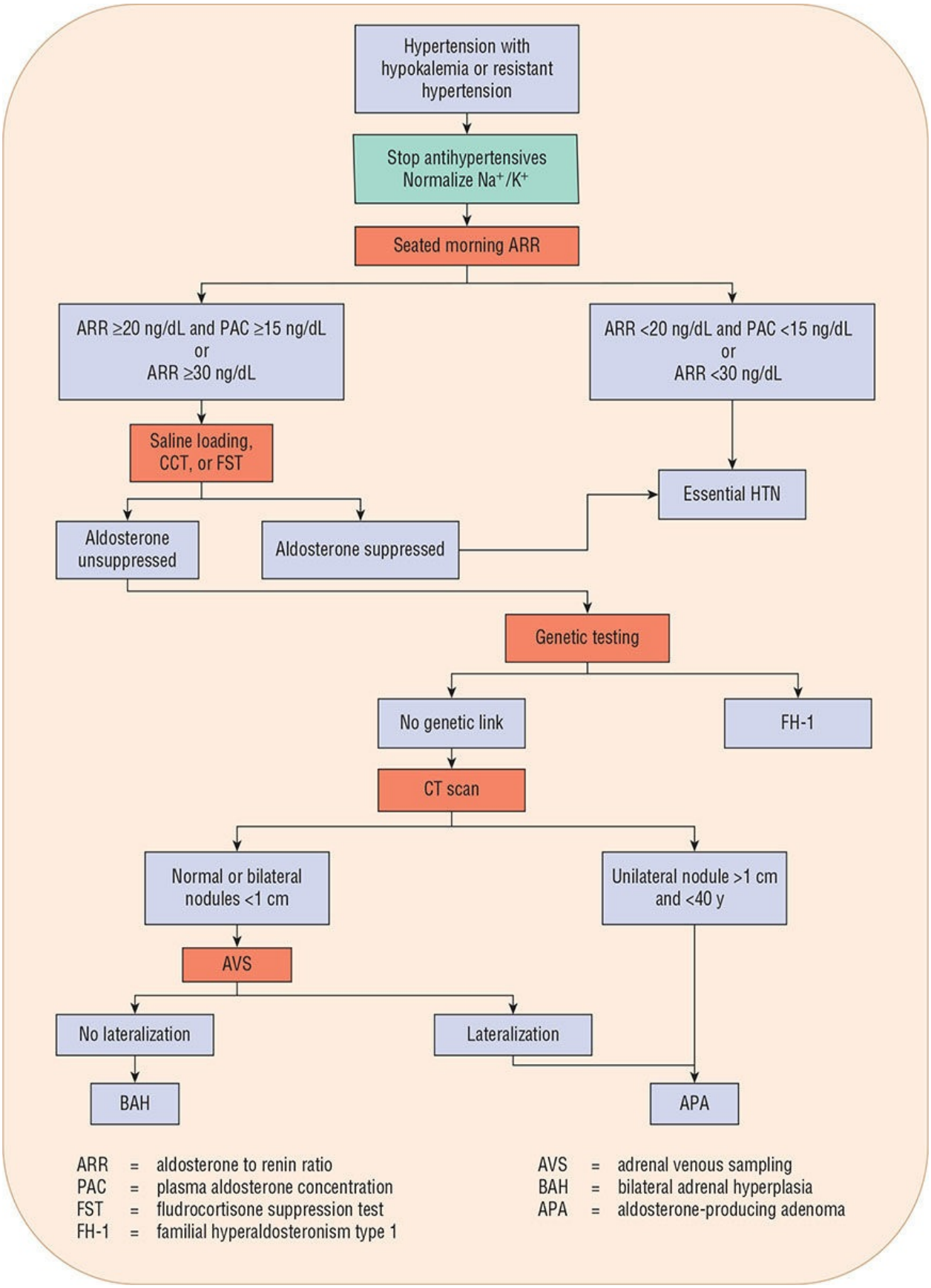

Hypertension with hypokalemia or resistant hypertension
Stop antihypertensives Normalize Na^+/K^+
Seated morning ARR
ARR ≥20 ng/dL and PAC ≥15 ng/dL or ARR ≥30 ng/dL
ARR <20 ng/dL and PAC <15 ng/dL or ARR <30 ng/dL
Saline loading, CCT, or FST
Essential HTN
Aldosterone unsuppressed
Aldosterone suppressed
Genetic testing
No genetic link
FH-1
CT scan
Normal or bilateral nodules <1 cm
Unilateral nodule >1 cm and <40 y
AVS
No lateralization
Lateralization
BAH
APA
ARR = aldosterone to renin ratio
PAC = plasma aldosterone concentration
FST = fludrocortisone suppression test
FH-1 = familial hyperaldosteronism type 1
AVS = adrenal venous sampling
BAH = bilateral adrenal hyperplasia
APA = aldosterone-producing adenoma

FIGURE 93-5 Algorithm for the diagnosis of primary aldosteronism. (ARR, aldosterone-to-renin ratio expressed in ng/dL per ng/(mL·h); APA, aldosterone-producing adenoma; AVS, adrenal venous sampling; BAH, bilateral adrenal hyperplasia; CCT, captopril challenge test; FH-1, familial hyperaldosteronism type 1; FST, fludrocortisone suppression test; HTN, hypertension; PAC, plasma aldosterone concentration [multiply values by 27.74 for units of pmol/L].).

TABLE 93-8 Differential Diagnosis of Primary Aldosteronism

Disease	Plasma Renin Activity	Plasma Aldosterone Concentration	Blood Pressure
Primary aldosteronism	Low	High	High
Edematous disorders	High	High	Normal
Malignant hypertension	High	High	High
Congenital adrenal hyperplasia	Low	Low	High
Cushing syndrome	Low to normal	Low to normal	High
Liddle syndrome	Low	Low	High
Bartter syndrome	High	High	Low to normal
Licorice ingestion	Low	Low	High
Low-renin essential hypertension	Low	Low to normal	High

Initial diagnosis is made by screening patients with suspected PA. Any patient with a blood pressure greater than 150/100 mm Hg measured on three separate days and those with resistant hypertension should be screened.[53] Additional patients at risk for PA include those with diuretic-induced hypokalemia, hypertension and adrenal incidentaloma, hypertension and sleep apnea, hypertension and a family history of early onset hypertension or cerebrovascular accident at an age less than 40 years, and all patients with hypertension and a first-degree relative diagnosed with PA.

Screening for PA is most often done by using the PAC-to-PRA ratio, otherwise known as the aldosterone-to-renin ratio (ARR). An elevated ARR is highly suggestive of PA; however, an optimal cutoff ratio remains elusive because testing conditions (posture, time, current drug therapy, recent dietary salt intake), patient characteristics, and assay variability can significantly alter test results.[54] ARR cutoffs of 20 to 40 ng/dL per ng/(mL·h) (550 to 1100 pmol/L per (mcg/(L·h)) to with an aldosterone concentration greater than 15 ng/dL (420 pmol/L) are used most often.[49,54-56]

Following a positive ARR screening test, confirmatory testing must be performed to exclude false-positive cases. Confirmatory tests include the oral

sodium loading test, saline infusion test (SIT), fludrocortisone suppression test (FST), and the captopril challenge test (CCT). Although individual tests can vary in sensitivity, specificity, and reliability, any test can be used depending on patient- and institution-specific considerations. FST generally is considered the most reliable but requires hospitalization. The SIT and CCT are both accurate alternatives to FST. However, a post-CCT evaluation of PAC is recommended to help interpret results of this confirmatory test.[57] Prior to performing these tests, potassium must be normalized and renin–angiotensin–aldosterone system (RAAS) inhibitors should be temporarily discontinued, if possible. Positive tests indicate autonomous aldosterone secretion under inhibitory pressures and are diagnostic for PA. After diagnosis, patients with confirmed PA before age 20 or with a family history of PA or strokes before age 40 should undergo genetic testing for GRA.[54]

Differentiating between an APA and BAH is imperative to formulate a proper treatment plan. Most adenomas are singular and small (<1 cm) and occur more often in the left adrenal gland than the right. Patients with APA generally have more severe hypertension, more profound hypokalemia, and higher plasma and urinary aldosterone concentrations compared with patients with BAH. Adrenal venous sampling (AVS) provides the most accurate means of differentiating unilateral from bilateral forms of PA. However, AVS is expensive, invasive, and often unavailable. CT scanning can detect most adenomas, although an incidentaloma can occasionally cause confusion. If CT scanning is inconclusive, AVS is performed to characterize lateralization.[49,58–60]

The underlying abnormality in BAH remains a mystery, but some investigators believe that a hormone factor stimulates the zona glomerulosa, resulting in increased sensitivity to angiotensin II. In contrast to those with an APA, patients with BAH are able to maintain control of the renin-angiotensin system, with little effect following doses of ACTH.

TREATMENT

6 BAH-Dependent Aldosteronism

Aldosterone-receptor antagonists are the treatment of choice in BAH. Drug dosing and monitoring parameters can be found in **Tables 93-9** and **93-10**. Spironolactone, a nonselective aldosterone-receptor antagonist, competes with aldosterone for binding at the aldosterone receptor, thus preventing the negative downstream effects of aldosterone-receptor activation. Additionally, spironolactone is capable of inhibiting aldosterone synthesis within the adrenal

gland; however, the magnitude of inhibition is relatively small and the effect only occurs above recommended doses.[61] Spironolactone is available in oral form, with most patients responding to doses between 25 and 400 mg/day. The clinician should wait 4 to 8 weeks before reassessing the patient for urinary electrolytes and blood pressure control. Adverse effects of spironolactone are dose-dependent and include GI discomfort, impotence, gynecomastia, menstrual irregularities, and hyperkalemia. Gynecomastia and menstrual irregularities observed with spironolactone therapy arise from activity at androgen and progesterone receptors and inhibition of testosterone biosynthesis. Additionally, because salicylates increase the renal secretion of canrenone, the active metabolite of spironolactone, patients should be advised to avoid concomitant therapy with salicylates. In patients intolerant of spironolactone, alternative options include eplerenone and amiloride.[50,51,62–64]

TABLE 93-9 Drug Dosing in the Treatment of Hyperaldosteronism

Drug	Brand Name	Initial Dose	Usual Range	Special Populations	Comments
Amiloride	Midamor®, 5 mg tablets	5 mg twice daily	20 mg/day in two divided doses	CrCl 10-50 mL/min (0.17-0.84 mL/s): reduce dose by 50%; CrCl <10 mL/min (0.17 mL/s): CI	Maximum: 30 mg/day
Eplerenone	Inspra®, 25 and 50 mg tablets	50 mg once daily	100-300 mg/day in single or divided doses; titrate at 4- to 8-week intervals	CrCl <30 mL/min (0.5 mL/s): CI	Maximum: 300 mg/day
Spironolactone	Aldactone®, 25, 50, and 100 mg tablets	25 mg once daily	100-400 mg/day in single or divided doses; titrate at 4- to 8-week intervals	CrCl 10-50 mL/min (0.17-0.84 mL/s): extend dosing interval to once daily; CrCl <10 mL/min (0.17 mL/s): CI	Maximum: 400 mg/day

CI, contraindicated; CrCl, creatinine clearance.

TABLE 93-10 Drug Monitoring in the Treatment of Hyperaldosteronism

Drug	Adverse Drug Reaction	Monitoring Parameters	Comments
Amiloride	Electrolyte abnormalities (hyperkalemia), hypotension, nausea, vomiting, diarrhea, headache	Serum creatinine, serum potassium, blood pressure	Electrolyte abnormalities (hyperkalemia) more pronounced with reduced renal function
Eplerenone	Electrolyte abnormalities (hyperkalemia), hypotension, dizziness, headache; gynecomastia and menstrual irregularities are uncommon	Serum creatinine, serum potassium, blood pressure	Electrolyte abnormalities (hyperkalemia) more pronounced with reduced renal function. CYP3A4 substrate; avoid use with potent CYP3A4 inhibitors
Spironolactone	GI discomfort, impotence, gynecomastia, menstrual irregularities, electrolyte abnormalities (hyperkalemia), hypotension	Serum creatinine, serum potassium, blood pressure	Electrolyte abnormalities (hyperkalemia) more pronounced with reduced renal function

CYP, cytochrome P450 enzyme; GI, gastrointestinal.

Eplerenone is a selective aldosterone-receptor antagonist with high affinity for the aldosterone receptor and low affinity for androgen and progesterone receptors. Consequently, eplerenone elicits fewer sex steroid–dependent effects than spironolactone. Randomized controlled trial data have been inconclusive with regard to whether eplerenone achieves similar blood pressure reductions to spironolactone and there are limited long-term data comparing these agents.[65,66] Eplerenone dosing starts at 50 mg daily, with titration to 50 mg twice a day; some patients may require total daily doses as high as 200 to 300 mg.[62] Titration should occur at 4- to 8-week intervals. In addition, eplerenone is a substrate of CYP3A4 and should not be taken with potent CYP3A4 inhibitors. Eplerenone is the preferred aldosterone antagonist during pregnancy since spironolactone can cause ambiguous genitalia in a male fetus.[67]

Amiloride, a potassium-sparing diuretic, is dosed at 5 mg twice a day up to 30 mg/day if necessary. Amiloride is less effective than spironolactone and patients often require additional therapy to adequately control blood pressure. Additional second-line options include calcium channel blockers, ACE inhibitors, and diuretics such as chlorthalidone, although all lack outcome data in PA.[60,63] However, some agents (eg, diuretics, calcium channel blockers) can promote a reactive rise in PRA, ultimately leading to increased aldosterone levels and potentially worsening PA. A prudent strategy would be to use these agents only in combination with RAAS inhibitors to mitigate the downstream aldosterone effects of any increase in PRA.

Aldosterone synthase inhibitors, currently under development, may offer additional therapeutic options in the future.

APA-Dependent Aldosteronism

The treatment of choice for APA-dependent aldosteronism remains laparoscopic resection of the adenoma.[68] Nearly 100% of patients show blood pressure improvement and up to 72% are permanently cured.[64,69] Because APAs are small and often occur in multiples, resection should target the entire adrenal gland. In successful cases, blood pressure control is achieved in 1 to 3 months. Medical management with an aldosterone receptor antagonist is often effective in this population if surgery is contraindicated. However, medical management may be significantly more expensive than unilateral resection.

Glucocorticoid-Remediable Aldosteronism

Glucocorticoids are very effective in treating GRA.[44] Low doses of long-acting glucocorticoids are used (0.125-0.5 mg/day of dexamethasone or 2.5-5 mg/day of prednisone) because complete suppression of ACTH-stimulated aldosterone release is unnecessary. If blood pressure fails to normalize with glucocorticoid therapy alone, the addition of spironolactone, eplerenone, or amiloride may help control symptoms.[49]

Secondary Aldosteronism

Secondary aldosteronism results from an appropriate response to excessive stimulation of the zona glomerulosa by an extra-adrenal factor, usually the renin-angiotensin system. Excessive potassium intake can promote aldosterone secretion as well as oral contraceptive use, pregnancy (aldosterone secretion 10 times normal by the third trimester), and menses. Congestive heart failure, cirrhosis, renal artery stenosis, and Bartter syndrome also can lead to elevated aldosterone concentrations.

Treatment of secondary aldosteronism is dictated by the etiology. Control or correction of the extra-adrenal stimulation of aldosterone secretion should resolve the disorder. Medical therapy with spironolactone is the mainstay of treatment until an exact etiology can be identified.

HYPOFUNCTION OF THE ADRENAL GLAND

Hypofunction of the adrenal gland can affect any or all adrenal hormones, depending on the etiology of the disorder. However, hypofunction does not

always lead to insufficient production of adrenal hormones. Some types of adrenal hypofunction can lead to excess production of certain hormones.

Addison's Disease

7 Primary adrenal insufficiency, or Addison's disease, most often involves the destruction of all regions of the adrenal cortex. Deficiencies arise in cortisol, aldosterone, and the various androgens and levels of CRH and ACTH increase in a compensatory manner. In developed countries, autoimmune dysfunction is responsible for most cases (80%-90%), whereas tuberculosis predominates as the cause in developing countries. Approximately 50% of patients with autoimmune etiologies present with one or more concomitant autoimmune disorders, usually involving other endocrine organs. Autoimmune thyroid disorders (eg, Hashimoto thyroiditis or Graves' disease) are the most common, but the ovaries, pancreas, parathyroid gland, and organs of the GI system can also be affected. This polyglandular failure syndrome, termed autoimmune polyendocrine syndrome (APS), is associated with the idiopathic etiology only and has not been seen with adrenal insufficiency associated with tuberculosis or other invasive diseases. Medications that inhibit cortisol synthesis (ketoconazole) or accelerate cortisol metabolism (phenytoin, rifampin, phenobarbital) can also cause primary adrenal insufficiency.[70]

8 Secondary insufficiency is characterized by reduced glucocorticoid production secondary to decreased ACTH levels. Low levels of ACTH most commonly result from exogenous steroid use, leading to suppression of the HPA axis and decreased release of ACTH, as well as impaired androgen and cortisol production. These effects occur with oral, inhaled, intranasal, and topical glucocorticoid administration.[71–73] Moreover, mirtazapine and progestins, such as medroxyprogesterone acetate and megestrol acetate, have been reported to induce secondary adrenal insufficiency.[74,75] Chronic suppression also can result in atrophy of the anterior pituitary and hypothalamus, impairing recovery of function if the exogenous steroid is reduced. Endogenous secondary insufficiency can occur with tumor development in the hypothalamic-pituitary region. Secondary disease classically presents with normal concentrations of mineralocorticoids since the zona glomerulosa is controlled by the renin-angiotensin system rather than ACTH levels.

Approximately 90% of the adrenal cortex must be destroyed before adrenal insufficiency symptoms occur.[76] Etiologies for both primary and secondary insufficiency are listed in **Table 93-11**. Adrenal hemorrhage can result from

multiple etiologies including traumatic shock, coagulopathies, ischemic disorders, and other situations of severe stress, but septicemia is the most common. Symptoms include truncal pain, fever, shaking, chills, hypotension preceding shock, anorexia, headache, vertigo, vomiting, rash, psychiatric symptoms, abdominal rigidity or rebound, and death in 6 to 48 hours if not treated. The most common organisms found on autopsy are *Neisseria meningitidis*, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, Group A *Streptococcus*, and *Haemophilus influenzae*.[76,77]

TABLE 93-11 Etiologies of Primary and Secondary Adrenal Insufficiency

Primary Insufficiency	Secondary Insufficiency
Slow onset	Craniopharyngioma
Acquired immunodeficiency syndrome	Cure of Cushing syndrome
Adrenomyeloneuropathy	Empty sella syndrome
Adrenoleukodystrophy	Tumors of the third ventricle
Amyloidosis	Histiocytosis
Autoimmune adrenalitis[a]	Hypothalamic tumors
Bilateral adrenalectomy	Hypopituitarism
Congenital adrenal hypoplasia	Long-term corticosteroid administration
Hemochromatosis	Lymphocytic hypophysitis
Isolated glucocorticoid deficiency	Pituitary surgery, radiation, or tumor
Metastatic neoplasia	Sarcoidosis
Systemic fungal, bacterial, or viral infections, tuberculosis[b]	Medications—progestins and glucocorticoid discontinuation
Medications—ketoconazole, etomidate, rifampin, phenytoin, phenobarbital	Postpartum pituitary necrosis Necrotic or bleeding pituitary macroadenoma
Fast onset	
Adrenal thrombosis, hemorrhage, sepsis, trauma, or necrosis	Head trauma, lesions of the pituitary stalk, pituitary or adrenal surgery for Cushing syndrome

[a]Accounts for approximately 70% of cases.

[b]Accounts for approximately 20% of cases.

Diagnosis

Distinguishing Addison's disease from secondary insufficiency is difficult; however, the following guidelines may be helpful:

1. Hyperpigmentation, commonly found in areas of skin exposed to increased friction, is seen only in Addison's disease because of excess secretion of ACTH and other proopiomelanocortin (POMC) peptides that induce melanocyte-stimulating hormone production. Secondary adrenal insufficiency is fundamentally characterized by deficient ACTH and POMC peptide secretion and a corresponding low level of melanocyte-stimulating hormone production. In fact, some patients with secondary insufficiency may exhibit pale-colored skin secondary to hypopigmentation.
2. Aldosterone secretion usually is preserved in secondary insufficiency.
3. Weight loss, dehydration, hyponatremia, hyperkalemia, and elevated blood urea nitrogen are common in Addison's disease.
4. Addison's disease will have an abnormal response to the short corticotropin stimulation test. Plasma ACTH levels are usually elevated (400-2,000 pg/mL [88-440 pmol/L]) in primary insufficiency, versus low to normal (5-50 pg/mL [1.1-11 pmol/L]; see Table 93-3) in secondary insufficiency. A normal corticotropin stimulation test does not rule out secondary adrenal insufficiency, particularly in mild cases.

The short corticotropin stimulation test, also known as the cosyntropin stimulation test, can be used to assess patients suspected of hypocortisolism. Patients are given 250 μg of synthetic ACTH intravenously or intramuscularly, with serum cortisol measured at baseline and 30 to 60 minutes after the injection. A resulting cortisol concentration ≥18 μg/dL (500 nmol/L) rules out adrenal insufficiency.[78] Because 250 μg represents a massive supraphysiologic dose, this test can elicit normal, elevated cortisol responses in some cases of mild secondary insufficiency. Thus, some suggest that higher cutoff values (≥22 μg/dL [610 nmol/L]) should be used to prevent false-negative test results.[79] Alternatively, a low-dose corticotropin stimulation test, using 1 μg of synthetic ACTH, can achieve similar results to the standard dose test. Neither test is very effective in ruling out secondary insufficiency.[80] Other tests include the insulin hypoglycemia test, the metyrapone test, and the CRH stimulation test.[70]

The standard cutoffs described above are of limited use in acutely ill patients.[70] Severe infection, trauma, burns, illnesses, or surgery can increase cortisol production by as much as a factor of 6, making the recognition of

adrenal insufficiency in this population extremely difficult. In the critically ill, a random cortisol concentration below 15 µg/dL (415 nmol/L) is suggestive of adrenal insufficiency, whereas a concentration greater than 34 µg/dL (940 nmol/L) suggests that adrenal insufficiency is unlikely.[70] For patients who fall between these two values, a poor response to corticotropin (<9 µg/dL [250 nmol/L] increase in plasma cortisol from baseline at 30 or 60 minutes) indicates the possibility of adrenal insufficiency and a need for corticosteroid supplementation.[70] A hypoproteinemic patient (albumin <2.5 g/dL [25 g/L]) will have markedly lower CBG, which can underestimate the actual free fraction of cortisol. These patients may benefit from measurement of free cortisol, although the assay may not be routinely available.[70]

TREATMENT

Treatment of Addison's disease must include adequate patient education, so that the patient is aware of treatment complications, the expected outcome, consequences of missed doses, and drug side effects. The agents of choice are hydrocortisone and cortisone acetate administered two or three times daily. The treatment goal is to establish the lowest effective dose while mimicking the normal diurnal adrenal rhythm.[78] Twice-daily dosing is usually adequate depending on the agent used. Once-daily prednisolone is an alternative when adherence to a multi-dose regimen is a concern.

Endogenous cortisol production varies between 5 and 10 mg/m^2/day.[81] Hence, the classically recommended 12 to 15 mg/m^2/day dose for cortisol supplementation will be excessive in most patients. Starting doses to properly mimic endogenous cortisol production are 15 to 25 mg of hydrocortisone daily, which is roughly equal to 20 to 35 mg of cortisone acetate daily, or 3 to 5 mg of prednisolone daily.[70,81] For hydrocortisone or cortisone, the majority of the dose (67%) is given in the morning and the remainder (33%) is given 6 to 8 hours later to duplicate the normal circadian rhythm of cortisol production. Recent data also suggest that continuous infusion of glucocorticoids delivered via infusion pump may provide a more physiological circadian maintenance of ACTH and cortisol concentration when compared to conventional oral replacement.[82] Since no laboratory test adequately determines the appropriateness of dosing, the patient's symptoms should be monitored every 6 to 8 weeks to assess proper glucocorticoid replacement. Monitoring parameters should include body weight, postural blood pressures, subjective energy levels, and signs of frank glucocorticoid excess.

In primary insufficiency, fludrocortisone acetate can be used to supplement mineralocorticoid loss. For most patients, a dose of 0.05 to 0.2 mg by mouth once a day is adequate to maintain volume status. If parenteral therapy is needed, 2 to 5 mg of deoxycorticosterone trimethylacetate in oil intramuscularly every 3 to 4 weeks can be substituted. Mineralocorticoid replacement attenuates the development of hyperkalemia, and patients on fludrocortisone therapy do not need to restrict salt intake. However, mineralocorticoid replacement may be unnecessary in some primary cases because glucocorticoids, particularly at large doses, also bind to mineralocorticoid receptors. For example, a daily dose of hydrocortisone 40 to 50 mg has similar mineralocorticoid effects to 0.1 mg of fludrocortisone. Adverse effects must be monitored closely and include gastric upset, edema, hypertension, hypokalemia, insomnia, excitability, and diabetes mellitus. In addition, patient weight, blood pressure, and electrocardiogram should be monitored regularly.[70]

Most adrenal crises occur secondary to glucocorticoid dose reduction or lack of stress-related dose adjustments. Patients receiving corticosteroid replacement therapy should receive an additional 5 to 10 mg of hydrocortisone shortly before strenuous activities such as exercise.[70] Likewise, during times of severe physical stress such as febrile illnesses or injury, patients should be instructed to double their daily dose until recovery.[70,83] For major trauma, surgery, or in critically ill patients, larger doses—up to 10 times the usual daily dose—may be required.[70] Parenteral therapy should be used for patients experiencing diarrhea or vomiting. In patients with concomitant, newly diagnosed, or uncontrolled hypothyroidism, thyroid replacement should take place only after adequate glucocorticoid replacement as euthyroidism can trigger an adrenal crisis by accelerating cortisol metabolism.[78]

The endpoint of therapy is difficult to assess in most patients, but a reduction in excess pigmentation is a good clinical marker. The development of features of Cushing syndrome indicates excessive replacement. Treatment of secondary adrenal insufficiency is similar to primary disease treatment, except that mineralocorticoid replacement usually is unnecessary. Patient education is paramount with emphasis placed on the medication regimen and adrenal crisis prevention.

CLINICAL PRESENTATION Adrenal Insufficency

Symptoms

- Patients commonly complain of weakness, weight loss, GI symptoms,

craving for salt, headaches, memory impairment, depression, and postural dizziness.

- Early symptoms of acute adrenal insufficiency also include myalgias, malaise, and anorexia. As the situation progresses, vomiting, fever, hypotension, and shock will develop.

Signs

- Increased pigmentation
- Hypotension (postural)
- Fever
- Decreased body hair
- Vitiligo
- Features of hypopituitarism (amenorrhea and cold intolerance)

Laboratory Tests

- The short cosyntropin stimulation test can be used to assess patients suspected of hypercortisolism.

Other Diagnostic Tests

- Other tests include the insulin hypoglycemia test, the metyrapone test, and the CRH stimulation test.

Acute Adrenal Insufficiency

Adrenal crisis, or Addisonian crisis, is characterized by an acute adrenocortical insufficiency and represents a true endocrine emergency. Anything that increases adrenal requirements dramatically can precipitate an adrenal crisis. Stressful situations, surgery, infection, and trauma all are potential triggering events, especially in the patient with some underlying adrenal or pituitary insufficiency. The most common cause of adrenal crisis is HPA-axis suppression brought on by abrupt withdrawal of chronic glucocorticoid use.

Treatment of adrenal crisis involves the administration of parenteral glucocorticoids. Hydrocortisone is the agent of choice owing to its combined glucocorticoid and mineralocorticoid activity. Hydrocortisone is initially administered at a dose of 100 mg IV through rapid infusion, followed by 200 mg

of hydrocortisone over 24 hours via a continuous infusion or intermittent bolus every 6 hours.[70] Intravenous administration is continued for an additional day at a reduced dose of 100 mg over 24 hours, at which time if the patient is stable, oral hydrocortisone can be administered at a dose of 50 mg every 6 to 8 hours, followed by tapering to the individual's chronic replacement needs. Fluid replacement often is required and can be accomplished with dextrose 5% in normal saline solution (D_5NS) at a rate to support blood pressure. If therapy is needed for hypoglycemia, dextrose 25% in water ($D_{25}W$) can be infused at a dose of 2 to 4 mL/kg (maximum single dose of 25 g dextrose). During initial treatment for adrenal crisis, mineralocorticoid replacement generally is unnecessary because of hydrocortisone's mineralocorticoid activity. If hyperkalemia is present after the hydrocortisone maintenance phase, additional mineralocorticoid supplementation can be achieved with 0.1 mg of fludrocortisone acetate daily.

Patients with adrenal insufficiency should be instructed to carry a card or wear a bracelet or necklace, such as MedicAlert, that contains information about their condition. Additionally, patients should have easy access to injectable hydrocortisone or glucocorticoid suppositories in case of an emergency or during times of physical stress, such as febrile illness or injury.[70]

Hypoaldosteronism

Hypoaldosteronism is rare and usually associated with low-renin status (hyporeninemic hypoaldosteronism), diabetes, complete heart block, or severe postural hypotension, or it can occur postoperatively following tumor removal. Hypoaldosteronism can be part of a multi-hormonal insufficiency or a stand-alone defect. In nonselective hypoaldosteronism, generalized adrenocortical insufficiency is the most likely etiology (see Addison's Disease). In selective hypoaldosteronism, insufficient aldosterone levels are precipitated by a specific defect in the stimulation of adrenal aldosterone secretion, with 21-hydroxylase deficiency being most common. Pseudohypoaldosteronism results from a defect in peripheral aldosterone action, whether from peripheral resistance or a reduced number of functional aldosterone receptors.

Laboratory analysis reveals hyponatremia, hyperkalemia, or both. Patients often will present with hyperchloremic metabolic acidosis. In most cases, the deficiency is in mineralocorticoid production and replacement with fludrocortisone in a dose of 0.1 to 0.3 mg is usually effective. Patients should be monitored for blood pressure response as well as electrolyte status.

Congenital Adrenal Hyperplasia

Because many enzyme systems are needed to complete the complex cholesterol-to-cortisol pathway, enzyme deficiencies can lead to disruptions of the normal cascade of events (see Fig. 93-2). This group of enzyme disorders is collectively referred to as congenital adrenal hyperplasia because of the resultant chronic adrenal gland stimulation that occurs following enzyme deficiency.[70,84,85] The most frequent cause of congenital adrenal hyperplasia is steroid 21-hydroxylase deficiency, accounting for more than 90% of cases. Any enzyme deficiency is capable of affecting any one or all three of the steroid pathways. Therefore, treatment focuses on replacement of the deficient hormone, psychological support, and surgical repair of the external genitalia in female patients.[86] Pediatric patients receiving glucocorticoid replacement (eg, with hydrocortisone and fludrocortisone) should be monitored for adverse outcomes, especially incident hypertension and decreased bone mineral density.[87,88] Six of the most common enzyme deficiencies are outlined briefly in **Table 93-12**.

TABLE 93-12 Congenital Adrenal Hyperplasia

Enzyme Deficiency (Disorder)	Symptoms	Laboratory Tests	Comments
21-Hydroxylase (nonvirilizing CAH)	Enlarged female genitalia and adrenal gland (caused by cholesterol)	All steroids are low in blood and urine	Poor prognosis for infants
17-Hydroxylase (nonvirilizing CAH)	Hypertension usually present	Low concentrations of cortisol and estrogens	Mineralocorticoid replacement not necessary
21-Hydroxylase (virilizing CAH)	Pubertal irregularities (acne, early pubic hair, voice lowering, and increased muscularity); mature normally with replacement	High progesterone, renin, 17-hydroxyprogesterone, and ACTH; low cortisol, sodium, and aldosterone	Most common form of CAH (90% of total), incidence of 1:10,000; monitor growth velocity, bone age, renin, and 17-hydroxyprogesterone
11-Hydroxylase (virilizing CAH)	Hypertension secondary to high deoxycortisol and virilism from androgen excess; mistaken for Cushing, but no glucose intolerance	Low plasma cortisone and aldosterone; high ACTH and MSH concentrations	Second most common form of CAH (9% of total), incidence of 1:100,000; final step in biosynthesis of corticosterone and cortisol; found only in adrenal cortex
3-Hydroxysteroid dehydrogenase (mixed CAH)	Both cortisol and aldosterone deficiencies	Decreased aldosterone, cortisol, estrogens, and androgens; increased pregnenolone and cholesterol	Defect affects both adrenals and gonads
18-Hydroxysteroid dehydrogenase (corticosterone methyloxidase deficiency)	Hypotension	Restricted to zona glomerulosa; sole aldosterone defect; hyponatremia, hyperkalemia, increased renin	Mineralocorticoid replacement without glucocorticoid replacement

ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia; MSH, melanocyte-stimulating hormone.

Adrenal Virilism

9 Virilism, excessive secretion of androgens from the adrenal gland, commonly occurs as a result of congenital enzyme defects. Depending on the enzyme deficiency, patients accumulate excess levels of a variety of androgens, most notably testosterone. The condition affects women more often than men, with hirsutism being the dominant feature. Additional coexisting features can include voice deepening, acne, increased muscle mass, menstrual abnormalities, clitoral enlargement, redistribution of body fat and loss of female body contour, breast atrophy, and hair recession and crown balding.[89]

Treatment of virilism centers on suppression of the pituitary–adrenal axis with exogenous glucocorticoids. In adults, the usual steroids used are dexamethasone (0.25-0.5 mg), prednisone (2.5-5 mg), or hydrocortisone (10-20 mg).[90]

Hirsutism

Women presenting with hirsutism exhibit excess terminal hair growth in an androgen-dependent distribution. Such growth has obvious cosmetic consequences, but also can adversely affect quality of life and psychological well-being.[91] Most cases of hirsutism occur in women with some degree of excess androgen production. Androgen excess can be derived from either the ovaries or the adrenal glands, or rarely from pituitary disorders. Polycystic ovarian syndrome (PCOS) is responsible for most cases of ovarian excess and is the most common cause of hirsutism.[92] Congenital adrenal hyperplasia accounts for 5% of cases while adrenal and ovarian tumors cause hyperandrogenemia in 0.2% of women.

Cosmetic approaches generally are tried first, with repeated photoepilation offering the greatest long-term success.[93] If these approaches are unsuccessful, subsequent treatment should include pharmacologic intervention. Oral contraceptives are the treatment of choice in most hirsute women, particularly in those requiring concurrent contraception. If oral contraceptives are used, a progestin with low androgen activity (norethindrone, ethynodiol diacetate) or antiandrogenic activity (drospirenone) should be chosen. Other antiandrogens, including spironolactone and finasteride, can supplement or replace oral contraceptive therapy in women who cannot or choose not to conceive. Antiandrogens can take 6 to 12 months to alleviate hirsutism and treatment should be continued for 2 years, followed by a slow dose reduction.[94] Dexamethasone (and other glucocorticoids) can be modestly effective if the androgen source is adrenal, but can induce cushingoid symptoms even at doses of 0.5 mg/day.

Gonadotropin-releasing hormone can be an effective adjunct or alternative to oral contraceptives if the source of androgen is ovarian. However, these products generally are not recommended due to excessive costs, injectable-only routes of administration, and adverse effects resulting from estrogen deficiency. Additionally, insulin sensitizers, such as metformin or thiazolidinediones, can show modest metabolic and glycemic improvement in women with PCOS, but their routine use is not recommended because their effects on hirsutism, acne, and infertility are limited.[92]

Eflornithine hydrochloride, an irreversible ornithine decarboxylase inhibitor, moderately reduces the rate of hair growth but does not remove hair already present. The drug is available as a topical cream applied as a thin layer to the affected area twice daily, at least 8 hours apart. Reduction in unwanted hair can

be noted within 6 to 8 weeks with a maximal effect at 8 to 24 weeks; therapy must be continued indefinitely to prevent hair regrowth.[90,94] Skin irritation can occur that resolves on discontinuation.

PRINCIPLES OF GLUCOCORTICOID ADMINISTRATION

The term *glucocorticoid* was initially given to these agents to describe their glucose-regulating properties. However, carbohydrate metabolism is only one of the myriad effects exhibited by steroids. The activity produced by these drugs is a function of the receptor activated (glucocorticoid vs mineralocorticoid), the location of the receptor, as well as the agent and dose prescribed.

The mechanism of action of glucocorticoids is complex and not fully known. The glucocorticoid enters the cell through passive diffusion and binds to its specific receptor. Between 5,000 and 100,000 receptors exist in each cell. Steroids exhibit various binding affinities to the vast number of receptors in almost every tissue and therefore elicit a wide variety of biologic effects.

Following receptor binding, a structural change occurs in the receptor, known as *activation*. After activation, the receptor–steroid complex binds to deoxyribonucleic acid sites in the cell called *glucocorticoid response elements* (GREs). This binding alters nearby gene expression and stimulates or, in some cases, inhibits transcription of specific mRNAs. Consequently, the resulting protein, which produces the stimulatory or inhibitory glucocorticoid action, varies according to the tissue and cell type in which the glucocorticoid receptor exists.

Pharmacokinetic properties of the glucocorticoids vary by agent and route of administration. In general, most orally administered steroids are well absorbed. Water-soluble agents are more rapidly absorbed following intramuscular injection than are lipid-soluble agents. Intravenous administration is recommended when a quick onset of action is needed. A summary of these agents is provided in **Table 93-13**.

TABLE 93-13 Relative Potencies of Glucocorticoids

Glucocorticoid	Anti-inflammatory Potency	Equivalent Potency (mg)	Approximate Half-Life (min)	Sodium-Retaining Potency
Cortisone	0.8	25	30	2
Hydrocortisone	1	20	90	2
Prednisone	3.5	5	60	1
Prednisolone	4	5	200	1
Triamcinolone	5	4	300	0
Methylprednisolone	5	4	180	0
Betamethasone	25	0.6	100-300	0
Dexamethasone	30	0.75	100-300	0

In addition to causing iatrogenic Cushing syndrome, systemic steroids can lead to increased susceptibility to infection, osteoporosis, sodium retention with resultant edema, hypokalemia, hypomagnesemia, cataracts, peptic ulcer disease, seizures, and generalized suppression of the HPA axis. Long-term complications tend to be insidious and less likely to respond to steroid withdrawal.

Suppression of the HPA axis is a major concern whenever systemic steroids are tapered or withdrawn. Single doses of glucocorticoids can prevent the axis from responding to major stressors for several hours. In general, steroid administration at a high dose for long periods of time causes suppression of the axis. However, the possibility of suppression occurs any time the patient is exposed to supraphysiologic steroid doses.[11,95] Symptoms of steroid withdrawal resemble those seen in a patient with adrenocortical deficiency.

A variety of recommendations for steroid tapering are available.[11,96–98] In general, patients who have been on long-term steroid therapy will need to be gradually withdrawn toward physiologic doses over months. On average, the normal adult produces approximately 10 to 30 mg of cortisol per day with the peak concentration occurring around 8:00 am. As the steroid or steroid-equivalent dose approaches the 20- to 30-mg level, the taper should be slowed and the patient checked for axis function. The primary modes to test HPA integrity are the ACTH test, either high or low dose, or a morning (8:00 am) serum cortisol. A normal morning serum cortisol (>20 μg/dL [550 nmol/L]) or a normal ACTH test indicates that daily steroid maintenance therapy may be discontinued. If morning serum cortisol is between 3 and 20 μg/dL (85 and 550 nmol/L), the ACTH or CRH stimulation test can be useful in the assessment of pituitary–adrenal function.[11] A morning cortisol less than 3 μg/dL (85 nmol/L) indicates axis suppression and the need for continued replacement therapy. Suppression can persist for up to a year in some patients. Caution should be used

to prevent disease exacerbation during the steroid taper and to avoid the need for another course of high-dose steroids.

Alternate-day therapy (ADT) regimens have been promoted as a means to lessen the impact of prolonged steroid administration.[11,98] ADT theoretically minimizes the hypothalamic-pituitary suppression as well as some of the adverse effects seen with once-daily therapy. This hypothetical advantage may be especially pertinent in treating children and young adults, in whom growth suppression is a major concern. ADT is not recommended for initial management, but rather in the management of the stabilized patient who needs long-term therapy. The patient is exposed to “on” and “off” days, with the “on” day dose gradually increased corresponding with a dose-reduction in the “off” day dose over a period of 14 days. After 2 weeks, no medication is taken on “off” days. Not all patients will have equivalent disease control on ADT, and it should be avoided in certain indications.[11,98]

EVALUATION OF THERAPEUTIC OUTCOMES

Successful glucocorticoid therapy involves counseling and monitoring the patient, as well as recognizing complications of therapy (**Table 93-14**). The risk-to-benefit ratio of glucocorticoid administration should always be considered, especially with concurrent disease states such as hypertension, diabetes mellitus, peptic ulcer disease, and uncontrolled systemic infections.

TABLE 93-14 Appropriate Use of Glucocorticoid Therapy

Monitoring	Glucose concentrations (serum and urine) Electrolytes (serum and urine) Ophthalmologic examinations Stool tests for occult blood loss Growth and development (children and adolescents)
Patient Education	Take with food to minimize GI discomfort Never discontinue medication on your own; check with your physician; gradual dose reduction is usually necessary Carry or wear medical identification indicating that you are on long-term glucocorticoid therapy Dosage increases can be necessary at times of increased stress (surgery or emergency treatments) Be aware of potential side effects (ie, visual disturbances, bruising, and delayed wound healing) What to do if you miss a dose: If your dosing schedule is: *Every other day*: Take as soon as possible if remembered that morning. If not remembered until later, skip that day. Take the next morning, and then skip the following day *Every day*: Take as soon as possible, but skip if almost time for the next dose. Never double doses
Recognizing complications	Early in therapy and essentially unavoidable: insomnia, enhanced appetite, weight gain Common in patients with underlying risk factors: hypertension, diabetes mellitus, peptic ulcer disease Long-term intense treatment: cushingoid habitus, hypothalamic pituitary–adrenal suppression, impaired wound healing Delayed and insidious: cataracts, atherosclerosis Rare and unpredictable: psychosis, glaucoma, pancreatitis

Data from References 99 and 100.

Postclass Engaged Learning Activity

Conduct a literature search and identify a primary research manuscript that has been published in the past 12 months regarding the treatment of Cushing syndrome, hyperaldosteronism, or hypoaldosteronism. If the manuscript is regarding a new patient care process, write a brief summary about the process, how feasible you believe the process would be to implement in practice, and what setting(s) the process would be best suited (eg, community pharmacy, ambulatory clinic, long-term care facility, hospital). If the manuscript is regarding a medication that is discussed in the book chapter, write a brief summary of the study methods, the major findings, and how this new information might change current practice. If the manuscript is regarding a new medication that is not described in the chapter, write a brief summary about the medication's mechanisms of action, how it is administered, and one potential advantage or disadvantage of this new medication compared to the current standard of care. This activity is intended to build your literature evaluation skills and ability to critically appraise research manuscripts.

Alternative: Create a table with mechanisms for drug-induced secondary adrenal insufficiency or drug-induced Cushing syndrome

ABBREVIATIONS

ACTH	adrenocorticotropic hormone
ADT	alternate-day therapy
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APA	aldosterone-producing adenoma
APS	autoimmune polyendocrine syndrome
ARR	aldosterone-to-renin ratio
AST	aspartate aminotransferase
AVS	adrenal venous sampling
BAH	bilateral adrenal hyperplasia
CAH	congenital adrenal hyperplasia
CBG	corticosteroid-binding globulin
CCT	captopril challenge test
CHD	coronary heart disease
CNS	central nervous system
CrCl	creatinine clearance
CRH	corticotropin-releasing hormone
CT	computed tomography
CYP	cytochrome P450
D_5NS	dextrose 5% in normal saline solution
$D_{25}W$	dextrose 25% in water
DDT	dichlorodiphenyltrichloroethane
DST	dexamethasone suppression test
FDA	Food and Drug Administration
FH	familial hyperaldosteronism
FST	fludrocortisone suppression test
GABA	*γ*-aminobutyric acid
GI	gastrointestinal
GRA	glucocorticoid-remediable aldosteronism
GRE	glucocorticoid response element
HPA	hypothalamic–pituitary–adrenal

INR	international normalized ratio
IPSS	inferior petrosal sinus sampling
IRMA	immunoradiometric assay
JVS	jugular venous sampling
LDL	low-density lipoprotein
MRI	magnetic resonance imaging
PA	primary aldosteronism
PAC	plasma aldosterone concentration
PAC-to-PRA	plasma-aldosterone-concentration–to–plasma-renin-activity
PCOS	polycystic ovarian syndrome
POMC	proopiomelanocortin
PRA	plasma renin activity
RAAS	renin–angiotensin–aldosterone system
RIA	radioimmunoassay
SIT	saline infusion test
sst	somatostatin receptor subtype
UFC	urinary free cortisol

REFERENCES

1. Conn JW. Primary aldosteronism, a new clinical syndrome. *J Lab Clin Med* 1955;45:6–17.
2. Albright F. Cushing syndrome. *Harvey Lect* 1942–1943;38:123–186.
3. Lacroix A, Feelders RA, Stratakis CA, Nieman LK. Cushing syndrome. *Lancet* 2015;386(9996):913–927.
4. Isidori AM, Kaltsas GA, Pozza C, et al. The ectopic adrenocorticotropin syndrome: Clinical features, diagnosis, management, and long-term follow-up. *J Clin Endocrinol Metab* 2006;91:371–377.
5. Boscaro M, Barzon L, Sonino N. The diagnosis of Cushing syndrome: Atypical presentations and laboratory shortcomings. *Arch Intern Med* 2000;160:3045–3053.
6. Arlt W. Disorders of the adrenal cortex. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J.eds. *Harrison's Principles of Internal Medicine*, 19th ed. New York, NY: McGraw-Hill; 2015. http://accessmedicine.mhmedical.com/content.aspx?

bookid=1130&Sectionid=79752055.

7. Catargi B, Rigalleau V, Poussin A, et al. Occult Cushing syndrome in type-2 diabetes. *J Clin Endocrinol Metab* 2003;88:5808–5813.
8. Findling JW, Raff H. Screening and diagnosis of Cushing syndrome. *Endocrinol Metab Clin North Am* 2005;34:385–402.
9. Nieman LK, Biller BMK, Findling JW, et al. The diagnosis of Cushing syndrome: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2008;93:1526–1540.
10. Terzolo M, Reimondo G, Chiodini I, et al. Screening of Cushing syndrome in outpatients with type 2 diabetes: Results of a prospective multicentric study in Italy. *J Clin Endocrinol Metab* 2012;97:3467–3475.doi:10.1210/jc.2012-1323.
11. Hopkins RL, Leinung MC. Exogenous Cushing syndrome and glucocorticoid withdrawal. *Endocrinol Metab Clin North Am* 2005;34:371–384.
12. Bolland MJ, Bagg W, Thomas MG, et al. Cushing syndrome due to interaction between inhaled corticosteroids and itraconazole. *Ann Pharmacother* 2004;38:46–49.
13. Samaras K, Pett S, Gowers A, et al. Iatrogenic Cushing syndrome with osteoporosis and secondary adrenal failure in human immunodeficiency virus-infected patients receiving inhaled corticosteroids and ritonavir-boosted protease inhibitors: Six cases. *J Clin Endocrinol Metab* 2005;90:4394–4398.
14. Newell-Price J, Trainer P, Besser M, Grossman A. The diagnosis and differential diagnosis of Cushing syndrome and pseudo-Cushing states. *Endocr Rev* 1998;19:647–672.
15. Nieman LK, Ilias I. Evaluation and treatment of Cushing syndrome. *Am J Med* 2005;118:1340–1346.
16. Lindsay JR, Nieman LK. Differential diagnosis and imaging in Cushing syndrome. *Endocrinol Metab Clin North Am* 2005;34:403–421.
17. Arnaldi G, Angeli A, Atkinson AB, et al. Diagnosis and complications of Cushing syndrome: A consensus statement. *J Clin Endocrinol Metab* 2003;88:5593–5602.
18. Jackson RV, Hockings GI, Torpy DJ, et al. New diagnostic tests for Cushing syndrome: Uses of naloxone, vasopressin and alprazolam. *Clin Exp Pharmacol Physiol* 1996;23:579–581.

19. Ambrosi B, Bochicchio D, Colombo P, et al. Loperamide to diagnose Cushing syndrome. *JAMA* 1993;270:2301–2302.
20. Papanicolaou DA, Mullen N, Kyrou I, Nieman LK. Nighttime salivary cortisol: A useful test for the diagnosis of Cushing syndrome. *J Clin Endocrinol Metab* 2002;87:4515–4521.
21. Viardot A, Huber P, Puder JJ, et al. Reproducibility of nighttime salivary cortisol and its use in the diagnosis of hypercortisolism compared with urinary free cortisol and overnight dexamethasone suppression test. *J Clin Endocrinol Metab* 2005;90:5730–5736.
22. Findling JW, Raff H, Aron DC. The low-dose dexamethasone suppression test: A reevaluation in patients with Cushing syndrome. *J Clin Endocrinol Metab* 2004;89:1222–1226.
23. Rockall AG, Babar SA, Sohaib SA, et al. CT and MR imaging of the adrenal glands in ACTH-independent Cushing syndrome. *Radiographics* 2004;24:435–452.
24. Peppercorn PD, Reznek RH. State-of-the-art CT and MRI of the adrenal gland. *Eur Radiol* 1997;7:822–836.
25. Nieman LK. Medical therapy of Cushing disease. *Pituitary* 2002;5:77–82.
26. Labeur M, Arzt E, Stalla GK, Paez-Pereda M. New perspectives in the treatment of Cushing syndrome. *Curr Drug Targets Immune Endocr Metabol Disord* 2004;4:335–342.
27. McEvoy GK ed. *American Hospital Formulary Service (AHFS) Drug Information*. Bethesda, MD: American Society of Health-System Pharmacists; 2015.
28. Nieman LK, Biller BMK, Findling JW, et al. Treatment of Cushing syndrome: An Endocrine Society Clinical Practice Guideline. *J Clin Endorcrinol Metab*. 2015;100:2807–2831.
29. Utz AL, Swearingen B, Biller BM. Pituitary surgery and postoperative management in Cushing disease. *Endocrinol Metab Clin North Am* 2005;34:459–478.
30. Dang CN, Trainer P. Pharmacological management of Cushing syndrome: An update. *Arq Bras Endocrinol Metabol* 2007;51:1339–1348.
31. Preda VA, Sen J, Karavitaki N, Grossman AB. Etomidate in the management of hypercortiolaemia in Cushing syndrome: A review. *Eur J Endocronol*. 2012;167:137–143.
32. Pivonello R, Ferone D, de Herder WW, et al. Dopamine receptor

expression and function in corticotroph pituitary tumors. *J Clin Endocrinol Metab* 2004;89:2452–2462.

33. Godbout A, Manavela M, Danilowicz K, et al. Cabergoline monotherapy in the long-term treatment of Cushing disease. *Eur J Endocrinol* 2010;163:709–716.
34. Tritos NA, Biller BMK, Swearingen B. Management of Cushing disease. *Nat Rev Endocrinol* 2011;7:279–289.
35. Tritos NA, Biller BM. Medical management of Cushing disease. *J Neurooncol* 2014;117(3):407–414.
36. Colao A, Petersenn S, Newell-Price J, et al. A 12-month phase 3 study of pasireotide in Cushing disease. *N Engl J Med* 2012;366:914–924.
37. Petersenn S, Salgado LR, Schopohl J, et al. Long-term treatment of Cushing's disease with pasireotide: 5-year results from an open-label extension study of a Phase III trial. *Endocrine*. 2017;57(1):156–165. doi: 10.1007/s12020-017-1316-3.
38. Guarnotta V, Pizzolanti G, Ciresi A, Giordano C. Insulin sensitivity and secretion and adipokine profile in patients with Cushing's disease treated with pasireotide. *J Endocrinol Invest*. 2018;2:1–1.
39. Feelders RA, de Bruin C, Pereira AM, et al. Pasireotide alone or with cabergoline and ketoconazole in Cushing disease. *N Engl J Med* 2010;362:1846–1848.
40. Nieman LK. Update in the medical therapy of Cushing disease. *Curr Opin Endocrinol Diabetes Obesm* 2013;20:330–334.
41. Fleseriu M, Biller BMK, Findling JW, et al. Mifepristone, a glucocorticoid receptor antagonist, produces clinical and metabolic benefits in patients with Cushing syndrome. *J Clin Endocrinol Metab* 2012;97:2039–2049.
42. Semple PL, Vance ML, Findling J, Laws ER. Transsphenoidal surgery for Cushing disease: Outcome in patients with a normal magnetic resonance imaging scan. *Neurosurgery* 2000;46:553–558.
43. Biller BMK, Grossman AB, Stewart PM, et al. Treatment of adrenocorticotropin-dependent Cushing syndrome: A consensus statement. *J Clin Endocrinol Metab* 2008;93:2454–2462.
44. Terzolo M, Angeli A, Fassnacht M, et al. Adjuvant mitotane treatment for adrenocortical carcinoma. *N Engl J Med* 2007;356:2372–2380.
45. Veytsman I, Nieman L, Fojo T. Management of endocrine manifestations and the use of mitotane as a chemotherapeutic agent for adrenocortical

carcinoma. *J Clin Oncol* 2009;27:4619–4629.

46. Morris D, Grossman A. The medical management of Cushing syndrome. *Ann N Y Acad Sci* 2002;970:119–133.
47. Stowasser M, Gordon RD. Primary aldosteronism: From genesis to genetics. *Trends Endocrinol Metab* 2003;14:310–317.
48. Stowasser M, Gordon RD. Primary aldosteronism. *Best Pract Res Clin Endocrinol Metab* 2003;17:591–605.
49. Wu V, Chao C, Kuo C, et al. Diagnosis and Management of Primary Aldosternoism. *Acta Nephrologica* 2012;26(3):111–120.
50. Chao C, Wu V, Kuo C, et al. Diagnosis and management of primary aldosteronism: An updated review. *Ann Med*. 2013;45:375–383.
51. Monticone S, D'Ascenzo F, Moretti C, et al. Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: A systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2018;6(1):41–50. doi: 10.1016/S2213-8587(17)30319-4.
52. Funder JW, Carey RM, Mantero F, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: An Endocrine Society Clinical Practice Guidelines. *J Clin Endocrinol Metab*. 2016;101(5):1889–1916. doi: 10.1210/jc.2015-4061.
53. Funder JW, Carey RM, Fardella C, et al. Case detection, diagnosis, and treatment of patients with primary aldosteronism: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2008;93:3266–3281.
54. Schwartz GL, Turner ST. Screening for primary aldosteronism in essential hypertension: Diagnostic accuracy of the ratio of plasma aldosterone concentration to plasma renin activity. *Clin Chem* 2005;51:386–394.
55. Kumar B, Swee M. Aldosterone-renin ratio in the assessment of primary aldosteronism. *JAMA* 2014;312(2):184–185.
56. Song Y, Yang S, He W, et al. Confirmatory tests for the diagnosis of primary aldosteronism: A prospective diagnostic accuracy study. *Hypertension*. 2018;71(1):118–124. 10.1161/HYPERTENSIONAHA.117.10197.
57. Mulatero P, Dluhy RG, Giacchetti G, et al. Diagnosis of primary aldosteronism: From screening to subtype differentiation. *Trends Endocrinol Metab* 2005;16:114–119.
58. Young WF, Stanson AW, Thompson GB, et al. Role for adrenal venous sampling in primary aldosteronism. *Surgery* 2004;136:1227–1235.

59. Nwariaku FE, Miller BS, Auchus R, et al. Primary hyperaldosteronism: Effect of adrenal vein sampling on surgical outcome. *Arch Surg* 2006;141:497–502.
60. Ye P, Yamashita T, Pollock DM, Rainey WE. Contrasting effects of eplerenone and spironolactone on adrenal cell steroidogenesis. *Horm Metab Res* 2009;41:35–39.
61. Nishizaka MK, Calhoun DA. Primary aldosteronism: Diagnostic and therapeutic considerations. *Curr Cardiol Rep* 2005;7:412–417.
62. Young WFJr. Primary aldosteronism: Management issues. *Ann N Y Acad Sci* 2002;970:61–76.
63. Young WF. Primary aldosteronism: Treatment options. *Growth Horm IGF Res*. 2003;13:S102–S108.
64. Parthasarathy HK, Menard J, White WB, et al. A double-blind, randomized study comparing the antihypertensive effect of eplerenone and spironolactone in patients with hypertension and evidence of primary aldosteronism. *J Hypertens*. 2011;29:980–990.
65. Karashima S, Yoneda T, Kometani M, et al. Comparison of eplerenone and spironolactone for the treatment of primary aldosteronism. *Hypertens Res*. 2016;39(3):133–137. doi: 10.1038/hr.2015.129.
66. Cabassi A, Rocco R, Berretta R, et al. Eplerenone use in primary aldosteronism during pregnancy. *Hypertension* 2012;49:e18–19.
67. Meria P, Kempf BF, Hermieu JF, et al. Laparoscopic management of primary aldosteronism: Clinical experience with 212 cases. *J Urol* 2003;169:32–35.
68. Meyer A, Brabant G, Behrend M. Long-term follow-up after adrenalectomy for primary aldosteronism. *World J Surg* 2005;29:155–159.
69. Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and treatment of primary adrenal insufficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2016;101(2):364–389. doi: 10.1210/jc.2015-1710.
70. Levin C, Maibach HI. Topical corticosteroid-induced adrenocortical insufficiency: Clinical implications. *Am J Clin Dermatol* 2002;3:141–147.
71. Bello CE, Garrett SD. Therapeutic issues in oral glucocorticoid use. *Lippincotts Prim Care Pract* 1999;3:333–341.
72. Sizonenko PC. Effects of inhaled or nasal glucocorticosteroids on adrenal function and growth. *J Pediatr Endocrinol Metab* 2002;15:5–26.
73. Goodman A, Cagliero E. Megestrol-induced clinical adrenal insufficiency.

Eur J Gynaecol Oncol 2000;21:117–118.

74. Schule C, Baghai T, Bidlingmaier M, et al. Endocrinological effects of mirtazapine in healthy volunteers. *Prog Neuropsychopharmacol Biol Psychiatry* 2002;26:1253–1261.
75. Alevritis EM, Sarubbi FA, Jordan RM, Peiris AN. Infectious cause of adrenal insufficiency. *South Med J* 2003;96:888–890.
76. Torrey SP. Recognition and management of adrenal emergencies. *Emerg Med Clin North Am* 2005;23:687–702.
77. Michels A, Michels N. Addison Disease: Early Detection and Treatment Principles. *Am Fam Physician* 2014;89(7):563–568.
78. Oelkers W. The role of high- and low-dose corticotropin tests in the diagnosis of secondary adrenal insufficiency. *Eur J Endocrinol* 1998;139:567–570.
79. Ospina NS, Al Nofal A, Bancos I, et al. ACTH stimulation tests for the diagnosis of adrenal insufficiency: Systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2016;101(2):427–434. doi: 10.1210/jc.2015-1700.
80. Crown A, Lightman S. Why is the management of glucocorticoid deficiency still controversial: A review of the literature. *Clin Endocrinol (Oxf)* 2005;63:483–492.
81. Oksnes M, Bjornsdottir S, Isaksson M. Continuous subcutaneous hydrocortisone infusion versus oral hydrocortisone replacement for treatment of Addison's disease: A randomized clinical trial. *J Clin Endocrinol Metab*. 2014;99(5):1665–1674.
82. Nieman LK, Turner MC. Addison's disease. *Clin Dermatol*. 2006;24:276–280.
83. Speiser PW, White PC. Congenital adrenal hyperplasia. *N Engl J Med* 2003;349:776–788.
84. Forest MG. Recent advances in the diagnosis and management of congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Hum Reprod Update* 2004;10:469–485.
85. Merke DP, Bornstein SR. Congenital adrenal hyperplasia. *Lancet* 2005;365:2125–2136.
86. Halper A, Sanchez B, Hodges JS, et al. Bone mineral density and body composition in children with congenital adrenal hyperplasia. *Clin Endocrinol (Oxf)*. 2018;88(6):813–819. doi: 10.1111/cen.13580.
87. Maccabee-Ryaboy N, Thomas W, Kyllo J, et al. Hypertension in children

with congenital adrenal hyperplasia. *Clin Endocrinol (Oxf)*. 2016;85(4):528–534. doi: 10.1111/cen.13086

88. Yildiz BO. Diagnosis of hyperandrogenism: Clinical criteria. *Best Pract Res Clin Endocrinol Metab* 2006;20:167–176.
89. Rosenfield RL. Hirsutism. *N Engl J Med* 2005;353:2578–2588.
90. Koulouri O, Conway GS. Management of hirsutism. *BMJ* 2009;338:823–826.
91. Azziz R. The evaluation and management of hirsutism. *Obstet Gynecol* 2003;101:995–1007.
92. Moghetti P. Treatment of hirsutism and acne in hyperandrogenism. *Best Pract Res Clin Endocrinol Metab* 2006;20:221–234.
93. United States Pharmacopeial Convention Inc. USPDI. *Advice for the Patient: Drug Information in Lay Language*, Vol. II, 19th ed. Taunton, MA: Rand-McNally; 1999:612–616.
94. Boumpas DT, Chrousos GP, Wilder RL, et al. Complications of therapy. In: Boumpas DT, moderator. Glucocorticoid therapy for immune-mediated diseases: Basic and clinical correlates. *Ann Intern Med*. 1993;119:1198–1208.
95. Arvat E, Giordano R, Ramunni J, et al. Adrenocorticotropin and cortisol hyperresponsiveness to hexarelin in patients with Cushing disease bearing a pituitary microadenoma, but not in those with macroadenoma. *J Clin Endocrinol Metab* 1998;83:4207–4211.
96. Martin KA, Chang RJ, Ehrmann DA, et al. Evaluation and treatment of hirsutism in premenopausal women: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2008;93: 1105–1120.
97. Henzen C, Suter A, Lerch E, et al. Suppression and recovery of adrenal response after short-term, high-dose glucocorticoid treatment. *Lancet* 2000;355:542–545.
98. Krasner AS. Glucocorticoid-induced adrenal insufficiency. *JAMA* 1999;282:671–676.
99. Kountz DS, Clark CL. Safely withdrawing patients from chronic glucocorticoid therapy. *Am Fam Physician* 1997;55:521–552.
100. Baxter JD. Advances in glucocorticoid therapy. *Adv Intern Med* 2000;45:317–349.

Pituitary Gland Disorders

Joseph K. Jordan, Amy Heck Sheehan, and Kashif M. Munir

KEY CONCEPTS

1. Pharmacologic therapy for acromegaly should be considered when surgery and irradiation are contraindicated, when there is a poor likelihood of surgical success, when rapid control of symptoms is needed, or when other treatments have failed to normalize growth hormone (GH) and insulin-like growth factor-1 (IGF-1) serum concentrations.
2. Pharmacotherapy for acromegaly using dopamine agonists has several advantages including oral administration and lower cost when compared to somatostatin analogs and pegvisomant. However, dopamine agonists effectively normalize IGF-1 serum concentrations in only 10% to 30% of patients. Therefore, somatostatin analogs remain the mainstay of therapy.
3. Blood glucose concentrations should be monitored frequently in the early stages of somatostatin analog therapy, especially pasireotide.
4. Pegvisomant appears to be the most effective agent for normalizing IGF-1 serum concentrations.
5. Recombinant growth hormone (GH) is currently considered the drug of choice for the treatment of children with growth hormone–deficient short stature. Prompt diagnosis of growth hormone deficiency (GHD) and initiation of replacement therapy with recombinant GH is crucial for optimizing final adult heights.
6. All GH products are equally effective. The recommended initial dose for treatment of GHD short stature in children is 0.16 to 0.24 mg/kg/wk.
7. Pharmacologic agents that antagonize dopamine or increase the release of prolactin can induce hyperprolactinemia. Discontinuation of the offending medication and initiation of an appropriate therapeutic alternative usually normalizes serum prolactin concentrations.

8. Cabergoline appears to be more effective than bromocriptine for the medical management of prolactinomas and offers the advantage of less-frequent dosing and fewer adverse effects.
9. Although preliminary data do not suggest that cabergoline has significant teratogenic potential, cabergoline is not recommended for use during pregnancy. Patients receiving cabergoline or bromocriptine who plan to become pregnant should discontinue the medication as soon as pregnancy is detected.
9. Pharmacologic treatment of panhypopituitarism includes the use of glucocorticoids, thyroid hormone, sex steroids, and recombinant GH, when appropriate, as lifelong replacement therapies.

Preclass Engaged Learning Activity

Create a diagram of anterior pituitary hormones, noting the upstream signals (ie, hypothalamic-releasing or inhibiting hormones) and downstream targets of the hormones secreted by the anterior pituitary. When applicable, note inhibitory or excitatory feedback mechanisms in this process.

INTRODUCTION

It wasn't until the 1950s that the physiologic importance of pituitary hormones was understood and the neurohormonal regulation of the pituitary by the hypothalamus described.[1] The pituitary gland plays an essential role in homeostasis, and for this reason, it is often referred to as the *master gland*. The hypothalamus and the pituitary gland are closely connected, and together they provide a means of communication between the brain and many of the body's endocrine organs. The hypothalamus uses input from the central nervous system and metabolic signals from the body to control the secretion of pituitary hormones that regulate growth, thyroid function, adrenal activity, reproduction, lactation, and fluid balance.

ANATOMY AND PHYSIOLOGY

The hypothalamus (**Fig. e94-1**) is a small region at the base of the brain that

receives autonomic nervous input from different areas of the body to regulate limbic functions, food and water intake, body temperature, cardiovascular function, respiratory function, and diurnal rhythms. In addition, the hypothalamus controls the release of hormones from the anterior and posterior regions of the pituitary gland. Neurons in the hypothalamus produce vasopressin and oxytocin and make many hormone-releasing factors that stimulate or inhibit the release of trophic hormones from the anterior pituitary that subsequently stimulate endocrine tissues to grow and release hormones. At the base of the hypothalamus, a projection known as the *median eminence* is rich with nerve axons and blood vessels and provides both chemical and physical connections between the hypothalamus and the pituitary gland.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

SECTION 11 GYNECOLOGIC AND OBSTETRIC DISORDERS

95

Pregnancy and Lactation: Therapeutic Considerations

Julie J. Kelsey and Kristina E. Ward

KEY CONCEPTS

1. Complex physiology surrounds the process of fertilization and pregnancy progression.
2. Drug characteristics and physiologic changes modify drug pharmacokinetics during pregnancy, including changes in absorption, protein binding, distribution, and elimination, requiring individualized drug selection and dosing.
3. Although drug-induced teratogenicity is a serious concern during pregnancy, most drugs required by pregnant women can be used safely. Informed selection of drug therapy is essential.
4. Healthcare practitioners must know where to find and how to evaluate evidence related to the safety of drugs used during pregnancy and lactation.
5. Health issues influenced by pregnancy, such as nausea and vomiting, can be treated safely and effectively with nonpharmacologic treatment or carefully selected drug therapy.
6. Some acute and chronic illnesses pose additional risks during pregnancy, requiring treatment with appropriately selected and monitored drug therapies to avoid harm to the woman and the fetus.
7. Management of the pregnant woman during the peripartum period not only can encompass uncomplicated pregnancies/deliveries, but can also include a wide variety of potential complications that require use of evidence-based treatments to maximize positive maternal and neonatal outcomes.
8. Understanding the physiology of lactation and pharmacokinetic factors affecting drug distribution, metabolism, and elimination can assist the

clinician in selecting safe and effective medications during lactation.

Preclass Engaged Learning Activity

Search the Food and Drug Administration (FDA) website (https://tinyurl.com/2ujhjm) for "Pregnancy and Lactation Labeling Rule." Choose one link to review and then summarize the key points about the new pregnancy and lactation labeling requirements. How do they differ from pregnancy categories? Do pregnancy categories still exist? This activity is useful to enhance student understanding about what type of pregnancy and lactation information to expect in drug product labeling.

INTRODUCTION

As drug use in pregnancy and lactation is a controversial and emotionally charged subject, due to medicolegal and ethical implications, it is often a topic underemphasized in the education of health professionals. However, clinicians are responsible for ensuring safe and effective therapy before conception, during pregnancy and parturition, and after delivery. Optimal treatments of illnesses during pregnancy sometimes differ from those used in the nonpregnant patient, and active patient participation in this process is essential.

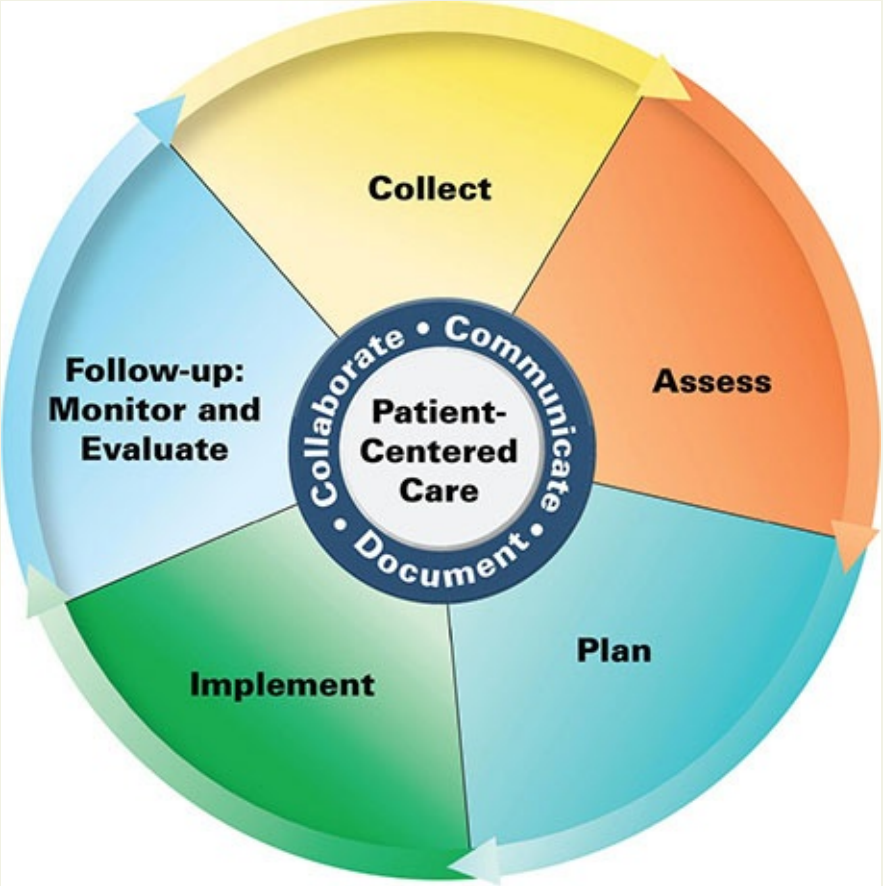
In many cases, medication dosing recommendations for acute or chronic illnesses in pregnant women are the same as for the general population. However, some cases require different dosing and selection of medications. Principles of drug use during lactation, although similar, are not the same as those applicable during pregnancy.

PHYSIOLOGY OF PREGNANCY

1 Fertilization and progression of pregnancy are complex, resulting in survival of only approximately 50% of embryos.[1] Because most losses occur early, usually in the first 2 weeks after fertilization, many women do not realize they were pregnant. Spontaneous loss of pregnancy later in gestation (ie, after 12 weeks) occurs in about 15% of pregnancies.[1]

Fertilization occurs when a sperm attaches to the outer protein layer of the

egg, the zona pellucida, and renders the egg nonresponsive to other sperm.[2] The attached sperm releases enzymes that allow the sperm to fully penetrate the zona pellucida and contact the egg's cell membrane. The membranes of the sperm and egg then combine to create a new, single cell called a *zygote*. Male and female chromosomes join in the zygote, fuse to create a single nucleus, and organize for cell division.



Patient Care Process for the Management of Gestational Diabetes

Collect

- Patient characteristics (eg, age, race)
- Characteristics of the pregnancy (eg, gestational age, gravidity and parity, weight gain to date)
- Characteristics of previous pregnancy(ies) (eg, prior gestational diabetes, birth weight of previous children, unexplained fetal demise)

- Patient history (past medical, family, social habits, physical activity habits, dietary discretion, her birth weight)
- Current medications (including complementary or alternative therapies) and adherence to medication schedules
- Social and cultural issues: preferences, values, and beliefs; health literacy
- Physical exam: height, weight, body mass index (BMI), blood pressure, heart rate
- Labs (A1C if at high risk, urine dipstick results for glucose, protein, and albumin)

Assess*

- High-risk factors and need for early screening and diagnosis (see Table 95-2)
- Screening and diagnostic testing between 24 and 28 weeks gestation (see Table 95-2)
- Achievement of target fasting and 2-hour postprandial glucose goals
- Efficacy and adherence to dietary modifications and current antihyperglycemic regimen and alternative therapies
- Achievement of goals for comorbidities (eg, blood pressure)
- Assess for depression, anxiety regarding treatment, dietary habits
- Screen for psychosocial problems and barriers to diabetes self-management

Plan

- Set appropriate blood glucose goals based on age, comorbidities, and other factors
- Tailored lifestyle modifications (eg, diet, exercise)
- Drug therapy regimen including specific antihyperglycemic agent(s), dose, route, frequency, and duration
- Monitoring parameters including efficacy (eg, self-monitored blood glucose[SMBG]), safety (medication-specific adverse events, hypoglycemia), and timeframe
- Patient education (eg, purpose of treatment, drug administration, dietary and lifestyle modifications)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence to the treatment plan
- Schedule follow-up clinic visits to adjust the treatment plan and monitor and evaluate adverse effects
- Determine glucose goal attainment
- Obtain fetal growth and estimated weight via ultrasound
- Encourage screening at 6 week postpartum visit and periodically throughout life

** Collaborate with patient, caregivers, and other healthcare professionals.*

Fertilization usually occurs in the fallopian tube.[3] The fertilized egg travels down the fallopian tube over 2 days, with cell division taking place. By day 3, the fertilized egg reaches the uterus. Cell division continues for another 2 to 3 days in the uterine cavity before implantation. Approximately 6 days after fertilization, the cell mass is termed a *blastocyst*. Human chorionic gonadotropin (hCG) can be detected in maternal urine 8 or 9 days after ovulation.[3] Implantation begins with the blastocyst sloughing the zona pellucida to rest directly on the endometrium, allowing initiation of growth into the endometrial wall. By day 10 postfertilization, the blastocyst is implanted under the endometrial surface and receives nutrition from maternal blood. On the first day of the third week postfertilization, it is called an *embryo*.[4,5]

After the embryonic period (between weeks 2 and 8 postfertilization), the embryo is renamed a *fetus*. Most body structures are formed during the embryonic period, and they continue to grow and mature during the fetal period. The fetal period continues until the pregnancy reaches term, approximately 40 weeks after the last menstrual period.[5]

Gravidity is the number of times that a woman has been pregnant. A multiple birth is counted as a single pregnancy. *Parity* refers to the number of pregnancies exceeding 20 weeks of gestation and relates information regarding the outcome of each pregnancy. In sequence, the numbers reflect (a) term deliveries, (b) premature deliveries, (c) aborted pregnancies, and (d) number of living children. For example, in a woman who has been pregnant four times; has experienced two term deliveries, one premature delivery, and one ectopic pregnancy; and has

three living children would be designated G_4P_{2113}.[3,6]

Characteristics of Pregnancy

Pregnancy lasts approximately 280 days (about 40 weeks or 9 months) with the time period being measured from the first day of the last menstrual period to birth. *Gestational age* refers to the age of the embryo or fetus beginning with the first day of the last menstrual period, which is about 2 weeks prior to fertilization. When calculating the estimated due date, add 7 days to the first day of the last menstrual period then subtract 3 months. Pregnancy is divided into three periods of 3 calendar months, each called a *trimester*.[3]

Early symptoms of pregnancy include fatigue and increased frequency of urination. After the first or second missed menstrual period, nausea and vomiting can occur. While commonly called *morning sickness*, this is a misnomer as it can happen at any time of the day; however, it usually resolves at 14 to 16 weeks of gestation. A pregnant woman can feel fetal movement in the lower abdomen at 14 to 20 weeks of gestation; multiparous women feel movement earlier than women who are primiparous. Signs of pregnancy include cessation of menses, change in cervical mucus consistency, bluish discoloration of the vaginal mucosa, increased skin pigmentation, and anatomic breast changes.[3,6]

Pharmacokinetic Changes During Pregnancy

2 Normal physiologic changes that occur during pregnancy may alter medication effects, resulting in the need to more closely monitor and, sometimes, adjust therapy. Physiologic changes begin in the first trimester and peak during the second trimester. For medications that can be monitored by blood or serum concentration measurements, monitoring should occur throughout pregnancy due to the many changes that occur during this time.

During pregnancy, maternal plasma volume, cardiac output, and glomerular filtration increase by 30% to 50% or higher, potentially lowering the concentration of renally cleared drugs.[7,8] With changes in maternal plasma volume and body weight, the volume of distribution of drugs may be affected. Plasma albumin concentration decreases, which increases the volume of distribution of drugs that are highly protein bound. However, unbound drugs are more rapidly cleared by the liver and kidney during pregnancy, resulting in little change in concentration. Hepatic perfusion also increases, which could theoretically increase the hepatic extraction of drugs; activity of metabolic

enzymes and drug transporters changes during pregnancy. Activity of cytochrome P450 3A4, 2C9, and 2D6 is increased while that of 1A2 is decreased.[7,9] Nausea and vomiting, as well as delayed gastric emptying, may alter the absorption of drugs. Hydrochloric acid secretion in the stomach is variable during pregnancy; however, gastrin production is increased, which increases gastric acidity and may affect absorption of drugs.[8]

Transplacental Drug Transfer

2 Although once thought to be a barrier to drug transfer, the placenta is the organ of exchange between the mother and fetus for a number of substances, including drugs. Most drugs move from the maternal circulation to the fetal circulation by diffusion.[10] Certain chemical properties, such as lipid solubility, electrical charge, molecular weight, and degree of protein binding of medications, may influence the rate of transfer across the placenta.

Drugs with molecular weight less than 500 Da readily cross the placenta, whereas larger molecules (600–1,000 Da) cross more slowly.[10] Drugs with molecular weight greater than 1,000 Da, such as insulin and heparin, do not cross the placenta in significant amounts. Lipophilic drugs, such as opioids and antibiotics, cross the placenta more easily than do water-soluble drugs. Maternal plasma albumin progressively decreases, while fetal albumin increases during the course of pregnancy, which may result in higher concentrations of certain protein-bound drugs in the fetus. Fetal pH is slightly more acidic than maternal pH, permitting weak bases to more easily cross the placenta. Once in the fetal circulation, the molecule becomes more ionized and less likely to diffuse back into the maternal circulation.[10]

DRUG SELECTION DURING PREGNANCY

3 Many misconceptions exist regarding the association of medications and birth defects. Although some drugs have the potential to cause teratogenic effects, most medications required by pregnant women can be used safely.

The baseline risk for congenital malformations is approximately 3% to 6%, with approximately 3% considered severe.[11,12] Medication exposure is estimated to account for less than 1% of all birth defects, as genetic causes are responsible for 15% to 25%, other environmental issues (eg, maternal conditions and infections) account for 10%, and the remaining 65% to 75% of congenital

malformations result from unknown causes.[11,12]

Factors such as the stage of pregnancy during exposure, medication route of administration, and dose can also affect outcomes.[12] In the first 2 weeks following conception, exposure to a teratogen may result in an “all-or-none” phenomenon, which could either destroy the embryo or cause no problems.[13] Organogenesis occurs during the embryonic period when organ systems are developing; therefore, teratogenic exposures may result in structural anomalies. For the remainder of the pregnancy, exposure to teratogens may result in growth retardation, central nervous system (CNS) abnormalities, or death. Examples of medications associated with teratogenic effects in the period of organogenesis include chemotherapy drugs (eg, methotrexate and cyclophosphamide), sex hormones (eg, androgens and progestational drugs), lithium, retinoids, thalidomide, certain antiepileptic drugs, and coumarin derivatives. Other medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and tetracycline derivatives, are more likely to exhibit effects in the second or third trimester.

Medications are necessary during pregnancy for treatment of acute and chronic conditions. Identifying patterns of medication use before conception, eliminating nonessential medications and discouraging self-medication, minimizing exposure to medications known to be harmful, and adjusting medication doses are all strategies to optimize the health of the mother while minimizing the risk to the fetus. In summary, a small number of medications have the potential to cause congenital malformations, and many can be avoided during pregnancy. In situations where a drug may be teratogenic but is necessary for maternal care, considerations related to route of administration, dosage form, and dosing may lessen the risk.

Methods and Resources for Determining Drug Safety in Pregnancy

4 When assessing the safety of using medications during pregnancy, evaluation of the quality of the evidence is important. Ideally, safety data from randomized, controlled trials are most desirable, but pregnant women are not usually eligible for participation in clinical trials. Other types of data commonly used to estimate the risk associated with medication use during pregnancy include animal studies, case reports, case–control studies, prospective cohort studies, historical cohort studies, and voluntary reporting systems.

Animal studies are a required component of drug testing, but extrapolation of

the results to humans is not always valid.[14] A prime example of this is thalidomide which was found to be safe in some animal models, but proved to have significant teratogenic effects in human offspring. The value of case reports is limited because birth defects in the offspring of women who used medication during pregnancy may occur by chance.[14] Case–control studies identify an outcome (congenital anomaly), match subjects with or without that outcome, and report how often exposure to a suspected agent occurred. Recall bias is a concern, as women with an affected pregnancy may be more likely to remember drugs used during the pregnancy than those with a normal outcome.

Cohort studies that evaluate the intervention (use of a particular drug) in a group of persons and compare outcomes in a similar group of subjects without the intervention are also possible.[14,15] Prospective studies eliminate some of the problems with recall bias, but require time and large numbers of participants. Despite these disadvantages, cohort studies are often used for evaluating the effects of a drug exposure on pregnancy outcomes.

Teratology information services provide pregnant women with information about potential exposures during pregnancy and follow these women throughout the pregnancy to assess the outcomes of the pregnancy.[14] These services may publish pooled data to facilitate information sharing about medications used during pregnancy. Some pharmaceutical companies have organized voluntary reporting systems (also called pregnancy registries) for drugs used during pregnancy.

4 Computerized databases (eg, http://www.motherisk.org, LactMed [http://www.toxnet.nlm.nih.gov], http://reprotox.org), tertiary compendia, and textbooks with information from large cohorts of treated women offer valuable assistance. New information regarding drug use in pregnancy and lactation can be obtained from searches of the primary literature for cohort and case–control studies.

The FDA-approved product-labeling requirements for drugs approved after June 20, 2015 include a subsection for pregnancy that provides information about pregnancy exposure registries, a risk summary, clinical considerations, and supporting data. The lactation subsection provides information about drug use during lactation. A new subsection includes information for females and males of reproductive potential. Prescription drugs approved after June 30, 2001 are required to have updated product labeling to meet the new labeling requirements; use of the new requirements will be phased in gradually. Drugs approved before June 30, 2001 do not have to implement the new labeling requirements, but must remove the pregnancy category from product labeling by

the end of June 2018. Because of multiple limitations of the pregnancy risk categories (ie, A, B, C, D, X, with A considered safe and X considered teratogenic) previously used to guide clinicians regarding medication risk during pregnancy, risk categories remain in product labeling only for over-the-counter (OTC) medications.[16]

In summary, determining drug safety during pregnancy is limited by the quality of data and the types of study designs that can be used. While information from product labeling may provide a rough estimate of risks for medication-related adverse fetal outcomes, careful evaluation of other available information sources is necessary to make decisions about medication use in pregnant women.

PRECONCEPTION PLANNING

Pregnancy outcomes are influenced by maternal health status, lifestyle, and history prior to conception. The goal of preconception care is health promotion, through modification of behavioral, biomedical, and social risks in all women of reproductive age to ensure optimal health and improve pregnancy outcomes.[17] Almost half of all pregnancies in the United States are unintended. Preconception planning is important, since some behaviors and exposures impart risk to the fetus during the first trimester, often before prenatal care is begun or even before pregnancy is detected. **Table 95-1** lists selected preconception risk factors, the potential adverse pregnancy outcomes, and management or prevention options.

TABLE 95-1 Selected Preconception Risk Factors for Adverse Pregnancy Outcomes

Preconception Risk Factor	Potential Adverse Pregnancy Outcomes	Management or Prevention Options
Use of known teratogens		
• Antiepileptic drugs	• Known teratogens; causes craniofacial, cardiac, and limb defects[a] • NTD • Fetal hydantoin syndrome	• Use lowest possible dose to maintain control • Folic acid 4 mg daily
• Isotretinoins	• Spontaneous abortion • Known teratogen; causes CNS, craniofacial, and cardiac defects[a]	• Use effective pregnancy prevention/contraception • Discontinue at least 1 month before attempting conception
• Oral anticoagulants	• Fetal warfarin syndrome	• Switch to nonteratogenic anticoagulant (eg, LMWH) before becoming pregnant
Lifestyle factors		
• Alcohol misuse	• Fetal alcohol syndrome	• Cease alcohol intake before conception
• Obesity	• NTD • Preterm delivery • Diabetes, HTN, VTE • Cesarean section	• Weight loss with appropriate nutritional intake before pregnancy

• Tobacco use	• Preterm birth
	• Low birth weight
	• Spontaneous abortion
	• Increased perinatal mortality
		• Ideally, cease tobacco use before conception
		• Nonpharmacologic therapies (eg, CBT, counseling, hypnosis)
		• No consensus for NRT product, dosing, or frequency:
		  • Intermittent forms (eg, gum)
		  • Transdermal patch (limit to 16 h/day)
		  • Bupropion risk may be less than risk posed by smoking; efficacy unclear
		  • Varenicline safety unknown

[a]List is not all-inclusive.

CBT, cognitive behavioral therapy; CNS, central nervous system; HTN, hypertension; LMWH, low-molecular-weight heparin; NRT, nicotine replacement therapy; NTD, neural tube defect; VTE, venous thromboembolism.

Data from References 17–20.

The most common major congenital abnormalities are neural tube defects (NTDs), cleft palate and lip, and cardiac anomalies. Each year in the United States approximately 7 in 10,000 infants are born with NTDs.[18] Folic acid supplementation in women substantially reduces the incidence of NTDs in their offspring. This is also true in women who have previously delivered babies with NTDs, as they occur within the first month of conception due to neural tube closure occurring during the first month of pregnancy. Folic acid supplementation between 0.4 and 0.8 mg daily is recommended throughout a woman's reproductive years, since many pregnancies are unplanned and may not be recognized until after the first month.[18]

Use of alcohol and recreational drugs during pregnancy is also associated with birth defects.[19] Smoking can cause preterm birth, low birth weight, and other adverse outcomes. Between 2009 and 2010 in the United States, alcohol use, illicit drug use, and cigarette use were reported in 10.8%, 4.4%, and 16.3% of pregnant women ages 15 to 44 years, respectively.[19] Use of nicotine replacement during pregnancy is controversial, since its use is not supported by clinical trial data; however, nicotine replacement theoretically imparts less risk than exposure to the over 4,000 chemicals found in cigarettes.[20]

PREGNANCY-INFLUENCED ISSUES

Pregnancy causes or exacerbates conditions that pregnant women commonly experience, including constipation, gastroesophageal reflux, hemorrhoids, and nausea and vomiting. Women with pregnancy-influenced gastrointestinal (GI) issues can be treated safely with lifestyle modification or medications, many of them nonprescription. Gestational diabetes, gestational hypertension, and venous thromboembolism (VTE) have the potential to cause adverse pregnancy consequences. Gestational thyrotoxicosis (GTT) is usually self-limiting.

Gastrointestinal Tract

5 Constipation during pregnancy is prevalent, affecting almost 40% of women and may contribute to the development or exacerbation of hemorrhoids which are more prevalent in pregnant women compared with the general population.[21] Conservative treatment (ie, high dietary fiber intake, adequate oral fluid intake, and use of sitz baths) or moderate physical activity should be tried first. Laxatives, supplemental fiber, and stool softeners can be used if conservative management is inadequate for preventing or treating constipation. Bulk-forming agents (eg, psyllium, methylcellulose, and polycarbophil) are safe for long-term use because they are not absorbed. Osmotic laxatives (eg, polyethylene glycol, lactulose, and sorbitol) are safe and polyethylene glycol is considered by some to be preferred during pregnancy.[21] Stimulant laxatives (ie, senna and bisacodyl) are also used but bisacodyl should be reserved for short-term use.[22] Use of magnesium and sodium salts may cause electrolyte imbalance. Castor oil and mineral oil should be avoided because they cause stimulation of uterine contractions and impairment of maternal fat-soluble vitamin absorption, respectively.[21,22] Data supporting other management options for hemorrhoids during pregnancy are limited. Topical anesthetics, skin protectants, and

astringents (eg, witch hazel) can be used for anal irritation and pain. Hydrocortisone may reduce inflammation and pruritis.[23]

Between 40% and 85% of pregnant women experience gastroesophageal reflux disease. An algorithm starting with lifestyle and dietary modifications (eg, small, frequent meals; alcohol and tobacco avoidance; food avoidance before bedtime; elevation of the head of the bed) should be used.[21] If symptoms are not relieved, antacids (eg, aluminum, calcium, magnesium preparations) or sucralfate are acceptable. However, sodium bicarbonate, magnesium trisilicate, and large aluminum doses should be avoided. Histamine-2 (H_2) receptor blockers can be used for patients unresponsive to lifestyle changes and antacids; evidence supports the use of ranitidine and cimetidine. Literature evaluating the use of famotidine and nizatidine is limited, but they are likely safe.[21,22] The use of proton pump inhibitors (PPIs) during pregnancy does not appear to increase the risk of major birth defects; however, most data comes from use of omeprazole.[21,22] Since more data and clinical experience are available for H_2 antagonists, use of PPIs should be reserved for women with inadequate response to H_2 antagonists.

Nausea and vomiting of pregnancy (NVP) is estimated to affect up to 80% of pregnant women. NVP usually begins between weeks 4 and 6 of gestation and usually resolves by weeks 16 to 20 with peak symptoms occurring between weeks 8 and 12.[21] Hyperemesis gravidarum (HG; ie, unrelenting vomiting causing weight loss of more than 5% prepregnancy weight, dehydration, electrolyte imbalance, and ketonuria) occurs in 0.3% to 2% of women. Dietary modifications, such as eating frequent, small, bland meals, and avoiding fatty or spicy foods, may be helpful.[21] Applying pressure at acupressure point P6 on the volar aspect of the wrist may be beneficial.[24] Ginger has shown efficacy for hyperemesis in randomized, controlled trials and is probably safe. Pharmacotherapeutic approaches for NVP that have shown efficacy include pyridoxine (vitamin B_6), and antihistamines (including doxylamine). The American College of Obstetricians and Gynecologists (ACOG) considers pyridoxine alone or in combination with doxylamine first-line and this drug combination was approved by the FDA in 2013.[24] Antihistamine-1 agents and phenothiazines can also be used first-line, but may cause sedation. Metoclopramide is second-line because of its potential to cause extrapyramidal effects, including dystonia, and sedation. Conflicting data exist regarding ondansetron use. While recent studies showed no increase in risk of congenital anomalies, a large case–control study found an increased risk of oral clefts.[21,24]

Corticosteroids may be effective for HG; use should be reserved until after the first trimester because of a small increase in the risk of oral clefts.[24]

Gestational Diabetes

5 Gestational diabetes mellitus (GDM) is diabetes diagnosed in the second or third trimester that is not overt diabetes.[25] It develops in >9% of pregnant women in the United States.[26] Risks of GDM are many and include fetal loss, fetal macrosomia, and birth trauma. The American Diabetes Association (ADA) and a consensus panel of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommend universal screening of pregnant women not previously diagnosed with diabetes.[25,27]

At the first prenatal visit, all women considered high-risk for diabetes (eg, BMI > 25, high-risk race or ethnicity [lowest rate in Caucasian women], previous gestational diabetes, hypertension or cardiovascular disease, and strong history of diabetes) should be screened for overt diabetes which would indicate pregestational origin. Overt diabetes occurs if the A1C is greater than or equal to 6.5% (0.065; 48 mmol HbA1C/mol Hgb), fasting plasma glucose (FPG) ≥ 126 mg/dL (7.0 mmol/L), or 2-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT), or if random plasma glucose (RPG) ≥ 200 mg/dL (11.1 mmol/L) in a patient with hyperglycemic crisis or classic hyperglycemic symptoms. If overt diabetes is not diagnosed or for women not at high risk for diabetes, screening for GDM should occur at weeks 24 to 28 using either the one-step (75-g OGTT) or two-step (50-g, 1-hour glucose challenge test followed by a 100-g, 3-hour OGTT) method.[25,28] **Table 95-2** summarizes screening and diagnosis of GDM.

TABLE 95-2 Screening and Diagnosis of Gestational Diabetes Mellitus

One-Step Method		Two-Step Method	
Give	75-g OGTT[a]	***Step 1***	Give 50-g OGTT[b]
	If any plasma glucose levels are met or exceeded, GDM is diagnosed		
Fasting	≥92 mg/dL (5.1 mmol/L)	1-hour	≥130 mg/dL (7.2 mol/L), ≥135 mg/dL (7.5 mmol/L) or ≥140 mg/dL (7.8 mmol/L)[c]
			If plasma glucose level is met or exceeded, proceed to Step 2[d]
1-hour	≥180 mg/dL (10 mmol/L)	***Step 2***	Give 100-g OGTT[a]
			If two or more plasma glucose levels are met or exceeded, GDM is diagnosed
2-hour	≥153 mg/dL (8.5 mmol/L)		Carpenter–Coustan Method[e]
		Fasting	95 mg/dL (5.3 mmol/L)[d]
		1-hour	180 mg/dL (10 mmol/L)
		2-hour	155 mg/dL (8.6 mmol/L)
		3-hour	140 mg/dL (7.8 mmol/L)

[a]Perform with plasma glucose measurement in a fasting state. Should be performed in the morning after at least 8-hours of fasting.

[b]Perform with plasma glucose measurement in a fasting or nonfasting state.

[c]Threshold set by individual practices; lower thresholds equate to higher false-positive results.

[d]If > 200 mg/dL (11.1 mmol/L), diagnosis of GDM is made; do not proceed to step 2.

[e]Carpenter and Coustan developed diagnostic criteria for gestational diabetes that lowered diagnostic plasma glucose levels compared to the National Diabetes Data Group.

OGTT, oral glucose tolerance test.

Data from References 27 and 28.

Dietary modification (medical nutrition therapy), exercise, and blood glucose monitoring are considered first-line therapies for all women who have GDM, since as many as 85% of women can achieve control with these interventions.[29] Self-monitoring of blood glucose four times daily (fasting, and 1 or 2 hours after each meal) is recommended until normoglycemia, at which time monitoring may be modified.[28] Drug therapy should be initiated if glycemic control is not achieved with lifestyle interventions. Glycemic control is fasting capillary glucose concentrations at or below 95 mg/dL (5.3 mmol/L) along with one of the following: a 1-hour postprandial glucose at or below 140 mg/dL (7.8 mmol/L) or a 2-hour postprandial glucose of 120 mg/dL (6.7 mmol/L) or below.[29]

Human insulin is the drug of choice for diabetes management during pregnancy because it does not cross the placenta. The ACOG considers insulin the preferred agent for treatment of GDM. Metformin is an alternative for insulin in women who decline insulin therapy due to either cost or inability to use

injections. Metformin may be more effective than insulin in reducing the risks of neonatal intensive care unit (NICU) admission, neonatal hypoglycemia, and excessive fetal growth.[30] Nevertheless, more than 40% of women on metformin will require supplemental insulin to control their blood glucose.[28–30] Glyburide has been used as first-line therapy for GDM for many years; however, recent studies have shown it to be inferior to insulin therapy in preventing neonatal morbidity, including higher rates of NICU admission, respiratory distress, birth trauma, and excessive fetal growth.[28,31]

Evidence supporting dietary modification, self-monitored blood glucose, exercise, and pharmacologic interventions for women with GDM is limited. Treatment of GDM with nutritional education, blood glucose monitoring, and pharmacologic treatments (if needed) has been assocaited with decreased occurance of newborns that are large for their gestational age, macrosomia, and shoulder dystocia.[30]

Screening with a 2-hour OGTT at 6 weeks postpartum is recommended for all women diagnosed with GDM to diagnose type 2 diabetes not recognized prior to pregnancy.[28] Women with GDM are at much higher risk of developing type 2 diabetes later in life and periodic screening is suggested.[29]

Hypertensive Disorders of Pregnancy

5 Hypertensive disorders of pregnancy (HDP) complicate approximately 10% of pregnancies. Four categories of HDP are established: (1) preeclampsia, (2) chronic hypertension (HTN; pre-existing hypertension or developing before 20 weeks of gestation), (3) chronic HTN with superimposed preeclampsia, and (4) gestational HTN (HTN without proteinuria developing after 20 weeks of gestation).[32,33] Hypertension in pregnancy is defined as either systolic blood pressure (sBP) above 140 mm Hg or diastolic blood pressure (dBP) above 90 mm Hg based upon two or more measurements at least 4 hours apart.[34] Severe hypertension is two measurements of an sBP > 160 mm Hg and/or dBP > 110 mm Hg at least 15 minutes apart. Nondrug management of HDP centers on stress reduction and light exercise or activity restriction. Exercise for at least 50 minutes 3 days a week can reduce the incidence of hypertension threefold over women who are more sedentary.[35] No evidence indicates that either stress reduction or activity restriction improves pregnancy outcome, and prolonged bed rest may increase the risk of complications (eg, venous thromboembolic disease).[32] Use of supplemental calcium or vitamin D has been shown to

decrease the risk of preeclampsia by 51% (RR 0.49, 95% CI: 0.35,0.69).[36] Calcium supplementation was most effective in women with high-risk pregnancies when taken for a duration less than 18 weeks. The ACOG states that the findings are not applicable to populations with adequate calcium intake, such as in the United States.[33] Antihypertensive drug therapy is discussed under Chronic Illnesses in Pregnancy.

While preeclampsia develops after 20 weeks of gestation, up to 20% of chronic and 35% of gestational hypertensive pregnancies are complicated by preeclampsia.[32] Preeclampsia is a multisystem syndrome that complicates 2% to 8% of pregnancies and can cause poorer outcomes, including renal failure, maternal morbidity/mortality, preterm delivery, and intrauterine growth restriction.[32,34] Risk factors are presented in **Table 95-3**. It can be divided into early onset, prior to 34 weeks or requiring delivery prior to 37 weeks, or late onset. Early onset preeclampsia is typically severe in nature and associated with more maternal morbidity.[37] Diagnosis of preeclampsia includes elevated blood pressure as with HDP and proteinuria (≥300 mg/24 hours or a protein/creatinine ratio of ≥ 300 mg/g (approximately 30 mg/mmol) are preferred, or urine dipstick of 1+). If proteinuria is not present, new onset of any of the following with new onset HTN is indicative of severe preeclampsia: thrombocytopenia (count less than 100,000/μL [100 × 10^9/L]), serum creatinine above 1.1 mg/dL (97 μmol/L) or a doubling of serum creatinine, elevated liver transaminases at least twice the upper limit of normal, or cerebral or visual symptoms (eg, scotomata, headache).[37,38] Women may also experience chest pain or dyspnea, vomiting, and epigastric pain. Other signs and symptoms of preeclampsia that would warrant delivery include: severe uncontrolled hypertension, eclampsia, persistent severe headache, pulmonary edema, placental abruption, disseminated intravascular coagulation, and HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelets) or evidence of adverse fetal effects, such as growth restriction.[32–34] Treatment of hypertension in women with preeclampsia depends upon the blood pressure measurement and follows the same principles discussed under “Chronic Illnesses in Pregnancy.”

TABLE 95-3 Risk Factors for Preeclampsia

High-Risk Factors	Moderate-Risk Factors
Preeclampsia in a prior pregnancy	Multiple gestation
Antiphospholipid antibody syndrome	Nulliparity
Underlying medical conditions	Family history of preeclampsia or early onset cardiovascular disease
Chronic hypertension	Obesity (BMI > 35 kg/m^2)
Renal disease	Maternal age > 40
Diabetes mellitus	Ethnicity (black greater than Caucasian or Hispanic)

Data from References 32 and 34.

Low-dose aspirin (60–81 mg/day) beginning between 12 and 28 weeks gestation (preferably before 16 weeks) in women with one high-risk factor or at least two moderate-risk factors reduces the incidence of severe preeclampsia (RR 0.47, CI 0.26,0.83) and fetal growth restriction. This corresponds to treating 50 high-risk women to prevent one case of preeclampsia.[39] Decreased risks of intrauterine growth restriction (20%) and preterm delivery (14%) also result from low-dose aspirin use.[40] The only cure for preeclampsia is delivery of the placenta. Signs and symptoms of preeclampsia can occur until 6 weeks postpartum and women with a history of preeclampsia are at high risk of future cardiovascular complications.[34,41]

Preeclampsia may progress rapidly to eclampsia, which is the occurrence of tonic–clonic seizures superimposed on preeclampsia. Eclampsia is a medical emergency that can occur antepartum, intrapartum, or postpartum. It is often preceded by a headache and visual changes.[34] Magnesium sulfate decreases the risk of progression to eclampsia by 50%,[32] and it is recommended to prevent eclampsia as well as to treat eclamptic seizures. The usual dose of magnesium sulfate is 4 to 6 g IV over 15 to 20 minutes followed by a 2 g/h continuous infusion. Duration of use varies, but the usual duration is throughout active labor and 12 to 24 hours postpartum. Diazepam and phenytoin should be avoided.[32,41]

Thyroid Abnormalities

5 Pregnant women with overt hyperthyroidism should be treated with a thioamide (ie, methimazole and propylthiouracil [PTU]), and those with overt hypothyroidism should receive thyroid replacement (ie, levothyroxine).[42]

During pregnancy, stimulation of the thyroid gland may occur because of hCG's structural similarity to thyroid-stimulating hormone (TSH; thyrotropin). In some women, gestational transient thyrotoxicosis (GTT) may result. Occurrence of GTT is often associated with HG. By 20 weeks of gestation, GTT usually resolves as production of hCG declines. Treatment with antithyroid medication is not usually needed.[42] Nausea and vomiting can be treated as for patients without this pseudo-hyperthyroid state.

Although not all women experience postpartum thyroiditis (PPT) similarly, the typical presentation is characterized by transient hyperthyroidism during the first several months postpartum, a period of transient hypothyroidism between 4 and 8 months postpartum, and, finally, euthyroidism within 1 year. The initial hyperthyroid state usually does not require treatment; however, β-blockers (propranolol, starting at 10–20 mg daily as needed) can provide symptomatic relief of adrenergic symptoms. Because PTT is from a destructive inflammation process and not overproduction of thyroid hormone, antithyroid drugs are ineffective. Levothyroxine replacement is suggested for a total of 6 to 12 months.[42] Up to one-third of women affected by PPT develop permanent hypothyroidism.

Thromboembolism

5 Thromboembolism is the most common cause of maternal death in developed countries. The risk of VTE in pregnant women is increased by fivefold to tenfold over nonpregnant women and increases to 15- to 35-fold during the first 6 weeks postpartum.[43] Low-molecular-weight heparin (LMWH) is recommended over unfractionated heparin (UFH) and warfarin for treatment of acute thromboembolism during pregnancy. Treatment should be continued throughout pregnancy and for 6 weeks after delivery; the minimum total duration should not be less than 3 months. Fondaparinux and injectable direct thrombin inhibitors (eg, lepirudin and bivalirudin) should be avoided unless a severe allergy to heparin (eg, heparin-induced thrombocytopenia) is present. The novel oral anticoagulants (eg, dabigatran, rivaroxaban, apixaban, and edoxaban) are not recommended.[43] Warfarin is not used because it causes nasal hypoplasia, stippled epiphyses, absence of the corpus callosum, eye abnormalities, microcephaly, fetal bleeding, and fetal demise at all stages of pregnancy. The risk period appears to be between 6 and 12 weeks of gestation, with the CNS anomalies being associated with second- and third-trimester exposure.

Recurrent VTE is divided into three categories: low risk, intermediate risk,

and high risk of recurrence. Antepartum monitoring is recommended for women with a single episode of VTE who have a low risk of recurrence such as those with one transient risk factor (ie, surgery, injury, lengthy travel, or immobility). For intermediate risk (ie, hormone-related, pregnancy-related, or unprovoked VTE) and high risk (ie, more than one unprovoked VTE or continuous risk factors), antepartum prophylaxis with LMWH plus 6-week postpartum prophylaxis with either LMWH or warfarin is recommended. Specific recommendations for thrombophilias (eg, antiphospholipid antibodies, Factor V Leiden, prothrombin G20201A, protein C and S deficiencies) can be found in the ACOG Practice Bulletin addressing thromboembolism in pregnancy.[44]

Women with mechanical heart valves should receive warfarin during pregnancy despite the teratogenic risk, as it appears to be lower with doses < 5 mg than with doses over 5 mg, and women can continue low-dose warfarin therapy during the first trimester. Women taking higher doses should be offered the option to use LMWH or UFH every 12 hours. Dose adjustment should be made to achieve a peak anti-Xa at 4 hours of 0.8 to 1.2 U/mL (kU/L) or a mid-interval aPPT at least twice the control value, respectively. The risk of warfarin teratogenicity ranges from 3.7% to 6.4% when used throughout the entire pregnancy.[45] Additionally women with mechanical heart valves should also receive low-dose aspirin (81–100 mg/daily).[45] Women with prosthetic valves have a lower risk of thromboembolism than those with mechanical valves; however, management of anticoagulation during pregnancy is similar. Warfarin appears to be superior to LMWH or UFH, so women can be offered warfarin after receiving LMWH or UFH during the first trimester.[46] Around 36 weeks, warfarin should be discontinued and therapy with a heparin should be initiated until delivery.

ACUTE CARE ISSUES IN PREGNANCY

In some cases, the risks associated with acute illness are magnified during pregnancy, and early screening and treatment become critical. In other cases, such as during treatment of certain sexually transmitted infections (STIs), the urgency regarding treatment comes from an increased likelihood of infection leading to preterm labor. Occasionally, common acute care issues, such as migraine headache, improve during pregnancy.

Urinary Tract Infection

6 The most common infections in pregnant and nonpregnant women are urinary tract infections (UTIs). Typically, UTIs are characterized as asymptomatic (eg, asymptomatic bacteriuria) or symptomatic (eg, lower [cystitis] or upper [pyelonephritis]). *Escherichia coli* is the primary cause of infection in 70% to 80% of cases. Other gram-negative rods, such as *Enterobacter*, *Klebsiella*, and *Proteus*, as well as Group B *Streptococcus* (GBS) account for some infections.[47] The presence of GBS in the urine indicates heavy colonization of the genitourinary tract, increasing the risk for GBS infection in the newborn.

The incidence of asymptomatic bacteriuria ranges from 2% to 10%. Untreated, bacteriuria progresses to pyelonephritis in approximately 40% of pregnant women.[47] Multiple organizations based in the United States recommend screening pregnant women for asymptomatic bacteriuria, although the timing is not universally agreed upon. Screening should occur early in pregnancy up to 16 weeks gestation with the urine culture being the gold standard. Use of rapid screening tests, such as dipsticks, should be avoided because of the potential for false-negative results, as the test is specific, but not sensitive.[47] Acute cystitis occurs in about 1% to 2% of pregnant women. Signs and symptoms of acute cystitis include urgency, frequency, hematuria, pyuria, and dysuria.[47]

Treatment of asymptomatic bacteriuria and acute cystitis is necessary to prevent pyelonephritis and preterm delivery; however, the agents of choice and treatment duration are not well defined. As no specific treatment appears superior to other commonly used treatments, local antibiograms should be used to direct empiric treatment. Treatment courses for asymptomatic bacteriuria and cystitis of 3 to 7 days are common.[47,48]

Beta-lactams (including penicillins and cephalosporins) have been widely used to treat asymptomatic bacteriuria and cystitis; nitrofurantoin is considered first-line by ACOG.[47,48] Beta-lactams are not known teratogens; however, increasing resistance to ampicillin and amoxicillin limits their use as single agents. Nitrofurantoin is not active against *Proteus* species and should not be used after week 37 in patients with glucose-6-phosphate dehydrogenase deficiency because of a theoretical risk for hemolytic anemia in the neonate. Sulfa-containing drugs can contribute to the development of newborn kernicterus; use should be avoided during the last weeks of gestation. Trimethoprim is a folate antagonist and is relatively contraindicated during the first trimester because of associations with cardiovascular malformations. Regionally, increased rates of resistance to trimethoprim-sulfa may limit its use.

Fluoroquinolones and tetracyclines are contraindicated because of potential associations with impaired cartilage development and deciduous teeth discoloration (if given after 5 months of gestation), respectively.[47]

Patients with pyelonephritis usually present with bacteriuria and systemic symptoms of costovertebral angle tenderness, dysuria, fever, flank pain, nausea, and vomiting. Complications of pyelonephritis include premature delivery, low infant birth weight, and maternal morbidity (eg, hypertension, anemia, acute kidney injury, sepsis, and acute respiratory distress syndrome). Hospitalization is the standard of care for pregnant women with pyelonephritis. Inpatient therapy has included parenteral administration of second- or third-generation cephalosporins (eg, cefuroxime and ceftriaxone), ampicillin plus gentamicin, or ampicillin–sulbactam. Switching to an oral antibiotic can be considered after the patient has been afebrile for 48 hours; nitrofurantoin should be avoided because it does not achieve therapeutic levels outside of the urine. Outpatient antibiotic therapy can be considered after initial inpatient observation in women who are afebrile and less than 24 weeks of gestation.[47] The total duration of antibiotic therapy for acute pyelonephritis is controversial with some recommending 7 to 14 days and others recommending 10 to 14 days.[47,49] Suppression therapy can be considered for use until week 37 of gestation.[47]

Sexually Transmitted Infections

6 Sexually transmitted infections in pregnant women range from infections that may be transmitted across the placenta and infect the infant prenatally (eg, syphilis) to organisms that may be transmitted during birth and cause neonatal infection (eg, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, or herpes simplex virus [HSV]) to infections that pose a threat for preterm labor (eg, bacterial vaginosis [BV]). Initial screening during the first prenatal visit is recommended for human immunodeficiency virus (HIV), hepatitis B surface antigen, and syphilis. Women younger than 25 years and older women with increased risk (eg, new sex partner, two or more sex partners, non-monogamous sex partner, or sex partner with an STI) should be screened for *C. trachomatis* and gonorrhea; women at high risk for hepatitis C should also be screened during the first prenatal visit.[50] Treatment for select STIs is summarized in **Table 95-4**.

TABLE 95-4 Management of Sexually Transmitted Infections in Pregnancy

STI	Drug Name (Brand Name)	Usual Dose	Monitoring	Comments
Bacterial vaginosis	*Recommended:* Metronidazole (Flagyl) **OR** Metronidazole 0.75% gel *Alternatives*[a]: Clindamycin (Cleocin)	 500 mg by mouth two times daily × 7 days 5 g intravaginally once daily × 5 days	Follow-up testing not required if symptoms resolve	No link between intravaginal clindamycin and newborn complications Oral or vaginal preparations can be used
Chlamydia	*Recommended:* Azithromycin (Zithromax) *Alternatives*[a]: Amoxicillin (Amoxil) Erythromycin base Erythromycin ethylsuccinate	 1 g by mouth × 1 dose	Test-of-cure at 3–4 weeks after therapy completion; retest all after 3 months	Gonorrheal coinfection common; both are treated concurrently Chlamydia is asymptomatic in men and women Women below age 25 years and those at high risk should be retested in the third trimester
Genital herpes	*Recommended:* Acyclovir (Zovirax) **OR** Valacyclovir	 400 mg by mouth three times a day 500 mg by mouth twice a day	Routine serologic testing for HSV-2 is not recommended	Start treatment at 36 weeks of gestation
Gonorrhea	*Recommended:* Ceftriaxone (Rocephin) *PLUS* Azithromycin (Zithromax)	 250 mg IM × 1 dose 1 g by mouth × 1 dose	Because of high reinfection rate, repeat testing for gonorrhea 3 months after treatment	Chlamydial coinfection common; both are treated concurrently Consult with infectious disease specialist in case of cephalosporin allergy
Syphilis[a]				
Primary, secondary, early latent	*Recommended:* Benzathine penicillin G (Bicillin L-A)	 2.4 million units IM × 1 dose; a second dose can be given 1 week after initial dose	Nontreponemal serologic evaluation[b] at 6 and 12 months	For treatment failure or reinfection, use same drug and dose but increase to 3 weekly doses unless neurosyphilis is present
Tertiary, late latent	*Recommended:* Benzathine penicillin G (Bicillin L-A)	 2.4 million units IM × 3 doses at 1-week intervals	Nontreponemal serologic evaluation[b] at 6, 12, and 24 months. CSF examination may be required	Use this regimen for late latent or latent syphilis of unknown duration
Neurosyphilis	*Recommended:* Aqueous penicillin G (Pfizerpen) *Alternative*[c]: Procaine penicillin (Wycillin, Pfizerpen-AS) *PLUS* Probenecid	3-4 million units IV every 4 hours or 18-24 million units IV continuously × 10-14 days 2.4 million units IM daily × 10-14 days 500 mg by mouth four times daily × 10-14 days	If initial elevation of leukocytes in CSF, repeat CSF examination every 6 months until normalization	Consider repeat treatment if CSF leukocytes or protein do not normalize after 2 years Use alternative regimen only if compliance can be ensured
Trichomoniasis	*Recommended:* Metronidazole	2 g by mouth × 1 dose	Rescreen HIV patients at 3 months after treatment	While tinidazole is an alternative for nonpregnant women, avoid during pregnancy

[a]Pregnant women with history of penicillin allergy should undergo penicillin desensitization as no proven alternatives exist.

[b]Nontreponemal evaluation consists of VDRL (Venereal Disease Research Laboratory) and RPR (rapid plasma regain).

[c]Refer to Reference 50 for specific dosing recommendations.

CSF, cerebrospinal fluid; IM, intramuscular; STI, sexually transmitted infection.

Data from Reference 50.

Syphilis

Syphilis is caused by *Treponema pallidum*; complications are many (eg, mucocutaneous lesions, altered mental status, visual and auditory abnormalities, gumma, cranial nerve palsies). For women who live in areas with a high prevalence of syphilis, are at high risk, have not been previously tested, or had positive serology in the first trimester, additional serologic testing early in the third trimester (around 28 weeks) and at delivery is recommended.[50] With the exception of neurosyphilis, which is treated with aqueous penicillin G, the drug of choice for all stages of syphilis is benzathine penicillin G. If a penicillin allergy is present, women with IgE-mediated hypersensitivity can undergo desensitization. Penicillin effectively prevents transmission to the fetus and treats the fetus, if already infected. Treatment during the second half of pregnancy may increase the risk for preterm labor and fetal distress because a Jarisch–Herxheimer reaction may occur; however, treatment should not be withheld or delayed.[50]

Chlamydia and Gonorrhea

Chlamydia is the most commonly reported STI in the United States; complications of *C. trachomatis* include pelvic inflammatory disease (PID), ectopic pregnancy, and infertility. *C. trachomatis* infects the newborn through exposure to the infected cervix during delivery. Perinatal infection most commonly causes conjunctivitis that develops 5 to 12 days postpartum. A subacute, afebrile pneumonia with an onset at ages 1 to 3 months may occur.[50]

Gonorrhea, an STI caused by *N. gonorrhoeae,* is the second- most commonly reported notifiable infection in the United States.[50] In women, recognizable symptoms may be absent initially, but gonorrheal infection can cause PID, a known risk for infertility. Perinatal gonococcal infection results from exposure to the infected cervix during birth. Symptoms usually manifest within 2 to 5 days after delivery. Milder manifestations include rhinitis, vaginitis, and urethritis. More severe presentations include ophthalmia neonatorum and sepsis.[50] Identification and treatment of the infection in neonates is crucial, as permanent sequelae such as blindness can occur.

Antimicrobial resistance rates among *N. gonorrhoeae* are increasing, which has prompted the Centers for Disease Control and Prevention to remove oral cephalosporins as a preferred treatment option.[50] Coinfection with *C. trachomatis* is common; treatment of most *N. gonorrhoeae* infections includes

treatment for *C. trachomatis*.[50]

Bacterial Vaginosis and Trichomoniasis

Bacterial vaginosis (BV) and trichomoniasis are STIs characterized by vaginal discharge. BV results from the lack of normal vaginal flora (ie, *Lactobacillus* species) and replacement with anaerobic bacteria, mycoplasmas, and *Gardnerella vaginalis*.[50] It is a risk factor for premature rupture of membranes, preterm labor, preterm birth, intraamniotic infection, and postpartum endometritis. In women at high or low risk for preterm delivery, data to support routine screening for asymptomatic BV at the first prenatal visit are equivocal.[50]

Trichomoniasis is caused by the protozoa, *Trichomonas vaginalis*, and infection is associated with an increased risk of premature rupture of the membranes, preterm delivery, and low birth weight. Treatment may prevent respiratory or genital infection in the neonate.[50]

Genital Herpes

Genital herpes is a chronic disease most frequently caused by herpes simplex virus-2 (HSV-2), although the number of anogenital herpes infections caused by HSV-1 is increasing. Neonatal herpes often occurs in infants born to women lacking histories of genital herpes. The risk of neonatal transmission is under 1% for women with a history of recurrent herpes at term or those who acquire herpes in the first half of pregnancy, but is 30% to 50% for women who initially acquire genital herpes near term.[50] However, because recurrent herpes occurs more commonly than new acquisition during pregnancy, it remains the cause for most cases of neonatal transmission. Prevention strategies include counseling uninfected women to avoid intercourse during the third trimester with partners having known or suspected genital herpes infection. Women with no history of orolabial herpes should avoid receptive oral sex during the third trimester with partners who have orolabial herpes. Prevention of genital herpes transmission to pregnant women using antiviral agents has not been studied.[50]

All women should be asked about symptoms of genital herpes at the time of delivery and should be examined for lesions. Women who have no symptoms (including prodromal symptoms) or lesions proceed with vaginal childbirth; however, in those with evidence of an outbreak it is recommended that a cesarean section be performed to decrease the risk of neonatal transmission. Use of suppressive acyclovir late in pregnancy decreases recurrence of genital herpes at term, which decreases the need for cesarean delivery.[50]

Maternal use of acyclovir during the first trimester has not demonstrated an increased risk for birth defects. Valacyclovir is an alternative, but is more expensive.[50] For initial or recurrent episodes, most women receive oral acyclovir therapy; IV acyclovir is reserved for severe infections. In women seropositive for HSV but who have not experienced an outbreak, no data suggest a treatment benefit.[50]

Headache

6 Primary headaches (eg, tension and migraine) in pregnant and nonpregnant women are the most common types of headache. Secondary headaches can also occur and include those caused by eclampsia, stroke, postdural puncture, cerebral angiopathy, and cerebral venous thrombosis.[51]

Migraine headaches are associated with estrogen fluctuations in women of childbearing age. More than 50% of pregnant women with a history of migraine headaches experience symptom improvement during pregnancy and 20% experience complete cessation. Migraineurs may experience worsening in the first trimester and lessening in later stages of pregnancy.[52,53] Improvement is more likely in women who have migraine without aura and in women with a history of menstrual migraine. Women with menstrual migraine are more likely to have postpartum recurrence.[53] Tension headaches are less studied; however, most women report no change in the frequency or intensity of tension headaches, although remission is possible.

Relaxation, stress management, and biofeedback are all effective nonpharmacologic treatment methods that should be attempted in pregnant women with migraines and tension headaches because these interventions pose a minimal risk. For tension headache, acetaminophen or ibuprofen can be used if nonpharmacologic treatments fail. While NSAIDs use may increase the risk of spontaneous abortion when used immediately prior to pregnancy and early in the first trimester, their use after this period is safe; they are contraindicated in the third trimester because of the potential for premature closure of the ductus arteriosus. Aspirin in general is not recommended for use in pregnancy for pain relief.[53,54] Opioids are rarely used.[54]

Pharmacologic treatment for migraines involves use of analgesics (ie, acetaminophen and ibuprofen). Opioids have been used but may contribute to migraine-associated nausea. Long-term use near the end of pregnancy can cause neonatal withdrawal. For migraines that are not responsive to other treatments, triptans may be used as no increase in teratogenic effects has been seen with the

drug class.[55] Sumatriptan is the triptan of choice because it is the least likely to cross the placenta.[53] Ergotamine and dihydroergotamine are contraindicated because of effects on uterine tone. Promethazine, prochlorperazine, and metoclopramide can be used for patients who have migraine-associated nausea.[54]

Tension-type headaches do not usually require prophylaxis. Chronic, preventive treatment is reserved for women with severe headaches (usually migraines) that are not responsive to other treatments. Dietary supplements, such as riboflavin, Coenzyme Q10, and pyridoxine may be effective as pharmacologic prophylactic therapies.[53] The agent of choice is propranolol given at the lowest effective dose. Alternatives include tricyclic antidepressants with amitriptyline and nortriptyline (each dosed 10–25 mg by mouth daily) being preferred over the selective serotonin reuptake inhibitors (SSRI) or serotonin–norepinephrine reuptake inhibitors (SNRI) because data on safe use of these agents during pregnancy are conflicting.[54]

CHRONIC ILLNESSES IN PREGNANCY

For the majority of women and their healthcare providers, pregnancy is a new consideration for a previously diagnosed health condition. Medications used to treat the chronic illness can often be used throughout the pregnancy and during breastfeeding. See **Table 95-5** for treatment of chronic illnesses during pregnancy.

TABLE 95-5 Treatment of Chronic Illnesses in Pregnancy

Chronic Illness	Treatment	Comments
Allergic rhinitis	• Intranasal corticosteroids • Intranasal cromolyn • Antihistamines (chlorpheniramine, diphenhydramine, hydroxyzine)	Budesonide and beclomethasone most widely studied intranasal corticosteroids Second-generation antihistamines do not appear to increase fetal risk, but are less extensively studied than first-generation products Use of external nasal dilator, short-term topical oxymetazoline, or ICS is preferable to oral decongestants
Asthma Step 1 (intermittent) Step 2 and above (persistent)	 • SABA (albuterol) • SABA (albuterol) • Step-appropriate ICS • LABA	Budesonide is the preferred ICS, but any may be used Alternatives are cromolyn (less effective), leukotriene receptor antagonists (less experience in pregnancy), and theophylline (more potential toxicity) Systemic corticosteroids recommended to gain control in patients with most severe disease
Epilepsy	Probably Safest AEDs • Carbamazepine • Lamotrigine • Levetiracetam • Phenytoin Lower risk than VPA • Gabapentin • Oxcarbazepine • Zonisamide Significant risk greater than other AEDs • Phenobarbital • Topiramate • VPA	Polytherapy carries higher risk of major malformations than monotherapy Rates of major malformation with AEDs range between 0.7 and 10 per 100 exposures Phenytoin, phenobarbital, and topiramate may cause cleft palate Phenobarbital is associated with cardiac malformations Risk for most AED-associated malformations is dose-dependent
HIV	Currently receiving ART: • Continue current regimen if viral load is suppressed • ART-naïve, no evidence of resistance, preferred regimen: • Dual NRTI backbone PLUS • Ritonavir-boosted PI • Integrase inhibitor	ARV drug resistance testing should be performed to guide ART if HIV RNA is > 500 copies/mL (0.5×10^6/L) for ART-naïve women For women already receiving ART with virologic failure and HIV RNA > 1,000 copies/mL (1.0×10^6/L), ARV drug-resistance testing should be performed to inform change in ARV therapy
Hypertension, chronic	Initial treatment: • Labetalol • Nifedipine • Methyldopa	ACE inhibitors, ARBs, renin inhibitors, mineralocorticoid receptor antagonists are not recommended Atenolol has been associated with fetal growth restriction Thiazide diuretics theoretically lower the increase in plasma volume during pregnancy, but are considered second-line
Thyroid disorders	Hypothyroid • Levothyroxine • Hyperthyroid • PTU • Methimazole	For hypothyroidism, attain a TSH of 0.1–2.5, 0.2–3, and 0.3–3 milli-international units/L (mIU/L) in the first, second, and third trimester, respectively Use PTU in first trimester followed by switch to methimazole in second and third trimester to balance the risk of PTU-induced hepatotoxicity and methimazole embryopathy

ACE, angiotensin converting enzyme; AED, antiepileptic drug; ARB, angiotensin receptor blocker; ART, antiretroviral therapy; ARV, antiretroviral; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NTD, neural tube defects; PI, protease inhibitor; PTU, propylthiouracil; SABA, short-acting beta agonist; TSH, thyroid-stimulating hormone; VPA, valproic acid.

Data from References 34, 42, 56, 57, 60, 61, and 65–67.

Allergic Rhinitis and Asthma

6 Asthma and rhinitis are common chronic illnesses in pregnancy. Asthma affects approximately 8% of pregnancies.[56] During pregnancy, almost equal proportions of patients have symptoms that worsen, improve, or remain unchanged. Diagnosis and staging of asthma during pregnancy is the same as in nonpregnant women, although more frequent follow-up is necessary because of changes in disease severity. Bronchoprovocation using methacholine as well as allergen skin testing should be avoided.[56] Health consequences of untreated or poorly treated asthma include preterm labor, preeclampsia, intrauterine growth restriction, premature birth, low birth weight, and stillbirth; therefore, the treatment goal is to achieve and maintain control of asthma symptoms. Asthma is controlled when there are no daytime symptoms, limitations of activities, nocturnal symptoms, short-acting β_2-agonist use, or exacerbations, and there is normal pulmonary function.[56]

Risks of medication use to the fetus are lower than the risks of untreated asthma; therefore, use of medications to achieve and maintain control is warranted. Treatment recommendations are divided into multiple steps based on symptom control and follow a stepwise approach. Once control is achieved, maintenance of control at the lowest controlling step is the overall goal; however, stepping down may be delayed until after delivery because of the potential effects of exacerbation on pregnancy outcomes.[56]

Pre-existing or newly developed allergic rhinitis occurs during pregnancy. Notably, nasal congestion can be caused by pregnancy because of vascular engorgement in the nasal passages and hormonal effects on mucus secretion. Treatment strategies for allergic rhinitis during pregnancy are similar to those used in nonpregnant women and include avoidance of allergens, immunotherapy, and pharmacotherapy. Oral antihistamines and leukotriene receptor antagonists as well as intranasal antihistamines, decongestants (limit duration because of the risk for drug-induced rhinitis), cromones, and corticosteroids can be used. Oral corticosteroids and inhaled ipratropium should be reserved for patients inadequately controlled with other pharmacotherapy; oral corticosteroids should be of short duration to limit exposure to the fetus. Immunotherapy is not contraindicated in pregnancy, but dose increases during pregnancy are not advised in order to lessen the risk for anaphylaxis.[57]

Diabetes

6 Poorly controlled diabetes can cause fetal malformations, fetal loss, and maternal morbidity. Women with diabetes should use effective contraception and attempt pregnancy after optimal glycemic control has been achieved. During pregnancy, diabetic retinopathy may worsen, hypertension may develop, and renal function may deteriorate during pregnancy, requiring enhanced monitoring for these target-organ problems.[29,58]

Glycemic control can change dramatically during pregnancy and frequent adjustment to management may be needed. Medical nutrition therapy, consisting of an individualized nutrition plan, and supervised physical activity programs should continue. Self-monitored fasting and postprandial blood glucose should occur with preprandial monitoring recommended for women with pre-existing diabetes who use basal-bolus therapy or insulin pumps to allow for adjustment of rapid-acting insulin analogs before a meal.[29] For patients with type 1 or 2 diabetes insulin is the treatment of choice. However no data have shown the use of insulin analogs (eg, insulin aspart, insulin detemir, insulin glargine, insulin lispro) to cause major safety concerns in pregnancy, a finding confirmed in a recent meta-analysis.[59] For women who refuse insulin, metformin (and to a lesser extent, glyburide) can be considered; however, both cross the placenta and long-term safety information is limited.[28,59]

Epilepsy

6 Seizure frequency does not change for most pregnant women with epilepsy. At least 79% of women who have been seizure free for at least 9 months prior to pregnancy remain seizure free during pregnancy. Studies have demonstrated no frequency change in 44% of women with epilepsy, while decreased seizure frequency occurs in 17% and increased in approximately 38%.[60] Seizure relapses are most common in the first few days postpartum. Seizures may become more frequent because of changes in maternal hormones, sleep deprivation, and medication adherence problems due to perceived teratogenic risk. Another potential cause is changes in free serum concentrations of antiepileptic drugs resulting from increased maternal volume of distribution, decreased protein binding from hypoalbuminemia, increased hepatic drug metabolism, and increased renal drug clearance. A woman’s clinical condition and her free serum concentrations of antiepileptic drug should be the basis for dose adjustments.

The risks of uncontrolled seizures, particularly tonic–clonic seizures, to the fetus are considered to be greater than those associated with antiepileptic drugs. However, major malformations are two to three times more likely to occur in children born to women taking antiepileptic drugs than to those who do not.[61] Teratogenic effects with many anticonvulsants are related to the dose, often with a threshold above which risks increase.[62] Major malformations with valproic acid are dose related and range from 6% to 9%. Use of valproic acid should be avoided during pregnancy to minimize the risk of neural tube defects, facial clefts, and cognitive teratogenicity.[60] Topiramate and zonisamide have been associated with lower birth weights and length.[63]

When possible, antiepileptic drug monotherapy is recommended with medication regimen optimization occurring before conception. If gradual drug withdrawal is attempted because of epilepsy remission, it should be fully completed and evaluated before trying to conceive. Medication change to avoid use of valproic acid and phenobarbital is suggested; however, if either is used during pregnancy because of treatment failure with other medications, the lowest effective dose should be used.[61,62] All women taking antiepileptic drugs should receive folic acid supplementation: 4 to 5 mg daily starting before pregnancy and continuing through at least the first trimester, but preferably through the entire pregnancy.[60,61]

Human Immunodeficiency Virus Infection

6 The rate of perinatal HIV transmission is below 2% as a result of national recommendations for universal prenatal HIV counseling and testing, antiretroviral therapy (ART) use, cesarean delivery, and breastfeeding avoidance. The primary goal for HIV-infected women who receive combination ART and desire pregnancy is to achieve sustained viral load suppression below the limits of detection before conception and throughout pregnancy. In women newly diagnosed with HIV or who have not previously received ART, pharmacotherapy should be initiated as soon as pregnancy is determined since risk of perinatal transmission is lower with earlier viral suppression. The treatment regimen should be selected from those suggested for nonpregnant adults, with special consideration given to the teratogenic and pharmacologic profile of each drug.[64] Women currently receiving ART should be continued on their regimen, provided that viral suppression below the level of detection is documented.[65] For ART-naïve women, use of a three-drug combination regimen is recommended; however, recommendations regarding combination ART change frequently as

new data becomes available. The clinical guidelines provided at https://aidsinfo.nih.gov are the most up-to-date.

For pregnant women with HIV RNA levels above 1,000 copies/mL (1.0×10^6/L) who are approaching delivery, a scheduled cesarean section at 38 weeks of gestation is recommended to reduce the risk of perinatal HIV transmission. Scheduled cesarean section is not recommended if HIV RNA levels are 1,000 copies/mL (1.0×10^6/L) or below because of risks for increased complications and the low rate of perinatal transmission. If maternal viral load is greater than 1,000 copies/mL (1.0×10^6/L) or not known, IV zidovudine should be initiated with a 1-hour loading dose (2 mg/kg) followed by a continuous infusion (1 mg/kg) for 2 hours (cesarean) or until delivery (for vaginal delivery). Intravenous zidovudine should still be administered in the presence of resistance to oral zidovudine. Consider administration of IV zidovudine to women with a viral load between 50 and 1000 copies/mL ($0.05–1.0 \times 10^6$/L). Although there is inadequate information that zidovudine provides additional protection, there may be benefit as there is a slightly higher rate of transmission with a viral load in this range. Women with a viral load below 50 copies/mL (0.05×10^6/L) near delivery do not require IV zidovudine, but they should continue their ART. Specific recommendations for different clinical scenarios during antepartum, intrapartum, and postpartum are provided in the clinical guidelines.[65]

Hypertension

6 Typically, a physiologic decrease in blood pressure occurs during the first part of pregnancy, reaching its lowest point between 16 and 18 weeks of gestation. This decrease may mask undiagnosed hypertension. By the third trimester, blood pressure usually returns to prepregnancy levels. Hypertension occurring before 20 weeks of gestation, the use of antihypertensive medications before pregnancy, or the persistence of hypertension beyond 12 weeks postpartum defines chronic hypertension in pregnancy. It is classified as mild/nonsevere (sBP 140–159 mm Hg or dBP 90–109 mm Hg) or severe (sBP 160 mm Hg or greater or dBP 110 mm Hg or greater).[66] Women can be divided into low-risk and high-risk hypertensives, with the high-risk category indicating end-organ damage from long-standing hypertension.

Chronic hypertension can cause fetal growth restriction, maternal complications, and hospital admission. There is no consensus on treatment thresholds in women with mild hypertension. Aggressive treatment of dBP (goal < 85 mm Hg) has not been shown to alter pregnancy outcomes when compared

to a goal < 100 mm Hg. Progression to preeclampsia is more likely with less aggressive treatment.[67] According to ACOG, drug therapy is recommended for women with persistent chronic hypertension with a blood pressure of 160/105 mm Hg and above. If no evidence of end-organ damage is present and sBP is below 160 mm Hg and dBP is below 105 mm Hg, pharmacologic treatment is not suggested.[33] When antihypertensive medication is used, maintenance of sBP between 120 and 160 mm Hg and dBP between 80 and 105 mm Hg is recommended.[33] No international consensus on management of chronic hypertension exists as definitions and recommendations vary.

Sustained severe hypertension in pregnancy requires treatment as maternal end-organ complications, such as stroke, can occur. Lowering of blood pressure should occur over a period of hours to prevent compromise of uteroplacental blood flow. Initial choice of pharmacologic agent varies, but recommended agents are parenteral labetalol and hydralazine; however, hydralazine is associated with more maternal and fetal adverse effects. Oral nifedipine may also be used.[68] Although still commonly used, limited evidence supports the use of magnesium sulfate to lower blood pressure except when being used concomitantly for preeclampsia. Nitroprusside, diazoxide, and nitroglycerin should be reserved for refractory hypertension in an appropriately monitored environment.[68]

Mental Health Conditions

6 Psychiatric illness affects approximately 500,000 pregnancies each year according to a practice guideline reaffirmed by ACOG in 2018.[69] Anxiety disorders, including panic disorder, obsessive-compulsive disorder, generalized anxiety disorder, posttraumatic stress disorder, social anxiety disorder, and phobias, can cause adverse maternal and fetal outcomes such as spontaneous abortion, preterm delivery, prolonged labor, and fetal distress.[69]

Depression occurs in approximately 20% of pregnant women.[70] Maternal depression is associated with greater risk for premature birth, low birth weight, miscarriage, and fetal growth restriction.[71] In addition to the potential impact of maternal depression on obstetric complications, untreated depression may have long-term implications for normal infant development.[69] Up to 3% of Americans have bipolar disorder, with men and women equally affected; the incidence in pregnancy is unclear although perinatal episodes tend toward depressive manifestations.[72] Schizophrenia occurs in 0.7% to 1% of women; however, the

incidence in pregnancy is unknown. Maternal schizophrenia is associated with increased risk of low birth weight, small-for-gestational-age infants, cardiovascular malformations, preterm delivery, stillbirth, and infant death.[69]

Up to 70% of women with mental health conditions discontinue or refuse treatment because of concerns about teratogenicity or because of paranoid or delusional thinking.[73] Therefore, the risks and benefits of psychotropic medication use during pregnancy must be discussed with the patient. Because most psychotropic medications are used to treat more than one condition, the reader should refer to other chapters for information about treatment of specific mental health diagnoses (see Psychiatric Disorders Section). In general, monotherapy is preferred over polytherapy even if higher doses are required.[69]

Through 2005, the use of SSRIs was considered relatively safe. Conflicting studies about the risk of cardiac malformations with paroxetine are published in the literature; however, if absolute risk is increased with paroxetine use, it appears small and clinically insignificant.[71,74] Despite this association, SSRIs are not considered major teratogens, as no consistent information supports an association with structural malformations,[71] and risks with SNRIs are less defined. Use of SSRIs and SNRIs in the latter part of pregnancy is causally associated with persistent pulmonary hypertension of the newborn and neonatal adaptation syndrome which encompasses cardiac, respiratory, neurological, GI, and metabolic complications from drug toxicity or withdrawal of drug therapy.[75] Tricyclic antidepressants were commonly used in pregnancy before the introduction of SSRIs and are not considered major teratogens, although they have also been associated with a neonatal withdrawal syndrome when used late in pregnancy.[69,73,76] Importantly, women who stop taking antidepressants are more likely to relapse, which can also have implications for the well-being of the fetus.

Studies completed over 30 years ago showed an increased risk of oral clefts with diazepam use during pregnancy; these findings were not confirmed in a meta-analysis that found the absolute risk of oral cleft changed from six cases to seven cases per 10,000 exposures (0.01%).[69] Benzodiazepine use in the third trimester can cause infant sedation and withdrawal symptoms (eg, restlessness, hypertonia, hyperreflexia, tremulousness, apnea, diarrhea, and vomiting). “Floppy baby syndrome,” consisting of low Apgar scores, hypothermia, poor muscle tone, feeding difficulties, and poor temperature adaptation, has also been described.[69]

Mood stabilizers, such as lithium, lamotrigine, carbamazepine, and valproic

acid, are often used to treat bipolar disorder.[69] The reader can find information related to the safety of seizure medications used for mood stabilization in Chapter 95. Lithium's place in the treatment of bipolar disorder during pregnancy is controversial because of concerns about cardiovascular anomalies, especially Ebstein's anomaly, in exposed infants.[69] It appears that the risk of cardiac malformation increases with doses higher than 900 mg daily with a risk ratio of 3.22. Risk with lower doses was not significant when compared to no therapy. Stated differently, for every 100 live births in women taking lithium during the first trimester, there would be up to two more cases of cardiac malformations compared to women not exposed to lithium.[77] It is no longer considered a major human teratogen, but careful monitoring of serum lithium concentrations along with renal and thyroid function during pregnancy is prudent.[74,78] Other reported neonatal side effects include floppy baby syndrome, nephrogenic diabetes insipidus, hypoglycemia, cardiac arrhythmias, thyroid dysfunction, polyhydramnios, and premature delivery. Lithium may cause lethargy, hypotonia, hypothermia, cyanosis, and changes in electrocardiogram in infants exposed through breastfeeding. If breastfeeding, the infant's lithium levels, thyroid function, and complete blood count should be monitored.[69]

While neither the typical nor atypical antipsychotics have been adequately studied for the risk of adverse pregnancy outcomes, the typical antipsychotics are considered to have minimum toxic or teratogenic potential. Chlorpromazine, haloperidol, and perphenazine have long histories of use during pregnancy with no reported significant teratogenic effects.[69] Atypical antipsychotics are considered first-line treatment for schizophrenia because of their more favorable side-effect profiles (see Chapter 84); therefore, use has increased during pregnancy. While one systematic review found no or minimal increases in risk of major malformations with atypical antipsychotics,[74] others have found a higher rate (10% vs 2%) of low-birth-weight infants with olanzapine, clozapine, quetiapine, paliperidone, lurasidone, ziprasidone, and risperidone compared with non-exposed infants and an increased risk of cardiovascular defects, especially with risperidone.[69,74,77] Atypical antipsychotics can cause weight gain, gestational diabetes, and metabolic syndrome which have implications for poorer obstetric outcomes.[74] Exposure to antipsychotic agents during pregnancy may increase preterm delivery and small-for-gestational-age newborns.[79]

Thyroid Disorders

6 Universal screening for thyroid disorders during pregnancy is not

recommended.[42] Hypothyroidism is present in 2 to 10 per 1,000 pregnancies. Untreated hypothyroidism increases the risk of preeclampsia, premature birth, miscarriage, and growth restriction; impaired neurological development in the fetus may also occur. Causes of hypothyroidism include autoimmune diseases (eg, Hashimoto's thyroiditis), iodine deficiency (uncommon in the United States), and thyroid dysfunction following surgery or ablative therapy for previous hyperthyroidism. If hypothyroidism is present, thyroid replacement should occur. A reasonable levothyroxine starting dose is 0.1 mg/day.[42] Women receiving thyroid replacement therapy before pregnancy may have an increased dosage requirement during pregnancy. Laboratory follow-up of TSH should occur every 4 to 6 weeks during pregnancy to allow for dose titration according to TSH levels.[42]

Hyperthyroidism affects approximately 0.2% of pregnancies and is associated with fetal death, low birth weight, intrauterine growth restriction, and preeclampsia. Graves' disease accounts for 95% of hyperthyroidism in pregnancy.[42] Therapy includes the thioamides (ie, methimazole and PTU). The risks of uncontrolled hyperthyroidism outweigh the risks of the thioamides. The goal of therapy is to attain free thyroxine concentrations near the upper limit of normal to allow for dose minimization and to limit fetal or neonatal hypothyroidism.[42] Iodine-131 is contraindicated because of the risk of thyroid damage in the fetus.

LABOR AND DELIVERY

Management of the pregnant woman during the perinatal period often requires drug therapy for pain and for potential complications associated with labor and delivery.

Preterm Labor

7 Preterm labor occurs between 20 and 37 weeks of gestation when changes in cervical dilation and/or effacement happen along with regular uterine contractions, or when the initial presentation includes regular contractions and cervical dilation of at least 2 cm.[80] Preterm birth is the leading cause of infant morbidity and mortality with an incidence that peaked in 2006 at 12.8% in the United States. Rates decreased to 9.8% in 2017 but are still higher than the European rate.[81] Risk factors for preterm delivery include previous preterm delivery, infections, multiple gestation, poverty, nonwhite race, maternal

complication factors (eg, smoking and use of illicit drugs or alcohol), and uterine functional causes (eg, cervical insufficiency). Age < 18 or > 35 years, and periodontal disease confer a higher risk.[82,83]

No adequate tests are available for monitoring and preventing preterm labor. Monitoring of uterine activity along with intensive surveillance does not minimize risk.[80] The presence of fetal fibronectin, a glycoprotein found in cervicovaginal secretions, indicates a high risk of preterm birth. Cervical shortening is also associated with preterm delivery. Fetal fibronectin determinations and cervical ultrasound have not helped to prevent preterm labor but have been useful for their negative predictive value.[80] Bed rest and hydration do not decrease the risk of preterm birth and should not be recommended routinely as they carry risks of VTE, bone demineralization, and deconditioning.

Tocolytic Therapy

The purposes of tocolytic therapy are threefold: (a) postpone delivery long enough to allow for the maximum effect of antenatal corticosteroid administration; (b) allow for transportation of the mother to a facility equipped to deal with high-risk deliveries; and (c) prolongation of pregnancy when there are underlying, self-limited conditions that can cause labor, such as pyelonephritis or abdominal surgery, that are unlikely to cause recurrent preterm labor.[80] However, the use of tocolytics has not reduced the number of premature deliveries and are generally not utilized beyond 34 weeks of gestation. The criteria for starting tocolysis are regular uterine contractions with cervical change. Tocolytic therapy should not be used in cases of previability, intrauterine fetal demise, a lethal fetal anomaly, intrauterine infection, fetal distress, severe preeclampsia, vaginal bleeding, or maternal hemodynamic instability.[80]

Four classes of tocolytics are available in the United States: β-agonists, magnesium, calcium channel blockers, and prostaglandin inhibitors (ie, NSAIDs). All four therapies prolong pregnancy between 48 hours to 1 week; however, this prolongation is not associated with a statistically significant reduction in overall rates of respiratory distress syndrome, neonatal death, or preterm birth before 37 weeks of gestation.[80,84] Prostaglandin inhibitors and calcium channel blockers may be preferable based on the probability of delaying delivery and improving neonatal outcomes.[84]

The β-agonists terbutaline and ritodrine have been used for tocolytic therapy; however, ritodrine is no longer available in the United States. Relative to other agents, β-agonists have a higher incidence of maternal side effects, including

hyperkalemia, arrhythmias, hyperglycemia, hypotension, and pulmonary edema. Recommended terbutaline doses vary because its use as a tocolytic agent is off-label; a commonly used dose is 250 mcg subcutaneously which may be repeated in 15 to 30 minutes for inadequate response with a maximum of 500 mcg given in a 4-hour period.[85] A black box warning was issued in 2011 recommending against oral dosing or prolonged parenteral use (beyond 48–72 hours) because of maternal cardiotoxicity and death.[80,85]

Intravenous magnesium sulfate has been used for tocolysis; however, a Cochrane review does not support its effectiveness.[85,86] Heterogeneity of study designs and results along with small treatment arms in the included studies may partially explain this finding; however, its use remains unsupported by evidence. These findings should not affect the use of magnesium sulfate for neuroprotection, as the incidence of cerebral palsy is increased in premature infants. Several studies evaluating the use of IV magnesium (6 g load followed by 2 g/h continuous infusion until delivery) during preterm labor (up to 34 weeks of gestation) found the occurrence of moderate or severe cerebral palsy was decreased by 45% to 50%.[85] Maternal side effects are common and include a general feeling of warmth, flushing, diaphoresis, blurred vision, nausea, weakness, and slurred speech. Difficulty in retaining and comprehending information, chest tightness, and pulmonary edema have also been reported. At toxic levels, hypotension, muscle paralysis, tetany, cardiac arrest, and respiratory depression may occur.[85] Magnesium undergoes renal excretion and therefore dose adjustment is required in women with impaired renal function.

Nifedipine is associated with fewer side effects than magnesium or β-agonist therapy and decreases risk of delivery within 7 days compared to β-agonists.[84,85] One concern with the use of nifedipine is its hypotensive effect and corresponding change in uteroplacental blood flow. However, a meta-analysis showed reduced neonatal morbidity with calcium channel blocker use. With the initial diagnosis of preterm labor, nifedipine loading doses range between 10 and 40 mg with subsequent dosing of 10 to 20 mg every 4 to 6 hours with dose adjustment based on patterns of preterm contractions.[85]

NSAIDs, such as indomethacin, have been used effectively for tocolysis.[80,84,85] Oral or rectal doses of 50 to 100 mg initially, followed by an oral dose of 25 to 50 mg every 6 hours for 48 hours, have been used. An increased rate of premature constriction of the ductus arteriosus has been noted in infants with indomethacin use after 32 weeks of gestation and with use exceeding 48 hours.[85] Indomethacin may be used when tocolysis is needed despite treatment with magnesium for neuroprotection because other agents,

such as calcium channel blockers and β-agonists, can cause hypotension when administered concurrently with magnesium.

Other Drug Therapies for Preterm Labor Prevention

Infection is a potential cause of preterm labor, and antibiotics have been used, in addition to tocolytics and corticosteroids, to improve the outcome of preterm labor. However, a Cochrane review showed no reduction in the incidence of preterm delivery, respiratory distress syndrome, or neonatal sepsis but a trend toward increased neonatal mortality.[80] Therefore, routine use of antibiotics is not recommended. However, if a patient experiences preterm premature rupture of membranes (PPROM) before 34 weeks of gestation, prophylactic antibiotics should be initiated because a reduction in major morbidities (ie, death, respiratory distress syndrome, early sepsis, severe intraventricular hemorrhage, and necrotizing enterocolitis) was demonstrated.[87,88] A 7-day course of broad-spectrum antibiotics should be used with the intent to prolong latency, which is the time from ruptured membranes to delivery. One recommended regimen is ampicillin (2 g IV every 6 hours) plus erythromycin (250 mg IV every 6 hours) for 48 hours, followed by amoxicillin (250 mg orally three times daily) and erythromycin base (333 mg orally every 8 hours), although multiple regimens have shown benefit.[87] Amoxicillin-clavulanate is not recommended since it causes increased rates of necrotizing enterocolitis. Induction of labor is recommended at 34 weeks gestation as prolonging delivery may increase the risk of chorioamnionitis.[87]

Progesterone administration in the setting of prior preterm birth is based upon its effects to diminish cervical ripening (softening of the cervix necessary for cervical dilation before birth), reduce uterine wall contractility, and modulate inflammation.[89] Evidence supports progesterone supplementation to prevent recurrent spontaneous preterm birth in singleton pregnancies. Use of intramuscular 17-α-hydroxyprogesterone weekly (250 mg) starting between weeks 16 and 24 continued through week 36 in women with a previous spontaneous preterm birth is recommended.[90]

Antenatal Corticosteroids

Use of antenatal corticosteroids for fetal lung maturation to prevent respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and death in infants delivered prematurely is supported by a Cochrane review and recommended by ACOG.[80,91,92] The current clinical recommendation is to

administer betamethasone 12 mg intramuscularly every 24 hours for two doses or dexamethasone 6 mg intramuscularly every 12 hours for four doses to pregnant women between 24 and 34 weeks of gestation who are at risk for preterm delivery within the next 7 days.[91] The greatest benefit from antenatal steroids is seen at 2 to 7 days after the initial dose.[91,93] In women less than 30 weeks gestation, delivery within 7 days confers the greatest reduction of respiratory distress syndrome, with no benefit if delivery occurs more than 14 days after the initial dose of corticosteroids.[93] Consideration of a single course of corticosteroids should be made in women between 34 and 37 weeks gestation if they have not previously received corticosteroids.[91] Administration of corticosteroids to women between 23 and 24 weeks gestation is controversial, but the decision should be based on the family's wishes regarding resuscitation.

Salvage ("rescue") treatment administered to women at risk of delivering within 7 days but who received a previous course of therapy is also supported by a Cochrane review. Risk of respiratory distress syndrome was lower with the administration of rescue steroids compared with placebo (RR 0.83, 95% CI 0.75,0.91).[91]

Group B *Streptococcus* Infection

7 Maternal infection with GBS is associated with invasive disease in the newborn.[94,95] Women colonized with GBS have an increased risk for pregnancy loss, premature delivery, and transmission of the bacteria to the infant during delivery. Between 10% and 30% of pregnant women are colonized with GBS. The rate of invasive infection (defined as isolation of GBS from blood or other sterile body site excluding urine) in pregnant women is 0.12 per 1,000 live births (range, 0.11–0.14 per 1,000 births). The incidence of early-onset disease in neonates, although higher than in pregnant women, has declined steadily from 1.5 per 1,000 live births in 1993 to approximately 0.24 cases per 1,000 live births in 2010. The consequences of neonatal infections include bacteremia, pneumonia, meningitis, and fatality in the newborn,[95] with the case-fatality rate being approximately 4%.

Recommendations for prevention of GBS infection were last updated in 2010.[96] Universal prenatal screening for GBS colonization is recommended. Antibiotics are given if the woman previously gave birth to an infant with invasive GBS disease or in the presence of GBS bacteriuria. All other pregnant women should have a vaginal/rectal culture at 35 to 37 weeks of gestation. If negative, antibiotics are not indicated. If a woman presents in labor and no

screening information is available, antibiotics are given for fever greater than 100.4°F (38°C), membrane rupture at least 18 hours prior, or gestation under 37 weeks.

Penicillin G 5 million units given IV, followed by 2.5 million units given every 4 hours until delivery is the recommended treatment regimen.[96] Alternatively, ampicillin 2 g can be given IV, followed by 1 g every 4 hours. For women with penicillin allergy but not at risk for anaphylaxis, cefazolin 2 g IV, followed by 1 g every 8 hours, is recommended. In women at high risk for anaphylaxis, clindamycin 900 mg IV every 8 hours is recommended. For penicillin-allergic women, GBS cultures should be sent for sensitivities. If resistant to clindamycin or erythromycin, vancomycin 1 g IV every 12 hours until delivery is appropriate. A minimum of 4 hours of therapy with a beta-lactam antibiotic is required for adequate prophylaxis.

Cervical Ripening and Labor Induction

7 Throughout gestation, the cervix is closed and firm. During the last few weeks of pregnancy, the cervix softens and thins to facilitate labor. This process is mediated by hormonal changes, including final mediation by prostaglandins E_2 and $F_2\alpha$, which increase collagenase activity in the cervix leading to thinning and dilation.

Approximately one in five women undergo labor induction, either elective or medically indicated. The most common indications for induction are post-term pregnancies (beyond 42 weeks) and pregnancy-induced hypertension, which account for 80% of inductions.[97–99] Other reasons for induction include fetal growth restriction or compromise, maternal hypertension, premature rupture of membranes with no active onset of labor, and social factors. Contraindications include placenta previa, oblique or transverse lie, pelvic structure abnormality, prolapsed umbilical cord, and active herpes. Concerns with induction of labor are ineffective labor and side effects, such as uterine hyperstimulation, that may adversely affect the infant and increase the likelihood of cesarean section.

Scoring systems have been used to determine the likelihood of successful labor induction. The Bishop scoring system is most commonly used and is based on five parameters: cervical dilation, cervical effacement (thinning), station of the baby's head, consistency of the cervix, and position of the cervix.[97,99] A Bishop score under 6 indicates the need for cervical ripening while a score above 8 corresponds to a likely successful vaginal delivery.

A number of nonpharmacologic methods are used for cervical ripening.

Castor oil, hot baths, sexual intercourse, and nipple stimulation all have been suggested for labor induction[100]; however, minimal evidence supports the efficacy of these methods. Use of a Foley catheter placed in an unfavorable cervix for ripening has been found as effective as prostaglandin E_2. Membrane stripping and amniotomy can also be performed and increase contractions via the release of prostaglandins.[99]

Prostaglandin E_2 analogs (eg, dinoprostone [Prepidil gel, Cervidil vaginal insert]) are commonly used for cervical ripening. Prepidil 500 mcg is administered intracervically and may be repeated after 6 hours to a maximum of three doses in 24 hours.[99] After administration, the patient remains supine for 30 minutes. Cervidil contains 10 mg dinoprostone with a slower, more constant release of medication than the gel.[99] The patient should remain in a recumbent position for 2 hours after placement and the insert should be removed when labor begins or after 12 hours. Patients must be attached to a fetal heart rate monitor for the duration of dinoprostone use and for 15 minutes after Cervidil removal.[100]

Misoprostol, a prostaglandin E_1 analog, is an effective and inexpensive drug for cervical ripening and labor induction. Intravaginal administration of 25 mcg misoprostol (oral tablets are split to obtain dose) given every 3 to 6 hours is at least as effective as other prostaglandin agents and results in a shorter time to delivery.[99,101] Oral misoprostol has been used successfully for cervical ripening and labor induction resulting in a quicker onset and shorter duration; dosing of 25 or 50 mcg can be given every 4 hours. There is little benefit of using misoprostol for longer than 24 hours. Sublingual and buccal routes of misoprostol administration have less information regarding the efficacy compared to other routes. The most commonly encountered side effects are uterine hyperstimulation and meconium-stained amniotic fluid. Use of misoprostol is contraindicated in women with a previous uterine scar because of its association with uterine rupture, a catastrophic medical event.

Oxytocin is the most commonly used agent for labor induction after cervical ripening. By the end of pregnancy, the number of oxytocin receptors has increased by 300-fold.[98,100] A solution of 10 mU/mL is used for infusion. Oxytocin is effective in both low-dose (physiologic) and high-dose (pharmacologic) regimens. Refer to the ACOG practice bulletin for detailed administration information.[99]

Labor Analgesia

7 The first phase of labor occurs from onset of labor to complete cervical dilation while the second phase of labor is the period of time between complete cervical dilation and delivery. During the first phase of labor, women perceive visceral pain caused by uterine contractions. Pain in the second phase of labor is somatic pain associated with perineal stretching.[102]

Nonpharmacologic Approaches to Analgesia

Women who receive continuous support from nurses, midwives, childbirth educators, or doulas (lay women trained in labor support) have fewer operative vaginal deliveries, cesarean deliveries, and requests for pain medication.[103] Warm water baths provide temporary pain relief and may decrease the length of the first stage of labor and use of pharmacologic pain treatments, but they do not decrease the rate of assisted vaginal deliveries or cesarean sections. Maternal and neonatal infection, umbilical cord avulsion, and neonatal water aspiration are potential risks if delivery occurs while submerged. Intradermal injections of sterile water in the sacral area provide short-term decreases in back pain during labor; however, requests for pain medication did not decrease in studies. Acupuncture has also been used for pain relief with several randomized, controlled trials showing that acupuncture decreases the need for analgesia, but more methodologically sound studies are needed. The use of visualization and breathing techniques, yoga postures, massage, acupressure, and facilitated partner support show more women delivering vaginally, and they have been shown to reduce epidural use and shorten the second stage of labor.[104] Use of audioanalgesia (music or white noise), relaxation and breathing techniques, application of heat and cold, aromatherapy, acupressure, transcutaneous electrical nerve stimulation (TENS), and hypnosis have little to no evidence of effectiveness derived from randomized, controlled trials.[103,105]

Pharmacologic Approaches to Labor Pain Management

Maternal request alone is a sufficient medical indication for labor analgesia.[102] The two main types of pharmacologic approaches in the United States are parenteral opioids and epidural analgesia. Use of nitrous oxide during labor is an alternative for pain management.

Parenteral opioids are commonly used to alleviate labor pain.[102] Up to 42% of

women receive parenteral drugs, although there is no consensus that one agent is more effective or safe than another.[106] They are less effective than epidural analgesia, have more side effects, and possibly less reliable pain response.[102]

Approximately 60% of women in the United States choose an epidural for pain relief during labor and report better pain relief than with other analgesic modalities.[106] With epidural analgesia, a catheter is introduced into the epidural space, and an opioid and/or an anesthetic (eg, fentanyl and/or bupivacaine) is administered. Combined spinal-epidural analgesia consists of injecting a single opioid bolus into the subarachnoid space to provide instant pain relief with additional use of a local anesthetic epidural. Compared with traditional epidurals, combined spinal-epidural anesthesia has a slightly shorter mean time to onset of effective analgesia.[102] Patient-controlled epidural analgesia allows the patient to control the amount and timing of the anesthetic. It results in a lower total dose of local anesthetics used over the course of labor compared with continuous epidural infusions and allows a reduction in the time between onset of pain and administration of analgesia.[107]

Side effects of regional anesthesia include hypotension, pruritus, and inability to void. Epidural analgesia is associated with prolongation of the second stages of labor, but it does not lead to higher numbers of instrumental deliveries, cesarean sections (for fetal distress), or maternal fever when compared to intravenous opioid therapy.[105,108] A rare complication of epidural anesthesia is puncture of the subarachnoid space leading to a severe headache, which occurs in approximately 1% of women. Other complications include hypotension, nausea, vomiting, itching, and urinary retention.[108] Low back pain has not been associated with the use of epidural analgesia.

Nitrous oxide, as a 50% mixture with oxygen, can be employed in women desiring a non-medicated labor. It is less effective than epidural anesthesia, but is quickly reversible and does not limit the woman’s mobility.[102,106]

Postpartum Hemorrhage

7 The placenta is delivered after the delivery of the baby and is referred to as the third stage of labor. Postpartum hemorrhage (PPH) is an obstetrical emergency and is a major cause of morbidity and mortality worldwide.[109] The traditional definition of PPH is loss of more than 500 mL of blood within 24 hours of a vaginal delivery or more than 1,000 mL after a cesarean section; however, ACOG now defines PPH as a cumulated blood loss of more than 1,000 mL regardless of delivery method or blood loss accompanied with signs and

symptoms of hypovolemia within 24 hours after delivery.[111] Risk factors include prior PPH, previous cesarean delivery, a macrosomic fetus or multiple gestation, preeclampsia, operative vaginal delivery, chorioamnionitis, abnormal placentation, and prolonged or augmented labor.[110]

A stepwise approach to the treatment of PPH is advised. After the exclusion of retained products of conception and cervical and vaginal lacerations, attention should be turned to the management of uterine atony, if present, as this is the most common cause of PPH.[110,111] Controlled traction of the cord, which involves gently pulling on the cut umbilical cord to remove the placenta, may reduce minor PPHs, but early clamping and cutting of the umbilical cord has no effect on rates of PPH.[110] Administration of oxytocin should be initiated before placental delivery to institute active management of labor after all uncomplicated vaginal deliveries, as this practice results in reduced maternal blood loss, fewer cases of PPH, and a shorter third stage of labor.[111,112] Other uterotonic agents should be used if an inadequate response is attained with oxytocin alone. Methylergonovine, carboprost, and rectal, sublingual, or oral misoprostol can all be used as second-line agents; none has been shown to be more effective than another.[111] Tranexamic acid (TXA), an antifibrinolytic agent, has been shown to reduce maternal deaths from obstetric hemorrhage if given within 3 hours of delivery. A limited amount of evidence has shown a modest decrease in blood loss when TXA is given prophylactically.[111] If uterotonic drug therapies fail to control the bleeding, uterine artery embolization, intrauterine balloon catheters, or a variety of different surgical techniques can be used.[110,111]

POSTPARTUM ISSUES

Drug Use During Lactation—General Concepts

8 A wide variety of benefits (eg, health, nutritional, immunologic, psychological, economic, developmental, and social) are imparted by breastfeeding, not only to the infants, but also mothers and the family. Women should breastfeed exclusively for 6 months and continue until at least 12 months of age while other foods are introduced.[113] Healthy People 2020 increased targets for breastfeeding to 81.9% for infants ever breastfed, 60.5% for infants at 6 months, and 34.1% for infants at 12 months.[113]

Adequate milk removal from the breast by breastfeeding or pumping is

necessary to maintain or increase milk production.[114] Relactation is the process of increasing the breast milk supply for women whose milk has not “come in,” who have inadequate milk production despite appropriate breastfeeding frequency or pumping, or who have weaned or never breastfed after delivery. Metoclopramide can be used if nonpharmacologic measures are ineffective due to its stimulation of prolactin secretion. The most common dose is 10 mg orally three times daily for 7 to 14 days.[114] Breast milk production may decrease after metoclopramide therapy is stopped, but production will continue if lactation has been established successfully.

Most drugs transfer into breast milk, but breastfeeding may be continued in most circumstances. Healthcare providers should encourage breastfeeding women who require medications to continue breastfeeding whenever possible. Passive diffusion is the primary mechanism for drug transfer into breast milk, but other drug-related factors influence drug transfer from maternal circulation into breast milk, including (a) degree of protein binding in maternal plasma, (b) molecular weight, (c) lipid solubility (and corresponding fat content of milk), (d) maternal plasma concentration, (e) drug half-life, and (f) drug pH.[115] The degree of protein binding to maternal plasma proteins is one of the most significant factors affecting drug transfer to breast milk; highly bound medications transfer in low amounts. Low-molecular-weight drugs passively diffuse into breast milk, but larger molecules are not likely to transfer in large amounts. Higher lipid solubility of drugs also increases the likelihood of transfer. Colostrum is secreted in the first couple of days after birth and has high quantities of immunoglobulins, maternal lymphocytes, and maternal macrophages. While greater amounts of drugs are present in colostrum, the amount received by the nursing infant is minimal because of the limited volume of colostrum produced. A greater volume of mature milk is produced, but drug transfer into mature milk is lower because of tight cell-to-cell junctions. The higher the concentration of drug in the mother’s serum, the higher the concentration in the breast milk. As the drug is metabolized and excreted by the mother, the mother’s serum concentration drops, and the drug in the breast milk may redistribute back into the mother’s bloodstream. Maternal plasma pH is 7.4, while the pH of breast milk ranges between 6.8 and 7. Weak bases are not ionized in the maternal circulation and easily transfer to breast milk.[115] In the lower pH of breast milk, molecules become ionized and are less likely to diffuse back into maternal circulation (“ion trapping”). Likewise, drugs with longer half-lives are more likely to maintain higher levels in breast milk, resulting in greater exposure to the infant.

Infant-related factors may also influence the amount of drug ingested through

breastfeeding as both the frequency of feedings and the amount of milk ingested are important considerations. Exclusively breastfed infants are more likely to ingest larger amounts of drugs than older infants who receive other foods. Drugs unstable in gastric acid (aminoglycosides, PPIs, heparin, and insulin) are less likely to be absorbed by infants.[115] Finally, infants may vary in their ability to metabolize and excrete ingested medication. Premature and full-term infants may not have full renal and liver function.

Strategies for reducing the risk to the infant include selection of medications that would be considered safe for use in the infant. Drugs with shorter half-lives accumulate less, and those that are more protein bound do not cross into breast milk as well as those that are less protein bound. When choosing between different pharmacotherapies, drugs with lower oral bioavailability and lower lipid solubility may be better choices to reduce infant exposure. If the mother is using a once-daily medication, administration before the infant's longest sleep period may be advised to increase the interval to the next feeding. For medications taken multiple times per day, administration immediately after breastfeeding provides the longest interval for back diffusion of drug from the breast milk to the mother's serum. During short-term drug therapy, the mother can pump and discard milk to preserve her milk-producing capability if the necessary medication is not considered compatible with breastfeeding.[116,117]

Information regarding drug use during breastfeeding is available from expert committees (eg, American Academy of Pediatrics Committee on Drugs) and evidence-based textbooks or databases (eg, LactMed [http://toxnet.nlm.nih.gov/newtoxnet/lactmed. htm]). All may be of assistance in determining safe and appropriate medications to use during breastfeeding.

Mastitis

8 Mastitis is inflammation of the breast that occurs in 3% to 20% of lactating women.[118] It can be infectious or noninfectious and the most common cause is milk stasis. Signs and symptoms include breast tenderness, redness, warmth, flulike symptoms, and fever (temperature 101.3°F [38.5°C] or greater). Risk factors for developing mastitis include breast engorgement, plugged milk ducts, oversupply of milk, and cracked nipples.[118]

Penicillin-resistant *Staphylococcus aureus* is the most common bacterial cause of mastitis; *E. coli* and *Streptococcus* have also been implicated.[118] A 10- to 14-day course of antibiotics is usually given for treatment of mastitis; penicillinase-resistant penicillins (eg, dicloxacillin, oxacillin) and cephalosporins

(eg, cephalexin) are frequently prescribed. Antiinflammatory drugs, such as ibuprofen, may provide some pain relief. Application of heat may also be helpful along with direct massage of the affected area, if tolerated. Affected women should be counseled to continue breastfeeding from both breasts throughout treatment and to pump if breasts are not emptied completely with feedings.[118]

Postpartum Depression

8 Mood disorders in the postpartum period may include postpartum blues, postpartum depression, and postpartum psychosis.[119] Postpartum blues ("baby blues") is common, usually affecting 15% to 85% of new mothers within the first 10 days of delivery, and generally does not require treatment. Symptoms include anxiety, anger, fatigue, insomnia, tearfulness, and sadness. Postpartum psychosis is more severe and can present as mania, psychotic depression, or schizophrenia but is rare, affecting less than 1% of new mothers; hospitalization is usually indicated.[119]

Postpartum depression affects up to 13% of women, with almost 5% experiencing major depression.[119] Symptoms may develop during pregnancy or up to 6 months after delivery, although the strict definition for major depressive disorder after delivery specifies symptom occurrence within 4 to 6 weeks. Psychotherapy, including interpersonal psychotherapy, cognitive behavioral therapy, and group/family therapy, has been shown to be effective for treatment of postpartum depression.[119]

Some suggest that the benefits of breastfeeding to the infant exceed the risks of antidepressant exposure in mothers with postpartum depression. In cases where pharmacotherapy is warranted, selection of medication with low transfer to breast milk is desirable.[116] Sertraline, paroxetine, fluoxetine, and nortriptyline are the most studied in the postpartum period. A Cochrane review found that SSRIs were more likely to be effective than placebo for treatment of postpartum depression, but the evidence with tricyclic antidepressants was insufficient to assess outcome. The review was limited by the number of studies meeting its inclusion criteria (n=6) which were based on study design quality.[119] Given that long-term effects of exposure to antidepressants are largely unknown, monitoring growth and neurodevelopment should be considered for children exposed to antidepressants present in breast milk.[116]

CONCLUSION

Pregnant women may experience pregnancy-influenced, acute, and chronic conditions during pregnancy, with some requiring drug therapy. Drug exposure during pregnancy can elicit fear since many believe that the risk of birth defects with exposure is high. With the potential for drug exposure before the discovery of pregnancy and the potential for unplanned pregnancies, anxiety may result.

While some medications convey risk, some medications are considered safe for use in pregnancy based on evidence from frequent use with no apparent increase in congenital malformations. Women using medications considered safe should be comforted that these choices are unlikely to increase the risk of birth defects. However, in some situations, ensuring mother's or fetus' health requires treatment with medications that have been associated with a higher risk of adverse effects to the fetus. The healthcare provider should provide realistic information about the types and likelihood of adverse effects to assist the patient and her family in making the best possible decisions based on their beliefs, concerns, and need for treatment.

Evidence-based resources, databases related to drug use in pregnancy, and primary and secondary literature provide healthcare practitioners with access to relevant and current medication information to manage drug therapy needs during pregnancy and lactation. Collaboration among healthcare providers who care for pregnant women is essential to seek, evaluate, and present the most contemporary and accurate information to their patients.

Postclass Engaged Learning Activity

Conduct a search of the literature to identify primary literature published within the last 12 months regarding the use of the selective serotonin receptor inhibitors during pregnancy and summarize the study methods, major findings, and potential limitations of the data. How has the new primary literature added to current knowledge about their use in pregnancy? Does this new information change clinical practice? If so, how? This activity is intended to enhance student ability to search for primary literature and to critically appraise research studies.

ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
ART	antiretroviral therapy

ARV	antiretroviral
BV	bacterial vaginosis
CNS	central nervous system
dBP	diastolic blood pressure
FPG	fasting plasma glucose
GBS	Group B *Streptococcus*
GDM	gestational diabetes mellitus
GI	gastrointestinal
GTT	gestational transient thyrotoxicosis
H_2	histamine-2
hCG	human chorionic gonadotropin
HDP	hypertensive disorders of pregnancy
HELLP	hemolysis, elevated liver enzymes, low platelets
HG	hyperemesis gravidarum
HIV	human immunodeficiency virus
HSV-1	herpes simplex virus 1
HSV-2	herpes simplex virus 2
HTN	hypertension
IADPSG	International Association of Diabetes and Pregnancy Study Groups
LMWH	low-molecular-weight heparin
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NSAID	nonsteroidal anti-inflammatory drug
NTD	neural tube defect
NVP	nausea and vomiting of pregnancy
OGTT	oral glucose tolerance test
PID	pelvic inflammatory disease
PPH	postpartum hemorrhage
PPI	proton pump inhibitor
PPROM	preterm premature rupture of membranes
PPT	postpartum thyroiditis
PTU	propylthiouracil

RPG	random plasma glucose
sBP	systolic blood pressure
SMBG	self-monitored blood glucose
SNRI	serotonin–norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
STI	sexually transmitted infection
TENS	transcutaneous electrical nerve stimulation
TSH	thyroid-stimulating hormone
UFH	unfractionated heparin
UTI	urinary tract infection
VTE	venous thromboembolism

REFERENCES

1. Benagiano G, Farris M, Grudzinskas G. Fate of fertilized human oocytes. *Reprod Biomed Online*. 2010;21:732–741.
2. Anifandis G, Messini CI, Dafopoulos K, et al. Sperm contributions to oocyte activation: More that meets the eye. *J Assist Reprod Genet*. 2016;33:313–316.
3. Prenatal care. In: Cunningham F, Leveno KJ, Bloom SL, et al., eds. *Williams Obstetrics*. 25th ed. [electronic version] 2018, *AccessMedicine*. Available at: http://accessmedicine.mhmedical.com/content.aspx?bookid=19188&sectionid=144148582. Accessed July 10, 2018.
4. Implantation and placental development. In: Cunningham F, Leveno KJ, Bloom SL, et al, eds. *Williams Obstetrics*. 25th ed. [electronic version] 2018, *AccessMedicine*. Available at: http://accessmedicine.mhmedical.com/content.aspx?bookid=19188&sectionid=185046233. Accessed July 10, 2018.
5. Embryogenesis and fetal development. In: Cunningham F, Leveno KJ, Bloom SL, et al., eds. *Williams Obstetrics*. 25th ed. [electronic version] 2018, *AccessMedicine*. Available at: http://accessmedicine.mhmedical.com/content.aspx?bookid=19188&sectionid=141464503. Accessed July 10, 2018.
6. Bernstein HB, VanBuren G. Normal pregnancy and prenatal care. In: DeCherney AH, Nathan L, Laufer N, et al., eds. *CURRENT Diagnosis &*

Treatment: Obstetrics & Gynecology. 11th ed. [electronic version] 2013, *AccessMedicine*. Available at: http://accessmedicine.mhmedical.com/content.aspx?bookid=498&sectionid=41008595. Accessed July 10, 2018.

7. Feghali MN, Mattison DR. Clinical therapeutics in pregnancy. *J Biomed Biotechnol*. 2011;2011:783528. doi:10.1155/2011/783528.
8. Flick AA, Kahn DA. Maternal physiology during pregnancy & fetal & early neonatal physiology. In: DeCherney AH, Nathan L, Laufer N, et al., eds. *CURRENT Diagnosis & Treatment: Obstetrics & Gynecology*. 11th ed. [electronic version] 2013, *AccessMedicine*. Available at: http://accessmedicine.mhmedical.com/content.aspx?bookid=498&sectionid=41008597. Accessed July 10, 2018.
9. Tasnif Y, Morado J, Hebert MF. Pregnancy-related pharmacokinetic changes. *Clin Pharmacol Ther*. 2016;100:53–62.
10. Syme MR, Paxton JW, Keelan JA. Drug transfer and metabolism by the human placenta. *Clin Pharmacokinet*. 2004;43:487–514.
11. Brent RL. Environmental causes of human congenital malformations: The pediatrician's role in dealing with these complex clinical problems caused by a multiplicity of environmental and genetic factors. *Pediatrics*. 2004;113(4 Suppl):957–968.
12. Brent RL. The role of the pediatrician in preventing congenital malformations. *Pediatr Rev*. 2011;32:411–421.
13. Adam MP. The all-or-none phenomenon revisited. *Birth Defects Res A Clin Mol Teratol*. 2012;94:664–669.
14. Kallen BA. Methodological issues in the epidemiological study of the teratogenicity of drugs. *Congenit Anom (Kyoto)*. 2005;45:44–51.
15. Schaefer C, Ornoy A, Clementi M, Meister R, Weber-Schoendorfer C. Using observational cohort data for studying drug effects on pregnancy outcome: Methodological considerations. *Reprod Toxicol*. 2008;26:36–41.
16. Food and Drug Administration. Content and format of labeling for human prescription drug and biological products: Requirements for pregnancy and lactation labeling (final rule). *Federal Register*. 2014;79(233):72064–72103.
17. Callegari LS, Ma EW, Schwarz EB. Preconception care and reproductive planning in primary care. *Med Clin North Am*. 2015;99:663–682.
18. Bibbins-Domingo K, Grossman DC, et al. U.S. Preventive Services Task Force. Folic acid supplementation for the prevention of neural tube

defects: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2017;317:183–189.

19. Behnke M, Smith VC. Committee on Substance Abuse. Prenatal substance abuse: Short- and long-term effects on the exposed fetus. *Pediatrics*. 2013;131:e1009–e1024.
20. De Long NE, Barra NG, Hardy DB, Holloway AC. Is it safe to use smoking cessation therapeutics during pregnancy? *Expert Opin Drug Saf*. 2014;13:1721–1731.
21. Gomes CF, Sousa M, Lourenco I, Martins D, Torres J. Gastrointestinal diseases during pregnancy: What does the gastroenterologist need to know? *Ann Gastroenterol*. 2018;31:385–394.
22. Briggs GG Freeman RK, Towers CV, Forinash AB. *Drugs in Pregnancy and Lactation*. 11 ed. New York, NY: Wolters Kluwer; 2017.
23. Zielinski R, Searing K, Deibel M. Gastrointestinal distress in pregnancy: Prevalence, assessment, and treatment of 5 common minor discomforts. *J Perinat Neonatal Nurs*. 2015;29:23–31.
24. Maltepe C, Koren G. The management of nausea and vomiting of pregnancy and hyperemesis gravidarum: A 2013 update. *J Popul Ther Clin Pharmacol*. 2013;20:e184–e192.
25. American Diabetes Association. Classification and diagnosis of diabetes. *Diabetes Care*. 2017;40(Suppl 1):S11–S24.
26. DeSisto CL, Kim SY, Sharma AJ. Prevalence estimates of gestational diabetes mellitus in the United States, Pregnancy Risk Assessment Monitoring System (PRAMS), 2007-2010. *Prev Chronic Dis*. 2014;11:E104. doi:10.5888/pcd11.130415.
27. Metzger BE, Gabbe SG, et al. International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care*. 2010;33:676–682.
28. Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin No. 190: Gestational diabetes mellitus. *Obstet Gynecol*. 2018;131:e49–e64.
29. American Diabetes Association. Management of diabetes in pregnancy: Standards of medical care in diabetes-2018. *Diabetes Care*. 2018;41(Suppl 1):S137–S143.
30. Farrar D, Simmonds M, Bryant M, et al. Treatments for gestational diabetes: A systematic review and meta-analysis. *BMJ Open*.

2017;7(6):e015557. doi:10.1136/bmjopen-2016-015557.

31. Camelo Castillo W, Boggess K, Sturmer T, et al. Association of adverse pregnancy outcomes with glyburide vs insulin in women with gestational diabetes. *JAMA Pediatr*. 2015;169:452–458.
32. Magee LA, Pels A, Helewa M, et al. The hypertensive disorders of pregnancy (29.3). *Best Pract Res Clin Obstet Gynaecol*. 2015;29:643–657.
33. American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol*. 2013;122:1122–1131.
34. Leeman L, Dresang LT, Fontaine P. Hypertensive disorders of pregnancy. *Am Fam Physician*. 2016;93:121–127.
35. Barakat R, Pelaez M, Cordero Y, et al. Exercise during pregnancy protects against hypertension and macrosomia: Randomized clinical trial. *Am J Obstet Gynecol*. 2016;214:649 e641–e648.
36. Khaing W, Vallibhakara SA, Tantrakul V, et al. Calcium and vitamin D supplementation for prevention of preeclampsia: A systematic review and network meta-analysis. *Nutrients*. 2017;91141. doi:10.3390/nu9101141.
37. Phipps E, Prasanna D, Brima W, Jim B. Preeclampsia: updates in pathogenesis, definitions, and guidelines. *Clin J Am Soc Nephrol*. 2016;11:1102–1113.
38. Jackson JR, Gregg AR. Updates on the recognition, prevention and management of hypertension in pregnancy. *Obstet Gynecol Clin North Am*. 2017;44:219–230.
39. ACOG Committee Opinion No. 743: Low-dose aspirin use during pregnancy. *Obstet Gynecol*. 2018;132:e44–e52.
40. Xu TT, Zhou F, Deng CY, et al. Low-dose aspirin for preventing preeclampsia and its complications: A meta-analysis. *J Clin Hypertens (Greenwich)*. 2015;17:567–573.
41. Jim B, Karumanchi SA. Preeclampsia: Pathogenesis, prevention, and long-term complications. *Semin Nephrol*. 2017;37:386–397.
42. American College of Obstetricians and Gynecologists. Practice Bulletin No. 148: Thyroid disease in pregnancy. *Obstet Gynecol*. 2015;125:996–1005.
43. Bates SM, Middeldorp S, Rodger M, et al. Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. *J Thromb*

Thrombolysis. 2016;41:92–128.

44. ACOG Practice Bulletin No. 196: Thromboembolism in pregnancy. *Obstet Gynecol*. 2018;132:e1–e17.
45. Bhagra CJ, D'Souza R, Silversides CK. Valvular heart disease and pregnancy part II: Management of prosthetic valves. *Heart*. 2017;103:244–252.
46. Wang J, Li K, Li H et al. Comparison of anticoagulation regimens for pregnant women with prosthetic heart valves: A meta-analysis of prospective studies. *Cardiovasc Ther*. 2017;35:e12292–doi:10.1111/1755-5922.12292.
47. Glaser AP, Schaeffer AJ. Urinary tract infection and bacteriuria in pregnancy. *Urol Clin North Am*. 2015;42:547–560.
48. Vazquez JC, Abalos E. Treatments for symptomatic urinary tract infections during pregnancy. *Cochrane Database Syst Rev*. 2011; (1):CD002256.
49. O'Dell KK. Pharmacologic management of asymptomatic bacteriuria and urinary tract infections in women. *J Midwifery Womens Health*. 2011;56:248–265.
50. Workowski KA, Bolan GA. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. 2015;64(RR-03):1–137.
51. Macgregor EA. Headache in pregnancy. *Neurol Clin*. 2012;30:835–866.
52. Calhoun AH. Migraine treatment in pregnancy and lactation. *Curr Pain Headache Rep*. 2017;21:46. doi:10.1007/s11916-017-0646-4.
53. Wells RE, Turner DP, Lee M, et al. Managing migraine during pregnancy and lactation. *Curr Neurol Neurosci Rep*. 2016;16:40. doi:10.1007/s11910-016-0634-9.
54. Negro A, Delaruelle Z, Ivanova TA, et al. Headache and pregnancy: A systematic review. *J Headache Pain*. 2017;18:106. doi:10.1186/s10194-017-0816-0.
55. Marchenko A, Etwel F, Olutunfese O, et al. Pregnancy outcome following prenatal exposure to triptan medications: A meta-analysis. *Headache*. 2015;55:490–501.
56. Kelly W, Massoumi A, Lazarus A. Asthma in pregnancy: Physiology, diagnosis, and management. *Postgrad Med*. 2015;127:349–358.
57. Ridolo E, Caminati M, Martignago I, et al. Allergic rhinitis:

Pharmacotherapy in pregnancy and old age. *Expert Rev Clin Pharmacol*. 2016;9:1081–1089.

58. Ballas J, Moore TR, Ramos GA. Management of diabetes in pregnancy. *Curr Diab Rep*. 2012;12:33–42.
59. Lv S, Wang J, Xu Y. Safety of insulin analogs during pregnancy: A meta-analysis. *Arch Gynecol Obstet*. 2015;292:749–756.
60. Block HS. Neurological complications of pregnancy. *Curr Neurol Neurosci Rep*. 2016;16:67. doi:10.1007/s11910-016-0665-2.
61. Kinney MO, Morrow J. Epilepsy in pregnancy. *BMJ*. 2016;353:i2880. doi:10.1136/bmj.i2880.
62. Tomson T, Battino D, Bonizzoni E, et al. Dose-dependent teratogenicity of valproate in mono- and polytherapy: An observational study. *Neurology*. 2015;85:866–872.
63. Hernandez-Diaz S, Mittendorf R, Smith CR, et al. Association between topiramate and zonisamide use during pregnancy and low birth weight. *Obstet Gynecol*. 2014;123:21–28.
64. Gilbert EM, Darin KM, Scarsi KK, McLaughlin MM. Antiretroviral pharmacokinetics in pregnant women. *Pharmacotherapy*. 2015;35:838–855.
65. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf. Accessed September 6, 2018.
66. Ankumah NE, Sibai BM. Chronic hypertension in pregnancy: Diagnosis, management, and outcomes. *Clin Obstet Gynecol*. 2017;60:206–214.
67. Podymow T, August P. New evidence in the management of chronic hypertension in pregnancy. *Semin Nephrol*. 2017;37:398–403.
68. Committee Opinion No. 692 Summary: Emergent therapy for acute-onset, severe hypertension during pregnancy and the postpartum period. *Obstet Gynecol*. 2017;129:769–770.
69. ACOG Committee on Practice Bulletins: Obstetrics. ACOG Practice Bulletin: Clinical management guidelines for obstetrician-gynecologists number 92, April 2008 (replaces practice bulletin number 87, November 2007). Use of psychiatric medications during pregnancy and lactation (reaffirmed 2018). *Obstet Gynecol*. 2008;111:1001–1020.

70. Ashley JM, Harper BD, Arms-Chavez CJ, LoBello SG. Estimated prevalence of antenatal depression in the US population. *Arch Womens Ment Health*. 2016;19:395–400.
71. Yonkers KA, Wisner KL, Stewart DE, et al. The management of depression during pregnancy: A report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. *Obstet Gynecol*. 2009;114:703–713.
72. Jones SC, Jones I. Pharmacological management of bipolar disorder in pregnancy. *CNS Drugs*. 2017;31:737–745.
73. Gentile S. Drug treatment for mood disorders in pregnancy. *Curr Opin Psychiatry*. 2011;24:34–40.
74. Pearlstein T. Use of psychotropic medication during pregnancy and the postpartum period. *Womens Health (Lond)*. 2013;9:605–615.
75. Alwan S, Bandoli G, Chambers CD. Maternal use of selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *Clin Pharmacol Ther*. 2016;100:34–41.
76. Ornoy A, Weinstein-Fudim L, Ergaz Z. Antidepressants, antipsychotics, and mood stabilizers in pregnancy: what do we know and how should we treat pregnant women with depression. *Birth Defects Res*. 2017;109:933–956.
77. Patorno E, Huybrechts KF, Bateman BT, et al. Lithium use in pregnancy and the risk of cardiac malformations. *N Engl J Med*. 2017;376:2245–2254.
78. Levey L, Ragan K, Hower-Hartley A, et al. Psychiatric disorders in pregnancy. *Neurol Clin*. 2004;22:863–893.
79. Coughlin CG, Blackwell KA, Bartley C, et al. Obstetric and neonatal outcomes after antipsychotic medication exposure in pregnancy. *Obstet Gynecol*. 2015;125:1224–1235.
80. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins: Obstetrics. Practice Bulletin No. 171: Management of preterm labor. *Obstet Gynecol*. 2016;128:e155–e164.
81. Martin JA, Hamilton BE, Osterman MJK, et al. Births: Final Data for 2016. *Natl Vital Stat Rep*. 2018;67:1–55.
82. Koullali B, Oudijk MA, Nijman TA, et al. Risk assessment and management to prevent preterm birth. *Semin Fetal Neonatal Med*. 2016;21:80–88.

83. Committee on Practice Bulletins: Obstetrics, The American College of Obstetricians and Gynecologists. Practice bulletin no. 130: Prediction and prevention of preterm birth. *Obstet Gynecol*. 2012;120:964–973.
84. Nijman TA, van Vliet EO, Koullali B, et al. Antepartum and intrapartum interventions to prevent preterm birth and its sequelae. *Semin Fetal Neonatal Med*. 2016;21:121–128.
85. Abramovici A, Cantu J, Jenkins SM. Tocolytic therapy for acute preterm labor. *Obstet Gynecol Clin North Am*. 2012;39:77–87.
86. Crowther CA, Brown J, McKinlay CJ, Middleton P. Magnesium sulphate for preventing preterm birth in threatened preterm labour. *Cochrane Database Syst Rev*. 2014(8):CD001060.
87. Committee on Practice Bulletins: Obstetrics. ACOG Practice Bulletin No. 188: Prelabor rupture of membranes. *Obstet Gynecol*. 2018;131:e1–e14.
88. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 120: Use of prophylactic antibiotics in labor and delivery. *Obstet Gynecol*. 2011;117:1472–1483.
89. Dodd JM, Crowther CA. The role of progesterone in prevention of preterm birth. *Int J Womens Health*. 2010;1:73–84.
90. Society for Maternal-Fetal Medicine (SMFM) Publications Committee. The choice of progestogen for the prevention of preterm birth in women with singleton pregnancy and prior preterm birth. *Am J Obstet Gynecol*. 2017;216:B11–B13.
91. Committee on Obstetric Practice. Committee Opinion No. 713: Antenatal corticosteroid therapy for fetal maturation. *Obstet Gynecol*. 2017;130:e102–e109.
92. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev*. 2017(3):CD004454.
93. Yasuhi I, Myoga M, Suga S, et al. Influence of the interval between antenatal corticosteroid therapy and delivery on respiratory distress syndrome. *J Obstet Gynaecol Res*. 2017;43:486–491.
94. Phares CR, Lynfield R, Farley MM, et al. Epidemiology of invasive group B streptococcal disease in the United States, 1999-2005. *JAMA*. 2008;299:2056–2065.
95. Verani JR, McGee L, Schrag SJ. Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention. Prevention of perinatal group B streptococcal

disease: Revised guidelines from CDC, 2010. *MMWR Recomm Rep*. 2010;59(RR-10):1–36.

96. American College of Obstetricians and Gynecologists Committee on Obstetric Practice. ACOG Committee Opinion No. 485: Prevention of early-onset group B streptococcal disease in newborns. *Obstet Gynecol*. 2011;117:1019–1027.
97. Swamy GK. Current methods of labor induction. *Semin Perinatol*. 2012;36:348–352.
98. Sanchez-Ramos L. Induction of labor. *Obstet Gynecol Clin North Am*. 2005;32:181–200.
99. Committee on Practice Bulletins: Obstetrics. ACOG Practice Bulletin No. 107: Induction of labor. (Reaffirmed 2016). *Obstet Gynecol*. 2009;114(2 Pt 1):386–397.
100. Tenore JL. Methods for cervical ripening and induction of labor. *Am Fam Physician*. 2003;67:2123–2128.
101. Penfield CA, Wing DA. Labor induction techniques: Which is the best? *Obstet Gynecol Clin North Am*. 2017;44:567–582.
102. Committee on Practice Bulletins: Obstetrics. Practice Bulletin No. 177: Obstetric analgesia and anesthesia. *Obstet Gynecol*. 2017;129:e73–e89.
103. Arendt KW, Tessmer-Tuck JA. Nonpharmacologic labor analgesia. *Clin Perinatol*. 2013;40:351–371.
104. Levett KM, Smith CA, Bensoussan A, Dahlen HG. Complementary therapies for labour and birth study: A randomised controlled trial of antenatal integrative medicine for pain management in labour. *BMJ Open*. 2016;6:e010691. doi:10.1136/bmjopen-2015-010691.
105. Jones L, Othman M, Dowswell T, et al. Pain management for women in labour: An overview of systematic reviews. *Cochrane Database Syst Rev*. 2012;(3):CD009234.
106. Koyyalamudi V, Sidhu G, Cornett EM, et al. New labor pain treatment options. *Curr Pain Headache Rep*. 2016;20:11. doi:10.1007/s11916-016-0543-2.
107. Heesen M, Bohmer J, Klohr S, et al. The effect of adding a background infusion to patient-controlled epidural labor analgesia on labor, maternal, and neonatal outcomes: A systematic review and meta-analysis. *Anesth Analg*. 2015;121:149–158.
108. Anim-Somuah M, Smyth RM, Cyna AM, Cuthbert A. Epidural versus

non-epidural or no analgesia for pain management in labour. *Cochrane Database Syst Rev*. 2018;(5):CD000331.

109. Mousa HA, Blum J, Abou El Senoun G, et al. Treatment for primary postpartum haemorrhage. *Cochrane Database Syst Rev*. 2014; (2):CD003249.
110. Evensen A, Anderson JM, Fontaine P. Postpartum hemorrhage: Prevention and treatment. *Am Fam Physician*. 2017;95:442–449.
111. Committee on Practice Bulletins: Obstetrics. Practice Bulletin No. 183: Postpartum hemorrhage. *Obstet Gynecol*. 2017;130: e168–e186.
112. Begley CM, Gyte GM, Devane D, McGuire W, Weeks A. Active versus expectant management for women in the third stage of labour. *Cochrane Database Syst Rev*. 2015;(3):CD007412.
113. Section on Breastfeeding. Breastfeeding and the use of human milk. *Pediatrics*. 2012;129:e827–e841.
114. Academy of Breastfeeding Medicine Protocol Committee. ABM Clinical Protocol #9: Use of galactogogues in initiating or augmenting the rate of maternal milk secretion (First Revision January 2011). *Breastfeed Med*. 2011;6:41–49.
115. Rowe H, Baker T, Hale TW. Maternal medication, drug use, and breastfeeding. *Child Adolesc Psychiatr Clin N Am*. 2015;24:1–20.
116. Sachs HC; Committee On Drugs. The transfer of drugs and therapeutics into human breast milk: An update on selected topics. *Pediatrics*. 2013;132:e796–e809.
117. Berlin CM Jr., van den Anker JN. Safety during breastfeeding: drugs, foods, environmental chemicals, and maternal infections. *Semin Fetal Neonatal Med*. 2013;18:13–18.
118. Amir LH, Academy of Breastfeeding Medicine Protocol C. ABM clinical protocol #4: Mastitis, revised March 2014. *Breastfeed Med*. 2014;9:239–243.
119. Molyneaux E, Howard LM, McGeown HR, Karia AM, Trevillion K. Antidepressant treatment for postnatal depression. *Cochrane Database Syst Rev*. 2014;(9):CD002018.

96

Menstruation-Related Disorders

Kai I. Cheang and Elena M. Umland

KEY CONCEPTS

1. While a urine pregnancy test should be one of the first steps in evaluating amenorrhea, the majority of primary amenorrhea case can be attributed to either physical anomalies of the gonads, outflow tract or anomalies of the hypothalamic–pituitary–ovarian (HPO) axis.
2. For hypoestrogenic conditions associated with primary and secondary amenorrhea, if correction of the underlying cause does not restore menses, estrogen (with a progestin) is recommended.
3. Heavy menstrual bleeding (HMB) is generally caused by either uterine structural abnormalities or nonstructural causes.
4. Pregnancy, including intrauterine pregnancy, ectopic pregnancy, and miscarriage, must be at the top of the differential diagnosis for any woman presenting with heavy menses.
5. When compared to other conventional medical therapies used for HMB, the levonorgestrel intrauterine system is associated with a 61% lower discontinuation rate and 82% fewer treatment failures.
6. Intrauterine systems (IUS) or devices are considered therapeutic options in a variety of menstruation-related disorders. Guidelines from the American College of Obstetricians and Gynecologists (ACOG) indicate that both nulliparous and multiparous women at low risk of sexually transmitted diseases are good candidates for IUS use.
7. Abnormal uterine bleeding associated with ovulatory dysfunction (AUB-O) is caused by oligo- or anovulation, leading to irregular, heavy menstrual bleeding due to chronic unopposed estrogen on the endometrium.
8. Polycystic ovary syndrome (PCOS) can present as AUB-O, and symptoms include amenorrhea, oligomenorrhea, intermenstrual bleeding, and HMB.

Although its exact definition continues to evolve, it is a disorder of androgen excess accompanied by ovulatory dysfunction and/or polycystic ovarian morphology. Insulin resistance is often present, and PCOS is a risk factor for the metabolic syndrome, type 2 diabetes, dyslipidemia, hypertension, and possibly cardiovascular disease.

9. Combined hormonal contraceptives (CHCs) alone should be recommended for the management of irregular menstrual cycles and clinical hyperandrogenism in adult women and adolescents with PCOS.
10. The selective serotonin reuptake inhibitors (SSRIs) are first-line pharmacologic treatment options for premenstrual dysphoric disorder (PMDD).

Preclass Engaged Learning Activity

Watch the video entitled “The Menstrual Cycle” https://tinyurl.com/szk3dt7. This 9-minute video provides an overview of a normal menstrual cycle and its hormonal regulation. The video is useful to enhance student understanding of the pathophysiology of various menstrual disorders.

INTRODUCTION

Problems related to the menstrual cycle are exceedingly common in women of reproductive age. This chapter discusses the most frequently encountered menstruation-related difficulties: amenorrhea; heavy menstrual bleeding (HMB); abnormal uterine bleeding associated with ovulatory dysfunction (AUB-O), including polycystic ovary syndrome (PCOS); dysmenorrhea; and premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD). The need for effective treatments of these disorders stems from their negative impact on any or all of the following: quality of life, reproductive health, and long-term detrimental health effects, such as increased risk of osteoporosis with amenorrhea and risk of diabetes with PCOS.

Before menstrual disorders are discussed, what constitutes a normal menstrual cycle needs to be considered. The American College of Obstetrics and Gynecologists recommends that clinicians should ask about an individual’s first day of her last menstrual period, as well as her pattern of menses, during every clinical encounter.[1] Identification of menstrual patterns should begin in

adolescence, which may improve the early detection of potential health concerns.[1]

In adolescents, immaturity of the hypothalamic–pituitary–ovarian axis in the early years after menarche may lead to longer cycles due to anovulation.[1] However, 90% of these cycles will be within the range of 21 to 45 days.[1] The following menstrual characteristics and patterns are considered normal:[1]

- Median age of menarche of 12.4 years, and menarche by age 15
- Menstrual cycle interval between 21 and 45 days
- Menstrual flow length 7 days or less
- Menstrual product use between 3 to 6 pads or tampons per day

In adult females not using hormonal contraception, a normal menstrual period lasts between 4.5 and 8 days, and cycle lengths range from 24 to 28 days.[2] Blood loss between 5 and 80 mL during each period is considered normal.[2]

AMENORRHEA

EPIDEMIOLOGY

Amenorrhea is defined as no menstrual bleeding in a 90-day period,[2] and can be either primary or secondary in nature. Primary amenorrhea is the absence of menses by age 15 years in women who have never menstruated.[3] Secondary amenorrhea is the absence of menses for three cycles or for 6 months in a previously menstruating woman.[3,4]

Primary amenorrhea occurs in less than 0.1% of the general population. Secondary amenorrhea, in comparison, has an incidence of 3% to 4% in the general population and occurs more frequently in women younger than 25 years with a history of menstrual irregularities and in those involved in competitive athletics.[5]

Etiology

In two-thirds of women, menses occur generally at 28 + 3 days, and cycle lengths of 18 to 40 days are considered within the normal range.[4] Amenorrhea is not itself a diagnosis, but a sign of a disorder.[4] There are three broad categories

of amenorrhea etiology:

- Anatomical causes, including pregnancy and uterine structural abnormalities
- Endocrine disturbances leading to chronic anovulation
- Ovarian insufficiency/failure

1 While a urine pregnancy test should be one of the first steps in evaluating amenorrhea, the majority of primary amenorrhea cases can be attributed to either anomalies involving (i) the hypothalamic–pituitary axis resulting in endocrine disturbances, (ii) ovarian function or (iii) outflow tract.[6] Similarly, greater than 50% of secondary amenorrhea cases are due to the impact of disturbances of the hypothalamic–pituitary–adrenal (HPA) axis or the hypothalamic–pituitary–ovarian (HPO) axis.[5] Therefore, in organizing an approach to diagnosis and treatment, it is helpful to consider the organ systems involved in the menstrual cycle, which include the uterus, ovaries, anterior pituitary, and hypothalamus.

PATHOPHYSIOLOGY

Ovulation is required for the follicle (an estrogen-secreting body) to become a corpus luteum (a progesterone-secreting body). Without ovulation, the proper sequence of estrogen production, progesterone production, and estrogen/progesterone withdrawal will not occur. This can result in amenorrhea. Anovulation can occur secondary to endocrine disturbances or ovarian insufficiency.

Each organ in the HPO axis, along with the uterus, is of importance in determining amenorrhea's etiology and pathophysiology. Beginning with the uterus/outflow tract and progressing caudally will result in a comprehensive differential diagnosis. However, coexisting physical signs and symptoms, and a thorough history, typically help the clinician prioritize evaluation steps. **Table 96-1** lists the pathophysiology of amenorrhea relative to the organ system(s) involved and the specific condition(s) that results in amenorrhea.

TABLE 96-1 Pathophysiology of Selected Menstrual Bleeding Disorders

Organ System	Condition	Pathophysiology/Laboratory Findings
Amenorrhea		
Uterus	Asherman's syndrome	Postcurettage/postsurgical uterine adhesions
	Congenital uterine abnormalities	Abnormal uterine development
Ovaries	Turner's syndrome	Lack of ovarian follicles
	Gonadal dysgenesis	Other genetic abnormalities
	Premature ovarian failure	Early loss of follicles
	Chemotherapy/radiation	Gonadal toxins
Anterior pituitary	Pituitary prolactin-secreting adenoma	↑ Prolactin suppresses the HPO axis
	Hypothyroidism	TRH causes ↑ prolactin, other abnormalities
	Medication (antipsychotics, verapamil)	↑ Prolactin suppresses the HPO axis
Hypothalamus	FHA	↓ Pulsatile GnRH secretion in the absence of other abnormalities
	Eating disorder	↓ Pulsatile GnRH secretion, ↓ FSH and LH secondary to weight loss
	Exercise	↓ Pulsatile GnRH secretion, ↓ FSH and LH secondary to low body fat
	Anovulation/PCOS	Asynchronous gonadotropin and estrogen production, abnormal endometrial growth
Abnormal Uterine Bleeding Associated with Ovulatory Dysfunction (AUB-O)		
Physiologic causes	Adolescence	Immaturity of the HPO axis: no LH surge
	Perimenopause	Declining ovarian function
Pathologic causes	Hyperandrogenic anovulation (PCOS)	Hyperandrogenism: high testosterone, high LH, hyperinsulinemia, and insulin resistance
	Hypothalamic dysfunction (physical or emotional stress, exercise, weight loss)	Suppression of pulsatile GnRH secretion and estrogen deficiency: low LH, low FSH
	Hyperprolactinemia (pituitary gland tumor, psychiatric medications)	High prolactin
	Hypothyroidism	High TSH
	Premature ovarian failure	High FSH
Heavy Menstrual Bleeding (HMB)		
Hematologic	von Willebrand disease	Factor VII defect causing impaired platelet adhesion and increased bleeding time
	Idiopathic thrombocytopenic purpura	Decrease in circulating platelets, can be acute or chronic
Hepatic	Cirrhosis	Decreased estrogen metabolism, underlying coagulopathy
Endocrine	Hypothyroidism	Alterations in the HPO axis
Uterine	Fibroids	Alteration of endometrium, changes in uterine contractility
	Adenomyosis	Alteration of endometrium, changes in uterine contractility
	Endometrial polyps	Alteration of endometrium
	Gynecologic cancers	Various dysplastic alterations of endometrium, uterus, cervix

FHA, functional hypothalamic amenorrhea; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; HPO, hypothalamic–pituitary–ovarian axis; LH, luteinizing hormone; PCOS, polycystic ovary syndrome; TSH, thyroid-stimulating hormone; TRH, thyrotropin-releasing hormone.

Data from References 3-13.

Uterus/Outflow Tract

For menstruation to occur, a uterus, functional endometrium, and patent vagina must be present. Several anatomic abnormalities may cause amenorrhea.[6] Congenital anomalies such as imperforate hymen or uterine agenesis may be discovered by physical examination. An acquired condition of the genital tract, such as Asherman's syndrome or cervical stenosis, is more likely in secondary amenorrhea.

Ovaries

Normal ovarian function is critical for menstruation to occur. The ovaries must respond appropriately to follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by secreting estrogen and progesterone in the proper sequence to influence endometrial growth and shedding (**Figure 96-1**).

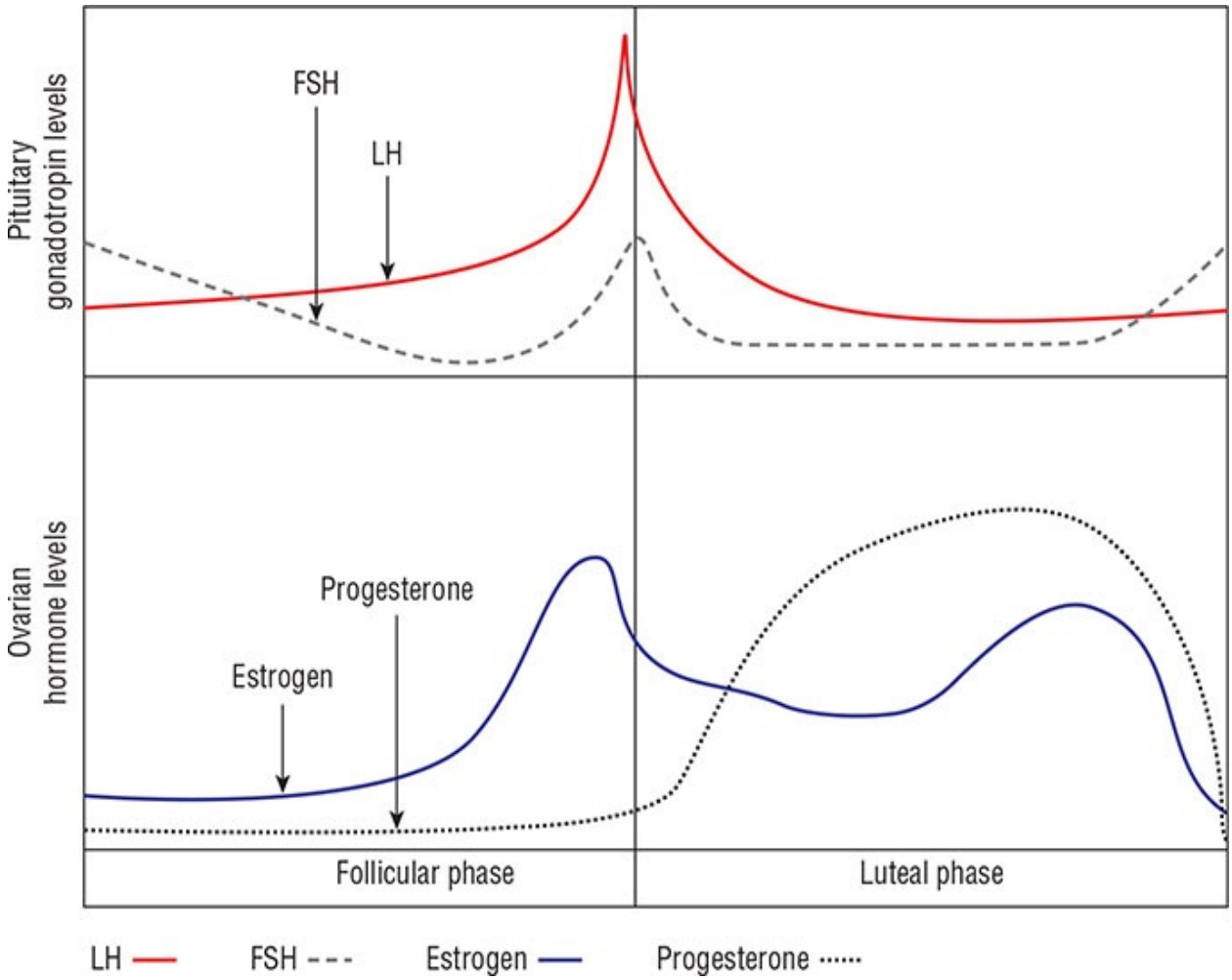


FIGURE 96-1 Hormonal fluctuations with the normal menstrual cycle. (FSH,

follicle-stimulating hormone; LH, luteinizing hormone.)

Primary ovarian insufficiency occurs when potentially viable primordial follicles in the ovaries have been depleted.[7] Estrogen production from the remaining ovarian follicles is insufficient to stimulate endometrial growth in the absence of follicles. The etiologies for primary ovarian insufficiency include bilateral oophorectomy,[14] genetic anomalies,[7] autoimmunity and iatrogenic causes as a result of radiation or chemotherapy.[15] However, in 90% of cases, the cause cannot be identified.[7]

CLINICAL PRESENTATION Amenorrhea

General

- Although patients may be concerned about the cessation of menses and implications for fertility, patients are generally not in acute physical distress.

Symptoms

- Patients will note cessation of menses.
- Patients may complain of infertility, vaginal dryness, or decreased libido.

Signs

- Cessation of menses for more than 6 months in women with established menstruation, absence of menses by age 16 in the presence of normal secondary sexual development, or absence of menses by age 14 in the absence of normal secondary sexual development.
- Recent significant weight loss or weight gain.
- Presence of acne, hirsutism, hair loss, or acanthosis nigricans may suggest androgen excess.

Laboratory Tests

- Pregnancy test
- Serum FSH and LH
- Thyroid-stimulating hormone

- Prolactin
- If hyperandrogenic state (eg, PCOS) is suspected, consider free and total testosterone, dehydroepiandrosterone, fasting glucose, and fasting lipid panel

Other Diagnostic Tests

- Progesterone challenge to confirm functional anatomy and adequate estrogenization.
- Pelvic ultrasound to evaluate for polycystic ovaries, presence/absence of uterus, and/or structural abnormalities of the reproductive tract organs.

Pituitary Gland

The anterior pituitary gland secretes FSH and LH in sequential fashion in response to hypothalamic stimulation and a complex ovarian feedback mechanism. Normal secretion of FSH and LH is altered by several endocrinologic and iatrogenic conditions, including thyroid disease, hyperprolactinemia, and dopaminergic drug administration.

Hypothalamus

The hypothalamus secretes cyclic gonadotropin-releasing hormone (GnRH), which causes the pituitary to produce FSH and LH. Disrupting this cyclic process interrupts the hormonal cascade that results in normal menstruation. Anorexia nervosa, bulimia, intense exercise, and stress may cause hypothalamic amenorrhea, known as functional hypothalamic amenorrhea (FHA). Further, recent research has confirmed the role of leptin insufficiency in causing hypogonadotropic hypogonadism leading to hypothalamic amenorrhea.[8]

TREATMENT

Desired Outcomes

In general, the treatment options for amenorrhea depend on its causes. Therapeutic modalities for amenorrhea should ensure the occurrence of normal puberty and restore the menstrual cycle. Treatment goals include bone density preservation, bone loss prevention, and ovulation restoration to improve fertility if desired. Hypoestrogenism may affect quality of life via hot flash induction

(premature ovarian failure), dyspareunia, and, in prepubertal females, lack of secondary sexual characteristics and absence of menarche. Treatment is targeted at reversing these effects.

General Approach to Treatment

The overall success of any intervention to treat amenorrhea depends on proper identification of the disorder's underlying cause(s). Once the cause is identified, the appropriate intervention(s) can be made. For patients experiencing amenorrhea secondary to hypoestrogenic states, a diet rich in calcium and vitamin D is essential to minimize any negative impact on bone health.

Nonpharmacologic Therapy

Nonpharmacologic therapy for amenorrhea varies depending upon the underlying cause. Amenorrhea secondary to anorexia may respond to weight gain. In young women for whom excessive exercise is an underlying cause, reduction of exercise quantity and intensity are important. Evaluation for a possible eating disorder may be appropriate (see Chapter 81 "Eating Disorders," for more information). Cognitive behavioral therapy has been shown to restore ovarian function in women with FHA.[9] In 2017, the Endocrine Society Clinical Practice Guideline recommended a reasonable trial of psychological, nutrition and/or modified exercise intervention prior to use of pharmacotherapy in patients with FHA.[16] In medication-induced hyperprolactinemia (**Table 96-2**),[17] the clinician may consider alternative agents that do not inhibit dopamine receptors or increase prolactin levels.

TABLE 96-2 Medications That May Induce Hyperprolactinemia

Drug Class	Agents
Typical antipsychotics	Phenothiazines (eg, prochlorperazine, chlorpromazine)
	Butyrophenones (eg, haloperidol)
	Thioxanthenes (eg, chlorprothixene)
Atypical antipsychotics	Risperidone
	Molindone
Antidepressants	Clomipramine
Monoamine oxidase inhibitors	Pargyline
	Clorgyline
Antihypertensives	Verapamil
Gastrointestinal promotility agents	Metoclopramide
	Domperidone

Data from Reference 17.

Pharmacologic Therapy

2 For hypoestrogenic conditions associated with primary or secondary amenorrhea, historically estrogen has been supplemented as an oral contraceptive, conjugated equine estrogen, or estradiol patch, in conjunction with progestin in an attempt to decrease osteoporosis risk. However, data supporting estrogen supplementation in FHA are based on a limited number of studies with small sample size and short follow-ups.[18] Therefore, the primary approach for FHA should be the correction of energy balance to restore HPO axis function.[18] The 2017 Endocrine Society Clinical Practice Guideline for FHA recommends the short-term use of transdermal estradiol with cyclic oral progestins, after an adequate trial of nonpharmacological therapy (eg, psychological and nutritional intervention).[16] Combined hormonal contraceptives (CHC) and synthetic ethinyl estradiol are no longer recommended as first-line agents for patients with FHA.[16] However, CHCs are also useful for pregnancy prevention, treatment of acne and other conditions in this population.[16] For women with primary ovarian insufficiency, a prospective study with estradiol 100 mcg/day transdermal patch suggested improvement in bone mineral density to normal population values.[19] **Table 96-3** lists therapeutic agents for amenorrhea treatment, including recommended doses. **Figure 96-2** illustrates a treatment algorithm for the management of amenorrhea.

TABLE 96-3 Therapeutic Agents for Selected Menstrual Disorders

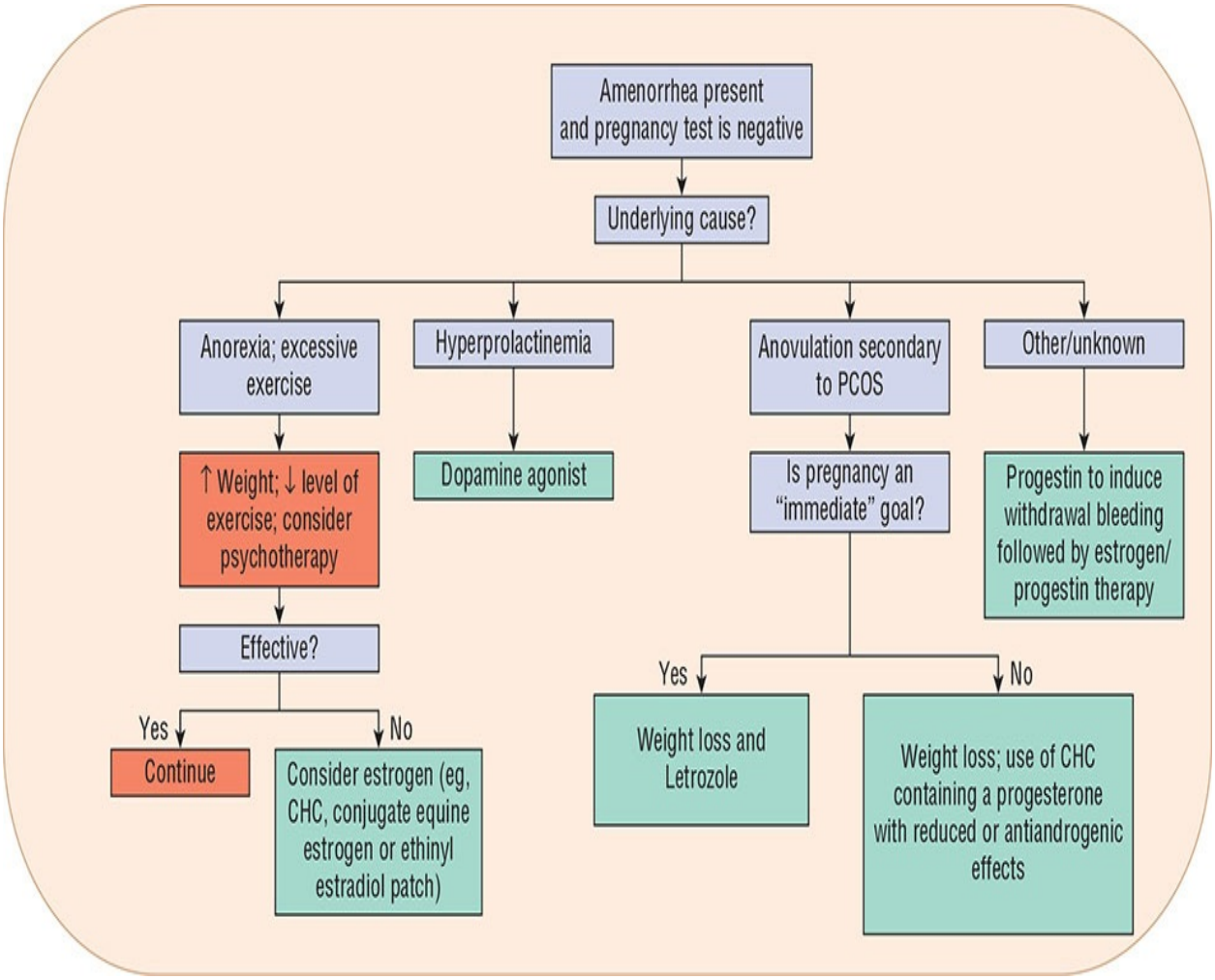
Specific Menstrual Disorder(s)	Agent(s)	Brand Name(s)	Usual Recommended Dose
Amenorrhea (primary or secondary)[6,11,20,16]	CEE	Premarin®, Cenestin®, Enjuvia®	0.625-1.25 mg by mouth daily on days 1-25 of the cycle
	Ethinyl estradiol patch	Alora®, Climara®, Estraderm®, Vivelle-Dot®	50 mcg/24 hours
	CHC	Various	30-40 mcg formulations
Amenorrhea (secondary)[3,20,16]	Oral MPA	Provera®	5-10 mg by mouth on days 14-25 of the cycle
	Progesterone vaginal gel	Crinone®	1.125 g of 4% gel intravaginally every other day for 6 doses; if no response, increase to 8% gel for 6 doses
	Norethindrone	Aygestin®	5 mg by mouth daily for 7-10 days
	Micronized progesterone	Prometrium®	400 mg by mouth daily for 7-10 days
Amenorrhea related to hyperprolactinemia[13,21]	Bromocriptine	Parlodel®, Parlodel® SnapTabs	2.5-15 mg daily in two to three divided doses
	Cabergoline	Dostinex®	0.25-2 mg by mouth once weekly or in two divided doses
Anovulatory bleeding[10]	CHC	Desogen 28®, Ortho-Cept 28®, Yasmin 28®, Yaz®, Beyaz®, and others	≤35 mcg ethinyl estradiol
Dysmenorrhea[22–24]	CHC	Examples include:Norgestrel containing: Cryselle 28®, Lo/Ovral 28®Levonorgestrel containing: Levora 28®, Nordette 28®, Aviane 28®, Lessina 28®Other progestins: Ortho Cyclen 28®, Ortho-Cept 28®, Yasmin 28®, Yaz®Extended-cycle: Introvale®, Quasense®, Seasonale®, Seasonique®, LoSeasonique®, Lybrel®	<35 mcg formulations; use of extended-cycle formulations may be beneficial for this indication
	Injectable MPA	Depo-Provera®, Depo-SubQ Provera 104®	150 mg intramuscularly or 104 mg subcutaneously every 12 weeks
	LNG-IUS	Mirena®	20 mcg released daily
	NSAIDs (any are acceptable); the most commonly studied/cited are included in this table	Ibuprofen (Motrin®, Advil®),	Ibuprofen 800 mg by mouth initially, followed by 400-800 mg every 8 hours as needed
		Naproxen (Naprosyn®)	Naproxen 440-550 mg by mouth initially, followed by 220-550 mg every 12 hours as needed
		Mefanamic acid (Ponstel®)	500 mg by mouth initially, followed by 250 mg every 6 hours as needed
		Celecoxib (Celebrex®)	400 mg by mouth initially, followed by 200 mg every 12 hours as needed
Heavy Menstrual Bleeding[25–30]	CHC	Various Estradiol valerate/dienogest (Natazia®)	Optimal dose unknown
	LNG-IUS	Mirena®	20 mcg released daily
	Oral MPA	Provera®	5-10 mg by mouth on days 5-26 of the cycle or during the luteal phase
	Tranexamic acid	Lysteda®	1,300 mg by mouth every 8 hours once heavy bleeding begins; dose for 4-7 days as needed per cycle
PCOS-related amenorrhea and/or AUB-O[31,32]	Injectable MPA CHC	Depo-Provera®, Depo-SubQ Provera 104®Desogestrel containing: Desogen 28®, Ortho-Cept 28®Norgestimate containing: OrthoTri-Cyclen Lo®Drospirenone containing: Yasmin 28®, Yaz®, Beyaz®	150 mg intramuscularly or 104 mg subcutaneously every 12 weeks ≤30 mcg ethinyl estradiol with either desogestrel, norgestimate or drospirenone
	Oral MPA	Provera®	10 mg by mouth for 10 days[5]
	Metformin	Glucophage®, Fortamet®, Glucophage XR®, Glumetza®	1,500-2,000 mg by mouth daily[21]
PMDD[33–37]	Clomipramine	Anafranil®	25-75 mg by mouth daily taken either continuously or only during the luteal phase
	Drospirenone	Yasmin 28®, Yaz®, Beyaz®	3 mg (+ ≤30 mcg ethinyl estradiol) by mouth on days 1-21 of the menstrual cycle[23]
	Leuprolide	Lupron Depot®	3.75 mg intramuscularly[22]

Specific Menstrual Disorder(s)	Agent(s)	Brand Name(s)	Usual Recommended Dose
PMDD	SSRIs	Citalopram = Celexa®; escitalopram = Lexapro®; fluoxetine = Prozac®, Sarafem®; paroxetine = Paxil®; sertraline = Zoloft®	Citalopram 10-30 mg; escitalopram 10-20 mg; fluoxetine 10-20 mg; fluvoxamine 50 mg; paroxetine 10-30 mg; sertraline 25-150 mg; all agents are given by mouth daily and can be dosed either continuously or during the luteal phase only
	SNRIs	Venlafaxine = Effexor®, Effexor XR®; duloxetine = Cymbalta®	Venlafaxine 50-200 mg, can be dosed continuously or during the luteal phase only; duloxetine 60 mg dosed continuously

CEE, conjugated equine estrogen; LNG-IUS, levonorgestrel intrauterine system; MPA, medroxyprogesterone acetate; NSAID, nonsteroidal anti-inflammatory drug; CHC, combined hormonal contraceptive; PCOS, polycystic ovary syndrome; PMDD, premenstrual dysphoric disorder; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin–norepinephrine reuptake inhibitors.

Data from References 3, 6,10,11,13,16, and 20-37.

FIGURE 96-2 Treatment algorithm for amenorrhea. (CHC, combined hormonal contraceptive; PCOS, polycystic ovary syndrome.)



When hyperprolactinemia is the cause of amenorrhea, dopamine agonists such as bromocriptine and cabergoline aid in reducing prolactin concentrations and the resumption of menses. Bromocriptine normalizes prolactin levels in 58% of affected women while cabergoline has the same effect in 85%.[16]

Progestins induce withdrawal bleeding in women with secondary amenorrhea and Table 96-3 outlines the doses for various progestins. Absence of withdrawal bleeding after a progestin challenge may suggest outflow tract obstruction or insufficient endometrial estrogen exposure.[16]

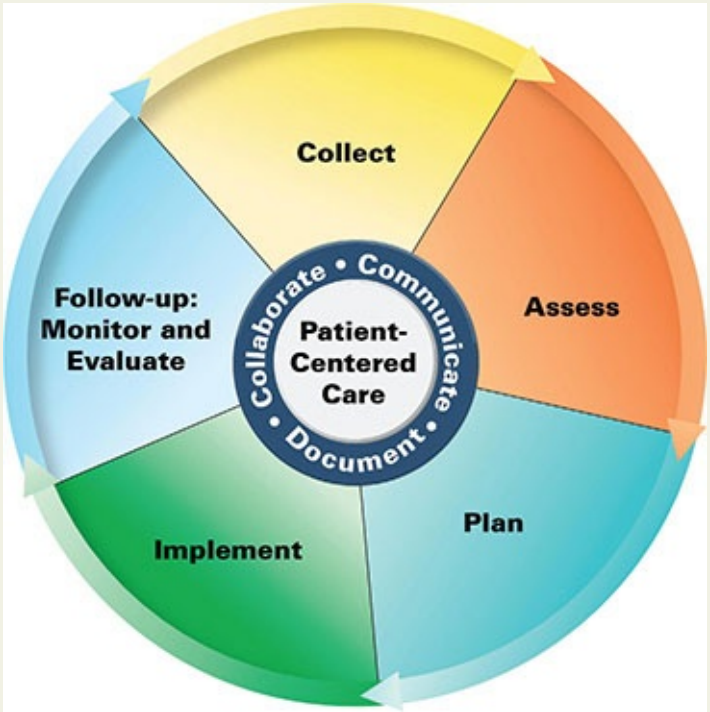
Progestin efficacy for secondary amenorrhea varies by formulation used. Progesterone in oil administered intramuscularly results in withdrawal bleeding in 70% of treated patients, whereas oral medroxyprogesterone acetate (MPA) induces withdrawal bleeding in 95% of treated patients.[38] Table 96-3 identifies the types and doses of progestins used for secondary amenorrhea treatment and Fig. 96-2 illustrates when to consider progestin use for amenorrhea treatment.

Amenorrhea related to PCOS-induced anovulation is discussed subsequently

in the “abnormal uterine bleeding” section.

Special Populations

Amenorrhea in the adolescent population is of concern because developmentally this is the time when peak bone mass is achieved. The cause of amenorrhea, whether primary or secondary, must be promptly identified, as amenorrhea and its related hypoestrogenism negatively affect bone development. In addition to treating or eliminating amenorrhea’s underlying cause, ensuring that the patient is receiving adequate amounts of calcium and vitamin D is imperative. Estrogen replacement is important for bone health.



Patient Care Process for Menstruation-Related Disorders

Collect

- Patient characteristics (age)
- Patient medical history
    - First day of the last menstrual cycle
    - Age of menarche
    - Cycle length and predictability

    - Number of days of each menstrual cycle, and the number of absorbent products used per day
    - History of current symptoms including relationship with menstrual cycles
    - Menstrual diary and recorded symptoms
- Social history (eg, tobacco/ethanol use), dietary and physical activity habits (especially for women with PCOS)
- Current medications including over-the-counter nonsteroidal anti-inflammatory drug (NSAID) use, herbal products, and dietary supplements
- Objective data
    - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight
    - Labs depend on suspected underlying conditions. Common labs include follicle stimulating hormone (FSH) and thyroid stimulating hormone (TSH) (see Table 96-1). Total and free testosterone, other androgen precursors, glucose tolerance test and fasting lipids may be obtained if PCOS is suspected. If anemia associated with heavy menstrual bleeding is suspected, obtain CBC with differential.

Assess

- Presence of severe anemia or acute bleeding that necessitates immediate treatment
- Presence of suicidal ideation associated with premenstrual dysphoric disorder that necessitates immediate psychiatric evaluation and treatment
- Whether the patient desires contraception or is attempting pregnancy
- Comorbid conditions that may affect treatment choice (eg, a nonestrogen-containing regimen should be considered in a patient with a history of deep venous thrombosis, and NSAID should not be an initial choice for a patient with a history of GI bleed).
- Acceptability of available treatment choice to the patient

Plan*

- Drug therapy regimen including specific agent(s), dose, route, frequency, and duration (see Table 96-3)
- Monitoring parameters including efficacy and safety (see Table 96-4)

- Patient education (eg, purpose of treatment, dietary and lifestyle modification, invasive procedures, drug-specific information)
- Referrals to other providers when appropriate (eg, thrombosis specialist to evaluate bleeding disorders, behavioral health, dietician)

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence in lifestyle interventions for women with PCOS

Follow-up: Monitor and Evaluate

- Resolution of symptoms
- Presence of adverse effects
- Patient adherence to treatment plan using multiple sources of information
- Reevaluate therapy as life goals change (eg, changing from desiring contraception to desiring fertility)

**Collaborate with patient, caregivers, and other healthcare professionals.*

EVALUATION OF THERAPEUTIC OUTCOMES

Table 96-4 identifies the mechanisms of action, expected outcomes, and monitoring parameters for pharmacologic agents used for amenorrhea management.

TABLE 96-4 Pharmacologic Properties and Monitoring Parameters for Select Agents or Classes of Medications Used in the Management of Menstrual Disorders

Therapeutic Agent or Drug Class	Mechanism of Action/Role in Particular Menstrual Disorders	Adverse Drug Reactions	Monitoring for Expected Outcomes of Specific Menstrual Disorders	Comments
Dopamine agonists (bromocriptine and cabergoline)	Suppresses prolactin production from pituitary tumors such that resumption of normal FSH and LH production occurs	Hypotension, nausea, constipation, anorexia, Raynaud's phenomenon, fatigue, headache	Amenorrhea related to hyperprolactinemia: Baseline and weekly prolactin levels should be measured with dosage increases until resumption of menses is observed. Continue therapy for 6-12 months following return of menses and continued normalization of serum prolactin levels	Inhibits CYP3A4 and is metabolized by CYP3A4 St John's Wort induces CP3A4; coadministration may lead to treatment failure
Tricyclic Antidepressants (clomipramine)	PMDD: Exact mechanism unknown	Dry mouth, constipation, fatigue, vertigo, sweating	Reduction in or absence of initial symptoms and improved quality of life within 1-3 menstrual cycles of therapy	
Oral combined hormonal contraception (CHC)	Exogenous estrogen and progesterone that suppresses FSH and LH production and thus inhibits ovulation Can be used to reduce menstrual flow (menorrhagia, dysmenorrhea), and control menstrual cycle (anovulatory bleeding secondary to hypoestrogenism)	Thromboembolism, breast enlargement, breast tenderness, bloating, nausea, GI upset, headache, peripheral edema	Amenorrhea: Resumption of menses within 1-2 months of therapy Anovulatory bleeding: Improvement in pattern of abnormal bleeding within 1-2 months of therapy Dysmenorrhea: Reduction in or absence of pelvic pain within 1-2 months of therapy Menorrhagia: Reduction in blood loss with menses over 1-2 months of therapy. Improvement in hemoglobin/hematocrit after 3 months of therapy compared to baseline	St John's Wort contributes to altered menstrual bleeding Rifampin induces estrogen metabolism, possibly contributing to treatment failure Sulfa-containing drugs may contribute to increased photosensitivity
Conjugated equine estrogen (CEE)	Estrogen replacement for hypoestrogenic states leading to anovulatory bleeding	As noted for oral CHC	Anovulatory bleeding: Improvement in pattern of abnormal bleeding within 1-2 months of therapy	Same as oral CHC
Drospirenone-containing CHCs	Progesterone with antimineralocorticoid and antiandrogenic properties; decreases emotional lability associated with PMDD	As noted for oral CHC; increased risk of hyperkalemia	PCOS-related amenorrhea or anovulatory bleeding: In addition to the improvement in the pattern of abnormal bleeding within 1-2 months of treatment, women should also experience an improvement in androgen-excess symptoms such as acne/oily skin and hirsutism	Same as oral CHC Coadministration of potassium-sparing diuretics or diets high in potassium may contribute to increased serum potassium concentrations, particularly in women with renal dysfunction
Ethinyl estradiol transdermal patch	Same as combination oral CHC and CEE	As noted for oral CHC; however, lesser effects on serum cholesterol concentrations because patch avoids first-pass metabolism	Amenorrhea: Resumption of menses within 1-2 months of therapy	Same as oral CHC
Leuprolide	GnRH agent that contributes to suppression of FSH and LH and ultimately a reduction in estrogen and progesterone, inhibiting the normal menstrual cycle/hormonal fluctuations	Hot flashes, night sweats, headache, nausea	PMDD: Improvement in PMDD signs and symptoms within 1-2 months of therapy	
Levonorgestrel Intrauterine System (LNG-IUS)	Suppresses FSH and LH and ultimately estrogen and progesterone, inhibiting the usual growth of the endometrium	Irregular menses, amenorrhea	Dysmenorrhea: Reduction in or absence of pelvic pain after 1-2 months of therapy Menorrhagia: Reduction in blood loss with menses over 1-2 months of therapy. Improvement in hemoglobin/hematocrit after 3 months of therapy compared to baseline	
Medroxyprogesterone acetate (MPA) (oral and injectable)	Suppresses FSH and LH and ultimately estrogen and progesterone, inhibiting the usual growth of the endometrium	Edema, anorexia, depression, insomnia, weight gain or loss, increase in serum total and LDL cholesterol, may reduce HDL cholesterol	Dysmenorrhea: Reduction in or absence of pelvic pain after 1-2 months of therapy Menorrhagia: Reduction in blood loss with menses over 1-2 months of therapy. Improvement in hemoglobin/hematocrit after 3 months of therapy compared to baseline PCOS-related amenorrhea and/or anovulatory bleeding: Resumption of menses over 1-2 courses of therapy	

Metformin	Inhibits hepatic glucose production and increases sensitivity of tissues to insulin, thus reducing insulin resistance	Anorexia, nausea, vomiting, diarrhea, flatulence, lactic acidosis (rare)	PCOS-related amenorrhea and/or anovulatory bleeding: If desired, monitor for ovulation after 3-6 months of therapy	IV contrast dye may increase the risk of lactic acidosis; stop metformin 1 day prior and restart when renal function is normal and stabilized following the IV dye
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Inhibits prostaglandin release that occurs with menses, thus reducing inflammatory response contributing to dysmenorrhea	GI upset, stomach ulcer, nausea, vomiting, heartburn, indigestion, rash, dizziness	Dysmenorrhea: Reduction in or absence of pelvic pain within hours of initiating.Menorrhagia: Reduction in blood loss with menses over 1-2 months of therapy	
Selective Serotonin Reuptake Inhibitors (SSRIs)	Exact mechanism in PMDD unknown	Sexual dysfunction (reduced libido, anorgasmia), insomnia, sedation, hypersomnia, nausea, diarrhea	Improvement in PMDD signs and symptoms observed within 1-3 months of therapy	
Tranexamic acid	Antifibrinolytic effects by reversibly blocking lysine binding sites on plasminogen, preventing fibrin degradation and a reduction in menstrual blood loss	Nausea, vomiting, diarrhea, dyspepsia	Menorrhagia: Reduction in blood loss with menses should be noticeable with the first month of therapy. Improvement in hemoglobin/ hematocrit after 3 months of therapy compared to baseline	
Venlafaxine	Exact mechanism in PMDD unknown		Improvement in PMDD signs and symptoms observed within 1-3 months of therapy	

CEE, conjugated equine estrogen; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LH, luteinizing hormone; LNG-IUS, levonorgestrel intrauterine system; MPA, medroxyprogesterone acetate; NSAID, nonsteroidal anti-inflammatory drug; PMDD, premenstrual dysphoric disorder; SSRI, selective serotonin reuptake inhibitor.

Data from References 10, 12-15, 21, 24, 27-29, 31-35, and 39.

HEAVY MENSTRUAL BLEEDING

EPIDEMIOLOGY

Heavy menstrual bleeding (HMB) is the term now used in place of menorrhagia.[12] The classical definition, however, remains the same: menstrual blood loss greater than 80 mL per cycle or menstrual bleeding lasting greater than 7 days per cycle.[12] This definition has been questioned because of difficulty

quantifying menstrual loss in clinical practice. Additionally, many women with "heavy menses" but whose blood loss is less than 80 mL merit treatment consideration because of flow containment issues, unpredictably heavy flow days, or other associated symptoms.[24,40] More recently, diagnosis has also been considered based upon the impact of HMB on quality of life and social, professional, familial, or sexual roles.

HMB is one of the most commonly encountered gynecological problems, accounting for 18% to 30% of gynecologic visits.[26] HMB affects a woman's physical, psychological, and social function. The amount of blood loss may make it impractical or embarrassing to leave home for fear of soiling outer garments, leading to decreased work productivity and limited social activities.[26]

ETIOLOGY

3 4 The International Federation of Gynecology and Obstetrics Menstrual Disorders Working Group created the PALM-COEIN classification system to define the causes of abnormal uterine bleeding (AUB).[41] The PALM group of classification includes structural causes of AUB: **P**olyp, **A**denomyosis (endometrial tissue within the myometrium), **L**eiomyoma (also known as Fibroids), and **M**alignancy.[41] The COEIN components include nonstructural causes: **C**oagulopathy, **O**vulatory disorders, and **E**ndometrial disorders, **I**atrogenic causes and **N**ot classified.[41] Combined the PALM-COEIN classification also characterizes intermenstrual bleeding as bleeding that occurs between predictable and clearly cyclic menses, while AUB is defined as bleeding that is abnormal in either regularity, timing, or volume.[26,41] Under these definitions, HMB specifically refers to an abnormally excessive volume of menstrual bleeding that affects the woman's quality of life. Causes of HMB may include AUB due to polyps (AUB-P), adenomyosis (AUB-A), leiomyoma (AUB-L), as well as nonstructural causes such as coagulopathy (AUB-C), and endometrial dysfunction (AUB-E).[26] Pregnancy, including intrauterine pregnancy, ectopic pregnancy, and miscarriage, must be at the top of the differential diagnosis list for any woman presenting with heavy menses.[8] Bleeding disorders including von Willebrand disease, symptomatic hemophilia, platelet dysfunction, and Factor VIII and IX deficiencies must also be considered as these were found to exist in 20% of women with HMB.[11] Hypothyroidism also may be associated with heavy menses.[11,42] Additionally, uterine structural abnormalities, such as polyps, adenomyosis, and leiomyoma, are not uncommon

in women with HMB,[26] with fibroids, specifically, being identified in as many as 40% of women with HMB.[29]

PATHOPHYSIOLOGY

HMB may be the result of one of several very diverse causes including hematologic, hepatic, endocrine, and/or uterine disorders. Table 96-1 lists the pathophysiology of HMB relative to the organ system(s) involved and the specific conditions that may result in HMB.

TREATMENT

Desired Outcomes

The primary goal of treatment for HMB is to reduce menstrual flow. Along with this, treatments should be initiated to improve the patient's quality of life, and defer the need for surgical intervention.

CLINICAL PRESENTATION Heavy Menstrual Bleeding

General

- Patients may or may not be in acute distress.

Symptoms

- Patients may complain of heavy/prolonged menstrual flow. They also may have signs of fatigue and lightheadedness in cases of severe blood loss. These symptoms may or may not occur with dysmenorrhea.

Signs

- Orthostasis, tachycardia, and pallor may be noted in cases of significant anemia or acute blood loss.

Laboratory Tests

- Complete blood count and ferritin levels; hemoglobin and hematocrit results may be low.
- If the history dictates, testing (eg, prothrombin time, activated partial thromboplastin time, international normalized ratio, von Willebrand

factor antigen, Factor VIII, factor IX activity) may be performed to identify coagulation disorder(s) as a cause.

Other Diagnostic Tests

- Pelvic ultrasound
- Pelvic magnetic resonance imaging
- Papanicolaou (Pap) smear
- Endometrial biopsy
- Hysteroscopy
- Sonohysterogram

General Approach to Treatment

As several treatment options exist for HMB, the choice regarding which specific agent to use depends on the patient's treatment history, concomitant concerns, and the side effect profile for the various agents.

Nonpharmacologic Therapy

Nonpharmacologic interventions for HMB include surgical procedures generally reserved for patients not responding to pharmacologic treatment. These interventions vary from conservative endometrial ablation to hysterectomy.[26,40]

Pharmacologic Therapy

While surgical treatment may be an option for HMB, effective medical treatments are recommended as the initial treatment choice. Estrogen is the recommended treatment for managing acute severe bleeding episodes in women without suspected or known bleeding disorders.[43] Following its initial use to control acute bleeding episodes, therapy continuation may be necessary to prevent future occurrences. Both estrogen-containing CHCs and progestin-only regimens can be used for maintenance therapy.[26] Although it is assumed that all CHCs will reduce menstrual blood loss, the only agent that has been FDA approved is a combination of estradiol valerate and dienogest.[26] Table 96-3 identifies the variety of pharmacologic treatment options and their recommended dosing for HMB management.

Among the agents used to treat HMB, the nonsteroidal anti-inflammatory drugs (NSAIDs) have the advantage of administration only during menses and are associated with a 10% to 51% reduction in blood loss.[26] For women desiring to avoid pregnancy, CHC should be considered as a 30% to 60% reduction in menstrual blood loss has been observed.[26] The one-year continuation rates of CHCs in women with HMB range from 72% to 84%.[26] The best studied CHC option for HMB, and the only agent approved by the FDA for the indication of HMB is the four-phasic formulation containing estradiol valerate and dienogest.[25,26]

For women with contraindications to CHCs, progestin-only methods induce amenorrhea and reduce menstrual blood loss.[26] Cyclic progesterone therapy for 14 days, administered as oral norethindrone acetate or medroxyprogesterone acetate, reduces menstrual blood loss in only 2% to 30% of women.[26] However, when administered as long course (for 21 days, starting on day 5 after onset of menses), they reduce menstrual blood loss in 63% to 78% of women.[26]

Another progestin-only treatment option for HMB is the levonorgestrel-releasing intrauterine system (LNG-IUS). This is considered the most effective treatment to reduce menstrual flow.[26] In particular, a 70% to 96% reduction in blood loss has been observed with its use,[26] and its use has also resulted in postponing or canceling scheduled endometrial ablation surgery or hysterectomy.[39] Among women using this treatment option, only 9% eventually opted for surgery.[39] Further, its therapeutic efficacy is similar to endometrial ablation up to 2 years following treatment.[30]

Tranexamic acid is also approved in the United States for primary HMB treatment. Its use is associated with 34% to 56% reduction in menstrual blood loss.[26] Compared to many of the other options, its use may be preferable among women desiring pregnancy or in whom hormonal therapy may not be appropriate.

5 For women in whom pregnancy is not an immediate goal, it is reasonable to start with either a CHC or the LNG-IUS. While either choice is acceptable for both nulligravid and multiparous women who desire a long-term reversible form of contraception, cost-effectiveness data suggest LNG-IUS is the best first-line choice for women desiring contraception.[29,40] Clinical trial data illustrate a higher failure rate with the oral CHCs (32%) compared to the LNG-IUS (11%) as the primary treatment method.[29] When compared to other conventional medical therapies used for HMB, the LNG-IUS is associated with a 61% lower discontinuation rate and 82% fewer treatment failures.[27]

For women who have HMB associated with ovulatory cycles and do not desire hormonal therapy and/or contraception, NSAIDs during menses is a reasonable choice in the absence of any contraindications or GI disorders such as peptic ulcer disease or gastroesophageal reflux disease. This choice is convenient (only taken during menses) and comparatively inexpensive. Given their side effects, reduced efficacy compared to the first-line agents, and/or cost, use of oral progesterone, and depot MPA should be reserved. Tranexamic acid is another treatment option that can be taken only during menses.[26] **Figure 96-3** presents an algorithm for HMB treatment.

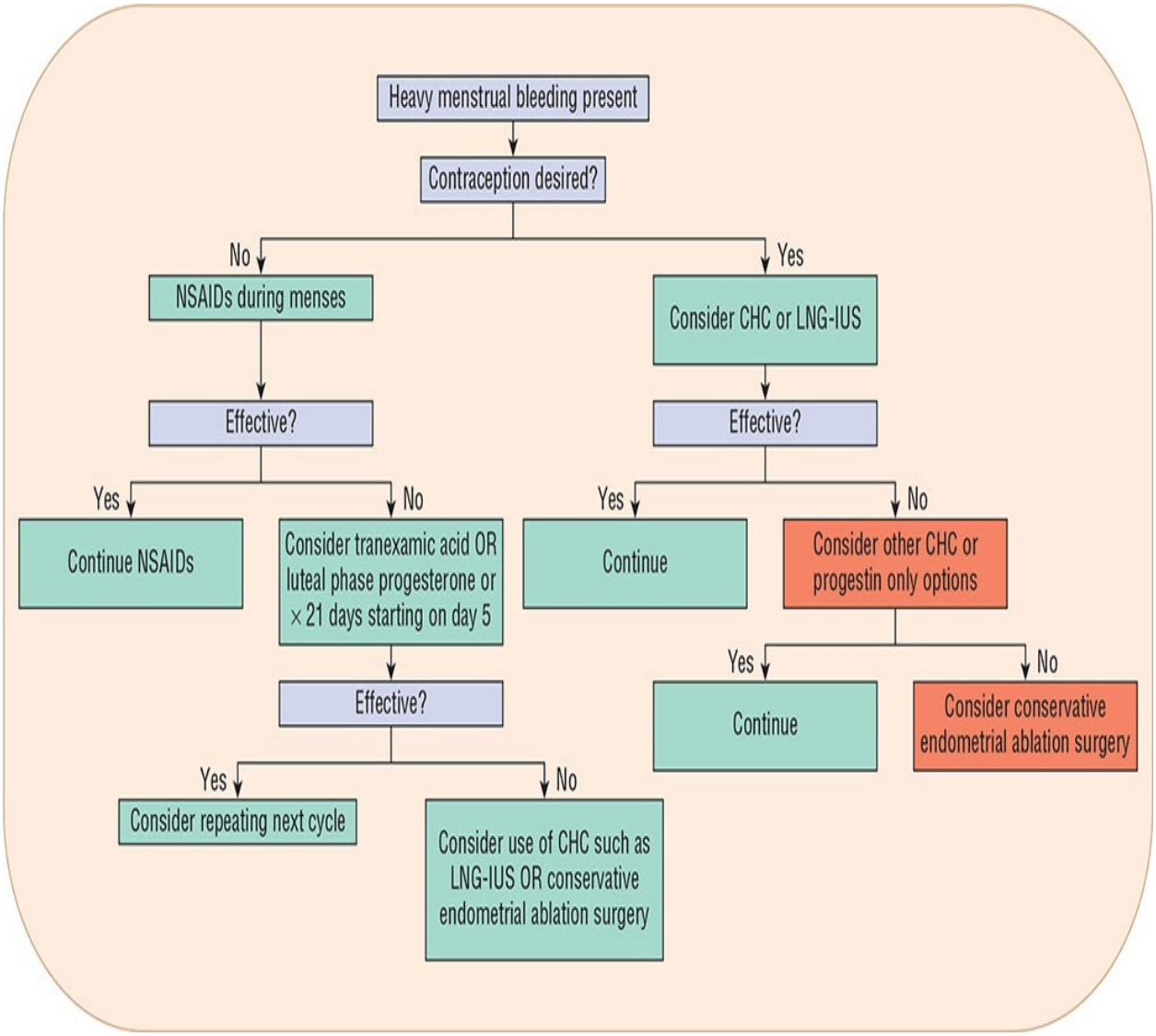


FIGURE 96-3 Treatment algorithm for HMB. (CHC, combined hormonal contraceptive; LNG-IUS, levonorgestrel-releasing intrauterine system; NSAIDs, nonsteroidal anti-inflammatory drugs.)

Special Populations

6 Although historically it was believed that IUS use should be avoided in nulliparous women, guidelines from the American College of Obstetricians and Gynecologists (ACOG) indicate that both multiparous and nulliparous women (including adolescents) at low risk of sexually transmitted diseases are good candidates for intrauterine system (IUS) use.[44] Therefore, any of the treatments discussed (including the LNG-IUS) are options in females presenting with HMB.

Dosage adjustment for tranexamic acid is recommended for reduced renal function. Women with serum creatinine between 1.4 and 2.8 mg/dL (124 and 248 µmol/L) should receive only 1,300 mg by mouth twice daily; women with serum creatinine between 2.9 and 5.7 mg/dL (256 and 504 µmol/L) should receive 1,300 mg by mouth once daily; those with serum creatinine above 5.7 mg/dL (504 µmol/L) should receive 650 mg by mouth once daily. Additionally, due to its potential to increase the risk for venous thromboembolism, it should be used with extreme caution in women with a history of thrombosis and should not be combined with estrogen-containing contraceptives.

EVALUATION OF THERAPEUTIC OUTCOMES

Table 96-4 identifies the significant pharmacologic properties of agents used for the management of HMB, the expected outcomes for each agent, and specific monitoring parameters for the treatment modalities used in HMB management.

ABNORMAL UTERINE BLEEDING WITH OVULATORY DYSFUNCTION

EPIDEMIOLOGY

7 Abnormal uterine bleeding associated with ovulatory dysfunction (AUB-O) is caused by oligo- or anovulation, leading to irregular, heavy menstrual bleeding due to chronic unopposed estrogen on the endometrium.[10] While it does encompass bleeding patterns such as HMB and amenorrhea, this section will focus specifically on AUB-O as it relates to oligo-anovulation.

The estimated annual prevalence of menstrual irregularities is 53 per 1,000

women.[45] In reproductive-age women, Polycystic Ovary Syndrome (PCOS) is one of the most common causes of AUB-O,[10] with a prevalence range of 8% to 13%.[46] In perimenopausal women, bleeding changes are due to normal menopausal transition, with the average age of menopause being 51 years in developed countries. In North America, the mean duration of menopausal transition is 4 years, and during this time period menstrual irregularity is commonly observed.[10]

ETIOLOGY

When considering the etiology of AUB-O, the patient's age must be taken into account. As previously discussed, all patients presenting with abnormal bleeding should be evaluated for pregnancy. In adolescents though, anovulation is the most common cause of AUB-O.[10] During the first 12 to 18 months after menarche, immaturity of the HPO axis is frequently the cause of AUB-O.[10] By the third year after the onset of menstruation, 60% to 80% of cycles are regular.[10] If regular menstrual cycles have not been established within 5 years of menarche, further evaluation for the cause, such as PCOS, should be considered.[32] When irregular menses is associated with significant bleeding, an inherited bleeding disorder should be considered as a cause, especially in adolescence.[10] Women experiencing AUB-O in their reproductive years should be evaluated for pathologic causes, including PCOS, thyroid dysfunction, hyperprolactinemia, primary pituitary disease, premature ovarian failure, hypothalamic dysfunction, disordered eating, adrenal disease, and androgen-producing tumors.[10] Women in their perimenopausal years may experience "physiologic" anovulatory cycles because of intermittently declining estrogen levels. Regardless of age, evaluation for endometrial hyperplasia and/or endometrial cancer should be considered when a woman experiences excessive bleeding with irregular menses.[10] When considering the etiology of AUB-O, more than one condition may coexist (eg, PCOS and hypothyroidism), each contributing to the woman's constellation of symptoms.

PATHOPHYSIOLOGY

Normal menstrual cycles occur through a complex interaction of the hypothalamus, pituitary gland, ovaries, and endometrium (see Fig. 96-1). In an ovulatory cycle, the ovary produces a mature, estrogen-secreting follicle in

response to FSH release from the pituitary. The endometrium proliferates under the influence of this estrogen production. At a critical level of estrogen concentration, the pituitary responds by producing an “LH surge,” which creates a cascade of ovarian events, culminating in ovulation. Upon oocyte release, the follicle becomes a progesterone-producing corpus luteum. The endometrium “organizes” into secretory endometrium in the presence of adequate progesterone, preparing itself for a possible pregnancy. If conception and implantation do not occur, corpus luteum involution causes a decline in estrogen and progesterone leading to predictable, organized menstrual flow as the endometrium sloughs.

If ovulation does not occur, progesterone is not produced, and the endometrium will continue to proliferate in an “unorganized” fashion under the influence of continued estrogen production. Eventually, the endometrium will become so thick that it can no longer be supported by continued estrogen production. This results in unorganized, sporadic sloughing of the endometrium, characteristic of the unpredictable and heavy bleeding associated with AUB-O.

Overall, AUB-O has various etiologies, which will require a careful history and examination along with laboratory assessments to elucidate. For example, in adolescence, HPO axis immaturity contributes to the absence of the LH surge required for ovulation. In patients with anorexia, the hypothalamus loses much of its pulsatile GnRH release, leading to low levels of FSH and LH, and in certain cases enough for estrogen production but not enough to induce ovulation. Oocyte decline and abnormal follicular development contribute to anovulatory cycles common among women in the perimenopause transition.[10]

8 In reproductive-age women, PCOS is one of the most common causes of AUB-O.[10] Generally, PCOS can present as AUB-O, and symptoms include amenorrhea, oligomenorrhea, intermenstrual bleeding, and HMB. Although its exact definition continues to evolve, it is a disorder of androgen excess accompanied by ovulatory dysfunction and/or polycystic ovarian morphology.[47,48] Insulin resistance is often present, and PCOS is a risk factor for the metabolic syndrome, type 2 diabetes, dyslipidemia, hypertension, and possibly cardiovascular disease.[32] Besides PCOS, common causes of AUB-O in reproductive-age women include hyperprolactinemia, hypothalamic amenorrhea, also known as hypogonadotropic hypogonadism, primary ovarian insufficiency, and thyroid dysfunction.[10]

The criteria for diagnosing PCOS in adolescents are controversial as the pathologic features used for the diagnosis in adults, specifically acne and irregular menses, may be normal pubertal occurrences. Adolescent

hyperandrogenism (as opposed to adult hyperandrogenism) may be a natural consequence of the lack of synchronicity within the HPO axis during prolonged anovulatory cycles that are typical during puberty. Additionally, there is a high background prevalence of polycystic ovarian morphology in this population.[49] Recent evidence suggests that menstrual irregularity for over 2 years, accurate assessment of hyperandrogenic as well as metabolic features, in addition to reduced reliance on ultrasound diagnosis of polycystic ovarian morphology, may be suitable strategies for PCOS diagnosis in the adolescent population.[49] More research is needed to definitively identify the appropriate diagnosis of PCOS among adolescents so that appropriate treatment(s) can be recommended.

TREATMENT

Desired Outcomes

The optimal therapy for AUB-O depends upon the underlying cause(s) and the treatment options for AUB-O are wide and varied. When applicable, control of excessive bleeding in the short term is paramount. Longer-term goals of therapy include restoring the natural cycle of orderly endometrial growth and shedding, preventing endometrial hyperplasia,[10] addressing fertility concerns, decreasing the risk of osteopenia in cases of ovarian insufficiency, and improving the overall quality of life. Table 96-3 identifies the agents used to manage AUB-O and their recommended doses. Medical treatment, as opposed to surgical management, to resolve AUB-O should be initiated, as AUB-O is primarily an endocrinologic abnormality.[10]

CLINICAL PRESENTATION Abnormal Uterine Bleeding with Ovulatory Dysfunction

General

- Patients typically will not be in acute distress.

Symptoms

- Irregular, heavy, or prolonged uterine bleeding.
- Perimenopausal symptoms (eg, hot flashes, night sweats, and vaginal dryness) in ovarian insufficiency or menopausal transition.

Signs

- Acne, hirsutism, and obesity in PCOS

Laboratory Tests

- Pregnancy testing
- If PCOS is suspected, consider free or total testosterone, fasting glucose, fasting lipid panel
- If perimenopause is suspected, measure FSH
- Thyroid-stimulating hormone

Other Diagnostic Tests

- Endometrial biopsy for women with risk factors for endometrial hyperplasia or malignancy
- Pelvic ultrasound to evaluate for polycystic ovaries

Nonpharmacologic Therapy

Nonpharmacologic treatment options for AUB-O depend on the underlying cause. In a woman of reproductive age with PCOS, weight loss of 5% to 10% may result in improved menstrual regularity and ovulatory function, reduced hirsutism, increased insulin sensitivity, and improved response to fertility treatments.[31] Further, sustained weight loss has resulted in a return to ovulatory cycles in women without PCOS who experienced anovulatory cycles.[10] In women with AUB-O who have completed childbearing or who have not responded to medical management, endometrial ablation or resection and hysterectomy are surgical options. In the short term, ablation results in less morbidity and shorter recovery periods compared to other surgical interventions. However, patients should be counseled about the risks regarding the ability to detect and diagnose endometrial cancer in the future.[10] Importantly, procedure choice involves shared decision-making with the patient.

Pharmacologic Therapy

Hormonal contraceptives prevent recurrent AUB-O by providing a progestin and suppressing ovarian hormones. The CHCs are also useful for cycle regulation, leading to predictable menstrual cycles. In women with contraindication(s) to estrogen or in whom the side effects are unacceptable, progesterone-only

products are an option. They should be strongly considered for women experiencing HMB associated with anovulatory cycles.[10] Depot and intermittent oral MPA provide endometrial protection through endometrial suppression.[3] Another progesterone option is placement of the LNG-IUS,[10] particularly if pregnancy is not desired. Studied specifically in women over 30 years of age, use of the LNG-IUS resulted in a greater than 95% reduction in menstrual blood loss by 2 years.[50] Patient satisfaction rates were greater than 80%, with 74% agreeing to recommend it to other women.[50]

9 For women with PCOS who have high androgen levels and its related signs (eg, hirsutism), CHCs also increase sex hormone-binding globulin (SHBG) which binds androgens and reduces their circulating free concentrations. The 2018 international PCOS guideline recommends that CHCs alone should be recommended in adult women and adolescents with PCOS for management of irregular menstrual cycles and clinical hyperandrogenism.[31] For women with PCOS, CHCs containing less than or equal to 35 mcg of ethinyl estradiol and a progesterone that exhibits minimal androgenic side effects (eg, norgestimate and desogestrel) or with antiandrogenic effects (eg, drospirenone) may be desirable.

The 2018 international PCOS guidelines also recommend that metformin should be considered in women and adolescents with PCOS for management of metabolic features when lifestyle changes do not achieve desired goals.[31] Although metformin improves insulin sensitivity, and can reduce circulating androgen concentrations and improve ovulation rates,[32,51] CHCs are more effective in cycle regulation and decreasing androgens. The 2018 international PCOS guidelines recommend that metformin can be used in combination with CHCs for treatment of hyperandrogenic-related alopecia or hirsutism if at least 6 months of CHCs and cosmetic therapy do not adequately improve symptoms.[31] While not typically an issue among the relatively young population of patients treated with metformin for PCOS, one must be cognizant of the risk of lactic acidosis in metformin users with renal impairment. As such, this drug should be avoided in women with serum creatinine greater than 1.4 mg/dL (124 µmol/L). In addition, metformin may lead to spontaneous ovulation, and birth control should be advised in women with PCOS not desiring pregnancy.[31]

Hormonal contraceptives containing antiandrogenic progesterones are very effective for managing the acne and hirsutism that accompany PCOS as they suppress ovarian androgen production and increase SHBG, thus reducing free testosterone concentrations. Controversy regarding their use in PCOS exists secondary to their potential adverse effects on insulin resistance and glucose

tolerance.[52] An increase in high-sensitivity C-reactive protein and an increase in homocysteine levels, both indicators of cardiovascular risk, have been observed with the use of CHCs.[53] Another trial found a reduction in brachial artery flow-mediated dilatation and an increase in carotid intima-media thickness, both indicators of endothelial dysfunction, following therapy with oral CHCs containing ethinyl estradiol and cyproterone acetate in women with PCOS.[54] Additional, longer-term clinical trials will clarify whether the benefits of these agents outweigh the risks. It has been suggested that cardiovascular risk calculators be employed as an adjunct to guidelines suggesting the use of oral CHCs in this patient population.[55]

If the treatment goal is fertility, in women with PCOS with anovulatory infertility and no other infertility factors, letrozole should be considered first-line treatment for ovulation induction.[31] In a double-blind, multicenter, randomized trial of letrozole and clomiphene for ovulation induction in women with PCOS, letrozole led to significantly more ovulatory cycles, pregnancies, and live births.[56] Letrozole is dosed at 2.5 mg daily for 5 days beginning on cycle day 3 after induced withdrawal bleeding with a progesterone such as MPA 10 mg daily orally for 10 days. If ovulation does not occur, doses can be increased in subsequent cycles to a maximum of 7.5 mg daily in up to 5 cycles.[56] As an alternative ovulation induction agent, clomiphene citrate is administered in a similar manner, initiated at 50 mg daily, with dose increase in subsequent cycles to a maximum of 150 mg daily.[56]

CLINICAL PRESENTATION Dysmenorrhea

General

- Patients may or may not be in acute distress, depending on the level of menstrual pain experienced

Symptoms

- Patients complain of crampy pelvic pain beginning shortly before or at the onset of menses. Symptoms typically last from 8 to 72 hours.
- Associated symptoms may include low back pain, headache, diarrhea, fatigue, and/or nausea and vomiting.

Laboratory Tests

- Pelvic examination should be performed to screen for sexually

transmitted diseases and/or pelvic inflammatory disease as a cause of the pain in sexually active females.

- Gonorrhea, Chlamydia cultures or polymerase chain reaction, wet mount.

Other Diagnostic Tests

- Transvaginal/pelvic ultrasound can be used to identify potential anatomic abnormalities such as masses/lesions or to detect ovarian cysts and endometriomas.

Overall, the treatment(s) of choice depends on accurate etiologic diagnosis as well as identification of the desired treatment outcome(s). Hormonal contraceptives are the first-choice treatment in women with AUB-O who do not desire pregnancy.[10] In women with PCOS, CHCs are first-line pharmacologic agents for cycle control and minimizing the androgenic signs and symptoms of PCOS, while metformin is primarily used for metabolic improvement when lifestyle interventions do not yield adequate improvements.[31] Letrozole is used for ovulation induction in PCOS.[31] Table 96-4 lists the important pharmacologic properties of agents used to treat AUB-O that require monitoring.

Special Populations

Anovulatory cycles are fairly common in the perimenarchal reproductive years. Ovulation typically is established 1 year or more following menarche. If excessive bleeding occurs, the patient should be evaluated for bleeding disorders, as HMB since menarche may indicate an undetected coagulopathy.[26] If identified, the specific bleeding disorders should be treated. Acute severe bleeding can be managed with intravenous conjugated equine estrogen, high-dose CHCs, or high-dose oral progestins.[43]

EVALUATION OF THERAPEUTIC OUTCOMES

Table 96-4 lists the expected outcomes and specific monitoring parameters for the treatment modalities used to manage AUB-O.

DYSMENORRHEA

EPIDEMOLOGY

Dysmenorrhea is one of the most commonly encountered gynecologic complaints and is defined as crampy pelvic pain occurring with or just prior to menses. Primary dysmenorrhea implies pain in the setting of normal pelvic anatomy and physiology,[57] while secondary dysmenorrhea is associated with underlying pelvic pathology.[58] Dysmenorrhea prevalence rates range from 16% to 90%,[58] and its presence may be associated with significant interference in work and school attendance. In addition, significant reductions in quality of life and lower overall life satisfaction and contentment ratings have been observed in women with dysmenorrhea compared to controls.[57] Risk factors include menarche before the age of 12 years, current age less than 30 years, heavy menses, nulliparity, low body mass index, and a history of sexual abuse.[58]

ETIOLOGY

For most patients, dysmenorrhea is accompanied by normal ovulatory cycles and normal pelvic anatomy. This is referred to as primary, or functional, dysmenorrhea. However, in approximately 10% of the adolescents and young adults presenting with painful menses, an underlying anatomic or physiologic cause exists.[58] Comparatively, secondary dysmenorrhea associated with pelvic pathology should be suspected in women over 30 years of age without a history of dysmenorrhea.[58]

PATHOPHYSIOLOGY

The most significant mechanism for primary dysmenorrhea is the release of prostaglandins and leukotrienes into the menstrual fluid, initiating an inflammatory response and vasopressin-mediated vasoconstriction.[11,24] Causes of secondary dysmenorrhea include endometriosis, current or history of pelvic inflammatory disease, uterine fibroids, and adenomyosis leiomyomata.[58] Pregnancy and miscarriage must be considered in new-onset dysmenorrhea.

TREATMENT

Desired Outcomes

Initial treatment choice is influenced by whether or not the woman desires pregnancy. Medical management of dysmenorrhea should relieve the pelvic pain, result in reducing lost school and work days, and contribute to an improved quality of life. Table 96-3 identifies the agents used to manage dysmenorrhea and their recommended doses. **Figure 96-4** shows a treatment algorithm for dysmenorrhea management.

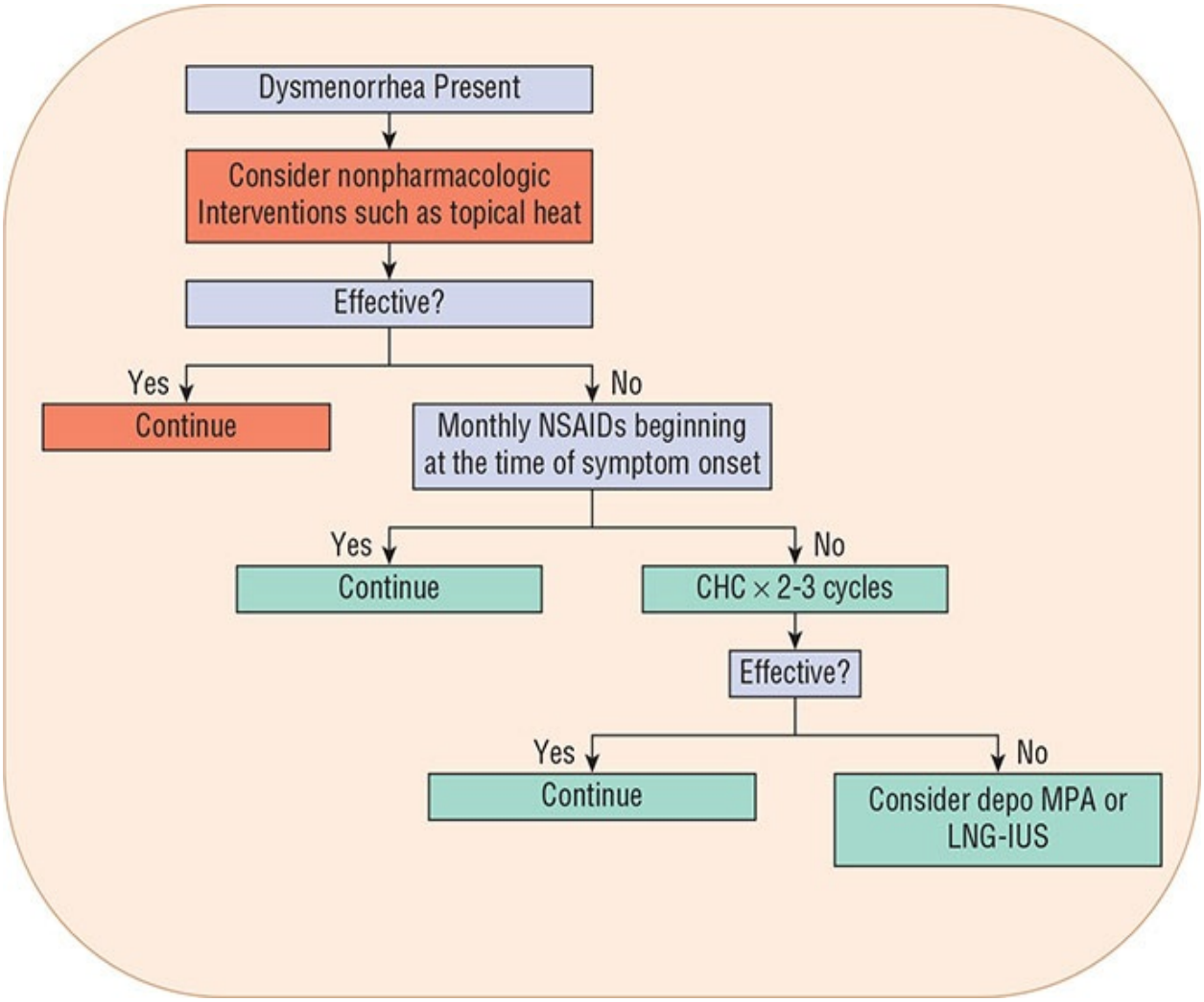


FIGURE 96-4 Treatment algorithm for dysmenorrhea. (LNG-IUS, levonorgestrel-releasing intrauterine system; MPA, medroxyprogesterone acetate; NSAIDs, nonsteroidal anti-inflammatory drugs; CHC, combined hormonal contraceptive.)

General Approach to Treatment

A variety of effective treatment options for dysmenorrhea are available,

including nonhormonal and hormonal pharmacologic options and noninvasive nonpharmacologic options. Treatment choice is influenced by the desire for contraception, the patient's level of sexual activity, potential for adverse effects, and cost.

Nonpharmacologic Therapy

Several nonpharmacologic interventions are used for managing dysmenorrhea. Among these, topical heat therapy, exercise, acupuncture, and a low-fat vegetarian diet have been shown to reduce dysmenorrhea intensity.[58–60] Dietary changes may shorten dysmenorrhea duration. Topical heat application via an abdominal patch is as effective as 400 mg of ibuprofen dosed three times daily.[59,61] Because topical heat, exercise, and dietary changes do not impart systemic effects, they are associated with little to no risk compared to the pharmacologic options. Although a variety of dietary supplements, including fenugreek, fish oil, vitamin B1, ginger, valerian, and zinc sulfate, have been evaluated for dysmenorrhea, a Cochrane analysis concluded that evidence supporting their use is of low or very low quality due to limited sample sizes and methodological concerns.[62] Similarly, although there is some evidence supporting the use of acupuncture and acupressure, a recent Cochrane analysis also concluded that the quality evidence was low or very low.[60]

Pharmacologic Therapy

Given the role of prostaglandins in dysmenorrhea pathophysiology, NSAIDs are the initial treatment of choice. These agents do not differ in efficacy with the most commonly used agents being naproxen and ibuprofen.

All NSAIDs have a propensity for causing GI distress and ulceration; their administration with food or milk minimizes these effects. In women who have a history of NSAID-induced gastric effects, the use of celecoxib, a cyclo-oxygenase-2 (COX-2) inhibitor, is an alternative.[24] Choice of one agent over another may be based on cost, convenience, and patient preference.[22] All NSAIDs should be dosed on an individual basis and are most effective if started 1 to 2 days prior to the onset of menses and continued through the first 2 to 3 days of menstrual bleeding.[22] Some research suggests that NSAID therapy should begin at the onset of menses or perhaps even the day before and continued around the clock instead of waiting until symptom onset; however, the data substantiating this are weak.[58] Acetaminophen is inferior to NSAID use in

the treatment of this disorder.[24] If an NSAID or celecoxib use is contraindicated or not desired, hormonal agents should be considered.

Overall, the CHCs improve dysmenorrhea by inhibiting endometrial tissue proliferation which reduces endometrial-derived prostaglandins and leukotrienes that cause the pelvic pain.[11,22] Significant improvements in mild, moderate, and severe dysmenorrhea have been noted with CHCs. Although one study suggested that a CHC containing a potent progestin (eg, levonorgestrel) may be more beneficial, other studies using CHCs with other progestins suggest that pain reduction is not limited to levonorgestrel-containing regimens.[23] Compared with cyclic regimens, continuous CHC regimens may result in more rapid pain reduction.[22] However, both cyclic and continuous regimens have been used successfully.[22]

Long-acting progesterones, such as depot MPA and the LNG-IUS, can be considered for dysmenorrhea treatment. Their efficacy is secondary to their ability to render most patients amenorrheic within 6 to 12 months of use.[11,23] Because the pelvic pain of dysmenorrhea is related to the prostaglandins released during menses, in the setting of amenorrhea the underlying cause of dysmenorrhea is removed.

Several factors influence the choice of first-line treatment for dysmenorrhea. If contraception is desired, then a hormonal option may be considered taking into account cost, adherence issues, and side effects. If contraception is not desired, then NSAID use would be desirable from both cost and convenience standpoints. If NSAIDs are not tolerated, celecoxib could be recommended. In patients for whom hormonal contraception, NSAIDs, or celecoxib are not an option, topical heat should be considered.

Special Populations

Dysmenorrhea is common in adolescent females. The College of Obstetricians and Gynecologists recommend that an NSAID should be the initial treatment choice for adolescents with dysmenorrhea. In adolescent patients desiring contraception, or in whom NSAIDs do not provide adequate relief, hormonal contraceptives can be used alone, or in combination with NSAIDs.[22] Prolonged use of depot MPA may lead to significant loss of bone mineral density (BMD), and BMD loss may not be completely reversible after depot MPA discontinuation.[23] Adolescence is a critical period for BMD accrual. Hence, depot MPA may not be the first choice in this population.[23] Table 96-4 identifies the significant pharmacologic properties for agents used to treat dysmenorrhea

that require monitoring.

EVALUATION OF THERAPEUTIC OUTCOMES

Table 96-4 lists the expected outcomes and specific monitoring parameters for the treatment modalities used in the management of dysmenorrhea.

PREMENSTRUAL SYNDROME AND PREMENSTRUAL DYSPHORIC DISORDER

EPIDEMIOLOGY

Premenstrual syndrome (PMS) is represented by a cyclic pattern of symptoms (**Table 96-5**) occurring in the last week of the menstrual cycle that resolve with menstrual flow. Diagnosis requires that at least one moderate-to-severe somatic or psychiatric symptom is present in the last week of the luteal phase for at least 3 months.[33,63] In addition to physical and psychological examinations, a prospective menstrual diary with recordings of symptoms for at least two cycles is used to confirm diagnosis.[33]

TABLE 96-5 Diagnostic Criteria for Premenstrual Syndrome

At least one of the following somatic or affective symptoms should be present during the 5 days before menses in the last three menstrual cycles

Somatic symptoms	Affective symptoms
Abdominal bloating	Angry outbursts
Breast swelling or tenderness	Anxiety
Headache	Depression
Muscle or joint pain	Difficulty in concentration, or confusion
Swelling of extremities	Irritability
Weight gain	Social withdrawal

Data from Reference 33.

Some women experience severe PMS symptoms known as premenstrual dysphoric disorder (PMDD). In PMDD, at least five symptoms are present in the last week prior to the onset of menses in the majority of the menstrual cycles, and these symptoms improve within a few days after the onset of menses.[33] At

least one of the five symptoms must be an affective symptom,[33] and for both PMS and PMDD, symptoms cannot be attributable to other medical causes or substance use, and must affect the patient's normal daily functioning.[33]

Women experiencing PMS and PMDD symptoms miss significantly more work and school compared to women without PMS or PMDD. They also report significant impairment of their ability to participate in social activities, hobbies, and in their relationships with others. Additionally, they also have a lower health-related quality of life and higher medical expenses.[33]

Up to 80% of menstruating women experience PMS symptoms.[33] However, most do not report impairment of their daily activities.[33] An exact PMS prevalence is difficult to ascertain, because symptoms and severity tend to fluctuate. The prevalence of PMDD ranges from 1.3% to 9%.[33,64]

ETIOLOGY

PMDD is a complex psychiatric disorder with multiple biological, psychological, and sociocultural determinants.[65] Although cyclic hormonal changes are in some way related to PMS and PMDD, the association is neither linear nor simple. When ovulation is suppressed medically or surgically, symptoms improve.

PATHOPHYSIOLOGY

Some evidence suggests that PMS and PMDD symptoms are related to low levels of the centrally active progesterone metabolite allopregnanolone in the luteal phase and/or lower cortical γ-aminobutyric acid levels in the follicular phase.[65] A number of studies suggest a link between PMS and PMDD and low serotonin levels.[65] Although several cross-cultural studies suggest that PMS physical symptoms are consistent across cultures, the negative affective symptoms are part of the negative "menstrual socialization" in western culture.[65]

TREATMENT

Desired Outcomes

Treatment of PMS and PMDD attempts to relieve psychiatric and somatic symptoms through ovulation suppression, or through affecting neurotransmitter

(eg, serotonin, norepinephrine, or dopamine) concentrations in the brain.[33] Therefore, PMS and PMDD interventions should alleviate the presenting symptoms and subsequently improve quality of life. Table 96-3 lists the various agents used in the managing PMS and PMDD and their recommended dosing.

CLINICAL PRESENTATION Premenstrual Dysphoric Disorder

A summary of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (*DSM-*5)* criteria for PMDD is as follows[66]:

- Symptoms are temporally associated with the last week of the luteal phase and remit with the onset of menses.
- At least five of the following symptoms are present: affective lability, anger or irritability often characterized by interpersonal conflicts, markedly depressed mood, anxiety, decreased interest in activities, fatigue, difficulty concentrating, changes in appetite, sleep disturbance, feelings of being overwhelmed, and physical symptoms, such as breast tenderness or bloating.
- One of the symptoms must be affective lability, irritability, markedly depressed mood, or anxiety.
- Symptoms interfere significantly with work and/or social relationships.
- Symptoms are not an exacerbation of another underlying psychiatric disorder.
- The criteria are confirmed prospectively by daily ratings over two menstrual cycles and must have occurred during most menstrual cycles in the past year.

General Approach to Treatment

A treatment modality that is minimally invasive or without systemic effects is desired for initial therapy. Key to the successful choice of pharmacologic therapy for PMS and PMDD is having the patient chart her specific symptoms for at least two menstrual cycles to assist in ruling out premenstrual exacerbation of underlying psychiatric disorders.

Nonpharmacologic Therapy

Some lifestyle changes for women with mild-to-moderate premenstrual symptoms include minimizing intake of caffeine, refined sugar, and sodium and increasing exercise.[34] Although exercise appears to improve PMS symptoms, definitive, evidence-based recommendations cannot be made due to methodological limitations of these studies.[34] Vitamin and mineral supplements, such as vitamin B_6 (50-100 mg daily) and calcium carbonate (1,200 mg daily), may help to reduce the physical symptoms associated with PMS; however, clinical trial data is limited and/or mixed precluding a definitive conclusion regarding their use.[34] Cognitive behavioral therapy has also been studied showing moderate efficacy.[34] However, the frequency and duration therapy have not been defined. Nonetheless, the results suggest that acceptance-based cognitive behavior therapy and mindfulness-based exercises may be helpful in reducing symptoms.[33] A Cochrane review of herbal supplements for PMS, including angelica root, bitter orange, dragon's teeth, ginkgo, peppermint, saffron, turmeric, tangerine leaf, vitex agnus-castus, among others, do not support their use.[67,68] Although acupuncture and acupressure appear to improve physical and psychological symptoms of PMS, evidence was from limited sample sizes and of low quality.[69]

Pharmacologic Therapy

Most recent investigations have focused on the selective serotonin reuptake inhibitors (SSRIs) for this disorder.[35] Studies have revealed positive results relative to most symptoms associated with PMDD. Other agents that have been studied and are alternatives include the selective serotonin–norepinephrine reuptake inhibitor (SNRI) venlafaxine, as well as CHCs and GnRH agonists.

10 The first-line pharmacologic treatment options for severe symptoms of PMS and PMDD are the SSRIs.[33,34] Among this class of agents, data support the use of citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. Current research evaluating the dosing of these agents continuously or only during the luteal phase has illustrated similar efficacy between the two regimens, such that one regimen cannot be recommended over another,[34] although more studies directly comparing continuous versus luteal phase administration are needed.[33] Most side effects also appear to be similar between continuous and luteal dosing, except decreased libido which occurs at a higher rate with continuous dosing.[34] In addition, abrupt cessation of SSRI at the end of

the menstrual cycle is not associated with discontinuation symptoms.[36] All SSRI doses appear to be effective for psychiatric symptoms, and should be titrated to individual patients' symptom improvement and tolerability.[33] The safety of SSRIs use during early pregnancy has been an active area of investigation. In a recent large-scale analysis, reassuring evidence was provided for some SSRIs, but birth defects (including anencephaly, atrial septal defects, right ventricular outflow tract obstruction, and gastroschisis) can be 2 to 3.5 times more frequent with paroxetine or fluoxetine use in early pregnancy.[70]

The SNRI, venlafaxine, has been studied for PMDD and, similar to the SSRIs, found to result in a 50% or greater improvement in symptoms in 60% of treated patients compared with only 35% in the control group.[34] The norepinephrine and dopamine reuptake inhibitor, bupropion, is not effective for PMS or PMDD.[33]

It is important that concomitant drug therapy of women prescribed any of the SSRIs or venlafaxine be evaluated closely for pharmacokinetic drug–drug interactions given the interface of these drugs with cytochrome P450 isoenzyme systems. Additional information regarding antidepressant dosing, side effects, pharmacokinetics, and drug–drug interactions can be found in Chapter 85, "Depressive Disorders."

The use of a monophasic oral CHC containing 20 mcg of ethinyl estradiol and 3 mg of drospirenone, a progesterone with antiandrogenic effects, improves premenstrual symptoms in women with PMDD, and is FDA approved for this indication.[34] The continuous cycle CHC regimen delivering 90 mcg of levonorgestrel and 20 mcg of ethinyl estradiol daily has also been studied in controlled trials resulting in a 30% to 59% improvement in PMDD symptoms.[37] For PMS symptoms, in a large-scale study, both triphasic and monophasic CHCs led to reduction in physical symptoms but not mood symptoms.[34] Superiority of one CHC relative to another has not been established.

If treatment with the above options is unsuccessful, hormonal treatment with a GnRH agonist, such as leuprolide, can be considered.[34] Leuprolide improves premenstrual emotional symptoms as well as some physical symptoms, such as bloating and breast tenderness. However, its cost, the need for intramuscular administration, and its hypoestrogenism side effects (eg, vaginal dryness, hot flashes, and bone demineralization) severely limit its use.[34] Table 96-4 lists the significant pharmacologic properties for agents used to treat PMDD that require monitoring.

EVALUATION OF THERAPEUTIC OUTCOMES

Table 96-4 lists the expected outcomes and specific monitoring parameters for the treatment modalities used in PMDD management.

CONCLUSION

Problems related to the menstrual cycle are very common in women of reproductive age. The most frequently encountered menstruation-related difficulties include amenorrhea; heavy menstrual bleeding (HMB); abnormal uterine bleeding associated with ovulatory dysfunction (AUB-O), including polycystic ovary syndrome (PCOS); dysmenorrhea; and premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD). The diagnosis of various menstruation-related disorders begins with a thorough history of the patient's menstrual patterns, co-occurring symptoms. Problems related to the menstrual cycle negatively affect quality of life, reproductive potential, and may have long-term detrimental health effects.

Postclass Engaged Learning Activity

Read the following article (available at https://tinyurl.com/uer57fk):

Almenning I, Rieber-Mohn A, Lundgren KM, Shetelig Lovvik T, Garnaes KK, Moholdt T. Effects of high intensity interval training and strength training on metabolic, cardiovascular and hormonal outcomes in women with polycystic ovary syndrome: A pilot study. *PLOS One* 2015;10(9):e138793.

Write a brief summary about the study methods, major findings, a potential advantage and disadvantage of the intervention, and how the intervention can be implemented in practice.

This activity is intended to build your skills in critically appraising research manuscripts and applying new knowledge to practice.

ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
AUB-O	abnormal uterine bleeding with ovulatory dysfunction
CHC	combined hormonal contraception

COX-2	cyclo-oxygenase-2
FHA	functional hypothalamic amenorrhea
FSH	follicle-stimulating hormone
GnRH	gonadotropin-releasing hormone
HC	hormonal contraceptive
HMB	heavy menstrual bleeding
HPA	hypothalamic–pituitary–adrenal
HPO	hypothalamic–pituitary–ovarian
IUSs	Intrauterine systems
hCG	human chorionic gonadotropin
LH	luteinizing hormone
LNG-IUS	levonorgestrel-releasing intrauterine system
MPA	medroxyprogesterone acetate
NSAID	nonsteroidal anti-inflammatory drug
PCOS	polycystic ovary syndrome
PMDD	premenstrual dysphoric disorder
PMS	premenstrual syndrome
SHBG	sex hormone-binding globulin
SNRI	serotonin–norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor

REFERENCES

1. The American College of Obstetricians and Gynecologists' Committee on Adolescent Health Care. Committee opinion 651: Menstruation in girls and adolescents using the menstrual cycle as a vital sign. Obstet Gynecol. Available at http://www.acog.org/-/media/Committee-Opinions/Committee-on-Adolescent-Health-Care/co651.pdf?dmc=1&ts=20170604T2324312143. Published 2015. Accessed November 21, 2018.
2. Fraser IS, Critchley HOD, Broder M, Munro MG. The FIGO recommendations on terminologies and definitions for normal and abnormal uterine bleeding. *Semin Reprod Med*. 2011;29(5):383–390.
3. Klein DA, Poth MA. Amenorrhea: An approach to diagnosis and

management. *Am Fam Physician*. 2013;87(11):781–788.

4. Rebar R. Evaluation of amenorrhea, anovulation, and abnormal bleeding [updated 2018 Jan 15]. In: De Groot KJ, Chrousos G, Kungan K, eds. *Endotext [Internet]*. South Dartmouth, MA: MDText.com, Inc; 2018.
5. Fourman LT, Fazeli PK. Neuroendocrine causes of amenorrhea: An update. *J Clin Endocrinol Metab*. 2015;100(3):812–824.
6. Marsh CA, Grimstad FW. Primary amenorrhea: Diagnosis and management. *Obstet Gynecol Surv*. 2014;69(10):603–612.
7. Nelson LM. Primary ovarian insufficiency. *N Engl J Med*. 2009;360:606–614.
8. Chou SH, Mantzoros C. Role of leptin in human reproductive disorders. *J Endocrinol*. 2014;223(1):T49–T62.
9. Michopoulos V, Mancini F, Loucks TL, Berga SL. Neuroendocrine recovery initiated by cognitive behavioral therapy in women with functional hypothalamic amenorrhea: A randomized, controlled trial. *Fertil Steril*. 2013;99(7):2084–2091.
10. The American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 136. Management of abnormal uterine bleeding associated with ovulatory dysfunction. *Obs Gynecol*. 2013;122(1):176–185.
11. Jamieson MA. Disorders of menstruation in adolescent girls. *Pediatr Clin North Am*. 2015;62(4):943–961.
12. Uhm S, Perriera L. Hormonal contraception as treatment for heavy menstrual bleeding: A systematic review. *Clin Obstet Gynecol*. 2014;57(4):694–717.
13. Arduc A, Gokay F, Isik S, et al. Retrospective comparison of cabergoline and bromocriptine effects in hyperprolactinemia: A single center experience. *J Endocrinol Invest*. 2015;38(4):447–453.
14. Sullivan SD, Sarrel PM, Nelson LM. Hormone replacement therapy in young women with primary ovarian insufficiency. *Fertil Steril*. 2016;106:1588–1599.
15. Sarrel PM, Sullivan SD, Nelson LM. Hormone replacement therapy in young women with surgical primary ovarian insufficiency and early menopause. *Fertil Steril*. 2016;106(7):1580–1587.
16. Gordon CM, Ackerman KE, Berga SL, et al. Functional hypothalamic amenorrhea: An Endocrine Society clinical practice guideline. *J Clin*

Endocrinol Metab. 2017;102(5):1413–1439.

17. Molitch ME. Medication-induced hyperprolactinemia. *Mayo Clin Proc*. 2005;80(8):1050–1057.
18. Altayar O, Al Nofal A, Carranza Leon BG, Prokop LJ, Wang Z, Murad MH. Treatments to prevent bone loss in functional hypothalamic amenorrhea: A systematic review and meta-analysis. *J Endocr Soc*. 2017;1(5):500–511.
19. Popat VB, Calis KA, Kalantaridou SN, et al. Bone mineral density in young women with primary ovarian insufficiency: Results of a three-year randomized controlled trial of physiological transdermal estradiol and testosterone replacement. *J Clin Endocrinol Metab*. 2014;99(9):3418–3426.
20. De Souza MJ, Nattiv A, Joy E, et al. 2014 Female Athlete Triad Coalition consensus statement on treatment and return to play of the female athlete triad. *Clin J Sport Med*. 2014;24(2):96–119.
21. Faje A, Nachtigall L. Current treatment options for hyperprolactinemia. *Expert Opin Pharmacother*. 2013;14(12):1611–1625.
22. The American College of Obstetricians and Gynecologists' Committee on Adolescent Health Care. ACOG Committee Opinion 760: Dysmenorrhea and endometriosis in the adolescent. *Obstet Gynecol*. 2018;132(6):e249–e258.
23. Harel Z. Dysmenorrhea in adolescents and young adults: Etiology and management. *Expert Opin Pharmacother*. 2012;13(15):2157–2170.
24. Marjoribanks J, Ayeleke RO, Farquhar C, Proctor M. Nonsteroidal anti-inflammatory drugs for dysmenorrhoea. *Cochrane Database Syst Rev*. 2015;(7):CD001751.
25. LYSTEDA [prescribing information]. Parsippany, NJ: Ferring Pharmaceuticals, Inc; 2016.
26. Sriprasert I, Pakrashi T, Kimble T, Archer DF. Heavy menstrual bleeding diagnosis and medical management. *Contracept Reprod Med*. 2017;2:20.
27. Qiu J, Cheng J, Wang Q, Hua J. Levonorgestrel-releasing intrauterine system versus medical therapy for menorrhagia: A systematic review and meta-analysis. *Med Sci Monit*. 2014;20:1700–1713.
28. Lethaby A, Hussain M, Jr R, Mc R. Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding. *Cochrane Database Syst Rev*. 2015;(4):CD002126.

29. Abu Hashim H. Medical treatment of idiopathic heavy menstrual bleeding. What is new? An evidence based approach. *Arch Gynecol Obstet*. 2013;287(2):251–260.
30. Kaunitz AM, Meredith S, Inki P, Kubba A, Sanchez-Ramos L. Levonorgestrel-releasing intrauterine system and endometrial ablation in heavy menstrual bleeding: A systematic review and meta-analysis. *Obstet Gynecol*. 2009;113(5):1104–1116.
31. Teede HJ, Misso ML, Costello MF, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Fertil Steril*. 2018;110(3):364–379.
32. Setji TL, Brown AJ. Polycystic ovary syndrome: Update on diagnosis and treatment. *Am J Med*. 2014;127(10):912–919.
33. Hofmeister S, Bodden S. Premenstrual syndrome and premenstrual dysphoric disorder. *Am Fam Physician*. 2016;94(3):236–240.
34. Maharaj S, Trevino K. A comprehensive review of treatment options for premenstrual syndrome and premenstrual dysphoric disorder. *J Psychiatr Pract*. 2015;21(5):334–350.
35. Marjoribanks J, Brown J, O'Brien PMS, Wyatt K. Selective serotonin reuptake inhibitors for premenstrual syndrome. *Cochrane database Syst Rev*. 2013;(6):CD001396.
36. Yonkers KA, Kornstein SG, Gueorguieva R, Merry B, Steenburgh KV, Altemus M. Symptom-onset dosing of sertraline for the treatment of premenstrual dysphoric disorder: A multi-site, double-blind, randomized, placebo-controlled trial. *JAMA Psychiatry*. 2015;72(10):1037–1044.
37. Freeman EW, Halbreich U, Grubb GS, et al. An overview of four studies of a continuous oral contraceptive (levonorgestrel 90 mcg/ethinyl estradiol 20 mcg) on premenstrual dysphoric disorder and premenstrual syndrome. *Contraception*. 2012;85(5):437–445.
38. Simon JA. Progestogens in the treatment of secondary amenorrhea. *J Reprod Med*. 1999;44(2 suppl):185–190.
39. Bitzer J, Heikinheimo O, Nelson AL, Calaf-Alsina J, Fraser IS. Medical management of heavy menstrual bleeding: A comprehensive review of the literature. *Obstet Gynecol Surv*. 2015;70(2):115–130.
40. Heliovaara-Peippo S, Hurskainen R, Teperi J, et al. Quality of life and costs of levonorgestrel-releasing intrauterine system or hysterectomy in the treatment of menorrhagia: A 10-year randomized controlled trial.

Obstet Gynecol Surv. 2014;69(4):204–205.

41. Munro MG, Critchley HOD, Fraser IS, FIGO Menstrual Disorders Working Group. The FIGO classification of causes of abnormal uterine bleeding in the reproductive years. *Fertil Steril*. 2011;95(7):2204–2208.
42. Ray S, Ray A. Non-surgical interventions for treating heavy menstrual bleeding (menorrhagia) in women with bleeding disorders. *Cochrane database Syst Rev*. 2014;(11):CD010338.
43. The American College of Obstetricians and Gynecologists. ACOG Committee on Gynecologic Practice No. 557: Management of acute abnormal uterine bleeding in nonpregnant reproductive-aged women. *Obs Gynecol*. 2013;121(4):891–896.
44. The American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 186. Long-acting reversible contraception: Implants and intrauterine devices. *Obstet Gynecol*. 2017;130(5):e251–e269.
45. Kjerulff KH, Erickson BA, Langenberg PW. Chronic gynecological conditions reported by US women: Findings from the National Health Interview Survey, 1984 to 1992. *Am J Public Health*. 1996;86(2):195–199.
46. Azziz R, Carmina E, Chen Z, et al. Polycystic ovary syndrome. *Nat Rev Dis Prim*. 2016;2:16057.
47. Legro RS, Arslanian SA, Ehrmann DA, et al. Diagnosis and treatment of polycystic ovary syndrome: An endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2013;98(12):4565–4592.
48. Goodman NF, Cobin RH, Futterweit W, Glueck JS, Legro RS, Carmina E. American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and PCOS Society disease state clinical review: Guide to the best practices in the evaluation and treatment of polycystic ovary syndrome—Part 1. *Endocr Pract*. 2015;21(12):1415–1426.
49. Hardy TSE, Norman RJ. Diagnosis of adolescent polycystic ovary syndrome. *Steroids*. 2013;78(8):751–754.
50. Mansukhani N, Unni J, Verma S, et al. Are women satisfied when using levonorgestrel-releasing intrauterine system for treatment of abnormal uterine bleeding? *J Midlife Health*. 2013;4(1):31.
51. Palomba S, Pasquali R, Orio F, Nestler JE. Clomiphene citrate, metformin or both as first-step approach in treating anovulatory infertility in patients with polycystic ovary syndrome (PCOS): A systematic review of head-to-head randomized controlled studies and meta-analysis. *Clin Endocrinol*

(Oxf). 2009;70(2):311–321.

52. Adeniji AA, Essah PA, Nestler JE, Cheang KI. Metabolic effects of a commonly used combined hormonal oral contraceptive in women with and without polycystic ovary syndrome. *J Womens Heal*. 2016;25(6):638–645.
53. Harmanci A, Cinar N, Bayraktar M, Yildiz BO. Oral contraceptive plus antiandrogen therapy and cardiometabolic risk in polycystic ovary syndrome. *Clin Endocrinol (Oxf)*. 2013;78(1):120–125.
54. Gode F, Karagoz C, Posaci C, et al. Alteration of cardiovascular risk parameters in women with polycystic ovary syndrome who were prescribed to ethinyl estradiol-cyproterone acetate. *Arch Gynecol Obstet*. 2011;284(4):923–929.
55. Beller JP, McCartney CR. Cardiovascular risk and combined oral contraceptives: Clinical decisions in settings of uncertainty. *Am J Obstet Gynecol*. 2013;208(1):39–41.
56. Legro RS, Brzyski RG, Diamond MP, et al. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. *N Engl J Med*. 2014;371(2):119–129.
57. Iacovides S, Avidon I, Bentley A, Baker FC. Reduced quality of life when experiencing menstrual pain in women with primary dysmenorrhea. *Acta Obstet Gynecol Scand*. 2014;93(2):213–217.
58. Osayande AS, Mehulic S. Diagnosis and initial management of dysmenorrhea. *Am Fam Physician*. 2014;89(5):341–346.
59. Potur DC, Kömürcü N. The effects of local low-dose heat application on dysmenorrhea. *J Pediatr Adolesc Gynecol*. 2014;27(4):216–221.
60. Smith CA, Armour M, Zhu X, Li X, Lu ZY, Song J. Acupuncture for dysmenorrhoea. *Cochrane Database Syst Rev*. 2016;(4):CD007854.
61. Navvabi Rigi S, Kermansaravi F, Navidian A, et al. Comparing the analgesic effect of heat patch containing iron chip and ibuprofen for primary dysmenorrhea: A randomized controlled trial. *BMC Womens Health*. 2012;12:25.
62. Pattanittum P, Kunyanone N, Brown J, et al. Dietary supplements for dysmenorrhoea. *Cochrane Database Syst Rev*. 2016;(3):CD002124.
63. The American College of Obstetricians and Gynecologists. *Guidelines for Women's Health Care: A Resource Manual*. 4th ed. Washington, D.C.: American College of Obstetricians and Gynecologists; 2014.

64. Robinson LLL, Ismail KMK. Clinical epidemiology of premenstrual disorder: Informing optimized patient outcomes. *Int J Womens Health*. 2015;7:811–818.
65. Matsumoto T, Asakura H, Hayashi T. Biopsychosocial aspects of premenstrual syndrome and premenstrual dysphoric disorder. *Gynecol Endocrinol*. 2013;29(1):67–73.
66. The American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition*. In: Washington, DC: American Psychiatric Association; 2013.
67. Jang SH, Kim DI, Choi M-S. Effects and treatment methods of acupuncture and herbal medicine for premenstrual syndrome/premenstrual dysphoric disorder. *BMC Complement Altern Med*. 2014;14:11.
68. Jing Z, Yang X, Ismail KMK, Chen X, Wu T. Chinese herbal medicine for premenstrual syndrome. *Cochrane Database Syst Rev*. 2009; (1):CD006414.
69. Armour M, Ee CC, Hao J, Wilson TM, Yao SS, Smith CA. Acupuncture and acupressure for premenstrual syndrome. *Cochrane Database Syst Rev*. 2018;(8):CD005290.
70. Reefhuis J, Devine O, Friedman JM, Louik C, Honein MA. Specific SSRIs and birth defects: Bayesian analysis to interpret new data in the context of previous reports. *BMJ*. 2015;350:h3190.

97

Endometriosis

Kathleen Vest and Sarah E. Lynch

KEY CONCEPTS

1. Endometriosis is a chronic condition in reproductive age women that can cause chronic pelvic pain and infertility.
2. Endometriosis is characterized by endometrial tissue outside the uterus, but the exact pathophysiology and biological mechanisms are multifactorial and still remain unclear.
3. Endometriosis should be suspected in any woman of reproductive age presenting with recurring pelvic pain or otherwise unexplained infertility. Failure of first-line treatment options like nonsteroidal anti-inflammatory drugs (NSAIDs) or combined hormonal contraceptives (CHCs) to relieve dysmenorrhea is highly suspect of endometriosis.
4. Definitive diagnosis of endometriosis requires direct surgical visualization; however, it is acceptable to empirically treat these symptoms without a definitive diagnosis.
5. Treatment strategies are based on patient symptoms and preferences with regards to desire for pregnancy.
6. Pharmacologic and surgical options are indicated to treat endometriosis-associated pain. Surgery/reproductive technology is the only treatment option for endometriosis-related infertility.
7. Treatment options are not curative of endometriosis and only provide symptom management.
8. First-line pharmacologic options include NSAIDs, CHCs, and progestins. Other options include gonadotropin-releasing hormone (GnRH) agonists, GnRH antagonists, danazol, and aromatase inhibitors.
9. Add-back therapy can be utilized with certain agents to minimize hypoestrogenic adverse events such as bone mineral density (BMD) loss

and vasomotor symptoms.

Preclass Engaged Learning Activity

Review the American College of Obstetricians and Gynecologists (ACOG) bulletin, European Society of Human Reproduction and Embryology (ESHRE) Guidelines and National Institute for Health and Care Excellence (NICE) guidelines to determine similarities and differences.

INTRODUCTION

Endometriosis is a common gynecologic condition that affects women during their reproductive years, defined as the growth of endometrial tissue outside the uterus. Clinically, endometriosis can cause several symptoms with the most common being dysmenorrhea, dyspareunia, and infertility. It is usually diagnosed in women in their thirties and forties; however, it is also common in adolescent age. Chronic pelvic pain is the most common complaint, especially in adolescents. Patients are often asymptomatic; therefore, it is difficult to confirm the true incidence of endometriosis.

While the pathophysiology of endometriosis isn't completely understood, it is believed that retrograde menstrual flow causes several endometriosis symptoms. This backflow of fluid often leads to endometrial deposits in various areas of the genitourinary tract including the bladder, ureter, and ovaries in addition to the gastrointestinal tract. Other theories include hematogenous or lymphatic transport, stem cells from bone marrow, and coelomic metaplasia (ACOG). Interventions are focused on the desire of the patient to become pregnant, relieve symptoms, or both. Pregnancies are often beneficial for improving symptoms.

EPIDEMIOLOGY

The incidence of endometriosis in the general population is approximately 10%.[1,2] It is a common cause of infertility and chronic pelvic pain and has an incidence of approximately 38% in women with infertility (with some estimates of around 50%); and more than 60% of patients with chronic pelvic pain have a diagnosis of endometriosis (with some reports of 71%-87%).[2] It is estimated that roughly one in ten women of reproductive age are diagnosed with endometriosis.

However, it is probable that approximately 11% of women are undiagnosed. There is a strong genetic predisposition, and it has been noted that women with a first degree relative with endometriosis have a 7- to 10-fold increased risk for developing endometriosis.[2]

ETIOLOGY

Endometriosis is characterized by the growth of endometrial tissue outside of the uterus,[1,2] and while it can be diagnosed in any age; it is most commonly found during the reproductive years. In addition to genetic predisposition, several risk factors have been identified. The risk of endometriosis is higher in those with early menarche (defined as the start of menses at 11 years old or younger), short menstrual cycles (less than 27 days) and heavy, prolonged menses. It is thought that environmental factors play a role in the pathogenesis of endometriosis. For example, dioxins, chemicals that have been found in the environment, have been thought to increase a woman's risk for developing endometriosis or worsening symptoms.[3,4] Multiple parity has been associated with a lower risk of endometriosis and/or improvement in endometriosis symptoms. Additionally, regular exercise of more than 4 hours per week has been associated with a lower risk of the development of endometriosis.[2,5]

In addition to infertility and chronic pain, endometriosis is a major cause of hysterectomy and hospitalization in the United States and can lead to decreased quality of life.

PATHOPHYSIOLOGY

2 While not well understood, the pathophysiology of endometriosis is related to the finding of endometrial implants (the tissue forming the lining of the uterus) outside of the uterus. It is thought that these implants occur outside of the uterus due to retrograde menstrual flow. Endometrial implants are often found in the peritoneum, ovaries, fallopian tubes, uterus, bladder, ureters, intestines and rectum.[6,7] The growth of implants is dependent on estrogen, and throughout a woman's menstrual cycle they grow and bleed just as the endometrium thickens and sheds during menstruation. When the implants proliferate, adhesions (collections of scar tissue) can form that can lead to further bleeding, inflammation, and scarring especially prior to and during menses.

While retrograde menstruation can explain the endometrial deposits in the

peritoneal cavity, there are also other theories regarding the development of endometriotic implants. Additionally, several women have retrograde menstruation, yet do not develop endometriosis. It is estimated that there is a 90% prevalence of retrograde menstruation, yet 10% prevalence of endometriosis.[8] Four well-supported hallmarks of the pathophysiology of endometriosis include genetic predisposition, estrogen dependence, progesterone resistance, and inflammation.[6,7,9,8,10]

In patients with endometriosis, there are alterations in estrogen- and progesterone-dependent processes including inflammatory and immune responses, angiogenesis, and apoptosis. These alterations lead to survival and replenishment of endometriotic tissue. Genetic alterations that have been noted include the upregulation of B-cell lymphoma **2** (*BCL-2*), which is an antiapoptotic gene and has been shown in both eutopic and ectopic endometrium from women with endometriosis.[8] An observation that has been found in endometriotic tissue is the increased expression of the aromatase enzyme and decreased expression of 17β-hydroxysteroid dehydrogenase (17β-HSD) type 2, which leads to an increase in the concentration of estradiol. Estradiol stimulates prostaglandin E2 that further can stimulate aromatase activity. It is also thought that estrogen can stimulate the release of other inflammatory cytokines such as cyclooxygenase 2 (COX-2). Additionally, endometriotic lesions have decreased progesterone receptor expression and an absence of progesterone receptor-B. This can lead to an incomplete transition of endometrium from the luteal phase to the secretory phase of the menstrual cycle. While estradiol tends to have proinflammatory and antiapoptotic effects on endometrial cells, progestins inhibit inflammatory pathways and induce apoptosis in endometriotic cells.

Endometriosis has been considered a pelvic inflammatory condition because the peritoneal fluid tends to contain several inflammatory markers that are believed to contribute to pain, formation of adhesions, tissue fibrosis, and scarring. In patients without endometriosis, the immune system clears refluxed endometrial tissue deposits from the peritoneum. Endometrial lesions can lead to inflammation with the activation of macrophages and proinflammatory cytokines. The peritoneal fluid of patients with endometriosis often contains proinflammatory cytokines such as tumor necrosis factor alpha and interleukins 1, 6, and 8 that lead to prostaglandin induction. There is also thought to be an increased density of nerve fibers and a high expression of nerve growth factor in endometriotic lesions which further increases pain. Compression of nerve fibers by endometrial implants along with bleeding from endometrial tissues can increase a patient’s pain. Lastly, endometriotic nerve fibers influence dorsal root

neurons thereby increasing pain perception.

Infertility and the reason for its development has been less well described, especially in mild cases of endometriosis. In more severe cases, inflammation and anatomic abnormalities such as ovarian cysts and adhesions can lead to blockage of the fallopian tubes and hindrance of oocyte and embryo development. The inflammatory cytokines can lead to damage of sperm DNA and cell membranes and the general inflammation seen may result in adhesions and scarring.[1] Hormonal dysregulation can also lead to irregularities in the menstrual cycle, alterations in endometrial receptivity and implantation, and altered oocyte and embryo quality, or issues with uterotubal transport.[8]

CLINICAL PRESENTATION

Symptoms

3 Endometriosis presents in a variable and unpredictable manner with regards to clinical presentation and clinical course. Dysmenorrhea and infertility are the most commonly reported symptoms in patients; however, several other symptoms are often present, or a patient can remain asymptomatic. Typical symptoms include abdominopelvic pain, dysmenorrhea, and dyspareunia; and women experiencing these classic symptoms are more likely to be diagnosed than those presenting without these symptoms. Deep pain during or after sexual intercourse, period-related or cyclical gastrointestinal symptoms, such as painful bowel movements, menorrhagia, ovulation pain, and chronic fatigue are other possible symptoms. Chronic pelvic pain can vary in severity and may be cyclic or acyclic. Pain can lead to a decreased quality of life depending on the severity; however, some patients may be asymptomatic.[2,6,7]

Signs

Physical examination of a patient with endometriosis often reveals pelvic tenderness, enlarged ovaries, pelvic masses or nodules, uterosacral ligaments, or a fixed, retroverted uterus. These signs are usually most significant during menses, so it is recommended to perform the examination at that time. Imaging studies such as transvaginal ultrasound or magnetic resonance imaging are also used to visualize endometrial lesions. If a patient with suspected endometriosis has normal imaging studies, laparoscopic surgery can be considered to further

evaluate the pelvis and endometrial lesions. Lesions can vary in size from small lesions in the ovaries or peritoneum to endometriomas, which are large cysts. The lesions are often described as “powder burn” or “gunshot” lesions; dark brown, black or blue lesions, nodules, and cysts; and blood containing endometriomas are called “chocolate cysts.”[11]

Diagnosis

4 The diagnosis of endometriosis can be challenging and may take several years due to variability of symptoms. Additionally, a definitive diagnosis can only be made by histological examination of lesions removed during surgery. Treatment guidelines do discuss ruling out all causes of pain and providing a nondefinitive diagnosis in patients with chronic pelvic pain. Ultrasonography, magnetic resonance imaging, computed tomography are often used to assess pelvic or adnexal masses, but have a lower sensitive for investigating endometrial lesions. However, in some cases pelvic and abdominal examinations can be used, especially during menstruations and positive findings include pelvic tenderness, enlarged ovaries, or a fixed, retroverted uterus. Imaging studies can be utilized to determine whether there is endometrial tissue in the bowel, bladder, or ureter. Transvaginal ultrasounds are used to determine if endometrial tissue is infiltrating the rectum. Cancer antigen 125 (CA 125) is a marker for ovarian and endometrial cancer, which has been noted to be elevated in some women with endometriosis but is not a diagnostic marker.[11] However, for diagnosis of endometriosis, the CA-125 measurement is limited due to the fact that an elevated level is not diagnostic.[2,11]

CLINICAL PRESENTATION Endometriosis

Physical Symptoms

- Dysmenorrhea
- Infertility
- Pelvic pain
- Dyspareunia (Deep pain during or after sexual intercourse)
- Period-related or cyclical gastrointestinal symptoms (eg, painful bowel movements)
- Menorrhagia

- Ovulation pain
- Chronic fatigue are other possible symptoms

Other considerations

- Chronic pelvic pain can vary in severity and may be cyclic or acyclic
- Pain can lead to a decreased quality of life depending on the severity
- Some patients may be asymptomatic

Signs: From physical examination of a patient with endometriosis

- Pelvic tenderness
- Enlarged ovaries
- Pelvic masses or nodules
- Uterosacral ligaments
- Fixed, retroverted uterus
- *Note: These signs are usually most significant during menses*

Data from references 2, 6, and 7.

Disease Staging

In general, endometriosis disease severity can be classified according to the American Society of Reproductive Medicine staging system which ranges from stage I [mild] to stage IV [severe]. This system stages endometriosis according to not only anatomic location, but also the severity of disease.[2] Although staging of disease can be helpful, it is limited in its clinical utility because it does not predict pregnancy after treatment and does not correlate well with symptoms of pain or dyspareunia.[2] Regardless, staging may be useful in guiding decisions regarding prognosis and treatment for infertility.[2,12]

TREATMENT

Multiple guidelines and expert opinions exist for the management of

endometriosis, with key guidelines coming from organizations such as the American College of Obstetricians and Gynecologists (ACOG), the American Society for Reproductive Medicine (ASRM), Society of Obstetricians and Gynecologists of Canada (SOGC), National Institute for Health and Care Excellence,[11] and the European Society of Human Reproduction and Embryology (ESHRE).[12,13] Table 97-1 is a summary of the ESHRE-graded recommendations.

TABLE 97-1 Evidence-based Recommendations for Treatment of Endometriosis-Related Pain

Treatment Options	Grade of Recommendation—ESHRE
CHCs	
Oral	B
Vaginal	C
Transdermal	C
Continuous use of CHC	C
Progestins	
Oral	A
Depot	A
LNG-IUS	B
Danazol	A
GnRH Agonist	A
Initiate add-back therapy with GnRH agonist initiation to prevent anti-estrogen side effects	A
NSAIDs	GPP
Aromatase inhibitors (in women in refractory endometriosis, used in combination with oral CHCs, progestins, GnRH agonists)	B
Surgical Treatment	A

A = Meta-analysis or multiple randomized trials (of high quality); B = Meta-analysis or multiple randomized trials of moderate quality, single randomized trial, large nonrandomized trials, or case-control/cohort studies of high quality; C = Single randomized trial, large nonrandomized trial(s), or case-control/cohort studies (of moderate quality); D = Nonanalytic studies or case reports/case series (of high or moderate quality); GPP = Good practice point based on expert opinion.

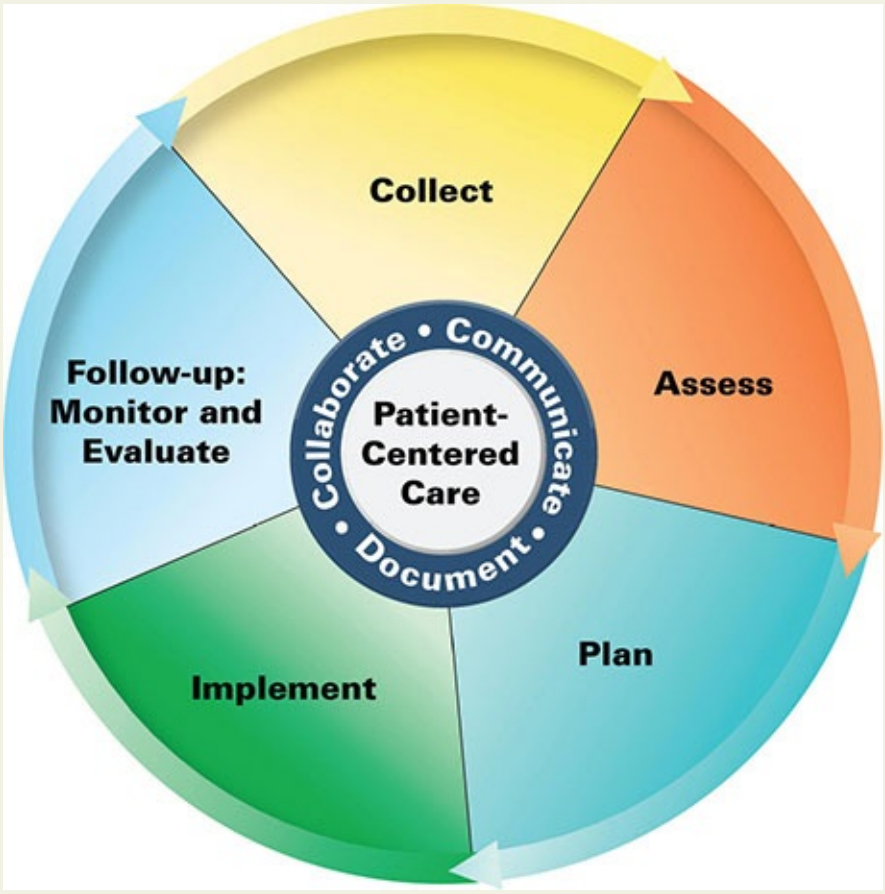
Source: Data from reference 12.

Desired Outcomes

75 Endometriosis is not curable with currently available treatment modalities; therefore, presently available options allow for the management of disease primarily through pain relief and correction of infertility treatment. Patient-specific goals and desired outcomes will vary and should be considered when making a treatment plan, as the individual patient's desires will greatly impact the treatment options available. Reducing pain and improving quality of life can be achieved through pharmacologic options and/or surgery.[2,10,14] Endometriosis-related infertility does not respond to available pharmacologic therapies and requires surgical intervention.[2,10]

General Approach to Treatment

Endometriosis-related pain can be managed with medical treatment, surgical treatment, or both. The best option for an individual patient will depend on their specific goals for treatment. Current medical therapies relieve endometriosis-related pain through induction of a pseudopregnancy or pseudo menopausal state, which reduces painful lesions, but does not improve fertility. Therefore, individuals looking to become pregnant will typically require surgical intervention and may also require the use of assisted reproductive technologies. Pregnancy success rates do increase after surgical procedures, but the exact magnitude is unclear due to the lack of well-designed clinical studies.[2,10,14]



Patient Care Process for Endometriosis

Collect

- Patient characteristics (age and pregnancy)
- Patient medical history (personal and family)
- Patient's desire and timeline for fertility
- Symptoms (type of pain, location, frequency, cyclic vs acyclic)
- Objective data:

  Imaging procedure results confirming diagnosis of endometriosis (if available)

Assess

- Whether patient is a candidate for drug therapy or surgical procedures
- Patient goals and treatment options (Tables 97-1 and 97-2)
- Presence of contraindications to treatment options

- Ability/willingness to use various formulations such as injections, vaginal ring, transdermal patch, intrauterine device
- Ability/willingness to pay for treatment options
- Likely adherence to options

Plan*

- Drug therapy regimen including specific medication(s), dose, route, frequency, and duration (Table 97-3)
- Monitoring parameters including efficacy and safety (pain relief, side effects) (Table 97-3)
- Prepare patient education
- Referrals to other providers

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up appointment (typically 2-3 months to determine treatment efficacy)

Follow-Up/Monitor

- Resolution of symptoms
- Presence of adverse drug events (Table 97-3)
- If using GnRH agonists: bone mineral density and serum lipids
- Patient adherence to treatment plan
- Duration of therapy depending on desire to become pregnant or patient entering menopause

**Collaborate with patient, caregivers, and other healthcare professionals.*

Medical management options include nonsteroidal anti-inflammatory drugs (NSAIDs), combined hormonal contraceptive (CHCs), progestins, gonadotropin-releasing hormone (GnRH) agonists, danazol, and aromatase inhibitors. In general, the NSAIDs, CHCs, and progestins are recommended first line due to their proven success in dysmenorrhea management, tolerability, and cost. The GnRH agonists and danazol are both highly effective but are considered second-

line options because of their side effect profiles. Aromatase inhibitors are considered last line after failure of other medical or surgical therapies.

The patient's chief complaint, possible side effects seen with various pharmacotherapeutic agents, extent of prescription drug coverage, contraindications to treatment, and adherence should all be considered when developing a treatment plan.[2,10,12,15] Information regarding drug therapy options can be seen in **Table 97-2**. Overall, the NSAIDs are appropriate to use in conjunction with each listed treatment option, barring the existence of contraindications to use, as endometriosis treatments are not typically guaranteed to provide full relief of symptoms and may require adjunctive analgesic use.

TABLE 97-2 Evidence- Based Considerations in Endometriosis Treatment

Treatment Considerations	Grade of Recommendation—ESHRE
Empirical treatment of pain (without specific diagnosis) with CHCs or progestins	GPP
Preoperative hormonal treatment should NOT be initiated prior to surgery with the primary goal to improve surgery outcomes	A
Postoperative hormonal treatment should NOT be initiated after surgery with the primary goal to improve surgery outcomes	A
CHCs and LNG-IUS are preferred treatment options for postoperative secondary prevention of dysmenorrhea	A
Operative laparoscopy is the preferred treatment option for women with infertility secondary to endometriosis who are looking to become pregnant	A
Hysterectomy–oophorectomy may be considered in women finished with childbearing who have failed more conservative options	GPP

A = Meta analysis or multiple randomized trials (of high quality); B = Meta analysis or multiple randomized trials of moderate quality, single randomized trial, large nonrandomized trials, or case-control/cohort studies of high quality; C = Single randomized trial, large nonrandomized trial(s), or case-control/cohort studies (of moderate quality); D = Nonanalytic studies or case reports/case series (of high or moderate quality); GPP = Good practice point based on expert opinion.

Source: Data from reference 12.

Asymptomatic patients with an incidental diagnosis of endometriosis do not

need treatment, but rather can be monitored for the development of pain or infertility and then managed at that point.[12]

Nonpharmacologic Therapy

6 Laparoscopic surgery is used as a diagnostic and therapeutic tool for endometriosis.[2,10,12] As part of this procedure, it is generally recommended that surgeons remove any visible lesions when performing a diagnostic surgery. Otherwise individuals may seek surgery if they are infertile or are not responding to available medical treatment options. A hysterectomy–oophorectomy is an option for individuals who do not desire future pregnancy, but, as with other treatment modalities, this surgery does not guarantee full relief of symptoms.[12]

For those undergoing surgery, pre- and posttreatment with hormone therapy does not improve outcomes related to surgery. The ESHRE guidelines separate postsurgical treatment into adjunctive (use for <6 months) and secondary prevention (use for >6 months) categories. These guidelines state that short-term adjunctive hormonal treatment will not improve the surgical outcomes after surgery, but long-term medical treatment may be started postsurgery for purposes of contraception or secondary prevention. Secondary prevention recommendations include using CHCs or the levonorgestrel-releasing intrauterine system (LNG-IUS) for at least 18-24 months to prevent recurrence of endometriomas.[12,16,17]

Pharmacologic Therapy

Pharmacologic therapy is typically the first choice for treatment of endometriosis-related pain to minimize risks from multiple surgeries such as scarring and tissue adhesions. First-line treatment options are such because they are equally effective but have an improved tolerability and cost compared to alternative therapy options (Table 97-3).[2,10,12,15]

TABLE 97-3 Drug Dosing/Adverse Drug Reactions (ADRs)/Monitoring/Comments

Drug Therapy Options	Brand Name	Dosing	Adverse Drug Reactions/Side Effects	Monitoring Parameters and Counseling Points
NSAID				
Ibuprofen	Motrin; Advil	200-800 mg orally 3 times daily	Gastrointestinal upset, dizziness, skin rash, tinnitus	Take with food to limit GI upset
Naproxen	Aleve, Naprosyn	200-220 mg orally 2-3 times daily up to 500-550 mg twice daily		Consider monitoring blood pressure if using regularly
Diclofenac	Voltaren	50 mg orally 3 times daily		
CHC				
Various (oral tablet)	Various	1 tablet orally daily	Nausea, vomiting, breast tenderness, weight gain, acne, oily skin, fatigue, BTB, spotting, elevated blood pressure, application site reaction (patch only), vaginal irritation (ring only)	Continuous dosing may improve outcomes
Etonogestrel/ethinyl estradiol (vaginal ring)	NuvaRing	Insert 1 ring vaginally for 3 weeks and remove for 1 week		Many ADRs improve after 2-3 cycles
Norelgestromin/ ethinyl estradiol (transdermal)	Ortho Evra; Xulane	Apply one patch weekly for 3 weeks and remove for 1 week		Measure blood pressure within 3 months of starting new method
Progestin				
Norethindrone (oral tablet)	Aygestin	5 mg orally daily; may titrate to 20 mg daily	Breast tenderness, nausea, peripheral edema, VTE	
MPA (oral tablet)	Provera	30 mg orally daily; may titrate to 60 mg daily	Menstrual irregularities, nausea, peripheral edema, VTE	
DMPA (IM or SubQ)	Depo-Provera IM	150 mg IM every 13 weeks	Menstrual irregularities, weight gain, acne, hirsutism, depression, decreased BMD	BMD testing not currently recommended
	Depo-SubQ Provera	104 mg SubQ every 12-14 weeks		
LNG-IUS	Mirena	Single insertion for up to 5 years	Menstrual irregularities, insertion-related complications, expulsion, pelvic inflammatory disease	
GnRH Agonist				
Goserelin	Zoladex	3.6 mg monthly SubQ implant	Acne, depression, hot flashes, mood swings, peripheral edema, vaginitis, BMD loss	Use add-back to prevent many ADRs
Leuprolide	Leupron Depot	3.75 mg IM monthly or 11.25 mg IM every 3 months	Acne, depression, hot flashes, mood swings, vaginitis, BMD loss, VTE, anaphylaxis, nausea/vomiting, headache, dizziness, triglyceride elevation	Consider BMD testing every 1-2 years and serum lipid levels every 6 months if treatment exceeds 12 months
Naferelin	Naferelin	400 mcg intranasally daily (one spray in one nostril AM and one spray in the opposite nostril PM); may titrate to 800 mcg daily	Acne, headache, hot flash, mood swing, vaginal dryness, BMD loss, VTE	
Triptorelin	Triptorelin	3.75 mg IM monthly	Headache, elevated blood pressure, hot flashes, anaphylaxis, angioedema	
GnRH Antagonist				
Elagolix	Orilissa	150 mg orally once daily or 200 mg orally twice daily	Headache, nausea, anxiety, hot flash, BMD loss, change in lipid levels, insomnia, mood swings, night sweats	
Androgen				
Danazol	Danocrine	100-200 mg orally twice daily; may titrate to 400 mg twice daily	Acne, peripheral edema, hirsutism, lipid abnormalities, weight gain, hepatic dysfunction	Liver function tests and serum cholesterol every 3-6 months
Aromatase Inhibitor				
Anastrozole	Arimidex	1 mg orally daily	Arthralgias, hot flashes, myalgias, nausea, diarrhea, decreased BMD	Use with CHC, progestin, or GnRH agonist
Letrozole	Femara	2.5 mg orally daily		Consider BMD testing every 1-2 years if treatment exceeds 12 months

ADR, adverse drug reaction; BMD, bone mineral density; BTB, breakthrough bleeding; CHC, combined hormonal contraceptive; IM, intramuscular; LNG-IUS, levonorgestrel-releasing intrauterine system; NSAID, nonsteroidal anti-inflammatory drug; SubQ, subcutaneous; VTE, venous thromboembolism.

Drug Treatments of First Choice

8 First-line therapy for endometriosis-associated pain includes oral CHCs, oral progestins (norethindrone acetate or medroxyprogesterone acetate), or depot progestin medroxyprogesterone acetate (DMPA). These medications tend to be well-tolerated and are safe for long-term use, which is important because endometriosis symptoms typically return shortly after treatment is discontinued.[2,10,12,15]

Studies demonstrating direct comparisons between these products are lacking, so the decision of which product to use should depend on patient preference, including formulation type, dosing schedule, and potential adverse events.[2]

Although laparoscopic imaging provides the only definitive diagnosis of endometriosis, these options may be initiated empirically for suspected endometriosis in patients of any age prior to laparoscopy.[2,10,12,15] Response to hormonal treatment does not predict the presence or absence of endometriosis, but use of these options before laparoscopy can avoid an invasive procedure.[12]

Nonsteroidal Anti-inflammatory Drugs Dysmenorrhea is a primary symptomatic feature of endometriosis and NSAIDs are indicated as the first-line treatment of menstrual pain with or without an endometriosis diagnosis. Individuals may initially self-treat with over-the-counter options, such as ibuprofen and naproxen; however, prescription strength versions of these are available as well, and individuals may find they need to use the upper end of the recommended dosing range in order to find relief from pain.[2,10,11]

Combined Hormonal Contraception Combined hormonal contraceptives (CHCs) are a first-line treatment option for suppression of endometriosis and are widely used due to their efficacy, tolerability, safety profile, and cost.[18] Their exact mechanism of action for endometrial pain relief is unclear because the pathogenesis of endometriosis is unclear. However, there are several widely accepted theories.[18] Overall, the CHCs alleviate dysmenorrhea, a common symptom of endometriosis, reduce the growth of endometrial tissue, decrease menstrual flow, and reduce prostaglandin generation.[18] They have also been shown to down-regulate cell proliferation and increase apoptosis in the eutopic endometrium.[18] Secondary benefits of CHCs include menstrual cycle regulation and contraception.

Oral CHCs have demonstrated efficacy in a small number of observational, placebo-controlled and active-comparator trials. The majority of studies on CHC

efficacy have been for oral products; however, one study demonstrated effectiveness of the CHC patch and vaginal ring, which may have appealing dosing schedules compared to their oral counterparts.[19] The decision between CHCs should be based upon patient preference, including adherence and cost.[2]

The CHCs have traditionally been dosed cyclically, with 3 weeks of active hormone followed by 1 week of placebo, allowing for a withdrawal bleed. However, some individuals prefer the option to dose continuously, either through commercially available "extended cycle" options or by skipping the placebo week of their CHC. A prospective trial demonstrated that continuous dosing may be more efficacious than cyclic dosing after individuals with recurrent postoperative dysmenorrhea were switched from cyclic to continuous CHC dosing and reported a significant reduction in pain.[20] Other studies have mimicked these results, and the ESHRE guidelines now specifically recommend continuous dosing as an option for patients.[12]

Due to the proposed estrogen dependency of endometriotic lesions, it has been proposed that the estrogen dose in CHCs should be limited to avoid feeding the endometriosis tissue. Even the lowest doses of commercially available CHCs are four to six times the physiologic dose of estrogen; therefore, clinicians should consider initiating patients on CHCs with the lowest effective estrogen dose to limit this possibility.

Progestins Progestins are another first-line option for suppression of endometriosis due to their efficacy in treating dysmenorrhea, the overall tolerability of progestins, and their reasonable price. Progestins suppress growth of endometriotic implants, eventually causing endometriotic atrophy. They have also demonstrated inhibition of blood vessel growth and anti-inflammatory action, in addition to their anovulatory effects, all which relieve the dysmenorrhea associated with endometriosis.[21–23]

Progestins may be administered orally (norethindrone acetate or medroxyprogesterone acetate), intramuscularly or subcutaneously (depot medroxyprogesterone acetate–DMPA) or as a levonorgestrel intrauterine system (LNG-IUS). As with other endometriosis treatment options, studies comparing progestin options directly are limited; therefore, selection should account for the individual's opinion about dosage form, as well as cost and potential side effects and risks.[24]

Oral Progestins Oral progestins are widely available as contraceptive and menopausal hormonal replacement products. Importantly, contraceptive progestin products have the added benefit of preventing pregnancy and

managing other menstrual-related side effects, such as acne.

Injectable Depot Medroxyprogesterone Acetate The downsides to injectable DMPA use include a slow return to fertility and potential bone mineral density loss, as DMPA carries a black box warning to avoid use for greater than 2 years due to the risk of potentially irreversible BMD loss. Controversy exists on the potential irreversibility of BMD loss and despite this labeling, the ACOG has stated that clinicians may continue its use beyond 2 years in patients who are responding well.[25] For those who wish to become pregnant shortly after discontinuing treatment, this option may not be preferred because of its associated slow return of normal ovulation. Overall, DMPA has a mean conception time of 10 months after discontinuation, compared to other hormonal products that have shorter return to fertility.[26]

Levonorgestrel Intrauterine System Insertion of an LNG-IUS is an option for those seeking long-acting reversible contraceptive benefits in addition to endometriosis pain relief. There are various forms of LNG-IUSs available in the market. Approximately 20% to 30% of women experience amenorrhea within the first year of using an LNG-IUS, reducing the major symptom of endometriosis, dysmenorrhea.[27] Despite their efficacy at reducing endometriosis-related pain, no LNG-IUSs are currently Food and Drug Administration (FDA) approved for the treatment of endometriosis.

The LNG-IUDs do not inhibit ovulation, yielding a potential for the growth of ovarian endometriomas. Other disadvantages of the LNG-IUS include potential difficulty of inserting the device into nulliparous women, a 5% expulsion rate, and cost of the procedure.[15]

Alternative Drug Treatments

Other options for treatment of endometriosis pain include gonadotropin-releasing hormone (GnRH) agonists, GnRH antagonists, danazol, and aromatase inhibitors.[2,12,15,28] Treatments fall into this category for several reasons: lack of data supporting their efficacy in treating endometriosis, proven efficacy but intolerable adverse events, or unknown long-term safety.

None of these methods is proven superior over others, so treatment decisions should be made based on patient preference of dosage form and dosing schedule, patient-specific response, potential side effects, and medication costs/insurance coverage.[2,10,12,15]

Several of the options in this category can be combined with other

medications to limit their adverse events. For example, GnRH agonists are used with estrogen-progestin products to limit anti-estrogenic side effects and aromatase inhibitors are prescribed with CHCs, progestins, or GnRH agonists.

Gonadotropin-Releasing Hormone Agonists The GnRH agonists are highly effective at treating endometriosis-associated pain, but their use is limited by side effects and cost. The ACOG guidelines recommend their empiric use in the event of NSAID or contraceptive failure.[2] Pharmacologically the GnRH agonists inhibit follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion, which effectively mimics an oophorectomy.

The GnRH agonists create a gonadotropic flare prior to their long-term receptor downregulation, which may increase pain during this period. This can be minimized by initiating therapy during the mid-luteal phase or overlapping therapy with a CHC or progestin for three weeks. Pain will recur quickly upon discontinuation, making GnRH agonists a chronic treatment option.[29,30] Although GnRH agonist are approved by the FDA currently for only 12-month courses of treatment, if a patient responds well to therapy it is often continued for longer with add-back therapy (subsequently discussed).[2]

Side effects seen with GnRH agonists are the result of the hypoestrogenic environment and include BMD loss and vasomotor symptoms, such as hot flushes, vaginal dryness, and insomnia. With long-term use (>6 months) BMD loss becomes a major concern. Utilization of add-back therapy minimizes this loss and other adverse events and has demonstrated safety for up to 10 years.[31,32] It is recommended to start add-back therapy on immediate initiation of GnRH agonist treatment.[2,12,15] Monitoring for this class of medications includes physical findings, bone density, and serum lipids.[2]

9 ***Add-Back Therapy*** Add-back regimens may consist of progestins alone, estrogens, and progestins and bisphosphonates and are utilized in combination with GnRH agonists to reduce or eliminate BMD loss and provide symptomatic relief against the anti-estrogenic effects of GnRH agonists. Several studies have recently shown that estrogen-progestin combinations are more effective than progestin monotherapy at protecting for BMD loss.[30,33,34]

Adding estrogen to a GnRH agonist has a potential to negate its anti-estrogenic effects that relieve endometriosis pain. Therefore, the dose of estrogen must be low enough to maintain a serum estrogen level <50 pg/mL (180 pmol/L) in order to prevent growth of new endometrial tissue while preventing anti-estrogenic side effects such as BMD loss and vasomotor symptoms. The

CHCs should not be used as add-back therapy because they will yield a higher serum level than recommended; therefore, menopausal preparations are typically appropriately dosed to reach this serum level.[15] Examples of regimens studied include oral conjugated equine estrogens 0.625 mg/day plus oral norethindrone acetate 5 mg/day, and transdermal estradiol 25 μg twice weekly plus oral medroxyprogesterone acetate 5 mg/day, and oral estradiol 2 mg/day plus oral norethindrone acetate 1 mg/day.[33]

Gonadotropin-Releasing Hormone Antagonists Elagolix is the most recently approved drug to treat endometriosis. It is a member of the class of GnRH antagonists, which competitively inhibit GnRH receptors in the pituitary in order to rapidly decreases circulating estradiol and gonadotropins.[35] GnRH antagonists may represent a class of medications with similar efficacy but better tolerability compared to the GnRH agonists: while effectively downregulating the same hormones as GnRH agonists, the GnRH antagonists differ in their quicker onset and avoidance of a painful gonadotropin flare upon initiation. Elagolix can be dosed to achieve partial or full suppression, which may minimize hypoestrogenic adverse events compared to GnRH agonists. It is not clear whether add-back therapy is appropriate to minimize these adverse events if they do occur.

Elagolix's side effects include headache, nausea, anxiety, hot flashes, and some breakthrough bleeding and spotting.[36] Hypoestrogenic side effects include hot flashes, increased serum lipid levels, and BMD loss. Because this drug is so new, it is still unknown whether this loss is reversible and what the long-term effects of use may be.

Elagolix does not fully suppress ovulation and the effect of GnRH antagonists on pregnancy is unknown at this time.[36] Individuals are recommended to use contraception to avoid pregnancy while on this class of medications until further information is known.

Androgens Danazol is an androgen that serves as a second-line hormonal treatment option. Danazol inhibits endometrial tissue growth, induces endometrial atrophy, and causes amenorrhea due to the hypo-estrogenic/hypo-progestogenic environment it creates. It is highly effective and was formerly considered the gold standard of endometriosis treatment, but is now used in a limited manner because of the androgenic properties of its side effect profile.[37]

Danazol should not be initiated in women with hyperlipidemia or liver disease. Barrier contraception must be used in conjunction with use of this medication due to its teratogenicity. Common side effects include hirsutism and acne, although some individuals may experience significant weight gain and

fluid retention.[37]

Three studies have looked at the use of vaginal danazol formulations in an effort to limit systemic drug exposure and limit androgenic side effects. Each study demonstrated improvements in dysmenorrhea, deep dyspareunia, and pelvic pain without systemic side effects. The vaginal formulation of danazol is not currently available in the United States.[38–40]

Aromatase Inhibitors Aromatase inhibitors are a more recent addition to the endometriosis-treatment toolkit. While the ACOG guidelines do not support their routine use based on limited data, the ESHRE guidelines support their use in women with endometriosis refractory to other medical or surgical treatment.[2,12] This class lowers overall estrogen concentrations by inhibiting aromatase, which is key enzyme in the conversion of adrenal androgens to estrogens. The resultant reduction of estrogen concentrations then diminishes endometrial lesions.

Numerous case reports and studies have looked at aromatase inhibitors in combination with progestins, oral combined hormonal contraceptives and GnRH agonists. Results of these studies have demonstrated decreased pain, improved quality of life, and reduced postoperative recurrence of disease in women refractory to other treatments.[40–44]

As the aromatase inhibitors reduce circulating estrogen levels, long-term use may impact bone mineral density, similar to other pharmacologic therapies. Safety information for this class of medications is mainly from studies in postmenopausal women with cancer, which differs from the typical woman of reproductive age who would be using these agents for endometriosis pain. Limited available data does indicate that the use of progestin monotherapy or combined hormonal contraceptives in addition to the aromatase inhibitor would limit BMD loss.[40,41] The progestin and combined OC may also limit the FSH release, which may lead to chronic ovarian stimulation.[2]

Special Populations

Endometriosis is most commonly diagnosed in women in their thirties and forties, but endometriosis is the most common diagnosis in adolescent patients presenting with secondary dysmenorrhea.[15] Endometriosis commonly presents as early stage in adolescents, so physical findings will often be normal and laparoscopic findings may be atypical compared to those seen in older women.[15]

Treatment of adolescent patients is similar to adult treatment guidelines, with the most notable difference related to the use of options that affect bone mineral

density (BMD).[15,28,45] Both DMPA and the GnRH agonists should be used with caution in adolescents due to BMD loss concerns and while they are not completely contraindicated, their use should be held off as long as possible and only started after full consideration of the risk/benefit profile.[45]

Dysmenorrhea in adolescents is typically treated empirically with first-line options including NSAIDs and CHCs. These can be trialed for 3 months to assess pain relief. If pain persists after 3 months, CHCs may be switched from cyclic to continuous dosing to instigate amenorrhea. The next step after failure of this first-line options typically includes consideration of laparoscopic diagnostic/treatment surgery because failure correlates highly to a diagnosis of endometriosis.

EVALUATION OF THERAPEUTIC OUTCOMES

Outcome monitoring for endometriosis is based upon subjective relief of symptoms. Factors such as size, number, and distribution of endometrial lesions does not correlate to pain symptoms or potential fertility, limiting the use of objective tests to measure response to treatment.

The Endometriosis Treatment Satisfaction Questionnaire is a patient-reported outcome instrument that was developed and validated to measure patient reported pain before and/or during periods, pain during and/or after sex, endometriosis pain, bleeding and spotting, tolerability, and overall satisfaction using a seven-point Likert scale. Another validated tool is the Medical Outcomes Study Questionnaire Short Form 36 Health Survey (SF-36).[2,46,47]

Medical treatment of endometriosis should relieve endometriosis-related pain within 2 months of initiation. If symptoms are not relieved, individuals may try another medical option and/or surgery.

Surgery is frequently required in endometriosis-related infertility. It is recommended that individuals allow 6 months postintervention to try to conceive. If pregnancy is not achieved within this time-span, assisted reproductive technologies are the next line in treatment.

CONCLUSION

1 5 7 Endometriosis is a common disease with implications ranging from pain and reduced quality of life to infertility. Treatment modalities are not curative but may be successful at diminishing discomfort and improving quality

of life. Treatment plans should be designed while taking into account patient-specific factors and goals.

Postclass Engaged Learning Activity

Perform a drug literature search for endometriosis treatments that are currently in the drug development pipeline and describe their mechanism of action. Using your knowledge of endometriosis pathophysiology, what are possible drug therapy targets?

ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
ESHRE	European Society of Human Reproduction and Embryology
CHC	combined hormonal contraceptive
DMPA	depot medroxyprogesterone acetate
GnRH	gonadotropin-releasing hormone
LNG-IUS	levonorgestrel-releasing intrauterine system
BMD	bone mineral density
MPA	medroxyprogesterone acetate
VTE	venous thromboembolism
BTB	breakthrough bleeding

REFERENCES

1. Bedaiwy MA, Alfaraj S, Yong P, Casper R. New developments in the medical treatment of endometriosis. *Fertil Steril*. 2017;107(3):555–565.
2. Committee on Gynecologic Practice. ACOG Practice Bulletin No. 114: Management of endometriosis. *Obstet Gynecol*. 2010;116(1):223–236.
3. Cano-Sancho G, Ploteau S, Matta K, et al. Human epidemiological evidence about the associations between exposure to organochlorine chemicals and endometriosis: Systematic review and meta-analysis. *Environment International*. 2019;123:209–223.
4. World Health Organization. Dioxins and their effects on human health.

Available at: https://www.who.int/en/news-room/fact-sheets/detail/dioxins-and-their-effects-on-human-health. Accessed December 8, 2018.

5. Signorello LB, Harlow BL, Cramer DW, et al. Epidemiologic determinants of endometriosis: A hospital-based case control study. *Ann Epidemiol*. 1997;7:267–741.
6. Bulun SE. Endometriosis. *N Engl J Med*. 2009;360(3):268–279.
7. American College of Obstetricians and Gynecologists. Endometriosis FAQs. Available at: https://www.acog.org/-/media/For-Patients/faq013.pdf?dmc=1&ts=20180123T1606195516. Accessed November 21, 2018.
8. Jones RK, Searle RF, Bulmer JN. Apoptosis and bcl-2 expression in normal human endometrium, endometriosis and ademomyosis. *Human Reprod*. 1998;13:3496–3502.
9. Peterson CM, Johnstone EB, Hammoud AO, et al. Risk factors associated with endometriosis: Importance of study population for characterizing disease in the ENDO study. *Am J Obstet Gynecol*. 2013;208(6):451.e1–451.e11.
10. Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis: A committee opinion. *Fertil Steril*. 2014;101(4):927–935.
11. National Institute for Health and Care Excellence. Endometriosis Diagnosis and Management. Available at: https://www.nice.org.uk/guidance/ng73. Accessed November 25, 2018.
12. Dunselman GAJ, Vermeulen N, Becker C, et al. ESHRE guideline: Management of women with endometriosis. *Human Reprod*. 2014;29(3):400–412.
13. Hirsch M, Begum M, Paniz É, et al. Diagnosis and management of endometriosis: A systematic review of international and national guidelines. *BJOG Int J Obstet Gyn*. 2017;125(5):556–564.
14. Ziegler D, Borghese B, Chapron C. Endometriosis and infertility: Pathophysiology and management. *Lancet*. 2010;376(9742):730–738.
15. Leyland N, Casper R, Laberge P, Singh SS. Endometriosis: Diagnosis and management. *J Obstet Gynaecol Can*. 2010;32(7 suppl 2):S1–S32.
16. Wu L, Wu Q, Liu L. Oral contraceptive pills for endometriosis after conservative surgery: A systematic review and meta-analysis. *Gynecol Endocrinol*. 2013;29(10):883–890.

17. Tanmahasamut P, Rattanachaiyanont M, Angsuwathana S, et al. Postoperative levonorgestrel-releasing intrauterine system for pelvic endometriosis-related pain. *Obstet Gynecol*. 2012;199(3):519–526.
18. Harada T, Momoeda M, Taketani Y, et al. Low-dose oral contraceptive pill for dysmenorrhea associated with endometriosis: A placebo-controlled, double-blind, randomized trial. *Fertil steril*. 2008;90(5):1583–1588.
19. Vercellini P, Barbara G, Somigliana E, et al. Comparison of contraceptive ring and patch for the treatment of symptomatic endometriosis. *Fertil Steril*. 2010;93(7):2150–2161.
20. Vercellini P, Frontino G, Giorgi OD, et al. Continuous use of an oral contraceptive for endometriosis-associated recurrent dysmenorrhea that does not respond to a cyclic pill regimen. *Fertil Steril*. 2003;80(3):560–563.
21. Schweppe K-W. Current place of progestins in the treatment of endometriosis-related complaints. *Gynecol Endocrinol*. 2001;15(S6):22–28.
22. Vercellini P, Fedele L, Pietropaolo G, et al. Progestogens for endometriosis: Forward to the past. *Hum Reprod Update*. 2003;9:387–396.
23. Gezer A, Oral E. Progestin therapy in endometriosis. *Women's Health*. 2015;11(5):643–652.
24. Brown J, Kives S, Akhtar M. Progestagens and anti-progestagens for pain associated with endometriosis. *Cochrane Database Syst Rev*. 2012;(3):CD002122. doi: 10.1002/14651858.CD002122.pub2.
25. Committee on Adolescent Health Care, Committee on Gynecologic Practice. Committee Opinion No. 602: Depot medroxyprogesterone acetate and bone effects. *Obstet Gynecol*. 2014;123(6):1398–1402.
26. Hatcher RA, Trussell J, Nelson AL, et al. *Contraceptive Technology*. 21st ed. Ardent New York: Median, Inc.; 2015.
27. Vercellini P, Aimi G, Panazza S, et al. A levonorgestrel-releasing intrauterine system for the treatment of dysmenorrhea associated with endometriosis: A pilot study. *Fertil Steril*. 1999;72(3):505–508.
28. Dovey S, Sanfilippo J. Endometriosis and the adolescent. *Clin Obstet Gynecol*. 2010;53(2):420–428.
29. Surrey ES. Gonadotropin-releasing hormone agonist and add-back therapy: What do the data show? *Curr Opin Obstet Gynecol*. 2010;22(4):283–288.

30. Divasta AD, Feldman HA, Gallagher JS, et al. Hormonal add-back therapy for females treated with gonadotropin-releasing hormone agonist for endometriosis. *Obstet Gynecol*. 2015;126(3):617–627.
31. Bedaiwy MA, Casper RF. Treatment with leuprolide acetate and hormonal add-back for up to 10 years in stage IV endometriosis patients with chronic pelvic pain. *Fertil Steril*. 2006;86(1):220–222.
32. Wu D, Hu M, Hong L, et al. Clinical efficacy of add-back therapy in treatment of endometriosis: A meta-analysis. *Arch Gynecol Obstet*. 2014;290(3):513–523.
33. Farmer JE, Prentice A, Breeze A, et al. Gonadotrophin-releasing hormone analogues for endometriosis: Bone mineral density. *Cochrane Database Syst Rev*. 2003;(4):CD001297.
34. DiVasta AD, Feldman HA, Gallagher JS, et al. The effect of hormonal add-back therapy in adolescents treated with a gonadotropin-releasing hormone (GnRH) agonist for endometriosis: A randomized trial. *J Adolescent Health*. 2015;56(2):S24.
35. Taylor HS. Use of elagolix in gynaecology. *J Obstet Gynaecol Can*. 2018;40(7):931–934.
36. Taylor HS, Giudice LC, Lessey BA, et al. Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist. *N Engl J Med*. 2017;377(1):28–40.
37. Barbieri RL, Evans S, Kistner RW. Danazol in the treatment of endometriosis: Analysis of 100 cases with a 4-year follow-up. *Fertility and Sterility*. 1982;37(6):737–746.
38. Razzi S, Luisi S, Calonaci F, et al. Efficacy of vaginal danazol treatment in women with recurrent deeply infiltrating endometriosis. *Fertil Steril*. 2007;88(4):789–794.
39. Bhattacharya SM, Tolasaria A, Khan B. Vaginal danazol for the treatment of endometriosis-related pelvic pain. *Int J Gynaecol Obstet*. 2011;115(3):294–295.
40. Ferrero S, Tramalloni D, Venturini PL, Remorgida V. Vaginal danazol for women with rectovaginal endometriosis and pain symptoms persisting after insertion of a levonorgestrel-releasing intrauterine device. *Int J Gynaecol Obstet*. 2011;113(2):116–119.
41. Pavone ME, Bulun SE. Aromatase inhibitors for the treatment of endometriosis. *Fertil Steril*. 2012;98(6):1370–1379.
42. Abushahin F, Goldman KN, Barbieri E, et al. Aromatase inhibition for

refractory endometriosis-related chronic pelvic pain. *Fertil Steril*. 2011;96(4):939–942.

43. Colette S, Donnez J. Are aromatase inhibitors effective in endometriosis treatment? *Expert Opin Investig Drugs*. 2011;20(7):917–931.
44. Nothnick WB. The emerging use of aromatase inhibitors for endometriosis treatment. *Reprod Biol Endocrinol*. 2011;9:87.
45. Stuparich MA, Donnellan NM, Sanfilippo JS. Endometriosis in the adolescent patient. *Semin Reprod Med*. 2017;35(1):102–109.
46. Deal LS, Williams VS, DiBenedetti DB, Fehnel SE. Development and psychometric evaluation of the endometriosis treatment satisfaction questionnaire. *Qual Life Res*. 2010;19(6):899–905.
47. Stull DE, Wasiak R, Kreif N, et al. Validation of the SF-36 in patients with endometriosis. *Qual Life Res*. 2014;23(1):103–117.

98

Hormone Therapy in Women

Devra K. Dang, Kathryn E. Wheeler, and Judy T. Chen

KEY CONCEPTS

1. The decision to use menopausal hormone therapy (MHT) and the type of formulation used must be individualized based on several factors, including personal preference, age, menopause onset, the severity of menopausal symptoms, and the risks of cardiovascular disease, breast cancer, osteoporotic fracture, and venous thromboembolic events (VTE).
2. Menopausal hormone therapy is the most effective treatment option for alleviating moderate-to-severe vasomotor symptoms.
3. Cardiovascular disease—including coronary artery disease, stroke, and peripheral vascular disease—is the leading cause of death among women, but MHT should not be used for reducing the risk of cardiovascular disease.
4. The risk of breast cancer associated with MHT appears to be associated with the addition of progestogen therapy to estrogen. Use of estrogen alone does not increase the risk of breast cancer.
5. Use of MHT at doses lower than those prescribed prior to the Women's Health Initiative (WHI) study appears to be effective in reducing bone loss and managing menopausal symptoms.
6. Use of transdermal MHT is preferred over oral preparations due to lower risk of thrombosis, and possibly stroke and coronary artery disease.
7. Because of the increased risk of endometrial hyperplasia and endometrial cancer with estrogen monotherapy (ie, unopposed estrogen), use of systemic estrogen in women with an intact uterus must always be accompanied by progestogen or tissue-selective estrogen complex (estrogen-bazedoxifene) for endometrial protection.
8. In women experiencing postmenopausal symptoms, initiation of systemic estrogen therapy should generally be limited to women younger than 60

years of age or within 10 years of menopause onset.

Preclass Engaged Learning Activity

What do you know about menopause? Before progressing in this lesson, create a list of all the information you currently know regarding menopause. It may be helpful to construct a “mind map,” a visual organization of the information to formulate connections between each item in your information list. When you have completed this task, identify needed information and consider how you might use this knowledge to improve a patient’s care.

INTRODUCTION

Menopause is the permanent cessation of menses following the loss of ovarian follicular activity. It is a natural life event, not a disease, as all women undergo menopause, and each experience it differently. Natural menopause occurs in stages including perimenopause (in the 5th decade), menopause, and postmenopause (1 year after menopause and beyond). Induced menopause can be experienced any time before natural menopause with bilateral oophorectomy (removal of both ovaries) or iatrogenic ablation of ovarian function (eg, chemotherapy, pelvic radiation). Symptoms of menopause can vary widely with induced menopause typically causing more severe symptoms. Due to the variability in duration, severity, and presence of menopausal symptoms among women, treatment should be individualized with treatment goals and decisions established in a shared decision-making process.

EPIDEMIOLOGY

The median age at the onset of menopause in the United States is 51 years, but can vary widely from 40 to 58 years.[1] An estimated 6,000 women in the United States reach menopause each day, and will spend approximately 40% of their lives in postmenopause.[2] It is estimated that by 2025, the number of postmenopausal women will be 1.1 billion worldwide.[1] By definition, menopause is a normal physiologic event that occurs after 12 consecutive months of amenorrhea, so the time of the final menses is determined retrospectively. Women who have undergone hysterectomy (removal of the

uterus) must rely on their symptoms to estimate the actual time of menopause, but typically occurs a few years earlier than natural menopause.

ETIOLOGY

A nomenclature and staging system for the female reproductive aging continuum was developed at the Stages of Reproductive Aging Workshop (STRAW) in 2001 and revised in 2011 with the STRAW+10 staging system.[3] The menopause transition refers to the span of time including menstrual, endocrine, and symptom changes starting with variation in menstrual cycle length and ending with the final menstrual period (FMP). Postmenopause occurs during the years beyond the FMP with stabilization of hormone levels and limited endocrine changes.

PATHOPHYSIOLOGY

A woman is born with approximately two million primordial follicles in her ovaries. During a normal reproductive life span, she ovulates fewer than 500 times; therefore, the vast majority of follicles undergo atresia.

The hypothalamic–pituitary–ovarian axis dynamically controls reproductive physiology throughout the reproductive years. The pituitary is regulated by pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH), produced by the pituitary in response to GnRH, regulate ovarian function. These gonadotropins also are influenced by negative feedback from estradiol and progesterone. Ovarian follicular activity is reflected by the circulating concentrations of sex steroids and by peptide hormones including inhibin, activin, and anti-Mullerian hormone (AMH). Overall, AMH is a product of growing ovarian follicles, which appears to be independent of the hypothalamic–pituitary–gonadal axis. It is a principal regulator of early follicular recruitment from the primordial pool such that the concentration of AMH in blood may also reflect the nongrowing follicle population. In general, AMH concentrations decline with age and while AMH levels may predict the median time to menopause, obtaining levels of AMH, FSH, and estradiol may be best reserved for women seeking fertility.[4] The sex steroids include estradiol, produced by the dominant follicle; progesterone, produced by the corpus luteum after maturation of the dominant ovarian follicle; and androgens, primarily testosterone and androstenedione, secreted by the ovarian stroma. These sex steroids are

important for the healthy functioning of many organs, including the bones, brain, skin, and reproductive and urogenital tracts as they act primarily by regulating gene expression.

Physiologic changes associated with menopause are caused by loss of ovarian follicular activity. Since ovarian primordial follicle numbers decrease with advancing age, by the time of menopause, few follicles remain in the ovary. Hence, the postmenopausal ovary is no longer the primary site of estradiol or progesterone synthesis as it secretes primarily androstenedione. In contrast to the acute fall in circulating estrogen at the time of menopause, circulating androgens begin to decline in the decade prior to the average age of natural menopause and closely parallels increasing age. Whether the ovary continues to secrete testosterone after menopause remains controversial. Hypertrophy of the ovarian stroma may develop after menopause, probably secondary to high LH concentrations, thereby resulting in increased ovarian testosterone production. Alternatively, the ovaries may become fibrotic and a poor source of sex steroids. No endocrine event clearly signals the time just prior to final menses.[5]

As women age, a progressive rise in circulating FSH and a concomitant decline in ovarian inhibin-B and AMH are observed. In women who continue to experience menstrual bleeding, FSH determinations on day 2 or 3 of the menstrual cycle exceeding 10 to 12 IU/L (mIU/mL) may indicate diminished ovarian reserve. Alternatively, low AMH concentrations, measured at any time in the cycle, predicts diminishing ovarian reserve. Clear elevations in serum FSH are seen in women approximately at age 40 years.[5] When ovarian function has ceased, serum FSH concentrations are greater than 40 IU/L (mIU/mL). Menopause is characterized by a 10- to 15-fold increase in circulating FSH concentrations compared with concentrations of FSH in the follicular phase of the cycle, a fourfold to fivefold increase in LH, and a greater than 90% decrease in circulating estradiol concentrations.[5] During the perimenopause, FSH concentrations may rise to the postmenopausal range during some cycles but return to premenopausal levels during subsequent cycles. Thus, high concentrations of FSH should not be used to diagnose menopause in perimenopausal women.

CLINICAL PRESENTATION

The perimenopause commences with the onset of menstrual irregularity and ends 12 months after the last menstrual period.[3] Approximately 90% of women have 4 to 8 years of menstrual cycle changes with heavier flow of longer duration

before natural menopause occurs.[1] The menstrual cycle irregularity is most often caused by the increased frequency of anovulatory cycles, but may also be due to thyroid abnormalities, hyperprolactinemia, or polycystic ovary syndrome. Women commonly experience symptoms during the perimenopause, which substantially impact their health and daily function. Vasomotor symptoms (eg, hot flashes and night sweats) develop in up to 80% of women and the symptoms on average can last 10 years, with longer duration in women experiencing menopause at an earlier age.[6] However, only less than one-third of women seek medical attention for treatment. While the frequency of vasomotor symptoms varies among individuals, women on average reports having 4 to 5 hot flashes per day with some women experiencing as many as 20 hot flashes per day.[6] Vasomotor symptoms persist for an average 7.4 years with moderate-to-severe vasomotor symptoms extending in 42% of women age 60 to 65 years.[6,7] Research has shown that 25% of women experience severe vasomotor symptoms, 30% experience severe psychological symptoms (eg, depression and anxiety), 88% of women experience sexual dysfunction, and 50% report moderate-to-severe symptoms of sleep disturbance, joint pain, or headache.[8,9] Genitourinary syndrome of menopause (GSM) is a collection of symptoms associated with decreased estrogen and other sex steroids that create changes to the labia, clitoris, vestibule/introitus, vagina, urethra, and bladder.[10] Resulting symptoms include genital dryness, burning, and irritation; sexual symptoms of lubrication difficulty, discomfort or pain, and impaired sexual function; and urinary urgency, dysuria, and recurrent urinary tract infections. Vaginal symptoms occur in 27% to 85% of women.[11] While majority of women report GSM negatively affect their sexual function and overall quality of life, many women are not aware these symptoms are related to menopause and therefore these symptoms remain untreated.[11]

CLINICAL PRESENTATION Hormone Therapy in Women

Signs

- Perimenopause: Abnormal uterine bleeding (AUB) as a result of anovulatory cycles (other gynecologic disorders should be excluded).
- Menopause: permanent cessation of menses

Symptoms

- Vasomotor symptoms (hot flashes and night sweats)

- Sleep disturbances
- Mood changes
- New-onset depression
- Problems with concentration and memory
- Arthralgia
- Genitourinary Syndrome of Menopause (GSM): vaginal dryness, burning and irritation of reproductive organs and structures, sexual dysfunction, dysuria, dyspareunia, urinary urgency, recurrent urinary tract infections

Laboratory Tests

- Perimenopause: FSH on day 2 or 3 of the menstrual cycle greater than 10 to 12 IU/L (mIU/mL)
- Menopause: FSH greater than 40 IU/L (mIU/mL) (high FSH is not required to make the diagnosis)

Other Relevant Diagnostic Tests

- Thyroid function tests
- Iron stores
- Serum prolactin
- Lipid profile
- Serum hCG

Women who experience severe symptoms, either from early in the menopause transition or from their FMP, are likely to continue to experience severe symptoms for several years.[8] The perimenopause is associated with a higher vulnerability to depression with the risk increasing from early-to-late perimenopause and decreasing during postmenopause.[12] Women who experience a major depressive episode during perimenopause often represents a reoccurrence of their major depressive disorder.[12]

In addition to the symptoms of menopause, loss of estrogen production results in significant metabolic changes including effects on body composition, cognition, lipids, vascular function, and bone metabolism. The menopause transition is associated with a significant increase in central abdominal fat

leading to an average weight gain during the menopausal transition of 5 lb; however, this is likely to be related to aging and lifestyle rather than menopause.[1] Skin changes including decreased thickness and elasticity, loss of collagen, and wrinkling, and hair changes including alopecia and hirsutism are also associated with menopause. Poor concentration and memory are common during the menopause transition and early postmenopause.[1] Memory performance and processing speed slightly decline during the menopausal transition, but reach premenopausal levels after menopause. It is important to note that these cognitive symptoms can be affected by other symptoms of menopause including sleep disturbances, hot flashes, depressed mood, fatigue, and midlife stressors.

Abnormal uterine bleeding (AUB) is characterized by a deviation of regularity, frequency, duration, or volume of menstrual fluid typical of a woman's menses. In general, AUB may occur during the perimenopausal years because of anovulatory cycles; however, unusual uterine bleeding always merits investigation when it cannot be simply explained by menopausal cyclical irregularity. Hormonal treatment options for AUB include insertion of an intrauterine progestin-only device, systemic progestogen therapy, or the combined oral contraceptive pill unless contraindicated.[1]

TREATMENT

Desired Outcomes

Menopause is a natural life event, not a disease. The primary goals of therapy for menopause are to relieve symptoms and improve quality of life while minimizing adverse effects. This can be best achieved by individualizing treatment based on medical, social, and family history as well as her symptoms and quality of life goals.

General Approach to Treatment

In women with mild vasomotor symptoms, nonpharmacologic therapy can be considered. In women with moderate-to-severe hot flashes and vulvovaginal symptoms, menopausal hormone therapy (MHT) is the treatment of choice unless contraindicated (**Table 98-1**). Topical vaginal products should be reserved for women exclusively experiencing vulvovaginal atrophy. Treatment of mild vulvovaginal symptoms should include nonhormonal lubricants and moisturizers. However, for some women these treatments are not effective.

Figure 98-1 outlines an algorithm for the general management of menopausal women.

TABLE 98-1 FDA-Labeled Indications and Contraindications for Menopausal Hormone Therapy with Estrogens and Progestins

Indications	
For systemic use	Treatment of moderate-to-severe vasomotor symptoms (ie, moderate-to-severe hot flashes)
For intravaginal use (low systemic exposure)	Treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy (ie, moderate-to-severe vaginal dryness, dyspareunia, and atrophic vaginitis)
Contraindications	
Absolute contraindications	Undiagnosed abnormal genital bleeding Known, suspected, or history of cancer of the breast Known or suspected estrogen- or progesterone-dependent neoplasia Active deep vein thrombosis, pulmonary embolism, or a history of these conditions Active or recent (eg, within the past year) arterial thromboembolic disease (eg, stroke, myocardial infarction) Liver dysfunction or disease
Relative contraindications	Elevated blood pressure Hypertriglyceridemia Impaired liver function and past history of cholestatic jaundice Hypothyroidism Fluid retention Severe hypocalcemia Ovarian cancer Exacerbation of endometriosis Exacerbation of asthma, diabetes mellitus, migraine, systemic lupus erythematosus, epilepsy, porphyria, and hepatic hemangioma

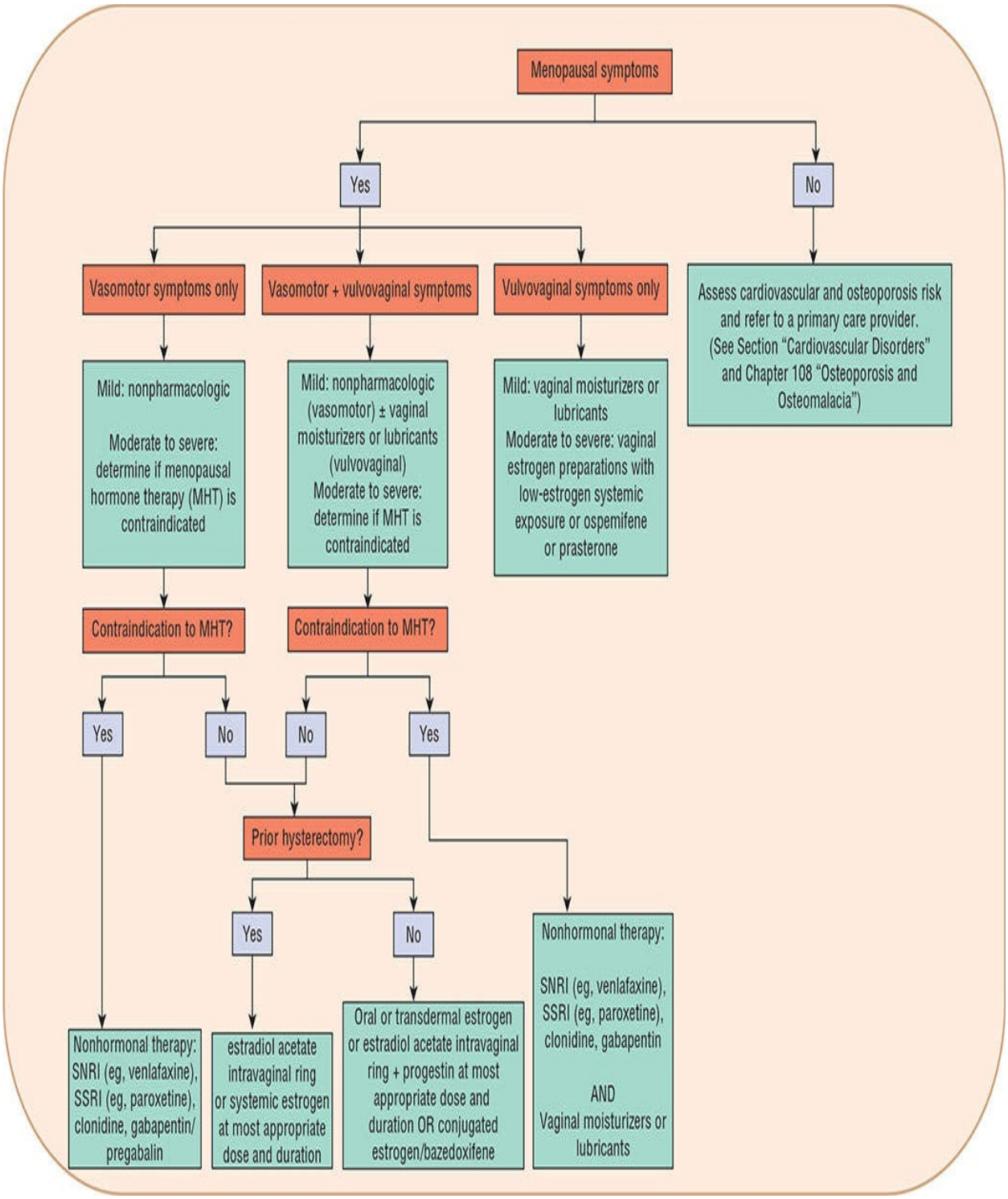
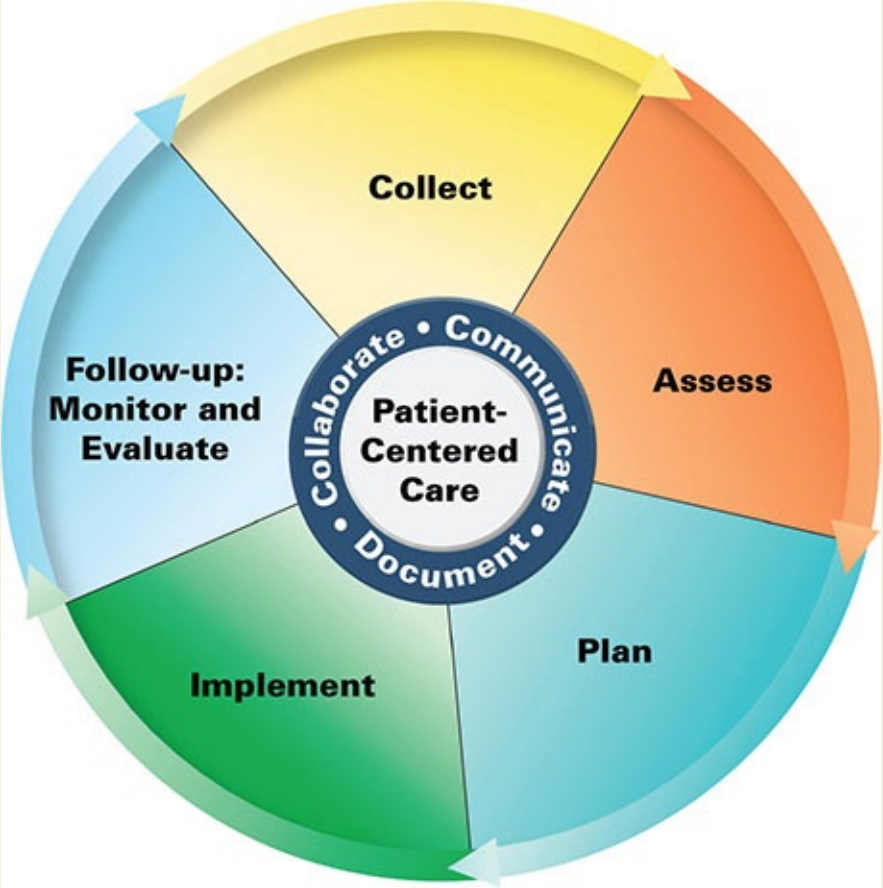


FIGURE 98-1 Algorithm for pharmacologic management of menopausal symptoms.

SNRI: serotonin norepinephrine reuptake inhibitor, SSRI: selective serotonin reuptake inhibitor.

1 The decision to use MHT and the type of formulation used must be individualized based on several factors, including personal preference, age, menopause onset, the severity of menopausal symptoms and the risks of cardiovascular disease, breast cancer, osteoporotic fracture, and venous thromboembolic events (VTE). Breast cancer risk is increased with concomitant progestogen use in menopausal women with an intact uterus,[13] and VTE may also increase with higher estrogen doses and oral administration.[14]

The duration of therapy also needs to be individualized according to severity of symptoms, health status, and concerns regarding risks. Approved indications of MHT include treatment of moderate-to-severe vasomotor symptoms, moderate-to-severe vulvovaginal atrophy, and prevention of postmenopausal osteoporosis. For treatment of vasomotor symptoms, systemic MHT is the most effective pharmacologic intervention (Fig. 98-1). For symptoms of vulvar and vaginal atrophy, such as vaginal dryness, intravaginal products should be considered.[14]



Patient Care Process for Hormone Therapy in Women

Collect

- Patient characteristics: age
- Personal and family medical history: cancer, cardiovascular disease, thromboembolic risks, osteoporosis, date of last menses, menstrual bleeding pattern, diabetes (Table 98-1)
- Gynecological surgical history
- Physical exam: breast and pelvic exam, Papanicolaou (PAP) cervical cytologic examination, mammography, liver function, assessment for gallbladder disease
- Bone mineral density results
- Current medication including prescription, nonprescriptions, and dietary supplements
- Social history: Tobacco use, ethanol use, caffeine use
- Symptoms: hot flashes, night sweats, irregular periods, sleep disturbances, mood changes, thinning of hair, difficulty with concentration or memory, arthralgia, and genitourinary syndrome of menopause (eg, vaginal dryness, burning and irritation of reproductive organs and structures, sexual dysfunction, dysuria, dyspareunia, urinary urgency, recurrent urinary tract infections) (See CLINICAL PRESENTATION box)
- Signs: Abnormal uterine bleeding, decreased vaginal moisture, vaginal tissue fragility, thinning hair, skin changes (See CLINICAL PRESENTATION box)
- Labs/Tests: Thyroid function tests, iron stores, serum prolactin, lipid profile, follicle stimulating hormone (FSH) levels
- Patient's expectations, preferences, and goals for therapy (eg, reduce frequency / predictability of menses, symptom relief)

Assess

- Evaluate woman's menstrual cycle history or menstrual calendar
- Stage of menopausal transition; perimenopause, menopause, postmenopause
- Does patient still have a uterus intact
- Rule out causes other than the menopausal transition for abnormal uterine

bleeding and amenorrhea (eg, pregnancy, hyperprolactinemia, and hyperthyroidism) (See CLINICAL PRESENTATION box)

- Emotional status (eg, anxiety, depression) (See CLINICAL PRESENTATION box)
- Define patient's risk for osteoporosis, coronary heart disease, thromboembolic risks, cancer
- Risks and benefits of various therapy options (Table 98-3)
- Insurance coverage and patient's ability to afford treatment options

Plan*

- Nonpharmacologic lifestyle interventions including smoking cessation, dress in layers, weight loss, exercise, limit intake of spicy foods, caffeine, and hot beverages
- Develop a drug therapy regimen (including specific medication, dose, route, frequency, duration) to provide symptom relief, maximize adherence, provide endometrial protection and minimize long-term risk (Table 98-3 through 98-7, Table 98-9, and Figure 98-1)
- Monitoring parameters for efficacy of therapy: reduction in vasomotor symptoms, improvement in genitourinary syndrome of menopause (GSM) signs and symptoms, mood stability, improved sleep (Table 98-8)
- Monitoring parameters for adverse effects: breast tenderness, bloating, premenstrual-like symptoms, mood changes, withdrawal bleeding or abnormal bleeding patterns (Table 98-8)
- Self-monitoring for vasomotor symptoms, GSM signs and symptoms, adverse effects, signs and symptoms of thrombosis

Implement*

- Provide patient education regarding all elements of treatment plan
- Educate patient regarding risks and benefits of treatment options, lifestyle modifications, drug-specific information
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Resolution of bothersome symptoms
- Presence of adverse effects
- Patient adherence to treatment
- Reevaluate need and continuation for therapy (Table 98-8)

**Collaborate with patient, caregivers, and other healthcare professionals.*

Nonpharmacologic Therapy

Mild menopausal symptoms may be managed effectively with lifestyle modifications, including wearing layered clothing that can be removed or added as necessary, lowering room temperature, decreasing intake of hot spicy foods, caffeine, and hot beverages, exercise, and other good general health practices. Some dietary supplements have been promoted as alternatives to MHT with conflicting results.[15]

Pharmacologic Therapy

Pharmacologic therapy is the mainstay of management of menopausal symptoms and includes both hormonal (estrogen with or without progestogen) and nonhormonal medications.

2 Drug Treatment of First Choice

Menopausal hormone therapy is the most effective treatment option for alleviating moderate-to-severe vasomotor symptoms. In women with an intact uterus, systemic MHT consists of an estrogen plus a progestogen or a tissue-selective estrogen complex (estrogen/bazedoxifene) to prevent endometrial hyperplasia. In women who have undergone hysterectomy, estrogen therapy is given unopposed by a progestogen (ie, as monotherapy). Mild vulvovaginal symptoms may be adequately managed with nonhormonal lubricants and moisturizers.[1] However, vaginal estrogen therapy (cream, tablet, and ring) may be needed for moderate-to-severe vulvovaginal symptoms. Progestogen therapy for endometrial protection is not recommended with the use of low-dose vaginal estrogens (ie, those with minimal systemic exposure) with the exception of one vaginal ring (Femring®) known to deliver adequate systemic estrogen concentration to treat vasomotor symptoms.[14]

A number of national and international guidelines and consensus statements

on the management of menopause are available.[14–23] The US Preventive Services Task Force also provides a recommendation statement on the use of MHT for the prevention of chronic medical conditions in postmenopausal women.[24]

Therapy for Perimenopausal Women

Despite a decline in fertility with age, sexually active women may become pregnant during the perimenopausal years. Furthermore, perimenopausal women can experience hot flashes despite having menstrual cycles. Combined hormonal contraceptives (containing low-dose estrogen and progestogen) provide contraception and vasomotor symptom relief. Perimenopausal women should not use estrogen-containing contraceptives if they smoke or have a history of estrogen-dependent cancer, cardiovascular or cerebrovascular disease, hypertension, diabetes with vascular disease, or risk factors for thromboembolism, liver disease, or migraine headaches. For perimenopausal women with AUB due to anovulatory cycles, a progestin-only intrauterine device may be a useful option. Combined hormonal contraceptives provide the additional benefit of reducing the risk of ovarian and endometrial cancer.

Menopausal Hormone Therapy for Vasomotor and Genitourinary Syndrome Symptoms

Menopausal hormone therapy remains the most effective treatment for moderate and severe vasomotor symptoms, impaired sleep quality, and vulvovaginal symptoms of menopause.[1,14,16–18]

Vasomotor Symptoms Fewer than 25% of women experience a menopausal transition without symptoms, whereas more than 25% suffer severe menopausal symptoms, most commonly hot flashes and night sweats. The average duration of vasomotor symptoms is 7.4 years with some women experiencing symptoms for more than 10 years.[6] Women with mild vasomotor symptoms can experience relief by lifestyle modification, and at least 25% of women in clinical trials reported significant improvement of vasomotor symptoms when taking placebo. The most effective treatment for vasomotor symptoms is MHT.[1,14,16–18] Benefits and risks of MHT should be weighed individually and assessed on an annual basis. Clinicians should select the most appropriate dose, duration, and routes of administration based on patient symptoms and medical history to provide the most benefits.

Genitourinary Syndrome of Menopause The lower genitourinary tract contains a high concentration of estrogen receptors and is particularly vulnerable to estrogen deficiency, resulting in symptoms which progressively worsen over time. Up to 85% of postmenopausal women report symptoms of vulvovaginal atrophy,[11] which results in vaginal dryness, burning, irritation, discomfort, and dyspareunia. Lower urinary tract symptoms include urethritis, recurrent urinary tract infection, urinary urgency, and frequency.

Most women with moderate-to-severe vulvovaginal symptoms require local or systemic estrogen therapy for symptom relief. Local (vaginal) estrogen delivery is preferred when vaginal symptoms are the only menopausal symptom complaint, as it minimizes systemic absorption and is more effective than oral estrogen therapy with 80% to 90% symptom relief compared to 75% with oral estrogen.[14,20] Vaginal estrogen has also been shown to improve atrophic symptoms and vaginal mucosal appearance, decrease vaginal pH, improve vaginal and/or urethral cytology, and reduce the risk of lower urinary tract symptoms and recurrent urinary tract infections possibly by modifying the vaginal flora.[14,20] Moderate-to-severe vulvovaginal symptoms can be treated with a vaginal estrogen cream, tablet, or ring; or with the selective estrogen receptor modulator (SERM) ospemifene given 60 mg orally per day.[25] Ospemifene has a nearly full estrogen agonist effect in the vaginal epithelium to improve dyspareunia, sexual function, and overall satisfaction in postmenopausal women with moderate-to-severe vaginal dryness and has been well tolerated.[25] Women with moderate-to-severe dyspareunia can also consider prescription intravaginal dehydroepiandrosterone (DHEA) prasterone.

Dose-related adverse effects of vaginal estrogen include vulvovaginal candidiasis, vaginal bleeding, breast pain, and nausea.[20] Concomitant progestogen therapy is unnecessary when low-dose vaginal estrogen is used with the exception of one vaginal ring (Femring®) which is known to deliver a systemic concentration of estrogen.[26] Therapeutic response to vaginal estrogen therapy is typically attained after 2 weeks of daily estrogen use. For maintenance therapy, the frequency of administration is generally decreased to two to three times weekly.

Assessing Benefits and Risks of Systemic Menopausal Hormone Therapy

The Women's Health Initiative (WHI) was a randomized, double-blind, placebo-controlled trial launched in 1991 to evaluate the effects of MHT on heart disease,

osteoporosis, and cancer. The WHI trial had two arms: the estrogen-plus-progestin arm involving women with an intact uterus and the estrogen-alone arm involving women with a history of hysterectomy.[13] The combined estrogen and progestin arm included 16,608 women aged 50 to 79 years (mean age 63 years), and the estrogen-only arm enrolled 10,739 women aged 50 to 79 years (mean age 64 years). The primary outcome was incidence of coronary heart disease (CHD) (nonfatal myocardial infarction or CHD death), and the primary safety outcome was invasive breast cancer. A global index was used to summarize the balance of risks and benefits, which included the two primary outcomes plus stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, and death due to other causes. The estrogen-plus-progestin arm was terminated prematurely after only 5.2 years (the planned duration was 8.5 years) because the global index statistic supported risks exceeding benefits on the major clinical outcomes. The estrogen-only arm also was terminated early (after 6.8 years) because of excess risk of stroke. Results of the WHI trial are shown in **Table 98-2**.[13] Upon discontinuation of the trial, participants were asked to discontinue study medication and invited to participate in a follow-up phase of the study that has resulted in multiple ancillary analyses.[13,26–29]

TABLE 98-2 Principal Results of the Women's Health Initiative Hormone Therapy Trial

	Estrogen + Progestogen Arm (Median duration 5.6 years)			Estrogen-only Arm (Median duration 7.2 years)		
	MHT (n = 8,506)	Placebo (n = 8,102)		MHT (n = 5,310)	Placebo (n = 5,429)	
Outcome	No. Patients (annualized %)	No. Patients (annualized %)	Hazard Ratio (Nominal 95% CI)	No. Patients (annualized %)	No. Patients (annualized %)	Hazard Ratio (Nominal 95% CI)
CHD	196 (0.41)	159 (0.35)	1.18 (0.95-1.45)	204 (0.55)	222 (0.58)	0.94 (0.78-1.14)
Stroke	159 (0.33)	109 (0.24)	1.37 (1.07-1.76)	169 (0.45)	130 (0.34)	1.35 (1.07-1.70)
Pulmonary Embolism	87 (0.18)	41 (0.09)	1.98 (1.36-2.87)	52 (0.14)	39 (0.10)	1.35 (0.89-2.05)
Invasive Breast Cancer	206 (0.43)	155 (0.35)	1.24 (1.01-1.53)	104 (0.28)	135 (0.35)	0.79 (0.61-1.02)
Colorectal Cancer	50 (0.10)	75 (0.17)	0.62 (0.43-0.89)	65 (0.17)	58 (0.15)	1.15 (0.81-1.64)
Endometrial Cancer	27 (0.06)	30 (0.07)	0.83 (0.49-1.40)	NA	NA	NA
Hip Fracture	53 (0.11)	75 (0.17)	0.67 (0.47-0.95)	48 (0.13)	74 (0.19)	0.67 (0.46-0.96)
Death	250 (0.52)	238 (0.53)	0.97 (0.81-1.16)	301 (0.80)	299 (0.77)	1.03 (0.88-1.21)
Global Index	876 (1.89)	736 (1.68)	1.12 (1.02-1.24)	753 (2.08)	755 (2.04)	1.03 (0.93-1.13)

CI, confidence interval; MHT, menopausal hormone therapy.

Data from Reference 13.

Use of MHT has greatly evolved to recognize the need to individualize therapy for women based on patient-specific factors (eg, age, risk factors, and goals of therapy). A summary of various clinical considerations described in the 2017 Hormone Therapy Position Statement of the North American Menopause Society is provided in **Table 98-3**.[1,14,15,19,20]

TABLE 98-3 Summary of North American Menopause Society Position Statement on Menopausal Hormone Therapy

Symptom/Condition	Summary Statement(s)
Vasomotor symptoms	Estrogen therapy (± progestogen) is the most effective therapy, including consequences of vasomotor symptoms such as sleep quality, irritability, difficulty concentrating, and quality of life
Vulvovaginal symptoms	Estrogen therapy is the most effective treatment for moderate-to-severe vulvovaginal symptoms. Local therapy is recommended for sole vaginal symptoms; progestogen generally not indicated
Sexual function	Low-dose local estrogen therapy may improve lubrication, blood flow and vaginal sensation; however, MHT is not recommended as treatment for other problems of sexual function (eg, libido, orgasmic response)
Osteoporosis	Standard-dose MHT reduces postmenopausal osteoporotic fractures (hip, vertebral, and nonvertebral) and many systemic MHT products are approved for prevention of osteoporosis. MHT is not indicated for treatment. Benefits of MHT dissipate when discontinued
Coronary heart disease	Observational and randomized control data are conflicting. Estrogen only therapy may reduce CHD risk when initiated in newly menopausal women (age 50-59 years). Estrogen + progestogen therapy initiated between ages 50 and 59 years or within 10 years of menopause does not appear to increase CHD risk. Women initiating therapy after 10 years since menopause have an increased risk of CHD. MHT is not recommended any time for coronary protection
Stroke	Increased risk of ischemic stroke (not hemorrhagic) exists with estrogen only and estrogen + progestogen use.
Venous thromboembolism (VTE)	Increased risk of VTE with oral MHT across all ages. Risk increases with personal risk factors including obesity, previous history of VTE, presence of Factor V Leiden mutation. The type of progestogen may impact risk. Transdermal formulations appear to have lower VTE risk than oral formulations

MHT: menopausal hormone therapy, CHD: coronary heart disease, VTE: venous thromboembolism.

Data from References 1, 14, 15, 19, and 20.

Furthermore, several national and international organizations have published guidelines or position statements to outline points of consensus regarding the safe and effective use of MHT.[14–23]

Overall, consensus recommendations regarding the use of MHT include:

- Menopausal hormone therapy is the most effective treatment for vasomotor symptoms. Healthy, recently menopausal women (before age 60 years or within 10 years of menopause) have the most favorable benefit-to-risk profile.
- Estrogen-only therapy may decrease heart disease and all-cause mortality

in 50- to 59-year-old women with a history of hysterectomy. In this age group, combined estrogen and progestogen therapy shows similar trends for mortality, but no significant difference in CHD.

- Estrogen alone is appropriate for women after hysterectomy; additional progestogen is required when a uterus is present.
- Use of MHT should be individualized based on the severity of menopausal symptoms and personal risk factors (eg, age, time since menopause, history of VTE, stroke, ischemic heart disease, osteoporosis risks, and breast cancer).
- Risk of VTE and stroke increases with oral MHT containing estrogen, but the absolute risk is low in women below 60 years of age. Based on observational studies, transdermal MHT and low-dose oral estrogen therapy appear to have a lower risk of VTE and stroke compared to standard-dose oral estrogen regimens.
- Menopausal hormone therapy is contraindicated in women with a personal history of breast cancer. The risk of MHT-related breast cancer appears to be associated with the addition of progestogen to estrogen and increases after 5 or more years of continuous combined use. However, use of estrogen alone appears to decrease rather than increase breast cancer risk.
- Select the most appropriate dose, duration, and routes of administration of hormone therapy to provide the most benefits and adequately manage menopausal symptoms. Duration of therapy should not be discontinued solely based on the patient's age.

3 ***Cardiovascular Disease*** Cardiovascular disease—including coronary artery disease, stroke, and peripheral vascular disease—is the leading cause of death among women, but MHT should not be used for reducing the risk of cardiovascular disease. Menopause is associated with the development of a more adverse lipid profile, and presence of vasomotor symptoms have been associated with an increased risk of cardiovascular disease.[30]

In the decade prior to the publication of the WHI results in 2002, an expectation of coronary benefit had been a major reason for use of postmenopausal hormones because observational studies indicated that women who use MHT have a 35% to 50% lower risk of CHD than nonusers. In addition, previous studies had shown that estrogen exerts protective effects on the cardiovascular system, including lipid-lowering, antioxidant, and vasodilating effects.[31] However, in the 2000s, published results of several randomized clinical

trials provided no evidence of cardiovascular disease protection and even some evidence of harm with MHT.[13,28]

The primary findings of the estrogen plus progestogen arm of the WHI trial showed an overall increase in the risk of CHD (HR 1.18, 95% CI 0.95-1.45) among healthy postmenopausal women receiving combined estrogen–progestogen MHT compared with those receiving placebo.[13] The primary findings of the estrogen-only arm of the WHI trial show no effect (either increase or decrease) on the risk of CHD in women taking estrogen alone.[13] In the extended postintervention follow-up of 13 years revealed that women who initiated MHT 10 or more years after the time of menopause tended to have increased CHD risk compared with women who initiated therapy within 10 years of menopause.[13] Estrogen plus progestogen was associated with a nonsignificantly elevated CHD events in women aged 50 to 59 years, whereas estrogen alone was associated with reduced risk of CHD in women who aged younger than 60 and/or who are within 10 years of menopause onset.[13,14] Older women (age 70-79) who are more than 20 years past menopause onset experience highest risk of CHD that is statistically significant compared with placebo group when estrogen plus progestogen therapy is initiated.[13,14] Most women who commence estrogen or estrogen plus progestogen therapy do so within the first few years of becoming menopausal.

A randomized controlled study of 1,006 recently menopausal women revealed that 10-year MHT was associated with a significantly reduced risk of cardiovascular disease.[32] In addition, studies of recently menopausal women showed that the presence and severity of hot flashes are associated with vascular endothelial dysfunction and vascular inflammation (markers of increased risk for CHD); MHT improved both of these parameters.[33]

In an attempt to resolve some of the controversy, the Kronos Early Estrogen Prevention Study (KEEPS) randomized 727 recently menopausal women (mean age 52 years and less than 3 years since FMP) to cyclic progestogen and either oral estrogen (conjugated estrogen 0.45 mg/day), transdermal estrogen (estradiol 50 mcg/day), or placebo to examine the rate of atherosclerosis.[34] During 4 years of treatment, there was no difference among the study arms on atherosclerotic progression as evidenced by carotid intima-media thickness and coronary artery calcium. However, in the Early versus Late Intervention Trial with Estradiol (ELITE) trial, use of hormone therapy (oral 17β-estradiol 1 mg/day plus progesterone vaginal gel administered sequentially in women with intact uterus) showed reduced carotid intima-media thickness progression in early postmenopausal women who initiated hormone therapy within 6 years of

menopause onset, but similar cardioprotective effect was not observed among postmenopausal women who initiated hormone therapy 10 years after menopause onset.[35] While results from the ELITE trial provides preliminary evidence for the "timing hypothesis," that the benefits of hormone therapy are dependent on the timing of initiation and hormone therapy may be cardioprotective if started around the time of menopause and therapy may be harmful when initiated in late postmenopausal women,[36] currently available clinical data remain inconsistent and additional research is still needed.

In light of the available data, current guidelines caution against initiating or continuing menopausal hormone therapy solely for the prevention of cardiovascular disease.[14,24] Adherence to a healthful lifestyle (smoking cessation, regular exercise, healthy diet, and body mass index less than 25 kg/m^2) may prevent the onset of cardiovascular disease in postmenopausal women.[15] It should be noted that use of vaginal estrogen is not associated with an increased risk of CHD.[26]

In the estrogen plus progestogen arm of the WHI study, the increased risk for stroke (HR 1.37, 95% CI 1.07-1.76) and pulmonary embolism (HR 1.98, 95% CI 1.36-2.87) was evident, even during the postintervention phase.[13] Increased risk was observed only for ischemic stroke and not for hemorrhagic stroke. In the estrogen-alone arm of the study, a similar increased risk (HR 1.35, 95% CI 1.07-1.70) for stroke was observed.[13] After the cessation of treatment, the risks for stroke remain higher compared with placebo groups at 13-year follow-up.[13] It should be noted that use of vaginal estrogen is not associated with an increased risk of stroke.[26]

It is worth noting that in the cumulative 18-year follow-up from WHI trials, hormone therapy combined estrogen–progestogen or estrogen alone have not been shown to increase all-cause mortality including death from CVD, CHD, and stroke.[27]

Venous Thromboembolism In general, VTE, including thrombosis of the deep veins of the legs and embolism to the pulmonary arteries, is uncommon in the general population. Conversely women taking oral estrogen therapy have a twofold increased risk for thromboembolic events, with the highest risk occurring in the first 1 to 2 years of use.[13,14,28] However, women with certain risk factors for VTE including those with a Factor V Leiden mutation, obesity, and history of previous thromboembolic events are at increased risk with MHT.[14] Lower doses of estrogen are associated with a decreased risk for thromboembolism as compared with higher doses. Oral administration of

estrogen increases the risk of VTE compared to the transdermal route.[14] Currently, there is no indication for thrombophilia screening before initiating MHT. However, MHT should be avoided in women at high risk for thromboembolic events.

The Endocrine Society clinical practice guideline recommends evaluating a woman's 10-year CVD risk before initiation of MHT using the ACC/AHA Cardiovascular Risk Calculator.[16,37] Regardless of years since menopause onset, the guideline recommends avoid hormone therapy for symptomatic women at high CV risk (>10%) and use of nonhormone therapy is advocated. For women at moderate risk of CVD (5%-10%), use of transdermal estrogen is preferred over oral formulations with oral micronized progesterone in women with an intact uterus.[16] It should be noted that use of vaginal estrogen is not associated with an increased risk of pulmonary embolism or VTE.[26]

4 ***Breast Cancer***The risk of breast cancer associated with MHT appears to be associated with the addition of progestogen therapy to estrogen, as use of estrogen alone does not increase the risk of breast cancer. The WHI trial found that combined estrogen plus progestogen oral therapy has an increased risk of invasive breast cancer (HR 1.24, 95% CI: 1.01-1.53) and a trend toward increasing risk with increasing duration of therapy.[13,14] After discontinuation of hormone therapy, study results demonstrated a year-to-year reduction in breast cancer risk but elevated risk persists at 13 years of extended follow-up (HR 1.32, 95% CI: 1.08-1.61).[13] On the contrary, the estrogen-only arm of the WHI trial found a nonsignificant decreased risk for breast cancer (HR 0.79, 95% CI: 0.61-1.02) during the intervention phase, which persisted after discontinuation of treatment.[13] Results from the 18 years of cumulative follow-up noted death from breast cancer was significantly lowered among postmenopausal women who took estrogen only therapy compared to placebo (HR 0.55, 95% CI: 0.33-0.92).[27] No significant difference in age or time since menopause was observed with breast cancer risks among postmenopausal women on hormone treatments.[13] Breast cancer risk appears to similar between low-dose (<0.625 mg) and conventional dose (0.625 mg) of conjugated equine estrogen but a lower risk of breast cancer is noted with the transdermal formulation.[29]

Addition of progestogens to estrogen may increase breast cancer risk beyond that observed with estrogen alone.[13,14] In the estrogen plus progestogen arm of the WHI, the increased breast cancer risk did not appear until after 3 years of study participation.[14] The breast cancers diagnosed in women in the MHT group had similar histology and grade but were more likely to be in an advanced stage

compared with women in the placebo group.[28] Despite increased incidence of breast cancer risk with combined estrogen plus progestogen therapy, no significant increased risk of death from breast cancer was noted during the 18 years of cumulative follow-up (HR 1.44, 95% CI: 0.97-2.15).[27]

For women in the United States, the lifetime risk of developing breast cancer is approximately one in eight, and the greatest incidence occurs in women older than 60 years.[38] The Endocrine Society clinical practice guideline recommends evaluating a woman's breast cancer risk before initiation of MHT using either the 5-year risk assessment tool from National Cancer Institute Breast Cancer Risk Assessment Tool (http://www.cancer.gov/bcrisktool/) or the 10-year International Breast Intervention Study calculator (http://ibis.ikonopedia.com).[16] In general, the guideline cautions against using hormone therapy for women in the intermediate-risk category, and advises against using systemic hormone therapy for women in the high-risk category, particularly women with personal history of breast cancer.[14,16] While use of vaginal estrogen with minimal systemic absorption has not been demonstrated to increase risk of breast cancer,[26] use of low-dose local vaginal estrogen may be considered only after unsuccessful trials of nonhormone therapies in conjunction with consultation with an oncologist.[14]

Endometrial Cancer It is well documented that systemic estrogen alone given to women with an intact uterus significantly increases uterine cancer risk.[14,28] The excess risk increases with dose and duration of estrogen and persists for many years after estrogen replacement is discontinued.[14,16] While estrogen alone is appropriate for women after hysterectomy; use of systemic estrogen in women with an intact uterus must always be accompanied by adequate dose and duration of progestogen for endometrial protection. Although results from the WHI trial's postintervention and follow-up phase demonstrated a reduced risk of endometrial cancer with combined oral MHT,[13] for symptomatic women with advanced cancer or higher risk for endometrial cancer, use of nonhormone therapies is still recommended.[14] Women preferring not to take progestogen may consider tissue-selective estrogen complex (estrogen/bazedoxifene) as an alternative to reduce risk of endometrial hyperplasia.

Ovarian Cancer Lifetime risk of ovarian cancer is low (1.7%) and results from the WHI trial suggested that orally administered combined MHT does not increase the risk of ovarian cancer (HR 1.41, 95% CI: 0.75-2.66) with the risk remain nonsignificant after 13 years of cumulative follow-up.[14] However,

limited observation data have reported inconsistent results.[14] An analysis of 52 epidemiological studies suggests that ovarian cancer risk is increased in current users of MHT, even with less than 5 years of use. The increased risk appears to decrease but not completely disappear a decade after discontinuation of MHT.[39] In a recent meta-analysis evaluating continuous versus sequential hormone therapies suggests hormone therapies are associated with an increased risk of ovarian cancer regardless of the types or regimen.[40] Further research is still needed to confirm these findings.

Lung Cancer The WHI trial found that combined oral estrogen–progestogen therapy did not increase lung cancer incidence,[13] but significantly increased deaths from lung cancer have been observed in the post hoc analysis of the WHI intervention, mainly from nonsmall cell lung cancers among past and current smokers over 60 years of age.[14] The estrogen-only arm of the WHI trial found no increased risk for lung cancer[13]; however, it should be noted that the WHI was not designed to assess lung cancer.

Osteoporosis Postmenopausal osteoporosis is a serious age-related condition that affects millions of women throughout the world. Menopause is accompanied by accelerated bone loss, and the central role of estrogen deficiency in postmenopausal osteoporosis is well established. The WHI was the first randomized trial to demonstrate that MHT reduces the risk of fractures at the hip, spine, and wrist.[14] Estrogen therapy reduces bone turnover and increases bone density in postmenopausal women of all ages. The protective effect persists as long as the treatment is maintained; however, bone protection is quickly lost with cessation of therapy. Although there is no evidence of rebound fracture.[14] The standard bone-sparing daily estrogen dose is equivalent to 0.625-mg conjugated equine estrogen (CEE). However, lower doses of estrogen have been shown to increase bone mass to the same extent as standard-dose estrogen therapy.[41,42] Whether lower doses of estrogen are safer (eg, lower incidence of VTE and breast cancer) remains to be proven.

In women who experience vasomotor symptoms and are younger than 60 years of age or within 10 years of menopause onset, systemic estrogen therapy may be indicated for the prevention of bone loss and osteoporotic fractures.[14] General protective health measures, such as regular weight-bearing exercise and avoidance of detrimental lifestyle habits such as smoking and alcohol abuse, are appropriate for all women. Some women require calcium supplementation to their usual dietary intake and adequate vitamin D intake and/or supplementation

are also needed. Appropriate risk assessment and evaluation is needed to determine appropriate treatment strategies in menopausal women. See Chapter 108, “Osteoporosis and Osteomalacia,” for a full discussion of osteoporosis prevention and treatment.

Mood, Cognition, and Dementia Menopausal hormone therapy appears to improve depressive symptoms in symptomatic menopausal women, most likely by relieving hot flash and improving sleep. Women with vasomotor symptoms receiving MHT have improved mental health and fewer depressive symptoms compared with women receiving placebo. However, MHT may worsen quality of life in women without flashes.[43]

More than 33% of women 65 years and older will develop dementia during their lifetime.[44] Several observational studies have suggested that estrogen therapy may be protective against Alzheimer’s disease. The WHI Memory Study (WHIMS, an ancillary study of the WHI trial) evaluated the effect of MHT on dementia and cognition in 4,532 women 65 to 79 years old.[45] The study found that postmenopausal women 65 years and older taking estrogen plus progestogen therapy had twice the rate of dementia, including Alzheimer disease, than women taking placebo (HR 2.05, 95% CI: 1.21-3.48).[45] In addition, estrogen plus progestogen therapy in these women did not prevent mild cognitive impairment, a cognitive and functional state between normal aging and dementia that frequently progresses to dementia.[45] The estrogen-alone arm of the WHI trial showed similar findings.[46,47]

In contrast, the Women’s Health Initiative Memory Study of Younger Women (WHIMSY) found that neither estrogen plus progestogen or estrogen-alone therapy confers any risk or benefit to cognitive function when taken by postmenopausal women aged 50 to 55 years old.[48] In another study, the ancillary Cognitive and Affective Study (KEEPS-Cog) of the Kronos Early Estrogen Prevention Cognitive Study (KEEPS) evaluated the effects of up to four years of MHT on cognition and mood in recently menopausal women (mean age 52.6 years and 1.4 years past FMP) with low cardiovascular risk.[49] Specifically, 693 women participated with 220 women randomized to receive 0.45 mg/day oral CEE plus 200 mg/day micronized progesterone for the first 12 days of each month, 211 women randomized to receive 50 mcg/day transdermal estradiol plus 200 mg/day micronized progesterone for the first 12 days of each month, and 262 women randomized to receive placebo pills and patches. After a mean length of follow-up of 2.85 years for cognition outcomes, no treatment-related benefits were observed. After a mean length of follow-up for 2.76 years

regarding mood outcomes, model estimates indicated that women treated with oral CEE showed improvements in depression and anxiety symptoms over the 48 months of treatment, compared to women on placebo.[49]

Diabetes In healthy postmenopausal women, hormone therapy appears to have a beneficial effect on fasting glucose levels in women with elevated fasting insulin concentrations.[50] Also, in women with coronary artery disease, hormone therapy reduces the incidence of diabetes by 35%.[51] Women who received estrogen plus progestogen in the WHI trial had a statistically significant 21% reduction (HR, 0.79; 95% CI, 0.67-0.93) in the incidence of type 2 diabetes requiring treatment.[52] These findings provide important insights into the metabolic effects of hormone therapy but are insufficient to recommend the long-term use of hormone therapy in women with diabetes.

Body Weight A meta-analysis of randomized controlled trials showed that unopposed estrogen or estrogen combined with a progestogen has no effect on body weight, suggesting that hormone therapy does not cause weight gain in excess of that normally observed at the time of menopause.[53]

Gallbladder Disease Gallbladder disease is a commonly cited complication of oral estrogen use. The WHI studies reported an increased risk for cholecystitis, cholelithiasis, and cholecystectomy among women taking oral estrogen or estrogen–progestogen therapy. Therefore, transdermal estrogen is an alternative to oral therapy for women at high risk for cholelithiasis.[14]

Estrogens

Estrogens are naturally occurring hormones or synthetic steroidal or nonsteroidal compounds with estrogenic activity. The primary indication for systemic estrogen-based MHT is the relief of moderate and severe vasomotor and vulvovaginal symptoms. The initial dose should be the lowest effective dose for symptom control.

Adverse Effects Common adverse effects of estrogen include nausea, headache, breast tenderness, and heavy bleeding. More serious adverse effects include increased risk for CHD, stroke, VTE, breast cancer, and gallbladder disease. Transdermal estradiol is associated with a lower incidence of breast tenderness and deep vein thrombosis than oral estrogen.[14,32]

5 ***Dosage and Administration*** Use of MHT at doses lower than those

prescribed historically (ie, prior to the WHI study) appears to be effective in reducing bone loss and managing menopausal symptoms (see Table 98-1).[41,42,54,55] Low-dose estrogen regimens include 0.3 to 0.45 mg conjugated estrogens, 0.5 mg micronized 17β-estradiol, and 0.014 mg to 0.0375 mg transdermal 17β-estradiol patch.[14] Topical gels, sprays, and creams are also available in low doses. Lower doses typically have fewer adverse effects and may have better overall benefit-risk profiles than standard doses. The lowest effective dose of estrogen, consistent with individualized patient treatment goals and assessment of safety and effectiveness, should be used.

Various systemically administered estrogens (typically oral and transdermal) are equally effective for replacement therapy (**Table 98-4**). Estrogens can be administered orally, percutaneously (transdermal patches and topical products), intravaginally (creams, tablets, rings, or inserts), intramuscularly, and even subcutaneously in the form of implanted pellets. The choice of estrogen delivery (product, route, and method) should be determined in consultation with the patient to ensure acceptability and enhance adherence. In general, the oral and transdermal routes are used most frequently.

TABLE 98-4 FDA-Approved Estrogen Products for Menopausal Hormone Therapy

Drug	Brand Name[a]	Initial Dose/Low Dose	Usual Dose Range	Comments
Systemic Estrogen Products (for the treatment of moderate and severe vasomotor symptoms ± urogenital symptoms)				
Oral estrogens[b]				
Conjugated equine estrogens	Premarin	0.3 or 0.45 mg once daily	0.3-1.25 mg once daily	Dosage form available as 0.3, 0.45, 0.625, 0.9, 1.25 mg
Esterified estrogens (75%-85% estrone + 6%-15% equilin)	Menest	0.3 mg once daily	0.3-1.25 mg once daily	Administer 3 weeks on and 1 week off Dosage form available as 0.3, 0.625, 1.25 mg
Estradiol acetate	Femtrace	0.45 mg once daily	0.45-1.8 mg once daily	Dosage form available as 0.45, 0.9, 1.8 mg
Micronized 17β-estradiol	Estrace Generics	1 mg once daily	1 or 2 mg once daily	Administer 3 weeks on and 1 week off Dosage form available as 0.5, 1, 2 mg
Transdermal estrogens patches				
17β-estradiol	Alora	0.025 mg/day (patch applied twice weekly)[c]	0.025-0.1 mg/day (patch applied twice weekly)[c]	Dosage form available as 0.025, 0.05, 0.075, 0.1 mg/day
	Climara	0.025 mg/day (patch applied once weekly)[c]	0.025-0.1 mg/day (patch applied once weekly)[c]	Dosage form available as 0.025, 0.0375, 0.05, 0.06, 0.075, 0.1 mg/day
	Menostar	0.014 mg/day (patch applied once weekly)[c,d]	0.014 mg/day (patch applied once weekly)[c,d]	Dosage form available as 0.014 mg/day
	Estraderm	-	0.05 or 0.1 mg/day (patch applied twice weekly)[c]	Dosage form available as 0.05, 0.1 mg/day
	Minivelle, Vivelle, Vivelle Dot	0.025 mg/day (patch applied twice weekly)[c]	0.025-0.1 mg/day, 0.05 is standard dose (patch applied twice weekly)[c]	Dosage form available as 0.025, 0.0375, 0.05 (standard dose), 0.075, 0.1 mg/day
Other topical forms of estrogen				
17β-estradiol topical emulsion	Estrasorb 0.25% emulsion	–	Two pouches once daily (which delivers 0.05 mg of estradiol per day)	Apply to legs
17β-estradiol topical gel	EstroGel 0.06% metered-dose pump	–	1.25 g/day once daily (contains 0.75 mg estradiol)	Apply from wrist to shoulder
	Elestrin 0.06% metered-dose pump	–	1-2 unit doses once daily (1 unit dose: 0.87 g, which contains 0.52-mg estradiol)	Apply to upper arm
	Divigel 0.1% (topical once daily)	0.25 g once daily	0.25-1 g (provides 0.25-1 mg of estradiol)	Apply to upper thigh. Dosage form available as 0.25, 0.5, 0.75, 1 mg
17β-estradiol transdermal spray	Evamist	1 spray once daily	1-3 sprays once daily (1.53 mg of estradiol per spray)	Apply to inner surface of forearm
Implanted estrogens[e]				
Implanted 17β-estradiol	Estradiol pellets	25-mg implanted subcutaneously every 6 months	50-100 mg implanted subcutaneously every 6 months	
Vaginal estrogens				
Estradiol acetate vaginal ring	Femring	12.4 mg every 3 months	12.4-, 24.8-mg ring (delivers 0.05- or 0.1-mg estradiol/day)	
Intravaginal Estrogen Products (for the treatment of urogenital symptoms only/low systemic exposure)				
Conjugated equine estrogens (CEE) vaginal cream	Premarin		0.5-2 g/day (contains 0.625 mg CEE per g)	Administer 21 days on and 7 days off
17β-estradiol vaginal cream	Estrace	2-4 g daily for 1 or 2 weeks then gradually reduced to ½ initial dosage for similar period	Maintenance dose of 1 g, one to three times weekly	Dosage form available as tube containing 1½ oz with calibrated applicator for delivery of 1, 2, 3, or 4 g
17β-estradiol vaginal ring	Estring	2 mg replaced every 90 days	2 mg ring (delivers 0.0075 mg/day) replaced every 90 days	
17β-estradiol vaginal insert	Imvexxy	1 vaginal insert daily for 2 weeks, then 1 insert twice weekly	4 or 10 mcg twice weekly	
Estradiol hemihydrate vaginal tablet	Vagifem Yuvafem Generics	10 mcg once weekly for 2 weeks, then twice weekly	10 mcg twice weekly	

[a]US brand names.

[b]Orally administered estrogens stimulate synthesis of hepatic proteins and increase circulating concentrations of sex hormone-binding globulin, which in turn may compromise the bioavailability of androgens and estrogens. Women with elevated triglyceride concentrations or significant liver function abnormalities are candidates for nonoral estrogen therapy.

[c]Do not apply estrogen patches on or near breasts. Avoid waistline as patch may rub off with tight-fitting clothing.

[d]FDA-approved for prevention of postmenopausal osteoporosis only.

[e]Not available in the United States.

Oral Estrogen Oral conjugated equine estrogen has been available for more than 70 years. Oral CEE is prepared from the urine of pregnant mares and is composed of estrone sulfate (50%-60%) and multiple other equine estrogens such as equilin and 17α-dihydroequilin.

Estradiol is the predominant and most active form of endogenous estrogens. A micronized form of estradiol (produced by a technique that yields extremely small particles of the pure hormone) is readily absorbed from the small intestines. When given orally, estradiol is metabolized by the intestinal mucosa and the liver during the first hepatic passage, and only 10% reaches circulation as free estradiol. Metabolism of estrogen is partly mediated by the cytochrome P450 3A4 isoenzyme. Gut and liver metabolism converts a large proportion of estradiol to the less potent estrone. Thus, measurement of serum estradiol is not useful for monitoring oral estrogen replacement. The principal metabolites of micronized estradiol are estrone and estrone sulfate. Administration of estradiol via the oral route results in estrone concentrations that are five to seven times those of estradiol.[17] Ethinyl estradiol is a highly potent semisynthetic estrogen that has similar activity following administration by the oral or nonoral route.

Orally administered estrogens stimulate the synthesis of hepatic proteins and increase the circulating concentrations of sex hormone-binding globulin, which, in turn, may compromise the bioavailability of androgens and estrogens.

Other Routes of Estrogen Administration Nonoral routes of estrogen administration may offer both advantages and disadvantages compared with the oral route, but long-term data are not available. As the nonoral forms of estrogens bypass the GI tract, they thereby avoid first-pass liver metabolism. These routes of estradiol delivery result in a more physiologic estradiol-to-estrone ratio (estradiol concentrations greater than estrone concentrations), as seen in the normal premenopausal state.

6 When compared with standard oral estrogen doses, transdermal therapy appears to offer no significant increase in triglycerides, C-reactive protein, sex hormone binding globulin, and blood pressure.[14] Use of transdermal estrogen has also been associated with a lower risk of deep vein thrombosis and possibly stroke and coronary artery disease.[14,17] Transdermal estrogen patches share the advantages of other nonoral estrogen routes and have the added advantage of delivering estradiol to the general venous circulation at a continuous rate. The matrix transdermal systems (estrogen in adhesive) generally are well tolerated, and fewer than 5% of women experience skin reactions. The incidence of skin irritation diminishes when the application site is rotated. Topical anti-

inflammatory products (eg, hydrocortisone cream) can be applied for managing the rashes, and switching to another transdermal patch is often a viable option.

Topical gels, sprays, and emulsions are convenient forms of systemic estrogen therapy, but variability in drug absorption has been noted with some formulations. Intravaginal creams, tablets, inserts, and rings are used for treatment of urogenital (vulvar and vaginal) atrophy. Pharmacologically they are sustained-release delivery systems that can maintain adequate estradiol concentrations. While most products provide local estrogen, one intravaginal-ring product (Femring®) is designed to achieve systemic concentrations of estrogen and is also indicated for treatment of moderate-to-severe vasomotor symptoms. Estradiol pellets (for subcutaneous implantation), containing pure crystalline 17β-estradiol, have been available for more than 60 years. They are inserted subcutaneously into the anterior abdominal wall or buttock. Pellets are difficult to remove and may continue to release estradiol for a long time after insertion. Implantation should not be repeated until serum estradiol concentrations have fallen to values similar to those at the midfollicular phase of the menstrual cycle. Estradiol pellets are not available in the United States.

7 Progestogens

Because of the increased risk of endometrial hyperplasia and endometrial cancer with estrogen monotherapy (ie, unopposed estrogen), use of systemic estrogen in women with an intact uterus must always be accompanied by a progestogen or tissue-selective estrogen complex (estrogen/bazedoxifene) for endometrial protection.[56] Some data suggest that progestins may also improve vasomotor symptoms,[57,58] but their use for this purpose is not considered first-line or standard therapy.

Progestogens reduce nuclear estradiol receptor concentrations, suppress DNA synthesis, and decrease estrogen bioavailability by increasing the activity of endometrial 17-hydroxysteroid dehydrogenase, an enzyme responsible for converting estradiol to estrone.[59]

The first generation of progestogens included the C-19 androgenic progestogens norethindrone (also known as norethisterone), norgestrel, and levonorgestrel. More recent preparations have included the C-21 progestogens dydrogesterone (not currently available in the United States) and medroxyprogesterone acetate (MPA), which are less androgenic. Drospirenone, a synthetic progestogen analog of the potassium-sparing diuretic spironolactone, has both antiandrogenic and antialdosterone properties. Micronized progesterone

also has become available for use in postmenopausal women. Although data are limited, oral micronized progesterone is considered as the first-line progestin (safe alternative) because it is effective for endometrial hyperplasia, is metabolically neutral, and does not appear to increase the risk of either breast cancer or CHD in studies to date.[17] The most commonly used oral progestogens are MPA, micronized progesterone, and norethindrone acetate.[60] The latter can be administered transdermally in the form of a combined estrogen–progestogen patch.

Adverse Effects Common adverse effects of progestogens include irritability, weight gain, bloating, and headache. Changing from a cyclic to a continuous-combined regimen or changing from one progestogen to another may decrease the incidence or severity of untoward effects. Adverse effects of progestogens are difficult to evaluate and can vary with the agent administered. Some women experience "premenstrual-like" symptoms, such as mood swings, bloating, fluid retention, and sleep disturbance. Newer methods and routes of progestogen delivery (eg, locally by an intrauterine device that releases levonorgestrel or a progesterone-containing bioadhesive vaginal gel) may be associated with fewer adverse effects.

Dosage and Administration Several progestogen regimens designed to prevent endometrial hyperplasia are available for use in women with an intact uterus (**Table 98-5**). Progestogens can be used continuously (resulting in endometrial atrophy) or cyclically (resulting in monthly withdrawal bleeding). For cyclic use, the progestogen must be taken for a sufficient period of time during each cycle. In general, a minimum of 12 to 14 days of progestogen therapy per month is required for complete protection against estrogen-induced endometrial hyperplasia. For women with a history of hysterectomy, use of progestogens is not needed. However, in women with endometriosis who have had a hysterectomy, the use of a progestogen along with estrogen may minimize endometriosis exacerbations.

TABLE 98-5 Progestogen Dosing for Endometrial Protection (Cyclic Administration)

Progestogen	Dosage
Medroxyprogesterone acetate	5-10 mg/day for 12-14 days per calendar month (oral dosage form available as 2.5-, 5-, 10-mg tablets)
Micronized progesterone	200 mg/day for 12-14 days per calendar month (oral dosage form available as 100- and 200-mg tablets)
Norethindrone acetate	5 mg/day for 12-14 days per calendar month (oral dosage form available as 2.5-, 5-mg tablets)

Menopausal Hormone Therapy Regimens

Many products have been used for MHT, and most include an estrogen and a progestogen in various regimens, routes, and administration schedules. Additionally, tissue-selective estrogen complex product (estrogen/bazedoxifene) is available for once-daily dosing. Common combination MHT regimens are described in **Table 98-6**.

TABLE 98-6 Common Combination Menopausal Hormone Therapy Regimens

Regimen	Brand name	Dosage
Oral Regimens		
Conjugated equine estrogen (CEE) + medroxyprogesterone acetate (MPA)	Prempro (continuous)	0.625 mg CEE/2.5 mg MPA, 0.625 mg CEE/5 mg MPA daily Low-dose: 0.3 mg CEE/1.5 mg MPA, 0.45 mg CEE/1.5 mg MPA daily
	Premphase (continuous sequential)	0.625 mg CEE daily only in the first 2 weeks of a 4-week cycle then 0.625 mg daily CEE + 5 mg MPA daily in the last 2 weeks of a 4-week cycle
Conjugated equine estrogen (CEE) + bazedoxifene	Duavee (continuous)	0.45/20 mg daily
Ethinyl estradiol (EE) + norethindrone acetate (NETA)	Generic, Femhrt (continuous) Fayvolv (continuous)	Femhrt: 2.5 mcg EE/0.5 mg NETA daily Fyavolv: 2.5 mcg EE/0.5 mg NETA daily, 5 mcg EE/1 mg NETA daily
Estradiol (E) + drospirenone (DRSP)	Angeliq (continuous)	1 mg E/0.5 mg DRSP daily Low dose: 0.5 mg E/0.25 mg DRSP daily
Estradiol (E) + norgestimate	Prefest (estrogen/intermittent progestogen)	1 mg E daily for first 3 days then 1 mg E/0.09 mg norgestimate daily for next 3 days; this pattern is repeated continuously
Estradiol (E) + norethindrone acetate (NETA)	Activella (continuous) Mimvey (continuous) Mimvey Lo (continuous) Amabelz (continuous) Lopreeza (continuous)	1 mg E/0.5 mg NETA daily Low-dose: 0.5 mg E/0.1 mg NETA daily
Estradiol (E) + progesterone	Bijuva (continuous)	1 mg E/100 mg progesterone daily
Transdermal Regimens		
Estradiol + norethindrone acetate patch	CombiPatch (continuous) CombiPatch (continuous sequential)	Continuous: 0.05/0.14 mg, 0.05/0.25 mg (apply 1 patch twice weekly) Continuous sequential: 0.05 mg of an estradiol only patch (apply 1 patch twice weekly) in the first 2 weeks of a 4-week cycle then either dose of the CombiPatch (apply 1 patch twice weekly) in the last 2 weeks of a 4-week cycle
Estradiol (E) + levonorgestrel patch	Climara Pro (continuous)	0.045 mg E/0.015 mg/day (apply 1 patch once weekly)

CEE, conjugated equine estrogen; DRSP, drospirenone; E, estradiol; EE, ethinyl estradiol; NETA, norethindrone acetate; MPA, medroxyprogesterone acetate.

Continuous Cyclic Estrogen–Progestogen (Sequential) Treatment Estrogen typically is administered continuously (daily). A progestogen is coadministered with the estrogen for at least 12 to 14 days of a 28-day cycle.[61] The progestogen causes scheduled withdrawal bleeding in approximately 90% of women. With this regimen, bleeding usually begins 1 to 2 days after the last progestogen dose. Occasionally, bleeding begins during the latter phase of progestogen

administration.

Continuous Combined Estrogen–Progestogen Treatment Continuous combined estrogen–progestogen administration results in endometrial atrophy and the absence of vaginal bleeding. Continuous combined MHT is more acceptable than traditional cyclic therapy. This method of treatment can be achieved by using either commercially available oral and transdermal preparations or by administering systemic estrogen along with the use of the levonorgestrel-releasing intrauterine system. This combination offers the best protection against endometrial hyperplasia and cancer.[17] The continuous combined estrogen–progestogen regimen (using conjugated equine estrogens 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day) was found to lead to a decreased risk of endometrial cancer in the WHI study.[13]

Continuous Long-Cycle Estrogen–Progestogen Treatment This modified sequential regimen was developed to decrease the incidence of uterine bleeding. In the continuous long-cycle (or cyclic withdrawal) estrogen–progestogen regimen, estrogen is given daily, and progestogen is given six times per year, every other month for 12 to 14 days, resulting in six periods per year. Bleeding episodes may be heavier and last for more days than withdrawal bleeding with continuous cyclic regimens. The effect of continuous long-cycle estrogen–progestogen treatment on endometrial protection is unclear.

Intermittent Combined Estrogen–Progestogen Treatment The intermittent combined estrogen–progestogen regimen, also called *continuous-pulsed estrogen–progestogen* or *pulsed-progestogen*, consists of 3 days of estrogen therapy alone, followed by 3 days of combined estrogen and progestogen, which is then repeated without interruption. This regimen is designed to lower the incidence of uterine bleeding. It is based on the assumption that pulsed-progestogen administration will prevent downregulation of progesterone receptors that can be produced by continuous combined regimens. The lower progestogen dose induces fewer side effects and can be better tolerated. The long-term effect of intermittent combined regimens in endometrial protection is undetermined.

Compounded Bioidentical Hormone Therapy

Bioidentical hormone products are those that contain hormones that are chemically identical molecules to those produced by the body. There are FDA-approved products containing bioidentical hormones (eg, 17β-estradiol).

Compounded bioidentical hormone therapy (CBHT) is terminology used to describe hormone therapy formulations that are custom-prepared (ie, compounded) for individual patients, often involving the use of measuring and monitoring hormone levels in blood and/or other body fluids such as saliva.[22] Hormones that are commonly used in CBHT include estrone, estradiol, estriol, progesterone, testosterone, DHEA, and thyroid hormone. Although claims have been made to suggest that compounded bioidentical hormones are safer and more "natural" alternatives to commercially available preparations, there is a paucity of evidence regarding the efficacy, safety, and pharmaceutical quality of these products.[62] Furthermore, saliva testing is often used to adjust hormone levels, and there is no scientific evidence to support this practice. Bioidentical hormones appear to carry the same risks as traditional hormone therapy products. Several major medical organizations have released statements to dissuade patients and clinicians from CBHT.[22,62,63]

Other Treatments for Menopause-Related Symptoms

In women who have contraindications to MHT use, prefer not to take estrogen and/or progestogen, or cannot tolerate estrogen and/or progestogen administration, a number of other medications may be considered, depending on the goals of therapy.[15,21] These include the prescription medications testosterone, SERMs, and tibolone (not currently available in the United States) as well as nonhormonal prescription medications (eg, selective serotonin reuptake inhibitors).

Alternatives to estrogen for treatment of hot flashes include tibolone, selective serotonin reuptake inhibitors (eg, paroxetine, fluoxetine, citalopram, escitalopram), dual serotonin and norepinephrine reuptake inhibitors (eg, venlafaxine, desvenlafaxine), clonidine, gabapentin, and pregabalin (**Table 98-7**). Progestogens (eg, MPA, megesterol acetate) alone may be an option for some women (eg, those with a history of VTE), but weight gain, vaginal bleeding, and other adverse effects often limit their use. Tibolone and progestogens cannot be considered nonhormonal agents for the treatment of hot flashes in women for whom MHT is contraindicated. For this group of patients, selective serotonin reuptake inhibitors such as paroxetine mesylate and serotonin-norepinephrine reuptake inhibitors such as venlafaxine are considered by some to be a first-line therapy.[15] However, in breast cancer patients, evidence suggests that certain selective serotonin reuptake inhibitors (paroxetine and fluoxetine) could interfere with metabolism of endocrine therapies, such as tamoxifen via cytochrome P450 2D6 inhibition (tamoxifen requires activation to its active metabolites by

cytochrome P450 2D6).[15,17] Gabapentin has demonstrated beneficial effect for reducing the frequency and severity of vasomotor symptoms. Higher effective doses may limit its use due to adverse events at such doses; including drowsiness, dizziness, and loss of coordination. However, it may be a reasonable option for women with disrupted sleep and hot flashes when administered in the evening. Pregabalin has demonstrated benefit at alleviating vasomotor symptoms, but is less well studied.[17] Clonidine has also been shown to be more effective for hot flashes compared to placebo but its side effects (eg, sedation, dry mouth, and hypotension) are not always well tolerated by women. It is also less effective than the previously described nonhormonal treatment options.[17]

TABLE 98-7 Alternatives to Estrogen for Treatment of Hot Flashes[a]

Drug	Brand Name[b]	Initial Dose	Usual Dose Range	Comments
Tibolone[c]	Livial (not available in the United States)	2.5 mg	2.5 mg/day	Tibolone is not recommended during the perimenopause period because it may cause irregular bleeding
Venlafaxine	Effexor, Effexor XR	37.5 mg	37.5-150 mg/day	Adverse effects include nausea, headache, somnolence, dizziness, insomnia, nervousness, xerostomia, anorexia, constipation, diaphoresis, weakness, and hypertension
Desvenlafaxine	Pristiq	100-150 mg	100-150 mg/day	Adverse effects include nausea, headache, somnolence, dizziness, insomnia, xerostomia, anorexia, constipation, diaphoresis, and weakness
Paroxetine, paroxetine CR[d]	Brisdelle,[e] Paxil, Paxil CR, Pexeva	7.5 mg/day (paroxetine),[e] 10 mg/day (paroxetine), or 12.5 mg/day (paroxetine CR)	7.5 mg/day,[e] 10-20 mg/day or 12.5–25 mg/day	Adverse effects include nausea, somnolence, insomnia, headache, dizziness, xerostomia, constipation, diarrhea, weakness, and diaphoresis
Citalopram		10 mg/day	10-20 mg/day	Adverse effects include drowsiness, insomnia, diaphoresis, nausea, xerostomia, dose-dependent QTc prolongation
Escitalopram		10 mg/day, start with 5 mg/day in sensitive or older women and titrate up	10-20 mg/day	Adverse effects include headache, insomnia, nausea, increased sweating, fatigue, and somnolence. Decreased libido and anorgasmia
Clonidine	Catapres and generic tablets (oral) Catapres-TTS (transdermal) Kapvay tablets (extended release; oral)	0.1 mg/day	0.1 mg/day	Adverse effects include drowsiness, dizziness, hypotension, and dry mouth, especially with higher doses
Pregabalin	Lyrica	150 mg/day	150-300 mg/day	Adverse effects include drowsiness, dizziness, dry mouth, edema, blurred vision, weight gain, impaired concentration
Gabapentin	Gralise, Neurontin	300 mg at bedtime	900 mg/day (divided in three daily doses), doses up to 2,400 mg/day (divided in three daily doses) have been studied	Adverse effects include somnolence and dizziness; these symptoms often can be obviated with a gradual increase in dosing

CR, controlled release; XR, extended release.

[a]Treatment of postmenopausal hot flashes is an off-label indication in the United States for all medications listed except for one formulation of paroxetine (paroxetine mesylate).

[b]US brand names.

[c]Not available in the United States.

[d]Other selective serotonin reuptake inhibitors (eg, citalopram, escitalopram, fluoxetine, and sertraline) have also been studied and may be used for the treatment of hot flashes.

[e]The brand Brisdelle contains 7.5 mg of paroxetine and is FDA-approved to treat moderate-to-severe vasomotor symptoms of menopause. This specific product is not FDA-approved for treating psychiatric conditions.

Androgens Androgens have important biologic effects in women, acting both directly via androgen receptors in tissues, such as bone, skin fibroblasts, hair follicles, and sebaceous glands, and indirectly via the aromatization of testosterone to estrogen in the ovaries, bone, brain, adipose tissue, and other tissues. There is a natural decline in androgen production with aging, and pathophysiologic states affecting ovarian and adrenal function, such as adrenal insufficiency and hypopituitarism, as well as bilateral oophorectomy, are associated with androgen deficiency in women. The therapeutic use of testosterone in women is controversial.

A cluster of symptoms that characterizes androgen insufficiency in women, manifested as diminished sense of well-being, persistent or unexplained fatigue, and sexual function changes such as decreased libido, decreased sexual receptivity, and decreased pleasure has been reported. However, studies designed to evaluate this have shown no relationships between serum total and free testosterone levels and either sexual function or well-being in women.[64,65] Thus, as data supporting an androgen deficiency syndrome are lacking, the American Endocrine Society in 2014 reaffirmed their recommendation against making a diagnosis of androgen deficiency in women.[66] However, large randomized placebo-controlled clinical trials involving naturally and surgically postmenopausal women presenting with low libido demonstrate that testosterone therapy, with and without concurrent estrogen therapy, may improve the quality of the sexual experience.[67]

Androgens should not be used during pregnancy or lactation or in women with suspected androgen-dependent neoplasia. Adverse effects from excessive dosage include virilization, fluid retention, and potentially adverse lipoprotein lipid effects, which are more likely with oral administration. Further studies are required to determine the long-term safety of testosterone in women.

Most of the earlier studies showing clinical improvement with testosterone therapy reported supraphysiologic concentrations. Other studies have used transdermal patch therapy to achieve free testosterone concentrations in the upper normal range for young women.[66,67] Evidence regarding efficacy and safety of testosterone in women is lacking, and the generalized use of testosterone is currently not recommended.[66] In the United States, there are currently no testosterone products FDA-approved for use in women.

Dehydroepiandrosterone (DHEA) DHEA is a precursor hormone in the synthesis of estrone, estradiol, and testosterone. DHEA is classified as a dietary

supplement in the United States and has been used off-label for a number of conditions, including fertility and treatment of menopausal symptoms. Intravaginal DHEA (cream, gel, suppositories) was previously only available as compounded formulations but a prescription version (in the form of an insert) has recently approved by the FDA for treatment of moderate-to-severe dyspareunia at a dose of 6.5 mg once daily at bedtime. Premarketing clinical trials reported a significant improvement in moderate-to-severe dyspareunia symptoms and decrease in vaginal dryness compared to placebo.[68] Intravaginal administration of prasterone conveys only a local effect on the vaginal tissue; the serum concentrations of estradiol, testosterone, and DHEA were within the normal range for postmenopausal women after 12 weeks of treatment in one clinical trial.[69] Prasterone's FDA labeling does not carry the same boxed warnings for VTE, endometrial hyperplasia, or other risks that are present in estrogen-containing products. However, the product labeling does warn against the use of prasterone in women with a history of, or suspected, breast cancer, given that prasterone is a precursor to estrogen. Prasterone is also contraindicated in women with undiagnosed AUB. The most common side effects of intravaginal prasterone are vaginal discharge and abnormal Pap smear.[70]

Selective Estrogen Receptor Modulators (SERMs) Selective estrogen receptor modulators are a group of nonsteroidal compounds that are chemically distinct from estradiol. They act as estrogen agonists in some tissues, such as bone, and as estrogen antagonists in other tissues, such as breast and endometrial tissue, through specific, high-affinity binding to the estrogen receptor. Individual SERMs differ in their activity and tissue specificity resulting in varying patterns of estrogen-receptor agonism in some tissues and estrogen-receptor antagonism in others.[71]

The ideal SERM would protect against osteoporosis and decrease the incidence of breast, endometrial, and colorectal cancer and CHD without exacerbating menopausal symptoms or increasing the risk of VTE or gallbladder disease. To date, no SERM meets these ideals. Tamoxifen, the first-generation SERM (a nonsteroidal triphenylethylene derivative), has estrogen antagonist activity on the breast and estrogen-like agonist activity on bone and endometrium. The second-generation SERM raloxifene, a nonsteroidal benzothiophene derivative, is used to reduce the risk of postmenopausal osteoporosis and invasive breast cancer, and also for treatment of postmenopausal osteoporosis. Raloxifene is antiestrogenic at the endometrium. However, it has an increased incidence of hot flashes compared to placebo.[72]

The third-generation SERM, bazedoxifene, in conjunction with conjugated estrogens forms a tissue-selective estrogen complex (TSEC) and is FDA-approved for use in moderate-to-severe vasomotor symptoms and prevention of osteoporosis.[71,73] This agent appears to have a favorable breast, endometrial, and ovarian safety profile, even after prolonged use.[74] While this TSEC has demonstrated high effectiveness for vasomotor symptoms (approximately 75% reduction),[74,75] SERMs alone do not alleviate, and may even exacerbate vasomotor symptoms, and also increase the risk for VTE.

Ospemifene is an orally administered third-generation SERM approved by the FDA for the treatment of moderate-to-severe dyspareunia and moderate-to-severe vaginal dryness from menopausal vulvar and vaginal atrophy due to menopause. Ospemifene's labeling carries a boxed warning about its estrogenic effect on the endometrium as there is an increased risk of endometrial hyperplasia and endometrial cancer in a woman with a uterus who takes unopposed estrogen therapy. Ospemifene labeling also includes a boxed warning about the possible risk of stroke and VTE.[76]

Adverse Effects Depending on the tissue selectivity, several SERMs are associated with hot flashes and less often with leg cramps. The SERMs can increase the risk of VTE and fatal stroke to a degree similar to that of oral estrogen, but the degree of risk is product specific.[14] Common adverse effects (greater than or equal to 5%) of bazedoxifene include muscle spasms, nausea, diarrhea, dyspepsia, upper abdominal pain, oropharyngeal pain, dizziness, and neck pain.[77] Common adverse effects of ospemifene include hot flashes, vaginal discharge, muscle spasm, headache, vaginal hemorrhage, and hyperhidrosis.[76]

Dose and Administration Conjugated estrogens/bazedoxifene is supplied as 0.45/20-mg tablets and is taken once daily. Ospemifene is a 60-mg tablet taken once daily with food. Other available SERMs are also dosed orally once daily.

Tibolone Tibolone is a gonadomimetic synthetic steroid in the norpregnane family with combined estrogenic, progestogenic, and androgenic activity. Tibolone has been used for three decades in Europe for treatment of menopausal symptoms and prevention of osteoporosis but is currently not approved in the United States. The hormonal effects of this synthetic steroid depend on its metabolism and activation in peripheral tissues. The parent compound has been described as a prodrug that is metabolized quickly in the gastrointestinal (GI) tract. It has several active metabolites, including a Δ4-isomer and 3α-OH and 3β-OH compounds. The Δ4-isomer metabolite confers significant progestogenic and

androgenic properties.

Tibolone has beneficial effects on mood and libido and improves menopausal symptoms and vaginal atrophy. Tibolone protects against bone loss and significantly reduces the risk of vertebral fractures in postmenopausal women with osteoporosis.[78] It has also been shown to decrease the risk of breast cancer and colon cancer in healthy women aged 60 to 85 years,[78] and appears to be more effective than conventional MHT for management of sexual dysfunction.[79]

Adverse Effects Tibolone use in elderly women has been reported to be associated with an increased risk of stroke,[78] and its use is also associated with breast cancer recurrence in breast cancer patients with vasomotor symptoms.[80] Tibolone lowers concentrations of total cholesterol, triglycerides, and lipoprotein (a), but may also decrease high-density lipoprotein (HDL) cholesterol.[81] The Million Women Study, an observational cohort study, found a greater risk of endometrial cancer (adjusted relative risk 1.79, 95% CI: 1.43-2.25) with tibolone use.[82] However, other randomized placebo-controlled studies have not shown an increased risk of endometrial cancer with tibolone and suggest that tibolone has an endometrial safety profile similar to continuous combined CEE and MPA.[83] The most commonly reported adverse effects of tibolone include weight gain and bloating.

Complementary and Alternative Medicine Some women prefer to use natural remedies due to a belief that they are safer. However, randomized, placebo-controlled trials of complementary and alternative therapies have been equivocal and have not established the safety and efficacy of herbal remedies, homeopathic treatments, or acupuncture for the prevention or treatment of hot flashes.

Phytoestrogens Phytoestrogens are plant compounds with estrogen-like biologic activity and relatively weak estrogen receptor-binding properties, resulting in physiologic effects in humans. Epidemiologic studies suggest that consumption of a phytoestrogen-rich diet, which is common in traditional Asian societies, may be associated with a lower risk of endometrial and ovarian cancer.[84]

The biologic potencies of phytoestrogens vary as most of these compounds are nonsteroidal and are less potent than synthetic estrogens. The main classes of phytoestrogens are isoflavones, lignans, coumestans, and prenylflavonoids.[84] The most commonly studied phytoestrogen is the isoflavone class, with genistein and daidzein being the most abundant active components of isoflavones. The concentration of isoflavones per gram of soy protein varies considerably among preparations. Also, a single plant often contains more than one class of

phytoestrogen. Common food sources of phytoestrogens include soybeans (isoflavones), oilseeds such as flaxseed (lignans), alfalfa sprouts and pinto beans (coumestans), and hops and beer (prenylflavonoids).[84]

Mild estrogenic effects have been seen in postmenopausal women with phytoestrogen consumption. A systematic review indicated that high levels of genistein extracts appear to reduce the number of daily hot flashes compared with placebo without harmful endometrial effects when used for up to 2 years.[85] A limitation of this review is that many of the studies included were of poor quality and short duration. A more recent meta-analysis of randomized, controlled trials concluded that compared to placebo, phytoestrogens reduce the frequency of hot flashes and vaginal dryness but not in night sweats.[86]

Phytoestrogens decrease low-density lipoprotein (LDL) cholesterol and triglyceride concentrations with no significant change in HDL cholesterol concentrations.[87] Furthermore, phytoestrogens have the ability to inhibit LDL oxidation and normalize vascular reactivity in estrogen-deprived primates.[87] Common adverse effects include constipation, bloating, and nausea.[88]

A meta-analysis reported that phytoestrogen use is not associated with increased rates of endometrial cancer, vaginal bleeding, and breast cancer.[88] Large, long-term studies are needed to further document the effects of phytoestrogens on the breast, bone, and endometrium. Furthermore, before phytoestrogens can be considered an alternative to conventional MHT in postmenopausal women, additional data are needed to clarify differences among classes of phytoestrogens, including dosing, biologic activity, safety, and efficacy.

Other Complementary and Alternative Options Black cohosh (*Cimicifuga racemosa* or *Actaea racemosa*), a widely used herbal supplement, may not offer substantial benefits for relief of vasomotor symptoms. A systematic review and meta-analysis concluded that black cohosh was not associated with a reduction in hot flashes.[86] This substance does not appear to have strong intrinsic estrogenic properties but may act through the serotonergic system. Black cohosh appears to be generally well tolerated, although hepatotoxicity has been reported. It is unclear if this is due to the herb itself or is a result of adulteration of the commercially available products.[89] The long-term effects of black cohosh are unknown. Other herbals and alternative treatments that may be used by women include dong quai, red clover leaf (contains phytoestrogens), and ginseng. These have not been shown to be effective in the treatment of menopausal symptoms and may carry the risk of adverse events.[15,90] Complementary and alternative

therapies should not be recommended to treat menopausal symptoms.

Personalized Pharmacotherapy

8 The severity of menopausal symptoms varies widely from woman to woman. The decision to use MHT must be individualized and based on several parameters, including vasomotor and vulvovaginal symptoms, age, fracture risk, cardiovascular disease risk, breast cancer risk, and thromboembolism risk. MHT is not indicated for prevention of chronic diseases of aging. The initiation of MHT should be considered for healthy symptomatic women who are within 10 years of the onset of menopause or age younger than 60 years and who do not have contraindications to therapy.[14,19] The treatment regimen (estrogen only or combined estrogen–progestogen, dose, route of administration) and duration should be based on the individualized risk versus benefit analysis for each woman.[14]

Long-term use of MHT or initiation in older women is associated with greater risks. Once advised of increased risks associated with continuing MHT beyond age 60 years, extending therapy may be acceptable under close medical supervision. For example, in women with severe and persistent menopausal symptoms, use should not be discontinued based solely on age but rather individualized based on assessment of potential risks and benefits.[14]

Estrogen therapy is the most effective treatment for moderate and severe vasomotor symptoms, impaired sleep quality, and vulvovaginal symptoms of menopause (Fig. 98-1). A thorough discussion of the risks and benefits of MHT should be completed with the patient so that she can weigh the risks and benefits versus alternatives and make a rational decision about whether to use MHT. For a healthy recently menopausal woman who has vasomotor symptoms, the benefits of hormonal therapy generally outweigh the risks. These benefits include the control of vasomotor symptoms, treatment of urogenital atrophy, and prevention of postmenopausal bone loss. Nonetheless, VTE and stroke are concerning short-term risks.

Menopausal hormone therapy should be tailored for optimal formulation, dose, route of delivery, and counseling should be based on age, years since menopause, and hysterectomy status. All types and routes of administration of estrogen are equally effective in relieving vasomotor symptoms and vulvovaginal atrophy.[14] A dose-dependent relationship between estrogen administration and suppression of hot flashes is well established. Some women, especially younger women, may require a higher than average dose of estrogen

to suppress symptoms. On the other hand, many women with hot flashes at the time of menopause require lower doses of estrogen.[91] Initiation of therapy with low doses of estrogen often will minimize adverse effects, such as breast tenderness and unscheduled bleeding. Transdermal estradiol is less likely than oral estrogen to cause nausea and headache. In many cases changing from one estrogen regimen to another can alleviate certain adverse effects.

Prior to initiating pharmacologic therapy, a complete medical history and physical examination should be performed. Medical history should include a personal and family history of cardiovascular disease and thrombotic risks. The physical examination should include a complete cardiovascular examination, clinical assessment of thyroid status, and breast and pelvic examinations. Papanicolaou cervical cytologic examination and screening mammography negative for malignancy are required before initiating MHT. Thyroid function tests and lipoprotein lipid profile also are performed at the discretion of the clinician. Oral estrogen should be avoided in women with hypertriglyceridemia, liver disease, and gallbladder disease. For these women, transdermal administration is a safer approach. Sequential estrogen-progestogen therapy results in scheduled vaginal withdrawal bleeding but often is scant or completely absent in older women. For many women, scheduled withdrawal bleeding is one of the main reasons for avoiding or discontinuing MHT. Because there is no physiologic need for bleeding, new MHT regimens that reduce monthly bleeding (eg, continuous long-cycle regimens) or prevent monthly bleeding (eg, continuous combined and intermittent combined regimens) were developed. Continuous combined estrogen–progestogen administration results in endometrial atrophy and the absence of vaginal bleeding. Initially, it causes unpredictable spotting or bleeding, which usually resolves within 6 to 12 months. Decreasing the estrogen dose or increasing the progestogen dose usually decreases or stops the spotting. Occasionally, a drug-free period of 1 or 2 weeks is useful to stop the bleeding. Women who recently have undergone menopause have a higher risk for excessive, unpredictable bleeding while receiving continuous therapy; thus, this regimen is best reserved for women who are at least 2 years postmenopause.

If MHT is to be initiated, the selection of the drug should also take into account the potential for drug interactions, including those involving the cytochrome P450 (CYP450) microsomal enzyme system. Estrogen is metabolized partly by the CYP 450 isoenzymes 1A2 and 3A4, and the progestin medroxyprogesterone is metabolized by CYP450 3A4. Inducers or inhibitors of these enzymes may either decrease or increase, respectively, the therapeutic

effects or result in side effects. Similarly, selection of nonhormonal drug therapy options should take into account the potential for interactions with other prescription and nonprescription medications the patient may be taking. Selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors can have major interactions with other drugs also affecting CYP450 2D6 and 3A4 (See Chapter 85, “Depressive Disorders”). Patients using vaginal estrogen creams or nonestrogen vaginal moisturizers should be warned that products with oil-based lubricants or vehicles can weaken latex condoms, which can decrease protection against sexually transmitted infections. Pharmacodynamic drug interactions (eg, additive side effects) should also be considered.

EVALUATION OF THERAPEUTIC OUTCOMES

The relief of moderate and severe hot flashes is the primary goal of MHT. In order to adequately assess treatment effect, women should be encouraged to continue their MHT regimen for at least 1 month. The main reasons for discontinuing MHT are side effects such as bleeding, breast tenderness, bloating, and “premenstrual-like symptoms.” Reducing the dose or changing the regimen or the route of administration can minimize these effects. Alternatively, if vasomotor symptoms are not controlled adequately with a lower-dose regimen, increasing the estrogen dose may be a reasonable option. Therefore, after the menopausal woman begins MHT, a brief follow-up visit 6 weeks later may be useful to discuss patient concerns about MHT and to evaluate the patient for symptom relief, adverse effects, and patterns of withdrawal bleeding. Women receiving MHT should be seen by the clinician for annual monitoring (**Table 98-8**).

TABLE 98-8 Management of Patients Taking Hormone Therapy Regimens

Initiation of Hormone Therapy

Hormone therapy should be used only as long as vasomotor symptom control is necessary

Six-Week Follow-up Visit

- To discuss patient concerns about hormone therapy
- To evaluate the patient for symptom relief, adverse effects, and patterns of withdrawal bleeding (if continuous sequential hormone therapy is given)

Drug	Adverse Drug Reaction	Monitoring Parameter	Suggested Change
Estrogen		Persistence of hot flashes	Increase estrogen dose
Estrogen	Breast tenderness		Reduce estrogen dose; switch to a transdermal regimen
Progestogen	Bloating Premenstrual-like symptoms		Switch to another progestogen or bazedoxifene

Annual Follow-up Visit

Annual monitoring: medical history, physical examination (including pelvic examination), blood pressure measurement, and routine endometrial cancer surveillance (as indicated). Additional follow-up is determined based on the patient's initial response to therapy and the need for any modification of the regimen

Breast examinations: annual mammograms (scheduled based on patient's age and risk factors)

Osteoporosis prevention: BMD should be measured in women 65 years and older and in women younger than 65 years with risk factors for osteoporosis. Repeat testing should be performed as clinically indicated.

In women taking sequential hormone therapy	Transvaginal ultrasound, and where indicated an endometrial biopsy should be performed if vaginal bleeding occurs at any time other than the expected time of withdrawal bleeding or when heavier or more prolonged withdrawal bleeding occurs (if endometrial pathology cannot be excluded by endovaginal ultrasonography, further evaluation may be required, such as hysteroscopy)
In women taking continuous combined hormone therapy	Endometrial evaluation should be considered when irregular bleeding persists for more than 6 months after initiating therapy

BMD, bone mineral density.

The main indication for MHT is relief of menopausal symptoms. Many women have no difficulty abruptly stopping MHT; others develop vasomotor symptoms after discontinuation. Although these symptoms may be mild and resolve over a few months, in some women the symptoms are severe and intolerable. There is no evidence that gradual discontinuation of MHT reduces the recurrence of hot flashes compared with sudden discontinuation.[14]

CONCLUSION

Menopause is a natural life event—not a disease. Therefore, the decision to use MHT must be individualized based on the severity of menopausal symptoms and the risk for cardiovascular disease, breast cancer, thromboembolism, and

osteoporotic fracture (Table 98-9).

TABLE 98-9 Evidence-Based Hormone Therapy Guidelines for Menopausal Symptom Management

Recommendation	Recommendation Level
In the absence of contraindications, estrogen-based postmenopausal hormone therapy should be used for treatment of moderate-to-severe vasomotor symptoms	Level 1
Systemic or vaginal estrogen therapy may be used for treatment of urogenital symptoms and vaginal atrophy. However, if a patient is only experiencing bothersome GSM, low-dose vaginal estrogen therapy is recommended as first-line therapy before systemic therapy	Level 1
The type of MHT, dose, formulation, route of administration, and duration of use should be carefully considered to meet individual treatment goals for a patient. Periodic reassessment of therapy should consider changes in a woman's health, and ongoing risks and benefits of the current therapy strategy	Level 3
Postmenopausal women taking estrogen-based therapy should be informed about potential risks. Benefits likely outweigh risks of initiating MHT for symptomatic women younger than 60 years of age or within 10 years of menopause onset	Level 1
Studies demonstrate varying risks for estrogen-only therapy and estrogen and progestin therapy (eg, breast cancer risk)	Level 2
Appropriate counseling and a decision regarding duration of MHT use includes assessment of a woman's risk (personal and familial) for hormone sensitive cancer, osteoporosis, stroke, venous thromboembolism, and coronary heart disease	Level 3
Endometrial protection is required for women with an intact uterus using systemic estrogen therapy. An adequate dose and duration of progestogen or combined estrogen and progestogen or CEE with bazedoxifene is recommended to avoid endometrial hyperplasia	Level 1
Progestogen therapy is not recommended with use of low dose (local) vaginal estrogen therapy.	Level 1
Lower doses or switching to transdermal delivery of hormone therapy may be considered as a woman ages or develops hypertriglyceridemia	Level 3
Compounded bioidentical hormone therapy is not recommended due to safety concerns regarding dosing, lack of studies demonstrating safety and efficacy	Level 1

North American Menopause Society's Level of Recommendation14: Level 1, based on good and consistent scientific evidence; Level 2, based on limited or inconsistent scientific evidence; Level 3, based primarily on consensus and expert opinion.

CEE, conjugated equine estrogen; GSM, Genitourinary Syndrome of Menopause; MHT, menopausal hormone therapy.

The WHI trial reported increased risk of cardiovascular disease, breast cancer, stroke, and thromboembolic disease among women using continuous combined therapy with CEE plus MPA compared with placebo. In the estrogen-alone arm of the study, CEE had no effect on cardiovascular disease or breast cancer risk compared to placebo, but an increased risk of stroke and thromboembolic disease was noted in those who received estrogen. The WHI trial also demonstrated that quality of life and cognition were no better in the group receiving MHT than in the placebo group, and that MHT increases dementia risk in women 65 years or older. Recent studies suggest dose, duration, and timing

(early or late menopause) of therapy may alter the benefit-risk profile and should be considered for individual patients.

In the absence of contraindications, MHT is the most effective treatment for managing postmenopausal symptoms, such as hot flashes, night sweats, and vaginal dryness. For many women, the benefits of short-term use of MHT for the relief of menopausal symptoms, far outweighs any risks. For symptoms of genital atrophy alone, the use of local, nonsystemic estrogen, nonhormonal lubricants and moisturizers, or ospemifene should be considered.

Long-term use of MHT cannot be recommended routinely for osteoporosis prevention given the availability of alternative therapies, such as bisphosphonates. For long-term MHT use, the potential harm (cardiovascular disease, breast cancer, and thromboembolism) outweighs the potential benefits. MHT should not be used for prevention of CHD. Women with cardiovascular risk factors (eg, hypertension and lipid abnormalities) can benefit from reduction of these risk factors through interventions such as weight loss, lipid-lowering therapy, use of aspirin, and physical activity.

Postclass Engaged Learning Activity

A patient asks for your advice regarding the symptoms she is experiencing due to menopause. She is considering her treatment options. What questions do you have for the patient? How would you identify the best treatment strategy for her?

ABBREVIATIONS

AUB	abnormal uterine bleeding
AMH	anti-Mullerian hormone
BMD	bone mineral density
CBHT	compounded bioidentical hormone therapy
CEE	conjugated equine estrogens
CHD	coronary heart disease
FMP	final menstrual period
FSH	follicle-stimulating hormone
GI	gastrointestinal

GnRH	gonadotropin-releasing hormone
GSM	genitourinary syndrome of menopause
HDL	high-density lipoprotein
HR	hazard ratio
LDL	low-density lipoprotein
LH	luteinizing hormone
MHT	menopausal hormone therapy
MPA	medroxyprogesterone acetate
NETA	norethindrone acetate
o-CEE	oral conjugated equine estrogens
SERM	selective estrogen receptor modulator
STRAW	Stages of Reproductive Aging Workshop
TSEC	tissue-selective estrogen complex
VTE	venous thromboembolism
WHI	Women's Health Initiative
WHIMSY	Women's Health Initiative Memory Study of Younger Women

REFERENCES

1. Shifren JL, Gass ML. The North American Menopause Society recommendations for clinical care of midlife women. *Menopause*. 2014;21:1038–1062.
2. Takahashi TA, Johnson KM. Menopause. *Med Clin North Am*. 2015;99:521–534.
3. Harlow SD, Gass M, Hall JE, et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: Addressing the unfinished agenda of staging reproductive aging. *J Clin Endocrinol Metab*. 2012;97:1159–1168.
4. Freeman EW, Sammel MD, Lin H, Gracia CR. Anti-mullerian hormone as a predictor of time to menopause in late reproductive age women. *J Clin Endocrinol Metab*. 2012;97:1673–1680.
5. Burger HG. The endocrinology of the menopause. *J Steroid Biochem Mol Biol*. 1999;69:31–35.
6. Avis NE, Crawford SL, Green R. Vasomotor symptoms across the menopause transition: Differences among women. *Obstet Gynecol Clin North Am*. 2018;45:629–640.

7. Gartoulla P, Worsley R, Bell RJ, Davis SR. Moderate to severe vasomotor and sexual symptoms remain problematic for women aged 60 to 65 years. *Menopause*. 2015;22:694–701.
8. Mishra GD, Kuh D. Health symptoms during midlife in relation to menopausal transition: British prospective cohort study. *BMJ*. 2012;344:e402.
9. Thornton K, Chervenak J, Neal-Perry G. Menopause and sexuality. *Endocrinol Metab Clin North Am*. 2015;44:649–661.
10. Portman DJ, Gass ML. Vulvovaginal Atrophy Terminology Consensus Conference Panel. Genitourinary syndrome of menopause: New terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. *Menopause*. 2014;21:1063–1068.
11. Shifren JL, Zincavage R, Cho EL, et al. Women's experience of vulvovaginal symptoms associated with menopause. *Menopause*. 2018;26(4):341–349.
12. Maki PM, Kornstein SG, Joffe H, et al. Guidelines for the evaluation and treatment of perimenopausal depression: Summary and recommendations. *Menopause*. 2018;25:1069–1085.
13. Manson JE, Chlebowski RT, Stefanick ML et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA*. 2013;310:1353–1368.
14. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24:728–753.
15. North American Menopause Society. Nonhormonal management of menopause-associated vasomotor symptoms: 2015 Position statement of The North American Menopause Society. *Menopause*. 2015;22:1155–1172.
16. Stuenkel CA, Davis SR, Gompel A, et al. Treatment of symptoms of the menopause: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2015;100:3975–4011.
17. Cobin RH, Goodman NF. American Association of Clinical Endocrinologists and American College of Endocrinology Position Statement on Menopause-2017 Update. *Endocr Pract*. 2017;23:869–880.
18. American College of Obstetrics and Gynecology. ACOG Practice Bulletin

No. 141: Management of menopausal symptoms. *Obstet Gynecol*. 2014;123:202–216. (Reaffirmed 2018).

19. North American Menopause Society. The North American Menopause Society statement on continuing use of systemic hormone therapy after age 65. *Menopause*. 2015;22:693.
20. North American Menopause Society. Management of symptomatic vulvovaginal atrophy: 2013 Position statement of The North American Menopause Society. *Menopause*. 2013;20:888–902.
21. Baber RJ, Panay N, Fenton A, et al.; International Menopause Society Writing Group. 2016 IMS recommendations on women's midlife health and menopause hormone therapy. *Climacteric*. 2016;19:109–150.
22. Santoro N, Braunstein GD, Butts CL, Martin KA, McDermott M, Pinkerton JV. Compounded bioidentical hormones in endocrinology practice: An Endocrine Society scientific statement. *J Clin Endocrinol Metab*. 2016;101:1318–1343.
23. de Villiers TJ, Hall JE, Pinkerton JV et al. Revised global consensus statement on menopausal hormone therapy. *Climacteric*. 2016;19:313–315.
24. Grossman DC, Curry SJ, Owens DK et al. Hormone therapy for the primary prevention of chronic conditions in postmenopausal women: US Preventive Services Task Force recommendation statement. *JAMA*. 2017;318:2224–2233.
25. Archer DF, Goldstein SR, Simon JA, et al. Efficacy and safety of ospemifene in postmenopausal women with moderate-to-severe vaginal dryness: A phase 3, randomized, double-blind, placebo-controlled, multicenter trial. *Menopause*. 2019;26(6):–611. 621.
26. Crandall CJ, Hovey KM, Andrews CA, et al. Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the Women's Health Initiative Observational Study. *Menopause*. 2018;25:11–20.
27. Manson JE, Aragaki AK, Rossouw JE, et al. Menopausal hormone therapy and long-term all-cause and cause-specific mortality: The Women's Health Initiative randomized trials. *JAMA*. 2017;318:927–938.
28. Marjoribanks J, Farquhar C, Roberts H, Lethaby A, Lee J. Long-term hormone therapy for perimenopausal and postmenopausal women. *Cochrane Database Syst Rev*. 2017;1:CD004143.
29. Shufelt C, Bairey Merz CN, Pettinger MB, et al. Estrogen-alone therapy

and invasive breast cancer incidence by dose, formulation, and route of delivery: Findings from the WHI observational study. *Menopause*. 2018;25:985–991.

30. Muka T, Oliver-Williams C, Colpani V, et al. Association of vasomotor and other menopausal symptoms with risk of cardiovascular disease: A systematic review and meta-analysis. *PLoS One*. 2016;11:e0157417.
31. Koh KK, Jin DK, Yang SH, et al. Vascular effects of synthetic or natural progestagen combined with conjugated equine estrogen in healthy postmenopausal women. *Circulation*. 2001;103:1961–1966.
32. Schierbeck LL, Rejnmark L, Tofteng CL, et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: Randomised trial. *BMJ*. 2012;345:e6409.
33. Bechlioulis A, Naka KK, Kalantaridou SN, et al. Short-term hormone therapy improves sCD40L and endothelial function in early menopausal women: Potential role of estrogen receptor polymorphisms. *Maturitas*. 2012;71:389–395.
34. Harman SM, Black DM, Naftolin F, et al. Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: A randomized trial. *Ann Intern Med*. 2014;161:249–260.
35. Hodis HN, Mack WJ, Henderson VW, et al. Vascular effects of early versus late postmenopausal treatment with estradiol. *N Engl J Med*. 2016;374:1221–1231.
36. Keaney JF Jr, Solomon CG. Postmenopausal hormone therapy and atherosclerosis: Time is of the essence. *N Engl J Med*. 2016;374:1279–1280.
37. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;129:S49–S73.
38. Breast cancer risk in American women. National Cancer Institute Website. Available at: https://www.cancer.gov/types/breast/risk-fact-sheet. Accessed February 14, 2019.
39. Beral V, Gaitskell K, Hermon C, Moser K, Reeves G, Peto R. Collaborative Group on Epidemiological Studies of Ovarian Cancer. Menopausal hormone use and ovarian cancer risk: Individual participant meta-analysis of 52 epidemiological studies. *Lancet*. 2015;385:1835–1842.

40. Shi LF, Wu Y, Li CY. Hormone therapy and risk of ovarian cancer in postmenopausal women: A systematic review and meta-analysis. *Menopause*. 2016;23:417–424.
41. Lindsay R, Gallagher JC, Kleerekoper M, Pickar JH. Effect of lower doses of conjugated equine estrogens with and without medroxyprogesterone acetate on bone in early postmenopausal women. *JAMA*. 2002;287:2668–2676.
42. Lindsay R, Gallagher JC, Kleerekoper M, Pickar JH. Bone response to treatment with lower doses of conjugated estrogens with and without medroxyprogesterone acetate in early postmenopausal women. *Osteoporos Int*. 2005;16:372–379.
43. Hlatky MA, Boothroyd D, Vittinghoff E, Sharp P, Whooley MA. Quality-of-life and depressive symptoms in postmenopausal women after receiving hormone therapy: Results from the Heart and Estrogen/Progestin Replacement Study (HERS) trial. *JAMA*. 2002;287:591–597.
44. Ott A, Breteler MM, van Harskamp F, Stijnen T, Hofman A. Incidence and risk of dementia. The Rotterdam Study. *Am J Epidemiol*. 1998;147:574–580.
45. Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women. The Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA*. 2003;289(20):2651–2662.
46. Espeland MA, Rapp SR, Shumaker SA et al. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. *JAMA*. 2004;291:2959–2968.
47. Shumaker SA, Legault C, Kuller L et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA*. 2004;291:2947–2958.
48. Espeland MA, Shumaker SA, Leng I et al. Long-term effects on cognitive function of postmenopausal hormone therapy prescribed to women aged 50 to 55 years. *JAMA Intern Med*. 2013;173:1429–1436.
49. Gleason CE, Dowling NM, Wharton W, et al. Effects of hormone therapy on cognition and mood in recently postmenopausal women: Findings from the randomized, controlled KEEPS-Cognitive and Affective Study. *PLoS Med*. 2015;12:e1001833. Discussion e1001833.
50. Espeland MA, Hogan PE, Fineberg SE et al. Effect of postmenopausal

hormone therapy on glucose and insulin concentrations. PEPI Investigators. Postmenopausal Estrogen/Progestin Interventions. *Diabetes Care*. 1998;21:1589–1595.

51. Kanaya AM, Herrington D, Vittinghoff E et al. Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/progestin Replacement Study. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 2003;138:1–9.
52. Margolis KL, Bonds DE, Rodabough RJ et al. Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. *Diabetologia*. 2004;47:1175–1187.
53. Norman RJ, Flight IH, Rees MC. Oestrogen and progestogen hormone replacement therapy for peri-menopausal and post-menopausal women: Weight and body fat distribution. *Cochrane Database Syst Rev*. 2000;CD001018.
54. Bachmann GA, Schaefers M, Uddin A, Utian WH. Lowest effective transdermal 17beta-estradiol dose for relief of hot flushes in postmenopausal women: A randomized controlled trial. *Obstet Gynecol*. 2007;110:771–779.
55. Haines C, Yu SL, Hiemeyer F, Schaefers M. Micro-dose transdermal estradiol for relief of hot flushes in postmenopausal Asian women: A randomized controlled trial. *Climacteric*. 2009;12:419–426.
56. Furness S, Roberts H, Marjoribanks J, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. *Cochrane Database Syst Rev*. 2012:CD000402.
57. Hitchcock CL, Prior JC. Oral micronized progesterone for vasomotor symptoms: A placebo-controlled randomized trial in healthy postmenopausal women. *Menopause*. 2012;19:886–893.
58. Prior JC, Hitchcock CL. Progesterone for hot flush and night sweat treatment: Effectiveness for severe vasomotor symptoms and lack of withdrawal rebound. *Gynecol Endocrinol*. 2012;28(suppl 2):7–11.
59. Casper RF. Estrogen with interrupted progestin HRT: A review of experimental and clinical studies. *Maturitas*. 2000;34:97–108.
60. Stute P, Neulen J, Wildt L. The impact of micronized progesterone on the endometrium: A systematic review. *Climacteric*. 2016;19: 316–328.
61. The Writing Group for the PEPI Trial. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The

Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA*. 1996;275:370–375.

62. American College of Obstetrics and Gynecologists Committee on Gynecologic Practice, American Society for Reproductive Medicine Practice Committee. Compounded bioidentical menopausal hormone therapy. *Fertil Steril*. 2012;98:308–312.
63. McBane SE, Borgelt LM, Barnes KN, Westberg SM, Lodise NM, Stassinos M. Use of compounded bioidentical hormone therapy in menopausal women: An opinion statement of the Women's Health Practice and Research Network of the American College of Clinical Pharmacy. *Pharmacotherapy*. 2014;34:410–423.
64. Bell RJ, Donath S, Davison SL, Davis SR. Endogenous androgen levels and well-being: Differences between premenopausal and postmenopausal women. *Menopause*. 2006;13:65–71.
65. Davis SR, Davison SL, Donath S, Bell RJ. Circulating androgen levels and self-reported sexual function in women. *JAMA*. 2005;294:91–96.
66. Wierman ME, Arlt W, Basson R, et al. Androgen therapy in women—a reappraisal: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2014;99:3489–3510.
67. Lebbe M, Hughes D, Reisch N, Arlt W. Androgen replacement therapy in women. *Expert Rev Endocrinol Metab*. 2012;7:515–529.
68. Portman DJ, Goldstein SR, Kagan R. Treatment of moderate to severe dyspareunia with intravaginal prasterone therapy: A review. *Climacteric*. 2019;22:65–72.
69. Ke Y, Labrie F, Gonthier R et al. Serum levels of sex steroids and metabolites following 12 weeks of intravaginal 0.50% DHEA administration. *J Steroid Biochem Mol Biol*. 2015;154:186–196.
70. Package insert. *Intrarosa (prasterone)*. Waltham, MA: AMAG Pharmaceuticals, Inc; 2018.
71. Santen RJ, Kagan R, Altomare CJ, Komm B, Mirkin S, Taylor HS. Current and evolving approaches to individualizing estrogen receptor-based therapy for menopausal women. *J Clin Endocrinol Metab*. 2014;99:733–747.
72. Package insert. *Evista (raloxifene)*. Indianapolis, IN: Lilly USA; 2018.
73. Palacios S, Mejia Rios A, Bazedoxifene/conjugated estrogens combination for the treatment of the vasomotor symptoms associated with menopause and for prevention of osteoporosis in postmenopausal women. *Drugs*

Today (Barc). 2015;51:107–116.

74. Mirkin S, Komm B, Pickar JH. Conjugated estrogen/bazedoxifene tablets for the treatment of moderate-to-severe vasomotor symptoms associated with menopause. *Womens Health*. 2014;10:135–146.
75. Pinkerton JV, Abraham L, Bushmakin AG et al. Evaluation of the efficacy and safety of bazedoxifene/conjugated estrogens for secondary outcomes including vasomotor symptoms in postmenopausal women by years since menopause in the Selective estrogens, Menopause and Response to Therapy (SMART) trials. *J Womens Health*. 2014;23:18–28.
76. Package insert. *Osphena (ospemifene)*. Bryn Mawr, PA, USA: Duchesnay; 2019 January.
77. Package insert. *Duavee (conjugated estrogens/bazedoxifene)*. Philadelphia, PA: Pfizer; 2017.
78. Cummings SR, Ettinger B, Delmas PD et al. The effects of tibolone in older postmenopausal women. *N Engl J Med*. 2008;359:697–708.
79. Nijland EA, Weijmar Schultz WC, Nathorst-Boos J, et al. Tibolone and transdermal E2/NETA for the treatment of female sexual dysfunction in naturally menopausal women: Results of a randomized active-controlled trial. *J Sex Med*. 2008;5:646–656.
80. Kenemans P, Bundred NJ, Foidart JM, et al. Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: A double-blind, randomised, non-inferiority trial. *Lancet Oncol*. 2009;10:135–146.
81. Christodoulakos GE, Lambrinoudaki IV, Panoulis CP, Papadias CA, Kouskouni EE, Creatsas GC. Effect of hormone replacement therapy, tibolone and raloxifene on serum lipids, apolipoprotein A1, apolipoprotein B and lipoprotein(a) in Greek postmenopausal women. *Gynecol Endocrinol*. 2004;18:244–257.
82. Beral V, Bull D, Reeves G. Endometrial cancer and hormone-replacement therapy in the Million Women Study. *Lancet*. 2005;365:1543–1551.
83. Langer RD, Landgren BM, Rymer J, Helmond FA. Effects of tibolone and continuous combined conjugated equine estrogen/medroxyprogesterone acetate on the endometrium and vaginal bleeding: Results of the OPAL study. *Am J Obstet Gynecol*. 2006;195:1320–1327.
84. Rietjens I, Louisse J, Beekmann K. The potential health effects of dietary phytoestrogens. *Br J Pharmacol*. 2017;174:1263–1280.
85. Lethaby A, Marjoribanks J, Kronenberg F, Roberts H, Eden J, Brown J. Phytoestrogens for menopausal vasomotor symptoms. *Cochrane Database*

Syst Rev. 2013:CD001395.

86. Franco OH, Chowdhury R, Troup J, et al. Use of plant-based therapies and menopausal symptoms: A systematic review and meta-analysis. *JAMA*. 2016;315:2554–2563.
87. Lissin LW, Cooke JP. Phytoestrogens and cardiovascular health. *J Am Coll Cardiol*. 2000;35:1403–1410.
88. Tempfer CB, Froese G, Heinze G, Bentz EK, Hefler LA, Huber JC. Side effects of phytoestrogens: A meta-analysis of randomized trials. *Am J Med*. 2009;122:939–946. e9.
89. National Institutes of Health Office of Dietary Supplements. Dietary supplements fact sheet: Black cohosh. Updated August 30, 2018. Available at: http://ods.od.nih.gov/factsheets/BlackCohosh-HealthProfessional. Accessed January 5, 2019.
90. Nedrow A, Miller J, Walker M, Nygren P, Huffman LH, Nelson HD. Complementary and alternative therapies for the management of menopause-related symptoms: A systematic evidence review. *Arch Intern Med*. 2006;166:1453–1465.
91. Ettinger B. Vasomotor symptom relief versus unwanted effects: Role of estrogen dosage. *Am J Med*. 2005;118(suppl 12B):74–78.

SECTION 12 UROLOGIC DISORDERS

99

Erectile Dysfunction

Mary Lee and Roohollah Sharifi

KEY CONCEPTS

1. The incidence of erectile dysfunction is low in men younger than 40 years of age. The incidence increases as men age likely as a result of concurrent medical conditions that impair the vascular, neurologic, psychogenic, and hormonal systems necessary for a normal penile erection.
2. Many commonly used drugs have sympatholytic, anticholinergic, sedative, or antiandrogenic effects that may exacerbate or contribute to the development of erectile dysfunction. Clinicians should be familiar with these agents and be prepared to make adjustments in drug regimens to minimize adverse effects of these drugs on a patient's erectile function.
3. The first step in clinical management of erectile dysfunction is to identify and, if possible, reverse the underlying causes. Risk factors for erectile dysfunction, including hypertension, diabetes mellitus, smoking, and chronic ethanol abuse, should be addressed and minimized.
4. Specific treatments for erectile dysfunction include vacuum erection devices (VEDs), pharmacologic treatments, psychotherapy, and surgery. Of these, phosphodiesterase type 5 inhibitors are the medications of first choice.
5. The ideal treatment of erectile dysfunction should have a fast onset, be effective, be convenient to administer, be cost effective, have a low incidence of serious adverse effects, and be free of serious drug interactions.
6. Specific treatment is first initiated with the least invasive forms of treatment, including VEDs or oral phosphodiesterase type 5 inhibitors, followed by intracavernosal injections or intraurethral inserts, and finally by surgical insertion of a penile prosthesis.

7. Vacuum erection devices can have a slow onset of action (up to 20 minutes) during initial use and are not discreet; therefore, they are most effective for a couple in a stable relationship.
8. Although phosphodiesterase type 5 inhibitors are convenient and effective regardless of the etiology of erectile dysfunction, they fail in 30% to 40% of patients. Also, phosphodiesterase type 5 inhibitors are contraindicated in patients taking any dosage formulation of nitrate.
9. Testosterone supplementation should be reserved for patients with primary, secondary, or mixed hypogonadism who have erectile dysfunction. Testosterone supplementation should not be used by patients with erectile dysfunction who have normal serum testosterone levels.
10. Although intracavernosal injections and intraurethral pellets of alprostadil are effective and independent of the etiology of erectile dysfunction, they fail in up to one-third of patients. To self-administer medication by these routes, patients require training to minimize administration-related adverse effects.

Preclass Engaged Learning Activity

Many medications may cause or worsen erectile dysfunction. Based on the physiology of a normal erection, create a table in which you identify various classes of medications that interfere with the hormonal, vascular, neurologic, or psychogenic factors that are essential for a normal penile erection. In a separate column, identify medications that are less likely to interfere with those physiologic factors and therefore have a lower propensity to cause erectile dysfunction.

INTRODUCTION

The National Institutes of Health Consensus Development Panel on Impotence[1] and the Fourth International Consultation on Sexual Medicine[2] define erectile dysfunction as the persistent or recurrent failure to achieve or maintain a penile erection to allow for satisfactory sexual intercourse. A persistent failure generally refers to erectile dysfunction for a minimum of 3 months. Patients may refer to the condition as impotence. Erectile dysfunction must be distinguished

from disorders of libido or ejaculation, and of infertility, all of which are caused by different pathophysiologic mechanisms and are treated with alternative agents (Table 99-1). A patient may have one or more disorders of sexual and reproductive function. For example, an older man with primary hypogonadism could have both decreased libido and erectile dysfunction. Diagnosis of the type of such disorders in patients is key to initiating the most appropriate treatment.

TABLE 99-1 Types of Sexual Dysfunction in Men

Type of Dysfunction	Definition
Decreased libido	Decreased sexual drive or desire
Increased libido	Inappropriate and excessive sexual drive or desire
Erectile dysfunction (impotence)	Failure to achieve a penile erection suitable for satisfactory sexual intercourse
Delayed ejaculation/ anejaculation	Commonly referred to as "dry sex"; ejaculation is delayed or absent
Retrograde ejaculation	Ejaculate passes retrograde into the bladder, instead of toward the anterior urethra (antegrade) and out of the penis
Infertility	Sperm are insufficient in number, have abnormal morphology, or have inadequate motility, and fail to fertilize the ovum

EPIDEMIOLOGY

1 The incidence of erectile dysfunction is low in men younger than 40 years of age, but increases as men age. The Massachusetts Male Aging Study, a cross-sectional survey of a random sample of 1,290 men in the Boston area, was conducted during the period from 1987 to 1989. The study reported an overall prevalence of 52% for any degree of erectile dysfunction in men aged 40 to 70 years, with an age-related increase in incidence ranging from 12.4 cases per 1,000 men per year in men aged 40 to 49 years, up to 46.4 cases per 1,000 men per year in men aged 60 to 69 years.[3] In men older than 70 years, the prevalence of erectile dysfunction increases and has been reported to be as high as 80%, depending on the population studied.[3] In the Health Professional Follow-Up Study of more than 31,000 male health professionals aged 53 to 90 years, the prevalence of erectile dysfunction was 33%.[4] Interestingly, although the prevalence of erectile dysfunction increases with patient age, many patients fail

to seek medical treatment.[5–7] This may be due to the decrease in sexual activity as males age from 57 years to 85 years.[7,8]

Erectile dysfunction is sometimes assumed to be a symptom of the aging process in men. However, more likely it results from concurrent medical conditions of the patient (eg, hypertension, arteriosclerosis, hyperlipidemia, diabetes mellitus, metabolic syndrome, or psychiatric disorders) or from medications that patients may be taking for these diseases.[1–3,5] For example, up to 50% of patients with diabetes mellitus develop erectile dysfunction, and medications such as diuretics are associated with a high incidence of erectile dysfunction.

PHYSIOLOGY OF A NORMAL PENILE ERECTION

A normal penile erection requires full functioning of several physiologic systems: vascular, nervous, and hormonal. The patient also must be psychologically receptive to sexual stimuli.[9]

Vascular System

The penis comprises two corpora cavernosa on the dorsal side and one corpus spongiosum on the ventral side. The corpus spongiosum surrounds the urethra and forms the glans penis. The corpora are composed of multiple interconnected sinuses, which can fill with blood to produce an erection. The corpora cavernosa are encased by the tunica albuginea, a fibrous tissue membrane, which has limited distensibility. In the flaccid state, arterial flow into and venous outflow from the corpora are balanced. During the erectile phase, arterial blood flow increases and blood fills the sinusoids within the corpora. Blood traps in the corpora as the outflow of the subtunical veins is compressed against the tunica albuginea. This prolongs the erection. (**Fig. 99-1**).

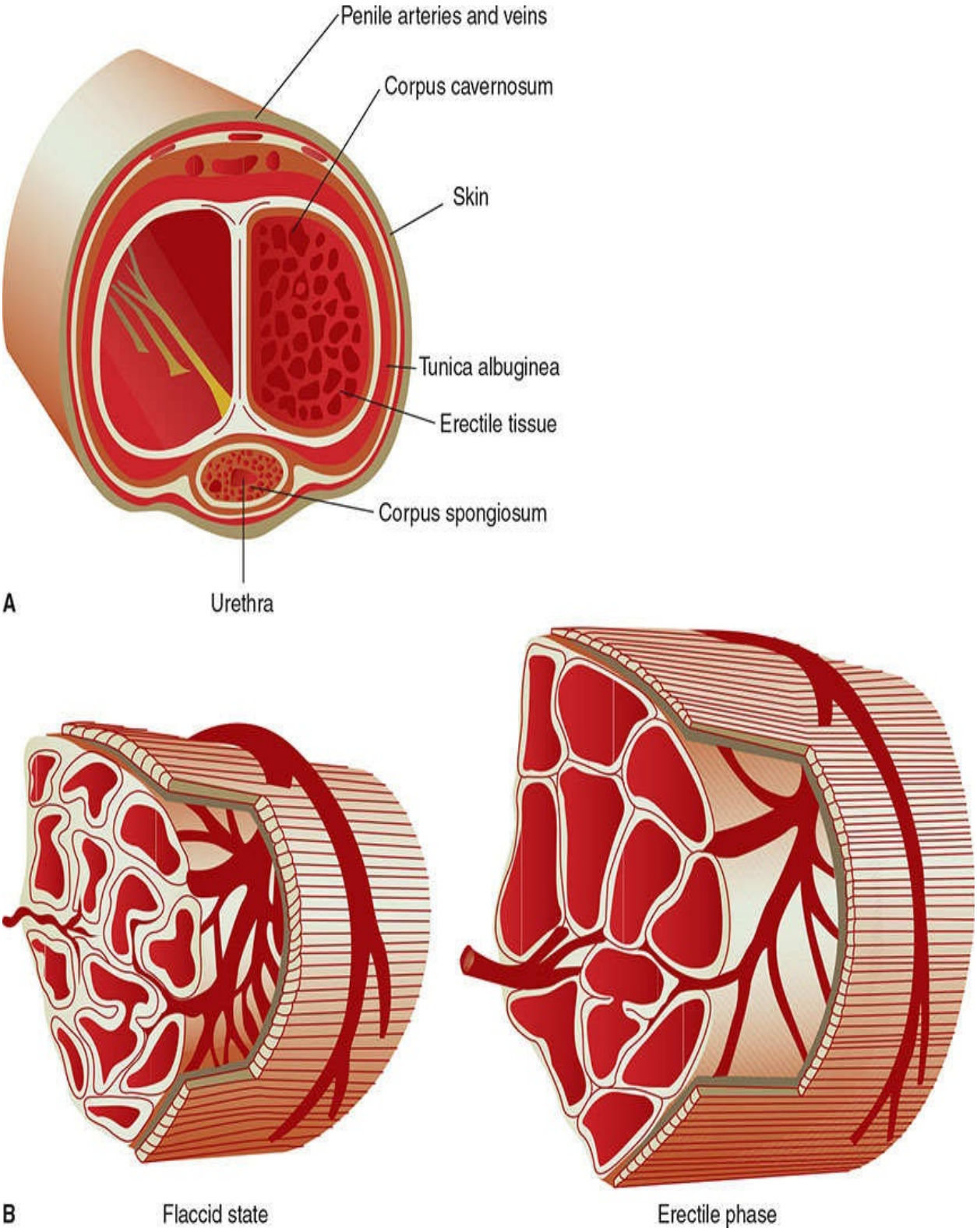


FIGURE 99-1 Microanatomy of and vascular changes in the penis in flaccid and erect states. In the flaccid state, arterial flow into and venous outflow from the corpora are balanced. During the erectile phase, arterial blood flow increases and

blood fills the sinusoids within the corpora, causing penile swelling and elongation. The erection is prolonged by a decrease in venous outflow from the corpora, which is caused by compression of subtunical venules by the swollen corpora. (*Reprinted with permission from Walsh PC, ed. Campbell's Urology, 8th ed. Philadelphia, PA: WB Saunders; 2002:1595, 1697. Copyright © 2002 from Elsevier.*)

Arterial flow into the corpora is enhanced by acetylcholine-mediated vasodilation. Acetylcholine indirectly enhances arterial flow to the corpora and increases sinusoidal filling of the corporal tissue. That is, acetylcholine is a co-neurotransmitter, which works along with other nonpeptidergic intracellular neurotransmitters— including cyclic guanosine monophosphate (cGMP), cyclic adenosine monophosphate (cAMP), or vasoactive intestinal polypeptide—to produce vasodilation. In effect, cGMP and cAMP are secondary messengers that direct desired effects in target tissues.

Specifically, acetylcholine produces an erection probably through two different pathways. Through one pathway, in the presence of sexual stimulation to genital tissue, acetylcholine enhances the production of nitric oxide by endothelial cells and nonadrenergic–noncholinergic neurons. Nitric oxide enhances the activity of guanylate cyclase, which increases the conversion of cyclic guanosine triphosphate to cGMP. cGMP activates a cGMP-dependent kinase, which decreases intracellular calcium concentrations in smooth muscle cells of penile arteries and cavernosal sinuses. As a result, smooth muscle relaxation occurs, which enhances arterial blood flow to and blood filling of the corpora.[9] An erection results.

In an alternative pathway, acetylcholine or prostaglandin E enhances the activity of adenyl cyclase, which increases the conversion of cyclic adenosine triphosphate to cAMP, a potent muscle relaxant. Similar to cGMP, cAMP decreases intracellular calcium concentrations to produce smooth muscle relaxation in cells of the arteries and cavernosal sinuses. Arterial blood flow to and blood filling of the corpora are enhanced, and a penile erection results.[9]

Nervous System and Psychogenic Stimuli

Some erections are mediated by a sacral nerve reflex arc (eg, erections can occur while the patient is sleeping). However, in the conscious patient, sensory sexual stimulation mediates erections via the central nervous system (CNS). That is, when a patient sees an attractive partner, hears sweet words, smells a particular scent, or tastes or touches a pleasant object, these situations can result in an

erection. In this case, the patient's brain processes this information and the nervous impulse is carried down the spinal cord to peripheral cholinergic nerves that innervate the vascular supply to the corpora, resulting in an erection.

The medial preoptic area of the hypothalamus is thought to be that portion of the brain responsible for integrating external stimuli. Here dopamine exerts a proerectogenic effect, whereas, α_2-adrenergic stimulation causes the penis to become and/or remain flaccid. After moving down the spinal cord, stimulatory nerve impulses travel to the penis by efferent peripheral nerves, including inhibitory sympathetic neurons (T_{11}-L_2), proerectogenic parasympathetic neurons (S_2-S_4), and proerectogenic somatic neurons (S_2-S_4).

In short, acetylcholine produces an erection by working along with other co-neurotransmitters, including cGMP and cAMP. Thus, an erection is mediated neurologically, maintained by arterial blood filling of the corpora, and sustained by occlusion of venous outflow from the corpora.

Detumescence, or the progression of an erect penis to a flaccid state, results from the actions of norepinephrine, which contracts vascular smooth muscle to decrease arterial inflow to the corpora and contracts sinusoidal tissue in the corpora. As a result, venous outflow from the corpora increases.

Hormonal System

Testosterone is principally produced by the testes at a daily rate of 4 to 8 mg and a normal physiologic serum concentration is 300 to 1,100 ng/dL (10.4-38.2 nmol/L). Production follows a circadian pattern with highest blood levels in the morning and lowest levels in the evening. Physiologically active (free) testosterone comprises only 2% of circulating blood levels. About 44% of testosterone in the bloodstream is tightly bound to sex hormone-binding globulin and is inactive. Approximately 50% is reversibly bound to albumin and 4% is reversibly bound to corticosteroid-binding globulin; both of these portions of testosterone are in equilibrium with the 2% of testosterone that is not bound. Thus, the bioavailable portion of testosterone is normally 56% and comprises testosterone bound to albumin and corticosteroid-binding globulin and the unbound, or free, portion.[10] However, the bioavailable percentage of testosterone can vary considerably with changes in sex hormone-binding globulin. Sex hormone-binding globulin increases with aging, hyperthyroidism, human immunodeficiency virus disease, and hepatic cirrhosis; and decreases with obesity, diabetes mellitus, hypothyroidism, nephrotic syndrome, and corticosteroid use.[10]

Testosterone stimulates libido (sexual drive) and increases muscle mass in males. In addition, androgen receptors have been identified in the penile arterial endothelium and are thought to increase cavernosal levels of nitric oxide and cGMP, thereby enhancing vascular processes essential for a penile erection.[9,11] In addition, androgens may enhance phosphodiesterase type 5 activity and may improve cavernosal nerve function.[12] In some target cells with 5-α reductase, testosterone is activated to dihydrotestosterone. Dihydrotestosterone, which is more potent than testosterone, stimulates prostate gland growth, increases facial and body hair, induces baldness, and causes acne. In adipose tissue, a small portion of testosterone is converted to estradiol that can lead to gynecomastia.

Beginning at age 40 years, men experience a gradual decrease in testicular production of testosterone, with an associated decrease in muscle mass and sexual function.[11] The Massachusetts Male Aging Study reported that 6% to 12% of elderly males had symptoms of hypogonadism.[3] The European Male Aging Study described three cardinal symptoms of low serum testosterone levels: decreased libido, erectile dysfunction, and loss of spontaneous morning erections.[12] Other symptoms include fatigue, malaise, depressed mood, decreased bone density, increased fat:muscle ratio, gynecomastia, anemia, and insulin resistance.

Within the normal physiologic serum total testosterone concentration, sexual drive is usually normal. Because of variability in circulating levels of sex hormone-binding globulin and the lack of precision of available assays,[10] a patient's serum concentration of testosterone should always be interpreted in the context of the patient's symptoms and physical exam findings. To confirm hypogonadism two serum total testosterone concentrations should be obtained on different days, or a serum-free (bioavailable) testosterone concentration could be obtained after an initial low or equivocal serum total testosterone level.[13–15]

The relationship between erectile dysfunction and serum testosterone levels is complicated. Patients with normal serum testosterone levels may have erectile dysfunction, and patients with subnormal serum testosterone levels may have normal sexual function.[14,15] When a patient has hypogonadism and libido is decreased, a patient may not develop erections. In this case, erectile dysfunction is considered secondary to a decreased libido.

As a result, although the Food and Drug Administration (FDA) defines hypogonadism as when the serum testosterone concentration is less than 300 ng/dL (10.4 nmol/L) in an adult man, treatment is indicated only in patients who have symptoms or signs of hypogonadism. Similarly, the European Association of Urology and the American Society of Andrology guidelines state that a serum

testosterone greater than 350 ng/dL (12.2 nmol/L) requires no treatment, a serum testosterone of 230 to 350 ng/dL (8.0-12.2 nmol/L) requires treatment if the patient is symptomatic, and a serum testosterone below 230 ng/dL (8.0 nmol/L) generally should be treated.[11,15]

ETIOLOGY/PATHOPHYSIOLOGY

Erectile dysfunction can result from any single abnormality or combination of abnormalities of the four systems necessary for a normal penile erection. Vascular, neurologic, or hormonal etiologies of erectile dysfunction are collectively referred to as *organic erectile dysfunction*. Approximately 80% of patients with erectile dysfunction have the organic type. Patients who do not respond to psychogenic stimuli and have no organic cause for dysfunction have *psychogenic erectile dysfunction*.[14]

Diseases that compromise vascular flow to the corpora cavernosum (eg, peripheral vascular disease, arteriosclerosis, and essential hypertension) comprise the most common causes of organic erectile dysfunction.[16] Diseases that impair nerve conduction to the brain (eg, spinal cord injury or stroke) or conditions that impair peripheral nerve conduction to the penile vasculature (eg, diabetes mellitus) can result in erectile dysfunction.

Diseases associated with hypogonadism, primary, secondary, or mixed, result in subphysiologic levels of testosterone, which cause diminished sexual drive (decreased libido) and secondary erectile dysfunction. Primary hypogonadism occurs with surgical removal of the testes for treatment of prostate or testicular cancer, or with testicular injury or disease. Secondary hypogonadism may result from hypothalamic or pituitary disorders of luteinizing hormone-releasing hormone or luteinizing hormone, respectively; or elevated prolactin levels, which can be associated with pituitary tumors or can occur in patients with chronic renal failure. In aging males, the etiology of hypogonadism is mixed. In addition to decreased Leydig cell function in the testes, the release of gonadotropin from the hypothalamus is reduced, the circadian pattern of luteinizing hormone release from the pituitary gland is impaired, and sex hormone-binding globulin production increases.[15]

Patients must be in the proper mental frame of mind to be receptive to sexual stimuli. Patients who suffer from malaise, have reactive depression or performance anxiety, are sedated, or have Alzheimer’s disease, hypothyroidism, or mental disorders commonly complain of erectile dysfunction. In most studies, patients with psychogenic erectile dysfunction generally exhibit a higher

response rate to various interventions than do patients with organic erectile dysfunction because the former have less severe disease.

Social habits of patients have been linked to erectile dysfunction. The vasoconstrictor effect of cigarette smoking may compromise blood flow to the corpora and decrease cavernosal filling. Excessive ethanol intake may lead to androgen deficiency, peripheral neuropathy, or chronic liver disease, all of which can contribute to erectile dysfunction.

2 Medications may cause erectile dysfunction through similar pathophysiologic mechanisms (Table 99-2).16–19 Medications are responsible for approximately 10% to 25% of cases of erectile dysfunction.

TABLE 99-2 Medication Classes That Can Cause Erectile Dysfunction

Drug Class	Proposed Mechanism by Which Drug Causes Erectile Dysfunction	Special Notes
Anticholinergic agents (antihistamines, antiparkinsonian agents, tricyclic antidepressants, phenothiazines)	Anticholinergic activity	• Second-generation nonsedating antihistamines (eg, loratadine, fexofenadine, or cetirizine) are associated with less erectile dysfunction than first-generation agents. • Selective serotonin reuptake inhibitor (SSRI) and multiple receptor reuptake inhibitor antidepressants cause less erectile dysfunction than tricyclic antidepressants. Of the SSRIs, paroxetine, sertraline, fluvoxamine, and fluoxetine cause erectile dysfunction more commonly than venlafaxine, nefazodone, trazodone, bupropion, duloxetine, mirtazapine, escitalopram, or vilazodone.[12] • Phenothiazines with less anticholinergic effect (eg, chlorpromazine) can be substituted in some patients if erectile dysfunction is a problem.
Dopamine antagonists (eg, metoclopramide, phenothiazines)	Inhibit prolactin inhibitory factor, thereby increasing prolactin levels	• Increased prolactin levels inhibit testicular testosterone production; depressed libido results.
Estrogens or drugs with antiandrogenic effects (eg, luteinizing hormone-releasing hormone superagonists, digoxin, spironolactone, ketoconazole, cimetidine)	Suppress testosterone-mediated stimulation of libido	• In the face of a decreased libido, a secondary erectile dysfunction develops because of diminished sexual drive.[16]
CNS depressants (eg, barbiturates, narcotics, benzodiazepines, short-term use of large doses of alcohol, anticonvulsants)	Suppress perception of psychogenic stimuli	
Agents that decrease penile blood flow (eg, diuretics, peripheral β-adrenergic antagonists, or central sympatholytics [methyldopa, clonidine, guanethidine])	Reduce arteriolar flow to corpora	• Any diuretic that produces a significant decrease in intravascular volume can decrease penile arteriolar flow. • Safer antihypertensives include angiotensin-converting enzyme inhibitors, postsynaptic α_1-adrenergic antagonists (terazosin, doxazosin), calcium channel blockers, and angiotensin II receptor antagonists.[16,17,19]
Miscellaneous • Finasteride, dutasteride • Lithium carbonate • Gemfibrozil • Interferon • Clofibrate • Monoamine oxidase inhibitors (eg, phenelzine, isocarboxazid, tranylcypromine) • Opiates	Unknown mechanism	

Data from References 17-19.

DIAGNOSIS

With the availability in the late 1990s of effective medications for erectile dysfunction independent of the etiology, diagnostic evaluation of erectile dysfunction became streamlined. Key assessments include a description of the severity of erectile dysfunction, complete medical, psychosocial, and surgical histories, review of concurrent medications, physical examination, assessment of cardiac reserve, and selected clinical laboratory tests.[20]

To assess the severity of erectile dysfunction, the patient should be asked about the quality of sexual intercourse for the past 4 weeks to 6 months. A self-administered standardized questionnaire, such as the International Index of Erectile Function (IIEF), is often used. It is administered before initiation of any treatment and repeated at regular intervals during treatment. It includes 15 questions about the quality of sexual function and satisfactoriness of sexual intercourse.[21] Questions include the following: How often were you able to maintain an erection? How difficult was it to sustain an erection? How satisfied are you with your sexual life? The physician should carefully assess the expectations for erectile function of the patient and the partner to ensure that expectations are reasonable. Shorter versions of the IIEF and other self-reporting questionnaires are also used in clinical practice. For example, the IIEF-EF comprises the six questions from the IIEF that focus on erectile function. The patient responds to each question; each response is scored on a range of 1 to 5. A score of 26 to 30 is considered normal function, 19 to 25 is mild erectile dysfunction, 13 to 18 is mild-to-moderate erectile dysfunction, 7 to 12 is moderate erectile dysfunction, and 6 or less is severe erectile dysfunction.[21]

A medical history should be obtained to identify concurrent medical illnesses (eg, hypertension, atherosclerosis, hyperlipidemia, diabetes mellitus, and depression) or surgical procedures (eg, perineal or pelvic) that are risk factors for or are associated with organic or psychogenic erectile dysfunction. Underlying diseases that do not optimally respond to treatment should be addressed before specific treatment for erectile dysfunction is initiated. If the patient smokes cigarettes, drinks excessive amounts of ethanol, or uses recreational drugs, these social habits should be discontinued before specific treatment for erectile dysfunction is started.[20,22,23]

A complete listing of the patient's prescription and nonprescription medications and dietary supplements should be reviewed by the clinician, who should identify drugs that may be contributing to erectile dysfunction. If possible, causative agents should be discontinued or the dose should be reduced.

CLINICAL PRESENTATION Erectile Dysfunction

General

- Men are affected emotionally in many different ways.
- Depression.
- Performance anxiety.
- Marital difficulties and avoidance of sexual intimacy (patients are often brought to a physician by their partners).
- Nonadherence to medications that the patient believes are causing erectile dysfunction.

Symptoms

- Erectile dysfunction or inability to have sexual intercourse, which may or may not be associated with decreased libido and ejaculatory disorders.

Signs

- IIEF survey results are consistent with low satisfaction with the quality of erectile function.
- Medical history may identify concurrent medical illnesses or past surgical procedures that interfere with good vascular flow to the penis, damaged nerve function to the corpora, or mental disorders associated with decreased reception of sexual stimuli.
- Medication history may reveal prescription or nonprescription medications that could cause or contribute to erectile dysfunction.
- Physical examination may reveal signs of hypogonadism (eg, gynecomastia, small testicles, decreased body hair or beard, and decreased muscle mass), which may contribute to erectile dysfunction. The patient may have an abnormally curved penis when erect, decreased pulses in the pelvic region (suggesting impaired vascular flow to the penis), or decreased anal sphincter tone (suggesting impaired nerve function to the corpora). Men older than 50 years should undergo a digital rectal examination to determine whether an enlarged prostate is contributing to the patient’s erectile dysfunction.

Assessments

- Conduct IIEF-EF, a validated self-assessment questionnaire to assess the

severity of the patient's erectile dysfunction.

- Conduct an assessment of cardiac reserve based on the patient's medical history, signs and symptoms of cardiovascular disease, and treadmill testing, if indicated.

Laboratory Tests

- If the patient has signs of hypogonadism and complains of decreased libido, a serum testosterone concentration may be below the normal range, which would be consistent with a hormonal cause of erectile dysfunction. A low serum testosterone level should always be confirmed with a repeat blood level.
- If the patient has an enlarged prostate noted on digital rectal examination, a blood test for prostate specific antigen should be run. If elevated, the patient should be evaluated for a prostate disorder, which could contribute to erectile dysfunction.

A physical examination of the patient should include a check for hypogonadism (ie, signs of gynecomastia, small testicles, and decreased beard or body hair). The penis should be evaluated for diseases associated with abnormal penile curvature (eg, Peyronie's disease), which are associated with erectile dysfunction. Femoral and lower extremity pulses should be assessed to provide an indication of vascular supply to the genital area. Anal sphincter tone and other genital reflexes should be checked for the integrity of the nerve supply to the penis. A digital rectal examination in patients 50 years or older is needed to rule out benign prostatic hyperplasia, which may contribute to erectile dysfunction.

Erectile dysfunction is a potential marker for arteriosclerotic cardiovascular disease.[24] Sexual intercourse and orgasm require cardiac work equivalent to that needed to vigorously climb two flights of stairs or to walk approximately 1.5 km. In addition, erectogenic drugs may stress the heart.[25,26] For this reason, a patient's cardiac reserve should be assessed before initiating treatment for erectile dysfunction. According to the Princeton Consensus Conference guideline, the clinician should take a careful cardiovascular disease history and check for signs and symptoms of cardiovascular disease. Drug treatment for erectile dysfunction is recommended only in patients at low risk of cardiovascular events. Drug treatment should be avoided in patients at high risk of cardiovascular events. For patients at intermediate risk, treadmill testing is indicated; results will stratify patients into low- and high-risk groups, which

should be managed accordingly. The risk assessment is described in Table 99-3 and detailed in the Third Princeton Consensus Panel recommendations.[27]

TABLE 99-3 Recommendations of the Third Princeton Consensus Conference for Cardiovascular Risk Stratification of Patients Being Considered for Phosphodiesterase Inhibitor Therapy[27]

Risk Category	Description of Patient's Condition	Management Approach
Low risk	Has asymptomatic cardiovascular disease with <3 risk factors for cardiovascular disease Has well-controlled hypertension Has mild congestive heart failure (NYHA class I or II) Has mild valvular heart disease Has had a myocardial infarction >8 weeks ago	Patient can be started on phosphodiesterase inhibitor
Intermediate risk	Has ≥3 risk factors for cardiovascular disease Has mild or moderate, stable angina Had a recent myocardial infarction or stroke within the past 2-8 weeks Has moderate congestive heart failure (NYHA class III) History of stroke, transient ischemic attack, or peripheral artery disease	Patient should undergo complete cardiovascular workup and treadmill stress test to determine tolerance to increased myocardial energy consumption associated with increased sexual activity. Then, reclassify in low- or high-risk category
High risk	Has unstable or refractory angina, despite treatment Has uncontrolled hypertension Has severe congestive heart failure (NYHA class IV) Has had a recent myocardial infarction or stroke within past 2 weeks Has moderate or severe valvular heart disease Has high-risk cardiac arrhythmias Has obstructive hypertrophic cardiomyopathy	Phosphodiesterase inhibitor is contraindicated; sexual intercourse should be deferred

NYHA, New York Heart Association.

Reprinted with permission from Nehra A, Jackson G, Miner M, et al. The Princeton III Consensus Recommendations for the Management of Erectile Dysfunction and Cardiovascular Disease. Mayo Clin Proc. 2012;87(8):766-778.

Selected laboratory tests should be obtained to identify the presence of underlying diseases that could cause erectile dysfunction. They include a fasting serum blood glucose and lipid profile. Serum testosterone levels should be checked in patients older than 50 years and in younger patients who complain of decreased libido and erectile dysfunction. At least two early morning serum testosterone levels on different days, approximately 4 weeks apart, are needed to confirm the presence of hypogonadism.[28]

TREATMENT

Erectile Dysfunction

Desired Outcomes

The goal of treatment is to improve the quantity and quality of penile erections suitable for intercourse and considered satisfactory by the patient and his partner. Simple as this may sound, healthcare providers must ensure that patients and their partners have reasonable expectations for any therapies that are initiated. Furthermore, only patients with erectile dysfunction should be treated. Patients who have normal sexual function should not seek—or be encouraged to seek—treatment in an effort to enhance sexual function or enable increased activity. Objective measures of improvement include an increase in four points in the IIEF-EF score[5,21] or achievement of a total score of at least 20. In addition, treatment should be well tolerated and be of reasonable cost.

General Approach to Treatment

3 The Third Princeton Consensus Conference recommendations are a widely accepted multidisciplinary approach to managing erectile dysfunction that maps out a stepwise treatment plan.[27] This approach is based on the knowledge that erectile dysfunction and cardiovascular disease and its risk factors coexist in many patients, and that sexual intercourse can precipitate serious cardiovascular consequences in high-risk patients. The first step in clinical management of erectile dysfunction is to identify and, if possible, reverse underlying causes. Risk factors for erectile dysfunction, including hypertension, coronary artery disease, dyslipidemia, diabetes mellitus, smoking, or chronic ethanol abuse, should be addressed and minimized. Patients should follow a heart-healthy lifestyle, which includes physical fitness, weight loss to achieve a normal body mass index, low cholesterol diet, no excessive ethanol intake, and no smoking.[16,28,29] In some cases, these types of interventions are sufficient to restore erectile function. However, if erectile dysfunction does not respond to these measures, specific treatment is indicated.

For patients with psychogenic erectile dysfunction, psychotherapy can be used as monotherapy or as an adjunct to specific treatments for the disorder. To enhance the relevance of psychotherapy, both the patient and the partner should be included in the counseling sessions.[5,12] Treatment should be individualized and should address immediate factors that may be causing performance anxiety or depression. The effectiveness of psychotherapy is generally low, and long-term psychotherapy is often necessary.

4 5 6 Specific treatments of erectile dysfunction include vacuum

erection devices (VEDs), pharmacologic treatments, and surgery. The ideal treatment of this disorder should have a fast onset, be effective, be convenient to administer, be cost-effective, have a low incidence of serious adverse effects, and be free of serious drug interactions (Table 99-4). Generally, when choosing from among treatment approaches, those that are least invasive are selected first; more invasive therapies are reserved for patients who do not respond to first-line agents.

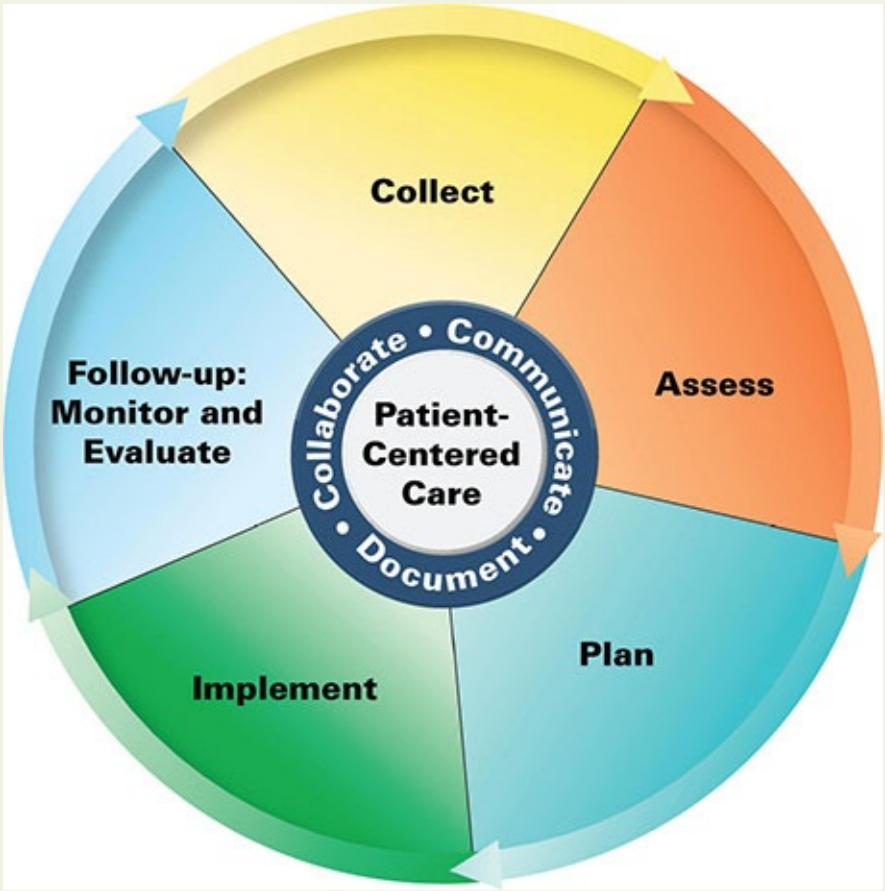
TABLE 99-4 Dosing Regimens for Selected Drug Treatments for Erectile Dysfunction

Drug	Brand Name®	Initial Dose	Usual Range	Special Population Dose	Other
Phosphodiesterase Inhibitor					
Sildenafil	Viagra	50 mg orally 1 hour before intercourse	25-100 mg 1 hour before intercourse. Limit to one dose per day	In patients age 65 years and older, start with 25 mg dose. In patients with creatinine clearance less than 30 mL/min (0.5 mL/s) or severe hepatic impairment, limit starting dose to 25 mg. In patients with mild-to-moderate hepatic impairment or those taking strong CYP3A4 inhibitors (eg, itraconazole, ketoconazole, or erythromycin), consider starting with 25 mg. In patients taking protease inhibitors, limit starting dose to 25 mg every 48 hours.	Generic formulations are available. Titrate dose so that erection lasts no more than 1 hour. High-fat foods decrease rate of absorption by 1 hour. Avoid taking dose with grapefruit juice. Contraindicated with nitrates by any route of administration.
Vardenafil	Levitra	5-10 mg orally 1 hour before intercourse	5-20 mg 1 hour before intercourse. Limit to one dose per day	In patients age 65 years and older, start with 5 mg Levitra. No dosage adjustment is required in patients with decreased creatinine clearance. In patients with moderate hepatic impairment, start with 5-mg Levitra. Use not recommended in patients with severe hepatic impairment. In patients taking strong P450 CYP3A4 inhibitors (eg, atazanavir, erythromycin, clarithromycin, ketoconazole, itraconazole), limit starting dose to 2.5 mg every 24 hours. In patients on ritonavir, limit dose to 2.5 mg every 72 hours. Not recommended in patients with congenital prolonged QT interval or in patients taking Type 1A or Type 3 antiarrhythmics.	Titrate dose so that erection lasts no more than 1 hour. High-fat foods decrease rate of absorption by 1 hour. Avoid taking dose with grapefruit juice. Contraindicated with nitrates by any route of administration.
	Staxyn	10-mg tablet to dissolve on the tongue 1 hour before intercourse	10-mg tablet to dissolve on the tongue 1 hour before intercourse. Limit to one dose per day	Dose of Staxyn requires no adjustment in patients 65 years or older, patients with creatinine clearance less than 30 mL/min (0.5 mL/s), or those with mild hepatic impairment. Do not use in patients with moderate or severe hepatic impairment or those taking moderately or highly potent P450 CYP3A4 inhibitors. Do not initiate Staxyn in patients taking α-adrenergic antagonists.	Staxyn should be taken without any liquid or food. The tablet should be placed on the tongue where it will dissolve. No up-titration of dose is recommended. Do not substitute Staxyn for Levitra, or vice versa.
Tadalafil	Cialis	5-10 mg orally at least 30 minutes before intercourse OR 2.5-5 mg orally once daily	10-20 mg at least 30 minutes before intercourse. Limit to one dose per day 2.5-5 mg once daily. Limit to one dose per day	Dose of tadalafil requires no dosage adjustment in patients 65 years or older. In patients with creatinine clearance of 30-50 mL/min (0.5-0.83 mL/s), limit starting dose to 10 mg every 48 hours; if less than 30 mL/min (0.5 mL/s), limit starting dose to 5 mg every 72 hours. In patients with mild-to-moderate hepatic impairment, limit starting dose to 10 mg every 24 hours. Do not use in patients with severe hepatic impairment. In patients taking potent P450 CYP3A4 inhibitors, limit starting dose to 10 mg every 72 hours (if using it on demand) or 2.5 mg daily (if using a continuous daily regimen).	Generic formulations are available. Titrate dose so that erection lasts not more than 1 hour. Food does not affect rate or extent of drug absorption. Avoid taking dose with grapefruit juice. Contraindicated with nitrates by any route of administration. When taken with large amounts of ethanol, tadalafil may cause orthostatic hypotension.
Avanafil	Stendra	100 mg orally 15-30 minutes before intercourse	50-200 mg orally 15-30 minutes before intercourse. Limit to one dose per day.	In patients with creatinine clearance of 30-89 mL/min (0.5-1.49 mL/s) or those with mild-to-moderate hepatic impairment, no dosage adjustment is needed. Not recommended if creatinine clearance is less than 30 mL/min (0.5 mL/s), if the patient has severe hepatic disease, or if the patient is taking potent P450 CYP3A4 inhibitors. If the patient is taking moderate P450 CYP3A4 inhibitors (eg, erythromycin, fluconazole), the maximum recommended dose is 50 mg every 24 hours.	May be taken with or without food. Avoid taking dose with grapefruit juice. When taken with large amounts of ethanol, avanafil may cause orthostatic hypotension.

Prostaglandin E_1					
Alprostadil intracavernosal injection	Caverject, Edex	2.5-mcg intracavernosally 5-10 minutes before intercourse	10-20 mcg 5-10 minutes before intercourse. Maximum recommended dose is 60 mcg. Limit to not more than one injection per day and not more than three injections per week with a 24-hour interval between doses	In older adults, use the lowest effective dose. No specific dosage adjustment provided in labeling for patients with hepatic or renal impairment.	Titrate dose to achieve an erection that lasts 1 hour Patient will require training on aseptic intracavernosal injection technique. Avoid intracavernosal injections in patients with sickle cell anemia, multiple myeloma, leukemia, severe coagulopathy, schizophrenia, poor manual dexterity, severe venous incompetence, severe cardiovascular disease, or Peyronie's disease.
Alprostadil intraurethral pellet	Muse	125-250 mcg intraurethrally 5-10 minutes before intercourse	250-1,000 mcg just before intercourse. Limit to not more than two doses per day	In older adults, use the lowest effective dose. No specific dosage adjustment provided in labeling for patients with hepatic or renal impairment.	Patient will require training on proper intraurethral administration techniques. Use applicator provided to administer medications to avoid urethral injury.
Testosterone Supplements					
Methyltestosterone	Android, Testred, Methitest	10 mg once daily	10-50 mg once daily	No dosage adjustment provided in labeling for patients with renal or hepatic impairment or older adults.	Not recommended for use due to extensive first-pass hepatic catabolism and because it is associated with hepatotoxicity. May cause fluid retention in patients with renal or hepatic disease.
Testosterone buccal system	Striant	30 mg every 12 hours, morning and evening	30 mg every 12 hours, morning and evening	No dosage adjustment provided in labeling for patients with renal or hepatic impairment or older adults.	Time the dose so that buccal system is removed before every morning and evening toothbrushing. Place buccal system just above incisor tooth in the mouth and hold in place for 30 seconds to adhere. To remove, slide buccal system down toward the tooth. With each dose, rotate site of administration to the alternate side of the mouth. Buccal tablet may become detached during eating. If this occurs, discard and replace with new buccal system. Do not chew or swallow buccal system.
Testosterone cypionate intramuscular injection	Depo-Testosterone	200-400 mg every 2-4 weeks	200-400 mg every 2-4 weeks (up to 6 weeks)	No dosage adjustment provided in labeling for patients with renal or hepatic impairment or older adults.	During the dosing interval, supraphysiologic serum concentrations of testosterone are produced during a portion of the dosing interval. This has been linked to mood swings.
Testosterone enanthate intramuscular injection	Delatestryl	200-400 mg every 2-4 weeks	200-400 mg every 2-4 weeks (up to 6 weeks)	No dosage adjustment provided in labeling for patients with renal or hepatic impairment or older adults.	During the dosing interval, supraphysiologic serum concentrations of testosterone are produced during a portion of the dosing interval. This has been linked to mood swings.
Testosterone undecanoate intramuscular injection	Aveed	750 mg as a single dose	750 mg as a single dose on Day 0, Week 4, and then 750 mg every 10 weeks	No dosage adjustment provided in labeling for patients with renal or hepatic impairment or older adults. Contraindicated in patients with serious hepatic or renal disease.	Only available in facilities certified through a Risk Evaluation and Mitigation Strategy Program. Administer by deep intramuscular injection into gluteal muscle. Avoid intravascular injection, which can lead to pulmonary oil embolism.

Testosterone transdermal patch	Androderm	4 mg as a single dose at bedtime	2-6 mg as a single dose at bedtime. Titrate dose 2 weeks after initiating a dose	No dosage adjustment is provided in labeling for patients with renal or hepatic impairment or older adults.	When administered at bedtime, serum concentrations of testosterone in the usual circadian pattern are produced. Apply to those sites recommended in the package labeling: upper arm, back, abdomen, and thigh. Rotate application sites every 7 days. May have to apply multiple patches at one time to achieve appropriate serum testosterone level. Avoid swimming, showering, or washing administration site for 3 hours after patch application.
Testosterone gel	AndroGel 1% (25 mg/2.5 g), Testim 1% (25 mg/2.5 g)	5-10 g of gel (equivalent to 50-100 mg testosterone, respectively) as a single dose in the morning	5-10 g of gel (equivalent to 50-100 mg testosterone, respectively) as a single dose in the morning. Titrate dose up at 14-day intervals	No dosage adjustment provided in labeling for patients with renal or hepatic impairment or older adults.	Cover application site to avoid inadvertent transfer to others. Avoid swimming, showering, or washing administration site for 2 hours after gel application. Apply to those sites recommended in the product labeling. For Androgel, apply to shoulders, upper arms, or abdomen. For Testim, apply to shoulders or upper arms only. Children and women should avoid contact with unclothed or unwashed application sites. Patients should wash hands with soap and water after administration of transdermal testosterone product. For patients who have difficulty measuring the appropriate dose using tubes of gel, it is also available in premeasured dose packets or from a pump dispenser. REMS assessments must be submitted to the FDA.
	AndroGel 1.6% (40.5 mg/2.5 g)	2 pumps (equivalent to 40.5 mg testosterone) as a single dose in the morning	2-4 pumps (equivalent to 40.5-81 mg) as a single dose in the morning. Titrate dose 14-28 days after starting treatment	No dosage adjustment provided in labeling for patients with renal or hepatic impairment or older adults.	Apply to shoulders and upper arms. Avoid swimming, showering, or washing administration site for 2 hours after application. Same precautions as listed above for 1% gel. REMS assessments must be submitted to the FDA.
Testosterone transdermal spray	Fortesta 2% (10 mg/actuation)	4 sprays (equivalent to 40-mg testosterone) every morning	4-7 sprays (equivalent to 40-70 mg testosterone) every morning. Titrate dose up at 14- to 35-day intervals	No dosage adjustment provided in labeling for patients with renal or hepatic impairment or older adults.	Must prime pump by pushing on pump three times. Apply to front or inner thighs only. Cover application site to avoid inadvertent transfer to others. Avoid swimming, showering, or washing administration site for 2 hours after spray application. Children and women should avoid contact with unclothed or unwashed application sites. Patients should wash hands with soap and water after administration of transdermal testosterone product. REMS assessments must be submitted to the FDA.
Testosterone transdermal solution	Axiron (30 mg/actuation)	One pump spray (equivalent to 30-mg testosterone) to left or right axilla daily	One to four pump sprays (equivalent to 30-120 mg testosterone, respectively) to left or right axilla daily. Titrate dose up at 14- to 35-day intervals	No dosage adjustment provided in labeling for patients with renal or hepatic impairment or older adults.	Limit application to axilla. Apply antiperspirant or deodorant before Axiron. If applying multiple spray doses, apply one spray, let dry, then apply second dose to each axilla. Avoid swimming, showering, or washing administration site for 2 hours after application. REMS assessments must be submitted to the FDA.
Testosterone subcutaneous implant pellet	Testopel	150-450 mg (equivalent to 2-6 pellets) as a single dose every 3-6 months.	150-450 mg as a single dose every 3-6 months	No dosage adjustment recommended for renal or hepatic impairment or older adults.	Trained health professional is required to administer the dose. Should use sterile implanter kit. Administration of the dose requires a forearm incision and subcutaneous dose implant under local anesthesia. Clinical onset is delayed for 3-4 months after initial dose. Generic formulations are available in higher strengths: 100 or 200 mg per pellet.

*Common brand names are included in this table. Medications may be available with other brand names.



Patient Care Process for the Management of Erectile Dysfunction

Collect

- Patient characteristics (eg, age, race)
- Patient history (past medical history, marital/partner status, family history, social—sexual history, situations in which erectile dysfunction occurs; tobacco, recreational drug, or alcohol use)
- Administer International Index of Erectile Function screening questionnaire if feasible (see “Diagnosis” section)
- Current and past medications, including prescription and nonprescription medications, or nonpharmacologic interventions for erectile dysfunction see Table 99-4)
- If patient is not responding to a phosphodiesterase type 5 inhibitor, details on how and when patient is using the medication (see “Efficacy”

subsection under “Phosphodiesterase Type 5 Inhibitor” section)

- Current psychologic status (emotional stressors, depression, performance anxiety) (see “Clinical Presentation” box)
- Objective data (see “Diagnosis” section)
  - BP, heart rate (HR), height, weight, and BMI
  - Physical examination to rule out hypogonadism and prostate dysfunction
  - Labs (eg, blood/serum glucose, lipids, testosterone)
  - Cardiovascular risk assessment, if indicated (see “Diagnosis” section and Table 99-3)

Assess

- Patient and partner’s expectations regarding therapy and costs
- Patient’s physical ability to engage in sexual intercourse
- Presence of conditions that are contraindications to sexual intercourse and to phosphodiesterase type 5 inhibitors (Table 99-3)
- Current use of medications contributing to erectile dysfunction (see Table 99-2)

Plan*

- Treatment selection must be individualized based on the patient’s preferences for and perception of the effectiveness of various treatment options, out-of-pocket costs for treatment, and potential adverse effects; patients generally prefer a discreet treatment not obvious to sexual partners and not requiring careful attention to administration timing relative to sexual activity.
- Optimize treatment for underlying causes of erectile dysfunction (eg, hypertension, coronary artery disease, dyslipidemia, diabetes mellitus, smoking, chronic ethanol abuse)
- Discontinue medications contributing to erectile dysfunction when possible (Table 99-2)
- Treat hypogonadism when present
- Counseling or psychotherapy for psychogenic causes of erectile dysfunction

- Drug therapy regimen including specific agent(s), dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Tables 99-4 and 99-5 and Figs. 99-2, 99-3, 99-5, and 99-6); consider presence of concomitant diseases treatable with agents for erectile dysfunction (eg, daily tadalafil in men who also have benign prostatic hypertrophy)
- Nonpharmacologic or surgical intervention when medications are contraindicated or are not effective (see Figs. 99-2 and 99-3)
- Patient reeducation to salvage patient nonresponders to phosphodiesterase type 5 inhibitor, if appropriate (see "Efficacy" subsection under "Phosphodiesterase Type 5 Inhibitor" section)
- Monitoring parameters including efficacy (eg, BP, cardiovascular events, kidney health), safety (medication-specific adverse effects), and time frame (see Tables 99-6 and 99-7)
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug therapy)
- Referrals to other providers when appropriate (eg, physician, urologist)

Implement*

- Provide patient education regarding all elements of treatment plan
- Schedule follow-up for several weeks after therapy initiation

Follow-up: Monitor and Evaluate

- Patient satisfaction with quality and quantity of penile erections
- Presence of adverse effects
- Adjust medication doses or change to alternative agent as clinically indicated
- Consider alternative devices, drugs, combinations of drugs, or surgical intervention in patients who fail treatment with a single approach

** Collaborate with patient, caregivers, and other healthcare professionals.*

The 2018 American Urological Association guideline on the management of erectile dysfunction,[20] the Fourth International Consultation of Sexual Medicine,[30] the 2010 European Urology Association guideline,[31] and the American College of Physicians[32] clearly identify oral phosphodiesterase type 5

inhibitors for first-line treatment. VEDs, intracavernosal injection of erectogenic agents, or intraurethral prostaglandin inserts are second-line treatments. Prescribing of a particular agent for a patient should be individualized. Surgical intervention should be reserved for patients who fail to respond to first- and second-line treatments. A sample algorithm that guides selection of treatment is shown in **Fig. 99-2**.

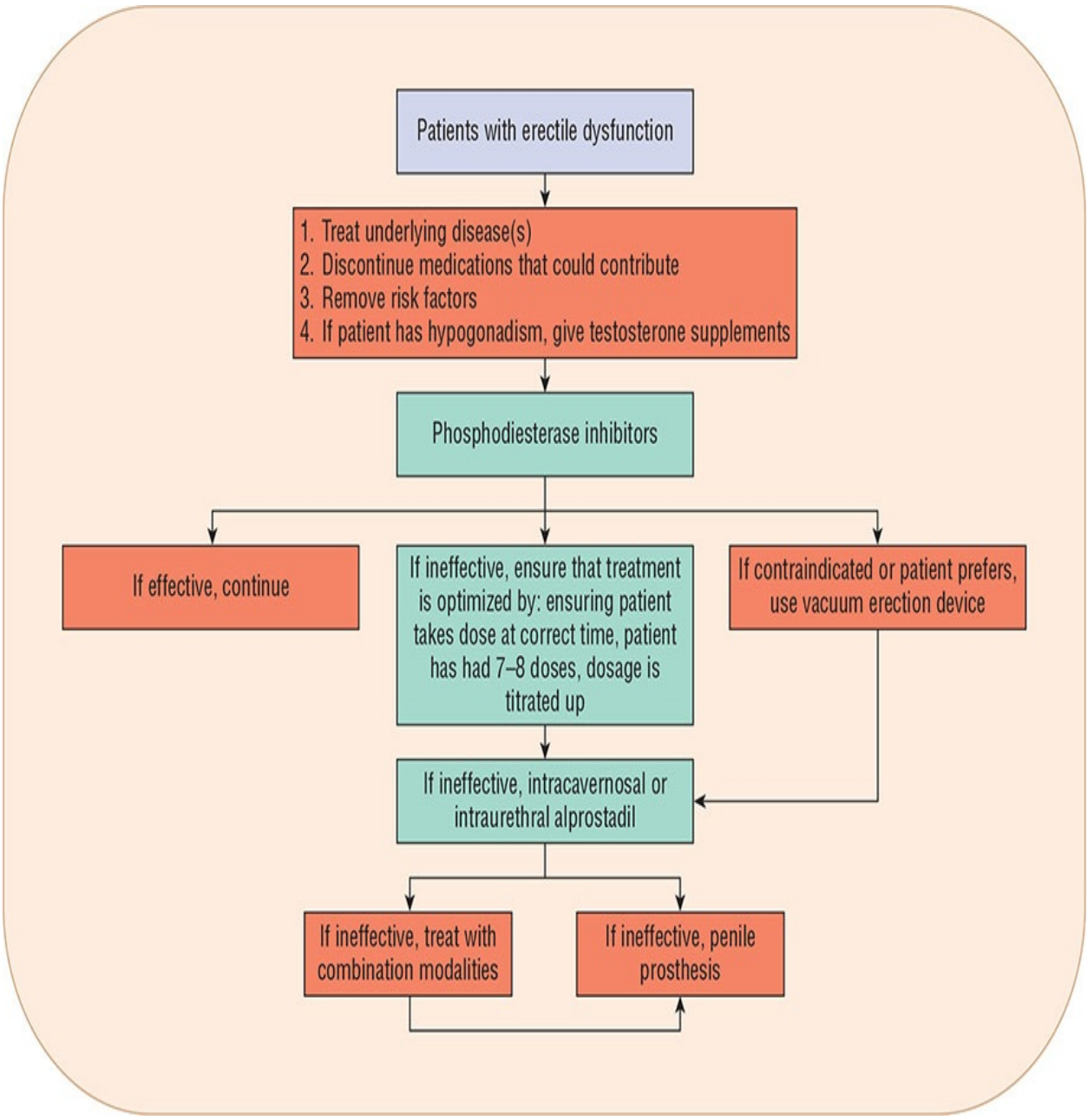
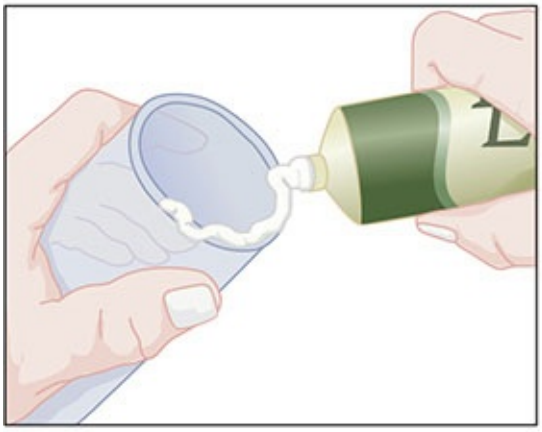


FIGURE 99-2 Algorithm for selecting treatment for erectile dysfunction.

Vacuum Erection Device

A vacuum erection device (VED) is a noninvasive medical device with few contraindications to use. A patient makes a one-time purchase and the device can be used repeatedly.

A VED has two parts: a pump, which generates a negative vacuum pressure; and a cylinder, which is closed at one end (**Fig. 99-3**). The patient inserts his penis into the open end of the cylinder, which is then pushed up flush against his lower abdomen to create a vacuum chamber. Then the patient activates the pump to produce a vacuum pressure, which draws arteriolar blood into the corpora cavernosa. To prolong the erection, the patient can use constriction bands or tension rings, which are placed at the base of the penis. The bands or rings keep the arteriolar blood in and reduce venous outflow from the penis. With the assistance of loading cones to protect the glans, these bands or rings can be rolled over the glans penis onto the erect penile shaft. Alternatively, the bands or rings can be first threaded onto the plastic cylinder before the penis is inserted. Once the penis is erect, the band or ring can be rolled off the cylinder onto the base of the penis. However, some patients prefer to apply the band or ring before the penis is erect.[33]



Assemble your system according to the two-step procedure.

Step 1

Apply Osbon Personal Lubricant™ to the following:

1. two inches inside the open end of the cylinder;
2. the rim of the cylinder that meets the body to form the vacuum seal; and
3. the entire head of the penis.

Applying lubricant properly will help you achieve the best erection possible.

Tip: Trimming the pubic hair around the base of the penis with a pair of scissors may also prove helpful in creating an airtight seal.

Step 2

It is recommended that you stand for this step (the system can also be used when you are sitting or lying down).

Place the lubricated penis inside the cylinder with the label on the cylinder facing up. With one hand, hold the cylinder at a downward 45° angle with the open end snugly against the body.

Tip: Rotate cylinder slightly back and forth to make an airtight seal against the body, make sure the testicles are not drawn into the cylinder.

FIGURE 99-3 Technique for using a vacuum erection device. (*Reprinted with permission from Osbon Erec Aid Esteem Vacuum Therapy System User Guide. Eden Prairie, MN: TIMM Medical Technologies.*)

7 The onset of action of the VED is 3 to 20 minutes; a faster onset of 2 to 3 minutes is associated with continued, more experienced use.[33] VEDs are not

discreet. That is, a patient's use of a VED is evident to the partner. For this reason, VEDs appear to work best in older patients who are married or who have stable sexual relationships. In this group, VEDs could be considered first-line therapy, and the overall satisfaction rate can be as high as 60% to 80% (range, 27%-94%).[33] VEDs may be used as second-line therapy in patients who do not respond to oral phosphodiesterase type 5 inhibitors,[34] which includes patients who have had radical prostatectomy or those who do not respond to injectable drug treatments for erectile dysfunction. The combination of a VED with intracavernosal or intraurethral alprostadil[34] or a phosphodiesterase type 5 inhibitor[35,36] is associated with a higher efficacy rate than use of the VED alone. As a result, combination therapy sometimes is attempted before penile prosthesis surgery is considered in the patient who fails to respond to a VED alone.[37]

Patients may discontinue using VEDs because they are inconvenient and not discreet. It has been reported that the dropout rate is as high as 56% during the first year of use.[33,34] Also, 6% to 11% of partners complain that the penis is cool to the touch or is discolored (bluish) in appearance, particularly when constriction bands are used.[36]

Vacuum erection devices are available with battery-operated pumps, which offer convenience, particularly in patients with arthritis of the hands. Patients may purchase these devices over-the-counter (OTC). When choosing a device, patients should select one with a pop-off safety valve that minimizes the likelihood of excessively high vacuum pressure, which can cause penile discomfort, petechiae, or hematoma.[33]

Penile pain, bruising, or injury from VEDs most often is caused by the constriction bands used to sustain an erection. Because these rings trap blood in the corpora and reduce arteriolar flow into the penis, the penile shaft may feel cold and numb. If the constriction bands are applied for longer than 30 minutes, the penile shaft may turn blue and hurt.[36] Patients may complain that a hinge-like erection is produced in that the penis pivots on the rubber ring or tension band. Patients sometimes fail to ejaculate.

Vacuum erection devices are contraindicated in patients with sickle cell disease or patients with a history of prolonged erections. These patients are prone to priapism, which can be exacerbated by the use of constriction bands with VEDs. The devices also should be used cautiously by patients taking warfarin, as this agent increases the likelihood of penile bruising during use of the device. Finally, VEDs are contraindicated in patients with severe penile curvature.

Phosphodiesterase Type 5 Inhibitors

Mechanism

In the presence of sexual stimulation, nitric oxide is released by neurons and endothelial cells in cavernosal tissue, thereby enhancing the activity of guanylate cyclase, the enzyme responsible for conversion of guanylate triphosphate to cGMP (Fig. 99-4).[38,39] cGMP is a vasodilatory secondary messenger that activates protein kinase G. This decreases intracellular calcium levels, resulting in smooth muscle relaxation, enhanced arterial flow to the corpora cavernosa, and increased blood filling of cavernosal sinuses.[38] Catabolism of cGMP in cavernosal tissue is mediated by phosphodiesterase isoenzyme type 5.[40]

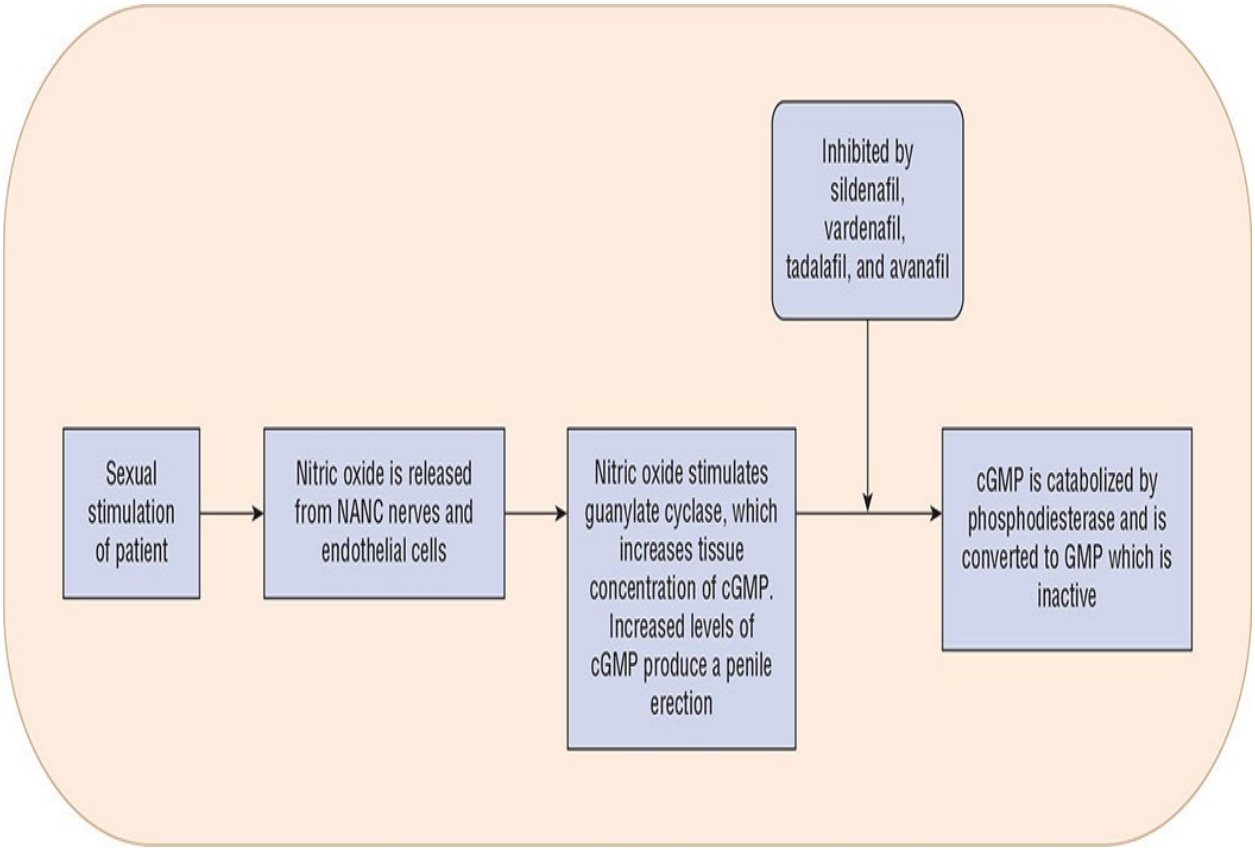


FIGURE 99-4 Mechanism of action of phosphodiesterase type 5 inhibitors. All inhibit catabolism of cGMP, a vasodilatory secondary messenger. (cGMP, cyclic guanosine monophosphate; NANC, nonadrenergic noncholinergic.)

Four competitive, reversible inhibitors of the phosphodiesterase isoenzyme type 5 are marketed for erectile dysfunction in the United States (Table 99-5). Chemically, they are nonhydrolyzable analogs of cGMP and they act by

decreasing catabolism and maintaining high concentrations of cGMP in the corpora cavernosa. In effect, this sustains a penile erectile. However, these medications are not specific for phosphodiesterase isoenzyme type 5. They also inhibit other phosphodiesterase isoenzymes in other tissues and organs, which produces some of the unwanted side effects of this medication class.[36,38,40]

TABLE 99-5 Pharmacodynamics and Pharmacokinetics of Phosphodiesterase Inhibitors

	Sildenafil (Viagra)	Vardenafil (Levitra/Staxyn)	Tadalafil (Cialis)	Avanafil (Stendra)
Inhibits PDE-5	Yes	Yes	Yes	Yes
Inhibits PDE-1	Yes	Yes	Minimally	Minimally
Inhibits PDE-6	Yes	Yes	No	Moderately
Inhibits PDE-11	No	No	Yes	No
Time to peak plasma level (hours)	0.5-1	0.7-0.9/1.5	2	0.5-0.8
Oral bioavailability (%)	40	15/21-44	36	15
Fatty meal decreases rate of oral absorption?	Yes	Yes/No[a]	No	No
Mean plasma half-life (hours)	3.7	4.4-4.8/4-6	18	4-5
Active metabolite	Yes	Yes/Yes	No	Yes
Is CYP 3A4 principally responsible for metabolism?	Yes	Yes	Yes	Yes
Other CYP enzymes responsible for metabolism	CYP 2C9, CYP 2C19, CYP 2D6	CYP 3A5, CYP 2C9	None	CYP 2C9
Percentage of dose excreted in feces	80	91-95/91-95	61	62
Percentage of dose excreted in urine	13	2-6/2-6	36	21
Clinical onset (minutes)	30	30/60	45	25-40
Duration (hours)	4-12	4-5/4-6	24-36	6+

[a]When Staxyn is taken with water, the area under the curve decreases by 29%.

Selectivity of Other Phosphodiesterase Isoenzymes

More than 11 different phosphodiesterase isoenzymes have been identified; however, the physiologic effects of stimulation and inhibition of some of these isoenzymes remain to be elucidated. Phosphodiesterase isoenzyme 1 is found in the peripheral vasculature. Inhibition of this isoenzyme has been linked with peripheral vasodilation, which can lower blood pressure, and cause flushing and reflex tachycardia in some patients.

Phosphodiesterase isoenzyme type 6 is localized to the rods and cones of the retina. Inhibition of this isoenzyme has been associated with blurred vision and cyanopsia. Sildenafil is the most potent inhibitor of phosphodiesterase isoenzyme type 6, vardenafil and avanafil are intermediate inhibitors, and tadalafil is the least potent inhibitor.[41]

Phosphodiesterase isoenzyme type 11 is localized to striated muscle. Inhibition of this isoenzyme has been associated with myalgia and back muscle pain. Tadalafil exerts the greatest inhibitory activity against phosphodiesterase type 11.[42]

The four marketed phosphodiesterase type 5 inhibitors differ in their degree of selectivity in inhibiting phosphodiesterase type 5 versus other phosphodiesterase isoenzymes. For example, avanafil has 100-fold greater selectivity for phosphodiesterase type 5 isoenzyme than phosphodiesterase isoenzyme type 1, 6, or 11.[41] In contrast, tadalafil shows unique selectivity for phosphodiesterase isoenzyme type 11[42] (see Table 99-5).

Efficacy

Because of their apparent effectiveness, convenient route of administration, and comparatively low incidence of serious adverse effects, phosphodiesterase type 5 inhibitors are considered first-line therapy for erectile dysfunction, particularly in younger patients. They allow for discreet use. Although not based on direct comparison trials, all four commercially available phosphodiesterase type 5 inhibitors are considered to be equally effective and comparable in safety and tolerability.[38,40] Patient preference studies show that some patients may prefer one agent over because of the preferences of the sexual partner; or the onset, duration, or cost of treatment.[43–45] Usual starting and maintenance dose regimens are included in Table 99-4.

In the presence of sexual stimulation and in doses of 25 to 100 mg, sildenafil produces satisfactory erections in 56% to 82% of patients, independent of the etiology of erectile dysfunction. Similar results are documented in the product labeling for the other agents in this class (65%-80% for vardenafil, 62%-77% for tadalafil, and 50%-55% for avanafil). Response rates in the lower range for phosphodiesterase type 5 inhibitors have been documented in patients with diabetes mellitus or after radical prostatectomy, or those with severe vascular disease, probably due to neuropathy, or surgery-related nerve damage.[45,46] The effectiveness of the drugs appears to be dose-related.

8 Approximately 30% to 40% of patients do not respond to

phosphodiesterase type 5 inhibitors.[5,20] At least half of nonresponders can benefit from education on proper use of the drugs.[36] Therefore, follow-up is always recommended after a phosphodiesterase type 5 inhibitor is initiated. Education of patients should include the following points: (a) patients must engage in sexual stimulation (foreplay) for the best response; (b) sildenafil and vardenafil should be taken on an empty stomach, at least 2 hours before meals, for the fastest response, but tadalafil and avanafil can be taken without regard to meals; (c) patients who do not respond to the first dose should continue with the phosphodiesterase type 5 inhibitor for at least five to eight doses before failure is declared, as increasing success rates are reported with sequential dose administration; (d) some patients require dosage titration up to 100-mg sildenafil, 20-mg vardenafil, 20-mg tadalafil, or 200-mg avanafil for a response; (e) patients should avoid excessive alcohol intake, which can cause drowsiness and hypotension and worsen erectile dysfunction; (f) involvement of the sexual partner can help improve the patient's response to treatment; (g) treatment of concomitant medical illnesses that contribute to erectile dysfunction (eg, diabetes mellitus, hypertension, and hypogonadism) should be optimized (if the patient has depression because of divorce or loss of a sexual partner, or has performance anxiety, psychologic counseling may be helpful).[20,28]

The phosphodiesterase type 5 inhibitors should not be used by patients with normal erectile function. Also, according to FDA-approved labeling, the drugs should not be used in combination with other forms of therapy for erectile dysfunction because prolonged erections (which may lead to priapism) may result.[20] Phosphodiesterase type 5 inhibitors should be avoided in patients predisposed to developing priapism, including men with sickle cell anemia, leukemia, or multiple myeloma.

Long-term use of phosphodiesterase type 5 inhibitors for up to 10 consecutive years continues to be effective and is not associated with tachyphylaxis.[45] The voluntary discontinuation rate among patients who respond to phosphodiesterase type 5 inhibitors is less than 2% per year in controlled clinical trials.[35,46,47] However, the actual voluntary discontinuation rate is probably closer to 35% to 47% after 6 to 24 months of treatment, despite a positive treatment response. This phenomenon is likely due to the high out-of-pocket costs of phosphodiesterase type 5 inhibitors, the inconvenient process of obtaining the medication, adverse drug effects, the patient's loss of interest in sexual intercourse, or the efficacy of the medication being below the patient's expectations.[47,48]

Despite the initial effectiveness of phosphodiesterase type 5 inhibitors and the

measures to salvage patients with reeducation, some patients with severe vascular or neurologic disease will show minimal or no response to maximum doses of a phosphodiesterase type 5 inhibitor. Various strategies have been attempted in this subgroup of patients, including the following:

1. The effectiveness of switching from one phosphodiesterase type 5 inhibitor to another when the patient does not respond to an initial agent is controversial. In one study, vardenafil was beneficial in 12% of patients who did not respond to sildenafil.[49] Controlled clinical trials in larger patient groups are needed before this strategy is used as routine treatment.
2. Switching the patient from an as-needed to a daily regimen of tadalafil may be reasonable in a patient who has difficulty coordinating the timing of tadalafil before meals or sexual intercourse.
3. High-dose phosphodiesterase type 5 inhibitor treatment (eg, sildenafil 200 mg) has been used anecdotally. However, such doses are also associated with a higher frequency of adverse effects.[50]
4. In older patients (age greater than or equal to 65 years) with late-onset hypogonadism and erectile dysfunction, correcting the former with testosterone supplementation improves the response to a phosphodiesterase type 5 inhibitor.[11,51]
5. Phosphodiesterase type 5 inhibitors have been combined with intracavernosal or intraurethral alprostadil in selected patients.[5,35,36]

Pharmacokinetics and Drug–Food Interactions

Pharmacokinetic parameters of the phosphodiesterase type 5 inhibitors are listed in Table 99-5.[42]

Sildenafil and the conventional oral formulation of vardenafil have similar pharmacokinetic profiles. Both drugs have a 1-hour onset of action and short duration of action. Oral absorption is significantly delayed by 1 hour when either drug is taken within 2 hours of a fatty meal.[42] In contrast, tadalafil has a slower onset of action of 2 hours, has a prolonged duration of action up to 36 hours, and food does not affect its rate of absorption. Thus, tadalafil offers greater spontaneity for patients, as one dose can last through an entire weekend and it allows for multiple acts of sexual intercourse over multiple days with a single dose. An oral disintegrating tablet formulation of vardenafil, which dissolves on the tongue, has 1.2- to 1.4-fold higher bioavailability than the conventional oral tablet. However, its clinical efficacy appears comparable to the conventional tablet. The oral disintegrating tablet formulation does not require the patient to

take it with water, and it is not susceptible to the drug–food interactions of the conventional oral tablet.[52] Avanafil has an onset of action of 15 minutes; its onset is faster than, but similar in duration to, sildenafil and vardenafil. Food does not significantly impact on absorption of avanafil. Further study is needed to determine if avanafil's duration of action is longer than 6 hours.

The onset of action of these agents has undergone reexamination to assess how soon after drug administration patients can expect to have an erection suitable for intercourse. Although up to 50% of patients may develop an erection within 20 to 30 minutes of sildenafil 100 mg, vardenafil 20 mg, tadalafil 20 mg, or avanafil 200 mg, the rest of the patients may require a full hour to achieve an adequate erectile response.[42] Therefore, patients should be instructed to allow adequate time for the drug to work. In addition, sildenafil and vardenafil have been reported to be effective in some patients up to 12 hours after dosing, and tadalafil is effective up to 36 hours after dosing, which is long after plasma concentrations have declined. It has been hypothesized that this may be due to the continued intracellular action of the phosphodiesterase type 5 inhibitor.

Concomitant ingestion of ethanol with phosphodiesterase type 5 inhibitors can result in orthostatic hypotension and drowsiness. Therefore, the manufacturer recommends that patients avoid ethanol when taking these medications.

All four phosphodiesterase type 5 inhibitors are hepatically catabolized principally by the cytochrome P450 3A4 microsomal isoenzyme, and other P450 isoenzymes (minor routes) and/or other hepatic enzymes (see Table 99-5). Sildenafil has an active metabolite, which is excreted primarily in the urine. Tadalafil has a clinically insignificant active metabolite. However, 36% of the parent drug is renally eliminated. Thus, both sildenafil and tadalafil doses should be reduced in patients with significant renal impairment. Vardenafil and avanafil have active metabolites that are largely excreted in feces. No specific dosage reduction of these medications is recommended in patients with reduced renal function because of the intermittent nature of the dosing schedule. Avanafil is not recommended when the creatinine clearance is less than 30 mL/min (0.5 mL/s) (see Table 99-4).

Dosing

The usual oral doses of the phosphodiesterase type 5 inhibitors are listed in Table 99-4. Sildenafil, vardenafil, and avanafil should be taken on demand at least 30 to 60 minutes before sexual intercourse. Tadalafil should be taken at least 2 hours before sexual intercourse. The durations of action for sildenafil,

vardenafil, and avanafil are approximately 4 to 6 hours, whereas tadalafil lasts 36 hours. The agents vary as to whether doses must be adjusted for patients 65 years and older and those with compromised hepatic or renal function. Patients should be advised to take no more than the amount prescribed and not more than one dose per day. Doses higher than those recommended have been described in the published literature (eg., sildenafil 200 mg).[50] However, such dosing regimens have not consistently produced improved erectile responses.

For patients who do not respond to an adequate course of on-demand phosphodiesterase type 5 inhibitors for erectile dysfunction, daily low dosing of tadalafil may improve endothelial function in cavernosal tissue. That is, regular use of phosphodiesterase type 5 inhibitors may activate endothelial nitric oxide synthase, increase local concentrations of cGMP, which may lead to increased oxygen tension, improved blood flow, and reduced endothelial damage and cavernosal fibrosis.[53] A preliminary clinical trial of daily dosing of tadalafil 5 mg showed a 86% frequency of successful sexual intercourse compared with conventional on-demand use of tadalafil 20 mg, which produced 95% global efficacy.[54] Other potential advantages of daily low dosing regimens include a lower potential for dose-related adverse effects and increased spontaneity of sexual intercourse. However, disadvantages of the daily low-dose regimen are the high cost of treatment and patients with more severe erectile dysfunction, who may require higher doses of a phosphodiesterase type 5 inhibitor, may not respond.[55] Although clinical trials of daily dosing of tadalafil 10 and 20 mg,[56,57] have been published, the only FDA-approved labeling is for daily dosing of tadalafil 2.5 or 5 mg.

Adverse Effects

Most adverse effects of the phosphodiesterase type 5 inhibitors are mild or moderate, are self-limited, and tolerance to the adverse effects develops with continued use.[5,55] The rates of drug discontinuation because of adverse effects are low, ranging from 2.1% to 25%, and are similar for all four agents. In usual doses, the most common adverse effects are headache (11%), facial flushing (12%), dyspepsia (5%), nasal congestion (3.4%), and dizziness (3%), all of which are dose-related and result from vasodilation or smooth muscle relaxation secondary to inhibition of phosphodiesterase isoenzyme type 1 or 5 in cardiac or vascular tissues.[55]

Sildenafil and vardenafil produce an 8- to 10-mm Hg decrease in systolic and a 5- to 8-mm Hg decrease in diastolic blood pressure starting approximately 1 hour after a dose is taken and lasting for 4 hours. Most patients are

asymptomatic as a result of these blood pressure changes, but some patients, particularly those taking multiple antihypertensives or nitrates or those with baseline hypotension, may develop clinical symptoms as a consequence of these peripheral vascular effects. Avanafil and tadalafil produce decreases in systolic and diastolic blood pressure that are smaller than those associated with sildenafil and vardenafil, although the decrements may be greater when they are used along with other antihypertensives or α-adrenergic antagonists.[55] All phosphodiesterase type 5 inhibitors must be used with caution in patients with cardiovascular disease because of the cardiac risk inherent to sexual activity. The management approach for such patients, as described in the recommendations of the Princeton Consensus Guideline Conference III,[27] should be applied to all the patients in whom phosphodiesterase type 5 inhibitors are being considered for use (see Table 99-3).

Sildenafil, vardenafil, and avanafil cause increased sensitivity to light, blurred vision, or loss of blue–green color discrimination in 2% to 3% of patients. This adverse effect is dose-related with the incidence increasing to 40% to 50% in patients taking sildenafil 200 mg.[55] These effects result from inhibition of phosphodiesterase type 6 in the photoreceptor cells of retinal rods and cones. Visual adverse effects commonly occur at the time of peak serum concentrations. Avanafil has moderate and tadalafil has minimal to no inhibitory activity against phosphodiesterase type 6, and they are associated with a lower incidence of visual adverse effects (less than 1%) when compared to sildenafil and vardenafil.[55] Nevertheless, according to current product labeling, all phosphodiesterase type 5 inhibitors should be used cautiously in patients at risk for retinitis pigmentosa, a genetic disease associated with retinal phosphodiesterase deficiency.

Nonarteritic anterior ischemic optic neuropathy (NAION) is a sudden, unilateral, painless blindness, which may be irreversible. Isolated cases of NAION have been associated with phosphodiesterase type 5 inhibitor use.[58] NAION has developed at variable and unpredictable times after starting a phosphodiesterase type 5 inhibitor, ranging from 6 hours to months or years after the first dose.[58] Although a cause–effect relationship has not been established, it has been proposed that the blood pressure-lowering effects of these medications may decrease blood flow to the optic nerve and lead to a sudden unilateral decrease in vision. Because NAION may lead to permanent vision loss, the FDA has required inclusion of warnings on the product labeling of phosphodiesterase type 5 inhibitors. Specifically, before receiving these agents, patients at risk for NAION should be evaluated by an ophthalmologist, risk factors for NAION

should be addressed, and the patient should be cautioned against using a phosphodiesterase type 5 inhibitor.[55,58,59]

Patients at risk of NAION include a wide variety of patients: those with glaucoma, macular degeneration, diabetic retinopathy, dyslipidemia, or hypertension, those who have undergone eye surgery or have experienced eye trauma, patients who are age 50 years or more, or smokers. A patient who experiences sudden vision loss in one eye while taking a phosphodiesterase type 5 inhibitor should be evaluated for NAION before continuing treatment. If NAION is present, the phosphodiesterase type 5 inhibitor should be discontinued as there is a 15% to 25% risk of developing NAION in the other eye in the ensuing 5 to 10 years.[54,58,60]

Tadalafil produces lower back and limb muscle pain, which occurs in a dose-related fashion in 7% to 30% of patients treated with doses of 10 to 100 mg.[42] The mechanism for this is not known. It has been linked to inhibition of type 11 phosphodiesterase, which is a unique characteristic of tadalafil.

Acute unilateral hearing loss has also been reported after use of a phosphodiesterase type 5 inhibitor. A cause–effect relationship has not been established. In the cases reported, the hearing loss occurred within 1 to 3 days of starting treatment; it was variably accompanied by tinnitus or vertigo, and often resulted in residual hearing loss despite discontinuation of the phosphodiesterase type 5 inhibitor.[55,61] The product labeling now includes a warning that a phosphodiesterase type 5 inhibitor should be immediately stopped and the patient should see a physician if sudden hearing loss develops.

Priapism is a rare adverse effect of phosphodiesterase type 5 inhibitors, particularly sildenafil and vardenafil, which have shorter plasma half-lives than tadalafil. Priapism has been associated with excessive doses of the phosphodiesterase type 5 inhibitor or concomitant use with other erectogenic drugs.

Recently, sildenafil use has been associated with an increased risk of melanoma.[62] The proposed mechanism theorized is that phosphodiesterase type 5 inhibition activates *BRAF*, a human gene that produces a protein that causes proliferation of melanoma cells. However, a cause–effect relationship has not been established.[62–64]

Recommendations for adverse effect monitoring are included in **Table 99-6**.

TABLE 99-6 Drug Monitoring Table

Drug	Adverse Drug Reaction	Monitoring Parameter	Comments
Phosphodiesterase Inhibitor			
Sildenafil	• Headache • Flushing • Dyspepsia • Nasal congestion • Cyanopsia • NAION • Hypotension • Priapism • Hearing loss	• Clinical symptoms of erectile dysfunction • Visual complaints, loss of vision • Hearing loss • Blood pressure • Pulse	• Discontinue sildenafil if the patient has any visual or hearing loss and refer the patient to a physician • If the patient is taking any antihypertensives, stabilize blood pressure before starting sildenafil • If the patient develops priapism, he should proceed to the emergency department • If the patient has a bleeding disorder, use cautiously
Vardenafil	• Headache • Flushing • Dyspepsia • Nasal congestion • Cyanopsia • NAION • Hypotension • QT interval prolongation on EKG • Priapism • Hearing loss	• Clinical symptoms of erectile dysfunction • Visual complaints, loss of vision • Hearing loss • Blood pressure • Pulse • Palpitations or dizziness	• Discontinue vardenafil if the patient has any visual or hearing loss and refer the patient to a physician • If the patient is taking any antihypertensives, stabilize blood pressure before starting vardenafil • If the patient has palpitations or dizziness, check EKG. If QT prolongation is present, refer the patient for appropriate medical care. • If the patient develops priapism, he should proceed to the emergency department • If the patient has a bleeding disorder, use cautiously
Tadalafil	• Headache • Flushing • Dyspepsia • Nasal congestion • Cyanopsia • Hearing loss • NAION • Hypotension • Low back or muscle pain • Priapism	• Clinical symptoms of erectile dysfunction • Visual complaints, loss of vision • Hearing loss • Blood pressure • Pulse • Palpitations or dizziness • Myalgia	• Discontinue tadalafil if the patient has any visual or hearing loss and refer the patient to a physician • If the patient is taking any antihypertensives, stabilize blood pressure before starting tadalafil • If the patient develops priapism, he should proceed to the emergency department • If the patient has a bleeding disorder, use cautiously • Muscle pain is dose-related
Avanafil	• Headache • Flushing • Dyspepsia • Nasal congestion • Cyanopsia • Hearing loss • NAION • Hypotension • Priapism	• Clinical symptoms of erectile dysfunction • Visual complaints, loss of vision • Blood pressure • Pulse • Palpitations or dizziness • Hearing loss	• Discontinue avanafil if the patient has any visual or hearing loss and refer the patient to a physician • If the patient is taking any antihypertensives, stabilize blood pressure before starting avanafil • If the patient develops priapism, he should proceed to the emergency department • If the patient has a bleeding disorder, use cautiously
Prostaglandin E_1			
Alprostadil, intracavernosal	• Penile pain • Hematoma at injection site • Priapism • Hypotension • Fibrotic nodules along penile shaft • Decreased blood pressure • Dizziness	• Clinical symptoms of erectile dysfunction • Presence of hematoma or fibrotic nodules • Blood pressure • Pulse	• Penile pain responds to acetaminophen • To avoid hematoma, apply pressure to injection site for 5-10 minutes after injection • If the patient develops priapism, he should proceed to the emergency department • Fibrotic nodules are rare but may occur after repeated injections. These may cause curvature of the penis during an erection and this requires assessment by a urologist • Hypotension and dizziness are uncommon and are associated with inadvertent venous injection of the drug
Alprostadil, intraurethral	• Aching pain in penis, testicles, legs, and perineum • Urethral burning, bleeding, or tearing • Priapism • Hypotension • Dizziness • Female partner may experience vaginal pain and burning sensation	• Clinical symptoms of erectile dysfunction • Urethral injury as evidenced by pain, bleeding, or tissue damage • Blood pressure • Pulse	• Burning pain usually resolves spontaneously. If urethral injury is suspected, this requires assessment by a urologist. Pain experienced by the female partner is due to leakage of medication from male urethra into vagina. Pain will usually resolve spontaneously • If the patient develops priapism, he should proceed to the emergency department • Hypotension and dizziness are uncommon, occurring in only 2%-3% of patients, and are associated with systemic absorption of the drugs • Alprostadil is embryotoxic and contact should be avoided if the female sex partner is pregnant. Males should use condoms if female is pregnant

Testosterone Supplements			
Methyltestosterone	• Sodium and water retention • Hyperlipidemia • Polycythemia • Gynecomastia • Sleep apnea, worsening • Increased libido • Mood swings • Oligospermia • Hepatotoxicity • Venous thromboembolism • Prostate enlargement	• Clinical symptoms of erectile dysfunction • Physical exam for edema • Blood pressure • Serum lipids, hematocrit, hepatic transaminases, prostate specific antigen, serum testosterone	• Discontinue if the patient has signs of hepatoxicity. If hematocrit exceeds 55% (0.55), methyltestosterone should be discontinued. Testosterone supplements may worsen lower urinary tract symptoms (LUTS) in patients with BPH. It is contraindicated in patients with untreated prostate cancer or men with breast cancer. May increase the risk of nonfatal myocardial infarction or death. Use precautiously in patients with a significant cardiovascular history. Discontinue if venous thromboembolism is suspected
Testosterone buccal system	• Sodium and water retention • Hyperlipidemia • Polycythemia • Gynecomastia • Sleep apnea, worsening • Increased libido • Mood swings • Oligospermia • Hepatotoxicity • Venous thromboembolism • Gum irritation and pain • Bitter taste • Prostate enlargement	• Clinical symptoms of erectile dysfunction • Physical exam for edema • Blood pressure • Serum lipids, hematocrit, hepatic transaminases, prostate-specific antigen, serum testosterone	• Discontinue if the patient has signs of hepatoxicity. If hematocrit exceeds 55% (0.55), testosterone buccal system should be discontinued. Testosterone supplements may worsen LUTS in patients with BPH. It is contraindicated in patients with untreated prostate cancer or men with breast cancer. May increase the risk of nonfatal myocardial infarction or death. Use precautiously in patients with a significant cardiovascular history. Discontinue if venous thromboembolism is suspected
Testosterone cypionate or enanthate Testosterone undecanoate	• Sodium and water retention • Hyperlipidemia • Polycythenia • Gynecomastia • Sleep apnea, worsening • Increased libido • Oligospermia • Mood swings • Hepatotoxicity • Venous thromboembolism • Prostate enlargement • Injection site pain, pruritis • Pulmonary oil microembolism (POME), testosterone undecanoate only • Anaphylactic reactions • Prostate enlargement • Sodium and water retention • Hyperlipidemia • Polycythemia • Gynecomastia • Sleep apnea, worsening • Increased libido • Oligospermia • Mood swings • Hepatotoxicity	• Clinical symptoms of erectile dysfunction • Physical exam for edema • Blood pressure • Serum lipids, hematocrit, hepatic transaminases, prostate-specific antigen • Clinical symptoms of erectile dysfunction • Physical exam for edema, cough, shortness of breath • Blood pressure • Serum lipids, hematocrit, hepatic transaminases, prostate-specific antigen	• Discontinue if the patient has signs of hepatoxicity. If hematocrit exceeds 55% (0.55), testosterone supplement should be discontinued. Testosterone supplements may worsen LUTS in patients with BPH. It is contraindicated in patients with untreated prostate cancer or men with breast cancer. These formulations produce supraphysiologic serum concentrations of testosterone. Mood swings have been reported with these agents. May increase the risk of nonfatal myocardial infarction or death. Use cautiously in patients with a significant cardiovascular history. Discontinue if venous thromboembolism is suspected • Discontinue if the patient has signs of hepatoxicity. If hematocrit exceeds 55% (0.55), testosterone supplement should be discontinued. Testosterone supplements may worsen LUTS in patients with BPH. It is contraindicated in patients with untreated prostate cancer or men with breast cancer. These formulations produce supraphysiologic serum concentrations of testosterone. Mood swings have been reported with these agents. May increase the risk of nonfatal myocardial infarction or death. Use cautiously in patients with a significant cardiovascular history. Discontinue if venous thromboembolism is suspected • Signs of POME include cough, dyspnea, chest pain, and syncope, usually within 30 minutes of testosterone undecanoate injection. This medication should only be administered by a healthcare provider or in setting which is certified through a Risk Evaluation and Mitigation Strategy program
Testosterone patch	• Sodium and water retention • Hyperlipidemia • Gynecomastia • Sleep apnea, worsening • Increased libido • Contact dermatitis • Application site erythema, pruritus • Prostate enlargement	• Clinical symptoms • of erectile dysfunction • Physical exam for edema • Blood pressure • Serum lipids, hematocrit, hepatic transaminases, prostate-specific antigen, serum testosterone	• Testosterone supplements may worsen LUTS in patients with BPH. It is contraindicated in patients with untreated prostate cancer or men with breast cancer. Contact dermatitis has been associated with the alcohol-based agent used to enhance transdermal drug absorption. It responds to topical corticosteroids. Of significance, hepatotoxicity has not been reported with transdermal patches. May increase the risk of nonfatal myocardial infarction or death. Use precautiously in patients with a significant cardiovascular history. Discontinue if venous thromboembolism is suspected. Adverse effects of mood swings and polycythemia are less likely with patch than with injectable formulations

Testosterone gel/ spray/axillary solution	• Sodium and water retention • Hyperlipidemia • Polycythemia • Gynecomastia • Sleep apnea, worsening • Increased libido • Dermatitis • Application site erythema • pruritis, • Prostate enlargement	• Clinical symptoms of erectile dysfunction • Physical exam for edema • Blood pressure • Serum lipids, hematocrit, hepatic transaminases, prostate specific antigen, serum testosterone	• Do not interchange topical formulations. Testosterone supplements may worsen LUTS in patients with BPH. It is contraindicated in patients with untreated prostate cancer or men with breast cancer Use is contraindicated in pregnant women or women who are likely to become pregnant, or women who breast feed infants. Women and children who have inadvertent skin exposure to these formulations may become virilized. If hematocrit exceeds 55% (0.55), testosterone supplement should be discontinued. May increase the risk of nonfatal myocardial infarction or death. Use precautiously in patients with a significant cardiovascular history. Discontinue if venous thromboembolism is suspected. With transdermal sprays, REMS assessments must be submitted to the FDA
Testosterone subcutaneous implant	• Sodium and water retention • Hyperlipidemia • Polycythemia • Gynecomastia • Sleep apnea, worsening • Increased libido • Mood swings • Oligospermia • Hepatotoxicity • Prostate enlargement • Pain and infection at the implant site	• Clinical symptoms of erectile dysfunction • Physical exam for edema • Blood pressure • Serum lipids, hematocrit, hepatic transaminases, prostate specific antigen, serum testosterone	• Subcutaneous implant pellet may be extruded with loss of the dose. Androgen-related adverse effects may persist for a long time after drug administration unless the implant is removed. If hematocrit exceeds 55% (0.55), testosterone implant should be removed. Testosterone supplements may worsen LUTS in patients with BPH. It is contraindicated in patients with untreated prostate cancer or men with breast cancer. May increase the risk of nonfatal myocardial infarction or death. Use cautiously in patients with a significant cardiovascular history. Discontinue if venous thromboembolism is suspected

LUTS, lower urinary tract symptoms.

Drug Interactions

Approximately 8% of patients taking organic nitrates may develop sudden, severe hypotension if they also take a phosphodiesterase type 5 inhibitor. Decreased blood pressure results from two major factors: (a) organic nitrates on their own produce hypotension, and (b) organic nitrates are nitric oxide donors, which can stimulate the activity of guanylate cyclase and increase tissue levels of cGMP.[27,42] For this reason, use of phosphodiesterase type 5 inhibitors is contraindicated in patients taking nitrates given by any route at scheduled times or intermittently.[65,66] Furthermore, nitrates should be withheld for 24 hours after sildenafil, vardenafil, or avanafil administration and for 48 hours after tadalafil administration.[27,42,65,66] Finally, if a patient who has taken a phosphodiesterase type 5 inhibitor requires medical treatment of angina, non-nitrate-containing agents (eg, calcium channel blocker, β-adrenergic antagonist, and morphine)

should be used.

If severe hypotension occurs after exposure to nitrates and a phosphodiesterase type 5 inhibitor, the patient should be placed in a Trendelenburg position and aggressive fluid administration initiated. If severe hypotension continues, parenteral β-adrenergic agonists (eg, dopamine) should be administered cautiously.[27,66]

Interestingly, dietary sources of nitrates, nitrites, or L-arginine (a precursor for nitrates) do not interact with phosphodiesterase type 5 inhibitors. This is because dietary sources do not increase circulating or tissue levels of nitric oxide in humans.

The phosphodiesterase type 5 inhibitors have a low potential to interact with antihypertensive medications.[66] In a retrospective analysis of patients taking sildenafil in combination with α-adrenergic antagonists, β-adrenergic antagonists, diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or calcium channel blockers, the incidence of hypotension was similar to that reported in patients taking sildenafil alone.[67] This finding was confirmed by a retrospective analysis of pooled data of more than 4,800 patients in 35 clinical trials.[66]

Small decreases in blood pressure with clinically symptomatic orthostatic hypotension have been described in some patients taking phosphodiesterase type 5 inhibitors and α-adrenergic antagonists. The degree of hypotension that develops is dependent on several factors: (a) stability of patient's blood pressure prior to taking both drugs; (b) dose of the α-adrenergic antagonist used; (c) particular α-adrenergic antagonist used; (d) particular phosphodiesterase type 5 inhibitor used; and (e) timing of administration of both drugs. The drug interaction produces less hypotension when the patient has stable blood pressure prior to taking both drugs; a low dose of α-adrenergic antagonist is taken; a uroselective (eg, tamsulosin or silodosin) or extended-release formulation of an α-adrenergic antagonist (eg, alfuzosin, or modified-release doxazosin) is used; tadalafil is preferentially prescribed over sildenafil, vardenafil, or avanafil; and when there is an interval of 4 to 6 hours between the dosing of the α-adrenergic antagonist and phosphodiesterase type 5 inhibitor.[66]

Hepatic metabolism of all four phosphodiesterase type 5 inhibitors can be inhibited by strong enzyme inhibitors of CYP 3A4, including fluvoxamine, fluoxetine, nefazodone, verapamil, diltiazem, cimetidine, erythromycin, clarithromycin, itraconazole, ketoconazole, fluconazole itraconazole, atazanavir, indinavir, ritonavir, saquinavir, and grapefruit juice.[41,66] Potent CYP 3A4 inhibitors may increase plasma levels of phosphodiesterase type 5 inhibitors by

threefold or more.[5] Lower starting doses of the phosphodiesterase type 5 inhibitor should be used in these patients to minimize dose-related adverse effects, including cyanopsia, hypotension, flushing, nasal congestion, and priapism (see Table 99-4). Similarly, CYP 3A4 inducers, including carbamazepine, phenytoin, and phenobarbital, can decrease plasma levels of phosphodiesterase type 5 inhibitors.

If used with type 1A antiarrhythmics (eg, quinidine or procainamide) or type 3 antiarrhythmics (eg, sotalol, amiodarone), vardenafil can prolong the QT interval. This is a unique drug interaction of vardenafil and not a pharmacologic class effect.[66,67]

Testosterone Replacement Regimens

Mechanism

Testosterone replacement regimens supply exogenous testosterone and restore serum testosterone levels to the normal range of 300 to 1,100 ng/dL (10.4-38.2 nmol/L). In so doing, testosterone replacement regimens correct symptoms of hypogonadism, which include malaise, loss of muscle strength, depressed mood, and decreased libido. Testosterone can directly stimulate androgen receptors in the CNS and is thought to be responsible for maintaining normal sexual drive. In addition, testosterone may stimulate nitric oxide synthase, thereby increasing cavernosal concentrations of nitric oxide, and enhancing the effects of phosphodiesterase type 5 in cavernosal tissue.[68]

Indications

Testosterone replacement regimens are indicated in symptomatic patients with primary, secondary, or mixed hypogonadism, as confirmed with serum concentrations of testosterone that are less than 230-350 ng/dL (8.0-12.2 nmol/L).[69–71] Mixed hypogonadism is characteristic of aging men who undergo andropause, in which the Leydig cells of the testes slowly and progressively decrease testosterone production, and hypothalamic and pituitary production of gonadotropin and luteinizing hormone, respectively, are altered.[68–70] Serum testosterone levels decrease starting at age 40 years by approximately 10% per decade of life. This is often referred to as late-onset hypogonadism, symptomatic late-onset hypogonadism andropause, or the male menopause. Thus, the prevalence of late-onset hypogonadism ranges from 3.2% and 5.1% in men aged

60 to 69 years and in men aged 70 to 79 years old, respectively.[68–71] Symptoms include decreased libido, erectile dysfunction, gynecomastia, small testes, reduced growth of body hair and beard, decreased muscle mass, and increased body fat. If left untreated, patients develop anemia and osteoporosis.

Serum testosterone concentrations typically are measured in the early morning between 7 am and 11 am because the secretion pattern of this hormone follows a circadian pattern, with highest serum concentrations in the morning hours and the lowest level at night (approximately 10 pm). A low measured serum testosterone level is confirmed with a repeat measurement on a separate day, optimally 4 weeks later. Confirmation of a low serum testosterone level is essential because of an approximate 10% intra-individual variation of measured levels and variable performance characteristics of various testosterone assays.[10,15] Simultaneous serum luteinizing hormone levels help to distinguish patients with primary hypogonadism, who have elevated luteinizing hormone levels, from those with secondary hypogonadism, who have decreased luteinizing hormone levels.[71]

Testosterone replacement regimens should never be administered to men with normal serum testosterone levels, patients who have asymptomatic hypogonadism, or patients with isolated erectile dysfunction as the only sign of hypogonadism.

Efficacy

Testosterone replacement regimens restore muscle strength and sexual drive, promote erythropoiesis, and improve mood, cognition, and bone density in adult patients with hypogonadism.[69–71] Testosterone replacement regimens do not directly correct erectile dysfunction; instead, they improve libido, thereby correcting secondary erectile dysfunction.[70] Although testosterone replacement regimens may correct the serum testosterone level within days, clinical improvements are generally observed within days or weeks of the start of testosterone replacement. While increased libido may be evident at 6 weeks, improvements in erectile dysfunction or increase in muscle mass may take months. For this reason, a minimum effective clinical trial is considered 3 to 6 months.[71]

No additional benefit has been demonstrated for large doses of testosterone, which can increase the serum testosterone level from the low end to the upper end of the normal range or to the above-normal range.[69–71]

Testosterone replacement regimens can be administered parenterally, orally,

buccally, or transdermally (see Tables 99-4). Intramuscular injections of testosterone enanthate and cypionate are the preferred treatment for symptomatic patients with primary or secondary hypogonadism because they are effective, inexpensive, and not associated with the bioavailability problems or hepatotoxic adverse effects of oral androgens.[69] Patients generally require dosing every 2 to 4 weeks. A longer-acting depot intramuscular formulation of testosterone undecanoate, which can be dosed every 10 weeks, offers greater convenience but is more expensive than testosterone enanthate or cypionate. Testosterone undecanoate has been associated with pulmonary oil embolism and anaphylactic reactions that can necessitate hospitalization.[72] For this reason, testosterone undecanoate is restricted to settings certified through a Risk Evaluation and Mitigation Strategy Program. A subcutaneous implant of testosterone pellets lasts 3 to 6 months, but it requires a surgical incision in the forearm. Extrusion has been reported in up to 8.5% of treated patients and results in loss of drug effect.

Oral formulations are associated with hepatotoxicity and are not recommended; and the buccal formulation must be dosed twice a day and is expensive.[73] Although convenient for the patient, testosterone patches, gels, and sprays are much more expensive than testosterone enanthate or cypionate.[74] Therefore, they should be reserved for patients who refuse injectable testosterone.

In the ideal testosterone replacement regimen, the medication would mimic the normal circadian pattern of serum testosterone concentrations such that peak and trough concentrations occur in the early morning and late afternoon, respectively; produce serum concentrations in the normal range; produce serum concentrations of dihydrotestosterone and estradiol, which are metabolites of testosterone, that mimic the normal physiologic pattern; and produce minimal adverse effects.[70] The ideal replacement regimen should be inexpensive and be convenient for the patient to use. Table 99-4 compares commercially available testosterone replacement regimens for these characteristics and shows that an ideal regimen has yet to be identified.

The dropout rate with testosterone supplementation is high. Approximately 30% and 85% of patients stop testosterone replacement after 6 and 12 months, respectively. The reasons for this include the cost of the medication, slow onset of response, and inadequate perceived benefit.[69–71]

Pharmacokinetics

Natural testosterone has poor oral bioavailability because of extensive first-pass hepatic metabolism; therefore, large doses must be taken. To improve oral bioavailability, alkylated derivatives were formulated. Of these derivatives, methyltestosterone and fluoxymesterone are more resistant to hepatic catabolism and can be taken in smaller daily doses, which are theoretically safer. However, oral alkylated derivatives of testosterone are not metabolized to dihydrotestosterone or estradiol, are associated with a higher incidence of serious hepatotoxicity, and therefore are not preferred for management of hypogonadism.

An alternative to oral administration is the testosterone buccal system (Striant), which is applied to the gum above the upper incisor teeth twice per day. Over time it forms a gel from which testosterone is absorbed. One advantage of this route of administration is that the drug bypasses first-pass hepatic catabolism, which allows for increased bioavailability of testosterone. Serum testosterone levels are maintained in the normal range for approximately 80% of the day.[73]

Several testosterone esters have been formulated for intramuscular injection, with different durations of action (see Table 99-4). The shorter-acting testosterone propionate, which requires dosing three times per week, has been replaced with testosterone cypionate or enanthate, which can be dosed every 2, 4, or 6 weeks in most patients. These testosterone formulations produce supraphysiologic serum testosterone levels 2 to 4 days after each dose, which have been linked to mood swings and polycythemia in some patients.

After the first and second dose, which are given 4 weeks apart, intramuscular injections of testosterone undecanoate generally last 10 weeks.[72] An even longer-acting parenteral testosterone is available as a subcutaneous implant for dosing every 3 to 6 months.

Transdermal testosterone replacement regimens can be delivered as once-daily patches or gel. For convenience, the gel is available in premeasured dose packets or in a pump dispenser. Testosterone patches increase serum testosterone levels into the normal range in 2 to 6 hours. Serum testosterone levels return to baseline 24 hours after patch or gel administration. However, unlike oral or injectable supplements, transdermal testosterone patches applied at bedtime or testosterone gel applied each morning produce physiologic patterns of serum testosterone levels throughout the day. Although these formulations are often described as producing more “natural” hormone levels, the clinical importance of this biochemical effect is unknown.[68–70]

The original Testoderm brand patch was formulated for scrotal application.

Scrotal skin is thinner and has a richer vascular supply than does the skin on the arms or thighs. Therefore, application of Testoderm patches produced excellent absorption of the hormone. However, the patch could detach when the scrotum became damp or moist, when the patient exercised, or if the scrotum was excessively hairy.[74] Due to its inconvenient site of application, the scrotal patch is no longer commercially available in the United States.

For improved convenience, Androderm patches were formulated for application to the upper arms, back, abdomen, or thighs. The addition of absorption enhancers and adhesives has been linked to a higher incidence of contact dermatitis with Androderm patches compared with the original Testoderm scrotal patch or to gel formulations.[74]

When compared to patches, testosterone gel 1% formulation (AndroGel) is applied in much larger doses (5 or 10 g each day) to the skin of the shoulders, upper arms, or abdomen. The hormone is absorbed quickly, within 30 minutes, but several hours may be required for complete absorption of the dose. For this reason, the patient should be reminded to wait at least 2 hours after application before showering. To prevent inadvertent transfer of testosterone gel to others, the patient should thoroughly wash his hands with soap and water after administration of a dose, allow the application site to dry undisturbed for several minutes before dressing or covering it, and ensure that there is no contact with clothing contaminated with the gel by children and female members of the household.

A high-strength testosterone gel (1.6%) formulation is also available. It allows administration of a daily dose with a smaller amount of gel. It should be applied to the shoulder or upper arms.

Dosing

Table 99-4 lists the usual doses for testosterone replacement regimens. Three to 6 months is considered as an adequate treatment trial with a particular dose.[68–71] Thus, a dose should not be increased until the patient has used one particular dose for at least this time period. The recommended target serum testosterone level is the mid normal range, or 450 to 600 ng/dL (15.6-20.8 nmol/L). Repeated serum testosterone levels that exceed the normal range or produce adverse effects will necessitate a dosage reduction or increased interval between drug doses. **Table 99-7** provides guidance on the timeline for monitoring serum testosterone levels based on the particular testosterone formulation used. After starting treatment, patients should be reassessed in 1 to 3 months. The patient's libido, mood, and quality of life may improve in 3 to 4 weeks, erectile function

may improve in 6 months, but other symptoms of hypogonadism (eg, bone density) may take longer to resolve. If the patient responds to treatment and serum testosterone levels have returned to normal, the patient can be followed up annually. At each visit, the use of a validated self-assessment tool (eg, Androgen Deficiency in Aging Men Questionnaire) can assist the physician in gauging the patient's response to treatment.[75]

TABLE 99-7 Timing of Serum Testosterone Level Monitoring in Patients on Testosterone Replacement Regimens

When to Monitor Serum Testosterone Levels	
Oral testosterone tablets/ capsules	2-3 hours after dose for peak level only
Intramuscular testosterone cypionate or enanthate	Midpoint of dosing interval or measure trough level right before the 4th dose
Intramuscular testosterone undecanoate	Just before each subsequent injection or measure level halfway between 10-week dosing interval
Transdermal gel	Depending on the formulation, just before dose in the morning 2-4 weeks after start of therapy or after a dose adjustment
Transdermal patch	Before the next dose 2 weeks after start of therapy or after a dose adjustment
Axillary solution	2-8 hours after application and 2 weeks after starting therapy or after a dosage adjustment
Testosterone subcutaneous implant	3-6 months after implantation, obtain trough level just before next dose
Buccal system	Before the morning dose, 4-12 weeks after initiating treatment.

Before initiating any testosterone replacement regimen in patients 40 years and older, patients should be screened for breast cancer, benign prostatic hyperplasia, and prostate cancer. All are testosterone-dependent conditions and theoretically could be worsened by exogenous administration of testosterone. However, no confirmed cases of prostate cancer caused by testosterone supplementation in a hypogonadal patient have been documented.[76–78] Nevertheless, untreated prostate cancer is a contraindication to androgen supplementation. To screen for prostate disorders, a prostate-specific antigen serum concentration should be obtained and a digital rectal examination of the

prostate performed. These tests are generally repeated at 1-year intervals after treatment is started. Also, since testosterone supplementation has been reported to worsen severe sleep apnea or edema of congestive heart failure, caution should be exercised in using testosterone in patients with these disorders.[14,20,71]

Other baseline tests that are recommended include hematocrit and liver function tests. These should be repeated 3 and 6 months after the start of a testosterone replacement regimen. If normal, these tests can be repeated annually thereafter. If the hematocrit exceeds 55% (0.55), the testosterone replacement regimen should be withheld to avoid polycythemia and its consequences.

Adverse Effects

Testosterone replacement regimens can cause sodium retention, which can lead to weight gain, or exacerbate hypertension, congestive heart failure, and edema (Table 99-6). Although serum lipoprotein perturbations may occur, testosterone replacement regimens have a neutral effect in that they decrease both total cholesterol and high-density lipoprotein cholesterol levels. Two recent retrospective studies have associated testosterone supplementation with an increased risk of myocardial infarction and stroke.[79,80] However, these studies did not prove a cause–effect relationship and are considered inconclusive. Nevertheless, the FDA has posted a warning that testosterone supplementation may lead to cardiovascular disease and physicians should discuss this potential risk with patients before initiating treatment. This was prompted by the significant increase in testosterone use in the United States, inadequate monitoring of serum testosterone levels prior to and during testosterone supplementation, and the potential hazards of using testosterone supplementation in elderly patients with cardiovascular risk factors.[81]

Gynecomastia can occur as a result of conversion of testosterone to estrogen in peripheral tissues. This has been reported most often in patients with liver cirrhosis or those who are obese.

Oral alkylated testosterone replacement regimens have caused hepatotoxicity, ranging from mild elevations of hepatic transaminases to serious liver diseases, including peliosis hepatis (hemorrhagic liver cysts), hepatocellular and intrahepatic cholestasis, and benign or malignant tumors. For this reason, parenteral or transdermal testosterone replacement regimens are preferred.

Transdermal testosterone patches may cause contact dermatitis, which responds well to topical corticosteroids. This adverse effect has been associated with the presence of permeation enhancers, which are added to patch formulations. If the dermatitis from the patch formulation becomes problematic,

testosterone gel is associated with a lower incidence of contact dermatitis.

Erythrocytosis occurs most often in patients receiving parenteral testosterone formulations. If the increase in hematocrit is mild, decreasing the dose of testosterone replacement is all that is needed. However, if the hematocrit exceeds 55% (0.55), of testosterone injections should be stopped and can be replaced with a transdermal testosterone product.[14,15,68,71]

Alprostadil

Mechanism

Alprostadil, also known as prostaglandin E_1, stimulates adenyl cyclase, resulting in increased production of cAMP, a secondary messenger that activates protein kinase A, which decreases intracellular calcium concentrations and causes smooth muscle relaxation of the arterial blood vessels and sinusoidal tissues in the corpora. This results in enhanced blood flow to and blood filling of the corpora.[82] Because it does not require nitric oxide to produce its clinical effects, patients with erectile dysfunction due to diseases that are associated with an impaired nitric oxide pathway (eg, diabetes mellitus, post radical prostatectomy, and failure of phosphodiesterase type 5 treatment) may respond to alprostadil. In one study, 88% of men who failed to respond to sildenafil responded to intracavernosal alprostadil.[35,83]

Alprostadil is commercially available as an intracavernosal injection (Caverject and Edex) and as an intraurethral insert (medicated urethral system for erection [MUSE]).

Indications

Both commercially available formulations of alprostadil are FDA approved as monotherapy for management of erectile dysfunction. Alprostadil is more effective by the intracavernosal route than the intraurethral route.

The enhanced efficacy of the intracavernosal injection may be related to the excellent bioavailability of the drug when injected directly into the corpora cavernosum. In contrast, intraurethral alprostadil doses generally are several hundred times larger than intracavernosal doses. This is because intraurethral alprostadil must be absorbed from the urethra, through the corpus spongiosum, and into the corpus cavernosum, where it exerts its full proerectogenic effect.

Although several other agents, including papaverine and phentolamine, have

been used off-label for intracavernosal therapy, alprostadil is preferentially prescribed. This is because intracavernosal alprostadil has been approved by the FDA for erectile dysfunction, it does not require extemporaneous compounding, and it has a low potential for causing prolonged erections and priapism.

Both formulations of alprostadil are considered more invasive than VEDs or phosphodiesterase type 5 inhibitors. For this reason, intracavernosal alprostadil is generally prescribed after patients do not respond to or cannot use less invasive interventions. Intracavernosal alprostadil is preferred over intraurethral alprostadil because of its greater effectiveness. Intracavernosal alprostadil may be preferred in patients with diabetes mellitus, who are accustomed to injectable drug therapy and may have peripheral neuropathies, which decrease the patient's perception of pain upon injection. Intraurethral alprostadil is generally reserved as a treatment of last resort for patients who do not respond to other less invasive and more effective forms of therapy, and who refuse surgery.

Intracavernosal Alprostadil

Efficacy The overall efficacy of intracavernosal alprostadil is 70% to 90%.[20,82,83] Three characteristics of intracavernosal alprostadil include the following:

1. The effectiveness of alprostadil is dose-related. The mean duration of erection is directly related to the dose of alprostadil administered and ranges from 12 to 44 minutes.
2. A higher percentage of patients with psychogenic and neurogenic erectile dysfunction respond to alprostadil at a lower dose compared to patients with vasculogenic erectile dysfunction.
3. Tolerance does not appear to develop with continued use of intracavernosal alprostadil at home.

10 Although 70% to 75% of patients respond to intracavernosal alprostadil, a high proportion of patients elect to discontinue its use over time. Depending on the study and the length of observation, 30% to 50% of patients voluntarily discontinue therapy, usually during the first 6 to 12 months, and this increases to 54% and 67% after 2 to 4 years, respectively.[5,20] After 10 years, fewer than 5% of patients continue intracavernosal injections.[84] Common reasons for discontinuation include lack of perceived effectiveness; inconvenience of administration; an unnatural, nonspontaneous erection; needle phobia; penile pain, loss of interest; or cost of therapy.[31,83]

Approximately one-third of patients do not respond to usual doses of

intracavernosal alprostadil. In these patients, intracavernosal alprostadil has been used successfully along with VEDs. Such combination therapy can be attempted by patients before transitioning to more invasive surgical procedures.[31,35,36] Alternatively, intracavernosal injections of synergistic combinations of vasoactive agents that act by different mechanisms have been used. For example, papaverine is a nonspecific phosphodiesterase inhibitor that increases cavernosal concentrations of cAMP and cGMP, and phentolamine is an α-adrenergic antagonist that blocks detumescence (thereby prolonging an erection). Intracavernosal drug combinations typically produce an erection that lasts longer than an erection produced by any one of the agents in the mixture. In addition, because of the low dosage of each agent in the combination, fewer systemic and local fibrotic adverse effects develop compared with high-dose monotherapy. For example, when used in low-dose combination regimens, papaverine is less likely to induce hypotension and liver dysfunction, and phentolamine is less likely to induce tachycardia and hypotension.[5,20] However, such intracavernosal drug combinations are not commercially available and must be extemporaneously compounded. Several different two- or three-drug formulations have been used, but no one formulation is considered a standard.[36] Finally, intracavernsoal alprostadil has been used in combination with phosphodiesterase type 5 inhibitors; however, this use is an unlabeled indication.[36,85]

Pharmacokinetics Intracavernosal injection should be administered into only one corpus cavernosum. From this injection site, the drug will reach the other corpus cavernosum through vascular communications between the two corpora. Alprostadil acts rapidly, with an onset of 5 to 15 minutes. The duration is directly related to the dose. Within the usual dosage range of 2.5 to 20 mcg, the duration of erection is not more than 1 hour. Higher doses are expected to exhibit a longer duration of action. Local 15-hydroxy dehydrogenase in the corpora cavernosum quickly converts alprostadil to inactive metabolites. Any alprostadil that escapes into the systemic circulation is deactivated on first pass through the lungs. Hence, the plasma half-life of alprostadil is approximately 5 to 10 minutes, and the potential for systemic and local adverse effects is negligible.[30,82] Dose modification is not necessary in patients with renal or hepatic disease.

Dosing The usual dose of intracavernosal alprostadil is 10 to 20 mcg, with a maximum recommended dose of 60 mcg. Doses greater than 60 mcg have not produced any greater improvement in penile erection but may cause hypotension

or prolonged erections lasting more than 1 hour.[82] The dose should be administered 5 to 10 minutes before intercourse. The manufacturer recommends that patients be slowly titrated up to the minimally effective dosage to minimize the likelihood of hypotension. Under a physician's supervision, patients should be started with a 1.25-mcg dose, which can be increased in increments of 1.25 to 2.50 mcg at 30-minute intervals up to the lowest dose that produces a firm erection for 1 hour and does not produce adverse effects. In clinical practice, this process is rarely done because it is time consuming. Thus, many physicians start the patient on 10 mcg and move quickly up the dosage range to identify the best dose for the patient. To avoid adverse effects, patients should receive not more than one injection per day and not more than three injections per week with a 24-hour interval between doses (see Table 99-4).

Intracavernosal injections should be performed using a 0.5-in. (1.3 cm), 27- or 30-gauge needle. A tuberculin syringe or a syringe prefilled with diluent as supplied by the manufacturer should be used to ensure precise measurement of doses. Patients with needle phobia, poor vision, or poor manual dexterity can use commercially available autoinjectors to facilitate administration of intracavernosal alprostadil.[30]

Intracavernosal injections require that the patient or the sexual partner practice good aseptic techniques (to avoid infection), have good manual skills and visual ability, and be comfortable with injection techniques. When practicing self-injection, the patient should use one hand to firmly hold the glans penis against his thigh to expose the lateral surface of the shaft. The injection should be made at right angles into one of the lateral surfaces of the proximal third of the penis. The injection should never be made into the dorsal or ventral surface of the penis. This will prevent inadvertent injection of the drug into arteries on the dorsal surface or the urethra on the ventral surface. After the injection, the penis should be massaged to help distribute the drug into the opposite corpus cavernosum. Injection sites should be rotated with each dose. Finally, manual pressure should be applied to the injection site for 5 minutes to reduce the likelihood of hematoma formation (**Fig. 99-5**).

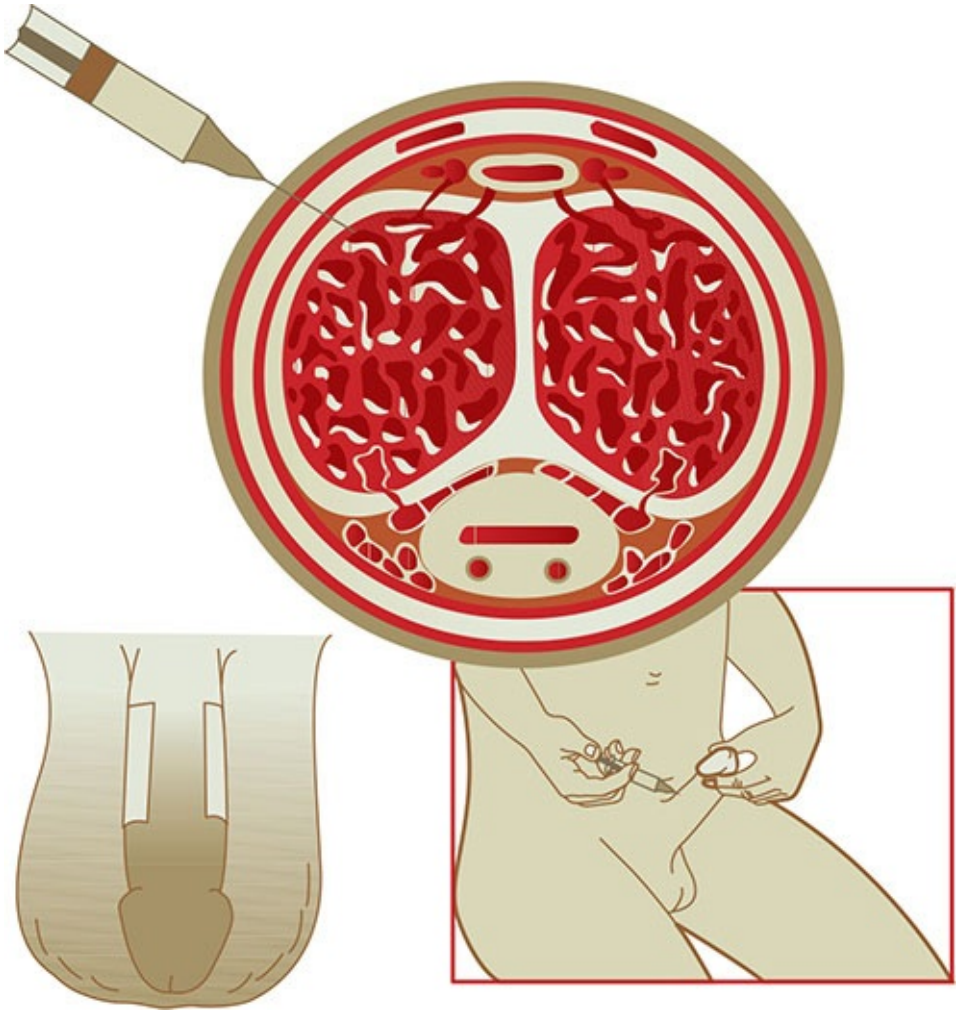


FIGURE 99-5 Technique for administration of intracavernosal injections. (*Source: From Caverject [package insert]. New York, NY: Pfizer Inc.; 2006.* http://www.Pfizer.com/files/products/USPi_caverject_impulse.pdf. *Accessed November 1, 2018.*)

Once the optimal dosage of intracavernosal alprostadil is established, the patient should return for routine medical follow-up every 3 to 6 months. Some patients subsequently require dosage adjustment, largely attributed to worsening of the underlying disease that is contributing to the erectile dysfunction.

Adverse Effects

Intracavernosal alprostadil is most commonly associated with local adverse effects. Hematoma and bruising at the injection site occur most often during the first year of therapy. These effects are largely the result of poor injection technique. To minimize the risk of injection site hematomas, patients should apply pressure to the injection site for 5 minutes after each dose. Similarly,

infection at the injection site has been reported. Meticulous aseptic technique is necessary to prevent this complication.

Cavernosal plaques or areas of fibrosis at injection sites form in approximately 2% to 12% of patients. When they occur, the patient should suspend further injections for 2 to 4 months or until the plaques resolve.[82] These plaques may cause penile curvature, similar to Peyronie's disease, which makes sexual intercourse difficult or impossible. The cause of corporal fibrosis and plaque formation is unknown. This adverse effect may be caused by poor injection technique or by alprostadil itself. Although patients have developed corporal fibrosis, alprostadil may be less likely to cause this adverse effect compared to other intracavernosal drug combinations, such as phentolamine or papaverine. Unlike cavernosal fibrosis associated with large doses and repeated administration of papaverine, penile scarring secondary to alprostadil appears to be unpredictable.

Alprostadil causes penile pain in approximately 10% to 44% of patients. The pain has been described as a burning discomfort or dull pain near the injection site or during the erection, which generally does not persist after the penis becomes flaccid. The pain usually is mild, generally does not require discontinuation of therapy, and often abates even with continued treatment. However, 2% to 5% of patients discontinue taking alprostadil because of severe pain. The pain can be managed by oral analgesics (eg, acetaminophen), if necessary. One investigator has recommended adding procaine to intracavernosal alprostadil, but this may mask the signs of more serious adverse effects of the drug or of penile injury during intercourse and is not recommended.[82] The mechanism of this adverse reaction is poorly understood. Alprostadil may intrinsically produce pain. In addition, the pain may be a result of the pH of the parenteral solution. Alprostadil is acidic, and the commercially available Caverject formulation is buffered with sodium citrate, a weak base, to reduce pain on injection.[82]

Priapism, a prolonged, painful erection lasting more than 1 hour, occurs in 1% to 15% of treated patients. It occurs most often during the dose titration period and is rare thereafter. Blood sludging in the corpora can lead to tissue hypoxia and irreversible cavernosal fibrosis and scarring. The risk for this complication is greatest for erections that persist beyond 4 to 6 hours. Patients are advised to seek medical attention immediately when drug-induced erections last more than 4 hours, as this may progress to a urologic emergency. Its management includes supportive care, including analgesics for pain and sedatives for anxiety. In addition, needle aspiration of sludged blood in the

corpora or intracavernosal injection of α-adrenergic agonists (eg, phenylephrine) has been used. These procedures facilitate venous drainage of the corpora, allowing venous outflow to "catch up" with arterial inflow.[30,31]

The likelihood of prolonged erections with intracavernosal alprostadil is dose-related. Therefore, to prevent this adverse effect, the lowest effective dose should be used, and the dose should be titrated to ensure that the duration of the erection is not more than 1 hour.

Intracavernosal alprostadil rarely causes systemic adverse effects, owing to the agent's local catabolism in cavernosal tissue and rapid deactivation in pulmonary tissue (if any of the drug escapes into the systemic circulation). However, large doses greater than 20 mcg are associated with dizziness and hypotension in some patients and is one reason why such large doses are not commonly used.

Intracavernosal injection therapy should be used cautiously by patients at risk for priapism, including patients with sickle cell disease, leukemia, or multiple myeloma. It should be used cautiously by patients who may develop bleeding complications secondary to injections, including patients with thrombocytopenia or those taking anticoagulants. It also should be used cautiously by patients who use poor-quality injection technique, including patients with psychiatric disorders, obese patients (who may not be able to reach or see the penile injection site), patients who are blind, patients with severe arthritis, or patients with abnormal penile anatomy.[20,36,82]

Intraurethral Alprostadil

10 **Efficacy** Intraurethral alprostadil inserts are marketed as MUSE, which contains a medication pellet inside a prefilled urethral applicator. Multiple studies show this product has an overall effectiveness rate of 43% to 65%[5,86] compared with 70% to 90% for intracavernosal alprostadil. Its decreased effectiveness and inconvenient administration method have resulted in this product being considered a third-line treatment option for patients with erectile dysfunction. However, some patients have responded to intraurethral alprostadil even though they did not respond to intracavernosal alprostadil[87] or sildenafil.[86]

Intraurethral alprostadil has been combined with a VED to improve treatment response.[30,31,35]

The voluntary dropout rate is high and has been reported to be 57% and 75% after 3 and 15 months, respectively.[86]

Intraurethral alprostadil should be avoided in patients with urethral stricture

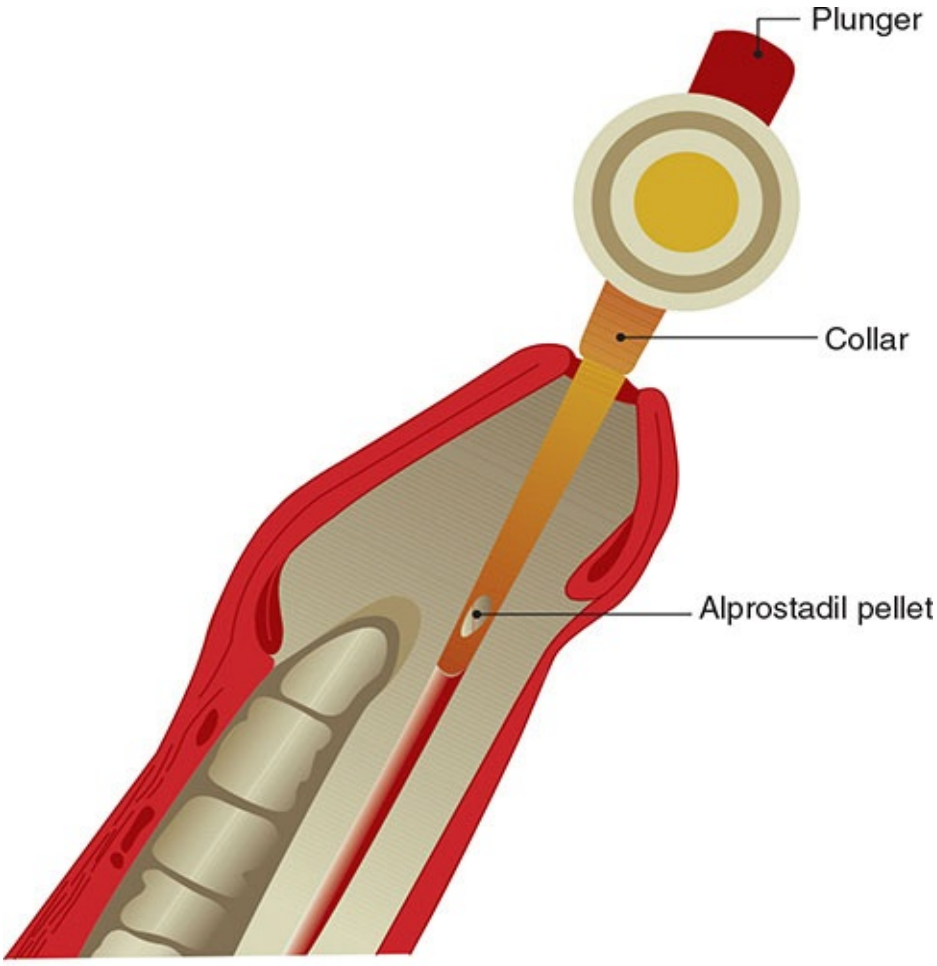
or urethritis, or if the female partner is pregnant.

Pharmacokinetics Following intraurethral instillation, alprostadil is absorbed quickly through the urethra, into the corpus spongiosum, and then into the corpora cavernosum. As much as 80% of each dose is absorbed by the urethra and corpus spongiosum in less than 10 minutes, with peak absorption occurring in 20 to 25 minutes. An estimated 20% of each dose is delivered to the corpora cavernosum. As with intracavernosal injections of alprostadil, any drug absorbed into the systemic circulation is rapidly metabolized on first pass through the lungs.

The onset after intraurethral insertion is similar to that of intracavernosal injection, 5 to 10 minutes, and the duration is 30 to 60 minutes.

Dosing The usual dosage range of intraurethral alprostadil is 125 to 1,000 mcg, but 500 mcg is typically needed in most patients.[86] The dose should be administered 5 to 10 minutes before sexual intercourse. Not more than two doses per day are recommended. Before administration, the patient should be advised to empty his bladder, voiding completely (see Table 99-3).

Similar to intracavernosal injection treatments, intraurethral insertion of alprostadil requires good manual and visual skills to minimize the risk of urethral injuries. Intraurethral alprostadil is supplied in a prefilled intraurethral applicator. The patient should void first to moisten the urethra. With one hand the patient holds the glans penis, and with the other hand the patient inserts the intraurethral applicator 0.5 in. (1.3 cm) into the urethra. The drug pellet is then pushed into the urethra. The penis should be massaged to enhance drug dissolution in the urethral fluids and drug absorption (**Fig. 99-6**).


Plunger
Collar
Alprostadil pellet

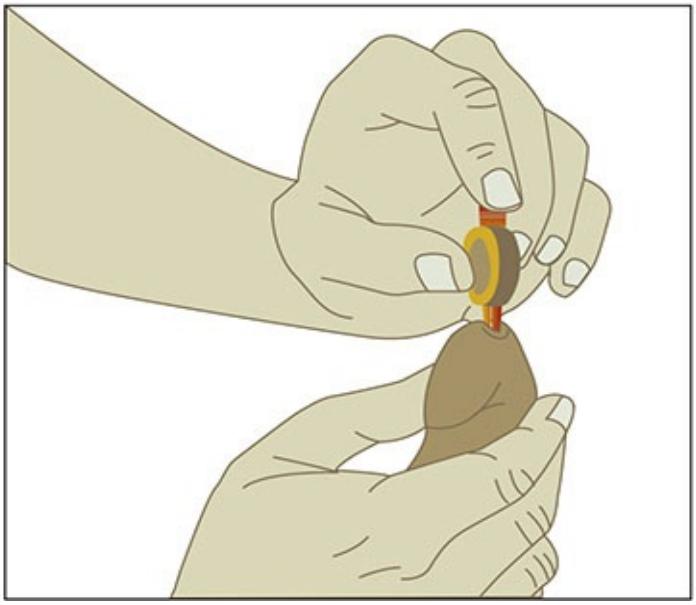


FIGURE 99-6 Technique for administration of intraurethral alprostadil with a medicated urethral system for erection applicator. (*Source: From Muse [package insert]. Mountain View, CA: Vivus, Inc.; 2003.* https://medlibrary.org/lib/rx/meds/muse. *Accessed November 1, 2018.*)

Adverse Effects

The urethra can be injured because of an improper administration technique. Injuries can lead to urethral bleeding or stricture and difficulty voiding. Patients should receive complete education about optimal administration procedures before starting treatment.

Urethral pain has been reported in 24% to 43% of patients. Usually it is mild and does not require discontinuation of treatment. Approximately 6% of female sexual partners may experience vaginal burning, itching, or pain, which probably is related to transfer of alprostadil from the man's urethra to the woman's vagina during intercourse.[30,31,86]

Prolonged painful erections (priapism) have been rarely reported. Syncope and dizziness have been reported rarely (only 2%-3% of patients) and likely are related to use of excessively large doses.

Unapproved Agents

A variety of other commercially available and investigational agents have been used for management of erectile dysfunction. Although it is beyond the scope of this chapter to discuss all of them, some of the more commonly used agents are discussed here.

Yohimbine

Yohimbine, a tree-bark derivative also known as *yohimbe*, is widely used as an aphrodisiac. Yohimbine is a central α_2-adrenergic antagonistic that increases catecholamines and improves mood. Some investigators believe that yohimbine has peripheral proerectogenic effects. Yohimbine may reduce peripheral α-adrenergic tone, thereby permitting a predominant cholinergic tone, which could result in a vasodilatory response.[20] The usual oral dose is 6 to 15 mg three times per day.

Based on a meta-analysis of published studies that concluded that yohimbine is only mildly efficacious for psychogenic erectile dysfunction,[5] the American Urological Association has cautioned against the use of yohimbine.[20] In

addition, yohimbine can cause many systemic adverse effects, including anxiety, insomnia, tachycardia, and hypertension.

Papaverine

Papaverine is a nonspecific phosphodiesterase type 5 inhibitor that decreases metabolic catabolism of cAMP in cavernosal tissue. As a result of enhanced tissue levels of cAMP, smooth muscle relaxation occurs. Cavernosal sinusoids fill with blood, and a penile erection results.

Papaverine is not FDA approved for erectile dysfunction. Intracavernosal papaverine alone is not commonly used for management of erectile dysfunction because the large doses required to achieve a therapeutic effect also produce dose-related adverse effects, such as priapism, corporal fibrosis, hypotension, and hepatotoxicity.[88] Papaverine is more often administered in lower doses combined with phentolamine and/or alprostadil. A variety of formulas have been used, but no one mixture has been proven better than other mixtures. Combination formulations are considered safer and are associated with the potential for fewer serious adverse effects than high doses of any one of these agents.

A portion of each papaverine dose is systemically absorbed, and its prolonged plasma half-life of 1 hour contributes to adverse effects. The usual dose of papaverine is 7.5 to 60 mg when used as a single agent for intracavernosal injection. When used in combination, the dose decreases to 0.5 to 20 mg.

If treated with papaverine, patients with a history of underlying liver disease or alcohol abuse should undergo liver function testing at baseline and every 6 to 12 months during continued treatment.

Phentolamine

Phentolamine is a competitive nonselective α-adrenergic blocking agent. It reduces peripheral adrenergic tone and enhances cholinergic tone. As a result, it improves cavernosal filling and is proerectogenic.[20]

Phentolamine has most often been administered as an intracavernosal injection. Monotherapy is avoided because large doses are required for an erection, and at these large doses systemic hypotensive adverse effects would be prevalent. Most often, phentolamine has been used in combination with other vasoactive agents for intracavernosal administration. A ratio of 30-mg papaverine to 0.5 to 1 mg phentolamine is typical, and the usual dose ranges from 0.1 to 1 mL of the mixture. Such a mixture promotes local effects of

phentolamine and minimizes systemic hypotensive adverse effects.

Hypotension is the most common adverse effect of intracavernosal phentolamine. It is more common and more severe with large doses or in patients with a poor injection technique who have injected into a vein (rather than the cavernosa). Prolonged erections have been reported in patients who used excessive doses of intracavernosal medications in combination.

Penile Prostheses

Surgical insertion of a penile prosthesis is the most invasive treatment of erectile dysfunction. It is reserved for patients who do not respond to or who are not candidates for less invasive medical treatments or devices.

Prosthesis insertion requires anesthesia and skilled urologists. Two prostheses are widely used: malleable and inflatable. Malleable or semirigid prostheses consist of two bendable rods that are inserted into the corpora cavernosa. The patient appears to have a permanent erection after the procedure; the patient is able to bend the penis into position at the time of intercourse.[5,20,89]

The inflatable prosthesis has several mechanical parts, including a pump, reservoir, and fillable cylinders. Once it is manually activated, a pump transfers fluid from a reservoir into the cylinders in the corpora cavernosa. The inflatable prosthesis produces a more natural erection, and for this reason, it is associated with a higher patient satisfaction rate than a malleable prosthesis.[89,90] The patient develops an erection only when the device is activated. Inflatable prostheses are available as 2- or 3-piece devices; fewer mechanical parts are associated with fewer malfunctions.[90] With improvements in technology, inflatable devices can be placed during shorter surgical procedures and have a low 10-year mechanical failure rate (5%-15%) as compared with the original inflatable prostheses (**Fig. 99-7**).[20,90]

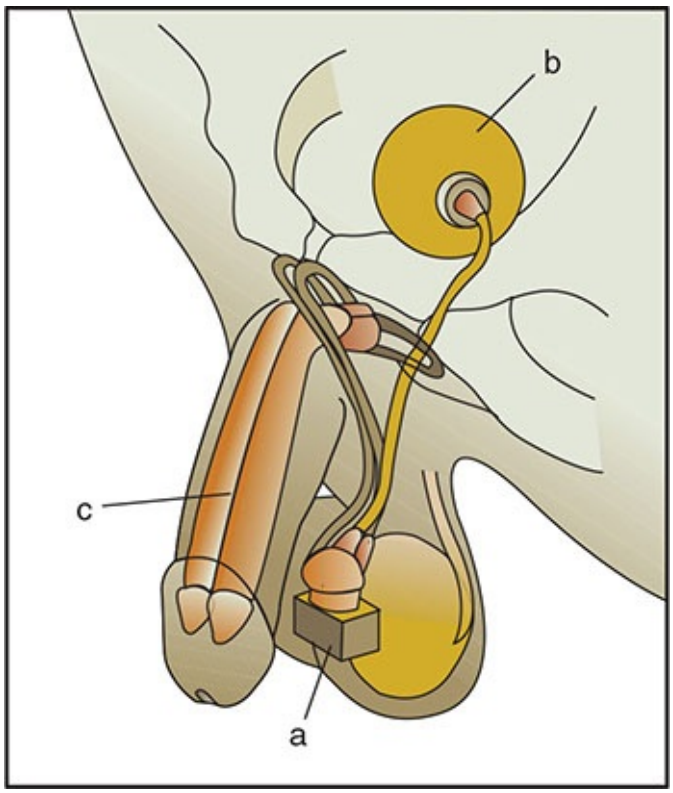


FIGURE 99-7 Example of surgically implanted penile prosthesis. (a, activation mechanism; b, reservoir with fluid for inflating prosthesis; c, inflatable rods in corpora.) (*From the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases.*)

Penile prostheses provide penile rigidity suitable for vaginal intercourse and are associated with a greater than 90% patient satisfaction rate, which is generally higher than that observed with any other drug treatment or VED.[90] The surgical success rate after insertion is 82% to 98%.[90]

Adverse effects of prosthesis insertion can occur early or late after the surgical procedure. The most common early complication is infection.[91] Late complications include mechanical failure of the prosthesis, erosion of the rods through the penis, or late-onset infection. Although some salvage procedures have been devised, in many cases the prosthesis requires removal.

EVALUATION OF THERAPEUTIC OUTCOMES

The primary therapeutic outcomes of specific treatments for erectile dysfunction include (a) improvement in the quantity and quality of penile erections suitable for intercourse and (b) avoidance of adverse drug reactions and drug

interactions.

At baseline and after the patient has completed a clinical trial period of several weeks with a specific treatment for erectile dysfunction, the physician should conduct assessments to determine whether the quality and quantity of penile erections has improved. A patient's level of satisfaction is highly individualized, depending on his lifestyle and expectations. Therefore, a patient who has successful intercourse once per week might be completely satisfied, whereas another patient might judge this to be unsatisfactory. Patients with unrealistic expectations in this regard must be identified and counseled by clinicians to avoid adverse effects of excessive use of erectogenic agents.

Failure to improve the quality and quantity of penile erections suitable for intercourse after an appropriate clinical trial period with a specific treatment for erectile dysfunction occurs in a significant percentage of patients. In this case, physicians generally take the following steps to:

1. Ensure that the patient has been prescribed a maximum tolerated dose and has an adequate clinical trial of a specific treatment before discarding it as ineffective.
2. Switch to another drug (see Fig. 99-2).
3. Reserve surgical treatment for patients who do not respond to drug treatment.

CONCLUSION

Erectile dysfunction is a common disorder of aging men. Its incidence is higher in patients with underlying medical disorders that compromise the vascular, neurologic, hormonal, or psychogenic systems necessary for a normal penile erection. Medications are common causes of erectile dysfunction. By correcting the underlying etiology, erectile dysfunction can often be reversed without the use of specific treatments. When treatment of erectile dysfunction is needed, the least invasive options should be used first because they produce the lowest incidence of serious adverse effects. Phosphodiesterase type 5 inhibitors are first-line treatment. If this fails or if the patient cannot use a phosphodiesterase type 5 inhibitor, a VED or intracavernosal alprostadil injection therapy can be initiated. If this treatment fails, the patient can attempt a combination of intracavernosal alprostadil and VED, combination intracavernosal therapy, or intraurethral alprostadil. If this treatment fails, the patient may require insertion of a penile prosthesis. Some insurance companies do not reimburse for drug treatments for erectile dysfunction, so cost is an important issue for patients.

Clinicians should provide clear and simple advice. Patient confidentiality and privacy, which are extremely important to men with erectile dysfunction, should be maintained at all times.

Postclass Engaged Learning Activity

Existing medical treatments for erectile dysfunction are being developed. Two such treatments include low intensity shock wave therapy and stem cell treatment. Conduct a literature search for the most recent 5-year period and retrieve an appropriate research or review article. After reading it, please summarize the mechanism of action, method of administration, and advantages and disadvantages of these treatment strategies.

ABBREVIATIONS

cAMP	cyclic adenosine monophosphate
cGMP	cyclic guanosine monophosphate
CNS	central nervous system
IIEF	International Index of Erectile Function
LUTS	lower urinary tract symptoms
NAION	nonarteritic anterior ischemic optic neuropathy
REMS	Risk Evaluation and Mitigation Strategies
VED	vacuum erection device

REFERENCES

1. NIH Consensus Development Panel on Impotence. Impotence. NIH Consensus Development Panel on Impotence. *JAMA*. 1993;270(1):83–90.
2. McCabe MP, Sharlip ID, Lewis R, et al. Incidence and prevalence of sexual dysfunction in women and men: A consensus statement from the Fourth International Consultation on Sexual Medicine 2015. *J Sex Med*. 2016;13(2):144–152.
3. Johannes CB, Aranjo AB, Feldman HA, et al. Incidence of erectile dysfunction in men 40–69 years old: Longitudinal results from the Massachusetts Male Aging Study. *J Urol*. 2000;163(2):460–463.

4. Bacon CG, Mittleman MA, Kawachi I, et al. Sexual function in men older than 50 years of age: Results from the Health Professionals Follow-up Study. *Ann Intern Med*. 2003;139(3):161–168.
5. Porst H. Burnett A, Brock G, et al. SOP conservative (medical and mechanical treatment of erectile dysfunction. *J Sex Med*. 2013;10(1):130–171.
6. Kim SC, Seo KK, Kim TH. Reasons and predictive factors for discontinuation of PDE-5 inhibitors despite successful intercourse in erectile dysfunction patients. *Int J Impot Res*. 2014;26(3):87–93.
7. Frederick LR, Cakir OO, Arora H, et al. Undertreatment of erectile dysfunction: Claims analysis of 6.2 million patients. *J Sex Med*. 2014;11(10):2546–2553.
8. Lindau ST, Schumm LP, Laumann EO, et al. A study of sexuality and health among older adults in the United States. *N Engl J Med*. 2007;357(8):762–774.
9. Andersson KE. Mechanisms of penile erection and basis for pharmacological treatment of erectile dysfunction. *Pharmacol Rev*. 2011;63(4):811–859.
10. Paduch DA, Brannigan RE, Fuchs EF, et al. The laboratory diagnosis of testosterone deficiency. *Urology*. 2014;83(5):980–988.
11. Khera M, Adaikan G, Buvat J, et al. Diagnosis and treatment of testosterone deficiency: Recommendations from the Fourth International Consultation for Sexual Medicine. *J Sex Med*. 2016;13(12):1787–1804.
12. Tajar A, Huhtaniemi IT, O'Neill TW, et al. Characteristics of androgen deficiency in late-onset hypogonadism: Results from the European Male Aging Study. *J Clin Endocrinol Metab*. 2012;97(5):1508–1516.
13. Mobley DF, Khera M, Baum N. Recent advances in the treatment of erectile dysfunction. *Postgrad Med J*. 2017;93 (1105):679–685.
14. Greenspan MB, Barkin J. Erectile dysfunction and testosterone deficiency syndrome: The portal to men's health. *Can J Urol*. 2012;19(suppl 1):18–27.
15. Lunenfeld B, Mskhalaya G, Zitzmann M, et al. Recommendations on the diagnosis, treatment, and monitoring of late onset hypogonadism in men-a suggested update. *Aging Male*. 2015;18(1):5–15.
16. Patel JP, Lee EH, Mena-Hurtado CI. Evaluation and management of erectile dysfunction in the hypertensive patient. *Curr Cardiol Rep*. 2017;19(9):89. doi: 10.1007/s11886-017-0889-z.

17. Chrysant SG. Antihypertensive therapy causes erectile dysfunction. *Curr Opin Cardiol*. 2015;30(4):399–390.
18. Clayton AH, Croft HA, Handiwala L. Antidepressants and sexual function: Mechanisms and clinical implications. *Postgrad Med*. 2014;126 (2):91–99.
19. Lee M, Sharifi R. Sexual dysfunction in men. In: Tisdale JE, Miller DA, eds. Drug-Induced Disease-Prevention, *Detection, and Management*. 2nd ed. Bethesda, MD: American Society of Health-System Pharmacists; 2010;686–701.
20. Burnett AL, Nehra A, Breau RH, et al. American Urological Association Guideline on the Management of Erectile Dysfunction 2018. Available at: http://www.auanet.org/guidelines/male-sexual-dysfunction-erectile-dysfunction. Accessed November 1, 2018.
21. Rosen RC, Riley A, Wagner G, et al. The International Index of Erectile Function (IIEF): A multidimensional scale for assessment of erectile dysfunction. *Urology*. 1997;49(6):822–830.
22. Baumann F, Hehli D, Makaloski V, et al. Erectile dysfunction-overview from a cardiovascular perspective. *Vasa*. 2017;46(5):347–353.
23. Capogrosso P, Ventimiglia E, Oreggia D, et al. Medical treatment of erectile dysfunction: Too many medical prescriptions. *Urologia*. 2017;84(3):121–129.
24. Polonsky TS, Taillon LA, Sheth H, et al. The association between erectile dysfunction and peripheral arterial disease as determined by screening ankle-brachial index testing. *Atherosclerosis*. 2009;207(2):440–444.
25. Gandaglia G, Briganti A, Montorsi P, et al. Diagnostic and therapeutic implications of erectile dysfunction in patients with cardiovascular disease. *Eur Urol*. 2016;70(2):219–222.
26. Handler J. Managing erectile dysfunction in hypertensive patients. *J Clin Hypertens*. 2011;13(6):450–454.
27. Nehra A, Jackson G, Miner M, et al. The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. *Mayo Clin Proc*. 2012;87(8):766–778.
28. Miner M, Rosenberg MT, Barkin J. Erectile dysfunction in primary care: A focus on cardiometabolic risk evaluation and stratification for future cardiovascular events. *Can J Urol*. 2014;21(suppl 2):25–38.
29. Najari B, Kashanian JA. Erectile dysfunction. *JAMA*. 2016;316(17):1838.

30. Hatzimouratidis K, Salonia A, Adaikan G, et al. Pharmacotherapy for erectile dysfunction: Recommendations from the Fourth International Consultation for Sexual Medicine (ICSM 2015). *J Sex Med*. 2016;13(4):465–488.
31. Hatzimouratidis K, Amar E, Eardley I, et al. Guidelines on male sexual dysfunction, erectile dysfunction and premature ejaculation. *Eur Urol*. 2010;57(5):804–814.
32. Pahlajani G, Raina R, Jones S, et al. Vacuum erection devices revisited: Its emerging role in the treatment of erectile dysfunction and early penile rehabilitation following prostate cancer therapy. *J Sex Med*. 2012;9(4):1182–1189.
33. Trost LW, Munarriz R, Wang R, et al. External mechanical devices and vascular surgery for erectile dysfunction. *J Sex Med*. 2016;13(11):1579–1617.
34. Sun L, Peng FL, Yu ZL, et al. Combined sildenafil with vacuum erection device therapy in the management of diabetic men with erectile dysfunction after failure of first-line sildenafil monotherapy. *Int J Urol*. 2014;21(12):1263–1267.
35. Dhir RR, Lin HC, Canfield SE, Wang R. Combination therapy for erectile dysfunction: An update review. *Asian J Androl*. 2011;13(3):382–390.
36. Lee M, Sharifi R. Non-invasive management options for erectile dysfunction when a phosphodiesterase type 5 inhibitor fails. *Drugs Aging*. 2018;35(3):175–187.
37. Bennett N. Sexual dysfunction-behavioral, medical, and surgical treatment. *Med Clin N Am*. 2018;102(2):349–360.
38. Uckert S, Kuczyk MA, Oelke M. Phosphodiesterase inhibitors in clinical urology. *Expert Rev Clin Pharmacol*. 2013;6(3):323–332.
39. Tsertsvadze A, Fink HA, Yazdi F, et al. Oral phosphodiesterase-5-inhibitors and hormonal treatments for erectile dysfunction: A systematic review and meta-analysis. *Ann Intern Med*. 2009;151(9):650–661.
40. Bruzziches R, Francomano D, Gareri P, et al. An update on pharmacological treatment of erectile dysfunction with phosphodiesterase type 5 inhibitors. *Expert Opin Pharmacother*. 2013;14(10):1333–1344.
41. Zurawin JL, Stewart CA, Anaissie JE, et al. Avanafil for the treatment of erectile dysfunction. *Expert Rev Clin Pharmacol*. 2016;9(9):1163–1170.
42. Hong JH, Kwon YS, Kim IY. Pharmacodynamics, pharmacokinetics, and clinical efficacy of phosphodiesterase-5 inhibitors. *Expert Opin Drug*

Metab Toxicol. 2017;13(2):199–192.

43. Mirone V, Fusco F, Rossi A, et al. Tadalafil and vardenafil vs sildenafil: A review of patient preference studies. *BJU Int*. 2009;103(9):1212–1217.
44. Tolra JR, Campana JM, Ciutat LF, Miranda EF. Prospective, randomized, open-label, fixed-dose, crossover study to establish preference of patients with erectile dysfunction after taking the three PDE-5 inhibitors. *J Sex Med*. 2006;3(5):901–909.
45. Lombardi G, Macchiarella A, Cecconi F, Del Popolo G. Ten-year follow-up of sildenafil use in spinal cord-injured patients with erectile dysfunction. *J Sex Med*. 2009;6(12):3449–3457.
46. Albersen M, Orabi H, Lue TF. Evaluation and treatment of erectile dysfunction in the aging male: A mini-review. *Gerontology*. 2012;58(1):3–14.
47. Carvalheira A, Forjaz V, Pereira NM. Adherence to phosphodiesterase type 5 inhibitors in the treatment of erectile dysfunction in long–term users: How do men use the inhibitors. *Sex Med*. 2014;2(2):96–102.
48. Yafi PA, Jenkins L, Albersen M, et al. Erectile dysfunction. *Nat Rev Dis Primers*. 2017;2:16003. doi: 10.1038/nrdp.2016.3.
49. Brisson TE, Broderick GA, Thiel DD, et al. Vardenafil rescue rates of sildenafil nonresponders: Objective assessment of 327 patients with erectile dysfunction. *Urology*. 2006;68(2):397–401.
50. McMahon CG. High dose sildenafil as a salvage therapy for severe erectile dysfunction. *Int J Impot Res*. 2002;14(6):533–538.
51. Aversa A, Francomano D, Lenzi A. Does testosterone supplementation increase PDE5-inhibitor responses in difficult-to-treat erectile dysfunction patients? *Expert Opin Pharmacother*. 2015;16(5):625–628.
52. Sperling H, Gittelman M, Norenberg C, et al. Efficacy and safety of an orodispersible vardenafil formulation for the treatment of erectile dysfunction in elderly men and those with underlying conditions: An integrated analysis of two pivotal trials. *J Sex Med*. 2011;8(1):261–271.
53. Lee KCJ, Brock GB. Daily dosing of PDE5 inhibitors: Where does it fit in? *Curr Urol Rep*. 2013;14(4):269–278.
54. Ricardi U, Gontero P, Ciammella P, et al. Efficacy and safety of tadalafil 20 mg on demand vs tadalafil 5 mg once-a-day in the treatment of post-radiotherapy erectile dysfunction in prostate cancer men: A randomized phase II trial. *J Sex Med*. 2010;7(8):2851–2859.

55. Ventimiglia E, Capogrosso P, Montorsi F, Salonia A. The safety of phosphodiesterase type 5 inhibitors for erectile dysfunction. *Expert Opin Drug Saf*. 2016;15(2):141–152.
56. McMahon C. Efficacy and safety of daily tadalafil in men with erectile dysfunction previously unresponsive to on demand tadalafil. *J Sex Med*. 2004;1(3):292–300.
57. McMahon C. Comparison, efficacy, and tolerability of on demand tadalafil and daily dosed tadalafil for the treatment of erectile dysfunction. *J Sex Med*. 2005;2(3):415–25.
58. Nathoo NA, Etminan M, Mikelberg FS. Association between phosphodiesterase-5-inhibitors and nonarteritic anterior ischemic optic neuropathy. *J Neuroophthalmol*. 2015;35(1):12–15.
59. Katz EG, Tan RB, Rittenberg D, et al. Avanafil for erectile dysfunction in elderly and young adults: Differential pharmacology and clinical utility. *Ther Clin Risk Manag*. 2014;10:701–711.
60. Pomeranz HD. The relationship between phosphodiesterase-5 inhibitors and nonarteritic anterior ischemic optic neuropathy. *J Neuroophthalmol*. 2016;36(1):193–196.
61. Okuyucu S, Guven OE, Akoglu E, et al. Effect of phosphodiesterase-5 inhibitor on hearing. *J Laryngol Otol*. 2009;123(7):718–722.
62. Loeb S, Ventigmiglia E, Salonia A, et al. Meta-analysis of the association between phosphodiesterase inhibitors (PDE5Is) and risk of melanoma. *J Natl Cancer Inst*. 2017;109(8):djx086. doi: 10.1093/jnci/djx086.
63. Li WQ, Qureshi AA, Robinson KC, Han J Sildenafil use and increased risk of incident melanoma. *JAMA Intern Med*. 2014;174 (6):964–970.
64. Loeb S, Folkvalijon Y, Lambe M, et al. Use of phosphodiesterase type 5 inhibitors for erectile dysfunction and risk of malignant melanoma. *JAMA*. 2015;313(24):2449–2455.
65. Levine GN, Steinke EE, Bakaeen FG, et al. Sexual activity and cardiovascular disease: A scientific statement from the American Heart Association. *Circulation*. 2012;125(8):1058–1072.
66. Schwartz BG, Kloner RA. Drug interactions with phosphodiesterase-5 inhibitors used for the treatment of erectile dysfunction or pulmonary hypertension. *Circulation*. 2010;122(1):88–95.
67. Kloner RA. Pharmacology and drug interaction effects of the phosphodiesterase 5 inhibitors: Focus on α blocker interactions. *Am J Cardiol*. 2005;96(12B):42M–46M.

68. Conners WP, Morgentaler A. The evaluation and management of testosterone deficiency: The new frontier in urology and men's health. *Curr Urol Rep*. 2013;14(6):557–564.
69. Afiadata A, Ellsworth P. Testosterone replacement therapy: Who to evaluate, what to use, how to follow and who is at risk? *Hosp Pract*. 2014;42(5):69–82.
70. Matsumoto AM. Testosterone administration in older men. *Endocrinol Metab Clin North Am*. 2013;42(2):271–286.
71. Hackett G, Kirby M, Edwards D, et al. British Society for Sexual Medicine guidelines on adult testosterone deficiency, with statements for UK practice. *J Sex Med*. 2017;14(12):1504–1523.
72. Corona G, Maseroli E, Maggi M. Injectable testosterone undecanoate for the treatment of hypogonadism. *Expert Opin Pharmacother*. 2014;15(13):1903–1926.
73. Wang C, Swerdloff R, Kipnes M, et al. New testosterone buccal system (Striant) delivers physiological testosterone levels: Pharmacokinetics study in hypogonadal men. *J Clin Endocrinol Metab*. 2004;89(8):3821–3829.
74. Ullah MI, Riche DM, Koch CA. Transdermal testosterone replacement therapy in men. *Drug Des Devel Ther*. 2014;8:101–112.
75. Morely JE, Charlton E, Patrick P, et al. Validation of a screening questionnaire for androgen deficiency in aging males. *Metabolism*. 2000;49(9):1239–1242.
76. Kang DY, Li HJ. The effect of testosterone replacement therapy on prostate-specific antigen levels in men being treated for hypogonadism: A systematic review and meta-analysis. *Medicine*. 2015;94(3):e410. doi: 10.1097/imd.0000000000000410.
77. Morgentaler A, Benesh JA, Denes BS, et al. Factors influencing prostate specific antigen response among men treated with testosterone therapy for 6 months. *J Sex Med*. 2014;11(11):2818–2825.
78. Dupree JM, Langille GM, Khera M, Lipshultz LI. The safety of testosterone supplementation therapy in prostate cancer. *Nat Rev Urol*. 2014;11(9):526–530.
79. Vigen R, O'Donnell CI, Baron AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA*. 2013;310(17):1829–1836.
80. Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of nonfatal

myocardial infarction following testosterone therapy prescription in men. *PLoS One*. 2014;9(1):e85805. doi: 10.1371/jouornal.pone.00885805.ecollection2014.

81. Garnick MB. Testosterone replacement therapy faces FDA scrutiny. *JAMA*. 2015;313(6):563–564.
82. Jakubczyk T. Intracavernosal injections in the diagnosis and treatment of PDE-5 resistant erectile dysfunction. *Cent European J Urol*. 2013;66(2):215–216.
83. Shabsigh R, Padma-Nathan H, Gittleman M, et al. Intracavernous alprostadil alfadex (EDEX/VIRIDAL) is effective and safe in patients with erectile dysfunction after failing sildenafil. *Urology*. 2000;55(4):477–480.
84. He L, Wen J, Jiang X, et al. Long-term efficacy and safety of self-intracavernous injection of prostaglandin E1 for treatment of erectile dysfunction in China. *Andrologia*. 2011;43(3): 208–212.
85. McMahon CG, Samali R, Johnson H. Treatment of intracorporeal injection nonresponse with sildenafil alone or in combination with triple agent intracorporeal injection therapy. *J Urol*. 1999;162(6):1992–1997.
86. Costa P, Potempa AJ. Intraurethral alprostadil for erectile dysfunction: A review of the literature. *Drugs*. 2012;72(17):2243–2254.
87. Engel JD, McVary KT. Transurethral alprostadil as therapy for patients who withdrew from or failed prior intracavernous injection therapy. *Urology*. 1998;51(5):687–692.
88. Brown SL, Haas CA, Koehler M, et al. Hepatotoxicity related to intracavernous pharmacotherapy with papaverine. *Urology*. 1998;52(5):844–847.
89. Shamlou R, Ghanem H. Erectile dysfunction. *Lancet*. 2013;381(9861):153–165.
90. Levine LA, Becher EF, Bella AJ, et al. Penile prosthesis surgery: Current recommendations from the International Consultation on Sexual Medicine. *J Sex Med*. 2016;13(14):489–518.
91. Mulcahy JJ, Kramer A, Brant WO, et al. Current management of penile implant infections, device reliability, and optimizing cosmetic outcome. *Curr Urol Rep*. 2014;15(6):413. doi: 10.107/s11934- 014-0413-6.

100

Benign Prostatic Hyperplasia

Mary Lee and Roohollah Sharifi

KEY CONCEPTS

1. Although symptomatic benign prostatic hyperplasia (BPH) is rare in men younger than 50 years, it is common in men 60 years and older. Prostate growth is androgen-dependent. Symptoms commonly result from both static and dynamic factors.
2. BPH symptoms may be exacerbated by medications, including antihistamines, phenothiazines, tricyclic antidepressants, and anticholinergic agents. In these cases, discontinuing the causative agent can relieve symptoms.
3. For patients with mild disease who are asymptomatic or have mildly bothersome symptoms and no complications of BPH disease, watchful waiting is indicated. Watchful waiting includes behavior modification, lifestyle modification, discontinuation of medications that contribute to voiding symptoms, and return visits to the physician at 6- or 12-month intervals for assessment of worsening symptoms or signs of bladder outlet obstruction.
4. If symptoms progress to a moderate or severe level, drug therapy or surgery is indicated. α_1-Adrenergic antagonists quickly relieve voiding symptoms, but do not prevent disease progression. 5α-Reductase inhibitors delay symptom progression and reduce the incidence of BPH-related complications in patients with prostates of at least 30 to 40 g, but may not reduce voiding symptoms for 3 to 6 months.
5. All α_1-adrenergic antagonists are equally effective in relieving BPH symptoms. Older second-generation immediate-release formulations of α_1-adrenergic antagonists (eg, terazosin, doxazosin) can cause adverse cardiovascular effects, mainly first-dose syncope, orthostatic hypotension, and dizziness. For patients who cannot tolerate these hypotensive adverse

effects, the third-generation, pharmacologically uroselective α_{1A}-adrenergic antagonists (eg, tamsulosin, silodosin) or an extended-release formulation of alfuzosin, a second-generation, functionally uroselective agent, are good alternatives.

6. 5α-reductase inhibitors are useful primarily for patients with large prostates greater than 30 to 40 g who wish to avoid surgery and cannot tolerate the side effects of α_1-adrenergic antagonists. 5α-Reductase inhibitors have a slow onset of action, taking up to 6 months to exert maximal clinical effects, which is a disadvantage of their use, especially as single-drug therapy for BPH. In addition, decreased libido, erectile dysfunction, and ejaculation disorders are common adverse effects, which may be troublesome problems in sexually active patients.

7. Phosphodiesterase type 5 inhibitors can be used in patients with moderate-to-severe BPH and erectile dysfunction. They improve obstructive and irritative voiding symptoms, but do not produce significant increases in urinary flow rate or reductions in postvoid residual (PVR) urine volume. Hence, a phosphodiesterase type 5 inhibitor is considered less effective than an α-adrenergic antagonist for BPH. A phosphodiesterase type 5 inhibitor may be used alone; however, symptom improvement and an increase in peak urinary flow rate have been demonstrated when it is used along with an α-adrenergic antagonist or a 5α-reductase inhibitor.

8. Anticholinergic agents are indicated in patients with moderate-to-severe lower urinary tract symptoms (LUTS) with a predominance of irritative voiding symptoms. In this case, the drugs are commonly added to an existing regimen of an α_1-adrenergic antagonist or a 5α-reductase inhibitor. Because older patients are at high risk of systemic and central nervous system anticholinergic adverse effects, uroselective anticholinergic agents or those with low potential to cross the blood brain barrier are preferred over nonuroselective agents. To minimize the risk of acute urinary retention, anticholinergics should be used cautiously in patients when baseline PVR urine volume is greater than 100 to 150 mL. In addition, the potential anticholinergic medication burden should be assessed before starting an anticholinergic agent.

9. Mirabegron is a β_3-adrenergic agonist that relaxes the detrusor muscle to increase the bladder's storage capacity and prolong the interval between voidings. Although not approved by the Food and Drug Administration (FDA) for management of BPH, it is indicated for treatment of overactive

bladder symptoms, including urgency and nocturia. These symptoms mimic irritative lower urinary tract voiding symptoms. Thus, mirabegron is used as an alternative to anticholinergic agents in patients with irritative voiding symptoms that do not respond to α_1-adrenergic antagonists or in patients who cannot tolerate anticholinergic adverse effects.

10 Surgery is indicated for moderate-to-severe symptoms of BPH for patients who do not respond to or do not tolerate drug therapy, or for patients with complications of BPH. It is the most effective mode of treatment because it relieves symptoms and increases peak urinary flow rate in the greatest number of men with BPH. However, the two standard techniques, transurethral resection of the prostate (TURP) and open prostatectomy, are associated with the highest rates of complications, including retrograde ejaculation and erectile dysfunction. Moreover, because medications are first-line treatment for patients with moderate-to-severe symptoms of BPH, patients who are surgical candidates are often older and more frail. Therefore, minimally invasive surgical procedures are often sought by patients and urologists. Such procedures relieve symptoms and are associated with a lower rate of adverse effects and do not require hospitalization, but they have higher reoperation rates than the standard procedures.

Preclass Engaged Learning Activity

Go to a reference text on anatomy and physiology and review the section on the male genitourinary tract. Draw a diagram of these organs that shows the anatomical relationship of the kidneys, ureters, urinary bladder, prostate, urethra, testicles. Then explain how an enlarged prostate could cause obstruction of urinary outflow from the bladder and lead to recurrent urinary tract infection and renal failure.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is the most common benign neoplasm of American men. A nearly ubiquitous condition among elderly men, BPH is of major societal concern, given the large number of men affected, the progressive nature of the condition, and the healthcare costs associated with it. This chapter

discusses BPH and its available treatments: watchful waiting, α1-adrenergic antagonists, 5α-reductase inhibitors, phosphodiesterase inhibitors, anticholinergic agents, mirabegron, and surgery. The limitations of phytotherapy are described.

EPIDEMIOLOGY

According to the results of autopsy studies, approximately 80% of older men develop histologic evidence of BPH. About half of the patients with microscopic changes develop an enlarged prostate gland, and as a result, they may develop symptoms including difficulty emptying urine from the urinary bladder. Approximately half of symptomatic patients eventually require treatment. Thus, the disease can be characterized by three stages: Benign prostatic hyperplasia (BPH), benign prostatic enlargement (BPE), and benign prostatic obstruction (BPO). While BPH itself may not require treatment, some patients with BPE, depending on the size of the prostate, will be at risk of developing complications of BPH. In these patients, 5α-reductase inhibitors can reduce disease complications and delay the need for prostate surgery. In patients with moderate-to-severe BPO, bothersome voiding symptoms require medical or surgical treatment.

1 The peak incidence of clinical BPH occurs between ages 63 and 65 years. Symptomatic disease is uncommon in men younger than 50 years, but some urinary voiding symptoms are present by the time men reach 60 years of age. The Boston Area Normative Aging Study estimated that the cumulative incidence of clinical BPH was 78% for patients at age 80 years.[1] Similarly, the Baltimore Longitudinal Study of Aging projected that approximately 60% of men at least 60 years old develop clinical BPO.[2]

NORMAL PROSTATE PHYSIOLOGY

Located anterior to the rectum, the prostate is a small heart-shaped, chestnut-sized gland located below the urinary bladder. It surrounds the proximal urethra like a doughnut.

Soft, symmetric, and mobile on palpation, a normal prostate gland in an adult man weighs 15 to 20 g. Physical examination of the prostate must be done by digital rectal examination during which the prostate is manually palpated by inserting a finger into the rectum. Thus, the prostate is examined through the

rectal wall.

The prostate has two major functions: (a) to secrete fluids that make up a portion (20%–40%) of the ejaculate volume and (b) to provide secretions with antibacterial effect possibly related to its high concentration of zinc.[2]

ETIOLOGY

The etiologies of BPH include: (a) patient age of 40 years or more; (b) the stimulatory effect of androgens; and (c) increased α-adrenergic tone in smooth muscle of the prostate and prostatic urethra

Patient Age of 40 Years or More

At birth, the prostate is the size of a pea and weighs approximately 1 g. The prostate remains that size until the boy reaches puberty. At that time, the prostate undergoes its first growth spurt, growing to its normal adult size of 15 to 20 g by the time the man is 25 to 30 years old. The prostate remains this size until the patient reaches age 40 years, when a second growth spurt begins and continues for the rest of his lifetime. During this period, the prostate can quadruple in size or grow even larger. This second growth spurt is when BPE develops.

Stimulatory Effect of Androgens and Increased α-Adrenergic Tone

The prostate gland comprises three types of tissue: epithelial tissue, stromal tissue, and the capsule. Epithelial tissue, also known as *glandular tissue*, produces prostatic secretions. These secretions are delivered into the urethra during ejaculation and contribute to the total ejaculate volume. Androgens stimulate epithelial tissue growth. Stromal tissue, also known as *smooth muscle tissue*, is embedded predominantly with α_1-adrenergic receptors, predominately of the α_{1A} subtype. Stimulation of these receptors by norepinephrine causes smooth muscle contraction, which results in an extrinsic compression of the urethra, reduction of the urethral lumen, and decreased urinary bladder emptying. The normal prostate is composed of a higher amount of stromal tissue than epithelial tissue, as reflected by a stromal-to-epithelial tissue ratio of 2:1. This ratio is exaggerated to 5:1 for patients with BPH, which explains why α_1-adrenergic antagonists are quickly effective in symptomatic management and

why 5α-reductase inhibitors reduce an enlarged prostate gland by only 25%.[2] The capsule, or outer shell of the prostate, is composed of fibrous connective tissue and smooth muscle, which also is embedded with α_1-adrenergic receptors. When stimulated with norepinephrine, the capsule contracts around the prostatic urethra (**Fig. 100-1**).

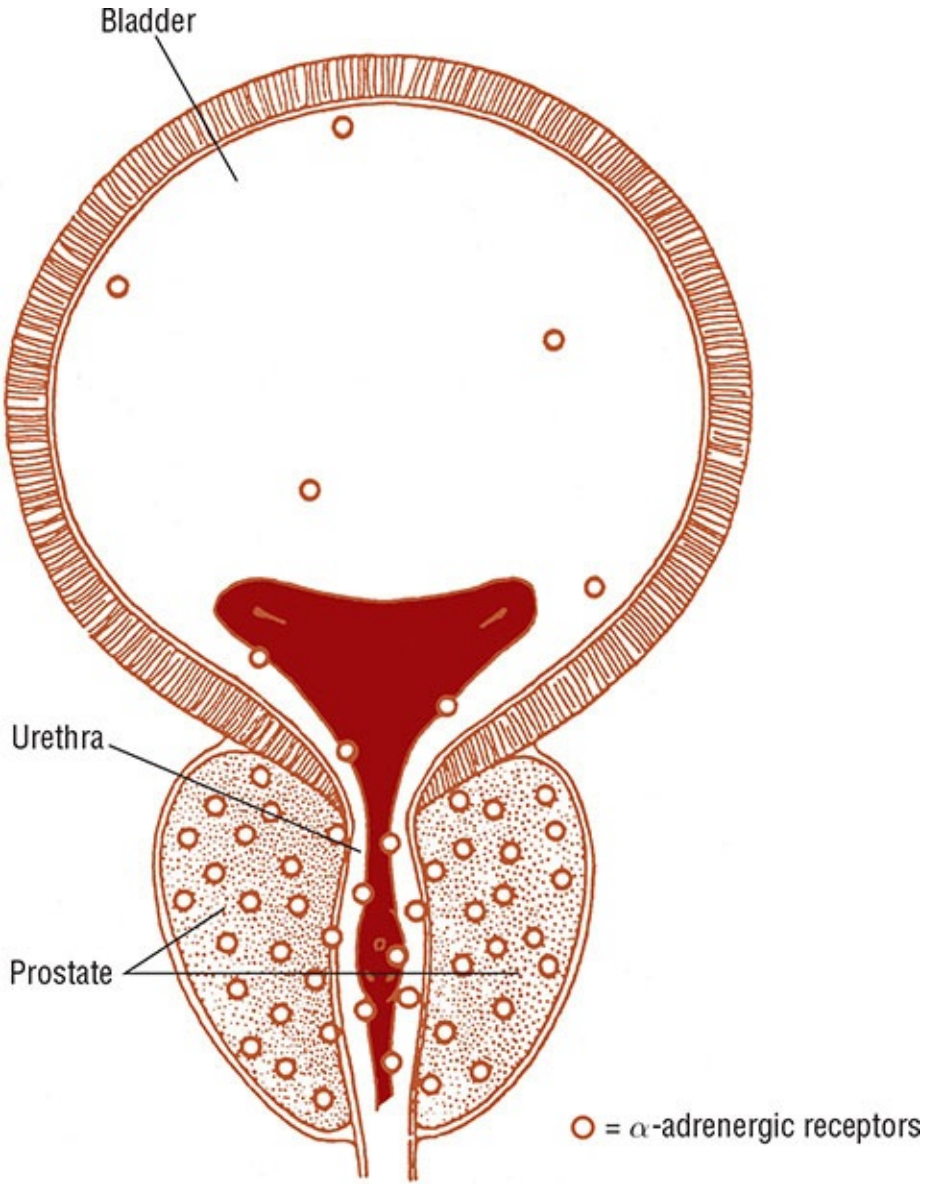


FIGURE 100-1 Representation of the anatomy of and α-adrenergic receptor distribution in the prostate, urethra, and bladder. *(Narayan P, Indudhara R. Pharmacotherapy for benign prostatic hyperplasia. Western Journal of Medicine. 1994;161(5):495-506. Copyright © 1994 with permission from BMJ Publishing Group Ltd.)*

Testosterone is the principal testicular androgen in males, whereas androstenedione is the principal adrenal androgen. These two hormones are responsible for penile and scrotal enlargement, increased muscle mass, and maintenance of the normal male libido. These androgens are converted by 5α-reductase in target cells to dihydrotestosterone (DHT), an active metabolite. Two types of 5α-reductase exist. Type I enzyme is localized to sebaceous glands in the frontal scalp, liver, and skin, although a small amount is in the prostate. DHT produced at these target tissues causes acne and increased body and facial hair. Type II enzyme is localized to the prostate, genital tissue, and hair follicles of the scalp. In the prostate, DHT induces growth and enlargement of the gland.[3]

In prostate cells, DHT has greater affinity for intraprostatic androgen receptors than testosterone, and DHT forms a more stable complex with the androgen receptor. Thus, DHT is considered a more potent androgen than testosterone in the prostate. Of note, despite the decrease in testicular androgen production in the aging male, intracellular DHT levels in the prostate remain normal, probably due to increased activity of intraprostatic 5α-reductase.[3]

Estrogen, a product of peripheral metabolism of androgens, is believed to stimulate the growth of the stromal portion of the prostate gland. Estrogens are produced when testosterone and androstenedione are converted by aromatase enzymes in peripheral adipose tissues. In addition, estrogens may induce the androgen receptor.[2] As men age, the ratio of serum levels of testosterone to estrogen decreases as a result of a decline in testosterone production by the testes and increased adipose tissue conversion of androgen to estrogen.

PATHOPHYSIOLOGY

Although the precise pathophysiologic mechanisms causing BPH remain unclear, the role of intraprostatic DHT and type II 5α-reductase in the development of BPH is evidenced by several observations:

1. BPH does not develop in men who are castrated before puberty.
2. Patients with type II 5α-reductase enzyme deficiency do not develop BPH.
3. Castration causes an enlarged prostate to shrink.
4. Administration of testosterone to orchiectomized dogs of advanced age produces BPH.

The pathogenesis of BPH is often described as resulting from both static and dynamic factors. Static factors relate to anatomic enlargement of the prostate gland, which produces a physical block at the bladder neck and thereby obstructs

urinary outflow. Enlargement of the gland depends on androgen stimulation of epithelial tissue and estrogen stimulation of stromal tissue in the prostate. Dynamic factors relate to excessive α-adrenergic tone of the stromal component of the prostate gland, bladder neck, and posterior urethra, which results in contraction of the prostate gland around the urethra and narrowing of the urethral lumen.[4]

Symptoms of BPH disease may result from static and/or dynamic factors, and this must be recognized when drug therapy is considered. For instance, some patients may present with obstructive voiding symptoms, but have prostates of normal size. In these patients, dynamic factors likely are responsible for the symptoms. However, for patients with enlarged prostate glands, static and dynamic factors likely are working in concert to produce the observed symptoms. Moreover, the likelihood of developing moderate-to-severe obstructive voiding symptoms is directly related to the increasing size of the prostate gland.[5]

Dynamic factors may be accentuated if the patient becomes stressed or is in pain. In these situations, increased α-adrenergic tone may precipitate excessive contraction of prostatic stromal tissue. When the stressful event resolves, voiding symptoms often improve.[2]

MEDICATION-RELATED SYMPTOMS

2 Medications in several pharmacologic categories should be avoided for patients with BPH because they may exacerbate symptoms. Testosterone replacement regimens, used to treat primary or secondary hypogonadism, deliver additional substrate that can be metabolized to DHT by the prostate. Although no cases of BPH have been reported because of exogenous testosterone administration, cautious use is advised for older patients with prostatic enlargement. α-Adrenergic agonists, used as oral or intranasal decongestants (eg, pseudoephedrine, ephedrine, or phenylephrine), can stimulate α-adrenergic receptors in the prostate, resulting in muscle contraction. By decreasing the caliber of the urethral lumen, bladder emptying may be compromised. β-Adrenergic agonists (eg, terbutaline) may cause relaxation of the bladder detrusor muscle, which prevents bladder emptying.[6] Drugs with significant anticholinergic adverse effects (eg, antihistamines, phenothiazines, tricyclic antidepressants, or anticholinergic drugs used as antispasmodics or to treat Parkinson’s disease) may decrease contractility of the urinary bladder detrusor muscle. For patients with BPH who have a narrowed urethral lumen, loss of

effective detrusor contraction could result in acute urinary retention, particularly for patients with significantly enlarged prostate glands and a PVR urine volumes greater than 150 mL. Diuretics, particularly in large doses, can produce polyuria, which may present as urinary frequency, similar to that experienced by patients with BPH.

CLINICAL PRESENTATION

Patients with BPH can present with a variety of symptoms and signs of disease. All symptoms of BPH can be divided into two categories: obstructive and irritative.

Obstructive symptoms, also known as *prostatism* or *bladder outlet obstruction*, result when dynamic and/or static factors reduce bladder emptying. The force of the urinary stream becomes diminished, urinary flow rate decreases, and bladder emptying is incomplete and slow. Patients report urinary hesitancy and straining and a weak urine stream. Urine dribbles out of the penis, and the urinary bladder always feels full, even after patients have voided. Some patients state that they need to press on their bladder to force out the urine. In severe cases, patients may go into urinary retention when bladder emptying is not possible. In these cases, suprapubic pain can result from bladder overdistension.

Approximately 50% to 80% of patients have irritative voiding symptoms, which typically occur late in the disease course. Irritative voiding symptoms result from long-standing obstruction of the bladder neck. The detrusor muscle cholinergic receptors become supersensitive to small volumes of urine in the bladder. Involuntary bladder contractions are triggered resulting in urinary urgency and frequency.[2,3] Patients report waking up every 1 to 2 hours at night to void (nocturia), which significantly reduces quality of life. As BPH progresses, the bladder muscle undergoes hypertrophy so that it can generate a greater contractile force to empty urine past the anatomic obstruction at the bladder neck. Decompensation eventually occurs, and the hypertrophied bladder muscle is no longer able to generate adequate contractile force; the bladder becomes ineffective in emptying urine. Acute urinary retention and recurrent urinary tract infections, and renal failure complicate progressive, untreated disease.

General

- A patient is in no acute distress unless he has moderate-to-severe symptoms or complications of BPH.

Symptoms

- Obstructive symptoms: Slow urinary stream, intermittency, hesitancy, straining to urinate, incomplete emptying, dribbling
- Irritative symptoms: Urgency, frequency, nocturia

Signs

- Digital rectal examination reveals an enlarged prostate (>20 g) with no nodules or indurations; prostate is soft, symmetric, and mobile.

Laboratory Tests

- Increased blood urea nitrogen (BUN) and serum creatinine with long-standing, untreated bladder outlet obstruction, elevated prostate-specific antigen (PSA) level.

Other Diagnostic Tests

- Increased American Urological Association (AUA) Symptom Score, decreased urinary flow rate (<10 mL/s), and increased PVR urine volume.

Other factors implicated in the pathophysiology of BPH include chronic prostatic inflammation, advanced atherosclerosis of the blood supply to the pelvis, and decreased release of nitric oxide and decreased production of cyclic guanosine monophosphate (cGMP) at the bladder neck and in the prostate.[7]

Symptoms of BPH vary over time. Symptoms may improve, remain stable, or worsen spontaneously. Thus, BPH is not necessarily a progressive disease; approximately 85% of patients with BPH have stable symptoms when evaluated 4 years after initial diagnosis.[8] Between one-third and two-thirds of men with mild disease stabilize or improve without treatment over 2.5 to 5 years.[2,9] However, worsening symptoms and complications of BPH develop in patients, particularly those with a prostate gland volume of 30 to 40 mL or PSA of 1.4 ng/mL (mcg/L) or greater.[2,9,10] A patient with a prostate volume of 30 mL or more is three times more likely to develop acute urinary retention.[10]

Collectively, obstructive and irritative voiding symptoms and their negative

impact on a patient's quality of life are referred to as *lower urinary tract symptoms* (LUTS). However, LUTS is not pathognomonic for BPH and may be caused by other diseases, such as neurogenic bladder or urinary tract infection.[2]

Another presentation of BPH is silent prostatism. Patients have LUTS but adapt to the symptoms and do not voluntarily complain about them. Such patients do not present for medical treatment until complications of BPH disease arise or a spouse brings in the symptomatic patient for medical care.

When BPH progresses, it can produce complications that include the following:

1. Acute, painful urinary retention, which can lead to acute renal failure.
2. Persistent or intermittent gross hematuria when tissue growth exceeds its blood supply.
3. Overflow urinary incontinence or unstable bladder.
4. Recurrent urinary tract infection that results from urinary stasis.
5. Bladder diverticula.
6. Bladder stones.
7. Chronic renal failure from long-standing bladder outlet obstruction.

Approximately 17% to 20% of patients with symptomatic BPH require treatment because of disease complications.[8,11] Men older than 70 years with large prostates of more than 40 g and a PVR urine volume greater than 100 mL are three times more likely to have severe symptoms or suffer from acute urinary retention and to require prostatectomy than patients with smaller prostates.[12] Thus, a serum PSA level of 1.4 ng/mL (mcg/L) or greater has been used as a surrogate marker for an enlarged prostate gland to identify patients at risk for developing complications of BPH disease and has been used to guide selection of the most appropriate treatment modality in some patients.[12,13]

DIAGNOSTIC EVALUATION

Because the obstructive and irritative voiding symptoms associated with BPH are not unique to the disease and can be presenting symptoms of other genitourinary tract disorders, including prostate or bladder cancer, neurogenic bladder, prostatic calculi, or urinary tract infection, the patient presenting with signs and symptoms of BPH must be thoroughly evaluated.

A careful medical history should be taken to ensure that a complete listing of symptoms is collected to identify concomitant disorders that may be contributing

to voiding symptoms. The medical history should be followed by a thorough medication history, including all prescription and nonprescription medications and dietary supplements that the patient is taking. Any drugs that could be causing or exacerbating the patient's symptoms should be identified. If possible, the suspected drugs should be discontinued or the dosing regimen modified to ameliorate the voiding symptoms.

The patient should undergo a physical examination, including a digital rectal examination, although the size of the prostate gland may not correspond to symptoms. BPH usually presents as an enlarged, soft, smooth, symmetric gland, greater than 20 g in size. Some patients have only a slightly enlarged gland and yet have bothersome or even serious voiding difficulties. Other patients have intravesical enlargement of the prostate gland (ie, the gland grows into the urinary bladder and produces a ball-valve blockage of the bladder neck). This type of prostate enlargement is not palpable on digital examination.

The patient's perception of the severity of BPH symptoms guides selection of a particular treatment modality in a patient. To evaluate the patient's perceptions objectively, validated instruments, such as the AUA Symptom Score (**Table 100-1**), are commonly used. Using the AUA Symptom Score, the patient rates the "bothersomeness" of seven obstructive and irritative voiding symptoms.[14] A patient's perception of bothersomeness is often based on how much these symptoms interfere with daily activities or cause worry or embarrassment in social settings. Each item is rated for severity on a scale from 0 to 5, such that 35 is the maximum score and is consistent with the most severe symptoms. Patients usually are stratified into the three groups shown in the table based on disease severity for the purposes of deciding a treatment approach.

TABLE 100-1 Categories of BPH Disease Severity Based on Symptoms and Signs

Disease Severity	AUA Symptom Score	Typical Symptoms and Signs
Mild	≤7	Asymptomatic
		Peak urinary flow rate <10 mL/s
		PVR urine volume >25–50 mL
Moderate	8-19	All of the above signs plus obstructive voiding symptoms and irritative voiding symptoms (signs of detrusor instability)
Severe	≥20	All of the above plus one or more complications of BPH

AUA, American Urological Association; BPH, benign prostatic hyperplasia; BUN, blood urea nitrogen; PVR, postvoid residual volume.

In addition, the patient can complete a voiding diary in which he records the number of voids, the volume of each void, and voiding symptoms for several days. This information is used to evaluate symptom severity and tailor recommendations for lifestyle modifications that may ameliorate symptoms.

The only clinical laboratory test that must be performed is a urinalysis. Because many of the voiding symptoms of BPH could be caused by other urologic disorders, a urinalysis can help screen for hematuria, urolithiasis, and infection. To screen for prostate cancer, another common cause of glandular enlargement, a PSA test should be performed for patients aged 40 years or more, with at least a 10-year life expectancy, in whom the potential benefit of diagnosing the disorder will be outweighed by the cost of the test.[14]

Objective measures of bladder emptying include peak and average urinary flow rate (normal is at least 10 mL/s). These measures are determined using an uroflowmeter, which checks the rate of urine flow out of the bladder. This is a quick noninvasive outpatient procedure in which the patient is instructed to drink water until his bladder feels full and then the patient's urinary flow is clocked during voiding. A low urinary flow rate (<10–12 mL/s) implies failure of bladder emptying due to obstruction or a functional disorder of the detrusor muscle. A patient with such a low urinary flow rate has a fourfold greater risk of acute urinary retention than patients with higher urinary flow rates.[10]

Another objective measure is PVR urine volume (normal is 0 mL), which is assessed using abdominal ultrasonography. A PVR urine volume of 25 to 50 mL or more implies failure of bladder emptying and a predisposition for urinary tract infections, whereas a PVR of 100 mL or more has been associated with

progressive worsening of BPH symptoms if no specific treatment is initiated.[15] Because of a weak correlation among voiding symptoms, prostate size, and urinary flow rate, most physicians use a combination of measures, including the patient's assessment of symptoms along with objective evaluation of urinary outflow, PVR, and presence of complications of BPH to determine the need for treatment.

Many other tests can be performed if additional information is needed to assess the severity of BPH disease and its complications, to assist in the preoperative assessment of the patient, or to distinguish prostate enlargement due to BPH from that caused by prostate cancer. Tests include a serum BUN and creatinine, voiding cystometrogram, transrectal ultrasound of the prostate, IV pyelogram, renal ultrasound, and prostate biopsy.

TREATMENT

The goals of treatment are to control symptoms, as evidenced by a minimum of a three-point decrease in the AUA symptom index, prevent progression of BPH disease by reducing the risk of developing complications, and delay the need for surgical intervention.

As a disease of symptoms, BPH is treated by relieving bothersome symptoms. However, selection of a single best treatment for a patient must consider the variable costs and adverse effects of treatment options, the inability to predict the course of the disease in an individual patient, and the potential benefit that may occur in a comparatively small number of treated patients.

The AUA Guidelines on Management of Benign Prostatic Hyperplasia is the principal tool used in the United States[14] and is similar to the European Guidelines[8] (**Fig. 100-2**) with the exception that the European Guidelines recommend tadalafil for moderate-to-severe LUTS in younger male patients (who are likely to be sexually active) who are physically trim; and that 5α-reductase inhibitors are recommended for long-term treatment of patients with BPH who have a prostate volume greater than 40 mL and a PSA greater than 1.4 ng/mL (mcg/L). The AUA Guidelines were originally published in 2010 and, although reaffirmed in 2014, were not revised since then. The European Guidelines were updated and published in 2015.

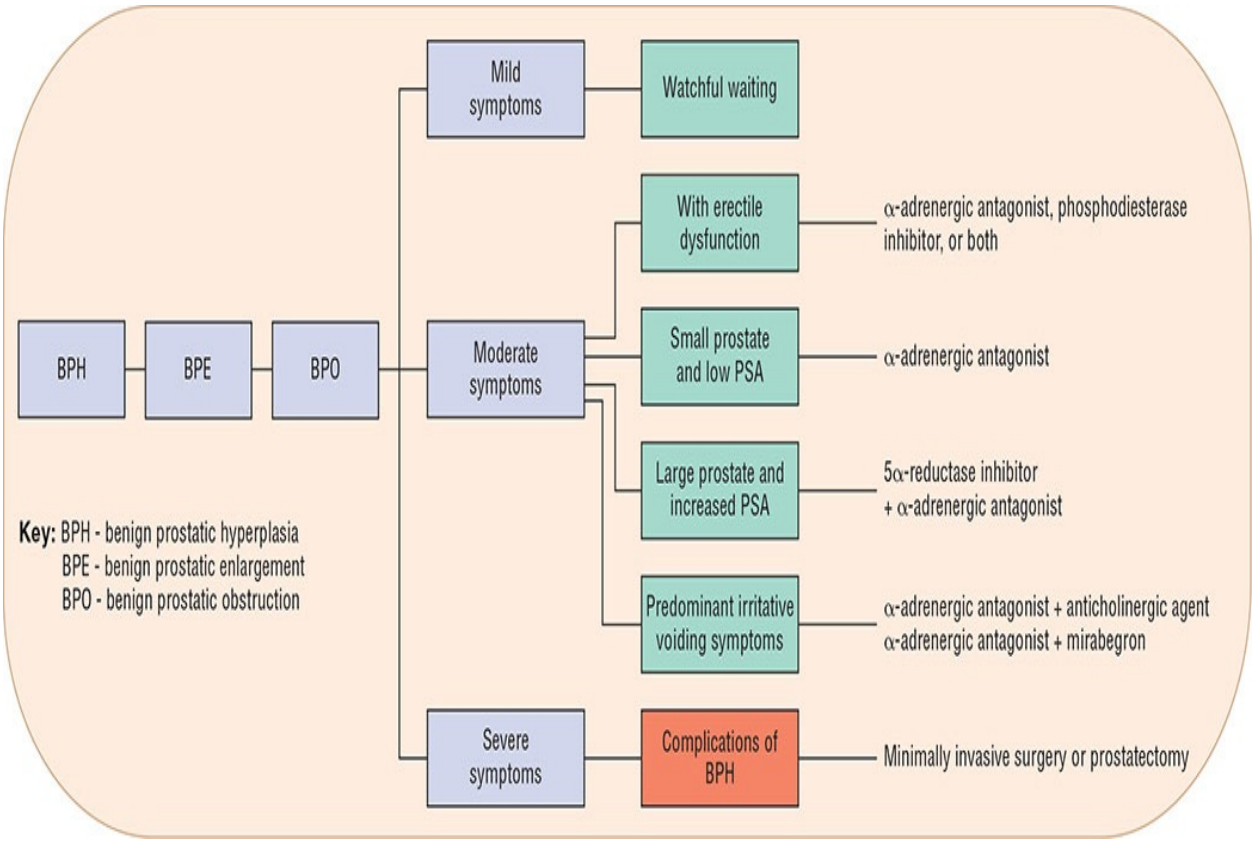


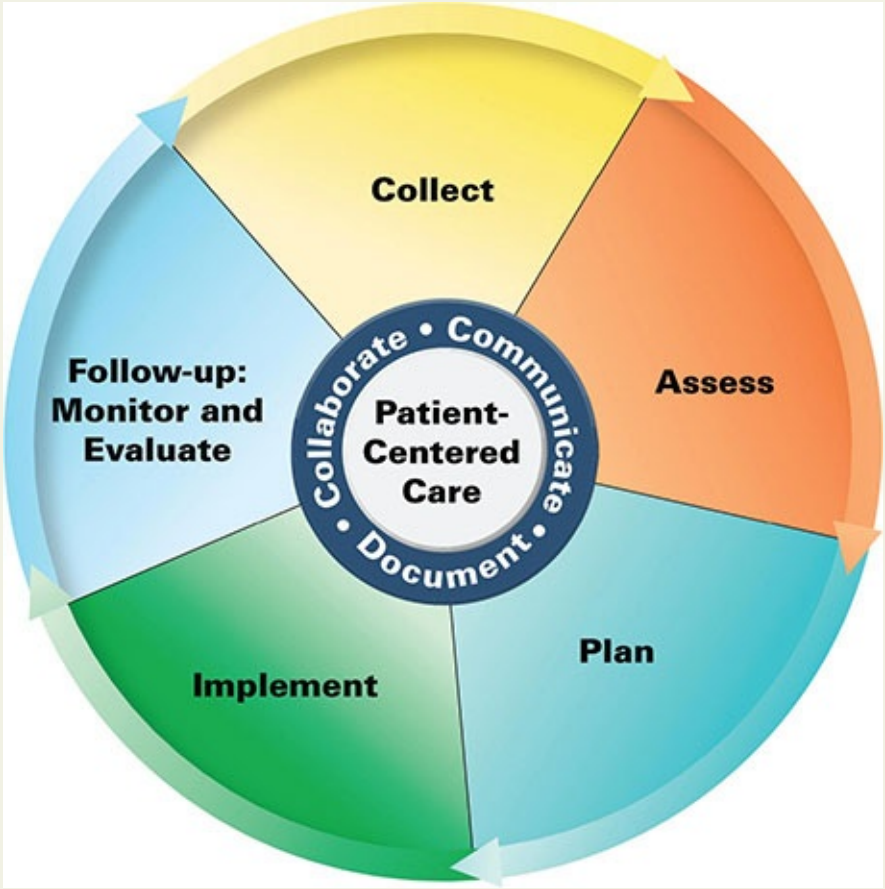
FIGURE 100-2 Management algorithm for benign prostatic hyperplasia (BPH).

Specific treatment options include watchful waiting, pharmacologic therapy, and surgical intervention. Although phytotherapy is used by some patients alone or along with conventional medications for BPH, head-to-head comparisons with FDA-approved treatments are lacking; consequently, such herbals cannot be recommended at this time.[14]

3 Patients with mild disease are asymptomatic or have mildly bothersome symptoms and have no complications of BPH disease. These patients can be managed with watchful waiting, which entails having the patient return for reassessment at intervals of 6 to 12 months. At each return visit, the patient should complete a standardized, validated survey tool to assess severity of symptoms, and objective signs of disease should be assessed using measurements of urinary flow rate and PVR urine volume. Watchful waiting should be accompanied by patient education about the disease and behavior modification to avoid practices that exacerbate voiding symptoms. Behavior modification includes restricting fluids close to bedtime, minimizing caffeine and alcohol intake, frequent emptying of the bladder during waking hours or before long trips (to avoid overflow incontinence and urgency), and avoiding

drugs that could exacerbate voiding symptoms.[16,17] At each visit, physicians should assess the patient's risk of developing acute urinary retention by evaluating the patient's prostate size or using PSA as a surrogate marker of prostate enlargement.[14]

4 If symptoms progress to the moderate or severe level, or the patient perceives his symptoms to be bothersome, the patient should be offered specific treatment. In these patients, watchful waiting delays—but does not decrease—the need for prostatectomy. In symptomatic patients, watchful waiting can lead to intractable urinary retention, increased PVR urine volumes, and significant voiding symptoms.[18,19] Recommended treatment options include drug therapy with an α_1-adrenergic antagonist or 5α-reductase inhibitor, a combination of an α_1-adrenergic antagonist and a 5α-reductase inhibitor, a phosphodiesterase inhibitor alone or combined with an α_1-adrenergic antagonist or 5α-reductase inhibitor, or the addition of an anticholinergic agent or mirabegron to an α_1-adrenergic antagonist or 5α-reductase inhibitor particularly if the patient has significant irritative voiding symptoms that are not responsive to an α_1-adrenergic antagonist or 5α-reductase inhibitor; or surgery.



Patient Care Process for Benign Prostatic Hyperplasia

Collect

- Patient characteristics (eg, age, race)
- Patient history (past medical history, family history, social—tobacco, recreational drug, or alcohol use)
- Presence of bladder symptoms that are obstructive (slow urinary stream, intermittency, hesitancy, straining to urinate, incomplete emptying, dribbling) and/or irritative (urgency, frequency, nocturia) (see Clinical Presentation box)
- Patient's perception of bothersomeness of voiding symptoms using American Urological Association (AUA) Symptom Score (see "Diagnostic Evaluation" section)
- Current and past medications, including prescription and nonprescription medications or nonpharmacologic interventions for BPH and medications perceived as causing BPH (see "Medication-Related Symptoms" section)

- Objective data (see “Diagnostic Evaluation” section and Clinical Presentation box)
    - BP, heart rate (HR), height, weight, and body mass index (BMI)
    - Digital rectal examination
    - Labs (eg, urinalysis, blood urea nitrogen, serum creatinine, prostate-specific antigen)
    - Urinary flow rates and postvoid residual volume

Assess

- Disease severity (see Table 100-1); patient views on watchful waiting (in mild cases), medical treatment (in moderate-to-severe cases), and surgery (in severe cases)
- Need for further evaluation based on laboratory and examination findings
- Size of prostate by digital rectal exam or transrectal ultrasound of the prostate
- Presence of BPH, prostate cancer, prostatitis, all of which can cause lower urinary-tract symptoms (LUTS)

Plan*

- Dietary and lifestyle modifications to avoid problematic symptoms and situations (see “Medication-Related Symptoms” section and Clinical Presentation box)
- Interventions as indicated to encourage heart-healthy lifestyle, smoking cessation, weight loss if needed, management of other chronic diseases
- Drug therapy regimen including specific agent(s), dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Fig. 100-2 and Tables 100-2, 100-3, and 100-4), advantage or disadvantage of single drug versus combination therapy
- Monitoring parameters including efficacy (symptom relief) and safety (medication-specific adverse effects) (see Table 100-5)
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug therapy)
- Comparison of during treatment responses by repeating AUA Symptom Score or using a voiding diary (see “Diagnostic Evaluation” section)
- Referrals to other providers when appropriate (eg, physician, urologist)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Determine BPH goal attainment
- Presence of adverse effects
- Patient adherence to treatment plan using multiple sources of information

**Collaborate with patient, caregivers, and other healthcare professionals.*

Patients with serious complications of BPH should be offered surgical correction (transurethral or open prostatectomy, or a minimally invasive surgical procedure). Drug therapy is considered an interim measure for such patients because it only delays worsening of complications and the need for surgical intervention.[14,18]

Desired Outcomes

The desired outcomes of treatment include reducing LUTS as evidenced by an improvement of AUA Symptom Score by at least three points, an increase in the peak urinary flow rate, and a normalization of PVR to less than 50 mL. In addition, treatment should prevent the development of disease complications and reduce the need for surgical intervention. Treatment should be well tolerated and be cost-effective.

General Approach to Treatment

In selecting the most appropriate treatment for an individual patient, consideration should be given to the severity and quality of the patient's LUTS, the likelihood of developing complications of BPH (based on size of the prostate gland or the PSA level), the patient's preference for medical versus surgical intervention, the patient's risk for adverse effects of treatment, and the cost of treatment.

Concurrent medical illnesses of the patient should also be considered. For

example, if the patient has erectile dysfunction and moderate LUTS, then a phosphodiesterase inhibitor might be preferred over an α_1-adrenergic antagonist. If the patient has overactive bladder syndrome and BPH, irritative voiding symptoms may require the addition of an anticholinergic agent or mirabegron. If medical treatment is initiated, the patient's level of renal function should be assessed, as the daily dose of some α-adrenergic antagonists and some anticholinergics require modification to avoid accumulation.

Nonpharmacologic Therapy

BPH is a chronic, nonfatal medical illness. All patients should be encouraged to initiate and maintain a heart-healthy lifestyle, including a low-fat diet, high intake of plenty of fresh fruits and vegetables, regular physical exercise, and no smoking.[16] The patient should avoid excess consumption of caffeine-containing beverages (which may induce diuresis). Patients should void before retiring to bed at night and before long car rides. If the patient is overweight, he should be encouraged to lose weight. If the patient has diabetes mellitus, dyslipidemia, or hypertension, he should be advised to optimize management of those disorders.[16]

Pharmacologic Therapy

Drug therapy for BPH can be categorized into three types: agents that relax prostatic smooth muscle (reducing the dynamic factor), agents that interfere with testosterone's stimulatory effect on prostate gland enlargement (reducing the static factor), and agents that relax bladder detrusor muscle (improving the urine storage capacity of the bladder) (**Tables 100-2** and **100-3**). Of the agents that relax prostatic smooth muscle, second- and third-generation α_1-adrenergic antagonists have been most widely used. These agents relax the intrinsic urethral sphincter and prostatic smooth muscle, thereby enhancing urinary outflow from the bladder. Phosphodiesterase inhibitors also relax bladder neck and prostatic smooth muscle. α_1-Adrenergic antagonists and phosphodiesterase inhibitors do not reduce prostate size. Of the agents that interfere with testosterone's stimulatory effect on prostate gland size, the only agents approved by the FDA are 5α-reductase inhibitors (eg, finasteride, dutasteride). Other agents that interfere with androgen stimulation of the prostate have not been popular in the United States because of the many adverse effects associated with their use. The luteinizing hormone-releasing hormone superagonists leuprolide and goserelin

decrease libido and can cause erectile dysfunction, gynecomastia, and hot flashes. Antiandrogens (eg, bicalutamide, flutamide) produce nausea, diarrhea, gynecomastia, and hepatotoxicity. Finally, antimuscarinic agents and mirabegron relax detrusor muscle, which reduces irritable voiding symptoms, improves urine storage capacity of the bladder, and increases the interval between voidings.[17,18]

TABLE 100-2 Medical Treatment Options for Benign Prostatic Hyperplasia

Category	Mechanism	Drug (Brand Name)
Reduces dynamic factor	Blocks α_1-adrenergic receptors in prostatic stromal tissue	Prazosin (Minipress) Alfuzosin (Uroxatral) Terazosin (Hytrin) Doxazosin (Cardura)
	Blocks α_{1A}-adrenergic receptors in prostatic stromal tissue	Tamsulosin (Flomax) Silodosin (Rapaflo)
	Causes smooth muscle relaxation of prostate, bladder neck, and prostatic urethra	All α_1-adrenergic antagonists Tadalafil (Cialis)
Reduce static factor	Blocks 5α-reductase enzyme	Finasteride (Proscar) Dutasteride (Avodart)
	Blocks dihydrotestosterone at its intracellular receptor	Bicalutamide (Casodex)* Flutamide (Eulexin)*
	Blocks pituitary release of luteinizing hormone	Leuprolide (Lupron)* Goserelin (Zoladex)*
	Blocks pituitary release of luteinizing hormone and blocks androgen receptor	Megestrol acetate (Megace)*
Relaxes smooth muscle of prostate and bladder neck	Inhibits phosphodiesterase type 5 in prostate, urethra, bladder, and pelvic blood vessels	Tadalafil (Cialis)
Relaxes detrusor muscle	Blocks muscarinic receptors in detrusor muscle of bladder	Tolterodine (Detrol) Oxybutynin (Ditropan) Trospium (Sanctura) Solifenacin (Vesicare) Darifenacin (Enablex) Fesoterodine (Toviaz)
Relaxes detrusor muscle	Stimulates β_3-adrenergic receptors in detrusor muscle of bladder	Mirabegron (Myrbetriq)

*Not FDA approved for treatment of benign prostatic hyperplasia.

TABLE 100-3 Comparison of α_1-Adrenergic Antagonists, 5α-Reductase Inhibitors, Phosphodiesterase Inhibitors, and Anticholinergic Agents and β_3-Adrenergic Agonists for Benign Prostatic Hyperplasia

	α_1-Adrenergic Antagonists	5α-Reductase Inhibitors
Relaxes prostatic smooth muscle	Yes	No
Decreases prostate size	No	Yes
Halts disease progression	No	Yes
Peak onset	1–6 weeks	3–6 months
Efficacy in relieving BOO	++	++ (for patients with enlarged prostates)
Frequency of dosing	One to two times per day, depending on the agent and dosage formulation	Once per day
Decreases PSA	No	Yes
Sexual dysfunction adverse effects	EJD	Decreased libido, ED, EJD
Cardiovascular adverse effects	Yes	No
	Phosphodiesterase Inhibitors	**Anticholinergic Agents**
Relaxes prostatic smooth muscle	Yes	No
Decreases prostate size	No	No
Halts disease progression	No	No
Peak onset	4 weeks	1-2 weeks
Efficacy in relieving BOO	+	0 (irritative symptoms only)
Frequency of dosing	Once per day	Once per day
Decreases prostate-specific antigen	No	No
Sexual dysfunction adverse effects	No	ED
Cardiovascular adverse effects	Yes (mild hypotension)	Yes (tachycardia)
	β_3-Adrenergic Agonists	
Relaxes prostatic smooth muscle	No	
Decreases prostate size	No	
Halts disease progression	No	
Peak onset	2 weeks, but may take up to 8 weeks	
Efficacy in relieving BOO	0 (irritative symptoms only)	
Frequency of dosing	Once per day	
Decreases prostate-specific antigen	No	
Sexual dysfunction adverse effects	No	
Cardiovascular adverse effects	Yes (hypertension)	

BOO, bladder outlet obstruction; BPH, benign prostatic hyperplasia; ED, erectile dysfunction; EJD, ejaculation disorder; PSA, prostate-specific antigen.

+ Notation is a quantitative assessment.

Selection of a medical treatment for a patient with moderate-to-severe symptoms should be determined on a case-by-case basis after the patient and provider discuss the risks, benefits, and costs of various treatments. With drug therapy for BPH, patients must understand that the benefits continue only as long as the medication is taken.

If possible, drug therapy should be initiated with a single agent, usually an α_1-adrenergic antagonist, which is faster acting and more effective than a 5α-reductase inhibitor. Some are also available as less expensive generic formulations. In addition, α_1-adrenergic antagonists are effective in reducing LUTS independent of prostate size and have no effect on PSA. A 5α-reductase inhibitor is a good first-choice agent for symptomatic patients with a significantly enlarged prostate (>40 g) and an elevated PSA greater than or equal to 1.4 ng/mL (mcg/L). Such patients are at risk for developing complications of BPH, and typically combination drug therapy with an α_1-adrenergic antagonist and a 5α-reductase inhibitor is prescribed. The pharmacologic rationale for such a combination is that using two drugs with different mechanisms of action can be more effective than either drug alone. Also combination drug therapy quickly relieves symptoms, delays disease progression, and reduces the need for surgical intervention. Since combination drug therapy is expensive and associated with more adverse effects than single-drug therapy, it should be reserved for those patients who will benefit the most from it.

For patients with both erectile dysfunction and BPH, a phosphodiesterase inhibitor alone or in combination with an α-adrenergic antagonist may be used. However, it should be noted that a phosphodiesterase inhibitor alone will only relieve LUTS, and will not produce a clinically significant increase in urinary flow rate or a decrease in PVR. Therefore, a phosphodiesterase inhibitor is generally considered less effective than an α-adrenergic antagonist.

For patients with a predominance of irritative voiding symptoms, an anticholinergic agent could be added to an existing drug regimen for BPH. To reduce the risk of developing systemic anticholinergic adverse effects, a uroselective anticholinergic agent may be prescribed. To avoid the risk of developing acute urinary retention, an anticholinergic agent should be used cautiously when the patient’s PVR is greater than 250 to 300 mL. Mirabegron is more expensive than many anticholinergic agents. Therefore, it should be reserved as an add-on treatment for patients with irritative voiding symptoms who cannot tolerate anticholinergic adverse effects.

α-Adrenergic Antagonists

Three generations of α-adrenergic antagonists have been used to treat BPH. They all relax smooth muscle in the prostate and bladder neck. Because antagonism of presynaptic α_2-adrenergic receptors produces tachycardia and arrhythmias, first-generation α-adrenergic agents, such as phenoxybenzamine, have been replaced by the second-generation postsynaptic α_1-adrenergic antagonists and third-generation uroselective postsynaptic α_{1A}-adrenergic antagonists.

5 The second- and third-generation α_1-adrenergic antagonists are considered equally effective for treatment of BPH.[14,17,19,20] These agents generally improve the AUA Symptom Score by 30% to 40%, decreasing the AUA Symptom Index by three to six points, within 2 to 6 weeks, depending on the need for dose titration; increase urinary flow rate by 2 to 3 mL/s in 60% to 70% of treated patients; and reduce PVR.[18,19] With continued use, durable clinical benefit has been demonstrated for years.[20] Their effectiveness in reducing BPH symptoms and the severity of adverse effects appear to be dose-dependent.[20] They have no effect on prostate volume. α_1-Adrenergic antagonists do not reduce PSA levels, preserving the utility of this prostate cancer marker in this high-risk population.[14]

Older, immediate-release, second-generation α_1-adrenergic antagonists and tamsulosin are available as inexpensive generic formulations, which may be desirable in selected patients.[18]

Second-Generation α-Adrenergic Antagonists

Second-generation agents include prazosin, terazosin, doxazosin, and alfuzosin. These are all nonselective α_1-adrenergic antagonists. At the usual doses used to treat BPH, immediate-release formulations of prazosin, terazosin, and doxazosin antagonize peripheral vascular α_1-adrenergic receptors in addition to those in the prostate. As a result, first-dose syncope, orthostatic hypotension, and dizziness are characteristic adverse effects. In older adults, such adverse effects could lead to falls and bone fractures.[21,22] To improve tolerance to these adverse effects, therapy should start with a low dose of 1 mg daily and then should be slowly titrated up to a full therapeutic dose over several weeks. Additive blood-pressure-lowering effects commonly occur when these agents are used with antihypertensive agents, which limit the use of these agents for some patients. These agents differ in terms of duration of action and dosage formulation.

Whereas prazosin requires dosing two to three times per day, terazosin, doxazosin, and alfuzosin offer more convenient once-daily dosing. Because prazosin requires twice- to thrice-daily dosing and has significant cardiovascular adverse effects, it is not recommended in the current AUA guidelines for treatment of BPH.[14] Extended-release dosage formulations are available for doxazosin and alfuzosin. These offer the convenience of once-daily dosing, treatment initiation with a full therapeutic dose, and decreased dose-related hypotension as the formulation produces lower peak serum concentrations than immediate-release products. An α_1-adrenergic antagonist is not preferred as single-drug therapy for treatment of both BPH and hypertension in a patient. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) of 24,000 patients with hypertension, doxazosin produced more congestive heart failure than amlodipine, lisinopril, or chlorthalidone.[23] Thus, both the AUA and the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure[14,24] recommend that patients with BPH and hypertension be treated with separate and appropriate drug treatment for each medical condition.

When using immediate-release formulations of the second-generation α_1-adrenergic antagonists terazosin and doxazosin, slow titration up to a therapeutic maintenance dose is necessary to minimize orthostatic hypotension and first-dose syncope. Conservatively, dosages should be increased in an orderly stepwise process, at 2- to 7-day intervals, depending on the patient's response to the medication. A faster titration schedule can be used as long as the patient does not develop orthostatic hypotension or dizziness. Two sample titration schedules for terazosin are as follows:

Schedule 1: Slow titration

- Days 4 to 14: 2 mg at bedtime
- Weeks 2 to 6: 5 mg at bedtime
- Weeks 7 and on: 10 mg at bedtime

Schedule 2: Quicker titration

- Days 1 to 3: 1 mg at bedtime
- Days 4 to 14: 2 mg at bedtime
- Weeks 2 to 3: 5 mg at bedtime
- Weeks 4 and on: 10 mg at bedtime

Patients should continue taking the drug as long as they continue to respond to it. Durable responses for 6 and 10 years have been reported for tamsulosin[25] and doxazosin,[26] respectively.

Alfuzosin is considered functionally and clinically uroselective in that usual doses used to treat BPH are less likely than other second-generation agents to cause cardiovascular adverse effects in animal or human models.[27] This clinical effect has been observed more often with the once-daily, extended-release formulation of alfuzosin, which is the only commercially available formulation in the United States, as compared with the immediate-release formulation that is dosed three times per day, which is available in Europe.[27] Its clinical uroselectivity has been postulated to be due to higher concentrations of alfuzosin achieved in the prostate versus serum after usual doses,[28,29] absence of high peak serum levels with the extended-release formulation, and the fixed dosing schedule of the extended-release formulation. The extended-release alfuzosin dosing is FDA approved for 10 mg daily, with no dose titration increase. This formulation is particularly convenient for patients who have difficulty remembering varying doses needed for up-titration dosing schedules.

Third-Generation α_1-Adrenergic Antagonists

Three subtypes of α_1-adrenergic receptors exist: (a) $\alpha_{1A,}$ which comprise 70% to 75% of the α-adrenergic receptors in the prostate, bladder neck, prostatic urethra, seminal vesicles, spermatic duct, and vas deferens (when stimulated, smooth muscle contraction and the emission phase of ejaculation occurs)[20,21]; (b) $\alpha_{1B,}$ which cause arterial smooth muscle contraction when stimulated; (c) $\alpha_{1D,}$ which are found in the urinary bladder and brain, but their function remains to be defined.[4]

Third-generation α_1-adrenergic antagonists preferentially inhibit α_{1A}-adrenergic receptors. Tamsulosin and silodosin are the only third-generation α_{1A}-adrenergic antagonists available in the United States. Blockade of these receptors relaxes smooth muscle of the prostate and bladder neck and improves bladder emptying in patients with BPH and are likely to cause ejaculatory disorders. In addition, both of these agents have low affinity for vascular α_{1B}-adrenergic receptors, which explains why hypotension is not as frequent with usual daily doses as compared with second-generation agents.[30]

Silodosin has 50-fold greater selectivity for the α_{1A}-adrenergic receptor than the α_{1D}-adrenergic receptor and has 100-fold greater selectivity for the α_{1A}-

adrenergic receptor than the α_{1B}-adrenergic receptor.[30] Silodosin demonstrates greater pharmacologic uroselectivity than tamsulosin, which has a 10-fold greater selectivity for the α_{1A}-adrenergic receptor than the α_{1D}-adrenergic receptor and has 2.5-fold greater selectivity for the α_{1A}-adrenergic receptor than the α_{1B}-adrenergic receptor.[29] These pharmacologic differences are not associated with a significant difference in efficacy, but there is a higher incidence of ejaculatory disorders as an adverse effect in silodosin-treated patients as opposed to tamsulosin-treated patients.[30]

The uroselectivity of α_{1A}-adrenergic receptors has multiple implications. Dose titration is minimal; therefore, patients can begin tamsulosin 0.4 mg daily or silodosin 8 mg daily. Patients can be instructed to take the dose anytime during the day, unlike immediate-release formulations of terazosin and doxazosin, which should be taken at bedtime so that patients can sleep through the time when peak cardiovascular adverse effects are most likely to occur. Tamsulosin and silodosin should be taken 30 minutes after the same meal every day because food decreases their bioavailability, reduces the peak serum concentration of the drug, and lowers the risk of hypotensive adverse effects. The onset of peak action is quick, in the range of 1 week. Increasing the daily dose of tamsulosin to 0.8 mg daily produces inconsistent improvements in effectiveness but does increase adverse effects.[31] These agents are well tolerated in patients with well-controlled hypertension; and the addition of tamsulosin to furosemide, enalapril, nifedipine, and atenolol does not result in hypotension.[32,33]

As compared with tamsulosin, silodosin requires dosage reduction in patients with a creatinine clearance of 30 to 50 mL/min (0.5–0.83 mL/s), is contraindicated in patients with severe hepatic insufficiency or a creatinine clearance less than 30 mL/min (0.5 mL/s), and has the potential to produce more adverse effects because of elevated plasma concentrations if used concurrently with potent CYP 3A4 inhibitors (eg, clarithromycin, itraconazole, ketoconazole, ritonavir) or P-glycoprotein inhibitors (eg, cyclosporine). Silodosin also causes more ejaculatory dysfunction than tamsulosin.[30,33] Finally, silodosin is commercially available from only one source, whereas tamsulosin is available as a generic formulation.

The usual doses of α_1-adrenergic antagonists are summarized in **Table 100-4**.

TABLE 100-4 Dosing of Drugs Used in Treatment of Benign Prostatic Hyperplasia

Drug	Brand Name	Initial Dose	Usual Dose	Special Population Dose
α-Adrenergic Antagonists				
Prazosin	Minipress	0.5 mg twice a day orally	1–5 mg twice a day orally	To uptitrate the dose, double the dose every 2 weeks.
Terazosin	Hytrin	1 mg at bedtime orally	10–20 mg daily orally	To uptitrate the dose, increase slowly to 2 mg, 5 mg, and then 10 mg daily in a stepwise fashion. Take extra care if the patient is taking other drugs that lower blood pressure.
Doxazosin	Cardura	1 mg daily orally	8 mg daily orally	For the immediate-release formulation, doses of 16 mg daily have been used for hypertension. For the XL formulation, increase from 4 to 8 mg daily after a 3- to 4-week interval. When switching from the immediate- to the extended-release formulation, start with 4 mg of the extended-release formulation no matter what maintenance dose of immediate-release doxazosin the patient is taking.
	Cardura XL	4 mg daily orally	4–8 mg daily	
Alfuzosin	Uroxatral	10 mg daily orally	10 mg daily orally (no dose titration)	This is an extended-release formulation, and it should not be chewed or crushed. The drug should be taken after meals and used cautiously in patients with creatinine clearance less than 30 mL/min (0.5 mL/s).
Tamsulosin	Flomax	0.4 mg daily orally	0.4–0.8 mg daily orally	This is an extended-release formulation, and it should not be chewed or crushed. The drug should be taken after meals. No dosage adjustment is needed in patients with renal or liver dysfunction. Allow several weeks after starting a dose before increasing to a higher dose.
Silodosin	Rapaflo	8 mg daily orally	8 mg daily orally (no dose titration)	This drug is contraindicated when creatinine clearance is less than 30 mL/min (0.5 mL/s). If creatinine clearance is 30–50 mL/min (0.5–0.83 mL/s), use 4 mg daily orally, preferably after the same meal each day. Should not be given to patients on potent CYP 3A4 inhibitors or with severe hepatic impairment.
5α-Reductase Inhibitors				
Finasteride	Proscar	5 mg daily orally	5 mg daily orally	No dosage adjustment in patients with renal impairment. Use cautiously in patients with hepatic impairment.
Dutasteride	Avodart	0.5 mg daily orally	0.5 mg daily orally	No dosage adjustment in patients with renal impairment. Use cautiously in patients with hepatic impairment.
Dutasteride + tamsulosin	Jalyn	1 tablet (equivalent to 0.5-mg dutasteride + 0.4-mg tamsulosin) daily orally	1 tablet daily orally	No dosage adjustment needed in patients with renal or moderate hepatic impairment.
Phosphodiesterase Inhibitor				
Tadalafil	Cialis	5 mg daily orally	5 mg daily orally	If creatinine clearance is 30–50 mL/min (0.5–0.83 mL/s), use 2.5 mg daily orally. Do not use if creatinine clearance is less than 30 mL/min (0.5 mL/s). Use cautiously in patients with mild-to-moderate hepatic impairment. Avoid in patients with severe hepatic impairment.
Anticholinergic Agents				
Darifenacin	Enablex	7.5 mg daily orally	7.5–15 mg daily orally	This is an extended-release formulation and it should not be chewed or crushed. To uptitrate the dose, double the dose after 2 weeks. If the patient is taking a potent CYP3A4 inhibitor (eg, ketoconazole, itraconazole, ritonavir, nelfinavir, and clarithromycin), do not exceed 7.5 mg daily orally. No dosage adjustment is needed for patients with renal impairment. Use a maximum dose of 7.5 mg daily for patients with moderate hepatic impairment. Do not use in patients with severe hepatic impairment.
Fesoterodine	Toviaz	4 mg daily orally	4–8 mg daily orally	This is an extended-release formulation, and it should not be chewed or crushed. If the patient is taking a potent CYP3A4 inhibitor (eg, ketoconazole, itraconazole, ritonavir, nelfinavir, and clarithromycin), do not exceed 4 mg daily orally. If the creatinine clearance is less than 30 mL/min (0.5 mL/s), do not exceed 4 mg daily orally. Use is not recommended in patients with severe hepatic impairment.
Oxybutynin	Ditropan	5 mg two to three times a day orally	5–10 mg two to three times a day orally	Increase daily dose at 5-mg increments at weekly intervals. No specific dosing modifications available for patients with renal or hepatic impairment; use cautiously in these patients.
	Ditropan XL	5 mg daily orally	5–30 mg daily orally	This is an extended-release formulation, and it should not be crushed or chewed. Increase daily dose at 5-mg increments at weekly intervals. No specific dosing modifications available for patients with renal impairment; use cautiously in these patients.
	Oxytrol TDS	1 patch (3.9-mg oxybutynin) twice weekly	1 patch (3.9 mg) twice weekly	This is a transdermal patch. Apply to abdomen, hip, or buttock. Rotate application site. Do not expose patch to sunlight. No specific dosing modifications available for patients with renal or hepatic impairment; however, use cautiously in these patients.
	Gelnique 10% gel	1-g gel (100-mg oxybutynin) daily	1-g gel (100-mg oxybutynin) daily	This is available as premeasured dose packets. Apply to abdomen, thighs, upper arms, or shoulders. Wash hands after application. Do not bathe, shower, or swim for 1 hour after application. Cover application site with clothing until medication dries on skin. Rotate application site daily. No specific dosing modifications available for patients with renal or hepatic impairment; use cautiously in these patients.

Drug	Brand Name	Initial Dose	Usual Dose	Special Population Dose
Solifenacin	VESIcare	5 mg daily orally	5–10 mg daily orally	If the creatinine clearance is less than 30 mL/min (0.5 mL/s) or the patient has moderate hepatic impairment, do not exceed 5 mg daily orally. Do not use if the patient has severe hepatic impairment. If the patient is taking a potent CYP3A4 inhibitor (eg, ketoconazole, itraconazole, ritonavir, nelfinavir, and clarithromycin), do not exceed 5 mg daily orally
Tolterodine	Detrol	2 mg twice daily orally	1–2 mg twice daily orally	If the patient has significant renal impairment or severe hepatic impairment, limit dose to 1 mg twice a day.
	Detrol LA	4 mg daily orally	2–4 mg daily orally	This is an extended-release formulation, and it should not be chewed or crushed. If the creatinine clearance is 10–30 mL/min (0.17–0.5 mL/s) or the patient has mild/moderate hepatic impairment, do not exceed 2 mg daily orally. If the creatinine clearance is less than 10 mL/min (0.17 mL/s), do not use Detrol LA. If the patient has severe hepatic impairment, use of the extended-release formulation is not recommended.
Trospium	Sanctura	20 mg twice daily orally	20 mg twice daily orally	Avoid alcohol ingestion for 2 hours after a dose. Use cautiously in patients with moderate or severe hepatic impairment. In patients older than 75 years, use the immediate-release formulation and start with 20 mg daily orally. If the creatinine clearance is less than 30 mL/min (0.5 mL/s), use 20-mg immediate-release formulation
	Sanctura XR	60 mg daily orally	60 mg daily orally	This is an extended-release formulation, and it should not be chewed or crushed. This is not recommended in patients with creatinine clearance less than 30 mL/min (0.5 mL/s). This should be used cautiously in patients with severe hepatic impairment.
β_3-Adrenergic Agonist				
Mirabegron	Myrbetriq	25 mg daily orally	25-50 mg daily orally	This is an extended-release formulation. Do not chew, crush, or divide tablet. In patients with a creatinine clearance of 15–29 mL/min (0.25–0.48 mL/s) or those with moderate hepatic impairment, the maximum daily dose should be 25 mg daily. This drug is not recommended in patients with creatinine clearance less than 15 mL/min (0.25 mL/s) or those with severe hepatic impairment.

Recommended Dosing Adjustments

With the exception of silodosin and alfuzosin, no dosage adjustments are recommended for α_1-adrenergic antagonists for patients with renal failure. A reduced starting dose of 4 mg daily of silodosin is recommended for patients with moderate renal impairment (creatinine clearance 30–50 mL/min [0.5–0.83 mL/s]). Alfuzosin should be used cautiously when the creatinine clearance is less than 30 mL/min (0.5 mL/s).

Because these drugs are hepatically catabolized, the lowest effective dose should be used for patients with hepatic dysfunction, and patients should be monitored carefully for adverse effects.

Adverse Effects

Approximately 10% to 12% of patients discontinue taking second-generation α_1-adrenergic antagonists because of adverse effects, especially those that affect the cardiovascular system (eg, syncope, dizziness, hypotension).[34] Patients who tolerate hypotension poorly should avoid immediate-release formulations of second-generation α_1-adrenergic antagonists. This includes patients with poorly controlled angina, serious cardiac arrhythmias, patients with reduced circulating volume, patients with untreated hypertension, and patients taking multiple antihypertensives.[21] These patients are candidates for alfuzosin, extended release doxazosin, or a third-generation α_1-adrenergic antagonist.

Tiredness and asthenia, anejaculation and retrograde ejaculation, flu-like symptoms, and nasal congestion are the most common dose-related adverse effects of tamsulosin and silodosin. These adverse effects are extensions of their α_{1A}-adrenergic antagonist activity and are dose-related, but with proper education patients likely will not discontinue treatment.[34] However, if the patient is sexually active and ejaculatory dysfunction is problematic, switching the patient from a third-generation to a second-generation α_1-adrenergic antagonist has been effective.[29,35,36]

Floppy iris syndrome has been associated with doxazosin, silodosin, and tamsulosin use, although the number of reported cases is highest with tamsulosin.[37] The mechanism for this adverse reaction is related to blockade of α_{1A}-adrenergic receptors in iris dilator muscles. As a result, during cataract surgery, pupillary constriction occurs despite the use of mydriatic agents and the iris billows out (floppy iris), both of which complicate the procedure or can increase the likelihood of postoperative complications, including posterior capsular rupture, retinal detachment, residual retained lens material, or endophthalmitis. Permanent loss of vision can result.[37]

Patients who are taking α_1-adrenergic antagonists and who plan to undergo cataract surgery should inform their ophthalmologist that they are taking this medication so that appropriate measures can be taken during eye surgery, for example, use of iris retractors, pupillary expansion rings, or potent mydriatic agents.[37] No benefit has been demonstrated with holding the α_1-adrenergic

antagonist preoperatively.

For patients who are scheduled to have cataract surgery, and who have not yet started an α_1-adrenergic antagonist, they should be advised to delay the start of the α_1-adrenergic antagonist until surgery has been completed.

Patients with severe sulfa allergy should avoid tamsulosin.

Drug Interactions

Caution is needed when CYP 3A4 inhibitors—for example, cimetidine and diltiazem—are used with α_1-adrenergic antagonists because a drug–drug interaction could lead to decreased metabolism of the latter agents. In contrast, concurrent use of potent CYP 3A4 stimulators such as carbamazepine and phenytoin may increase hepatic catabolism of α_1-adrenergic antagonists.

Phosphodiesterase inhibitors (eg, sildenafil, vardenafil, tadalafil) may produce hypotension if used in large doses along with α_1-adrenergic antagonists. The mechanisms for this interaction are related to the intrinsic vasodilatory effects of phosphodiesterase inhibitors and the higher susceptibility of elderly patients to venous pooling because of autonomic incompetence.[27,38] The prevalence of hypotension depends on the specific phosphodiesterase inhibitor and α_1-adrenergic antagonist agent, specifically the combination of tadalafil and a third-generation α_{1A}-adrenergic antagonist is least likely to produce a clinically significant drug interaction, as compared with other combinations.[38] Therefore, a patient's blood pressure should be stabilized on the α_1-adrenergic antagonist before starting a phosphodiesterase inhibitor. In addition, patients who are taking phosphodiesterase inhibitors with α_1-adrenergic antagonists should have their blood pressure monitored closely when initiating combined drug use.

5α-Reductase Inhibitors

6 Finasteride competitively inhibits type II 5α-reductase, the predominant isoform of the enzyme in the prostate, which suppresses intraprostatic DHT by 80% to 90%, and decreases serum DHT levels by 70%.[14,39] Dutasteride is a nonselective inhibitor of type I and II 5α-reductase. It more quickly and completely suppresses intraprostatic DHT production and decreases serum DHT levels by 90%.[39] However, direct comparison clinical trials show no advantages of these pharmacodynamic differences between these two agents.[40] 5α-Reductase inhibitors are indicated for management of moderate-to-severe BPH

disease for patients with enlarged prostate glands of at least 40 g.[8,41,42] For such patients, 5α-reductase inhibitors may slow disease progression and decrease the risk of disease complications, thereby decreasing the ultimate need for surgical intervention. When taken continuously for 4 years or 6 years, dutasteride or finasteride, respectively, has been shown to decrease the risk of acute urinary retention and prostatectomy.[43,44] For patients with severe disease, these agents generally should be used with a 6-month short course of an α_1-adrenergic antagonist; the latter will provide fast symptom relief until the 5α-reductase inhibitor starts to work. 5α-Reductase inhibitors may be preferred for patients with BPH and an enlarged prostate gland who have uncontrolled arrhythmias, have poorly controlled angina, are taking multiple antihypertensive agents, or are unable to tolerate hypotensive adverse effects of α_1-adrenergic antagonists.

5α-Reductase inhibitors also reduce or stop prostate-related bleeding by inhibiting prostatic vascular endothelial growth factor. Thus, the prevalence of gross hematuria in patients with BPH may be reduced with treatment of 5α-reductase inhibitors.[14]

5α-Reductase inhibitors reduce prostate size by 25%, increase peak urinary flow rate by 1.6 to 2.0 mL/s, improve voiding symptoms in approximately 30% of treated patients, and produce few serious adverse effects.[42] Compared with α_1-adrenergic antagonists, 5α-reductase inhibitors have several disadvantages. 5α-Reductase inhibitors have a delayed peak onset of clinical effect, which is undesirable for patients with bothersome symptoms. Long-term treatment is needed; an adequate minimum period for a clinical trial is 6 to 12 months. In addition, patients experience less objective improvement of the AUA Symptom Score and urinary flow rate with 5α-reductase inhibitors than with α_1-adrenergic antagonists.[14] 5α-Reductase inhibitors cause more sexual dysfunction than α_1-adrenergic receptor antagonists; therefore, physicians consider 5α-reductase inhibitors to be the second-line agents for treatment of BPH in sexually active males (**Tables 100-3** and **100-5**).[14,45]

TABLE 100-5 Monitoring of Drugs Used in Treatment of Benign Prostatic Hyperplasia

Drug	Adverse Reaction	Monitoring Parameter	Comment
α_1-Adrenergic antagonists	Syncope Lightheadedness Orthostatic hypotension Tachycardia Nasal congestion Ejaculatory dysfunction Priapism Floppy iris syndrome	Blood pressure Heart rate	If prescribing an immediate-release formulation, start the patient on the lowest possible dose and instruct the patient to take the first dose at bedtime. Slowly uptitrate the dose over several weeks. Stabilize the patient's blood pressure on the α-adrenergic antagonist before adding any other hypotensive agent. If the patient needs cataract surgery, instruct the patient to inform the ophthalmologist so that appropriate measures can be taken during the procedure to prevent intraoperative complications. If the patient has a painful erection lasting longer than 4 hours, the patient should seek immediate medical attention.
5α-Reductase inhibitors	ED Decreased libido Ejaculatory dysfunction Gynecomastia	PSA	The patient's PSA level should decrease by 50% if he is adherent to therapy.
Phosphodiesterase inhibitor	Headache Dizziness Nasal congestion Dyspepsia Back pain Myalgia Hearing loss Vision loss	Blood pressure Pulse Hearing loss Changes in vision	If the patient experiences hearing or vision loss, discontinue tadalafil.
Anticholinergic agents	Dry mouth Constipation Headache Tachycardia Blurry vision Acute urinary retention Drowsiness Confusion Angioedema Anaphylaxis ED	Mental status Bowel habits Ability to urinate	Adverse effects are dose-related and generally reversible. Patients with signs of severe allergic reaction need immediate medical attention.
β_3-adrenergic agonist	Hypertension Tachycardia Dry mouth Nausea Constipation Diarrhea Headache Nasopharyngitis Impaired cognition	Blood pressure Bowel habits	Adverse effects are dose-related and generally reversible.

ED, erectile dysfunction; PSA, prostate-specific antigen.

Prostate Cancer and 5α-Reductase Inhibitors

In the Prostate Cancer Prevention Trial, patients with BPH who had large prostate glands and a PSA level less than 3 ng/mL (mcg/L) were prescribed finasteride 5 mg daily for up to 7 years. Finasteride reduced the 7-year prevalence of prostate cancer by 25%.[46] However, finasteride was associated with a 27% increase in the number of patients who developed high-grade prostate cancer, which usually is invasive. Although originally thought to be a disadvantage of finasteride use, it is now thought that the higher incidence of prostate cancer was due to biopsy sampling bias. That is, since finasteride reduces the size of the prostate gland, this results in increased sensitivity of sampling biopsies to detect prostate cancer.[47]

Another clinical trial produced similar results. The Reduction by Dutasteride in Prostate Cancer Events (REDUCE) study compared the effect of 4 years of continuous use of dutasteride versus placebo on reducing the incidence of prostate cancer in more than 6,700 men at high risk for developing prostate cancer. At the end of the study, dutasteride-treated patients had a 22.8% decreased relative risk of prostate cancer. Of the patients with biopsy-positive prostate cancer, a similar number of patients in each treatment group developed high-grade tumors (Gleason grade 7–10) with no statistical difference between the groups.[48]

Thus, when finasteride is administered long-term to patients with BPH, it could be useful as chemoprophylaxis in patients with a family history of prostate cancer or in men of African descent who have an increased risk of developing prostate cancer. The possibility of developing a high-grade prostate cancer should be discussed with the patient before treatment is initiated with a 5α-reductase inhibitor for prevention of prostate cancer.[46,49]

Dosing

Finasteride is well absorbed from the gastrointestinal (GI) tract (95%), and its absorption is unaffected by food. Peak serum concentrations are reached 1 to 2 hours after the dose. Finasteride is highly protein bound. The liver extensively metabolizes finasteride to inactive metabolites, which are largely excreted in stool. The plasma half-life is 4.7 to 7.1 hours, but its biologic half-life probably is longer, as decreased serum DHT levels persist for up to 2 weeks after finasteride dosing is stopped.

For BPH, finasteride is given in doses of 5 mg by mouth daily. The dose can

be taken with meals or on an empty stomach. No dosage adjustment is needed for patients with renal dysfunction. Although no dosage reduction is recommended for patients with hepatic insufficiency, patients should be monitored carefully. Maximal reductions in prostate volume or symptom improvement may not be evident for 12 months, but noticeable changes from baseline should occur after 6 months of continuous treatment. No clinically relevant drug interactions have been reported with 5α-reductase inhibitors.

Patients must continue to take 5α-reductase inhibitors as long as they respond. Durable responses to finasteride and dutasteride have been reported with continued treatment for 6 years[44] and 4 years,[40] respectively. Upon discontinuation of the drug, prostate size and voiding symptoms generally return to baseline.

Adverse Effects

5α-Reductase inhibitors can produce sexual dysfunction, and this has led to discontinuation of therapy in up to 12% of treated patients in one-pooled analysis.[40] Although sexual dysfunction often improves with time as the patient continues to take the medication, decreased libido and erectile dysfunction may persist after discontinuation of the 5α-reductase inhibitors.[50–52] Erectile dysfunction has been reported in 3% to 16% of patients.[40,45] It may be secondary to ejaculation disorders or may be due to a drug-induced decrease in dihydrotestosterone and subsequent inhibition of nitric oxide synthase (which is needed to produce nitric oxide, a vasodilatory substance) in cavernosal tissue.[36,51] The role of 5α-reductase inhibitors in causing erectile dysfunction is not clear, as older adult men with BPH commonly develop erectile dysfunction as they age or have concurrent medical illnesses or concomitant drug therapies that may predispose to the development of sexual dysfunction. Decreased libido has been reported in 2% to 10% of treated patients.[45] Ejaculation disorders (dry sex or delayed ejaculation) have been reported in 3% to 8% of treated patients.[45] These disorders, which are possible results of decreased prostatic secretion, are reversible with drug discontinuation. In one analysis, dutasteride was associated with a higher frequency of sexual dysfunction than finasteride.[53]

Other minor adverse effects include nausea, abdominal pain, asthenia, dizziness, flatulence, headache, rash, muscle weakness, and gynecomastia.

5α-Reductase inhibitors are in FDA pregnancy category X, which means that they are contraindicated in pregnant females. Exposure of the male fetus to finasteride may produce pseudohermaphroditic offspring with ambiguous

genitalia, similar to those of patients with a rare genetic deficiency of type II 5α-reductase. Because of this teratogenic effect, women who are pregnant or seeking to become pregnant should not handle 5α-reductase inhibitor tablets and should not have contact with semen from men being treated with 5α-reductase inhibitors. Women health professionals of childbearing age should handle this product with protective gloves if they might be pregnant.

Effects of 5α-Reductase Inhibitors on PSA

Usual doses of 5α-reductase inhibitors produce a median reduction of serum PSA levels of 50% at months 6 to 12 after the start of treatment. To interpret a PSA level in a patient being treated with a 5α-reductase inhibitor, it is generally recommended that the actual measured level be doubled to get an estimate of the true level.[14] For this reason, PSA levels must be measured and a digital rectal examination should be performed before treatment begins. After 6 months of therapy, the patient should have a repeat PSA. This PSA level can be used as the new baseline for the patient. Alternatively, when compared to the pretreatment PSA, if the during treatment level does not decline by 50% and the patient has been adherent to the 5α-reductase inhibitor regimen, he should be evaluated for prostate cancer. Annually thereafter, the patient should have a PSA assay and digital rectal examination if the patient has a 10-year life expectancy. Patients with an increase in PSA level of 0.3 ng/mL (mcg/L) or more above the baseline nadir level should be evaluated for prostate cancer[14,53] or noncompliance to the prescribed regimen.

Phosphodiesterase Type 5 Inhibitors

7 Several observations led to the use of phosphodiesterase type 5 inhibitors for management of BPH. (1) BPH and erectile dysfunction are often present concurrently in the same patient. (2) The pathophysiology of BPH and erectile dysfunction may be common in so far as both disorders may be associated with increased smooth muscle contraction and pelvic atherosclerosis.[54] (3)Improvement of BPH symptoms has been reported to ameliorate erectile dysfunction; and vice versa.[55] (4) Using a phosphodiesterase type 5 inhibitor with a 5α-reductase inhibitor is reasonable as the former will effectively treat include erectile dysfunction due to the latter.[56]

Phosphodiesterase type 5 inhibitors relax smooth muscle in the prostate, urethra, bladder neck, and pelvic blood vessels, probably by increasing cGMP. By so doing, phosphodiesterase type 5 inhibitors interrupt the Rho-protein

kinase pathway (which regulates smooth muscle contraction mediated by endothelin and α-adrenergic stimulation), improve oxygenation to tissue, and possibly decrease inflammation.[4,57,58]

In multiple clinical trials of patients with moderate LUTS, tadalafil caused a mean two-point improvement in both obstructive and irritative voiding symptoms using the AUA Symptom Index Score or International Prostate Symptom Score (IPSS), with the level of improvement similar to that observed with α_1-adrenergic antagonists.[15,59,60] However, no or minimal increase in urinary flow rate or reduction in PVR occurred with tadalafil alone.[61,62] Tadalafil 2.5 mg was inferior to 5 mg, and doses of 10 or 20 mg were not superior to 5 mg.[59,60,63,64] This is the basis of the current product labeling dose of tadalafil 5 mg daily for BPH. The onset of clinical symptom improvement is within 4 weeks.[59,64]

When tadalafil is combined with an α-adrenergic antagonist, patients experienced significant improvements in LUTS, increased urinary flow rates, and decreased PVR volume[61,63,64]; however, the improvement was similar to that observed with an α-adrenergic antagonist alone.[64] When tadalafil is combined with a 5α-reductase inhibitor, the former can offset the sexual dysfunction adverse effects of the latter. In addition, their actions are complementary. Tadalafil can reduce LUTS within a week, while the 5α-reductase inhibitor can delay BPH progression.[65]

A few other BPH studies have employed sildenafil 50 mg or 100 mg daily or vardenafil 10 mg twice a day.[61–64] Based on a recent meta-analysis, all phosphodiesterase type 5 inhibitors produce comparable improvements of LUTS, but tadalafil is the only one that has been FDA approved for the treatment of BPH.[66] Tadalafil has the longest plasma half-life and longest duration of action among the phosphodiesterase type 5 inhibitors. This pharmacokinetic characteristic is conducive for the treatment of BPH, which is a chronic illness.

Dosing Recommendations

The recommended tadalafil dose is 5 mg daily. Based on the limited clinical benefit, cost, and potential adverse effects of tadalafil, its use should be reserved for patients with both BPH and erectile dysfunction. Patients with known cardiovascular disease should be assessed and stratified according to the Princeton Consensus Panel guidelines[4,67] to identify those patients who can safely use tadalafil. If used in combination with an α-adrenergic antagonist, precautions should be taken to minimize hypotension, specifically, the patient’s

blood pressure should be stabilized on the α_1-adrenergic antagonist before adding tadalafil.[38] If used in combination with a 5α-reductase inhibitor, tadalafil may be used instead of an α-adrenergic antagonist, and the combination may be associated with less sexual dysfunction, particularly in younger, sexually active patients.

Adverse Effects

The most common adverse effects with tadalafil are headache, flushing, gastroesophageal reflux, sinusitis, visual disturbances, and back pain, which are generally mild and reversible and do not require discontinuation of therapy. Headache and dizziness are related to the vasodilatory effect of tadalfil. If tadalafil is an add-on to an existing α_1-adrenergic antagonist and the patient is at risk of hypotensive adverse effects, it is recommended that: (a) the patient's blood pressure be stabilized on the α_1-adrenergic antagonist before tadalafil is started; (b) once tadalafil is started, separate its administration from the α_1-adrenergic antagonist by 4 hours; and (c) preferentially prescribe tamsulosin, silodosin, or alfuzosin as opposed to other α_1-adrenergic antagonists. Back pain has been linked to tadalafil's inhibition of phosphodiesterase type 11. This usually responds to acetaminophen or a nonsteroidal anti-inflammatory agent.

Drug Interactions

Nitrates by any route of administration are contraindicated in patients taking tadalafil.

Anticholinergic Agents

Five types of muscarinic receptors have been identified: (1) M_1 that concentrate in the brain, stomach, and salivary glands; (2) M_2 that comprise 71% to 75% of the muscarinic receptors in the urinary bladder and also are found in the gastrointestinal tract and the atrioventricular node of the heart; (3) M_3 comprise 25% to 29% of the muscarinic receptors in the urinary bladder, and are also distributed in salivary glands, gastrointestinal tract, airways, and eyes; (4) M_4 that are found in the urinary bladder and central nervous system; and (5) M_5 that are found in the brain and eyes.[68] Although M_2 receptors predominate in the urinary bladder, increased M_3 receptor stimulation has been linked with irritative bladder symptoms and overactive bladder syndrome. For this reason, M_3

selective anticholinergic agents are considered uroselective. However, since M_3 receptors are widely distributed in other organ systems, this explains why darifenacin, a uroselective anticholinergic agent, causes dry mouth, constipation, and mydriasis.

8 Treatment with an α_1-adrenergic antagonist, 5α-reductase inhibitor, or surgery may improve urinary flow rate and bladder emptying; however, the patient may still complain of irritative voiding symptoms (eg, urinary frequency, urgency, and nocturia), which mimic those of overactive bladder syndrome. A variety of anticholinergic agents, including oxybutynin or tolterodine, have been added to an α-adrenergic antagonist regimen to relieve these symptoms.[4,29,69]

By blocking muscarinic receptors in the detrusor muscle, anticholinergic agents can reduce uninhibited detrusor contractions, a sequela of prolonged bladder outlet obstruction. Thus, irritative voiding symptoms including urinary frequency, urgency, and incontinence, are reduced. The peak clinical effect is observable in several weeks. It is recommended that a patient should be reevaluated 4 to 6 weeks after starting an anticholinergic agent for BPH. These agents do not improve urinary flow rate or consistently improve AUA symptom scores.[58] Because older patients are sensitive to the central nervous system adverse effects and dry mouth, such patients should be started on the lowest effective dose and then slowly titrated up.[66,70] Anticholinergic agents are contraindicated in patients with narrow angle glaucoma, urinary or gastric retention, or severely decreased intestinal motility. The total anticholinergic burden should be considered prior to making the decision to initiate an anticholinergic agent if the patient is already taking other anticholinergic agents (eg, antipsychotic, antidepressant, antihistamine, antiparkinsonian agents). When multiple anticholinergic agents are taken concurrently, anticholinergic adverse effects, including dry mouth, nausea, constipation, blurred vision, and confusion, will more likely occur and be more severe.

For patients who poorly tolerate systemic anticholinergic adverse effects, the best options are darifenacin, which is a uroselective M_3 receptor antagonist; anticholinergics, which preferentially inhibit M_3 receptors more than other receptors (eg, solifenacin)[68]; transdermal oxybutynin, which bypasses first-pass hepatic metabolism to an active metabolite with anticholinergic adverse effects; or extended-release formulations of anticholinergic agents (eg, tolterodine), which produce lower peak plasma concentrations as compared to immediate-release formulations. For older adults at risk of sedation and confusion from anticholinergic agents, trospium or fesoterodine has a lower propensity to cross

the blood brain barrier and may be a good choice.[4]

In the presence of BPH, anticholinergic agents can cause acute urinary retention in patients with poor detrusor contractility. Therefore, before prescribing an anticholinergic agent, a PVR urine volume should be measured; it should be 100 to 150 mL or less.[14,68,70] By so doing, patients at high risk of acute urinary retention would be excluded from treatment.

Mirabegron

Approximately 95% of the β-adrenergic receptors in the urinary bladder are of the β_3 subtype. When stimulated, β_3-adrenergic receptors increase production of cyclic adenosine monophosphate (cAMP), which relaxes the detrusor muscle.[58,68,70,71]

9 Mirabegron is a β_3-adrenergic agonist. As a result of relaxing the detrusor muscle during the storage phase of the micturition cycle, mirabegron reduces irritative voiding symptoms, increases urinary bladder capacity, and increases the interval between voidings. Mirabegron does not inhibit voiding or reduce urinary flow rate, nor does it increase PVR urine volume or cause acute urinary retention.[15,72] The clinical efficacy of mirabegron for LUTS is comparable to that of anticholinergic agents, but mirabegron is better tolerated.[58,72] Mirabegron does not produce anticholinergic adverse effects, nor does it cause acute urinary retention.

Mirabegron is indicated for symptomatic management of overactive bladder syndrome, which presents with symptoms that overlap with the irritative component of LUTS. For this reason, mirabegron is used as an alternative to anticholinergic agents in patients with LUTS, when irritative symptoms persist despite treatment with an α_1-adrenergic antagonist or 5α-reductase inhibitor.[72] The usual starting dose of mirabegron is 25 mg daily, increasing to 50 mg daily if needed. Increasing the dose to 100 mg appears no more effective than 50 mg.[68] A usual daily dose of 25 mg daily is recommended for patients with impaired renal function (creatinine clearance of 15-20 mL/min [0.25-0.33 mL/s]) or moderate hepatic impairment. Mirabegron should not be used in patients with severe hepatic dysfunction or a creatinine clearance less than 15 mL/min (0.25 mL/s).

Adverse effects of mirabegron include mild headache, dry mouth, nausea, diarrhea, constipation, nasopharyngitis, and in rare cases QT-interval prolongation. None of these adverse effects cause discontinuation of treatment. Mirabegron increases systolic blood pressure by 0.5 to 1 mm Hg and heart rate

by 1 bpm. Although these increases are generally small, older adults with BPH often have essential hypertension and the concern is that this may be worsened by mirabegron. Therefore, patients with uncontrolled hypertension or a systolic or diastolic blood pressure of 180 mm Hg or 110 mm Hg or higher, respectively, should avoid mirabegron. Regular blood pressure monitoring is advised in patients with poorly controlled blood pressure, significant congestive heart failure, cardiomyopathy, or patients who are 80 years of age or older.[72]

Combination Drug Therapy

Many drug combinations have been used for BPH. With an α_1-adrenergic antagonist as initial therapy, medications are often added when the patient's symptoms are still bothersome. To reduce irritative symptoms, an anticholinergic agent, mirabegron, or a phosphodiesterase type 5 inhibitor may be added. Similarly, a 5α-reductase inhibitor has a slow onset of action. To achieve faster symptom relief, an α_1-adrenergic antagonist,[14] mirabegron[73], or a phosphodiesterase inhibitor[74,75] can be added. These combinations do not reduce the need for prostate surgery or reduce the risk of disease progression. When such combinations are used, the benefit of reducing bothersome symptoms must be balanced by the increased risk of adverse effects and drug interactions, higher cost of treatment, and lower rates of adherence to treatment.[75]

However, the combination of an α_1-adrenergic antagonist and a 5α-reductase inhibitor is ideal for patients with both severe symptoms and an enlarged prostate gland of at least 40 g and PSA of at least 1.4 ng/mL (mcg/L), a surrogate marker for an enlarged prostate gland.[11,14] Such patients appear to be at high risk for disease progression, as evidenced by symptom worsening and development of disease complications, including acute urinary retention, recurrent urinary tract infection, or the need for surgical intervention.[11]

In the landmark Multiple Treatment of Prostate Symptoms Study (MTOPS), a regimen of finasteride and doxazosin for 5 years was shown to prevent symptom progression by 66%, decrease the risk of developing acute urinary retention by 81%, and decrease the need for prostate surgery by 67%. Moreover, urinary symptom improvement and higher urinary flow rates at 15 to 18 months were observed in patients treated with combination therapy, as compared with monotherapy with finasteride alone or doxazosin alone.[11] In another key clinical trial, the Combination of Avodart and Tamsulosin (COMBAT) study, dutasteride versus tamsulosin versus a combination of dutasteride and tamsulosin were evaluated in patients with prostate glands of 40 mL or greater and PSA of 1.5

ng/mL (mcg/L) or higher. The combination regimen was more effective in reducing symptoms 9 months after the start of treatment than dutasteride alone or tamsulosin alone. In addition, after a long-term follow-up of 4 years, the combination of dutasteride and tamsulosin prevented disease progression and reduced the need for prostate surgery.[76,77]

Although not proven by direct comparison trials, any combination of 5α-reductase inhibitor and α_1-adrenergic antagonist probably is similarly effective for patients with the aforementioned characteristics. The disadvantages of a combination regimen include increased medication cost, decreased adherence to multidrug treatment regimens, and an increased incidence of adverse drug effects (eg, sexual dysfunction).[14,64,75]

Surgical Intervention

10 The gold standard for treatment of patients with complications of BPH is prostatectomy performed either transurethrally or as an open surgical procedure.[8,14] Surgical intervention is indicated for patients with moderate-to-severe symptoms, who are not responsive to or cannot tolerate adverse effects of drug therapy, who are noncompliant with drug therapy, or who prefer surgical intervention.[78] Surgical intervention is always indicated for patients with complications of BPH, including acute urinary retention not responsive to drug treatment, chronic urinary retention associated with decreased renal function or overflow urinary incontinence, urolithiasis, recurrent urinary tract infection, or recurrent hematuria.[79] Surgical removal of the prostatic adenoma offers the highest rate of symptom improvement, but it also has the highest complication rate.

With TURP, an endoscopic resectoscope inserted through the urethra is used to remove the inside core of the prostatic adenoma. This enlarges the opening at the bladder neck and prostatic urethra. Often performed as outpatient surgery, this procedure produces on average a peak urinary flow rate increase of 125%, improves the AUA Symptom Score by 10 to 18 points, and improves voiding symptoms by almost 90% in approximately 90% of patients. A common complication of TURP is retrograde ejaculation, occurring in up to 75% of patients. Bleeding, urinary incontinence, and erectile dysfunction occur in smaller, but significant numbers of patients (2%–15%).[79,80] Approximately 2% to 10% and 12% to 15% of patients require second surgeries within 5 and 8 years, respectively.[80]

Alternatively, an open surgical procedure (open prostatectomy) can be

performed retropubically or suprapubically. This procedure is usually reserved for men with prostate glands larger than 80 mL. This necessitates hospitalization for at least a few days, anesthesia, and a longer recuperation time. Adverse effects of open prostatectomy include bleeding, urinary and soft-tissue infection, retrograde ejaculation in 77% of patients, erectile dysfunction in 16% to 33% of patients, and urinary incontinence in 2% of patients. The reoperation rate is 3% to 5% at 10 years.[14,79]

Transurethral incision of the prostate (TUIP) is an alternative surgical procedure for patients with moderate-to-severe voiding symptoms who have an enlarged prostate gland less than 30 g in size. In the short term TUIP is as effective as TURP but requires less operation time, causes less blood loss, and produces fewer adverse effects.[14,79] TUIP involves using an endoscopic resectoscope to make one or two incisions at the bladder neck to widen the opening. In limited long-term studies, the reoperation rate for TUIP is slightly higher than with TURP.

Minimally invasive surgical procedures are highly desirable by patients. The procedures do not require hospitalization, are associated with less blood loss, have a lower potential to produce adverse effects, and are less expensive than continuous drug therapy regimens lasting years.[81,82] In addition, medical treatment is considered first line for patients with moderate-to-severe symptoms. Patients may receive such medical treatment for years before their BPH progresses to the point that surgical intervention is required. At this stage, patients are often at an advanced age, are frail or debilitated, may have more comorbidities, may be on anticoagulants (which complicates prostatectomy procedures), and may have larger prostates. Minimally invasive surgical procedures may be particularly useful for these patients These procedures typically use heat energy from microwaves, water, or laser (holmium, potassium titanyl phosphate, or thulium) to destroy prostate tissue.[83] Commonly used procedures include transurethral needle ablation of the prostate, green light laser ablation, and transurethral microwave thermotherapy of the prostate.[81,82] A disadvantage of all minimally invasive surgical procedures is the high percentage of patients who may develop acute urinary retention in the immediate postoperative period. In addition, patients who undergo minimally invasive procedures generally experience smaller improvements in voiding symptoms and urinary flow rates, and they are more likely to require reoperation after an initial improvement in symptoms than patients who undergo TURP or open prostatectomy.[81,82]

Phytotherapy

Although phytotherapy is widely used in Europe for the management of BPH, the published data on herbal agents are largely inconclusive and conflicting. Studies often lack placebo controls, which are essential for assessing treatments for BPH because spontaneous regression of mild symptoms can occur. Furthermore, because these agents are marketed under the Dietary Supplements Health and Education Act, their efficacy, safety, and quality are not regulated by the FDA. For these reasons, herbal products—including saw palmetto berry (*Serenoa repens*), stinging nettle (*Urtica dioica*), South African star grass (*Hypoxis rooperi*), pumpkin seed (*Cucurbita pepo*), and African plum (*Pygeum africanum*)—are not recommended for treatment of BPH.[14] Excellent reviews on phytotherapy for BPH have been published.[83,84]

EVALUATION OF THERAPEUTIC OUTCOMES

The primary therapeutic outcome of BPH therapy is improvement of voiding symptoms with minimal treatment-related adverse effects. As a disease for which therapy is directed at the voiding symptoms that the patient finds most bothersome, assessment of outcomes depends on the patient's perceptions of the effectiveness of therapy. Use of a validated, standardized instrument, such as the AUA Symptom Score, for assessing patient's voiding symptoms is important in this process.[14] A clinically significant improvement is generally associated with a decrease in score of three points or more. The efficacy of any new medication or medication combination for treatment of BPH should be assessed 6 to 12 weeks after its start. Symptomatic improvement of LUTS is expected, although 5α-reductase inhibitors will require at least 6 months to shrink an enlarged prostate.[14,15]

For patients being considered for surgical treatment, objective measures of bladder emptying are useful and include the urinary flow rate and PVR urine volume (see "Diagnostic Evaluation").

Because this patient population is at high risk for prostate cancer, PSA should be measured and a digital rectal examination performed annually if a patient has a life expectancy of at least 10 years. For patients taking 5α-reductase inhibitors, a second PSA taken 6 months after the start of treatment should be compared with baseline measurements. If the patient is suspected of having developed renal impairment as a consequence of long-standing bladder outlet obstruction, then BUN and serum creatinine should be evaluated at regular intervals.

CONCLUSION

A ubiquitous disease of aging men, symptomatic BPH requires medical attention to preserve the patient's quality of life and to prevent disease complications, many of which can be life-threatening in this patient population. In men who have no or mildly bothersome symptoms, watchful waiting and behavior modification are the best treatment approach, as BPH remains stable or even regresses in approximately half of these men.

For patients with voiding symptoms that are moderate to severely bothersome, pharmacotherapy is indicated. An α_1-adrenergic antagonist is the agent of first choice. Second-generation agents include terazosin, doxazosin, and alfuzosin, and third-generation agents include tamsulosin and silodosin. Immediate-release formulations of terazosin and doxazosin cause more cardiovascular adverse effects than do extended-release formulations (eg, doxazosin or alfuzosin), or uroselective α_{1A}-adrenergic agents (eg, tamsulosin, silodosin, or alfuzosin). 5α-Reductase inhibitors are preferred drug treatment for patients with enlarged prostates greater than 40 g who poorly tolerate the hypotensive adverse effects of α_1-adrenergic antagonists. However, 5α-reductase inhibitors have a slow onset of action. For patients who do not respond to monotherapy, combination drug therapy could be attempted. Alternatively, surgery is an option.

For patients with both moderate-to-severe BPH and erectile dysfunction, a phosphodiesterase inhibitor alone or combined with an α-adrenergic antagonist may be prescribed. For patients with moderate-to-severe BPH with a predominance of irritative voiding symptoms, an anticholinergic agent, mirabegron, or a phosphodiesterase inhibitor may be added to an existing drug treatment regimen for BPH. Before starting an anticholinergic agent in a patient with BPH, the patient's PVR should be less than 100 to 150 mL.

For patients who have complications of BPH, surgery is required. Although it has more adverse complications than pharmacotherapy or watchful waiting, TURP is considered the gold standard.

Postclass Engaged Learning Activity

Based on the pharmacologic mechanism of 5α-reductase inhibitors, it has been suggested that they may increase the risk of breast cancer and congestive heart failure. Conduct a literature search and identify one to two articles on either of

these topics. Read through the article and summarize the proposed mechanism for the adverse effect, clinical findings, and any limitations of the findings. Then describe how you would respond to a patient who might ask questions about these potential adverse effects of drug treatment.

ABBREVIATIONS

ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
AUA	American Urological Association
BPE	benign prostatic enlargement
BPO	benign prostatic obstruction
BPH	benign prostatic hyperplasia
BUN	blood urea nitrogen
cAMP	cyclic adenosine monophosphate
cGMP	cyclic guanosine monophosphate
COMBAT	Combination of Avodart and Tamsulosin (Study)
CYP	cytochrome P-450
DHT	dihydrotestosterone
GI	gastrointestinal
IPSS	International Prostate Symptom Score
LUTS	lower urinary tract symptoms
MTOPS	Multiple Treatment of Prostate Symptoms (Study)
PSA	prostate-specific antigen
PVR	postvoid residual (pertains to urine volume)
REDUCE	Reduction by Dutasteride in Prostate Cancer Events
TURP	transurethral resection of the prostate
TUIP	transurethral incision of the prostate

REFERENCES

1. Glynn RJ, Campion EW, Bouchard GR, Silbert JE. The development of benign prostatic hyperplasia among volunteers in the Normative Aging Study. *Am J Epidemiol*. 1985;121(1):78–90.

2. Egan KB. The epidemiology of benign prostatic hyperplasia associated with lower urinary tract symptoms: Prevalence and incident rates. *Urol Clin North Am*. 2016;43(3):289–297.
3. Roehrborn CG. Pathology of benign prostatic hyperplasia. *Int J Impot Res*. 2008;20 (suppl 3):S11–S18.
4. Albisinni S, Biaou I, Marcelis Q, et al. New medical treatments for lower urinary tract symptoms due to benign prostatic hyperplasia and future perspectives. *BMC Urol*. 2016;16(1):58. doi: 10.1186/s12894-016-0176-0.
5. St. Sauver JL, Jacobson DJ, Girman CJ, et al. Tracking of longitudinal changes in measures of benign prostatic hyperplasia in a population based cohort. *J Urol*. 2006;175 (3 Pt 1):1018–1022.
6. Wuerstle MC, Van Den Eeden SK, Poon KT, et al.; Urologic Diseases in American Project. Contribution of common medications to lower urinary tract symptoms in men. *Arch Intern Med*. 2011;171(18):1680–1682.
7. Lythgoe C, McVary K. The use of PDE-5 inhibitors in the treatment of lower urinary tract symptoms due to benign prostatic hyperplasia. *Curr Urol Rep*. 2013;14(6):585–594.
8. Gratze C, Bachmann A, Descazeaud A, et al. EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. *Eur Urol*. 2015;67(6):1099–1109.
9. Wasson JH, Reda DJ, Bruskewitz RC, et al. A comparison of transurethral surgery with watchful waiting for moderate symptoms of benign prostatic hyperplasia. The Veterans Affairs Cooperative Study Group on Transurethral Resection of the Prostate. *N Engl J Med*. 1995;332(2):75–79.
10. Jacobsen SJ, Jacobson DJ, Girman CJ, et al. Natural history of prostatism: Risk factors for acute urinary retention. *J Urol*. 1997;158(2):481–487.
11. McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med*. 2003;349(25):2387–2398.
12. Roehrborn CG. Male lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH). *Med Clin North Am*. 2011;95(1): 87–100.
13. Rosenberg MT, Witt ES, Miner M, Barkin J. A practical primary care approach to lower urinary tract symptoms caused by benign prostatic hyperplasia (BPH-LUTS). *Can J Urol*. 2014;21(suppl 2):12–24.

14. McVary KT, Roehrborn CG, Avins AL, et al. American Urological Association Guideline: Management of Benign Prostatic Hyperplasia (BPH). 2010, reviewed and validity confirmed 2014. Available at: http://www.auanet.org/education/guidelines/benign-prostatic-hyperplasia.cfm. Accessed October 1, 2018.
15. Unnikrishnan R, Almassi N, Fareed K. Benign prostatic hyperplasia: evaluation and medical management in primary care. *Cleve Clin J Med*. 2017;84(1):53–64.
16. Newman DK, Guzzo T, Lee D, Javadevappa R. An evidence-based strategy for the conservative management of the male patient with incontinence. *Curr Opin Urol*. 2014;24(6):553–559.
17. Strittmatter F, Gratzke C, Stief CG, Hedlund P. Current pharmacological treatment options for male lower urinary tract symptoms. *Expert Opin Pharmacother*. 2013;14(8):1043–1054.
18. Hollingsworth JM, Wilt T. Lower urinary tract symptoms in men. *BMJ*. 2014;349:g4474. doi: 10.1136/b,j.g4474.
19. Djavan B, Marberger M. A meta-analysis on the efficacy and tolerability of alpha1-adrenoceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction. *Eur Urol*. 1999;36(1):1–13.
20. Lepor H, Kazzazi A, Djavan B. α-Blockers for benign prostatic hyperplasia: The new era. *Curr Opin Urol*. 2012;22(1):7–15.
21. Welk B, McArthur E, Fraser LA, et al. The risk of fall and fracture with the initiation of a prostate-selective α antagonist: A population based cohort study. *BMJ*. 2015;351:h5398.
22. Albisinni S, Aoun F, Roumequere T, et al. New treatment strategies for benign prostatic hyperplasia in the frail elderly population: A systematic review. *Minerva Urol Nefrol*. 2017;69(2):119–132.
23. ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2000;283(15):1967–1975.
24. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NM/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults-a report of the American College of Cardiology/American Heart Association Task Froce on Clinical Practice

Guidelines. *J Am Coll Cardiol*. 2019;71(19):e248. doi: 10.1016/jack.2017.11.006.

25. Narayan P, Evans CP, Moon T. Long-term safety and efficacy of tamsulosin for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia. *J Urol*. 2003;170 (2 Pt 1):498–502.
26. Dutkiewicz S. Long term treatment with doxazosin in men with benign prostatic hyperplasia: 10 year follow-up. *Int Urol Nephrol*. 2004;36(2):169–173.
27. Zhang LT, Lee SW, Park K, et al. Multicenter, prospective, comparative cohort study evaluating the efficacy and safety of alfuzosin 10 mg with regard to blood pressure in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia with or without antihypertensive medications. *Clin Interv Aging*. 2015;10:277–286.
28. Mottet N, Bressolle F, Delmas V, et al. Prostatic tissue distribution of alfuzosin in patients with benign prostatic hyperplasia following repeated oral administration. *Eur Urol*. 2003;44(1):101–105.
29. Lepor H. Alpha-blockers for the treatment of benign prostatic hyperplasia. *Urol Clin North Am*. 2016;43(3):311–323.
30. Osman NI, Chapple CR, Cruz F, et al. Silodosin: A new subtype selective alpha-1-antagonist for the treatment of lower urinary tract symptoms in patients with benign prostatic hyperplasia. *Expert Opin Pharmacother*. 2012;13(14):2085–2096.
31. Aharony S, Lam O, Corcos J. Is there a demonstrated advantage to increase tamsulosin dosage in patients with benign prostatic hyperplasia? *Urology*. 2014;84(2):493–494.
32. Bird ST, Delaney JA, Brophy JM, et al. Tamsulosin treatment for benign prostatic hyperplasia and risk of severe hypotension in men aged 40-85 years in the United States: Risk window analyses using between and within patient methodology. *BMJ*. 2013;347:f6320. doi: 10.1136/bmj.f6320.
33. Roehrborn CG, Cruz F, Fusco F. α1-Blockers in men with lower urinary tract symptoms suggestive of benign prostatic obstruction: Is silodosin different? *Adv Ther*. 2017;33(12):2110–2121.
34. Michel MC. The forefront for novel therapeutic agents based on the pathophysiology of lower urinary tract dysfunction: Alpha-blockers in the treatment of male voiding dysfunction—how do they work and why do they differ in tolerability? *J Pharmacol Sci*. 2010;112(2):151–157.

35. Herberts M, Butcher M, Kohler T. The effect of LUTS/BPH and treatments on ejaculatory function. *Curr Urol Rep*. 2016;17(7):48. doi: 10.1007/s11934-016-0604-4.
36. Welliver C, Essa A. Sexual side effects of medical and surgical benign prostatic hyperplasia treatments. *Urol Clin North Am*. 2016;43(3):393–404.
37. Yaycioglu O, Altan-Yaycioglu R. Intraoperative floppy iris syndrome: Facts for the urologist. *Urology*. 2010;76(2):272–276.
38. Goldfischer E, Kowalczyk JJ, Clark WR, et al. Hemodynamic effects of once-daily tadalafil in men with signs and symptoms of benign prostatic hyperplasia on concomitant α1-adrenergic antagonist therapy: Results of a multicenter randomized, double-blind, placebo-controlled trial. *Urology*. 2012;79(4):875–882.
39. Wu C, Kapoor A. Dutasteride for the treatment of benign prostatic hyperplasia. *Expert Opin Pharmacother*. 2013;14(10):1399–1408.
40. Nickel JC, Gilling P, Tammela TL, et al. Comparison of dutasteride and finasteride for treating benign prostatic hyperplasia: The Enlarged Prostate International Comparator Study (EPICS). *BJU Int*. 2011;108(3):388–394.
41. Zatton R, Ficarra V, Novara G. Risk stratification for benign prostatic hyperplasia. *Urologia*. 2017;84(3):153–157.
42. Fullhase C, Schneider MP. 5-alpha-reductase inhibitors and combination therapy. *Urol Clin North Am*. 2016;43(3):325–336.
43. Roehrborn CG, Nickel JC, Andriole GL, et al. Dutasteride improves outcomes of benign prostatic hyperplasia when evaluated for prostate cancer risk reduction: Secondary analysis of the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial. *Urology*. 2011;78(3):641–646.
44. Roehrborn CG, Bruskewitz R, Nickel JC, et al. Sustained decrease in incidence of acute urinary retention and surgery with finasteride for 6 years in men with benign prostatic hyperplasia. *J Urol*. 2004;171:1194–1198.
45. Welliver C, Butcher M, Potini Y, McVary KT. Impact of alpha blockers, 5-alpha reductase inhibitors and combination therapy on sexual function. *Curr Urol Rep*. 2014;15(10):441. doi: 10.1007/s11934-014-0441-2.
46. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med*. 2003;349(3):215–224.
47. Thompson IM, Tangen CM, Goodman PJ, et al. Finasteride improves the

sensitivity of digital rectal examination for prostate cancer detection. *J Urol*. 2007;177(5):1749–1752.

48. Andriole GL, Bostwick DG, Brawley OW, et al. for the REDUCE Study Group. Effect of dutasteride on the risk of prostate cancer. *N Engl J Med*. 2010;362(13):1192–1202.
49. Theoret MR, Ning YM, Zhang JJ, et al. The risks and benefits of 5α-reductase inhibitors for prostate cancer prevention. *N Engl J Med*. 2011;365(2):97–99.
50. Irwig MS. Persistent sexual side effects of finasteride: Could they be permanent? *J Sex Med*. 2012;9(11):2927–2932.
51. Liu L, Zhao S, Li F, et al. Effect of 5α-reductase inhibitors on sexual function: A meta-analysis and systematic review of randomized controlled trials. *J Sex Med*. 2016;13(9):1297–1310.
52. Corona C, Tirabassi G, Santi D, et al. Sexual dysfunction in subjects treated with inhibitors of 5α-reductase for benign prostatic hyperplasia: A comprehensive review and meta-analysis. *Andrology*. 2017;5(4):671–678.
53. Kaplan SA, Chung DE, Lee RK, et al. A 5-year retrospective analysis of 5alpha-reductase inhibitors in men with benign prostatic hyperplasia: Finasteride has comparable urinary symptom efficacy and prostate volume reduction, but less sexual side effects and breast complications than dutasteride. *Int J Clin Pract*. 2012;66(11):1052–1055.
54. Kirby M, Chapple C, Jackson G. Erectile dysfunction and lower urinary tract symptoms: A consensus on the importance of co-diagnosis. *Int J Clin Pract*. 2013;67(7):606–618.
55. Shelbaia A, Elsaied WM, Elghamrawy H, et al. Effect of selective alpha-blocker tamsulosin on erectile function in patients with lower urinary tract symptoms due to benign prostatic hyperplasia. *Urology*. 2013;82(1):130–135.
56. Laydner HK, Oliveira P, Oliveira CR, et al. Phosphodiesterase 5 inhibitors for lower urinary tract symptoms secondary to benign prostatic hyperplasia: A systematic review. *BJU Int*. 2011;107(7):1104–1109.
57. Egerdie RB, Auerbach S, Roehrborn CG, et al. Tadalafil 2.5 mg or 5 mg administered once daily for 12 weeks in men with both erectile dysfunction and signs and symptoms of benign prostatic hyperplasia: Results of a randomized, placebo-controlled, double-blind study. *J Sex Med*. 2012;9(1):271–281.
58. Chughtai B, Thomas D, Kaplan S. α-Blockers, 5α-reductase inhibitors,

acetylcholine, β-3 agonists, and phosphodiesterase-5s in medical management of lower urinary tract symptoms/benign prostatic hyperplasia: How much do the different formulations actually matter in the classes? *Urol Clin North Am*. 2016;43(3):351–56.

59. Oelke M, Shinghal R, Sontag A, et al. Time to onset of clinically meaningful improvement with tadalafil 5 mg once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: Analysis of data pooled from 4 pivotal, double-blind placebo-controlled studies. *J Urol*. 2015;193(5):1581–1589.
60. Oelke M, Giuliano F, Mirone V, et al. Monotherapy with tadalafil or tamsulosin similarly improved lower urinary tract symptoms suggestive of benign prostatic hyperplasia in an international, randomized, parallel, placebo-controlled clinical trial. *Eur Urol*. 2012;61(5): 917–925.
61. Gacci M, Corona G, Salvi M, et al. A systematic review and meta-analysis on the use of phosphodiesterase 5 inhibitors alone or in combination with α-blockers for lower urinary tract symptoms due to benign prostatic hyperplasia. *Eur Urol*. 2012;61(5):994–1003.
62. Roehrborn CG, Chapple C, Oelke M, et al. Effects of tadalafil once daily on maximum urinary flow rate in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia. *J Urol*. 2014;191(4):1045–1050.
63. Gacci M, Andersson K-E, Chapple C, et al. Latest evidence on the use of phosphodiesterase type 5 inhibitors for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. *Eur Urol*. 2016;70(1):124–133.
64. Yan H, Zong H, Cui Y, et al. The efficacy of PDE5 inhibitors alone or in combination with alpha-blockers for the treatment of erectile dysfunction and lower urinary tract symptoms due to benign prostatic hyperplasia: A systematic review and meta-analysis. *J Sex Med*. 2014;11(6):1539–1545.
65. Schauer I, Madersbacher S. Medical treatment of lower urinary tract symptoms/benign prostatic hyperplasia: Anything new in 2015. *Curr Opin Urol*. 2015;25(1):6–11.
66. Yuan JQ, Mao C, Wong SY, et al. Comparative effectiveness and safety of monodrug therapies for lower urinary tract symptoms associated with benign prostatic hyperplasia: A network meta-analysis. *Medicine*. 2015;94(27):e974. doi: 10.1097/MD.0000000000000974.
67. Nehra A, Jackson G, Miner M, et al. The Princeton III Consensus

Recommendations for the management of erectile dysfunction and cardiovascular disease. *Mayo Clin Proc*. 2012;87(8):766–778.

68. Osman NI, Aldamanhori R, Mangera A, Chapple CR. Antimuscarinics, β3 agonists, and phosphodiesterase inhibitors in the treatment of male lower urinary tract symptoms: An evolving paradigm. *Urol Clin North Am*. 2016;43(3):337–349.
69. Kim HJ, Sun HY, Choi H, et al. Efficacy and safety of initial combination treatment of an alpha blocker with an anticholinergic medication in benign prostatic hyperplasia patients with lower urinary tract symptoms: Updated meta-analysis. *Plos One*. 2017;12(1):e0169248. doi: 10.1371/journal.pone.0169248.
70. Nitti VW, Rosenberg S, Mitcheson DH, et al. Urodynamics and safety of the β3-adrenoceptor agonist mirabegron in males with lower tract symptoms and bladder outlet obstruction. *J Urol*. 2013;190(4):1320–1327.
71. Russo A, La Croce G, Capogrosso P, et al. Latest pharmacotherapy options for benign prostatic hyperplasia. *Expert Opin Pharmacother*. 2014;15(16):2319–2328.
72. Robinson D, Thiagamoorthy G, Cardozo L. A drug safety evaluation of mirabegron in the management of overactive bladder. *Expert Opin Drug Saf*. 2016;15(5):689–696.
73. Maeda T, Kikuchi E, Hasegawa M, et al. Solifenacin or mirabegron could improve persistent overactive bladder symptoms after dutasteride treatment in patients with benign prostatic hyperplasia. *Urology*. 2015;85(5):1151–1155.
74. Casabe A, Roehrborn CG, DaPozzo LF, et al. Efficacy and safety of the coadministration of tadalafil once daily with finasteride for 6 months in men with lower urinary tract symptoms and prostatic enlargement secondary to benign prostatic hyperplasia. *J Urol*. 2014;191(3):727–733.
75. Cindolo L, Pirozzi L, Sountoulides P, et al. Patient’s adherence on pharmacological therapy for benign prostatic hyperplasia (BPH)-associated lower urinary tract symptoms (LUTS) is different: Is combination therapy better than monotherapy? *BMC Urol*. 2015;15:96. doi: 10.1186/5121894-015-0090-x.
76. Roehrborn CG, Siami P, Barkin J, et al.; CombAT Study Group. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4 year results from the COMBAT study. *Eur Urol*. 2010;57(1):123–131.

77. Roehrborn CG, Barkin J, Siami P, et al. Clinical outcomes after combined therapy with dutasteride plus tamsulosin or either monotherapy in men with benign prostatic hyperplasia (BPH) by baseline characteristics: 4-year results from the randomized, double-blind Combination of Avodart and Tamsulosin (CombAT) trial. *BJU Int*. 2011;107(6):946–954.
78. Presicce F, De Nunzio C, Tubaro A. Can long-term LUTS/BPH pharmacological treatment alter the outcomes of surgical intervention? *Curr Urol Rep*. 2017;18(9):72. doi: 10.1007/s11934-017-0721-8.
79. Mandeville J, Mourtzinos A. Surgical management of male voiding dysfunction. *Surg Clin North Am*. 2016;96(3):491–501.
80. Kim EH, Larson JA, Andriole GL. Management of benign prostatic hyperplasia. *Annu Rev Med*. 2016;67:137–51.
81. Foster HE, Barry MJ, Gandhi MC, et al. American Urological Association. Surgical management of lower urinary tract symptoms attributed to benign prostatic hyperplasia (2018). Available at: https://www.auanet.org/guidelines/benign-prostatic-hyperplasia/lower-urinary-tract-symptoms. Accessed September 29, 2018.
82. Presicce F, DE Nunzio C, Gacci M, et al. The influence of the medical treatment of LUTS on benign prostatic hyperplasia surgery: Do we operate too late? *Minerva Urol Nefrol*. 2017;69(3):242–252.
83. Pagano E, Laudata M, Griffo M, Capasso R. Phytotherapy of benign prostatic hyperplasia. A minireview. *Phytother Res*. 2014;28:949–955.
84. Keehn A, Taylor J, Lowe FC. Phytotherapy for benign prostatic hyperplasia. *Curr Urol Rep*. 2016;17:53. doi: 10.1007/s11934-016-0609-z.

101

Urinary Incontinence

Eric S. Rovner, Jean F. Wyman, and Sum Lam

KEY CONCEPTS

1. In evaluating urinary incontinence (UI), drug-induced or drug-aggravated etiologies must be ruled out.
2. Accurate diagnosis and classification of UI type are critical to the selection of appropriate pharmacotherapy.
3. Goals of treatment for UI are reduction of symptoms, minimization of adverse effects, and improvement in quality of life.
4. Nonpharmacologic, nonsurgical treatment is the first-line treatment for several types of UI, and should be continued even when drug therapy is initiated.
5. Antimuscarinic agents are second-line treatments for urgency incontinence. Choice of agent should be based on patient characteristics (eg, age, comorbidities, concurrent medications, and ability to adhere to the prescribed regimen).
6. Mirabegron, a β_3-adrenergic agonist, is another second-line treatment for urgency incontinence, and can be considered in patients who failed to achieve optimal efficacy or cannot tolerate adverse effects of antimuscarinic agents.
7. Duloxetine (approved in Europe only), α-adrenergic receptor agonists, and topical (vaginal) estrogens (alone or together) are the drugs of choice for urethral underactivity (stress incontinence).
8. Assessment of patient outcomes should include efficacy, adverse effects, adherence, and quality of life.
9. Management of UI should target individualized goals and treatment preferences, which may change over time. If therapeutic goals are not achieved with a given agent at optimal dosage for an adequate duration of

trial, consider switching to an alternative agent.

Preclass Engaged Learning Activity

Read or listen to the topic summary on urinary incontinence from *Quick Pharmacy Answers* in Access Pharmacy by Lauren Roller. The summary is based on the 10th edition of this textbook chapter. This exercise allows the learners to gain a concise overview of the topic.

INTRODUCTION

Urinary incontinence (UI) is defined as involuntary leakage of urine.[1] It is frequently accompanied by other bothersome lower urinary tract symptoms, such as urgency, increased daytime frequency, and nocturia. It is one of the most common health conditions occurring in adults, and yet it is an underdetected and under-reported problem that can significantly affect quality of life. Patients with UI may have depression as a result of the perceived lack of self-control, loss of independence, and lack of self-esteem, and they often curtail their activities for fear of an "accident." UI may also have serious medical and economic ramifications for untreated or undertreated patients, including perineal dermatitis, worsening of pressure ulcers, urinary tract infections, and falls.

This chapter highlights the epidemiology, etiology, pathophysiology, treatment of stress, urgency, mixed, and overflow UI in men and women.

EPIDEMIOLOGY

UI is highly prevalent, and the impact of this condition is substantial, crossing all racial, ethnic, and geographic boundaries. In addition, lower urinary tract symptoms (eg, urgency, urinary frequency, and nocturia) associated with overactive bladder (OAB) are also quite debilitating.[2] Evidence from several studies indicates that UI is associated with reduced levels of social and personal activities, increased psychological distress, and overall decreased quality of life.[3] The condition can affect people of all age groups, but the peak incidence of UI, at least in women, appears to occur around the age of menopause, with a slight decrease in the age group 55 to 60 years, and then a steadily increasing prevalence after age 65 years.

Determining the true prevalence of UI is difficult because of problems with definition, reporting bias, and other methodological issues. Prevalence estimates vary by age, gender, and racial/ethnic group, setting (noninstitutionalized vs institutionalized), and incontinence subtype (stress, urgency, mixed, and overflow UI). Prevalence tends to be highest in women, those of advanced age, and living in long-term care settings.[3,4] The National Health and Nutrition Examination Survey (NHANES) reported a prevalence rate of 43.8% in noninstitutionalized adults age 65 years and over, with more than half of women and one-quarter of men reporting urine leakage.[3] Twelve percent of older women had severe or very severe scores on a validated incontinence severity index representing daily urine leakage with more than drops or small splashes, whereas, older men had slight or moderate incontinence scores representing less frequent urine leakage.[3]

Relatively little is known about differences in clinical and epidemiologic characteristics of incontinence across racial or ethnic groups, especially in men. Almost all population-based studies comparing UI prevalence across racial and ethnic groups is from the United States which limits generalizability. The majority of studies report that white women have a higher prevalence of UI overall and stress UI.[5] There is less consistency regarding prevalence of UI subtypes in black women. In the BACH study, black women had higher rates of mixed UI,[6] and in the EPI study, black women had higher rates of urgency UI.[7] Using data from the NHANES program, no racial or ethnic differences were found in UI prevalence in men.[8] However, differences in access to healthcare as well as cultural attitudes and mores may contribute to these differences.[9,10]

UI prevalence is highest in nursing home residents, with 36.7% of short-stay residents and 70.3% of long-term residents having bladder control problems.[3] Residents who were aged 85 years and more compared to those aged 65 to 74 years had rates 1.5 times higher for short-term residents and 1.2 higher for long-term residents.

ETIOLOGY AND PATHOPHYSIOLOGY

Anatomy

The lower urinary tract consists of the bladder, urethra, urinary or urethral sphincter, and surrounding musculofascial structures, including connective tissue, nerves, and blood vessels. The urinary bladder is a hollow organ composed of smooth muscle and connective tissue located deep in the bony

pelvis in men and women. The urethra is a hollow tube that acts as a conduit for urine flow out of the bladder. An epithelial cell layer termed the *urothelium*, which is in constant contact with urine, lines the interior surface of both the bladder and the urethra. Previously considered inert and inactive, the urothelium may play an active role in the pathophysiology of many lower urinary tract disorders, including interstitial cystitis/bladder pain syndrome and UI[11] and may be a targeted location for future pharmacologic therapeutic interventions for some types of lower urinary tract dysfunction.[12] The urinary or urethral sphincter is a combination of smooth and striated muscle within and surrounding the proximal portion of the urethra adjacent to the bladder. In the male, the prostate gland lies just beyond the bladder outlet and is intimately associated with the urethral sphincter. Its location accounts for both the favorable effects of pharmacological manipulation on male lower symptoms as well as the risk of UI in males following some types of prostate surgery.

To understand the principles of pharmacotherapy for UI, an understanding of the neuroanatomy and neurophysiology of the bladder and urethra is needed. The primary motor (efferent) input to the detrusor muscle of the bladder is parasympathetic and travels along the pelvic nerves emanating from spinal cord segments S2 to S4. Acetylcholine appears to be the primary neurotransmitter at the neuromuscular junction in the human lower urinary tract. Both volitional and involuntary detrusor contractions are mediated by activation of postsynaptic muscarinic receptors by acetylcholine. Of the five known subtypes of muscarinic receptors, the majority of bladder smooth muscle cholinergic receptors are of the M_2 variety. In humans, the ratio of M_2/M_3 receptor numbers is approximately 3:1. However, M_3 receptors are the subtype responsible for both emptying contractions of normal micturition as well as involuntary bladder contractions that may result in UI.[11] Thus, most pharmacologic antimuscarinic therapy is primarily anti-M_3 based. Administration of such agents results in detrusor smooth muscle relaxation and a reduction of bladder overactivity.

Beta-3-adrenergic receptors are found in the lower urinary tract at the level of the detrusor muscle and the urothelium.[11] Although found elsewhere, stimulation of these receptors in the detrusor results in smooth muscle relaxation. Clinically, administration of β_3-agonists is associated with attenuation of bladder contractility and, similarly to antimuscarinics, is used clinically to treat overactive bladder and related urgency incontinence. β-Receptors are also located on the urethra but their clinical significance is considered to be negligible.

Clinically relevant α-adrenergic receptors are located at the level of the bladder outlet on the smooth and striated muscle of the urethra.[11] Stimulation of these receptors with α-adrenergic agonists results in increased urethral closure pressure. Such effects are usually not pronounced enough to treat stress urinary incontinence; however, use of these agents may result in unwanted adverse effects such as aggravation of bladder outlet obstruction and result in poor bladder emptying (urinary retention) especially in men.

Other potentially relevant motor and sensory pathways, neurotransmitters, and receptors have been identified in the lower urinary tract (eg, transient receptor potential channels, E-series prostaglandin receptors). However, the exact role of such targets, as well as ways of modulating their activity pharmacologically in humans has yet to be elucidated and further discussion is beyond the scope of this chapter.

Urinary Continence

To prevent incontinence during the bladder filling and storage phase of the micturition cycle, the urethra, or more accurately the urethral sphincter, must maintain adequate closure in order to resist the flow of urine from the bladder at all times until voluntary voiding is initiated. Urethral closure or resistance to flow is maintained to a large degree by the proximal (under involuntary control) and distal (under both voluntary and involuntary control) urinary sphincters. Variable contributions to urethral closure may also come from the urethral mucosa, submucosal spongy tissue, and the overall length of the urethra. During bladder filling and urinary storage, the bladder accommodates to increasing volumes of urine flowing in from the upper urinary tract without a significant increase in bladder (intravesical) pressure. The maintenance of a low intravesical pressure despite increasing volumes of urine is a unique property of the bladder and is termed *compliance*. In addition, bladder or detrusor smooth muscle activity is normally suppressed during the filling phase by centrally mediated neural reflexes. Normal bladder emptying occurs with opening of the urethral sphincters concomitant with a volitional bladder contraction. Bladder contraction occurs in a coordinated fashion, resulting in a rise in intravesical pressure. The rise in intravesical pressure is ideally of adequate magnitude and duration to empty the bladder to completion. Opening and funneling of the bladder outlet results in urine flow into the urethra until the bladder is emptied to near completion.

The bladder and urethra normally operate in unison during the bladder filling

and storage phase, as well as the bladder emptying phase of the micturition cycle. The smooth and striated muscles of the bladder and urethra are organized during the micturition cycle by a number of reflexes coordinated at the pontine micturition center in the midbrain. Disturbances in the neural regulation of micturition at any level (brain, spinal cord, or pelvic nerves) often lead to characteristic changes in lower urinary tract function that may result in UI.[13,14]

Mechanisms of Urinary Incontinence

Simply stated, UI may occur as a result of abnormalities of only the urethra (including the bladder outlet and urinary sphincter) or only the bladder or as a combination of abnormalities in both. Abnormalities may result in either overactivity or underactivity of the bladder and/or urethra, with resulting development of UI. Although this simple classification scheme excludes extremely rare causes of UI such as congenital ectopic ureters and urinary fistulas, it is useful for gaining a working understanding of the condition and understanding the basis for therapeutic intervention including pharmacotherapy of various lower urinary tract disorders.

Urethral Underactivity (Stress Urinary Incontinence) This type of incontinence is characterized by brief bursts of UI concomitant with exertional activities such as exercise, running, lifting, coughing, and sneezing. The pathophysiology of *stress urinary incontinence* (SUI) is related to decreased or inadequate urethral closure forces. In individuals with SUI, the muscular tissues surrounding the urethra that form the urethral sphincter are compromised and thus not able to resist the expulsive forces resulting from transient increases in intra-abdominal pressure during physical activity. Such forces are transmitted to the bladder (an intra-abdominal organ), compressing it to such an extent as to cause the egress of urine through the urethra. SUI is characterized by episodic, usually low volume urinary leakage but is clearly proportional to the amount of physical exertion or other increases in abdominal pressure such as that related to coughing and sneezing as well as the ambient urethral closure forces.

Risk factors for SUI in the woman include pregnancy, childbirth, menopause, cognitive impairment, obesity, and aging.[15] In men, SUI is most commonly the result of prior lower urinary tract surgery and injury to the sphincter mechanism within and external to the urethra. Radical prostatectomy for treatment of adenocarcinoma of the prostate and transurethral resection of the prostate (TURP) are probably the most common proximate causes of SUI in the male. Notably, compared with its prevalence in women, SUI in men is actually quite

rare.

SUI may be caused or aggravated by some pharmacologic agents such as α-antagonists and angiotensin-converting enzyme (ACE) inhibitors.[16] α-Antagonists may relax the smooth muscle at the level of the urethral sphincter, resulting in a weakened closure mechanism and the onset of SUI. Alternatively, some α-agonists, such as those used clinically for nasal congestion or weight loss, may improve SUI in some individuals, and may even potentially aggravate some types of voiding problems such as those related to bladder outlet obstruction from an enlarged prostate. An adverse effect of some ACE inhibitors is chronic cough, which can also aggravate existing SUI.

Bladder Overactivity (Urgency Urinary Incontinence [UUI]) Urgency UI is defined as the leakage of urine associated with urgency, a compelling desire to void.[1] This is most often related to detrusor (bladder) overactivity due to involuntary bladder contractions. Bladder overactivity describes the condition in which the detrusor muscle contracts inappropriately during urinary storage that, in the neurologically normal individual, results in a sense of urinary urgency. The terms *overactive bladder* and *detrusor (bladder) overactivity* are distinct and should not be used interchangeably.

The International Continence Society defines OAB as a symptom syndrome characterized by urinary urgency, with frequency and nocturia, with/without associated UI in the absence of a known pathologic condition that may result in similar symptoms (eg, urinary tract infection, bladder cancer).[11] *Frequency* is defined as micturition more than eight times per day. *Urgency* is described as a sudden compelling desire to urinate that is difficult to delay.[1] People suffering from OAB typically have to empty their bladder frequently, and, when they experience a sensation of urgency, they may leak urine if they are unable to reach the toilet quickly. Many patients have associated nocturia (>1 micturition per night) and/or nocturnal incontinence (enuresis). Patients with urgency urinary incontinence (UUI) often, but invariably, experience high-volume urine leakage when it occurs. Although detrusor overactivity may be related to OAB, the former diagnosis requires urodynamic testing while the latter is symptomatically defined.

Most patients with OAB and UUI have no identifiable underlying etiology and thus are classified as “idiopathic.” Patients with a relevant neurologic condition and with UI related to involuntary bladder contractions demonstrated on urodynamic testing are classified as having neurogenic detrusor overactivity. Clearly identifiable risk factors for UUI include normal aging, neurologic

disease (including stroke, Parkinson disease, multiple sclerosis, and spinal cord injury), and bladder outlet obstruction resulting in pathological changes to the detrusor muscle (eg, due to benign prostatic hyperplasia [BPH] or prostate cancer).[5]

The pathophysiology of OAB and UUI is not well understood but is likely related to either neurogenic or myogenic factors or combination of both.[17] A full discussion of these differences is complex and beyond the scope of this chapter. However, in practice, although the cause of UUI is difficult to define, the treatment is identical regardless of etiology and pathophysiology.

Some pharmacologic agents may cause or aggravate UUI. Diuretics will cause the rapid accumulation of urine in the bladder with resulting urinary urgency and frequency that can result in UUI. Alcohol will have similar effects. Anticholinesterase inhibitors may also produce urgency and frequency.

Urethral Overactivity and/or Bladder Underactivity (Overflow Incontinence) Overflow incontinence is urinary leakage resulting from an overfilled and distended bladder that is unable to empty. This type of UI occurs when the bladder is filled to capacity at all times but is unable to empty, causing urine to leak from a distended bladder past a normal or even overactive sphincter. Another term related to overflow incontinence is *chronic urinary retention*.[17]

Overflow incontinence is the result of urethral overactivity, bladder underactivity, or a variable combination of both. Clinically and practically, the most common causes of urethral overactivity in men are anatomic urethral obstruction, including that due to BPH and prostate cancer. In women, urethral overactivity is rare but may result from cystocele formation (with resultant kinking or obstruction of the urethra) or surgical overcorrection following surgery for the repair of SUI (iatrogenic obstruction). In both men and women, overflow UI may be associated with systemic neurologic dysfunction or diseases, such as spinal cord injury or multiple sclerosis.

Bladder underactivity occurs as a result of the detrusor muscle of the bladder becoming suddenly or progressively weakened and eventually losing the ability to voluntarily contract and expel urine during voiding. In the absence of adequate contractility, the bladder is unable to empty completely, and large volumes of residual urine are left after voiding. Both myogenic and neurogenic factors have been implicated in producing the impaired contractility seen in this condition. Clinically, overflow incontinence is most commonly seen in the setting of long-term chronic bladder outlet obstruction in men, such as that due

to BPH or prostate cancer, diabetes mellitus, or denervation due to radical pelvic surgery, such as abdominopelvic resection or radical hysterectomy.

There are numerous pharmacologic agents that can result in urinary retention and overflow incontinence. Agents that increase urethral resistance or closure pressure include α-agonists and tricyclic antidepressants. Over-the-counter cold and cough remedies as well as diet pills may contain agents with α-adrenergic properties and/or antihistaminic properties that can result in voiding dysfunction and urinary retention. Agents that can decrease bladder contractility include anticholinergics, tricyclic antidepressants, calcium channel blockers, narcotic analgesics, and antipsychotics.

Mixed Incontinence and Other Types of Urinary Incontinence Various types of UI may coexist in the same patient. The combination of bladder overactivity resulting in urinary incontinence (urgency UI) and urethral underactivity resulting in urinary incontinence (SUI or stress UI) is termed *mixed incontinence*. The diagnosis is often difficult because of the confusing array of presenting symptoms. Bladder overactivity may also coexist with impaired bladder contractility. This occurs most commonly in the elderly and is termed *detrusor hyperactivity with impaired contractility*.[18]

Functional incontinence is not caused by bladder- or urethra-specific factors. Rather, in patients with conditions such as dementia or cognitive or mobility deficits, the UI is linked to the primary disease process more than any extrinsic or intrinsic deficit of the lower urinary tract. An example of functional incontinence occurs in the postoperative orthopedic surgery patient. Following extensive orthopedic reconstructions such as total hip arthroplasty, patients are often immobile secondary to pain or traction. Therefore, patients may be unable to access toileting facilities in a reasonable amount of time and may become incontinent as a result. Treatment of this type of UI may involve simple interventions such as placing a urinal or commode at the bedside that allows for uncomplicated access to toileting. Pharmacologically, functional incontinence can be induced by sedative-hypnotics, narcotic analgesics, and other medications with cognitive adverse effects.

Many localized or systemic illnesses may result in UI because of their effects on the lower urinary tract or the surrounding structures:

1. Dementia/delirium
2. Depression
3. Urinary tract infection (cystitis)
4. Postmenopausal atrophic urethritis or vaginitis

5. Diabetes mellitus
6. Neurologic disease (eg, stroke, Parkinson disease, multiple sclerosis, spinal cord injury)
7. Pelvic malignancy
8. Constipation
9. Congenital malformations of the urinary tract

1 As noted above, many commonly used medications may precipitate or aggravate existing voiding dysfunction and UI (Table 101-1).[19]

TABLE 101-1 Medications That Influence Lower Urinary Tract Function

Medications	Effect
Diuretics, acetylcholinesterase inhibitors	Polyuria resulting in urinary frequency, urgency
α-Receptor antagonists	Urethral muscle relaxation and stress urinary incontinence
α-Receptor agonists	Urethral muscle contraction (increased urethral closure forces) resulting in urinary retention (more common in men)
Calcium channel blockers	Urinary retention due to reduced bladder contractility
Narcotic analgesics	Urinary retention due to reduced bladder contractility
Sedative hypnotics	Functional incontinence caused by delirium, immobility
Antipsychotic agents	Anticholinergic effects resulting in reduced bladder contractility and urinary retention
Anticholinergics	Urinary retention due to reduced bladder contractility
Antidepressants, tricyclic	Anticholinergic effects resulting in reduced bladder contractility (urinary retention), and α-antagonist effects resulting in reduced urethral smooth muscle contraction (stress incontinence)
Alcohol	Polyuria resulting in urinary frequency, urgency
ACEIs	Cough as a result of ACEIs may aggravate stress urinary incontinence

ACEIs, angiotensin-converting enzyme inhibitors.

Generally, stress UI is considered the most common type of UI and probably accounts for at least a portion of UI in more than half of all incontinent women. Some studies have found that mixed UI (stress UI and urgency UI) is the most common type of UI. However, the proportions of SUI, UUI, and mixed UI vary considerably with age group and gender of patients studied, study methodology, and a variety of other factors.

CLINICAL PRESENTATION

[2] UI may present in a number of ways, depending on the underlying pathophysiology. A complete medical and medication history, including an assessment of symptoms and a physical examination, is essential for correctly classifying the type of incontinence and thereby assuring appropriate therapy.

Urine Leakage

UI represents a spectrum of severity in terms of both volume of leakage and degree of bother to the patient. It is important to carefully consider the level of patient discomfort and bother when discussing urine leakage as each individual may or may not desire therapy. A careful and complete history during the patient interview is essential to accurately determine the precise nature of the problem. The onset, nature, timing, and volume of incontinence are recorded as is the use of pads. Use of absorbent products, such as panty liners, pads, or briefs, is an important point of discussion, but the clinician must keep in mind that use of these products varies among patients. The number and type of pads may not relate to the amount or type of incontinence, as their use is a function of personal preference and hygiene. A high number of absorbent pads may be used every day by a patient with severe, high-volume UI or, alternatively, by a fastidiously hygienic patient with low-volume leakage who simply changes pads often to prevent wetness or odor. Nevertheless, a large number of pads that are described by the patient as “soaked” is indicative of high-volume urine loss.

CLINICAL PRESENTATION	Urinary Incontinence Related to Urethral Underactivity (SUI)

General

- The patient usually notes UI during activities such as exercise, running, lifting, coughing, and sneezing. Occurs much more commonly in women

(generally seen only in men with prior lower urinary tract surgery, neurologic disease, or other injury compromising the sphincter).

Symptoms

- Urine leakage with physical activity (volume is proportional to activity level). No UI with physical inactivity, especially when supine (minimal or no nocturia). May develop urgency and frequency as a compensatory mechanism (or as a separate component of bladder overactivity).

Diagnostic Tests

- Observation of urethral meatus while patient coughs or strains (cough stress test).

CLINICAL PRESENTATION — Urinary Incontinence Related to Bladder Overactivity (UUI)

General

- Can have bladder overactivity and UI without urgency if sensory input from the lower urinary tract is absent.

Symptoms

- Urinary frequency (>8 micturitions per day), urgency with or without UI; nocturia (≥1 micturition per night) and enuresis may be present.

Diagnostic Tests

- Urodynamic studies are the gold standard for diagnosis of detrusor overactivity when the finding of involuntary bladder contractions on the study reproduces the patient's symptoms. Urinalysis and urine culture should be negative (rule out urinary tract infection as the cause of frequency).

CLINICAL PRESENTATION — Overflow Incontinence (Chronic Urinary Retention)

General

- Important but uncommon type of UI in both men and women. Urethral overactivity is usually due to prostatic enlargement (men) or cystocele formation or surgical overcorrection following stress incontinence surgery in women. Bladder underactivity resulting in overflow incontinence can result from many causes including neurogenic disease, diabetes, and postoperatively from pelvic surgery (eg, radical hysterectomy).

Symptoms

- Lower abdominal fullness, hesitancy, straining to void, decreased force of stream, interrupted stream, sense of incomplete bladder emptying. May have urinary frequency and urgency. Abdominal pain if acute urinary retention is present.

Signs

- Increased postvoid residual urine volume.

Diagnostic Tests

- Assessment of postvoid residual urine either by imaging (ultrasound, etc.) or catheterization. Renal function tests to rule out renal failure due to chronic urinary retention.

Regardless of the volume of urine loss, the desire to seek evaluation for UI in the majority of patients is most commonly elective and therapy is often contingent on the degree of bother to the individual patient. As with the use of absorbent products, patients differ with regard to the amount of urine loss they will tolerate before considering the condition bothersome enough to seek assistance. However, it is critically important that in some individuals new-onset UI may be the first manifestation of an undiagnosed illness (eg, diabetes, multiple sclerosis), or may occur as a result of treatment or drug therapy of an unrelated condition. It is these individuals who mandate a full evaluation and treatment.

Symptoms

Under the best of circumstances, UI is difficult to categorize based on symptoms alone (**Table 101-2**).[20] In a study of patients who appeared to have SUI based on symptoms and patient history, urodynamics showed that only 72% of patients had SUI as the sole cause of incontinence.[21]

TABLE 101-2 Differentiating Bladder Overactivity-Related UI (Urgency Urinary Incontinence) from Urethral Underactivity Related UI (Stress Urinary Incontinence)

Symptoms	Bladder Overactivity (UUI)	Urethral Underactivity (SUI)
Urgency (strong, sudden desire to void)	Yes	Not common
Frequency with urgency	Yes	Rarely
Leaking during physical activity (eg, coughing, sneezing, lifting)	No	Yes
Amount of urinary leakage with each episode of incontinence	Large if present	Usually small
Ability to reach the toilet in time following an urge to void	No or just barely	Yes
Nocturnal incontinence (presence of wet pads or undergarments in bed)	Yes	Rare
Nocturia (waking to pass urine at night)	Usually	Seldom

Patients with SUI characteristically complain of urinary leakage with physical activity. Volume of leakage is proportional to the level of activity. They will often leak urine during periods of exercise, coughing, sneezing, lifting, or even when rising from a seated to a standing position. Patients with pure SUI will not have leakage when physically inactive, especially when they are supine. Often they will have little or no UI at night, will not awaken to void during the night (nocturia), will not wet the bed, and often do not even wear absorbent products during the night. Urinary urgency and frequency may be associated with SUI, either as a separate component caused by bladder overactivity (mixed incontinence) or as a compensatory mechanism wherein the patient with SUI learns to toilet frequently to prevent large-volume urine loss during physical activity.

Typical symptoms of UUI and bladder overactivity include frequency, urgency, and high-volume incontinence. Nocturia and nocturnal incontinence are often present. Urine leakage is unpredictable, and the volume loss may be quite large. Patients often wear protection both day and night. Urinary frequency can be affected by a number of factors unrelated to bladder overactivity, including excessive fluid intake (polydipsia) and bladder hypersensitivity states such as interstitial cystitis and urinary tract infection. In some patients, bladder overactivity manifests as UI without awareness in the absence of a sense of

urinary urgency or frequency. *Urinary urgency*, a sensation of impending micturition, requires intact sensory input from the lower urinary tract. In patients with spinal cord injury, sensory neuropathies, and other neurologic diseases, a diminished ability to perceive or process sensory input from the lower urinary tract may result in bladder overactivity and UI without urgency or urinary frequency. When bladder contraction occurs without warning and sensation is absent, the condition is referred to as *reflex incontinence*.

Patients with overflow incontinence may present with lower abdominal fullness as well as considerable obstructive urinary symptoms, including hesitancy, straining to void, decreased force of urinary stream, interrupted stream, and a vague sense of incomplete bladder emptying. These patients may also have a significant component of urinary frequency and urgency. In patients with acute urinary retention and overflow incontinence, lower abdominal pain may be present. Although these symptoms are not specific for overflow incontinence, they may warrant further investigation, including an assessment of postvoid residual urine volume.

Signs A presenting complaint of UI mandates a directed physical examination and a brief neurologic assessment. The workup ideally includes an abdominal examination to exclude a distended bladder, neurologic assessment of the perineum and lower extremities, pelvic examination in women (looking especially for evidence of prolapse or hormonal deficiency), and genital and prostate examination in men. Perineal skin maceration, erythema, breakdown, and ulceration may be indicative of chronic, severe UI. Patients with chronic incontinence, especially those who are obese, may also manifest fungal infections of the skin of the perineum and upper thighs.

SUI can usually be objectively demonstrated by having the patient cough or strain during the examination and observing the urethral meatus for a sudden spurt of urine (cough stress test). In women, SUI may be associated with varying degrees of vaginal prolapse, including cystourethrocele (bladder and urethral prolapse).

In both men and women, digital rectal examination provides an opportunity to assess neurological integrity by checking ambient rectal tone, perianal sensation, and the integrity of the sacral reflex arc (eg, anal wink) as well as assess the patient’s ability to perform a voluntary pelvic floor muscle contraction (ie, Kegel exercise), which may be an important factor in deciding on appropriate therapy. In men, a digital examination of the prostate assesses for the presence of prostate cancer, inflammation, and BPH.

A targeted neurologic examination includes assessment of reflexes, rectal

tone, and sensory or motor deficits in the lower extremities, which might be indicative of systemic or localized neurologic disease. Neurologic diseases have the potential to affect bladder and sphincter function and thus may have significant implications in the incontinent patient.

Prior Medical or Surgical Illness UI may present in the setting of concurrent, seemingly unrelated illnesses. New-onset UI may be the initial manifestation of systemic illnesses such as diabetes mellitus, metastatic malignancies, and neurologic diseases such as Parkinson disease, brain tumors, and multiple sclerosis. Central nervous system (CNS) disease, or injury above the level of the pons, generally results in symptoms of bladder overactivity and UUI. Spinal cord injury or disease may manifest as bladder overactivity and UUI or as overflow incontinence, depending on the spinal level and completeness of the injury or disease.

Medications may have wide-ranging effects on lower urinary tract function (see Table 101-1). A thorough inquiry into the use of new medications in the setting of recent-onset UI may show a relationship.

Acute UI manifesting in the immediate postoperative setting may be secondary to a number of factors, including surgical manipulation and immobility, and to a number of medications, especially opioid analgesics and sedative-hypnotics.

Prior surgery may have effects on lower urinary tract function. UI following prostate surgery in men is highly suggestive of injury to the sphincter and resultant SUI. Pelvic surgery for benign and malignant conditions may result in denervation or injury to the lower urinary tract. This includes bowel surgery and gynecologic procedures. For example, new-onset total UI following gynecologic surgery suggests intraoperative urinary tract injury and subsequent development of a postoperative genitourinary fistula. Radiation therapy to the pelvis for malignant disease (eg, prostate cancer or cervical cancer) may result in injury to the bladder or urethra and subsequent UI.

In women, UI may be related to several gynecologic factors including childbirth, hormonal status, and prior gynecologic surgery, although recently the relationship of some of these factors to UI has come under debate.[22] Pregnancy and childbirth, particularly vaginal delivery, are associated with SUI and pelvic prolapse. Significant SUI in the nulliparous woman is uncommon. UI that becomes progressive at or around menopause suggests a hormonal component that may be responsive to estrogen or hormone replacement therapy.

UI may present in the setting of other significant pelvic floor disorders, signs, and symptoms. Constipation, diarrhea, fecal incontinence, dyspareunia, sexual

dysfunction, and pelvic pain may be related to UI. A history of gross hematuria in the setting of UI mandates further urologic investigation, including radiologic imaging of the upper urinary tract and cystoscopy. Acute dysuria with or without hematuria in the setting of UI suggests cystitis. Urinalysis and urine culture should be performed in these patients.

TREATMENT

Desired Outcomes

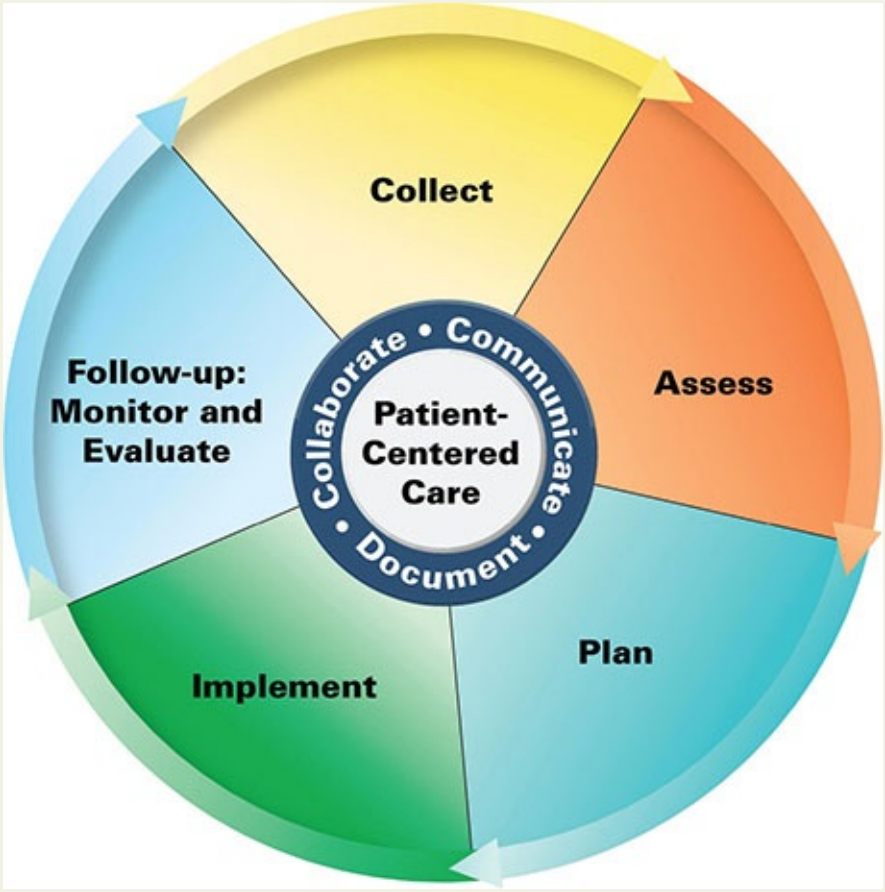
3 The efficacy goals for the management of UI include restoration of continence, reduction of the number of UI episodes, and prevention of complications (perineal dermatitis, pressure ulcers, falls, etc.). Other desired outcomes are minimization of adverse treatment consequences and cost, improvement in the patient's quality of life, and reduced risk of nursing home placement.

General Approach to Treatment

Nonsurgical, nonpharmacologic intervention is the first-line treatment for UI. Drug therapy may be considered in patients whose UI is not adequately controlled by nonpharmacologic therapies and in those who have no major contraindications to drug treatment. In general, pharmacotherapy provides a better response when combined with behavioral interventions. Selection of agent should be based on the type of UI, and patient characteristics (eg, age, comorbidities, concurrent drug therapies, ability to maintain medication adherence). Surgery can be considered when the degree of bother or lifestyle compromise is sufficient and other nonsurgical interventions are undesired or ineffective.

Antimuscarinic agents have been the mainstay of pharmacotherapy for OAB and UUI. According to the American Urological Association (AUA) guideline,[23] clinicians should avoid antimuscarinic agents in patients with narrow-angle glaucoma unless approved by the treating ophthalmologist. Antimuscarinic agents should be cautiously used in patients with frailty, impaired gastric emptying, or a history of urinary retention, or in those who are taking other drugs with anticholinergic properties. When one agent offers inadequate symptom control and/or unacceptable adverse drug events, consider a dose modification or switching to another agent. Before initiating antimuscarinic

therapy, patients should be informed of adverse effects and strategies to minimize them. Before abandoning effective antimuscarinic therapy, clinicians should manage constipation and dry mouth (bowel regimen, fluid management, dose modification, or alternative antimuscarinics).[23] Beta-3 agonists are a relatively new class of agent for the pharmacological therapy of UUI. These are discussed in detail later in the chapter.



Patient Care Process for Urinary Incontinence

Collect

- Patient characteristics (eg, age, sex, pregnancy status, drug allergy profile)
- Patient medical and genitourinary surgical history including coexisting conditions that may influence UI
- Obstetric and menstrual history in women
- Past conservative, medical, and surgical treatment of UI
- Social history (tobacco/ethanol use; caffeine and fluid intake;

environmental issues; exercise; availability of family caregiver, if relevant)

- Current medications (see Table 101-1) including over-the-counter (OTC), herbal products, and dietary supplements
- Objective data
  - Lab tests: urinalysis ± urine culture; if infected, treat and reassess if appropriate
  - Cough stress test to demonstrate stress UI (if appropriate)
  - Postvoid residual urine by bladder ultrasound or catheterization (if suspected urinary retention/overflow incontinence)

Assess

- Urinary symptoms including bladder diary (see Table 101-2)
- Presence of bowel symptoms or vaginal prolapse symptoms (in women); estrogen status in women
- Quality of life, treatment preferences, and goals
- Mental status, body mass index, physical dexterity and mobility
- Abdominal, rectal, prostate (in men), neurological, and pelvic examination (in women)

Plan*

- Nonpharmacological interventions based on UI severity and subtype (see Table 101-3)
- Drug therapy regimen for urgency UI, if indicated (see Table 101-5)
- Monitoring parameters (see Tables 101-6 and 101-7); frequency and timing of follow-up
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug-specific information)
- Self-monitoring for resolution of UI symptoms and drug adverse events (if indicated)
- Referrals to other providers when appropriate (eg, urologist, urogynecologist, continence nurse practitioner, physical therapist)

Implement*

- Provide patient education regarding all elements of treatment plan

- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (eg, adherence assessment, treatment response)

Follow-up: Monitor and Evaluate

- Monitor for patient response in 1 or 2 weeks after therapy initiation
- Assess efficacy after a minimum of 4 weeks to assess drug efficacy
- Resolution of UI symptoms
- Presence of adverse effects (eg, Table 101-7), or drug interactions
- Patient adherence to treatment plan using multiple sources of information
- Reevaluate efficacy and necessary duration of therapy every 3 to 6 months

**Collaborate with patient, caregivers, and other healthcare professionals.*

Nonpharmacologic Therapy

Nonsurgical Treatment

4 Nonpharmacologic, nonsurgical treatment of UI is recommended as the first-line treatment at a primary care level. It is the only option for patients in whom pharmacologic and/or surgical management is inappropriate or undesired. Examples of patients who fulfill these criteria for nonpharmacologic treatment include those with mild-to-moderate symptoms and who do not want to take medication; those with comorbid conditions that place them at high risk for adverse effects from drug therapy; those who are not medically fit for surgery; those who plan future pregnancies (which may adversely affect long-term surgical outcomes); those with overflow incontinence whose condition is not amenable to surgery or drug therapy; and those who are delaying surgery or do not want to undergo surgery.[24,25]

Nondrug interventions for UI include behavioral interventions, external neuromodulation, anti-incontinence devices, and supportive interventions (**Table 101-3**).[24,25] Behavioral interventions are generally the first-line treatment for SUI, UUI, and mixed UI. Interventions include lifestyle modifications, voiding schedule regimens, and pelvic floor muscle rehabilitation. Because the key to success with any type of behavioral intervention is motivation of patients or caregivers, these individuals must be active participants in developing a treatment plan. Regular follow-up is needed to help motivate patients and

caregivers, provide reassurance and support, and monitor treatment outcomes.

TABLE 101-3 Nonpharmacologic Management of Urinary Incontinence

Intervention	Description	Patient Characteristics
Lifestyle Modifications		
Behavioral changes (eg, fluid and caffeine modifications, smoking cessation, weight loss, constipation prevention)	Self-management strategies targeted toward reducing or eliminating risk factors that cause or exacerbate UI	Used as first-line therapies or in combination with pharmacological treatment in patients with stress, urgency, and mixed incontinence
Scheduling Regimens		
Timed voiding	Toileting on a fixed schedule where interval does not change, typically every 2 hours during waking hours	Used for patients with cognitive or physical impairments
Habit retraining	Scheduled toiletings with adjustments of voiding intervals (longer or shorter) based on patient's voiding pattern	Used for institutionalized or homebound patients with cognitive or physical impairments
Prompted voiding	Scheduled toiletings that require prompts to void from a caregiver, typically every 2 hours; patient assisted in toileting only if response is positive; used in conjunction with operant conditioning techniques for rewarding patients for maintaining continence and appropriate toileting	Used for patients who are functionally able to use toilet or toilet substitute, able to feel urge sensation, and able to request toileting assistance appropriately; primarily used in institutional settings or in homebound patients with an available caregiver
Bladder training	Scheduled toiletings with progressive voiding intervals; includes teaching urgency suppression strategies using relaxation and distraction techniques, self-monitoring, and use of reinforcement techniques; sometimes combined with drug therapy	Used for stress, urgency, and mixed incontinence in patients who are cognitively intact, able to toilet, and motivated to comply with training program
Pelvic Floor Muscle Rehabilitation		
Pelvic floor muscle exercises (eg, Kegel exercises)	Regular practice of pelvic floor muscle contractions; may involve use of pelvic floor muscle contraction for prevention of stress leakage and urge inhibition	Used for stress, urgency, and mixed incontinence in patients who can isolate and correctly contract pelvic floor muscles; requires cognitively intact and highly motivated patient
Biofeedback	Use of electronic or mechanical instruments to display visual or auditory information about neuromuscular or bladder activity; used to teach correct pelvic floor muscle contraction or urge inhibition; home trainers available	Used for stress, urgency, and mixed incontinence in patients who have the capability to learn voluntary control through observation and are motivated; used in conjunction with pelvic floor muscle exercises
Vaginal weight training	Active retention of increasing vaginal weights; typically used in combination with pelvic floor muscle exercises at least twice per day	Women with stress incontinence who are cognitively intact, can correctly contract pelvic floor muscles, able to stand, and have sufficient vaginal vault and introitus to retain cone, and are highly motivated; contraindicated in patients with moderate-to-severe pelvic organ prolapse
External Neuromodulation		
Nonimplantable electrical stimulation	Application of electrical current through vaginal, anal, surface, or fine needle electrodes; used to inhibit bladder overactivity and improve awareness, contractility, and efficacy of pelvic floor muscle contraction; handheld stimulators for home use are available	Used for stress, urgency, and mixed incontinence in patients who are highly motivated; contraindicated in patients with diminished sensory perception; urinary retention, history of cardiac arrhythmia, cardiac pacemakers, implantable defibrillators, pregnant or attempting pregnancy; vaginal or anal electrodes are contraindicated in moderate or severe pelvic organ prolapse
Percutaneous tibial nerve stimulation	Application of a pulsed electrical current through a fine needle electrode placed externally near the tibial nerve	Used for treatment of overactive bladder with urinary urgency, frequency, and urgency incontinence; contraindicated in patients with pacemakers or implantable defibrillators, prone to excessive bleeding, or women who are pregnant
Extracorporeal magnetic electrical stimulation	Pulsed magnetic stimulation to pelvic floor musculature causing depolarization of motor neurons, thus inducing pelvic floor muscle contraction; stimulation is provided through a specially designed chair that contains a device for producing a pulsing magnetic field	Used for treatment of stress, urgency, and mixed incontinence; contraindicated in patients with demand cardiac pacemakers or metallic joint replacements; may be useful treatment option when other approaches fail or are not feasible
Alternative Medicine Therapies		
Acupuncture	Involves insertion of disposable sterile fine stainless steel needles into points on the skin that are thought to suppress or stimulate spinal and/or supraspinal reflexes to the bladder and/or urethra	Used for stress, urgency, and mixed incontinence and UI due to spinal cord injury

Anti-Incontinence Devices		
Bed or pant alarms	Sensor devices that respond to wetness; used to awaken or alert individuals via noise or vibrating mechanism	Primarily used for nocturnal enuresis in children; system available for monitoring incontinence in home care and institutional environments
Pessaries	Intravaginal devices designed to support the bladder neck, relieve minor-to-moderate pelvic organ prolapse, and change pressure transmission to the urethra	Used for female stress incontinence and mild-to-moderate pelvic organ prolapse; in postmenopausal women, topical estrogen therapy is typically prescribed to prevent ulceration and breakdown of vaginal tissue; requires good manual dexterity to manipulate device
Urethral insert (women only)	Intraurethral device	Used in female stress incontinence with stress incontinence who are cognitively intact and have good manual dexterity
Urethral compression device (men only)	Penile clamp	Used in men patients with stress incontinence who are cognitively intact and have good manual dexterity
External collection devices (men only)	Condom catheter with leg bag	Used in men with urgency, stress, and overflow incontinence and in those with functional impairments
Catheters	Disposable, intermittent urethral catheters and indwelling urethral and suprapubic catheters	Used for overflow incontinence; used in patients who are bed-bound or with significant mobility impairments and severe incontinence; those with terminal illness; those with sacral pressure ulcers until healing occurs
Supportive Interventions		
Toileting substitutes and other environmental modifications	Female and male urinals, bedside commodes, elevated toilet seats	Used for patients with mobility impairments that make reaching toilet in timely fashion difficult
Absorbent products	Variety of reusable and disposable liners, pads, male drip collectors, male guard, collector undergarment, fitted brief, and pant systems; some products contain a polymer that absorbs and wicks urine away from the body	Used for all types of incontinence
Physical therapy	Gait and/or strength training	Used for older patients with mobility impairments that make reaching a toilet in timely fashion difficult

External neuromodulation may include nonimplantable electrical stimulation (EStim), percutaneous tibial nerve stimulation (PTNS), or extracorporeal magnetic stimulation (MStim). Electrical stimulation is typically prescribed when traditional pelvic floor muscle rehabilitation has failed. Anti-incontinence devices such as bed alarms, catheters, pessaries, penile clamps, and external collection devices are reserved for special situations depending on patients' UI symptoms, cognitive and mobility status, and overall health status. Supportive interventions such as physical therapy may be beneficial for patients with muscle

weakness and slow gait to reach the toilet in a timelier manner, and absorbent products will provide greater confidence in dealing with unpredictable urine loss. Penile clamps and external collection devices (“condom catheter”) have a role for some male patients with stress UI.

Surgical Treatment

Only rarely does surgery play a role in the initial management of UI. In the absence of secondary complications from UI (eg, skin breakdown or infection), the decision to surgically treat symptomatic UI should be based on the premise that the degree of bother or lifestyle compromise to the patient is great enough to warrant an elective operation, and that nonsurgical therapy either is undesired or has been ineffective.

Successful application of surgery depends mostly on defining the underlying abnormalities responsible for UI (bladder vs urethra, underactivity vs overactivity). Once the underlying factors are determined, other considerations include renal function, sexual function, severity of leakage, history of abdominal or pelvic surgery, presence of concurrent abdominal or pelvic pathology requiring surgical correction, and finally the patient’s suitability for the procedure and willingness to accept the risks of surgery.

If patients with uncomplicated SUI become dissatisfied with the initial management approaches of pelvic floor exercises, medications, and/or behavioral modification, surgical treatment assumes the primary role.

Surgical correction of female SUI (urethral underactivity) is directed toward either (a) repositioning the urethra and/or creating a backboard of support, or otherwise stabilizing the urethra and bladder neck in a well-supported retropubic (intra-abdominal) position that is receptive to changes in intra-abdominal pressure; or (b) improving the sealing mechanism and/or creating compression or otherwise augmenting the urethral resistance provided by the intrinsic sphincteric unit, with (ie, sling) or without (ie, periurethral injectable bulking agents) urethral and bladder neck support.

Bulking agents are injected into the urethra at the level of the urinary sphincter as an office-based procedure and are generally considered quite safe. However, their durability and efficacy are likely inferior to other options.[26]

Midurethral synthetic slings have become the most common approach to the treatment of SUI in women in the United States.[27] These can be inserted as outpatient procedures that have shorter convalescence periods and allow faster return to usual activities compared with many of the older procedures. These procedures are generally felt to be highly durable and efficacious. However,

safety concerns have been expressed regarding the implantation of surgical mesh in some patients, the implications of which are yet to be fully clarified.[28]

SUI in men is very rare in the absence of prior pelvic surgery, injury, or neurologic disease. When it occurs, SUI in men can be treated in a number of ways.[29] Bulking agents can be injected periurethrally and submucosally into the region of the external urinary sphincter but have fallen out of favor due to poor short- and long-term outcomes. This approach is less effective and far less durable than alternative surgical procedures, although it can be performed in the office setting without the need for general anesthesia.

The artificial urinary sphincter is generally considered to be the gold standard for treatment of male SUI.[28] Placement of this manually operated silicone device has been associated with very high long-term success and satisfaction rates.[30] Male slings and external urethral compression devices.[31] placed through a perineal incision are alternatives to the artificial urinary sphincter. However, long-term efficacy and safety data on large numbers of patients are lacking.[32]

Most patients with UUI are managed nonsurgically with a combination of behavioral modification, pelvic floor exercises, and pharmacologic therapy. However, for patients refractory to such measures, invasive therapy can be beneficial. Posterior tibial nerve stimulation is an office-based percutaneous treatment for UUI or OAB. Therapy consists of weekly 30-minute treatments with a needle placed posteriorly to the medial malleolus of the ankle for 3 months. Efficacy appears similar to or slightly better than oral pharmacotherapy.[33] However, long-term efficacy and safety data are lacking.[34]

Surgery for the treatment of UUI generally consists of implantation of a sacral nerve stimulator (neuromodulation) or endoscopic office-based injection of botulinum toxin directly into the detrusor muscle.[35,36] Neuromodulation is a staged surgical procedure in which a neurostimulator lead is placed transforaminally at the level of sacral spinal cord root S3. Its exact mechanism is unknown, but the device may exert its favorable effects on urination and UUI by rebalancing the afferent and efferent nerve impulses to the lower urinary tract and pelvic floor. The injection of botulinum toxin is performed in the office generally with local anesthesia. Following transurethral injection directly into the detrusor muscle using a small needle in a template fashion, the toxin is taken up by the local neurons. The intracellular toxin cleaves SNAP-25, a cystoplasmic protein critical for the attachment of neurotransmitter containing vesicles to the cell membrane at the nerve terminal. As the vesicles containing neurotransmitter are unable to fuse to the cell membrane and release its contents into the synaptic cleft, neural transmission to the postsynaptic muscle fascicle is

interrupted. This results in a graded, initially irreversible but transient weakness and paralysis of the affected muscle. The duration of effect of the toxin is about 4 to 8 months, after which repeat injection is necessary to maintain effect. The therapeutic algorithm involving these two choices for treatment of refractory UUI is evolving, and is determined largely by patient preference.[37]

Few surgical treatments for bladder underactivity are effective. After an appropriate evaluation for reversible causes, the most effective management of this condition is intermittent self-catheterization performed by the patient or a caregiver three or four times per day. Sacral nerve stimulation (neuromodulation) has shown some efficacy in this patient population, but success rates for detrusor underactivity (nonobstructive urinary retention) are inferior to that seen for the indication of urgency UI with urinary frequency and urgency.[38] Proper patient selection for this therapy remains poorly defined. Alternative methods of management that are less satisfactory or more invasive include indwelling urethral or suprapubic catheters and urinary diversion.

Urethral overactivity is most commonly caused by anatomic obstruction. Anatomic obstruction in men is most often caused by benign prostatic enlargement. Treatments may include transurethral surgical resection of the prostate (see Chapter 100, “Benign Prostatic Hyperplasia”).

Rarely, bladder outlet obstruction is caused by a functional obstruction at the level of the bladder neck or external sphincter. Hypertrophy of the smooth muscle fibers at the level of the bladder neck in men and women may result in obstruction to the flow of urine. In patients who do not respond to pharmacologic therapy with α-adrenergic receptor antagonists, endoscopic incision using the cystoscope (resectoscope) is highly effective in treating this very uncommon condition.

Pharmacologic Therapy

Urgency Urinary Incontinence

5 Antimuscarinic agents and β_3-adrenergic agonists are the second-line drug treatments for urgency UI. **Table 101-4** summarizes AUA recommendations for treating OAB in adults.[23] **Table 101-5** lists the usual dosage for approved agents for OAB or UUI. **Table 101-6** suggests common monitoring parameters for these agents.

TABLE 101-4 AUA Guideline for Treatment of Overactive Bladder in

Adults

Recommendation	Evidence Strength Grade[a]
First-Line Treatments	
Behavioral therapies (eg, bladder training, bladder control strategies, pelvic floor muscle training, fluid management)	B
Behavioral therapies may be combined with antimuscarinic therapies	C
Second-Line Treatments	
Oral antimuscarinics or β_3-adrenergic agonist as second-line therapy	B
If an IR and an ER formulation are available, prefer ER formulations because of lower rates of dry mouth	B
Transdermal oxybutynin (patch or gel) may be offered	C
Third-Line Treatments	
Intradetrusor onabotulinum toxin A (100 units) in carefully selected patients who have been refractory to first- and second-line OAB treatments[b]	B/C
Peripheral tibial nerve stimulation in a carefully selected patient population	C
Sacral neuromodulation in carefully selected patients with severe refractory OAB symptoms or in those who are not candidates for second-line therapy and are willing to undergo a surgical procedure	C

AUA, American Urological Association; ER, extended-release; IR, immediate-release; OAB, overactive bladder.

[a]When sufficient evidence existed, the body of evidence for a particular treatment was assigned a strength rating of A (high), B (moderate), or C (low). Both B and C indicate that benefits outweigh risks/burdens.

[b]The patient must be able and willing to return for frequent postvoid residual evaluation and able and willing to perform self-catheterization if necessary.

TABLE 101-5 Dosing of Medications Approved for OAB or UUI

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Comments
Anticholinergics/Antimuscarinics					
Oxybutynin IR	Ditropan	2.5 mg twice daily	2.5-5 mg two to four times daily		Titrate in increments of 2.5 mg/day every 1-2 months; available in oral solution
Oxybutynin XL	Ditropan XL	5-10 mg once daily	5-30 mg once daily		Adjust dose in 5-mg increments at weekly interval; swallow whole
Oxybutynin TDS	Oxytrol Oxytrol for Women (OTC)		3.9 mg/day apply one patch twice weekly		Apply every 3-4 days; rotate application site
Oxybutynin gel 10%	Gelnique		One sachet (100 mg) topically daily		Apply to clean and dry, intact skin on abdomen, thighs or upper arms/ shoulders; contains alcohol
Oxybutynin gel 3%	Gelnique 3%		Three pumps (84 mg) topically daily		Same as above
Tolterodine IR	Detrol		1-2 mg twice daily	1 mg twice daily if patient is taking CYP3A4 inhibitors, or with renal/hepatic impairment	
Tolterodine LA	Detrol LA		2-4 mg once daily	2 mg once daily in those who are taking CYP3A4 inhibitors or with renal/hepatic impairment	Swallow whole; avoid in patients with creatinine clearance ≤10 mL/min (0.17 mL/s)
Trospium chloride IR	Sanctura		20 mg twice daily	20 mg once daily in patient age ≥75 years or creatinine clearance ≤30 mL/min (0.5 mL/s)	Take 1 hour before meals or on empty stomach; patient age ≥75 years should take at bedtime
Trospium chloride ER	Sanctura XR		60 mg once daily	Avoid in patient age ≥75 years or creatinine clearance ≤30 mL/min (0.5 mL/s)	Take 1 hour before meals or on empty stomach; swallow whole
Solifenacin	VESIcare	5 mg daily	5-10 mg once daily	5 mg daily if patient is taking CYP3A4 inhibitors or with creatinine clearance ≤30 mL/min (0.5 mL/s) or moderate hepatic impairment; avoid in severe hepatic impairment	Swallow whole
Darifenacin ER	Enablex	7.5 mg once daily	7.5-15 mg once daily	7.5 mg daily if patient is taking potent CYP3A4 inhibitors or with moderate hepatic impairment; avoid in severe hepatic impairment	Titrate dose after at least 2 weeks; swallow whole
Fesoterodine ER	Toviaz	4 mg once daily	4-8 mg once daily	4 mg daily if patient is taking potent CYP3A4 inhibitors or with creatinine clearance ≤30 mL/min (0.5 mL/s); avoid in severe hepatic impairment	Prodrug (metabolized to 5-hydroxymethyl tolterodine); swallow whole
β_3-Adrenergic Agonist					
Mirabegron ER	Myrbetriq	25 mg once daily	25-50 mg once daily	25 mg once daily if creatinine clearance 15-29 mL/min (0.25-0.49 mL/s) or moderate hepatic impairment; avoid in patients with ESRD or severe hepatic impairment	Swallow whole

CYP, cytochrome P450 enzyme; ER, extended-release; ESRD, end-stage renal disease; IR, immediate release; LA, long acting; OAB, overactive bladder; OTC, over-the-counter; TDS, transdermal system; UUI, urge urinary incontinence; XL, extended release.

TABLE 101-6 Monitoring of Medications Approved for OAB or UUI

Drug	Adverse Drug Reaction	Monitoring Parameters	Comments
Antimuscarinic			
Oxybutynin IR Oxybutynin XL Oxybutynin TDS Oxybutynin gel 10% Oxybutynin gel 3% Tolterodine IR Tolterodine LA Trospium chloride IR Trospium chloride ER Solifenacin Darifenacin ER Fesoterodine ER	Anticholinergic adverse effects: dry mouth, constipation, headache, dyspepsia, dry eyes, blurred vision, cognitive impairment, tachycardia, sedation, orthostatic hypotension Application site reactions (topical agents): pruritus, erythema	Contraindications and precautions: urinary retention, gastric retention, severely decreased GI motility, angioedema, myasthenia gravis, uncontrolled narrow-angle glaucoma Worsening of renal/hepatic condition or concomitant drug therapy, which may necessitate dosage reduction or drug cessation Mental status change or risk for falls in elderly or frail patients	In general, ER, LA, XL, and topical products are associated with fewer anticholinergic adverse effects, particularly dry mouth Possible transference of drug from topical application Avoid open fire or smoke until alcohol-based gel has dried
β_3-Adrenergic Agonist			
Mirabegron ER	Hypertension, nasopharyngitis, urinary tract infection, headache	Precautions: urinary retention, severe uncontrolled hypertension Worsening of renal/hepatic condition, which may necessitate dosage reduction or drug cessation Increased effect of narrow therapeutic index drugs that are CYP2D6 substrates QT prolongation	Mirabegron is a CYP2D6 inhibitor

CYP, cytochrome P450 enzyme; ER, extended-release; IR, immediate release; LA, long acting; OAB, overactive bladder; TDS, transdermal system; UUI, urge urinary incontinence; XL, extended release.

Antimuscarinic agents (see Table 101-5) antagonize muscarinic receptors and suppress premature detrusor contractions, thereby enhance bladder storage. They have similar contraindications, precautions, and side-effect profiles, with incidence/severity varies with each individual agent.[39] These agents improve quality of life, and are considered equally effective based on clinical efficacy in reducing UI episodes, decreasing micturitions per day, and increasing urine volume voided per micturition.[40] Antimuscarinic agents may worsen cognitive function, especially in older adults. Caution should be exercised as these agents may antagonize the therapeutic effects of acetylcholine esterase inhibitors indicated for dementia.

Oxybutynin Oxybutynin immediate release (IR) is the oldest and least expensive treatment for UUI. It gives substantial nonurinary antimuscarinic effects, including orthostatic hypotension, sedation, and weight gain (see Table 101-6).[41] These adverse effects, when significant, may jeopardize medication

adherence and prevent dose escalation. Its multiple daily dosing may be too complicated for patients with cognitive impairment or those who are taking multiple medications. Oral solution formulation is available for patients who have difficulty with swallowing. To optimize tolerability, initiate dose at no more than 2.5 mg twice daily, increase to 2.5 mg three times daily after 1 month, then titrate in increments of 2.5 mg/day every 1 to 2 months until the desired response or the maximum recommended dosage. Side effects may be managed by dose reduction. Dry mouth may be relieved by use of sugarless hard candy, gum, or a saliva substitute. Constipation can be minimized by increasing fluid/fiber intake, physical activity, and/or laxative therapy.

An extended-release (XL) formulation of oxybutynin is an alternative therapy in patients who cannot tolerate IR formulation. It delivers a controlled amount of oxybutynin over a 24-hour period, and has a reduced first-pass metabolism. The lower plasma concentration of active metabolite, *N*-desethyloxybutynin may explain the lower dry mouth incidence associated with the XL product.[42] In short-term studies, oxybutynin XL was better tolerated than oxybutynin IR, and at least as effective as tolterodine IR or long acting (LA) in managing urinary symptoms.[42] Oxybutynin XL should be administered once daily, and should not be crushed or chewed. Elderly patients should start with a dose of 5 mg once daily and titrate gradually to desired effects, which may take at least 4 weeks after dose initiation or escalation. Drug interactions may occur when oxybutynin is used with other anticholinergic drugs, potent CYP3A4 inhibitors (eg, itraconazole, miconazole, erythromycin, and clarithromycin), and acetylcholinesterase inhibitors via pharmacodynamic antagonism.[42]

The oxybutynin transdermal system (TDS) is a nonoral option for patients who cannot tolerate IR oxybutynin. It was approved as the first over-the-counter treatment for OAB in women aged 18 years and over. The patch allows oxybutynin to bypass first-pass hepatic and gut metabolism, and gives a more tolerable adverse effect profile with similar efficacy as oxybutynin IR or tolterodine LA.[43,44] A large multicenter trial reported improved quality of life and good tolerability in patients 65 years or older; increase in work productivity was noted among younger patients.[45,46] Patients should apply oxybutynin TDS to dry, intact skin on the abdomen, hip, or buttocks every 3 to 4 days (twice weekly). Rotating application site at least weekly may help minimize local side effects. The most common adverse effects are pruritus (14%-17%), erythema (6%-9%) at the application site and anticholinergic side effects (<10%).[43]

Oxybutynin topical gel (available in 10% or in 3%) causes significantly less dry mouth than oxybutynin (6.1% vs 73.1%).[47–49] Although it did not cause

cognitive impairment in older adults in short-term studies, clinicians should monitor for anticholinergic effects during long-term therapy, particularly in frail patients.[50] The most common adverse events include dry mouth (8%-12%), application site reactions (5%-11%), and dizziness (3%).[47,48] Clinicians should counsel patients to avoid applying sunscreen within half an hour before or after application and to avoid showering within 1 hour after application. The transfer of gel between individuals may occur if vigorous skin contact is made at the application site; patients should avoid open fires or exposure to smoking until this alcohol-based gel has dried.[47,48]

Tolterodine Tolterodine is a competitive muscarinic receptor antagonist that is as effective as oxybutynin IR, but gives better tolerability and thus medication adherence.[51] Tolterodine is predominantly eliminated by hepatic metabolism, which is partially under the control of genetic polymorphism.[52] The principal metabolic pathway in extensive metabolizers involves oxidation of the parent drug by CYP isoenzyme 2D6 to the active 5-hydroxymethyl metabolite (DD01). In CYP2D6 poor metabolizers (approximately 7% of the US population), the principal metabolic pathway involves CYP3A4. Because tolterodine is principally metabolized by CYP3A4 in this case, its elimination may be impaired by CYP3A4 inhibitors (eg, fluoxetine, sertraline, fluvoxamine, macrolide antibiotics, azole antifungals, and grapefruit juice). Concurrent use of fluoxetine, a dual inhibitor of CYP2D6 and 3A4 can significantly increase tolterodine level.[52] Caution is also advised with individuals who carry nonfunctional CYP2D6*13 allele.[52,53]

Tolterodine IR can be given 1 to 2 mg twice daily with or without food. It is not recommended in patients with creatinine clearance less than 10 mL/min (0.17 mL/s) or severe hepatic impairment. The dose should be reduced to 2 mg in patients with mild-to-moderate hepatic impairment, or creatinine clearance 10 to 30 mL/min (0.17-0.50 mL/s), or in those taking potent CYP3A4 inhibitors. The maximum benefit from tolterodine may take up to 8 weeks after therapy initiation or dose escalation.[52] The most common adverse effects of tolterodine are dry mouth, dyspepsia, headache, constipation, and dry eyes. Of note, patients who have known hypersensitivity to fesoterodine fumarate should not receive tolterodine because both agents are metabolized to DD01. Monitoring of QT prolongation is advisable in patients who are also taking Class IA (eg, quinidine, procainamide) or Class III (eg, amiodarone, sotalol) antiarrhythmic medications.[52]

Tolterodine long acting offers a convenient once-daily dosing, and causes less

dry mouth than taking IR products.[54] It also improves OAB symptoms in men who were taking α-adrenergic blockers.[55] It should be given once daily, and should not be crushed or chewed. The dose should be limited to 2 mg once daily in patients with mild-to-moderate hepatic impairment (Child-Pugh class A or B), severe renal impairment creatinine clearance 10 to 30 mL/min (0.17-0.50 mL/s), or taking drugs that are potent CYP3A4 inhibitors (ketoconazole, itraconazole, clarithromycin, or ritonavir). Patients with creatinine clearance less than 10 mL/min (0.17 mL/s) or severe hepatic impairment (Child-Pugh class C) should avoid taking the drug. Patients should be counseled that it takes up to 8 weeks to see maximum benefit after starting therapy or dose escalation.[54]

Fesoterodine Fumarate Fesoterodine fumarate is also indicated for symptoms of urinary frequency, urgency, or urgency incontinence. It is a prodrug that is metabolized to its active metabolite, 5-hydroxymethyl tolterodine (also a metabolite of tolterodine), by nonspecific plasma esterases.[56] In a short-term study, fesoterodine was better than tolterodine ER 4 mg and placebo on reducing UUI episodes, micturitions, urgency, and improving health-related quality of life. However, fesoterodine caused more dry mouth (28% vs 13%), and constipation (4% vs 3%) than tolterodine ER. It has been associated with higher discontinuation rates due to adverse events (5% vs 3%).[57]

The usual starting dose is 4 mg daily, increasing to 8 mg daily, as needed and tolerated. The dose of fesoterodine should not exceed 4 mg daily in the presence of severe renal impairment (creatinine clearance <30 mL/min [0.50 mL/s]) or in patients also taking potent CYP3A4 inhibitors. Fesoterodine is not recommended in patients with severe hepatic impairment. It is available in XL tablets, which should be swallowed whole; patients should not chew, crush, or divide the product.[56] The most common adverse effects of fesoterodine are dry mouth (27%), constipation (5.1%), dyspepsia (2%), and dry eyes (1.6%). Anticholinergic adverse effects associated with fesoterodine are dose-related.[56]

Trospium Chloride Trospium chloride, a quaternary ammonium anticholinergic, is a second-generation antimuscarinic agent for urgency UI. Trospium chloride is poorly absorbed after oral administration (<10%), and food reduces bioavailability by 70% to 80%. It is principally cleared by the renal route (60%). Metabolites account for approximately 40% of the excreted dose following oral administration. The major metabolic pathway is hypothesized as ester hydrolysis with subsequent conjugation. CYP is not expected to contribute significantly to the elimination of trospium. The plasma half-life is approximately 20 hours; with renal clearance about 30 L/hr. Active tubular

secretion is a major route of elimination for trospium. When creatinine clearance is less than 30 mL/min (0.50 mL/s), drug exposure and drug concentration are significantly increased.[58] Trospium chloride IR was noninferior to oxybutynin IR, but was associated with less dry mouth.[59]

Anticholinergic side effects occur more often in patients 75 years and older due to pharmacodynamics changes (ie, increased sensitivity). Trospium may interact with other drugs that are eliminated by active tubular secretion via competition (eg, procainamide, pancuronium, morphine, vancomycin, and tenofovir).[58] Trospium IR is dosed 20 mg twice daily, and should be taken on an empty stomach. Dosage reduction (by 50% of the daily dose) is recommended when creatinine clearance is less than 30 mL/min (0.50 mL/s). In older patients (75 years and older), dose reduction to 20 mg once daily should be considered based upon tolerability.[58]

Trospium chloride extended-release offers once-daily dosing. Its efficacy and safety have been demonstrated in patients with OAB, including those who are older and taking multiple medications.[60,61] Trospium is eliminated primarily unchanged in the urine. It is not recommended in patients with severe renal impairment (creatinine clearance ≤ 30 mL/min [0.50 mL/s]). Alcohol should not be consumed within 2 hours of trospium ER administration. Coadministration with antacid may increase or decrease trospium exposure. In addition, coadministration of immediate-release (IR) metformin 500 mg twice daily may reduce its systemic exposure and drug level (29% and 34%, respectively).[61] The usual dosage of trospium ER is 60 mg daily. Because food decreases the bioavailability by 35% to 60%, XL trospium chloride must be taken on an empty stomach (1 hour before or 2 hours after meals).[60] Common adverse effects with trospium chloride ER are dry mouth (11%), constipation (9%), dizziness (2%), dry eyes (1.6%), flatulence (1.6%), nausea (1.4%), and abdominal pain (1.4%). Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents.[61]

Solifenacin Succinate Solifenacin succinate is a second-generation antimuscarinic agent indicated for the treatment of OAB with urgency incontinence, urgency, and urinary frequency.[62] Solifenacin is associated with less dry mouth than oxybutynin IR (35% vs 83%).[63–66] It is well absorbed (mean absolute bioavailability, 88%), and food has no clinically relevant effect on absorption. It is principally eliminated via metabolism and renal excretion of metabolites, with renal excretion of parent compound less than 10% of the dose. With a mean terminal disposition half-life of 50 to 60 hours, the drug can be

dosed once daily.[62] The primary pathway for elimination of solifenacin is via CYP3A4.

The recommended dose of solifenacin is 5 mg once daily. If the drug is well tolerated but the effectiveness is not optimal, the dose can be increased to 10 mg once daily. Little additional benefit is generally achieved with doses exceeding 5 mg daily. Solifenacin can be administered with or without food. For patients with creatinine clearance rates less than 30 mL/min (0.50 mL/s) or with moderate hepatic impairment (Child-Pugh class B), the daily dosage should not exceed 5 mg. Patients who have severe hepatic impairment (Child-Pugh class C) should avoid using this drug. If the patient is receiving concurrent therapy with one or more potent CYP3A4 inhibitors, the daily dose should not exceed 5 mg. The most common adverse reactions of solifenacin are dry mouth (11%-28%), constipation (5%-13%), urinary tract infection (4%-5%), and blurred vision (3%-5%). It interacts with CYP3A4 inhibitors and inducers; close patient monitoring is required. Prolonged corrected QT intervals have been reported with high-dose solifenacin.[62]

Darifenacin Darifenacin is another second-generation antimuscarinic for the management of OAB or UUI. It improves urinary symptoms, and quality of life.[67,68] The bioavailability of extended-release (ER) formulation is low (25%), and is affected by CYP2D6 genotype, treatment dose, and race/ethnicity. Darifenacin is extensively metabolized, with cumulative urinary excretion of the parent compound less than 10%. The 2D6 and 3A4 isoenzymes of CYP are responsible for darifenacin metabolism. Thus, pharmacogenomic profile may impact the clinical response to darifenacin.[69] With a mean terminal disposition half-life of 3 to 5 hours (depending on CYP2D6 metabolizer status), an ER formulation is needed to allow once-daily dosing.[70] Darifenacin ER should be initiated at 7.5 mg once daily, and may be increased to 15 mg once daily after 2 weeks to target clinical response. The dosage should be limited to 7.5 mg daily in patients with moderate hepatic impairment (Child-Pugh class B), taking potent CYP3A4 inhibitors. It should be avoided in patients with severe hepatic impairment (Child-Pugh class C). It must be swallowed whole without chewing, dividing, or crushing. Common adverse reactions are constipation (21%), dry mouth (19%), headache (7%), dyspepsia (5%), and nausea (4%). Darifenacin may interact with substrates of CYP2D6 (flecainide, thioridazine, and tricyclic antidepressants).[70]

Mirabegron Mirabegron has been approved by FDA in June 2012 for the treatment of OAB with symptoms of UUI, urgency, and urinary frequency.

6 Mirabegron is another second-line treatment for managing UUI. It increases bladder capacity by relaxing the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle through the activation of β_3-adrenergic receptors. Similar to antimuscarinic agents, it is modestly effective and reduces urinary frequency and incontinence episodes by less than one per day. It is associated with nonsignificant improvements in UUI, urgency episodes, and quality-of-life measures. It has been shown to have similar efficacy as with tolterodine ER.[23,71] It reduces mean number of incontinence episodes per 24 hours, mean number of micturitions per 24 hours, and increased mean volume voided per micturition. The efficacy is usually seen during 4 to 8 weeks of therapy.[71] The efficacy and safety of combination therapy with mirabegron and solifenacin have been evaluated in clinical trials.[72–74] Other β_3-adrenergic agonists in development are solabegron, ritobegron, vibegron and others.[75–77]

Mirabegron reaches its peak plasma concentrations at approximately 3.5 hours and has an oral bioavailability of 29% to 35%. It achieves steady state within 7 days of therapy. It can be taken with or without food. Mirabegron is extensively distributed in the body, with a volume of distribution of approximately 1,670 L. It has protein binding of approximately 71% to both albumin and α_1-acid glycoprotein. Mirabegron is metabolized via multiple pathways involving dealkylation, oxidation, glucuronidation, and amide hydrolysis. It has two inactive metabolites (16% and 11% of total exposure), respectively. Isoenzymes CYP2D6 and 3A4 play a limited role in its elimination. Poor metabolizers of CYP2D6 had an increased mean peak concentration and drug exposure compared to extensive metabolizers of CYP2D6 (16% and 17%, respectively). Other enzymes that are involved in mirabegron metabolism include butylcholinesterase, uridine diphospho-glucuronosyltransferases (UGT), and possibly alcohol dehydrogenase.

Total body clearance of mirabegron is about 57 L/hr, with a terminal elimination half-life of 50 hours. Renal clearance equals approximately 13 L/hr, primarily through active tubular secretion along with glomerular filtration. The urinary elimination of unchanged mirabegron is dose-dependent and ranges from 6% to 12% after a daily dose of 25 to 100 mg.[71]

Mirabegron should be initiated at 25 mg once daily, and may titrate upward to 50 mg once daily after 8 weeks, based on individual efficacy and tolerability; limit dose to 25 mg once daily in patients with severe renal impairment or moderate hepatic disease. Mirabegron is available in ER tablets, and should be swallowed whole with water without chewing, dividing, or crushing. It should be

avoided in patients with end-stage renal disease, severe hepatic impairment, or severe uncontrolled hypertension (≥180/110 mm Hg). Most commonly reported adverse reactions were hypertension (7%-11%), nasopharyngitis (4%), urinary tract infection (3%-6%), and headache (3%-4%). Patient should be monitored for increased blood pressure and urinary retention, particularly in patients with bladder outlet obstruction or those who are taking anticholinergic drugs.[71] Mirabegron has similar adverse effects (except less dry mouth) when compared with tolterodine ER. Blood pressure and heart rate changes were minimal (<1 mm Hg and <2 beats per minutes, respectively).[23] Mirabegron is a moderate inhibitor of CYP2D6, and may affect the dosage requirement for some 2D6 substrates (eg, metoprolol and desipramine). Thus, drug level monitoring for certain medications with a narrow therapeutic range, such as thioridazine, flecainide, and propafenone, is advised. When initiating a combination of mirabegron and digoxin, start with the lowest possible dose of digoxin and titrate based on drug level and clinical effect.[71]

Other Anticholinergics and Antimuscarinics Other drugs for treatment of UUI are less effective, are not safer, or have not been adequately studied.[24] Tricyclic antidepressants are generally no more effective than oxybutynin IR, and give bothersome and potentially serious adverse effects (eg, orthostatic hypotension, cardiac conduction abnormalities, dizziness, and confusion). They are also potentially life-threatening in overdose. Therefore, their use should be limited to individuals who have one or more additional medical indications for these agents (eg, depression or neuropathic pain); patients with mixed UI (because of their effect of decreasing bladder contractility and increasing outlet resistance); and possibly those with nocturnal incontinence associated with altered sleep patterns. Because of the lower incidence of adverse effects, desipramine and nortriptyline may be preferred over imipramine and doxepin. However, due to their lower anticholinergic activity, they may not be as effective. Other agents that are not recommended for urgency UI include propantheline, flavoxate, dicyclomine, and hyoscyamine.

Comparative Data Several systematic reviews with meta-analyses have examined the comparative effectiveness and adverse effects of antimuscarinic drugs for UI and OAB.[37,78,79] In general, higher doses of a particular drug were associated with greater adverse effects, particularly dry mouth. LA products (oxybutynin and tolterodine) had less dry mouth as compared to IR formulations.

Oxybutynin IR was associated with lower tolerability, particularly dry mouth, than tolterodine IR or LA. Oxybutynin IR, TDS (patch), and tolterodine LA

produced similar reductions in the number of incontinence episodes. However, the oral agents were associated with higher frequencies of dry mouth and constipation. In contrast, the patch formulation was associated with higher frequencies of local (application site) reactions.[78] Solifenacin had greater clinical efficacy (patient-reported cure or improvement, UI episodes, urgency episodes, and quality of life) than did tolterodine, although constipation was more common. Darifenacin 15 mg daily dose had similar efficacy to oxybutynin in reducing OAB symptoms but a lower occurrence of dry mouth. When comparing darifenacin 30 mg with oxybutynin 30 mg, dry mouth rates were similar, but constipation was more frequent in patients treated with darifenacin 30 mg.[78,79]

In a systematic review of 94 randomized controlled trials involving drugs for UUI, all drugs showed similar small benefits.[37] More data are needed to assess long-term adherence and drug safety, quality-of-life improvements, and comparative effectiveness among drugs.[37] In a meta-analysis, mirabegron and antimuscarinics had similar efficacy in reducing UI and UUI, with the exception of solifenacin 10 mg that was more efficacious in improving frequency of micturition and UUI. However, mirabegron was associated with the least dry mouth.[38] Selection of an initial drug therapy most likely depends on side-effect profile, comorbidities, concurrent drug therapy, and patient preference in drug delivery methods. **Table 101-7** lists the frequencies for the most common adverse events for all approved treatment agents based on manufacturers' product information.

TABLE 101-7 Adverse Event Incidence Rates with Approved Drugs for Bladder Overactivity[a]

Drug	Dry Mouth	Constipation	Dizziness	Vision Disturbance
Oxybutynin IR	71	15	17	10
Oxybutynin XL	61	13	6	14
Oxybutynin TDS	7	3	NR	3
Oxybutynin gel	10	1	3	3
Tolterodine	35	7	5	3
Tolterodine LA	23	6	2	4
Trospium chloride IR	20	10	NR	1
Trospium chloride XR	11	9	NR	2
Solifenacin	20	9	2	5
Darifenacin ER	24	18	2	2
Fesoterodine ER	27	5	NR	3
Mirabegron ER	3	3	3	NR

IR, immediate release; LA, long acting; TDS, transdermal system; XL, extended release; XR/ER, extended release; NR, not reported.

[a]All values constitute mean data, predominantly using product information from the manufacturers.

Botulinum Toxin A Enthusiasm is considerable for the application of botulinum toxin A for treatment of voiding dysfunction. Botulinum toxin is a naturally occurring powerful muscle relaxant produced by *Clostridium botulinum*.

Injected into smooth or striated muscle, botulinum toxin acts as a neurotoxin by temporarily paralyzing the muscle. The mechanism of action of the paralytic effect is generally ascribed to prevention of the release of the neurotransmitter acetylcholine into the synapse at the neuromuscular junction, although other pathways in neurotransduction may also be affected.

This compound is commercially produced for medical use in a number of conditions such as muscle spasticity, hyperhidrosis, and cosmetic reduction of skin wrinkles. It is currently indicated for the treatment of detrusor overactivity associated with neurologic condition and OAB.[80–82] Intradetrusor onabotulinumtoxin A is recommended by AUA as the third-line treatment in adult patients with refractory OAB.[23] In the lower urinary tract, it has also been used to treat external urethral sphincter spasticity by direct injection into the external urethral sphincter.

Botulinum toxin is delivered into the detrusor muscle (intravesical injection) using a cystoscope equipped with a needle. The usual dosage is between 100 and 300 units per session. It is injected through the needle directly into the bladder muscle in 10 to 30 injections spaced over 5 to 10 minutes. The procedure is carried out as an outpatient procedure without general anesthesia. The duration of therapeutic effect varies, lasting usually from 4 to 8 months. Repeat injections are necessary to maintain the beneficial effects.[81]

The adverse effects of botulinum toxin A when used in the urinary tract most frequently include dysuria, hematuria, urinary tract infection, and urinary retention. Urinary retention occurs in up to 20% of treated individuals and persists until the paralytic effects have worn off (up to 6-8 months). Therapeutic and adverse effects may not become evident for 3 to 7 days, presumably because this period of time is required for uptake of the toxin following injection.[81,82]

Intravesical (ie, bladder) injection of botulinum toxin A in patients with refractory OAB resulted in increased bladder capacity, increased bladder compliance, and improved quality of life.[81,82] Adverse effects include urinary tract infection and urinary retention.[81] Comparative data with placebo and other interventions, long-term safety and efficacy outcomes, and data regarding the optimal dose of botulinum toxin for idiopathic OAB are needed.

An alternative mechanism of delivery other than intravesical injection would greatly improve the appeal of this agent as needle injection can be painful in some individuals. Results of an open-label trial of intravesical botulinum toxin A in dimethylsulfoxide in 21 women with refractory idiopathic detrusor overactivity demonstrated a significant reduction in the frequency of incontinence episodes without any effect on postvoid residual urine volumes.[83] Further studies are needed in this regard.

Catheterization Combined with Medications Patients with UUI and an elevated postvoid residual urine volume due to retention may require intermittent self-catheterization along with frequent voiding between catheterizations. If intermittent catheterization is not possible, surgical placement of a suprapubic catheter may be necessary. Use of a chronic indwelling catheter should be avoided because of the increased occurrence of urinary tract infections and nephrolithiasis.

Regardless of catheterization status, patients may experience symptom relief with judicious use of oxybutynin (IR, XL, or TDS formulations), tolterodine (IR or LA formulations), trospium chloride, solifenacin, fesoterodine, darifenacin, or mirabegron, as these agents relax the detrusor muscle and enhance bladder

storage. Patients with UUI and symptoms of urinary retention may also benefit from an α-adrenergic receptor antagonist that relaxes the internal bladder sphincter (eg, prazosin, terazosin, doxazosin, tamsulosin, silodosin, and alfuzosin). Although theoretically of benefit, bethanechol, a cholinergic agonist, has not been demonstrated effective in improving bladder emptying in well-done trials. In addition, it causes numerous bothersome (eg, muscle and abdominal cramping and diarrhea) and potentially life-threatening adverse effects and should not be used in patients with asthma or heart disease.[24]

Urethral Underactivity

7 Urethral underactivity, or SUI, may be aggravated by agents with α-adrenergic receptor blocking activity, including prazosin, terazosin, doxazosin, tamsulosin, alfuzosin, silodosin, methyldopa, clonidine, guanfacine, and labetalol. The goal of therapy for SUI is to improve the urethral closure mechanism by stimulating *α*-adrenergic receptors in the smooth muscle of the bladder neck and proximal urethra, enhancing the supportive structures underlying the urethral epithelium, or enhancing the positive effects of serotonin and norepinephrine in the afferent and efferent pathways of the micturition reflex.[84]

Estrogens Local and systemic estrogens have been used extensively for the pharmacologic management of SUI since the 1940s. Estrogens are believed to work via several mechanisms, including enhancement of the proliferation of urethral epithelium, local circulation, and numbers and/or sensitivity of urogenital α-adrenergic receptors. However, a trial has questioned whether estrogens exert a stimulatory effect on vaginal collagen production, at least over the short-term.[85]

A meta-analysis of 34 trials evaluating the use of local or systemic estrogen therapy on UI in postmenopausal women found that systematic administration of estrogen alone or in combination with progesterone resulted in UI worsening.[86] In fact, observational studies have documented that oral or systemic estrogen use is associated with an increased risk of UI compared with that in nonusers.[87] There was some evidence that vaginal estrogen (vaginal cream or pessaries) may improve UI, and reduce urgency and frequency. The long-term effects of this therapy in older women are unknown. A recent meta-analysis of 17 trials of local estrogen compared to placebo or no treatment found beneficial effects on UI and OAB symptoms and some urodynamic parameters.[88] Different forms of vaginal estrogen (ring, pessary) appear to have similar improvements in urinary

symptoms (SUI, UUI, frequency, urgency). Studies comparing vaginal estrogen alone or in combination with antimuscarinic drugs (tolterodine or oxybutynin) or pelvic floor muscle exercises found greater improvement in subjective measures of UI in the combination approach. If estrogens are to be used for treatment of UI or OAB in postmenopausal women, only topical products should be administered, potentially combined with other treatment modalities such as pelvic floor muscle exercises or antimuscarinic drugs.

***α*-Adrenergic Receptor Agonists** Numerous open trials have supported the use of a variety of α-adrenergic receptor agonists in SUI, including ephedrine, norfenefrine, phenylpropanolamine, and midodrine. Phenylpropanolamine was withdrawn from the US market in 2000 because of a risk for stroke in women using the agent.[88] Patients may obtain the drug from international sources or via Internet. If so, individuals with the contraindications listed later in the chapter (especially coronary artery disease and/or cardiac arrhythmias) should be warned against self-treatment with this or other α-adrenergic receptor agonists.

Placebo-controlled comparative trials with phenylpropanolamine, norfenefrine, and norephedrine support the modest efficacy of these agents for treatment of mild or moderate SUI.[89,90] These agents have been found to variably affect maximum urethral closure pressure and functional urethral length. Adverse effects include hypertension, headache, dry mouth, nausea, insomnia, and restlessness. Contraindications to the use of these agents include the presence of hypertension, tachyarrhythmias, coronary artery disease, myocardial infarction, cor pulmonale, hyperthyroidism, renal failure, and narrow-angle glaucoma.

Several studies have evaluated whether the clinical and urodynamic effects of a combination of estrogen and an α-adrenergic receptor agonist exceed those of the individual therapies in SUI.[90] In general, combination therapy has resulted in somewhat superior clinical and urodynamic responses compared with monotherapy, including severity of complaints, amount of urine lost per episode, number of daily voluntary micturitions, number of leakage episodes per day, patient preference, pad use, maximum urethral closure pressure, functional urethral length, and pressure transmission ratio.

Duloxetine Duloxetine, a dual inhibitor of serotonin and norepinephrine reuptake (SNRI), was approved in 2004 for treatment of depression and painful diabetic neuropathy in the United States.[91] It is approved for SUI in Europe only. It is believed to affect central serotoninergic and noradrenergic regions, which are involved in ascending and descending control of urethral smooth muscle and

the external urethral sphincter. These mechanisms facilitate the bladder-to-sympathetic reflex pathway, increasing urethral and external urethral sphincter muscle tone during the storage phase.

Duloxetine is metabolized by CYP2D6 and 1A2 enzymes to form multiple metabolites and then eliminated in the urine. Duloxetine may increase the concentrations, drug exposure and half-lives of CYP2D6 substrates (eg, desipramine). Meanwhile, the drug concentration of duloxetine can be increased by CYP2D6 inhibitors (eg, paroxetine) and CYP1A2 inhibitors (eg, fluvoxamine).[91] Moderate hepatic dysfunction (Child-Pugh class B) significantly increases mean AUC and terminal disposition half-life of duloxetine. Mild or moderate renal impairment (creatinine clearance 30-80 mL/min [0.50-1.33 mL/s]) does not affect drug disposition. In severe renal impairment (hemodialysis patients), mean peak plasma concentration and AUC are both increased 100%, whereas metabolite concentrations are increased up to 900%.[91]

In six large, double-blinded, randomized, placebo-controlled clinical trials that evaluated duloxetine for SUI, duloxetine therapy produced significant reductions in UI episode frequency and number of micturitions per day, improvement in incontinence quality-of-life questionnaire scores and patient self-assessment, and increase in mean micturition interval. Results were independent of baseline UI severity (severity based on incontinent episode frequency). Significant intergroup differences were seen by week 4. However, cure rates were generally not improved by duloxetine. When evaluating the absolute differences between treatments, the actual benefit of duloxetine was generally quite modest.[83] Duloxetine also reduced incontinence episodes and improved quality of life in men with SUI after radical prostatectomy.[92]

A randomized, placebo-controlled clinical trial evaluated the effects of duloxetine (80 mg daily), pelvic floor muscle training (PFMT), and the combination of both modalities on incontinent episode frequency, incontinence-related quality of life, pad use, and patient global impression of change. Sham PFMT was used in the placebo group. Results indicated that duloxetine plus PFMT were probably additive in effect and that combination therapy afforded greater improvement than either monotherapy.[93]

The adverse events associated with duloxetine may make adherence problematic. In the SUI trials, treatment-emergent adverse events occurred in 68% to 93% of duloxetine and 50% to 72% of placebo recipients. Premature study withdrawal rates (due to adverse events) were as high as up to 33%. The most common adverse events reported with duloxetine were nausea (≤46%), headache (≤27%), constipation (≤27%), dry mouth (≤22%), and insomnia

(≤14%). Of interest, the drug may be associated with small increases in blood pressure (such as venlafaxine, another SNRI) and withdrawal symptoms (sleep disturbances). Unfortunately, adherence to long-term therapy is quite poor due to a combination of adverse events and lack of efficacy.[94]

Despite these negatives, duloxetine is the first drug approved by a regulatory agency for treating SUI in Europe. Based on studies conducted to date, a dosage regimen of 40 to 80 mg/day (in one or two doses) appears reasonable. Gradual dose titration (40 mg daily for 2 weeks, then 80 mg daily) helps reduce the risks of nausea, dizziness, and premature drug discontinuation. If cessation of duloxetine is desired, consider tapering the dosage by 50% for 2 weeks before discontinuation to avoid withdrawal symptoms.

Venlafaxine Venalfaxine is another SNRI. A double-blind, randomized, placebo-controlled clinical trial has demonstrated the benefit of venlafaxine 75 mg once daily for 12 weeks over placebo in terms of incontinence episode frequency, voiding interval, quality of life, and patient global impression of improvement. Nausea occurred in 40% of the venlafaxine group compared with 15% of the placebo group.[95]

Overflow Incontinence

Overflow incontinence secondary to benign or malignant prostatic hyperplasia may be amenable to pharmacotherapy. For management of malignant prostatic disease, see Chapter 148, “Prostate Cancer.” The pharmacotherapy of BPH is discussed in Chapter 100.

Nocturia

Desmopressin (DDAVP) Nocturia may be caused by uncontrolled diabetes mellitus, congestive heart failure, bladder/prostate diseases, and use of diuretics. Desmopressin is a synthetic vasopressin analog in intranasal formulation that was approved in March 2017 in the United States for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least two times per night to void.

The product carries multiple contraindications that may limit its use: hyponatremia, polydipsia, primary nocturnal enuresis, concomitant use of loop diuretics or glucocorticoids (systemic or inhaled), renal impairment, syndrome of inappropriate antidiuretic hormone secretion, during illness that can cause fluid or electrolyte imbalance, moderate-to-severe heart failure, and uncontrolled

hypertension.

The dose of intranasal desmopressin for patients who are not at risk for hyponatremia is 1.66 mcg in either nostril 30 minutes before bedtime. In patients who are at risk for hyponatremia, the starting dose is 0.83 mcg in either nostril 30 minutes before bedtime. The dose may be increased to 1.66 mcg after at least 1 week of therapy.[96] The dose of sublingual formulation is 27.7 mcg (for females) or 55.3 mcg (for males) once daily 1 hour before bedtime.[97]

PERSONALIZED PHARMACOTHERAPY

Patient factors (eg, age, comorbidities, concurrent drug therapies, ability to adhere to prescribed regimen, etc.) and preferences should be considered when selecting pharmacotherapy for patients with UI.

All anticholinergic/antimuscarinic drugs have similar contraindications and precautions, including urinary retention, gastric retention, uncontrolled narrow-angle glaucoma, CNS effects, angioedema, and myasthenia gravis. IR formulations of older agents (oxybutynin and tolterodine) have been associated with higher rates of anticholinergic adverse effects (dry mouth, constipation, headache, dyspepsia, dry eyes, cognitive impairment, tachycardia, and urinary retention). Older patients are particularly susceptible to these adverse events, thus require close monitoring. Significant dry mouth may lead to dental caries, ill-fitting dentures, and swallowing difficulty. Orthostatic hypotension and sedation may lead to falls in patients with baseline cognitive or cardiac conditions. Constipation is prevalent among the older patients because of polypharmacy and age-related physiologic changes.

All patients on anticholinergics should be warned about risk of somnolence and advised not to drive or operate heavy machinery until they know how the drugs affect them. Women with mixed UI or UUI plus urethritis or vaginitis may benefit from a topical estrogen (alone or in combination with an anticholinergic drug). Men with irritative symptoms of BPH that are nonresponsive to drug therapy may benefit from anticholinergic therapy while being closely monitored for the risk of precipitating acute urinary retention.

Antimuscarinic drugs should be considered for the management of UUI as monotherapy or in combination with nonpharmacologic interventions. None of the currently available antimuscarinic agents appears to have a clear advantage in efficacy over others. Selection of an agent should be based on patient factors, including renal/hepatic function, concomitant diseases, concurrent drug therapy, medication adherence, drug tolerability, dosing convenience, cost considerations,

and patient preference of formulation. Pharmacogenetic testing on CYP2D6 activity may be helpful to guiding the dosing or monitoring of antimuscarinics that are metabolized via the enzyme. In general, LA or ER products given once daily are preferable over IR ones because of better tolerability. Dose escalation of IR formulations may result in improved efficacy, albeit limited, at the cost of an increase in adverse event frequency and severity. Newer antimuscarinic agents and mirabegron may be good choices for patients who are intolerable of CNS adverse effects associated with older agents. Topical formulations, such as oxybutynin TDS or gel, may offer favorable systemic adverse effect profiles and convenient dosing. It is advisable to review concomitant medications for any possibility of additive, synergistic, antagonistic drug interactions in cholinergic system and liver enzymes (CYP3A4 and 2D6).

EVALUATION OF THERAPEUTIC OUTCOMES

8 Assessment of patient outcomes should include efficacy, side effects, adherence, and quality of life. During long-term management of UI, patient-specific clinical signs and symptoms of most distress (“bother”) to the individual must be monitored. A daily diary may be useful in this regard. Some of the short-form instruments used in incontinence research for measuring symptom impact and condition-specific quality of life can be used in clinical monitoring. In addition, quantitating the use of ancillary supplies, such as pads, may be useful.

9 The main goal of therapy is to minimize the signs and symptoms most bothersome to the patient, as well as the use of pads and other ancillary supplies or devices. Total elimination of UI signs and symptoms may not be possible, and patients and practitioners need to mutually establish realistic goals of therapy. Because the therapies for UI frequently have nuisance adverse effects (eg, anticholinergic effects such as dry mouth, constipation, sedation, etc.) that may compromise regimen adherence, the presence and severity of adverse effects must be carefully elicited at each visit to the healthcare practitioner. Queries of the patient and caregiver regarding CNS effects are important in elderly or frail patient as these effects can be severe enough to cause loss of independent living skills. Emergence of adverse effects may necessitate drug dosage adjustment or use of alternative strategies (eg, chewing sugarless gum, sucking on hard sugarless candy, or use of saliva substitutes in xerostomia) or even drug discontinuation. Patient should be encouraged to persist with a particular treatment for 4 to 8 weeks before declaring treatment failure. Nonresponders to

an antimuscarinic should be offered at least one other antimuscarinic and/or dose modification attempted to obtain a better balance between efficacy and side effects.

Postclass Engaged Learning Activity

Conduct a literature search and identify at least three emerging beta-3 adrenergic agents that are under investigation for the treatment of urinary incontinence. Describe the differences and similarities in their mechanism of action, pharmacokinetic parameters, dosage and side effects. Select one clinical study, write a brief summary about the study method, major findings and the role of therapy of this new agent in the treatment of urinary incontinence. This activity is intended to build your literature research skills and ability to critically evaluate clinical studies.

ABBREVIATIONS

ACE	angiotensin-converting enzyme
AUA	American Urological Association
AUC	area under the plasma or serum concentration-versus-time curve
BPH	benign prostatic hyperplasia
CYP	cytochrome P450
DD01	5-hydroxymethyl metabolite
ER	extended-release
EStim	electrical stimulation
FDA	Food and Drug Administration
IR	immediate release
LA	long acting
MStim	magnetic stimulation
OAB	overactive bladder
PFMT	pelvic floor muscle training
PTNS	peripheral tibial nerve stimulation
SNRI	serotonin and norepinephrine reuptake

SUI	stress urinary incontinence
TDS	transdermal system
UI	urinary incontinence
UGT	uridine diphospho-glucuronosyltransferases
UUI	urgency urinary incontinence
XL	extended release

REFERENCES

1. Milsom I, Altman D, Cartwright R, et al. Epidemiology of urinary incontinence (UI) and other lower urinary tract symptoms (LUTS), pelvic organ prolapse (POP) and anal incontinence (AI). In: Abrams P, Cardozo L, Khoury S, Wein A, eds., et al. *Incontinence*. 5th ed. International Consultation on Urological Disease European Association of Urology (ICUD-EAU); 2013;15–108.
2. Milsom I, Kaplan SA, Coyne KS, et al. Effect of bothersome overactive bladder symptoms on health-related quality of life, anxiety, depression, and treatment seeking in the United States: Results from EpiLUTS. *Urology*. 2012;80(1):90–96.
3. Gorina Y, Schappert S, Bercovitz A, et al. Prevalence of incontinence among older Americans. National Center for Health Statistics. *Vital Health Stat*. 2014;3(36):1–33.
4. Malmsten UG, Milsom I, Molander U, Norlen LJ. Urinary incontinence and lower urinary tract symptoms: An epidemiological study of men aged 45–99 years. *J Urol*. 1997;158:1733–1737.
5. Milson I, Altman D, Cartwright R, et al. Epidemiology of urinary incontinence (UI) and other lower urinary tract symptoms (LUTS), pelvic organ prolapse (POP), and anal (AI) incontinence. In: Abrams P, Cardozo L, Wagg A, Wein A, et al., eds. *Incontinence*. 6th ed. Paris: Health Publications Ltd; 2006;17–24.
6. Tennsted SL, Link CL, Steers WD, et al. Prevalence of and risk factors for urine leakage in a racially and ethnically diverse population of adults: The Boston Area Community Health (BACH) Survey. *Am J Epidemiol*. 2008;167:390–399.
7. Fenner DE, Trowbridge ER, Patel DA, et al. Establishing the prevalence of incontinence study: Racial differences in women’s patterns of urinary

incontinence. *J Urol*. 2008;179:1455–1460.

8. Markland AD, Goode PS, Redden DT, et al. Prevalence of urinary incontinence in men: Results from the National Health and Nutrition Examination Survey. *J Urol*. 2010;184:1022–1027.
9. Bump RC. Racial comparisons and contrasts in urinary incontinence and pelvic organ prolapse. *Obstet Gynecol*. 1993;81:421–425.
10. Burgio KL, Matthews KA, Engel BT. Prevalence, incidence and correlates of urinary incontinence in healthy, middle-aged women. *J Urol*. 1991;146:1255–1259.
11. Andersson KE, Chapple C, Cardozo L, et al. Pharmacological treatment of urinary incontinence. In: Abrams P, Cardozo L, Khoury S, Wein A, eds.*Incontinence*. 5th ed. International Consultation on Urological Disease European Association of Urology (ICUD-EAU); 2013:623–672.
12. Kanai A, Wyndaele JJ, Andersson KE, et al. Researching bladder afferents-determining the effects of β(3)-adrenergic receptor agonists and botulinum toxin type-A. *Neurourol Urodyn*. 2011;30(5):684–691.
13. Fowler C. Integrated control of the lower urinary tract—Clinical perspective. *Br J Pharmacol*. 2006;147(Suppl 2):s14–s24.
14. Blok BF. Brain control of the lower urinary tract. *Scand J Urol Nephrol Suppl*. 2002;(210):11–15.
15. Abrams P, Andersson KE, Apostolidis A, et al. 6th International Consultation on Incontinence. Recommendations of the International Scientific Committee: Evaluation and treatment of urinary incontinence, pelvic organ prolapse and faecal incontinence. *Neurourol Urodyn*. 2018;37:2271–2272.
16. Ruby CM, Hanlon JT, Boudreau RM, et al. Health, aging and body composition study. The effect of medication use on urinary incontinence in community-dwelling elderly women. *J Am Geriatr Soc*. 2010;58(9):1715–1720.
17. Haylen BT, de Ridder D, Freeman RM, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Int Urogynecol J*. 2010;21:5–26.
18. Resnick NM, Yalla S. Detrusor hyperactivity with impaired contractile function. An unrecognized but common cause of incontinence in the elderly patient. *JAMA*. 1987;257:3076–3081.
19. Hall SA, Yang M, Gates MA, et al. Associations of commonly used

medications with urinary incontinence in a community based sample. *J Urol*. 2012;188(1):183–189.

20. Rovner ES, Wein AJ. Today's treatment of overactive bladder and urge incontinence. *Womens Health Prim Care*. 2000;3:179–192.
21. James M, Jackson S, Shepard A, Abrams P. Pure stress leakage symptomatology: Is it safe to discount detrusor instability? *Br J Obstet Gynaecol*. 1999;106:1255–1258.
22. Fritel X, Ringa V, Quiboeuf E, Fauconnier A. Female urinary incontinence, from pregnancy to menopause: A review of epidemiological and pathophysiological findings. *Acta Obstet Gynecol Scand*. 2012;91(8):901–910.
23. Gormley EA, Lightner DJ, Burgio KL, Chai TC, et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment. 2014. Available at: http://www.auanet.org/common/pdf/education/clinical-guidance/Overactive-Bladder.pdf. Accessed June 3, 2016.
24. Cottenden A, Bliss DZ, Buckley B, et al. Management using continence products. In: Abrams P, Cardozo L, Khoury S, Wein A, et al., eds. *Incontinence*. 5th ed. International Consultation on Incontinence: European Urological Association; 2013;1651–1786.
25. Shamliyan T, Wyman J, Bliss DZ, Kane RL, Wilt TJ. Prevention of Urinary and Fecal Incontinence. Prepared by the Minnesota Evidence-based Practice Center under Contract 290-02-0009. Publication No. 08-E003. Rockville, MD: Agency for Healthcare Policy and Research; 2007.
26. Kirchin V, Page T, Keegan PE, Atiemo K, Cody JD, McClinton S. Urethral injection therapy for urinary incontinence in women. *Cochrane Database Syst Rev*. 2012;2:CD003881.
27. Suskind AM, Kaufman SR, Dunn RL, et al. Population-based trends in ambulatory surgery for urinary incontinence. *Int Urogynecol J*. 2013;24:207–211.
28. Koski ME, Rovner ES. Implications of the FDA statement on transvaginal placement of mesh: The aftermath. *Curr Urol Rep*. 2014;15(2):380.
29. Sandhu JS. Treatment options for male stress urinary incontinence. *Nat Rev Urol*. 2010;7(4):222–228.
30. Wilson LC, Gilling PJ. Post-prostatectomy urinary incontinence: A review of surgical treatment options. *BJU Int*. 2011;107(Suppl 3):7–10.
31. Nash S, Aboseif S, Gilling P, et al. Four-year follow-up on 68 patients

with a new post-operatively adjustable long-term implant for post-prostatectomy stress incontinence: ProACT™. *Neurourol Urodyn*. 2019;38:248–253.

32. Welk BK, Herschorn S. The male sling for post-prostatectomy urinary incontinence: A review of contemporary sling designs and outcomes. *BJU Int*. 2012;109(3):328–344.
33. Peters KM, Macdiarmid SA, Wooldridge LS, et al. Randomized trial of percutaneous tibial nerve stimulation versus extended-release tolterodine: Results from the overactive bladder innovative therapy trial. *J Urol*. 2009;182(3):1055–1061.
34. Abrams P, Cardozo L, Khoury S, Wein A, et al. Recommendations of the International Scientific Committee: Evaluation and treatment of urinary incontinence, pelvic organ prolapse, and faecal incontinence. *Incontinence*. 3rd ed. Plymouth, UK: Health Publications Ltd; 2005;1589–1630.
35. Van Kerrebroeck PE, Marcelissen TA. Sacral neuromodulation for lower urinary tract dysfunction. *World J Urol*. 2012;30(4):445–450.
36. Rovner E, Kennelly M, Schulte-Baukloh H, et al. Urodynamic results and clinical outcomes with intradetrusor injections of onabotulinum toxin A in a randomized, placebo-controlled dose-finding study in idiopathic overactive bladder. *Neurourol Urodyn*. 2011;30(4):556–562.
37. Shepherd JP, Lowder JL, Leng WW, Smith KJ. InterStim sacral neuromodulation and botox botulinum—a toxin intradetrusor injections for refractory urge urinary incontinence: A decision analysis comparing outcomes including efficacy and complications. *Female Pelvic Med Reconstr Surg*. 2011;17(4):199–203.
38. van Kerrebroeck PE, van Voskuilen AC, Heesakkers JP, et al. Results of sacral neuromodulation therapy for urinary voiding dysfunction: Outcomes of a prospective, worldwide clinical study. *J Urol*. 2007; 178(5):2029–2034.
39. Shamliyan T, Wyman JF, Ramakrishnan R, Sainfort F, Kane RL. Benefits and harms of pharmacologic treatment for urinary incontinence in women: A systematic review. *Ann Intern Med*. 2012;156(12):861–874,W301–W310.
40. Maman K, Aballea S, Nazir J, et al. Comparative efficacy and safety of medical treatments for the management of overactive bladder: A systematic review and mixed treatment comparison. *Eur Urol*.

2014;65:755–765.
41. Ortho-McNeil-Janssen Pharmaceuticals. *Ditropan (Oxybutynin) Package Insert*. Raritan, NJ: Ortho-McNeil-Janssen; 2012.
42. Janssen Pharmaceuticals. *Ditropan XL (Oxybutynin Chloride) Extended-Release Tablets Package Insert*. Titusville, NJ: Janssen Pharmaceuticals; 2015.
43. Activis Pharma. *Oxytrol (Oxybutynin Transdermal System) Package Insert*. Parsippany, NJ: Activis Pharma; 2015.
44. Cartwright R, Srikrishna S, Cardozo L, Robinson D. Patient-selected goals in overactive bladder: A placebo controlled randomized double-blind trial of transdermal oxybutynin for the treatment of urgency and urge incontinence. *BJU Int*. 2011;107(1):70–76.
45. Pizzi LT, Talati A, Gemmen E, et al. Impact of transdermal oxybutynin on work productivity in patients with overactive bladder: Results from the MATRIX study. *Pharmacoeconomics*. 2009;27(4):329–339.
46. Newman DK. The MATRIX study: Evaluating the data in older adults. *Director*. 2008;16(2):21–24.
47. Activis Pharma. *Gelnique 3% (Oxybutynin Chloride 3% Gel) Package Insert*. Parsippany, NJ: Activis Pharma; 2015.
48. Activis Pharma. *Gelnique (Oxybutynin Chloride 10% Gel) Package Insert*. Corona, CA: Activis Pharma; 2015.
49. Sand PK, Davila GW, Lucente VR, et al. Efficacy and safety of oxybutynin chloride topical gel for women with overactive bladder syndrome. *Am J Obstet Gynecol*. 2012;206(2):168.e1–e6.
50. Esin E, Ergen A, Cankurtaran M, et al. Influence of antimuscarinic therapy on cognitive functions and quality of life in geriatric patients treated for overactive bladder. *Aging Ment Health*. 2015;19:217–223.
51. Gomes T, Juurlink DN, Mamdani MM. Comparative adherence to oxybutynin or tolterodine among older patients. *Eur J Clin Pharmacol*. 2012;68(1):97–99.
52. Pharmacia & Upjohn. *Detrol (Tolterodine) Package Insert*. New York, NY: Pharmacia & Upjohn; 2012.
53. Pharmacogenomic effect/ADR for tolterodine. Available at: https://www.drugbank.ca/pharmaco/genomics/DBSNPE004890. Accessed March 6, 2019.
54. Pharmacia & Upjohn. *Detrol LA (Tolterodine Tartrate Extended Release*

Capsule). New York, NY: Pharmacia & Upjohn; 2011.

55. Chapple CR, Herschorn S, Abrams P, et al. Efficacy and safety of tolterodine extended-release in men with overactive bladder symptoms treated with an α-blocker: Effect of baseline prostate-specific antigen concentration. *BJU Int*. 2010;106(9):1332–1338.
56. Pfizer Laboratories. *Toviaz (Fesoterodine Fumarate Extended-Release Tablets) Package Insert*. New York, NY: Pfizer; 2014.
57. Kaplan SA, Schneider T, Foote JE, et al. Superior efficacy of fesoterodine over tolterodine extended release with rapid onset: A prospective, head-to-head, placebo-controlled trial. *BJU Int*. 2011;107(9):1432–1440.
58. Allergan. *Sanctura (Trospium Chloride) Tablets Package Insert*. Irvine, CA: Allergan; 2012.
59. Zellner M, Madersbacher H, Palmtag H, et al. Trospium chloride and oxybutynin hydrochloride in a German study of adults with urinary urge incontinence: Results of a 12-week, multicenter, randomized, double-blind, parallel-group, flexible-dose noninferiority trial. *Clin Ther*. 2009;31(11):2519–2539.
60. Sand PK, Rovner ES, Watanabe JH, Oefelein MG. Once-daily trospium chloride 60 mg extended release in subjects with overactive bladder syndrome who use multiple concomitant medications: Post hoc analysis of pooled data from two randomized, placebo-controlled trials. *Drugs Aging*. 2011;28(2):151–160.
61. Allergan. *Sanctura XR (Trospium Chloride Extended-Release Capsules) Package Insert*. Irvine, CA: Allergan; 2012.
62. Astellas Pharma Technologies. *Vesicare (Solifenacin Succinate) Package Insert*. Norman, OK: Stellas Pharma Technologies; 2013.
63. Chapple CR, Martinez-Garcia R, Selvaggi L, et al. A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: Results of the STAR trial. *Eur Urol*. 2005;48:464–470.
64. Kelleher CJ, Cardozo L, Chapple CR, Haab F, Ridder AM. Improved quality of life in patients with overactive bladder symptoms treated with solifenacin. *BJU Int*. 2005;95:81–85.
65. Herschorn S, Pommerville P, Stothers L, et al. Tolerability of solifenacin and oxybutynin immediate release in older (>65 years) and younger (≤65 years) patients with overactive bladder: Sub-analysis from a Canadian, randomized, double-blind study. *Curr Med Res Opin*. 2011;27(2):375–

382.

66. Herschorn S, Stothers L, Carlson K, et al. Tolerability of 5 mg solifenacin once daily versus 5 mg oxybutynin immediate release 3 times daily: Results of the VECTOR trial. *J Urol*. 2010;183(5):1892–1898.
67. Dwyer P, Kelleher C, Young J, et al. Long-term benefits of darifenacin treatment for patient quality of life: Results from a 2-year extension study. *Neurourol Urodyn*. 2008;27(6):540–547.
68. Abrams P, Kelleher C, Huels J, et al. Clinical relevance of health-related quality of life outcomes with darifenacin. *BJU Int*. 2008;102(2):208–213.
69. Darifenacin. Available at: https://www.drugbank.ca/drugs/db00496. Accessed March 6, 2019.
70. Warner Chilcott. *Enablex (Darifenacin Extended Release) Package Insert*. Rockaway, NJ: Warner Chilcott; 2013.
71. Astellas Pharma Technologies. *Myrbetriq (Mirabegron) Package Insert*. Norman, OK: Astellas Pharma Technologies; 2015.
72. Abrams P, Kelleher C, Staskin D, et al. Combination treatment with mirabegron and solifenacin in patients with overactive bladder: Exploratory responder analyses of efficacy and evaluation of patient-reported outcomes from a randomized, double-blind, factorial, dose-ranging, Phase II study (SYMPHONY). *World J Urol*. 2017;35:827–838.
73. Gratzke C, van Maanen R, Chapple C, et al. Long-term safety and efficacy of mirabegron and solifenacin in combination compared with monotherapy in patients with overactive bladder: A randomised, multicentre phase 3 study (SYNERGY II). *Eur Urol*. 2018;74:501–509.
74. Drake MJ, Chapple C, Esen AA, et al. BESIDE study investigators. Efficacy and safety of mirabegron add-on therapy to solifenacin in incontinent overactive bladder patients with an inadequate response to initial 4-Week solifenacin monotherapy: A randomised double-blind multicentre phase 3B study (BESIDE). *Eur Urol*. 2016;70:136–145.
75. Thiagamoorthy G, Cardozo L, Robinson D. Current and future pharmacotherapy for treating overactive bladder. *Expert Opin Pharmacother*. 2016;17:1317–25.
76. Mitcheson HD, Samanta S, Muldowney K, et al. Vibegron (RVT-901/MK-4618/KRP-114V) administered once daily as monotherapy or concomitantly with tolterodine in patients with an overactive bladder: A multicenter, phase IIb, randomized, double-blind, controlled trial. *Eur Urol*. 2019;75:274–282.

77. Yoshida M, Takeda M, Gotoh M, et al. Efficacy of novel β(3)-adrenoreceptor agonist vibegron on nocturia in patients with overactive bladder: A post-hoc analysis of a randomized, double-blind, placebo-controlled phase 3 study. *Int J Urol*. 2019;26:369–375.
78. Madhuvrata P, Cody JD, Ellis G, Herbison GP, Hay-Smith EJ. Which anticholinergic drug for overactive bladder symptoms in adults. *Cochrane Database Sys Rev*. 2012;1:CD005429.
79. Novara G, Galfano A, Secco S, et al. A systematic review and meta-analysis of randomized controlled trials with antimuscarinic drugs for overactive bladder. *Eur Urol*. 2008;54:740–764.
80. Anger JT, Weinberg A, Suttorp MJ, et al. Outcomes of intravesical botulinum toxin for idiopathic overactive bladder symptoms: A systematic review of the literature. *J Urol*. 2010;183(6):2258–2264.
81. Dmochowski R, Chapple C, Nitti VW, et al. Efficacy and safety of onabotulinum toxin A for idiopathic overactive bladder: A double-blind, placebo controlled, randomized, dose ranging trial. *J Urol*. 2010;184(6):2416–2422.
82. Duthie JB, Vincent M, Herbison GP, Wilson DI, Wilson D. Botulinum toxin injections for adults with overactive bladder syndrome. *Cochrane Database Syst Rev*. 2011;(12):CD005493.
83. Petrou SP, Parker AS, Crook JE, et al. Botulinum A toxin/dimethylsulfoxide bladder instillations for women with refractory idiopathic detrusor overactivity: A phase I/II study. *Mayo Clin Proc*. 2009;84:702–706.
84. Tsakiris P, de la Rosette JJ, Michel MC, et al. Pharmacologic treatment of male stress urinary incontinence: Systematic review of the literature and levels of evidence. *Eur Urol*. 2008;53:53–59.
85. Jackson S, James M, Abrams P. The effect of oestradiol on vaginal collagen metabolism in postmenopausal women with genuine stress incontinence. *BJOG*. 2002;109:339–344.
86. Cody JD, Jacobs ML, Richardson K, et al. Oestrogen therapy for urinary incontinence in post-menopausal women. *Cochrane Database Syst Rev*. 2012;(10):CD001405.doi:10.1002/14651858. CD001405.pub2.
87. Grady D, Brown JS, Vittinghoff E, et al. Postmenopausal hormones and incontinence: The Heart & Estrogen/Progestin Replacement Study. *Obstet Gynecol*. 2001;97:116–120.
88. Weber MA, Kleijn MH, Langendam M, et al. Local oestrogen for pelvic

floor disorders: A systematic review. *PLOS One*. 2015;10(9):e013625.

89. Kernan WN, Viscoli CM, Brass LM, et al. Phenylpropanolamine and the risk of hemorrhagic stroke. *N Engl J Med*. 2000:343:1826–1832.
90. Alhasso A, Glazener CM, Pickard R, N'dow J. Adrenergic drugs for urinary incontinence in adults. *Cochrane Database Syst Rev*. 2005;3:CD001842.
91. Eli Lilly Canada Inc. *Cymbalta (duloxetine) Package Insert*. Toronto, Ontario. 2016.
92. Cornu JN, Merlet B, Ciofu C, et al. Duloxetine for mild to moderate postprostatectomy incontinence: Preliminary results of a randomised, placebo-controlled trial. *Eur Urol*. 2011;59(1):148–154.
93. Ghoneim GM, VanLeeuwen JS, Elser DM, et al. A randomized controlled trial of duloxetine alone, pelvic floor muscle training alone, combined treatment and no active treatment in women with stress urinary incontinence. *J Urol*. 2005;173:1647–1653.
94. Bump RC, Voss S, Beardsworth A, et al. Long-term efficacy of duloxetine in women with stress urinary incontinence. *Br J Urol Int*. 2008;102:214–218.
95. Erdinc B, Gurates B, Celik H, et al. The efficacy of venlafaxine in the treatment of women with stress urinary incontinence. *Arch Gynecol Obstet*. 2009;279:343–348.
96. Serenity Pharmaceuticals. *Noctiva® (Desmopressin Acetate) Package Insert*. Milford, PA: Serenity Pharmaceuticals; 2017.
97. Ferring Pharmaceuticals. *Nocdurna® (Desmopressin Acetate) Sublingual Tablets Package Insert*. Parsippany, NJ: Ferring Pharmaceuticals; 2018.

SECTION 13 IMMUNOLOGIC DISORDERS

Function and Evaluation of the Immune System

Daniel A. Zlott and Geoffrey M. Thiele

KEY CONCEPTS

1. Cells of the immune system are derived from the pluripotent stem cell. Hematopoiesis is closely regulated to assure adequate numbers of different cell types. The development of these different cells or cell lineages depends on cell-to-cell interactions and hematopoietic growth factors.
2. Upon activation, dendritic cells (DCs) express higher concentrations of major histocompatibility complex class II molecules, B7-1, B7-2, CD40, ICAM-1, and LFA-3 molecules than other antigen-presenting cells (APCs). They also produce more IL-12. These differences may explain why, in vitro, DCs are the most efficient APC.
3. A T lymphocyte expresses hundreds of T-cell receptors (TCRs). All the TCRs expressed on the surface of an individual T lymphocyte have the same antigen specificity.
4. An immature B lymphocyte expresses thousands of membrane-bound surface immunoglobulin (sIg) as IgM (monomeric) or IgD, all with the same specificity (ie, antigen-binding site). Upon antigen stimulation and T-cell help, the immature B lymphocyte matures (proliferates, class-switches and becomes a plasma cell) to secrete different isotypes (eg, IgM [pentamer], IgA, immunoglobulin G [IgG], and IgE) with the same specificity as the original membrane-bound sIg.
5. Serum protein electrophoresis determines the total concentration of all circulating proteins, including the immunoglobulins (ie, IgG, IgA, IgM, IgD, and IgE). The concentration of the individual isotypes can be determined with isotype-specific quantification methods. Most clinical laboratories quantitate only IgG, IgM, and IgA because they are the most

prevalent isotypes in the bloodstream. In patients with allergic disorders, quantification of IgE is rarely useful.

6. An understanding of the mechanism of action of immunomodulators allows a clinician to anticipate potential adverse effects. The benefit of manipulating immune responses must be balanced with the potential consequences and long-term sequela (eg, tumor growth, infections, autoimmune reactions) of such manipulation.

Preclass Engaged Learning Activity

Watch the following video to learn more about the different ways clinicians use the immune system to treat cancer. IMMUNOTHERAPY: The Path to a Cancer Cure (For Clinicians): https://tinyurl.com/wrqz4q9. As you read the chapter, note which strategies for modulating the immune response for therapeutic purposes were discussed in the video.

INTRODUCTION

The immune system is a complex network of barriers, organs, cellular elements, and molecules that interact to defend the body against invading pathogens. The *immune system* is actually composed of two distinct systems of immunity: innate immunity and adaptive immunity. In brief, innate immunity includes a series of nonspecific barriers (physical and chemical), along with cellular and molecular elements strategically deployed and positioned to prevent or quickly neutralize infection. Adaptive immunity works in concert with the innate immune system. In contrast to innate immunity, adaptive immunity constantly evolves and adapts to the invading pathogens. The hallmarks of the adaptive immune response are *diversity*, *memory*, *mobility*, *self-versus-nonself discrimination*, *redundancy*, *replication*, and *specificity*.[1] *Diversity* indicates the capability of the immune system to respond to many different pathogens or strains of pathogens. Immunological *memory* ensures a quicker and more vigorous response to a subsequent encounter with the same pathogen. If an individual has seen something before, the odds are good that he or she will see it again, so the individual will make more of these cells and have them ready. *The mobility* of components of the immune system enables local reactions to provide systemic protection. *Discrimination of self-versus-nonself* helps prevent the immune

system from responding to ourselves, and thus results in tolerance to our own tissues. *Redundancy* refers to the ability of the immune system to produce components with similar biological effects from multiple cell lines, such as inflammatory cytokines. *Replication* of the cellular components of the immune system amplifies the immune response. *Specificity* describes the ability of the immune system to distinguish between dissimilar antigens.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

103

Systemic Lupus Erythematosus

Beth H. Resman-Targoff

KEY CONCEPTS

1. Systemic lupus erythematosus (SLE) is considered a disease primarily of young women, but it can occur in anyone. The prevalence and severity vary with sex, race, ethnicity, and socioeconomic factors.
2. Understanding the etiology of SLE and environmental factors that can initiate or exacerbate the disease may make it possible to avoid those triggers.
3. SLE is an autoimmune disease characterized by the presence of autoantibodies, some of which may play a role in the pathogenesis of the disease. An understanding of disease mechanisms can lead to targeted drug therapy.
4. SLE is a multisystem disease that can involve almost any organ and may present in many different ways. Therapy is determined by the manifestations in each patient, which may change and fluctuate in severity over time.
5. Lifestyle changes can modify risk factors for SLE flares and complications.
6. The overall goals of therapy are to prevent disease flares and involvement of other organs, decrease disease activity and prevent damage, achieve and maintain remission, reduce use of corticosteroids, and improve quality of life, while minimizing adverse effects and costs. Most patients with SLE should receive hydroxychloroquine alone or in combination with other therapy appropriate for the disease manifestations.
7. Pregnancy planning is essential for good outcomes. Pregnancy outcomes are best when the disease is controlled before conception. Drugs used to treat SLE may adversely affect fertility and the fetus.
8. Antiphospholipid antibodies are associated with arterial and venous

thrombosis and obstetric complications.

9. Many drugs can induce a lupus-like syndrome. The manifestations and laboratory findings may be different between the traditional drug-induced lupus and that seen with use of tumor necrosis factor-alpha inhibitors.
10. Since SLE can present in many different ways, it is difficult to design standard response criteria. Development of appropriate criteria is essential for the approval of new drugs.

Preclass Engaged Learning Activity

Go to lupus organization Websites that are designed for patients:

World Lupus Federation (https://tinyurl.com/smmwg2k): review the document, "Lupus Knows No Boundaries e-Report" (https://tinyurl.com/tgasjgo)

Lupus Foundation of America (https://tinyurl.com/yyz8etzd): explore the section, Understanding Lupus (https://tinyurl.com/tkjxavy)

Lupus Canada (https://tinyurl.com/r34lghm): review the Living with Lupus Section (https://tinyurl.com/uf2sxmd)

Summarize what you learned about SLE from the Personal Stories section (https://tinyurl.com/r7dxhmo).

What questions would you have if you developed lupus?

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease associated with autoantibody production. The term "lupus" (Latin for wolf) was first used in the 13th century to describe erosive lesions that looked like skin that had been gnawed by a wolf. In the 1800s, it was recognized that other organs may be affected and we now know that SLE is a multisystem disease. The common finding in SLE is production of autoantibodies.[1] This is an exciting time in the management of SLE because a better understanding of disease mechanisms has led to the development of new drugs. In addition, new response criteria are being developed to show efficacy of drugs, even with the background of standard therapy. This led to the first approval of a drug for the treatment of SLE in over 50 years. Despite these advances, the management of this disease remains a

challenge. It has a myriad of manifestations and many of the drugs used to treat it are not approved for this indication. As a result, the dosing of many of the drugs considered to be standard-of-care therapy must be personalized.

EPIDEMIOLOGY

1 Systemic lupus erythematosus is generally considered to occur most frequently in women of reproductive age (15–50 years old). This is especially characteristic of the disease in nonwhite women. Statistics regarding SLE depend on the population studied and sampling and recruitment criteria.[2] These have profound effects on estimates of incidence and prevalence, disease activity and severity, and mortality. The incidence is 0.3 to 23.7 per 100,000 person-years and the prevalence is 6.5 to 178 per 100,000 persons. Rates are nine times higher in women than in men so overall population statistics can be rather misleading. It is affected by ethnicity, which includes genetic, geographic, cultural, social, and other aspects within a group. Rates are higher in nonwhites than in the white population.[3] It is most common in those of African origin, but is also more common in people of Asian, Arab, and Hispanic background, and Native Americans (called First Nations in Canada) than in whites.[3,4] Most people are of mixed race, so race by itself can be difficult to analyze. Nonwhites tend to have an earlier onset, more severe disease, and a higher mortality rate, but it can be difficult to separate out the influence of socioeconomic factors and access to medical care. The disease tends to be more severe in men and children, and those with onset at a later age (over 50 years) have poor outcomes.[3]

Survival rates have improved recently with better therapy and earlier diagnosis and initiation of treatment. The standardized mortality ratio for SLE is 2.6 to 3 times higher than in the general population, most related to more cardiovascular and renal disease and infections.[3] Overall SLE survival is 95% at 5 years and 92% at 10 years after diagnosis. This is reduced to about 88% at 10 years with lupus nephritis and even less than that in African Americans with lupus nephritis.[5] The survival rate may be lower in men, but the small number of males in most studies makes this difficult to determine.[3]

ETIOLOGY

2 The exact etiology for SLE is unknown but many factors have been identified that appear to play a role in the disease. Some are predisposing factors

and others are involved in the disease mechanisms. Categories of these elements include genetic influences, epigenetic regulation of gene expression, environmental factors, hormones, and abnormalities in immune cells and cytokines.[6]

The incidence of SLE is increased in affected families. First-degree relatives of patients with SLE are 20 times more likely to develop the disease than those in a general population.[7] Ten percent of patients with SLE have relatives with the disease. The concordance rate is 24% to 69% for identical twins and 2% to 5% for fraternal twins and other full siblings.[8] The genetic predisposition to SLE is a result of the interplay of a combination of genes. In rare cases, it is thought to result primarily from a single abnormal gene.[6] The major histocompatibility complex (MHC) class II alleles HLA-DR2 and HLA-DR3 are known to be linked to SLE. An increasing number of other gene loci are being identified as having associations with the disease.[2] Gene expression is regulated by deoxyribonucleic acid (DNA) methylation and histone modifications. These epigenetic changes can cause alterations that may influence SLE. Interestingly, hydralazine and procainamide, two drugs that may induce lupus, inhibit DNA methylation.[9]

In a genetically susceptible individual, environmental triggers can initiate the disease. It is possible that the type of trigger may influence specific organ involvement. Cigarette smoke has many components, such as hydrazine, that may affect the immune system. Chronic smokers and former smokers are more likely to have elevated titers of anti-double-stranded DNA (anti-dsDNA) antibodies. Cigarette smoking is phototoxic and associated with cutaneous lupus.[10] Ultraviolet light can cause keratinocytes in the skin to release nuclear material that can further stimulate the immune system and autoantibody production by B cells.[10] Viruses may trigger SLE. Studies have suggested a potential role for the Epstein–Barr virus.[2] Other implicated triggers include infections, medications (eg, vaccines and biologics), psychological stress, silica dust, hydrazines, petroleum, solvents (eg, nail polish remover and metal cleaners), dyes, and pesticides.[10,11]

The higher prevalence in women suggests that hormones such as estrogens and progesterones play a role in SLE, but the presence of the X chromosome may also contribute. The incidence of SLE is increased 10-fold in men with Klinefelter (XXY) syndrome and decreased in women with Turner (XO) syndrome.[2]

PATHOPHYSIOLOGY

3 Systemic lupus erythematosus is a multisystem disease characterized by disorders of the innate and adaptive immune systems (**Fig. 103-1**). T and B lymphocyte activation and signaling are altered in SLE and there is abnormal clearance of apoptotic debris containing nuclear material which can stimulate immune responses.[2] The number of plasma cells is increased in active SLE and these cells produce autoantibodies, which can cause tissue damage. Neutrophil dysfunction can increase the risk for infection.[12] Antibodies directed at dsDNA are seen in about 60% to 70% of patients with SLE and less than 0.5% of patients without the disease.[2] The titers of anti-dsDNA may fluctuate with disease activity and may predict disease flare. Some autoantibodies may play a role in the pathogenesis of clinical features of SLE; these autoantibodies may target Ro/SSA (antigen Ro/Sjögren syndrome A, ribonucleoprotein complex), La/SSB (antigen La/Sjögren syndrome antigen B, RNA-binding protein), C1q (subunit of the C1 complement component), Sm (nuclear particles), *N*-methyl-D-aspartate (NMDA) receptor (amino acid released by neurons), phospholipids, nucleosomes (from apoptotic cellular debris), and histones (protein core of nucleosomes). The autoantibodies can be present for many years before SLE is clinically apparent and they may be associated with specific organ involvement, such as anti-dsDNA, anti-Ro, anti-La, anti-C1q, and anti-Sm with lupus nephritis, and anti-NMDA associated with central nervous system (CNS) lupus.[2]

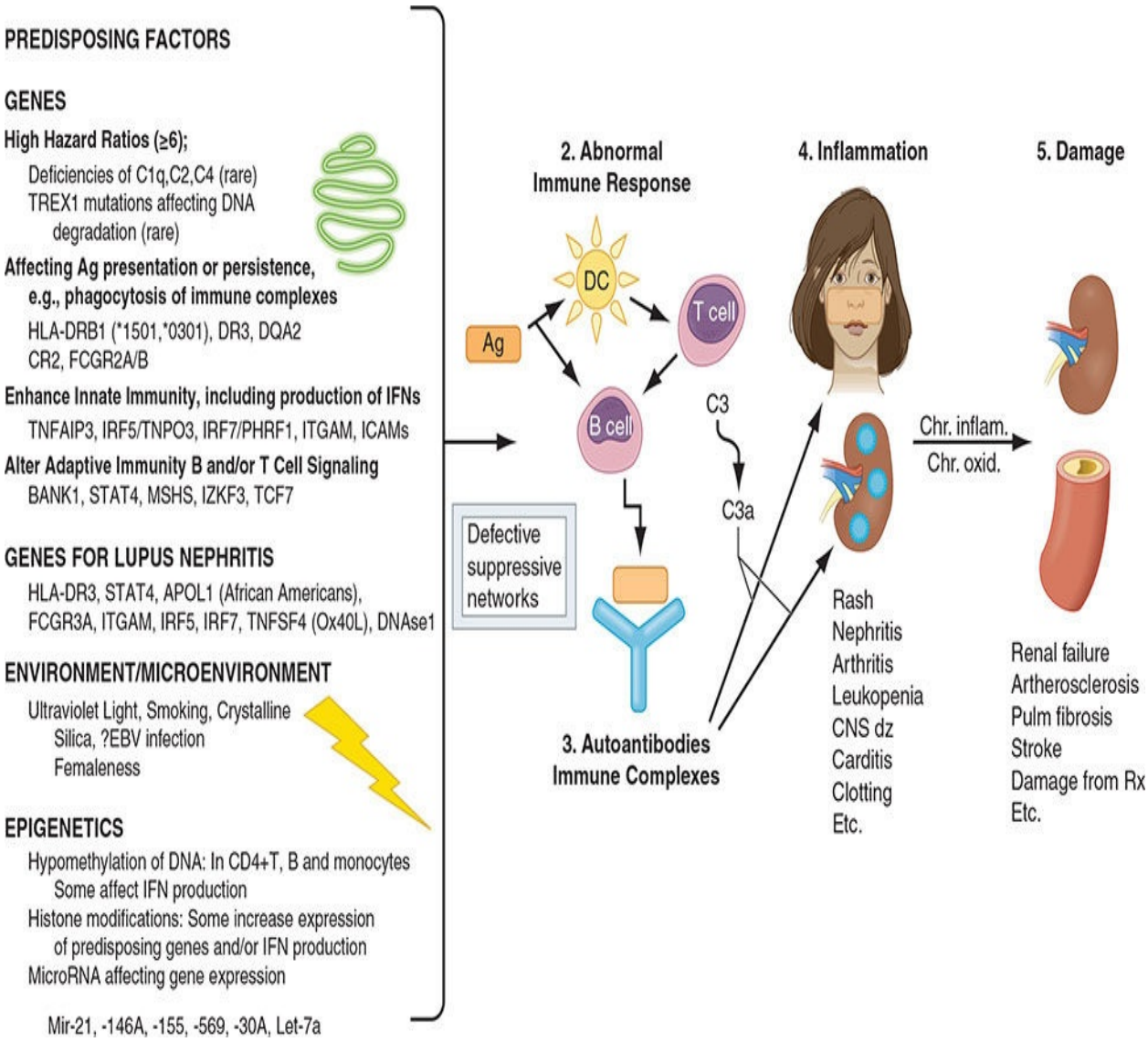


FIGURE 103-1 Pathogenesis of systemic lupus erythematosus (SLE). Pathogenesis is related in large part to production of increased quantities and immunogenic forms of nucleic acids and other self-antigens, which drive autoimmune-inducing activation of innate immunity, autoantibodies, and T cells. Interactions between genes, environment, and epigenetic changes drive increased autophagy, Ag presentation, neutrophil NETosis, autoantibody formation with increased plasma cells, and production of pathogenic effector T cells in Th1, Th17, and Tfh subsets, with ineffective regulatory networks. (Ag, antigen; C1q, complement system; C2,C4, complement components; CNS, central nervous system; DC, dendritic cell; EBV, Epstein-Barr virus; HLA, human leukocyte antigen; IFN, interferon UV, ultraviolet.) (*Reproduced, with permission, from Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 20th ed. New York, NY: McGraw-*

Hill; 2019.)

The exact mechanism of autoantibody tissue destruction is unclear. Immune complexes form when autoantibodies bind to nuclear material and deposit in tissues.[2] They activate the complement cascade, leading to an influx of inflammatory cells and tissue injury.[12] Autoantibodies might also directly react with proteins in tissues. Antibodies to blood cells can cause cytopenias.[2] Antibodies against phospholipids can lead to thrombosis and fetal loss.[13]

T-cell abnormalities contribute to the immune disorders observed in SLE. There are increased T helper cells type 2 and 17 and diminished number and function of T regulatory (Treg) cells. Cytokines, such as tumor necrosis factor-alpha (TNF-α), interferon-gamma, and interleukin-10, produced by activated T cells can stimulate B cells.[2]

Cytokines play multiple roles in SLE and contribute to inflammation and tissue damage. Interleukin-10 stimulates B cell proliferation and autoantibody production in renal cells and may affect skin and joint symptoms.[2] Increased T-cell production of interleukin-17 correlates with disease activity and may contribute to kidney and other tissue damage.[2,12] There is a decrease in interleukin-2 which is important for Treg function and restriction of interleukin-17.[12] Plasmacytoid dendritic cells secrete type 1 interferon which has a role in the pathogenic mechanism of SLE.[2] B-lymphocyte stimulator (BLyS), also known as B cell activating factor of the TNF family (BAFF), increases survival and promotes differentiation of B cells.[14] Interleukin-6 promotes production of antibodies and may play a role in lupus nephritis.[2] The role of TNF-α in SLE is unclear. It appears to be harmful in some patients, and in others, protective.[2]

CLINICAL PRESENTATION

4 Systemic lupus erythematosus is an autoimmune disease that can involve almost any organ and may present in many different ways. This can make it difficult to establish a diagnosis and an extensive workup may be needed to determine the full extent of involvement and to exclude other possible etiologies for the manifestations. More common features include involvement of the skin and mucus membranes, joints, kidneys, CNS, serous membranes, cardiovascular system, and hematologic cell lines. Fatigue and depression are frequent symptoms and can adversely affect quality of life.[15] Arthritis or arthralgias are experienced by 75% to 95% of patients with SLE.[9] SLE may present differently

in men and women. For example, men are more likely to have renal and hematologic involvement but have fewer dermatologic features. Race and ethnicity may also affect the specific manifestations.[16]

Disease manifestations fluctuate with periods of remission, flares, and progression.[17] The presence of ANA may be used as a screening test for SLE. Most patients with SLE have these antibodies, but they are not specific for the disease.[18]

An international group of SLE researchers developed and validated criteria for classification of SLE in 2012. These are referred to as the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria and were developed to identify patients with the disease for clinical studies. They are not intended to establish a diagnosis in an individual patient but may help assess the likelihood that a patient has SLE. The widely used American College of Rheumatology (ACR) criteria were developed in 1982 and revised in 1997. The 1997 version was not validated. The SLICC criteria are more clinically relevant and sensitive than the ACR criteria. When validated, the SLICC criteria had a sensitivity of 97% and specificity of 84% compared to 83% and 96% for the ACR criteria. The number of criteria was expanded from 11 to 17 and, unlike the ACR criteria, they are divided into clinical and immunologic parameters. The ACR criteria required 4 of the 11 elements to be present, serially or simultaneously. To satisfy the SLICC criteria, a patient must still meet at least four of the elements, but now these must include at least one clinical and one immunologic criterion or the patient must have biopsy-proven lupus nephritis with positive ANA or anti-dsDNA antibodies. An abbreviated version of the SLICC criteria, with comparison to the ACR criteria, is shown in **Table 103-1**.[18,19] It may be possible to classify patients earlier in their disease course as having SLE with the SLICC criteria.[19] New classification criteria that focus on early diagnosis were developed through collaboration of the ACR and the European League Against Rheumatism (EULAR).[20]

TABLE 103-1 2012 Systemic Lupus International Collaborating Clinics Classification Criteria for Systemic Lupus Erythematosus (SLICC)

CLINICAL PRESENTATION

Systemic Lupus Erythematosus

Symptoms

- Fatigue, depression, anxiety, photosensitivity, joint pain, headache, weight loss, nausea/abdominal pain

Signs

- Rash, alopecia, fever, oral and nasal ulcers, arthritis, renal dysfunction, seizure, psychosis, pleuritis, pleural effusion, cardiovascular disease, pericarditis/ myocarditis, heart murmur, hypertension, anemia, leukopenia, thrombocytopenia, lymphadenopathy, Raynaud's phenomenon, vasculitis

Diagnostic Tests

- Serology: autoantibodies, antiphospholipid antibodies, complement; inflammatory markers: C-reactive protein, erythrocyte sedimentation rate; blood chemistries; complete blood count; urinalysis; lumbar puncture; renal biopsy

1. Acute/subacute cutaneous lupus/malar rash[a]/photosensitive rash[a]
2. Chronic cutaneous lupus/discoid rash
3. Oral OR nasal ulcers
4. Nonscarring alopecia
5. Arthritis/synovitis or tenderness
6. Serositis (pleuritis, pericarditis)
7. Renal (urine protein-to-creatinine ratio [or 24-hour urine protein] representing 500-mg protein/24 hr OR red blood cell casts)
8. Neurologic (seizure, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, acute confusional state)
9. Hemolytic anemia[b]
10. Leukopenia (<4,000 cells/mm^3 [4 × 10^9/L]) OR lymphopenia (<1,000 cells/mm^3 [1 × 10^9/L])[b]
11. Thrombocytopenia (<100,000/mm^3 [100 × 10^9/L])[b]

Immunologic Criteria

1. Antinuclear antibody (ANA)
2. Anti-double-stranded DNA (dsDNA)[c]
3. Anti-Sm[c]
4. Antiphospholipid antibody (lupus anticoagulant, anticardiolipin, anti-β_2-glycoprotein I, false positive rapid plasma reagin test for syphilis)[c]
5. Low complement (C3, C4, CH50)
6. Direct Coombs test (without hemolytic anemia)

[a]In the ACR Criteria, malar rash and photosensitivity are two separate criteria.

[b]In the ACR Criteria, hemolytic anemia, leukopenia, lymphopenia, and thrombocytopenia count as one criterion.

[c]In the ACR Criteria, anti-dsDNA, anti-Sm, and antiphospholipid antibody count as one criterion.

At least four criteria, including at least one clinical and one immunologic criterion OR biopsy-proven lupus nephritis with positive ANA or anti-dsDNA required for diagnosis.

Data from References 18 and 19.

An international working group of SLE experts devised a consensus definition of SLE flare: “A flare is a measurable increase in disease activity in one or more organ systems involving new or worse clinical signs and symptoms and/or laboratory measurements. The assessor must consider the increase in disease activity to be clinically significant, sufficient to consider a change or an increase in treatment.”[21]

Some skin involvement is seen in about 50% to 70% of patients with SLE.[9] This can be disfiguring and affect a patient’s health-related quality of life.[22] Three main types of cutaneous lupus erythematosus have been observed. They may occur with or without SLE. Acute cutaneous lupus erythematosus is

typically seen in patients with SLE and is characterized by a photosensitive malar rash over the cheeks and nose with sparing of the nasolabial folds. The malar rash is present in 52% of patients with SLE at the time of diagnosis. The arms and trunk may be involved. The manifestations usually wax and wane without scarring.[23] Severe SLE is less common with the other forms of cutaneous lupus. Subacute cutaneous lupus erythematosus is highly photosensitive and is manifested by annular or papulosquamous lesions that usually heal without scarring. It can be accompanied by musculoskeletal complaints and 70% of patients have anti-Ro/SSA autoantibodies. It is more common than other types of cutaneous lupus erythematosus in patients with drug-induced lupus. About half of patients with subacute cutaneous lupus erythematosus meet criteria for SLE.[23] Many subtypes of chronic cutaneous lupus erythematosus have been identified. The most common is discoid lupus, which is confined to the head and neck in about two-thirds of patients, but it can be generalized.[24] Chronic discoid lupus is the first manifestation of SLE in up to 10% of cases. Discoid lupus progresses to SLE in about 5% to 10% of patients. It is more common in smokers and African Americans. It may be associated with scarring, scarring alopecia, malar rash, photosensitivity, oral ulcers, leukopenia, vasculitis, and chronic seizures. Chronic discoid lupus is associated with a lower incidence of arthritis, end-stage renal disease, and immunologic markers such as ANA, anti-dsDNA, and antiphospholipid antibodies.[25]

Lupus nephritis is present at the time of SLE diagnosis in about 35% of adult patients and 50% to 60% of patients develop it by 10 years. It is more common in African American and Hispanic patients than in whites and more prevalent in men than in women. The International Society of Nephrology/Renal Pathology Society devised a classification system for lupus nephritis based on histologic findings: Class I: minimal mesangial, Class II: mesangial proliferative; Class III: focal (less than 50% of glomeruli involved); Class IV: diffuse (50% or more of glomeruli involved); Class V: membranous; and Class VI: advanced sclerosing (at least 90% globally sclerosed glomeruli without residual activity). Patients with nephritis may also have hypertension and atherosclerosis.[5]

The central and peripheral nervous systems can be involved in SLE. The prevalence of this involvement is around 19% to 38%, but can range from 6.4% to 93% depending on the population studied and methods for detecting the occurrence.[26] About 50% of neuropsychiatric events appear within the first 2 years after the diagnosis of SLE. Although mild nonspecific neuropsychiatric findings such as headache, mood disorders, and mild cognitive dysfunction are common in SLE (10%–20%), they may not reflect overt CNS disease activity.

Findings more indicative of neuropsychiatric lupus include cerebrovascular disease (ischemic stroke and/or transient ischemic attack), anxiety, and seizures in 5% to 10% of patients; severe cognitive dysfunction, acute confusional state, peripheral neuropathy, and psychosis in 3% to 5%; and chorea, movement disorders, cranial nerve neuropathies, and aseptic meningitis in less than 1% to 2% of patients. Risk factors include general SLE disease activity, prior neuropsychiatric events, and presence of antiphospholipid antibodies. It is important to assess contributing factors and to rule out other possible etiologies of these manifestations such as medication use, infection, and metabolic abnormalities. The diagnostic approach will vary depending on the clinical presentation and preliminary findings, but can include a thorough history and physical, lumbar puncture with cerebrospinal fluid analysis (mostly to exclude infection), electroencephalogram, serology, complete blood count, blood chemistries, neuropsychological assessment of cognitive function, nerve conduction studies, and magnetic resonance imaging. An attribution algorithm to determine the likelihood of neuropsychiatric SLE was developed by a study group of the Italian Society of Rheumatology. It scores on timing with respect to SLE onset, nonspecific events, confounding factors, and favoring factors.[27]

Cardiovascular disease is a leading cause of death in patients with SLE. Not only are there cardiac manifestations of SLE, such as pericarditis and myocarditis, but patients with SLE are also at increased risk for accelerated atherosclerosis. This is probably related to the chronic inflammation associated with the disease and adverse effects of the drugs (eg, high-dose corticosteroids) used to treat it. Antiphospholipid antibodies and type I interferons may play a role in the pathogenesis. Drugs such as hydroxychloroquine and mycophenolate mofetil may have a cardioprotective effect.[28]

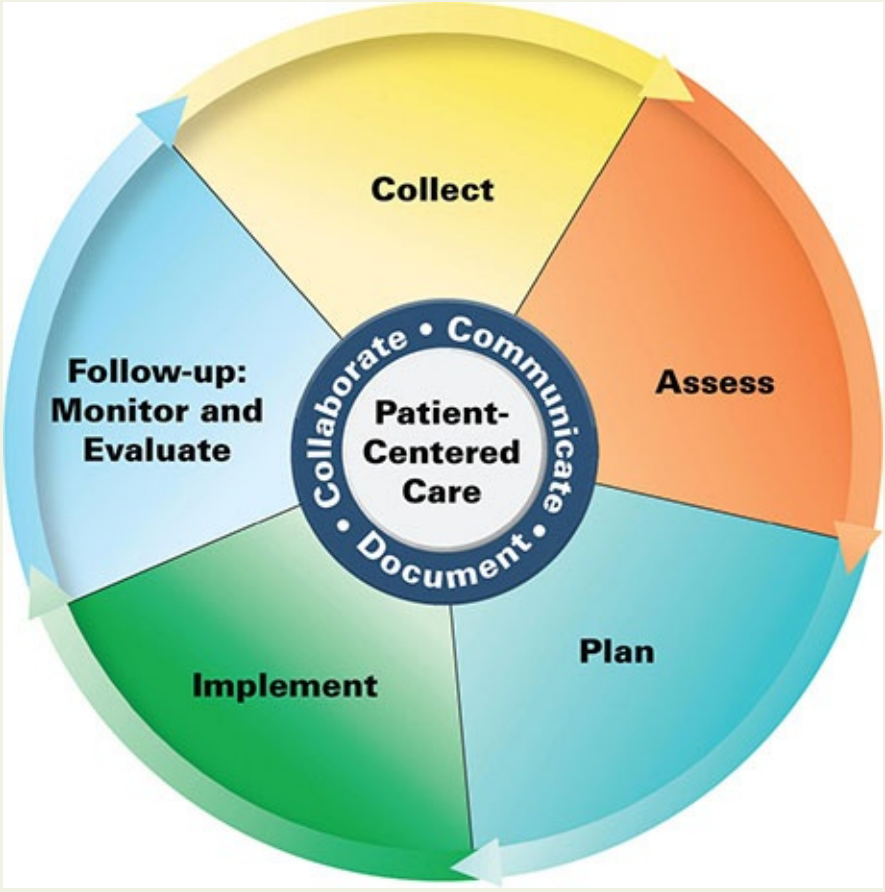
TREATMENT

Treatment of SLE is determined by the patient's symptoms, organ involvement, comorbidities, and other patient-specific factors.

Desired Outcomes

The target of therapy should be identified. Ideally, the goal should be remission, but achieving low disease activity is also beneficial. Remission is categorized as with or without treatment other than hydroxychloroquine. Patients should be involved in treatment decisions, taking into account their preferences, priorities, and pregnancy plans. Therapy should be designed to prevent disease flares and

involvement of other organs, decrease disease activity and prevent damage, achieve and maintain remission, reduce use of corticosteroids, and improve quality of life, while minimizing adverse effects and costs. Success in achieving these outcomes depends on disease severity and the type and extent of organ impairment. In general, the prognosis is better if lupus is limited to skin and musculoskeletal findings. The worst prognosis is seen with renal or CNS involvement.[5,27] Many of the desired outcomes have been observed with antimalarials, although most patients require additional therapy.[29] Survival and quality of life have improved with a better understanding of disease mechanisms and new therapeutic options. Mortality is affected by SLE disease activity, cardiovascular risks, and infections.



Patient Care Process for Systemic Lupus Erythematosus

Collect

- Patient characteristics (eg, age, race, sex, pregnancy status)
- Patient history (past medical, pregnancies and outcomes, symptoms,

family, social—dietary habits, alcohol and tobacco use)

- Current medications and prior lupus medication use
- Immunization history
- Objective data (see Clinical Presentation box and Table 103-1)
  - BP, heart rate, height, weight, and BMI; other physical exam findings
  - Labs (metabolic panel, Scr, BUN, urinalysis, CBC, ANA, antiphospholipid antibodies, direct Coombs test, other lupus-associated antibodies, complement, inflammatory markers (ESR, CRP)
  - Other diagnostic tests when indicated (eg, ECG, CXR, skin or kidney biopsy)

Assess

- Presence of cutaneous, renal, neurologic, hematologic, cardiac, or pleural manifestations of lupus
- Evidence of antiphospholipid syndrome (thromboembolic events, miscarriages)
- Current medications that could be associated with drug-induced lupus
- Appropriateness and effectiveness of current lupus regimen (see Figs. 103-2 and 103-3)
- Psychological effects of lupus

Plan*

- Tailored lifestyle modifications (eg, diet, exercise, weight management, protection from sun, smoking cessation, keeping warm if Raynaud's phenomenon occurs)
- Drug therapy regimen including specific medications based on disease manifestations, dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Figs. 103-2 and 103-3 and Tables 103-2 and 103-3)
- Monitoring parameters including efficacy (eg, skin manifestations, cardiovascular events, thromboembolic events, miscarriages, kidney health, neurologic events), safety (medication-specific adverse effects), and time frame

- Patient education (eg, purpose of treatment, dietary and lifestyle modifications, drug therapy, pregnancy considerations, osteoporosis prevention if taking corticosteroids)
- Self-monitoring of skin and BP—where and how to record results
- Immunizations as needed; consider timing of live vaccines with respect to immunosuppressive drug use and pregnancy
- Referrals to other providers when appropriate (eg, physician, dietician, counselor)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Determine goal attainment based on disease manifestations
- Presence of adverse effects
- Occurrence of cardiovascular events and development/progression of kidney or other organ impairment
- Patient adherence to treatment plan using multiple sources of information

**Collaborate with patient, caregivers, and other healthcare professionals.*

General Approach

Patients with SLE should be counseled about the importance of lifestyle modifications such as protection from the sun, smoking cessation, exercise, and weight control. The need for immunizations should be assessed with consideration of appropriate timing with respect to immunosuppressive drug use. The effects of disease activity and treatment on pregnancy outcomes should be discussed. Patients should be evaluated and treated for any comorbidities such as hypertension, hyperlipidemia, and depression. Mild symptoms can be managed with nonsteroidal anti-inflammatory drugs (NSAIDs) with or without other analgesics.[30] Antimalarial drugs have numerous beneficial effects in SLE and many experts feel that most patients with the disease should always receive one

of these drugs.[31] Corticosteroids are used to treat most forms of SLE and up to 57% to 86% of patients receive continuous/chronic therapy.[32] The need for osteoporosis prevention should be assessed.[33] If the above therapy is ineffective or major organs are involved, immunosuppressive or immunomodulatory drugs are added.[30] The specific treatment is determined by the organs involved and severity of the disease. It is summarized in **Fig. 103-2**.[17] Patients must be educated about the importance of adherence to treatment. Studies have shown that only 25% to 57% of patients with SLE are adherent to taking their medications and up to 33% discontinue therapy after 5 years.[34] The expected time for response to lupus medications also needs to be discussed because patients may interpret delayed onset as ineffectiveness.

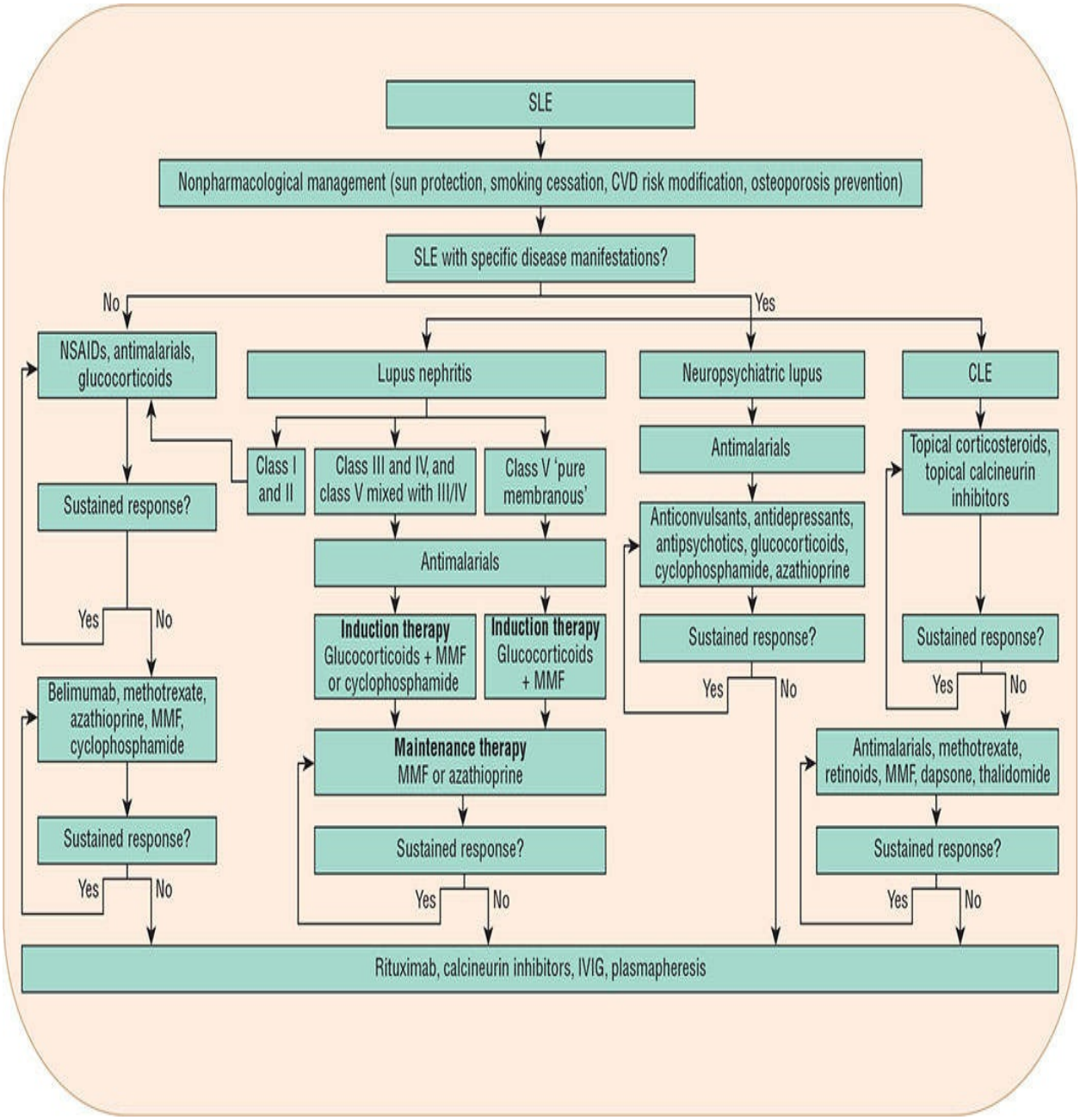


FIGURE 103-2 Algorithm for the treatment of SLE. (CLE, cutaneous lupus erythematosus; CVD, cardiovascular disease; IVIG, intravenous immunoglobulin; MMF, mycophenolate mofetil; SLE, systemic lupus erythematosus.) (*Reprinted with permission from Xiong W, Lahita RG. Pragmatic approaches to therapy for systemic lupus erythematosus. Nat Rev Rheumatol. 2014;10:97-107.*)

Nonpharmacologic Therapy

5 Patient perceptions of well-being and quality of life are affected not only by disease activity, but also by social support, coping mechanisms, feelings of helplessness, and abnormal illness-related behaviors.[30] Good social support can improve outcomes, in part by making it easier for patients and their families to navigate the healthcare system and utilize resources.[35] Counseling and support groups may help patients' mental well-being and coping mechanisms, but do not affect SLE disease activity. Limited data suggest that aerobic exercise may help decrease patients' risk for cardiovascular events and osteoporosis and may also improve fatigue, depression, anxiety, and sleep disturbances, which are frequently experienced in SLE.[36] Exercise can also help with weight loss. Obesity is associated with worse patient-reported outcomes including quality of life and disease activity.[37]

Since photosensitivity is common in SLE, patients should wear protective clothing and hats and use sunscreens to protect themselves from the sun. They should avoid tanning salons.[24] The FDA issued regulations for testing and labeling of sunscreens that took effect in 2012. Sunscreens labeled as broad spectrum protect against ultraviolet A and B radiation. They have sun protection factors (SPFs) of 15 to 50+.[38] Patients with SLE should use sunscreens with high SPF values and apply them every 2 hours while in the sun.[24]

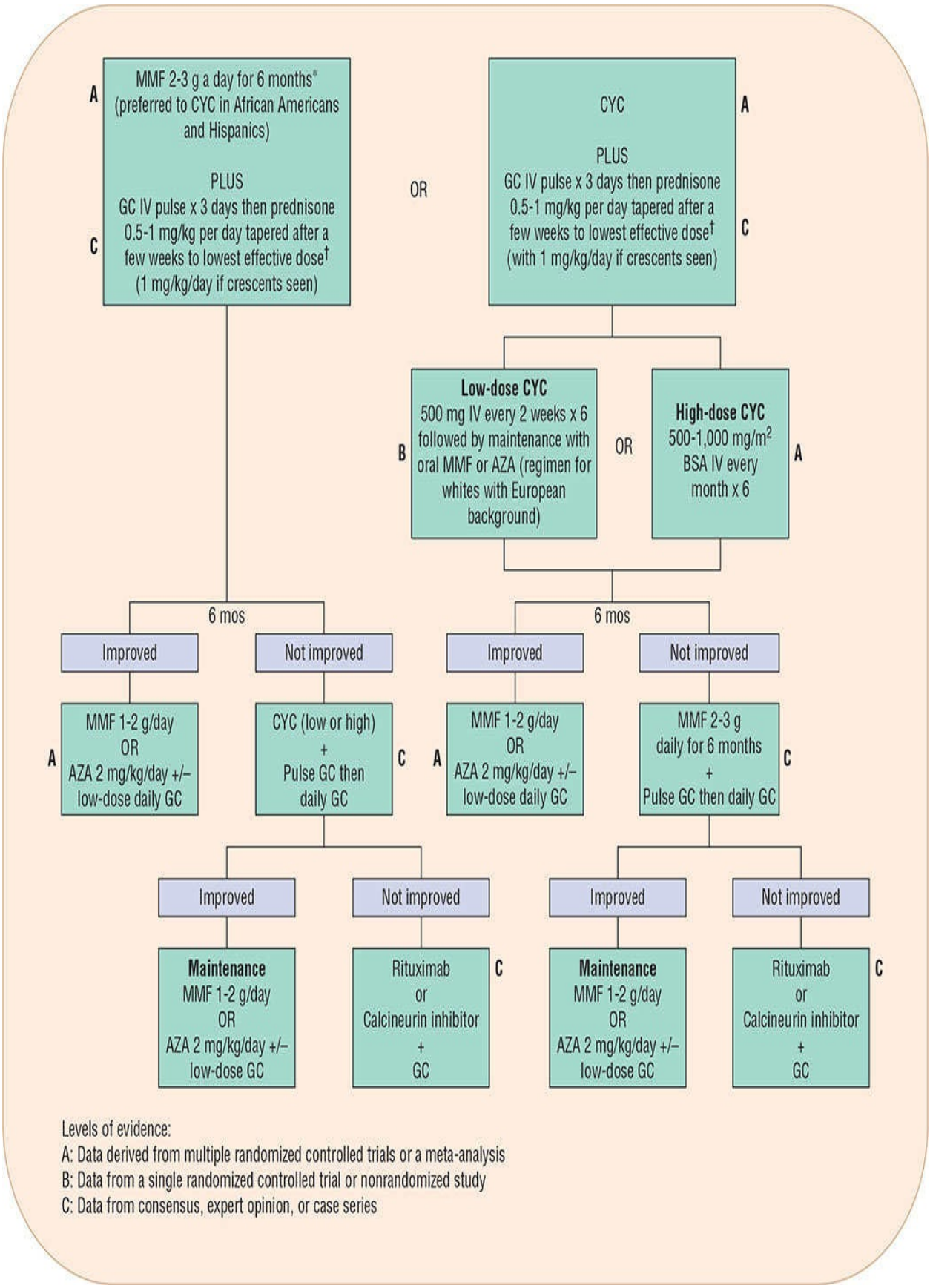
Patients should be counseled to stop smoking. Smoking cessation is important, not only because it decreases cardiovascular risk, but because smoking can exacerbate SLE and diminish the effectiveness of antimalarials and belimumab.[39,40] Smokers also have a higher incidence of active rashes with skin damage and scarring.[39]

Pharmacologic Therapy

6 Treatment is personalized based on the manifestations of SLE in the patient. It consists of a combination of immunosuppression and symptomatic and supportive therapies. The only drugs approved by the FDA for treatment of SLE are aspirin, prednisone, hydroxychloroquine, and belimumab. The use of other drugs for SLE, even those considered "standard of care," is considered to be "off-label" use. For many of these drugs, the optimal doses and duration of therapy for induction and maintenance of response in SLE have not been determined.

Organization or expert task force treatment recommendations have been published for lupus nephritis, neuropsychiatric lupus, and antiphospholipid

antibody carriers.[5,41,42] A committee of the ACR developed guidelines for screening, treatment, and management of lupus nephritis. All patients with nephritis should receive hydroxychloroquine to reduce damage and flares. An angiotensin-converting enzyme inhibitor or angiotensin receptor blocker can reduce proteinuria by about 30% in those with proteinuria of 0.5 g/day or more, and delay progression of renal disease. Blood pressure should be maintained at no more than 130/80 mm Hg. Patients with low-density lipoprotein cholesterol greater than 100 mg/dL (2.59 mmol/L) should receive a statin to prevent accelerated atherosclerosis. More specific treatment is based on the type of nephritis. The first two classes, minimal mesangial and mesangial proliferative lupus nephritis do not usually need immunosuppressive therapy. Focal and diffuse lupus nephritis (Classes III and IV) are treated similarly with aggressive use of glucocorticoids and immunosuppressive therapy. **Figure 103-3** shows the induction regimens for these patients and the levels of evidence to support the recommendations. In studies of lupus nephritis, whites with Western or Southern European backgrounds respond as well to low-dose IV cyclophosphamide ("Euro-Lupus" regimen of 500 mg every 2 weeks for six doses) as to high-dose regimens (500-1,000 mg/m^2 body surface area once a month for six doses) (Level B evidence). African Americans and Hispanics respond less well to IV cyclophosphamide than do whites or Asians. Patients of African or Hispanic origin may respond better to mycophenolate mofetil than to cyclophosphamide. Asians require lower doses of mycophenolate mofetil (Level C evidence).[5] Patients with a combination of Class V with III or IV would be treated similarly to those with only III or IV. The initial cyclophosphamide or mycophenolate mofetil therapy should be continued for 6 months unless proteinuria or serum creatinine worsens by 50% or more at 3 months (Level A evidence). After 6 months of induction therapy, patients who have improved can be maintained on mycophenolate mofetil or azathioprine, with low doses of corticosteroids if needed. Patients with pure Class V, membranous lupus nephritis, and nephrotic range proteinuria of more than 3 g/day should receive induction therapy with mycophenolate mofetil 2 to 3 g/day with prednisone 0.5 mg/kg/day for 6 months (Level A evidence). Those who improve can be maintained on mycophenolate mofetil 1 to 2 g/day or azathioprine 2 mg/kg/day. Patients who do not respond should be treated with cyclophosphamide 500 to 1,000 mg/m^2/month for 6 months with IV pulse glucocorticoids, followed by prednisone 0.5 to 1 mg/kg/day.[5] Maintenance therapy should be continued for at least 3 years.[43] Patients with advanced sclerosing lupus nephritis (Class VI) should be considered for renal replacement therapy.[5]



Levels of evidence:
A: Data derived from multiple randomized controlled trials or a meta-analysis
B: Data from a single randomized controlled trial or nonrandomized study
C: Data from consensus, expert opinion, or case series

FIGURE 103-3 American College of Rheumatology guidelines for therapy for Class III/IV lupus nephritis. (AZA, azathioprine; BSA, body surface area; GC, glucocorticoids; MMF, mycophenolate mofetil; *, preference of MMF over cyclophosphamide (CYC) in patients who desire to preserve fertility; †, recommended background therapies discussed in text.) (*Reprinted with permission from Reference 5.*)

A task force of the European League Against Rheumatism (EULAR) developed recommendations for the management of neuropsychiatric lupus. Treatment depends on the manifestations. Symptomatic therapy (eg, anticonvulsants and antidepressants) should be given as needed. More specific treatment depends on whether the problem is determined to be inflammatory or thrombotic or both. If there is inflammation or neurotoxic damage in the presence of generalized SLE activity, glucocorticoids alone or in conjunction with immunosuppressive drugs such as azathioprine or cyclophosphamide should be given (Strong evidence). If the condition does not respond, other treatments such as plasma exchange, IV immunoglobulin, or rituximab can be tried. If the problem is related to moderate-to-high titers of antiphospholipid antibodies and/or thrombosis, anticoagulants and/or inhibitors of platelet aggregation should be used (Sufficient evidence).[41]

For patients with intermittent joint pain associated with SLE, NSAIDs are good initial therapy. If the pain is more severe or persistent, prednisone in a dose of 10 mg/day or less in combination with hydroxychloroquine should be instituted. Intra-articular corticosteroid injections can be used for localized joint pain. If this therapy is inadequate, methotrexate can be added to hydroxychloroquine therapy. For patients who fail or are intolerant of these therapies, mycophenolate mofetil or azathioprine can be tried. If alternative treatment is needed, leflunomide, belimumab, rituximab, abatacept, or TNF-α inhibitors may be considered.[44]

The first step in the management of cutaneous lupus erythematosus is counseling patients to protect themselves from ultraviolet light as described above.[24] Drug treatment is personalized based on the extent and severity of involvement. Topical corticosteroids are commonly used and may relieve symptoms such as itching or burning, but may not provide adequate clearing of lesions when used alone.[24] The choice of corticosteroid depends on the location of application. Low potency corticosteroids (eg, fluocinolone acetonide 0.01% and hydrocortisone 1%) should be used on areas with thin skin such as the face and groin, mid-potency (eg, triamcinolone acetonide) for trunk and extremities,

and high potency (eg, clobetasol propionate) for thick-skin areas such as scalp, soles, and palms. Creams or, for more severe disease, ointments are used on the body, and foams or solutions on the scalp.[23] Intralesional corticosteroids may be used in discoid lupus, but should not be repeated more often than every 4 to 6 weeks.[24] To avoid the adverse effects of topical corticosteroids, such as skin atrophy, telangiectasias, and steroid-induced dermatitis, the lowest effective potency and duration of therapy should be used.[23] Alternatively, topical calcineurin inhibitors may be used instead. Pimecrolimus is more lipophilic than tacrolimus and has greater affinity for the skin. Antimalarials have photoprotective effects and are commonly used as first-line systemic therapy in the management of cutaneous lupus. If hydroxychloroquine alone is ineffective, quinacrine, available from compounding pharmacies, may be added.[24] For refractory disease, systemic immunosuppressive drugs (eg, corticosteroids, methotrexate, mycophenolate mofetil, or azathioprine), immunomodulatory drugs (eg, dapsone, thalidomide, or lenalidomide), biologics (eg, rituximab or belimumab), or oral retinoids may be added. Patients should be screened for glucose-6-phosphate dehydrogenase (G6PD) deficiency before getting dapsone. The evidence to support use of these drugs in management of cutaneous lupus is mainly from case reports rather than controlled studies. The choice of agents may be guided by other organ involvement.[23]

Dosing information for selected drugs is shown in **Table 103-2**. Since most of the drugs used to treat SLE are not FDA-approved for that indication, the doses given are based on other uses for those drugs. **Table 103-3** lists adverse effects and drug monitoring parameters. Selected issues concerning the drugs are discussed below.

TABLE 103-2 Dosing of Drugs Used to Treat Systemic Lupus Erythematosus

Drug	Brand Name	Initial or Starting Dose	Usual Range or Maintenance Dose	Special Population Doses	Comments (adverse drug reactions, special populations)
NSAIDs/salicylates	Various drugs				Caution in patients with renal insufficiency, cardiovascular disease, gastrointestinal problems
Glucocorticoids	Deltasone (prednisone), Medrol (prednisolone)	0.1-1 mg/kg/day PO	Prefer <7.5-10 mg/day PO		Dose depends on organ involvement and severity; initial dose may be given for 4-6 weeks, then tapered down for maintenance; no standard dose
	Solu-Medrol (methylprednisolone)	100-1,000 mg IV daily × 3			Severe disease; later, dose tapered and changed to PO
Hydroxychloroquine	Plaquenil	400 mg PO daily or 200 mg twice daily	200-400 mg PO daily	Dosing adjustment may be needed with renal or hepatic dysfunction	Dose should not exceed 5 mg/kg/day actual weight to minimize retinopathy risk
Belimumab	Benlysta	10 mg/kg IV every 2 weeks × 3 or 200 mg SC weekly	10 mg/kg IV every 4 weeks or 200 mg SC weekly	Use with caution in African Americans; no data on use in hepatic impairment; no adjustment for renal impairment if CrCl ≥15 mL/min (0.25 mL/s); no studies in pregnant or breastfeeding women	IV infusion over 1 hour; consider premedication to prevent infusion and hypersensitivity reactions; hypersensitivity reactions up to 4 hours after administration; most common with first two infusions
Cyclophosphamide	Cytoxan	500-1,000 mg/m² BSA IV every month × 6 or 500 mg IV every 2 weeks × 6		Dosing adjustment might be needed with renal dysfunction; low and high doses may have equivalent efficacy in white patients with European background	Infertility in women and men, teratogenicity of concern
Mycophenolate mofetil	Cellcept Myfortic (enteric coated mycophenolate sodium)	2-3 g/day PO	0.5-3 g/day PO	Lower doses may be needed in Asians than non-Asians; may be more effective than cyclophosphamide in African Americans and Hispanics	Contraindicated in pregnancy
Azathioprine	Imuran	2 mg/kg/day PO	1.5-2 mg/kg/day PO		Lower dose if thiopurine methyltransferase (TPMT) deficient
Methotrexate	Rheumatrex, Trexall, Otrexup, Rasuvo		15-25 mg PO or SC weekly		Decrease toxicity by giving with folic acid
Rituximab	Rituxan	375 mg/m² BSA IV weekly × 4 or 500-1,000 mg IV on days 1 and 15		Variable doses have been used	Alternative for patients refractory to other treatments; may be more effective in African Americans

BSA, body surface area; CrCl, creatinine clearance; IV, intravenously; NSAIDs, nonsteroidal anti-inflammatory drugs; PO, orally.

TABLE 103-3 Monitoring of Drugs Used to Treat Systemic Lupus Erythematosus

Drug	Adverse Drug Reaction	Monitoring Parameter	Comments
NSAIDs/salicylates	Gastrointestinal bleeding, hepatic toxicity, renal toxicity, hypertension, cardiovascular events, aseptic meningitis	CBC[a], platelets[a], creatinine[a], urinalysis, AST/ALT[a], blood pressure[a]	Antihypertensive effects of calcium channel blockers affected less than other classes
Glucocorticoids, systemic	Osteoporosis, cataracts, glaucoma, hyperglycemia/diabetes, hypertension, dyslipidemia, thinning of the skin, weight gain, fat redistribution, sleep/mood disturbances	Blood pressure[a], serum glucose[a], lipid panel[a], bone densitometry, ophthalmic examinations	Patients should receive osteoporosis preventive therapy; high doses of systemic corticosteroids are associated with infections, myopathy, psychological disturbances, osteonecrosis, and stroke
Glucocorticoids, topical	Skin atrophy, telangiectasias	Skin appearance	Avoid prolonged use, especially of high-potency steroids
Hydroxychloroquine	Retinal toxicity	Funduscopic and automated visual field examinations, consider spectral domain optical coherence tomography, multifocal electroretinogram, or fundus autofluorescence (frequency depends on level of risk), CBC, AST/ALT, albumin, chemistry panel, creatinine	Risk for retinal toxicity increased with doses >5 mg/kg/day actual body weight, more than 5 years therapy, renal or macular disease, or concurrent tamoxifen use
Belimumab	Infusion reactions, hypersensitivity, nausea, diarrhea, fever, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine	Monitor for serious infections, hypersensitivity/infusion reactions, worsening depression, mood changes, or suicidal thoughts	No live vaccines 30 days before or during belimumab therapy; not recommended with other biologics or IV cyclophosphamide; consider premedication with acetaminophen and diphenhydramine
Cyclophosphamide	Myelosuppression, opportunistic infections, hemorrhagic cystitis, bladder malignancy, infertility	CBC[b], platelets[b], creatinine, AST/ALT, urinalysis[b], urine cytology[a], PAP test[a]	Greater risk for cystitis with oral form than IV; decrease with hydration and mesna
Mycophenolate mofetil	Myelosuppression, nausea, vomiting, diarrhea	CBC[c], platelets[c], creatinine, chemistry panel, AST/ALT, chest x-ray	Gastrointestinal side effects may limit use and compliance; these symptoms may be less with use of an enteric-coated form
Azathioprine	Myelosuppression, hepatotoxicity	CBC[c,d], platelets[c,d], creatinine[e], AST/ALT[c,f], chemistry panel[e], albumin, TPMT assay, PAP test	Test thiopurine methyltransferase (TPMT) before starting; toxicity greatly increased if deficient
Methotrexate	Hepatic, hematologic, pulmonary toxicity; stomatitis	CBC[c,g], platelets[c,g], creatinine[c,g], AST/ALT[c,g], albumin[c,g], bilirubin, chemistry panel[h], alkaline phosphatase[c], chest x-ray	Check hepatitis B and C serologies before starting if at risk
Rituximab	Infusion reactions, infections, neutropenia, mucocutaneous reactions, fever, fatigue, progressive multifocal leukoencephalopathy	CBC[i], platelets[i], creatinine, vital signs, human antichimeric antibody (HACA) titers	Consider pretreatment with acetaminophen, diphenhydramine, corticosteroid to decrease infusion reactions

Monitoring parameters should be checked at baseline and at interval noted:

[a]52 weeks

[b]4 weeks

[c]12 weeks

[d]every 1-2 weeks after dose change

[e]26 weeks

[f]every 2 weeks after dose change

[g]2-4 weeks during 3 months after dose change

[h]8 weeks

[i]8-16 weeks.

Source: Data from references 48 and 67; and from Yazdany J, Panopalis P, Gillis JZ, et al. Systemic Lupus Erythematosus Quality Indicators Project Expert Panels. A quality indicator set for systemic lupus erythematosus. *Arthritis Rheum* 2009;61:370-377.

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs are used as first-line treatment for arthritis, musculoskeletal complaints, fever, and serositis.[17] Low-dose aspirin is used in patients with antiphospholipid antibodies.[13] One concern with NSAIDs is that they can decrease renal function, which can complicate evaluation of lupus nephritis. They have the potential to increase cardiac events in patients who already are at elevated risk. Other adverse effects include hepatotoxicity, gastrointestinal (GI) bleeding, and aseptic meningitis.[17]

Corticosteroids

Corticosteroids as monotherapy or as adjuncts to other treatments can control flares and maintain low disease activity in SLE. Their effects have a rapid onset, whereas other therapies may take months or over a year to achieve their maximum benefits. The corticosteroids can be used topically or systemically.

Although corticosteroids have been used in the management of SLE since the 1950s, optimal doses, duration of therapy, and tapering regimens have not been determined. High doses given in a pulse IV administration regimen are used to treat flares and quickly reduce inflammation. Doses should slowly be tapered down to the lowest effective dose.[32] Corticosteroids are the foundation for treatment of most forms of SLE, but it is increasingly being recognized that high-dose oral corticosteroid use is associated with increased lupus organ damage accrual, infection, and death. Oral maintenance doses should be kept as low as possible with pulse methylprednisolone doses used for disease flares and in combination with other drugs that are steroid-sparing.[31]

Common adverse effects of low (prednisone less than 7.5 mg/day) to moderate (7.5-30 mg/day) doses are shown in Table 103-3. Although higher doses may be divided, single morning doses may be associated with fewer adverse effects and less adrenal suppression. Chronic use of any dose is associated with cardiovascular complications, psychological disturbances, glaucoma, cataracts, hyperglycemia, weight gain, avascular necrosis of bone, and osteoporosis.[32] Corticosteroids decrease absorption of vitamin D and increase catabolism of 25(OH) vitamin D and $1,25(OH)_2$ vitamin D. According to the 2017 American College of Rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis, all patients taking prednisone at a dose of 2.5 mg daily or more for at least 3 months should optimize calcium and vitamin D intake in addition to lifestyle changes such as balanced diet,

maintenance of recommended weight, smoking cessation, and limiting alcohol intake. Additional treatment is based on Fracture Risk Assessment Tool (FRAX) score. (Conditional recommendation-limited data).[33] To avoid adrenal insufficiency, patients on chronic corticosteroid therapy should not have treatment stopped abruptly and they may need increased doses at times of stress such as surgery.[45] Prolonged use of topical corticosteroids can lead to atrophy of the skin and telangiectasias (small dilated blood vessels).[23]

Antimalarials

The antimalarials chloroquine and hydroxychloroquine have long been used in rheumatology practice. Hydroxychloroquine is thought to have fewer adverse reactions and is the preferred drug. In the past, hydroxychloroquine was primarily used for skin and joint manifestations of SLE, but most experts believe that all patients, including pregnant women, with SLE should receive hydroxychloroquine. There is high-quality evidence that it can prevent lupus flares and improve long-term survival; moderate-quality evidence that it protects against bone mass loss, and has protective effects against thrombosis and irreversible organ damage.[46] It has a beneficial effect on lipids and fasting blood glucose, decreases the risk of thrombosis in patients with antiphospholipid antibodies, and decreases infections.[31,46] It can allow corticosteroid doses to be decreased.[46] When given to patients with some findings consistent with SLE, it can delay the time for them to fully meet criteria for the disease. Patients receiving hydroxychloroquine often have disease flares when the drug is discontinued.[29]

Hydroxychloroquine has anti-inflammatory, immunomodulatory, and antithrombotic effects. It reduces concentrations of inflammatory cytokines such as interleukins 1, 2, 6, 17, and 22, interferon alpha and gamma, and TNF-α. It alters antigen presentation and T-cell proliferative responses. Its key activity may be decreasing activation of toll-like receptors, which are important in innate immunity and autoimmune diseases. It reduces platelet aggregation and thrombosis.[29] Finally, it may reduce cardiovascular risk factors such as hyperlipidemia and diabetes mellitus and improve survival.[29] The LUMINA (LUpus in MInorities, NAture vs nurture) multiethnic study found that hydroxychloroquine has a protective effect on survival. It may delay the development of renal damage and the occurrence of integument damage (severe skin damage including scarring, ulcers, and scarring alopecia), and decrease accrual of damage.[29,46]

Although some studies showed reduced disease activity and flares with hydroxychloroquine whole blood concentrations over 1,000 ng/mL (mcg/L; 2,980 nmol/L), other studies where doses were adjusted to achieve that concentration did not show better disease control. Studies of cutaneous lupus showed good improvement at 750 ng/mL (mcg/L; 2230 nmol/L), while others considered 500 ng/mL (mcg/L; 1490 nmol/L) to be the minimum therapeutic concentration. It has been suggested that hydroxychloroquine concentration monitoring be used as a measure of adherence to therapy.[47] The drug is primarily eliminated by the kidneys and has a long tissue half-life of about 40 to 50 days. Low concentrations may therefore be an indicator of consistent nonadherence or abnormal metabolism.[47] It may take 2 to 8 weeks to see the therapeutic effects of hydroxychloroquine and up to 3 to 6 months for maximum clinical efficacy.[47]

Adverse effects with hydroxychloroquine are usually mild. Most common are GI and skin reactions and they usually improve with dose reduction.[29] The main concern is retinal toxicity, but the incidence is low and may be less than that seen with chloroquine. The incidence is less than 1% in patients receiving the drug at recommended doses for 5 years and less than 2% up to 10 years. Major risk factors are duration of use over 5 years, daily doses more than 5 mg/kg actual body weight, concurrent use of tamoxifen, or patients with kidney dysfunction or preexisting macular disease. Advanced retinal damage has a characteristic bull's-eye appearance on funduscopic examination and is irreversible, but this should not be seen with appropriate monitoring. Patterns of damage are different in Asians. Early recognition of damage may minimize vision loss. The current American Academy of Ophthalmology monitoring recommendations are to have several baseline screening tests within the first year including fundus examination and if maculopathy is present, visual fields and spectral domain optical coherence tomography (SD OCT). After 5 years, patients should begin annual examinations unless the patient is considered to be at high risk, in which case yearly testing would begin earlier. Tests include automated visual fields and SD OCT, and, if needed, other tests such as multifocal electroretinogram and fundus autofluorescence. If toxicity is suspected, the drug should be stopped or the patient counseled about risks of blindness versus disease flares.[48]

Biologic Agents

Since autoantibody formation is an important feature of SLE, B cells are a logical target for SLE therapy. B-lymphocyte stimulator (BLyS) is a cytokine that is important for B cell survival, maturation, and differentiation. Belimumab is a fully human IgG1-λ monoclonal antibody that binds to soluble BLyS, which

prevents BLyS from binding to receptors on B cells and promotes apoptosis of B lymphocytes. Belimumab is FDA-approved for treatment of autoantibody-positive active SLE in addition to standard therapy. It is the first drug approved by the FDA in over 50 years for management of SLE.[49] Approval of belimumab was based on two international phase III trials: BLISS-76, conducted primarily in Western Europe and North America, and BLISS-52, which was carried out in Eastern Europe, Latin America, and the Asia-Pacific region. These trials had strict entry criteria and used the new SLE Responder Index (SRI) assessment criteria. For both studies, the primary efficacy endpoint was the SRI at 52 weeks. Entry requirements included positive ANA or anti-dsDNA, and active SLE (SELENA-SLEDAI [measure of disease activity] score of 6 or greater) while receiving standard treatment (prednisone, NSAIDs, antimalarials, and/or immunosuppressive drugs [but not IV cyclophosphamide or other biologics]). Patients had to be on stable therapy for at least 30 days. The most common organ systems involved were musculoskeletal and mucocutaneous. Patients with severe active lupus nephritis or CNS lupus were excluded. Patients received belimumab 1 mg/kg, 10 mg/kg, or placebo by IV infusion every 2 weeks for two doses, then every 4 weeks, in addition to their standard therapy. There were restrictions on concomitant medications, and those became stricter as the studies progressed. The response rate was significantly higher in the group receiving belimumab 10 mg/kg as compared to placebo in both studies.[49] Patients receiving belimumab also had greater improvement in health-related quality of life.[14] Patients of African descent did not appear to benefit from belimumab. Subsequent experience from academic clinical practice found favorable responses to belimumab in all racial and ethnic groups and ongoing studies are further exploring this.[50]

Rituximab is a chimeric monoclonal antibody directed at the CD20 antigen on B cells.[51] Although many case reports and open-label trials have reported beneficial effects of rituximab in SLE, randomized, placebo-controlled trials of rituximab have not demonstrated efficacy in SLE. The largest of these were the EXPLORER (Efficacy and Safety of Rituximab in Moderately-to-Severely Active Systemic Lupus Erythematosus) trial which evaluated patients with extrarenal involvement treated with rituximab and immunosuppressive drugs and the LUNAR (LUpus Nephritis Assessment with Rituximab) trial that examined use of rituximab with mycophenolate mofetil and corticosteroids in patients with lupus nephritis. Failure to show significant benefit could be due to the short duration of the trials or the choice of endpoints. Further improvement has been observed in the second year of therapy. Exploratory analyses of specific patient

subgroups or use of different response criteria suggested some benefit. Rituximab may be more effective in patients of African descent and Hispanics with lupus nephritis than those of other races, or in combination with cyclophosphamide instead of mycophenolate mofetil.[51–53] In a small lupus nephritis study of rituximab with mycophenolate mofetil and pulse doses of methylprednisolone, about half the patients achieved complete renal remission without using oral corticosteroids.[54] It may serve as an alternative therapy in treatment of refractory lupus nephritis, severe hematological lupus, and some CNS manifestations of the disease. It may also prove useful for maintenance therapy, as a steroid-sparing agent, or when preservation of fertility is desired.[51]

Other drugs targeting B cells are being investigated in SLE. Examples of these are blisibimod, which inhibits soluble and membrane BLyS, and atacicept which blocks both BLyS- and APRIL (a proliferation-inducing ligand)–mediated B cell stimulation. Sifalimumab and anifrolumab target type 1 interferons. Other biologic agents have been tried in SLE with varying degrees of success, such as abatacept, which inhibits T-cell costimulation. The observed efficacy of drugs may depend on the definition of response used. Interestingly, a study of abatacept for lupus nephritis failed to show efficacy, but when other investigators applied endpoint criteria used in different studies of the disease to that data, very different results were observed.[54]

As discussed later, there is concern about TNF-α inhibitors inducing lupus. However, short-term induction therapy with infliximab may confer long-lasting benefits in patients with lupus nephritis. When TNF-α inhibitors are used to treat lupus arthritis, patients respond but relapse within a few months after the drug is stopped.[55] Good results have been observed with etanercept as long-term treatment of refractory lupus arthritis.[56] Biologic drugs should not be combined. There are, however, ongoing trials of rituximab with cyclophosphamide followed by belimumab for lupus nephritis.[54]

Immunosuppressive Drugs

Cyclophosphamide has long been used to treat severe organ involvement in SLE such as lupus nephritis, neuropsychiatric lupus, and severe systemic vasculitis.[17] Its role in therapy is being redefined because of the availability of newer drugs, as discussed elsewhere in this chapter. Response rate and dosing requirements may vary with patient race. Cyclophosphamide is an alkylating agent that causes cross-linkage of DNA leading to cell death. It may also suppress B cells and IgG production and decrease production of adhesion molecules and cytokines.

Cyclophosphamide has an oral bioavailability of 75% to 100%. It is a prodrug that is metabolized to active and inactive metabolites via the cytochrome P450 enzyme system. Cyclophosphamide is primarily cleared by the liver, but its active metabolites may persist in renal failure.[57]

Cyclophosphamide can potentially cause hemorrhagic cystitis and bladder cancer due to acrolein, a metabolite of the drug that concentrates in the bladder. The risk appears to be greater with oral administration, higher cumulative doses, and in smokers. The association with intermittent pulse IV doses in SLE patients is less clear. Hydration and frequent voiding may decrease the risk of these adverse effects. With oral administration, patients are advised to take the drug in the morning and to drink fluids for several hours. Adherence is not good with this regimen. With IV administration, IV fluids are begun before administration of the cyclophosphamide and continued for several hours after. Patients are encouraged to maintain oral hydration for 72 hours. Another method to decrease bladder toxicity is to use sodium-2-mercaptoethane sulfonate (mesna), which binds acrolein and prevents its harmful effects on the bladder. Although mesna is sometimes used with high-dose cyclophosphamide, it is only FDA-approved for use with ifosfamide. Use of mesna with daily oral cyclophosphamide is expensive and inconvenient based on available dosage forms. The recommended mesna regimen with IV pulse doses of cyclophosphamide is to give IV doses, each equivalent to 20% of the cyclophosphamide dose, 15 to 30 minutes before the cyclophosphamide, then 4 and 8 hours after. Since oral mesna is about 50% bioavailable, the 4- and 8-hour mesna doses after cyclophosphamide may be given orally, each in doses equivalent to 40% of the administered dose of cyclophosphamide.[57] In practice, a variety of mesna regimens are used. The effectiveness of mesna for uroprotection in patients receiving cyclophosphamide for rheumatologic diseases has been questioned.[58]

Mycophenolic acid (MPA) reversibly inhibits the enzyme inosine 5-monophosphate dehydrogenase (IMPDH), which is important for de novo synthesis of purine (guanosine) nucleotides. This inhibits lymphocyte proliferation, chemotaxis, and antibody production. Genetic polymorphisms of the IMPDH proteins may influence the effects of MPA, but they are not well enough understood to recommend routine measurement.[47] The drug also has other immunomodulating effects such as induction of activated T-cell apoptosis, inhibition of adhesion molecule expression, and antifibrotic and antiproliferative effects on cells such as fibroblasts, dendritic cells, and vascular smooth muscle cells.[59]

Mycophenolate mofetil is about 94% absorbed and is hydrolyzed to MPA, its

active form. MPA is bound to albumin, so unbound drug concentrations can be affected by changes in albumin. MPA is glucuronidated in the liver to an inactive metabolite, mycophenolic glucuronide. The metabolite is excreted in the urine but also undergoes enterohepatic recycling, with conversion back to the active form. Some studies have shown better lupus nephritis response to MPA with higher trough concentrations or 12-hour MPA areas under the curve, but optimal values have not been determined and these did not correlate with toxicity, so measurement is not common practice.[47]

Mycophenolate mofetil has been most studied in the treatment of lupus nephritis. It has been shown to be at least as effective as cyclophosphamide for induction therapy and as azathioprine for maintenance treatment.[60,61] The Aspreva Lupus Management Study (ALMS) was a multinational study of lupus nephritis in 370 patients. The 6-month induction phase showed mycophenolate mofetil to be equivalent in efficacy to monthly IV pulse doses of cyclophosphamide, including in a small group of patients with an estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m^2.[59] The response to therapy at 6 months correlated with the baseline complement C4 concentration, time since diagnosis of lupus nephritis, and eGFR. Normalization of complement C3 and/or C4 and reduction in proteinuria of at least 25% at 8 weeks also predicted renal improvement at 6 months.[62] Responders at 6 months entered a 36-month maintenance phase in which mycophenolate mofetil was superior to azathioprine in maintaining renal response to treatment and preventing disease relapse. Although adverse events occurred in more than 97% of patients in both groups, more patients receiving azathioprine withdrew from the study due to toxicity than those receiving mycophenolate mofetil.[63] The MAINTAIN trial did not find a difference in the rate of renal flare with mycophenolate mofetil compared to azathioprine 5 and 10 years after induction with low-dose IV cyclophosphamide. The difference in these results compared to the ALMS trial may be due to the difference in induction therapy, selection of patients for the maintenance phase, and in populations studied. The MAINTAIN trial studied 105 predominantly (83%) white European patients, whereas the larger ALMS trial included a more racially diverse population (56% non-Caucasians). The MAINTAIN trial did find a correlation between achieving a proteinuria value of less than 0.5 g/day at 12 months and good long-term renal outcome.[64]

Mycophenolate mofetil may also be useful for nonrenal manifestations of SLE such as arthritis, cutaneous lupus, and hematologic and cardiorespiratory involvement, and can be steroid sparing.[65]

The most common adverse effects observed with mycophenolate mofetil are infections and GI, including nausea, vomiting, and diarrhea. These may be severe enough to require discontinuation of therapy. Hematologic effects such as red cell aplasia may also be seen. The side effects may be diminished with a reduction in dose.[59] Use of an enteric-coated form of mycophenolate sodium may decrease GI symptoms.[65] Numerous congenital malformations have been reported with mycophenolate mofetil and it is contraindicated in pregnancy.[65]

Azathioprine is a purine analog that is metabolized to mercaptopurine. It inhibits nucleic acid synthesis and affects cellular and humoral immune functions.[17,66] Mercaptopurine is inactivated by thiopurine methyltransferase (TPMT). Patients should have TPMT testing before receiving azathioprine.[64] If the activity of that enzyme is low, patients may experience more severe toxicity. Myelosuppression and GI adverse effects correlate with TPMT polymorphism, but hepatotoxicity may not. Other metabolic pathways are also involved in the elimination of azathioprine.[66] The metabolism of azathioprine and mercaptopurine is inhibited by allopurinol and febuxostat. If the combination of these drugs is to be used, a reduction in dose is required.[67] Azathioprine is less effective than cyclophosphamide for induction therapy in lupus nephritis, but it can be useful as an alternative to mycophenolate mofetil for maintenance treatment.[5] Azathioprine may also be used for SLE-related arthritis, serositis, and mucocutaneous manifestations. It has steroid-sparing effects, allowing use of lower doses of corticosteroids.[17]

Methotrexate is an inhibitor of dihydrofolate reductase, which is needed for DNA synthesis and cell proliferation.[30] Its toxicities are reduced by folic acid administration. It is important to note that it is dosed once weekly in the management of SLE. It is used for arthritis and skin disease and as a steroid-sparing drug.[17]

Numerous other immunosuppressive drugs have been used in SLE, especially in patients who have contraindications to use of the agents already discussed or who cannot tolerate them, or those whose disease is refractory to conventional treatment.

Alternative Treatments

Studies have shown that SLE patients receiving conventional treatment frequently feel they have unmet needs. Often these are psychosocial and may include anxiety or depression. These needs can lead patients to try alternative therapies. It is important for healthcare providers to have an open dialogue with

patients about these therapies so that patients will report them. This allows practitioners to monitor for interactions with other treatments and to guide patients to therapies with greater potential for benefit and less for harm.[68]

Complementary and alternative medicine includes health systems, products, and practices that are outside the realm of conventional medicine. In general, these have not been evaluated in randomized controlled trials involving SLE patients.[68]

Concentrations of dehydroepiandrosterone (DHEA), a weak adrenal androgen, are typically decreased in SLE. Some small studies have suggested that DHEA supplementation may offer some limited benefit for patients' assessment of disease activity, steroid effects on bone mineral density, and time to flares in SLE.[68]

Vitamin D concentrations are decreased in SLE, especially in patients with high disease activity and those with darker skin pigmentation (eg, African Americans). A contributing factor to the deficiency is that patients are told to protect themselves from sunlight because of the photosensitivity that accompanies SLE.[69] Another factor may be polymorphisms in the gene that is involved in vitamin D degradation. Vitamin D deficiency is associated with high concentrations of inflammatory cytokines. Deficiencies not only affect bone health, but some studies show that low concentrations of vitamin D may also be associated with greater SLE disease activity, insulin resistance, and fatigue.[70] Low concentrations also correlate with increased cardiovascular risk factors such as hypertension and hyperlipidemia. B and T lymphocytes, dendritic cells, macrophages, and neutrophils have vitamin D receptors, which suggests a role for vitamin D in both innate and adaptive immune processes.[70] Some experts suggest that most patients with SLE should receive vitamin D supplements of at least 400 IU/day of vitamin D3, and those on glucocorticoids for 3 months or more, 600 to 800 IU/day.[24,33] One recommendation is to check a baseline 25(OH) vitamin D concentration with a current goal of 30 ng/mL (75 nmol/L). An optimal goal has not yet been determined.[70] The concentration should be rechecked 3 months after a change in vitamin D dosing since that is the time required to reach steady state.[71]

Special Populations

Pregnancy and Contraception

7 Pregnancy planning with assessment of risk factors is key for achieving good

outcomes for women with SLE and healthy babies. EULAR issued recommendations for women's health, pregnancy, reproduction, and menopause for patients with SLE with or without antiphospholipid antibodies.[72] Timing of pregnancies with respect to disease activity and use of teratogenic medications makes contraception counseling very important. Women should be educated about fertility issues related to age and effects of alkylating agents.[72] Cyclophosphamide therapy is associated with ovarian failure and infertility. This is especially of concern in older women who wish to conceive.[5] Estrogen-containing oral contraceptives or hormone replacement therapy are associated with thrombosis, especially in women with antiphospholipid antibodies or other risk factors. However, combined estrogen-progestin or progestin-only oral contraceptives can be offered to women whose SLE is inactive or stable active and who do not have antiphospholipid antibodies. (1/A rating for level of evidence and grade of recommendation)[72] Hormone replacement therapy may be considered for women with severe symptoms of menopause who have stable/inactive disease and do not have antiphospholipid antibodies. (1/A rating)[72] Although SLE flares have been a concern with use of hormonal contraceptives, recent studies in mild-to-moderate disease did not show such an association, but the results may be influenced by study inclusion and exclusion criteria.[73] Progestin-only contraceptives may be used but the adverse effects of acne, hirsutism, and abnormal bleeding may make them less desirable and the risk of osteoporosis increases after 2 years of use.[73,74] Intrauterine devices may be better choices for contraception.[72]

Pregnancy during SLE is considered to be high risk. The risk of maternal mortality, cesarean delivery, preterm labor, and preeclampsia and the risk of thrombotic, infectious, and hematologic complications are increased.[30,75] Fetal loss, intrauterine growth restriction, and early preeclampsia may relate to uterine-placental insufficiency with poor placental blood flow.[76] Preeclampsia occurs in 16% to 30% of women with SLE and is defined as hypertension and proteinuria (greater than 300 mg/24 hr) that develop for the first time after 20 weeks of gestation.[75,77] This can be difficult to distinguish from lupus nephritis. The risk for preterm preeclampsia may be decreased by 90% with daily use of low-dose aspirin begun before 16 weeks' gestation.[76] Flares during pregnancy may be difficult to identify since they may share characteristics of a normal pregnancy.[75] The complications are more likely in patients with active disease, especially lupus nephritis. If the mother has anti-Ro/SSA or anti-La/SSB antibodies, the fetus is at risk for neonatal lupus with rash, hematologic, hepatic,

and cardiac abnormalities including heart block. These risks are significantly decreased with continued use of hydroxychloroquine.[75] Treatment of pregnant women with antiphospholipid antibodies is discussed below. Pregnancy should be discouraged in patients with severe pulmonary hypertension, advanced renal insufficiency, severe restrictive lung disease, heart failure, or a history of severe preeclampsia. It also is not advised within 6 months of a severe SLE flare, active lupus nephritis, or a stroke. The best pregnancy outcomes are observed in patients who have had inactive disease for at least 6 months prior to the pregnancy. Drugs used to control the SLE should be those such as hydroxychloroquine, which can be continued throughout the pregnancy and may decrease the incidence of flares, disease activity, and risk of heart block in at-risk pregnancies.[75] Any potentially teratogenic drugs (eg, methotrexate, leflunomide, mycophenolate, cyclophosphamide, and thalidomide) should be stopped at least 3 months before attempting pregnancy.[78] Leflunomide should be removed through the oral cholestyramine elimination procedure (8 g three times a day for 11 days with confirmation of undetectable serum concentrations) prior to conception.[75] Close monitoring and disease management of the mothers and fetuses are essential during pregnancy. The risks of drug use and harmful effects of disease flare both need to be considered.[72] If a flare occurs and an immunosuppressive drug is required during the pregnancy, azathioprine may be considered, since the fetal liver is unable to metabolize it to its active form. The dose should not exceed 2 mg/kg/day.[79] Calcineurin inhibitors (cyclosporine, tacrolimus) are alternative choices. Supplements with calcium, vitamin D, and folic acid should be offered.[72] If corticosteroids are needed, maintenance doses should be kept as low as possible to decrease the risk of gestational diabetes mellitus, hypertension, infections, and premature rupture of membranes.[75] Patients on long-term steroid therapy may need stress doses at the time of delivery. Fluorinated corticosteroids (such as dexamethasone or betamethasone) should be avoided unless they are being used to treat the fetus, since they cross the placenta.[78] Cyclophosphamide should only be used during the second or third trimester of pregnancy if alternatives failed and the mother’s life is in danger.[72] If treatment of hypertension is needed, methyldopa, labetalol, nifedipine, or hydralazine are preferred, although there are concerns about growth retardation with labetalol and impaired uteroplacental blood flow with hydralazine.[78] Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may cause fetal malformations, neonatal arterial hypertension, and renal failure.[78] Diuretics are generally avoided but if one is needed, furosemide is preferred.[80] NSAIDs should be used with caution during early

pregnancy. Congenital malformations have been reported with use in the first trimester and impaired fetal renal function after 20 weeks. They should not be used after 32 weeks of gestation because they increase the risk of premature closure of the ductus arteriosus by almost 15-fold.[78] Data on the safety of biologics are limited. First trimester use of belimumab does not appear to be harmful. Rituximab given during the second or third trimester can cause neonatal B cell depletion and should be avoided.[81]

SLE–Antiphospholipid Syndrome Overlap

8 The antiphospholipid antibodies consist of anticardiolipin, anti-β-2-glycoprotein I, and lupus anticoagulant and others have been proposed. They can promote clotting and pregnancy morbidity.[82] Complement also plays a key role in antiphospholipid syndrome (APS) pathogenesis.[13] The diagnosis of APS requires at least one clinical and one laboratory feature. The clinical aspects are vascular events such as venous or arterial thrombi and/or obstetric complications. The obstetric complications meeting the criteria are three or more unexplained consecutive miscarriages before the 10th week of gestation, one or more unexplained deaths of fetuses at or beyond the 10th week of gestation, and one or more births of infants before the 34th week of gestation associated with eclampsia or severe preeclampsia or features of placental insufficiency.[83] Adverse pregnancy outcomes after 12 weeks of gestation are especially associated with the presence of lupus anticoagulant.[84] Laboratory criteria are the presence of antiphospholipid antibodies on two separate occasions, 12 weeks apart.[83] Antiphospholipid antibodies are found in about 40% of patients with SLE, but less than 40% of those experience thrombotic events.[13] Patients with lupus anticoagulant or persistently positive anticardiolipin at medium-high titers are at high risk for thrombosis, and those with all three antibodies (triple positivity) are at highest risk. Patients with isolated, intermittently positive anticardiolipin or anti-β_2-glycoprotein I at low-medium titers are considered to be at low risk. Patients with thrombosis often have other cardiovascular risk factors (such as hypertension, hyperlipidemia, smoking, or use of estrogen-containing medications) or an underlying autoimmune disease such as SLE. It is recommended that any modifiable factors be controlled. In deciding choice, intensity, and duration of treatment, the clinician should balance benefits with the patient's risk of bleeding. Consideration should also be given to whether thrombotic events are associated with identified transient precipitating factors. An international group of physicians who had clinical and research experience

with APS reviewed the literature and developed consensus guidelines for management of thrombosis in patients with antiphospholipid antibodies (**Table 103-4**).[42] A EULAR Task Force is developing new management recommendations that consider individual risk assessments.[82]

TABLE 103-4 Recommendations for Thromboprophylaxis in Patients with Systemic Lupus Erythematosus and Antiphospholipid Antibodies

Recommendation	Grade of Recommendation
1. General measures for aPL carriers	
Control cardiovascular risk factors if high-risk aPL profile	Nongraded
Thromboprophylaxis with low molecular weight heparin in high risk situations such as surgery, prolonged immobilization, and after childbirth	1C
2. Primary thromboprophylaxis	
Regularly assess patients for presence of aPL	Nongraded
Thromboprophylaxis with hydroxychloroquine (1) and low-dose aspirin (2) for patients with positive LA or persistent aCL at medium-high titers	1B (1) 2B (2)
3. Secondary thromboprophylaxis	
Treat patients with arterial or venous thrombosis and aPL who do not meet APS criteria with standard thrombosis treatment	1C
Treat patients with definite APS and first venous event with warfarin to target INR 2-3	1B
Treat patients with definite APS and arterial thrombosis with warfarin at INR greater than 3 or combined antiaggregant-warfarin (INR 2-3) therapy	Nongraded
Assess bleeding risk before high-intensity warfarin or combined antiaggregant-warfarin therapy	Nongraded
4. Duration of treatment	
Indefinite antithrombotic therapy in patients with definite APS and thrombosis	1C
For first venous event, low-risk APS profile and known transient precipitating factor, anticoagulate for 3-6 months	Nongraded
5. Refractory and difficult cases	
If recurrent thrombosis, fluctuating INR, major bleeding or high risk for major bleeding, consider an alternative such as low molecular weight heparin, hydroxychloroquine, or statins	Nongraded

aPL, antiphospholipid antibodies; LA, lupus anticoagulant; aCL, anticardiolipin; APS, antiphospholipid syndrome; INR, international normalized ratio.

Grades of recommendation: 1B: Strong recommendation, moderate-quality evidence, 1C: Strong recommendation, low or very low-quality evidence; 2B: Weak recommendation, moderate-quality evidence

Adapted with permission from Reference 42.

Patients with antiphospholipid antibodies may also have a false-positive test for syphilis (rapid plasma reagin).[18] Other common manifestations of APS are cognitive impairment, thrombocytopenia, stroke or transient ischemic attack, chorea, migraine, glomerulonephritis, avascular necrosis of bones, heart valve lesions, and livedo reticularis.[82]

It is not clear how to treat pregnant women with antiphospholipid antibodies. Those with no history of thrombosis who have experienced early fetal loss may be treated with low-dose aspirin (75-100 mg) alone or in combination with prophylactic doses of heparin or low-molecular-weight heparin.[82] Not only does heparin have anticoagulant effects, but it also has anti-inflammatory and immunomodulating properties and can inhibit complement activation.[85] Hydroxychloroquine should also be considered. Those without thrombosis who have had later miscarriages or premature births associated with preeclampsia or placental insufficiency may receive low dose aspirin plus prophylactic or intermediate doses of heparin or prophylactic doses of low-molecular-weight heparin. Pregnant patients with APS and a history of thrombosis should receive low-dose aspirin with therapeutic doses of heparin or low-molecular-weight heparin.[82] Warfarin is teratogenic and should be avoided during pregnancy; especially during the first trimester.[75] If low-molecular-weight heparin is used, it should be switched to unfractionated heparin 4 weeks before the anticipated delivery date. The heparin should be stopped at the start of labor or 8 hours before a planned cesarean delivery.[80] All women with APS should receive anticoagulation with prophylactic doses of heparin, low-molecular-weight heparin, or warfarin for 6 weeks postpartum. Women without thrombosis risks may benefit from just 7 to 10 days of low-molecular-weight heparin.[82] Both heparin and warfarin are safe during breastfeeding.[13]

Better control of APS can be achieved by adding hydroxychloroquine, statins, and vitamin D to standard therapy.[13] For patients who do not respond to conventional APS treatment or for whom it is contraindicated, alternative therapies include other platelet inhibitors, corticosteroids, rituximab, and the complement inhibitor, eculizumab. The role of direct-acting oral anticoagulants is not yet clear. There is concern about their adequacy of effects for arterial thrombi.[82]

The most severe form of APS is called catastrophic and is associated with widespread thrombosis, multiorgan failure, and up to 48% mortality.[82]

Drug-Induced Lupus

About 10% to 15% of cases of SLE can be attributed to drugs.[86] There are about 15,000 to 30,000 new cases each year in the United States.[9] These are idiosyncratic reactions precipitated by the interplay of genetic predisposition, concurrent illnesses, environmental factors, and other drugs or foods. Various pathophysiologic mechanisms have been proposed for different drugs in inducing lupus. Most drugs are small molecules that can induce an immune response by binding to larger molecules such as proteins, a process called haptenization. Another proposed mechanism is interfering with macrophage uptake of apoptotic or necrotic cells, leading to accumulation of self-antigens. A more recently described pathway is stimulation of neutrophil extracellular traps (NETs; NETosis), a form of neutrophil cell death that also results in self-antigens that stimulate autoreactive T or B cells.[87] Other proposed mechanisms are altered T-cell function due to DNA hypomethylation and interference with T-cell maturation.[86]

Because the manifestations of drug-induced lupus are so diverse, there are no standard diagnostic criteria. The diagnosis is based on lupus-like findings in a patient with no history of the disease and the temporal relationship with the drug, including onset at least one month after initiation and improvement in symptoms within days to months after the drug is discontinued. The time frame, however, can be variable. The patient will often have laboratory findings such as a positive ANA or anti-histone antibodies, but usually not anti-dsDNA or anti-Sm antibodies.[86]

Many drugs of varied classes have been implicated. The drugs considered to have the highest risk for inducing traditional symptomatic drug-induced lupus are procainamide (20%) and hydralazine (5%-8%), especially with hydralazine doses over 200 mg/day or a cumulative dose of more than 100 g.[86] It is more common in patients who are slow acetylators.[87] The incidence of positive ANAs with these drugs is 80% to 90% and 50% respectively.[86] Common manifestations include arthralgias, arthritis, and myalgias. Constitutional symptoms such as fever, fatigue, anorexia, and weight loss are common.[9] Other clinical features include rash, pleuritis, pericarditis, and autoimmune hepatitis. Glomerulonephritis, CNS disease, and hematologic abnormalities are rare in drug-induced lupus.[9] The incidence and types of reactions vary depending on the offending drug. Laboratory abnormalities associated with drug-induced lupus include positive ANA (90%-100%) and antibodies to histones (90%-95%). Other antibodies such as anti-Sm, anti-dsDNA, and antineutrophil cytoplasmic

antibodies (ANCA) may be seen with some drugs. A drug with moderate risk for lupus is quinidine. The incidence of quinidine- and procainamide-induced lupus is declining because of decreased prescribing of the drugs and use of lower doses. The other over 100 drugs of many different classes that have been implicated are considered to be of low risk. Other drugs with well-established links to lupus are minocycline, isoniazid, methyldopa, carbamazepine, and chlorpromazine.[9] A variant of the syndrome is drug-induced subacute cutaneous lupus, which has been associated with calcium channel antagonists, thiazide diuretics, angiotensin-converting enzyme inhibitors, leflunomide, TNF inhibitors, chemotherapeutic agents, statins, interferon, terbinafine, and, most recently, proton pump inhibitors.[9,87,88] The mean age for this syndrome is 59 years; more patients are women, and positive ANA, anti-Ro/SSA, and anti-La/SSB are common. It may occur after weeks to years of therapy.[87] Chronic cutaneous lupus has been reported with fluorouracil, capecitabine, and NSAIDs.[87,88] Drug-induced lupus can take weeks to months for skin lesions to resolve after the offending drug has been stopped.[9]

A separate category of drug-induced lupus is that involving TNF-α inhibitors, such as infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol.[9] This is called TAILS or TNF-α inhibitor-induced lupus syndrome. These drugs, especially chimeric infliximab, are known to induce autoantibodies. Other theories explaining the mechanism for TNF-α inhibitor-induced lupus are that they induce cell apoptosis, increase the risk for bacterial infection, or suppress T-helper 1 immune response and favor T-helper 2 response. It is common for patients receiving these drugs to develop positive ANAs, anti-dsDNA of the IgM subtype, and extractable nuclear antibodies. Antihistone antibodies are less commonly seen than with other drug-induced lupus (17%-57%). As with traditional drug-induced lupus, the incidence of clinical lupus is low compared to the numbers that develop autoantibodies.[86] Rashes and hypocomplementemia are more common features with TNF-α inhibitors than traditional drug-induced lupus.[88] Arthralgias, arthritis, fever, and weight loss are also seen. Renal, hematologic, and neurologic disorders are rare.[9] The underlying diseases being treated with these drugs may be a factor in the development of the observed reactions.

The primary treatment for drug-induced lupus is stopping the implicated drug. Some patients require treatment with corticosteroids or other topical or systemic drugs based on the type and severity of the manifestations. If patients do not improve, a diagnosis of idiopathic SLE should be considered.[9]

Immunizations

Patients with SLE are at increased risk for infections because of immune dysfunction caused by the disease itself and the immunosuppressive therapy the patients receive. It is important to try to protect patients against these infections, but there are areas of concern regarding the safety and efficacy of vaccines in patients with SLE. SLE cases developing or flaring after vaccine administration have been reported, but the actual risk appears low when considering how many people receive immunizations.[89] These reactions may be a response to adjuvants added to increase the immunogenicity of vaccines and could be part of the syndrome called "ASIA—Autoimmune/inflammatory Syndrome Induced by Adjuvants."[90] Another concern is that immunosuppressed patients may have an impaired response to vaccines as compared with healthy individuals. This can be assessed by checking titers after immunization. Revaccination may be needed in some cases. Whenever possible, to achieve the best response, vaccines should be administered when SLE is stable and prior to initiating immunosuppressive medications. Killed vaccines are considered safe in immunosuppressed patients. It is recommended that SLE patients receive pneumococcal vaccine because they are particularly susceptible to *Streptococcus pneumoniae* infections. They should also receive annual influenza vaccines. Hydroxychloroquine may improve the response to vaccines and decrease the risk of infections. Patients with splenectomy should receive Haemophilus influenzae and meningococcal vaccines. Those considered to be at risk should be immunized against hepatitis B.[89] Live-attenuated virus vaccines, such as measles–mumps–rubella, varicella, zoster, intranasal influenza, and yellow fever, are contraindicated in patients receiving biologic agents. They should be avoided with consideration of risks versus benefits in patients taking high doses of other immunosuppressive drugs.[91] Doses of corticosteroids equivalent to prednisone 20 mg/day or more given for at least 2 weeks are considered immunosuppressive.[92] Inactivated vaccines should preferably be given 2 weeks before starting immunosuppressive drugs.[93] Live vaccines should be given at least 4 weeks before starting immunosuppressive drugs or 1 month after stopping them, depending on the duration of drug effects.[91,92] The recombinant zoster vaccine can be given during therapy with immunosuppressive drugs but should not be given during pregnancy. The same pregnancy delay should be observed for live vaccines and the human papilloma vaccine. The meningococcal serogroup B vaccine should only be given during pregnancy if benefits outweigh risks.[92]

EVALUATION OF THERAPEUTIC OUTCOMES

10 Patients must be assessed for the activity and extent of lupus and monitored for adverse drug effects. Monitoring for specific drugs is listed in Table 103-3. Many instruments have been developed and modified over the years to assess SLE therapy in trials. It is difficult to assess SLE therapy because milder forms of the disease may fluctuate, regardless of treatment. Examples of measures of disease activity include the Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI), and British Isles Lupus Assessment Group (BILAG). The SELENA-SLEDAI is a measure of disease activity that scores the severity of 24 manifestations. BILAG measures clinical disease activity in eight organ systems compared to the prior assessment. The organ domains are given scores of A-E based on severity with A being severe. Updates of these instruments are the SLEDAI-2K and the BILAG-2004. Individually, these indices were inadequate for showing superiority of new drugs over standard therapy. To overcome this problem, belimumab investigators developed the SRI assessment criteria. The SRI has three components: (a) Reduction in disease activity by SELENA-SLEDAI by at least 4 points; (b) No new BILAG A (severe disease activity) and no more than one new BILAG B score; and (c) less than 0.3 point increase (worsening) in physician global assessment (PGA). The PGA assesses patients' general health status.[94] Another important assessment of therapy is health-related quality of life (HRQoL), which may use a tool such as the generic 36-item Health Survey Short Form (SF-36).[22]

A British Society for Rheumatology working group developed guidelines for managing SLE in adults. Patients should regularly be evaluated for SLE manifestations, drug toxicity, and comorbidities. Those with active disease should be assessed at least every 1 to 3 months with blood pressure, urinalysis, renal function, anti-dsDNA antibodies, complement concentrations, C-reactive protein, complete blood count, and liver function tests with further testing as warranted. Clinical and laboratory assessments should be performed every 6 to 12 months in patients with inactive disease and no organ damage, and more frequently if abnormalities are found.[95]

The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) may be used to assess disease activity and damage in cutaneous lupus erythematosus and response to therapy.[94]

Postclass Engaged Learning Activity

A female patient in her twenties comes to see you. She has had multiple miscarriages and has not been feeling well, physically and emotionally. She went to see a physician and had tests done. She was told that she has SLE and antiphospholipid antibodies. She asks you what kind of drug therapy she might need to take and what the considerations are for the different agents. She also wants to know about any lifestyle changes she needs to make and what drug and disease considerations there are if she decides to try again to get pregnant.

ABBREVIATIONS

ACR	American College of Rheumatology
ALMS	Aspreva Lupus Management Study
ANA	antinuclear antibody
ANCA	antineutrophil cytoplasmic antibodies
Anti-dsDNA	anti-double-stranded DNA
APRIL	a proliferation-inducing ligand
APS	antiphospholipid syndrome
BAFF	B cell activating factor of the TNF family
BILAG	British Isles Lupus Assessment Group
BLyS	B-lymphocyte stimulator
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CNS	central nervous system
DHEA	dehydroepiandrosterone
DNA	deoxyribonucleic acid
eGFR	estimated glomerular filtration rate
EULAR	European League Against Rheumatism
G6PD	glucose-6-phosphate dehydrogenase
HRQoL	health-related quality of life
IMPDH	inosine 5-monophosphate dehydrogenase
IL	interleukin

La/SSB	antigen La/Sjögren syndrome B antigen
Mesna	sodium-2-mercaptoethane sulfonate
MHC	major histocompatibility complex
MPA	mycophenolic acid
NET	neutrophil extracellular trap
NMDA	*N*-methyl-D-aspartate
NSAID	nonsteroidal anti-inflammatory drug
PGA	physician global assessment
Ro/SSA	antigen Ro/Sjögren syndrome A antigen
SD OCT	Spectral domain optical coherence tomography
SELENA-SLEDAI	Safety of Estrogens in Lupus Erythematosus: National Assessment-Systemic Lupus Erythematosus Disease Activity Index
SF-36	Medical Outcomes Survey Short Form-36
SLE	systemic lupus erythematosus
SLICC	Systemic Lupus International Collaborating Clinics
SPF	sun protection factor
SRI	SLE Responder Index
TAILS	TNF-α inhibitor-induced lupus syndrome
TNF-α	tumor necrosis factor-alpha
TPMT	thiopurine methyltransferase
Treg	T regulatory cell

REFERENCES

1. Fortuna G, Brennan MT. Systemic lupus erythematosus: epidemiology, pathophysiology, manifestations, and management. *Dent Clin North Am*. 2013;57:631–655.
2. Azevedo PC, Murphy G, Isenberg DA. Pathology of systemic lupus erythematosus: the challenges ahead. *Methods Mol Biol*. 2014;1134:1–16.
3. Pons-Estel GJ, Ugarte-Gil MF, Alarcon GS. Epidemiology of systemic lupus erythematosus. *Expert Rev Clin Immunol*. 2017;13:799–814.
4. Stojan G, Petri M. Epidemiology of systemic lupus erythematosus. *Curr Opin Rheumatol*. 2018;30:144–150.

5. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res (Hoboken)*. 2012;64:797–808.
6. Lim SS, Drenkard C. Epidemiology of lupus: An update. *Curr Opin Rheumatol*. 2015;27:427–432.
7. Niewold TB. Advances in lupus genetics. *Curr Opin Rheumatol*. 2015;27:440–447.
8. Chen LY, Shi ZR, Tan GZ, et al. Systemic lupus erythematosus with and without a family history: A meta-analysis. *Lupus*. 2018;27:716–721.
9. Vaglio A, Grayson PC, Fenaroli P, et al. Drug-induced lupus: traditional and new concepts. *Autoimmun Rev*. 2018;17:912–918.
10. Zandman-Goddard G, Solomon M, Rosman Z, et al. Environment and lupus-related diseases. *Lupus*. 2012;21:241–250.
11. Gulati G, Brunner HI. Environmental triggers in systemic lupus erythematosus. *Semin Arthritis Rheum*. 2018;47:710–717.
12. Tsokos GC, Lo MS, Reis PC, Sullivan KE. New insights into the immunopathogenesis of systemic lupus erythematosus. *Nat Rev Rheumatol*. 2016;12:716.
13. Pons-Estel GJ, Andreoli L, Scanzi F, et al. The antiphospholipid syndrome in patients with systemic lupus erythematosus. *J Autoimmun*. 2017;76:10–20.
14. Strand V, Levy RA, Cervera R, et al. Improvements in health-related quality of life with belimumab, a B-lymphocyte stimulator-specific inhibitor, in patients with autoantibody-positive systemic lupus erythematosus from the randomised controlled BLISS trials. *Ann Rheum Dis*. 2014;73:838–844.
15. Choi ST, Kang JI, Park IH, et al. Subscale analysis of quality of life in patients with systemic lupus erythematosus: Association with depression, fatigue, disease activity and damage. *Clin Exp Rheumatol*. 2012;30:665–672.
16. Tan TC, Fang H, Magder LS, Petri MA. Differences between male and female systemic lupus erythematosus in a multiethnic population. *J Rheumatol*. 2012;39:759–769.
17. Xiong W, Lahita RG. Pragmatic approaches to therapy for systemic lupus erythematosus. *Nat Rev Rheumatol*. 2014;10:97–107.
18. Petri M, Orbai AM, Alarcon GS, et al. Derivation and validation of the

Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum*. 2012;64:2677–2686.

19. Inês L, Silva C, Galindo M, et al. Classification of Systemic Lupus Erythematosus: Systemic Lupus International Collaborating Clinics versus American College of Rheumatology Criteria. A comparative study of 2,055 patients from a real-life, international systemic lupus erythematosus cohort. *Arthritis Care Res (Hoboken)*. 2015;67:1180–1185.
20. Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. *Arthritis Rheumatol*. 2019;71:1400–1412.
21. Ruperto N, Hanrahan LM, Alarcon GS, et al. International consensus for a definition of disease flare in lupus. *Lupus*. 2011;20:453–462.
22. Ogunsanya ME, Kalb SJ, Kabaria A, Chen S. A systematic review of patient-reported outcomes in patients with cutaneous lupus erythematosus. *Br J Dermatol*. 2017;176:52–61.
23. Okon LG, Werth VP. Cutaneous lupus erythematosus: Diagnosis and treatment. *Baillieres Best Pract Res Clin Rheumatol*. 2013;27:391–404.
24. Hansen CB, Dahle KW. Cutaneous lupus erythematosus. *Dermatol Ther*. 2012;25:99–111.
25. Santiago-Casas Y, Vila LM, McGwin G Jr., et al. Association of discoid lupus erythematosus with clinical manifestations and damage accrual in a multiethnic lupus cohort. *Arthritis Care Res (Hoboken)*. 2012;64:704–712.
26. Jafri K, Patterson SL, Lanata C. Central nervous system manifestations of systemic lupus erythematosus. *Rheum Dis Clin North Am*. 2017;43:531–545.
27. Govoni M, Bortoluzzi A, Padovan M, et al. The diagnosis and clinical management of the neuropsychiatric manifestations of lupus. *J Autoimmun*. 2016;74:41–72.
28. Knight JS, Kaplan MJ. Cardiovascular disease in lupus: Insights and updates. *Curr Opin Rheumatol*. 2013;25:597–605.
29. Costedoat-Chalumeau N, Dunogué B, Morel N, et al. Hydroxychloroquine: A multifaceted treatment in lupus. *Presse Med*. 2014;43:e167–e180.
30. Lisnevskaia L, Murphy G, Isenberg D. Systemic lupus erythematosus. *Lancet*. 2014;384:1878–1888.

31. Ugarte A, Danza A, Ruiz-Irastorza G. Glucocorticoids and antimalarials in systemic lupus erythematosus: An update and future directions. *Curr Opin Rheumatol*. 2018;30:482–489.
32. Kasturi S, Sammaritano LR. Corticosteroids in lupus. *Rheum Dis Clin North Am*. 2016;42:47–62,viii.
33. Buckley L, Guyatt G, Fink HA, et al. 2017 American College of Rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Care Res (Hoboken)*. 2017;69:1095–1110.
34. Mehat P, Atiquzzaman M, Esdaile JM, et al. Medication nonadherence in systemic lupus erythematosus: A systematic review. *Arthritis Care Res (Hoboken)*. 2017;69:1706–1713.
35. Mazzoni D, Cicognani E, Prati G. Health-related quality of life in systemic lupus erythematosus: A longitudinal study on the impact of problematic support and self-efficacy. *Lupus*. 2017;26:125–131.
36. Rodriguez Huerta MD, Trujillo-Martin MM, Rua-Figueroa I, et al. Healthy lifestyle habits for patients with systemic lupus erythematosus: A systematic review. *Semin Arthritis Rheum*. 2016;45:463–470.
37. Patterson SL, Schmajuk G, Jafri K, Yazdany J, Katz P. Obesity is independently associated with worse patient-reported outcomes in women with systemic lupus erythematosus. *Arthritis Care Res (Hoboken)*. 2019;71:126–133.
38. Food and Drug Administration, HHS. Labeling and effectiveness testing; sunscreen drug products for over-the-counter human use. Final rule. *Fed Regist*. 2011;76:35620–35665.
39. Kuhn A, Sigges J, Biazar C, et al. Influence of smoking on disease severity and antimalarial therapy in cutaneous lupus erythematosus: Analysis of 1002 patients from the EUSCLE database. *Br J Dermatol*. 2014;171:571–579.
40. Parodis I, Sjowall C, Jonsen A, et al. Smoking and pre-existing organ damage reduce the efficacy of belimumab in systemic lupus erythematosus. *Autoimmun Rev*. 2017;16:343–351.
41. Bertsias GK, Ioannidis JP, Aringer M, et al. EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: Report of a task force of the EULAR standing committee for clinical affairs. *Ann Rheum Dis*. 2010;69:2074–2082.
42. Ruiz-Irastorza G, Cuadrado MJ, Ruiz-Arruza I, et al. Evidence-based

recommendations for the prevention and long-term management of thrombosis in antiphospholipid antibody-positive patients: Report of a Task Force at the 13th International Congress on Antiphospholipid Antibodies. *Lupus*. 2011;20:206–218.

43. van Vollenhoven RF, Mosca M, Bertsias G, et al. Treat-to-target in systemic lupus erythematosus: Recommendations from an international task force. *Ann Rheum Dis*. 2014;73:958–967.
44. Artifoni M, Puechal X. How to treat refractory arthritis in lupus? *Joint Bone Spine*. 2012;79:347–350.
45. Duru N, van der Goes MC, Jacobs JW, et al. EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases. *Ann Rheum Dis*. 2013;72:1905–1913.
46. Ponticelli C, Moroni G. Hydroxychloroquine in systemic lupus erythematosus (SLE). *Expert Opin Drug Saf*. 2017;16:411–419.
47. Mok CC. Therapeutic monitoring of the immuno-modulating drugs in systemic lupus erythematosus. *Expert Rev Clin Immunol*. 2017;13:35–41.
48. Marmor MF, Kellner U, Lai TYY, et al. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). *Ophthalmology*. 2016;123:1386–1394.
49. Dennis GJ. Belimumab: A BLyS-specific inhibitor for the treatment of systemic lupus erythematosus. *Clin Pharmacol Ther*. 2012;91:143–149.
50. Hui-Yuen JS, Reddy A, Taylor J, et al. Safety and efficacy of belimumab to treat systemic lupus erythematosus in academic clinical practices. *J Rheumatol*. 2015;42:2288–2295.
51. Eko SL, van Vollenhoven RF. Rituximab and lupus—a promising pair? *Curr Rheumatol Rep*. 2014;16:444.
52. Coca A, Sanz I. Updates on B-cell immunotherapies for systemic lupus erythematosus and Sjogren's syndrome. *Curr Opin Rheumatol*. 2012;24:451–456.
53. Fattah Z, Isenberg DA. Recent developments in the treatment of patients with systemic lupus erythematosus: Focusing on biologic therapies. *Expert Opin Biol Ther*. 2014;14:311–326.
54. Lazaro E, Scherlinger M, Truchetet ME, et al. Biotherapies in systemic lupus erythematosus: New targets. *Joint Bone Spine*. 2017;84:267–274.
55. Aringer M, Smolen JS. Therapeutic blockade of TNF in patients with

SLE-promising or crazy? *Autoimmun Rev*. 2012;11:321–325.

56. Cortés-Hernández J, Egri N, Vilardell-Tarrés M, Ordi-Ros J. Etanercept in refractory lupus arthritis: An observational study. *Semin Arthritis Rheum*. 2015;44:672–679.
57. Monach PA, Arnold LM, Merkel PA. Incidence and prevention of bladder toxicity from cyclophosphamide in the treatment of rheumatic diseases: A data-driven review. *Arthritis Rheum*. 2010;62:9–21.
58. Yilmaz N, Emmungil H, Gucenmez S, et al. Incidence of cyclophosphamide-induced urotoxicity and protective effect of mesna in rheumatic diseases. *J Rheumatol*. 2015;42:1661–1666.
59. Dall'Era M. Mycophenolate mofetil in the treatment of systemic lupus erythematosus. *Curr Opin Rheumatol*. 2011;23:454–458.
60. Liu LL, Jiang Y, Wang LN, et al. Efficacy and safety of mycophenolate mofetil versus cyclophosphamide for induction therapy of lupus nephritis: A meta-analysis of randomized controlled trials. *Drugs*. 2012;72:1521–1533.
61. Maneiro JR, Lopez-Canoa N, Salgado E, Gomez-Reino JJ. Maintenance therapy of lupus nephritis with mycophenolate or azathioprine: Systematic review and meta-analysis. *Rheumatology*. 2014;53: 834–838.
62. Dall'Era M, Stone D, Levesque V, et al. Identification of biomarkers that predict response to treatment of lupus nephritis with mycophenolate mofetil or pulse cyclophosphamide. *Arthritis Care Res*. 2011;63:351–357.
63. Dooley MA, Jayne D, Ginzler EM, et al. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. *N Engl J Med*. 2011;365:1886–1895.
64. Tamirou F, D'Cruz D, Sangle S, et al. Long-term follow-up of the MAINTAIN Nephritis Trial, comparing azathioprine and mycophenolate mofetil as maintenance therapy of lupus nephritis. *Ann Rheum Dis*. 2016;75:526–531.
65. Ordi-Ros J, Saez-Comet L, Perez-Conesa M, et al. Enteric-coated mycophenolate sodium versus azathioprine in patients with active systemic lupus erythematosus: A randomised clinical trial. *Ann Rheum Dis*. 2017;76:1575–1582.
66. Liu YP, Xu HQ, Li M, et al. Association between thiopurine S-methyltransferase polymorphisms and azathioprine-induced adverse drug reactions in patients with autoimmune diseases: A meta-analysis. *PLoS ONE*. 2015;10:e0144234.

67. Schmajuk G, Yazdany J. Drug monitoring in systemic lupus erythematosus: A systematic review. *Semin Arthritis Rheum*. 2011;40:559–575.
68. Greco CM, Nakajima C, Manzi S. Updated review of complementary and alternative medicine treatments for systemic lupus erythematosus. *Curr Rheumatol Rep*. 2013;15:378.
69. Dall'Ara F, Cutolo M, Andreoli L, et al. Vitamin D and systemic lupus erythematous: A review of immunological and clinical aspects. *Clin Exp Rheumatol*. 2018;36:153–162.
70. Shoenfeld Y, Giacomelli R, Azrielant S, et al. Vitamin D and systemic lupus erythematosus: The hype and the hope. *Autoimmun Rev*. 2018;17:19–23.
71. Kamen DL. Vitamin D in lupus—new kid on the block? *Bull NYU Hosp Jt Dis*. 2010;68:218–222.
72. Andreoli L, Bertsias GK, Agmon-Levin N, et al. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. *Ann Rheum Dis*. 2017;76:476–485.
73. Sammaritano LR. Contraception in patients with rheumatic disease. *Rheum Dis Clin North Am*. 2017;43:173–188.
74. Cravioto MD, Jiménez-Santana L, Mayorga J, Seuc AH. Side effects unrelated to disease activity and acceptability of highly effective contraceptive methods in women with systemic lupus erythematosus: A randomized, clinical trial. *Contraception*. 2014;90:147–153.
75. Lateef A, Petri M. Systemic lupus erythematosus and pregnancy. *Rheum Dis Clin North Am*. 2017;43:215–226.
76. Ostensen M, Clowse M. Pathogenesis of pregnancy complications in systemic lupus erythematosus. *Curr Opin Rheumatol*. 2013;25:591–596.
77. Moroni G, Doria A, Giglio E, et al. Maternal outcome in pregnant women with lupus nephritis. A prospective multicenter study. *J Autoimmun*. 2016;74:194–200.
78. Lateef A, Petri M. Managing lupus patients during pregnancy. *Baillieres Best Pract Res Clin Rheumatol*. 2013;27:435–447.
79. Saavedra MA, Sánchez A, Morales S, et al. Azathioprine during pregnancy in systemic lupus erythematosus patients is not associated with poor fetal outcome. *Clin Rheumatol*. 2015;34:1211–1216.

80. Baer AN, Witter FR, Petri M. Lupus and pregnancy. *Obstet Gynecol Surv*. 2011;66:639–653.
81. Teng YKO, Bredewold EOW, Rabelink TJ, et al. An evidence-based approach to pre-pregnancy counselling for patients with systemic lupus erythematosus. *Rheumatology (Oxford)*. 2018;57:1707–1720.
82. Uthman I, Noureldine MHA, Ruiz-Irastorza G, Khamashta M. Management of antiphospholipid syndrome. *Ann Rheum Dis*. 2019;78:155–161.
83. Gómez-Puerta JA, Cervera R. Diagnosis and classification of the antiphospholipid syndrome. *J Autoimmun*. 2014;48-49:20–25.
84. Lockshin MD, Kim M, Laskin CA, et al. Prediction of adverse pregnancy outcome by the presence of lupus anticoagulant, but not anticardiolipin antibody, in patients with antiphospholipid antibodies. *Arthritis Rheum*. 2012;64:2311–2318.
85. Alijotas-Reig J. Treatment of refractory obstetric antiphospholipid syndrome: The state of the art and new trends in the therapeutic management. *Lupus*. 2013;22:6–17.
86. Araújo-Fernández S, Ahijón-Lana M, Isenberg DA. Drug-induced lupus: Including anti-tumour necrosis factor and interferon induced. *Lupus*. 2014;23:545–553.
87. He Y, Sawalha A. Drug-induced lupus erythematosus: An update on drugs and mechanisms. *Curr Opin Rheumatol*. 2018;30:490–497.
88. Lomicova I, Suchy D, Pizinger K, Cetkovska P. A case of lupus-like syndrome in a patient receiving adalimumab and a brief review of the literature on drug-induced lupus erythematosus. *J Clin Pharm Ther*. 2017;42:363–366.
89. Pasoto SG, Ribeiro AC, Bonfa E. Update on infections and vaccinations in systemic lupus erythematosus and Sjögren's syndrome. *Curr Opin Rheumatol*. 2014;26:528–537.
90. Garg M, Mufti N, Palmore TN, Hasni SA. Recommendations and barriers to vaccination in systemic lupus erythematosus. *Autoimmun Rev*. 2018;17:990–1001.
91. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis*. 2014;58:e44–e100.
92. Kim DK, Hunter P, on behalf of the Advisory Committee on Immunization Practices. Recommended adult immunization schedule,

United States, 2019. *Ann Intern Med*. 2019;170:182–192.

93. Friedman MA, Winthrop K. Vaccinations for rheumatoid arthritis. *Curr Opin Rheumatol*. 2016;28:330–336.
94. Thanou A, Merrill JT. Top 10 things to know about lupus activity measures. *Curr Rheumatol Rep*. 2013;15:334.
95. Gordon C, Amissah-Arthur MB, Gayed M, et al. The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults. *Rheumatology (Oxford)*. 2018;57:e1–e45.

Drug Allergy

Christopher M. Bland and Bruce M. Jones

KEY CONCEPTS

1. Drug allergy accounts for 6% to 10% of adverse reactions to medications. Most of these immune events are mediated by IgE or activated T cells.
2. Two theories—the prohapten/hapten concept and the p-i concept—have been proposed to explain how drugs stimulate the immune response.
3. Anaphylaxis is an acute, life-threatening allergic reaction involving multiple organ systems that generally begins within 1 hour but almost always within 2 hours after exposure to the inciting allergen. Anaphylaxis requires prompt treatment to restore respiratory and cardiovascular functions. Epinephrine is the drug of first choice and should be administered to counteract bronchoconstriction and peripheral vasodilation. IV fluids should be administered aggressively to restore intravascular volume.
4. Factors that influence the likelihood of drug allergy are the chemical composition of the drug, whether the drug contains proteins of nonhuman origin, the route of drug administration, and the sensitivity of the individual as determined by genetics or environmental factors. For some drugs, the presence of specific human leukocyte antigen alleles is a risk factor for allergic-mediated skin reactions.
5. Ideally, cephalosporins should be avoided in patients with a history of an immediate penicillin allergy, but the risk of an allergic response to a cephalosporin, even in a person with a positive penicillin skin test result, is low. Similarities in the R1 side chain of the agents should be considered when assessing the risk of cross-reactivity.
6. Fewer than 1% of patients receiving nonionic radiocontrast agents experience some type of adverse reaction. Of the variety of reactions reported, about 90% are nonimmediate and mostly urticarial, with severe

immediate reactions occurring as infrequently as 0.02%.

7. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) can produce two general types of reactions, urticaria/angioedema and rhinosinusitis/asthma, in susceptible patients. Most patients with aspirin sensitivity who require aspirin for prevention of cardiovascular disease can safely undergo and complete a graded challenge or desensitization.
8. Cross-reactivity between sulfonamide antibiotics and nonantibiotics is low. The low cross-reactive rate may be explained by differences in the chemical structures and reactive metabolites of the sulfonamide antibiotics and nonantibiotics.
9. The basic principles of management of allergic reactions to drugs or biologic agents include (a) discontinuation of the medication or offending agent when possible; (b) treatment of the adverse clinical signs and symptoms; and (c) substitution, if necessary, of another agent.
10. The reference standard for evaluating the risk of an immediate hypersensitivity to penicillin is the penicillin skin test. Skin testing can demonstrate the presence of penicillin-specific immunoglobulin E, if present, and predict immediate reactions. Skin testing is not indicated for non-IgE-mediated reactions.
11. When an allergenic drug is considered medically necessary and no therapeutic alternative or reliable skin testing method exists, two options are available to the clinician: induction of drug tolerance (previously known as desensitization) and graded dose challenge or rechallenge.

Preclass Engaged Learning Activity

Listen to the podcast series entitled “The Itch: An SIDP Podcast Miniseries on Penicillin Allergy”: https://sidp.org/podcasts/. These podcasts led by drug allergy experts in the pharmacy field discuss various topics including myth busting with regards to penicillin allergies, how to successfully implement penicillin skin testing, and finally “lessons learned from the front-line” to help those interested in developing a comprehensive penicillin allergy assessment and skin test program.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

105

Solid Organ Transplantation

Douglas L. Jennings and Heather J. Johnson

KEY CONCEPTS

1. Generally, patients receive a combination of two to four immunosuppressive drugs in order to minimize individual drug toxicities as well as block different aspects of the immune response.
2. While the calcineurin inhibitors (CI) tacrolimus and cyclosporine, inhibitors of interleukin (IL)-2 and thus T-cell activation, are the backbone of immunosuppressive regimens, they are associated with serious adverse effects, primarily nephrotoxicity and neurotoxicity.
3. Calcineurin inhibitor-induced nephrotoxicity is one of the most common adverse effects observed in solid organ transplant recipients. Therapeutic drug monitoring is used to optimize the use of calcineurin inhibitors and prevent toxicity.
4. Corticosteroids are a key component of most immunosuppressive strategies because they block the initial steps in allograft rejection. Their significant adverse effects have led to steroid-minimizing and steroid-free immunosuppressive protocols. Corticosteroids, however, remain first-line treatment for allograft rejection.
5. Azathioprine and mycophenolic acid derivatives inhibit T-cell proliferation by altering purine synthesis. Bone marrow suppression is the most significant adverse effect associated with these agents.
6. Sirolimus and everolimus inhibit the mTOR (mammalian target of rapamycin) receptor, which alters T-cell response to IL-2. The adverse effects associated with these agents include leukopenia, thrombocytopenia, anemia, and hyperlipidemia.
7. Antibody preparations that target specific receptors on T cells are classified based on their ability to deplete lymphocyte counts. Most lymphocyte-

depleting antibodies are associated with significant infusion-related reactions, whereas nondepleting agents are generally better tolerated.

8. Long-term allograft and patient survival are limited by chronic rejection, cardiovascular disease, infection, and long-term immunosuppressive complications such as malignancy.
9. Multiple factors impact immunosuppressant systemic exposure in transplant patients. Recognition of these factors by clinicians will facilitate optimization of drug therapy.

Preclass Engaged Learning Activity

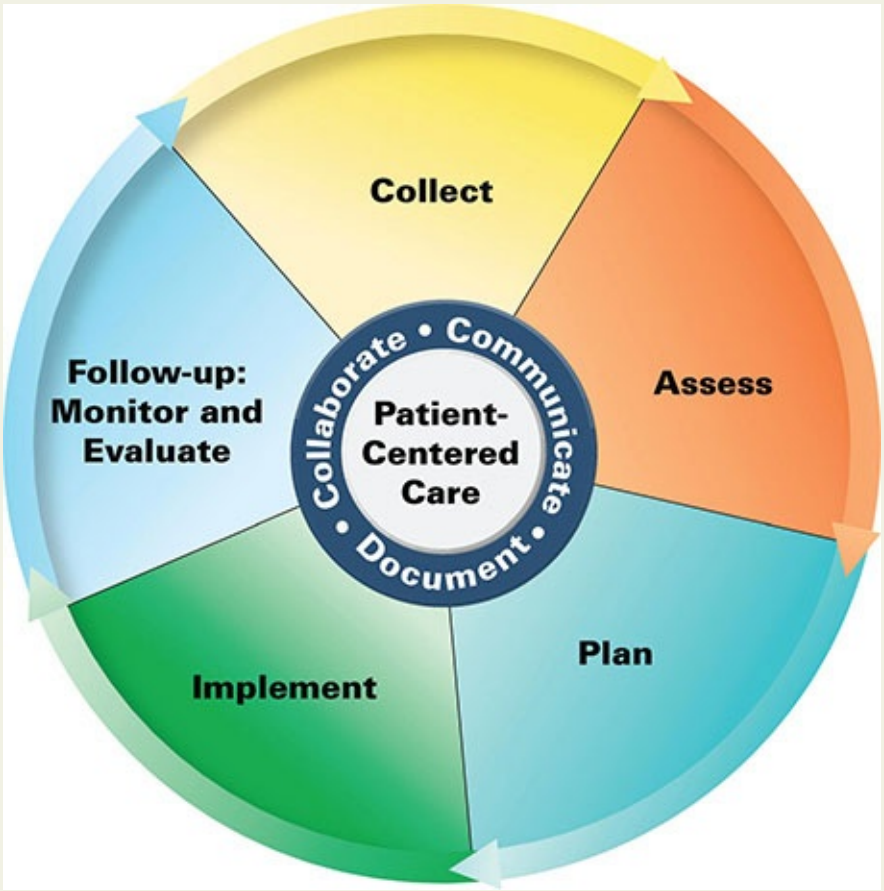
Visit the International Society for Heart and Lung Transplantation website <https://ishlt.org>. This website contains several useful links, including links to many registries that track outcomes in patients who have undergone heart or lung transplantation. Access the International Thoracic Organ Transplant (TTX) Registry Data slides <https://ishltregistries.org/registries/slides.asp>, and review the Adult Heart Transplantation Statistics information. Focus on the slides that pertain to immunosuppression regimens and outcomes. This will aid in the ASSESS and PLAN steps in the patient care process.

INTRODUCTION

Solid organ transplantation provides a lifesaving treatment for patients with end-stage cardiac, kidney, liver, lung, and intestinal disease. Over 300 US hospitals offer transplant services, and pharmacists are often an integral part of the transplant team.[1] In 2016, almost 600 pharmacists were members of the American College of Clinical Pharmacy's Transplant Interest Group and more that 65% of responding centers reported a pharmacist on their transplant teams.[2] The Centers for Medicare and Medicaid Services regulations require that transplant programs have a multidisciplinary team including medicine, nursing, nutrition, social services, transplant coordination and someone with experience in pharmacology. While the regulations may not specifically state that each center must have a pharmacist, a pharmacist could provide the desired expertise in transplant pharmacotherapy that the regulations mandate.[1]

Since 1980 over 630,000 transplants have been performed, with over half

being kidney transplants. A recent analysis estimated that since 1987 over 2.27 million life years have been saved by transplantation, with an average of 4.3 years per patient.[3] In 2016, more than 33,000 solid organ transplants were performed. Kidneys remain the most commonly transplanted organs; 13,431 from cadaveric donors and 5,629 from living donors in 2016. The next most frequently transplanted organ was the liver, with 7,496 from cadaveric donors and 345 from living donors. Heart transplants account for almost 3,200 transplants and about 2,300 lung transplants were performed in 2016. Pancreas (or combined kidney–pancreas) transplants account for just over 1,100 transplants. Small numbers of intestinal (147) and vascular composite allografts (13) were also performed in 2016.[1] Demand for transplantation continues to grow, but the number waiting continues to grow. In 2016, almost 115,000 persons in the United States were waiting for a transplant (over 101,000 people were awaiting a kidney, 15,000 a liver, 4,100 and 1,500 respectively were on the list for a heart or lung). Almost half of kidney transplant recipients had been receiving dialysis for more than 5 years.[1] The median waiting time for a liver transplant is about 1 year whereas the median wait for a heart transplant is about 2.5 months. For heart, liver, and lung transplantation clinical status is an important factor affecting waiting times, with the sickest patients receiving priority for available organs.[1]



Patient Care Process for Solid Organ Transplant Recipient*

Collect

- Patient characteristics (eg, age, sex, pregnant)
- Patient medical history (personal and family)
- Social history (eg, tobacco/ethanol use/marijuana), dietary habits
- Current medications including OTC use, herbal products, dietary supplements
- Objective data
    - Blood pressure (BP), heart rate (HR), respiratory rate (RR), temperature (T), height, weight, O_2-saturation
    - Labs including measures of end-organ function, hemoglobin (Hgb), platelets, serum creatinine (SCr), immunosuppressant concentrations, white blood cell count (WBC)

Assess

- Presence of over immunosuppression: infection, adverse drug events
- Presence of under immunosuppression: evidence of end-organ compromise
- Assess risk based on patient-specific risk factors and time posttransplant

Plan†

- Drug therapy regimen including specific immunosuppressive agents, dose, route, frequency, and duration (see Tables 105-3 and 105-4)
- Monitoring parameters including efficacy (eg, Scr, electrolytes, INR, Total Bili) and safety (eg, sign and symptoms of rejection, CBC, SCr, constitutional symptoms); frequency and timing of follow-up
- Patient education (eg, purpose of treatment, dietary and lifestyle restriction, drug-specific information, medication administration)
- Signs and symptoms of rejection (urine output, BP, pain, fever) or infection (temperature)
- Self-monitoring for sign/symptoms adverse effects (see Table 105-6)
- Referrals to other providers when appropriate

Implement

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (eg, CI concentration, Scr)

Follow-up: Monitor and Evaluate

- Maintenance of graft functions
- Presence of adverse effects (eg, nephrotoxicity, tremor, hyperglycemia, hypertension, nausea, vomiting; see Tables 105-6 and 105-7)
- Immunosuppressant TDM results (TAC, CSA, SIR, EVR); adjust IS dose as needed to keep at goal (see Tables 105-8 and 105-10)
- Patient adherence to treatment plan using multiple sources of information
- Reevaluate IS/anti-infective goal of therapy every 3 months

**New solid organ transplant recipient in the immediate post-op period.*

†Collaborate with patient, caregivers, and other healthcare professionals.

To increase the number of organs available for transplantation, several strategies have been employed in the past several years. Living donors account for one-third of all kidney transplants, more than any other organ. Living-donor transplantation is also becoming increasingly important for those with end-stage liver and lung disease. Efforts to expand the cadaveric donor pool have included relaxation of age restrictions, development of better preservation solutions, use of “extended-criteria” and nonheart-beating donors, and, in the case of liver transplants, the transplantation of one liver to more than one recipient or implantation of only a segment of a liver. An increase in deaths related to drug overdose has also resulted in an increased number of organ donors, often times infected with the hepatitis C virus. With the availability of current treatments for hepatitis C virus, some transplant recipients may be willing to accept a transplant from an HCV-infected donor. Although very controversial, some have advocated the creation of a regulated system for compensating individuals (paying them) for the “donation” of a kidney.[4]

Despite these efforts, thousands of people on transplantation waiting lists die each year. Efforts to improve organ allocation have included allocation primarily on “medical necessity” versus time on the waiting list. Dialysis can be used for an extended period of time to partially replace the function of the kidneys, and more than half of recent heart transplant recipients had left ventricular assist devices as a bridge to transplantation. Such options are not readily available for liver and lung transplant candidates.[5]

Patient and graft survival rates following transplantation have improved significantly over the past 30 years as a result of advances in pharmacotherapy, surgical techniques, organ preservation, and the postoperative management of patients (**Table 105-1**). In this chapter the epidemiology of end-stage kidney, liver, lung, and heart disease is briefly reviewed, the pathophysiology of organ rejection is presented, the pharmacotherapeutic options for individualized immunosuppressive regimens are critiqued, and the unique complications of these regimens along with the therapeutic challenges they present are discussed.

TABLE 105-1 Organ-Specific Patient and Graft Survival Rates[1]

	Patient Survival (%)		Graft Survival (%)	
Organ	**1 year**	**5 years**	**1 year**	**5 years**
Kidney				
Living donor	97.9	89.4	97.5	85.6
Deceased donor	94.3	80.4	93.2	74.46
Liver				
Living donor	90.1	77.6	88	77.3
Deceased donor	86.2	71.9	89.1	71.9
Heart				
Cardiomyopathy			91.6	79.4
Coronary Artery Disease			89.1	71.9
Lung				
Single	85.8	35.8	85.4	45.5
Double	83.3	47.3	87.3	55.7

EPIDEMIOLOGY AND ETIOLOGY

The epidemiology and etiology associated with solid organ transplant is specific to the type of organ transplant.

Kidney

Kidney transplantation is the preferred long-term therapeutic option for most patients with end-stage kidney disease because it provides the greatest potential improvement in quality of life. Dialysis catheter-related infections, peritoneal dialysis-associated peritonitis, and scheduled dialysis treatments are avoided, and dietary restrictions are fewer. Patients who receive a kidney transplant before the initiation of dialysis have markedly improved quality of life and prolonged life expectancy compared to those who were sustained on dialysis prior to their transplant.[6] The expanded use of living-donor transplantation has made this increasingly possible. Although the analysis of quality of life is complex, patients generally report improved quality of life following transplantation as compared with patients on maintenance dialysis.[7]

Diabetes mellitus, hypertension, and glomerulonephritis are the three leading causes of end-stage kidney disease and account for more than 70% of patients (see Chapter 61).[1] Patients with medical conditions such as unstable cardiac

disease or recently diagnosed malignancy, for whom the risk of surgery or chronic immunosuppression would be greater than the risks associated with chronic dialysis, are generally excluded from consideration for transplantation. Since dialysis is an available option for virtually all patients with end-stage kidney disease, risk of death without transplantation cannot drive organ allocation.

Liver

Noncholestatic cirrhosis (hepatitis C, alcoholic cirrhosis, hepatitis B, nonalcoholic steatohepatitis, and autoimmune hepatitis) is the primary cause of end-stage liver disease and more than 70% of liver transplant recipients have been diagnosed with one of these conditions.[1] Other indications for transplantation include acute liver failure, primary biliary cirrhosis, primary sclerosing cholangitis, as well as hepatocellular carcinoma. Nonalcoholic steatohepatitis represents a growing indication for liver transplantation, while hepatitis C–related indications are declining.[1] Livers are allocated based on a United Network for Organ Sharing-adapted, Model for End-stage Liver Disease (MELD) score.[8] This score, calculated from the patient's serum creatinine concentration, total serum bilirubin concentration, international normalized ratio, and etiology of cirrhosis, has been demonstrated to be a useful tool to predict impending mortality.

In general, active substance abuse has been a contraindication to liver transplantation, but given the high mortality for acute alcoholic hepatitis and the current lack of viable treatments, this is an area of growing research worldwide and a number of US centers have expanded transplantation in this patient population.[9] Although hepatitis B and C can recur in the transplanted liver, these are not absolute contraindications to liver transplantation. Moreover, recent guidelines suggest that patients with hepatitis C await treatment until after transplantation.[5,10]

Heart

Heart transplant candidates are typically patients with New York Heart Association class III or IV signs and symptoms despite maximal medical management and have an expected 1-year mortality risk of 50% or greater without a transplant.[11] Idiopathic cardiomyopathy and ischemic heart disease account for heart failure in more than 90% of heart transplantation recipients.[1]

Other etiologies include valvular disease, retransplantation for graft atherosclerosis or dysfunction, and congenital heart disease. The role of heart transplant as a therapeutic option for patients with heart failure is discussed in Chapter 35.

Absolute contraindications to heart transplantation include the presence of an active infection (except in the case of an infected ventricular assist device, which is an indication for urgent transplantation) or the presence of other diseases (eg, malignancy) that may limit survival and/or rehabilitation, and severe irreversible pulmonary hypertension.

Lung

Lung transplantation is becoming an increasing viable life-saving option for patients with end-stage pulmonary failure not amenable to other treatment. The primary indications for lung transplantation are chronic obstructive lung disease/emphysema, idiopathic pulmonary arterial hypertension, cystic fibrosis, and idiopathic pulmonary fibrosis. The vast majority of lung transplants are cadaveric (greater than 99%) and bilateral lung transplants accounted for 67% of lung transplants in 2012. Lungs are allocated on the basis of the complex lung allocation score (LAS) which is used to prioritize candidates based on medical need and expected posttransplant survival given patient-specific characteristics such as antecedent disease, age, body mass index, kidney function, diabetes as well as measures of current functional status.[1,12]

PHYSIOLOGIC CONSEQUENCES OF TRANSPLANTATION

Transplantation is truly lifesaving for heart, liver, and lung transplantation recipients, whereas kidney transplantation is associated with improved quality of life and survival when compared with dialysis.[13] Although not all heart transplant recipients return to work, 89.9% of patients consider themselves to have no activity limitations at 1-year follow-up.[14] The specific physiologic consequences of kidney, liver, heart, and lung transplantation are discussed below.

Kidney Transplantation

The glomerular filtration rate of a successfully transplanted kidney may be near

normal almost immediately after transplantation. In some patients, however, the concentration of standard biochemical indicators of kidney function, such as serum creatinine and blood urea nitrogen, may remain elevated for several days. Standard formulas used to predict drug dosing rely on a stable serum creatinine and may be inaccurate immediately following transplantation (see Chapter e59).

Although the allograft is able to remove uremic toxins from the body, it may take several weeks for other physiologic complications of ESRD, such as anemia, calcium and phosphate imbalance, and altered lipid profiles, to resolve. The renal production of erythropoietin and 1-hydroxylation of vitamin D may return toward normal early in the postoperative period. Because the onset of physiologic effects may be delayed, continuation of the patient's pretransplantation vitamin D, calcium supplementation, and/or phosphate binders may be warranted. Patients should be monitored for hypophosphatemia and hypercalcemia for the first few days to weeks after kidney transplantation.

Primary nonfunction of a kidney allograft or delayed graft function (DGF) is characterized by the need for dialysis in the first postop week or the failure of the serum creatinine to fall by 30% of the pretransplantation value. The incidence of DGF in cadaveric kidney transplantation ranges from 8% to 50% and results in a slower return of the kidney's excretory, metabolic, and synthetic functions. DGF is associated with prolonged hospital stays, higher costs, difficult management of immunosuppressive therapy, slower patient rehabilitation, and poor graft survival.[15] Other early causes of impaired kidney function such as urethral obstruction or arterial or venous stenosis or thrombosis should be distinguished from DGF.

The primary cause of DGF is acute tubular necrosis (ATN). The incidence of ATN is higher when kidneys are harvested from donors who recently experienced a cardiac arrest, those who were hypotensive or on vasopressors, or older donors (age greater than 55 years). While cyclosporine and tacrolimus have been implicated in the prolongation of ATN, a clear cause-and-effect relationship has not been established. Nonetheless, many clinicians will decrease calcineurin inhibitor doses in patients with ATN. DGF predisposes patients to acute rejection, possibly as a consequence of decreased calcineurin inhibitor concentrations and a resultant reduction in the level of immunosuppression.[16] The kidney donor profile index (KDPI) is a scoring system that incorporates donor factors to quantify risk of graft failure. The number expressed as a percentage denotes that a given kidney with a KDPI of X% has a higher expected risk of graft failure than X% of all kidneys from the previous year. Donor age, race, height, weight, presence of HTN, DM, HCV, cause of death,

and DCD status are incorporated into the KDPI score.[17]

Liver Transplantation

The physiologic consequences of liver transplantation are complex, involving changes in both its metabolic and synthetic function. Postoperatively, the liver transplant recipient will likely have many fluid, electrolyte, and nutritional abnormalities. Biliary tract dysfunction may alter the absorption of fats and fat-soluble drugs.[18] Poor absorption of the lipid-soluble drug cyclosporine improves after successful liver transplantation and reestablishment of bile flow. Vitamin E deficiency and its neurologic complications are usually reversed after successful liver transplantation. In stable adult liver transplant patients, the concentrations of retinol and tocopherol are similar to those seen in normal healthy subjects, indicating recovery of liver production and excretion of bile salts needed for fat-soluble vitamin absorption. Table 105-2 summarizes the effects of liver transplantation on metabolism and renal elimination that are seen in the immediate postoperative period. Most of these changes resolve as liver function normalizes.

TABLE 105-2 Perioperative Changes in Drug Disposition and Elimination Following Liver Transplantation

	Result	Comment
Serum proteins		
↓ Albumin	↑ Free fraction of drugs usually bound to albumin	Diazepam, salicylic acid binding greater in liver transplant than chronic liver disease because of endogenous binding inhibitors (up to 45 days posttransplant)
↑ Alpha-1-acid glycoprotein	Lower unbound fraction of drugs	Lidocaine
Metabolism/elimination		
Microsomal enzymes	↑ CYP2E1 activity	Increased drug metabolism (induction)
	↔ CYP2D6	Unaffected
	↓ CYP activity	Decreased drug elimination (inhibition)
Oxidation	Stable	
Conjugation	Normalizes after transplant	
Biliary function	↓ Absorption of lipophilic compounds	
	↑ Cyclosporine metabolites in blood	
Renal elimination	Elimination of gentamicin, vancomycin, cephalosporins less than predicted by serum creatinine	Renal elimination of metabolites limited

Failure of the newly transplanted liver to function occurs in 10% to 15% of recipients. Early graft failure can result from preexisting disease in the donor, and even coagulation defects have been acquired through donor organs. The technical complexity of the operation can produce flaws in revascularization that also lead to graft nonfunction. Surgical complications include portal vein or hepatic artery thrombosis and bile duct leaks. Ischemic injury can also result in early graft dysfunction. While hyperacute rejection in liver transplantation rarely occurs, graft failure in the first 2 postoperative weeks may indicate antibody-

mediated graft destruction.

Heart Transplantation

The transplanted heart is denervated and no longer responds to physiologic stimuli and pharmacologic agents in a normal manner.[13] In situations requiring an increased heart rate such as exercise or hypotension, the denervated heart is unable to increase heart rate but instead relies on increasing the stroke volume. Later in the course of exercise or hypotension, heart rate increases in response to circulating catecholamines. While the maximum exercise capacity of heart transplant recipients is below normal, most patients are able to resume normal lifestyles and participate in reasonably vigorous activities.[14] Partial reinnervation may occur over time, thereby facilitating more normal physiologic and pharmacologic responses and better exercise capacity.[14]

A number of autoregulatory and physiologic responses present in the normal heart are interrupted or blunted for the first 6 weeks after transplantation. The donor sinus node function may be impaired as the result of the preservation regimen, direct surgical trauma at excision, the presence of long-acting antiarrhythmics (eg, amiodarone) taken prior to transplant by the recipient, and a lack of “conditioning” responsiveness to catecholamines.[14] Consequently, the transplanted heart generally requires chronotropic support with either dobutamine, dopamine, or pacing in the perioperative period to maintain a heart rate greater than 110 beats/min and satisfactory hemodynamics (ie, blood pressure, urine output, and tissue perfusion).[19] Isoproterenol was historically used to increase heart rate, but the high cost and wide availability of alternative agents like dobutamine have led to a significant decline in the use of this agent after heart transplant. Approximately 10% to 20% of transplant patients will have persistent chronotropic incompetence requiring short courses of medications, such as terbutaline; implantation of a permanent cardiac pacemaker is reserved for rare cases of severe, symptomatic bradycardia or persistent advanced heart block.

Right ventricular function is frequently impaired, presumably as a result of preservation regimen injury and elevated pulmonary vascular resistance. A “restrictive” hemodynamic pattern may be present initially but usually improves in 6 weeks following transplantation. Donor–recipient size mismatch may contribute to early posttransplantation hemodynamic abnormalities characterized by higher right and left ventricular end-diastolic pressures. Supraventricular arrhythmias are usually transient and may result from use of catecholamines or

milrinone.

Myocardial depression frequently occurs and generally requires inotropic support with agents such as dobutamine, milrinone, and epinephrine. Common treatments for right-heart failure include intra- or postoperative administration of pulmonary vasodilators (eg, nitric oxide) and inotropic agents like milrinone and dobutamine.[19]

Persistent abnormalities of diastolic function in the transplanted heart can increase intracardiac pressures in an exaggerated fashion in response to exercise and/or volume infusion.[19] These abnormalities are due in part to denervation, but also to acute rejection or to the scarring secondary to previously treated rejection episodes, hypertension, or cardiac allograft vasculopathy.

Hypertension may occur following surgery secondary to the effect of elevated catecholamine concentrations and systemic vascular resistance as the residual effects of end-stage heart failure on the healthy heart. Systolic blood pressure should be maintained at 110 to 140 mm Hg to enhance cardiac function. In the acute posttransplantation period, intravenous nicardipine may be needed, with transition to oral calcium channel blockers like amlodipine once the patient can ingest oral medications.

Lung Transplantation

Lung transplant recipients experience more complications than other solid organ transplant recipients as evidenced by a higher rate of posttransplant re-hospitalization. Primary graft dysfunction with a mortality of 30% to 40% occurs within 72 hours of transplant in up to 20% of recipients. It presents as noncardiogenic pulmonary edema and is thought to be a manifestation of ischemia-reperfusion injury and may be associated with prolonged cold ischemia (greater than 6 hours) as well as a number of other factors including female gender. Airway complications include ischemia and associated anastomotic dehiscence, bronchial stenosis, and bronchiolitis obliterans. Dehiscence may result in mediastinitis, pneumothorax, or hemorrhage. Bronchial stenosis which may occur in up to 24% of patients results in a narrowing the bronchus that is usually managed by bronchoscopy and balloon dilation. Respiratory infections are especially problematic in lung transplant recipients as their newly transplanted organ is in direct contact with the outside environment. Additionally, the absence of a cough reflex as well as a reduction in mucociliary clearance as the result of denervation and lymphatic interruption also contribute to the risk of pulmonary infections. Patients with cystic fibrosis are susceptible

to the pathogens with which they were colonized before transplant.[12,20]

PATHOPHYSIOLOGY OF REJECTION

Rejection of a transplanted organ can take place at any time following surgery and is classified clinically as hyperacute, acute cellular, and/or humoral or chronic rejection.

General Concepts

Rejection is primarily mediated by activation of alloreactive T cells and antigen-presenting cells such as B lymphocytes, macrophages, and dendritic cells. Acute allograft rejection is caused primarily by the infiltration of T cells into the allograft, which triggers inflammatory and cytotoxic effects on the graft. Complex interactions between the allograft and cellular cytokines, cell-to-cell interactions, CD4+ and CD8+ T cells, and B cells ultimately lead to chronic rejection and graft loss if adequate immunosuppression is not maintained.[21]

The sequence of events that underlies graft rejection is recognition, via MHC class I and II antigens, of the donor's histocompatibility differences by the recipient's immune system, recruitment of activated lymphocytes, initiation of immune effector mechanisms, and finally graft destruction. The specifics of this immune cascade of organ rejection are discussed in Chapter e102. The complex nature of cytokine interactions makes it very difficult to design drugs with exclusive actions (**Fig. 105-1**).

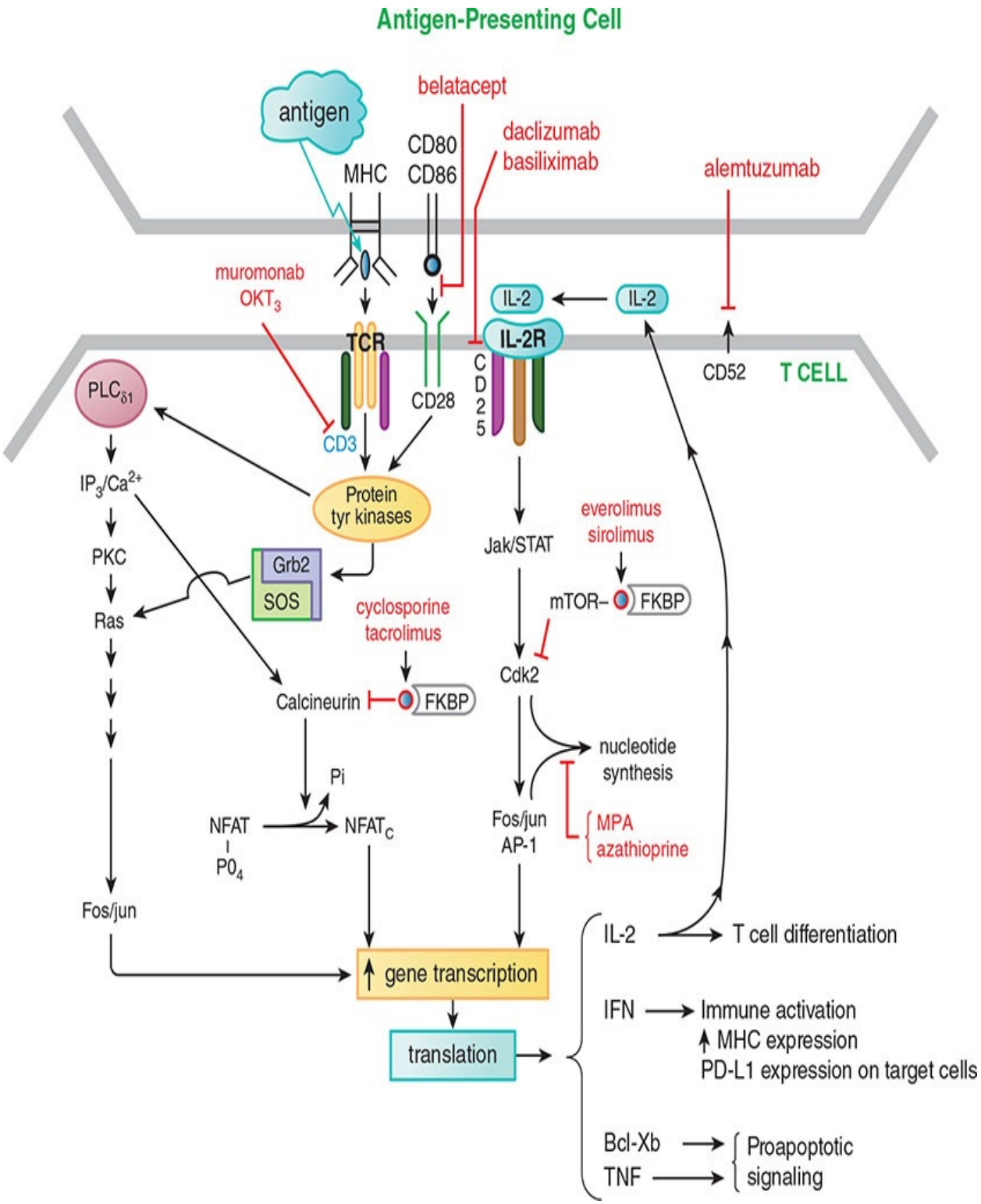


FIGURE 105-1 T-cell activation and sites of action of immunosuppressive agents. The TCR recognizes antigens bound to the MHC. A costimulatory signal is required for T-cell activation: the CD80/CD86-CD28 interaction from the APC to the T cell. Activation leads to IL-2 production (in a positive-feedback

loop) and a host of other events, some of which are bracketed in the lower right-hand corner. Numerous agents are available to suppress T-cell activation. Belatacept blocks the CD80/CD86-CD28 interaction. Cyclosporine and tacrolimus bind to immunophilins (cyclophilin and FKBP, respectively), forming a complex that inhibits the phosphatase calcineurin and the calcineurin-catalyzed dephosphorylation that permits translocation of NFAT into the nucleus. NFAT is required for transcription of IL-2 and other growth– and differentiation-associated cytokines (lymphokines). Sirolimus (rapamycin) and everolimus work downstream of the IL-2R, binding to FKBP; the FKBP-sirolimus complex binds to and inhibits the mTOR, a kinase involved in cell cycle progression (proliferation). Mycophenolate (MPA) and azathioprine inhibit nucleic acid synthesis, thereby inhibiting T-cell proliferation. The antibody muromonab (OKT3) inhibits TCR function via interaction with its CD3 component. Daclizumab and basiliximab block IL-2 signaling by interacting with the alpha subunit of the IL-2R complex (CD25). Several antibodies can block the systemic effects of released TNF. Alemtuzumab, by binding to CD52, marks the cell for destruction, thereby depleting $CD52^+$ cells. (APC, antigen-presenting cell; FKBP, FK506-binding protein; IFN, interferon; IL-2R, interleukin 2 receptor; MHC, histocompatibility complex; mTOR, mammalian target of rapamycin; NFAT; nuclear factor of activated T lymphocytes; OKT3, muromonab CD3; PD-L1, programmed death ligand 1.) (*Adapted from Brunton LL, Hilal-Dandan R, Knollmann BC, eds. Goodman & Gilman's the Pharmacological Basis of Therapeutics. 13th ed. New York, NY: McGraw-Hill; 2018.*)

Efforts to allocate well-matched kidneys, according to human leukocyte antigens (HLA)-A, -B, and -DR, are foundational to minimize rejection and enhance survival. However, the benefit of having no recipient donor mismatches may be negated by excessive cold ischemia time (greater than 36 hours) and donor age older than 60 years. HLA tissue matching is not performed routinely before transplantation for livers and hearts because organ availability is more limited and the optimal cold ischemia time is shorter.[22] However, if the potential recipient's blood is reactive against a panel of random donor blood samples (ie, panel reactive antibody [PRA] greater than 10%-20%), a negative T-cell crossmatch is required prior to transplantation. Transplanted organs must be matched for ABO blood-group compatibility with the recipient. Liver transplantation may be carried out in emergency situations across ABO blood groups, but survival is lower.

Hyperacute Rejection

Hyperacute rejection may be evident within minutes of the transplantation procedure when preformed donor-specific antibodies are present in the recipient at the time of the transplant. It can also be induced by immunoglobulin G antibodies that bind to antigens on the vascular endothelium, such as class I MHC, ABO, and vascular endothelial cell antigens. Tissue damage can be mediated through antibody-dependent, cell-mediated cytotoxicity or through activation of the complement cascade. If present the ischemic damage to the microvasculature rapidly results in tissue necrosis.

Hyperacute rejection has become uncommon in kidney and heart transplants. A positive crossmatch presents a serious risk for graft failure even if hyperacute rejection does not occur. A negative lymphocytotoxicity crossmatch does not entirely rule out the possibility of hyperacute rejection because non-MHC antigens on the vascular endothelium can serve as targets of donor-specific antibodies. Early graft dysfunction is treated with supportive care and retransplantation if possible. The reason for the rarity of hyperacute rejection in liver transplantation is not fully understood, but the local release of cytokines may alter the immunologic reaction in the liver.[23]

Acute Cellular Rejection

Acute cellular rejection (ACR) is most common in the first few months following transplantation but can occur at any time during the life of the allograft. It is mediated by alloreactive T-lymphocytes that appear in the circulation and infiltrate the allograft through the vascular endothelium. After the graft is infiltrated by lymphocytes, the cytotoxic cells specifically target and kill the functioning cells in the allograft. At the same time, local release of lymphokines attracts and stimulates macrophages to produce tissue damage through a delayed hypersensitivity-like mechanism. These immunologic and inflammatory events lead to nonspecific signs and symptoms including pain and tenderness over the graft site, fever, and lethargy.

Kidney

Acute rejection, which may affect up to 20% of patients during the first 6 months following transplantation, is evidenced by an abrupt rise in serum creatinine concentration of greater than or equal to 30% over baseline. A specific histologic diagnosis can be obtained via biopsy of the allograft and is often used to guide

rejection therapy. A biopsy specimen with a diffuse lymphocytic infiltrate is consistent with ACR. After the diagnosis of rejection has been confirmed, the potential risks and benefits of specific antirejection therapies must be evaluated. Hypertension often worsens during an episode of rejection, and edema and weight gain are common as a result of sodium and fluid retention. Symptomatic azotemia may also develop in severe cases.

Liver

Fewer than 15% of liver transplantation recipients will experience a rejection episode in the first posttransplant year. The clinical signs of ACR include leukocytosis and a change in the color or quantity of bile for those who still have an external drainage tube in place. A serum bilirubin 50% over baseline or increases in hepatic transaminases to values more than three times the upper limit of normal are sensitive markers of rejection. Although a liver biopsy provides definitive evidence of the diagnosis of rejection, a prompt response to antirejection medication has also proven useful as a means to differentiate rejection from other causes of hepatic dysfunction.

Heart

Approximately 16% of heart transplantation recipients will experience at least one episode of acute rejection during the first year.[24] Because rejection of the cardiac allograft is not necessarily accompanied by overt clinical signs or symptoms and because the incidence of acute rejection is highest during the first year posttransplant, endomyocardial biopsies are often performed at regularly scheduled intervals following transplantation.[19] A typical biopsy schedule would be weekly for the first postoperative month, biweekly for the next 2 months, and monthly to bimonthly through the remainder of the first posttransplant year. Nonspecific symptoms, including low-grade fever, malaise, mild reduction in exercise capacity, heart failure, or atrial arrhythmias may also be evident and if present are reflective of a more severe rejection episode.

Lung

Up to 36% of lung transplant recipients will experience acute rejection in the first year.[20] Patients with acute rejection often present with nonspecific symptoms including fatigue, fever, cough, dyspnea, hypoxemia, mucus as well as a diminished FEV1. Because spirometry and radiography cannot delineate the cause of these nonspecific symptoms, bronchoscopy and transbronchial biopsy

are the standard for establishing a diagnosis of rejection. Eosinophilia, lymphocyte proliferation, and infiltration are hallmark signs of rejection. Routine assessment after transplantation includes pulmonary function tests as well as clinical and radiologic evaluations.[12,20]

Antibody-Mediated Rejection

Antibody-mediated rejection (AMR), sometimes referred to as vascular or humoral rejection, is characterized by the presence of antibodies directed against HLA antigens present on the donor vascular endothelium. The antibodies activate complement, which creates a membrane attack complex that directly damages the organ and further attracts inflammatory cells to the allograft. The resultant damage is histologically distinct from cellular rejection and involves microvascular injury, often to the peritubular capillaries.[25] Definitive diagnosis of AMR is based on the presence of three criteria: presence of donor-specific antibodies, immunofluorescence staining of C4d deposits in the peritubular capillaries, and evidence of allograft dysfunction.[26] Circulating immune complexes often precede humoral rejection. This form of rejection is less common than ACR and generally occurs in the first 3 months after transplantation. It is associated with an increased fatality rate and appears to be more common when antilymphocyte antibodies are used for rejection prophylaxis. An increased risk of humoral rejection is associated with female sex, elevated PRA, cytomegalovirus seropositivity, and a positive crossmatch.[27] Strategies to reverse humoral rejection include plasmapheresis, often in combination with intravenous immunoglobulin, high-dose intravenous corticosteroids, antithymocyte globulin (ATG), bortezomib or carfilzomib, rituximab, and mycophenolate mofetil.

Chronic Rejection

Chronic rejection is a major cause of graft loss. It presents as a slow and indolent form of ACR, in which the involvement of the humoral immune system and antibodies against the vascular endothelium appear to play a role. Persistent perivascular and interstitial inflammation is a common finding in kidney, liver, and heart transplantation. As a result of the complex interaction of multiple drugs and diseases over time, it is difficult to delineate the true nature of chronic rejection. Unlike acute rejection, chronic rejection is not reversible with any immunosuppressive agents currently available.

Kidney

While advances in immunosuppression have reduced the rates of acute rejection in the first year posttransplant from over 50% to about 10%, chronic allograft nephropathy remains the most common cause of graft loss in the late posttransplantation period (greater than 1 year).[26] The syndrome is characterized in histological terms as interstitial fibrosis and tubular atrophy (IFTA) of unknown etiology. As many as two-thirds of allografts will be affected 5 years after transplantation.[28] Hypertension, proteinuria, and a progressive decline in kidney function represent the classic clinical triad of chronic allograft nephropathy. Factors that contribute to the development of chronic allograft nephropathy include calcineurin inhibitor nephrotoxicity, polyomavirus infection, hypertension, donor-related factors including ischemia time and undetected kidney disease in the donor kidney, and recurrence of the primary kidney disease in the recipient.

Liver

Approximately 3% to 5% of transplant livers are affected by chronic rejection, which is characterized by an obliterative arteriopathy and the gradual loss of bile ducts, often referred to as the vanishing bile duct syndrome. Initially patients experience an asymptomatic rise in the alkaline phosphatase and γ-glutamyl transpeptidase. As concentrations of bilirubin increase, patients become jaundiced and may experience itching.

Heart

Cardiac allograft vasculopathy, characterized by accelerated intimal thickening or development of atherosclerotic plaques, is the leading cause of graft failure and death in heart transplant recipients.[29] Endothelial injury, caused by both cell-mediated and humoral responses, is the first step in the process. Vasculopathy is restricted to the transplanted allograft. Routine surveillance with coronary angiography, intravascular ultrasound, or other procedures can aid in the diagnosis of vasculopathy. Evidence of cardiac allograft vasculopathy can be seen in as many as 14% of patients within 1 year of transplantation and up to 50% of patients within 5 years.[29] While chronic rejection of the kidney or liver allograft is generally not amenable to treatment, 3-hydroxy-3-methylglutaryl-coenzyme A (HMGCoA) reductase inhibitors are given to all heart transplant recipients to decrease the incidence of vasculopathy and prolong survival (**Table 105-3**).[29] The proliferation signal inhibitors (PSI) sirolimus and everolimus

reduce the incidence and slow progression of cardiac allograft vasculopathy; however, these agents are hampered by significant side effects and cannot be used in the early posttransplant setting (Table 105-3).[29] Percutaneous transluminal coronary angioplasty and coronary artery bypass grafting have been used in severe cases of vasculopathy; these procedures, however, are of limited value because of their association with increased mortality compared with the general population.[29]

TABLE 105-3 Strategies for Preventing Cardiac Allograft Vasculopathy (CAV)

Intervention	Drugs	Dose	Timing of Initiation
Statins	Pravastatin Simvastatin Atorvastatin Rosuvastatin	20-40 mg daily 5-20 mg daily 10-40 mg daily 5-20 mg daily	Prior to hospital discharge
Proliferation signal inhibitors	Everolimus Sirolimus	0.75 mg twice daily 1-2 mg daily	Not recommended to initiate within 6 months of transplant due to impaired wound healing; however, greatest benefit is realized if started within 1-2 years
Glycemic control	Insulin	Titrate to euglycenmia	Immediately posttransplant
Prevent ACR[1]	Tacrolimus Cyclosporine	Titrate to center-specific trough values	Immediately posttransplant
Prevent CMV infection[2]	Valganciclovir	900 mg daily (adjusted for kidney function)	Immediately posttransplant

ACR, acute cellular rejection; CMV, cytomegalovirus.

[1]Episodes of acute cellular rejection increase the subsequent risk of developing CAV

[2]CMV infection has been linked to accelerated development of CAV. Prophylaxis with valganciclovir is only recommended in recipients at high risk of infection posttransplant.

Lung

Chronic rejection in the lung is known as bronchiolitis obliterans syndrome, a fibroproliferative disease which impacts the small airways. It is characterized by a reduction of FEV1 greater than 20% and occurs in up to 50% of patients in the first 5 years posttransplant. The long-term prognosis is poor and survival is limited. Treatments are lacking, but chronic use of the azithromycin has shown some promise.[12,20]

TREATMENT OF REJECTION

Immunosuppression achieved with a variety of agents is the cornerstone to

rejection management and the accepted regimens for most solid organs are usually comprised of two or more agents.

Desired Outcomes

Immediately following surgery, the primary goal of therapy is to prevent hyperacute and acute rejection. The high doses of immunosuppressants required to achieve this goal, if maintained long term, may result in serious complications such as nephrotoxicity, infection, thrombocytopenia, and drug-induced diabetes. Therefore, rapid dosage reductions are frequently used to minimize these effects. Transplant immunosuppression must be balanced to optimize both graft and patient survival.

General Approach to Treatment

1 A multidrug approach is rational from an immunomechanistic viewpoint because the many agents have overlapping and potentially synergistic mechanisms of action. Furthermore, the use of a multidrug immunosuppression regimen may allow the use of lower doses of individual agents, thus reducing the severity of dose-related adverse effects (**Fig. 105-2**). The protocols and individual drug regimens tend to be medical center specific.[19,23,30] Although induction therapy may not be uniformly used, in almost every setting, patients receive IV methylprednisolone intraoperatively. Patients may also receive a descending dose of methylprednisolone over the first 5 to 7 postoperative days before beginning oral prednisone. Protocols generally combine a drug from two or three of the following classes: calcineurin inhibitors, antimetabolites or proliferation signal inhibitors, and corticosteroids (**Table 105-4**).

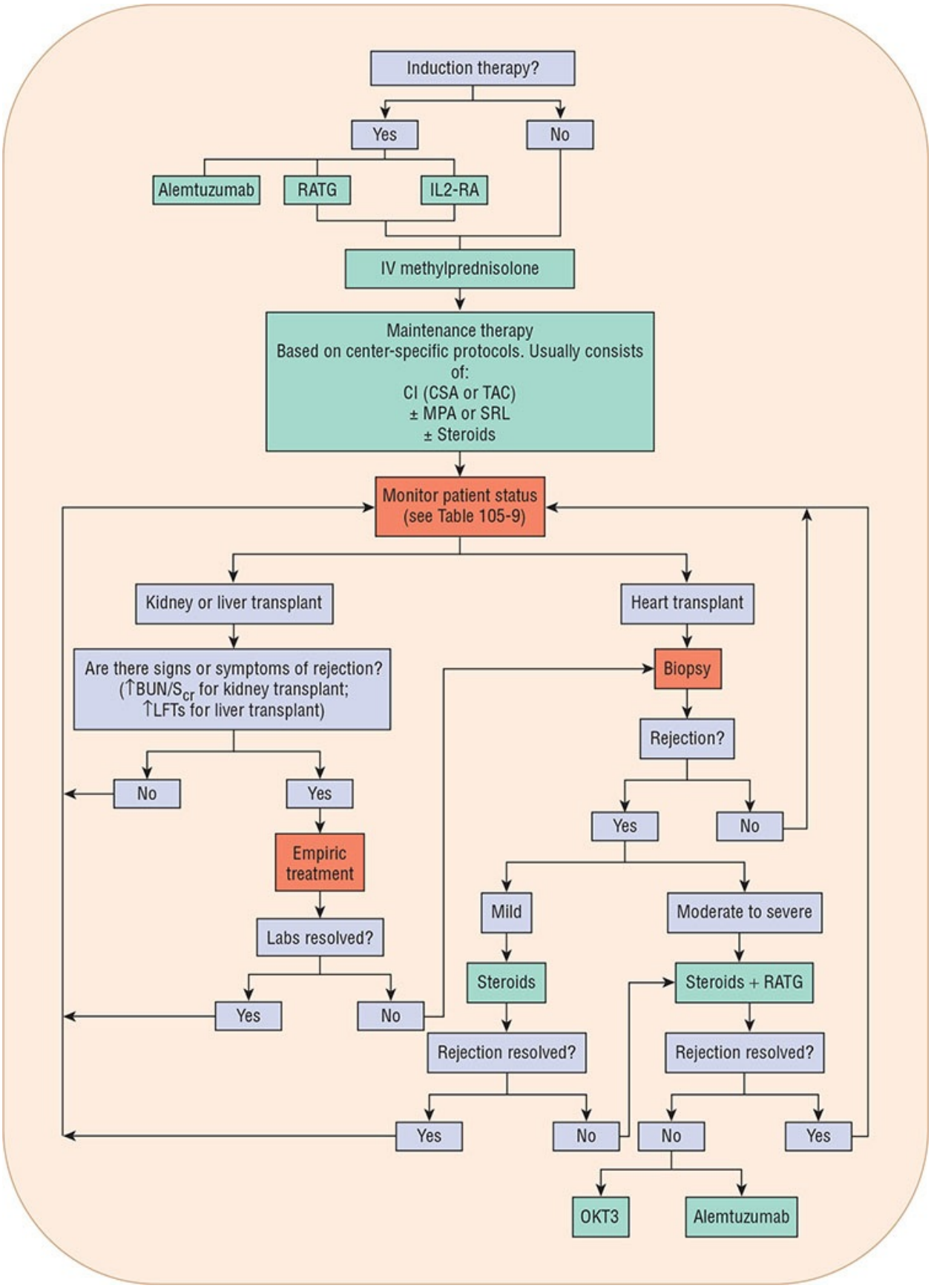

Induction therapy?
Yes
No
Alemtuzumab
RATG
IL2-RA
IV methylprednisolone
Maintenance therapy
Based on center-specific protocols. Usually consists of:
CI (CSA or TAC)
± MPA or SRL
± Steroids
Monitor patient status
(see Table 105-9)
Kidney or liver transplant
Heart transplant
Are there signs or symptoms of rejection?
(↑BUN/S_{cr} for kidney transplant;
↑LFTs for liver transplant)
Biopsy
Rejection?
No
Yes
Yes
No
Empiric treatment
Mild
Moderate to severe
Labs resolved?
Steroids
Steroids + RATG
Yes
No
Rejection resolved?
Rejection resolved?
Yes
No
No
Yes
OKT3
Alemtuzumab

FIGURE 105-2 General approach to solid organ transplant immunosuppression. (BUN, blood urea nitrogen; CI, calcineurin inhibitor; CSA, cyclosporine; IL2RA, interleukin-2 receptor antagonist; LFTs, liver function tests; MPA, mycophenolic acid; OKT3, muromonab CD3; RATG, rabbit antithymocyte immunoglobulin; S_{cr}, serum creatinine; SRL, sirolimus; TAC, tacrolimus.)

TABLE 105-4 Example of Maintenance Immunosuppression Regimen After Heart Transplant

Tacrolimus	Mycophenolate Mofetil	Prednisone
Start 0.05 mg/kg by mouth twice daily on POD1 Titrate to target trough based on daily serum concentrations Target trough: 1-3 months: 12-15 ng/mL (mcg/L) 3-6 months: 10-12 ng/mL (mcg/L) 6-12 months: 8-10 ng/mL (mcg/L) >12 months: 6-8 ng/mL (mcg/L)	1,500 mg by mouth twice daily No empiric dose adjustment needed in the early posttransplant phase unless side effects develop Taper dose periodically over the first year, goal for long-term maintenance of 500-750 mg twice daily	POD1: 50 mg by mouth twice daily POD2: 40 mg by mouth twice daily POD3: 30 mg by mouth twice daily POD4: 20 mg by mouth twice daily POD5: 20 mg by mouth once daily Stop taper at 20 mg once daily Continue to taper after each routine biopsy if no evidence of rejection Goal is to be off steroids by the end of the first posttransplant year

POD, postoperative day.

If rejection is suspected, a biopsy can be done to ascertain the definitive diagnosis or the patient may be empirically treated for rejection. Empiric treatment generally involves administration of high-dose corticosteroids, usually 500 to 1,000 mg of methylprednisolone intravenously for one to three doses.[12,19,23,30] If signs and symptoms of rejection are resolved with empiric therapy, the maintenance immunosuppressive regimen is generally modified to provide a greater level of overall immunosuppression. If rejection is confirmed by biopsy, treatment may be based on the severity of rejection with polyclonal antibodies being reserved for moderate-to-severe rejections or for those patients

who have not responded to a course of corticosteroids.

Induction Therapy

Induction therapy provides a high level of immunosuppression, at the time of transplantation, with or without the immediate introduction of cyclosporine or tacrolimus (see Fig. 105-2). Two perioperative immunosuppressive strategies have been predominantly utilized to achieve this goal: (a) the provision of a highly intense immunosuppression, often on the basis of patient-specific risk factors such as age and race, or (b) the use of antibody therapy to provide enough immunosuppression to delay the initiation of therapy with the potentially nephrotoxic calcineurin inhibitors. The rationale for delayed calcineurin inhibitor administration varies slightly depending on the type of transplant. In kidney transplantation, the newly transplanted kidney is very susceptible to nephrotoxic injury, whereas in liver and heart transplantation, the idea is to protect patients with preexisting kidney impairment from further insults during the perioperative period. Additionally, calcineurin inhibitor dosage adjustment to maintain target concentrations may be difficult in the perioperative period secondary to fluctuations in gastrointestinal (GI) absorption and enteral intake.[23,30,31]

Acute Rejection

The primary goal of acute rejection therapy is to minimize the intensity of the immune response and prevent irreversible injury to the allograft. The available options include (a) increasing the doses of current immunosuppressive drugs, (b) starting “pulse” corticosteroids with subsequent dosage taper, (c) addition of another immunosuppressant indefinitely, or (d) short-term treatment with a polyclonal or monoclonal antibody. The treatment of acute rejection almost always begins with “pulse” corticosteroid therapy for several days (oral or intravenous). However, African American kidney transplant recipients may not respond as well to corticosteroids; thus, ATG may be preferable for this patient population.[32]

Cytolytic agents like ATG are often reserved for those with corticosteroid-resistant rejection, signs of hemodynamic compromise (heart), or more severe rejections. Other innovative forms of therapy for persistent or intractable rejection have been investigated, including mycophenolate mofetil, tacrolimus, low-dose methotrexate, sirolimus, cyclophosphamide, total lymphoid irradiation, and plasmapheresis and intravenous immunoglobulin. Prophylactic agents such

as valganciclovir, nystatin, trimethoprim-sulfamethoxazole, H_2-receptor antagonists or proton-pump inhibitors, and/or antacids may be added to minimize adverse effects associated with these intensive immunosuppression regimens.[33]

Maintenance Therapy

The goal of maintenance immunosuppression is to prevent acute and chronic rejection while minimizing drug-related toxicity. As patients progress through the posttransplant course, the risk of acute rejection decreases, thus allowing the clinician to gradually reduce the doses of immunosuppressants or in some cases totally withdraw them over a period of 6 to 12 months. Transplant organ and type (cadaveric vs living-donor), the degree of HLA mismatch, time after transplantation, posttransplantation complications (including the number of acute rejections), previous immunosuppressive adverse reactions, compliance, and financial considerations are among the patient-specific factors considered in individualizing maintenance immunosuppression. Calcineurin inhibitors are generally a central component in most maintenance regimens, although calcineurin inhibitor-free immunosuppression remains a future goal because of the significant nephrotoxicity associated with these agents. Ideally, immunosuppression should be optimized to prevent acute rejection episodes, minimize the occurrence of chronic rejection, and prevent long-term toxicities.

Calcineurin Inhibitors

2 Cyclosporine and tacrolimus are the two calcineurin inhibitors (CIs) currently used for most solid organ transplant recipients. More than 90% of transplant recipients receive tacrolimus as part of their immunosuppressive regimen.[1]

Pharmacology/Mechanism of Action Calcineurin inhibitors block T-cell proliferation by inhibiting the production of IL-2 and other cytokines by T cells (see Fig. 105-1). Cyclosporine and tacrolimus bind to unique cytoplasmic immunophilins: cyclophilin and FK-binding protein-12 (FKBP12), respectively. The drug–immunophilin complex inhibits the action of calcineurin, an enzyme that activates the nuclear factor of activated T cells, which is, in turn, responsible for the transcription of several key cytokines necessary for T-cell activity, including IL-2. IL-2 is a potent T-cell growth factor and ultimately is responsible for activation and clonal expansion.

Pharmacokinetics The calcineurin inhibitors are highly lipophilic compounds, with variable but generally low bioavailability of approximately 30% (range: 5%-60%). Unlike tacrolimus, cyclosporine depends on bile for intestinal absorption, which lends to more interpatient and intrapatient variability. Liver recipients with a T-tube for diversion of bile may thus experience incomplete and erratic absorption of cyclosporine.[31]

Because of the significant variability in absorption of cyclosporine, and its associated pharmacokinetic problems, a microemulsion formulation was developed. Both forms are available commercially in the United States and are referred to as “cyclosporine, USP” and “cyclosporine, USP [MODIFIED].” The two formulations are not bioequivalent and should not be used interchangeably. The microemulsion formulation is self-emulsifying and forms a microemulsion spontaneously with aqueous fluids in the gastrointestinal tract, making it less dependent on bile for absorption. The result is a significantly greater rate and extent of absorption and decreased intraindividual variability in pharmacokinetic parameters. The relative bioavailability of the microemulsion formulation is 60% and peak concentrations are generally reached within 1.5 to 2 hours after oral administration. Tacrolimus, on the other hand, has a more predictable absorption pattern, reaching peak concentrations within 1 to 3 hours but still with a variable bioavailability ranging from 4% to 93% (average 20%).[31]

Following oral absorption, both cyclosporine and tacrolimus are highly protein bound. Ninety percent of cyclosporine is bound to lipoproteins in the blood while 99% of tacrolimus is bound primarily to albumin and α_1-acid glycoprotein. Cyclosporine is distributed widely into tissue and body fluids, resulting in a large and variable volume of distribution, ranging from 3 to 5 L/kg. Because of the high concentration of FKBP12 that is found in red blood cells, tacrolimus is distributed primarily in the vasculature, with a volume of distribution of 0.8 to 1.9 L/kg. Both drugs are extensively metabolized by the cytochrome P450 3A4 (CYP3A4) in both the gut and the liver, which accounts for their poor bioavailability and numerous drug interactions that are highlighted in **Table 105-5**.[31,34–36]

TABLE 105-5 The Impact of Concomitant Medications on Immunosuppressive Concentrations

Medications	TAC	CSA	MPA	PSI
Anti-Infectives				
Clotrimazole	↑	↑		↑
Fluconazole	↑	↑		↑
Ketoconazole	↑	↑		↑
Voriconazole	↑	↑		↑
Itraconazole	↑	↑		↑
Posaconazole	↑	↑		↑
Erythromycin	↑	↑		↑
Clarithromycin	↑	↑		↑
Azithromycin	↑	↑		↑
Levofloxacin	↑	↑		
Ofloxacin	↑	↑		
Norfloxacin			↓	
Metronidazole			↓	
Selective gut decontamination			↓	
Nafcillin	↓	↓	↓	↓
Rifampin	↓	↓	↓	↓
Lopinavir/Ritonavir	↑	↑		
Nelfinavir				
Saquinavir				
Efavirenz	↓	↓		
Simeprevir		↑		
Glecaprevir/pibrentasvir	↑			
Cardiovascular				
Verapamil	↑	↑		↑
Diltiazem	↑	↑		↑
CNS				
Nefazodone	↑	↑		
Carbamazepine	↓	↓		↓
Phenytoin	↓	↓		↓
Phenobarbital	↓	↓		↓
Immunosuppressants				
Cyclosporine			↓	↑
Tacrolimus				
Sirolimus		↑		
Everolimus		↑		
Mycophenolic acid		↓		

Data from References 27, 28, 34-36.

Efficacy Both cyclosporine and tacrolimus are currently approved for prophylaxis of organ rejection in kidney, liver, and heart transplantation. The microemulsion formulation of cyclosporine has demonstrated equivalent or superior efficacy in kidney, liver, and heart transplantation recipients. Tacrolimus and cyclosporine demonstrate equivalent efficacy as primary immunosuppression in all transplantation situations.

Adverse Effects The adverse effects of calcineurin inhibitors, cyclosporine and tacrolimus, and other immunosuppressants are presented in **Table 105-6**. The nephrotoxic potential of both drugs is equal and is often related to the dose and duration of exposure. Neurotoxicity typically manifests as tremors, headache, and peripheral neuropathy; occasionally, however, seizures have been observed. Tacrolimus may be associated with an increased occurrence of neurologic complications compared with cyclosporine.

TABLE 105-6 Comparison of Common Adverse Effects of Maintenance Immunosuppressants

System/Adverse Effect	AZA	MPA	CI	Steroids	PSI	Bela
Neurologic						
Headache			X			
Tremors			X			
Seizures			X			
Mood changes				X		
Cardiovascular						
Hypertension			X	X		
Hyperlipidemia			X	X	X	
Peripheral edema						X
Gastrointestinal						
Nausea	X	X	TAC	X		
Diarrhea		X	TAC			X
Vomiting	X					
Bleeding				X		
Hepatotoxicity	X		TAC			
Renal						
Nephrotoxicity			X		X	
Hyperkalemia			X			
Hypomagnesemia			X			
Urinary tract infection						X
Hematologic						
Anemia						X
Leukocytosis						
Leukopenia	X	X			X	
Neutropenia						X
Thrombocytopenia	X	X			X	
Cosmetic						
Acne				X		
Alopecia			TAC			
Gingival hyperplasia			CSA			
Hirsutism			CSA			
Weight gain				X		
Endocrine						
Hyperglycemia			X	X		
Osteoporosis				X		

AZA, azathioprine; Bela, belatacept; CI, calcineurin inhibitor; CSA, cyclosporine; MPA, mycophenolic acid; PSI, proliferation signal inhibitor; TAC, tacrolimus.

Cyclosporine has a greater propensity to cause hypertension and hyperlipidemia compared with tacrolimus.[37,38] Conversely, hyperglycemia is more common with tacrolimus than with cyclosporine but is often reversible when doses of tacrolimus and/or corticosteroids are reduced.[37] Cyclosporine is associated with cosmetic effects, such as hirsutism and gingival hyperplasia, which may be managed by converting from cyclosporine to tacrolimus or by improving hygiene in patients who cannot be switched to tacrolimus. Tacrolimus, in contrast, has been reported to cause alopecia, which is usually self-limiting and reversible.

3 ***Calcineurin Inhibitor Nephrotoxicity*** Two types of nephrotoxicity can occur with calcineurin inhibitors. Acute nephrotoxicity is frequently seen early and is dose dependent and reversible, but chronic nephropathy is more common. Clinical manifestations of calcineurin inhibitor nephrotoxicity include elevated serum creatinine and blood urea nitrogen concentrations, hyperkalemia, hyperuricemia, mild proteinuria, and a decreased fractional excretion of sodium. Calcineurin inhibitor nephrotoxicity is the leading cause of impaired kidney function following nonrenal solid organ transplant.

The predominant mechanism for calcineurin inhibitor nephrotoxicity is renal vasoconstriction, primarily of the afferent arteriole, resulting in increased renal vascular resistance, decreased renal blood flow by up to 40%, reduced glomerular filtration rate by up to 30%, and increased proximal tubular sodium reabsorption with a reduction in urinary sodium and potassium excretion. A number of other mechanisms have been implicated, including changes in the renin–angiotensin–aldosterone system, prostaglandin synthesis, nitrous oxide production, sympathetic nervous system activation, and calcium handling.[39]

Several approaches have been proposed to reduce calcineurin inhibitor nephrotoxicity including delaying administration immediately postoperatively in patients at high risk for nephrotoxicity (using alternative induction protocols including an IL-2 receptor antagonist or antilymphocyte globulin), monitoring calcineurin inhibitor trough blood concentrations, reducing the calcineurin inhibitor dosage if the vasoconstrictive effects are problematic, and avoiding other nephrotoxins (eg, aminoglycosides, amphotericin B, and nonsteroidal anti-inflammatory agents) when possible[15,39] Currently, no proven therapies consistently prevent or reverse the nephrotoxic effects of calcineurin inhibitors.

In patients who have received a kidney transplant, it is often difficult to differentiate calcineurin inhibitor nephrotoxicity from kidney allograft rejection.

Because the clinical features of acute kidney allograft rejection and calcineurin inhibitor nephrotoxicity overlap considerably, a kidney biopsy is often necessary to differentiate the two (Table 105-7). However, differentiating between chronic kidney allograft rejection and calcineurin inhibitor nephrotoxicity may be more difficult because, in addition to clinical signs and symptoms, biopsy findings may also be similar.

TABLE 105-7 Differential Diagnosis of Acute Rejection and Cyclosporine or Tacrolimus Nephrotoxicity

	Nephrotoxicity in Renal Transplant Recipients	
	Acute Rejection	**CSA or TAC Nephrotoxicity**
History	Often <4 weeks postoperatively	Often >6 weeks postoperatively
Clinical presentation	Fever	Afebrile
	Hypertension	Hypertension
	Weight gain	
	Graft swelling/ tenderness	Graft nontender
	Decreased daily urine volume	Good urine output
Laboratory biopsy	Rapid rise in serum Cr (0.3 mg/dL/day [27 µmol/L/day])	Gradual rise in serum Cr (>0.15 mg/dL/day [13 µmol/L/day])
	Normal CSA or TAC concentration	Elevated CSA or TAC concentration
	Interstitial lymphocytic infiltrates	Interstitial fibrosis, tubular atrophy, glomerular thrombosis, arterial inflammation

Cr, creatinine; CSA, cyclosporine; TAC, tacrolimus.

Drug–Drug and Drug–Food Interactions Drug interactions occur frequently with the calcineurin inhibitors because they are substrates for CYP3A4 and P-glycoprotein.[34–36] The most commonly administered drugs that are known to significantly alter cyclosporine and tacrolimus concentrations are highlighted in Table 105-5. Inhibitors of CYP3A4, such as diltiazem or erythromycin, can

increase drug concentrations up to 82%, whereas drugs that induce CYP3A4 activity, such as phenytoin or rifampin, can decrease drug concentrations by 50%.[36] While in vitro data suggest that drugs that increase the pH of the GI tract, such as magnesium-, aluminum-, or calcium-containing antacids, sodium bicarbonate, and magnesium oxide, can cause a pH-mediated degradation of tacrolimus by physically adsorbing tacrolimus in the GI tract, this is not supported by clinical studies.[40] Some clinicians suggest separating such compounds from tacrolimus administration by at least 2 hours to avoid any potential interaction.

Cyclosporine and, to a lesser extent, tacrolimus, are inhibitors of CYP3A4 and P-glycoprotein.[31,41] The inhibitory effects of cyclosporine and tacrolimus on CYP3A4 can be seen with weaker substrates, such as the HMG-CoA reductase inhibitors ("statins"). Concomitant administration of a calcineurin inhibitor with an HMG-CoA reductase inhibitor results in an increase in the HMG-CoA reductase inhibitor concentrations, which increases the risk of HMG-CoA reductase inhibitor adverse effects, most notably myopathy.[42] Patients should be monitored for clinical signs of myopathy when receiving HMG-CoA reductase inhibitors in combination with cyclosporine and tacrolimus. The interaction appears to be more pronounced between cyclosporine and HMG-CoA reductase inhibitors due to inhibition of organic anion-transporter proteins (OATP) by cyclosporine.[43]

Consistency in administration of the calcineurin inhibitors with regard to meals and food intake is important to sustain an effective concentration time profile. High-fat meals can enhance both plasma clearance and the volume of distribution of cyclosporine by more than 60%.[44] Food reduces the rate and extent of tacrolimus absorption, and a high-fat meal may further delay gastric emptying and reduce the maximum achieved serum concentration (C_{max}), and the area under the concentration–time curve (AUC).[31] Furocoumarins, such as quercetin, naringin, and bergamottin, found in grapefruit juice, are potent inhibitors of CYP3A4 and have been reported to increase both cyclosporine and tacrolimus concentrations significantly. The AUC and C_{max} of cyclosporine have been reported to be increased by more than 55% and 35%, respectively. In addition, the components of green tea as well as turmeric and ginger have been noted to increase calcineurin exposure.[31]

Dosing and Administration Initial oral cyclosporine doses range from 8 to 18 mg/kg/day administered every 12 hours. Higher doses of cyclosporine are used more commonly in two-drug regimens, whereas lower doses are part of triple-

drug regimens. Oral tacrolimus doses usually are in the range of 0.1 to 0.3 mg/kg/day given every 12 hours. An extended-release tablet formulation of tacrolimus (Envarsus®) has greater bioavailability than the immediate-release formulation and thus a lower recommended daily starting dose range of (0.11-0.17 mg/kg/day).[45] Children require higher doses to maintain therapeutic drug concentrations, up to 14 to 18 mg/kg/day for cyclosporine and 0.3 mg/kg/day for tacrolimus. The two once-daily formulations of tacrolimus are not interchangeable. Astagraf XL® or Advagraf® (tacrolimus extended-release capsule) is generally converted from standard tacrolimus formulations on a mg:mg basis whereas the more recently developed extended-release form of tacrolimus, Envarsus® XR (tacrolimus prolonged release tablets) has greater bioavailability than the immediate-release tacrolimus and the recommended conversion factor is 1-mg immediate release to 0.8-mg prolonged release, that is, a 20% reduction in total daily dose.[31,45,46] When patients were converted from immediate-release tacrolimus to extended Astagraf XL® on a mg:mg conversion based on total daily dose, about one-third of patients required downward dose adjustments to maintain the same 24-trough serum concentrations.[46] If oral administration is not possible, both CSA and TAC can be administered intravenously at approximately one-third the oral dosage, since administration by this route avoids first-pass metabolism. The usual intravenous dose of cyclosporine is 2 to 5 mg/kg/day, given as a continuous infusion or as single or twice-daily injection. Intravenous tacrolimus doses range from 0.05 to 0.1 mg/kg/day and must be administered by continuous infusion.

Therapeutic Drug Monitoring Calcineurin inhibitor trough blood concentrations should be measured routinely to optimize therapy (**Table 105-8**). Radioimmunoassay (RIA) and fluorescence polarization immunoassay are among the methods to measure cyclosporine concentrations. Tacrolimus concentrations are most commonly measured by microparticle enzyme immunoassays or enzyme-linked immunoassays. Both drugs can be measured by high-performance liquid chromatography (HPLC), which is recognized as the reference procedure.[44] Therapeutic target ranges are assay specific because some quantitate parent plus metabolite concentration, while others only measure the parent compound. Thus, the target concentrations will be lower for the specific assays (LC-MS/MS) compared with nonspecific assays (RIA and microparticle enzyme immunoassays) by approximately 20% to 25%. The specific goal concentration for both drugs is dependent on transplant type, time after transplantation, concomitant immunosuppression, and transplantation center.

One review of the role of tacrolimus in kidney transplantation suggests that target 12-hour whole blood concentrations for tacrolimus should be 15 to 20 ng/mL (mcg/L; 18.6 to 24.8 nmol/L) 0 to 1 month after transplantation, 10 to 15 ng/mL (mcg/L; 12.4 to 18.6 nmol/L) 1 to 3 months after transplantation, and 5 to 12 ng/mL (mcg/L; 6.2 to 14.9 nmol/L) greater than 3 months after transplantation.[38] Blood drug concentrations should be measured frequently (daily or three times per week) following initiation of the drug and during the stabilization period after transplantation. With time, blood concentrations can be measured less frequently.

TABLE 105-8 Therapeutic Concentrations of Immunosuppressants

		Concentrations (ng/mL or mcg/L)	
Drug	**Sampling medium**	**HPLC**	**RIA**
Cyclosporine	Whole blood	100-300	375-400
	Plasma	75-100	150-250
Tacrolimus	Whole blood	8-13	5-20
	Plasma		0.2-0.8
Sirolimus (with CIs)	Whole blood	10-15	15-20
Sirolimus (without CIs)	Whole blood	15-25	20-30
Everolimus (with CIs)	Whole blood	3-8	

CIs, calcineurin inhibitors; HPLC, high-performance liquid chromatography; RIA, radioimmunoassay.
For expression of immunosuppressant drugs in SI units of nmol/L multiply levels in ng/mL(or mcg/L) by 0.832 for cyclosporine, 1.24 for tacrolimus, 1.094 for sirolimus, and 1.044 for everolimus.

Cyclosporine trough concentrations are poorly predictive of rejection.[47] Alternative strategies, including AUC and peak concentration determination, have been suggested to better correlate with rejection.[44,47] Limited sampling techniques using two to five blood samples within the first 4 hours after an oral dose have been used to determine AUC and it was observed that AUC values greater than 4,400 ng/mL (mcg/L; 3,661 nmol/L) per hour correlated with a reduction in rejection.[44,47] Cyclosporine peak concentration (C_{peak}) has also been found to correlate with rejection and toxicity. Some transplantation centers have adopted this strategy to manage cyclosporine concentrations because of the convenience and reduced cost associated with the measurement of a single blood concentration. The suggested therapeutic range for C_{peak} cyclosporine

concentrations is 1,500 to 2,000 ng/mL (mcg/L; 1,248-1,664 nmol/L) for the first few months after transplant and 700 to 900 ng/mL (mcg/L; 582-749 nmol/L) after 6 to 12 months.[44]

Current therapeutic drug monitoring does not ensure complete avoidance of either toxicity or rejection. Intra-patient variability with tacrolimus has been associated with both graft rejection and development of *de novo* donor-specific antibodies. Other measures of CI exposure such as time in therapeutic range (TTR), commonly employed to measure adequacy of warfarin monitoring, has been reported to be positively associated with superior outcomes in lung transplant recipients. Prospective implementation of these findings has not been employed to drive outcomes, but may be an opportunity to identify patients at heightened risk and modify monitoring.[47–49]

Corticosteroids

4 Corticosteroids have been used since the beginning of the modern transplantation era. Despite their many adverse events, they continue to be a cornerstone of immunosuppression regimens in many transplant centers, with 30% and 60% of liver and kidney transplant patients, respectively, receiving corticosteroids for at least the first year after transplantation.[1] The most commonly used corticosteroids are methylprednisolone and prednisone.

Pharmacology/Mechanism of Action Corticosteroids block cytokine activation by binding to corticosteroid response elements, thereby inhibiting IL-1, IL-2, IL-3, IL-6, γ-interferon, and tumor necrosis factor-α synthesis (see Fig. 105-1). Additionally, corticosteroids interfere with cell migration, recognition, and cytotoxic effector mechanisms.[50]

Pharmacokinetics Prednisone is converted to prednisolone, its active moiety, in the liver and has multiple effects on the immune system. Prednisone is rapidly absorbed from the GI tract, achieving peak concentrations in 1 to 3 hours in transplant recipients. Bioavailability is greater than 90%. In kidney transplant recipients the pharmacokinetic half-life is short, 2 to 4 hours, but the pharmacodynamic effects extend beyond the time that concentrations are measurable, permitting daily administration.[50]

Efficacy The efficacy of corticosteroids is irrefutable based on the decades of clinical experience. Systematic studies comparing corticosteroid-free immunosuppressive agent combinations with conventional therapy are difficult to perform because of the hundreds of potential combinations that now exist.

Nevertheless, corticosteroid-free immunosuppressive agent combinations with newer, more specific immunosuppressants hold promise and may be more commonly used in the future.[51]

Adverse Effects Adverse effects of prednisone that occur in more than 10% of patients include increased appetite, insomnia, indigestion (bitter taste), and mood changes. Side effects that occur less often but which are seen with high doses or prolonged therapy include cataracts, hyperglycemia, hirsutism, bruising, acne, sodium and water retention, hypertension, bone growth suppression, and ulcerative esophagitis. The adverse effects of corticosteroids are summarized in Table 105-6.

Drug–Drug and Drug–Food Interactions Barbiturates, phenytoin, and rifampin induce hepatic metabolism of prednisolone and thus may decrease the effectiveness of prednisone. Prednisone decreases the effectiveness of vaccines and toxoids.[50]

Dosing and Administration An intravenous corticosteroid, commonly high-dose methylprednisolone (250-1,000 mg), is given at the time of transplantation. The dose of methylprednisolone is tapered rapidly and usually discontinued within 3 to 5 days when oral prednisone is initiated. Prednisone doses are tapered progressively over several weeks to months, depending on the type of additional immunosuppression and organ function. It is preferable to administer corticosteroids between 7 AM and 8 AM to mimic the body's diurnal release of cortisol. While conversion to alternate-day regimens or complete withdrawal of prednisone in patients with stable posttransplantation courses has been used with success in some transplantation centers, corticosteroids are often continued for the entire life of the functional graft.[50]

The first-line therapy for the treatment of acute graft rejection is high-dose intravenous methylprednisolone (250-1,000 mg) daily for 3 days or oral prednisone (200 mg) daily for 3 days. Doses of oral prednisone are then tapered over 5 days to 20 mg/day. Prednisone should be taken with food to minimize GI upset. Corticosteroids should never be discontinued abruptly; tapering should be gradual because of suppression of the hypothalamic–pituitary–adrenal axis. Corticosteroids slow the growth rate of children, prompting clinicians to use alternate-day dosing or to withhold corticosteroids until rejection occurs.

Antimetabolites

5 Antimetabolites have been used since the early days of transplantation

because they prevent proliferation of lymphocytes. Azathioprine, long considered a part of the “gold standard” regimen with cyclosporine and corticosteroids, has largely been supplanted by mycophenolic acid derivatives which are more specific in their effects on lymphocytes and have fewer side effects.

Mycophenolic Acid Derivatives Two formulations of mycophenolic acid (MPA) are currently available in the United States: mycophenolate mofetil, the morpholinoethyl ester of MPA, and mycophenolate sodium, which is available as an enteric-coated formulation of the sodium salt of MPA.

Pharmacology/Mechanism of Action The immunosuppressive effect of MPA is exerted through noncompetitive binding to inosine monophosphate dehydrogenase (IMPDH), the key enzyme responsible for guanosine nucleotide synthesis via the de novo pathway. Inhibition of IMPDH results in decreased nucleotide synthesis and diminished DNA polymerase activity, ultimately reducing lymphocyte proliferation.[52] Although MPA inhibits both types of IMPDH, IMPDH I, expressed by all cells in the body, and IMPDH II, which is expressed only in T and B lymphocytes, it is more specific for IMPDH II.[52] In addition to this, T and B lymphocytes only use the de novo pathway for nucleotide synthesis (see Fig. 105-1), making MPA very specific for these cells. Other cells within the body have a salvage pathway by which they can synthesize nucleotides, making them less susceptible to the actions of MPA and thereby reducing, but not eliminating, the potential for the hematologic adverse effects seen with azathioprine. In addition to decreasing lymphocyte proliferation, MPA may also down regulate activation of lymphocytes.[53]

Pharmacokinetics Because MPA is unstable in an acidic environment, mycophenolate mofetil acts as a prodrug that is readily absorbed from the GI tract, after which it is rapidly and completely converted to MPA in the liver. The enteric coating of mycophenolate sodium protects MPA from the acidic gastric pH and allows MPA to be released directly into the small intestine for absorption. The absolute bioavailability of mycophenolate mofetil and mycophenolate sodium is 94% and 72% of the active moiety, respectively. Peak concentrations of mycophenolate mofetil are reached within 1 to 2 hours following oral administration, while the enteric coating of mycophenolate sodium delays absorption and peak concentrations are not reached until 4 hours after administration.[53]

MPA is extensively bound (97%) to albumin and is eliminated by the kidney

and also undergoes glucuronidation in the liver to an inactive glucuronide metabolite (MPAG) that is subsequently excreted in the bile and urine. Enterohepatic cycling of MPAG can lead to deconjugation, thereby recirculating MPA into the bloodstream. This can account for 10% to 60% of total MPA exposure and results in a second peak 6 to 12 hours after oral administration.[53] The half-life of MPA is 18 hours.

Efficacy Currently, mycophenolate mofetil is approved for use in kidney, liver, and heart transplantation and is recommended as a component of maintenance immunosuppression regimens for most kidney and heart transplant recipients.[19,30] Compared to azathioprine, mycophenolate treatment in patients receiving cyclosporine and corticosteroids leads to a significant improvement in patient and graft survival at 1 and 3 years.[53] Mycophenolate is also effective in combination with tacrolimus, and has demonstrated efficacy in the treatment of acute rejection.[53]

Mycophenolic acid derivatives are a key component of calcineurin inhibitor–sparing protocols. MPA monotherapy has been associated with an unacceptable rejection rate. Combination of MPA with sirolimus, on the other hand, resulted in improved kidney function with no change in acute rejection incidence or/and patient and graft survival.[53]

Adverse Effects Unlike cyclosporine and tacrolimus, MPA is not associated with nephrotoxicity, neurotoxicity, or hypertension. The most common side effects are related to the GI tract, including nausea, vomiting, diarrhea, and abdominal pain (see Table 105-5), which occur with similar frequency during intravenous and oral therapy. Strategies to reduce GI symptoms are not well studied. Changing formulation may or may not improve symptoms and it is clear that dose reduction and discontinuation increase the risk of rejections.[53] Mycophenolic acid also has hematologic effects, such as leukopenia and anemia, particularly with higher doses. Recently, the rare but serious adverse event of progressive multifocal leukoencephalopathy (PML) has been reported, but could not be substantiated in further analyses.[53] Because peripheral intravenous mycophenolate administration is associated with local edema and inflammation, central venous administration may be the preferred route.

Drug–Drug and Drug–Food Interactions Food has no effect on MPA AUC, but it delays the absorption and decreases MPA C_{max} by 40% and 33% when mycophenolate mofetil and mycophenolate sodium, respectively, are administered. Concomitant administration with aluminum- and magnesium-

containing antacids or cholestyramine significantly decreases the AUC of MPA and should be avoided.[53] It has been suggested that administration of iron may produce similar results, but this has not been tested. Concomitant administration of mycophenolate mofetil with pantoprazole has been reported to decrease MPA concentrations by 57% and AUC by 12% in healthy volunteers. The same effect was not observed with mycophenolate sodium. Reduced MPA exposure has not been shown to impact graft outcomes in all patients. However, Knorr et al. demonstrated an increased risk of BPAR with PPI use in black patients.[54]

Acyclovir, commonly used in kidney transplant recipients for the treatment and prevention of viral infections, competes with MPAG for renal tubular secretion. AUCs of both entities are increased during concomitant acyclovir and MPA administration. No pharmacokinetic interaction with other antiviral agents has been demonstrated, but, there is potential for additive pharmacodynamic effects such as bone marrow suppression.

Decreased MPA trough concentrations have been reported when MPA is administered with cyclosporine compared with those achieved when MPA is given with tacrolimus or sirolimus.[53] This interaction is most likely a result of cyclosporine inhibition of multidrug-resistance-associated protein 2 (MRP2), which inhibits the enterohepatic recycling of MPAG, resulting in decreased MPA concentrations.[53] Cyclosporine decreases MPA concentrations by approximately 40% to 50% compared to tacrolimus.[35] To achieve equivalent MPA and MPAG serum concentrations, it may be necessary to administer higher doses of MPA with cyclosporine compared to tacrolimus. Antibiotics may also interfere with enterohepatic recycling of MPAG by decreasing bacterial-mediated deglucuronidation in the colon.[53]

Dosing and Administration Mycophenolate mofetil is currently available in both oral and intravenous formulations. Although intravenous administration of equal doses closely mimics oral administration, the two cannot be considered bioequivalent. Mycophenolate sodium is only available as an oral formulation. To optimize immunosuppression and minimize adverse effects, MPA is administered in two divided doses given every 12 hours. The total daily dose for kidney and liver transplants is typically 2 g/day for mycophenolate mofetil and 1.44 g/day for mycophenolate sodium. The total daily dose in heart transplant recipients is commonly 3 g/day, with a target trough concentration of greater than 1.5 mcg/mL (mg/L; 4.7 μmol/L).[19] The recommended pediatric dose is 600 mg/m^2 for mycophenolate mofetil and 400 mg/m^2 for mycophenolate sodium, in two divided doses.

While an increasing body of literature suggests that therapeutic drug monitoring of MPA is of value, it remains controversial.[54–56] Plasma appears to be the most appropriate medium in which to measure MPA for therapeutic drug monitoring, due to the relationship between target plasma MPA concentrations and improved clinical outcomes in patients receiving concomitant CIs and corticosteroids. For example, patients with trough MPA concentrations between 1.0 and 3.5 mcg/mL (mg/L; 3.1-10.9 μmol/L) experience fewer significant complications. Unbound concentrations as opposed to total MPA concentrations may be the most relevant to measure, especially in patients with liver disease, hypoalbuminemia, and severe infection.[53] Trough concentrations may not be accurate in predicting total drug exposure during a 12-hour interval and thus AUC monitoring has been proposed as the most appropriate measure of MPA drug exposure to guide therapy.[53] Better outcomes are associated with MPA AUC concentrations of greater than 42.8 mcg/mL (mg/L; 134 μmol/L) per hour (by HPLC),[56] although a reference range of 30 to 60 mcg/mL (mg/L; 94-188 μmol/L) has been proposed. The correlation between MPA AUC values and adverse effects is low. The best means to evaluate MPA concentrations, the acceptable targets for each, and the appropriate strategy to monitor MPA concentrations remain unclear.[56]

Azathioprine Azathioprine, a prodrug for 6-mercaptopurine (6-MP), has been used as an immunosuppressant in combination with corticosteroids since the earliest days of the modern transplantation era. Its use has dramatically declined with the availability of newer immunosuppressants, but it remains an option for patients intolerant of other medications.[19,30]

Pharmacology/Mechanism of Action Azathioprine is an inactive compound that is converted rapidly to 6-MP in the blood and is subsequently metabolized by three different enzymes. Xanthine oxidase, found in the liver and GI tract, converts 6-MP to the inactive final end product, 6-thiouric acid. Thiopurine *S*-methyltransferase (TPMT), found in hematopoietic tissues and red blood cells, methylates 6-MP to an inactive metabolite, 6-methylmercaptopurine. Finally, hypoxanthine-guanine phosphoribosyltransferase is the first step responsible for converting 6-MP to 6-thioguanine nucleotides (6-TGNs), the active metabolites, which are incorporated into nucleic acids, ultimately disrupting both the salvage and de novo pathways of DNA, RNA, and protein synthesis. This process is toxic to the cell and renders the cell unable to proliferate (see Fig. 105-1). Eventually, 6-TGNs are catabolized by xanthine oxidase and thiopurine *S*-methyltransferase to inactive products.[55]

Pharmacokinetics Oral bioavailability of azathioprine is approximately 40%. Metabolism of 6-MP is primarily by xanthine oxidase to inactive metabolites, which are excreted by the kidneys. The half-life of azathioprine is very short, approximately 12 minutes. The half-life of 6-MP is longer, ranging from 0.7 to 3 hours. However, it is the activity of the 6-TGNs that determines the pharmacodynamic half-life of the drug which has been estimated to be 9 days.[57]

Adverse Effects Dose-limiting adverse effects of azathioprine are often hematologic (see Table 105-5). Leukopenia, anemia, and thrombocytopenia can occur within the first few weeks of therapy and can be managed by dose reduction or discontinuation of azathioprine. Other common adverse effects include nausea and vomiting, which can be minimized by taking azathioprine with food. Alopecia, hepatotoxicity, and pancreatitis are less common adverse effects of azathioprine and are reversible on dose reduction or discontinuation. Activity of TPMT can affect the occurrence of adverse effects with azathioprine. Approximately 10% of the population has intermediate TPMT activity and 0.3% has low activity of the enzyme. In both scenarios, the incidence of leukopenia and hepatotoxicity is increased. As a result, TPMT genotyping may be useful to guide dosing of azathioprine to minimize adverse effects.[55]

Drug–Drug and Drug–Food Interactions The xanthine oxidase inhibitors allopurinol and febuxostat can increase azathioprine and 6-MP concentrations by as much as fourfold.[57] The metabolic pathways shift to favor production of 6-TGNs, which ultimately results in increased bone marrow suppression and pancytopenia. Doses of azathioprine should be reduced by 50% to 75% when allopurinol is added to a patient's drug regimen.

Dosing and Administration Usual initial doses of azathioprine range from 3 to 5 mg/kg/day. Individualization to maintain the white blood cell count between 3,500 and 6,000 cells/mm^3 (3.5 and 6.0 × 10^9/L) may be accomplished in some patients with doses as low as 0.25 mg/kg/day. Patients are often instructed to take azathioprine in the evening when initiating or titrating therapy to allow for dose adjustments based on morning determinations of their white blood cell count.

Proliferation Signal Inhibitors

Two PSIs have been approved in the United States for use in transplantation. Sirolimus, also known as rapamycin, is an immunosuppressive macrolide antibiotic that is structurally similar to tacrolimus, and is effective in reducing

the risk of acute rejection. Everolimus, a synthetic derivative of sirolimus, was developed to improve upon the pharmacokinetics of sirolimus. Everolimus was approved in the United States in 2009 and has a significantly shorter half-life than sirolimus.

Pharmacology/Mechanism of Action Sirolimus and everolimus both bind to FKBP12, forming a complex that binds to the mammalian target of rapamycin (mTOR), which inhibits the body's response to cytokines (see Fig. 105-1). As such, the drugs are commonly referred to as mTOR inhibitors. IL-2 stimulates mTOR to activate kinases that ultimately advance the cell cycle from G1 to the S phase. Thus, these drugs reduce T-cell proliferation by inhibiting the cellular response to IL-2 and progression of the cell cycle.[58,59]

Pharmacokinetics Bioavailability after oral administration is low for both, only 14% to 20%, with peak concentrations being reached within 1 to 2 hours.[58,59] Both have large volumes of distribution, 5.6 to 16.7 L/kg for sirolimus and approximately 110 L (about 1.5 L/kg for a 70-kg individual) for everolimus. Both are metabolized primarily by CYP3A4 in the gut and the liver. Likewise, both are also substrates for P-glycoprotein. The half-life for sirolimus is reported to be 60 hours but can be as long as 110 hours in patients with liver dysfunction, while that of everolimus is much shorter, 18 to 35 hours.[58,59]

Efficacy Sirolimus is only approved for the prevention of rejection in kidney transplant recipients when given in combination with corticosteroids and cyclosporine or after withdrawal of cyclosporine in patients with low-to-moderate immunologic risk. Because of the risks of delayed wound healing sirolimus is usually not started until 3 months after transplantation or once the surgical wound has healed. Sirolimus has also been demonstrated to be effective in combination with tacrolimus or mycophenolate in kidney transplants, with patient survival rates greater than 99% and graft survival rates greater than 96%.[50] Combination therapy with sirolimus and mycophenolate can be used to avoid the use of calcineurin inhibitors and decrease the risk of nephrotoxicity. Everolimus is approved for use in both kidney and liver transplantation. In kidney transplant recipients it was studied in combination with basiliximab, cyclosporine, and corticosteroids, whereas in liver transplant recipients it was initiated at least 30 days after transplantation in combination with reduced-dose tacrolimus and corticosteroids. Everolimus has also been used with tacrolimus with similar results as sirolimus.[60] Everolimus appears to have less of an effect on wound healing and thus may potentially be used earlier after transplantation.

Early cyclosporine withdrawal has been studied in patients receiving sirolimus-based immunosuppressive protocols. Ideal candidates are patients who have not had a recent or severe rejection episode and have adequate kidney function 3 months after transplant. Rejection occurred in 5.6% of patients after discontinuation of cyclosporine and no difference in graft survival was noted. Long-term follow-up (2 years) showed improved kidney function and blood pressure without an increase in acute rejection or graft loss in patients who discontinued cyclosporine.[50] Similar results have been demonstrated with everolimus.[60]

PSIs have demonstrated efficacy to reduce CI use and nephrotoxicity in liver,[59] heart,[58] and lung transplant patients.[59] PSIs are also being investigated in liver transplant patients as a means to reduce the recurrence of hepatitis C and hepatocellular carcinoma.[59] They may also reduce the incidence of chronic rejection after heart transplantation.[29]

Adverse Effects Both everolimus and sirolimus are associated with dose-related myelosuppression. Thrombocytopenia is usually seen within the first 2 weeks of sirolimus therapy but generally improves with continued treatment; leukopenia and anemia are also typically transient.[58,59] Sirolimus trough serum concentrations greater than 15 ng/mL (mcg/L; 16 nmol/L) have been correlated with thrombocytopenia and leukopenia.[58] Hypercholesterolemia and hypertriglyceridemia are also common in patients receiving everolimus or sirolimus. It is postulated that the mechanism of this adverse effect is related to an overproduction of lipoproteins or inhibition of lipoprotein lipase. Peak cholesterol and triglyceride concentrations are often seen within 3 months of sirolimus initiation but usually decrease after 1 year of therapy and can be managed by reducing the dose, discontinuing sirolimus, or initiating therapy with an HMG-CoA reductase inhibitor or fibric acid derivative. Dyslipidemia associated with sirolimus may not be a major risk factor for early cardiovascular complications following kidney transplantation.[58] Delayed wound healing and dehiscence could be a result of inhibition of smooth muscle proliferation and intimal thickening.[58] Mouth ulcers are reported in as many as 60% of patients treated with sirolimus and appear to be dose-related.[58] Reversible interstitial pneumonitis has been described in kidney, liver, and heart–lung transplantation recipients.[50] Despite their similarities, everolimus and sirolimus do have some differences likely related to difference in distribution. Sirolimus appears to enhance CSA neurotoxicity and both CSA and TAC nephrotoxicity, whereas everolimus did not.[59] Other adverse effects reported with sirolimus include

increased liver enzymes, hypertension, rash, acne, diarrhea, and arthralgia (see Table 105-6).

Drug–Drug and Drug–Food Interactions The major metabolic pathway for everolimus and sirolimus is CYP3A4; thus, the drug interactions mediated by induction or inhibition of the CYP3A4 enzyme system are similar to those seen with cyclosporine and tacrolimus (see Table 105-5). Administration of the microemulsion formulation of cyclosporine with sirolimus significantly increases the AUC and trough sirolimus serum concentrations: this has not been observed with the standard formulation of cyclosporine. Conversely, cyclosporine concentrations and AUC are increased when it is given concomitantly with sirolimus. The mechanism is proposed to be competitive binding to CYP3A4 and P-glycoprotein.[58,59] Concomitant administration of tacrolimus does not affect sirolimus concentrations.[58] Although everolimus AUC was increased by the administration of a single dose of the microemulsion cyclosporine formulation, no specific recommendations for dose timing are given. It should be expected, however, that any changes in CSA dose may also necessitate a modification of everolimus dose and increased attention to therapeutic drug monitoring.[59]

As with cyclosporine and tacrolimus, grapefruit juice increases sirolimus concentrations. Administration of sirolimus with a high-fat meal is associated with a delayed rate of absorption, decreased C_{max}, and increased AUC, indicating an increased drug exposure, whereas the half-life remains unchanged.[58] Conversely, administration of everolimus with a high-fat meal was associated with decreases in both C_{max} and AUC.[59]

Dosing and Administration The fixed sirolimus dosing regimen, approved for concomitant use with cyclosporine includes a loading dose of 6 to 15 mg followed by 2 or 5 mg daily, respectively. Therapeutic monitoring of sirolimus is advocated using whole-blood concentrations measured by HPLC, which is specific for the parent compound (see Table 105-7). For everolimus a starting dose of 0.75 mg twice daily is indicated in regimens that contain cyclosporine, corticosteroids, and basiliximab. Target serum concentrations are 3 to 8 ng/mL (mcg/L; 3-8 nmol/L).

Costimulatory Signal Inhibitor

Belatacept, derived from abatacept, is the only drug currently approved in this class of immunosuppressive agents. Belatacept may ultimately replace

calcineurin inhibitors in the majority of immunosuppressive regimens, since its use has not been associated with toxicities seen with CIs, namely nephrotoxicity.[61] As of the fall of 2018, belatacept is only approved for kidney transplantation.

Pharmacology/Mechanism of Action Belatacept is a selective costimulation blocker that binds costimulatory ligands (CD80 and CD86) on antigen presenting cells, preventing interaction with CD28 on T cells. The interaction of CD80 and CD86 with CD28 is required for the initiation of "signal 2," the costimulatory signal that produces calcineurin, protein kinases, and nuclear factor-κ β that lead to activation and proliferation of T-cells. Thus, blockade of CD80 and CD86 prevents T-cell activation.[62]

Pharmacokinetics Belatacept which is only available as an intravenous formulation has a volume of distribution of 0.11 L/kg, half-life of approximately 11 days and is not affected by reduced kidney or liver function.[61]

Efficacy A phase III clinical trial comparing belatacept to cyclosporine in first time kidney transplant patients demonstrated similar efficacy in terms of both patient and graft survival. Cyclosporine users experienced more chronic allograft nephropathy at month 12, while the belatacept group experienced more frequent and more severe ACR. Despite this, the measured GFR was 13 to 15 mL/min (0.22-0.25 mL/s) higher in the belatacept group compared to the cyclosporine group, a trend that persisted for 7 years.[61]

Additionally, belatacept-treated patients had better blood pressure control and lower lipid concentrations as well as less diabetes than CI-treated patients. It is unclear whether this translates long term to less cardiovascular mortality.[62] Conversion from CI-based regimens to belatacept in kidney transplant recipients with stable kidney function leads to improved GFR from baseline.[63,64] However, acute rejection occurs more frequently in patients who switch to belatacept, compared with no acute rejection in the patients who remain on CIs.[61]

Early studies with belatacept in liver transplant patients were associated with increased graft loss and death, which lead to the subsequent termination of ongoing studies.[65] There is limited postmarketing experience with belatacept in liver transplant recipients with poor kidney function as a bridge to future calcineurin therapy.[66]

Adverse Effects The most common adverse effects of belatacept include anemia, neutropenia, diarrhea, urinary tract infections, headache, and peripheral

edema.[61] Patients who are Epstein Barr virus (EBV) naïve experience a significantly higher incidence of posttransplant lymphoproliferative disease (PTLD). Most cases of PTLD occur within the first 18 months of treatment and the majority occur in the central nervous system. There is no increase in incidence of PTLD in patients who are EBV-seropositive. As a result, belatacept carries a black box warning for PTLD and is contraindicated in patients who are EBV-seronegative. Progressive multifocal leukoencephalopathy (PML) is also reported with belatacept.[61]

Drug–Drug and Drug–Food Interactions No drug or food interactions have been reported with belatacept.

Dosing and Administration Patients for whom belatacept is being considered must be screened for EBV-serostatus prior to initiation of therapy. Only patients who are EBV-seropositive should receive belatacept due to the increased risk of PTLD in EBV-seronegative patients. The risk evaluation and mitigation strategy (REMS) for belatacept involves screening for symptoms of PTLD and PML with counseling and education. As a primary immunosuppressant for first time kidney transplants, belatacept is administered as 10 mg/kg intravenously over 30 minutes on days 0, 4, 14, 28, and at the end of weeks 8 and 12. Thereafter, the dose is reduced to the maintenance dose of 5 mg/kg administered IV over 30 minutes every 4 weeks beginning at week 16.

When converting to belatacept from a CI-based regimen, the proposed dosing schedule is 5 mg/kg IV administered every 2 weeks for 5 doses on days 0, 14, 28, 42, and 56, then every 4 weeks thereafter. The CI dose should be decreased by 50% after the second dose of belatacept and then discontinued after the fourth dose.[61]

Antibody Agents

7 Both polyclonal and monoclonal antibody preparations are used in transplantation. These agents can be differentiated by their level of specificity, that is, particular receptor(s) they effect, or their downstream effects.

Depleting Antibodies

Antithymocyte Globulin Two ATG formulations are available in the United States: ATG (Atgam, Pfizer, New York, NY), an equine polyclonal antibody, and RATG (Thymoglobulin, Genzyme, Cambridge, MA), a rabbit polyclonal antibody. The rabbit preparation is less immunogenic and may have other

advantages over the equine preparation. Both ATG and RATG are often used as induction therapy to prevent acute rejection. In 2016, over 60% of kidney transplant recipients received RATG induction whereas fewer than 20% of liver and heart transplant recipients did.[1]

PHARMACOLOGY/MECHANISM OF ACTION Because of their polyclonal antibody nature, both ATG and RATG exert their immunosuppressive effect by binding to a wide array of lymphocyte receptors such as CD2, CD3, CD4, CD8, CD25, and CD45. Binding of ATG or RATG to the various receptors results in complement-mediated lysis and subsequent lymphocyte depletion. While T cells are the major lymphocytic target for the compounds, other blood cell components such as B cells and other leukocytes are also affected (see Fig. 105-1). Damaged T cells are subsequently removed by the spleen, liver, and lungs.

PHARMACOKINETICS ATG is poorly distributed into lymphoid tissue and binds primarily to circulating lymphocytes, granulocytes, and platelets. The terminal half-life of ATG is 5.7 days. RATG has a volume of distribution of 0.12 L/kg, and its terminal half-life in kidney transplant recipients is significantly longer than ATG at 30 days.[33] Peak plasma concentrations are reached after 5 to 7 days of ATG or RATG infusions. Antiequine antibodies have been noted in up to 78% of patients who are receiving ATG therapy. Similarly, antirabbit antibodies have been reported in up to 68% of patients who are receiving RATG therapy. The effects of preformed antibodies on the efficacy and safety of these preparations have not been well studied.

EFFICACY ATG and RATG are used most commonly for the treatment of acute allograft rejection or as induction therapy to prevent acute rejection. ATG is currently approved for both indications in kidney transplants. RATG is approved only for the treatment of acute allograft rejection in kidney transplantations. Both drugs have been studied extensively for both indications.[27,33]

Use of RATG as part of quadruple therapy in liver transplantation is associated with similar rates of patient and graft survival and acute rejection compared with dual therapy. In kidney transplant, RATG is associated with improved graft survival at 5 years as compared with equine ATG. Quadruple-drug therapy results in similar rates of patient and graft survival in heart transplant recipients, with a significantly lower rate of acute rejection at 1 year compared with triple-drug therapy. Increased risk of cytomegalovirus (CMV) infection is a limitation of this strategy, but routine prophylaxis is successful in preventing its development.[59]

Adverse Effects Most adverse effects reported with ATG and RATG are related to the lack of specificity for T cells. Dose-limiting myelosuppression (leukopenia, anemia, and thrombocytopenia) occurs frequently. Other adverse effects include anaphylaxis, hypotension, hypertension, tachycardia, dyspnea, urticaria, and rash. Serum sickness is seen more frequently with ATG than with RATG. Nephrotoxicity has been reported but is rare in the absence of serum sickness. Infusion-related febrile reactions are common; therefore, all patients should be premedicated with acetaminophen, diphenhydramine, and corticosteroids. Finally, as with any immunosuppressive agent, ATG and RATG are associated with an increased risk of infections, particularly viral infections, and malignancy.

Drug–Drug and Drug–Food Interactions No drug or food interactions have been reported with ATG or RATG.

Dosing and Administration ATG doses range from 10 to 30 mg/kg/day as a single dose for 7 to 14 days. RATG is a more potent compound and is administered at doses of 1 to 1.5 mg/kg/day as a single daily dose for 7 to 14 days for acute rejection or for 5 to 10 days for induction of immunosuppression. It is recommended that both ATG and RATG be administered through a central line or through a high-flow vein with an in-line 0.22-micron filter over at least 4 hours to minimize phlebitis and thrombosis.[33] Heparin and hydrocortisone are commonly added to the infusion to minimize phlebitis and thrombosis.[33]

Alemtuzumab Alemtuzumab is approved for use in B-cell chronic lymphocytic leukemia.[67] However, its effects on depleting both T and B lymphocytes make it useful in solid organ transplants. While alemtuzumab is not FDA approved for solid organ transplantation, it is increasingly recognized as a viable therapeutic option for induction or treatment of acute rejection. In 2012, commercial distribution of alemtuzumab ceased for transplantation and leukemia, requiring centers to enroll in the manufacturer's distribution program for these indications.[68]

Pharmacology/Mechanism of Action Alemtuzumab is a humanized monoclonal antibody against the CD52 surface antigen found on both T and B lymphocytes, as well as macrophages, monocytes, eosinophils, and natural killer cells. When alemtuzumab binds to the CD52 surface antigen, antibody-dependent lysis occurs, which removes both T and B lymphocytes from the blood, bone marrow, and organs, resulting in complete lymphocyte depletion.[67]

Pharmacokinetics The pharmacokinetics of alemtuzumab in solid organ transplantation patients have not been investigated. In patients with B-cell chronic lymphocytic leukemia, the volume of distribution of alemtuzumab after repeated dosing is 0.18 L/kg. The mean half-life after the first 30-mg dose is 11 hours, but increases to 6 days after 12 weeks of therapy. The extrapolation of these pharmacokinetic data to solid organ transplantation is difficult because of the differences in dosing strategies (single or multiple 30-mg doses in solid organ transplantation vs weekly to thrice weekly dosing in B-cell chronic lymphocytic leukemia). One or two doses of alemtuzumab result in complete and prolonged lymphocyte depletion. Following administration, B lymphocyte counts return to normal within 3 to 12 months. T lymphocytes, however, remain depressed for as long as 3 years following administration.[35,67]

Efficacy Alemtuzumab is effective as induction therapy for the prevention of acute rejection in kidney, liver, heart, pancreas, intestinal, and lung transplants.[34] Additionally, alemtuzumab has been used to successfully treat acute rejection following transplantation and is effective for corticosteroid- and antibody-resistant rejection.[27]

Adverse Effects Adverse effects of alemtuzumab are primarily infusion related, hematologic, and infectious. Because alemtuzumab causes complete lymphocyte depletion and associated cytokine release, infusion-related reactions include rigors, hypotension, fever, shortness of breath, bronchospasms, and chills. The potential for developing these reactions can be reduced by administering premedications such as acetaminophen, corticosteroids, and diphenhydramine or by administering smaller doses and escalating the dose gradually. Hematologic effects include pancytopenia, neutropenia, thrombocytopenia, and lymphopenia.

Drug–Drug and Drug–Food Interactions No drug or food interactions have been reported with alemtuzumab.

Dosing and Administration Several dosing regimens have been proposed for alemtuzumab in solid organ transplantation. The most common dosing strategy is 30 mg as a single dose; some centers administer a second dose 1 to 5 days after transplantation.[67] Other studied dosing strategies include 0.3 mg/kg per dose, as a single- or multiple-dose regimen, and, finally, two 20-mg doses given on the day of transplantation and the first postoperative day.[67]

Nondepleting Antibodies

Interleukin-2 Receptor Antagonists Basiliximab, a chimeric monoclonal antibody (25% murine) is the only available IL-2 receptor antagonist currently marketed in the United States. It is approved for use in kidney transplantation, but is also extensively used in other organ transplants as well.[69]

PHARMACOLOGY/MECHANISM OF ACTION Basiliximab exerts its immunosuppressive effect by specifically binding with high affinity to the α-chain (CD25) on the surface of activated T lymphocytes (see Fig. 105-1). Binding of basiliximab to the IL-2 receptor prevents IL-2-mediated activation and proliferation of T cells, a critical step in clonal expansion of T cells and the development of allograft rejection. Saturation of the IL-2 receptor occurs rapidly and confers an immunosuppressive effect that lasts for 4 to 6 weeks after administration.[69]

PHARMACOKINETICS Most of the pharmacokinetic data available for basiliximab was derived following administration to kidney transplantation patients. Caution must be used when extrapolating these data to nonrenal transplantation recipients. The volume of distribution is approximately 8 L and it has a half-life of approximately 7 days. Clearance is increased in patients who have received a liver transplant, and therefore it is recommended that patients with greater than 10 L of ascites receive an additional dose of basiliximab on postoperative day 8.[70]

EFFICACY Basiliximab is approved for use in kidney transplantation in combination with cyclosporine and corticosteroids, although induction therapy has also been studied extensively in liver and heart transplant recipients. In 2016 over 20% of kidney, liver, and heart transplant recipients received an IL-2 receptor antagonist at the time of transplant.[1] Use of basiliximab in liver transplant recipients has been increasing as a means of delaying CI initiation in the setting of acute kidney injury. A meta-analysis of basiliximab efficacy in kidney transplantation concluded that IL-2 receptor antagonists reduced the risk of rejection significantly with no increases in graft loss, infectious complications, malignancy, or death.[69] Similar results were seen in liver and heart transplant patients.[70]

IL-2 receptor antagonists offer a reasonable addition to calcineurin inhibitor—or corticosteroid-sparing protocols. While CI therapy cannot be completely avoided in most cases, IL-2 receptor antagonists allow for delayed use or reduced doses of CIs, thus minimizing the risk of nephrotoxicity in the early posttransplantation period. Similar rates of rejection and corticosteroid-resistant

rejection were seen in patients with DGF who received an IL-2 receptor antagonist in conjunction with lower tacrolimus doses compared with patients without DGF who received standard tacrolimus doses and no IL-2 receptor inhibitor induction.[70]

Adverse Effects Relatively few adverse effects have been reported with basiliximab. In contrast to lymphocyte-depleting agents, basiliximab is not associated with infusion-related reactions. However, since the marketing of basiliximab, an increased number of hypersensitivity reactions have been reported. Development of anti-idiotypic antibodies to the murine portion occurs rarely.[70] No increased risk of malignancy has been reported.

DRUG–DRUG AND DRUG–FOOD INTERACTIONS While, cyclosporine and tacrolimus serum concentrations may increase in patients receiving concomitant basiliximab therapy, this interaction is not considered clinically significant.[69]

DOSING AND ADMINISTRATION Basiliximab is usually administered as two 20-mg intravenous doses, intraoperatively and again on postoperative day 4. Basiliximab is compatible with both 0.9% sodium chloride and 5% dextrose and can be administered either centrally or peripherally over 20 to 30 minutes in a volume of 50 mL. This regimen results in saturation of the IL-2 receptor for 30 to 45 days.

Investigational Agents

Rituximab Rituximab is a chimeric monoclonal antibody against the CD20 receptor found on B cells. While it is FDA approved for non-Hodgkin lymphoma and rheumatoid arthritis, it has also been used for the treatment of antibody mediated rejection and posttransplant lymphoproliferative disorder as well as suppression of alloantibodies prior to transplantation.[71] Rituximab has been shown to improve graft survival when given in combination with plasmapheresis and IVIG in patients with AMR.[27] In highly sensitized patients, rituximab administration prior to transplantation has been shown to suppress alloantibodies and even allow transplantation across ABO-incompatibility.[71] In PTLD, rituximab is most effective in patients with CD20 positive malignancies.[71] The optimal dose of rituximab in transplantation has not been defined.

Bortezomib Bortezomib, a proteosomal inhibitor that is FDA approved for the treatment of multiple myeloma, has been used in the treatment of AMR. In one series, 20 patients with AMR received four doses of bortezomib 1.3 mg/m^2 on

days 1, 4, 7, and 11 with plasmapheresis. Bortezomib was effective in lowering donor specific antibodies by 50%.[27] Another series showed benefit of bortezomib over rituximab.[27] However, bortezomib is associated with a high incidence of side effects (up to 33% required hospitalization) that primarily effect the GI tract; diarrhea that leads to dehydration, nausea, edema, vomiting, infections, and peripheral neuropathy.[27]

Janus Kinase Inhibitors Janus kinases are important for transduction of intracellular signals in lymphocytes to stimulate proliferation and lymphocyte activity. Tofacitinib is a Janus Kinase 3 (JAK3) inhibitor that has been compared to cyclosporine in combination with mycophenolate mofetil and steroids. Tofacitinib show similar efficacy to cyclosporine, but is associated with an increased incidence of cytomegalovirus and BK virus infections.[72]

EVALUATION OF THERAPEUTIC OUTCOMES

8 The success of transplantation can be measured in terms of length of graft and patient survival as well as improvements in quality of life. Several donor and recipient factors that have an impact on graft and patient survival have been identified (**Table 105-9**). The greatest risk to short-term graft survival is acute rejection. Routine surveillance of appropriate biochemical markers and serum drug concentrations are essential to minimize the potential for acute rejection. These parameters should be assessed daily to weekly for the first 1 to 3 months after transplantation. Monitoring should include complete blood counts, serum electrolyte concentrations, serum creatinine and blood urea nitrogen concentrations, and the appropriate serum drug concentrations. Liver function tests should also be evaluated using the same schedule in liver transplantation recipients. Routine biopsies are necessary to monitor for acute rejection in heart and lung transplantation recipients. As the time after transplantation increases, the frequency of monitoring decreases. Once 3 months have elapsed after transplantation, monitoring of these parameters can be reduced to biweekly or monthly for most patients. **Table 105-10** depicts a typical posttransplantation laboratory monitoring plan.

TABLE 105-9 Factors Negatively Effecting Allograft and Patient Survival

	Kidney	Liver	Heart
Donor factors	Decreased HLA matching	Size mismatch	Size mismatch
		Age (youngest, oldest)	Increased age
	Increased age		Prolonged ischemia time
	Increased serum creatinine		
	Cardiac instability		
	Prolonged ischemia time		
	History of hypertension		
Recipient factors	Age <15, >50 years	Increased age	Age <5, >60 years
	Retransplantation	Retransplantation	ICU pretransplant
	African race	African race	Mechanical ventilation
	Elevated PRA	ICU pretransplant	LVAD
	Multiparous women	ABO blood type	IABP
	Poor drug adherence	Poor drug adherence	Poor drug adherence

HLA, human leukocyte antigens; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; PRA, panel of reactive antibodies.

TABLE 105-10 Laboratory Monitoring after Transplantation

	1-2 Weeks	1 Month	2-4 Months	4-12 Months	>12 Months
SCr/BUN	Daily	1-2 times per week	Every 1-2 weeks	Monthly	Every 1-2 months
Chemistries[a]	Daily	1-2 times per week	Every 1-2 weeks	Monthly	Every 1-2 months
Liver function tests[b]					
Kidney or heart recipient	Once	Once	Monthly	Every 1-3 months	Every 1-3 months
Liver recipient	Daily	1-3 times per week	Every 1-2 weeks	Monthly	Every 1-2 months
Immunosuppressant concentrations	Daily	1-2 times per week	Every 1-2 weeks	Monthly	Every 1-2 months
Complete blood count[c]	Daily	1-2 times per week	Every 1–2 weeks	Monthly	Every 1-2 months
Lipid panel[d]	Once	Every 3 months	Every 3 months	Every 3 months	Every 3 months
HbA_{1c}	Once	Every 3 months	Every 3 months	Every 3 months	Every 3 months

BUN, blood urea nitrogen; HbA_{1c}, hemoglobin A1c; SCr infusion, serum creatinine.

[a]Chemistries include sodium, potassium, chloride, CO_2 content, magnesium, calcium, phosphorus, and blood glucose.

[b]Liver function tests include total bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamyl transpeptidase (GGTP), alkaline phosphatase.

[c]Complete blood count includes white blood cells (WBC), red blood cells (RBC), platelets, and/or differential.

[d]Lipid panel includes total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride, and/or very low-density lipoprotein (VLDL).

Long-term graft survival is limited by chronic rejection. Overall survival rates

for solid organ transplantations are described in terms of half-life, or the time after transplantation at which only 50% of transplanted organs are still functioning. Estimated half-lives for kidneys are 26.9 years for HLA-identical grafts, and ranges from 10.8 to 12.2 for grafts from a sibling or parent who are 1-haplotype matches. The estimated half-life for HLA-matched grafts was 17.3 years while a markedly lower value of 7.8 years has been noted with mismatched kidneys.[1] The overall median patient survival time for heart transplant recipients is 9.8 years, but in these patients surviving the first year after transplantation, the median survival increases to 12 years.[1] The highest rate of mortality occurs within the first year after liver transplantation due to the risks of surgery and early postoperative complications.

PHARMACOTHERAPY CONSIDERATIONS

Individualization of drug therapy starts with identifying the patient's risk of rejection prior to transplantation. Most clinicians will use induction therapy with a lymphocyte depleting agent for patients at high risk of rejection, including those patients who are sensitized to more HLA antigens due to previous exposure to blood products or previous transplant, younger patients, and African Americans. Similarly, organs associated with a higher risk of rejection, including heart and lung transplants, require higher doses of immunosuppressants as maintenance therapy.

9 Therapeutic drug monitoring is paramount to ensure adequate immunosuppressant exposure while minimizing drug-related toxicities. Blood concentrations are routinely monitored for CIs and PSIs throughout the duration of therapy. Studies are ongoing to determine the correlation between blood concentrations and MPA. Consensus guidelines suggest that MPA monitoring may be warranted when MPA is used as the primary immunosuppressant, CI doses are reduced or discontinued, the patient has altered liver or kidney function, or medications that interact with MPA are administered concomitantly.[35]

Other patient-specific factors can influence CI pharmacokinetics and thus dosing requirements. Children require significantly higher CI doses on weight basis than do their adult counterparts, up to threefold higher in the youngest of patients. Advancing age appears to decrease CI requirements, presumably through increased absorption and decreased metabolic activity. Patients greater than 64 years required lower doses than younger recipients.[31] Beyond these factors, some transplant dependent factors can also impact immunosuppressant

exposure. Ischemic reperfusion injury in the setting of liver transplantation has been shown to increase P-glycoprotein expression and thus decrease CI absorption whereas uremia seen in the setting of delayed graft function in kidney transplantation is associated with decreased P-glycoprotein and thus higher CI concentrations.[31]

Pharmacogenetic assessment to optimize immunosuppressive therapy regimens is slowly emerging. Cytochrome P450 genetic polymorphisms are important for CI metabolism. Both cyclosporine and tacrolimus are metabolized by CYP3A5, which contributes to the interpatient variability associated with CIs. It is estimated that 30% of Caucasians and 50% of African Americans express high levels of CYP3A5 enzymes. Patients who express CYP3A5 require significantly higher doses of CIs to achieve therapeutic concentrations.[73] There are ethnic differences in CYP3A5 expressions that impact tacrolimus exposure as well as ultimate graft outcome. Up to 73% of patients of African descent express *CYP3A5*1* which is associated with a twofold reduction in dose normalized tacrolimus concentrations, that is, patients require higher doses to achieve the same target as nonexpressers.[31] This has been shown to result in higher TAC peak concentrations which may alter the adverse effect profile in these patients. Moreover, in *CYP3A5*1* expressers, recommended dose conversions result in higher AUC and C_{min} with the extended-release formulation versus immediate-release.[74] In African Americans who do not achieve target tacrolimus trough concentrations, the risks of antibody-mediated rejection and ACR are significantly elevated.[49] Furthermore, African Americans may require monitoring of MPA concentrations due to more rapid clearance of MPA compared to Caucasians.[75] CYP3A5 genotyping may help to identify patients who require higher doses of CIs to optimize immunosuppressive therapy earlier after transplantation and potentially decrease the risk of rejection.

Pharmacodynamic monitoring of immunosuppressants of the specific targets of immunosuppressants rather than blood concentrations is in its infancy. Research is ongoing to determine the value of monitoring calcineurin activity for CIs[76] and IMPDH activity for MPA.[53]

Generic Substitution

In recent years a number of generic versions of immunosuppressants have entered the market. While generic versions of corticosteroids and azathioprine have long been available, there are now generic versions of cyclosporine, USP [MODIFIED], tacrolimus, and both mycophenolic acid derivatives. While these

formulations have demonstrated bioequivalence to the innovator product in healthy individuals, bioequivalence testing in transplant patients is not required for approval.[77]

Several potential factors including the complexity of the regimens and the impact of end-organ disease could alter absorption and result in PK variability not seen in healthy volunteers. The presence of diabetes may delay gastric emptying, whereas cystic fibrosis may lead to differences in tacrolimus or cyclosporine secondary to fat malabsorption. Finally, none of the available generic formulations have been studied in pediatric patients.[78]

As generic medications may offer a significant cost advantage compared with the innovator product, their use will increase over time. Much of the concern with generic substitution for immunosuppressant and other narrow therapeutic index medications relates to the potential for increased or decreased systemic exposure that, although within the “acceptable” regulatory range, may put patients at risk because of inadequate maintenance of the desired serum concentrations. Systems that alert patients and prescribers to changes in formulation (eg, labels on medications, direct notification to physicians) could trigger clinicians to more closely monitor patients for efficacy and toxicity as well as heighten therapeutic drug monitoring during a switch. However, the extent to which increased monitoring could offset cost savings associated with generic substitution has not been fully delineated.

IMMUNOSUPPRESSION-RELATED COMPLICATIONS

Comorbidities such as cardiovascular disease and malignancy, recurrent disease, drug toxicities (namely nephrotoxicity), and chronic rejection are the primary causes of mortality in patients who have a functioning graft for 5 or more years after transplantation.[1]

Cardiovascular Disease

Cardiovascular disease is a leading cause of morbidity and mortality in transplant patients.[79] Hypertension, hyperlipidemia, and diabetes are common complications in transplantation recipients and are independent risk factors for cardiovascular disease. Chronic rejection has been linked to hypertension and hyperlipidemia.[37,79]

Hypertension

Corticosteroids, cyclosporine, tacrolimus, and impaired kidney graft function may cause posttransplantation hypertension. Calcineurin inhibitor–associated hypertension may be due to increased endothelin production as well as stimulation of the sympathetic and renin angiotensin systems.[80] In addition to the propensity to cause peripheral vasoconstriction, CIs promote sodium retention, resulting in extracellular fluid volume expansion. Tacrolimus appears to have less potential to induce hypertension following transplantation than cyclosporine.[38,80,81]

Calcium channel blockers have traditionally been the first-line agents to treat hypertension after transplantation.[30,80] They may ameliorate the nephrotoxic effects of cyclosporine, improve renal hemodynamics, decrease the incidence of DGF and the development of allograft atherosclerosis, and enhance the degree of immunosuppression.

ACEIs and angiotensin II receptor blockers have traditionally been avoided in kidney transplantation recipients, especially in the perioperative period, because of the potential for hyperkalemia and negative influence on glomerular filtration rate. They are now, however, considered to be an equivalent alternative to calcium channel blockers for the treatment of hypertension in all transplant recipients, and are preferred in patients with proteinuria.[30] When ACEIs or angiotensin II receptor blockers are used in patients after transplant, serum creatinine and potassium concentrations should be monitored closely. If the increase in serum creatinine is greater than 30% within 1 to 2 weeks after initiating ACEIs or angiotensin II receptor blockers, other alternatives must be considered (see Chapter 63).

Multiple antihypertensive agents are usually necessary to achieve the goal blood pressure in transplant recipients; consequently, the addition of a β-blocker, diuretic, or centrally acting antihypertensive may also be necessary. Calcineurin inhibitor–induced hypertension is often salt-sensitive, making it very responsive to diuretics. Central-acting agents (eg, clonidine) are used often as adjunctive therapy in transplantation recipients who are unable to achieve blood pressure control with calcium channel blockers or ACEIs. There are no universal goals for blood pressure in transplant recipients. Most indicate a goal blood pressure between 130/80 and 140/90 mm Hg depending on other compelling indications.[80]

Hyperlipidemia

Hyperlipidemia may be exacerbated by corticosteroids, calcineurin inhibitors, and sirolimus.[23,30] Corticosteroids promote insulin resistance and a decrease in lipoprotein lipase activity, as well as excessive triglyceride production. The mechanism of CIs may decrease the activity of the low-density lipoprotein (LDL) receptor or lipoprotein lipase, altering LDL catabolism.[23] Tacrolimus appears to have less potential than cyclosporine to induce hyperlipidemia.[38] It is controversial whether the management of hyperlipidemia in transplant recipients should be more aggressive than current guidelines for the general population (see Chapter 31).[30,82] Aggressive lipid lowering may not only arrest the progress or prevent the complications of atherosclerosis but may also promote graft survival in kidney and heart transplant recipients. Current recommendations suggest monitoring lipid panels 2 to 3 months after transplantation and annually thereafter.[19,30]

HMG-CoA reductase inhibitors should be used with caution in transplantation recipients because of several reports of rhabdomyolysis when these agents are combined with calcineurin inhibitors.[42] However, beyond their impact on hyperlipidemia, HMG-CoA reductase inhibitors also have immunomodulatory effects on MHC expression and T-cell activation and reduce cardiac allograft rejection.[42]

Concurrent use of simvastatin and cyclosporine is contraindicated, due to the increased risk of rhabdomyolysis.[83] The concurrent use of medications known to increase the risk of myopathy (such as gemfibrozil) should be avoided.[42] Baseline and follow-up creatinine phosphokinase measurements (every 6 months) have proven useful to identify patients with subclinical rhabdomyolysis. Pravastatin may be preferred as a result of its lower interactive potential with CIs because it is not metabolized by CYP3A4. The potential for hepatotoxicity from HMG-CoA reductase inhibitors warrants close monitoring of liver function in all transplant recipients[30,82]

Bile acid-binding resins may be used to lower cholesterol in transplant patients, but adequate doses are difficult to achieve without the development of GI adverse effects. Because the absorption of cyclosporine is dependent on the presence of bile in the GI tract, patients should be instructed to separate dosing of bile acid-binding resins and cyclosporine and most other immunosuppressants by at least 2 hours. For transplant patients who have hypertriglyceridemia refractory to dietary intervention, fish oil and fibric acid derivatives are well-tolerated, effective alternatives (see Chapter 31). Fibric-acid derivatives are most effective in lowering serum triglyceride concentrations.

New-Onset Diabetes after Transplantation

Corticosteroids and CIs can impair glucose control in patients with preexisting diabetes, as well as cause new-onset diabetes after transplantation (NODAT) in 5% to 30% of patients.[25,30] Corticosteroids induce insulin resistance and impair peripheral glucose uptake, whereas CIs appear to inhibit insulin production.[23] Tacrolimus seems to be more diabetogenic than cyclosporine, although recent studies have failed to show a statistical difference.[38] Other possible risk factors that have been identified for NODAT include African American or Hispanic ethnicity, age greater than 40 years at time of transplant, family history, and weight, as well as CMV and Hepatitis C virus infection.[23]

Up to 40% of patients with NODAT will require insulin therapy.[23] In patients with diabetes who can be managed with an oral hypoglycemic agent, glipizide, which is metabolized extensively by the liver, may be preferred over renally eliminated agents such as glyburide. Metformin should be used with caution because of the risk of lactic acidosis in those with impaired kidney function. Frequent blood glucose monitoring is imperative in the early postoperative phase to improve glucose control and to identify those with NODAT. Changes in kidney function secondary to CI nephrotoxicity or DGF or acute rejection in kidney transplant recipients affect the elimination of many hypoglycemic agents, including insulin, and may result in hyper- or hypoglycemia. Dose changes of immunosuppressant drugs also affect glycemic control. Tapering of immunosuppressive medications may result in reduced insulin requirements, whereas corticosteroid pulses for the treatment of rejection may result in increased insulin requirements.

Infection

Increased risk of infection is a natural consequence of therapeutic immunosuppression. Many infections, including cytomegalovirus and fungal infections, in solid organ transplant recipients are reviewed in Chapter 140.[84]

Polyomavirus-associated nephropathy (PVAN) is an important cause of impaired kidney function in kidney transplant recipients. Primary infection with BK virus occurs in childhood as an asymptomatic infection in 50% to 90% of the general population. The precise mechanism of transmission is not clear but is suspected to be via the oral or respiratory routes. The virus may remain latent primarily in the genitourinary tract until reactivation as the result of compromised immune function and is common in kidney transplant recipients.

Reactivation can be detected by measuring the presence of BK virus in the urine, a finding that is seen in approximately 30% to 40% of kidney transplant recipients, although it does not progress to nephropathy in the majority of patients. However, BK viremia if it develops has been noted to progress to allograft nephropathy in 50% of patients.[84] The development of BK virus nephropathy results in graft loss in about 46% of effected patients.[84]

All kidney transplant recipients should be screened for urinary BK virus replication monthly for the first 3 to 6 months after transplant, and every 3 months thereafter for the first year.[30,84] Screening for BK virus presence in serum should also occur any time the serum creatinine is elevated without known cause and after treatment of acute rejection. Treatment of BK virus should be initiated when plasma concentrations persist above 10,000 copies/mL(10×10^6/L).[30,84] The first line of treatment is to reduce immunosuppressive medications, targeting tacrolimus trough concentrations of <6 ng/mL (mcg/L; 7.4 nmol/L), cyclosporine <150 ng/mL (mcg/L; 125 nmol/L), sirolimus troughs <6 ng/mL (mcg/L; 6.6 nmol/L) or total daily mycophenolate mofetil doses of <1,000 mg. Other treatment strategies may include the addition of cidofovir, leflunomide, or fluoroquinolones.[84]

Hepatitis C virus (HCV) recurs almost universally following liver transplantation and the course of the disease is accelerated. Within 5 years, 10% to 20% of liver transplant recipients with HCV recurrence will progress to cirrhosis requiring retransplantation, compared to the general population where 20% to 30% will develop cirrhosis over 20 to 30 years. Recipient risk factors for recurrence include HCV viremia either before or in the first 3 month posttransplant, interleukin-28B TT genotype, and female sex. Advanced donor age and the presence of graft steatosis have also been associated with HCV progression.[10,85] Recommendations for the treatment of HCV were developed in 2014 by the American Association for the Study of Liver Diseases and the Infectious Disease Society of America and continue to rapidly evolve.[86] Additionally pretransplant antiviral therapy may reduce the risk of recurrent HCV post-liver transplant.[87] Management of drug–drug interactions with immunosuppressants and the direct acting antivirals (DAAs) is an important consideration for clinicians. Glecaprevir/pibrentasvir resulted in a 40% increase in tacrolimus AUC, but empiric dose reduction is not recommended. Elbasvir/grazoprevir and sofosbuvir/velpatasvir/voxilaprevir on the other hand are contraindicated with CSA due to a 15-fold and 9-fold increase in grazoprevir and voxilaprevir exposure, respectively. Simeprevir, an intestinal CYP3A4 and P-glycoprotein inhibitor, is contraindicated with cyclosporine-based regimens

due to a sixfold increase in simeprevir exposure when coadministered with cyclosporine. Conversely, ledipasvir, velpatasvir, sofosbuvir, and daclatasvir do not appear to significantly impact immunosuppressant concentrations. Only elbasvir/grazoprevir and glecaprevir/pibrentasvir are indicated for patients with creatinine clearance <30 mL/min (0.5 mL/s). Ribavirin does not have any direct pharmacokinetic interactions with immunosuppressants; however, clinicians should note the overlapping toxicities, especially anemia as well as the need to adjust doses of ribavirin in patients with reduced kidney function. The DAAs have been generally well-tolerated, but elbasvir/grazoprevir and glecaprevir/pibrentasvir should not be used in patients with decompensated cirrhosis.[86]

In the absence of preventative therapy, hepatitis B recurs in approximately 75% of patients after transplant in the absence of preventative treatment. Administration of hepatitis B immunoglobulin (HBIg) at the time of transplant reduces the rate of infection significantly.[88] Common strategies include intravenous HBIg 10,000 units during the anhepatic phase followed by 10,000 units daily for 6 days. Antihepatitis B surface titer should be monitored weekly to ensure adequate levels for protection as well as to optimize HBIg use. HBIg has been typically dosed to maintain titers greater than 100 to 500 international units/L. Long-term HBIg therapy is extremely costly, estimated at $100,000 for the first postoperative year and $50,000 for each subsequent year. Combination therapy with antiviral agents appears to be synergistic and is the current standard. Entecavir and tenofovir have emerged as first-line agents post-liver transplant due to lamivudine resistance. With the availability of highly active antiviral agents, there is growing interest in long-term regimens that don’t include HBIg. Treatment for active hepatitis B virus graft infection should include HBIg, antiviral therapy, and concomitant reduction in immunosuppression.[88]

Malignancy

Although advances in immunosuppression have decreased the incidence of acute rejection and increased patient survival, they have also increased the patient’s lifetime exposure to immunosuppression. While the precise mechanism is unclear, posttransplantation malignancy seems to be related to the overall level of immunosuppression, as evidenced by a difference in the rates of malignancy associated with quadruple versus triple versus dual immunosuppressant regimens. The risk of de novo malignancy in transplantation recipients is

increased threefold to fivefold over the general population.[53] The risk of lung and colon cancers may be as much as doubled in kidney transplant recipients.[89] A number of cancers that are uncommon in the general population occur with much higher prevalence in transplantation recipients: posttransplantation lymphomas and lymphoproliferative disorders (PTLDs), Kaposi sarcoma, renal carcinoma, in situ carcinomas of the uterine cervix, hepatobiliary tumors, and anogenital carcinoma are a few examples.[89] Skin cancers are the most common tumors. Factors that may predispose transplant recipients to skin cancers include copious sun exposure and therapy with azathioprine.[53] While too early to definitively assess the impact of MPA derivatives on malignancy, one analysis showed a lower risk of PTLD with MMF compared with AZA.[53] Proliferation signal inhibitors have a theoretical benefit in terms of the development of malignancy. In addition to immunosuppressive properties, PSIs also have antiproliferative effects. In fact, a decreased incidence of malignancy was reported in patients receiving PSIs versus CIs, and conversion to PSIs from CIs can result in regression of Kaposi sarcoma.[89]

PTLD encompasses a broad spectrum of disorders, ranging from benign polyclonal hyperplasia to malignant monoclonal lymphomas. Factors that predispose patients to PTLD include Epstein-Barr virus seronegativity at transplantation and intense immunosuppression, particularly with lymphocyte-depleting agents. Nonrenal transplantation recipients are more likely to develop PTLD secondary to the intensive immunosuppression used to reverse rejection. Administration of ganciclovir or acyclovir preemptively during antilymphocyte therapy may decrease the risk of EBV seroconversion and infection, reducing the eventual risk of PTLD. Treatment of life-threatening PTLD generally includes severe reduction or cessation of immunosuppression. Other options include systemic chemotherapy or rituximab.[89]

Posttransplantation malignancies appear an average of 5 years after transplantation and increase with the length of follow-up. As many as 72% of patients surviving greater than 20 years may be affected. Malignancy accounts for 11.8% of deaths after cardiac transplantation and is the single most common cause of death in the 6th to the 10th posttransplant years.[89]

CLINICAL BOTTOM LINE

Transplantation is a lifesaving therapy for several types of end-organ failure. Advances in the understanding of transplant immunology have produced an

unprecedented number of choices in terms of immunosuppression. The increasing number of effective immunosuppressive therapies offers clinicians diverse ways to prevent allograft rejection.

However, the vast array of currently available immunosuppressive agents make it increasingly difficult to evaluate their long-term efficacy. Clinicians must be keenly aware of the adverse effects of immunosuppressive medications and their management in order to optimize the care of the transplanted patient.

Postclass Engaged Learning Activity

Conduct a literature search and identify a manuscript that has been published in the past 24 months that compares various immunosuppression regimens in a patient after heart transplantation. Write a brief summary of study's primary hypothesis and the major findings. Compare and contrast the findings of this paper with what you learned in the pre-activity slides from the registry. This activity is intended to build your experience with accessing the primary biomedical literature for patients after solid organ transplant, and to enhance your appreciation for differences in large registry data versus individual clinical trials.

ABBREVIATIONS

ACEI	angiotensin-converting enzyme inhibitor
ACR	acute cellular rejection
AMR	antibody-mediated rejection
APC	antigen-presenting cell
ATG	antithymocyte globulin
ATN	acute tubular necrosis
AUC	area under the concentration curve
C_2	concentration 2 hours after dose
C_{peak}	peak concentration
CI	calcineurin inhibitors
CMV	cytomegalovirus
CYP	cytochrome P450 liver enzyme system
DAA	direct acting antivirals

DGF	delayed graft function
EBV	Epstein Barr virus
FKBP	FK506-binding protein
GI	gastrointestinal
HBIg	hepatitis B immunoglobulin
HLA	human leukocyte antigen
HMG-CoA	hydroxy-3-methylglutaryl-coenzyme A
HPLC	high-performance liquid chromatography
IFN	interferon
IFTA	interstitial fibrosis and tubular atrophy
IL-2R	Interleukin 2 receptor
IMPDH	inosine monophosphate dehydrogenase
LAS	lung allocation score
LDL	low-density lipoprotein
MELD	model for end-stage liver disease
MHC	major histocompatibility complex
6-MP	6-mercaptopurine
MPA	mycophenolic acid
MPAG	mycophenolic acid glucuronide
MRP2	multidrug-resistance-associated protein 2
mTOR	mammalian target of rapamycin
NFAT	nuclear factor of activated T lymphocytes
NODAT	new-onset diabetes after transplantation
OATP	organic anion-transporter proteins
OKT3	muromonab-CD3
PD-L1	programmed death ligand 1
PML	progressive multifocal leukoencephalopathy
PRA	panel of reactive antibodies
PSI	proliferation signal inhibitor
PTLD	posttransplantation lymphoproliferative disorder
PVAN	polyomavirus associated nephropathy
RIA	radioimmunoassay
REMS	risk evaluation and mitigation strategy

TPMT	thiopurine S-methyltransferase

REFERENCES

1. U.S. Department of Health and Human Services, Health Resources and Services Administration, OPTN/SRTR Annual Data Report. 2019. Available at: https://srtr.transplant.hrsa.gov/annual_reports/Default.aspx. Accessed April 7, 2019.
2. Alloway RR, Dupuis R, Gabardi S, et al. Evolution of the role of the transplant pharmacist on the multidisciplinary transplant team. *Am J Transplant*. 2011;11(8):1576–1583.
3. Rana A, Gruessner A, Agopian VG, et al. Survival benefit of solid-organ transplant in the United States. *JAMA Surg*. 2015;150(3):252–259.
4. Working Group on Incentives for Living Donation; Living D, Matas AJ, Satel S, et al. Incentives for organ donation: Proposed standards for an internationally acceptable system. *Am J Transplant*. 2012;12(2):306–312.
5. Tritto G, Davies NA, Jalan R. Liver replacement therapy. *Semin Respir Crit Care Med*. 2012;33(1):70–79.
6. U.S. Renal Data System, USRDS 2012 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. 2012. Available at: https://www.usrds.org/2012/view/. Accessed April 7, 2019.
7. Jansz TT, Bonenkamp AA, Boereboom FTJ, van Reekum FE, Verhaar MC, van Jaarsveld BC. Health-related quality of life compared between kidney transplantation and nocturnal hemodialysis. *PLoS One*. 2018;13(9):e0204405.
8. Quante M, Benckert C, Thelen A, Jonas S. Experience since MELD implementation: How does the new system deliver? *Int J Hepatol*. 2012;2012:264015.
9. Weeks SR, Sun Z, McCaul ME, et al. Liver transplantation for severe alcoholic hepatitis, updated lessons from the world's largest series. *J Am Coll Surg*. 2018;226(4):549–557.
10. Sheiner P, Rochon C. Recurrent hepatitis C after liver transplantation. *Mt Sinai J Med*. 2012;79(2):190–198.
11. McCalmont V, Ohler L. Cardiac transplantation: Candidate identification,

evaluation, and management. *Crit Care Nurs Q*. 2008;31(3):216–229. quiz 230-211.

12. Hartert M, Senbaklavacin O, Gohrbandt B, Fischer BM, Buhl R, Vahld CF. Lung transplantation: A treatment option in end-stage lung disease. *Dtsch Arztebl Int*. 2014;111(7):107–116.
13. Deng MC. Cardiac transplantation. *Heart*. 2002;87(2):177–184.
14. Wright M, Takeda K, Mauro C, et al. Dose-dependent association between amiodarone and severe primary graft dysfunction in orthotopic heart transplantation. *J Heart Lung Transplant*. 2017;36(11):1226–1233.
15. Wagner SJ, Brennan DC. Induction therapy in renal transplant recipients: How convincing is the current evidence? *Drugs*. 2012;72(5):671–683.
16. Wojciechowski D, Chandran S, Vincenti F. Early post-transplant conversion from tacrolimus to belatacept for prolonged delayed graft function improves renal function in kidney transplant recipients. *Clin Transplant*. 2017;31(5):.doi:10.1111/ctr.12930.
17. U.S. Department of Health and Human Services, Health Resources and Services Administration, Organ Procurement and Transplantation Network. Kidney Donor Profile Index (KDPI) Guide for Clinicians. 2019. Available at: https://optn.transplant.hrsa.gov/resources/guidance/kidney-donor-profile-index-kdpi-guide-for-clinicians/. Accessed April 7, 2019.
18. Venkataramanan R, Habucky K, Burckart GJ, Ptachcinski RJ. Clinical pharmacokinetics in organ transplant patients. *Clin Pharmacokinet*. 1989;16(3):134–161.
19. Costanzo MR, Dipchand A, Starling R, et al. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. *J Heart Lung Transplant*. 2010;29(8):914–956.
20. Thompson ML, Flynn JD, Clifford TM. Pharmacotherapy of lung transplantation: An overview. *J Pharm Pract*. 2013;26(1):5–13.
21. Cozzi E, Colpo A, De Silvestro G. The mechanisms of rejection in solid organ transplantation. *Transfus Apher Sci*. 2017;56(4):498–505.
22. U.S. Department of Health and Human Services, Health Resources and Services Administration, Organ Procurement and Transplantation Network. How Organ Allocation Works. 2019. Available at: https://optn.transplant.hrsa.gov/learn/about-transplantation/how-organ-allocation-works/. Accessed April 7, 2019.
23. Lucey MR, Terrault N, Ojo L, et al. Long-term management of the successful adult liver transplant: 2012 Practice guideline by the American

Association for the Study of Liver Diseases and the American Society of Transplantation. *Liver Transpl*. 2013;19(1):3–26.

24. Lund LH, Khush KK, Cherikh WS, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-fourth Adult Heart Transplantation Report-2017; Focus Theme: Allograft ischemic time. *J Heart Lung Transplant*. 2017;36(10):1037–1046.
25. Haas M. Pathologic features of antibody-mediated rejection in renal allografts: An expanding spectrum. *Curr Opin Nephrol Hypertens*. 2012;21(3):264–271.
26. Fehr T, Gaspert A. Antibody-mediated kidney allograft rejection: Therapeutic options and their experimental rationale. *Transpl Int*. 2012;25(6):623–632.
27. Kim M, Martin ST, Townsend KR, Gabardi S. Antibody-mediated rejection in kidney transplantation: A review of pathophysiology, diagnosis, and treatment options. *Pharmacotherapy*. 2014;34(7):733–744.
28. Birnbaum LM, Lipman M, Paraskevas S, et al. Management of chronic allograft nephropathy: A systematic review. *Clin J Am Soc Nephrol*. 2009;4(4):860–865.
29. Chih S, Chong AY, Mielniczuk LM, Bhatt DL, Beanlands RS. Allograft vasculopathy: The Achilles' Heel of Heart Transplantation. *J Am Coll Cardiol*. 2016;68(1):80–91.
30. Kasiske BL, Zeier MG, Craig JC, et al. Kidney disease: Improving Global Outcomes Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant*. 2009;9(suppl 3):S1–S155.
31. Knops N, Levtchenko E, van den Heuvel B, Kuypers D. From gut to kidney: Transporting and metabolizing calcineurin-inhibitors in solid organ transplantation. *Int J Pharm*. 2013;452(1-2):14–35.
32. Malat GE, Culkin C, Palya A, Ranganna K, Kumar MS. African American kidney transplantation survival: The ability of immunosuppression to balance the inherent pre- and post-transplant risk factors. *Drugs*. 2009;69(15):2045–2062.
33. Petite SE, Bollinger JE, Eghtesad B. Antithymocyte globulin induction therapy in liver transplant: Old drug, new uses. *Ann Pharmacother*. 2016;50(7):592–598.
34. Jasiak NM, Park JM. Immunosuppression in solid-organ transplantation: Essentials and practical tips. *Crit Care Nurs Q*. 2016;39(3):227–240.

35. Kuypers DR. Immunotherapy in elderly transplant recipients: A guide to clinically significant drug interactions. *Drugs Aging*. 2009;26(9):715–737.
36. Trofe-Clark J, Lemonovich TL. AST Infectious Diseases Community of Practice. Interactions between anti-infective agents and immunosuppressants in solid organ transplantation. *Am J Transplant*. 2013;13(suppl 4):318–326.
37. Shivaswamy V, Boerner B, Larsen J. Post-transplant diabetes mellitus: Causes, treatment, and impact on outcomes. *Endocr Rev*. 2016;37(1):37–61.
38. Lee RA, Gabardi S. Current trends in immunosuppressive therapies for renal transplant recipients. *Am J Health Syst Pharm*. 2012;69(22):1961–1975.
39. Salvadori M, Bertoni E. Is it time to give up with calcineurin inhibitors in kidney transplantation? *World J Transplant*. 2013;3(2):7–25.
40. Chisholm MA, Mulloy LL, Jagadeesan M, DiPiro JT. Coadministration of tacrolimus with anti-acid drugs. *Transplantation*. 2003;76(4):665–666.
41. Amundsen R, Asberg A, Ohm IK, Christensen H. Cyclosporine A- and tacrolimus-mediated inhibition of CYP3A4 and CYP3A5 in vitro. *Drug Metab Dispos*. 2012;40(4):655–661.
42. Olyaei A, Greer E, Delos Santos R, Rueda J. The efficacy and safety of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors in chronic kidney disease, dialysis, and transplant patients. *Clin J Am Soc Nephrol*. 2011;6(3):664–678.
43. Heeney SA, Tjugum SL, Corkish ME, Hollis IB. Safety and tolerability of high-intensity statin therapy in heart transplant patients receiving immunosuppression with tacrolimus. *Clin Transplant*. 2019;33(1):e13454.
44. Schiff J, Cole E, Cantarovich M. Therapeutic monitoring of calcineurin inhibitors for the nephrologist. *Clin J Am Soc Nephrol*. 2007;2(2):374–384.
45. Kuypers DR. Immunosuppressive drug monitoring—what to use in clinical practice today to improve renal graft outcome. *Transpl Int*. 2005;18(2):140–150.
46. Envarsus XR® (tacrolimus extended-release tablets) [product information]. Cary, NC: Veloxis Pharmaceuticals, Inc; 2018.
47. Ensor CR, Iasella CJ, Harrigan KM, et al. Increasing tacrolimus time-in-therapeutic range is associated with superior one-year outcomes in lung

transplant recipients. *Am J Transplant*. 2018;18(6):1527–1533.

48. Del Bello A, Congy-Jolivet N, Danjoux M, et al. High tacrolimus intra-patient variability is associated with graft rejection, and de novo donor-specific antibodies occurrence after liver transplantation. *World J Gastroenterol*. 2018;24(16):1795–1802.
49. Taber DJ, Gebregziabher MG, Srinivas TR, Chavin KD, Baliga PK, Egede LE. African-American race modifies the influence of tacrolimus concentrations on acute rejection and toxicity in kidney transplant recipients. *Pharmacotherapy*. 2015;35(6):569–577.
50. Bergmann TK, Barraclough KA, Lee KJ, Staatz CE. Clinical pharmacokinetics and pharmacodynamics of prednisolone and prednisone in solid organ transplantation. *Clin Pharmacokinet*. 2012;51(11):711–741.
51. Pascual J, Royuela A, Galeano C, Crespo M, Zamora J. Very early steroid withdrawal or complete avoidance for kidney transplant recipients: A systematic review. *Nephrol Dial Transplant*. 2012;27(2):825–832.
52. de Jonge H, Naesens M, Kuypers DR. New insights into the pharmacokinetics and pharmacodynamics of the calcineurin inhibitors and mycophenolic acid: Possible consequences for therapeutic drug monitoring in solid organ transplantation. *Ther Drug Monit*. 2009;31(4):416–435.
53. Staatz CE, Tett SE. Pharmacology and toxicology of mycophenolate in organ transplant recipients: An update. *Arch Toxicol*. 2014;88(7):1351–1389.
54. Knorr JP, Sjeime M, Braitman LE, Jawa P, Zaki R, Ortiz J. Concomitant proton pump inhibitors with mycophenolate mofetil and the risk of rejection in kidney transplant recipients. *Transplantation*. 2014;97(5):518–524.
55. van Gelder T, van Schaik RH, Hesselink DA. Pharmacogenetics and immunosuppressive drugs in solid organ transplantation. *Nat Rev Nephrol*. 2014;10(12):725–731.
56. Kuypers DR, Le Meur Y, Cantarovich M, et al. Consensus report on therapeutic drug monitoring of mycophenolic acid in solid organ transplantation. *Clin J Am Soc Nephrol*. 2010;5(2):341–358.
57. Imuran® (azathioprine) [product information]. San Diego, CA: Prometheus Laboratories Inc; 2011.
58. Shihab F, Christians U, Smith L, Wellen JR, Kaplan B. Focus on mTOR inhibitors and tacrolimus in renal transplantation: Pharmacokinetics,

exposure-response relationships, and clinical outcomes. *Transpl Immunol*. 2014;31(1):22–32.

59. Klawitter J, Nashan B, Christians U. Everolimus and sirolimus in transplantation-related but different. *Expert Opin Drug Saf*. 2015;14(7):1055–1070.
60. Dantal J. Everolimus: Preventing organ rejection in adult kidney transplant recipients. *Expert Opin Pharmacother*. 2012;13(5):767–778.
61. Vincenti F, Rostaing L, Grinyo J, et al. Belatacept and long-term outcomes in kidney transplantation. *N Engl J Med*. 2016;374(4):333–343.
62. Masson P, Henderson L, Chapman JR, Craig JC, Webster AC. Belatacept for kidney transplant recipients. *Cochrane Database Syst Rev*. 2014;(11):CD010699.
63. Iasella CJ, Winstead RJ, Moore CA, et al. Maintenance belatacept-based immunosuppression in lung transplantation recipients who failed calcineurin inhibitors. *Transplantation*. 2018;102(1):171–177.
64. Kumar D, LeCorchick S, Gupta G. Belatacept as an alternative to calcineurin inhibitors in patients with solid organ transplants. *Front Med (Lausanne)*. 2017;4:60.
65. Nulojix® (belatacept) [product information]. Princeton, NJ: Bristol-Myers Squibb Company; 2014.
66. LaMattina JC, Jason MP, Hanish SI, et al. Safety of belatacept bridging immunosuppression in hepatitis C-positive liver transplant recipients with renal dysfunction. *Transplantation*. 2014;97(2):133–137.
67. Morgan RD, O'Callaghan JM, Knight SR, Morris PJ. Alemtuzumab induction therapy in kidney transplantation: A systematic review and meta-analysis. *Transplantation*. 2012;93(12):1179–1188.
68. US Campath (alemtuzumab) Distribution Program. 2019. Available at: https://www.campathproviderportal.com. Accessed April 7, 2019.
69. Simulect® (basiliximab) [product information]. East Hanover, NJ: Novartis Pharmaceutical Corporation; 2018.
70. Cillo U, Bechstein WO, Berlakovich G, et al. Identifying risk profiles in liver transplant candidates and implications for induction immunosuppression. *Transplant Rev (Orlando)*. 2018;32(3):142–150.
71. Ramanath V, Nistala R, Chaudhary K. Update on the role of rituximab in kidney diseases and transplant. *Expert Opin Biol Ther*. 2012;12(2):223–233.

72. Wojciechowski D, Vincenti F. Tofacitinib in kidney transplantation. *Expert Opin Investig Drugs*. 2013;22(9):1193–1199.
73. Adams SM, Crisamore KR, Empey PE. Clinical pharmacogenomics: Applications in nephrology. *Clin J Am Soc Nephrol*. 2018;13(10):1561–1571.
74. Trofe-Clark J, Brennan DC, West-Thielke P, et al. Results of ASERTAA, a randomized prospective crossover pharmacogenetic study of immediate-release versus extended-release tacrolimus in African American kidney transplant recipients. *Am J Kidney Dis*. 2018;71(3):315–326.
75. Tornatore KM, Meaney CJ, Wilding GE, et al. Influence of sex and race on mycophenolic acid pharmacokinetics in stable African American and Caucasian renal transplant recipients. *Clin Pharmacokinet*. 2015;54(4):423–434.
76. van Rossum HH, de Fijter JW, van Pelt J. Pharmacodynamic monitoring of calcineurin inhibition therapy: Principles, performance, and perspectives. *Ther Drug Monit*. 2010;32(1):3–10.
77. Christians U, Klawitter J, Clavijo CF. Bioequivalence testing of immunosuppressants: Concepts and misconceptions. *Kidney Int Suppl*. 2010;(115):S1–S7.
78. Uber PA, Ross HJ, Zuckermann AO, et al. Generic drug immunosuppression in thoracic transplantation: An ISHLT educational advisory. *J Heart Lung Transplant*. 2009;28(7):655–660.
79. Webber A, Hirose R, Vincenti F. Novel strategies in immunosuppression: Issues in perspective. *Transplantation*. 2011;91(10):1057–1064.
80. Weir MR, Burgess ED, Cooper JE, et al. Assessment and management of hypertension in transplant patients. *J Am Soc Nephrol*. 2015;26(6):1248–1260.
81. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311(5):507–520.
82. Florentin M, Elisaf MS. Simvastatin interactions with other drugs. *Expert Opin Drug Saf*. 2012;11(3):439–444.
83. Fishman JA. Infection in organ transplantation. *Am J Transplant*. 2017;17(4):856–879.
84. Hirsch HH, Randhawa P, Practice ASTIDCo. BK virus in solid organ transplant recipients. *Am J Transplant*. 2009;9(suppl 4):S136–S146.

85. Mitchell O, Gurakar A. Management of hepatitis C post-liver transplantation: A comprehensive review. *J Clin Transl Hepatol*. 2015;3(2):140–148.
86. AASLD/IDSA HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. 2019. Available at: https://www.hcvguidelines.org. Accessed April 7, 2019.
87. Martin P, DiMartini A, Feng S, Brown R Jr, Fallon M. Evaluation for liver transplantation in adults: 2013 Practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Hepatology*. 2014;59(3):1144–1165.
88. Saab S, Chen PY, Saab CE, Tong MJ. The management of hepatitis B in liver transplant recipients. *Clin Liver Dis*. 2016;20(4):721–736.
89. Bottomley MJ, Harden PN. Update on the long-term complications of renal transplantation. *Br Med Bull*. 2013;106:117–134.

SECTION 14 RHEUMATOLOGIC DISORDERS

106

Osteoarthritis

Lucinda M. Buys and Sara A. Wiedenfeld

KEY CONCEPTS

1. Osteoarthritis (OA) is a very common disease. OA prevalence increases with age and number of other chronic conditions, with women more commonly affected than men.
2. Contributors to OA are systemic (age, genetics, hormonal status, obesity, occupational or recreational activity) and/or local (injury, overloading of joints, muscle weakness, or joint deformity).
3. OA is primarily a disease of cartilage that reflects a failure of the chondrocyte to maintain proper balance between cartilage formation and destruction. This leads to loss of cartilage in the joint, local inflammation, pathologic changes in underlying bone, and further damage to cartilage triggered by the affected bone.
4. The most common symptom associated with OA is pain, which leads to decreased function and motion. Pain relief is the primary objective of medication therapy.
5. Manifestations of OA are local, affecting one or a few joints; the knees are most commonly affected, as well as the hips and hands.
6. Nonpharmacologic therapy is the foundation of the treatment plan for all patients with OA. Nonpharmacologic therapy should be initiated before or concurrently with pharmacologic therapy.
7. Based upon efficacy, safety, and cost considerations, scheduled acetaminophen, up to 4 g/day, should be tried initially for pain relief in knee and hip OA. If this fails, nonsteroidal anti-inflammatory drugs (topical or oral) are recommended, if there are no contraindications.
8. Topical NSAIDs, in lieu of oral NSAIDs, are recommended for patients older than 75 years of age to decrease the risks of systemic toxicity.

9. Strategies to reduce NSAID-induced GI toxicity include the use of nonacetylated salicylates, COX-2 selective inhibitors, or the addition of misoprostol or a proton pump inhibitor.
10. Other agents useful in treating knee OA include intra-articular injections of corticosteroids, duloxetine, or tramadol.

Preclass Engaged Learning Activity

This activity is designed to build skills in developing a safe and effective patient specific plan as part of the patient care process.

Create a table of drug treatment options for the plan as part of the patient care process for a patient with knee, hip, and hand osteoarthritis in a patient with a history of a myocardial infarction, a patient with stage 3 chronic kidney disease, a patient with a history of a gastric ulcer and age of more than 80 years.

INTRODUCTION

Osteoarthritis (OA) is the most common joint disease and one of the leading causes of disability in the United States.[1] Knee OA alone is as important a contributor to disability as cardiovascular disease and more important than other comorbidities. OA is a common co-occurrence with other chronic health conditions that adversely affect quality of life.[1]

The progressive destruction of articular cartilage has long been appreciated in OA, but OA involves the entire diarthrodial joint, including articular cartilage, synovium, capsule, and subchondral bone, with surrounding ligaments and muscles also playing important roles. Changes in structure and function of these tissues produce clinical OA, characterized by joint pain and tenderness, with decreased range of motion, weakness, joint instability, and disability.

This chapter will review the epidemiology, etiology, pathophysiology, and clinical presentation of OA. It then will focus on nonpharmacologic and pharmacologic treatments for OA. Because millions of persons take medications for OA, the overall risks posed by these medications require careful consideration, particularly by clinicians who treat or advise patients on drug therapy for OA. This chapter examines the risks and benefits of OA treatments,

with emphasis on those individuals who have the highest risk for adverse events, to help clinicians maximize benefits and minimize risks to their patients with OA.

EPIDEMIOLOGY

During 2013 to 2015, an estimated 54.4 million adults in the United States reported doctor-diagnosed arthritis (osteoarthritis, rheumatoid arthritis, gout, lupus or fibromyalgia) with 23.7 million reporting arthritis-attributable activity limitation (AAAL).[1] The prevalence of AAAL among adults with arthritis increased by almost 20% over time (2002-2015).[1] Arthritis is projected to affect 78.4 million adults by 2040.[2] OA imposes a tremendous cost burden with combined arthritis-attributable medical expenditures and earnings losses totaling approximately $303 billion dollars in 2013.[3] The US Medical Expenditure Panel Survey found that arthritis-attributable medical expenditures were $139.8 billion, representing 11% of the total medical expenditures in 2013.[3] Among all adults in the US population, adults with arthritis had the highest overall average cost per person ($9,233), followed by adults with at least one nonarthritis chronic condition ($6,272) and those with no chronic conditions ($1,369).[3] Total hospital costs associated with the specific diagnosis of osteoarthritis were $16.5 billion attributed to 1 million hospital stays in 2013.[4] Arthritis-attributable lost earnings were $163.7 billion with almost half of lost earnings due to lower adjusted per-person earnings for those with arthritis.[3]

Prevalence by Age, Sex, and Race

Prevalence estimates for OA vary depending on the age group of interest, gender, ethnic group, and the specific joint involved. Estimates also depend on the specific means by which OA is assessed and documented. Clinical OA is based on physical exam and patient history, whereas radiographic OA is determined by x-ray or other imaging, and symptomatic OA is based on patient history and physical exam plus x-ray. OA is more prevalent with increasing age. In the United States, the prevalence of self-reported doctor-diagnosed arthritis in the 2013 to 2015 National Health Interview Survey (NHIS) is 22.7% for all persons over age 18, but 49.6% for persons age 65 and older.[1] Prevalence for AAAL among persons with doctor-diagnosed arthritis is 43.5% for all persons over age 18 and 44% for persons age 65 and older.[1] Radiologically confirmed

hip OA shows clear trends through all age groups, affecting 1.6% of those between ages 30 and 39, up to a prevalence of 14% in those over 85 years of age.[5] Radiographic hand OA is found in 5% of those aged 40, but in 65% of those older than 80 years of age.[6]

Prevalence of physician-diagnosed arthritis is 26.3% in white populations, and ranges from 11.1% for Asian populations to 21.8% for black populations.[1] African-American men are approximately 35% more likely to have radiographic knee OA and twice as likely to have more severe knee OA than white men.[7] No significant differences were found between the prevalence of knee OA in black women and white women, but black women were 50% more likely than white women to have more severe involvement.[7] Among adults with arthritis, the prevalence of severe joint pain is significantly higher in women (29.7%), non-Hispanic blacks (45.6%), those with less than a high school education (40.2%) and those unable to work (51.9%).[8] Women are also more likely to have inflammatory OA of the proximal and distal interphalangeal joints of the hands, giving rise to the formation of Bouchard and Heberden nodes, respectively (**Fig. 106-1**).

FIGURE 106-1 Heberden nodes (distal interphalangeal joint) noted on all fingers and Bouchard nodes (proximal interphalangeal joint) noted on most fingers. *(From Johnson BE. Arthritis: Osteoarthritis, Gout and Rheumatoid Arthritis. In: South-Paul JE, Matheny SC, Lewis EL, eds. CURRENT Diagnosis and Treatment in Family Medicine, 4th ed. New York, NY: McGraw-Hill; 2015.).*

Incidence

As the incidence of a disease describes the number of newly diagnosed cases each year, OA poses a challenging situation for determining disease incidence. These reasons include: (1) not all patients with OA seek medical treatment, (2) OA is very common within the population, (3) many effective treatments are available over the counter, promoting self-treatment, (4) not all radiographically diagnosed OA is symptomatic and patients may not be formally diagnosed with OA and (5) many patients have multiple affected joints, making it difficult to track the overall occurrence of OA in these individuals.

ETIOLOGY

2 The etiology of OA is multifactorial and complex, with development of OA depending on interplay between person-level risk factors and joint-level risk factors.[9] Many patients have more than one risk factor for the development of OA. The most common risk factors for the development of OA include age, obesity, sex, occupation, participation in certain sports, history of joint injury or surgery, and genetic predisposition.

Obesity

Obesity is the most important preventable risk factor for OA. This linkage is strongest for knee OA, although hip OA and even hand and wrist OA may be linked with obesity. The etiology of this association of OA in nonweight bearing joints is thought to be the adverse metabolic and inflammatory effects produced by obesity.[10] As the epidemic of obesity spreads in the United States and in other developed countries, so will the burdens imposed by OA. For every five unit increase in BMI, the risk of knee OA increases 35%.[9] Obesity often precedes OA and contributes to its development, rather than occurring as a result of inactivity from joint pain. In an 11-year study of approximately 30,000 Norwegian men and women, obesity significantly increased the risk of developing OA.[11] Men who were obese at baseline had a 2.8-fold increase in developing knee OA compared to the nonobese men, whereas women who were obese at baseline had a 4.4-fold increased risk in developing knee OA compared to the nonobese women. Also, there was an increased risk for severe knee OA in obese subjects.[11]

Occupation, Sports, and Trauma

OA risk is increased for people in occupations involving excessive mechanical stress. Work that involves prolonged standing, kneeling, squatting, lifting or moving of heavy objects increases risk of OA. Such occupations include construction, mining, healthcare assistance, factory work, carpentry, and farming.[9] Repetitive motion also contributes to hand OA, with the dominant hand usually affected. Risk for OA depends on the type and intensity of physical activity and whether injury incurred in the activity. Increased risk of OA is associated with participation in activities such as wrestling, soccer, weight lifting, football and hockey, although recreational participants do not have the increased risk seen in the professional athlete.[12] Studies that have included running, including long-distances have produced decidedly mixed results.[12] In the study of 30,000 Norwegians, exercise intensity was not associated with any increased risk in the obese subjects compared to those of normal weight.[11]

Traumatic knee injury, either during sports or in accidents, significantly increases the risk of knee OA over a 10-year period.[12] These injuries include anterior cruciate ligament tears, meniscal tears, and direct cartilage injuries.[9] Meniscal damage increases the risk of knee OA because of the loss of proper load bearing and shock absorption, increased focal load on cartilage and on subchondral bone. Quadriceps muscle weakness is also recognized to increase the risk for knee OA, as these muscles are important in maintaining joint stability.[10] As proper alignment of the joint structures is critical to proper function of the joint, knee malalignment increases risk of developing OA. In the person who already has OA, knee malalignment is strongly associated with faster progression of OA.[10]

Genetic Factors

OA is a complex disease with a strong genetic component. The genetic contribution to OA has been supported by many studies and it is estimated that 30% of the risk of OA is genetically determined.[13] There is not a single genetic variant responsible for OA, but likely thousands of loci associated with the complex nature of the disease. Identification of these genetic loci may promote development of agents to prevent OA or to slow or halt its progression. Heberden nodes are 10 times more prevalent in women than in men, for example, with a twofold higher risk if the woman’s mother had them. Genetic links have been shown with OA of the first metatarsophalangeal joint and with

generalized OA. Twin studies indicate that OA can be attributed substantially to genetic factors.[14]

One approach OA researchers have used is the candidate gene approach which is hypothesis based and focuses on genes with known function which could be plausibly linked with the OA. This approach requires *a priori* knowledge of disease etiology and only very small regions of the genome can be studied at a time. Recent studies of 199 candidate genes found that only 2 variants (COL11A1 and VEGF genes) reached significance.[13] These results confirm that using existing joint biology knowledge to identify genetic variants is unlikely to facilitate the understanding of the genetic risks of OA.

Genome-wide association studies (GWAS) use an hypothesis-free methodology that involves scanning hundreds of thousands or millions of genetic markers, in the form of single nucleotide polymorphisms (SNP's). Using GWAS studies at least 21 independent susceptibility loci to OA have been found.[13] A meta-analysis of GWA studies with 6,709 knee OA cases and 44,439 controls revealed that the Chrom7Q22 locus was very highly significantly associated with knee OA. The locus also included six genes which code for proteins that are known to be expressed in joint tissues.[15]

It is quite likely that the genetic risk of developing OA, like many other diseases, is determined by a combination of genetic differences. This underscores the point that understanding of the genetics and pathology of OA is in its early stages.

PATHOPHYSIOLOGY

OA falls into two major etiologic classes. *Primary* (*idiopathic*) *OA*, the more common type, has no identifiable cause. *Secondary OA* is that associated with a known cause such as inflammation, trauma, metabolic or endocrine disorders, and congenital factors.[16]

The old view of OA as a "wear-and-tear" or degenerative disease, largely focused on joint cartilage, has long been superseded by an appreciation of the dynamic nature of OA and that it represents a failure of the joint and surrounding tissues.[10] Some changes in the OA joint may reflect compensatory processes to maintain function in the face of ongoing joint destruction. Not only biomechanical forces but also inflammatory, biochemical, and immunologic factors are involved. An appreciation of the biology and function of normal cartilage can aid in understanding osteoarthritic cartilage and is summarized

below.

Normal Cartilage

Function, Structure, and Composition of Cartilage

Articular cartilage possesses viscoelastic properties that provide lubrication with motion, shock absorbency during rapid movements, and load support. In synovial joints, articular cartilage is found between the synovial cavity on one side and a narrow layer of calcified tissue overlying subchondral bone on the other side (**Fig. 106-2**).[16,17] The layer of cartilage is narrow, with human medial femoral articular cartilage being approximately 2 to 3 mm thick. Despite this, healthy articular cartilage in weight-bearing joints withstands millions of cycles of loading and unloading each year. Cartilage is easily compressed, losing up to 40% of its original height when a load is applied. Compression increases the area of contact and disperses force more evenly to underlying bone, tendons, ligaments, and muscles. In addition, cartilage is almost frictionless, and together with its compressibility, this enables smooth movement in the joint, distributes load across joint tissues to prevent damage, and stabilizes the joint.

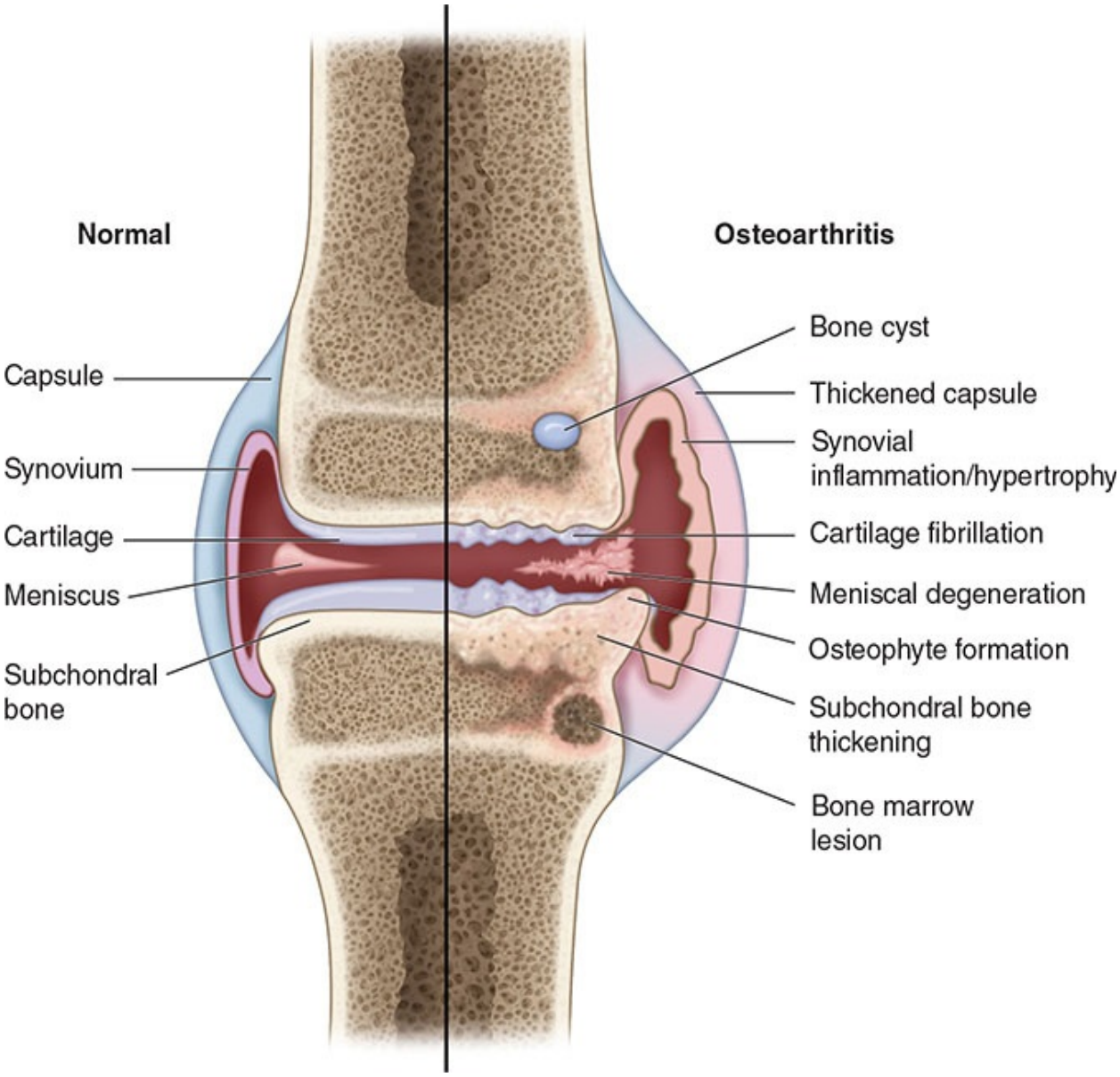


FIGURE 106-2 Characteristics of osteoarthritis in the diarthrodial joint. (*Used with permission from Loeser RF. Age-related changes in the musculoskeletal system and the development of osteoarthritis. Clin Geriatr Med. 2010;26(3):371-386.).*

Strength, a low coefficient of friction, and compressibility of cartilage derive from its unique structure. Cartilage is a complex, hydrophilic, extracellular matrix (ECM). It is approximately 70% water, 10% collagen, 8% proteoglycans, chondrocytes, other proteins, and long hyaluronic acid molecules.[18] The two major structural components in articular cartilage are type II collagen and aggrecans.[16] Type II collagen has a tightly woven triple helical structure, which

provides the tensile strength of cartilage. Aggrecan is a proteoglycan linked with hyaluronic acid, providing the long aggrecan molecules a high negative charge. These are squeezed together by surrounding fibrils of type II collagen. The strong electrostatic repulsion of proteoglycans held in close proximity gives cartilage the ability to withstand further compression. Within the cartilage ECM are the chondrocytes, the only cells in cartilage, responsible for laying down all the components of cartilage.

Normal cartilage turnover helps repair and restore cartilage in response to demands of joint loading and during physical activity. In adults, cartilage chondrocyte metabolism is slow and is regulated by growth factors, including bone morphogenetic protein 2, insulin-like growth factor-1, and transforming growth factor, and by catabolism and proteolysis stimulated by matrix metalloproteinases (MMPs), tumor necrosis factor-α (TNF-α), interleukin-1, and other cytokines. Tissue inhibitors of metalloproteinase (TIMP) also contribute to the balance by restraining the catabolic actions of MMPs. If cartilage is injured, chondrocytes react by removing the damaged areas and increasing synthesis of matrix constituents to repair and restore cartilage.[17]

Another component supporting healthy joints are the joint protective mechanisms, such as muscles bridging the joint, sensory receptors in feedback loops to regulate muscle and tendon function, supporting ligaments, and subchondral bone that has shock-absorbent properties.

Finally, it is important to note that adult articular cartilage is avascular, with chondrocytes nourished by synovial fluid. With movement and cyclic loading and unloading of joints, nutrients flow into the cartilage, whereas immobilization reduces nutrient supply. This is one of the reasons that normal physical activity is beneficial for joint health.

Osteoarthritic Cartilage

3 Important contributors to the development of OA are local mechanical influences, genetic factors, inflammation, and aberrant chondrocyte function leading to loss of articular cartilage.[16,19] At a molecular level, OA pathophysiology involves the interplay of dozens, if not hundreds, of extracellular and intracellular molecules with roles including chondrocyte regulation, phenotypic changes, proteolytic degradation of cartilage components, and interactions between articular cartilage, underlying subchondral bone, and the joint synovium.[10,19]

OA most commonly begins with damage to articular cartilage, through trauma

or other injury, excess joint loading from obesity or other reasons, or instability or injury of the joint that causes abnormal loading. In response to cartilage damage, chondrocyte activity increases in an attempt to remove and repair the damage. Depending on the degree of damage, the balance between breakdown and resynthesis of cartilage can be lost, and a vicious cycle of increasing breakdown can lead to further cartilage loss and apoptosis of chondrocytes.[10,19] Recent studies have revealed several respects of the very complex nature of OA.

There is increased appreciation of the role of tissues beyond cartilage, within the joint and surrounding it, subchondral bone.[19] Subchondral bone undergoes pathologic changes that may precede, coincide with, or follow damage to the articular cartilage. In OA, subchondral bone releases vasoactive peptides and MMPs, and damage to subchondral bone may trigger further damage to articular cartilage.[18] Neovascularization and subsequent increased permeability of the adjacent cartilage occur and contributes further to cartilage loss.

Joint space narrowing results from loss of cartilage, which can lead to a painful, deformed joint (**Fig. 106-3**). Remaining cartilage softens and develops fibrillations (vertical clefts into the cartilage), followed by splitting off of more cartilage and exposure of underlying bone.[18] During this time, adjacent subchondral bone undergoes further pathologic changes, cartilage is eroded completely, leaving denuded subchondral bone, which becomes dense, smooth, and glistening (eburnation). A more brittle, stiffer bone results, with decreased weight-bearing ability and development of sclerosis and microfractures. New bone formations or osteophytes also appear at joint margins, distant from cartilage destruction and are thought to arise from local and humoral factors. There is direct evidence that osteophytes can help stabilize osteoarthritic joints.[16]

FIGURE 106-3 Plain x-ray films of the knee demonstrating joint space narrowing. *(From Johnson BE. Arthritis: Osteoarthritis, Gout and Rheumatoid Arthritis. In: South-Paul JE, Matheny SC, Lewis EL, eds. CURRENT Diagnosis and Treatment in Family Medicine, 4th ed. New York, NY: McGraw-Hill; 2015.).*

In the joint capsule and synovium, inflammatory changes and pathologic changes can occur.[19] Contributors to inflammation may include crystals or cartilage shards in synovial fluid. Other possible factors are interleukin-1, prostaglandin E_2, TNF-α, and nitric oxide that are found in synovial fluid. With inflammatory changes in the synovium, effusions and synovial thickening occur.

4 The pain of OA is not related to the destruction of cartilage but arises from the activation of nociceptive nerve endings within the joint by mechanical and chemical irritants.[10,16] OA pain may result from distension of the synovial capsule by increased joint fluid, microfracture, periosteal irritation, or damage to ligaments, synovium, or the meniscus. Consequently, x-ray changes in OA correlate poorly with pain severity.

CLINICAL PRESENTATION

Diagnosis

5 The diagnosis of OA is made through history, physical examination,

characteristic radiographic findings, and laboratory testing.[20] The major diagnostic goals are (1) to discriminate between primary and secondary OA and (2) to clarify the joints involved, severity of joint involvement, and response to prior therapies, providing a basis for a treatment plan. The American College of Rheumatology has published traditional diagnostic criteria and "decision trees" for OA diagnosis.[20] As with all guidelines, the authors stress these are for assisting the clinician rather than replacing clinical judgment. For example, traditional criteria are as follows: (1) For hip OA, a patient must have pain in the hip and at least two of the following three: an erythrocyte sedimentation rate <20 mm/hr (5.6 µm/s), femoral or acetabular osteophytes on radiography, or joint space narrowing on radiography. This provides a sensitivity of 89% and a specificity of 91%. For a clinical diagnosis of knee OA, a patient must have pain at the knee and osteophytes on radiography plus one of the following: age older than 50 years, morning stiffness no more than 30 minutes, crepitus on motion, bony enlargement, bony tenderness, or palpable warmth. This provides a sensitivity of 95% and a specificity of 69%. The addition of laboratory or radiographic data further improves accuracy of diagnosis. Criteria for hand OA have also been published.[21]

Prognosis

The prognosis for patients with primary OA is variable and depends on the joint involved. If a weight-bearing joint or the spine is involved, considerable morbidity and disability are possible. In the case of secondary OA, the prognosis depends on the underlying cause. Treatment of OA may relieve pain or improve function but does not reverse preexisting damage to the joint.

TREATMENT

Desired Outcome

Management of the patient with OA begins with a diagnosis based on a careful history, physical examination, radiographic findings, and an assessment of the extent of joint involvement. Treatment should be tailored to each individual. Goals are (1) to educate the patient, family members, and caregivers; (2) to relieve pain and stiffness; (3) to maintain or improve joint mobility; (4) to limit functional impairment; and (5) to maintain or improve quality of life.[22,23] About half of the US population has one chronic health condition, with 25% having two

or more conditions.[24] With nearly 25% of the US adults with a least one chronic health condition having arthritis, it is essential that comprehensive patient-centered medication management is provided to these patients to maximize treatment goals for OA and other chronic conditions, while minimizing medication related adverse outcomes.

CLINICAL PRESENTATION Osteoarthritis

Age

- Usually occurs in older adults (≥65 years of age)

Gender

- Age <45 years more common in men
- Age >45 years more common in women

Symptoms

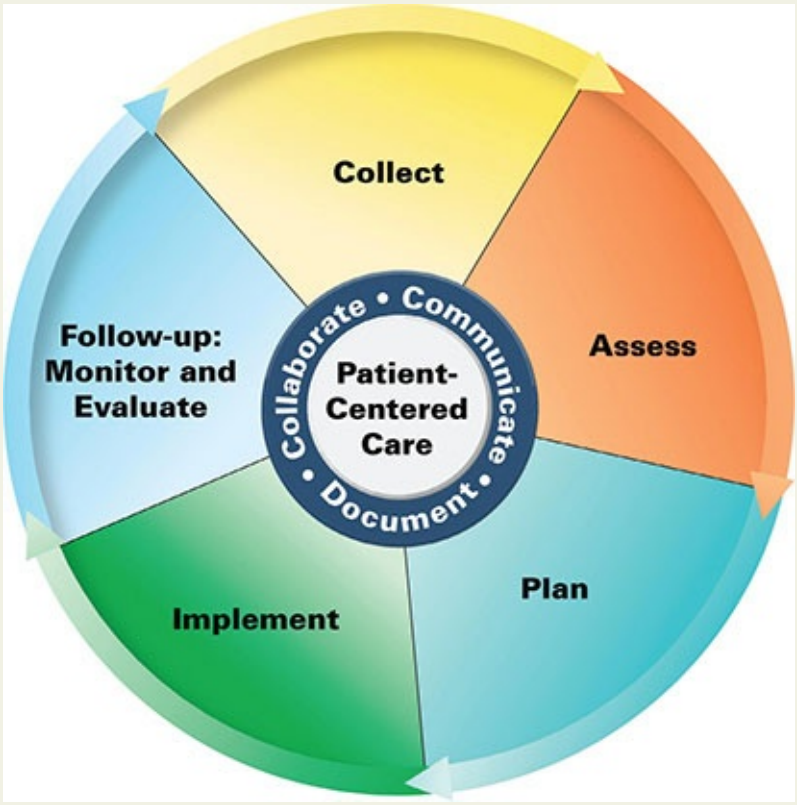
- Pain
- Deep, aching character
- Pain on motion
- Stiffness in affected joints
- Resolves with motion, recurs with rest (“gelling phenomenon”)
- Usually duration <30 minutes
- Often related to weather
- Limited joint motion
- May result in limitations of activities of daily living
- Instability of weight bearing joints

Signs, history, and physical examination

- Monoarticular or oligoarticular, asymmetrical involvement
- Hands
  - Distal interphalangeal joints
    - Herberden nodes (osteophytes or bony enlargements) (Fig. 106-1)
  - Proximal interphalangeal joints

        - Bouchard’s nodes (osteophytes)
    - First metacarpal joint
        - Osteophytes give characteristic square appearance to hands
- Knee
    - Pain related to climbing stairs
        - Transient joint effusion
        - Genu varum (“bow-legged”)
    - Hips
        - Groin pain during weight bearing exercises
        - Stiffness, especially after activity
        - Limited joint movement
    - Spine
        - Lumbar involvement is most common at L3 and L4
        - Paresthesia
        - Loss of reflexes
    - Feet
        - Typically involves the first metatarsophalangeal joint
    - Shoulder, elbow, acromioclavicular, sternoclavicular, temporomandibular joints may also be affected.
- Observation on joint examination
    - Bony proliferation or occasional synovitis
    - Local tenderness
    - Crepitus
    - Limited motion with passive/active movement
    - Deformity
- Radiologic Evaluation
    - Early Mild OA
        - Radiographic changes often absent
    - Progressive OA
        - Joint space narrowing (Fig. 106-3)
        - Subchondral bone sclerosis
        - Marginal osteophytes
    - Late OA
        - Abnormal alignment of joints

- Effusions



Patient Care Process for the Management of Osteoarthritis

Collect

- Patient characteristics (eg, age, weight, height, race, sex, pregnant)
- Patient history (past medical, family, social—trauma, diet, exercise, alcohol use)
- Symptom information: type and location of pain, duration, effect of motion and rest, range of motion and limitations on activities, joint instability
- Current and past medications, including nonprescription agents and dietary supplements, and medications' relief of symptoms
- Objective data
    - Physical examination, appearance of joints
    - Radiologic evaluation—changes in joints, subchondral bone sclerosis, effusions

- Body mass index (presence of overweight or obesity)

Assess

- Distribution and severity of joint involvement
- Impact of symptoms on patients' movements, health-related quality of life, amount of disability

Plan

- Patient education about disease, prognosis, treatment options, application and use of topical products
- Nonpharmacologic therapy (see Table 106-1)—weight loss (if overweight or obese), exercise, surgery (for severe pain or functional disability)
- Drug therapy regimen including specific analgesics, dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Figs. 106-4 and 106-5 and Tables 106-2 and 106-3)
- Monitoring parameters including efficacy (eg, symptom relief), safety (medication-specific adverse effects) (see Table 106-3)
- Self-monitoring of symptoms, exercise, and weight—where and how to record results
- Referrals to other providers when appropriate (eg, physician, orthopedic surgeon, physical therapist, dietician)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Assess symptom relief, effectiveness of weight loss and exercise programs
- Presence of adverse effects (see Table 106-3), including cardiovascular and renal effects of NSAIDs and hepatic effects of acetaminophen
- Closely monitor proper use of opioids, including dependence, addiction, tolerance, hyperalgesia, and diversion (see text); joint replacement may be preferred to chronic opioids

- Patient adherence to treatment plan using multiple sources of information

** Collaborate with patient, caregivers, and other healthcare professionals.*

General Approach to Treatment

Treatment for each OA patient depends on the distribution and severity of joint involvement, comorbid disease states, concomitant medications, and allergies. Management for all individuals with OA should begin with both oral and written patient education, a customized activity and exercise program, and weight loss, if the patient is overweight or obese.[22,23] A multidisciplinary intervention for knee OA initiated by pharmacists has been shown to improve adherence to OA guideline recommendations, decrease pain scores and improve functional assessment scores.[25] These types of multidisciplinary disease state management programs that implement strategies to provide comprehensive care should be offered to all OA patients to maximize outcomes.

The primary objective of medication is to alleviate pain.[22,23] Scheduled acetaminophen, up to 4 g/day, should be tried initially (knee, hip), if contraindications are not present. Application of topical NSAIDs over specific joints (knee, hands) and topical capsaicin (hands) are recommended as initial therapy. Nonsteroidal anti-inflammatory drugs (NSAIDs) or possibly a cyclooxygenase-2 (COX-2)–selective inhibitor (celecoxib) can be prescribed after careful risk assessment if additional pain control is needed. Intra-articular corticosteroid injections (knee or hip) can relieve pain and are offered concomitantly with oral analgesics or after failed trials of first-line medications, depending on the practitioner's preference. With centrally acting serotonin reuptake inhibition and analgesic properties, tramadol can also be considered if acetaminophen or topical treatment is ineffective or not tolerated.

Consideration may also be given to duloxetine or rarely, hyaluronic acid injections when additional pain control is needed for knee OA. When symptoms are persistent or there is significant loss of function, joint replacement can be appropriate if the patient is a surgical candidate.

There is general agreement that glucosamine and/or chondroitin and topical medications lack uniform efficacy in the treatment of hip and knee OA pain and are not preferred treatment options.

Nonpharmacologic Therapy

6 Nonpharmacologic therapy is an integral part of the treatment plan for all

patients with OA.[22,23,26] Nonpharmacologic therapy is the only available treatment that has been shown to delay the progression of OA.[2,27] Delaying the progression of OA through active participation in nonpharmacologic therapy is critical to prevent future functional impairment. Patient specific characteristics such as (1) number and location of affected joints, (2) degree of functional impairment, (3) body mass index, (4) motivation, and (5) overall health status determine which nonpharmacologic therapies should be offered. Nonpharmacologic therapy should be ongoing treatment for all patients, even those who require pharmacologic therapy for pain control (Table 106-1).[2,26,27]

TABLE 106-1 Nonpharmacologic Interventions in the Treatment of OA[28,29]

Intervention	Strength of Recommendation
Exercise	Strong
Weight loss (if overweight)	Strong
Patient education	Strong
Use of assistive device (ie, cane)	Moderate
Use of shoe insoles	Moderate
Application of heat	Moderate
Use of fitted knee braces	Minimal
Lateral patellar taping	Minimal
Passive exercise alone	Minimal

Robustness of recommendation: Strong–fully supported by evidence-based guidelines, Moderate–supported by evidence-based guidelines, Minimal–little support by evidence-based guidelines.

Patient Education

The first step in OA treatment is patient education about the disease process, the extent of OA, the prognosis, and treatment options. Education is paramount in that OA is often seen as a wear-and-tear disease, an inevitable consequence of aging for which nothing helps. Even worse, patients may resort to the use of alternative but unproven medications or treatments. Organizations such as the Arthritis Foundation provide a wealth of educational information for patients regarding OA, OA medications, information about local clinics and agencies offering physical and economic assistance. Exercise, weight loss, and nutritional information are also available. Most educational information is readily available online for patient use. Several mobile applications are available to provide

education, track symptoms and exercise, and encourage better self-management of OA.

The benefits of patient education have been documented in a variety of programs.[26,28] These programs are provided across a wide spectrum of delivery methods: from trained volunteers using telephone calls to group sessions for patient support to one-on-one educational sessions with physical therapists or nurse educators. While nearly all of these delivery methods are effective, cost of delivery is highly variable. Long-term cost-effectiveness is very important for sustainability of these patient education programs.

Weight Loss

The association between OA and obesity has been well established. Studies also indicate a strong association between increasing BMI and surgical replacement of the hip and knee joints.[30] Weight loss of amounts as small as 4% body weight can lessen OA pain in the knee.[31] Greater amounts of weight loss, especially when associated with regular exercise improve joint function and substantially lessen pain.[2,27] Modest weight loss (5%) has been shown to provide some relief in obese patients with OA but the goal weight loss should be an initial decrease in body weight of at least 10% to provide significant reductions in pain.[30] The Intensive Diet and Exercise for Arthritis trial (IDEA) found that after 18 months, overweight and obese adults with knee OA who participated in the diet and exercise treatment group had less inflammation, less pain, better function and better quality of life.[32] Weight loss requires a motivated patient, but it should be encouraged and supported for all obese and overweight patients with OA. Effective behavior change strategies should be employed to promote weight loss in patients with OA.[27]

Exercise

Exercise programs can improve joint function and can decrease disability, pain, and analgesic use by OA patients.[2,33] Low-impact aerobic exercise including both land- and water-based methods are preferred.[34] Exercises can be taught and then observed before the patient exercises at home. The frequency, types of exercise and setting of exercise are still uncertain, but patients who exercise have decreased pain and increased physical function.[35] The patient should be instructed to decrease the number of repetitions if severe pain develops with exercise.

Some regular exercise should be encouraged for all patients with OA.[23] With

weak or deconditioned muscles, the load is transmitted excessively to the joints; weight-bearing activities can exacerbate symptoms. Many patients fear that exercise will promote further joint damage and avoid exercise as a means to protect the joint. However, avoidance of regular exercise by those with hip or knee OA leads to further deconditioning and/or weight gain. Further weight gain and deconditioning leads to more pain and impaired joint function, promoting a downward spiral of disability. Exercise therapy in addition to patient education has been shown to decrease or postpone the need for hip replacement surgery in patients with hip OA.[36]

Referral to the physical and/or occupational therapist is especially helpful for developing a customized exercise plan for patients with functional disabilities. The therapist can assess muscle strength and joint stability and recommend exercises and assistive and orthotic devices, such as canes, walkers, braces, heel cups, splints, or insoles for use during exercise or daily activities. Heat or cold treatments help to maintain and restore joint range of motion and to reduce pain and muscle spasms. Warm baths or warm water soaks may decrease pain and stiffness. Heating pads should be used with caution, especially in the elderly. Patients should be warned not to fall asleep on the heat source or to lie on it for more than brief periods to avoid burns.

Surgery

Surgery can be recommended for OA patients with functional disability and/or severe pain unresponsive to medical therapy.[37] Total joint replacement surgeries are quite common and expected to increase. Over 1 million total hip and knee replacements procedures are performed each year in the United States. It is estimated that there are 7 million individuals living with an artificial knee or hip including 620,000 people who have both.[29] Although total knee arthroplasty can decrease pain and improve function for many patients, about 20% experience little or no improvement in pain, disability and/or quality of life.[38] Patients who are obese are less likely to have improvement in symptoms from knee arthroplasty. Patients also experience less pain and decreased length of hospitalization after surgery if they participate in a supervised exercise program for the first two months that begins on the day of surgery.[39]

Total joint arthroplasty is responsible for a large portion of the direct medical costs associated with OA in the United States. The cost-effectiveness of total knee arthroplasty has been evaluated for a Medicare-age population.[40] Calculations were based on Medicare claims data and costs and outcomes data. Cost projections were calculated for lifetime costs as well as quality-adjusted life

expectancy (QALE) for different risk populations and across low-volume to high-volume hospitals. Although total knee arthroplasty was found to be cost-effective across hospital settings and patient risk categories, the procedure was found to be most cost-effective when performed in high-volume centers. The cost-effectiveness of knee arthroplasty was evaluated against nonsurgical management. Knee arthroplasty was found to be cost-effective at both low and high levels of improvement in pain and function in patients with severe knee OA.[41] It is anticipated that direct medical costs associated with joint replacement will continue to increase at higher than predicted rates due to increasing willingness of patients to undergo joint replacement surgery.[3]

TABLE 106-2 Dosing of Medications for Osteoarthritis

Drug	Brand Name	Starting Dose	Usual Range	Special Population Dose	Other
Oral analgesics					
Acetaminophen	Tylenol	325-500 mg three times a day	325-650 mg every 4-6 hours or 1 g 3-4 times/day	Chronic alcohol intake, hepatic disease	Contained in many combination analgesics
Tramadol Tramadol ER	Ultram Ultram ER	25 mg in the morning 100 mg daily	Titrate dose in 25 mg increments to reach a maintenance dose of 50-100 mg three times a day. Titrate to 200-300 mg daily	Creatinine clearance <30 mL/min (0.5 mL/s)—maximum dose is 200 mg daily Do not use if creatinine clearance <30 mL/min (0.5 mL/s)	May need to taper dose upon discontinuation to prevent withdrawal symptoms
Hydrocodone/ acetaminophen	Lortab, Vicodin, Norco	5 mg/325 mg three times daily	2.5-10 mg/325-650 mg 3-5 times daily	Titrate dose slowly in older adults (age >65 years)	Maximum dose limited by total daily dose of acetaminophen
Oxycodone/ acetaminophen	Percocet	5 mg/325mg three times daily	2.5-10 mg/325-650 mg 3-5 times daily	Titrate dose slowly in older adults (age >65 years)	Maximum dose limited by total daily dose of acetaminophen
Topical analgesics					
Capsaicin 0.025% or 0.15%	Capzasin-HP		Apply to affected joint 3-4 times per day		—
Diclofenac 1% gel	Voltaren		Apply 2 or 4 g per site as prescribed, 4 times daily		
Diclofenac 1.3% patch	Flector		Apply one patch twice daily to the site to be treated, as directed.		
Diclofenac 1.5% solution	Pennsaid		Apply 40 drops to the affected knee, applying and rubbing in 10 drops at a time. Repeat for a total of four times daily		
Diclofenac 2% solution	Pennsaid		Apply 40 mg (two pump actuations) twice daily		
Intra-articular Corticosteroids					
Triamcinolone	Kenalog	5-15 mg/joint	10-40 mg/large-joint (knee, hip, shoulder)	If multiple joints injected, maximum total dose is usually 80 mg	Often administered concomitantly with a local anesthetic
Methylprednisolone acetate	Depo-Medrol	10-20 mg/joint	20-80 mg/large-joint (knee, hip, shoulder)	10-40 mg for medium joints (elbows, wrists)	
Nonsteroidal anti-inflammatory drugs (NSAIDs)					
Aspirin, plain, buffered, or enteric-coated	Bayer, Ecotrin, Bufferin	325 mg three times a day	325-650 mg four times a day		Doses of 3,600 mg/day are needed for anti-inflammatory activity
Celecoxib	Celebrex	100 mg daily	100 mg twice daily or 200mg daily		
Diclofenac XR	Voltaren-XR	100 mg daily	100-200 mg daily		
Diclofenac IR	Cataflam	50 mg twice a day	50-75 mg twice a day		
Diflunisal	Dolobid	250 mg twice a day	500-750 mg twice a day		
Etodolac	Lodine	300 mg twice a day	400-500 mg twice a day		
Fenoprofen	Nalfon	400 mg three times a day	400-600 mg 3-4 times a day		
Flurbiprofen	Ansaid	100 mg twice a day	200-300 mg/day 2-4 divided doses		
Ibuprofen	Motrin, Advil	200 mg three times a day	1,200-3,200 mg/day in 3-4 divided doses		Available OTC and Rx
Indomethacin	Indocin	25 mg twice a day	Titrate dose by 25-50 mg/day until pain controlled or maximum dose of 50 mg three times a day		
Indomethacin SR	Indocin SR	75 mg SR once daily	Can titrate to 75 mg SR twice daily if needed		

Ketoprofen	Orudis	50 mg three times a day	50-75 mg 3-4 times a day	
Meclofenamate	Meclomen	50 mg three times a day	50-100 mg three to four times a day	
Mefenamic acid	Ponstel	250 mg three times a day	250 mg four times a day	FDA approval for 1 week of therapy
Meloxicam	Mobic	7.5 mg daily	15 mg daily	
Nabumetone	Relafen	500 mg daily	500-1000 mg 1-2 times a day	
Naproxen	Naprosyn	250 mg twice a day	500 mg twice a day	
Naproxen sodium Naproxen sodium DR	Anaprox, Aleve Naprelan	220 mg twice a day	220–550 mg twice a day 375-750 mg twice a day	Available OTC and Rx
Oxaprozin	Daypro	600 mg daily	600-1200 mg daily	
Piroxicam	Feldene	10 mg daily	20 mg daily	
Salsalate	Disalcid	500 mg twice a day	500-1000 mg 2-3 times a day	

Pharmacologic Therapy

Drug therapy in OA is targeted at relief of pain. OA is commonly seen in older individuals who have other medical conditions, and OA treatment is often long term. As such, a conservative and patient-centered approach to drug treatment is warranted (see **Figs. 106-4**, **106-5**).[22,23,26] Even when pharmacologic therapy is initiated, appropriate nondrug therapies should be continued and reinforced. Specific drug therapy recommendations depend on which joint(s) are affected, response to previous trials of medication and patient comorbidities.

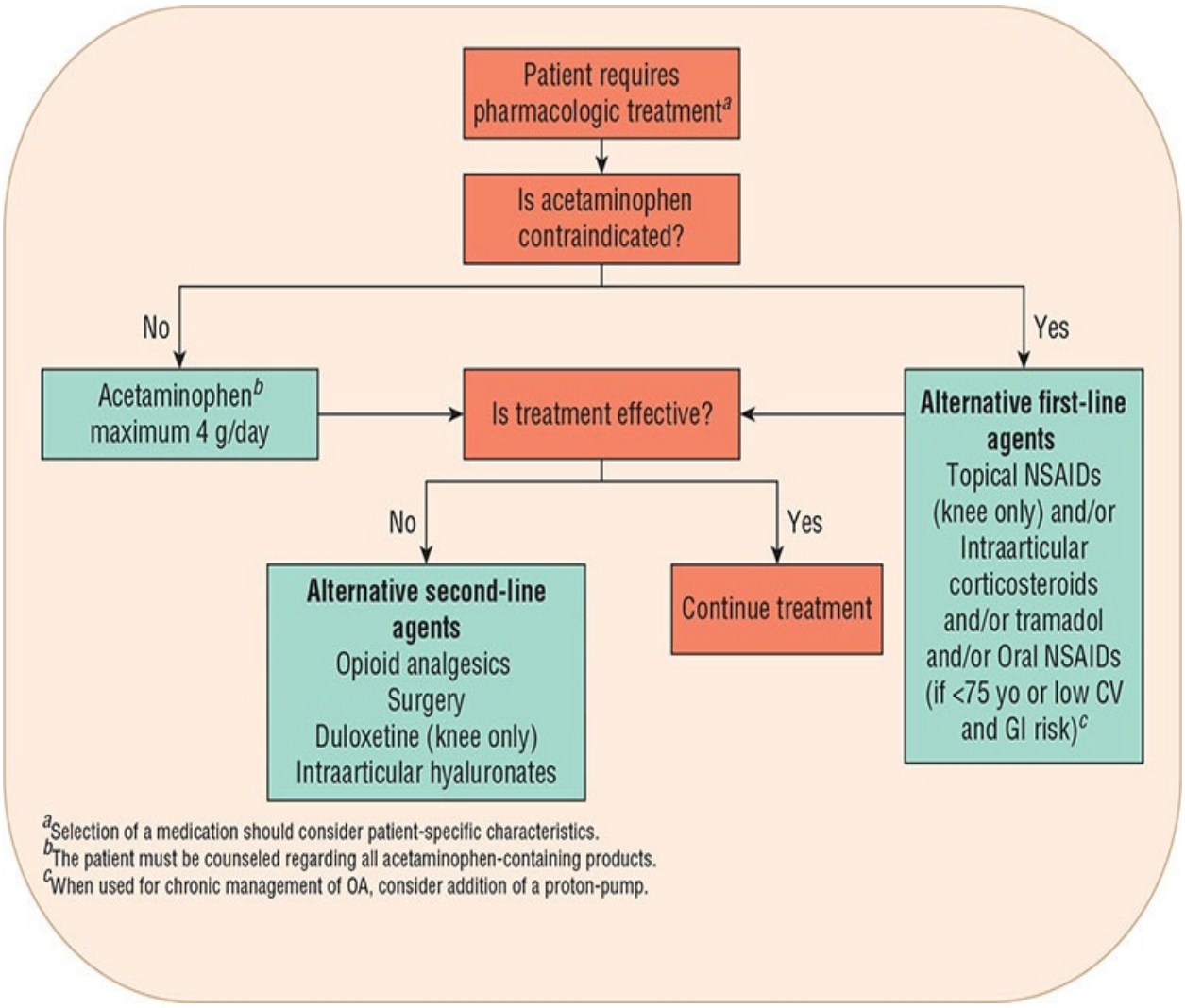


FIGURE 106-4 Treatment recommendations for knee and hip osteoarthritis. (CV, cardiovascular; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.).

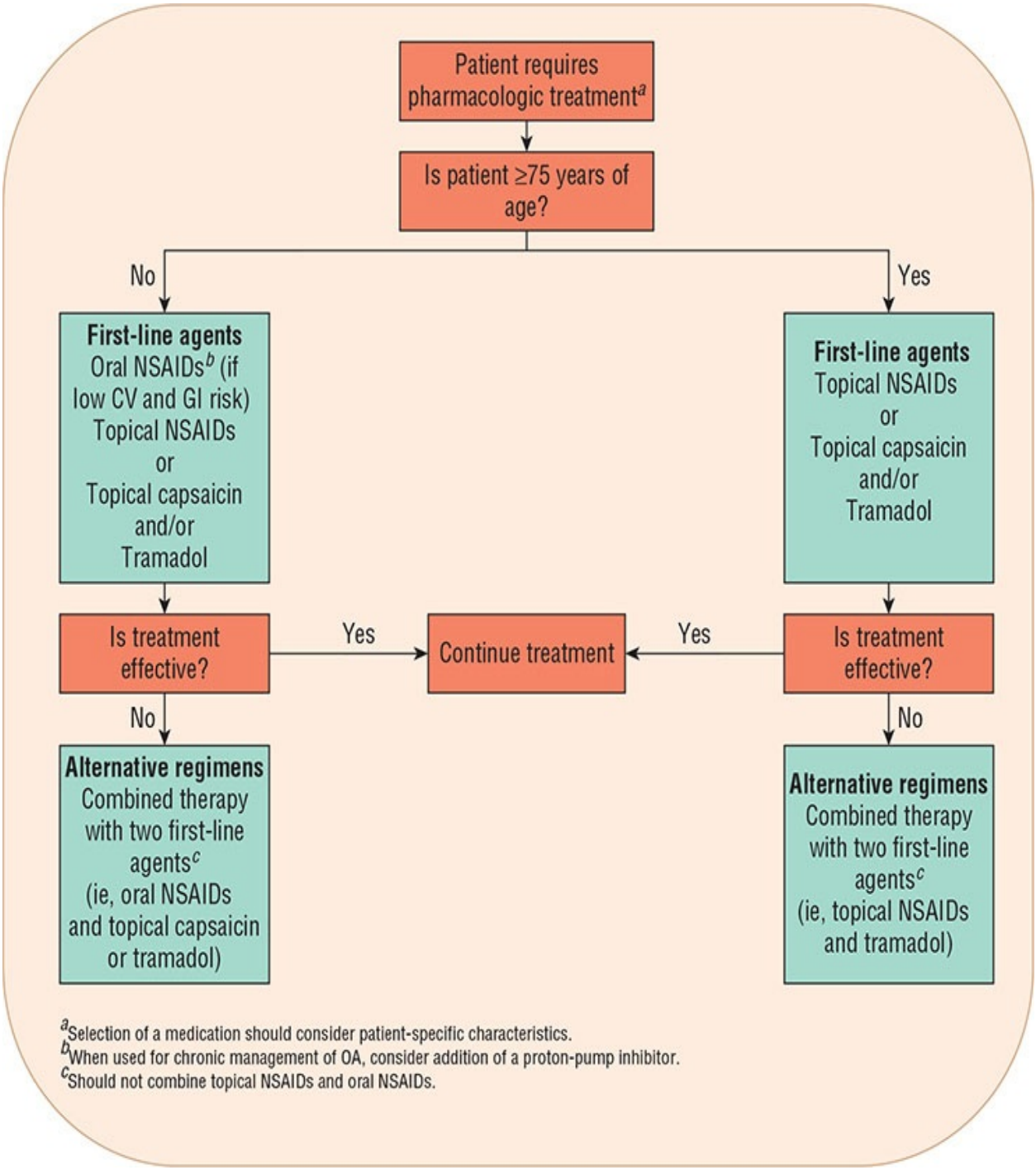


FIGURE 106-5 Treatment recommendations for hand osteoarthritis. (NSAID, nonsteroidal anti-inflammatory drug.).

Knee and Hip OA

First-Line Treatments

7 ***Acetaminophen*** The American College of Rheumatology, as well as others,

recommend acetaminophen as a first-line treatment for knee and hip OA.[22,23,42] Acetaminophen has been extensively studied in the treatment of knee and hip OA and is more effective than placebo in controlling OA pain.[43] Compared with oral NSAIDs, acetaminophen may be modestly less effective, but have lower risk of serious gastrointestinal and cardiovascular adverse events and as a consequence is preferred over oral NSAIDs as first-line treatment.[26,42]

Oral NSAIDs The American College of Rheumatology and other key groups recommend nonspecific or COX-2 selective NSAIDs, depending on patient risk factors, as a first-line option for knee and hip OA if the patient fails acetaminophen.[23,24,41] Nonselective and COX-2 selective NSAIDs pose higher risks for gastrointestinal, renal, and cardiovascular adverse events compared to acetaminophen. COX-2 inhibitors carry less risk for both minor and serious gastrointestinal adverse events in comparison to nonselective NSAIDs (with the exception of diclofenac).[42]

8 ***Topical NSAIDs—Knee Only*** The American College of Rheumatology and other authorities recommend topical NSAIDs as a first-line option for knee OA if the patient fails acetaminophen and is preferred over oral NSAIDs for those older than age 75 years.[22,23,42] Randomized trials have demonstrated that topical NSAIDs provide pain relief for OA similar to that obtained with oral NSAIDs but with fewer gastrointestinal adverse events. Topical NSAIDs offer a favorable safety profile and aren't associated with systemic adverse effects. The most common adverse effect of topical NSAIDs is a localized skin reaction.[44]

Intra-articular Corticosteroids Intra-articular corticosteroid injections are recommended as alternative first-line treatment for both knee and hip OA when pain control with acetaminophen or NSAIDs is suboptimal.[22,23] Injections can also be administered with concomitant oral analgesic therapy as needed for additional pain control. Intra-articular corticosteroids are generally safe and well tolerated, but should not be administered more frequently than once every three months due to risks of systemic adverse effects.

Tramadol Tramadol is recommended as an alternative first-line treatment of knee and hip pain due to OA in patients who have failed treatment with scheduled full-dose acetaminophen and topical NSAIDs, who are not appropriate candidates for oral NSAIDs and are not able to receive intra-articular corticosteroids.[23] Tramadol can also safely be added to partially effective acetaminophen or oral NSAID therapy. Less data are available to support the use

of tramadol as monotherapy for OA pain.

Second-Line Treatments

Opioid Analgesics The American College of Rheumatology recommends opioid analgesics as the primary second-line medication for both knee and hip OA.[23] Opioids may be considered in patients who have not had an adequate response to both nonpharmacologic and first-line pharmacologic therapies. Patients who are at high surgical risk, precluding joint arthroplasty are also candidates for opioid therapy. When compared to nonopioid medications in a 12-month randomized trial, opioids were not found to be superior in improving pain related function.[45] Adverse effects, including serious events, limit the routine use of opioids in the treatment of OA pain.

TABLE 106-3 Monitoring of Medications Used in Osteoarthritis Treatment

Drug	Adverse Drug Reactions	Monitoring Parameters	Comments
Oral Analgesics			
Acetaminophen	Hepatotoxicity	Total daily dose limits	Use caution with multiple acetaminophen-containing products—total 4 g limit (or less in patients with hepatic dysfunction)
Tramadol	Nausea, vomiting, somnolence	No routine labs recommended	Drug–drug interaction with other serotonergic medications
Opioids	Sedation, constipation, nausea, dry mouth, hormonal changes	No routine labs recommended	Risks of addiction, dependence, and drug diversion
NSAIDs	Dyspepsia, CV events, GI bleeding, renal impairment	BUN/Creatinine, Hgb/Hct, blood pressure	Risks higher in those older than 75 years of age
Topical Analgesics			
Capsaicin	Skin irritation and burning	Inspection of areas of application	Wash hands thoroughly after application
NSAIDs	Skin itching, rash, irritated Dyspepsia, CV events, GI bleeding, renal impairment	Inspection of areas of application. As needed: BUN/Creatinine, Hgb/Hct, blood pressure	Wash hands thoroughly after application. Avoid oral NSAID or aspirin other than cardioprotective dose. Ensure patient applying gel, solution, or patch correctly
Injectable drugs			
Intra-articular corticosteroids	Hypertension, hyperglycemia	Glucose, blood pressure	HPA axis suppression if used too frequently
Intra-articular hyaluronates	Local joint swelling, stiffness, pain	No routine labs recommended	Less effective than intra-articular corticosteroids; expensive

Duloxetine—Knee Only Duloxetine can be used as adjunctive treatment in patients with knee OA who have had a partial response to first-line analgesics.[22,23] It may be a preferred second-line medication in patients with both neuropathic and musculoskeletal OA pain. Duloxetine has demonstrated efficacy primarily as add-on therapy when there has been less than optimal response to acetaminophen or oral NSAIDs.[46,47] Reduction in pain occurs at about 4 weeks after initiation.[48] Adverse events associated with duloxetine in the treatment of knee OA are most commonly gastrointestinal with nausea, vomiting and constipation being the most common. The recommended dose is 60 mg once daily. However, some patients may benefit from higher doses, up to a maximum dose of 120 mg daily.[48] Adverse events have not been reported in OA trials that

most commonly used doses of 60 mg/day. A higher dose is associated with an increased risk of adverse reactions.

Intra-articular Hyaluronic Acid The American College of Rheumatology, NICE, and others do not routinely recommend the use of intra-articular hyaluronic acid injections for knee OA pain.[22,23,26] HA injections do not appear to provide clinically meaningful improvement in pain and/or function scores, although some studies may report statistical differences in scores. These agents may be associated with serious adverse events such as increased pain, joint swelling and stiffness. Limited efficacy and risks of serious events limit the routine use of these agents.

Hand OA

First-Line Treatments

NSAIDs The American College of Rheumatology and NICE recommend topical NSAIDs as a first-line option for hand OA.[26] Application of diclofenac gel compared to placebo topical product for hand OA provided significant relief.[21] No difference was found between the efficacy of oral and topical NSAIDs. Local adverse effects were seen more with topical verses oral NSAIDs but gastrointestinal adverse effects were more common with oral NSAIDs.[49,50] Efficacy with topical NSAIDs was reported quickly, within 1 to 2 weeks.[21]

Oral NSAIDs are recommended as an alternative first-line treatment for hand OA by the American College of Rheumatology and as second-line therapy in the NICE guidelines.[23,26] For the person who cannot tolerate local skin reactions or who received inadequate relief from topical NSAIDs, oral NSAIDs can offer relief, but the patient then faces increased risk for GI, renal, and cardiovascular adverse events.

Topical Capsaicin Capsaicin cream is recommended as an alternative first-line treatment for hand OA.[23] Clinical trial data supporting the use of capsaicin for the treatment of hand OA is limited to small studies, but demonstrates about 50% reduction in pain scores.[21] Adverse effects associated with capsaicin are primarily skin irritation and burning, therefore it is a reasonable therapeutic alternative for patients not able to take oral NSAIDs.

Tramadol Tramadol is recommended by the American College of Rheumatology as an alternative first-line treatment for OA of the hand.[23] No studies in hand OA with tramadol have been performed.[21] In clinical practice, tramadol is a

therapeutic option for patients who do not respond to topical therapy and are not candidates for oral NSAID treatment due to high GI, CV, or renal risks. Tramadol may also be used in combination with partially effective acetaminophen, topical therapy or oral NSAIDs.

Drug Class Information

Highlighted drug information will be reviewed below. This section is not intended to be all inclusive but aims to provide pertinent drug information to facilitate the safe and effective use of these medications in patients with OA.

First-Line Treatments

Acetaminophen

Pharmacology and Mechanism of Action Acetaminophen is understood to act within the central nervous system (CNS) by inhibiting synthesis of prostaglandins, agents that enhance pain sensations. Acetaminophen prevents prostaglandin synthesis by blocking the action of central cyclooxygenase (COX). Acetaminophen is well absorbed after oral administration, with a bioavailability of 60% to 98%. It achieves peak concentrations within 1 to 2 hours, it is inactivated in the liver by conjugation with sulfate or glucuronide, and its metabolites are renally excreted.

Adverse Effects Although acetaminophen is one of the safest analgesics for younger individuals without comorbidities, it carries greater risk in frail older adults.[51] Serious hepatotoxicity, including fatalities, have been well documented with acetaminophen overdose (see Chapter e7, “Clinical Toxicology,” for treatment of acetaminophen overdose).[52] Unintentional overdoses of acetaminophen are due to a variety of circumstances including narrow therapeutic window at the maximum dose (4 g/day), interpatient differences in sensitivity to liver injury from acetaminophen, a wide array of nonprescription and prescription products that contain acetaminophen, which may be hard for patients to identify on the label, and consumers’ lack knowledge about the association of acetaminophen and serious liver injury.

Acetaminophen related hepatotoxicity is dose-dependent. Even at therapeutic doses, acetaminophen may cause transient liver enzyme elevations and potentially hepatotoxicity.[53,54] The most common risk factor for liver failure in patients who take acetaminophen is chronic alcohol intake.[55] The FDA has

recommended that chronic alcohol users (three or more drinks daily) avoid acetaminophen intake as it increases the risk of liver damage or GI bleeding. Other individuals do not appear to be at increased risk of GI bleeding.

Drug–Drug Interactions and Drug–Food Interactions Drug interactions with acetaminophen can occur; for example, isoniazid can increase the risk of hepatotoxicity. Chronic ingestion of maximal doses of acetaminophen may intensify the anticoagulant effect for patients taking warfarin; such individuals may need closer monitoring. Although food decreases the maximum serum concentration of acetaminophen by approximately half, the overall efficacy is unchanged.

Dosing and Administration When used for chronic OA, acetaminophen should be administered in a scheduled manner. It may be taken with or without food. Acetaminophen can be taken at 325 to 650 mg every 4 to 6 hours, but the total dose must not exceed 4 g daily (see Adverse Effects above). FDA labeling requirements warn patients about potential liver toxicity if they inadvertently ingest more than the recommended dose when using multiple products containing acetaminophen. Additionally, prescription analgesics containing acetaminophen are limited to 325 mg/tablet to further decrease the opportunity for inadvertent overdose. Acetaminophen should be avoided in the setting of chronic alcohol intake or in those with underlying liver disease.

Oral Nonsteroidal Anti-inflammatory Drugs

Pharmacology and Mechanism of Action NSAIDs reduce pain, inflammation, and fever by preventing synthesis of tissue prostaglandins and related prostanoids, which play a role in triggering these symptoms. All NSAIDs bind (reversibly) to the cyclooxygenase 2 (COX-2) enzyme, blocking its action and thus prostanoid production. Blockade of prostaglandin synthesis by inhibiting COX enzymes (mainly COX-2) is thought to account for NSAIDs ability to relieve pain and inflammation (**Fig. 106-6**).[56] Nonselective NSAIDs were developed prior to extensive knowledge of COX enzymes, but in fact they block both COX-2 and COX-1. COX-1 has required “housekeeping” functions such as gastroprotection. COX-2 inhibitors selectively block COX-2 but not COX-1 activity.

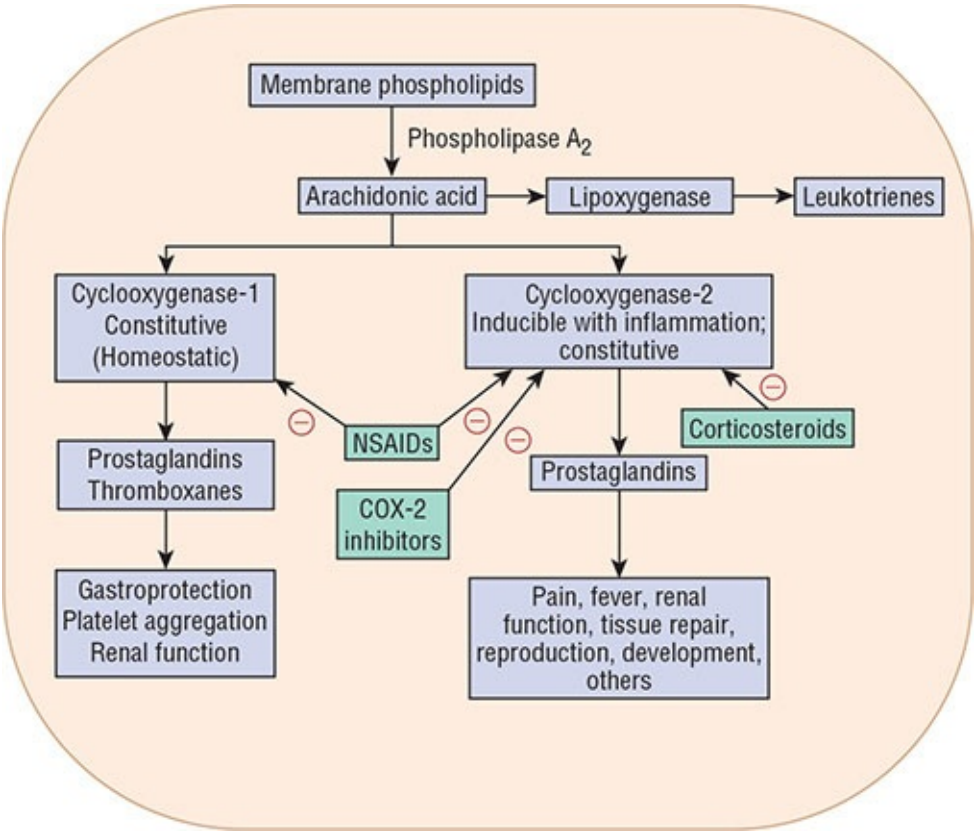


FIGURE 106-6 Pathway of synthesis for prostaglandins and leukotrienes. COX-1 and COX-2 are cyclooxygenase-1 and cyclooxygenase-2 enzymes, respectively. The minus (–) sign indicates inhibitory influence. Prostaglandins include PGE_2 and PGI_2; the latter is also known as prostacyclin.

The various NSAIDs exhibit several pharmacokinetic similarities, including high oral availability, high protein binding, and absorption as active drugs (except for sulindac and nabumetone, which require hepatic conversion for activity). There is a broad range of serum half-lives for different NSAIDs, which influence dosing frequency, and potentially, compliance with therapy.[57] Elimination of NSAIDs largely depends on hepatic inactivation, with a small fraction of active drug being renally excreted. NSAIDs penetrate joint fluid, reaching approximately 60% of blood levels.

Adverse Effects

Gastrointestinal Effects of Nonselective NSAIDs The most common adverse effects of NSAIDs involve the GI tract. NSAIDs can cause minor symptoms such as nausea and dyspepsia as well as more serious effects such as ulcers and bleeding.[58–60] All NSAIDs increase ulcer risk, but the serious GI complications associated with NSAIDs include perforations, gastric outlet obstruction, and

bleeding. These important GI complications occur in 1.5% to 4% of patients per year. NSAIDs are so widely used that these small percentages translate into substantial morbidity and mortality. Moreover, the risk increases substantially for patients with risk factors including a longer duration of NSAID usage, higher dosage, age older than 60 years, past history of peptic ulcer disease of any cause, history of alcohol use, concomitant use of glucocorticoids, and/or anticoagulants.[56] A patient treated with NSAIDs has a three to five times higher risk of developing gastrointestinal complications than a patient not treated with these medications.[61]

9 Options are available to reduce the GI risk of traditional NSAIDs. (1) Take the lowest dose possible and take only when needed. (2) Take the prostaglandin analog, misoprostol four times daily that reduces the rate of ulcers and serious GI complications. Many patients cannot tolerate the GI adverse events of misoprostol, especially diarrhea. (3) Take a proton pump inhibitor (PPI) or a full dose H2 blocker daily. The PPI and the H2 blocker do reduce minor GI complaints and reduce the risk of ulcers but are not rigorously proven to decrease the serious complications, possibly because of lack of power to detect rare events.[61]

Another choice that is available to reduce risk of GI events with an NSAID is to take a COX-2 selective inhibitor ("coxib").[58,60] Celecoxib is the only coxib available in the United States. Because this drug does not block the "housekeeping" gene, it may not have the same GI risks, but it is important to note it is not without GI risk.[55] A meta-analysis showed that COX-2 selective inhibitors were associated with significantly fewer gastro-duodenal ulcers and clinically important ulcer complications. Celecoxib has been shown to be as safe to the upper GI tract as a nonselective NSAID plus a PPI.[62] Another concern is the risk associated with NSAID use in patients taking aspirin for cardioprotection. It appears the GI risk is lower in patients taking a coxib medication and low-dose aspirin than a nonselective NSAID. However, in patients with high GI risk the combination may still be harmful and gastroprotection is appropriate.[62]

Cardiovascular Risk of COX-2 Inhibitors and Traditional NSAIDs Both nonselective and selective NSAIDs are associated with an increased risk for hypertension, stroke myocardial infarction and death. NSAIDs should be avoided in patients with known active ischemic heart disease, cerebrovascular disease and moderate-to severe heart failure.[56] It is not entirely clear the mechanism for the cardiovascular effects of NSAIDs.[61] NSAIDs are associated

with hypertension, increased preload, volume expansion and reduced sodium excretion.[63] A large meta-analysis showed some differences among NSAIDs in terms of vascular risk. The risk of diclofenac and ibuprofen were similar to that of coxibs but naproxen was not associated with an increased risk of major vascular events. Overall, coxibs were found to increase vascular risk by approximately one-third.[64] Several recent randomized controlled trials have compared NSAIDs to evaluate cardiovascular safety and found celecoxib to be noninferior to other NSAIDs in terms of cardiovascular events. However the celecoxib dose in these trials was lower than the doses previously reported to be associated with increased cardiovascular risk. In these trials, more patients also discontinued celecoxib due to lack of efficacy compared to other NSAIDs.[64,65]

In February 2014, an advisory committee to the FDA met to discuss the data relating the cardiovascular risk and NSAIDs. After their review it was decided to strengthen the warning label for nonaspirin NSAIDs, warning patients on the risk of heart attack and stroke. The updated labeling warns that cardiovascular events can happen at any point during NSAID therapy and the risk may increase with longer treatment and higher doses. The FDA concluded that there was insufficient evidence that the risk of any NSAID was higher or lower than another. An increased risk for cardiovascular events is present even in patients with no underlying cardiovascular disease. The data reviewed also showed patients taking a NSAID following a first MI were more likely to die in the first year following the MI.[66] Strategies to reduce cardiovascular risk with NSAIDs are not well documented. Naproxen may present less cardiovascular risk than coxibs and diclofenac at higher doses and therefore seems prudent to consider this when choosing a specific NSAID.[61,62,66]

Other Toxicities Associated with NSAIDs NSAIDs may cause kidney diseases, including acute renal insufficiency, sodium retention, acute interstitial nephritis, renal papillary necrosis and accelerated chronic kidney disease. In a trial evaluating NSAID safety, serious renal events occurred at a significantly lower rate in the celecoxib group compared to the ibuprofen group but when celecoxib was compared to naproxen the difference in renal events was not significant.[67] Sodium retention has been reported to occur in up to 25% of NSAID-treated patients. This effect may be clinically important to cause exacerbations of congestive heart failure.[63] Clinical features of these NSAID-induced renal syndromes include increased serum creatinine and blood urea nitrogen, hyperkalemia, elevated blood pressure, peripheral edema, and weight gain. Patients at high risk are those with conditions associated with decreased renal

blood flow or taking certain medications. Examples are those with chronic renal insufficiency, congestive heart failure, severe hepatic disease, and nephrotic syndrome, those of advanced age, or those taking diuretics, angiotensin-converting enzyme inhibitors, cyclosporine, or aminoglycosides (**Fig. 106-7**).

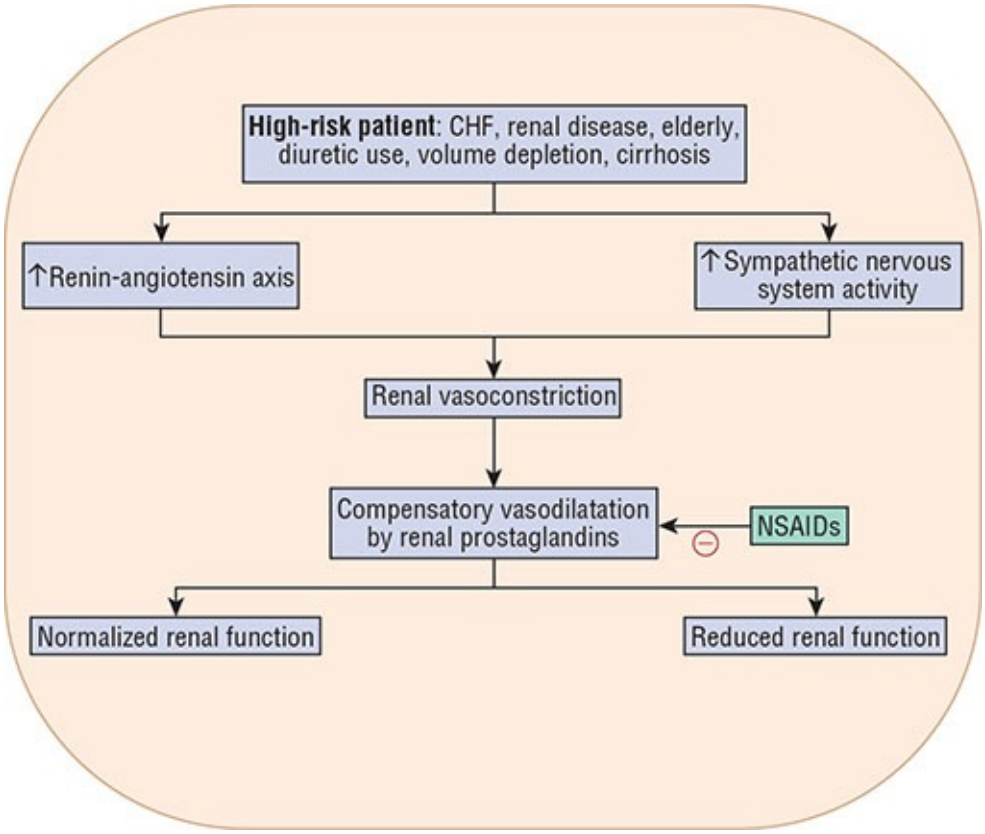


FIGURE 106-7 Mechanisms implicated in NSAID-induced renal injury. The minus (–) sign indicates inhibitory influence. (CHF, congestive heart failure; NSAIDs, nonsteroidal anti-inflammatory drugs.).

Close monitoring is advisable for high-risk patients taking an NSAID, with monitoring of serum creatinine at baseline and within 3 to 7 days of drug initiation. For those with impaired renal function, the National Kidney Foundation recommends acetaminophen over NSAIDs, although acetaminophen may pose risks, as discussed above.

Coxibs and NSAIDs uncommonly cause drug-induced hepatitis; the two NSAIDs most frequently implicated are diclofenac and sulindac. Patient monitoring should include periodic liver enzymes (aspartate aminotransferase and alanine aminotransferase), with cessation of therapy if these values exceed two to three times the upper limit of normal. A review of hepatotoxicity associated with NSAIDs use found them to be responsible for about 10% of

medication induced liver injury.[68]

Other toxic effects of NSAIDs include hypersensitivity reac- tions, rash, and CNS complaints of drowsiness, dizziness, headaches, depression, confusion, and tinnitus.[57] It is also recommended that NSAIDs be avoided for patients with asthma who are aspirin-intolerant.

All nonspecific NSAIDs inhibit COX-1–dependent thromboxane production in platelets and thus increase bleeding risk. Unlike aspirin, celecoxib and nonspecific NSAIDs inhibit thromboxane formation reversibly, with normalization of platelet function one to three days after the drug is stopped. Warfarin and celecoxib are metabolized by the cytochrome P450 isoenzyme CYP2C9, thus patients receiving warfarin and COX-2 inhibitors should be followed closely.

Finally, if misoprostol is taken for GI protection, great care is indicated. Because of its abortifacient properties, misoprostol is contraindicated in pregnancy and in women of childbearing age who are not maintaining adequate contraception. It must be dispensed in its original container, which carries a warning for these individuals. Misoprostol is also available in a combination product with diclofenac, which bears the same restrictions as misoprostol alone.

Drug–Drug Interactions Avoidance of concomitant use, or anticipation and careful monitoring can often prevent serious events when potentially interacting drugs are being considered. The most potentially serious interactions include the use of NSAIDs with lithium, warfarin, other agents that increase bleeding risk, oral hypoglycemics, methotrexate, antihypertensives, angiotensin-converting enzyme inhibitors, β-blockers, and diuretics.[57] In addition, there are probable drug interactions with tacrolimus for ibuprofen, naproxen, diclofenac, and possibly other NSAIDs.

Specific drug interactions are also seen with celecoxib.[69] Celecoxib metabolism is primarily via CYP2C9.[69] Cytochrome P450 inducers such as rifampin, carbamazepine, and phenytoin have the potential to reduce celecoxib levels. Concomitant administration of celecoxib with fluconazole can increase plasma concentrations of celecoxib, due to fluconazole inhibition of the CYP2C9 isoenzyme. Because warfarin and celecoxib are both metabolized by CYP2C9, patients receiving warfarin and COX-2 inhibitors should be followed closely. Because celecoxib inhibits CYP2D6, it has the potential to increase concentrations of a variety of agents, including antidepressants. Celecoxib is a sulfonamide and is thus noted to be contraindicated for those with sulfa allergies.[69]

Another drug interaction has been noted for those taking some NSAIDs and cardioprotective doses of aspirin. Ibuprofen, used at doses of 400 mg or more, may block aspirin's antiplatelet effect if it is taken prior to aspirin. Patients taking ibuprofen have been advised to take a single dose of ibuprofen at least 30 minutes after taking aspirin, or to take their aspirin at least 8 hours after taking ibuprofen. It is possible that other nonselective NSAIDs, such as naproxen, also may cause such interactions. Currently, the ACR recommends that patients taking aspirin who need an oral NSAID for OA choose an NSAID other than ibuprofen or COX-2 selective inhibitors.[23] Acetaminophen does not appear to interfere with the antiplatelet effect of aspirin.

Dosing and Administration Administration of NSAIDs must be tailored to the individual patient with OA. Selection of an NSAID depends on the prescriber's experience, medication cost, patient preference, allergies, toxicities, and adherence issues. Individual patient response differs among NSAIDs, so if an inadequate response is obtained with one NSAID, another NSAID may yet provide benefit.[23,26]

Topical NSAIDs

Pharmacology and Mechanism of Action The mechanism of action of topical NSAIDs is considered to be through inhibition of the COX-2 enzyme in tissues near the site of application. Studies show significant placebo effects which could result from rubbing the product into the skin, which may have a counterirritant effect. Topical NSAIDs are significantly more efficacious compared to placebo vehicle in reducing pain due to musculoskeletal conditions, including osteoarthritis. Most trials have shown topical diclofenac to be as effective as oral NSAIDs, including both oral diclofenac and other comparators.[42,50,70] Diclofenac 1% gel as well as the newer diclofenac solution, and diclofenac patches are currently approved in the United States for osteoarthritis.

Adverse Effects Compared to oral NSAIDs, topical NSAIDs are associated with many fewer gastrointestinal adverse events and fewer adverse events overall, except for local application site reactions. In comparison to placebo or oral NSAIDs, topical NSAID use is associated with more local adverse events, most often mild skin reactions such as itching or rash, but with very few serious adverse effects. Meta-analyses and reviews have found similar tolerability between topical NSAIDs and placebo. Topical NSAIDs have not shown a significant link between their use and increased risk of cardiovascular events.[44]

It is estimated that from 1% to 15% of topical NSAID enters the systemic circulation, usually less than 5% that contributes to its greater safety profile.[70,71]

Drug–Drug Interactions Interactions listed for topical diclofenac are the same as for oral NSAIDs, which are listed above for oral NSAIDs. The most potentially serious interactions include the use of NSAIDs with lithium, warfarin and other agents that increase bleeding risk, oral hypoglycemics, methotrexate, antihypertensives, angiotensin-converting enzyme inhibitors, β-blockers, and diuretics. Other topical agents have not been studied with the product and there could be changes in tolerability and absorption of the diclofenac. For all of these interactions, as there is only a small percentage of diclofenac absorbed, the risks are likely significantly less than with oral drug, but the patient and provider would be wise to monitor appropriately for these interactions with any of these drugs the patient is taking. Patients should avoid oral NSAIDs while using topical products to minimize potential for additive adverse effects. Care should be taken to avoid contact with the eyes or open wounds and to wash hands after application (except when treating hand OA).

Dosing and Administration Diclofenac 1% gel (Voltaren®) can be used for hand or knee OA or other joints amenable to topical application (eg, not the hip). It is applied four times daily using the dose measuring cards provided by the manufacturer. Four grams of gel is recommended for application to the affected area in the lower limb four times daily, and for upper extremities, the dose is 2 g four times daily. Diclofenac solution (Pennsaid®), only approved for knee OA, is available in 1.5% and 2% solution. Forty drops of the 1.5% solution are to be applied four times a day to each affected knee. The solution should be applied to the back, front, and sides of the knee. For each dose, the patient places 10 drops at a time directly onto the painful knee (or first into the hands and then immediately spreads onto the knee) and rubs the solution in. The patient then repeats this process three more times until 40 drops worth have been applied to the painful knee for that particular dose. The 2% diclofenac solution is available in a meter-dose pump. Two actuations or 40 mg are applied twice daily to the affected knee(s). The entire dose should be pumped into the palm of the hand then applied evenly to the knee. The diclofenac patch (180 mg diclofenac epolamine) is applied twice daily. If the patch doesn’t stick well, the patient can tape edges with first-aid tape. Patient counseling is important to carefully explain how to apply the topical products and how long to wait before dressing, putting on gloves, showering, and so forth.

Pharmacoeconomic Impact of NSAIDs The highest costs associated with the

pharmacotherapy of OA are hospitalization for treatment of NSAID-related complications, particularly serious GI adverse events. Historically, gastroprotective therapy or the use of COX-2–selective inhibitors for low-risk patients has not been cost-effective because of the large number needed to treat to prevent serious events, but most PPI's are generic, multisource products, making concomitant treatment with PPI's effective.[72] Pharmacoeconomic considerations for OA involve the selection of therapy for the initial treatment of patients with OA. Use of the nonprescription analgesic acetaminophen as initial therapy has greatly reduced medication costs in comparison with the use of NSAIDs, many of which are by prescription only. Oral NSAID costs vary considerably, depending on the medication, daily dose, and regimen selected. As oral NSAIDs as a class are therapeutically similar, the use of a less-expensive agent such as nonprescription ibuprofen or naproxen or a multisource generic product may minimize the cost. More expensive NSAIDs can be prescribed if neither of these offers benefit after a 2-week trial at sufficient doses. Topical NSAIDs are significantly more costly than oral agents, although may still be cost-effective in patients at high-risk for costly complications associated with oral NSAID therapy.

Intra-articular Corticosteroids

10 **Pharmacology and Mechanism of Action** The anti-inflammatory properties of corticosteroids as a class are the primary mechanism of pain relief in the treatment of OA. These properties decrease the formation and release of prostaglandins, kinins, liposomal enzymes and histamine. These actions decrease erythema, swelling, heat and tenderness of the inflamed joints.[23,73] Aspiration of the effusion and injection of glucocorticoid are carried out aseptically, with examination of the aspirate recommended to exclude crystalline arthritis or infection. Several randomized, placebo-controlled, double-blind studies have shown that intra-articular corticosteroids are superior to placebo in alleviating knee pain and stiffness caused by OA but with a relatively short duration.[73] The most commonly used corticosteroids for intra-articular use are triamcinolone acetonide and methylprednisolone acetate. The branched esters of triamcinolone and methylprednisolone are preferred by practitioners because of the reduced solubility that allows the agents to remain in the joint space longer.[74,75]

Adverse Events Adverse events associated with intra-articular injection of corticosteroids can be local or systemic in nature. Systemic adverse events are the same as with any other systemic corticosteroid and can include

hyperglycemia, edema, elevated blood pressure, flushing, dyspepsia and hypercortisolism. Evidence shows an acute two to three day rise in blood glucose in patients with diabetes following a single corticosteroid injection. The risk of systemic side effects can be lessened by limiting the dose of the corticosteroid since doses greater than 40 mg for triamcinolone or methylprednisolone have not been shown to provide any additional benefit.[74] Local adverse effects can include infection in the affected joint, osteonecrosis, tendon rupture, and skin atrophy at the injection site. Systemic corticosteroid therapy is not recommended in OA, given the lack of proven benefit and the well-known adverse effects with long-term use.

Dosing and Administration Average doses for injection of large joints in adults are 40 mg of triamcinolone and methylprednisolone acetate. Local anesthetics such as lidocaine or bupivacaine are commonly combined with corticosteroids to provide rapid pain relief.[74] This therapy is generally limited to three or four injections per year due to the potential systemic effects of corticosteroids and because the need for more frequent injections indicates little response to the therapy.

After injection, the patient should minimize activity and stress on the joint for several days. Initial pain relief may be seen within 24 to 72 hours after injection, with peak pain relief about 7 to 10 days after injection and lasting up to 4 to 8 weeks.

Capsaicin

Pharmacology and Mechanism of Action Capsaicin, isolated from hot peppers, releases and ultimately depletes substance P from afferent nociceptive nerve fibers. Substance P has been implicated in the transmission of pain in arthritis, and capsaicin cream has demonstrated to have moderate efficacy compared to placebo in clinical trials.[51] Due to the larger surface area and distance from the site of application to the joint, it is not expected that application of capsaicin would provide efficacy in the treatment of hip OA.

Adverse Effects Adverse events associated with capsaicin are primarily local including burning, stinging, and/or erythema that usually subsides with repeated application. Systemic effects are rare.[51] The FDA has issued a public drug safety communication notifying consumers that rare cases of severe burns have been reported.[76] Some patients may experience coughing associated with application.

Dosing and Administration To be effective, capsaicin must be used regularly,

and it may take up to 2 weeks to take effect. Use is recommended four times a day.[51] Patients should be counseled not to get the cream in their eyes or mouth. Patients should also notify their healthcare provider immediately if they experience pain, swelling or blistering skin at the site of application.

Capsaicin is a nonprescription product available as a cream, gel, solution lotion, or patch in concentrations ranging from 0.025% to 0.15%.

Tramadol

Pharmacology and Mechanism of Action Tramadol, an analgesic with affinity for the μ-opioid receptor, as well as weak inhibition of the reuptake of norepinephrine and serotonin neurotransmitter, has shown moderate pain improvement for patients with OA when compared with placebo.[77,78] Tramadol is also modestly effective as add-on therapy for patients taking concomitant acetaminophen, NSAIDs, or COX-2–selective inhibitors. Tramadol may be helpful for patients who cannot take NSAIDs or COX-2–selective inhibitors.

Adverse Events Opioid-like adverse effects such as nausea, vomiting, dizziness, constipation, headache, and somnolence are common with tramadol. These occur in 45% to 84% of treated patients.[79] Although the frequency of adverse effects is high, the severity of these effects is less than for NSAIDs, as tramadol use is not associated with life-threatening gastrointestinal bleeding, cardiovascular events, or renal failure. The most notable serious adverse event associated with tramadol use is seizures. Withdrawal symptoms can occur if tramadol is stopped abruptly. Older adults are significantly more likely to experience adverse events.[79] Tramadol was initially not classified as a controlled substance but was rescheduled as a class IV controlled substance due to its potential for dependence, addiction, and diversion.

Drug-Drug Interaction Medications that lower the seizure threshold should be used with caution in patients taking tramadol. These include tricyclic antidepressants, first-generation antipsychotic medications and cyclobenzaprine, as well as others. There is also an increased risk of serotonin syndrome (see Chapter 85, “Depressive Disorders,” for description) when tramadol is used concomitantly with other serotonergic medications, including duloxetine.

Dosing and Administration Tramadol should be initiated at a lower dose (100 mg/day) and may be titrated as needed for pain control to a dose of 200 mg/day, with a maximum dose of 400 mg/day. Tramadol is available in a combination tablet with acetaminophen and as an extended-release tablet or capsule.

Second-Line Treatments

Opioid Analgesics

Opioid analgesics may be useful for patients who experience limited pain relief with acetaminophen, oral NSAIDs, intra-articular injections, or topical therapy or who cannot tolerate the side effect profile of these agents.[55] For patients with underlying conditions that limit the use of first-line analgesics, opioid analgesics can effectively relieve acute OA pain. A common clinical scenario includes the patient who cannot take oral NSAIDs because of renal failure or cardiovascular disease. Patients in whom all other treatment options have failed and who are at high surgical risk, precluding joint arthroplasty are also candidates for opioid therapy. It is important to carefully use opioids to promote safety. The CDC recommends only prescribing opioids if the benefits from pain control and function outweigh the risk. The best practice for opioid prescribing include: using the lowest effective dose and the smallest quantity needed, providing patients with information on how to use, store, and dispose of opioid medications, and avoiding combinations of opioids and sedating medications unless there is a specific indication to do so. Opioid use should be assessed at least every three months, evaluating patient progression toward functional treatment goals, risks of harm, and adverse effects.[80]

Adverse effects are common in opioid-treated patients with OA. More than 75% of patients in clinical trials experience at least one typical opioid-related (ie, nausea, somnolence, constipation, dry mouth and dizziness) adverse effect. Although this is not an unexpected finding, it serves as a reminder to use opioids cautiously in elderly patients who may be more susceptible to adverse effects.

Opioid dependence, addiction, tolerance, hyperalgesia and issues surrounding drug diversion are more serious adverse effects associated with long-term treatment. Prescription opioid misuse/abuse/addiction is a major public health concern with the CDC reporting around 46 deaths every day from prescription opioid overdose.[81] Patients should be educated on the risks of taking opioids, including addiction, overdose, and death.

If pain is poorly controlled and limits activities of daily living, and the patient has sufficiently good cardiopulmonary health to undergo major surgery, joint replacement may be preferable to continued reliance on opioids.

Duloxetine

Duloxetine is a centrally acting dual-reuptake inhibitor of both serotonin and

norepinephrine, although norepinephrine reuptake inhibition does not occur until doses reach 60 mg/day. While the most common pain target in OA is peripheral nociceptive pain, there is some evidence that chronic nociceptive pain leads to central pain sensitization thereby lowering the pain threshold.[47] Duloxetine provides pain relief through the blocking of central pain transmitters, including serotonin and norepinephrine.

Adverse effects commonly associated with duloxetine therapy include nausea, dry mouth, constipation, and anorexia. Expected neurologic adverse effects include fatigue, somnolence, and dizziness. Rare, but serious adverse events associated with duloxetine include Stevens-Johnson syndrome and liver failure. Patients should be notified to contact their healthcare provider immediately if they develop a rash while taking duloxetine.

Particular care should be taken to avoid the use of duloxetine with other serotonergic medications including tramadol. As tramadol is a first-line treatment recommendation for OA, the likelihood of encountering this combination is high. Concomitant use of duloxetine with other medications that increase serotonin concentrations increases the risk of serotonin syndrome.

Hyaluronic Acid Injections

Hyaluronate is a naturally occurring component of cartilage and synovial fluid. Exogenous intra-articular hyaluronate is available as a treatment for the symptoms of knee OA. The goal of intra-articular HA is to provide and maintain intra-articular lubrication. HA may also have anti-inflammatory, analgesic and chondroprotective effects on the articular cartilage and joint synovium.[82] Evidence has not shown intra-articular HA to have a clinically significant benefit involving pain relief and functional improvement and therefore does not support the routine use of HA.[83] Most HA products are injected once weekly for either three or five weeks, depending on the specific agent administered. Patients are generally advised to repeat the injection schedule by 6 months if they are satisfied with the previous course.[73] Strenuous or prolonged weight-bearing activities should be avoided for 48 hours after treatment. Routinely, the most improvement is expected from 5 to 13 weeks after injection with some effect still occurring at 24 weeks.[82] Injections are generally well tolerated, although acute joint swelling, effusion, and stiffness can occur as well as local skin reactions, including rash, ecchymoses and pruritus have been reported. Local adverse effects are more frequent in products from animal origin. Rarely, systemic adverse events including hypersensitivity reactions have occurred. Joint infections are rare but have been reported.

At this time, the effect of HA injections on knee OA appears to be modest at best.[82] These agents are expensive because the treatment includes both drug costs and administration costs. Patient expectations and cost effectiveness must be considered before choosing HA injection.[73]

Glucosamine and Chondroitin

Interest in chondroitin and glucosamine was spurred initially by anecdotal reports of benefit in animals and humans and by the ability of these substances to stimulate proteoglycan synthesis from articular cartilage in vitro. Over the last decade, enthusiasm for these agents has waned as additional efficacy data has become available to the point that the American College of Rheumatology conditionally recommends against the use of glucosamine and chondroitin.[23] Glucosamine, alone or in combination, has not been shown to provide uniform improvements in pain control or functional status in patients with OA of the knee or hip.[84]

Numerous trials have examined the safety and efficacy of glucosamine and chondroitin; however, the duration of these studies has been relatively short. The efficacy of glucosamine and chondroitin was evaluated after two years and found not to be statistically superior to placebo.[85] The combination of glucosamine and chondroitin was well tolerated. There has previously been some concern that glucosamine may worsen diabetes or asthma; however, with 2-year follow-up this was not substantiated.[85] When the combination of glucosamine and chondroitin was compared to celecoxib in patients with knee OA, it was found to be noninferior in the reduction of pain at 6 months. The combination was well tolerated and the authors suggest glucosamine and chondroitin as a potential safe alternative for patients with cardiovascular or gastrointestinal conditions.[86]

Because glucosamine and chondroitin are marketed in the United States as dietary supplements, neither the products nor their purity is adequately regulated by the FDA. The potential consequences related to the lack of regulatory oversight for these products can affect both efficacy and safety. Products containing less than labeled doses can compromise efficacy, while those containing ingredients not included on the labeling can compromise safety. A variety of brand name and generic products are available in various doses and formulations.

EVALUATION OF THERAPEUTIC OUTCOMES

For the person with OA, treatment decisions and pharmacotherapy monitoring is patient specific. The patient's situation and individual needs should be considered when devising a treatment plan. Is the patient bothered primarily by pain, by limitations in activity, or with concerns about side effects from medications? Does the patient understand what OA is and why certain treatments are useful?

When the patient is first being assessed for the possibility of OA, the diagnosis is often straightforward, including history and physical exam, plain films of the affected joint(s), and lab tests. The older patient with unilateral knee pain, limited range of motion, no palpable warmth, crepitus, without prolonged morning stiffness and without other suspicious findings, is highly likely to have knee OA. It is still reasonable to obtain x-rays that may help follow disease over time (although joint space narrowing often does not correlate with the extent of pain or difficulty walking). Basic labs to help decide what pharmacologic therapy is possible (eg, no NSAIDs with poor renal function), assessment of pain using a visual analog scale, range of motion for affected joints. Additional tests of OA severity may include measurement of grip strength, 50 ft walking time, patient and physician global assessment of OA severity, and assessment of ability to perform activities of daily living. Once the patient is assessed and diagnosed, patient and family education is essential. Nondrug therapy may include a referral for physical and/or occupational therapy services, where the therapists can help to maintain and improve range of motion. Referral for nutritional counseling and weight loss may also be necessary if the patient is overweight or obese. These interventions may decrease pain and facilitate improved activity for OA patients.

Although all patients must be provided with nonpharmacologic therapies, results from these interventions usually require weeks to months. In the meantime, the patient needs pain relief. First-line therapy continues to be acetaminophen. Adverse events with acetaminophen are uncommon, although it is important that the patient understand the maximum daily dose limits and all possible sources of acetaminophen containing products. Although some do well on acetaminophen, many do not achieve sufficient pain relief. A step up to oral NSAIDs or second-line therapy might be necessary but poses significant risks beyond acetaminophen. A switch to NSAIDs requires careful consideration of the patient's age and comorbidities, renal function, history of GI problems, hypertension, and cardiovascular health. Periodic monitoring would include open ended questions followed by direct questions relating to the commonest adverse effects associated with the respective medication. For an oral NSAID,

symptoms of abdominal pain, heartburn, nausea, or change in stool color provide valuable clues to the presence of GI complications, although serious GI complications can occur without warning. Patients should be monitored for the development of hypertension, weight gain, edema, skin rash, and CNS adverse effects such as headaches and drowsiness. Baseline serum creatinine, complete blood count, and serum transaminases are repeated at 6- to 12-month intervals to identify GI, renal, and hepatic toxicities.

Topical NSAIDs have demonstrated efficacy in OA of the hand and knee and are as effective as oral NSAIDs. Although they carry the same cardiovascular, renal, and GI warnings, their AUC for a typical dose is only a few percent of the AUC from an equivalent dose of oral NSAID. Topical NSAIDs' most common side effects are local, with irritated skin, rash, or itching, usually mild, and with many fewer adverse effects of CV, GI, or renal nature. These agents are a welcome addition to the limited treatment modalities for the very common, costly, painful, and often disabling disease of OA. It is important that the patient apply the topical products appropriately to achieve maximum benefit and avoiding adverse events.

For patients receiving intra-articular corticosteroids, pain relief should begin with 2 to 3 days and last 4 to 8 weeks. Patients should be advised about possible injection site reactions, as well as possible systemic effects, especially for those with hypertension or diabetes, as there is a potential for increased blood pressure or blood glucose. For patients receiving opioids or tramadol, relief from pain should occur rapidly. Frail or elderly patients should be monitored carefully and cautioned about sedation, dysphoria, nausea, risk of falls, and constipation. Special additional monitoring should include strategies to assess development of opioid tolerance, addiction, misuse, and diversion.

CONCLUSION

OA is a very common, slowly progressive disorder that affects diarthrodial joints and is characterized by progressive deterioration of articular cartilage, subchondral sclerosis, and osteophyte production. Clinical manifestations include gradual onset of joint pain, stiffness, and limitation of motion. The primary treatment goals are to reduce pain, maintain function, and prevent further destruction. An individualized approach based on education, rest, exercise, weight loss as needed, and analgesic medication can succeed in meeting these goals. Recommended drug treatment starts with acetaminophen ≤4 g/day and topical analgesics as needed. If acetaminophen is ineffective, oral

NSAIDs may be used in appropriately selected patients, often providing satisfactory relief of pain and stiffness. Individuals at increased risk for toxicity from NSAIDs, especially for GI, cardiovascular, or renal events, deserve special attention. Celecoxib may have safety advantages in some OA patients, but its safety relative to other NSAIDs and its role in OA remains poorly defined. Adjunctive therapy with tramadol, intra-articular corticosteroids and duloxetine may be helpful in patients with poorly controlled pain. Experimental therapy aimed at preventing the progression of OA requires further clinical investigation before entering widespread clinical use.

Postclass Engaged Learning Activity

This activity is designed to build skills in literature evaluation and ability to critically appraise research manuscripts.

Conduct a literature search to identify a primary research manuscript in the past 18 months on a nonpharmacologic intervention for the treatment osteoarthritis. If the manuscript is regarding a lifestyle intervention, write a brief summary about the study methods, the major findings, and how a pharmacist may be able to facilitate or participate as part of the intervention. If the manuscript is regarding an intervention not described in the chapter, write a brief summary about the study methods, the major findings and one potential advantage or disadvantage of the intervention.

ABBREVIATIONS

AAAL	Arthritis-Attributable Activities Limitations
BMI	Body mass index
COX	cyclooxygenase
ECM	extracellular matrix
FDA	Food and Drug Administration
GI	gastrointestinal
GWAS	genome-wide linkage studies
HA	hyaluronic acid
IDEA	Intensive Diet and Exercise for Arthritis
IR	immediate release

MI	Myocardial infarction
MMP	matrix metalloproteinase
NICE	National Institute for Health and Clinical Excellence
NSAID	nonsteroidal anti-inflammatory drug
OA	osteoarthritis
OARSI	Osteoarthritis Research International
PPI	proton pump inhibitor
QALE	quality-adjusted life expectancy
SNP’s	single nucleotide polymorphisms
SR	sustained release
TIMP	tissue inhibitors of metalloproteinase

REFERENCES

1. Barbour KE, Helmick CG, Boring M, Brady TJ. Vital signs: Prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation—United States, 2013-2015. *MMWR Morb Mortal Wkly Rep*. 2017;66(9):246–253.
2. Hootman JM, Murphy LB, Omura JD, et al. Health care provider counseling for physical activity or exercise among adults with arthritis—United States, 2002 and 2014. *MMWR Morb Mortal Wkly Rep*. 2018;66(5152):1398–1401.
3. Murphy LB, Cisternas MG, Pasta DJ, Helmick CG, Yelin EH. Medical expenditures and earnings losses among US adults with arthritis in 2013. *Arthritis Care Res (Hoboken)*. 2018;70(6):869–876.
4. Torio C (AHRQ), Moore B (Truven Health Analytics). National inpatient hospital costs: The most expensive conditions by payer, 2013. HCUP statistical brief #204.
5. Dagenais S, Garbedian S, Wai EK. Systematic review of the prevalence of radiographic primary hip osteoarthritis. *Clin Orthop Relat Res*. 2009;467(3):623–637.
6. Feydy A, Pluot E, Guerini H, Drape JL. Osteoarthritis of the wrist and hand, and spine. *Radiol Clin North Am*. 2009;47(4):723–759.
7. Jordan JM. An ongoing assessment of osteoarthritis in African Americans and Caucasians in North Carolina: The Johnston county osteoarthritis

project. *Trans Am Clin Climatol Assoc*. 2015;126:77–86.

8. Barbour KE, Boring M, Helmick CG, Murphy LB, Qin J. Prevalence of severe joint pain among adults with doctor-diagnosed arthritis—United States, 2002-2014. *MMWR Morb Mortal Wkly Rep*. 2016;65(39):1052–1056.
9. Johnson VL, Hunter DJ. The epidemiology of osteoarthritis. *Best Pract Res Clin Rheumatol*. 2014;28(1):5–15.
10. Glyn-Jones S, Palmer AJ, Agricola R, et al. Osteoarthritis. *Lancet*. 2015;386(9991):376–387.
11. Mork PJ, Holtermann A, Nilsen TI. Effect of body mass index and physical exercise on risk of knee and hip osteoarthritis: Longitudinal data from the norwegian HUNT study. *J Epidemiol Community Health*. 2012;66(8):678–683.
12. Vina ER, Kwoh CK. Epidemiology of osteoarthritis: Literature update. *Curr Opin Rheumatol*. 2018;30(2):160–167.
13. Warner SC, Valdes AM. Genetic association studies in osteoarthritis: Is it fairytale? *Curr Opin Rheumatol*. 2017;29(1):103–109.
14. Munk HL, Svendsen AJ, Hjelmborg J, Sorensen GL, Kyvik KO, Junker P. Heritability assessment of cartilage metabolism. A twin study on circulating procollagen IIA N-terminal propeptide (PIIANP). *Osteoarthritis Cartilage*. 2014;22(8):1142–1147.
15. Evangelou E, Valdes AM, Kerkhof HJ, et al. Meta-analysis of genome-wide association studies confirms a susceptibility locus for knee osteoarthritis on chromosome 7q22. *Ann Rheum Dis*. 2011;70(2):349–355.
16. Felson DT, Neogi T. Osteoarthritis. In: Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, eds. *Harrison's principles of internal medicine*. 20th ed. New York, NY: McGraw-Hill Education; 2017. accessmedicine.mhmedical.com/content.aspx?aid=1155953712.
17. Loeser RF. Age-related changes in the musculoskeletal system and the development of osteoarthritis. *Clin Geriatr Med*. 2010;26(3):371–386.
18. Kumar V, Abbas AK, Aster J. Bones, joints, and soft tissue tumors. Robbins Basic Pathology. 10th ed. New York: Elsevier, Inc.; 2018.
19. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: A disease of the joint as an organ. *Arthritis Rheum*. 2012;64(6):1697–1707.
20. American College of Rheumatology. Available at http://www.rheumatology.org/publications/.

21. Kloppenburg M. Hand osteoarthritis-nonpharmacological and pharmacological treatments. *Nat Rev Rheumatol*. 2014;10(4):242–251.
22. Bennell KL, Hunter DJ, Hinman RS. Management of osteoarthritis of the knee. *BMJ*. 2012;345:e4934.
23. Hochberg MC, Altman RD, April KT, et al. American college of rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)*. 2012;64(4):455–474.
24. Qin J, Theis KA, Barbour KE, et al. Impact of arthritis and multiple chronic conditions on selected life domains—United States, 2013. *MMWR Morb Mortal Wkly Rep*. 2015;64(21):578–582.
25. Marra C, Cibere J, Grubisic M, et al. Pharmacist initiated intervention trial in osteoarthritis (PhIT-OA): A multidisciplinary intervention for knee osteoarthritis. Arthritis Care Res (Hoboken). 2012;64(12):1837–1845.
26. National Institute for Health and Care Excellence. Osteoarthritis care and management in adults. Available at https://www.nice.org.uk/guidance/cg177. Updated 2014. Accessed 8/25, 2015.
27. Guglielmo D, Hootman JM, Murphy LB, et al. Health care provider counseling for weight loss among adults with arthritis and overweight or obesity—United States, 2002-2014. *MMWR Morb Mortal Wkly Rep*. 2018;67(17):485–490.
28. Zhang W, Doherty M, Leeb BF, et al. EULAR evidence based recommendations for the management of hand osteoarthritis: Report of a task force of the EULAR standing committee for international clinical studies including therapeutics (ESCISIT). *Ann Rheum Dis*. 2007;66(3):377–388.
29. Maradit Kremers H, Larson DR, Crowson CS, et al. Prevalence of total hip and knee replacement in the United States. *J Bone Joint Surg Am*. 2015;97(17):1386–1397.
30. Bliddal H, Leeds AR, Christensen R. Osteoarthritis, obesity and weight loss: Evidence, hypotheses and horizons—a scoping review. *Obes Rev*. 2014;15(7):578–586.
31. Vincent HK, DeJong G, Mascarenas D, Vincent KR. The effect of body mass index and hip abductor brace use on inpatient rehabilitation outcomes after total hip arthroplasty. *Am J Phys Med Rehabil*. 2009;88(3):201–209.

32. Messier SP, Mihalko SL, Legault C, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: The IDEA randomized clinical trial. *JAMA*. 2013;310(12):1263–1273.
33. Qin J, Barbour KE, Nevitt MC, et al. Objectively measured physical activity and risk of knee osteoarthritis. *Med Sci Sports Exerc*. 2018;50(2):277–283.
34. Nelson AE, Allen KD, Golightly YM, Goode AP, Jordan JM. A systematic review of recommendations and guidelines for the management of osteoarthritis: The chronic osteoarthritis management initiative of the U.S. bone and joint initiative. *Semin Arthritis Rheum*. 2014;43(6):701–712.
35. Regnaux JP, Lefevre-Colau MM, Trinquart L, et al. High-intensity versus low-intensity physical activity or exercise in people with hip or knee osteoarthritis. Cochrane Database Syst Rev. 2015;(10):CD010203. doi: 10.1002/14651858.CD010203.pub2.
36. Svege I, Nordsletten L, Fernandes L, Risberg MA. Exercise therapy may postpone total hip replacement surgery in patients with hip osteoarthritis: A long-term follow-up of a randomised trial. *Ann Rheum Dis*. 2015;74(1):164–169.
37. Gossec L, Paternotte S, Maillefert JF, et al. The role of pain and functional impairment in the decision to recommend total joint replacement in hip and knee osteoarthritis: An international cross-sectional study of 1909 patients. report of the OARSI-OMERACT task force on total joint replacement. *Osteoarthritis Cartilage*. 2011;19(2):147–154.
38. Skou ST, Roos EM, Laursen MB, et al. Total knee replacement plus physical and medical therapy or treatment with physical and medical therapy alone: A randomised controlled trial in patients with knee osteoarthritis (the MEDIC-study). *BMC Musculoskelet Disord*. 2012;13:67.
39. Weber KL, Jevsevar DS, McGrory BJ. AAOS clinical practice guideline: Surgical management of osteoarthritis of the knee: Evidence-based guideline. *J Am Acad Orthop Surg*. 2016;24(8):e94–e96.
40. Losina E, Walensky RP, Kessler CL, et al. Cost-effectiveness of total knee arthroplasty in the united states: Patient risk and hospital volume. *Arch Intern Med*. 2009;169(12):1113–1121. discussion 1121-2.
41. Waimann CA, Fernandez-Mazarambroz RJ, Cantor SB, et al. Cost-effectiveness of total knee replacement: A prospective cohort study.

Arthritis Care Res (Hoboken). 2014;66(4):592–599.

42. Chou R, McDonagh MS, Nakamoto E, Griffin J. Analgesics for osteoarthritis: An update of the 2006 comparative effectiveness review. comparative effectiveness review no. 38. (prepared by the oregon evidence-based practice center under contract HHSA 290 2007 10057 I). *Agency for Healthcare Research and Quality*. 2011;No. 11(12)-EHC076-EF.
43. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: A systematic review and network meta-analysis. *Ann Intern Med*. 2015;162(1):46–54.
44. Barkin RL. Topical nonsteroidal anti-inflammatory drugs: The importance of drug, delivery, and therapeutic outcome. *Am J Ther*. 2015;22(5):388–407.
45. Krebs EE, Gravely A, Nugent S, et al. Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: The SPACE randomized clinical trial. *JAMA*. 2018;319(9):872–882.
46. Frakes EP, Risser RC, Ball TD, Hochberg MC, Wohlreich MM. Duloxetine added to oral nonsteroidal anti-inflammatory drugs for treatment of knee pain due to osteoarthritis: Results of a randomized, double-blind, placebo-controlled trial. *Curr Med Res Opin*. 2011;27(12):2361–2372.
47. Hochberg MC, Wohlreich M, Gaynor P, Hanna S, Risser R. Clinically relevant outcomes based on analysis of pooled data from 2 trials of duloxetine in patients with knee osteoarthritis. *J Rheumatol*. 2012;39(2):352–358.
48. Brown JP, Boulay LJ. Clinical experience with duloxetine in the management of chronic musculoskeletal pain. A focus on osteoarthritis of the knee. *Ther Adv Musculoskelet Dis*. 2013;5(6):291–304.
49. Altman RD. Pharmacological therapies for osteoarthritis of the hand: A review of the evidence. *Drugs Aging*. 2010;27(9):729–745.
50. Altman RD, Barthel HR. Topical therapies for osteoarthritis. *Drugs*. 2011;71(10):1259–1279.
51. Taylor N. Nonsurgical management of osteoarthritis knee pain in the older adult. *Clin Geriatr Med*. 2017;33(1):41–51.
52. Department of Health and Human Services. *Federal Register*. 2009; 81.

53. Watkins PB, Kaplowitz N, Slattery JT, et al. Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily: A randomized controlled trial. *JAMA*. 2006;296(1):87–93.
54. Larson AM, Polson J, Fontana RJ, et al. Acetaminophen-induced acute liver failure: Results of a United States multicenter, prospective study. *Hepatology*. 2005;42(6):1364–1372.
55. O'Neil CK, Hanlon JT, Marcum ZA. Adverse effects of analgesics commonly used by older adults with osteoarthritis: Focus on non-opioid and opioid analgesics. *Am J Geriatr Pharmacother*. 2012;10(6):331–342.
56. Meara AS, Simon LS. Advice from professional societies: Appropriate use of NSAIDs. *Pain Med*. 2013;14(suppl 1):S3–S10.
57. McEvoy GK. AHFS Drug Information. Bethesda, MD: American Society of Health-System Pharmacists, Inc.; 2012. ISBN 978-1-58528-247-0.
58. Lanas A. Nonsteroidal anti-inflammatory drugs and cyclooxygenase inhibition in the gastrointestinal tract: A trip from peptic ulcer to colon cancer. *Am J Med Sci*. 2009;338(2):96–106.
59. Moore N, Scheiman JM. Gastrointestinal safety and tolerability of oral non-aspirin over-the-counter analgesics. *Postgrad Med*. 2018;130(2):188–199.
60. Rostom A, Moayyedi P, Hunt R; Canadian Association of Gastroenterology Consensus Group. Canadian consensus guidelines on long-term nonsteroidal anti-inflammatory drug therapy and the need for gastroprotection: Benefits versus risks. *Aliment Pharmacol Ther*. 2009;29(5):481–496.
61. Patricio JP, Barbosa JP, Ramos RM, Antunes NF, de Melo PC. Relative cardiovascular and gastrointestinal safety of non-selective non-steroidal anti-inflammatory drugs versus cyclo-oxygenase-2 inhibitors: Implications for clinical practice. *Clin Drug Investig*. 2013;33(3):167–183.
62. Scarpignato C, Lanas A, Blandizzi C, et al. Safe prescribing of non-steroidal anti-inflammatory drugs in patients with osteoarthritis—An expert consensus addressing benefits as well as gastrointestinal and cardiovascular risks. *BMC Med*. 2015;13:55. doi: 10.1186/s12916-015-0285-8.
63. Crofford LJ. Use of NSAIDs in treating patients with arthritis. *Arthritis Res Ther*. 2013;15(suppl 3):S2.
64. Coxib and traditional NSAID Trialists' (CNT) Collaboration; Bhala N, Emberson J, Merhi A, et al. Vascular and upper gastrointestinal effects of

non-steroidal anti-inflammatory drugs: Meta-analyses of individual participant data from randomised trials. *Lancet*. 2013;382(9894):769–779.

65. Antman EM. Evaluating the cardiovascular safety of nonsteroidal anti-inflammatory drugs. *Circulation*. 2017;135(21):2062–2072.
66. Bello AE, Holt RJ. Cardiovascular risk with non-steroidal anti-inflammatory drugs: Clinical implications. *Drug Saf*. 2014;37(11):897–902.
67. Nissen SE. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. *N Engl J Med*. 2017;376(14):1390.
68. Meunier L, Larrey D. Recent advances in hepatotoxicity of non steroidal anti-inflammatory drugs. *Ann Hepatol*. 2018;17(2):187–191.
69. Celebrex®[package insert]. Pfizer, Inc. N.Y., N.Y.; May 2016. Available at http://labeling.pfizer.com/ShowLabeling.aspx?id=793. Accessed June 2016.
70. Derry S, Moore RA, Rabbie R. Topical NSAIDs for chronic musculoskeletal pain in adults. *Cochrane Database Syst Rev*. 2012;9:CD007400.
71. Conaghan PG, Dickson J, Grant RL, Guideline Development Group. Care and management of osteoarthritis in adults: Summary of NICE guidance. *BMJ*. 2008;336(7642):502–503.
72. Latimer N, Lord J, Grant RL, et al. Cost effectiveness of COX 2 selective inhibitors and traditional NSAIDs alone or in combination with a proton pump inhibitor for people with osteoarthritis. *BMJ*. 2009;339:b2538.
73. Ayhan E, Kesmezacar H, Akgun I. Intraarticular injections (corticosteroid, hyaluronic acid, platelet rich plasma) for the knee osteoarthritis. *World J Orthop*. 2014;5(3):351–361.
74. Law TY, Nguyen C, Frank RM, Rosas S, McCormick F. Current concepts on the use of corticosteroid injections for knee osteoarthritis. *Phys Sportsmed*. 2015;43(3):269–273.
75. Pyne D, Ioannou Y, Mootoo R, Bhanji A. Intra-articular steroids in knee osteoarthritis: A comparative study of triamcinolone hexacetonide and methylprednisolone acetate. *Clin Rheumatol*. 2004;23(2):116–120.
76. FDA Drug Safety Communication, September 13, 2012. Available at http://fda.gov./Drugs/DrugSafety/ucm318858.htm. Accessed September 10, 2015.
77. Cepeda MS, Camargo F, Zea C, Valencia L. Tramadol for osteoarthritis: A

systematic review and metaanalysis. *J Rheumatol*. 2007;34(3):543–555.

78. Howes F, Buchbinder R, Winzenberg TB. Opioids for osteoarthritis? weighing benefits and risks: A cochrane musculoskeletal group review. *J Fam Pract*. 2011;60(4):206–212.
79. Langley PC, Patkar AD, Boswell KA, Benson CJ, Schein JR. Adverse event profile of tramadol in recent clinical studies of chronic osteoarthritis pain. *Curr Med Res Opin*. 2010;26(1):239–251.
80. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA*. 2016;315(15):1624–1645.
81. Centers for Disease Control and Prevention (CDC). 2018 annual surveillance report of drug-related risks and outcomes—United States; surveillance special report. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. Accessed August 8, 2018 from https://www.cdc.gov.drugoverdose/pdf/pubs/2018cdc-drug-surveillance-report.pdf.
82. Hunter DJ. Viscosupplementation for osteoarthritis of the knee. *N Engl J Med*. 2015;372(11):1040–1047.
83. Jevsevar D, Donnelly P, Brown GA, Cummins DS. Viscosupplementation for osteoarthritis of the knee: A systematic review of the evidence. *J Bone Joint Surg Am*. 2015;97(24):2047–2060.
84. Wandel S, Juni P, Tendal B, et al. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: Network meta-analysis. *BMJ*. 2010;341:c4675.
85. Sawitzke AD, Shi H, Finco MF, et al. The effect of glucosamine and/or chondroitin sulfate on the progression of knee osteoarthritis: A report from the glucosamine/chondroitin arthritis intervention trial. *Arthritis Rheum*. 2008;58(10):3183–3191.
86. Hochberg MC, Martel-Pelletier J, Monfort J. Combined chondroitin sulfate and glucosamine for painful knee osteoarthritis: A multicentre, randomised, double-blind, non-inferiority trial versus celecoxib. *Ann Rheum Dis*. 2015;75(1):37–44.

Rheumatoid Arthritis

Stephanie Gruber, Bianca Lezcano, and Susan Hylland

KEY CONCEPTS

1. The etiology of rheumatoid arthritis is unknown but is thought to result from a combination of genetic and environmental factors.
2. Rheumatoid arthritis is a systemic autoimmune condition in which inappropriate activation of innate and adaptive immune responses cause inflammation leading to bone, cartilage, and synovium erosion.
3. The primary goal of treatment includes targeting disease remission/low disease activity ultimately aiming at enhancing quality of life.
4. Care should be provided by a rheumatology-trained clinician.
5. Optimizing mental health and completing physical therapy are both crucial nonpharmacologic therapies in addition to providing comprehensive disease and treatment education.
6. Drug treatment should be started as soon as a diagnosis is established.
7. Choice of therapy depends on the level of disease activity, comorbid health conditions, patient preference, and often insurance coverage.
8. Nonsteroidal anti-inflammatory drugs, analgesics, and corticosteroids are used as adjunctive therapy to disease-modifying antirheumatic drug therapy.
9. Response to therapy is evaluated by patient subjective reports, physical examination, laboratory markers, and imaging.

Preclass Engaged Learning Activity

In 2009, the US Congress created an abbreviated pathway for approval and

licensure of biologic products that are verified to have no clinically meaningful differences with a biologic product already approved by the US Food and Drug Administration (FDA). Agents approved through this abbreviated pathway are known as *biosimilars*. As the generic versions of small-molecule drugs, the goal in developing biosimilars is to increase the number of treatment options without increasing drug costs. Biosimilars provide formulary options to hospitals, health systems, and pharmacy benefit managers for use in patients with rheumatoid arthritis and other conditions treatable with biologic agents.

Explore the FDA Website on biosimilars: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelc Particularly focus on the “Patient and Prescriber” video materials provided through the website. Through watching these presentations, the learner will become familiar with basic biosimilar verbiage, requirements on the approval pathway, and implication of biosimilars in current clinical practice.

INTRODUCTION

Autoimmune conditions cause the body to produce an inappropriate immune response against its own healthy tissue. Rheumatoid arthritis (RA) is a common, chronic, progressive autoimmune condition that primarily affects the joint and synovium but can also have detrimental effects on organ systems throughout the body. It can have substantial and devastating effects on one’s ability to function and complete basic activities of daily living. The exact etiology of RA is unknown, but treatment options are numerous. Comprehensive treatment plans are developed under the guidance of a rheumatology specialist and through a process of shared decision-making with the patient.

EPIDEMIOLOGY

RA is one of the more common autoimmune conditions. The annual incidence is about 40 individuals per 100,000 Worldwide disease prevalence is approximately 1% with some variance for race and geographic location.[1] Epidemiologic studies have shown that this prevalence corresponds most closely with North American and Northern European countries; however, native American-Indian populations have the highest prevalence noted (approximately 5%-6%). Southern European, Eastern Asian, and African countries have a lower

prevalence.[2,3] Women are twice as likely to develop the disease compared with men.[1,2]

RA generally presents in the fifth decade of life with increasing prevalence up to the eighth decade of life.[4] RA can affect children age 16 years or younger; in these patients, the condition is referred to as juvenile RA. This chapter focuses only on the clinical management of adult RA. Compared with the general population, individuals with RA have higher rates of disability claims and workplace limitations and lower rates of employment.[5] Loss of productivity has been associated with lower annual earnings.[3,5]

The mortality rate in patients with RA is higher than that of the general population. Cardiovascular (CV) disease is the leading cause of death in RA and presents the greatest concern. Patients with RA have a higher risk of major adverse CV events, and RA disease activity is a predictor of increased CV risk. The risk of death is also increased by infections, malignancy, depression, and pulmonary disease. The expected life expectancy of patients with RA is 3 to 10 years less than the general population.[1,6,7]

Despite advancements in therapy in recent years, mortality trends have not changed drastically, though one could argue additional time is required to detect changes in survival data. Other common comorbid autoimmune diseases include insulin-dependent diabetes mellitus and autoimmune thyroid disease.[6,7]

ETIOLOGY

1 The specific cause of RA is unknown. The disease results from a mix of genetic susceptibility and nongenetic factors combined with a triggering event. Genetic polymorphisms seem to play a large role based on descriptive epidemiologic studies. There is a thought that multiple genes are involved, specifically those of the human leukocyte antigen (HLA) system.[8] Genetics also seems to play a role based on familial studies. In studies of the development of RA in twins, monozygotic twins had a higher concordance than dizygotic twins.[9] Patients with a first-degree relative with RA are at a higher risk of having RA themselves when nongenetic factors are standardized.[10]

Studies show some variability regarding the role of hormonal regulation and the likelihood of RA development, particularly with estrogen. Evidence is conflicting as to whether pregnancy status affects the risk of RA. Pregnancy is often associated with disease remission in the last trimester, but flares commonly occur in the acute postpartum period.[8] There is also controversial evidence

showing female oral contraceptives may protect against or postpone disease development. Men with low testosterone levels are more likely to have RA, suggesting testosterone may provide a protective effect as well.[2,8]

Nongenetic or environmental factors possibly associated with RA include cigarette use, coffee consumption, and obesity.[8] Cigarette smoking has been tied to increased disease activity, increased biomarkers, and poor prognoses.[2,6] Ties are weaker for disease development with heavy coffee consumption and obesity.[11] An omega-3 rich diet seems to provide a favorable impact on disease development.[2] Occupational hazards, such as exposure to silica, may also play a role in susceptibility to disease.[12]

Additional factors, aside from those mentioned above, are thought to be needed to trigger the disease itself. An infectious process is hypothesized to be the primary trigger. The Epstein–Barr virus and retroviruses are most commonly associated with the disease.[8] Infections of *Mycoplasma* spp. and *Porphyromonas gingivalis* have been suspected as bacterial triggers, but no true link has been found to show their causality.[13]

Further studies are required to help uncover the exact etiology of RA.

PATHOPHYSIOLOGY

2 The role of the immune system is to detect foreign matter, build a response, and neutralize the threat. In RA, the immune system cannot discriminate between self and nonself. This results in cell proliferation, inflammation, and destruction of tissues and fluids throughout one's own body.

The immune cascade and inflammatory pathway dysregulation associated with RA is multifactorial (**Fig. 107-1**). Overstimulation of the innate immune system is thought to be one of the earliest histologic changes in RA. T cells display an activated surface phenotype with high allele expression of HLA and CD 27, increasing their affinity for lymphokines. Activated T cells stimulate B cells, causing production of autoantibodies. These autoantibodies form large complexes that deposit throughout the body. Antibodies to immunoglobulin G (IgG) have a strong correlation to the pathogenesis and poor prognosis of RA and are known as rheumatoid factor (RF). B cells also produce proinflammatory cytokines, including tumor necrosis factor (TNF) and the interleukin (IL) system, which are responsible for inducing expression of adhesion molecules on the endothelium, further enhancing T-cell proliferation and differentiation, encouraging cell migration, and regulating matrix modeling.[14–16]

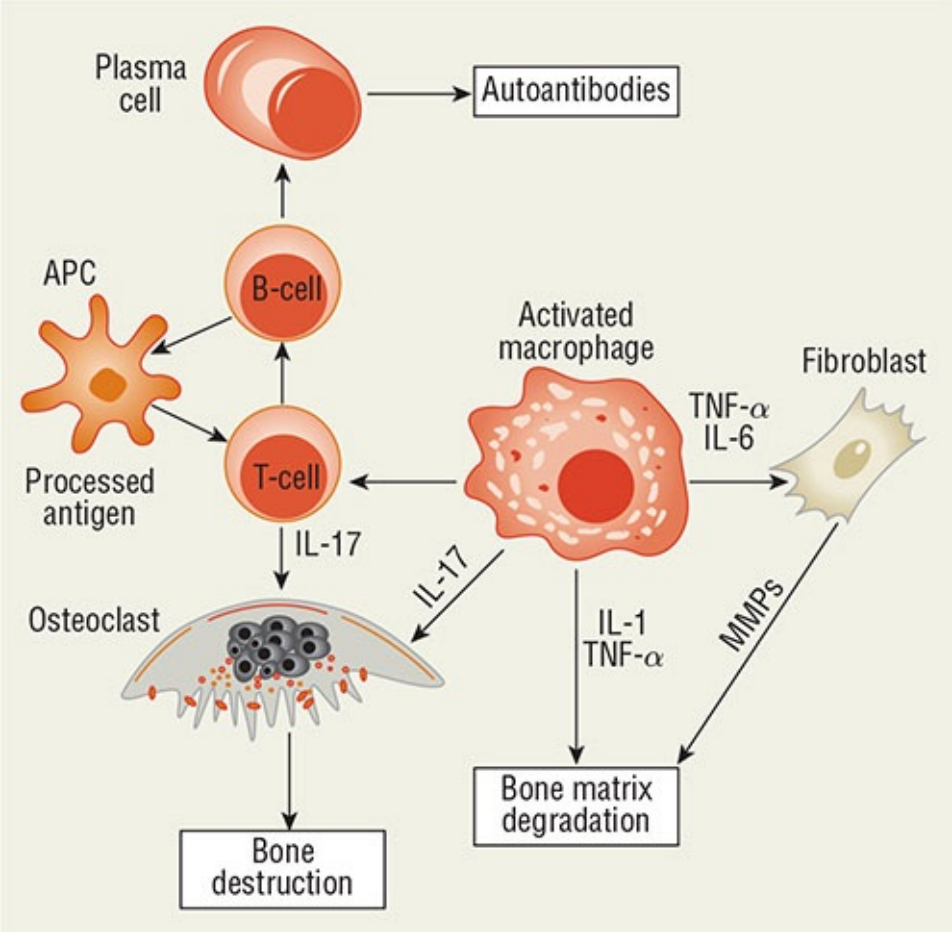


FIGURE 107-1 Pathogenesis of the inflammatory response. Antigen-presenting cells process and present antigens to T cells, which may stimulate B cells to produce antibodies and osteoclasts to destroy and remove bone. Macrophages stimulated by the immune response can stimulate T cells and osteoclasts to promote inflammation. They also can stimulate fibroblasts, which produce matrix metalloproteinases to degrade the bone matrix and produce proinflammatory cytokines. Activated T cells and macrophages release factors that promote tissue destruction, increase blood flow, and result in cellular invasion of synovial tissue and joint fluid. (APC, antigen-presenting cell; IL, interleukin; MMP, matrix metalloproteinase; TNF-α, tumor necrosis factor α.)

Other mechanisms of pathogenesis include overexpression of tumor suppressor gene *p53*, which prevents normal DNA repair and interferes with appropriate cell apoptosis (programmed cell death), and increased presence of anti-citrullinated protein antibodies (ACPA). ACPA positivity is associated with a poorer prognosis in patients with RA.[17,18]

A variety of histological changes occur within the synovium given the above

pathological processes. Synovial tissue typically attaches to the skeletal tissues and the bone-cartilage joint cavity and provides a protective shield for the synovial interstitium and a nutrient-rich environment for cartilage. Migration of lymphocytes, macrophages, and mononuclear cells into the synovium and synovial cavity are some of the earliest histologic changes in RA. With the increased mass to the synovium comes hypertrophy and subsequently angiogenesis, which is needed to bring the necessary oxygen and nutrients to the environment. Angiogenesis is initiated by the proinflammatory cytokines and driven by factors such as IL-8, prostaglandins, vascular endothelial growth factor, and macrophage angiogenic factor. As the vessels develop, cytokines also stimulate further migration of both innate and adaptive immune systems into the synovium, causing inflammation. The inflamed, fibrotic synovium found in RA is known as a pannus. The pannus invades cartilage and bone around it, thereby promoting further destruction and dysregulation.[19–22]

Cytokines in the cartilage drive the generation of reactive nitrogen and oxygen species while increasing chondrocyte catabolism, inhibiting chondrocyte anabolism, and increasing extracellular matrix destruction. Proinflammatory cytokines travel to the bone, provide the source for receptor activator of NFkB ligand (RANKL), and enhance the differentiation and activity of osteoclasts leading to bone matrix destruction.[23–26]

Circulating immune complexes and T cells have been found in the extra-articular involvement of RA. Chronic inflammation in vascular endothelial and visceral, cutaneous, and pleural tissues leads to complications including vasculitis, fibrosis, anemia, and renal amyloidosis.[19,27]

CLINICAL PRESENTATION

Joint Involvement

Patients with RA often present with involvement of synovial-lined peripheral joints, typically in a symmetrical fashion (**Fig. 107-2**). The joints of the hands, feet, wrists, and ankles are most commonly involved. Elbows, knees, shoulders, hips, cervical spine, and temporomandibular joints may also be affected.

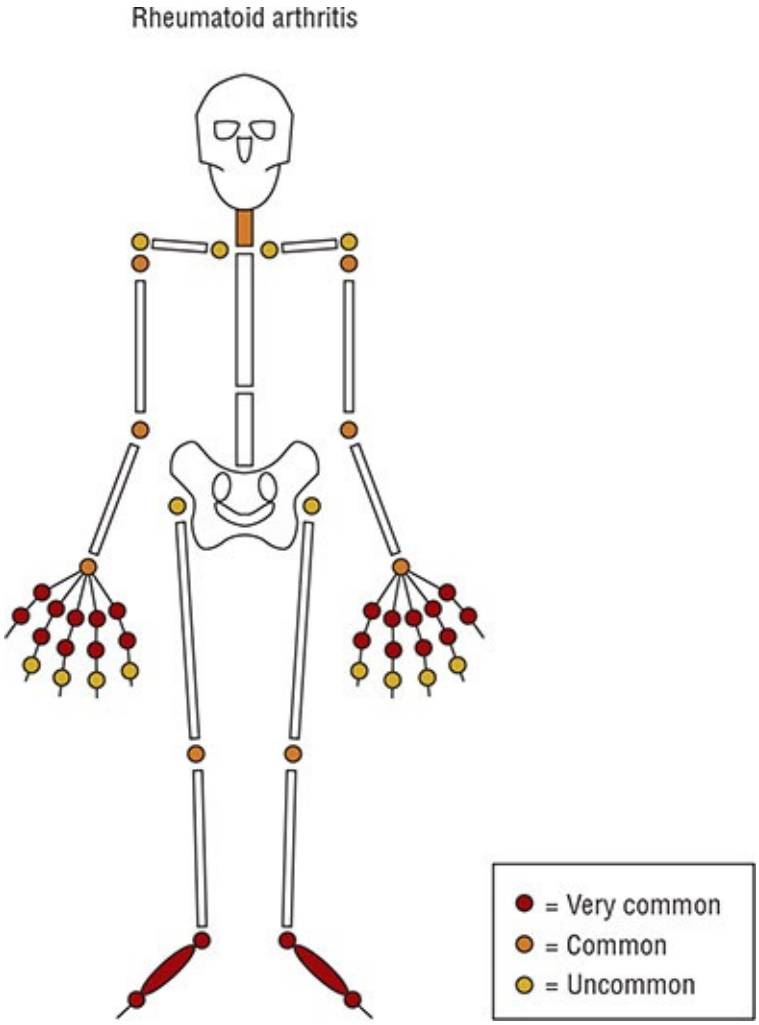


FIGURE 107-2 Patterns of joint involvement in rheumatoid arthritis.

Classic features of RA are the presence of swelling and prolonged morning stiffness, often for more than 30 minutes. Joint swelling is caused by proliferation of synovium or effusion within the joint capsule. On physical examination, joint swelling may be visible or detected by palpation of soft spongy tissue along joint lines. A swollen joint may appear erythematous, and the overlying skin may feel warmer than surrounding tissue. In contrast, the swelling associated with osteoarthritis is due to bony enlargement and not typically associated with signs of inflammation.

CLINICAL PRESENTATION Rheumatoid Arthritis

Joint Involvement

- Hands, wrists, ankles, and feet most commonly affected, often

bilaterally

- Presence of warmth and swelling with or without pain
- Prolonged morning stiffness, often for longer than 30 minutes in duration
- Decreased functionality
- Symptoms present for 6 weeks or more
- Subluxations and deformities possible with advanced disease

Extra-articular Involvement

- Generalized fatigue, weakness, and decreased mood are nonspecific implications of disease
- Rheumatoid nodules can be found on extensor or pleural lining surfaces
- Interstitial lung disease or pleural disease
- Vasculitis
- Keratoconjunctivitis sicca, scleritis, or Sjögren's syndrome
- Pericarditis, cardiac conduction abnormalities, or myocarditis
- Felty syndrome or anemia

Laboratory Findings

- Rheumatoid factor is detected in 70% to 80% of patients with RA with higher titers, which reflects increased sensitivity and more progressive disease
- Anti-cyclic citrullinated antibodies are more specific for disease, particularly early stage, and generally indicate more aggressive disease
- Erythrocyte sedimentation rate and C-reactive proteins may indicate the presence of a nonspecific inflammatory process
- Synovial fluid analysis through joint aspiration typically demonstrates a high white blood cell count in the absence of crystals or infection

Radiography

- In early stages of RA, it may show soft-tissue swelling and joint space narrowing
- In late-stage disease, it may show joint subluxations, deviations, and

secondary arthritis

RA of the hands more specifically involves the metacarpophalangeal, proximal interphalangeal, and wrist joints, while sparing distal interphalangeal joints (**Fig. 107-3**). Pain and swelling commonly affect joint range of motion and grip strength. Wrist swelling may lead to focal nerve compression, causing symptoms of carpal tunnel syndrome. Untreated, long-term joint inflammation may lead to bony erosions, subluxations, and deformities (**Figs. 107-4 and 107-5**). These changes may alter the mechanics of hand function, reducing grip strength and making it difficult to perform usual daily activities.

FIGURE 107-3 Typical hand deformities of rheumatoid arthritis showing ulnar deviation of the fingers and swelling of the metacarpophalangeal and proximal interphalangeal joints. (*Reproduced with permission from Brunicardi FC, Anderson DK, Billiar TR, et al. Schwartz's Principles of Surgery. 8th ed. New York: McGraw-Hill; 2005.*)

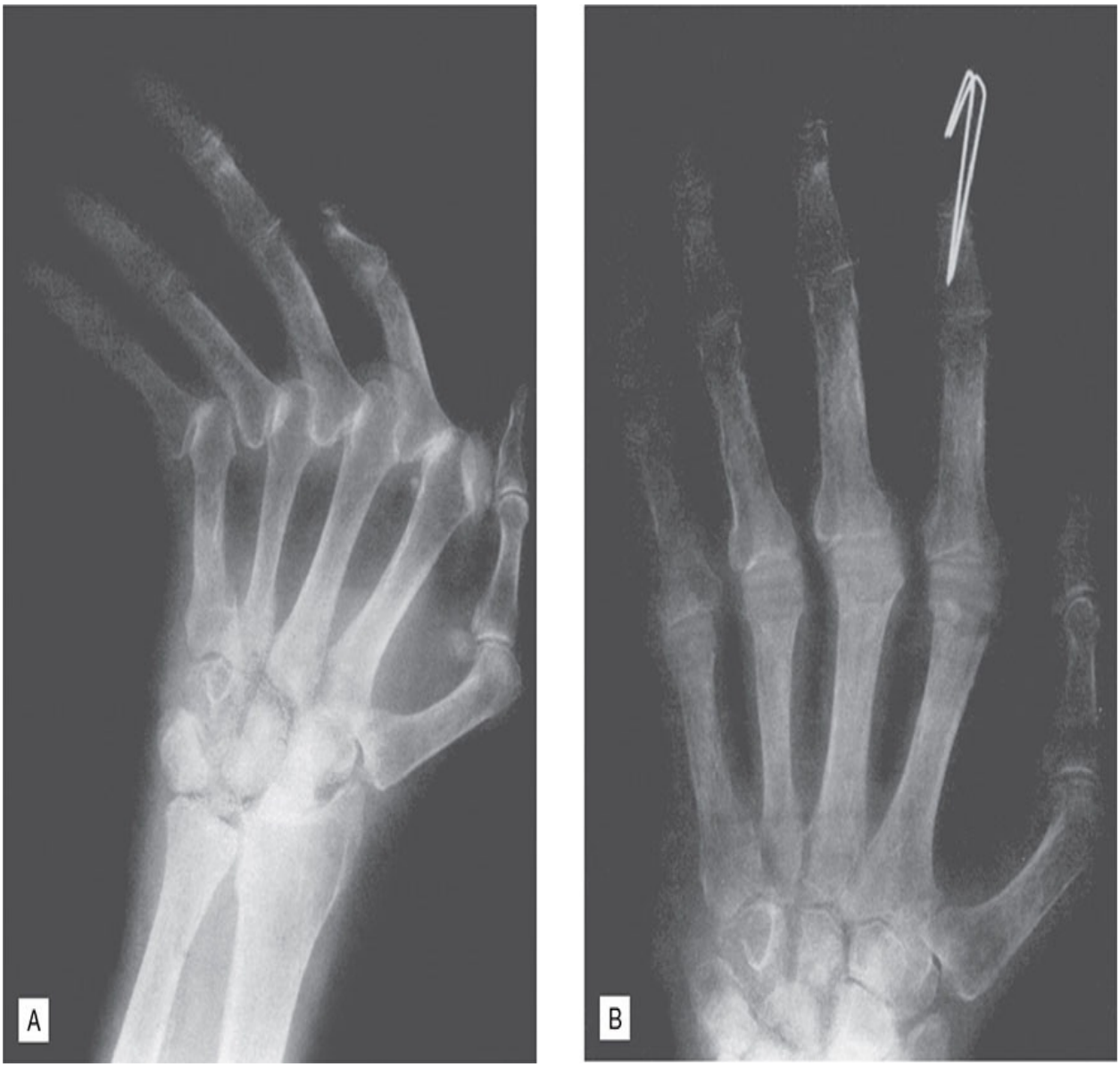


FIGURE 107-4 Radiographs of hands of patient with rheumatoid arthritis showing erosions and subluxations of the metacarpophalangeal joints with ankylosis of the carpal bones of both wrists. (*Reproduced, with permission, from Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 20th ed. New York, NY: McGraw-Hill; 2019.*)

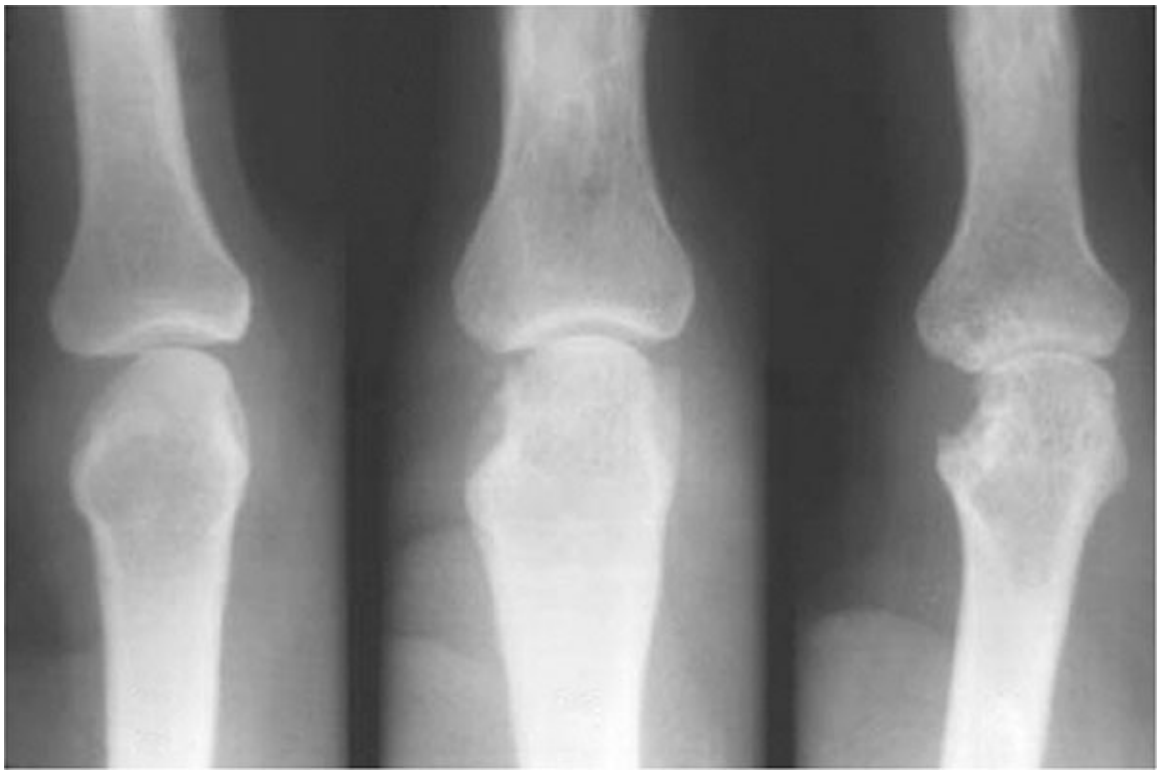


FIGURE 107-5 Radiograph showing soft tissue swelling, joint space narrowing, and erosions in the metacarpophalangeal joints. (*Reprinted with permission from Jonsson A, Borg A, Hannesson, et al. Film-screen vs digital radiography in rheumatoid arthritis of the hand: An ROC analysis. Acta Radiologica. 1994;35(4):312.*)

When patients with RA have involvement of the joints of the feet, walking may be difficult because of metatarsophalangeal, midfoot, and ankle joint inflammation. Untreated long-term inflammation may lead to subluxations of the metatarsal heads causing bunion formation, hammer toe deformities, or overlapping digits (Figs. 107-4 and 107-5). Affected joints are then subject to ulceration of the skin overlying joint deformities secondary to pressure caused by footwear.

Other parts of the body are also affected by pathophysiologic changes in RA. Pain and decreased range of motion in the elbow and shoulder joints may be the result of joint inflammation or inflammation of the tendons and bursae around the joints. Chronic synovial inflammation of the knee may lead to effusions, pain, and loss of range of motion. Synovitis of the knee may cause the formation of a fluid collection behind the knee called a popliteal (Baker) cyst. Eventually, chronic knee joint inflammation may lead to cartilage loss and muscle atrophy, which can result in laxity of the ligamentous structures that support the knee and

ultimately instability. The hip joint, a large axial joint, is less commonly involved in RA, but may manifest with joint effusion and long-term accelerated cartilage loss.

Spinal involvement in RA, when present, occurs in the upper cervical vertebrae. Inflammation of the synovial-lined portions of the first and second cervical vertebrae (C1-C2) can lead to neck pain and stiffness. Long-term RA activity at this joint may lead to instability and subluxation, putting patients at risk for spinal cord compression, although this complication is rare.

The temporomandibular joint of the jaw is also a synovial lined joint and, when affected, patients with RA may experience malocclusion and difficulty chewing.

Extra-articular Involvement

Although joint involvement is the hallmark finding in RA, it is important to recognize that this is ultimately a multisystem inflammatory disease. Patients with high-titer RF or ACPA have a higher likelihood of extra-articular manifestations.

Rheumatoid Nodules

Rheumatoid nodules occur in 20% to 35% of patients with RA at some point during their disease course.[28] Rheumatoid nodules are subcutaneous collections of palisading macrophages surrounded by lymphocytes and fibroblasts, which can vary in size from several millimeters to several centimeters. They are most commonly found on the extensor surfaces of the elbows, forearms, and hands but also may be seen on the feet and at other pressure points. They also may develop in the lung or pleural lining of the lung. Rheumatoid nodules usually are asymptomatic and do not require any special intervention. They do not necessarily improve with treatments targeting RA activity and can accelerate in growth during treatment with methotrexate.[29]

Pulmonary Complications

Interstitial lung disease (ILD) is the most common pulmonary manifestation of rheumatoid disease. Frequently ILD is not overtly clinically apparent, but it can be seen on high-resolution CT imaging in up to 33% of patients with RA without symptoms of cough or dyspnea.[30] The most frequent patterns of ILD seen in RA are the usual interstitial pneumonia and nonspecific interstitial pneumonia.

Smoking increases the risk of this complication.[31]

Pleural disease is common in RA, and while most commonly asymptomatic, it may result in pleural effusion.[32] Rheumatoid nodules may also develop in lung tissue and may be difficult to distinguish from infection or malignancy on chest imaging. Interstitial pneumonitis is a rare but potentially life-threatening complication of RA. Treatments directed at treating articular manifestations of rheumatoid arthritis frequently do not control pulmonary manifestations.

Vasculitis

Rheumatoid vasculitis is a rare complication of RA seen in patients with long-standing seropositive disease. Invasion of arterial walls by inflammatory cells results in narrowing of the vessel lumen, producing tissue ischemia and infarct. Skin is the most common tissue involved, and infarcts of distal fingers or toes are usually of little consequence. Vasculitis may also involve skin in the lower extremities, producing ulcers that may first appear to be stasis ulcers but are painful due to the ischemic arterial component.

When more severe or visceral rheumatoid vasculitis is present, patients commonly show constitutional symptoms such as weight loss, fever, or failure to thrive. Infarction of vessels supplying blood to nerves can cause motor deficits, such as a foot drop. Renal involvement of vasculitis may lead to a necrotizing glomerulonephritis. Rarely, involvement of medium-sized vessels can result in life-threatening complications with visceral involvement similar to that seen in polyarteritis nodosa.

Rheumatoid vasculitis requires aggressive immunosuppressive therapy to prevent serious complications. Fortunately, the incidence of rheumatoid vasculitis has dramatically decreased with the advent of the routine use of disease-modifying antirheumatic drugs (DMARDs) and biologic therapies with the intent of treating patients with RA to target remission.[33]

Ocular Manifestations

Ocular manifestations of RA include keratoconjunctivitis sicca and inflammation of the sclera, episclera, cornea, and uveal tract. Inflammation and subsequent atrophy of the lacrimal glands may result in decreased tear formation, causing dry and itchy eyes, a condition usually termed *keratoconjunctivitis sicca*. When this condition is observed in association with RA, it is referred to as secondary Sjögren’s syndrome.

Inflammation of the superficial layers of the sclera is called *episcleritis* and is

a generally self-limiting manifestation. *Scleritis* is a more serious vascular inflammation of the cornea, episclera, and uvea, as it is painful and threatens vision. Scleritis in RA is typically a sign of uncontrolled systemic inflammation and warrants prompt and aggressive immunosuppression to preserve vision.

Cardiac Involvement

RA is believed to be an independent risk factor for coronary artery disease and is associated with an increased risk of cardiovascular mortality. A meta-analysis published in 2008 concluded that the risk of cardiovascular mortality was 59% higher in patients with RA than in the general population.[34]

The risk for cardiovascular disease appears to be higher in those with more active inflammation and is reduced with treatment, particularly with methotrexate.[35] Pericarditis may occur, although the development of clinically evident pericarditis with tamponade is a rare complication. Cardiac conduction abnormalities and aortic valve incompetence, caused by aortic root dilation, may occur. Myocarditis is a rare complication of RA.

Hematologic Involvement

A small subset of patients with more severe, long-standing, seropositive RA will go on to develop splenomegaly and neutropenia; this is known as *Felty syndrome*. Neutropenia leads to an increased susceptibility to recurrent bacterial infection. Treatment with immunosuppressive therapy, typically methotrexate, with the goal of reversing immune system dysfunction, will usually improve granulocyte counts.

Large granular lymphocyte leukemia (LGL) is an indolent leukemia characterized by a clonal proliferation of large granular lymphocytes. Often patients with LGL require no therapy, unless neutropenia is severe leading to recurrent infections. LGL is treated with immunosuppression. The majority of experience has involved the use of methotrexate, cyclophosphamide, or cyclosporine.[36]

Other Complications

Lymphadenopathy may occur in patients with RA, and when present, it warrants a work-up for infection or malignancy. Amyloidosis is a rare complication of longstanding RA and may lead to renal and gastrointestinal complications. Osteoporosis in patients with RA is almost 2 times higher than in patients without RA.[37]

Laboratory Findings

The complete blood count can be altered by RA or its treatment. A mild-to-moderate normocytic anemia is commonly due to anemia of chronic disease. It is important to differentiate anemia of chronic disease from anemia associated with complications of therapy, such as gastritis induced by nonsteroidal anti-inflammatory drugs (NSAIDs) or bone marrow suppression from immunosuppressive therapy. Thrombocytosis is a common finding with active RA since platelets are generally considered an acute phase reactant and tend to rise and fall in correlation with inflammation in many patients. Thrombocytopenia may also result as a side effect of immunosuppressive therapy. Neutropenia is associated with Felty syndrome and LGL, but it also may be a side effect of immunosuppressive drugs. Leukocytosis is seen commonly as a result of corticosteroid treatment.

The erythrocyte sedimentation rate (ESR) and C-reactive proteins (CRP) are nonspecific markers of inflammation that are usually elevated in patients with active RA. They may be used as an aid in following RA activity.

A positive RF is detected in 70% to 80% of patients with RA. In general, higher titers of RF increase the sensitivity and indicate a potentially more severe disease course. A positive RF (two times the upper limit of normal) in a patient with consistent clinical features of inflammatory arthritis is fairly specific for rheumatoid arthritis. However, a positive RF, especially with a low titer in a patient without clinical evidence of inflammatory arthritis, has low specificity for RA. Many patients with hepatitis C have a positive rheumatoid factor, as do many patients with Sjögren's syndrome, sarcoidosis, and certain infections.

Anticyclic citrullinated antibodies have a slightly lower sensitivity to the RF, being found in 57% (range, 12%-93%) of patients with RA, but ACPAs are more specific (96%) and may be detectable very early in the disease.[38] The presence of ACPA in general predicts a more aggressive course of disease and increased risk of joint erosions. In contrast to RF, ACPAs are not typically present in patients with hepatitis C. Many rheumatologists order both tests in evaluating new patients.

Antinuclear antibodies (ANAs) are detected in 25% of patients with RA as a result of their disease. The presence of a positive ANA in a work-up of polyarthritis may initially lead to a diagnostic challenge, since they are more commonly seen in systemic lupus erythematosus, systemic sclerosis, and mixed connective tissue disease, all of which can have arthritis as a presenting feature. However, patients with RA who have a positive ANA would not be expected to be positive for more specific antibodies for connective tissue disorders,

including anti-ds DNA antibodies, anti-smith antibodies, anti-SCL 70 antibodies, or anti-RNP antibodies.

Synovial fluid analysis may be performed during the initial diagnosis or follow-up in patients with RA to rule out crystalline disease or infection in swollen joints (especially joints that are swollen out of proportion to the rest of the clinical examination). Synovial fluid analysis of involved joints typically reveals white blood cell counts of 1,500 to 25,000/mm^3 (1.5×10^9 to 25×10^9/L) but may be higher in those with very active RA.[39]

Plain radiographs in RA are often normal at the time of disease presentation. The earliest plain radiographic findings typically include soft-tissue swelling and periarticular osteoporosis on hand and foot x-rays. As RA progresses, joint space narrowing occurs as a result of cartilage degradation, and marginal erosions (at the margins of the joint capsules) may occur, typically in the ulnar styloid, metacarpophalangeal and proximal interphalangeal joints of the hands (Fig. 107-5), and the metatarsophalangeal joints of the feet. In advanced stages of RA, radiographs may show deformities including joint subluxations, ulnar deviation of the metacarpophalangeal joints, and secondary osteoarthritis. Many DMARD and biologic therapies have been shown to halt the progression of erosive changes in RA. Serial joint radiographs may be used in addition to clinical findings as a way of evaluating disease progression and adequacy of therapy.

DIAGNOSTIC CRITERIA

In 2010, the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) updated their classification criteria for RA.[40] The revised criteria allow for identification of patients at an earlier stage of disease, such as synovitis of one small joint in the absence of an alternative diagnosis. It is widely acknowledged that early identification of patients with RA may allow for earlier treatment geared toward preventing structural damage to joints.

The criteria use a scoring system which assigns points based upon the number and types (small and large) of joints involved. The presence of RF or ACPA and elevated acute phase reactants (CRP and ESR) result in additional points. A duration of symptoms of 6 weeks or more provides an additional point. A total score of 6 or more out of a possible total score of 10 is considered diagnostic for RA (**Table 107-1**).[40] Not all patients with RA will score 6 or greater initially but may evolve to higher scores over time.

TABLE 107-1 ACR/EULAR Rheumatoid Arthritis Classification Criteria

Criteria	Score
Low-positive RF or ACPA	2
High-positive RF or ACPA	3
High ESR or CRP	1
Duration of symptoms ≥6 weeks	1
Joint Involvement (at least one joint not explained by another disease)	
2-10 large joints	1
1-3 small joints (± large joint)	2
4-10 small joints (± large joint)	3
>10 joints (at least one small joint)	5

ACR/EULAR, American College of Rheumatology/European League Against Rheumatism; ACPA, anti-citrullinated protein antibodies; CRP, C-reactive protein; ESR, eosinophil sedimentation rate; RF, rheumatoid factor.

Patients with inflammatory arthritis who have negative RF and ACPA may be diagnosed with RA if they fulfill further criteria otherwise characteristic of RA. In addition, a number of other inflammatory arthritic conditions are managed similarly to seropositive rheumatoid arthritis; these include psoriatic arthritis, reactive arthritis, ankylosing spondylitis, and arthritis associated with inflammatory bowel disease.

TREATMENT

Desired Outcomes

The ACR as well as the EULAR guidelines suggest a treat-to-target approach when treating patients with RA rather than a nontargeted treatment approach. This approach to treatment suggests that if remission cannot be achieved, low disease activity is an acceptable alternative target.[41,42] This treatment approach is supported by several randomized controlled trials that have shown superior clinical outcomes compared with usual care. In general, RA treatment is directed toward reducing inflammation and symptoms, including joint pain and stiffness. Most of the therapies used to treat RA slow the disease progression and thus the progression of irreversible joint damage, which can help decrease disability and improve quality of life.[43]

General Approach To Treatment

3 4 Available pharmacologic therapies do not reverse joint damage that has already occurred. Therefore, early aggressive treatment of RA is imperative. Several studies have supported that early treatment of RA results in improved outcomes and have shown that patients with a shorter disease duration are more likely to respond to treatment.[44,45] Nonpharmacologic therapies also play a role in the management of RA and encourage patients to take an active role in managing their disease.[46] Therefore, the approach to the treatment of RA should include both pharmacologic and nonpharmacologic methodologies. Ultimately, care should be coordinated by a healthcare provider trained in rheumatology.

Nonpharmacologic Treatment

5 Nonpharmacologic approaches for the treatment of RA include referrals to occupational and physical therapy, mental health, social work, reviewing pain coping skills, and providing patient education. Both mental and physical health are important in patients with RA, as some data suggest that central neuroendocrine and dopaminergic pathways may be involved in both RA disease activity and physical and mental health. Patients with RA are also more likely to be affected by mood disorders.[47]

Patient education should involve disease state education as well as medication education related to potential adverse effects and how to appropriately administer injectable agents. Physical therapy is beneficial for reducing pain and inflammation while preserving joint function. The benefits of exercise and physical activity, including aerobic activity and muscle-strengthening exercises, have been demonstrated to improve RA-related disease outcomes. Assistive devices and orthoses such as braces and supports are useful to improve pain and function. Occupational therapy can be effective and provide several benefits such as exercises, appropriate footwear, and splinting.[46] Weight loss can help decrease the stress on joints. Surgical options, including joint replacements, are reserved for patients with more severe disease where there may have significant cartilage loss.

Pharmacologic Therapy

Currently available therapies used to treat RA and also slow the progression of the disease include conventional and biologic DMARDs and the small-molecule

agent tofacitinib. Conventional DMARDs include methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine. Biologic DMARDs fall into two categories: tissue necrosis factor (TNF) inhibitor biologics (adalimumab, etanercept, certolizumab, golimumab, and infliximab) and non-TNF biologics (abatacept, tocilizumab, rituximab, anakinra, and sarilumab). Tofacitinib is an oral synthetic DMARD that is also a Janus Kinase (JAK) inhibitor. Many of the therapies used to treat RA are also indicated and used in the treatment of other conditions such as psoriatic arthritis and ankylosing spondylitis, conditions that are outside of the scope of this chapter. **Table 107-2** includes RA-indicated dosages for the agents discussed in this chapter.

TABLE 107-2 Usual Doses for Disease-Modifying Antirheumatic Drugs

Drugs	Brand Names	Routes of Administration	Starting Doses	Usual Ranges or Maintenance Doses	Comments
Methotrexate	Rasuvo Trexall Otrexup (SubQ)	Oral, SubQ, IM	Oral: 7.5 mg once weekly or 2.5 mg every 12 hours 3 days/week SubQ/IM: 7.5 mg once weekly	7.5-20 mg every week	May be given with folic acid 1-5 mg/day to reduce adverse reactions
Leflunomide	Arava	Oral	Loading dose: 100 mg daily for 3 days, then 20 mg daily or 10-20 mg daily without loading dose	10-20 mg daily	Not recommended in liver disease (ALT >3 times ULN)
Hydroxychloroquine	Plaquenil	Oral	200 mg twice daily or 400 mg daily	200 mg twice daily or 400 mg daily	Take with food or milk; use with caution in renal or hepatic impairment
Sulfasalazine	Azulfidine	Oral	500 mg once or twice daily	1,000 mg twice daily (maximum dose is 3,000 mg/day if inadequate response after 12 weeks of 2,000 mg/day)	Not recommended in renal or hepatic impairment
Etanercept	Enbrel	SubQ	50 mg once weekly or 25 mg twice weekly	Same as starting dose	
Infliximab	Remicade	IV	3 mg/kg at 0, 2, 6 weeks, and then every 8 weeks	3-10 mg/kg every 4-8 weeks	Given in combination with methotrexate therapy; pretreat with methylprednisolone, acetaminophen, and antihistamine
Adalimumab	Humira	SubQ	40 mg every 2 weeks	40 mg every 2 weeks (may increase to 40 mg once weekly if not taking methotrexate)	
Certolizumab	Cimzia	SubQ	400 mg at 0, 2, 4 weeks	200 mg every other week or 400 mg every 4 weeks	
Golimumab	Simponi	SubQ	50 mg once monthly	Same as starting dose	
Rituximab	Rituxan	IV	1,000 mg in 2 doses given 2 weeks apart	Initial dose may be repeated every 16-24 weeks based on response	Pretreat with methylprednisolone, acetaminophen, and antihistamine
Abatacept	Orencia	IV, SubQ	IV: <60 kg: 500 mg, 60-100 kg: 750 mg, >100 kg: 1,000 mg at 0, 2, and 4 weeks or initial IV dose followed by 125 mg subcutaneously within 24 hours SubQ: 125 mg weekly	IV: dose based on weight every 4 weeks SubQ: 125 mg weekly	
Tocilizumab	Actemra	IV, SubQ	IV: 4 mg/kg every 4 weeks SubQ: <100 kg: 162 mg every other week, >100 kg 162 mg weekly	IV: 4-8 mg/kg every 4 weeks (maximum 800 mg per infusion) Subcutaneously: <100 kg: 162 mg every other week, followed by an increase to weekly injections if needed, >100 kg: 162 mg weekly	Can increase the metabolism of CYP3A4 substrates
Tofacitinib	Xeljanz	Oral	IR: 5 mg twice daily ER: 11 mg daily	Same as starting dose	5 mg once daily in moderate-to-severe renal insufficiency, moderate hepatic impairment, or concomitant CYP3A4 or CYP2C19 inhibitors
Anakinra	Kineret	SubQ	100 mg once daily	Same as starting dose	
Sarilumab	Kevzara	SubQ	200 mg every 2 weeks	Same as starting dose	

ALT, alanine transaminase; CYP, cytochrome P; ER, extended release; IR, immediate release; ULN, upper limit of normal; IM, intramuscular; SubQ, subcutaneous; IV, intravenous.

6 7 The current guidelines for treatment of RA recommend initiation of conventional DMARDs irrespective of disease activity in treatment-naive patients (**Fig. 107-6**) once a diagnosis is established. The preferred conventional DMARD is methotrexate unless a contraindication to its use exists.[41,42] In practice though choice of therapy may ultimately be dependent on level of disease activity, comorbid health conditions, patient preference, and often insurance coverage.

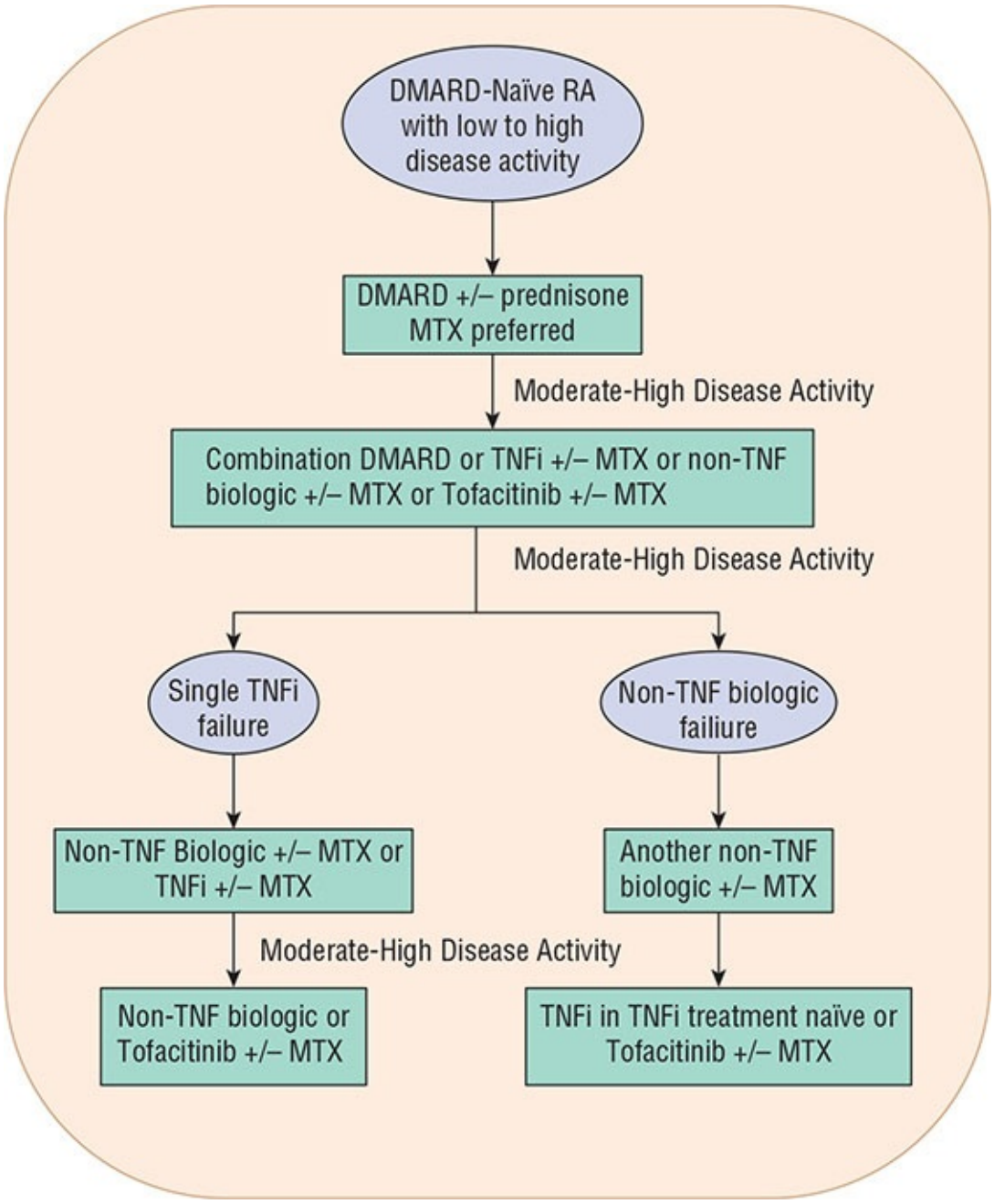


FIGURE 107-6 Treatment algorithm for rheumatoid arthritis based on the American College of Rheumatology guidelines. (DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; TNF, tumor necrosis factor.) *(Data from Reference 41.)*

In patients with early RA—defined as duration of disease/symptoms of less than 6 months—and with low disease activity, treatment with DMARD monotherapy is recommended. Double or triple DMARD therapy is recommended if disease activity is moderate or high. A biologic agent can be used as monotherapy or with conventional DMARD(s) in patients with moderate or high disease activity. Tofacitinib would be an alternate option if disease activity remains moderate or high with combination conventional DMARDs. If disease activity remains moderate or high despite DMARD or biologic agents, a low-dose glucocorticoid can be added for the shortest duration of time necessary. Low-dose glucocorticoid is defined as prednisone 10 mg/day or less or an equivalent amount of another glucocorticoid. If patients achieve remission, DMARDs and biologic agents can be tapered; however, patients should remain on DMARD therapy at some level.[41]

In patients with established RA (duration of disease/symptoms for 6 months or more), treatment with DMARD monotherapy is recommended despite disease activity in DMARD-naive patients. Combination conventional DMARDs or a biologic DMARD or tofacitinib can be used if disease activity remains moderate or high after an adequate trial with DMARD monotherapy. In patients who are on TNF inhibitor monotherapy with moderate or high disease activity, one or two DMARDs can be added to the TNF inhibitor. A non-TNF biologic can be used in place of a TNF inhibitor if disease activity remains moderate or high on a TNF inhibitor. This is recommended over tofacitinib. Therapy can be switched to another non-TNF biologic if a single non-TNF biologic is unable to adequately control disease activity. If courses of two TNF inhibitors have not adequately controlled disease activity, a non-TNF biologic can be initiated. Tofacitinib can be initiated if disease activity persists despite multiple TNF inhibitors in patients for whom non-TNF biologics are not an option. Glucocorticoids can be added if disease flares occur or are inadequately controlled despite DMARD, TNF inhibitor, or non-TNF biologic therapy.[41]

8 DMARDs can take weeks to months to take effect in patients with RA. NSAIDs and/or glucocorticoids, as well as other analgesics such as acetaminophen, can provide symptomatic relief and have a more rapid onset of action than DMARDs; they are often used as “bridge” therapy. NSAIDs do not

impact disease progression, and corticosteroids have several side effects associated with their use, making both less desirable choices for long-term use.

Conventional Disease-Modifying Antirheumatic Drugs

Methotrexate

Methotrexate is the DMARD of choice for most patients unless its use is contraindicated.[41] Methotrexate has been used in the treatment of RA for several decades and has a sustained clinical response over time and a glucocorticoid-sparing effect.[48] It can be taken as monotherapy or in combination with other DMARDs.

Methotrexate is a structural analogue of folic acid that inhibits dihydrofolate reductase. Dihydrofolate reductase is the enzyme responsible for reducing dihydrofolic acid to folinic acid, the active intracellular metabolite. Through this action, methotrexate inhibits DNA synthesis and repair and cellular replication.[49]

Methotrexate is taken once weekly and is typically given in either tablet form or as a subcutaneous injection. It is also available as an intramuscular injection. The absorption of oral methotrexate is highly variable. At low doses (≤30 mg/m^2), oral bioavailability is about 60%, and this decreases at higher doses. Methotrexate is about 50% protein bound and is excreted by the kidney, about 80% to 90% unchanged.[49] Injectable methotrexate has a higher bioavailability compared with oral methotrexate and thus provides superior clinical efficacy. Injectable methotrexate is typically better tolerated and has less potential to cause gastrointestinal side effects as well.[50] The doses used for the treatment of RA typically range from 7.5 to 20 mg weekly. Doses exceeding 20 mg weekly can increase the risk for toxicities.[49] At doses higher than 15 mg weekly, oral methotrexate may not have significant added clinical benefit; changing to subcutaneous methotrexate may increase bioavailability and clinical benefit.[8] Clinical benefit can be seen 3 to 6 weeks after starting methotrexate therapy.[49]

Methotrexate is teratogenic and is therefore contraindicated in pregnancy and breastfeeding. Additional contraindications include alcoholism, alcoholic liver disease or other chronic liver disease, immunodeficiency, and preexisting hematologic disorders, such as leukopenia and thrombocytopenia. Methotrexate excretion is reduced in renal impairment and may require dose reduction or discontinuation in some cases. Excretion is also reduced in ascites or pleural

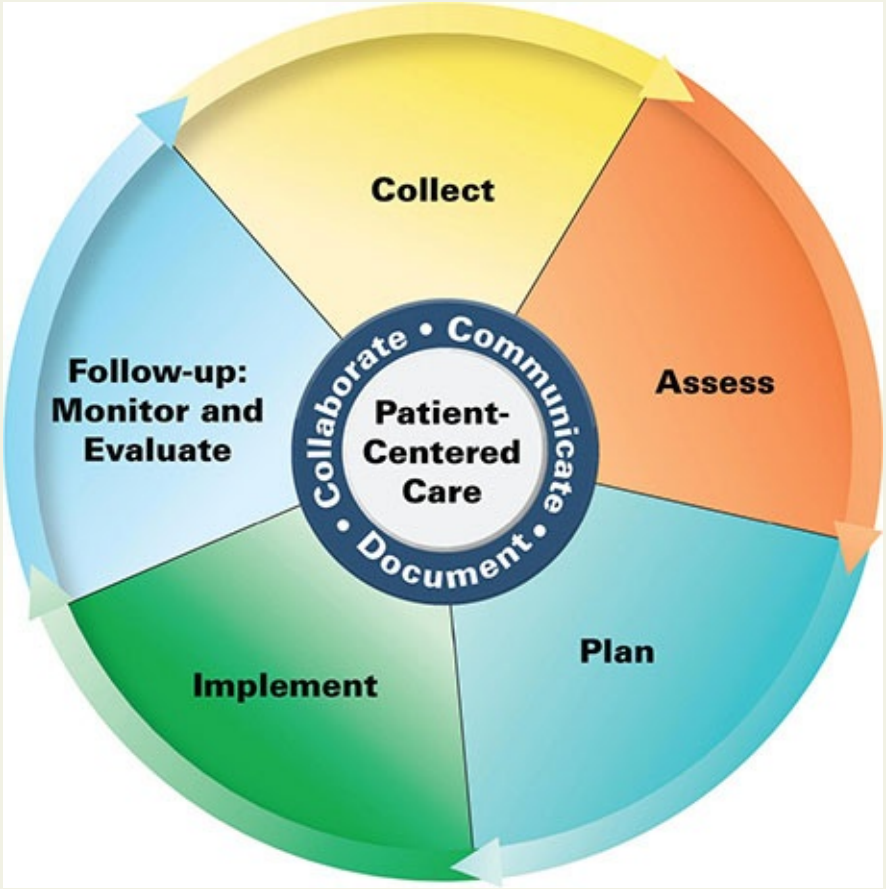
effusions.[49]

Recommended laboratory monitoring prior to starting methotrexate includes a complete blood count (CBC) with differential, alanine transaminase (ALT), aspartate transaminase (AST), and renal function. These should be monitored every 2 to 4 weeks for 3 months after initiation or following a dose increase, then every 8 to 12 weeks during 3 to 6 months of therapy, and every 12 weeks after 6 months of therapy.[1] A chest x-ray film can be considered before starting methotrexate in patients with underlying lung disease. Hepatitis B, hepatitis C, and tuberculosis screenings should be obtained at baseline in high-risk patients.[51]

Adverse effects of methotrexate include infection, pulmonary complications (eg, interstitial pneumonitis and chronic obstructive pulmonary disease [COPD]), gastrointestinal problems (eg, perforation and diarrhea), hematologic changes (eg, thrombocytopenia and leukopenia), and hepatic toxicities (eg, elevated liver enzymes and cirrhosis). Because methotrexate is a structural analogue of folic acid, it can cause folic acid deficiency; methotrexate should be given with folic acid 1 to 5 mg daily to reduce the incidence of toxicities associated with methotrexate.[49]

Leflunomide

Leflunomide, an oral DMARD that inhibits pyrimidine synthesis, can be used as monotherapy or in combination with other DMARDs to treat RA. Leflunomide has been shown to reduce signs and symptoms of RA, inhibit structural damage, and improve physical function. It is significantly protein bound (>99.3%). The typical maintenance dose used to treat RA is 20 mg daily; the dose can be decreased to 10 mg daily if patients are unable to tolerate higher doses. A loading dose can be given of 100 mg for 3 days to achieve steady state more rapidly, but this may increase the risk for toxicities.



Patient Care Process for Rheumatoid Arthritis

Collect

- Patient characteristics (eg, age, sex, pregnancy status, insurance)
- Social history (eg, tobacco/alcohol use, activity)
- Patient medical history (eg, health conditions, immunizations, recent infections)
- Family medical history (eg, autoimmune conditions)
- Current medications
- Past RA medication trials
- Subjective symptom report
- Objective data such as blood pressure, labs (eg, ESR, CRP, CBC), imaging (eg, DEXA, x-ray films, ultrasound), physical examination (eg, number of tender/swollen joints)

Assess

- Patient subjective report (eg, pain score, duration of morning joint stiffness, adherence to therapy, injection technique/medication storage, side effects to drug therapy, disability, fatigue)
- Change in number of tender/swollen joints, labs, or imaging
- Cardiovascular risk factors
- Infection risk and upcoming procedures
- Patient treatment preference (utilize motivational interviewing as appropriate)

Plan*

- Drug therapy (see Table 107-2)
- Referrals when appropriate (eg, tobacco treatment clinic, podiatry, mental health, social work, physical and/or occupational therapy)
- Patient education (eg, dosing, side effects, infection risk management, symptom self-monitoring)
- Order follow-up labs based on therapy chosen (see Table 107-4)

Implement*

- Provide patient education regarding rationale for and follow-up of treatment plan
- Provide patient with written medication changes, time frame for follow-up, and clinic/emergency contact information
- Coordinate and schedule follow-up

Follow-up: Monitor and Evaluate

- Subjective symptom changes and impact on daily activities
- Presence of adverse effects and infections
- Laboratory results as indicated for therapy
- Patient adherence to treatment plan
- Time frame dependent on treatment plan (generally every 1-3 months)

**Collaborate with a rheumatologist.*

Leflunomide has a half-life of about 2 weeks and may require washout with cholestyramine if rapid elimination is required due to toxicity or incidental pregnancy. Leflunomide is excreted by the kidneys as well as through direct biliary excretion.[9] Baseline monitoring should include a tuberculosis screening, CBC with differential, ALT, AST, and renal function. These should be monitored every 2 to 4 weeks for 3 months after initiation or following a dose increase, then every 8 to 12 weeks during 3 to 6 months of therapy, and every 12 weeks after 6 months of therapy.[41]

Adverse reactions associated with leflunomide include diarrhea, elevated liver enzymes, alopecia, elevated blood pressure, and rash. If ALT is three times the upper limit of normal (ULN), leflunomide should be discontinued. Leflunomide should not be used in pregnant or nursing mothers or in patients with severe hepatic impairment.[52]

Sulfasalazine

Sulfasalazine is a prodrug with two metabolites, 5-aminosalicylic acid (5-ASA) and sulfapyridine. The exact mechanism of action of sulfasalazine for the treatment of RA is unknown, but it has been shown to have immunomodulating and anti-inflammatory properties. Sulfasalazine can be used as monotherapy or in combination with other DMARDs to treat RA. The typical starting dose of sulfasalazine is 500 mg daily or 1 g daily in two divided doses; this can be increased weekly to 2 g daily in two divided doses to minimize the risk of adverse events. Clinical benefit can be seen in 4 weeks, but some individuals may need to be on sulfasalazine for 12 weeks before clinical benefit is achieved. If clinical benefit is not sufficient after 12 weeks of therapy, the dose can be further titrated to 3 g/day in evenly divided doses.

Sulfasalazine is primarily eliminated by the kidney and should be used with caution in renal impairment. Sulfasalazine is contraindicated in sulfonamide or salicylate allergy.[53] Baseline monitoring should include a CBC with differential, ALT, AST, and renal function.[41,53] These should be monitored every 2 to 4 weeks for 3 months after initiation or following a dose increase, then every 8 to 12 weeks during 3 to 6 months of therapy, and every 12 weeks after 6 months of therapy.[41] Glucose-6-phosphate dehydrogenase deficiency can cause hemolytic anemia; therefore, screening for this prior to initiation should be considered.[53]

Sulfasalazine use is limited by its potential to cause gastrointestinal adverse effects, including diarrhea, nausea, vomiting, and anorexia. Less common adverse effects associated with sulfasalazine include rash, urticaria, blood cell

abnormalities (including leukopenia, anemia, and thrombocytopenia), severe hypersensitivity reactions (including Stevens-Johnson syndrome), photosensitivity, elevated liver enzymes, and alopecia. Sulfasalazine can also cause urine and skin discoloration. Sulfasalazine crosses the placenta and is present in breast milk but can be used in pregnant and nursing mothers with caution.[53]

Hydroxychloroquine

Hydroxychloroquine is typically used in combination with other DMARDs in patients with RA, but it can be used as monotherapy in mild cases. The mechanism of action in the treatment of RA is not fully understood, but a proposed mechanism for its anti-inflammatory properties is its interference with antigen processing in macrophages and other antigen-presenting cells.[54] Hydroxychloroquine's oral absorption is incomplete and inconsistent, varying from 25% to 100%. It is about 40% protein bound and excreted predominately in the urine.[55]

The typical dose of hydroxychloroquine is 400 mg daily either as one dose or as two divided doses. Clinical benefit is delayed and may take several weeks. The main advantage of hydroxychloroquine use is that it does not require frequent, routine laboratory monitoring because it is not generally associated with infection risk or hepatic, renal, or blood cell abnormalities. The most common adverse effects with hydroxychloroquine are gastrointestinal side effects, including nausea, vomiting, and diarrhea; these can sometimes be mitigated by taking the medication with food or splitting the dose into two doses.[46]

Irreversible retinal damage can occur with hydroxychloroquine use. For patients with risk factors for developing retinal damage, such as low body weight and renal and hepatic impairment, ophthalmologic exams should be conducted annually throughout the treatment with this drug. If patients do not have risk factors for developing retinal damage, an ophthalmologic examination should be completed within 5 years of starting hydroxychloroquine and then repeated annually.[46,56]

Hydroxychloroquine can be continued during pregnancy as no studies have shown an increased risk of birth defects or ocular toxicities. Hydroxychloroquine is excreted into the breast milk, and caution should be exercised in nursing mothers.[57]

Biologic Disease-Modifying Antirheumatic Drugs

Biologics agents are genetically engineered protein molecules that have varying mechanisms by which they decrease inflammation. They can be separated into two groups: TNF inhibitor biologics including adalimumab, etanercept, certolizumab, golimumab, and infliximab; and non-TNF biologics including abatacept, tocilizumab, rituximab, anakinra, and sarilumab.

Biologic DMARDs are associated with an increased risk of infection due to their immunosuppressant effects. A tuberculin skin test or interferon gamma release assay (IGRA) blood test should be obtained before starting a biologic to detect and treat latent or active tuberculosis. Patients should also be screened for hepatitis B before starting biologic therapy because of the risk for reactivation.

Biologic agents can be used in combination with conventional DMARDs, but multiple biologics should not be used concomitantly due to additive immunosuppressive effects. In general, if patients are switched from one biologic to another, the new agent should be initiated when the patient is due for a dose of the previous biologic to avoid potential adverse effects. Because of the immunosuppressive effects of these agents, patients should notify their providers if they are being treated for an infection or plan to undergo major surgery while on a biologic or before starting a biologic. A patient's therapy may need to be held until appropriate postsurgical healing and/or resolution of infection can be confirmed.

TNF Inhibitor Biologics

TNF inhibitors block the proinflammatory cytokine TNF-α. Elevated levels of TNF-α are found in the synovial fluid of individuals with RA as well as other rheumatologic conditions. Adalimumab, etanercept, golimumab, certolizumab, and infliximab can take several weeks for clinical benefit to be noted and up to 3 months to achieve full clinical benefit.[58] The place in therapy for these agents is typically when disease activity remains moderate or high despite conventional DMARD therapy.

A major limitation to the use of TNF inhibitors is cost, as they are more expensive than conventional DMARDs. To optimize the use of TNF inhibitors, medication education should include site of administration, expected time to benefit, safe storage, proper disposal, and possible side effects.

Although these agents have similar side effect profile and contraindications, the TNF inhibitors all have differing structures, pharmacokinetics, and dosing schemes. The selection of an agent depends on cost and patient preference for

route and frequency of administration. TNF inhibitors should not be used in patients with moderate-to-severe heart failure (New York Heart Association [NYHA] class III/IV), as new-onset and worsening heart failure has been reported with TNF inhibitors. These agents increase the risk of serious infection and malignancies such as lymphoma and skin cancers.[41]

New-onset or exacerbation of demyelinating disorders such as multiple sclerosis has been observed with TNF-α inhibitors. Therapy should be discontinued in patients who develop symptoms of demyelinating disorders, and caution should be exercised in using these agents in this patient population. Before starting TNF inhibitors, patients should be screened for tuberculosis and hepatitis B. During therapy, a CBC with differential should be monitored periodically as TNF inhibitors can cause blood cell disorders including pancytopenia. Other monitoring includes signs/symptoms of malignancy and serious infections.[58]

Certolizumab

Certolizumab is a pegylated humanized antibody Fab fragment of TNF-α monoclonal antibody. Because it is not a complete antibody and lacks the Fc region, it does not induce complement activation, antibody-dependent cell-mediated cytotoxicity, or apoptosis. Pegylation allows for delayed elimination and extended half-life. It is available as a prefilled syringe for subcutaneous injection. A loading dose of 400 mg at week 0, 2 and 4 can be given followed by a maintenance dose of 200 mg every other week or 400 mg every 4 weeks.

The most common adverse effects associated with certolizumab are upper respiratory tract infection, rash, and urinary tract infection. The safety and efficacy of certolizumab were evaluated in multiple studies that found that adult patients with moderate-to-severe RA treated with certolizumab had improved clinical response compared with placebo. These studies also showed that structural damage and RA progression was inhibited by certolizumab as compared with placebo plus methotrexate. Patients had improved function when treated with certolizumab compared with placebo.[59]

Adalimumab

Adalimumab binds to TNF-α and blocks its interaction with the p55 and p75 cell surface TNF receptors. It is available as a prefilled syringe or pen for subcutaneous injection. Typical dosing for RA is 40 mg every 2 weeks when used with methotrexate. The dose can be increased to 40 mg weekly if it is not

being used with methotrexate. Local injection site reactions are the most common adverse event and usually manifest as redness, itching, pain, and swelling.

Adalimumab has been studied as monotherapy, with methotrexate, or as combination therapy with other DMARDs in patients with RA. It has been shown to improve clinical response, delay the progression of structural damage, and improve function.[58]

Etanercept

Etanercept is a recombinant DNA-derived protein composed of TNF receptor linked to the Fc fragment of human IgG1. It is available as a prefilled syringe or pen for subcutaneous injection. Typical dosing for RA is 50 mg once weekly.[60]

The most common adverse effects associated with etanercept use include infections and injection site reactions. Studies have shown that patients treated with etanercept monotherapy and etanercept with methotrexate have improved clinical response. Clinical response was noted within 1 to 2 weeks of starting etanercept, but some patients required 3 months of therapy to demonstrate clinical response. Etanercept plus methotrexate was shown to decrease structural damage and progression of RA compared with monotherapy with etanercept or methotrexate. Function was also improved in patients treated with etanercept as compared with placebo.[60]

Golimumab

Golimumab is a human monoclonal antibody that binds to human TNF-α. It is available as a prefilled syringe or pen for subcutaneous injection and is typically dosed at 50 mg once monthly. It is also available as an intravenous product that dosed 2 mg/kg at weeks 0 and 4, and then every 8 weeks thereafter.

The most common adverse effects associated with golimumab use are upper respiratory tract infections and nasopharyngitis. Compared with methotrexate monotherapy, golimumab plus methotrexate has been shown to improve clinical response in patients with RA. Golimumab has also been shown to improve function in patients as compared with placebo.[61]

Infliximab

Infliximab is a chimeric monoclonal antibody that binds to human TNF-α. Infliximab is administered as an IV infusion and typical dosing is 3 mg/kg at weeks 0, 2, and 6, followed by every 8 weeks.

The most common adverse effects associated with infliximab use are infections, infusion-related reactions, headache, and abdominal pain.[39] Studies have shown that about 15% of patients develop antibodies to infliximab. Patients who develop these antibodies typically have a higher likelihood of developing an infusion reaction, have increased clearance of infliximab, and therefore decreased efficacy. An electrochemiluminescence immunoassay (ECLIA) can be used to measure infliximab antibodies if this is suspected. When infusion reactions occur with infliximab, they typically begin within 2 hours of infusion. Concomitant use with immunosuppressants such as methotrexate can lessen the likelihood of developing antibodies to infliximab. Premedication with an antihistamine, acetaminophen, and/or a glucocorticoid can help decrease the likelihood of patients developing infusion-related reactions. Patients on infliximab plus methotrexate have been shown to have an improved clinical response as compared with patients on methotrexate alone. Structural damage and progression of RA was also delayed.[62]

Non-TNF Biologics

Abatacept

Abatacept is a selective co-stimulation modulator that inhibits T-cell activation by binding to CD80 and CD86. This binding blocks the interaction between T cells CD28, thus inhibiting the activation of T cells. Activated T cells are found in the synovial fluid of patients with rheumatologic conditions such as RA and are thought to play a role in the disease. Abatacept is indicated for moderate-to-severe RA and can be used as monotherapy or in conjunction with conventional DMARDs.[63]

Abatacept is typically initiated if disease activity persists in patients after conventional DMARD monotherapy and can be an alternative to TNF inhibitors with or without methotrexate. It can also be initiated in patients who have failed or have had an inadequate response to TNF inhibitors.[41] Abatacept plus methotrexate has similar efficacy and incidence of adverse events as compared with adalimumab plus methotrexate in biologic-naive patients who had an incomplete response to methotrexate.[64]

Abatacept is available in a prefilled syringe or auto-injector for subcutaneous injection and is given at a dose of 125 mg once weekly. It is also available as a 30-minute IV infusion that is dosed according to body weight (<60 kg: 500 mg; 60-100 kg: 750 mg; >100 kg: 1,000 mg); it is given at 0, 2, and 4 weeks and every 4 weeks thereafter.[63]

The most common side effects associated with abatacept include headache, upper respiratory tract infection, nasopharyngitis, and nausea. Abatacept should be used with caution in patients with COPD; exacerbations have been observed in patients with both COPD and RA on abatacept. Like other biologics, abatacept has also been associated with serious infections and malignancy. Infusion reactions are rare but can include anaphylaxis, hypotension, dyspnea, and urticaria and can occur within 24 hours of intravenous administration.[63]

Tocilizumab

Tocilizumab is a monoclonal antibody that inhibits the binding of the proinflammatory cytokine IL-6 to its receptor. Tocilizumab can be used in patients with moderate-to-severe RA who have had an incomplete response to one or more conventional DMARDs and/or TNF inhibitor and can be used as monotherapy or in combination with DMARDs.[41,65] A study that included patients with severe RA who could not use methotrexate found that tocilizumab monotherapy was more effective in the symptom management of RA compared to adalimumab monotherapy.[66]

Tocilizumab is available as a prefilled syringe for subcutaneous injection with dosing dependent on weight (<100 kg: 162 mg every other week, followed by an increase to weekly injections if needed based on clinical response; >100 kg: 162 mg weekly). It is also available as a 1-hour intravenous infusion at a dose of 4 mg/kg every 4 weeks; the dose can be increased to 8 mg/kg every 4 weeks if needed based on clinical response.[65]

The most common side effects associated with tocilizumab include upper respiratory tract infections, nasopharyngitis, headache, hypertension, increased liver enzymes, and injection site reactions. Infusion reactions can also occur, typically within 24 hours of infusion; these are manifest as headache, rash, pruritus, and urticaria. Tocilizumab can also cause gastrointestinal perforation, neutropenia, and thrombocytopenia as well as serious infections and malignancy. Baseline monitoring recommended should include neutrophils, platelets, lipid panel, AST, and ALT. Neutrophils, platelets, and liver enzymes should also be monitored 4 to 8 weeks after starting therapy and every 3 months thereafter. A lipid panel should be repeated after 4 to 8 weeks of treatment and every 6 months during treatment.[65]

Tocilizumab should not be initiated in patients with an absolute neutrophil count (ANC) of less than 2,000/mm^3 (2×10^9/L) or platelet count less than 100,000/mm^3 (100×10^9/L); treatment should be discontinued if ANC is less

than 500/mm^3 (0.5 × 10^9/L) or platelet count is less than 50,000/mm^3 (50 × 10^9/L). Treatment should not be initiated if liver enzymes are greater than 1.5 times ULN and should be discontinued if liver enzymes are greater than 5 times ULN. Tocilizumab has the potential to increase the metabolism of drugs that are CYP450 substrates, particularly CYP3A4.[65]

Rituximab

Rituximab is a monoclonal antibody that binds the CD20 antigen found on the surface of B cells. Rituximab can be given as monotherapy or in combination with methotrexate and can be initiated in patients with moderate-to-severe RA who have had an incomplete response to one or more TNF inhibitors.[67] An observational cohort study showed that patients who failed one TNF inhibitor had greater reductions in disease activity scores when treated with rituximab than with a second TNF inhibitor.[68]

Rituximab is available as an intravenous infusion and can be given as two 1,000-mg infusions separated by 2 weeks. The recovery of B-cells can take several months; therefore, rituximab can be given every 24 weeks. Some patients may not need to receive another dose as often as every 24 weeks; the decision to re-dose should be based on the return of RA symptoms. Rituximab should not be given more frequently than every 16 weeks.[67]

Methylprednisolone 100 mg administered intravenously is recommended 30 minutes before each infusion as well as acetaminophen and an antihistamine to reduce the development and severity of infusion reactions. Side effects that could occur with rituximab treatment include upper respiratory tract infection, nasopharyngitis, urinary tract infection, serious infections, bronchitis, infusion reactions, bowel obstruction/perforation, blood cell disorders, and cardiovascular events.[67] A CBC with differential should be obtained before treatment, with each infusion, and every 2 to 4 months.

Anakinra

Anakinra inhibits IL-1, which is involved in inflammatory responses. It can be used in patients with moderate-to-severe RA who have failed one or more DMARDs; however, the ACR did not include this drug in its 2015 RA treatment recommendations due to its infrequent use for the treatment of RA and lack of new data to support its use since 2012. It is a once-daily subcutaneous injection dosed at 100 mg.[69]

Sarilumab

Sarilumab is a more recently approved IL-6 receptor antagonist that is indicated in the treatment of patients with moderate-to-severe RA who have had an incomplete response to one or more DMARDs. The ACR did not include this drug in their RA treatment recommendations because it had been approved recently when the 2015 recommendations were issued. Sarilumab can be used as monotherapy or with conventional DMARDs. It is a subcutaneous injection of 200 mg administered every 2 weeks.[70]

The most common adverse effects with sarilumab include neutropenia, increased liver enzymes, injection site reactions, and upper respiratory and urinary tract infections. It can also be associated with gastrointestinal perforation and serious infections. Monitoring of this medication should include a baseline tuberculosis screening, CBC with differential, and liver enzymes at baseline, 4 to 8 weeks later, and every 3 months thereafter, and a lipid panel at baseline, 4 to 8 weeks after starting therapy, and then every 6 months. Sarilumab should not be initiated in patients with ANC less than 2,000/mm^3 (2×10^9/L), platelets less than 150,000/mm^3 (150×10^9/L), or liver enzymes greater than 1.5 times ULN.[70]

The MOBILITY study included patients treated with sarilumab plus methotrexate compared with methotrexate plus placebo; sarilumab plus methotrexate produced a decrease in symptoms, improvement in function, and less progression of RA compared with placebo plus methotrexate.[71] The TARGET study showed that sarilumab plus a DMARD reduced the symptoms of RA and improved function compared with placebo plus DMARD.[72]

Target-Specific DMARDs

Tofacitinib

Tofacitinib is an oral Janus kinase (JAK) inhibitor that is indicated for the treatment of moderate-to-severe RA in patients who have had an incomplete response to methotrexate. It can be used as monotherapy or in combination with conventional DMARDs and should not be used with biologic DMARDs. It is available as a 5-mg immediate-release tablet and an 11-mg extended-release tablet. The recommended dosing is either 5 mg twice daily or 11 mg daily unless a dose reduction is recommended due to hepatic or renal impairment or if used concomitantly with CYP3A4 or CYP2C19 inhibitors.[73]

A common measure in studies of RA is *ACR 20* improvement, which is

defined as at least a 20% improvement in seven ACR core measures of disease activity, including tender and swollen joints as well as patients' assessment of disease activity and physical function. It has been widely used to measure disease activity and response to therapy in clinical trials. In one study using this measure, tofacitinib with methotrexate, adalimumab with methotrexate, or placebo with methotrexate showed that after 6 months, patients receiving tofacitinib had similar ACR 20 response compared with adalimumab and a higher ACR 20 response compared with placebo.[74,75]

Adverse effects that can occur with tofacitinib include upper respiratory tract infection, cardiovascular effects, gastrointestinal perforation, serious infections, ILD, malignancy, nasopharyngitis, diarrhea, and headache. Because tofacitinib can be associated with bone marrow suppression, it should not be initiated when lymphocytes are less than 500 cells/mm^3 (0.5×10^9/L) or when ANC is less than 1,000 cells/mm^3 (1×10^9/L). Use should be avoided when hemoglobin is less than 9 g/dL (90 g/L; 5.59 mmol/L), and therapy should be interrupted if hemoglobin is less than 8 g/dL (80 g/L; 4.97 mmol/L) or decreases more than 2 g/dL (20 g/L; 1.24 mmol/L). Lymphocyte count should be monitored at baseline and every 3 months thereafter. ANA, platelet counts, and hemoglobin should be monitored at baseline, after 4 to 8 weeks of therapy, and every 3 months thereafter. Tofacitinib can also cause hyperlipidemia; lipids should be monitored 4 to 8 weeks after starting therapy and periodically thereafter. Hepatotoxicity can occur with treatment, and liver function test monitoring is recommended. Use in severe hepatic impairment is not recommended.[73]

Other Disease-Modifying Antirheumatic Drugs

Therapies such as azathioprine, cyclosporine, minocycline, and gold salts were previously used to treat RA. With the development of other DMARDs and biologics, they are now used infrequently and have no recent data to support their use.[41]

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs inhibit prostaglandin synthesis and can provide anti-inflammatory as well as analgesic effects. However, they do not slow disease progression and should not be used as monotherapy. NSAIDs can provide symptomatic relief of pain and stiffness and can be effective as adjuncts to DMARD therapy in patients with RA. They have a more rapid onset of action than DMARDs and

may be beneficial to “bridge” patients while DMARDs take effect.

Although these agents are available without prescription, they still possess potentially serious risks to use. In the United States, NSAIDs carry a Boxed Warning because they have been found to increase the risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke.[76] Their use is also associated with serious gastrointestinal bleeding and ulcerations.

For more details on NSAIDs, see Chapter 106, “Osteoarthritis.”

Glucocorticoids

Glucocorticoids have been used in the treatment of RA for their anti-inflammatory and immune-modulating effects.[77] Although these agents have been found to slow the progression of RA, glucocorticoids should not be used as monotherapy in the treatment of RA, particularly due to the potential for serious, long-term adverse effects. Therefore, they should be used at the lowest effective dose for the shortest period of time. According to the ACR, short-term glucocorticoid is defined as less than 3 months of therapy and low-dose glucocorticoid is defined as prednisone 10 mg/day or less or its equivalent.[41]

Glucocorticoids can be administered orally or intramuscularly. They act systemically to decrease inflammation and pain. Intra-articular injections administered directly into joints can provide a local decrease in inflammation and pain relief. The intra-articular route is associated with fewer systemic adverse effects because of the limited systemic action. Intra-articular injections should not be repeated more often than every 3 months because of the potential for accelerated loss of cartilage in the joint. Oral glucocorticoids are absorbed almost completely in the gastrointestinal tract, metabolized in the liver, and eliminated in the urine. Typically, oral glucocorticoids, such as prednisone, are taken once daily. Intramuscular glucocorticoids such as triamcinolone acetonide and methylprednisolone acetate can be administered instead of oral steroids based on patient preference or in patients who may not adhere to daily oral therapy. This can also be used in place of an intra-articular injection when multiple joints are involved. To avoid withdrawal associated with hypothalamus–pituitary–adrenal (HPA) axis suppression, glucocorticoids should not be stopped abruptly but should be tapered, especially when used for long term or at high doses. Intramuscular glucocorticoids provide patients with a physiologic taper.

Similar to NSAIDs, glucocorticoids can be used to “bridge” patients while

DMARDs take effect. They can also be used as adjuncts to DMARDs at the lowest dose possible in patients with refractory disease. High-dose, short-term bursts can be used as needed for acute flares of RA symptoms, followed by tapering to the lowest effective dose to control symptoms or until discontinued over several days.[77]

Use of long-term glucocorticoids is limited by adverse effects, which include fluid retention, hyperglycemia, hypertension, behavioral and mood changes, increased appetite, weight gain, electrolyte imbalances, impaired healing, hirsutism, Cushing syndrome, HPA axis suppression, osteonecrosis of femoral and humeral heads, osteoporosis and fractures, myopathy, glaucoma, and cataracts.[78,79] The lowest effective dose for the shortest period of time should be used to minimize the potential for these adverse effects. Patients with RA are at a higher risk of developing osteoporosis, and the use of long-term glucocorticoids doubles this risk. In a study of prednisone 7.5 mg daily, patients lost an average of 9.5% of bone in the spine over 20 weeks of treatment.[79]

For more information on glucocorticoid-induced bone loss, see Chapter 108, “Osteoporosis and Osteomalacia.”

Special Populations

Pregnancy and Lactation

Data on the safety of using a majority of the medications used to treat RA during pregnancy and breastfeeding are limited, and a majority of medications with available safety data in this population have been associated with adverse effects. The potential risks of becoming pregnant should be discussed with women of childbearing age who are being treated for RA, and contraception counseling should be discussed for those not currently planning on becoming pregnant. Recent studies have shown that 20% to 40% of patients with RA achieve remission during the third trimester of pregnancy and remission is more common in women with RF-negative RA.[80]

Because of risks associated with paternal exposure to DMARDs, family planning for male patients should also be taken into account when developing treatment plans.[80]

In women who want to become pregnant, therapies that are contraindicated in pregnancy such as methotrexate and leflunomide should be discontinued. Medications that have been found unsafe during pregnancy or have inadequate data to determine safety, such as abatacept, tocilizumab, rituximab, tofacitinib

and anakinra, should also be discontinued. Disease activity should then be monitored. For symptom control, NSAIDs, acetaminophen, and glucocorticoids can be considered. DMARDs that can be used during pregnancy include hydroxychloroquine and sulfasalazine.[80]

Current evidence suggests no increase in congenital malformations with TNF inhibitors and therefore they can also be considered for use during the first part of pregnancy.[80,81] Specifically, etanercept and certolizumab may be continued throughout pregnancy.[81]

For women who are breastfeeding, methotrexate and leflunomide would be contraindicated. NSAIDs, acetaminophen, hydroxychloroquine, sulfasalazine, and glucocorticoids would be preferred. TNF inhibitors, anakinra, abatacept, rituximab, tocilizumab, and tofacitinib do not have sufficient evidence to recommend safe use during breastfeeding.[80] However, since TNF inhibitors are large protein molecules, little to no drug is likely to be found in breastmilk.[81]

For male patients with RA, methotrexate should be held for 3 months before conception, and sulfasalazine may need to be held if the patient is having difficulty with fertility. Data are insufficient to suggest adverse outcomes with leflunomide. TNF inhibitors can disrupt spermatogenesis, but overall data suggest use could be considered. Adverse outcomes have been reported with rituximab and abatacept.[80]

Serious Infections

In patients with a history of serious infections, combination DMARDs are recommended over TNF inhibitors. Abatacept can be considered over TNF inhibitors; in a study of patients hospitalized for an infection while on TNF inhibitors, abatacept was associated with the lowest risk of a subsequent infection compared with other biologics.[41]

In patients who screen positive for tuberculosis via either a tuberculin skin test or interferon gamma release assay, a chest x-ray film should be obtained to determine if the patient has latent or active tuberculosis infection. If the chest x-ray film is positive, a sputum for acid-fast bacillus (AFB) can be collected to rule out active tuberculosis. If this is negative, then the patient likely has latent tuberculosis and a biologic DMARD or tofacitinib can be started or resumed after completing at least 1 month of treatment for latent tuberculosis. If the test is positive, then the patient likely has active tuberculosis and a biologic DMARD or tofacitinib can be started or resumed after the patient has completed treatment for active tuberculosis.[41]

Hepatitis

In patients with hepatitis B infection who are currently receiving treatment for hepatitis B, treatment of RA should be the same as in patients without a history of hepatitis. In patients with prior exposure to hepatitis B, RA treatment should be the same as unexposed patients with monitoring of viral load every 6 to 12 months. In patients with history of untreated hepatitis B, treatment of hepatitis B should be considered prior to initiating immunosuppressive therapies.

Patients who are being treated for hepatitis C should not be treated differently than patients without hepatitis C. TNF inhibitors can be used in patients with hepatitis C when they are being treated for this viral infection. In patients with untreated hepatitis C, DMARDs are recommended over TNF inhibitors. Methotrexate and leflunomide should be avoided due to potential effects on the liver; instead, hydroxychloroquine or sulfasalazine should be considered.[41]

Malignancy

In patients with previous melanoma and nonmelanoma skin cancer, DMARDs are preferred over biologic agents and tofacitinib. DMARDs are less immunosuppressive than biologics, decreasing the risk of skin cancer with DMARDs compared with other RA therapies. However, in patients with low-grade skin cancer with history of prior treatment, biologics could be considered with close monitoring of the skin by a dermatologist.

In patients with previously treated lymphoproliferative disorders, rituximab use is recommended over TNF inhibitors because of the known increased risk of lymphoma with TNF inhibitors. Also, rituximab is an FDA-approved treatment for some lymphoproliferative disorders. Combination DMARDs, abatacept, or tocilizumab can be considered over TNF inhibitors. Patients with a history of previously treated solid organ malignancy should be treated as patients without this history.[41]

Heart Failure

TNF inhibitors should be avoided in patients with NYHA II, III, or IV heart failure because of the potential for TNF inhibitors to worsen heart failure or cause new-onset heart failure. If patients develop signs of worsening heart failure on TNF inhibitors, this therapy should be discontinued. Combination DMARDs, non-TNF biologics, or tofacitinib would be recommended as alternative therapies.[41]

Comorbidity Management

Cardiovascular Risk Reduction

RA poses as a risk factor for CV disease; this is likely the result of multiple factors present in patients with RA, including chronic inflammation. Therefore, part of RA management is to also manage cardiovascular disease risk. To lower CV disease risk, RA disease activity should be as low as possible. Lifestyle recommendations should be discussed with patients including smoking cessation, regular exercise, and healthy diet.

Other factors that contribute to CV disease—such as hypertension, hyperlipidemia, and diabetes—should be screened for and treated appropriately. NSAIDs should be used with caution, especially in patients with established CVD. Glucocorticoid use should be minimized and tapered to the lowest possible dose due to their potential ill effects on blood glucose and blood pressure.[82]

Osteoporosis

RA is associated with an increased incidence of osteoporosis, falls, and fractures. Glucocorticoid use can increase the potential for these risks. Published recommendations for osteoporosis screening in patients with RA vary greatly. The American Association of Clinical Endocrinologists suggests screening all postmenopausal women with an increased risk of secondary osteoporosis, including those with RA. Canadian recommendations suggest osteoporosis screening for all patients older than 50 years of age who have RA.[83]

In patients with RA who are found to have low bone mineral density, treatment should be considered based on estimated 10-year probability of a major osteoporotic fracture or hip fracture risk.[83] Vitamin D supplementation and calcium intake should also be assessed and optimized.

According to the ACR, patients on long-term glucocorticoids who are 40 years of age or older should have bone mineral density testing at least within 6 months of initiating glucocorticoids and fracture risk should be estimated using FRAX. In patients younger than 40 years of age, bone mineral density testing should be considered at least within 6 months of initiating glucocorticoids if the patient has a history of an osteoporotic fracture or has significant risk factors for developing osteoporosis.[84]

Immunizations

Live vaccines should not be given during treatment with biologics but instead should be given before starting therapy when possible and avoided for at least 3 months after immunosuppressants are discontinued.[6] This is because of the inability of the immunocompromised patient to mount an appropriate immune response to the vaccine. Live vaccines can be given to patients on methotrexate (the doses used in RA typically do not produce enough immunosuppression to cause concern), leflunomide, sulfasalazine, and hydroxychloroquine. Inactivated vaccines can be administered while patients are on conventional DMARDs, TNF and non-TNF biologics, and tofacitinib; however, efficacy of the vaccine may be reduced if patient is on methotrexate or biologic agents.[41]

Several influenza vaccines are available, including inactivated influenza vaccine (IIV), recombinant influenza vaccine (RIV), and the intranasal live-attenuated influenza vaccine (LAIV). Patients with RA should receive the influenza vaccine yearly before initiating and during therapy. The IIV and RIV can be administered to all patients on conventional DMARDs, TNF inhibitors, non-TNF biologics, and tofacitinib who do not have other contraindications to the vaccine. The high-dose inactivated influenza vaccine that is licensed for individuals 65 years of age or older can be given to RA patients regardless of concomitant RA drug therapy.

The available hepatitis B vaccines—either a three-dose series over 6 months (Recombivax HB, Engerix-B), a newer recombinant product (Heplisav-B) that is given in two doses 1 month apart, or a three-dose series in combination with hepatitis A protection (Twinrix)—are licensed for use in adults. These can be given before initiating or while on therapy for RA, but patients on immunosuppressive agents may have a reduced response to the vaccine. The series can be completed as directed in product labeling without regard for RA therapy. The 2019 Centers for Disease Control and Prevention immunization schedule states that Heplisav-B can be used as a substitute for a dose of a three-dose series hepatitis B vaccine; however, two doses of Heplisav-B still need to be given at least 4 weeks between doses in order for the series to be complete.

Tetanus, diphtheria, acellular pertussis (Tdap) is an inactivated vaccine that should be given to adults who have not received a dose of Tdap as an adult or child. A dose of Td or Tdap is then recommended every 10 years.

The two inactivated pneumococcal vaccines, the pneumococcal polysaccharide vaccine (PPSV, Pneumovax 23) and the pneumococcal conjugated vaccine (PCV, Prevnar 13), should be administered to patients with acquired immunodeficiencies, including patients with RA who are receiving biologic therapy. PCV13 is administered to such patients who are 19 to 64 years

of age followed by PPSV23 at least a year later. Another dose of PPSV23 should be given 5 years later. At age 65 or older, an additional dose of PPSV23 should be given at least 5 years after the most recent dose of PPSV23.[85,86]

A recombinant, adjuvanted zoster vaccine to prevent herpes zoster was approved in 2017 (Shingrix) and is recommended for adults aged 50 years and older. It is administered as two doses at 0 and 2 to 6 months. The safety of this vaccine in patients with certain comorbid conditions, including RA, still needs to be determined.[85,87] An older zoster vaccine, Zostavax, is a live vaccine that is contraindicated in patients with RA who are on immunosuppressive therapies; Shingrix is now the preferred vaccine over Zostavax, according to the US Centers for Disease Control and Prevention.[85]

Future Directions

Over the past few decades, the treatment of RA has evolved. Numerous drug therapies are undergoing phase II or III studies for the treatment of RA. Some of these include other JAK inhibitors currently approved for other indications such as Crohn's disease and IL-1 receptor agonists. In 2018, a JAK inhibitor, baricitinib, was approved for the treatment of RA. It is taken orally once daily as monotherapy or in combination with conventional DMARDs[88]; its place in therapy is not yet clear.

Biosimilars

In recent years, biosimilars have been approved for the treatment of RA and several other rheumatic conditions. Biosimilars are products that have been verified to have no clinically meaningful differences compared with an FDA-approved reference biologic product. These agents can increase access to RA treatment because their costs are lower than the originator products.

Despite the availability of more than a dozen biosimilar products for a variety of conditions, several challenges have limited their use in clinical practice, including a lack of regulatory guidelines about switching from the original biologic product to the biosimilar. Clinicians are also uncertain about the extrapolation of indications for biosimilars from the original biologic product. Postmarketing surveillance is needed to provide additional information regarding adverse reactions and any potentially meaningful differences between biologics and biosimilars to help guide their incorporation into clinical practice.[89]

EVALUATION OF THERAPEUTIC OUTCOMES

9 An assessment of disease activity should be conducted at baseline and at each follow-up visit for patients with RA to evaluate disease control and therapeutic response. The evaluation of therapeutic outcomes should be based largely on the patient's subjective improvement of RA symptoms with respect to joint pain, swelling and tenderness, morning stiffness, and fatigue, as well as on a patient's ability to perform activities of daily living. A physical examination should also be conducted at each visit to evaluate the number of swollen and/or tender joints to obtain objective data. This can also help clinicians evaluate loss of joint mobility and deformity. As detailed in **Table 107-3**, several useful tools can guide clinicians in the objective measurement of disease activity.

Laboratory monitoring of acute phase reactants such as CRP and ESR can be useful in assessing inflammation. Plain radiographs of the hands, wrists, and forefeet should be obtained at baseline as well as every 2 years in patients with low disease activity or in remission. Little-to-no evidence of RA disease progression should be evident on this imaging if drug therapy is effective. Imaging may be needed more frequently in patients with moderate or high disease activity. If patients have radiographic changes on imaging suggestive of RA disease progression—such as periarticular osteopenia, bone erosions, or joint space narrowing—drug therapy should be modified.[90]

TABLE 107-3 Assessment Tools to Measure Rheumatoid Arthritis Disease Activity

Assessment Tool	Scale	High Disease Activity	Moderate Disease Activity	Low Disease Activity	Remission
Clinical Disease Activity Index (CDAI)	0 to 76	>22	>10 to 22	>2.8 to 10	≤2.8
Disease Activity Score (DAS28)	0 to 9.4	>5.1	≥3.2 to ≤5.1	≥2.6 to <3.2	<2.6
Patient Activity Scale (PAS) or PASII	0 to 10	≥8.0	>3.7 to <8.0	>2.5 to 3.7	0 to 2.5
Routine Assessment of Patient Index Data 3 (RAPID-3)	0 to 10	>4.0 to 10	>2 to 4	>1.0 to 2.0	0 to 1.0
Simplified Disease Activity Index (SDAI)	0 to 86	>26	>11 to ≤26	>3.3 to ≤11.0	≤3.3

It is also important to monitor and assess for adverse effects of the medications used to treat RA as detailed in **Table 107-4**.

TABLE 107-4 Adverse Drug Reactions and Monitoring Recommended for Disease-Modifying Antirheumatic Drugs

Drugs	Adverse Drug Reactions	Initial Monitoring	Maintenance Monitoring
NSAIDs	GI ulceration, bleeding, and perforation, renal damage	SCr, CBC every 2-4 weeks after starting therapy	Same as initial plus stool guaiac every 6-12 months
Corticosteroids	Fluid retention, hyperglycemia, hypertension, behavioral and mood changes, increased appetite, weight gain, electrolyte imbalances, impaired healing, hirsutism, Cushing syndrome, HPA axis suppression, osteonecrosis of femoral and humeral heads, osteoporosis and fractures, myopathy, glaucoma, cataracts	Glucose, CBC periodically, blood pressure every 3-6 months	Same as initial
Hydroxychloroquine	Retinal damage, rash, diarrhea	Ophthalmologic exam (fundus examination plus visual fields and spectral-domain optical coherence tomography if maculopathy present) within 5 years of starting therapy	Ophthalmologic exam annually if risk factors for retinal damage present or annually beginning after 5 years of use if no risk factors
Methotrexate	Infection, hepatic fibrosis, cirrhosis, interstitial pneumonitis, stomatitis, rash, GI perforation, diarrhea, thrombocytopenia, leukopenia	SCr, CBC with differential, AST, ALT, hepatitis B and C screening, tuberculosis screening	SCr, CBC with differential, AST, ALT, every 2-4 weeks for 3 months after starting or following a dose increase, then every 8-12 weeks during 3-6 months of therapy, and every 12 weeks after 6 months of therapy, signs of infection
Leflunomide	Hepatitis, diarrhea/nausea, alopecia, elevated blood pressure	CBC with differential, SCr, ALT, AST, blood pressure	CBC with differential, SCr, ALT, AST every 2-4 weeks for 3 months after starting or following a dose increase, then every 8-12 weeks during 3-6 months of therapy, and every 12 weeks after 6 months of therapy; blood pressure periodically

Sulfasalazine	Rash, nausea, vomiting, diarrhea, photosensitivity, alopecia	CBC with differential, SCr, ALT, AST	CBC with differential, SCr, ALT, AST every 2-4 weeks for 3 months after starting or following a dose increase, then every 8-12 weeks during 3-6 months of therapy, and every 12 weeks after 6 months of therapy
Tocilizumab	Local injection-site reactions, infection, malignancy, GI perforation, neutropenia, thrombocytopenia	Tuberculosis screening, hepatitis B screening, CBC with differential, AST, ALT, FLP	AST, ALT, CBC with differential every 4-8 weeks after starting then every 3 months; FLP after 4-8 weeks of starting then every 6 months, signs/symptoms of infection and malignancy
Anakinra	Local injection-site reactions, infection, malignancy	CBC with differential, tuberculosis screening, SCr, hepatitis B screening	CBC with differential every 3 months up to 1 year, SCr periodically, signs/symptoms of infection and malignancy
Etanercept, adalimumab, golimumab, certolizumab	Local injection-site reactions, infection, malignancy	Tuberculosis screening, hepatitis B screening, CBC with differential	Periodic skin examination, signs/symptoms of infection and malignancy, CBC with differential periodically
Infliximab	Immune reactions, infection, malignancy	Tuberculosis screening, hepatitis B screening, CBC with differential, LFTs	CBC with differential, LFTs, signs/symptoms of infection and malignancy
Rituximab	Immune reactions, infection, malignancy	Tuberculosis screening, hepatitis B screening, CBC with differential	CBC with differential prior to each treatment course and at 2- to 4-month intervals, signs/symptoms of infection
Abatacept	Immune reactions, infection, malignancy	Tuberculosis screening, hepatitis B screening	Signs/symptoms of infection and malignancy
Tofacitinib	Infection, malignancy, GI perforations, upper respiratory tract infections, headache, diarrhea, nasopharyngitis	Tuberculosis screening, hepatitis B screening, CBC with differential, Hgb, LFTs, FLP, HR, and blood pressure	CBC with differential and Hgb after 4-8 weeks and every 3 months, FLP after 4-8 weeks and periodically, LFTs periodically, periodic skin examinations, HR and blood pressure, signs/symptoms of infection and malignancy
Sarilumab	Local injection-site reactions, infection, malignancy	Tuberculosis screening, hepatitis B screening, CBC with differential, LFTs, lipid panel	CBC with differential and LFTs 4-8 weeks after starting and then every 3 months, FLP 4-8 weeks after starting and every 6 months during therapy, signs/symptoms of infection and malignancy

ALT, alanine transaminase; AST, aspartate transaminase; CBC, complete blood count; FLP, fasting lipid panel; GI, gastrointestinal; HPA, hypothalamic–pituitary–adrenal; LFTs, liver function tests; SCr, serum creatinine.

CONCLUSION

Rheumatoid arthritis is an autoimmune condition that impacts approximately 1% of the population. It is a systemic, progressive disease that can lead to disability and decreased quality of life. The course of therapy is variable but includes both

nonpharmacologic and pharmacologic therapies. A patient-centered, comprehensive treatment plan should be initiated as soon as a diagnosis is established to target disease remission or low disease activity. Though a treatment plan should be created with a trained rheumatologist, other clinics should be utilized for their expertise, such as social work, mental health, and physical/occupational therapy. Chosen pharmacologic treatment is dependent on level of disease activity, past medication trials, comorbidities, and patient-preference. Though the etiology of RA is unclear, we can expect further research to be conducted to determine its cause to help design additional targeted therapies.

Postclass Engaged Learning Activity

Direct-to-consumer advertising refers to the marketing of products to patients rather than healthcare professionals. This is a common marketing strategy, particularly for pharmaceutical products. Watch the following advertisements for “a common biologic product” and https://tinyurl.com/rh47uoy https://www.ispot.tv/ad/wrWz/humira-food-drive.

Reflect on the promotional materials by considering the following questions:

- What is the general feeling generated by the commercials?
- What actions or activities do the commercials focus on?
- What additional concerns might one have after hearing about the possible side effects of this biologic product?
- In your view, what other pertinent information should have been included in these commercials?

After seeing commercials on TV, patients may do their own medication research. Watching one of the above commercials would lead patients to the following site: https://www.humira.com. Explore the website and reflect on the following questions:

- How user-friendly is the website?
- What resources are available for patients? What specifically is HUMIRA Complete?
- Where is the injection education video located on the Website? Would you direct patients to watch this video?

- What resources would you use from this Website, if any, for your patient education in clinic?

One of the counseling points for adalimumab (Humira) is to contact your provider prior to having any surgeries or receiving any vaccinations. Make a chart of which immunizations a patient can and cannot receive while using this injectable medication.

ABBREVIATIONS

ACPA	anti-citrullinated protein antibodies
ACR	American College of Rheumatology
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ANA	antinuclear antibody
ANC	absolute neutrophil count
ANTI-CCP	anti-citrullinated C protein
BID	twice daily
CBC	complete blood count
CRP	C-reactive protein
CT	computerized tomography
CYP450	cytochrome P450
DEXA	dual-energy x-ray absorptiometry
DMARDs	disease-modifying antirheumatic drugs
eGFR	estimated glomerular filtration rate
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
EX	extended release
FDA	Food and Drug Administration
GI	gastrointestinal
HLA	human leukocyte antigen
Hgb	hemoglobin
HPA	hypothalamic–pituitary–adrenal
IgG	immunoglobulin G

IL	interleukin
IM	intramuscular
IR	immediate release
IV	intravenous
ILD	interstitial lung disease
JAK	Janus kinase
LFTs	liver function tests (includes AST/ALT, T bilirubin, Alkaline Phosphatase)
LGL	large granular lymphocyte leukemia
MO	month
MTX	methotrexate
NSAIDs	nonsteroidal anti-inflammatory drugs
NYHA	New York Heart Association
PBM	Pharmacy Benefit Managers
RA	rheumatoid arthritis
RANKL	receptor activator of NFkB ligand
RF	rheumatoid factor
SCr	serum creatinine
SubQ	subcutaneous
TNF	tumor necrosis factor
ULN	upper limit of normal
US	ultrasound

REFERENCES

1. Gibofsky A. Overview of epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis. *Am J Manag Care*. 2012;18:S295–S302.
2. Alamanos Y, Drosos AA. Epidemiology of adult rheumatoid arthritis. *Autoimmun Rev*. 2005;4:130–136.
3. Sullivan P, Ghushchyan V, Huang X, Globe D. Influence of rheumatoid arthritis on employment, function, and productivity in a nationally representative sample in the United States. *J Rheumatol*. 2010;37(3):544–549.
4. Silman AJ, Hochberg MC. Descriptive epidemiology of rheumatoid

arthritis. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, eds. *Rheumatoid Arthritis*. Philadelphia, PA: Mosby Elsevier; 2009;15–22.

5. Martikainen JA, Kautiainen H, Rantalaiho V, Puolakka K. Long-term work productivity costs due to absenteeism and permanent work disability in patients with early rheumatoid arthritis: A Nationwide Register Study of 7831 Patients. *J Rheumatol*. 2016;34(26):2101–2015.
6. Myasoedova E, Davis JIII, Crowson C, Gabriel S. Epidemiology of rheumatoid arthritis: Rheumatoid arthritis and mortality. *Curr Rheumatol Rep*. 2010;12:379–385.
7. Carmona L, Cross M, Williams B, et al. Rheumatoid arthritis. *Best Pract Res Clin Rheumatol*. 2010;24:733–745.
8. Silman AJ, Pearson JE. Epidemiology and genetics of rheumatoid arthritis. *Arthritis Res Ther*. 2002;4(3):S265.
9. Silman AJ, MacGregor AJ, Thomson W, et al. Twin concordance rates for rheumatoid arthritis: Results from a nationwide study. *Br J Rheumatol*. 1993;32(10):903.
10. Hemminki K, Li X, Sundquist J, Sundquist K. Familial associations of rheumatoid arthritis with autoimmune diseases and related conditions. *Arthritis Rheum*. 2009;60(3):661.
11. Pedersen M, Jacobsen S, Garred P, et al. Strong combined gene-environment effects in anti-cyclic citrullinated peptide-positive rheumatoid arthritis: A nationwide case-control study in Denmark. *Arthritis Rheum*. 2007;56(5):1446.
12. Khuder SA, Peshimam AZ, Agraharam S. Environmental risk factors for rheumatoid arthritis. *Rev Environ Health*. 2002;17(4):307.
13. Wegner N, Lundberg K, Kinloch A, et al. Autoimmunity to specific citrullinated proteins gives the first clues to the etiology of rheumatoid arthritis. *Immunol Rev*. 2010;233(1):34.
14. Jiang H, Chess L. Regulation of immune response by T cells. *N Engl J Med*. 2006;354:1166–1176.
15. Youinou P, Taher TE, Pers J-O, et al. B lymphocyte cytokines and rheumatoid autoimmune disease. *Arthritis Rheum*. 2009;60:1873–1880.
16. Uesugi M, Hayashi T, Jasin HE. Covalent cross-linking of immune complexes by oxygen radicals and nitrite. *J Immunol*. 1998;161:1422.
17. Firestein GS, Echeverri F, Yeo M, et al. Somatic mutations in the p53

tumor suppressor gene in rheumatoid arthritis synovium. *Proc Natl Acad Sci USA*. 1997;94:10895.

18. Huizinga TW, Amos CI, van der Helm-van Mil AH, et al. Refining the complex rheumatoid arthritis phenotype based on specificity of the HLA-DRB1 shared epitope for antibodies to citrullinated proteins. *Arthritis Rheum*. 2005;52:3433.
19. John Hopkins Arthritis Center. RA Pathophysiology. Available at: https://www.hopkinsarthritis.org/arthritis-info/rheumatoid-arthritis/ra-pathophysiology-2/. Last accessed, September 14, 2018.
20. Deane KD, O'Donnell CI, Hueber W, et al. The number of elevated cytokines and chemokines in preclinical seropositive rheumatoid arthritis predicts time to diagnosis in an age-dependent manner. *Arthritis Rheum*. 2010;62:3161.
21. Hill JA, Southwood S, Sette A, et al. Cutting edge: The conversion of arginine to citrulline allows for a high-affinity peptide interaction with the rheumatoid arthritis-associated HLA-DRB1*0401 MHC class II molecule. *J Immunol*. 2003;171:538.
22. Hitchon CA, El-Gabalawy HS. The synovium in rheumatoid arthritis. *Open Rheumatol J*. 2011;5(1:M3):107–114.
23. Brennan FM, McInnes IB. Evidence that cytokines play a role in rheumatoid arthritis. *J Clin Invest*. 2008;118:3537–3545.
24. Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. *N Engl J Med*. 2001;344(12):907–916.
25. Catrina AI, af Klint E, Ernestam S, et al. Anti-tumor necrosis factor therapy increases synovial osteoprotegerin expression in rheumatoid arthritis. *Arthritis Rheum*. 2006;54:76.
26. Gravallese EM. Bone destruction in arthritis. *Ann Rheum Dis*. 2002;61(S2):ii84–ii86.
27. Jasin HE, Taurog JD. Mechanisms of disruption of the articular cartilage surface in inflammation. Neutrophil elastase increases availability of collagen type II epitopes for binding with antibody on the surface of articular cartilage. *J Clin Invest*. 1991;87:1531.
28. Turesson C, Jacobsson LT. Epidemiology of extra-articular manifestations in rheumatoid arthritis. *Scand J Rheumatol*. 2004;33(2):65.
29. Patatanian E, Thompson DF. A review of methotrexate-induced accelerated nodulosis. *Pharmacotherapy*. 2002;22(9):1157.

30. Gochuico BR, Avila NA, Chow CK, et al. Progressive preclinical interstitial lung disease in rheumatoid arthritis. *Arch Intern Med*. 2008;168(2):159.
31. Lake F, Proudman S. Rheumatoid arthritis and lung disease: From mechanisms to a practical approach. *Semin Respir Crit Care Med*. 2014;35(2):222–238.
32. Balbir-Gurman A, Yigla M, Nahir AM, Braun-Moscovici Y. Rheumatoid pleural effusion. *Semin Arthritis Rheum*. 2006;35(6):368.
33. Bartels C, Bell C, Rosenthal A, Shinki K, Bridges A. Decline in rheumatoid vasculitis prevalence among US veterans: A retrospective cross-sectional study. *Arthritis Rheum*. 2009;60(9):2553.
34. Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: A meta-analysis of observational studies. *Arthritis Rheum*. 2008;59(12):1690.
35. Wallberg-Jonsson S, Johansson H, Ohman ML, Rantapaa-Dahlqvist S. Extent of inflammation predicts cardiovascular disease and overall mortality in seropositive rheumatoid arthritis. A retrospective cohort study from disease onset. *J Rheumatol*. 1999;26(12):2562–2571.
36. Lamy T, Loughran TPJr. How I treat LGL leukemia. *Blood*. 2011;117(10):2764.
37. Hauser B, Riches PL, Wilson JF, Horne AE, Ralston SH. Prevalence and clinical prediction of osteoporosis in a contemporary cohort of patients with rheumatoid arthritis. *Rheumatology (Oxford)*. 2014;53(10):1759.
38. Whiting PF, Smidt N, Sterne JA, et al. Systematic review: Accuracy of anti-citrullinated Peptide antibodies for diagnosing rheumatoid arthritis. *Ann Intern Med*. 2010;152(7):456.
39. Dougados M. Synovial fluid cell analysis. *Baillieres Clin Rheumatol*. 1996;10(3):519.
40. Aletaha D, Neogi T, Silman AJ, et al. Arthritis 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Rheum*. 2010;62(9):2569.
41. Singh JA, Saag KG, Bridges SL, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res*. 2015. doi:10.1002/acr.22783.https://www.rheumatology.org/Portals/0/Files/ACR9

42. Smolen JS, Landewe R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 Update. *Ann Rheum Dis*. 2017;0:1–18.
43. Solomon DH, Bitton A, Katz JN, et al. Treat to Target in rheumatoid arthritis: Fact, fiction or hypothesis? *Arthritis Rheumatol*. 2014;66(4):775–782.
44. Demoruelle MK, Deane KD. Treatment strategies in early rheumatoid arthritis and prevention of rheumatoid Arthritis. *Curr Rheumatol Rep*. 2012;14(5):472–480.
45. Anderson JJ, Wells G, Verhoeven AC, et al. Factors predicting response to treatment in rheumatoid arthritis: The importance of disease duration. *Arthritis Rheum*. 2000;43:22–29.
46. Vliet Vlieland TP, Van Den Ende CH. Nonpharmacological treatment of rheumatoid arthritis. *Curr Opin Rheumatol*. 2011; 23(3):259–264.
47. Sturgeon JA, Finan PH, Zautra AJ. Affective disturbance in rheumatoid arthritis: Psychological and disease-related pathways. *Nat Rev Rheumatol*. 2016;12(9):532.
48. Weinblatt ME. Efficacy of methotrexate in rheumatoid arthritis. *Br J Rheumatol*. 1995;34(Suppl 2):43–48.
49. Methotrexate [package insert]. Huntsville, AL: DAVA Pharmaceuticals, Inc; https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/008085s066lbl
50. Bianchi G, Caporali R, Todoerti M, et al. Methotrexate and rheumatoid arthritis: Current evidence regarding subcutaneous versus oral routes of administration. *Adv Ther*. 2016;33:369–378.
51. Kremer JM, Alarcon GS, Lightfoot RWJr, et al. Methotrexate for rheumatoid arthritis. Suggested guidelines for monitoring liver toxicity. American College of Rheumatology. *Arthritis Rheum*. 1994;37(3):316–328.
52. Arava [package insert]. Bridgewater, NJ: Sanofi-Aventis U.S. LLC; 2011, https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020905s022lbl
53. Azulfidine [package insert]. New York, NY: Pfizer; 2012, https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/007073s125lbl
54. Fox RI. Mechanism of action of hydroxychloroquine as an antirheumatic drug. *Semin Arthritis Rhem*. 1993;23(2 Suppl 1):82–91.

55. Tett SE, Day RO, Cutler DJ. Concentration-effect relationship of hydroxychloroquine in rheumatoid arthritis: A cross sectional study. *J Rheumatol*. 1993;20(11):1874–1879.
56. Marmor MF, Kellner U, Lai TY, et al. American Academy of Ophthalmology. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). *Ophthalmology*. 2016;123(6):1386–1394.
57. Plaquenil [package insert]. St. Michael, Barbados: Concordia Pharmaceuticals; January 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009768s037s0
58. Humira [package insert]. North Chicago, IL: Abbvie: August 2018. Available at: https://www.rxabbvie.com/pdf/humira.pdf.
59. Cimzia [package insert]. Smyrna, GA: UCB; May 2018, https://www.cimzia.com/sites/default/files/docs/CIMZIA_full_prescribing_
60. Enbrel [package insert]. Thousand Oaks, CA: Immunex Corporation; December 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103795s5503ll
61. Simponi [package insert]. Horsham, PA: Janssen Biotech; August 2011, https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125289s0064ll
62. Remicade [package insert]. Horsham, PA: Janssen Biotech; November 2013. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/103772s5359ll
63. Orencia [package insert]. Princeton, NJ: Bristol-Meyers Squibb; March 2017. Available at: https://packageinserts.bms.com/pi/pi_orencia.pdf.
64. Weinblatt ME, Schiff M, Valente R, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: Findings of a phase IIIb, multinational, prospective, randomized study. *Arthritis Rheum*. 2013;65(1):28–38.
65. Actemra [package insert]. South San Francisco, CA: Genentech; May 2018. Available at: https://www.gene.com/download/pdf/actemra_prescribing.pdf.
66. Gabay C, Emery P, van Vollenhoven R, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): A randomised, double-blind, controlled phase 4 trial. *Lancet*. 2013;381(9877):1541–1550.
67. Rituxan [package insert]. South San Francisco, CA: Genentech; June 2018. Available at:

https://www.gene.com/download/pdf/rituxan_prescribing.pdf.
68. Chatzidionysiou K, van Vollenhoven RF. Rituximab versus anti-TNF in patients who previously failed one TNF inhibitor in an observational cohort. *Stand J Rheumatol*. 2013;42(3):190–195.
69. Kineret [package insert]. Stockholm, Sweden: Swedish Orphan Biovitrum AB; December 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103950s5136l
70. Kevzara [package insert]. Bridgewater, NJ: Sanofi-Aventis U.S.; May 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761037s000lb
71. Genovese MC, Fleischmann R, Kivitz AJ, et al. Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate: Results of a phase III study. *Arthritis Rheumatol*. 2015;67(6):1424–1437.
72. Strand V, Really M, Chen CI, et al. Sarilumab improves patient-reported outcomes in rheumatoid arthritis patients with inadequate response/intolerance to tumor necrosis factor inhibitors. *RMD Open*. 2017;3:e000416.
73. Xeljanz [package insert]. New York, NY: Pfizer; May 2018. Available at: http://labeling.pfizer.com/ShowLabeling.aspx?id=959.
74. van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med*. 2012; 367(6):508–519.
75. Felson DT, LaValley MP. The ACR20 and defining a threshold for response in rheumatic disease: Too much of a good thing. *Arthritis Res Ther*. 2017;16(1):101.
76. Kineret [package insert]. Stockholm, Sweden: Swedish Orphan Biovitrum AB; December 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103950s5136l
77. Kavanaugh A, Wells AF. Benefits and risks of low-dose glucocorticoid treatment in the patient with rheumatoid arthritis. *Rheumatology (Oxford)*. 2014;53(10):1742–1751.
78. Rayos [package insert]. Deerfield, IL: Horizon Pharma USA; July 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202020s000lb
79. Da Silva JAP, Jacobs JWG, Kirwan JR, et al. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: Published evidence and

prospective trial date. *Ann Rheum Dis*. 2006;65(3):285–293.

80. Krause ML, Makes A. Management of rheumatoid arthritis during pregnancy: Challenges and solutions. *Open Access Rheumatol*. 2016;8:23–26.
81. Skorpen CG, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis*. 2016;75:795–810.
82. Agca R, Heslinga SC, Rollefstad S, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 Update. *Ann Rheum Dis*. 2016;0:1–12.
83. Jeremiah MP, Unwin BK, Greenawald MH, et al. Diagnosis and management of osteoporosis. *Am Fam Physician*. 2015;92(4):261–268.
84. Buckley L, Guyana G, Fink HA, et al. 2017 American College of Rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Rheumatol*. 2017;69(8):1521–1537.
85. Centers for Disease Control and Prevention. Recommended immunization schedule for adults aged 19 years or older, United States, 2018. Available at: https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf. Last assessed, September 10, 2018.
86. Centers for Disease Control and Prevention. Pneumococcal vaccine timing for adults. Available at: https://www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf. Last assessed, September 10, 2018.
87. Shingrix [package insert]. Research Triangle Park, NC: GlaxoSmithKline Biologicals; October 2017. Available at: https://gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescr
88. Olumiant [package insert]. Indianapolis, IN: Eli Lilly; May 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/207924s000lbl
89. Dorner T, Strand V, Cornes P, et al. The changing landscape of biosimilars in rheumatology. *Ann Rheum Dis*. 2016;75(6):974–982.
90. Khanna D, Ranganath VK, Fitzgerald J, et al. Increased radiographic damage scores at the onset of seropositive rheumatoid arthritis in older patients are associated with osteoarthritis of the hands, but not with more rapid progression of damage. *Arthritis Rheum*. 2005;52(8):2284.

108

Osteoporosis

Mary Beth O'Connell, Jill S. Borchert, Erin M. Slazak, and Joseph P. Fava

KEY CONCEPTS

1. Osteoporosis is a public health epidemic that affects all ages, genders, races, and ethnicities. Lifestyle behaviors, diseases, and medications should be reviewed to identify risk factors for developing osteoporosis and osteoporotic fractures. Healthcare professionals should identify and resolve reversible risks. Secondary causes of bone loss should be explored, especially for patients with early onset or severe osteoporosis.
2. Bone physiology and pathophysiology are complex involving coupled bone resorption and formation in bone remodeling processes. These processes result from many different cell lines, transmitters, pathways, and biofeedback systems. As these processes become more delineated, additional targets are identified for medications.
3. All patients taking medications known to increase bone loss, falls, and fractures should practice a bone-healthy lifestyle, be evaluated for a switch to a safer alternative medication, and/or be considered for osteoporosis therapy. The most common causes of medication-induced osteoporosis are long-term oral glucocorticoids and certain chemotherapeutic agents.
4. Ten-year probabilities for a major osteoporotic and hip fracture can be estimated for women (postmenopausal to age 90 years old) and men (50-90 years old) with the fracture risk assessment tool (FRAX) tool. This tool is a questionnaire that can be used in any setting, including pharmacies, health fairs, and clinics. Central bone mass densitometry can determine bone mass, predict fracture risk, and influence patient and provider treatment decisions.
5. Throughout life, everyone should practice a bone-healthy lifestyle, which emphasizes regular exercise, nutritious diet, tobacco avoidance, minimal

alcohol use, and fall prevention to prevent and treat osteoporosis.

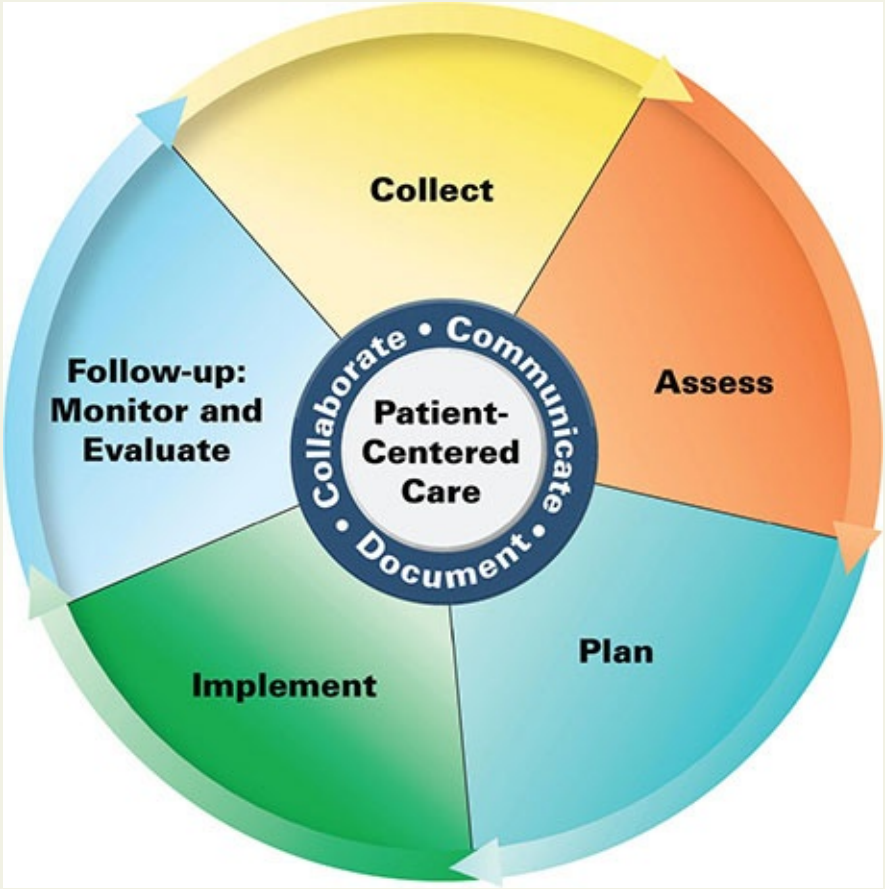
6. Treatment should be considered for postmenopausal women and men older than 50 years who have a low-trauma hip or vertebral fracture, T-score of −2.5 or less at the femoral neck, total hip, or spine, or low bone mass (T-score between −1.0 and −2.5) and a FRAX 10-year probability of major osteoporotic fracture of 20% or more or hip fracture of 3% or more. Patients with secondary causes might receive therapy at younger ages or higher T-scores.
7. The recommended dietary calcium intake for American adults is 1,000 to 1,200 mg of elemental calcium daily with diet as the preferred source. Supplements are added when diet is insufficient.
8. The recommended daily dietary vitamin D intake for American adults is 600 units and for older adults 800 units. Some organizations and guidelines recommend higher doses of at least 800 to 1,000 units daily. Vitamin D intake is achieved through sun exposure, fortified foods, and supplements. Vitamin D insufficiency and deficiency, defined as 25-hydroxyvitamin D (25[OH] vitamin D) concentrations of less than 30 ng/mL (mcg/L; 75 nmol/L) and less than 20 ng/mL (mcg/L; 50 nmol/L) respectively, are common in Americans. Higher vitamin D daily intakes and/or replenishment dosing is then required.
9. Alendronate, risedronate, zoledronic acid, and denosumab decrease vertebral, hip, and nonvertebral fractures and are first-line osteoporosis treatments. Therapy continues for about five years in mild osteoporosis and 5 to 10 years in moderate-to-severe osteoporosis. Other antiresorptive (ibandronate, raloxifene), anabolic (abaloparatide, teriparatide), and combination anabolic and antiresorptive (romosozumab) medications are alternatives. These medications decrease osteoporotic fracture risk but not hip fractures. Calcitonin is an agent of last resort. Adherence to osteoporosis medications is suboptimal. Poor adherence is associated with less fracture prevention. Healthcare professionals should assess medication administration technique and adherence at each visit, provide education, and resolve medication-related problems.

Preclass Engaged Learning Activity

To better understand a bone-healthy lifestyle and risk factors for osteoporosis,

please complete these two activities.

1. Use the International Osteoporosis Foundation calcium calculator (https://www.iofbonehealth.org/calcium-calculator) to calculate your dietary calcium intake, which will help you learn about foods high in calcium that you could recommend to your patients. Compare your calcium intake to the recommended calcium daily allowance (see Table 108-5). Now use the National Osteoporosis Foundation calcium calculator (https://www.nof.org/patients/treatment/calciumvitamin-d/steps-to-estimate-your-calcium-intake/) to calculate your own calcium daily intake. Compare and contrast these two calculators. Which calculator would you use for a patient: (a) at risk for osteoporosis? (b) who experienced an osteoporotic fracture? (c) with limited health literacy?
2. Think about an older adult, such as a grandparent or neighbor. Enter her/his health information into this decision aid https://osteoporosisdecisionaid.mayoclinic.org/ to learn about osteoporosis risk factors, fracture risk assessment tools, and patient education materials describing fracture prevention effects with medication.



Patient Care Process for Osteoporosis

Collect

- Patient characteristics (eg, age, sex, postmenopausal status)
- Medical history (personal and family; eg, maximum height, falls, fractures, dental issues, gastroesophageal reflux/heartburn, and for women age at menarche and menopause)
- Social history (eg, tobacco and alcohol use, physical activity, and dietary habits, including calcium-containing food intake)
- Current medications including calcium and vitamin D, dietary supplements, multivitamins, and herbal product use
- Past medications (eg, hormone therapy and medications causing osteoporosis; see Table 108-3)
- Objective data
    - Height, weight

- Laboratory results (see Table 108-4) and secondary causes
- Central dual-energy x-ray absorptiometry (DXA) at the spine and hip
- Fracture evidence (eg, vertebral fracture assessment, radiographs)

Assess

- Adequacy of dietary calcium and calcium/vitamin D supplement intakes
- Bone mineral density (BMD): Categorize lowest T-score as normal, low bone mass, or osteoporosis
- FRAX 10-year risk of major osteoporotic fractures and hip fracture
- Laboratory data and presence of secondary causes (see Tables 108-2 and 108-3)
- Patient preferences including injectable medications and concern about adverse effects
- Potential barriers to adherence (eg, administration route, frequency, cost, health literacy)

Plan

- Medication regimen including specific agent, dose, route, frequency, and duration (see Fig. 108-3, Tables 108-7 and 108-8), and calcium and vitamin D supplements as necessary.
- Monitoring parameters including efficacy (eg, BMD, fracture, 25(OH)-vitamin D concentration), and safety (eg, common and serious adverse effects, serum creatinine, calcium). Include frequency and timing of follow-up

Implement*

- Provide patient education regarding treatment plan (eg, purpose of treatment, dietary calcium sources, medication-specific administration/injection technique in patient's primary language) (see Tables 108-7 and 108-8)
- Consider risk communication tool to explain medication benefit and rare adverse effects
- Schedule laboratory tests as needed, and DXA (generally 2-5 years after initiation)

- Schedule referrals when appropriate (eg, physical therapist for fall prevention, dietitian)
- For zoledronic acid, coordinate with infusion center for administration
- For nongeneric therapies, coordinate prior authorization process as necessary

Follow-up: Monitor and Evaluate*

- Patient adherence to treatment plan and administration instructions
- Presence of adverse effects (see Table 108-8)
- Bone mass density, fractures, falls, and laboratory parameters
- Changes in habits (eg, dietary calcium, exercise, alcohol and tobacco use)
- Re-evaluate duration of therapy after 1 year (romosozumab), 2 years (teriparatide, abaloparatide), 3 years (intravenous bisphosphonate), 5 years (oral bisphosphonate), or as suggested by response to therapy and adverse effects

**Collaborate with patient, caregivers, and other healthcare professionals.*

INTRODUCTION

1 Osteoporosis is a bone disorder characterized by low bone density, impaired bone architecture, and compromised bone strength that predisposes a person to increased fracture risk. Osteoporosis is a major public health threat,[1] with about 50% of people 50 years of age and older expected to develop this disease.[2] In the United States, 10.2 million Americans are estimated to have osteoporosis.[3] An additional 43.4 million Americans are estimated to have low bone density and are at risk for osteoporosis. Attention to bone health is required throughout life. Osteoporosis and osteoporotic fractures are multifactorial conditions, beginning at birth with genetics and continuing throughout life due to health behaviors that influence bone growth and maintenance, skeletal factors that lead to compromised bone strength, and nonskeletal factors that lead to falls (**Fig. 108-1**). Healthcare professionals should educate people about bone-healthy lifestyles and empower them to practice these health behaviors. Currently, osteoporosis is underdiagnosed and undertreated.[4] Bone health screenings, osteoporosis prevention programs, accurate diagnoses, and optimal medication management are needed to prevent and treat osteoporosis and prevent fractures.

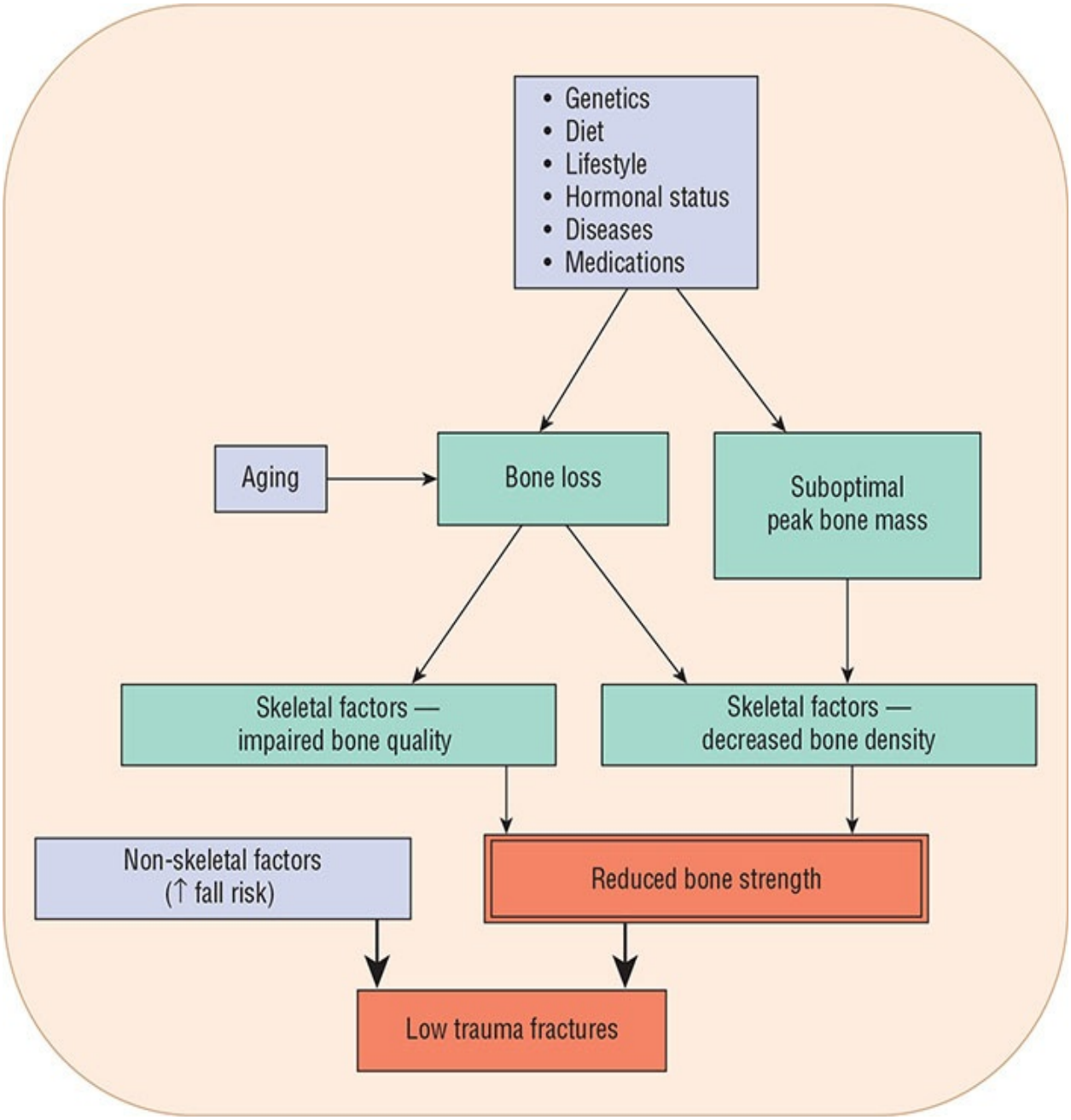


FIGURE 108-1 Etiology of osteoporosis and osteoporotic fractures.

EPIDEMIOLOGY

1 Low bone density, osteoporosis, and osteoporotic fractures are very common and affect all races and ethnic groups. Low bone density is estimated to occur in 53% of non-Hispanic White, 48% of Mexican American, and 36% of non-Hispanic Black women age 50 and older.[5] Osteoporosis affects 16% of non-

Hispanic White, 20% of Mexican American, and 8% of non-Hispanic Black women age 50 and older. Disease prevalence greatly increases with age; from 7% in women 50 to 59 years of age to 35% in women 80 years of age and older. White and Hispanic women have the highest fragility fracture rate followed by Native American, African American, and Asian women when the data are adjusted for weight, bone mineral density (BMD), and other factors.[6] Approximately 35% of men aged 50 years and older have low bone density rising to 53% in men 80 years and older. Osteoporosis prevalence in non-Hispanic White men is 4%, Mexican American men is 6%, non-Hispanic Black men is 1%. Osteoporosis prevalence rises to 11% in men 80 years and older. Although osteoporosis is common in adults with fractures, 12% of fracture patients have normal BMD and 52% have low bone density, supporting fractures occur at any BMD.[4]

Fragility wrist and vertebral fractures are common throughout adulthood, with hip fractures more common in older adults. While women experience the majority of fractures, approximately 29% to 40% of fractures due to osteoporosis occur in men.[3,7,8] One of two women and one of five men will have a fracture in their life.[1] In a woman's lifetime, she has a 17% likelihood of a hip fracture, 16% likelihood of a vertebral fracture and 16% likelihood of a forearm fracture. In a man's lifetime, osteoporotic fracture risk is 13% to 30%.[7,8,9] The incidences of hip fracture and BMD are decreasing for both sexes, possibly due to better efforts at osteoporosis prevention (eg, bone-healthy lifestyle) and use of osteoporosis medications. However, rates in the United States remain higher than those in other developed countries, suggesting a need for continued focus on bone health.[10]

Osteoporosis creates an economic health burden. In 2011, 1.7 million hospitalizations occurred for fragility fractures with 3 million osteoporotic fractures expected in 2025.[11,12] By 2025, osteoporosis treatment costs are estimated to be about $25.3 billion.[2,12] Because of associated morbidity, hip fracture is the most costly complication of osteoporosis, accounting for almost 72% of fracture costs.[1]

ETIOLOGY

Figure 108-1 depicts a model describing osteoporosis and fracture etiology. The major risk factors (see **Tables 108-1**,[1,3,4,6,8,10,13–19] **108-2**[1,3,8,13–16, 21] and **108-3**[20–25]) influencing bone loss are hormonal status, genetics, exercise, aging,

nutrition, lifestyle, concomitant diseases, and medications. Nonhormonal risk factors are similar between women and men.

TABLE 108-1 Risk Factors for Osteoporosis and Osteoporotic Fractures

Low bone mineral density[a]
Female sex[a]
Advanced age[a]
Race/ethnicity[a]
History of a previous fragility (low-trauma) fracture as an adult[a] (especially clinical vertebral fracture or hip fracture)
Osteoporotic fracture in a first-degree relative (especially parental hip fracture[a])
Low body weight or body mass index[b]
Premature menopause (before 45[a,b] years old)
Secondary osteoporosis[a,b]
Rheumatoid arthritis[a]
Past or present systemic oral glucocorticoid therapy[a,c]
Current cigarette smoking[a,c]
Alcohol intake of 3 or more drinks/day[a,c]
Low calcium intake
Low physical activity or immobilization
Vitamin D insufficiency and deficiency
Recent falls
Cognitive impairment
Impaired vision

[a]Factors included in World Health Organization fracture risk assessment tool (FRAX).

[b]Secondary causes included in the FRAX tool are type 1 diabetes, osteogenesis imperfecta as an adult, long-standing untreated hyperthyroidism, hypogonadism, premature menopause (<45 years old), chronic malnutrition, malabsorption, and chronic liver disease.

[c]Risk is larger with greater exposure.

Data from References 1, 3, 4, 6, 8, 10, and 13–19.

TABLE 108-2 Select Medical Conditions Associated with Osteoporosis in Children and Adults

Primary or secondary ovarian failure
Testosterone deficiency
Hyperthyroidism
Cushing's syndrome
Growth hormone deficiency (in children)
Primary hyperparathyroidism
Diabetes, type 1 and type 2
Gastrointestinal
Nutritional disorders (eg, anorexia nervosa)
Malabsorptive states (eg, Crohn's disease, celiac disease, gastrectomy, and bariatric surgery)
Chronic liver disease (eg, primary biliary cirrhosis)
Disorders of Calcium Balance
Hypercalciuria
Vitamin D deficiency
Inflammatory Disorders
Rheumatoid arthritis
Chronic Illness
Chronic kidney disease
Malignancies (eg, multiple myeloma, lymphoma, and leukemia)
Human immunodeficiency virus infection/acquired immunodeficiency syndrome
Organ transplant
Disuse/Immobility
Muscular dystrophy
Multiple sclerosis
Stroke/cerebrovascular accident
Genetic
Osteogenesis imperfecta
Cystic fibrosis
Hemochromatosis
Hypophosphatasia

Data from References 1, 3, 8, 13–16, 20, and 21.

TABLE 108-3 Select Medications Associated with Increased Bone Loss and/or Fracture Risk

Medications	Comments
Antiseizure therapy (phenytoin, carbamazepine, phenobarbital, and valproic acid)	↓ BMD and ↑ fracture risk; increased vitamin D metabolism leading to low 25(OH) vitamin D concentrations
Antiretroviral therapy (ART) (nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) (tenofovir disoproxil fumarate > other NRTIs), protease inhibitors (PI) (ritonavir > other PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs)	↓ BMD (NRTIs > PIs), fracture risk unknown; increased osteoclast activity and decreased osteoblast activity
Aromatase inhibitors (eg, letrozole and anastrozole)	↓ BMD and ↑ fracture risk; reduced estrogen concentrations
Calcineurin inhibitors (eg, cyclosporine and tacrolimus)	↓ BMD and ↑ fracture risk; increase osteoclast activity
Furosemide	↑ fracture risk; increased calcium renal elimination
Glucocorticoids (long-term oral therapy)	↓ BMD and ↑ fracture risk; increased bone resorption and decreased bone formation, and decreased calcium absorption; dose and duration dependent; see special populations section
Gonadotropin-releasing hormone agonists or analogs (eg, leuprolide and goserelin)	↓ BMD and ↑ fracture risk; decreased sex hormone production
Heparin (unfractionated, UFH) or low molecular weight heparin (LMWH)	↓ BMD and ↑ fracture risk (UFH >>> LMWH) with long-term use (eg, >6 months); decreased osteoblast replication and increased osteoclast function
Medroxyprogesterone acetate depot administration	↓ BMD, fracture risk unknown; possible BMD recovery with discontinuation; decreased estrogen concentrations
Proton pump inhibitor therapy (long-term therapy)	↓ BMD and ↑ fracture risk; possible calcium malabsorption secondary to acid suppression for carbonate salts
Selective serotonin reuptake inhibitors	↓ BMD and ↑ fracture risk; decreased osteoblast activity
Sodium glucose cotransporter 2 (SGLT2) inhibitors	↓ BMD and ↑ fracture risk; alteration in calcium and phosphate homeostasis; increased bone resorption
Thiazolidinediones (pioglitazone and rosiglitazone)	↓ BMD and ↑ fracture risk; decreased osteoblast function
Thyroid—excessive supplementation	↓ BMD and ↑ fracture risk; risk increases with TSH concentration <0.1 mIU/L; possible increase in bone resorption
Vitamin A—excessive intake (>1.5 mg of retinol form)	↓ BMD and ↑ fracture risk; decreased osteoblast activity and increased osteoclast activity

BMD, bone mineral density; TSH, thyroid-stimulating hormone; DXA, dual-energy x-ray absorptiometry.

Data from References 20–25.

Low Bone Density

BMD is a major predictor of fracture risk. Every standard deviation decrease in BMD in women represents a 10% decrease in bone mass and a 1.5- to 3-fold increase in fracture risk.[3,6,26] In contrast, increasing peak bone mass in younger years by 10% was estimated to create 13 more years without a fracture in older women.[11] Low BMD can occur as a result of failure to reach a normal peak bone mass, bone loss or both. Genetics accounts for 60% to 80% of peak bone mass variability.[6,27] Bone loss occurs when bone resorption exceeds bone formation, which also can result from high bone turnover when the number or depth of bone resorption sites greatly exceeds the rate and ability of osteoblasts to form new bone. Women and men begin to lose a small amount of bone mass starting in the third to fourth decade of life, about 0.5% to 1% per year.[3] During perimenopause and menopause, bone loss occurs predominantly due to increases in bone resorption. By age 70 to 80, 30% to 40% of bone mass is lost in women. Older adults steadily lose bone mass as a consequence of an accelerated rate of bone remodeling combined with reduced bone formation. Bone loss for both women and men have decreased from 2005 to 2014.

Impaired Bone Quality

Bone strength is highly affected by the quality of the bone's composition and its structure, and is a better predictor of fracture than BMD.[11] Changes in bone mass do not fully reflect changes in bone thinning and decreased connectivity, both related to strength. BMD explains only 70% of femur and 44% of spine bone strength. Women with normal bone mass (3.4%) and low bone mass (5.3%) fracture, which is a slightly lower rate than with osteoporotic bone mass (6.8%). Accelerated bone turnover can increase the amount of immature bone that is not adequately mineralized. Sex differences exist with thinning of trabeculae, with aging in men causing less bone quality damage and impaired bone strength than in women. With aging, fracture risk increases for a given T-score, partly related to bone quality changes; for example, at a T-score of −2.5, a 50-year-old postmenopausal woman has about a 4% probability of a hip fracture, whereas a 70-year-old woman has about a 9% probability.[28]

Falls

One-third to one-half of older adults fall each year.[29,30] In older adults, 87% of fractures resulted from a fall. In 2013, 2.5 million older adults were treated in the emergency department for falls resulting in 734,000 hospitalizations and incurred about $30 billion healthcare costs. Costs for inpatient and outpatient fall care were about $50 billion in 2015. The risk factors for falls overlap with the risk factors for osteoporosis and osteoporotic fractures.[1]

PHYSIOLOGY

Bone Physiology

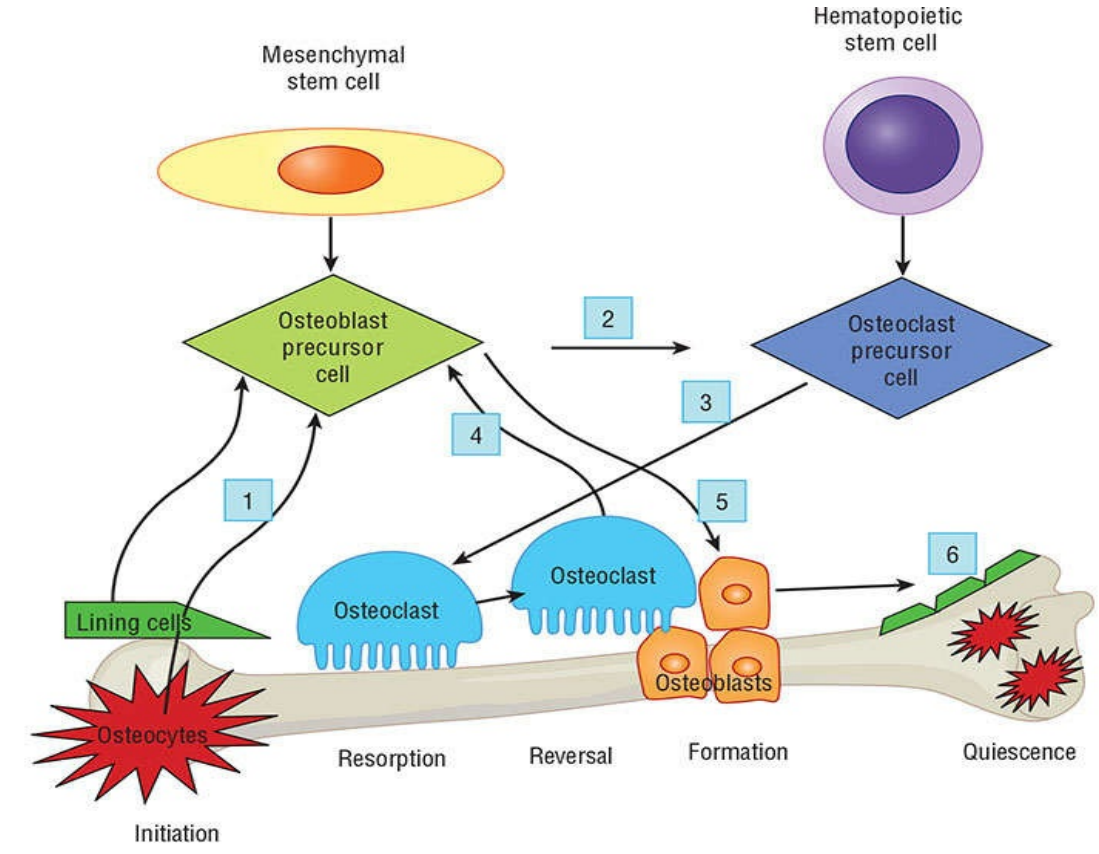
2 The skeleton has two types of bone. Cortical bone makes up the majority of the skeleton (80%) and is found mostly in the long bones (eg, forearm and hip).[31] Trabecular bone is found mostly in the vertebrae and ends of long bones. This bone type is metabolically more active compared with cortical bone due to a much higher bone turnover rate because of its large surface area and honeycomb-like shape.

Bone is made of collagen and mineral components.[31,32] The collagen component gives bone its flexibility and energy-absorbing capability. The mineral component gives bone its stiffness and strength. The correct balance of these substances is needed for bone to adequately accommodate stress and strain and resist fractures. Imbalances can impair bone quality and lead to reduced bone strength.[33]

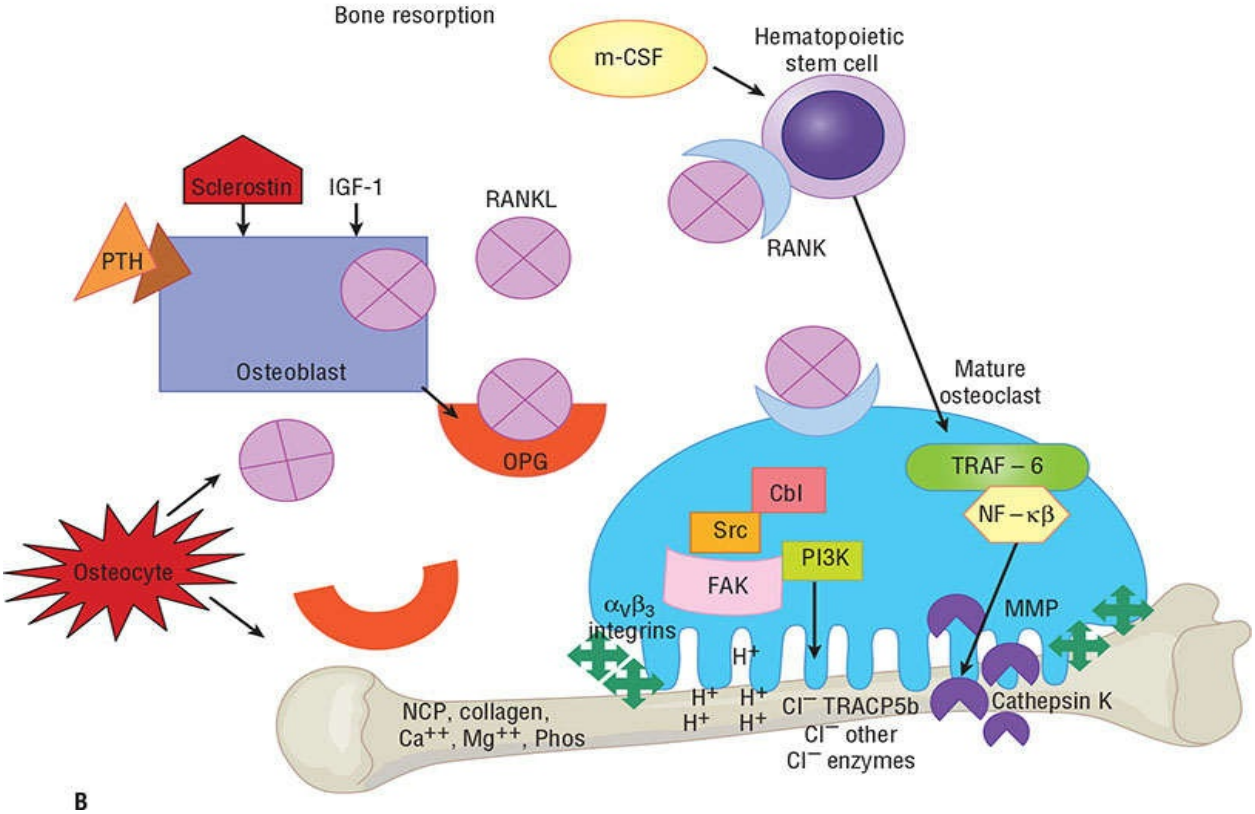
Bone strength reflects the integration of bone mass, bone strength and quality (composition and microarchitecture). Bone mass increases rapidly throughout childhood and adolescence. Peak bone mass is attained by age 18 to 25 years.[1,11,34] Peak bone mass is highly dependent on genetic factors, which accounts for 60% to 80% of the variability.[27] The remaining 20% to 40% is influenced by modifiable factors such as nutritional intake (eg, calcium, vitamin D, and protein), exercise, adverse lifestyle practices (eg, smoking), hormonal status, and certain diseases and medications (see Tables 108-2 and 108-3). Optimizing peak bone mass is important for preventing osteoporosis. The higher the peak bone mass, the more bone one can lose before being at an increased fracture risk. As the microarchitecture of bone deteriorates, the bone strength greatly decreases. Women lose more structure than men.

Bone remodeling is a dynamic process that occurs continuously throughout life (see **Fig. 108-2A-C**).[35–40] One to two million tiny sections of bone are in the

process of remodeling at any given time. Within these sections, the bone remodeling activities of bone resorption and bone formation are coupled and balanced. Bone remodeling is triggered to repair microdamage to the skeleton and serves to support calcium homeostasis through maintaining a normal serum calcium by releasing calcium from the bone into the blood stream. Within an active bone remodeling unit, osteoclasts (bone resorbing cells) work to resorb bone during the resorptive phase, then this process reverses and osteoblasts (bone-forming cells) work to form bone during the formation phase. Osteoblasts then become incorporated into the bone matrix as osteocytes or cover the surface as lining cells, both with bone-communication activities. The unit then becomes inactive and enters a quiescent phase. If remodeling becomes unbalanced and bone resorption surpasses bone formation or if the phases become uncoupled and bone resorption occurs without adequate formation, a decrease in BMD results. Osteocytes and lining cells play key roles in the process and can trigger a new remodeling cycle.


Mesenchymal stem cell
Hematopoietic stem cell
Osteoblast precursor cell
Osteoclast precursor cell
2
3
4
1
5
6
Lining cells
Osteoclast
Osteoclast
Osteoblasts
Osteocytes
Resorption
Reversal
Formation
Quiescence
Initiation

A


Bone resorption
m-CSF
Hematopoietic stem cell
Sclerostin
IGF-1
RANKL
PTH
RANK
Osteoblast
Mature osteoclast
OPG
TRAF – 6
Cbl
NF – κβ
Src
PI3K
FAK
Osteocyte
αvβ3 integrins
MMP
H+
H+ H+
H+ H+
Cl− TRACP5b
Cl− other
Cl− enzymes
Cathepsin K
NCP, collagen,
Ca++, Mg++, Phos

B

The signaling of the bone remodeling cycle through the steps from resorption through quiescence is highly complex; many cytokines, growth factors, and hormones influence each step.[36,39,40] The complete physiology of bone remodeling is not fully known, but appears to begin with signals from lining cells or osteocytes that are triggered by stress, microfractures, biofeedback systems responsive to cytokines and growth factors, and potentially certain diseases and medications (see **Fig. 108-2B**, step 1). A major stimulus for hematopoietic stem cell differentiation to become mature osteoclasts is the receptor activator of nuclear factor kappa β ligand (RANKL), which is a cytokine emitted from osteoblasts or osteocytes in step 2. Interleukins 1 and 6 (IL-1, IL-6), macrophage colony stimulating factor (m-CSF), parathyroid hormone (PTH), parathyroid-releasing protein (PTHrP), 1,25(OH) vitamin D, tissue growth factor-β (TGF-β), prostaglandin E_2, insulin-like growth factor (IGF), sclerostin, and tumor necrosis factor-α (TNF-α) stimulate RANKL release whereas estrogen and calcitonin inhibit RANKL release. The RANKL then binds to the receptor activator of nuclear factor kappa β (RANK) on the surface of osteoclast precursors initiating differentiation. The RANKL also stimulates mature osteoclast activation and bone adherence via $\alpha_v\beta_3$ integrins to resorb bone (step 3). This step is influenced by TGF-β, IGF 1 and 2, platelet-derived growth factor, bone morphometric proteins (BMP), and fibroblast growth factor (FGF). After bone attachment, the osteoclasts secrete proteinases, such as cathepsin K, collagenase, gelatinase, tartrate-resistant acid phosphate isoenzyme 5 (TRACP5b), and matrix metalloproteases (MMP), and hydrogen and chloride ions to dissolve the mineralized bone. The hydrogen ion production is under nonreceptor tyrosine kinase (Src) control, which needs to be bound to other compounds such as E3 ubiquitin ligase (Cbl), focal adhesion kinase (FAK), and phosphatidylinositol 3-kinase (Pl3K).

After bone is resorbed and a cavity is created, osteoclasts produce cytokines and growth factors to elicit osteoblast differentiation from mesenchymal stem cells, maturation and activity (step 4).[40] Osteoblast differentiation can be inhibited by PPARγ, which directs mesenchymal cell maturation to adipocytes instead of osteoblasts. However, leptin produced by adipocytes can stimulate bone formation. Mature osteoblasts and osteocytes produce osteoprotegerin (OPG) that binds to RANKL, thereby stopping bone resorption.

The process of bone formation is complicated (see **Fig. 108-2C**).[36,37,40] First, wingless tail ligands (Wnt) bind to low- density lipoprotein receptor–related protein 5 or 6 (LRP5/6) and a frizzled coreceptor. Wnt binding is influenced by

IGF-1, and PTH and PTHrP, which fit into the same receptor PTH1R. Next, LRP5/6 binds to disheveled cytoplasmic protein (DSH), which then binds to axin. Axin cannot bind to glycogen synthase kinase-3β (GSK-3β); this prevents degradation of β-catenin by casein kinase 1α (Csk1α) (step 5). Accumulated β-catenin then enters the nucleus and binds to T-cell-specific transcription factor 4/lymphoid enhancer factor 1 (TCF/LEF). This complex signals target genes to create proteins to fill the resorption cavity with osteoid. Growth hormone and IGF-1 also increase bone collagen production. Next mineralization of bone with calcium, magnesium, and phosphorus follows to give the new matrix strength.

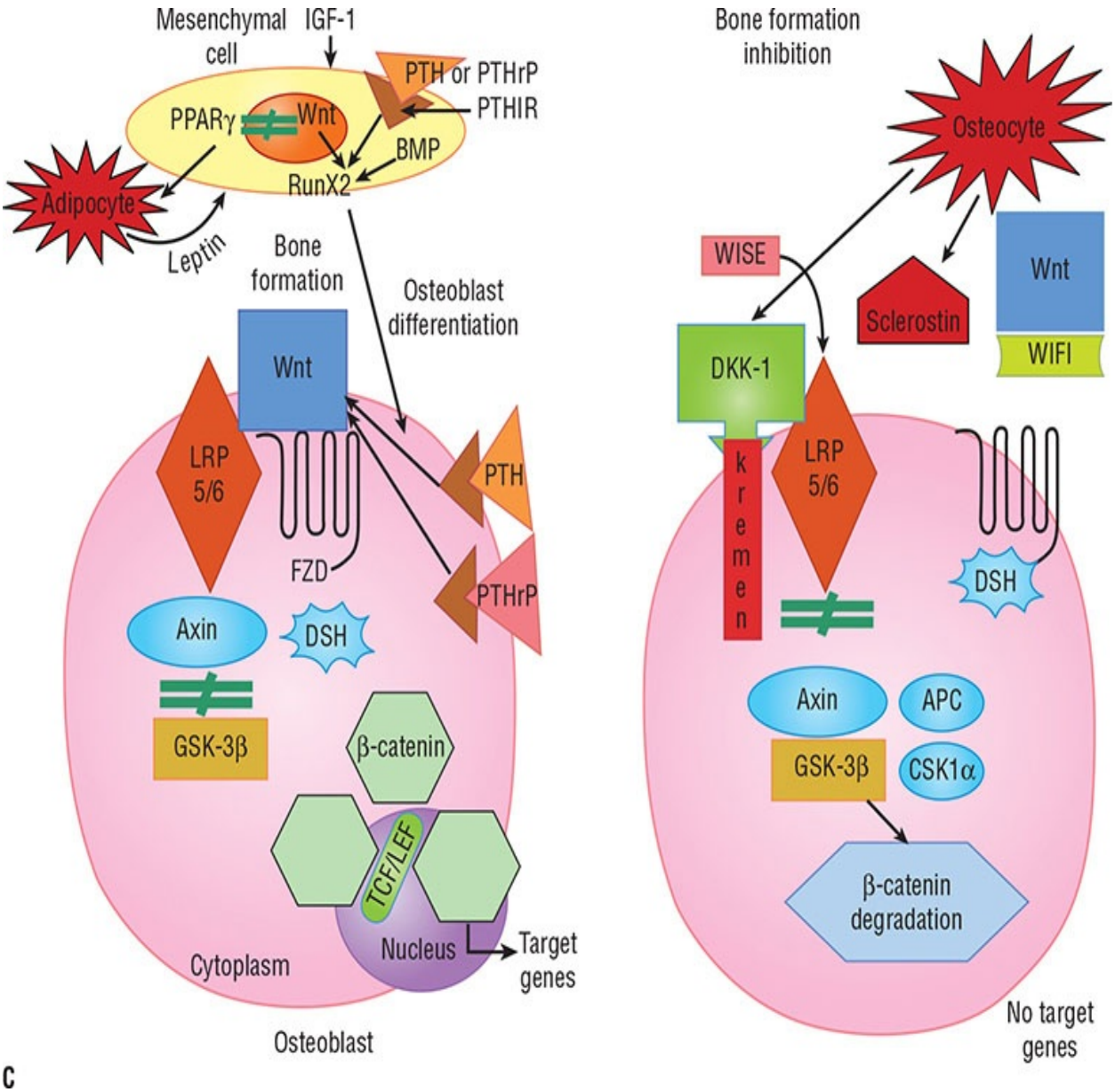


FIGURE 108-2 Bone remodeling cycle. (A) Overview of remodeling process,

Step 1 = initiation, Step 2 and 3 = resorption, Step 4 = reversal, Step 5 = formation, and Step 6 = quiescence; (B) Molecular level detail of major pathways during bone resorption steps 2 and 3, which also showcase osteoporosis medication targets; (C) Molecular level detail of major pathways during bone formation steps 4 and 5, which also showcase osteoporosis medication targets. APC, adenomatous polyposis coli; BMP, bone morphogenetic protein; Ca^{++}, elemental calcium; Cbl, E3 ubiquitin ligase; Cl^{-}, chloride ion; Csk1α, casein kinase 1α; Dkk-1, Dickkoff1; DSH, disheveled cytoplasmic protein; FAK, focal adhesion kinase, GSK-3β, glycogen synthase kinase-3β; H^{+}, hydrogen ion; IGF-1, insulin-like growth factor 1; LRP5/6, lipoprotein-receptor–related protein 5 or 6; m-CSF, macrophage-colony-stimulating factors; Mg^{++}, magnesium; MMP, matrix metalloproteinases; NF-kβ, nuclear factor kappa beta; NCP, noncollagenous proteins; OPG, osteoprotegerin; Phos, phosphorous; Pl3K, phosphatidylinositol 3-kinase; PPARγ, peroxisome proliferator-activated receptor; PTH, parathyroid hormone; PTH1R, PTH and PTHrP receptor; PTHrP, parathyroid hormone-related protein; RANK, receptor activator of nuclear factor-kβ; RANKL, receptor activator of nuclear factor-kβ ligand; runX2, runt-related transcription factor; Scr, nonreceptor tyrosine kinase; sFRP, secreted frizzled-related proteins; TCF/LEF, T cell specific transcription factor 4/lymphoid enhancer factor 1; TRACP 5b, tartrate-resistant acid phosphate isoenzyme 5; TRAF-6, tumor necrosis factor receptor associated factor 6; WIFI, Wnt inhibitory factor 1; WISE, Wnt modulator insurface ectoderm; Wnt, wingless tail ligands. *Data from References 35–40*.

Once the cavity is mineralized, bone formation can be stopped through multiple signaling processes.[36,37,40] Secreted frizzled-related proteins (sFRP) or Wnt inhibitory factor 1 (WIF1) can bind to Wnt, preventing it from binding to LRP 5/6. Both sclerostin and Dickkopf-1 (Dkk-1 or Kremen) are secreted from osteocytes and bind to LRP5/6, which also prevents Wnt from binding with LRP 5/6. Axin can then bind to adenomatous polyposis coli (APC), Csk1α, and GSK-3β, which then can cause β-catenin degradation, osteoblast apoptosis, and the end of osteoblastic activity (step 6). The mature osteoblasts can become lining cells or osteocytes.

Quiescence is the phase when bone is at rest until another remodeling cycle is initiated. Later, osteocytes may trigger initiation of a new remodeling cycle through secretion of sclerostin or RANKL to stimulate osteoclasts and bone resorption.

Hormones can influence the remodeling steps. Estrogen has many positive

effects on the bone remodeling process in people of both genders, and most of its actions help to maintain a normal bone resorption rate.[9,31] Estrogen suppresses the proliferation and differentiation of osteoclasts and increases osteoclast apoptosis. Estrogen decreases the production of several cytokines that are potent stimulators of osteoclasts, including IL-1, IL-6, TNF-α, and m-CSF, and increases TGF-α, which increases osteoclast apoptosis. Estrogen also decreases the production of RANKL to reduce osteoclastogenesis.

Testosterone's role in bone health is becoming more apparent with recent identification of some direct effects on bone resorption and osteoblasts.[9,31,41] Most of testosterone's bone effects relate to its metabolism to estradiol and the above estrogen bone effects. Testosterone can also increase OPG production, which will inhibit bone resorption. Increased osteoblast proliferation and differentiation are direct effects. These effects might be from increasing TGF-β, TGF mRNA, FGF, and IGF-2, and decreasing IL-6.

Bone physiology has many genomic and genetic influences; isolating one or a few genes for correction will unlikely resolve the problems in an aging population for whom osteoporosis is a common problem.[27,37] Genetic mutations do result in bone disorders such as osteoporosis, osteogenesis imperfecta, and juvenile idiopathic osteoporosis. Heredity is important since family history, especially of a hip fracture in a parent, is a strong risk factor for osteoporosis development.

At this time, 56 loci have been identified that influence BMD and 14 loci for fracture risk, ranging from impacts on bone resorption (RANKL, OPG) to formation (Wnt, LRP5, and sclerostin).[38] Calcium, vitamin D, and estrogen receptors are also under genetic influence. Studies are conflicting as to whether an association exists between response to currently available antifracture medications and genetic profiles. Genetic modulation is in its infancy for osteoporosis prevention and treatment, but genomics and gene editing might lead to the creation of new medications and/or the ability to tailor medication choices to an individual's genetic profile.

Calcium Homeostasis, Vitamin D, and Parathyroid Hormone

2 Calcium homeostasis is maintained by vitamin D and PTH, which influence calcium gastrointestinal (GI) absorption and renal reabsorption.[33,35] Calcium absorption under normal conditions is approximately 30% and is improved with

vitamin D sufficiency.[42] Calcium absorption is lower in the winter due to decreased exposure to required ultraviolet light that converts cholesterol in the skin to vitamin D. Absorption is reported to be higher in obesity, which is associated with greater vitamin D storage. Calcium absorption is predominantly an active rate-limited process in the duodenum and jejunum, which is controlled by many hormones, such as 1,25-dihydroxyvitamin D [1,25(OH) vitamin D], estrogen, and transient receptor potential cation channel subfamily V member 6 (TRPV6). A calcium transporter (calmodulin or calbindin) is required to bring calcium from the gut into the tissue wall and then across the enterocyte. Calcium is extruded into the circulation via calcium (Ca^{++}) adenosine triphosphatase (ATPase) and the sodium-calcium exchanger. Throughout the intestine, paracellular passive calcium diffusion occurs. This diffusion accounts for less than 15% of absorbed calcium, is not rate limited, and possibility is sensitive to 1,25(OH) vitamin D. Solvent drag plays a minor role in calcium absorption.

When the calcium-sensing receptor on parathyroid cells detects low serum calcium, PTH production increases.[33,35] PTH then directly (minimal effect) and indirectly (predominant effect via increasing calcitriol production) causes calcium reabsorption by the kidney. Calcium reabsorption increases as 25(OH) vitamin D concentrations increase, plateauing around 10 to 15 ng/mL (mcg/L; 25-37 nmol/L). Loop diuretics decrease, and thiazide diuretics increase calcium resorption in the kidney.

Sometimes the increased fractional calcium absorption is insufficient to maintain normal serum calcium, requiring bone resorption for correction.[35] Consistent and high concentrations of PTH and calcitriol increase RANKL and decrease OPG, resulting in increased osteoclast activity, which releases calcium from bone to restore calcium homeostasis. Of note, low PTH concentrations for a short time (eg, teriparatide) increase bone formation.

Active 1,25(OH) vitamin D concentrations depend on skin conversion, dietary and supplemental intake, and PTH control.[33,35] The sun's ultraviolet B rays convert 7-dehydrocholesterol in the skin to cholecalciferol (vitamin D_3), which is the most abundant vitamin D source. A few foods contain ergocalciferol (vitamin D_2). Supplements and multivitamins include cholecalciferol or ergocalciferol. Subsequent conversion of cholecalciferol and ergocalciferol to 25-hydroxyvitamin D (25[OH] vitamin D; calcidiol) occurs in the liver, and then PTH stimulates conversion of 25(OH) vitamin D via 25(OH) vitamin D-1α-hydroxylase (CYP27B1) to its final active form, 1,25-dihydroxyvitamin D (calcitriol), in the kidney. Calcitriol binds to the intestinal vitamin D receptor (VDR) and then increases the action of calcium-binding proteins calmodulin and

calbindin. As a result, the intestinal absorption of calcium and phosphorous are increased. The feedback system is completed with CYP27B1 activity inhibited by adequate calcium and phosphorus, and FGF23 inhibiting PTH synthesis.

PATHOPHYSIOLOGY

Postmenopausal Osteoporosis

2 Estrogen deficiency causes significant bone density loss and compromises bone architecture. Estrogen deficiency increases proliferation, differentiation, and activation of new osteoclasts and prolongs survival of mature osteoclasts.[6,9,10] Interleukins, prostaglandin E_2, TNF-α, and interferon γ also increase resulting in more RANKL and less OPG. Loss of estrogen also increases calcium excretion and decreases calcium gut absorption through decreases in TRPV6 activity and 1,25(OH) vitamin D binding proteins. Estrogen deficiency can also be seen in other settings such as anorexia nervosa and lactation, and from medications, such as prolonged depot medroxyprogesterone acetate implants, aromatase inhibitors, and gonadotropin releasing hormone agonists.[22,23,34,43]

Accelerated bone loss of both mass and strength begins during perimenopause and continues up to 8 years after menopause due to increased bone resorption that exceeds bone formation.[9,11,34] During this time bone loss can be as high as 2% per year, with total BMD loss due to menopause about 10% to 30%.[3,9,11] Bone strength decreases by about 2.5% per year. The number of remodeling sites increases and resorption pits are deeper and inadequately filled by normal osteoblastic function. During menopause, trabecular bone is most susceptible, leading predominantly to vertebral and wrist fractures.[6,13] Initially, women with early menopause (ie, before age 40) due to natural or induced causes have lower BMD than matched premenopausal women. After the age 70, risk for fractures and low bone density becomes the same.

Male Osteoporosis

2 Men are at a lower risk for developing osteoporosis and osteoporotic fractures because of larger bone size, greater peak bone mass, increase in bone width with aging, fewer falls, and shorter life expectancy.[8,9,13,41,44] However, the mortality rate after a fracture is greater for men than women. With aging, sex

hormone binding globulin increases, which results in less free testosterone and thereby less testosterone available for conversion to estrogen. Estrogen inhibits bone resorption in men; however, androgen deficiency increases RANKL release and bone resorption.

Male osteoporosis results from aging or secondary causes (see Tables 108-2 and 108-3).[1,3,8,13,15,16,44] The most common risk factors for men are smoking, alcohol abuse, low body weight, weight loss, age, long-term glucocorticoid use, androgen deprivation therapy, and low-testosterone concentrations. Medical conditions and medications that cause hypogonadism can increase bone loss.[45]

Age-related Osteoporosis

2 Age-related bone mass and strength loss begin after peak bone mass is reached.[29,32,34] About 0.5% BMD is loss each year after age 30 years, increasing to 1.6% after 85 years. Age-related osteoporosis occurs in older adults because of accelerated bone turnover rate and reduced osteoblast bone formation, with a greater effect on cortical bone. These bone changes occur from hormone deficiencies; calcium and vitamin D deficiencies due to changes in intake, absorption, and metabolism; decreased production or function of cytokines or other bone biochemicals; decreased molecular signaling; increase in redox status and free radical formation; increase in adipocytes; decreased body water; telomere shortening; and less exercise. Fracture risk for a given BMD value increases with aging.[28] Hip fracture risk rises dramatically in older adults as a consequence of the cumulative loss of cortical and trabecular bone and an increased risk for falls. Falls accounted for 87% of fractures in older adults.[29,30] Aging is associated with muscle changes as well, resulting in weakness, balance instability, and greater likelihood of falls.

Illness-Induced Secondary Causes of Osteoporosis

1 2 A secondary medical cause of osteoporosis is common (see Table 108-2).[1,3,8,13–16, 21] Symptoms, initial screening laboratory test results, medication profile review, and/or a decreased Z-score from a DXA test can suggest a secondary cause, warranting a more comprehensive work-up.

Medication-Induced Secondary Causes of Osteoporosis

1 3 Medication-related reductions in BMD and associated fractures are a common secondary cause of osteoporosis.[20–25] Table 108-3 lists select medications associated with bone loss and/or fracture risk as well as the proposed mechanisms of bone loss.[20–25] Alternative medications should be used when possible, with consideration given to patients' individual risk and baseline BMD status. When these medications cannot be avoided, periodic re-assessment of benefits and risks should be performed, as reversal of bone loss might be possible upon discontinuation of some of these medications. Two of the most common causes of medication-induced osteoporosis, glucocorticoids and certain cancer chemotherapies, are discussed later in this chapter.

CLINICAL PRESENTATION

Table 108-4 outlines the clinical presentation of osteoporosis.[1,3,8,13,14,21,28] Osteoporosis is a silent disease, frequently not detected until a fracture is experienced or noticed on x-ray. Many vertebral fractures are asymptomatic, with patients sometimes attributing mild back pain to old age. Some new vertebral fractures present with moderate-to-severe back pain that can radiate down the leg. The pain usually subsides after 2 to 4 weeks; however, residual chronic back pain can persist. Multiple vertebral fractures decrease height and sometimes curve the spine (kyphosis or lordosis). Patients with a nonvertebral fracture frequently present with severe pain, swelling, and reduced function and mobility at the fracture site.

TABLE 108-4 Clinical Presentation of Osteoporosis

General
- Many patients are unaware they have osteoporosis until testing or fracture.
- Fractures can occur after bending, lifting, or falling, or independent of any activity.

Symptoms
- Frequently asymptomatic
- Pain
- Immobility
- Depression, fear, and low self-esteem from physical limitations and deformities

Signs
- Shortened stature (>1.5 in. [4 cm] loss from maximum height; >0.8 in. [2 cm] in 1 year), kyphosis, or lordosis
- Fragility (low-trauma) vertebral, hip, wrist, or forearm fracture

Laboratory tests
- Routine tests: comprehensive metabolic profile (creatinine, calcium, phosphorous, electrolytes, alkaline phosphatase, and albumin), 25(OH) vitamin D, thyroid-stimulating hormone, complete blood count, total testosterone (for men), and 24-hour urine calcium and creatinine concentrations
- Bone turnover markers (eg, urinary or serum NTX, serum CTX, and serum PINP) are sometimes used, especially to determine if high bone turnover exists
- Additional testing if the patient's history, physical examination, or initial laboratory and or diagnostic tests suggest a specific secondary cause (eg, intact parathyroid hormone, free testosterone, serum protein electrophoresis, serum parathyroid, and celiac panel)

Other diagnostic tests
- Spine and hip bone density measurement using central dual-energy x-ray absorptiometry (DXA)
- Vertebral fracture assessment (VFA) with DXA technology
- Radiograph ordered for other reasons that shows low bone density
- Radiograph to confirm fracture
- Balance and mobility tests

CTX, C-terminal crosslinking telopeptide of type 1 collagen; NTX, N-terminal crosslinking telopeptide of type 1 collagen; PINP, procollagen type 1 N-terminal propeptide.

Data from References 1, 3, 8, 13, 14, 21, and 28.

CONSEQUENCES OF OSTEOPOROSIS

Osteoporosis can lead to fragility/low-trauma fractures, defined as fracture that

occurs as a result of a fall from standing height or less or with minimal to no trauma. Fractures of the vertebrae, hip, forearm, and humerus are considered major osteoporotic fractures whereas other fractures are generally not considered osteoporosis-related. Osteoporotic fractures can lead to increased morbidity and mortality and decreased quality of life. Pain and physical deformity are common, and these changes can lead to other health consequences. For example, severe kyphosis can lead to respiratory problems as a result of compression of the thoracic region and GI complications such as poor nutrition from intra-abdominal compression. Depression is common because of fear of falling/fracture, pain, loss of self-esteem from physical deformity, and loss of independence and mobility postfracture.

Hip fractures are associated with the greatest increase in morbidity and mortality. After a hip fracture, 40% of patients have mobility limitations, 20% become totally dependent or require long-term care, and about 20% die within the year from complications of the hip fracture or other comorbid disease processes.[1,3,44] Men have a higher 1-year mortality rate after hip fracture than women.[41]

Wrist fractures occur more commonly in younger postmenopausal women and are frequently a result of a fall on an outstretched hand.[1] Although they cause less disability than other fracture sites, negative outcomes include prolonged pain and weakness, and decreased activities of daily living such as cooking and shopping.

Once a low-trauma fracture has occurred, the risk for subsequent fractures goes up exponentially.[1] Vertebral fractures, even if asymptomatic, are a major predictor of a future fracture with up to a fivefold increase in future vertebral fractures and a doubling of the risk at other sites. Hip fractures are associated with a twofold or greater increase in risk for future fracture.

PATIENT ASSESSMENT

Laboratory tests and other assessments are described in Table 108-4.[1,3,8,13,14,21,28] Height should be measured annually using a wall-mounted stadiometer. Low bone density (sometimes called osteopenia) reported on routine radiographs is a sign of significant bone loss and requires further evaluation for osteoporosis. Additional tests will be required that are specific to potential secondary causes (Table 108-3). In addition to physical examination and laboratory tests, patients can be assessed with risk factor assessment tools, osteoporosis quality of life questionnaires, peripheral and central DXA,

ultrasonography, and bone turnover markers (BTM).

Risk Factor Assessment

The aim of an initial osteoporosis risk assessment screening is to identify those patients who are at risk for osteoporosis and osteoporotic fractures (see Table 108-1), and/or would benefit from further evaluation or pharmacologic intervention. The most commonly used assessment is the fracture risk assessment (FRAX) tool, with the Garvan tool as another option.

4 The FRAX tool was created to be used for screening and diagnosis. It can be used without DXA results, however, estimates improve when T-scores are available.[3,10,28] This tool uses 11 risk factors: age, race/ethnicity, sex, previous fracture, parent history of hip fracture, body mass index, glucocorticoid use (current use or past use for 3 or more months of the equivalent of at least 5 mg of prednisolone daily), current smoking, alcohol use of 3 or more drinks per day, rheumatoid arthritis, and select secondary causes of osteoporosis (see Table 108-1); with optional entry for femoral neck BMD. The FRAX tool calculates an individual's percent probability of any major osteoporotic fracture and hip fracture in the next 10 years. Each country establishes cut-off points for fracture risk treatment decisions. For the United States they are 20% or higher for major osteoporotic fracture and 3% or higher for hip fracture. Most guidelines use these universal cutoffs, but others are beginning to recommend age-adjusted FRAX cutoffs[10] to prevent undertreatment of younger people and overtreatment of older people or create a middle zone[14] in which BMD would be needed to determine treatment. For example, for a 55-year-old person, a 10% 10-year risk of major osteoporotic fracture would be used and for an 80-year-old person, 30% would be used. For postmenopausal women younger than 65 years of age, a 10-year major osteoporotic fracture risk of greater than 8.4% would result in a referral for a DXA.[46] Some important risk factors for fracture, for example, falls, multiple fractures, recent fracture, or other common secondary causes, are not accommodated in the FRAX model.

The Garvan calculator uses four risk factors (age, sex, low-trauma fracture, and falls) with the option to also use BMD.[13,47] It calculates 5- and 10-year risk estimates of any osteoporotic/fragility fracture and hip fracture. This tool corrects some disadvantages of the FRAX tool since it includes falls and number of previous fractures, but it does not use as many other risk factors.

Screening Using Peripheral Bone Mineral Density Devices

Peripheral bone density devices that use DXA (pDXA) or quantitative ultrasonography (QUS) are helpful as screening tools to determine which patients require further evaluation with central DXA or for decision making if central DXA testing is not available.[1,48] Peripheral DXA of the forearm, heel, or finger uses a low amount of radiation and requires personnel with special training. Quantitative ultrasonography at the heel and other peripheral sites uses sound waves without radiation or need for specially trained personnel. The heel is the only skeletal site at which QUS has been validated. The QUS has better fracture predictive value than pDXA and has demonstrated the ability to predict fractures in postmenopausal women and in men 65 years of age or older. The specific peripheral T-score threshold for referral is not universally defined and varies by device. These tests should not be used for diagnosis or for monitoring response to therapy.

Peripheral devices are considerably less expensive than central DXA, easy to use, portable, fast (less than 5 minutes), and can predict general fracture risk. They are popular for screening patients at health fairs and community pharmacies. Patients already identified as being at high risk for osteoporosis based on risk factors, fragility fracture, or secondary causes for osteoporosis should be referred for central DXA testing.

Central Dual-Energy X-Ray Absorptiometry

4 BMD measurements at the hip or spine can be used to assess fracture risk, establish the diagnosis and severity of osteoporosis, and confirm osteoporosis following a low-trauma fracture.[1,3,8,28,48] Multiple techniques are available for measurement of BMD and include DXA, quantitative computed tomography (QCT), digital x-ray radiogrammetry, and radiographic absorptiometry. Central DXA is the mostly widely used technique. It is considered the gold standard for measuring BMD because of its high precision, short scan times, low-radiation dose (comparable to the average daily dose from natural background), and stable calibration. Measurements of lumbar spine, femoral neck, and total hip BMD are recommended with the lowest BMD value used for diagnosis. The forearm (distal third of the radius) can be used as an alternative if the preferred areas cannot be scanned. Trabecular bone score (TBS) is a newer technology available on some densitometers that can provide measurements of bone quality and

microarchitecture. Low TBS is independently associated with increased fractures and can be used in combination with BMD and FRAX scores to better identify those at increased fracture risk.[28,48]

Several consensus guidelines and position statements are consistent in recommending central BMD testing for all women aged 65 years or older, men aged 70 years or older, postmenopausal women younger than 65 years old and men 50 to 69 years old with risk factors for fracture, and patients with an identified secondary cause for bone loss.[1,3,8,13,14,28,48] The United States Preventive Services Task Force (USPSTF) provides similar recommendations for screening in women 65 years or older and in women under the age of 65 with additional risk factors as determined by a clinical risk assessment tool, such as FRAX.[49] This group, however, has concluded that current data are insufficient to make recommendations for men. Patients with a fragility fracture do not need a DXA for an osteoporosis diagnosis, but the results are helpful for determining the severity of osteoporosis and as a baseline for monitoring response to therapy. The DXA results can also help patients make decisions about the need for lifestyle changes and prescription osteoporosis medications. In the absence of a suspected or known secondary cause for osteoporosis or a history of a low-trauma fracture, central BMD testing is not recommended for children, premenopausal women, or men younger than 50 years of age.

A central DXA BMD report provides the actual bone density value, T-score, and Z-score.[1,3,48] The actual bone density value (g/cm^2) is most useful for serial monitoring of therapy response, which is typically performed 1 to 2 years after medication initiation. The T-score is used for diagnosis and is a comparison of the patient's BMD to the mean BMD of a healthy, young (20-29 year old), sex-matched white reference population. It is not adjusted for age, race, or ethnicity. The T-score is the number of standard deviations from the mean of the reference population. The Z-score is similar but compares the patient's BMD to the mean BMD for a healthy sex- and age-matched population. Patient's race and ethnicity should be used for the Z-score if available. The Z-score is sometimes helpful in determining whether a secondary cause for osteoporosis is present and is used for diagnosis (value ≤ -2.0) in children, premenopausal women, and men younger than 50 years of age. Follow-up monitoring had been every 2 years[3] after initiation of pharmacotherapy; however, newer guidelines are recommending 5 years[2] in postmenopausal women. The postmedication initiation scan results need to be above the machine's least significant change to be clinically relevant.[3] Most insurance carriers, including Medicare, cover BMD testing every 2 years. For patients with normal bone density or those in the upper

range of low bone mass, time between follow-up scans can be lengthened.[2,3,50]

Using the spine DXA image, a vertebral fracture assessment (VFA) can be performed to assess for vertebral fractures that might otherwise go undetected.[1,3,8,13,48] Each vertebra is visually evaluated for fracture and fractures are assessed for severity. This result becomes important for treatment decisions in patients with low bone mass. Because many vertebral fractures are asymptomatic, VFA is recommended for those at high risk of an undiagnosed vertebral fracture. This includes patients with a T-score less than −1.0 when one or more of the following criteria are also present: women over age of 70 or men over the age of 80; a historical height loss of more than 1.5 in. (4 cm); a self-reported but undocumented prior vertebral fracture; or patients on glucocorticoid therapy (≥5 mg prednisone or equivalent daily for 3 months or more).[3,48]

Laboratory Tests

Routine laboratory testing (see Table 108-4) is used for initial bone health assessment.[1,3,8,13–15, 21,51] To evaluate secondary causes, additional testing is conducted, which will be specific to the suspected secondary cause.

Bone Turnover Markers

Bone turnover markers (BTM) are commonly used in clinical trials and sometimes in clinical practice.[3,8,52] They can be used to assess bone pathophysiology, predict fracture risk, monitor response to osteoporosis medications, evaluate medication adherence, and determine the need for reinitiation of osteoporosis medications after a drug holiday. Markers of bone formation are bone-specific alkaline phosphatase (BAP), osteocalcin (OCN), and procollagen type 1 propeptides (PINP, PICP). Markers of bone resorption obtained from blood samples are C-terminal type 1 collagen telopeptide (CTX), C-terminal telopeptide (ICTP), and tartrate resistant acid phosphatase isoenzyme 5b (TRACP5b), and from urine samples are deoxypyridinoline (DPD) and N-terminal type 1 collagen telopeptide (NTX). Response to osteoporosis therapy can be measured as early as 2 to 3 months. Circadian variability, seasonal variations, food intake, recent exercise, some diseases and conditions, and assay variability can affect results and decrease utility in clinical practice. For serum BTM, fasting morning samples should be obtained with repeat tests done at the same facility with the same assay. Coverage for these tests varies by health insurance.

Diagnosis of Osteoporosis

6 The diagnosis of osteoporosis is based on a low-trauma fracture or femoral neck, total hip and/or spine DXA using World Health Organization (WHO) T-score thresholds.[1–3,8,13–15] Low bone mass (preferred term) or osteopenia is a T-score between –1 and –2.5, and osteoporosis is a T-score at or below –2.5. Although these definitions are based on data from postmenopausal white women, they are also applied to perimenopausal women, men age 50 years and older, and adults from different races and ethnicities. The diagnosis of osteoporosis in children, premenopausal women, and men under 50 years of age should be based on a Z-score at or less than –2.0 in combination with other risk factors or fracture.[8,17,18,34,48] Without a history of clinically significant fracture, children and premenopausal women are given a diagnosis of bone mass below the expected range for age.

PREVENTION AND TREATMENT

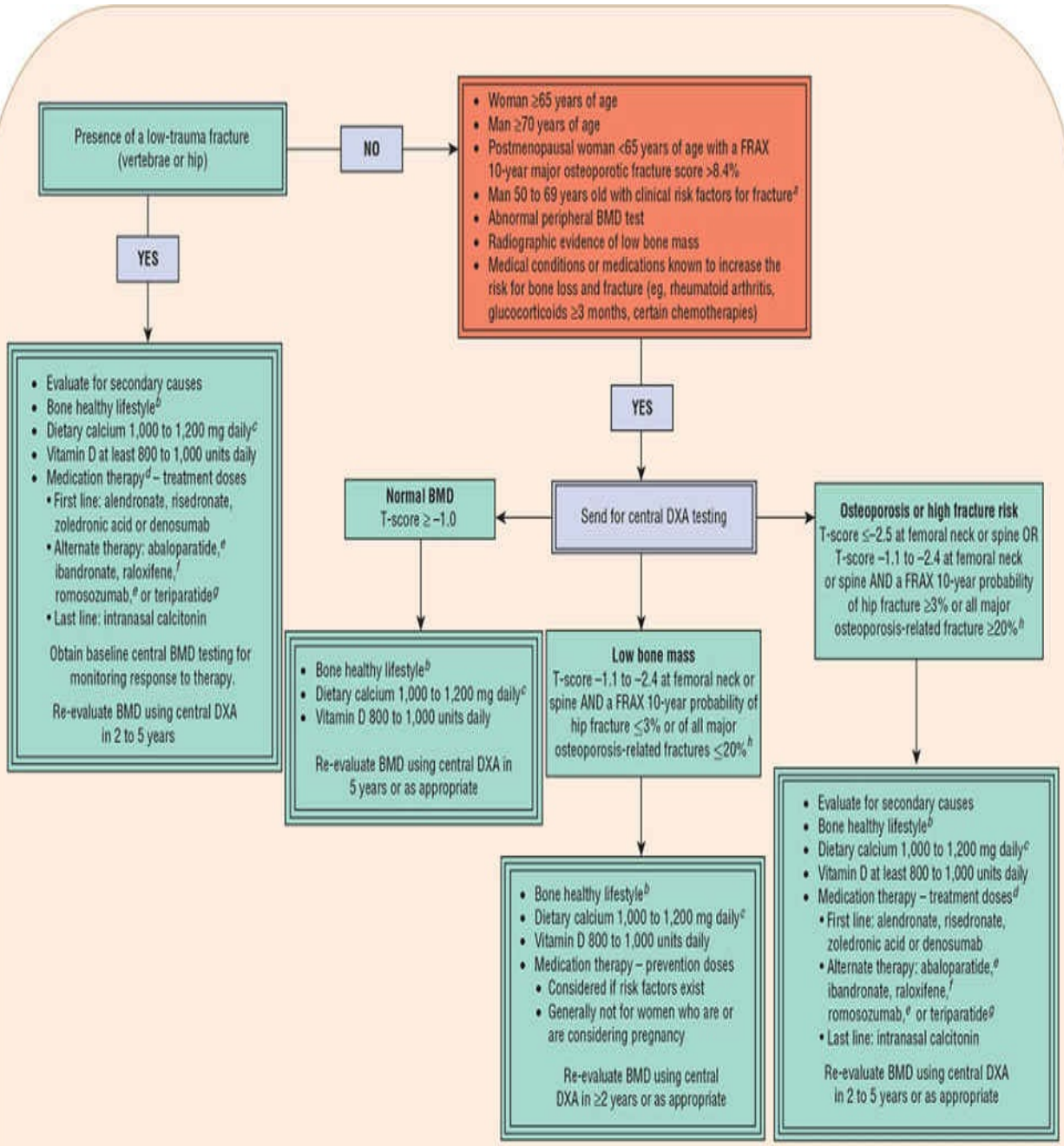
Desired Outcomes

The primary goal of osteoporosis care should be prevention. Optimizing skeletal development and peak bone mass accrual in childhood, adolescence, and early adulthood will ultimately reduce the future incidence of osteoporosis. Once low bone mass or osteoporosis develops, the objective is to stabilize or improve bone mass and strength and prevent fractures. In patients who have already suffered osteoporotic fractures, reducing pain and deformity, improving functional capacity, improving quality of life, and reducing future falls and fractures are the main goals.

General Approach to Prevention and Treatment

5 6 A bone-healthy lifestyle should begin at birth and continue throughout life, and provides the foundation for osteoporosis prevention and treatment. Supplements and medications are used when lifestyle habits are insufficient or suboptimal, osteoporosis has developed, or a low-trauma fracture occurs. Guidelines and position statements recommend considering prescription therapy in any postmenopausal woman or man age 50 years and older presenting with one of the following scenarios: a hip or vertebral fracture; T-score of −2.5 or lower at the femoral neck, total hip, or spine; or low bone mass (T-score between

−1.0 and −2.5 at the femoral neck, total hip, or spine) with a FRAX 10-year probability of hip fracture of 3% or more, or a FRAX 10-year probability of any major osteoporosis-related fracture of 20% or more.[1–3,14] **Figure 108-3** provides an osteoporosis management algorithm for postmenopausal women and men 50 years and older that incorporates both nonpharmacologic and pharmacologic approaches.[1–3,46]



[a]Major clinical risk factors for fracture: current smoker, low body weight or body mass index, personal history of fracture as an adult (after age 50 years), history of osteoporosis/low trauma fracture in a first-degree relative, excessive alcohol intake.

[b]Bone-healthy lifestyle includes well-balanced diet with adequate calcium, vitamin D, and protein intakes; smoking cessation; limited alcohol intake; weight-bearing/resistance exercises; and fall prevention.

[c]Dietary calcium preferred. If diet is inadequate, supplement as necessary.

[d]Sometimes men with hypogonadism also receive testosterone replacement; sometimes women with menopausal symptoms receive low dose hormone therapy for a short time.

[e]Newer agents marketed after osteoporosis guidelines published; similar uses as teriparatide.

[f]Raloxifene can be a good option in women at high risk for breast cancer.

[g]Teriparatide can be considered a first-line option in patients with a very high risk of fracture (e.g, T-score ≤3.5 or multiple low trauma fractures) or intolerant to other medications.

[h]Some providers use age adjusted FRAX thresholds versus set thresholds for all age groups.

FIGURE 108-3 Algorithm for the management of osteoporosis in postmenopausal women and men aged 50 and older. (BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; FRAX, World Health Organisation fracture risk assessement tool.) (*Data from References 1–3, 8, and 46.*).

NONPHARMACOLOGIC THERAPY

5 Nonpharmacologic therapy, referred to as a bone-healthy lifestyle, includes proper nutrition, moderation of alcohol intake, smoking cessation, exercise, and fall prevention.[3] A bone-healthy lifestyle that is employed early in life will help to optimize peak bone mass, and if continued throughout life it will minimize bone loss over time. A bone-healthy lifestyle not only maintains or increases BMD, but it also helps decrease falls and fragility fractures.

Diet

5 Overall, a diet well balanced in nutrients and minerals with limited salt, alcohol, and caffeine use are important for bone health. Adequate amounts of calcium and vitamin D have documented impacts on bone health. Protein is required for bone, thus the recommended dietary allowances (RDAs) of 0.8 g/kg body weight per day is recommended for adults increasing to 1 to 1.2 g/kg body weight in older adults.[10] Magnesium, boron, and vitamin K have a physiologic role in bone development and maintenance but either no or insufficient data exist to establish them independently as supplemental agents for prevention and treatment of osteoporosis.[3] Some of these agents are included in calcium combination products and are found in multivitamins. Strontium ranelate has documented positive bone effects and is marketed in Europe for prevention of osteoporosis.

Eating disorders are associated with increased bone loss and fractures. Being thin or having anorexia nervosa are well known to decrease bone mass.[16,43] In the past, obesity was thought protective due to increased estrogen production and stimulation of bone remodeling due to weight bearing; however, emerging literature suggests adipocytes have negative impacts on bone health.

Calcium

5 7 Adequate calcium intake is necessary for calcium homeostasis

throughout life, bone development during growth, and bone maintenance.[42] The Institute of Medicine (IOM) recommended calcium intakes are based on age and gender (**Table 108-5**).[42,53] These values represent the average daily amount needed to meet requirements for 97% to 98% of healthy people. Higher intakes might be needed when concomitant diseases and medications known to negatively affect calcium and vitamin D homeostasis exist. Ingesting calcium-containing and/or calcium-fortified foods and beverages is the preferred method to achieve daily calcium requirements. Dairy products generally have the highest amount of calcium per serving and are available in low-fat options. Some food sources are absorbed well but have low elemental calcium content (eg, broccoli). Carbohydrates increase calcium absorption whereas phylates (eg, beans, seeds, wheat bran) and oxalates (eg, spinach and rhubarb) decrease absorption.[54]

TABLE 108-5 Calcium and Vitamin D Recommended Dietary Allowances (RDAs) and Tolerable Upper Intake Levels (ULs)

Group and Ages	Elemental Calcium RDA (mg)	Calcium Tolerable Upper Intake Level (mg)	Vitamin D RDA (Units)[a]	Vitamin D Tolerable Upper Intake Level (Units)
Infants				
Birth to 6 months	200[b]	1,000	400[b]	1,000
7-12 months	260[b]	1,500	400[b]	1,500
Children				
1-3 years	700	2,500	600	2,500
4-8 years	1,000	2,500	600	3,000
9-18 years	1,300	3,000	600	4,000
Adults				
19-50 years	1,000	2,500	600[b,c]	4,000
51-70 years (men)	1,000	2,000	600[b,c]	4,000
51-70 years (women)	1,200	2,000	600[b,c]	4,000
>70 years	1,200	2,000	800[b,c]	4,000

[a]Some guidelines recommend intake to achieve a 25(OH) vitamin D concentration of >30 ng/mL (mcg/L; 75 nmol/L),[1,3,8] which is higher than the Institute of Medicine goal of >20 ng/mL (mcg/L; 50 nmol/L).[53]

[b]Adequate intake (evidence insufficient to determine an RDA).

[c]Guidelines recommend 800 to 1,000 units[1] or 1,000 to 2,000 units[3,8] for adults with osteoporosis.

Data from References 42 and 53.

People should be encouraged to evaluate their food and beverage intake to determine if they are receiving adequate amounts of calcium. To calculate the amount of calcium in a serving of food, consumers can add a zero to the percentage of the daily value listed on food labels. For example, a serving of milk (8 oz. [~240 mL]) has 30% of the daily value of calcium. This translates to 300-mg calcium per serving. Websites can be used to identify foods and beverages high in calcium.[42,55]

Although many foods and beverages are high in calcium, the average daily dietary calcium intake is insufficient in several age groups, including children aged 9 to 13, adolescents aged 14 to 18 and women 51 to 70 years, and adults older than 70 years.[55] In addition, lactose intolerance limits dietary calcium

intake. Approximately 25% of the US population has some level of lactose intolerance, with the incidence in Asian (85%) and African American (50%) populations higher than in whites (10%). Patients with lactose-intolerance have several options to increase dietary calcium intake, including products containing lactase (Lactaid®), lactose-reduced milk, lactose-free milk, calcium-fortified milk alternatives (eg, soy and almond milk), certain aged cheeses, or yogurt with active cultures along with other nondairy calcium-fortified products (eg, orange juice, breakfast cereals, and energy bars). Vegan diets sometimes have insufficient calcium intake, but products such as tofu, calcium-fortified milk alternatives, and juices can be used. When diet cannot be enhanced to achieve adequate intakes, calcium supplements will be required.

Vitamin D

Table 108-5 also lists the IOM recommended adequate intakes for Vitamin D. The three main sources of vitamin D are sunlight (conversion of 7-dehydrocholesterol to vitamin D3), diet, and supplements.[53] Vitamin D3 comes from oily fish, eggs, and fortified dairy products. Vitamin D2 comes from fungi and eggs (chickens given vitamin D2 in their diet). Websites can be used to identify the few foods high in vitamin D. To calculate the amount of vitamin D in a serving of food, consumers can multiply the % daily value of vitamin D listed on the food label by 4 (eg, 20% vitamin D = 80 units).

Overall prevalence of hypovitaminosis D (<20 ng/mL [mcg/L; 50 nmol/L]) in American adults has been estimated at 29%; with higher prevalence ratios observed in those who are older than 60 years of age, race/ethnic minorities, of lower education levels, obese, physically inactive, and current smokers.[56] Low vitamin D concentrations can result from insufficient intake, dietary fat malabsorption, decreased sun exposure, decreased skin production, and/or decreased liver and renal metabolism. Endogenous synthesis of vitamin D can be decreased by factors that affect exposure to or decrease skin penetration of ultraviolet B light rays. Sunscreen use, full body coverage with clothing (eg, women wearing veiled and full-length dresses), and darkly pigmented skin can all decrease vitamin D production. Seasonal variations in vitamin D concentrations are also seen with nadirs in late winter and peaks in late summer. Because few foods are naturally high or fortified with vitamin D, most people, especially older adults, require supplementation to achieve IOM recommended adequate intakes.

Isoflavones

5 Phytoestrogens (isoflavones, lignans, and coumestans) are plant-derived compounds that possess weak estrogenic agonist and antagonist effects throughout the body.[57] Isoflavones are found in soy products, lignans in seeds, berries, and grains, and coumestans in broccoli and sprouts. Genistein is the most abundant and biologically active isoflavone in soybeans. Isoflavones, genistein, and daidzein are also available as single-agent or combination supplements. The evidence supporting a positive bone benefit from phytoestrogen intake is conflicting with most studies showing little or no effect.[1,6,57] Doses of at least 75-mg isoflavones increased spine but not hip BMD when compared to placebo. Isoflavones from soy foods appear safe; however, more information is needed, especially in women with breast cancer and for isoflavone supplements versus food sources.

Alcohol

3 Excessive but not moderate alcohol consumption is associated with an increased risk for osteoporosis and fractures.[3,8,10] Alcohol increases bone resorption by increasing RANKL and decreases bone formation by inhibiting Wnt signaling pathway and increasing oxidative stress that results in osteoblast apoptosis. Patients with alcohol use disorder might also have poor nutrition, decreased calcium absorption, altered vitamin D metabolism, decreased testosterone production, and balance impairments resulting in more falls and fractures. Alcohol consumption should not exceed 1 to 2 drinks per day for women and 2 to 3 drinks per day for men.

Caffeine

5 Although results are conflicting, excessive caffeine consumption is associated with increased calcium excretion, increased rates of bone loss, and a modestly increased risk for fracture.[3] Ideally, caffeine consumption should be limited to two servings or less per day. For those with greater intakes, the increased calcium excretion might be compensated by additional calcium intake.

Smoking

5 Counseling patients of all ages on smoking cessation can help to optimize

peak bone mass, minimize bone loss, and ultimately reduce fracture risk.[3,8] Cigarette smoking is an independent risk factor for osteoporosis and is associated with increased relative risk for fracture at all sites. The effect is dose and duration dependent, but even passive smoking shows adverse effects on BMD. The negative bone effects are associated with reduced intestinal calcium absorption, lower 25(OH) vitamin D concentrations possibly due to increased hepatic metabolism, an increase in bone resorption from a decrease in production and increase in metabolism of estradiol, increase in RANKL and decrease in OPG, decrease in osteoblasts and bone formation secondary to increase in cortisol and dehydroepiandrosterone sulfate, and impairment of osteoid production and mineralization. The detrimental effects of smoking on physical function and balance can contribute to an increased risk of falls.

Exercise

5 Physical activity or exercise is an important nonpharmacologic approach to preventing osteoporotic fractures.[11] Exercise can decrease the risk of falls and fractures by stabilizing bone density and improving muscle strength, coordination, balance, and mobility. Physical activity is especially important early in life since 50% of peak bone mass is gained at that time and lack of exercise during growth can lead to suboptimal loading/straining, decreased stimulation of bone deposition, and reduced peak bone mass. Although bone mass might not increase, bone strength will increase in older adults. All people of any age who are medically fit should be encouraged to perform a moderate-intensity weight-bearing activity (eg, running, plyometric training [jumping, hopping, bounding]) and resistance activity (eg, weight machines, free weights, or elastic bands). Walking, swimming, cycling, and yoga have less impact on osteogenics but are still important. People at risk of osteoporosis should participate in exercise, including weight-bearing activities, at least three to four times weekly for 30 to 40 minutes per session.[8,11] Older adult recommendations from the American Heart Association can be advocated as well (accumulate 30-60 minutes of moderate-intensity aerobic exercise daily or 20-30 minutes of vigorous-intensity exercise daily).[10]

Fall Prevention

5 Risk of falling increases with advanced age predominantly as a result of balance, gait, and mobility problems, poor vision, reduced muscle strength,

impaired cognition, multiple medical conditions (eg, arrhythmias, postural hypotension, Alzheimer's disease, and Parkinson disease), and polypharmacy (especially psychoactive, cardiovascular, diabetes, seizure, and pain medications).[29,30] The ability to adapt to falls also decreases with aging. Older adults are more likely to sustain a hip or pelvic fracture because they tend to fall backward or sideways instead of forward.

Because of the link between falls and fractures, all older adults should be asked at least annually if they have fallen.[29,30] The Centers for Disease Control and Prevention have created an assessment tool. If an older adult scores 4 or more, a comprehensive falls assessment should be conducted. Many other assessment tools exist to evaluate falls.

Generally, intervention programs that are multifactorial have greater effects on decreasing falls, fractures, other injuries, and nursing home and hospital admissions than single interventions.[3,29,30] Medication profiles should also be reviewed for any unnecessary medications that can affect cognition and balance and potentially increase fall risk. Consideration should be given to replacing high-risk medications with safer alternatives. Although Vitamin D supplementation has been advocated to reduce falls and fractures in some guidelines, the most recent USPSTF recommendation states the evidence is inadequate to prescribe this therapy for fall[58] and fracture[59] prevention. Maintenance of a regular individualized exercise program, such as tai chi, should be recommended to improve body strength, balance, and agility.[29,30] Other recommendations include resolving vision, low blood pressure, heart rate/rhythm, and foot problems and using proper footwear. External hip protectors are specialized undergarments designed to pad the area surrounding the hip, decreasing the force of impact from a sideways fall. Conflicting results and poor adherence limit their use.

VERTEBROPLASTY AND KYPHOPLASTY

During vertebroplasty and kyphoplasty cement is injected into fractured vertebra(e) for patients with debilitating pain from vertebral compression fractures.[60] Although used to stabilize damaged vertebrae, reduce pain, and decrease opioid intake, this therapy is decreasing based on recent research including a meta-analysis showing the effects are similar to sham interventions, are short-term, have no major pain benefit, and are associated with vertebral fracturing around the cement, cement leakage into the spinal column, and nerve damage (rare).

PHARMACOLOGIC THERAPY

9 Because nonpharmacologic interventions alone are frequently insufficient to prevent or treat osteoporosis, medication therapy is often necessary. Osteoporosis medication effects on fracture risk and BMD, dosing, and adverse effects and monitoring are described in **Tables 108-6**,[6,26,61] **108-7** (product prescribing information), and **108-8** (product prescribing information), respectively. Medication use should be combined with a bone-healthy lifestyle.

TABLE 108-6 Fracture and Bone Mineral Density Effects of Osteoporosis Medications from Pivotal Fracture Trials*a* in Postmenopausal Women

Medication	Vertebral Fracture	Nonvertebral Fracture	Hip Fracture	% Change in Spine BMD[b]	% Change in Hip BMD[b,c]
Abaloparatide	86%↓	43%↓	↔	10.4%↑	4.3%↑
Bazedoxifene	35%-40%↓	↔[d]	↔	2.2%↑	0.5%↑
Bazedoxifene with conjugated equine estrogens	ND	ND	ND	0.24%-1.6%↑	0.2%-1.5%↑
Bisphosphonates	40%-70%↓	25%-40%↓[e]	40%-53%↓[f]	4.3%-6.7%↑	2.8%-6.0%↑
Calcitonin	33%↓	↔	↔	3%↑	↔
Denosumab	68%↓	20%↓	40%↓	9.2%↑	6.0%↑
Estrogen with or without a progestogen	33%- 40%↓	13%-27%↓	30%-50%↓	3.5%-7%↑[f]	1.7%-5%↑[g]
Raloxifene	30%-68%↓[h]	↔	↔	2.6%↑	2.1%↑
Romosozumab	73%↓	25%↓	ND	13.3%↑	6.8%↑
Teriparatide	65%↓	53%↓	↔	8.6%-9.7%↑	3.5%↑

[a]Fracture reductions are relative risk reductions, no head to head fracture studies except for raloxifene and bazedoxifene, data should only be used for relative between class comparisons, clinical trials have different patient samples and study designs, most pivotal fracture trials were of 3-year duration except for abaloparatide (2 year), romosozumab (1 year) and teriparatide studies (18 months).

[b]Relative to placebo; may vary based on duration of therapy and timing relative to menopause.

[c]Total hip (alendronate, ibandronate, zoledronic acid, bazedoxifene, denosumab, estrogen, abaloparatide, teriparatide, romosozumab) or femoral neck (calcitonin, estrogen, risedronate, and raloxifene).

[d]50% decreases in nonvertebral fractures in subgroup of high-risk postmenopausal women (very low BMD and or previous fractures).

[e]Risedronate and zoledronic acid only; nonvertebral fracture reductions with ibandronate were not significant.

[f]Alendronate, risedronate, and zoledronic acid only; hip fracture data not reported with ibandronate.

[g]Data obtained from nonpivotal fracture trials.

[h]Plus data from a pivotal bazedoxifene trial with raloxifene as one of the comparators.

%, percent; BMD, bone mineral density; ↓, decrease; ↑, increase; ↔, no significant change; ND, no data.

Data from References 6, 26, and 61.

TABLE 108-7 Drug Dosing Table

Medication	Brand Name	Dose	Comments
Antiresorptive Medications—Nutritional Supplements			
Calcium	Various	Adequate daily intake: *IOM:* 200-1,200 mg/day, varies per age; see Table 108-5); supplement dose is the difference between required adequate intake and dietary intake. Immediate-release doses should be <500-600 mg.	Recommend food first to achieve goal intake. Available in different salts including carbonate and citrate, absorption of other salts not fully quantified. Different formulations including chewable, liquid, gummy, softgel, drink, and wafer; different combination products. Review package to determine number of units per serving size and desired amount of elemental calcium. Give calcium carbonate with meals to improve absorption.
Vitamin D D3 (cholecalciferol) D_2 (ergocalciferol)	Over the counter • Tablets, 400, 1,000, and 2,000 units • Capsules, 400, 1,000, 2,000, 5,000, and 10,000 units • Gummies, 300, 500, and 1,000 units • Drops, 300, 400, 1,000, and 2,000 units/mL or drop • Solution, 400 and 5,000 units/mL • Spray, 1,000 and 5,000 units/spray • Creams and lotions, 500 and 1,000 units per ¼ teaspoonful Prescription • Capsule, 50,000 units • Solution, 8,000 units/mL	Adequate daily intake: IOM: 400-800 units/day to achieve adequate intake (see Table 108-5); NOF: 800-1,000 units orally daily; if low 25(OH) vitamin D concentrations, malabsorption, or altered metabolism higher doses (>2,000 units daily) might be required. Vitamin D deficiency: 50,000 units orally once to twice weekly for 8-12 weeks; repeat as needed until therapeutic concentrations.	Vegetarians and vegans need to read label to determine if the vitamin D source is a plant-based product. Slight of D3 over D2 for increasing serum 25(OH) vitamin D concentrations. For drops, make sure measurement is correct for desired dose. Ability of sprays, lotions, and creams to resolve deficiencies or maintain adequate intakes is unknown.
Antiresorptive Prescription Medications			
Bisphosphonates			
Alendronate	Fosamax Fosamax Plus D Binosto (effervescent tablet)	Treatment: 10 mg orally daily or 70 mg orally weekly Prevention: 5 mg orally daily or 35 mg orally weekly	Generic available for daily and weekly tablet product. 70-mg dose is available as a tablet, effervescent tablet, or combination tablet with 2,800 or 5,600 units of vitamin D3. Administered in the morning on an empty stomach with 6-8 ounces (180-240 mL) of plain water. Do not eat and remain upright for at least 30 minutes following administration. Do not coadminister with any other medication or supplements, including calcium and vitamin D.
Ibandronate	Boniva	Treatment: 150 mg orally monthly, 3-mg intravenous quarterly Prevention: 150 mg orally monthly	Generics available. Administration instructions same as for alendronate, except must delay eating and remain upright for at least 60 minutes.
Risedronate	Actonel Atelvia (delayed-release)	Treatment and prevention: 5 mg orally daily, 35 mg orally weekly, 150 mg orally monthly	Generics available. 35-mg dose is also available as a delayed-release product. Administration instructions same as for alendronate, except delayed-release product is taken immediately following breakfast.
Zoledronic acid	Reclast	Treatment: 5-mg intravenous infusion yearly Prevention: 5-mg intravenous infusion every 2 years	Generic available. Can premedicate with acetaminophen to decrease infusion reactions. Contraindicated if CrCl <35 mL/min (0.58 mL/s). Also marketed under the brand name Zometa (4 mg) with different dosing for treatment of hypercalcemia of malignancy, multiple myeloma, and prevention of skeletal-related events from bone metastases from solid tumors.

RANK Ligand Inhibitor			
Denosumab	Prolia	Treatment: 60-mg subcutaneously every 6 months	Administered by a healthcare practitioner. Correct hypocalcemia before administration. Also marketed under the brand name Xgeva (70 mg/mL) with different dosing for treatment of hypercalcemia of malignancy, multiple myeloma, and prevention of skeletal-related events from bone metastases from solid tumors.
Estrogen Agonist/Antagonist and Tissue Selective Estrogen Complex			
Raloxifene	Evista	60 mg daily	Generic available.
Bazedoxifene with conjugated equine estrogens (CEE)	Duavee	20 mg plus 0.45 mg CEE daily	For postmenopausal women with a uterus; no progestogen needed. Bazedoxifene monotherapy available in some countries.
Calcitonin			
Calcitonin (salmon)	Fortical	200 units (1 spray) intranasally daily, alternating nares every other day.	Only available as a generic. Refrigerate nasal spray until opened for daily use, then room temperature. Prime with first use. Also available as a subcutaneous injection.
Formation Medications			
Recombinant human parathyroid hormone (PTH 1-34 units)			
Teriparatide	Forteo PF708 approved biosimilar; under investigation to determine therapeutic equivalence	20-mcg subcutaneously daily for up to 2 years	First dose sitting or lying. Refrigerate before and after each use. Use new needle with each dose. Inject in thigh or abdomen. Discard after 28 days or if cloudy.
Human parathyroid hormone–related peptide (PTHrP[1-34]) analog			
Abaloparatide	Tymlos	80-mcg subcutaneously daily for up to 2 years	First dose sitting or lying. Refrigerate before use then keep at room temperature. Use new needle with each dose. Inject in abdomen. Discard after 30 days.
Formation and Antiresorptive Medication			
Sclerostin inhibitor			
Romosozumab	Evenity	210-mg subcutaneously monthly for 1 year; administered as two single use 105-mg/1.17-mL prefilled syringes	Correct hypocalcemia before administration. Refrigerate. Leave at room temperature for at least 30 minutes before use. Provider administration, exploring patient administration. Inject in abdomen, thigh, or upper arm; preferably each injection at a different site.

IOM, Institute of Medicine; NOF, National Osteoporosis Foundation; NSAID, nonsteroidal anti-inflammatory drug.

Data from product prescribing information.

TABLE 108-8 Medication Monitoring Table

RANK Ligand Inhibitor			
Denosumab	Prolia	Treatment: 60-mg subcutaneously every 6 months	Administered by a healthcare practitioner. Correct hypocalcemia before administration. Also marketed under the brand name Xgeva (70 mg/mL) with different dosing for treatment of hypercalcemia of malignancy, multiple myeloma, and prevention of skeletal-related events from bone metastases from solid tumors.
Estrogen Agonist/Antagonist and Tissue Selective Estrogen Complex			
Raloxifene	Evista	60 mg daily	Generic available.
Bazedoxifene with conjugated equine estrogens (CEE)	Duavee	20 mg plus 0.45 mg CEE daily	For postmenopausal women with a uterus; no progestogen needed. Bazedoxifene monotherapy available in some countries.
Calcitonin			
Calcitonin (salmon)	Fortical	200 units (1 spray) intranasally daily, alternating nares every other day.	Only available as a generic. Refrigerate nasal spray until opened for daily use, then room temperature. Prime with first use. Also available as a subcutaneous injection.
Formation Medications			
Recombinant human parathyroid hormone (PTH 1-34 units)			
Teriparatide	Forteo PF708 approved biosimilar; under investigation to determine therapeutic equivalence	20-mcg subcutaneously daily for up to 2 years	First dose sitting or lying. Refrigerate before and after each use. Use new needle with each dose. Inject in thigh or abdomen. Discard after 28 days or if cloudy.
Human parathyroid hormone–related peptide (PTHrP[1-34]) analog			
Abaloparatide	Tymlos	80-mcg subcutaneously daily for up to 2 years	First dose sitting or lying. Refrigerate before use then keep at room temperature. Use new needle with each dose. Inject in abdomen. Discard after 30 days.
Formation and Antiresorptive Medication			
Sclerostin inhibitor			
Romosozumab	Evenity	210-mg subcutaneously monthly for 1 year; administered as two single use 105-mg/1.17-mL prefilled syringes	Correct hypocalcemia before administration. Refrigerate. Leave at room temperature for at least 30 minutes before use. Provider administration, exploring patient administration. Inject in abdomen, thigh, or upper arm; preferably each injection at a different site.

IOM, Institute of Medicine; NOF, National Osteoporosis Foundation; NSAID, nonsteroidal anti-inflammatory drug.

Data from product prescribing information.

The Endocrine Society guideline for postmenopausal women (2019),[96] American College of Physicians guideline for women and men (2017),[2] the American Association of Clinical Endocrinologists and American College of Endocrinology guideline for postmenopausal women (2016),[3] National Osteoporosis Foundation's clinician's guideline for women and men (2014),[1] and the Endocrine Society guideline for men (2012)[8] provide guidance on osteoporosis oprevention and treatment strategies. Older guidelines such as the North American Menopause Society position statement for postmenopausal women (2010)[6] and recent guidelines from the United Kingdom (2017)[14] and Europe (2019)[28] also provide insight into diagnosis and treatment.

Drug Treatments of First Choice

9 Combined with adequate calcium and vitamin D intakes, alendronate, risedronate, zoledronic acid, and denosumab are the prescription medications of choice because they reduce both hip and vertebral fracture risks.[3,96] Abaloparatide, bazedoxifene/conjugated equine estrogens, ibandronate, raloxifene, romosozumab, and teriparatide are alternatives since they decrease vertebral but not hip fracture risks. Calcitonin is last-line therapy. Estrogen and testosterone therapies are not used for osteoporosis treatment, but when prescribed for other conditions will have a positive bone effect. The algorithm (see Fig. 108-3) helps determine for whom medication therapy should be used.[1–3,46,96] In general, prescription therapy should be considered in any postmenopausal woman or man age 50 years and older presenting with a fragility fracture, osteoporosis, or low bone mass combined with a FRAX 10-year probability of hip fracture of 3% or more or a FRAX 10-year probability of any major osteoporosis-related fracture of 20% or more. The use of osteoporosis prescription medications in children, premenopausal women, and men younger than 50 years old occurs in special cases and is generally related to secondary medical and medication causes or genetic disorders.

Antiresorptive Therapies

Antiresorptive therapies include calcium, vitamin D, bisphosphonates, denosumab, estrogen agonists/antagonists (EAA), tissue selective estrogen complexes (TSEC), calcitonin, estrogen, and testosterone.

Calcium Supplementation

7 Calcium imbalance can result from inadequate dietary intake, decreased fractional calcium absorption, enhanced calcium excretion, and diseases and medications altering these processes. Adequate calcium intake (see Table 108-5) is considered a foundation for osteoporosis prevention and treatment in the guidelines and should be combined with vitamin D, especially when osteoporosis medications are taken.[1,3,8,28] If dietary intake cannot be increased to achieve adequate intake, calcium supplements can be used.

Efficacy Calcium generally maintains BMD, although small BMD increases (0.6%-1.8%) have been documented.[3,8] These BMD effects are less than those observed with other osteoporosis medications. The most recent USPSTF report states insufficient data to support using calcium and vitamin D supplementation to reduce fracture incidence.[59]

Adverse Events Calcium's most common adverse reaction, constipation, can first be treated with increased water intake, dietary fiber, and exercise. If still unresolved, smaller and more frequent administration or a lower total daily dose can be tried. Calcium carbonate can create gas and cause upset stomach. Calcium citrate, a formulation with fewer GI side effects, is often recommended if calcium carbonate is not tolerated.

Calcium supplementation when combined with vitamin D can increase the risk of kidney stone formation.[42,59] However, in some cases, calcium binds to oxalate in the gut, which decreases urinary oxalate excretion thereby decreasing kidney stones. Increased fluid intake and decreased salt intake might be warranted to prevent kidney stones. While previous concerns existed regarding calcium supplements slightly increasing coronary artery calcifications and cardiovascular disease events, a recent meta-analysis did not demonstrate a significant difference in cardiovascular events with calcium supplementation.[2,59]

Interactions Since calcium carbonate requires acid for disintegration, medications such as proton pump inhibitors and histamine type-2 receptor antagonists can decrease absorption from the carbonate product. Fiber laxatives can also decrease the absorption of calcium if given concomitantly. Calcium can decrease the oral absorption of some medications including iron, tetracyclines, quinolones, bisphosphonates, and thyroid supplements.

Dosing and Administration Many patients, especially those aged 60 years or older, do not ingest sufficient dietary calcium and therefore require supplements.

To ensure adequate calcium absorption, 25(OH) vitamin D concentrations should be at least 10 to 15 ng/mL (mcg/L; 25-37 nmol/L). Because fractional calcium absorption is dose-limited, maximum single doses of 500 to 600 mg or less of elemental calcium are recommended.[3] Despite this, slow-release and/or absorbable calcium formulations (eg, Citrical Slow Release 1200) are available in doses of 1,200 mg and advertised to be taken once daily. These high-dose products are sometimes as two 600-mg tablets that can be taken at different times. In addition, supplemental doses this high are usually not needed unless a severe dietary deficiency of calcium exists. Calcium carbonate is the salt of choice as it contains the highest amount of elemental calcium (40%) and is typically the least expensive. Calcium carbonate should be taken with meals, which increases gastric acidity resulting in product dissolution and disintegration. Calcium citrate (21% elemental calcium) has acid-independent absorption and does not need to be administered with meals. Although tricalcium phosphate contains 38% elemental calcium, calcium-phosphate complexes could limit overall calcium absorption. This product might be helpful in patients with hypophosphatemia that cannot be resolved with increased dietary intake.

Disintegration and dissolution rates vary significantly between products and lots. Products labeled United States Pharmacopeia “USP Verified” should be recommended. This indicates that the products have undergone the voluntary USP verification program, which ensures that the product contains the ingredients shown on the label at the stated strength/potency, and has been produced using safe, clean, and controlled manufacturing processes as specified by the USP and the US Food and Drug Administration (FDA). Products from unrefined oyster shell or coral calcium should not be recommended because of concerns for high concentrations of lead and other heavy metals. Some calcium products come in alternative dosage forms (eg, chewable tablets, dissolvable tablets, and liquid), which can be beneficial for select patients with issues such as swallowing large tablets. For all products, encourage patients to read the labeling carefully as the serving size is often more than just one tablet. In addition, product labeling sometimes recommends taking doses providing 1,000 to 1,200 mg/day, which often provides more calcium than needed to meet IOM requirements, even in patients with small amounts of dietary intake, and could exceed tolerable upper limits when dietary calcium intake is adequate.

Some commercial calcium supplements contain other nutrients associated with bone physiology such as magnesium, vitamin K, “natural estrogens,” or isoflavones. Minimal BMD and no fracture data exist for these combination products. These products are also typically more expensive. Additionally,

combining too many vitamins and supplements might exceed upper-tolerable nutrient limits and increase toxicities.

Vitamin D Supplementation

8 The IOM recommends adequate intakes of vitamin D from diet and/or supplementation for all ages (see Table 108-5).[53] Current osteoporosis guidelines recommend slightly higher vitamin D maintenances doses (800-2,000 units daily).[1,3,28]

The desired therapeutic range for vitamin D is controversial. The IOM defines 20 ng/mL (50 nmol/L; 1 ng/mL = 2.5 nmol/L) as the cut point for normal 25(OH) vitamin D, below which a patient would be considered deficient.[53] Current guidelines recommend treating patients with osteoporosis to a concentration of approximately 30 ng/mL (mcg/L; 75 nmol/L)[1] or 30 to 50 ng/mL (mcg/L; 75-125 nmol/L).[3] Concentrations higher than 50 to 60 ng/mL (mcg/L; 125-150 nmol/L) can be associated with adverse effects.[53]

Current evidence suggests that the major effects of vitamin D are achieved with 25(OH) vitamin D concentrations between 6 and 20 ng/mL (mcg/L; 15-50 nmol/L), including increasing calcium absorption (10-15 ng/mL [mcg/L; 25-37 nmol/L]) and decreasing BMD loss (up to 20 ng/mL [mcg/L; 50 nmol/L]).[62] Daily vitamin D doses of 500 to 700 units generally are sufficient to achieve vitamin D concentrations more than 20 ng/mL (mcg/L; 50 nmol/L), leading some experts to suggest the higher daily doses recommended in guidelines are not warranted. Other experts state not everyone achieves a 25(OH) vitamin D concentration greater than 30 ng/mL (mcg/L; 75 nmol/L), and therefore recommend 800 to 1,000 units[1] or 1,000 to 2,000 units[3,8] daily, especially in adults at high risk or with osteoporosis. Furthermore, since most products are inexpensive and safe, the higher recommended doses are appropriate. These higher recommendations are within the upper limit for vitamin D in adults, which is 4,000 units daily.

Serum 25(OH) vitamin D is the best indicator of total body vitamin D status.[1] Interassay variability exists; thus, the same laboratory should be used for repeat testing. Measurement of 25(OH) vitamin D concentration can be considered in anyone with high risk for low vitamin D, low bone density, history of a low-trauma fracture, frequent falls, unexplained muscle weakness, and/or bone pain.

Efficacy Supplemental vitamin D given at doses of 700 to 800 units per day has been shown to significantly reduce the incidence of both hip and nonvertebral

fractures.[3] Small increases in BMD, improvement in muscle strength, and improvement in balance have also been observed. Several studies have analyzed the effect of supplemental vitamin D on falls; however, the USPSTF recommends against the use of supplemental vitamin D specifically for fall prevention.[58]

Interactions Some medications can induce vitamin D metabolism including rifampin, phenytoin, barbiturates, valproic acid, and carbamazepine. Vitamin D absorption can be decreased by cholestyramine, colestipol, orlistat, and mineral oil. Vitamin D can enhance the absorption of aluminum; therefore aluminum-containing products should be avoided to prevent aluminum toxicity.

Dosing and Administration Dosing of supplemental vitamin D should be based on IOM adequate intakes (see Table 108-5), or to achieve a 25(OH) vitamin D concentration of ≥30 ng/mL (mcg/L; 75 nmol/L), especially in those with osteoporosis.[1,3] Almost 30% of older adults have hypovitaminosis D (≤20 ng/mL [mcg/L; 50 nmol/L]), with higher prevalence in Blacks (72%) and Hispanics (43%).[56] Replacement doses will first be required in these patients before recommended maintenance doses.

Vitamin D can be taken as a single-agent or combination product. Supplements and multivitamins contain vitamin D3 or D2. Synthesized vitamin D3 can be made from irradiated sheep's wool and vitamin D2 from irradiated mushrooms. Guidelines suggest either for prevention and treatment of vitamin D deficiency. Higher-dose prescription vitamin D regimens administered weekly, monthly, or quarterly can be used for replacement therapy.[1,3] For example, one strategy is 50,000 units given once weekly for 8 to 12 weeks, or until the 25(OH) vitamin D concentration reaches 30 ng/mL (mcg/L; 75 nmol/L), followed by 1,000 to 2,000 units daily to maintain this concentration. More than one multivitamin or large doses of cod liver oil daily are no longer advocated because of the risk of hypervitaminosis A, which can increase bone loss. Because the half-life of vitamin D is about 1 month, approximately 3 months of therapy are required before a new steady state is achieved and a repeat 25(OH) vitamin D concentration should be obtained to assess efficacy of therapy.

Individuals with deficient concentrations of vitamin D are at risk for osteomalacia, a condition that can be mistaken for osteoporosis, which is characterized by decreased mineralization or "softening" of bone matrix.[28] In patients who are pregnant, obese, or with disorders (eg, celiac disease, cystic fibrosis, Crohn's disease, chronic kidney disease) or medications (eg, anticonvulsants, glucocorticoids, antifungals, and antiretroviral medications used

in treatment of acquired immunodeficiency syndrome) affecting vitamin D absorption and/or metabolism, higher doses and more frequent monitoring might be required.

Bisphosphonates

9 Alendronate, risedronate, and intravenous zoledronic acid are approved by the FDA for postmenopausal, male, and glucocorticoid-induced osteoporosis. Intravenous and oral ibandronate and some specialized oral formulations of other bisphosphonates are indicated only for postmenopausal osteoporosis.

Pharmacology Bisphosphonates mimic pyrophosphate, an endogenous bone resorption inhibitor.[63] Bisphosphonate antiresorptive activity results from blocking prenylation and inhibiting guanosine triphosphatase-signaling proteins, which lead to decreased osteoclast maturation, number, recruitment, bone adhesion, and life span.

Pharmacokinetics Oral bisphosphonate bioavailability is less than 1%; and is greatly decreased with concomitant food and beverages.[63,64] Within 24 hours of administration, bisphosphonates undergo rapid skeletal uptake and any medication not incorporated into bone is renally excreted. Elimination decreases linearly with declining renal function. Incorporation into bone gives bisphosphonates long biologic half-lives of up to 10 years. Bisphosphonates differ in the strength of binding to bone (zoledronic acid greater than alendronate which is greater than ibandronate which is greater than risedronate) with zoledronic acid having the greatest bone absorption and longest bone retention.

Efficacy Bisphosphonates consistently provide fracture risk reduction and BMD increases (see Table 108-6) with noted difference in sites of fracture reduction between agents. Fracture clinical trial data are from daily oral bisphosphonate or annual intravenous therapy, not weekly, monthly, or quarterly regimens.[64] Bisphosphonate comparative fracture prevention trials do not exist. Hip-fracture reduction has not been demonstrated with daily oral ibandronate; however, the study might have been underpowered.[3] Because of the lack of hip-fracture reduction data, ibandronate is not a first-line therapy (see Fig. 108-3). Annual intravenous zoledronic acid has documented secondary fracture prevention and a decrease in mortality when given after a first hip fracture.[10] Administration of intravenous zoledronic acid at an extended 18-month interval in women 65 years of age or older with osteopenia also decreased both vertebral and nonvertebral fractures over 6 years.[65]

Bone turnover reaches an equilibrium with a lower rate of bone turnover evident within 3 to 6 months of starting therapy, which results in BMD increases and a reduced fracture risk seen within the first 6 to 12 months.[26,64] For all bisphosphonates, increases in BMD are typically greater at the spine than at the hip.[26] Small increases in BMD continue for 4 to 5 years before plateauing. After discontinuation, the increased BMD is sustained for a prolonged period of time that varies based on different binding affinities of the individual bisphosphonates.[51] Because of the sustained effects, drug holidays can be considered for bisphosphonates.

The BMD increases with alendronate, risedronate, zoledronic acid, and oral ibandronate in men are similar to those in postmenopausal women.[8,13] Because of a lack of fracture data from pivotal trials in men, bisphosphonates are only FDA indicated to increase BMD, not to reduce fracture risk in men. A meta-analysis combining data from published randomized controlled trials showed reductions in vertebral and nonvertebral fractures in men.[50]

Adverse Effects Oral bisphosphonates are well tolerated if patients are selected for therapy appropriately and the patient takes them correctly (see Table 108-8).[3,15] Patients with creatinine clearances (CrCl) less than 30 to 35 mL/min (0.50-0.58 mL/s), who have serious GI conditions (abnormalities of the esophagus that delay emptying, such as stricture or achalasia), or who are pregnant should not take bisphosphonates. Some evidence suggest bisphosphonates can be used in select patients with age-related decline in renal function without added adverse effects.[63]

GI complaints, including heartburn and dyspepsia, are one of the most common reasons cited by patients for discontinuing therapy.[3,64] While these mild GI effects are common, bisphosphonates are also associated with rare severe GI events, such as esophageal erosion, ulcer, or GI bleeding. If GI adverse events occur, switching to a different bisphosphonate or less frequent administration schedule might resolve the problem. Patients should be encouraged to discuss GI complaints with a healthcare provider. Intravenous zoledronic acid or ibandronate can be used for patients with GI contraindications or intolerances to oral bisphosphonates. Other common bisphosphonate adverse effects include injection reactions and musculoskeletal pain. If severe musculoskeletal pain occurs, the medication can be discontinued temporarily or permanently. Acute phase reactions (eg, fever, flu-like symptoms, myalgias, and arthralgias) are typically associated with intravenous administration, but rarely reported with oral bisphosphonates. This reaction usually diminishes with subsequent

administration.

Rare adverse effects include osteonecrosis of the jaw (ONJ) and subtrochanteric femoral (atypical) fractures.[64,66] ONJ occurs more commonly in patients with cancer, receiving higher-dose intravenous bisphosphonate therapy and other risk factors including glucocorticoid therapy and diabetes mellitus. In osteoporosis, the incidence of ONJ is 0.001% to 0.01%, which is slightly higher than the incidence in the general population (0.001%). Maxillary or mandibular bone surgery and poor oral hygiene are dental-specific risk factors for development of ONJ. When possible, major dental work should be completed before bisphosphonate initiation. For patients already on therapy, some practitioners withhold bisphosphonate therapy during and after major dental procedures, but no data exist to support any benefit of such practice.[3] Atypical femoral shaft fractures are rare; some evidence suggests the risk could increase with longer duration of bisphosphonate use.[64] Since some patients with atypical fracture experience prodromal thigh or hip pain, any such pain should be evaluated.

Interactions Because of poor bioavailability, oral bisphosphonates should not be administered at the same time as other medications. The administration instructions described below should be followed.

Dosing and Administration Because bioavailability is very poor for bisphosphonates (less than 1%) and to minimize GI side effects, each oral tablet should be taken with at least 6 ounces (~180 mL) of plain water (not coffee, juice, mineral water, or milk) at least 30 minutes (60 minutes for ibandronate) before consuming any food, supplements (including calcium and vitamin D), or medications (see Table 108-7). The patient should also remain upright (ie, either sitting or standing) for at least 30 minutes after alendronate and risedronate and 1 hour after ibandronate administration. For patients with swallowing difficulties (eg, stroke and tube feeding), an effervescent tablet form of alendronate, which is dissolved in 4 ounces (~120 mL) of room temperature water, could be used. This formulation has the same food restrictions as traditional oral tablets. In contrast, delayed-release risedronate is available and it is administered immediately following breakfast with at least 4 ounces (~120 mL) of plain water. A patient who misses a weekly dose can take it the next day. If more than 1 day has lapsed, that dose is skipped. If a patient misses a monthly dose, it can be taken up to 7 days before the next administration.

Before intravenous bisphosphonates are used, the patient’s serum calcium concentration must be normal. Serum creatinine should be monitored before

each dose of zoledronic acid. The intravenous products need to be administered by a healthcare provider. The quarterly ibandronate injection is given intravenously over 15 to 30 seconds or can be diluted and given with a syringe pump. Zoledronic acid should be infused once yearly over at least 15 minutes with a pump. Acetaminophen can be given to decrease acute phase reactions.

Although these medications are effective, adherence is poor and results in decreased effectiveness.[10,64] Adherence is improved with once-weekly bisphosphonate administration over daily therapy; however, it is unclear if once-monthly therapy improves adherence more. While dosing frequency is a common barrier to adherence, adverse effects and concerns about adverse effects remain important predictors of adherence and persistence. Using decision aids in discussions about medication therapy choices and periodic follow-up with a healthcare professional could improve adherence and persistence to therapy. These decision aids help to visually display the pros of bisphosphonate therapy (ie, fracture avoidance) to the cons (ie, adverse effects) based on an individualized fracture risk (eg, https://osteoporosisdecisionaid.mayoclinic.org/). To help overcome the barrier associated with dosing frequency, intravenous ibandronate and zoledronic acid could be used as replacements if cost is not an issue, which is less of a concern with generic medication availability.[67]

Duration The ideal duration of bisphosphonate therapy is not known. Bisphosphonates are deposited into the bone and continue to suppress bone turnover after discontinuation, and some adverse effects, such as atypical fracture, are associated with duration of therapy.[51] To balance risk and benefit, some clinicians recommend a “bisphosphonate holiday,” defined as disruption of therapy during which medication effects exist with a plan for medication reinstitution. Two randomized, double-blind studies with a bisphosponate holiday after therapy with alendronate for 5 years or zoledronic acid for 3 years showed a continued fracture benefit after discontinuation of therapy. Because a beneficial response was predicted by hip T-score, experts recommend that a bisphosphonate holiday could be considered in postmenopausal women after 5 years of oral bisphosphonates or 3 years of intravenous bisphosphonates if no significant fracture history, hip BMD T-score is above –2.5, and fracture risk is not high.[96] In women with a high-fracture risk or lower hip BMD T-scores, continuing oral bisphosphonates for 10 years or intravenous bisphosphonates for 6 years should be considered. These recommendations are based on limited data and questions remain regarding what therapy to reinitiate and the applicability of this approach for men and patients with glucocorticoid-induced osteoporosis. Bisphosponate holidays should last for 5 or fewer years with BMD and patient

assessment done every 2 to 4 years.[96]

Denosumab

9 Denosumab is FDA indicated for treatment of osteoporosis in women and men at high risk for fracture. It is also approved for glucocorticoid-induced osteoporosis and to increase bone mass in men receiving androgen deprivation therapy for nonmetastatic prostate cancer and in women receiving adjuvant aromatase inhibitor therapy for breast cancer who are at high risk for fracture.

Pharmacology Denosumab is a fully human monoclonal antibody that binds to RANKL, blocking its ability to bind to its RANK receptor on the surface of osteoclast precursor cells and mature osteoclasts.[68] Denosumab inhibits osteoclastogenesis and increases osteoclast apoptosis.

Pharmacokinetics Following subcutaneous injection, rapid suppression of bone turnover occurs within 12 hours.[68,69] Denosumab achieves peak concentration in approximately 10 days. The half-life is approximately 25 days and the concentration slowly declines over a period of 4 to 5 months. The medication does not accumulate with repeated dosing at 6-month intervals. No dosage adjustment is necessary in renal impairment; however, hypocalcemia is more common in severe renal impairment.[68] No studies have been conducted in hepatic impairment.[69]

Efficacy Over 3 years, denosumab significantly decreased vertebral fractures, nonvertebral fractures, and hip fractures in postmenopausal women with low bone density (see Table 108-6).[26] Continued increases in BMD are demonstrated with long-term treatment with no plateau in the effects on BMD over 10 years. For postmenopausal women previously treated with oral bisphosphonates, switching to denosumab for 1 year provided greater increases in BMD at the spine and hip over switching to zoledronic acid; however, fracture outcomes are unknown. Denosumab is not incorporated into bone. Upon medication discontinuation, a rapid increase in bone turnover above baseline is noted with a corresponding increase in the vertebral fracture rate. Therefore, for those with high fracture risk, denosumab therapy should be continued or alternative antiresorptive therapy (ie, bisphosphonate) should be initiated if denosumab is discontinued.[15,26]

Adverse Events In trials up to 10 years in duration, denosumab was generally well tolerated (see Table 108-8).[26] Dermatologic reactions not specific to the

injection site such as dermatitis, eczema, and rashes were more common than with placebo.[15] Serious infections were noted in initial clinical trials, although an increased incidence has not been noted in long-term, follow-up trials.[15,68]

As with bisphosphonates, rare, serious adverse effects from bone turnover suppression have been reported with denosumab including ONJ and atypical femoral fracture.[68] Major dental work should be completed before use when possible. Hypocalcemia can occur and any existing hypocalcemia should be corrected prior to use. Severe hypocalcemia is more common in patients with underlying kidney dysfunction and the manufacturer recommends monitoring of serum calcium, magnesium, and phosphorus within 14 days of administration in those with a CrCl less than 30 mL/min (0.50 mL/s).

Interactions No interactions have been identified with denosumab.

Dosing and Administration Denosumab is administered subcutaneously in the upper arm, upper thigh, or abdomen by a healthcare professional including pharmacists in some states. The product is available as a refrigerated prefilled syringe that can be stored at room temperature up to 14 days before administration (see Table 108-7).

Duration After 5 to 10 years of therapy, patients should be reevaluated for medication continuation, discontinuation, or switching to a different medication.[96]

Mixed Estrogen Agonists/Antagonists and Tissue Selective Estrogen Complexes

Raloxifene is a second-generation mixed estrogen agonist/antagonist (EAA; previously known as a selective estrogen receptor modulator, or SERM) approved by the FDA for prevention and treatment of postmenopausal osteoporosis and for reducing the risk of invasive breast cancer in postmenopausal women with and without osteoporosis. Bazedoxifene is a third-generation EAA combined with conjugated equine estrogens (CEE) making it a tissue selective estrogen complex (TSEC) that is approved by FDA for prevention of postmenopausal osteoporosis and vasomotor menopausal symptoms.[70,71] Raloxifene's breast cancer–prevention benefits make this medication desirable for younger postmenopausal women at risk for or with osteoporosis and breast cancer. Bazedoxifene with CEE is a good choice for younger postmenopausal women with menopausal symptoms at risk for

osteoporosis.

Pharmacology EAAs bind with α- and β-estrogen receptors and coactivators or corepressors to cause varying agonist or antagonist effects at different tissue sites.[70] Raloxifene is an agonist at bone receptors and antagonist at breast receptors and has minimal effect on the uterus. Bazedoxifene is an agonist at bone, and antagonist at the uterus and breast; however, it has no breast cancer prevention effects.

Pharmacokinetics Food has a nonsignificant effect on absorption, which is about 2% for raloxifene and 6% for bazedoxifene due to extensive presystemic glucuronidation. Raloxifene is 95% protein bound. The half-life of raloxifene is 28 hours and of bazedoxifene is 30 hours. EAAs are predominantly metabolized via glucuronidation and eliminated in the feces.

Efficacy Raloxifene and bazedoxifene decrease vertebral but not hip fractures.[70,72] In a post hoc analysis of the Multiple Outcomes with Raloxifene Evaluation trial, raloxifene decreased nonvertebral fractures in postmenopausal women with the most severe vertebral fractures at baseline and in a subgroup of high-risk postmenopausal women. Bazedoxifene decreased nonvertebral fractures. The fracture prevention effects of bazedoxifene combined with CEE are not known. EAAs increase spine and hip BMD, but to a lesser extent than bisphosphonates (see Table 108-6). Raloxifene's vertebral fracture prevention is greater in women without previous fracture. Bazedoxifene's BMD increases are greater than with raloxifene, but vertebral fracture prevention rates are similar. Bazedoxifene with CEE produced significantly greater increases in spine and hip BMD than raloxifene and placebo.[70,71] Raloxifene 7- and 8-year data and bazedoxifene 5- and 7-year data support long-term effects. After discontinuation, however, the medication effect is lost, with bone loss returning to age- or disease-related bone loss rates. EAAs have a positive impact on the lipid profile but have not demonstrated a benefit on cardiovascular disease.[70–72]

Adverse Events Hot flushes are common with raloxifene but decreased with bazedoxifene with CEE (see Table 108-8).[70–72] Raloxifene rarely causes endometrial thickening and bleeding; bazedoxifene decreases these adverse events making progestogen therapy unnecessary when it is combined with CEE. Leg cramps and muscle spasms are also common with both medications. Thromboembolic events are uncommon (less than 1.5%), but can be fatal. In large trials, no change in overall death, cardiovascular death, or overall stroke incidence was seen with raloxifene; however, a slight increase in fatal stroke

(0.7/1,000 women–year difference) was documented, which resulted in a boxed warning for raloxifene.[70] Fatal stroke with raloxifene occurred most frequently in women with an increased risk of stroke at baseline. Bazedoxifene with CEE also has all the adverse effects listed for estrogens as a class including increased thromboembolic events.

Interactions Because of raloxifene's highly protein bound nature (95%), when given concomitantly with other highly protein bound medications, like warfarin, a potential for binding interactions exists and, therefore, monitoring of both medications is suggested. Cholestyramine can decrease raloxifene absorption. Rifampin, phenytoin, carbamazepine, and phenobarbital can decrease bazedoxifene concentrations by inducing intestinal and liver uridine diphosphate glucuronosyltransferase (UGT) metabolism. Estrogen metabolism is decreased with CYP3A4 inhibitors.

Dosing and Administration EAAs/TSECs are administered orally once daily (see Table 108-7). They are contraindicated for women with an active or past history of venous thromboembolic disease, pregnancy, or childbearing potential. Therapy should be stopped if a patient anticipates extended immobility. Women at high risk for a stroke or coronary events and those with known coronary artery disease, peripheral vascular disease, atrial fibrillation, or a prior history of cerebrovascular events might not be good candidates for EAAs/TSECs. These medications should be used with caution in patients with severe liver impairment or moderate-to-severe renal impairment due to a lack of data. Bazedoxifene with CEE has all the contraindications and precautions for estrogens as a class.

Calcitonin

9 Calcitonin is FDA indicated for osteoporosis treatment for women who are at least 5 years past menopause. While an FDA Advisory Committee Panel voted against continued calcitonin use for postmenopausal osteoporosis, it remains on the market for patients in which alternative therapies are not appropriate.[73] Only vertebral fractures have been documented to decrease with intranasal calcitonin therapy (see Table 108-6).[6] Recent meta-analyses have revealed a weak relationship between calcitonin and cancer with no consistency in dose–response relationship or cancer cell line. While evidence was insufficient to establish the risk of cancer, due to a lack of efficacy calcitonin is considered a last-line therapy.[3] Intranasal calcitonin might provide some short-term pain relief to some patients with acute vertebral fractures.

Dosing and Administration Some patients do not like to administer medications intranasally (see Table 108-7). In clinical trials of calcitonin, a high dropout rate exists. If the nasal product is used for vertebral fracture pain, calcitonin should be prescribed for short-term (4 weeks) treatment and should not be used in place of other more effective and less-expensive analgesics nor should it preclude the use of more appropriate osteoporosis therapy.

Hormone Therapies

Estrogens were the first FDA-indicated medications for prevention of osteoporosis for women at significant risk and for whom other, nonestrogen osteoporosis medications cannot be used.[3] However, based on the Women's Health Initiative trial results about estrogen harms, these agents are not generally used solely for osteoporosis.

Hormone therapies will have positive bone effects when used for other indications.[6,74] Estrogen therapy can be a good choice for women going through early menopause when protection against bone loss is needed in addition to reduction of vasomotor symptoms, reserving other anti-osteoporosis therapy until treatment is reassessed closer to the average age of menopause.[6] Testosterone is used to treat hypogonadism in men, but an osteoporosis medication should be added when risk for osteoporotic fracture is high.[8] A complete discussion of adverse events, drug interactions, dosing, and administration for estrogen and testosterone products for women can be found in Chapter 98, "Hormone Therapy in Women," and for testosterone products for men in Chapter 99, "Erectile Dysfunction."

Estrogen In women, estrogens with or without a progestogen significantly decrease fracture risk and bone loss (see Table 108-6).[1,3,6] Oral and transdermal estrogens at equivalent doses and continuous or cyclic hormone therapy regimens have similar BMD effects. Effect on BMD is dose dependent, with some benefit seen with lower estrogen doses. Fracture risk reduction has not been demonstrated with the lower doses. When estrogen therapy is discontinued, bone loss accelerates and fracture protection is lost.

Testosterone No fracture data are available, but some data support minor bone loss prevention for testosterone use in men and women.[6,8,45]

Formation Medications

Parathyroid Hormone Analogs

9 Abaloparatide is an analog of PTHrP and teriparatide and the biosimilar PF708 are analogs of PTH. These agents are FDA indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture defined as multiple risk factors for fracture, a history of osteoporotic fracture, or failed or intolerant to other therapies. Teriparatide is additionally FDA indicated for men with idiopathic or hypogonadal osteoporosis who are at high risk for fracture, men intolerant to other osteoporosis medications, and patients with glucocorticoid-induced osteoporosis. Patients who have a history of osteoporotic fracture, multiple risk factors for fracture, very low bone density (eg, T-score less than –3.5), or have failed or are intolerant of previous bisphosphonate therapy could be candidates for PTH analog therapy.[3,75]

Pharmacology Teriparatide is a recombinant human product representing the first 34 amino acids in human PTH.[75,76] Unlike continuous PTH effects from primary hyperparathyroidism that can decrease BMD, when administered intermittently (ie, subcutaneously once daily) teriparatide increases bone formation with a minor increase in bone resorption for a net anabolic effect. Abaloparatide is a synthetic analog of PTHrP sharing the first 22 amino acids but with differing amino acids at positions 23–34. While both agents bind to the PTH type I receptor, abaloparatide binds with higher affinity to the RG confirmation, which results in an increased anabolic effect. Further, abaloparatide demonstrates less of an effect on activating bone resorption and remodeling than teriparatide. With both medications bone mass is improved. Teriparatide also demonstrated increased surface mineralization suggesting increased osteoblast activity.

Pharmacokinetics Bioavailability for teriparatide and abaloparatide are 95% and 36%, respectively. The peptides are cleared through hepatic and extrahepatic pathways, with a half-life of 1 hour and 1.7 hours, respectively. Increases in the area under the curve are noted with decreasing renal function but there are no dosage adjustments noted in renal insufficiency. No studies have been performed in hepatic impairment. Alternative delivery formulations are being investigated.[76]

Efficacy Two years of teriparatide or abaloparatide reduce vertebral and nonvertebral fracture risk in postmenopausal women (see Table108-6).[6,26] Compared with alendronate, teriparatide has demonstrated reductions in vertebral fracture rates in patients taking glucocorticoids; however, no reductions

in nonverterbral fractures were evident.[77] Lumbar spine BMD increases are greater than with antiresorptive agents. Observational data for teriparatide suggest a similar fracture benefit in men while no data are available regarding abaloparatide use in men.[13] Discontinuation of parathyroid hormone analog therapy results in a decrease in BMD, which can be alleviated with subsequent antiresorptive therapy.[76] PF708 is biosimilar to teriparatide with investigations ongoing to determine therapeutic equivalency.

Adverse Events Transient hypercalcemia can occur and is less common with abaloparatide than with teriparatide (3.4% vs 6.4%, respectively) (see Table 108-8).[14,15,75,76] Because of an increased incidence of osteosarcoma in rats, both medications contain a box warning against use in patients at increased baseline risk for osteosarcoma (eg, Paget's bone disease, unexplained elevations of alkaline phosphatase, pediatric patients, young adults with open epiphyses, or patients with prior radiation therapy involving the skeleton). This adverse effect has not been seen in people.

Interactions An increased calcium concentration could be a concern if on digoxin therapy.

Dosing and Administration Teriparatide and abaloparatide are commercially available as a prefilled pen delivery device (see Table 108-7). A daily subcutaneous injection is delivered to the abdominal area with site rotation. Teriparatide can also be given in the thigh. The administration of the first dose should take place with the patient either sitting or lying down in case orthostatic hypotension occurs. Both medications should be stored in the refrigerator before first use. After first use, abaloparatide can be kept at room temperature for up to 30 days. In contrast, teriparatide must be returned for storage in the refrigerator after each use and special precautions must be taken for travel. The teriparatide pen should be discarded after 28 days. Due to the theoretical risk for osteosarcoma, these medications should not be used for more than 2 years cumulatively in a patient's lifetime. Suboptimal adherence is documented to decrease efficacy.

Besides the conditions listed above, parathyroid hormone analogs should not be used in patients with hypercalcemia, metabolic bone diseases other than osteoporosis, metastatic or skeletal cancers, or premenopausal women of childbearing potential.

Formation and Antiresorptive Medication

Romosozumab

9 Romosozumab is FDA indicated for postmenopausal women at high risk for fracture defined as multiple risk factors for fracture, a history of osteoporotic fracture, or failed or intolerant to other therapies.

Pharmacology Romosozumab is a humanized monoclonal antibody that binds to sclerostin to prevent inhibition of bone formation and decrease bone resorption, an activity that separates this medication from other anabolic medications.[40,61] By binding sclerostin, Wnt signaling can continue to increase gene transcription, which results in increased osteoblast synthesis, differentiation, and bone matrix building. This medication inhibits bone resorption by decreasing RANKL and m-CSF and increasing OPG.

Pharmacokinetics About 50% to 70% of a dose is absorbed.[61] Peak serum concentrations after subcutaneous administration are reached within 3 to 4.5 days, with no accumulation with subsequent doses. Romosozumab has a half-life of 6 to 7 days.[78]

Efficacy After 1 year of romosozumab, vertebral fractures are statistically decreased by 73%, with a nonsignificant decrease in nonvertebral fractures by 25% in postmenopausal women (see Table 108-6).[61] Fracture prevention was higher if the Latin American female study participants were removed from the multicountry study analysis because this cohort had lower fracture rates even in the placebo arm. Fracture risk was also decreased by 48% for vertebral fractures, 19% for nonvertebral fractures and 38% for hip fractures after 1 year of romosozumab followed by 1 year of alendronate. Lumbar spine and hip BMD statistically increased after one year of romosozumab treatment. To prevent BMD loss after discontinuation, 1 year of denosumab or alendronate after romosozumab resulted in BMD continuing to increase at both sites. Vertebral, femoral neck, and hip BMD and hip bone strength increased after romosozumab therapy in postmenopausal women who had received at least 3 years of prior bisphosphonate therapy.[79] These BMD increases were not as large as reported in bisphosphonate naïve women but were greater than teriparatide therapy BMD effects after bisphosphonate therapy. Romosozumab increased BMD in men by 12.1% at the lumbar spine, 2.5% total hip, and 2.2% femoral neck, all significantly different than placebo after 1 year of therapy.[7] Fracture data were not captured in men.

Adverse Effects Headache and arthralgia were the most common adverse

effects, followed by hypercalcemia (<1%) (see Table 108-8).[61,79] Mild injection site irritation occurred in 6% to 8% of patients.[7,61,79] Romosozumab antibodies developed in 10% to 20% patients, sometimes being transient. The antibodies generally are not neutralizing antibodies nor did they alter efficacy. Serious cardiovascular events have been reported in a few trials, but the incidence is low (<2.5%) and not much higher nor significantly different from the alendronate treatment arm (1.9%) in postmenopausal women at 1 year; increasing to 6.5% and 6.1%, respectively after both arms were switched to alendronate for year 2.[61] In men the cardiovascular event rates were 4.9% in men receiving romosozumab versus 2.5% receiving placebo.[7] Myocardial infarction, stroke, and cardiovascular death are listed as a boxed warning. Romosozumab should not be used within one year of a myocardial infarction or stroke and benefit risk evaluation should be conducted in patients at risk for these conditions or with these conditions in their past medical history. Rare cases of ONJ and atypical femoral fractures have been reported. Because Wnt signaling is also related to malignancies, the medication-induced increased activity could be a concern; however, this adverse effect has not been identified in the premarketing clinical trials.

Interactions None

Dosing and Administration The medication comes as two prefilled syringes refrigerated until consecutively administered by a healthcare provider into two different sites (see Table 108-7). Patient self-administration is being explored.

Sequential and Combination Therapy

9 In sequential therapy, an anabolic agent is given first to increase bone remodeling units and bone mass, followed by an antiresorptive agent to continue with bone formation.[80] Although this sequential therapy is recommended in the guidelines, in practice this regimen is generally reserved for patients with severe osteoporosis because of the cost of anabolic agents.[1] Starting with an antiresorptive first and then switching to teriparatide results in lower BMD increases. However, this therapy will be used, especially for patients who have fractured or continue to lose bone mass while on antiresorptive therapy. Small increases in BMD can be seen when switching from an oral bisphosphonate to denosumab. This sequential therapy can be used during a bisphosphonate drug holiday or for bisphosphonate treatment failures (no BMD changes or fracture).

Because of no documented fracture benefit, increased cost, concern for dual

suppression of bone turnover, and potential for more adverse effects, combination therapy is rarely used.[3,80] Combination therapy of two antiresorptive agents or two anabolic agents did not increase bone mass compared to monotherapy even though they have different pharmacologic properties. Combination of teriparatide with oral bisphosphonates resulted in less BMD gains than monotherapy, and thus is not used. Teriparatide and denosumab combined did result in greater hip BMD effects, but long-term results are generally similar to sequential therapy. Estrogen therapy combined with a bisphosphonate did not increase bone mass further than monotherapy, so bisphosphonates can be initiated after estrogen discontinuation to help negate the accelerated bone loss that occurs once estrogen is stopped. However, sometimes they will be used concomitantly because they are treating different conditions. When raloxifene is used for breast cancer prevention, sometimes another antiresorptive agent will be prescribed, especially if hip fracture risk is high.

SPECIAL POPULATIONS

Osteoporosis is a particular threat in some subgroups because of age, genetic abnormalities, diseases, and medications.

Children and Adolescents

6 Osteoporosis in children and adolescents is uncommon but can lead to significant pain, deformity, and chronic disability. Pediatric osteoporosis is due to genetic disorders such as osteogenesis imperfecta and idiopathic juvenile osteoporosis, or secondary causes including growth hormone deficiency and glucocorticoid use (see Tables 108-2 and 108-3).[16,18,27,81] Female athlete triad and anorexia nervosa, which are common in this age group, can lead to osteoporosis and fractures.

The diagnosis and treatment of osteoporosis in children and adolescents are challenging.[18,48] Low bone mass is defined as a Z-score of −2.0 or less (adjusted for gender, age, and race/ethnicity) using central DXA of the spine or total body. Ability to lie still during the test and radiation doses of some tests create concerns for this age group. An osteoporosis diagnosis requires a DXA Z-score of −2.0 or less and 2 long-bone fractures by age of 10 or 3 long-bone fractures by the age of 19.

The first management step is correcting any underlying causes and instituting a bone-healthy lifestyle, which also includes weight gain for anorexia nervosa

and decreased exercise intensity for those with the female athlete triad.[16,81] Pharmacologic treatment has been used for children and adolescents with low bone mass and fragility fractures.[18] Growth hormone can be helpful in children with a documented deficiency but has no effect without an underlying deficit. The optimal osteoporosis medication, dose, and duration of therapy are unknown, and more safety data are needed. A major concern with bisphosphonates is their effect on longitudinal bone growth and modeling; however, fracture healing, skeletal growth/maturation, or the appearance of growth plates does not appear to be impaired. Because bisphosphonates are released from bone for many years and cross the placenta, teratogenic effects are also a concern. Teriparatide has a box warning for children due to a concern for osteosarcoma. Pediatric experience with denosumab is limited but positive. Newer agents have not been evaluated in pediatric patients.

Premenopausal Women

6 Clinically significant bone loss and fractures in healthy premenopausal women are rare. Risk factors are similar between premenopausal and postmenopausal osteoporosis.[34,43] While bone loss occurs during pregnancy and lactation, it is usually gained back 6 to 12 months after breastfeeding is complete. Fifty percent to 90% of premenopausal women with osteoporosis have a secondary cause (see Tables 108-2 and 108-3) for the bone loss. Common secondary causes in this group are amenorrhea, anorexia nervosa, glucocorticoid use, and celiac disease. A retrospective review reported a normal BMD in 28% of premenopausal women suffering low-trauma fractures. Premenopausal fractures predict postmenopausal osteoporotic fractures.

Routine bone density screening should not be performed in healthy premenopausal women.[34,48] Premenopausal women with known osteoporosis risk factors and low-trauma fractures can undergo central DXA examinations. In this case, the Z-score is used, with Z-scores of −2.0 or less defined as bone mass below the expected range for age. The categorization of osteopenia or osteoporosis based on T-score alone should be avoided in premenopausal women unless there is a history of low-trauma fracture or a secondary cause of osteoporosis.

Pharmacologic therapy for osteoporosis should be used with caution in premenopausal women as efficacy and safety have not been adequately demonstrated.[34,43] All premenopausal women should practice a bone-healthy lifestyle. Secondary causes of bone loss should be resolved. For example,

gaining weight and resumed menses are more effective in correcting bone loss secondary to anorexia nervosa than oral contraceptives. If the contributing factor cannot be eliminated, for example, chemotherapy or glucocorticoids, pharmacological therapy can be considered. Women with an unidentified cause for osteoporosis and no history of fracture should be treated with a bone-healthy lifestyle and watchful waiting.

Osteoporosis medication safety during pregnancy and breastfeeding have not been determined. A theoretical concern is risk for fetal harm with pregnancies that occur during and after bisphosphonate therapy due to the long half-lives of these agents and the potential for fetal exposure after therapy is discontinued. While some data suggest that use prior to conception and during the first trimester of pregnancy is safe, bisphosphonates are generally not used in women of childbearing age. Sometimes bisphosphonates are prescribed along with contraceptive agents to reduce the likelihood of becoming pregnant during therapy.[16,17]

Older Adults

Although osteoporosis, osteoporotic fractures, and postfracture morbidity and mortality increase with age, osteoporosis is underdiagnosed and undertreated in older adults.[44] More than 50% of women older than 75 years old have osteoporosis.[3] In a Medicare study, only 28% of older adults received osteoporosis medications after a fracture.[82] Only 33% of nursing home residents with an osteoporosis diagnosis or past fracture received an osteoporosis medication, even though 89% of them were considered at high risk for a fracture.[19] Sarcopenia resulting in decreased muscle mass and function is prevalent in older adults (1%-29% community dwelling and 14%-33% long-term care older adults), and is associated with increased falls and fractures.[83]

Guidelines recommend DXA for adults 65 and older; however, all older adults are not evaluated for osteoporosis.[1,4,15,44] Universal screening of older women was found to be cost effective, with more cost savings generated with greater age.[84] Reference standards for osteoporosis assessment tools are generally not available for the oldest older adults (eg, maximum age for FRAX is 90 years). In clinical practice, estimates for a 90-year-old person are applied to those adults older than 90 years. FRAX slightly overestimated whereas ultrasound underestimated osteoporosis in nursing home residents.[85] In an older adult with falls, the Garvan calculator might be better since it includes falls whereas FRAX does not.[13]

Older adults should practice a bone-healthy lifestyle, ingest adequate calcium and vitamin D,[44] and implement measures to prevent falls (see above sections).[29,30] While some guidelines recommend adequate amounts of calcium and vitamin D, the USPSTF feels evidence is insufficient to support fall[58] and fracture[59,86] prevention with supplementation. Exercise might be difficult in older adults due to osteoarthritis, and or limited by underlying cardiac and respiratory diseases. However, walking and lifting light weights can still stimulate bone remodeling. Lactose intolerance and hypercholesterolemia increase with aging and can lead to lower calcium intake from dairy products, which can increase the need for calcium supplements. Limited sun exposure due to frailty and institutional residence can increase the need for vitamin D supplementation for bone and muscle health. Encouraging older adults to do a home safety evaluation for falls can assist with fracture prevention.[29,30] Multidisciplinary fall prevention programs with multiple interventions generally have greater impact on fall prevention than single discipline or single intervention. Many fall prevention materials are free on the internet.

Osteoporosis medication efficacy and safety data are limited in the oldest older adults.[16,44] However, some data exist to support benefit of the older agents with no data available yet for abaloparatide or romosozumab. In the Medicare study, antiosteoporotic medications after a fracture lowered subsequent fracture risk by 21%.[82] When deciding whether or not to use prescription medications in older adults, the following factors need to be taken into consideration: remaining life span, ability to take and afford medications, cognitive function, swallowing ability, GI disorders, polypharmacy, desire to avoid additional medications, and regimen complexity. Challenges with oral bisphosphonate administration requirements exist for older adults who are bed bound, have difficulties swallowing, have fluid restrictions for cardiovascular or kidney diseases, or forget to drink adequate amounts of fluid or stay upright for the given time. Sometimes not initiating or stopping osteoporosis medications might be warranted for older adults with conditions such as severe Alzheimer disease or during palliative or hospice care. Osteoporosis medications can put an older adult into the Medicare Part D medication insurance plan coverage gap, “the donut hole,” the time frame older adults pay most of the medication expenses out of pocket, which might create adherence problems.

Chronic Kidney Disease

Low BMD and fractures occur in patients with chronic kidney disease (CKD;

glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2 [0.58 mL/s/m^2], dialysis, and after kidney transplant. Fractures occur earlier and have greater 1-year mortality rates (64%).[16] Osteoporosis due to aging and other secondary causes are different from chronic kidney disease-mineral and bone disorders (CKD-MBD) such as renal osteodystrophy (see Chapters 67, "Calcium and Phosphorus Homeostasis," and 61, "Chronic Kidney Disease"), which can be related to high bone turnover, adynamic bone, or a combination of both.[16,87,88] In the new nephrology guidelines, DXA can be used to assess bone loss and FRAX can be used to determine fracture risk; however, this later tool does not account for renal failure as a risk factor. Neither assessment distinguishes between renal and nonrenal causes of bone loss. When the diagnosis of the underlying cause could influence treatment, a bone biopsy is indicted. Laboratory tests such as serum calcium, 25 (OH) vitamin D, intact PTH, and serum phosphorus can help with identifying underlying CKD-MBD.

Limited data exist on osteoporosis medications for patients with CKD, dialysis, and/or post kidney transplant.[16,43,87,88] Calcium intake is preferred by diet with supplements used only to achieve RDAs. Vitamin D concentrations are measured and insufficient concentrations replenished with choleciferol or ergocalciferol, 1,25 $(OH)_2$ vitamin D, or a combination of products. Osteoporosis medication studies have not been done or generally show little to no effect on BMD except for bisphosphonates used after kidney transplant that showed lumbar spine BMD increases and fracture risk reduction, and for raloxifene reducing vertebral fractures; however, these studies had insufficient sample sizes to document change. Oral bisphosphonates are not recommended and zoledronic acid is contraindicated if CrCl is less than 30 or 35 mL/min (0.50 or 0.58 mL/s). Some healthcare professionals will use bisphosphonates at regular or lower doses for shorter durations (to account for decreased renal bisphosphonate elimination) in patients with renal function decreased due to aging versus underlying kidney disorders.[63] More healthcare professionals are beginning to use bisphosphonates off label in patients with mild and moderate CKD or on dialysis. Denosumab is not renally eliminated and when used in CKD-MBD, serum calcium needs to be monitored since these patients can develop hypocalcemia, especially if also receiving calcium sensing receptor agonists. Teriparatide can help patients with adynamic bone and those with low PTH and BMD. A role for abaloparatide and romosozumab could exist since these medications are not renally eliminated, do not accumulate in bone, and can overcome some CKD-MBDs; however, there are no data yet. Kidney and or bone specialists usually provide care to patients with significant kidney disease

and osteoporosis.

Drug-Induced Disease

Glucocorticoid-Induced Osteoporosis

3 Glucocorticoid use is the most common cause of medication-induced osteoporosis. Up to 40% of patients taking chronic oral glucocorticoids will experience a clinical fracture or show evidence of vertebral fracture on x-ray.[77,89] In patients who take 2.5 to 7.5 mg/day of prednisone or the equivalent, the relative risk of vertebral fracture doubles and the relative risk of hip fracture increases by 50%. All glucocorticoid doses and formulations have been associated with increased bone loss and fractures; however, risk is much greater with prednisone doses of 5 mg or more daily or equivalent and oral therapy versus inhaler and intranasal therapy. Although a well-documented risk, many patients receiving glucocorticoids are not evaluated and or treated for glucocorticoid-induced osteoporosis (GIO); therefore, greater vigilance by all healthcare professionals is needed.[77,89]

Bone losses with glucocorticoids are rapid with up to 12% loss over the first year, with the greatest decrease occurring in the first 3 to 6 months of therapy. Afterward, bone loss is about 2% to 3% per year.[77,89,90] The risk of fracture increases within three months of initiating glucocorticoid therapy and peaks at one year. Trabecular bone is affected more than cortical bone; therefore, vertebral fractures are more common. The pathophysiology of glucocorticoid-induced bone loss is multifactorial. Glucocorticoids decrease bone formation through decreased proliferation and differentiation and enhanced apoptosis of osteoblasts. They can interfere with the bone's natural repair mechanism through increased apoptosis of osteocytes. Glucocorticoids increase RANKL and decrease OPG, leading to an increase in the number of osteoclasts and increased bone resorption. They can reduce estrogen and testosterone concentrations. A negative calcium balance is created from decreased calcium absorption and increased urinary calcium excretion via alterations in calcium transporters. The underlying disease requiring glucocorticoids (see Table 108-2) also can negatively affect bone metabolism.

FRAX and central DXA are recommended by current guidelines for evaluation.[89] Since FRAX does not account for specific dose, duration or accumulation of glucocorticoids, scores must be adjusted based on prednisone dose or equivalent. For those taking more than 7.5 mg or equivalent per day, FRAX risk of major osteoporotic fracture should be increased by 15% (ie,

multiplied by 1.15) and FRAX risk of hip fracture by 20% (ie, multiplied by 1.2). Based on glucocorticoid-adjusted FRAX estimates of the 10-year risk of major osteoporotic fracture and hip fracture, the patients are risk stratified into low, moderate, and high risk for fracture. Criteria for classification into a risk category is detailed in **Table 108-9**.[89] An initial BMD assessment is recommended prior to or within 6 months of glucocorticoid initiation for adults 40 years of age or older and for adults under the age of 40 with a history of fragility fracture or other risk factors. Repeat BMD testing is recommended every 2 to 3 years during osteoporosis therapy for those taking very high-glucocorticoid doses (30 mg of prednisone or more per day or a cumulative dose greater than 5 g in the past year), a fracture 18 months or more after starting osteoporosis therapy, medication adherence or absorption concerns, or other risk factors for osteoporosis. A vertebral fracture assessment (VFA) is suggested for patients with significant height loss, pain consistent with a vertebral fracture or spine, or receiving 5 mg or more prednisone or equivalent daily.

TABLE 108-9 Classification of Fracture Risk in Patients Treated with Glucocorticoids

Fracture Risk	Adults ≥40 years old	Adults <40 years old
Low	FRAX[a] 10-year risk of major osteoporotic fracture <10% FRAX[a] 10-year risk of hip fracture ≤1%	No prior osteoporotic fracture None of the risk factors listed for moderate- or high-fracture risk (below)
Moderate	FRAX[a] 10-year risk of major osteoporotic fracture 10%-19% FRAX[a] 10-year risk of hip fracture >1% and <3%	Hip or spine BMD Z-score <–3.0, or Rapid bone loss (≥10% at the hip or spine over 1 year) And continuing glucocorticoid therapy with ≥7.5 mg/day for ≥6 months
High	History of osteoporotic fracture, or Hip or spine BMD T-score ≤–2.5 in men ≥50 years old and postmenopausal women, or FRAX[a] 10-year risk of major osteoporotic fracture ≥20%, or FRAX[a] 10-year risk of hip fracture ≥3%	Prior osteoporotic fracture

[a]If glucocorticoid treatment is >7.5-mg prednisone or equivalent per day, the FRAX risk score should be multiplied by 1.15 for major osteoporotic fracture and by 1.2 for hip fracture and then used to determine overall fracture risk per the guideline.

Data from Reference 89.

All patients using glucocorticoids should practice a bone-healthy lifestyle (described above) and minimize glucocorticoid exposure when possible.[77,89] All patients starting or receiving glucocorticoid therapy (any dose or duration) should consume 1,000 to 1,200 mg elemental calcium and 600 to 800 units of vitamin D daily or more to achieve therapeutic 25 (OH) vitamin D concentrations. Minimizing fall risk is important. Counseling should occur for all patients using this medication for three months or more regardless of dose. Glucocorticoids should be used at the lowest dose and for the shortest duration possible. Upon discontinuation of glucocorticoid therapy, fracture risk decreases

and BMD increases, though not to baseline levels.[90]

The current guidelines from the American College of Rheumatology divide recommendations for prescription osteoporosis medication use in GIO by fracture risk and age (see Tables 108-9 and 108-10).[89] Alendronate, risedronate, zoledronic acid, denosumab, and teriparatide have FDA indications for GIO.[77] Therapy recommendations are based on comparative efficacy, potential for toxicity, and cost. Oral bisphosphonates are recommended first-line, though intravenous bisphosphonates can be used in patients who are not adherent or unable to take the oral preparations. Teriparatide is recommended for patients who cannot use a bisphosphonate, and denosumab is recommended if neither a bisphosphonate nor teriparatide can be used. Denosumab is not recommended first-line for GIO due to limited safety data in this population. Consideration should be given to potential risk of infection in patients taking immunosuppressive agents or biologic therapies. Raloxifene does not have an FDA indication for GIO, but does have some clinical data documenting improved BMD at the lumbar spine in patients taking glucocorticoids.[89] It is recommended only in postmenopausal women if no other osteoporosis medications can be used. Standard osteoporosis therapy doses are used. The recommendations are similar for women of childbearing potential who do not plan to become pregnant and are using an effective contraceptive or are not sexually active. Patients receiving glucocorticoids are considered high risk, and, therefore, a bisphosphonate drug holiday is generally not considered after 5 years. Bisphosphonate treatment for 7 to 10 years is recommended if patients continue glucocorticoid use. Since glucocorticoids can cause hypogonadism, sometimes hormone therapy will be prescribed. The hormonal therapy for correcting hypogonadism symptoms most likely will have some positive bone effects as well.

TABLE 108-10 Therapy to Prevent or Treat Glucocorticoid-Induced Osteoporosis in Adults Beginning Long-Term Glucocorticoid Treatment (≥2.5-mg prednisone or equivalent per day for ≥3 months)

Patient Population	Low-Fracture Risk	Moderate-Fracture Risk	High-Fracture Risk
All	Optimize calcium and vitamin D intake Lifestyle modifications	Optimize calcium and vitamin D intake Lifestyle modifications	Optimize calcium and vitamin D intake Lifestyle modifications
Adults age ≥40 years	No prescription osteoporosis therapy	Oral bisphosphonate Alternatives:[a] IV bisphosphonate, teriparatide, denosumab, or raloxifene[b]	Oral bisphosphonate Alternatives:[a] IV bisphosphonate, teriparatide, denosumab, or raloxifene[b]
Adults age <40 years	No prescription osteoporosis therapy	Oral bisphosphonate Alternatives:[a] IV bisphosphonate, teriparatide or denosumab	Oral bisphosphonate Alternatives:[a] IV bisphosphonate, teriparatide or denosumab
Women of childbearing potential[c,d]	No prescription osteoporosis therapy	Oral bisphosphonate Alternative: teriparatide	Oral bisphosphonate Alternatives: teriparatide, IV bisphosphonate, or denosumab

[a]Alternatives listed in order of preference; abaloparatide and romosozumab were not yet approved during guideline development.

[b]Raloxifene recommended only for postmenopausal women when other alternative therapies cannot be used.

[c]Women of childbearing potential who do not intend to become pregnant during the osteoporosis treatment period and are using effective birth control or are not sexually active.

[d]Potential fetal risks from osteoporosis medications during pregnancy.

Data from Reference 89.

Cancer Treatment–Induced Bone Loss

3 Cancers, metastatic bone disease, and their associated treatments can cause bone loss and osteoporosis.[16,43,91] Medications used to treat hormone-responsive cancers, such as aromatase inhibitors and androgen deprivation therapy, as well as some cytotoxic chemotherapies, are associated with a reduction in BMD. Chemotherapy-induced ovarian failure can enhance bone loss. Glucocorticoids used as chemotherapy, chemotherapy premedication, and/or treatment for chemotherapy-induced nausea and vomiting also increase bone loss in patients with cancer.

DXA screening is advocated for patients at high risk for osteoporosis, which would include certain chemotherapies and cancers. When using FRAX, secondary osteoporosis can be checked “yes” when premature menopause and hypogonadism caused by chemotherapy and cancer are present, though fracture risk is likely still underestimated in this group.[16]

Certain osteoporosis medications are used to prevent bone loss or treat osteoporosis due to chemotherapy, cancer, and metastases.[91] Bisphosphonates and denosumab decrease chemotherapy-induced bone loss and in some trials, fractures. These medications might also decrease cancer progression. Most

research has been conducted in women with breast cancer and men with prostate cancer. Raloxifene decreases the risk of invasive breast cancer in high-risk women. Due to risk of osteosarcoma, teriparatide and abaloparatide are specifically contraindicated in patients with bone metastases or prior radiation to the skeleton.[1,91] Zoledronic acid and denosumab are used for cancer-related hypercalcemia and skeletal-related events and are marketed with different product names for these indications since dosages are much higher than for osteoporosis.

EVALUATION OF THERAPEUTIC OUTCOMES

Monitoring of Patient-Centered Care Plan

Assessment of adherence and tolerability of medication should be performed at each visit. Having a patient repeat back instructions for medication administration will help identify administration problems and enable timely correction. Assessment of fracture, back pain, and height loss can help identify worsening osteoporosis.

The role of routine monitoring of BMD via central DXA is controversial and recommendations vary since change in BMD is only one component of fracture risk.[3,15] Nonetheless, decreases in BMD while on treatment are associated with increases in fracture risk compared to stable or increased BMD. Since BMD continues to decrease with aging, no change from baseline can be an acceptable response. However, if BMD significantly decreases while on treatment this can indicate nonadherence, a lack of response, or the presence of secondary causes that could be contributing to continued bone loss. To evaluate efficacy, a central DXA BMD measurement can be obtained after 1 to 2 years,[1,3] 3 to 5 years,[96] or 5 years[2] after initiating a medication to monitor response. To minimize test variability, BMD testing should be performed on the same DXA machine. A statistical change needs to be greater than the least significant change for that specific piece of equipment. Central DXAs are repeated every 1 to 2 years[1,3] until BMD is stable at which time the interval for reassessment could be lengthened; however, other guidelines recommend to wait until 5 years after initiation.[2] Financial support for testing at intervals less than 2 years might not be provided by insurance plans. In patients with conditions associated with higher rates of bone loss (eg, glucocorticoid use and certain chemotherapy agents), more frequent monitoring might be warranted.

Bone turnover markers have been used to determine response to an osteoporosis prescription medication but do not help to predict individual fracture risk.[1,3,15,52] Like central DXA, BTM can be used to identify nonadherence and lack of response to therapy. The markers are measured 6 months after therapy initiation and compared to baseline values.[52] Significant changes need to be greater than the least significant change for that test and, for P1NP, below pre-identified thresholds. Because no consensus on result interpretation and high-test variability exists, these tests are not routinely ordered.

Osteoporosis Services

Despite the availability of effective therapies, many patients (approximately 70%) are not being evaluated or do not receive appropriate osteoporosis therapy.[1,4,15] In fact, the proportion of patients receiving osteoporosis medication following a hip fracture has decreased. To combat this trend, many institutions are implementing an Own the Bone program[4] or a fracture liaison service, which is generally an interprofessional, multifaceted program to increase treated patient numbers, enhance adherence, and improve osteoporosis treatment outcomes.[15,92] Community pharmacists and other healthcare professionals can provide osteoporosis screenings using the FRAX tool to estimate fracture risk in the community, especially at health fairs. Osteoporosis prevention and treatment services have been clinically successful in community pharmacies[93,94] and in ambulatory care settings.[94] At 1 year, only 26% to 56% of patients still use their osteoporosis medications.[10] Thus, all healthcare professionals should identify and resolve barriers to optimal medication initiation and adherence. The main reasons for nonadherence are medication cost, fear of adverse effects, resistance to medication use, and perceived lack of medication need.[10] Routine follow-up with healthcare professionals and enhanced risk-benefit communication tools could improve treatment and adherence rates.[3,64,67] Databases can be used to identify patients after a low-trauma fracture who have not had a DXA exam or osteoporosis medication started. Patient medication assistance programs can be used to decrease cost.

To improve patient care, the Centers for Medicare and Medicaid Services have created this quality measure—the percentage of women 50 to 85 years old with a recent fracture that is screened or treated within 6 months.[95] Financial incentives tied to these measures could help bridge the gap in quality of care.

CONCLUSION

Osteoporosis prevention begins at birth and continues throughout life by practicing a bone-healthy lifestyle (adequate calcium and vitamin D intake, exercise, no smoking, minimal alcohol use, and fall prevention). Generally, osteoporosis occurs in postmenopausal women and older men; however, the disease can occur in all ages as a result of secondary causes such as genetics, diseases, and medications. Central DXA can be used for screening, diagnosis, and monitoring and the FRAX tool can be used for screening and to assist in identifying patients at high risk for fracture requiring treatment.

Alendronate, risedronate, zoledronic acid, and denosumab are first-line therapies since these medications decrease hip, nonvertebral, and vertebral fractures. Abaloparatide, romosozumab, and teriparatide are the only medications that can build bone; however, cost, subcutaneous administration, and lack of hip fracture prevention limit their use. Although medications decrease fracture risk, prescribing osteoporosis medications and patient adherence to them is suboptimal. All healthcare professionals need to be actively involved with people of all ages to provide osteoporosis education and counseling, prevent osteoporosis development across the lifespan, treat osteoporosis, and improve medication adherence to prevent osteoporotic fractures.

Postclass Engaged Learning Activity

1. Critique recent abaloparatide and romosozumab clinical trials to evaluate new data on fracture prevention and adverse effects. How will you use this new information to determine when to use these medications compared to previously marketed osteoporosis medications?
2. What can you do to help patients with osteoporosis increase medication adherence? What can you do to help patients afford their anabolic medications?
3. What therapy will you recommend for a patient who has had a fracture while on a bisphosphonate to prevent a second fracture?

ABBREVIATIONS

25(OH)	25-hydroxyvitamin D/calcidiol

vitamin D	
APC	adenomatous polyposis coli
ATPase	adenosine triphosphatase
BAP	Bone-specific alkaline phosphatase
BMD	bone mineral density
BMP	bone morphometric proteins
BTM	bone turnover markers
Calcium	Ca^{++}
Cbl	E3 ubiquitin ligase
CEE	conjugated equine estrogens
Csk1α	casein kinase 1α
CKD-MBD	chronic kidney disease-mineral and bone disorder
CrCl	creatinine clearance
CTX	c-terminal type 1 collagen telopeptide
Dkk-1	Dickkoff-1
DPD	deoxypyridinoline
DSH	Disheveled cytoplasmic protein
DXA	dual-energy x-ray absorptiometry
EAA	estrogen agonist antagonist
FAK	focal adhesion kinase
FDA	Food and Drug Administration
FGF	fibroblast growth factor
FRAX	World Health Organization fracture risk assessment tool
GFR	glomerular filtration rate
GI	gastrointestinal
GIO	glucocorticoid-induced osteoporosis
GSK-3β	glycogen synthase kinase-3β
ICTP	c-terminal telopeptide
IGF	insulin-like growth factor
IOM	Institute of Medicine
LRP5/6	lipoprotein-receptor related protein
m-CSF	macrophage-colony stimulating factor
MMP	matrix metalloproteases

NF-κβ	nuclear factor kappa β
NHANES	national health and nutrition examination survey
NTX	N-terminal type 1 collagen telopeptide
OCN	osteocalcin
ONJ	osteonecrosis of the jaw
OPG	osteoprotegerin
P13K	phosphatidyl inositol 3-kinase
pDXA	peripheral dual-energy x-ray absorptiometry
PINP/PICP	procollagen type 1 N-terminal propeptide
PPARγ	peroxisome proliferator-activated receptor γ
PTH	parathyroid hormone
PTHrP	parathyroid hormone-related protein
QCT	quantitative computed tomography
QUS	quantitative ultrasound
RANK	receptor activator of nuclear factor-kappa β
RANKL	receptor activator of nuclear factor-kappa β ligand
RDA	recommended dietary allowances
runX2	runt-related transcription factor
Scr	nonreceptor tyrosine kinase
sFRP	secreted frizzled related proteins
TBS	trabecular bone score
TCF/LEF	T cell specific transcription factor 4/lymphoid enhancer factor 1
TGF-β	tissue growth factor-β
TNF-α	tumor necrosis factor-α
TRACP5b	tartrate-resistant acid phosphatase isoenzyme 5
TRPV6	transient receptor potential cation channel subfamily V member 6
TSEC	tissue selective estrogen complex
UL	upper limits
USP	United States Pharmacopeia
USPSTF	United States Preventive Services Task Force
VDR	vitamin D receptor
VFA	vertebral fracture assessment

WIFI	Wnt inhibitory factor 1
WISE	Wnt modulator insurface estoderm
WHO	World Health Organization
Wnt	wingless tail ligand

REFERENCES

1. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int.* 2014;10:2359–2381.
2. Qaseem A, Forciea MA, McLean RM, Denberg TD. Clinical Guidelines Committee of the American College of Physicians. Treatment of low bone density or osteoporosis to prevent fractures in men and women: A clinical practice guideline update from the American college of physicians. *Ann Intern Med.* 2017;11:818–839.
3. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists and American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis, 2016—executive summary. *Endocr Pract.* 2016;9:1111–1118.
4. Carlson BC, Robinson WA, Wanderman NR, et al. The American Orthopaedic association's own the bone(r) database: A national quality improvement project for the treatment of bone health in fragility fracture patients. *Osteoporos Int.* 2018;9:2101–2109.
5. Wright NC, Looker AC, Saag KG, et al. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. *J Bone Miner Res.* 2014;11:2520–2526.
6. North American Menopause Society. Management of osteoporosis in postmenopausal women: 2010 Position statement of the North American Menopause Society. *Menopause*. 2010;1:25–54.
7. Lewiecki EM, Blicharski T, Goemaere S, et al. A phase III randomized placebo-controlled trial to evaluate efficacy and safety of romosozumab in men with osteoporosis. *J Clin Endocrinol Metab.* 2018;9:3183–3193.
8. Watts NB, Adler RA, Bilezikian JP, et al. Osteoporosis in men: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2012;6:1802–1822.

9. Drake MT, Clarke BL, Lewiecki EM. The pathophysiology and treatment of osteoporosis. *Clin Ther.* 2015;8:1837–1850.
10. Rizzoli R. Postmenopausal osteoporosis: Assessment and management. *Best Pract Res Clin Endocrinol Metab.* 2018;5:739–757.
11. Troy KL, Mancuso ME, Butler TA, Johnson JE. Exercise early and often: Effects of physical activity and exercise on women's bone health. *Int J Environ Res Public Health*. 2018;15:878
12. Xu Y, Wu Q. Decreasing trend of bone mineral density in US multiethnic population: Analysis of continuous NHANES 2005-2014. *Osteoporos Int.* 2018;29(11):2437–2446. doi:10.1007/s00198-018-4648-9.
13. Adler RA. Update on osteoporosis in men. *Best Pract Res Clin Endocrinol Metab*. 2018;5:759–772.
14. Compston J, Cooper A, Cooper C, et al. UK clinical guideline for the prevention and treatment of osteoporosis. *Arch Osteoporos*. 2017;12:43.
15. Compston JE, McClung MR, Leslie WD. Osteoporosis. *Lancet*. 2019;10169:364–376.
16. Gielen E, Bergmann P, Bruyere O, et al. Osteoporosis in frail patients: A consensus paper of the Belgian Bone Club. *Calcif Tissue Int.* 2017;2:111–131.
17. Langdahl BL. Osteoporosis in premenopausal women. *Curr Opin Rheumatol.* 2017;4:410–415.
18. Marrani E, Giani T, Simonini G, Cimaz R. Pediatric osteoporosis: Diagnosis and treatment considerations. *Drugs*. 2017;6:679–695.
19. Zarowitz BJ, Cheng LI, Allen C, O'Shea T, Stolshek B. Osteoporosis prevalence and characteristics of treated and untreated nursing home residents with osteoporosis. *J Am Med Dir Assoc.* 2015;4:341–348.
20. Miller PD. Unrecognized and unappreciated secondary causes of osteoporosis. *Endocrinol Metab Clin North Am.* 2012;3:613–628.
21. Mirza F, Canalis E. Management of endocrine disease: Secondary osteoporosis: Pathophysiology and management. *Eur J Endocrinol*. 2015;3:R131–151.
22. O'Sullivan S, Grey A. Adverse skeletal effects of drugs—beyond glucocorticoids. *Clin Endocrinol (Oxf)*. 2015;1:12–22.
23. Panday K, Gona A, Humphrey MB. Medication-induced osteoporosis: Screening and treatment strategies. *Ther Adv Musculoskelet Dis.* 2014;5:185–202.

24. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV, Department of Health and Human Services. Available at: https://aidsinfo.nih.gov/guidelines. Accessed February 18, 2019.
25. Ruanpeng D, Ungprasert P, Sangtian J, Harindhanavudhi T. Sodium-glucose cotransporter 2 (sglt2) inhibitors and fracture risk in patients with type 2 diabetes mellitus: A meta-analysis. *Diabetes Metab Res Rev.* 2017;33:e2903.
26. Lorentzon M. Treating osteoporosis to prevent fractures: Current concepts and future developments. *J Intern Med.* 2019. doi:10.1111/joim.12873.
27. Boudin E, Van Hul W. Mechanisms in endocrinology: Genetics of human bone formation. *Eur J Endocrinol*. 2017;2:R69–R83.
28. Kanis JA, Cooper C, Rizzoli R, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int.* 2019;1:3–44.
29. Ambrose AF, Cruz L, Paul G. Falls and fractures: A systematic approach to screening and prevention. *Maturitas*. 2015;1:85–93.
30. Phelan EA, Ritchey K. Fall prevention in community-dwelling older adults. *Ann Intern Med.* 2018;11:ITC81–ITC96.
31. Walsh JS. Normal bone physiology, remodeling and hormonal regulation. *Surgery*. 2015;1–6.
32. Burr DB. Changes in bone matrix properties with aging. *Bone*. 2019;85–93.
33. Stewart AF. Normal physiology of bone and mineral homeostasis. In: Benjamin IJ, Wing EJ, Fitz JG, eds. *Andreoli and Carpenter's Cecil Essentials of Medicine*. Philadelphia, PA: Saunders; 2016;732–740.
34. Cohen A. Premenopausal osteoporosis. *Endocrinol Metab Clin North Am.* 2017;1:117–133.
35. Bringhurst FR, Demay MB, Krane SM, Kronenberg HM, et al. Bone and mineral metabolism in health and disease. In: Jameson JL, Fauci AS, Kasper DL, eds., et al. *Harrison's Principles of Internal Medicine*. 20th ed. McGraw-Hill Companies, Inc.; 2018.
36. Iniguez-Ariza NM, Clarke BL. Bone biology, signaling pathways, and therapeutic targets for osteoporosis. *Maturitas*. 2015;2:245–255.
37. Lerner UH, Ohlsson C. The Wnt system: Background and its role in bone. *J Intern Med.* 2015;6:630–649.

38. Marini F, Brandi ML. Pharmacogenetics of osteoporosis. *Best Pract Res Clin Endocrinol Metab*. 2014;6:783–793.
39. Ono T, Nakashima T. Recent advances in osteoclast biology. *Histochem Cell Biol*. 2018;4:325–341.
40. Russow G, Jahn D, Appelt J, Mardian S, et al. Anabolic therapies in osteoporosis and bone regeneration. *Int J Mol Sci*. 2018;20:83.
41. Mohamad NV, Soelaiman IN, Chin KY. A concise review of testosterone and bone health. *Clin Interv Aging*. 2016;1317–1324.
42. United States Department of Health and Human Services. Calcium fact sheet for health professionals. Available at: https://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/. Accessed February 18, 2019.
43. McLendon AN, Woodis CB. A review of osteoporosis management in younger premenopausal women. *Womens Health (Lond)*. 2014;1:59–77.
44. Vandenbroucke A, Luyten FP, Flamaing J, Gielen E. Pharmacological treatment of osteoporosis in the oldest old. *Clin Interv Aging*. 2017;1065–1077.
45. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: An endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2018;5:1715–1744.
46. US Preventive Services Task Force, Curry SJ, Krist AH, et al. Screening for osteoporosis to prevent fractures: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;24:2521–2531.
47. Garvan Institute. Fracture risk calculator. Available at: https://www.garvan.org.au/promotions/bone-fracture-risk/calculator/. Accessed February 18, 2019.
48. International Society for Clinical Densitometry. Official positions 2015 adult and pediatric. 2015;1–24.
49. Viswanathan M, Reddy S, Berkman N, et al. Screening to prevent osteoporotic fractures: Updated evidence report and systematic review for the us preventive services task force. *JAMA*. 2018;24:2532–2551.
50. Nayak S, Greenspan SL. Osteoporosis treatment efficacy for men: A systematic review and meta-analysis. *J Am Geriatr Soc*. 2017;3:490–495.
51. Adler RA, El-Hajj Fuleihan G, Bauer DC, et al. Managing osteoporosis in patients on long-term bisphosphonate treatment: Report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res*.

2016;1:16–35.

52. Szulc P. Bone turnover: Biology and assessment tools. *Best Pract Res Clin Endocrinol Metab.* 2018;5:725–738.
53. National Institutes of Health Office of Dietary Supplements. Vitamin D fact sheet for health professionals. Available at: https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/#en1. Accessed February 18, 2019.
54. Ramsubeik K, Keuler NS, Davis LA, Hansen KE. Factors associated with calcium absorption in postmenopausal women: A post hoc analysis of dual-isotope studies. *J Acad Nutr Diet.* 2014;5:761–767.
55. Foundation IO. Calcium calculator. Available at: https://www.iofbonehealth.org/calcium-calculator. Accessed February 18, 2019.
56. Liu X, Baylin A, Levy PD. Vitamin D deficiency and insufficiency among US adults: Prevalence, predictors and clinical implications. *Br J Nutr.* 2018;8:928–936.
57. Nie Q, Xing M, Hu J, et al. Metabolism and health effects of phyto-estrogens. *Crit Rev Food Sci Nutr.* 2017;11:2432–2454.
58. United States Preventive Services Task Force, Grossman DC, Curry SJ, et al. Interventions to prevent falls in community-dwelling older adults: US Preventive Services Task Force recommendation statement. *JAMA.* 2018;16:1696–1704.
59. Kahwati LC, Weber RP, Pan H, et al. Vitamin D, calcium, or combined supplementation for the primary prevention of fractures in community-dwelling adults: Evidence report and systematic review for the US Preventive Services Task Force. *JAMA.* 2018;15:1600–1612.
60. Buchbinder R, Johnston RV, Rischin KJ, et al. Percutaneous vertebroplasty for osteoporotic vertebral compression fracture. *Cochrane Database Syst Rev.* 2018. CD006349.
61. Solling ASK, Harslof T, Langdahl B. The clinical potential of romosozumab for the prevention of fractures in postmenopausal women with osteoporosis. *Ther Adv Musculoskelet Dis.* 2018;5-6:105–115.
62. Bouillon R, Van Schoor NM, Gielen E, et al. Optimal vitamin D status: A critical analysis on the basis of evidence-based medicine. *J Clin Endocrinol Metab.* 2013;8:E1283–1304.
63. Cremers S, Drake MT, Ebetino FH, et al. Pharmacology of bisphosphonates. *Br J Clin Pharmacol.* 2019. doi:10.1111/bcp.13867.

64. Maraka S, Kennel KA. Bisphosphonates for the prevention and treatment of osteoporosis. *BMJ*. 2015;351:h3783.
65. Reid IR, Horne AM, Mihov B, et al. Fracture prevention with zoledronate in older women with osteopenia. *N Engl J Med*. 2018;25:2407–2416.
66. Nicolatou-Galitis O, Schiodt M, Mendes RA, et al. Medication-related osteonecrosis of the jaw: Definition and best practice for prevention, diagnosis, and treatment. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2019;2:117–135.
67. Durden E, Pinto L, Lopez-Gonzalez L, Juneau P, Barron R. Two-year persistence and compliance with osteoporosis therapies among postmenopausal women in a commercially insured population in the United States. *Arch Osteoporos*. 2017;12:22.
68. Anastasilakis AD, Polyzos SA, Makras P. Therapy of endocrine disease: Denosumab vs bisphosphonates for the treatment of postmenopausal osteoporosis. *Eur J Endocrinol*. 2018;1:R31–R45.
69. Zaheer S, LeBoff M, Lewiecki EM. Denosumab for the treatment of osteoporosis. *Expert Opin Drug Metab Toxicol*. 2015;3:461–470.
70. Pinkerton JV, Thomas S. Use of SERMs for treatment in postmenopausal women. *J Steroid Biochem Mol Biol*. 2014;142–154.
71. Umland EM, Karel L, Santoro N. Bazedoxifene and conjugated equine estrogen: A combination product for the management of vasomotor symptoms and osteoporosis prevention associated with menopause. *Pharmacotherapy*. 2016;5:548–561.
72. Peng L, Luo Q, Lu H. Efficacy and safety of bazedoxifene in postmenopausal women with osteoporosis: A systematic review and meta-analysis. *Medicine (Baltimore)*. 2017;49:e8659.
73. United States Food and Drug Administration. Questions and answers: Changees to the indicated population for miacalcin (calcitonin-salmon). 2015. Available at: https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformation Accessed February 18, 2019.
74. Gartlehner G, Patel SV, Feltner C, et al. Hormone therapy for the primary prevention of chronic conditions in postmenopausal women: Evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2017;22:2234–2249.
75. Anagnostis P, Gkekas NK, Potoupnis M, et al. New therapeutic targets for osteoporosis. *Maturitas*. 2019;120:1–6.

76. Canalis E. Management of endocrine disease: Novel anabolic treatments for osteoporosis. *Eur J Endocrinol*. 2018;2:R33–R44.
77. Buckley L, Humphrey MB. Glucocorticoid-induced osteoporosis. *N Engl J Med.* 2018;26:2547–2556.
78. Padhi D, Allison M, Kivitz AJ, et al. Multiple doses of sclerostin antibody romosozumab in healthy men and postmenopausal women with low bone mass: A randomized, double-blind, placebo-controlled study. *J Clin Pharmacol*. 2014;2:168–178.
79. Langdahl BL, Libanati C, Crittenden DB, et al. Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: A randomised, open-label, phase 3 trial. *Lancet*. 2017;10102:1585–1594.
80. McClung MR. Using osteoporosis therapies in combination. *Curr Osteoporos Rep.* 2017;4:343–352.
81. Female athlete issues for the team physician: A consensus statement-2017 update. *Curr Sports Med Rep.* 2018;5:163–171.
82. Keshishian A, Boytsov N, Burge R, et al. Examining the treatment gap and risk of subsequent fractures among females with a fragility fracture in the US Medicare population. *Osteoporos Int.* 2017;8:2485–2494.
83. Woo J. Sarcopenia. *Clin Geriatr Med.* 2017;3:305–314.
84. Schousboe JT, Ensrud KE, Nyman JA, et al. Universal bone densitometry screening combined with alendronate therapy for those diagnosed with osteoporosis is highly cost-effective for elderly women. *J Am Geriatr Soc.* 2005;10:1697–1704.
85. Greenspan SL, Perera S, Nace D, et al. FRAX or fiction: Determining optimal screening strategies for treatment of osteoporosis in residents in long-term care facilities. *J Am Geriatr Soc.* 2012;4:684–690.
86. United States Preventive Services Task Force, Grossman DC, Curry SJ, et al. Vitamin D, calcium, or combined supplementation for the primary prevention of fractures in community-dwelling adults: US Preventive Services Task Force recommendation statement. *JAMA.* 2018;15:1592–1599.
87. Covic A, Vervloet M, Massy ZA, et al. Bone and mineral disorders in chronic kidney disease: Implications for cardiovascular health and ageing in the general population. *Lancet Diabetes Endocrinol*. 2018;4:319–331.
88. Wilson LM, Rebholz CM, Jirru E, et al. Benefits and harms of osteoporosis medications in patients with chronic kidney disease: A

systematic review and meta-analysis. *Ann Intern Med.* 2017;9:649–658.

89. Buckley L, Guyatt G, Fink HA, et al. American College of Rheumatology Guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Care Res.* 2017;8:1095–1110.
90. Whittier X, Saag KG. Glucocorticoid-induced osteoporosis. *Rheum Dis Clin North Am.* 2016;1:177–189.
91. Rizzoli R, Body JJ, Brandi ML, et al. Cancer-associated bone disease. *Osteoporos Int.* 2013;12:2929–2953.
92. Osuna PM, Ruppe MD, Tabatabai LS. Fracture liaison services: Multidisciplinary approaches to secondary fracture prevention. *Endocr Pract.* 2017;2:199–206.
93. Elias MN, Burden AM, Cadarette SM. The impact of pharmacist interventions on osteoporosis management: A systematic review. *Osteoporos Int.* 2011;10:2587–2596.
94. Bowers BL, Drew AM, Verry C. Impact of pharmacist-physician collaboration on osteoporosis treatment rates. *Ann Pharmacother*. 2018;9:876–883.
95. Centers for Medicare and Medicaid Services. Merit-based incentive payment system. Quality measures requirements. 2019 quality measures. Available at: https://qpp.cms.gov/mips/explore-measures/quality-measures?py=2019#measures. Accessed February 18, 2019.
96. Eastell R, Rosen CJ, Black DM, Cheung AM, Murad MH, Shoback D. Pharmacological management of osteoporosis in postmenopausal women: An Endocrine Society* Clinical Practice Guideline. *J Clin Endocrinol Metab.* 1, 2019;104(5):1595–1622. doi:10.1210/jc.2019-00221.

109

Gout and Hyperuricemia

Michelle A. Fravel and Michael E. Ernst

KEY CONCEPTS

1. In the absence of a history of gout, asymptomatic hyperuricemia is not usually treated.
2. Acute gouty arthritis may be treated effectively with short courses of high-dose nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or colchicine.
3. Initiation of a xanthine oxidase inhibitor may be considered in patients with gout and one of the following indications for urate-lowering therapy (ULT): (a) two or more gout attacks per year, (b) the presence of one or more tophus, (c) a history of urolithiasis, (d) high-risk comorbidities including chronic kidney disease, hypertension, ischemic heart disease, or heart failure, (e) first diagnosis of gout at age <40 years, or (f) serum uric acid concentrations >8.0 mg/dL.
4. According to the treat-to-target approach supported by the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) Guidelines, the goal serum urate concentration is less than 6 mg/dL [less than 357 μmol/L], or less than 5 mg/dL [less than 297 μmol/L] if signs of gout persist at a concentration of 6 mg/dL.
5. Xanthine oxidase inhibitors are preferred agents for the prophylaxis of recurrent gout attacks because they are effective in both underexcreters and overproducers of uric acid.
6. Uricosuric drugs are contraindicated for patients with impaired kidney function (a creatinine clearance less than 45-50 mL/min).
7. Due to increased risk of acute kidney injury when used as monotherapy, lesinurad is only approved to be taken in combination with a xanthine oxidase inhibitor.

8. Low-dose colchicine, NSAID, or corticosteroid therapy should be administered during the first 6 months of urate-lowering therapy (ULT) to minimize the risk of acute gout attacks that may occur during this initiation period.
9. Uric acid nephrolithiasis should be treated with adequate hydration (2-3 L/day), a daytime urine-alkalinizing agent, and 60 to 80 mEq/day (mmol/day) of potassium bicarbonate or potassium citrate.
10. Patients with hyperuricemia or a history of gouty arthritis should undergo comprehensive evaluation for signs and symptoms of cardiovascular disease, and aggressive management of cardiovascular risk factors (eg, weight loss, reduction of alcohol intake, control of blood pressure, glucose, and lipids) should be attempted.

Preclass Engaged Learning Activity

Create a summary table of the pharmacotherapy options available for each of the following three indications: (1) treatment of an acute attack of gouty arthritis; (2) management of hyperuricemia in patients with recurrent gout; and (3) prevention of acute gout during initiation of urate-lowering therapy. In the table, highlight the differences in dosing when a medication can be used for multiple indications. For indication (1), identify patient comorbidities that would favor selection of one drug class over another.

INTRODUCTION

The term *gout* describes a heterogeneous clinical spectrum of diseases including elevated serum urate concentration (hyperuricemia), recurrent attacks of acute arthritis associated with monosodium urate (MSU) crystals in synovial fluid leukocytes, deposits of monosodium urate crystals (tophi) in tissues in and around joints, interstitial kidney disease, and uric acid nephrolithiasis.[1]

The underlying metabolic disorder of gout is hyperuricemia, defined physiochemically as serum that is supersaturated with monosodium urate. At 37°C (98.6°F), serum urate concentrations above (or around) 7 mg/dL (416 µmol/L) begin to exceed the limit of solubility for monosodium urate.[1] For determination of the risk of gout, hyperuricemia is defined statistically as serum

urate concentrations greater than two standard deviations above the population means for age- and sex-matched healthy populations, usually 7 mg/dL (416 μmol/L) for men and 6 mg/dL (357 μmol/L) for women.[1,2] Although hyperuricemia is fundamental to the development of gout, the mere presence of hyperuricemia itself is often an asymptomatic condition.

EPIDEMIOLOGY

Historically, gout has been referred to as the "disease of kings" since it was often associated with affluent societies and lifestyles of overindulgence, gluttony, and intemperance. Although the prevalence of gout continues to be highest in high-income countries, the overall global burden of gout in both developed and developing countries is increasing due to the aging population and increasing rates of obesity.[3] According to the most recently available data on gout from the National Health and Nutrition Examination Survey (NHANES), NHANES 2007 to 2008, the prevalence of gout in US adults is 3.9%, which corresponds to an estimated 8.3 million people. This represents a 1.2% increase in prevalence compared with NHANES survey data from 1988 to 1994.[4]

Elevated serum urate concentrations are the single most important risk factor for the development of gout, and the relationship between the risk of an attack of acute gouty arthritis and serum urate concentration is linearly correlated. The 5-year cumulative risk of gout for patients with serum urate concentrations less than 7 mg/dL (less than 416 μmol/L) is 0.6%, compared with a risk of 30.5% for those with urate concentrations more than 10 mg/dL (more than 595 μmol/L).[5] Sustained elevation of serum urate is virtually essential for the development of gout; however, hyperuricemia does not always lead to gout, and many patients with hyperuricemia remain asymptomatic.[2] The prevalence of hyperuricemia in the United States mirrors the trend seen with gout, affecting 21.4% of adults (43.3 million people) according to NHANES 2007 to 2008, compared to just 18.2% in NHANES 1988 to 1994.[4]

Gout and hyperuricemia are more common in older adults, with the highest prevalence of 12.6% observed in those 80 years and older, compared with just 0.4% in those between ages 20 and 29 years.[4] Obese persons are twice as likely to have gout as nonobese counterparts.[6] Dietary and lifestyle factors linked to obesity have also been independently associated with gout. These include consumption of alcohol, sugary beverages, and red meat along with a sedentary lifestyle.[7]

Gout affects men about three times more often than women.[4] The lowest rates of gout are observed in women younger than 45 years, approximately 0.6 cases per 1,000 person-years.[8] Serum uric acid concentrations in women approach those of men once menopause has occurred given loss of estrogen-influenced uricosuria; thus, in older age groups the gender gap narrows, and approximately half of newly diagnosed cases of gout are found in women.[9] Gout in men younger than 30 years or in premenopausal women may indicate an inherited enzyme defect or the presence of kidney disease.

ETIOLOGY AND PATHOPHYSIOLOGY

In humans, the production of uric acid is the terminal step in the degradation of purines (**Fig. 109-1**). Uric acid serves no known physiologic purpose and is regarded as a waste product. Normal uric acid concentrations are near the limits of urate solubility, because of the delicate balance that exists between the amount of urate produced and excreted.[2] Humans have higher uric acid concentrations than other mammals because they do not express the enzyme uricase, which converts uric acid into the more soluble allantoin.[9]

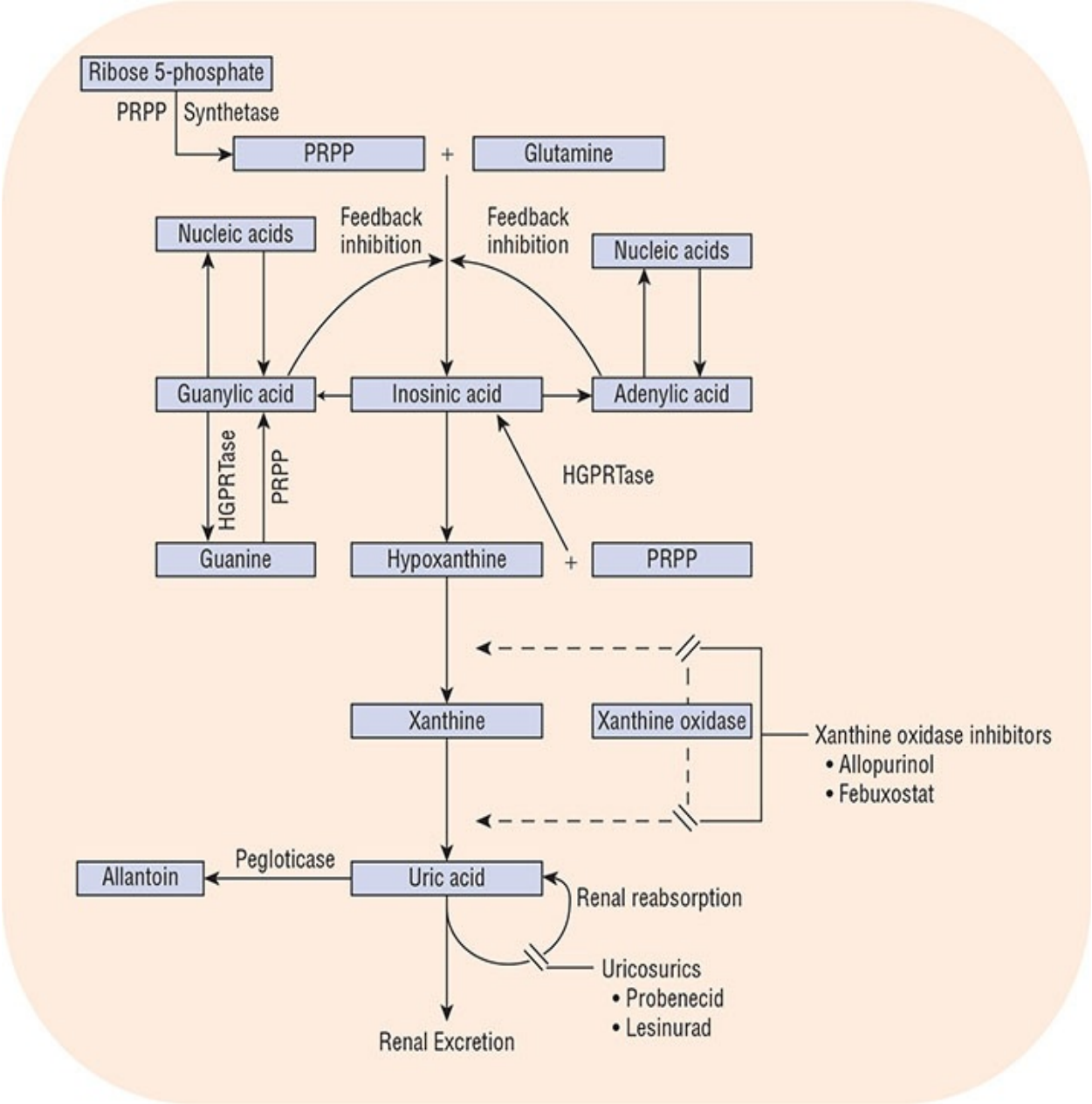


FIGURE 109-1 Uric acid pathway and targets of drug action. (HGPRT, hypoxanthine-guanine phosphoribosyltransferase; PRPP, phosphoribosyl pyrophosphate.)

Gout occurs exclusively in humans in whom a miscible pool of uric acid exists. Under normal conditions, the amount of accumulated uric acid is about 1,200 mg in men and about 600 mg in women. The size of the urate pool is increased several fold in individuals with gout. This excess accumulation may result from either overproduction or underexcretion of uric acid. Several conditions are associated with either decreased kidney clearance or an

overproduction of uric acid, leading to hyperuricemia. Table 109-1 lists some of these conditions.

TABLE 109-1 Conditions Associated with Hyperuricemia

Primary gout	Obesity
Diabetic ketoacidosis	Sarcoidosis
Myeloproliferative disorders	Congestive heart failure
Lactic acidosis	Impaired kidney function
Lymphoproliferative disorders	Down syndrome
Starvation	Lead toxicity
Chronic hemolytic anemia	Hyperparathyroidism
Toxemia of pregnancy	Acute alcoholism
Pernicious anemia	Hypoparathyroidism
Glycogen storage disease type 1	Acromegaly
Psoriasis	Hypothyroidism
Hypoxanthine-guanine phosphoribosyltransferase deficiency	Phosphoribosylpyrophosphate synthetase overactivity
Polycythemia vera	Berylliosis
Kidney transplantation	

Overproduction of Uric Acid

The purines from which uric acid is produced originate from three sources: dietary purine, conversion of tissue nucleic acid into purine nucleotides, and de novo synthesis of purine bases. The purines derived from these three sources enter a common metabolic pathway leading to the production of either nucleic acid or uric acid. Under normal circumstances, uric acid may accumulate excessively if production exceeds excretion. The average human produces about 600 to 800 mg of uric acid each day. Dietary purines play an unimportant role in the generation of hyperuricemia in the absence of some derangement in purine metabolism or elimination. However, diet modifications are an important first step for patients with such problems who develop symptomatic hyperuricemia.

Several enzyme systems regulate purine metabolism. Abnormalities in these regulatory systems can result in overproduction of uric acid. Uric acid may also be overproduced as a consequence of increased breakdown of tissue nucleic acids and excessive rates of cell turnover, as observed with myeloproliferative

and lymphoproliferative disorders, polycythemia vera, psoriasis, and some types of anemias. Cytotoxic medications used to treat these disorders can result in overproduction of uric acid secondary to lysis and breakdown of cellular matter.

Two enzyme abnormalities resulting in an overproduction of uric acid have been well described (Fig. 109-1). The first is an increase in the activity of phosphoribosyl pyrophosphate (PRPP) synthetase, which leads to an increased concentration of PRPP. PRPP is a key determinant of purine synthesis and uric acid production. The second is a deficiency of hypoxanthine-guanine phosphoribosyltransferase (HGPRT). HGPRT is responsible for the conversion of guanine to guanylic acid and hypoxanthine to inosinic acid. These two conversions require PRPP as the co-substrate and are important reactions involved in the synthesis of nucleic acids. A deficiency in the HGPRT enzyme leads to increased metabolism of guanine and hypoxanthine to uric acid and to more PRPP to interact with glutamine in the first step of the purine pathway.[2] Complete absence of HGPRT results in the childhood Lesch–Nyhan syndrome, characterized by choreoathetosis, spasticity, intellectual disability, and markedly excessive production of uric acid. A partial deficiency of the enzyme may be responsible for marked hyperuricemia in otherwise normal, healthy individuals.

Underexcretion of Uric Acid

Normally, uric acid does not accumulate as long as production is balanced with elimination. About two-thirds of the daily uric acid production is excreted in the urine and the remainder is eliminated through the gastrointestinal (GI) tract after enzymatic degradation by colonic bacteria. The vast majority of patients (90%) with gout have a relative decrease in the renal excretion of uric acid for an unknown reason (primary idiopathic hyperuricemia).[2]

A decline in the urinary excretion of uric acid to a concentration below the rate of production leads to hyperuricemia and an increased miscible pool of sodium urate. Almost all the urate in plasma is freely filtered across the glomerulus. The concentration of uric acid appearing in the urine is determined by multiple renal tubular transport processes in addition to the filtered load. Evidence favors a four-component model including glomerular filtration, tubular reabsorption, tubular secretion, and postsecretory reabsorption.

Approximately 90% of filtered uric acid is reabsorbed in the proximal tubule, probably by both active and passive transport mechanisms. There is a close linkage between proximal tubular sodium reabsorption and uric acid reabsorption, so conditions that enhance sodium reabsorption (eg, dehydration)

also lead to increased uric acid reabsorption. The exact site of tubular secretion of uric acid has not been determined; this too appears to involve an active transport process. Postsecretory reabsorption occurs somewhere distal to the secretory site. **Table 109-2** lists the drugs that decrease renal clearance of uric acid through modification of filtered load or one of the tubular transport processes. By enhancing renal urate reabsorption, insulin resistance is also associated with gout.

TABLE 109-2 Drugs Capable of Inducing Hyperuricemia and Gout

Diuretics	Ethanol	Ethambutol
Nicotinic acid	Pyrazinamide	Cytotoxic drugs
Salicylates (<2 g/day)	Levodopa	Cyclosporine

The pathophysiologic approach to the evaluation of hyperuricemia requires determining whether the patient is overproducing or underexcreting uric acid. This can be accomplished by placing the patient on a purine-free diet for 3 to 5 days and then measuring the amount of uric acid excreted in the urine in 24 hours. As it is very difficult to maintain a purine-free diet for several days, this test is done infrequently in clinical practice. Nevertheless, when it is performed, individuals who excrete more than 600 mg on a purine-free diet may be considered overproducers. Hyperuricemic individuals who excrete less than 600 mg of uric acid per 24 hours on a purine-free diet may be classified as underexcreters of uric acid. On a regular diet, excretion of more than 1,000 mg per 24 hours reflects overproduction; less than this is probably normal.

CLINICAL PRESENTATION

1 Gout is diagnosed clinically by the presence of symptoms, rather than laboratory tests of uric acid. In fact, asymptomatic hyperuricemia discovered incidentally generally requires no therapy because many individuals with hyperuricemia will never experience an attack of gout. These patients should still be encouraged to implement lifestyle measures to reduce serum urate concentrations.

Acute Gouty Arthritis

A classic acute attack of gouty arthritis is characterized by rapid and localized onset of excruciating pain, swelling, and inflammation. The attack is typically

monoarticular at first, most often affecting the first metatarsophalangeal joint (great toe) and then, in order of frequency, the insteps, ankles, heels, knees, wrists, fingers, and elbows. In one half of initial attacks, the first metatarsophalangeal joint is affected, a condition commonly referred to as *podagra* (**Fig. 109-2**). Up to 90% of patients with gout will experience podagra at some point in the course of their disease.[2]

FIGURE 109-2 Acute gout attack of the first metatarsophalangeal joint. (*Reproduced with permission from Imboden J, Hellmann DB, Stone JH. Current Rheumatology Diagnosis and Treatment, 2nd ed. New York: McGraw-Hill, 2004:316.*)

Atypical presentations of gout also occur. For elderly patients, gout can present as a chronic polyarticular arthritis that can be confused with rheumatoid arthritis or osteoarthritis. Additionally, the onset of gout may be less dramatic than the typical acute attack and with fewer clinical findings.[10] Multiple small joints in the hands may be involved, especially in elderly women.[9] **Table 109-3** summarizes the different clinical manifestations of gout.

TABLE 109-3 Clinical Manifestations of Gout

Classic acute gout ("podagra")	Monoarticular arthritis Frequently attacks the first metatarsophalangeal joint, although other joints of the lower extremities are also frequently involved Affected joint is swollen, erythematous, and tender
Interval gout	Asymptomatic period between attacks
Tophaceous gout	Deposits of monosodium urate crystals in soft tissues Complications include soft tissue damage, deformity, joint destruction, and nerve compression syndromes such as carpal tunnel syndrome
Atypical gout	Polyarthritis affecting any joint, upper or lower extremity May be confused with rheumatoid arthritis or osteoarthritis
Gouty nephropathy	Nephrolithiasis Acute and chronic kidney disease

The predilection of acute gout for peripheral joints of the lower extremity is probably related to the low temperature of these joints combined with high intra-articular urate concentration. Synovial effusions are likely to occur transiently in weight-bearing joints during the course of a day with routine activity. At night, water is reabsorbed from the joint space, leaving behind a supersaturated solution of monosodium urate, which can precipitate attacks of acute arthritis. Attacks generally begin at night with the patient awakened from sleep by excruciating pain.

CLINICAL PRESENTATION Acute Gouty Arthritis

General

- Gout classically presents as an acute inflammatory monoarthritis. The first metatarsophalangeal joint is often involved ("podagra"), but any joint of the lower extremity can be affected and occasionally gout will present as a monoarthritis of the wrist or finger. The spectrum of gout also includes nephrolithiasis, gouty nephropathy, and aggregated deposits of sodium urate (tophi) in cartilage, tendons, synovial membranes, and elsewhere.

Signs and Symptoms

- Fever, intense pain, erythema, warmth, swelling, and inflammation of involved joints.

Laboratory Tests

- Elevated serum uric acid concentrations; leukocytosis.

Other Diagnostic Tests

- Observation of MSU crystals in synovial fluid or a tophus.
- For patients with long-standing gout, radiographs may show asymmetric swelling within a joint or subcortical cysts without erosions.

The development of crystal-induced inflammation involves several chemical mediators causing vasodilation, increased vascular permeability, complement activation, and chemotactic activity for polymorphonuclear leukocytes.[2] Phagocytosis of urate crystals by the leukocytes results in rapid lysis of cells and a discharge of lysosomal and proteolytic enzymes into the cytoplasm. The ensuing inflammatory reaction is associated with intense joint pain, erythema, warmth, and swelling. Fever is common, as is leukocytosis. Untreated attacks may last from 3 to 14 days before spontaneous recovery.

Although acute attacks of gouty arthritis may occur without apparent provocation, several conditions may precipitate an attack. These include stress, trauma, alcohol ingestion, infection, surgery, rapid lowering of serum uric acid by ingestion of uric acid-lowering agents, and ingestion of certain drugs known to elevate serum uric acid concentrations (Table 109-2). The natural course of an acute flare, if left untreated, varies among patients and may resolve after several hours or may take up to two weeks. Furthermore, acute flares of gouty arthritis may initially occur infrequently. Over time the duration of untreated attacks may become longer and the interval between attacks may shorten if appropriate measures to correct hyperuricemia are not undertaken. Later in the disease, tophaceous deposits of MSUs in the skin or subcutaneous tissues may be found. These tophi are often found on the hands, wrists, elbows, or knees. It is estimated to take 10 or more years for tophi to develop.

Diagnostic Evaluation

Table 109-4 lists the differential diagnosis of an acute monoarthritis.[11] A

definitive diagnosis of gout requires aspiration of synovial fluid from the affected joint and identification of intracellular crystals of monosodium urate monohydrate in synovial fluid leukocytes.[2] Identification of MSUs is highly dependent on the experience of the observer. Crystals are needle-shaped, and when examined under polarizing light microscopy, they are strongly negatively birefringent (**Fig. 109-3**). Crystals can be observed in synovial fluid during asymptomatic periods.[12] If an affected joint is tapped, the resulting synovial fluid may have white cells and appear purulent. Such findings should always raise the question of infection. If any clinical features of infection are present, such as high fever, elevated white blood cell count, multiple joints affected, or an identified source of infection, proper diagnosis and treatment are critical. Patients with gout can have septic arthritis. Diabetes, alcohol abuse, and advanced age increase the likelihood of septic arthritis.

TABLE 109-4 Differential Diagnosis of Acute Monoarthritis

1. Pseudogout (pyrophosphate crystal-related arthritis)
2. Palindromic rheumatism
3. Seronegative inflammatory arthritis
4. Trauma or hemarthrosis
5. Septic arthritis
6. Cellulitis
7. Type II dyslipidemia
8. Unrelated hyperuricemia (as in psoriasis, hypertension) when joint pain is not caused by gout

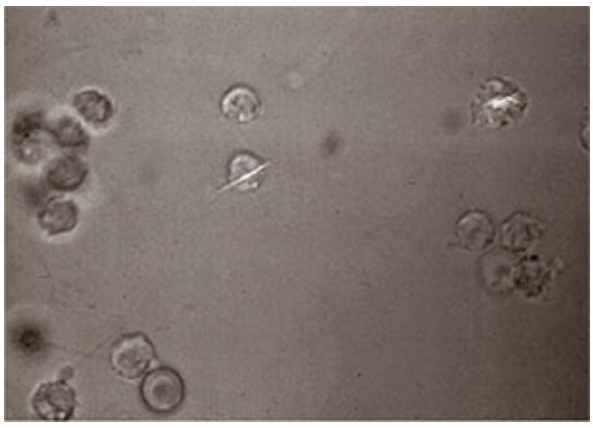


FIGURE 109-3 Urate crystal ingested by a polymorphonuclear leukocyte in synovial fluid. (*Reproduced with permission from Imboden J, Hellmann DB, Stone JH. Current Rheumatology Diagnosis and Treatment, 2nd ed. New York: McGraw-Hill, 2004:317.*)

In lieu of obtaining a synovial fluid sample from an affected joint to inspect for urate crystals, the clinical triad of inflammatory monoarthritis, elevated serum uric acid concentration, and response to colchicine can be used to diagnose gout. However, this approach has limitations, including a failure to recognize atypical gout presentations and the fact that serum uric acid concentrations can be normal or even low during an acute gout attack.[2,5] In addition, use of colchicine as a diagnostic tool for gout is limited by lack of sensitivity and specificity for the disease. Other conditions such as psoriatic arthritis, sarcoidosis, pseudogout, and Mediterranean fever can respond to colchicine therapy. For patients with long-standing gout, radiographs may show punched-out marginal erosions and secondary osteoarthritic changes; however, in an acute first attack radiographs will be unremarkable.[11,13] The presence of chondrocalcinosis on radiographs may indicate pseudogout (see additional discussion on pseudogout below). Some studies have recently examined the use of magnetic resonance imaging and computed tomography to obtain images for patients with gout; however, this is not currently considered part of normal practice. **Table 109-5** shows the European League Against Rheumatism (EULAR) evidence-based diagnostic principles.[13]

TABLE 109-5 EULAR Evidence-Based Recommendations for Gout: Diagnostic Principles

1. In acute attacks the rapid development of severe pain, swelling, and tenderness that reaches its maximum within just 6-12 hours, especially with overlying erythema, is highly suggestive of crystal inflammation though not specific for gout
2. For typical presentations of gout (such as recurrent podagra with hyperuricemia), a clinical diagnosis alone is reasonably accurate but not definitive without crystal confirmation
3. Demonstration of MSU crystals in synovial fluid or tophus aspirates permits a definitive diagnosis of gout
4. A routine search for MSU crystals is recommended in all synovial fluid samples obtained from undiagnosed inflamed joints
5. Identification of MSU crystals from asymptomatic joints may allow definite diagnosis in intercritical periods
6. Gout and sepsis may coexist. When septic arthritis is suspected, gram staining and culture of synovial fluid should still be performed, even if MSU crystals are identified
7. While the most important risk factor for gout, serum uric acid levels do not confirm or exclude gout, as many people with hyperuricemia do not develop gout, and during acute attacks serum levels may be normal
8. Renal uric acid excretion should be determined in selected gout patients, especially those with a family history of young onset gout, onset of gout under age 25 years, or with renal calculi
9. Although radiographs may be useful for differential diagnosis and may show typical features in chronic gout, they are not useful in confirming the diagnosis of early or acute gout
10. Risk factors for gout and associated comorbidity should be assessed, including features of the metabolic syndrome (obesity, hyperglycemia, hyperlipidemia, hypertension)

EULAR, The European League Against Rheumatism; MSU, monosodium urate.

Data from Reference 13.

The American College of Rheumatology (ACR) and EULAR jointly developed recommendations for the classification of gout to assist in identifying subjects potentially eligible for enrollment into clinical trials of gout treatments.[14] Although it is specifically stated that the recommendations should not be used clinically to diagnose gout, the classification system may be a useful reference when evaluating a patient presenting with symptoms suggestive of gout. The recommendations include a point-based system that includes clinical, laboratory, and imaging information, which can be used when a patient presents with at least one episode of swelling, pain, or tenderness in a peripheral joint or bursa but has no evidence of MSU crystals. An online calculator is available at http://goutclassificationcalculator.auckland.ac.nz/.

Other crystal-induced arthropathies that may resemble gout on clinical presentation are caused by calcium hydroxyapatite crystals and calcium pyrophosphate dihydrate crystals (calcium pyrophosphate deposition disease [CPDD] or “pseudogout”), which are associated with calcific periarthritis, tendinitis, and arthritis.[15–17] Pseudogout is relatively common, occurring in up to 7% of all adults in Europe and the United States. Furthermore, its prevalence increases with age, doubling with every decade over 60 years.[15] Identification of calcium pyrophosphate crystals in the synovial fluid of an affected joint in combination with positive radiology findings (eg, chondrocalcinosis, hook-like osteophytes, and axial skeletal involvement) are key methods used for diagnosis of pseudogout. Importantly, calcium pyrophosphate crystals differ from uric acid crystals in that they are positively birefringent when exposed to light microscopy. Furthermore, the clinical picture may provide clues as pseudogout rarely presents with podagra and more commonly affects the knee or wrist. Although initial management of an acute flare of pseudogout is similar to the approach used for treatment of traditional gout, management of chronic pseudogout may require use of hydroxychloroquine, methotrexate, and, ultimately, joint replacement. Recommended therapies used to prevent gout by lowering uric acid will not impact the progression of pseudogout. For these reasons, differentiating between pseudogout and gout, although challenging, is important to ensure successful clinical outcomes.

Uric Acid Nephrolithiasis

Clinicians should be suspicious of hyperuricemic states for patients who present with kidney stones, as nephrolithiasis occurs in approximately 15% of patients with gout.[18] The frequency of urolithiasis depends on serum uric acid concentrations, acidity of the urine, and urinary uric acid concentration. Typically, patients with uric acid nephrolithiasis have a urinary pH of less than 6. Uric acid has a negative logarithm of the acid ionization constant of 5.5. Therefore, when the urine is acidic, uric acid exists primarily in the unionized, less soluble form. At a urine pH of 5, urine is saturated at a uric acid concentration of 15 mg/dL (0.89 mmol/L). When the urine pH is 7, the solubility of uric acid in urine is increased to 200 mg/dL (11.9 mmol/L).[1] For patients with uric acid nephrolithiasis, urinary pH typically is less than 6 and frequently less than 5.5. When acidic urine is saturated with uric acid, spontaneous precipitation of stones may occur.

Other factors that predispose individuals to uric acid nephrolithiasis include

excessive urinary excretion of uric acid and highly concentrated urine. The risk of renal calculi approaches 50% in individuals whose renal excretion of uric acid exceeds 1,100 mg/day (6.5 mmol/day). In addition to pure uric acid stones, hyperuricosuric individuals are at increased risk for mixed uric acid–calcium oxalate stones and pure calcium oxalate stones.

Gouty Nephropathy

There are two types of gouty nephropathy: acute uric acid nephropathy and chronic urate nephropathy.[2] In acute uric acid nephropathy, acute kidney injury occurs as a result of blockage of urine flow secondary to massive precipitation of uric acid crystals in the collecting ducts and ureters. This syndrome is a well-recognized complication for patients with myeloproliferative or lymphoproliferative disorders and is a result of massive malignant cell turnover, particularly after initiation of chemotherapy.

Chronic urate nephropathy is caused by the long-term deposition of urate crystals in the renal parenchyma. Microtophi may form, with a surrounding giant-cell inflammatory reaction. A decrease in the kidneys' ability to concentrate urine and the presence of proteinuria may be the earliest pathophysiologic disturbances. Hypertension and nephrosclerosis are common associated findings. Although kidney failure occurs in a higher percentage of gouty patients than expected, it is not clear if hyperuricemia per se has a harmful effect on the kidneys. The chronic kidney disease seen in individuals with gout may result largely from the coexistence of hypertension, diabetes mellitus, and atherosclerosis.

Tophaceous Gout

Tophi (urate deposits) are uncommon in the general population of gouty subjects and are a late complication of hyperuricemia. The most common sites of tophaceous deposits for patients with recurrent acute gouty arthritis are the base of the fingers, olecranon bursae, ulnar aspect of the forearm, Achilles tendon, knees, wrists, and hands (**Fig. 109-4**).[2] Eventually, even the hips, shoulders, and spine may be affected. In addition to causing obvious deformities, tophi may damage surrounding soft tissue, cause joint destruction and pain, and even lead to nerve compression syndromes including carpal tunnel syndrome.

FIGURE 109-4 Tophaceous gout with subcutaneous nodule almost breaking through the skin. (*Reproduced with permission from South-Paul JE, Matheny SC, Lewis EL. Current Diagnosis and Treatment in Family Medicine. New York: McGraw-Hill, 2004:275.*)

TREATMENT

Guideline Overview

The goals in the treatment of gout are to terminate the acute attack, prevent recurrent attacks of gouty arthritis, and prevent complications associated with chronic deposition of urate crystals in tissues. These can be accomplished through a combination of pharmacologic and nonpharmacologic methods, including focused patient education efforts. Several organizations, including The American College of Rheumatology (ACR), the European League Against Rheumatism (EULAR), and the American College of Physicians (ACP), have developed guidelines for the management of gout. These guidelines have been published and, in some cases, undergone revision since their original publication.

The first-ever ACR evidence- and consensus-based guidelines for the management of gout were published in 2012.[19,20] These guidelines provide specific recommendations for treatment of acute gout attacks, management of hyperuricemia in gout, and anti-inflammatory prophylaxis of acute gout during initiation of urate-lowering therapy (ULT). The original 2006 EULAR gout guidelines, which address the same aspects of care included in the ACR guidelines, were updated in 2016 with 11 novel recommendations and three overarching principles.[21] In addition, the ACP developed a guideline for management of acute and recurrent gout in 2017. This guideline consists of four recommendations and identification of six-specific areas with inconclusive evidence.[22] While the various guidelines share many similarities, there are several differences, particularly with regard to the management of

hyperuricemia, which will be highlighted throughout the treatment section. **Tables 109-6** and **109-7** summarize dosing and monitoring information for available pharmacotherapy used in management and prevention of gout.

TABLE 109-6 Pharmacotherapy of Acute Gout, Anti-Inflammatory Prophylaxis during Initiation of Urate-Lowering Therapy and Hyperuricemia in Gout[a]

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Other
Acute Gout					
NSAIDs					In general, not recommended in patients with advanced kidney disease as NSAID use may decrease kidney function; use with caution in patients with mild-to-moderate kidney impairment
Etodolac	Lodine, various	300 mg twice daily	300-500 mg twice daily		
Fenoprofen	Nalfon, various	400 mg three times daily	400-600 mg three to four times daily		
Ibuprofen	Advil, various	400 mg three times daily	400-800 mg three to four times daily		
Indomethacin	Indocin	50 mg three times daily	50 mg three times daily initially until pain is tolerable then rapidly reduce to complete cessation		
Ketoprofen	Orudis, various	75 mg three times daily or 50 mg four times daily	50-75 mg three to four times daily	Severe kidney impairment (GFR <25 mL/min [0.42 mL/s]): 100 mg maximum daily dose Mildly impaired kidney function: 150 mg maximum daily dose Impaired liver function with serum albumin <3.5 g/dL (<35 g/L): 100 mg maximum daily dose	
Naproxen	Naprosyn, various	750 mg followed by 250 mg every 8 hours until the attack has subsided		Not recommended in severe kidney impairment (creatinine clearance <30 mL/min [<0.5 mL/s])	
Piroxicam	Feldene	20 mg once daily or divided twice daily			
Sulindac	Clinoril	200 mg twice a day	150-200 mg twice daily for 7-10 days		
Meloxicam	Mobic	5 mg daily	7.5-15 mg daily	Not recommended if creatinine clearance <15 mL/min	
Celecoxib	Celebrex	800 mg followed by 400 mg on day one then 400 mg twice daily for 1 week			Option for patients with GI contraindications to nonselective NSAIDs; unclear risk-to-benefit ratio at this time due to cardiovascular concerns
Oral colchicine	Colcrys	1.2 mg initially, followed by 0.6 mg 1 hour later		See Table 109-8	Dose adjustment recommended when used with selected CYP3A4 and P-glycoprotein inhibitors
Corticosteroids					
Oral		0.5 mg/kg prednisone equivalent daily for 5-10 days followed by discontinuation or 0.5 mg/kg daily for 2-5 days followed by tapering for 7-10 days	30-60 mg prednisone equivalent once daily for 3-5 days, then taper in 5-mg decrements spread over 10-14 days until discontinuation		The use of an oral methylprednisolone dose pack may be considered
Intramuscular		Triamcinolone acetonide 60 mg IM once; methylprednisolone 100 mg IM once	Triamcinolone acetonide 60 mg IM once; methylprednisolone 100-150 mg IM daily for 1-2 days		Administration of intramuscular triamcinolone is to be followed by oral prednisone or prednisolone
Intra-articular	Kenalog	Triamcinolone acetonide 10 mg (large joints), 5 mg (small joints)	Triamcinolone acetonide 10-40 mg (large joints), 5-20 mg (small joints)		Intra-articular administration is acceptable when only one to two joints involved and should be used in combination with NSAIDs, colchicine, or oral corticosteroids

Corticotropin	H.P. Acthar Gel	40 units IM or SC every 72 hours	40-80 units IM or SC every 24-72 hours		Contraindicated for IV administration
Interleukin-1 inhibitors					Reserve use for refractory cases; use for gout is an off-label indication
Anakinra	Kineret	100-mg SC daily for 3 days			
Canakinumab	Ilaris	Single dose 150-mg SC			
Anti-Inflammatory Prophylaxis During Initiation of Urate-Lowering Therapy					
NSAIDs			Lowest effective dosage		
Oral colchicine	Colcrys	0.6 mg daily	0.6 mg once or twice daily	See Table 109-8	
Prednisone or prednisolone		≤10 mg daily			Second-line therapy; recommended only if colchicine and NSAIDs are both contraindicated, ineffective, or not tolerated
Interleukin-1 inhibitors					Reserve use for refractory cases Studied for 16-week duration
Rilonacept	Arcalyst	320-mg loading dose followed by 160 mg weekly (SC)			
Canakinumab	Ilaris	Single SC dose (50-300 mg) or four times weekly SC dosing (50 mg—50 mg—25 mg—25 mg)			
Hyperuricemia in Gout					
Xanthine oxidase inhibitors					
Allopurinol	Lopurin, Zyloprim	100 mg daily	100-800 mg daily to achieve serum urate concentration <6 mg/dL (<357 µmol/L)	Start at dose of 50 mg daily for patients with a glomerular filtration rate <30 mL/min/1.73 m^2 (<0.29 mL/s/m^2)	
Febuxostat	Uloric	40 mg daily	40-80 mg/daily	No dosage adjustment necessary for patients with mild-to-moderate kidney impairment (creatinine clearance 30-89 mL/min [0.5-1.49 mL/s]) Insufficient data in patients with creatinine clearance <30 mL/min (<0.5 mL/s)	
Uricosurics					
Probenecid	Probalan	250 mg twice daily for 1 week	500-2,000 mg/day (target serum urate concentration <6 mg/dL [<357 mol/L])	Not recommended if creatinine clearance <50 mL/min (<0.83 mL/s)	
Lesinurad	Zurampic	200 mg once daily in combination with a xanthine oxidase inhibitor		Not recommended if creatinine clearance <45 mL/min (<0.75 mL/s) Not studied in patients with severe hepatic disease Contraindicated in tumor lysis syndrome and Lesch-Nyhan syndrome	Should be used in combination with a xanthine oxidase inhibitor due to increased risk of acute kidney injury with lesinurad monotherapy Use is not recommended in patients taking allopurinol doses <300 mg daily (normal kidney function) or <200 mg daily (creatinine clearance <60 mL/min)

Combination Therapy				
Lesinurad/ Allopurinol	Duzallo	Lesinurad 200 mg/ allopurinol 300 mg: one tablet daily	Lesinurad 200 mg/ allopurinol 200 mg: one tablet daily recommended if creatinine clearance is 45-60 mL/min Not recommended if creatinine clearance <45 mL/min (<0.75 mL/s)	See above for lesinurad and allopurinol comments
Other				
Pegloticase	Krystexxa	8 mg IV every 2 weeks		Optimal treatment duration has not been established

[a]Agents available in the United States.

CYP, cytochrome P; GFR, glomerular filtration rate; IM, intramuscular; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; SC, subcutaneous.

TABLE 109-7 Drug Monitoring

Drug	Adverse Drug Reaction	Monitoring Parameter	Comments
NSAIDs	Impaired kidney function (acute and chronic [Chapter 61], gastritis (worse with concurrent aspirin), fluid retention, blood pressure elevation	Therapeutic Resolution of pain Avoidance of gout attacks when used for prophylaxis Toxic Blood pressure Kidney function Edema Dark stools	Avoid for patients with peptic ulcer disease, active bleeding Use caution in congestive heart failure, dehydration, impaired kidney function Consider coadministration with a proton-pump inhibitor when used long term for patients at risk for GI bleeding
Systemic corticosteroids	GI upset, increased appetite, nervousness/restlessness, transient glucose intolerance, fluid retention, blood pressure elevation	Therapeutic Resolution of pain Avoidance of gout attacks when used for prophylaxis Toxic Glucose levels in patients with diabetes	Limit duration of therapy in patients with diabetes
Intra-articular corticosteroids	Injection pain, rebound arthritis	Therapeutic Resolution of pain Toxic Signs of rebound arthritis (pain relief followed by reemergence of pain)	Avoid if joint sepsis cannot be ruled out
Corticotropin	Increased appetite, nervousness/restlessness, transient glucose intolerance, fluid retention, blood pressure elevation	Therapeutic Resolution of pain	Requires intact pituitary–adrenal axis Less effective for patients receiving long-term oral corticosteroid therapy
Colchicine	Dose-dependent GI adverse effects (diarrhea, nausea, vomiting), rare myelosuppression, and reversible neuromyopathy	Therapeutic Resolution of pain Avoidance of gout attacks when used for prophylaxis Toxic GI symptoms Complete blood count	
Interleukin-1 inhibitors	Injection site reaction, neutropenia, immune hypersensitivity reaction, infectious disease, malignancy	Therapeutic Resolution of pain Avoidance of gout attacks when used for prophylaxis Toxic Neutrophil count (prior to initiation, monthly for the first 3 months of therapy then after 6, 9, and 12 months of therapy) Temperature (periodically to detect infection)	Safety for use in acute gout and gout prophylaxis during initiation of urate-lowering therapy has not yet been established; not FDA approved for use in gout
Allopurinol	Rash, potential for fatal hypersensitivity syndrome	Therapeutic Serum urate level Reduced frequency of gout attacks Toxic Rash Kidney function	Can be used in both urate overproduction and urate underexcretion
Febuxostat	Liver enzyme elevation, nausea, arthralgias, rash, cardiovascular risk	Therapeutic Serum urate level Reduced frequency of gout attacks Toxic Liver function tests Kidney function	Can be used in both urate overproduction and urate underexcretion
Probenecid	Urolithiasis	Therapeutic Serum urate level Reduced frequency of gout attacks Toxic Kidney function	Useful in urate underexcretion Avoid for patients with history of urolithiasis
Pegloticase	Acute gout attack during treatment initiation, anaphylaxis, GI symptoms (constipation, nausea, vomiting), chest pain, nasopharyngitis	Therapeutic Serum urate levels Reduced frequency of gout attacks Toxic Signs/symptoms of anaphylaxis following infusion	Reserved for patients with gout refractory to conventional therapies Can be used in both urate overproduction and urate underexcretion
Lesinurad	Acute gout attack during treatment initiation, headache, GERD, acute kidney injury, major adverse cardiovascular events have been observed, although a causal relationship has not been established	Therapeutic Serum urate levels Reduced frequency of gout attacks Toxic Kidney function	Reserved for patients with hyperuricemia associated with gout who do not achieve target serum uric acid levels with conventional therapies Can be used in both urate overproduction and urate underexcretion Must be used in combination with a xanthine oxidase inhibitor due to increased risk of acute kidney injury with monotherapy

FDA, Food and Drug Administration; GERD, gastroesophageal reflux disease; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.

Acute Gouty Arthritis

Nonpharmacologic Therapy

Nonpharmacologic therapies have an important role in modifying the underlying hyperuricemia and reducing the risk of an acute gout attack before one occurs. There are limited effective nonpharmacologic therapies for treatment of an acute gout attack; therefore, they are recommended strictly as adjuvants.

Local ice application to the affected joint is the most effective.[20] Adjunctive ice application results in significantly greater pain reduction in those receiving the therapy compared with those not treated with ice.[23] Complementary and alternative medicines, including flaxseed, cherry, and celery root, are not recommended for treatment of acute gout in guidelines.[20]

Pharmacologic Therapy

2 For most patients, acute attacks of gouty arthritis may be treated successfully with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or colchicine. The ACR, EULAR, and ACP guidelines recognize these three monotherapies as first line for the treatment of acute gout.[20–22] Treatment should commence as soon as possible after the onset of an attack. In more severe cases, those affecting multiple joints or causing higher intensity pain, combination or off-label use of IL-1 inhibitor therapy may be used (**Fig. 109-5**).[20,21]

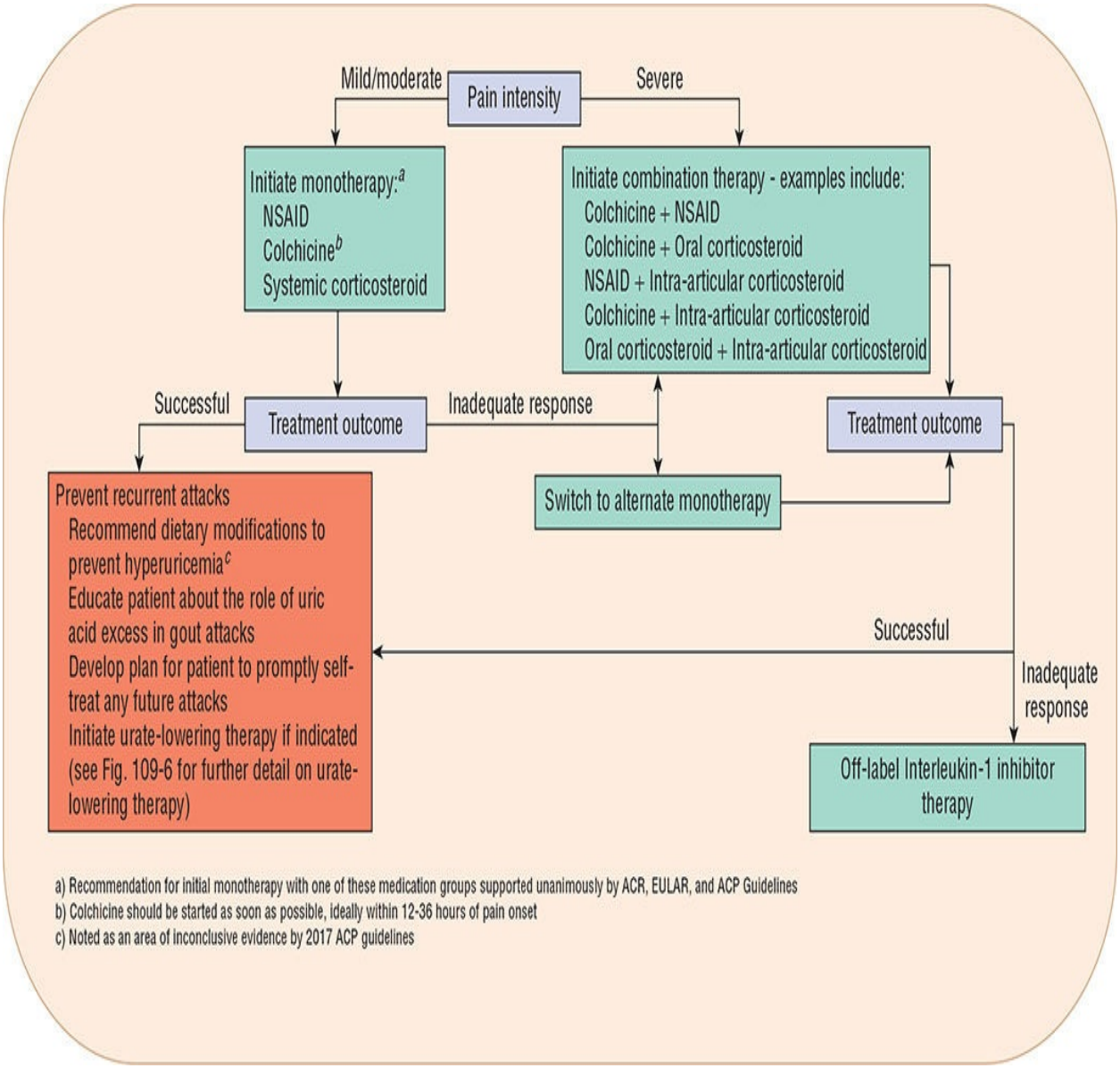
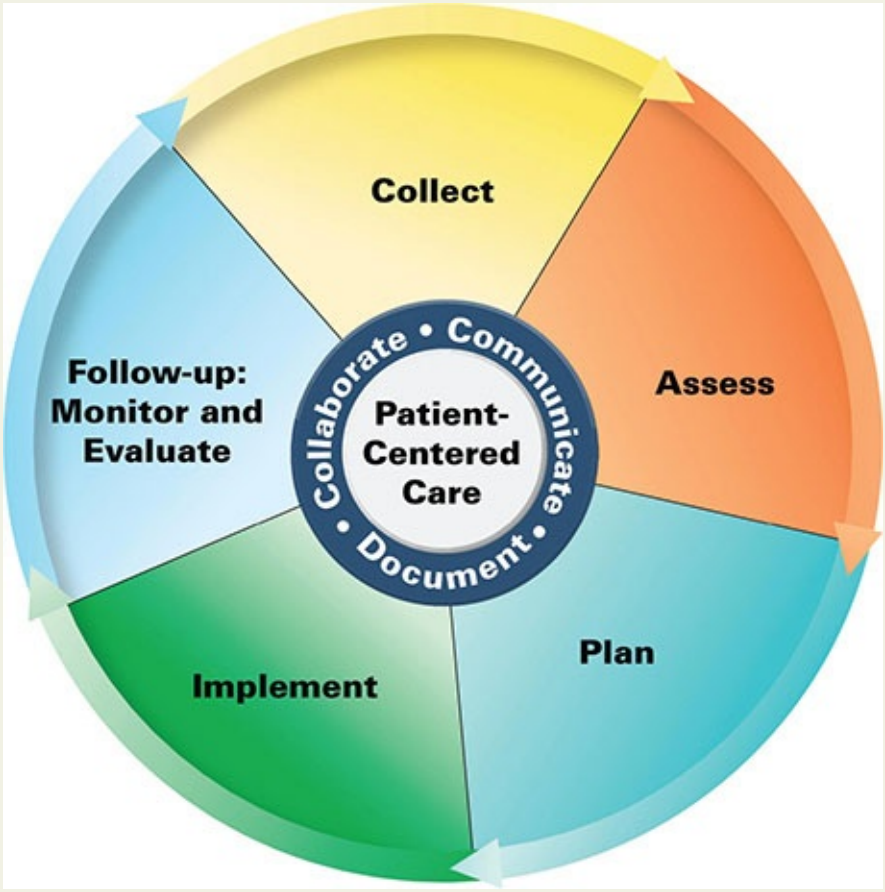


FIGURE 109-5 Algorithm for management of an acute gout attack. (*Algorithm derived from 2017 ACP, 2016 EULAR and 2012 ACR gout guidelines.*)

Nonsteroidal Anti-Inflammatory Drugs NSAIDs are a mainstay of therapy for acute attacks of gouty arthritis because of their excellent efficacy and minimal toxicity with short-term use. Indomethacin has been historically favored as the NSAID of choice for acute gout flares, but there is little evidence to support one NSAID as being more efficacious than another. Three agents (indomethacin, naproxen, and sulindac) have US Food and Drug Administration (FDA)–approved labeling for the treatment of gout, although several others are likely to be effective.[20] The most important determinant of therapeutic success is not which NSAID is chosen, but rather, how soon it is initiated. Therapy initiated

within 24 hours of onset is more likely to be effective than if delayed.[20] Following resolution of the attack, tapering of NSAID therapy may be considered, especially in patients with comorbidities such as impaired hepatic or kidney function where prolonged therapy would be undesirable.[20] Resolution of an acute attack for most patients generally occurs within 5 to 8 days after initiating therapy.



Patient Care Process for Gout

Collect

- Patient characteristics (eg, age, sex, ethnicity)
- Patient medical history (see Table 109-1)
- Dietary habits that may lead to increased uric acid concentrations, including alcohol consumption, intake of high-purine foods and products containing high-fructose corn syrup
- Current medications that may contribute to hyperuricemia (see Table 109-

2)

- Subjective report of acute gout symptoms
- Objective data
  - Blood pressure (BP), height, weight
  - Labs including uric acid, serum creatinine (SCr)
  - Synovial fluid aspirate

Assess

- Presence of acute gout (see Tables 109-3 and 109-5)
- Presence of hyperuricemia (>7.0 mg/dL)
- Indication for urate-lowering therapy (see Table 109-6)
- Optimal therapy given patient-specific factors (see Table 109-9)
- Presence of other cardiovascular risk factors (eg, hypertension, diabetes)

Plan*

- Drug therapy regimen including specific agent for treatment of acute gout: dose, route, frequency, and duration (see Table 109-6)
- Monitoring parameters for efficacy (eg, resolution of pain) and safety (eg, sign and symptoms of adverse effects associated with selected therapy), frequency and timing of follow-up
- Drug therapy regimen including specific agent for treatment of hyperuricemia if indicated: dose, route, frequency, and duration (see Table 109-6)
- Patient education (eg, purpose of treatment vs prevention, dietary and lifestyle modification, drug-specific information, medication counseling; see Table 109-6)
- Self-monitoring for resolution of gout symptoms and occurrence of medication side effects
- Referrals to other providers when appropriate (eg, rheumatologist, dietitian)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize

adherence

- Schedule follow-up (eg, assessment of uric acid, SCr, adherence)

Follow-up: Monitor and Evaluate

- Resolution of gout symptoms (eg, pain)
- Presence of adverse effects (eg, diarrhea [colchicine], agitation [corticosteroids], allopurinol hypersensitivity syndrome [allopurinol])
- Uric acid concentrations (allopurinol, febuxostat) (adjust dose as needed to achieve uric acid <5.0-6.0 mg/dL)
- Patient adherence to treatment plan using multiple sources of information

**Collaborate with patient, caregivers, and other healthcare professionals.*

All NSAIDs have the potential to cause similar adverse effects. The most common areas affected include the GI system (gastritis, bleeding, perforation), kidneys (renal papillary necrosis, reduced glomerular filtration rate), cardiovascular system (sodium and fluid retention, increased blood pressure), and central nervous system (CNS) (impaired cognitive function, headache, dizziness). Caution should be exercised when using NSAIDs for individuals with a history of peptic ulcer disease, congestive heart failure, uncontrolled hypertension, impaired kidney function, coronary artery disease, or who are concurrently receiving anticoagulants or antiplatelets. Patients with active peptic ulcer disease, uncompensated congestive heart failure, chronic kidney disease, or a history of hypersensitivity to aspirin or other NSAIDs should not be prescribed an NSAID.

Selective cyclooxygenase-2 (COX-2) inhibitors present a potentially less risky alternative to nonselective NSAIDs in patients with GI issues.[24] Specific COX-2 inhibitors, etoricoxib and lumiracoxib, have demonstrated efficacy in the treatment of acute gout in numerous controlled trials; however, these agents are not available in the United States. One study has established effectiveness of high-dose celecoxib (1,200 mg on day 1 followed by 400 mg twice daily thereafter) in the treatment of acute gout, but concerns regarding the cardiovascular risk of COX-2 inhibitors must be considered when using these agents (see Chapter 106, “Osteoarthritis,” for further discussion of COX-2 inhibitors).[25] The ACR guidelines recommend celecoxib as an option for patients unable to take traditional NSAIDs but note that the risk-to-benefit ratio of celecoxib use in acute gout is unclear.[20]

Corticosteroids Corticosteroids have historically been reserved for treatment of acute gout flares when contraindications to other therapies exist, largely due to lack of evidence from controlled clinical trials. However, more recent evidence indicates that corticosteroids are equivalent to NSAIDs in the treatment of acute gout flares.[26,27] They can be used either systemically or by intra-articular injection. The ACR and EULAR guidelines recommend that the number of joints involved be considered when choosing the route of corticosteroid administration. If only one or two joints are involved, either intra-articular or oral corticosteroids are recommended. If an attack is polyarticular, systemic therapy is necessary.[20,21] A hypothetical risk exists for a rebound attack upon steroid withdrawal; therefore, gradual tapering is often employed when discontinuing steroid therapy. The ACR guidelines suggest two different dosing strategies for oral corticosteroid therapy (prednisone or prednisolone) in the treatment of acute gout: (a) 0.5 mg/kg daily for 5 to 10 days followed by abrupt discontinuation or (b) 0.5 mg/kg daily for 2 to 5 days followed by tapering for 7 to 10 days. The guidelines also support the use of a methylprednisolone dose pack for acute treatment of gout, a 6-day regimen that starts with 24 mg on day 1 and decreases by 4 mg each day.[20] EULAR guidelines recommend prednisolone at a dose of 30 to 35 mg/day for 5 days.[21]

Intra-articular administration of triamcinolone acetonide in a dose of 20 to 40 mg may be useful in treating acute gout limited to one or two joints. Injection should be done under an aseptic technique in a joint determined not to be infected. Per ACR guideline recommendations, intra-articular corticosteroid therapy should be used in conjunction with either an NSAID, colchicine, or oral corticosteroid therapy; however, case reports suggest that combination therapy may be no more effective than intra-articular injection monotherapy.[20,28] A single intramuscular injection of a long-acting corticosteroid, such as methylprednisolone, followed by a short course of oral corticosteroid therapy is recognized as a reasonable therapeutic approach to the treatment of acute gout by the ACR guidelines.[20] EULAR guidelines do not specify that intra-articular corticosteroid injections should be part of combination therapy.[21] Alternatively, intramuscular corticosteroid monotherapy could be considered in patients with multiple affected joints who are unable to take oral therapy.

The adverse effects of corticosteroids are generally dose and duration dependent. Short-term use for treatment of acute attacks is generally well tolerated. Corticosteroids should be used with caution for patients with diabetes as they can increase blood sugar. In addition, patients with a history of GI problems, bleeding disorders, cardiovascular disease, and psychiatric disorders

should be monitored closely. Long-term corticosteroid use should be avoided because of the risk for osteoporosis, hypothalamic–pituitary axis suppression, cataracts, and muscle deconditioning that can occur with their use.

Corticotropin, or adrenocorticotropic hormone (ACTH), which stimulates the adrenal cortex to produce cortisol and corticosterone, can be administered in acute gout. The ACR guidelines support the use of ACTH in the treatment of acute gout in patients unable to take oral medications.[20] Doses of 40 to 80 United States Pharmacopeia (USP) units are given intramuscularly with repeat doses as clinically indicated for 2 to 3 days, and then discontinued. Studies with ACTH are limited, but it appears to provide similar efficacy to systemic anti-inflammatory doses of corticosteroids.[29] When administered alone or in combination with colchicine, ACTH may provide earlier efficacy compared with indomethacin but with fewer adverse effects.[30] Because the studies have several limitations, the regimen should be considered only as an alternative, especially for patients with comorbidities where other regimens are contraindicated.[31] Examples of patients where ACTH has been used safely when other first-line gout therapies were contraindicated include those with congestive heart failure, chronic kidney disease, and history of GI bleeding.[32] Unfortunately, access to ACTH has been impacted following changes in the manufacturer of ACTH in 2007. This change in ownership resulted in a dramatic increase in the price of the medication such that it is no longer a viable treatment option.

Colchicine Colchicine is an antimitotic drug that is highly effective at relieving acute attacks of gout.[33] When begun within the first 24 hours of an acute attack, colchicine produces a response in two-thirds of patients within hours of administration.[34] If the initiation of colchicine is delayed; however, the probability of success with the drug diminishes substantially. For this reason, the ACR guidelines advocate use of colchicine for treatment of acute gout only if started within 36 hours of attack onset, while EULAR guidelines encourage colchicine use within 12 hours of an attack.[20,21]

Although it is a highly effective therapy, oral colchicine can cause dose-dependent GI adverse effects, including nausea, vomiting, and diarrhea. Other important non-GI adverse effects include neutropenia and axonal neuromyopathy, which may be worsened for patients taking other myopathic drugs such as β-hydroxy-β-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) or for those with impaired kidney function.

Colchicine was used for many years to treat acute gouty arthritis, but as an unapproved drug without having undergone formal FDA review for safety and

efficacy. In 2009, the FDA approved a 0.6-mg tablet of colchicine (under the brand name Colcrys®) for oral use, which was followed by an order for all unapproved colchicine products to stop manufacturing within 90 days. Following enforcement of market exclusivity for the branded colchicine product, use of colchicine to treat acute gouty arthritis declined immediately thereafter due to the significant cost.[35] Colchicine is now once again available generically.

One benefit of the FDA approval of Colcrys® was new information on dosing. Data submitted in support of the safety and efficacy of colchicine in acute gout flares demonstrated that a substantially lower dose of colchicine (1.2 mg initially, followed by a single 0.6-mg dose one hour later) was as effective as higher doses traditionally used (continued hourly dosing until symptoms subside or GI symptoms become intolerable).[36] These findings suggested that use of high-dose colchicine regimens may unnecessarily expose patients to increased GI toxicity with no additional efficacy.[33] In addition to the low-dose regimen, the ACR guidelines also suggest that colchicine 0.6 mg once or twice daily can be started 12 hours following the initial 1.2-mg dose and continued until the acute attack resolves.[20] This off-label dosing recommendation is based upon pharmacokinetic data that suggest that colchicine concentrations begin to decline 12 hours after administration.[36]

Comprehensive review of postmarketing safety data revealed an increased risk of adverse events for patients receiving colchicine administered concurrently with P-glycoprotein or cytochrome P450 3A4 inhibitors (including protease inhibitors and medications listed in **Table 109-8**).[37] These interactions are thought to result in an increased colchicine concentration. Colchicine should also be used carefully for patients with impaired kidney and hepatic function. Colchicine dosing recommendations in select situations are listed in Table 109-8. Please refer to the colchicine prescribing information for an entire listing of drug/disease interactions and corresponding dosing adjustments.

TABLE 109-8 Colchicine Dosing in Special Situations/Colchicine Drug Interactions

	Treatment of Acute Gout Flares	Prophylaxis of Gout Flares
Impaired Kidney Function[a]		
Mild/moderate (creatinine clearance = 30-80 mL/min [0.5-1.33 mL/s])	Dose adjustment not required	Dose adjustment not required
Severe (creatinine clearance <30 mL/min [<0.5 mL/s])	Dose adjustment not required; treatment course should be repeated no more than once every 2 weeks	0.3 mg daily (starting dose)
Dialysis	Single 0.6-mg dose; treatment course should not be repeated more than once every 2 weeks	0.3 mg twice weekly (starting dose)
Hepatic Impairment[b]		
Mild/moderate	Dose adjustment not required	Dose adjustment not required
Severe	Dose adjustment not required; treatment course should be repeated no more than once every 2 weeks	Dose reduction should be considered
Colchicine Drug Interactions		
Strong CYP3A4 inhibitors • Atazanavir • Clarithromycin • Darunavir/ritonavir • Indinavir • Itraconazole • Ketoconazole • Lopinavir/ritonavir • Nefazodone • Nelfinavir • Ritonavir • Saquinavir • Telithromycin • Tipranavir/ritonavir	Single 0.6-mg dose followed by 0.3 mg 1 hour later; dose to be repeated no earlier than 3 days	0.3 mg once every other day to 0.3 mg once daily
Moderate CYP3A4 inhibitors • Amprenavir • Aprepitant • Diltiazem • Erythromycin • Fluconazole • Fosamprenavir • Grapefruit juice and related citrus products • Verapamil	Single 1.2-mg dose; dose to be repeated no earlier than 3 days	0.3-0.6 mg daily (0.6-mg dose may be given as 0.3 mg twice daily)
P-glycoprotein inhibitors • Cyclosporine • Ranolazine	Single 0.6-mg dose; dose to be repeated no earlier than 3 days	0.3 mg once every other day to 0.3 mg once daily

[a]Treatment of gout flares with colchicine is not recommended in patients with impaired kidney function who are receiving colchicine for prophylaxis.

[b]Treatment of gout flares with colchicine is not recommended in patients with hepatic impairment who are receiving colchicine for prophylaxis.

IV colchicine has resulted in fatalities and is no longer available.[38]

Management of Hyperuricemia in Gout

Nonpharmacologic Therapy

Following treatment and resolution of the intense pain associated with an acute gout attack, the focus should shift to the prevention of future episodes. Recurrent gout attacks can be prevented by maintaining low uric acid concentrations. Although both nonpharmacologic and pharmacologic efforts to maintain low uric acid concentrations are critical in the management of gout, trials have shown high rates of nonadherence with ULT.[39] A likely explanation for this lack in patient adherence is the silent nature of intercritical gout (the period of time between two gout attacks). Patient education, therefore, is a critical first step in the management of hyperuricemia.[19] Education should address the recurrent nature of the disease and reinforce the objective of each lifestyle/dietary modification and medication therapy recommended.

Weight loss through caloric restriction and exercise should be promoted in all patients with gout and hyperuricemia, as this may enhance renal excretion of urate.[19] Specifically, the urate lowering effect of the DASH diet (Dietary Approaches to Stop Hypertension) has been examined. This diet includes vegetables, fruits, whole grains, reduced-fat dairy, lean meats, beans, and nuts along with avoidance of foods high in saturated fats and sweetened beverages/foods. Studies have demonstrated a serum uric acid lowering effect of ~1.0 mg/dL in patients with hyperuricemia at baseline who adhere to the diet.[40,41] Restriction of alcohol intake is also of great importance, as this is closely correlated with gout attacks.[42] Acute ingestions of alcohol cause lactic acidemia, which reduces renal urate excretion, and long-term alcohol intake promotes production of purines as a by-product of the conversion of acetate to acetyl coenzyme A in the metabolism of alcohol.[43] The ACR guidelines recommend limiting alcohol use in all gout patients and avoidance of any alcohol during periods of frequent gout attacks and in those with advanced gout under poor control, while EULAR guidelines recommend avoidance of alcohol in every person with gout.[19,21] Both guidelines also recommend limiting consumption of high-fructose corn syrup and purine-rich foods (organ meats and some seafood), which have been linked to uric acid elevation, and encourage the consumption of low-fat dairy products, which have been shown to have urate-lowering effects.[19,21] In contrast to ACR and EULAR guidelines, the ACP guidelines note there is insufficient evidence to support recommendations for

dietary counseling in patients with gout. They cite the existence of only one systemic review and one randomized trial showing urate lowering with dietary counseling, but no studies showing that dietary intervention improved clinical outcomes (such as reduction in gout flares).[22]

Consumption of cherry-containing products, such as cherries and tart cherry extract, for both the prevention and treatment of gout, has received considerable attention and a wide variety of non-FDA regulated supplements promoting benefits for gout are available. Uric acid lowering effects associated with cherry consumption have been demonstrated, although a physiologic mechanism for this effect has not been described.[44] In a large trial involving 633 individuals, self-reported cherry intake over a 2-day period was associated with a 35% lower risk of gout attacks compared with no intake.[45] Randomized controlled trials are needed to better establish the role of cherry products before they can be recommended for management of hyperuricemia. Furthermore, the caloric and sugar content of each cherry-containing product should be considered. Since many patients with hyperuricemia can benefit from weight loss, use of these caloric-dense products is not optimal.

Another strategy to lower uric acid before initiating urate-lowering pharmacotherapy is to evaluate the patient's medication list for potentially unnecessary drugs that may elevate uric acid concentrations (Table 109-2). The ACR guidelines recommend the elimination of unnecessary uric acid-elevating medications for all gout patients with hyperuricemia; noting that the benefit of therapies must be considered in tandem. Examples of these medications include thiazide and loop diuretics, calcineurin inhibitors, niacin, and low-dose aspirin. Importantly, the ACR guidelines specifically highlight the importance of continuing low-dose aspirin used for cardiovascular prevention in patients with gout who are at increased cardiovascular risk, noting that aspirin's effect on elevating serum uric acid is negligible.[19]

The presence of gout should not be an absolute contraindication to the use of thiazide diuretics in hypertensive patients, although clinicians should be aware that diuretics can increase serum uric acid concentrations and initiation of a diuretic has been repeatedly demonstrated as independent risk factor for an acute gout attack.[8] It may be important to avoid using diuretics if other agents can be used to control blood pressure, particularly if the patient has had frequent gout attacks or continues to have an elevated serum uric acid concentration despite appropriate therapy for gout. Of note, beta-blockers have also been linked to elevated uric acid and increased risk for gout when compared to other anti-hypertensives in small studies.[46] Although the mechanism of this effect is

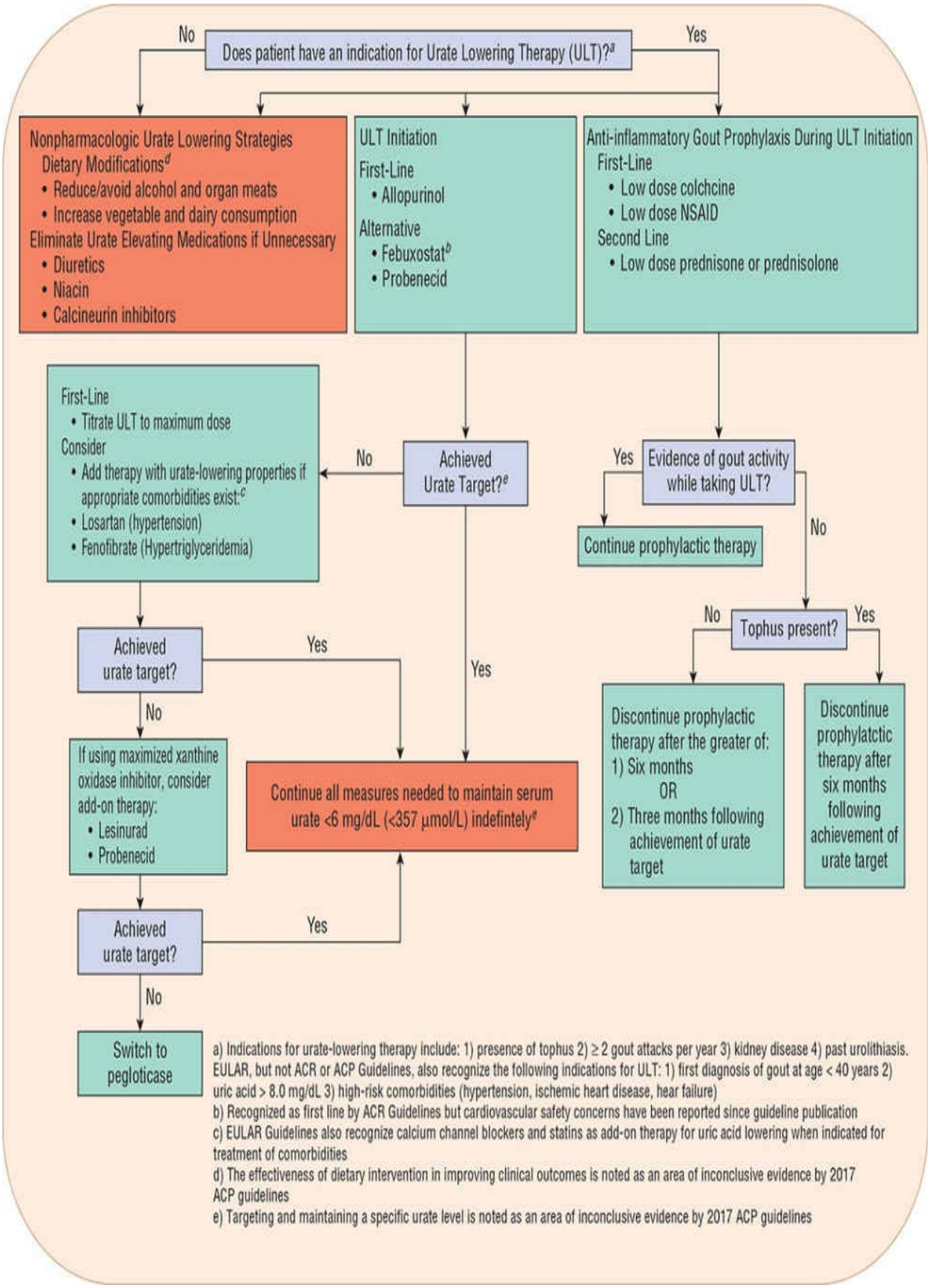
unknown, avoidance of this class should be considered if there is no compelling indication for a beta-blocker and an alternative antihypertensive can be used.

Pharmacologic Therapy

After the first attack of acute gouty arthritis, a decision to institute prophylactic urate-lowering pharmacotherapy may be considered. This decision should carefully balance risk and benefit.

3 The ACR, EULAR, and ACP guidelines recognize the occurrence of two or more gout attacks per year as an indication for pharmacologic ULT. Other indications include the presence of one or more tophus, kidney disease, or a history of uric acid urolithiasis.[19,21,22] The EULAR guidelines also recognize the following additional indications for ULT initiation: first diagnosis of gout at age <40 years, serum uric acid concentrations >8.0 mg/dL and/or high-risk comorbidities (hypertension, ischemic heart disease, and heart failure).[21]

ACR guidelines suggest that pharmacologic ULT can be safely started during an acute gout attack if appropriate anti-inflammatory prophylaxis has been initiated (see “Anti-inflammatory Gout Prophylaxis during Initiation of Pharmacologic Urate-Lowering Therapy” section and **Fig. 109-6**).[19] EULAR guidelines cite evidence from two small trials, which found that initiation of allopurinol 200 to 300 mg during an acute attack did not prolong duration or worsen severity of the attack compared to delayed initiation; however, the guidelines fall short of fully endorsing this approach because of limitations related to sample size and generalizability of the trials.[21]



a) Indications for urate-lowering therapy include: 1) presence of tophus 2) ≥ 2 gout attacks per year 3) kidney disease 4) past urolithiasis. EULAR, but not ACR or ACP Guidelines, also recognize the following indications for ULT: 1) first diagnosis of gout at age < 40 years 2) uric acid > 8.0 mg/dL 3) high-risk comorbidities (hypertension, ischemic heart disease, hear failure)

b) Recognized as first line by ACR Guidelines but cardiovascular safety concerns have been reported since guideline publication

c) EULAR Guidelines also recognize calcium channel blockers and statins as add-on therapy for uric acid lowering when indicated for treatment of comorbidities

d) The effectiveness of dietary intervention in improving clinical outcomes is noted as an area of inconclusive evidence by 2017 ACP guidelines

e) Targeting and maintaining a specific urate level is noted as an area of inconclusive evidence by 2017 ACP guidelines

FIGURE 109-6 Algorithm for management of hyperuricemia in gout. (*Algorithm derived from 2017 ACP, 2016 EULAR and 2012 ACR gout guidelines.*)

Reduction of serum urate concentrations can be accomplished pharmacologically by decreasing the synthesis of uric acid (xanthine oxidase inhibitors) or by increasing the renal excretion of uric acid (uricosurics).

4 The ACR and EULAR guidelines provide a step-wise approach in the treatment of hyperuricemia in gout (Fig. 109-6).[19,21] Within this strategy, xanthine oxidase inhibitors are recommended as first-line therapy with uricosurics reserved as second-line therapy for those intolerant to xanthine oxidase inhibitor therapy. In refractory cases, combination therapy including a xanthine oxidase inhibitor plus an agent with uricosuric properties is suggested. Finally, in severe cases, in which the patient cannot tolerate or is not responding to other therapies, pegloticase is recommended. The target serum uric acid concentration identified by ACR and EULAR guidelines is less than 6 mg/dL (357 μmol/L), and preferably below 5 mg/dL (297 μmol/L) if gout is severe or if signs and symptoms of gout persist.[19,21] In contrast, ACP guidelines do not identify a serum uric acid target and, instead, highlight the "treat-to-target" approach as an area of inconclusive evidence, suggesting that studies are needed to compare the traditional approach of targeting a serum uric acid concentration to a "treat-to-avoid-symptoms" approach which would involve no monitoring of urate concentrations.[21]

Given that the factors associated with uric acid elevation are typically not reversible, urate-lowering therapy is typically prescribed for long-term use. Furthermore, long-term ULT administration has been demonstrated to be more effective in controlling gouty attacks compared to intermittent administration in clinical trials.[19,47] For these reasons, ACR and EULAR guidelines recommend long-term, as opposed to intermittent, ULT administration in patients in whom therapy is indicated.[19,21] In contrast, the ACP guidelines state that evidence is inconclusive in this area and suggest that studies are needed to investigate if patients with annual urate concentrations <7.0 mg/dL may be able to stop ULT after "about 5 years."[22]

Despite nuances among the guidelines in their interpretation of available evidence about treatment targets, all patients at increased risk of recurrent gout attacks should be identified and considered for treatment with urate-lowering medication.

Xanthine Oxidase Inhibitors Xanthine oxidase inhibitors reduce uric acid by impairing the ability of xanthine oxidase to convert hypoxanthine to xanthine and xanthine to uric acid (Fig. 109-1). Because they are efficacious for prophylaxis in both underexcreters and overproducers of uric acid, xanthine oxidase inhibitors are the most widely prescribed agents for the long-term prevention of recurrent attacks of gout. There are currently two commercially available xanthine oxidase inhibitors, allopurinol and febuxostat.

Allopurinol is an effective urate-lowering agent,[48] but up to 5% of patients are unable to tolerate it because of adverse effects, and long-term adherence with allopurinol is low.[39,49] Mild adverse effects such as skin rash, leukopenia, GI problems, headache, and urticaria can occur with allopurinol administration. A more severe adverse reaction known as “allopurinol hypersensitivity syndrome”, which includes severe rash (toxic epidermal necrolysis, erythema multiforme, or exfoliative dermatitis), hepatitis, interstitial nephritis, and eosinophilia, reportedly occurs in approximately 1:1,000 patients and is associated with a 20% to 25% mortality rate.[19] In a large population-based study in Taiwan including almost 500,000 patients using allopurinol for the first time, the annual incidence rate of allopurinol hypersensitivity was 4.68 per 1,000 patients. Risk factors associated with the development of allopurinol hypersensitivity included female gender, age above 60 years, initial starting dose of allopurinol exceeding 100 mg/day, kidney disease, cardiovascular disease, and use of allopurinol for treatment of asymptomatic hyperuricemia.[50] Additionally, the presence of the *HLA-B*5801* allele is associated with increased risk for allopurinol hypersensitivity syndrome.

As evidence has linked higher starting doses of allopurinol with an increased incidence of allopurinol hypersensitivity syndrome, conservative initial dosing is important.[51] ACR and EULAR guidelines both recommend that allopurinol be started at a dose no greater than 100 mg daily in patients with normal kidney function and ACR guidelines further recommend that the starting dose should be limited to 50 mg daily in patients with chronic kidney disease (stage 4 or worse).[19,21]

Ideally, the dose of allopurinol should be gradually titrated every 2 to 5 weeks up to a maximum dose of 800 mg/day until the serum urate target is met.[19] When the dose of allopurinol is maximized beyond 300 mg/day, patients should be educated about the signs and symptoms of a serious reaction, including pruritus and rash. These patients should also undergo routine monitoring for elevation of hepatic enzymes and signs of eosinophilia.[19]

In clinical practice, allopurinol is often arbitrarily capped at a dose of 300 mg/day, resulting in achieving serum urate target concentration of less than 6.0 mg/dL (less than 357 μmol/L) in fewer than 50% of patients.[52] In patients with impaired kidney function, the maximum daily dose of allopurinol is typically reduced even further; however, this recommendation comes from a nonevidence-based algorithm and is therefore not supported by the ACR guidelines.[19] EULAR guidelines acknowledge that data exists to show that allopurinol dose escalation beyond limits of creatinine clearance based dosing algorithms does not result in serious cutaneous adverse events; however, given the limited number of patients and events in these trials, the task force did not feel the evidence was strong enough to reverse the 2006 recommendation to adjust allopurinol dose based on kidney function.[21] Since publication of the EULAR guidelines, one additional randomized controlled trial including 183 patients was published which concluded that higher than creatinine clearance based dosing of allopurinol in patients with impaired kidney function was safe and effective.[53] The small number of patients in the trial remains a limitation; however, the accruing evidence that allopurinol can be safely used in patients with impaired kidney function may guide decision making in practice and in the future, may prompt a more rigorous trial in this area.

Similar to allopurinol, febuxostat lowers serum urate concentrations in a dose-dependent manner.[54] In clinical trials, 40 mg/day of febuxostat was noninferior to conventionally dosed allopurinol (300 mg/day) in achieving the primary endpoint of serum urate concentration less than 6 mg/dL (less than 357 μmol/L), while 80 mg/day of febuxostat was more effective. The incidence of gout flares occurring during long-term follow-up was similar for both drugs.[55]

One criticism of the studies comparing allopurinol and febuxostat is that a fixed dose of allopurinol was used, rather than titrating the dose to achieve the targeted serum urate concentration. An advantage of febuxostat is that it has been studied in patients with impaired hepatic and kidney function and does not require dose adjustment in these patients. One concern with febuxostat is recent clinical trial evidence that demonstrated an increase in all-cause mortality and cardiovascular mortality compared to allopurinol.[56] These findings are reflected in updated FDA labeling for febuxostat.[57]

EULAR guidelines currently recommend reserving febuxostat use for patients who have an intolerance or fail to meet uric acid goals with allopurinol given European cost effectiveness analyses; whereas, ACR guidelines do not acknowledge preferential use of one agent over the other.[19,21] It should be noted, however, that both of these guidelines were published prior to publication of the

aforementioned cardiovascular safety trial. Given the lack of evidence supporting improved efficacy with febuxostat compared to equivalent dosed allopurinol, cardiovascular safety concerns, and increased cost, febuxostat remains a secondary choice in practice.

6 **Uricosuric Drugs** Uricosuric drugs increase the renal clearance of uric acid by inhibiting postsecretory renal proximal tubular reabsorption of uric acid. Two uricosurics, lesinurad and probenecid, are available for use in the United States. An alternative uricosuric, benzbromarone, is available in Europe but not in the United States. Uricosurics offer an alternative and complementary mechanism to xanthine oxidase inhibitors to enhance serum uric acid lowering. Although this class of medications is well tolerated overall, uricosuric therapy is associated with adverse renal outcomes and, therefore, limited to patients with creatinine clearance above 45 to 50 mL/min.

Probenecid Probenecid is given initially at a dose of 250 mg twice a day for 1 to 2 weeks and then 500 mg twice a day for 2 weeks. Thereafter, the daily dose is increased by 500-mg increments every 1 to 2 weeks until satisfactory control is achieved or a maximum dose of 2 g is reached. Uricosuric therapies, through their action to increase the elimination of uric acid (Fig. 109-1), cause marked uricosuria and may cause stone formation. Probenecid, specifically, has been associated with a 9% to 11% risk of urolithiasis.[19] For this reason, patients with a history or urolithiasis should not use potent uricosuric drugs.[19] The maintenance of adequate urine flow and alkalinization of the urine during the first several days of probenecid therapy may help diminish the possibility of uric acid stone formation.[19]

In addition to urolithiasis, major adverse effects associated with uricosuric therapy include GI irritation, rash and hypersensitivity, and precipitation of acute gouty arthritis. A disadvantage of uricosurics is that salicylates may interfere with this mechanism and result in treatment failure; however, low doses (325 mg/day or less) of enteric-coated aspirin may be used cautiously. In addition, probenecid can inhibit the tubular secretion of other organic acids; thus, increased plasma concentrations of penicillins, cephalosporins, sulfonamides, and indomethacin can occur.

Lesinurad Lesinurad (Zurampic®) is the first FDA-approved selective uric acid reabsorption inhibitor (SURI). It works by inhibiting urate transporter 1 (URAT1), a transporter found in the proximal renal tubule. Inhibition of URAT1 results in uric acid excretion (Fig. 109-1).

In one 4-week randomized controlled trial, the addition of lesinurad 200 mg, 400 mg, or 600 mg to daily allopurinol therapy (200-600 mg) demonstrated efficacy in reducing serum uric acid in patients with gout and an inadequate response to allopurinol therapy (defined as serum uric acid more than or equal to 6 mg/dL on more than or equal to 2 occasions more than or equal to 2 weeks apart while on allopurinol 200-600 mg daily for more than or equal to 6 weeks).[58] Patients taking 200 mg, 400 mg, and 600 mg of lesinurad achieved serum uric acid reduction of 16%, 22% and 30%, respectively, compared to 3% with placebo ($P < 0.0001$ for all comparisons).[58] Adverse effects noted with lesinurad therapy included serum creatinine elevation, elevated lipase, increased creatinine kinase, and urticaria.[58]

7 Lesinurad is approved as combination therapy with a xanthine oxidase inhibitor (including allopurinol and febuxostat) for treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid concentrations with xanthine oxidase inhibitor monotherapy. Because lesinurad works by increasing renal uric acid secretion, it has been associated with adverse renal events, particularly when used as monotherapy.[59] In one study examining lesinurad monotherapy in patients intolerant to xanthine oxidase inhibitor therapy, kidney stones occurred in 4.2% of patients and serum creatinine elevation occurred in 30.8% of patients taking lesinurad.[60] For these reasons, lesinurad carries a black box warning which highlights the increased risk of acute kidney injury when used in the absence of xanthine oxidase inhibitor therapy.[60] Lesinurad has been studied in combination with xanthine oxidase inhibitor therapy in multiple placebo-controlled trials for up to 12 months. Although other doses have been studied, the only approved dose of lesinurad is 200 mg daily due to increased risk of renal events when used at higher doses.[59] Lesinurad should not be used in patients with creatinine clearance less than 45 mL/min.[59] Lesinurad is commercially available as a single-entity product (Zurampic®, 200-mg tablet) and in combination with two different allopurinol strengths (Duzallo®, 200-mg lesinurad/200-mg allopurinol [approved for patients with creatinine clearance 45-59 mL/min] and 200 mg lesinurad/300 mg allopurinol [approved for patients with creatinine clearance >59 mL/min).[61]

Because the ACR and EULAR guidelines were published prior to the approval of a URAT1 inhibitor, lesinurad's place in therapy is not yet well established. Given lesinurad's ease of use (once daily oral tablet) and, thus far, reasonable safety profile, the medication may serve as first-line add-on therapy for the treatment of hyperuricemia in patients with gout who are unable to

achieve target serum uric acid concentrations despite maximization of xanthine oxidase inhibitor therapy.[77] Limitations to widespread use may include high cost, until patent expiration, and renal adverse events. Given the lack safety data beyond 12 months of use, postmarketing surveillance will also be important in guiding future use.

Pegloticase Pegloticase (Krystexxa®) is a pegylated recombinant uricase that works to reduce serum uric acid by converting uric acid to allantoin, a water-soluble and easily excreted substance (Fig. 109-1).

In randomized controlled trials, biweekly pegloticase therapy has demonstrated efficacy in reducing serum uric acid and resolving tophi in patients with severe gout and hyperuricemia (uric acid more than or equal to 8 mg/dL [more than or equal to 476 μmol/L]) who have failed or have a contraindication to allopurinol therapy.[62] Severe gout refers to patients who meet at least one of the following criteria: (a) three or more gout flares within the most recent 18 months, (b) one or more tophi, or (c) joint damage due to gout. Although clearly efficacious, pegloticase has several drawbacks that limit widespread use. One is the route of administration. The biweekly IV infusions of pegloticase must be given over no less than 2 hours, a potential inconvenience to many patients. Furthermore, given potential infusion-related allergic reactions, patients must be treated with antihistamines and corticosteroids before therapy. Cost is another major consideration. Pegloticase is estimated to cost several thousand dollars per month, not including administration costs associated with an IV infusion.[63] This represents a significantly greater cost burden compared with other ULT.[63]

The ideal duration of pegloticase therapy is currently unknown. Other ULTs, xanthine oxidase inhibitors for example, are typically used indefinitely in patients with gout and hyperuricemia. Immunogenicity issues associated with pegloticase therapy may limit the duration with which pegloticase therapy may be used effectively. In the previously cited 6-month pegloticase trials, 134 of 150 patients developed pegloticase antibodies that, for most patients, resulted in a loss of efficacy by month 4.[62]

Given these many limitations and the narrow patient population in which the drug has been studied, pegloticase is an agent of last resort that should be reserved for patients with refractory gout who are unable to take or have failed all other ULTs.

Miscellaneous Urate-Lowering Agents Lipid-lowering agents, in particular fenofibrate, can also be prescribed for patients with gout. Although dyslipidemia is common in gout patients, the fibrates are believed to exert their effects as an

ancillary benefit by increasing the clearance of hypoxanthine and xanthine, leading to a sustained reduction in serum urate concentrations. Reductions of 20% to 30% in urate concentrations are observed with fenofibrate use.[64] Importantly, fenofibrate does not appear to not cause an acute gout flare when initiated and is well tolerated overall.[65] Although less potent than fenofibrate therapy, atorvastatin and rosuvastatin have also been linked to serum uric acid lowering, and while the mechanism of this effect remains unclear, it is thought to be due to decreased renal reabsorption of uric acid.[66]

Losartan, an angiotensin II receptor antagonist, has also demonstrated benefit in reducing serum urate concentrations independent of angiotensin receptor antagonism.[67] Losartan inhibits renal tubular reabsorption of uric acid and increases urinary excretion, and this effect seems to be a unique property of losartan that is not shared with other angiotensin II receptor antagonists.[68] In addition, it alkalinizes the urine, which helps reduce the risk for stone formation. In addition to losartan, calcium channel blockers have been associated with lower risk of gout which is purported to be linked to increased renal elimination of uric acid. Specifically, amlodipine, nifedipine, and diltiazem were associated with a 15% to 20% risk reduction in one population-based case-control study.[69]

The EULAR and ACR guidelines support the preferential use of fenofibrate or losartan when indicated in patients with refractory disease, while the EULAR guidelines support calcium channel blocker and statin use as well.[19,21]

Anti-Inflammatory Gout Prophylaxis during Initiation of Pharmacologic Urate-Lowering Therapy

8 Initiation of ULT can prompt an acute attack of gout due to remodeling of urate crystal deposits in joints as a result of rapid lowering of urate concentrations.[20] The frequency of this phenomenon is inconsistently reported in clinical trials and may occur in as many of 75% of patients initiating ULT or as few as 25%.[70] Prophylactic anti-inflammatory pharmacotherapy is often recommended to prevent gout attacks and, secondarily, to assist in ensuring patient acceptance of and adherence with ULT. The ACR and EULAR guidelines recommend low-dose oral colchicine (0.6 mg twice daily) or low-dose NSAIDs (eg, naproxen 250 mg twice/day) as first-line prophylactic therapies, with stronger evidence supporting use of colchicine.[20,21] EULAR guidelines specifically list low-dose colchicine as first-line therapy and low-dose NSAIDs as second-line therapy if colchicine is contraindicated or not tolerated.[21] Low-

dose corticosteroid therapy (eg, less than or equal to 10 mg/day prednisone) is recommended by ACR guidelines as an alternative in patients with intolerance, contraindication, or lack of response to first-line therapy.[20] EULAR guidelines recommend 6 months of prophylaxis while ACR guidelines recommend continuation at least 3 months after achieving target serum uric acid or 6 months total, whichever is longer, and 6 months following achievement of serum urate target in patients with one or more tophi (Fig. 109-6).[20,21]

Given the considerable duration of therapy required for acute gout prophylaxis during initiation of ULT, adverse effects of the pharmacologic agents employed must be seriously considered. Although the risk for gastric ulceration and bleeding is relatively small with short-term NSAID therapy normally employed when treating acute gout flares, administration of a proton-pump inhibitor or other acid-suppressing therapy is indicated to protect from NSAID-induced gastric problems for patients on long-term prophylactic therapy.[20] Prolonged corticosteroid therapy is clearly linked to many severe adverse effects (ie, hyperglycemia, Cushing syndrome, fluid retention, hypertension, osteoporosis, glaucoma, depression/euphoria) and, as suggested above, is not appropriate for first-line therapy for this reason.

Cost is another major consideration when selecting prophylactic pharmacotherapy given the need for an extended duration of therapy (6 months of therapy compared to approximately 1 week for acute gout treatment). Although generic colchicine again became commercially available in 2015, the lack of competition among manufacturers of generic colchicine have allowed the cost per tablet to remain high.[71] The cost of colchicine, if not covered by insurance, remains a potential challenge to therapy for certain patients making NSAIDs and corticosteroids more affordable options for patients.

Investigational Drugs

Prior to the release of febuxostat in 2009, pegloticase in 2010, and lesinurad in 2015, several decades passed without the release of a new pharmacotherapeutic agent for the treatment of gout. Given the increased prevalence of gout and the presence of both treatment intolerance and treatment refractory cases, several new agents are currently under investigation.[72]

Interleukin-1 Inhibitors

During acute gout attacks, urate crystals elicit an inflammatory response that triggers the production of interleukin-1 (IL-1).[73] This finding has led to the

investigational use of IL-1 inhibitors in the treatment and prevention of acute gout.

In small trials, two IL-1 inhibitors, anakinra and canakinumab, have demonstrated efficacy in the treatment of acute gout. Neither is approved for treatment of acute gout by the FDA, and their use remains off-label. The EULAR and ACR guidelines suggest that IL-1 inhibitors can be considered for treatment of severe acute gout attacks refractory to other treatments. However, due to a lack of randomized controlled trials and an uncertain risk-to-benefit ratio, the ACR guidelines note that the role of IL-1 inhibitors in the treatment of acute gout is unclear.[20,21]

Limited evidence also suggests efficacy of IL-1 inhibitors in the prevention of acute gout during the first 16 weeks of ULT initiation (subcutaneous rilonacept 320-mg loading dose followed by 160 mg weekly and subcutaneous canakinumab single dose [50-300 mg] or four times weekly dosing [50 mg—50 mg—25 mg—25 mg]).[74–76] Given the limited evidence and lack of FDA approval for this indication, the ACR and EULAR guidelines do not provide a recommendation for the use of IL-1 inhibitors for anti-inflammatory prophylaxis during initiation of ULT.

Other Investigational Agents

Several investigational agents intended to be used for the management of gout are at various stages of development. Additional URAT1 inhibitors are currently in development (verinurad, levotofisopam, arhalofenate).[77] Arhalofenate also suppresses the production of IL-1β which may potentially lead to a reduction in gout flares in addition to urate lowering.[77] Other novel mechanisms of action include purine nucleoside phosphorylase (PNP) inhibition (ulodesine) and glucose transporter 9 (GLUT9) inhibition (tranilast).[75,76] Continued research will ultimately define the role of these agents in the management of gout and hyperuricemia.

Nephrolithiasis

9 The medical management of uric acid nephrolithiasis includes hydration sufficient to maintain a urine volume of 2 to 3 L/day, alkalinization of urine, avoidance of purine-rich foods, moderation of protein intake, and reduction of urinary uric acid excretion.

Maintenance of a 24-hour urine volume of 2 to 3 L with an adequate intake of

fluids is desirable for all gout patients, but especially for those with excessive uric acid excretion (more than 1 g/day [more than 6 mmol/day]). Alkalinizing agents should be used with the objective of making the urine less acidic. Urine pH should be maintained at 6 to 6.5. In this pH range, up to 85% of uric acid will be in the form of the soluble urate ion.

Reduction of urine acidity is usually accomplished by the administration of potassium bicarbonate or potassium citrate 60 to 80 mEq/day (mmol/day).[78,79] Administration of alkali via sodium salts is a less desirable option for two reasons. First, the sodium-induced volume expansion will increase sodium excretion and can secondarily cause hypercalcemia because calcium passively follows the reabsorption of sodium in the proximal tubule and loop of Henle. In the presence of uric acid, the resultant hypercalcemia can lead to calcium oxalate stone formation. Second, older patients with uric acid kidney stones may also have hypertension, congestive heart failure, or impaired kidney function. Because of these conditions, they should not be overloaded with alkalinizing sodium salts or unlimited fluid intake, as these can worsen these conditions.

Acetazolamide, a carbonic anhydrase inhibitor, produces rapid and effective urinary alkalinization and sometimes is used in conjunction with alkali therapy. When a 250-mg dose of acetazolamide is given at bedtime, the excretion of acidic urine in the early morning hours is avoided. The usual tachyphylaxis (rapid tolerance) to this drug is obviated by a daily repletion dose of bicarbonate.

Since the advent of xanthine oxidase inhibitors, a low-purine, low-protein diet for the patient with uric acid nephrolithiasis is no longer as critical as it once was; however, it is still advisable to instruct the patient to avoid foods rich in purine and to limit protein to no more than 90 g/day. Such a diet is still palatable and reduces appreciably the amount of uric acid in the urine.

The mainstay of drug therapy for recurrent uric acid nephrolithiasis is xanthine oxidase inhibitors. They are effective in reducing both serum and urinary uric acid concentrations, thus preventing the formation of calculi. Xanthine oxidase inhibitors are recommended as prophylactic treatment for patients who will receive cytotoxic agents for the treatment of lymphoma or leukemia. The marked increase in uric acid production associated with cytolysis of a neoplasm predisposes a patient to the development of uric acid nephrolithiasis.

Uric Acid Lowering in the Absence of Gout

Asymptomatic Hyperuricemia

Questions are often raised regarding the use of drug therapy for asymptomatic hyperuricemia. The purported benefits include prevention of acute gouty arthritis, tophi formation, nephrolithiasis, and chronic urate nephropathy. As hyperuricemia does not always lead to gout attacks, drug treatment of asymptomatic hyperuricemia on these grounds is not clearly justifiable. The prevention of urate nephropathy might be a stronger indication because it is irreversible even with proper treatment. Available data indicate, however, that gouty nephropathy is extremely rare in the absence of clinical gout, and evidence that elevation of uric acid by itself may cause kidney disease is weak and inconclusive. Kidney disease associated with hyperuricemia is very rare in the absence of concurrent hypertension and atherosclerosis. In addition, it is unclear whether uric acid–lowering therapy protects kidney function in such individuals.

Uric Acid and Cardiovascular Risk

The relationship between elevated serum urate concentrations and cardiovascular disease is controversial. In observational studies, hyperuricemia has been shown to be a risk factor for ischemic heart disease.[80] However, hyperuricemia is also associated with other known risk factors for cardiovascular disease, such as diabetes mellitus, dyslipidemia, and hypertension, and the individual contribution of hyperuricemia on the risk for cardiovascular disease is difficult to separate from these associated factors. A 12-year follow-up of the Health Professionals Study revealed a 28% higher risk of death from all causes, 38% higher risk of cardiovascular disease death, 55% higher risk of death from coronary heart disease, and a 59% higher risk of nonfatal myocardial infarction for men with a self-reported history of gout compared with those without this reported history.[81] These associations remained significant even after adjusting for age, body mass index, smoking, family history of myocardial infarction, and comorbidities such as diabetes and hypertension. Emerging data from additional prospective trials supports this relationship between hyperuricemia and increased risk for atherosclerotic cardiovascular disease.[82,83]

Given the epidemiologic relationship between uric acid and cardiovascular risk, the potential effects of urate lowering on various cardiovascular parameters have been investigated in several small trials. Multiple small trials, for example, have demonstrated reduction in carotid intima-media thickness with allopurinol use in patients with asymptomatic hyperuricemia.[84,85] Effects of ULT on blood pressure and vasculature are one of the mechanisms studied to explain these positive associations with cardiovascular outcomes. In one trial, the addition of

allopurinol in blacks receiving chlorthalidone further improved clinic blood pressure control (4.3 mm Hg mean decrease in systolic blood pressure after 4 weeks of therapy).[86] Similar effects on blood pressure have been demonstrated with allopurinol in other clinical studies.[87–89] The mechanism by which allopurinol may decrease blood pressure is not clear but may be mediated through decreases in oxidative stress brought on as a result of inhibiting oxidant generation during the reaction between hypoxanthine and xanthine with xanthine oxidase.[86]

While empirically initiating ULT in patients with asymptomatic hyperuricemia and elevated cardiovascular risk may seem attractive on the basis of epidemiologic studies and small prospective trials using surrogate markers, no prospective randomized controlled trials examining clinical outcomes have provided clear evidence that drug treatment of asymptomatic hyperuricemia or gout reduces cardiovascular morbidity and mortality. At this time, it is premature to implement therapy for patients with asymptomatic hyperuricemia in the absence of a history of gout. Risks of therapy must also be considered, such as the increased incidence of allopurinol hypersensitivity syndrome when allopurinol is used for the treatment of asymptomatic hyperuricemia. Whether or not ULT is implemented, efforts should be directed toward aggressive management of cardiovascular risk factors in all patients with hyperuricemia.

Pharmacotherapy Considerations

While the EULAR and ACR guidelines provide clear recommendations regarding use of pharmacotherapy in the management of gout and hyperuricemia, application of these recommendations requires personalization to fit the needs of a specific patient. When making therapeutic choices for an individual, it is critical to evaluate the adverse effect profile of a particular pharmacotherapeutic agent while considering a patient’s baseline risk for those unwanted effects. This involves an analysis of patient demographics and comorbidities.[10]

Allopurinol hypersensitivity syndrome is perhaps the most concerning adverse effect of all potential side effects associated with gout therapies, given the high-mortality rate associated with this reaction. As such, it would be ideal if patients at high risk for developing this syndrome could be screened for and, consequently, guided to alternative therapy. Recent research has identified a genetic link in certain populations that increases risk for the development of allopurinol hypersensitivity syndrome. Korean patients with chronic kidney

disease (stage 3 or worse), Han Chinese patients, and Thai patients have been identified as being at increased risk for allopurinol hypersensitivity syndrome if found to have a specific genotype (HLA-B*5801 positive).[90] The ACR guidelines recommend that HLA-B*5801 testing be considered before allopurinol initiation in these specific subpopulations; for those found to be positive, alternative therapy should be used. EULAR guidelines do not include recommendations for screening given the lack of data supporting cost effectiveness of this practice in populations with low frequency of this genotype, as in Europe.[19,21]

Certain comorbidities may warrant dose adjustment of some gout therapies or, in certain instances, complete avoidance of certain medications. For example, patients with impaired kidney function should, in general, avoid NSAID therapy and must receive colchicine at reduced doses. Patients with GI disease should also avoid NSAID therapy and may not be able to tolerate colchicine therapy and, therefore, may find most success with corticosteroid therapy. In addition to comorbidities, polypharmacy and cost considerations may affect treatment decisions in an individual patient. The comprehensive management of gout provides ample opportunity for pharmacists to apply medication expertise, and care models incorporating pharmacists in the management of gout have demonstrated improved outcomes compared to standard practice.[91] Refer to **Table 109-9** for an overview of important factors to consider when tailoring pharmacotherapy to an individual patient with gout.

TABLE 109-9 Pharmacotherapy Considerations in Gout

Conditions and Situations	Limitations to Pharmacotherapy	Alternative Therapies
Impaired Kidney Function	NSAIDs may lead to exacerbation of kidney impairment	Consider reduced-dose colchicine or corticosteroids for short-term treatment of acute gout Consider reduced-dose colchicine for prophylaxis during initiation of urate-lowering therapy
	Uricosuric therapy is ineffective in patients with impaired kidney function	Consider allopurinol or febuxostat
	Lesiurad is not indicated in patients with impaired kidney function	Consider allopurinol or febuxostat for first-line urate lowering therapy; consider pegloticase for refractory cases
GI disease	Colchicine may cause GI upset and diarrhea	Consider corticosteroids for treatment of acute gout If monoarticular, consider joint injection
	NSAIDs may cause GI bleeding or ulceration	Consider gastroprotection with coadministration of proton-pump inhibitor when NSAID therapy is used Consider colchicine or corticosteroids for treatment of acute gout Consider low-dose colchicine for prophylaxis during initiation of urate-lowering therapy
Congestive heart failure	NSAIDs may cause a congestive heart failure exacerbation	Consider colchicine for treatment of acute gout Consider colchicine for prophylaxis during initiation of urate-lowering therapy
	Concurrent use of diuretic may increase serum urate	If diuretic remains necessary, consider initiating urate-lowering therapy Consider losartan as a therapy for congestive heart failure given its uricosuric properties
Hypertension	Diuretics may increase uric acid	Consider losartan as alternative or additional antihypertensive therapy given its uricosuric properties Consider addition of urate-lowering therapy if diuretic remains necessary
	NSAIDs may worsen blood pressure control	Consider colchicine or corticosteroids for treatment of acute gout Consider colchicine for prophylaxis during initiation of urate-lowering therapy
Polypharmacy	CYP3A4 inhibitors and P-glycoprotein inhibitors interact with colchicine leading to elevated colchicine levels	Reduce the dose of colchicine used for the treatment and prophylaxis of acute gout Consider NSAIDs or corticosteroids for treatment of acute gout Consider NSAIDs for prophylaxis during initiation of urate-lowering therapy
	Added pharmacotherapy may be undesirable in a patient with a large medication burden	Consider losartan as urate-lowering therapy in patients with comorbid hypertension Consider fenofibrate as urate-lowering therapy in patients with hypertriglyceridemia
Financial limitations	Febuxostat and colchicine are considerably more costly compared with other gout treatments	Consider allopurinol as urate-lowering therapy Consider NSAIDs or corticosteroids for treatment of acute gout Consider NSAIDs for prophylaxis of gout during initiation of urate-lowering therapy

CYP, cytochrome P450; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.

Evaluation of Therapeutic Outcomes

Follow-up of patients with gout depends on the frequency of attacks and on the medications used to treat symptoms. For a patient who is experiencing a first attack of gout, long-term therapy is generally not indicated. As previously mentioned, guidelines recommend that urate-lowering pharmacotherapy be reserved for patients at increased risk for recurrent attacks because the treatment is long-term, there is potential for adverse drug effects, and medication adherence for patients without symptoms is generally poor.[19,21,22,49] Patients having a first attack should be educated about the likelihood of recurrence and what to do if another attack occurs. Approximately 60% of patients have a second attack within the first year, and 78% have a second attack within 2 years. Only 7% of patients do not have a recurrence within a 10-year period.[92]

10 Baseline blood work for patients receiving hypouricemic medications chronically should include kidney function (serum creatinine, blood urea nitrogen), liver enzymes (aspartate aminotransferase, alanine aminotransferase), complete blood count, and electrolytes. There is generally no need to recheck these laboratory parameters for patients undergoing acute therapy with an NSAID or colchicine of limited duration. However, for patients requiring long-term therapy or prophylaxis, they should be rechecked every 6 to 12 months or as clinically indicated. For patients suspected of having an acute attack of gouty arthritis, it is reasonable to check a serum uric acid concentration, particularly if it is not the first attack and a decision is to be made regarding initiation of prophylactic therapy. However, clinicians should be mindful that acute gouty arthritis can occur in the presence of normal serum uric acid concentrations.[1,2] During titration of ULT, uric acid should be monitored every 2 to 5 weeks; once the urate target is achieved, uric acid should be monitored every 6 months.[19] This monitoring regimen is recommended not only to ensure appropriate dosing of ULT, but also to serve as an assessment of patient adherence given the known adherence issues with ULTs. Because of the high rates of comorbidities associated with gout, including diabetes mellitus, chronic kidney disease, hypertension, obesity, myocardial infarction, heart failure, and stroke, elevated uric acid concentrations or gout should prompt evaluations for signs of cardiovascular disease and the need for appropriate risk reduction measures.[93] Additionally, clinicians should look for a possible correctable cause of hyperuricemia, such as medications (eg, thiazide and loop diuretics, niacin, calcineurin inhibitors), obesity, malignancy, and alcohol abuse.

Nonpharmacologic options include encouraging patients to exercise, lose weight, reduce alcohol intake, reduce consumption of syrup-sweetened sodas and increase consumption of low-fat dairy foods and vegetables, and have periodic follow-up to address progress on these goals.

CONCLUSION

Hyperuricemia can be asymptomatic without complications, or it may lead to acute attacks of gouty arthritis, chronic gout, and uric acid nephrolithiasis. Asymptomatic hyperuricemia is not generally treated, although lifestyle modifications (eg, weight loss, reduction of alcohol intake, control of blood pressure) should be encouraged to help reduce serum urate and overall cardiovascular health.

Acute gouty arthritis responds well to short courses of NSAIDs, colchicine, or corticosteroids to treat the underlying inflammatory condition. The management of uric acid nephrolithiasis includes hydration and alkalinization of the urine. Prevention of recurrent gouty arthritis or recurrent nephrolithiasis and treatment of chronic gout require hypouricemic therapy with either a uricosuric drug, a xanthine oxidase inhibitor, or a combination of both therapies. Xanthine oxidase inhibitors are effective in both underexcreters and overproducers of uric acid, making them the hypouricemic drugs of choice for most patients with gout. Finally, anti-inflammatory prophylaxis with low-dose colchicine or NSAID therapy is indicated during the initiation of ULT to prevent the development of acute gout due to rapid mobilization of urate.

Postclass Engaged Learning Activity

Conduct a literature search and identify a primary research manuscript that has been published in the past 12 months regarding a medication used to treat or prevent gout. Write a brief summary of the study methods, the major findings, and how this new information might change current practice. This activity is intended to build your literature evaluation skills and ability to critically appraise research manuscripts.

ABBREVIATIONS

ACR	American College of Rheumatology

ACP	American College of Physicians
ACTH	adrenocorticotropic hormone
CNS	central nervous system
COX-2	cyclooxygenase-2
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
GI	gastrointestinal
GLUT9	glucose transporter 9
HGPRT	hypoxanthine-guanine phosphoribosyltransferase
IL-1	interleukin-1
MSU	monosodium urate
NSAID	nonsteroidal anti-inflammatory drug
PNP	purine nucleoside phosphorylase
PRPP	phosphoribosyl pyrophosphate (synthetase)
SURI	selective uric acid reabsorption inhibitor
ULT	urate-lowering therapy
URAT1	urate transporter 1
USP	United States Pharmacopeia

REFERENCES

1. Wortmann RL, et al. Chapter 87: Gout and hyperuricemia. In: Firestein GS, Budd RC, Harris ED, Jr, et al., eds. *Kelley's Textbook of Rheumatology*. 8th ed. Philadelphia, PA: WB Saunders; 2008.
2. Edwards NL, Choi HK, Terkeltaub RA, et al. Chapter 12: Gout. In: Klippel JH, Stone SH, Crofford LJ, et al., eds. 13th ed. New York, NY: Springer Scientce+Business Media; 2008.
3. Smith E, Hoy D, Cross M, et al. The global burden of gout: Estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis*. 2014;73:1470–1476.
4. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: The National Health and Nutrition Examination Survey 2007–2008. *Arthritis Rheum*. 2011;63:3136–3141.
5. Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia.

Risks and consequences in the Normative Aging Study. *Am J Med*. 1987;82:421–426.

6. Juraschek SP, Miller ER, Gelber AC. Body mass index, obesity, and prevalent gout in the United States in 1988–1944 and 2007–2010. *Arthritis Care Res*. 2013;65:127–132.
7. Choi HK. A prescription for lifestyle change in patients with hyperuricemia and gout. *Curr Opin Rheumatol*. 2010;22:165–172.
8. Hak AE, Curhan GC, Grodstein F, et al. Menopause, postmenopausal hormone use and risk of incident gout. *Ann Rheum Dis*. 2010;69:1305–1309.
9. Neogi T. Gout. *N Engl J Med*. 2011;364:443–452.
10. Fravel MA, Ernst ME. Management of gout in the older adult. *Am J Geriatr Pharmacother*. 2011;9:271–285.
11. Eggebeen AT. Gout: An update. *Am Fam Physician*. 2007;76:801–808.
12. Agudelo CA, Weinberger A, Schumacher HR, et al. Definitive diagnosis of gout by identification of urate crystals in asymptomatic metatarsophalangeal joints. *Arthritis Rheum*. 1979;22:559–560.
13. Zhang W, Doherty M, Pascual E, et al. EULAR evidence based recommendations for gout. Part I. Diagnosis. Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis*. 2006;65:1301–1311.
14. Neogi T, Jansen T, Dalbeth N, et al. 2015 Gout classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis*. 2015;74:1789–1798.
15. Rosenthal AK, Ryan LM. Calcium pyrophosphate deposition disease. *N Engl J Med*. 2016;374:2575–84.
16. Schumacher HR. Crystal-reduced arthritis: An overview. *Am J Med*. 1996;100(suppl 2A):46S–52S.
17. MacMullan P, McCarthy G. Treatment and management of pseudogout: Insights for the clinician. *Ther Adv Musculoskel Dis*. 2012;4:121–131.
18. Kramer HM, Curhan G. The association between gout and nephrolithiasis: The National Health and Nutrition Examination Survey III, 1988–1994. *Am J Kid Dis*. 2002;40:37–42.
19. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to

hyperuricemia. *Arthritis Care Res*. 2012;64:1431–1446.

20. Khanna D, Khanna PP, Fitzgerald JD, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: Therapy and anti-inflammatory prophylaxis of acute gouty arthritis. *Arthritis Care Res*. 2012;64:1447–1461.
21. Richette R, Doherty M, Pascual E, et al. 2016 Updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis*. 2017;76:29–42.
22. Qaseem A, Harris RP, Forciea MA. Management of acute and recurrent gout: A clinical practice guideline from the American college of physicians. *Ann Intern Med*. 2017;166:58–68.
23. Schlesinger N, Detry MA, Holland BK, et al. Local ice therapy during bouts of acute gouty arthritis. *J Rheumatol*. 2002;29:331–334.
24. van Durme CMPG, Wechalekar MD, Buchbinder R, et al. Non-steroidal anti-inflammatory drugs for acute gout. *Cochrane Database Syst Rev*. 2014;(9):CD010120. doi:10.1002/14651858.CD010120.pub2.
25. Schumacher HR, Berger MF, Li-Yu J, et al. Efficacy and tolerability of celecoxib in the treatment of acute gouty arthritis: A randomized controlled trial. *J Rheumatol*. 2012;39:1859–1866.
26. Rainer TH, Cheng CH, Janssens H, et al. Oral prednisolone in the treatment of acute gout: A pragmatic, multicenter, double-blind, randomized trial. *Ann Intern Med*. 2016;164:464–471.
27. Xu L, Liu S, Guan M, et al. Comparison of prednisolone, etorcoxib, and indomethacin in treatment of acute gouty arthritis: An open-label, randomized, controlled trial. *Med Sci Monit*. 2016;22:810–817.
28. Fernandez D, Noguera R, Gonzalez JA, et al. Treatment of acute attacks of gout with a small dose of intraarticular triamcinolone acetonide. *J Rheumatol*. 1999;26:2285–2286.
29. Siegel LB, Alloway JA, Nashel DJ. Comparison of adrenocorticotropic hormone and triamcinolone acetonide in the treatment of acute gouty arthritis. *J Rheumatol*. 1994;21:1325–1327.
30. Axelrod D, Preston S. Comparison of parenteral adrenocorticotropic hormone with oral indomethacin in the treatment of acute gout. *Arthritis Rheum*. 1988;31:803–805.
31. Taylor CT, Brooks NC, Kelley KW. Corticotropin for acute management of gout. *Ann Pharmacother*. 2001;35:365–368.

32. Ritter J, Kerr LD, Valeriano-Marcet J, Spiera H. ACTH revisited: Effective treatment for acute crystal induced synovitis in patients with multiple medical problems. *J Rheumatol*. 1994;21:696–699.
33. van Echteld I, Wechalekar MD, Schlesinger N, et al. Colchicine for acute gout. *Cochrane Database Syst Rev*. 2014;(8):CD006190. doi:10.1002/14651858.CD006190.pub2.
34. Ahern MJ, Reid C, Gordon TP, et al. Does colchicine work? The results of the first controlled study in acute gout. *Aust NZ J Med*. 1987;17:301–304.
35. Kesselheim A, Franklin J, Kim S, et al. Reductions in use of colchicine after FDA enforcement of market exclusivity in a commercially insured population. *J Gen Intern Med*. 2015;30:1633–8.
36. Terkeltaub RA, Furst DE, Bennett K, et al. High versus low dosing of oral colchicine for early acute gout flare: Twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. *Arthritis Rheum*. 2010;62:1060–1068.
37. COLCRYS. *Colchicine*. Deerfield, IL: Takeda Pharmaceuticals, 2012.
38. Bonnel RA, Villalba ML, Karwoski CB, Beitz J. Deaths associated with inappropriate intravenous colchicine administration. *J Emerg Med*. 2002;22:385–387.
39. Harrold LR, Andrade SE, Briesacher BA, et al. Adherence with urate-lowering therapies for the treatment of gout. *Arthritis Res Ther*. 2009;11:R46.
40. Juraschek SP, Gelber AC, Choi HK, et al. Effects of the dietary approaches to stop hypertension (DASH) diet and sodium intake on serum uric acid. *Arthritis Rheum*. 2016;68:3002–3009.
41. Tang O, Miller ER, Gelber AC, et al. DASH diet and change in serum uric acid over time. *Clin Rheum*. 2017;36:1413–1417.
42. Zhang Y, Woods R, Chaisson CE, et al. Alcohol consumption as a trigger of recurrent gout attacks. *Am J Med*. 2006;119:800.e13-18.
43. Schlesinger N. Management of acute and chronic gouty arthritis: Present state-of-the-art. *Drugs*. 2004;64:2399–2416.
44. Haidari F, Mohammad SM, Keshavarz SA, et al. Inhibitory effects of tart cherry (prunus cerasus) juice on xanthine oxidoreductase activity and its hypouricemic and antioxidant effects on rats. *Malays J Nutr*. 2009;15:53–64.
45. Zhang Y, Neogi T, Chen C, et al. Cherry consumption and the risk of

recurrent gout attacks. *Arthritis Rheum*. 2012;64: 4004–4011.

46. Reyes AJ. Cardiovascular drugs and serum uric acid. *Cardiovasc Drugs Ther*. 2003;17:397–414.
47. Bull PW, Scott JT. Intermittent control of hyperuricemia in the treatment of gout. *J Rheumatol*. 1989;16:1246–1248.
48. Seth R, Kydd ASR, Buchbinder R, et al. Allopurinol for chronic gout. *Cochrane Database Syst Rev*. 2014;(10):CD006077.
49. Riedel AA, Nelson M, Joseph-Ridge N, et al. Compliance with allopurinol therapy among managed care enrollees with gout: A retrospective analysis of administrative claims. *J Rheumatol*. 2004;31:1575–1581.
50. Yang C, Chen C, Deng S, et al. Allopurinol use and risk of fatal hypersensitivity reactions. A nationwide population-based study in Taiwan. *JAMA*. 2015;175:1550–1557.
51. Stamp LK, Taylor WJ, Jones PB, et al. Starting dose is a risk factor for allopurinol hypersensitivity syndrome: A proposed safe starting dose of allopurinol. *Arthritis Rheum*. 2012;64:2529–2536.
52. Chao J, Terkeltaub R. A critical reappraisal of allopurinol dosing, safety, and efficacy for hyperuricemia in gout. *Curr Rheumatol Rep*. 2009;11:135–140.
53. Stamp LK, Chapman PT, Barclay ML, et al. Allopurinol dose escalation to achieve serum urate below 6 mg/dL: An open-label extension study. *Ann Rheum Dis*. 2017;76:2065–2070.
54. Becker MA, Schumacher HR, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med*. 2005;353:2450–2461.
55. Tayar JH, Lopez-Olivo MA, Suarez-Almazor ME. Febuxostat for treating chronic gout. *Cochrane Database Syst Rev*. 2012;(11):CD008653.
56. White WB, Saag KG, Becker MA, et al. Cardiovascular safety of febuxostat or allopurinol in patients with gout. *N Engl J Med*. 2018;310:1200–1210. PMID: 29527974.
57. ULORIC. *Febuxostat*. Deerfield, IL: Takeda Pharmaceuticals, 2018.
58. ZURAMPIC. *Lesinurad*. Wilmington, DE: AstraZeneca Pharmaceuticals; 2015.
59. Perez-Ruiz F, Sundy JS, Miner JN, et al. Lesinurad in combination with allopurinol: Results of a phase 2, randomised, double-blind study in patients with gout with an inadequate response to allopurinol. *Ann Rheum*

Dis. 2016;75:1074–1080.

60. Tausche AK, Alten R, Dalbeth N, et al. Lesinurad monotherapy in gout patients intolerant to a xanthine oxidase inhibitor: A 6-month phase 3 clinical trial and extension study. *Rheumatol*. 2017;56:2170–2178.
61. DUZALLO. *Lesinurad/Allopurinol*. Cambridge, MA: AstraZeneca Pharmaceuticals; 2017.
62. Sundy JS, Baraf HS, Yood RA, et al. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: Two randomized controlled trials. *JAMA*. 2011;306:711–720.
63. Shannon JA, Cole SW. Pegloticase: A novel agent for treatment-refractory gout. *Ann Pharmacother*. 2012;46:368–376.
64. Feher MD, Hepburn AL, Hogarth MB, et al. Fenofibrate enhances urate reduction in men treated with allopurinol for hyperuricaemia and gout. *Rheumatol*. 2003;42:321–325.
65. Hepburn AL, Kaye SA, Feher MD. Long-term remission from gout associated with fenofibrate therapy. *Clin Rheumatol*. 2003;22:73–76.
66. Ogata N, Fujimori S, Oka Y, et al. Effects of three strong statins (atorvastatin, pitavastatin, and rosuvastatin) on serum uric acid levels in dyslipidemic patients. *Nucleosides Nucleotides Nucleic Acids*. 2010;29:321–4.
67. Wurzner G, Gerster JC, Chiolero A, et al. Comparative effects of losartan and irbesartan on serum uric acid in hypertensive patients with hyperuricaemia and gout. *J Hypertens*. 2001;19:1855–1860.
68. Shahinfar S, Simpson RL, Carides AD, et al. Safety of losartan in hypertensive patients with thiazide-induced hyperuricemia. *Kidney Int*. 1999;56:1879–1885.
69. Choi HK, Soriano LC, Zhang Y, et al. Antihypertensive drugs and risk for incident gout among patients with hypertension: Population based case-control study. *BMJ*. 2012;344:d8190.
70. Borstad G, Bryant L, Abel M, et al. Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. *J Rheumatol*. 2004;31:2429–2432.
71. RetailMeNot RxSaver. Colchicine. Available at: https://rxsaver.retailmenot.com/prescriptions/prices?distance=20&filter=allopurinol&zipCode=52240. Accessed 3/12/2019.

72. Kotz J. The gout pipeline crystallizes. *Nat Rev Drug Discov*. 2012;11:425–426.
73. Tran T, Pham J, Shafeeq H, et al. Role of interleukin-1 inhibitors in the management of gout. *Pharmacotherapy*. 2013;33:744–753.
74. Schumacher HR, Sundy JS, Terkeltaub R, et al. Rilonacept (interleukin-1 trap) in the prevention of acute gout flares during initiation of urate-lowering therapy: Results of a phase II randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2012;64:876–884.
75. Schlesinger N, Mysler E, Lin HY, et al. Canakinumab reduces the risk of acute gouty arthritis flares during initiation of allopurinol treatment: Results of a double-blind, randomised study. *Ann Rheum Dis*. 2011;70:1264–1271.
76. Sundy J, Schumacher R, Kivitz A, et al. Rilonacept for gout flare prevention in patients receiving uric acid-lowering therapy: Results of RESURGE, a phase III, international safety study. *J Rheumatol*. 2014;41:1703–1711.
77. Shahid H, Singh J. Investigational drugs for hyperuricemia. *Expert Opin Investig Drugs*. 2015;24:1013–1030.
78. Riese RJ, Sakhaee K. Uric acid nephrolithiasis: Pathogenesis and treatment. *J Urol*. 1992;148:765–771.
79. Pak CY, Sakhaee K, Fuller C. Successful management of uric acid nephrolithiasis with potassium citrate. *Kidney Int*. 1986;30:422–428.
80. Freedman DS, Williamson DF, Gunter EW, et al. Relation of serum uric acid to mortality and ischemic heart disease. The NHANES I Epidemiologic Follow-up Study. *Am J Epidemiol*. 1995;141:637–644.
81. Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. *Circulation*. 2007;116:894–900.
82. Zuo T, Liu X, Jian L, et al. Hyperuricemia and coronary heart disease mortality: A meta-analysis of prospective cohort studies. *BMC Cardiovasc Disord*. 2016;16:207–216.
83. Gaubert M, Marlinge M, Alessandrini M, et al. Uric acid levels are associated with endothelial dysfunction and severity of coronary atherosclerosis during a first episode of acute coronary syndrome. *Purinergic Signal*. 2018;14:191–99.
84. Liu SC, Xia L, Zhang J, et al. Gout and risk of myocardial infarction: A systematic review and meta-analysis of cohort studies. *PLoS ONE*. 2015;10:e0134088.

85. Higgins P, Dawson J, Lees KR, et al. Xanthine oxidase inhibition for the treatment of cardiovascular disease: A systematic review and meta-analysis. *Cardiovasc Ther*. 2012;30:217–26.
86. Segal M, Srinivas T, Mohandas R, et al. The effect of the addition of allopurinol on blood pressure control in African Americans treated with a thiazide-like diuretic. *J Am Soc Hypertens*. 2015;9:610–619.
87. Beattie C, Fulton R, Higgins P, et al. Allopurinol initiation and change in blood pressure in older adults with hypertension. *Hypertension*. 2014;64:1102–1107.
88. Agarwal V, Hans N, Messerli F. Effect of allopurinol on blood pressure: A systematic review and met-analysis. *J Clin Hypertens*. 2013;15:435–442.
89. Tausche A, Christoph M, Forkmann M, et al. As compared to allopurinol, urate-lowering therapy with febuxostat has superior effects on oxidative stress and pulse wave velocity in patients with severe chronic tophaceous gout. *Rheumatol Int*. 2014;34:101–109.
90. Quach C, Galen BT. *HLA-B*5801* Testing to prevent allopurinol hypersensitivity syndrome: A teachable moment. *JAMA Intern Med*. 2018;178:1260–1261.
91. Latif Z, Abhishek A. Are doctors the best people to manage gout? Is there a role for nurses and pharmacists? *Curr Rheumatol Rep*. 2018;20:14.
92. Gutman AB. The past four decades of progress in the knowledge of gout, with an assessment of the present status. *Arthritis Rheum*. 1973;16:431–445.
93. Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007–2008. *Am J Med*. 2012;125:679–687.

SECTION 15 OPHTHALMIC DISORDERS

110

Glaucoma

Richard G. Fiscella, Timothy S. Lesar, Ohoud A. Owaidhah, and Deepak P. Edward

KEY CONCEPTS

1. Primary open-angle glaucoma (POAG) or ocular hypertension is more prevalent outside Asia than primary angle-closure glaucoma (PACG).
2. In any form of glaucoma, reduction of intraocular pressure (IOP) is essential.
3. IOP is a very important risk factor for glaucoma, but the most important considerations are progression of glaucomatous changes in the back of the eye (optic disk and nerve fiber layer) and visual field changes when diagnosing and monitoring for POAG or ocular hypertension.
4. Optic nerve changes often occur before visual field changes are exhibited.
5. Recent studies demonstrate that reduction in IOP prevents progression or even onset of glaucoma.
6. Newer medications simplify treatment regimens for patients. Prostaglandin analogs are considered the most potent topical medications for reducing IOP and flattening diurnal variations in IOP.
7. Local adverse events are common with topical glaucoma medications, but patient education and reinforcing adherence are essential to prevent glaucoma progression.

Preclass Engaged Learning Activity

Watch the video from Dr Henry Jampel, a leading glaucoma specialist, entitled “Using Eye Drops to Treat Glaucoma” from The Wilmer Eye Institute https://tinyurl.com/vzeg9dh. Proper administration of eye drops is critical

prior to discussing glaucoma medication with a patient. The video presents very common mistakes associated with eye drop administration, the proper technique for administering eye drops and frequently asked questions about using eye drops in glaucoma. It is a very useful tool for the student to help ensure that the proper use of eye drops in glaucoma in the ASSESS and IMPLEMENT steps for the Patient Care Process.

INTRODUCTION

The glaucomas are a group of ocular disorders that lead to an optic neuropathy characterized by changes in the optic nerve head (optic disk) that is associated with loss of visual sensitivity and field. Increased intraocular pressure (IOP) is thought to play an important role in the pathogenesis of glaucoma, but it is not a diagnostic criterion for glaucoma. Consistently elevated IOP without signs or symptoms of glaucoma is called ocular hypertension (OHT).

Two major types of glaucoma have been identified: open angle and closed angle. Primary open-angle glaucoma (POAG) accounts for the great majority of cases in North America, while primary angle-closure glaucoma (PACG) is more prevalent in Asia. Either type can be a primary inherited disorder, congenital, or secondary to disease, trauma, or drugs and can lead to serious complications. Both primary and secondary glaucomas may be caused by a combination of open-angle and closed-angle mechanisms (**Table 110-1** and **Fig. 110-1**). Patients with consistently high intraocular pressure, or patients with clinical findings suspicious of early glaucomatous changes are called “glaucoma suspects.”[1–6]

TABLE 110-1 General Classification of Glaucoma

I. Primary glaucoma
   a. Open angle
   b. Angle closure
      1. With pupillary block
      2. Without pupillary block
II. Secondary glaucoma
   a. Open angle
      1. Pretrabecular
      2. Trabecular
      3. Posttrabecular
   b. Angle closure
      1. Without pupillary block
      2. With pupillary block
III. Congenital glaucoma
IV. Other

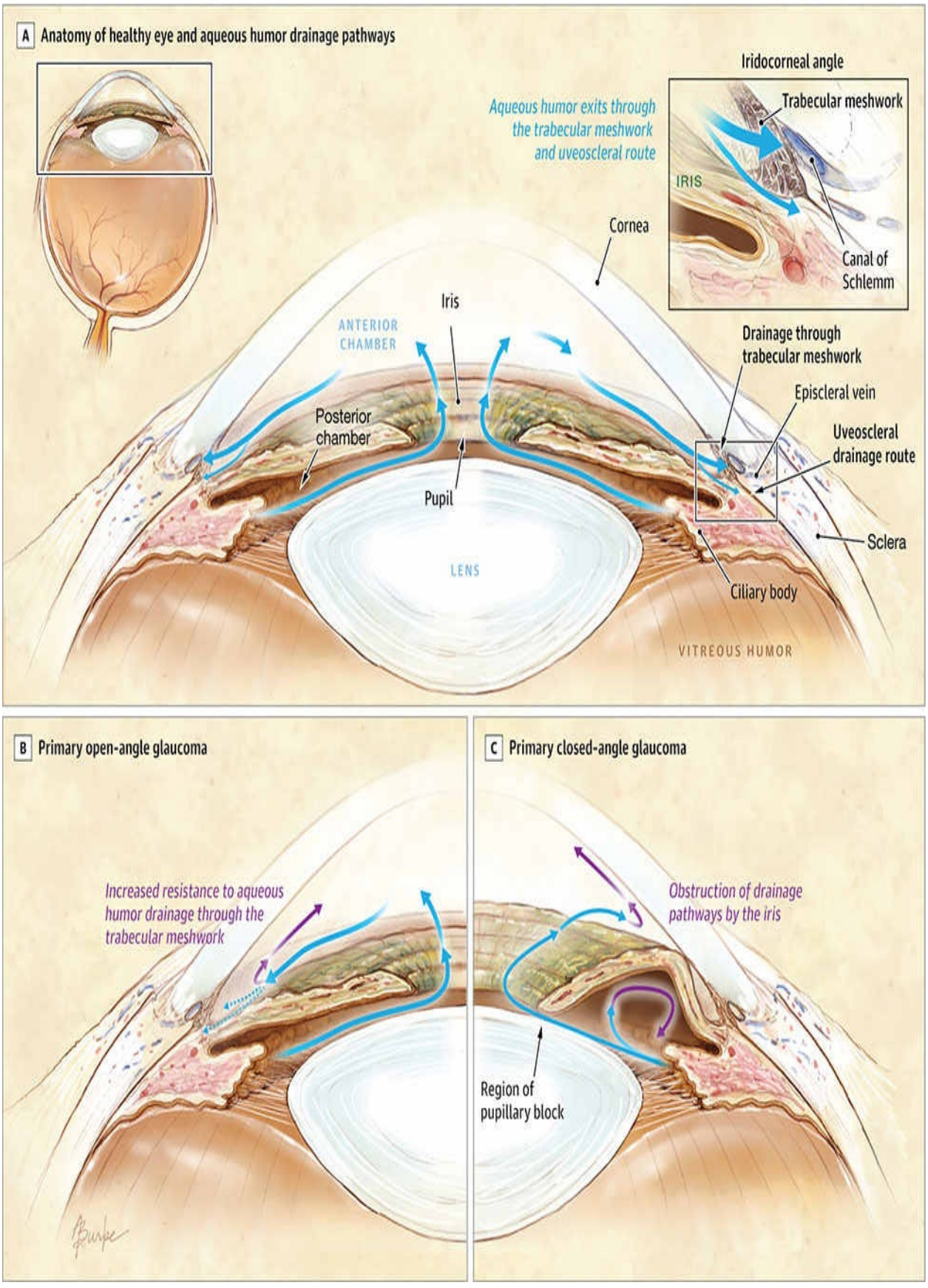

A Anatomy of healthy eye and aqueous humor drainage pathways
Iridocorneal angle
Trabecular meshwork
IRIS
Canal of Schlemm
Aqueous humor exits through the trabecular meshwork and uveoscleral route
Cornea
Iris
ANTERIOR CHAMBER
Drainage through trabecular meshwork
Episcleral vein
Posterior chamber
Uveoscleral drainage route
Pupil
Sclera
LENS
Ciliary body
VITREOUS HUMOR
B Primary open-angle glaucoma
Increased resistance to aqueous humor drainage through the trabecular meshwork
C Primary closed-angle glaucoma
Obstruction of drainage pathways by the iris
Region of pupillary block

FIGURE 110-1 Aqueous humor drainage pathways of healthy and glaucomatous eyes. (*Reprinted with permission from Weinreb RN, Aung T, Madeiros FA. The pathophysiology and treatment of glaucoma. JAMA. 2014;311:1901-1911.*)

BASIC CONCEPTS

Aqueous Humor Dynamics and Intraocular Pressure

An understanding of IOP and aqueous humor dynamics will assist the reader in understanding the drug therapy of glaucoma.[1–3]

Aqueous humor is a clear fluid and ultrafiltrate of the serum that fills and helps form the anterior and posterior chambers of the eye.[7] It is formed in the ciliary body and its epithelium (Fig. 110-1) through both filtration and secretion. Because ultrafiltration depends on pressure gradients, blood pressure and IOP changes influence aqueous humor formation. Osmotic gradients produced by active secretion of sodium and bicarbonate and possibly by other solutes such as ascorbate from the ciliary body epithelial cells into the aqueous humor result in movement of water from the pool of ciliary stromal ultrafiltrate into the posterior chamber, forming aqueous humor. Carbonic anhydrase (primarily isoenzyme type II), α- and β-adrenergic receptors, and sodium- and potassium-activated adenosine triphosphatases are found on the ciliary epithelium and appear to be involved in this secretion of the solutes sodium and bicarbonate.

Receptor systems controlling aqueous inflow have not been elucidated fully. Pharmacologic studies suggest that β-adrenergic agents increase inflow, whereas α_2-adrenergic blocking, β-adrenergic blocking dopamine-blocking, carbonic anhydrase-inhibiting, melatonin-1 agonist, and adenylate cyclase-stimulating agents decrease aqueous inflow. Aqueous humor produced by the ciliary body is secreted into the posterior chamber at a rate of approximately 2 to 3 μL/min. The pressure in the posterior chamber produced by the constant inflow pushes the aqueous humor between the iris and lens and through the pupil into the anterior chamber of the eye (see Fig. 110-1).[1–3,8–10]

Aqueous humor in the anterior chamber leaves the eye by two routes: (a) filtration through the trabecular meshwork (conventional outflow) to the Schlemm's canal (80%-85%) and (b) through the ciliary body and the suprachoroidal space (uveoscleral outflow or unconventional outflow) (see Fig. 110-1). Cholinergic agents such as pilocarpine appear to increase outflow by

physically opening the meshwork pores secondary to ciliary muscle contraction. The nitric oxide group on latanoprost bunod is believed to cause trabecular relaxation and increased trabecular meshwork outflow. ROCK inhibitors are believed to increase aqueous humor outflow through the trabecular meshwork. Prostaglandins are thought to result in remodeling of extracellular matrix in the meshwork, thereby increasing mainly uveoscleral outflow. The uveoscleral outflow of aqueous humor is increased by prostaglandin analogs, β- and α_2-adrenergic agonists. Constant inflow of aqueous humor from the ciliary body and resistance to outflow result in an IOP great enough to produce an outflow rate equal to the inflow rate (see Fig. 110-1). Novel adenosine receptor agonists, cannabinoids, serotonin agents, and dopamine agonists also increase aqueous humor outflow and reduce IOP.[1–4,8–10]

The median IOP measured in large populations is 15.5 ± 2.5 mm Hg (2.1 ± 0.3 kPa); however, the distribution of pressures around the mean is skewed to the right (toward higher readings). IOP is not constant and changes with pulse, blood pressure, forced expiration or coughing, neck compression, and posture. Gender, general health and lifestyle (eg, smoking) are some factors that may have a long-term effect on the IOP.[1–6] The amount of caffeine in one cup of caffeinated coffee (182 mg) increases IOP by about 1 mm Hg (0.1 kPa) after 90 minutes, this increase in IOP is not clinically relevant. Patients who have thinner corneas, have had laser refractory eye surgery (LASIK), or have had cataract surgery demonstrate falsely low IOP readings. IOP is measured by tonometry: indentation tonometry, applanation tonometry, or a noncontact method using an air pulse. Newer methods of tonometery include the Pascal tonometer, Icare™ rebound tonometer, and a contact lens-based investigational device that can remotely monitor 24-hour IOP changes from baseline.[1–5,11,12] These methods may result in slightly different pressure readings. IOPs consistently greater than 21 mm Hg (2.8 kPa) are found in 5% to 8% of the general population. The incidence increases with age, such that “abnormal” (ie, >22 mm Hg [2.9 kPa]) IOP is found in 15% of those 70 to 75 years of age. Intermittently very high IOP (>40 mm Hg [5.3 kPa]) is found in patients with PACG.

IOP demonstrates considerable circadian variation (often referred to as *diurnal* IOP or the IOP during the daily 24-hour cycle) primarily because of changes in the rate of aqueous humor formation. This circadian variation results in a minimum IOP at approximately 6 pm and a maximum IOP at awakening, although some studies suggest that both healthy and glaucoma patients may have their highest IOP at night after falling asleep.[1–3] Low systemic blood pressure in conjunction with high IOPs (decreased ocular perfusion pressure) at night can

result in optic nerve head damage. Generally, the circadian IOP variation is less than 3 to 4 mm Hg (0.4-0.5 kPa); however, it may be greater for patients with glaucoma. This circadian variation and the variable relationship of IOP with visual loss make measurement of IOP a poor screening test for glaucoma. Controlling circadian increases in IOP is thought to be important in prevention of disease progression. Prostaglandin analogs and carbonic anhydrase inhibitors (CAIs) reduce nocturnal IOP, whereas beta blockers and alpha-2 adrenergic agents have minimal effects.[1,3,13]

Although increased IOP within any range is associated with a higher risk of glaucomatous damage, it is both an insensitive and nonspecific diagnostic and monitoring tool. Of individuals with IOP between 21 and 30 mm Hg (2.8 and 4.0 kPa), only 0.5% to 1% per year will develop optic disk changes and visual field loss (ie, glaucoma) over 5 to 15 years. However, more subtle retinal damage, such as alteration of color vision or decreased contrast sensitivity, occurs in a higher percentage of patients with IOPs greater than 21 mm Hg (2.8 kPa), and the incidence of visual field defects increases to as high as 28% in individuals with IOPs above 30 mm Hg (4.0 kPa). For a given IOP finding, the risk of developing glaucoma increases with older age, family history of glaucoma, lower ocular perfusion pressure, lower blood pressure, thinner central cornea, optic disc hemorrhage, larger cup-to-disk ratio, and specific visual fields findings. For patients with preexisting optic nerve damage, the worse the existing damage, the more sensitive the eye is to a given IOP. As many as 20% to 30% of patients with glaucomatous visual field loss have an IOP of less than 21 mm Hg (2.8 kPa) (called *normal-tension glaucoma*, referring to the normal IOP). Thus, the absolute IOP is a less-precise predictor of optic nerve damage. More direct measurements of therapeutic outcome, such as optic disk examination and visual field evaluation, also must be used as monitors of disease progression. Taking the above factors into consideration, glaucoma medications that provide maximal reduction of IOP over 24 hours and have minimal influence on blood pressure may be advantageous in treating glaucoma patients.[1–5,14–18]

Optic Disk and Visual Fields

The optic disk is the portion of the optic nerve ophthalmoscopically visible as it leaves the eye. It consists of approximately 1 million retinal ganglion nerve cell axons, blood vessels, and supporting connective tissue structures (lamina cribrosa). The small depression within the disk is termed the *cup* (**Fig. 110-2**). A

normal physiologic cup does not extend beyond the optic nerve rim and has a varying diameter of less than one-third to one-half that of the disk (cup-to-disk ratio: 0.33-0.5). **Table 110-2** lists the common alterations of the optic disk found in glaucoma. These disk changes result from optic nerve axonal degeneration and remodeling of the supporting structures. As the nerve axons die, the cup becomes larger in relation to the whole disk. A loss of retinal nerve fiber layer might be visualized in glaucoma patients with detectable visual field loss (see **Fig. 110-3**). This pattern of changes is consistent with visual field losses and loss of visual sensitivity seen in glaucoma.[1–4] Damage to the optic nerve can be documented by optic disk photographs, and disease stability or progression may be monitored by examining sequential photographs. Newer methods of assessing damage to the retinal nerve fiber layer and optic disk have been described. These include scanning laser polarimetry (GDX), confocal laser ophthalmoscopy (Heidelberg retinal tomography, or HRT), and optical coherence tomography (OCT). These methods offer the ability to assess the damage to the optic nerve quantitatively.

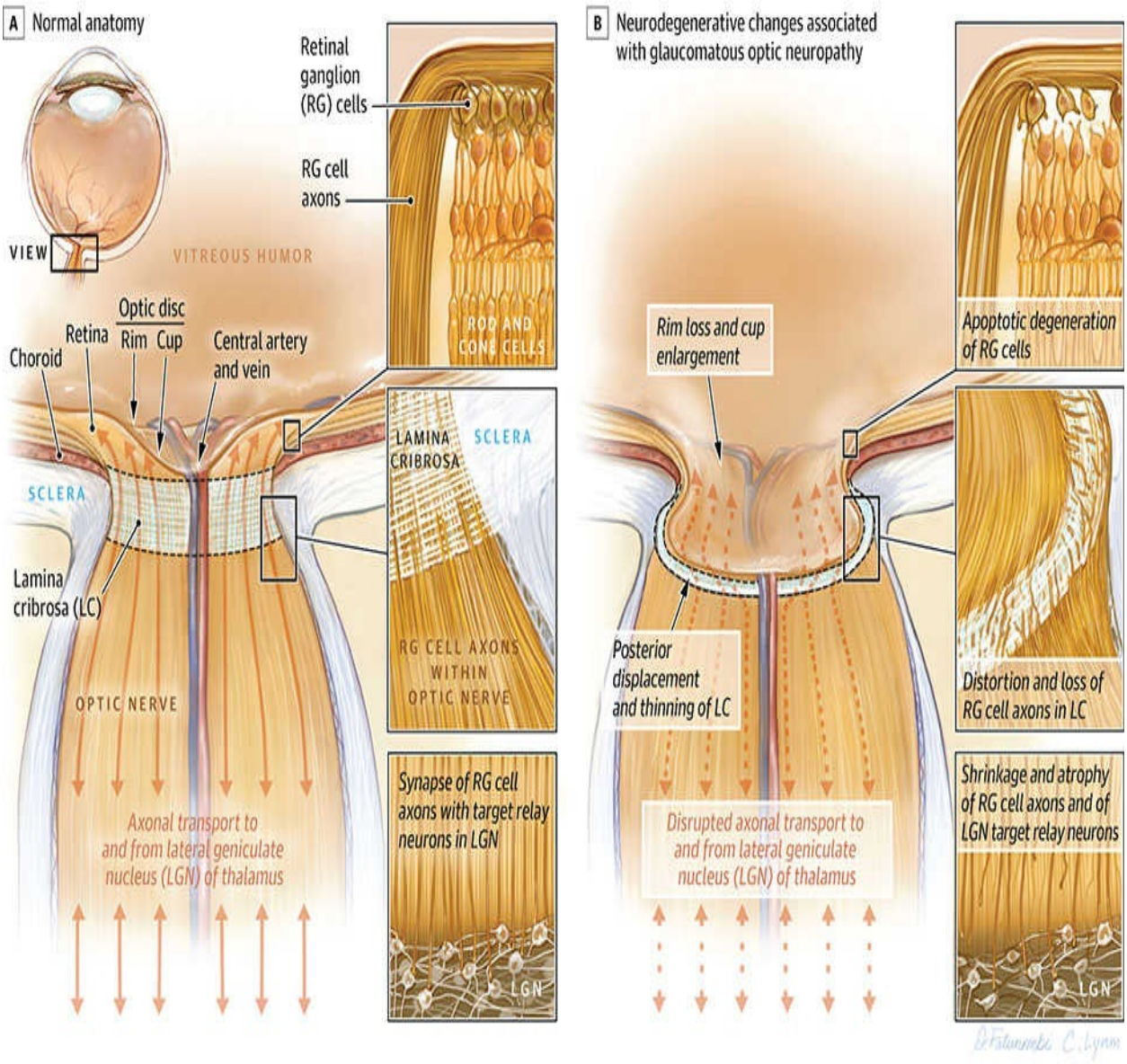


FIGURE 110-2 Schematic illustration of normal anatomy and neurodegenerative changes associated with glaucomatous optic neuropathy. (*A*) The optic disc is composed of neural, vascular, and connective tissues. The convergence of the axons of retinal ganglion (RG) cells at the optic disc creates the neuroretinal rim; the rim surrounds the cup, a central shallow depression in the optic disc. Retinal ganglion cell axons exit the eye through the lamina cribrosa (LC), forming the optic nerve, and travel to the left and right lateral geniculate nucleus, the thalamic relay nuclei for vision. (*B*) Glaucomatous optic neuropathy involves damage and remodeling of the optic disc tissues and LC that lead to vision loss. With elevated intraocular pressure, the LC is posteriorly displaced and thinned, leading to deepening of the cup and narrowing of the rim.

Distortions within the LC may initiate or contribute to the blockade of axonal transport of neurotrophic factors within the RG cell axons followed by apoptotic degeneration of the RG cells. Strain placed on this region also causes molecular and functional changes to the resident cell population in the optic nerve (eg, astrocytes, microglia), remodeling of the extracellular matrix, alterations of the microcirculation, and to shrinkage and atrophy of target relay neurons in the lateral geniculate nucleus. (*Reprinted with permission from Weinreb RN, Aung T, Madeiros FA. The pathophysiology and treatment of glaucoma. JAMA. 2014;311:1901-1911*.)

TABLE 110-2 Optic Disk and visual Field Findings

Optic disk
Cup-to-disk ratio >0.5
Progressive increase in cup size
Cup-to-disk ratio asymmetry >0.2
Vertical elongation of the cup
Excavation of the cup
Increased exposure of lamina cribrosa
Pallor of the cup
Splinter hemorrhages
Cupping to edge of disk
Notching of the cup (usually superior or inferior)
Nerve fiber defects
Visual field findings
General peripheral field constriction
Isolated scotomas (blind spots)
Nasal visual field depression ("nasal step")
Enlargement of blind spot
Large arc-like scotomas
Reduced contrast sensitivity
Reduced peripheral acuity
Altered color vision

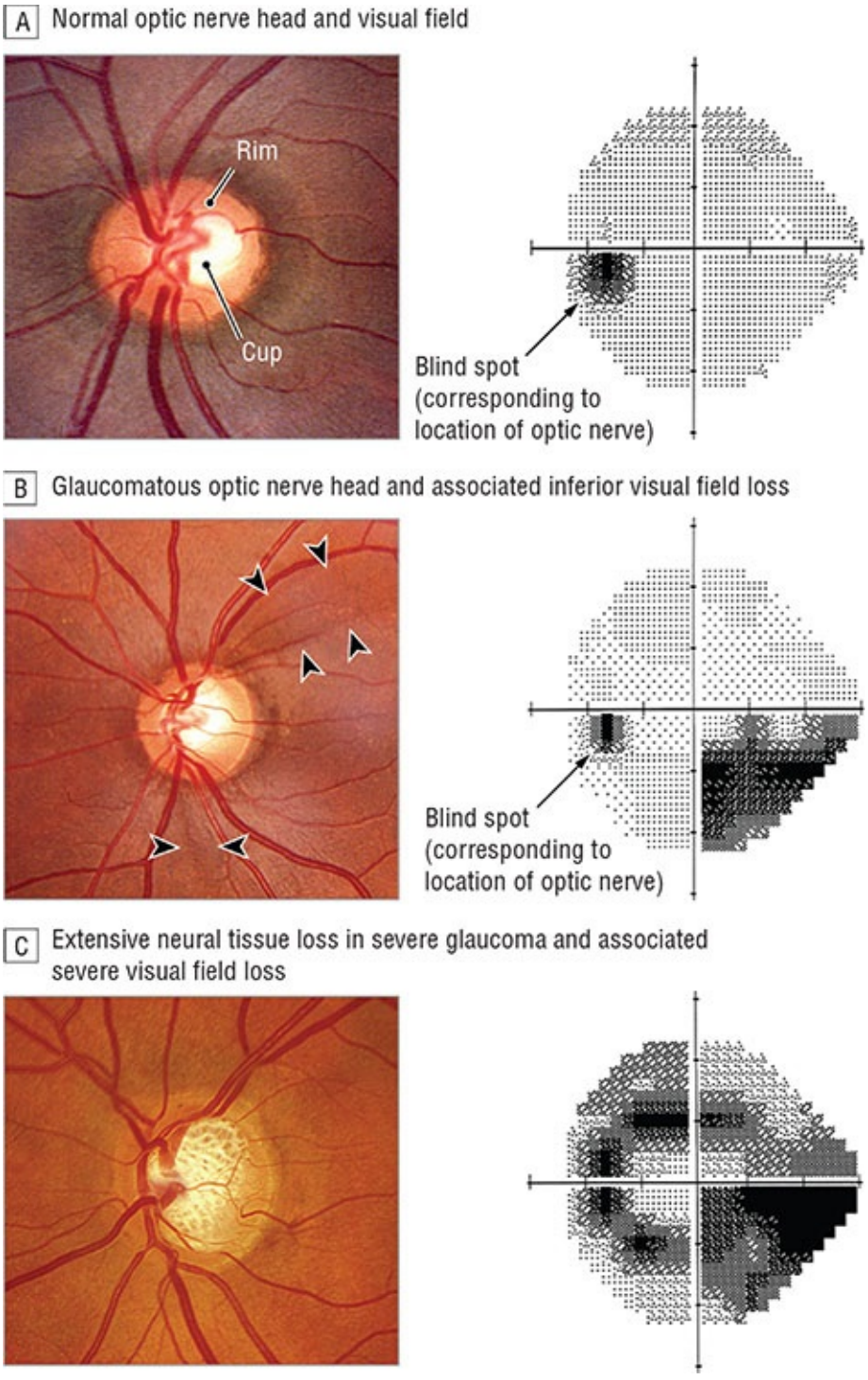


FIGURE 110-3 Normal, glaucomatous, and severe glaucomatous optic nerve heads and visual field test results. (*A*) The pink area of neural tissue forms the neuroretinal rim, whereas the central empty space corresponds to the cup. (*B*) Glaucomatous optic nerve showing loss of superior neural retinal rim (thinning) and excavation with enlargement of the cup. The arrowheads point to an

associated retinal nerve fiber layer defect, which appears as a wedge-shaped dark area emanating from the optic nerve head. The superior neural losses correspond to the inferior defect (black scotoma) seen on the visual field. There is also a small retinal nerve fiber layer defect inferiorly, but the corresponding hemifield of the visual field remains within normal limits. (*C*) More extensive neural tissue loss from glaucoma with severe neuroretinal rim loss, excavation, and enlargement of the cup. There is severe loss of visual field both in the superior as well as in the inferior hemifield. (*Reprinted with permission from Weinreb RN, Aung T, Madeiros FA. The pathophysiology and treatment of glaucoma. JAMA. 2014;311:1901-1911*.)

Determination of the visual field allows assessment of optic nerve damage and is an important monitoring parameter in treatment. However, visual field changes typically lag behind optic disk changes, and a loss of 25% to 35% of retinal ganglion cells is usually required before detectable visual field defects are noted. The peripheral visual field is measured using a visual field instrument called a *perimeter*. Characteristic visual field loss occurs in glaucoma (Fig. 110-3; see also Table 110-2), but loss of central visual acuity usually does not occur until late in the disease. Other indicators, such as color vision changes and contrast sensitivity, may allow earlier and more sensitive detection of glaucomatous changes.[1–4]

Genetics

Glaucoma is often inherited as a complex multifactorial disease, but it can also be inherited as a Mendelian autosomal-dominant or autosomal-recessive trait form. The common age-related adult-onset glaucoma, like POAG, although containing heritability of some significance, is more complex and is influenced by environmental factors. Genetic studies have more clearly defined the underlying molecular events responsible for the Mendelian forms of the disease. However, the chromosome locations identified may play some factor in the more complex forms. A number of major gene loci associated with POAG have been identified. The molecular mechanism of how mutations in any of these genes result in increased IOP with loss of visual field has not been determined. The future of genetic studies in glaucoma will include discovery of new glaucoma genes, determination of clinical phenotypes associated with these genes and mutations, understanding how environmental factors interact, and developing a database that can be used for further testing.

Genome-wide association studies have identified new loci that are associated

with clinically relevant optic disc parameters, including the optic disc area and vertical cup-to-disc ratio. Genes associated with chronic angle-closure glaucoma have also been identified. Improved understanding of the genetic origins of POAG may lead to new diagnostic tools and therapies that target the underlying causes of the disease.[1–4,19]

Epidemiology of Ocular Hypertension, Glaucoma Suspects, and Open-Angle Glaucoma

1 Overall OHT occurs in 4.5% of non-Hispanic whites in the United States. The frequency increases to 7.7% of those over age 79 years.[20–23] The number of glaucoma suspects (ie, consistently high IOP or suspicious eye findings) is thought to be 3 to 6 million individuals in the United States. Left untreated, approximately 2% of glaucoma suspects will progress to glaucoma each year.[1–4]

Open-angle glaucoma (OAG) is the second leading cause of blindness, affecting up to 4 million individuals in the United States and up to 70 million individuals worldwide. It is estimated that more than 135,000 persons in the United States and about 6 to 7 million in the world have glaucoma-related bilateral blindness. The prevalence rate varies with age, race, diagnostic criteria, and other factors. In the United States, OAG occurs in 1.5% of the population older than 30 years of age, 1.3% of whites and 3.5% of blacks. Recent study data have also suggested that the prevalence of OAG and ocular hypertension is also high among Latinos of Mexican ancestry, with approximately 4.74% and 3.56% of people affected, respectively.[24]

The incidence of OAG increases with increasing age. The incidence of the disease for patients 80 years of age is 3% in whites and 5% to 8% in blacks. In addition to increased IOP, age and ethnicity, the risk of glaucoma increases with family history, thinner central corneal thickness, lower ocular perfusion pressure, Type II diabetes, myopia, and certain genetic mutations.[1–5,19–23]

Etiology of Open-Angle Glaucoma

2 The specific cause of glaucomatous optic neuropathy is presently unknown. Previously, increased IOP was considered to be the sole cause of the damage; however, it is now recognized that IOP is only one of many factors associated with the development and progression of glaucoma. Increased susceptibility of the optic nerve to ischemia (a reduced or dysregulated blood flow), excitotoxicity, autoimmune reactions, and other abnormal physiologic processes

are likely additional contributory factors. Damage of the optic nerve ganglion occurs at the point at which ganglion and blood vessels pass through the perforated supportive collagen lamina cribosa of the optic disc. The final outcome of these processes is believed to be apoptosis of the retinal ganglion cells, which results in axonal degeneration and finally permanent loss of vision. Neuronal loss also extends beyond the optic nerve to the lateral geniculate nucleus and visual cortex. POAG may represent a number of distinct diseases or conditions that simply manifest the same symptoms. Susceptibility to visual loss at a given IOP varies considerably; some patients do not demonstrate damage at high IOPs, whereas other patients have progressive visual field loss despite an IOP in the normal range (normal-tension glaucoma).[1–4,6]

Although IOP poorly predicts which patients will have visual field loss, the risk of visual field loss clearly increases with increasing IOP within any range. In fact, recent studies demonstrate that lowering IOP, no matter what the pretreatment IOP, reduces the risk of glaucomatous progression or may even prevent the onset to early glaucoma in patients with ocular hypertension.[1–4,6,14–18]

The mechanism by which a certain level of IOP increases the susceptibility of a given eye to nerve damage remains controversial. Multiple mechanisms are likely to be operative in a spectrum of combinations to produce the death of retinal ganglion cells and their axons in glaucoma. Pressure-sensitive astrocytes and other cells in the optic disk supportive matrix may produce changes and remodeling of the disk, resulting in axonal death. Vasogenic theories suggest that optic nerve damage results from insufficient blood flow to the retina secondary to the increased perfusion pressure required in the eye, dysregulated perfusion, or vessel wall abnormalities, and results in degeneration of axonal fibers of the retina. Another theory suggests that the IOP may disrupt axoplasmal flow at the optic disk.[1–3]

Recently, focus on the mechanisms of the retinal ganglion cell apoptosis and the role of excessive glutamate and nitric oxide found in glaucoma patients has broadened the focus of drug therapy research to include evaluation of agents that act as neuroprotectants. Such agents may be particularly useful for patients with normal-pressure glaucoma, in whom pressure-independent factors may play a relatively larger role in disease progression. These agents would target risk factors and underlying pathophysiologic mechanisms of disease other than IOP.[2,9,13–15,25–28]

Pathophysiology of Open-Angle Glaucoma

3 As stated previously, optic nerve damage in POAG can occur at a wide range of IOPs, and the rate of progression is highly variable. Patients may exhibit pressures in the 20 to 30 mm Hg (2.7-4.0 kPa) range for years before any disease progression is noticed in the optic disk or visual fields. That is why POAG is often referred to as the “sneak thief of sight.”

Clinical Presentation of Open-Angle Glaucoma

POAG is a bilateral, often asymmetric, genetically determined disorder constituting 60% to 70% of all glaucomas and 90% to 95% of primary glaucomas in the United States (see Clinical Presentation above). An increased IOP is not required for diagnosis of POAG. Symptoms do not present until substantial visual field constriction occurs. Central visual acuity typically is maintained, even in the late stages of the disease. Even though POAG is a bilateral disease, it may have greater IOP and progression and severity in one eye. As such, each eye is treated individually.[1–4,6]

4 Detection and diagnosis involve evaluation of the optic disk and retinal nerve fiber layer, assessment of the visual fields, and measurement of IOP. The presence of characteristic disk changes and visual field loss with or without increased IOP confirms the diagnosis of glaucoma. Typical disk changes and field loss occurring at an IOP of less than 21 mm Hg (2.8 kPa) account for 20% to 30% of patients and are referred to as *normal-tension glaucoma*. Elevated IOP (>21 mm Hg [2.8 kPa]) without disk changes or visual field loss is observed in 5% to 7% of individuals (*glaucoma suspects*) and is referred to as *ocular hypertension*. New technologies such as OCT, retinal nerve fiber analyzers, or confocal scanning laser tomography of the optic nerve head may allow early identification of signs of glaucomatous retinal changes in ocular hypertensives, thus allowing for earlier initiation of therapy.[1–5]

Secondary OAG has many causes, including exfoliation syndrome, pigmentary glaucoma, systemic diseases, trauma, surgery, ocular inflammatory diseases, and medications. A system for classifying secondary glaucomas into pretrabecular, trabecular, and posttrabecular forms has been proposed. This classification allows drug therapy to be chosen on the basis of the pathogenic mechanism involved. In pretrabecular forms, a normal meshwork is covered and does not permit aqueous humor outflow. Trabecular forms of secondary glaucoma result from either an alteration of meshwork or an accumulation of

material in the intertrabecular spaces. The posttrabecular forms result primarily from disorders causing increased episcleral venous blood pressure.[1]

CLINICAL PRESENTATION Glaucoma

General

- Glaucoma can be detected in otherwise asymptomatic patients, or patients can present with characteristic symptoms, especially vision loss. Primary open-angle Glaucoma (POAG) is a chronic, slowly progressive disease found primarily in patients older than 50 years of age, whereas primary angle-closure glaucoma (PACG) is more typically associated with symptomatic acute episodes or may be slowly progressive like POAG

Symptoms

- POAG: None until substantial visual field loss occurs
- PACG: Nonsymptomatic or prodromal symptoms (blurred or hazy vision with halos around lights that is caused by a hazy, edematous cornea, and occasionally headache) may be present. Acute episodes produce symptoms associated with a cloudy, edematous cornea, ocular pain, or discomfort, nausea, vomiting, abdominal pain, and diaphoresis

Signs

- POAG: Disk changes and visual field loss (see Table 110-2); IOP can be normal or elevated (>21 mm Hg [2.8 kPa])
- Mild: Optic disk abnormalities with normal visual field with standard perimetry
- Moderate: Optic disk changes plus visual field abnormalities in one hemifield that are not within 5 degrees of central visual fixation.
- Severe: Optic disk changes with visual field loss in both hemifields and loss within 5 degrees of central fixation and abnormalities in at least one hemifield.
- Acute Angle-Closure Glaucoma (ACG): Acute, hyperemic conjunctiva, cloudy cornea, shallow anterior chamber, and occasionally an edematous and hyperemic optic disk; IOP is generally elevated markedly (40-90 mm Hg [5.3-12.0 kPa]) when symptoms are present.

- Chronic (CACG): Disk changes and visual field loss (see Table 110-2); IOP can be normal or elevated (>21 mm Hg [2.8 kPa])

Laboratory Tests

- None

Other Diagnostic Tests

- Emerging tests include optical coherence tomography, retinal nerve fiber analyzers, and confocal scanning laser tomography of the optic nerve. Pachymetry is crucial to detect a thin cornea that has been proved to be associated with visual field progression in Open-Angle Glaucomas.

Prognosis of Open-Angle Glaucoma

5 In most cases of POAG, the overall prognosis is excellent when it is discovered early and treated adequately. Even patients with advanced visual field loss can have continued visual field loss reduced if the IOP is maintained at low enough pressures (often <10-12 mm Hg [1.3-1.6 kPa]). Medications will control IOP successfully in 60% to 80% of patients over a 5-year period. Progression of visual field loss still occurs in 8% to 20% of patients despite reaching standard therapy IOP goals. However, for untreated patients and for those who fail to achieve target IOP reduction, up to 80% have continued visual field loss. Estimates of progression to bilateral blindness in treated patients range from 4% to 22%. Compared to placebo, each 1 mm Hg (0.1 kPa) in IOP reduction reduces risk of disease progression by at least 10% and up to 19%.[1–4,14–18,29] After 2 years, visual field loss occurred in 25.6% of placebo patients compared to 15.2% of those treated with latanoprost.[29] Thus, the keys to medical treatment of POAG are an effective, well-tolerated drug regimen, close monitoring of therapy, and adherence.[1–4]

Epidemiology of Primary Angle-Closure Glaucoma (PACG)

The incidence of PACG varies by the ethnic group, with a higher incidence in individuals of Inuit, Chinese, and Asian-Indian descent. Incidence rates of 1% to 4% have been reported in these populations.[1,2] Because of the high frequency of PACG in populous Asia, PACG accounts for approximately one-third of

glaucoma worldwide. PACG accounts for a disproportionately high proportion of blindness (estimated at up to 50%) worldwide.[1–3,30]

Etiology of Primary Angle-Closure Glaucoma (Acute Angle-Closure Glaucoma and Chronic Angle -Closure Glaucoma)

In North America, primary angle-closure glaucoma (PACG) accounts for a minority of primary glaucomas. When severe acute angle-closure glaucoma (ACG) occurs, it may need to be treated as an emergency to avoid visual loss. PACG results from mechanical blockage of the (usually normal) trabecular meshwork by the peripheral iris. Partial or complete blockage of the meshwork occurs intermittently, potentially resulting in extreme fluctuations between normal IOP with no symptoms and very high IOP with symptoms of acute PACG. Between attacks of PACG, the IOP is usually normal unless the patient has concomitant POAG or nonreversible blockage of the meshwork with synechiae (“creeping” angle closure) that develops over time in the narrow-angle eye. PACG occurs in patients with inherited shallow anterior chambers (often seen in small eyes), which produce a narrow angle between the cornea and iris or tight contact between the iris and lens (pupillary block) (see Fig. 110-1C). The presence of a narrow angle is determined mainly by visualization of the angle by gonioscopy. Other tests for PACG involve provocation of an angle-closure–induced IOP increase. These tests, which attempt to produce angle closure through mydriasis (darkroom test or mydriasis test) or gravity (prone test), are rarely performed in the clinical setting.

Two major types of classic, reversible PACG have been described: PACG with pupillary block and PACG without pupillary block. PACG with pupillary block results when the iris is in firm contact with the lens. This produces a relative block of aqueous flow through the pupil to the anterior chamber (pupillary block), resulting in a bowing forward of the iris, which blocks the trabecular meshwork. PACG with pupillary block occurs most commonly when the pupil is in mid-dilation. In this position, the combination of pupillary block and relaxed iris allows the greatest bowing of the iris; however, angle closure may occur during miosis or mydriasis.

PACG can occur without significant pupillary block for patients with an abnormality called a *plateau iris*. The ciliary processes in these cases are situated anteriorly, which indent the iris forward and cause closure of the trabecular meshwork, especially during mydriasis. The mydriasis produced by

anticholinergic drugs or any other drug results in precipitation of both types of PACG glaucoma, whereas drug-induced miosis may produce pupillary block.[1–3,30]

Pathophysiology of Primary Angle-Closure Glaucoma

The mechanism of IOP elevation in PACG is clearer than that of POAG. In PACG, a physical blockage of trabecular meshwork is present. In many cases, single or multiple episodes of high IOP that in some patients may exceed 40 mm Hg (5.3 kPa) and result in optic nerve damage. Very high IOP (>60 mm Hg [8.0 kPa]) may result in permanent loss of visual field within a matter of hours to days.

One type of CAG, known as “creeping” angle closure, occurs in patients with narrow angles in which the iris adheres to the trabecular meshwork and may result in continuously increased IOP in ranges more similar to those of POAG, and the clinical behavior is similar to POAG, with individuals differing in the degree and rapidity of visual loss from any given elevated IOP.[1,30]

Clinical Presentation of Angle-Closure Glaucoma

Most patients with untreated PACG typically experience intermittent nonsymptomatic or prodromal symptoms brought on by precipitating events (see Clinical Presentation above). Increased IOP during such prodromal episodes is not great enough or long enough to produce the other symptoms of a full-blown attack. Such prodromal attacks last 1 to 2 hours, at which time pupillary block is broken by further mydriasis or miosis, or when miosis or mydriasis occurs in patients with plateau iris. The rate at which IOP increases may be a determinant of when full-blown symptoms occur. Visual fields demonstrate generalized constriction or typical glaucomatous defects as seen in POAG. In approximately 25% of patients, severe attacks may occur and if prolonged, total loss of vision may occur if the IOP is high enough. Tonometry reveals IOPs as high as 40 to 90 mm Hg (5.3-12.0 kPa). Patients who have developed adhesions between the iris and meshwork (anterior synechiae) may have chronic IOP elevation with intermittent spikes of high IOP when angle closure occurs.[1,2,30]

Drug-Induced Glaucoma

A number of medications are associated with increased IOP or carry labeling that cautions against use of the medication in glaucoma patients. The potential for a

medication to produce or worsen glaucoma depends on the type of glaucoma and whether the patient is treated adequately.[1–5,31–32] Patients with treated, controlled POAG are at minimal risk of induction of an increase in IOP by systemic medications with anticholinergic properties or vasodilators; however, for patients with untreated glaucoma or uncontrolled POAG, the potential of these medications to increase IOP should be considered. Topical anticholinergic agents used to produce mydriasis may result in an increase in IOP. Potent anticholinergic agents such as atropine or homatropine are most likely to increase IOP. Weaker anticholinergics, such as tropicamide, that produce less cycloplegia are less likely to increase IOP and are favored, along with phenylephrine, when mydriasis is desired for POAG patients. Inhaled, nasal, topical, or systemic glucocorticoids may increase IOP for both normal individuals and patients with POAG.

Patients with POAG appear to be particularly susceptible to glucocorticoid-induced increases in IOP. Glucocorticoids reduce the facility of aqueous humor outflow through the trabecular meshwork. The decreased facility of outflow appears to result from the accumulation of extracellular material blocking the trabecular channels. The potential of a glucocorticoid to increase IOP is related to its anti-inflammatory potency and intraocular penetration. Thus, patients should be treated with the lowest potency and dose and for the shortest time possible when steroids are indicated.

For patients predisposed to CAG (ie, narrow anterior chambers), angle closure may be produced by any drug that causes mydriasis (eg, anticholinergics). A wide range of sulfa compounds causes idiosyncratic reactions that result in lens swelling and anterior choroidal effusions with anterior movement of the iris and lens, resulting in angle closure. The topical use of anticholinergics or sympathomimetic agents most likely will result in angle closure. Systemic and inhaled anticholinergic and sympathomimetic agents also must be used with caution in such patients. As discussed previously, potent miotic agents such as echothiophate may produce angle closure by increasing pupillary block. **Table 110-3** lists the drugs associated with potentiation of glaucoma.

TABLE 110-3 Drugs That May Induce or Potentiate Increased Intraocular Pressure

Open-angle glaucoma
Ophthalmic corticosteroids (high risk)
Systemic corticosteroids
Nasal/inhaled corticosteroids
Fenoldopam
Ophthalmic anticholinergics
Succinylcholine
Vasodilators (low risk)
Cimetidine (low risk)

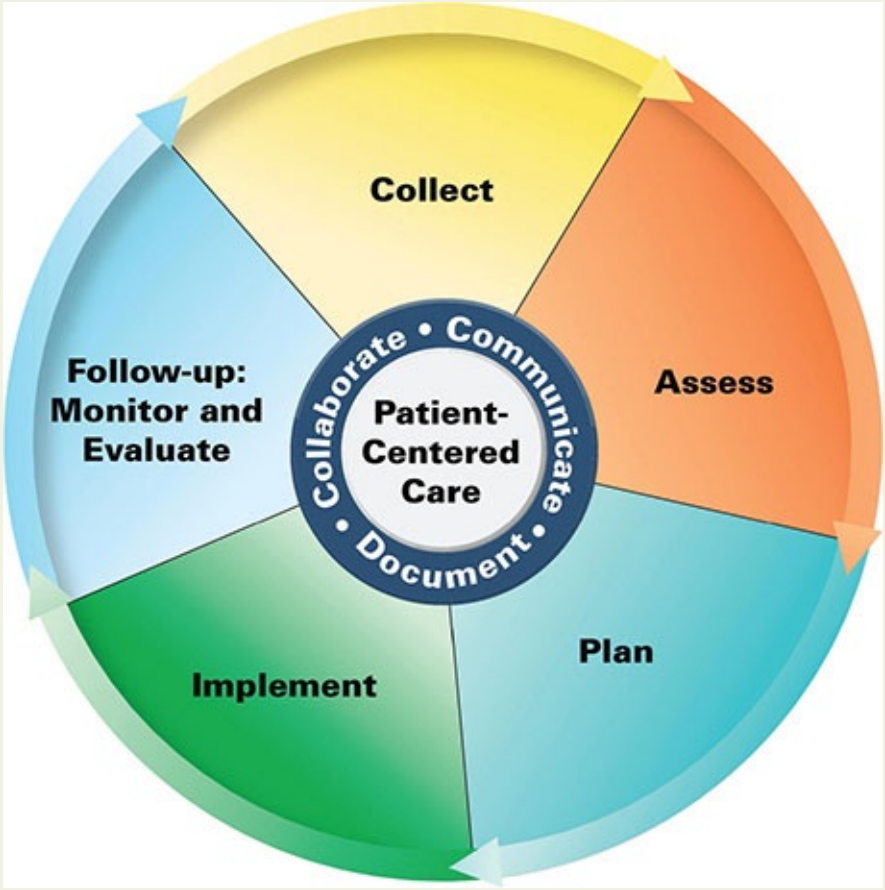
Closed-angle glaucoma
Topical anticholinergics
Topical sympathomimetics
Systemic anticholinergics
Heterocyclic antidepressants
Low-potency phenothiazines
Antihistamines
Ipratropium
Benzodiazepines (low risk)
Theophylline (low risk)
Vasodilators (low risk)
Systemic sympathomimetics (low risk)
CNS stimulants (low risk)
Serotonin-selective reuptake inhibitors
Imipramine
Venlafaxine
Topiramate
Tetracyclines (low risk)
Carbonic anhydrase inhibitors (low risk)
Monoamine oxidase inhibitors (low risk)
Topical cholinergics (low risk)

TREATMENT

Glaucoma Suspect and Ocular Hypertension

Treatment of the patient with possible glaucoma (ocular hypertension; ie, patients with IOP >22 mm Hg [2.9 kPa]) is less controversial with the recent results of the Ocular Hypertensive Treatment Study (OHTS) than it was in the past.[14] The OHTS helped to identify risk factors for treatment. Patients with IOPs higher than 25 mm Hg (3.3 kPa), vertical cup-to-disk ratio of more than 0.5, and central corneal thickness of less than 555 µm are at greater risk for developing glaucoma. Risk factors such as family history of glaucoma, black, Latino/Hispanic ethnicity, severe myopia, and patients with only one eye must also be taken into consideration when deciding which individuals need

treatment.



Patient Care Process for the Management of Glaucoma

Collect

- Patient characteristics (eg, age, race, sex, pregnant)
- Patient history (past medical, family history of glaucoma, social; date and results of past eye examinations)
- Changes in vision (see Fig. 110-3)
- Current medications, including nonprescription agents and topically applied products, including eye drops (see Table 110-3 for agents that affect intraocular pressure (IOP)
- Objective data (see Clinical Presentation box)
    - IOP measurements
    - Disc changes and abnormalities—bilateral, symmetrical?

- Visual field changes and losses

Assess

- If primary angle-closure glaucoma is suspected, manage or refer as ophthalmologic emergency
- Presence of conditions that can produce secondary cases of open-angle glaucoma (eg, exfoliation syndrome, pigmentary glaucoma, systemic diseases, trauma, surgery, ocular inflammatory diseases, and medications [see Table 110-3])
- Current medications that may contribute to or worsen glaucoma (see Table 110-3)
- Past history of adverse effects to agents used in treatment of glaucoma
- Identify target IOP goal based on past history and current situation

Plan*

- Drug therapy regimen designed to achieve target IOP, including specific agent(s), dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Fig. 110-4 and Table 110-4)
- Monitor IOP for target reductions (usually at least 20% reduction from baseline IOP, if not a reduction of 25%-30%, at 4-6 weeks after therapy begins, and for adverse effects (eg, local intolerance or reactions, altered iris pigmentation within 2 years of treatment initiation, hypertrichosis, hyperpigmentation of lids or lashes)
- Referrals to other providers when appropriate (eg, ophthalmologist)

Implement*

- Provide patient education regarding all elements of treatment plan
- Provide extensive education about administration of eye drops, separation of doses, and reinforcement of importance of adherence to preservation of vision
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up, usually 4 to 6 weeks after therapy starts and every 3 to 4 months once target IOPs are achieved

Follow-up: Monitor and Evaluate

- Measure intraocular pressure
- Optic disc and visual fields
- Adverse effects to medications
- Adherence to treatment and drug administration technique

*Collaborate with patient, caregivers, and other healthcare professional.

Patients without risk factors typically are not treated and are monitored for the development of glaucomatous changes. The use of risk calculators has been suggested as a means of determining who are at greatest risk in developing glaucoma. It is hoped that with future improvement in such calculators, one would be able to tailor treatment to those at greatest risk for developing glaucoma.

Patients with significant risk factors usually are treated with a well-tolerated topical agent such as a prostaglandin analog or β-blocking agent. Other options include a α_2-agonist (brimonidine), a topical carbonic anhydrase inhibitor (CAI), or netasudil, depending on individual patient characteristics. Therapy may be initiated in one eye to assess tolerance and efficacy compared to the contralateral eye; however, because each eye may respond differently to a medication as well as possible contralateral effects, IOP response may be compared to baseline in individual eyes.

The goal of therapy is to lower the IOP to a level associated with a decreased risk of optic nerve damage, usually at least a 20%, if not a 25% to 30% decrease from the baseline IOP. Greater decreases may be required in high-risk patients or those with higher initial IOPs. Drug therapy should be monitored by measurement of IOP, examination of the optic disk, assessment of the visual fields, and evaluation of the patient for drug adverse effects and compliance with therapy. Patients who are unresponsive to or intolerant of a drug should be switched to an alternative agent rather than given an additional drug. Partial responders may be treated with combinations of well-tolerated topical medications (prostaglandins, beta-blockers, brimonidine, or a CAI). Use of multiple combinations of topical agents or when first-line agents fail to reduce IOP depends on the risk-to-benefit assessment of each patient. Some clinicians prefer to discontinue all medications for patients who fail to respond adequately to simple topical therapy, closely monitor for development of disk changes or visual field loss, and treat again when such changes occur.[6] The cost, inconvenience of frequent adverse effects of multiple-combination therapies, pilocarpine, cholinesterase inhibitors, and oral CAIs generally result in an

unfavorable risk-to-benefit ratio for glaucoma suspect patients.[1–4,6,32–35]

TREATMENT

Open-Angle Glaucoma

All patients with elevated IOP and characteristic optic disk changes and/or visual field defects not caused by other factors (ie, glaucoma by definition) should be treated. Recent findings that one in five patients with “normal” IOP and glaucomatous retinal nerve findings (ie, normal-tension glaucoma) do not have progression of visual field loss if left untreated have prompted recommendations to monitor normal-tension glaucoma patients without immediate threat of loss of central vision and to treat only when progression is documented. Some controversy exists as to whether the initial therapy of glaucoma should be surgical trabeculectomy (filtering procedure), argon or selective laser trabeculectomy, or medical therapy.[1–4,32–44] Presently, drug therapy remains the most common initial treatment modality. Drug therapy of patients with documented glaucomatous change with either elevated or normal IOP is initiated in a stepwise manner (**Fig. 110-4**), starting with a single, well-tolerated topical agent. The goal of therapy is to prevent further visual loss. A “target” IOP is chosen based on a patient baseline IOP and the amount of existing visual field loss. Typically, an initial target IOP reduction of 25% to 30% is desired. Greater reductions may be desired for patients with very high baseline IOPs or advanced visual field loss. Patients with normal baseline IOPs (normal-tension glaucoma) may have target IOPs of less than 10 to 12 mm Hg (1.3-1.6 kPa).[1–4]

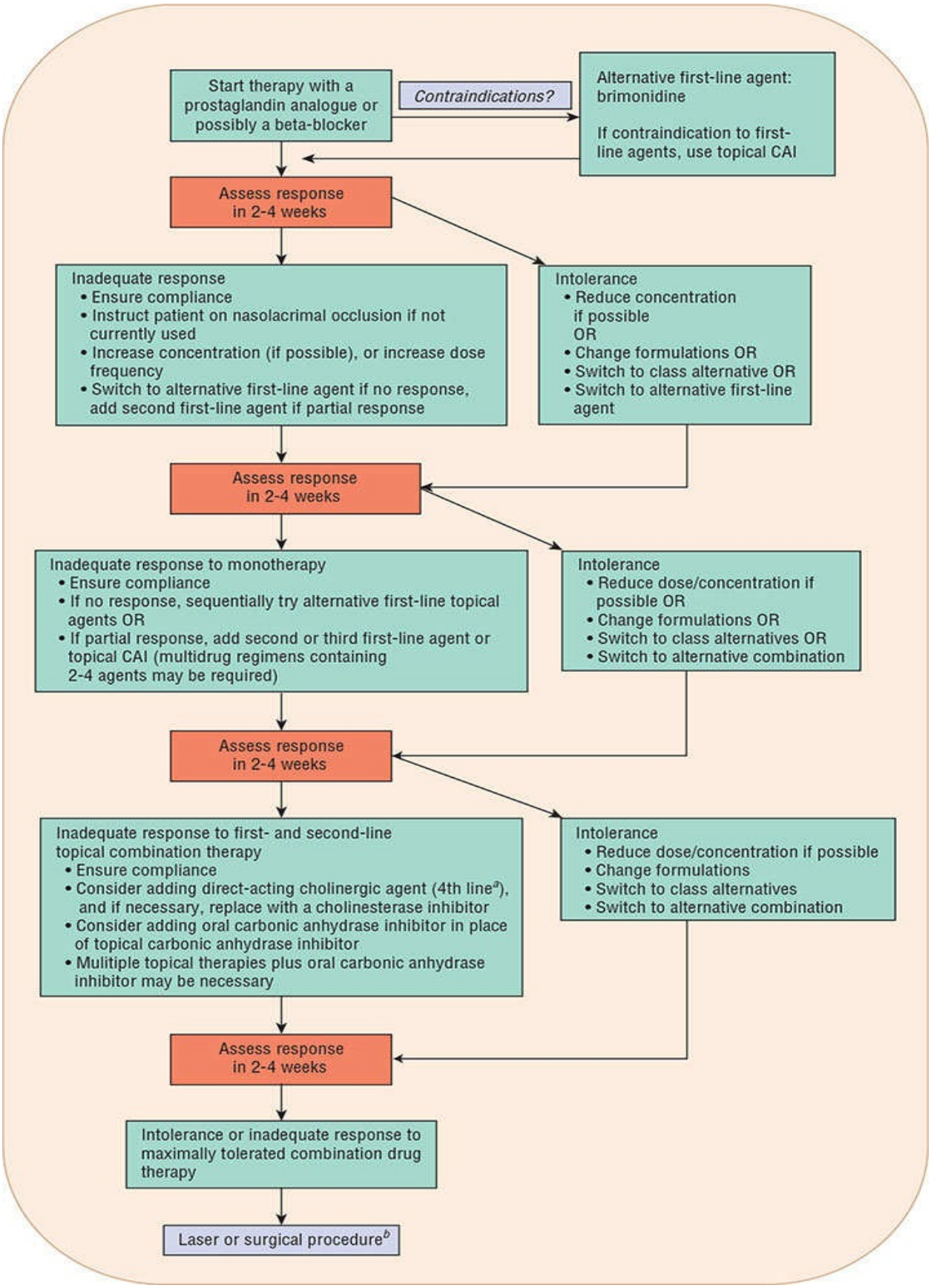

Start therapy with a prostaglandin analogue or possibly a beta-blocker
Contraindications?
Alternative first-line agent: brimonidine
If contraindication to first-line agents, use topical CAI
Assess response in 2-4 weeks
Inadequate response
• Ensure compliance
• Instruct patient on nasolacrimal occlusion if not currently used
• Increase concentration (if possible), or increase dose frequency
• Switch to alternative first-line agent if no response, add second first-line agent if partial response
Intolerance
• Reduce concentration if possible OR
• Change formulations OR
• Switch to class alternative OR
• Switch to alternative first-line agent
Assess response in 2-4 weeks
Inadequate response to monotherapy
• Ensure compliance
• If no response, sequentially try alternative first-line topical agents OR
• If partial response, add second or third first-line agent or topical CAI (multidrug regimens containing 2-4 agents may be required)
Intolerance
• Reduce dose/concentration if possible OR
• Change formulations OR
• Switch to class alternatives OR
• Switch to alternative combination
Assess response in 2-4 weeks
Inadequate response to first- and second-line topical combination therapy
• Ensure compliance
• Consider adding direct-acting cholinergic agent (4th line[a]), and if necessary, replace with a cholinesterase inhibitor
• Consider adding oral carbonic anhydrase inhibitor in place of topical carbonic anhydrase inhibitor
• Mulitiple topical therapies plus oral carbonic anhydrase inhibitor may be necessary
Intolerance
• Reduce dose/concentration if possible
• Change formulations
• Switch to class alternatives
• Switch to alternative combination
Assess response in 2-4 weeks
Intolerance or inadequate response to maximally tolerated combination drug therapy
Laser or surgical procedure[b]

FIGURE 110-4 Algorithm for the pharmacotherapy of open-angle glaucoma. *a*Fourth-line agents are not commonly used any longer or are commercially unavailable. *b*Most clinicians believe the laser procedure should be performed earlier (eg, after three-drug maximum, poorly adherent patient). (CAI, carbonic anhydrase inhibitor.)

Pharmacotherapeutic Approach

6 Medications most commonly used to treat glaucoma are the prostaglandin analogs, nonselective β-blockers, brimonidine (a α_2-agonist), the topical CAIs, and the fixed combination products of timolol/dorzolamide, timolol/brimonidine, brimonidine/brinzolamide, or timolol/prostaglandins (non-United States). Recently introduced effective and acceptable safety profiles include latonoprostene bunod and netarsudil.[1–4,32–35]

The prostaglandin analogs are often recommended as first-line therapy. They offer once-daily dosing, better IOP reduction, better 24-hour IOP control, good tolerance, and availability of lower-cost generics (see Fig. 110-4). The topical β-blockers have a long history of successful use, providing a combination of clinical efficacy and general tolerability. Brimonidine and topical CAIs are also well tolerated and effective agents, but often considered second-line agents (to prostaglandins and beta blockers).[1–4] The role of newer agents such as latanoprostene bunod and netarsudil are not established but will likely be used (individually or in combination) in patients not inadequately responding to or intolerant of other agents. Therapy optimally is started as a single agent; it can be started in one eye (except for patients with very high IOP or advanced visual field loss) to evaluate drug efficacy and tolerance, although response may differ between contralateral eyes. Monitoring of therapy should be individualized. Initial check for IOP response to therapy is typically done 4 to 6 weeks after the medication is started. Once IOPs reach acceptable levels, the IOP is monitored every 3 to 4 months or longer if there is prolonged control (over 6-12 months) without progression. More frequent monitoring is necessary if IOP target is not achieved, disease progression is noted, and after any change in drug therapy.[1–4,6]

Visual fields and disk changes are typically monitored every 6 to 12 months or earlier if the glaucoma is unstable or there is suspicion of disease worsening. Patients should always be questioned regarding adherence to and tolerance of prescribed therapy. Initial IOP response does not predict long-term IOP control, as tachyphylaxis to IOP reduction and or disease progression may occur.

The value of an agent with which the patient has shown a drop in IOP

following an initial response can be measured by discontinuing the medication completely and determining if an increase in IOP occurs. Patients responding to but intolerant of initial therapy may be switched to another drug. For patients failing to respond to an initial drug, a switch to an alternative agent should be considered. If only a partial response occurs, addition of another topical drug to be used in combination is a possibility. A number of drugs or drug combinations may need to be tried before an effective and well-tolerated regimen is identified. Prostaglandin agonists, beta blockers, brimonidine, CAI, and pilocarpine may be used in various combinations. Generally adding a second drug results in a less than additive reduction in IOP. Using more than one drop per dose does not improve response, and it increases the likelihood of adverse effects and the cost of therapy. When using more than one medication, separation of drop instillation of each agent by at least 5 minutes is suggested to provide optimal ocular absorption. Combination products reduce the number of daily doses, possibly improving adherence and preventing washout effect seen when a second medication is administered too soon after the initial medication. Use of combination products also reduces exposure to ophthalmic preservatives. Ocular surface disease (OSD) secondary to glaucoma therapy will often manifest as superficial punctate keratitis, tear-film instability, or allergy.[45] In-vivo and animal studies have demonstrated the toxic effects of preservatives, often benzalkonium chloride through various mechanisms. However, extrapolating these results to clinical use is difficult because these studies must control for effects such as blinking, tear dilution and turn over, buffering capabilities, etc. of the human eye. While many crossover clinical trials show benefit to preservative-free therapies, there are a multitude that demonstrate no improvement. Patients with medication-related OSD may try treatment with artificial tears, anti-inflammatory therapy, or possibly preservative-free therapy if feasible.

The IOP response to ocular hypotensive medication may vary with corneal thickness. The response might be better in those with normal or thin corneas than in those with thicker structures.

Because of the frequency of adverse effects, dipivefrin, carbachol, topical cholinesterase inhibitors, and oral CAIs are considered last-line agents to be used for patients who fail less-toxic combination topical therapy.

Nonpharmacologic Therapy: Laser and Surgical Procedures

When drug therapy fails, is not tolerated, or is excessively complicated, surgical procedures such as laser trabeculoplasty (argon or selective) or a surgical trabeculectomy (filtering procedure) may be performed to improve outflow. Laser trabeculoplasty is usually an intermediate step between drug therapy and trabeculectomy. The newer selective laser trabeculoplasty (SLT) procedure has demonstrated similar IOP reduction as argon laser trabeculoplasty (ALT) and may be repeatable. Recent studies have demonstrated good efficacy for this procedure in comparison with medical treatment options for POAG. Procedures with higher complication rates, such as those involving placement of draining tubes or destruction of the ciliary body (cyclodestruction), may be required when other methods fail (see Figs. 110-1 and 110-2).[1–4]

Surgical methods for reduction of IOP involve the creation of a channel through which aqueous humor can flow from the anterior chamber to the subconjunctival space (filtering bleb), where it is reabsorbed by the vasculature. A major reason for failure of the procedure is healing and scarring of the site. The use of aqueous shunts or valves to manage glaucoma has been increasing, and the results of a recent study have demonstrated improved safety and efficacy of these devices. However, glaucoma surgery is still plagued with the shortcomings despite modifications and improvements over the past century, including potentially vision-threatening complications like hypotony, wound leaks, and infections.[38,39,46] MIGS (Minimally Invasive Glaucoma Surgery) offer micro incisions and implants that reduce intraocular pressure by targeting various areas of the outflow pathway.[46] These can either be approached from inside the eye (ab-interno) (eg, iStent, Hydrus, Trabectome, XEN 45, suprachoroidal shunts) or outside the eye (ab-externo) (eg, canaloplasty, Gold micro shunt, and Stegman Canal Expander).[46] MIGS can be considered as an alternative to medical therapy in an effort to address adherence challenges, adverse events, and quality-of-life (QOL) issues with topical medications. They are usually performed in combination with cataract surgery (eg, iStent, Hydrus) or as a solo procedure (XEN 45).

Modification of the healing process to maintain patency is possible with the use of antiproliferative agents. The antiproliferative agents' 5-fluorouracil and mitomycin C are used for patients undergoing glaucoma-filtering surgery to improve success rates by reducing fibroblast proliferation and consequent scarring. Although used most commonly for patients with increased risk for suboptimal surgical outcome (after cataract surgery and a previous failed filtering procedure), use of these agents also improves success in low-risk patients.[38,39,46] A standardized formulation of mitomycin C (MMC) that is

prepacked in a kit with a fixed dose and concentration was approved by FDA in 2012 and is commercially available under the name “Mitosol.” Off-label use of mitomycin C prepared by compounding pharmacies is also common.

TREATMENT

Acute Angle-Closure Crisis (AACC)

The goal of initial therapy for acute AACC with high IOP is rapid reduction of the IOP to preserve vision and to avoid surgical or laser iridectomy on a hypertensive, congested eye. Iridectomy (laser or surgical) is the definitive treatment of PACG; it produces a hole in the iris that permits aqueous humor flow to move directly from the posterior chamber to the anterior chamber, opening up the block at the trabecular meshwork. Drug therapy of an AACC typically involves administration of one or more topical antiglaucoma medications including miotics (eg, pilocarpine), secretory inhibitors (β-blockers, α_2-agonist, or topical/systemic CAIs), or a prostaglandin agonist.[5,30] The miosis produced by pilocarpine pulls the peripheral iris away from the meshwork. However, miotics may worsen angle closure by increasing pupillary block and producing anterior movement of the lens because of drug-induced accommodation. The aqueous secretory inhibitors and pilocarpine may not be effective due to ischemia of the ciliary body and pupillary sphincter, respectively. During this time, the urge to use excessive amounts of topical agents must be resisted. A hyperosmotic agent such as mannitol or glycerin may be needed to temporarily reduce IOP and restore response to the topical agents.

An osmotic agent also is commonly administered because these drugs produce the most rapid decrease in IOP. Oral glycerin 1 to 2 g/kg can be used if an oral agent is tolerated; if not, IV mannitol 1 to 2 g/kg should be used. Osmotic agents reduce IOP by withdrawing water from the eye secondary to the osmotic gradient between the blood and the eye. These drugs are among the first-line agents in the short-term treatment of an AACC or other forms of acute very high IOP elevations. Topical corticosteroids often are used to reduce the ocular inflammation and reduce the development of synechiae in PACG eyes. Patients failing therapy altogether will require an emergency iridectomy. Once the IOP is controlled, iridectomy is performed on the affected eye as well as the contralateral eye (if narrow angles are present).

Peripheral iridectomy essentially “cures” primary PACG without significant synechiae. Long-term drug therapy is not used unless IOP remains high because of the presence of synechiae blocking the trabecular meshwork or concurrent

POAG. In such cases, the pharmacotherapeutic approach is essentially identical to that for the POAG patient, or laser or surgical procedures are performed.[1,2,5,30]

PHARMACOLOGIC AGENTS USED IN GLAUCOMA

Prostaglandin Analogs

The prostaglandin analogs, including latanoprost, travoprost, bimatoprost, and tafluprost, reduce IOP by increasing the uveoscleral and, to a lesser extent, trabecular outflow of aqueous humor. Some differences in receptor sites and mechanisms of action may exist between the two prostaglandins (latanoprost, travoprost, and tafluprost) and the prostamide (bimatoprost). However, both classes appear to produce collagen changes in the matrix of the ciliary body and trabecular meshwork. Bimatoprost may be slightly more effective in lowering IOP, getting a larger percentage of patients to lower IOPs, and for patients unresponsive to latanoprost. If the patient does not respond to one prostaglandin agonist, a switch to another may be beneficial.[37,40,41] Generic forms of some prostaglandin analogs are now available, reducing the cost to patients for these agents. Tafluprost is available as a preservative-free solution, which may be useful in patients intolerant of common ophthalmic preservatives or those with corneal surface disorders.

Reduction in IOP with once-daily doses of prostaglandin analogs (a 25%-35% reduction) is often greater than that seen with timolol 0.5% twice daily. In addition, nocturnal control of IOP is improved compared with timolol.[2,40,41] The drugs are administered at nighttime, although they are probably as effective if given in the morning.

Prostaglandin analogs are well tolerated and produce fewer systemic adverse effects than timolol. Local ocular tolerance generally is good, but ocular reactions such as punctate corneal erosions and conjunctival hyperemia do occur. Local intolerance occurs in 10% to 25% of patients with these agents.[1–3,10,33–35]

With prostaglandin analogs, altered iris pigmentation occurs in 15% to 30% of patients, particularly those with mixed-color irises (blue-brown, green-brown, blue-gray-brown, or yellow-brown eyes), which become browner in color over 3 to 12 months. The change in iris pigmentation will often appear within 2 years, and long-term consequences of this pigment change appear to be mostly

cosmetic but irreversible upon discontinuation. Hypertrichosis is common and reverses upon discontinuation of the drug. Hyperpigmentation around the lids and lashes has also been reported and appears to reverse upon discontinuation. Loss of periorbital fat has been reported, which may lead to apparent enophthalmos and sunken eye, especially when used unilaterally.

Topical prostaglandin analogs may produce rates of corneal thinning that are slightly higher than ongoing age-related changes. This effect is unlikely to be clinically relevant.[8–10,33–35]

These agents have occasionally been associated with uveitis, and caution is recommended for patients with ocular inflammatory conditions. Cases of cystoid macular edema and worsening of herpetic keratitis have been reported.

Prostaglandin analogs can be used in combination with other antiglaucoma agents for additional IOP control because of their unique mechanism of action. Given their excellent efficacy and side-effect profile, prostaglandin analogs provide effective monotherapy or adjunctive therapy for patients who are not responding to or tolerating other agents. Long-term studies demonstrate these agents are safe, efficacious, and well tolerated in glaucoma therapy.[8–10,33–35] Various fixed combination prostaglandin products, often with timolol are available in Canada and overseas.

Latanoprostene bunod is a newer agent approved for use in patients with OAG and OHT.[10,28,41,43] This agent is a prodrug of latanoprost and is also metabolized to a nitric-oxide–donating moiety, thus providing dual mechanisms for increasing aqueous outflow. This agent produces IOP reduction similar to or greater than that with timolol. Adverse effects are similar to that seen with pure prostaglandin analogs.

β-Blocking Drugs

The topical β-blocking agents are one of the most commonly used antiglaucoma medications (**Table 110-4**). β-Blockers lower IOP by 20% to 30% with a minimum of local ocular adverse effects. Beta blockers have minimal effects on nocturnal IOP. These are commonly one of the agents of first choice—along with prostaglandin analogs—in treating POAG if no contraindications exist.[1–4,10,33–35]

TABLE 110-4 Topical Drugs Used in the Treatment of Open-Angle Glaucoma

Drug	Pharmacologic Properties	Common Brand Names/Generic	Dose Form	Strength (%)	Usual Dose[a]	Mechanism of Action
β-Adrenergic Blocking Agents						
Betaxolol	Relative β_1 selective	Generic	Solution	0.5	One drop twice a day	All reduce aqueous production of ciliary body
		Betoptic-S	Suspension	0.25	One drop twice a day	
Carteolol	Nonselective, intrinsic sympathomimetic activity	Generic	Solution	1	One drop twice a day	
Levobunolol	Nonselective	Betagan/Generic	Solution	0.25, 0.5	One drop twice a day	
Metipranolol	Nonselective	OptiPranolol	Solution	0.3	One drop twice a day	
Timolol	Nonselective	Timoptic, Betimol, Istalol/Generic	Solution	0.25, 0.5	One drop every day—one to two times a day	
		Timoptic-XE/ Generic	Gelling solution	0.25, 0.5	One drop every day[a]	
Adrenergic Agonists						
α_2-Adrenergic Agonists						
Apraclonidine	Specific α_2-agonists	Iopidine	Solution	0.5, 1	One drop two to three times a day	Both reduce aqueous humor production; brimonidine known to also increase uveoscleral outflow; only brimonidine has primary indication
Brimonidine		Alphagan P 0.1/ Generic 0.2, 0.15	Solution	0.2, 0.15, 0.1	One drop two to three times a day	
Cholinergic Agonists Direct Acting						
Carbachol	Direct and indirect acting	Carboptic, Isopto Carbachol	Solution	1.5, 3	One drop two to three times a day[a]	All increase aqueous humor outflow through trabecular meshwork
Pilocarpine	Direct acting	Isopto Carpine, Pilocar/Generic	Solution	1, 2, 4	One drop two to three times a day[a]	
					One drop four times a day	
Cholinesterase Inhibitors						
Echothiophate	Indirect acting cholinesterase inhibitor	Phospholine Iodide	Solution	0.125	Once or twice a day	
Carbonic Anhydrase Inhibitors						
Topical						
Brinzolamide	Carbonic anhydrase type II inhibition	Azopt	Suspension	1	Two to three times a day	All reduce aqueous humor production of ciliary body
Dorzolamide		Trusopt/Generic	Solution	2	Two to three times a day	
Systemic						
Acetazolamide		Generic	Tablet	125 mg, 250 mg	125–250 mg two to four times a day	
			Injection	500 mg/vial	250-500 mg	
		Diamox Sequels	Capsule	500 mg	500 mg twice a day	
Methazolamide		Generic	Tablet	25 mg, 50 mg	25–50 mg two to three times a day	
Prostaglandin Analogs						
Latanoprost	Prostanoid agonist	Xalatan/Generic	Solution	0.005	One drop every night	Increases aqueous uveoscleral outflow and to a lesser extent trabecular outflow
Latanoprostene Bunod	Prostanoid agonist	Vyzulta	Solution	0.024	One drop every night	
Bimatoprost	Prostamide agonist	Lumigan 0.01/ Generic 0.03	Solution	0.01, 0.03	One drop every night	

Travoprost	Prostanoid agonist	Travatan Z / GenericTravoprost	Solution	0.004	One drop every night
Tafluprost	Prostanoid agonist	Zioptan	Preservative free solution	0.0015	One drop every night
Rho Kinase Inhibitors					
Netarsudil	Rho Kinase Inhibitor	Rhopressa	Solution	0.02	One drop every night
Combinations					
Timolol–dorzolamide		Cosopt Generic	Solution	Timolol 0.5/ Dorzolamide 2	One drop twice daily
Timolol–brimonidine		Combigan	Solution	Timolol 0.5/ Brimonidine 0.2	One drop twice daily
Brinzolamide–brimonidine		Simbrinza	Suspension	Brinzolamide 1/ Brimonidine 0.2	One drop three times daily
Netarsudil-latanoprost		Rocklatan	Solution	Netarsudil 0.02/ Latanoprost 0.005	One drop every night

[a]Use of nasolacrimal occlusion will increase the number of patients successfully treated with longer dosage intervals.

The β-blocking agents produce ocular hypotensive effects by decreasing the production of aqueous humor by the ciliary body without producing substantial effects on aqueous humor outflow facility. The mechanism by which β-blockers decrease aqueous humor inflow remains controversial, but it is most frequently attributed to β_2-adrenergic receptor blockade in the ciliary body.

Five ophthalmic β-blockers are presently available: timolol, levobunolol, metipranolol, carteolol, and betaxolol. Timolol, levobunolol, and metipranolol are nonspecific β-blocking agents, whereas betaxolol is a relatively β_1-selective agent. Carteolol is a nonspecific blocker with intrinsic sympathomimetic activity. Despite differences in potency, selectivity, lipophilicity, and intrinsic sympathomimetic activity, the five agents reduce IOP to a similar degree, although betaxolol has been reported to produce somewhat less lowering of IOP than timolol and levobunolol. Levobunolol, which possesses alpha-adrenergic effects, may be more effective than timolol and betaxolol in reducing postcataract surgery IOP increases and may be more effective in controlling IOP than other agents when given as aqueous solutions on a once-daily schedule (up to 70% of patients). Timolol in the form of a gel-forming solution (Timoptic-XE) provides equivalent IOP control with once-daily administration when compared with the same concentration of the aqueous solution administered twice daily.

The choice of a specific β-blocking agent generally is based on differences in adverse effect potential, individual patient response, and cost. Treatment with topical β-blockers may result in tachyphylaxis (short-term escape and long-term drift) in 20% to 25% of patients. The mean IOP reduction from baseline may be smaller for patients receiving topical β-blockers with concurrent systemic β-blockers.[33–35]

Local adverse effects with β-blockers usually are tolerable, although stinging on application occurs commonly, particularly with betaxolol solution (less with betaxolol suspension) and metipranolol. Other local effects include dry eyes, corneal anesthesia, blepharitis, blurred vision, and, rarely, conjunctivitis, uveitis, and keratitis. Some local reactions may be a result of preservatives used in the commercially available products. Switching from one agent to another or switching the type of formulation may improve tolerance in patients experiencing local adverse effects.

Systemic effects are the most important adverse effects of β-blockers. Drug absorbed systematically may produce decreased heart rate, reduced blood pressure, negative inotropic effects, conduction defects, bronchospasm, CNS effects, and alteration of serum lipids and may block the symptoms of hypoglycemia. The β_1-specific agents' betaxolol and possibly carteolol (as a consequence of intrinsic sympathomimetic activity) are less likely to produce the systemic adverse effects caused by β-adrenergic blockade, such as the cardiac effects and bronchospasm, but a real risk still exists. The use of timolol as a gel-forming liquid or betaxolol as a suspension allows for administration of fewer drugs per day and, therefore, reduces the chance for systemic adverse effects compared with the aqueous solutions.

Because of their systemic adverse effects, all ophthalmic β-blockers should be used with caution for patients with pulmonary diseases, sinus bradycardia, second- or third-degree heart block, congestive heart failure, atherosclerosis, diabetes, and myasthenia gravis, as well as for patients receiving oral β-blocker therapy. Use of the nasolacrimal occlusion (ELC; see Patient Education below for description) technique during administration reduces the risk or severity of systemic adverse effects, as well as optimizes response. Overall, β-adrenergic blocking agents are well tolerated by most patients, and most potential problems can be avoided by appropriate patient evaluation, drug choice, and monitoring of drug therapy. For patients failing or having an inadequate response to single-drug therapy with a β-blocking agent, the addition of a topical CAI, prostaglandin analog, or the α_2-adrenergic receptor agonist brimonidine usually will result in additional IOP reduction.[1–5,10,33–35]

α_2-Adrenergic Agonists

Brimonidine and the less lipid-soluble and less receptor-selective apraclonidine are α_2-adrenergic agonists structurally similar to clonidine. Apraclonidine is indicated and brimonidine is effective for prevention or control of postoperative or postlaser treatment increases in IOP. Brimonidine has a primary indication in open-angle glaucoma and is considered a second-line agent (often after a prostaglandin or beta blocker) or adjunctive agent. Apraclonidine is generally used only in short term after ocular surgery due to high incidence of loss of control of IOP (tachyphylaxis) and a more severe and prevalent ocular allergy rate.

Alpha-2 agonists reduce IOP by decreasing the rate of aqueous humor production (some increase in uveoscleral outflow also occurs with brimonidine). The drugs reduce IOP by 18% to 27% at peak (2-5 hours) and by 10% at 8 to 12 hours. Comparative trials demonstrate a reduction in IOP similar to that obtained with 0.5% timolol. Use of brimonidine 0.2% every 8 to 12 hours appears to provide maximum IOP-lowering effects in long-term use. Use of ELC (see Patient Education below) may improve response and allow the longer dosing frequency (ie, every 12 hours). These agents have minimal effects on nocturnal IOP. Combinations of α_2-agonists with β-blockers, prostaglandin analogs, or CAIs produce additional IOP reduction.

An allergic-type reaction characterized by lid edema, eye discomfort, foreign-object sensation, itching, and hyperemia occurs in approximately 30% of patients with apraclonidine. Brimonidine produces this adverse effect in up to 8% of patients. This reaction commonly necessitates drug discontinuation. Systemic adverse effects with brimonidine include dizziness, fatigue, somnolence, dry mouth, and possibly a slight reduction in blood pressure and pulse. α_2-Agonists should be used with caution for patients with cardiovascular diseases, renal compromise, cerebrovascular disease, and diabetes, as well as in those taking antihypertensives and other cardiovascular drugs, monoamine oxidase inhibitors, and tricyclic antidepressants.

Brimonidine is also contraindicated in infants because of apneic spells and hypotensive reactions. In terms of overall efficacy and tolerability, brimonidine approximates that achieved with β-blockers.[1–4,10,33–35]

Brimonidine Purite 0.15% or 0.1% is a formulation of brimonidine in a lower concentration than the original product that contains a less corneal-toxic preservative than the commonly employed benzalkonium chloride. The newer formulations are as effective as the original because the more neutral pH of

brimonidine Purite (0.15% pH 7.2; 0.1% pH 7.7) allows for higher concentrations of brimonidine in the aqueous humor with a similar reduction in IOP and a reduced incidence of ocular allergy.

A randomized clinical trial of topical brimonidine 0.2% twice daily preserved visual field better than treatment with topical timolol maleate 0.5% in patients with OAG and statistically normal IOP.[25] The IOP-lowering efficacy was similar between the two medications, suggesting that this finding was consistent with a non-IOP-related mechanism, possibly a neuroprotective action. However, validation of a neuroprotective role for brimonidine requires further research to confirm these results.[25,26] The combination product timolol 0.5% and brimonidine 0.2% (Combigan) may provide additional IOP lowering than either agent alone.[42]

Carbonic Anhydrase Inhibitors

Topical Agents

CAIs reduce IOP by decreasing ciliary body aqueous humor secretion. CAIs appear to inhibit aqueous production by blocking active secretion of sodium and bicarbonate ions from the ciliary body to the aqueous humor.[1,2,10,33] The topical CAIs dorzolamide and brinzolamide are well tolerated and are considered second line (after prostaglandins and beta blockers) for monotherapy or adjunctive therapy of POAG and ocular hypertension. These drugs reduce IOP by 15% to 26%.

Topical CAIs generally are well tolerated. Local adverse effects include transient burning and stinging, ocular discomfort and transient blurred vision, tearing, and, rarely, conjunctivitis, lid reactions, and photophobia. A superficial punctate keratitis occurs in 10% to 15% of patients. Brinzolamide produces more blurry vision but is less stinging than dorzolamide. Systemic adverse effects are unusual despite the accumulation of drug in red blood cells. Because of their favorable adverse-effect profile, topical CAIs provide a useful alternative agent for monotherapy or adjunctive therapy for patients with inadequate response to or who are unable to use other agents. The drugs may add additional IOP reduction for patients using other single or multiple topical agents. The usual dose of a topical CAI is one drop every 8 to 12 hours. Administration every 12 hours produces somewhat less IOP reduction than administration every 8 hours. Use of ELC should optimize response to CAI given at any interval.[1–3,33] The combination product timolol 0.5% and dorzolamide 2% (Cosopt) is dosed twice daily and produces equivalent IOP lowering to each product dosed separately.

Both dorzolamide and timolol/dorzolamide (Cosopt) are now available as generic formulations. The combination product brimonidine 0.2% and brinzolamide 1% (Simbrinza) is available dosed three times daily.

Systemic CAI Agents

Systemic CAIs are indicated for patients failing to respond to or tolerate maximum topical therapy. Systemic and topical CAIs should not be used in combination because no data exist concerning improved IOP reduction, and the risk for systemic adverse effects is increased. Oral CAIs reduce aqueous humor inflow by 40% to 60% and IOP by 25% to 40%. The available systemic CAIs (see Table 110-4) produce equivalent IOP reduction but differ for potency, adverse effects, dosage forms, and duration of action. Despite their excellent effects on elevated IOP of any etiology, the systemic CAIs frequently produce intolerable adverse effects. As a result, CAIs are considered third-line agents in the treatment of POAG and often used for short-term administration to lower IOP.

On average, only 30% to 60% of patients are able to tolerate oral CAI therapy for prolonged periods. Intolerance to CAI therapy results most commonly from a symptom complex attributable to systemic acidosis and including malaise, fatigue, anorexia, nausea, weight loss, altered taste, depression, and decreased libido. Other adverse effects include renal calculi, increased uric acid, blood dyscrasias, diuresis, and myopia. Elderly patients do not tolerate CAIs as well as younger patients. The available CAIs produce the same spectrum of adverse effects; however, the drugs differ in the frequency and severity of the adverse effects listed.

CAIs should be used with some caution in patients with sulfa allergies (all CAIs, topical or systemic, contain sulfonamide moieties, although cross-sensitivity is thought to be very low), sickle cell disease, respiratory acidosis, pulmonary disorders, renal calculi, electrolyte imbalance, hepatic disease, renal disease, diabetes mellitus, or Addison's disease. Concurrent use of a CAI and a diuretic may rapidly produce hypokalemia. High-dose salicylate therapy may increase the acidosis produced by CAIs, whereas the acidosis produced by CAIs may increase the toxicity of salicylates.[1–4,10,33–35]

Rho Kinase Inhibitors

Netarsudil is the first approved agent in a new class of antiglaucoma medications, Rho kinase inhibitors.[10,28,42,43] Netarsudil reduces IOP by

increasing trabecular meshwork outflow. Once-daily (in the evening) administration of a 0.02% solution reduces both daytime and nighttime IOP. Efficacy appears to be similar to that of beta blockers. Netarsudil may be used in combination with other antiglaucoma agents. The most common local side effects are conjunctival hyperemia, conjunctival hemorrhage, and corneal verticillate. Systemic effects are rare.

A combination of netarsudil/latanoprost ophthalmic solution 0.02%/0.005% (Rocklatan) was approved in the United States.

Parasympathomimetic Agents

The parasympathomimetic (cholinergic) agents reduce IOP by increasing aqueous humor trabecular outflow. The increase in outflow is a thought to be a result of physically pulling open the trabecular meshwork secondary to ciliary muscle contraction, thereby reducing resistance to outflow. These agents may actually reduce uveoscleral outflow. Their use as primary or even adjunctive agents in the treatment of glaucoma has decreased significantly because of local ocular adverse effects and/or frequent dosing requirements.

Pilocarpine, the parasympathomimetic agent of choice in POAG, is available as an ophthalmic solution (see Table 110-4). Pilocarpine produces similar (20%-30%) reductions in IOP as those seen with β-blocking agents. Pilocarpine in POAG is initiated as 1% solution, one drop three to four times daily. The use of ELC improves response and reduces the need for an every 6-hour dosing frequency. The use of one drop of 2% pilocarpine every 6 to 12 hours and ELC provides optimal response in many patients. Both drug concentration and frequency may be increased if IOP reduction is inadequate. Patients with darkly pigmented eyes frequently require higher concentrations of pilocarpine than do patients with lightly pigmented eyes. Concentrations of pilocarpine above 4% rarely improve IOP control in patients.

Ocular adverse effects of pilocarpine include miosis, which decreases night vision and vision in patients with central cataracts. Visual field constriction may be seen secondary to miosis and should be considered when evaluating visual field changes in a glaucoma patient. Pilocarpine ciliary muscle contraction produces accommodative spasm, particularly in young patients still able to accommodate (prepresbyopic). Pilocarpine may also produce frontal headache, brow ache, periorbital pain, eyelid twitching, and conjunctival irritation or injection early in therapy, which tends to decrease in severity over 3 to 5 weeks of continued therapy.

Cholinergics produce a breakdown of the blood–aqueous humor barrier and may result in a worsening of an ocular inflammatory reaction or condition. Systemic cholinergic adverse effects of pilocarpine such as diaphoresis, nausea, vomiting, diarrhea, cramping, urinary frequency, bronchospasm, and heart block can be seen. Other adverse effects associated with direct-acting miotics include retinal tears or detachment, allergic reaction, permanent miosis, cataracts, precipitation of CAG, and, rarely, miotic cysts of the pupillary margin.

Carbachol is a potent direct-acting miotic agent; its duration of action is longer than that of pilocarpine (8-10 hours) because of resistance to hydrolysis by cholinesterases. This drug also may act as a weak inhibitor of cholinesterase. Patients with an inadequate response to or intolerance of pilocarpine as a result of ocular irritation or allergy frequently do well on carbachol. The ocular and systemic adverse effects of carbachol are similar to but more frequent, constant, and severe than those of pilocarpine.[33] Clinical use of carbachol is limited.

Echothiophate is a cholinesterase inhibitor and is used in the treatment of POAG. It is a long-acting, relatively irreversible agent (limited commercial availability; see Table 110-4). This agent is a potent inhibitor of pseudocholinesterase, but also inhibits true cholinesterase. Because of the serious ocular and systemic toxic effects of echothiophate, it is reserved primarily for patients who are either not responding to or are intolerant of other therapy. Because of its cataractogenic properties, most ophthalmologists use this agent only for patients without lenses (aphakia) and for patients with artificial lenses (pseudophakia). The ocular and periocular parasympathomimetic adverse effects are more common and more severe than with pilocarpine or carbachol.

In addition to the parasympathomimetic effects, echothiophate may produce severe fibrinous iritis (particularly with the irreversible inhibitors), synechiae, iris cysts, conjunctival thickening, occlusion of the nasolacrimal ducts, and cataracts. The inhibition of systemic pseudocholinesterase by echothiophate decreases the rate of succinylcholine hydrolysis, resulting in prolonged muscle paralysis. Echothiophate should be discontinued at least 2 weeks before procedures in which succinylcholine is used.

The role of echothiophate in glaucoma is limited by its frequency and potential toxicity. For phakic patients, cholinesterase inhibitors should be administered only if intolerance or failure results with other antiglaucoma medications. Echothiophate has been shown to provide additional IOP-lowering effects when used with β-blockers, CAIs, and sympathomimetic (adrenergic) agents. Only one concentration of this agent (0.125%) is currently available. A once-daily administration frequency should be used for most patients unless very

high IOP is present.

Use of ELC likely improves response, reduces systemic adverse effects, and should be performed by all patients administering echothiophate. The drug should be used with caution for patients with asthma, retinal detachments, narrow angles, bradycardia, hypotension, heart failure, Down's syndrome, epilepsy, Parkinsonism, peptic ulcer, and ocular inflammation, as well as in those receiving cholinesterase inhibitor therapy for myasthenia gravis or exposure to carbamate or organophosphate insecticides and pesticides.

Future Drug Therapies

It is hoped that new agents, improved formulations, and novel approaches to the reduction of IOP and other methods of prevention of glaucomatous visual field loss will provide more effective and better-tolerated therapies. Most areas of glaucoma development continue to focus on drugs that reduce IOP by either reducing aqueous production or increasing outflow. Classes of drugs in development include adenosine-1 receptor agonists, cannabinoids, serotonin agonists, dopamine agonists, nitric oxide/carbon dioxide modulators, and hydroxysteroid dehydrogenase inhibitors. Agents with dual ROCK inhibition and norepinephrine transport inhibition are in later clinical phase trials. Agents that are neuroprotective and act through mechanisms other than IOP reduction are also in development and are likely to be part of glaucoma therapy in the future.[8,9,26,28,43]

Development of new long-acting topical formulations (such as nanoparticulates), implants, ocular inserts, and drug-eluting punctal plugs may provide improved patient convenience and medication adherence in the future.

EVALUATION OF THERAPEUTIC OUTCOMES

The ultimate goal of drug therapy for the patient with glaucoma is to preserve visual function through reduction of IOP to a level at which no further optic nerve damage occurs. Because of the poor relationship between IOP and optic nerve damage, no specific target IOP exists. Indeed, drugs used to treat glaucoma may act in part to halt visual field loss through mechanisms separate from or in addition to IOP reduction, such as improvements in retinal or choroidal blood flow. Often a 25% to 30% reduction is desired, but greater reductions (40%-50%) may be desired for patients with initially high IOPs. For patients with glaucoma, an IOP of less than 21 mm Hg (2.8 kPa) generally is

desired, with progressively lower target pressures needed for greater levels of glaucomatous damage. Even lower IOPs (possibly even below 10 mm Hg [1.3 kPa]) are required for patients with very advanced disease, those showing continued damage at higher IOPs, and those with normal-tension glaucoma and pretreatment pressures in the low-to-middle teens. The IOP considered acceptable for a patient is often a balance of desired IOP and acceptable treatment-related toxicity and of patient quality of life.

PATIENT EDUCATION

7 An important consideration for patients failing to respond to drug therapy is adherence. Poor adherence or nonadherence occurs in 25% to 60% of glaucoma patients.

A large percentage of patients also fail to use topical ophthalmic drugs correctly. Patients should be taught the following procedure:

1. Wash and dry the hands; shake the bottle if it contains a suspension.
2. With a forefinger, pull down the outer portion of the lower eyelid to form a “pocket” to receive the drop.
3. Grasp the dropper bottle between the thumb and fingers with the hand braced against the cheek or nose and the head held upward.
4. Place the dropper over the eye while looking at the tip of the bottle; then look up and place a single drop in the eye.
5. The lids should be closed (but not squeezed or rubbed) for 5 minutes after instillation. This increases the ocular availability of the drug and reduces systemic absorption.
6. Recap bottle and store as instructed.

Note that many patients are physically unable to administer their own eye drops without assistance. ELC also should be used to improve ocular bioavailability and reduce systemic absorption.[1–4] The patient induces ELC for 5 minutes by gently closing the eyes. ELC decreases nasolacrimal drainage of drug, thereby decreasing the amount of drug available for systemic absorption by the nasopharyngeal mucosa. The use of ELC may improve drug response significantly, reduce adverse effects, and allow less-frequent dosing intervals and the use of lower drug concentrations.

Use of more than one drop per dose increases costs, does not improve response significantly, and may increase adverse effects. When two drugs are to be administered, instillations should be separated by at least 5 minutes

(preferably 10 minutes) to prevent the drug administered first from being washed out. The patient should be taught not to touch the dropper bottle tip with eye, hands, or any surface.

Adherence to glaucoma therapy usually is inadequate, and it always should be considered as a possible cause of drug therapy failure. Assessment of adherence by healthcare providers generally is poor; so all patients should be encouraged continually to administer prescribed therapy diligently as instructed. To improve adherence, the patient, family, and care providers should be fully informed of the expectations of therapy and the need to continue therapy despite a lack of symptoms. Possible adverse effects of the medication and ways to reduce them should be discussed. Adherence will be improved by good communication, simplified and well-tolerated dosing regimens, reminder devices, education, close monitoring, and individualized care planning.[1–4,44]

Postclass Engaged Learning Activity

Conduct a literature search and identify a primary research manuscript that has been published in the past 12 months regarding the treatment of glaucoma with new topical agents or by new routes of administration. If the manuscript is about a topical medication that is discussed in the book chapter, write a brief summary about the study methods, the major findings, and how this new medication may be implemented in current practice. If the manuscript is regarding a new medication that is either not described in the chapter or a new route of administration, write a brief summary about the medication's mechanisms of action, how it is administered, and one potential advantage or disadvantage of this new medication compared to the current standard of care. This activity is intended to build your literature evaluation skills and ability to critically appraise research manuscripts.

ABBREVIATIONS

CAG	closed-angle glaucoma
CAI	carbonic anhydrase inhibitor
IOP	intraocular pressure
ELC	Eyelid closure
OAG	open-angle glaucoma

OHT	ocular hypertension
OHTS	Ocular Hypertensive Treatment Study
POAG	primary open-angle glaucoma

REFERENCES

1. Jonas JB, Aung T, Bourne RR, Bron AM, Ritch R. Glaucoma. *Lancet*. 2017:390:2183–2193.
2. Weinreb RN, Aung T, Madeiros FA. The pathophysiology and treatment of glaucoma. *JAMA*. 2014;311:1901–1911.
3. Kwon YH, Fingert JH, Kuehn MH, Alward WLM. Primary open-angle glaucoma. *N Engl J Med*. 2009;360:1113–1124.
4. American Academy of Ophthalmology Glaucoma Panel. *Preferred Practice Pattern Guidelines. Primary Open Angle Glaucoma*. San Francisco, CA: American Academy of Ophthalmology; 2015. www.aao.org/ppp.
5. American Academy of Ophthalmology Glaucoma Panel. *Preferred Practice Pattern Guidelines. Primary Angle Closure*. San Francisco, CA: American Academy of Ophthalmology; 2015. www.aao.org/ppp.
6. American Academy of Ophthalmology Glaucoma Panel. *Preferred Practice Pattern Guidelines. Primary Open Angle Glaucoma Suspect*. San Francisco, CA: American Academy of Ophthalmology; 2015. www.aao.org/ppp.
7. Goel M, Picciani G, Lee RK, Bhattacharya SK. Aqueous humor dynamics: A review. *The Open Ophthalmology Journal*. 2010;4:52–59.
8. Bucolo C, Salomone S, Drago F, Reibaldi M, Longo A, Uva MG. Pharmacological management of ocular hypertension: Current approaches and future perspective. *Curr Opin Pharmacol*. 2013;13:50–55.
9. Kolko M. Present and new treatment strategies in the management of glaucoma. *The Open Ophthalmol J*. 2015:9(suppl 1:M5):89–100.
10. Schmidl D, Schmetterer L, Gashofer G, Pops-Cherecheanu A. Pharmacotherapy of glaucoma. *J Ocul Pharmcol Thera*. 2015;31:63–77.
12. Mansouri K, Medeiros FA, Tafreshi A, Weinreb RN. Continuous 24-hour monitoring of intraocular pressure patterns with a contact lens sensor: Safety, tolerability, and reproducibility in patients with glaucoma. *Arch Ophthalmol*. 2012;13:1–6. doi:10.1001/archophthalmol.2012.2280.

13. Wax MB, Camras CB, Fiscella RG, et al. Emerging perspectives in glaucoma: Optimizing 24-hour control of intraocular pressure. *Am J Ophthalmol*. 2002;133:S1–S10.
14. Kass MA, Heuer DK, Higginbotham EJ, et al. The ocular hypertension treatment study: A randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002;120:701–713. discussion 829, 830.
15. Leske MC, Heijl A, Hussein M, et al. Factors for glaucoma progression and the effect of treatment: The early manifest glaucoma trial. *Arch Ophthalmol*. 2003;121:48–56.
16. Van Veldhuisen PC, Schwartz AL, Gaasterland DE, et al. The advanced glaucoma intervention study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. *Am J Ophthalmol*. 2000;130:429–440.
17. Collaborative Normal-Tension Glaucoma Study Group. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. *Am J Ophthalmol*. 1998;126:487–497.
18. Chauhan BC, Mikelberg FS, Balaszi AG, et al. Canadian glaucoma study 2. Risk factors for the progression of open-angle glaucoma. *Arch Ophthalmol*. 2008;126:1030–1036.
19. Wiggs JL. Genetic etiologies of glaucoma. *Arch Ophthalmol*. 2007;125:30–37.
20. Brandt JD, Beiser JA, Gordon MO, et al. Ocular Hypertension Treatment Study (OHTS) Group. Central corneal thickness and measured IOP response to topical ocular hypotensive medication in the Ocular Hypertension Treatment Study. *Am J Ophthalmol*. 2004;138:717–722.
21. Gordon MO, Torri V, Miglior S, et al. Ocular Hypertension Treatment Study Group; European Glaucoma Prevention Study Group;. Validated prediction model for the development of primary open-angle glaucoma in individuals with ocular hypertension. *Ophthalmology*. 2007;114:10–19.
22. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol*. 2006;90:262–267.
23. Brandt JD, Gordon MO, Beiser JA, et al. Ocular Hypertension Treatment Study Group. Changes in central corneal thickness over time: The ocular hypertension treatment study. *Ophthalmology*. 2008;115:1550–1556.

24. Miller MA, Fingert JF, Bettis DI. Genetics and genetic testing for glaucoma. *Curr Opin Ophthalmol*. 2017, 28:133–138.
25. Krupin T, Liebmann JM, Greenfield DS, et al. A randomized trial of brimonidine versus timolol in preserving visual function: Results from the Low-pressure Glaucoma Treatment Study. *Am J Ophthalmol*. 2011;151:671–681.
26. Nucci C, Russo R, Martucci A, et al. New strategies for neuroprotection in glaucoma, a disease that affects the central nervous system. *Eur J Pharmacol*. 2016;787:119–126.
27. Li T, Lindsley K, Rouse B, et al. Comparative effectiveness of first line medications for primary open-angle glaucoma. A systematic review and network meta-analysis. *Ophthalmology*. 2016;123:129–140.
28. Dikopf MS, Vajaranant TS, Edward DP. Topical treatment of glaucoma: Established and emerging pharmacology. *Exp Opin Pharmacol*. 2017;18:885–898.
29. Garway-Heath DF, Crabb DP, Bunce C, et al. Latanoprost for open angle glaucoma (UKGTS): A randomized, multicenter, placebo controlled trial. *Lancet*. 2015;385:1295–1304.
30. Wright C, Tawfik MA, Waisbourd M, Katz LJ. Primary angle-closure glaucoma: An update. *Acta Ophthalmologica*. 2016;94(3):217–225.
31. Tripathi RC, Tripathi BJ, Haggerty C. Drug-induced glaucomas. *Drug Saf*. 2003;26:749–767.
32. Zheng W, Dryja TP, Wei Z, et al. Systemic medication associations with presumed advanced or uncontrolled primary open-angle glaucoma. *Ophthalmology*. 2018;125(7):984–993.
33. Murphy RM, Bakir B, O'Brien C, et al. Drug-induced bilateral secondary angle-closure glaucoma: A literature synthesis. *J Glaucoma*. 2016;25:99–105.
34. Kanner E, Tsai JC. Glaucoma medications. Use and safety in the elderly population. *Drugs Aging*. 2006;23:321–332.
35. Han JA, Frishman WH, Sun SW, et al. Cardiovascular and respiratory considerations with pharmacotherapy of glaucoma and ocular hypertension. *Cardiol Rev*. 2008;16:95–108.
36. Katz LJ, Steinmann WC, Kabir A, et al. Selective laser trabeculoplasty versus medical therapy as initial treatment of glaucoma: A prospective, randomized trial. *J Glaucoma*. 2012;21:460–468.

37. Law SK. Switching within glaucoma medication class. *Curr Opin Ophthalmol*. 2009;111:1439–1448.
38. Habash AA, Aljasim LA, Owaidhah O, Edward DP. A review of the efficacy of mitomycin C in glaucoma filtration surgery. *Clin Ophthalmol*. 2015;9:1945–1951.
39. Singh K, Mehta K, Shaikh NM, et al. Trabeculectomy with intraoperative mitomycin C versus 5-fluorouracil. *Ophthalmology*. 2000;107:2305–2309.
40. van der Valk R, Webers CA, Schouten JSAG, et al. Intraocular pressure-lowering effects of all commonly used glaucoma drugs. A meta-analysis of randomized clinical trials. *Ophthalmology*. 2005;112:1177–1185.
41. Hoy SM. Latanoprosene bunod. Ophthalmic solution 0.024%: A review in open angle glaucoma and ocular hypertension. *Drugs*. 2018;78:773–780.
42. Hoy SM. Netarsudil Ophthalmic Solution 0.02%: First global approval. *Drugs*. 2018;78:389–396.
43. Schehlein EM, Novack GD, Robin AL. New classes of glaucoma medications. *Curr Opin Ophthalmol*. 2017;28:161–168.
44. Gray TA, Orton LC, Henson D, et al. Interventions for improving adherence to ocular hypotensive therapy. *Cochrane Database Syst Rev*. 2009;2:CD006132. doi:10.1002/14651858.CD006132.pub2.
45. Anwar Z, Wellik SR, Galor A. Glaucoma therapy and ocular surface disease: Current literature and recommendations. *Curr Opin Ophthalmol*. 2013;24:136–143.
46. Pillunat LE, Erb C, Junemann AGM, Kimmich F. Micro-invasive glaucoma surgery (MIGS): A review of surgical procedures using stents. *Clin Ophthalmol*. 2017;11:1583–1600.

111

Age-Related Macular Degeneration

Alisa K. Escano and Casey S. Washington

KEY CONCEPTS

1. The hallmark sign of age-related macular degeneration (AMD) is the development of drusen in the macula. Drusen are yellow deposits of lipids between the retinal pigment epithelial and Bruch's membrane that can develop with age.
2. AMD is identified as the leading cause of blindness in the industrialized world and a top cause of blindness worldwide.
3. The two most important risk factors for AMD are age and smoking.
4. The goal of treatment is to slow progression of AMD and prevent severe visual impairment or blindness.
5. Smoking cessation is the main modifiable risk factor that will slow progression of AMD. Pharmacists and other health professionals can play a vital role in helping people stop smoking.
6. Antioxidant vitamins and minerals may prevent cellular damage in the retina caused by the formation of free radicals through light absorption. Use may benefit patients the most with medium or large sized drusen and/or geographic atrophy in at least one eye.
7. For most patients with wet AMD and choroidal neovascularization, the use of intravitreal vascular endothelial growth factor (VEGF) inhibitors and other inhibitor-like drugs have led to improvement in visual acuity.
8. The appeal of the ranibizumab treat and extend (TREX) approach is the reduction of office visits and medication cost.
9. VEGF inhibitors and antioxidant vitamins and minerals are the only pharmacologic therapies available that have been shown to improve and stabilize visual acuity in patients with intermediate to advanced AMD.

Preclass Engaged Learning Activity

Watch the three age-related macular degeneration videos on the National Eye Institute. These short videos totaling 3 minutes provide a brief overview to age-related macular degeneration and animation of the pathophysiology. These videos are useful to enhance student understanding regarding the COLLECT and ASSESS steps in the patient care process.

INTRODUCTION

Age-related macular degeneration (AMD) is a neurodegenerative disease that produces irreversible loss of central vision due to damage to the macula, the center region of the retina. AMD is a leading cause of blindness due to age-related changes in the macula and, specifically, the photoreceptor–retinal pigment epithelial (RPE) complex.[2]

A general familiarity with the anatomy of the eye including the macula and photoreceptor–RPE complex will aid in understanding the disease and treatment mechanisms (**Figs. 111-1** and **111-2**).[3,4] The macula in the middle of the retina is responsible for all central vision, a significant part of color vision, and the fine detail images. The photoreceptor cells of the macula identify light and then transfer the information to the brain to produce an image. Central vision is needed to read, write, drive, watch television, and other typical activities of daily living. AMD reduces central vision, visual acuity, and blue-yellow color sensitivity leading to significant disability (**Fig. 111-3**).[5]

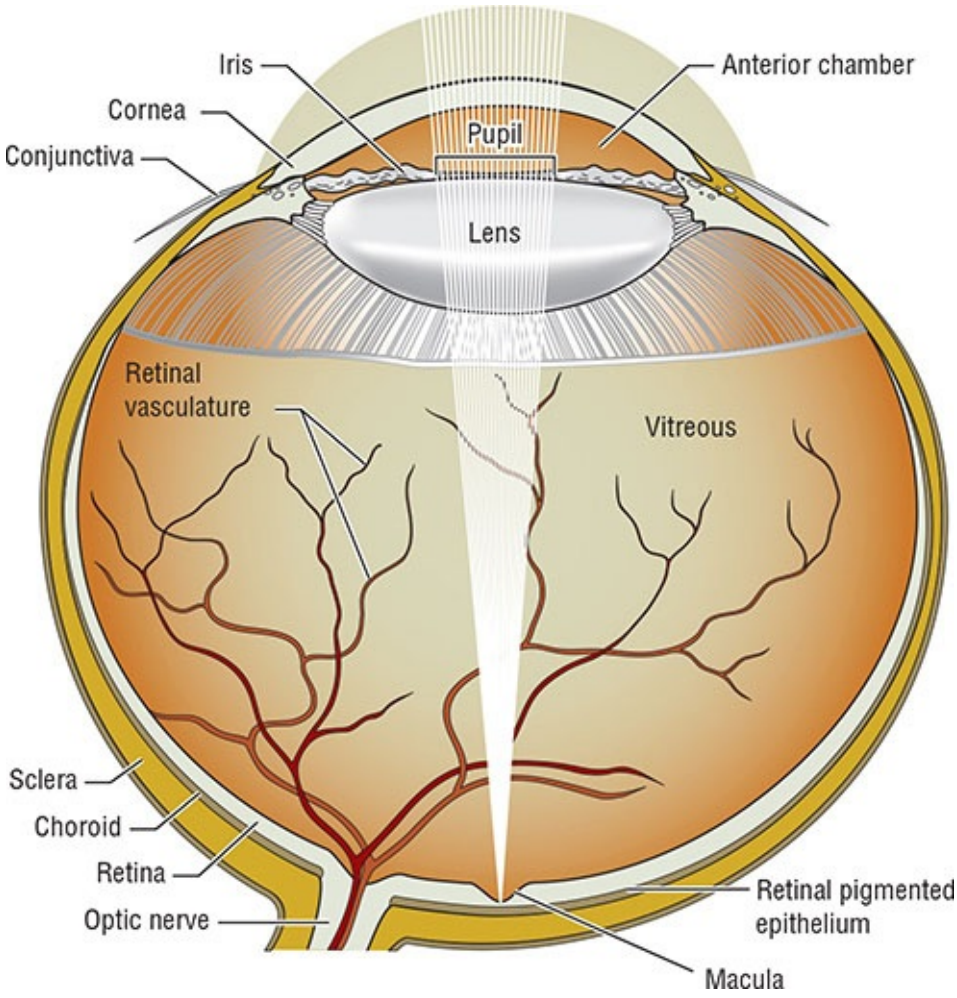


FIGURE 111-1 Anatomy of the eye. The macula, in the center of the retina, is responsible for central vision, color vision, and fine details.

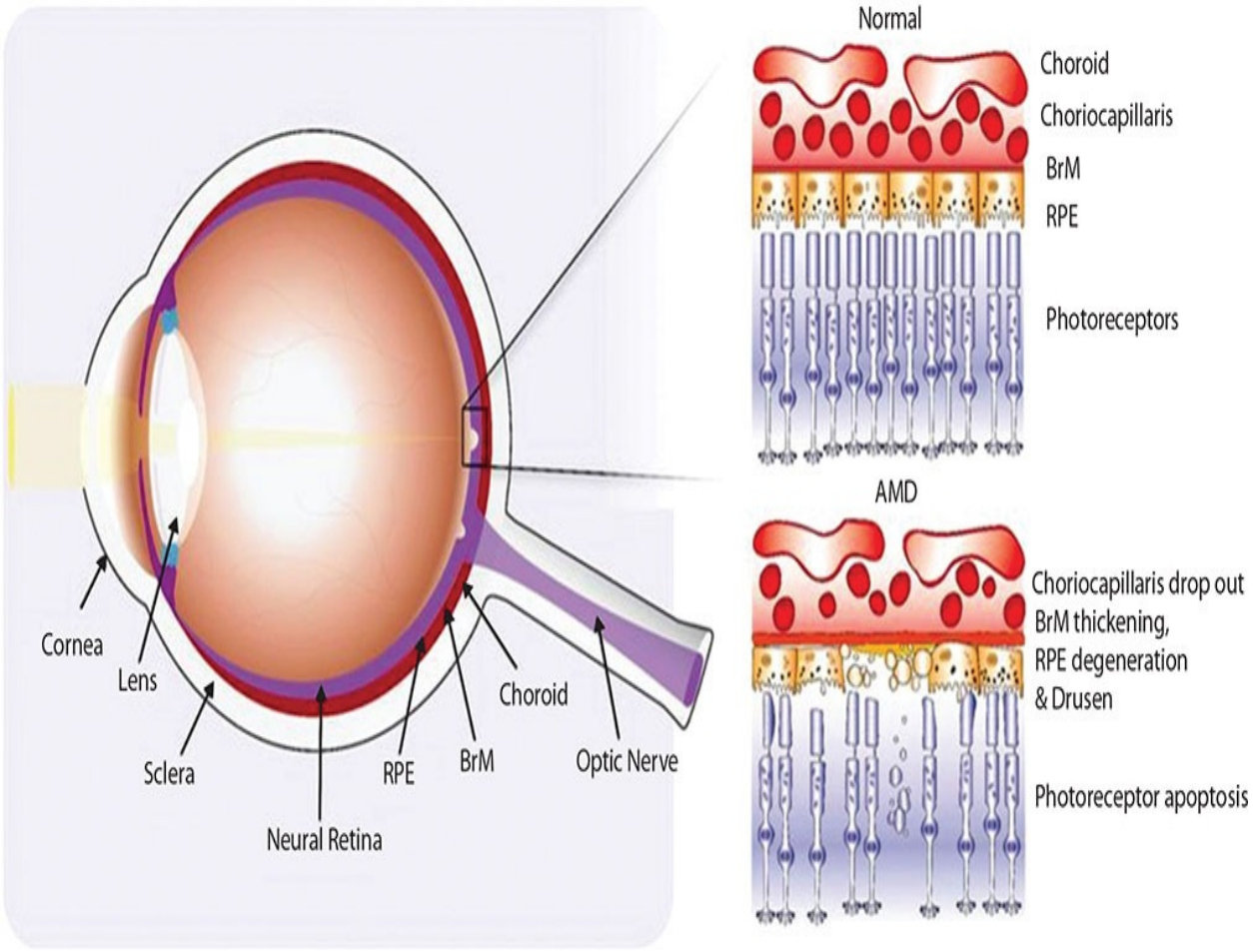
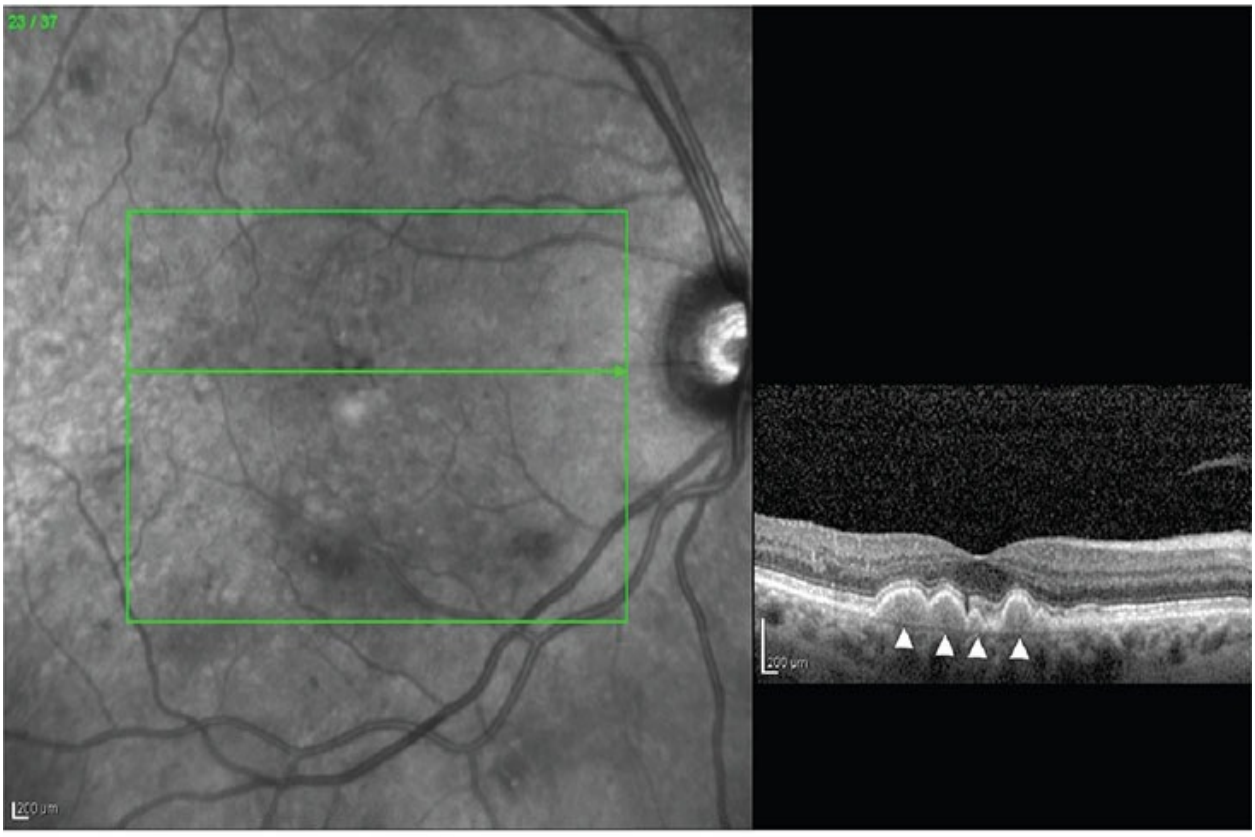


FIGURE 111-2 Detailed anatomy of the photoreceptor–retinal pigment epithelial (RPE) complex. The photoreceptor–RPE complex in the normal state and in a state with AMD that shows the breakdown of the RPE with drusen formation and apoptosis of photoreceptors contributing to the loss of vision with AMD. (*Reproduced, with permission, from Chichagova V, Hallam D, Collin J, Zerti D, Dorgau B, Felemban M, Lako M, Steel DH. Cellular regeneration strategies for macular degeneration: past, present and future. Eye (Lond). 2018 May;32(5):946-971.*)

FIGURE 111-3 Effects of the loss of central vision with AMD. (*From National Eye Institute, National Institutes of Health, Washington, DC.*)

1 The hallmark sign of AMD is the development of drusen in the macula. Drusen are yellow deposits of lipids between the RPE and Bruch's membrane that can develop with age (**Fig. 111-4**). Bruch's membrane is an extracellular layer separating the RPE from choroidal capillaries in the eye. Small drusen without additional abnormalities have a lower risk of progression to severe disease than large drusen.

A



B

FIGURE 111-4 Age-related macular degeneration (AMD). (*A*) Discrete **(small arrow)** and large confluent **(large arrow)** drusen. (*B*) Optical coherence tomography scan of large confluent drusen **(arrowheads)**. (*Reproduced, with permission, from Riordan-Eva P, Augsburger JJ, eds. Vaughan & Asbury's General Ophthalmology. 19th ed. New York: McGraw-Hill; 2018.*)

Two distinct types of AMD have been identified: geographic atrophy (GA) "dry" and choroidal neovascularization (CNV), exudative "wet" (**Fig. 111-5**). Disease progression is unpredictable as visual disturbances do not correlate with drusen formation. Patients can monitor visual changes with an Amsler grid by using one eye at a time and looking for any distortions in the grid (**Fig. 111-6**).

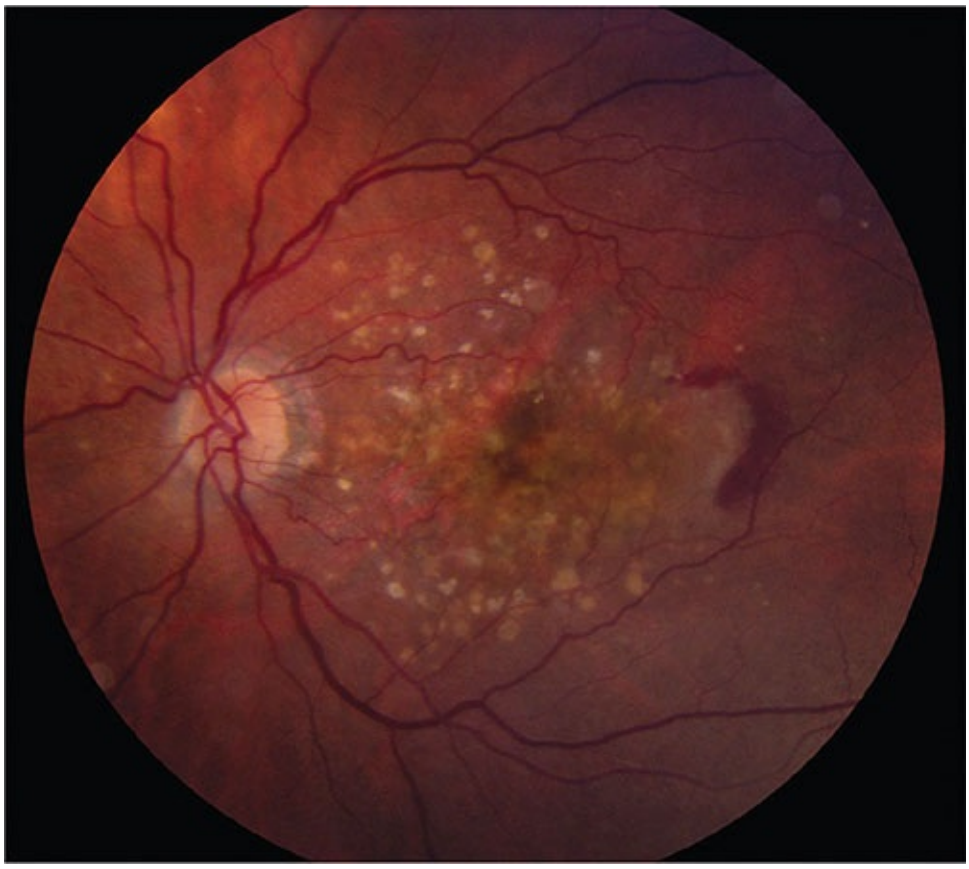


FIGURE 111-5 Age-related macular degeneration consisting of scattered yellow drusen in the macula (dry form) and a crescent of fresh hemorrhage temporal to the fovea from a subretinal neovascular membrane (wet form). (*Reproduced, with permission, from Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 20th ed. New York, NY: McGraw-Hill; 2019.*)

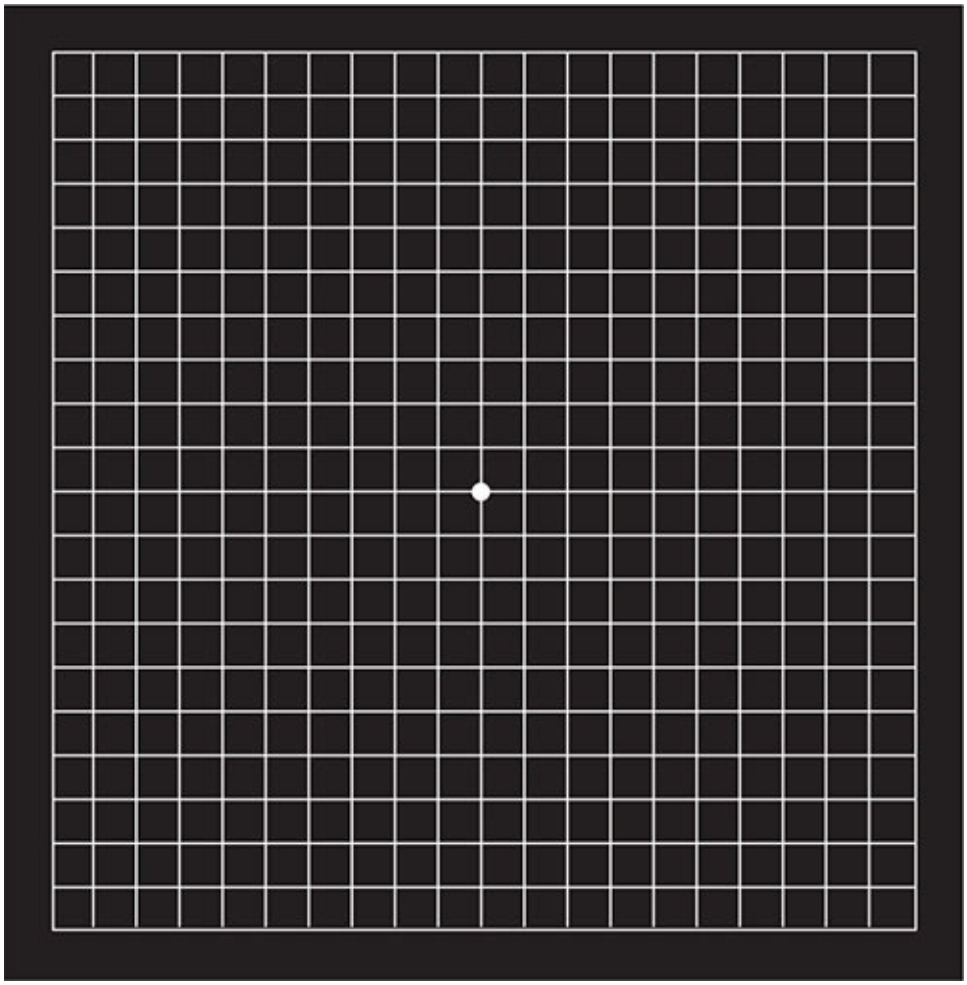


FIGURE 111-6 Amsler grid for monitoring vision by tracking any distortions in the grid lines while focusing on the center dot. (*Reproduced, with permission, from Riordan-Eva P, Augsburger JJ, eds. Vaughan & Asbury's General Ophthalmology. 19th ed. New York: McGraw-Hill; 2018.*)

The American Academy of Ophthalmology defines AMD by the presence of one of the following criteria[1]:

- Presence of at least intermediate-size drusen (63 µm or larger in diameter)
- RPE abnormalities (hypopigmentation or hyperpigmentation)
- Reticular pseudodrusen
- Presence of any of the following features: RPE GA, CNV, polypoidal choroidal vasculopathy, retinal angiomatous proliferation

EPIDEMIOLOGY

2 With longer life expectancy, the incidence of vision impairment from macular diseases increased 62% from 1990 to 2010.[6] AMD is identified as the leading cause of blindness in the industrialized world and a top cause of blindness worldwide, in addition to diabetic retinopathy, glaucoma, cataracts, and under-correction of refraction error.[7–9] Drusen development and AMD diagnosis can occur at any age, although usually after the age of 50. The prevalence of AMD is 8.69% for adults 45 to 85 years of age.[10] Rates of AMD increase nonlinearly with age affecting 6% to 10% of people aged 65 years or older and more than 20% to 25% of who have reached age 75 years.[11,12]

Dry AMD is the most common type diagnosed in 80% to 90% of patients and 10% to 20% may progress to wet AMD.[7,11] The more severe wet AMD is associated with progressive vision loss and makes up only 10% to 20% of AMD diagnoses yet is responsible for 90% of the vision loss of AMD.[8]

In the United States, 2.8 million individuals have advanced or intermediate forms of AMD, with expectations to reach 3 million by 2020 and continuing to increase.[10,11] Cases of early AMD in the United States totaled 9.1 million in 2010 with expectations to increase to 17.8 million by 2050.[10]

Risk Factors

3 The two most important risk factors for AMD are age and smoking. Additional risk factors for AMD include ethnicity and genetics, both of which are nonmodifiable. In addition to smoking, modifiable risk factors include hypertension, body-mass index (BMI), and cardiovascular disease (**Table 111-1**).[13]

TABLE 111-1 Risk Factors for AMD

Factor		Increased Risk	Protective
Age (years)	<55		✓
	55-75	✓	
	>75	✓	
Ethnicity	European	✓	
Race[a]	White	✓	
	Black		✓
Genetics	Y402H	✓	
	ARMS2/HtrA1	✓	
	LIPC	✓	
	rs3775291	✓	
Gender[b]	Female	✓	
Smoking	Active	✓	
	History	✓	
Diet	Omega-3 fatty acids		✓
	High fat	✓	
	Lutein		✓
	Fruit and Vegetables		✓
	Nitrates		✓
Physical activity			✓
Medications	Statins		✓

[a]Take into consideration race is a socially created categorization and not determinable by genetic testing.

[b]Gender nonbinary inclusive studies have not been performed; consult www.transhealth.ucsf.edu/guidelines.[41]

The risk of development of AMD increases exponentially with age, with risk at the age of 75 years 2 to 3 times that at 65 years. A 2014 worldwide meta-analysis found a higher prevalence of AMD in European compared to Asian, Hispanic, and African populations.[6,8] The Salisbury Eye Evaluation evaluated prevalence of AMD of white and black Americans and found higher prevalence of large drusen, focal hyperpigmentation, and GA in white participants, suggesting there may be a mechanism of protection against fundus abnormalities in the central zone for black participants.[9]

Genetics

Several genetic factors are associated with increasing risk, progression, and protection from AMD.[8] The complement factor H (CFH)–related gene on chromosome 1 binds to factor C3b and is involved in regulation of the innate immune system. This regulation is defective with a homozygous Y402H polymorphism of *CFH*, causing alteration at the C3b site leading to an up-regulation of inflammation, affecting vascular endothelial growth factor (VEGF) expression, and increasing the risk of AMD by 7.4-fold.[14]

Other genetic variants associated with increased risk of AMD include the ARMS2/HtrA serine peptidase 1 (*HtrA1*) genes, hepatic lipase (*LIPC*) gene, and the rs3775291 variant in the toll-like receptor 3 (*TLR3*) gene.[8,14] Despite publications suggesting genetic testing may be helpful, genetic tests are not recommended in patient care at this time because of inconclusive data.[15,16]

Smoking

Because it is a modifiable risk factor, smoking is important for health professionals to address; it is associated with a 32% increased risk of AMD.[17] Studies have consistently found an increased risk across different populations of early, wet, and dry AMD with current smoking, duration of smoking of more than 40 years, histories of smoking of 11 pack-years or more, and former smoking.[18,19]

Smoking cessation is a staple in the care plan for patients at risk for and with prior diagnosis of AMD due to the ability to slow progression. The Australian government added warnings to cigarette packs regarding the risk of blindness related to data from AMD.[20] In 2014, the United States Department of Health & Human Services published a report of the damage smoking can do to health; however, the warnings on cigarettes in the United States are opposed by the tobacco industry.[21,22]

Diet

Diets higher in saturated, transunsaturated, polyunsaturated, and monounsaturated fatty acid (FA) are associated with higher prevalence and progression of AMD compared to diets with lower intake of fat.[23] Interestingly, FA in nuts and fish were found to be protective. Omega-3 FA intake was found to decrease the risk of AMD by 22% and the risk was increased in participants

that had low-dietary omega-6 FA.[17]

Antioxidant intake has also proven important in AMD.[24] Lutein, zeaxanthin, zinc, and vitamins C and E had varying results when evaluating supplements and dietary intake. Combining types of antioxidants, through a varied diet, tends to have better results.[25–27] A recent population-based cohort study found that patients who followed a diet consisting of 200 g of vegetables per day, fruit twice daily, and fish twice a week had a significantly reduced risk of AMD.[25] Dietary nitrate intake of 142 g/day, from vegetable and nonvegetable sources, was also found to reduce incidence of early AMD.[28]

Additional Risk Factors

AMD can loosely be linked to atherosclerosis and cardiovascular disease.[29,30] Risk factors of these disease states overlap, including hypertension, which is associated with a higher incidence of wet AMD. Obesity and inactivity are also associated with increased risk of early and late AMD.[31] 3-Hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are associated with 17% reduction in risk of early AMD and a protective effect against wet AMD; the drugs show no benefit or harm with respect to risk of dry AMD.[32] Aspirin was thought to increase the chance of developing wet AMD, but results have been conflicting and the minimal increase in the risk of wet AMD is less than the benefit in using aspirin for cardiovascular disease in older adults.[8,33,34]

Ultraviolet radiation exposure, especially in people with light-colored eyes, has also shown an increase in the risk of AMD.[35,36] Thyroid dysfunction and thyroxine use have both shown an association with increased AMD diagnosis.[37] Other medications have also been associated with AMD including nitroglycerin, beta-blockers, chloroquine derivatives, and phenothiazines.[38] Environmental safety is a prudent component to evaluate due to unsafe chemicals and the need for a focus on sustainability in healthcare.[39] Pesticide exposure was correlated to AMD diagnosis in the Agriculture Health Study reporting that exposure to insecticides and herbicides are a modifiable risk factor for AMD.[40]

ETIOLOGY

AMD is a neurodegenerative disease with ocular inflammation and autoimmunity in combination with additional causes of RPE dysfunction and atrophy including the effects of aging, external environmental factors, and

genetic factors.[42,43] Abnormal processing of complement, lipid, angiogenic, inflammatory, and extracellular matrix pathways contribute to the detrimental changes, but the pathogenesis of AMD is not fully understood. Oxidative stress and complement activation can increase RPE secretion of VEGF-A, which is associated with angiogenesis.

Wet AMD has CNV, which are new blood vessels created in the choroidal region of the eye. There are different types of wet AMD determined by how the CNV occurs and how it affects the RPE.[44] In type 1, formerly referred to as "occult," CNV is categorized by lesions with leakage of blood or plasma proteins from immature choroidal blood vessels that remain below the RPE.[42] The extra volume may cause pigment epithelial detachment. Type 1 can progress to type 2. In type 2, often referred to as classic, lesions push through and are visible above the RPE. Type 3 has retinal angiomatous proliferation meaning the choroidal and retinal vessels link together. Retinal macrophages are increased and are a hallmark sign of CNV.[45]

Dry AMD has been labeled a metabolic storage disease, due to the excessive buildup of lipofuscin, a nondegradable debris that accumulates in the RPE with age or other toxic accumulations between the RPE and Bruch's membrane.[46] The deposits on the semipermeable Bruch's membrane interfere with efflux, increasing stress and inflammation on the RPE (Fig. 111-3). This stress, in addition to cigarette smoking and aging, increases lipofuscin that interferes with lipid metabolism. The extra volume shifts the original layers of the RPE complex resulting in GA.

Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease are other common neurodegenerative diseases of aging potentially related to AMD.

A reduction in quality of life is common with AMD.[47] Clinical depression is reported in one-third of patients, twice the rate of peers without AMD, and this risk increases as vision deteriorates.[48,49] A significant decline in participation in valued activities such as hobbies occurs in 60% of patients, which has been found to increase the risk of depression.[50,51]

PATHOPHYSIOLOGY

The presence and type of drusen on the retina upon examination can predict the progression of AMD. Drusen are yellow-white deposits made up of protein and lipids that appear on a layer of the retina known as the Bruch's membrane, a

thin, semipermeable membrane that operates as a basement membrane for the retinal epithelium and mediates the metabolic exchange between the retina and the choroid (Fig. 111-3). While the exact cause of drusen is unknown, several hypotheses suggest that drusen are composed of lipids and cellular debris accumulation from the rods and cones of the retina that are not fully eliminated. While drusen are not a cause of or diagnostic of AMD, the presence of drusen on examination can increase a person's risk of developing AMD. Only patients over the age of 50 with the presence of drusen can carry the diagnosis of early AMD. Patients younger than 50 years of age should consider hereditary factors for macular disease if signs and symptoms similar to AMD are present.[13]

Drusen can be classified as hard or soft (Fig. 111-4). Drusen that are small, round, well-defined spots located far away from one another on the retina are called "hard" drusen. Hard drusen are not a large cause for concern for vision loss or AMD as they may never progress to AMD or may be very slow to progress. Most people over the age of 50 years have hard drusen present on their retina, and these are considered a natural consequence of aging. Soft drusen increase the risk for AMD (specifically wet AMD); these are larger drusen, are not well-defined with blurred edges, and are often clustered closer together on the retina. The presence of large, soft drusen is associated with vision loss and an increased risk for progression to AMD. Soft drusen can also lead to RPE detachment through the disruption of the retinal layers.

Dry AMD

Atrophic or dry AMD is a painless disease of the macula resulting in a gradual loss of vision. The most common form of AMD, dry AMD can progress very slowly and is less threatening to central vision loss compared to wet AMD. Dry AMD is characterized by subretinal hard and soft drusen deposits, the thinning of the macula, RPE atrophy, and hyperpigmentation of the retina. The cause of dry AMD is unknown, but studies indicate that it may be related to inflammation, genetics, and environmental factors such as smoking and diet.[29–32]

Dry AMD is usually diagnosed in patients older than 50 years of age. As the eye ages, the macula begins to thin and break down. Early detection, self-care, and reduction of risk factors through better diet, smoking cessation, and vitamin supplementation can help to slow progression of the disease.

Dry AMD that progresses to the advanced stage is called geographic atrophy (GA). GA occurs when there is progressive and irreversible loss of RPE,

choriocapillaris, and photoreceptors leading to a loss of central vision.[52,53] Severe GA can also progress to wet AMD.

Dry AMD usually affects both eyes, but in some patients, only one eye is affected. Patients with dry AMD in one eye may not have noticeable symptoms because the healthier eye will overcompensate for the eye affected by AMD. The patient's peripheral vision is not affected by dry AMD, so the vision loss may not be obvious in the early stages of the disease.

Symptoms of dry AMD are[54,55]:

- Difficulty reading or driving (eg, increasing blurriness of written words)
- Visual distortion (eg, straight lines appearing bent)
- Blurred images (eg, difficulty recognizing faces)
- Difficulty seeing in low or dim light; bright light may be needed to see better
- Decreasing central vision
- Colors may not appear as bright as they once were

Wet AMD

Choroidal neovascularization (CNV), or exudative AMD, is typically referred to as wet AMD, and is advanced AMD.[56] Wet AMD is characterized by the loss of central vision caused by CNV, which is the abnormal growth of new blood vessels from the choroid into the macula and retina. These abnormal blood vessels can leak blood or fluid into the retina and can form pockets of fluid between the choroid and the RPE; these can be seen as bumps in the macula and cause a disruption in central vision.[57] The patient will see dark spots in their central vision because of the pockets of fluid and wavy lines instead of straight lines because their macula is no longer smooth.[58] The presence of drusen that are large and soft and RPE hyperpigmentation increases the risk of development of wet AMD.

VEGF plays an important role in the pathogenesis of wet AMD. VEGF is a specific and potent regulator of angiogenesis and is responsible for the abnormal growth of blood vessels. One isoform, VEGF-A, is most strongly associated with angiogenesis in ocular diseases and is therefore a target for VEGF inhibitors for the treatment of wet AMD.[59–61]

Like dry AMD, wet AMD may affect one or both eyes. Once the patient has progressed to wet AMD, vision loss may be rapid if treatment is not initiated

promptly to address the leaky blood vessels. Symptoms of wet AMD are similar to dry AMD and also include presence of dark spots in the patient's central vision; peripheral vision is not affected. Patients at high risk of wet AMD should have regular eye examinations to assess functional change.

Classification of AMD

AMD can be classified using different systems. Most practitioners use the Age-Related Eye Disease Study (AREDS) classification or the more recently developed Beckman Classification system (**Table 111-2**), which is based on the presence and size of drusen and pigmentary changes.[62,63]

TABLE 111-2 Classification of Age-Related Macular Degeneration

Clinical Classification	Characteristics
Normal aging changes	Small drusen ≤63 µm No pigmentary abnormalities
Early AMD	Medium-sized drusen >63 µm and ≤125 µm No pigmentary abnormalities
Intermediate AMD	Large drusen >125 µm and/or any pigmentary abnormalities
Late AMD	Neovascular AMD and/or geographic atrophy
AREDS Classification	
No AMD (Category 1)	No or few small drusen
Early AMD (Category 2)	Multiple small drusen Few intermediate drusen Mild abnormalities in the retinal pigment epithelium
Intermediate AMD (Category 3)	Any of the following: • Numerous intermediate drusen • At least one large drusen • Geographic atrophy
Advanced AMD (Category 4)	One or more of the following: • Geographic atrophy of the retinal pigment epithelium involving the foveal center • Neovascular maculopathy that includes the following: • Choroidal neovascularization • Serous and/or hemorrhagic detachment of the neurosensory retina or retinal pigment epithelium • Retinal hard exudates • Subretinal and subretinal pigment epithelium fibrovascular proliferation • Disciform scar (subretinal fibrosis)

AREDS, Age-Related Eye Disease Study; AMD, age-related macular degeneration.

Early AMD

AREDS defines early AMD based on presence of a few small (<63 µm) to medium (63-124 µm) drusen. The patient may or may not have pigment epithelial abnormalities in the macula. Patients diagnosed with early AMD have a very low risk of progressing to advanced AMD after 5 years of stable

disease.[62]

Intermediate AMD

Intermediate AMD has been defined by the AREDS as having one or more large drusen (≥125 µm in diameter) or evidence of extensive medium drusen (63-124 µm) or in one or both eyes. Patients with intermediate AMD have a much greater chance of progression to advanced AMD if left untreated. If, at baseline diagnosis, drusen are present only in one eye, there is approximately an 18% chance that the disease will progress to advanced AMD after 5 years. If medium to large drusen are present in both eyes, the risk of progression to advanced AMD increases to 26% after 5 years.[62] Upon diagnosis, patients should begin a discussion with their physician about the risks and benefits of delayed progression or stabilized visual acuity with the available treatment options.

Reticular pseudodrusen, also called subretinal drusenoid deposits, may appear in patients with intermediate AMD. These are difficult to identify upon examination, and diagnosis may require the use of fundus autofluorescence, infrared reflectance, and/or spectral domain optical coherence tomography (SD-OCT). The presence of pseudodrusen is associated with the progression of intermediate AMD.[64–67]

Advanced AMD

AREDS defines advanced AMD as neovascular AMD or GA present in the macula. In patients with advanced AMD, at least one eye is affected, with a complete loss of visual acuity. According to AREDS, the risk of progression of visual acuity loss in the unaffected eye is 35% to 50% at 5 years.[68] Patients with GA may have a slower loss of visual acuity compared with patients with neovascular AMD.[8]

CLINICAL PRESENTATION

AMD can present without symptoms, or patients may have complaints of central vision loss, including scotoma (a dark patch in the middle of their vision), or distorted vision. Patients are typically older than 50 years of age. In dry AMD, patients may complain of the need for a bright light or a magnifying glass while reading or trouble seeing while driving. Wet AMD presents as metamorphopsia, the distortion of straight lines. Acute vision loss requires urgent evaluation and care.

TREATMENT

4 The goal of treatment is to slow progression of AMD and prevent severe visual impairment or blindness. It should be noted that while pharmacotherapeutic options do exist, there is not enough supportive evidence to advocate for one treatment option over another to prevent progression to advanced AMD. For patients with intermediate AMD, studies support use of antioxidant vitamins and minerals to slow progression to advanced AMD. In patients with wet AMD, the use of anti-VEGF agents, photodynamic therapy (PDT), and even surgery has been studied in an attempt to slow progression to vision loss. Assessment of the patient by the physician and informed discussion with the patient evaluating the risks and benefits of treatment are necessary before treatment begins.

Smoking Cessation

5 For all patients with dry AMD, smoking cessation is very important to include as first-line nonpharmacotherapeutic treatment option. Smoking cessation is the primary modifiable risk factor that can slow progression of AMD.

Health professionals, particularly pharmacists, can play a vital role in providing patient counseling and assistance with choosing the appropriate over-the-counter (OTC) nicotine replacement therapy (NRT) options for patients. A Cochrane review evaluated evidence supporting the effectiveness of community pharmacists and their role in helping patients achieve smoking cessation. Well-trained, community pharmacists that provide behavioral counseling and education on choosing the appropriate NRT were able to help patients achieve smoking cessation goals. In the community setting, behavioral counseling and education for at least 1 month yielded positive smoking cessation rates.[52,69] Because most smoking cessation products in the United States are widely available OTC, community pharmacists have an opportunity to make a significant impact by helping a patient choose the appropriate NRT agent and dose while also providing the necessary counseling to support the patient (see Chapter 83, “Substance-Related Disorders: Alcohol, Nicotine, and Caffeine”).

CLINICAL PRESENTATION Age-Related Macular Degeneration

Signs

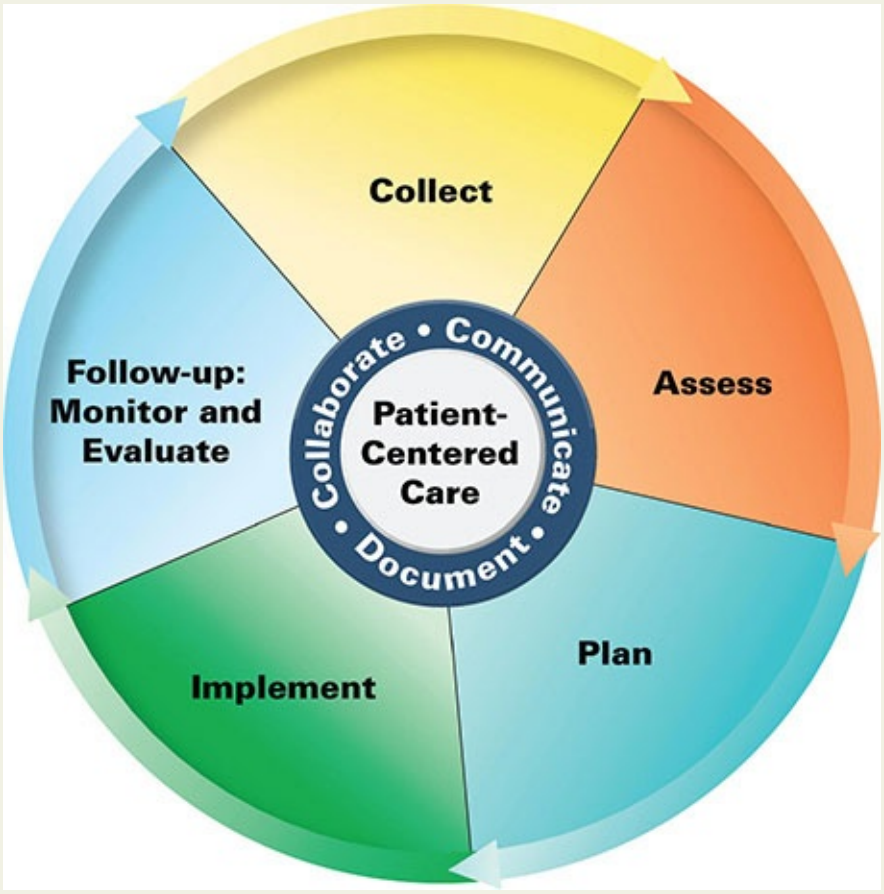
- Distortion when viewing the Amsler grid (Fig. 111–6)
- Dilated eye examination with a slit-lamp instrument to observe and measure
  - Dry: drusen, GA present as hypopigmentation or hyperpigmentation
  - Wet: subretinal fluid or hemorrhage, which requires other diagnostic tests

Laboratory Tests

- None

Diagnosis Tests

- Subretinal evaluation using fluorescein dye retinal angiography, optical coherence tomography, or fundus autofluorescence



Patient Care Process for Management of Age-Related Macular

Degeneration

Collect

- Patient characteristics (age, sex,)
- Patient history (past medical, family history of AMD, social, smoking; date and results of past eye examinations)
- Changes in vision (see Fig. 110-4 in the Glaucoma chapter and Fig. 111-5 in this chapter)
- Current medications
- Objective data (see Clinical Presentation box)
- Visual field changes and losses
- Macula changes

Assess

- Smoking status
- Current treatment

Plan

- Drug therapy regimen designed to prevent progression of the disease and preserve visual acuity, including specific agent(s), dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Table 111-4)
- Referral to ophthalmologist as needed

Implement*

- Provide patient education regarding all elements of treatment plan
- Provide education on diet and lifestyle changes, adherence to medications, and use of the Amsler grid
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up, usually 4 to 8 weeks, or as needed for specific medications

Follow-up: Monitor and Evaluate

- Monitor vision with Amsler grid (Fig. 111-6)

- Visual fields and diagnostic tests
- Adverse effects to medications
- Adherence to treatment

**Collaborate with patient, caregivers, and other healthcare professionals.*

Antioxidant Vitamins and Minerals

6 Several studies looked at the benefit of antioxidant vitamins and minerals in slowing the progression of AMD.[62] These trials are based on the hypothesis that antioxidant vitamins and minerals may prevent cellular damage in the retina caused by the formation of free radicals through light absorption. Use may benefit patients the most with medium or large drusen and/or GA in at least one eye.

Patient-specific factors must be considered before recommending available antioxidant vitamins and minerals to patients with dry AMD (**Table 111-3**). AREDS evaluated the effects of high doses of vitamins E, C, and beta-carotene plus zinc (once-daily doses of vitamin E 400 IU, vitamin C 500 mg, beta carotene 15 mg, zinc 80 mg as zinc oxide, and copper 2 mg as cupric oxide) in patients with AMD with an average follow-up of 6.3 years. Compared with placebo, the supplements decreased the progression to visual acuity loss significantly in patients with intermediate and advanced disease in both the wet and dry forms of AMD. Patients with mild or borderline AMD did not demonstrate a benefit. The use of zinc alone in patients with AMD has significantly lowered the risk of progression to advanced AMD.[62]

TABLE 111-3 Commercially Available Vitamin Products Useful in Age-Related Macular Degeneration

Brand Names	Active Ingredients	Dosage Forms	Directions
	AREDS Formulation		
Preservision AREDS	Vitamin E 400 IU, vitamin C 452 mg, beta carotene 28,640 IU, zinc 69.6 mg as zinc oxide, and copper 1.6 mg as cupric oxide	Softgel, tablet	**Softgels**: 1 softgel twice daily **Tablets**: 2 tablets twice daily
	AREDS 2 Formulation		
Preservision AREDS 2	Vitamin E 400 IU, vitamin C 500 mg, zinc 80 mg as zinc oxide, and copper 2 mg as cupric oxide, lutein 10 mg, zeaxanthin 2 mg	Softgel, chewable	1 softgel twice daily
	Miscellaneous formulations containing components of the AREDS and AREDS 2 ingredients		
Pro-Optic	Vitamin E 200 IU, vitamin C 500 mg, zinc 25 mg, copper 2 mg, lutein 10 mg, zeaxanthin 2 mg	Capsule	1 capsule daily
Equate Vision Formula with Lutein, Zexanthin & Omega-3 50+	Vitamin E 30 IU, vitamin C 150 mg, zinc 9 mg, copper 1 mg, omega-3 250 mg, lutein 5 mg, zexanthin 1 mg	Tablet, softgel	1 tablet/softgel daily with food
Equate Vision Formula with Lutein	Vitamin A 1,000 IU, vitamin C 200 mg, vitamin E 60 IU, zinc 40 mg, selenium 55 mcg, copper 2 mg, lutein 2 mg	Tablet	1 tablet daily
Visivite AREDS 2 Eye Vitamin	Vitamin C 500 mg, vitamin E 400 IU, zinc 40 mg as zinc oxide, copper 1 mg as copper oxide, lutein 10 mg, zeaxanthin 2 mg	Capsule	1 capsule twice daily with meals
ActiveEyes AREDS 2	Vitamin E 266 mg, vitamin C 500 mg, zinc 80 mg as zinc oxide, copper 2 mg as copper gluconate, lutein 10 mg, zeaxanthin 2 mg (per 2 capsules)	Capsule	1 capsule twice daily
EyePromise AREDS 2	Vitamin C 500 mg, vitamin D3 2,000 IU, vitamin E 400 IU, fish oil EE 250 mg, mixed tocopherols 20 mg, alpha lipoic acid 10 mg, zeaxanthin 10 mg, lutein 10 mg	Softgel	1 softgel twice daily
Viteyes classic AREDS 2	Vitamin C 500 mg, vitamin E 400 IU, zinc 25 mg as zinc oxide, copper 1.2 mg as cupric oxide, lutein 10 mg, zeaxanthin 2 mg	Capsule	1 capsule twice daily with meals
Dr. Krawitz Eye Vitamins Macular Support	Vitamin E 100IU, vitamin C 500 mg, zinc 40 mg, copper 1 mg, lutein 15 mg, zeaxanthin 3 mg, calcium 115 mg, vitamin B6 20 mg, selenium 200 mcg, bilberry 50 mg, alpha lipoic acid 20 mg, grape seed extract 20 mg, L-gluthione 10 mg	Soy free, GMO free, gluten free, sugar free vegetarian capsule	2 capsules daily
MaxiVision Ocular Formula	Vitamin C 500 mg, vitamin D3 600 IU, vitamin E 400 IU, zinc 25 mg, copper 1.6 mg, lutein 20 mg, zeaxanthin 4 mg	Capsule	2 capsules per day during a meal
Systane I-Caps AREDS	Vitamin E 400 IU, vitamin C 425 mg, beta carotene 28640 IU, zinc 69.6 mg, copper 1.6 mg	Softgel, coated tablet	1 tablet/softgel twice daily
Systane I-Caps AREDS 2	Vitamin E 400 IU, vitamin C 500 mg, zinc 25 mg, copper 2 mg, lutein 10 mg, zeaxanthin 2 mg	Softgel, chewable tablet	1 softgel/tablet twice daily
Ocuvite Eye Vitamin & Mineral supplement 50+	Vitamin E 20 mg, vitamin C 150 mg, zinc 9 mg, copper 1 mg, lutein 5 mg, zeaxanthin 1 mg, omega-3 fatty acids 250 mg	Softgel	1 softgel twice daily

Previous studies have shown that the use of beta-carotene is associated with an increased risk of lung cancer in smokers, thus limiting its use in this population to nonsmokers only.[70] In the AREDS 2 study, beta-carotene was replaced with the carotenoids lutein 10 mg and zeaxanthin 2 mg; other components of the AREDS formulation of antioxidant vitamins and minerals remained the same. The replacement combination reduced the progression of AMD and therefore would be a reasonable substitute for beta-carotene in patients with AMD who smoke.[71]

The antioxidant property of saffron and its effect on visual acuity in AMD was studied in a small number of patients older than 50 years with mild-to-moderate AMD. Study participants received saffron 20 mg/day for 3 months and were followed for 6 months. Participants who received saffron and the antioxidant vitamin cocktail studied in the AREDS study demonstrated a modest improvement in visual function compared with placebo. Continued study of saffron in a larger sample of this patient population is needed to fully support its use in improving visual acuity in AMD.[72]

Specific Treatments for Wet AMD

Decisions about specific therapies for wet AMD must take into account the risks and benefits of the various therapies and the likelihood of visual recovery. Patients with smaller, more recent drusen are more likely to benefit from therapy. Therapies discussed below—VEGF inhibitors, PDT, and surgical therapy—are specific for wet AMD.

VEGF Inhibitors and Inhibitor-like Drugs

For most patients with wet AMD and CNV, the use of intravitreal VEGF inhibitors and other inhibitor-like drugs has improved visual acuity. VEGF is a potent endothelial cell-specific mitogen and vascular permeability factor that is produced by many cells in the body including tumor cells, macrophages, and platelets.[73] As discussed earlier, VEGF-regulated CNV is a major cause of vision loss caused by the growth of new abnormal blood vessels through the Bruch membrane into the subretinal space. VEGF inhibitors play a pivotal role in preventing neovascularization in patients with wet AMD by preventing the growth of new blood vessels into the retina. Inhibition of VEGF in AMD can limit progression of AMD and stabilize or reverse vision loss. Early initiation of VEGF inhibitors can have a significant effect on vision outcomes. Delay in therapy of as little as 21 weeks after early AMD symptoms have appeared has

been associated with poor vision outcomes at 6 months post-VEGF inhibitor initiation.[74]

Two recombinant humanized monoclonal antibodies, bevacizumab and ranibizumab, exert their mechanism of action as VEGF inhibitors. By acting as VEGF inhibitors in AMD, bevacizumab and ranibizumab inhibit neovascularization within the retina by preventing the growth and leakage of new blood vessels into the retina.

Bevacizumab is a humanized monoclonal antibody approved by the US Food and Drug Administration (FDA) for ovarian, nonsmall-cell lung, glioblastoma, and colorectal cancers and is used off label intravitreally for wet AMD. It exerts its effect on all isoforms of VEGF. Compared with ranibizumab, bevacizumab is much less expensive (approximately $50 an injection vs $2,000 an injection for ranibizumab).[75,76] Structurally, ranibizumab and bevacizumab are different but related monoclonal antibodies.

Ranibizumab is a fragmented monoclonal antibody that was genetically engineered to have an increased binding affinity for all biologically active forms of VEGF, allowing for increased VEGF inhibition. This is achieved by a modification of the amino acid sequence in ranibizumab.[75] Off-label use of these monoclonal antibodies in patients with AMD appears to be safe and effective when used short term based on limited data from controlled trials.[76,77]

Several studies compare the efficacy of bevacizumab to ranibizumab given monthly or as needed.[78–82] The studies have found that both drugs improve visual acuity, with no significant differences seen in efficacy. Both drugs also demonstrated similar safety data, with no differences seen in mortality, hospitalizations, or atherothrombotic events.

8 Ranibizumab has been studied for efficacy in increasing and maintaining visual acuity using a treat and extend (TREX) approach to dosing compared to the traditional monthly dosing (**Table 111-4**). The appeal of the ranibizumab TREX approach is the reduction of office visits and cost of the medication. Ranibizumab can cost the patient an average of $2,000 a dose, which does not include the costs of administration and monitoring for efficacy.[83] Visual acuity was maintained with the TREX approach in patients with wet AMD following the initial monthly injections for 3 months, and costs associated with monthly office visits for treatment and ophthalmic examinations were decreased.[84] The TREX method in patients using ranibizumab is thus preferred over monthly injections.[82,84] Premedication prior to injection is not generally necessary with bevacizumab or ranibizumab.

TABLE 111-4 Medications Used in the Treatment of Age-Related Macular Degeneration

Medication	Brand Names	Usual Doses	Notes
Antioxidant Vitamins: described in Table 111-3			
Monoclonal Antibody VEGF inhibitors: inhibit neovascularization within the retina by preventing the growth and leakage of new blood vessels into the retina			
Bevacizumab	Avastin	Intravitreal: 1.25 mg monthly for 3 months, then may be given monthly or as needed	
Ranibizumab	Lucentis	Intravitreal: 0.5 mg once a month (approximately every 28 days) TREX dosing Frequency may be reduced (eg, 4-5 injections over 9 months) after the first 3 injections or may be reduced after the first 4 injections to once every 3 months if monthly injections are not feasible	A regimen averaging 4-5 doses over 9 months is expected to maintain visual acuity and an every 3-month dosing regimen has reportedly resulted in a ~5 letter (1 line) loss of visual acuity over 9 months, as compared to monthly dosing which may result in an additional ~1-2 letter gain
Nonmonoclonal antibody VEGF inhibitors			
Aflibercept	Eylea	Intravitreal: 2 mg once every 4 weeks for the first 12 weeks, followed by 2 mg once every 8 weeks	Some patients may require every 4 week dosing after the first 12 weeks
Pegaptanib	Macugen	Intravitreal: 0.3 mg once every 6 weeks	Does not improve visual acuity in patients with new-onset wet AMD

The VEGF inhibitor drugs aflibercept and pegaptanib are also administered intravitreally in wet AMD. These drugs are pharmacologically classified as VEGF inhibitors and are not monoclonal antibodies like bevacizumab or ranibizumab. Aflibercept and pegaptanib are primarily used in patients who have insufficient response in visual acuity improvement to ranibizumab and bevacizumab.

The first VEGF inhibitor approved by the FDA for use in wet AMD was pegaptanib. Pegaptanib is a selective antagonist specifically designed to bind and block the activity of extracellular VEGF-A with high specificity and affinity.[85] The first anti-VEGF treatment available for wet AMD, it was approved by the FDA in 2004. Randomized controlled trials at the time of approval demonstrated efficacy with the 0.3-mg dose injected into the vitreous every 6 weeks, but pegaptanib does not improve visual acuity in patients with new-onset wet AMD compared with other VEGF inhibitors.[8] For these reasons, it is rarely used in clinical practice.

Aflibercept is a pan-VEGF-A and placental growth factor blocker that exerts its action in wet AMD by competing for binding with VEGF-A. It was approved by the FDA in 2011 for the treatment of wet AMD based on randomized trials

that demonstrated aflibercept to be noninferior to other VEGF inhibitors such as ranibizumab after 1 year of treatment.[86] Aflibercept has not thus far been compared directly with bevacizumab, which is much less expensive per dose.

Aflibercept is dosed by intravitreal injections of three monthly loading doses, followed by 2 mg injected intravitreally every 4 to 8 weeks. While some patients may require every 4-week injections, there was no additional efficacy noted in the clinical trials in doses administered every 4 weeks compared with every 8 weeks. Therefore, in patients receiving aflibercept 2 mg every 8 weeks, the benefit is improvement of visual acuity without the burden and risk of monthly intravitreal injections or monitoring.

Efficacy and safety tolerability are similar between the two VEGF inhibitors, with the advantage being that aflibercept had the potential for a reduced administration schedule at every 2 months and a reduced monthly cost compared with aflibercept. Overall, it is unknown if there is a standard optimal dosing schedule for VEGF inhibitors.

Adherence with these medications is imperative to maintain the visual acuity gains achieved.[87] If therapy is not continued, the gains can be lost. Counseling patients on the importance of adherence, risks of nonadherence, and options if cost is prohibitive are needed for continued benefit of VEGF therapy.

Photodynamic Therapy for Wet AMD

PDT is initiated in patients with wet AMD who fail to demonstrate an improvement in visual acuity with the use of VEGF inhibitors alone. PDT for AMD is performed by the intravenous injection of a photosensitizing dye, verteporfin, followed by activation of the dye using a photo laser applied through the use of a specialized contact lens. A physician then shines a laser into the patient’s eye, focused on a localized area. The laser activates the dye, causing the formation of a thromboembolism within the abnormal blood vessels below the macula. The thromboembolism seals off the abnormal blood vessels, preventing further leakage of the fluid into the retina that is causing difficulty in vision.

PDT may be used with or without VEGF inhibitors in patients whose visual acuity has worsened while on treatment with VEGF inhibitors alone.[88] When used at least once in combination with the VEGF inhibitors ranibizumab or bevacizumab, it can help improve and maintain visual acuity with continued VEGF inhibitor administration. Several randomized controlled trials with verteporfin and ranibizumab indicate that the combination therapy of VEGF inhibitors with PDT was more effective in improving and maintaining visual

acuity and required fewer PDT treatments than with PDT alone.[88–90]

Randomized clinical trials of bevacizumab and PDT are under way; a number of smaller retrospective case series examining this combination have indicated that it may be effective in improving and maintaining visual acuity.[91–93] Results have been conflicting with aflibercept plus PDT usage and changes in visual acuity. A randomized trial was unable to demonstrate benefit in combination over monotherapy alone due to insufficient patients meeting criteria for dual therapy.

Side effects of PDT are light sensitivity for several days following the procedure and pain in the eye. Patient counseling should include instructions on avoiding exposure to direct sunlight, wearing dark sunglasses and protective clothing when outside, and using OTC analgesics such as acetaminophen for pain. Patients may experience blurry vision that is temporary and will subside. However, worsening vision or increasing eye pain should be reported to a physician.

Surgical Therapy

Management of AMD using surgical techniques is varied and requires further investigation. Surgical therapy is usually reserved in patients with substantial macular hemorrhages that lack a response to VEGF inhibitor therapy.

The most effective surgery for these patients has been the removal of submacular hemorrhages following administration of tissue plasminogen activator (tPa) into the retina.[91–94] Visual acuity improves following surgery; however, it declines over time without the continued use of a VEGF inhibitor to decrease CNV.

Thermal laser photocoagulation is a surgical procedure that involves the use of a thermal laser seal to stop the leakage of fluid from abnormal blood vessel growth under the macula. The heat from the laser seals the abnormal, leaky blood vessels, preventing further fluid leakage and subsequent loss of visual acuity. The negative aspect of this procedure is that it can also destroy surrounding healthy retinal tissue as it seals the leaky blood vessels. Because of this risk, thermal laser photocoagulation is not used to seal vessels located directly under the center of the macula. Thermal laser photocoagulation does not restore vision loss in advanced AMD and should be used as early as possible in therapy to help prevent progression of the disease. Currently, because of these limitations, thermal laser photocoagulation is rarely used in clinical practice.

Antioxidant Vitamins, Beta Carotene, and Zinc

As discussed earlier, studies have demonstrated that antioxidant vitamins and minerals may be useful in delaying progression to advanced AMD in patients with the presence of drusen. The choice of vitamin formulation should be considered based on the patient's history of smoking. Smokers with AMD should be counseled to use only the vitamin formulation that contains lutein and zeaxanthin, whereas nonsmokers can use the formulations containing either beta-carotene or lutein and zeaxanthin. Attention should be paid to amount of vitamin E the patient is consuming daily to avoid vitamin E overdose with use of other multivitamin supplements.

Daily doses should consist of vitamin C 500 mg, vitamin E 400 IU, lutein 10 mg, zeaxanthin 2 mg, zinc oxide 80 mg, and copper (cupric oxide) 2 mg. Beta-carotene 15 mg may be used in lieu of lutein and zeaxanthin in nonsmokers.

Statin Therapy

The use of statins to prevent onset of AMD and progression of early AMD to late AMD has been evaluated in several randomized placebo controlled studies. Epidemiologic data suggests a link between patients with atherosclerotic disease and AMD, and the use of statins may exert a protective effect in patients with AMD.[32,95] The rationale is that drusen are composed of lipid deposits that accumulate within the retinal layers. The effects of statins on drusen are hypothesized to be through a number of different mechanisms. Through the serum lipid lowering, statins may alter the formation of lipid deposits on the Bruch's membrane.[21] Statins may also exert a protective effect against atherosclerosis and AMD by preserving the vascular supply to the outer retina.[22] There may also be an intraocular anti-inflammatory effect through inhibition of VEGF. In AMD, elevated levels of VEGF may play a role in the development of CNV. By inhibiting VEGF intraocularly, statins may prevent CNV and reduce its progression.[23] Finally, statins may interfere with secretion of metalloproteinases, which when released play a role in the rupture of lipid plaques and neovascular development.[24]

Several studies have examined the effect of statins on preventing or reducing progression of AMD to vision loss. Studies evaluating simvastatin indicated there may be a benefit in patients with early AMD; however, sample sizes were small in one study and in the largest study, 30% of patients were lost to follow-up.[21,25] In both studies, no benefit was observed in patients with advanced AMD to support statin therapy. In a small pilot study of patients with advanced AMD,

intensive therapy with atorvastatin 80 mg daily indicated a possible regression in drusen size and vision improvement, but a larger study should be conducted to confirm these effects.[26]

Overall, statin therapy is not recommended for treatment of patients with AMD alone, as results from larger studies would be needed to support use. Statins may be used in AMD patients with other indications such as a diagnoses of atherosclerosis, coronary artery disease, or hyperlipidemia.

Prevention of AMD

Antioxidant vitamins and minerals have not been proven to prevent the onset of AMD in patients with risk factors such as drusen.[96] One trial indicated that there may be some benefit in the use of B vitamins in preventing the onset of AMD. The study compared folic acid 2.5 mg/day, pyridoxine 50 mg/day, and cyanocobalamin 1 mg/day to placebo in women with an increased risk of cardiovascular disease without AMD. After 7 years of follow-up, more women in the placebo group had evidence of AMD compared to the treatment group. Additional studies with larger patient populations are needed to confirm these results. However, it is promising that the use of B vitamins may be beneficial in reducing the risk of AMD in women with cardiovascular disease.[97]

Diets rich in the omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) found in fish, and plant-based omega-3 FA, such as alpha-linolenic acid (ALA), may play a role in decreasing the progression to advanced AMD in patients with intermediate AMD, as seen in several subsets of studies.[17,98–101] However, there is insufficient evidence to say that dietary modification can prevent AMD formation.[98–102]

As previously discussed, smoking cessation is imperative (Table 111-1).

EVALUATION OF THERAPEUTIC OUTCOMES

The overall goal of therapy for macular degeneration is to prevent vision loss through slowing down progression of the disease and preserving visual acuity.

9 VEGF inhibitors and antioxidant vitamins and minerals are the only pharmacologic therapies available that have been shown to improve and stabilize visual acuity in patients with intermediate to advanced AMD. It is important to counsel the patient when discussing the treatment options that they are not curative and may only serve to improve visual acuity from baseline. Current

pharmacologic therapy options will require repeated long-term administration to maintain visual acuity.

Currently, no pharmacologic therapy has been shown to prevent AMD in patients with high-risk factors for development. Studies are conflicting regarding the implementation of a diet high in omega-3 fatty acids such as EPA and DHA found in fish, and plant-based omega 3 fatty acid supplements, such as ALA for prevention of AMD. More studies are needed to fully support this indication.

CONCLUSION

Age-related macular degeneration remains one of the leading causes of blindness globally. Its impact on the quality of life of the aging adult can be tremendous. Early detection of this disease is the key to preserving visual acuity and allows early initiation of pharmacologic therapy to help stabilize and slow vision loss.

Postclass Engaged Learning Activity

Conduct a literature search and identify two primary research manuscripts that have been published in the past 12 months regarding medications for the treatment of macular degeneration. Create a table including inclusion and exclusion criteria, methods, and major findings. Compare the two trials to determine which patients would be ideal for each treatment and make a list of which patients should not use each treatment. If either article is about a new medication that is not described in the chapter, write a brief summary about the medication's mechanisms of action, administration, and one potential advantage or disadvantage of this new medication compared with another treatment option. This activity is intended to build your literature evaluation skills and ability to accurately apply research findings to patient care.

ABBREVIATIONS

ALA	alpha-linolenic acid
AMD	age-related macular degeneration
AREDS	Age-Related Eye Disease Study
CFH	complement factor H
CNV	choroidal neovascularization

DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
FA	fatty acid
FDA	Food and Drug Administration
GA	geographic atrophy
HtrA1	ARMS2/HtrA serine peptidase 1
LIPC	hepatic lipase
NRT	nicotine replacement therapy
OTC	over the counter
PDT	photodynamic therapy
RPE	retinal pigment epithelium
TLR3	toll-like receptor 3
TREX	treat and extend
US	United States
VEGF	vascular endothelial growth factor

REFERENCES

1. Shah N, Dakin SC, Dobinson S, Tufail A, Egan CA, Anderson RS. Visual acuity loss in patients with age-related macular degeneration measured using a novel high-pass letter chart. *Br J Ophthalmol*. 2016;100(10):1346–1352. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26846435.
2. Hunt LA, Nijjar B, Stead A. Chapter 14: Sensory function, function related to the skin and pain: Health conditions. In: Bonder B, Bello-Haas VD, eds. *Functional Performance in Older Adults*. Philadelphia, PA: F. A. Davis Company; 2018.
3. Mathew R, Sivaprasad S, Augsburger JJ, Corrêa ZM. Retina. In: Riordan-Eva P, Augsburger JJ, eds. *Vaughan & Asbury's General Ophthalmology*. 19th ed. New York, NY: McGraw-Hill. Available at: http://accessmedicine.mhmedical.com.proxy.library.vcu.edu/content.aspx?bookid=2186&sectionid=165517649.
4. Horton J. Disorders of the eye. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 20th ed. New York, NY: McGraw-Hill. Available at:.http://accessmedicine.mhmedical.com.proxy.library.vcu.edu/content.asp

bookid=2129&sectionid=192011900.

5. Chang DF. Ophthalmologic examination. In: Riordan-Eva PAJ, ed. *Vaughan & Asbury's General Ophthalmology*. 19th ed. New York, NY: McGraw-Hill. Available at:.http://accessmedicine.mhmedical.com.proxy.library.vcu.edu/content.aspbookid=2186&sectionid =165516032.
6. Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: A systematic review and meta-analysis. *Lancet Glob Health*. 2014;2(2):106. Accessed November 16, 2018.doi:10.1016/S2214-109X(13)70145-1.
7. Chou R, Dana T, Bougatsos C, Grusing S, Blazina I. Screening for impaired visual acuity in older adults: Updated evidence report and systematic review for the US preventive services task force. *JAMA*. 2016;315(9):915–933. Accessed November 16, 2018.doi:10.1001/jama.2016.0783.
8. American Academy of Ophthalmology Retina/Vitreous Panel. *Preferred Practice Pattern® Guidelines: Age-Related Macular Degeneration*. San Francisco, CA: American Academy of Ophthalmology; 2015. Available at:.www.aao.org/ppp.
9. Bressler SB, Muñoz B, Solomon SD, West SK. Racial differences in the prevalence of age-related macular degeneration: The salisbury eye evaluation (SEE) project. *Arch Ophthalmol*. 2008;126(2):241–245. Accessed November 19, 2018.doi:10.1001/archophthalmol.2007.53.
10. Jonas JB, Bourne RRA, White RA, et al. Visual impairment and blindness due to macular diseases globally: A systematic review and meta-analysis. *Am J Ophthalmol*. 2014;158(4):808–815. Accessed November 16, 2018.doi:10.1016/j.ajo.2014.06.012.
11. Al-Zamil WM, Yassin SA. Recent developments in age-related macular degeneration: A review. *Clin Interv Aging*. 2017;12:1313. Accessed November 13, 2018.doi:10.2147/CIA.S143508.
12. Kahn HA, Leibowitz HM, Ganley JP, et al. The framingham eye study. I. Outline and major prevalence findings. *Am J Epidemiol*. 1977;106(1):17–32. Accessed November 18, 2018.
13. Fine SL, Berger JW, Maguire MG, Ho AC. Age-related macular degeneration. *N Engl J Med*. 2000;342(7):483–492. Available at: http://content.nejm.org/cgi/content/extract/342/7/483.
14. Kumaramanickavel G. Age-related macular degeneration: Genetics and

biology. *Asia Pac J Ophthalmol (Phila)*. 2016;5(4):229–235. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27488064.

15. Chew EY, Klein ML, Clemons TE, Agrón E, Abecasis GR. Genetic testing in persons with age-related macular degeneration and the use of the AREDS supplements: To test or not to test? *Ophthalmology*. 2015;122(1):212–215. Available at: https://www.clinicalkey.es/playcontent/1-s2.0-S0161642014010124.
16. Wittes J, Musch DC. Should we test for genotype in deciding on age-related eye disease study supplementation? *Ophthalmology*. 2015;122(1):3–5. Available at: https://www.clinicalkey.es/playcontent/1-s2.0-S0161642014010392.
17. Seddon JM, George S, Rosner B. Cigarette smoking, fish consumption, omega-3 fatty acid intake, and associations with age-related macular degeneration: The US twin study of age-related macular degeneration. *Arch Ophthalmol*. 2006;124(7):995–1001. Available at: http://dx.doi.org/10.1001/archopht.124.7.995.
18. Huan J Chang. The prevalence of age-related macular degeneration and associated risk factors. JAMA. 2010;304(8):838. Available at: https://search.proquest.com/docview/750862838.
19. Velilla S, García-Medina JJ, García-Layana A, et al. Smoking and age-related macular degeneration: Review and update. *J Ophthalmol*. 2013;2013:895147–11. Available at: http://dx.doi.org/10.1155/2013/895147.
20. Adams A, Gelles EB. *Letters*. New York, NY: Library of America; 2016;275:1386–1387. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1772857/.
21. US Department of Health & Human Services. The health consequences of Smoking—50 years of progress: A report of the surgeon general, 2014 | SurgeonGeneral.gov. Available at: https://www.surgeongeneral.gov/library/reports/50-years-of-progress/index.html. Updated 2014. Accessed November 20, 2018.
22. Products CfT. Labeling - cigarette graphic health warnings. Available at: https://www.fda.gov/tobaccoproducts/labeling/labeling/ucm257774.htm. Web site. https://www.fda.gov/tobaccoproducts/labeling/labeling/ucm257774.htm. Accessed November 20, 2018.
23. Parekh N, Voland RP, Moeller SM, et al. Association between dietary fat

intake and age-related macular degeneration in the carotenoids in age-related eye disease study (CAREDS): An ancillary study of the women's health initiative. *Arch Ophthalmol*. 2009;127(11):1483–1493. Available at: http://dx.doi.org/10.1001/archophthalmol.2009.130.

24. Ranard KM, Jeon S, Mohn ES, Griffiths JC, Johnson EJ, Erdman JW. Dietary guidance for lutein: Consideration for intake recommendations is scientifically supported. *Eur J Nutr*. 2017;56(suppl 3):37–42. Accessed November 20, 2018.doi:10.1007/s00394-017-1580-2.
25. de Koning-Backus APM, Buitendijk GHS, Kiefte-de Jong JC, et al. Intake of vegetables, fruit, and fish is beneficial for age-related macular degeneration. *Am J Ophthalmol*. 2018. Accessed November 20, 2018.doi:10.1016/j.ajo.2018.09.036.
26. Chew EY, Clemons TE, Sangiovanni JP. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: The age-related eye disease study 2 (AREDS2) randomized clinical trial. *JAMA*. 2013;309(19):Available at: http://parlinfo.aph.gov.au/parlInfo/search/display/display.w3p;query=librar
27. Zampatti S, Ricci F, Cusumano A, Marsella LT, Novelli G, Giardina E. Review of nutrient actions on age-related macular degeneration. *Nutr Res*. 2014;34(2):95–105. Available at:.https://www.clinicalkey.es/playcontent/1-s2.0-S0271531713002674.
28. Gopinath B, Liew G, Kifley A et al. Association of dietary nitrate intake with the 15-year incidence of age-related macular degeneration. J Acad Nutr Diet. 2018. Available at: https://jandonline.org/article/S2212-2672(18)30276-4/fulltext.
29. Wu J, Uchino M, Sastry SM, Schaumberg DA. Age-related macular degeneration and the incidence of cardiovascular disease: A systematic review and meta-analysis. *PLoS ONE*. 2014;9(3):e89600. Available at: https://www.openaire.eu/search/publication?articleId=dedup_wf_001::591efe6bcfc631a2f27e50df59cf19dc.
30. Klein R, Cruickshanks KJ, Myers CE, et al. The relationship of atherosclerosis to the 10-year cumulative incidence of age-related macular degeneration: The beaver dam studies. *Ophthalmology*. 2013;120(5):1012–1019. Accessed November 20, 2018.doi:10.1016/j.ophtha.2012.11.003.
31. McGuinness MB, Le J, Mitchell P, et al. Physical activity and age-related macular degeneration: A systematic literature review and meta-analysis.

Am J Ophthalmol. 2017;180:29–38. Available at: https://www.clinicalkey.es/playcontent/1-s2.0-S0002939417302180.

32. Ma L, Wang Y, Du J, Wang M, Zhang R, Fu Y. The association between statin use and risk of age-related macular degeneration. *Sci Rep*. 2015;5:18280. Accessed November 20, 2018.doi:10.1038/srep18280.
33. Christen WG, Glynn RJ, Ajani UA, et al. Age-related maculopathy in a randomized trial of low-dose aspirin among US physicians. *Arch Ophthalmol*. 2001;119(8):1143–1149. Available at: http://dx.doi.org/10.1001/archopht.119.8.1143.
34. Liew G, Mitchell P, Wong TY, Rochtchina E, Wang JJ. The association of aspirin use with age-related macular degeneration. *JAMA Internal Medicine*. 2013;173(4):258–264. Available at: http://dx.doi.org/10.1001/jamainternmed.2013.1583.
35. Bressler NM, Munoz B, Maguire MG, et al. Five-year incidence and disappearance of drusen and retinal pigment epithelial abnormalities: Waterman study. *Arch Ophthalmol*. 1995;113(3):301–308. Accessed November 20, 2018.
36. Klein BEK, Howard KP, Iyengar SK, et al. Sunlight exposure, pigmentation, and incident age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2014;55(9):5855–5861. Accessed November 20, 2018.
37. Gopinath B, Liew G, Kifley A, Mitchell P. Thyroid dysfunction and ten-year incidence of age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2016;57(13):5273–5277. Accessed November 20, 2018.doi:10.1167/iovs.16-19735.
38. Smith JL. Chloroquine macular degeneration. *Arch Ophthalmol*. 1962;68(2):186–190. Available at: https://jamanetwork.com/journals/jamaophthalmology/fullarticle/626946.
39. Gilden RC. Pesticides use in hospitals: Health protection, health hazards, and viable alternatives. *Nurs Adm Q*. 2010;34(4):320–326. Accessed November 20, 2018.doi:10.1097/NAQ.0b013e3181f56330.
40. Montgomery MP, Postel E, Umbach DM, et al. Pesticide use and age-related macular degeneration in the agricultural health study. *Environ Health Perspect*. 2017;125(7):077013. Accessed November 20, 2018.doi:10.1289/EHP793.
41. Center of Excellence for Transgender Health, Department of Family and Community Medicine, University of California San Francisco., ed.

Guidelines for the primary and gender-affirming care of transgender and gender nonbinary people. 2nd ed.; 2016. Deutsch M.B., ed. Available at: www.transhealth.ucsf.edu/guidelines.

42. Ambati J, Fowler B. Mechanisms of age-related macular degeneration. *Neuron*. 2012;75(1):26–39. Available at: https://www.sciencedirect.com/science/article/pii/S0896627312005806.
43. Morohoshi K, Goodwin AM, Ohbayashi M, Ono SJ. Autoimmunity in retinal degeneration: Autoimmune retinopathy and age-related macular degeneration. *J Autoimmun*. 2009;33(3-4):247–254. Accessed Nov 20, 2018. doi:10.1016/j.jaut.2009.09.003.
44. Jones BW, Marc RE, Pfeiffer RL. Retinal degeneration, remodeling and plasticity. *Webvision: The Organization of the Retina and Visual System*. Salt Lake City (UT): University of Utah Health Sciences Center; 1995. Available at: http://www.ncbi.nlm.nih.gov/books/NBK482309/.
45. Jager MJ. Macrophages and macular degeneration. *J Ophthalmic Vis Res*. 2014;9(1):1–2. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4074466/.
46. Bowes Rickman C, Farsiu S, Toth CA, Klingeborn M. Dry age-related macular degeneration: Mechanisms, therapeutic targets, and imaging. *Invest Ophthalmol Vis Sci*. 2013;54(14):ORSF68. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24335072.
47. Chatziralli I, Mitropoulos P, Parikakis E, Niakas D, Labiris G. Risk factors for poor quality of life among patients with age-related macular degeneration. *Semin Ophthalmol*. 2017;32(6):772–780. Available at: https://doi-org.proxy.library.vcu.edu/10.1080/08820538.2016.1181192.
48. Brody BL, Gamst AC, Williams RA, et al. Depression, visual acuity, comorbidity, and disability associated with age-related macular degeneration. *Ophthalmology*. 2001;108(10):1893–1900. Available at: https://www.sciencedirect.com/science/article/pii/S0161642001007540.
49. Casten R, Rovner B. Depression in age-related macular degeneration. *J Vis Impair Blind*. 2008;102(10):591. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20011131.
50. Rovner BW, Casten RJ, Hegel MT, Hauck WW, Tasman WS. Dissatisfaction with performance of valued activities predicts depression in age-related macular degeneration. *Int J Geriatr Psychiatry*. 2007;22(8):789–793. Accessed November 15, 2018.
51. Rovner BW, Casten RJ. Activity loss and depression in age-related

macular degeneration. *Am J Geriatr Psychiatry*. 2002;10(3):305–310. Available at: https://www.sciencedirect.com/science/article/pii/S106474811261361X.

52. Sadda SR, Chakravarthy U, Birch DG, Staurenghi G, Henry EC, Brittain C. Clinical endpoints for the study of geographic atrophy secondary to age-related macular degeneration. *Retina (Philadelphia, Pa.)*. 2016;36(10):1806–1822. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27652913.
53. Bonilha VL. Age and disease-related structural changes in the retinal pigment epithelium. *Clin Ophthalmol*. 2008;2(2):413–424. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19668732.
54. Quillen DA. Common causes of vision loss in elderly patients. *American family physician*. 1999;60(1):99. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10414631.
55. Jager RD, Mieler WF, Miller JW. Age-related macular degeneration. *N Engl J Med*. 2008;358(24):2606–2617. Accessed November 20, 2018.doi:10.1056/NEJMra0801537.
56. Smith W, Assink J, Klein R, et al. Risk factors for age-related macular degeneration: Pooled findings from three continents. *Ophthalmology*. 2001;108(4):697–704. Available at: https://www.sciencedirect.com/science/article/pii/S0161642000005807.
57. Gass JDM, Agarwal A, Lavina AM, Tawansy KA. Focal inner retinal hemorrhages in patients with drusen: An early sign of occult choroidal neovascularization and chorioretinal anastomosis. *Retina (Philadelphia, Pa.)*. 2003;23(6):741–751. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14707822.
58. Fine AM, Elman MJ, Ebert JE, Prestia PA, Starr JS, Fine SL. Earliest symptoms caused by neovascular membranes in the macula. *Arch Ophthalmol*. 1986;104(4):513–514. Available at: https://jamanetwork.com/journals/jamaophthalmology/fullarticle/635985.
59. Barakat MR, Kaiser P. VEGF inhibitors for the treatment of neovascular age-related macular degeneration. *EXPERT OPIN INV DRUG*. 2009;18(5):637–646. Available at: http://www.ingentaconnect.com/content/apl/eid/2009/00000018/00000005/
60. de Oliveira Dias JR, Rodrigues EB, Maia M, Magalhaes O, Penha FM, Farah ME. Cytokines in neovascular age-related macular degeneration: Fundamentals of targeted combination therapy. *Br J Ophthalmol*.

2011;95(12):1631–1637. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21546514.

61. Bhisitkul RB. Vascular endothelial growth factor biology: Clinical implications for ocular treatments. *Br J Ophthalmol*. 2006;90(12):1542–1547. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17114590.
62. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol*. 2001;119(10):1417–1436. Accessed November 13, 2018.
63. Ferris FL, Wilkinson CP, Bird A, et al. Clinical classification of age-related macular degeneration. *Ophthalmology*. 2013;120(4):844–851. Accessed November 13, 2018.doi:10.1016/j.ophtha.2012.10.036.
64. Curcio CA, Messinger JD, Sloan KR, McGwin G, Medeiros NE, Spaide RF. Subretinal drusenoid deposits in non-neovascular age-related macular degeneration: Morphology, prevalence, topography, and biogenesis model. *Retina (Philadelphia, Pa.)*. 2013;33(2):265–276. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23266879.
65. Sarks J, Arnold J, Ho I, Sarks S, Killingsworth M. Evolution of reticular pseudodrusen. *Br J Ophthalmol*. 2011;95(7):979–985. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21109695.
66. Zweifel SA, Imamura Y, Spaide TC, Fujiwara T, Spaide RF. Prevalence and significance of subretinal drusenoid deposits (reticular pseudodrusen) in age-related macular degeneration. *Ophthalmology*. 2010;117(9):1775–1781. Available at: https://www.clinicalkey.es/playcontent/1-s2.0-S0161642010000552.
67. Ueda-Arakawa N, Ooto S, Tsujikawa A, Yamashiro K, Oishi A, Yoshimura N. Sensitivity and specificity of detecting reticular pseudodrusen in multimodal imaging in japanese patients. *Retina (Philadelphia, Pa.)*. 2013;33(3):490–497. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23403515.
68. Ferris FL, Davis MD, Clemons TE, et al. A simplified severity scale for age-related macular degeneration: AREDS report no. 18. *Arch Ophthalmol*. 2005;123(11):1570–1574. Available at: http://dx.doi.org/10.1001/archopht.123.11.1570.
69. Sinclair HK, Bond CM, Stead LF. Community pharmacy personnel interventions for smoking cessation. *Cochrane Database Syst Rev*.

2004;1:CD003698. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14974031.

70. Druesne-Pecollo N, Latino-Martel P, Norat T, et al. Beta-carotene supplementation and cancer risk: A systematic review and meta-analysis of randomized controlled trials. *Int J Cancer*. 2010;127(1):172–184. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/ijc.25008.
71. Chew EY, Clemons T, et al. ; AREDS2 Research Group. The age-related eye disease study 2 (AREDS2): Study design and baseline characteristics (AREDS2 report number 1). *Ophthalmology*. 2012;119(11):2282–2289.
72. Broadhead GK, Grigg JR, McCluskey P, Hong T, Schlub TE, Chang AA. Saffron therapy for the treatment of mild/moderate age-related macular degeneration: A randomised clinical trial. *Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie*. 2018;1–10. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30343354.
73. Duffy AM, Bouchier-Hayes DJ, Harmey JH. *Vascular Endothelial Growth Factor (VEGF) and Its Role in Non-Endothelial Cells: Autocrine Signalling by VEGF*. Austin, TX: Landes Bioscience; 2013. Available at: https://www.ncbi.nlm.nih.gov/books/NBK6482/.
74. Lim JH, Wickremasinghe SS, Xie J, et al. Delay to treatment and visual outcomes in patients treated with anti-vascular endothelial growth factor for age-related macular degeneration. *Am J Ophthalmol*. 2012;153(4):2.
75. Steinbrook R. The price of sight—ranibizumab, bevacizumab, and the treatment of macular degeneration. *N Engl J Med*. 2006;355(14):1409–1412. Available at: http://content.nejm.org/cgi/content/extract/355/14/1409.
76. Rosenfeld PJ. Intravitreal avastin: The low cost alternative to lucentis? *Am J Ophthalmol*. 2006;142(1):141–143. Available at: https://www.sciencedirect.com/science/article/pii/S000293940600420X.
77. Bashshur ZF, Bazarbachi A, Schakal A, Haddad ZA, El Haibi CP, Noureddin BN. Intravitreal bevacizumab for the management of choroidal neovascularization in age-related macular degeneration. *Am J Ophthalmol*. 2006;142(1):1–9. Available at: https://www.sciencedirect.com/science/article/pii/S0002939406003321.
78. Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: 2-year results: Comparison of age-related macular degeneration treatments trials

(CATT) research group. 2012. Available at: https://www.openaire.eu/search/publication?articleId=od267:39c58b43de5c6fecb30babd56cc5591b.doi:10.1016/j.ophth

79. Chakravarthy U, Harding SP, Rogers CA, et al. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-Year findings of the IVAN randomised controlled trial. *Lancet*. 2013;382(9900):1258–1267. Available at: https://www.clinicalkey.es/playcontent/1-s2.0-S0140673613615019.
80. Kodjikian L, Souied EH, Mimoun G, et al. Ranibizumab versus bevacizumab for neovascular age-related macular degeneration: Results from the GEFAL noninferiority randomized trial. *Ophthalmology*. 2013;120(11):2300–2309. Available at: https://www.clinicalkey.es/playcontent/1-s2.0-S0161642013005241.
81. Berg K, Pedersen TR, Sandvik L, Bragadóttir R. Comparison of ranibizumab and bevacizumab for neovascular age-related macular degeneration according to LUCAS treat-and-extend protocol. *Ophthalmology*. 2015;122(1):146–152. Available at: doi:10.1016/j.ophtha.2014.07.041. https://www.clinicalkey.es/playcontent/1-s2.0-S016164201400685X.
82. Wykoff CC, Croft DE, Brown DM, et al. Prospective trial of treat-and-extend versus monthly dosing for neovascular age-related macular degeneration: TREX-AMD 1-year results. *Ophthalmology*. 2015;122(12):2514. Available at.https://www.ncbi.nlm.nih.gov/pubmed/26391465.
83. Spaide R. Ranibizumab according to need: A treatment for age-related macular degeneration. *Am J Ophthalmol*. 2007;143(4):679–680. Available at: doi:10.1016/j.ajo.2007.02.024. https://www.clinicalkey.es/playcontent/1-s2.0-S0002939407001900.
84. Silva R, Berta A, Larsen M, Macfadden W, Feller C, Monés J. Treat-and-extend versus monthly regimen in neovascular age-related macular degeneration. *Ophthalmology*. 2018;125(1):57–65. Available at: https://www.sciencedirect.com/science/article/pii/S0161642017310254.
85. Gragoudas ES, Adamis AP, Cunningham ET, Feinsod M, Guyer DR. Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med*. 2004;351(27):2805–2816. Available at: https://doi.org/10.1056/NEJMoa042760.
86. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-

eye) in wet age-related macular degeneration. *Ophthalmology*. 2012;119(12):2537–2548. Available at: https://www.clinicalkey.es/playcontent/1-s2.0-S0161642012008652.

87. Ehlken C, Helms M, Böhringer D, Agostini HT, Stahl A. Association of treatment adherence with real-life VA outcomes in AMD, DME, and BRVO patients. *Clin Ophthalmol*. 2018;12:13–20.
88. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: One-year results of 2 randomized clinical Trials—TAP report 1. *Arch Ophthalmol*. 1999;117(10):1329–1345. Available at: http://dx.doi.org/10.1001/archopht.117.10.1329.
89. Brown DM, Michels M, Kaiser PK, Heier JS, Sy JP, Ianchulev T. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study. *Ophthalmology*. 2009;116(1):65.e5. Available at: http://www.sciencedirect.com/science/article/pii/S0161642008010750.
90. Antoszyk AN, Tuomi L, Chung CY, Singh A. Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration (FOCUS): Year 2 results. *Am J Ophthalmol*. 2008;145(5):874.e3. Available at: https://www.clinicalkey.es/playcontent/1-s2.0-S0002939408000081.
91. Kaiser PK. Verteporfin photodynamic therapy combined with intravitreal bevacizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2009;116(4):755.e1. Available at: https://www.clinicalkey.es/playcontent/1-s2.0-S0161642008013572.
92. Lazic R, Gabric N. Verteporfin therapy and intravitreal bevacizumab combined and alone in choroidal neovascularization due to age-related macular degeneration. *Ophthalmology*. 2007;114(6):1179–1185. Available at: https://www.clinicalkey.es/playcontent/1-s2.0-S016164200700231X.
93. Costa R, Jorge R, Calucci D, Melo L Jr, Cardillo J, Scott I. Intravitreal bevacizumab (avastin) in combination with verteporfin photodynamic therapy for choroidal neovascularization associated with age-related macular degeneration (IBeVe study). *Graefes Arch Clin Exp Ophthalmol*. 2007;245(9):1273–1280. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17333238.
94. Chang W, Garg SJ, Maturi R, et al. Management of thick submacular hemorrhage with subretinal tissue plasminogen activator and pneumatic

displacement for age-related macular degeneration. *Am J Ophthalmol*. 2014;157(6):1250–1257. Available at: https://www.clinicalkey.es/playcontent/1-s2.0-S0002939414000701.

95. Vavvas DG, Daniels AB, Kapsala ZG, et al. Regression of some high-risk features of age-related macular degeneration (AMD) in patients receiving intensive statin treatment. *EBioMedicine*. 2016;5:198–203. Available at: https://www.sciencedirect.com/science/article/pii/S2352396416300299.
96. Evans JR, Lawrenson JG. Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. *Cochrane Database Syst Rev*. 2017;7:CD000253. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28756617.
97. Christen WG, Glynn RJ, Chew EY, Albert CM, Manson JE. Folic acid, vitamin B6, and vitamin B12 in combination and age-related macular degeneration in a randomized trial of women. *Arch Intern Med*. 2009;169(4):335–341.
98. SanGiovanni JP, Chew EY, Agrón E, et al. The relationship of dietary ω-3 long-chain polyunsaturated fatty acid intake with incident age-related macular degeneration: AREDS report no. 23. *Arch Ophthalmol*. 2008;126(9):1274–1279. Available at: http://dx.doi.org/10.1001/archopht.126.9.1274.
99. Christen WG, Schaumberg DA, Glynn RJ, Buring JE. Dietary ω-3 fatty acid and fish intake and incident age-related macular degeneration in women. *Arch Ophthalmol*. 2011;129(7):921–929. Available at: http://dx.doi.org/10.1001/archophthalmol.2011.34.
100. Chong EW, Kreis AJ, Wong TY, Simpson JA, Guymer RH. Dietary ω-3 fatty acid and fish intake in the primary prevention of age-related macular degeneration: A systematic review and meta-analysis. *Arch Ophthalmol*. 2008;126(6):826–833. Available at: http://dx.doi.org/10.1001/archopht.126.6.826.
101. Chua B, Flood V, Rochtchina E, Wang JJ, Smith W, Mitchell P. Dietary fatty acids and the 5-year incidence of age-related maculopathy. *Arch Ophthalmol*. 2006;124(7):981–986. Available at: http://dx.doi.org/10.1001/archopht.124.7.981.
102. Lawrenson JG, Evans JR. Omega 3 fatty acids for preventing or slowing the progression of age-related macular degeneration. *The Cochrane Database of Syst Rev*. 2015;(4):CD010015. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25856365.

Drug-Induced Ophthalmic Disorders

Rena Gosser

KEY CONCEPTS

1. The eye is highly susceptible to drug toxicity due to its extensive vasculature.
2. When ophthalmic disorders occur, all medications and biologic agents, irrespective of route of administration, are potential causes.
3. It is difficult to fully quantify the incidence of drug-induced ophthalmic disorders due to the variety of causative factors and side-effect reporting behaviors of clinicians.
4. The most common drug-induced ophthalmic disorders include dry eye, cataract, intraoperative floppy iris syndrome, optic neuropathy, and retinopathy.
5. The severity of drug-induced ophthalmic disorders varies and depends on dose, pharmacokinetics, genetic predisposition, age, extremes of body weight, and/or duration of exposure.
6. Health professionals and patients should discuss potential drug-induced ophthalmic disorders to ensure awareness, prompt identification, management, and treatment.

Preclass Engaged Learning Activity

Watch the following videos available from the US National Library of Medicine MedlinePlus for a brief overview of the anatomy and function of the eye. These videos provide necessary foundation and will assist in understanding the mechanisms of drug-induced ophthalmic disorders.

Seeing: https://medlineplus.gov/ency/anatomyvideos/000109.htm (3:22)

Blinking: https://medlineplus.gov/ency/anatomyvideos/000010.htm (1:01)

INTRODUCTION

1 The eye is an important, complex organ of the nervous system. It is composed of specialized tissues and complex structures that collectively contribute to the body's ability to visually process the environment (**Fig. e112-1**).[1–3] The sequence for normal, functioning eyes begins with the eyelid, which opens to allow exposure to light, bathes the eye with tear film, and helps remove waste. The eye receives light through the cornea, a clear tissue at the front of the eye. The light then proceeds through the aqueous humor and enters the pupil. The light continues through the pupil, which regulates the amount of light entering the eye to the lens. The lens changes thickness and shape to bend the received light and send it through the vitreous humor to the retina at the back of the eye.[1–3] The retina then transforms the light into electrical impulses, which travel through the optic nerve to the brain. The brain then translates these impulses into the image that is seen. The function of each structure of the eye is summarized in **Table e112-1**.[2,3]

1 2 Disruption at any structure or step in the process can lead to dysfunction of the eye. This can result from many factors. Exposure to toxic substances, including medications, is one such cause of dysfunction. The combination of a rich blood supply and extensive vasculature allows for ocular exposure to systemically administered medication. The blood-aqueous and blood-retinal barriers are capable of keeping most compounds away from the eye; however, some medications are able to bypass the junctions within cells and reach the eye.[4] The eye is the second most common organ to display drug toxicities, with the liver considered most common.[5]

3 It is difficult to accurately quantify the incidence of drug-induced ophthalmic disorders overall.[4,6] All medications have the potential to induce side effects, irrespective of the mode of administration. Side effects may range from mild to severe and can affect any area of the eye. It is important to note that many but not all drug-induced ophthalmic disorders are well documented in the literature; lack of clinician or patient reports is a limiting factor. Despite any potential gaps in the literature, it is important to establish causality between an ophthalmic side effect and medication use. A popular tool used by clinicians to establish the likelihood of causality is the adverse drug reaction (ADR)

probability scale, commonly known as the Naranjo scale.[7] The Naranjo scale is composed of scored questions the clinician should use to assess an ADR. Categories of definite, probably, possible, and doubtful are assigned based on the score.[7]

This chapter will discuss drug-induced ophthalmic disorders seen with commonly prescribed medications in clinical practice. A review of drug-induced glaucoma will not be covered in this chapter, as it is discussed in Chapter 110, "Glaucoma."

DRUG-INDUCED OPHTHALMIC REACTIONS

Dry Eye Disease

4 Dry eye disease (DED), also known as dry eye syndrome or keratoconjunctivitis sicca, is a common ophthalmic disorder that affects the quality of life for millions of people around the world.[6,8] In addition to the discussion of DED in this chapter, nonprescription therapies for the condition are detailed in Chapter e10, "Minor Ophthalmic Disorders."

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

SECTION 16 DERMATOLOGIC DISORDERS

Acne Vulgaris

Debra Sibbald

KEY CONCEPTS

1. Acne is a highly prevalent disorder affecting adolescents and adults, with a large psychosocial impact.
2. The etiology of this complex disease originates from multiple causative and contributory factors, including genetics and environment. The diagnosis is based on the patient's history and clinical presentation.
3. Acne is a disease of the pilosebaceous unit. Elements of pathogenesis involve defects in epidermal keratinization, androgen secretion, sebaceous function, bacterial growth, inflammation, and immunity.
4. Acne vulgaris is a chronic disorder which cannot be "cured." Goals of treatment and prevention include control and alleviation of symptoms by reducing the number and severity of lesions, slowing progression, limiting disease duration and recurrence, prevention of long-term disfigurement associated with scarring and hyperpigmentation and avoidance of psychologic suffering. Targeting goals may increase patient adherence to therapy.
5. The most critical target for treatment is the microcomdedone. Minimizing or reversing follicular occlusion will arrest the pathogenic acne cascade and involve combining treatment measures to target all pathogenic elements.
6. Nondrug measures are aimed at long-term prevention and treatment. Patients should eliminate aggravating factors, maintain a balanced, low-glycemic load diet, and control stress. Cleanse twice daily with mild soap or soapless cleanser and use only oil-free cosmetics. Comedone extraction in approximately 10% of patients produces immediate cosmetic improvement. Shave infrequently as possible, using a sharp blade or electric razor.

7. First-, second-, and third-line therapies should be appropriate for the severity and staging of the clinical presentation and directed toward control and prevention.
8. Treatment regimens should be tapered over time, adjusting to response. Combine the smallest number of agents at the lowest possible dosages to ensure efficacy, safety, avoidance of resistance, and patient adherence.
9. Once control is achieved, maintenance regimens should be simplified to continue with some suppressive therapy. Therapy must be continued beyond 8 weeks: efficacy is assessed through comedonal and inflammatory lesion count, control or progression of severity, and management of associated anxiety or depression. Safety end points include monitoring for treatment adverse effects.
10. Motivate the patient to continue long-term therapy through empathic and informative counseling.

Preclass Engaged Learning Activity

Watch the video entitled “Acne” by Dr Sheilagh Maguiness, pediatric dermatologist, available on the Society for Pediatric Dermatology Website (https://tinyurl.com/saa9t4s). This 5-minute video provides a brief overview regarding information patients need to know about acne vulgaris. The video is useful to enhance student understanding regarding what information to provide to patients regarding causes of acne, triggers, cleansing, over the counter and prescription options, directions for use and precautions. It gives a brief summary of take-home points useful to direct counseling.

INTRODUCTION

In this chapter, I review the latest developments in understanding acne vulgaris and its treatment. The contents provide an analysis of the physiology of the pilosebaceous unit; the epidemiology, etiology, and pathophysiology of acne; relevant treatment with nondrug measures; and comparisons of pharmacologic agents, including drugs of choice recommended in best-practice guidelines. Options include a variety of alternatives such as retinoids, antimicrobial agents, hormones, and light therapy. Formulation principles are discussed in relation to

drug delivery. Patient assessment, general approaches to individualized therapy plans, and monitoring evaluation strategies are presented.

EPIDEMIOLOGY

1 Acne vulgaris is a chronic disease and the most common one treated by dermatologists. There is a high degree of variability in prevalence, age of onset, distribution, severity, and age of resolution.

The lifetime prevalence of acne approaches 90%, with the highest incidence in adolescents. Prevalence data available from the European Union, United States, Australia, and New Zealand show that acne affects 80% of individuals between puberty and 30 years of age, depending on the method of lesion counting (50%-95% prevalence range reported for adolescents and 20%-30% prevalence range for ages 20-40).[1] Other studies have reported acne in 28% to 61% of school children aged 10 to 12 years; 79% to 95% of those 16 to 18 years of age; and even in children aged 4 to 7 years. If mild manifestations were excluded and only moderate or severe manifestations were considered, the frequency in epidemiological studies in Western industrialized countries was still 20% to 35%.[2–5]

The onset of acne vulgaris during puberty occurs at a younger chronologic age in girls than boys (12% age 25-58 vs 3% in males of the same age) and periodic premenstrual flares may continue until menopause. It is triggered in children by the initiation of androgen production by the adrenal glands and gonads, and it usually subsides after the end of growth. However, to some degree, most patients continue to have symptoms into their mid-twenties, and there is evidence that the duration of acne may last into middle age for most women, recorded in 54% of women and 40% of men older than 25 years of age.[6] In puberty, acne is often more severe in boys in about 15% of cases, which is 10-fold greater than in girls. Women often have more severe forms during adulthood. When untreated, acne usually lasts for several years until it spontaneously remits. After the disease has ended, scars and dyspigmentation are not uncommon permanent negative outcomes.

Genetic factors have been recognized; there is a high concordance among identical twins, and there is also a tendency toward severe acne in patients with a positive family history of acne.

There are believed to be no gender differences in acne prevalence, although such differences are often reported and may represent social biases. In urban clinics, there is a clear preponderance of girls seeking treatment. There is also a

perception that acne is less prevalent in rural populations. This is supported by the data from Varanasi, India, where 21.35% of boys (13-18 years) from rural areas had acne versus 37.5% of those from the urban areas.[7]

An international group of epidemiologists, community medicine specialists, and anthropologists have questioned whether acne might be predominantly a disease of Western civilization.[8] They assert that since acne vulgaris is nearly universal in westernized societies (afflicting 79%-95% of the adolescent population), one causative factor might be the Western glycemic diet. While this hypothesis is based on the observation that primitive societies subsisting on traditional (low glycemic) diets have no acne, the theory awaits validation and acceptance by the dermatologic community.

ETIOLOGY

2 Acne is a multifactorial disease. Genetic, racial, hormonal, dietary, and environmental factors have been implicated in its development. Its psychologic impact can be severe.

Four major etiologic factors are involved in the development of acne: increased sebum production, due to hormonal influences; alteration in the keratinization process and hyperproliferation of ductal epidermis; bacterial colonization of the duct with *Propionibacterium acnes*; and production of inflammation with release of inflammatory mediators in acne sites. These are reviewed in the Pathophysiology section later in this chapter.

The role of heredity in acne has not been clearly defined; however, there is a significant tendency toward more serious involvement if one or both parents had severe acne during their youth.

Environmental factors play a major role in determining the severity and extent of acne and may influence the choice of topical treatments. Heat and humidity may induce comedones; pressure or friction caused by protective devices such as helmets, shoulder pads, or pillows, and excessive scrubbing or washing can exacerbate existing acne by causing microcomedones to rupture. Pressure may cause acne lesions to form in patients who do not have acne vulgaris: this variant is called *mechanical acne*. Friction, wool, or other rough textured fabrics and occlusive clothing may also be mechanical irritants. Hair styles that are low on the forehead or neck may cause excessive sweating and occlusion, exacerbating acne. In most cases acne is worse in winter and improves during the summer, suggesting a salutary effect of sunlight. However, in some cases, exposure to sunlight worsens the disease.[9] Studies examining the

relationship between tobacco smoking and acne show inconsistent results; however, dermatologists have begun to counsel people to quit tobacco smoking as a potential auxiliary treatment for acne.

The importance of psychologic factors in this prolonged and capricious condition has been repeatedly stressed. Two-thirds of affected teenagers wish that they could speak with their physician and healthcare provider about acne, but only one-third do. Emotions, such as intense anger and stress, can exacerbate acne, causing flares or increasing mechanical manipulation: picking, excoriating, or pinching lesions sometimes subconsciously or in sleep. This is probably the result of increased glucocorticoid secretion by the adrenal glands, which appears to potentiate the effects of androgens.[10]

Dietary influences Current investigations explore associations between dietary influences and acne. Under study are dietary influences as factors in acne development as well as potential treatment modalities. This follows the dismissal of over-interpreted 40-year-old, poorly designed studies that disavowed potential effects of dietary ingestions on acne.[11–14] Three primary influences on development include dairy and growth factors in milk; whey protein in milk; and hyperglycemic-load diets.

A series of studies have linked consumption of dairy products with acne.[15,16] Acne has been positively associated with the reported quantity of milk ingested, particularly skim milk.[17] The Nurses Health Retrospective Study examining diet during high school in 47,355 women found an association between acne and milk intake, suggesting natural hormonal components of milk and/or other bioactive molecules in milk could exacerbate acne.[18]

Lactoferrin is a whey milk protein with anti-inflammatory activity. Lactoferrin-enriched fermented milk ameliorated acne vulgaris, selectively decreasing triacylglycerols in skin surface lipids.[18] Lactoferrin administered as a dietary supplement twice daily in mild-to-moderate acne vulgaris led to an overall improvement in acne lesion counts in adolescents and young adults.[19]

A recent meta-analysis of observational studies examined association of dairy intake and acne in children, adolescents, and young adults. Any dairy product—including milk, yogurt, and cheese—was associated with an increased odds ratio for acne in individuals aged 7 to 30 years; however, studies were heterogenous in design, making comparisons difficult.[20]

Other studies suggest a role for insulin-like growth factor (IGF), increased by ingestion of high glycemic loads.[21,22] The strongest evidence supports a high glycemic load (HGL) diet as a significant factor in acne. In a randomized

controlled trial, patients who eliminated high glycemic index foods showed a significant reduction in acne. Those who consumed a low-glycemic-load diet compared with a conventional HGL diet had improvements of facial acne after 12 weeks. Accompanying changes in physical and endocrinologic parameters suggest that decreases in total energy intake, body weight, and indices of androgenicity and insulin resistance may also be associated with observed improvements in acne.[23] Another study reported an improvement in acne and insulin sensitivity in low-glycemic-load diets compared with controls, suggesting nutrition-related lifestyle factors play a role in acne etiology.[24] Independent effects of weight loss versus dietary intervention need to be isolated. In an Australian study, participants who consumed low glycemic load diets had no reported cases of acne.[17]

Other studies showed correlations between increases in the ratio of saturated to monounsaturated fatty acids, acne lesion counts and increased sebum outflow, suggesting a possible role of desaturase enzymes in sebaceous lipogenesis and the clinical manifestation of acne. These require further investigation.[25]

Univariate and multivariate analyses were used to examine results of a 2015 French survey of individuals (age 15-24 years) reporting or not reporting acne with associated epidemiologic variables. Daily consumption of chocolate and sweets (odds ratio 2.38) and regular use of cannabis (odds ratio 2.88) was independently and highly associated with acne. Smoking tobacco (>10 cigarettes daily) was highly protective. Respective roles of sugar, lipids, and milk were not investigated.[26]

The role of dietary factors in the development or progression of acne vulgaris cannot be dismissed. Currently, practical recommendations would be to avoid excess sugar and skim milk. Further studies are ongoing, including reviewing antioxidants from nutritional and topical sources and probiotics as potential acne-fighting agents.[17]

PATHOPHYSIOLOGY

3 The pathogenesis of acne includes hyperseborrhea, abnormal follicular keratinization, and *Propionibacterium acnes* proliferation in the pilosebaceous unit. Recent research has shed some new light on the involvement of the sebaceous gland, as well as on the pro-inflammatory activity of the cutaneous microbiome. Acne progresses through the following four major stages:

1. Increased sebum production by the sebaceous gland

2. *P. acnes* follicular colonization (and bacterial lipolysis of sebum triglycerides to free fatty acids)
3. Release of inflammatory mediators
4. Increased follicular keratinization

Improved understanding of acne development on a molecular level suggests that acne is a disease that involves both innate and adaptive immune systems and inflammatory events. Receptors that regulate sebaceous lipid metabolism work in concert with receptors regulating epidermal growth and differentiation. Acne can be considered as a model of immune-mediated chronic inflammatory skin disease: an innate immune response that is not able to control *P. acnes* followed by a Th1-mediated adaptive immune response that becomes self-maintaining independently from *P. acnes* itself.[27]

Acne usually begins in the prepubertal period, when the adrenal glands mature, and progresses as androgen production and sebaceous gland activity increase with gonad development. During puberty, alteration of the sebaceous lipid profile, called dysseborrhoea, together with stress, irritation, cosmetics, and potential dietary factors lead to inflammation and formation of different types of acne lesions.[28]

As shown in **Fig. 113-1**, acne results from the development of an obstructed sebaceous follicle, called a *microcomedone*. Sebaceous glands increase their size and activity in response to circulating androgens. Most patients with acne do not overproduce androgens (with some exceptions); instead, they have sebaceous glands that are hyperresponsive to androgens.[29] Patients with acne have a significantly greater number of lobules per gland compared with unaffected individuals.

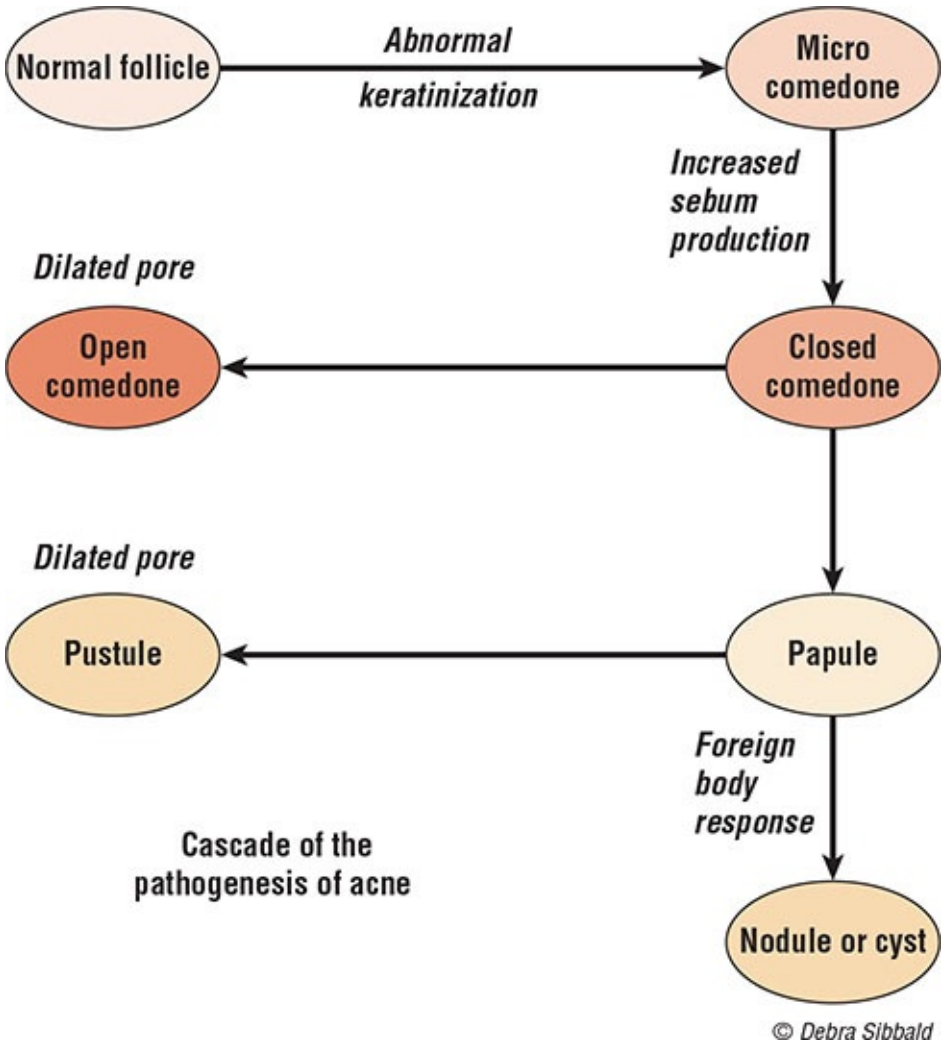


FIGURE 113-1 Cascade of the pathogenesis of acne. (*Reprinted with permission from Mills OH, Kligman AM. Comedogenicity of sunscreens: experimental observations in rabbits. Arch Dermatol 1982;18(6):417-419.*)

Sebum production is induced by different receptors expressed by the sebaceous gland. Involved are the histamine receptor (activated by histamines), the hormonal DHT receptor, (activated by androgens); the neuromodulator receptor (mainly substance P); and corticotrophin-releasing hormone (CRH) receptor (mainly activated by stress); recent molecular research has identified three other receptors that are expressed by the sebocyte and control sebum production. Each of these newly identified receptors is activated by a dietary substance.[28]

The peroxisome proliferator-activated receptors are stimulated by free fatty acids and cholesterol, which act in concert with retinoid X receptors to regulate epidermal growth and differentiation as well as lipid metabolism.

The insulin-like growth factor (IGF)-1 receptor is stimulated by sugar to increase lipid formation, mediated by sterol response element binding proteins. The leptin receptor is stimulated by fat. Leptin is responsible for creating lipid droplets within the sebocyte and induces pro-inflammatory enzyme and cytokine (interleukin (IL)-6 and IL-8) secretion as well.[28]

The sebaceous gland also acts as an endocrine organ in response to changes in androgens and other hormones. Oxidized squalene can stimulate hyperproliferative behavior of keratinocytes, and lipoperoxides produce leukotriene B4, a powerful chemoattractant.[29] The composition of sebum is changed, with a reduction in linoleic acid. The growth of keratinocytes changes. The infrainfundibulum increases its keratinization of cells with hypercornification and development of the microcomedone, the primary lesion of both noninflammatory and inflammatory acne.[27] Cells adhere to each other in an expanding mass, which forms a dense keratinous plug. Androgen hormones could be a stimulus to pilosebaceous duct hypercornification. Sebum, produced in increasing amounts by the active gland, becomes trapped behind the keratin plug and solidifies, contributing to open or closed comedone formation.

Interleukin-1-α upregulation contributes to the development of comedones independently of colonization with *P. acnes*. A relative linoleic acid deficiency has also been described.[29]

A prominent role is played by the follicular colonization by *P. acnes. P. acnes* displays several activities which promote the development of acne lesions, including the promotion of follicular hyperkeratinization; the induction of sebogenesis; and the stimulation of an inflammatory response by the secretion of proinflammatory molecules and by the activation of innate immunity, followed by a *P. acnes*-specific adaptive immune response. In addition, *P. acnes*-independent inflammation mediated by androgens or by a neurogenic activation, followed by the secretion in the skin of proinflammatory neuropeptides, can occur in acne lesions.[27]

The pooling of sebum in the follicle provides ideal substrate conditions for proliferation of the anaerobic bacterium *P. acnes*, generating a T-cell response, which results in inflammation.[30] *P. acnes* produces a lipase that hydrolyzes sebum triglycerides into free fatty acids. These free fatty acids may trigger the changes that lead to an increase in keratinization and microcomedone formation.[31,32] This closed comedone, or whitehead, is the first clinically visible lesion of acne. It takes approximately 5 months to develop. The closed comedone is almost completely obstructed to drainage and has a tendency to rupture.[33–35]

As the plug extends to the upper canal and dilates its opening, an open comedone, or blackhead, is formed. Its dark color is not due to dirt but to either oxidized lipid and melanin or to the impacted mass of horny cells. The cylindrically shaped, open comedone is very stable and may persist for a long time as soluble substances and liquid sebum escape more easily. Acne that is characterized by open and closed comedones is termed *noninflammatory acne*.

Acne produces chemotactic factors and promotes the synthesis of tumor factor-α and interleukin-1β. Cytokine induction by *P. acnes* occurs. Both recruitment of polymorphs into the follicle during the inflammatory process and release of *P. acnes*–generated chemokines lead to pus formation. The pus eventually bursts on the surface with resolution of the inflammation or into the dermis. *P. acnes* also produces enzymes that increase the permeability of the follicular wall, causing it to rupture, releasing keratin, hair, and lipids and irritating free fatty acids into the dermis. Several different types of inflammatory lesions may form, including pustules, nodules, and cysts and may lead to scarring.

Postinflammatory hyperpigmentation (PIH) and scarring are two sequelae of acne. A time delay of up to 3 years between acne onset and adequate treatment correlates to degree of scarring and emphasizes the need for early therapy.[11,12]

CLINICAL PRESENTATION

To correctly diagnose acne vulgaris, the clinician considers patient assessment, which includes distinguishing all the presenting signs and symptoms of the clinical presentation, reviewing diagnostic and assessment considerations (see Clinical Presentation box), as well as considering psychosocial issues, differential diagnosis, and the possibility of drug-induced acne.

Psychosocial Issues

Acne causes profound negative psychological and social effects on the quality of life (QOL) of patients. Assessment of acne's impact on QOL is an important consideration in clinical decision-making. The negative impact of facial acne is one of the primary motivators for patients to seek and to adhere to treatment.[40] The European Dermatology Forum S3-Guideline for the Treatment of Acne recommended adopting a QOL measure as an integral part of acne management.[41] Specific QOL indicators represent patients' perceptions of and reactions to their health. Assessing QOL impairment in patients with acne may

aid in management by evaluating psychologic impact, which may not correlate with clinical severity; aid in detection of depression or need for psychologic care; and improve therapeutic outcomes.

Acne adversely affects all aspects of QOL. In addition to documentation regarding acne-specific QOL impairment, acne impact on general health and psychologic status has been assessed for relationship between sociodemographic variables, disease severity, and mental status on QOL of acne sufferers. In a report of 195 cases, acne impact on health status was worse compared to other chronic diseases. Authors concluded acne is not a minor disease in comparison with other chronic conditions. Age of onset is capable to influence general health quality (GHQ status), which in turn affects QOL.[42] Patients with acne experience functioning and emotional effects from their skin disease comparable with those experienced by patients with psoriasis, and patients with severe acne reported levels of social, psychological, and emotional problems as great as those reported by patients with chronic disabling asthma, epilepsy, diabetes, back pain or arthritis.[41]

The European Academy of Dermatology and Venereology Task Force on QOL and Patient Oriented Outcomes and the Task Force on Acne, Rosacea and Hidradenitis Suppurativa have documented the QOL instruments that have been used in acne patients, with information on validation, purposes of their usage, description of common limitations and mistakes in their usage and overall recommendations.[41]

There are many global scales that have been used to evaluate acne. Some include the World Health Organization Quality of Life (WHOQOL), Skindex,[43] the Dermatology QOL Index,[44] and the Children's Dermatology Life Quality Index (CDLQI). Examples of acne-specific scales include the Acne-specific QOL questionnaire,[45] the Acne QOL Scale,[46] the Acne Disability Index (ADI), and the Cardiff Acne Disability Index (CADI).[41] The Acne QOL Scale was developed to measure the impact of facial acne across four domains (acne symptoms, role-emotional, self-perception, and role-social) of health-related QOL. Health-state utilities (such as time trade-off [TTO]) are quantitative measures of patient preferences of health outcomes ranging from 0 (death) to 1 (perfect health) and can be used in clinical trials as outcome measures of treatment effects. TTO utilities for acne in the range of 0.94 to 0.96 can be compared with those of other diseases (eg, 0.92 for epilepsy, 0.94 for myopia), and help to identify the impact of acne on self-perception and psychologic functioning.[47]

Differential Diagnosis

Acne vulgaris is rarely misdiagnosed. The conditions most commonly mistaken for acne vulgaris include rosacea, perioral dermatitis, gram-negative folliculitis, and drug-induced acne.[48]

Acne rosacea (adult acne) is a chronic, progressive relapsing condition occurring after age of 30 years in fair-complexioned persons. The diagnosis is clinical and based on history and physical findings. There are four subtypes: erythemato-telangietactic changes (erythema, flushing, telangiectasia [spider veins], stinging and burning); progressing to papular-pustular changes (inflammatory lesions, with edema, papules, and pustules on central facial areas such as nose, cheeks, chin, and forehead); phymatous changes (thickened skin and prominent pores on nose, ears, chin, and eyelids; and ocular changes (foreign body sensation, dryness, burning, eyelid erythema).

Rosacea has key differences from acne vulgaris. Onset is not linked to androgens or endocrine changes; and comedones are not usually present. Aggravating factors include endogenous triggers: ingestion of alcohol, spicy foods, or hot drinks (especially those containing caffeine), smoking; and exogenous triggers: overexposure to sunlight; exposure to temperature extremes, heat and humidity, friction, irritating cosmetics, and steroids. Treatment may include antibiotics, particularly doxycycline (low, anti-inflammatory dose) or erythromycin, topical metronidazole, pimecrolimus or azelaic acid as well as agents to reduce erythema (alpha adrenergics).[49]

Perioral dermatitis occurs primarily in young women and adolescents and is characterized by erythema, scaling, and papulopustular lesions commonly clustered around the nasolabial folds, mouth, and chin. The cause is unknown.[50]

Gram-negative folliculitis (*Proteus, Pseudomonas, Klebsiella*) may complicate acne, with a sudden change to pustules or large inflammatory cysts occurring after long-term treatment of acne with oral antibiotics. Folliculitis may be caused by staphylococci. There is a sudden onset of superficial pustules around the nose, chin, and cheeks. Patients with suspected folliculitis should be referred.[51]

Several conditions include acne vulgaris as a characteristic component, and understanding the mechanisms involved in these syndromes provides insight into the pathogenesis of acne. These include polycystic ovary syndrome (elevated androgen levels); PAPA syndrome (pyogenic arthritis, pyoderma gangrenosum, acne; early onset arthritis with increased inflammatory activity), and SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis syndrome; sterile

inflammatory arthro-osteitis, with *P. acnes* as a possible trigger).[30]

CLINICAL PRESENTATION Acne Vulgaris

Lesion Type: Acne Vulgaris Can Be Noninflammatory or Inflammatory

- Noninflammatory acne is characterized by open and closed comedones that develop from the subclinical microcomedo
- The closed comedo is visible as a 1-2 mm whitehead most easily seen when the skin is stretched. It is often inconspicuous with no visible follicular opening.
  - Is the first clinical sign of acne
  - Has a tendency to rupture
- The open comedo or blackhead is large, approximately 2-5 mm, and dark-topped with contents extruding
  - is relatively stable
- Inflammatory acne is traditionally characterized as having papulopustular and/or nodular lesions, which may arise from the microcomedo or from noninflammatory clinically apparent lesions
- A pustule is formed from a superficial aggregation of neutrophils.
  - Appears as a raised white lesion filled with pus, usually less than 5 mm in diameter
  - Superficial pustules usually resolve within a few days without scarring
- A nodule is produced through deeper, dermal, inflammatory infiltration
  - Is the most severe variant of acne
  - Appears as warm, tender, firm lesions, with a diameter of 5 mm or greater
  - May be suppurative or hemorrhagic within the dermis, may involve adjacent follicles and sometimes extend down to fat
- Cysts are suppurative nodules named because they resemble inflamed epidermal cysts
  - Cystic acne may show double comedones, resulting from prior inflammation and fistulous links between neighboring sebaceous units
- Progression of inflammatory lesions

- Pustules and cysts often rupture spontaneously and drain a purulent or bloody but odorless discharge[36]
- Inflammatory lesions may itch as they erupt and can be tender or painful. Nodules may develop exudative sinus tracts resulting in tissue destruction
- Often resolution of these lesions leaves erythematous or pigmented macules that can persist for months or longer, especially in dark-skinned individuals

- Nodules and deep lesions may result in scarring

Regions of Involvement

- Acne lesions can occur anywhere on the body apart from the palms and soles
  - Are usually located on the face, back, neck, shoulders, and chest
- May extend to buttocks or extremities
- One or more anatomic areas may be involved in any given patient
- The pattern of involvement, once present, tends to remain constant
- Comedones frequently have a midfacial distribution in childhood and, when evident early, are indicative of a poor prognosis
- Skin, scalp, and hair are frequently oily

Severity Grading Taxonomies

***US Food and Drug Administration (FDA) Investigator Global Assessment 2005*37,38**

Type 1	Almost clear: rare noninflammatory lesions with no more than 1 small IL
Type 2	Mild, some noninflammatory lesions, no more than a few inflammatory lesions (papules/pustules only, no nodules)
Type 3	Moderate: many noninflammatory lesions, some inflammatory lesions, no more than one nodule
Type 4	Severe: up to many noninflammatory and inflammatory lesions, but no more than a few nodular lesions

European Union Guidelines Clinical Classification[29,39]

I	Comedonal acne
II	Mild-to-moderate papulopustular (MMPP) acne
III	Severe papulopustular acne, moderate nodular acne (*this level combines FDA types 3 and 4, above*)
IV	Severe nodular acne, conglobate acne (*this is an additional level beyond the FDA types above*)

Diagnostic and Assessment Considerations

Palliating factors	Sunlight
Provoking factors	Premenstrual flares, humid environments, excessive sweating; exposure to chemicals; occlusive clothing; friction; oily cosmetics; manual manipulation; stress; diet (high glycemic load, dairy)
Associated symptoms	Itch, pain, fever
Medical conditions	May contribute to or coexist with acne, including endocrine factors (eg, irregular menses, hirsutism, alopecia), pregnancy, atopy
Allergies	May cause acne symptoms, or present a contraindication to therapy
Medication history	Products may cause or interact with acne signs and symptoms
Social habits	Diet or smoking
Family history	Genetic predisposition to acne
Psychosocial issues	Assess global and disease specific quality of life (QOL) indicators or health-state utilities

Drug-Induced Acne

In addition to the conditions induced by drugs that are presented in Chapter e117, “Drug-Induced Dermatologic Disorders,” acneiform eruptions can also be caused by medications. Drug-induced acne is monomorphic, either comedonal with some inflammation or papular–pustular. Drugs most commonly implicated in inducing comedonal/inflammatory acne include those with hormonal effects (steroids, OCP), halogens (iodide, bromide), vitamins (B_2, B_6, B_{12}), tuberculostatic drugs (isoniazid, ethambutol), lithium salts, antiepileptics

(phenytoin), cyclosporine, and azathioprine. Drugs that most commonly induce papular–pustular reactions include anti-inflammatory medications (NSAIDs), sulfamethoxazole–trimethoprim, cephalosporins, and diltiazem.

Systemic corticosteroids can cause a pustular inflammatory form of acne, especially on the trunk. Onset is abrupt at 2 to 6 weeks after initiation of therapy. Acne has also been associated with most of the potent topical steroids, but not with hydrocortisone, which lacks the ability to inhibit protein synthesis. Discontinuation of the steroid results in an initial worsening of appearance due to removal of the anti-inflammatory action of the steroid itself. Caution patients about this reaction, which can be subdued through judicious use of topical hydrocortisone.[50–53]

Antiepileptics and tuberculostatics are the most commonly implicated in drug-induced acne, followed by lithium. Other heavy metals inducing acne include cobalt (in vitamin B_{12}).[54] Halogens, especially an excess of iodide in seafood, salt, and health foods, can exacerbate acne. In addition, halogens can provoke de novo acne lesions in individuals who have increased external exposure often due to occupational contact, or pool or hot tub disinfection; this variant is called *chloracne*.

In addition, certain minor ingredients in cosmetics have been implicated in cosmetic acne, including isopropyl myristate, cocoa butter, and fatty acids.

TREATMENT

The first step in determining a safe and efficacious treatment regimen for acne vulgaris is to establish desired outcomes for the patient, regarding both short- and long-term goals.

Desired Outcomes (Goals of Treatment)

4 Acne vulgaris is treated as a chronic disease, as it demonstrates typical chronicity characteristics: manifests as either acute outbreaks or slow onset; patterns of recurrence or relapse; a prolonged course; and psychologic and social impact. There are two governing principles: the chronic nature warrants early and aggressive treatment, and maintenance therapy is often needed for optimal outcomes.

Acne requires long-term control. This must be stressed with the patient to encourage adherence to lengthy treatment regimens, which address management of current symptoms and signs and preventive measures.

Basic goals of treatment include alleviation of symptoms by reducing the number and severity of lesions (objective and subjective grading) and improving appearance, slowing progression, limiting duration and recurrence, prevention of long-term disfigurement associated with scarring and hyperpigmentation, and avoidance of psychologic suffering.

A significant percentage change in lesion counts is desirable: most patients empirically validate a margin of 10% to 15% reduction in facial lesion counts as appropriate. Patient global self-assessment of acne improvement is a primary outcome.

General Approach to Treatment

5 The most critical treatment target is the microcomedone. Eliminating follicular occlusion will arrest the whole acne cascade. Nondrug and pharmacologic treatment and preventive measures should be directed toward cleansing, reducing triggers, and combination therapy targeting all four pathogenic mechanisms. Combination therapy is often more effective than single therapy and may decrease side effects and minimize resistance or tolerance to individual treatments.

The approach to acne management is largely determined by:

1. Severity index
2. Lesion type: predominantly noninflammatory or inflammatory
3. Treatment preferences including patient choices
4. Cost implications
5. Skin type and/or ethnic group
6. Patient age
7. Adherence
8. Response to previous therapy
9. Presence of scarring
10. Psychologic effects
11. Family history of persistent acne

Topical therapy is the standard of care for mild-to-moderate acne. Those with moderate-to-severe acne will require systemic therapy.

Topical treatments work only where applied. To reduce new lesion development, they must be applied to the entire affected area rather than

individual spots. Most cause initial skin irritation, which may result in nonadherence or discontinuation. Irritation can be minimized by starting with lower strengths and gradually increasing frequency or dose. Where irritation persists, changing formulation from alcoholic solutions to washes, gels, or more moisturizing creams or lotions might help.

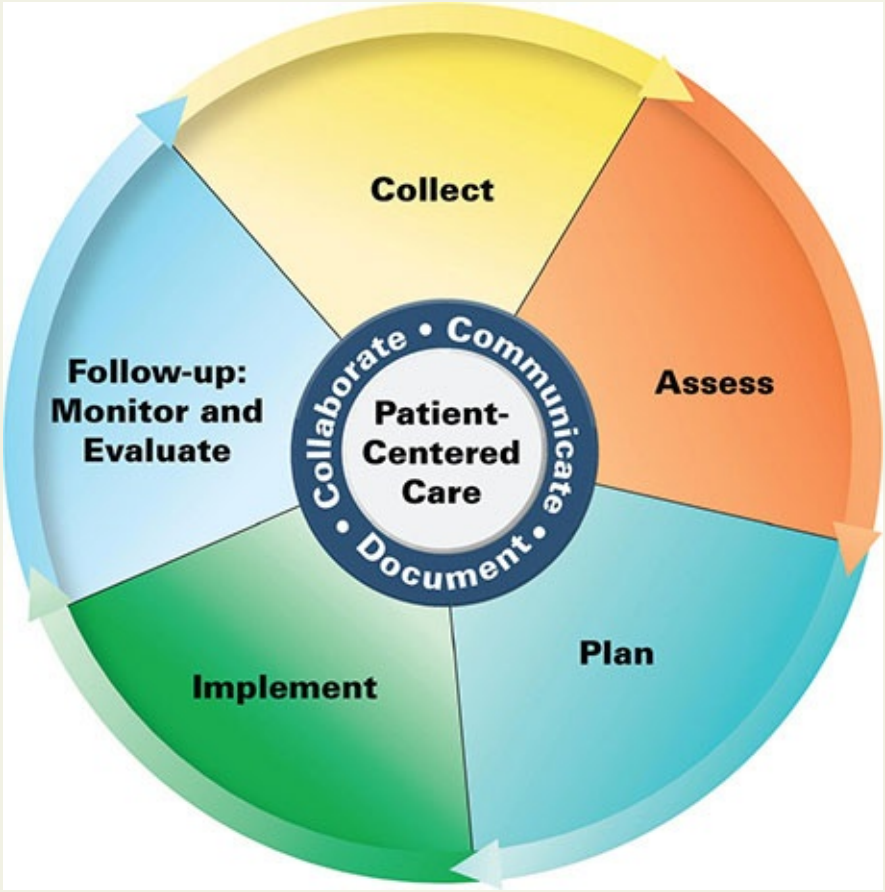
6 7 First-line, second-line, and third-line therapies should be selected and altered as appropriate for the severity and staging of the clinical presentation. Treatment is directed at control, not cure. Regimens should be tapered over time, adjusting to response. Combine the smallest number of agents at the lowest possible dosages to ensure efficacy, safety, avoidance of resistance, and patient adherence. Once control is achieved, simplify the regimen but continue with some suppressive therapy. As it takes 8 weeks for a microcomedone to mature, therapy must be continued beyond this duration to assess efficacy.[52] With the exception of topical antibiotics, most topical preparations may be used for years as needed.

Lesions typically recur for years. Microcomedones significantly decrease during therapy but rebound almost immediately after therapy is discontinued. The strategy for treating acne includes an induction phase followed by a maintenance phase, further supported by adjunctive treatments and/or cosmetic routines. Routine maintenance therapy involves regular use of appropriate agents to ensure remission and reduce potential for recurrence of visible lesions.

For successful long-term treatment, maintenance therapy must be tolerable, appropriate for the patient's lifestyle and convenience, continuing months to years, depending on age. Education about pathophysiology of acne and the psychosocial benefits of clearer skin are compelling reasons for patient adherence to consistent therapy to sustain remission.

Nonpharmacologic Therapy

8 9 Encourage patients with acne to discontinue or avoid aggravating factors, including occlusion from mechanical factors or cosmetics, maintain a balanced, low-glycemic-load diet, and control stress. Evidence shows that by being empathic and informative during counseling, the health professional may motivate the patient to continue long-term therapy.[8,9,49] One of the first approaches to nondrug management of acne is attention to cleansing techniques. Shaving recommendations, comedone extraction, dietary considerations, issues relating to ultraviolet light, and prevention of cosmetic acne should be reviewed with patients.



Patient Care Process for Acne Vulgaris

Collect

- Patient characteristics (eg, age, race, sex, weight [body mass index], pregnant)
- Patient medical history (personal and family history, especially of acne or scarring, adrenal abnormalities)
- Social history (eg, psychosocial issues) and dietary habits including intake of glycemic foods, dairy, and sugary drinks (see Clinical Presentation/Diagnostic and Assessment Considerations; also section “Etiology”)
- Current medications including OTC drug and nondrug measures, prescription drugs (eg, contraceptives) sunscreens, herbal products, dietary supplements, and prior acne medication use
- Current cosmetic use, including makeup, coverups, and cleansers
- Current use of devices (eg, comedone extractors)

- Inhaled systemic or contact allergies to drugs, cosmetics, foods, vehicle ingredients or excipients
- Objective data
  - Fitzpatrick phototype
  - Labs if relevant to monitoring for hepatic or renal function

Assess

- Presence of provoking factors or contributing factors (see Clinical Presentation/Diagnostic and Assessment Considerations) (eg, hormonal or adrenal anomalies: presence of vellus hair on females; in children: early age of onset [age 1-7 years], body odor, hair in axillary and public areas and adrenal: rapid growth in children)
- Severity: number, type, and region of lesions; presence of scarring
- Hyperpigmentation of healed lesions (postinflammatory hyperpigmentation)
- Ability/willingness to adhere to long-term therapy
- Emotional status (eg, presence of anxiety, depression)

Plan*

- Goals: clear existing and prevent new lesions; reduce scarring, hyperpigmentation, and psychological impact
- Discontinuation of provoking habits, botanicals or drug or nondrug measures
- Cleansing routine
- Drug therapy regimen including dietary, nonpharmacologic and pharmacologic approaches
- Monitoring parameters including efficacy (eg, improvement or resolution of lesions and time frame) and safety (eg, sign and symptoms worsening, irritation, or allergy); frequency and timing of follow-up
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug-specific information, medication administration or application technique)
- Self-monitoring for resolution of acne symptoms, occurrence of scarring, when to seek emergency medical attention

- Referrals to other providers when appropriate (eg, behavioral health, dietitian)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up, adherence assessment

Follow-up: Monitor and Evaluate

- Improvement or resolution of acne symptoms (eg, noninflammatory or inflammatory lesions)
- Prevention of complications (eg, scarring, infection)
- Slow progression
- Presence of adverse effects
- Patient adherence to treatment plan using multiple sources of information
- Reevaluate duration of therapy every 3 months

**Collaborate with patient, caregivers, and other healthcare professionals.*

Cleansing

A systematic review of clinical evidence for washing and cleansers reported that they are common interventions. Cleansers are indicated in all patients with acne. However, the clinical evidence for their efficacy is not well understood.[55]

Twice-daily face washing may be superior to either once-daily or more frequent washing. Washing too frequently in an attempt to remove surface oils has shown no added benefit and is not likely helpful, as surface lipids do not affect acne. Contributory lipids are deep in the follicle and are not removed through washing. Antiseptic cleansers, while producing a clean, refreshed feeling, remove only surface dirt, oil, and aerobic bacteria. They do not affect *P. acnes*. Patients should wash no more than twice daily with a mild, nonfragranced opaque or glycerin soap or a soapless cleanser.

Bar soaps are subclassified into true soaps, comprising an alkali and a fatty acid, syndet bars, which use synthetic surfactants, and combars, which include features of both. A study has suggested syndet bars may be superior to true soaps as an acne vulgaris cleansing agent.[56]

Soapless cleansers are an alternative to soaps.[57] Soaps are the most widely used cleansing products, but do not lend themselves to efficient delivery of active drug. Two main disadvantages exist. As soaps are rinsed off, the deposit of active agent is limited, and the high pH required in soaps may degrade some active ingredients and be less tolerable on sensitive skin. Soaps produce a drying effect on the skin due to detergent action. As medicated cleansers require increased contact time, this drying action is pronounced, especially with peeling agents.

Gentle liquid cleansers often contain surfactant systems to remove dirt, sebum, bacteria, and corneocytes from the skin surface. Oil is dispersed from the skin into the surfactant system; however, the active ingredient is sometimes trapped and removed upon rinsing. The balance between cleanliness and drying or irritation should also be considered. Most patients prefer products with foaming action, and these must contain additional secondary surfactants to enhance the foam and condition the skin.

There is no evidence that any particular washing regimen is superior. Evidence-based studies on the use of cleanser or medicated cleansers are lacking or poorly designed with small numbers of patients.[56] It is also difficult to compare studies of different nonprescription formulations even when the same active ingredient is used, as differences in the composition of vehicle may affect cutaneous penetration and vehicles themselves may affect acne. Avoid cream-based cleansers. Scrubbing should be minimized to prevent follicular rupture.

Because the acid pH of skin has an antimicrobial effect, it has been proposed that lowering lesional surface pH (with products such as Herpifix, marketed in Europe) may be correlated to the number of acne lesions. Studies are planned.

Synthetic polyester cleansing sponges abrade the skin surface, removing superficial debris. Considering the structure of comedones, they are unlikely to unseat these lesions. Sponges are available in soft or coarse textures, with or without soap. Circular or rubbing motions will increase irritation. Instruct patients to use single, gentle, continuous strokes on each side of the face, from the midline out toward the ears.

Cationic-bond strips are activated by water. As the strip dries, the cation bonds with the anionic dirt and oil in the pores and removes it when the strip is peeled off.

Shaving

Boys and men with acne should try electric and safety razors to determine which is more comfortable for shaving. When using a safety razor, the beard should be

softened with soap and warm water or shaving gel. Shaving should be done as lightly and infrequently as possible, using a sharp blade and being careful to avoid nicking lesions. Strokes should be in the direction of hair growth, shaving each area only once, to minimize irritation.

Comedone Extraction

Comedone extraction has not been widely tested in clinical trials despite long-standing clinical use; however, it is painless and results in immediate cosmetic improvement. Pretreatment with a peeler for 4 to 6 weeks often facilitates the procedure.[53] Following cleansing with hot water, a comedone extractor is placed over the lesion and gentle pressure applied until the contents are expressed. This removes unsightly lesions, preventing progression to inflammation. A correctly sized extractor allows the central keratin plug to extrude through the opening. The small end of a plastic eye dropper, with bulb removed, may also be used. These instruments should be cleaned with alcohol after each use. Some initial reddening may be apparent. If the contents are not expressed with modest pressure, patients should not continue since improper extraction may further irritate the skin. A physician should be consulted if this technique is too difficult for the patient to manage. Since the follicle is difficult to remove completely, comedones may recur between 25 and 50 days following expression. Fewer than 10% of comedone extractions are a complete success, but the process is useful when done properly.[36]

Comedo removal may be helpful in the management of comedones resistant to other therapies. While the procedure cannot affect the clinical course of the disease, it can improve the patient’s appearance, which may encourage adherence with the treatment program.

Ultraviolet Light

Although ultraviolet light was recommended in the past for desquamation, the practice is no longer advisable because of the well-established carcinogenic and photoaging effects of ultraviolet exposure. Moreover, inflamed skin is more susceptible to the damaging effects of ultraviolet light. Patients taking tretinoin may show heightened sensitivity.[58]

Before exposure to sunlight, patients with acne should apply sunscreens (sun protection factor [SPF] 15) in alcohol- or oil-free bases and avoid using the acnegenic benzophenones. Sunscreen should be applied as the first product.

Prevention of Cosmetic Acne

Persistent low-grade acne is frequently caused by heavy cosmetic use in women after their mid-twenties. Adolescent acne in younger women may be exacerbated with makeup overuse. The problem is perpetuated when resultant blemishes are concealed with more cosmetics.

Patients should be advised to discontinue oil-containing cosmetics and avoid cosmetic multistep regimens applying various cream-based cleansers and cover-ups. These are commercially advertised and often available with promotional bonuses through Internet shopping. Three-step basic systems usually combine medicated and nonmedicated ingredients. The product names used in marketing these preparations may not make apparent the inclusion of therapeutic agents. Initial steps usually involve cleansers, in lotions or creams, which may contain a multitude of unnecessary ingredients, including medicated peelers, oils, fragrances, and preservatives. Active ingredients including salicylic acid, sulfur, or benzoyl peroxide are often included in subtherapeutic or low doses. The second step is generally a water- or alcohol-based “toner” or “refresher,” which might contain medicated mild comedolytic agents such as α-hydroxy acids (eg, glycolic acid), or even a humectant such as glycerin. The final product, often called intensive or repairing solutions, usually contains the lowest strength of peelers such as benzoyl peroxide, sulfur, or salicylic acid; plus potentially sensitizing fragrances and preservatives; or oil-soluble sunscreens not identified on the label. Bases may have significant oil content. There may be additional products such as masks or spot treatments that supplement the base routine of three steps. Multiple-step cosmetic programs are often costly and should be avoided in favor of simple cleansers and more effective single-ingredient peelers at optimal concentrations.

The term *noncomedogenic* may refer to either water-based vehicles or products that are free of substances known to induce comedones. They are not necessarily oil-free. Water-based cosmetics may contain significant amounts of oil in the form of undiluted vegetable oils, lanolin, fatty acid esters (butyl stearate, isopropyl myristate), fatty acids (stearic acid), fatty acid alcohols, cocoa butter, coconut oil, red veterinary petrolatum, and sunscreens containing benzophenones. Water-based products are more likely to contribute to pore blockage than oil-free products.

Oil-free makeups are well-tolerated and lipstick, eye shadow, eyeliner, eyebrow pencils, and loose face powders are relatively innocuous. Heavier, oil-based preparations, particularly moisturizers and hairsprays, clog pores and accelerate comedone formation.[59]

Patients should restrict cosmetic use including makeup, moisturizers, or sunscreens to products labeled oil-free rather than water-based. Cover-up cosmetics for acne are available in several skin tones and in lotion and cream forms. They often contain peeling agents, antibacterial agents, or hydroquinone. Most contain sulfur. They may be applied as cosmetics two or three times daily, over the entire face or to individual lesions. Because the spread time of oil-free makeup is decreased, best results are achieved if applied to one-quarter of the face at a time. Topical medication should be applied after gentle cleansing and a foundation lotion may be used sparingly as a concealer.[60–62]

Because the action of most therapeutic acne agents is to dry the skin, the use of nonspecific moisturizers is counterproductive. Active agents, such as α-hydroxy acids (glycolic, lactic, pyruvic, and citric acids), may be present in a cosmetic formulation, since they reduce corneocyte adhesion.[63] Patients with acne should be restricted to oil-free α-hydroxy acid products unless necessary because of treatment with strong drying agents or isotretinoin.

Cosmetics, if correctly prescribed, may improve the performance of the therapy, whereas incorrect procedures and/or inadequate cosmetics may worsen acne. Clinicians should make informed decisions about the role of various cosmetics and to identify the appropriate indications and precautions. The choice of the most effective product should take into consideration the ongoing pharmacologic therapy and acne type/severity as well.[64]

Vehicles

Topical medication is a staple in treating mild-to-moderate acne because it is an efficient way to deliver medication to the site of action and involves decreased risk of exposure to ingredients. Since local irritation from the vehicle can lead to poor adherence and outcomes, it is essential to choose a vehicle which is effective and well tolerated. Topical agents are absorbed primarily through passive diffusion via appendageal transcellular or intracellular pathways. As the active drug travels, it may undergo chemical changes in the skin or by the vehicle.[65]

The formulation of an acne vehicle must consider the technical characteristics of maintaining and delivering the drug in an active state together with the need for an elegant product that is well tolerated and the patient will enjoy using, so that it is more likely to be applied as required and deliver the full benefit. Physically and chemically, the vehicle will be used with one or more of the following goals: reduce excess oil, control bacteria associated with acne, reduce the effects of hyperkeratinization, and unclog pores. Performance, safety, and

stability should be maximized while addressing technical and commercial factors.

Immiscible liquids might be delivered in oil-in-water or water-in-oil emulsions. In addition to having undesirable oil content, these vehicles also contain humectants, thickeners, preservatives, and fragrance, all of which may be problematic.

Solutions are simpler formulations. They are often used as the soaking liquid for fibrous cloth wipe products. The shelf-life depends upon whether multiple wipe packages are resealable, and whether the solvent volatility will affect storage and active agent availability or cause crystallization. Solutions are used mainly with topical antibiotics, which are often dissolved in specific types of alcohol. Although some antibiotics are only soluble in ethyl alcohol, isopropyl alcohol is generally better able to remove oil from the skin surface and is preferred for nonmedicated vehicles. Solutions and washes can be more easily applied to large areas such as the back.[66]

Nongreasy solutions, gels, lotions, and creams should be selected as bases for topical acne preparations. Lotions and creams will contain some oil-phase ingredients. Discourage moisturizers and oil-based products. Lotions are slightly less drying than gels, and creams are more emollient. Gels are very useful as they are mixtures of water or alcohol and totally oil free. Many gels contain ethanol or isopropyl alcohol. Propylene glycol is sometimes present in small amounts to add viscosity and lessen the drying effects of strong peeling agents. Gels are drying but may cause a burning irritation in some patients and may prevent certain kinds of cosmetics from adhering to the skin.[59] Propylene glycol gels are easy to apply and dry without a visible or sticky film. Nonalcoholic gels may be so effective and less drying than alcoholic solutions. Alcoholic or acetone gels are usually more drying and provide better penetration of the active ingredient.

Consider the patient’s skin type and preferences in the choice of vehicle for topical agents. Patients with oily skin often prefer vehicles with higher proportions of alcohol (solutions and gels), while those with dry or sensitive skin prefer nonirritating lotions and creams. Hydrating and emollient products are often recommended to patients using drying treatment therapies, such as isotretinoin, to control adverse effects and improve adherence to treatment. Lotions can be used with any skin type and can be easily spread over hair-bearing skin, but they will cause burning or dryness if they contain propylene glycol. Compatibility of vehicles and agents with cosmetics should also be considered.

The focus of innovation has been optimal formulations of problematic drugs. A fixed topical alcohol-free aqueous gel combination of clindamycin phosphate 1.2% and tretinoin 0.025% given once daily simplifies administration and encourages adherence. Creamy wash and gel hydrophase options for benzoyl peroxide reduce the irritation of this drug.[67]

The importance of vehicle effects in topical therapy has been demonstrated in placebo effect literature.[67] The percent contribution of vehicle (placebo) toward efficacy of reduction of lesions counts of eight commonly prescribed topical preparations at the end of 10 to 12 weeks of daily administration has been reported as a mean value of 55% (range 35%-82%).

How to Use Topical Preparations

Topical preparations should not be applied to individual lesions but to the whole area affected by acne to prevent new lesions from developing. Care should be advised in applying around the eyelid, mouth, and neck (to avoid chafing). Lotions should be applied with a cotton swab once or twice a day after washing or at bedtime if they leave a visible residue. Skincare products may cause skin dryness and redness particularly at the early stages of the treatment. Should this occur, the product should be applied more infrequently, the treatment should be stopped for a while or another topical product tried. To reduce irritation a topical vehicle with high water content may be applied over the medicinal product after a few minutes; the irritation usually subsides as the skin becomes accustomed to the topical skincare product.

Psychologic Approaches, Hypnosis, and Biofeedback

The psychologic effects of acne may be profound. The American Academy of Dermatology expert workgroup unanimously concluded that effective acne treatment can improve the emotional outlook of patients.[68] There is weak evidence of the possible benefit of biofeedback-assisted relaxation and cognitive imagery.[69,70]

Dressings

A pilot double-blind, randomized study of 20 patients has shown some benefit of treatment with a hydrocolloid acne dressing when compared with tape dressings for improving mild-to-moderate inflammatory acne vulgaris. Results showed greater reduction over 3 to 7 days in the overall severity of acne and inflammation, along with greater improvement in redness, oiliness, dark

pigmentation, and sebum casual level. Less ultraviolet B light reaches the skin surface with the hydrocolloid dressing in place.[71,72]

Pharmacologic Therapy

Successful pharmacologic therapy must address one of the four mechanisms involved in the pathogenesis of acne. Numerous agents are available that prove one or more of these actions and are therefore effective. However, the choice of active pharmacologic therapy depends on severity.

Mechanisms of drug action relating to acne pathogenesis are illustrated in Fig. 113-2.

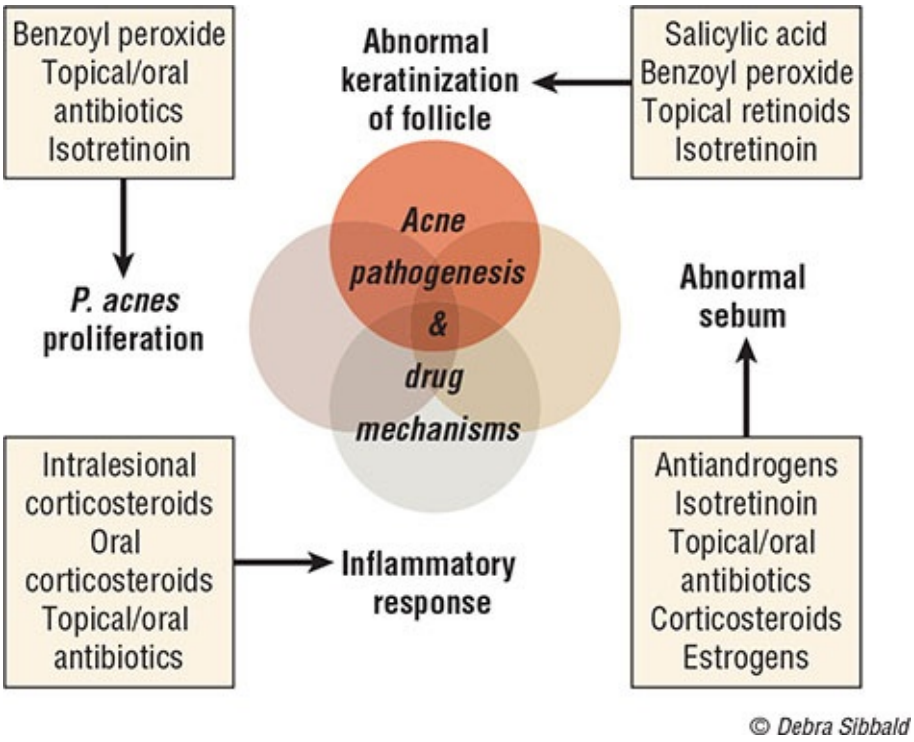


FIGURE 113-2 Acne pathogenesis and drug mechanisms.

Drug Treatments of First Choice

There is concordance among key opinion leaders in different settings regarding recommendations for drugs of choice for management of acne—the Global Alliance 2018 and the 2016 European Guidelines.[29,39,73]

Managing Acne

For comedonal, noninflammatory acne Active agents of first choice include

those that correct the defect in keratinization by producing exfoliation most efficaciously. Topical retinoids, in particular, adapalene, or a fixed combination with a retinoid (eg, adapalene plus benzoyl peroxide) can be recommended as drugs of choice.[29,39] Benzoyl peroxide or azelaic acid or salicylic acid can be considered, as alternatives (lower strength recommendation).[29,39] Limitations can apply that may necessitate the use of a treatment with a lower strength of recommendation as a first-line therapy (eg, financial resources and reimbursement limitations, legal restrictions, availability, drug licensing). Because the comedone is the initial lesion even in inflammatory acne, these agents are used to correct the defect in keratinization in all cases of acne.

For mild-to-moderate papulopustular inflammatory acne It is important to reduce the population of *P. acnes* in the follicle and the generation of its extracellular products and inflammatory effects. Either the fixed-dose combination (adapalene and benzoyl peroxide) or benzoyl peroxide or topical retinoid or azelaic acid are strongly recommended as first choice therapy (high strength recommendation).[29,39,73] In case of more widespread disease, for the treatment of **moderate papulopustular inflammatory acne**, the fixed-dose combination is preferred, with or without hormonal therapy and/or antibiotic, particularly if the trunk is involved.[73]

Low-strength recommendations are offered as considerations for treatment in the event of limitations that apply in selecting a first-choice agent. The choices would be blue light monotherapy, alternate combination therapy (such as fixed-dose combination of erythromycin and tretinoin, fixed-dose combination of isotretinoin and erythromycin) or oral zinc. In case of more widespread disease, a combination of a systemic antibiotic with either benzoyl peroxide or with adapalene in fixed combination with benzoyl peroxide can be considered.[29,39]

For moderately severe or severe papulopustular or moderate nodular acne The fixed-dose combination with an oral antibiotic is preferred. Alternatively, oral isotretinoin or oral hormonal therapy can also be added.[74] In the event of limitations to use of these agents, considerations could be given to oral antiandrogens in combination with oral antibiotics or topical treatments, or systemic antibiotics in combination with benzoyl peroxide (low strength recommendation).

Managing Very Severe Acne

For nodular or conglobate acne In males, monotherapy with oral isotretinoin is strongly recommended as the drug of first choice (high strength

recommendation).[29,39] As alternative agents, a retinoid fixed combination or oral antibiotics can be recommended. For females, oral isotretinoin plus antiandrogenic hormonal therapy is preferred. Alternatively a fixed combination retinoid with oral antibiotics (consider high dose) and/or oral antiandrogenic hormonal therapy can be recommended.[74]

For maintenance therapy for acne The most frequently recommended agents are topical retinoids or retinoid and benzoyl peroxide fixed dose combinations.[73] The most extensively studied maintenance treatment (four controlled trials) has been adapalene regimens.[29,39] Other published options include tazarotene or tretinoin. In general, maintenance therapy is begun after a 12-week induction and continues for 3 to 4 months. Continuing improvement using this schema is achieved, with relapse occurring when patients stop treatment, suggesting a longer duration of maintenance therapy is likely to be beneficial. Topical azelaic acid is an alternative to topical retinoids for acne maintenance therapy, with advantageous efficacy and safety profiles for long-term therapy. To minimize antibiotic resistance, long-term therapy with antibiotics is not recommended as an alternative to topical retinoids. If an antimicrobial effect is desired, the addition of benzoyl peroxide to topical retinoid therapy is preferred.

Published Guidelines

In general, recommendations should be based on critical appraisal and interpretation of the literature combined with clinical experience. There is considerable heterogeneity in the acne literature. The large number of products and product combinations, and the scarcity of comparative studies, has led to disparate opinions and few recommendations are evidence-based. Various evidence-based guidelines, available from multiple American, Canadian, European, Scandinavian, and South African sources from 2005 to 2018, do not provide concordance or clarity on all issues.

The 2016 European Guidelines for the Treatment of Acne focus primarily on major treatments, but do not review general management issues such as psychologic determinants, scarring, diet, and so forth.[29,75] Where relevant, specific information from multiple sources will be integrated into the therapy section that follows.

An expert committee of the American Academy of Dermatology redefined guidelines for acne therapy in 2016 (**Table 113-1**).[74] These guidelines address the management of adolescent and adult patients presenting with acne but not the

consequences of disease, including the scarring, postinflammatory erythema, or postinflammatory hyperpigmentation. In 2009, the Global Alliance to Improve Outcomes in Acne updated their 2003 recommendations to review new information about pathophysiology and treatment and included current published data on relevant issues.[76] In 2018, the Global Alliance published a further update providing relevant clinical guidance to healthcare practitioners managing patients with acne, with an emphasis on areas where the evidence base may be sparse or needs interpretation for daily practice. They provided 10 consensus recommendations, based on the 2016 American Academy and European Guidelines.[73]

TABLE 113-1 Evidence Chart for Recommendations for Managing Acne Vulgaris

Recommendation	Strength of Recommendation	Level of Evidence
Grading/classification system	B	II, III
Microbiologic testing	B	II, III
Endocrinologic testing	B	I, II
Topical therapies		
Benzoyl peroxide	A	I, II
Topical antibiotics (eg, clindamycin and erythromycin)	A	I, II
Combination of topical antibiotics and benzoyl peroxide	A	I
Topical retinoids (eg, tretinoin, adapalene, and tazarotene)	A	I, II
Combination of topical retinoids and benzoyl peroxide/topical antibiotic	A	I, II
Azelaic acid	A	I
Dapsone	A	I, II
Salicylic acid	B	II
Systemic antibiotics		
Tetracyclines (eg, tetracycline, doxycycline, and minocycline)	A	I, II
Macrolides (eg, azithromycin and erythromycin)	A	I
Trimethoprim (with or without sulfamethoxazole)	B	II
Limiting treatment duration and concomitant/maintenance topical therapy	A	I, II
Hormonal agents		
Combined oral contraceptives	A	I
Spironolactone	B	II, III
Flutamide	C	III
Oral corticosteroids	B	II
Isotretinoin		
Conventional dosing	A	I, II
Low-dose treatment for moderate acne	A	I, II
Monitoring	B	II
iPLEDGE and contraception	A	II
Miscellaneous therapies and physical modalities		
Chemical peels	B	II, III
Intralesional steroids	C	III
Complementary and alternative therapies (eg, tea tree oil, herbal, and biofeedback)	B	II
Role of diet in acne effect of glycemic index	B	II
Dairy consumption	B	II

Data from Reference 74.

The Alliance recommendations statements were as follows[73]:

1. Retinoids have an essential role in treatment of acne. For most patients with inflammatory acne, comedonal acne, or both, a topical retinoid plus benzoyl peroxide is first-line therapy.[29,74,75]
2. The role of antibiotics in acne therapy has changed. Neither topical nor systemic antibiotics should be used as monotherapy for acne treatment.[75,77]
3. Oral isotretinoin should be first-line therapy for very severe (cystic and conglobate) acne.[75]
4. Oral isotretinoin therapy should proceed until full clearance of acne. Additional studies are needed to define a total cumulative dose that maintains remission.
5. Acne flare with oral isotretinoin can be minimized by initiating therapy at a low dose.
6. Most patients with acne should receive maintenance therapy with a topical retinoid.
7. Azelaic acid cream 20% or gel 15% is a useful acne treatment in pregnant women and patients with acne and PIH.
8. At present, devices that use laser, intense pulsed light, or photodynamic therapy should not be considered first-line treatment for inflammatory acne.
9. A minority of women 25 years of age have acne lesions localized only to the lower face. Topical retinoids with or without benzoyl peroxide are important components in therapy of adult acne.
10. Early and effective treatment is important to minimize potential risk for acne scarring.

General Information Regarding Efficacy and Safety

The guidelines and recommendations of the American Academy of Dermatology considered the efficacy and safety of various treatments, such as topical agents, systemic antibacterial agents, hormonal agents, isotretinoin, miscellaneous therapies, complementary and alternative therapies, and dietary restriction, based on levels of evidence and best clinical practice.[74] More specific information about the efficacy and safety of each of these specific modalities is outlined below in sections on each individual agent.

Alternative Drug Treatments

Complementary and Alternative Medications People with acne often turn to complementary and alternative medicine (CAM), such as herbal medicine, acupuncture, and dietary modifications, because of their concerns about the adverse effects of conventional medicines. Although these products might be well tolerated, very limited data exist regarding their safety and efficacy.

A systematic review of CAM treatments for acne in 2006 identified 15 randomized controlled trials covering diverse approaches such as *Aloe vera*, pyridoxine, fruit-derived acids, kampo (Japanese herbal medicine), and ayurvedic herbal treatments.[78] Although mechanisms of potential benefit for some were biologically plausible, the included studies were of poor quality and inconclusive.

Another systematic review of 17 traditional Chinese medicine randomized controlled trials found some benefit for acupuncture with moxibustion that was better than Western medicines, but the quality of included studies was limited.[78,79]

A review of studies published from 2007 to 2010 showed most studies were level of evidence grade D. Two studies of grade A concluded that topical tea tree oil 5% gel and gluconolactone are efficacious in mild-to-moderate acne, with the latter agent comparable with benzoyl peroxide 5%. No data supported these claims, and one study predated the review dimensions (published in 1992). Tea tree oil contains terpinen-4-ol, which appears to have some antimicrobial activity. One grade B study compared tea tree oil 5% against benzoyl peroxide 5% without placebo and concluded tea tree oil provided slower relief but less discomfort.[80]

A systematic review of four randomized controlled trials of tea tree oil in 2000 did not find conclusive evidence of benefit.[81] Tea tree oil continues to be studied for its efficacy and safety in acne.[82,83]

There is increasing interest in the use of CAM as adjuvant or single therapies: in America, 7% people report using a complementary medicine, and 2% report seeing a complementary medicine practitioner.[84] Traditional Chinese medicine has been widely used to treat acne for many years, based on a diagnosis from a traditional Chinese medicine perspective according to the different syndromes of acne.

The Cochrane collaboration undertook a systematic review, reported in 2015, to assess the effectiveness and safety of any CAM in the management of acne vulgaris.[83] This included 35 studies, with a total of 3,227 participants in parallel-group randomized controlled trials (or the first phase data of randomized cross-over trials) of any kind of CAM, compared with no treatment, placebo, or other

active therapies, in people with a diagnosis of acne vulgaris. The primary outcome was improvement of clinical signs assessed through skin lesion counts. Some evidence from single studies showed low-glycemic load diet, tea tree oil, and pollen bee venom (PBV) may have an effect reducing total skin lesion counts and acne severity scores. However, small sample sizes and poor methodological quality limited the strength of the evidence. Evidence from other existing randomized controlled trials does not support the use of herbal medicine, acupuncture, or wet-cupping therapy for the treatment of acne vulgaris. The evidence for a secondary outcome (number of participants with remission) for herbal medicine versus antibiotic was uncertain. Two trials reported QOL showed the benefit of herbal medicine compared with western drugs. From the review of 31 studies, the Cochrane review cautioned there is a lack of evidence to support the use of other CAMs, such as aloe vera, copaiba essential oil, dried fruit of *Berberis vulgaris*, or seaweed oligosaccharides for the treatment of this condition. Most studies were done in a traditional Chinese medicine context; therefore, results might be less generalizable to western medicine. The review highlights potential adverse effects from herbal medicine (dizziness, dry mouth, nausea, diarrhea, or stomach upset); acupuncture (pain, itchiness, or redness) and tea tree oil gel (pruritus, dryness, burning sensations, and skin flaking).[83]

A 2018 review focused on the use of essential oils and aromatherapy in acne, examining existing evidence from small pilot studies.[85] It reaffirmed there is only weak clinical evidence that tea tree oil 5% may be used as an alternative acne therapy. Several agents may be helpful as complementary therapy due to biologic plausibility, including lactobacillus-fermented *Chamaecyparis obtuse*, copaiba, sandalwood oil, rosemary extract, jeju essential oil, and Korean citrus, but concluded there is little supportive clinical evidence.

The use of botanical preparations that are nonstandardized should be discouraged in favor of traditional quality-controlled preparations that have evidence of efficacy. The lack of appropriate data, absence of quality assessment, and inconsistencies in search methodology suggest that CAM cannot be recommended for acne therapy at this time.

Glycolic Acid Another agent considered alternative therapy for acne vulgaris is glycolic acid. The efficacy and tolerability of a 0.1% retinaldehyde/6% glycolic acid combination (Diacneal) has been evaluated for mild-to-moderate acne vulgaris.[86] Physician and patient ratings of acne symptom severity and tolerance performed at baseline and months 1, 2, and 3 showed mean numbers of papules, pustules, and comedones were significantly reduced from month 1 on,

demonstrating that glycolic acid is effective and well tolerated in mild-to-moderate acne vulgaris.

Both glycolic acid-based, salicylic acid or salicylic acid derivative-based, (eg, lipohydroxyacid) and amino fruit acid-peeling preparations have been used in the treatment of acne. There is very little evidence from clinical trials published in peer-reviewed literature supporting the efficacy of peeling regimens.[68] Topical corneolytics, including retinaldehyde/glycolic acid or lactic acid, induce a comedolytic effect and may also facilitate skin absorption of topical drugs.[64] Further research on the use of peeling in the treatment of acne needs to be conducted to establish best practices for this modality.

Hydroquinone To control pigmentation, hydroquinone, which reversibly damages melanocytes, has been used as a hypopigmenting agent in concentrations of 2% to 4%, in preparations of clear or tinted gels, which are more drying, and as vanishing or opaque, flesh-tinted creams, with or without α-hydroxy acids or sunscreens. Hydroquinone causes fading of epidermal but not dermal pigmentation. Onset of response is usually 3 to 4 weeks, and the depigmentation lasts for 2 to 6 months but is reversible. While effective in the removal of melanin, hydroquinone has been clinically found to be a possible carcinogen and causes a blue-black discoloration known as ochronosis.[87]

After considering new data and information on the safety of hydroquinone, the FDA issued a proposed ruling in 2006 about hydroquinone products. The FDA proposed reversing earlier rules that hydroquinone is generally recognized as safe and effective. The FDA has not yet issued a final ruling on the status of nonprescription hydroquinone, and many physicians consider a ban unnecessary, given the lack of convincing evidence of carcinogenic risk to humans and the rarity of ochronosis occurrence.

Treatment of Scarring Drug and nondrug measures for scar resolution are important in acne vulgaris because many patients are scarred despite adequate treatment and scarring carries an emotional toll. Interventions for atrophic scars might be aided through early identification of patients at risk using a risk assessment tool for scar development. One such tool incorporates four factors: worst ever severity of acne, duration of acne, family history of atrophic acne scars, and lesion manipulation behaviors.[88]

Effective procedures for treatment of scarring focus on resurfacing techniques. For patients with mild scarring, nonprescription α-hydroxy acids may be used, while severe scarring may be corrected with other treatment modalities that require consultation with a dermatologist. Dermabrasion, local or

subcuticular excision, collagen implants, chemical peels (eg, 70% glycolic acid, trichloroacetic acid), and laser therapy have been used to improve scarring. Atrophic scars can be treated with laser resurfacing. Usually the scar is not completely removed, but a more cosmetically acceptable result is achieved. Keloids and hypertrophic scars can be treated with intralesional triamcinolone, cryotherapy, topical steroids, and silicone sheeting. Surgical options for scars include excision, augmentation with collagen or fat, chemical peels, subcision, and injection of autologous fibroblasts.

Special Populations

About 20% of young infants (2-3 months of age) develop papules, pustules, and less commonly closed or open comedones, primarily on the cheeks, due to placental transfer of maternal androgens (neonatal acne). The acne subsides within a few months with regular maturation. Boys are affected more often than girls because of a transient increase in testosterone secretion during the third and fourth month of intrauterine life. *Malassezia* spp. may be involved in pathogenesis.[36] Resolution occurs without therapy.[89] Infants with neonatal acne may have more severe teenage acne.[36]

The treatment of acne in children is similar to treatment for adults. Because topical therapies may be more irritating in children, initiation with low concentrations is preferred. Systemic treatments should be reserved for more extensive cases. Erythromycin is preferred over tetracyclines for children younger than 9 years of age because tetracyclines can affect growing cartilage and teeth.

Although treatment with isotretinoin has numerous potential minor adverse effects in patients of all ages, an uncommon complication in young patients is premature epiphyseal closure. This generally occurs when isotretinoin is administered in high doses, thus limiting long-term therapy.

There is a growing population of women seeking acne therapy and a clinical perception that acne in women requires systemic treatment. Recent analyses of clinical trials have shown that topical therapy can be efficacious in this group. Most patients have an acne presentation similar to adolescent acne, with mixed inflammatory and noninflammatory lesions on multiple facial areas (not limited to the mandibular area). Topical therapy with a retinoid and antimicrobial can be a good option. Data support the use of retinoids, including adapalene/benzoyl peroxide in both 0.1% and 0.3% concentrations, tretinoin 0.04%, and a retinaldehyde 0.1%/glycolic acid/6% cream. Among antimicrobial agents, both dapsone and clindamycin/benzoyl peroxide have shown efficacy if a topical

retinoid is added. Azelaic acid 15% gel has also shown good results in a small study. Hormonal therapy, including oral contraceptives (OCs), can play an important role in management of acne in women and is typically used in combination with topical acne therapy.[73]

Selecting appropriate treatment in pregnant women can be challenging because many acne therapies are teratogenic; all topical and especially oral retinoids should be avoided. Oral therapies, such as tetracyclines and antiandrogens, are also contraindicated in pregnancy. Topical and oral treatment with erythromycin may be considered.

Acne in skin of color is an increasing problem, presenting unique challenges. Postinflammatory hyperpigmentation (PIH), a hypermelanotic reaction to skin inflammation, is a common occurrence in patients with acne, particularly in those with darker skin and those who excoriate their lesions, affecting all genders and ages. It has a prolonged duration and can be more bothersome than active acne lesions. Prevention (including sun protection) and early treatment of underlying acne-associated inflammation effectively is a primary approach to PIH management. Chemical peels, lasers, and other light therapies may also be used for PIH; however, these methods can also cause pigmentation problems so should be used with care. Topical retinoids also improve pigmentation by inhibiting melanosome transfer to keratinocytes and increasing epidermal turnover, lessening pigmentation. It is important for the patient to be aware that many PIH lesions resolve spontaneously, but slowly.[73]

Although combination therapy is now the standard of care in acne, concerns exist with the increased potential irritation and dryness in skin of color. Although individual medications can be titrated or applied at different times of day to avoid irritation, this is not always practical or desirable. There is a paucity of clinical studies that evaluate the safety and efficacy of acne medications in skin of color. One study has examined susceptibility to irritation in Fitzpatrick skin types I to III versus types IV to VI and found subjects with darker skin were not more susceptible and tolerability was comparable across the two groups. Hispanic subjects were not more susceptible to irritation compared with total study groups.[90]

Drug Class Information

This section reviews the pharmacology and mechanisms as related to pathophysiology for pharmacologic options recommended in the guidelines for mild, moderate, and severe acne. It will also review evidence of efficacy and safety as well as kinetics, interactions, dosing, and administration when relevant.

Topical Therapies Topical therapy agents that are available over the counter or by prescription. The choice of therapy can be influenced by age of the patient, site of involvement, extent and severity of disease, and patient preference. Topical therapies may be used as monotherapy, in combination with other topical agents, or in combination with oral agents in both initial control and maintenance. Strength of recommendations for treatment of acne with topical therapies is shown in **Table 113-2**. Commonly used topical acne therapies include benzoyl peroxide, salicylic acid, antibiotics, combination antibiotics with benzoyl peroxide, retinoids, retinoid with benzoyl peroxide, retinoid with antibiotic, azelaic acid, and sulfone agents.[73]

TABLE 113-2 Monitoring of Medications Used in Acne Treatment and Maintenance Therapy

Medications	Adverse Drug Effects	Monitoring Parameters	Comments
Exfoliants			
Resorcinol	Irritant and sensitizer.	Degree and/or changes in signs or symptoms of irritancy (redness, discomfort, peeling, skin breakdown, or dermatitis).	Should not be applied to large areas of the skin or on broken skin.
Sulfur	Avoid eye contact—slight ophthalmic and skin irritation.	Degree and/or changes in signs or symptoms of irritancy (redness, discomfort, peeling, skin breakdown, or dermatitis). Use should be discontinued if excessive irritation results.	
Salicylic acid	Mild irritant—burning and reddening, local skin peeling.	Degree and/or changes in signs or symptoms of irritancy (redness, discomfort, peeling, skin breakdown, or dermatitis).	Begin with a low concentration and increase as tolerance develops. Not a sensitizer.
Retinoids			
Isotretinoin	Side effects: mucocutaneous (most common), musculoskeletal, and ophthalmic systems. Common: dryness of mucus membranes (lips, mouth, eyes, nose) dry skin, itching, hair loss, thirst, back pain, myalgia, headaches, and central nervous system effects. Increased cholesterol. Teratogenic. Sun sensitivity. Depression and suicide—controversial.	Test for pregnancy twice before starting. Contraceptive measures must be started 1 month prior, continued during the 2 months of treatment and for at least 1 month after stopping treatment (but normally 4 months). Laboratory monitoring during therapy should include triglycerides, cholesterol, transaminases, and complete blood counts (before, during and after treatment). Degree and/or changes in signs or symptoms of irritancy to skin (redness, discomfort, peeling, skin breakdown, or dermatitis). Degree and/or changes in signs or symptoms of irritancy to mucous membranes (mouth, nose, eyes). Instances of headache or central nervous system symptoms. Note prior psychiatric symptoms, monitor patients at each visit for early recognition of changes in mood or psychological well-being (before, during, and after treatment).	Drying agents must be discontinued. Sun-avoidance strategies and sunscreen use recommended. Vitamin A supplementation. Use moisturizers (lip balm, nasal moisturizers, eye lubricants, temporary removal of contacts). Most adverse effects, such as cheilitis, and dry nose, eyes and mouth, are temporary and resolve after the drug is discontinued. Advise patients about a possible risk of depression and suicidal behavior.
Tretinoin/retinoic acid	Common: erythema, dryness, burning, photosensitization. Rare: true contact allergy. Use cautiously in pregnancy. (Irritation: tazarotene > retinoic acid > adapalene)	Degree and/or changes in signs or symptoms of irritancy to skin (redness, discomfort, peeling, skin breakdown, or dermatitis). Skin changes in areas of sun exposure—dermatitis or hives.	Additive effects with concomitant topical drying medications, such as products with high concentrations of alcohol, astringents, or abrasive soaps. Gels and creams are less irritating than solutions. Sun-avoidance strategies and sunscreen use recommended.
Adapalene	Side effects include erythema, xerosis, burning and desquamation. Less irritation than other retinoids. Photoirritation or sensitization.	Degree and/or changes in signs or symptoms of irritancy to skin (redness, discomfort, peeling, skin breakdown, or dermatitis). Skin changes in areas of sun exposure—dermatitis or hives.	Less photosensitivity than other agents. Sun-avoidance strategies and sunscreen use recommended.
Tazarotene	Side effects include irritation, erythema, xerosis, burning, and desquamation.	Skin changes in areas of sun exposure—dermatitis or hives.	Contraindicated in pregnancy due to the large surface area. Short contact therapy, 1-5 minutes every other night, gradually increasing to overnight advocated for dosing in patients with sensitive skin. Oily complexions may tolerate twice daily, short contact time.
Topical Antimicrobial Agents			
Benzoyl peroxide	Dryness and peeling appear after a few days, erythema, burning, pruritus. Rare reports of contact allergic dermatitis. May bleach hair and clothing. Body odor, odor on clothes and bedsheets. Irritation is concentration dependent—most frequent with 10% gel. Irritation from gels used as vehicles—water-based < alcohol = acetone	Once tolerance is achieved, the strength may be increased to 5% or the base changed to the acetone or alcohol gels, or to paste. Degree and/or changes in signs or symptoms of irritancy to skin (redness, discomfort, peeling, skin breakdown, or dermatitis). Hives.	Increased skin irritation or drying effect with other medications, soaps, and cosmetics with strong drying effect. Chemically incompatible with retinoic acid. Cross-reactions with other sensitizers, such as Peruvian balsam, cinnamon, and other benzoic acid derivatives (topical anesthetics).
Clindamycin	Erythema, peeling, itching, dryness, and burning.	Signs or symptoms of irritancy to skin (redness, discomfort, peeling, skin breakdown, or dermatitis).	

Oral Antibiotics			
Erythromycin	Gastrointestinal upset (nausea, vomiting, diarrhea). Vaginal candidiasis.	If gastrointestinal adverse effects occur, monitor hydration. Vaginal discharge.	Drug interactions: Inhibits CYP1A2 and CYP3A4: carbamazepine, cyclosporine, theophylline, and warfarin. Safe in pregnant women and children.
Tetracyclines	Gastrointestinal intolerance: (tetracycline > erythromycin > doxycycline = minocycline). Vaginal candidiasis. Photosensitivity is dose-dependent (doxycycline > tetracycline).	Vaginal discharge. Skin changes in areas of sun exposure—dermatitis or hives.	Contraindicated in pregnant women or in children younger than 9 years of age. Absorption decreased by food, chelated by antacids and milk. To be taken on an empty stomach.
Minocycline	Drug-induced lupus. Pigment changes in skin, mucous membranes, and teeth. Hepatitis. Urticaria. Dose-related dizziness (resolves with dose titration). Autoimmune hepatitis and hypersensitivity syndrome.	Vaginal discharge. Skin changes in areas of sun exposure—dermatitis or hives. Changes or discoloration of skin, teeth, or mucous membranes. Monitor degree of dizziness as dose is titrated. Signs of hypersensitivity syndrome: fever, dermatitis, blistering reactions; systemic symptoms such as malaise, changes in blood pressure, or renal function.	Contraindicated in pregnant women or in children younger than 9 years of age. Decreased gastrointestinal absorption with Fe, Ca, Mg, Al. Sun-avoidance strategies and sunscreen use recommended.
Doxycycline	Gastrointestinal upset. Photosensitizer (especially at higher doses).	If gastrointestinal side effects occur, monitor hydration. Skin changes in areas of sun exposure—dermatitis or hives.	Contraindicated in pregnant women or in children younger than 9 years of age. Sun-avoidance strategies and sunscreen use recommended.
Antisebum			
Combination oral contraceptives	Breakthrough bleeding, headache. Serious: venous thromboembolism, hepatotoxicity.	Spotting or bleeding.	Oral antibiotics may decrease contraceptive efficacy—(significance controversial).
Spironolactone	Common: hyperkalemia, menstrual irregularity, gynecomastia, breast tenderness	Menstrual signs. Breast changes.	
Anti-inflammatory			
Azelaic acid	Primary: pruritus, burning, stinging, and tingling. Other: erythema, dryness, rash, peeling, irritation, dermatitis, and contact dermatitis in less than 1% of patients.	Skin changes in areas of sun exposure—dermatitis or hives.	Adverse reactions are generally transient and mild in nature.
Dapsone	Short- and long-term safety and efficacy demonstrated. Peeling, dryness, and erythema.	Skin changes in areas of sun exposure—dermatitis or hives.	Does not induce phototoxicity or photoallergy in human dermal safety studies. Medications such as rifampin, anticonvulsants, trimethoprim/sulfamethoxazole, and St John's wort may increase formation of dapsone hydroxylamine (toxicity).

Al, aluminum; Ca, calcium; CYP, cytochrome P450; Fe, iron; Mg, magnesium.

Exfoliants (Peeling Agents) Exfoliants induce continuous mild drying and peeling by primary irritation, damaging the superficial layers of the skin, and inciting inflammation. This stimulates mitosis, thickening the epidermis, and increasing horny cells, scaling, and erythema. A decrease in sweating results in a dry, less oily surface and may superficially resolve pustular lesions.

In the past, a rabbit model was used to study the efficacy of topical exfoliants in retarding tar-induced comedone formation and accelerating their loss (comedolysis). In this animal model, retinoic acid (tretinoin) was most active, compared with benzoyl peroxide and salicylic acid, which were respectively less active. Data from peer-reviewed literature regarding the efficacy of sulfur, resorcinol, sodium sulfacetamide, aluminum chloride, and zinc are limited. Traditional nonprescription exfoliants, including phenol, resorcinol, beta-naphthol, sulfur, Vleminckx solution, and sodium thiosulfate, are weak or ineffective. These agents are not comedolytic given that they affect the superficial epidermis rather than the hair canal. They have been supplanted by superior effective agents. Linoleic acid-rich phosphatidylcholine combined with 4% nicotinamide is suggested as an emulsion treatment that may be effective in normalization of follicular hyperkeratinization, and also provide anti-inflammatory effects.[91,92]

Resorcinol Although sulfur and resorcinol have been used for many years in the treatment of acne, evidence from peer-reviewed literature supporting their efficacy is lacking.[73] The phenol derivative resorcinol is less keratolytic than salicylic acid. It is noted to be both bactericidal and fungicidal. Products containing resorcinol 1% to 2% have been used for acne, often in combination with other peeling agents such as sulfur or salicylic acid. The FDA considers resorcinol 2% and resorcinol monoacetate 3%, in combination with sulfur 3% to 8%, to be safe and effective and that the combination may enhance the activity of sulfur. However, the FDA is not convinced that resorcinol and resorcinol acetate are safe and effective when used as single ingredients, and has placed such products in category II (not generally recognized as safe and effective, or misbranded).[92]

Resorcinol is an irritant and sensitizer and should not be applied to large areas of the skin or on broken skin. It produces a reversible, dark brown scale on some dark-skinned individuals.

Protective packaging is important as resorcinol is reactive to light and oxygen. It has good solubility in both water and alcohol and is heat stabile. Thus, it is incorporated into a variety of products, including emulsions.[93]

Salicylic Acid Salicylic acid, a β-hydroxy acid, is a comedolytic agent that is available over the counter in 0.5% to 2% strengths. Clinical trials demonstrating the efficacy or safety of salicylic acid in acne are limited, although it has been used for many years.[73] It is a natural ingredient in many plants such as willow tree or willow bark, and it penetrates the pilosebaceous unit. The comedolytic action depends on concentration: concentrations in commercial preparations (<2%-3%) are generally low. Concentrations less than 2% may in fact increase keratinization, while those between 3% and 6% are keratolytic, softening the horny layer and producing shedding of scales. Its mechanism remains unresolved, attributed to either reduced cohesion of corneocytes or shedding of epidermal cells, rather than breakdown of keratin.

Salicylic acid has no effect on the mitotic activity of normal epidermis and does not influence disordered cornification.[94] It may provide mild antibacterial value, as it is active against *P. acnes*. It offers slight anti-inflammatory activity at concentrations ranging from 0.5% to 5%. Its efficacy against comedones helps to prevent development of inflamed lesions, thus providing a delayed efficacy.[95]

Salicylic acid is effective. As a peeling agent, its relative strength compared with others in this class varies according to the model used in measurement. It is slightly *less* potent than equal-strength benzoyl peroxide when measured with the rabbit ear animal model, and slightly *more* potent when measured with a biologic microcomedone model.[95] Its anti-inflammatory properties may help dry inflammatory lesions.[93] Its comedolytic properties are considered less potent than topical retinoids. It is often used when patients cannot tolerate a topical retinoid because of skin irritation.[96]

Its keratolytic effect may enhance the absorption of other agents. Salicylic acid is a mild irritant and may cause some degree of local skin peeling and discomfort (burning or reddening). It is not a sensitizer. Although the FDA recognizes salicylic acid as safe and effective, the compound offers no advantages over more modern topical agents such as benzoyl peroxide.[92,94,96]

Salicylic acid products are often used as first-line therapy for mild acne because of their widespread availability without a prescription. They are often available in alcohol–detergent impregnated pads as well as washes, bars, and semisolid vehicles. Both wash-off and leave-on preparations are well tolerated. Lower concentrations are sometimes combined with sulfur to produce an additive keratolytic effect. Concentrations up to 5% to 10% can be used for acne, beginning with a low concentration and increasing as tolerance to the irritation develops. However, the maximum strength allowed in nonprescription acne products is 2%. In high concentrations of 20% to 30% in hydroethanolic

vehicles, salicylic acid, either alone or in combination, can be used as a peeling agent for comedonal acne and hyperpigmentation. It has been shown to extrude closed and open comedones several days after peel, but it must be applied under strict control to offer this adjunctive benefit when treating acne vulgaris.[97]

Sulfur Sulfur medications often lessen the severity of acne, presumably because of keratolytic and antibacterial action. Sulfur helps to resolve comedones by an exfoliant action. Its popularity is due to its ability to quickly resolve pustules and papules, mask and conceal lesions (as a thick foundation lotion), and produce irritation leading to skin peeling and mild antibacterial action. Sulfur is used in the precipitated or colloidal form in concentrations of 2% to 10%, because it is practically insoluble in water and must be well dispersed. Its stability depends on effective maintenance of the dispersion.[93] Sulfur compounds (eg, sulfides, thioglycolates, sulfites, thiols, cysteines, and thioacetates) are also available and somewhat weaker. Sulfur can cause slight ophthalmic and dermatologic irritation, and patients should be cautioned to avoid eye contact. Use should be discontinued if excessive irritation results. Although it is often combined with salicylic acid or resorcinol to increase its effect, its use is limited by its offensive odor and the availability of more effective agents.[98]

Sulfur has met the criteria of the FDA Advisory Review Panel for nonprescription topical acne products and is considered safe and effective when used alone, although its antibacterial effects were not recognized by this panel. Sodium thiosulfate, zinc sulfate, and zinc sulfide were not considered safe and effective.

Topical Retinoids Topical retinoids are prescription vitamin A derivatives with well-documented, randomized, double-blind, placebo-controlled trials supporting their use for acne treatment.[74] Three active agents are available: tretinoin (0.025%-0.1% in cream, gel, or microsphere gel vehicles), adapalene (0.1%, 0.3% cream, or 0.1% lotion[98,99]), and tazarotene (0.05%, 0.1% cream, gel, or foam). Each retinoid binds to a different set of retinoic acid receptors conferring slight differences in activity, tolerability, and efficacy: tretinoin to alpha, beta, and gamma; and tazarotene and adapalene, selectively, to beta and gamma. Binding to specific nuclear receptors reduces inflammation, and inhibits sebocyte proliferation and differentiation, which reduces sebum production.

Retinoids are the most powerful available peeling agents since normal epithelial cell differentiation is a vitamin A–dependent process. There is no consensus about the relative efficacy of currently available topical retinoids (tretinoin, adapalene, tazarotene) and oral isotretinoin. Retinoids are the core of

topical therapy because of their ability to target key stages in the development of the disease: they are comedolytic, resolve the precursor microcomedone lesion, and are anti-inflammatory.

These agents act to reduce obstruction within the follicle and therefore are useful in the management of both comedonal and inflammatory acne. As a group, the retinoids are highly active peelers as they reverse abnormal keratinocyte desquamation.[99] They improve acne vulgaris by inhibiting microcomedone formation, diminishing the number of mature comedones and subsequently, inflammatory lesions. They also normalize follicular epithelium maturation and desquamation. The third-generation retinoids (ie, adapalene and tazarotene) are receptor specific. Topical retinoids, unlike isotretinoin, do not decrease production of sebum, but primarily decrease inflammation, normalize keratinocyte differentiation, and increase keratinocyte proliferation and migration.[99]

Retinoids facilitate acne clearance through secondary effects of loosening and decreasing corneocytes. This increases skin permeability, facilitates absorption of other agents, such as antimicrobials or benzoyl peroxide, and increases penetration of oral antibiotics into the follicular canal. As a result, the overall duration of antibiotic treatment decreases, and the possibility of resistance lessens. Therefore, combination products with oral or topical antimicrobials are available for increased efficacy, faster onset of effects, decreased total antibiotic use and risk of resistance, and shorter duration of treatment.[99] Retinoids may also improve and prevent postinflammatory hyperpigmentation often seen in people with darker complexions who have acne.

Retinoic acid (vitamin A acid or tretinoin) is a powerful exfoliant that slows the desquamation process, reducing numbers of both microcomedones and comedones.[31] It is not to be used in pregnant women because of risk to the fetus. Gels and creams are less irritating than solutions.

Adapalene is a stable, fast-acting, antiacne treatment that has significant anti-inflammatory and comedolytic properties.[99–103] It causes epidermal and follicular epithelium hyperplasia, increased desquamation, keratinocyte differentiation, and loosening of corneocyte connections. Its anti-inflammatory effect is due to the inhibition of oxidative metabolism of arachidonic acid and inhibition of chemotactic reponses.[103] It is better at reducing inflammatory lesions and total lesion count[104] and causes less local irritation because of its mechanisms and receptor specificity than tretinoin or tazarotene.[101–108] Release from lotions and hydroalcoholic gels is more effective than from creams and aqueous gels and a microsphere gel formulation may be less irritating.[99,104] It is

a good first-line therapy for colder climates or in patients with sensitive skin.[87]

Adapalene is generally regarded as the topical retinoid of first choice for both treatment and maintenance therapy, as it is as effective but less irritating than other topical retinoids.[60,76] It is available in fixed-dose combinations in specialized gel vehicles with benzoyl peroxide to increase the efficacy in comparison with monotherapies. This strategy allows for the synergy of adapalene effects on normalizing desquamation with reduction of inflammation due to benzoyl peroxide action against *P. acnes*. Adapalene gel 0.1% has been approved as a nonprescription product for once-daily application by patients aged 12 years and older.

Tazarotene is also a specific agent with superior efficacy to parent retinoids, reducing both noninflammatory and ILs.[53] While its exact mechanism is unknown, it is thought to activate retinoid receptors and thereby affect keratinocyte differentiation, and inhibit proinflammatory transcription factors to decrease cell proliferation and inflammation.[53] It penetrates skin but accumulates in the upper dermis. It is as effective as adapalene in reducing noninflammatory and IL counts when applied half as frequently. Compared with tretinoin, it is as effective for comedonal and more effective for inflammatory lesions when applied once daily.[107–109] Tazarotene foam 0.1% has been studied as an alternative vehicle to the gel with less systemic absorption and is a safe and effective formulation.[110,111] Tazarotene is not degraded by sunlight.[31]

The retinoid class includes the systemic agent isotretinoin, which has effects on comedogenesis and sebum control, and is reviewed below under Antisebum Agents.

Retinoids tend to produce remissions that are maintained for extended periods of time, provided the accompanying irritation does not impede patient adherence. Side effects, including dryness, peeling, erythema, and irritation, can be mitigated by reduced frequency of application. Given any single agent, higher concentrations may be more efficacious, but with greater side effects. The vehicle of any particular retinoid may also decrease tolerability.[102,103] Most retinoids are unstable and insoluble in water.

Topical retinoids are not teratogenic; however, tretinoin should be used cautiously in pregnancy and tazarotene is contraindicated. Tretinoin and adapalene are in FDA category C, while tazarotene, based on large-surface-area use in psoriasis (see Chapter 114, “Psoriasis,” is in FDA category X.[36]

Skin type and age may influence tolerability in addition to the choice of vehicle. Oily skin may be more resistant, and darker skin is more prone to

postinflammatory hyperpigmentation due to retinoid dermatitis. To decrease irritation, start with the lowest concentration and increase as tolerated. Application of retinoids should be at night, a half hour after cleansing, starting with every other night for 1 to 2 weeks to adjust to irritation. Short contact time starting with 2 minutes and adding 30 seconds per dose can be advised for patients with sensitive skin or in the winter, discontinuing and resuming after a 3-day rest if undue irritation results. Doses can be increased only after beginning with 4 to 6 weeks of the lowest concentration and least irritating vehicle. Gels and creams are less irritating than solutions. Adapalene and tazarotene are photo-irritants (not photosensitizers), and sun avoidance and sunscreen use are imperative.[99]

These agents enhance any other topical acne regimen and allow for maintenance of clearance after discontinuation of oral therapy. Since retinoids are ideal for comedonal acne, when used in combination with other agents, they can address all acne variants. Three topical agents are available that contain retinoids in combination with other products: adapalene 0.1%/ benzoyl peroxide 2.5%, approved for use in patients aged 9 years or older, and two agents with fixed combination clindamycin phosphate 1.2%/tretinoin 0.025% gel, approved for those age 12 years or older.[73]

Some formulations of tretinoin are not photostable and should be applied in the evening. Tretinoin also may be oxidized and inactivated by the coadministration of benzoyl peroxide. It is recommended that the two agents be applied at different times. Tretinoin microsphere formulation, adapalene, and tazarotene do not have similar restrictions. Topical retinoids have been associated with an increased risk of photosensitivity; concurrent daily sunscreen can be used to reduce the risk of sunburn.

The therapy of acne in children younger than 12 years of age with products approved by the FDA has expanded. Fixed combination benzoyl peroxide 2.5%/adapalene 1% gel is approved for patients 9 years of age or older, and tretinoin 0.05% micronized tretinoin gel for patients 10 years of age or older. All other retinoids are approved by the FDA for patients 12 years of age or older. Current data show that retinoids in younger patients are effective and are not associated with increased irritation or risk.[73]

Overall, topical retinoids are the cornerstone of acne treatment and provide safe, effective, and economical means of treating all but the most severe cases of acne vulgaris. They should be the first step in moderate acne, alone or in combination with antibiotics and benzoyl peroxide, reverting to retinoids alone for maintenance once adequate results are achieved. Their lack of effect in

inducing bacterial resistance enables long-term maintenance of remission.

A Cochrane systematic evidence-based assessment of all issues regarding acne treatment with topical retinoids is planned to establish optimal treatment regimens, compare efficacy and tolerability of combination therapy, assess effect on *P. acnes* resistance, and evaluate safety.[109]

Antibacterial Agents Choices for antibacterial therapy include benzoyl peroxide, prescription topical and systemic antibiotics, and combination products. These drugs kill *P. acnes* and inhibit the production of proinflammatory mediators by organisms that are not killed.[31]

Benzoyl Peroxide Benzoyl peroxide is a bactericidal agent that has proven effective in the treatment of acne. It kills *P. acnes* through the release of free oxygen radicals and is also mildly comedolytic. No resistance to this agent has been reported, and the addition of benzoyl peroxide to regimens of antibiotic therapy enhances results and may reduce resistance development.

Benzoyl peroxide is a derivative of coal tar and was first used for acne vulgaris in the mid-1960s, becoming popular once stable formulations aimed at its heat-lability were developed in the mid-1970s.[105] These preparations are the single most useful group of topical nonprescription drugs. Used alone or in combination, benzoyl peroxide is the standard of care for mild-to-moderate papular-pustular acne.[29,39,73] It is an agent of first choice when combined with adapalene for most patients with mild-to-moderate inflammatory acne vulgaris and a second choice alternative for patients with noninflammatory comedonal acne.[29,39,73] A systematic review of 22 trials using benzoyl peroxide for acne vulgaris provided evidence that it reduces acne-lesion count, although high-quality evidence is not robust enough for firm conclusions.[112]

Benzoyl peroxide is well absorbed through the stratum corneum and concentrates in the pilosebaceous unit.[113] It has three principle actions useful in both noninflammatory and inflammatory acne. It produces powerful anaerobic antibacterial activity due to slow release of oxygen, thereby acting against gram-positive and gram-negative bacteria, yeasts, and fungi. This nonspecific antibacterial mechanism does not induce resistance with long-term use.[113] It has a rapid (within 2 hours) bactericidal effect that lasts at least 48 hours. As a result, it may decrease the number of inflamed lesions within 5 days. As an indirect effect, it induces suppression of sebum production; it does not reduce skin surface lipids, but is effective in reducing free fatty acids, which are comedogenic agents and triggers of inflammation.[113] Topical benzoyl peroxide

5% lowers free fatty acids 50% to 60% after daily application for 14 days and decreases aerobic bacteria by 84% and anaerobic bacteria (primarily *P. acnes*) by 98%.

It also produces comedolysis. While earlier rabbit model studies showed a benzoyl peroxide effect greater than that of salicylic acid, these animal comedones were not physiologic but induced by tar. More recent studies using native microcomedones show an anticomedogenic effect that is only comparatively slight, compared with tretinoin or salicylic acid.[114–116]

Finally, a supplementary benefit of benzoyl peroxide is an indirect anti-inflammatory action, which is due either to its antibacterial or oxidizing effects. This has been reported in several studies and thus can be used to support treatment of predominantly inflamed lesions.[113] The drug's antiacne effect is augmented by increased blood flow, dermal irritation, local anesthetic properties, and promotion of healing.[117–120] Because the primary effect of benzoyl peroxide is antibacterial, it is most effective for inflammatory acne. Many patients with noninflammatory comedonal acne will respond to its peeling action.

Benzoyl peroxide is available in a variety of preparations such as topical washes, foams, creams, or gels, and can be used as leave-on or wash-off agents. There is no clear superiority of different preparations in terms of effectiveness. Newer delivery systems to enhance efficacy and tolerability are also being investigated. Strengths available for acne therapy range from 2.5% to 10%. Total skin contact time and formulation can affect efficacy. Lower concentrations (eg, 2.5%-5%), water-based, and wash-off agents may be better tolerated in patients with more sensitive skin.

Cleansers containing benzoyl peroxide are available as nonprescription liquid washes and solid bars of various strengths. The desquamative and antibacterial effectiveness in a soap or wash is minimized by limited contact time and removal with proper rinsing. Alcohol and acetone gels facilitate bioavailability and may be more effective, while water-based vehicles are less irritating and better tolerated. Paste vehicles are stiffer and more drying than ointments or creams, which facilitate absorption and allow the active ingredients to stay localized.

Concentrations of 2.5%, 5%, and 10% in a water-based gel have been compared with the vehicle alone. The 2.5% formulation is equivalent to the 5% and 10% formulation in reducing the number of inflammatory lesions. The lower strength may not be as effective a peeler compared to higher strengths, which is due to an irritancy reaction. Thus, irritant side effects with the 2.5% gel are less frequent than with the 10% gel but are equivalent to the 5% gel. The lowest

concentration of benzoyl peroxide should be used for treating patients with easily irritated skin and may lessen irritation when used in combination topical therapy with comedolytic agents.

Therapy is limited by staining and bleaching of hair, bedsheets, and clothing, concentration-dependent irritation, and uncommonly contact allergy. It produces a mild primary irritant dermatitis that subsides with continued use and is more likely to occur in those with fair complexions, a tendency to irritancy, or propensity to sunburn. This irritation is dependent on the concentration and the vehicle, being higher with alcoholic gels compared with emulsion bases.[114] There are rare reports of contact allergic dermatitis. Cross-reactions with other sensitizers, notably Peruvian balsam and cinnamon, are well established. It may cross-sensitize to other benzoic acid derivatives such as topical anesthetics. Concomitant use of an abrasive cleanser may initiate or enhance sensitization.[121]

Another side effect is body odor from breakdown of the benzoyl peroxide that remains on clothing and bedsheets.

There is no indication that the normal use of benzoyl peroxide in the treatment of acne is associated with an increased risk of facial skin cancer. Although links have been made in experiments with mice, human relevance has not been established. The weak in vitro genotoxic potential is not manifested in vivo based on a lack of initiating or complete carcinogenic activity.[113] Overall, the cutaneous use of benzoyl peroxide is relatively safe, and is recognized by the FDA as category III, which means that more information is required to make a final determination of safety and efficacy for nonprescription use.[122–125] Safety is also confirmed by the American Academy of Dermatology and the German Best Guideline Acne (BGA) Monograph.[113]

Benzoyl peroxide has been used in combination with other antiacne medications, such as sulfur and chlorhydroxyquinoline, or in formulations with urea to facilitate drug delivery. No significant improvement has been demonstrated.

Benzoyl peroxide has also been combined with prescription agents to improve efficacy, reduce dosing strengths, decrease irritation, and reduce resistance of antibiotics.[126–129]

Benzoyl peroxide is often combined with topical retinoid for an antimicrobial effect or used in conjunction with an antimicrobial. It reduces the likelihood of antibiotic resistance. For long-term maintenance therapy, it is recommended as a highly efficient bactericidal agent to be added to a topical retinoid.[29,39]

Combining topical antibiotics with benzoyl peroxide has efficacy and

tolerability advantages over using either agent alone; most trials have assessed benzoyl peroxide in combination with clindamycin. Combination with erythromycin show advantages over oral tetracycline monotherapy.[130]

The adjunctive use of clindamycin/benzoyl peroxide gel with tazarotene cream promotes greater efficacy and may also enhance tolerability. Increased tolerability might be attributed to emollients in the clindamycin/benzoyl peroxide gel formulation.[131] A patented gel formulation of benzoyl peroxide 5%/clindamycin phosphate 1% (clindamycin) containing dimethicone and glycerin was studied both as a monotherapy and in combination with topical retinoid use. Certain additives, such as silicates and specific humectants, reduced irritation by maintaining barrier integrity.[132]

All single-agent preparations of benzoyl peroxide are now available without prescription. Recommend the weakest concentration (2.5%) in a water-based formulation, for anyone with a history of skin irritation, or who must use combination therapy.[132] There are many suggested routines to initiate therapy. One is to gently cleanse the skin and apply the preparation for 15 minutes the first evening, avoiding the eyes and mucous membranes. A mild stinging and reddening will appear. Each evening the time should be doubled until the product is left on for 4 hours and subsequently all night. Dryness and peeling will appear after a few days. Once tolerance is achieved, the strength may be increased to 5% or the base changed to the acetone or alcohol gels, or to paste. Alternatively, benzoyl peroxide can be applied for 2 hours for four nights, 4 hours for four nights, and then left on all night. It is important to wash the product off in the morning. Other drying agents should be discontinued. Patients with very sensitive skin or demonstrated sensitivity to benzoyl peroxide should not use the product, and it should be discontinued if irritation becomes severe upon use. Contact with eyes, lips, or mouth should be avoided.

A sunscreen is recommended if benzoyl peroxide is used. To avoid interactions, apply the sunscreen during the day and the benzoyl peroxide at night.

Comparison of Salicylic Acid and Benzoyl Peroxide Although both salicylic acid and benzoyl peroxide are used for mild-to-moderate acne, their mechanisms differ and therefore different types of acne respond to each. Benzoyl peroxide is a strong antibacterial agent, while salicylic acid acts primarily through keratolysis.

Studies have shown salicylic acid to be equal or slightly superior to benzoyl peroxide in reducing number of comedones and subsequently number of

inflammatory lesions. Any superiority salicylic acid demonstrates is likely because it interferes with an earlier step in pathogenesis—formation of the primary lesion of acne, the microcomedone.[94,96] However, studies of the compound did not use identical formulations. Instead, they compared salicylic acid cleansers to benzoyl peroxide washes and salicylic acid solutions to benzoyl peroxide creams. The effect of different bases is critical in determining differences in efficacy and therefore comparability of action since the base itself has an effect and influences penetration and duration of action.

In summary, the two products have similar efficacy, with salicylic acid noted as stronger in terms of retarding comedone formation. Benzoyl peroxide, as an antibacterial with some peeling effects, is considered the nonprescription and cosmetic gold standard for milder versions of the condition, used alone or in combination to increase efficacy and improve tolerability; however, salicylic acid is included in many of these products because of the perception of efficacy and safety for comedonal acne of type 1 or milder presentation.[95]

Topical Antibacterials Topical antibiotics for acne accumulate in the follicle, where they are thought to work through both antibacterial effects (the primary mechanism for efficacy in acne) and anti-inflammatory mechanisms. These agents are best used in combination with benzoyl peroxide (wash-off or leave-on), which increases efficacy and decreases the development of resistant bacterial strains. Monotherapy with topical antibiotics in the management of acne is not recommended because of the development of antibiotic resistance.[133,134] Macrolides, including topical erythromycin and topical clindamycin, are effective and well-tolerated, well-established acne treatments.

Clindamycin 1% solution or gel is currently the preferred topical antibiotic for acne therapy. Topical erythromycin in 2% concentration is available as a cream, gel, lotion, or pledget, but it has reduced efficacy in comparison with clindamycin because of resistance of cutaneous staphylococci and *P. acnes*.[74] Findings suggest topical erythromycin use for acne has essentially ceased. By contrast, clindamycin use is increasing.[135] More than 50% of *Propioni bacterium* acnes strains are resistant to topical macrolides. Resistant strains are usually resistant to all macrolides.[136]

Current recommendations discourage topical antibiotic monotherapy in favor of combination therapy with benzoyl peroxide and topical retinoids. Addition of benzoyl peroxide or topical retinoids to the macrolide antibiotic regimen is more effective than monotherapy and mitigates against survival of resistant *P. acnes* populations.

Clindamycin is the preferred macrolide because of potent action, lack of absorption, and its systemic use is limited because it can cause pseudomembranous colitis when given orally or by injection. It is available as a single ingredient topical preparation and can also be combined with benzoyl peroxide. A topical fixed-dose clindamycin phosphate 12% and benzoyl peroxide 30% combination gel once daily was more effective and twice daily at least as effective as clindamycin alone twice daily, with an early onset of action and an acceptable safety and tolerability profile.[135] Erythromycin is available alone and in combination with retinoic acid or benzoyl peroxide. Stable, fixed-combination agents are available with erythromycin 3%/benzoyl peroxide 5%, clindamycin 1%/benzoyl peroxide 5%, and clindamycin 1%/benzoyl peroxide 3.75%. Combination agents may enhance adherence with treatment regimens. Some topical antibiotic–benzoyl peroxide combinations require refrigeration.[68] Tolerance with these agents is excellent; clindamycin alone is pregnancy category B.[74]

Other topical antibiotics that are being studied include fluoroquinolones, such as 1% nadifloxacin cream, but are not available in the American market. Research approaches for developing new antibiotics against *P. acnes* include combining ribosomal effects of aminoglycosides molecules with bacteria-selective membrane-permeabilizing abilities in one drug.[137]

Oral Antibacterials Overview: a systematic evidence-based review of scientific evidence of the efficacy of oral antibiotics for acne was published in 2017. Due to heterogeneity in trials, there is insufficient evidence to support one type, dose, or duration of oral antibiotic over another in terms of efficacy and summarized key points.[138]

- The use of oral antibiotics is reserved for patients with moderate-to-severe inflammatory acne.
- Tetracyclines are considered first-line therapy, while macrolides and trimethoprim/sulfamethoxazole are acceptable alternative agents.
- It is recommended that oral antibiotics be prescribed with concurrent topical therapy for improved efficacy and to combat antibiotic resistance.
- The choice of antibiotic should be determined based on the side effect profile, resistance, cost, and consensus guidelines.
- Oral antibiotics used in the treatment of acne may have unintended effects on nontarget bacteria, and the clinical implications of this warrant further exploration.

Systemic antibiotics are a standard of care in the management of moderate and severe acne and treatment-resistant forms of inflammatory acne. There is evidence to support the use of tetracycline, doxycycline, minocycline, erythromycin, trimethoprim-sulfamethoxazole, trimethoprim, and azithromycin. Studies do not exist for the use of ampicillin, amoxicillin, or cephalexin. However, any antibiotic that can reduce the *P. acnes* population in vivo and interfere with the organism's ability to generate inflammatory agents should be effective.[68] Although erythromycin is effective, use should be limited to those who cannot use one of the tetracyclines (ie, pregnant women or children under 8 years of age because of the potential for damage to the skeleton or teeth). Ciprofloxacin, trimethoprim-sulfamethoxazole, and trimethoprim alone are also effective in instances where other antibiotics cannot be used or for patients who do not respond to conventional treatment.[92,139] A comparison of azithromycin with doxycycline reported doxycycline is a better option for treatment of acne vulgaris.[140]

The tetracycline antibiotic family has multiple modes of action, well-understood antibacterial effects, and anti-inflammatory effects that target an additional aspect of pathogenesis.[133,139,141] Agents, such as tetracycline, minocycline, and doxycycline, are used only as systemic agents. Through calcium chelation, they inhibit neutrophil and monocyte chemotaxis. Concentrations below the antibiotic threshold still inhibit inflammation and improve both acne vulgaris and acne rosacea.

Tetracycline is no longer the drug of choice in this family; its disadvantages include diet-related effects on absorption and the drug's lower anti-inflammatory and antibacterial activity.

The incidence of significant adverse effects with oral antibiotic use is low. However, adverse effect profiles may be helpful for each systemic antibiotic used in the treatment of acne. Vaginal candidiasis may complicate the use of all oral antibiotics.[68] Doxycycline is very commonly a photosensitizer especially at higher doses.

Minocycline has been associated with pigment deposition in the skin, mucous membranes, and teeth, particularly among patients receiving long-term therapy and/or higher doses of the medication. In some instances this is irreversible. Pigmentation occurs most often in acne scars, anterior shins, and mucous membranes. Minocycline may cause dose-related dizziness, which resolves with dose titration; urticaria; hypersensitivity syndrome, autoimmune hepatitis, a systemic lupus erythematosus-like syndrome; and serum sickness-like reactions.[68,133]

The Cochrane collaboration has conducted a review into the efficacy and safety of minocycline, examining 39 randomized controlled trials. These studies show that minocycline is an effective treatment for moderate-to-severe inflammatory acne but present no evidence to support the first-line use of minocycline in acne treatment. The drug is more lipophilic, may act more quickly, and can be taken once daily. However, people treated with minocycline are at a significantly greater risk of developing an autoimmune syndrome than those given tetracycline or no treatment.[142]

Sarecycline (Seysara) is a new, oral, narrow-spectrum tetracycline-derived antibiotic with anti-inflammatory properties. It is specifically indicated for the treatment of inflammatory lesions of non-nodular moderate-to-severe acne vulgaris in patients 9 years of age or older. The mechanism of action of in treating acne vulgaris is not known. Sarecycline should be taken once daily, with or without food, and the recommended daily dose is based on the patient's body weight (60 mg if 33-54 kg, 100 mg if 55-84 kg, and 150 mg if 85-136 kg). To reduce the risk of esophageal irritation and ulceration, sarecycline should be administered with adequate amounts of fluid.

The FDA approval of sarecycline in October 2018 was based on two identically designed, large, multicenter, randomized, double-blind, placebo-controlled, phase III studies that assessed use in a total of 2,002 participants 9 years of age or older with moderate-to-severe facial acne vulgaris. Data demonstrated that once-daily sarecycline 1.5 mg/kg significantly improved acne severity based on Investigator's Global Assessment (IGA) success and significantly reduced inflammatory lesion count versus placebo at week 12. Study 1: IGA success, 21.9% versus 10.5%, and mean absolute reduction in number of inflammatory lesions, 15.3 versus 10.2. Study 2: IGA success, 22.6% versus 15.3%, and mean absolute reduction in inflammatory lesions, 15.5 versus 11.1.[143–145]

The majority of oral antibiotic course durations follow guidelines. Costs of antibiotic therapy are reported lower for shorter courses and those using generic medications.[146]

Bacterial resistance to antibiotics It is an increasing problem particularly because therapy is directed at control over a long period of time.[133] The development of strains with unidentified mutations suggest new mechanisms of resistance are evolving. Combined resistance to clindamycin and erythromycin is much more common than resistance to tetracycline. Use of topical antibiotics can lead to resistance largely confined to the skin of treated sites, whereas oral antibiotics can lead to resistance in commensal flora at all body sites. Resistance

is more common in patients with moderate-to-severe acne and in countries with high outpatient antibiotic sales. Resistance is disseminated primarily by person-to-person contact, and thus the spread occurs frequently.

There have been an increasing number of reports of systemic infections caused by resistant *P. acnes* in nonacne patients after surgery. A transmission of factors conferring resistance to bacteria other than *P. acnes* has been described.

The most likely effect of resistance is to reduce the clinical efficacy of antibiotic-based treatment regimens to a level below that in patients with fully susceptible flora. This has been shown as a decreased clinical efficacy of topical erythromycin in clinical trials; there is no evidence to date of this effect in treatments with oral tetracycline or topical clindamycin.

Studies on *P. acnes* resistance have highlighted the need for treatment guidelines to restrict the use of antibiotics to limit the emergence of resistant strains. Patients with less severe forms of acne should not be treated with oral antibiotics, and where possible such therapy should be limited to the shortest feasible duration (eg, 6-8 weeks). Local patterns of resistance should be considered.[130] The use of systemic antibiotics should be limited (both indication and duration) and topical antibiotic monotherapy should be avoided.

There should be early use of combination therapy with retinoids. Often, when oral antibiotics are combined with topical agents, the antibiotic may be discontinued after 6 months of therapy.[147] Nearly 70% of patients with acne require antibiotics for 12 weeks or less if aggressive retinoid therapy is used during that time.[133]

Another potential strategy that had been suggested is to eliminate the use of antibiotics and combine other topical agents. Neither retinoids nor benzoyl peroxide creates selective pressure for resistance and is one combination option. Although this approach has been evaluated for efficacy and safety, there is limited evidence of its effect on microbial resistance. In one open label study of adapalene and benzoyl peroxide, baseline counts of antibiotic resistant strains of *P. acnes* were reduced by week 4.[133]

The high sensitivity of *P. acnes* to acidified nitrite suggests a useful role in the treatment of antibiotic resistant acne. Nitric oxide and its intermediates diffuse as well as oxygen and would be expected to penetrate the inflammatory lesions well. The newly developed topical nitric oxide–releasing agent holds potential in limiting antibiotic resistance.[148] Further work to optimize the pharmacokinetic delivery of nitric oxide releasers could increase bactericidal effectiveness.[149]

Stricter cross-infection control measures are recommended when assessing acne. Any topical or systemic antibiotic therapy should be combined when

possible with broad-spectrum antibacterial agents such as benzoyl peroxide. In addition, isotretinoin use should be initiated earlier in indicated patients, rather than prolonging antibiotic courses.[29,75]

Azelaic Acid Azelaic acid is mildly effective as a comedolytic, antibacterial, and anti-inflammatory agent. The agent has been used in patients with sensitive skin or of Fitzpatrick skin types IV or greater because of the lightening effect of the product on dyspigmentation.[73]

Azelaic acid possesses activity against all four pathogenic factors that produce acne. It has anti-inflammatory and antibacterial activities. Azelaic acid also normalizes keratinization, which accounts for its anticomedogenic effect. It is a competitive inhibitor of mitochondrial oxidoreductases and of 5-α-reductase, inhibiting the conversion of testosterone to 5-dehydrotestosterone. It also possesses bacteriostatic activity to both aerobic and anaerobic bacteria including *P. acnes*. Azelaic acid is an antikeratinizing agent, displaying antiproliferative cytostatic effects on keratinocytes and modulating the early and terminal phases of epidermal differentiation.[117] It may produce hypopigmentation. Inhibition of thioredoxin reductase by azelaic acid provides a rationale for its depigmenting property.

Azelaic acid 20% cream is used in the treatment of mild-to-moderate inflammatory acne, has an excellent safety profile with minimal adverse effects, and is well-tolerated in comparison with other acne treatments. The most common adverse effects, occurring in approximately 1% to 5% of patients, are pruritus, burning, stinging, and tingling. Adverse reactions are generally transient and mild in nature. Other adverse reactions, such as erythema, dryness, rash, peeling, irritation, dermatitis, and contact dermatitis, have been reported in less than 1% of patients.[150]

Azelaic acid has been shown effective in clinical trials studied with topical 2% erythromycin, topical 5% benzoyl peroxide gel, and topical 0.05% tretinoin cream in the treatment of mild-to-moderate inflammatory acne. However, the agent has limited efficacy, compared with other antiacne therapies.[68] It is an alternative to first choice therapy for comedonal and all types inflammatory acne, particularly in combination. It is an alternative to topical retinoids for maintenance therapy as its efficacy and safety profile are advantageous for long-term therapy.[29,39,73]

Azelaic acid should be applied twice a day, in the morning and evening. A majority of patients with inflammatory lesions may experience an improvement in their acne within 4 weeks of beginning treatment. However, treatment may be

continued over several months, if necessary.

Azelaic acid is in a pregnancy category B and should only be used in pregnant women if medically necessary. Patients with dark complexions should be monitored for early signs of hypopigmentation.

Dapsone Topical dapsone, a synthetic sulfone, is available as an agent for acne. Sulfones have both anti-inflammatory and antibacterial properties and may be used in sulfonamide-allergic patients. Dapsone's utility is attributable to its anti-inflammatory and antimicrobial properties that improve both inflammatory and noninflammatory acne, with more prominent effects occurring in inflammatory lesions. In clinical trials, topical dapsone showed modest-to-moderate efficacy, primarily in the reduction of inflammatory lesions.[181] Short- and long-term safety and efficacy have been demonstrated.[151,152]

Topical dapsone gel 5% was shown to be safe, minimally irritating, and effective after 12 weeks in the treatment of mild-to-moderate inflammatory facial acne in 101 adult women with sensitive skin.[153] The response to dapsone 5% gel appears to be influenced by gender, with female patients experiencing a significantly greater reduction in acne lesion counts and a significantly higher clinical success rate following 12 weeks of treatment.[154]

Topical dapsone 5% gel is available as a twice-daily agent for acne. Dapsone 7.5% gel is a once-daily reformulation of the 5% product administered twice daily. It received FDA approval for use in patients aged 12 years and older based on two 12-week, double-blind, placebo-controlled, randomized trials totaling more than 4,300 patients with acne. The studies showed the stronger once-daily product was extremely well tolerated, with application site dryness and itching rates similar to placebo. In terms of efficacy, a Global Acne Assessment Score of 0 or 1 with at least a two-grade improvement was achieved in 30% of patients assigned to dapsone 7.5% gel, compared with 21% of vehicle-treated controls.[155]

Topical dapsone is a novel addition to the treatment armamentarium, especially for patients exhibiting sensitivities or intolerance to conventional antiacne agents.[156]

Combination therapy with dapsone and topical retinoids may be indicated if comedonal components are present. Topical dapsone 5%, alone or in combination, with adapalene 0.1% or benzoyl peroxide 4% has been shown to be safe and efficacious but may be more irritating than other topical agents.[157,158]

Intralesional Steroids Intralesional corticosteroid injections are effective in the treatment of individual inflammatory acne nodules. The effect of intralesional

injection with corticosteroids (eg, triamcinolone acetonide) is a well-established and recognized treatment for large inflammatory lesions. Cystic acne improved in patients receiving intralesional steroids.[68] Rapid improvement and decreased pain are noted.

Systemic absorption of steroids may occur with intralesional injections. Adrenal suppression was observed in one study. The injection of intralesional steroids may be associated with local atrophy. Lowering the concentration and/or volume of steroid may minimize these complications.

Antisebum Agents No topical agents directly influence the production of sebum. Systemic drugs that influence sebum production include high-dose estrogens, antiandrogens (cyproterone acetate), spironolactone, and the retinoid isotretinoin. Antioxidants, such as sodium l-ascorbyl-2-phosphate 5%, may act to prevent the oxidation of sebum and studies are in preliminary stages.

Oral antiandrogens, such as spironolactone and cyproterone acetate, can also be useful in the treatment of acne. Flutamide is a nonsteroidal selective androgen receptor blocker used in the treatment of prostate cancer. It is not approved by the FDA for use in acne. While flutamide can be effective, hepatotoxicity is limiting. There is no evidence to support the use of finasteride. Use of flutamide in the treatment of acne is discouraged except where benefit warrants the risk.[74]

There are limited data to support the effectiveness of oral corticosteroids in the treatment of acne. Oral corticosteroid therapy is of temporary benefit in patients who have severe inflammatory acne. In patients who have well-documented adrenal hyperandrogenism, low-dose oral corticosteroids may be useful in treatment of acne.[68]

Oral Contraceptives Estrogen-containing oral contraceptives can be useful in the treatment of acne in some women. Those currently approved by the FDA for the management of acne contain norgestimate with ethinyl estradiol and norethindrone acetate with ethinyl estradiol. There is good evidence and consensus opinion that other estrogen-containing oral contraceptives are also equally effective.[68]

The mechanism of action of combination oral contraceptives (COCs) in the treatment of acne is based on their antiandrogenic properties. These hormones decrease androgen production at the level of the ovary and also increase sex hormone-binding globulin, binding free circulating testosterone and rendering it unavailable to bind and activate the androgen receptor. In addition, COCs reduce 5-alfa-reductase activity and block the androgen receptor.[74]

The risks of COCs must be weighed against the risks of the condition that

they are treating or preventing. If COCs are used exclusively for acne, their risks must be compared to the risks of acne. It is important to remember that FDA approval of all COCs for acne specifies that they are approved for the treatment of acne in women who also desire contraception. COCs carry cardiovascular risks, and breast cancer risks in some women, and low estrogen may affect bone mass. However, decreased risks of colorectal, ovarian, and endometrial cancers have been shown.

Oral contraceptives may improve acne for many women with clinical and laboratory findings of hyperandrogenism and in women without these findings. They may be used alone or in combination with other acne treatments.[74]

The Cochrane collaboration conducted a review in 2012 to determine the effectiveness of COCs for the treatment of facial acne compared with placebo or other active therapies. Thirty-one trials with a total of 12,579 women were reviewed.[158]

Combination oral contraceptive use reduced inflammatory and noninflammatory facial lesion counts, severity grades, and self-assessed acne in nine placebo comparison trials, according to the review. Progestins included levonorgestrel, norethindrone acetate, norgestimate, drospirenone, dienogest, and chlormadinone acetate. There were fewer clear differences in trials that compared varying progestin types, showing no superiority, little differences, or conflicting results. No conclusions could be reached regarding the effect of a COC compared with an antibiotic because there was only one underpowered trial.[158]

Most studies assessed women over six treatment cycles, which might not be adequate for a chronic condition like acne. In two trials, patients were more likely to discontinue because of adverse events, suggesting even if COCs improve acne, women might not be willing to accept long-term use for acne because of other side effects.

The review concluded that COCs should be considered for women with acne who also want an oral contraceptive.

A meta-analysis review of 32 randomized controlled trials comparing use of antibiotics to oral contraceptive agents for acne concluded that although antibiotics may be superior at 3 months, oral contraceptive agents are equivalent to antibiotics at 6 months in reducing acne lesions and may be a better first-line alternative to systemic antibiotics for long-term acne management in women.[159]

There is a need for more research into comparative effectiveness of COCs in randomized control trials, and into the acceptability and need for long-term use of COCs for acne.[158]

Spironolactone At higher doses, spironolactone is an antiandrogenic compound that decreases testosterone production and competitively inhibits binding of testosterone and dihydrotestosterone to androgen receptors in the skin. Dosages of 50 to 200 mg have been shown to be effective in acne. Spironolactone may cause hyperkalemia, particularly when higher doses are prescribed or when there is cardiac or renal compromise. It occasionally causes menstrual irregularity. A 5% spironolactone gel, studied in patients with increased sebum secretion, resulted in a decrease in the total acne lesions with no significant efficacy under the acne severity index.[160] Its use as an antiandrogen is not approved by the FDA for the treatment of acne. Given the small number and size of available studies, a 2009 Cochrane database review concluded that there are insufficient data to support the efficacy of spironolactone in the treatment of acne. Despite the lack of published data, relying on available evidence, experience, and expert opinion, the 2016 AAD work group supports the use of spironolactone in the management of acne in select women.[74]

Cyproterone Acetate Cyproterone combined with ethinyl estradiol (in the form of an oral contraceptive) has been found effective in the treatment of acne in females. Higher doses have been found more effective than lower doses. No cyproterone/estrogen-containing oral contraceptives are approved for use in the United States.[158]

Oral Corticosteroids Oral corticosteroids have two potential modes of activity in the treatment of acne. One study demonstrated that low-dose corticosteroids suppress adrenal activity in patients who have proven adrenal hyperactivity.[161] Low-dose prednisone in doses ranging from 5 to 15 mg daily, administered alone or with high estrogen containing COCs, has shown efficacy in the treatment of acne and seborrhea. Expert opinion is that short courses of higher dose oral corticosteroids may be beneficial in patients with highly inflammatory disease. Long-term adverse effects of corticosteroids prohibit use as a primary therapy for acne.[74]

Oral Isotretinoin Isotretinoin revolutionized the treatment of acne, yet its use and availability are increasingly complex. The risk of potential adverse effects must be weighed against its ability to prevent lifelong and permanent physical and psychologic scarring.[162]

Oral isotretinoin, an isomer of retinoic acid, has been used in the United States for the treatment of acne for more than 30 years and is approved by the FDA for the treatment of severe recalcitrant acne vulgaris. Its use has proven

successful for most patients with severe acne, resulting in decreased sebum production, acne lesions, and acne scarring, along with a decrease in symptoms of anxiety and depression. It has also been effectively used in the treatment of moderate acne that is either treatment-resistant or that relapses quickly after the discontinuation of oral antibiotic therapy.[68] It is the consensus of the 2016 AAD guidelines that the presence of moderate acne that is either treatment-resistant or that produces physical scarring or significant psychosocial distress is an indication for treatment with oral isotretinoin.[74]

A good understanding of this agent's mechanisms and adverse effects is important. Oral isotretinoin is a natural metabolite of vitamin A. Its mechanism is elusive, as it does not bind to retinoid receptors. It has been shown to reduce sebogenesis and may also inhibit sebaceous gland activity, growth of *P. acnes*, inflammation, and improve follicular epithelial differentiation.[163] Systemic isotretinoin exerts a primary effect on comedogenesis, causing a decrease in size and reduction in formation of new comedones.[31] Isotretinoin is the only drug treatment for acne that produces prolonged remission.

The teratogenic effects of oral retinoid therapy are well documented. Because of its teratogenicity and the potential for many other adverse effects, this drug should be prescribed only by those physicians knowledgeable in its appropriate administration and monitoring. Female patients of child-bearing potential must only be treated with oral isotretinoin if they are participating in the approved pregnancy prevention and management program (ie, iPLEDGE). Two different forms of contraception must be started 1 month before and continue at least 1 month (but normally 4 months) after therapy and pregnancy monitoring undertaken before, during, and after therapy.[162]

The efficacy of conventional isotretinoin treatment (0.5-1.0 mg/kg/day for 16-32 weeks, reaching a cumulative dose of 120 mg/kg) for acne has been well established. The approved dosage of isotretinoin is 0.5 to 2.0 mg/kg/day. The drug is usually given over a 20-week course.

Initial flaring can be minimized with a beginning isotretinoin dose of 0.5 mg/kg/day or less. There are many reports regarding the efficacy of low-dose and intermittent isotretinoin treatment. Lower doses can be used for longer time periods, with a total cumulative dose of 120 to 150 mg/kg or the dose can be lowered to 20 mg on alternate days after an initial 2 months of therapy with higher dosage.[164–166] Reports suggest that low-dose regimens are superior to other regimens (conventional or intermittent) in terms of patient satisfaction, tolerability, and efficacy for patients with moderate acne. In patients with severely inflamed acne, an even greater initial dose reduction may be required.

In the most severe cases of acne, consideration of pretreatment with oral corticosteroids may also be appropriate. Some patients experience a relapse of acne after the first course of treatment with isotretinoin. Relapses are more common in younger adults or when lower doses are used.

The 2016 AAD guidelines supports initiation of isotretinoin at 0.5 mg/kg/day when appropriate, subsequently increasing to a full dose of 1 mg/kg/day after the first month as tolerated, with a goal cumulative dose between 120 and 150 mg/kg. One recent study of 116 patients found that a cumulative dose of 220 mg/kg or more may result in lower relapse rates, but confirmation will require study in larger populations.[74]

Isotretinoin is highly lipophilic and is best absorbed when taken with food. One novel formulation is less dependent on the presence of fat in the gut for absorption.[167] When used, drying agents must be discontinued and replaced with moisturizers.

Because isotretinoin is a vitamin A derivative, it interacts with many of the biologic systems of the body, and consequently has a significant pattern of adverse effects. The pattern is similar to that seen in hypervitaminosis A. Side effects include those of the mucocutaneous (most common), musculoskeletal, and ophthalmic systems, as well as headaches and central nervous system effects. Most of the adverse effects, such as cheilitis and dry nose, eyes, and mouth, are temporary and resolve after the drug is discontinued.[162] Laboratory monitoring during therapy should include triglycerides, cholesterol, transaminases, and complete blood counts.

Mood disorders, depression, suicidal ideation, and suicides have been reported sporadically in patients taking this drug. A causal relationship has not been established. These symptoms are quite common in adolescents and young adults, the age range of patients who are likely to receive isotretinoin.

Issues regarding responsible and informed use Published data and expert opinion differ with respect to the use of isotretinoin as first-line or reserve therapy, optimal dosing, and risk of depression.[162]

Although some persist in reserving isotretinoin use only for severe acne, nodular or conglobate acne that has not responded to appropriate antibiotics and topical therapy, delaying use of isotretinoin, the most effective choice, poses an ethical problem.[168] Opinions vary on whether or not to restrict use to patients under 12 years and whether to avoid lasers, peelers, or wax epilation for at least 6 months after discontinuation of therapy.[169]

The causal relationship between the use of isotretinoin and risk of depression continues to be scrutinized with no consensus. The issue is complex as

depression and suicidal ideation occur with severe acne in the absence of isotretinoin.

There are instances in which withdrawal of isotretinoin has resulted in improved mood, and reintroduction of isotretinoin has resulted in the return of mood changes. Treatment of severe acne with isotretinoin is often associated with mood improvement.[68] There is epidemiologic evidence that the incidence of these events is lower in patients treated with isotretinoin than in an age-matched general population. There is also evidence that the risk of depressed mood is no greater during isotretinoin therapy than during therapy of an age-matched acne group treated with conservative therapy.[68]

A systematic review published in 2005 did not find any evidence to support worsening of depression after use, and some depressive scores improved with use; however, nine of these studies had limitations.[170] A retrospective cohort study in Sweden found attempted suicide increased in users, but an increased risk was present before treatment. An increased risk of attempted suicide was present 6 months after isotretinoin, suggesting patients should be monitored for suicidal behavior after treatment discontinuation.[171] A 2016 review on isotretinoin controversies, facts, and recommendations concluded despite common misperceptions, there is weak evidence for increased incidence of depression, suicidality, or inflammatory bowel disease with isotretinoin use and data indicate that transient increases in transaminases and lipid levels do not typically necessitate discontinuation of therapy.[172]

In 2017, a systematic review and meta-analysis of the literature, with 31 studies, concluded isotretinoin treatment for acne did not appear to be associated with an increased risk for depression and that the treatment of acne appears to ameliorate depressive symptoms.[173] Current literature regarding the association with depression and suicide was reexamined in 2018. It reconfirmed that while those with a personal or family history of mental disorder might be at risk, further studies are needed and no conclusions can be drawn.[174] The current literature is insufficient to support a meaningful causative association, but important study limitations exist. In the absence of definitive evidence, an idiosyncratic effect cannot be excluded. This disputed association remains an important area for future research. Given the prevalence of depression, anxiety, and suicidal ideation/suicide in the general population, and especially the adolescent population who may be candidates for isotretinoin therapy, the prescribing physician should continue to monitor for these symptoms at each visit for early recognition, advise patients about a possible risk of depression and suicidal behavior, and make therapeutic decisions within the context of each

individual patient.[74,170,171]

Light Therapy Light therapies are believed to work by killing *P. acnes* and by damaging and shrinking sebaceous glands, reducing sebum output and have few[175] or temporary[176,177] adverse effects. Light therapies may be used once or twice weekly as a course of 6 to 10 treatments, with each irradiation lasting 10 to 20 minutes.[177] *P. acnes* produce endogenous porphyrins that absorb light to form highly reactive singlet oxygen, which destroys the bacteria.[177] There is still debate about the effectiveness of different wavelengths.[177] Since porphyrins have peak absorption at blue light wavelengths, blue light is often used to treat acne. Red light is also absorbed by porphyrins and can penetrate deeper into the skin,[178] where it may directly affect inflammatory mediators. Other light therapies attempt to selectively target and damage sebaceous glands directly, reducing their size and thus sebum output.[179] These include infrared lasers, low-energy pulsed dye lasers, and radiofrequency devices.[177]

Photodynamic therapy (PDT) uses specific light-activating creams, which are absorbed into the skin and amplify the response to light therapy but tend to produce more severe adverse effects. There are concerns that PDT may interfere with the skin's natural immune mechanisms[180,181] and cause long-term skin damage.

Light therapies, previously expensive and accessed privately via dermatologists or clinics, are increasingly popular. Home-use blue light therapy is now available. Patients find it easier to comply with light treatments because of their short duration.

Very few trials compare light therapy with conventional acne treatments. The European evidence-based guidelines concluded published evidence is scarce and standardized treatment protocols and widespread experience are lacking. Due to conflicting or insufficient evidence, these guidelines did not make a recommendation for or against treatment of comedonal, MMPP, or severe papulopustular/nodular acne with monotherapy visible light, visible or infrared wavelength lasers, or intense pulsed light or PDT. Blue light has a low strength recommendation as a consideration for MMPP.[29,75] An ongoing Cochrane review protocol continues to investigate the current state of evidence for use of light therapy in acne.[182]

Pharmacologic Cleansing Options

Medicated Soaps and Washes Medicated soaps, washes, and foams may

contain topical antiseptics such as triclosan; peeling agents such as salicylic acid, sulfur; antimicrobials such as benzoyl peroxide, clindamycin, or azelaic acid, alone or in combination in low concentrations. They may be nonprescription or prescription status.[183] Most washes should remain on the skin from 15 seconds to 5 minutes followed by thorough rinsing. This limits the amount of time the active ingredient is in contact with the skin. Other cleansers are applied after washing and left on the skin without rinsing.

Quaternary ammonium compounds are cationic detergents that are inactivated quickly in the presence of organic material such as sebum. The duration of action of these products is short.

Antiseptic cleansers that have been studied include hexachlorophene, chlorhexidine, and povidone-iodine. Use of hexachlorophene has since been banned in nonprescription products by the UFDA because of neurotoxicity concerns. Bacteriostatic soaps containing hexachlorophene, carbanilides, and salicylanilides (halogenated hydroxyphenols) may alter normal flora or be acnegenic. Few ordinary soaps induce acne. However, acne patients are particularly susceptible to comedogenic contactants, and if these soaps are applied several times daily for long periods, they may become troublesome.

Soaps containing coal tar, which can induce folliculitis, are not indicated for acne.

In a very small group of patients in an 8-week, double-blind, randomized clinical trial, a combination cleanser containing triclosan, azelaic acid, and salicylic acid produced a greater histopathologic decrease in inflammatory response compared with a nonmedicated cleanser, but there was no significant difference in noninflammatory lesions in either group.[184] A rebound tendency was noted for the nonmedicated cleanser with respect to inflammatory lesions at 4 weeks. Authors concluded that nonmedicated cleansers were an easier and cheaper way of managing patients with mild acne.

Chlorhexidine inhibits in vitro growth of *P. acnes*.[185] A 4% chlorhexidine gluconate preparation in a detergent base has been shown to be as effective as benzoyl peroxide washes in patients with mild acne, and both preparations reduced the number of inflammatory and noninflammatory lesions after 8 and 12 weeks, compared with vehicle alone.[184] However, further evidence is lacking, and irritation is a side effect.[55]

Glycolic 1%, an alpha-hydroxy acid (AHA), has been used as a cleanser. Alpha-hydroxy acids cause desquamation by decreasing basal corneocyte cohesion and limiting follicular occlusion. AHA-containing formulations may be considered in the treatment of acne in light of mechanistic similarities with better

validated antikeratinization agents such as retinoids.[55]

Alcohol-detergent medicated pads, impregnated with salicylic acid 0.5%, have reduced inflammatory lesions and open comedones in mild-to-moderate acne. This type of medication is less abrasive, not rinsed off, and convenient.[186]

Alcohol-detergent wipes, swabs, or “pledgets” impregnated with antibiotics, such as clindamycin or lincomycin, are available. The antibiotic is deposited in low concentrations on the surface of the skin and may not penetrate to the depths of the pilosebaceous duct. Although patients may like the convenience and perception of using an active agent, they should not be recommended over simple cleansing.

Abrasives consist of finely divided particles of fused aluminum or plastic together with cleansing and wetting agents. Abrasives peel and remove surface debris and may assist resorption of papules and pustules. Despite vigorous rubbing, removal of comedones is not accomplished. Particles containing active agents, such as sodium tetraborate decahydrate, dissolve on use, and their abrasiveness is therefore limited.[186] The effectiveness of an abrasive cleanser with and without polyethylene granules showed no difference in results in patients with mild-to-moderate acne. These products are not indicated in most cases but may be used in a patient who responds empirically.[187]

Personalized Pharmacotherapy

The individualized treatment of certain patient groups, including infants, children, pregnant women, and persons of color, is described under Special Populations.

Providers and patients must also weigh costs and drug availability in choosing a treatment regimen. One study showed that the average total cost of treatment per episode across all age groups is US $689.06.[188] Topical retinoids and fixed-dose combination therapies are in general more expensive than benzoyl peroxide preparations. A retrospective analysis investigated adherence to oral antibiotic guideline recommendations and opportunities for cost-savings. Of 17,448 courses, 84.5% aligned with duration guidelines, although 69.0% of courses did not include concomitant topical retinoid therapy. Costs of antibiotic therapy were lower for shorter courses and those using generic medications. Mean savings of $592.26 per person could result if prolonged courses met guidelines.[189]

Laser treatments and cosmetic procedures are also very costly. The economics of long-term maintenance therapy should be borne in mind when selecting a regimen. Patients should not spend large amounts on herbals and botanicals, as

well as home remedies, given the lack of current good evidence to support their use. As acne is a chronic disease extending over many years, total cost implications are important and affect adherence and response.

Other practical considerations include the need for refrigeration of some products such as antibiotics. Local patterns of resistance should be kept in mind in choosing antibiotics. Extent and area of lesion involvement when large or inaccessible (eg, the back or trunk) as well as ease of application may determine the choice of route between topical and systemic therapy. The natural skin predilection toward oiliness versus dryness may dictate the choice of vehicle. Dietary interactions should be born in mind with certain drugs such as oral tetracycline. Sunscreens will need to be used with photosensitizers and applied as the first topical agent.

Regimens that may require more frequency of application may be difficult for students or patients whose occupation limits flexibility. The frequency of primary nonadherence to acne treatment has been characterized in terms of the complexity of multidrug acne regimens. Overall, 27% of patients did not fill all their prescriptions; with one, two, or three or more treatments, 9%, 40%, and 31%, respectively, did not fill all their prescriptions. Authors concluded some patients may not complete acne treatment because one or more of their medications were never obtained. Primary adherence to an acne treatment regimen is better when only one treatment is prescribed.[190] History of poor adherence because of intolerance of topical treatments may be countered by reducing the strength of treatment, using a different preparation of the drug, or switching to an alternative topical agent that causes less irritation.

EVALUATION OF THERAPEUTIC OUTCOMES

10 Provide a monitoring framework for patients with acne. Parameters should be monitored by the patient and recorded in a diary. Therapy should be appropriately tapered in response to improvement or resolution. The healthcare professional should be responsible for ensuring that the treatment plan remains on schedule and is effective with no adverse effects. The patient should be contacted within 2 to 3 weeks to determine progress.

Acne is poorly understood by adolescents. These patients often lack knowledge of the cause of the disorder and aggravating factors, indications for self-care versus prescription treatment, expected onset of effect, sequence of the healing process, duration of treatment, appropriate application of topical agents, maximal achievable effects, expected adverse effects, safety concerns, and the

benefit to QOL. Clinicians should review patient understanding of each of these important factors to ensure patient adherence. There is often a need to supplement counseling sessions with written materials to which the patient can refer at home.

Good adherence is the key to treatment success. Other strategies to increase adherence include use of once-daily regimens, online follow-up visits, and remote digital imaging for ongoing lesion assessment.[188,191,192] A randomized controlled trial compared the effectiveness of automated online counseling to standard web-based education on improving acne knowledge. While both models had a significant increase in knowledge from baseline, after 12 weeks, mean improvement in knowledge was higher in the automated counseling group than in the standard Website group. The automated counseling Website group rated their educational material more useful and more enjoyable to view than did the standard Website group. Internet-based patient education appears to be an effective method of improving acne knowledge among adolescents.[193]

Monitoring of the Pharmaceutical Care Plan

Tables 113-2 to 113-4 provide a guide for monitoring patients with acne. Table 113-2 outlines individual drugs, their most common adverse effects, parameters to monitor, and issues to note. **Table 113-3** outlines general effectiveness and safety end points, monitoring parameters, and degree of change and time frames for short- and long-term outcomes. **Table 113-4** is a guide for monitoring acne patients with consideration to the severity grading of acne types I through IV.

TABLE 113-3 Monitoring Therapy for Acne: Parameters and Frequency

Person Responsible and Frequencies for Monitoring:		
Patient: daily while on drug therapy; Pharmacist: every 4-8 weeks of therapy or next pharmacy visit		
Parameter	**Time Frame / Degree of Change**	**Actions**
Short-Term Effectiveness End Points (Acne Resolution/Control)		
Lesion count	Decrease by 10%-25% within 4-8 weeks, with control, or more than a 50% decrease within 2-4 months	If end points are not achieved, refer to a physician for further therapy.
Comedones	Resolve by 3-4 months	
Inflammatory lesions	Resolve within a few weeks	
Anxiety, depression	Achieve control or improvement within 2-4 months	
Long-Term Effectiveness End Points (Acne Resolution/Control)		
Progression of severity	No progression of severity	If end points are not achieved, refer to a physician for further therapy.
Recurrent episodes	Lengthening of acne-free periods throughout therapy	
Scarring or pigmentation	No further scarring or pigmentation throughout therapy	
Safety End Points (Treatment Side Effects)		
Dermatitis, increased dryness, gastrointestinal upset, photosensitivity	No adverse effects	Refer to a physician for alternate therapy, dose reduction, discontinuation or additive palliative treatment, or preventative measures for adverse effects.

TABLE 113-4 Monitoring Care Plans for Acne Types I Through IV

Acne Type	Description	Suggested Options	Follow-up Action If Patient Responds	Follow-up Action If Patient Does Not Respond in 3 Months	Adjustment in Therapy If Patient Does Not Respond Adequately to Previous Action
Type I	Mainly comedones with an occasional small inflamed papule or pustule; no scarring present	Topical retinoid or a fixed combination with a retinoid is the drug of choice; can also consider benzoyl peroxide or azelaic acid or salicylic acid	Continue until lesions are completely cleared and then stop or taper therapy	Treat as Type II acne	
Type II	Comedones and more numerous papules and pustules (mainly facial); mild scarring	Fixed-dose combination (adapalene and benzoyl peroxide) or benzoyl peroxide or topical retinoid or azelaic acid; if more severe, fixed-dose combination is preferred, with or without hormonal therapy and/or antibiotic, particularly if the trunk is involved	Continue until lesions are completely cleared and then stop or taper therapy	Treat as Type III acne	
Type III	Numerous comedones, papules and pustules, spreading to the back, chest, and shoulders, with an occasional cyst or nodule; moderate scarring	Fixed-dose combination with an oral antibiotic is preferred, oral isotretinoin or oral hormonal therapy can also be added	Oral antibiotics typically are prescribed for daily use over 4-6 months, with subsequent tapering and discontinuation as acne improves. Other agents can also be stopped or tapered at this time	Add oral contraceptive or antiandrogen (women only)	Oral isotretinoin (except in women who are or who may become pregnant); consider safety end points (potential adverse effects) before initiating therapy
Type IV	Numerous large cysts on the face, neck, and upper trunk; severe scarring	For males, monotherapy with oral isotretinoin or a retinoid fixed combination or oral antibiotics; for females, oral isotretinoin plus antiandrogenic hormonal therapy is preferred, or a fixed combination retinoid with oral antibiotics (consider high dose) and/or oral antiandrogenic hormonal therapy	Oral antibiotics typically are prescribed for daily use over 4–6 months, with subsequent tapering and discontinuation as acne improves Other agents can also be stopped or tapered at this time	If no response after 3-6 months, oral isotretinoin (except in women who are or who may become pregnant). Consider safety end points (potential adverse effects) before initiating therapy	

Data from Reference 74.

CONCLUSION

Considerable gaps remain in the understanding of acne, despite all that is known about the pathogenesis of acne and the mechanisms of effective drugs for controlling its symptoms, progression, and complications at structural, biochemical, and physiologic levels. It is still not possible to precisely define the cause of one of the most common skin diseases, nor is it possible to identify a cure for a condition that affects a very large proportion of the global population.

Postclass Engaged Learning Activity

This activity is intended to build your self-assessment skills and your ability to critically evaluate key relevant information and/or misconceptions in the patient care process, as applied to a select patient scenario. After reflecting on what you have learned about clinical presentation of acne, triggers, patients at risk, and guidelines about best practice therapy, create a small case scenario followed by a series of multiple-choice questions and answers based on a patient with noninflammatory comedonal acne. In each lead-in question, try to test key elements such as essential decisions, common misconceptions or errors. Lead-ins can address patient assessment, differential diagnosis, patient communication, investigations, drug therapy problem identification, risk factors, nonpharmacologic treatment, nonprescription treatment, prescription treatment, referral or triage, or safety. Continue the case example with sequential questions, changing the situation to provide further case details, such as complications, altered circumstances, variations. You can also retest with another variation (eg, a relative). Next, provide a second case and series of 5 to 6 questions, where the patient presents with mild-to-moderate inflammatory acne. Sequential questions can provide further circumstances, such as progressing to moderate or severe forms. Style tips: Use single best answer style (the distractors should have some element of truth to be attractive to the test-taker, but not be the most appropriate response). Have one correct answer with two distractors, or three if necessary: do not have five answer options. Avoid true-or-false and all-or-none-of-the-above items, and keep options same length. Example: Which is the most relevant information to interpret about this patient's needs when eliciting the history of their signs and symptoms? (List three choices, with one best answer.)

ABBREVIATIONS

BGA	best guideline acne
CAM	complementary and alternative medicine
COC	combination oral contraceptive
CRH	corticotropin-releasing hormone
FDA	Food and Drug Administration
GHQ	general health quality

HGL	high glycemic load
IGF	insulin-like growth factor
MMPP	mild-to-moderate papulopustular
P. acnes	*Propionibacterium acnes*
PAPA	pyogenic arthritis, pyoderma gangrenosum, acne
PBV	pollen bee venom
PDT	photodynamic therapy
QOL	quality of life
SAPHO	synovitis, acne, pustulosis, hyperostosis, osteitis syndrome
SPF	sun protection factor
TTO	time trade-off

REFERENCES

1. Cunliffe WJ, Gould DJ. Prevalence of facial acne vulgaris in late adolescence and in adults. *Br Med J*. 1979;1:1109–1110.
2. Rademaker M, Garioch JJ, Simpson NB. Acne in schoolchildren: No longer a concern for dermatologists. *BMJ*. 1989;298:1217–1219.
3. Kilkenny M, Merlin K, Plunkett A, Marks R. The prevalence of common skin conditions in Australian school children, III: Acne vulgaris. *Br J Dermatol*. 1998;139:840–845.
4. Nijsten T, Rombouts S, Lambert J. Acne is prevalent but use of its treatments is infrequent among adolescents from the general population. *J Eur Acad Dermatolog Venereol*. 2007;21:163–168.
5. Bhate K, Williams HC. Epidemiology of acne vulgaris. *Br J Dermatol*. 2013;168(3):474–485.
6. Smithard A, Glazebrook C, Williams HC. Acne prevalence, knowledge about acne and psychological morbidity in mid-adolescence: A community-based study. *Br J Dermatol*. 2001;41:577–580.
7. Pandey SS. Epidemiology of acne vulgaris. *Indian J Dermatol*. 1983;28:109–110.
8. Kubba R, Bajaj AK, Thappa DM, et al. Acne in India: Guidelines for management—IAA Consensus Document: Epidemiology of acne. *Indian J Dermatol Venereol Leprol*. 2009;75(suppl 1):S3.
9. Shalita AR. Acne vulgaris: Pathogenesis and treatment. *Cosmet Toiletries*.

1983;98:57–60.

10. Malus M, LaChance PA, Lamy L, Macaulay A, Vanasse M. Priorities in adolescent health care: The teenagers' viewpoint. *J Fam Pract*. 1987;25:159–162.
11. Rosenberg EW. Acne diet reconsidered. *Arch Dermatol*. 1981;117(4):193–195.
12. Fulton JE, Plewig G, Kligman AM. Effect of chocolate on acne vulgaris. *JAMA*. 1969;210:2071–2074.
13. Anderson PC. Foods as the cause of acne. *Am Fam Physician*. 1971;3(3): n102–n103.
14. Fulton JE, Plewig G, Kligman AM. Effect of chocolate on acne vulgaris. *JAMA*. 1969;210(11):2071–2074.
15. Adebamowo CA, Spiegelman D, Danby FW, Frazier AL, Willett WC, Holmes MD. High school dietary dairy intake and teenage acne. *J Am Acad Dermatol*. 2005;52(2):207–214.
16. Danby FW. Acne and milk, the diet myth, and beyond. *J Am Acad Dermatol*. 2005;52(2):360–362.
17. Bowers J. Diet and acne. *Dermatology World*. 2011:31–34.
18. Kim J, Ko Y, Park YK, et al. Dietary effect of lactoferrin-enriched fermented milk on skin surface lipid and clinical improvement of acne vulgaris. *Nutrition*. 2010;26(9):902–909.
19. Mueller EA, Trapp S, Frentzel A, et al. Efficacy and tolerability of oral lactoferrin supplementation in mild to moderate acne vulgaris: An exploratory study. *Curr Med Res Opin*. 2011;27(4):793–797.
20. Juhl CR, Bergholdt HKM, Miller IM, Jemec GBE, Kanters JK, Ellervik C. Dairy intake and acne vulgaris: A systematic review and meta-analysis of 78,529 children, adolescents, and young adults. *Nutrients*. 2018;10(8):1049. doi:10.3390/nu10081049.
21. Thiboutot D. Acne: Hormonal concepts and therapy. *Clin Dermatol*. 2004;22:419–428.
22. Cappel M, Mauger D, Thiboutet D. Correlation between serum levels of insulin-like growth factor 1, dehydroepiandrosterone sulfate, and dihydrotestosterone and acne lesion counts in adult women. *Arch Dermatol*. 2005;141(3):333–338.
23. Smith RN, Mann NJ, Braue A, et al. The effect of a high protein, low-glycemic load diet versus a conventional high-glycemic load diet on

biochemical parameters associated with acne vulgaris: A randomized, investigator-masked controlled trial. *J Am Acad Dermatol*. 2007;57(2):247–256.

24. Smith RN, Mann NJ, Braue A, Mäkeläinen H, Varigos GA. A low-glycemic-load diet improves symptoms in acne vulgaris patients: A randomized controlled trial. Am J Clin Nutr. 2007;86(1):107–115. doi: 10.1093/ajcn/86.1.107.
25. Smith RN, Braue A, Varigos GA, Mann NJ. The effect of a low glycemic load diet on acne vulgaris and the fatty acid composition of skin surface triglycerides. *J Dermatol Sci*. 2008;50(1):41–52.
26. Wolkenstein P, Misery L, Amici JM, et al. Smoking and dietary factors associated with moderate-to-severe acne in French adolescents and young adults: Results of a survey using a representative sample. *Dermatology*. 2015;230(1):34–39.
27. Antiga E, Verdelli A, Bonciani D, et al. Acne: A new model of immune-mediated chronic inflammatory skin disease. *Giornale Italiano di Dermatologia e Venereologia*. 2015;150(2):247–254.
28. Dréno B. What is new in the pathophysiology of acne, an overview. *J Eur Acad Dermatol Venereol*. 2017;31(S5):8–12. https://doi.org/10.1111/jdv.14374.
29. Gollnick HP, Bettoli V, Lambert J, et al. A consensus-based practical and daily guide for the treatment of acne patients. *J Eur Acad Dermatol Venereol*. 2016;30(9):1480–1490. doi:10.1111/jdv.13675.
30. Chu A. Acne vulgaris. In: Lebwohl MG, Heyman WR, Berth-Jones J, Couslon I,eds. *Treatment of Skin Diseases*. 2nd ed. Philadelphia, PA: Mosby Elsevier; 2006:6–12.
31. Dreno B, Poli F. Epidemiology of acne. *Dermatology*. 2003;206:7–10.
32. Tucker SB, Rogers S, Winkleman RK. Inflammation in acne vulgaris: Leukocyte attraction and cytotoxicity by comedonal material. *J Invest Dermatol*. 1985;74:21–25.
33. Winston MH, Shalita AR. Acne vulgaris. *Pediatr Clin North Am*. 1991;38(4):889–903.
34. Plewig G, Kligman AM. The dynamics of primary comedo formation. In: Plewig G, Kligman AM,eds.*Acne: Morphogenesis and Treatment*. New York: Springer-Verlag; 1975:58–107.
35. Puissegur-Lupo M. Acne vulgaris, treatments and their rationale. *Postgrad Med*. 1985;78(7):76–88.

36. Batra RS. Acne. In: Arndt KA, Tsu JTS,eds.*Manual of Dermatologic Therapeutics*. 7th ed. Philadelphia, PA: Lippincott, Williams and Wilkins; 2007:3–18.
37. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry. Acne vulgaris: developing drugs for treatment. 2005. Available at: http://www.fda.gov/dowloads/Drugs/GuidanceComplianceRegulatoryInfor
38. Pochi PE, Shalita AR, Straus JC, et al. Report of the consensus conference on acne classification. *J Am Acad Dermatol*. 1991;24(3):495–500.
39. Nast A, Rosumeck S, Erdmann R, Alsharif U, Dressler C, Werner RN. Methods report on the development of the European evidence-based (S3) guideline for the treatment of acne: Update 2016. *J Eur Acad Dermatol Venereol*. 2016;30(8):e1–e28. doi:10.1111/jdv.13783.
40. Harrison-Atlas R, Bernhard JD, O'Connor RC, Weinraub LF. What to do when typical teenage acne strikes. *JCOM*. 1996;3:9.
41. Chernyshov PV, Zouboulis CC, Tomas-Aragones L, et al. Quality of life measurement in acne. Position paper of the European Academy of Dermatology and Venereology Task Forces on Quality of Life and Patient Oriented Outcomes and Acne, Rosacea and Hidradenitis Suppurativa. *J Eur Acad Dermatol Venereol*. 2018;32(2):194–208. doi:10.1111/jdv.14585.
42. Pagliarello C, Di Pietro C, Tabolli S. A comprehensive health impact assessment and determinants of quality of life, health and psychological status in acne patients. *Giornale Italiano di Dermatologia e Venereologia*. 2015;150(3):303–308.
43. Chren MM, Lasek RJ, Quinn LM, et al. Skindex, a quality-of-life measure for patients with skin disease. Reliability, validity and responsiveness. *J Invest Dermatol*. 1996;107(5):707–713.
44. Finlay AY, Khan GK. Dermatology Quality of Life Index (DLQI): A simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994;19(3):210–106.
45. Girman CJ, Hartmaier S, Thiboutot D, et al. Evaluating health-related quality of life in patients with facial acne: Development of a self-administered questionnaire for clinical trials. *Qual Life Res*. 1996;5(5):481–490.
46. Gupta MA, Johnson AM, Gupta AK. The development of an acne quality of life scale: Reliability, validity and relationship to subjective acne

severity in mild to moderate acne vulgaris. *Acta Derm Venereol*. 1998;78(6):451–456.

47. Wang KC, Zane LT. Recent advances in acne vulgaris research: Insights and clinical implications. In: James WD, ed.*Advances in Dermatology*. Philadelphia, PA: Elsevier; 2008:197–209.
48. Johnson BA, Nunley JR. Topical therapy for acne vulgaris: How do you choose the best drug for each patient? *Postgrad Med J*. 2000; 107(3):69–80.
49. Steinhoff M, Schauber J, Leyden JJ. New insights into rosacea pathophysiology: A review of recent findings. *J Am Acad Dermatol*. 2013;69:S15–S26.
50. Habif TP. Acne, rosacea, and related disorders. In: Klein EA, Menczer BS,eds.*Clinical Dermatology*. Toronto: Mosby, 1990:756.
51. Kelly AP. Acne and related disorders. In: Sams WM, Lynch PJ,eds.*Principles and Practice of Dermatology*. New York: Churchill Livingstone; 1990:1014.
52. MacDonald Hull S, Sunliffe WJ. The use of a corticosteroid cream for immediate reduction in the clinical signs of acne vulgaris. *Acta Derm Venereol*. 1989;69(5):452–453.
53. Brodell RT, O'Brien MR. Topical corticosteroid-induced acne: Three treatment strategies to break the "addiction cycle". *Postgrad Med*. 1999;106(6):225–229.
54. Hitch JM. Acneform eruption induced by drugs and chemicals. *JAMA*. 1969;200:879.
55. Stringer T, Nagler A, Orlow SJ, Oza VS. Clinical evidence for washing and cleansers in acne vulgaris: A systematic review. *J Dermatol Treatment*. 2018;29(7):688–693. doi:10.1080/09546634.2018.1442552.
56. Choi YS, Suh HS, Yoon MY, et al. A study of the efficacy of cleansers for acne vulgaris. *J Dermatol Treat*. 2010;21(3):201–205.
57. Boothroyd S. Topical therapy and formulation principles. In: Webster GF, Rawlings AV,eds.*Acne and Its Therapy*. New York: Informa Healthcare USA; 2007:253–274.
58. Food and Drug Administration. Non-prescription drugs. 2009. Available at: http://www.fda.gov/OHRMS/DOCKETS/98fr/78n-0065-npr0003.pdf.
59. Russell JJ. Topical therapy for acne. *Am Fam Physician*. 2000;61(2):357–365.

60. Epinette WW, Gresit MC. Osols II. The role of cosmetics in postadolescent acne. *Cutis*. 1982;29(5):500–514.
61. Plewig G, Kligman AM. Acne cosmetica. In: Plewig G, Kligman AM,eds.*Acne: Morphogenesis and Treatment*. New York: Springer-Verlag; 1975;226–229.
62. Mills OH, Kligman AM. Comedogenicity of sunscreens. Experimental observations in rabbits. *Arch Dermatol*. 1982;18(6):417–419.
63. Cappel M, Mauger D, Thiboutet D. Correlation between serum levels of insulin-like growth factor 1, dehydroepiandrosterone sulfate, and dihydrotestosterone and acne lesion counts in adult women. *Arch Dermatol*. 2005;141:333–338.
64. Dall'oglio F, Tedeschi A, Fabbrocini G. Cosmetics for acne: Indications and recommendations for an evidence-based approach. *Giornale Italiano di Dermatologia e Venereologia*. 2015;150(1):1–11.
65. Hoffman LK, Bhatia N, Zeichner J, Kircik LH. Topical vehicle formulations in the treatment of acne. *J Drugs Dermatol*. 2018;17(6 suppl):s6–s10.
66. Thiboutot DM. New treatments and therapeutic strategies for acne. *Arch Fam Med*. 2000;9(2):179–187.
67. Chiou WL. Low intrinsic drug activity and dominant vehicle (Placebo) effect in the topical treatment of acne vulgaris. *Int J Clin Pharmacol Therapeut*. 2012;50(6):434–437.
68. Strauss JS, Kowchk DP, Leyden JJ, et al. Guidelines of care for acne vulgaris management. *J Am Acad Dermatol*. 2007;56:651–663.
69. Ellerbroek WC. Hypotheses toward a unified field theory of human behavior with clinical application to acne vulgaris. *Perspect Biol Med*. 1973;16:240–262.
70. Hughes H, Brown BW, Lawlis GF, Fulton JE Jr. Treatment of acne vulgaris by biofeedback relaxation and cognitive imagery. *J Psychosom Res*. 1983;27:185–191.
71. Chao CM, Lai WY, Wu BY, Chang HC, Huang WS, Chen YF. A pilot study on efficacy treatment of acne vulgaris using a new method: Results of a randomized double-blind trial with Acne Dressing. *J Cosmet Sci*. 2006;57(2):95–105.
72. Rhei LD, Zatz JL, Motwani MR. Targeted delivery of actives from topical treatment products to the pilosebaceous unit. In: Webster GF, Rawlings AV,eds.*Acne and Its Therapy*. New York: Informa Healthcare USA;

2007:223–252.

73. Thiboutot DM, Dréno B, Abanmi A, et al. Practical management of acne for clinicians: An international consensus from the Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol*. 2018;78(2 suppl 1):s1–s23.e. doi:10.1016/j.jaad.2017.09.078.
74. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol*. 2016;74(5):945–973. doi:10.1016/j.jaad.2015.12.037.
75. Nast A, Dréno B, Bettoli V, et al. European evidence-based (S3) guideline for the treatment of acne: Update 2016—short version. *J Eur Acad Dermatol Venereol*. 2016;30(8):1261–1268. doi:10.1111/jdv.13776.
76. Thiboutot D, Gollnick H, Bettoli V, et al. New Insights into the management of acne: An update from the Global Alliance to Improve Outcomes in Acne Group. *J Am Acad Dermatolog*. 2009;60:S1–S50.
77. Dréno B, Thiboutot DM, Gollnick H, et al. Antibiotic stewardship in dermatology: Limiting antibiotic use in acne. *Eur J Dermatol*. 2014;24(3):330–334. doi:10.1684/ejd.2014.2309.
78. Magin PJ, Adams J, Pond CD, et al. Topical and oral CAM in acne: A review of the empirical evidence and a consideration of its context. *Complement Ther Med*. 2006;14:62–76.
79. Li B, Chair H, Du YH, Xiao L, Xiong J. Evaluation of therapeutic effect and safety for clinical randomized and controlled trials of treatment of acne with acupuncture and moxibustion. *Zhongguo Zhen Jiu*. 2009; 29(3):247–251.
80. Reuter J, Merfort I, Schempp CM. Botanicals in dermatology: An evidence-based review. *Am J Clin Dermatol*. 2010;11:247–67.
81. Ernst E, Huntley A. Tea-tree oil: A systematic review of randomized clinical trials. *Forsch Komplementarmed Klass Natureheilkd*. 2000;7: 17–20.
82. Hammer KA. Treatment of acne with tea tree oil (melaleuca) products: A review of efficacy, tolerability and potential modes of action. *Int J Antimicrob Agents*. 2015;45(2):106–110.
83. Cae H, Liu JP, Smith CA, et al. Complementary therapies for acne vulgaris (Review). The Cochrane collaboration, issue 1. New York: Wiley; 2015. Available at: http://www.thecochranelibrary.com.
84. Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990–1997: Results of a follow-up national

survey. *JAMA*. 1998;280(18):1569–1575.

85. Winkelman WJ. Aromatherapy, botanicals, and essential oils in acne. *Clin Dermatol*. 2018;36(3):299–305. doi:10.1016/j.clindermatol.2018.03.004.
86. Poli F, Ribet V, Lauze C, Adhoute H, Morinet P. Efficacy and safety of 0.1% retinaldehyde/6% glycolic acid (Diacneal) for mild to moderate acne vulgaris. A multicentre, double-blind, randomized, vehicle-controlled trial. *Dermatol*. 2005;210(suppl 1):14–21.
87. Food and Drug Administration. Non-prescription drugs. 2009. Available at: http://www.fda.gov/OHRMS/DOCKETS/98fr/78n-0065-npr0003.pdf.
88. Tan J, Thiboutot D, Gollnick H, et al. Development of an atrophic acne scar risk assessment tool. *J Eur Acad Dermatol Venereol*. 2017;31(9):1547–1554. doi:10.1111/jdv.14325.
89. Katsambas AD, Katoulis AC, Stavropoulos P. Acne neonatorum: A study of 22 cases. *Int J Dermatol*. 1999;38(2):128–130.
90. Callender VD. Fitzpatrick skin types and clindamycin phosphate 1.2%/benzoyl peroxide gel: Efficacy and tolerability of treatment in moderate to severe acne. *J Drugs Dermatol*. 2012;11(5):643–648.
91. Brown S. Therapeutic potpourri. *Dermatol Clin*. 1989;7(1):71–74.
92. Sykes NL, Webster GF. Acne: A review of optimum treatment. *Drugs*. 1994;48(1):59–70.
93. Zouboulis CC. Moderne aknetherapie. *Akt Dermatol*. 2003;29:49–57.
94. Zander E, Weisman S. Treatment of acne vulgaris with salicylic acid pads. *Clin Ther*. 1992;14:247–253.
95. Gross G. Benzoyl peroxide and salicylic acid therapy. In: Webster GF, Rawlings AV,eds.*Acne and Its Therapy*. New York: Informa Healthcare USA; 2007:117–136.
96. Shalita AR. Treatment of mild and moderate acne vulgaris with salicylic acid in an alcohol-detergent vehicle. *Cutis*. 1981;28:556–561.
97. Kligman D, Kligman AM. Salicylic acid as a peeling agent for the treatment of acne. *Cosmetic Dermatol*. 1997;10:44–47.
98. Lin AN, Reimer RJ, Carter DM. Sulfur revisited. *J Am Acad Dermatol*. 1988;18:553–558.
99. Kroshinsky D, Shalita AR. Topical retinoids. In: Webster GF, Rawlings AV,eds.*Acne and Its Therapy*. New York: Informa Healthcare USA; 2007:103–112.
100. Galvin SA, Gilbert R, Baker M, Guibal F, Tuley MR. Comparative

tolerance of adapalene 0.1% gel and six different tretinoin formulations. *Br J Dermatol*. 1998;139(suppl 52):34–40.

101. Mills OHJr., Berger RS. Irritation potential of a new topical tretinoin formulation and a commercially-available tretinoin formulation as measured by patch testing in human subjects. *J Am Acad Dermatol*. 1998;38:S11–S16.
102. Jeremy AHT, Holland DB, Roberts SG, et al. Inflammatory events are involved in acne lesion initiation. *J Invest Dermatol*. 2003;139:897–900.
103. Shroot B, Michel S. Pharmacology and chemistry of adapalene. *J Am Acad Dermatol*. 1997;36(6):S96–S103.
104. Brogden R, Goa K. Adapalene: A review of its pharmacological properties and clinical potential in the management of mild to moderate acne. *Drugs*. 1997;53(3):511–519.
105. Weiss JS, Shavin JS. Adapalene for the treatment of acne vulgaris. *J Am Acad Dermatol*. 1998;39(2):50–54.
106. Verschoore M, Langner A, Wolska M, Jablonska S, Czernielewski J, Schaefer H. Vehicle controlled study of CD 271 lotion in the topical treatment of acne vulgaris. *J Invest Dermatol*. 1993;100:221.
107. Russell JJ. Topical therapy for acne. *Am Fam Physician*. 2000;61(2): 357–365.
108. Kakita L. Tazarotene versus tretinoin or adapalene in the treatment of acne vulgaris. *J Am Acad Dermatol*. 2000;43(2 pt 3):851–854.
109. Tzellos T, Toulis KA, Dessinioti C, et al. Topical retinoids for the treatment of acne vulgaris (protocol). The Cochrane collaboration, issue 12. New York: Wiley, 2011. Available at: http://www.thecochranelibrary.com.
110. Jarratt M, Werner CP, Alio Saenz AB. Tazarotene foam versus tazarotene gel: A randomized relative bioavailability study in acne vulgaris. *Clin Drug Investig*. 2013;33(4):283–289.
111. Feldman SR, Werner CP, Alio Saenz AB. The efficacy and tolerability of tazarotene foam, 0.1%, in the treatment of acne vulgaris in 2 multicenter, randomized, vehicle-controlled, double-blind studies. *J Drugs Dermatol: JDD*. 2013;12(4):438–446.
112. Mohd Nor NH, Aziz Z. A systematic review of benzoyl peroxide for acne vulgaris. *J Dermatolog Treat*. 2013;24(5):397–386.
113. Gross G. Benzoyl peroxide and salicylic acid therapy. In: Webster GF,

Rawlings AV,eds.*Acne and Its Therapy*. New York: Informa Healthcare USA; 2007:117–136.

114. Zander E, Weisman S. Treatment of acne vulgaris with salicylic acid pads. *Clin Ther*. 1992;14:247–253.
115. Zouboulis CC. Moderne aknetherapie. *Akt Dermatol*. 2003;29:49–57.
116. Gollnick H, Schramm M. Topical drug treatments in acne. *Dermatol*. 1998;196:119–125.
117. Cotterill JA. Benzoyl peroxide. *Acta Derm Venereol*. 1980;89(suppl): 57–63.
118. Cunliffe WJ, Holland KT. The effect of benzoyl peroxide on acne. *Acta Derm Venereol*. 1981;61(3):267–269.
119. Lassus A. Local treatment of acne. A clinical study and evaluation of the effect of different concentrations of benzoyl peroxide gel. *Curr Med Res Opin*. 1981;7(6):370–373.
120. Cunliffe WJ, Dodman B, Eady R. Benzoyl peroxide in acne. *Practitioner*. 1978;220(3):470–482.
121. Maddin S. Benzoyl peroxide. *Can J Dermatol*. 1989;1(4):92.
122. Report of the Expert Advisory Committee on Dermatology. The carcinogenic activity of benzoyl peroxide. Information Letter Ottawa: Health Protection Branch (Canada); 1987;711:1–9.
123. Cunliffe WJ, Burke B. Benzoyl peroxide: Lack of sensitization. *Acta Derm Venereol*. 1982;62(5):458–459.
124. Tkach JR. Allergic contact urticaria to benzoyl peroxide. *Cutis*. 1982;29(2):187–188.
125. Rietschel RL, Duncan SH. Benzoyl peroxide reactions in an acne study group. *Contact Dermatitis*. 1982;8:323–326.
126. Bowman S, Gold M, Nasir A, Vamvakias G. Comparison of clindamycin/benzoyl peroxide, tretinoin plus clindamycin, and the combination of clindamycin/benzoyl peroxide and tretinoin plus clindamycin in the treatment of acne vulgaris: A randomized, blinded study. *J Drug Dermatol*. 2005;4(5):611–618.
127. Korkut C, Piskin S. Benzoyl peroxide, adapalene, and their combination in the treatment of acne vulgaris. *J Dermatol*. 2005;2(3):169–173.
128. Bikowski JB. Clinical experience results with clindamycin 1% benzoyl peroxide 5% gel (Duac) as monotherapy and in combination. *J Drug Dermatol*. 2005;4(2):164–171.

129. Burkhart CG, Burkhart CN. Treatment of acne vulgaris without antibiotics: Tertiary amine-benzoyl peroxide combination vs. benzoyl peroxide alone (Proactiv Solution). *Int J Dermatol*. 2007;46(1):89–93.
130. Gamble R, Dunn J, Dawson A, et al. Topical antimicrobial treatment of acne vulgaris: An evidence-based review. *Am J Clin Dermatol*. 2012;13(3):141–152.
131. Tanghetti E, Abramovits W, Solomon B, Loven K, Shalita A. Tazarotene versus tazarotene plus clindamycin/benzoyl peroxide in the treatment of acne vulgaris: A multicenter, double-blind, randomized parallel-group trial. *J Drugs Dermatol*. 2006;5(3):256–261.
132. Del Rosso JQ, Tanghetti E. The clinical impact of vehicle technology using a patented formulation of 5%/clindamycin 1% gel: Comparative assessments of skin tolerability and evaluation of combination use with a topical retinoid. *J Drug Dermatol*. 2006;5(2):160–164.
133. Webster G. Antimicrobial therapy in acne. In: Webster GF, Rawlings AV,eds.*Acne and Its Therapy*. New York: Informa Healthcare USA; 2007:97–102.
134. Austin BA, Fleischer AB Jr.. The extinction of topical erythromycin therapy for acne vulgaris and concern for the future of topical clindamycin. *J Dermatolog Treat*. 2017;28(2):145–148. doi:10.1080/09546634.2016.1214234.
135. Kawashima M, Hashimoto H, Alio Saenz AB, et al. Clindamycin phosphate 12%-benzoyl peroxide 30% fixed-dose combination gel has an effective and acceptable safety and tolerability profile for the treatment of acne vulgaris in Japanese patients: A phase III, multicentre, randomised, single-blinded, active-controlled, parallel-group study. *Br J Dermatol*. 2015;172(2):494–503.
136. Walsh TR, Efthimiou J, Dréno B. Systematic review of antibiotic resistance in acne: An increasing topical and oral threat. *Lancet Infect Dis*. 2016;16(3):e23–33. doi:10.1016/S1473-3099(15)00527-7.
137. Schmidt NW, Agak GW, Deshayes S, et al. Pentobra: A potent antibiotic with multiple layers of selective antimicrobial mechanisms against propionibacterium acnes. *J Invest Dermatol*. 2015;135(6):1581–1589.
138. Bienenfeld A, Nagler AR, Orlow SJ. Oral antibacterial therapy for acne vulgaris: An evidence-based review. *Am J Clin Dermatol*. 2017;18(4):469–490. doi:10.1007/s40257-017-0267-z.
139. Bottomly WW, Cunliffe WJ. Oral trimethoprim as a third line antibiotic in

the management of acne vulgaris. *Dermatol*. 1993;187:193–196.

140. Ullah G, Noor SM, Bhatti Z, et al. Comparison of oral azithromycin with oral doxycycline in the treatment of acne vulgaris. *J Ayub Med Coll, Abbottabad: JAMC*. 2014;26(1):64–67.
141. Dalzeil K, Dykes PJ, Marks R. The effect of tetracycline and erythromycin in a model of acne-type inflammation. *Br J Exp Pathol*. 1987;68:67–70.
142. Garner SE, Eady A, Bennett C, et al. Minocycline for acne vulgaris: Efficacy and safety (review). The Cochrane Collaboration, Issue 9. New York: Wiley; 2012. Available at: http://www.thecochranelibrary.com.
143. Deeks ED. Sarecycline: First global approval. *Drugs*. 2019;79(3):325–329. doi:10.1007/s40265-019-1053-4.
144. Zhanel G, Critchley I, Lin L-Y, Alvandi N. Microbiological profile of sarecycline, a novel targeted spectrum tetracycline for the treatment of acne vulgaris. *Antimicrob Agents Chemother*. 63(1):pii: e01297-18. doi:10.1128/AAC.01297-18.
145. Moore A, Green LJ, Bruce S, et al. Once-daily oral sarecycline 1.5 mg/kg/day is effective for moderate to severe acne vulgaris: Results from two identically designed, phase 3, randomized, double-blind clinical trials. *J Drugs Dermatol*. 2018;17(9):987–996.
146. Straight CE, Lee YH, Liu G, et al. Duration of oral antibiotic therapy for the treatment of adult acne: A retrospective analysis investigating adherence to guideline recommendations and opportunities for cost-savings. *J Am Acad Dermatol*. 2015;72(5):822–827.
147. Hughes BR, Murphy CE, Barnett J, Cunliffe WJ. Strategy of acne therapy with long-term antibiotics. *Br J Dermatol*. 1989;121:623–628.
148. Aslam I, Fleischer A, Feldman S. Emerging drugs for the treatment of acne. *Expert Opin Investig Drugs*. 2015;20(1):91–101.
149. Weller R, Price RJ, Ormerod AD, et al. Antimicrobial effect of acidified nitrite on dermatophyte fungi, Candida and bacterial skin pathogens. *J Appl Microbiol*. 2001;90(4):648–652.
150. Passi S, Picardo M, De Luca C, Nazzaro-Porro M. Mechanism of azelaic acid action in acne. *G Ital Dermatol Venereol*. 1989;10:455–463.
151. Draelos ZD, Carter E, Maloney JM, et al. Two randomized studies demonstrate the efficacy and safety of dapsone gel, 5% for the treatment of acne vulgaris. *J Am Acad Dermatol*. 2007;56(3):439.e1–10.
152. Tan J. Dapsone 5% gel: A new option in topical therapy for acne. *Skin*

Therapy Letter. 2012;17(8):1–3.

153. Lynde CW, Andriessen A. Cohort study on the treatment with dapsone 5% gel of mild to moderate inflammatory acne of the face in women. *SKINmed*. 2014;12(1):15–21.
154. Tanghetti E, Harper JC, Oefelein MG. The efficacy and tolerability of dapsone 5% gel in female vs male patients with facial acne vulgaris: Gender as a clinically relevant outcome variable. *J Drugs Dermatol: JDD*. 2012;11(12):1417–1421.
155. Jancin B. New topical agents for acne rolling out. *Clinician Reviews.* 2017. Available at: https://www.mdedge.com/clinicianreviews/article/131086/acne/new-topical-agents-acne-rolling-out. Accessed March 2, 2019.
156. Fleischer AB Jr, Shalita A, Eichenfield LF, et al. Dapsone gel 5% in combination with adapalene gel 0.1%, benzoyl peroxide gel 4% or moisturizer for the treatment of acne vulgaris: A 12-week, randomized, double-blind study. *J Drugs Dermatol*. 2010;9(1):33–40.
157. Gamble R, Dunn J, Dawson A, et al. Topical antimicrobial treatment of acne vulgaris: An evidence-based review. *Am J Clin Dermatolgol*. 2012;13(3):141–152.
158. Arowojolu AO, Gall MR, Lopez LM, et al. Combined oral contraceptive pills for treatment of acne. The Cochrane Collaboration, Issue 7. New York: Wiley; 2012. Available at: http://www.thecochranelibrary.com.
159. Koo EB, Petersen TD, Kimball AB. Meta-analysis comparing efficacy of antibiotics versus oral contraceptives in acne vulgaris. *J Am Acad Dermatol*. 2014;71(3):450–9.
160. Afzli BM, Yaghoobi E, Yaghoobi R, et al. Comparison of the efficacy of 5% topical spironolactone gel and placebo in the treatment of mild and moderate acne vulgaris: A randomized controlled trial. *J Dermatol Treat*. 2012;23(1):21–25.
161. Nader S, Rodriguez-Rigau LJ, Smith KD, Steinberger E. Acne and hyperandrogenism: Impact of lowering androgen levels with glucocorticoid treatment. *J Am Acad Dermatol*. 1984;11:256–259.
162. Lowenstein EB, Lowenstein EJ. Isotretinoin systemic therapy and the shadow cast upon dermatology's downtrodden hero. *Clin Dermatol*. 2011;29:652–661.
163. Rawlings AV. The molecular biology of retinoids and their receptors. In: Webster GF, Rawlings AV,eds.*Acne and Its Therapy*. New York: Informa

Healthcare USA; 2007:45–53.

164. Agarwal US, Besarwal RK, Bhola K. Oral isotretinoin in different dose regimens for acne vulgaris: A randomized comparative trial. *Indian J Dermatol Venereol Leprol*. 2011;77(6):688–94.
165. Lee JW, Yoo KH, Park KY, et al. Effectiveness of conventional, low-dose and intermittent oral isotretinoin in the treatment of acne: A randomized, controlled comparative study. *Br J Dermatol*. 2011;164(6):1369–1375.
166. Berk DR. Effectiveness of conventional, low-dose and intermittent oral isotretinoin in the treatment of acne: A randomized, controlled comparative study—comment. *Br J Dermatol*. 2011;165(1):205.
167. Webster GF, Leyden JJ, Gross JA. Results of a Phase III, double-blind, randomized, parallel-group, non-inferiority study evaluating the safety and efficacy of isotretinoin-Lidose in patients with severe recalcitrant nodular acne. *J Drugs Dermatol: JDD*. 2014; 13(6):665–670.
168. European Directive for systemic isotretinoin prescription. EMEA—Committee for Proprietary Medicinal Products (CPMP). 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_docun WC500010882.pdf.
169. Layton AM, Dreno B, Gollnick HPM, et al. A review of the European Directive for prescribing systemic isotretinoin for acne vulgaris. *J Eur Acad Dermatol Venereol*. 2006;20:773–776.
170. Marqueling AL, Zane LT. Depression and suicidal behavior in acne patients treated with isotretinoin: A systematic review. *Semin Cutan Med Surg*. 2005;24:92–102.
171. Sundstrom A, Alfredsson L, Sjolin-Forsberg G, Gerdén B, Bergman U, Jokinen J. Association of suicide attempts with acne and treatment with isotretinoin: Retrospective Swedish cohort study. *Br Med J*. 2010;341:c5812.
172. Bauer LB, Ornelas JN, Elston DM, Alikhan A. Isotretinoin: Controversies, facts, and recommendations. *Expert Rev Clin Pharmacol*. 2016;9(11):1435–1442. doi:10.1080/17512433.2016.1213629.
173. Huang YC, Cheng YC. Isotretinoin treatment for acne and risk of depression: A systematic review and meta-analysis. *J Am Acad Dermatol*. 2017;76(6):1068–1076.e9. doi:10.1016/j.jaad.2016.12.028.
174. Oliveira JM, Sobreira G, Velosa J, Telles Correia D, Filipe P. Association of isotretinoin with depression and suicide: A review of current literature.

J Cutan Med Surg. 2018;22(1):58–64. doi:10.1177/1203475417719052.

175. Elman M, Slatkine M, Harth Y. The effective treatment of acne vulgaris by a high-intensity, narrow band 405–420 nm light source. *J Cosmet Laser Ther*. 2003;5:111–117.
176. Friedman PM, Jih MH, Kimyai-Asadi A, Goldberg LH. Treatment of inflammatory facial acne vulgaris with the 1450-nm diode laser: A pilot study. *Dermatol Surg*. 2004;30:147–151.
177. Mariwalla K, Rohrer TE. Use of lasers and light-based therapies for treatment of acne vulgaris. *Lasers Surg Med*. 2005;37(5):333–342.
178. Ross EV. Optical treatments for acne. *Dermatol Ther*. 2005;18(3):253–266.
179. Lloyd JR, Mirkov M. Selective photothermolysis of the sebaceous glands for acne treatment. *Lasers Surg Med*. 2002;31(2):115–120.
180. Böhm M, Luger TA. The pilosebaceous unit is part of the skin immune system. *Dermatol*. 1998;196(1):75–79.
181. Seaton E, Mouser PE, Charakida A, Alam S, Seldon PM, Chu AC. Investigation of the mechanism of action of nonablative pulsed-dye laser therapy in photorejuvenation and inflammatory acne vulgaris. *Br J Dermatol*. 2006;155(4):748–755.
182. Car J, Car M, Hamilton F, et al. Light therapies for acne (protocol). The Cochrane Collaboration, Issue 4. New York: Wiley; 2009. Available at: http://www.thecochranelibrary.com.
183. Choi YS, Suh HS, Yoon MY, et al. A study of the efficacy of cleansers for acne vulgaris. *J Dermatol Treat*. 2010;21(3):201–205.
184. Shalita AR. Treatment of mild and moderate acne vulgaris with salicylic acid in an alcohol-detergent vehicle. *Cutis*. 1982;28(11): 556–568.
185. Stoughton RB, Leyden JJ. Efficacy of 4 percent chlorhexidine gluconate skin cleanser in the treatment of acne vulgaris. *Cutis*. 1987;39(6):551–553.
186. Arndt KA. Acne. In: Arndt KA, ed.*Manual of Dermatologic Therapeutics*. 4th ed. Toronto: Little Brown; 1989:3–13.
187. Fulgha CC, Caltalano PM, Childers RC, et al. Abrasive cleansing in the management of acne vulgaris. *Arch Dermatol*. 1982;118(9):658–659.
188. Yentzer BA, Ade RA, Fountain JM, et al. Simplifying regimens promotes greater adherence and outcomes with topical acne medications: A randomized controlled trial. *Cutis*. 2012;86(2):103–108.
189. Straight CE, Lee YH, Liu G, et al. Duration of oral antibiotic therapy for

the treatment of adult acne: A retrospective analysis investigating adherence to guideline recommendations and opportunities for cost-savings. *J Am Acad Dermatol*. 2015;72(5):822–827.

190. Anderson KL, Dothard EH, Huang KE, et al. Frequency of primary nonadherence to acne treatment. *JAMA Dermatology*. 2015;151(6):623–626.
191. Watson AJ, Bergman H, Williams CM, et al. A randomized trial to evaluate the efficacy of online follow-up visits in the management of acne. *Arch Dermatol*. 2010;146(4):406–411.
192. Bergman H, Tsai KY, Seo SJ, et al. Remote assessment of acne: The use of acne grading tools to evaluate digital skin images. *Telemed J E Health*. 2009;15(5):426–430.
193. Tuong W, Wang AS, Armstrong AW. Comparing the effectiveness of automated online counseling to standard web-based education on improving acne knowledge: A randomized controlled trial. *Am J Clin Dermatol*. 2015;16(1):55–60.

114

Psoriasis

Rebecca M. Law and Wayne P. Gulliver

KEY CONCEPTS

1. Patients with psoriasis have a lifelong illness that may be very visible and emotionally distressing. There is a strong need for empathy and a caring attitude in interactions with these patients.
2. Psoriasis is a progressive T-lymphocyte–mediated systemic inflammatory disease that results from a complex interplay between multiple genetic factors and environmental influences. Genetic predisposition and precipitating "trigger" factors play a role in the "march of psoriasis." This march of innate and adaptive immune responses results in clinical expressions (eg, keratinocyte proliferation) and is possibly responsible for psoriatic comorbidities.
3. Diagnosis of psoriasis is usually based on recognition of the characteristic psoriatic lesion and not based on laboratory tests.
4. Treatment goals for patients with psoriasis are to minimize signs such as plaques and scales, alleviate symptoms such as pruritus, reduce the frequency of flare-ups, ensure appropriate treatment of associated comorbid conditions such as metabolic syndrome, psoriatic arthritis or clinical depression, and minimize treatment-related morbidity.
5. Management of patients with psoriasis generally involves both nonpharmacologic and pharmacologic therapies.
6. Nonpharmacologic alternatives such as stress reduction and the liberal use of moisturizers may be very beneficial and should always be considered and initiated when appropriate.
7. Pharmacologic alternatives for psoriasis include topical agents, phototherapy, and systemic agents (both traditional and newer biologic agents).

8 Pharmacologic therapy is generally guided by the severity of disease, advancing from topical agents to phototherapy to systemic agents as needed.

9 Rotational therapy (ie, rotating systemic drug interventions) is a means to minimize drug-associated toxicities. However, continuous treatment has replaced rotational or sequential therapy and is now the standard of care for many dermatologists. Sequential therapy may be needed for biologics.

10 Some biologic agents have proven efficacy for psoriasis; however, there are differences among these agents, including mechanism of action, duration of remission, and adverse-effect profile. Biologics are often used for moderate-to-severe psoriasis and may be first-line therapy especially if comorbidities exist.

Preclass Engaged Learning Activity

What does psoriasis look like? Search online for images of the skin manifestations of the various types of psoriasis (as described in Table 114-1). In particular, for plaque psoriasis (the most common phenotype), search for images of scalp, trunk/limb, hands, and nail involvement (oil spots).

INTRODUCTION

Psoriasis is a chronic disease that waxes and wanes. It is never cured, and it is now known to be associated with multiple comorbidities including heart disease, diabetes, and the metabolic syndrome. The signs and symptoms of psoriasis may subside totally (go into remission) and then flare up again (exacerbation). Triggers include stress, seasonal changes, and some drugs. Disease severity may vary from mild to disabling. Psoriasis imposes a burden of disease that extends beyond the physical dermatologic manifestations.

1 Patients with psoriasis often have a lifelong illness that may be very visible and emotionally distressing. There is a strong need for empathy and a caring attitude in interactions with these patients. Thus, management of this condition is necessarily long-term and multifaceted, and management modalities may change according to the severity of illness at the time.

EPIDEMIOLOGY

Psoriasis is likely the most common immune-mediated inflammatory disease in North America and Europe, as it is thought to affect 17 million people, or approximately 2% of the population.[2,3] Worldwide prevalences vary between 0.1% and 3%, with reasons for variation ranging from racial to geographic and environmental.[3] Climate, sun exposure, and ethnicity are thought to affect prevalence, but correlation between latitude and prevalence is weak.[4] According to the largest population-based survey—the Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP)—the prevalence of psoriasis ranges from 1.4% in Spain to 3.3% in Canada, with the United States at 2.2% and the overall prevalence of psoriasis at 1.9%.[5] Lower frequencies of between 0.4% and 0.7% are seen for people of African and Asian descent.[4] Of interest is the fact that psoriasis is seldom seen in North and South American aboriginal Indians. It affects males and females equally.[3] Psoriasis can present at any age.[5] The majority of patients (approximately 75%) have onset before the age of 40 years,[3] but psoriasis has been observed at birth and as late as the ninth decade of life.[3] Prevalence increases are roughly linear over the life course (about 0.12% at age 1 year to 1.2% at age 18).[4] Many studies report two peak ages of onset: at 20 to 30 and again at 50 to 60 years of age.[3,5]

ETIOLOGY

2 Psoriasis is a T-lymphocyte–mediated systemic inflammatory disease that results from a complex interplay between multiple genetic factors and environmental influences. Genetic predisposition coupled with some precipitating factor triggers an abnormal immune response, resulting in the initial psoriatic skin lesions. This has been called the “march of psoraisis”[2,6] to reflect the innate and adaptive immune responses that are present. This march leads to expressions of psoriasis with keratinocyte proliferation being central to the clinical presentation of psoriasis, and is likely responsible for various comorbidities as a consequence of the chronic inflammation associated with psoriasis.[2,4] For example, there is an association between psoriasis and cardiovascular disease, which appears to be an ongoing, two-way interplay.[2,6] The concept is that systemic inflammation enhances insulin resistance, causing endothelial dysfunction, leading to atherosclerosis and coronary events.[7]

Genetics

Dermatologists have recognized the familial tendencies of psoriasis for many years. Approximately 30% of patients have a first-degree relative with psoriasis, and the risk of psoriasis increases with the number of affected relatives a patient has.[5] Monozygotic twins have a concordance rate in the 80% range. Rates of family history in a psoriasis family range between 36% and 91%.[8,9] A study using the founder population of Newfoundland and Labrador noted that more than 80% of the patients had a positive family history.

The bimodal distribution of this disease (prevalence peaking at 20-30 years and again at 50-60 years) may represent two distinct forms of psoriasis, with early onset psoriasis much more likely to possess a genetic marker highly associated with psoriasis.[5]

There are psoriasis susceptibility genes and variants that reside on various chromosomes. The psoriasis susceptibility locus 1 (*PSORS1*) on chromosome 6p is a key gene locus, accounting for up to 50% of disease heritability.[4] In 2009, studies of the Newfoundland and Labrador population confirmed that major histocompatibility complex antigen HLA-Cw6 and tumor necrosis factor (TNF)-α as major psoriasis susceptibility genes, along with interleukin (IL)-23 loci that had previously been reported.[3,10] The findings have been confirmed in multiple populations worldwide.[11]

Currently, roughly 40 additional loci are thought to be associated with psoriasis.[4] Corresponding genes to these loci are involved in pathogenesis pathways in the immune system (adaptive and innate). There appears to be a general role for T cells and a specific role for TH17 lymphocytes in psoriasis pathogenesis and as indicators of psoriasis risk.[4]

Predisposing Factors and Precipitating Factors

Injury to the skin, infection, drugs, smoking, alcohol consumption, obesity, and psychogenic stress have been implicated in the development of psoriasis. Examples of these precipitating factors include a horsefly bite causing skin trauma and resulting in new-onset psoriasis (known as the *Koebner phenomenon*),[12] a viral or streptococcal infection, or the use of β-adrenergic blockers.[13] Factors exacerbating preexisting psoriasis include drugs[13] (eg, lithium, nonsteroidal anti-inflammatory drugs [NSAIDs], antimalarials such as chloroquine, β-adrenergic blockers, fluoxetine, and withdrawal of corticosteroids), and psoriatic patients commonly have exacerbations during

times of stress.[1,4,13] Smoking cigarettes has been shown in two international studies to be a risk factor for psoriasis.[14] Lifestyle intervention to mitigate risk factors has been recommended.[15]

PATHOPHYSIOLOGY

Psoriasis is a common chronic inflammatory disease that involves both adaptive and innate immunity.[4] It is an immune-mediated disease in which the skin inflammatory changes are dependent on immune cells and their cytokines.[5] The interaction between dermal dendritic cells, activated T cells of the TH-1, TH-17 lineage in concert with a multitude of cytokines and growth factors are responsible for the epidermal hyperplasia and dermal inflammation that is seen in the skin of patients with psoriasis. Cross-talk between the innate and adaptive immune system mediated by cytokines including TNF-α, interferon gamma, and interleukin 1 is a major research focus.[4]

Comorbidities

It is well documented that psoriasis patients have significant associated comorbidities.[2,4–6,14] Approximately 75% of patients will have at least one comorbid condition, and many will have multiple comorbidities.[5] Psoriatic arthritis is one of the most common and well-known extracutaneous manifestations of disease.[5,14] Other associated comorbidities include metabolic syndrome, other immune-mediated disorders such as Crohn's disease, multiple sclerosis, and some psychological illnesses (anxiety, depression, and alcoholism).[16] Also, malignancies such as cutaneous T-cell lymphoma are associated with psoriasis, and melanoma and nonmelanoma skin cancer are associated with psoriasis treatments.

The National Psoriasis Foundation published a clinical consensus on psoriasis comorbidities with recommendations for screening and addressing issues such as cardiovascular risk, metabolic syndrome, and obesity.[17] The importance of screening for comorbidities in psoriasis patients cannot be overemphasized: Nearly half of the psoriatic patients older than age 65 have at least three comorbidities, (with two-thirds of this patient population having two or more comorbidities).[18] The presence of a specific comorbidity in a patient with psoriasis may influence the choice of pharmacotherapy.

Psoriatic arthritis (PsA) usually develops after the onset of psoriasis,[3]

typically 10 years later,[16] with a range of 5 to 12 years.[5] However, 10% to 15% of patients report that the PsA appeared first.[3] The prevalence of PsA in psoriatic patients is about 30%[4,16] but varies by disease severity.[16] In one US study, the prevalences were 14% for patients with mild psoriasis, 18% for those with moderate psoriasis, and 56% for patients with severe psoriasis.[19] PsA most commonly presents as polyarticular peripheral arthritis but can vary widely with peripheral and/or axial, monoarticular, or polyarticular patterns.[5] The severity of PsA also varies widely and does not necessarily correlate with severity of skin findings.[5] TNF-α and HLA-Cw6 are linked to both PsA and psoriasis.[20] Although immunomodulating treatments for psoriasis (such as methotrexate or TNF-α inhibitors) are useful for PsA, NSAIDs effective for joint symptoms of PsA may exacerbate psoriasis.

Metabolic syndrome is a cluster of risk factors including abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance or glucose intolerance, prothrombotic state, and proinflammatory state.[17] Patients with psoriasis are at increased risk of developing the metabolic syndrome.[4,17] The syndrome is a strong predictor of cardiovascular diseases, stroke, and diabetes.[17,21,22] Patients with this syndrome are three times as likely to have a myocardial infarction (MI) or stroke, twice as likely to die from the MI or stroke, and five times as likely to develop type 2 diabetes.[17] A 2010 retrospective analysis of pooled data from three clinical trials (M02-528, CHAMPION, and REVEAL) showed that patients with psoriasis have a 28% and 12% increased 10-year risks of coronary heart disease (CHD) and stroke, respectively.[22]

Psychiatric/psychologic comorbidities include depression, suicidal ideation and suicide, anxiety, and poor self-esteem.[14] A recent meta-analysis reported that more than 25% of psoriasis patients had depressive symptoms and more than 10% were clinically depressed.[14,23] In comparison to control subjects, psoriasis patients had significantly more depression symptoms with an odds ratio (OR) of 1.57% (95% CI 1.40–1.76) for clinical depression (using the International Classification of Diseases codes) and had an OR of 4.24 (95% CI 1.53–11.76) for antidepressant use.[14,23]

Patients with psoriasis also have a decreased life expectancy and increased rates of mortality. Psoriasis is an independent risk factor for atherosclerosis, especially for younger patients with severe disease.[17] A 2006 study found that a relative risk (RR) of death for a 30-year-old person with severe psoriasis was 3.10, after controlling for traditional cardiovascular risk factors (eg, age, gender, hypertension, dyslipidemia, diabetes mellitus, smoking, body mass index [BMI],

C-reactive protein [CRP], and family history of cardiovascular disease).[17,24] Three epidemiological meta-analyses identified increased cardiovascular mortality risk (relative risk: 1.39, 1.37, 1.2) and stroke (relative risk 1.56, 1.59, and 1.21) for psoriatic patients.[4] Only patients with severe psoriasis are associated with a higher cardiovascular disease risk.[14] Moderate-to-severe psoriasis may be associated with an increased risk of chronic kidney disease.[14]

Systemic treatment of psoriasis with anti-inflammatory agents—in particular, methotrexate and some biologic therapies—may have protective effects against cardiovascular death, MI, and stroke/cerebrovascular disease.[25,26] However, the use of systemic retinoids does not.[26]

Types of Psoriasis

Plaque psoriasis, also known as *psoriasis vulgaris*, is the most common type of psoriasis (Table 114-1) and is seen in about 90% of psoriasis patients. Plaque psoriasis presents as shown in the Clinical Presentation box.

TABLE 114-1 Phenotypic Classifications of Psoriasis

Plaque (psoriasis vulgaris)
Flexural and/or intertriginous (inverse psoriasis)
Seborrheic
Scalp
Acrodermatitis of Hallopeau
Palm and/or soles
Generalized pustular psoriasis
Guttate
Erythrodermic

Up to 30% of patients with psoriasis have associated psoriatic arthritis[4] but this varies by disease severity.[16] Although nail involvement (psoriatic onychodystrophy) can occur with any type of psoriasis, it is seen in up to 90% of patients with psoriatic arthritis.[14] Fingernails are involved in about 50% of all patients with psoriasis and toenails are involved in 35% of patients.[14]

CLINICAL PRESENTATION: PSORIASIS

Signs and Symptoms of Plaque Psoriasis	Description (from Reference 14)
Lesions (plaques)	Erythematous
	Red-violet in color
	At least 0.5 cm in diameter
	Well demarcated—clearly distinguished from normal skin
	Typically covered by silver, flaking scales—scale removal is accompanied by fine points of bleeding (the "Auspitz sign")
	Lesions may develop at sites of trauma or injury (the "Koebner phenomenon")
Skin involvement	Either as single lesions at predisposed areas (eg, knees, elbows)
	Or
	Generalized over a wide BSA
	Mild psoriasis: ≤5% BSA involvement
	Moderate psoriasis: PASI ≥8 (higher in trials of biologics)
	Severe psoriasis: The rule of tens: PASI ≥10 or DLQI ≥10 or BSA ≥10% (in some phototherapy trials, BSA ≥20% used as lower limit)
	Categories in the European consensus: Mild psoriasis: BSA ≤10 and PASI ≤10 and DLQI ≤10. Moderate-to-severe psoriasis: (BSA >10 or PASI >10) and DLQI >10

Signs and Symptoms of Plaque Psoriasis	Description (from Reference 14)
Pruritus	More than 50% of patients with psoriasis have associated pruritus
	May be severe in some patients and may require treatment to minimize excoriations from constant scratching
Other associated concerns	This condition may also be physically debilitating or socially isolating
	Potential comorbidities: PsA, depression, hypertension, obesity, diabetes mellitus, Crohn's disease, anxiety, alcoholism

BSA, body surface area; DLQI, Dermatology Life Quality Index; PASI, psoriasis area and severity index; PsA, psoriatic arthritis.

DIAGNOSTIC CONSIDERATIONS

3 The diagnosis of psoriasis is a diagnosis based on recognition of the characteristic psoriatic lesion and not on laboratory tests. Diagnostic testing is rarely performed as a biopsy may be suggested but is not diagnostic of psoriasis.

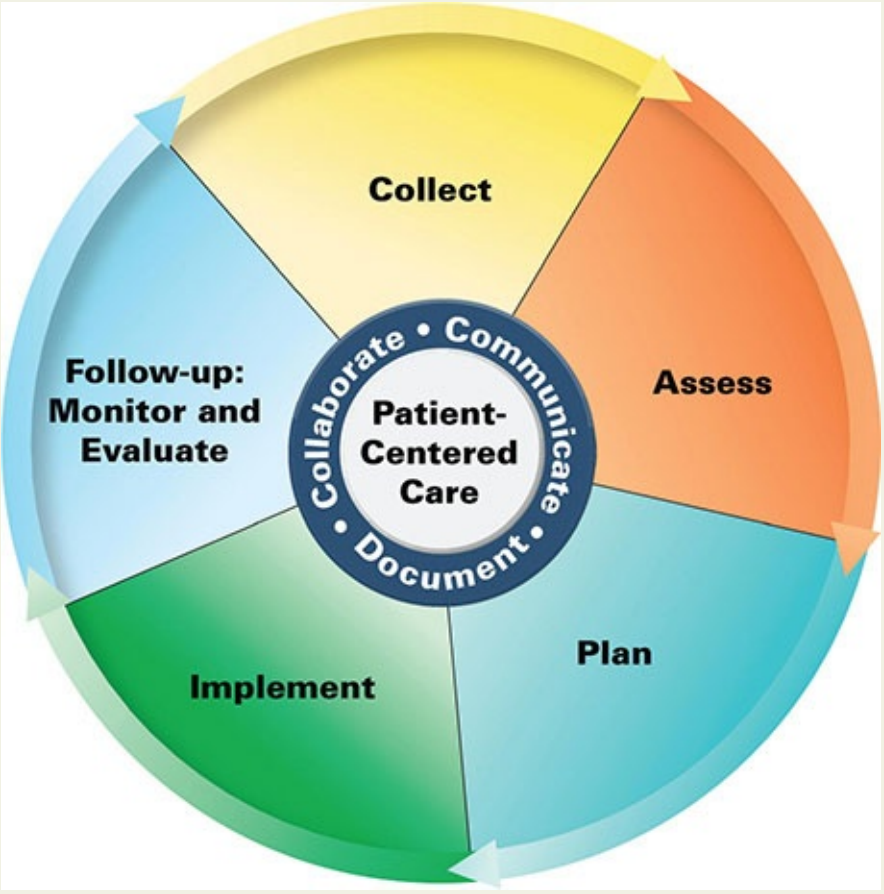
Psoriasis is traditionally classified into mild, moderate, or severe disease. In 2011, a European consensus (19 countries) formalized the definition of disease severity and treatment goals and defined plaque psoriasis severity as two main categories: mild versus moderate-to-severe. This became the basis for defining treatment goals in the 2015 European guidelines.[27,28] Both classification systems are in use today. Most recently, in 2017 the Medical Board of the National Psoriasis Foundation (NPF) used a consensus-building (Delphi) process to establish treatment goals/targets in psoriasis (discussed later).[29] In clinical practice, assessment of the severity of disease includes both an objective evaluation of the extent and symptoms as well as a subjective evaluation of the impact of disease on the patient's quality of life.[14] Assessment typically includes measures of symptom and involvement such as body surface area (BSA), Psoriasis Area and Severity Index (PASI), or Physician's Global Assessment (static PGA), as well as quality-of-life measures such as the Dermatology Life Quality Index (DLQI) or the Short Form (SF-36) Health Survey.[5,14]

Classification of psoriasis as mild, moderate, or severe disease is generally based on BSA or PASI measurements (see Clinical Presentation box). Practically, to give a rough estimate of BSA involvement, palm size is

approximately 1% BSA, head and neck involvement is approximately 10% BSA, both upper limbs approximately 20% BSA, trunk involvement (front and back) approximately 30% BSA, and both lower limbs approximately 40% BSA.

TREATMENT

Treatment of psoriasis is based on managing the underlying pathophysiology. Agents that modulate the abnormal immune response, such as topical corticosteroids and biologic agents, are important treatment strategies for psoriasis. Topical therapies that affect cell turnover, such as retinoids, are also effective for psoriasis. In addition, nonpharmacologic therapies are effective adjuncts and should be considered for all patients with psoriasis. A treatment regimen should always be individualized, taking into consideration severity of disease, patient responses, and tolerability to various interventions. Furthermore, if comorbidities exist, they must be taken into treatment considerations and managed early. Optimal psoriasis care needs to maintain a focus on the patient's overall health-related quality of life.



Patient Care Process for Management of Psoriasis

Collect

- Patient characteristics (eg, age, sex, pregnancy status)
- Patient medical history (personal and family)
- Patient description of history of psoriasis, subjective complaints of itch, and other symptoms
- Signs associated with severity of psoriasis (eg, areas of involvement, etc.)
- Signs associated with severity of itch (eg, excoriations, sleep disturbances)
- Signs of other comorbid illnesses (psoriatic arthritis, depression, anxiety, poor self-esteem, Crohn's disease, and metabolic syndrome–associated diseases, eg, dyslipidemia, hypertension, obesity, etc.)
- Signs of secondary skin infections
- Symptoms of stress or distress (personal and family/caregiver)

Assess

- Type of psoriasis (plaque psoriasis being most common)
- Severity of psoriasis—classify into mild, moderate, or severe disease. Mild psoriasis: ≤5% BSA involvement. Moderate psoriasis: PASI ≥8 (higher in trials of biologics). Severe psoriasis: The rule of tens: PASI ≥10 or DLQI ≥10 or BSA ≥10% (in some phototherapy trials, BSA ≥20% used as lower limit). Categories in the European consensus: Mild psoriasis: BSA ≤10 and PASI ≤10 and DLQI ≤10. Moderate-to-severe psoriasis: (BSA >10 or PASI >10) and DLQI >10. Both classifications are in use in North America.
- Severity of itch
- Ability/willingness to pay for medical treatment options
- Emotional concerns for patient and caregiver (if any)

Plan

- Determine an appropriate treatment approach, that is, topical or phototherapy or systemic therapy or a combination of treatments
- Determine specific therapeutic agents/treatments of choice
- Recommend the most appropriate therapies (nonpharmacologic and pharmacologic) for psoriasis
- Manage the itch with appropriate nonpharmacologic and pharmacologic

therapies

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Provide information about prevention of future flare-ups

Follow-up: Monitor and Evaluate

- Contact patient/caregiver in 1-2 weeks to follow-up about the efficacy of recommended therapies and any issues with the treatment regimen
- Ensure that appropriate monitoring parameters for efficacy and potential adverse effects have been put in place (eg, follow-up lab tests as needed)
- Reinforce preventive measures including continuation of maintenance therapy
- Ensure that patient/caregiver has been connected to other health resources as needed for follow-up (eg, a psychologist for stress reduction therapy)

**Collaborate with patient, caregivers, and other healthcare professionals.*

Desired Outcomes

4 Goals of treatment[1]:

- Minimizing or eliminating the visible signs of psoriasis, such as plaques and scales
- Alleviating pruritus and minimizing excoriations
- Reducing the frequency of flare-ups
- Ensuring appropriate treatment of associated comorbid conditions such as psoriatic arthritis, hypertension, dyslipidemia, diabetes, or clinical depression
- Screening for and managing lifestyle factors which may trigger exacerbations (eg, stress, smoking, obesity)[30]
- Minimizing nonspecific triggers such as mild trauma (scratching, piercings, tattoos), sunburn, chemical irritants, environmental/workplace factors[4]

- Providing guidance or counseling as needed (eg, stress-reduction techniques, smoking cessation programs)
- Avoiding or minimizing adverse effects from treatments used (topical, phototherapy, and/or systemic)
- Providing cost-effective therapy
- Maintaining or improving the patient's quality of life

Evaluation of Therapeutic Outcomes

Successful management of psoriasis should include not only clearance of skin lesions, which may take weeks to months depending on the severity of disease, but also control of associated conditions such as itching, and, importantly, comorbidities, including dyslipidemia, hypertension, psoriatic arthritis, and clinical depression as discussed earlier. The ultimate goal is to provide enough control of this chronic disease and its comorbidities, (if present) so that the patient's quality of life is minimally affected.

The 2011 European consensus defined induction and maintenance phases and provided separate treatment goals for induction and maintenance.[27,28] The induction phase is defined as the first 16 weeks of treatment for drugs with a rapid induction to remission (such as adalimumab or infliximab), extending the phase to 24 weeks of treatment for less rapidly effective drugs (such as methotrexate or etanercept).[28] To be considered successful therapy, a treatment regimen should result in a reduction of PASI greater than or equal to 75%, or PASI of 50% to 75% coupled with a DLQI less than 5.[28] Otherwise, treatment modifications should be considered. Treatment goals should be assessed at 10 to 16 weeks and then every 8 weeks thereafter.[28]

In 2017, the NPF-led US consensus recommended earlier treatment response targets: An acceptable treatment response at 3 months after starting new therapies (ie, induction phase) is either BSA 3% or less, or BSA improvement 75% or more from baseline; the target response at 3 months after starting new therapies is BSA 1% or less.[29] During the maintenance phase, evaluation should occur every 6 months with the target response being BSA 1% or less at every 6 months maintenance evaluation.[29]

It is important to treat beyond clearing visible skin lesions. In fact, "psoriasis is the first dermatological inflammatory disorder where the goal is to manage skin lesions and associated diseases.[30]" Comorbidities and trigger factors must be managed as early as possible.

General Approach to Treatment

5 Management of patients with psoriasis generally involves both nonpharmacologic and pharmacologic therapies. Nonpharmacologic management strategies are important and should be used for all patients with psoriasis, regardless of the severity of disease. Pharmacologic therapies are always tailored to the individual patient with psoriasis, and different treatment strategies would be used depending on psoriatic disease severity, presence or absence of comorbid illnesses, and any special considerations such as hepatic or renal dysfunction.

Nonpharmacologic Management Strategies

6 Nonpharmacologic alternatives may be very beneficial and should always be considered and initiated when appropriate.[1] These include stress-reduction strategies, moisturizers, oatmeal baths, and skin protection using sunscreens.[31]

In particular, stress reduction has been shown to improve both the extent and severity of psoriasis, and includes methods such as guided imagery and stress-management clinics. Liberal use of nonmedicated moisturizers, applied ad lib, helps to maintain skin moisture, reduces skin shedding, controls associated scaling, and may reduce pruritus. Oatmeal baths further reduce pruritus and with regular use may minimize the need for systemic antipruritic drugs.

Sunscreens, preferably with a sun protection factor (SPF) of 30 or more, should be regularly used because sunburns can trigger an exacerbation of psoriasis. Irritation to the skin should be minimized—harsh soaps or detergents should not be used. Cleansing should be done with tepid water and preferably with lipid-free and fragrance-free cleansers.[1,31]

For patients with comorbidities such as dyslipidemia, obesity, or cardiovascular disease, cessation of nicotine and alcohol consumption, diet control, and increasing physical activity are all important interventions.[2,30]

Pharmacologic Therapies

7 Pharmacologic alternatives for psoriasis are topical agents, phototherapy, and systemic agents, including biologic agents (formerly referred to as biologic response modifiers or BRMs).

Drug Treatments of First Choice

8 9 For limited or mild-to-moderate disease, topical treatments are the mainstay of care.[32] Phototherapy and photochemotherapy are used in moderate-to-severe cases.[33] For patients presenting with extensive or moderate-to-severe disease, systemic therapies with or without the use of topical treatments are the usual standard of care.[34,35] Newer systemic treatments such as biologic agents may be the treatments of choice, especially for patients with comorbidities such as PsA or if traditional systemic treatments (such as methotrexate or cyclosporine) are contraindicated.[35] See section "Systemic Therapy with Biologics" about guidelines for transitioning from traditional systemic agents to biologics. Once the disease is under control, it would be important to step down to the least potent, least toxic agent(s) that maintain(s) control. Rotational therapy (ie, rotating systemic drug interventions) may minimize drug-associated toxicities; however, continuous treatment has replaced rotational or sequential therapy and is now the standard of care for many dermatologists. Sequential therapy may be needed for biologics. Different treatment algorithms are used, depending on the severity of the plaque psoriasis (**Figs. 114-1** and **114-2**). The European consensus categorizes psoriasis as mild or moderate-to-severe with mild disease treated topically and moderate-to-severe disease treated systemically. The Canadian Psoriasis Guidelines Addendum Committee[14] and the British Association of Dermatologists have recommended first and alternate choices for biologics (if used)—see section "Systemic Therapy with Biologics" for details.

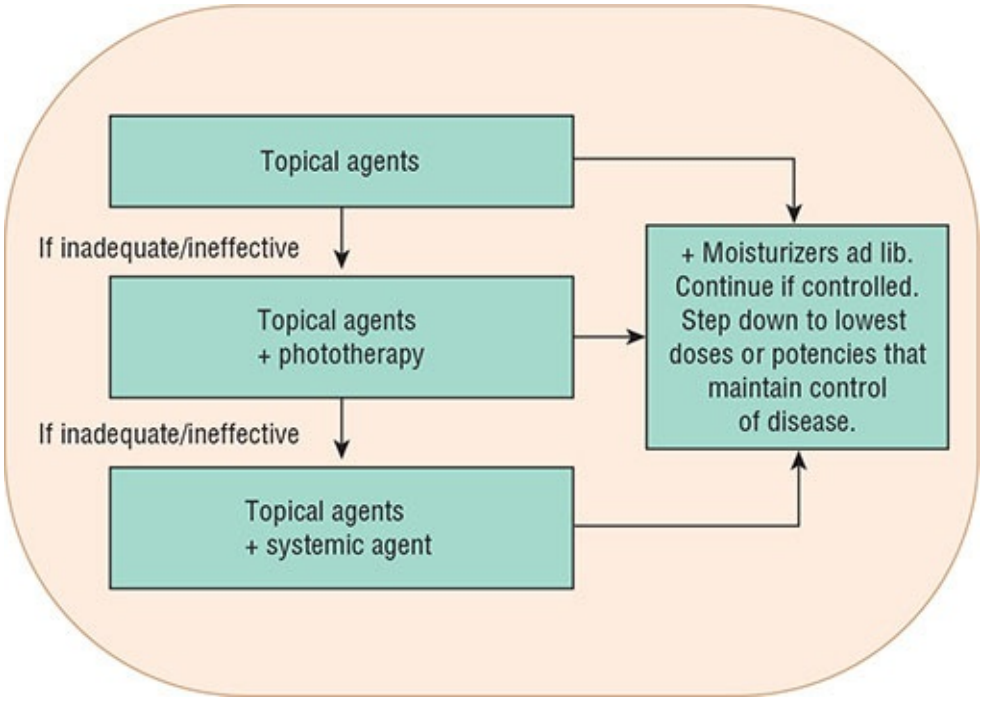


FIGURE 114-1 Treatment algorithm for mild-to-moderate psoriasis.

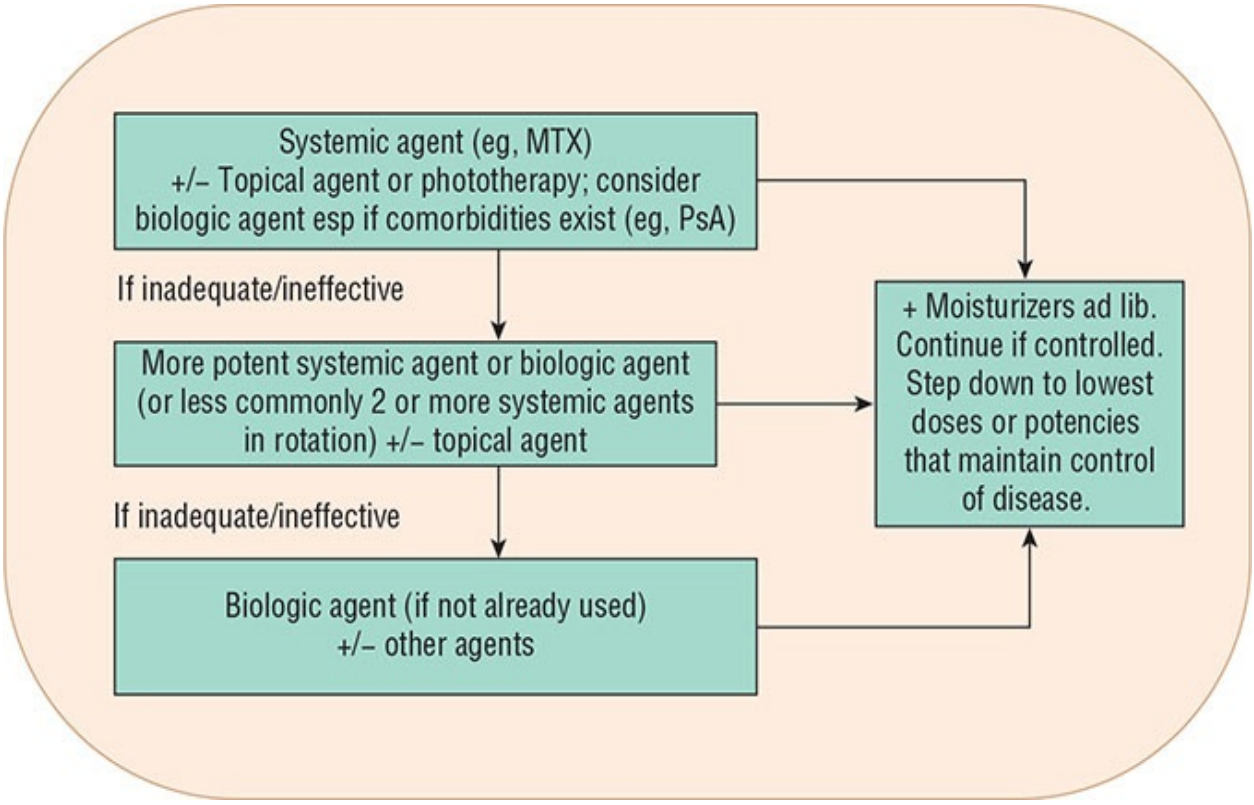


FIGURE 114-2 Treatment algorithm for moderate-to-severe psoriasis. (See section "Systemic Therapy with Biologic Agents" for details: choosing a biologic and guidelines for transitioning from traditional systemic therapies to biologics.)

Published Guidelines or Treatment Protocols There are treatment guidelines for both Canada (the Canadian Dermatology Association (CDA))[14] and the United States (American Academy of Dermatology (AAD)).[36–39] In addition, the National Psoriasis Foundation (NPF) has guidelines for use of cyclosporine and methotrexate.[40,41] In 2011, a 19-country European conference provided a consensus document focusing on disease severity and treatment goals, which ultimately resulted in updated European treatment guidelines in 2015.[27] In 2016, the CDA provided a guideline addendum which updated each chapter of the 2009 guidelines, and in particular provided more information on use of biologics for treatment of psoriasis.[14] This was followed by new biologics guidelines from the British Association of Dermatologists (BAD) in 2017,[42] and joint AAD-NPF biologics guidelines[43] with special attention paid to comorbidities in 2019.[44] As mentioned earlier, the NPF provided guidance about psoriasis treatment targets

in 2017 via a consensus study (Delphi method).[29] These guidelines represent the current standards of care.

Topical Therapies

Approximately 80% of patients with psoriasis have mild-to-moderate disease,[38] and the majority of these patients can be treated with topical therapies alone.[38] Individualized approaches are essential because of the wide variation in patients' presentations, their psychosocial health, and their personal opinions as to what would be acceptable treatment.[13,14] Traditional topical therapies include corticosteroids, vitamin D_3 analogs, retinoids, anthralin, and coal tar. In addition, topical calcineurin inhibitors may be useful for difficult-to-treat sites such as the intertriginous areas or the face. Topical biologic agents are being developed and marketed. Topical agents are also used as adjunctive therapy for patients with more extensive disease who are being treated concurrently with phototherapy or systemic agents.

To determine the quantity of topical agents required, the fingertip unit[45,46] can be used. One fingertip unit is approximately 500 mg,[38,45] which is sufficient to cover one hand (front and back) or about 2% BSA.[46] The trunk (front and back) is about 30% BSA; to cover the entire trunk once, about 15 fingertip units, or 7,500 mg (7.5 g), would be required.

In the United States, the current (2009) treatment guidelines recommend topical corticosteroids (TCS) of varying strengths as first-line treatment for limited psoriasis,[38,47] used either as monotherapy or in conjunction with nonsteroidal topical agents; and potency can be enhanced with different vehicles, and as needed by occlusion.[47] Case-based discussions illustrating the guidelines were published in 2010.[47]

In a 2012 systematic review of topical and phototherapies for psoriasis by dermatologists in France, nine recommendations based on evidence and expert opinion are offered. However, quality literature was limited, and the recommendations relating to optimal steroid use and optimal first-line treatment for psoriasis did not reach 80% consensus.[45]

Corticosteroids Topical corticosteroids (TCS) have been the mainstay of therapy for the majority of patients with psoriasis for over half a century. They are generally well tolerated, although adverse effects can occur, including systemic ones on occasion. **Table 114-2** provides a summary of topical corticosteroid formulations—including ointments, creams, gels, foams, lotions,

sprays, shampoos, tape, and solutions—and potencies.

TABLE 114-2 Topical Corticosteroid Potency Chart

Potency Rating	Corticosteroid—Topical Preparations
Class 1: Superpotent	Betamethasone dipropionate 0.05% ointment (Diprolene and Diprosone ointment) Clobetasol propionate 0.05% lotion/spray/shampoo/foam (Clobex lotion/spray/shampoo, OLUX and OLUX-E foam) Clobetasol propionate 0.05% cream, gel, solution (scalp), ointment (Cormax, Temovate, Dermovate) Diflorasone diacetate 0.05% ointment (Florone, Psorcon, ApexiCon) Halobetasol propionate 0.05% cream, lotion, ointment (Ultravate) Flurandrenolide tape 4 mcg/cm^2 (Cordran)
Class 2: Potent	Amcinonide 0.1% ointment (Cyclocort, Amcort) Betamethasone dipropionate 0.05% cream/gel (Diprolene cream, gel, and Diprosone cream) Desoximetasone 0.25% cream, gel, ointment (Topicort) Diflorasone diacetate 0.05% ointment (ApexiCon, Florone, Psorcon) Fluocinonide 0.05% cream, gel, ointment (Lidex) Halcinonide 0.1% cream (Halog)
Class 3: Upper mid-strength	Amcinonide 0.1% cream (Cyclocort) Betamethasone valerate 0.1% ointment (Betnovate/Valisone) Diflorasone diacetate 0.05% cream (Psorcon, Florone, ApexiCon) Fluticasone propionate 0.005% ointment (Cutivate) Mometasone furoate 0.1% ointment (Elocon) Triamcinolone acetonide 0.5% cream and ointment (Aristocort)
Class 4: Mid-strength	Betamethasone valerate 0.12% foam (Luxiq) Betamethasone dipropionate 0.05% spray (Sernivo) Clocortolone pivalate 0.1% cream (Cloderm) Desoximetasone 0.05% cream and gel (Topicort LP) Fluocinolone acetonide 0.025% ointment (Synalar) Fluocinolone acetonide 0.2% cream (Synalar-HP) Hydrocortisone valerate 0.2% ointment (Westcort) Mometasone furoate 0.1% cream, lotion, solution (Elocon) Triamcinolone acetonide 0.1% ointment (Kenalog)
Class 5: Lower mid-strength	Betamethasone dipropionate 0.05% lotion (Diprosone) Betamethasone valerate 0.1% cream and lotion (Betnovate/Valisone) Desonide 0.05% lotion, ointment, gel (DesOwen, Tridesilon) Fluocinolone acetonide 0.01% shampoo (Capex) Fluocinolone acetonide 0.01%, 0.025%, 0.03% cream (Synalar) Flurandrenolide 0.05% cream and lotion (Cordran) Fluticasone propionate 0.05% cream and lotion (Cutivate) Hydrocortisone butyrate 0.1% ointment, lotion, cream (Locoid, Locoid Lipocream) Hydrocortisone probutate 0.1% cream (Pandel) Hydrocortisone valerate 0.2% cream (Westcort) Prednicarbate 0.1% cream and ointment (Dermatop) Triamcinolone acetonide 0.1% cream, ointment and lotion (Kenalog)
Class 6: Mild (low potency)	Alclometasone dipropionate 0.05% cream and ointment (Aclovate) Betamethasone valerate 0.05% cream and ointment (Valisone) Desonide 0.05% cream, ointment, gel (DesOwen, Desonate, Tridesilon) Desonide 0.05% foam (Verdeso) Fluocinonide acetonide 0.01% cream and solution (Synalar) Fluocinonide acetonide 0.01% FS oil (Derma-Smoothe)
Class 7: Least Potent	Hydrocortisone 0.5%, 1%, 2%, 2.5% cream, lotion, spray, and ointment (various brands)

Data from The National Psoriasis Foundation—Mild Psoriasis: Steroid potency chart, http://www.psoriasis.org/netcommunity/sublearn03_mild_potency. Rosso JD, Friedlander SF. Corticosteroids: Options in the era of steroid-sparing therapy. J Am Acad Dermatol 2005;53:S50–S58; Leung DYM, Nicklas RA, Li JT, et al. Disease management of atopic dermatitis: An updated practice parameter. Ann Allergy Asthma Immunol 2004;93:S1–S17.; Jeon C, Sekhon S, Bhutani T, Koo J. Topical Treatments. In Bhutani T, Liao W, Nakamura M, editors. Evidence-Based Psoriasis, Diagnosis and Treatment. Table 2.1 (A textbook in the series Updates in Clinical Dermatology, with series editors Berth-Jones J, Gob CL, and Maibach HI., at http://www.springer.com/series/13203). Springer International Publishing AG, Gewerbestrassee 11, 6330 Cham, Switzerland. 2018. pp. 19-21.

The most important distinction between corticosteroids is their potency differences. Superpotent (class I) TCS provides rapid onset of efficacy but have the greatest risk of adverse effects. Their use should be limited in scope (body area) and duration (2-4 weeks). Clobetasol-17-propionate and betamethasone dipropionate were effective in clearing or markedly improving psoriasis in 75% to 80% of patients in about 3 weeks.[48] Lowest potency TCS should be used on the face and skin folds.

Salt forms of corticosteroids affect potency. For example, betamethasone dipropionate is superpotent to high potency (formulation dependent), whereas betamethasone valerate is medium to lower-mid potency (formulation dependent).

The choice of vehicle affects corticosteroid potency: Ointments, being the most occlusive, enhance drug penetration and provide the most potent formulations. However, patients may prefer a less greasy formulation, such as a cream or lotion for daytime use, although they may be willing to apply the more effective ointment-based corticosteroid during the night.[38] Providing additional occlusion will increase drug penetration of a topical preparation, resulting in enhanced potency. For example, flurandrenolide cream and lotion are potency class 5, but flurandrenolide tape was found to have higher efficacy than diflorasone diacetate ointment (potency class 1).[38,49,50]

Despite their widespread use, there have been few large-scale, randomized placebo-controlled corticosteroid trials and even fewer head-to-head comparisons with other therapies. The most comprehensive review to date is the analysis of topical psoriasis therapies done in 2002 but recent studies aren’t included so this review was already somewhat out of date when published.[14,51] This systematic review found that all topical corticosteroid treatments considered were efficacious and significantly better than placebo; and that the highest potency corticosteroids were the most efficacious, followed by vitamin D_3 analogs.[14] The French group in 2012 found variable efficacy in their systematic review, noting that recommendations about topical steroid use should be mostly based on expert opinion, and that maintenance intermittent treatment may prolong remission.[52] In addition, TCS used in combination with other agents—topical or systemic or biologic—may be mutually beneficial. For example, the concomitant use of a second agent may provide a steroid-sparing effect; or the TCS may enhance the efficacy of the second agent. Specifics are discussed in various sections below.

Corticosteroids have anti-inflammatory, antiproliferative,

immunosuppressive, and vasoconstrictive effects.[32,38] These are mediated through a variety of mechanisms. Mechanisms of action include binding to intracellular corticosteroid receptors and regulation of gene transcription (in particular those which code for proinflammatory cytokines).[32,38]

Appropriate use of TCS should include an assessment of disease severity and disease location as well as knowledge of the patient's preference and age. Lower potency TCS should be used for infants and for lesions on the face, intertriginous areas, and areas with thin skin. For other areas of the body in adults, mid- to high-potency agents are generally recommended as initial therapy.[38] The highest potency TCS are generally reserved for patients with very thick plaques or recalcitrant disease, such as plaques on palms and soles. The use of potency class 1 corticosteroids should be limited to a duration of 2 to 4 weeks,[38] recognizing that the risk of cutaneous and systemic side effects increases with continued use.

Cutaneous adverse effects include skin atrophy, acne, contact dermatitis, hypertrichosis, folliculitis, hypopigmentation, perioral dermatitis, striae, telangiectases, and traumatic purpura.[14,38] Systemic adverse effects have been reported not only with superpotent corticosteroids but also with extended or widespread use of mid-potency agents.[38] Systemic adverse effects include hypothalamic–pituitary–adrenal (HPA) axis suppression and less commonly Cushing's syndrome, osteonecrosis of the femoral head, cataracts, and glaucoma.[38]

Tachyphylaxis can occur with prolonged use, although its clinical significance is difficult to verify.[14] It is recommended that the frequency of use be gradually reduced once clinical response is seen, although there are no established tapering regimens.[38] The French group recommended twice-weekly maintenance therapy.[45] Other approaches include transitioning to weaker potency agents or combination with other nonsteroidal topical therapies.[38] Pulse dosing has also been used to minimize tachyphylaxis and adverse effects.[53]

Vitamin D_3 Analogs Topical vitamin D_3 analogs include calcipotriol (calcipotriene), calcitriol (the active metabolite of vitamin D), and tacalcitol. Calcipotriol and calcitriol are currently available in the United States and Canada and tacalcitol is available in the United Kingdom. Calcitriol is only available in ointment form; however, calcipotriol is available in ointment, cream, foam, solution, and gel suspension formulations.[32] Other analogs currently under study include maxacalcitol and becocalcidiol.[38] Their mechanisms of action include

binding to vitamin D receptors, which results in inhibition of keratinocyte proliferation and enhancement of keratinocyte differentiation.[14,38] They also have immunosuppressive properties such as inhibiting proinflammatory cytokine production (eg, IL-2 and IFN-gamma) leading to inhibition of T-lymphocyte activity.[14]

Topical calcitriol can be used as first-line monotherapy or in combination regimens for patients with mild plaque psoriasis.[14] The efficacy of calcitriol has been established in large, randomized, double-blind clinical trials.[14] The efficacy of calcipotriol for patients with mild psoriasis is also well established in randomized double-blind placebo-controlled trials. In head-to-head comparison studies with other topical agents, calcipotriol was found to be more effective than anthralin (dithranol)[54] and comparable or slightly more effective than potency class 3 (upper mid-strength) topical corticosteroid ointments such as betamethasone valerate 0.1% ointment.[14,55,56] In an analysis of topical psoriasis therapies done in 2002,[51] calcipotriol was found to be as effective as all but the most potent TCS.[14,51] Combination therapy with a TCS is particularly effective[57] and is also discussed later in the chapter.

Vitamin D_3 analogs are generally well tolerated and have a good safety profile in comparison with other topical therapies.[57] They have been considered the safest long-term topical treatments.[4] Cutaneous adverse effects most commonly include a mild irritant contact dermatitis; others include burning, pruritus, edema, peeling, dryness, and erythema.[14,38] These adverse effects may be mitigated with continued use.[38] Systemic adverse effects, including hypercalcemia and parathyroid hormone suppression, are rare unless patients are using more than the recommended maximum of 5-mg calcipotriol (100 g of calcipotriol 50 mcg/g cream or ointment) per week[14,38] or if there is underlying renal disease or impaired calcium metabolism.[38] When applied sparingly over a BSA <30%, the risk of hypercalcemia is remote.[45]

Calcipotriol is inactivated by ultraviolet A (UVA) light, thus it should be applied after rather than before UVA light exposure.[38] Calcipotriol can be inactivated by acidic substances and thus should not be used with salicylic acid in treating psoriasis.[32] It may also be partially degraded by hydrocortisone valerate.[32] However, calcipotriol is stable with other TCS[57] and stable combinations available in the United States include: calcipotriol and betamethasone dipropionate ointment and suspension (Taclonex) and calcipotriol and betamethasone dipropionate foam (Enstilar).[32] The combination of calcipotriol with betamethasone dipropionate in either ointment or foam results

in enhanced efficacy when compared with either agent used alone.[32]

Retinoids Tazarotene is a topical retinoid that acts through the following mechanisms: normalizing abnormal keratinocyte differentiation, diminishing keratinocyte hyperproliferation, and clearing the inflammatory infiltrate in the psoriatic plaque.[14,38] It is effective in clearing psoriatic plaque lesions and achieving remission.

In a placebo-controlled trial of tazarotene 0.1% and 0.05% gels for patients with plaque psoriasis, tazarotene provided a 50% or greater improvement in 63% (0.1% gel) and 50% (0.05% gel) of patients, respectively, after 12 weeks of use.[58] The therapeutic benefit appears to be maintained for 12 weeks after cessation of therapy.[58] Later clinical trials with tazarotene 0.1% and 0.05% creams versus a placebo vehicle provided similar findings.[59] The 2012 systematic review similarly found that about 50% of patients experienced a 50% or more improvement with no difference in formulations.[45] In comparison to other agents, tazarotene 0.1% gel has similar efficacy to calcipotriol 0.005% ointment (in a small study) but less effective than clobetasol propionate 0.05% cream.[14] It may be combined with TCS to enhance efficacy and reduce irritation.[32] Fixed combinations are marketed, for example, halobetasol propionate and tazarotene lotion 0.01%/0.045% (Duobrii) received FDA approval in April 2019.

Adverse effects of tazarotene include a high incidence of irritation at the site of application, a dose-dependent effect.[14] This results in burning, itching, and erythema, which can occur in lesional and perilesional skin.[38] Irritation may be reduced by using the cream formulation, lower concentration, alternate-day application, or short-contact (30-60 minutes) treatment.[38] Ad lib use of moisturizers is also beneficial. Tazarotene is also potentially photosensitizing, due to thinning of the epidermis that can occur with continued use.[38]

Tazarotene is contraindicated in pregnancy and should not be used in women of childbearing age unless effective contraception is being used. (All retinoids are potentially teratogenic including topically applied agents. See under section “Retinoids” for further details.)

Anthralin Anthralin is not as commonly used as other topical therapies currently available for psoriasis; however, there are situations where its use is appropriate and efficacious. It has a direct antiproliferative effect on epidermal keratinocytes,[14,32] normalizing keratinocyte differentiation.[38] Although the exact mechanism of action is unknown, it may have a direct effect on

mitochondria[38,60] and reduce the mitotic activity of epidermal cells.[32] It also prevents T-lymphocyte activation.[38] Small placebo-controlled studies demonstrated efficacy for anthralin used continuously or as very short contact (1 minute of treatment).[38]

Currently, short-contact anthralin therapy (SCAT) is usually the preferred regimen, where the anthralin ointment is applied only to the thick plaque lesions for 2 hours or less and then wiped off.[1,38] To minimize irritation, it can be applied for 5 to 10 minutes daily initially then titrating up the application time to 20 to 30 minutes or more as tolerated.[32] Because lesions are generally well demarcated, zinc oxide ointment or a nonmedicated stiff paste should be applied to the surrounding normal skin to protect it from irritation and burning. Anthralin should be used with caution, if at all, on the face and intertriginous areas because of the risk of severe skin irritation.[38]

Concentrations for SCAT range from 1% to 4% or as tolerated; concentrations for continuous anthralin therapy vary from 0.05% to 0.4%. Aside from significant and often severe skin irritation, other adverse effects include folliculitis and allergic contact dermatitis, but these are uncommon.

Anthralin powder causes skin irritation. People who handle the dry anthralin powder should avoid skin contact (eg, by wearing gloves while compounding).[1]

Coal Tar Coal tar was one of the earliest agents used to treat psoriasis. It is keratolytic and may have antiproliferative and anti-inflammatory effects.[1,32] Coal tar formulations include crude coal tar and tar distillates (liquor carbonis detergens—LCD) in ointments, creams, and shampoos. Because of limited efficacy coupled with patient acceptance and compliance issues, coal tar preparations are less commonly used today, especially in North American and European[45] countries.

A 2007 comparative study in Thailand reported that betamethasone valerate was significantly more effective than coal tar.[14,61] Although coal tar may have similar efficacy as calcipotriol,[14] it has a slower onset of action.[14] In addition, coal tar has an unpleasant odor and will stain clothing; thus, it may be cosmetically unappealing to patients. LCD 15% solution was shown to be cosmetically acceptable, well tolerated and effective when compared with calcipotriol 0.005% cream.[14,62]

Adverse effects include folliculitis, acne, local irritation, and phototoxicity.[14] It is carcinogenic in animals, but for humans no convincing data have emerged regarding carcinogenicity with topical use.[38]

Coal tar concentrations as used in psoriasis treatments (0.5%-5%) are considered safe by the FDA.[63] However, occupational exposure to coal tar, especially in very high concentrations such as coal tar used in industrial paving, was reported to increase the risk of lung cancer, scrotal cancer, and skin cancer.[38] The risk of teratogenicity when used in pregnancy is likely to be small, if it exists.[38,63]

Salicylic Acid Salicylic acid has keratolytic properties and has been used in various formulations including shampoos or bath oils for patients with scalp psoriasis. In combination with topical corticosteroids, it enhances steroid penetration, thus increasing efficacy.[32] It should not be used in combination with ultraviolet B (UVB) light phototherapy because of a filtering effect that may reduce UVB efficacy.[32] It should not be used with calcipotriol as it inactivates calcipotriol upon contact.[32] Systemic absorption and toxicity can occur, especially when applied to more than 20% BSA[32] or when used for patients with renal impairment.

Avoid the use of salicylic acid in children. However, it may be used for limited and localized plaque psoriasis in pregnancy.[38]

Calcineurin Inhibitors Topical calcineurin inhibitors such as pimecrolimus 1% cream (Elidel) are marketed for the treatment of inflammatory skin diseases such as atopic dermatitis.[64–66] They are not FDA approved for psoriasis but are used off label. Pimecrolimus was found effective for plaque psoriasis when used under occlusion[65] and also effective for patients with moderate-to-severe inverse psoriasis (intertriginous areas are affected).[66] Because this cream is less irritating than calcipotriol and also avoids steroid adverse effects such as skin atrophy, it may be a useful alternative for patients with lesions in intertriginous areas or on the face.[32]

Phototherapies and Photochemotherapy

Phototherapy has been used for treating psoriasis for years and is still an important treatment modality today. It has been known for centuries that some skin diseases improve with sun exposure, and clinical studies with phototherapies have been reported since the late 19th century.[36] Phototherapy consists of using nonionizing electromagnetic radiation, either UVA or UVB, as light therapy to treat psoriatic lesions.[67]

UVB is given alone as either broadband or narrowband UVB (NB-UVB), currently with NB-UVB being the preferred method. UVB is also given as

photochemotherapy with topical agents such as crude coal tar (Goeckerman regimen)[67] or anthralin (Ingram regimen) for enhanced efficacy.[36]

UVA is generally given with a photosensitizer, such as an oral psoralens, to enhance efficacy—this regimen is known as PUVA (photochemotherapy with oral methoxypsoralen and ultraviolet A light).[67]

With respect to comparative efficacy, NB-UVB is more efficacious than broadband UVB, but may be slightly less effective than PUVA.[36,68] PUVA is very effective in the majority of patients, with the potential for long remissions.[36] A meta-analysis showed that more patients are still clear at 6 months with PUVA versus with NB-UVB.[68] However, because of greater availability of UVB treatment centers, more evidence available now of the efficacy of UVB treatments for psoriasis (in particular, NB-UVB), and especially the increasing concerns about PUVA toxicities (including skin cancers), phototherapy for psoriasis currently uses UVB or NB-UVB where available. Failure of NB-UVB may justify PUVA therapy.[67]

UVB interferes with protein and nucleic acid synthesis, leading to decreased proliferation of epidermal keratinocytes.[36] UVA has similar effects on epidermal keratinocytes. However, because of deeper penetration into the dermis, it also has effects on dermal dendritic cells, fibroblasts, endothelial cells, mast cells, and skin-infiltrating inflammatory cells including granulocytes and T lymphocytes.[36]

Adverse effects of phototherapy include erythema, pruritus, xerosis, hyperpigmentation, and blistering, especially with higher dosages. It should be used with caution for patients with photosensitivity concerns, and drug interactions include photosensitizing medications such as tetracyclines. Patients must be provided with eye protection during UVB, NB-UVB, or PUVA treatments, and for 24 hours[67] or the remainder of the day[36] after PUVA treatments. In addition, patients receiving PUVA therapy may experience gastrointestinal symptoms such as nausea or vomiting, which may be minimized by taking the oral psoralens with food or milk.[36] For patients also receiving oral retinoids plus PUVA (RE-PUVA), the UVA dose should be reduced by one-third.[36] Long-term PUVA use can lead to photoaging and the development of PUVA lentigines. Psoralens bind to proteins in the lens of the eye; thus, there is a potential for increased cataract formation.

Furthermore, although UVB has a theoretical risk of photocarcinogenesis, the risk is significantly higher with PUVA and is dose related.[36,67] A meta-analysis reported a 14-fold increase in the incidence of squamous cell carcinoma (SCC)

in patients receiving high-dose PUVA when compared with low-dose PUVA, with SCC of the male genitalia particularly elevated.[36,69] PUVA may also increase the risk of basal cell carcinoma and possibly melanoma,[36] which may occur 15 years after the first treatment.[67] Thus, the use of phototherapy or photochemotherapy is contraindicated in patients with a history of melanoma or multiple nonmelanoma skin cancers.

Targeted phototherapy using excimer lasers that selectively target psoriatic lesions without affecting normal skin is an option being studied and early results appear promising, although blistering and burning of treated lesions are more common, and long-term safety has not been established.[36]

Systemic Therapies

Systemic therapies are the mainstay of treatment for patients with moderate-to-severe psoriasis, with topical therapies remaining as useful adjuncts. However, as discussed below under combination therapies, topical calcipotriol and betamethasone dipropionate ointment may provide sufficient disease control for some patients.[14,70] Conversely, a subset of patients with limited disease may have debilitating symptoms, and the use of systemic therapies would be warranted.[37] Systemic therapies include the following traditional agents: acitretin, cyclosporine, methotrexate, mycophenolate mofetil (MMF), and hydroxyurea; as well as the biologic agents, specifically adalimumab, alefacept, etanercept, infliximab, ustekinumab, secukinumab, and newer agents certolizumab, ixekixumab, brodalumab, guselkumab, tildrakizumab, risankizumab, and others at various stages of development.

Acitretin In the 1980s, etretinate became the first oral retinoid, or vitamin A acid derivative, available for the treatment of psoriasis. It has since been replaced by acitretin, its active metabolite.

Retinoids may be less effective than methotrexate or cyclosporine when used as monotherapy, although the initial response may be more rapid than methotrexate for patients with severe inflammatory forms of psoriasis. Currently, acitretin is more commonly used in combination with topical calcipotriol or phototherapy.[14,37] Its efficacy appears to be dose dependent.[37] Although low-dose acitretin (25 mg/day) is safer and better tolerated than higher-dose (50 mg/day) therapy,[14] low-dose acitretin is not recommended as monotherapy for psoriasis.

Common adverse effects of acitretin include hypertriglyceridemia and mucocutaneous adverse effects such as dryness of the eyes, nasal and oral

mucosa, chapped lips, cheilitis, epistaxis, xerosis, brittle nails, and burning or sticky skin.[14,37] Less commonly, “retinoid dermatitis” may occur. Ophthalmologic changes include photosensitivity, decreased color vision and impaired night vision.[27] GI side effects including hepatitis and jaundice are rare with liver enzyme elevations usually being transient.[27] Periungual pyogenic granulomas are sometimes seen after long-term use of acitretin.[37] Rarely, skeletal abnormalities—such as disseminated idiopathic skeletal hyperostosis (DISH) syndrome—may occur.[14]

All retinoids are teratogenic and are absolutely contraindicated in pregnancy, including topical retinoids. Acitretin should not be used for women of childbearing age unless they are able and willing to use effective birth control not only for the duration of acitretin therapy but also for at least 2 years after discontinuing the agent.[14,27,37] Blood donation (men and women) is not permitted during and for at least a year after treatment.[27] Ethanol should be avoided during therapy and for 2 months after drug discontinuation because it causes the transesterification of acitretin to etretinate, which has a much longer elimination half-life.

Cyclosporine Cyclosporine is a systemic calcineurin inhibitor. The more bioavailable microemulsion formulation, Neoral, was approved by the FDA in 1997 for the treatment of psoriasis and rheumatoid arthritis.[40]

Cyclosporine is efficacious for both inducing remission and as maintenance therapy for patients with moderate-to-severe plaque psoriasis. It is also effective in treating pustular, erythrodermic, and nail psoriasis.[40] The 2009 Canadian Guidelines recommended that cyclosporine be normally reserved for intermittent use in periods up to 12 weeks for most patients with psoriasis,[14] although other recommendations are for periods of 1 year or up to 2 years.[40] Risk of toxicity increases with treatment duration: intermittent short-course therapy (<12 weeks) is preferable since this appears to significantly reduce the risk of nephrotoxicity as compared to continuous therapy.[14,27,40]

In comparative randomized controlled trials (RCTs), cyclosporine was significantly more effective than etretinate[71] and similar or slightly better in efficacy than methotrexate.[14,40,72] After inducing remission, maintenance therapy using low doses (1.25-3.0 mg/kg/day) may prevent relapse.[40] The dose should always be titrated to the lowest effective dose for maintenance. In one placebo-controlled study, the relapse rate was 42% for patients on 3.0 mg/kg/day versus 84% for patients on placebo.[73] For patients discontinuing cyclosporine, a

gradual taper of 1 mg/kg/day each week may prolong the time before relapse, as compared with abrupt discontinuation.[37,40] Abrupt discontinuation resulted in a dramatic rebound of psoriasis in a few cases.[14] Because more than half of patients discontinuing cyclosporine will relapse within 4 months, patients should be provided with appropriate alternative treatments shortly before or after discontinuing cyclosporine therapy.[40]

Adverse effects of cyclosporine include cumulative renal toxicity, hypertension, and hypertriglyceridemia. The latter two are particularly significant for patients with prior elevation of diastolic blood pressure or triglycerides.[14] Hypertriglyceridemia can occur in up to 15% of patients with psoriasis who are treated with cyclosporine, although this effect is generally reversible upon cessation of therapy.[37] The cyclosporine-induced blood pressure elevation is dose-related, based on a Cochrane systematic review.[74]

The risk of SCC and other nonmelanoma skin cancers increases with duration of treatment[14] and with prior PUVA treatments.[37] Thus, although continuous therapy for up to 2 years may be efficacious,[40] it should be used only in a subset of patients[14] in whom renal function is monitored with annual determinations of glomerular filtration rate (GFR) and monthly measurements of blood pressure and creatinine clearance, with more frequent measurements during the initial 6 weeks of treatment.[14]

Baseline blood pressure, serum creatinine, serum urea nitrogen, triglycerides, complete blood count, uric acid, potassium, and magnesium should be obtained before initiating therapy, every 2 weeks for the first 12 weeks of therapy, and monitored monthly thereafter during therapy.[14,40] If the serum creatinine increases to 25% above the patient's baseline on two occasions (2 weeks apart), the cyclosporine dosage needs to be decreased by 25% to 50% and serum creatinine rechecked as often as every other week for 1 month. If the serum creatinine does not return to within 10% of the patient's baseline value, a further dose decrease of 25% to 50% should be considered. If the value continues to be greater than 10% above the patient's baseline value, consider discontinuing cyclosporine therapy.[40] (*Note*: A 25% above-baseline cutoff for dosage reduction is the manufacturer's recommendation; the NPF consensus guidelines continue to recommend a 30% cutoff).[40] Age-appropriate malignancy screening should also be done, and patients should be seen for dental examinations at least yearly because of the risk of gingival hyperplasia.[40]

As a cytochrome P450 isoenzyme 3A4 (CYP3A4) substrate, cyclosporine has significant drug interactions. Serum concentration monitoring is not routinely

needed for patients with psoriasis because doses used are lower than in transplant recipients, although monitoring may be advisable for patients taking interacting drugs.

Drugs that can increase cyclosporine concentrations include calcium channel blockers (verapamil, diltiazem, and nicardipine), amiodarone, thiazide diuretics, macrolide antibiotics, allopurinol, oral contraceptives, ezetimibe, selective serotonin reuptake inhibitors (fluoxetine, sertraline), fluoroquinolones (ciprofloxacin, norfloxacin), antifungals (ketoconazole, itraconazole, fluconazole, voriconazole), and cimetidine.[40] Grapefruit juice will also increase cyclosporine concentrations.

Drugs that can reduce cyclosporine concentrations include anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin, valproic acid), rifampin, efavirenz, and St. John's wort.[40]

Conversely, cyclosporine may also affect the drug levels of some drugs. Concurrent use of potentially interacting drugs should be avoided when possible.

Methotrexate For decades, methotrexate has been the mainstay of systemic therapy for patients with moderate-to-severe psoriasis. It has direct anti-inflammatory benefits due to its effects on T-cell gene expression and also has cytostatic effects.[14] It is more efficacious than acitretin and similar or slightly less efficacious than cyclosporine.[14,41]

Although it also has a significant adverse-effect profile, methotrexate is generally considered a safer alternative than cyclosporine unless there are preexisting contraindications such as liver disease. In some head-to-head clinical studies more patients dropped out of the cyclosporine treatment arms due to adverse effects.[37,41] While biologic agents are undoubtedly more efficacious, they are much more costly, and some insurance companies require an inadequate response or intolerance to methotrexate (the gold standard) as a prerequisite for approving their use.[41] In a recent placebo-controlled comparative study with adalimumab (CHAMPION), the efficacy of methotrexate was 36% versus 80% for adalimumab and 19% for placebo.[75] Adalimumab also provided a more rapid response; however, the duration of remission is unclear.

Initial doses of 7.5 to 15 mg/week may be increased to 20 to 25 mg/week if the response is inadequate at 8 to 12 weeks, with appropriate adverse effect monitoring. Methotrexate can be used continuously for years or decades with sustained benefits.[14] Methotrexate inhibits folate biosynthesis; and the use of folate supplementation during prolonged methotrexate therapy as seen in dermatology remains controversial. Although some experts recommend folate

supplementation for all patients receiving methotrexate for psoriasis, others add folate only when patient issues occur, such as gastrointestinal adverse effects or early bone marrow toxicity (as manifested by an increased mean corpuscular volume) that can be caused by megaloblastic anemia.[37,41] Lack of folate supplementation has also been listed as a risk factor for hepatotoxicity from methotrexate use.[41] One small placebo-controlled study suggested that folate supplementation may result in a slight decrease in efficacy of treatment,[76] but the study methodology has been questioned.[37,41]

The most significant adverse effect is cumulative liver toxicity; and total lifetime dose of methotrexate must be monitored. Traditionally, patients received a pretreatment liver biopsy and subsequent biopsies when a cumulative dose of 1.5 g is reached. Liver biopsy is the gold standard for assessing histological changes and provides an invasive marker of liver fibrosis. Currently, it is recognized that pretreatment liver biopsies may not be practical or appropriate in all cases[14,41] and that baseline liver biopsies only be considered for patients with a history of significant liver disease.[41] It has also been recommended that a baseline liver biopsy be delayed for 2 to 6 months so that medication efficacy and tolerability can first be established[41] (ie, intention to continue with methotrexate use). Risk factors for hepatotoxicity from methotrexate include the following: a history of or current alcohol consumption, persistent abnormal liver chemistry studies, history of liver disease including chronic hepatitis B or C, family history of inheritable liver disease, history of significant exposure to hepatotoxic drugs or chemicals, diabetes mellitus, obesity, and hyperlipidemia.[37,41] For patients without preexisting risk factors for hepatotoxicity, it is recognized that they would likely have a low risk of fibrosis and would not require a baseline liver biopsy; furthermore, consideration can be made to continue methotrexate treatment for these patients without biopsies at all, to perform a liver biopsy after 3.5 to 4.0 g total cumulative dose, or to switch therapy to an alternate drug at that point.[37,41]

There are noninvasive markers of liver fibrosis, in particular the procollagen type III N-terminal peptide (P3NP or PIIINP) serum level, and the 2015 European recommendation for MTX monitoring is PIIINP determination prior to starting MTX and every 3 months thereafter.[27] However, a systematic review and meta-analysis of the diagnostic accuracy of noninvasive markers of liver fibrosis in patients with psoriasis taking methotrexate reported that: (1) the likelihood ratios for P3NP were suboptimal for it to be considered a “good test” and (2) liver function tests demonstrate low-diagnostic accuracy for the detection of fibrosis; and the conclusion was that the clinical utility of LFTs, P3NP, and

liver ultrasound is poor, and that if these tests are used in isolation, a significant proportion of patients with liver fibrosis may remain unidentified.[77] Thus, MTX monitoring recommendations currently differ between continents.

Other adverse effects include significant nausea, pulmonary toxicity, pancytopenia, acute myelosuppression, megaloblastic anemia, and a small but significant increase in lymphoma.[14] Although rare, pancytopenia can occur anytime with the use of low-dose weekly methotrexate and even after single doses of methotrexate.[37] Informing patients about the early symptoms of pancytopenia (dry cough, nausea, fever, dyspnea, cyanosis, stomatitis/oral symptoms, and bleeding) may aid early detection.[27] Methotrexate is an abortifacient and is teratogenic and is absolutely contraindicated in pregnancy. After methotrexate therapy is discontinued, it is recommended that men continue an effective birth control for 3 months (since one cycle of spermatogenesis is 74 days), and women should be on effective birth control for at least one ovulatory cycle.[14,37]

Significant drug interactions include serum albumin binding interactions with salicylates, phenytoin, sulfonamides/trimethoprim, ciprofloxacin, and thiazide diuretics, potentially increasing toxicity. Drugs that can reduce methotrexate renal elimination (such as acidic drugs, including salicylates or vitamin C) will also increase serum methotrexate levels and hence increase toxicity. In addition, drugs with hepatotoxic potential may pose an additive risk with methotrexate use.[37]

Janus Kinase (JAK) Inhibitors: Tofacitinib *Tofacitinib* is a potent and selective inhibitor of the JAK family of kinases. It inhibits JAK1, JAK2, JAK3, and to a lesser extent TyK2.[120] Inhibition of JAK1 and JAK3 blocks signaling through common receptors for cytokines including IL2, IL4, IL7, IL9, IL15, and IL21.[120] JAK1 inhibition also attenuates signaling by other pro-inflammatory cytokines (ie, IL6 and Type I interferons).[120]

Tofacitinib is an oral agent with a recommended dosage of 5 mg twice daily (or 11 mg of the tofacitinib XR once daily) taken with or without food; the XR tablets must be swallowed whole and cannot be split, crushed, or chewed.[120] Potential drug interactions involve CYP450 substrates. Potent CYP3A4 inhibitors (eg, ketoconazole) or modest CYP3A4 plus potent CYP2C19 inhibitions (eg, with fluconazole) may increase tofacitinib exposure, and potent CYP3A4 inducers (eg, rifampin) may reduce tofacitinib exposure.[120]

Systemic Therapy with Biologic Agents

10 Biologic agents have exploded onto the treatment scenario for many immune conditions, including psoriasis. More and more biologic agents have proven efficacy for psoriasis and are indicated for use; however, there are differences among these agents, including mechanism of action, duration of remission, and adverse-effect profile. In addition to biologic agents, there are biosimilars to established biologic agents (eg, Amjevita is a biosimilar to Adalimumab [Humira]). The NPF provides and updates a Treatment Comparison chart on their website which lists biologics and biosimilars in the United States[78]; this is a useful link as new ones become available at: https://www.psoriasis.org/sites/default/files/treatment_comparison_chart_1.pdf

The *Pharmaceutical Journal* provided a discussion about the economic impact of adalimumab being off patent in October 2018 in the UK and the use of biosimilars.[79]

General Concerns & Precautions What precautions are needed when using biologics for treating psoriasis? In general, because of their immunomodulatory effects, there is an increased risk of infection with most of these agents, including serious infections such as sepsis, new-onset or reactivation of tuberculosis, and opportunistic infections such as histoplasmosis, cryptococcosis, aspergillosis, candidiasis, and pneumocystis. The use of live or live-attenuated vaccines during therapy is generally contraindicated. Because biologics are relatively new on the market, the risks of rare but serious adverse effects or those with a longer latency period may still be unrecognized or unreported. Further, we are still relying mostly on clinical trial experience, thus safety data on vulnerable populations such as children or women planning pregnancy are usually absent.[80] There may be more safety data with earlier biologics which had approval for use in rheumatoid arthritis; however, it is the newer classes of biologics which are showing most promise. A 2018 publication concisely addresses the adverse reactions known to-date of biologics used in dermatology—both as indicated and off-label use.[81]

A more recently recognized concern about using biologics is that their efficacy may not be sustainable for much more than three years, that is, there is a loss of effect over time. For example, the British Association of Dermatologists (BAD) Biologic Interventions Register (BAD-BIR) has registered a 53% overall probability of drug survival by year 3, that is, about 50% failure.[80] (BAD-BIR currently has >10,000 registrations including children.[80]) Current data also suggest that failure of one biologic may negatively impact the efficacy of the next, as seen in psoriasis studies.[80] From experience with biologics for

rheumatoid diseases, it appears that, after three biologic agents are used, other agents are less likely to be efficacious—there may be a similar phenomenon with their use in psoriasis.

Place in Therapy & Transitioning from Other Therapies Currently, biologics are often considered for patients with moderate-to-severe psoriasis when other systemic agents are inadequate or relatively contraindicated, or if comorbidities such as active PsA exists. Biologic agents are sometimes recommended for first-line therapy, alongside conventional systemic agents, for patients with moderate-to-severe psoriasis; however, in practice, drug access due to cost considerations may be a limiting factor. The availability of biosimilars may mitigate this to some extent. British Association of Dermatologists (BAD) recommends biologics in methotrexate and cyclosporine failure / intolerance / contraindication; when psoriasis has significant impact on physical, psychological, or social functioning and (a) the psoriasis is extensive (BSA >10 or PASI >=10) or (b) the psoriasis is severe at localized sites and associated with significant functional impairment and/or high levels of distress (eg, nail disease or involvement of high-impact and difficult-to-treat sites such as the face, scalp, palms, soles, flexures, and genitals).[42]

Are there guidelines for transitioning from traditional systemic therapies to biologics? BAD provides some transitioning strategies in their 2017 guidelines[42]: (1) In stable disease, aim to allow 1 month to elapse between the last dose of any current standard systemic immunosuppressive therapy (except MTX) and the planned date of biologic initiation; (2) start a biologic with no drug washout period in patients taking MTX, or on other therapies where a drug washout period would lead to unstable disease; (3) when standard systemic immunosuppressant therapy cannot be stopped (eg, if a disease flare would be severe or hazardous), rationalize use of therapy and stop as soon as possible (eg, when a minimum response has been achieved).[42]

Biologics may be appropriate/preferred as first-line therapy if comorbidities exist. For example, biologics such as infliximab or adalimumab would be an appropriate treatment option for patients with both plaque psoriasis and active PsA. Biologics currently available for treatment of psoriasis include adalimumab, etanercept, infliximab, ustekinumab, secukinumab, certolizumab, ixekixumab, brodalumab, guselkumab, tildrakizumab, risankizumab, and others which may be at various stages of development.[35,78]

Choosing Between Biologics With the plethora of biologics currently available and more on the horizon, how does one choose between them? This is an

important consideration for managing a chronic disease such as psoriasis. The Canadian Psoriasis Guidelines Addendum Committee[14] and BAD[42] both recommend ustekinumab and adalimumab as first-line biologic therapies: ustekinumab for ameliorating moderate-to-severe plaque psoriasis[14] and adalimumab particularly when psoriatic arthropathy is a consideration.[42] Both ustekinumab and adalimumab can be considered for potential clearance: some patients on adalimumab achieve 100% PASI reduction within 16 weeks of treatment, and some patients on ustekinumab may achieve 90% or greater PASI reduction by week 12 of treatment.[14] These recommendations are based on sustainable efficacy results; for example, adalimumab had a 3-year open-label extension of a 1-year phase 3 trial (REVEAL) which demonstrated sustained response at 3 years with continuous use in initial PASI 75 responders.[82] British guidelines also suggest considering secukinumab as a first-line biologic, with other biologics being second line if the patient has not responded to a first-line biologic.[42] These biologics and others are discussed below, grouped based on their classification / immune target.

Individual & Classes of Biologic Agents

Alefacept Alefacept was the first biologic to receive approval for the treatment of psoriasis, in January 2003 in the United States and in October 2004 in Canada. In comparison with other biologics, alefacept monotherapy provides only limited control of psoriasis, although it has an extensive and reassuring safety record. Due to its modest response, alefacept had been voluntarily withdrawn by the manufacturer from the United States and Canadian markets in 2011 and 2012, respectively.

Tumor Necrosis Factor-α Inhibitors Dysregulation of TNF-α production is associated with various inflammatory conditions, including rheumatoid arthritis, inflammatory bowel disease, ankylosing spondylitis, PsA, and psoriasis.[14,35,39,42,43] Elevated TNF-α levels are seen in both the affected skin and serum of patients with psoriasis; and these elevated levels have a significant correlation with psoriasis severity.[39] The biologic agents adalimumab, etanercept, infliximab and certolizamab are TNF-α inhibitors; this class of agents is effective for psoriasis and psoriatic arthritis.[14,35,39,42,43,82,83]

There are safety concerns common to TNF-α inhibitors, mainly from observations made through their use in rheumatoid arthritis and inflammatory bowel disease and more recently in psoriasis.[82–84] One concern is an increased risk of bacterial, mycobacterial, invasive fungal (disseminated or

extrapulmonary histoplasmosis, aspergillosis, coccidioidomycosis), viral, parasitic, or other opportunistic infections—most commonly upper respiratory tract infections, and less commonly serious infections including sepsis, new-onset or reactivation tuberculosis, and opportunistic infections.[14,39,82–85] There have been reports of serious pulmonary and disseminated histoplasmosis, coccidioidomycosis, and blastomycosis infections, sometimes with fatal outcomes when these infections were not consistently recognized and promptly treated in the patients taking TNF-α inhibitors.[85]

A second concern is the development or worsening of autoimmune diseases such as peripheral and central demyelinating disorders including multiple sclerosis and drug-induced lupus-like syndromes.[14,39,84] Although there is no definitive causal relationship, it is recommended that anti-TNF agents be avoided in patients with established demyelinating diseases (eg, multiple sclerosis), and treatment discontinued in patients with suspected demyelination during therapy.[84] A third concern is the potential increased risk of malignancies such as lymphoma,[14,84,85] melanoma, and nonmelanoma skin cancer.[39] A fourth concern is the potential for other cutaneous adverse effects including vasculitis, granulomatous reactions, cutaneous infections, psoriasiform eruptions, and infusion or injection site reactions.[83] Flares of pustular psoriasis have been reported primarily for patients undergoing treatment for nondermatologic conditions such as rheumatoid arthritis.[14] A fifth concern is the risk of hematologic toxicity including neutropenia (more commonly reported)[84,85] and rare reports of other hematologic events including pancytopenia and aplastic anemia.[85]

There is also a sixth concern about chronic heart failure (CHF): worsening congestive heart failure (CHF) and new-onset CHF have been reported during use of these agents. TNF-α inhibitors are contraindicated in patients with preexisting moderate-to-severe CHF (NYHA class III/IV),[27,39,85], and those with milder CHF should have their TNF-α inhibitors withdrawn at the onset of new symptoms or worsening of preexisting CHF.[39]

Although the above are safety concerns common to etanercept, adalimumab, infliximab and certolizumab, their safety profiles are not identical. For example, the risk for tuberculosis (TB) appears lowest with etanercept and may be highest with infliximab.[14] Nonetheless, they are contraindicated in patients with active TB.[27] Patients should be evaluated for active or latent TB prior to therapy and considered for a yearly PPD.[14,39] CBC and LFTs are also recommended prior to and periodically during therapy.[27] In addition, pretreatment C-reactive protein

(CRP), hepatitis serology (HBV, HCV), and HIV testing have been recommended.[27] They are safe to use in pregnancy.[39] However, some manufacturers have cautioned that, since these agents cross the placenta, infants exposed in utero may be at higher risk of infections and live vaccines would therefore be contraindicated for several months after birth.[85]

Adalimumab is a human monoclonal antibody that provides rapid and efficacious control of psoriasis.[14,39] Adalimumab is currently a first-line biologic recommended by BAD[42] and CDA[14] for adults with psoriasis, particularly when psoriatic arthropathy is a consideration.[42] Clinical trials in patients with moderate-to-severe psoriasis have shown dramatic results. A 2006 12-week RCT with open-label extension to 52 weeks showed significant improvement within 1 week of therapy, with complete or nearly complete clearance in some patients, and clinical benefits were maintained for at least 1 year with continuous therapy for most patients.[14,86] Currently, there is evidence that some patients may achieve / maintain PASI 90 through at least 160 weeks of treatment.[14]

A pivotal 2008 52-week RCT (REVEAL) with an initial 16-week double-blind placebo-controlled (DBPC; period A) phase followed by a 17-week open-label phase (period B) followed by a 19-week DBPC phase (period C) showed a 71% PASI 75 response for adalimumab-treated patients versus 7% for placebo-treated patients at week 16. All patients received open-label adalimumab from weeks 17 through 32. At week 33, patients achieving PASI 75 were rerandomized to adalimumab or placebo; patients achieving PASI 50 but <75 were continued on open-label adalimumab; and therapy for patients with PASI <50 was discontinued. At week 52, 5% of patients rerandomized to adalimumab lost adequate response versus 28% of patients rerandomized to placebo. Adalimumab was continued at 40 mg every other week. The study showed that adalimumab can produce rapid and dramatic results which can be sustained on continued use, in patients with moderate-to-severe psoriasis.[87]

An additional 3-year open-label extension study for patients in REVEAL showed that in patients with sustained initial PASI 75 responses, adalimumab efficacy was maintained for more than 3 years of continuous therapy and maintenance was best at PASI 100. Some patients with PASI <75 in REVEAL also achieved long-term PASI 75 responses.[82]

For comparative studies, as discussed in section “Methotrexate,” a head-to-head study showed that adalimumab was significantly more efficacious than methotrexate.[75] For patients who have an inadequate response to other psoriasis treatments (including etanercept), adalimumab is a good alternative.[14]

Adalimumab is given as 80 mg subcutaneously in the first week, then 40 mg the following week, and thereafter 40 mg every other week continuously.[14,27,39,85] More frequent dosing has been explored.[14]

Adverse effects in adalimumab clinical trials including the 3-year extension were similar to those already described for this class of biologics.[85]

Etanercept was one of the earliest biologics available on the market for use in inflammatory diseases. It has demonstrated efficacy for rheumatoid arthritis. It was approved for use in PsA in the United States in June 2002 and approved in 2004 for use in moderate-to-severe psoriasis. It is also approved for treatment of juvenile rheumatoid arthritis and ankylosing spondylitis. Thus, as opposed to some of the other biologics approved for psoriasis, etanercept has been extensively used in rheumatology both for adults and children.

The dosing of etanercept in psoriasis differs from its other indications, reflective of the dosing regimens found to be effective for psoriasis in clinical trials. Etanercept is used continuously, given as 50 mg subcutaneously twice weekly for the first 12 weeks, followed by 25 mg twice weekly[14] or 50 mg once weekly.[27,39] Significant improvement was seen in about 50% of patients in clinical trials by week 12 and more than 50% of participants by week 24; with continuing therapy, weaker responders continued to improve for up to 1 year.[14,39,88] Continuing therapy using 50 mg twice weekly regimens are being explored and may provide greater benefit.[14] Etanercept was efficacious in children and adolescents (aged 4-17 years) with plaque psoriasis dosed at 0.8 mg/kg (maximum 50 mg) once weekly.[89]

Infliximab also received approval for rheumatologic diseases before psoriasis and was on the market before adalimumab. Infliximab is more efficacious than etanercept. A 2011 open-label study showed that psoriatic patients with an inadequate response to etanercept had rapid and sustained improvement when switched to infliximab.[90] Unlike etanercept or adalimumab, infliximab is a chimeric antibody with both murine and human components; thus, antibodies to the drug can develop, resulting in infusion reactions[39,43] and loss of clinical efficacy.[43] The standard dosing regimen is three IV infusions of 5 mg/kg given over a 6-week induction period, followed by regular infusions every 8 weeks.[39] This 8-week gap between infusions is longer than with other agents, thus increasing the risk of infusion reactions and loss of efficacy due to antibody development in comparison to other biologics.[43]

Clinical response is seen rapidly. In a pivotal phase III RCT, 76% and 70% of patients achieved PASI 75 by week 10 (after 3 doses of infliximab at 5 mg/kg

and 3 mg/kg respectively), and PASI 90 was achieved by 45% and 37%, respectively[43,91]; however, the response dropped to about 50% by week 50.[91,92] Combining infliximab with other therapies may enhance response. Methotrexate can reduce the immunogenicity of infliximab, which minimizes the risk of antibody development to infliximab and a consequent loss of clinical response.[43] Enhanced clinical response has been seen in psoriasis and in psoriatic arthritis.[43] Thus, the joint AAD-NPF guidelines recommend that the addition of methotrexate to infliximab should be considered strongly for all patients.[43] They caution that the long-term safety of this combination is currently unknown.[43] Infliximab has been combined with TCS and a vitamin D analogue to augment efficacy but rigorous evidence supporting this combination is currently lacking.[43]

In addition to antibody development and infusion reactions, serious adverse events, including fatal cases of hepatosplenic T-cell lymphomas, have been reported rarely with infliximab use.[39] Cutaneous adverse effects include nonmelanoma skin cancers; however, these were mostly seen in patients with prior exposure to UV therapy, including NB-UVB and PUVA.[84] Other rare instances of cholecystitis and autoimmune hepatitis, which may be a class effect for TNF-α inhibitors, have also been reported.[14]

Certolizumab pegol is a humanized antigen-binding fragment of a monoclonal antibody that is further conjugated with a polyethylene glycol moiety. This binds to TNF-α, blocking its interaction with TNF receptors.[43] A phase II RCT showed PASI 75 achieved in 75% and 83% of patients by week 10, on doses of 200 mg or 400 mg every other week, respectively, versus 7% for the placebo group.[43,93] Recommended certolizumab dosing is 400 mg (as 2 × 200-mg SC injections) every 2 weeks, with a dose-reduced regimen for patients under 90 kg (198 lb): 400 mg (as 2 × 200-mg SC injections) initially and at weeks 2 and 4, followed by 200 mg every other week.[43,94]

IL-12/IL-23 Inhibitors: Ustekinumab *Ustekinumab* is an IL-12/23 monoclonal antibody approved for the treatment of psoriasis in adults 18 years or older with moderate-to-severe plaque psoriasis.[14,24] Ustekinumab is currently a first-line biologic recommended by BAD[42] and CDA[14] for adult psoriasis patients. It has a higher drug survival rate than TNF-α inhibitors, that is, longer duration of efficacy with continued treatment.[43] There is evidence that some patients may maintain PASI 90 through at least 244 weeks of treatment.[14] One study found that patients who had not used a biologic before (ie, biologic-naïve) or were

using methotrexate concomitantly had longer survival.[43,95]

Ustekinumab selectively targets IL-12 and IL-23, two cytokines that play a role in the pathogenesis of psoriasis.[27,43] It binds to their shared p40 protein subunit, thus preventing interaction with their cell surface IL-12Rβ1 receptor.[96] This shared binding may allow ustekinumab to exert its clinical effects in both psoriasis and psoriatic arthritis through interruption of the TH1 and TH17 cytokine pathways, central to both disease conditions.[96]

Ustekinumab can provide a rapid response that is seen within two weeks of initiating treatment.[43,97,98] Two large randomized placebo-controlled trials (PHOENIX 1[97] and PHOENIX 2[98]) demonstrated clinical efficacy of ustekinumab, with approximately 70% of patients achieving 75% skin clearance after two doses and maintaining the response for 1 year with continued treatment. The improvements were dramatic. Ustekinumab is effective in treating difficult-to-treat areas, such as hand and foot (either palmoplantar plaque or pustular), nail, and scalp psoriasis.[43]

The impact of ustekinumab on patients' health-related quality of life (QOL) was evaluated in the PHOENIX 2 trial.[99] Patients showed a significant improvement not only in skin-related QOL, but also in symptoms of anxiety and depression (as assessed by the Hospital Anxiety and Depression Scale).[98] The subset of patients with PsA in PHOENIX 1 and PHOENIX 2 also showed significant improvement in QOL, anxiety, and depression.[100]

Weight-based dosing rather than fixed-dose was found to be clinically significant for efficacy in PHOENIX 1 and PHOENIX 2—heavier patients required a higher dose.[101] Serum ustekinumab concentrations were also affected by weight.[101] Clinical response appears to be related to serum ustekinumab levels achieved.[96] Dosing is 45 mg for patients weighing 100 kg (220 lb) or less, and 90 mg for those of higher weights. Ustekinumab is administered subcutaneously at weeks 0 and 4, then every 12 weeks thereafter as maintenance therapy.[14,96] In cases where a loss of response is detected in the patient, the dose can be increased from 45 mg every 12 weeks to 90 mg every 8 weeks to improve response.[14]

Cumulative 3-year safety data from PHOENIX 1 & 2 have been published[102,103] and to-date there is 5-year safety data.[84] Common adverse effects include upper respiratory infections, headache, fatigue, pruritus, back pain, injection site reactions, and arthralgia, with the most common events being headache and nasopharyngitis.[102] Ustekinumab does not appear to exacerbate atopic diseases.[102] Serious adverse effects include those seen with other

biologics, including serious tubercular, fungal, viral infections, and cancers. No evidence of a dose-response to infection rates was seen.[103] Serious infections and malignancy rates did not increase with long-term ustekinumab treatment up to 3 years.[102,103] In addition, a reversible posterior leukoencephalopathy syndrome (RPLS) has been reported.[83,84] Regarding major adverse cardiovascular events (MACE), 5-year follow-up of clinical trials did not show an increased risk with ustekinumab.[84,104]

IL-17 Inhibitors: Secukinumab, Ixekizumab, and Brodalumab IL-17 a proinflammatory cytokine. It is a key cytokine in the pathogenesis of psoriasis—binding to receptors on keratinocytes leads to increased inflammation and recruitment of inflammatory cell types, resulting in the characteristic psoriatic plaques.[35]

IL-17 inhibitors are useful in blocking this process. These agents have comparable efficacies, and some adverse effects are similar, such as an increased risk of infection—in particular mucocutaneous *Candida* infection.[43] Patients with a history of or active inflammatory bowel disease (IBD) may experience worsening or reactivation, and IL-17 inhibitors should be avoided in these patients.[43] Neutralizing antibodies to specific IL-17 inhibitors have been reported, and their presence may be associated with lower serum concentrations of the biologic and reduced efficacy.[43]

Secukinumab is a fully human IgG1κ monoclonal antibody that selectively binds and inhibits IL-17A, thus inhibiting the release of chemokines and other proinflammatory mediators. It was approved in the United States and Canada in 2015 for the treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.[43,105] The approval was based on the results of four RCTs (including ERASURE and FIXTURE)[106] that included more than 2,000 patients. Secukinumab was shown to induce a rapid response with clinically significant greater PASI rates by week 12, and continued treatment was associated with sustained high responses through week 52.[106]

The CLEAR study compared secukinumab to ustekinumab and found greater efficacy at week 16 with secukinumab.[107] Secukinumab showed greater efficacy at 300 mg than at 150 mg in several RCTs and appeared to be equally safe.[43] Thus, the recommended dosing regimen is 300 mg (as two subcutaneous injections of 150 mg) at weeks 0, 1, 2, and 3, followed by 300 mg as a maintenance dose starting at week 4.[43,105] However, a 150-mg dose may be acceptable for some patients.[43,106] The 300-mg dose may be more effective in

treating head, neck, nail, palmoplantar, erythrodermic, and generalized pustular psoriasis.[43,108–111] Adverse effects from clinical trials commonly included nasopharyngitis, headache, upper respiratory tract infection, diarrhea, and uncommonly included neutropenia and detection of anti-secukinumab antibodies.[43,105,106]

Ixekizumab is a humanized IgG4 monoclonal antibody that neutralizes IL-17A.[43] Binding to IL-17A prevents it from binding to its target IL-17 receptor, thus reducing/attenuating the expression of cytokines including interferon gamma, IL-17, IL-22, and Il-23.[35] It is indicated for moderate-to-severe psoriasis; pivotal clinical trials include UNCOVER-1, UNCOVER-2, UNCOVER-3, and IXORA-S.[35,43] UNCOVER-3 was a phase 3 RCT that showed that ixekizumab was superior to etanercept after a 12-week induction phase.[32,112] The percentages of patients achieving PASI 75, PASI 90, and PASI 100 were 84%, 65%, and 35% with ixekizumab versus 53%, 26%, and 7% with etanercept, respectively.[43,112] Placebo responses were 7%, 3.1%, and 0%, respectively.[112] IXORA-S was a phase 3 RCT comparing efficacy of ixekizumab with ustekinumab at the label doses. At week 12, patients achieving PASI 90 were 73% with ixekizumab versus 42% with ustekinumab.[43,113] Ixekizumab also appears efficacious for palmoplantar (nonpustular), nail, scalp, erythrodermic, inverse, and generalized pustular psoriasis.[43]

Recommended dosing for ixekizumab is an initial dose of 160 mg (self-administered subcutaneously) followed by 80 mg every 2 weeks until week 12, followed by a maintenance phase of 80 mg every 4 weeks thereafter.[35,43] Adverse events from clinical trials include nasopharyngitis, URTI, injection site reactions, with the most serious being cellulitis (0.4%); MACE was rare (one patient with a stroke).[35] Neutralizing anti-ixekizumab antibodies develop over time and are associated with reduced drug concentrations and loss of efficacy.[43]

Brodalumab is a fully human IgG2 anti-IL-17RA monoclonal antibody that binds to the IL-17 receptor A and blocks the biologic activities of cytokines including IL-17A, IL-17F, IL-17A/F, IL-17A/F heterodimer, IL-17C, and IL-17E (also known as IL-25).[35,43] Pivotal clinical trials include IMAGINE-1, IMAGINE-2, and IMAGINE-3. In both IMAGINE-2 and IMAGINE-3, brodalumab at 210-mg doses had higher PASI 90 and PASI 100 response rates than ustekinumab.[35,43] Brodalumab is also efficacious in erythrodermic, nail, scalp, generalized pustular psoriasis, and psoriatic arthritis.[43] Recommended dosing is 210 mg subcutaneously self-injected on weeks 0, 1, and 2 then 210 mg every 2 weeks.[43]

The most frequent adverse effects in clinical trials of brodalumab were arthralgia, headache, fatigue, diarrhea, oropharyngeal pain, nausea, and infections were seen in 25% of patients (mostly URTI, nasopharyngitis, UTI, bronchitis, influenza, and nonserious skin and mucosal *Candida* infections.)[35] The most serious potential risk is suicidal ideation or behavior which occurred in 34 of 4,464 patients treated with brodalumab (ie, a rate of 0.37 per 100 participant-years.)[35] Thus, brodalumab has a black box warning, and it is contraindicated in patients with suicidal ideation, recent suicidal behavior, or history of suicidal ideation. In addition, brodalumab is only available through a risk evaluation and mitigation strategy (REMS) program,[35,43] the SILIQ REMS.[43]

IL-23 Inhibitors: Guselkumab, Tildrakizumab, Risankizumab Acting through a transcription pathway, IL-23 induces a population of T-helper cells (designated as TH17 cells) with a unique inflammatory gene signature that is important in the pathogenesis of psoriasis and other autoimmune diseases.[114] IL-23 inhibitors block/bind to the p19 subunit of IL-23.[43] Neutralizing antibodies to specific IL-17 inhibitors have been reported and their presence may be associated with lower serum concentrations of the biologic and reduced efficacy.[43] In patients on these agents who are not responding adequately, dose escalation may be needed or other modalities (eg, TCS, vitamin D analogues, methotrexate, or UVB) added.[43]

Guselkumab is a fully human IgG1 lambda monoclonal antibody that blocks the p19 subunit of IL-23.[43] A phase 3 RCT (VOYAGE 2) comparing guselkumab with adalimumab and placebo found greater efficacy at week 16 (PASI 90 was 70% vs 47% for adalimumab and 2.4% for placebo).[115] Furthermore, 66% of adalimumab nonresponders switched to guselkumab reached PASI 90 at week 48.[43,115] The recommended dose is 100-mg SC at weeks 0 and 4, and every 8 weeks thereafter.[43] The agent has also been shown to be effective for scalp, nail, and plaque-type palmoplantar psoriasis.[43]

Tildrakizumab is a humanized IgG1 monoclonal antibody designed to selectively block IL-23 by binding to the p19 subunit.[43] A phase 3 RCT (reSURFACE 2) comparing 2 doses of tildrakizumab (200 mg and 100 mg) to etanercept and placebo found greater efficacy at week 12 with either dose of tildrakizumab than with etanercept (66% of patients on tildrakizumab 200 mg achieving PASI 75 and 61% for tildrakizumab 100 mg, compared with 48% for etanercept and 6% with placebo).[116] PASI 90 was achieved by 37% (200-mg dose), 39% (100-mg dose), 21% (etanercept), and 1% (placebo) of

participants.[43,116] The recommended dose is 100 mg subcutaneously administered *only by a healthcare provider* at weeks 0 and 4, and every 12 weeks thereafter.[43]

Risankizumab is a humanized IgG1 monoclonal antibody that selectively inhibits IL-23 by binding to the p19 subunit; it appears to be more efficacious than ustekinumab.[43,117–119] The agent received FDA and Health Canada approvals in April 2019 for treatment of moderate-to-severe plaque psoriasis. The approval decisions were supported by positive results from four phase 3 RCTs: ultIMMa-1, ultIMMa-2, IMMhance, and IMMvent.[117–119] From clinical trials, at week 12, PASI 90 for risankizumab was about 75% (90 mg and 180 mg doses pooled) versus about 40% to 45% for ustekinumab (weight-based dosing).[43,118] Recommended dosing is risankizumab 75 mg for 2 doses (totaling 150 mg) at weeks 0 and 4, followed by 150 mg as two injections every 12 weeks thereafter.

Switching Between Biologic Agents Switching between biologic agents to possibly improve efficacy, safety, and/or tolerability is a useful consideration. Biologics that develop neutralizing antibodies may have reduced efficacy over time (secondary failure),[43] and sustainability for more than 3 years is currently a treatment target for a biologic agent—and 3 years is not that long a time for a chronic disease such as psoriasis.

Switching to another biologic even within its own class of biologics may restore efficacy. However, not all switches result in improvement, and currently there are no recommendations for specific switches in US guidelines, nor recommendations for the duration interval between discontinuing one biologic and starting another.[43]

BAD provided some general recommendations in its 2017 guidelines: Consider using a 1-month washout period, or the length of the treatment cycle (whichever is longer), between the last dose of the current biologic therapy and the planned date of a new biologic initiation.[42] BAD also recommended taking into consideration the pharmacology of the agents, the patient's clinical circumstances, and the patient's views on the risks and benefits of transitioning option(s).[42]

Another strategy to increase biologic drug survival is the concomitant use of other agents (eg, methotrexate) as further discussed below.

Combination Therapies

Combination therapies may be beneficial in the management of plaque psoriasis: generally to either enhance efficacy or minimize toxicity. As shown in Figs. 114-1 and 114-2 above, combinations can include two topical agents, a topical agents plus phototherapy, a systemic agent plus topical therapy, a systemic agent plus phototherapy, two systemic agents used in rotation, or a biologic agent with either a systemic agent or a topical agent.

The combination of a topical corticosteroid and a topical vitamin D_3 analog is particularly useful. This was shown in several studies to be efficacious and safe, with less skin irritation than monotherapy with either agent, and the combination product containing calcipotriol and betamethasone dipropionate ointment has demonstrated efficacy in RCTs for patients with relatively severe psoriasis.[14,38] The combination may also be steroid sparing.[38]

The combination of retinoids with phototherapy has also been shown to increase efficacy. Because retinoids may be photosensitizing and increase the risk of burning after ultraviolet (UV) light exposure, doses of phototherapy should be reduced to minimize adverse effects. A RCT with tazarotene and broadband UVB not only showed significant enhancement of UVB efficacy but also reduced the number of UVB treatment sessions needed for response.[36,38,121] The combination of acitretin and broadband UVB reduced the number of needed treatments, compared with UVB alone.[14,122] Acitretin with NB-UVB (RE-UVB) was highly effective for patients with difficult-to-control psoriasis.[38,123] The combination of acitretin and PUVA (RE-PUVA) also showed greater efficacy than monotherapy with either agent.[36,124] RE-PUVA can be used to achieve clearance with up to a twofold reduction in total UV exposure.[14] Phototherapy has also been used with other topical agents, such as UVB with coal tar (Goeckerman regimen)[67] to increase treatment response, because coal tar is also photosensitizing.

Cyclosporine and calcipotriol/betamethasone dipropionate in combination is superior to cyclosporine alone.[27] Cyclosporine may also be successfully used with SCAT; however, it should not be used with PUVA due to reduced efficacy and the potential increase risk of cutaneous malignancies.[40]

The combination of MTX and UVB appears to be synergistic.[37,41] There is also evidence that MTX in combination with biologics is beneficial. MTX has been effectively used in conjunction with etanercept, infliximab, adalimumab, ustekinumab, and others. MTX in combination with adalimumab or infliximab is widely used in rheumatology, and low-dose MTX (eg, 7.5-10 mg once per week) is likely sufficient to reduce formation of anti-biologic-antibodies and increase

the respective trough levels of adalimumab or infliximab.[27] Infliximab given concurrently with MTX or azathioprine may result in a lower incidence of infusion reactions to infliximab.[39]

Biologics used in combination with nonbiologic therapies are being explored and recommended, sometimes with just a theoretical rationale (ie, without RCT backup yet). In particular, the concept of increasing biologic survival with the addition of an immunosuppressive agent that reduces the development of neutralizing biologic antibodies is gaining acceptance as experience and clinical evidence accumulates with their use. Newer biologics whose use is associated with neutralizing antibodies are often used together with an immunosuppressive agent such as MTX.[43]

Other Drug Treatments

Selective Phosphodiesterase-4 (PDE4) Inhibitors: Crisaborole, Apremilast A relatively new approach to management of inflammatory skin conditions such as psoriasis and atopic dermatitis (AD) is targeted inhibition of phosphodiesterase 4 (PDE4).[125] PDE4 inhibition causes an increase in intracellular cyclic AMP (cAMP), which leads to multiple effects, including reduced production of pro-inflammatory mediators.[125] Currently, two selective PDE4 inhibitors have been marketed with different approved indications. Apremilast is a systemic agent for psoriasis and PsA, Crisaborole is a topical ointment which has been approved for AD; it has only limited clinical trial evidence in plaque psoriasis.[126]

Apremilast is an oral tablet approved in the United States and Canada for patients with active PsA or moderate-to-severe psoriasis. It has shown efficacy and safety in 2 Phase III RCT (ESTEEM 1 and ESTEEM 2) for patients with psoriasis.[127] Recommended dosing is 10 mg on day 1, 10 mg twice daily on day 2, 10 mg in the morning and 20 mg in the evening on day 3, 20 mg twice daily on day 4, 20 mg in the morning and 30 mg in the evening on day 5, then 30 mg twice daily thereafter. Dosing if renally impaired (CrCl <30 mL/min [0.5 mL/s]) is 10 mg in the morning on days 1 to 3; titrate using morning doses only (skip evening doses) to 20 mg on days 4 and 5, with maintenance dose of 30 mg once daily in the morning thereafter.

Apremilast may be taken without regard to food; however, it should not be crushed, chewed, or split. There are drug interactions: the levels/effects of apremilast may be decreased by bosentan, CYP3A4 inducers (moderate and strong); dabrafenib, deferasirox, ivosidenib, lorlatinib, pitolisant, sarilumab, siltuximab, tocilizumab, and St. John’s wort.[128]

Mycophenolate Mofetil Mycophenolate mofetil (MMF) is a systemic agent occasionally used for patients with resistant cases of moderate-to-severe psoriasis.[14] This is currently not an approved indication in either Canada or the United States (off-label use).

A few reports and small studies are available describing the efficacy of MMF when used as monotherapy or adjuvant therapy.[129] In addition, one small study evaluated the switch for eight patients with severe psoriasis from cyclosporine to MMF after a washout period of 2 to 4 weeks. On cyclosporine, seven of these patients had deteriorating renal function and hypertension, and one experienced loss of efficacy.[130] After the switch to MMF, there was significant loss of psoriasis control in five of the eight patients but also significant improvement in renal function for six patients.[129,130]

Conversely, another small study evaluated the sequential use of MMF followed by cyclosporine in eight patients with moderate-to-severe psoriasis.[131] There was significant improvement with MMF in all patients, and all patients further improved when switched to cyclosporine.[131]

MMF has some uncommon but significant adverse effects, including increased incidence of opportunistic infections such as cytomegalovirus, cryptococcosis, candidiasis, and *Pneumocystis jirovecii*.[4,129] Cases of progressive multifocal leukoencephalopathy have also been reported.[129] There may be an associated risk of malignancy.[132]

Hydroxyurea Hydroxyurea is an antimetabolite usually used for cancer treatments, but it has also been used in the systemic treatment of psoriasis for more than 30 years.[14,37] It is still occasionally tried for patients with recalcitrant severe psoriasis, although biologics may be a better option for these patients.

Hydroxyurea has been compared with MTX for patients with moderate-to-severe psoriasis.[133] Weekly regimens showed greater efficacy for MTX with a faster clearance rate, although hydroxyurea was also efficacious. The authors concluded that weekly doses of hydroxyurea may be an alternative to MTX for patients experiencing intolerable MTX side effects or have reached the recommended cumulative MTX dose.[133]

Adverse effects of hydroxyurea include significant bone marrow suppression, lesional erythema, localized tenderness, and reversible hyperpigmentation.[14,133]

Complementary and Alternative Medicines

The use of complementary and alternative medicine (CAM) among patients with

psoriasis is common, with a prevalence of 43% to 69% in various studies.[134] Most of these patients use herbs, special diets, or dietary supplements in conjunction with their usual antipsoriatic medications and not as replacements. Most patients do not discuss CAM use with their physicians.[134]

A 2009 systematic review of RCTs found that, although there is a large body of literature on CAM use in psoriasis, the quality of most studies was relatively low.[134] CAM agents and interventions with documented clinical efficacy in psoriasis include *Mahonia aquifolium*, fish oil, climatotherapy (Dead Sea salts), and stress reduction techniques.

Mahonia aquafolium (Oregon grape, Mountain grape, or barberry but *not* European barberry) is an evergreen native to southern British Columbia, western Oregon, and northern Idaho. The rhizome and root contain berberine as the primary active constituent. Berberine is an alkaloid that inhibits keratinocyte growth and reduces keratinocyte proliferation, and it also has antibacterial and antifungal activities. In at least two clinical trials *Mahonia aquifolium* was efficacious in reducing disease severity: In one randomized placebo-controlled study a *Mahonia aquifolium* 10% preparation applied topically twice daily resulted in a significant improvement in the PASI score and the Quality of Life Index (QLI), compared with placebo.[135] Adverse effects in clinical trials included rash, burning sensation, redness, and itching.

Fish oil contains two important long-chain polyunsaturated fatty acids—eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA and DHA are omega-3 fatty acids. They act as substrates competing with arachidonic acid for cyclooxygenase and lipoxygenase, thus reducing the production of proinflammatory molecules in psoriatic plaques.[134] Several randomized placebo-controlled and/or comparative trials for patients with psoriasis have demonstrated efficacy of fish oils. One study comparing EPA plus etretinate to etretinate monotherapy found significantly greater efficacy with the combination of EPA plus etretinate.[136]

Climatotherapy refers to the practice of traveling to the Dead Sea and sunbathing and/or bathing in the sea—the beneficial effects are likely from the high salinity of the sea and UV rays.[134] Several studies have demonstrated efficacy, including two studies using saline spa baths. One study used highly concentrated (25%-27%) saline spa baths plus UVB compared with UVB alone, and the other used low concentrated (4.5%-12%) saline spa bath plus UVB again compared with UVB alone. In both studies the clinical response was significantly better with the saline spa bath plus UVB combination.[134,137,138]

Stress-reduction techniques have inconsistently shown some benefit. One

randomized study demonstrated that both meditation or meditation and imagery were efficacious as adjunctive treatments for patients with scalp psoriasis.[139] A second randomized study for patients with psoriasis receiving either UVB or PUVA therapy showed that the addition of a mindfulness-based stress-reduction audiotape played during light treatments reduced response times for patients receiving UVB but not PUVA therapy.[140] This confirmed the belief that psychological stress plays a role in psoriasis. More recently, in a case-control study of risk factors during the year before the onset of psoriasis, stressful life events were found to be significant.[141,142]

Personalized Pharmacotherapy

Despite the availability of good quality evidence and clinical practice guidelines, patients with psoriasis are still often undertreated or inappropriately managed.[28] A 2007 study in the United States involving 1,657 patients from National Psoriasis Foundation surveys found that 40% of patients with psoriasis were receiving no current treatment; of those, 27% had psoriasis involving >10% BSA.[143] In addition, those receiving care may be undertreated.[143] Early access to care and adherence may also be issues.

Patient-specific therapies that take into consideration comorbid illnesses, adherence, and pharmacoeconomic issues in addition to the patient's psoriatic manifestations and responses to treatments are important, and will ultimately improve the quality of care. Treatment goals need to be patient-specific and defined for both short-term and long-term management time frames.[28] Without optimizing patient care, the concern is that patients with poorly managed psoriasis may follow a "diminished" life course compared with the course they might have taken if they did not have psoriasis, as the disease has significant psychological, social, and economic impacts in addition to its physical manifestations.[144]

To this end, a current focus is defining frameworks,[144] specific treatment goals[27,28] and targets[29] for implementation of practice guidelines, as described earlier in this chapter. The reader is encouraged to review the noted references for further information.

Special Populations

Psoriasis in Children Every year, an estimated 20,000 children under 10 years of age are diagnosed with psoriasis.[145] Psoriasis in infants is uncommon, but it does occur.[145] Pediatric psoriasis is more often attributable to direct precipitating

factors such as skin trauma, infections, drugs, or stress.[14,146] Compared with adults, plaque lesions in children are often smaller, thinner, and less scaly, which can make diagnosis more difficult. Face and flexures are more commonly involved than for adults. Psoriatic diaper rash can occur up to age 2. PsA is rare.[14]

Psoriasis in children is associated with cardiovascular risk factors and the metabolic syndrome.[14] Cardiovascular risk factors include being overweight, obesity, hyperlipidemia, hypertension, high blood glucose, and diabetes.[14] Obesity and excessive waist circumference (central adiposity) are higher in children with severe psoriasis, and in general are higher in childhood psoriasis than in adults.[14,149] Adolescent girls who are overweight are at increased risk of later developing moderate-to-severe psoriasis, suggesting that obesity precedes the onset of psoriasis.[14,150]

Thus, nonpharmacologic management strategies in children also include minimizing cardiovascular risk factors and the development of the metabolic syndrome. The importance of maintaining a healthy lifestyle with good eating habits, exercise, and weight balance is crucial information to communicate to the child/adolescent and caregivers.

Topical treatment is the standard of care for children with psoriasis.[14,147] Calcipotriol with or without TCS has been recommended as treatment of first choice[14,147] because it produces minimal adverse effects.[14] Since children's skin is thinner and better hydrated than that of adults, they are at higher risk of drug absorption leading to systemic adverse effects. If a TCS is needed, the lowest potency TCS that provides control should be used, and it should be tapered as the lesions improve. If long-term calcipotriol is used, monitoring of ionized calcium is recommended because of the risk of hypercalcemia.[14] For treatment-resistant or moderate-to-severe psoriasis, anthralin is suggested, followed by short-term UVB in adolescents.[14,147]

Systemic therapies are reserved for children with severe and recalcitrant psoriasis.[14,147] MTX can provide near to complete clearance[147] and has been recommended as the systemic treatment of choice.[14] MTX can be safely used to control severe childhood psoriatic episodes and then withdrawn as lesions improve.[14] Regular monitoring for liver and blood toxicity is required.[14] Etanercept has been recommended as a third-line option[14]; an RCT in 211 children and adolescents (4-17 years) with moderate-to-severe plaque psoriasis showed that etanercept significantly reduced disease severity; however, four serious adverse events occurred (ovarian cyst requiring removal, gastroenteritis,

gastroenteritis-associated dehydration, and left basilar pneumonia).[148] Etanercept has been studied in children with polyarticular juvenile rheumatoid arthritis without new safety concerns emerging.[14] Currently, ustekinumab and adalimumab are being studied in childhood psoriasis.[14]

Phototherapy should be used with caution, especially for younger children, because of long-term carcinogenic risks and phototoxicities. For older children and adolescents with severe, extensive, or treatment-resistant disease, UVB may be a treatment option.[14]

Psoriasis in Pregnancy Hormonal changes in pregnancy can improve symptoms for patients with plaque psoriasis. In one study, 55% of patients showed improvements during pregnancy.[14,151] For patients with more than 10% BSA involvement who reported improvement, lesions decreased by more than 80% during pregnancy.[151] This appeared to correlate with high estrogen but not progesterone levels.[151] Thus, some pregnant women may require minimal treatment for their psoriasis.

Some antipsoriatic drugs have significant teratogenic risks, making them contraindicated in pregnancy. Thus, women of childbearing potential must use effective birth control during therapy, and may need to continue effective contraception after discontinuing therapy for a period of time, as discussed in detail throughout this chapter. In addition, some drugs may carry known teratogenic risks in animal studies or have limited available data for use in pregnancy in humans.

UVB has been considered the safest treatment for extensive psoriasis during pregnancy. It is recommended for patients with widespread disease not controlled by topical agents. One problem with this therapy is an increased potential for reactivation of herpes simplex, which may be transmitted to the infant at delivery.[14]

For more detailed information about antipsoriatic drugs in pregnancy, a systematic, drug-by-drug review of case reports and case-control studies is available.[152] The 2009 Canadian Guidelines provides a drug-by-drug summary of recommendations for topical agents, phototherapy, and systemic agents in pregnancy.[14] The 2015 European S3 Guidelines provides a discussion about most appropriate treatments for women with a wish for pregnancy in the near future, and which treatments to avoid.[27]

Psoriasis in Older Adults Age-related changes in organ function / drug clearance and greater drug sensitivity increase the risk of adverse drug events for

elderly patients with psoriasis.

MTX is hepatotoxic and should be used with caution in older adults. Cyclosporine has nephrotoxic potential and may also increase blood pressure. Both drugs have significant drug interactions, and polypharmacy, common in older patients, make management of interactions challenging.

In addition, older patients may have preexisting comorbidities, such as hyperlipidemia and metabolic syndrome, and this may further limit drug selection. Adalimumab appears equally efficacious in patients age 65 years or older who may have higher incidences of hypertension, hyperlipidemia, depression, obesity, and diabetes.[153] Adverse-effect profiles were similar between subgroups (various weights and comorbidities) with no significant differences in serious adverse events.[153] Ustekinumab requires no dosage adjustments for renal or hepatic impairments and geriatric dosing is the same as for adults younger than 65, with the dose based on weight. Secukinumab also requires no dosage change in older adults and those with renal/hepatic impairment.

Topical psoriasis treatments are often prescribed for older adults as first-line therapy[14]; however, even with topicals, adverse effects—including systemic ones—can occur with greater frequency in these patients.[14]

Psoriasis in Patients with a History of Solid Tumors As discussed throughout this chapter, many antipsoriatic therapies carry significant cancer risks. PUVA, systemic therapies such as cyclosporine, and some biologics are associated with increased risks of oncologic disorders.

A systematic review of the risk of malignancy associated with therapies for moderate-to-severe psoriasis confirmed the following[132]: PUVA is associated with an increased risk of cutaneous SCC and malignant melanoma; UVB is a much safer therapeutic modality than PUVA; cyclosporine increases risks of lymphoma, internal malignancies, and skin cancers; methotrexate may be associated with increased melanoma and Epstein-Barr virus–associated lymphomas; MMF may be associated with lymphoproliferative disorders; and the malignancy risk may be increased for biologic agents, especially the TNF-α inhibitors.[132]

The 2009 Canadian guidelines recommend that TNF-α inhibitors be used with caution for patients with a history of malignancy or existing malignancies, and the T-cell modulator alefacept (now voluntarily withdrawn from the United States and Canadian markets) is contraindicated for these patients.[14] There are currently registry safety databases (PSOLAR,[154] BADBIR,[155] PsoBest[156,157]) for

biologics; over time, these will provide biologic-specific and updated safety information.[157] Known risks in general include the development of neoplasms such as nonmelanoma skin cancer.[84]

Pharmacoeconomic Considerations

10 The wide gap in costs of agents for psoriasis makes economics and availability of insurance or other coverage important considerations in formulating a therapeutic plan.

Currently, the biologics are often considered for patients with moderate-to-severe psoriasis when less expensive traditional systemic agents are inadequate or relatively contraindicated. Biologics have also been recommended as first-line therapy, alongside conventional systemic agents, for patients with moderate-to-severe psoriasis; however, in practice, drug access secondary to cost considerations can limit use. These agents may be needed early, though, for some patients with comorbidities, such as PsA.

A pharmacoeconomic analysis of biologics in the treatment of psoriasis suggests that the cost-to-benefit ratio for biologics may be favorable.[158] This analysis was performed in 2009 when available biologics were fewer and more expensive than today; thus the conclusions would likely still be applicable today, especially with the availability of less expensive biosimilars for many biologics. There are of course cost differences among the biologics. In 2012, cost and efficacy comparisons of the TNF-α inhibitors and ustekinumab were presented as follows: etanercept was the least costly, followed by adalimumab than infliximab.[159] However, etanercept was less efficacious. Adalimumab (at doses of 40 mg every other week) was significantly less costly than ustekinumab, with similar efficacies, in patients with suboptimal response to etanercept.[160]

CONCLUSIONS

Psoriasis is a lifelong illness with no known cure. Significant comorbidities may coexist. Treatment should be patient-specific, with consideration given to disease severity, patient risk factors, age, and comorbidities. Newer treatment modalities, including numerous biologics, are now parts of the armamentarium available in the management of this disease.

Postclass Engaged Learning Activity

There is a plethora of information readily available online for the patient with psoriasis, some of which are housed at more trustworthy and unbiased locations (such as the National Psoriasis Foundation in the United States). Review patient education material available online and identify patient education materials that you would provide to your patients.

ABBREVIATIONS

BAD	British Association of Dermatologists
BADBIR	British Association of Dermatologists Biologic Interventions Register
BMI	body mass index
BRM	biologic response modifier (This term has been replaced by “biologic agents.”)
BSA	body surface area
CAM	complementary and alternative medicine
CDA	Canadian Dermatology Association
CHD	coronary heart disease
CHF	chronic heart failure
CRP	C-reactive protein
CYP3A4	cytochrome P450 isoenzyme 3A4
DBPC	double-blind placebo-controlled
DHA	docosahexaenoic acid
DISH	disseminated (or diffuse) idiopathic skeletal hyperostosis
DLQI	Dermatology Life Quality Index
EPA	eicosapentaenoic acid
FDA	Food and Drug Administration
GFR	glomerular filtration rate
HLA-C	major histocompatibility complex antigen
HPA	hypothalamic–pituitary–adrenal
IL	interleukin
MACE	major adverse cardiovascular events

MMF	mycophenolate mofetil
MI	myocardial infarction
NPF	National Psoriasis Foundation
NSAIDs	nonsteroidal anti-inflammatory drugs
NB-UVB	narrowband ultraviolet B (311-nm ultraviolet B light)
OR	odds ratio
PASI	psoriasis area and severity index
PGA	Physician's Global Assessment
PsA	psoriatic arthritis
PUVA	psoralens with ultraviolet A light
QOL	quality of life
QLI	Quality of Life Index
RCT	randomized controlled trial
RE-PUVA	retinoid plus PUVA (as combination therapy)
RE-UVB	retinoid plus NBUVB (as combination therapy)
RPLS	reversible posterior leukoencephalopathy syndrome
RR	relative risk
SCAT	short-contact anthralin therapy
SCC	squamous cell carcinoma
SF-36	Short Form Health Survey
SPF	sun protection factor
TB	tuberculosis
TNF-α	Tumor necrosis factor-α
UV	ultraviolet
UVA	ultraviolet A (315-400 nm ultraviolet A light)
UVB	ultraviolet B, or broadband UVB (28-315 nm ultraviolet B light)

REFERENCES

1. Law RM. Chapter 64: Psoriasis. In: Chisholm-Burns M, ed. *Pharmacotherapy Principles and Practice*. 3rd ed. New York: McGraw-Hill; 2013:1127–1141.
2. Reich K. The concept of psoriasis as a systemic inflammation:

Implications for disease management. *J Eur Acad Dermatol Venereol*. 2012;26(suppl 2):3–11.

3. Gulliver WP, Pirzada SM. Psoriasis: More than skin deep. In: Saeland S, ed. *Recent Advances in Skin Immunology*. Kevala, India: Research Signpost; 2008:167–179.
4. Boehncke WH, Schon MP. Psoriasis. *Lancet*. 2015; 386:983–994.
5. Kimmel GW, Lebwohl M. Psoriasis: Overview and diagnosis. In: Bhutani T, Liao W, Nakamura M, eds. *Evidence-Based Psoriasis, Diagnosis and Treatment*. Cham, Switzerland: Springer International Publishing AG; 2018;1–16. A textbook in the series Updates in Clinical Dermatology, with series editors Berth-Jones J, Gob CL, and Maibach HI.http://www.springer.com/series/13203.
6. Boehncke WH, Boehncke S, Tobin AM, Kirby B. The 'psoriatic march': A concept of how severe psoriasis may drive cardiovascular comorbidity. *Exp Dermatol*. 2011;147:1031–1039.
7. Grozdev I, Korman N, Tsankov N. Psoriasis as a systemic disease. *Clinics in Dermatology*. 2014;32:343–350.
8. Farber E, Bright R, Nall M. Psoriasis: A questionnaire survey of 2144 patients. *Arch Dermatol*. 1974;98:248–259.
9. Farber EM, Nall ML, Watson W. Natural history of psoriasis in 61 twin pairs. *Arch Dermatol*. 1974;109:207–211.
10. Nall L, Gulliver WP, Charmley P, et al. Search for the psoriasis susceptibility gene: The Newfoundland Study. *Cutis*. 1999;64:323–329.
11. Nair RP, Duffin KC, Helms C, et al. Genome-wide scan reveals association of psoriasis with IL-23 and NF-κB pathways. *Nat Genet*. 2009;41:199–204.
12. Raychaudhuri SP, Jiang W-Y, Raychaudhuri SK. Revisiting the Koebner phenomenon. *Am J Pathol*. 2008;172:961–971.
13. Basavaraj KH, Ashok NM, Rashmi R, Praveen TK. The role of drugs in the induction and/or exacerbation of psoriasis. *Int J Dermatol*. 2010;49:1351–1361.
14. Papp KA, Gulliver W, Lynde CW, Poulin Y(Steering Committee). Canadian Guidelines for the Management of Plaque Psoriasis. 1st Edition, June 2009. Available at: https://dermatology.ca/dermatologists/guidelines/psoriasis. Also see: Canadian Psoriasis Guidelines Addendum Committee. Addendum to the Canadian Guidelines for the Management of Plaque Psoriasis, May 2016.

J Cutan Med Surg. 2016;20(5):375-431. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5014087/. Accessed Mar. 26, 2019.

15. Boehncke S, Boehncke WH. 'Upgrading' psoriasis responsibly. *Experimental Dermatology*. 2014;23:710–711.
16. Guenther L, Gulliver W. Psoriasis comorbidities. *J Cutan Med Surg*. 2009;13(suppl 2>):S77–S87.
17. Kimball AB, Gladman D, Gelfand JM, et al. National Psoriasis Foundation clinical consensus on psoriasis comorbidities and recommendations for screening. *J Am Acad Dermatol*. 2008;58:1031–1042.
18. Gulliver WP. Importance of screening for comorbidities in psoriasis patients. *Expert Rev Dermatol*. 2008;3:133–135.
19. Gelfand JM, Gladman Dd, Mease PJ, et al. Epidemiology of psoriatic arthritis in the population of the United States. *J Am Acad Dermatol*. 2005;53:573–577.
20. Rahman P, O'Reilly DD. Psoriatic arthritis genetic susceptibility and pharmacogenetics. *Pharmacogenomics*. 2008;9:195–205.
21. Wilson PW, D'Agostino RB, Parise H, et al. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation*. 2005;112:3066–3072.
22. Kimball AB, Guerin A, Latremouille-Viau D, et al. Coronary heart disease and stroke risk in patients with psoriasis: Retrospective analysis. *Am J Med*. 2010;123:350–357.
23. Dowlatshani EA, Wakkee M, Arends LR, et al. The prevalence and odds of depressive symptoms and clinical depression in psoriasis patients: A systematic review and meta-analysis. *J Invest Dermatol*. 2014;136(6):1542–1551.
24. Gelfand JM, Neimann AL, Shin DB, et al. Risk of myocardial infarction in patients with psoriasis. *JAMA*. 2006;296:1735–1741.
25. Ahlehoff O, Skov L, Gislason G, et al. Cardiovascular disease event rates in patients with severe psoriasis treated with systemic anti-inflammatory drugs: A Danish real-world cohort study. *J Intern Med*. 2013;273(2):197–204.
26. Lan CC, Ko YC, Yu HS, et al. Methotrexate reduces the occurrence of cerebrovascular events among Taiwanese psoriatic patients: A nationwide population-based study. *Acta Derm Venereol*. 2012;92(4):349–352.

27. European S3-Guidelines on the systemic treatment of psoriasis vulgaris. Updated 2015. EDF in cooperation with EADV and IPC. *J Eur Acad Dermatol Venereol*. 2015;29(12):e1–22. Available at: https://www.edf.one/dam/jcr:d0c615a6-0631-4bf7-9f87-c8f95c21ab9b/European%20S3-Guidelines%20on%20the%20systemic%20treatment%20of%20psoriasis%
28. Mrowietz U. Implementing treatment goals for successful long-term management of psoriasis. *J Eur Acad Dermatol Venereol*. 2012;26(suppl 2):12–20.
29. Armstrong AW, Siegel MP, Bagel J, et al. From the Medical Board of the National Psoriasis Foundation: Treatment targets for plaque psoriasis. *J Am Acad Dermatol*. 2017;76(2):290–298.
30. Mrowietz U, Steinz K, Gerdes S. Psoriasis: To treat or to manage? *Experimental Dermatology*. 2014;23:705–709.
31. Law RMT, Gulliver WP. Chapter 110: Psoriasis. In: Schwinghammer TL, Koehler JM, eds. *Pharmacotherapy Casebook and Instructor's Guide: A Patient-Focused Approach*. 11th ed. New York: McGraw-Hill; 2019.
32. Jeon C, Sekhon S, Bhutani T, Koo J. Topical treatments. In: Bhutani T, Liao W, Nakamura M, eds. *Evidence-Based Psoriasis, Diagnosis and Treatment. (A textbook in the series Updates in Clinical Dermatology, with series editors Berth-Jones J, Gob CL, and Maibach HI, at http://www.springer.com/series/13203)*. Cham, Switzerland: Springer International Publishing AG; 2018;17–29.
33. Griffith JL, Zarbo AJ, Lim HW. Phototherapy and photochemotherapy. In: Bhutani T, Liao W, Nakamura M, eds. *Evidence-Based Psoriasis, Diagnosis and Treatment. (A textbook in the series Updates in Clinical Dermatology, with series editors Berth-Jones J, Gob CL, and Maibach HI., at http://www.springer.com/series/13203)*. Cham, Switzerland: Springer International Publishing AG; 2018;31–53.
34. Beck KM, Yang EJ, Afifian L, et al. Oral agents for psoriasis. In: Bhutani T, Liao W, Nakamura M, eds., et al. *Evidence-Based Psoriasis, Diagnosis and Treatment. (A textbook in the series Updates in Clinical Dermatology, with series editors Berth-Jones J, Gob CL, and Maibach HI., at http://www.springer.com/series/13203)*. Cham, Switzerland: Springer International Publishing AG; 2018;55–71.
35. Sekhon S, Jeon C, Liao W. Biologics. In: Bhutani T, Liao W, Nakamura M, eds. *Evidence-Based Psoriasis, Diagnosis and Treatment. (A textbook*

in the series Updates in Clinical Dermatology, with series editors Berth-Jones J, Gob CL, and Maibach HI., at http://www.springer.com/series/13203). Cham, Switzerland: Springer International Publishing AG; 2018;73–92.

36. Menter A, Korman NJ, Elmets CA, et al. 2009 Guidelines of care for the management of psoriasis and psoriatic arthritis—section 5. Guidelines of care for the treatment of psoriasis with phototherapy and photochemotherapy. *J Am Acad Dermatol*. 2010;62:114–135.
37. Menter A, Korman NJ, Elmets CA, et al. 2009 Guidelines of care for the management of psoriasis and psoriatic arthritis—section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. *J Am Acad Dermatol*. 2009;61:451–485.
38. Menter A, Korman NJ, Elmets CA, et al. 2009 Guidelines of care for the management of psoriasis and psoriatic arthritis—section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. *J Am Acad Dermatol*. 2009;60:643–659.
39. Menter A., Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis—section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2008;58:826–850.
40. Rosmarin DM, Lebwohl M, Elewski BE, et al. Cyclosporine and psoriasis: 2008 National psoriasis Foundation Consensus Conference. *J Am Acad Dermatol*. 2010;62:838–853.
41. Kalb RE, Strober B, Weinstein G, Lebwohl M. Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. *J Am Acad Dermatol*. 2009;60:824–837.
42. Smith CH, Jabbar-Lopez ZK, Yiu ZZ, et al. British Association of Dermatologists guidelines for biologic therapy for psoriasis 2017. *Br J Dermatol*. 2017;177(3):628–636.
43. Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2019;80(4):1029–1072.
44. Elmets CA, Leonardi CL, Davis DMR, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. *J Am Acad Dermatol*. 2019;80(4):1073–1113.
45. Paul C, Gallini A, Archier E, et al. Evidence-based recommendations on topical treatment and phototherapy of psoriasis: Systematic review and

expert opinion of a panel of dermatologists. *J Eur Acad Dermatol Venereol*. 2012;26(suppl 3):1–10.

46. Long CC, Finlay AY. The finger-tip unit—a new practical measure. *Clin Exp Dermatol*. 1991;16:444–447.
47. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: Case-based presentations and evidence-based conclusions. *J Am Acad Dermatol*. 2011;65:137–174.
48. Katz HI, Hien NT, Prawer SE, et al. Superpotent topical steroid treatment of psoriasis vulgaris – clinical efficacy and adrenal function. *J Am Acad Dermatol*. 1987;16(4):804–811.
49. Menter Kamili. Topical treatment of psoriasis. In: Yawalkar N, ed. *Current Problems in Dermatology*. Basel, Switzerland: S. Karger AG; 2009.
50. Krueger GG, O'Reilly MA, Weidner M, et al. Comparative efficacy of once-daily flurandrenolide tape versus twice-daily diflorasone diacetate ointment in the treatment of psoriasis. *J Am Acad Dermatol*. 1998;38:186–190.
51. Mason J, Mason AR, Cork MJ. Topical preparations for the treatment of psoriasis: A systemic review. *Br J Dermatol*. 2002;146: 351–364.
52. Castela E, Archier E, Devaux S, et al. Topical corticosteroids in plaque psoriasis: A systematic review of efficacy and treatment modalities. *J Euro Acad Dermatol Venereol*. 2012;26(suppl 3):36–46.
53. Katz HI, Prawer SE, Medansky RS, et al. Intermittent corticosteroid maintenance treatment of psoriasis: A double-blind multicenter trial of augmented betamethasone dipropionate ointment in a pulse dose treatment regimen. *Dermatol*. 1991;183:269–274.
54. Wall ARJ, Poyner TF, Menday AP. A comparison of treatment with dithranol and calcipotriol on the clinical severity and quality of life in patients with psoriasis. *Br J Dermatol*. 1998;139:1005–1011.
55. Cunliffe WJ, Berth-Jones J, Claudy A, et al. Comparative study of calcipotriol (MC 903) ointment and betamethasone 17-valerate ointment in patients with psoriasis vulgaris. *J Am Acad Dermatol*. 1992;26:736–743.
56. Kragballe K, Gjertsen BT, De Hoop D, et al. Double-blind, right/left comparison of calcipotriol and betamethasone valerate in treatment of psoriasis vulgaris. *Lancet*. 1991;337:193–196.

57. Devaux S, Castela A, Archier E, et al. Topical vitamin D analogues alone or in association with topical steroids for psoriasis: A systematic review. *J Euro Acad Dermatol Venereol*. 2012;26(suppl 3):52–60.
58. Weinstein GD, Krueger GG, Lowe NJ, et al. Tazarotene gel, a new retinoid, for topical therapy of psoriasis: Vehicle-controlled study of safety, efficacy, and duration of therapeutic effect. *J Am Acad Dermatol*. 1997;37:85–92.
59. Weinstein GD, Koo JY, Krueger GG, et al. Tazarotene cream in the treatment of psoriasis: Two multicenter, double-blind, randomized, vehicle-controlled studies of the safety and efficacy of tazarotene cream 0.05% and 0.1% applied once daily for 12 weeks. *J Am Acad Dermatol*. 2003;48:760–767.
60. McGill A, Frank A, Emmett N, et al. The anti-psoriatic drug anthralin accumulates in keratinocyte mitochondria, dissipates mitochondrial membrane potential, and induces apoptosis through a pathway dependent on respiratory competent mitochondria. *FASEB J*. 2005;19:1012–1014.
61. Thawornchaisit P, Harncharoen K. A comparative study of tar and betamethasone valerate in chronic plaque psoriasis: A study in Thailand. *J Med Assoc Thai*. 2007;90:1997–2002.
62. Alora-Palli MB, Perkins AC, Van Cott A, et al. Efficacy and tolerability of a cosmetically acceptable coal tar solution in the treatment of moderate plaque psoriasis: A controlled comparison with calcipotriene (calcipotriol) ream. *Am J Cli Dermatol*. 2010;11(4):275–283.
63. Cosmetic Ingredient Review Expert Panel. Final safety assessment of coal tar as used in cosmetics. *Int J Toxicol*. 2008;27(suppl 2):1–24.
64. Stuetz A, Grassberger M, Meingassner JG. Pimecrolimus (Elidel, SDZ ASM 981)—preclinical pharmacologic profile and skin selectivity. *Semin Cutan Med Surg*. 2001;20:233–241.
65. Mrowietz U, Graeber M, Brautigam M, et al. The novel azomycin derivative SDZ ASM 981 is effective for psoriasis when used topically under occlusion. *Br J Dermatol*. 1998;139:992–996.
66. Gribetz C, Ling M, Lebwohl M, et al. Pimecrolimus cream 1% in the treatment of intertriginous psoriasis: A double-blind, randomized study. *J Am Acad Dermatol*. 2004;51:731–738.
67. Matz H. Phototherapy for psoriasis: What to choose and how to use: Facts and controversies. *Clin Dermatol*. 2010;28:73–80.
68. Archier E, Devaux S, Castela E, et al. Efficacy of Psoralen UV-A therapy

vs. narrowband UV-B therapy in chronic plaque psoriasis: A systematic literature review. *J Euro Acad Dermatol Venereol*. 2012;26(suppl 3):11–21.

69. Stern RS. Genital tumors among men with psoriasis exposed to psoralens and ultraviolet A radiation (PUVA) and ultraviolet B radiation: The photochemotherapy follow-up study. *N Engl J Med*. 1990;322:1093–1097.
70. Anstey AV, Kragballe K. Retrospective assessment of PASI 50 and PASI 75 attainment with a calcipotriol/betamethasone dipropionate ointment. *Int J Dermatol*. 2006;45:970–975.
71. Mahrie G, Schulze HJ, Farber L, et al. Low-dose short-term cyclosporine versus etretinate in psoriasis: Improvement of skin, nail, and joint involvement. *J Am Acad Dermatol*. 1995;32:78–88.
72. Heydendael VM, Spuls POL, Opmeer BC, et al. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. *N Engl J Med*. 2003;349:658–665.
73. Shupack J, Abel E, Bauer E, et al. Cyclosporine as maintenance therapy in patients with severe psoriasis. *J Am Acad Dermatol*. 1997;36:423–432.
74. Robert N, Wong GWK, Wright JM. Effect of cyclosporine on blood pressure. *Cochrane Database Syst Rev*. 2010;(1):CD007893.
75. Saurat JH, Stingl G, Dubertret L, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *Br J Dermatol*. 2008;158:558–566.
76. Salim A, Tan E, Ilchyshyn A, et al. Folic acid supplementation during treatment of psoriasis with methotrexate: A randomized, double-blind, placebo-controlled trial. *Br J Dermatol*. 2006;154:1169–1174.
77. Maybury CM, Samarasekera E, Douriri A, et al. Diagnostic accuracy of noninvasive markers of liver fibrosis in patients with psoriasis taking methotrexate: A systematic review and meta-analysis. *Br J Dermatol*. 2014;170(6):1237–1247. doi:10.1111/bjd.12905.
78. Treatment Comparison chart. National Psoriasis Foundation. Available at: https://www.psoriasis.org/sites/default/files/treatment_comparison_chart_1 Accessed May 3, 2019.
79. Robinson J. Preparing for the big biologic switch. The Pharmaceutical Journal. August 16, 2018. Available at: https://www.pharmaceutical-journal.com/news-and-analysis/features/preparing-for-the-big-biologic-switch/20205278.article?firstPass=false. Accessed May 3, 2019.

80. Smith CH. Biologics for psoriasis: More drugs, new patient categories, but fresh challenges for clinical dermatologists. *Br J Dermatol*. 2017;177:7–8.
81. Puig L, Gulliver W. eds. Volume 53: Adverse Reactions to Biologics. Part of the series Current Problems in Dermatology. Series editors Itin P, Jemec GBE. Karger AG, Basel (Switzerland), 2018. ISBN 978-3-318-06100-0.
82. Gordon K, Papp K, Poulin Y, et al. Long-term efficacy and safety of adalimumab in patients with moderate to severe psoriasis treated continuously over 3 years: Results from an open-label extension study for patients from REVEAL. *J Am Acad Dermatol*. 2012;66:241–251.
83. Moustou A-E, Matekovits A, Dessinioti C, et al. Cutaneous side effects of anti-tumor necrosis factor biologic therapy: A clinical review. *J Am Acad Dermatol*. 2009;61:486–504.
84. Lockwood SJ, Prens LM, Kimball AB. Adverse reactions to biologics in psoriasis. In: Puig L, Gulliver W. eds. Adverse Reactions to Biologics. Part of the series Current Problems in Dermatology. Series editors Itin P, Jemec GBE. Karger AG, Basel (Switzerland), 2018. Vol 53:1-14. ISBN 978-3-318-06100-0.
85. Adalimumab (Humura) product monograph. Date of Revision: January 23, 2019. Available at: http://www.abbvie.ca/content/dam/abbviecorp/ca/en/docs/HUMIRA_PM_I Assessed May 6, 2019.
86. Gordon KB, Langley RG, Leonard C, et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: Double-blind, randomized controlled trial and open-label extension study. *J Am Acad Dermatol*. 2006;55:598–606.
87. Menter A, Tyring SK, Gordon K, et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. *J Am Acad Dermatol*. 2008;58:106–115.
88. Leonardi CL, Powers JL, Matheson RT, et al. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med*. 2003;349:2014–2022.
89. Paller AS, Siegfried EC, Langley RG, et al. Etanercept treatment for children and adolescents with plaque psoriasis. *N Engl J Med*. 2008;358:241–251.
90. Gottlieb AB, Kalb RE, Blauvelt A, et al. The efficacy and safety of infliximab in patients with plaque psoriasis who had an inadequate response to etanercept: Results of a prospective, multicenter, open-label study. *J Am Acad Dermatol*. 2011;67:642–650.

91. Menter A, Feldman SR, Weinstein GD, et al. A randomized comparison of continuous vs intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *J Am Acad Dermatol*. 2007;56:e1–e15.
92. Reich K, Nestle FO, Papp K, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: A phase III, multicenter, double-blind trial. *Lancet*. 2005;366:1367–1374.
93. Reich K, Ortonne JP, Gottlieb AB, et al. Successful treatment of moderate to severe plaque psoriasis with the PEGylated Fab' certolizumab pegol: Results of a phase II randomized, placebo-controlled trial with a re-treatment extension. *Br J Dermatol*. 2012;167(1):180–190.
94. Goffe B, Papp K, Gratton D, et al. An integrated analysis of thirteen trials summarizing the long-term safety of alefacept in psoriasis patients who have received up to nine courses of therapy. *Clin Ther*. 2005;27:1912–1921.
95. Shalom G, Cohen AD, Ziv M, et al. Biologic drug survival in Israeli psoriasis patients. *J Am Acad Dermatol*. 2017;76(4):662–666. e661.
96. Stelara (ustekinumab injection). Available at: http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/STELARA-pi.pdf and https://www.stelarahcp.com/plaque-psoriasis. Accessed May 10, 2019.
97. Leonardi C, Kimball AB, Papp K, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-Week results from a randomized, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet*. 2008;371:1665–1674.
98. Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-Week results from a randomized, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet*. 2008;371:1675–1684.
99. Langley RG, Feldman SR, Han C, et al. Ustekinumab significantly improves symptoms of anxiety, depression, and skin-related quality of life in patients with moderate-to-severe psoriasis: Results from a randomized, double-blind, placebo-controlled phase III trial. *J Am Acad Dermatol*. 2010;63:457–465.
100. Sofen H, Wasel N, Yeilding N, et al. Ustekinumab improves overall skin response and health-related quality of life, in a subset of moderate to severe psoriasis patients with psoriatic arthritis: Analysis of PHOENIX 1

and 2. *J Am Acad Dermatol*. 2011 Feb;64(2 suppl 1):AB156.

101. Lebwohl M, Yeilding N, Szapary P, et al. Impact of weight on the efficacy and safety of ustekinumab in patients with moderate to severe psoriasis: Rationale for dosing recommendations. *J Am Acad Dermatol*. 2010;63:571–579.
102. Lebwohl M, Leonardi C, Griffiths CEM, et al. Long-term safety experience of ustekinumab in patients with moderate-to-severe psoriasis (part I of II): Results from analyses of general safety parameters from pooled phase 2 and 3 clinical trials. *J Am Acad Dermatol*. 2012;66:731–741.
103. Gordon KB, Papp KA, Langley RG, et al. Long-term safety experience of ustekinumab in patients with moderate to severe psoriasis (part II of II): Results from analyses of infections and malignancy from pooled phase II and III clinical trials. *J Am Acad Dermatol*. 2012;66:742–751.
104. Bissonnette R, Kerdel F, Naldi L, Papp K, et al. Evaluation of risk of major adverse cardiovascular events with biologic therapy in patients with psoriasis. *J Drugs Dermatol*. 2017;16(10):1002–1013.
105. Secukinumab (Cosentyx) product monograph. Available at: https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/fil Accessed May 11, 2019.
106. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis: Results of two Phase 3 trials. *New Engl J Med*. 2014;371(4):326–338. Available at: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1314258.
107. Blauvelt A, Reich K, Tsai TF, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: Results from the CLEAR study. *J Am Acad Dermatol*. 2017;76(1):60–69. e69.
108. Kircik L, Fowler J, Weiss J, et al. Efficacy of secukinumab for moderate-to-severe head and neck psoriasis over 52 weeks: Pooled analysis of four phase 3 studies. *Dermatol Ther (Heidelv)*. 2016;6(4):627–738.
109. Polesie S, Lidjolm AG. Secukinumab in the treatment of generalized pustular psoriasis: A Case report. *Acta Derm Venereol*. 2017;97(1):124–125.
110. Weng HJ, Wang TS, Tsai TF. Clinical experience of secukinumab in the treatment of erythrodermic psoriasis: A case series. *Br J Dermatol*. 2018;178(6):1439–1440.

111. Mugheddu C, Atzori L, Lappi A, et al. Successful secukinumab treatment of generalized pustular psoriasis and erythrodermic psoriasis. *J Eur Acad Dermatol Venereol*. 2017;31(9):e420–e421.
112. Griffiths CE, Reich K, Lebwohl M, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): Results from two phase 3 randomized trials. *Lancet*. 2015;386(9993):541–551.
113. Reich K, Pinter A, Lacour JP, et al. Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24-Week results from IXORA-S, a phase III study. *Br J Dermatol*. 2017;177(4):1014–1023.
114. Gaffen SL, Jain R, Garg AV, Cua DJ. IL-23-IL-17 immune axi: Discovery mechanistic understanding, and clinical testing. *Nat Rev Immunol*. 2014;14(9):585–600.
115. Reich K, Armstrong AW, Foley P, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. *J Am Acad Dermatol*. 2017;76(3):418–431.
116. Reich K, Papp KA, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): Results from two randomised controlled, phase 3 trials. *Lancet*. 2017;390(100091):276–288.
117. Gingerich CP. FDA approves Risankizumab for plaque psoriasis. MD Magazine April 24, 2019. Available at: https://www.mdmag.com/medical-news/fda-approves-risankizumab-for-plaque-psoriasis. Accessed May 11, 2019.
118. Gordon KB, Strober B, Lebwohl M, et al. Efficacy and safety of Risankizumab in moderate-to-severe plaque psoriasis (UltiMMa-1 and UltiMMa-2): Results from two double-blind, randomized, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet*. 2018 Aug 25;392(10148):650–661.
119. Al-Janabi A, Jabbar-Lopez ZK, Griffiths CEM, Yiu ZZN. Risankizumab vs. ustekinumab for plaque psoriasis: A critical appraisal. *Br J Dermatol*. 2019;180(6):1348–1351.
120. Tofacitinib product monograph. February 2019. Available at: https://www.pfizer.ca/sites/g/files/g10050796/f/201902/XELJANZ_PM_E_

121. Koo JY, Lowe NJ, Lew-Kaya DA, et al. Tazarotene plus UVB phototherapy in the treatment of psoriasis. *J Am Acad Dermatol*. 2000;43:821–828.
122. Lowe NJ, Prystowsky JH, Bourget T, et al. Acitretin plus UVB therapy for psoriasis: Comparisons with placebo plus UVB and acitretin alone. *J Am Acad Dermatol*. 1991;24:591–594.
123. Spuls PI, Rozenblit M, Lebwohl M. Retrospective study of the efficacy of narrowband UVB and acitretin. *J Dermatol Treat*. 2003;14(suppl):17–20.
124. Tanew A, Guggenbichler A, Honigsmann H, et al. Photochemotherapy for severe psoriasis without or in combination with acitretin: A randomized, double-blind comparison study. *J Am Acad Dermatol*. 1991;25:682–684.
125. Kitzen JM, Pergolizzi JV, Taylor R, Raffa RB. Crisaborole and apremilast: PDE4 inhibitors with similar mechanism of action, different indications for management of inflammatory skin conditions. *Pharmacology & Pharmacy*. 2018;9:357–381.
126. Pfizer (2017) AN2728 Topical ointment to treat mild-to-moderate plaque-type psoriasis (NCT01300052). Vol 2018, ClinTrials.gov, Phase 2 Clinical Trial, a multi-center, ramdomized, double-blind, 12-week study of the safety and efficacy of AN2728 versus AN2728 vehicle in the treatmet of patients with mild-to-moderate plaque-type psoriasis.
127. Crowley J, Thaci D, Joly P, et al. Long-term safety and tolerability of apremilast in patients with psoriasis: Pooled safety analysis for >/=156 weeks from 2 Phase 3, randomized, controlled trials (ESTEEM 1 and 2). *J Am Acad Dermaol*. 2017;77:310–317.
128. Lexi-Drugs: Apremilast. Lexicomp 2019, Wolters Kluwer Clinical Drug Information, Inc.
129. Orvis AK, Wesson SK, Breza TS, et al. Mycophenolate mofetil in dermatology. *J Am Acad Dermatol*. 2009;60:183–199.
130. Davidson SC, Morris-Jones R, Powles AV, et al. Change of treatment from cyclosporin to mycophenolate mofetil in severe psoriasis. *Br J Dermatol*. 2000;143:405–407.
131. Pedraz J, Dauden E, Delgado-Jimenez Y, et al. Sequential study on the treatment of moderate-to-severe chronic plaque psoriasis with mycophenolate mofetil and cyclosporin. *J Eur Acad Dermatol Venereol*. 2006;20:702–706.
132. Patel RV, Clark LN, Lebwohl M, et al. Treatments for psoriasis and the risk of malignancy. *J Am Acad Dermatol*. 2009;60:1001–1017.

133. Ranjan N, Sharma NL, Shanker V, et al. Methotrexate versus hydroxycarbamide (hydroxyurea) as a weekly dose to treat moderate-to-severe chronic plaque psoriasis: A comparative study. *J Dermatol Treat*. 2007;18:295–300.
134. Smith N, Weymann A, Tausk FA, et al. Complementary and alternative medicine for psoriasis: A qualitative review of the clinical trial literature. *J Am Acad Dermatol*. 2009;61:841–856.
135. Bernstein S, Donsky H, Gulliver W, et al. Treatment of mild to moderate psoriasis with Relieva, a Mahonia aquifolium extract—a double-blind, placebo-controlled study. *Am J Ther*. 2006;13:121–126.
136. Danno K, Sugie N. Combination therapy with low-dose etretinate and eicosapentaenoic acid for psoriasis vulgaris. *J Dermatol*. 1998;25:703–705.
137. Brochow T, Schiener R, Franke A, et al. A pragmatic randomized controlled trial on the effectiveness of highly concentrated saline spa water baths followed by UVB compared to UVB only in moderate to severe psoriasis. *J Altern Complement Med*. 2007;13:725–732.
138. Brochow T, Schiener R, Franke A, et al. A pragmatic randomized controlled trial on the effectiveness of low concentrated saline spa water baths followed by ultraviolet B (UVB) compared to UVB only in moderate to severe psoriasis. *J Eur Acad Dermatol Venereol*. 2007;21:1027–1037.
139. Gaston L, Crombez J, Lassonde M, et al. Psychological stress and psoriasis: Experimental and prospective correlational studies. *Acta Derm Venereol*. 1991;156:37–43.
140. Kabat-Zinn J, Wheeler E, Light T, et al. Influence of a mindfulness meditation-based stress reduction intervention on rates of skin clearing in patients with moderate to severe psoriasis undergoing phototherapy (UVB) and photochemotherapy (PUVA). *Psychosom Med*. 1998;60:625–632.
141. Treloar V. Integrative dermatology for psoriasis: Facts and controversies. *Clin Dermatol*. 2010;28:93–99.
142. Naldi L, Chatenoud L, Linder D, et al. Cigarette smoking, body mass index, and stressful life events as risk factors for psoriasis: Results from an Italian case-control study. *J Invest Dermatol*. 2005;125:61–67.
143. Horn EJ, Fox KM, Patel V, et al. Are patients with psoriasis undertreated? Results of National Psoriasis Foundation survey *J Am Acad Dermatol*.

2007;57:957–962.

144. Augustin M, Alvaro-Gracia JM, Bagot M, et al. A framework for improving the quality of care for people with psoriasis. *J Euro Acad Dermatol Venereol*. 2012;26(suppl 4):1–16.
145. Psoriasis in children. National Psoriasis Foundation. Available at: https://www.psoriasis.org/about-psoriasis. Accessed May 8, 2019.
146. Benoit S, Hamm H. Childhood psoriasis. *Clin Dermatol*. 2007;25:555–562.
147. De Jager MEA, de Jong EMG, van de Kerkhof PCM, et al. Efficacy and safety of treatments for childhood psoriasis: A systemic literature review. *J Am Acad Dermatol*. 2010;62:1013–1030.
148. Paller AS, Siegfried EC, Langley RG, et al. Etanercept treatment for children and adolescents with plaque psoriasis. *N Engl J Med*. 2008;358:241–251.
149. Paller AS, Mercy K, Kwasny MJ, et al. Association of pediatric psoriasis severity with excess and central adiposity: An international cross-sectional study. *JAMA Dermatol*. 2013;149(2):166–176.
150. Bryld LE, Sorensen TI, Andersen KK, et al. High body mass index in adolescent girls precedes psoriasis hospitalization. *Acta Derm Venereol*. 2010;90(5):488–493.
151. Murase JE, Chan KK, Garite TJ, et al. Hormonal effect on psoriasis in pregnancy and postpartum. *Arch Dermatol*. 2005;141:601–606.
152. Lam J, Polifka JE, Dohil MA. Safety of dermatologic drugs used in pregnant patients with psoriasis and other inflammatory skin diseases. *J Am Acad Dermatol*. 2008;59:295–315.
153. Menter A, Gordon KB, Leonardi CL, et al. Efficacy and safety of adalimumab across subgroups of patients with moderate to severe psoriasis. *J Am Acad Dermatol*. 2010;63:448–456.
154. Papp KA, Strober B, Augustin M, et al. PSOLAR: Design, utility, and preliminary results of a prospective, international disease-based registry of patients with psoriasis who are receiving, or are candidates for, conventional systemic treatments or biologic agents. *J Drugs Dermatol*. 2012;11:1210–1217.
155. Islandar IY, Ashcroft DM, Warren RB, et al. Patterns of biologic therapy use in the management of psoriasis: Cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *Br J Dermatol*. 2017;176:1297–1307.

156. Augustin M, Spehr C, Radtke MA, et al. German psoriasis registry PsoBest: Objectives, methodology and baseline data. *J Ktsch Dermatol Ges*. 2014;12:48–57.
157. Reich K, Mrowietz U, Radtke MA, et al. Drug safety of systemic treatments for psoriasis: Results from the German Psoriasis Registry PsoBest. *Arch Dermatol Res*. 2015;307:875–883.
158. Poulin Y, Langley R, Teiseira HD, et al. Biologics in the treatment of psoriasis: Clinical and economic overview. *J Cutan Med Surg*. 2009;13(suppl 2):S49–S57.
159. Bonafede M, Watson C, Fox K. Cost of tumor necrosis factor blocker per treated psoriatic arthritis patient using drug utilization data from a US managed care population. *J Am Acad Dermatol*. 2012;66(4):suppl 1: AB189 (poster reference no 5165. Poster abstracts. American Academy of Dermatology 70th Annual Meeting, San Diego, California, March 15–20, 2012.).
160. Augustin M, Sundaram M, Mulani PM, et al. Cost per responder with adalimumab versus ustekinumab treatment for moderate to severe psoriasis with suboptimal response to etanercept. *J Am Acad Dermatol*. 2012;66(4):suppl 1: AB189 (poster reference no. 5056. Poster abstracts. American Academy of Dermatology 70th Annual Meeting, San Diego, California, March 15–20, 2012.).

115

Atopic Dermatitis

Rebecca M. Law, Wayne P. Gulliver, and Poh Gin Kwa

KEY CONCEPTS

1. Atopic dermatitis is a chronic skin disorder involving inflammation associated with intense pruritus (itching), a hallmark symptom. Management of atopic dermatitis must always include appropriate management of the associated pruritus.
2. Atopic dermatitis is associated with other atopic diseases such as asthma and allergic rhinitis in the same patient or family. The three conditions are known as the *atopic triad*.
3. The prevalence of atopic dermatitis appears to have increased two- to threefold in many developed and developing countries during the past three decades. Recent data indicate age and country or regional differences, with some countries showing no change or even a decrease. Rural areas appear to have lower prevalence rates.
4. There are genetic and environmental factors in the pathogenesis and pathophysiologic manifestations of atopic dermatitis. The inheritance pattern is not straightforward. More than one gene may be involved in the disease, with the filaggrin gene (*FLG*) being a key player. Other genes coding for specific cytokines are also involved.
5. Atopic dermatitis usually presents in infants and young children. The clinical presentation differs somewhat depending on the age of the patient.
6. Disease severity can be determined by using SCORAD (Severity Scoring of Atopic Dermatitis). This composite index assesses both signs and symptoms to classify overall disease severity as mild, moderate, or severe, which is useful in determining appropriate treatment approach.
7. Secondary bacterial skin infections are common in patients with atopic dermatitis and must be promptly treated.

8. Management of atopic dermatitis must always include appropriate nonpharmacologic management of any controllable environmental factors, such as avoidance of identified triggers. These may include aeroallergens (eg, mold, grass, pollen), foods (eg, peanuts, eggs, tomatoes), chemicals (eg, detergents, soaps), clothing material (eg, wool, polyester), temperature (eg, excessive heat), and humidity (eg, low humidity).
9. Nonpharmacologic management of atopic dermatitis entails managing the symptoms associated with pruritus and encouraging appropriate skin care habits such as proper bathing techniques and the copious use of moisturizers, which is a standard of care.
10. Topical corticosteroids (TCS) are the drugs of first choice for atopic dermatitis.
11. Topical calcineurin inhibitors (TCI), that is, tacrolimus and pimecrolimus, are alternate treatment options for adults and children over the age of 2 years.
12. Phototherapy is a second-line treatment when TCS and TCI fail.
13. Biologic agents (eg dupilumab) may be an option for severe atopic dermatitis in adults and adolescents (not currently approved in children).
14. This chronic illness has substantial socioeconomic impact. The burden of disease is significant and the societal cost is magnified by undertreatment.

Preclass Engaged Learning Activity

Some of the treatment modalities for atopic dermatitis are also used in psoriasis. Review the discussion about topical corticosteroids (including the corticosteroid potency chart) in Chapter 114, “Psoriasis” in this textbook.

INTRODUCTION

1. Atopic dermatitis (AD) is a chronic, pruritic inflammatory skin disease. It is often referred to as *eczema*, which is a general term for several types of skin inflammation. AD is the most common type of eczema (**Table 115-1**).[1] Pruritus is the hallmark symptom and presentation and is responsible for much of the disease burden borne by patients and their families.[2]

TABLE 115-1 Types of Eczema (Dermatitis)

- **Allergic contact eczema (dermatitis):** A red, itchy, weepy reaction where the skin has come into contact with a substance that the immune system recognizes as foreign, such as poison ivy or certain preservatives in creams and lotions.
- **Atopic dermatitis:** A chronic skin disease characterized by itchy, inflamed skin.
- **Contact eczema (dermatitis):** A localized reaction that includes redness, itching, and burning where the skin has come into contact with an allergen (an allergy-causing substance) or with an irritant such as an acid, cleaning agent, or other chemical.
- **Dyshidrotic eczema:** Irritation of the skin on the palms of hands and soles of the feet characterized by clear, deep blisters that itch and burn.
- **Neurodermatitis:** Scaly patches of the skin on the head, lower legs, wrists, or forearms caused by a localized itch (such as an insect bite) that become intensely irritated when scratched.
- **Nummular eczema:** Coin-shaped patches of irritated skin—most common on the arms, back, buttocks, and lower legs—that may be crusted, scaling, and extremely itchy.
- **Seborrheic eczema:** Yellowish, oily, scaly patches of skin on the scalp, face, and occasionally other parts of the body.
- **Stasis dermatitis:** A skin irritation on the lower legs, generally related to circulatory problems.

Source: Data from Reference 1.

2 This form of dermatitis is commonly associated with a personal or family history of other atopic disorders, such as allergic rhinitis and asthma[2] (collectively known as the *atopic triad*). AD has been considered the start of the "atopic march"[2]; however, the association with other atopic conditions is multifactorial and complex since this progression does not happen in all cases.[2] The disease can have periods of exacerbation, or flare-ups, followed by periods of remission. These flare-ups may be disruptive to the patient's quality of life and may affect the entire family. Disease flare-ups may be difficult to manage and may be complicated by secondary infections. About one-half (estimate up to 65%) of cases in children first manifest before age 1 year[1–4]; these cases are termed *early onset atopic dermatitis*.[3,5] Onset of AD is most common between 3 and 6 months of age.[2] Approximately 85% to 90% of patients develop symptoms before age 5 years.[2]

Ten to 30 percent of children with AD will have the same skin condition continuing into their adulthood.[2] Early and severe onset, family history of AD, and early allergen sensitizations are risk factors for a prolonged course.[3]

Furthermore, patients who have apparently outgrown their disease may continue to have sensitive hyper-reactive skin and might have recurrences after long symptom-free periods.[3] However, onset after age 30 years is much less common and is often caused by exposure to harsh or wet conditions[1] such as repeated skin trauma or exposure to harsh chemicals.

EPIDEMIOLOGY

3 The prevalence of AD is generally said to have increased two- to threefold in developed and developing countries during the past three decades.[5] In developed countries, an estimated 15% to 30% of children and 2% to 10% of adults are affected.[3,5,6] The prevalence appears to have increased worldwide, as earlier prevalence rates were estimated at 10% to 15% in children.[4] In developed countries, the lifetime prevalence seems to have plateaued at 10% to 20%, whereas in many developing countries, the lifetime prevalence may be lower but continues to increase.[3]

3 The largest international study of the prevalence of AD found both age and country differences in prevalence rates.[7] This was the International Study of Asthma and Allergies in Childhood (ISAAC), which was conducted in three phases.[8] The strength of this study was the use of a uniformly validated methodology that allowed a direct comparison of results from pediatric populations worldwide.[9] ISAAC Phase One included 700,000 children from 156 centers in 56 countries between 1992 and 1998. ISAAC Phase Two studied allergic causes from 30 centers in 22 countries. ISAAC Phase Three repeated a multicountry cross-sectional survey (1999–2004) and included 187,943 children aged 6 to 7 years from 64 centers in 35 countries and 302,159 adolescents aged 13 to 14 years from 105 centers in 55 countries. For children aged 6 to 7 years, most countries showed an increase of two standard deviations (SDs) in mean annual prevalence over a 5- to 10-year period. In contrast, for adolescents aged 13 to 14 years, the trends differ from country to country. Large increases in prevalence were seen in developing countries (eg, Mexico, Chile, Kenya, and Algeria, and seven countries in Southeast Asia). But in other countries with formerly very high prevalences, the mean annual prevalence in eczema symptoms has either leveled off or decreased. Most of the largest decreases (SD ≥2) in prevalence were reported from developed countries in northwest Europe (eg, the United Kingdom, Ireland, Sweden, Germany) and New Zealand.[7] The ISAAC study has suggested that a maximum prevalence plateau of

approximately 20% has emerged.[7,8]

There were no differences according to the sex of the study participant, or with gross national income at a country level.[7] This is consistent with other reports that AD affects males and females at approximately the same rate.[1] There appears to be a lower prevalence of AD in rural areas when compared with urban areas,[2] suggesting a link to the *hygiene hypothesis*,[10,11] which postulates that the absence of early childhood exposure to infectious agents increases susceptibility to allergic diseases.[10–12] In contrast, children attending daycare centers before 3 months of age have less atopy and asthma in later childhood,[11,12] and areas with diffuse and chronic helminth infestations have a low prevalence of allergic diseases.[12] In addition, a European birth cohort study involving 1,133 newborns showed that children born to farm families had a lower prevalence of sensitization to seasonal inhaled allergens such as grass pollen.[11,13] Maternal exposure during pregnancy (ie, prenatal exposure) to animal sheds correlated with the lower prevalence rate in the farm children. However, there were no differences in prevalence related to inhaled perennial allergens. Parasitic infections decreased the risk of allergen sensitization.[11] A systematic review reported that exposures to endotoxin, farm animals, and dogs may protect against AD.[14]

Reported risk factors associated with higher prevalence include urban environment, higher socioeconomic status, higher level of family education, a family history of AD, female gender (after age 6 years), and smaller family size.[8] However, more recent studies are conflicting. There are no consistent findings that higher socioeconomic status or male/female gender affect the risk of AD.[2] Urban living does appear to increase the risk of AD, but studies attempting to identify causative environmental agents have been inconclusive.[2] Strongly associated risk factors include a family history of AD, and functional mutations in the *FLG* gene.[2]

ETIOLOGY

4 AD is a complex genetic disease that arises from gene–gene and gene–environment interactions. There are two major groups of genes involved. First, there are the genes encoding for epidermal or other epithelial structural proteins. Second, there are genes encoding for the major elements of the immune system.[5] However, the diagnosis of AD currently still remains clinical, as there is currently no reliable biomarker to distinguish AD from other inflammatory

conditions.[15]

The inheritance pattern is not straightforward. More than one gene is likely involved in the disease. There is an increased risk for a child to have AD if there is a family history of other atopic diseases, such as hay fever or asthma. The risk of AD is two- to threefold higher in children with one atopic parent and three- to fivefold higher if both parents are atopic.[2] Studies of identical twins show that a person whose identical twin has AD is seven times more likely to have AD than someone in the general population.[1] And a person whose fraternal twin has AD is three times more likely to have AD than someone in the general population.[1] Another estimate is 80% concordance in monozygous twins and 20% in heterozygous twins.[10]

Thus, genetic predispositions to developing AD exist. There is a genetic predisposition in patients with atopy to demonstrate T-helper (Th_2) predominance—hence increased Th_2 cell activity.[3] At least 32 susceptibility loci have been identified through gene-mapping studies, but they explain less than 20% of the estimated heritability.[3] The strongest known genetic risk factor for AD is null mutations in filaggrin (FLG).[3] The filaggrin gene (*FLG*) on chromosome 1q21.3 encodes for a key structural protein in epidermal differentiation.[3] FLG mutations also cause the semidominant skin-scaling disorder ichthyosis vulgaris, characterized by abnormal skin dryness and palmer hyperlinearity, which are features often found in AD.[3] More specifically, there are several possible genes on the chromosomes 3q21, 1q21, 16q, 17q25, 20p, and 3p26. Of these chromosomes, 1q21 has the highest linkage region. This region has a family of epithelium-related genes called the epidermal differentiation complex.[5] One of these genes is the *FLG*, on chromosome 1q21.3, which encodes for profilaggrin that degrades to filaggrin proteins.[2] Filaggrin proteins play key roles in epidermal differentiation, including terminal differentiation of the epidermis and formation of the skin barrier (including the stratum corneum).[2,16] Filaggrin breakdown products are natural moisturizers and contribute to epidermal hydration and barrier function.[2] Mutations or deficiency of *FLG* result in an abnormality in permeability barrier function.[16] Patients with AD who carry FLG mutations have more persistent disease, a higher incidence of skin infections with herpes virus (eczema herpeticum) and a greater risk for multiple allergies.[16] However, FLG mutation is neither necessary nor sufficient to cause AD. Up to 60% of carriers will not develop AD, and many patients with AD do not carry a FLG mutation.[3]

Epidermal barrier dysfunction is a prerequisite for the penetration of high-

molecular-weight allergens in pollens, house dust mite products, microbes, and food.[5] In mice studies, this barrier abnormality lowers irritability thresholds, and enhanced cutaneous allergen penetration.[16] In humans, two common FLG variants (*R501X* and *2282de14*) with an estimated combined allele frequency of about 6% have been identified in individuals of European descent.[17] Eighteen other less common variants have also been identified in Europeans, with an additional 17 mutations restricted to individuals of Asian descent.[17] Each of these variants leads to nonsense mutations that either prevent or severely diminish the production of filaggrin in the epidermis.[17] Mutations of FLG occur mainly in patients with early onset AD and may be associated with the development of asthma in patients with AD.[5,17] However, FLG mutations are identified in only 30% of European patients with AD, implying that other genetic mutations affecting other epidermal structures may be important (eg, changes in the cornified envelope proteins involucrin and loricrin, or lipid composition).[5]

4 There are other genes encoding for the immune system that may be associated with AD, especially those on chromosome 5q31-33.[5] These genes code for cytokines that regulate IgE synthesis. Cytokines are produced by helper T cells ($TH_{0,}$ TH_1, TH_2, TH_3).[11] T-helper type 1 (TH_1) cells produce cytokines that suppress immunoglobulin E (IgE) production (eg, interferon-γ and interleukin-12 [IL-12]).[5] T-helper type 2 (TH_2) cells produce cytokines that increase IgE production (eg, IL-5 and IL-13).[5,18] In patients with AD, there is an imbalance between TH_1 and TH_2 immune responses. These patients are genetically predisposed to TH_2 predominance, seen as increased TH_2 cell activity.[2,5,9,18] Increased TH_2 activity causes the release of IL-3, IL-4, IL-5, IL-10, and IL-13, resulting in blood eosinophilia, increased total serum IgE, and increased growth and development of mast cells.[2,5,11,18] This is seen in the initial and acute phase of AD.[9] In addition, these cytokines affect the maturation of B cells and cause a genomic rearrangement in these cells that favors isotype class switching from immunoglobulin M (IgM) to IgE.[5] As discussed below, epidermal Langerhans cells (LCs) and dendritic cells (DCs) with high-affinity IgE receptors uptake allergens and mediate the inflammatory response.[11]

In summary, FLG deficiency alone can provoke a barrier abnormality in the epidermis and predispose to the development of AD by enhancing allergen absorption through the skin.[19] Furthermore, there appears to be complex relationships, including genetic and nongenetic risk factors, that modify an

individual's susceptibility to allergic disease.[20] Complex genetic factors contribute to the increased susceptibility to AD (FLG mutations and gene–gene interactions). These, along with environmental factors such as food allergens[21] (gene–environment interactions), result in the pathophysiologic changes and clinical presentations associated with AD.

PATHOPHYSIOLOGY

4 The initial mechanisms that trigger inflammatory changes in the skin in patients with AD are unknown. Neuropeptides, irritation, or pruritus-induced scratching may be causing the release of proinflammatory cytokines from keratinocytes. Alternatively, allergens in the epidermal barrier or in food[21] may cause T-cell mediated but IgE-independent reactions. Allergen-specific IgE is not a prerequisite.[5] Characteristic features in pathophysiology are skin barrier dysfunction, and immune deviation toward TH_2 with subsequent increased IgE.[10] The disease is further complicated by microbial colonization with pathologic organisms resulting in increased susceptibility for skin infections.[10]

As discussed above, skin barrier dysfunction plays a critical role in the development of AD,[10,11,16,22] with loss of function mutations in *filaggrin* being a major risk factor.[16,22] Other factors may include a deficiency of skin barrier proteins, increased peptidase activity, lack of certain protease inhibitors, and lipid abnormalities.[22] There must be epidermal barrier dysfunction for high-molecular-weight allergens in pollens, house dust mite particles, microbes, and foods to penetrate the skin barrier. Atopic skin has reduced antimicrobial peptides (AMPs). AMPs are normally produced by keratinocytes, sebocytes, and mast cells, and they form a chemical shield on the surface of the skin. Reduced AMPs result in a diminished antimicrobial barrier, which correlates with increased susceptibility to infections and superinfections seen in these patients.[23]

Upon penetration of the epidermal barrier, allergens are met by DCs. DCs are antigen-presenting cells populating the skin, respiratory tract, and mucosa of the GI tract (ie, at the front line of pathogen entry).[24] DCs then enhance TH_2 polarization, resulting in increased production of IgE. Keratinocytes in the skin of patients with AD also produce high levels of an IL-7–like protein, which again drives DCs to enhance TH_2 polarization. Epidermal DCs in patients with AD bear IgE and express its high-affinity receptor (FcεRI).[25–27] Total serum IgE is often elevated in patients with AD,[1,2] especially during an exacerbation.

However, on initial presentation, patients with early onset AD generally do not have increased total serum IgE levels (ie, there is no detectable IgE-mediated allergic sensitization). IgE-mediated allergic sensitization may occur several weeks or months after the initial AD lesions appear, although in some children—mostly girls—this sensitization never occurs.[5] Furthermore, elevated total serum IgE is not specific to AD and can be associated even with nonatopic conditions.[2]

Other potential biomarkers currently discovered include serum CD30, macrophage-derived chemoattractant (MDC), interleukins (IL)-12, -16, -18, and -31, and thymus and activation-regulated chemokine (TARC); however, to date none of them have shown reliable sensitivity nor specificity for clinical use.[2]

Predisposing Factors

4 Several factors can predispose patients to development of AD. These include climate, infection, genetics, environmental aeroallergens, urban versus rural living, breastfeeding and time of weaning, obesity, pollution/tobacco smoke, and food/diet. A Western diet with high amounts of sugar and polyunsaturated fatty acids, a small family size, a high education level in the household, living in urban settings, and living in regions with low exposure to UV radiation and low humidity are all factors that may increase the risk of AD.[3]

Hot and extremely cold climates are both poorly tolerated by patients with AD. Dry weather, common in the winter, causes increased skin dryness. Hot weather causes increased sweating, resulting in pruritus.

Patients with AD are commonly colonized by *Staphylococcus aureus* bacteria. Clinical infections with *S. aureus* frequently cause flare-ups of AD.

As discussed previously, genetics plays a role in AD. Family history of AD is a strong risk factor.

4 Exposure to environmental aeroallergens is another risk factor. Dust mites, pollens, molds, cigarette smoke, and dander from animal hair or skin may worsen the symptoms of AD.[13]

The role of food as antigens in the pathogenesis of AD is still not fully understood.[3,21] Preliminary results (mostly animal studies) indicate that defects in the skin and gut barrier function may facilitate sensitization to food allergens.[21] Small amounts of environmental foods (low-dose exposure from foods on tabletops, hands, dust) may penetrate the skin barrier and be taken up by LCs, leading to TH_2 responses and IgE production.[28] However, early high-dose oral food consumption induces oral tolerance. The timing and balance of

cutaneous and oral exposure determines whether a child will have allergy or tolerance.[28] Increased serum IgE antibodies to a particular food is evidence of sensitization to a food and is consistent with—although not proof of—a food allergy.[1,29] Eczema may frequently be a manifestation of food allergy,[28] and patients with AD have a higher prevalence of food allergy than those in the general population.[1] Conversely, there is a belief that food allergy may be caused by AD, and in most patients with coexisting AD and food allergy, AD precedes the food allergy. (The assumption is that AD is a causal risk factor for asthma and systemic allergen sensitization in the context of FLG mutations.[16]) Regardless, the two conditions coexist, and the likelihood of an infant or child with AD also having food allergy or other allergies must be kept in mind.[29]

There is a known epidermal barrier dysfunction in AD, allowing for increased low-level skin permeability to allergenic foods. Certain foods may trigger acute reactions including urticaria and anaphylaxis. The most commonly reported allergenic foods are hen's eggs, cow's milk, peanuts, wheat, soy, tree nuts, shellfish, and fish.[1,30] Individual food allergies, such as peanut allergy, have increased in prevalence in the past decade[28,29]; new food allergies may also be increasing in prevalence, particularly kiwi allergy[28,31] and sesame seed allergy.[28,32] Allergies to seafood, peanuts, and tree nuts are more likely to persist into adulthood, while allergies to cow's milk, hen's eggs, wheat, and soy generally resolve by late-childhood.[21] Consistent with the oral tolerance concept, early results from recent studies using sublingual and oral immunotherapy to specific food allergens (eg, cow's milk or peanut) indicate that it may be possible to induce oral tolerance, and that it may be possible to desensitize children to some allergenic foods.[33] Nine to 12 months of immunotherapy were needed to observe the beneficial effect and "the present evidence does not warrant routine recommendation" by the AAD.[34] Injectable allergen-specific immunotherapy is also being studied.[34] National Institute of Allergy and Infectious Diseases (NIAID) suggests limited food allergy testing (ie, cow's milk, eggs, wheat, soy, peanut) if a child <5 years old has moderate-to-severe AD and persistent disease despite optimal therapy.[29,34] For more information about management of food allergies the reader is directed to the 2010 NIAID-sponsored expert panel's report, available at www.niaid.nih.gov.[29]

CLINICAL PRESENTATION: ATOPIC DERMATITIS

Diagnosis of AD is generally based on clinical presentation (Table 115-2).[1] There is currently no objective diagnostic test or reliable biomarker for the clinical confirmation of AD.[1–3] On occasion, skin biopsy specimens or other tests (eg, total and/or allergen-specific serum IgE, potassium hydroxide preparation, patch testing, and/or genetic testing) may be used to rule out other or associated skin conditions.[2] *Filaggrin* gene mutations may be associated with persistent and more severe AD as well as early onset cases.[22]

TABLE 115-2 Skin Features Associated with Atopic Dermatitis

- **Atopic pleat (Dennie–Morgan fold):** An extra fold of skin that develops under the eye.
- **Headlight sign:** Sparing of the skin on top of the nose.
- **Herthoge's sign:** Thinning or absence of the lateral portions of the eyebrows.
- **Cheilitis:** Inflammation of the skin on and around the lips.
- **Hyperlinear palms:** Increased number of skin creases on the palms.
- **Hyperpigmented eyelids:** Eyelids that have become darker in color from inflammation or hay fever.
- **Ichthyosis:** Dry, rectangular scales on the skin.
- **Keratosis pilaris:** Small, rough bumps, generally on the face, upper arms, and thighs.
- **Lichenification:** Thick, leathery skin resulting from constant scratching and rubbing.
- **Papules:** Small raised bumps that may open when scratched and become crusty and infected.
- **Urticaria:** Hives (red, raised bumps) that may occur after exposure to an allergen, at the beginning of flares, or after exercise or a hot bath.

Source: Data from Reference 1.

Atopic dermatitis follows a relapsing course.[34,35] Studies reviewing the natural course of the disease usually describe the disease pattern as persistent, intermittent, or in remission.[8] A 2004 study found that 43% were in complete remission after age 2 years, with 19% having persistent disease and 38% an intermittent pattern.[8]

5 The clinical presentation of AD differs depending on the age of the patient. In infancy, the earliest onset of AD usually occurs between 3 and 6 months of age, with 60% of patients developing symptoms within the first year of life, and 85% to 90% having developed symptoms before the age of 5 years.[1,2] The initial presentation in infancy is an erythematous, papular skin eruption that may first appear on the cheeks and chin as a patchy facial eruption which may progress to red, scaling, oozing skin.[1] The eruption shows a

centrifugal distribution affecting the malar region of the cheeks, forehead, scalp, chin, and behind the ears while sparing the central areas (ie, the nose and paranasal creases). Sparing of the skin on top of the nose is a characteristic feature (known as the “headlight sign”), and there is thinning or absence of the lateral portions of the eyebrows (known as the Herthoge’s sign).[3] Lesions occur in the flexor surfaces, such as antecubital and popliteal fossae. Over the next few weeks and as the infant becomes more mobile and begins crawling, the lesions spread to the extensors of the lower legs, and eventually the entire body may be involved, with sparing of the groin, axillary region, and the nose.[1,2,35] These lesions are associated with uncontrollable itchiness, and the infant will become irritable and may try to rub his or her face to relieve the itch. Scratching may occur quite early, and infants with AD may scratch themselves continuously, even during sleep.[2] Sleep disruption occurs in up to 60% of children with AD, increasing to 80% or more during exacerbations.[2] Excessive rubbing or scratching may result in excoriation and predispose the patient to secondary infections.

In childhood, the skin often appears dry, flaky, rough, cracked, and may bleed because of scratching. With repeated scratching and rubbing, the skin becomes lichenified. Lichenification, usually localized to the flexural folds of the extremities, is characteristic of childhood AD in older children and in adults.[35] Lichenification signifies repeated rubbing of the skin and is seen mostly over the folds, bony protuberances, and forehead.[35] Excoriations and crusting are also commonly seen, along with secondary infections. Sometimes increased folds are seen underneath the eyes (so-called Dennie–Morgan folds).[35] Lesions are still most commonly seen in the flexor surfaces of the body, particularly the flexural creases of the antecubital and popliteal fossae.[35]

Sleep disturbances also occur. One study reported that there are both brief and longer awakenings associated with scratching episodes that affect sleep efficiency in school-age children with AD.[36]

In adulthood, lesions are more diffuse with underlying erythema. The face is commonly involved and may be dry and scaly. Lichenification may again be seen. A brown macular ring around the neck, representing a localized deposit of amyloid, is typical but not always present.[35]

Although no objective diagnostic test confirms presence of AD,[1,2] some signs, symptoms, and other factors are commonly used in its diagnosis. These include pruritus, early age of onset, eczematous skin lesions that vary with age, chronic and relapsing courses, dry and flaky skin, IgE reactivity, family or

personal history of asthma or hay fever, or other atopic diseases (Tables 115-3 and 115-4).[2,35] Allergy skin testing has little utility in AD, although negative results may help rule out certain substances as triggers; however, positive results may be unrelated to disease activity, and false positives are common.[1]

TABLE 115-3 Clinical Features in the Diagnosis of Atopic Dermatitis

Essential Features (Must Be Present):

- Pruritus
- Eczema (acute, subacute, chronic)
  - Typical morphology and age-specific patterns
    Facial, neck, external involvement (infants, children)
    Flexural lesions (any age group)
    Sparing of groin and axillary regions
  - Chronic or relapsing history

Important Features (Seen in Most Cases, Supports the Diagnosis of AD):

- Early age of onset
- Atopy
  - Personal/family history
  - IgE reactivity
- Xerosis

Source: Data from Reference 2.

TABLE 115-4 Major and Minor Signs and Symptoms of Atopic Dermatitis

Major Indicators

- Pruritus (intense itching)
- Characteristic rash in locations typical of the disease
- Chronic or repeatedly occurring symptoms
- Personal or family history of atopic disorders (eczema, hay fever, asthma)

Selected Minor Indicators

- Early age of onset
- Dry skin that may also have patchy scales or rough bumps
- Increased serum IgE
- Numerous skin creases on the palms
- Hand or foot involvement
- Inflammation around the lips
- Nipple eczema
- Susceptibility to skin infection
- Positive allergy skin tests

Source: Data from Reference 1.

1 Pruritus is a quintessential feature of AD, and a diagnosis cannot be made

if there is no history of itching.[1–4,35] Scratching and rubbing itchy atopic skin further irritates the skin, increases inflammation, and exacerbates itchiness.[3] Atopic skin can itch during sleep. This nighttime itching is a problem for many infants and children with the disease, since there is no conscious control of scratching during sleep.[1,2] Pruritus is the symptom that most affects the health-related quality of life for most patients with AD. In studies, more than 50% of patients rated their pruritus as very bothersome or extremely bothersome and reported that they often or always experienced intolerable symptoms.[35]

Pruritus can be triggered by a variety of factors. The most common triggers of itch have been reported as heat and perspiration (96%), wool (91%), emotional stress (81%), certain (usually vasodilatory) foods (49%), alcohol (44%), upper respiratory infections (36%), and house dust mites (>35%).[35,36]

Once pruritus occurs, the surrounding normally nonpruritic skin area (whether inflamed or noninflamed) may be very sensitive and react to light stimuli and begin itching (a process known as *allokinesis*). Allokinesis is typical of AD.[35,36] As a result of allokinesis, patients with AD may experience pruritic attacks when their skin is touched accidentally by mechanical factors such as clothing, especially wool products.[36]

Elevated serum IgE may be seen, consistent with the genetically predetermined dominance of TH_2 cytokines causing increased IgE. In addition, increased serum IgE antibodies to a particular food, consistent with a food allergy, is common in patients with AD. Serum-based tests for allergen-specific IgE (formerly a radioallergosorbent test referred to as RAST) are used to screen for allergy to a specific substance or substances.[34] (Currently, most labs use large autoanalyzers that rely on fluorescent or chemiluminesent labels rather than radiolabels to identify reactions, so RAST does not describe the technique used). In some cases, allergen-specific IgE tests may be used to monitor immunotherapy or to see if a child has outgrown a specific allergy. The negative predictive value is high (>95%) but the specificity and positive predictive value are low (40%-60%).[34] Negative results help to rule out a food allergy, whereas positive (elevated) allergen-specific IgE test results only signify sensitization and require clinical correlation and confirmation.[34] The level of IgE may not correlate with the severity of an allergic reaction or with the severity of AD.

With respect to IgE reactivity, several candidate genes that encode cytokines involved in the regulation of IgE synthesis have been identified, notably on chromosome 5q31-33.[2] Increased Th_2 activity leads to release of IL-3, IL-4, IL-5, IL-10, and IL-13, which causes eosinophilia, increases IgE, and increases the

growth and development of mast cells.[35] In addition to eosinophils and mast cells, basophils and newly identified innate immune cells called group 2 innate lymphoid cells (ILC2s) have been shown to underlie the pathogenesis of AD.[35] The above cytokines also affect B-cell maturation, causing a genomic rearrangement that favors isotype class switching from IgM to IgE.[2] More recently, Th17 cells have been found to be elevated, with its role not yet clearly defined.[35]

A clinically useful set of criteria for the diagnosis of AD is as follows: atopy, pruritus, eczema, and altered vascular reactivity.

Disease Severity

6 Disease severity can be classified as mild, moderate, or severe. Assessing the severity of AD includes subjective symptoms and objective signs—in particular, the subjective evaluations relating to pruritus and sleep disturbance are particularly important. Composite scores assessing both signs and symptoms must be used to assess overall disease severity.[36] SCORAD (Scoring of Atopic Dermatitis) is a composite score developed by the European Task Force of Atopic Dermatitis (ETFAD), where a SCORAD score >50 defines severe AD, and one <25 considered mild AD.[36] There is also a Patient-Oriented SCORAD (PO-SCORAD) which is also useful since it can be administered independent of the physician; and the PO-SCORAD correlates well with SCORAD.[36] In addition, there is an objective assessment tool for visible lesions called EASI (Eczema Area and Severity Score) which is often used together with a subjective symptom assessment tool called POEM (Patient-Oriented Eczema Measures); this pair of tests is especially useful in the clinical trial setting.[36] Both SCORAD and PO-SCORAD are available as apps from the Eczema Foundation at https://www.fondation-dermatite-atopique.org/en/healthcare-professionals-space (**Fig. 115-1**).

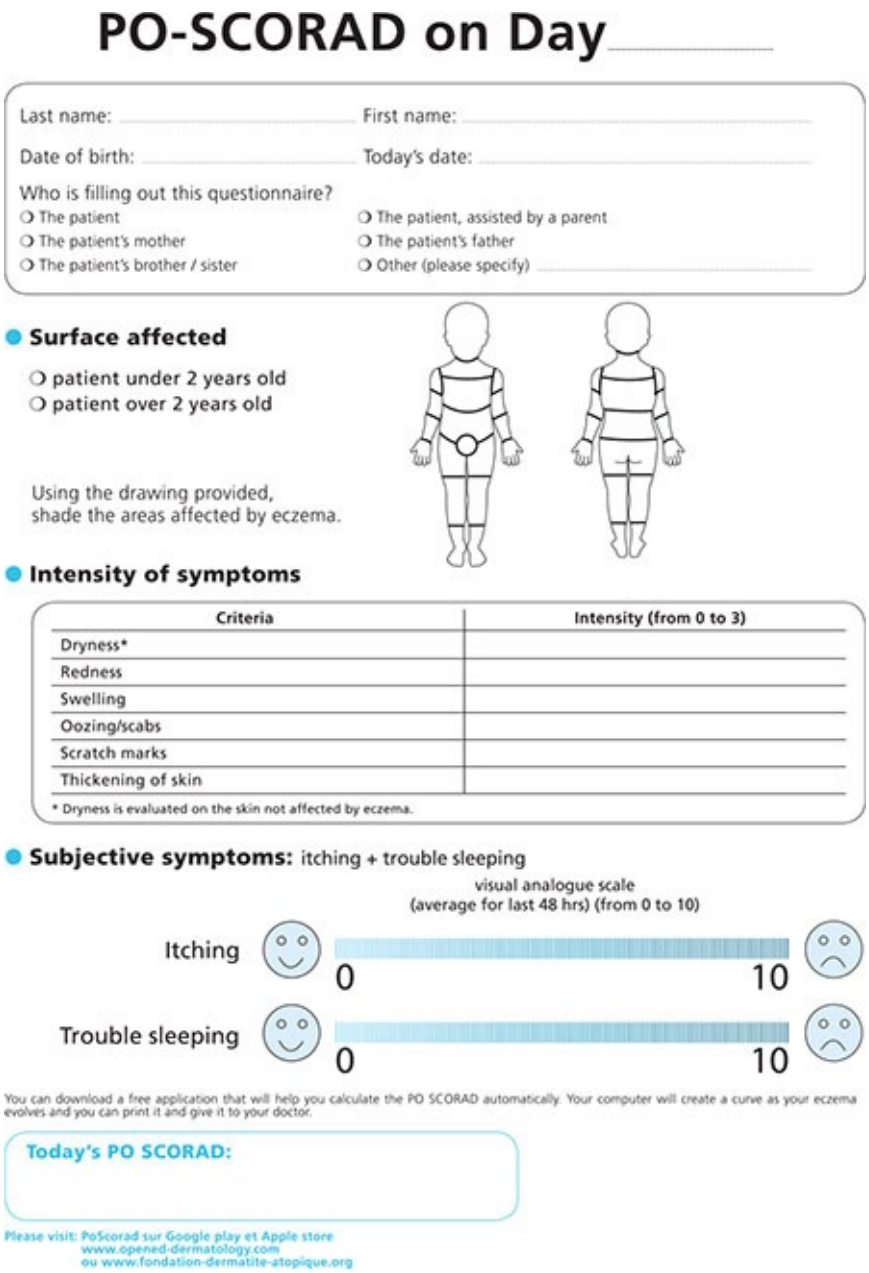


FIGURE 115-1 Example of use of SCORAD tool for atopic dermatitis disease severity assessment. A composite score of 40.8 would be consistent with moderate disease. (*SCORAD and POSCORAD copyright © Pr JF Stalder, Eczema Foundation, 2020. Reprinted with permission.*)

Complications

7 Patients with AD are prone to skin infections. Atopic skin is drier and the stratum corneum has weakened protective abilities; combined with the abnormal skin barrier function and immune defense, there is an increased risk of secondary

bacterial skin infections with staphylococci or streptococci, and viral infections such as herpes simplex or even fungal infections.[1,2] Constant scratching to relieve pruritus may cause excoriations, further compromising the integrity of the skin barrier. *S. aureus* is a common cause of secondary bacterial infections in AD.[3,10] Binding of *S. aureus* is enhanced by skin inflammation as seen in AD. Many patients with AD are colonized with *S. aureus* and may have exacerbations after skin infections of this organism.[10] Secondary bacterial infections may present as yellowish crusty lesions and should be promptly treated. Oral (systemic) antibiotics are generally more effective than topical treatment.[1]

Patients with AD are also more prone to disseminated infections with herpes simplex or vaccinia virus. Severe viral infections such as eczema herpeticum or eczema vaccinatum might be linked to the severity of atopy. Eczema herpeticum is a severe widespread skin infection with herpes simplex virus (HSV) that occurs in up to 3% of patients, in particular those with severe disease.[3] *Molluscum contagiosum* virus infection may be seen in children and adolescents with AD.[3] Smallpox vaccination is contraindicated in patients with AD.

TREATMENT

Desired Outcomes

In treating patients with AD, clinicians generally have the following clinical goals in mind:

1. Provide symptomatic relief—control the itching.
2. Control the AD.
3. Identify and, when possible, eliminate triggers and environmental aeroallergens.
4. Identify and minimize predisposing factors for exacerbations including any stressors.
5. Prevent future exacerbations.
6. Provide any social and psychological support needed for the patient, family, and caregivers.
7. Minimize or prevent adverse events from medications and other treatment modalities.
8. Treat to cure any secondary skin infections, if present.

Successful management of AD should include not only clearance of skin

lesions, which may take days to weeks depending on the severity of disease—and this determines the type of treatment regimen—but also control of the itch, minimizing or eliminating triggers, monitoring the patient to minimize or prevent adverse events from medications or other treatment modalities, and providing adequate social and psychological support for the patient, family, and caregivers.

The ultimate goal is to provide enough control of this chronic disease so that future exacerbations are prevented, thus ensuring that the patient's quality of life is minimally affected by AD. Because the course of the disease evolves over time, management strategies may change. Mild disease can be managed by reactive therapy, moderate-to-severe disease will require proactive therapy to maintain disease control.[36]

8 Both nonpharmacologic and pharmacologic therapies are important in managing the signs and symptoms of AD. Nonpharmacologic strategies include identifying and minimizing or eliminating preventable risk factors, such as known triggers and allergens, as well as appropriate skin care.[30,36]

Treatment guidelines and protocols for AD are available. These are listed in **Table 115-5**.

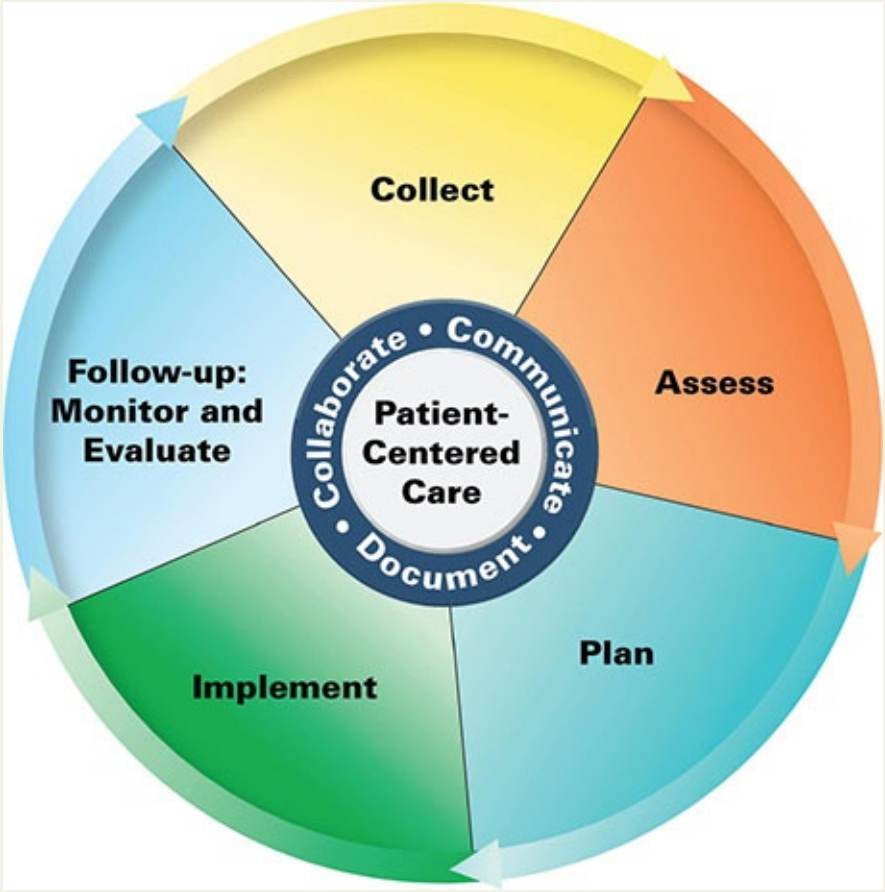
TABLE 115-5 Useful Sources of Information about Treatment of Atopic Dermatitis

Published Guidelines or Treatment Protocols

- Wollenberg A, Barbarot S, Bieber T, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I & part II. *J Eur Acad Dermatol Venereol* 2018;32(5):657–682 & 850–878.
- Wong ITY, Tsuyuki RT, Cresswell-Melville A, et al. Guidelines for the management of atopic dermatitis (eczema) for pharmacists. *Can Pharm J (Ott)* 2017;150(5):285-297.
- Gooderham M, Lynde CW, Papp K, et al. Review of systemic treatment options for adult atopic dermatitis. *J Cutan Med Surg* 2017;21(1):31-39.
- Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis. Section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol* 2014;70:338-351.
- Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis. Section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol* 2014;71:116-132.
- Sidbury R, Davis DM, Cohen DE, et al. Guidelines of care for the management of atopic dermatitis. Section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol* 2014;71:327-349.
- Sidbury R, Tom WL, Bergman JN, et al. Guidelines of care for the management of atopic dermatitis. Section 4. Prevention of disease flares and use of adjunctive therapies and approaches. *J Am Acad Dermatol* 2014; published online September 25, 2014. http://dx.doi.org/10.1016/j.jaad.2014.08.038.
- Eichenfield LF, Boguniewicz M, Simpson E, et al. Translating atopic dermatitis management guidelines into practice for primary care providers. *Pediatrics* 2015;136(3). http://www.pediatrics.org/cgi/doi/10.1542/peds.2014-3678.
- Rubel D, Thirumoorthy T, Soebaryo W, et al. Consensus guidelines for the management of atopic dermatitis: An Asia-Pacific perspective. *J Dermatol* 2013;40:160-171.
- Baron SE, Cohen SN, Archer CB. British Association of Dermatologists and Royal College of General Practitioners. Guidance on the diagnosis and clinical management of atopic eczema. *Clin Exp Dermatol* 2012;37(suppl 1):7-12.
- Izadi N, Leung DYM. Clinical approach to the patient with refractory atopic dermatitis. *Ann Allergy Asthma Immunol* 2018;120:23-33.
- Simpson EL. Atopic dermatitis: A review of topical treatment options. *Curr Med Res Opin* 2010;26(3):633-640.
- Carbone A, Siu A, Patel R. Pediatric atopic dermatitis: A review of the medical management. *Ann Pharmacother* 2010;44:1448-1458.
- National Institute of Arthritis and Musculoskeletal and Skin Diseases. Handout on Health: Atopic Dermatitis. US Department of Health and Human Services. NIH Publication No. 09-4272. May 2013, www.niams.nih.gov/Health_Info/Atopic_Dermatitis/default.asp.
- Lynde C, Barber K, Claveau J, et al. Canadian practical guide for the treatment and management of atopic dermatitis. *J Cutan Med Surg* 2005;8 (suppl 5):1-9. http://www.springerlink.com/content/r5432000056r2748/fulltext.html.

Useful Websites

- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), US National Institutes of Health: http://www.niams.nih.gov/Health_Info/Atopic_Dermatitis/default.asp
- American Academy of Allergy Asthma & Immunology (AAAAI): http://www.aaaai.org/conditions-and-treatments/allergies/Skin-Allergy.
- American Academy of Dermatology: https://www.aad.org/education/clinical-guidelines, http://www.jaad.org/article/S0190-9622(13)01095-5/fulltext.
- DermNet NZ: http://dermnetnz.org/dermatitis/atopic.html.



Patient Care Process for Atopic Dermatitis

Collect

- Patient characteristics (eg, age, sex, pregnancy status)
- Patient medical history (personal and family)
- Patient/caregiver description of history of atopic dermatitis, subjective complaints of itch and other symptoms
- Signs associated with severity of itch (eg, excoriations, sleep disturbances)
- Signs associated with severity of atopic dermatitis (eg, areas of involvement)
- Signs of secondary skin infections
- Signs of caregiver stress or distress

Assess

- Severity of atopic dermatitis—classify into mild, moderate, or severe disease (eg, using SCORAD)
- Severity of itch
- Ability/willingness to pay for medical treatment options
- Emotional/psychological concerns (for patient and caregiver, if any)

Plan*

- Determine an appropriate treatment approach, that is, proactive versus reactive therapy
- Recommend the most appropriate therapies (nonpharmacologic and pharmacologic) for atopic dermatitis and itch
- Recommend the most appropriate treatment (treat to cure) and ongoing preventative strategies for secondary skin infection, if present
- Recommend management strategies for caregiver stress or distress, if needed

Implement

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Provide information about prevention of future flare-ups

Follow-up: Monitor and Evaluate

- Contact patient/caregiver in 1 to 2 weeks to follow-up about the efficacy of recommended therapies and any issues with the treatment regimen
- Ensure that appropriate monitoring parameters for efficacy and potential adverse effects have been put in place (eg, follow-up lab tests as needed)
- Reinforce preventive measures including continuation of proactive therapy, if implemented
- Ensure that patient/caregiver has been connected to other health resources as needed for follow-up (eg, a dermatologist, psychologist)

**Collaborate with patient, caregivers, and other healthcare professionals.*

Nonpharmacologic Therapy

8 9 Nonpharmacologic approaches to the treatment of infants and children with AD include the following[30,36,37]:

1. Apply moisturizers frequently throughout the day. Moisturizers are a standard of care for AD and there is strong evidence that their use can reduce disease severity and the need for pharmacologic intervention.[30,36,37] Long-term moisturizer therapy improves AD associated xerosis.[36] Even stand-alone use of moisturizers for 1 week improves mild-to-moderate AD flares.[38] There is evidence to suggest that daily use of moisturizers from birth may reduce the development of AD in a high-risk population.[36,39]
2. Give lukewarm baths. Currently, there is insufficient evidence for patients with AD to recommend the addition of oils, emollients, or most other additives to bath water, or the use of acidic spring water.[37]
3. Apply moisturizer immediately after bathing. Currently, there is no standard for the frequency or duration of bathing appropriate for those with AD.[37]
4. Use nonsoap cleansers (which are neutral to low pH, hypoallergenic, fragrance free). Limited use.[37]
5. Use wet-wrap therapy (with or without TCS) during flare-ups for patients with moderate-to-severe AD. “Wet wrap” is applying damp tubular elasticized bandages and occlusive dressing to the limbs—this promotes skin hydration and absorption of emollients and TCS,[11] reducing disease severity and water loss.[11,37]
6. Keep child’s fingernails filed short.
7. Select clothing made of soft cotton fabrics.
8. Consider using sedating antihistamines to reduce scratching at night.
9. Keep the child cool; avoid situations in which overheating occurs.
10. Learn to recognize skin infections and seek treatment promptly.
11. Attempt to distract the child with activities to keep him or her from scratching.
12. Identify and remove irritants and allergens.

Hydration is crucial, and adequate skin hydration is a fundamental part of managing AD.[30,36,37] Transepidermal water loss is greater in atopic skin than in normal skin. Thus, any measures to improve skin moisturization, such as liberal use of moisturizers, would be beneficial. Moisturizers are a standard of care and may be steroid-sparing.[10,36,37] They are useful for both prevention and

maintenance therapy.[10,37,40,41] They can be categorized based on their specific effects on the skin:

1. *Occlusives*: These agents provide an oily layer on the skin surface to slow transepidermal water loss, increasing the moisture content of the stratum corneum. These are the best moisturizers for patients with AD.
2. *Humectants*: In the stratum corneum, these agents increase the water-holding capacity. However, they are not useful in patients with AD because they have a stinging effect on open skin.
3. *Emollients*: These agents smooth out the surface of the skin by filling the spaces with droplets of oil. These are the least effective moisturizers.

However, note that the term "emollients" is often more broadly used to mean *all* nonmedicated moisturizers, including occlusives.[36] More recently, nonmedicated "emollients" may also include active ingredients, softening the delineation of emollients from topical drugs.[36] The 2018 European consensus guideline defines *emollients* as "topical formulations with vehicle-type substances lacking active ingredients" and *emollients plus* as "topical formulations with vehicle-type substances and additional active, nonmedicated substances."[36] Usual ingredients in emollients can include mineral oil, petrolatum, and urea.[36] Emollient-plus products may contain active ingredients such as saponins, flavonoids, riboflavins from protein-free oat plantlet extracts, or bacterial lysates from *Aquaphilus dolomiae* or *Vitreoscilla filiformis*.[36,42] These lysates both improve AD and positively influence the skin microbiome.[36,43] A cream based on *Aquaphilus dolomiae* extracts alleviates nonhistaminergic pruritus.[44] Ceramide-containing OTC moisturizers and prescription emollient devices (PEDs) with distinct ratios of lipids mimic endogenous compositions. However, to date these have not shown superiority in AD.[37]

The humidity in the home should be kept at or above 50% and the room temperature kept on the cool side.[45]

Appropriate skin care is crucial in preventing flare-ups.[1] A daily skin care routine should include the following[45]:

1. Using scent-free moisturizers liberally as needed each day. Large quantities can be used.
2. Bathing in lukewarm water (never hot) for 5 to 10 minutes, once or twice daily.[30,36,37]. Adding a capful of emulsifying oil[10] may help the body retain

moisture; baths are better than showers. Bathing daily for 10 to 20 minutes may be desirable as long as a thick moisturizer is applied afterward. A 20-minute soak followed by immediate application of topical anti-inflammatory agents (eg, TCS) without towel drying is known as the “soak and smear” technique and is useful when the topical anti-inflammatory agent alone is inadequate.[37] Bathing twice daily during disease flares may also be a useful method for enhancing skin penetration of topical therapies and for debridement of crusting and staphylococcal colonization. The skin should be lightly towel dried (pat to dry, avoid rubbing or brisk drying).[1,45]

3. Scent-free moisturizer should then be applied while the skin is still moist or slightly damp (eg, within 3 minutes of towel drying).[45] Some fragrance-free moisturizers include Aveeno Baby Soothing Relief Moisture Cream, CeraVe lotion, Cetaphil, Neutrogena Hand Cream, and Vanicream products. Lotions may be used on the scalp and other hairy areas and for mild dryness on the face, trunk, and limbs; creams are more occlusive than lotions; ointments are the most occlusive and can be used for drier, thicker, or more scaly areas.[45]
4. Using nonsoap skin cleansers[1] may cause less skin irritation. Lipid- and fragrance-free skin cleansers may be particularly advantageous (eg, CeraVe facial cleansers [Foaming, Hydrating], CeraVe Eczema Body Wash, Cetaphil Gentle Skin Cleanser, Free and Clear Liquid Cleanser, Spectro Derm Cleanser, and Trisan Antibacterial Skin Cleanser). Aquanil, Dove, Neutrogena, and pHisoderm sensitive skin products have also been recommended as low-irritant products, and some are lipid free.
5. Avoiding alcohol-containing topical products including lotions, swabs, and wipes, as they may be drying.
6. Clothing should be double-rinsed. Mild detergents should be used to wash clothing, with no bleach or fabric softener.

Pharmacologic Therapy

Current treatment recommendations are based on disease severity, with reactive therapy appropriate for mild disease, and proactive therapy for moderate or severe AD—severe disease most appropriately managed initially with systemic therapy in a hospital setting (see **Fig. 115-2**).

(a) Treatment recommendation for atopic eczema: adult

- For every phase, *additional* therapeutic options should be considered
- Add antiseptics / antibiotics in cases of superinfection
- Consider compliance and diagnosis, if therapy has insufficient effect
- Refer to guideline text for restrictions, especially for treatment marked with[1]
- Licensed indication are marked with[2], off-label treatment options are marked with[3]

SEVERE: SCORAD >50 / or persistent eczema	Hospitalization; systemic immunosuppression: cyclosporine A[2], short course of oral glucocorticosteroids[2], dupilumab[1,2], methotrexate[3], azathioprin[3], mycophenolate mofetil[3]; PUVA[1]; alitretinoin[1,3]
MODERATE: SCORAD 25-50 / or recurrent eczema	Proactive therapy with topical tacrolimus[2] or class II or class III topical glucocorticosteroids[3], wet wrap therapy, UV therapy (UVB 311 nm, medium dose UVA1), psychosomatic counseling, climate therapy
MILD: SCORAD <25 / or transient eczema	Reactive therapy with topical glucocorticosteroids class II[2] or depending on local cofactors: topical calcineurin Inhibitors[2], antiseptics incl. silver[2], silver coated textiles[1]
BASELINE: Basic therapy	Educational programmes, emollients, bath oils, avoidance of clinically relevant allergens (encasings, if diagnosed by allergy tests)

(b) Treatment recommendation for atopic eczema: children

- For every phase, *additional* therapeutic options should be considered
- Add antiseptics / antibiotics in cases of superinfection
- Consider compliance and diagnosis, if therapy has insufficient effect
- Refer to guideline text for restrictions, especially for treatment marked with[1]
- Licensed indication are marked with[2], off-label treatment options are marked with[3]

SEVERE: SCORAD >50 / or persistent eczema	Hospitalization, systemic immunosuppression: cyclosporine A[3], methotrexate[3], azathioprin[3], mycophenolate mofetil[1,3]
MODERATE: SCORAD 25-50 / or recurrent eczema	Proactive therapy with topical tacrolimus[2] or class II or III topical glucocorticosteroids[3], wet wrap therapy, UV therapy (UVB 311 nm)[1], psychosomatic counseling, climate therapy
MILD: SCORAD <25 / or transient eczema	Reactive therapy with topical glucocorticosteroids class II[2] or depending on local cofactors: topical calcineurin inhibitors[2], antiseptics incl. silver, silver coated textiles
BASELINE: Basic therapy	Educational programmes, emollients, bath oils, avoidance of clinically relevant allergens (encasings, if diagnosed by allergy tests)

FIGURE 115-2 Stepwise treatment for atopic dermatitis in adults and children. (*Reprinted with permission from Reference* 10.)

Reactive therapy is the traditional treatment modality where anti-inflammatory agents are used only during disease flares with moisturizers used alone between flare-ups. Proactive therapy includes a predefined, long-term, anti-inflammatory treatment applied intermittently (usually twice weekly) together with moisturizers and a predefined appointment schedule for clinical examinations which begins *after* all lesions have been successfully treated. The duration of proactive therapy is usually adapted to disease severity and persistence.[36]

Topical Corticosteroids

10 *Topical corticosteroids* (TCS) are the standard of care to which other treatments are compared.[10,11,30,36,37,41] They remain the drug treatment of choice for AD. However, despite their extensive use, supporting data are limited regarding optimal corticosteroid concentrations, duration and frequency of therapy, and quantity of application.[10,37] The use of long-term intermittent application of TCS was beneficial and safe in two randomized controlled trials (RCTs); however, independent studies of other formulations are needed.

To maximize the anti-inflammatory benefit and minimize adverse effects, the choice of TCS should be matched with the severity and site of disease. Low-potency TCS, such as hydrocortisone 1%, are suitable for the face, and medium-potency TCS, such as betamethasone valerate 0.1%, may be used for the body. For longer-duration maintenance therapy, low-potency TCS are recommended.[37] Mid-strength and high-potency TCS should be used for short-term management of exacerbations.[37] Currently, there is no established optimum regimen for controlling flare-ups—starting with a short burst of high-potency TCS to rapidly control active disease followed by a rapid taper in potency is equally acceptable as using the lowest-potency agent thought to be needed then adjusting upward in potency if treatment fails.[37] Although twice-daily application is the usual clinical practice, there is some evidence of efficacy with once-daily use of some potent TCS.[37] Daily TCS applications are recommended until the inflammatory lesions are significantly improved—which may take up to several weeks at a time. Once control is achieved, either (a) stop the TCS and use moisturizers alone until the next flare-up, or (b) apply a TCS once or twice weekly to areas of the patient's body where frequent/repeated flare-ups occur—this method has reduced rates of

relapse for those patients who experience frequent flare-ups at the same body sites[37] and should be used as proactive therapy in patients with moderate-to-severe AD.[36] There are different potencies for corticosteroids which should be used to guide therapy. (For a corticosteroid potency comparison chart, see Table 114–2 in Chapter 114, or visit the National Psoriasis Foundation Website at http://www.psoriasis.org/netcommunity/sublearn03_mild_potency.) Children should be treated with less potent corticosteroids than adults.[36] Ultrahigh- and high-potency TCS, such as betamethasone dipropionate 0.05% or clobetasone propionate 0.05%, are typically reserved for short-term treatment of lichenified areas in adults.[40] After the lesions have cleared or significantly improved, a lower-potency agent (the least potent TCS that is effective)[37] should be used for maintenance when appropriate.[40] Potent fluorinated TCS should be avoided not only on the face, but also the genitalia and the intertriginous areas, and in young infants.[36]

It is also important to remember that altering the local environment through hydration and/or occlusion (eg, wet-wrap therapy)[11] as well as changing the vehicle[46] may alter the absorption and effectiveness of the TCS.[10] Some vehicles are better suited for certain body areas,[46] such as a lotion for the scalp and hairy areas. Foams may be more cosmetically pleasing to some patients, as they easily disappear into the skin. The surface area of the skin involved and the skin thickness also play a role. In addition, tachyphylaxis is a clinical concern, but there is little experimental documentation.

TCS are efficacious for the itch in addition to improving lesions, and itch is the key symptom for evaluation of response to treatment.[36] Tapering should not be initiated before the itch has largely improved.[36] Dose tapering has been suggested to avoid withdrawal rebound—with various tapering strategies such as to a less potent TCS or by reducing the frequency of application to intermittent treatment (eg, twice weekly).[36] Dose tapering also minimizes side effects.

Adverse effects of TCS may be systemic in nature, and they are directly related to the steroid potency, duration of use, and other factors as discussed above. Local adverse effects include striae distendae (stretch marks) and skin atrophy, perioral dermatitis, acne, rosacea, telangiectasias (rubeosis steroidica), purpura, focal hypertrichosis, a “dirty neck” (cutis punctata linearis colli), spontaneous scars (pseudocicatrices stellaires), and allergic contact dermatitis (often related to the vehicle but may be due to the corticosteroid).[36,37,47] Inappropriate, long-term use of potent TCS on the face can cause a facial rosacea-like disease with persistent erythema, burning and stinging sometimes

called the “red face syndrome” or “corticosteroid addiction syndrome.”[36] In infants, inappropriate use of high-potency TCS can cause granuloma gluteal infantum or iatrogenic Cushing’s disease.[36] The potential for systemic adverse effects is related to the potency of the TCS, the site of application, the occlusiveness of the preparation, the percentage of body surface area covered, and the duration of use. Potential systemic side effects include hypothalamic-pituitary-adrenal (HPA) axis suppression, infections, hyperglycemia, cataracts, glaucoma, and growth retardation (in children).[1,36,37,45,47] However, growth retardation may also be related to the chronicity of the illness rather than to TCS use or dietary factors. Although less likely, systemic adverse effects can occur with low-potency TCS. For example, a phase II study of a mild-potency corticosteroid (desonide 0.05% foam) in children and adolescents 3 months to 17 years showed that 4% (3 out of 75) of patients experienced mild reversible HPA-axis suppression after a 4-week treatment period.[48]

When TCS therapy has failed for efficacy or safety reasons, numerous agents and interventions can be used as alternative or add-on therapy in patients with AD. Some of these interventions are steroid-sparing.

Topical Calcineurin Inhibitors

11 Topical immunomodulators, such as the topical calcineurin inhibitors (TCIs): tacrolimus ointment (Protopic) and pimecrolimus cream (Elidel), have been shown to reduce the extent, severity, and symptoms of AD in adults and children.[10,36,37,40,41] TCIs inhibit the activation of key cells involved in AD, including T cells and mast cells, blocking the production of proinflammatory cytokines and mediators.[37] Tacrolimus also decreases the number and costimulatory ability of epidermal DCs.[37] Pimecrolimus has more favorable lipophilic characteristics and, in animal studies, appears to preferentially distribute to the skin as opposed to the systemic circulation.[49] Both tacrolimus ointment and pimecrolimus cream are approved for AD in adults and children older than age 2 years.[10,36,37,40,41] Although clinical trials conducted in younger infants (eg, 2-23 months old) showed significant efficacy without appreciable adverse effects, use in children younger than age 2 years is not FDA approved.[50] Tacrolimus 0.03% ointment is approved for moderate-to-severe AD for ages 2 years and older, with the 0.1% ointment limited to ages 16 years and older; pimecrolimus 1% cream is approved for mild-to-moderate AD for ages 2 years and older.[50] There is limited data comparing TCS with tacrolimus or pimecrolimus. However, it is known that simultaneous combination of TCS with

TCI at the same site does not seem to provide greater benefit.[36] Using a TCI at sensitive skin sites such as face and skin folds while using TCS at other sites may be a useful strategy. Unlike TCS, long-term use of TCI does not cause skin atrophy[37]; however, an initial acute site reaction is fairly common.[36]

Proactive therapy (intermittent) using TCI is cost-effective for patients with moderate and severe AD.[36,51,52] However, cost-effectiveness of first-line treatment with TCI has not yet been conclusively demonstrated.[36]

The FDA has a black-box warning for both tacrolimus ointment and pimecrolimus cream about their potential cancer risk, but no causal relationship has been proven between use of a TCI and the development of lymphoma or nonmelanoma skin cancer in humans.[43] However, there is a theoretical potential of local skin carcinogenesis as discussed below. Thus, both tacrolimus and pimecrolimus are recommended for use as second-line treatments for short-term and noncontinuous chronic use in AD,[10,36,37,40,41] when the continued use of TCS is ineffective or inadvisable.[36,37] They may be appropriate in patients with corticosteroid-related adverse effects, patients with large body-surface areas of disease, patients unresponsive to TCS, or other reasons where treatment with TCS is inadvisable. Children and adults with a weakened or compromised immune system should not be treated with these agents.[37] Unlike TCS, TCI can be used on all body locations for prolonged periods,[36] although episodic use is recommended. They may be used as twice-weekly long-term therapy for maintenance.[11,36,51,52] They may be used as steroid-sparing agents (sequentially or concomitantly with TCS).[36,37]

The most common adverse effect of TCI is transient discomfort (burning sensation) at the application site.[36,37] Some patients may experience a transient worsening of skin conditions; and these transient side effects are more often seen with tacrolimus than pimecrolimus, and if applying to acutely inflamed skin.[36] Generalized viral infections (eg, eczema herpeticum, eczema molluscatum) have been reported.[36] There is a theoretical potential for local skin carcinogenesis as seen in animal studies, or for systemic effects if high blood levels are reached (eg, increased susceptibility to infections due to immunosuppressive effects).[50] Because of the theoretical possible risk of cutaneous malignancy in humans,[36,37] and the known long-term use of systemic cyclosporine being associated with increased photocarcinogenicity in solid organ transplant patients, sun protection is recommended.[11,36,45] However, it may be that the use of TCI has no association with increased risk of nonmelanoma skin cancer, other malignancies, or photocarcinogenicity.[53,54] Nonetheless, patients should be encouraged to

apply a high sun protection factor (SPF) broad-spectrum sunblock daily to all exposed skin (ie, SPF 30 or higher); and this counseling should especially be emphasized for those patients with the highest risk of developing skin cancer, including patients with red hair and/or Fitzpatrick skin types I and II, and patients receiving phototherapy or using tanning beds.[45]

TCI are effective in relieving the associated pruritus. Both tacrolimus and pimecrolimus significantly relieve pruritus even after the first few days of treatment, in both children and adults (studies report relief after just 3 days).[10]

Coal Tar

Although tar preparations had been widely used for AD and have been recommended as alternative topical therapy, few RCTs support their efficacy.[37] Their anti-inflammatory properties are not well characterized, and part of the improvement may be the result of a placebo effect, which can be significant in AD.

Coal tar products are also staining and malodorous, although newer products may be more cosmetically acceptable. They are not recommended on acutely inflamed skin, since this may result in additional skin irritation.

The use of coal tar in pregnancy has not been studied. Few data are available about tar excretion into breast milk; in addition, safety in children has not been established.[55] Adverse effects include tar folliculitis, acneiform eruptions, irritant dermatitis, burning, stinging, photosensitivity, and a risk of tar intoxication if used extensively in a young child.[55] Although animal studies showed that tar components can be converted to carcinogenic and mutagenic entities, there is inconclusive epidemiologic evidence supporting the claim that human use of topical tar preparations in dermatology leads to skin cancer.[55]

Selective Phosphodiesterase 4 Inhibitors

Crisaborole and apremilast are small-molecule phosphodiesterase (PDE) 4 inhibitors. Cyclic nucleotide PDEs break down cAMP and cGMP into inactive metabolites and there is increased PDE activity in AD, creating a proinflammatory state that may result in stimulation of Th_2 cells to release inflammatory mediators.[56,57] PDE 4 inhibitors inhibit the increased PDE activity; and currently, crisaborole ointment is FDA approved for treatment of mild-to-moderate AD in adults and children 2 years of age or older.[36] (Apremilast is currently approved for psoriasis and psoriatic arthritis [see Chapter 114, “Psoriasis,” in this textbook].)[56] However, a pilot study of

apremilast in patients with moderate-to-severe AD demonstrated moderate improvement of skin lesions, pruritus, and quality of life,[57] and it has also shown success for moderate-to-severe AD in children.[58]

Other Topical Therapies

Patients with moderate-to-severe AD who have frequent bacterial infections may benefit from dilute bleach baths with intranasal mupirocin—one study showed enhanced clinical improvement.[37] Tofacitinib is a Janus kinase (JAK) inhibitor which has promising clinical trial data.[36]

Phototherapy

12 Phototherapy is effective for AD and is recommended[10,11,36,59] as second-line treatment when the disease is not controlled by TCS and/or TCI.[36,59] Although rarely used in prepubertal children, it is not contraindicated.[36] Both natural (heliotherapy) or artificial sources of UV radiation are effective.[36] UV light sources on the skin have immunosuppressive, immunomodulating, anti-inflammatory, and antipruritic effects.[36] A known mechanism of action is immunomodulation through apoptosis of inflammatory cells, inhibition of LCs, and alteration of cytokine production.[36] There are other potential benefits. Phototherapy may be steroid sparing, allowing for the use of lower-potency TCS, or even eliminating the need for maintenance by TCS in some cases. Phototherapy can be used for acute or maintenance therapy in children and adults with AD.[59] Phototherapy may also help prevent secondary bacterial skin infections, commonly seen in patients with AD. UVB radiation reduces *S. aureus* skin colonization.[36,60] However, in a few patients, phototherapy may worsen the AD; it is not recommended in patients whose disease flares up when exposed to sunlight. Relapse following cessation of therapy frequently occurs.[10]

Phototherapy may consist of either ultraviolet light therapy alone, or ultraviolet light therapy alongside drug or topical ointment (commonly called photochemotherapy). Psoralens plus ultraviolet A light (PUVA) is one type of photochemotherapy. The photosensitizer (psoralens) is administered either topically or in a bath immediately prior to ultraviolet A (UVA) light therapy. Topical ointments (such as crude coal tar) may also be used concomitantly with ultraviolet light therapy (eg, Crude coal tar + ultraviolet B [UVB] light) to increase efficacy.

Ultraviolet lamps include UVA (315-400 nm), UVA1 (340-400 nm),

broadband UVB (BB-UVB) (280-315 nm), and narrowband UVB (NB-UVB) (311 nm). Phototherapies used for AD have included PUVA, high- or medium-dose UVA1, BB-UVB, and NB-UVB.[10,59] Currently, no definitive recommendation can be made to differentiate between the various phototherapies.[59] NB-UVB is more effective than BB-UVB therapy and is generally the most commonly recommended light treatment and it has a better side-effect profile than UVA or PUVA.[10,59] BB-UVB may not effectively treat the scalp and skinfold areas. Medium-dose UVA1 is very effective for patients with an acute exacerbation of severe AD; however, the effect may be relatively short-lived and symptoms may recur within 3 months of stopping therapy.[59] Currently, medium-dose UVA1 is considered similar in efficacy as NB-UVB; and high-dose UVA1 is preferred in severe cases when available.[10] There is weaker evidence supporting the use of PUVA in AD[46] and it is not first-choice.[10]

Patients need to wear eye protection during ultraviolet (UV) light therapy to prevent damage to the retina. Short-term adverse effects include erythema, skin pain, skin burning or sunburn, pruritus, and pigmentation.[59] Long-term adverse effects include premature aging of the skin (photoaging), lentigines, photosensitive eruptions, folliculitis, photo-onycholysis, HSV reactivation, facial hypertrichosis, and skin cancer.[59] For example, PUVA has been associated with squamous cell carcinoma and possibly melanoma, which may occur years after PUVA therapy has ceased. UVA therapy may also cause cataract formation.[59]

To minimize a possible initial flare-up, co-medication of TCS and moisturizers has been suggested at the beginning of phototherapy.[36]

Other light therapies include short-wave visible light (>380 nm) (“blue light”) —currently in uncontrolled pilot studies, photopheresis, and devices such as 308-nm monochromatic excimer lasers and pulsed-dye lasers—currently experimental.[36]

Systemic Therapies

Systemic therapies for the treatment of AD are generally not well studied. Small case series or open studies are available for some agents, but few well-conducted RCTs exist. Agents described in published papers have included systemic corticosteroids, cyclosporine, interferon-γ, azathioprine, methotrexate, mycophenolate mofetil, intravenous immunoglobulin (IVIG), and biologic agents.[10,59] Systemic therapies are indicated in AD care only for the subset of adult and pediatric patients in whom optimized topical regimens and/or phototherapy do not adequately control the disease, or where the quality of life is

substantially affected.[59]

Systemic corticosteroids, although sometimes used for rapid disease suppression, are generally not recommended due to an unfavorable risk-benefit profile.[11,36,40,59] A 2017 systematic review of systemic treatment options for adults with AD gave no recommendations for use of systemic corticosteroids due to limited available evidence.[15] The 2018 European consensus guidelines recommended the following regarding oral corticosteroids for patients with AD: (1) restricted use, largely limited to adult patients; (2) short-term use (up to 1 week) in acute flare-ups only in exceptional cases; (3) daily dose not to exceed 0.5 mg/kg bodyweight; (4) use even more cautiously in children than in adults; (5) no long-term use.[36] Short courses of oral corticosteroids may lead to atopic flares/rebound.[11,59]

Cyclosporine is effective for AD and is considered the first-line treatment option when systemic therapy for AD is warranted, that is, for severe, recalcitrant AD,[10,11,15,36,59] but its usefulness is also limited by significant side effects, including hypertension and nephrotoxicity. Combination with UV therapy is not recommended, and effective UV protection should be used.[36] There is also the potential for significant drug–drug and drug–food (eg, grapefruit juice) interactions. It should be reserved for short-term use in adults (and more cautiously in children) with severe refractory disease.[11,59] Maximal benefit is usually seen after 2 to 6 weeks of use and relapse may occur quickly after cessation of therapy.[10,11,59] Treatment durations currently recommended are 6 to 9 months[11] and up to 1 year—this is off-label use in the United States and Canada.[59] European guidelines are for 2 years then to switch to another treatment if possible, but shorter intervals of 3 to 6 months are usually recommended; and cyclosporine is approved for AD in many European countries.[36] In a meta-analysis of eight RCTs, cyclosporine was more efficacious than placebo, with reduced body surface area, erythema, sleep loss, and glucocorticoid use. However, all scores were back to pretreatment levels 8 weeks after ending cyclosporine therapy.[10] An earlier study (2000) comparing intermittent to continuous cyclosporine therapy in children 12 to 16 years of age showed efficacy in some children on intermittent therapy (thus with a lower cumulative cyclosporine dose and minimizing toxicity); however, continuous cyclosporine therapy provided enhanced sustained improvement.[36,61]

Recombinant interferon-γ may be effective in a subset of patients with AD.[10] It may be an alternative for refractory AD (adults and children).[59] Two randomized placebo-controlled trials in patients with severe AD demonstrated

significant improvement in symptoms.[62,63] Short-term adverse effects, such as headache, myalgias, and chills, occurred in substantial proportions of study patients. Transient liver transaminase elevations and granulocytopenia have also occurred. There is no recommended optimal dose.[59]

Azathioprine,[59,64] *methotrexate*,[59,65] *mycophenolate mofetil*,[59] and IVIG have shown efficacy in small case series or open-label studies primarily in adults with recalcitrant AD. There are two RCTs with azathioprine as monotherapy which showed efficacy, improving both QOL and AD.[59,64] Additional RCTs are needed. Oral methotrexate, with a long history of pediatric use for various inflammatory conditions, appeared to be effective in a case series of children (aged 2-16 years) with severe AD[65] and has also shown efficacy in adults.[59]

13 *Biologic agents* are beginning to be approved for AD in some countries. The safety and efficacy of various biologic agents in patients with AD have been studied, mostly in case reports, small case series, or open-label studies with a limited number of patients; however, larger randomized, placebo-controlled trials are now available.[36] Dupilumab, a fully human monoclonal antibody that blocks the common α-chain of the receptor for interleukin-4 and intereukin-13, was approved by the FDA in April 2017 for treating moderate-to-severe adult AD.[36] Dupilumab is a down-regulator of the JAK-STAT pathway. Clinical outcomes (SCORAD, EASI, IGA, BSA) as well as patient-reported outcomes (DLQI, pruritus rating scales) were improved in various phase I-III clinical trials in adults with AD.[66] Clinical trials in children are ongoing at the time of writing (NCT02407756) as well as open-label studies evaluating long-term safety and efficacy of repeat doses in children, adolescents, and adults with previous participation in dupilumab clinical trials (NCT02612454, NCT01949311).[15] Dupilumab's safety profile currently appears to be superior to conventional immunosuppressives such as cyclosporine or methotrexate; its most relevant side effects being conjunctivitis and injection site reactions.[66] Safety in pregnancy is unknown at the time of writing. A recent review of systemic treatment options for adults with AD discussed trials with other biologics including infliximab, mepolizumab, omalizumab, rituximab, and ustekinumab.[15] Some of these trials showed little to no improvement; however, a case series of ustekinumab use showed promising results and was well tolerated.[15] Nemolizumab is another biologic with some promise in a recent clinical trial especially in reducing pruritus.[36] The TNF-α inhibitors infliximab and etanercept appeared effective in a few patients but not others, and adverse events have included infusion reactions with flushing and dyspnea, urticaria, and recurrent skin infections of

methicillin-resistant *S. aureus*. Similarly, omalizumab, rituximab, and alefacept have been shown in a few case reports and small case series to be somewhat effective. A case report series of omalizumab plus IVIG showed significant clinical improvement.[67] However, an RCT with omalizumab showed no clinical improvement in AD despite reducing IgE levels.[59] Currently, therapy of AD with traditional biologics (eg, rituximab, omalizumab, or ustekinumab) is not recommended.[36]

Alitretinoin is a retinoid with anti-inflammatory and antiproliferative effects licensed in some European countries for treatment of hand eczema.[36] It may improve both extrapalmar and hand lesions in AD patients and may be used for atopic hand eczema in adult patients of non-childbearing potential unresponsive to TCS therapy.[36]

Oral antihistamines are used widely; however, there is mixed evidence of efficacy in AD control.[36,59] There is some evidence that oral sedating antihistamines used at night may benefit patients with AD with poor sleep due to pruritus.[11,59]

Complementary and Alternative Therapies

Traditional Chinese herbal therapy has been studied in placebo-controlled trials and appeared to provide temporary benefit for patients with severe AD. However, the effectiveness may wear off despite continued treatment, and long-term toxicity is unknown.[10,68] A recent meta-analysis of seven RCTs attempted to evaluate the efficacy and safety of oral Chinese medicines for AD and concluded that traditional Chinese herbal medicines significantly improved symptom severity and was well tolerated; however, the studies were of poor quality and did not allow for valid conclusions to be drawn about tolerability and routine use.[69] Additional studies are needed.

Probiotics and *prebiotics* may prove to be beneficial for prevention and treatment of AD. Probiotics are live microorganisms (bacteria or fungi) that confer a health benefit on the host when administered in adequate amounts.[70] Prebiotics are nondigestable compounds that lead to favorable changes in the gut microbiome.[70] The term “synbiotics” refers to products that contain both probiotics and prebiotics.[70]

Although earlier studies of *probiotics* had mixed results, more recent clinical trials showed evidence of benefit in both prevention and treatment of AD.[70–73] The most common species of probiotics used include *L. rhamnosus GG, Lactobacillus casei, Lactobacillus plantarum, Lactobacillus johnsonii,*

Bifidobacterium lactis, and *Saccaromues boulardii*.[70] A meta-analysis of 25 clinical trials concluded that probiotics significantly reduced the risk of atopic sensitization when given prenatally.[70,71] A double-blind RCT showed that probiotics reduced the SCORAD index and serum cytokines in AD patients.[70,72] A randomized trial of oral *Bifidobacterium bifidum* in 40 infants newly diagnosed with AD noted a significant reduction in the SCORAD index posttreatment in the infants receiving the probiotic versus no change in those who did not.[73]

Prebiotics are nondigestible oligosaccharides including fructooligosaccharides, galactooligosaccharides, lactulose, and inulin. These can stimulate the growth of selective beneficial gut bacteria, in particular lactobacilli and bifidobacteria.[70] In the colon, prebiotics are fermented into short chain fatty acids (SCFAs) including butyrate, acetate, and propionate. The SCFAs may alter the gut microbiome. For example, transgalactooligosaccharides increase the number of bifidobacteria and modify the colonic fermentation metabolism of the gut flora.[74] Prebiotics have shown benefits for various disease conditions including hypercholesterolemia, *Clostridium difficile*–associated diarrhea, and allergic conditions such as AD.[70] Two recent meta-analyses have shown a 32% reduced incidence of pediatric AD[75] and that the combination of galactooligosaccharide and fructooligosaccharide reduced AD incidence.[76]

Immunotherapy using allergen-specific desensitization techniques in controlled settings for patients with AD may also be beneficial, and much research is ongoing including RCTs. A recent review and meta-analysis of immunotherapy in patients with AD showed significant efficacy.[11,77] More research is also needed to adequately assess the role of homeopathy, hypnotherapy, acupuncture, massage therapy, and biofeedback therapy in the treatment of AD.

Patient Considerations

14 AD may have significant implications not only for the patients themselves, but also their families and caregivers. The burden of AD needs to be addressed. In addition, patients with refractory AD may need further follow-up to rule out other diagnoses, confirm adequate/appropriate first-line therapy use, rule out/minimize exacerbating factors, implement second-line therapies, etc.[78]

In 2006, an international study of 2,002 patients and caregivers from 8 countries addressed the effect of AD on the lives of patients and society.[79] This European study found that, on average, patients experienced 9 flares per year,

with those having severe disease experiencing more flares and taking significantly longer to clear. The flares were associated with disturbed sleep, and 86% of patients avoided at least one type of everyday activity. Schoolwork performance and productivity were negatively affected. Patients missed an average of 2.5 days of school or work per year, and an analysis of adult patient performance at work and occupational absence showed that the social cost of lost productivity could amount to more than 2 billion Euros per year across the European Union. There were also emotional consequences; half of the patients experienced depression or unhappiness about their condition, and one-third reported that AD had eroded their self-confidence. In addition, concern about adverse effects from TCS treatments resulted in poor adherence to therapy. On average, patients endured the symptoms of AD without initiating specific treatment 47% of the time they had an exacerbation. Approximately one-half of the respondents were concerned about using TCS, and 58% restricted them to particular sites, 39% used them less frequently or for shorter time periods than prescribed, and 66% used them as a last resort. The study concluded that AD is "an undertreated disease that has a significant, yet mostly avoidable, negative effect on patients, their caregivers, and society."[79]

The above conclusion is echoed in more recent reports. In 2018 and 2019, studies relating to the burden of disease from the United States, Canada, and internationally were published. In a 2018 US cross-sectional study, 1,519 adult patients with AD reported a multidimensional burden of disease that is higher with greater disease severity and inadequate disease control.[80] Patients with moderate/severe AD (830/1519) reported more severe itching and pain, greater adverse effects on sleep, higher prevalence of anxiety and depression, and greater health-related QoL impairment. 103/1519 patients had inadequate disease control despite treatment with systemic immunomodulators or phototherapy, and they reported higher burdens of itch and sleeping symptoms versus those with controlled disease.[80] Sleep symptoms included trouble sleeping (significant on PO-SCORAD), longer sleep latency, more frequent sleep disturbances, and greater need for OTC sleep medications.[80] Results from two 2018 Canadian online national cross-sectional surveys included the burden of moderate-to-severe AD on pediatric patients.[81] For the adult patients: 87% (187/216) reported that their daily life was negatively affected by their disease, with experiences ranging from dysfunctional sleep (79%, ie, 148/187), anxiety (64%, ie, 120/187), avoidance of social activities (48%, ie, 90/187), avoidance of physical activity (47%, ie, 88/187), and avoidance of intimacy (40%, ie, 75/187). In addition, 32% reported difficulty accessing treatments and 41% felt that their treatment

needs were unmet. Only 9% reported that their disease was well controlled, and 78% reported they had lived for over one year with inadequate treatment for their disease. For the pediatric patients: 78% (253/361) had sleep disturbances, 51% avoided social activities, 30% had anxiety issues, 20% missed school due to their AD—and of these, 23% have missed 10 days or more within the past year.[81] Regardless of treatment modalities, most survey respondents felt that their child's AD is not well controlled—85% have used three or more treatment modalities for their child's AD, and 80% of respondents find the recommended care regimen for their child's AD challenging.[81]

Most recently, in 2019, data from a 2016 National Health and Wellness Survey conducted in France, Germany, Italy, Spain, and the United Kingdom was published with comparisons between controls without AD matched to patients with self-reported AD (both $n = 1860$).[82] Self-reported comorbidities were significantly more prevalent in patients with AD compared to those without AD and these included anxiety, depression, and sleep disturbances. There was reduced health-related QoL as well as a significant impact on work productivity (ie, presenteeism and overall work impairment) and the ability to undertake activities. There was also greater healthcare utilization.[82]

Even though there is likely selection bias due to the self-reporting nature of these surveys, the results from these (and others) should alert healthcare professionals to the continuing unmet health, psychosocial, and educational needs associated with AD.

Patient communication may be a key step—treating them as partners in their own (or their child's) care, with regular contact, advice, and support. Healthcare professionals play an integral role in providing patient and caregiver education and support about this disease and specific treatment plans. The importance of adequate and appropriate education for the patient, family, and caregivers about AD and its management cannot be overemphasized. Patients should be involved in their own care whenever possible. Timely access to dermatology consultation may be another key factor—in the above Canadian survey only 27% (123/451) of respondents are managed by a dermatologist—wait times for appointments were 3 months or longer (46%) and in 25% of cases were 6 months or longer.[79] Limited access to care is a societal issue.

EVALUATION OF THERAPEUTIC OUTCOMES

- Contact patient/caregiver in 1 to 2 weeks to follow-up about the efficacy of

recommended therapies and any issues with the treatment regimen. Continuing regular follow-up is recommended to monitor for adherence and address other issues and patient concerns (eg, QoL issues as discussed above).

- Ensure that appropriate monitoring parameters for efficacy and potential adverse effects have been put in place (eg, follow-up lab tests as needed).
- Reinforce preventive measures including continuation of proactive therapy, if implemented.
- Ensure that patient/caregiver has been connected to other health resources as needed for follow-up (eg, a dermatologist, psychologist, and social worker).

CONCLUSION

AD is a chronic skin condition that generally presents at an early age. It affects the patient, family, caregivers, and our society and is optimally managed by multidisciplinary care. Nonpharmacologic management strategies are important in treatment; these include appropriate skin care, hydration, avoidance of triggers, and psychosocial support and management. Community pharmacists are in a prime position to support patients, physicians, and other health professionals because patients with AD (and caregivers of children with AD) may initially seek nonprescription treatments.[30] The pharmacologic treatment strategy may be proactive or reactive depending on disease severity. Treatment alternatives continue to emphasize TCS as the standard of care; others being TCIs and other topical agents, wet wrap therapy, and UV therapy. For severe/recalcitrant disease, systemic therapies including cyclosporine and biologics may be warranted. A 2018 review provides a step-wise clinical approach to the patient with refractory AD which include ruling out other diagnoses, confirming first-line therapies, and ruling out exacerbating factors before using second-line therapies; further, a multidisciplinary approach to address behavioral factors (poor adherence, improper technique, habitual scratching, depression, sleep disturbance, stress) is described (eg, habit reversal training for the itch-scratch cycle).[78] Patient and caregiver education and support about AD and treatment strategies is critical to optimize treatment outcomes. Successful outcomes result when patients and caregivers are partners with healthcare professionals in the management of this chronic disease.

Postclass Engaged Learning Activity

Can atopic dermatitis be prevented? Research into primary prevention of allergy and allergic diseases in high-risk populations has been occurring. Currently, there is much interest and research focus into the gut microbiome and skin microbiome as they relate to allergic diseases, and limited evidence exists that probiotics are beneficial by altering the gut microbiome. In 2015, the World Allergy Organization (WAO) partnered with McMaster University to produce Guidelines for Allergic Disease Prevention (GLAD-P) as they relate to the use of probiotics.[83] Review these guidelines and perform a literature review to update the state of knowledge about prevention of allergic diseases.

ABBREVIATIONS

AD	atopic dermatitis
AMP	antimicrobial peptide
BB-UVB	broadband ultraviolet B light (280-315 nm)
DC	dendritic cell
ETFAD	European Task Force of Atopic Dermatitis
FDA	Food and Drug Administration
FLG	filaggrin gene
GI	gastrointestinal
HPA	hypothalamic-pituitary-adrenal
IgE	immunoglobulin E
IgM	immunoglobulin M
IL	interleukin
ISAAC	International Study of Asthma and Allergies in Childhood
IVIG	intravenous immunoglobulin
JAK	Janus kinase
MDC	macrophage-derive chemoattractant
NB-UVB	narrowband ultraviolet B light (311 nm)
NIAID	National Institute of Allergy and Infectious Diseases

PDE	phosphodiesterase
PUVA	psoralens plus ultraviolet A light
RAST	radioallergosorbent test
RCT	randomized controlled trial
SCFAs	short chain fatty acids
SCORAD	Scoring of Atopic Dermatitis
SD	standard deviation
SPF	sun protection factor
TARC	thymus and activation-regulated chemokine
TCIs	topical calcineurin inhibitors
TCS	topical corticosteroids
TH_1	T-helper cell type 1
TH_2	T-helper cell type 2
UV	ultraviolet
UVA	ultraviolet A
UVB	ultraviolet B

REFERENCES

1. National Institute of Arthritis and Musculoskeletal and Skin Diseases. Atopic Dermatitis. US Department of Health and Human Services. 2018. Available at: https://www.niams.nih.gov/health-topics/atopic-dermatitis/advanced. Accessed December 15, 2018.
2. Eichenfield LE, Tom WL, Chamlin SI, et al. Guidelines of care for the management of atopic dermatitis. Section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol*. 2014;70:338–351.
3. Weidinger S, Novak N. Atopic dermatitis. *The Lancet*. 2016 (March 12);387(10023):1109–1122.
4. Hanifin JM. Epidemiology of atopic dermatitis. *Immunol Allergy Clin North Am*. 2002;22:1–24.
5. Bieber T. Mechanisms of disease: Atopic dermatitis. *N Engl J Med*. 2008;358:1483–494.
6. Williams H, Flohr C. How epidemiology has challenged 3 prevailing concepts about atopic dermatitis. *J Allergy Clin Immunol*. 2006;118:209–

213.

7. Williams H, Stewart A, von Mutius E, Cookson W, et al. Is eczema really on the increase worldwide? *J Allergy Clin Immunol*. 2008;121:947–954.
8. DaVeiga SP. Epidemiology of atopic dermatitis: A review. *Allergy Asthma Proc*. 2012;23:227–234.
9. Nutten S. Atopic dermatitis: Global epidemiology and risk factors. *Ann Nutr Metab*. 2015;66(suppl 1):8–16.
10. Wollenberg A, Barbarot S, Bieber T, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: Part I & part II. *J Eur Acad Dermatol Venereol*. 2018;32(5):657–682.
11. Plotz SG, Wiesender M, Todorova A, Ring J. What is new in atopic dermatitis/eczema? *Expert Opin Emerging Drugs*. 2014;19(4):441–458.
12. Akdis CA. New insights into mechanisms of immunoregulation in 2007. *J Allergy Clin Immunol*. 2008;122:700–709.
13. Ege MJ, Herzum I, Buchele G, et al. Prenatal exposure to a farm environment modifies atopic sensitization at birth. *J Allergy Clin Immunol*. 2008;122:407–412.
14. Flohr C, Yeo L. Atopic dermatitis and the hygiene hypothesis revisited. *Curr Probl Dermatol*. 2011;41:1–34.
15. Gooderham M, Lynde CW, Papp K, et al. Review of systemic treatment options for adult atopic dermatitis. *J Cutan Med Surg*. 2017;21(1):31–39.
16. Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. *N Eng J Med*. 2011;365(4):1315–1327.
17. Rodriguez E, Baurecht H, Herberich E, et al. Meta-analysis of filaggrin polymorphisms in eczema and asthma: Robust rick factors in atopic disease. *J Allergy Clin Immunol*. 2009;123:1361–1370.
18. Honey B, Steinhoff M, Ruzicka T, Leung DYM. Cytokines and chemokines orchestrate atopic skin inflammation. *J Allergy Clin Immunol*. 2006;118:178–189.
19. Leung DYM. Our evolving understanding of the functional role of filaggrin in atopic dermatitis. *J Allergy Clin Immunol*. 2009;124:494–495.
20. Steinke JW, Rich SS, Borish L. Genetics of allergic disease. *J Allergy Clin Immunol*. 2008;121(suppl):S384–S387.
21. Heratizadeh A, Wichmann K, Werfel T. Food allergy and atopic dermatitis: How are they connected? *Curr Allergy Asthma Rep*.

2011;11:284–291.

22. Sicherer SC, Leung DYM. Advances in allergic skin disease, anaphylaxis and hypersensitivity reactions to foods, drugs, and insects in 2008. *J Allergy Clin Immunol*. 2009;123:319–327.
23. Schauber J, Gallo RL. Antimicrobial peptides and the skin immune defense system. *J Allergy Clin Immunol*. 2008;122:261–266.
24. Novak N, Bieber T. Dendritic cells as regulators of immunity and tolerance. *J Allergy Clin Immunol*. 2008;121(suppl):S370–S374.
25. Biebe T, de la Salle H, Wollenberg A, et al. Human epidermal Langerhans cells express the high affinity receptor for immunoglobulin E (Fc epsilon RI). *J Exp Med*. 1992;175:1285–1290.
26. Wang B, Rieger A, Kilgus O, et al. Epidermal Langerhans cells from normal human skin bind monomeric IgE via Fc epsilon RI. *J Exp Med*. 1992;175:1353–1365.
27. Novak N, Bieber T. The role of dendritic cell subtypes in the pathophysiology of atopic dermatitis. *J Am Acad Dermatol*. 2005;53(suppl 2):S171–S176.
28. Lack G. Epidemiologic risks for food allergy. *J Allergy Clin Immunol*. 2008;121:1331–1336.
29. Boyce JA, Assa'ad AH, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States. Report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol*. 2010;126(6 suppl):S1–S58. Available at: http://www.niaid.nih.gov/topics/foodAllergy/clinical/Pages/default.aspx.
30. Wong ITY, Tsuyuki RT, Cresswell-Melville A, et al. Guidelines for the management of atopic dermatitis (eczema) for pharmacists. *Can Pharm J*. 2017;150(5):285–297.
31. Lucas JSA, Lewis SA, Jourihane JO'B. Kiwi fruit allergy: A review. *Pediatr Allergy Immunol*. 2003;14:420–428.
32. Cohen A, Goldberg M, Levy B, et al. Sesame food allergy and sensitization in children: The natural history and long-term follow-up. *Pediatr Allergy Immunol*. 2007;18:217–223.
33. Burks AW, Laubach S, Jones SM. Oral tolerance, food allergy, and immunotherapy: Implications for future treatment. *J Allergy Clin Immunol*. 2008;121:1344–1350.
34. Sidbury R, Tom WL, Bergman JN, et al. Guidelines of care for the

management of atopic dermatitis. Section 4. Prevention of disease flares and use of adjunctive therapies and approaches. *J Am Acad Dermatol*. 2014. published online September 25, 2014. Available at: http://dx.doi.org/10.1016/j.jaad.2014.08.038.

35. Kim BS. Atopic Dermatitis. Medscape eMedicine updated Oct 30, 2018. Available at: http://emedicine.medscape.com/article/1049085-overview. Accessed November 19, 2018.
36. Wollenberg A, Barbarot S, Bieber T, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: Part I. *J Eur Acad Dermatol Venereol*. 2018;32:657–682.
37. Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis. Section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol*. 2014;71:116–132.
38. Angelova-Fischer I, Neufang G, Jung K, et al. A randomized, investigator-blinded efficacy assessment study of stand-alone emollient use in mild to moderately severe atopic dermatitis flares. *J Eur Acad Dermatol Venereol*. 2014;(suppl 3):9–15.
39. Horimukai K, Morita K, Narita M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol*. 2014;134:824–830. e6.
40. Rubel D, Thirumoorthy T, Soebaryo W, et al. Consensus guidelines for the management of atopic dermatitis: An Asia-Pacific perspective. *J Dermatol*. 2013;40:160–171.
41. Baron SE, Cohen SN, Archer CB. British Association of Dermatologists and Royal College of General Practitioners. Guidance on the diagnosis and clinical management of atopic eczema. *Clin Exp Dermatol*. 2012;37(suppl 1):7–12.
42. Aries MF, Hernandez-Pigeon H, Vaissiere C, et al. Anti-inflammatory and immunomodulatory effects of *Aquaphilus dolomiae* extract on in vitro models. *Clin Cosmet Investig Dermatol*. 2016;9:421–434.
43. Bianchi P, Theunis J, Casas C, et al. Effects of a new emollient-based treatment on skin microflora balance and barrier function in children with mild atopic dermatitis. *Pediatr Dermatol*. 2016;33:175–171.
44. Fostini AC, Georgescu V, Decoster CI, Girolomini G. A cream based on *Aquaphilus dolomiae* extracts alleviates non-histaminergic pruritus in humans. *Eur J Dermatol*. 2017;27:317–318.

45. Law RM, Kwa PG, Maibach HI, et al. Atopic dermatitis: The itch that erupts when scratched. In: Schwinghammer TL, ed., et al. *Pharmacotherapy Casebook: A Patient-Focused Approach*. 11th ed. New York: McGraw-Hill; 2020.
46. Rosso JD, Friedlander SF. Corticosteroids: Options in the era of steroid-sparing therapy. *J Am Acad Dermatol*. 2005;53:S50–S58.
47. Hengge UR, Ruzicka T, Schwartz RA, et al. Adverse effects of topical glucocorticosteroids. *J Am Acad Dermatol*. 2006;54:1–15.
48. Hebert AA; Desonide Foam Phase III Clinical Study Group. Desonide foam 0.05%: Safety in children as young as 3 months. *J Am Acad Dermatol*. 2008;59:334–340.
49. Stuetz A, Grassberger M, Meingassner JG. Pimecrolimus (Elidel, SDZ ASM 981)—Preclinical pharmacologic profile and skin selectivity. *Semin Cutan Med Surg*. 2001;20:233–241.
50. Berger TG, Duvic M, Van Voorhees AS, Frieden IJ. The use of topical calcineurin inhibitors in dermatology: Safety concerns. *J Am Acad Dermatol*. 2006;54:818–823.
51. Healy E, Bentley A, Fidler C, Chambers C. Cost-effectiveness of tacrolimus ointment in adults and children with moderate and severe atopic dermatitis: Twice-weekly maintenance treatment vs. standard twice-daily reactive treatment of exacerbations from a third party payer (U.K. National Health Service) perspective. *Br J Dermatol*. 2011;164:387–395.
52. Thaci D, Chambers C, Sidu M, et al. Twice-weekly treatment with tacrolimus 0.03% ointment in children with atopic dermatitis: Clinical efficacy and economic impact over 12 months. *J Eur Acad Dermatol Venereol*. 2010;24:1040–1046.
53. Margolis DJ, Abuabara K, Hoffstad OJ, et al. Association between malignancy and topical use of pimecrolimus. *JAMA Dermatol*. 2015;151:594–599.
54. Deleuran M, Vewtergaard C, Volund A, et al. Topical calcineurin inhibitors, topical glucocorticoids and cancer in children: A nationwide study. *Acta Derm Venereol*. 2016;96:834–835.
55. Pughdal KV, Schwartz RA. Topical tar: Back to the future. *J Am Acad Dermatol*. 2009;61:294–302.
56. Kitzen JM, Pergolizzi JV, Taylor R, et al. Crisaborole and apremilast: PDE4 inhibitors with similar mechanism of action, different indications for management of inflammatory skin conditions. *Pharmacology &*

Pharmacy. 2018;9:357–381. Available at: https://file.scirp.org/pdf/PP_2018090714540152.pdf.

57. Samrao A, Berry TM, Goreshi R, Simpson EL. A pilot study of an oral phosphodiesterase inhibitor (apremilast) for atopic dermatitis in adults. *Arch Dermatol*. 2012;148:890–1108.
58. Saporito RC, Cohen DJ. Apremilast use for moderate-to-severe atopic dermatitis in pediatric patients. *Case Rep Dermatol*. 2016;8:179–184.
59. Sidbury R, Davis DM, Cohen DE, et al. Guidelines of care for the management of atopic dermatitis. Section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol*. 2014;71:327–349.
60. Dotterud LK, Wilsgaard T, Vorland LH, et al. The effect of UVB radiation on skin microbiota in patients with atopic dermatitis and health controls. *Int J Circumpolar Health*. 2008;67:254–260.
61. Harper JI, Ahmed I, Barclay G, et al. Cyclosporin for severe childhood atopic dermatitis: Short course versus continuous therapy. *Br J Dermatol*. 2000;142:52–58.
62. Hanifin JM, Schneider LC, Leung DY, et al. Recombinant interferon gamma therapy for atopic dermatitis. *J Am Acad Dermatol*. 1993;28:189–197.
63. Jang IG, Yang JK, Lee HJ, et al. Clinical improvement and immunohistochemical findings in severe atopic dermatitis treated with interferon gamma. *J Am Acad Dermatol*. 2000;42:1033–1040.
64. Meggitt SJ, Gray JC, Reynolds NJ. Azathioprine doses by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomized controlled trial. *Lancet*. 2006;367:839–846.
65. Rouse C, Siegfried E. Methotrexate for atopic dermatitis in children. *J Am Acad Dermatol*. 2008;58(2 suppl 2):AB7, abstract P608.
66. Seegraber M, Srour J, Walter A, et al. Dupilumab for treatment of atopic dermatitis. *Expert Rev Clin Pharmacol*. 2018;11(5):467–474.
67. Toledo F, Silvestre JF, Munoz C. Combined therapy with low-dose omalizumab and intravenous immunoglobulin for severe atopic dermatitis. Report of four cases. *J Eur Acad Dermatol Venereol*. 2012;26:1325–1327.
68. Koo J, Arain S. Traditional Chinese medicine for the treatment of dermatologic disorders. *Arch Dermatol*. 1998;134:1388–1393.
69. Tan HY, Zhang AL, Chen DC, et al. Chinese herbal medicine for atopic

dermatitis: A systematic review. *J Am Acad Dermatol*. 2013;69:295–230.

70. Patel R, DuPont HL. New approaches for bacteriotherapy: prebiotics, new-generation probiotics, and synbiotics. *Clin Infect Dis*. 2015;60(suppl 2):S108–S121.
71. Elazab N, Mendy A, Gasana J, et al. Probiotic administration in early life, atopy, and asthma: A meta-analysis of clinical trials. *Pediatrics*. 2013;132:e666–e676.
72. Yesilova Y, Calka O, Akdeniz N, et al. Effect of probiotic on the treatment of children with atopic dermatitis. *Ann Dermatol*. 2012;24:189–193.
73. Lin RJ, Qiu LH, Guan RZ, et al. Protective effect of probiotics in the treatment of infantile eczema. *Experimental and Therapeutic Medicine*. 2015;9:1593–1596.
74. Bouhnik Y, Flourie B, D'Agay-Abensour L, et al. Administration of transgalato-oligosaccharides increases fecal bifidobacteria and modifies colonic fermentation metabolism in healthy humans. *J Nutr*. 1997;127:444–448.
75. Baquerizo Nole KL, Yim E, Keri JE. Probiotics and prebiotics in dermatology. *J Am Acad Dermatol*. 2014;71:814–821.
76. Osborn DA, Sinn J. Prebiotics in infants for prevention of allergy. *Cochrane Database Syst Rev*. 2013;3.
77. Bae JM, Choi YY, Park CO, et al. Efficacy of allergen-specific immunotherapy for atopic dermatitis: A systematic review and meta-analysis of randomized controlled trials. *J Allergy Clin Immunol*. 2013;132:110–117.
78. Izadi N, Leung DYM. Clinical approach to the patient with refractory atopic dermatitis. *Ann Allergy Asthma Immunol*. 2018;120(1):23–33.e1. doi:10.1016/j.anai.2017.09.061.
79. Zuberbier T, Orlow SJ, Paller AS, et al. Patient perspectives on the management of atopic dermatitis. *J Allergy Clin Immunol*. 2006;118:226–232.
80. Simpson EL, Guttman-Yassky E, Margolis DJ, et al. Association of inadequately controlled disease and disease severity with patient-reported disease burden in adults with atopic dermatitis. *JAMA Dermatol*. 2018;154(8):903–912. doi:10.1001/jamadermatol.2018.1572.
81. Bridgman AC, Eshtiaghi P, Cresswell-Melville A, Ramien M, Drucker AM. The burden of moderate to severe atopic dermatitis in Canadian children: A cross-sectional survey. *J Cutan Med Surg*. 2018;22(4):443–

444. doi:10.1177/1203475418761859.

82. Eckert L, Gupta S, Gadkari A, Mahajan P, Gelfand JM. Burden of illness in adults with atopic dermatitis: Analysis of National Health and Wellness Survey data from France, Germany, Italy, Spain, and the United Kingdom. *J Am Acad Dermatol*. 2019;81(1):187–195. doi:10.1016/j.jaad.2019.03.037.

83. Fiocchi A, Pawankar R, Cuello-Garcia C, et al. World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): Probiotics. *World Allergy Organ J*. 2015;8(1):4. doi:10.1186/s40413-015-0055-2.

116

Alopecia

Rebecca M. Law, Le Hanh Dung Do, and Howard I. Maibach

KEY CONCEPTS

1. The hair cycle consists of three phases: anagen, catagen, and telogen. These are not synchronized across all hair follicles. Different factors regulate each phase of the hair cycle.
2. Pattern hair loss (or androgenetic alopecia) is an inherited condition in which androgens play a key role.
3. Inflammation plays an important role in alopecia. Inflammatory infiltrates are evident in androgenetic alopecia and alopecia areata. Alopecia areata is the most frequent cause of inflammation-induced alopecia. Chronic inflammation may lead to the destruction of the hair follicle, resulting in irreversible hair loss.
4. Scarring hair loss (or cicatricial alopecia) leading to irreversible hair loss can be caused by chronic inflammation or secondary to burns, cancer, trauma, radiation, or other diseases such as lichen planopilaris and chronic cutaneous lupus erythematosus.
5. Thinning of hair or hair loss is usually the only clinical sign of alopecia. Other symptoms (eg, itching, pain, burning, or prickly discomfort) would suggest other underlying disease conditions. Dermatologic diseases can cause hair loss, which varies from mild, nonscarring, and reversible to scarring and irreversible.
6. Alopecia can be distressing, affecting the quality of life and causing psychological problems. Psychosocial support and counseling must not be overlooked.
7. Treatment and management strategies of alopecia should be as cause-specific as possible. Identified causes (eg, iron deficiency, tinea capitis) should be treated and/or eliminated as soon as practically feasible.

8. Treatment for androgenetic alopecia includes topical minoxidil, oral 5α-reductase inhibitors (finasteride, dutasteride) for men, hormonal therapy for women, and miscellaneous therapies including nutritional supplements and laser light therapy with variable efficacy.
9. Treatment for alopecia areata includes intralesional corticosteroids, topical corticosteroids, high-dose oral corticosteroids, topical minoxidil, topical immunotherapy, topical and systemic biologic agents (in particular JAK inhibitors), azathioprine and other immunosuppressive agents, and other miscellaneous therapies.

Preclass Engaged Learning Activity

Read this continuing medical education article: "Hair Loss: Common Causes and Treatment," by T. Grant Phillips, W. P. Slomiany, and R. Allison.[1]

INTRODUCTION

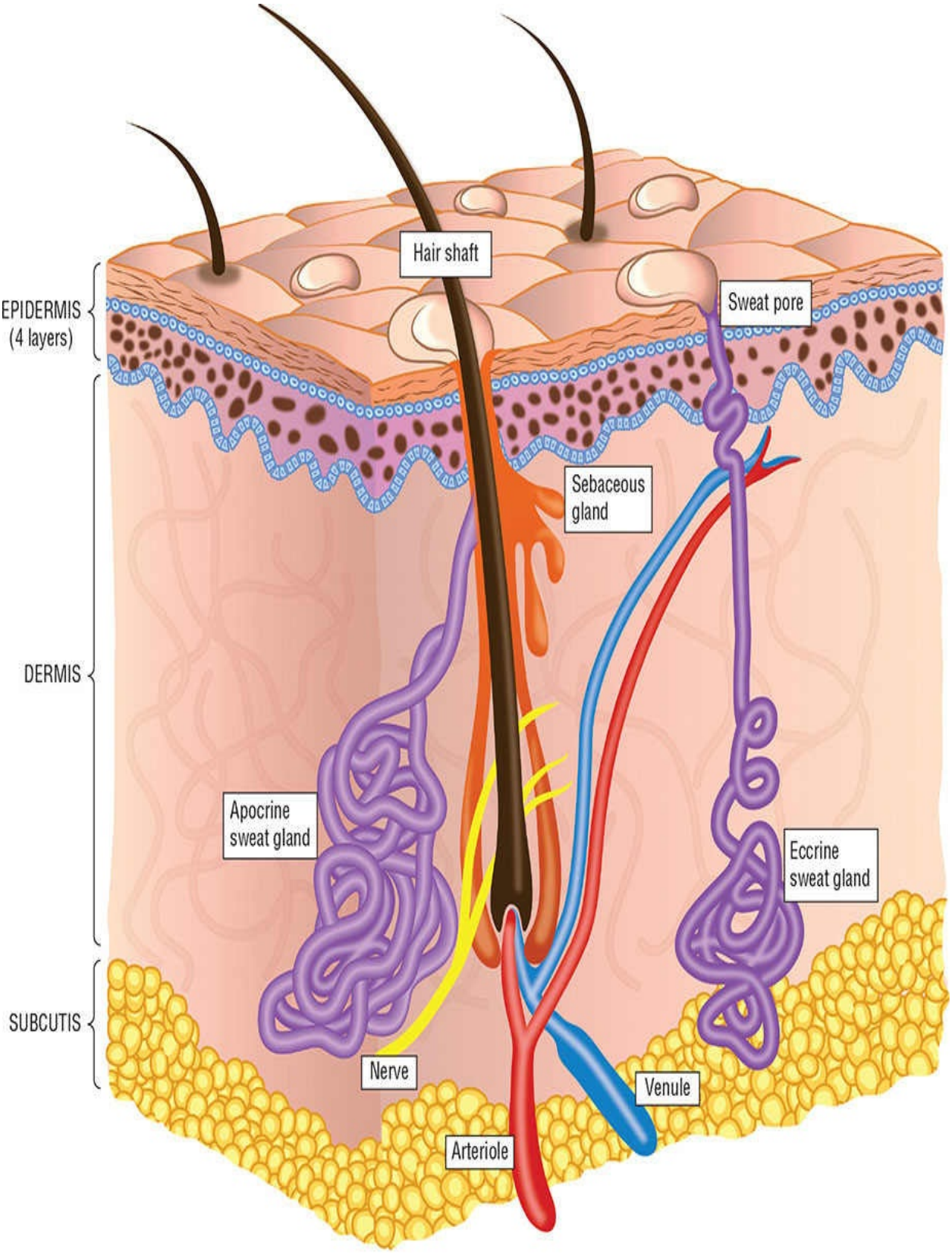
Having a full head of hair is of some importance to most adults and children. Alopecia, defined in the Oxford Dictionary as "the partial or complete absence of hair from areas of the body where it normally grows," is a condition with a myriad of causes. This chapter reviews normal hair growth and physiology and discusses some of the known causes and types of alopecia.

ANATOMY AND PHYSIOLOGY OF THE HAIR FOLLICLE

Hair covers most of the human body and grows both outside and inside of the skin. The external part is keratinized nonliving hair shaft, and the living follicles are located below the skin surface. The visible dead shaft mostly remains constant, while the living follicles continuously regenerate.[2,3]

The hair follicle is part of the human skin. It begins in the dermis with the hair bulb and the hair shaft, which extend through the epidermis and out into the external environment. The dermis provides support for the hair bulb, hair shaft, and other skin structures and appendages. The hair follicle and the sebaceous gland form a pilosebaceous unit with a common duct opening into the

environment (**Fig. 116-1**). (For discussions of other components in skin, refer to Chapter e117, “Drug-Induced Dermatologic Disorders.”)



Original artwork courtesy of Rebecca Law, ©2018 by R Law, all rights reserved.

FIGURE 116-1 The hair follicle and its relationship to other structures and appendages of the human skin. Refer to Chapter e117, "Drug-Induced Dermatologic Disorders," for discussions about other components in skin. (*Original artwork courtesy of Rebecca Law, ©2018 by R Law, all rights reserved.*)

The hair shaft comprises three layers from outside to inside: the cuticle, the cortex, and the medulla. The cuticle consists of hard, colorless cells that overlap. This outermost layer is responsible for elasticity and resiliency; it determines the general condition of the hair. The cortex contains melanin and thus determines hair color. It also contains keratin and determines whether the hair is straight or curly. The innermost layer is the medulla, which plays an important role in supporting the structure of hair.

Below the skin surface, the hair follicle is divided into upper and lower segments by the insertion site of the arrector pili muscle. The upper segment comprises the infundibulum and the isthmus (**Fig. 116-2**). The infundibulum is a funnel-shaped cavity that serves as a reservoir of the sebaceous gland. It is filled with sebum, and covered by an impermeable stratum corneum. The isthmus lies below the infundibulum, and it connects the duct of the sebaceous gland to the arrector pili muscle. The lower segment of the hair follicle contains the stem and the hair bulb. Adamson's fringe is the boundary between anucleate cells in the stem and nucleated cells in the bulb. The hair bulb contains nerve fibers, a capillary network, and loose connective tissue called the dermal papilla. Nerves and arterioles that supply the follicles are arranged as a plexus, arising from the subcutaneous fat to the dermis. The dermal papilla is a pear-shaped structure that consists of active cells and growth factors, which can induce hair growth and pigmentation.

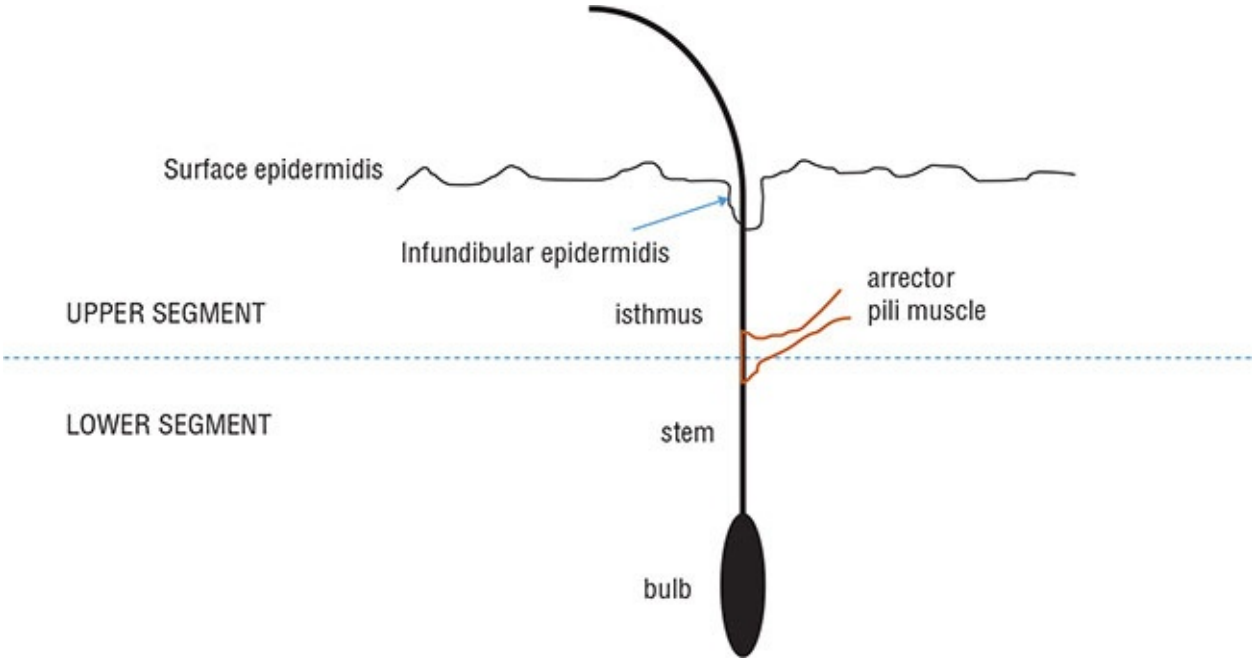


FIGURE 116-2 The hair follicle.

The Hair Cycle

1 The hair cycle consists of three phases; these are not synchronized among all hair follicles. The phases are the anagen, catagen, and telogen phases, followed by an intermediary "returning to anagen" phase (**Fig. 116-3**).[4]

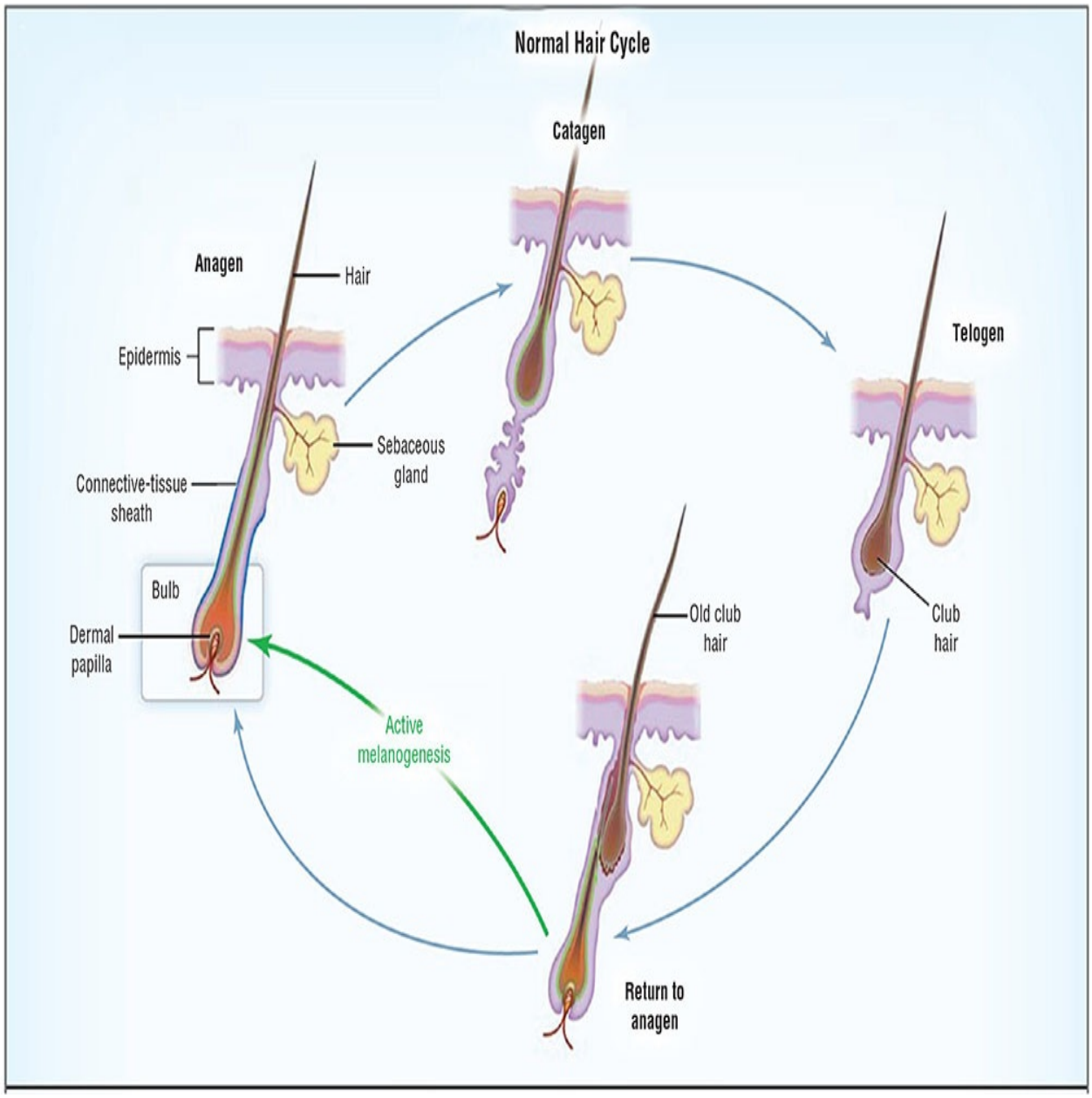


FIGURE 116-3 The normal hair cycle. (*Reprinted with permission from Reference 4.*)

Most of the hairs are in the ***anagen phase*** (also known as the growth phase). At the beginning of this phase, hair stem cells multiply, grow downward into the dermis and differentiate into the hair shaft,[5] where the melanocytes start producing pigment. While the anagen phase of short hairs (eg, eyelashes, eyebrows, hairs on arms and legs) lasts around 1 month, those of longer scalp hairs can last up to 6 years. Scalp hairs of an adult grow at a rate of about 1 mm per 3 days.

The anagen phase is regulated by factors as listed in column 1 of **Table 116-1**. Since hairs in this phase are growing, regulation is mostly by growth factors.

TABLE 116-1 Regulatory Factors of Three Phases in the Hair Cycle

Anagen Phase	Catagen Phase	Telogen Phase
Bone morphogenetic protein (BMP)	FGF-5	Androgens
Sonic hedgehog	Transforming growth factor β1 (TGF-β1)	Prolactin
WNT proteins and receptors	Interleukin 1b (IL-1b)	Adrenocorticotropic hormone (ACTH)
Insulin-like growth factor-1 (IGF-1)	Neurotrophins NT-3, NT-4	Retinoids and thyroid hormones
Fibroblast growth factor-7 (FGF-7)	Bone morphogenetic protein BMP2/4	Estrogen
Hepatic growth factor (HGF)	Tumor necrosis factor α (TNF-α)	FGF-5
Vascular endothelial growth factor (VEGF)		BMP-4[6]

Overall, about 1% to 3% of hairs are in the ***catagen phase*** (also known as the transition phase). It begins when the anagen phase ends. The hair follicle starts to undergo apoptosis and reduces in size. The keratinocytes decrease proliferation, melanocytes decrease the production of pigments, and the hair shaft is no longer lengthened. The dermal papilla is transformed into a cluster of inactive cells along with the shrinking hair follicle. This phase lasts about 2 to 3 weeks.

The catagen phase is regulated by factors as listed in column 2 of Table 116-1.[7] Note that Interleukin 1b (IL-1b) and tumor necrosis factor α (TNF-α) aid the inhibition of growth factors, leading to a decrease in proliferation of hair follicles.

The ***telogen phase*** begins after the catagen phase ends, and lasts for 1 to 3 months, with 10% to 15% of hairs. The hair and the dermal papilla go into a resting phase, and melanocytes go into apoptosis.

This phase is regulated by various hormones (thyroid hormones, androgens, prolactin, ACTH, and others) as listed in column 3 of Table 116-1. In the end, the hair falls out (***exogen phase***) at a usual rate of 50 to 100 scalp hairs per day.

The follicle rests for a few weeks and then proceeds to the growth phase with the multipotent stem cells from the bulge area. Generally, hair grows until the fourth decade of life. After that age period, the majority of hair follicles are in the catagen and telogen phases, which leads to thinning of the hair, and baldness.

PATHOPHYSIOLOGY

Hormones

2 Androgens play a key role in pattern hair loss, which is an inherited condition characterized by scalp sensitivity to dihydrotestosterone (DHT). Testosterone is converted into DHT by the enzyme 5α-reductase. DHT binds to androgen receptors in the same manner as testosterone, but with much greater affinity. DHT shortens the telogen phase, leading to more rapid hair loss. With aging, new hairs become insufficient to replace the shed ones and contribute to alopecia. This mechanism is observed both in male and female pattern hair loss. Treatment protocols for alopecia using inhibitors of 5α-reductase are proven to be effective.[8]

Genetic Association

2 In the 1990s and early 2000s, observations that there is a resemblance between alopecia in fathers and sons led to suggestions that genes from some autosomal chromosomes were the cause of male pattern baldness. Postulated genes included the insulin gene, the 5α-reductase genes, and the hairless gene.[9] However, further investigations by Ellis et al.[10,11] and Hillmer et al.[12] found only a weak association between those genes and male pattern alopecia.

In 2005, Hillmer et al.[13] demonstrated maternal inheritance of male pattern alopecia with their investigation of variants of androgen receptor locus on the X chromosome. This implied that the phenotypic resemblance should be higher between affected males and their maternal grandfathers than between affected males and their fathers. However, the attributable risk from this case–control study was only 0.46, which indicated that the remaining risk fraction was due to other autosomal loci, which may explain the similarity of the alopecia pattern between fathers and sons.

Genetic predisposition has been shown for alopecia areata (AA) through a genome-wide association study that identified eight susceptibility loci and 139 single-nucleotide polymorphisms associated with the activation and proliferation of T-cells, IL-2 receptors, natural killer cell receptors, genes expressed in the hair follicle, and other factors.[14] A follow-up study established IL-13 and KIAA0350/CLEC16A as susceptibility loci for AA.[15] Research is ongoing.

Hair Cycle Dynamics

In 1994, Courtois et al. proposed that the hair cycle itself was one of the key factors in alopecia.[16] As mentioned above, maximal hair length is achieved in the *anagen phase*. If this phase is too short, patients may present with shortened hair. In some cases, the *anagen* duration may significantly decline, which may lead to empty follicular pores.[17] A shortened *anagen phase* leads to a premature progression to the *telogen phase*, which contributes to a decrease in hair diameter (clinically seen as fine hair) and hair loss. Patients also present with longer duration of the *telogen phase* and latency to the next hair cycle. This lag worsens the effect of alopecia.

Inflammation

3 Inflammation plays an important role in alopecia. A 1998 study by Whiting et al. showed lymphohistiocytic infiltrate in the perifollicular area, with collagen deposition four times higher in patients with male pattern alopecia than in normal controls.[18] In 1999, Sueki et al. performed morphometric and ultrastructural analyses of the transitional zones in patients with male pattern alopecia and found a significant increase in the number of mast cells and lymphocytes around the follicular epithelium.[19]

A study in 2012 also showed greater eosinophilic infiltration around lower hair follicles and mononuclear cell count in diffuse AA.[20] A 2012 review described AA as an autoimmune inflammatory disorder in which hair follicles are attacked by a mixed inflammatory cell infiltrate containing T-cells, natural killer cells, mast cells, and dendritic cells.[4]

Scarring

3 Chronic inflammation may lead to the destruction of the hair follicle and irreversible hair loss.[21] In this case, the hair follicle is replaced by fibrous tissue and the epithelial stem cells in the bulge are destroyed, leading to the hair follicle losing the ability to regenerate.[22]

4 Scarring alopecia (or cicatricial alopecia) leading to irreversible hair loss can be caused by chronic inflammation or secondary to burns, cancer, trauma, radiation, or other diseases such as lichen planopilaris and chronic cutaneous lupus erythematosus. This type of scarring alopecia is discussed further in the “Scarring Hair Loss” subsection below.

CLINICAL PRESENTATION

5 Thinning of hair or hair loss is usually the only sign of alopecia. Other symptoms such as itching, pain, burning, or prickly discomfort may suggest other underlying conditions.

Anagen Hair Loss

Anagen hair loss or anagen effluvium usually has a sudden onset.[23] Patients present with the chief complaint of short hair and the inability to grow longer hair. The hair can be thin, sparse, but usually not fragile. Empty follicles can also be seen. Most cases of anagen effluvium are reversible and hair can regrow in 6 months. Common causes and presentations of anagen effluvium are listed in Table 116-2.

TABLE 116-2 Characteristics of Hair Loss in Anagen Effluvium

Causes	Presentations
Autoimmune disease—severe diffuse alopecia areata[20]	Diffuse and rapid hair shedding with exclamation point hairs, usually starts with a round patch, then spreads in a multilocular pattern.
Chemotherapy-induced alopecia[24]	Patients who recently received anticancer chemotherapeutic agents, radiation treatment, and other medications. Not all anticancer agents/treatments cause hair loss.
	Usually, recovery occurs within 6 months of treatment completion/drug discontinuation.
Inherited/congenital condition—loose anagen syndrome[25]	Predominantly seen in young girls between 2 and 6 years, but sometimes in boys. Diffuse or patchy alopecia often seen in the occiput.

Telogen Hair Loss

Telogen hair loss or telogen effluvium starts with thinning of hair, especially at the temples. It is a noninflammatory alopecia, usually of sudden onset.[2] Patients can lose 300 to 500 hairs a day, which is 2 to 3 times more than usual hair loss in a healthy individual. Hairs appear to be short, thin, and lacking melanin.

Telogen effluvium is usually seen 3 months after a medical condition that stops hair growth, such as childbirth, surgery, hormonal imbalance, or medications. The *telogen phase* normally lasts for about 3 months; if the condition is caused by drugs, hair can regrow after 4 months of drug withdrawal. The various systemic medical conditions affect the scalp, resulting in nonscarring alopecia. Medical causes include iron deficiency, thyroid hormone deficiency, systemic lupus erythematosus, syphilis, bacterial infections, and viral infection (herpes zoster). Medical and other causes are listed in **Table 116-3**.

TABLE 116-3 Causes of Telogen Effluvium

Pregnancy
Psychological stress
Fever, infection, hemorrhage, surgery
Weight loss
Autoimmune diseases (most common is systemic lupus erythematosus), thyroid hormone deficiency
Localized telogen effluvium following hair transplantation[26]
Vitamin or mineral deficiency—iron deficiency is a common cause of hair loss in women
Medications: contraceptives, anticoagulants, anticonvulsants, isotretinoin, warfarin

Androgenetic Alopecia (AGA)

Distinct patterns of hair loss are seen in boys/men and girls/women (**Table 116-4**).

TABLE 116-4 Male and Female Pattern Hair Loss

Male pattern hair loss	Female pattern hair loss
Gradual loss of the frontal hairline early in the process.	The frontal hairline is often preserved. Gradual thinning leading to widening of the part line.
Gradual thinning in the vertex and temporal areas.	Thinning hair on the mid-frontal area of the scalp. Diffuse pattern. Hair loss is generally less severe than that which occurs in males.

2 Male pattern hair loss, or androgenetic alopecia (AGA), is the most

common type of hair loss; it most often occurs in adult males.[23] AGA is caused by the effects of DHT in specific areas of the scalp such as the vertex and the temporal scalp. Patients usually have a vivid memory of a transitional time from having thick, long pigmented hairs to thinner, shorter hairs with less pigment.

A few women present with male pattern hair loss (AGA) caused by excessive levels of androgens, which leads to thinning hair on the mid-frontal area, but the condition is usually milder than in men. Polycystic ovarian syndrome (PCOS) and congenital adrenal hyperplasia are the common causes of male pattern hair loss in women.

Female pattern hair loss (FPHL or female AGA) usually presents with preservation of the frontal hairline with widening of the part line and reduced hair volume. These women are mostly losing their hair with age and hormone tests are normal. The Ludwig Classification is often used to describe FPHL, with Type I being minimal thinning that can be camouflaged with hair styling techniques and Type III being diffuse thinning with a see-through appearance on the top of the scalp.[27]

Dermatological Disease

3 4 5 Dermatological conditions on the scalp may result in scarring or nonscarring patchy hair thinning and alopecia. **Table 116-5** provides some common diseases and their presentations.

TABLE 116-5 Dermatological Diseases That Can Cause Hair Loss

Diseases	Presentations
Tinea capitis[28]	Gray patch (scaling with patchy hair loss), black dot, and diffuse alopecia. But on occasions, severely inflammatory and raised lesions can occur.
Psoriatic alopecia[29]	Often nonscarring and regrows after a few months. Complete destruction of the follicle leads to the inability to regrow.
Seborrheic dermatitis of the scalp[30]	From mild desquamation to honey-colored crusts attached to scalp and hair leading to alopecia. May reach into forehead as scaly erythematous border known as "corona seborrheica."
Allergic contact dermatitis of the scalp[31]	Mild hair loss 2 to 4 months after the episode of scalp dermatitis.
Pityriasis rubra pilaris[32]	Eczematous changes of the skin, ichthyosiform scale on lower extremities, coarse laminated palmoplantar keratoderma, and alopecia.
Erythroderma (a generalized disease)	Generalized erythema and exfoliation, patients sometimes present with malaise, fever or hypothermia, pruritus, diffuse alopecia, keratoderma, nail dystrophy, ectropion, pitting edema, lymphadenopathy, tachycardia, and high-output cardiac failure.[33]

Scarring Hair Loss

3 4 Scarring hair loss, or cicatricial alopecia, can be primary or secondary to indirect causes, such as burns, cancer, trauma, or radiation. Table 116-6 provides common causes of scarring hair loss and their presentations.

TABLE 116-6 Characteristics of Scarring Hair Loss

Causes	Presentations
Lichen planopilaris	<10% scalp involvement (localized) Generalized Rapidly progressing Itchy, multifocal, or central patches with follicular hyperkeratosis and perifollicular erythema; nonscalp areas may be affected
Chronic cutaneous lupus erythematosus	Single or multifocal patches with pronounced activity in the center of the patch, ulceration, follicular plugging, atrophy, and depigmentation
Frontal fibrosing alopecia	Band-like distribution around the frontal hairline; may be present in eyebrows
Central centrifugal cicatricial alopecia	Resembles lichen planopilaris; burning, scaling, and itchiness may occur
Brocq pseudopelade	Small and/or large, irregular patches of hair loss on the scalp with no detectable symptoms or inflammation; end-stage burnout
Folliculitis decalvans	Single patch of complete alopecia that expands circumferentially, slowly over years; typically found on hair-bearing periphery of scalp; pustules, honey-colored crusting, tufting; nonscalp involvement is rare
Dissecting cellulitis of the scalp	Multiple fluctuant nodules found across the scalp, often interconnected by sinus tracts; may be associated with acne conglobata: discharge is common and should be cultured

Alopecia Areata (AA)

3 Alopecia areata (AA) is the most frequent cause of inflammation-induced hair loss, affecting perhaps 4.5 million people in the United States.[4] AA affects both children and adults, with prevalence rates peaking between the ages of 20 to 40 years; up to 66% of AA patients are younger than 30 and only 20% are older than 40.[4] Although AA generally occurs equally in males and females,[4,34] one study involving subjects 21 to 30 years found male dominance.[35]

AA is a nonscarring, autoimmune inflammatory disease that manifests in the hair follicles and can affect the nails in up to two-thirds of patients.[36] Due to the autoimmune nature of the disease, hair-follicle specific autoantibodies may be detected and other autoimmune conditions may be associated. There is a familial

tendency with an especially high concordance rate in monozygotic twins, and genetic polymorphisms have been identified in multiple regions of the human genome.[34]

AA presents as an acute, patchy alopecia (with a well-circumscribed solitary or multiple patches) that is most commonly seen in the scalp but can be elsewhere in the body.[36,37] Patches up to 2 cm (~0.8 inch) in diameter can suddenly appear overnight then extend circumferentially at a rate of about 1 cm/week (0.4 inch/week); the hair loss consists of hair breakage close to or just below the skin surface. As a result, black dots can be seen on dermoscopy, with characteristic "exclamation mark" hairs—that is, hairs where the distal hair shaft is broader than the proximal end—around the margins of the patch of hair loss.[4] **Table 116-7** lists the types of AA.

TABLE 116-7 Classifications of Alopecia Areata

Types	Descriptions
Patchy AA	The most common type; localized hair loss; patchy; most commonly on scalp, sometimes involving beard area
AA totalis	Total hair loss on the scalp
AA universalis	Complete hair loss in all hair-bearing areas
Acute diffuse and total alopecia	Short clinical course ranging from a little hair loss to total baldness; favorable prognosis; rapid disease resolution, sometimes without treatment
Diffuse AA	Diffuse hair loss; can mimic telogen effluvium
Ophiasis	Hair loss only on the sides of the scalp (occipital areas) and the nape
Sisapho	A rare condition in which hair loss spares the sides of the scalp (occipital areas) and the nape and usually affects the central scalphis
Reticular patches	Several patches of AA coalescing to form a reticular pattern

Source: Data from references 4 and 34.

AA involves abnormality in the hair cycle (shortened and disordered) due to the activity of inflammatory mediators released by a mixed inflammatory cell infiltrate (**Fig. 116-4**).[4]

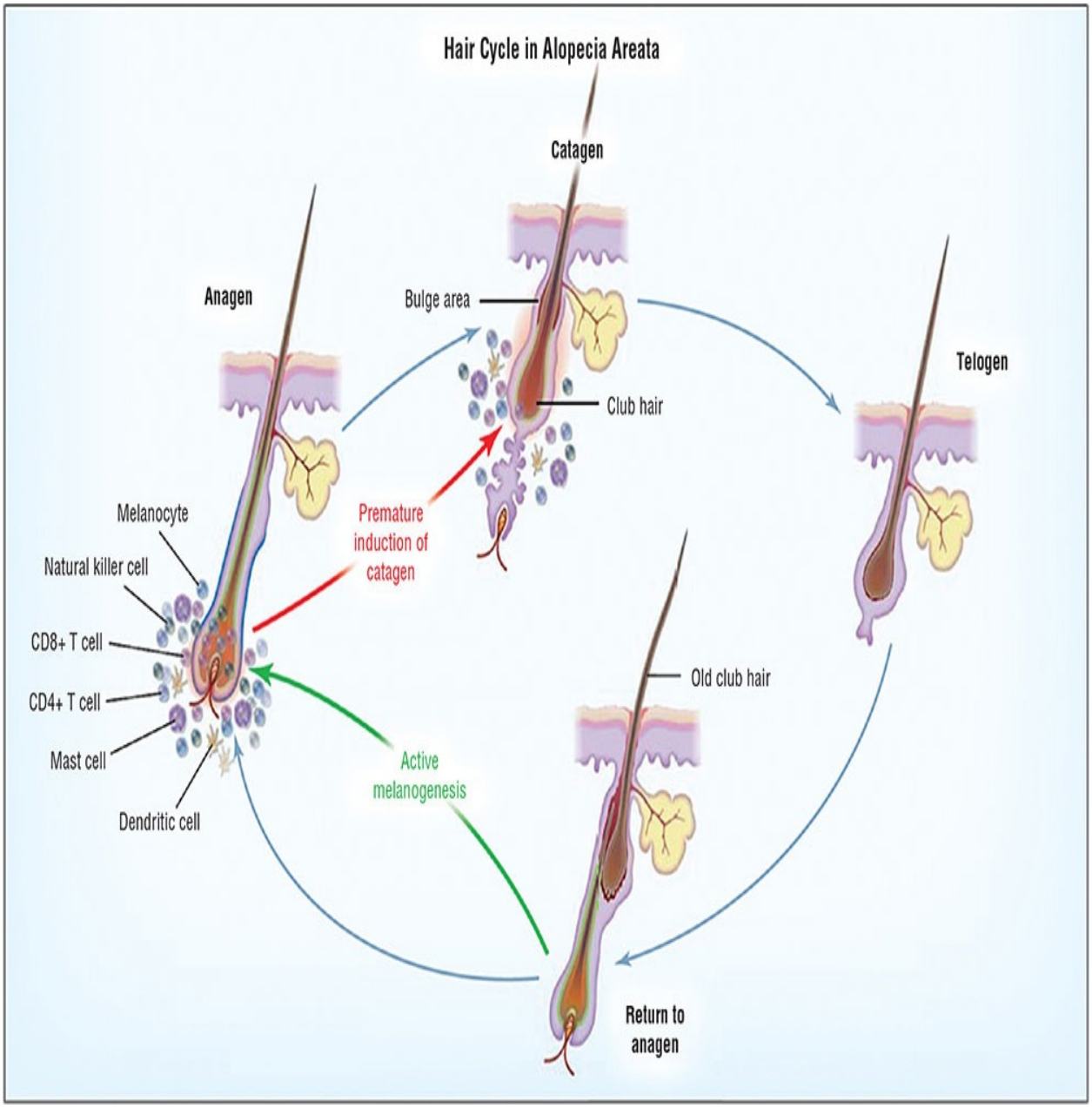


FIGURE 116-4 The hair cycle in alopecia areata. (*Reprinted with permission from Reference4.*)

Alopecia in Children

Hair loss in the pediatric population is more common than expected—about 7.5% of pediatric patients in dermatology practices, according to Al-Refu.[38] Although sharing many features with alopecia in adults, children may present with unique associations that require further examination.

A 5-year study in Jordan[38] showed that the three most common causes of

alopecia in children are tinea capitis (40.5%), AA (17.6%), and telogen effluvium (17%). Tinea capitis is often straightforward with additional findings, such as itchy erythema and scaly border. However, in some communities, parents use unknown topical/herbal creams, some of which contain corticosteroids, and these can mask the presentation of tinea capitis. Therefore, KOH testing plays an important role in etiologic diagnosis.

Autoimmune diseases were found in 13.5% of the pediatric AA cases, including diabetes, hypothyroidism, and vitiligo. In pediatric AA, the male:female ratio is 3:2,[38] compared to 1:2.3 in adults.[39]

Telogen effluvium in children is commonly caused by a prior low-grade fever.[38] All of these cases presented with a healthy scalp, normal hair texture, and regular bulb of telogen hair. This condition was seen more in female children, usually within 4 to 6 months before coming to the clinic.

Approximately 20% of the examined cases had some elements of traction alopecia,[38] with female predominance and occurring at the hairline. Moreover, some cases showed follicular pustules and perifollicular inflammation. This type of hair loss may be more common than the 20% seen, as traction alopecia is easily noticed by parents and reversed by wearing a loosened hair style, perhaps making it underrepresented in the clinic.

Trichotillomania is an impulse-control disorder where patients consciously or unconsciously pull, twist, or twirl their hair. It is a relatively common disorder in children. The mean age of onset is at about age 13 years, and it affects an estimated 4% of the population. Patients usually present with frontoparietal patches of alopecia that progress posteriorly and bare patches are typical. Trichoscopy shows broken hair shafts of various lengths typically with frayed “split ends.” The condition is associated with problems of self-esteem and social avoidance. Complications include infection, skin damage, and scarring.[1,40]

The above and other causes of hair loss in children are listed in **Table 116-8**.

TABLE 116-8 Common Causes of Hair Loss in Children

Tinea capitis
Alopecia areata
Telogen effluvium
Traction alopecia
Diffuse hair loss with abnormal texture
Trichotillomania
Hair abnormalities with atopic eczema
Folliculitis decalvans

COMPLICATIONS

6 Like other medical conditions, alopecia can be distressing, affecting the quality of life and causing psychological problems.[41] Loss of normal scalp hair increases the risk of sunburn and injury. Moreover, studies have shown that hair loss can be associated with depression, low self-esteem, and feelings of unattractiveness. Some studies show that men with hair loss are perceived, based solely on appearance, to be not as attractive and successful as men without hair loss. This is further discussed below in the “Hair Stigma” section.

DIAGNOSIS

Diagnosis of alopecia usually can be made clinically: by a meticulous patient history plus skin and hair examination. In cases of less certainty, further workup may be warranted.

Regarding patient history, the essential points to obtain include time of onset, course of hair loss, past medical history (autoimmune disease, medications, procedures, or surgery), and family history of alopecia. In children, physical and mental development should also be obtained. Then, an extensive physical evaluation can be performed to assess whether the patient has hypotrichosis or alopecia, the type of alopecia, hair shaft anomalies, hair quality, and other conditions of the scalp, including erythema, edema, pustules, scaling, atrophy, or scarring.

For hair examination, the hair tug and pull test is clinically popular since it is quick and easy to use, and it can also be done at multiple locations on the scalp for a more thorough assessment. This test distinguishes between loss from follicles and loss due to hair shaft fragility. First, the patient’s hairs are separated into a 4- to 6-mm diameter bundle (approximately 50-60 hairs). The tug portion

of the test involves gentle holding of hairs between the thumb and index finger near their root, then tugging with the other hand on the same strand at its distal part. The tug test is positive if more than 10% of the hairs fracture, suggesting hair shaft fragility. The pull test involves holding a hair close to the root between the thumb and index finger, then use a slight force to pull the hair out, causing mild discomfort but not pain. In general, telogen hairs are more likely to be extracted than anagen hairs. Furthermore, microscopic observation of the hair root can help distinguish anagen hairs (long sheath shaped) and telogen hairs (club shaped).[42]

In the case of suspected fungal infection, the wood lamp examination is an efficient test. For the test to be accurate, the hairs should be free of all hair applications such as deodorants or moisturizers. After the surroundings are darkened, the wood lamp is turned on and held about 5 to 10 inches (~12 to 25 cm) away from the skin. Some common fluorescent colors are listed in **Table 116-9**.

TABLE 116-9 Common Colors Shown on Wood Lamp Examination

Conditions/Organisms	Fluorescent color
Pityriasis versicolor by *Malassezia*	Yellowish or orange
Malassezia folliculitis	Bluish-white
Tinea capitis by *Microsporum* species	Blue-green
Tinea capitis by *Trichophyton schoenleinii*	Dull blue

Bacterial or viral infection usually can be further diagnosed with swabs for stain or culture.

In suspected cases of iron deficiency, complete blood count, ferritin, total iron-binding capacity, and transferrin saturation should be tested. If a female patient presents with alopecia along with virilization, clinicians should order dehydroepiandrosterone (DHEA) sulfate and testosterone analysis. Other systemic conditions such as lupus or hypothyroidism/hyperthyroidism can be assessed using their specific laboratory findings.

Alopecia in general does not need a biopsy for diagnosis, but this is sometimes performed for research purposes. Hairs can be biopsied transversely and may show miniaturization, especially in cases of AGA or telogen effluvium.

Genetic Testing in Androgenetic Alopecia

As mentioned in the pathophysiology section, many genetic factors may

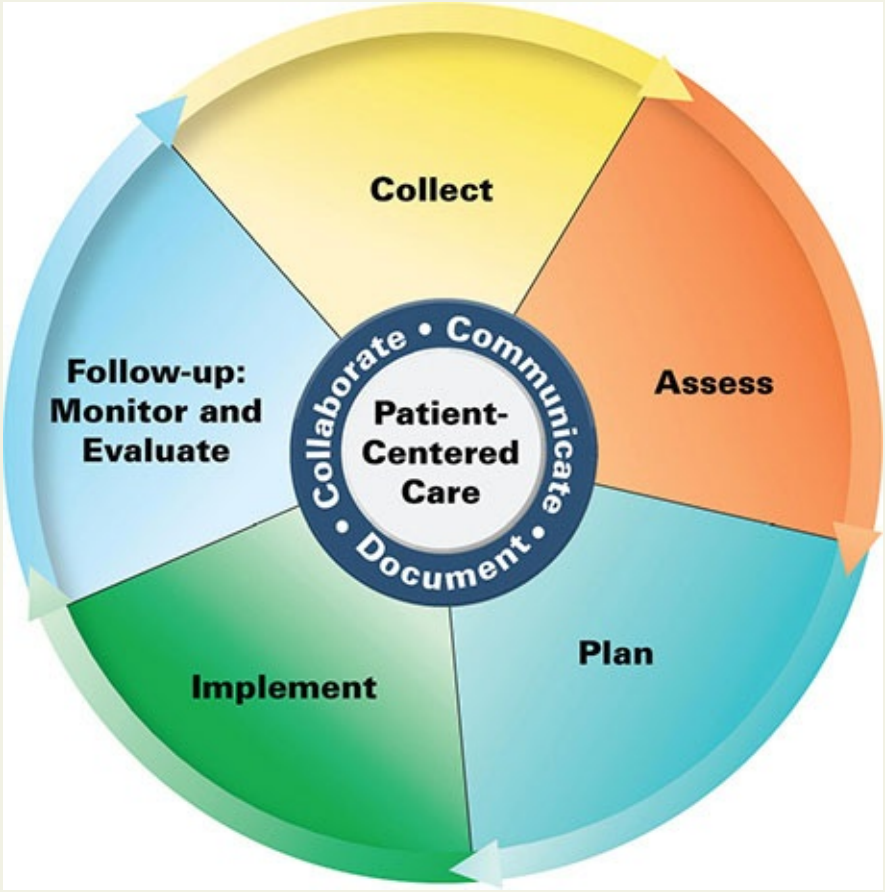
contribute to alopecia. However, more research is still needed before clinicians can reach a consensus in the screening test for AGA. Therefore, currently no genetic testing is officially recommended.

TREATMENT

7 There are a myriad of distinct and diverse causes and types of alopecia as discussed above; thus, treatment or management strategies should be as cause-specific as possible. Identified causes should be treated and/or eliminated as soon as practically feasible. Cause-specific management/treatment strategies include several considerations—infections, chemotherapy, iron deficiency, other nutritional deficiencies, physiological or emotional trauma, trichotillomania, and autoimmune diseases.

Infectious causes should be treated with the appropriate anti-infective agent(s) and treatment regimen (whether systemic or topical therapy as appropriate). Tinea capitis, which commonly manifests as patchy alopecia and usually caused by a *Trichophyton* species, requires a systemic antifungal with oral terbinafine or itraconazole and not a topical agent (it does not penetrate hair follicles sufficiently). See Chapter 138, "Superficial Fungal Infections," for further discussion of the treatment of mycotic infections of the scalp.

Chemotherapy-induced alopecia is generally a reversible and temporary condition. However, for the patient undergoing chemotherapy, having their hair fall out—seeing clumps of hair on pillows and brushes and bald areas on their head—may be emotionally distressing. Cold caps and scalp cooling systems reduce the amount of chemotherapeutic agents reaching the hair follicles and have been shown to significantly reduce the amount of hair loss[43] without increasing the risk of scalp skin metastases.[44] Other nondrug strategies include wigs, scarves/hats or other head coverings, and counseling/psychological support. Very limited studies of topical or systemic drug therapies for prevention and treatment (using alopecia treatments discussed below) have not been that promising especially in preventing hair loss,[24] and the risk for affecting chemotherapy efficacy or toxicity must be kept in mind, even with nutraceuticals.[24] Reassuring the patients that hair regrowth will happen may be comforting and letting them know that occasionally the hair grows back differently (eg, may be fuller or curlier) can provide a positive outlook.



Patient Care Process for Androgenetic Alopecia

Collect

- Patient characteristics (eg, age, sex, pregnancy status if female)
- Patient medical history (personal and family)
- Patient description of history of the alopecia
- Signs associated with severity of androgenetic alopecia (eg, areas of involvement)
- Signs or symptoms of other conditions (ie, differential diagnosis—could this be a condition other than androgenetic alopecia? Symptoms such as itching, pain, burning, or prickly discomfort may suggest underlying conditions. If the alopecia is seen in a female, is polycystic ovarian syndrome [PCOS] or congenital adrenal hyperplasia present?)

Assess

- Severity of androgenetic alopecia—can quantify using hair counts, hair

density measurements, and assessing the areas of involvement

- Relevant lab work, if needed (eg, check parameters that would rule out PCOS. Refer to the Acne case in the Casebook for discussion of relevant labs for PCOS.)
- Ability/willingness to pay for treatment options
- Emotional/psychological concerns

Plan

- Determine an appropriate treatment approach or various optional approaches (ie, topical vs systemic pharmacotherapy vs natural health products/nutritional supplements vs other approaches [mesotherapy, low-level laser light therapy, hair restoration surgery, cosmetic coverings]). Determine if psychosocial support is needed.
- Discuss with the patient various options to determine the most appropriate therapies (nonpharmacologic and pharmacologic) for the patient. Discuss options for psychosocial support if needed.

Implement*

- Provide patient education regarding all elements of treatment plan. Patient counseling points for various agents follow.
    - If topical therapy with minoxidil lotion is used: (1) Transient hair shedding may initially occur (indicating that minoxidil is stimulating hair follicles to re-enter a growth phase called anagen). This usually normalizes within a few weeks to months of starting therapy and treatment should be continued and not stopped. (2) To minimize drug contamination of the pillow and then inadvertent transfer to the face during sleep, use minoxidil lotion at least 2 hours before going to bed.
    - If systemic therapy with finasteride or dutasteride is used: (1) The medication must be swallowed whole and not chewed or crushed. (2) The medication may harm a growing fetus; pregnant women should not ingest or touch broken tablets. This also includes women seeking to become pregnant (including pharmacists, other health professionals, and caregivers). (3) The medication may cause sexual dysfunction. (4) Bloodwork may be needed (liver function tests) to monitor for potential side effects. (5) There are potential interactions

with other medications—please check with your physician or pharmacist.

- Use motivational interviewing and coaching strategies to maximize adherence when needed.
- Provide information about prevention/minimization of further hair loss (eg, appropriate hair care). Provide information about psychosocial support options, if needed.

Follow-up: Monitor and Evaluate

- Contact patient in 3 and 6 months to follow-up about the efficacy of recommended therapies and any issues with the treatment regimen.
- Ensure that appropriate monitoring parameters for efficacy and potential adverse effects have been put in place. Ensure follow-up lab tests if needed are in place (eg, liver function tests when finasteride or dutasteride is used).
- Reinforce preventive measures including appropriate hair care.

**Collaborate with patient, caregivers, and other healthcare professionals.*

Iron deficiency is a known and reversible cause of alopecia. In this case, appropriate treatment is iron replacement therapy followed by iron supplementation once iron stores are replenished. Iron-deficiency anemia is further discussed in Chapter 118, "Anemias."

Other *nutritional deficiencies* including specific trace element deficiencies should be corrected if found, as these may possibly play a role in alopecia. For example, there may be an association between copper deficiency and AGA; decreased copper level in the frontal zones of scalp hair and serum were found in both men and women with AGA when compared with their respective matched controls and the differences were statistically significant.[45] There may also be an association between defective copper metabolism and trichorrhexis nodosa, although there are many other possible causes, including hypothyroidism and Menkes disease.[1]

Any physiologic or emotional *trauma or stressors* that preceded the alopecia could be the inciting cause. If the traumatic events or stressors are still present and ongoing, management strategies to ameliorate them would be helpful (eg, mindfulness techniques, relaxation clinics, counseling, or psychotherapy).

Trichotillomania may be treated via nonpharmacologic and/or

pharmacotherapy—the optimal treatment is unknown, and psychiatric referral may be indicated. Cognitive behavior therapy and selective serotonin reuptake inhibitors (SSRIs) may be effective, and using both together may be more effective than either treatment used alone. Olanzapine and clomipramine may also be effective.[46]

Alopecia that is thought to be associated with *autoimmune diseases* as discussed above (eg, SLE, hypothyroidism) sometimes improves with treatment of the specific autoimmune disorder. Antibodies (eg, thyroid-antimicrosomal antibodies) may be involved in the pilar follicles, as antifollicular antibodies have been reported in alopecia.[47]

Pattern Baldness: Androgenetic Alopecia

8 There are recent reviews[1,48,49] and evidence-based guidelines[50,51] on the treatment of AGA in women and in men. Treatments include topical minoxidil, oral 5α-reductase inhibitors (finasteride, dutasteride) for men, hormonal therapies for women, and miscellaneous therapies including nutritional supplements and laser light therapy, with variable efficacy.

Male Baldness

Topical Therapy: Minoxidil Minoxidil (2% or 5%) topical solution is the most common treatment for male baldness. It can prevent the progression of baldness and improve hair density and thickness, with hair regrowth being more robust at the vertex than in the frontal area of the head.[52] Its exact mechanism of action on hair follicles remains unclear. However, the main benefits seen may be prolongation of the anagen phase and hair shaft diameter.[51]

The 5% concentration has been recommended for greater efficacy; a randomized controlled trial (RCT) comparing 5% versus 2% minoxidil in men ages 18 to 49 found 45% higher hair counts in those given 5% versus those given 2%.[53] There is currently insufficient evidence to recommend the 5% foam over the 5% solution.[50] The response to treatment should be assessed at 6 months.[50] If successful, treatment needs to continue indefinitely as hair loss recurs when treatment is interrupted or discontinued.[1,50]

Side effects of minoxidil lotion includes transient telogen hair shedding—an indication that minoxidil is stimulating telogen follicles to re-enter anagen[50]—this usually normalizes within a few weeks to months and therapy should be continued and not stopped.[50] Hypertrichosis is more common with the 5%

concentration and may reflect incorrect application. To minimize drug contamination of the pillow and inadvertent contact with the face during sleep, patients should be advised to use the medication at least 2 hours before going to bed.[50] Irritant and contact dermatitis sometimes occur. Minoxidil is an antihypertensive agent when used systemically, and uncommon to rare side effects of topical administration are related to its systemic effects on blood pressure: dizziness, headache, hypotension, tachycardia, or chest pain.

Systemic Therapy: Finasteride, Dutasteride The 5α-reductase enzyme converts testosterone to DHT, the main androgen causing AGA. There are two types of 5α-reductases in humans: type I is primarily found in liver, skin, and scalp; and type II is found in the prostate, genitourinary tract, and hair follicle.[50] 5α-reductase inhibitors were originally marketed for treatment of benign prostatic hyperplasia (BPH), and their efficacy for AGA was an incidental finding based on a "side effect" of BPH treatment.

Finasteride is a selective type II 5α-reductase inhibitor that reduces scalp production of DHT. Multiple RCTs have shown significant increases in total hair counts and/or other hair growth benefits in men at 6 months,[54,55] 12 months,[56,57] and 24 months.[58] A dose-ranging study found benefits at all doses greater than 0.2 mg/day but no greater difference between 5 mg/day versus 1 mg/day.[54] Thus, the recommended dose for male pattern baldness is finasteride 1 mg/day (the dose for BPH is 5 mg/day). A 4-year study (2-year observation, 2-year finasteride) found that hair follicles that can still produce a thick hair fiber responded to finasteride 1 mg/day by reducing the hair cycle lag phase by 40% (thus initiating active growth more rapidly) and increasing the duration of the anagen phase by 23%.[58] However, miniaturized hair follicles (ie, those that were producing thinner hair, defined as <40 microns thick) did not respond to finasteride.[58] This may be useful in future for patient selection and may be an explanation for nonresponders. In 2019, a follow-up study by the same investigators assessing finasteride pharmacodynamics in responders found finasteride-dependency and a rebound effect when finasteride was discontinued: after 12-months off-treatment, viable drug-responsive hair follicles began to rapidly miniaturize; and by 30 months off-treatment, 94% had miniaturized, which worsened the alopecia.[59] The authors concluded that drug dependency and a rebound phenomenon are new findings for finasteride use in alopecia.[59]

Side effects of finasteride include orthostatic hypotension, dizziness, decreased libido, impotence, and ejaculatory disorder. Two recent systematic reviews identified growing concerns about sexual dysfunctions[8,60] and patient

counseling should be provided prior to starting treatment.[8] Finasteride is extensively metabolized; monitoring parameters include liver function tests (LFTs) prior to starting therapy and repeated every 6 months.[61] Finasteride is teratogenic (risk category X), and crushed or broken tablets should not be touched by pregnant women or women seeking to become pregnant (including pharmacists, other health professionals, and caregivers), as exposure to the active ingredient can occur.

Dutasteride is a double inhibitor of both type I and type II 5α-reductase. It is currently only approved for BPH in men (and not for AGA) in the United States and Canada, although it is approved in other countries (eg, Korea) for AGA. RCTs have shown that dutasteride 0.5 mg/day has efficacy in 6 months without significant side effects[62] and that in comparison with finasteride 1 mg/day or placebo, it is significantly more efficacious.[55] Total hair counts (2.54 and 1.13 cm diameter [1 and 0.44 inch diameter]) and hair width but not terminal hair counts (2.54 cm diameter [1 inch diameter]) were significantly greater at 24 weeks with dutasteride compared with finasteride or placebo.[55] Incidences of sexual dysfunction and breast disorders were similar between dutasteride and finasteride but lower in the placebo group.

Also similar to finasteride, dutasteride is teratogenic (risk category X), and skin contact with the active ingredient (if tablet is broken or crushed) should be avoided. Tablets should be swallowed whole and not chewed or crushed. There is a potential association with high-grade prostate cancer, but the risk is low. Dutasteride is also extensively metabolized; its already-long half-life (5 weeks) increases with age. Its concentration/pharmacodynamic effects may be increased during concomitant therapy with strong CYP3A4 inhibitors.

The most concerning side effect for 5α-reductase inhibitors (finasteride, dutasteride) appears to be sexual dysfunction. A 2019 systematic review and meta-analysis of adverse sexual effects of finasteride or dutasteride as treatment for male AGA evaluated 15 RCTs (4,495 participants).[60] This study found an overall 1.57-fold risk of any adverse sexual effects associated with the use of either finasteride 1 mg/day or dutasteride 0.5 mg/day; when analyzed separately, finasteride had a 1.66-fold risk and dutasteride had an increased risk that was not statistically significant (RR 1.37, 95% CI 0.81–2.32).[60] But there were many fewer dutasteride RCTs, which may account for the wide CI.

Miscellaneous Therapies Many other cosmetic, pharmaceutical, nutraceutical, and food products are marketed as alternative therapies for alopecia. But most of these have little to no clinical evidence of efficacy, especially robust RCTs.

However, health practitioners should be somewhat knowledgeable about alternative therapies, as patients may be using them and/or have questions—for instance, if they have heard of or are considering these options.[50]

Mesotherapy is the microinjection of medications, vitamins, or other substances into the mesoderm (the middle layer of skin). Medications have included dutasteride, minoxidil, or other active ingredients. An RCT comparing mesotherapy to topical 5% minoxidil found little difference in the two types of treatments, the only difference being a variation of hair shaft diameter at 1 month that was not present at 4 months (the end of the study).[63] The mesohair solution contained 56 ingredients, including 24 amino acids, 13 vitamins, 4 coenzymes, 4 nucleic acids, 5 minerals, and 2 reducing agents, and the active ingredients decapeptide 4, acetyl decapeptide, and copper tripeptide.[63] A study of mesotherapy using 1 mL of dutasteride 0.01% demonstrated significant improvement after 9 months, but only 6 patients (5 males, 1 female) participated in the trial.[64]

Low-level laser light (LLLL) therapy can stimulate hair growth by scalp vasodilatation, but the exact mechanism is unclear.[65] LLLL therapy devices are currently available commercially for home or clinic use in the United States and Canada.[66]

Platelet-rich plasma (PRP) therapy involves intradermal injections of autologous PRP into the scalp. A 2017 systematic review found that 7 of 14 studies reported a significant increase in hair density, ranging from 12.3 to 45.9 hairs/cm^2 (80 to 300 hairs/sq. in.) with variable hair thickness and hair loss results.[67] The beneficial effects seem to begin with the first treatment and peak after 3 to 5 treatments, then attenuates and treatments must be continued to maintain benefits. Side effects include local irritation and pain.[66,67]

PRP is concentrated autologous platelets in plasma, and contains more than 20 growth factors, including platelet-derived growth factors. In AGA, PRP is thought to induce stem cell differentiation, prolong dermal papilla cell survival, prolong the anagen phase, and other mechanisms.[68] PRP has been compared to topical minoxidil and at 6 months, the PRP group scored higher in both global photography and patient satisfaction with a hair growth questionnaire.[69]

Ketoconazole inhibits the DHT pathway, and ketoconazole shampoo has been considered for use in combination with oral finasteride.[70]

Prostaglandin F2 analogues latanoprost and bimatoprost topical therapy are being studied for use in AGA. Early results seem promising.[70]

Topical valproic acid 8.3% spray was found to increase hair count in a recent

RCT.[71] Alopecia is a fairly common adverse effect of systemic valproic acid.

Hair restoration surgery involves hair transplantation, scalp reduction surgery, or a combination of both.

Natural health products—including biotin, melatonin, saw palmetto, black cohosh, dong quai, false unicorn, chaste berry, and red clover—have been used in treatment of alopecia. Some of these may have anti-androgenic or estrogen-promoting activities.[65] However, there is scant evidence of efficacy as hair growth promoters in men, as shown in these summaries:

1. A small 2017 RCT of a combination traditional Chinese medicine (TCM) containing six herbal ingredients (*Ginseng Radix, Astragali Radix, Angelicae Sinensis Radix, Ligustri Fructus, Rehmannia glutinosa*, and *Eclipta prostrata* Linn.) versus placebo showed that 9 of 17 patients receiving TCM had increased hair growth versus 2 of 17 in the placebo group, a statistically significant difference. However, of the 9 responders in the TCM group, 1 minimally improved, 5 moderately improved, and only 3 showed significant improvement.[72]
2. Biotin is popularly used for AGA; however, although it is known that genetic biotinidase deficiency results in hair loss, and biotin was found to reverse valproic acid–induced alopecia in a few patients, robust evidence is lacking.[73]
3. In contrast, a well-designed 2017 RCT of a commercially available product called Lambdapil (1,000 mg L-Cysteine, 100 mg *Serenoa repens*, 7.14 mg *Equisetum arvense L*, 0.5 mg silicon, 10 mg zinc, 16 mg vitamin B3, 6 mg vitamin B5, 1.4 mg vitamin B6, 50 µg D-biotin, 40 mg taurine), which enrolled both men and women in a 6 month placebo-controlled RCT using high-level methodology, found that Lambdapil increased the anagen/telogen ratio in men, with a 3.7% increase in anagen hair and an increase in hair volume. Quality of life was also improved.[74] (Results of the use of this product in women are discussed in the next section.)

Female Hair Loss

The majority of female hair loss is FPHL or female pattern AGA; however, women with PCOS also can develop male pattern baldness. A 2016 Cochrane review of interventions for FPHL reported moderate- to low-quality evidence of efficacy for minoxidil, low-quality evidence of efficacy for finasteride, and moderate- to low-quality evidence of efficacy for LLLL therapy.[49] Hormonal therapy, nutraceuticals, and mesotherapy were not included in the review,

although there are promising RCTs of these approaches. Other possibilities such as prostaglandin analogs are too early in development for review.

Topical *minoxidil* 2% lotion has been approved for use in females with AGA, but not the 5% concentration. Many RCTs using 2% minoxidil in women have shown efficacy, and pooled data from six studies (5 using 2%, 1 using 1%) confirmed the observation, with 157 of 593 patients demonstrating a moderate-to-marked increase in hair growth when compared with placebo (RR 1.93, 95% CI 1.51-2.47).[49] In 8 pooled studies (1,242 participants), there was a significant increase in total hair count (13.18/cm^2 [85/sq. in.]) compared with placebo.[49] Four studies (1,006 participants) comparing minoxidil 2% versus 5% did not show a difference, although the quality of the evidence was moderate to low.[49] Minoxidil, including topical use, is contraindicated in pregnancy and lactation.

Topical and oral prostaglandin analog treatments may be promising. Latanoprost, travoprost, and bimatoprost are prostaglandin analogs that are used for glaucoma, which caused eyelashes to grow as a side effect; they promote hair growth by prolonging the anagen phase. Blocking the prostaglandin D2 receptor (GPR44) may help to increase hair growth; setipiprant (KITH-105) is an oral GPR44 receptor inhibitor. Studies are ongoing.

5α-reductase inhibitors are not approved for use in females. One RCT showed efficacy with *finasteride* 1 mg in women with AGA while two others did not.[49] Patient selection may be key—four women with hyperandrogenism showed improvement with finasteride[75] but not postmenopausal women without hyperandrogenism.[48,76] Studies in premenopausal women have shown conflicting results.[76] *Dutasteride* is a more potent 5α-reductase inhibitor that can lower serum DHT levels by more than 90%[76] and effectiveness has been reported in a 46-year-old woman.[77] Precautions and concerns with handling broken tablets are even more of an issue if used by a woman, as the drug is contraindicated in pregnancy and in women of childbearing age.

Hormonal therapy with antiandrogens with or without estrogens has shown some efficacy. In particular, *cyproterone acetate* was compared with topical minoxidil; results showed greater efficacy for minoxidil in women without hyperandrogenism and greater efficacy for cyproterone acetate in women with multiple symptoms of hyperandrogenism.[78] Cyproterone acetate may be more effective in a birth control formulation (eg, Diane or Diane-35, which is available in Canada and Europe but not in the United States.)

Spironolactone has antiandrogenic activities and has been considered the most commonly used, off-label antiandrogen for the treatment of FPHL and

hirsutism[48]; however, published studies are limited. An open intervention study found spironolactone to be equally effective when compared with cyproterone acetate.[79]

Flutamide has potent antiandrogenic effects and has shown efficacy for FPHL in clinical trials. In a 4-year prospective cohort study in which flutamide was used in annually reduced doses of 250 mg/day, 125 mg/day, and 62.5 mg/day, flutamide used either alone or with an oral contraceptive reduced alopecia scores. The maximum drug effect occurred after 2 years and was maintained for the duration of the 4-year study.[80] The regimen of annually reduced doses was a dose-ranging attempt to minimize side effects; the study showed that the dose of 62.5 mg/day maintained efficacy with complete hepatic tolerability and high adherence. At the dose of 250 mg/day, the dropout rate was 4% due to drug-related hepatic changes.[80]

Natural health products and nutritional supplements may be beneficial. RCTs showing efficacy are as follows[81]:

1. A 2015 RCT of a nutritional supplement combination (460-mg fish oil [exact amounts of EPA and DHA unspecified], 460-mg black currant seed oil, antioxidants [1-mg lycopene, 30-mg vitamin C, 5-mg vitamin E])[81,82] versus placebo in 120 women found that 62% of the supplement group had increased hair density compared with 28% in the placebo group. Anagen hair increased significantly and telogen hair decreased significantly in the supplement group.[81,82]
2. The well-designed 2017 RCT of Lambdapil as discussed in an earlier section enrolled both women with acute Telogen effluvium (aTE) and men with AGA in a 6-month, placebo-controlled design using high-level methodology. Results in women showed an increase in hair volume (slight to moderate) and an improved quality of life.[74]
3. A topical botanical lotion that acts by increasing Bcl-2, perifollicular Langerhans and mast cells, and perifollicular collagen was found in a 2018 single-blinded RCT to increase hair density, improve Dermatology Life Quality Index, and increase the anagen:telogen ratio at 24 weeks.[83]

LLLL therapy increased the total hair count in women with FPHL in several studies.[49]

Mesotherapy containing nutritional supplements has been compared with topical minoxidil 5% lotion. No significant differences were found with regard to hair density or hair loss, but the mesotherapy group had a greater increase in

the number of hair follicles.[84]

Hair transplantation is a viable option if other medical therapies are unsuccessful. Cosmetic methods such as wigs, scarves, and hats are other alternatives.

Androgenetic Alopecia in Children

Familial predisposition may be present. Nonetheless, if AGA is seen in a prepubertal child, an endocrine evaluation is strongly recommended.[85] AGA in an adolescent is not uncommon and topical minoxidil may be effectively used.[42,86] One case report of AGA seen in a 15-year-old girl was successfully treated with topical minoxidil and oral contraceptives.[87]

Alopecia Areata

Alopecia areata (AA) can be emotionally devastating to a person and can cause a significant impact on the patient's quality of life and self-esteem.[4] It can cause stigmatization.[34] (See the section below on "Hair Stigma.") It may lead to clinical depression and/or anxiety and/or social phobia. Management and treatment of the psychological impact of AA must not be overlooked.

9 Curative therapy for AA does not yet exist; however, there is a high rate of spontaneous remission even with no pharmacotherapy.[4] Alopecia totalis and alopecia universalis are more resistant to treatment. Due to the autoimmune and inflammatory nature of AA, effective pharmacotherapy primarily involves immunosuppressive agents used systemically, intralesionally, and/or topically. Treatments that may be effective include high-dose oral corticosteroids, intralesional corticosteroids, topical corticosteroids, topical minoxidil, topical immunotherapy, systemic and topical biologic agents (in particular the Janus kinase inhibitors discussed later in this section), azathioprine and other immunosuppressive agents, and a few miscellaneous agents. Robust RCTs are lacking or limited for some of these therapies; some treatments may not be suitable for children with AA.

Intralesional corticosteroids are the treatment of choice in adults.[34] The best-tested immunosuppressive treatment is intradermal (intralesional) triamcinolone acetonide (5-10 mg/mL) every 2 weeks[4] or every 4 to 6 weeks.[34] Monthly intervals would be more convenient for the patient. An effective method is to inject 0.1 mL of solution into multiple sites at 1 cm (0.4 inch) apart, into the deep dermis, with a maximum volume of 20 mL injected at each clinic visit.[34]

This treatment stimulates regrowth in more than 60% of patients.[4] If there is no improvement at 6 months or if significant atrophy is noted, treatment should be discontinued.

Hydrocortisone acetate (25 mg/mL) is an alternative. Side effects include pain at injection sites, localized skin atrophy, and hypopigmentation. Dermal atrophy usually recovers over 3 to 6 months.[34] Relapses are common with treatment discontinuation.[4]

Topical corticosteroids (TCS) are commonly used, especially in children (since scalp injections are painful) and in those adults with less than 50% scalp involvement.[4] High-potency TCS such as clobetasol propionate used under occlusion are more effective since this may further increase potency. (As an aside, although keloid is an entirely different disease entity, a recent RCT found that clobetasol propionate 0.05% cream under silicone occlusion dressing was equally efficacious and had fewer adverse effects compared with intralesional triamcinolone.[88]) Treatment for AA may need to be continued for 3 months before regrowth is seen.[34] Monitor for topical and potentially systemic side effects since potent TCS are being used.[89] Folliculitis is a common side effect. Refer to Chapter 114, "Psoriasis," for a corticosteroid potency comparison chart and for a detailed discussion of TCS side effects. A recent article about rational and ethical use of TCS also provides a summary.[89]

Systemic corticosteroids are efficacious in patients with AA. However, their side effects profile limits their use to short treatment periods of 2 to 3 months. Pulse dosing (eg, once weekly) is used to minimize systemic side effects. Regimens include prednisolone 0.5 mg/kg/day (usually of 40-50 mg/day) daily for 3 months,[34] prednisolone 200 mg once weekly for 3 months,[4] or dexamethasone 0.1 mg/kg/day (mean dose about 8 mg) on two consecutive days once weekly for at least 4 months and then slowly tapered or discontinued (with some patients on treatment for 2 years).[90] This dexamethasone regimen was used in 31 patients with alopecia totalis or alopecia universalis, and complete response was seen in 22 patients (71%) and partial response in 3 (10%). The mean time to response was 1.55 months and the mean duration of therapy was 12.9 months (range 4-24 months). Adverse effects were seen in 10 of 31 patients (32%), including weight gain in 9 patients and Cushing syndrome, striae, and irritability in 1 patient each.

Relapses are seen after treatment is discontinued and sometimes during treatment.[90] Pulse therapy with high-dose systemic steroids have been used in other studies and may be an option for severe, extensive, or recalcitrant AA.

Biologic agents have exploded on the treatment scene for many dermatologic inflammatory disorders such as psoriasis, atopic dermatitis (AD), and AA, including the subtypes alopecia totalis (AT) and alopecia universalis (AU). Some biologic agents may be used topically for AA, and some have been successfully used in children and adolescents.

Janus kinase (JAK) inhibitors (tofacitinib, ruxolitinib, baricitinib) are a promising new class of biologic treatment for AA.[91,92] A JAK-STAT (signal transducer and activator of transcription) signaling pathway is important in the hair growth cycle, with key genes being highly expressed in the catagen and telogen phases but suppressed in the anagen phase.[91] JAK inhibitors inhibit the JAK-STAT pathway, resulting in various immunologic changes that result in prolonging the anagen phase, angiogenesis, stimulating/activating the proliferation of hair stem cells, and other changes, which all manifests in hair regrowth, as shown in these studies[91]:

1. Studies and case reports of oral and topical *tofacitinib* demonstrate efficacy in adults and children with AA, including AA subtypes AT and AU.[92] Patients with AA may have greater response than patients with AA subtypes. Systemic treatments may be more effective than the topical route. Using the Severity of Alopecia Tool (SALT), a cohort study of oral tofacitinib 5 to 10 mg twice daily in 90 adults with AA and subtypes, found that 58% improved their SALT score by 50% or more over 4 to 18 months of treatment. Patients with AA showed a greater degree of change in SALT than those with alopecia totalis or universalis (82% vs 59%).[92] A retrospective review of 13 adolescents with AA treated with tofacitinib 5 mg twice daily found a 90% median improvement in SALT score (1%-100%), and there are many other recent studies.[92] A retrospective review of children under 12 with AA, AT, or AU treated with tofacitinib identified 3 children 5 years or younger who failed previous treatment before tofacitinib and who responded to tofacitinib 2.5 mg daily for 4 days then 5 mg daily for 3 days each week (1 child with >90% hair regrowth after 12 months of treatment and the other 2 children with >50% improvement by 6 months and 21 months, respectively).[93] Results with topical JAK inhibitors are poorer than with oral agents. Topical tofacitinib or ruxolitinib were applied to eyebrow regions/upper eyelids/scalp in 6 pediatric patients ages 3 to 17 with AA, and responses were only seen in 3 patients.[94] Additional clinical studies are under way.
2. Fewer reports and studies have examined use of *ruxolitinib;* however, there

are reports of efficacy in hair regrowth in a few patients with AT who had failed therapy with tofacitinib.[95] Encouraging results and additional studies are under way.

3. There is one case report of oral *baricitinib* being effective in AA as an incidental finding, and other JAK inhibitors are on the horizon, including filgotinib and decernotinib, which are currently being tested for rheumatoid arthritis.

Dupilumab is a new class of biologic agent (an IL-4 receptor-α-antagonist) currently marketed for AD. It was found to trigger hair regrowth in two case reports of AD patients using dupilumab for AD: one case was a patient with long-standing AT[96] and the other case was a patient with long-standing AU.[97]

Azathioprine has been successfully used to treat AU including recalcitrant cases in adults (nonresponders to oral corticosteroids and topical immunotherapy with diphencyprone). A case study of 14 adult patients showed a complete response in 6 of 14 patients (43%). No identifiable prognostic factors were found, and adverse effects included elevated liver enzymes (1 patient), pancreatitis (1), bone marrow suppression (1), and diarrhea (2); treatment had to be discontinued in 4 patients.[98]

Other agents have been tried for treating AA over the years with varying levels of success, including topical anthralin,[99,100] topical diphenylcyclopropenone,[100] topical calcineurin inhibitors, and oral cyclosporine. None of these is commonly used today because of inconsistent efficacy and/or side effects.

HAIR CARE IN THE PATIENT WITH ALOPECIA

Patients suffering from alopecia may attempt to manipulate their hair to hide their hair loss and to make their head of hair appear fuller; however, most methods may actually further damage the hair and are not recommended. Chemical processing such as hair weaving or hair straightening can further damage the hair and cause hair breakage.

All hair dyes can damage the hair with the exception of temporary hair dyes. Temporary hair dyes have particle sizes that are too large to penetrate through the cuticle, which minimizes hair damage and accounts for their temporary nature (they are removed by a single shampooing).

Heat denatures the keratin protein structure of the hair shaft and turns the water in the hair shaft into steam. This can physically remove the cuticular scale

as the steam escapes from the hair shaft. Without the structural protection afforded by the cuticular scale, the hair breaks easily. Heat-damaged hair is known as bubble hair and cannot be repaired. Frequent hair combing or brushing may also damage the hair by encouraging cuticle removal.[101]

Hair should be combed or brushed only when dry, and excessive combing or brushing should be avoided. Brushing the hair 100 strokes a day and massaging the scalp vigorously with the brush are not appropriate for the patient with alopecia.[101]

Hair conditioners coat the hair shaft and smooth the cuticle, and they should be routinely used. Instant conditioners that are applied after shampooing and rinsed out coat the hair shaft with a thin dimethicone or quaternary ammonium compound to temporarily "glue down" loosened cuticular scales. Supplementing these with a leave-in conditioner can provide a thicker coating to further protect the hair until the next shampoo. Hair conditioners reduce combing friction, improve hair shine, increase hair softness, minimize static electricity, and reduce frizziness.[101]

HAIR STIGMA

"Beauty standards of hair are a form of bias."[102] Men, women, adolescents, and children are often distressed when there is hair loss, or when their hair is perceived as "different" from the societal norm. Adolescents and children in particular may be subject to bullying by their peers, sometimes just for having a head of hair that looks different.[103] In 2019, an anti-bullying song/video was released and a cosmetic manufacturer partnered in an anti-bullying campaign.[102,103]

Imagine the potential stigmatization/bullying situation if the person had patchy AA or AA totalis? This is involuntary hair loss which is quite different from people who have chosen to shave their heads such as monks. Stigmatization affects adults as well. Healthcare professionals should be cognizant of the psychosocial impact on their patient's quality of life. A 2015 review of the burden of disease for patients with AA reported rates for depression (8.8%) and generalized anxiety disorder (18.2%), both significantly higher than in the general population (about 1%-2%).[41] This review also found that the rate of psychiatric comorbidity was influenced by the age of onset of AA, with an increased risk of depression in patients aged <20 years and increased risks of anxiety and obsessive-compulsive disorder in patients aged 40

to 59 years.[41]

Similarly, in patients with AGA or other forms of alopecia, the psychosocial impact must not be overlooked. Even with temporary anagen hair loss (such as chemotherapy-induced alopecia), the onset is usually sudden and may be absolutely traumatizing to the patient.

CONCLUSION

Alopecia is the visible result of many diverse causes, some of which may be temporary and easily reversible and others refractory to therapy. Identifying the cause is key. Management/treatment of alopecia should be as cause specific as possible. In addition, psychosocial support should always be kept in mind.

Postclass Engaged Learning Activity

Complete the continuing medical education quiz for the article read in the Preclass Engaged Learning Activity ("Hair Loss: Common Causes and Treatment" by T. Grant Phillips, W. P. Slomiany, and R. Allison. *Am Fam Physician* 2017;96(6):371-378; Quiz questions on page 360).

Review the patient information handout for this topic (from *American Family Physician* and related to above activities), available at: http://www.aafp.org/afp/2009/0815/p373.html.

ABBREVIATIONS

ACTH	adrenocorticotropic hormone
AA	alopecia areata
AD	atopic dermatitis
AGA	androgenetic alopecia
AT	alopecia totalis (or alopecia areata totalis)
aTE	acute telogen effluvium
AU	alopecia universalis (or alopecia areata universalis)
BMPs	bone morphogenetic proteins
BPH	benign prostatic hyperplasia
CI	confidence interval

DHEA	dehydroepiandrosterone
DHT	dihydrotestosterone
F	female
FGF	fibroblast growth factor
FPHL	female pattern hair loss
HGF	hepatic growth factor
IGF	insulin-like growth factor
IL	interleukin
JAK-STAT	Janus Kinase-signal transducer and activator of transcription
KOH	potassium hydroxide
LFTs	liver function tests
LLLL	low-level laser light
M	male
NT	neurotrophins
PCOS	polycystic ovarian syndrome
PRP	platelet-rich plasma
QoL	quality of life
RCT	randomized controlled trial
RR	risk ratio
SALT	severity of Alopecia Tool
SLE	systemic lupus erythematosus
SSRI	selective serotonin reuptake inhibitor
TCM	traditional Chinese medicine
TCS	topical corticosteroids
TGF	transforming growth factor
TNF	tumor necrosis factor
WNT	aportmanteau created from the name Wingless and the name Int-1
VEGF	vascular endothelial growth factor

REFERENCES

1. Phillips TG, Slomiany WP, Allison R. Hair loss: Common causes and

treatment. *Am Fam Physician*. 2017;96(6):371–378.

2. Buffoli B, Rinaldi F, Labanca M, et al. The human hair: From anatomy to physiology. *Int J Dermatol*. 2014;53(3):331–341. doi:0.1111/ ijd.12362.
3. Mandt N, Troilius A, Drosner M. Epilation today: Physiology of the hair follicle and clinical photo-epilation. *J Investig Dermatol Symp Proc*. 2005 Dec;10(3):271–274.
4. Gilhar A, Etzioni A, Paus R. Alopecia areata. *N Engl J Med*. 2012;366(16):1515–1525. doi:10.1056/NEJMra1103442.
5. Yang CC, Cotsarelis G. Review of hair follicle dermal cells. *J Dermatol Sci*. 2010;57(1):2–11. doi:10.1016/j.jdermsci.2009.11.005.
6. Erdoğan B. (2017, May 03). Anatomy and Physiology of Hair. Retrieved May 22, 2019, from https://www.intechopen.com/books/hair-and-scalp-disorders/anatomy-and-physiology-of-hair.
7. Schneider MR, Schmidt-Ullrich R, Paus R. The hair follicle as a dynamic miniorgan. *Curr Biol*. 2009;19(3):R132–R142. doi:10.1016/j.cub.2008.12.005.
8. Mysore V, Shashikumar BM. Guidelines on the use of finasteride in androgenetic alopecia. *Indian J Dermatol Venereol Leprol*. 2016;82(2):128–134. doi:10.4103/0378-6323.177432.
9. Juárez-Rendón KJ, Rivera Sánchez G, Reyes-López MÁ, et al. Alopecia Areata. Current situation and perspectives. *Arch Argent Pediatr*. 2017;115(6):e404–e411. doi:10.5546/aap.2017.eng.e404.
10. Ellis JA, Stebbing M, Harrap SB. Insulin gene polymorphism and premature male pattern baldness in the general population. *Clin Sci (Lond)*. 1999;96(6):659–662.
11. Ellis JA, Stebbing M, Harrap SB. Genetic analysis of male pattern baldness and the 5alpha-reductase genes. *J Invest Dermatol*. 1998;110(6):849–853.
12. Hillmer AM, Kruse R, Macciardi F, et al. The hairless gene in androgenetic alopecia: Results of a systematic mutation screening and a family-based association approach. *Br J Dermatol*. 2002;146(4):601–608.
13. Hillmer AM, Hanneken S, Ritzmann S, et al. Genetic variation in the human androgen receptor gene is the major determinant of common early-onset androgenetic alopecia. *Am J Hum Genet*. 2005;77(1):140–148. doi:10.1086/431425.
14. Petukhova L, Duvic M, Hordinsky M, et al. Genome-wide association

study in alopecia areata implicates both innate and adaptive immunity. *Nature*. 2010;466(7302):113–117. doi:10.1038/nature09114.

15. Jagielska D, Redler S, Brockschmidt FF, et al. Follow-up study of the first genome-wide association scan in alopecia areata: IL13 and KIAA0350 as susceptibility loci supported with genome-wide significance. *J Invest Dermatol*. 2012;132(9):2192–2197. doi:10.1038/jid.2012.129.
16. Courtois M, Loussouarn G, Hourseau C, Grollier JF. Hair cycle and alopecia. *Skin Pharmacol*. 1994;7(1-2):84–89.
17. Guarrera M, Rebora A. Anagen hairs may fail to replace telogen hairs in early androgenic female alopecia. *Dermatology*. 1996;192(1):28–31.
18. Kibar M, Aktan S, Bilgin M. Scalp dermatoscopic findings in androgenetic alopecia and their relations with disease severity. *Ann Dermatol*. 2014;26(4):478–484. doi:10.5021/ad.2014.26.4.478.
19. Cranwell W, Sinclair R, et al. Male androgenetic alopecia. [Updated 2016 Feb 29]. In: Feingold KR, Anawalt B, Boyce A, eds., et al. *Endotext [Internet]*. South Dartmouth (MA): MDText.com, Inc; 2000. Available at: https://www.ncbi.nlm.nih.gov/books/NBK278957/.
20. Zhao Y, Zhang B, Caulloo S, Chen X, Li Y, Zhang X. Diffuse alopecia areata is associated with intense inflammatory infiltration and CD8+ T cells in hair loss regions and an increase in serum IgE level. *Indian J Dermatol Venereol Leprol*. 2012;78(6):709–714.
21. Filbrandt R, Rufaut N, Jones L, Sinclair R. Primary cicatricial alopecia: Diagnosis and treatment. *CMAJ*. 2013;185(18):1579–1585. doi:10.1503/cmaj.111570.
22. Harries MJ, Sinclair RD, Macdonald-Hull S, Whiting DA, Griffiths CE, Paus R. Management of primary cicatricial alopecias: Options for treatment. *Br J Dermatol*. 2008;159(1):1–22. doi:10.1111/j.1365-2133.2008.08591.x.
23. Piraccini BM, Alessandrini A. Androgenetic alopecia. *G Ital Dermatol Venereol*. 2014;149(1):15–24.
24. Rubio-Gonzalez B, Juhász M, Fortman J, Mesinkovska NA. Pathogenesis and treatment options for chemotherapy-induced alopecia: A systematic review. *Int J Dermatol*. 2018;57(12):1417–1424. doi:10.1111/ijd.13906.
25. Dhurat RP, Deshpande DJ. Loose anagen hair syndrome. *Int J Trichology*. 2010;2(2):96–100. doi:10.4103/0974-7753.77513.
26. Loh SH, Lew BL, Sim WY. Localized telogen effluvium following hair transplantation. *Ann Dermatol*. 2018;30(2):214–217.

doi:10.5021/ad.2018.30.2.214.

27. Harvard Health Publishing. Harvard Medical School. Treating female pattern hair loss. https://www.health.harvard.edu/staying-healthy/treating-female-pattern-hair-loss. November 14, 2018; August 24, 2019.
28. Hay RJ. Tinea capitis: Current status. *Mycopathologia*. 2017;182(1-2): 87–93. doi:10.1007/s11046-016-0058-8.
29. Almeida MC, Romiti R, Doche I, Valente NY, Donati A. Psoriatic scarring alopecia. *An Bras Dermatol*. 2013;88(6 suppl 1):29–31. doi:10.1590/abd1806-4841.20132241.
30. Borda LJ, Wikramanayake TC. Seborrheic dermatitis and dandruff: A comprehensive review. *J Clin Investig Dermatol*. 2015;3(2):10.13188/2373-1044.1000019. doi:10.13188/2373-1044.1000019.
31. Tosti A, Piraccini BM, van Neste DJ. Telogen effluvium after allergic contact dermatitis of the scalp. *Arch Dermatol*. 2001;137(2):187–190.
32. Brown F, Badri T. Pityriasis Rubra Pilaris. [Updated 2019 February 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019. Available at: https://www.ncbi.nlm.nih.gov/books/NBK482436/.
33. Rothe MJ, Bialy TL, Grant-Kels JM. Erythroderma. *Dermatol Clin*. 2000 Jul;18(3):405–415.
34. Perera E, Yip L, Sinclair R. Alopecia Areata. In: Ioannides D, Tosti A, eds. Alopecias—Practical Evaluation and Management. Curr Probl Dermatol, Basel, Karger, 2015;47:67–75. doi:10.1159/000369406.
35. Kyriakis KP, Paltatzidou K, Kosma E, Sofouri E, Tadros A, Rachioti E. Alopecia areata prevalence by gender and age. *J Eur Acad Dermatol Venereol*. 2009;23(5):572–573. doi:10.1111/j.1468-3083.2008.02956.x.
36. Amin SS, Sachdeva S. (n.d.). Alopecia areata: An update. Retrieved May 22, 2019, from http://jpad.com.pk/index.php/jpad/article/view/346.
37. Seetharam KA. Alopecia areata: An update. *Indian J Dermatol Venereol Leprol*. 2013;79(5):563–575. doi:10.4103/0378-6323.116725.
38. Al-Refu K. Hair loss in children: Common and uncommon causes; clinical and epidemiological study in jordan. *Int J Trichology*. 2013;5(4):185–189. doi:10.4103/0974-7753.130393.
39. Lundin M, Chawa S, Sachdev A, Bhanusali D, Seiffert-Sinha K, Sinha AA. Gender differences in alopecia areata. *J Drugs Dermatol*. 2014;13(4):409–413.

40. Lacarrubba F, Micali G, Tosti A. Scalp dermoscopy or trichoscopy. In: Ioannides D, Tosti A, eds. *Alopecia—Practical Evaluation and Management. Curr Probl Dermatol. Basel, Karger*, 2015, vol 47, pp 21–32. doi:10.1159/000369402.
41. Villasante Fricke AC, Miteva M. Epidemiology and burden of alopecia areata: A systematic review. *Clin Cosmet Investig Dermatol*. 2015;8:397–403. doi:10.2147/CCID.S53985.
42. Xu L, Liu KX, Senna MM. A practical approach to the diagnosis and management of hair loss in children and adolescents. *Front Med (Lausanne)*. 2017;4:112. doi:10.3389/fmed.2017.00112.
43. Torborg L. Mayo Clinic Q & A: Cold cap therapy can reduce hair loss caused by chemotherapy. January 30, 2018. Mayo Clinic. Available at: https://newsnetwork.mayoclinic.org/discussion/mayo-clinic-q-and-a-cold-cap-therapy-can-reduce-hair-loss-caused-by-chemotherapy/. Accessed May 19, 2019.
44. Cold caps and scalp cooling systems. March 11, 2019. BreastCancer.org. Available at: https://www.breastcancer.org/tips/hair_skin_nails/cold-caps. Accessed May 19, 2019.
45. Skalnaya MG. Chapter 17: Copper deficiency a new reason of androgenetic alopecia? Pharmacology and Nutritional Intervention in the Treatment of Disease. Available at: http://dx.doi.org/10.5772/58416. Accessed April 30, 2019.
46. Ninan PT, Rothbaum BO, Marsteller FA, et al. A placebo-controlled trial of cognitive-behavioural therapy and clomipramine in trichotillomania. *J Clin Psychiatry*. 2000;61(1):47–50.
47. Likhitkar M, Shakur AA, Bansal KK, Pande M. Alopecia—Reason and possible treatments. *MOJ Drug Design Development & Therapy*. 2018;2(5):198–208.
48. Fabbrocini G, Cantelli M, Masarà A, Annunziata MC, Marasca C, Cacciapuoti S. Female pattern hair loss: A clinical, pathophysiologic, and therapeutic review. *Int J Womens Dermatol*. 2018;4(4):203–211. doi:10.1016/j.ijwd.2018.05.001.
49. van Zuuren EJ, Fedorowicz Z, Schoones J. Interventions for female pattern hair loss. *Cochrane Database Syst Rev*. 2016;2016(5):CD007628. doi:10.1002/14651858.CD007628.pub4.
50. Blumeyer A, Tosti A, Messenger A, et al. ; European Dermatology Forum (EDF). Evidence-based (S3) guideline for the treatment of androgenetic

alopecia in women and in men. *J Dtsch Dermatol Ges*. 2011;9(suppl 6):S1–S57. doi:10.1111/j.1610-0379.2011.07802.x.

51. Lee WS, Lee HJ, Choi GS, et al. Guidelines for management of androgenetic alopecia based on BASP classification—The Asian Consensus Committee guideline. *J Eur Acad Dermatol Venereol*. 2013;27(8):1026–1034. doi:10.1111/jdv.12034.
52. Torres F. Androgenetic, diffuse and senescent alopecia in men: Practical evaluation and management. In: Ioannides D, Tosti A, eds. Alopecia—Practical Evaluation and Management. Curr Probl Dermatol. Basel, Karger, 2015;47:33–44. doi:10.1159/000369403.
53. Olsen EA, Dunlap FE, Funicella T, et al. A randomized clinical trial of 5% topical minoxidil versus 2% topical minoxidil and placebo in the treatment of androgenetic alopecia in men. *J Am Acad Dermatol*. 2002;47(3):377–385.
54. Roberts JL, Fiedler V, Imperato-McGinley J, et al. Clinical dose ranging studies with finasteride, a type 2 5alpha-reductase inhibitor, in men with male pattern hair loss. *J Am Acad Dermatol*. 1999;41(4): 555–563.
55. Gubelin Harcha W, Barboza Martínez J, Tsai TF, et al. A randomized, active- and placebo-controlled study of the efficacy and safety of different doses of dutasteride versus placebo and finasteride in the treatment of male subjects with androgenetic alopecia. *J Am Acad Dermatol*. 2014;70(3):489–498 e3.doi:10.1016/j.jaad.2013.10.049.
56. Stough DB, Rao NA, Kaufman KD, Mitchell C. Finasteride improves male pattern hair loss in a randomized study in identical twins. *Eur J Dermatol*. 2002;12(1):32–37.
57. Van Neste D, Fuh V, Sanchez-Pedreno P, et al. Finasteride increases anagen hair in men with androgenetic alopecia. *Br J Dermatol*. 2000;143(4):804–810.
58. Van Neste D. Natural scalp hair regression in preclinical stages of male androgenetic alopecia and its reversal by finasteride. *Skin Pharmacol Physiol*. 2006;19(3):168–176.
59. Neste DV. (2019, May 12). Maintenance of optimised hair growth from viable terminal scalp hair follicles at baseline with oral finasteride in male pattern hair loss and first evidence of a “drug dependency” and a post-finasteride “rebound effect”. Retrieved May 22, 2019. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1111/srt.12707.
60. Lee S, Lee YB, Choe SJ, Lee WS. Adverse sexual effects of treatment

with finasteride or dutasteride for male androgenetic alopecia: A systematic review and meta-analysis. *Acta Derm Venereol*. 2019;99(1):12–17. doi:10.2340/00015555-3035.

61. Torres F. Androgenetic, and senescent alopecia in men: Practical evaluation and management. In: Ioannides D, Tosti A, eds. Alopecia—Practical Evaluation and Management. Curr Probl Dermatol, Basel, Karger, 2015;47:33–44. doi:10.1159/000369403.
62. Eun HC, Kwon OS, Yeon JH, et al. Efficacy, safety, and tolerability of dutasteride 0.5 mg once daily in male patients with male pattern hair loss: A randomized, double-blind, placebo-controlled, phase III study. *J Am Acad Dermatol*. 2010;63(2):252–258. doi:10.1016/j.jaad.2009.09.018.
63. Gajjar PC, Mehta HH, Barvaliya M, Sonagra B. Comparative study between mesotherapy and topical 5% minoxidil by dermoscopic evaluation for androgenic alopecia in male: A randomized controlled trial. *Int J Trichology*. 2019;11(2):58–67. doi:10.4103/ijt.ijt_89_18.
64. Saceda-Corralo D, Rodrigues-Barata AR, Vañó-Galván S, Jaén-Olasolo P. Mesotherapy with dutasteride in the treatment of androgenetic alopecia. *Int J Trichology*. 2017;9(3):143–145. doi:10.4103/ijt.ijt_73_16.
65. McElwee KJ, Shapiro JS. Promising therapies for treating and/or preventing androgenic alopecia. *Skin Therapy Lett*. 2012;17(6):1–4.
66. Jones MC. (2018, August 17). Treatment Options for Androgenetic Alopecia. Retrieved May 22, 2019. Available at: https://www.uspharmacist.com/article/treatment-options-for-androgenetic-alopecia.
67. Picard F, Hersant B, Niddam J, Meningaud JP. Injections of platelet-rich plasma for androgenic alopecia: A systematic review. *J Stomatol Oral Maxillofac Surg*. 2017;118(5):291–297. doi:10.1016/j.jormas.2017.06.011.
68. Cervelli V, Garcovich S, Bielli A, et al. The effect of autologous activated platelet rich plasma (AA-PRP) injection on pattern hair loss: Clinical and histomorphometric evaluation. *Biomed Res Int*. 2014;2014. doi:10.1155/2014/760709.
69. Verma K, Tegta GR, Verma G, Gupta M, Negi A, Sharma R. A study to compare the efficacy of platelet-rich plasma and minoxidil therapy for the treatment of androgenetic alopecia. *Int J Trichology*. 2019;11(2):68–79. doi:10.4103/ijt.ijt_64_18.
70. Kelly Y, Blanco A, Tosti A. Androgenetic alopecia: An update of treatment options. *Drugs*. 2016;76(14):1349–1364. doi:10.1007/s40265-

016-0629-5.

71. Jo SJ, Shin H, Park YW, et al. Topical valproic acid increases the hair count in male patients with androgenetic alopecia: A randomized, comparative, clinical feasibility study using phototrichogram analysis. *J Dermatol*. 2014;41(4):285–291.
72. Lee CY, Wei CC, Yu MC, et al. Hair growth effect of traditional Chinese medicine BeauTop on androgenetic alopecia patients: A randomized double-blind placebo-controlled clinical trial. *Exp Ther Med*. 2017;13(1):194–202. doi:10.3892/etm.2016.3935.
73. Sonthalia S, Daulatabad D, Tosti A. (2016, January 23). Hair Restoration in Androgenetic Alopecia: Looking Beyond Minoxidil, Finasteride and Hair Transplantation. Retrieved May 22, 2019. Available at: https://www.omicsonline.org/open-access/hair-restoration-in-androgenetic-alopecia-looking-beyond-minoxidil-finasteride-and-hair-transplantation-jctt1000105.php?aid=68395.
74. Narda M, Aladren S, Cestone E, Nobile V. (2017, November 30). Efficacy and Safety of a Food Supplement Containing L-cystine, Serenoa repens Extract and Biotin for Hair Loss in Healthy Males and Females. A Prospective, Randomized, Double-blinded, Controlled Clinical Trial. Available at: https://www.omicsonline.org/open-access/efficacy-and-safety-of-a-food-supplement-containing-lcystine-serenoa-repens-extract-and-biotin-for-hair-loss-in-healthy-males-and-2471-9323-1000127-96167.html.
75. Shum KW, Cullen DR, Messenger AG. Hair loss in women with hyperandrogenism: Four cases responding to finasteride. *J Am Acad Dermatol*. 2002;47(5):733–739.
76. Ioannides D, Lazaridou E. Female pattern hair loss. In: Ioannides D, Tosti A, eds. Alopecias: Practical Evaluation and Management. Curr Probl Dermatol. Basel, Karger 2015:47:45–54. doi:10.1159/000369404.
77. Olszewska M, Rudnicka L. Effective treatment of female androgenic alopecia with dutasteride. *J Drugs Dermatol*. 2005;4(5):637–640.
78. Vexiau P, Chaspoux C, Boudou P, et al. Effects of minoxidil 2% vs. cyproterone acetate treatment on female androgenetic alopecia: A controlled, 12-month randomized trial. *Br J Dermatol*. 2002;146(6):992–999.
79. Sinclair R, Wewerinke M, Jolley D. Treatment of female pattern hair loss with oral antiandrogens. *Br J Dermatol*. 2005;152(3):466–473.

80. Paradisi R, Porcu E, Fabbri R, Seracchioli R, Battaglia C, Venturoli S. Prospective cohort study on the effects and tolerability of flutamide in patients with female pattern hair loss. *Ann Pharmacother*. 2011;45(4):469–475. doi:10.1345/aph.1P600.
81. Le Floc'h C, Cheniti A, Connétable S, Piccardi N, Vincenzi C, Tosti A. Effect of a nutritional supplement on hair loss in women. *J Cosmet Dermatol*. 2015;14(1):76–82. doi:10.1111/jocd.12127.
82. Torkos S, Gazella K. (2015, April). Essential Fatty Acids and Antioxidants Benefit Women With Female Pattern Hair Loss. Retrieved May 22, 2019. Available at: https://www.naturalmedicinejournal.com/journal/2015-04/essential-fatty-acids-and-antioxidants-benefit-women-female-pattern-hair-loss.
83. Katoulis AC, Liakou AI, Alevizou A, et al. Efficacy and safety of a topical botanical in female androgenetic alopecia: A randomized, single-blinded, vehicle-controlled study. *Skin Appendage Disord*. 2018;4(3):160–165. doi:10.1159/000480024.
84. Hunter N, Sayed K, Hay RA, Allam R, Hussein N. Comparing the efficacy of mesotherapy to topical minoxidil in the treatment of female pattern hair loss using ultrasound biomicroscopy: A randomized controlled trial. *Acta Dermatovenerol Croat*. 2019;27(1):1–7.
85. Tosti A, Iorizzo M, Piraccini BM. Androgenetic alopecia in children: Report of 20 cases. *Br J Dermatol*. 2005;152(3):556–559.
86. Price VH. Androgenetic alopecia in adolescents. *Cutis*. 2003;71(2):115–121.
87. Rodrigues M, Antunes I, Magalhães S, et al. Androgenic alopecia: An entity to consider in adolescence Case Reports 2017; 2017:bcr-2017-220679.
88. Nor NM, Ismail R, Jamil A, Shah SA, Imran FH. A randomized, single-blind trial of clobetasol propionate 0.05% cream under silicone dressing occlusion versus intra-lesional triamcinolone for treatment of keloid. *Clin Drug Investig*. 2017;37(3):295–301. doi:10.1007/s40261-016-0484-x.
89. Rathi SK, D'Souza P. Rational and ethical use of topical corticosteroids based on safety and efficacy. *Indian J Dermatol*. 2012;57(4):251–259. doi:10.4103/0019-5154.97655.
90. Vañó-Galván S, Hermosa-Gelbard Á, Sánchez-Neila N, et al. Pulse corticosteroid therapy with oral dexamethasone for the treatment of adult alopecia totalis and universalis. *J Am Acad Dermatol*. 2016;74(5):1005–

1007.

91. Triyangkulsri K, Suchonwanit P. Role of janus kinase inhibitors in the treatment of alopecia areata. *Drug Des Devel Ther*. 2018;12:2323–2335. doi:10.2147/DDDT.S172638.
92. Liu LY, Craiglow BG, Dai F, King BA. Tofacitinib for the treatment of severe alopecia areata and variants: A study of 90 patients. *J Am Acad Dermatol*. 2017;76(1):22–28. doi:10.1016/j.jaad.2016.09.007.
93. Dai YX, Chen CC. Tofacitinib therapy for children with severe alopecia areata. *J Am Acad Dermatol*. 2019;80(4):1164–1166. doi:10.1016/j.jaad.2018.12.041.
94. Bayart CB, DeNiro KL, Brichta L, Craiglow BG, Sidbury R. Topical Janus kinase inhibitors for the treatment of pediatric alopecia areata. *J Am Acad Dermatol*. 2017;77(1):167–170. doi:10.1016/j.jaad.2017.03.024.
95. Liu LY, King BA. Ruxolitinib for the treatment of severe alopecia areata. *J Am Acad Dermatol*. 2019;80(2):566–568. doi:10.1016/j.jaad.2018.08.040.
96. Penzi LR, Yasuda M, Manatis-Lornell A, Hagigeorges D, Senna MM. Hair regrowth in a patient with long-standing alopecia totalis and atopic dermatitis treated with dupilumab. *JAMA Dermatol*. 2018;154(11):1358–1360. doi:10.1001/jamadermatol.2018.2976.
97. Smogorzewski J, Sierro T, Compoginis G, Kim G. Remission of alopecia universalis in a patient with atopic dermatitis treated with dupilumab. *JAAD Case Rep*. 2019;5(2):116–117. doi:10.1016/j.jdcr.2018.11.007.
98. Vañó-Galván S, Hermosa-Gelbard Á, Sánchez-Neila N, et al. Treatment of recalcitrant adult alopecia areata universalis with oral azathioprine. *J Am Acad Dermatol*. 2016;74(5):1007–1008. doi:10.1016/j.
99. Fiedler-Weiss VC, Buys CM. Evaluation of anthralin in the treatment of alopecia areata. *Arch Dermatol*. 1987;123(11):1491–1493.
100. Spano F, Donovan JC. Alopecia areata: Part 2: treatment. *Can Fam Physician*. 2015;61(9):757–761.
101. Draelos ZD. Hair care and dyeing. In: Ioannides D, Tosti A, eds. Alopecias: Practical Evaluation and Management. Curr Probl Dermatol, Basel, Karger, 2015;47:121–127. doi:10.1159/000368412.
102. Dove US (a skin care product company). YouTube. Beauty standards of hair are a form of bias. Available at: https://www.youtube.com/watch?v=agptI1_1C40. August 25, 2019.
103. Rowland K. YouTube. Crown. Available at:

https://www.youtube.com/watch?v=LUkqY-pR5EU. August 25, 2019.

Dermatologic Drug Reactions, Contact Dermatitis, and Common Skin Conditions

Rebecca M. Law, David T.S. Law, and Howard I. Maibach

KEY CONCEPTS

1. Patients presenting with a skin condition should be interviewed thoroughly regarding signs and symptoms, urgency, other subjective complaints, and medication history. The skin eruption should be carefully assessed to help distinguish between a disease condition and a drug-induced skin reaction.
2. Drug-induced skin reactions may be caused by systemic or topical medications and can be irritant (if topical route) or allergic (topical or systemic route) in nature.
3. Allergic drug reactions can be classified into exanthematous, urticarial, blistering, and pustular eruptions. Exanthematous reactions include maculopapular rashes and drug hypersensitivity syndrome. Urticarial reactions include urticaria, angioedema, and serum sickness-like reactions. Blistering reactions include fixed drug eruptions, Stevens-Johnson syndrome, and toxic epidermal necrolysis (SJS/TEN). Pustular eruptions include acneiform drug reactions and acute generalized exanthematous pustulosis. Other drug-induced skin reactions include hyperpigmentation and photosensitivity.
4. Not all skin reactions are drug induced. In clinical practice, a diagnosis of drug-induced skin reaction is often a diagnosis of exclusion (ie, the diagnosis is reached after other possible diagnoses have been ruled out).
5. Contact dermatitis is a common skin disorder caused either by an irritant contactant or an allergic/sensitizing contactant, resulting in an irritant contact dermatitis (ICD) or an allergic contact dermatitis (ACD).

6. An ICD is confined to the area of chemical contact whereas an ACD may extend beyond the areas of contact. However, it may sometimes be difficult to differentiate an ICD from an ACD.
7. Patch testing is a criterion standard for the diagnosis of ACD—the crucial investigative and diagnostic method used together with a detailed clinical history and physical exam/workup.
8. The first goals of therapy in the management of contact dermatitis involve identification, withdrawal, and avoidance of the offending agent. A thorough history, including occupational history, must be carefully reviewed for potential contactants.
9. Other goals of therapy for contact dermatitis include providing symptomatic relief, implementing preventive measures, and providing coping strategies and other information for patients and caregivers.
10. Photoaging is premature skin aging most commonly due to sun exposure.
11. Skin cancers include squamous cell carcinoma, basal cell carcinoma, and malignant melanoma.

Preclass Engaged Learning Activity

Review Chapter e16 – Skin Care and Minor/Self-Treatable Dermatologic Conditions in this textbook, *Pharmacotherapy: A Pathophysiologic Approach*, 11th ed., for background on skin structure and function, transdermal drug absorption, and definitions of macules, papules, nodules, and nevi.

INTRODUCTION

As the fictional character Lois Lane said, "… the light always returns to show us things familiar … and things entirely new, or long overlooked. It shows us new possibilities, and challenges us to pursue them … you can see it. All you have to do is look …" (Justice League movie 2017).[1]

This chapter builds on concepts from Chapter e16: Skin Care and Minor Dermatologic Conditions—the first concept in dermatology is learning how to look at skin. The reader is strongly encouraged to review that chapter prior to reading this one.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

SECTION 17 HEMATOLOGIC DISORDERS

118

Anemias

Kristen M. Cook and Devon M. Greer

KEY CONCEPTS

1. Anemia is a group of diseases characterized by a decrease in either hemoglobin (Hb) or the volume of red blood cells (RBCs), which results in decreased oxygen-carrying capacity of the blood. Anemia is defined by the World Health Organization (WHO) as Hb less than 13 g/dL (130 g/L; 8.07 mmol/L) in men and less than 12 g/dL (120 g/L; 7.45 mmol/L) in women.
2. Acute-onset anemias are most likely to present with tachycardia, lightheadedness, and dyspnea. Chronic anemia often presents with weakness, fatigue, headache, vertigo, and pallor.
3. Iron-deficiency anemia (IDA) is characterized by decreased levels of ferritin (most sensitive marker) and serum iron, and decreased transferrin saturation. Hb and hematocrit decrease later. RBC morphology includes hypochromia and microcytosis. Most patients are adequately treated with oral iron therapy, although parenteral iron therapy is necessary in some patients.
4. Vitamin B_{12} deficiency, a macrocytic anemia, can be due to inadequate intake, malabsorption syndromes, and inadequate utilization. Anemia caused by lack of intrinsic factor, resulting in decreased vitamin B_{12} absorption, is called *pernicious anemia*. Neurologic symptoms can be present and can become irreversible if the vitamin B_{12} deficiency is not treated promptly. Oral or parenteral therapy can be used for replacement.
5. Folic acid deficiency, a macrocytic anemia, results from inadequate intake, decreased absorption, and increased folate requirements. Treatment consists of oral administration of folic acid, even for patients with absorption problems. Adequate folic acid intake is essential in women of childbearing age to decrease the risk of neural tube defects in their children.

6. Anemia of inflammation (AI) is a newer term used to describe both anemia of chronic disease and anemia of critical illness. AI is a diagnosis of exclusion. It results from chronic inflammation, infection, or malignancy and can occur as early as 1 to 2 months after the onset of the disease. The serum iron level usually is decreased, but in contrast to IDA the serum ferritin concentration is normal or increased. Treatment is aimed at correcting the underlying pathology. Anemia of critical illness occurs within days of acute illness.
7. Anemia is one of the most prevalent clinical problems in the elderly, although not an inevitable complication of aging. Low Hb concentrations are not “normal” in the elderly. Anemia is associated with an increased risk of hospitalization and mortality, reduced quality of life, and decreased physical functioning in the elderly.
8. IDA is a leading cause of infant morbidity and mortality. Age- and sex-adjusted norms must be used in the interpretation of laboratory results for pediatric patients. Primary prevention of IDA is the goal. A therapeutic trial of oral iron is the standard of care.

Preclass Engaged Learning Activity

Watch the Khan Academy video on the pathophysiology of anemia:
https://tinyurl.com/u624ufn

INTRODUCTION

Anemia affects a large part of the world’s population. According to the World Health Organization (WHO), almost 1.6 billion people (25% of the world’s population) are anemic. Anemia is defined by the WHO as hemoglobin (Hb) less than 13 g/dL (130 g/L; 8.07 mmol/L) in men or less than 12 g/dL (120 g/L; 7.45 mmol/L) in women. In the United States, about 3.5 million people have anemia based on self-reported data from the National Center for Health Statistics. It is estimated that millions of people are unaware they have anemia, making it one of the most underdiagnosed conditions in the United States. Iron deficiency is the leading cause of anemia worldwide, accounting for as many as 50% of cases.[1] Recent data show that the overall prevalence of anemia has declined in

the United States in preschool-aged children and women of childbearing age over the past 20 years, but the prevalence of iron deficiency anemia (IDA) did not change significantly in these same groups. The reasons for these changes remain unclear.[2] Although nutritional deficiencies occur less often in the United States, obesity surgery, which can cause deficiencies, is becoming increasingly common. Gastric bypass may result in folate, vitamin B_{12}, and iron deficiencies. Prevalence data are confounded by the lack of a standardized definition of anemia and lack of screening guidelines for most populations. The United States Preventive Services Task Force (USPSTF) guidelines for pregnant women recommend routine screening for IDA.

Anemia is not an innocent bystander because it can affect both length and quality of life. Retrospective observational studies of hemodialysis patients and heart failure patients suggest that anemia is an independent risk factor for mortality.[3] In addition, anemia significantly influences morbidity in patients with end-stage renal disease, chronic kidney disease, and heart failure.[4] Anemia is associated with psychomotor and cognitive abnormalities in children. Similarly, anemia is associated with cognitive dysfunction in patients with renal failure or cancer, and among community-dwelling elders.[5] Anemia during pregnancy is associated with increased risk for low birth weights, preterm delivery, and perinatal mortality.[6] Maternal IDA may be associated with postpartum depression in mothers and poor performance by offspring on mental and psychomotor tests. Global goals of treatment in anemic patients are to alleviate signs and symptoms, correct the underlying etiology, and prevent recurrence of anemia.

1 Anemia is a group of diseases characterized by a decrease in either Hb or circulating red blood cells (RBCs), resulting in reduced oxygen-carrying capacity of the blood. Anemia can result from inadequate RBC production, increased RBC destruction, or blood loss. It can be a manifestation of a host of systemic disorders, such as infection, chronic renal disease, or malignancy. Because anemia is a sign of underlying pathology, rapid diagnosis of the cause may be essential.

The functional classification of anemia is shown in **Fig. 118-1.** This chapter focuses on the most common causes of anemia—IDA, anemia associated with vitamin B_{12} or folic acid deficiency, and anemia of inflammation (AI) (eg, anemia of chronic disease [ACD]). Some of the other causes of anemia are addressed in other chapters.

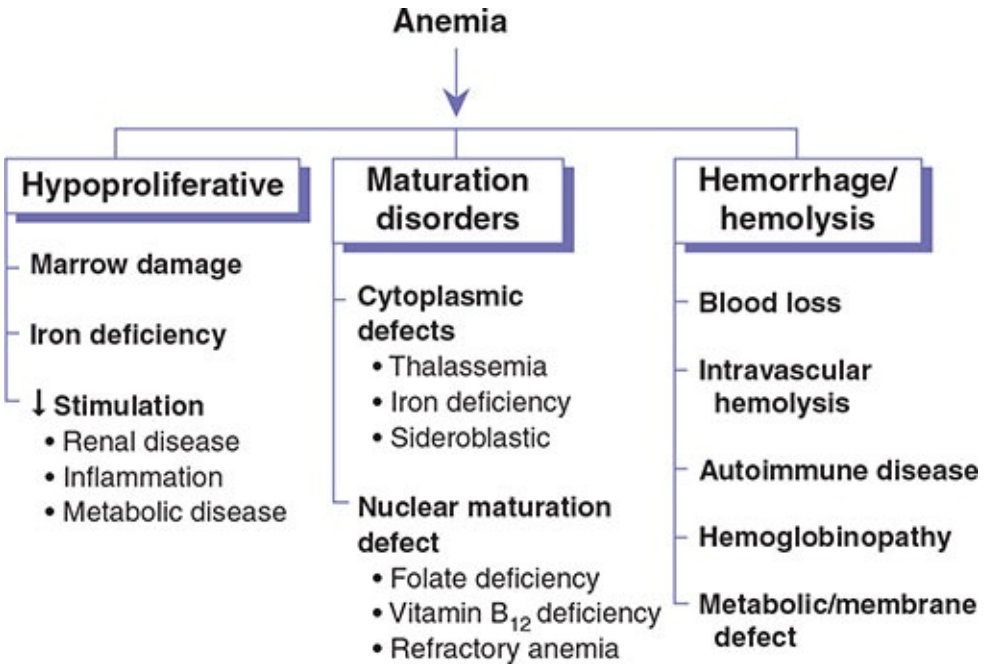


FIGURE 118-1 Functional classification of anemia. Each of the major categories of anemia (hypoproliferative, maturation disorders, and hemorrhage/hemolysis) can be further subclassified according to the functional defect in the several components of normal erythropoiesis.

Characteristic changes in the size of RBCs seen in erythrocyte indices can be the first step in the morphologic classification and understanding of the anemia. Anemia can be classified by RBC size as macrocytic, normocytic, or microcytic. Vitamin B_{12} deficiency and folic acid deficiency both are macrocytic anemias. An example of a microcytic anemia is iron deficiency, whereas a normocytic anemia may be associated with recent blood loss or chronic disease. More than one etiology of anemia can occur concurrently. Inclusion of the underlying cause of the anemia makes diagnostic terminology easier to understand (eg, microcytic anemia secondary to iron deficiency).

Microcytic anemias are a result of a quantitative deficiency in Hb synthesis, usually due to iron deficiency or impaired iron utilization. As a result, erythrocytes containing insufficient Hb are formed. Microcytosis and hypochromia are the morphologic abnormalities that provide evidence of impaired Hb synthesis.

Macrocytic anemias can be divided into megaloblastic and nonmegaloblastic anemias. The type of macrocytic anemia can be distinguished microscopically by peripheral blood smear examination. Megaloblasts are distinctive cells that express a biochemical abnormality of retarded DNA synthesis, resulting in unbalanced cell growth. Megaloblastic anemias may affect all hematopoietic cell

lines. The most common causes of megaloblastic anemia are vitamin B_{12} and folate deficiency. Nonmegaloblastic macrocytic anemias may arise from liver disease, hypothyroidism, hemolytic processes, and alcoholism. Hemolytic anemias often are macrocytic, reflecting the increased numbers of circulating reticulocytes, which are larger on average than mature red cells.

MATURATION AND DEVELOPMENT OF RED BLOOD CELLS

In adults, RBCs are formed in the marrow of the vertebrae, ribs, sternum, clavicle, pelvic (iliac) crest, and proximal epiphyses of the long bones. In children, most bone marrow space is hematopoietically active to meet increased RBC requirements.

In normal RBC formation, a pluripotent stem cell yields an erythroid burst-forming unit. Erythropoietin (EPO) and cytokines such as interleukin-3 and granulocyte-macrophage colony-stimulating factor stimulate this cell to form an erythroid colony-forming unit in the marrow (**Fig. 118-2**). During this process, the nucleus becomes smaller with each division, finally disappearing in the normal erythrocyte. Hb and iron are incorporated into the gradually maturing RBC, which eventually is released from the marrow into the circulating blood as a reticulocyte. The maturation process usually takes about 1 week. The reticulocyte loses its nucleus and becomes an erythrocyte within several days. The circulating erythrocyte is a non-nucleated, nondividing cell. More than 90% of the protein content of the erythrocyte consists of the oxygen-carrying molecule Hb. Erythrocytes have a normal survival time of 120 days.[7]

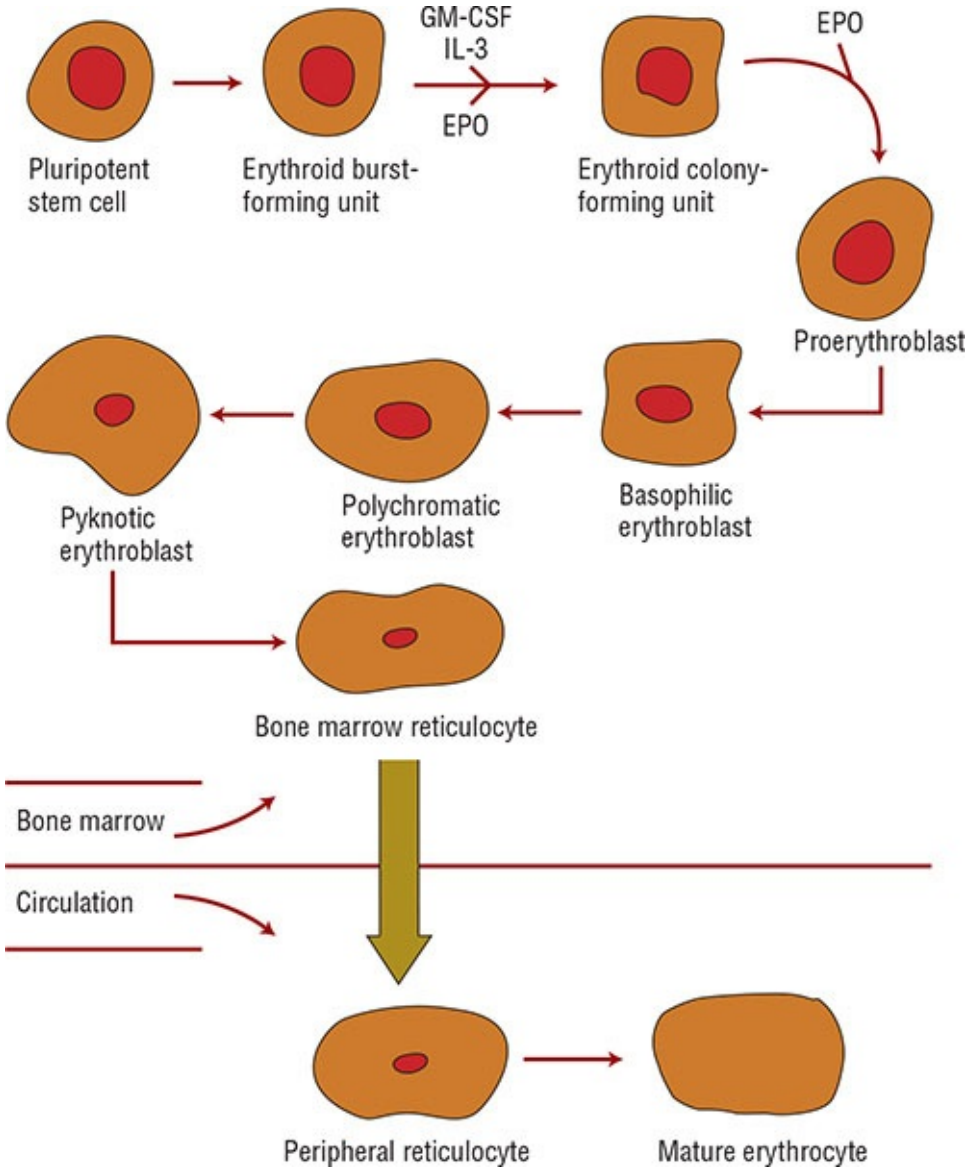


FIGURE 118-2 Erythrocyte maturation sequence. (EPO, erythropoietin; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-3, interleukin-3.)

Stimulation of Erythropoiesis

The hormone EPO, 90% of which is produced by the kidneys, initiates and stimulates the production of RBCs. Erythropoiesis is regulated by a feedback loop. The main mechanism of action of EPO is to prevent apoptosis, or programmed cell death, of erythroid precursor cells and allow their proliferation and subsequent maturation. A decrease in tissue oxygen concentration signals the kidneys to increase the production and release of EPO into the plasma, which increases production and maturation of RBCs. Under normal circumstances, the

RBC mass is kept at an almost constant level by EPO matching new erythrocyte production to the natural rate of loss of RBCs. A summary of erythropoiesis is shown in **Fig. 118-3**. Early appearance of large quantities of reticulocytes in the peripheral circulation (reticulocytosis) is an indication of increased RBC production.[7]

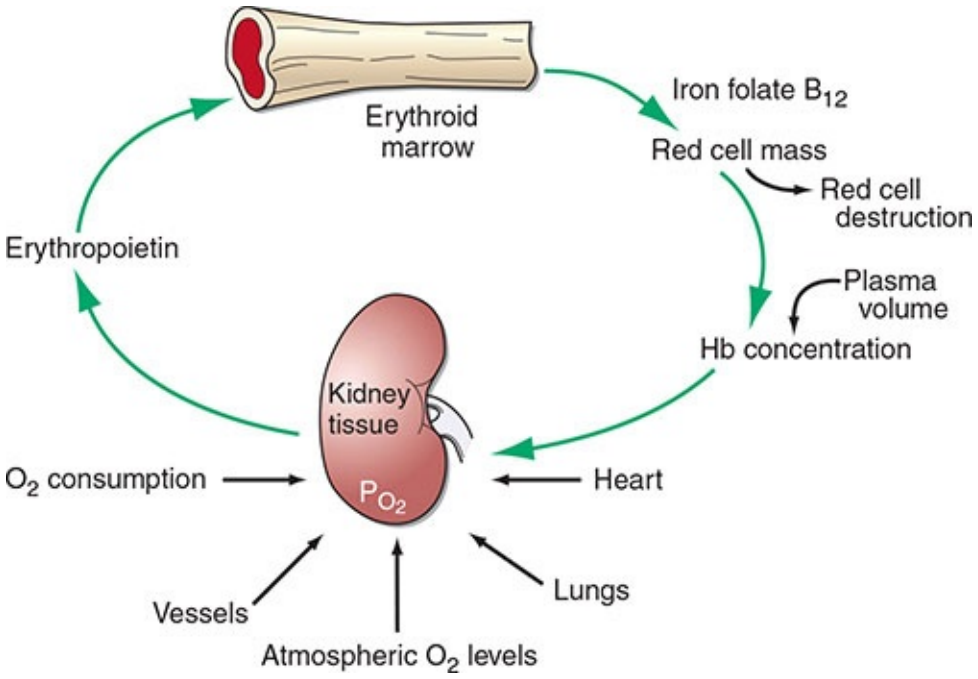


FIGURE 118-3 Physiologic regulation of red cell production by tissue oxygen tension. *(Reproduced with permission from Adamson JW, Longo DL. Anemia and polycythemia. In: Longo DL, Fauci AS, Kasper DL, et al., eds. Harrison's Principles of Internal Medicine. 18th ed. New York: Copyright © McGraw-Hill; 2012.)*

Synthesis of Hemoglobin

Hb contains a protein component with two α-chains and two β-chains. Each chain is linked to a heme group consisting of a porphyrin ring structure with an iron atom chelated at its center, which is capable of binding oxygen. The initial step in the synthesis of heme from the substrate succinyl CoA and glycine requires the presence of pyridoxine phosphate (vitamin B_6) as a catalyst.

Following its synthesis in the cytoplasmic mitochondria of the RBC, heme diffuses into the extramitochondrial space, where it combines with the completed α- and β-chains and forms Hb. When hemolytic destruction of RBCs exceeds marrow production capacity and anemia develops, the Hb value decreases to a

steady-state level at which production is equal to destruction.

Incorporation of Iron into Heme

Iron is an essential part of Hb. The specific plasma transport protein transferrin delivers iron to the bone marrow for incorporation into the Hb molecule. Transferrin enters cells by binding to transferrin receptors, which circulate and then attach to cells needing iron. Fewer transferrin receptors are present on the surface of cells that do not need iron, thus preventing iron-replete cells from receiving excess iron.[8]

Circulating transferrin normally is about 30% saturated with iron. Transferrin delivers extra iron to other body storage sites, such as the liver, marrow, and spleen, for later use. This iron is stored within macrophages as ferritin or hemosiderin. Ferritin consists of a Fe^{3+} hydroxyphosphate core surrounded by a protein shell called *apoferritin*. Hemosiderin can be described as compacted ferritin molecules with an even greater iron-to-protein shell ratio. Physiologically it is a more stable, but less available, form of storage iron. Since total body iron storage is generally reflected by ferritin levels, low serum levels of ferritin provide strong evidence of IDA.[9]

Normal Destruction of Red Blood Cells

Phagocytic breakdown destroys older blood cells, primarily in the spleen but also in the marrow (**Fig. 118-4**). Amino acids from the globin chains return to an amino acid pool; heme oxygenase acts on the porphyrin heme structure to form biliverdin and to release its iron. Iron returns to the iron pool to be reused, although biliverdin is further catabolized to bilirubin. The bilirubin is released into the plasma, where it binds to albumin and is transported to the liver for glucuronide conjugation and excretion via bile. If the liver is unable to perform the conjugation, as occurs with intrinsic liver disease or oversaturation of conjugation enzymes by excessive cell hemolysis, the result is an elevated *indirect* (unconjugated) bilirubin. If the biliary excretion pathway for conjugated bilirubin is obstructed, an elevated *direct* bilirubin results. Comparison of direct and indirect bilirubin values helps to determine if the defect in bilirubin clearance occurs before or after bilirubin enters the liver. The Hb in RBCs destroyed by intravascular hemolysis becomes attached to haptoglobin and is carried back to the marrow for processing in the normal manner.[10]

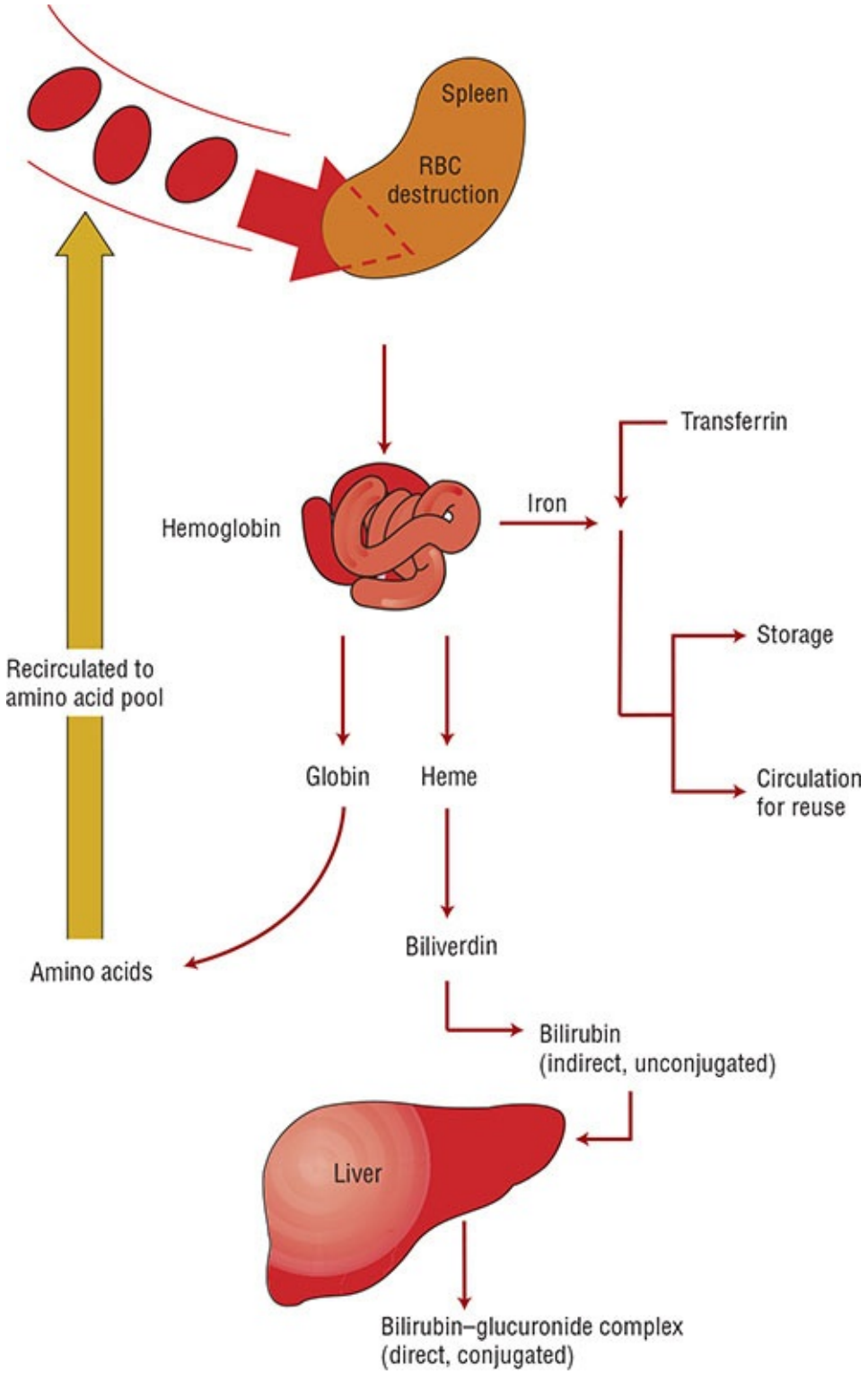


FIGURE 118-4 Destruction of red blood cells (RBCs).

DIAGNOSIS OF ANEMIA

General Presentation

History, physical examination, and laboratory testing are used in the evaluation of the patient with anemia. The workup determines if the patient is bleeding and investigates potential causes of the anemia, such as increased RBC destruction, bone marrow suppression, and iron deficiency. Diet can also be important in identifying causes of anemia. Additionally, information about concurrent nonhematologic disease states and a drug history are essential when evaluating the cause of the anemia (Chapter e121, Drug-Induced Hematologic Disorders). History of blood transfusions and exposure to toxic chemicals also should be obtained.

Presenting signs and symptoms of anemia depend on its rate of development and the age and cardiovascular status of the patient. Severity of symptoms does not always correlate with the degree of anemia. Healthy patients may acclimate to very low Hb concentrations if the anemia develops slowly. Mild anemia often is associated with no clinical symptoms and may be found incidentally upon obtaining a complete blood count (CBC) for other reasons. The signs and symptoms in elderly patients with anemia may be attributed to their age or concomitant disease states. The elderly may not tolerate levels of Hb in the same way that younger persons do. Similarly, patients with cardiac or pulmonary disease may be less tolerant of mild anemia. Premature infants with anemia may be asymptomatic or have tachycardia, poor weight gain, increased supplemental oxygen needs, or episodes of apnea or bradycardia.

2 Anemia of rapid onset is most likely to present with cardiorespiratory symptoms such as palpitations, angina, orthostatic lightheadedness, and breathlessness due to decreased oxygen delivery to tissues or hypovolemia in those with acute bleeding. The patient also may have tachycardia and hypotension.

If onset is more chronic, presenting symptoms may include fatigue, weakness, headache, orthopnea, dyspnea on exertion, vertigo, faintness, sensitivity to cold, pallor, and loss of skin tone. Traditional signs of anemia, such as pallor, have limited sensitivity and specificity and may be misinterpreted. With chronic bleeding, there is time for equilibration within the extravascular space, so faintness and lightheadedness are less common.

Possible manifestations of IDA include glossal pain, smooth tongue, reduced salivary flow, pica (compulsive eating of nonfood items), and pagophagia (compulsive eating of ice). These symptoms are not likely to appear unless the anemia is severe.

Neurologic findings in vitamin B_{12} deficiency may precede hematologic changes. Early neurologic findings may include numbness and paraesthesias. Ataxia, spasticity, diminished vibratory sense, decreased proprioception, and imbalance may occur later as demyelination of the dorsal columns and corticospinal tract develop. Vision changes may result from optic nerve involvement. Psychiatric findings include irritability, personality changes, memory impairment, depression, and infrequently, psychosis.

Anemia associated with folate deficiency is typically macrocytic but, unlike B_{12} deficiency, occurs without neurological symptoms. Although the symptoms of anemia will improve with folate replacement and a partial hematologic response will occur, the neurologic manifestations of vitamin B_{12} deficiency will not be reversed with folic acid replacement therapy and consequently may progress or become irreversible if not treated appropriately.

CLINICAL PRESENTATION Anemia

General

- Patients may be asymptomatic or have vague complaints
- Patients with vitamin B_{12} deficiency may develop neurologic consequences
- In AI, signs and symptoms of the underlying disorder often overshadow those of the anemia

Symptoms

- Decreased exercise tolerance
- Fatigue
- Dizziness
- Irritability
- Weakness
- Palpitations
- Vertigo
- Shortness of breath
- Chest pain

- Neurologic symptoms in vitamin B_{12} deficiency

Signs

- Tachycardia
- Pale appearance (most prominent in conjunctivae)
- Decreased mental acuity
- Increased intensity of some cardiac valvular murmurs
- Diminished vibratory sense or gait abnormality in vitamin B_{12} deficiency

Laboratory Tests

- Hemoglobin, hematocrit, and RBC indices may remain normal early in the disease and then decrease as the anemia progresses
- Serum iron is low in IDA and AI
- Ferritin levels are low in IDA and normal or elevated in AI
- Total iron-binding capacity is high in IDA and is low or normal in AI
- Mean cell volume is elevated in vitamin B_{12} deficiency and folate deficiency
- Vitamin B_{12} and folate levels are low in their respective types of anemia
- Homocysteine is elevated in vitamin B_{12} deficiency and folate deficiency
- Methylmalonic acid is elevated in vitamin B_{12} deficiency

LABORATORY EVALUATION

The initial evaluation of anemia involves a CBC (including RBC indices), reticulocyte index, and possibly an examination of a stool sample for occult blood. The results of the preliminary evaluation determine the need for other studies, such as examination of a peripheral blood smear. Based on laboratory test results, anemia can be categorized into three functional defects: RBC production failure (hypoproliferative), cell maturation ineffectiveness, or increased RBC destruction or loss (see Fig. 118-1).

Figure 118-5 shows a broad, general algorithm for the diagnosis of anemia based on laboratory data. There are many exceptions and additions to this algorithm, but it can serve as a guide to the typical presentation of common types and causes of anemia. The algorithm is less useful in the presence of more than one cause of anemia.

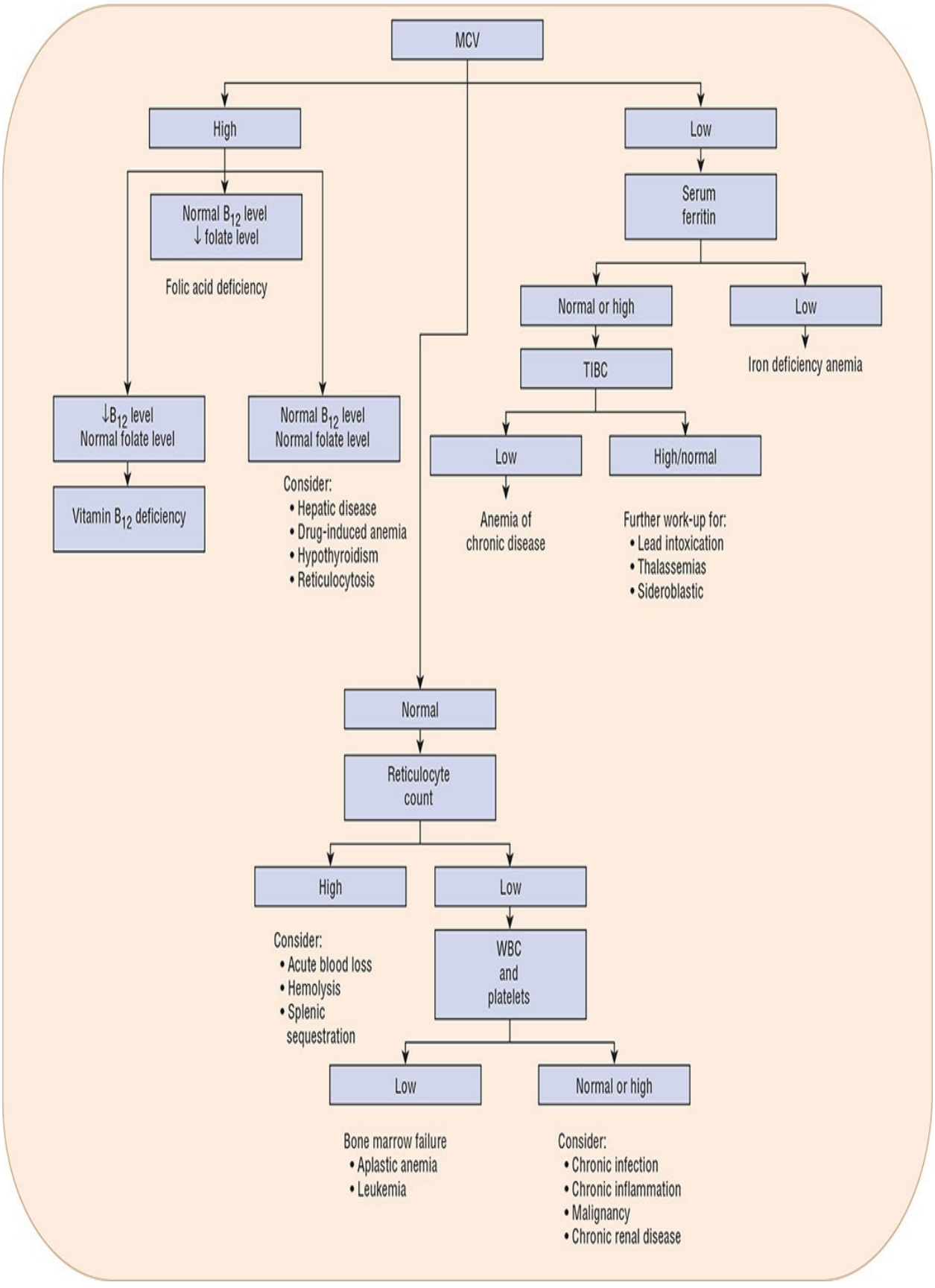

MCV
High
Low
Normal B_{12} level
↓ folate level
Folic acid deficiency
Serum ferritin
Normal or high
Low
Iron deficiency anemia
TIBC
↓B_{12} level
Normal folate level
Vitamin B_{12} deficiency
Normal B_{12} level
Normal folate level
Consider:
• Hepatic disease
• Drug-induced anemia
• Hypothyroidism
• Reticulocytosis
Low
High/normal
Anemia of chronic disease
Further work-up for:
• Lead intoxication
• Thalassemias
• Sideroblastic
Normal
Reticulocyte count
High
Low
Consider:
• Acute blood loss
• Hemolysis
• Splenic sequestration
WBC and platelets
Low
Normal or high
Bone marrow failure
• Aplastic anemia
• Leukemia
Consider:
• Chronic infection
• Chronic inflammation
• Malignancy
• Chronic renal disease

FIGURE 118-5 General algorithm for diagnosis of anemias. (↓, decreased; MCV, mean corpuscular volume; TIBC, total iron-binding capacity; and WBC, white blood cells.)

Hemoglobin

Values given for Hb represent the amount of Hb per volume of whole blood. The higher values seen in males are due to stimulation of RBC production by androgenic steroids, whereas the lower values in females reflect the decrease in Hb as a result of blood loss during menstruation. The Hb level can be used as a very rough estimate of the oxygen-carrying capacity of blood. Hb levels may be diminished because of a decreased quantity of Hb per RBC or because of a decrease in the actual number of RBCs.

Hematocrit

Expressed as a percentage, hematocrit (Hct) is the actual volume of RBCs in a unit volume of whole blood. In general, it is about three times the Hb value (when Hb is expressed in g/dL). An alteration in this ratio may occur with abnormal cell size or shape and often indicates pathology. A low Hct indicates a reduction in either the number or the size of RBCs or an increase in plasma volume.

Red Blood Cell Count

The RBC count is an indirect estimate of the Hb content of the blood; it is an actual count of RBCs per unit of blood.

Red Blood Cell Indices

Wintrobe indices describe the size and Hb content of the RBCs and are calculated from the Hb, Hct, and RBC count. RBC indices, such as mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH), are single mean values that do not express the variation that can occur in cells.

Mean Cell Volume

MCV represents the average volume of RBCs. It may reflect changes in MCH. Cells are considered macrocytic if they are larger than normal, microcytic if they are smaller than normal, and normocytic if their size falls within normal limits.

Folic acid– and vitamin B_{12}–deficiency anemias yield macrocytic cells, whereas iron deficiency and thalassemia are examples of microcytic anemias. When IDA (decreased MCV) is accompanied by folate deficiency (increased MCV), the overall MCV may be normal. Failure to understand that the MCV represents an average RBC size can cause the clinician to potentially overlook some causes of the anemia.

Mean Cell Hemoglobin

MCH is the amount of Hb in a RBC, and usually increases or decreases with the MCV. Two morphologic changes, microcytosis and hypochromia, can reduce MCH. A microcytic cell contains less Hb because it is a smaller cell, while a hypochromic cell has a low MCH because of the decreased concentration of Hb present in the cell. Cells can be both microcytic and hypochromic, as seen with IDA. The MCH alone cannot distinguish between microcytosis and hypochromia. The most common cause of an elevated MCH is macrocytosis (eg, vitamin B_{12} or folate deficiency).

Mean Cell Hemoglobin Concentration

The concentration of Hb per volume of cells is the mean cell Hb concentration (MCHC). Because MCHC is independent of cell size, it is more useful than MCH in distinguishing between microcytosis and hypochromia. A low MCHC indicates hypochromia; a microcyte with a normal Hb concentration will have a low MCH but a normal MCHC. A decreased MCHC is seen most often in IDA.

Total Reticulocyte Count

The total reticulocyte count is an indirect assessment of new RBC production. It reflects how quickly immature RBCs (reticulocytes) are produced by bone marrow and released into the blood. Reticulocytes circulate in the blood about 2 days before maturing into RBCs. About 1% of RBCs are normally replaced daily, representing a reticulocyte count of 1% (or 0.01 as a fraction). The reticulocyte count in normocytic anemia can differentiate hypoproliferative marrow from a compensatory marrow response to an anemia. A lack of reticulocytosis in anemia indicates impaired RBC production. Examples include iron deficiency, B_{12} deficiency, ACD, malnutrition, renal insufficiency, and malignancy. A high reticulocyte count may be seen in acute blood loss or hemolysis. The reticulocyte index can aid in determining the functional

classification of an anemia (see Fig. 118-5).

Red Blood Cell Distribution Width

The higher the red blood cell distribution width (RDW), the more variable is the size of the RBCs. The RDW increases in early IDA because of the release of large, immature, nucleated RBCs to compensate for the anemia, but this change is not specific for IDA. The RDW also can be helpful in the diagnosis of a mixed anemia. A patient can have a normal MCV yet have a wide RDW. This finding indicates the presence of microcytes and macrocytes, which would yield a "normal" average RBC size. The use of RDW to distinguish IDA from ACD is not recommended.

Peripheral Blood Smear

The peripheral blood smear can supplement other clinical data and help establish a diagnosis. Peripheral blood smears provide information on the functional status of the bone marrow and defects in RBC production. Additionally, it provides information on variations in cell size (anisocytosis) and shape (poikilocytosis). Automated blood counters, used for the CBC, can flag specific RBC changes that can be confirmed by a peripheral blood smear. Blood smears are placed on a microscope slide and stained as appropriate. Morphologic examination includes assessment of size, shape, and color. The extent of anisocytosis correlates with increased range of cell sizes. Poikilocytosis can suggest a defect in the maturation of RBC precursors in the bone marrow or the presence of hemolysis.

Serum Iron

The level of serum iron is the concentration of iron bound to transferrin. Transferrin is normally about one-third bound (saturated) to iron. The serum iron level of many patients with IDA may remain within the lower limits of normal because a considerable amount of time is required to deplete iron stores. Serum iron levels show diurnal variation (higher in the morning, lower in the afternoon), but this variation is probably not clinically significant in timing of levels.[9] Since serum iron levels are decreased by infection and inflammation, serum iron levels are best interpreted in conjunction with the total iron-binding capacity. The serum iron level decreases with IDA and ACD and increases with hemolytic anemias and iron overload.

Total Iron-Binding Capacity

An indirect measurement of the iron-binding capacity of serum transferrin, total iron-binding capacity (TIBC) evaluation, is performed by adding an excess of iron to plasma to saturate all transferrin with iron. Each transferrin molecule can carry two iron atoms. Normally, about 30% of available iron-binding sites are filled. With this laboratory test, all binding sites are filled to measure TIBC; the excess (unbound) iron is then removed and the serum iron concentration determined. Unlike the serum iron level, the TIBC does not fluctuate over hours or days. TIBC usually is higher than normal when body iron stores are low. The finding of a low serum iron level and a high TIBC suggests IDA. The TIBC is actually a measurement of protein serum transferrin, which can be affected by a variety of factors. Patients with infection, malignancy, inflammation, liver disease, and uremia may have a decreased TIBC and a decreased serum iron level, which are consistent with the diagnosis of ACD.

Percentage Transferrin Saturation

The ratio of serum iron level to TIBC indicates transferrin saturation. It reflects the extent to which iron-binding sites are occupied on transferrin and indicates the amount of iron readily available for erythropoiesis. It is expressed as a percentage, as described in the following formula:

$$\text{Transferrin saturation} = \frac{\text{serum iron}}{\text{TIBC}} \times 100$$

Transferrin normally is 20% to 50% saturated with iron. In IDA, transferrin saturation of 15% or lower is commonly seen.[10] Transferrin saturation is a less sensitive and specific marker of iron deficiency than are ferritin levels.

Serum Ferritin

The serum concentration of ferritin (storage iron) is proportional to total iron stores and therefore is the best indicator of iron deficiency or iron overload. Ferritin levels indicate the amount of iron stored in the liver, spleen, and bone marrow cells. Low serum ferritin levels are virtually diagnostic of IDA. In contrast, serum iron levels may decrease in both IDA and ACD. Since serum ferritin is an acute phase reactant, chronic infection or inflammation can increase its concentration independent of iron status, masking depleted tissue stores. This limits the utility of the serum ferritin if the level is normal or high for a

chronically ill patient. For these patients, iron, even if present in these tissue stores, may not be available for erythropoiesis.

Soluble Transferrin Receptor

The soluble transferrin receptor (sTfR) assay is a laboratory test considered a sensitive, early, highly quantitative marker of iron depletion. The sTfR concentration is inversely correlated with tissue iron stores, and elevated levels are predictive of iron deficiency. Unlike ferritin, the sTfR is not an acute phase reactant; so its level remains normal for patients with chronic disease. It may be a useful test for distinguishing ACD from IDA.[9] The major limitation of this test is that it is not widely available in many laboratories.

Folic Acid

The results of folic acid measurements vary depending on the assay method used. Decreased serum folic acid levels (less than 4 ng/mL [9 nmol/L]) indicate a folate deficiency megaloblastic anemia that may coexist with a vitamin B_{12}–deficiency anemia. Erythrocyte folic acid levels are less variable than serum levels because they are slow to decrease in an acute process such as drug-induced folic acid deficiency and slow to increase with oral folic acid replacement. In addition, erythrocyte folic acid levels have the theoretical advantage of less susceptibility to rapid changes in diet and alcohol intake. Limitations with sensitivity and specificity do exist with measurements of erythrocyte folate. If the serum folate concentration is normal for a patient with suspected folate deficiency, then the erythrocyte folate level should be measured.[11]

Vitamin B_{12}

Low levels (less than 200 pg/mL [148 pmol/L]) of vitamin B_{12} (cyanocobalamin or cobalamin) indicate deficiency. However, a deficiency may exist prior to the recognition of low serum levels. Serum values are maintained at the expense of vitamin B_{12} tissue stores. Vitamin B_{12} and folate deficiency may overlap, thus serum levels of both vitamins should be determined. Vitamin B_{12} levels may be falsely low with folate deficiency and pregnancy.[12]

Schilling Test

This test used to be the “gold standard” for assessing vitamin B_{12} absorption. Due to its cost, unavailable test components, and complexity, the test is rarely used today. Tests to replace it are under investigation.[13]

Homocysteine

Vitamin B_{12} and folate both are required for conversion of homocysteine to methionine. Increased serum homocysteine may suggest vitamin B_{12} or folate deficiency. Homocysteine levels also can be elevated in patients with vitamin B_6 deficiency, renal failure, hypothyroidism, or a genetic defect in cystathionine β-synthase.[14]

Methylmalonic Acid

A vitamin B_{12} coenzyme is needed to convert methylmalonyl coenzyme A to succinyl coenzyme A. Patients with vitamin B_{12} deficiency have increased concentrations of serum methylmalonic acid (MMA), which is a more specific marker for vitamin B_{12} deficiency than homocysteine. MMA levels are not elevated in folate deficiency because folate does not participate in MMA metabolism. Levels of both MMA and homocysteine usually are elevated prior to the development of hematologic abnormalities and reductions in serum vitamin B_{12} levels.[12] MMA levels must be interpreted cautiously for patients with renal disease and hypovolemia because the levels may be elevated due to decreased urinary excretion.

IRON-DEFICIENCY ANEMIA

Epidemiology

Iron deficiency is the most common nutritional deficiency in developing and developed countries. Data from the National Health and Nutrition Examination Survey (NHANES) indicate the prevalence of IDA in the United States in young children and women of childbearing age is 1.2% and 4.5%, respectively.[2] The normal ranges for Hb and Hct are so wide that a patient may lose up to 15% of RBC mass and still have a Hct within the normal range. Therefore, iron

deficiency may precede the appearance of anemia.

Iron Balance

The normal iron content of the body is about 3 to 4 g. Iron is a component of Hb, myoglobin, and cytochromes. About 2 g of the iron exists in the form of Hb, and about 130 mg exists as iron-containing proteins such as myoglobin. About 3 mg of iron is bound to transferrin in plasma, and 1,000 mg of iron exists as storage iron in the form of ferritin or hemosiderin. The rest of the iron is stored in other tissues such as cytochromes.[9] Due to the toxicity of inorganic iron, the body has an intricate system for iron absorption, transport, storage, assimilation, and elimination. Hepcidin is a regulator of intestinal iron absorption, iron recycling, and iron mobilization from hepatic stores. It is a peptide hormone made in the liver, distributed in plasma, and excreted in urine. Hepcidin inhibits efflux of iron through ferroportin. Hepcidin synthesis is increased by iron loading and inflammation and decreased by iron deficiency and erythropoietic activity. Hepcidin is induced during infections and inflammation, which allows iron to sequester in macrophages, hepatocytes, and enterocytes.[15] As a result, hepcidin is likely an important mediator of AI. Hepcidin is usually suppressed in IDA.[16] Hepcidin testing is not routinely available.[17]

Most people lose about 1 mg of iron daily. Menstruating women can lose up to 0.6% to 2.5% more per day. Pregnancy requires an additional 700 mg of iron and a blood donation can result in as much as 250 mg of iron loss;[18] these patients are at higher risk for deficiency.

Iron is best absorbed in its ferrous (Fe^{2+}) form. The normal daily Western diet contains mainly the ferric (Fe^{3+}) nonabsorbed form. After iron is ionized by stomach acid and then reduced to the Fe^{2+} state, it is absorbed primarily in the duodenum, and to a smaller extent in the jejunum, via intestinal mucosal cell uptake. Subsequently, it is transferred across the cell into the plasma. Iron absorption is not directly proportional to iron intake. Rather as physiologic iron levels decrease, GI absorption of iron increases.

The daily recommended dietary allowance for iron is 8 mg in adult males and postmenopausal females and 18 mg in menstruating females. Children require more iron because of growth-related increases in blood volume, and pregnant women have an increased iron demand brought about by fetal development. In the absence of hemochromatosis, iron overload does not occur, because only the amount of iron lost per day is absorbed. The amount of iron absorbed from food depends on the body stores, the rate of RBC production, the type of iron

provided in the diet, and the presence of any substances that may enhance or inhibit iron absorption.

Heme iron, which is found in meat, fish, and poultry, is about three times more absorbable than the nonheme iron found in vegetables, fruits, dried beans, nuts, grain products, and dietary supplements. Gastric acid and other dietary components such as ascorbic acid increase the absorption of nonheme iron. Dietary components that form insoluble complexes with iron (phytates, tannates, and phosphates) decrease absorption. Phytates, a natural component of grains, brans, and some vegetables, can form poorly absorbed complexes and partially explain the increased prevalence of IDA in poorer countries, where grains and vegetables compose a disproportionate amount of the normal diet. Polyphenols bind iron and decrease nonheme iron absorption when large amounts of tea or coffee are consumed with a meal. Although the mechanism is unknown, calcium inhibits absorption of both heme and nonheme iron. Finally, because gastric acid improves iron absorption, patients who have undergone a gastrectomy or have achlorhydria have decreased iron absorption.[19]

Etiology

Iron deficiency results from prolonged negative iron balance, which can occur due to increased iron demand or hematopoiesis, increased loss, or decreased intake/absorption. The onset of iron deficiency depends on an individual's initial iron stores and the imbalance between iron absorption and loss. Multiple etiologic factors usually are involved. Certain groups at higher risk for iron deficiency include children younger than 2 years, adolescent girls, pregnant/lactating females, and those older than 65 years. Patients older than 65 years of age with IDA should be considered for testing for occult GI bleeding.[18] Blood loss must initially be considered a cause of IDA in adults. Blood loss may occur as a result of many disorders, including trauma, hemorrhoids, peptic ulcers, gastritis, GI malignancies, arteriovenous malformations, diverticular disease, copious menstrual flow, nosebleeds, and postpartum bleeding. In less industrialized nations, the risk of IDA is largely related to dietary factors.

The USPSTF recommends routine screening for IDA in all pregnant women.[20] The USPSTF has concluded that evidence is insufficient to recommend for or against routine iron supplementation for nonanemic pregnant women.[18] However, iron deficiency in pregnant women is so common that the Centers for Disease Control and Prevention (CDC) guidelines recommend initiation of low-dose iron supplements or prenatal vitamins with 30 mg/day of

iron at each woman's first prenatal visit.

Medication history, specifically regarding recent or past use of iron, alcohol, corticosteroids, warfarin or other anticoagulants, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs), is a vital part of the history to assess bleeding risk. Other possible causes of hypochromic microcytic anemia include AI, thalassemia, sideroblastic anemia, and heavy metal (mostly lead) poisoning (see Fig. 118-4).

Pathophysiology

Iron is vital to the function of all cells. Without iron, cells lose their capacity for electron transport and energy metabolism. Iron deficiency usually is the result of a long period of negative iron balance. Manifestations of iron deficiency occur in three stages. In the initial stage, iron stores are reduced without reduced serum iron levels and can be assessed with serum ferritin measurement. The stores allow iron to be utilized when there is an increased need for Hb synthesis. Once stores are depleted, there still is adequate iron from daily RBC turnover for Hb synthesis. Further iron losses would make the patient vulnerable to anemia development. In the second stage, iron deficiency occurs when iron stores are depleted, and Hb is above the lower limit of normal for the population but may be reduced for a given patient. This can be determined by serial CBC measurements. Findings include reduced transferrin saturation and increased TIBC. The third stage occurs when the Hb falls to less than normal values.

Laboratory Findings

3 Abnormal laboratory findings for patients with IDA generally include low serum iron and ferritin levels and high TIBC. In the early stages of IDA, RBC size is not changed. Low ferritin concentration is the earliest and most sensitive indicator of iron deficiency. However, ferritin may not correlate with iron stores in the bone marrow because renal or hepatic disease, malignancies, infection, or inflammatory processes may increase ferritin values.[9] Hb, Hct, and RBC indices usually remain normal in early stages. In the later stages of IDA, Hb and Hct fall below normal values, and a microcytic hypochromic anemia develops. Microcytosis may precede hypochromia, as erythropoiesis is programmed to maintain normal Hb concentration in preference to cell size. As a result, even slightly abnormal Hb and Hct levels may indicate significant depletion of iron stores and should not be ignored. In terms of RBC indices, MCV is reduced earlier in IDA than Hb concentration.

Transferrin saturation (ie, serum iron level divided by the TIBC) is useful for assessing IDA. Low values may indicate IDA, although low serum transferrin saturation values also may be present in inflammatory disorders. The TIBC may help to differentiate the diagnosis in these patients. TIBC levels that are elevated suggest IDA, while values that are low represent inflammatory disease.

TREATMENT

Desired Outcomes

The outcomes for all types of anemia in this chapter include reversal of hematologic parameters to normal, return of normal function and quality of life, and prevention or reversal of long-term complications such as neurologic complications of vitamin B_{12} deficiency.

Dietary Supplementation and Oral Iron Preparations

The severity and cause of IDA determine the approach to treatment. Treatment is focused on replenishing iron stores. Because iron deficiency can be an early sign of other illnesses, treatment of the underlying disease may aid in the correction of iron deficiency.

Treatment of IDA usually consists of dietary supplementation and administration of oral iron preparations. Examples of foods that are high in iron include animal liver, fortified cereals/oatmeal, beef, eggs, spinach, lentils, tofu, and beans. Iron is best absorbed from meat, fish, and poultry. These foods as well as certain iron-fortified cereals can help treat IDA. Orange juice and other ascorbic acid–rich foods can be included with meals to potentially increase absorption. Milk and tea reduce absorption and should be consumed in moderation. In most cases of IDA, oral administration of iron therapy with soluble Fe^{2+} iron salts is appropriate.

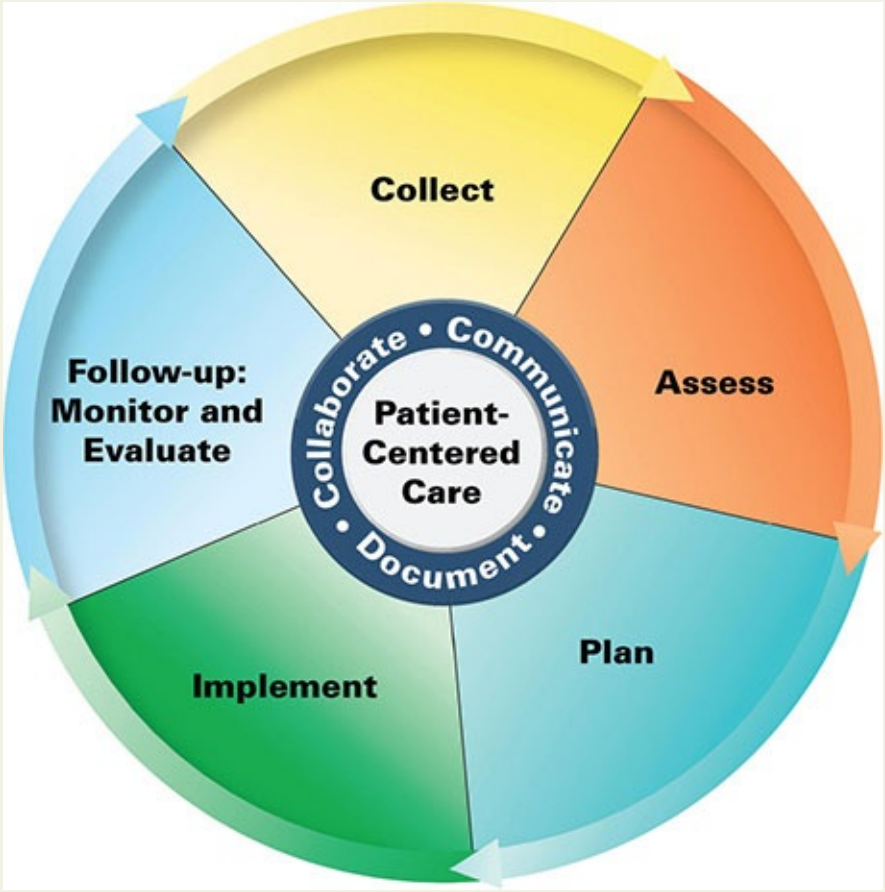
Fe^{2+} sulfate, succinate, lactate, fumarate, glutamate, and gluconate are absorbed similarly. Ferric citrate was approved by the FDA in 2017 for treatment of IDA in adults with chronic kidney disease who are not on dialysis (see Chapter 61, Chronic Kidney Disease). The addition of copper, cobalt, molybdenum, or other minerals provides no advantage but increases cost of the product. Iron is best absorbed in the reduced Fe^{2+} form, with maximal absorption occurring in the duodenum, primarily due to the acidic medium of the stomach. Slow-release, sustained-release, or enteric coated iron preparations may not undergo sufficient dissolution until they reach the small intestine. In the

alkaline environment of the small intestine, iron tends to form insoluble complexes, which significantly reduces absorption. The dose of iron replacement therapy depends on the patient's ability to tolerate the administered iron. Tolerance of iron salts improves with a small initial dose and gradual escalation to the full dose. For patients with IDA, the generally recommended dose is about 150 to 200 mg of elemental iron daily, usually in two or three divided doses to maximize tolerability. If patients cannot tolerate this daily dose of elemental iron, smaller amounts of elemental iron (eg, single 325-mg tablet of Fe^{2+}sulfate) usually are sufficient to replace iron stores, although at a slower rate. **Table 118-1** lists the percentage of elemental iron of commonly available iron salts. Iron preferably is administered at least 1 hour before meals because food can interfere with iron absorption. Many patients must take iron with food because they experience GI upset when iron is administered on an empty stomach.

TABLE 118-1 Oral Iron Products

Iron Salt	Percent Elemental Iron	Common Formulations and Elemental Iron Provided
Ferrous sulfate	20	60-65 mg/324-325 mg tablet 60 mg/5 mL syrup 44 mg/ 5 mL elixir 15 mg/1 mL drops
Ferrous sulfate (exsiccated)	30	65 mg/200 mg tablet 50 mg/160 mg tablet
Ferrous gluconate	12	38 mg/325 mg tablet 28-29 mg/240-246 mg tablet
Ferrous fumarate	33	66 mg/200 mg tablet 106 mg/324-325 mg tablet

Recent evidence suggests that lower amounts of iron can be given and produce similar results with better tolerability. Hepicidin, a protein that helps regulate iron absorption, may play a role in oral iron dosing. Some studies have found that a large dose of iron in the morning may elevate hepicidin levels and prevent further iron absorption of subsequent doses for at least the rest of the day, potentially up to 48 hours later.[21] Furthermore, once daily dosing of iron may result in a lower amount of iron being absorbed versus every other day dosing.[22] These studies have led some to propose that oral iron could be dosed every other day to achieve the same results as the previous recommended dosing. However, no long-term studies have been conducted to support this change in dosing.



Patient Care Process for Anemia

Collect

- Patient characteristics (eg, age, race, sex, pregnant)
- Patient history (past medical, dietary habits, activity)
- Symptoms of anemia (fatigue, weakness, chest pain, dizziness, paleness, etc. (see “CLINICAL PRESENTATION: ANEMIA” box)
- Current medications (including over-the-counter and supplements)
- Objective data (see “Clinical Presentation: Anemia” box)
    - Blood pressure (BP), heart rate (HR)
    - Labs (CBC, iron studies, vitamin B_{12}, foliate, homocysteine, MMA, etc.)

Assess

- Underlying disease states (blood loss, heart failure, chronic renal disease,

HIV, malignancy; see **Table 118-1**)

- Dietary habits and potential social factors contributing to nutritional deficiencies
- Acuity of symptoms and need for transfusion or hospitalization
- Current medications that may contribute to or worsen anemia or blood loss
- Lab results to determine underlying etiology of anemia for proper treatment selection or attainment of treatment goals

Plan*

- Dietary interventions for nutritional deficiencies
- Initiate appropriate drug therapy treatment based on etiology (correct formulation, strength, dosing, frequency, and pertinent drug interactions [see **Table 118-4** for iron product selection/drug interactions])
- Monitoring for efficacy and safety (lab and symptom improvement, corrected etiology if possible, adverse effects)
- Patient education (expectations/purpose of treatment, adverse effects, diet, etc.)
- Improved treatment of underlying pathologies if contributing to anemia of chronic disease

Implement*

- Educate patient on treatment interventions and treatment expectations
- Reinforce adherence to treatment plan for short and long term success
- Schedule patient for follow-up at appropriate intervals

Follow-up: Monitor and Evaluate

- Lab values within 4 weeks after treatment initiation
- Tolerability of medications (eg, adverse effects)
- Symptom improvement
- If minimal improvement or worsening, whether etiology of anemia is correct

**Collaborate with patient, caregivers, and other healthcare professionals.*

Adverse reactions to therapeutic doses of iron are primarily GI in nature and

consist of dark discoloration of feces, constipation or diarrhea, nausea, and vomiting. GI side effects usually are common, dose related, and are similar among iron salts when equivalent amounts of elemental iron are administered. Dark stools do not interfere with testing for occult blood in the GI tract. Administration of smaller amounts of iron with each dose or administration with meals may minimize these adverse effects. Histamine-2 blockers or proton-pump inhibitors reduce gastric acidity and may impair iron absorption. **Table 118-2** lists drug interactions with iron.

TABLE 118-2 Iron Salt–Drug Interactions

Drugs That Decrease Iron Absorption	Drugs Affected by Iron
Al-, Mg-, and Ca^{2+}-containing antacids	Levodopa ↓ (chelates with iron)
Tetracycline and doxycycline	Methyldopa ↓ (decreases efficacy of methyldopa)
$Histamine_2$ antagonists	Levothyroxine ↓ (decreased efficacy of levothyroxine)
Proton-pump inhibitors	Penicillamine ↓ (chelates with iron)
Cholestyramine	Fluoroquinolones ↓ (forms ferric ion quinolone complex)
	Tetracycline and doxycycline ↓ (when administered within 2 hours of iron salt)
	Mycophenolate ↓ (decreases absorption)

Failure to respond to appropriate treatment regimens necessitates reevaluation of the patient's condition. Common causes of treatment failure include poor patient adherence, inability to absorb iron, incorrect diagnosis, continued bleeding, or a concurrent inflammatory condition that impairs a full response. Even when iron deficiency is present, response may be impaired when a coexisting cause for anemia exists. Rarely a patient has diminished ability to absorb iron, most often due to previous gastrectomy, such as gastric bypass surgery, or celiac disease. Regardless of the form of oral therapy used, treatment should continue for 3 to 6 months after the anemia is resolved to allow for repletion of iron stores and to prevent relapse. Patients should be instructed to store oral iron out of reach of children and pets as small amounts can result in a fatal overdose. There are carbonyl iron products that may have slower absorption and have less risk in overdose for children. Products containing more than 30 mg of elemental iron are required to be packaged as individual dosage units to prevent toxicity. Treatment for acute iron poisoning is discussed in Chapter e7, Clinical Toxicology.

Parenteral Iron Therapy

Indications for parenteral iron therapy include intolerance to oral, malabsorption, and nonadherence. Patients with significant blood loss who refuse transfusions and cannot take oral iron therapy also may require parenteral iron therapy. Parenteral iron therapy should also be considered, possibly first line, in patients with inflammatory bowel disease and those with gastric bypass/gastric resection due to poor oral absorption.[23] Parenteral iron therapy is also used for patients with chronic kidney disease (see Chapter 61), especially those undergoing hemodialysis, and for some cancer patients receiving chemotherapy on erythropoiesis-stimulating agents (ESAs; Chapter 144, Cancer Treatment and Chemotherapy). Five different parenteral iron preparations currently available in the United States are iron dextran, sodium ferric gluconate, iron sucrose, ferumoxytol, and ferric carboxymaltose (Table 61-10). They differ in their molecular size, pharmacokinetics, bioavailability, and adverse effect profiles. Although toxicity profiles of these agents differ, clinical studies indicate that each is efficacious. Iron dextran parenteral preparations have been associated with more anaphylactic reactions and this product requires a test dose prior to full dose administration. Fatal reactions have also occurred in patients who tolerated the test dose. Iron dextran and ferumoxytol products have black box warnings in their labeling regarding severe allergic reactions. The safety profile of parenteral iron is largely assessed by spontaneous reports to the FDA and observational studies. All parenteral iron preparations carry a risk for anaphylactic reactions but likely to a lesser extent than iron dextran.[24,25] The FDA recommends that resuscitation equipment and trained staff be available during administration of all iron dextran preparations. A concern with parenteral iron is that iron may be released too quickly and overload the ability of transferrin to bind it, leading to free iron reactions that can interfere with neutrophil function. The following formula can be used to estimate the total dose of parenteral iron needed to correct anemia:

$$\text{Dose of iron (mg)} = \text{whole blood hemoglobin deficit (g/dL)} \times \text{body weight (lb)} \text{ or}$$

$$\text{Dose of iron (mg)} = \text{whole blood hemoglobin deficit (g/L)} \times \text{body weight (kg)} \times 0.22$$

An additional quantity of iron to replenish stores should be added (about 600 mg for women and 1,000 mg for men).[9]

Iron dextran, a complex of Fe^{3+} hydroxide and the carbohydrate dextran,

contains 50 mg of iron per milliliter and can be given via the intramuscular or IV route. Different brands of iron dextran are available and differ in their molecular weight. They are not interchangeable. The intramuscular route is no longer used routinely and requires Z-tract injection technique.[26]

Methods of IV administration include multiple injections or an infusion of a diluted preparation. This latter method often is referred to as total dose infusion.

Total replacement doses of IV iron dextran have been given as a single dose, but this method of administration is not FDA approved. A test dose still is required. Patients who receive total dose infusions are at higher risk for adverse reactions, such as arthralgias, myalgias, flushing, malaise, and fever. Other adverse reactions of iron dextran include staining of the skin, pain at the injection site, allergic reactions, and rarely, anaphylaxis. Patients with preexisting immune-mediated diseases, such as active rheumatoid arthritis or systemic lupus erythematosus, are considered at high risk for adverse reactions because of their hyperreactive immune response.[27]

Sodium ferric gluconate is a complex of iron bound to one gluconate and four sucrose molecules in a repeating pattern. Its molecular weight is 289 to 440 kDa. Sodium ferric gluconate is available in an aqueous solution. No direct transfer of iron from the Fe^{3+} gluconate to transferrin occurs. The complex is taken up quickly by the mononuclear phagocytic system and has a half-life of about 1 hour in the bloodstream. Sodium ferric gluconate appears to produce fewer anaphylactic reactions than iron dextran does. Adverse effects of sodium ferric gluconate include cramps, nausea, vomiting, flushing, hypotension, intense upper gastric pain, rash, and pruritus.[28]

Iron sucrose is a polynuclear iron (III) hydroxide in sucrose complex with a molecular weight of 34 to 60 kDa. Following IV administration of iron sucrose, the iron is released directly from the circulating iron sucrose to transferrin and is taken up by the mononuclear phagocytic system and metabolized. The half-life is about 6 hours, with a volume of distribution similar to that of iron dextran. Iron sucrose injection should not be administered concomitantly with oral iron preparations because it will reduce the absorption of oral iron.[29] Adverse effects include leg cramps and hypotension.

Ferumoxytol was FDA-approved in 2009 to treat iron deficiency in adults with chronic kidney disease who are on or off dialysis and in 2018 was approved to include all adults with IDA who have not responded to oral iron. Typical dosing is 510 mg IV dose followed by a second 510 mg dose 3 to 8 days later. The dose can be readministered after 1 month if anemia persists. No test dose is required but anaphylaxis can occur and patients should be observed for at least

30 minutes after each dose. A black-box warning was also added in 2015 due to case reports of fatal and nonfatal anaphylactic reactions to the product. It should not be used in patients who previously had an allergic reaction to other iron preparations.[30]

Ferric carboxymaltose is the newest approved parenteral iron product, receiving FDA approval in 2013. The approval of this product was delayed due to hypophosphatemia seen in clinical trials. No additional warnings were required and no clinical issues related to hypophosphatemia have been reported. This product received approval for treatment of IDA in those who have failed oral iron therapy or who have intolerance for oral therapy. It is also approved for chronic kidney disease patients not on hemodialysis.[31]

Increased risk for infection is a concern with parenteral iron preparations because iron is a growth factor for some bacteria, but a recently published meta-analysis concluded that IV iron does not increase risk for infection.[32] Parenteral iron products are discussed in more detail in Chapter 61.

MEGALOBLASTIC ANEMIAS

Macrocytic anemias are divided into megaloblastic and nonmegaloblastic anemias. Macrocytosis, as seen in megaloblastic anemias, is caused by abnormal DNA metabolism resulting from vitamin B_{12} or folate deficiency. It also can be caused by administration of various drugs, such as hydroxyurea, zidovudine, cytarabine, methotrexate, azathioprine, 6-mercaptopurine, and cladribine. In vitamin B_{12}- or folate-deficiency anemia, megaloblastosis results from interference with folic acid– and vitamin B_{12}–interdependent nucleic acid synthesis in the immature erythrocyte. The rate of RNA and cytoplasm production exceeds the rate of DNA production. The maturation process is impaired, resulting in immature large RBCs (macrocytosis). RNA and DNA synthesis depend on a series of reactions catalyzed by vitamin B_{12} and folic acid because of their role in the conversion of uridine to thymidine. As shown in **Fig. 118-6**, dietary folates are absorbed in this process and converted to 5-methyl-tetrahydrofolate (A), which then is converted via a B_{12}-dependent reaction (B) to tetrahydrofolate (C). After gaining a carbon, tetrahydrofolate is converted to 5,10-methyl-tetrahydrofolate (D), a folate cofactor used by thymidylate synthetase (E) in the biosynthesis of nucleic acids. The 5,10-methyl-tetrahydrofolate cofactor is converted to dihydrofolate (F) during biosynthesis. Dihydrofolate reductase normally reduces dihydrofolate back to tetrahydrofolate

(C), which can again pick up a carbon and be recycled to produce more 5,10-methyl-tetrahydrofolate (D).

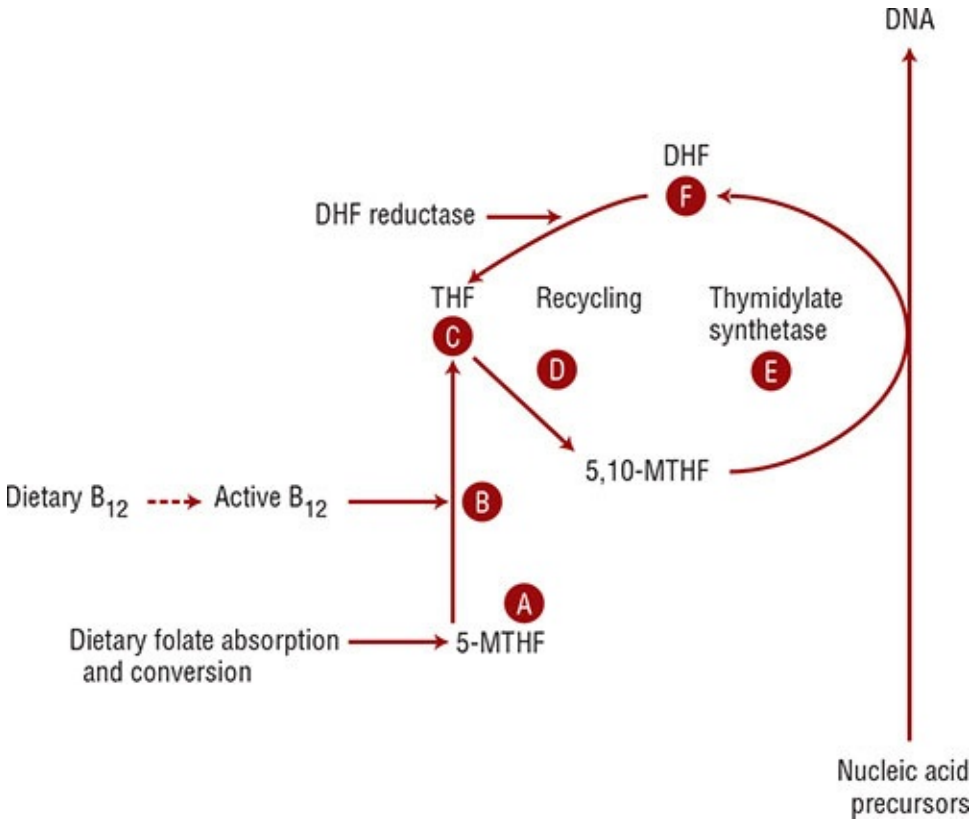


FIGURE 118-6 Drug-induced megaloblastosis. (DHF, dihydrofolate; 5-MTHF, 5-methyl-tetrahydrofolate; 5,10-MTHF, 5,10-methyl-tetrahydrofolate; THF, tetrahydrofolate.)

Although vitamin B_{12} and folate deficiency are common causes of macrocytosis, other possible causes must be considered if these deficiencies are not found. Other causes of macrocytosis include (1) a shift to immature or stressed RBCs as seen in reticulocytosis, aplastic anemia, and pure RBC aplasia; (2) a primary bone marrow disorder such as myelodysplastic syndromes, congenital dyserythropoietic anemias, and large granular lymphocyte leukemia; (3) lipid abnormalities as seen with liver disease, hypothyroidism, or hyperlipidemia; and (4) unknown mechanisms resulting from alcohol abuse and multiple myeloma. Macrocytosis is the most typical morphologic abnormality associated with excessive alcohol consumption. Even with adequate folate and vitamin B_{12} levels and the absence of liver disease, patients with high alcohol intake may present with an alcohol-induced macrocytosis. Cessation of alcohol ingestion results in resolution of the macrocytosis within a couple of months.

Vitamin B_{12}–Deficiency Anemia

The prevalence of vitamin B_{12}–deficiency anemia in the United States is unknown. Risk increases with age.[33] The use of gastric acid–suppressing agents, which may inhibit cobalamin release from food, is associated with an increased risk. Older adults in the United States have a high prevalence (up to 15%) of elevated MMA levels and associated low or low-normal vitamin B_{12} levels, likely due to atrophic gastritis and malabsorption of food-bound vitamin B_{12}.[33]

Etiology

4 The three major causes of vitamin B_{12} deficiency are inadequate intake, malabsorption syndromes, and inadequate utilization. Inadequate dietary consumption of vitamin B_{12} is rare. It usually occurs only in patients who are strict vegans and their breast-fed infants, chronic alcoholics, and elderly patients who consume a “tea and toast” diet because of financial limitations or poor dentition. Decreased vitamin B_{12} absorption can occur with loss of intrinsic factor by autoimmune mechanisms (such as pernicious anemia, in which gastric parietal cells are selectively damaged), chronic atrophic gastritis, or stomach surgery. One of the most frequent causes of low serum B_{12} levels results from the inability of vitamin B_{12} to be cleaved and released from proteins in food because of inadequate gastric acid production. Treatment of *Helicobacter pylori* may improve vitamin B_{12} status because this bacterial infection is a cause of chronic gastritis.[34] Vitamin B_{12} deficiency may occasionally result from overgrowth of bacteria in the bowel that use vitamin B_{12} or from injury or removal (from Crohn’s disease or small bowel surgery, respectively) of ileal receptor sites where vitamin B_{12} and the intrinsic factor complex are absorbed. Blind loop syndrome, Whipple disease, Zollinger–Ellison syndrome, tapeworm infestations, intestinal resections, tropical sprue, surgical resection of the ileus, pancreatic insufficiency, inflammatory bowel disease, advanced liver disease, tuberculosis, and Crohn’s disease may contribute to the development of vitamin B_{12} deficiency.[33] Metformin may reversibly decrease B_{12} absorption, likely due to its effects on the intestinal mucosa in the ileum. It rarely causes anemia on its own but can contribute to deficiency. Proton pump inhibitors and histamine 2 receptor antagonists may also contribute to vitamin B_{12} deficiency because an acidic environment is needed for vitamin B_{12} to be absorbed in the GI tract from

food.[35] A recent study suggested that these medications have a greater effect on deficiency in those who have taken them for two or more years.[35]

Pathophysiology

Vitamin B_{12} works closely with folate in the synthesis of building blocks for DNA and RNA, is essential in maintaining the integrity of the neurologic system, and plays a role in fatty acid biosynthesis and energy production. It is a water-soluble vitamin obtained exogenously by ingestion of meat, fish, poultry, dairy products, and fortified cereals. The body stores several years of vitamin B_{12}, of which about 50% is in the liver. The recommended daily allowance is 2 mcg in adults and 2.6 mcg in pregnant or breast-feeding women. The average Western diet provides 5 to 15 mcg of vitamin B_{12} daily, of which 1 to 5 mcg is absorbed.[33] Vitamin B_{12} deficiency usually takes several years to develop following vitamin deprivation.

Once dietary cobalamin enters the stomach, pepsin and hydrochloric acid release the cobalamin from animal proteins. The free cobalamin then binds to R-protein, which is released from parietal and salivary cells. In the duodenum, the cobalamin-R-protein complex is degraded, releasing free cobalamin. The cobalamin then binds with intrinsic factor that serves as a cell-directed carrier protein similar to transferrin for iron. This complex attaches to mucosal cell receptors in the distal ileum, the intrinsic factor is discarded, and the cobalamin is bound to transport proteins (transcobalamin I, II, and III). The cobalamin bound to transcobalamin II is secreted into the circulation and is taken up by the liver, bone marrow, and other cells. Most circulating cobalamin is bound to transcobalamin I and transcobalamin III. Passive diffusion is an alternate pathway for vitamin B_{12} absorption independent of intrinsic factor or an intact terminal ileum and accounts for about 1% of vitamin B_{12} absorption.[33]

Vitamin B_{12} deficiency can cause neurologic and hematologic complications. These usually start with bilateral paraesthesia in extremities; deficits in proprioception and vibration can also be present. If not treated, this can progress to ataxia, dementia-like symptoms, psychosis, and vision loss. In children prolonged deficiency can lead to poor brain development.[13,36] Patients with unexplained neuropathies should be evaluated for vitamin B_{12} deficiency.

Laboratory Findings

In macrocytic anemias, MCV is elevated greater than 100 fL, but some patients

deficient in vitamin B_{12} may have a normal MCV. If there is a coexisting cause of microcytosis, the MCV may not be elevated.[32] Mild leukopenia and thrombocytopenia are often present because abnormal DNA synthesis can affect all blood cell lines. A peripheral blood smear demonstrates macrocytosis accompanied by hypersegmented polymorphonuclear leukocytes (one of the earliest and most specific indications of this disease), oval macrocytes, anisocytosis, and poikilocytosis. Serum lactate dehydrogenase and indirect bilirubin levels may be elevated as a result of hemolysis or ineffective erythropoiesis.[13] Other laboratory findings include a low reticulocyte count, low serum vitamin B_{12} level (less than 200 pg/mL [148 pmol/L]), and low Hct.

In the early stages of vitamin B_{12} deficiency, classic signs and symptoms of megaloblastic anemia may not be evident, and serum levels of vitamin B_{12} may be within normal limits. Therefore, measurement of MMA and homocysteine may be useful because these parameters are typically the first to change. Because MMA and homocysteine are involved in enzymatic reactions that depend on vitamin B_{12}, a deficiency in vitamin B_{12} leads to accumulation of these metabolites. Elevations in MMA are more specific for vitamin B_{12} deficiency. Homocysteine is also elevated in several other situations including folate deficiency, chronic renal disease, alcoholism, smoking, and use of steroid or cyclosporine therapy.[36] Low levels of vitamin B_{12} result in hyperhomocysteinemia, which some studies have reported to be an independent risk factor for cerebrovascular, peripheral vascular, coronary, and venous thromboembolic disease.[37]

Blood levels of vitamin B_{12} should be drawn for all patients with suspected vitamin B_{12} deficiency. Vitamin B_{12} values less than 200 pg/mL (148 pmol/L) are suggestive of B_{12} deficiency. Subclinical vitamin B_{12} deficiency is sometimes used with vitamin B_{12} levels of 200 to 300 pg/mL (148-221 pmol/L).[38] Some patients with clinical B_{12} deficiency manifesting as neurological disease may have normal hematological parameters.

A Schilling test may theoretically be performed to diagnose pernicious anemia, but the usefulness of this test is questionable and rarely alters the clinical management of the vitamin B_{12} deficiency. The Schilling test was once performed to determine whether replacement of vitamin B_{12} should occur via an oral or parenteral route, but evidence now shows that oral replacement is as efficacious as parenteral supplementation because of the vitamin B_{12} absorption

pathway independent of intrinsic factor.[33,39]

TREATMENT

The goals of treatment for vitamin B_{12} deficiency include reversal of hematologic manifestations, replacement of body stores, and prevention or resolution of neurologic manifestations. Early treatment is of paramount importance because neurologic damage may be irreversible if the deficiency is not detected and corrected within months. In addition to replacement therapy, any underlying etiology that is treatable, such as bacterial overgrowth, should be corrected. Indications for starting oral or parenteral therapy include megaloblastic anemia or other hematologic abnormalities and neurologic disease from deficiency.[36] Those with borderline low levels of B_{12} but no hematologic abnormalities should be followed at yearly intervals.[36] Patients should be counseled on the types of foods high in vitamin B_{12} content such as fortified cereals, fish, animal liver, milk, clams, and yogurt. Orally administered vitamin B_{12} can be used effectively to treat pernicious anemia because of the previously discussed alternate pathway of passive absorption, independent of intrinsic factor.[14] Daily oral doses (1,000-2,000 mcg) of vitamin B_{12} is as effective as intramuscular administration in achieving hematologic and neurologic responses.[33,39] If vitamin B_{12} levels are marginally low and either MMA or both MMA and homocysteine levels are elevated, administration of 1,000 mcg of oral vitamin B_{12} daily should be strongly considered.[40] Timed-release preparations of oral cobalamin should be avoided.[41] Nonprescription 1,000 mcg cobalamin tablets are available, among several other strengths. A commonly used initial parenteral vitamin B_{12} regimen consists of daily injections of 1,000 mcg of cyanocobalamin for 1 week to saturate vitamin B_{12} stores in the body and resolve clinical manifestations of the deficiency. Thereafter, it can be given weekly for 1 month and monthly thereafter for maintenance. The series of daily parenteral injections may be omitted if administration is difficult or inconvenient. In this case the parenteral injection is then given weekly, sometimes for a longer than 1 month. Parenteral therapy is preferred for patients exhibiting neurologic symptoms until resolution of symptoms and normalization of hematologic indices because the most rapid-acting therapy is necessary.[42] When patients are converted from the parenteral to the oral form of cobalamin, 1,000 mcg of oral cobalamin daily can be initiated on the due date of the next

injection. Vitamin B_{12} should be continued for life in patients with pernicious anemia.

In addition to the oral and parenteral forms, vitamin B_{12} is available as a nasal spray for patients in remission following intramuscular vitamin B_{12} therapy who have no nervous system involvement. The nasal spray is administered once weekly. Intranasal administration should be avoided for patients with nasal diseases or those receiving medications intranasally in the same nostril. Patients should not administer the spray 1 hour before or after ingestion of hot foods or beverages, which can impair cobalamin absorption. The efficacy of the nasal spray formulation has not been well studied, and it should be used for maintenance therapy only after hematologic parameters have normalized.

Potential adverse effects with vitamin B_{12} replacement therapy are rare. Uncommon side effects include hyperuricemia and hypokalemia due to marked increase in potassium utilization during production of new hematopoietic cells.

Folic Acid Deficiency Anemia

Epidemiology

Folic acid deficiency is one of the most common vitamin deficiencies occurring in the United States, largely because of its association with excessive alcohol intake and pregnancy.

Etiology

5 Major causes of folic acid deficiency include inadequate intake, decreased absorption, and increased folate requirements. Poor eating habits make this deficiency more common in elderly patients, teenagers whose diets consist of “junk food,” alcoholics, food faddists, the impoverished, and those who are chronically ill or demented. Folic acid absorption may decrease for patients who have malabsorption syndromes or those who have received certain drugs. In alcoholics with poor dietary habits, alcohol interferes with folic acid absorption, interferes with folic acid utilization at the cellular level, and decreases hepatic stores of folic acid.

Increased folate requirements may occur when the rate of cellular division is increased, as seen in pregnant women; patients with hemolytic anemia, myelofibrosis, malignancy, chronic inflammatory disorders such as Crohn’s disease, rheumatoid arthritis, or psoriasis; patients undergoing long-term

dialysis; burn patients; and adolescents and infants during their growth spurts. This hyperutilization eventually can lead to anemia, particularly when the daily intake of folate is borderline, resulting in inadequate replacement of folate stores.

Several drugs have been reported to cause a folic acid deficiency. Some drugs (eg, azathioprine, 6-mercaptopurine, 5-fluorouracil, hydroxyurea, and zidovudine) directly inhibit DNA synthesis. Other drugs are folate antagonists; the most toxic is methotrexate (other examples include pentamidine, trimethoprim, and triamterene). A number of drugs (eg, phenytoin, phenobarbital, and primidone) antagonize folate via poorly understood mechanisms but are thought to reduce vitamin absorption by the intestine (see Chapter e121). Since folic acid doses as low as 1 mg/day may affect serum phenytoin levels, routine folic acid supplementation is not generally recommended. The decline in phenytoin concentration usually occurs within the first 10 days and may decrease phenytoin levels by 15% to 50%.[43] Alcohol can also interfere with folic acid and vitamin B_{12} absorption likely through its effects on the intestinal mucosa.[35]

Pathophysiology

Folic acid is a water-soluble vitamin readily destroyed by cooking or processing. It is necessary for the production of DNA and RNA. It acts as a methyl donor to form methylcobalamin, which is used in the remethylation of homocysteine to methionine. Because humans are unable to synthesize sufficient folate to meet total daily requirements, they depend on dietary sources. Major dietary sources of folate include fresh, green leafy vegetables, citrus fruits, yeast, mushrooms, dairy products, and animal organs such as liver and kidney. Most folate in food is present in the polyglutamate form, which must be broken down into the monoglutamate form prior to absorption in the small intestine. Once absorbed, dietary folate must be converted to the active form tetrahydrofolate through a cobalamin-dependent reaction. In 1997, the United States mandated that grain products be fortified with folic acid in an attempt to increase the dietary intake of folate. This amount of supplementation was chosen to decrease the incidence of neural tube defects without masking occult vitamin B_{12} deficiency.

As a result of grain product fortification, neural tube defect frequency has decreased by 25% to 30%.[44] Although body demands for folate are high because of high rates of RBC synthesis and turnover, the minimum daily requirement is 50 to 100 mcg. In the general population, the recommended daily allowance for

folate is 400 mcg in nonpregnant females, 600 mcg in pregnant females, and 500 mcg in lactating females.[40] Because the body stores about 5 to 10 mg of folate, primarily in the liver, cessation of dietary folate intake can result in deficiency within 3 to 4 months.

Laboratory Findings

It is of paramount importance to rule out vitamin B_{12} deficiency when folate deficiency is suspected. Laboratory changes associated with folate deficiency are similar to those seen in vitamin B_{12} deficiency, except vitamin B_{12} and MMA levels are normal. Serum folate levels decrease to less than 3 ng/mL (7 nmol/L) within a few days of reduced dietary folate intake. The RBC folate level (less than 150 ng/mL [340 nmol/L]) also declines, and levels remain constant throughout the life span of the erythrocyte.[12] If serum or erythrocyte folate levels are borderline, serum homocysteine usually is increased with a folic acid deficiency. If serum MMA levels also are elevated, vitamin B_{12} deficiency must be ruled out given that folate does not participate in MMA metabolism.

TREATMENT

Therapy for folic acid deficiency consists of administration of exogenous folic acid to induce hematologic remission, replace body stores, and resolve signs and symptoms. In most cases, 1 mg daily is sufficient to replace stores, except in cases of deficiency due to malabsorption, in which case doses of 1 to 5 mg daily may be necessary. Parenteral folic acid is available but rarely necessary. Synthetic folic acid is almost completely absorbed by the GI tract and is converted to tetrahydrofolate without cobalamin. Therapy should continue for about 4 months if the underlying cause of the deficiency can be identified and corrected to allow for clearance of all folate-deficient RBCs from the circulation. Examples of foods high in folic acid include beef liver, fortified cereals, lentils, green leafy vegetables, orange juice, and rice. They should be encouraged in the diet. Long-term folate administration may be necessary in chronic conditions associated with increased folate requirements. Low-dose folate therapy (500 mcg daily) can be administered when anticonvulsant drugs produce a megaloblastic anemia so that discontinuation of anticonvulsant therapy may not be necessary. Adverse effects have not been reported with folic acid doses used for replacement therapy. It is considered nontoxic at high doses and is rapidly excreted in the urine.

Although megaloblastic anemia during pregnancy is rare, the most common

cause is folate deficiency. The condition usually manifests as an underweight premature infant and suboptimal health of the mother. Periconceptional folic acid supplementation is recommended to decrease the occurrence and recurrence of neural tube defects, specifically anencephaly and spinal bifida. Folic acid supplementation at a dose of 400 mcg daily is recommended for all women. Women who have previously given birth to offspring with neural tube defects or those with a family history of neural tube defects should ingest 4 mg daily of folic acid.[43–45] Higher levels of folic acid supplementation should not be attained via ingestion of excess multivitamins because of the risk for fat-soluble vitamin toxicity.[45] Prenatal vitamins usually have a higher amount of folic acid as compared with general multivitamins to ensure adequate supplementation is attained. It is essential that women in their childbearing years maintain adequate folic acid intake.

ANEMIA OF INFLAMMATION

Epidemiology

6 AI is a term used to describe both ACD and anemia of critical illness. This term was developed to reflect the inflammatory process resulting in disturbances in iron homeostatis underlying both types of anemia. The onset of anemia of critical illness is rapid, generally over days, and often occurs in a hospital setting due to tissue damage and acute inflammatory changes. ACD has a similar mechanism, but develops over months to years from an underlying chronic condition. Globally, AI is one of the most common forms of anemia, particularly among the elderly; however, detailed statistics are not available due to the complex and multifaceted nature of the disease. ACD is associated with common disease states that may mimic the symptoms of anemia, which causes the diagnosis of ACD to sometimes be overlooked in the outpatient setting. Anemia of critical illness is a common complication in critically ill patients and is found almost universally in this patient population.[46]

Etiology

AI is an anemia traditionally associated with infectious or inflammatory processes, tissue injury, and conditions associated with the release of proinflammatory cytokines. The etiology of AI can be multifactorial and the diagnosis is usually one of exclusion. An in depth history of the illness is

important to help rule out other potential causes of anemia. Although it may be difficult to delineate between IDA and AI, it is important to exclude IDA as the true or competing etiology. Various conditions associated with ACD may predispose patients to blood loss (malignancy, GI blood loss from treatments with aspirin, NSAIDs, or corticosteroids). ACD is often observed in patients with diseases containing an inflammatory component lasting longer than 1-2 months, although it can occur in conditions with a more rapid onset of several weeks, such as pneumonia. Anemia associated with human immunodeficiency virus (HIV), autoimmune conditions, cancer, and heart failure are common forms of AI. The degree of anemia in ACD generally reflects the severity of underlying disease. **Table 118-3** lists common diseases associated with AI.

TABLE 118-3 Diseases Causing Anemia of Inflammation

Common causes
Chronic infections
Tuberculosis
Other chronic lung infections (eg, lung abscess, bronchiectasis)
Human immunodeficiency virus
Subacute bacterial endocarditis
Osteomyelitis
Chronic urinary tract infections
Chronic inflammation
Rheumatoid arthritis
Systemic lupus erythematosus
Inflammatory bowel disease
Inflammatory osteoarthritis
Gout
Other (collagen vascular) diseases
Chronic inflammatory liver diseases
Malignancies
Carcinoma
Lymphoma
Leukemia
Multiple myeloma
Less common causes
Alcoholic liver disease
Congestive heart failure
Thrombophlebitis
Chronic obstructive pulmonary disease
Ischemic heart disease

Factors that may contribute to anemia in critically ill patients include sepsis, frequent blood sampling, surgical blood loss, immune-mediated functional iron

deficiency, decreased production of endogenous EPO, reduced RBC life span, and active bleeding, especially in the GI tract. A combination of these factors often exists, creating a rapid anemic state over days. Additional comorbid factors include coagulopathies and nutritional deficits such as poor oral intake and altered absorption of vitamins and minerals, including iron, vitamin B_{12}, and folate.[47] Deleterious effects of anemia include an increased risk of cardiac-related morbidity and mortality, especially for patients with known cardiovascular disease. Persistent tissue hypoxia can result in cerebral ischemia, myocardial ischemia, multiple organ deterioration, lactic acidosis, and death. Consequences of anemia in critically ill patients may be enhanced because of the increased metabolic demands of critical illness. Weaning anemic patients from mechanical ventilation may be more difficult, as low hemoglobin has been identified as a potential risk factor for poor outcomes.[48,49] This is likely due to hemoglobin's critical role in oxygen delivery; low hemoglobin has been associated with increased work of breathing and cardiac output.[50–52]

Pathophysiology

AI is a hypoproliferative response to stimulation of the cellular immune system by various underlying disease processes. The pathogenesis of AI is multifactorial and is characterized by a blunted EPO response to anemia, an impaired proliferation of erythroid progenitor cells, and a disturbance of iron homeostasis. Increased iron uptake and retention occur within cells. The RBCs have a shortened life span, and the bone marrow's capacity to respond to EPO is inadequate to maintain normal Hb concentration. The cause of this defect is uncertain but appears to involve blocked release of iron from cells in the bone marrow. Iron availability to erythroid progenitor cells then is limited. Various cytokines, such as interleukin-1, interferon-γ, interleukin-6, and tumor necrosis factor released during illness, may inhibit the production or action of EPO or the production of RBCs.[53] These cytokines also upregulate hepcidin, which inhibits iron absorption from the gastrointestinal tract and prevents release from macrophages which are elevated during inflammation. Inflammation also increases the uptake of iron by macrophages reducing free iron for erythropoiesis.[53,54]

Laboratory Findings

ACD tends to be a mild (Hb greater than 9.5 g/dL [95 g/L; 5.90 mmol/L]) or

moderate (Hb greater than 8 g/dL [80 g/L; 4.97 mmol/L]) anemia.[53] No definitive test can confirm the diagnosis of AI. The clinician should maintain a high index of suspicion for any patient with a chronic inflammatory or neoplastic disease. AI may coexist with IDA and folic acid deficiency because many patients with these conditions have poor dietary intake. Examination of the bone marrow, although not routinely performed, reveals an abundance of iron, suggesting that the release mechanism for iron is the central defect. Patients with AI usually have a decreased serum iron level, but unlike patients with IDA, their TIBC is decreased and their serum ferritin level is normal or increased. Ferritin is an acute phase reactant and is often elevated during inflammation, helping to delineate AI from IDA. Transferrin saturation is typically decreased. AI usually is normocytic and normochromic with mildly depressed Hb. Patients with concurrent AI and IDA usually have microcytes and a more severe anemia. **Table 118-4** shows lab values seen in AI and IDA. Erythrocyte survival may be reduced for patients with AI, but a compensatory erythropoietic response does not occur. A low reticulocyte count indicates underproduction of RBCs.[53] As discussed in the IDA section, hepcidin levels are not routinely used for diagnosis but would likely be elevated in a patient with ACD.[55]

TABLE 118-4 Laboratory Value Differences between Anemia of Inflammation and Iron-Deficiency Anemia

	Anemia of Inflammation	Iron-Deficiency Anemia
Iron	↓	↓
Transferrin	↓ or NL	↑
Transferrin saturation	↓	↓
Ferritin	↑ or NL	↓
Soluble transferrin receptor	NL	↑

NL, Normal limits.

TREATMENT

Treatment of AI often depends on the underlying etiology. Resolution of the underlying condition may prompt recovery from anemia. Guidelines exist for management of anemia in patients with cancer or chronic kidney disease (see Chapters 61 and 144). Although the goals of therapy should include treating the underlying disorder and correcting reversible causes of anemia, accomplishment of these goals may not be feasible nor completely reverse hematologic and

physiologic abnormalities. AI is usually mild and does not affect the patient's lifestyle; therefore, additional therapy is unnecessary.

Iron supplementation is effective only if iron deficiency is present and should not be utilized for AI in its absence. During inflammation, oral or parenteral iron therapy may not be as effective. Absorption is impaired because of downregulation of ferroportin and iron diversion mediated by cytokines.[53] Because iron is a required nutrient for proliferating microorganisms, supplementation may also theoretically increase the risk of infections. Therefore, iron therapy should be reserved for patients with an established iron deficiency.[53]

Erythropoiesis-stimulating agents have been used to stimulate erythropoiesis for patients with symptomatic AI since a relative EPO deficiency exists in comparison to the degree of anemia. Similar to endogenous erythropoietin, response to exogenous ESA may be blunted in AI. Two agents are available: recombinant epoetin alfa and recombinant darbepoetin alfa. Although both agents share the same mechanism of action, darbepoetin alfa has a longer half-life and can be administered less frequently. ESAs have FDA approval for the use in AI due to CKD and HIV infection, as well as anemia due to malignancy, but are sometimes use off label for AI due to other underlying causes. The initial dosages of epoetin alfa and darbepoetin alfa are typically 50 to 100 units per kilogram three times per week and 0.45 mcg per kilogram once weekly, respectively. Response to ESAs varies depending on dose and cause of the anemia. Higher doses may be required to overcome hyporesponsiveness. ESA treatment is effective when the marrow has an adequate supply of iron, cobalamin, and folic acid; therefore, these agents should be used in combination with iron therapy.

Iron deficiency can occur in patients treated with ESAs, so close monitoring of iron levels is necessary. Some patients develop "functional" iron deficiency, in which the iron stores are normal but the supply of iron to the erythroid marrow is less than necessary to support the demand for RBC production. Therefore, many practitioners routinely supplement ESA therapy with oral or IV iron therapy. Potential toxicities of exogenous ESA administration include increases in blood pressure, nausea, headache, fever, bone pain, and fatigue. Less common adverse effects include seizures, thrombotic events, and allergic reactions such as rashes and local reactions at the injection site. Tumor progression with these agents can also occur and is discussed in Chapter 144. Further discussion of dosing guidelines and potential adverse outcomes of ESA treatment in populations for which treatment is FDA approved are discussed in Chapters 61 and 144. If ESAs are used, the practitioner must monitor to ensure the patient's Hb does not

exceed 12 g/dL (120 g/L; 7.45 mmol/L) with treatment or that Hb does not rise greater than 1 g/dL (10 g/L; 0.62 mmol/L) every 2 weeks since both of these events have been associated with increased mortality and cardiovascular events.[56] Continued monitoring of Hb should be considered every 2-4 weeks thereafter. If no rise in Hb is seen after 8 weeks of optimal therapy, the patient should be considered EAS nonresponsive and therapy may be discontinued.

Transfusions of packed red blood cells are effective but should be limited to situations in which oxygen transport is inadequate due to concomitant medical problems and symptomatic patients with insufficient time to respond to other methods. RBC transfusions should be strongly considered for severe AI with complications involving bleeding. Liberal use of transfusions for correction of anemia in critical illness has shown to have deleterious effect on patient outcomes.[46] Transfusion risks may include transmission of blood-borne infections, development of autoantibodies, transfusion reactions, and iron overload. Transfusions are typically considered for those with severe anemia (Hb less than 7-8 g/dL [70-80 g/L; 4.34-4.97 mmol/L]).

Patients who are critically ill require the necessary substrates of iron, folic acid, and vitamin B_{12} for RBC production. Parenteral iron is generally preferred in this population because patients often are undergoing enteral therapy or because of concerns regarding inadequate iron absorption. The disadvantage of parenteral therapy is the theoretical risk of infection, hypersensitivity reactions, including anaphylaxis, and hypotension during infusion.

Pharmacologic doses of ESAs have been used to treat the anemia of critical illness. In critically ill patients, the use of ESAs did not show a significant reduction in mortality or length of ICU stay.[57] The few randomized controlled trials which evaluated ESAs in this patient population did not consistently shown a decrease in transfusion requirements in ESA-treated patients.[58] Additionally, their use is often limited by the rapid progression of anemia in this setting and the increased risk of thrombotic events with their use. Further investigation is necessary to determine the effectiveness of ESAs in critically ill patients. These agents are not FDA approved in this setting.

Many critically ill patients receive RBC transfusions despite the inherent risks associated with transfusions. Stored RBCs may not function as well as endogenous blood. Although RBC transfusions may increase oxygen delivery to tissues, cellular oxygen may not increase.[59] Transfusion practices in ICUs vary, and clinicians use different Hb concentrations as thresholds for administering transfusions. The decision to use transfusions must consider the risks, including transmission of infections; volume overload, especially for patients with renal or

heart failure; iron overload; and immune-mediated reactions such as febrile reactions, hemolysis, and anaphylaxis. The clinician also must consider administrative, logistic, and economic factors, including the shortage of blood supplies.

The recognition of hepcidin in the regulation of iron homeostasis and its role in ACD has led to interest in new agents targeted at hepcidin, including direct hepcidin antagonists and other novel agents. Use of these agents awaits further clarification in clinical studies.[55]

ANEMIA IN THE ELDERLY

Epidemiology

7 One of the most common clinical problems observed in the elderly is anemia. Anemia is a prevalent and increasing problem in the elderly, with about 20% of people 85 years and older affected.[60] Elderly patients with the highest incidence of anemia are those who are hospitalized, followed by residents of nursing homes and other institutions, with an estimated rate of 31% to 40%.[61] Although the incidence of anemia is high in the elderly, anemia should not be regarded as an inevitable outcome of aging. The body's set point of Hb does not fall with age. An underlying cause can be identified in about two-thirds of older patients. Undiagnosed and untreated anemia has been associated with adverse outcomes, including all-cause hospitalization, hospitalization secondary to cardiovascular disease, and all-cause mortality.[62] Anemia is an independent predictor of death and major clinical adverse events in elderly patients with stable symptomatic coronary artery disease.[63] Anemia can exacerbate neurologic and cognitive conditions and can adversely influence quality of life and physical performance in the elderly.[64] Anemia may be an indication of serious diseases such as cancer.

Pathophysiology

Aging is associated with a progressive reduction in hematopoietic reserve, which makes individuals more susceptible to developing anemia in times of hematopoietic stress.[65] Dysregulation of proinflammatory cytokines, most notably interleukin-6, may inhibit EPO production or interact with EPO receptors.[66] Although Hb levels may remain normal, the diminished marrow reserve leaves the elderly patient more susceptible to other causes of anemia.

Renal insufficiency, which also is common in elderly patients, may reduce the ability of the kidneys to produce EPO. Older patients often have a normal creatinine level but a diminished glomerular filtration rate. Myelodysplastic syndromes are another common cause of anemia in the elderly, but most anemia cases in the elderly are multifactorial.

Etiology

In the acute care setting, the top three causes of anemia in the elderly are chronic disease (35%), unexplained (17%), and iron deficiency (15%), whereas in community-based outpatient clinics, the most common causes are unexplained (36%), infection (23%), and chronic disease (17%).[67] Another common problem in the elderly is vitamin B_{12} deficiency. The most common causes of clinically overt vitamin B_{12} deficiency are food/cobalamin malabsorption (more than 60% of cases) and pernicious anemia (15%-20% of cases).[68]

One often-overlooked major factor that may contribute to anemia in the older population is nutritional status. Cognitive and functional impairments in the older population may create barriers for patients to obtain and prepare a nutritious diet. Nutritional deficiencies that are not severe enough to affect the hematopoietic system in the younger population may contribute to anemia in the elderly. Edentulous or infirm elderly who may be too ill to prepare their meals are at risk for nutritional folate deficiency. Risk factors for inadequate folate intake in the elderly include low caloric intake, inadequate consumption of fortified cereals, and failure to take a vitamin/mineral supplement. However, unlike cobalamin levels, folate levels often increase rather than decline with age. High folic acid intake can occur if the elderly patient regularly uses a supplement and consumes fortified cereals.[69,70]

Bleeding with resultant iron deficiency in the elderly may be due to carcinoma, peptic ulcer, atrophic gastritis, drug-induced gastritis, postmenopausal vaginal bleeding, or bleeding hemorrhoids. Elderly women have a much lower incidence of IDA compared with younger, menstruating women. Until proven otherwise, iron deficiency in the elderly should be considered a sign of chronic blood loss. Steps should be taken to rule out bleeding, especially from the GI or female reproductive tract. AI is more common in the elderly, as diseases that contribute to AI such as cancer, infection, and rheumatoid arthritis are more prevalent in this population.

Laboratory Findings

For practical purposes, it is best to use usual adult reference values and WHO criteria for laboratory tests in the elderly. Anemia in elderly persons usually is normocytic and mild, with Hb values ranging between 10 and 12 g/dL (100-120 g/L; 6.21-7.45 mmol/L) in most anemic patients.[60] Evaluation of an elderly patient should be similar to strategies described previously for younger adults, perhaps with more emphasis on identifying occult blood loss and vitamin B_{12} deficiency. Vitamin B_{12} deficiency may be present even when plasma levels of vitamin B_{12} are within the normal range, but elevated MMA levels will reveal the deficiency. A refractory macrocytic anemia in the elderly should raise suspicion of a myelodysplastic syndrome.

TREATMENT

Treatment of anemia in the elderly is the same as that described for each type of anemia discussed in this chapter. With IDA it is essential to treat the underlying cause, if known (ie, bleeding), and administer iron supplementation. Lower doses of iron supplementation are often recommended in the elderly (eg, 325 mg of ferrous sulfate once daily) to decrease the incidence of GI adverse effects, which can lead to additional morbidity and poor adherence. Reticulocytosis typically occurs within a week of oral iron initiation. If reticulocyte count increases without a subsequent improvement in anemia, a trial of intravenous iron may be indicated as this may represent poor oral absorption. Vitamin B_{12} can be repleted orally or parenterally. The dosage for oral therapy is 1,000-2,000 mcg daily and has been shown to be as effective as intramuscular injections. As with oral iron therapy, reticulocytosis often occurs within a week of Vitamin B_{12} therapy. Folate deficiency is treated with folic acid supplementation at 1 mg daily. The goal of treatment of AI is resolution of the underlying cause, although curing the underlying chronic illness in elderly patients can be difficult. Routine treatment with ESAs is not currently standard of care for AI in the elderly.

ANEMIA IN PEDIATRIC POPULATIONS

Epidemiology

Globally, anemia is a significant cause of morbidity and mortality in pediatrics with an incidence as high as 47% in pre-school aged children and the

highest concentration of patients found in Africa and Southeast Asia.[71] In the United States, the WHO reported the incidence of anemia in the pediatric population as 6% in 2011.[72] Children ages 12-17 months have the highest risk of developing the condition. IDA accounts for the vast majority of anemia in children and the prevalence of iron deficiency has been reported as high as 20% in patients of low income families, likely due to diet.[73] IDA is a leading cause of infant mortality around the world.[74] Data from NHANES III indicated that 9% of children ages 12 to 36 months in the United States had iron deficiency and 3% had IDA.[75,76] Lack of a normal Hb at birth directly affects nonstorage iron and increases the risk of IDA in the first 3 to 6 months of life. African American or Hispanic American children have a higher incidence of anemia.[77] Requirements for iron absorption peak during puberty. An anemia of prematurity can occur 3 to 12 weeks after birth in infants younger than 32 weeks' gestation and spontaneously resolves by 3 to 6 months. The prevalence of vitamin B_{12} deficiency has been identified as 1 in 1,255 for levels less than 100 pg/mL (74 pmol/L) and 1 in 200 for levels less than 200 pg/mL (148 pmol/L), with the lowest levels in non-Hispanic whites.[78] Additional causes of anemia in pediatrics include "physiologic anemia" in newborns, G6PD deficiency, and thalassemia.

Etiology

The age of the child can yield some clues regarding the etiology of the anemia. From birth to 3 months, a "physiologic anemia" is the most common cause of anemia. At 3 to 6 months, hemoglobinopathy more often encountered as IDA is rare prior to 6 months of age. Iron deficiency becomes the most frequent etiology of anemia in toddler through adolescent years. The optimal amount of nutritional iron and folate required varies among individuals based on life-cycle stages. Two peak periods place children at risk of developing IDA. The first peak occurs during late infancy and early childhood, when children undergo rapid body growth, have low levels of dietary iron, and exhaust stores accumulated during gestation. The second peak occurs during adolescence, which is associated with rapid growth, poor diets, and onset of menses in girls. Some studies suggest that overweight children are at significantly higher risk for IDA. Proposed factors include genetic influences; physical inactivity, leading to decreased myoglobin breakdown and lower amounts of released iron into the blood; and inadequate diet with limited intake of iron-rich foods.[79]

Conditions in the newborn period that can lead to IDA include prematurity, low iron intake, and insufficient maternal iron consumption, particularly during

the third trimester of pregnancy when 60-80% of fetal iron storage occurs. However, there is insufficient data to suggest that treatment of IDA in pregnant women will prevent IDA in newborn. Premature infants are at increased risk for IDA because of their smaller total blood volume, increased blood loss through phlebotomy, and poor GI absorption. Factors leading to unbalanced iron metabolism in infants include insufficient iron intake, early introduction of cow's milk, intolerance of cow's milk, medications, and malabsorption. Dietary deficiency of iron in the first 6 to 12 months of life is less common today because of the increased use of iron supplementation during breast-feeding and use of iron-fortified formulas. Iron deficiency becomes more common when children change to regular diets.

When screening for iron deficiency in young children, a careful dietary history can help identify children at risk. High iron needs and the tendency to eat fewer iron-containing foods contribute to the etiology of iron deficiency during adolescence.

Other causes of microcytic anemia include thalassemia, lead poisoning, and sideroblastic anemia. Use of homeopathic or herbal medications and exposure to paint or certain cooking materials may place children at risk for lead exposure. Normocytic anemias in children include infection with human parvovirus B19 and glucose-6-phosphate dehydrogenase (G6PD) deficiency. In the setting of G6PD deficiency, a thorough review of potential drug and toxin exposure around the onset of anemia will be helpful to determine an offending agent. Macrocytic anemias are caused by deficiencies in vitamin B_{12} and folate, chronic liver disease, hypothyroidism, and myelodysplastic disorders. Folic acid deficiency usually is due to inadequate dietary intake, but human milk and cow's milk provide adequate sources. Folic acid deficiency may be seen in infants and children who primarily consume goat's milk or health food milk alternatives, or in children with insufficient intake of green leafy vegetables. Vitamin B_{12} deficiency due to nutritional reasons is rare but may occur due to a congenital pernicious anemia.

Pathophysiology

In contrast to anemias in adults, which tend to be manifestations of a broader underlying pathology, anemias in the pediatric population are more often due to a primary hematologic abnormality. In newborn infants, "physiologic anemia" is often due to a reduction in EPO production.[80] Erythropoiesis also decreases during this time as a result of increased tissue oxygenation. The nadir of

“physiologic anemia” is usually reached 6 to 9 weeks after birth and is mild in most infants (nadir of approximately Hgb 11 g/dL [110 g/L; 6.83 mmol/L).

Hemoglobinopathy is often suspected in infants with anemia between the ages of three to 6 months as IDA is rare during this period. Potential causes include sickle cell anemia, thalassemia, and G6PD deficiency. Thalassemia is an inherited condition in which the structure of Hgb is compromised leading to anemia of various degrees based on the subtype of thalassemia. This condition is most frequently seen in patients of Mediterranean and Southeast Asian heritage.[73] G6PD deficiency is an X-linked disorder most frequently seen in patients of Asian, Mediterranean, and African descent.[81] The lack of this enzyme reduces the red blood cell’s protection to oxidative injury by limiting the glutathione available. Glutathione in red blood cells rapidly inactivates oxidants preventing cellular injury. G6PD is an important enzyme in the formation of glutathione and a deficiency in this enzyme ultimately leads to hemolysis and anemia after exposure to an oxidant, such as dapsone, primaquine, or fava beans.

IDA should be suspected in microcytic anemia of children after 6 months of age. The amount of iron present at birth depends on gestational length and weight. Iron stores from birth are mostly depleted by 6 months of age. The addition of iron supplements and iron-enriched foods is important to maintain iron levels and prevent the development of IDA.

Laboratory Findings

When evaluating laboratory values for pediatric patients, the clinician must use age- and sex-adjusted norms. It is important to know that many blood samples are capillary samples, such as heel or finger sticks, which may have slightly different results than venous samples. The USPSTF has concluded that evidence is insufficient to recommend for or against routine screening for IDA in asymptomatic low-risk children aged 6 to 12 months. Hb is a sensitive test for iron deficiency, but it has low specificity in childhood anemias. If an abnormality is found, a CBC should be ordered to evaluate MCV and determine whether the anemia is microcytic, normocytic, or macrocytic. A peripheral blood smear and reticulocyte count also may be helpful. The peripheral blood smear can indicate the etiology based on RBC morphology, and the reticulocyte count helps differentiate between decreased RBC production and increased RBC destruction or loss. Other laboratory tests include serum iron, ferritin, TIBC, and transferrin saturation. Laboratory markers of hemolysis, including increased bilirubin, lactate dehydrogenase, and decreased haptoglobin, help to identify

hemolytic anemias, including G6PD deficiency and thalassemia. A G6PD deficiency screening test may be indicated if hemolysis is present. Mild hereditary anemias may produce a mild hypochromic microcytic anemia that can be confused with IDAs. The RDW may be high with iron deficiency and is more likely to be normal with thalassemia. Laboratory features of anemia of prematurity include normocytic normochromic cells, low reticulocyte count, low serum EPO concentrations, and decreased RBC precursors in bone marrow. Laboratory diagnosis of vitamin B_{12} and folate deficiency in children is similar to that of adults.

TREATMENT

Primary prevention of IDA in infants, children, and adolescents is the most appropriate goal because delays in mental and motor development are potentially irreversible. In 2015, the USPSTF published revised recommendations to screen and supplement iron deficiency in the United States, focusing on children and pregnant women. The routine screening of asymptomatic children and pregnant women and routine use of iron supplementation in pregnancy to improve fetal outcomes were found to have insufficient evidence to support.[82] Routine iron supplementation for exclusively breastfed infants at 1 mg/kg/day is recommended by the American Academy of Pediatrics (AAP) beginning at 4 months until appropriate iron-containing foods are introduced. Fair evidence was found that iron supplementation (eg, iron-fortified formula or iron supplements) might improve neurodevelopmental outcomes in children at risk for IDA. Due to the widespread use of iron-enriched formula, additional supplementation is rarely necessary in formula-fed infants.[72]

Interventions likely to prevent anemia include diverse foods with bioavailable forms of iron, food fortification for infants and children, and individual supplementation. Routine screening for iron deficiency in nonpregnant adolescents is recommended only for those with risk factors, which include vegetarian diets, malnutrition, low body weight, chronic illness, or history of heavy menstrual blood loss.

For infants aged 9 to 12 months with a mild microcytic anemia, the most cost-effective treatment is a therapeutic trial of iron. Fe^{2+} sulfate at a dose of 3 to 6 mg/kg/day of elemental iron divided once or twice daily between meals for 4 weeks is recommended. In children who respond, iron should be continued for two more months to replace storage iron pools, along with dietary intervention and patient education.[83] Liquid iron preparations can occasionally stain teeth.

Kids should be advised to brush teeth or rinse out their mouth after administration. Parenteral iron therapy has a limited role and is rarely necessary.

For the macrocytic anemias in children, folate can be administered in a dose of 1 mg daily. However, vitamin B_{12} deficiency due to congenital pernicious anemia requires lifelong vitamin B_{12} supplementation. Dose and frequency should be titrated according to clinical response and laboratory values. No data regarding the use of oral vitamin B_{12} supplementation in children is available.

Treatment of normocytic anemias is based on underlying cause.

EVALUATION OF THERAPEUTIC OUTCOMES

For IDA, a positive response to a trial of oral iron therapy is characterized by a modest reticulocytosis in days, with an increase in Hb starting after about 2 weeks with continued rapid rise in Hb. As the Hb level approaches normal, the rate of increase slows progressively. Hb should reach a normal level after about 2 months of therapy and often sooner.[9] If the patient does not develop reticulocytosis, reevaluation of the diagnosis or iron replacement therapy is necessary. Iron therapy should continue for a period sufficient for complete restoration of iron stores. Serum ferritin concentrations should return to the normal range prior to discontinuation of iron. The time interval required to accomplish this goal varies, although at least 6 to 12 months of therapy usually is warranted.

When large amounts of parenteral iron are administered, by either total dose infusion or multiple intramuscular or IV doses, the patient's iron status should be closely monitored. Patients receiving regular IV iron should be monitored for clinical or laboratory evidence of iron toxicity or overload. Iron overload may be indicated by abnormal hepatic function tests, serum ferritin greater than 800 ng/mL (800 mcg/L [1,800 pmol/L]), or transferrin saturation greater than 50%. Serum ferritin and transferrin saturation should be measured in the first week after larger IV iron doses. Hb and Hct should be measured weekly, and serum iron and ferritin levels should be measured at least monthly.

In the treatment of vitamin B_{12}–deficiency anemia, most patients respond rapidly to vitamin B_{12} therapy. The typical patient will experience an improvement in strength and well-being within a few days of treatment initiation. Reticulocytosis is evident in 3 to 5 days. Hb begins to rise after the first week and should normalize in 1 to 2 months. CBC count and serum cobalamin levels usually are drawn 1 to 2 months after initiation of therapy and

3 to 6 months thereafter for surveillance monitoring. Homocysteine and MMA levels can be repeated 2 to 3 months after initiation of replacement therapy to evaluate for normalization of levels, although levels begin to decrease in 1 to 2 weeks. Neuropsychiatric signs and symptoms can be reversible if treated early. If permanent neurologic damage has resulted, progression should cease with replacement therapy. Slow response to therapy or failure to observe normalization of laboratory results may suggest the presence of an additional abnormality such as iron deficiency, thalassemia trait, infection, malignancy, nonadherence, or misdiagnosis.

In folic acid deficiency anemia, symptomatic improvement, as evidenced by increased alertness and appetite, often occurs early during the course of treatment. Reticulocytosis begins in the first week. Hct begins to rise within 2 weeks and should reach normal levels within 2 months. MCV initially increases because of an increase in reticulocytes but gradually decreases to normal.

One of the earliest responses with ESA use is an increase in blood reticulocyte count, which usually occurs in the first few days. Baseline iron status should be checked before and during treatment, as many patients receiving ESAs require supplemental iron therapy. The optimal form and schedule of iron supplementation are not known. Hb levels should be monitored twice a week until stabilized. Hb should also be monitored twice weekly for 2 to 6 weeks after a dose adjustment.[47] A fall in Hb during ESA therapy may indicate a need for iron supplementation or signal occult blood loss. Baseline and periodic monitoring of iron, TIBC, transferrin saturation, or ferritin levels may be useful in optimizing iron repletion and limiting the need for ESAs. Patients who do not respond to 8 weeks of optimal dosage should not continue taking ESAs. Target Hb levels should be 11 to 12 g/dL (110-120 g/L; 6.83-7.45 mmol/L). Cost is an issue with ESA therapy. Therefore, drug cost must be weighed against the effects on transfusions and hospitalizations.

Responses and monitoring of treatment are similar in the elderly as described for the general adult population earlier in the chapter. If the reticulocyte count rises but the anemia does not improve, inadequate absorption of iron or continued blood loss should be suspected. As with any form of anemia, symptomatic improvement should be evident shortly after starting therapy and Hb/Hct should begin to rise within a few weeks of initiating therapy. A key component of symptom assessment among older adults is the functional domain. Patients should be asked about changes in self-care abilities, mobility, and stamina.

Therapeutic outcomes are assessed in children by monitoring Hb, Hct, and

RBC indices 4 to 8 weeks after initiation of iron therapy. For premature infants, Hb or Hct should be monitored weekly.

Postclass Engaged Learning Activity

Listen to the podcast about a specific patient population:
https://tinyurl.com/wna37x3

ABBREVIATIONS

ACD	anemia of chronic disease
AI	anemia of inflammation
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
EPO	erythropoietin
ESA	erythropoiesis-stimulating agent
Fe^{2+}	ferrous iron
Fe^{3+}	ferric iron
G6PD	glucose-6-phosphate dehydrogenase
Hb	hemoglobin
Hct	hematocrit
HIV	human immunodeficiency virus
IDA	iron-deficiency anemia
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MMA	methylmalonic acid
NHANES	National Health and Nutrition Examination Survey
NSAID	nonsteroidal anti-inflammatory drugs
RBC	red blood cell
RDW	red blood cell distribution width
TIBC	total iron-binding capacity
USPSTF	United States Preventive Services Task Force

WHO World Health Organization

REFERENCES

1. Benoist B, McLean E, Egli M, et al. *Worldwide Prevalence of Anaemia 1993-2005: WHO Global Database on Anaemia*. World Health Organization; 2008. https://www.who.int/vmnis/anaemia/prevalence/en/.
2. Cusick SE, Mei Z, Freedman DS, et al. Unexplained decline in the prevalence of anemia among US children and women between 1988-1994 and 1999-2002. *Am J Clin Nutr*. 2008;88:1611–1617.
3. Nissenson A. Anemia not just an innocent bystander. *Arch Intern Med*. 2003;163:1400–1404.
4. Mozaffarian D. Anemia predicts mortality in severe heart failure: The prospective randomized amlodipine survival evaluation (PRAISE). *J Am Coll Cardiol*. 2003;41:1933–1939.
5. Chaves PHM, Carlson MC, Ferrucci L,, et al. Association between mild anemia and executive function impairment in community-dwelling older women: The Women's Health and Aging Study II. *J Am Geriatr Soc*. 2006;54:1429–1435.
6. Anemia in pregnancy. ACOG Practice Bulletin No. 95. American College of Obst and Gynecologists. *Obstet Gynecol.* 2008; 112 : 201–207.
7. Prchal JT, Thiagarajan P. Erythropoiesis. In: Kaushansky K, Lichtman MA, Beutler E, *et al*, eds. *Williams Hematology*, 8th ed. New York: McGraw-Hill; 2010:453–458.
8. Wians FH, Urban JE, Keffer JH, Kroft SH. Discriminating between iron deficiency anemia and anemia of chronic disease using traditional indices of iron status vs. transferrin receptor concentration. *Am J Clin Pathol*. 2001;115:112–118.
9. Beutler E. Disorders of iron metabolism. In: Kaushansky K, Lichtman MA, Beutler E, *et al*, eds. *Williams Hematology*, 8th ed. New York: McGraw-Hill; 2010:565–606.
10. Beutler E. Destruction of erythrocytes. In: Kaushansky K, Lichtman MA, Beutler E, *et al*, eds. *Williams Hematology*, 8th ed. New York: McGraw-Hill; 2010:449–454.
11. Galloway M, Rushworth L. Red cell or serum folate? Results from the National Pathology Alliance benchmarking review. *J Clin Pathol*.

2003;56:924–926.

12. Snow CF. Laboratory diagnosis of vitamin B_{12} and folate deficiency. *Arch Intern Med*. 1999;159:1289–1298.
13. Green R. Folate, cobalamin, and megaloblastic anemias. In: Kaushansky K, Lichtman MA, Beutler E, *et al*, eds. *Williams Hematology*, 8th ed. New York: McGraw-Hill; 2010:533–564.
14. Dharmarajan TS, Norkus EP. Approaches to vitamin B_{12} deficiency. Early treatment may prevent devastating complications. *Postgrad Med*. 2001;110:99–105.
15. Ganz T. Hepcidin—A regulator of intestinal iron absorption and iron recycling by macrophages. *Best Pract Res Clin Haematol*. 2005;18:171–182.
16. Goodnough LT, Nemeth E, Gan T. Detection, evaluation, and management of iron restricted erythropoiesis. *Blood*. 2010;116:4754–4761.
17. Camaschella C. Iron-deficiency anemia. *N Engl J Med*. 2015;372: 1832–1843.
18. Killip S, Bennett J, Chambers M. Iron deficiency anemia. *Am Fam Physician*. 2007;75:671–678.
19. Hershko C, Ianculovich M, Souroujon M. A hematologist's view of unexplained iron deficiency anemia in males: Impact of *Helicobacter pylori* eradication. *Blood Cells Mol Dis*. 2007;38:45–53.
20. U.S. Preventive Services Task Force (USPSTF). Screening for Iron Deficiency Anemia—Including Iron Supplementation for Children and Pregnant Women. Rockville, MD: Agency for Healthcare Research and Quality (AHRQ); 2006.
21. Moretti D, Goede JS, et al. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. Blood. 2015;126:1981–1989. doi.10.1182/blood-2015-05-642223.26289639.
22. Stoffel NU, Cercamondi CI, Brittenham G,et al. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials. Lancet Haematol. 2017;4(11):e524–e533.doi:10.1016/S2352-3026(17)30182-5.29032957.
23. Gasche C, Berstad A, Befrits R, et al. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel

diseases. *Inflamm Bowel Dis*. 2007;13:1545–1553.

24. Faich G, Strobos J. Sodium Fe^{3+} gluconate complex in sucrose: Safer IV iron therapy than iron dextrans. *Am J Kidney Dis*. 1999;33:464–470.
25. Chandler G, Harchowal J, Macdougall IC. Intravenous iron sucrose: Establishing a safe dose. *Am J Kidney Dis*. 2001;38:988–991.
26. Silverstein SB, Gilreath JA, Rodgers GM. Intravenous iron therapy: A summary of treatment options and review of guidelines. *J Pharm Practice*. 2008;21:431–443.
27. Munoz M, Garcia-Erce JA, Remacha AF. Disorders of iron metabolism: Part II: Iron deficiency and iron overload. *J Clin Pathol*. 2011;64:287–296.
28. Ferrlecit [package insert]. Morristown, NJ: Watson Pharma; 2015.
29. Venofer [package insert]. Shirley, NY: American Regent; 2015.
30. Feraheme [package insert]. Lexington, MA: AMAG Pharmaceuticals; 2015.
31. Injectafer [package insert]. Shirley, NY: American Regent; 2013.
32. Avni T, Bieber A, Grossman A, et al. The safety of intravenous iron preparations: Systematic review and meta-analysis. *Mayo Clin Proc*. 2015;90:12–23.
33. Oh RC, Brown DL. Vitamin B_{12} deficiency. *Am Fam Physician*. 2003;67:979–986, 993–994.
34. Kaptan K, Beyan C, Ural AU, et al. *Helicobacter pylori*—Is it a novel causative agent in vitamin B_{12} deficiency? *Arch Intern Med*. 2000;160:1349–1353.
35. Hesdorffer CS, Longo DL. Drug-induced megaloblastic anemia. *NEJM*. 2015;373:1649–58.
36. Hoffbrand AV. Megaloblastic Anemias. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds.*Harrison's Principles of Internal Medicine*. 18th ed. New York: McGraw-Hill; 2012:chap 105.
37. Aronow WS. Homocysteine. The association with atherosclerotic vascular disease in older persons. *Geriatrics*. 2003;58:22–28.
38. Green R. Indicators for assessing folate and vitamin B-12 status and for monitoring the efficacy of intervention strategies. *Am J Clin Nutr*. 2011;94(Suppl):666S–672S.
39. Vidal-Alaball J, Butler CC, Cannings-John R, et al. Oral vitamin B_{12}

versus intramuscular vitamin B_{12} for vitamin B_{12} deficiency. *Cochrane Database Syst Rev*. 2005;3:CD004655.

40. Cravens DD, Nashelsky J, Oh RC. How do we evaluate a marginally low B_{12} level? *J Fam Pract*. 2007;56:62–63.
41. Solomon LR. Oral vitamin B_{12} therapy: A cautionary note. *Blood*. 2004;103:2863.
42. Lane LA, Rojas-Fernandez C. Treatment of vitamin B_{12}-deficiency anemia: Oral versus parenteral therapy. *Ann Pharmacother*. 2002;36:1268–1272.
43. Yerby MS. Clinical care of pregnant women with epilepsy: Neural tube defects and folic acid supplementation. *Epilepsia*. 2003;44(Suppl 3):33–40.
44. Pitkin RM. Folate and neural tube defects. *Am J Clin Nutr*. 2007;85:285S–288S.
45. American College of Obstetricians and Gynecologists (ACOG). Neural Tube Defects. ACOG Practice Bulletin No. 44. Washington, DC: American College of Obstetricians and Gynecologists; 2003.
46. Corwin HL, Gettinger A, Pearl RG, et al. The CRIT Study: Anemia and blood transfusion in the critically ill—Current clinical practice in the United States. *Crit Care Med*. 2004;32:39–52.
47. Rodriguez RM, Corwin HL, Gettinger A, et al. Nutritional deficiencies and blunted erythropoietin response as cause of anemia of critical illness. *J Crit Care*. 2001;16:36–41.
48. Silver MR. Anemia in the long-term ventilator-dependent patient with respiratory failure. *Chest*. 2005;128(Suppl):568S–575S.
49. Lai YC, Ruan SY, Huang CT, Kuo PH, Yu CJ. Hemoglobin levels and weaning outcome of mechanical ventilation in difficult-to-wean patients: A retrospective cohort study. PLoS One. 2013;8:e73743. 10.1371/journal.pone.0073743.24015310.
50. Schönhofer B, Wenzel M, Geibel M, Köhler D. Blood transfusion and lung function in chronically anemic patients with severe chronic obstructive pulmonary disease. Crit Care Med. 1998;26:1824–1828.
51. Leach RM, Treacher DF. The pulmonary physician in critical care * 2: oxygen delivery and consumption in the critically ill. Thorax. 2002;57:170–177.
52. Ouellette DR. The impact of anemia in patients with respiratory failure.

Chest. 2005;128(5 Suppl 2):576S–582S.doi:10.1378/chest.128.5_suppl_2.576S.16306056.

53. Weiss GW, Goodnough LT. Anemia of chronic disease. *N Engl J Med*. 2005;352:1011–1023.
54. Adamson J. The anemia of inflammation/malignancy: Mechanisms and management. *Hematol Am Soc Hematol Educ Program*. 2008;159–165.
55. Poggiali E, Migone De Amicis M, Motta I. Anemia of chronic disease: A unique defect of iron recycling for many different chronic diseases. *Eur J Intern Med*. 2014;25:12–17.
56. Procrit [package insert]. Thousand Oaks, CA: Amgen, 2009.
57. Zarychanski R, Turgeon AF, McIntyre L, Fergusson DA. Erythropoietin-receptor agonists in critically ill patients: A meta-analysis of randomized controlled trials. CMAJ. 2007;177:725–734. doi.10.1503/cmaj.071055.17823140.
58. Rudis M, Jacobi J, Hassan E, et al. Managing anemia in the critically ill patient. *Pharmacotherapy*. 2004;24:229–247.
59. Hébert PC, Wells G, Martin C, et al. Do blood transfusions improve outcomes related to mechanical ventilation? *Chest*. 2001;119:1850–1857.
60. Guralnik JM, Eisenstaedt RS, Ferrucci L, et al. Prevalence of anemia in person 65 years and older in the United States: Evidence for a high rate of unexplained anemia. *Blood*. 2004;104:2263–2268.
61. Carmel R. Anemia and aging: An overview of clinical, diagnostic, and biological issues. *Blood Rev*. 2001;15:9–18.
62. Culleton BF, Manns BJ, Zhang J, et al. Impact of anemia on hospitalization and mortality in older adults. *Blood*. 2006;107:3841–3846.
63. Muzzarelli S, Pfisterer M, TIME Investigators. Anemia as independent predictor of major events in elderly patients with chronic angina. *Am Heart J*. 2006;152:991–996.
64. Woodman R, Ferrucci L, Guralnik J. Anemia in older adults. *Curr Opin Hematol*. 2005;12:123–128.
65. Balducci L, Hardy CL, Lyman GH. Hematopoietic growth factors in the older cancer patient. *Curr Opin Hematol*. 2001;8:170–187.
66. Eisenstaedt R, Penninx BW, Woodman RC. Anemia in the elderly: Current understanding and emerging concepts. *Blood Rev*. 2006;20:213–226.
67. Balducci L. Epidemiology of anemia in the elderly: Information on diagnostic evaluation. *J Am Geriatr Soc*. 2003;51(Suppl):S2–S9.

68. Andres E, Loukili N, Noel E, et al. Vitamin B_{12} (cobalamin) deficiency in elderly patients. *CMAJ*. 2004;171:251–259.
69. Mulligan JE, Greene GW, Caldwell M. Sources of folate and serum folate levels in older adults. *J Am Diet Assoc*. 2007;107:495–499.
70. Ford ES, Bowman BA. Serum and red blood cell folate concentrations, race, and education: Findings from the third National Health and Nutrition Examination Survey. *Am J Clin Nutr*. 1999;69:476–481.
71. McLean E, Cogswell M, Egli I, Wojdyla D, de Benoist B. Worldwide prevalence of anaemia, WHO Vitamin and Mineral Nutrition Information System, 1993-2005. Public Health Nutr. 2009;12:444–454. doi.10.1017/S1368980008002401.18498676.
72. Wang M. Iron deficiency and other types of anemia in infants and children. Am Fam Physician. 2016;93:270–278. 26926814.
73. Khan L. Anemia in childhood. Pediatr Ann. 2018;47(2):e42–e47.doi:10.3928/19382359-20180129-01.29446792.
74. Milman N. Iron prophylaxis in pregnancy—General or individual and in which dose? *Ann Hematol*. 2006;85:821–828.
75. Recommendations to prevent and control iron deficiency in the United States. *Morb Mortal Wkly Rep*. 1998;47:1–36.
76. Moy RJ. Prevalence, consequences and prevention of childhood nutritional iron. *Clin Lab Haematol*. 2006;28:291–298.
77. Coyer S. Anemia: Diagnosis and management. *J Pediatr Health Care*. 2005;19:380–385.
78. Wright JD, Bialostosky K, Gunter EW, et al. Blood folate and vitamin B_{12}: United States, 1988-94. *Vital Health Stat*. 1998;11:1–78.
79. Nead KG, Halterman JS, Kaczorowski JM, et al. Overweight children and adolescents: A risk group for iron deficiency. *Pediatrics*. 2004;114:104–108.
80. Palis J, Segel GB. Hematology of the fetus and newborn. In: Prchal JT, Kaushansky K, Lichtman MA, Kipps TJ, Seligsohn U,, eds.*Williams Hematology*. 8th ed. New York: McGraw-Hill; 2010.
81. Nkhoma ET, Poole C, Vannappagari V, Hall SA, Beutler E. The global prevalence of glucose-6-phosphate dehydrogenase deficiency: A systematic review and meta-analysis. Blood Cells Mol Dis. 2009;42(3):267–278.doi:10.1016/j.bcmd.2008.12.005.19233695.
82. Siu AL. Screening for iron deficiency anemia and iron supplementation in

pregnant women to improve maternal health and birth outcomes: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2015;163(7):529–536.doi:10.7326/M15-1707.26344176.

83. Kazal LA. Prevention of iron deficiency in infants and toddlers. *Am Fam Physician*. 2002;66:1217–1224.

119

Coagulation Disorders

Heidi Trinkman, Timothy L. McCavit, and Lauren Duran

KEY CONCEPTS

1. Hemophilia is an inherited bleeding disorder resulting from a congenital deficiency in factor VIII or IX.
2. The goal of therapy for hemophilia is to prevent bleeding episodes and their resulting long-term complications, and to arrest bleeding if it occurs.
3. Recombinant factor concentrates usually are the first-line treatment of hemophilia because they have the lowest risk of infection.
4. Inhibitor formation is the most significant treatment complication in hemophilia and is associated with significant morbidity and decreased quality of life.
5. Recombinant factor VIIa is effective for the treatment of acute bleeds in patients with hemophilia A or B who have developed inhibitors.
6. The goal of therapy for von Willebrand disease (vWD) is to increase von Willebrand factor (vWF) and factor VIII levels to prevent bleeding during surgery or arrest bleeding when it occurs.
7. Factor VIII concentrates that contain vWF are the agents of choice for treatment of type 3 vWD and some type 2 vWD, and for serious bleeding in type 1 vWD.
8. Desmopressin acetate often is effective for the treatment of type 1 vWD. It also may be effective for the treatment of some forms of type 2 vWD in addition to mild-to-moderate hemophilia A.

Preclass Engaged Learning Activity

Create a Venn diagram to compare hemophilia A and B. Within the diagram,

be sure to include pertinent disease state information such as clinical manifestations, incidence, and recommended treatment. Name specific short- and long-acting products which may be used in each type, as well as treatment modalities which may be common to both.

INTRODUCTION

The coagulation system is intricately balanced and designed to stop bleeding at the site of vascular injury through complex interactions between the vascular endothelium, platelets, procoagulant proteins, anticoagulant proteins, and fibrinolytic proteins. Hemostasis stops bleeding at the site of vascular injury through the formation of an impermeable platelet and fibrin plug. Three key mechanisms facilitate hemostasis including vascular constriction, primary platelet plug formation (primary hemostasis), and clot propagation through fibrin formation (secondary hemostasis). Derangements in this system can lead to either bleeding or thrombosis. Bleeding disorders are the result of a coagulation factor defect, a quantitative or qualitative platelet defect or enhanced fibrinolytic activity.

COAGULATION FACTORS

Secondary hemostasis facilitates propagation and stabilization of the initial platelet plug formed in primary hemostasis through the formation of fibrin on the activated platelet surface. This step is initiated via the tissue factor pathway and is vital for adequate hemostasis. Coagulation factors circulate as inactive precursors (zymogens). Activation of these coagulation proteins leads to a cascading series of proteolytic reactions. At each step, a clotting factor undergoes limited proteolysis and becomes an active protease (designated by a lowercase “a,” as in Xa).

The coagulation factors can be divided into three groups based on biochemical properties: vitamin K–dependent factors (II, VII, IX, and X), contact activation factors (XI and XII, prekallikrein, and high-molecular-weight kininogen), and thrombin-sensitive factors (V, VIII, XIII, and fibrinogen). Biologic half-life and blood product source varies by coagulation factor.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The diagnosis of coagulation disorders is established from a detailed clinical history, physical examination, and laboratory test results. The clinical history should ascertain if there is a family history of bleeding or known bleeding disorders. Laboratory testing can distinguish bleeding disorders caused by defects in the coagulation pathways, fibrinolytic pathways, or alterations in the number or function of platelets. **Table 119-1** describes common coagulation tests.

TABLE 119-1 Laboratory Procedures

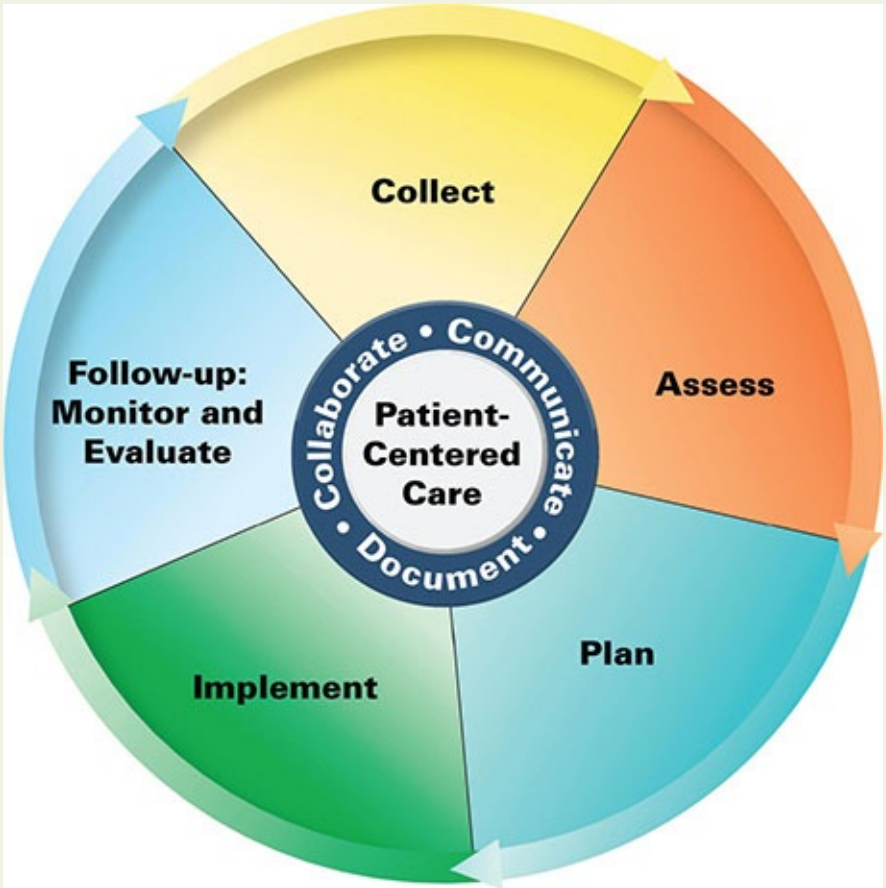
Procedure	Identifies	Possible Cause of Abnormal Value	Clinical Manifestations
Prothrombin time (PT)	Factors I, II, V, VII, X	Newborn Vitamin K deficiency Inherited factor deficiencies* Warfarin therapy Liver disease Lupus anticoagulant (rare) Afibrinogenemia Dysfibrinogenemia	Bleeding following surgery, trauma, etc. Easy bruising
Activated partial thromboplastin time (aPTT)	Factors I, II, V, VIII, IX, X	Inherited factor deficiencies* Lupus anticoagulant Heparin therapy Liver disease Afibrinogenemia Dysfibrinogenemia	Joint and muscle bleeding Bleeding after surgery, trauma, etc.
	HMWK, prekallikrein		No bleeding manifestations
	Factor XII		Increased incidence of thrombotic disease possible with severe factor XII deficiency
	Factor XI		Variable bleeding tendency Bleeding following surgery, trauma, etc.
Thrombin time (TT)	Fibrinogen Inhibitors of fibrin aggregation	Afibrinogenemia Dysfibrinogenemia Heparin therapy	Lifelong hemorrhagic disease Variable clinical symptoms from asymptomatic to either a bleeding diathesis or prothrombotic
Platelet count	Thrombocytopenia	Quantitative platelet disorder, type 2B von Willebrand disease, immune thrombocytopenia, other cause of thrombocytopenia	Mucocutaneous bleeding
Platelet function analyzer	Platelet function	Qualitative platelet defects, von Willebrand disease, antiplatelet therapy Also prolonged in anemia and thrombocytopenia *Insensitive to mild platelet defects and has fallen out of favor as a screening test*	Mucocutaneous bleeding
Platelet aggregation	Gold standard to assess platelet function	Qualitative platelet defects, antiplatelet medications	Mucocutaneous bleeding
Euglobulin clot lysis time (ECLT)	Fibrinolytic defect	A decreased ECLT indicates hyperfibrinolysis, which indicates an abnormality in the fibrinolytic pathway including plasminogen activator inhibitor 1 deficiency, α_2-plasminogen inhibitor deficiency Hypofibrinogenemia	Bleeding after trauma or surgical procedures especially in oral and urogenital areas

*Bleeding manifestations depend on factor levels.

HMWK, high-molecular-weight kininogen.

HEMOPHILIA

1 Hemophilia is a bleeding disorder that results from a congenital deficiency in a plasma coagulation protein. Hemophilia A (classic hemophilia) is caused by a deficiency of factor VIII and hemophilia B (Christmas disease) is caused by a deficiency of factor IX. Hemophilia affects about 400,000 males worldwide.[1] The incidence of hemophilia A is about 1 in 5,000 male births and hemophilia B occurs in 1 in 30,000 male births.[2] Hemophilia A constitutes 80% to 85% of all patients with hemophilia with the other 15% to 20% being hemophilia B.[1] The incidence of hemophilia is not affected by race.



Patient Care Process for Coagulation Disorders

Collect

- Patient characteristics (age, sex, etc.)

- Patient medical history (including family history and bleeding history)
- Patient surgical history (including dental procedures)
- Social history (level of activity, extracurricular activities)
- Medication list, especially aspirin, NSAIDs, other antiplatelet medications and anticoagulants
- Objective data
    - Vital signs (blood pressure, heart rate, respiratory rate, etc.)
    - Labs vary dependent on likely cause: prothrombin time (PT), activated partial thromboplastin time (aPTT), platelets, hemoglobin (Hgb), factor VIII level, factor IX level, von Willebrand factor antigen and activity

Assess

- Presence of active bleeding (see section "Clinical Manifestations and Diagnosis" and Table 119-1)
- Presence of common clinical manifestations in bleeding disorders (easy bruising, bleeding after surgery, mucocutaneous bleeding, prolonged menses, etc. and Table 119-1).
- Factor level and the need for prophylactic management.

Plan*

- Determine drug therapy regimen (dose, route, frequency, and duration)
    - Appropriate factor therapy (Table 119-2, 119-3)
    - Rescue and/or as-needed therapy (factor, desmopressin, aminocaproic acid, tranexamic acid, etc.)
- Monitoring parameters (signs/symptoms of bleeding, frequency of bleeding episodes)
- Patient education/counseling (control of bleeding episodes, administration of drug therapy, when to seek medical attention)
- Continued care at a Hemophilia Treatment Center (or comparable clinic with a comprehensive care team)

Implement

- Provide education and reinforcement of the treatment plan

- Improve adherence through motivational interviewing and open discussions about patient care and the treatment plan
- Schedule regular clinic appointments to assess adherence, bleeding episodes, and to tailor patient therapy

Follow-up: Monitor and Evaluate

- Control and resolution of bleeding signs and symptoms
- Number of bleeding episodes (improvement since beginning care, need for adjustment in the treatment plan)
- Factor level activity (tailor factor doses to patient-specific levels)
- Adherence to the treatment plan (prophylactic and as-needed therapy, seeking medical attention)

**Collaborate with patient, caregivers, and other healthcare professionals.*

About one-third of patients with hemophilia have a negative family history, presumably representing a spontaneous mutation.[1] Both hemophilia A and hemophilia B are recessive X-linked diseases, which means that the defective gene is located on the X chromosome. The disease primarily affects only males while females are carriers. Since affected males have the abnormal allele on their X chromosome and no matching allele on their Y chromosome, their sons would be normal (assuming the mother is not a carrier) and their daughters would be obligatory carriers. Female carriers have one normal allele and, therefore, do not usually have a bleeding tendency, although female carriers have lower factor VIII levels than females who are not carriers.[3] Sons of a female carrier and a normal male have a 50% chance of having hemophilia and daughters have a 50% chance of being carriers. Thus, there is a “skipped generation” mode of inheritance in which the female carriers do not express the disease but can pass it on to the next male generation. Hemophilia has been observed in a small number of females. It can occur if both factor VIII and IX genes are defective or if a female patient has only one X chromosome as in Turner syndrome.[4]

In 1984, researchers isolated and cloned the human factor VIII gene. It is a large gene, consisting of 186 kilobases (kb).[5] More than 2,000 unique mutations in the factor VIII gene, including point mutations, deletions, and insertions, have been reported.[6] Deletions and nonsense mutations are often associated with the more severe forms of factor VIII deficiency because functional factor VIII is not produced. In 1993, researchers identified an inversion in the factor VIII gene at

intron 22 that accounts for almost 50% of severe hemophilia A gene abnormalities.[7] That discovery has greatly simplified carrier detection and prenatal diagnosis in families with this gene mutation.

The factor IX gene, cloned and sequenced in 1982, consists of only 34 kb and is significantly smaller than the factor VIII gene.[5] Unlike the factor VIII gene in patients with severe hemophilia A, the factor IX gene in patients with hemophilia B has no predominant mutation. Direct gene mutation analysis is simpler in hemophilia B because of the smaller gene size, and to date more than 1,000 different mutations have been reported.[8] Most of these mutations are single base-pair substitutions. About 3% of factor IX gene mutations are deletions or complex rearrangements, and the presence of these mutations is associated with a severe phenotype.[7]

Hemophilia B Leyden is a rare variant in which factor IX levels initially are low but rise at puberty.[7] The mechanism of this disorder is controversial. Some propose that the binding of the androgen receptor and other transcription factors are responsible. Other molecular mechanisms for age-related gene regulation have been recently discovered and implicated in factor IX Leyden.[9] Identification of this genotype is clinically important because it confers a better prognosis.

Clinical Presentation and Diagnosis

The characteristic bleeding manifestations of hemophilia include palpable ecchymosis, bleeding into joint spaces (hemarthroses), muscle hemorrhages, and excessive bleeding after surgery or trauma. The severity of clinical bleeding generally correlates with the degree of deficiency of either factor VIII or factor IX. Factor VIII and factor IX activity levels are measured in units per milliliter, with 1 unit/mL representing 100% of the factor found in 1 mL of normal plasma.[2,10] Normal plasma levels range from 0.5 to 1.5 units/mL (50%-150%). Patients with less than 0.01 units/mL (1%) of either factor are classified as having severe hemophilia, those with between 0.01 and 0.05 units/mL (1%-5%) are moderate, and those with between 0.05 and 0.4 units/mL (5%-40%) have mild hemophilia.

Patients with severe disease experience frequent spontaneous hemorrhages, while those with moderate disease have excessive bleeding following mild trauma and rarely experience spontaneous hemarthroses. Patients with mild hemophilia may have few symptoms that their condition can be undetected for many years and they usually have excessive bleeding only after significant

trauma or surgery. Disease severity does not always correlate with disease manifestations. Those with severe disease (<1% factor activity) may occasionally not display a severe phenotype, while some with milder forms of the disease may have more severe bleeding. Prolonged bleeding after circumcision is a common presenting sign. Most patients will have some manifestation of the disease sometime after their first year of life when they begin to walk and increase their risk of bleeding due to falling.[1,7]

CLINICAL PRESENTATION Hemophilia

Signs and Symptoms

- Ecchymoses (palpable/raised)
- Hemarthroses (especially knee, ankle, and elbow)
- Joint pain
- Joint swelling and erythema
- Decreased range of motion
- Muscle hemorrhage
- Swelling at the site of muscle bleeding
- Pain with motion of affected muscle
- Signs of nerve compression
- Significant anemia from an iliopsoas or thigh bleed
- Oral bleeding with dental extractions or trauma
- Hematuria
- Intracranial hemorrhage (spontaneous or following trauma)
- Excessive bleeding with surgery

Laboratory Testing

- Prolonged activated partial thromboplastin time (aPTT)
- Decreased factor VIII or factor IX level
- Normal prothrombin time (PT)
- Normal platelet count
- Normal von Willebrand factor antigen and activity

- Normal bleeding time

The diagnosis of hemophilia should be considered in any male with unusual bleeding. A family history of bleeding is helpful in the diagnosis but is absent in up to 50% of patients with about one-third representing spontaneous mutations and the remaining secondary to unrecognized family history.[5] Brothers of patients with hemophilia should be screened; sisters should consider undergoing carrier testing. Laboratory testing in patients with hemophilia will usually reveal an isolated prolonged partial thromboplastin time (PTT) and they will have a decreased factor VIII or factor IX level.

Patients with severe hemophilia A should be tested for the common factor VIII gene inversions. In patients with severe hemophilia A who lack an inversion mutation or in patients with moderate or mild hemophilia A, the gene can be sequenced to determine the exact mutation if needed. The exact mutation can determine carrier status but is not done routinely because it is very costly and does not change therapy. Techniques to determine the genetic mutation in patients with hemophilia B are similar, but no predominant mutation like the factor VIII inversion has been found. The smaller size of the factor IX gene facilitates direct DNA mutational analysis.[7]

Hemophilia can be diagnosed prenatally, if desired, by chorionic villus sampling in gestational weeks 9 to 14 or by amniocentesis after 15 to 17 weeks of gestation.[1,11] These are invasive procedures with a 0.5% to 1% chance for pregnancy loss so it is not routinely done.[11] A new noninvasive method uses cell-free fetal DNA in maternal circulation to determine the sex of the fetus; more invasive testing is required for a male fetus.[11] This method was used to successfully identify hemophilia mutations but is still experimental and requires further validation.[12]

TREATMENT: HEMOPHILIA

The comprehensive care of hemophilia requires an interprofessional team approach. The patient is best managed in specialized centers with trained personnel and appropriate laboratory, radiologic, and pharmaceutical services.[1] The healthcare team should include hematologists, orthopedic surgeons, nurses, physical therapists, dentists, genetic counselors, psychologists, pharmacists, case managers, and social workers who have experience in caring for patients with bleeding disorders. The goal for comprehensive hemophilia care is to prevent

bleeding episodes and their long-term sequelae so that patients with hemophilia can live full, active, and productive lives.

2 Intravenous factor replacement therapy for the treatment or prevention of bleeding is the mainstay of treatment for hemophilia. Parents of children with hemophilia usually learn how to infuse factor concentrate to facilitate home treatment peripherally or via central venous access device. Older children and adult patients learn self-administration. Home healthcare nursing support may be helpful, particularly for the youngest patients in whom venous access may be difficult. In the setting of poor venous access, venous access devices may be indicated. Administration of factor at home is more convenient for families and allows for earlier treatment of acute bleeding episodes. However, serious bleeding episodes always require evaluation by medical personnel.

Patients with hemophilia should receive routine immunizations, including immunization against hepatitis B. Hepatitis A vaccine is also recommended for patients with hemophilia because of the risk (albeit small) of transmitting the causative agent through factor concentrates. The administration of vaccines is preferred subcutaneously in patients with severe disease.[1,13] If intramuscular administration is required, the use of a small-gauge needle with cold compresses and pressure to the site can prevent excessive bleeding.

A few special considerations apply to the perinatal care of male infants of hemophilia carriers. Intracranial or extracranial hemorrhage has been estimated to occur in 1% to 2% of newborns with hemophilia.[7] Vacuum extraction and forceps delivery increase the risk of cranial bleeding. Elective cesarean section has not been shown to prevent intracranial bleeding. The optimal mode of delivery or the use of prophylactic factor replacement in male infants of hemophilia carriers is controversial.[1] Circumcision should be postponed until a diagnosis of hemophilia is excluded. Factor levels can be assayed from cord blood samples or from peripheral venipuncture. Arterial puncture should be avoided because of the risk of hematoma formation. If an infant has hemophilia, many clinicians recommend a screening head ultrasound to rule out an intracranial hemorrhage prior to discharge from the nursery.

History

Therapy for hemophilia has undergone dramatic advances over the past few decades. Fifty years ago, the administration of fresh-frozen plasma was the only available treatment. The introduction of cryoprecipitate in the early 1960s allowed more specific therapy for hemophilia A.[14] Intermediate-purity factor

VIII and IX plasma-derived concentrates became available in the 1970s.[14] Plasma-derived factor concentrates are made from the donations of thousands of people. Contamination of plasma pools with hepatitis B, hepatitis C, and the human immunodeficiency virus (HIV) during the late 1970s and early 1980s resulted in transmission to a large portion of patients with hemophilia. Since the mid-1980s, plasma-derived concentrates have been manufactured with a variety of virus- inactivating techniques, including dry heat, pasteurization, and treatment with chemicals (eg, solvent detergent mixtures).[5] Since 1986, no transmission of HIV through factor concentrates to patients with hemophilia in the United States has been reported.[5] Protein purification techniques, introduced in the 1990s, led to the production of high-purity plasma-derived concentrates with increased amounts of factor VIII or factor IX relative to the product's total protein content. Recombinant factor VIII and then factor IX also became available in the 1990s.[14] Significant improvements have been made with recombinant products in limiting the risk of infectious transmission from albumin used to stabilize some of the products. Like plasma-derived products, these products use viral inactivation steps. With each subsequent generation of recombinant factor VIII products, the use of human proteins has been reduced.[14]

Significant advancements have taken place in the development of long-acting factor VIII and IX products some of which are FDA approved and commercially available. Methods for prolonging the half-life of these products include pegylation and Fc fusion.[15–17] Pegylation is thought to increase half-life by protecting the factor from receptor-mediated uptake and enzymatic catabolism. It reduces renal clearance and levels of neutralizing antibodies due to steric hindrance.[14] Protein fusion has also been a successful approach to prolonging the half-life of factor products. This method fuses factor VIII or IX to another human protein with a long circulatory half-life such as albumin or IgG. These fused proteins then bind to the neonatal Fc receptor (FcRn) present in the acidified endosomes of the endothelial cells. This binding protects the factor fusion product from targeted lysosomal degradation and facilitates recycling of the FcRn ligands at the endothelial surface resulting in a prolonged systemic half-life of the factor.[18,19]

Hemophilia A

Table 119-2 summarizes many of the factor VIII products currently available in the United States. Most patients are treated with high-purity products, which generally have the lowest risk of transmitting infectious disease and are therefore

recommended as first-line agents.[1] Recombinant products, when available, are generally used rather than plasma-derived products.

TABLE 119-2 Factor Concentrates

Plasma Derived	Recombinant	Extended Half-Life (EHL)

• **Factor VIII**
  • Hemofil M
  • Koate DVI
  • Monoclate P
• **Factor VIII + vWF**
  • Alphanate
  • Humate P
  • Wilate
• **Factor IX**
  • AlphaNine
  • Mononine
• **PCC**
  • Bebulin
  • Kcentra
  • Profilnine
• **aPCC**
  • FEIBA
	• **Factor VIII**
	  • Advate
	  • Afstyla
	  • Helixate
	  • Kogenate
	  • Kovaltry
	  • Obizur (PS)
	  • Recombinate
	  • Nuwiq
	  • NovoEight (BDD)
	  • Xyntha (BDD)
	• **Factor IX**
	  • BeneFIX
	  • Ixinity
	  • Rixubis
	• **Factor VII**
	  • NovoSeven
	• **vWF**
	  • Vonvendi
		• **Factor VIII**
		  • Adynovate (PEG)
		  • Jivi (PEG)
		  • Eloctate (Fc-IgG)
		• **Factor IX**
		  • Alprolix (Fc-IgG)
		  • Idelvion (FP)
		  • Rebinyn (PEG)

aPCC, activated prothrombin complex concentrate; PCC, prothrombin complex concentrate; vWF, von Willebrand factor; PS, porcine sequenced; BDD, B-domain deleted; PEG, pegylated; Fc, Fc fusion protein IgG; FP fusion protein–albumin.

Recombinant Factor VIII

3 Recombinant factor VIII is produced with recombinant DNA technology and is derived from cultured Chinese hamster ovary cells or baby hamster kidney cells transfected with the human factor VIII gene.[5] Since these products are not derived from blood donations, the risk of transmitting infections through administration of recombinant factor VIII is low and recombinant products are generally favored over plasma-derived products. A very small risk of viral infection of the cell lines used to produce the clotting factor still remains. Furthermore, human or animal proteins are used in the production process of some recombinant products.[14] Therefore, these products have a theoretical risk of transmitting infection, although hepatitis and HIV infection have never been reported with their use.[5] First-generation recombinant factor VIII products

contain human albumin as a stabilizing protein.[5] Second-generation recombinant factor VIII products add sugar instead of human albumin as a stabilizer, but human albumin is used in the culture process. Several products are manufactured specifically with the B domain of the factor VIII gene deleted, yielding a smaller protein product.[5,20] This B domain does not appear to be necessary for coagulation function and may serve as a binding site for neutralizing antibodies. Third-generation recombinant factor VIII products do not contain human protein either in the culture or in the stabilization processes.[14]

Plasma-Derived Factor VIII Products

Clinical trials have demonstrated that recombinant factor VIII products are comparable in effectiveness to plasma-derived products.[5] Several different plasma-derived factor VIII products are available (Table 119-2). These products are derived from the pooled plasma of thousands of donors and therefore have the potential to transmit infection. Donor screening, testing of plasma pools for evidence of infection, viral reduction through purification steps, and viral inactivation procedures (eg, dry heat, pasteurization, and solvent detergent treatment) have resulted in a safer product. No cases of HIV transmission from factor concentrates have been reported since 1986.[5] However, isolated cases of hepatitis C infection with the use of plasma-derived products have been reported.[5] Additionally, outbreaks of hepatitis A viral infections associated with plasma-derived products have been reported, likely because solvent detergent treatment does not inactivate this nonenveloped virus. Finally, possible infection with unidentified viruses not inactivated by currently used methods remains a concern. In addition, Prion disease may be present in plasma-derived factor products.[21]

Factor VIII concentrates can be classified according to their level of purity, which refers to the specific activity of factor VIII in the product. Cryoprecipitate is a low-purity product that also contains vWF, fibrinogen, and factor XIII. The current American Association of Blood Banks standards call for a minimum of 80 international units of factor VIII per cryoprecipitate pack.[5] This product is no longer considered a primary treatment of factor VIII deficiency in countries where factor VIII concentrates are available because cryoprecipitate does not undergo a viral inactivation process. Intermediate-purity products have a specific factor VIII activity of 5 units/mg of protein and high-purity products have up to 2,000 units/mg of protein.[5] Ultrahigh-purity plasma-derived products are prepared with monoclonal antibody purification steps and have a specific

activity of 3,000 units/mg of protein prior to addition of albumin as a stabilizer.

Factor VIII Concentrate Replacement

Appropriate dosing of factor VIII concentrate depends on the half-life of the infused factor, the patient's body weight, and the location and severity of the bleed. The presence or absence of an inhibitory antibody to factor VIII and the titer of this antibody also influence treatment. Recovery studies, which measure the immediate postinfusion factor level, and survival studies, which assess the half-life of the factor, can establish patient-specific pharmacokinetics. The location and magnitude of the bleeding episode determine the percent correction to target as well as the duration of treatment.[7] Serious or life-threatening bleeding requires peak factor levels of greater than 0.75 to 1 units/mL (75%-100%); less severe bleeding may be treated with a goal of 0.3 to 0.5 units/mL (30%-50%) peak plasma levels. **Table 119-3** provides general guidelines for the management of bleeding in different locations.

TABLE 119-3 Guidelines for Factor Replacement Therapy for Hemorrhage in Hemophilia A and B

Site of Hemorrhage	Desired Hemostatic Factor Level (% of Normal)	Comments
Joint	50%-70%, 2-3 days	Rest/immobilization/physical therapy rehabilitation following bleed; several doses may be necessary to prevent or treat target joint
Muscle	30%-50% for most sites 70%-100% for thigh, iliopsoas, or nerve compression	Risk of significant blood loss with a thigh or iliopsoas bleed; bed rest for iliopsoas or thigh bleeding
Oral mucosa	30%-50%	May try antifibrinolytic or topical thrombin prior to factor replacement for minor bleeding; higher factor levels are needed for tongue swelling or risk of airway compromise; antifibrinolytic therapy should be used following factor replacement
GI	Initially 100%, then 40%-60%	Endoscopy is highly recommended; antifibrinolytic therapy may be useful. Continue until healing occurs
Hematuria	30%-50% if no trauma 70%-100% if traumatic	If no pain or trauma, consider bed rest and fluids for 24 hours; factor should be given if hematuria persists; evaluate if hematuria persists; if trauma to abdomen or back, perform imaging and give aggressive factor replacement
CNS	Initially 100%, then 50%-100% for 10-21 days	Lumbar puncture requires prophylactic factor coverage
Trauma or surgery	Initially 100%, then 50%-100% until wound healing complete	The perioperative and postoperative management plan must be in place preoperatively; evaluation for inhibitors is crucial prior to elective surgery

aPCC, activated prothrombin complex concentrate; PCC, prothrombin complex concentrate.

Factor VIII is a large molecule that remains in the intravascular space. Therefore, the plasma volume (about 50 mL/kg) can be used to estimate the volume of distribution. In general, each unit of factor VIII concentrate infused per kilogram of actual body weight results in a 2% rise in plasma factor VIII levels.[7] The following equation can be used to calculate an initial dose of factor VIII:

Factor VIII (units) = (Desired level - Baseline level) × 0.5 × (Weight [in kilograms])

The baseline level usually is omitted from the equation when it is negligible compared to the desired level. The half-life of factor VIII ranges from 8 to 15 hours. It is generally necessary to administer 50% of the initial dose about every 12 hours to sustain the desired level of factor VIII. A single treatment may be adequate for minor bleeding such as oral bleeding or slight muscle hemorrhages. However, because of the potential for long-term joint damage with hemarthroses, 2 or 3 days of treatment is often recommended for these bleeds. Serious bleeding episodes may require maintenance of 70% to 100% factor activity for 1 week or longer. As previously mentioned, factor VIII dosing depends on several variables, and each case must be considered individually. Individualized pharmacokinetics may help guide treatment, particularly for serious bleeding episodes.

Alternatively, factor VIII can be administered as a continuous infusion when prolonged treatment is required (eg, in the perioperative period or for serious bleeding episodes). Infusion rates ranging from 2 to 4 units/kg/hr usually are given in fixed-dose continuous infusion protocols, with the aim of maintaining a steady-state level of 60% to 100%.[22] Administration of factor concentrate via continuous infusion may reduce factor requirements by 20% to 50% because unnecessarily high peaks of factor VIII that occur with bolus injections are avoided. A gradual decrease in factor VIII clearance during the first 5 to 6 days of treatment contributes to the lower factor concentrate requirements. Daily monitoring of factor level can help determine the appropriate rate of infusion.

Administration of factor VIII concentrate via continuous infusion is safe and effective, and it may be more convenient than bolus therapy for hospitalized patients.[23] Concerns about the stability of the formulations appear to be unwarranted, as most high-purity factor VIII concentrates have been shown to remain stable for at least 7 days after reconstitution.[23] However, exposure of factor VIII to light for 10 hours after reconstitution can decrease activity by 30%.[23] Therefore, it would be prudent to shield the container with foil wrap or an appropriate bag.

Other Pharmacologic Therapy

Treatment with desmopressin acetate often is adequate for minor bleeding episodes in patients with mild hemophilia A. A synthetic analog of the antidiuretic hormone vasopressin, desmopressin causes the release of vWF and factor VIII from endogenous endothelial storage sites. It appears to be most effective in patients with higher baseline factor VIII levels (0.1-0.15 units/mL [10%-15%]).[22] The recommended dose of desmopressin is 0.3 mcg/kg diluted in 50 mL of normal saline and infused IV over 15 to 30 minutes.[22] Patients with mild or moderate hemophilia A should undergo a desmopressin trial to determine their response to this medication. At least a twofold rise in factor VIII to a minimal level of 0.3 units/mL (30 %) within 60 minutes is considered an adequate response.[1,22] Infusion of desmopressin can be repeated daily for up to 2 to 3 days. Tachyphylaxis, an attenuated response with repeated dosing, may develop after that time due to the depletion of factor stores. The factor increase after the second dose of desmopressin is about 30% lower than after the initial dose.[24] Factor concentrate therapy may be necessary if the patient requires additional treatment. Factor levels should be monitored to ensure that an adequate response has been achieved. Treatment with desmopressin will not result in hemostasis in patients who have severe hemophilia and those who are only marginally responsive. Desmopressin should not be used as primary therapy for life-threatening bleeding episodes such as intracranial hemorrhage or for major surgical procedures.[1]

Desmopressin can be administered intranasally via a concentrated nasal spray.[22] It elicits a slower and less marked response, with a peak effect in 60 to 90 minutes after administration, which is somewhat longer than with IV administration.[22,24] The dosage is one spray (150 mcg) in one nostril for patients who weigh less than 50 kg and two sprays (one in each nostril, 300 mcg total) for those who weigh more than 50 kg.[22] The nasal spray may serve as an alternative to the IV formulation, especially in patients with mild bleeding episodes. Few adverse effects are associated with desmopressin. The most commonly observed side effect is facial flushing.[24] Less frequently reported side effects include mild headaches, increased heart rate, and decreased blood pressure. Desmopressin can cause water retention because of its antidiuretic effects, which may lead to severe hyponatremia. This may be a particular problem in children younger than 2 years and, therefore, should be used with caution in this age group.[22] Fluid restriction for 24 hours after the desmopressin dose and monitoring of urine output are recommended with desmopressin

administration.[22]

Antifibrinolytic therapy inhibits clot lysis and therefore is a useful adjunctive therapy for the treatment of hemophilia, primarily with mucocutaneous bleeding. Antifibrinolytic agents are particularly beneficial for the treatment of oral bleeding because of a high concentration of fibrinolytic enzymes in saliva. Antifibrinolytic therapy can also be helpful as adjuvant therapy in GI bleeding, epistaxis, and menorrhagia. Antifibrinolytic therapy should be used with caution in patients with urinary bleeding, due to the risk of obstruction and subsequent renal toxicity. The two currently available antifibrinolytics include aminocaproic acid and tranexamic acid. Aminocaproic acid is given at a dosage of 100 mg/kg (maximum 6 g) every 6 hours and can be administered orally or IV.[5] The dosage of tranexamic acid is 25 mg/kg (maximum 1.5 g) orally every 6 to 8 hours.[5]

Hemophilia B

Therapeutic options for hemophilia B have improved greatly over the past several years, first with the development of monoclonal antibody-purified plasma-derived products and then with the licensure of recombinant factor IX. Products currently available in the United States for treatment of hemophilia B are listed in Table 119-2.

Recombinant Factor IX

Recombinant factor IX was not available until 1998, which is 6 years after the first recombinant factor VIII product.[14] Recombinant factor IX is produced in Chinese hamster ovary cells transfected with the factor IX gene. Since blood and plasma products are not used to produce recombinant factor IX or to stabilize the final product, recombinant factor IX has an excellent viral safety profile.[5] Clinical trials have shown the product to be safe and efficacious in the treatment of acute bleeding episodes and in the management of bleeding associated with surgical procedures.[5] Although the half-life of recombinant factor IX is similar to that of the plasma-derived products, recovery is about 30% lower.[22] As a result, doses of recombinant factor IX concentrate must be higher than those of plasma-derived products to achieve equivalent plasma levels. Because individual pharmacokinetics may vary, recovery and survival studies should be performed to determine optimal treatment.[5] Recombinant factor IX is considered the treatment of choice for hemophilia B.[1]

Plasma-Derived Factor IX Products

High-purity factor IX plasma concentrates have been available in the United States since the early 1990s.[5,14] These products are derived from plasma through biochemical purification and monoclonal immunoaffinity techniques. Other viral inactivation measures, such as solvent detergent or chemical treatment, are also used. High-purity factor IX concentrates have excellent efficacy in the treatment of bleeding episodes and in the control of bleeding associated with surgical procedures.[22] Their viral safety profile has been reported to be excellent and the risk of thromboembolic complications is low.

Before the high-purity products were approved for use, hemophilia B patients were treated with factor IX concentrates that also contained other vitamin K–dependent proteins (factors II, VII, and X), known as prothrombin complex concentrates (PCCs). These products contain small amounts of activated factors generated during processing, and their use has been associated with thrombotic complications, including deep-vein thrombosis, pulmonary embolism, myocardial infarction, and disseminated intravascular coagulation.[5,22] The risk of these complications is highest in patients receiving high or repeated doses of PCCs, in those with hepatic disease (the liver produces antithrombotic factors and removes the activated factors from circulation), in neonates, and in patients who have experienced crush injuries or who are undergoing major surgery.[5] Concomitant use of PCCs and antifibrinolytics should be avoided because of the risk for thrombosis. Because of the lower purity of PCCs and their thrombogenic potential, these products are not first-line treatment for hemophilia B.

Factor IX Concentrate Replacement

Factor IX is a relatively small protein. Unlike factor VIII, it is not limited to the intravascular space; it also passes into the extravascular compartment.[5] Therefore, it has a volume of distribution that is about twice that of factor VIII. For plasma-derived factor IX concentrates, each unit of factor IX infused per kilogram of actual body weight results in about a 1% rise in the plasma level of factor IX (range, 0.67%-1.28%).[5] The following equation can be used to calculate the initial dose:

> Plasma-derived factor IX (units) = (Desired level - Baseline level) × (Weight [in kilograms])

As with the factor VIII dose calculation, the baseline level term can be omitted from the formula if it is negligible compared to the desired level.

Because recovery of recombinant factor IX is lower than that of the plasma-derived products, the following adjustment is made:

Pediatric dosing:

Recombinant factor IX (units) = (Desired level - Baseline level) × 1.4 × (Weight [in kilograms])

Adult dosing:

Recombinant factor IX (units) = (Desired level - Baseline level) × 1.2 × (Weight [in kilograms])

A recovery study to determine optimal dosing is recommended for patients who receive recombinant factor IX because of the wide interpatient variability in pharmacokinetics. Because the half-life of factor IX is about 24 hours, dosing can be less frequent than with factor VIII. Table 119-3 provides general guidelines for dosing factor IX based on the site and severity of the bleeding episode.[22]

Prophylaxis Versus On-Demand Therapy

One approach to treating hemophilia patients is to administer the necessary factor only for acute bleeding episodes; this is referred to as *on-demand therapy*. However, recurrent joint bleeding can damage the joint and lead to the development of severe physical disability. It is therefore advisable to prevent bleeding episodes and avoid the resultant damage. This is the rationale for the second approach to treatment known as *prophylactic factor replacement therapy.* The goal of this approach is to maintain a patient's minimum factor level at or above 0.01 units/mL (1%) with regular infusions of factor products. In developed countries, prophylaxis for patients with severe hemophilia is considered the standard of care. It is also recommended by the World Health Organization and the World Federation of Hemophilia.[1] Prophylaxis is sometimes required in patients with moderate hemophilia and is rarely used in patients with mild hemophilia.

Prophylactic replacement therapy converts severe hemophilia into a milder form of the disease. The rationale for this approach is that patients with moderate hemophilia rarely experience spontaneous hemarthroses, and they have a much lower risk of chronic arthropathy. Many clinical trials have demonstrated the efficacy of a prophylactic approach in pediatric patients both in previously treated and untreated patients. The common finding is that prophylaxis

prevented joint damage and decreased the frequency of joint and other hemorrhages.[25–27]

The dosing for prophylactic regimens varies considerably and no one regimen has been proven to be superior.[25] A common regimen for patients with hemophilia A is 20 to 40 units/kg of factor VIII given every other day or three times per week. For hemophilia B, the usual dosage ranges between 25 and 60 units/kg of factor IX given twice weekly because of the intrinsically longer half-life of factor IX.[25] The recent introduction of longer-lasting factor products has made prophylaxis a more feasible approach (see Table 119-2). Patients with hemophilia A can now be dosed with an extended half-life product at a dose of 25 to 65 units/kg at 3-to-5 day intervals depending on their individual response.[26,28] Similarly, patients with hemophilia B can be dosed with an extended half-life product at either 50 units/kg once weekly or 100 units/kg every 10 days.[28]

Controversy exists regarding the ideal timing for the initiation of prophylaxis. Primary prophylaxis is regular replacement therapy started at a young age (usually before age 2 years), prior to the onset of joint bleeding.[27] Secondary prophylaxis begins after significant joint bleeding has already occurred.[27] In 2001, the Medical and Scientific Advisory Council of the National Hemophilia Foundation of the United States recommended primary prophylaxis beginning at age 1 to 2 years for children with severe hemophilia. Prophylaxis regimens are best administered in the morning to protect the patient during daily activities.[1]

Prophylaxis therapy comes with its own set of challenges. In addition to the paucity of evidence regarding dosing and initiation, a prohibitive challenge is the high cost of this approach. The cost to treat a patient with hemophilia A in the United States has been estimated to be about $300,000 per year.[29] Other issues to consider are the inconvenience to families and possible difficulties with adherence. Central venous lines may be necessary for frequent administration of factor concentrates, particularly in children younger than 2 years, who are at the age when primary prophylaxis is considered. Potential complications of central venous access include surgical risks, infection, and catheter-related deep-vein thrombosis. Finally, routine use of primary prophylaxis may initially overtreat some patients with severe hemophilia who do not have a severe clinical phenotype.

Treatment of Inhibitors

4 Neutralizing antibodies to factors VIII and IX, known as *inhibitors*, develop

in a subset of patients with hemophilia. The development of an inhibitor is the most serious complication of factor replacement therapy and is associated with considerable morbidity and a decreased quality of life. The incidence of new factor VIII inhibitors in patients with severe factor VIII deficiency is about 30%.[30] Inhibitors are less common in patients with mild or moderate hemophilia occurring in about 5% to 10% of patients.[1] The risk of developing inhibitors in patients with hemophilia B is much lower, occurring in only 3% of patients.[5]

Most inhibitors develop in childhood, after relatively few exposure days (median 9-12 days).[31] Patients with severe hemophilia are much more likely to develop inhibitors than those with milder forms of the disease.[32] It is possible that the low levels of factor produced in patients with mild or moderate hemophilia induce immune tolerance in these individuals. In contrast, factor levels are undetectable in patients with severe hemophilia, so infused factor VIII is regarded as a foreign protein, which may provoke an antibody response. The rate of inhibitor formation varies even among patients with identical mutations, which suggests that host factors modify the risk. The development of an inhibitor is the result of a complex interaction between a patient's immune system and genetic and environmental risk factors.

The type of factor product administered to patients may influence the risk of developing inhibitors. An international, multicenter, randomized, open-label clinical trial named Survey of Inhibitors in Plasma-Product Exposed Toddlers (SIPPET) was designed to evaluate the incidence of inhibitor development in previously untreated or minimally treated patients with hemophilia A exposed to plasma-derived factor products compared to recombinant products. The results of this pivotal trial showed that patients receiving recombinant factor VIII products had a significantly higher incidence of developing inhibitors compared to those receiving plasma-derived products.[33]

An inhibitor is a polyclonal high-affinity immunoglobulin G (IgG) directed against the factor VIII or IX protein. Inhibitors interfere with infused factor concentrate, rendering them ineffective. The presence of an inhibitor is suspected when a decreased clinical response to factor replacement is observed or it may be discovered incidentally on routine laboratory screening. Inhibitors are measured with the Bethesda assay, and titers are reported in Bethesda units (BUs). One BU is the amount of inhibitor needed to inactivate half of the factor VIII or factor IX in a mixture of inhibitor-containing plasma and pooled normal plasma.[5] Patients with inhibitors to factor VIII or factor IX are divided into two groups: low responders, who have low levels of inhibitors (<5 BU/mL) and generally have little or no rise in antibody titers after exposure to the factor; and

high responders (>5 BU/mL), who have higher inhibitor levels and develop an increase in antibody titer after exposure (anamnestic response).[5,32]

Therapy for patients with inhibitors involves the treatment of acute bleeding episodes and treatment directed at eradicating the inhibitor. The inhibitor titer, the site and magnitude of bleeding, and the patient's past response to bypassing therapy determine the approach to the treatment of acute bleeding. For patients with a low inhibitor titer, the administration of high doses of the specific factor often can control bleeding episodes. Two to three times the usual replacement dose and more frequent dosing intervals are often necessary to overcome the antibody. Factor-level monitoring and clinical assessments help to evaluate the adequacy of treatment. Additional supportive measures, such as immobilization and administration of antifibrinolytic agents, should be used, where appropriate.

Inhibitor development can also complicate the administration of prophylactic therapy for patients with hemophilia. A novel agent was recently approved for this specific indication. Emicizumab is a recombinant, humanized, bispecific monoclonal antibody that bridges activated factor IX and factor X, performing the function of the missing activated factor VIII in maintaining hemostasis. Due to its unique structure, the risk of developing neutralizing antibodies to the drug is low and it is not affected by the patient's preexisting inhibitors to factor VIII. It is administered in a single subcutaneous injection once weekly. The safety and efficacy of emicizumab has been demonstrated in children and adults with hemophilia A for prophylaxis therapy in the HAVEN 1-4 trials. It is FDA approved for prophylaxis therapy in patients both with and without inhibitors.[34,35]

Treatment of acute bleeds in patients with high-titer inhibitors can be complicated and require the use of alternative agents. In the presence of a high-titer inhibitor, it is impossible to administer enough factor VIII or factor IX to neutralize the antibody and achieve a hemostatic plasma level. Therefore, the treatment of bleeding episodes consists of agents that bypass the factor to which the antibody is directed. These bypassing agents include PCCs, activated prothrombin complex concentrates (aPCCs), and recombinant factor VIIa. PCCs contain the vitamin K–dependent factors II, VII, IX, and X. Small quantities of activated factors are present in these products. Activated PCCs contain greater quantities of the activated factors primarily factor X and prothrombin. The only available aPCC product in the United States is FEIBA® (Factor Eight Inhibitor Bypassing Agent). The recommended dosage is 50 to 100 units/kg administered every 8 to 12 hours, depending on the severity of the bleeding episode and the maximum dose should not exceed 200 units/kg/day.[28] Activated PCCs appear to

be more effective than PCCs and are preferred in patients with inhibitors. As previously mentioned, serious thrombotic complications, including pulmonary emboli, deep-vein thrombosis, and myocardial infarction have been associated with the use of PCCs and aPCCs.[28] Other minor side effects include dizziness, nausea, hives, flushing, and headaches. Patients with factor IX inhibitors occasionally develop severe allergic reactions in response to infusion of factor IX-containing products, so these patients should be monitored closely.[32]

5 Recombinant factor VIIa is effective for the treatment of acute bleeds in patients with hemophilia A or B who have developed inhibitors. Recombinant factor VIIa is a bypassing agent that is thought to be hemostatically active only at the site of tissue injury where the tissue factor is present. Recombinant factor VIIa is not a plasma-derived product, so both viral transmission and anamnestic responses to factor VIII or factor IX are unlikely. The initial recommended dose for bleeding episodes is 90 mcg/kg.[28] However, depending on a patient's response, higher doses up to 300 mcg/kg can be used. A drawback is the product's short half-life, which necessitates initial dosing every 2 hours. Continuous infusion of recombinant factor VIIa, which may be more convenient and cost-effective, has been reported.[36] Patients treated with bypassing agents must be monitored clinically because no laboratory test directly measures the effectiveness of treatment.

Both recombinant factor VIIa and aPCCs are effective in the treatment of bleeding for patients with inhibitors. In determining which bypassing product to use in an individual patient, the clinician must consider multiple factors. In a patient with a newly diagnosed inhibitor, it is prudent to use recombinant factor VIIa because aPCCs contain a small amount of factor VIII or IX and have been shown to increase the inhibitor titer. It is also important to consider an individual's response to specific bypassing agents because of the significant variability in response between individuals. In some patients, bleeding can be unresponsive to monotherapy and may require alternating products.[38] Due to the risk of developing thrombosis or disseminated intravascular coagulation from alternating bypassing agents, this therapy should be used with caution and only in an inpatient setting.[28]

In the past, plasma-derived porcine factor VIII was an alternative therapeutic option for patients who have hemophilia A and inhibitors. It was removed from the market secondary to contamination with porcine parvovirus. The rationale for its use is that porcine factor VIII is enough like human factor VIII to participate in the coagulation cascade, yet most factor VIII inhibitors have absent or only weak neutralizing activity against nonhuman factor VIII making this an

effective agent to treat an acute bleed. Unfortunately, cross-reactivity with porcine factor VIII does occur, and a high titer of antibody against porcine factor VIII can develop and hypersensitivity to porcine proteins can occur. Recently a recombinant porcine factor VIII has been approved, but only for the treatment of acute bleeds in patients with acquired hemophilia A.[28,39]

The current hemostatic therapies for patients with an inhibitor have limited effectiveness leading to significant morbidity and a decreased quality of life. The ideal therapy for patients with an inhibitor is total eradication so that optimal hemostatic treatment with either factor VIII or IX is possible. At this time, the only proven method for inhibitor eradication is immune tolerance induction (ITI), which involves the regular infusion of factor VIII to induce antigen-specific tolerance. This approach is not recommended for patients with hemophilia B who have developed inhibitors due to the risk of hypersensitivity reactions and anaphylaxis associated with factor IX administration in this group.

Multiple immune tolerance registries were established to help determine patient- and treatment-related factors associated with immune tolerance outcome.[40] Across these registries, a patient's peak historical factor VIII inhibitor titer (<200 BU) and the inhibitor titer at the time of ITI induction (<10 BU) were associated with successful immune tolerance. The overall ITI success rate from these registries ranges from 51% to 79%; the variability is likely related to a lack of standardization in study methodologies, treatment protocols, and eradication definitions.[40,41]

The relationship between factor VIII dose and ITI success rate is not clear. A variety of different dosing regimens, ranging from 25 units/kg every other day to more than 200 units/kg every day, have been used. The International Immune Tolerance Registry demonstrated improved ITI success with high doses (200 IU/kg), while the North American and Spanish Immune Tolerance Registries showed improved success with lower dosing strategies.[41] The International Immune Tolerance Study is a multicenter randomized clinical trial that compared high-dose (200 units/kg/day) to low-dose (50 units/kg three times/wk) regimens in patients with severe hemophilia A and high titer inhibitors (>5 BU).[40,42] This study was stopped early due to an increased risk of bleeding events in the low-dose arm. At the stopping point, the proportion of ITI success was not significantly different between the two arms, but the time to achieve ITI success was shorter in the high-dose arm. Because the study was stopped early, it lacked statistical power to demonstrate therapeutic equivalence below the 30% boundary of equivalence. It appears that a high-dose strategy achieves tolerance at a faster rate, which explains the lower bleeding rate.

Some studies report better success rates for ITI in patients receiving plasma-derived factor products containing vWF, which may be related to the role of vWF in factor VIII function, stabilization, and immunogenicity.[43] vWF binding to the C2 domain of factor VIII, a common site for inhibitor formation, may result in epitope masking and decreased inhibitor activity. The use of vWF-containing products may also extend the plasma half-life of factor VIII during ITI; thus, increasing antigen presentation and possibly contributing to its overall success.[43]

Although not commonly used in ITI protocols, immune modulation can improve tolerance success. Agents such as cyclophosphamide and intravenous immune globulin have been used in an effort to reduce inhibitor titers and make ITI more successful.[7] Another immune modulating agent, rituximab, an anti-CD20 monoclonal antibody that inhibits B-cells and interferes with IgG production, has been used with some success. In a phase II trial of rituximab in patients with high titer inhibitors, only 3 out of 16 subjects (18.8%) had a major response (decline in the inhibitor to <5 BU without an increase in the inhibitor titer after rechallenge to factor VIII).[44] When used as a single agent in previously treated patients with inhibitors, rituximab had a modest effect, but further studies are needed to determine the activity of rituximab combined with ITI. **Figure 119-1** summarizes the therapeutic options in the management of acute bleeding in patients with hemophilia A and inhibitors.

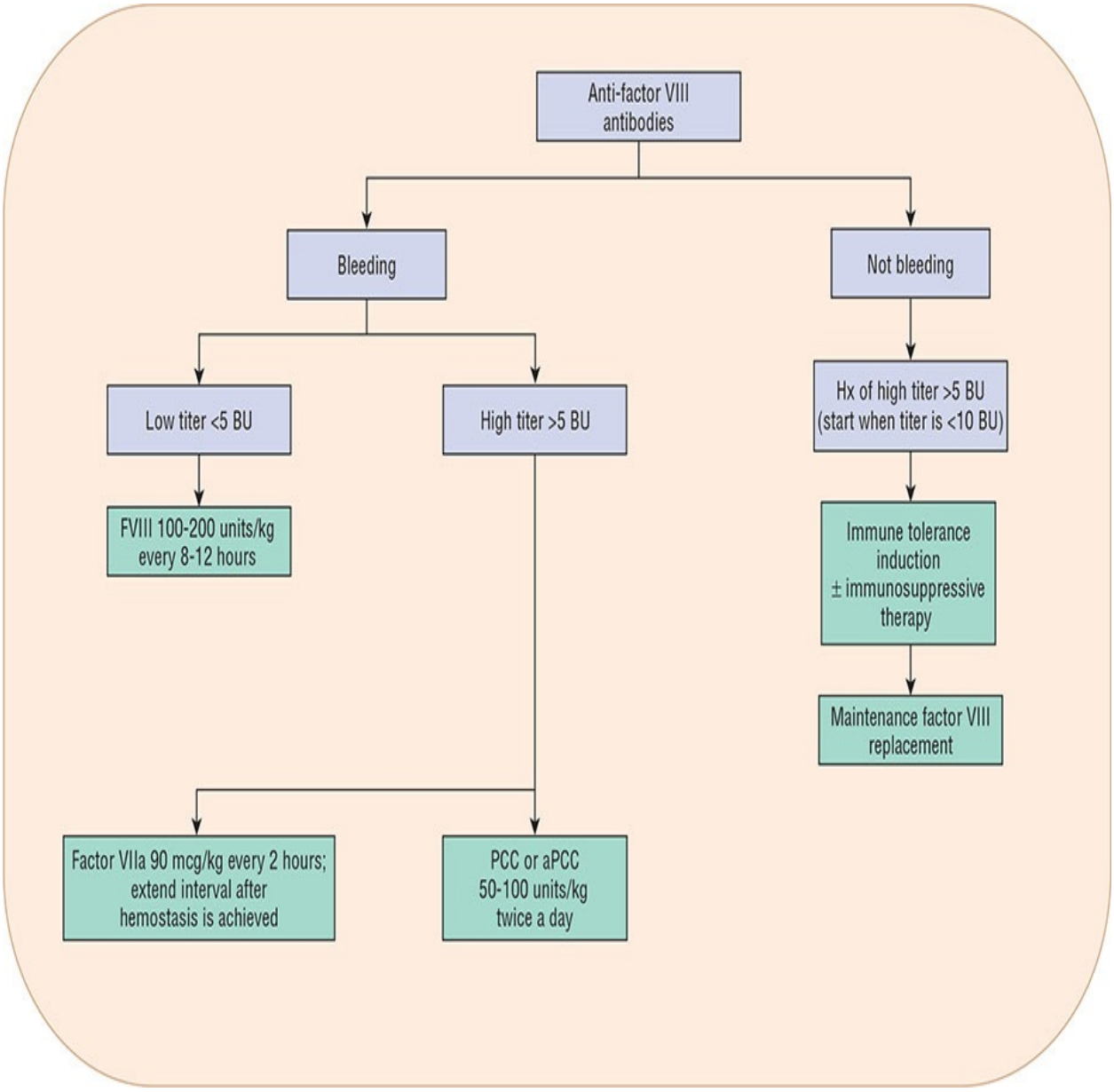


FIGURE 119-1 Treatment algorithm for the management of patients with hemophilia A and factor VIII antibodies. (aPCC, activated prothrombin complex concentrate; BU, Bethesda unit; PCC, prothrombin complex concentrate.)

Gene Therapy

Hemophilia is an excellent candidate for gene therapy because tight control of gene expression is not required. Even low levels of factor expression can reduce bleeding episodes in patients with severe hemophilia, which is similar to the rationale for prophylactic factor replacement. The goal of gene therapy is to achieve a sustainable factor activity level of over 5% (0.05 units/mL), which is

sufficient to convert patients with severe disease to a much milder phenotype.[45,46] If a treatment strategy could produce consistent factor activity levels of around 50% (0.5 units/mL), it would be considered curative.[46] Gene therapy for the treatment of hemophilia remains in the early clinical stages. Advances are most apparent in hemophilia B, which has been attributed to the smaller size (about 1.4 kb) of its complementary DNA (cDNA).[46] Recently, a landmark clinical trial reported the results of a single peripheral venous infusion of an adenovirus associated factor IX transgene vector under the control of a liver-restricted promoter in six patients with severe hemophilia B.[47] All of the study subjects demonstrated long-term (over 2 years) expression of the factor IX transgene with therapeutic levels of factor IX (plateau factor IX levels from 1% to 6% [0.01-0.06 units/mL]).[48] At this time, gene therapy for factor VIII deficiency has not progressed as far due to the considerably larger size of its cDNA (about 9 kb).[46] Potential benefits to gene therapy include patient convenience, viral safety, and decreased cost. Possible drawbacks to gene therapy include a risk of inhibitor formation, tumorigenesis related to possible integration of the viral vector, possible germline transmission of the viral vector, and concerns about long-term gene expression.

Other areas of gene therapy are being explored for the treatment of hemophilia. Platelets derived from hematopoietic stem cells may be able to deliver factor VIII or IX directly into the circulation. Lentiviral vectors are being explored for gene therapy due to their much larger packaging capacities compared to the adeno-associated viral vector (AAV). The area of gene editing is also being explored for patients with hemophilia using zinc finger nucleases or clustered regularly interspaced short palindromic repeats (CRISPR) approaches.[47]

Pain Management

Pain, both acute and chronic, can be a common occurrence in patients with hemophilia. The most likely cause of acute pain is bleeding, and treatment should include factor replacement to stop the bleeding, and PRICE (Protect, Rest, Ice, Compression, and Elevation).[7,49] Acetaminophen can be used for mild pain, although narcotic analgesia may be required for more severe pain. Nonsteroidal anti-inflammatory drugs (NSAIDs) impair platelet function and may complicate bleeding. For this reason, nonspecific NSAIDs are not routinely recommended during acute bleeding episodes. Cyclooxygenase-2 inhibitors have less antiplatelet activity and are an option for acute and chronic pain

management.[1,49]

Chronic pain in patients with hemophilia is typically secondary to hemophilic arthropathy. Hemophilic arthropathy is the direct result of recurrent hemarthrosis. Persistent blood in the joint leads to inflammation, synovial hypertrophy and inflammation, cartilage destruction, and finally bony erosion. Cyclooxygenase-2 inhibitors can also be helpful in managing chronic pain. Surgical interventions may help to alleviate chronic pain. Synovectomy (removal of the hypertrophied synovium) can reduce chronic pain from recurrent bleeding. Patients with more advanced joint disease could benefit from joint replacement.

Surgery

In patients with severe hemophilia, the dose of replacement factor required in the perioperative period will depend on the surgery, the inhibitor status, and the patient's previous response to factor products. Ideally, the patient's factor activity level should be maintained in the range of 50% to 100% (0.5 to 1.0 units/mL) depending on clinical status and type of procedure. Intermittent dosing or continuous infusion factor replacement may accomplish this goal.[1,36,50] Before surgery, factor concentrate is usually infused to obtain a plasma level of 1 unit/mL (100%). Replacement therapy is continued to maintain plasma levels greater than 0.5 units/mL (50%) for 5 to 7 days or longer, depending on the type of surgery and the patient's clinical response. Preoperative evaluation for elective procedures should include measurement of an inhibitor titer no longer than 2 weeks prior to procedure and assessment of the recovery and half-life of infused factor in the patient.[1] For those patients with inhibitors undergoing surgical procedures, there is evidence to support the use of both activated factor VII and aPCCs.[1,36]

Evaluation of Therapeutic Outcomes

The main goal in the treatment of hemophilia is to control and prevent bleeding episodes and their long-term sequelae such as chronic arthropathies. Pharmacologic and nonpharmacologic interventions should be aimed at achieving this goal. Treatment response can be monitored through clinical parameters such as cessation of bleeding and resolution of symptoms. Monitoring plasma factor levels also may be helpful, particularly for severe bleeding episodes. Home therapy for administration of factor concentrates is common among patients with hemophilia because this approach can lead to

earlier treatment and more independence for the patient. Diaries in which the patient documents symptoms, the dose of factor replacement, adjuvant therapies used, and treatment response can help the caregiver to evaluate the success of home therapy. Monitoring the number and type of bleeding episodes and trough plasma factor levels can evaluate the adequacy of prophylactic regimens. Pharmacokinetically driven dosing for prophylactic factor could optimize therapy, reduce bleeding and decrease overall factor consumption for the patient.[51] Physical examination with evaluation of joint range of motion and radiographic imaging of target joints can evaluate the long-term success of preventing and treating arthropathies.[52]

Clinicians should check for the development of inhibitors, especially in patients with severe disease and exposure to factor concentrates, at least yearly and with any suspicion of poor treatment response. The development of inhibitors challenges the management and control of bleeding episodes. A full understanding of the clinical situation and the titer of the inhibitor are mandatory to address all treatment options for each patient. Because no laboratory test measures the effectiveness of bypassing therapy in patients with inhibitors, close clinical monitoring for worsening or resolution of symptoms is essential for optimizing the outcome.

VON WILLEBRAND DISEASE

von Willebrand disease (vWD) is the most common congenital bleeding disorder in the United States and in the world, with a prevalence of 0.1% to 1%.[53,54] vWD refers to a family of disorders caused by a quantitative and/or qualitative defect of von Willebrand factor (vWF), a glycoprotein that plays a role in both platelet aggregation and coagulation (**Table 119-4**). vWF mediates platelet adhesion to injured blood vessel sites and promotes platelet aggregation. It binds factor VIII and protects it from degradation by plasma proteases, thus prolonging its half-life. Unlike hemophilia, vWD has an autosomal inheritance pattern, resulting in an equal frequency of disease in males and females.

TABLE 119-4 von Willebrand Disease

von Willebrand factor (vWF)
Large multimeric glycoprotein that is necessary for normal platelet adhesion, normal bleeding time, and stabilization of factor VIII

von Willebrand factor antigen (vWF:Ag)
Antigenic determinant(s) on vWF measured by immunoassays; usually low in types 1 and 2; virtually absent in type 3

Ristocetin cofactor activity (RCo)
Functional assay of vWF activity based on platelet aggregation with ristocetin. Reduced by the same degree as vWF:Ag in types 1 and 3, but to a greater extent in type 2 disease (except 2B)

The gene for vWF is located on chromosome 12 and is 178 kb in length.[53,57] Transcription and translation produce a large primary product that subsequently undergoes complex modifications, resulting in vWF multimers of various sizes with molecular weights ranging from 500 to over 10,000 kDa.[55,56] vWF is synthesized in endothelial cells, where it is either stored in Weibel–Palade bodies or secreted constitutively. It is also synthesized in megakaryocytes and stored in α-granules, from which it is released following platelet activation.[54,57]

vWF is important for both primary and secondary hemostases. In response to vascular injury, it promotes platelet adhesion by interacting with the glycoprotein Ib receptor on platelets.[57] It can facilitate platelet aggregation by binding to the platelet glycoprotein IIb/IIIa receptor, although fibrinogen is the main ligand for this receptor.[59] The highest-molecular-weight vWF multimers appear to be the most important in platelet adhesion because their large surface area contains numerous binding sites for various ligands and receptors. vWF is also the carrier molecule for circulating factor VIII, protecting it from premature degradation and removal.[54,57] A deficiency of vWF reduces the half-life of factor VIII and decreases plasma factor VIII levels. Therefore, vWF plays a dual role in hemostasis, affecting both platelet function and coagulation.

CLASSIFICATION OF VON WILLEBRAND DISEASE

vWD consists of a heterogeneous group of disorders that can be classified into three major subtypes. The National Institutes of Health has developed a classification scheme that characterizes vWD according to both the quantity of the von Willebrand clotting factors and their functionality (**Fig.119-2**). Types 1 and 3 are associated with quantitative defects in vWF; type 2 mutations refer to functional abnormalities in vWF.[57,59] It is important to determine disease

subtype because it influences treatment.

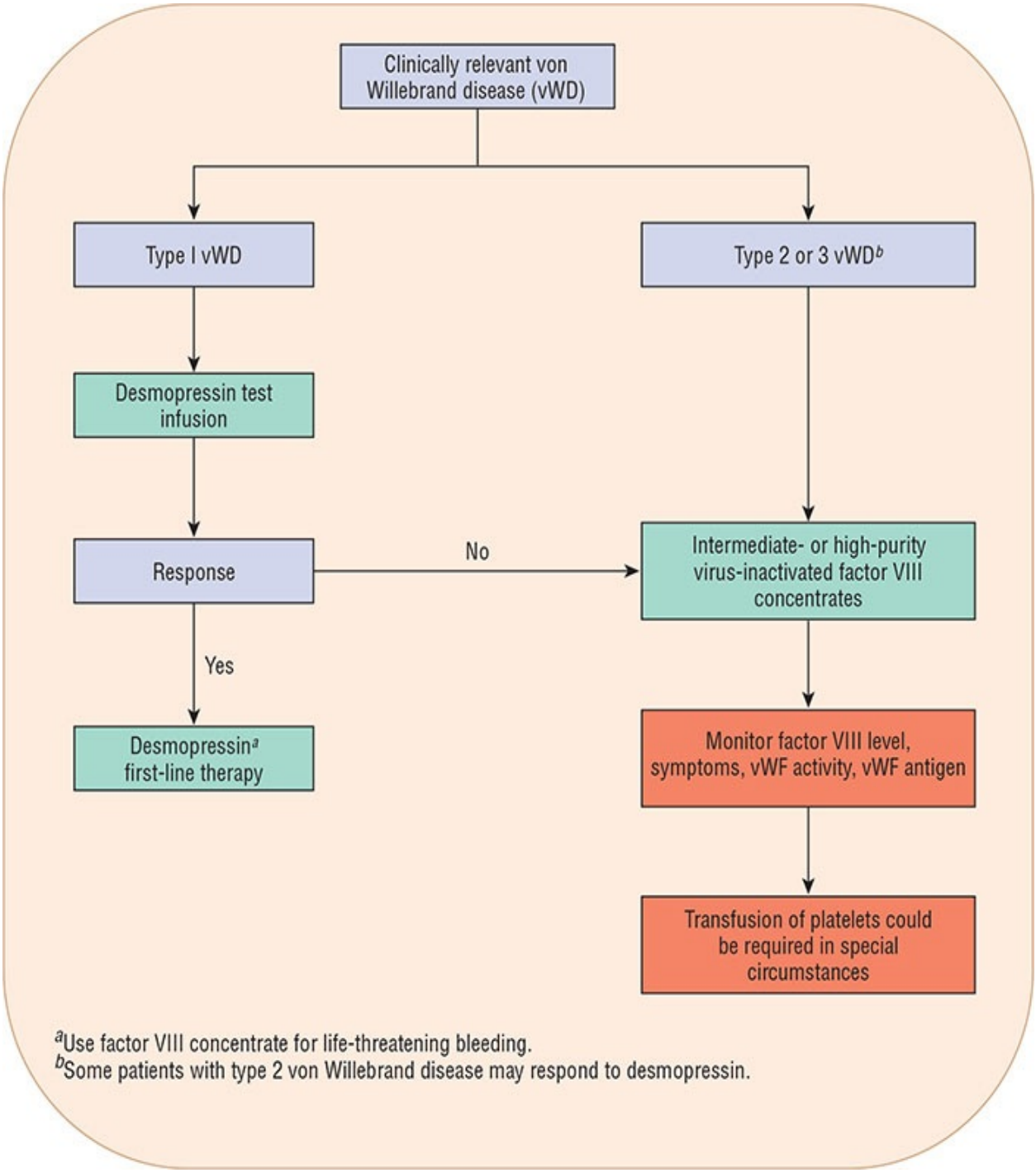


FIGURE 119-2 Diagnosis and Classification of von Willebrand Disease.

Type 1 vWD is the most common type, accounting for 70% to 80% of cases.[59–61] It is characterized by a mild-to-moderate quantitative reduction in the level of vWF (although its multimeric structure is normal) and a similar

reduction in the level of factor VIII. It usually is inherited in an autosomal dominant fashion with variable penetrance and expression.[57] Bleeding symptoms often are very mild to moderate.[57] Patients with vWD can experience mucocutaneous bleeding such as nosebleeds, bruising, gastrointestinal, or menstrual bleeding. Subjects may be at risk of bleeding following surgery, traumatic injury, or childbirth.[57]

Type 2 vWD, diagnosed in 20% to 30% of affected patients, is characterized by a qualitative abnormality of vWF.[61] Bleeding manifestations may be more severe than with type 1 disease. Inheritance most often is autosomal dominant but may be recessive.[57] Type 2 vWD can be subdivided into four variants. Type 2A is the most frequent subtype and is characterized by a reduced vWF–platelet interaction and an absence of high- and intermediate-molecular-weight factor multimers. Type 2B is a less common variant characterized by an abnormal vWF that has an increased affinity for the platelet glycoprotein Ib receptor. This subtype is associated with thrombocytopenia, which is usually mild. In addition, high-molecular-weight forms of vWF are usually absent. A platelet-type pseudo-vWD has been characterized in which vWF is normal but a defect in the platelet glycoprotein Ib receptor causes an increased affinity for normal vWF.[57] As a result, platelet-type pseudo-vWD is phenotypically similar to type 2B disease but should be distinguished from it because the treatment is different. Type 2M arises from a qualitative defect in vWF that impairs its binding to platelets; it is similar to type 2A, except there is no measurable reduction in the high-molecular-weight multimers.[57] Finally, type 2N vWD (Normandy) is a rare form of the disease in which vWF has a markedly reduced affinity for factor VIII. This subtype leads to a moderate-to-severe reduction of factor VIII plasma levels with normal vWF levels.[57]

Type 3 vWD refers to a severe quantitative variant of the disease in which vWF is nearly undetectable and factor VIII levels are very low (<20 IU/dL [0.2 IU/mL]). It is often inherited in an autosomal recessive fashion.[60] Type 3 vWD is rare and accounts for less than 5% of all cases.[61] The clinical phenotype is severe, reflecting major deficits in primary hemostasis and coagulation.

Acquired vWD is a rare bleeding disorder that is similar to the congenital form of the disease. It is primarily associated with autoimmune disorders, such as systemic lupus erythematosus, lymphoproliferative disorders, myeloproliferative disorders, hypothyroidism, and certain neoplastic diseases such as Wilms' tumor and lymphoma. It has been reported in situations of high shear stress such as aortic stenosis.[62] Certain medications have been associated

with acquired vWD, including valproic acid, griseofulvin, hydroxyethyl starch, and ciprofloxacin.[62] Bleeding manifestations vary from mild to severe, and the condition often resolves with treatment of the underlying disease. Various mechanisms have been proposed, including autoantibodies to vWF resulting in rapid removal from the plasma, adsorption to tumor cells or activated platelets, increased proteolysis, or mechanical destruction.[62]

CLINICAL PRESENTATION Von Willebrand Disease

Signs and Symptoms

- Clinical manifestations are variable; some patients are asymptomatic
- Mucocutaneous bleeding: epistaxis, gingival bleeding with minor manipulation, menorrhagia
- Easy bruising
- Postoperative bleeding

Clinical Presentation and Diagnosis

When a patient has a lifelong history of mucocutaneous bleeding and a family history of abnormal bleeding, vWD should be suspected. For a review of clinical questions to ask the patient, refer to the National Heart, Lung, and Blood Institute guidelines (Table 119-5).[63]

TABLE 119-5 Questions to Ask Patients

1. Have you or a blood relative ever needed medical attention for a bleeding problem or been told you have a bleeding disorder or problem?
   - During or after surgery?
   - With dental procedures or extractions?
   - During childbirth or for heavy menses?
   - Ever had bruises with lungs?
2. Do you have or have you ever had:
   - Liver or kidney disease?
   - A blood or bone marrow disorder?
   - A high or low platelet count?
3. Do you take aspirin, NSAIDs, clopidogrel, warfarin, heparin?

If yes to any of the above questions, ask additional questions:

1. Do you have a blood relative who has a bleeding disorder, such as von Willebrand disease or hemophilia?
2. Have you ever had prolonged bleeding from trivial wounds, lasting more than 15 minutes or recurring spontaneously during the 7 days after the wound?
3. Have you ever had heavy, prolonged, or recurrent bleeding after surgical procedures, such as tonsillectomy?
4. Have you ever had bruising, with minimal or no apparent trauma, especially if you could feel a lump under the bruise?
5. Have you ever had a spontaneous nosebleed that required more than 10 minutes to stop or needed medical attention?
6. Have you ever had heavy, prolonged, or recurrent bleeding after dental extractions that required medical attention?
7. Have you ever had blood in your stool, unexplained by a specific anatomic lesion (such as an ulcer in the stomach or polyp in the colon) that required medical attention?
8. Have you ever had anemia requiring treatment or received a blood transfusion?
9. For women, have you ever had heavy menses, characterized by the presence of clots greater than an inch in diameter and/or changing a pad or tampon more than hourly or resulting in anemia or low iron level?

NSAID, nonsteroidal anti-inflammatory drug.

Source: Adapted from Nichols WL, Rick ME, Ortel TL. Clinical and laboratory diagnosis of von Willebrand disease: A synopsis of the 2008 NHLBI/NIH guidelines. Am J Hematol. 2009;84:366-370.

Several different laboratory tests are helpful in the diagnosis of this hemostatic abnormality. Initial screening tests include determinations of PT, activated partial thromboplastin time (aPTT), and platelet count. PT is normal, while aPTT may be normal or prolonged in relation to the reduction in plasma factor VIII levels. A normal aPTT does not rule out vWD; specific laboratory

assessment of the vWF is required. The platelet count usually is normal, although thrombocytopenia is common in type 2B and platelet-type pseudo-vWD. The platelet function analysis (PFA-100), or the less commonly used bleeding time, may be prolonged but can be normal in patients with milder forms of the disease.[57,64]

Specific laboratory tests for the diagnosis of vWD include measurement of vWF antigen (vWF:Ag) level, factor VIII assay, determination of vWF ristocetin cofactor (vWF:RCo) activity, and vWF multimer analysis (see Table 119-4). Unfortunately, these levels vary considerably and often indeterminate or unreliable results can lead to confusion in the diagnosis. For example, the cutoff normal values for vWF:Ag, vWF:RCo, and other specialized tests vary between laboratories. This coupled with the natural variation of plasma concentrations of vWF can complicate interpretation of these results.[57] Plasma concentrations of vWF have been shown to increase with age, stress, cigarette smoking, exercise, pregnancy starting in the second trimester, infection, and with the use of certain medications such as corticosteroids, high-dose estrogen birth control pills, and desmopressin. Repeated test measurements may be necessary due to this physiologic variability.[57]

Electroimmunoassay, immunoradiometric assay, or enzyme-linked immunosorbent assay (ELISA) can be used to quantify vWF:Ag.[57] vWF:Ag levels are known to vary with different ABO blood types. Individuals with type O blood exhibit up to a 25% decrease in vWF levels when compared to those with type A due to increased plasma protein clearance.[57] The vWF:Ag level is usually low in types 1 and 2 vWD and virtually absent in type 3 disease. Factor VIII levels are normal or mildly decreased in patients with type 1 or 2 disease and very low (<10%) in those with type 3 disease.[57]

Ristocetin, an antibiotic that causes platelet aggregation in the presence of functional vWF, is used to measure vWF activity. The assay is performed by mixing platelet-free patient plasma, normal formalin-fixed platelets, and ristocetin and then quantitating the extent of platelet agglutination.[56] Ristocetin cofactor activity usually is reduced in parallel to vWF:Ag levels in types 1 and 3 disease and decreased to a greater extent than vWF:Ag in type 2 disease (except type 2B).[57] Low-dose ristocetin-induced platelet agglutination (LD-RIPA) is useful for further distinguishing type 2B disease, as a low concentration of ristocetin induces excessive aggregation in type 2B disease (see Fig.119-2).[57] When this measure in used, there is the potential for false results due to defects in vWF's ability to bind ristocetin.[59]

A newer assay functions independently of ristocetin and instead introduces gain-of-function mutations to GPIbα (glycoprotein Ib alpha); therefore, allowing it to bind vWF in vitro, spontaneously. The vWF:GPIbM assay provides greater precision with lower limits of detection compared to previous tests but is available only in limited locations in the United States.[59]

vWF, secreted as high-molecular-weight multimers, is cleaved in plasma to increasingly small protein fragments. The distribution of these multimer sizes can be helpful in determining the type of vWD. All multimer sizes are present in type 1 disease, whereas reduced levels of intermediate- and high-molecular-weight multimers are characteristic of type 2 disease. Type 3 patients lack all types of vWF multimers. Molecular genetic testing for vWD is now a feasible option in some instances. Genetic testing may clarify diagnostic uncertainty that may remain after coagulation testing and clinical evaluation.[57]

TREATMENT: VON WILLEBRAND DISEASE

6 The specific type of vWD and the location and severity of bleeding determine the approach to treatment. The comprehensive care of patients with vWD requires an interprofessional team approach. The desired outcome is to prevent bleeding episodes and their short-term and long-term consequences so that patients with vWD can live active and productive lives. Local measures, including prolonged pressure, ice, and topical thrombin, often can control superficial bleeding. Systemic treatment is used for bleeding that cannot be controlled in this manner and for the prevention of bleeding with surgery. The goal of systemic therapy is to correct platelet adhesion and coagulation defects by stimulating the release of endogenous vWF or by administering products that contain vWF and factor VIII or vWF alone.[54] General guidelines for the treatment of vWD are shown in **Fig. 119-3**.

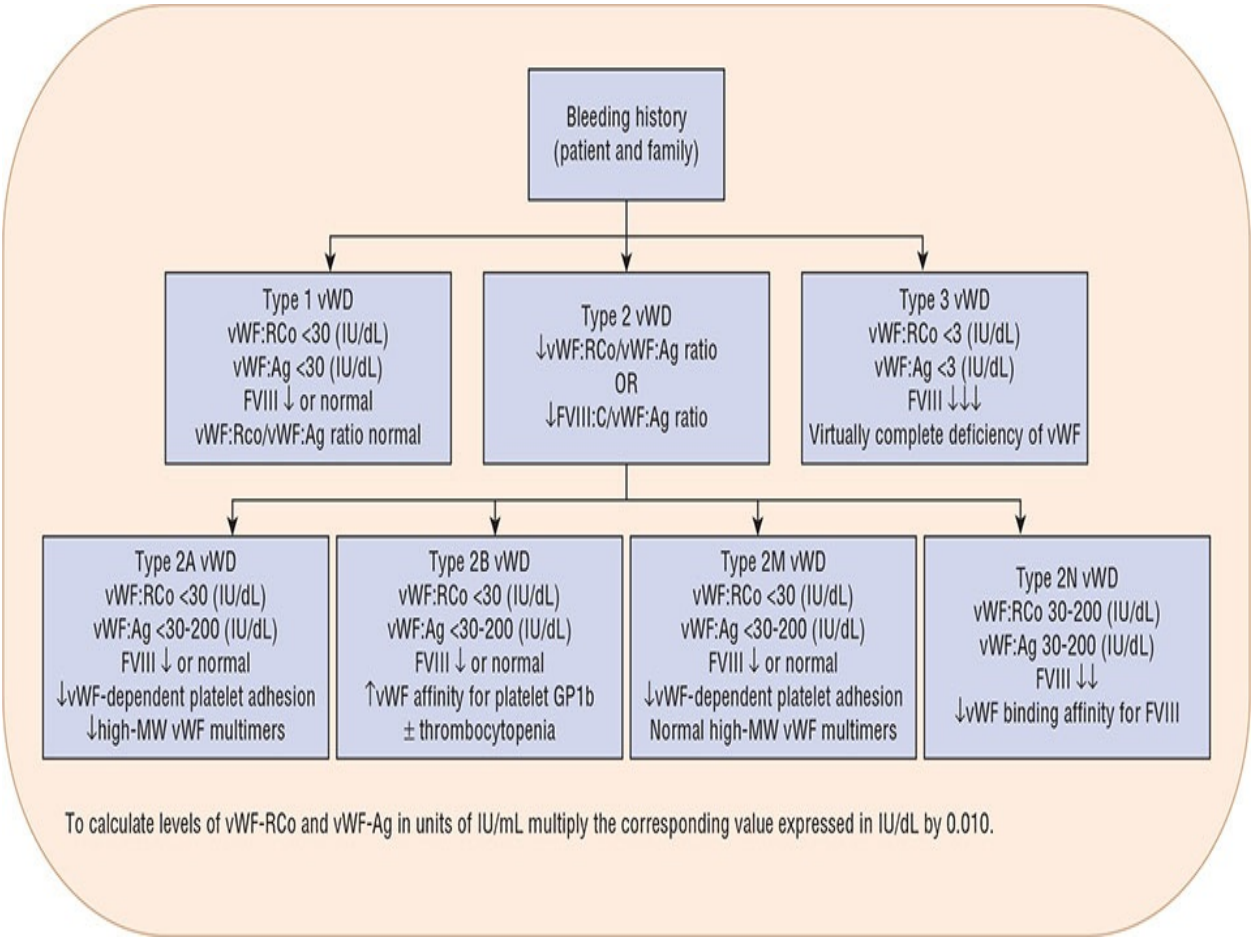


FIGURE 119-3 Guidelines for treatment of von Willebrand disease. (vWF, von Willebrand factor; RCo, ristocetin cofactor; FVIII:C, factor VIII activity.) (*Data from Reference 63.*)

Replacement Therapy

7 The treatment of choice for patients with types 2B, 2M, and 3 vWD and for patients with type 1 or 2A vWD who are unresponsive to desmopressin (which is discussed in the next section) is replacement therapy with plasma-derived vWF-containing products.[60] Several virus-inactivated, intermediate- or high-purity plasma-derived factor VIII concentrates contain sufficient amounts of functional vWF for treatment in this patient population (see Table 119-2). Ultrahigh-purity (monoclonal antibody-derived) plasma-derived products contain only negligible amounts of vWF and recombinant factor VIII products contain no vWF and are inadequate for treatment of vWD. Developing improved factor replacement products is an active area of research at this time. A prospective first-in-human clinical trial of a combination of recombinant vWF and recombinant factor VIII

in a fixed ratio was completed in 2013. That study showed the combination product to be safe and well tolerated with only minor and transient adverse effects similar to those seen in patients receiving plasma-derived products. The pharmacokinetics of the recombinant combination were also comparable to the plasma-derived vWF with the added benefit of enhanced factor VIII stabilization, resulting in no additional factor VIII product required for adequate hemostasis.[66]

Recombinant vWF alone was approved by the FDA in 2015 for on-demand treatment and control of bleeding episodes as well as perioperative management of bleeding in patients with vWD. Unlike plasma-derived vWF, recombinant products have no exposure to the ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13) which cleave large multimers.[68] Ultralarge and high-molecular-weight multimers are necessary for optimal platelet plug formation, making recombinant products ideal.[68]

Cryoprecipitate contains about 80 to 100 units of vWF per unit (5-10 times more vWF and factor VIII than fresh-frozen plasma), and historically it was the mainstay of therapy for vWD. However, because cryoprecipitate is not virally inactivated, it should not be used as first-line treatment. General guidelines for the dosing of replacement therapy in patients with vWD unresponsive to desmopressin are provided in **Table 119-6**. The vWD guidelines are also available at the National Heart, Lung and Blood Institute Website (https://www.nhlbi.nih.gov/health-topics/diagnosis-evaluation-and-management-of-von-willebrand-disease). In addition, a consensus guideline for the treatment of vWD and other bleeding disorders in women was published in 2009.[65]

TABLE 119-6 Replacement Therapy in von Willebrand Disease*

Condition	Therapy
Major surgery	Maintain factor VIII level ≥50% for 1 week
	Prolonged treatment in type 3 patients (>7 days)
Minor surgery	Maintain factor VIII level ≥50% for 1-3 days
	Maintain factor VIII level >20%-30% for an additional 4-7 days
Dental extraction	Single infusion to achieve factor VIII level >50%
	Desmopressin prior to procedure for type I
Spontaneous or posttraumatic bleeding	Usually single infusion of 20-40 units/kg

*The yield of factor VIII after first infusion is similar to that observed in hemophilia A (about 2% increment over baseline amount for every 1 unit/kg of factor VIII infused).

Other Pharmacologic Therapy

8 Desmopressin stimulates the endothelial cell release of vWF and factor VIII. It is temporarily effective for patients with vWD who have adequate endogenous stores of functional vWF, which includes most patients with type 1 disease and some patients with type 2A disease. Conversely, desmopressin is not appropriate for patients with type 3 disease, who lack stores of vWF. Desmopressin usually is not recommended for the treatment of type 2B disease because the release of additional abnormal vWF may exacerbate thrombocytopenia, but it has been reported to be beneficial in some patients with type 2B disease.[64] If desmopressin is used for the treatment of type 2B disease, close monitoring is necessary.

The dose of desmopressin used for treatment of vWD is identical to that used for treatment of mild factor VIII deficiency, 0.3 mcg/kg given IV over 15 to 30 minutes.[28] Patients with vWD generally have a better response to desmopressin than those with hemophilia, with an average three- to fivefold increase in vWF and factor VIII levels.[59] These levels remain elevated for about 6 to 8 hours. The response to desmopressin in a given patient usually is consistent, and a desmopressin trial should determine if the medication likely will be effective for the individual. Desmopressin is preferable to use of plasma-derived products for patients who have an adequate response because desmopressin does not carry a risk of viral transmission. An added benefit is the substantially lower cost of desmopressin compared to the plasma-derived products. (For a discussion of the

side effects of desmopressin, see Treatment of Hemophilia A.)

Desmopressin can be administered every 12 to 24 hours, but the response diminishes with repeated treatment. After three to four doses, desmopressin often is no longer effective and alternative replacement therapy may be necessary if prolonged treatment is required. Laboratory monitoring, including vWF:Ag measurements, factor VIII assays, vWF:activity assessments, and clinical examinations, will determine the adequacy of treatment.[64] Intranasal administration of desmopressin, at the same dosage as that used for mild factor VIII deficiency, can be useful for the treatment of mild bleeding episodes. One or two doses administered at the start of menses may be helpful in controlling menorrhagia. Oral contraceptives may also be very effective in controlling this symptom. Antifibrinolytic agents, such as aminocaproic acid and tranexamic acid, may be of special value in bleeds associated with tissues rich in plasminogen activators, such as the mouth, especially with tooth extractions.[64] These agents can also be used in the management of epistaxis, GI bleeding, and menorrhagia. However, these agents should be avoided in urinary tract bleeding because of the risk of thrombosis and obstruction.

In acquired vWD, low levels of plasma vWF are the result of accelerated removal of protein from plasma through the action of different pathogenic mechanisms. Acquired vWD may be associated with monoclonal gammopathy, lymphoproliferative or myeloproliferative syndromes, or cardiovascular disease. The treatment of the underlying lymphoproliferative disease with rituximab, a monoclonal antibody against CD20 on lymphocytes, has been reported to be relatively ineffective in the management of acquired vWD.[62] IV immune globulin remains a therapeutic option in acquired vWD, along with vWF concentrate and/or desmopressin.

Gene Therapy

Patients with the most severe bleeding phenotypes of vWD (type 3 and some severe cases of types 1 and 2) may be the most likely candidates for gene therapy, which offers the potential of a long-term, if not lifelong, correction of vWF deficiency. Preclinical trials are being conducted to test the feasibility of gene transfer in the management of vWD.[69]

Evaluation of Therapeutic Outcomes

Since the main goal in the treatment of vWD is to prevent or control bleeding

and the consequences of such bleeding, bleeding episodes can be monitored via clinical and laboratory parameters. Monitoring the number and types of bleeding episodes and measurement of plasma concentrations of vWF and factor VIII make it possible to evaluate the effectiveness of specific prophylactic and treatment regimens. As with hemophilia patients, assessment of patients' activities of daily living gives clinicians a better appreciation of the success of the treatment plan.

OTHER CONGENITAL FACTOR DEFICIENCIES

Rare bleeding disorders constitute 3% to 5% of all inherited coagulation factor deficiencies.[67] These rare bleeding disorders include congenital deficiencies in fibrinogen, in factors II, V, VII, X, XI, and XIII, and in combinations of factor deficiencies. Contact factor abnormalities, including deficiencies in factor XII, high-molecular-weight kininogen, and prekallikrein, prolong the aPTT but do not lead to any bleeding diathesis. Identification of these disorders is important so that inappropriate treatment is not given. The only contact factor deficiency associated with bleeding symptoms is factor XI deficiency. Also known as hemophilia C, this deficiency is particularly common in people of Ashkenazi Jewish descent.[70] Bleeding manifestations are variable. Bleeding usually does not occur spontaneously, but excessive bleeding may occur after trauma or surgery. Most other deficiencies are inherited as autosomal recessive disorders and are rare. Some patients with abnormal molecules, such as a dysfibrinogenemia, may have an increased tendency to develop thromboembolic disease. Most of these deficiencies are treated with fresh-frozen plasma. Newer specific concentrates are becoming available. For example, a factor XIII plasma-derived concentrate is available, and recombinant factor VIIa is approved for use in patients with congenital VII deficiency. Cryoprecipitate, which is rich in fibrinogen, or fibrinogen concentrates (RiaSTAP®), can be used to treat patients with fibrinogen deficiency or dysfunctional fibrinogen (dysfibrinogenemia).

COMPLICATIONS OF REPLACEMENT THERAPY

As discussed previously, the transmission of bloodborne infectious diseases is a concern when blood and blood-derived products are used. Most patients with hemophilia who received plasma-derived products were infected with hepatitis

viruses and HIV during the 1980s prompting the development of viral inactivation methods for use during the manufacturing of factor concentrates.[28] All currently available plasma-derived factor concentrates come from screened donors and undergo viral inactivation procedures in an effort to reduce the risk of viral transmission. Heat treatment, which includes dry and wet heat, is one method of viral inactivation. Wet heat is applied while the concentrate is in suspension or in solution (pasteurization) and appears to be more effective than dry heat. Other methods of viral inactivation include chemical (solvent detergent) and affinity chromatography with monoclonal antibodies. Solvent detergent treatment inactivates lipid-coated viruses, such as HIV and hepatitis B and C, but it is not effective against parvovirus B19, transfusion transmitted virus, hepatitis A, or prions.[5] Parvovirus B19 has been found in both plasma-derived and recombinant factor VIII concentrates (due to the use of albumin as a stabilizer in some recombinant products).[5,14] Parvovirus B19 may be particularly important for patients with hemophilia and HIV infection because it can cause chronic anemia in patients with immune deficiency. Prions are not inactivated by either solvent detergent treatment or by heat, so there is a risk of transmission.[7]

Other complications associated with factor administration include allergic reactions, fever, chills, urticaria, and nausea. PCCs and aPCCs also have the potential to cause thromboembolic complications, including deep-vein thrombosis, pulmonary embolism, myocardial infarction and DIC, likely related to the presence of activated factors.[28] Antifibrinolytic agents should not be given to patients receiving PCCs or aPCCs to avoid thrombotic complications.

Porcine factor VIII, used in the treatment of patients with inhibitors to factor VIII, is not known to transmit human viruses. However, allergic-type reactions (eg, fever, chills, skin rashes, nausea, and headaches) have been reported.[28] Patients who experience these reactions can be treated with steroids and/or diphenhydramine. Thrombocytopenia is another potential complication of porcine factor VIII use.[28]

CONCLUSION

Coagulation disorders, such as hemophilia and vWD, affect a small subset of the overall population, but their treatment can be costly and complicated, requiring knowledgeable healthcare professionals and an interprofessional team approach for optimal outcomes to be achieved. Exciting progress is being made in the development of new strategies for treating these types of disorders. The

development of new factor products with improved pharmacokinetic properties as well as the advances in gene therapy may soon redefine the therapeutic landscape for these patients and improve their overall experience.

Postclass Engaged Learning Activity

Perform a literature review to identify a primary research article published within the last 12 months. The article should identify a new therapy (eg, novel factor product or monoclonal antibody or similar) or treatment approach (eg, dosing based on pharmacokinetics). Write a brief summary of the article including advantages and disadvantages to the new therapy or approach. Compare this therapy to current guidelines and propose how this product may (or may not) impact the current management of coagulation disorders.

ABBREVIATIONS

ADAMTS13	a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13
aPCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
BU	Bethesda unit
ELISA	enzyme-linked immunosorbent assay
HIV	human immunodeficiency virus
ITI	immune tolerance induction
LD-RIPA	low-dose ristocetin-induced platelet agglutination
PCC	prothrombin complex concentrate
PT	prothrombin time
PRICE	Protect, Rest, Ice, Compression, and Elevation
SIPPET	Survey of Inhibitors in Plasma-Product Exposed Toddlers
vWD	von Willebrand disease
vWF:Ag	von Willebrand factor antigen
vWF:RCo	von Willebrand factor ristocetin cofactor
vWF:GPIbM	von Willebrand factor glycoprotein Ib mutational assay

REFERENCES

1. Srivastava A, Brewer AK, Mauser-Bunschoten EP, *et al* Guidelines for the management of hemophilia. *Haemophilia*. 2013;19:e1–e47.
2. Wynn TT, Gumuscu B. Potential role of a new PEGylated recombinant factor VIII for hemophilia. *J of Blood Medicine*. 2016;7:121–128.
3. http://www1.wfh.org/publication/files/pdf-1471.pdf.
4. Shahriari M, Bazrafshan A, Moghadam M, Karimi M. Severe hemophilia in a girl infant with mosaic Turner syndrome and persistent hyperplastic primary vitreous. *Blood Coagul Fibrinolysis*. 2016;27:352–353.
5. Lee C, Berntorp E, Hoots W,eds.*Textbook of Hemophilia*. 3rd ed. Chichester, West Sussex, UK: Wiley-Blackwell; 2014.
6. http://www.factorviii-db.org.
7. Benavides S, Nahata MC, eds.*Pediatric Pharmacotherapy*. American College of Clinical Pharmacy, Lenexa, Kansas, USA: 2013. Hemophilia in Turner's.
8. http://www.factorix.org.
9. Funnell APW, Crossley M. Hemophilia B Leyden and once mysterious cis-regulatory mutations. *Trends in Genetics*. 2014;30:18–23.
10. Franchini M, Frattini F, Crestani S, Bonfanti C. Haemophilia B: Current pharmacotherapy and future directions. *Expert Opin Pharmacother*. 2012;13:2053–2063.
11. Davies GA, Poon MC, Rydz N, Goodyear D. Attitudes toward prenatal diagnosis and pregnancy management in carriers of hemophilia: A qualitative analysis exploring the views of carriers in Southern Alberta. *Blood*. 2016;128:4742.
12. Xu XP, Gan HY, Li FX, *et al* A method to quantify cell-free fetal DNA fraction in maternal plasma using next generation sequencing: Its application in non-invasive prenatal chromosomal aneuploidy detection. *PLoS ONE*. Jan 14, 2016;11:1–13.
13. Carpenter SL, Soucie JM, Presley MV, *et al* Hepatitis B vaccination is effective by subcutaneous route in children with bleeding disorders: a universal data collection database analysis. *Haemophilia*. 2015;21:e39–43.
14. Aledort LM. The evolution of comprehensive haemophilia care in the United States: perspectives from the frontline. *Haemophilia*. 2016;22:676–683.

15. Berntorp E, Shapiro AD. Modern haemophilia care. *Lancet*. 2012;379:1447–1456.
16. Escobar MA. Advances in the treatment of inherited coagulation disorders. *Haemophilia*. 2013;19:648–659.
17. Bensen-Kennedy D. Bringing new therapy options to the hemophilia community. *Thromb Res*. 2013;131:S15–S18.
18. Negrier C, Karim FA, Lepatan LM, *et al* Efficacy and safety of long-acting recombinant fusion protein linking factor IX with albumin in haemophilia B patients undergoing surgery. *Haemophilia*. 2016;22:e259–e266.
19. Nolan B, Mahlangu J, Perry D, *et al* Long-term safety and efficacy of recombinant factor VIII Fc fusion protein (rFVIIIFc) in subjects with hemophilia A. *Haemophilia*. 2015;22:72–80.
20. Dube E, Bonnefoy A, Merien C, *et al* A prospective surveillance study of inhibitor development in haemophilia A patients following a population switch to a third-generation B-domain-deleted recombinant factor VIII. *Haemophilia*. 2018;24:236–244.
21. Urwin P, Thanigaikumar K, Ironside JW, *et al* Sporadic Creutzfeldt-Jakob disease in 2 plasma product receipients, United Kingdom. *Emerging Inf Diseases*. 2017;23:893–897.
22. Micromedex® Healthcare Series. Greenwood Village, CO: Thomson Reuters (Healthcare). Updated November 19, 2014.
23. Prelog T, Dolnicar MB, Kitanovaski L. Low-dose continuous infusion of factor VIII in patients with haemophilia A. *Blood Transfus*. 2016;14:474–480.
24. Loomans JI, Kruip MJHA, Carcao M, *et al* Desmopressin in moderate hemophilia A patients: A treatment worth considering. *Haematologica*. 2018;103:550–557.
25. Collins PW. Personalized prophylaxis. *Haemophilia*. 2012;18:131–135.
26. Berntorp E, Andersson NG. Prophylaxis for haemophilia in the era of extended half-life factor VIII/factor IX products. *Semin Thromb Hemost*. 2016;42:518–525.
27. Acharya SS. Advances in hemophilia and the role of current and emerging prophylaxis. *Am J Manag Care*. 2016;22:S116–S125.
28. Lexicomp Online® , Pediatric & Neonatal Lexi-Drugs ® , Hudson, Ohio: Lexi-Comp, Inc.; 2018.

29. Chen SL. Economic costs of hemophilia and the impact of prophylactic treatment on patient managent. *Am J Manag Care*. 2016;22 (5 suppl):s126–s133.
30. Shima M, Lillicrap D, Kruse-Jarres R. Alternative therapies for the management of inhibitors. *Haemophilia*. 2016;22:36–41.
31. Konkle BA. Impacting inhibitor development in hemophilia A. *Blood*. 2017;130:1689–1690.
32. Ljung RCR. How I manage patients with inherited haemophilia A and B and factor inhibitors. 2018;180:501–510.
33. Peyvandi F, Manucci PM, Garagiola I, *et al* A randomized trial of factor VIII and neutralizing antibodies in hemophilia A. *N Engl J Med*. 2016;374:2054–2064.
34. Oldenburg J, Mahlangu JN, Kim B, *et al* Emicizumab prophylaxis in hemophilia A with inhibitors. *N Engl J Med*. 2017;377:809–818.
35. Mahlangu J, Oldenburg J, Paz-Priel I, *et al* Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. *N Engl J Med*. 2018;379:811–822.
36. Santagostino E, Escobar M, Ozelo M, *et al* Recombinant activated factor VII in the treatment of bleeds and for the prevention of surgery-related bleeding in congenital haemophilia with inhibitors. *Blood Rev*. 2015;29(suppl 1):S9–S18.
37. Holme PA, Tjonnfjord GE, Batorova A. Continuous infusion of coagulation factor concentrates during intensive treatment. *Haemophilia*. 2018;24:24–32.
38. Antunes SV, Tangada S, Stasyshyn O, *et al* Randomized comparison of prophylaxis and on-demand regimens with FEIBA NF in the treatment of haemophilia A and B with inhibitors. *Haemophilia*. 2014;20:65–72.
39. Mannucci PM, Franchini M. Porcine recombinant factor VIII: An additional weapon to handle anti-factor VIII antibodies. *Blood Transfus*. 2017;15:365–368.
40. Valentino LA, Kempton CL, Kruse-Jarres R, *et al* US guidelines for immune tolerance induction in patients with haemophilia a and inhibitors. *Haemophilia*. 2015;21:559–567.
41. Collins P, Chalmers E, Alamelu J, *et al* First-line immune tolerance induction for children with severe haemophilia A: A protocol from the UK Haemophilia Centre Doctors' Organisation Inhibitor and Paediatric Working Parties. *Haemophilia*. 2017;23:654–659.

42. Hay CR, DiMichele DM. The principal results of the International Immune Tolerance Study: A randomized dose comparison. *Blood*. 2012;119:1335–1344.
43. Batsuli G, Meeks SL, Herzog RW, *et al* Innovating immune tolerance induction for haemophilia. *Haemophilia*. 2016;22(S5):31–35.
44. Jiang L, Liu Y, Zhang L, *et al* Rituximab for treating inhibitors in people with inherited severe hemophilia. *Cochrane Database Syst Rev*. 2017;7:1465–1858.
45. Giangrande P. The future of hemophilia treatment: Longer-acting factor concentrates versus gene therapy. *Semin Thromb Hemost*. 2016;42:513–517.
46. Walsh CE, Batt KM. Hemophilia clinical gene therapy: Brief review. *Transl Res*. 2013;161:307–312.
47. van den Berg HM. A cure for hemophilia within reach. *N Engl J Med*. 2017;377:2592–2593.
48. High KA. The gene therapy journey for hemophilia: Are we there yet? *Hematology Am Soc Hematol Educ Program*. 2012;2012:375–381.
49. Auerswald G, Dolan G, Duffy A, *et al* Pain and pain management in haemophilia. *Blood Coagul Fibrinolysis*. 2016;27:1–10.
50. Mensah PK, Gooding R. Surgery in patients with inherited bleeding disorders. *Anaesthesia*. 2015;70(suppl 1):112–120.
51. Collins PW. Personalized prophylaxis. *Haemophilia*. 2012;18(suppl 4): 131–135.
52. Pasca S, Milan M, Sarolo L, Zanon E. PK-driven prophylaxis versus standard prophylaxis: When tailored treatment may be a real and achievable cost-saving approach in children with severe hemophilia A. *Thrombosis Research*. 2017;157:58–63.
53. Blomback M, Eikenboom J, Lane D, Denis C, Lillicrap DP. von Willebrand disease biology. *Haemophilia*. 2012;18(suppl 4:141–147.
54. Swami A, Kaur V. von Willebrand disease: a concise review and update for the practicing physician. *Clin Appl Thromb Hemost*. 2017;23:900–910.
55. Stockschlaeder M, Schneppenheim R, Budde U. Update on von Willebrand factor multimers: focus on high-molecular-weight multimers and their role in hemostasis. *Blood Coagul Fibrinolysis*. 2014;25:206–216.
56. Bolton-Maggs PH, Favaloro EJ, Hillarp A, Jennings I, Kohler H. Difficulties and pitfalls in the laboratory diagnosis of bleeding disorders.

Haemophilia. 2012;18(suppl 4):66–72.

57. Ng C, Motto DG, Di Paola J. Diagnostic approach to von Willebrand disease. *Blood*. 2015;125:2029–2037.
58. Buga-Corbu I, Arion C, Davila C, *et al* Up to date concepts about von Willebrand disease and the diagnose of this hemostatic disorder. *J Med Life*. 2014;7:327–334.
59. Sharma R, Flood VH. Advances in the diagnosis and treatment of von Willebrand disease. *Blood*. 2017;130:2386–2391.
60. Federici AB, James P. Current management of patients with severe von Willebrand disease type 3: A 2012 update. *Acta Haematol*. 2012;128:88–99.
61. Leebeek FWG, Eikenboom JCJ. von Willebrand disease. *N Engl J Med*. 2016;375:2067–2080.
62. Callaghan MU, Wong TE, Federici AB. Treatment of acquired von Willebrand syndrome in childhood. *Blood*. 2013;122:2019–2022.
63. Nichols WL, Rick ME, Ortel TL. Clinical and laboratory diagnosis of von Willebrand disease: A synopsis of the 2008 NHLBI/NIH guidelines. *Am J Hematol*. 2009;84:366–370.
64. Laffan MA, Lester W, O'Donnell JS, *et al* The diagnosis and management of von Willebrand disease: A United Kingdom Haemophilia Centre Doctors Organization guideline approved by the British Committee for Standards in Haematology. *Br J Haematol*. 2014;167:453–465.
65. James AH, Kouides PA, Abdul-Kadir R. Von Willebrand disease and other bleeding disorders in women: Consensus on diagnosis and management from an international expert panel. *Am J Obstet Gynecol*. 2009;201:12e1–12e8.
66. Mannucci PM, Kempton C, Millar C, *et al* Pharmacokinetics and safety of a novel recombinant human von Willebrand factor manufactured with a plasma-free method: A prospective trial. *Blood*. 2013;122:648–657.
67. James P, Salomon O, Mikovic D, *et al* Rare bleeding disorders—bleeding assessment tools, laboratory aspects and phenotype and therapy of FXI deficiency. *Haemophilia*. 2014;20:71–75.
68. Gill JC, Castaman G, Windyga J, *et al* Hemostatic efficacy, safety, and pharmacokinetics of a recombinant von Willebrand factor in severe von Willebrand disease. *Blood*. 2015;126:2038–2046.
69. Portier I, Vanhoorelbeke K, Verhenne S, *et al* High and long-term von

Willebrand factor expression after *Sleeping Beauty* transposon-mediated gene therapy in a mouse model of severe von Willebrand disease. *J Thromb Haemost*. 2018;16:592–604.

70. Franchini M, Marano G, Pupella S, *et al* Rare congenital bleeding disorders. *Ann Transl Med*. 2018;6:331.

120

Sickle Cell Disease

C. Y. Jennifer Chan and Melissa Frei-Jones

KEY CONCEPTS

1. Sickle cell disease is an inherited disorder caused by a defect in the gene for β-globin, a component of hemoglobin, and is considered a qualitative hemoglobinopathy. Patients can have one defective gene (sickle cell trait) or two defective genes (sickle cell disease).
2. Although sickle cell disease usually occurs in persons of African ancestry, other ethnic groups can be affected. Multiple mutation variants are responsible for differences in clinical manifestations.
3. Sickle cell disease involves multiple organ systems. Usual clinical signs and symptoms include anemia, pain, splenomegaly, and pulmonary symptoms. Sickle cell disease is identified through routine newborn screening programs available in all 50 states. Early diagnosis allows early preventive and comprehensive care.
4. Patients with sickle cell disease are at risk for infection. Prophylaxis against pneumococcal infection reduces death during childhood in children with sickle cell anemia or hemoglobin SS.
5. Hydroxyurea decreases the risk of painful episodes, but patients treated with hydroxyurea require careful monitoring.
6. Neurologic complications caused by vasoocclusion can lead to stroke. Screening with transcranial Doppler ultrasound to identify children at risk accompanied by chronic transfusion therapy programs can decrease the risk of overt and silent stroke in children with sickle cell disease.
7. Patients with fever greater than 38.5°C (101.3°F) should be evaluated, and appropriate antibiotics administered immediately, including coverage for encapsulated organisms, especially pneumococcal organisms.
8. Pain episodes can often be managed at home. Hospitalized patients require

parenteral analgesics. Analgesic options include opioids, nonsteroidal anti-inflammatory agents, and acetaminophen. The patient characteristics and the severity of the pain should determine the choice of agent and regimen.

9 Patients with sickle cell disease should be followed regularly for healthcare maintenance issues and monitored for changes in organ function.

Preclass Engaged Learning Activity

https://tinyurl.com/vb4g9ye

https://tinyurl.com/tel4648

Watch the short video entitled “Sickle Cell Anemia” in the DNA Learning Center. This short 1-minute video provides 3D animation of the gene mutation resulting in sickle cell disease. Then listen to the podcast in EM Basic by Dr Jared Walker on evaluation and management of sickle cell disease in the emergency room.

INTRODUCTION

1 Sickle cell syndromes, which can be divided into sickle cell trait (SCT) and sickle cell disease (SCD), are a group of hereditary conditions characterized by the presence of sickle cell hemoglobin (HbS) in red blood cells. SCT is the heterozygous inheritance of one normal β-globin gene producing hemoglobin A (HbA) and one sickle gene, producing HbS (HbAS). Individuals with SCT are asymptomatic. SCD can be of homozygous or compounded heterozygous inheritance. Homozygous HbS (HbSS) has historically been referred to as sickle cell anemia (SCA), which now also includes HbSβ^0-thal due to similarities in clinical severity. The heterozygous inheritance of HbS with another qualitative or quantitative β-globin mutation results in sickle cell hemoglobin C (HbSC), sickle cell β-thalassemia (HbSβ^+-thal and HbSβ^0-thal), and some other rare phenotypes.[1–4]

Over the years, much progress has been made in our understanding of the relationship between clinical severity and genotype, as well as the pathological cascades leading to complications and morbidities associated with SCD. Ongoing research focuses on disease modification, organ damage prevention, and curative treatment. Advances in the care of SCD patients have increased life

expectancy to adulthood. Therefore, the transition from pediatric to adult medical care has become a focus to further improve survival and quality of life.[1–7]

SCD is a chronic illness with significant financial and emotional challenges for patients and their caregivers and high economic impact for society. Frequent hospitalizations can interrupt schooling and result in employment difficulties.[8,9] Acute complications of the disease can be unpredictable, rapidly progressive, and life threatening. Later in life, chronic organ damage and cognitive or emotional impairment can develop.[3,7,10,11] Because of the complexity of the illness, it is essential that comprehensive care is available to all patients and that all providers have a good understanding of disease progression and management.[1,10,11]

EPIDEMIOLOGY

2 SCD affects millions of people worldwide and is most common in people with African heritage.[2,3] The most common SCD genotype is HbSS (60%-65%), followed by HbSC (25%-30%), HbSβ^+-thal, and HbSβ^0-thal (5%-10%). Other variants account for less than 1% of patients.[1,2,5] The prevalence of SCD is highest in sub-Saharan Africa. The sickle mutation can also be found in the Arabian Peninsula, the Indian subcontinent, and the Mediterranean region.[1,3-5] An estimated 300,000 children are born each year with SCD-HbSS and another 50,000 to 100,000 births per year for other forms of SCD.[8] In the United States, about 100,000 Americans have SCD with a prevalence of 1 in 2,500 newborns, 1 in 365 African Americans, and 1 in 36,000 Hispanic births.[1,5]

The prevalence of SCD in a region is determined by the frequency of SCT. An estimated 300 million people are carriers worldwide.[12] The distribution of SCT reflects the survival advantage in regions where malaria is endemic as the gene mutation offers partial protection against serious malarial infection. Since red blood cells (RBCs) carrying the abnormal sickle hemoglobin prevent the normal growth and development of *Plasmodium falciparum* within RBCs, individuals with SCT are more likely to survive acute malarial illness.[13] The overall incidence of SCT reported in the United States is 15.5 per 1,000 newborns, with a rate of 7.3% in African Americans, 0.6% in Hispanics, 0.3% in white.[14,15]

ETIOLOGY

Normal hemoglobin (HbA) is composed of two α chains and two β chains (α_2 β_2). The biochemical defect that leads to the development of HbS involves the substitution of valine for glutamic acid as the sixth amino acid in the β-polypeptide chain. Another abnormal hemoglobin, hemoglobin C (HbC), is produced by the substitution of lysine for glutamic acid as the sixth amino acid in the β-chain. Structurally, the α chains of HbS, HbA, and HbC are identical. Therefore, it is the chemical differences in the β-chain that account for sickling and its related sequelae.[1-4]

Homozygous HbSS is the most common form of SCD and occurs when an individual inherits both maternal and paternal β-globin alleles that code for HbS. **Figures 120-1** to **120-4** show the probability of inheritance with each pregnancy for the offspring of parents with HbA, SCT, and HbSS. β-Thalassemia is a quantitative hemoglobinopathy resulting from a genetic defect in β-globin production. β-Thalassemia can be co-inherited with HbS and may vary from no β-globin production (β^0) to some β-globin production (β^+). Individuals with HbSS and HbSβ^0-thal have a more severe course than those with HbSC and HbSβ^+-thal and are now both referred to as SCA.[2,4,10]

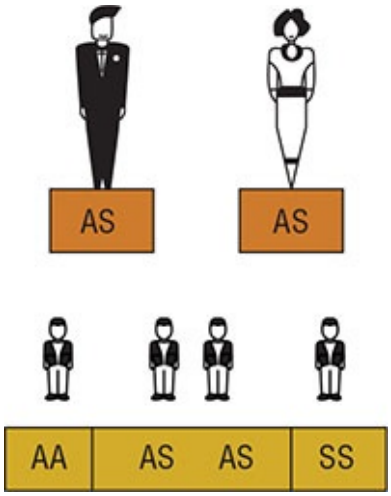


FIGURE 120-1 Sickle cell gene inheritance scheme for both parents with sickle cell trait (SCT). Possibilities with each pregnancy: 25% normal (AA); 50% SCT (AS); 25% sickle cell anemia (SS). (A, normal hemoglobin; S, sickle cell hemoglobin.)

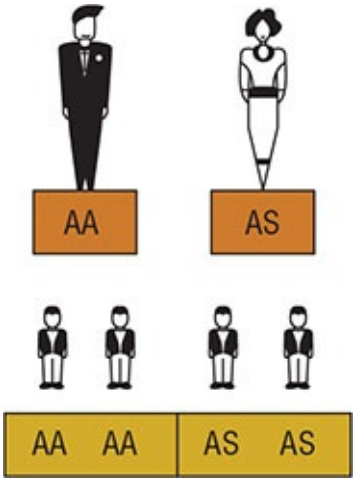


FIGURE 120-2 Sickle cell gene inheritance scheme for one parent with sickle cell trait (SCT) and one parent with no sickle cell gene. Possibilities with each pregnancy: 50% normal (AA); 50% SCT (AS). (A, normal hemoglobin; S, sickle cell hemoglobin.)

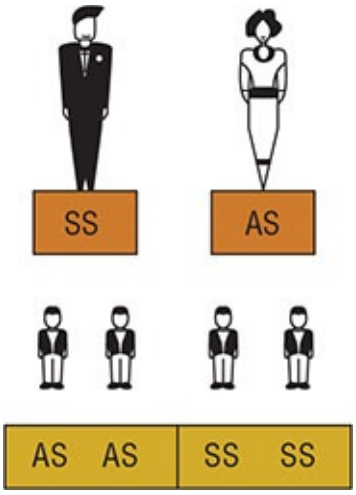


FIGURE 120-3 Sickle cell gene inheritance scheme for one parent with sickle cell trait (SCT) and one parent with sickle cell anemia (SCA). Possibilities with each pregnancy: 50% SCA (SS); 50% SCT (AS). (A, normal hemoglobin; S, sickle cell hemoglobin.)

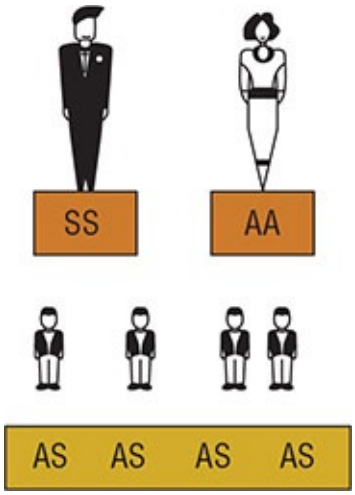


FIGURE 120-4 Sickle cell inheritance scheme for one parent without sickle cell gene and one parent with sickle cell anemia (SCA). Possibilities with each pregnancy: 100% SCT (AS). (A, normal hemoglobin; S, sickle cell hemoglobin.)

SCD is common among those with ancestors from sub-Saharan Africa, India, Saudi Arabia, and Mediterranean countries. Genetic analysis shows that the mutation found in Arabic patients differs from the mutation in those of African descent. SCD gene variants associated with different geographic regions may be responsible for variations in the clinical manifestations and response to therapy.[1-3,7] Several haplotypes characterize the sickle gene, resulting in different clinical and hematologic courses. The three most common haplotypes in the United States are the Bantu haplotype, characterized by severe disease; the Senegal haplotype, characterized by mild disease; and the Benin haplotype, characterized by a course intermediate to that of the other two haplotypes. Although there are a number of other haplotypes seen around the world, the major types outside of the United States are found in Saudi Arabia and Cameroon, both with milder courses of illness.[1–3,7,10,16]

PATHOPHYSIOLOGY

Normal adult RBCs contain predominantly HbA (96%-98%). Other forms of hemoglobin are HbA_2 (2%-3%) and fetal hemoglobin (<1%). Normal RBCs are biconcave shape and able to deform to squeeze through capillaries. Fetal hemoglobin (HbF) is present predominantly in fetal RBCs and is a tetramer of two α-globin chains and two γ-globin chains ($\alpha_2\gamma_2$).[2,3,7,13] Prior to birth, HbF is the predominant hemoglobin type. At around 32-week gestation, a switch from the production of γ chains to β chains occurs and consequently an increase in

HbA production occurs. Increased HbF production occurs under severe erythroid stress, such as anemia, after hematopoietic stem cell transplantation or chemotherapy or in the hereditary condition, hereditary persistence of fetal hemoglobin (HPFH), where a mutation in the β-globin gene cluster results in continued HbF production after birth. HPFH is a benign, asymptomatic condition.[2,3,17]

In the pathogenesis of SCD, the following are responsible for the various clinical manifestations: impaired circulation, destruction of RBCs, stasis of blood flow and ongoing inflammatory responses. These changes result directly from two major disturbances involving RBCs: abnormal hemoglobin polymerization and membrane damage (**Fig. 120-5**).

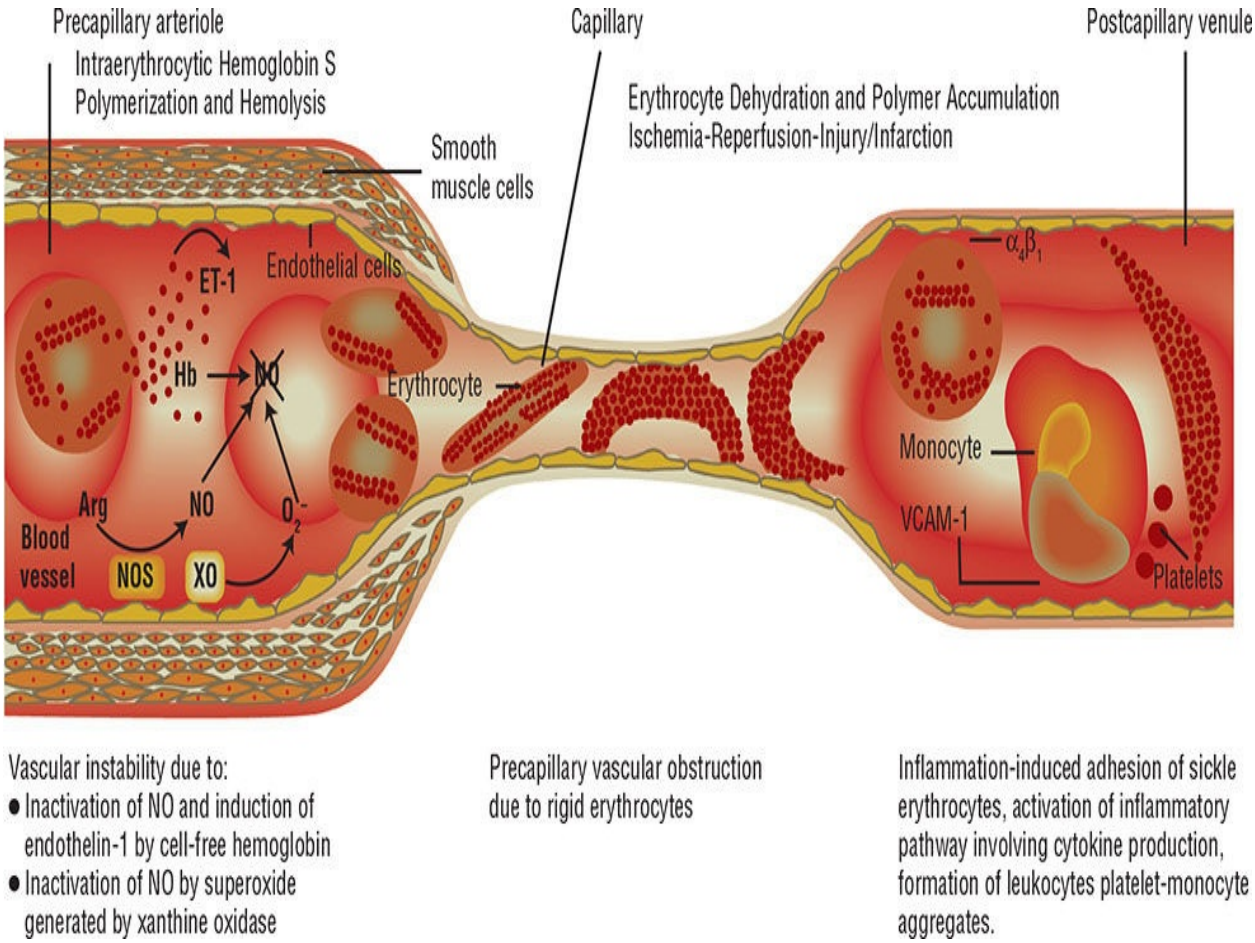


FIGURE 120-5 Pathophysiology of sickle cell disease. (Arg, arginine; ET-1, endothelin-1; Hb, hemoglobin; NO, nitric oxide; NOS, nitrous oxide synthase; VCAM-1, vascular cell adhesion molecule 1; XO, xanthine oxidase.) (*Reproduced with permission from Kato GJ, Gladwin MT. Sickle cell disease. In: Hall JB, Schmidt GA, Wood LDH. Principles of Critical Care, 3rd ed. New York:*

McGraw-Hill, 2005:1658.)

The solubilities of HbS and HbA are the same under conditions of normal oxygenation, but the solubility of deoxygenated HbS is reduced because of the valine substitution. Saturation of deoxy-HbS leads to intermolecular binding and formation of thin bundles of fibers, which initially are unstable. However, the increased binding of deoxy-HbS eventually results in cross-linked fibers and stable polymers. This process is influenced by mean corpuscular hemoglobin concentration (MCHC), temperature, intracellular pH, and the circulating amount of HbS. Polymerization allows deoxygenated hemoglobin molecules to exist as a semisolid gel that protrudes into the cell membrane, leading to distortion of RBCs (sickle shaped) and loss of deformability. The presence of sickled RBCs increases blood viscosity and encourages sludging in the capillaries and postcapillary venules. Such obstructive events lead to local tissue hypoxia, which tends to accentuate the pathologic process.[4,18,19]

When reoxygenated, polymers within the RBCs are lost and the RBCs eventually return to normal shape. This process contributes to vasoocclusion because the HbS-containing RBCs are able to enter the microvasculature when oxygenated, but sickle when deoxygenated. The cycle of sickling and unsickling results in damage to the cell membrane, loss of membrane flexibility, and rearrangement of surface phospholipids. Membrane damage also alters ion transport, resulting in potassium and water loss, which can lead to a dehydrated state enhancing the formation of sickled forms. After continual repetitions of the process, the RBC membrane develops into rigid irreversibly sickled cells (ISC). Unlike the reversible sickled cells (RSC), which have normal morphology when oxygenated, ISCs are elongated cells and remain sickled when oxygenated. More rigid membranes of HbS-containing RBCs retard flow, particularly through the microcirculation. In addition, sickled RBCs tend to adhere to vascular endothelial cells, which further increase polymerization and obstruction.[1,6,18,19]

Intermolecular binding and polymer formation are reduced by HbF and to a lesser degree by HbA_2. RBCs that contain HbF sickle less readily than cells without. ISCs, not surprisingly, have a low HbF level. Increased levels of HbF, as in the case of the Saudi Arabian haplotype, result in a more benign form of SCD. The amount of HbF and HbA_2 in relation to HbS influences the clinical manifestations and accounts for some of the variability in severity among SCD genotypes.[2,3,5]

Intravascular destruction of sickle cells can occur at an accelerated rate. The stresses of circulation and repetitive sickle–unsickle cycles lead to cell

fragmentation. Damage to the cell membrane promotes cell recognition by macrophages. Rigid ISCs are easily trapped, resulting in short circulatory survival and chronic hemolysis. The typical sickled cell survives for about 10 to 20 days, while the life span of a normal RBC is 120 days.[7,10] Anemia triggers the release of immature RBCs (reticulocytes) from the bone marrow prematurely. Surface adhesion proteins that maintain the reticulocytes inside the marrow adhere to the endothelium in postcapillary venules, further blocking the mature HbS-containing RBCs leading to complete occlusion of microvessels.[1–3]

SCD is a complex disease of inflammation as evidenced by leukocytosis, particularly an increase in monocytes and neutrophil counts. Coagulation abnormalities in SCD are the result of continuous activation of the hemostatic system or disorganization of the membrane layer. Sickled cells interact with leukocytes, endothelial cells, and platelets to form an occlusive clot. Hemolysis releases free hemoglobin resulting in generation of reactive oxygen species, nitric oxide (NO) depletion, and vascular inflammation. Chronic NO depletion contributes to vasoconstriction, activation of platelet, and adhesion molecules such as vascular cell adhesion molecule 1 (VCAM-1) and production of the potent vasoconstrictor peptide endothelin-1 (ET-1).[2,3,6,13,20]

Obstruction of blood flow to the spleen by sickle cells can result in functional asplenia, defined as the loss of splenic function with an intact spleen. These patients can also have deficient opsonization. Impaired splenic function increases susceptibility to infection by encapsulated organisms, particularly pneumococcal bacteria.[1,5,13]

CLINICAL PRESENTATION

3 Since 2006, universal newborn screening for SCD is performed in all 50 states. The sensitivity and specificity of screening methods such as isoelectric focusing high-performance liquid chromatography and hemoglobin electrophoresis approaches 100%. For infants with a positive screening result, a second test should be performed before 2 months of age to confirm the diagnosis. More than 98% newborns in the United States are screened for SCD to identify the disease. Some infants with SCD may not be identified because of extreme prematurity, prior blood transfusion, inability to contact family and/or immigration from countries where universal screening are not performed.[4,8,21]

SCD involves multiple organ systems, and its clinical manifestations vary greatly between genotypes (**Table 120-1**).[2,21,22] Persons with SCT are usually

asymptomatic and SCT is not considered a disease. However, under certain extreme situations where hemoglobin oxygenation is altered, RBC sickling can occur. Sickling of RBCs in the renal medulla, an area with low-oxygen tension, can result in the inability to concentrate urine. Individuals with such impairment can be at risk of dehydration. Microscopic hematuria has been observed, and gross hematuria can occur after heavy exercise. Other reported complications associated with SCT are delayed hemorrhage after eye trauma, venous thromboembolism, particularly pulmonary embolism, and chronic kidney disease.[12,23] Individuals with SCT should be cautious when participating in exercise under extreme conditions, such as athletic or military training. The US Sudden Death in Athletes Registry reported that 0.9% of 2,462 deaths occurred in athletes with SCT. The events in those 23 athletes with SCT were sudden cardiovascular collapse followed by several minutes of gradually worsening symptoms including dyspnea, fatigue and weakness during or after vigorous physical activity.[24] Preventive strategies such as gradual conditioning, adequate rest and hydration are recommended to minimize risk of sudden death in personnel undergoing athletic or military training.[12,24]

TABLE 120-1 Clinical Features of Sickle Cell Trait and Common Types of Sickle Cell Disease

Type	Clinical Features
Sickle cell trait (SCT)	Rare painless hematuria; heavy exercise under extreme conditions can provoke gross hematuria and complications (normal Hb)
Sickle cell anemia (SCA- HbSS)	Pain episodes, microvascular disruption of organs (spleen, liver, bone marrow, kidney, brain, and lung), gallstones, priapism, leg ulcers; anemia (Hb 6-9 g/dL [60-90 g/L; 3.72-5.59 mmol/L])
Sickle cell hemoglobin C (HbSC)	Painless hematuria and rare aseptic necrosis of bone; pain episodes are less common and occur later in life; other complications are ocular disease and pregnancy-related problems; mild anemia (Hb 9-14g/dL [90-140 g/L; 5.59-8.69 mmol/L])
Sickle cell β^+-thalassemia (HbSβ^+-thal)	Rare pain; milder severity than HbSS because production of some HbA; Hb 9-12 g/dL (90-120 g/L; 5.59-7.45 mmol/L) with microcytosis
Sickle cell β^0-thalassemia (HbSβ^0-thal)	No HbA production; severity similar to SCA; Hb 7-9 g/dL (70-90 g/L; 4.34-5.59 mmol/L) with microcytosis

Hb, hemoglobin; HbA, hemoglobin A.

Data from References 1-4, and 22-24.

The cardinal features of SCD are hemolytic anemia and vasoocclusion. In individuals with HbSS, anemia usually develops from 4 to 6 months after birth. The delay is due to the presence of HbF in fetal RBCs. HbF production is gradually replaced by HbS, leading to the clinical manifestations of the disease, such as pain and swelling of the hands and feet, commonly referred to as *hand-and-foot syndrome* or *dactylitis* in infants.[4,5,10]

The common clinical signs and symptoms associated with HbSS include chronic anemia and pallor, fever, arthralgia, scleral icterus, abdominal pain, weakness, anorexia, fatigue, hematuria, and enlargement of the liver, spleen, and heart. Laboratory findings include low hemoglobin level around 6 to 9 g/dL (60-90 g/L; 3.72-5.59 mmol/L), elevated reticulocytes of 10% to 25%, and elevated platelet and white blood cell (WBC) counts. Mean corpuscular volume (MCV) is normal. The peripheral blood smear demonstrates sickled red cell forms.[4,22]

Individuals with HbSC disease present with less severe symptoms than that of HbSS and the disease is characterized primarily by mild anemia (hemoglobin levels of 9-14 g/dL [90-140 g/L; 5.59-8.69 mmol/L] and reticulocytes of

5%-10%), infrequent episodes of pain, persistence of splenomegaly into adult life, and excessive target cells in the peripheral blood smear. In individuals with heterozygous HbSβ-thalassemia syndrome, severity of disease depends on the thalassemia mutation involved.[4,22]

Many factors can influence disease severity and mortality in children and adults with SCD. Previous markers for disease severity in children are dactylitis before 1 year of age, average hemoglobin less than 7 g/dL (70 g/L; 4.34 mmol/L) in the second year of life, and leukocytosis in the absence of infection have not been validated in more recent systemic reviews, largely due to improved care during childhood. Reticulocytosis has been associated with increased death and morbidity in both children and adults.[25,26] Early acute chest syndrome during the first 3 years of life is a predictor for recurrent episodes throughout childhood. Children with concomitant SCD and asthma have increased risk of acute chest syndrome and pain episodes and increased mortality. Factors associated with decreased survival in adults with SCD include frequency of sickle cell pain, elevated WBC, cerebrovascular events, renal failure, proteinuria and pulmonary hypertension.[25–28] With improved survival for SCD, chronic manifestations of the disease contribute to the increased morbidity later in life.

COMPLICATIONS

Acute Complications

Fever and Infection

Functional asplenia and failure to make antibodies against encapsulated organisms contribute to the high risk of overwhelming sepsis in individuals with SCD. Penicillin prophylaxis and vaccination have significantly reduced the overall risk of *Streptococcus pneumonia* bacteremia, but nonvaccine serotypes of *Streptococcus pneumonia* has been reported.[4,6,13,29] Children with SCD remain at a greater risk of invasive pneumococcal infections when compared to those with other underlying diseases or healthy children.[29,30] Other encapsulated organisms are *Haemophilus influenzae*, *Neisseria meningitidis*, and *Salmonella*, with the latter known to cause osteomyelitis and pneumonia in SCD. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* should be considered in older children with infiltrates on chest radiograph. Viral infections such as respiratory syncytial virus (RSV), influenza and parvovirus B19, can result in severe morbidity.[4,31] In children with SCD admitted for bacteremia, coagulase-

negative *Staphylococcus* was associated with central venous access; and should be considered for those with a permanent indwelling venous catheter. In adults, overt pneumococcal bacteremia is less common and pathogens such as *Staphylococcus aureus* and gram-negative organisms are associated with immunosuppression, indwelling catheter, and bone and joint infections.[5,32]

Children with SCD may experience a severe complication due to infection that results in impaired production of RBCs. An aplastic crisis is characterized by a decrease in the reticulocyte count and the rapid development of severe anemia (**Table 120-2**). The bone marrow becomes hypoplastic and is most often associated with a viral infection, particularly parvovirus B19.[3,4] All SCD patients with fever greater than 38.5°C (101.3°F) must be evaluated to determine the risk of infection or sepsis; and those with temperature 39.5°C (103.1°F) and appear ill should be hospitalized. Lumbar puncture may be needed, especially in young and toxic-appearing children.[3,4,22,32]

TABLE 120-2 Acute Sickle Cell Complications

Acute chest syndrome[a]

Clinical features: Peak incidence between ages 2 and 4 years. Clinically resemble pneumonia. Viral causes are more common in children than adults. Hypoxia is associated with outcome.

Signs and symptoms: New radiographic pulmonary infiltrate with one or more of the following: cough, dyspnea, tachypnea, chest pain, fever, wheezing, and new-onset hypoxia (greater than 2% decrease from baseline).

Evaluation: Chest x-ray, CBC, Type and Screen, frequent O_2 monitoring, sputum culture, serology for respiratory organisms.

Acute splenic sequestration[b]

Clinical features: Acute exacerbation of anemia due to sequestration of large blood volume by the spleen. More commonly seen in patients with functioning spleens (eg, infants with HbSS and older children and rarely adults with HbSC disease); onset often is associated with viral or bacterial infections; recurrences are common and can be fatal.

Signs and symptoms: Sudden onset of fatigue, dyspnea, and distended abdomen; rapid decrease in Hb and Hct with elevated reticulocyte count, abdominal pain, splenomegaly, vomiting, hypotension, and shock.

Evaluation: Close monitoring of vital signs, spleen size, and oxygen saturation, CBC, reticulocyte count, type and screen and blood cultures.

Aplastic crisis[c]

Clinical features: Acute decrease in Hb with decreased reticulocyte count (usually <1%); transient suppression of RBC production in response to bacterial or viral infection, most common being parvovirus B19.

Signs and symptoms: Headache, fatigue, dyspnea, pallor, and tachycardia; can also present with fever, upper respiratory or gastrointestinal infection symptoms.

Evaluation: CBC, reticulocyte count, Type and Screen, cultures (blood, urine, and throat), evaluation of viral infection (eg, parvovirus titers).

Overt Stroke[d]

Clinical features: Sudden onset but often proceeded by transient ischemic attack. Commonly seen in patients with HbSS and HbSβ^0-thal genotypes.

Signs and symptoms: headache, paralysis or weakness, aphasia, visual disturbances, facial droop and convulsions:

Evaluation: Imaging, CBC, reticulocyte count, HbS quantification, Type and Screen, prothrombin time, activated partial thromboplastin time and basic chemistry

Vasoocclusive pain episodes[e]

Clinical features: Acute painful infarction without changes in Hb; almost all patients with SCA will have episodes of acute pain. Recurrent acute pain results in bone, joint, and organ damage and chronic pain. Vasoocclusive episodes most commonly involve the bones, liver, spleen, brain, lungs, and penis. Acute pain in long bones can be accompanied by signs of inflammation, making it difficult to differentiate from osteomyelitis. Abdominal involvement can resemble a surgical abdomen. Precipitating factors include infection, extreme weather conditions, swimming, excessive physical activity, dehydration, and stress.

Signs and symptoms: Deep throbbing pain; local tenderness, erythema, and swelling can be seen. Fever and leukocytosis are common. Dactylitis usually occurs in young infants. Jaundice and increased transaminases can be present if the liver is involved.

Evaluation: Frequent physical examination, CBC, reticulocyte count, and urinalysis. Based on symptomatology, the following may be needed: needle aspiration to rule out osteomyelitis, abdominal studies (radiograph, computed tomography scan, etc.), liver function tests, bilirubin, blood culture, and chest radiograph.

[a] *Data from References 1, 4, 33, and 34.*

[b] *Data from References 1, 4, 13, 22, and 35.*

[c] *Data from References 2-4, 22, and 32.*

[d] *Data from References 1, 2, 4, 22, and 36.*

[e] *Data from References 1, 2, 4, 22, and 37.*

CBC, complete blood count; Hb, hemoglobin; HbS, sickle cell hemoglobin; HbSβ^0-thal, hemoglobin sickle cell β^0-thalassemia; HbSC, sickle cell hemoglobin C; HbSS, Homozygous; Hct, hematocrit; RBC, red blood cell; SCA, sickle cell anemia

Neurologic

Neurologic abnormalities and cognitive deficits are well documented in patients with SCD. Vasoocclusive processes can lead to cerebrovascular occlusion that manifests as signs and symptoms of overt stroke (Table 120-2). The risk of stroke is highest for HbSS and lowest for HbSβ^+-thal. The incidence of cerebral infarct in HbSS is 11% by age 20 years and 24% by age 45 years with a recurrence rate as high as 70% in 3 years. The highest risk occurs during the first decades, in particular ages 2 to 5. The risk is lowest before age 2 secondary to the protective effect of HbF. Ischemic strokes occur in 54% of cerebrovascular accidents with the highest risk before age 10 years and after 30 years of age, whereas hemorrhagic strokes are more common when patients are in their twenties and is associated with poor outcome.[1,4,19,36,38]

In addition to neurologic examination, evaluation of acute events include computed tomography (CT) scan and magnetic resonance imaging (MRI). Asymptomatic or silent infarcts are detected by screening MRI. Transcranial Doppler ultrasound (TCD) is important in primary stroke prevention to identify children between 2 and 16 years with abnormal cerebral velocities, which is associated with a 40% risk of overt stroke in the subsequent 3 years. Other imaging studies are magnetic resonance angiogram (MRA) to evaluate for cerebral vasculopathy in patients with persistently abnormal TCD, overt stroke or silent stroke; and magnetic resonance venography (MRV) to evaluate for cerebral vein thrombosis. In addition, electroencephalography (EEG) can be helpful in patients with a history of seizure.[4,5,22,36]

About 10% to 30% of individuals who have HbSS with no prior history of stroke have changes on MRI of the brain consistent with infarction or ischemia. Silent cerebral infarcts can be associated with increased risk of stroke, decreased neurocognitive functions, behavioral changes, and poor academic performances.[39] Neurological complications predispose aging adult patients to dementia. Finally, lower intelligence, visual-motor impairments, and neuropsychological dysfunction have been reported in patients not affected by acute or silent strokes and are associated with severity of anemia.[4,5,22,39]

Acute Chest Syndrome

Acute chest syndrome (ACS), defined as a new pulmonary infiltrate associated with fever and/or respiratory symptoms, is the second most common cause of hospitalization and leading cause of deaths among individuals with SCD (Table

120-2).[1,33,34] The primary etiology for ACS is pulmonary vascular occlusion. Infections, fat emboli released from bone marrow or direct adhesion of RBCs to the pulmonary vasculature resulting in the viscous cycle of inflammation, hypoxia, and injury to the lung. The most common cause of ACS is infection. Pathogens identified are *Mycoplasma pneumonia*, *RSV, Chlamydia pneumoniae*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*.[1,4,33,34]

Risk factors for ACS and recurrence include young age, lower HbF, higher leukocytes, history of asthma or bronchial hyper-responsiveness, smoke exposure, and recent history of stroke (overt or silent) or vasoocclusion. Genotype and haplotype also influence risk. Patients with HbSS and HbSβ^0-thal have higher risk than those with HbSC and HbSβ^+-thal and the risk is higher with African haplotypes than that of Saudi Arabia.[1,4,33,34]

ACS is more common in children but more severe in adults. Hypoxia is a predictor for severity and outcome. In severe cases, CT scan, perfusion scintigraphy, transthoracic echocardiography, and bronchoscopy may be helpful to exclude other etiologies. Pulmonary changes often involve the lower lobes of the lungs and may cause pleural effusions. Bilateral infiltrates or multiple lobe involvement is associated with poor prognosis.[4,33,34] Pulmonary manifestations must be recognized early and managed aggressively as ACS can rapidly progress to pulmonary failure and death.[33,34]

Priapism

Stasis and sickling of RBCs within the sinusoids of the corpora cavernosa is the primary mechanism of priapism, a sustained painful erection. In recent years, a better understanding of pathophysiology of priapism has identified other mechanisms at the molecular level, such as abnormal NO signaling as the result of chronic NO depletion. Stuttering priapism is repeated intermittent attacks up to several hours before remission; ischemic priapism is a persistent painful erection greater than 4 hours and should be considered an emergency. Thirty percent to 45% of males with SCD will present with at least one episode of priapism during their lifetime and the first episodes often occur during childhood. Impotence has been reported after repeated episodes and is directly related to the duration prior to treatment.[1,22,40]

Sickle Cell Pain

Acute episodes of pain are the most common symptoms and reason for seeking treatment in SCD (Table 120-2). Sickle cell pain may be caused by bone or

muscle infarction due to vasoocclusion. Although fever, infections, dehydration, hypoxia, acidosis, and sudden temperature alterations can precipitate pain, episodes are often unpredictable with no known triggers.[1,4,22] Dactylitis (hand-and-foot syndrome) is a subtype of sickle cell pain, occurring in infancy and early childhood and usually do not result in permanent damage.[1,22] Each painful episode is associated with residual damage from inflammation that worsen with recurrence leading to more serious complication such as ACS.[37]

Sickle cell pain may be localized or migratory and is continuous and throbbing. The most common locations are the back, chest, and extremities but can occur in any location such as the abdomen or the head and lead to confusion with other acute complications such as stroke.[1,22] Individuals with HbSS experience more frequent episodes of pain than those with HbSC or other variants. Risk factors associated with painful episodes include older age, iron overload, higher Hb, and lower HbF.[2,4,37]

Splenic Sequestration

Splenic sequestration is the sudden massive enlargement of the spleen resulting from the sequestration of sickled RBCs in the splenic parenchyma (Table 120-2). Hematocrit and hemoglobin concentrations dramatically fall, with reticulocytosis and no evidence of marrow failure or accelerated hemolysis. The trapping of the sickled RBCs by the spleen also leads to a decrease in circulating blood volume, which can result in hypotension and shock. The condition is most often seen in infants and children because their spleens are intact and can cause sudden death in young children due to hypovolemia. Splenic enlargement may also be acutely painful due to rapid capsular expansion. Over time, repeated splenic infarctions lead to autosplenectomy and the spleen can no longer become engorged. Sequestration usually occurs between 1 and 4 years of age for children with HbSS and HbSβ^0-thal because autoinfarction usually is completed by then. For HbSC and HbSβ^+-thal, autoinfarction is delayed and sequestration can occur even during adulthood.[1,4,13,22,35]

Venous Thromboembolism

Patients with SCD are susceptible to venous thromboembolism (VTE) due to hypercoagulable state, endothelial dysfunction and impaired blood flow. In addition to inflammation and hemostatic abnormalities associated with the disease, other risk factors for thrombosis include central venous access, abnormal mobility, and frequent hospitalizations. Recent studies have reported

an increased risk of VTE, deep vein thrombosis (DVT), and pulmonary embolism (PE), independent of hospitalization frequency.[7,11,13,41] Prevalence rates of 7.4% by age 30 and 11.3% by age 40 were reported in one study.[7] In addition, a recurrence rate of about 25% has been reported.[11] D-dimer testing cannot be used to detect DVT because elevated D-dimers are found in more than 90% of patients with SCD as a result of hemolysis.[13] Awareness of VTE is essential when evaluating patients presenting with ACS or vasoocclusive episodes. Management of VTE is based on the anticoagulation guidelines for the general public and the role of prophylaxis in patients with SCD is unclear.[7]

Chronic Complications

Pulmonary

Over 90% of children survive into adulthood, increasing the contribution of pulmonary manifestations to the morbidity and mortality of SCD. Physical exam and history should be performed to identify signs and symptoms of respiratory conditions such as asthma, restrictive lung disease, and chronic obstructive pulmonary disease. Pulmonary function testing is recommended in symptomatic patients but not as a routine screening tool.

Pulmonary hypertension, defined as a resting mean pulmonary arterial pressure (PAP) 25 mm Hg or greater by right heart catheterization, is associated with increased morbidity and mortality in SCD. Symptoms of pulmonary hypertension include shortness of breath during normal activities, fatigue, syncope, and peripheral edema. A less invasive test, tricuspid regurgitant jet velocity by Doppler echocardiography, is frequently performed initially to estimate PAP. Serum NT-pro-BNP measurement is an alternative test that can be used in patients with normal renal function when Doppler echocardiography is not an option. The American Thoracic Society recommends assessment of mortality risk using noninvasive (indirect) or invasive direct measurement to guide management of pulmonary hypertension (Table 120-3).[22,42,43]

TABLE 120-3 Risk Stratification and Management Recommendation for Pulmonary Hypertension

	Recommendations	Strength	Evidence Quality
Increased risk for mortality[a]	Hydroxyurea	Strong	Moderate
Increased risk for mortality, unresponsive or not candidates for hydroxyurea	Chronic transfusion therapy	Weak	Low
RHC-confirmed PH, venous thromboembolism, no risk factors for hemorrhage	Indefinite anticoagulant therapy	Weak	Low
Elevated TRV alone	No PAH therapy[b]	Strong	Moderate
Elevated NT-pro-BNP alone	No PAH therapy[b]	Strong	Moderate
RHC-confirmed marked elevation of pulmonary vascular resistance, normal pulmonary artery wedge pressure, presence of related symptoms	• A trial of prostacyclin agonist or endothelin receptor antagonist	Weak	Very low
	• Phosphodiesterase-5 inhibitor should not be used as first-line therapy	Moderate	Moderate

[a]Increased risk for mortality: (1) Tricuspid regurgitant jet velocity (TRV) greater than or equal to 2.5 m/s, (2) an N-terminal pro-brain natriuretic peptide (NT-pro-BNP) level greater than or equal to 16 pg/mL (ng/L; 1.9 pmol/L) or (3) right heart catheterization (RHC)-confirmed pulmonary hypertension (PH).

[b]PAH therapy: (1) prostacyclin agonist (epoprostenol, treprostinil, iloprost), (2) soluble guanylate cyclase stimulator (riociguat), (3) endothelin receptor antagonist (bosentan, macitentan, ambrisentan), (4) phosphodiesterase-5 inhibitor (sildenafil, vardenafil, tadalafil).

Data from References 42 and 43.

Airway inflammation and hyper-responsiveness are common in SCD. Therefore, careful screening for respiratory symptoms in adults and children with SCD is essential. Asthma and wheezing (with or without a diagnosis of asthma) in individuals with SCD have been associated with ACS and vasoocclusive pain episodes and increased mortality. Symptoms of asthma exacerbation can overlap with ACS making it difficult to differentiate the two.[1,4,13,27] For the management of asthma, the National Asthma Education and Prevention Program asthma management guideline should be utilized and inhaled corticosteroids are first line for persistent symptoms.[27]

Skeletal and Skin Diseases

Musculoskeletal complications from vasoocclusion are common in SCD and have significant impact on quality of life. Osteonecrosis, particularly of the femoral or humeral heads, causes chronic pain, permanent damage, and disability.[11,44] Low bone mineral density can occur early with a prevalence of over 70% reported in adults with SCD. Osteopenia and osteoporosis associated with low bone formation have been reported in both males and females with SCD.[4,45] Children with SCD also have an increased incidence of osteomyelitis; the organism most often responsible is *Salmonella*.[4,45] Septic arthritis occurs up to 5% in children but is rare in adults.[44] In addition to necrosis of joints, chronic

leg ulcers most commonly seen in the medial and lateral malleolus (ankles) can become a difficult and painful problem for adults. Ulcers are often seen after trauma or infection and are usually slow to heal.[5,22]

Ocular Manifestations

Ocular problems seen in patients with SCD include orbital and retinal manifestation. The incidence of proliferative sickle retinopathy and vitreous hemorrhage is up to 50%. Vasoocclusion in the eye can occur as early as 20 months of age, and clinically detectable retinal diseases usually occur during adolescence and early adulthood. Orbital involvement is uncommon but has a high potential for severe vision loss. Despite the less systemic manifestations, individuals with HbSC develop serious retinal complications more often and earlier than those with HbSS. Lack of visual symptoms does not indicate the absence of ocular manifestations. Annual retinal examination starting at age 10 is recommended for patients with SCD to prevent blindness from retinopathy and other complications.[22,46]

Hepatobiliary Diseases

Cholelithiasis is a common complication of SCD resulting from chronic hemolysis and increased bilirubin production, leading to biliary sludge and/or stone formation. The risk of gallstones increases with age: 12% for age 2 to 4 years, 43% by age 15 to 18 years, and 70% to 75% in adults. Cholecystitis, exemplified by pain in the right upper quadrant, can be confused with an acute sickle pain episode in the abdomen. Mild baseline hepatomegaly and elevation of lever function tests can occur in individuals with SCD. Cirrhosis occurred in 18% of young adults with SCD. Causes for development of chronic hepatic disease include repeated occlusion in the liver, iron overload, and hepatitis.[22,47]

Cardiac Diseases

Cardiovascular complications associated with anemia, including cardiac enlargement and various murmurs, can occur in patients with SCD. Patients experience varying degrees of exertional dyspnea, tachycardia, and palpitation because of the decreased oxygen-carrying capacity of the blood. Left ventricular diastolic dysfunction has been reported in 18% of adults with SCD and is associated with increased mortality, especially in patients with pulmonary hypertension. Left ventricular stiffness and left ventricular hypertrophy have been reported, and the progression is speculated to lead to diastolic dysfunction

later in life. Acute myocardial infarction in adults with SCD may be under-recognized due to the high incidence of sickle cell acute chest pain.[1,10,48]

Renal Diseases

Renal dysfunction in SCD begins during infancy, as evidenced by glomerular hyperfiltration. Other manifestations include inability to concentrate urine, hematuria, tubular acidosis, papillary necrosis, glomerulonephritis, microalbuminuria, and proteinuria. Enuresis, as a result of increased urine production, occurs in 42% of children ages 6 to 8 and 9% in young adults age 18 to 20. Microalbuminuria is typically the first sign of chronic kidney disease, which has been associated with increased mortality.[7,22,49,50]

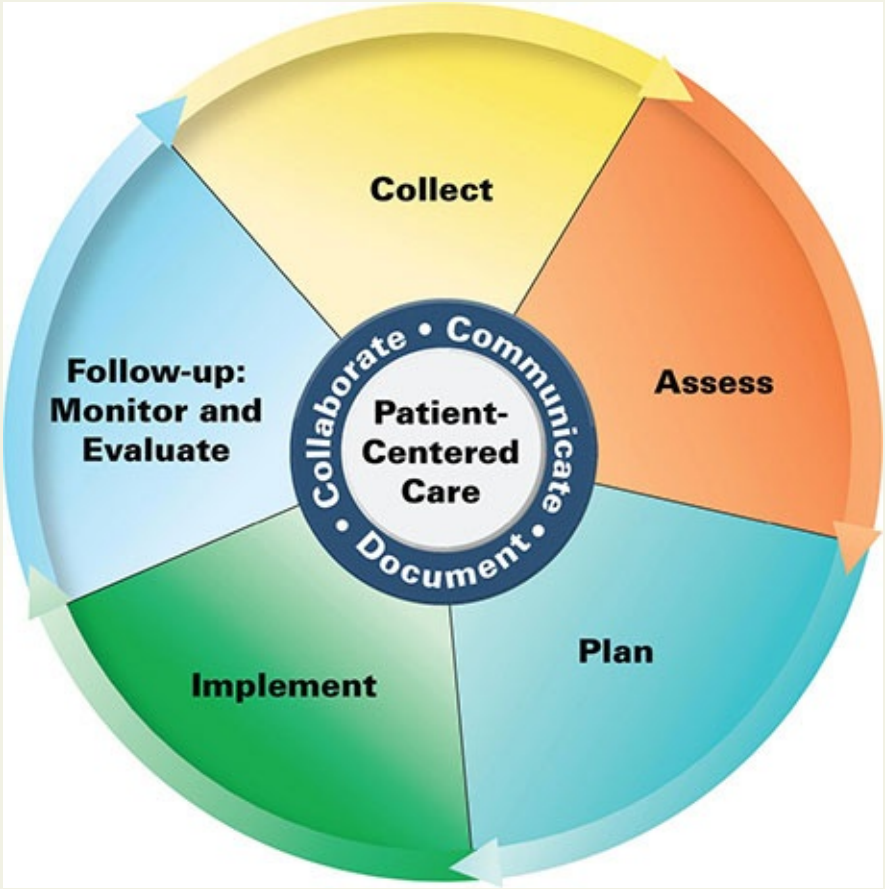
TREATMENT

Desired Outcomes

The goal of treatment is to reduce hospitalizations, complications, and mortality as well as improve quality of life. Management involves the use of general measures to meet the unique demands with the goal of preventing or treating complications of the disease. When an acute complication occurs, the type and severity of the episode determines the appropriate therapeutic plan.

With the availability of public health programs and comprehensive care, most children in developed countries survive through childhood and the burden of reducing mortality has shifted to focus on adults with SCD.[1,7,10] The median survival for HbSS and HbSC are 58 years and 66 years, respectively.[7] Nevertheless, the life expectancy for individuals with SCD remains lower than the general population by at least 20 years; and the most vulnerable period appears to be during the transition to adult medical care.[4,7] Outcome evaluation for management of SCD should include assessment of health-related quality of care in both adults and children.

All patients with SCD should receive regularly scheduled comprehensive medical evaluations. Because of the complexity of the disease, an interprofessional team is needed to provide high-quality medical care, education, counseling, and psychosocial support. Appropriate comprehensive care can have a positive impact on both longevity and quality of life. This care includes the use of evidence-based treatment combining general symptomatic supportive care, preventative medical therapies, and specific disease modifying therapies aimed at altering hematologic capacity and function.



Patient Care Process for Vasooclusive Episodes

Collect

- Patient characteristics (eg, age, sex, SCD genotypes)
- Patient medical history (include organ function and psychosocial issues)
- Immunization history
- Social history (eg, tobacco use)
- Pain diary
- Objective data
    - Vital signs: blood pressure, heart rate, respiratory rate, height, weight, O_2 saturation
    - Labs: CBC, Basic chemistry,
    - Additional labs or imaging per presenting symptoms (see Table 120-2)

Assess

- Hemodynamic stability
- Pain scale
- Adherence to home medication
- Sign or symptoms associated with sickle cell acute complications (see Table 120-2)

Plan*

- Fluid
- Pain management (see Table 120-6)
- Initiate antibiotics if febrile
- Oxygen

Implement

- Provide education on current pain regimen
- Develop individualized plan for pain management
- Evaluate if initiation of hydroxyurea or glutamine
- Schedule follow-up

Follow-Up: Monitor and Evaluation

- Ongoing evaluation of pain level
- Monitor for side effects of pain medication and initiate supportive care if needed

**Collaborate with patient, caregivers, and other healthcare professionals.*

Routine Health Maintenance

SCD is a complex chronic disease involving multiple organs. In addition to the preventive care recommended for the general population, individuals with SCD also need health maintenance and screenings that focus on minimizing complications (**Table 120-4**).

TABLE 120-4 Health Maintenance

Invasive Pneumococcal Infection Prevention

1. Oral penicillin until age 5 for children with HbSS/Sβ°-thal
   a. Discontinue penicillin prophylaxis at age 5 unless have had splenectomy or invasive pneumococcal infection
2. Consider no penicillin prophylaxis for children with HbSC disease and HbSβ⁺-thal unless they have had a splenectomy

Immunization

1. All individuals should receive immunization according to The Advisory Committee on Immunization Practices
2. Pneumococcal Vaccine
   a. All infants should receive complete series of PCV13.
   b. All children should receive PPSV23 at age 2 years and second dose at age 5 years.
   c. Children age 2 to 5 years with incomplete PCV13 vaccination
      i. Unvaccinated or less than 3 doses PCV13: 2 doses of PCV13 with second dose 8 weeks apart
      ii. Received 3 doses of PCV13 but none after 12-month of age: 1 dose of PCV 13
      iii. Give 2 doses of PPSV23 after the PCV13 series completed. First dose at least 8 weeks after PCV13 and second dose at least 5 years later
   d. Children age 6 to 18 years not received PCV13 should receive 1 dose of PCV13.
   e. Children age 6 to18 years not received PPSV23 should receive 2 doses of PPSV23. First dose at least 8 weeks after PCV13 and second dose at least 5 years later
   f. Adults age 19 to 64 years not previously received PCV13 or PPSV23:
      i. 1 dose PCV13
      ii. 2 doses PPSV23. First dose at least 8 weeks after PCV13 and second dose at least 5 years later
   g. Adults 19 to 64 years previously received PPSV23
      i. 1 dose PCV13 at least 1 year after last PPSV23
      ii. 1 dose of PPSV23 at least 5 years after first dose and no sooner than 8 weeks after PCV13
3. Haemophilus Influenza (Hib) Vaccine
   a. Children age greater than 5 years who have not previously received Hib vaccine should receive one dose
4. Meningococcal Vaccine (indicated for persons have functional or anatomic asplenia)[a]
   a. 4-dose primary series to be administered with MenACWY-CRM (2, 4, 6, and 12 months)
   b. Booster dose to be administered with MenACWY-CRM or MenACWY-D
      i. Primary series completed prior to age 7: booster dose 3 years after primary series and repeat every 5 years thereafter
      ii. Primary series completed age 7 or older: booster dose 5 years after primary series and repeat every 5 years thereafter
   c. Unvaccinated children 7-23 months: 2 doses of MenACWY-CRM with second dose at least 12 weeks after the first dose AND after first birthday
   d. Unvaccinated children age 2 years or older and adults: 2 doses of MenACWY-CRM or MenACWY-D 8-12 weeks apart
      i. MenACWY-D to be given at least 4 weeks after completion of all PCV13 doses
   e. Adults previously vaccinated should receive MenACWY-CRM or MenACWY-D every 5 years
   f. Serogroup B Meningococcal (MenB): age 10 or older
      i. MenB-FHbp (Trumenba®): 3-dose series (at 0, 1 to 2, and 6 months); or 2-dose series (at 0 and 6 months)
      ii. MenB-4C (Bexsero®): 2-dose series at least 1 month apart
5. Influenza vaccine annually for age 6 months and older

Renal

1. Screen for proteinuria by age 10 and annually if negative
2. Initiate ACE inhibitor for adults with microalbuminuria or proteinuria without apparent cause

Pulmonary Hypertension (PH)

1. Noninvasive tests (Doppler echocardiography or alternatively, serum NT-pro-BNP measurement) can be used to assess mortality risk
2. Echocardiogram to screen for PH and associated cardiac problems by age 8 for those with frequent cardiorespiratory symptoms
3. The optimal frequency for Doppler echocardiography is unknown but every 1-3 years seems to be reasonable
4. Children with evidence of PH by echocardiogram should be further evaluated: pulmonary function test, polysomnography, oxygenation assessment, and thromboembolic disease
5. Cardiac catheterization should be performed before initiation of PAH-specific therapy

Ophthalmological Evaluation

1. Dilated eye examination begins at age 10 and rescreen at 1-2 year intervals

Stroke Prevention

1. Children with SCA: transcranial Doppler (TCD) annually beginning at age 2 until at least age 16
2. Chronic transfusion therapy for stroke prevention in children with elevated (>200 cm/s) TCD results

[a]Brand name for meningococcal vaccine: MenACWY-CRM (Menveo®), and MenACWY-D (Menactra®)

Data from References 22,32,35,42,51–54.

PCV13, 13-valent conjugate pneumococcal vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; ACE Inhibitor, angiotensin converting enzyme inhibitor; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary artery hypertension; PH, pulmonary hypertension.

Growth and development in children with SCD should be monitored as delayed growth and sexual maturation are common.[4,10,39] Depression, anxiety, and other behavior issues are more common in children and adults with SCD than in the general population and have a significant impact on quality of life. Psychosocial supports are essential elements of care for individuals with SCD as well as their caretakers.[9,55] Pregnancy introduces an increased risk for the mother with SCD and for the fetus. Reproductive counseling and education should be incorporated in the care of individuals with SCD.[22,56]

Immunizations

Administration of routine immunizations is crucial preventive care in managing SCD. Children 6 months and older and adults with SCD should receive influenza vaccine annually. The most updated immunization and catch-up schedules are provided by the Centers for Disease Control and Prevention (http://www.cdc.gov/vaccines/schedules).

Impaired splenic function increases susceptibility to infection by encapsulated organisms, particularly *S. pneumoniae*. Prior to the routine use of penicillin prophylaxis and the development of pneumococcal vaccines, invasive pneumococcal disease was 20- to 100-fold more common in children with SCD than in healthy children. Reduced mortality has been associated with the introduction of pneumococcal vaccines.[1,4]

Two different pneumococcal vaccines are available. The 13-valent pneumococcal conjugate vaccine (PCV13; Prevnar®) induces good antibody responses in infants and children less than 2 years of age. Immunization with the PCV13 is recommended for all children, regardless of SCD status, younger than 24 months of age. Infants should receive the first dose after 6 weeks of age. Two additional doses should be given at 2-month intervals, followed by a fourth dose at age 12 to 15 months. The 23-valent pneumococcal polysaccharide vaccine (PPSV23; Pneumovax®23) is recommended for all children with functional or acquired asplenia but must be given after 2 years of age because of poor antibody response. To cover different serotypes, PPSV23 should be given starting at 2 years of age, and be administered 2 months after the last dose of the PCV13. A booster dose of PPSV23 is recommended 5 years after the first dose. Both pneumococcal vaccines are recommended for adults with certain medical conditions, including SCD (Table 120-4).[51,53]

The risk of meningococcal disease is also higher in SCD and vaccination is recommended for individuals with functional or acquired asplenia. Two types of

meningococcal vaccines are available: (1) quadrivalent (serogroups A, C, Y, and W-135) meningococcal conjugate vaccines (MenACWY-CRM and MenACWY-D) and (2) meningococcal group B vaccine (MenB-FHbp and Menb-4C). Infants with functional asplenia should receive 4-dose series with MenACWY-CRM at 2, 4, 6, and 12 months. Children over 2 years and adults with functional or acquired asplenia should receive a primary immunization series with two doses of the quadrivalent vaccine given 8 weeks apart. MenACWY-D should be given at age 2 years or older and at least 4 weeks after completion of all PCV13. A booster is recommended every 5 years for individuals with SCD.[22,52,54] Group B meningococcal vaccination is given to children with functional asplenia 10 years of age or older as a 2-dose (MenB-FHbp or Menb-4C) or 3-dose (MenB-FHbp) immunization series and these two vaccines are not interchangeable (Table 120-4).[52,54]

Penicillin

4 Penicillin prophylaxis until at least 5 years of age is recommended in children with SCD HbSS or HbSβ^0-thal, even if they have received PCV13 or PPSV23 immunization, as prophylaxis against invasive pneumococcal infections. An effective regimen that reduces the risk of pneumococcal infections by 84% is penicillin V potassium at a dosage of 125 mg orally twice daily until the age of 3 years, followed by 250 mg twice daily until the age of 5 years. Individuals who are allergic to penicillin can be given erythromycin 20 mg/kg/day. Penicillin prophylaxis is not routinely given in older children, based on a study demonstrating no benefit over placebo beyond the age of 5 years. However, continuation of oral pneumococcal prophylaxis should be considered on a case-by-case basis and is recommended for anyone with a history of invasive pneumococcal infection or surgical splenectomy.[22,32]

Hydroxyurea

HbF reduces polymer formation of HbS due to its high-oxygen affinity. Higher HbF levels are associated with decreased RBC sickling and RBC adhesion and observational studies show a relationship between HbF concentration and severity of SCD. Individuals with SCD and low HbF levels experience more frequent pain and higher mortality. HbF levels of 20% or greater are associated with lower risk of acute sickle cell complications. Based on these observations, HbF induction has become a treatment modality for patients with SCD.

Hydroxyurea (HU), a chemotherapeutic agent, stimulates HbF production and

increases the number of HbF-containing reticulocytes and intracellular HbF. The drug inhibits DNA synthesis by blocking the conversion of ribonucleoside to deoxyribonucleotides. The exact mechanism of HbF production is unknown but is postulated that its myelosuppressive effect stimulates stress erythropoiesis and triggers rapid erythroid regeneration and shifts erythrocyte hemoglobin production to HbF. In addition, HU increases NO levels, reduces neutrophils and monocytes, has antioxidant properties, alters the RBC membrane, increases RBC deformability by increasing intracellular water content, and decreases RBC adhesion to the endothelium.

HU is FDA approved for patients 2 years of age and older with recurrent moderate-to-severe painful crises to reduce the frequency of painful crises and the need for blood transfusions. The Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH Trial) was the first double-blind, placebo-controlled randomized controlled trial of HU in SCD. In that study, HU significantly reduced the frequency of painful episodes, risk of ACS, need for blood transfusions, and number of hospitalizations in adults with SCD. The incidence of death, stroke, and hepatic sequestration in the HU and placebo groups was not significantly different during the evaluation period. However, a follow-up study showed a 40% reduction in mortality with HU over a 9-year period. The original 299 patients from the MSH study were followed for 17.5 years and the results suggest improved survival with the long-term use of HU.[10,26,57,58]

Studies in pediatric patients have reported similar results to the MSH Trial with no adverse effects on growth and development. In addition, some patients treated with HU therapy had possible recovery or preservation of splenic and brain functions, including cognitive performance. The Transcranial Doppler with Transfusions Converting to Hydroxyurea study (TWiTCH) closed early after interim analysis showed that HU was not inferior to chronic blood transfusions to prevent primary stroke. However, the Stroke with Transfusions Changing to Hydroxyurea (SWiTCH) trial also closed early when the interim analysis showed that HU was inferior to chronic transfusions to prevent recurrent stroke. Therefore, chronic transfusions with iron chelation remain the preferred therapy to prevent stroke.[10,26,57,58] Initiating HU early and prior to development of complications may be beneficial. The Pediatric HU Phase III Clinical Trial (BABY HUG) randomized young children ages 9 to 18 months to HU or placebo. Although investigators found no significant difference in the primary endpoints (splenic and renal function), children treated with HU had fewer episodes of pain and dactylitis with no significant toxicities.[6,57,59] HU reduced the risk of painful events, ACS, renal enlargement, hospitalizations, and

transfusions. In addition, improved urine concentration ability as demonstrated by higher urine osmolality was reported.[57,58] In a retrospective study of children aged 3 to 18 years with SCD, significant reduction in mortality, fewer hospitalizations and emergency visits, and shorter admissions were reported.[60]

The most common adverse effect of HU is bone marrow suppression, resulting in neutropenia, thrombocytopenia, anemia, and decreased reticulocyte count. These hematologic adverse effects usually recover within 2 weeks of therapy discontinuation. Other adverse effects include dry skin and hyperpigmentation of skin or nails.[4,22,57,59] Long-term adverse effects of HU therapy in patients with SCD are not fully known, although no serious adverse effects were reported in the long-term (17.5 years) follow-up study of the MSH trial. Studies in children have not demonstrated delays in growth or puberty, increased risk of infections, or genotoxicity.[61] Myelodysplasia, acute leukemia, and chronic opportunistic infection associated with T-lymphocyte abnormalities have been reported in other patient populations treated with higher doses of HU. Reproductive toxicity is also a concern. High-dose HU has been shown to be teratogenic in animals, but normal pregnancies have been reported in women with SCD who received HU during pregnancy.[57]

Although HU was only FDA approved for patients age 2 years and older with SCD in 2017, the agent has been used in pediatric patients for years.[1,3,4,22] Clinical indications for HU include frequent painful episodes, severe symptomatic anemia, a history of ACS, or other severe vasoocclusive complications (**Table 120-5**). The starting dose for adult is 15 mg/kg/day rounded to the nearest 500 mg as a single daily dose. A lower dose of 5 to 10 mg/kg/day is used for patients with chronic disease. The recommended dose for children is 20 mg/kg. Dosage can be increased by 5 mg/kg up to a maximum of 35 mg/kg in 8-week intervals if the patient does not demonstrate significant adverse effects and blood counts are stable (**Fig. 120-6**). HU dosage should be individualized based on response and toxicity. In general, 3 to 6 months of therapy are required before improvement is observed. Medication adherence can be an issue. Since the MCV generally increases as the level of HbF increases, monitoring MCV is an inexpensive and convenient method to monitor response and adherence.[1,3,4,22,57]

TABLE 120-5 Recommendations on Hydroxyurea Therapy

	Recommendation	Strength	Evidence Quality
Adults with HbSS or Sβ^0-thalassemia			
• Three or more sickle cell–associated moderate-to-severe pain crises per year	Treat with hydroxyurea	Strong	High
• Sickle cell–associated pain that interferes with daily activities and quality of life		Strong	Moderate
• History of severe and/or recurrent ACS		Strong	Moderate
• Severe symptomatic chronic anemia that interferes with daily activities or quality of life		Strong	Moderate
Infants 9 months of age and older, children, and adolescents with HbSS or Sβ^0-thalassemia regardless clinical severity	Offer hydroxyurea	Strong	High (age 9-42 months); Moderate (>42 months)
Sickle nephropathy with persisting proteinuria despite therapy	Consider hydroxyurea	Weak	Low
Chronic hypoxia	Treat with hydroxyurea	Strong	Low
HbSC or HbSβ$^+$-thalassemia with recurrent sickle cell–associated pain that interferes with daily activities or quality of life	Consider hydroxyurea	Moderate	Low
History of stroke and unable to implement chronic transfusion	Initiate hydroxyurea	Moderate	Low

Data from References 57 and 58.

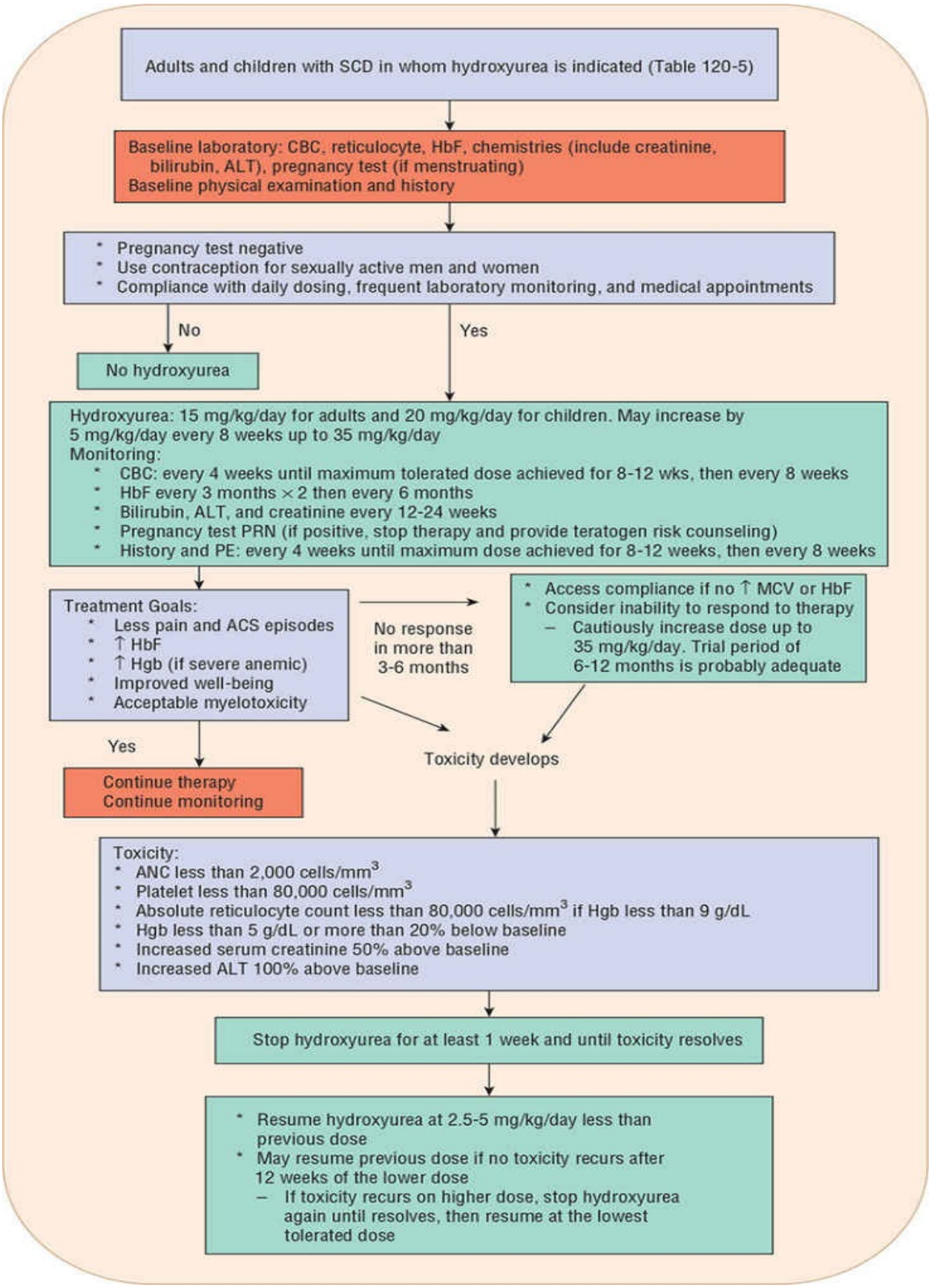

Adults and children with SCD in whom hydroxyurea is indicated (Table 120-5)
Baseline laboratory: CBC, reticulocyte, HbF, chemistries (include creatinine, bilirubin, ALT), pregnancy test (if menstruating)
Baseline physical examination and history
* Pregnancy test negative
* Use contraception for sexually active men and women
* Compliance with daily dosing, frequent laboratory monitoring, and medical appointments
No
Yes
No hydroxyurea
Hydroxyurea: 15 mg/kg/day for adults and 20 mg/kg/day for children. May increase by 5 mg/kg/day every 8 weeks up to 35 mg/kg/day
Monitoring:
* CBC: every 4 weeks until maximum tolerated dose achieved for 8-12 wks, then every 8 weeks
* HbF every 3 months × 2 then every 6 months
* Bilirubin, ALT, and creatinine every 12-24 weeks
* Pregnancy test PRN (if positive, stop therapy and provide teratogen risk counseling)
* History and PE: every 4 weeks until maximum dose achieved for 8-12 weeks, then every 8 weeks
Treatment Goals:
* Less pain and ACS episodes
* ↑ HbF
* ↑ Hgb (if severe anemic)
* Improved well-being
* Acceptable myelotoxicity
No response in more than 3-6 months
* Access compliance if no ↑ MCV or HbF
* Consider inability to respond to therapy
– Cautiously increase dose up to 35 mg/kg/day. Trial period of 6-12 months is probably adequate
Yes
Continue therapy
Continue monitoring
Toxicity develops
Toxicity:
* ANC less than 2,000 cells/mm3
* Platelet less than 80,000 cells/mm3
* Absolute reticulocyte count less than 80,000 cells/mm3 if Hgb less than 9 g/dL
* Hgb less than 5 g/dL or more than 20% below baseline
* Increased serum creatinine 50% above baseline
* Increased ALT 100% above baseline
Stop hydroxyurea for at least 1 week and until toxicity resolves
* Resume hydroxyurea at 2.5-5 mg/kg/day less than previous dose
* May resume previous dose if no toxicity recurs after 12 weeks of the lower dose
– If toxicity recurs on higher dose, stop hydroxyurea again until resolves, then resume at the lowest tolerated dose

FIGURE 120-6 Hydroxyurea use in sickle cell disease. Blood test results expressed in SI units that are consistent with toxicity are <2 x 10^9/L for ANC; <80 x 10^9/L for platelets; <80 x 10^9/L for absolute reticulocyte count if Hbg <90 g/L (5.59 mmol/L); and Hbg <50 g/L (3.10 mmol/L). (ACS, acute chest syndrome; ALT, alanine aminotransferase; ANC, absolute neutrophil count; CBC, complete blood cell count; Hb, hemoglobin; HbF, fetal hemoglobin; HbSS, homozygous sickle cell hemoglobin; HbSSβ^0, sickle cell β^0-thalassemia; MCV, mean corpuscular volume; PE, physical examination; PRN, as needed; RBC, red blood cell.) (*Data from References 1, 3, 4, and 22.*)

5 Patients receiving HU should be closely monitored for toxicity. Blood counts should be checked every 4 weeks during dose titration and every 8 weeks thereafter. Treatment should be interrupted if hematologic indices fall below the following values: absolute neutrophil count, 2,000 cells/mm^3 (2 × 10^9/L); platelet count, 80,000 cells/mm^3 (80 × 10^9/L); hemoglobin, 5 g/dL (50 g/L; 3.1 mmol/L); or reticulocytes, 80,000 cells/mm^3 (80 × 10^9/L) if the hemoglobin concentration is less than 9 g/dL (90 g/L; 5.59 mmol/L). Other laboratory abnormalities warranting temporary discontinuation of therapy are a 50% increase in serum creatinine and a 100% increase in transaminases. After recovery has occurred, treatment should be resumed at a dose that is 5 mg/kg/day lower than the dose associated with toxicity. If no toxicity occurs after 12 weeks with the lower dose, the dose can be increased by 2.5 to 5 mg/kg/day. If the increased dose produces hematologic toxicity, the patient should be maintained at the last tolerated dose with no further escalation except for normal growth or weight gain.[22,57,58]

Glutamine

Sickled RBCs are susceptible to oxidative damage leading to hemolysis and vasoocclusion. Glutamine, an essential amino acid, is a precursor for nicotinamide adenine dinucleotide (NAD^+) synthesis. Early studies have shown increased uptake of glutamine by sickle RBCs, mainly to produce NAD^+. Children with SCD have lower glutamine levels; an increase of NAD^+ can potentially restore the redox balance in oxidative stressed cells.

In a phase III double-blind, placebo-controlled trial, 230 adult and pediatric patients with SCD and a history of two or more pain crisis were enrolled. The median number of pain episodes over the study period of 48 weeks was significantly lower for the L-glutamine group. In addition, fewer hospitalizations

were also reported but no difference in emergency room visits not resulting in hospitalization. L-glutamine was well tolerated overall but nausea, noncardiac chest pain, fatigue, and musculoskeletal pain were more commonly reported in the L-glutamine group.[62]

L-glutamine (Endari®) was FDA-approved in July 2017, becoming the first product approved for pediatric patients with SCD and the first new treatment for adults in almost 20 years. It is indicated for SCD patients age 5 and older to reduce the acute complications of SCD. The product is available in 5-g packets and should be mixed with 8 ounces of liquid (~240 mL) or 4 to 6 ounces (~110-170 g) of food. The recommended dose is based on weight: 5 g twice a day for less than 30 kg; 10 g twice a day for 30 to 65 kg and 15 g twice a day for greater than 65 kg. The most common gastrointestinal side effects are constipation, abdominal pain, and nausea.[63]

Disease Modifying Therapies

Only hydroxyurea and glutamine are currently approved by the FDA for the management of SCD. With the expanded knowledge on the pathophysiologic mechanisms, multiple clinical trials with different therapeutic approaches are being studied. These agents target cell adhesion, inflammatory pathways, HbF modification and hemoglobin oxygen affinity modification (antisickling agent). With the complexity of the disease, a combination of agents with different mechanisms of action to modify the disease process may provide optimal therapy in the future.

Chronic Transfusion Therapy

RBC transfusions play an important role in the management of SCD. In acute illness, transfusions can be life-saving and the guidelines for acute transfusion are discussed later. Chronic transfusion programs can prevent serious complications of SCD. The primary indication for chronic transfusion is primary and secondary stroke prevention and amelioration of organ damage.[4,64] Blood transfusions can be administered as a simple transfusion, a manual exchange or an automated exchange called erythrocytapheresis. Exchange transfusion frequently requires permanent venous access and is associated with higher cost but has the advantage of increasing normal (donor) HbA, limiting volume, minimizing hyperviscosity, and transfusional iron overload.[22]

6 In children with an overt stroke, chronic transfusions are used as

secondary stroke prevention and reduce stroke recurrence from about 50% to about 10% over 3 years. An initial stroke in SCD can be devastating and transfusions can be given for primary stroke prevention. Prophylactic transfusions significantly reduced the incidence of first stroke (primary stroke prevention) over a 2-year period in children 2 to 16 years of age who were at an increased risk for stroke based on abnormal annual screening TCD. The risk of stroke was reduced from 16% in patients receiving usual care to 2% in those who received prophylactic transfusions.[64] Chronic transfusions should be considered in children and adults with previous stroke or children with abnormal TCD measurements.[22] Chronic transfusions may also be useful in patients with severe or recurrent ACS, debilitating pain, chronic organ failure, intractable leg ulcers, severe chronic anemia with cardiac failure, and complicated pregnancies, although data supporting the efficacy of chronic transfusion in these situations are limited.[65]

The goal of transfusions is to achieve and maintain an HbS concentration of less than 30% of total hemoglobin in the primary and secondary prevention of neurologic complications. Transfusions are usually given every 3 to 4 weeks, but the frequency of transfusion is adjusted to maintain the desired HbS levels. The risk of recurrent stroke decreases after 2 years of transfusion therapy and, in the absence of recurrent stroke, many clinicians will liberalize the HbS goal to less than 50%.[4,64] The optimal duration of primary prophylactic transfusion therapy in children with abnormal TCD is not clear, but discontinuation of transfusions has been associated with a 50% stroke recurrence rate within 12 months and abnormal blood flow velocity on TCD in children with SCD. The results of the TWiTCH trial suggest that some patients can safely transition to HU therapy after normalization of TCD and no evidence of cerebral vasculopathy with at least a 6-month overlap in transfusions and HU therapy. For secondary stroke prevention, transfusions should be continued indefinitely.[4,57,64] A pilot study suggested that HU could be started prior to discontinuation of transfusion for secondary stroke prevention with at least a 6-month overlap with transfusions. However, the phase III trial of switching HU for transfusion in secondary stroke prevention, the SWiTCH trial, was closed early due to an increased risk of recurrent strokes in the HU arm when compared to the transfusions arm.[38] The NIH recommends HU for prevention of recurrent stroke only if implementation of a transfusion program is not possible.[22]

Although the benefits of transfusion therapy are clear in some clinical situations, its role in other situations such as priapism or an acute pain episode remains controversial.[22] The risks of transfusion therapy must be weighed

against possible benefits. The risks associated with transfusion therapy include alloimmunization (sensitization to the blood received), hyperviscosity, transfusion transmitted viral infections, volume overload, iron overload, and nonhemolytic transfusion reactions. The use of leukocyte-reduced RBC transfusions in chronically transfused patients can reduce the risk of nonhemolytic transfusion reactions and viral transmission.[4,64,65] Transfusion-related infections remain a concern. All patients should be immunized with hepatitis A and B vaccines. Other viruses that can be transmitted through blood products are parvovirus B19, hepatitis, and cytomegalovirus. The risk of contracting human virus (HIV) from blood transfusions, although still of concern, has decreased with routine blood screening.[32,64]

Alloimmunization or alloantibody formation occurs in 19% to 37% of SCD patients who receive RBC transfusions and results from antigen differences on the red cell surface between the primarily Caucasian donor pool and recipients with SCD. Alloimmunization can make it difficult to find cross-matched blood and cause delayed hemolytic transfusion reactions. To prevent alloimmunization, patients receiving chronic transfusions should receive the best cross-matched blood including extended typing of other red cell antigens especially C, E, and Kell or full RBC phenotyping.[22,64,65]

The development of alloimmunization can be life threatening for individuals with SCD. Delayed hemolytic transfusion reactions (DHTR) usually occur within 7 to 10 days after transfusion but can occur as early as 2 days or as late as 20 days after transfusion. During a DHTR, patients develop symptoms consistent with hemolysis such as worsening pain, especially abdominal pain, severe anemia due to hemolysis of the transfused unit and reticulocytopenia, further aggravating the anemia. Subsequent transfusions can further worsen the clinical situation because of the presence of multiple antibodies making cross-matching difficult. Life-threatening events can be treated with steroids and intravenous immunoglobulin. Recombinant erythropoietin has been used in patients with reticulocytopenia.[22,64,65] Recovery, as evidenced by reticulocytosis with a gradual increase in the hemoglobin level, may occur only after further transfusions are withheld. Although some patients tolerate further transfusions after recovery, especially if the donor unit is negative for the offending alloantibody, others cannot avoid recurrent transfusions and may experience another hemolytic transfusion reaction. Rituximab has been used to prevent recurrent DHTR. It is generally preferable to prevent the development of DHTR by performing RBC phenotyping and, at a minimum, transfusing individuals with blood that is C, E, and Kell negative.[4,22,65]

Transfusional iron overload is another complication of RBC transfusions and patients should be instructed to avoid excess dietary iron.[64,65] Abnormal liver biopsy results showing mild-to-moderate inflammation or fibrosis have been reported. Iron overload assessments include liver function test annually or semiannually and serum ferritin. Iron overload can be confirmed by liver biopsy or less invasively by MRI.[22,65] Three chelating agents are available. Deferoxamine has been used as a chelating agent for decades but must be administered by subcutaneous or intravenous infusion. The oral chelation agents, deferasirox and deferiprone, are as effective as deferoxamine with acceptable safety profiles in long-term studies up to 5 years.[66–68] Deferasirox is available in two forms. Exjade® is a dissolving tablet given once daily on an empty stomach starting at 20 mg/kg/day. Jadenu® is given as a film-coated tablet or sprinkle granule once daily on an empty stomach or with a light meal starting at a lower dose of 14 mg/kg/day. The common side effects for deferasirox are transient skin rash and gastrointestinal symptoms such as nausea, vomiting, diarrhea, and abdominal pain. However, some patients may prefer film coated tablets as it is more palatable and can be taken with food. Deferiprone has good oral bioavailability but a short half-life. The usual starting dose for deferiprone is 75 mg/kg/day, given in three divided dose. Similar to deferasirox, the common adverse effects for deferiprone are rashes and gastrointestinal symptoms but the most concerning side effects are neutropenia and agranulocytosis. For patients who require more aggressive management, deferoxamine in combination with either oral agents has been reported.[66–69]

Allogeneic Hematopoietic Stem Cell Transplantation

Allogeneic hematopoietic stem cell transplantation (HSCT) is currently the only therapy that can cure patients with SCD. The overall survival rate and disease-free survival rate for children and young adults with HLA-matched sibling donors, has been reported at 95% to 98% and 87% to 92%, respectively.[70,71] The reported incidences of acute and chronic GVHD ranged from 5% to 17% and 0% to 3%, respectively. Other complications included seizures, marrow rejection, and sepsis. Improved growth, stabilization or improvement of CNS abnormalities, and recovery of splenic dysfunction were observed in posttransplant SCD patients, but gonadal failure and delayed sexual development in females requiring hormonal replacement have been reported.[72]

The optimal candidates for matched sibling donor transplant are SCD patients with severe disease (HbSS and HbSB°) prior to onset of SCD symptoms, stroke,

elevated TCD velocity, recurrent ACS, recurrent pain, red cell alloimmunization on chronic transfusion protocol, pulmonary hypertension, and sickle nephropathy.[73,74] Unfortunately, many children who are eligible for HSCT do not have an HLA-matched sibling donor and unrelated HLA-matched transplants are associated with higher transplant-related mortality. However, unrelated matched allogeneic HSCT is considered in SCD patients who are younger than 16 years of age, have a severe form of SCD and complications such as stroke, elevated TCD velocity, recurrent ACS despite supportive care, recurrent pain despite supportive care, red cell alloimmunization with indication for chronic transfusion, pulmonary hypertension, and sickle nephropathy. Because allogeneic HSCT performed in young children before organ damage and alloimmunization occur is associated with increased success, counseling and screening for HLA-matched sibling donors during the first year of life is now recommended. The risks associated with allogeneic HSCT must be carefully considered, as the transplant-related mortality rate is about 5% to 10%, and graft rejection is about 10%. Other risks associated with allogeneic HSCT include secondary malignancies. Neurologic events, such as intracranial hemorrhage and seizures during transplant, were seen more frequently in patients with a history of stroke.[73,74]

Umbilical cord blood is another potential donor source with some advantages over marrow donors including a lower incidence of severe GVHD and a larger donor pool from which to select donors, but such advantages are offset by longer time to engraftment and a higher rate of graft rejection.[72–74] Newer protocols are currently under investigation using haploidentical donors such as parents for patients with recurrent stroke on chronic transfusions or severe SCD symptoms with no sibling or unrelated matched donor. Use of nonmyeloablative allogeneic HSCT in adults and pediatric patients reported mixed donor-recipient chimerism and reversal of SCD in several clinical trials and has the advantage of less acute toxicity.[70–72,74]

Treatment of Complications

Parents and older children should be educated on the signs and symptoms of complications and conditions that require urgent evaluation. During acute illness, patients should be evaluated promptly because deterioration can occur rapidly. Fluid balance should be maintained because dehydration and fluid overload can worsen complications associated with SCD. Oxygen saturation by pulse oximetry should be maintained at least 92% or at baseline. New or increasing

supplemental oxygen requirements should be investigated.

Episodic Transfusions for Acute Complications

Indications for acute blood transfusions include (1) acute exacerbation of baseline anemia, such as aplastic crisis if the anemia is severe, hepatic or splenic sequestration, or severe hemolysis; (2) ACS, stroke, intrahepatic cholestasis, or acute multisystem organ failure; and (3) preparation for procedures that require the use of general anesthesia.[22] Acute transfusion is not indicated for priapism, uncomplicated pain or asymptomatic anemia. Simple transfusion or partial exchange transfusion can be used, though red cell exchange has been shown to have superior outcomes when compared to simple transfusion in overt stroke. If simple transfusion is used, volume overload leading to congestive heart failure can occur if anemia is corrected too rapidly in patients with severe anemia. In addition, increases in hemoglobin levels to greater than 10 g/dL (100 g/L; 6.21 mmol/L) can cause hyperviscosity and should be avoided.[3,22]

Infection and Fever

Fever in a patient with SCD should be considered a medical emergency with rapid administration of intravenous antibiotics due to the risk of overwhelming sepsis. Patients with SCD should be evaluated as soon as possible for any fever greater than 38.5°C (101.3°F). Criteria for hospitalization include an infant younger than 1 year, history of previous bacteremia or sepsis, temperature greater than 39.5°C (103.1°F), WBC greater than 30,000 cells/mm^3 (30×10^9/L) or less than 5,000 cells/mm^3 (5×10^9/L) and/or platelets less than 100,000 cells/mm^3 (100×10^9/L), and evidence of other acute complications or toxic appearance. Outpatient management can be considered in older nontoxic children with reliable family caregivers. Antibiotic choice should provide adequate coverage for encapsulated organisms.[4,22,32,75]

7 Ceftriaxone should be used for outpatient management because it provides coverage for 24 hours unless the patient has received ceftriaxone in the previous 8 weeks and then ampicillin should be given due to ceftriaxone-induced hemolysis.[76] For patients with cephalosporin allergy, clindamycin can be used. Vancomycin should be considered for acutely ill children or if *Staphylococcus* is suspected. A macrolide antibiotic should be added if *Mycoplasma pneumoniae* is suspected such as in ACS. Penicillin prophylaxis should be discontinued while the patient is receiving broad-spectrum antibiotics. Acetaminophen or ibuprofen can be used for fever control. Increased fluid requirement may be present

because of poor oral intake and/or increased insensible losses contributing to dehydration.[13,32]

Cerebrovascular Accidents

Patients with acute neurologic events must be hospitalized and monitored closely. Physical and neurologic examination should be performed every 2 hours. Acute treatment for children should include exchange transfusion to maintain hemoglobin at about 10 g/dL (100 g/L; 6.21 mmol/L) and HbS less than 30%, anticonvulsants for patients with a seizure history, and therapy for increased intracranial pressure if needed. Chronic transfusion therapy should be initiated for children with ischemic stroke as discussed earlier. In adults presenting with ischemic stroke related to atherosclerotic disease and not occlusion by sickled red cells, thrombolytic therapy should be administered if it is less than 3 hours since the onset of symptoms.[13,22,36,77]

Acute Chest Syndrome

Patients with ACS should use incentive spirometry frequently (eg, at least every 2 hours while awake) to reduce atelectasis development. In addition, proper management of pain is important. The goal is to provide relief while avoiding analgesic-induced hypoventilation. Appropriate fluid therapy is important as overhydration can cause pulmonary edema and exacerbate respiratory distress. Early use of broad-spectrum antibiotics, including a macrolide or quinolone in adults, is also recommended. Studies indicate that infection is the most common cause of ACS and can involve gram-positive, gram-negative, or atypical bacteria. Oxygen therapy is indicated for all patients who are hypoxic or in acute distress. In a patient with a history of reactive airway disease, asthma or wheezing on examination, a trial of bronchodilators is appropriate. Transfusions are indicated for severe ACS with worsening hypoxia and increased work of breathing.[13,33,34]

Steroids can decrease inflammation and endothelial cell adhesion. Glucocorticoids can decrease the duration of hospitalization and need for transfusions and other supportive care but can also increase the readmission rate for other sickle cell–related complications. Another potential therapy is the use of NO, which relaxes and dilates blood vessels. Its hematologic effects include inhibition of platelet aggregation and reduction in the polymerization tendency of HbS. Marked improvement of pulmonary status and cardiac output were reported in case reports of patients with ACS.[33,34]

Priapism

Stuttering priapism, episodes that last a few minutes to 2 hours, may resolve spontaneously with exercise, warm bath, and oral analgesics. Prolonged episodes lasting more than 2 to 3 hours require prompt medical attention. The initial goals of treatment are to provide appropriate analgesic therapy, reduce anxiety, produce detumescence, and preserve testicular function and fertility. Treatment given within 4 to 6 hours can usually reduce erection. Aggressive hydration and adequate pain control should be initiated. Heat (hot water bottles, hot packs, or sitz baths) can provide comfort without precipitating pain crisis. Although transfusions have been given to these patients, they are not recommended for this use because they have not been shown to be efficacious and are associated with severe neurologic sequelae.[40,78]

Clinicians have used both vasoconstrictors and vasodilators in the treatment of priapism. Vasoconstrictors, such as diluted phenylephrine (10 mcg/mL) or epinephrine (1 mcg/mL), are thought to work by forcing blood out of the corpus cavernosum into the venous return. In one uncontrolled, open-label study, aspiration followed by intrapenile irrigation of epinephrine was well tolerated and effective in 37 of 39 episodes. Detumescence can be achieved more rapidly using penile irrigation than simple transfusion but the procedure should be performed by an urologist with experience in the treatment of priapism.[13,40,78]

Vasodilators, such as terbutaline and hydralazine, relax the smooth muscle of the vasculature. This relaxation allows oxygenated arterial blood to enter the corpus cavernosum, which displaces or washes out the damaged sickle cells. Terbutaline has been used to treat priapism, but it has not been formally studied in patients with SCD.[40,78] Antiandrogens, bicalutamide and finasteride, have been used in SCD for treatment of recurrent or refractory priapism without major side effects.[78] Surgical interventions used in severe refractory priapism have included a variety of shunt procedures. These surgical procedures have been successful in some cases, but they have a high failure rate and potentially serious complications, which include impotence, skin sloughing, cellulitis, and urethral fistulas.[40,78]

Modalities to prevent priapism are limited and not well studied. Pseudoephedrine (30 or 60 mg/day given orally at bedtime) and leuprolide, a gonadotropin-releasing hormone, have been used. In one case report, a single oral sildenafil dose at onset of priapism aborted episodes. However, long-term studies of sildenafil have shown an increase in the frequency of pain episodes.[40,78] The results of a randomized, double-blind, placebo-controlled trial

to evaluate efficacy and safety of sildenafil at a dose of 50 mg/day to prevent recurrent episodes was inconclusive partly due to a small sample size.[79] The effect of HU promotes NO release but its effect on priapism has not been established.[80] Some clinicians transfuse patients to maintain an HbS level less than 30% to prevent recurrent priapism. Duration of such regimens should be limited to 6 to 12 months. Long-term chronic transfusions to prevent priapism are not recommended.[22,78]

Aplastic Crisis

Treatment of aplastic crisis is primarily supportive, and most patients recover spontaneously within 5 to 10 days. The only treatment may be blood transfusion if the anemia is severe or symptomatic. The reticulocyte count is used to detect the suppression of red cell production and the need for transfusion. The most common cause, parvovirus B19, is contagious and infected patients should be placed in isolation. In addition, contact with pregnant healthcare providers should be avoided because parvovirus infection during the midtrimester of pregnancy can result in hydrops fetalis and stillbirth.[4,13,32]

Splenic Sequestration

Splenic sequestration is a major cause of mortality in young children with SCD. The sequestration of RBCs in the spleen can result in a rapid drop of hemoglobin, leading to hypovolemia, shock, and death. Immediate treatment with fluid resuscitation and blood transfusions is indicated to correct hypovolemia. Broad-spectrum antibiotic therapy, which includes coverage for *S. pneumoniae* and *H. influenzae*, can also be beneficial if the patient is febrile as infection can precipitate sequestration.[1,4,22]

Recurrent episodes occur in about half of patients and are associated with increased mortality. Options for management of recurrence include observation and splenectomy.[22] Increased risk of invasive infection after splenectomy is a concern in very young children, but most experts agree individuals with HbSS develop splenic dysfunction as early as 6 months of age and have acquired asplenia by 5 years of age and by 10 to 12 years for those with HbSC. Splenectomy is probably indicated, even after a single sequestration crisis, if that sequestration was life threatening. Splenectomy should be considered after repetitive episodes, even if they are less serious. For children younger than 2 years of age, some experts recommend chronic blood transfusions to prevent sequestration and delay splenectomy until the age of 2 years, when the risk of

postsplenectomy septicemia is lower and pneumococcal vaccination has been completed. Finally, splenectomy should also be considered for patients with chronic hypersplenism.[4,13,22,35]

Acute Sickle Cell Pain

Hydration and analgesia are the mainstays of treatment for vasoocclusive (painful) episodes (**Table 120-6**). Patients with mild pain crisis can be treated as outpatients with rest, increased fluid intake, warm compresses, and oral analgesics. Hospitalization is necessary for moderate-to-severe pain or when oral analgesics fail to relieve pain. A pain episode may be precipitated by several risk factors including infection. In the setting of pain and fever, an infectious etiology should be considered and appropriate empiric therapy should be initiated. In patients with severe symptomatic anemia, transfusions may be indicated. Fluid replacement given intravenously or orally to correct or prevent hydration at 1 to 1.5 times the maintenance requirement is recommended. Close monitoring of fluid status is essential as aggressive hydration, particularly with sodium-containing fluids, can lead to volume overload, ACS, and heart failure.[4,10,13,22]

TABLE 120-6 Management of Acute Pain of Sickle Cell Disease

Principles

1. Treat underlying precipitating factors
2. Avoid delays in analgesia administration
   a. Initiate analgesic within 30 minutes of triage or 60 minutes of registration
3. Use pain scale to assess severity
4. Choice and dose of initial analgesic should be based on home regimen, previous pain pattern, history of response, current status, and other medical conditions. The following initial dosages may be considered if individualized plan unavailable:
   a. Morphine (IV): 0.1-0.15 mg/kg/dose for less than 50 kg; 5-10 mg/dose for greater than 50 kg
   b. Hydromorphone (IV): 0.015-0.02 mg/kg for less than 50 kg; 1.5 mg/dose for greater than 50 kg
   c. Ketorolac 0.5 mg/kg IV up to 30 mg/dose
5. Schedule pain medication; avoid as-needed dosing
6. Provide rescue dose for breakthrough pain
7. If adequate pain relief can be achieved with one or two doses of morphine, consider outpatient management with a weak opioid; otherwise hospitalization is needed for parenteral analgesics
8. Frequently assess to evaluate pain severity and side effects; titrate dose as needed
9. Treating adverse effects of opioids is part of pain management
10. Consider nonpharmacologic intervention (eg, relaxation techniques, guided imagery, deep breathing)
11. Transition to oral analgesics as the patient improves; choose an oral agent based on previous history, anticipated duration, and ability to swallow tablets; if sustained-release products are used, a product with a rapid onset is also needed for breakthrough pain

Analgesic regimens

Mild-to-moderate pain: nonopioid ± weak opioid
Moderate-to-severe pain: weak opioid or low dose of a strong opioid ± nonopioid
Severe pain: strong opioid + nonopioid

Other adjunct therapy

Hydration, heating pads, relaxation, and distraction
Laxatives for constipation
Antihistamine for itching
Antiemetics for nausea or vomiting

Data from References 4, 10, 11, 81-84.

The frequency and severity of acute pain episodes associated with SCD are variable. Pain should be assessed and analgesic therapy should be tailored for each patient and each individual episode. Several verbal and nonverbal pain

assessment tools are available to measure the intensity of pain. Unfortunately, validation for sickle cell pain is limited. Pain scales validated for use in children, such as the Wong-Baker FACES scale, should be used in pediatric patients with SCD pain. The healthcare provider should choose one tool appropriate for age and use it to assess pain. However, numeric scales alone should not be the only assessment of pain severity. Other useful information to guide the choice of analgesics should include previous effective agents and their dosages, response to therapy and previous clinical course, and duration of pain episodes.[10,85,86] Individualized patient-specific protocols and standardized pathway have been shown to improve the quality of pain management.[81,83,87]

8 Aggressive therapy that relieves pain and enables the patient to attain maximum functional ability should be initiated in patients with acute pain. Mild-to-moderate pain should be treated with nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, unless there are contraindications to their use. Ketorolac may be useful for patients requiring intravenous therapy. Because of increased risk of gastrointestinal bleeding, the duration of therapy should be limited to 5 days or less. NSAIDs has been associated with acute nonreversible kidney failure in a patient with SCD and should be used with caution and renal function should be monitored appropriately.[84] When acetaminophen is used, it is important to monitor the total dose of acetaminophen administered in patients who may also be receiving the agent for fever or another acetaminophen-containing product for pain. If mild-to-moderate pain persists, an opioid can be added.[10,22,81,82,85]

Severe pain should be treated aggressively until the pain is tolerable. Commonly used opioids include morphine, hydromorphone, fentanyl, and methadone. The weak opioids, codeine, and hydrocodone are used to manage mild-to-moderate pain usually in the outpatient setting. Some patients have clinically demonstrated inadequate relief to analgesic dosing with codeine. Some individuals who failed oral therapy with codeine were found to have a polymorphism in the *CYP2D6* gene resulting in a poor metabolizer phenotype. The CYP2D6 enzyme mediates the metabolism of codeine to morphine.[85,88] These results have led to early discontinuation of codeine analgesics if no response is seen after their first dose and use of alternative oral analgesics for the treatment of pain at home. Meperidine has no advantages as an analgesic and many disadvantages. Meperidine toxicity is caused by accumulation of the metabolite normeperidine, which can cause central nervous system side effects, ranging from dysphoria to seizures. Effective combination therapy, such as an NSAID and an opioid, can enhance analgesic efficacy while decreasing side

effects.

Both prior history and current assessment should be considered in the management of acute sickle cell pain. For patients whose typical pain improves in a short time, preparations with a short duration of action are appropriate. For patients whose pain requires many days to resolve, sustained-release preparations combined with a short-acting product for breakthrough pain are more appropriate. If the patient has been on long-term opioid therapy at home, tolerance can develop. In these cases, the acute pain should be treated with an opioid of different potency or a larger dose of the same medication. Low dose ketamine has been evaluated as an adjunct therapy for individuals with severe pain despite high dose opioid therapy. The consensus guidelines on the use of intravenous ketamine for acute pain management concluded that ketamine may be considered for opioid-dependent or -tolerant patients with acute or chronic sickle cell pain. The dosing range is not well defined but the guideline recommended the bolus dose not to exceed 0.35 mg/kg and the infusion rate of 0.1 to 0.5 mg/kg not to exceed 1 mg/kg/hr.[89]

Intravenous administration provides a rapid onset of action and therefore is preferred for severe pain. Intramuscular injections should be avoided. Children may actually deny pain due to fear of injections. Analgesics should be titrated to pain relief. In patients with continuous pain, the analgesic should be given as a scheduled dose or continuous infusion. Continuous infusion has the advantage of less fluctuation of blood levels between dosing intervals. As needed dosing is only indicated for breakthrough pain. Patient-controlled analgesia (PCA) is commonly prescribed for severe pain episodes. When used properly, PCA allows patients to have control over pain therapy and minimizes the lag time between perception of pain and administration of analgesics. PCA use reduces the cumulative dosage required for pain control. Another route of administration to produce rapid pain relief in timely manner is intranasal administration of an opioid such as fentanyl. The transdermal fentanyl patch has also been used successfully, but its role in sickle cell acute pain crisis is unclear because of its slow onset of onset of pain relief (12-16 hours) and fixed dosage form, which makes it difficult to titrate the dose.[4,10,11,13,82,85]

With better understanding of NO and inflammation on vasculopathy, therapy targeting blood rheology, endothelium adhesion or inflammation has been explored as adjunct therapy. Inhaled NO has been studied but no differences in duration of episodes, hospital stay, or opioid use when given to hospitalized adult and pediatric patients were observed.[90] In a randomized controlled trial in children hospitalized for painful episodes, arginine, the precursor for NO,

reduced total opioid use by more than 50%. The length of hospital stay was not reduced but the total parenteral opioid need and pain scores at discharge were significantly lower when compared to placebo.[91] Therapies targeting the pathophysiology of SCD may have additional benefits in the management of acute episodes. Rivipansel (GMI-1079) is currently in phase III trials for the treatment of vasoocclusive crisis in hospitalized patients.[19]

Chronic Sickle Cell Pain

As the number of adults living with SCD increases due to improved survival, the prevalence of disease morbidities including chronic pain also increases. Fifty-five percent of adults reported pain in more than half of the days and 29% of adults reported pain on 95% of the days. The 2014 Export Panel Report described pain as chronic when it lasted more than 3 months. A recent publication established the diagnostic criteria for chronic SCD pain syndrome.[92]

Treatment of chronic pain in SCD requires an interprofessional team approach and most physicians with expertise in treating SCD recommend following established guidelines for chronic pain. Most of the research has focused on the prevention of pain and the management of acute pain episodes. Central sensitization, neurogenic inflammation, and peripheral neural sensitization have been hypothesized to play a role in the development of chronic SCD pain.[34,40] Currently, evidence is available to support other medications such as selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, and anticonvulsants commonly used to treat chronic pain in patients with SCD. In a pilot study, pregabalin was found to reduce pain and improve quality of life scores.[93] Nonpharmacological interventions such as acupuncture, massage, cognitive behavioral therapy, and relaxation therapy have also been used as adjunct therapy.

EVALUATION OF THERAPEUTIC OUTCOMES

9 For infants younger than 1-year-old, medical evaluations every 2 to 4 months are recommended. Beyond 2 years of age, evaluation can be extended to every 6 to 12 months with modifications depending on severity of the illness. Routine laboratory evaluation including complete blood cell counts and reticulocyte counts every 3 to 6 months up to 2 years of age, then every 6 to 12 months; HbF level should be screened annually until 2 years of age. Renal, hepatobiliary, and pulmonary function should be evaluated annually. TCD screening is

recommended to start at age 2 years and performed annually for children with HbSS and HbSβ. Ophthalmologic examination to screen for retinopathy is recommended at around age 10 to 12 years for those with HbSC and 14 years for HbSS. In patients with recurrent ACS, pulmonary function tests should be done to establish baseline values and identify declines in lung function as well as an evaluation by pulmonology to screen for lower airway hyper-responsiveness.

It is essential that immunizations and prophylactic antibiotics be given. When infections do occur, appropriate antibiotic therapy should be initiated, and the patient should be monitored for laboratory and clinical improvement. The efficacy of HU can be measured as a decrease in the number, severity, and duration of sickle cell pain episodes. HbF concentrations or MCV values can be used as a biomarker of the patient's response to therapy. When painful episodes do occur, the effectiveness of analgesics can be measured by subjective assessments made by the patient, and healthcare practitioners. The success of poststroke blood transfusions can be measured by clinical progression or the occurrence of subsequent strokes. Finally, indicators can be used to measure quality of care for children with SCD.

SCD is a complex disorder that requires interprofessional comprehensive care. All patients should receive regular medical evaluation to provide preventive care, establish baseline symptoms and laboratory values, monitor changes, and provide education appropriate for age. A process to transition from the pediatric to adult healthcare setting is essential to ensure continuity of care. The aging population represents another challenge for management of SCD due to comorbidities. Management by specialists should be coordinated with the primary care physician to achieve comprehensive care. Current understanding of the pathophysiology of SCD has expanded treatment options for individuals with SCD, from disease modifying targeting cell adhesion to curative therapies such as transplantation and gene therapy.

Postclass Engaged Learning Activity

Review literature and compile a list of challenges encountered by teenagers and adults with sickle cell disease. Compile an overview of resources and programs available in your local area for this patient population. Then identify gaps that need further development in your community.

ABBREVIATIONS

ACS	acute chest syndrome
CT	computed tomography
DHTR	delayed hemolytic transfusion reactions
DVT	deep vein thrombosis
ET-1	endothelin-1
GVHD	graft-versus-host disease
HbA	hemoglobin A
HbAS	one normal (hemoglobin A) and one sickle cell hemoglobin (hemoglobin S) gene
HbC	hemoglobin C
HbF	fetal hemoglobin
HbS	sickle cell hemoglobin
HbSβ^+-thal	hemoglobin sickle cell β^+-thalassemia
HbSβ^0-thal	hemoglobin sickle cell β^0-thalassemia
HbSC	sickle cell hemoglobin C
HbSS	homozygous sickle cell hemoglobin (hemoglobin S)
HLA	human leukocyte antigen
HPFH	hereditary persistence of fetal hemoglobin
HSCT	hematopoietic stem cell transplantation
HU	hydroxyurea
ISC	irreversibly sickled cell
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MRA	magnetic resonance angiogram
MRI	magnetic resonance imaging
MRV	magnetic resonance venography
MSH	Multicenter Study of Hydroxyurea in Sickle Cell Anemia
MTD	maximum tolerated dose
NIH	National Institutes of Health
NO	nitric oxide
NSAID	nonsteroidal anti-inflammatory drug
NT-pro-BNP	N-terminal pro-brain natriuretic peptide

PAH	pulmonary artery hypertension
PAP	pulmonary arterial pressure
PCA	patient-controlled analgesia
PCV13	13-valent pneumococcal conjugate vaccine
PE	pulmonary embolism
PPSV23	23-valent pneumococcal polysaccharide vaccine
RBC	red blood cell
RSC	reversible sickled cell
SCA	sickle cell anemia
SCD	sickle cell disease
SCT	sickle cell trait
TCD	transcranial Doppler ultrasound
VCAM-1	vascular cell adhesion molecule 1
VTE	venous thromboembolism
WBC	white blood cell

REFERENCES

1. Alrayyes S, Baghdan D, Haddad RY, et al. Sickle cell disease: An overview of the disease and its systemic effects. *Dis Mon*. 2018;64:283–289.
2. Piel FB, Steinberg MH, Rees DC. Sickle cell disease. *N Engl J Med*. 2017;376:1561–1573.
3. Ware RE, de Montalembert M, Tshilolo L, Abboud MR. Sickle cell disease. *Lancet*. 2017;390:311–323.
4. Quinn CT. Sickle cell disease in childhood: From newborn screening through transition to adult medical care. *Pediatr Clin North Am*. 2013;60:1363–1381.
5. Brousse V, Makani J, Rees DC. Management of sickle cell disease in the community. *BMJ*. 2014;348:1765–1773.
6. Meier ER. Treatment options for sickle cell disease. *Pediatr Clin North Am*. 2018;65:427–443.
7. Thein MS, Igbineweka NE, Thein SL. Sickle cell disease in the older adult. *Pathology*. 2017;49:1–9.

8. Chakravorty S, Williams TN. Sickle cell disease: A neglected chronic disease of increasing global health importance. *Arch Dis Child*. 2015;100:48–53.
9. Madani BM, Raddadi R, Jaouni S, et al. Quality of life among caregivers of sickle cell disease patients: A cross sectional study. *Health Qual Life Outcomes*. 2018;16:176–184.
10. Kanter J, Kruse-Jarres R. Management of sickle cell disease from childhood through adulthood. *Blood Rev*. 2013;27:279–287.
11. Lanzkron S, Haywood CJr. The five key things you need to know to manage adult patients with sickle cell disease. *Hematology Am Soc Hematol Educ Program*. 2015;2015:420–425.
12. Key NS, Connes P, Derebail VK. Negative health implications of sickle cell trait in high income countries: From the football field to the laboratory. *Br J Haematol*. 2015;170:5–14.
13. Lovett PB, Sule HP, Lopez BL. Sickle cell disease in the emergency department. *Hematol Oncol Clin North Am*. 2017;31:1061–1079.
14. Dueker ND, Della-Morte D, Rundek T, et al. Sickle cell trait and renal function in Hispanics in the United States: The Northern Manhattan Study. *Ethn Dis*. 2017;27:11–14.
15. Ojodu J, Hulihan MM, Pope SN, Grant AM. Incidence of sickle cell trait —United States, 2010. *MMWR Morb Mortal Wkly Rep*. 2014;63:1155–1158.
16. Saraf SL, Molokie RE, Nouraie M, et al. Differences in the clinical and genotypic presentation of sickle cell disease around the world. *Paediatr Respir Rev*. 2014;15:4–12.
17. Serjeant GR, Serjeant BE, Hambleton IR, et al. A plea for the newborn diagnosis of Hb S-hereditary persistence of fetal hemoglobin. *Hemoglobin*. 2017;41:216–217.
18. Kuypers FA. Hemoglobin s polymerization and red cell membrane changes. *Hematol Oncol Clin North Am*. 2014;28:155–179.
19. Telen MJ. Beyond hydroxyurea: New and old drugs in the pipeline for sickle cell disease. *Blood*. 2016;127:810–819.
20. Conran N, Belcher JD. Inflammation in sickle cell disease. *Clin Hemorheol Microcirc*. 2018;68: 263–299.
21. Therrell BLJr, Lloyd-Puryear MA, Eckman JR, Mann MY. Newborn screening for sickle cell diseases in the United States: A review of data

spanning 2 decades. *Semin Perinatol*. 2015;39:238–251.

22. National Institutes of Health, National Heart Lung and Blood Institute. Evidence-Based Management of Sickle Cell Disease: Expert Panel Report. Available at http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines/. Accessed October 15, 2018.
23. Naik RP, Derebail VK, Grams ME, et al. Association of sickle cell trait with chronic kidney disease and albuminuria in African Americans. *JAMA*. 2014;312:2115–2125.
24. Maron BJ, Zipes DP, Kovacs RJ, et al. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Preamble, principles, and general considerations: A scientific statement from the American heart association and American College of Cardiology. *Circulation*. 2015;132:e256–261.
25. Maitra P, Caughey M, Robinson L, et al. Risk factors for mortality in adult patients with sickle cell disease: A meta-analysis of studies in North America and Europe. *Haematologica*. 2017;102:626–636.
26. Meier ER, Fasano RM, Levett PR. A systematic review of the literature for severity predictors in children with sickle cell anemia. *Blood Cells Mol Dis*. 2017;65:86–94.
27. De A, Manwani D, Rastogi D. Airway inflammation in sickle cell disease: A translational perspective. *Pediatr Pulmonol*. 2018;53: 400–411.
28. Elmariah H, Garrett ME, De Castro LM, et al. Factors associated with survival in a contemporary adult sickle cell disease cohort. *Am J Hematol*. 2014;89:530–535.
29. Martin OO, Moquist KL, Hennessy JM, Nelson SC. Invasive pneumococcal disease in children with sickle cell disease in the pneumococcal conjugate vaccine era. *Pediatr Blood Cancer*. 2018;65:e26713
30. Payne AB, Link-Gelles R, Azonobi I, et al. Invasive pneumococcal disease among children with and without sickle cell disease in the United States, 1998 to 2009. *Pediatr Infect Dis J*. 2013;32:1308–1312.
31. Sadreameli SC, Reller ME, Bundy DG, et al. Respiratory syncytial virus and seasonal influenza cause similar illnesses in children with sickle cell disease. *Pediatr Blood Cancer*. 2014;61:875–878.
32. Sobota A, Sabharwal V, Fonebi G, Steinberg M. How we prevent and manage infection in sickle cell disease. *Br J Haematol*. 2015;170:757–767.

33. Farooq S, Abu Omar M, Salzman GA. Acute chest syndrome in sickle cell disease. *Hosp Pract*. 2018;46:144–151.
34. Howard J, Hart N, Roberts-Harewood M, et al. Guideline on the management of acute chest syndrome in sickle cell disease. *Br J Haematol*. 2015;169:492–505.
35. Brousse V, Elie C, Benkerrou M, et al. Acute splenic sequestration crisis in sickle cell disease: Cohort study of 190 paediatric patients. *Br J Haematol*. 2012;156:643–648.
36. Kassim AA, Galadanci NA, Pruthi S, DeBaun MR. How I treat and manage strokes in sickle cell disease. *Blood*. 2015;125:3401–3410.
37. Darbari DS, Ballas SK, Clauw DJ. Thinking beyond sickling to better understand pain in sickle cell disease. *Eur J Haematol*. 2014;93:89–95.
38. Brousse V, Kossorotoff M, de Montalembert M. How I manage cerebral vasculopathy in children with sickle cell disease. *Br J Haematol*. 2015;170:615–625.
39. Glass P, Brennan T, Wang J, et al. Neurodevelopmental deficits among infants and toddlers with sickle cell disease. *J Dev Behav Pediatr*. 2013;34:399–405.
40. Anele UA, Le BV, Resar LM, Burnett AL. How I treat priapism. *Blood*. 2015;125:3551–3558.
41. Brunson A, Lei A, Rosenberg AS, White RH, et al. Increased incidence of venous thromboembolism in sickle cell disease patients: risk factors, recurrence and impact on mortality. *Br J Haematol*. 2017;178:319–326.
42. Abman SH, Hansmann G, Archer SL, et al. Pediatric Pulmonary Hypertension: Guidelines from the American Heart Association and American Thoracic Society. *Circulation*. 2015;132:2037–2099.
43. Klings ES, Machado RF, Barst RJ, et al. An official American Thoracic Society clinical practice guideline: Diagnosis, risk stratification, and management of pulmonary hypertension of sickle cell disease. *Am J Respir Crit Care Med*. 2014;189:727–740.
44. Vanderhave KL, Perkins CA, Scannell B, Brighton BK. Orthopaedic manifestations of sickle cell disease. *J Am Acad Orthop Surg*. 2018;26:94–101.
45. Osunkwo I. An update on the recent literature on sickle cell bone disease. *Curr Opin Endocrinol Diabetes Obes*. 2013;20:539–546.
46. Do BK, Rodger DC. Sickle cell disease and the eye. *Curr Opin*

Ophthalmol. 2017;28:623–628.

47. Shah R, Taborda C, Chawla S. Acute and chronic hepatobiliary manifestations of sickle cell disease: A review. *World J Gastrointest Pathophysiol*. 2017;8:108–116.
48. Gladwin MT. Cardiovascular complications and risk of death in sickle-cell disease. *Lancet*. 2016;387:2565–2574.
49. Nath KA, Hebbel RP. Sickle cell disease: Renal manifestations and mechanisms. *Nat Rev Nephrol*. 2015;11:161–171.
50. Sharpe CC, Thein SL. How I treat renal complications in sickle cell disease. *Blood*. 2014;123:3720–3726.
51. Bennett N. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2012;61:816–819.
52. Patton ME, Stephens D, Moore K, MacNeil JR. Updated Recommendations for Use of MenB-FHbp Serogroup B Meningococcal Vaccine: Advisory Committee on Immunization Practices, 2016. *MMWR Morb Mortal Wkly Rep*. 2017;66:509–513.
53. Cohn AC, MacNeil JR, Clark TA, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among children aged 6-18 years with immunocompromising conditions: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2013;62:521–524.
54. Cohn AC, MacNeil JR, Clark TA, et al. Prevention and control of meningococcal disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2013;62(RR-2):1–28.
55. Sehlo MG, Kamfar HZ. Depression and quality of life in children with sickle cell disease: The effect of social support. *BMC Psychiatry*. 2015;15:78–85.
56. Smith-Whitley K. Reproductive issues in sickle cell disease. *Hematology Am Soc Hematol Educ Program*. 2014;2014:418–424.
57. Qureshi A, Kaya B, Pancham S, et al. Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease: A British Society for Haematology Guideline. *Br J Haematol*. 2018;181:460–475.
58. Wong TE, Brandow AM, Lim W, Lottenberg R. Update on the use of

hydroxyurea therapy in sickle cell disease. *Blood*. 2014;124:3850–3857.

59. Thornburg CD, Files BA, Luo Z, et al. Impact of hydroxyurea on clinical events in the BABY HUG trial. *Blood*. 2012;120:4304–4310.
60. Lobo CL, Pinto JF, Nascimento EM, Moura PG, Cardoso GP, Hankins JS. The effect of hydroxcarbamide therapy on survival of children with sickle cell disease. *Br J Haematol*. 2013;161:852–860.
61. Rana S, Houston PE, Wang WC, et al. Hydroxyurea and growth in young children with sickle cell disease. *Pediatrics*. 2014;134:465–472.
62. Niihara Y, Miller ST, Kanter J, et al. A Phase 3 Trial of l-Glutamine in Sickle Cell Disease. *N Engl J Med*. 2018;379:226–235.
63. Endari™ [package insert]. Torrance, CA: Emmaus Medical; 2017.
64. Chou ST. Transfusion therapy for sickle cell disease: A balancing act. *Hematology Am Soc Hematol Educ Program*. 2013;2013:439–446.
65. Smith-Whitley K, Thompson AA. Indications and complications of transfusions in sickle cell disease. *Pediatr Blood Cancer*. 2012;59:358–364.
66. Calvaruso G, Vitrano A, Di Maggio R, et al. Deferiprone versus deferoxamine in sickle cell disease: Results from a 5-year long-term Italian multi-center randomized clinical trial. *Blood Cells Mol Dis*. 2014;53:265–271.
67. Chaudhary P, Pullarkat V. Deferasirox: appraisal of safety and efficacy in long-term therapy. *J Blood Med*. 2013;4:101–110.
68. Vichinsky E, Torres M, Minniti CP, et al. Efficacy and safety of deferasirox compared with deferoxamine in sickle cell disease: Two-year results including pharmacokinetics and concomitant hydroxyurea. *Am J Hematol*. 2013;88:1068–1073.
69. Ware HM, Kwiatkowski JL. Evaluation and treatment of transfusional iron overload in children. *Pediatr Clin North Am*. 2013;60:1393–1406.
70. Fitzhugh CD, Abraham AA, Tisdale JF, Hsieh MM. Hematopoietic stem cell transplantation for patients with sickle cell disease: Progress and future directions. *Hematol Oncol Clin North Am*. 2014;28:1171–1185.
71. Walters MC, De Castro LM, Sullivan KM, et al. Indications and results of HLA-identical sibling hematopoietic cell transplantation for sickle cell disease. *Biol Blood Marrow Transplant*. 2016;22:207–211.
72. Thompson LM, Ceja ME, Yang SP. Stem cell transplantation for treatment of sickle cell disease: Bone marrow versus cord blood transplants. *Am J*

Health Syst Pharm. 2012;69:1295–1302.

73. Angelucci E, Matthes-Martin S, Baronciani D, et al. Hematopoietic stem cell transplantation in thalassemia major and sickle cell disease: Indications and management recommendations from an international expert panel. *Haematologica*. 2014;99:811–820.
74. King A, Shenoy S. Evidence-based focused review of the status of hematopoietic stem cell transplantation as treatment of sickle cell disease and thalassemia. *Blood*. 2014;123:3089–3094.
75. Ellison AM, Smith Whitley K, Kittick M, et al. A standardized clinical pathway to decrease hospital admissions among febrile children with sickle cell disease. *J Pediatr Hematol Oncol*. 2018;40:111–115.
76. Neuman G, Boodhan S, Wurman I, et al. Ceftriaxone-induced immune hemolytic anemia. *Ann Pharmacother*. 2014;48:1594–1604.
77. Adams RJ, Cox M, Ozark SD, et al. Coexistent sickle cell disease has no impact on the safety or outcome of lytic therapy in acute ischemic stroke: Findings from Get With The Guidelines-Stroke. *Stroke*. 2017;48:686–691.
78. Olujohungbe A, Burnett AL. How I manage priapism due to sickle cell disease. *Br J Haematol*. 2013;160:754–765.
79. Burnett AL, Anele UA, Trueheart IN, et al. Randomized controlled trial of sildenafil for preventing recurrent ischemic priapism in sickle cell disease. *Am J Med*. 2014;127:664–668.
80. Anele UA, Mack AK, Resar LMS, Burnett AL. Hydroxyurea therapy for priapism prevention and erectile function recovery in sickle cell disease: A case report and review of the literature. *Int Urol Nephrol*. 2014;46:1733–1736.
81. Krishnamurti L, Smith-Packard B, Gupta A, Campbell M, et al. Impact of individualized pain plan on the emergency management of children with sickle cell disease. *Pediatr Blood Cancer*. 2014;61:1747–1753.
82. Telfer P, Bahal N, Lo A, Challands J. Management of the acute painful crisis in sickle cell disease: A re-evaluation of the use of opioids in adult patients. *Br J Haematol*. 2014;166:157–164.
83. Tanabe P, Silva S, Bosworth HB, et al. A randomized controlled trial comparing two vaso-occlusive episode (VOE) protocols in sickle cell disease (SCD). *Am J Hematol*. 2018;93:159–168.
84. Han J, Saraf SL, Lash JP, Gordeuk VR. Use of anti-inflammatory analgesics in sickle-cell disease. *J Clin Pharm Ther*. 2017;42:656–660.

85. Brandow AM, DeBaun MR. Key components of pain management for children and adults with sickle cell disease. *Hematol Oncol Clin North Am*. 2018;32:535–550.
86. Naegeli AN, Heath L, Zhou C, et al. Psychometric properties of a modified version of the faces pain scale-revised (Modified FPS-R) to evaluate worst pain in children and adolescents with sickle cell anemia. *J Pediatr Hematol Oncol*. 2018;40:499–503.
87. Kavanagh PL, Sprinz PG, Wolfgang TL, et al. Improving the management of vaso-occlusive episodes in the pediatric emergency department. *Pediatrics*. 2015;136:e1016–1025.
88. Yee MM, Josephson C, Hill CE, et al. Cytochrome P450 2D6 polymorphisms and predicted opioid metabolism in African American children with sickle cell disease. *J Pediatr Hematol Oncol*. 2013;35:e301–e305.
89. Schwenk ES, Viscusi ER, Buvanendran A, et al. Consensus guidelines on the use of intravenous ketamine infusions for acute pain management from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Reg Anesth Pain Med*. 2018;43:456–466.
90. Tran H, Gupta M, Gupta K. Targeting novel mechanisms of pain in sickle cell disease. *Blood*. 2017;130:2377–2385.
91. Morris CR, Kuypers FA, Lavrisha L, et al. A randomized, placebo-controlled trial of arginine therapy for the treatment of children with sickle cell disease hospitalized with vaso-occlusive pain episodes. *Haematologica*. 2013;98:1375–1382.
92. Dampier C, Palermo TM, Darbari DS, et al. AAPT diagnostic criteria for chronic sickle cell disease pain. *J Pain*. 2017;18:490–498.
93. Schlaeger JM, Molokie RE, Yao Y, et al. Management of sickle cell pain using pregabalin: A pilot study. *Pain Manag Nurs*. 2017;18:391–400.

Drug-Induced Hematologic Disorders

Elisa M. Greene and Tracy M. Hagemann

KEY CONCEPTS

1. The most common drug-induced hematologic disorders are aplastic anemia, agranulocytosis, megaloblastic anemia, hemolytic anemia, and thrombocytopenia.
2. Drug-induced hematologic disorders are rare adverse effects associated with drug therapy.
3. The incidence of rare adverse drug reactions (ADRs) is usually established by postmarketing surveillance and reporting.
4. Re-challenging a patient with an agent suspected of inducing a blood disorder is not generally recommended.
5. Drug-induced hematologic disorders can occur by two mechanisms: direct drug or metabolite toxicity or an immune reaction.
6. The primary treatment of drug-induced hematologic disorders is the removal of the drug in question and symptomatic support of the patient.

Preclass Engaged Learning Activity

Watch the video entitled “Part 1: Anemia: Pathophysiology and Diagnostic Approach” in AccessMedicine by Scott Stern, MD. This can be found by clicking on Multimedia, Lectures, Diagnostic Reasoning, then Anemia. This 21-minute video provides an overview of the foundational knowledge of anemia, the approach to evaluate a patient with anemia, common causes of anemias, and differential diagnosis for different types of anemias. This video increases student understanding regarding the COLLECT and ASSESS steps in the patient care process.

INTRODUCTION

1 Hematologic disorders have long been a potential risk of modern pharmacotherapy. Granulocytopenia (agranulocytosis) was reported in association with one of medicine's early therapeutic agents, sulfanilamide, in 1938.[1] Some agents cause predictable hematologic disease (eg, antineoplastics), but others induce idiosyncratic reactions not directly related to the drugs' pharmacology. The most common drug-induced hematologic disorders are aplastic anemia, agranulocytosis, megaloblastic anemia, hemolytic anemia, and thrombocytopenia.

2 The incidence of idiosyncratic drug-induced hematologic disorders varies depending on the condition and the associated drug. Few epidemiologic studies have evaluated the actual incidence of these adverse reactions, but these reactions appear to be rare. Women are generally more susceptible than men to the hematologic effects of drugs. The incidence varies based on geography, which suggests that genetic differences may be important determinants of susceptibility. Drug-induced thrombocytopenia is the most common drug-induced hematologic disorder, with reports suggesting that between 0.1% and 5% of patients who receive heparin develop heparin-induced thrombocytopenia (HIT).[2,3] The Berlin Case-Control Surveillance Study was conducted from 2000 to 2009 to assess the incidence and risks of drug-induced hematologic disorders and found that almost 30% of all cases of blood dyscrasias were "possibly" attributable to drug therapy.[4]

Although drug-induced hematologic disorders are less common than other types of adverse reactions, they are associated with significant morbidity and mortality. Aplastic anemia is the leading cause of death followed by thrombocytopenia, agranulocytosis, and hemolytic anemia.[5] Similar to most other adverse drug reactions (ADRs), drug-induced hematologic disorders are more common in elderly adults than in the young; the risk of death also appears to be greater with increasing age.

3 The MedWatch program supported by the Food and Drug Administration[6] is the most common avenue for postmarketing surveillance to establish the incidence of ADRs. Many facilities have similar drug-reporting programs to follow ADR trends and to determine whether an association between a drug and an ADR is causal or coincidental. These programs enable practitioners to confirm that an adverse event is the result of drug therapy rather than one of many other potential causes; general guidelines are readily available.[7,8]

4 Because drug-induced blood disorders are potentially dangerous, re-challenging a patient with a suspected agent in an attempt to confirm a diagnosis is not recommended. In vitro studies with the offending agent and cells or plasma from the patient's blood can be performed to determine causality.[9] These methods are often expensive, however, and require facilities and expertise that are not generally available. Although the diagnosis of HIT requires laboratory testing,[10] laboratory confirmation of drug causation is not always necessary to warrant interruption or discontinuation of therapy. Therefore, it is extremely important that practitioners be able to clinically evaluate suspect drugs quickly and to interrupt therapy when necessary.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

SECTION 18 INFECTIOUS DISEASES

Laboratory Tests to Direct Antimicrobial Pharmacotherapy

Brian J. Werth, Katie E. Barber, Jordan R. Smith, and Michael J. Rybak

KEY CONCEPTS

1. Understanding the difference between normal host microbiota and typical pathogens will help to determine whether a patient is truly infected or merely colonized.
2. Direct examination of tissue and body fluids by Gram stain provides rapid information about the causative pathogen.
3. Isolation of the offending organism by culture or rapid diagnostic testing assists in the diagnosis of infection and allows for more definitive directed treatment.
4. Development of molecular testing systems (or rapid diagnostic testing) has improved our ability to diagnose infection and determine the antimicrobial susceptibilities for numerous pathogens, including fastidious or slow-growing mycobacteria and viruses.
5. *In vitro* antimicrobial susceptibility testing has limitations and often cannot truly mimic the conditions found at the site of an infection. This can cause discordance between *in vitro* susceptibility results and *in vivo* response to therapy.
6. Laboratory evaluation of antimicrobial activity is an important component of the pharmacotherapeutic management of infectious diseases.
7. When used appropriately, rapid automated susceptibility test systems appear to improve therapeutic outcomes of patients with infection, especially when they are linked with other clinical information systems.
8. Understanding the fundamentals of antimicrobial pharmacodynamic

properties will help the clinician to make drug selection and dosing decisions in situations where robust clinical data are lacking.

9. Routine monitoring of serum concentrations is currently used for a select few antimicrobials, eg, aminoglycosides and vancomycin, in an attempt to minimize toxicity and maximize efficacy.
10. Appropriate timing for the collection of serum samples when measuring antimicrobial serum concentrations is crucial to ensure that valid pharmacokinetic data are generated.
11. Monitoring of aminoglycoside serum concentrations and the use of extended-interval doses can help to maximize the probability of therapeutic success and minimize the probability of aminoglycoside-related toxicity for certain infections.
12. Vancomycin and aminoglycoside serum concentration monitoring should be routinely done to ensure adequate serum concentrations, minimize toxicity, and avoid the potential for resistance.
13. Antimicrobial pharmacodynamics has become a crucial consideration for the selection of both empirical and pathogen-directed therapy in the current era of antimicrobial resistance.
14. Optimization of antimicrobial pharmacodynamic parameters such as the ratio of the peak serum concentration to minimum inhibitory concentration (MIC) or the time that the antibiotic serum concentration remains above the MIC or the ratio of the area under the concentration-time curve to the MIC can improve infection treatment outcomes.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

123

Antimicrobial Regimen Selection

Grace C. Lee and David S. Burgess

KEY CONCEPTS

1. Every attempt should be made to obtain specimens for culture and sensitivity testing prior to initiating antibiotics.
2. Empirical antibiotic therapy should be based on knowledge of likely pathogens for the site of infection, information from patient history (eg, recent hospitalizations, work-related exposure, travel, and pets), and local susceptibility.
3. Patients with delayed dermatologic reactions (ie, rash) to penicillin generally can receive cephalosporins. Patients with type I hypersensitivity reactions (ie, anaphylaxis) to penicillins should not receive cephalosporins. Alternatives to the cephalosporins inveclude aztreonam, quinolones, sulfonamide antibiotics, or vancomycin based on type of coverage indicated.
4. Creatinine clearance should be estimated for every patient who is to receive antibiotics and the antibiotic dose interval adjusted accordingly. Hepatic function should be considered for drugs eliminated through the hepatobiliary system, such as clindamycin, erythromycin, and metronidazole.
5. All concomitant drugs and nutritional supplements should be reviewed when an antibiotic is added to a patient's therapy to ensure drug–drug interactions will be avoided.
6. Combination antibiotic therapy may be indicated for polymicrobial infections (eg, intra-abdominal and gynecologic infections), to produce synergistic killing (such as β-lactam plus aminoglycoside vs *Pseudomonas aeruginosa*), or to prevent the emergence of resistance.
7. All patients receiving antibiotics should be monitored for resolution of

infectious signs and symptoms (eg, decreasing temperature and white blood cell count) and adverse drug events.

8. Antibiotics with the narrowest effective spectrum of activity are preferred. Antibiotic route of administration should be evaluated daily, and conversion from IV to oral therapy should be attempted as signs of infection improve for patients with functioning GI tracts (general exceptions are endocarditis and CNS infections).

9. Patients not responding to an appropriate antibiotic treatment in 2 to 3 days should be reevaluated to ensure (a) the correct diagnosis, (b) that therapeutic drug concentrations are being achieved, (c) that the patient is not immunosuppressed, (d) that the patient does not have an isolated infection (ie, abscess and foreign body), or (e) that resistance has not developed.

10. The main goals of antimicrobial stewardship programs (ASPs) are to optimize antimicrobial selection, dosing, duration, and route of administration while minimizing adverse drug events and the emergence of antimicrobial resistance.

INTRODUCTION

Antimicrobials are among the most widely used classes of drugs. In the United States, expenditures for antimicrobial agents exceed $10 billion annually. Approximately 20% to 40% of hospitalized patients receive antibiotics. The use of antibiotics is the main driver in creating selective pressure for the emergence of antimicrobial resistant pathogens; nevertheless, antibiotic overuse remains common. Selecting appropriate antimicrobial agent(s) to treat an infection has proven to be a challenging task.[1,2] Although the choice of a single agent or a combination of agents should be individualized for each patient, certain general principles of therapy should guide the selection of specific drugs (**Table 123-1**).

TABLE 123-1 Systematic Approach for Selection of Antimicrobials

Confirm the presence of infection
- Careful history and physical examination
- Signs and symptoms
- Predisposing factors

Identification of the pathogen (see Chapter e122)
- Collection of infected material
- Stains
- Serologies
- Culture and sensitivity

Selection of presumptive therapy considering every infected site
- Host factors
- Drug factors

Monitor therapeutic response
- Clinical assessment
- Laboratory tests
- Assessment of therapeutic failure

The initial selection of antimicrobial therapy is nearly always empirical, which is prior to documentation and identification of the offending organism. Infectious diseases generally are acute, and a delay in antimicrobial therapy can result in serious morbidity or even mortality. Thus, empirical antimicrobial therapy selection should be based on information gathered from the patient's history and physical examination and results of Gram stains or of rapidly performed tests on specimens from the infected site. This information, combined with knowledge of the most likely offending organism(s) and an institution's local susceptibility patterns, should result in a rational selection of antibiotics to treat the patient. This chapter introduces a systematic approach to the selection of antimicrobial therapeutic regimens.

CONFIRMING THE PRESENCE OF INFECTION

An infectious disease diagnosis is determined by assessing the presence of signs and symptoms of an infection, determining the site of infection, and establishing a microbiological diagnosis, when possible.

Fever

The presence of a temperature greater than the expected 37°C (98.6°F) "normal" body temperature is considered a hallmark of infectious diseases. Body temperature is controlled by the hypothalamus. In addition, the circadian rhythm,

a built-in temperature cycle, is also operational. The daily temperature rhythm can vary for each individual. In a healthy person, the internal thermostat is set between the morning low temperature and the afternoon peak as controlled by the circadian rhythm. During fever, the hypothalamus is reset at a higher temperature level.

Fever is defined as a controlled elevation of body temperature above the normal range. The average normal body temperature range taken orally is 36.7°C to 37°C (98°F–98.6°F). Body temperatures obtained rectally generally are 0.6°C (1°F) higher and axillary temperatures are 0.6°C (1°F) lower than oral temperatures, respectively. Skin temperatures are also less than the oral temperature but can vary depending on the specific measurement method. Fever can be a manifestation of disease states other than infection. Collagen vascular (autoimmune) disorders and several malignancies can have fever as a manifestation. Fever of unknown or undetermined origin is a diagnostic dilemma and is reviewed extensively elsewhere.[3]

Many drugs have been identified as causes of fever. *Drug-induced fever* is defined as persistent fever in the absence of infection or other underlying condition. The fever must coincide temporally with the administration of the offending agent and disappear promptly on its withdrawal, after which the temperature remains normal. Possible mechanisms of drug-induced fever are either a hypersensitivity reaction or development of antigen–antibody complexes that result in the stimulation of macrophages and the release of interleukin 1 (IL-1). While fever is not a common drug effect (accounting for no more than 5% of all drug reactions), it should be suspected when obvious reasons for fever are not present. Almost any medication can produce fever, but β-lactam antibiotics, anticonvulsants, allopurinol, hydralazine, nitrofurantoin, sulfonamides, phenothiazines, and methyldopa appear to be responsible more often than others.

Noninfectious etiologies of fever can be referred to as “false-positives.” Although these certainly can confuse the clinician, even more troublesome are false-negatives: the absence of fever in a patient with signs and symptoms consistent with an infectious disease. Careful questioning of the patient or family is vital to assess the ingestion of any medication that can mask fever (eg, aspirin, acetaminophen, nonsteroidal anti-inflammatory agents, and corticosteroids). The use of antipyretics should be discouraged during the treatment of infection unless absolutely necessary because they can mask a poor therapeutic response. Moreover, elevated body temperature, unless very high (greater than 40.5°C [105°F]), is not harmful and may be beneficial.

White Blood Cell Count

Most infections result in elevated white blood cell (WBC) counts (leukocytosis) because of the increased production and mobilization of granulocytes (neutrophils, basophils, and eosinophils), lymphocytes, or both to ingest and destroy invading microbes. The generally accepted range of normal values for WBC counts is between 4,000 and 10,000 cells/mm^3 (4×10^9 and 10×10^9/L). Values above or below this range hold important prognostic and diagnostic value.

Bacterial infections are associated with elevated granulocyte counts, often with immature forms (band neutrophils) seen in peripheral blood smears. Mature neutrophils are also referred to as *segmented neutrophils* or *polymorphonuclear* (PMN) *leukocytes*. The presence of immature forms (left shift) is an indication of an increased bone marrow response to the infection. With infection, peripheral WBC counts can be very high, but they are rarely higher than 30,000 to 40,000 cells/mm^3 (30×10^9/L to 40×10^9/L). Because leukocytosis indicates the normal host response to infection, low leukocyte counts after the onset of infection indicate an abnormal response and generally are associated with a poor prognosis.

The most common granulocyte defect is neutropenia, a decrease in absolute numbers of circulating neutrophils. A thorough description of the consequences of neutropenia is given in Chapter 140. Lymphocytosis, even with normal or slightly elevated total WBC counts, generally is associated with tuberculosis and viral or fungal infections. Increases in monocytes can be associated with tuberculosis or lymphoma, and increases in eosinophils can be associated with allergic reactions to drugs or infections caused by metazoa. Many types of infections can be accompanied by a completely normal WBC count and differential.

Local Signs

The classic signs of pain and inflammation can manifest as swelling, erythema, tenderness, and purulent drainage. Unfortunately, these are only visible if the infection is superficial or in a bone or joint. The manifestations of inflammation in deep-seated infections (eg, meningitis, pneumonia, endocarditis, and urinary tract infection) must be ascertained by examining tissues or fluids. For example, the presence of neutrophils in spinal fluid, lung secretions (sputum), or urine is highly suggestive of a bacterial infection.

Symptoms referable to an organ system must be sought out carefully because

not only do they help in establishing the presence of infection, but they also aid in narrowing the list of potential pathogens. For example, a febrile patient with complaints of flank pain and dysuria can well have pyelonephritis. In this situation, enteric gram-negative bacilli, especially *Escherichia coli*, are the predominant pathogens. If a febrile patient has no symptoms suggestive of an organ system but only constitutional complaints, the list of possible infectious diseases is lengthy.[3] A febrile individual with cough and sputum production probably has a pulmonary infection. What is not so evident, however, is the etiologic organism in this situation, because it can be caused by bacteria, mycobacteria, viruses, *Chlamydia*, or mycoplasmas.[4] In this situation, attention to the patient's history and background disease states is important. Even more important is a careful examination of the infected material (in this case sputum) to ascertain the identity of the pathogen.

IDENTIFICATION OF THE PATHOGEN

Microbiological Studies

1 Identification and antimicrobial susceptibility of a suspected pathogen are the most important factors in determining the choice of antimicrobial therapy. Generally, infected body materials must be sampled, if at all possible or practical, before or concurrently with institution of any antimicrobial therapy for two reasons. First, a Gram stain of the material might reveal bacteria, or an acid-fast stain might detect mycobacteria or actinomycetes. Second, the premature use of antimicrobials can suppress the growth of pathogens that might result in false-negative cultures results or alterations in the cellular and chemical composition of infected fluids. This is particularly true in patients with vertebral osteomyelitis, urinary tract infections, subacute endocarditis, meningitis, and septic arthritis.[5–9]

Blood cultures usually should be performed in the acutely ill febrile patient. Blood culture collection should coincide with sharp elevations in temperature, suggesting the possibility of microorganisms or microbial antigens in the bloodstream. Ideally, blood should be obtained from peripheral sites as two sets (one set consists of an aerobic bottle and one set an anaerobic bottle) from two different sites approximately 1 hour apart. In selected infections, bacteremia is qualitatively continuous (eg, endocarditis), so cultures can be obtained at any time.[9]

In addition to the infected materials produced by the patient (eg, blood,

sputum, urine, stool, and wound or sinus drainage), other less accessible fluids or tissues must be obtained if they are suspected to be the infected site (eg, spinal fluid in meningitis and joint fluid in arthritis). Abscesses and cellulitic areas also should be aspirated.

When a pathogenic microorganism is identified, the next step for the majority of clinical microbiological laboratories is antimicrobial susceptibility testing that measures the ability of a select organism to grow in the presence of an antimicrobial agent. These methods are described in detail in Chapter e122. Once a microorganism is identified and its susceptibilities are known, specific definitive antimicrobial therapy should be promptly administered.

Over the last decade, there has been an explosion in the development of rapid diagnostic methods that provide simultaneous organism identification and resistance marker detection. These methods include nonamplified probe technologies (peptide nucleic-acid-fluorescence in situ hybridization), proteomics, and nucleic acid amplification methods combined with microarray technologies. These tests can significantly reduce time to organism identification; thereby, can reduce time to effective antimicrobial therapy, overall antimicrobial use, and health outcomes among patients with infectious diseases.[10–12]

Interpreting Results

After a positive Gram stain, culture results, or both are obtained, the clinician must be cautious in determining whether the organism recovered is a true pathogen, a contaminant, or a part of the normal flora (see Chapter e122). The latter consideration is especially problematic with cultures obtained from the skin, oropharynx, nose, ears, eyes, throat, and perineum. These surfaces are heavily colonized with a wide variety of bacteria, some of which can be pathogenic in certain settings. For example, coagulase-negative staphylococci are found in cultures of all the aforementioned sites, yet are seldom regarded as pathogens unless recovered from blood, venous access catheters, or prosthetic devices.

Importantly, cultures of specimens from purportedly infected sites that are obtained by sampling from or through one of these contaminated areas might contain significant numbers of the normal flora. For urine cultures, the urinalysis should be used in combination with culture results to assess the presence of WBCs, nitrite, and leukocyte esterase to help confirm infection and rule out colonization.[13]

Particularly problematic are expectorated sputum specimens that must be evaluated carefully by determination of the presence of squamous epithelial cells and leukocytes.[4] A predominance of epithelial cells in sputum specimens reduces the likelihood that recovered bacteria are pathogenic, especially when multiple types of organisms are seen on Gram stain. In contrast, the discovery of leukocytes in large numbers with one predominant type of organism is a more reliable indicator of a valid collection. In general, however, sputum evaluation has poor sensitivity and specificity as a diagnostic test.

Gram-staining techniques, culture methods, and serologic identification, as well as susceptibility testing, are discussed in detail in Chapter e122. Emphasis must be placed on the proper collection and handling of specimens and careful assessment of Gram stain or other test results in guiding the clinician toward appropriate selection of initial antimicrobial therapy.[14]

SELECTION OF PRESUMPTIVE THERAPY

2 In many instances, empiric therapy must be instituted before microbiological results are available. To select rational antimicrobial therapy for a given clinical situation, a variety of factors must be considered. These include the severity and acuity of the disease, local epidemiology and antibiogram, patient history, host factors, factors related to the drugs used, and the necessity for using multiple agents. In addition, there are generally accepted drugs of choice for the treatment of most pathogens (see Appendix 123-1).

Antibiogram

Drugs of choice are compiled from a variety of sources and are intended as guidelines rather than as specific rules for antimicrobial use. These choices are influenced by local antimicrobial susceptibility data rather than information published by other institutions or national compilations. Each institution should publish an annual summary of antibiotic susceptibilities (antibiogram) for organisms cultured from patients. Antibiograms contain both the number of nonduplicate isolates for common species and the percentage susceptible to the antibiotics tested. To further guide empirical antibiotic therapy, some hospitals publish unit-specific antibiograms in unique patient care areas, such as intensive care units or burn units.

Susceptibility of bacteria can differ substantially among hospitals within a community. For example, the prevalence of hospital-acquired methicillin-

resistant *Staphylococcus aureus* (HA-MRSA) in some centers is quite high, whereas in other centers the problem might be nonexistent. This particular situation will influence the selection of therapy for possible *S. aureus* infection, where the clinician must choose either a β-lactam or vancomycin. The problem of differing susceptibilities is not limited only to gram-positive bacteria but also is evident in gram-negative organisms, and all drug classes are affected.

Patient History

Empirical therapy is directed at organisms that are known to cause the infection in question. These organisms are discussed for different sites of infection in Chapters 124–143. To define the most likely infecting organisms, a careful history and physical examination must be performed. The place where the infection was acquired should be determined, for example, the home (community acquired), nursing home environment, or hospital acquired (nosocomial). Nursing home patients can be exposed to potentially more resistant organisms because they are often surrounded by ill patients who are receiving antibiotics. Important considerations when selecting empiric antimicrobial therapy include: (1) prior knowledge of colonization or infections, (2) previous antimicrobial use, (3) the site of infection and the most likely pathogens, and (4) local antibiogram and resistance patterns for important pathogens. Other questions to ask infected patients regarding the history of present illness include: (1) Are any other people sick at home, especially children? (2) Are any unusual pets kept in the home? (3) Where are you employed (ie, are you exposed to contaminated meat or infectious biohazards)? and (4) Has there been any recent travel (ie, to endemic areas of fungal infections or developing countries)?

Host Factors

Several host factors should be considered when evaluating a patient for antimicrobial therapy. The most important factors are drug allergies, age, pregnancy, genetic or metabolic abnormalities, renal and hepatic function, site of infection, concomitant drug therapy, and underlying disease states.

Allergy

3 Allergy to an antimicrobial agent generally precludes its use. Careful assessment of allergy histories must be performed because many patients

confuse common adverse drug effects (ie, GI disturbance) with true allergic reactions.[15–17] Among the most commonly cited antimicrobial allergies are those to penicillin, penicillin-related compounds, or both. In the absence of complete penicillin skin testing capabilities, a rule of thumb for giving cephalosporins to patients allergic to penicillin is to avoid giving them to patients who give a good history for immediate or accelerated reactions (eg, anaphylaxis, laryngospasm) and to give them under close supervision in patients with a history of delayed reactions, such as a rash.[18] If a gram-negative infection is suspected or documented, therapy with a monobactam may be appropriate because cross-reactivity with other β-lactams is nonexistent.

Age

The patient's age is an important factor both in trying to identify the likely etiologic agent and in assessing the patient's ability to eliminate the drug(s) to be used. The best example of an age determinant of organisms is in bacterial meningitis, where the pathogens differ as the patient grows from the neonatal period through infancy and childhood into adulthood.[5,19]

For neonates, hepatic and liver functions are not well developed. Therefore, bilirubin excretion is decreased resulting in increased concentration of unconjugated bilirubin that can cause kernicterus. Neonates (especially when premature) can develop kernicterus when given sulfonamides. This results from displacement of bilirubin from serum albumin. In addition, neonates have more body water content that results in a larger volume of distribution leading to adjustments in antibiotic dosing regimens. Additional special drug considerations for pediatric patients include low frequency of adverse effects and compliance-enhancing features (eg, absorption not affected by food, once- to twice-daily dosing, and good taste).[7,20,21]

The major physiologic change in persons older than 65 years of age is a decline in the number of functioning nephrons that, in turn, results in decreased renal function.[22] This is usually manifested by an increased incidence of side effects caused by antimicrobials that are eliminated renally. For example, renal toxicity caused by aminoglycosides may be apparent much sooner during therapy in older adults than in younger patients.

Pregnancy

During pregnancy, not only is the fetus at risk for drug teratogenicity, but the

pharmacokinetic disposition of certain drugs can be altered.[23] Penicillins, cephalosporins, and aminoglycosides are cleared from the peripheral circulation more rapidly during pregnancy. This is probably a result of marked increases in intravascular volume, glomerular filtration rate, and hepatic and metabolic activities. The net result is that maternal serum antimicrobial concentrations can be as much as 50% lower during this period than in the nonpregnant state. Increased dosages of certain compounds might be necessary to achieve therapeutic levels during late pregnancy.[24]

Metabolic or Genetic Variation

Inherited or acquired metabolic abnormalities will influence the therapy of infectious diseases in a variety of ways. For example, patients with impaired peripheral vascular flow may not absorb drugs given by intramuscular injection. In addition, certain metabolic states can predispose patients to enhanced drug toxicity. For instance, patients who are phenotypically slow acetylators of isoniazid are at greater risk for peripheral neuropathy.[25] Patients with severe deficiency of glucose-6-phosphate dehydrogenase can develop significant hemolysis when exposed to such drugs as sulfonamides, nitrofurantoin, nalidixic acid, antimalarials, and dapsone. Although mild deficiencies are found in African Americans, the more severe forms of the disease generally are confined to persons of eastern Mediterranean origin. Another example is the antiretroviral drug abacavir, which is associated with a severe hypersensitivity reaction, consisting of fever, rash, abdominal pain, and respiratory distress. This risk has been associated with the presence of a human leukocyte antigen allele HLA-B*5701. Routine screening for the presence of this allele before initiating treatment with abacavir is a recommendation in the current HIV treatment guidelines. Furthermore, the hepatic cytochrome P450 system is a major pathway for a large number of antimicrobials. While differential host expressions of these enzymes occur, insufficient clinical data are currently available to recommend routine screening for antimicrobial therapy.

Organ Dysfunction

4 Patients with diminished renal or hepatic function or both will accumulate certain drugs unless the dosage is adjusted. It is common for patents requiring antimicrobial therapy to have some degree of renal impairment. Because many of the commonly used antimicrobials are primarily cleared by the kidneys, it is

imperative to adjust the dosing regimen or therapy.[26,27] Recommendations for dosing antibiotics in patients with liver dysfunction are not as formalized as guidelines for patients with renal dysfunction. Antibiotics that should be adjusted in severe liver disease include clindamycin, erythromycin, metronidazole, and rifampin. Significant accumulation can occur when both liver dysfunction and renal dysfunction are present for the following drugs: cefotaxime, nafcillin, piperacillin, and sulfamethoxazole.[28]

Concomitant Drugs

5 Any concomitant therapy that the patient is receiving can influence the drug selection, dose, and monitoring. For instance, administration of isoniazid to a patient who is also receiving phenytoin can result in phenytoin toxicity secondary to inhibition of phenytoin metabolism by isoniazid. Furthermore, drugs that possess similar adverse effect profiles can increase the risk for effects (ie, two drugs that cause nephrotoxicity or neutropenia). A detailed review of drug interactions is beyond the scope of this chapter, but an excellent textbook on this subject is available.[29] Lists of potentially severe drug–drug interactions are provided in **Table 123-2**.

TABLE 123-2 Major Drug Interactions with Antimicrobials

Antimicrobial	Other Agent(s)	Mechanism of Action/Effect	Clinical Management
Aminoglycosides	Neuromuscular blocking agents	Additive adverse effects	Avoid
	Nephrotoxins (N) or ototoxins (O) (eg, amphotericin B [N], cisplatin [N/O], cyclosporine [N], furosemide [O], NSAIDs [N], radiocontrast [N], vancomycin [N])	Additive adverse effects	Monitor aminoglycoside SDC and renal function
Amphotericin B	Nephrotoxins (eg, aminoglycosides, cidofovir, cyclosporine, foscarnet, pentamidine)	Additive adverse effects	Monitor renal function
Azoles	See Chapter 139		
Chloramphenicol	Phenytoin, tolbutamide, ethanol	Decreased metabolism of other agents	Monitor phenytoin SDC, blood glucose
Foscarnet	Pentamidine IV	Increased risk of severe nephrotoxicity/ hypocalcemia	Monitor renal function/serum calcium
Isoniazid	Carbamazepine, phenytoin	Decreased metabolism of other agents (nausea, vomiting, nystagmus, ataxia)	Monitor drug SDC
Macrolides/azalides	Digoxin	Decreased digoxin bioavailability and metabolism	Monitor digoxin SDC; avoid if possible
	Theophylline	Decreased metabolism of theophylline	Monitor theophylline SDC
Metronidazole	Ethanol (drugs containing ethanol)	Disulfiram-like reaction	Avoid
Penicillins and cephalosporins	Probenecid, aspirin	Blocked excretion of β-lactams	Use if prolonged high concentration of β-lactam desirable
Ciprofloxacin/ norfloxacin	Theophylline	Decreased metabolism of theophylline	Monitor theophylline
Quinolones	Classes Ia and III antiarrhythmics	Increased Q-T interval	Avoid
	Multivalent cations (antacids, iron, sucralfate, zinc, vitamins, dairy, citric acid), didanosine	Decreased absorption of quinolone	Separate by 2 hours
Rifampin	Azoles, cyclosporine, methadone propranolol, PIs, oral contraceptives, tacrolimus, warfarin	Increased metabolism of other agent	Avoid if possible
Sulfonamides	Sulfonylureas, phenytoin, warfarin	Decreased metabolism of other agent	Monitor blood glucose, SDC, PT
Tetracyclines	Antacids, iron, calcium, sucralfate	Decreased absorption of tetracycline	Separate by 2 hours
	Digoxin	Decreased digoxin bioavailability	Monitor digoxin SDC; avoid if possible

PI, protease inhibitor; PT, prothrombin time; SDC, serum drug concentrations.

Azalides: azithromycin; azoles: fluconazole, itraconazole, ketoconazole, and voriconazole; macrolides: erythromycin and clarithromycin; protease inhibitors: amprenavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, and saquinavir; quinolones: ciprofloxacin, gemifloxacin, levofloxacin, and moxifloxacin.

Concomitant Disease States

Concomitant disease states can influence the selection of therapy. Certain diseases will predispose patients to a particular infectious disease or will alter the type of infecting organism. For example, patients with diabetes mellitus and the resulting peripheral vascular disease often develop infections of the lower extremity soft tissue. Moreover, the alterations in peripheral blood flow associated with the disease and perhaps altered immunity make such infections more difficult to treat than in nondiabetics. Patients with chronic lung disease or cystic fibrosis develop frequent pulmonary infections that can be caused by somewhat different microorganisms than are found in otherwise normal hosts.

Patients with immunosuppressive diseases, such as malignancies or acquired immunologic deficiencies, are highly predisposed to infections, and the types of causative or pathogenic organisms can be vastly different from what would be expected (see Chapter 140). For instance, patients undergoing chemotherapy for acute forms of leukemia often are profoundly granulocytopenic and are predisposed to infections caused by bacteria and fungi.[30] Patients with the acquired immunodeficiency syndrome (AIDS) often become infected with an enormous variety of organisms (see Chapter 143). Many factors predisposing to infection are related to disruption of the host's integumentary barriers. For example, trauma, burns, and iatrogenic wounds induced in surgery can lead to a substantial risk of infection depending on the severity and location of the injury or disruption. For a complete discussion of the various risks involved in surgical procedures, see Chapter 141.

Drug Factors

Pharmacokinetic and Pharmacodynamic Considerations

Integration of both pharmacokinetic and pharmacodynamic properties of an agent is important when choosing antimicrobial therapy to ensure efficacy and to prevent resistance.[31] Early researchers relied solely on pharmacokinetic properties such as the area under the (drug concentration) curve (AUC), maximum observed concentration (peak), and drug half-life to optimize therapy. Pharmacodynamics is the study of the relationship between drug concentration and the effects on the microorganism. There is an important relationship between both pharmacokinetic and microbiologic parameters that has resulted in measurements such as AUC:minimal inhibitory concentration (MIC) ratio, peak:MIC ratio, and time (*T*) the concentration is above MIC (*T*> MIC).[32–35]

Aminoglycosides exhibit concentration-dependent bactericidal effects. An example of the integration of pharmacokinetics and microbiologic activity is the use of high-dose, once-daily aminoglycosides. For these regimens, the drug is given as a single large daily dose to maximize the peak:MIC ratio. Aminoglycosides also possess a postantibiotic effect (persistent suppression of organism growth after concentrations decrease below the MIC) that appears to contribute to the success of high-dose, once-daily administration. Fluoroquinolones exhibit concentration-dependent killing activity, but optimal killing appears to be characterized by the AUC:MIC ratio.

β-Lactams display time-dependent bactericidal effects. Killing activity is enhanced only marginally if drug concentration exceeds the MIC. Therefore, the important pharmacodynamic relationship for these antimicrobials is the duration that drug concentrations exceed the MIC (*T*> MIC). Effective dosing regimens require serum drug concentrations to exceed the MIC for at least 40% to 50% of the dosing interval. Frequent small doses, continuous infusion, or prolonged infusion of β-lactams appear to be correlated with positive outcomes. A detailed discussion on antimicrobial pharmacokinetics–pharmacodynamics is beyond the scope of this chapter. However, excellent sources of information on this topic are available.[31,32,35]

Tissue Penetration

The importance of tissue penetration varies with site of infection. Some of the difficulties in interpreting data include a lack of correlation with clinical outcomes and poor understanding of whether the antimicrobial agents are present in a biologically active form. An example of the former problem is the recognized efficacy of drugs with low biliary fluid concentrations in the treatment of cholecystitis, cholangitis, or both and the absence of the enhanced efficacy of drugs whose primary route of elimination is biliary excretion of active drug. An example of the latter difficulty is with penetration to deep infections, such as abscesses, where various factors such as acid pH, WBC products, and various enzymes can inactivate even high concentrations of certain drugs. The CNS is one body site where antimicrobial penetration is relatively well defined, and correlations with clinical outcomes are established.[5,36] CSF concentrations of antimicrobial agents necessary to cure bacterial meningitis have been defined, and drugs that do not reach significant concentrations in the CSF should be either avoided or instilled directly, if feasible. Caution must be exercised when selecting an antimicrobial agent for clinical use on the basis of

tissue or fluid penetration. Body fluids where drug concentration data are clinically relevant include CSF, urine, synovial fluid, and peritoneal fluid. Apart from these areas, more attention should be paid to clinical efficacy, antimicrobial spectrum, toxicity, and cost than to comparative data on penetration into a given body site.

The proper route of administration for an antimicrobial depends on the site of infection. Parenteral therapy is warranted when patients are being treated for febrile neutropenia or deep-seated infections such as meningitis, endocarditis, and osteomyelitis. Severe pneumonia often is treated initially with IV antibiotics and switched to oral therapy as clinical improvement is evident.[4,37,38] Patients treated in the ambulatory setting for upper respiratory tract infections (eg, pharyngitis, bronchitis, sinusitis, and otitis media), lower respiratory tract infections, skin and soft-tissue infections, uncomplicated urinary tract infections, and selected sexually transmitted diseases can usually receive oral therapy.

Drug Toxicity

It is incumbent on health professionals to avoid toxic drugs whenever possible. Antibiotics associated with CNS toxicities, usually when not dose-adjusted for renal function, include penicillins, cephalosporins, quinolones, and imipenem. Hematologic toxicities generally are manifested with prolonged use of nafcillin (neutropenia), piperacillin (platelet dysfunction), cefotetan (hypoprothrombinemia), chloramphenicol (bone marrow suppression, both idiosyncratic and dose-related toxicity), and trimethoprim (megaloblastic anemia). Reversible nephrotoxicity classically is associated with aminoglycosides and vancomycin. Irreversible ototoxicity can occur with aminoglycosides. In the outpatient setting, patients must be counseled regarding photosensitivity with azithromycin, quinolones, tetracyclines, pyrazinamide, sulfamethoxazole, and trimethoprim. Lastly, all antibiotics have been implicated in causing diarrhea and colitis secondary to *Clostridium difficile* (see Chapter 131).[39] List of potential antibiotic adverse drug reactions is provided in **Table 123-3**.

TABLE 123-3 Antimicrobial Adverse Drug Reactions

Antimicrobial Class	Adverse Drug Reaction	Monitoring Parameters	Comments
Penicillins	Hypersensitivity reactions and rash, drug fever, diarrhea, emesis, abdominal pain, hepatitis, interstitial nephritis, leukopenia, thrombocytopenia, Coomb's positive-hemolytic anemia, *C. difficile* colitis, electrolyte abnormalities, seizures	Monitor for hypersensitivity reactions (eg, bronchospasm, anaphylaxis, angioneurotic edema, immediate urticaria). During prolonged therapy and/or high-dose regimens, periodically monitor renal function, hepatic function, and CBC	Most serious reaction is immediate IgE-mediated anaphylaxis. Incidence is 0.05%, but 5%-10% can be fatal
Cephalosporins	Hypersensitivity reactions and rash, drug fever, diarrhea, interstitial nephritis, Coomb's positive-hemolytic anemia, leukopenia, thrombocytopenia, coagulopathy, hepatitis, *C. difficile* colitis	Monitor for hypersensitivity reactions (eg, bronchospasm, anaphylaxis, angioneurotic edema, immediate urticaria) and rash, renal function, hepatic function, and CBC	Patients with a history of IgE-mediated allergic reactions to penicillins should not receive a cephalosporin
Carbapenems	Hypersensitivity reactions and rash, headache, nausea, diarrhea, seizures, drug fever, eosinophilia, thrombocytopenia, hepatitis, *C. difficile* colitis	Monitor for hypersensitivity reactions (eg, bronchospasm, anaphylaxis, angioneurotic edema, immediate urticaria) and rash, renal function, hepatic function, and CBC	Skin test cross-sensitivity with penicillin reported to be up to 50%, but clinically significant cross-sensitivity reactions in penicillin-allergic patients reported to be as low as 1% Highest incidence of seizures with use of imipenem–cilastatin. More frequent in patients who are elderly, have history of seizure disorders and renal dysfunction
Monobactams	Rash, diarrhea, nausea, hepatitis, thrombocytopenia, *C. difficile* colitis	Monitor renal and hepatic function	May be used in patients with allergy to penicillins/cephalosporins
Aminoglycosides	Tubular necrosis and renal failure, vestibular and cochlear toxicity, neuromuscular blockade, vertigo, anemia, hypersensitivity	Monitor renal function, SDC, serum calcium, magnesium, sodium. Monitor for nausea, vomiting, nystagmus, and vertigo	Nephrotoxicity can be reversible. More frequent in patients with the following risk factors: elderly, history of renal dysfunction, concomitant administration of nephrotoxic drug (ie, cyclosporine, amphotericin B, radiocontrast, vancomycin), and duration of therapy Ototoxicities can be irreversible
Glycopeptides	Red man syndrome, phlebitis, renal dysfunction, neutropenia, leukopenia, eosinophilia, thrombocytopenia, drug fever	Monitor renal function, CBC, and SDC	Red man syndrome is associated with rapid infusion and nonspecific histamine release. May be prevented by prolonging infusions to over at least 60 minutes and pretreatment with antihistamines
Lipopeptides (daptomycin)	Hepatotoxicity, CPK elevation with or without myopathy, diarrhea, eosinophilic pneumonia, *C. difficile* colitis	Monitor LFTs, development of muscle pain/weakness, or neuropathy Obtain serum CPK levels at baseline and weekly (or more frequently in patients with prior or concomitant statin, renal dysfunction, or patients with elevations in CPK)	CPK elevation is dose-dependent. Obtain baseline and weekly CPK levels. Discontinue daptomycin if CPK exceeds 10 times normal level or if patient develops myopathy and CPK >1,000 IU/L (16.7 µkat/L). Consider stopping statin therapy during treatment with daptomycin
Oxazolidinones	Myelosuppression (thrombocytopenia, leukopenia, and anemia), peripheral neuropathy, optic neuropathy, blindness, lactic acidosis, diarrhea, nausea, serotonin syndrome, interstitial nephritis	Monitor for signs and symptoms of serotonin syndrome particularly in patients with prior or concomitant serotonergic agents, CBC with differential. For prolonged therapy, perform visual function tests, monitor visual acuity and visual field defect	Myelosuppression is reversible and associated with treatment duration >2 weeks
Tetracyclines	GI upset, nausea, vomiting, diarrhea, hepatotoxicity, esophageal ulcerations, photosensitivity, azotemia, visual disturbances, vertigo, hyperpigmentation, deposition on teeth, hemolytic anemia, pseudotumor cerebri, pancreatitis, *C. difficile* colitis	Monitor CBC with differential, LFTs, and renal function	Doxycycline preferred in patients with renal dysfunction Vestibular symptoms more frequent in women than in men Avoid use during pregnancy and in children
Chloramphenicol	Myelosuppression, aplastic anemia, "gray baby syndrome," optic neuritis, peripheral neuropathy, digital paresthesias, GI upset, *C. difficile* colitis, hypersensitivity	Obtain baseline CBC with differential and every 2 days during therapy. Monitor SDC (particularly in children and in patients with hepatic or renal insufficiency), liver and renal function	Bone marrow suppression associated with doses >4 g/day. Serum levels >50 mcg/mL (mg/L; 155 µmol/L) are associated with increased risk for "gray baby syndrome"
Rifamycines	Discoloration of urine, tears, contact lens, sweat, hepatotoxicity, GI upset, flu-like syndrome, hypersensitivity, thrombocytopenia, leukopenia, drug fever, interstitial nephritis, thrombocytopenia	Monitor LFTs, bilirubin, renal function, CBC at baseline; continue to monitor every 2-4 weeks in patients with hepatic impairment or receiving concomitant hepatotoxic drugs	Increased potential for hepatitis with concomitant hepatotoxic drugs (ie, TB drugs)

Antimicrobial Class	Adverse Drug Reaction	Monitoring Parameters	Comments
Macrolides/azalide	GI intolerance, diarrhea, prolonged QTc, cholestatic hepatitis, reversible ototoxicity, torsade de pointes, rash, hypothermia, exacerbation of myasthenia gravis	Monitor LFTs and ECG in high-risk patients	
Clindamycin	Diarrhea, *C. difficile* colitis, nausea, vomiting, generalized rash, hypersensitivity	For prolonged therapy, monitor liver and renal function	
Fluoroquinolones	GI intolerance, headache, malaise, insomnia, dizziness, photosensitivity, QTc prolongation, tendon rupture, peripheral neuropathy, crystalluria, seizure, interstitial nephritis, Stevens-Johnson syndrome, allergic pneumonitis, *C. difficile* colitis	Monitor renal function, encephalopathic changes (eg, confusion, hallucinations, and tremor)	Tendon rupture more frequently seen in the elderly and kidney, heart, and lung transplant recipients, and with concurrent use of corticosteroids
Polymyxins	Nephrotoxicity, neurotoxicity (paresthesia, vertigo, ataxia, blurred vision, slurred speech), neuromuscular blockade, bronchospasm (administered via inhalation)	Obtain baseline renal function tests and regularly during therapy. Monitor for signs of neuromuscular blockade (eg, respiratory depression, apnea, muscle weakness)	Nephrotoxicity is dose-dependent
Sulfonamides and trimethoprim	GI intolerance, rash, hyperkalemia, bone marrow suppression (anemia with folate deficiency, thrombocytopenia, and leukopenia), serum sickness, hepatitis, photosensitivity, crystalluria with azotemia, urolithiasis, methemoglobinemia, Stevens-Johnson syndrome, toxic epidermal necrolysis, aseptic meningitis, pancreatitis, interstitial nephritis, Sweet syndrome, neurologic toxicity	Monitor for hypersensitivity reactions and rash, CBC, renal and hepatic function, serum potassium, serum glucose	HIV-infected patients are at increased risk for developing adverse drug reactions Methemoglobinemia due to severe G6PD deficiency
Metronidazole	GI intolerance, headache, metallic taste, dark urine, peripheral neuropathy, disulfiram reactions with alcohol, insomnia, stomatitis, aseptic meningitis, dysarthria	Monitor hepatic function, mental/ neurologic status	Peripheral neuropathy is reversible and associated with prolonged treatment

CBC, complete blood count; CPK, creatine phosphokinase; LFT, liver function test; SDC, serum drug concentrations; TB, tuberculosis.

Aside from consideration of drug toxicity, some antimicrobial use requires more intensive risk–benefit analysis. An example of this is the decision to use isoniazid prophylactically to prevent tuberculosis. Because the hepatotoxicity of

isoniazid increases in frequency with age, older persons (greater than 45 years of age) who are candidates for isoniazid prophylaxis (positive skin test) must have additional risk factors for tuberculosis to balance the potential toxic effects. These include evidence of recent skin test conversion, immunosuppression, or previous gastrectomy. Older patients without additional risk factors are more likely to suffer toxicity from isoniazid than derive benefit from its use.

Combination Antimicrobial Therapy

6 In selecting a drug regimen for a given patient, consideration must be given to the necessity of using more than one drug. Inappropriate or inadequate antimicrobial therapy has been associated with increased morbidity and mortality.[40] Combinations of antimicrobials generally are used to broaden the spectrum of coverage for empirical therapy, achieve synergistic activity against the infecting organism, and prevent the emergence of resistance.

Broadening the Spectrum of Coverage

Increasing the coverage of antimicrobial therapy generally is necessary in two scenarios. First is in mixed infections where multiple organisms are likely to be present. This is the case in intra-abdominal and female pelvic infections, in which a variety of aerobic and anaerobic bacteria can produce disease.[41] Traditionally, a combination of a drug active against aerobic gram-negative bacilli (such as an aminoglycoside) and a drug active against anaerobic bacteria (such as metronidazole or clindamycin) is selected. Newer compounds, which possess good activity against both of these types of organisms, such as the β-lactam/β-lactamase inhibitor combinations, carbapenems, or glycylcyclines, might be adequate to replace the combination and thereby reduce the cost of therapy. The second scenario is for critically ill patients with presumed healthcare-associated infections in which an increased spectrum of activity is desirable.[37] Healthcare-associated infections are frequently caused by multi-drug resistant pathogens; combination therapy is used in this setting to ensure that at least one of the antimicrobials will be active against the pathogen(s).

Synergism

The achievement of synergistic antimicrobial activity is advantageous for infections caused by enteric gram-negative bacilli in immunosuppressed patients. Laboratory tests to identify synergy between antibiotic combinations

are described in Chapter e122. Traditionally, combinations of aminoglycosides and β-lactams have been used because these drugs together generally act synergistically against a wide variety of bacteria. However, the data supporting superior efficacy of synergistic over nonsynergistic combinations are weak. At best, synergistic combinations appear to produce better results in infections caused by *Pseudomonas aeruginosa* and *Enterococcus* species.[33,42–44]

The most obvious example of the use of synergy is the treatment of enterococcal endocarditis. The causative organism is usually only inhibited by penicillins, but it is killed rapidly by the addition of streptomycin or gentamicin to a penicillin. The need for bactericidal activity in the treatment of endocarditis underscores the need for these synergistic combinations.[9,45]

Preventing Resistance

The use of antimicrobial combinations to prevent the emergence of resistance is applied widely but not often realized. The only circumstance where this has been clearly effective is in the treatment of tuberculosis. The prevalence of resistance to a first-line drug such as isoniazid or rifampin in a population of organisms may be as high as 1 in 10^6 to 10^8. Because the bacterial load in a patient with active tuberculosis often exceeds this, two drugs are given to reduce the likelihood of encountering resistance to less than 1 in 10. There is ample evidence from in vitro data and experimental bacterial infections that combinations of drugs with different mechanisms are effective in the prevention of the emergence of resistance. Data from clinical trials, however, either are conflicting or do not convincingly support this concept.[42]

Disadvantages of Combination Therapy

Although there are potentially beneficial effects from combining drugs, there also are potential disadvantages, including increased cost, greater risk of drug toxicity such as nephrotoxicity with aminoglycosides, amphotericin, and possibly vancomycin, and superinfection with even more resistant bacteria.[42,44,46]

The combination of two or more antibiotics can result in antagonistic effects. For example, the effect of antagonism may be evident when one drug induces β-lactamase production and another drug is β-lactamase unstable. Cefoxitin and imipenem are examples of drugs capable of inducing β-lactamases and may result in more rapid inactivation of penicillins when used together.

MONITORING THERAPEUTIC RESPONSE

7 After antimicrobial therapy has been instituted, the patient must be monitored carefully for a therapeutic response. Culture and sensitivity reports from specimens sent to the microbiology laboratory must be reviewed and the therapy changed accordingly. Use of agents with the narrowest spectrum of activity against identified pathogens is recommended. If anaerobes are suspected, even if they are not identified, anti-anaerobic therapy should be continued.

Patient monitoring should include many of the same parameters used to diagnose the infection. The WBC count and temperature should start to normalize. Physical complaints from the patient also should diminish (ie, decreased pain, shortness of breath, cough, or sputum production). Appetite should improve. However, radiologic improvement can lag behind clinical improvement.

Determinations of serum (or other fluid) levels of antimicrobials can be useful in ensuring outcome, preventing toxicity, or both. There are only a few antimicrobials that require serum concentration monitoring and then only in selected situations. These include the aminoglycosides, vancomycin, flucytosine, and chloramphenicol. Achievement of adequate aminoglycoside concentrations within the first few days of therapy of gram-negative infection has been correlated with better therapeutic outcome.[47]

Changes in the volume of distribution can have a significant impact on the efficacy, safety, or both of therapy. An unexpectedly low volume of distribution (such as in the dehydrated patient) will result in higher, potentially toxic drug concentrations, whereas a larger-than-expected volume of distribution (such as in patients with edema or ascites) will result in low, potentially subtherapeutic concentrations. The most effective methods use measured serum concentrations of the drugs rather than estimations from renal function tests to assess true drug clearance from the body.

8 As patients improve clinically, the route of administration should be reevaluated. Streamlining therapy from parenteral to oral (switch therapy) has become an accepted practice for many infections.[5] Criteria that should be present to justify a switch to oral therapy include (a) overall clinical improvement, (b) lack of fever for 8 to 24 hours, (c) decreased WBC count, and (d) a functioning GI tract. Drugs that exhibit excellent oral bioavailability when compared with IV formulations include ciprofloxacin, clindamycin, doxycycline, levofloxacin, metronidazole, moxifloxacin, linezolid, and trimethoprim–sulfamethoxazole.

FAILURE OF ANTIMICROBIAL THERAPY

9 A variety of factors may be responsible for an apparent lack of response to therapy. Patients who fail to respond over 2 to 3 days require a thorough reevaluation. It is possible that the disease is not infectious or is nonbacterial in origin, or there is an undetected pathogen in a polymicrobial infection. Other factors include those directly related to drug selection, the host, or the pathogen. Laboratory error in identification, susceptibility testing, or both (presence of inoculum effect or resistant subpopulations) is a rare cause of antimicrobial failure.

Failures Caused by Drug Selection

Factors related directly to the drug selection include an inappropriate drug selection, dosage, or route of administration. Malabsorption of a drug product because of GI disease (such as a short-bowel syndrome) or a drug interaction (such as complexation of fluoroquinolones with multivalent cations resulting in reduced absorption) can lead to potentially subtherapeutic serum concentrations. Accelerated drug elimination is also possible. This can occur in patients with cystic fibrosis or during pregnancy, when more rapid clearance or larger volumes of distribution can result in low serum concentrations, particularly for aminoglycosides. A common cause of failure of therapy is poor penetration into the site of infection. This is especially true for sites such as the CNS, eye, and prostate gland. Drug failure also can result from drugs that are highly protein bound or that are chemically inactivated at the site of infection.

Failures Caused by Host Factors

Host defenses must be considered when evaluating a patient who is not responding to antimicrobial therapy. Patients who are immunosuppressed (eg, granulocytopenia from chemotherapy or AIDS) may respond poorly to therapy because their defenses are inadequate to eradicate the infection despite seemingly adequate drug regimens. A good example is the poor response of infection in granulocytopenic patients that is seen when their WBC counts remain low during therapy. This contrasts with a much better response when granulocyte counts increase during therapy. Other host factors are related to the need for surgical drainage of abscesses or removal of foreign bodies, necrotic tissue, or both. If these situations are not corrected, they result in persistent infection and, occasionally, bacteremia despite adequate antimicrobial therapy.

Failures Caused by Microorganisms

There are two types of resistance, intrinsic and acquired resistance. Intrinsic resistance is when the antimicrobial agent never had activity against the bacterial species. For example, gram-negative bacteria are naturally resistant to vancomycin because the drug cannot penetrate the outer membrane of gram-negative bacteria. Acquired resistance is when the antimicrobial agent was originally active against the bacterial species but the genetic makeup of the bacteria has changed so the drug can no longer be effective.[48] The strategies used by bacteria to develop acquired resistance are primarily classified into four general mechanisms of resistance: (a) alteration in the target site, (b) change in membrane permeability, (c) efflux pump, and (d) drug inactivation. Bacteria can use one or more of these mechanisms against a specific antibiotic class. Furthermore, a single mechanism of resistance can result in resistance to multiple related or unrelated classes of antibiotics.

Drug inactivation through either β-lactamases or aminoglycoside-modifying enzymes is the predominant mechanism of resistance. For example, β-lactamases can be either plasmid or chromosomally mediated. In addition, the expression of β-lactamases can be induced or constitutive. There are now multiple types and classes of β-lactamases identified, which is beyond the scope of this chapter. However, there are several outstanding papers discussing all of the different types of β-lactamases.[49–51] The increase in resistance among bacteria is believed to be a result of continued overuse of antimicrobials in the community, as well as in hospitals, and the increasing prevalence of immunosuppressed patients receiving long-term suppressive antimicrobials for the prevention of infections. These resistance patterns are regionally variable, and susceptibility patterns in the community (or hospital) should be monitored closely to promote rational antimicrobial selection.[48]

Enterococci have been isolated with multiple resistance patterns. They may be resistant to β-lactams (by virtue of β-lactamase production, altered penicillin-binding proteins [PBPs], or both), vancomycin (via alterations in peptidoglycan synthesis), and high levels of aminoglycosides (via enzymatic degradation). Pneumococci resistant to penicillins, certain cephalosporins, and macrolides are increasingly common. These organisms generally are susceptible to vancomycin, the new fluoroquinolones, and cefotaxime or ceftriaxone. However, antimicrobial agents such as linezolid, daptomycin, telavancin, and tigecycline have been targeted at resistant gram-positive bacteria.

Treatment of an infection caused by *Enterobacter*, *Citrobacter*, *Serratia*, or *P.*

aeruginosa with a third-generation cephalosporin or aztreonam may produce an initial clinical response by eradicating all the susceptible bacteria in the population. Within a few days, however, the highly resistant subpopulations have a selective advantage and can overgrow the infection site to produce a relapse. These bacteria usually retain susceptibility to aminoglycosides, carbapenems, and fluoroquinolones but are resistant to all other β-lactams. Host defenses are extremely important in this scenario. Debilitated patients with pulmonary infections, abscesses, or osteomyelitis are at high risk for drug failure. In these situations, a combination regimen to prevent the emergence of resistance or the use of carbapenem or a fluoroquinolone may be warranted for empirical therapy.

ANTIMICROBIAL STEWARDSHIP

10 The importance of the selection and continuation of appropriate antimicrobial therapy in acute care hospitals are part of a wide movement that is referred to as “antimicrobial stewardship.” Antimicrobial stewardship programs are aimed at “optimizing antimicrobial selection, dosing, route, and duration of therapy to maximize clinical cure or prevention of infection while limiting the unintended consequences, such as the emergence of resistance, adverse drug events, and cost.” Many institutions have developed an antibiotic stewardship program. The team is generally a multidisciplinary group including representation from microbiology, infection control, administration, information technology, pharmacy including infectious disease-trained clinical pharmacists, and physicians from several disciplines, including infectious disease. Components of antimicrobial stewardship activities include formulary restriction, prospective audit and feedback of antimicrobial prescriptions to clinicians, education, use of clinical order sets and guidelines, de-escalation of therapy, and intravenous to oral antimicrobial conversion.[52,53]

Antibiotic Formulary

One of the main roles of an antimicrobial stewardship team is to decide which antibiotics to include on their formularies. The decision to have a formulary remains controversial; however, restricting choices does encourage familiarity with a core of antibiotics for residents and attending physicians. Open formularies allow the empirical use of any commercially available antibiotics, with recommended guidelines for changes when culture and sensitivity results are finalized. The implementation of the guidelines and restrictions requires the

cooperation of the entire medical staff. Education is vital to the success of the antibiotic formulary.

Attention must be paid to the literature on antimicrobials to assist in the selection of therapy. Evidence-based practice guidelines from the Infectious Diseases Society of America can aid clinicians to direct appropriate therapy for specific infectious disease syndromes. In addition, the results from prospective, controlled, randomized clinical trials should be evaluated whenever possible when considering appropriate antimicrobial therapy. Results from prelicensing open trials offer only limited information that can be useful in this regard because patients in these trials generally are not seriously ill and are not infected with multiple resistant bacteria. Other confounding factors found in most clinical situations are excluded by virtue of the study design. Therefore, comparative data in more seriously ill patients are essential for the appropriate application of new agents.

Postmarketing trials are also important because results can demonstrate superiority of one regimen over another, in efficacy, safety, or cost-effectiveness. Appropriate antimicrobial therapy can change as new organisms are discovered, susceptibility patterns change, new drugs become available, and new clinical trial results are published. Classical thinking in the treatment of infectious diseases will continue to change and evolve to maintain antimicrobial efficacy. Optimal use of modern antimicrobials is just beginning to be defined.

ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
AST	antimicrobial susceptibility testing
AUC	area under the curve
CSF	cerebrospinal fluid
HA-MRSA	hospital-acquired methicillin-resistant *Staphylococcus aureus*
IL-1	interleukin 1
MIC	minimal inhibitory concentration
PBP	penicillin-binding protein
PMN	polymorphonuclear
WBC	white blood cell

REFERENCES

1. Boucher HW, Talbot GH, Bradley JS, et al. Bad bugs, no drugs: No ESKAPE! An update from the Infectious Diseases Society of America. *Clin Infect Dis* 2009;48:1–12.
2. Spellberg B, Guidos R, Gilbert D, et al.; Infectious Diseases Society of America. The epidemic of antibiotic-resistant infections: A call to action for the medical community from the Infectious Diseases Society of America. *Clin Infect Dis*. 2008;46:155–164.
3. Wright WF, Mackowiak PA. Fever of unknown origin. In: Bennett JE, Dolin R, Blaser MJ, eds. *Principles and Practice of Infectious Diseases*. 8th ed. New York: Churchill Livingstone; 2015;721–731.
4. Mandell LA, Wunderink RG, Anzueto A, et al.; Infectious Diseases Society of America, American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(Suppl 2):S27–72.
5. Brouwer MC, Tunkel AR, van de Beek D. Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. *Clin Microbiol Rev*. 2010;23:467–492.
6. van de Beek D, Drake JM, Tunkel AR. Nosocomial bacterial meningitis. *N Engl J Med*. 2010;362:146–154.
7. Liu C, Bayer A, Cosgrove SE, et al. Infectious Diseases Society of A. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis* 2011;52:e18–55.
8. Berbari EF, Kanj SS, Kowalski TJ, et al.; Infectious Diseases Society of America. 2015 Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. *Clin Infect Dis*. 2015;61(6):e26–46.
9. Baddour LM, Wilson WR, Bayer AS, et al.; Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease; Council on Cardiovascular Disease in the Young; Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia; American Heart Association; Infectious Diseases Society of America. Infective endocarditis: Diagnosis, antimicrobial therapy, and management of complications: A statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and

Cardiovascular Surgery and Anesthesia, American Heart Association: Endorsed by the Infectious Diseases Society of America. *Circulation*. 2005;111:e394–434.

10. Jenkins SG, Schuetz AN. Current concepts in laboratory testing to guide antimicrobial therapy. *Mayo Clin Proc* 2012;87:290–308.
11. Goff DA, Jankowski C, Tenover FC. Using rapid diagnostic tests to optimize antimicrobial selection in antimicrobial stewardship programs. *Pharmacotherapy*. 2012;32:677–687.
12. Avdic E, Carroll KC. The role of the microbiology laboratory in antimicrobial stewardship programs. *Infect Dis Clin North Am*. 2014;28:215–235.
13. Gupta K, Hooton TM, Naber KG, et al. ; Infectious Diseases Society of A, European Society for M, Infectious D. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis*. 2011;52:e103–120.
14. Croft AC WG. Specimen collection and handling for diagnosis of infectious diseases. In: McPherson RA PM, ed. *Henry's Clinical Diagnosis and Management by Laboratory Methods*. Pennsylvania, PA: Elsevier Saunders; 2011:1239–1254.
15. Granowitz EV, Brown RB. Antibiotic adverse reactions and drug interactions. *Crit Care Clin* 2008;24:421–42,xi.
16. Macy E. Penicillin and beta-lactam allergy: Epidemiology and diagnosis. *Curr Allergy Asthma Rep* 2014;14:476.
17. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: A cohort study. *J Allergy Clin Immunol*. 2014;133:790–796.
18. Gruchalla RS, Pirmohamed M. Clinical practice. Antibiotic allergy. *N Engl J Med*. 2006;354:601–609.
19. Hameed N, Tunkel AR. Treatment of drug-resistant pneumococcal meningitis. *Curr Infect Dis Rep*. 2010;12:274–281.
20. Bradley JS, Byington CL, Shah SS, et al.; Pediatric Infectious Diseases S, the Infectious Diseases Society of A. The management of community-acquired pneumonia in infants and children older than 3 months of age: Clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis*.

2011;53:e25–76.

21. Bradley JS LS. Principles of anti-infective therapy. *Principles and Practice of Pediatric Infectious Diseases*. Philadelphia, PA: Elsevier Saunders; 2012;1412–1518.
22. Weber S, Mawdsley E, Kaye D. Antibacterial agents in the elderly. *Infect Dis Clin North Am*. 2009;23:881–898. viii.
23. Crider KS, Cleves MA, Reefhuis J, Berry RJ, Hobbs CA, Hu DJ. Antibacterial medication use during pregnancy and risk of birth defects: National birth defects prevention study. *Arch Pediatr Adolesc Med*. 2009;163:978–985.
24. Briggs GG FR, Yaffe SJ. Drugs in Pregnancy and Lactation. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.
25. Roy PD, Majumder M, Roy B. Pharmacogenomics of anti-TB drugs-related hepatotoxicity. *Pharmacogenomics*. 2008;9:311–321.
26. Patel N, Scheetz MH, Drusano GL, Lodise TP. Determination of antibiotic dosage adjustments in patients with renal impairment: elements for success. *J Antimicrob Chemother*. 2010;65:2285–2290.
27. Matzke GR, Aronoff GR, Atkinson AJ Jr, et al. Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2011;80:1122–1137.
28. Verbeeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. *Eur J Clin Pharmacol*. 2008;64:1147–1161.
29. Piscitelli S. RK, Pai MP. *Drug Interactions in Infectious Diseases*. 3rd ed. New York: Springer Science; 2012.
30. Freifeld AG, Bow EJ, Sepkowitz KA, et al.; Infectious Diseases Society of A. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;52:427–431.
31. Drusano GL. Pharmacokinetics and pharmacodynamics of antimicrobials. *Clin Infect Dis* 2007;45 Suppl 1:S89–95.
32. Ambrose PG, Bhavnani SM, Rubino CM, et al. Pharmacokinetics-pharmacodynamics of antimicrobial therapy: It’s not just for mice anymore. *Clin Infect Dis*. 2007;44:79–86.
33. DeRyke CA, Lee SY, Kuti JL, Nicolau DP. Optimising dosing strategies of antibacterials utilising pharmacodynamic principles: Impact on the

development of resistance. *Drugs* 2006;66:1–14.

34. George JM, Towne TG, Rodvold KA. Prolonged infusions of beta-lactam antibiotics: Implication for antimicrobial stewardship. *Pharmacotherapy*. 2012;32:707–721.
35. Nightingale CH AP, Drusano GL, Murakawa T. *Antimicrobial Pharmacodynamics in Theory and Clinical Practice*. 2nd ed. New York: Informa Healthcare; 2007.
36. Sinner SW, Tunkel AR. Antimicrobial agents in the treatment of bacterial meningitis. *Infect Dis Clin North Am* 2004;18:581–602,ix.
37. American Thoracic S, Infectious Diseases Society of A. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005;171:388–416.
38. Bradley JS, Byington CL, Shah SS, et al.; Pediatric Infectious Diseases S, the Infectious Diseases Society of A. Executive summary: The management of community-acquired pneumonia in infants and children older than 3 months of age: Clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;53:617–630.
39. Cohen SH, Gerding DN, Johnson S, et al.; Society for Healthcare Epidemiology of A, Infectious Diseases Society of A. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). *Infect Control Hosp Epidemiol*. 2010;31:431–455.
40. Shorr AF, Micek ST, Welch EC, Doherty JA, Reichley RM, Kollef MH. Inappropriate antibiotic therapy in Gram-negative sepsis increases hospital length of stay. *Crit Care Med* 2011;39:46–51.
41. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: Guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Surg Infect (Larchmt)* 2010;11:79–109.
42. Tamma PD, Cosgrove SE, Maragakis LL. Combination therapy for treatment of infections with gram-negative bacteria. *Clin Microbiol Rev*. 2012;25:450–470.
43. Leekha S, Terrell CL, Edson RS. General principles of antimicrobial therapy. *Mayo Clin Proc*. 2011;86:156–167.

44. Paul M, Leibovici L. Combination antimicrobial treatment versus monotherapy: The contribution of meta-analyses. *Infect Dis Clin North Am*. 2009;23:277–293.
45. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: Executive summary. *Clin Infect Dis*. 2011;52:285–292.
46. Bliziotis IA, Samonis G, Vardakas KZ, Chrysanthopoulou S, Falagas ME. Effect of aminoglycoside and beta-lactam combination therapy versus beta-lactam monotherapy on the emergence of antimicrobial resistance: A meta-analysis of randomized, controlled trials. *Clin Infect Dis*. 2005;41:149–158.
47. Turnidge J. Pharmacodynamics and dosing of aminoglycosides. *Infect Dis Clin North Am*. 2003;17:503–528. v.
48. Chen LF, Chopra T, Kaye KS. Pathogens resistant to antibacterial agents. *Med Clin North Am*. 2011;95:647–676. vii.
49. Patel G, Bonomo RA. "Stormy waters ahead": Global emergence of carbapenemases. *Front Microbiol* 2013;4:1–17.
50. Bush K, Jacoby GA. Updated functional classification of beta-lactamases. *Antimicrob Agents Chemother*. 2010;54:969–976.
51. Bush K. The ABCD's of beta-lactamase nomenclature. *J Infect Chemother*. 2013;4:549–559.
52. Dellit TH, Owens RC, McGowan JE Jr, et al.; Infectious Diseases Society of A, Society for Healthcare Epidemiology of A. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis*. 2007;44:159–177.
53. Srinivasan A, Fishman N. Antimicrobial stewardship 2012: Science driving practice. *Infect Control Hosp Epidemiol*. 2012;33:319–321.

APPENDIX 123-1

Drugs of Choice, First Choice, *Alternative(s)*

GRAM-POSITIVE COCCI

Enterococcus faecalis (generally not as resistant to antibiotics as *Enterococcus*

faecium)

- Serious infection (endocarditis, meningitis, pyelonephritis with bacteremia)
  - Ampicillin (or penicillin G) + (gentamicin or streptomycin)
  - Vancomycin + (gentamicin or streptomycin), daptomycin, linezolid, tedizolid, telavancin, tigecycline*a*
- Urinary tract infection
  - Ampicillin, amoxicillin
  - *Fosfomycin* or *nitrofurantoin*

E. faecium (generally more resistant to antibiotics than *E. faecalis*)

- Recommend consultation with infectious disease specialist
  - Linezolid, quinupristin/dalfopristin, daptomycin, tigecycline[a]

Staphylococcus aureus/*Staphylococcus epidermidis*

- Methicillin (oxacillin)-sensitive
  - Nafcillin or oxacillin
  - *FGC,b,c trimethoprim–sulfamethoxazole, clindamycin, BL/BLId*
- Hospital-acquired methicillin (oxacillin)–resistant
  - Vancomycin ± (gentamicin or rifampin)
  - *Ceftaroline, daptomycin, linezolid, telavancin, tigecycline,a trimethoprim–sulfamethoxazole, quinupristin–dalfopristin*
- Community-acquired methicillin (oxacillin)–resistant
  - Clindamycin, trimethoprim–sulfamethoxazole, doxycycline*a*
  - *Ceftaroline, dalbavancin, daptomycin, linezolid, oritivancin, tedizolid, telavancin, tigecycline,*[a] or *vancomycin*

Streptococcus (groups A, B, C, G, and *Streptococcus bovis*)

- Penicillin G or V or ampicillin
- *FGC,*[b,c] *erythromycin, azithromycin, clarithromycin*

Streptococcus pneumoniae

- Penicillin-sensitive (minimal inhibitory concentration [MIC] <0.1 mcg/mL [mg/L])

    - Penicillin G or V or ampicillin
    - *FGC,b,c doxycycline,a azithromycin, clarithromycin, erythromycin*
- Penicillin intermediate (MIC 0.1-1 mcg/mL [mg/L])
    - High-dose penicillin (12 million units/day for adults) or ceftriaxone*c* or cefotaxime*c*
    - *Levofloxacin,a moxifloxacin,a gemifloxacin,a or vancomycin*
- Penicillin-resistant (MIC ≥1.0 mcg/mL [mg/L])
    - Recommend consultation with infectious disease specialist.
        - *Vancomycin ± rifampin*
        - *Per sensitivities: ceftaroline, cefotaxime, ceftriaxone,*[c] *levofloxacin,*[a] *moxifloxacin,*[a] *or gemifloxacin*[a]

Streptococcus, viridans group

- Penicillin G ± gentamicin*e*
- *Cefotaxime,*[c] *ceftriaxone,*[c] *erythromycin, azithromycin, clarithromycin*, or *vancomycin ± gentamicin*

GRAM-NEGATIVE COCCI

Moraxella (Branhamella) catarrhalis

- Amoxicillin–clavulanate, ampicillin–sulbactam
- *Trimethoprim–sulfamethoxazole, erythromycin, azithromycin, clarithromycin, doxycycline,*[a] *SGC,*[c, f] *cefotaxime,*[c] *ceftriaxone,*[c] or *TGCPO*[c,g]

Neisseria gonorrhoeae (also give concomitant treatment for *Chlamydia trachomatis*)

- Disseminated gonococcal infection
    - Ceftriaxone*c* or cefotaxime*c*
    - *Oral follow-up: cefpodoxime,c ciprofloxacin,a* or *levofloxacina*
- Uncomplicated infection
    - Ceftriaxone,*c* cefotaxime,*c* or cefpodoxime*c*
    - *Ciprofloxacin*[a] or *levofloxacin*[a]

Neisseria meningitides

- Penicillin G
- *Cefotaxime*[c] or *ceftriaxone*[c]

GRAM-POSITIVE BACILLI

Clostridium perfringens

- Penicillin G ± clindamycin
- *Metronidazole,*[a] *clindamycin, doxycycline,*[a] *cefazolin,*[c] *carbapenem*[h,i]

Clostridioides (formerly Clostridium) difficile

- *oral vancomycin or fidaxomicin*
- *oral metronidazole*

GRAM-NEGATIVE BACILLI

Acinetobacter spp.

- Doripenem, imipenem, or meropenem ± aminoglycoside*j* (amikacin usually most effective)
- *Ampicillin–sulbactam, polymyxins,*[i] or *tigecycline*[a]

Bacteroides fragilis (and others)

- Metronidazole*a*
- *BL/BLI,*[d] *clindamycin, cefoxitin,*[c] *cefotetan,*[c] *ceftolozane-azobactam, ceftazidime-avibactam,* or *carbapenem*[h,i]

Enterobacter spp.

- Carbapenem*h* or cefepime ± aminoglycoside*j*
- *Ceftolozane-tazobactam, ceftazidime-avibactam, ciprofloxacin,*[a] *levofloxacin,*[a] *piperacillin–tazobactam, ticarcillin–clavulanate*

Escherichia coli

- Meningitis

    - Cefotaxime,*c* ceftriaxone,*c* meropenem
- Systemic infection
    - Cefotaxime*c* or ceftriaxone*c*
    - *BL/BLI,d fluoroquinolone,a,k carbapenemh,i*
- Urinary tract infection
    - Most oral agents: check sensitivities
    - Ampicillin, amoxicillin–clavulanate, doxycycline,*a* or cephalexin*c*
    - *Aminoglycoside,*[j] *FGC,*[b,c] *nitrofurantoin, fluoroquinolone*[a,k]

Gardnerella vaginalis

- Metronidazole*a*
- *Clindamycin*

Haemophilus influenzae

- Meningitis
    - Cefotaxime*c* or ceftriaxone*c*
    - *Meropenemi*
- Other infections
- BL/BLI,*d* or if β-lactamase-negative, ampicillin or amoxicillin
    - *Trimethoprim–sulfamethoxazole, cefuroxime,*[c] *azithromycin, clarithromycin*, or *fluoroquinolone*[a,k]

Klebsiella pneumoniae

- BL/BLI,*d* cefotaxime,*c* ceftriaxone,*c* cefepime*c*
- Carbapenem,[h,i] *ceftolozane-tazobactam, ceftazidime-avibactam*, fluoroquinolone[a,k]

Legionella spp.

- Azithromycin, erythromycin ± rifampin, or fluoroquinolone*a,k*
- Trimethoprim–sulfamethoxazole, clarithromycin, or doxycycline[a]

Pasteurella multocida

- Penicillin G, ampicillin, amoxicillin

- *Doxycycline,*[a] *BL/BLI,*[d] *trimethoprim–sulfamethoxazole* or *ceftriaxone*[c]

Proteus mirabilis

- Ampicillin
- *Trimethoprim–sulfamethoxazole*

Proteus (indole-positive) (including *Providencia rettgeri*, *Morganella morganii*, and *Proteus vulgaris*)

- Cefotaxime,*c* ceftriaxone,*c* or fluoroquinolone*a,k*
- *BL/BLI,*[d] *aztreonam,*[l] *aminoglycosides,*[j] *carbapenem,*[h,i] *ceftolozane-tazobactam, ceftazidime-avibactam*

Providencia stuartii

- Amikacin, cefotaxime,*c* ceftriaxone,*c* fluoroquinolone*a,k*
- *Trimethoprim–sulfamethoxazole, aztreonam,*[l] *carbapenem*[h,i]

Pseudomonas aeruginosa

- Urinary tract infection only
  - Aminoglycoside*j*
  - *Ciprofloxacin,a levofloxacina*
- Systemic infection
  - Cefepime,*c* ceftazidime,*c* doripenem,*i* imipenem,*i* meropenem,*i* piperacillin–tazobactam, or ticarcillin–clavulanate + aminoglycoside*j*
  - *Aztreonam,*[l] *ceftolozane-tazobactam, ceftazidime-avibactam, ciprofloxacin,*[a] *levofloxacin,*[a] *polymyxin*[i]

Salmonella typhi

- Ciprofloxacin,*a* levofloxacin,*c* ceftriaxone,*c* cefotaxime*c*
- *Trimethoprim–sulfamethoxazole*

Serratia marcescens

- Ceftriaxone,*c* cefotaxime,*c* cefepime,*c* ciprofloxacin,*a* levofloxacin*a*
- *Aztreonam,*[l] *carbapenem,*[h,i] *piperacillin–tazobactam, ticarcillin–clavulanate*

Stenotrophomonas (Xanthomonas) maltophilia (generally very resistant to all antimicrobials)

- Trimethoprim–sulfamethoxazole.
- *Check sensitivities to ceftazidime,*[c] *doxycycline,*[a] *minocycline,*[a] and *ticarcillin–clavulanate*

MISCELLANEOUS MICROORGANISMS

Chlamydia pneumoniae

- Doxycycline*a*
- *Azithromycin, clarithromycin, erythromycin, or fluoroquinolone*[a,k]

C. trachomatis

- Azithromycin or doxycycline*a*
- *Levofloxacin,*[a] *erythromycin*

Mycoplasma pneumoniae

- Azithromycin, clarithromycin, erythromycin, fluoroquinolone*a,k*
- *Doxycycline*[a]

SPIROCHETES

Treponema pallidum

- Neurosyphilis
  - Penicillin G
  - *Ceftriaxone*[c]
- *Primary* or *secondary*
  - Benzathine, penicillin G
  - *Ceftriaxone*[c] or *doxycycline*[a]

Borrelia burgdorferi (choice depends on stage of disease)

- Ceftriaxone*c* or cefuroxime axetil,*c* doxycycline,*a* amoxicillin
- *High-dose penicillin, cefotaxime*[c]

*a*Not for use in pregnant patients or children.

*b*First-generation cephalosporins—IV: cefazolin; orally: cephalexin, cephradine, or cefadroxil.

*c*Some penicillin-allergic patients may react to cephalosporins.

*d*β-Lactam/β-lactamase inhibitor combination—IV: ampicillin–sulbactam, piperacillin–tazobactam, and ticarcillin–clavulanate; orally: amoxicillin–clavulanate.

*e*Gentamicin should be added if tolerance or moderately susceptible (MIC >0.1 mcg/mL [mg/L]) organisms are encountered; streptomycin is used but can be more toxic.

*f*Second-generation cephalosporins—IV: cefuroxime; orally: cefaclor, cefditoren, cefprozil, cefuroxime axetil, and loracarbef.

*g*Third-generation cephalosporins—orally: cefdinir, cefixime, cefetamet, cefpodoxime proxetil, and ceftibuten.

*h*Carbapenem: doripenem, ertapenem, imipenem/cilastatin, and meropenem.

*i*Reserve for serious infection.

*j*Aminoglycosides: gentamicin, tobramycin, and amikacin; use per sensitivities.

*k*Fluoroquinolones IV/orally: ciprofloxacin, levofloxacin, and moxifloxacin.

*l*Generally reserved for patients with hypersensitivity reactions to penicillin.

124

Central Nervous System Infections

Christina Koutsari, Thomas J. Dilworth, Jessica Holt, Ramy Elshaboury, and John C. Rotschafer

KEY CONCEPTS

1. The four most common pathogens of acute community-acquired bacterial meningitis in the United States are *Streptococcus pneumoniae*, group B *Streptococcus*, *Neisseria meningitidis*, and *Haemophilus influenzae* type b, although routine vaccinations are having a dramatic effect on the incidence and distribution of these pathogens.
2. In cases of bacterial meningitis, initial findings can include (a) presenting signs and symptoms: fever, headache, nuchal rigidity (the classic triad), Brudzinski's or Kernig's sign, and altered mental status; and (b) abnormal cerebrospinal fluid (CSF) chemistries: elevated white blood cell (WBC) count (>1,000 cells/mm^3 [1.0 x 10^9/L]), elevated protein (>50 mg/dL [500 mg/L]), and decreased glucose levels (<45 mg/dL [2.5 mmol/L]).
3. Main microbiologic tests that should be obtained include a Gram stain and culture of the CSF and blood. In patients with negative CSF Gram stain and culture, molecular testing such as polymerase chain reaction (PCR) has additive value in the pathogen(s) identification.
4. Three primary goals of treatment in meningitis include (a) eradication of infection, (b) amelioration of signs and symptoms, and (c) prevention of the development of neurologic sequelae, such as seizures, deafness, coma, and death.
5. When selecting antibiotics, the clinician must consider the antibiotic concentration at the site of infection as well as the spectrum of antibacterial activity. Empirical choices should be based on age, predisposing conditions, vaccination history, comorbidities, and local susceptibility patterns. (a) Ceftriaxone or cefotaxime and vancomycin are reasonable initial choices for empirical coverage of community-acquired meningitis in

adult patients. (b) Meningitis due to *Listeria monocytogenes* is more common in infants and elderly. Therefore, ampicillin with or without gentamicin should be empirically added to antimicrobial regimens in these age categories.

6. Empirical coverage with an appropriate antibiotic should be started as soon as possible when clinical suspicion of meningitis exists. If there is a delay in obtaining a lumbar puncture (even 30-60 minutes), or if the patient is to undergo neuroimaging, the first dose of antibiotic(s) should not be withheld.
7. Antibiotic dosages for the treatment of meningitis should be optimized to ensure adequate CNS therapeutic concentrations.
8. The duration of antibiotic treatment for acute bacterial meningitis has not been standardized. However, it is generally based on the causative organism and the individual case, and may range from 7 to 21 days.
9. Close contacts and relatives of the index case should be assessed for appropriate chemoprophylaxis and vaccinations, particularly for *N. meningitidis* and *H. influenza* meningitis.
10. Steroid treatment includes dexamethasone of 0.15 mg/kg per dose given four times daily for 2 to 4 days in infants and children with proven or strongly suspected *H. influenzae* type b meningitis. Steroids should be started 10 to 20 minutes prior to, or at least concomitant with, the first dose of antibiotics.

Preclass Engaged Learning Activity

Find the Centers for Disease Control and Prevention (CDC) guidelines for the treatment of CNS infection due to *Naegleria fowleri*. Assume that a female patient who is 50 kg and has normal kidney function requires treatment. Create a table with dose (both in mg/kg and in mg), dosing interval, and monitoring parameters for each recommended anti-infective agent. Which form of amphotericin B is preferred according to the CDC guidelines and why? The purpose of this activity is to enhance your ability to find evidence-based guidelines and apply them to clinical practice.

INTRODUCTION

Central nervous system (CNS) infections are caused by a variety of pathogens, including bacteria, viruses, fungi, and parasites. CNS infections result from hematogenous spread from a primary infection site, seeding from a parameningeal focus, reactivation from a latent site, trauma, neurosurgery, or congenital defects within the CNS. Newer diagnostic techniques have enabled more rapid and definitive diagnosis, thus reducing the number of unknown "aseptic meningitis" diagnoses and improving targeted therapy. Bacteria resistant to multiple antibiotics present new challenges in the management of CNS infections. This chapter presents the epidemiology, etiology, pathophysiology, therapy, and prophylaxis of common CNS infections.

EPIDEMIOLOGY

The incidence of acute, community-acquired bacterial meningitis is approximately 1 to 3 per 100,000 persons annually in developed countries, including the United States and Western Europe.[1–3] In the United States this corresponded to approximately 4,100 annual cases of acute community-acquired bacterial meningitis, excluding epidemics, between 2003 and 2007 resulting in approximately 500 deaths.[2] In stark contrast, incidence rates of meningitis due to *Neisseria meningitidis* alone can reach 1,000 cases per 100,000 people per year in a region of sub-Saharan Africa known as the "meningitis belt." This region is characterized by seasonal and explosive epidemics putting at least 350 million individuals at risk for meningitis annually.[4]

The estimated incidence of brain abscesses is 0.3 to 1.3 per 100,000 people per year but can be considerably higher in high risk groups, such as patients with HIV/AIDS.[5] The global reported incidence of encephalitis varies according to the population studied, and due to differences in definitions and research methodology. The reported incidence in western settings ranges from 0.7 to 13.8 per 100,000 for all ages: 0.7 to 12.6 per 100,000 adults and 10.5 to 13.8 per 100,000 children. The incidence peaks in the young and the elderly.[6,7] In the United States there are approximately 20,000 encephalitis-related hospitalizations and 1,400 deaths per year.[8,9]

ETIOLOGY

Streptococcus pneumoniae remains the leading cause of acute community-acquired bacterial meningitis in the United States with an incidence rate of 0.3 per 100,000 people in 2010.[2,10] *Neisseria meningitidis* and *Haemophilus influenzae* type b (Hib) have also been important causes of acute bacterial meningitis but their incidence has decreased substantially over time to 0.123 per 100,000 people and 0.058 per 100,000 people, respectively, mainly due to introduction of effective vaccinations.[10] Between 2003 and 2007 in the United States, *S. pneumoniae* accounted for 58% of all acute community-acquired bacterial meningitis cases, followed by group B *Streptococcus* (18.1%), *Neisseria meningitidis* (13.9%), *Haemophilus influenzae* (6.7%), and *L. monocytogenes* (3.4%).[2]

Hib was the most commonly identified cause of bacterial meningitis until the introduction of the Hib conjugate vaccine in 1987 (at 18 months of age) and 1991 (at 2 months of age) in the United States. Hib vaccination had a profound population-wide effect in all-age incidence of *Haemophilus influenzae* meningitis reducing it by 97% between 1986 and 2007 to a near elimination level.[11] Targeted meningococcal vaccination for high-risk infants, adolescents, and adults have similarly impacted the epidemiology and risk of meningococcal meningitis, and further changes are expected following the availability of meningococcal group B vaccines in the United States.[12] As a result of the rapid decline of acute community-acquired bacterial meningitis rates in children, the median age of patients increased from <5 years in 1986 to 42 years in 2007 in the United States.[11]

There may be a genetic predisposition to bacterial meningitis. A genome-wide association study reported three single-nucleotide polymorphisms (SNPs) within complement factor H that were associated with 30% lower risk of meningococcal disease.[13] This reduction appeared to be independent of the meningococcal strain. Complement factor H regulates the alternative complement pathway and is exploited by *Neisseria meningitis* to escape host immune control. The protective alleles of the reported SNPs appear to be least common in Africa, where the incidence of meningococcal disease is the highest, suggesting that these variants may explain, at least to some degree, population differences in meningococcal disease rates.

Organisms causing healthcare-associated ventriculitis and meningitis differ markedly from those causing community-acquired bacterial meningitis. The most likely pathogens associated with CSF shunt and drain infections are coagulase-negative staphylococci, *Staphylococcus aureus*, *Propionibacterium (now Cutibacterium) acnes*, and Gram-negative bacilli (including *Escherichia*

coli, *Enterobacter* species, *Citrobacter* species, *Serratia* species, and *Pseudomonas aeruginosa*).[14]

Infectious encephalitis can be caused by many viruses, bacteria (especially intracellular bacteria, such as *Mycoplasma pneumoniae*), parasites, and fungi.[6,15,16] Noninfectious processes can also cause encephalitis and, as a result, the etiology remains unknown in more than 50% of encephalitis cases. Herpes simplex virus (HSV) encephalitis is the most commonly diagnosed viral encephalitis in the United States.[8,17]

Zika virus sparked global attention in 2016 after the first cases of brain developmental disorders in newborns were linked to Zika virus infection of their mothers during pregnancy. Epidemiologic and experimental studies have now provided strong support for causality between Zika virus infection during pregnancy and congenital structural abnormalities of the brain.[18,19]

ANATOMY AND PHYSIOLOGY OF THE CENTRAL NERVOUS SYSTEM

Meninges

The skull and vertebrae protect the CNS from blunt or penetrating trauma (**Fig. 124-1**). The brain is suspended in these structures by cerebrospinal fluid (CSF) and is surrounded by the meninges. The meninges are made up of three separate membranes: dura mater, arachnoid, and pia mater.[20] Dura mater, or pachymeninges, lies directly beneath and is adherent to the skull. The other two membranes are referred to collectively as leptomeninges. Pia mater lies directly over brain tissue. Arachnoid, the middle layer, lies between the dura mater and the pia mater. The subarachnoid space, located between the arachnoid and the pia mater, is the conduit for CSF. Meningitis refers to inflammation of the subarachnoid space or spinal fluid, whereas encephalitis is an inflammation of the brain tissue itself. Since infectious microorganisms frequently are an underlying cause of these inflammatory processes, the terms meningitis, encephalitis, and meningoencephalitis are frequently used to denote an infectious process.

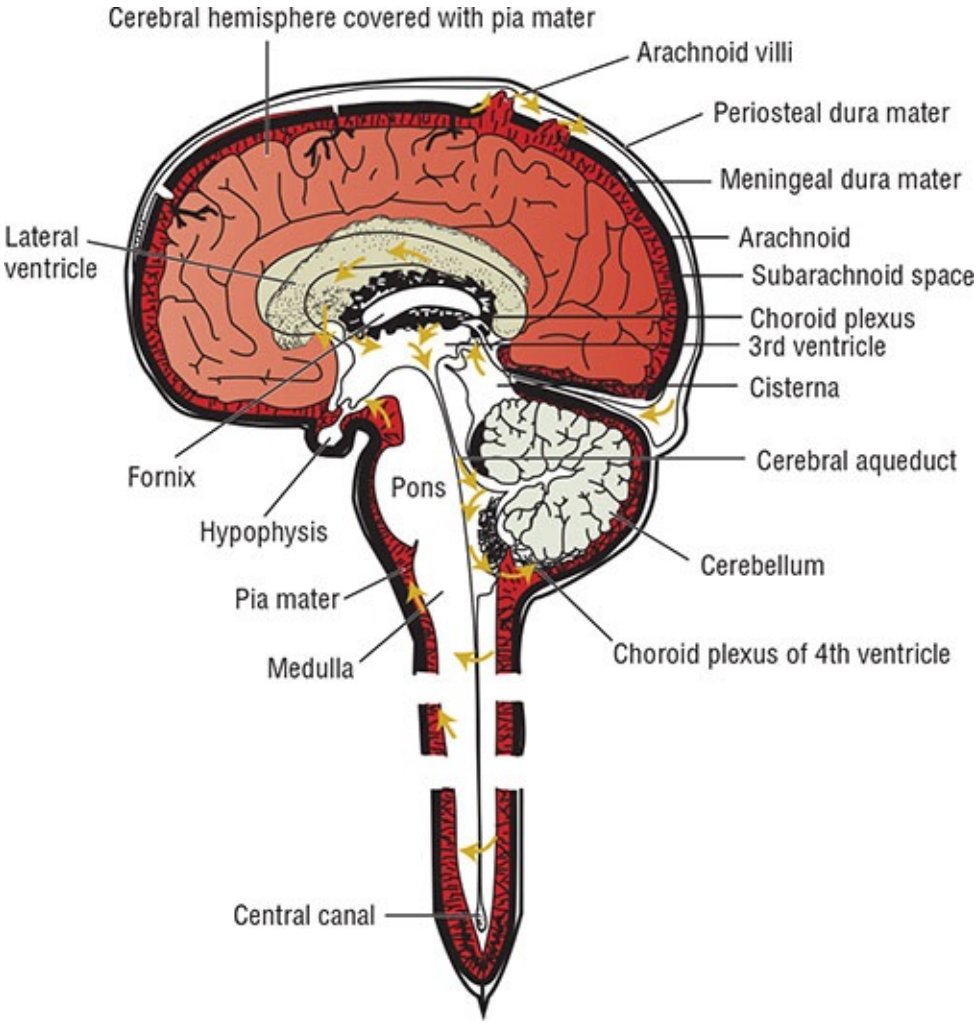


FIGURE 124-1 Diagram of the central nervous system.

Cerebrospinal Fluid

Approximately 85% of the CSF is produced within the third, fourth, and lateral ventricles by the choroid plexus (Fig. 124-1). CSF volume in the CNS is related to patient age: infants have approximately 40 to 60 mL of CSF, older children have 60 to 100 mL, while adults have 115 to 160 mL. Normally, CSF is produced at the rate of approximately 500 mL/day and flows unidirectionally downward through the spinal cord. The CSF is removed by the arachnoid villi and vertebral venous plexus located in the spinal cord and does not recommunicate with the point of production.[20]

2 The CSF normally is clear, with a protein content of less than 50 mg/dL (500 mg/L), a glucose concentration of approximately 50% to 60% of the simultaneous peripheral serum glucose concentration, and a pH of approximately

7.4. Also, it typically contains fewer than 5 WBCs per mm^3 (5×10^6/L), all of which should be lymphocytes (Table 124-1).[4,21] As meninges become inflamed, CSF abnormalities can be used diagnostically as markers of CNS infections.

TABLE 124-1 Mean Values of the Components of Normal and Abnormal Cerebrospinal Fluid[4,21]

Type	Normal	Bacterial	Viral	Fungal	Tuberculosis
WBC (cells/mm^3 or 10^6/L)	<5 (<30 in newborns)	1,000-5,000	50-1,000	20-500	25-500
Differential[a]	Monocytes	Neutrophils	Lymphocytes	Lymphocytes	Lymphocytes
Protein (mg/dL)	<50 (<500 mg/L)	Elevated	Mild elevation	Elevated	Elevated
Glucose (mg/dL)	45-80 (2.5-4.4 mmol/L)	Low	Normal	Low	Low
CSF/blood glucose ratio	50%-60%	Decreased	Normal	Decreased	Decreased

[a]Initial cerebrospinal fluid (CSF), while blood cell (WBC) count may reveal a predominance of polymorphonuclear neutrophils (PMNs). In CNS infection due to tuberculosis, "therapeutic paradox" may occur in which a lymphocytic predominance becomes neutrophilic during antituberculous treatment.

Blood–Brain Barrier/Blood–CSF Barrier

Natural barriers to the exchange of drugs and endogenous compounds among the blood, brain, and CSF are the blood–brain barrier (BBB) and the blood–CSF barrier (BCSFB) (Fig. 124-2). The BBB consists of tightly joined capillary endothelial cells. Drug entry into brain tissue is accomplished by direct passage through the capillary endothelial cells and further penetration of the glial cells that envelop the capillary structure.[20] Passage of drugs into the CSF is controlled by the BCSFB. This barrier is created by ependymal cells of the choroid plexus, which function as an active-transport system similar to the renal tubular epithelial cells. The inflammatory process associated with meningitis can also inhibit the active-transport system of the choroid plexus.

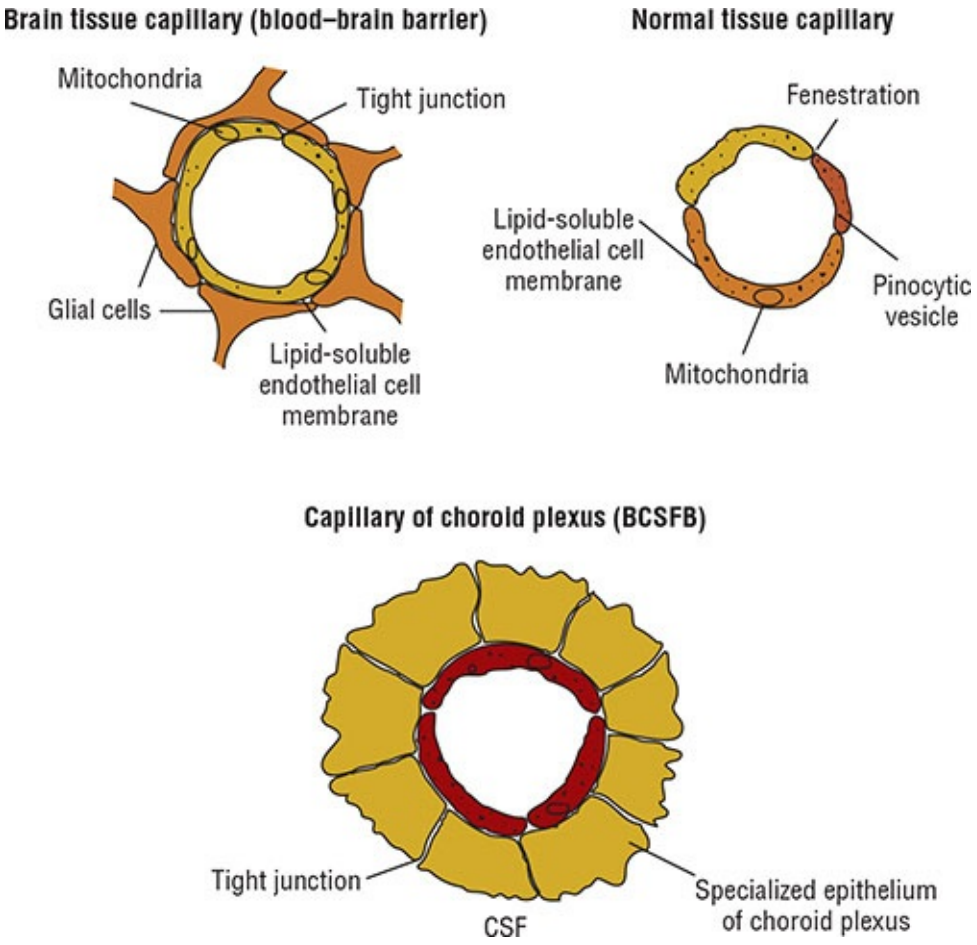


FIGURE 124-2 Schematic representation of a blood–cerebrospinal fluid barrier capillary, brain tissue capillary, and normal tissue capillary.

PATHOPHYSIOLOGY OF THE CNS INFECTION

The development of bacterial meningitis involves four main processes: (i) mucosal colonization and bacterial invasion of the host and CNS, (ii) bacterial replication in the subarachnoid space; (iii) pathophysiologic alterations resulting in progressive inflammation, and (iv) increased intracranial pressure (ICP) and cerebral edema leading to neuronal damage.[4,22] Many bacteria that cause meningitis initially colonize the mucous membranes of the upper respiratory tract. Immunoglobulins (Ig), such as secretory IgA, are found in high concentrations within nasopharyngeal secretions and work to inhibit bacterial colonization. However, this mucus barrier is deteriorated by IgA proteases secreted by bacteria, which allows bacteria to adhere to the host cell surface receptors.

Bacterial pathogens tightly attach to nasopharyngeal epithelial cells and are

then phagocytized into the host's bloodstream. Invasion into the bloodstream occurs either trans-cellularly (passing through the cells) or para-cellularly (between cells). After accessing the patient's bloodstream, bacteria must overcome the host's defense mechanisms. Commonly, CNS bacterial pathogens produce an extensive polysaccharide capsule resistant to neutrophil phagocytosis and complement opsonization. Capsular polysaccharides activate the alternate complement pathway, which promotes phagocytosis and clearance of infecting pathogens. Patients unable to activate the alternative complement pathway, such as those with asplenia or sickle cell anemia, are predisposed to bacterial infections caused by encapsulated microorganisms and, therefore, are at increased risk for meningitis. Most cases of acute bacterial meningitis probably occur following bacteremia but the high incidence of pneumococcal meningitis in patients with sinusitis and otitis media suggests that direct spread to the CNS can also occur.[4]

Although the exact site and mechanism of bacterial invasion into the CNS is unknown, invasion into the subarachnoid space may occur by continuous exposure of the CNS to large bacterial inoculum. Micro-organisms utilize three main mechanisms to directly transit the blood brain barrier: trans-cellular route, para-cellular route, and lytic mechanism.[23] Host defense mechanisms within the subarachnoid space are inadequate to combat bacterial pathogens. Therefore, bacteria replicate freely within the CSF. Although in most cases of bacterial meningitis the neurological syndrome is caused by the pathogen having invaded into the CNS, some bacteria such as the Shiga toxin-producing *E. coli* attack from outside the CNS using toxins.[24]

The effects of meningitis, namely inflammation within the subarachnoid space and the ensuing neurologic damage, are not necessarily a direct result of the pathogens themselves. The neurologic sequelae occur due to the activation of the host's inflammatory pathways, a process induced by the pathogen or its products. Bacterial cell lysis and subsequent death can result in the release of cell-wall components, such as lipopolysaccharide (LPS), lipid A (endotoxin), lipoteichoic acid, teichoic acid, and peptidoglycan, depending on whether the pathogen is Gram-positive or Gram-negative (**Fig. 124-3**). These cell-wall components cause capillary endothelial cells and CNS macrophages to release cytokines (interleukin-1 [IL-1] and tumor necrosis factor [TNF]) and other inflammatory mediators (IL-6, IL-8, platelet-activating factor [PAF], nitric oxide, arachidonic acid metabolites [eg, prostaglandin and prostacycline], and macrophage-derived proteins). Proteolytic products and toxic oxygen radicals are released from the capillary endothelium, causing an alteration in the

permeability of the BBB. Platelet-activating factor activates the coagulation cascade, and arachidonic acid metabolites stimulate vasodilation. These events propagate other sequential events that can lead to cerebral edema, ICP, CSF pleocytosis, decreased cerebral blood flow, cerebral ischemia, and possibly death.

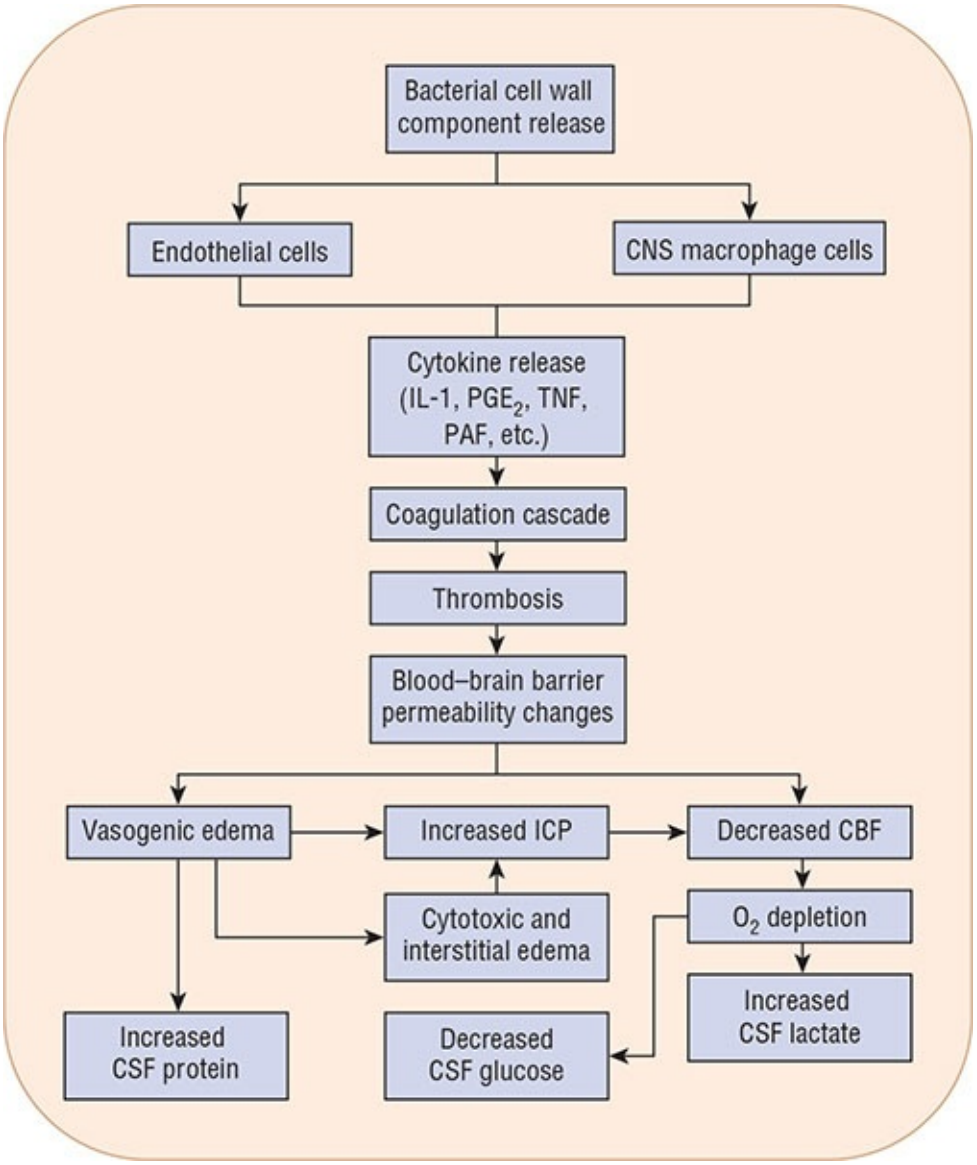


FIGURE 124-3 Hypothetical schema of pathophysiologic events that occur during bacterial meningitis. (CBF, cerebral blood flow; CSF, cerebrospinal fluid; ICP, intracranial pressure; IL-1, interleukin-1; PAF, platelet-activating factor; PGE_2, prostaglandin E_2; TNF, tumor necrosis factor.)

CLINICAL PRESENTATION AND DIAGNOSIS

Clinical presentation of CNS infections varies with host age, immune status, duration of illness, and the specific pathogen causing the infection.

Signs and Symptoms

2 Classic signs and symptoms of acute bacterial meningitis include fever, nuchal rigidity, altered mental status (the classic triad), chills, vomiting, photophobia, and severe headache. Kernig's and Brudzinski's signs may also be present but are poorly sensitive and frequently absent in children (**Figs. 124-4 and 124-5**). Additionally, clinical signs and symptoms in young children may include bulging fontanelle, apneas, purpuric rash, irritability, refusal to eat, and convulsions. The classic triad occurs in <50% of adult patients with acute bacterial meningitis.[25] However, up to 95% of patients exhibit at least two of following symptoms: fever, nuchal rigidity, headache, and altered mental status. Purpuric and petechial skin lesions may indicate meningococcal involvement, although lesions may also be present with *H. influenzae* meningitis.[26]

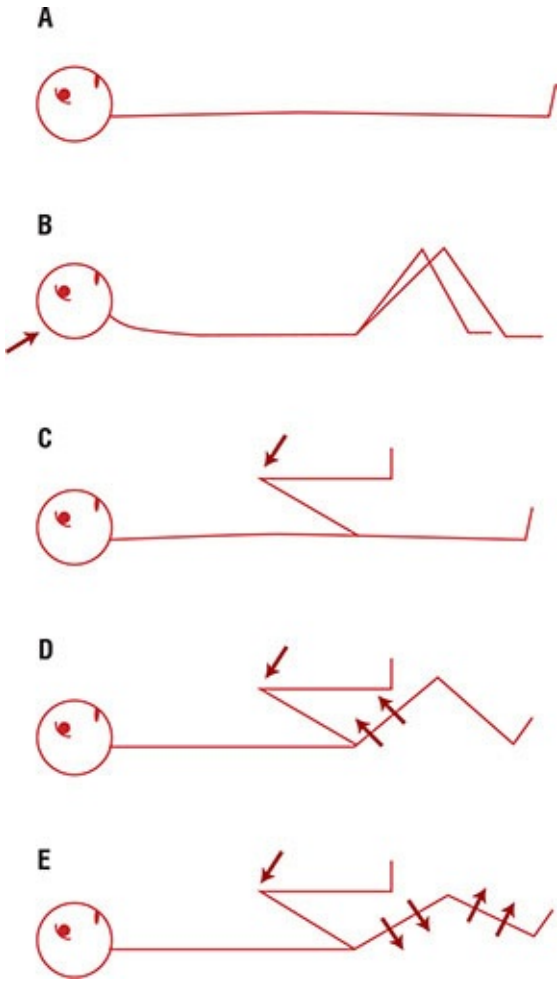


FIGURE 124-4 (A and B) Brudzinski's neck signs. (B) Hip and knee flexion occurs as a result of flexion of the neck. (C to E) Brudzinski's leg signs. (C) Patient's leg is flexed by examiner (*arrow*). (D) The contralateral leg begins to flex—identical contralateral sign (*arrows*). (E) The contralateral leg now begins to extend spontaneously, resembling a little kick (*arrows*).

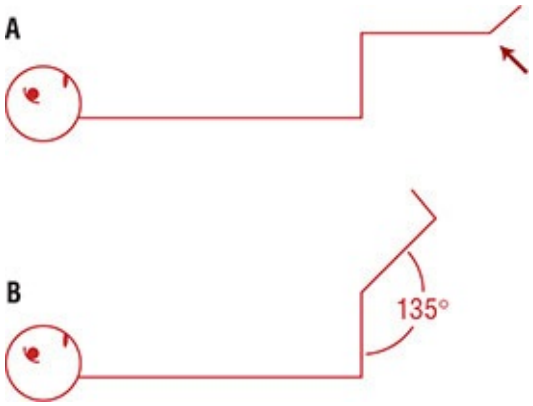


FIGURE 124-5 Kernig's sign. (A) Knees are raised to form a 90-degree angle relative to the trunk, and the examiner attempts to extend the knees. (B) Once the

knee angle reaches approximately 135 degrees, contracture or extensor spasm occurs.

As opposed to acute bacterial meningitis, symptoms of chronic meningitis, defined as 4 weeks of symptoms of meningitis or meningoencephalitis, can be present over weeks and months. Examples include *Mycobacterium tuberculosis* and fungal meningitis (eg, due to *Cryptococcus*, *Histoplasma*, *Aspergillus* species). Early symptoms of chronic meningitis may include headache, nausea, and decreased memory or comprehension, while later symptoms may include double vision, cranial nerve palsies, unsteady gait, emesis, and confusion.[21]

The clinical manifestations of brain abscess depend on the size and location of the space-occupying lesion. Common symptoms include headache, focal neurologic deficits, motor speech disorder, ataxia, fever, nystagmus, seizures, and vomiting. The clinical course can be indolent or fulminant depending on the virulence of the pathogen.

The classical clinical features of infective encephalitis in adults include fever, abnormal mental status (often with severe headache), nausea and vomiting. Seizures can also be the initial presenting feature of patients with infectious encephalitic processes affecting the cortex.[6,16] Lastly, ill children cannot often adequately describe symptoms such as headache, whereas infants commonly have nonspecific symptoms similar to those for other acute illnesses including feeding and respiratory difficulties.[15]

Diagnostic Tests

3 CSF examination is essential for establishing diagnosis of bacterial meningitis, identifying the pathogen, and performing susceptibility testing. CSF polymorphonuclear pleocytocis, an elevated CSF protein of 50 mg/dL (500 mg/L), and a CSF glucose concentration of <50% of the simultaneously obtained peripheral value suggest bacterial meningitis (Table 124-1).[4,21] However, the values for CSF glucose, protein, and WBC found with bacterial meningitis overlap significantly with those with viral, tuberculous, and fungal meningitis (Table 124-1). Therefore, CSF WBC counts and CSF glucose and protein concentrations cannot always distinguish the different etiologies of meningitis. CSF culture is the gold standard for diagnosis of bacterial meningitis and is positive in 80% to 90% of patients with community-acquired bacterial meningitis if the CSF sample is obtained before the start of antimicrobial therapy.[27] In addition, Gram stain is a rapid, inexpensive, and accurate method to

assess the presence of bacteria in CSF. However, the sensitivity of the Gram stain depends on the causative micro-organism, so that its aggregate diagnostic yield is 90% in pneumococcal meningitis, 70% to 90% in meningococcal, 50% in *H. influenza*, and only 25% to 35% in *L. monocytogenes* meningitis.[26]

In patients presenting with new-onset seizures, signs of space-occupying lesions, or moderate-to-severe impairment of consciousness, cranial imaging via magnetic resonance imaging (MRI) or cranial computed tomography (CT) should precede a lumbar puncture. MRI is generally preferred, as it more clearly identifies areas of cerebral edemas and has higher specificity and sensitivity than CT.[28] Neuroimaging should not delay initiation of appropriate antibiotic therapy as doing so can result in a poor outcome in this disease.

3 In patients with suspected CNS bacterial infection, blood cultures are strongly recommended and should be collected before the first dose of antibiotics. Blood cultures identify the causative organism in 50% to 80% of cases, although the yield decreases by 20% if the patient has received antibiotics.[27] CSF viral cultures are insensitive for the diagnosis of viral encephalitis/meningitis. Patients with suspected encephalitis should have a CSF PCR test for HSV1, HSV2, VZV, and enteroviruses, as this will identify 90% of cases due to known viral pathogens.[29]

Models have been developed in an attempt to predict the likelihood of acute community-acquired bacterial versus viral meningitis. Expert opinion articles and guidelines have systematically evaluated these models and identified concerns that limit use in clinical practice.[27,29] Limitations include <100% sensitivity (risk of false negative results), application limited to age-specific cohorts in which the models were developed, and ability to only differentiate between acute bacterial versus viral meningitis when in clinical practice other causes are also considered.

CSF lactate may be useful in differentiating between bacterial and other types of meningitis.[14,29] In a meta-analysis of 1,881 adult and pediatric patients, CSF lactate had a sensitivity of 93% and a specificity of 96% in differentiating bacterial from aseptic meningitis, when the specimen was collected before antibiotics. However, administration of antibiotics reduced sensitivity to 49%, suggesting that the usefulness of CSF lactate is compromised in patients who have already received antimicrobial therapy.[30] CSF and/or serum procalcitonin (PCT) may be useful markers for bacterial cause in community-acquired and healthcare-associated meningitis.[29,31] However, more studies are needed to confirm the impact of PCT monitoring on clinical outcomes, establish cut off

values, and evaluate cost-effectiveness.

3 Polymerase chain reaction (PCR) techniques can rapidly diagnose CNS infections and may be particularly useful in patients who have received antimicrobial therapy before lumbar puncture, have negative cultures, or when the organism is fastidious or fails to grow in conventional culture.[6,14,29] In addition to individual PCR tests, a multiplex PCR panel can simultaneously and rapidly (within ~1 hour) detect six bacterial, seven viral, and two yeast targets directly from CSF specimens; however, more studies are needed to establish performance in clinical practice.[32] Cultures continue to be necessary for the detection of pathogens not covered by the multiplex PCR panel and for antibiotic susceptibilities. 16S rRNA molecular testing and next generation sequencing are also emerging as useful diagnostic tools for CNS infections.[33,34] Ribosomal 16S is part of the 30s ribosomal subunit in bacteria. By identifying species-level 16s sequences, this testing can detect a causative pathogen for patients whose cultures are negative. Results may take several days to return.

Latex agglutination has little incremental value and is not a recommended routine diagnostic modality for rapid determination of bacterial etiology of meningitis.[14,28,29] More studies are needed to determine whether immunochromatographic antigen testing has incremental value in the diagnosis of bacterial meningitis.

Diagnosis of tuberculous meningitis employs acid-fast stain, culture, and PCR of the CSF. The standard diagnostic tests for fungal meningitis include culture, direct microscopic examination of stained and unstained specimens of CSF, antigen detection of cryptococcal or histoplasma antigens, and antibody assay of serum and/or CSF.

TREATMENT

Desired Outcome

4 Goals for the treatment of CNS infections should include prompt and effective eradication of infection, amelioration of signs and symptoms, and reduction of morbidity and mortality. Key elements include initiation of appropriate anti-infective and supportive care, and prevention of disease through timely introduction of vaccination and chemoprophylaxis. Understanding appropriate selection of anti-infective agents and the issues surrounding their CNS penetration will assist in meeting the goals of treatment.

General Approach to Treatment, Nonpharmacologic and Supportive Therapy

5 Until a pathogen is identified, prompt empirical antibiotic coverage is needed. Based on the patient's profile (ie, allergies, age, and concurrent medical conditions), extent of antibiotic CNS penetration, spectrum of activity, and local susceptibility patterns appropriate recommendations should be made. Therapy should last at least 48 to 72 hours or until an infectious process has been ruled out (**Tables 124-2** and **124-3**).[28,29,35]

TABLE 124-2 Bacterial Meningitis: Most Likely Etiologies and Empiric Therapy by Age Group[28,29]

Age	Most Likely Organisms	Empirical Therapy[a]
<1 month	*S. agalactiae* Gram-negative enterics[b] *L. monocytogenes*	Ampicillin + cefotaxime *or* ampicillin + aminoglycoside
1-23 months	*S. pneumoniae* *N. meningitidis* *H. influenzae* *S. agalactiae*	Vancomycin[c] + 3rd generation cephalosporin (cefotaxime *or* ceftriaxone)
2-50 years	*N. meningitidis* *S. pneumoniae*	Vancomycin[c] + 3rd generation cephalosporin (cefotaxime *or* ceftriaxone)
>50 years	*S. pneumoniae* *N. meningitidis* Gram-negative enterics[b] *L. monocytogenes*	Vancomycin[c] + ampicillin + 3rd generation cephalosporin (cefotaxime *or* ceftriaxone)

[a]All recommendations are A-III.

[b]*E. coli*, *Klebsiella* spp., *Enterobacter* spp. common.

[c]Vancomycin use should be based on local incidence of penicillin-resistant *S. pneumoniae* and until cefotaxime or ceftriaxone minimum inhibitory concentration results are available.

Strength of recommendation: (A) Good evidence to support a recommendation for use; should always be offered. (B) Moderate evidence to support a recommendation for use; should generally be offered.[15]

Quality of evidence: (I) Evidence from one or more properly randomized, controlled trial. (II) Evidence from one or more well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from one or more center) or from multiple time-series. (III) Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.[15]

TABLE 124-3 Penetration of Anti-infective Agents into the CSF[a],[35]

Therapeutic Levels in CSF With or Without Inflammation	
Acyclovir	Levofloxacin
Chloramphenicol	Linezolid
Ciprofloxacin	Metronidazole
Fluconazole	Moxifloxacin
Flucytosine	Pyrazinamide
Foscarnet	Rifampin
Fosfomycin	Sulfonamides
Ganciclovir	Trimethoprim
Isoniazid	Voriconazole
Therapeutic Levels in CSF With Inflammation of Meninges	
Ampicillin ± sulbactam	Imipenem
Aztreonam	Meropenem
Cefepime	Nafcillin
Cefotaxime	Ofloxacin
Ceftazidime	Penicillin G
Ceftriaxone	Piperacillin/tazobactam[b]
Cefuroxime	Pyrimethamine
Colistin	Quinupristin/dalfopristin
Daptomycin	Ticarcillin ± clavulanic acid[b]
Ethambutol	Vancomycin
Nontherapeutic Levels in CSF With or Without Inflammation	
Aminoglycosides	Cephalosporins (second generation)[d]
Amphotericin B	Doxycycline[e]
β-Lactamase inhibitors[c]	Itraconazole[f]
Cephalosporins (first generation)	

[a]Using recommended CNS dosing and compared to MIC of target pathogens.

[b]May not achieve therapeutic levels against organisms with higher MIC, as in *P. aeruginosa*. Tazobactam does not penetrate BBB.

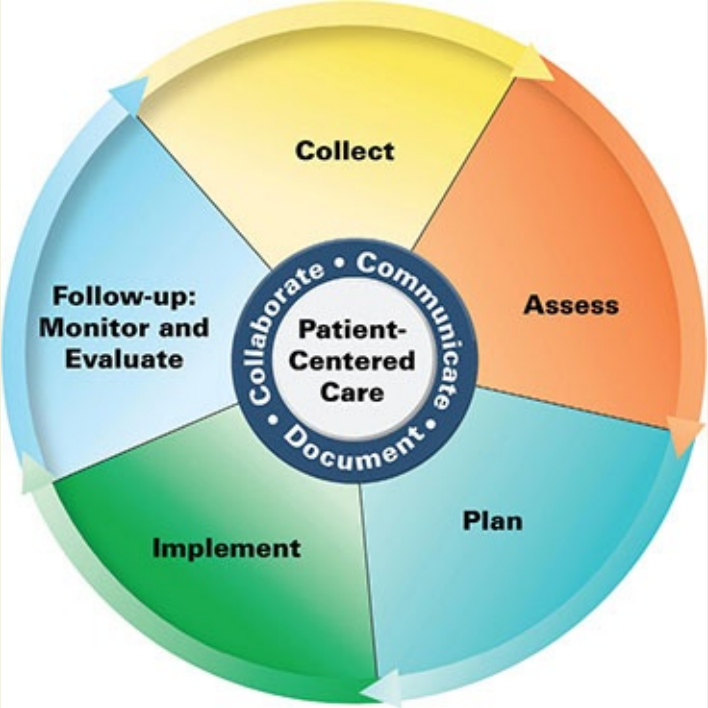
[c]Includes clavulanic acid, sulbactam, and tazobactam.

[d]Cefuroxime is an exception.

[e]Documented effectiveness for *B. burgdorferi*.

[f]Achieves therapeutic concentrations for *Cryptococcus neoformans* therapy.

6 Acute bacterial meningitis is a neurologic emergency and empiric antimicrobial therapy should be initiated as soon as possible after a diagnosis is suspected.[28] The first dose of antibiotics should not be withheld, even when lumbar puncture is delayed or neuroimaging is being performed. It is strongly recommended that the time period from suspected diagnosis to initiation of antibiotic treatment should not exceed 1 hour.[29]



Patient Care Process for CNS Infections

Collect

- Patient characteristics (eg, age, sex, weight, height, pregnancy status, allergies)
- Patient medical history (personal and family)
- Social history (eg, ethanol/IV drug use, recent travel, home residence, exposure to animals) and dietary habits including intake of unpasteurized dairy products
- Current medication use including anti-infective and immunomodulating agents
- Vaccination history (eg, PCV13, PPV23, Hib, MenACWY, MenB)

- Objective data
  - Temperature, blood pressure, respiratory rate, white blood cell count, lactate, procalcitonin, serum creatinine, blood urea nitrogen
  - Blood/CSF examination, cultures, gram stain, PCR, 16s rRNA, smear, AFB, serology
  - Radiologic imaging (MRI, CT)

Assess

- Presence of risk factors (eg, vaccination history, immunocompromised status, asplenia, recent dental procedure, endocarditis, consumption of unpasteurized dairy products, central venous catheter, CSF shunt)
- Signs and symptoms (eg, temperature >100.4 ^{o}F (38 ^{o}C), nuchal rigidity, headache, Kernig's and Bruzinski's signs [Figs. 124-4 and 124-5], CSF characteristics [Table 124-1], radiographic evidence, pathogen identification)
- Local susceptibilities of suspected/proven pathogen(s)
- Source control of focal infection (eg, minimally invasive aspiration of brain abscess)
- Barriers for successful completion of therapeutic regimen
- Candidates for chemoprophylaxis

Plan*

- Evidence-based empiric drug therapy regimen including anti-infective agent(s) with good CNS penetration (Table 124-3), dose, route, frequency, and duration (see Tables 124-2 and 124-5, the sections "Healthcare-Associated Ventriculitis and Meningitis," "Bacterial Brain Abscess," "Viral Encephalitis," and "CNS Infections in Special Populations").
- Definitive anti-infective therapy if specific pathogen identified (Tables 124-4 and 124-5, sections as above)
- Corticosteroid use when indicated
- Monitoring parameters including efficacy (eg, fever, mental status, meningismus, white blood cell count, radiologic resolution of focal infection, drug monitoring) and safety (eg, renal function, drug-drug interactions); frequency and timing of follow-up
- Patient education (eg, purpose of treatment, invasive procedures, drug-

specific information)

- Referrals to other providers when appropriate (eg, infectious diseases, neurologist, interventional radiologist)

Implement*

- Provide patient education regarding all elements of treatment plan
- Ensure effective transitions of care
- Schedule follow-up if treatment continues as outpatient (eg, SCr, adherence assessment, radiographic imaging)

Follow-up: Monitor and Evaluate

- Resolution of CNS infection symptoms (eg, fever, nuchal rigidity, headache, altered mental status)
- Presence of adverse effects (eg, acute renal injury, electrolyte abnormalities, QT interval prolongation)
- Patient adherence to treatment plan using multiple sources of information
- Duration of therapy based on evidence-based guidelines, clinical and radiologic progress

**Collaborate with patient, caregivers, and other healthcare professionals.*

Supportive care, particularly early in the course of treatment, is important. Administration of fluids, electrolytes, antipyretics, and analgesics may be indicated for patients presenting with a possible CNS infection. Additionally, venous thromboembolism prophylaxis, antiepileptic therapy, and ICP monitoring may be needed. Patients may require the administration of osmotic diuretics such as mannitol 25% or hypertonic 3% saline to maintain an ICP of less than 15 mm Hg (2 kPa) and a cerebral perfusion pressure of 60 mm Hg (8 kPa) or more. Other supportive care measures may include respiratory and circulatory supports, gastrointestinal (GI) care and maintaining normal body temperature.

Although supportive treatment may be indicated in certain patients with acute bacterial meningitis, the routine use of adjuvant mannitol, acetaminophen, antiepileptic agents or hypertonic saline is not recommended according to the European guidelines.[29] Furthermore, therapeutic hypothermia and glycerol are contraindicated because they have been associated with a higher mortality rate.[29–38] However, a Cochrane meta-analysis including 1,272 patients (mostly children under 16 years) demonstrated no effect of glycerol on mortality.[39]

7 Several factors influence the transfer of antibiotic from capillary blood into the CNS. Notably, antibiotic penetration is increased through inflamed meninges due to damage to tight junctions between capillary endothelial cells and reduction of the activity of energy-dependent efflux pumps in the choroid plexus responsible for movement of penicillins and, to a lesser extent, fluoroquinolones and aminoglycosides (Table 124-3).[35] Antibiotics having low molecular weights are passed more easily through biologic barriers than compounds of higher molecular weight. Furthermore, only nonionized antibiotics at physiologic or pathologic pH are capable of diffusion. Highly lipid-soluble compounds penetrate more readily than water-soluble compounds. Antibiotics not extensively bound to plasma proteins provide a larger free fraction of drug capable of passing into the CSF. However, passage of large, polar antibiotics into the CSF may be assisted by a carrier transport system. Antibiotic dosages in the treatment of CNS infections must be optimized to ensure adequate penetration to the site of infection.

Challenges of CSF penetration were traditionally overcome by direct instillation of antibiotics intrathecally or intraventricularly. Advantages of direct instillation, however, must be weighed against the risks of invasive CNS procedures and adverse effects. Intraventricular delivery may be necessary in patients who have shunt infections that are difficult to eradicate or who cannot undergo the surgical components of therapy.[28] Antimicrobial agents often utilized for bacterial meningitis treatment have adequate CSF penetration, which has limited the need for direct CNS instillation for this type of infection. The Infectious Diseases Society of America (IDSA) guidelines for healthcare-associated meningitis and ventriculitis recommend considering the use of intraventricular antibiotics only in patients who fail or respond poorly to systemic treatment.[14]

8 Although the length of treatment for acute bacterial meningitis is generally based on the causative organism, there is no universally accepted standard (**Table 124-4**).[14,28,29] Meningitis caused by *S. pneumoniae* has been treated successfully with 10 to 14 days of antibiotic therapy, while cases caused by *N. meningitidis* or *H. influenzae* usually can be treated with a 7-day course. In contrast, a longer duration (21 days or more) has been recommended for patients with *L. monocytogenes*, Gram-negative or pseudomonal meningitis. Nonetheless, antibiotic treatments for bacterial meningitis should be individualized, and some patients may require enduring courses.

TABLE 124-4 Antimicrobial Agents of First Choice and Alternative Choice

in the Treatment of Meningitis Caused by Gram-Positive and Gram-Negative Microorganisms[14,28,29]

Organism	Antibiotics of First Choice	Alternative Antibiotics	Recommended Duration of Therapy
Gram-Positive Organisms			
Streptococcus pneumoniae[a]			10-14 days
Penicillin susceptible MIC ≤0.06 mcg/mL (mg/L)	Penicillin G or Ampicillin (A-III)	Cefotaxime (A-III), Ceftriaxone (A-III), Cefepime (B-II), or Meropenem (B-II)	
Penicillin resistant MIC >0.06 mcg/mL (mg/L)	Vancomycin[b,c] + Cefotaxime or Ceftriaxone (A-III)	Moxifloxacin (B-II)	
Ceftriaxone resistant MIC >0.5 mcg/mL (mg/L)	Vancomycin[b,c] + Cefotaxime or Ceftriaxone (A-III)	Moxifloxacin (B-II)	
Staphylococcus aureus			14-21 days
Methicillin susceptible	Nafcillin or Oxacillin (A-III)	Vancomycin (A-III) or Meropenem (B-III)	
Methicillin resistant	Vancomycin[b,c] (A-III)	TMP-SMX or Linezolid (B-III)	
Group B *Streptococcus*	Penicillin G or Ampicillin (A-III) ± Gentamicin[b,c]	Ceftriaxone or Cefotaxime (B-III)	14-21 days
S. epidermidis	Vancomycin[b,c] (A-III)	Linezolid (B-III)	14-21 days[d]
L. monocytogenes	Penicillin G or Ampicillin ± Gentamicin[b,c,e] (A-III)	Trimethoprim-sulfamethoxazole (A-III), Meropenem (B-III)	≥21 days
Gram-Negative Organisms			
Neisseria meningitis			7-10 days
Penicillin susceptible	Penicillin G or Ampicillin (A-III)	Cefotaxime or Ceftriaxone (A-III)	
Penicillin resistant	Cefotaxime or Ceftriaxone (A-III)	Meropenem or Moxifloxacin (A-III)	
Haemophilus influenzae			7-10 days
β-lactamase negative	Ampicillin (A-III)	Cefotaxime (A-III), Ceftriaxone (A-III), Cefepime (A-III) or Moxifloxacin (A-III)	
β-lactamase positive	Cefotaxime or Ceftriaxone (A-I)	Cefepime (A-I) or Moxifloxacin (A-III)	
Enterobacteriaceae[f]	Cefotaxime or Ceftriaxone (A-II)	Cefepime (A-III), Moxifloxacin (A-III), Meropenem (A-III) or Aztreonam (A-III)	21 days
Pseudomonas aeruginosa	Cefepime or Ceftazidime (A-II) ± Tobramycin[b,c] (A-III)	Ciprofloxacin (A-III), Meropenem (A-III), Piperacillin plus Tobramycin[a,b] (A-III), Colistin sulfomethate[g] (B-III), Aztreonam (A-III)	21 days

[a]European Guidelines recommend considering the addition of rifampin to vancomycin therapy.

[b]Direct CNS administration maybe considered if failed conventional treatment.

[c]Monitor serum drug levels.

[d]Based on clinical experience; no clear recommendations.

[e]European guidelines recommend adding gentamicin for the first 7 days of treatment.

[f]Includes *E. coli and Klebsiella* spp.

[g]Should be reserved for multidrug-resistant pseudomonal or *Actinetobacter* infections for which all other therapeutic options have been exhausted.

See Table 124-2 footnotes for rating scale of evidence.

ACUTE BACTERIAL MENINGITIS

Causative Organisms

Streptococcus pneumoniae (Pneumococcus or Diplococcus)

9 *S. pneumoniae* continues to be the leading cause of community-acquired bacterial meningitis in patients 2 months of age or older. Approximately 40% to 50% of bacterial meningitis cases in the United States with an overall case-fatality rate of ~6% to 18%.[2,10] Despite declining rates of pneumococcal meningitis since the introduction of PCV7 and PCV13 vaccinations in 2000 and 2010, respectively, case-fatality rate has not significantly changed from the pre-PCV7 era.[2,40,1] Pneumonia, endocarditis, CSF leak secondary to head trauma, splenectomy, alcoholism, sickle cell disease, and bone-marrow transplantation may predispose the patient to the development of pneumococcal meningitis. Coma, hearing impairment, and seizures are common neurologic complications due to *S. pneumoniae* meningitis.

5 Based on resistance patterns, penicillin should not be used as empiric therapy if *S. pneumoniae* is a suspected pathogen. Furthermore, appropriate Clinical Laboratory Standards Institute (CLSI)-approved testing of all CSF isolates for penicillin resistance is recommended. Ceftriaxone and cefotaxime have served as alternatives to penicillin in the treatment of penicillin-nonsusceptible pneumococci. Of note, higher minimum inhibitory concentration (MIC) with cephalosporins and higher cephalosporin resistance rates were noted in penicillin-resistant isolates, with the exception of ceftaroline.[42] Therapeutic approaches to cephalosporin-resistant pneumococci include the addition of vancomycin or rifampin. The combination of vancomycin and ceftriaxone can be used as empirical treatment until antimicrobial susceptibility is available.[28,29]

Given the limited therapeutic options for penicillin- and cephalosporin-resistant pneumococcal meningitis, newer agents have been evaluated. Meropenem is approved for the treatment of bacterial meningitis in children aged 3 months and older and has shown similar clinical and microbiologic efficacies to cefotaxime or ceftriaxone. Meropenem is recommended as an alternative to a third-generation cephalosporin in penicillin-nonsusceptible isolates. Some caution is warranted with the use of imipenem for CNS infections

given the risk of drug-induced seizures, especially when doses are not properly adjusted for declining renal function. Of note, seizures may be caused by meningitis itself or imipenem, and the cause is often difficult to differentiate. Levofloxacin and moxifloxacin represent additional therapeutic options with favorable activity against multidrug-resistant pneumococci and good penetration into the CSF.[14, 43]

Intravenous linezolid, daptomycin, and ceftaroline have also emerged as viable therapeutic options for treating multidrug-resistant Gram-positive infections. Linezolid in combination with ceftriaxone has been used to treat a limited cases of pneumococcal meningitis with outcomes similar to standard treatment.[44,45] Further research is required to delineate the clinical utility of therapeutic options such as daptomycin and ceftaroline and determine their place in therapy.

Pneumococcal vaccines help reduce the risk of invasive pneumococcal disease (IPD). Virtually all serotypes of *S. pneumoniae* exhibiting intermediate or complete resistance to penicillin are included in the 23-serotype pneumococcal polysaccharide vaccine (PPV23). Use of the heptavalent pneumococcal conjugate vaccine (PCV7), introduced in 2000, significantly reduced the incidence of invasive pneumococcal infections, including sepsis and meningitis.[46] However, in the decade following its introduction, rate of invasive disease caused by non-PCV7 strains increased considerably, especially serotype 19A, leading to the development of a newer vaccine with expanded coverage.[46] In 2010, the FDA approved a PCV13 to replace PCV7. In the first 3 years after the introduction of PCV13 in the United States, investigators estimated over 30,000 cases of IPD and 3,000 deaths were potentially averted.[47] Notably, the first study to examine the impact of PCV13 on pneumococcal meningitis in the United States showed the total number of cases remained the same, yet the proportion of PCV13 serotypes and antibiotic-resistant strains have significantly decreased, mainly serotype 19A.[40] A national prospective study in England and Wales reported a rapid increase in IPD in the last 3 to 4 years due to highly virulent, non-PCV13 serotypes (serotypes 8, 12F, and 9N).[48] The reasons for this increase remain unknown.

For current recommendations on vaccinations against pneumococcal disease and high-risk groups, the reader is referred to Chapter 142 “Vaccines, Toxoids, and Other Immunobiologics” in this text and the current guidelines by the Advisory Committee on Immunization Practices (ACIP).

Neisseria Meningitidis (Meningococcus)

1 *N. meningitidis* is a leading cause of bacterial meningitis among children and young adults in the United States and around the world.[2,49–51] *N. meningitidis* accounted for 13.9% of all meningitis cases in the United States during 2003 to 2007, with a case-fatality rate of approximately 10%.[2] Overall incidence of meningococcal disease in the United States has been declining from 1.2 cases per 100,000 population in late 1990s to 0.12 cases per 100,000 population in 2016. Incidence peaks in infants <1 year old (0.93 cases per 100,000 population) with a second peak in adolescents and young adults 16 to 23 years of age (0.23 cases per 100,000 population).[50] Five of the thirteen serogroups of *N. meningitidis* (A, B, C, Y, and W-135) are primarily responsible for invasive meningococcal disease. The proportion of cases caused by each serogroup varies by age group in the United States. Serogroup B causes ~60% of meningococcal disease among children <5 years old, while serogroups C, Y, and W account for approximately two thirds of meningococcal disease in patients 11 years old.

N. meningitidis is spread by direct person-to-person close contact, including respiratory droplets and pharyngeal secretions. Close contacts of patients contracting meningococcal meningitis are at an increased risk of developing meningitis. Secondary cases of meningitis usually develop within the first week following exposure but may take up to 60 days after contact with the index case.[12] Clusters of disease are associated with crowding as in schools, dormitories, and military barracks. Other significant risk factors for meningococcal disease include complement deficiency, anatomic or functional asplenia, HIV infection, and passive or active smoking.[12]

The presence of petechiae may be the primary clue that the underlying pathogen is *N. meningitidis*.[26] Patients may also have an obvious or subclinical picture of disseminated intravascular coagulation (DIC). Deafness unilaterally or bilaterally may develop early or late in the disease course.

5 Third-generation cephalosporins (ie, cefotaxime and ceftriaxone) are the recommended empiric treatment for meningococcal meningitis (Table 124-4).[14,28,29] When final culture results are available, penicillin G or ampicillin is recommended for penicillin-susceptible isolates. Meropenem and fluoroquinolones are also suitable alternatives for the treatment of penicillin nonsusceptible meningococci. The recommended duration of therapy is typically 7 days if there is good clinical response.[28] Antimicrobial chemoprophylaxis of close contacts should be started as soon as possible (ideally <24 hours after identification of the index patient). In general, rifampin, ceftriaxone, and ciprofloxacin are recommended for prophylaxis, however, an increase in

rifampin-resistant and ciprofloxacin-resistant isolates was reported.[52] For further discussion of who should receive prophylaxis interested readers are referred to current recommendations by the CDC.[12]

Two quadrivalent meningococcal polysaccharide-protein conjugate vaccines that provide protection against meningococcal serogroups A, C, W, and Y are licensed in the United States (MenACWY-D and MenACWY-CRM). A quadrivalent meningococcal polysaccharide vaccine (MPSV4) is the only vaccine licensed for use among persons aged ≥56 years. A bivalent meningococcal polysaccharide-protein conjugate combination vaccine is licensed in the United States that contains antigens to serogroups C and Y, and *H. influenzae* type b (Hib-MenCY-TT). Finally, two recombinant protein vaccines against serogroup B are licensed in the United States: MenB-FHbp and MenB-4C. For full details on vaccine availability and vaccination recommendations in various age groups and for those with significant risk factors, readers are referred to the Chapter 142 "Vaccines, Toxoids, and Other Immunobiologics" in this text and the current recommendations from the ACIP.

Haemophilus influenzae type b

1 Widespread vaccination of infants and children has effectively decreased the incidence of bacterial meningitis due to Hib in children between the ages of 1 month and 5 years, resulting in a significant decline in all cases of bacterial meningitis.[2] Interested readers are referred to Chapter 142 "Vaccines, Toxoids, and Other Immunobiologics" in this text for information on recommended Hib vaccine dosing and administration schedules. In children older than 3 years and in adults, meningitis caused by Hib may indicate a parameningeal focus of infection, such as middle ear infection, paranasal sinus infection, or CSF leakage. Spread of the organism occurs either through direct spread from infected sinuses, draining of these areas via the veins, or bacteremia originating from the local focus of infection.

5 Third-generation cephalosporins (cefotaxime and ceftriaxone) are the drugs of choice for empirical therapy for *H. influenzae* type b meningitis as they are active against β-lactamase–producing and non-β-lactamase–producing strains.[28,29] Cefepime and fluoroquinolones are suitable alternatives regardless of β-lactamase activity. Recommended duration of treatment is 7 days (adults) or 7 to 10 days (children).[28,53]

Dexamethasone is beneficial for treatment of infants and children with Hib meningitis to diminish the risk of hearing loss, if given before or concurrently

with the first dose of antimicrobial agent(s).[53] All invasive (including meningitis) cases should be reported to the local public health department.

9 Chemoprophylaxis is indicated to reduce the risk of secondary invasive Hib disease in close contacts by eliminating nasopharyngeal and oropharyngeal carriages of *H. influenzae*. For prophylaxis, rifampin should be administered orally, once a day for 4 days (20 mg/kg/dose; maximum, 600 mg). For information on who should receive prophylaxis (adults and children), refer to the recommendations of the American Academy of Pediatrics.[53]

Streptococcus agalactiae (Streptococcus Group B)

1 Streptococcus group B (GBS) is a leading cause of neonatal meningitis in the United States and around the world.[2,54,55] Neurologic sequelae include sight or hearing loss and cerebral palsy. Death may occur in 5% of infants and adults. Neonates acquire this infection through vertical transmission while passing through the vaginal canal during birth. GBS is an inhabitant of the human GI and genitourinary tracts. Colonization in pregnant women ranges from 15% to 35%. Neonatal GBS meningitis survivors carry substantial long-term morbidity with up to 11% mortality before the age of 3 years.[56]

Early-onset disease occurs within the first 24 hours of life (range 0-6 days), whereas late-onset disease typically occurs at 3 to 4 weeks of age (range 7-89 days).[53] Universal prenatal screening and intrapartum antimicrobial prophylaxis of GBS-colonized pregnant women have significantly decreased the rate of early onset invasive disease. Recommended agents for intrapartum prophylaxis are penicillin or ampicillin, cefazolin (if penicillin allergy and not at high risk for anaphylaxis), or vancomycin (if penicillin allergy and at high risk for anaphylaxis). Given the high prevalence of resistance among invasive GBS isolates in the United States (13%-20%), clindamycin should only be used if the GBS isolate is clindamycin-susceptible, as confirmed by antimicrobial susceptibility testing.[57]

5 Ampicillin plus an aminoglycoside is the treatment of choice for a newborn infant with presumptive early-onset GBS meningitis. For empirical therapy of late-onset meningitis, ampicillin and an aminoglycoside or cefotaxime is recommended.[53] Ampicillin or penicillin G are the recommended agents in adults. Addition of an aminoglycoside could also be considered.[28] Alternative agents are third generation cephalosporins and vancomycin. Vancomycin is reserved for patients with severe penicillin allergy. While some GBS isolates are less sensitive to penicillin (MIC 0.12-1.0 mcg/mL), the optimal regimen for

these isolates has not been established.[58] For infants with uncomplicated meningitis, 14 days of treatment is satisfactory, but longer periods of treatment may be necessary for patients with prolonged or complicated courses.[53] For adults, the recommended duration of antibiotics is 14 to 21 days.[28]

Listeria monocytogenes

L. monocytogenes is a facultative anaerobic, Gram-positive diphtheroid-like organism that multiplies intracellularly. Meningitis due to *L. monocytogenes* primarily affects neonates, alcoholic or immunocompromised individuals (including pregnant women), and the elderly. Invasive infections in healthy young individuals remain rare. *L. monocytogenes* is implicated in approximately 10% of meningitis cases in patients older than 65 years of age and carries a case-fatality rate of approximately 18% in the United States.[2]

Transmission usually involves colonization of the patient's GI tract with the organism, which then penetrate the gut lumen. Soft cheeses and raw produce are common causes of listeriosis outbreaks. Coleslaw, unpasteurized milk, ready-to-eat foods, and raw beef and poultry have also been identified as sources of this foodborne pathogen. Invasive disease includes bacteremia, meningitis, meningoencephalitis, or cerebritis. Infection of the CNS may be diffuse or localized.

5 8 Treatment of *L. monocytogenes* meningitis should consist of penicillin G or ampicillin. The addition of aminoglycoside is also recommended in proven infection in both children and adults.[28,29,53] Trimethoprim-sulfamethoxazole and meropenem are recommended alternative agents, whereas there is less clinical experience with linezolid and fluoroquinolones. Despite *in vitro* activity against *L. monocytogenes*, intravenous vancomycin has been associated with high failure rates in patients with *L. monocytogenes* meningitis. Also, third-generation cephalosporins lack *in vitro* activity against *L. monocytogenes*. Patients should be treated for a minimum of 21 days.[28]

Dexamethasone as an Adjunctive Treatment for Acute Bacterial Meningitis

In addition to antibiotics, dexamethasone is a commonly used adjunctive therapy in the treatment of acute bacterial meningitis to immunomodulate the inflammatory response. Corticosteroids inhibit the production of TNF and IL-1, both potent proinflammatory cytokines.

A systematic review of 25 randomized controlled trials involving 4,121 participants showed that corticosteroid use in bacterial meningitis was associated with lower rates of hearing loss and short-term neurological sequelae in adults and children, but there was no mortality benefit in high income countries. No beneficial effects were observed in low-income countries. Additionally, subgroup analyses demonstrated a 16% reduction in overall mortality in pneumococcal meningitis and a 66% reduction in severe hearing loss in children with *H. influenzae* meningitis.[59]

Routine use of dexamethasone in meningitis is not without controversy. A potential concern is that adjunctive dexamethasone therapy may reduce the penetration of antibiotics into the CSF by inhibiting or reducing meningeal inflammation. Appropriate concentrations of vancomycin in CSF may be obtained even when adjunctive dexamethasone is used, but the small number of subjects studied limits the generalization of these findings.[60] The use of adjunctive corticosteroids may be of particular concern in patients who depend on treatment with vancomycin because of pneumococcal meningitis caused by penicillin- or cephalosporin-resistant strains. For these patients and for any patient who is not improving as expected after 48 hours of appropriate antimicrobial therapy, repeat lumbar puncture is recommended to document the sterility of CSF.[28]

1 Recommendations by the IDSA call for the use of adjunctive dexamethasone in infants and children (6 weeks of age and older) with *H. influenza* meningitis.[28] The recommended intravenous dose is 0.15 mg/kg every 6 hours for 2 to 4 days, initiated 10 to 20 minutes prior to or concomitant with, the first dose of antibiotics. In infants and children with pneumococcal meningitis, adjunctive dexamethasone may be considered after weighing the potential benefits and possible risks.[28,53] If pneumococcal meningitis is suspected or proven, adults should receive dexamethasone 0.15 mg/kg (up to 10 mg) every 6 hours for 2 to 4 days with the first dose administered 10 to 20 minutes prior to first dose of antibiotics.[28] It is often difficult to ascertain the responsible pathogen on presentation. Therefore, some clinicians and the European guidelines recommend initiating dexamethasone in all patients (adults and children) presenting with suspected or proven community-acquired bacterial meningitis and consider discontinuation only if pathogens other than *H. influenza* or *S. pneumoniae* are identified. Another difference between the IDSA and European guidelines is that according to the European guidelines, dexamethasone can still be administered up to 4 hours after initiation of antibiotics.[29]

HEALTHCARE-ASSOCIATED VENTRICULITIS AND MENINGITIS

Healthcare-associated meningitis and ventriculitis, formerly referred to as nosocomial meningitis, is a subclass of bacterial meningitis that largely occurs in neurosurgical patients.[14] The disease process in these patients can be more indolent compared to those with community-acquired bacterial meningitis. The most likely pathogens associated with CSF shunt and drain infections are coagulase-negative staphylococci (especially *Staphylococcus epidermidis*), *S. aureus*, *Propionibacterium acnes*, and Gram-negative bacilli; including *E. coli*, *Enterobacter* species, *Citrobacter* species, *Serratia* species, and *Pseudomonas aeruginosa*. In the presence of prosthetic devises, some of the microorganisms form biofilms which compromise antibiotic penetration.

Diagnosis of healthcare-associated meningitis and ventriculitis can be challenging and should focus on CSF fluid analysis and culture. However, patients may have only modest abnormalities in CSF cell counts. Additionally, CSF Gram-stain may be unreliable—particularly in the setting of systemic antibiotic exposure. If possible, antibiotic therapy should be delayed until CSF can be recovered for culture. A negative CSF culture following antimicrobial therapy is not sufficient to exclude healthcare-associated meningitis or ventriculitis. Use of extended hold cultures is encouraged to increase recovery of slow-growing pathogens such as *P. acnes.* If a CSF drain or shunt is removed due to possible infection then these components should be cultured as well. Blood cultures may be considered in those with ventriculopleural or ventriculoperitoneal shunts but are recommended in those with ventriculoatrial shunts.[14] 1-3-β-D-glucan may be useful to diagnosis fungal meningitis and ventriculitis because of the low sensitivity of CSF culture for fungal pathogens.[61,62]

Empiric use of broad-spectrum antibiotic therapy is critical for the treatment of healthcare-associated meningitis and ventriculitis because of the variety of organisms implicated in these cases. Empiric treatment should include intravenous vancomycin coupled with an anti-pseudomonal β-lactam such as meropenem, cefepime, or ceftazidime. All agents should be dosed to maximize CNS penetration.[14] Piperacillin-tazobactam is not recommended given the suboptimal CNS penetration of tazobactam. Intermittent vancomycin should be dosed to achieve a serum trough of 15 to 20 mg/L (10.4 to 13.8 µmol/L). Continuous infusion vancomycin may optimize vancomycin exposure in the

CSF but clinical data remain scant.[63]

Once culture results are available, antibiotic therapy can be tailored. *Staphylococcus* spp. are important causative pathogens in healthcare-associated meningitis and ventriculitis, particularly among patients with intracranial or spinal hardware. For methicillin-susceptible *S. aureus* (MSSA) the treatment of choice is nafcillin or oxacillin. Importantly, cefazolin penetration into the CNS is suboptimal and should be avoided. For methicillin-resistant *S. aureus* (MRSA) vancomycin, targeting a serum trough of 15 to 20 mg/L (10.4 to 13.8 µmol/L) is preferred. Rifampin may be considered for staphylococcal infections if the isolate is susceptible. Rifampin is indicated when there is hardware involved for optimal biofilm penetration. If β-lactam or vancomycin therapy is not possible then clinicians may consider linezolid or trimethoprim-sulfmethoxazole.[14] Daptomycin may also be considered although given its limited CNS penetration aggressive dosing is probably necessary (eg, 10-12 mg/kg/day).[14,64]

5 The treatment of meningitis due to *P. aeruginosa* remains a challenge because antibiotics showing good antibacterial activity, such as antipseudomonal penicillins and aminoglycosides, penetrate the CSF moderately or poorly (Table 124-3). Initially, cases of *P. aeruginosa* meningitis should be treated with an extended-spectrum β-lactam such as ceftazidime or cefepime, or alternatively aztreonam, ciprofloxacin, or meropenem depending on local susceptibility patterns. The addition of an aminoglycoside, usually tobramycin, to one of the aforementioned agents can also be considered. Since aminoglycosides penetrate the CSF poorly, their inclusion is to predominantly aid in the treatment of extracerebral infections.

Multidrug-resistant *P. aeruginosa*, *Acinetobacter*, and carbapenem-resistant *Enterobacteriaceae* infections are of concern to clinicians because of the limited therapeutic options available. This concern has led to the reemergence of the use of older antibiotics, such as colistin and polymyxin B. Colistin can be used, both intravenously and intrathecally, in the treatment of multidrug-resistant *P. aeruginosa* or *Acinetobacter* CNS infections. The use of colistin should be reserved for only the most severe cases.

New cephalosporin-β-lactamase inhibitor combination agents (ceftolozane-tazobactam and ceftazidime-avibactam) have yet to be formally studied in patients with CNS infections, but may be future alternative therapies for multidrug resistant Gram-negative organisms. For instance, ceftazidime/avibactam resulted in successful treatment of post-neurosurgical meningitis caused by a KPC-producing *Klebsiella pneumoniae*.[65] Additionally, two patients with extensively-drug resistant *P. aeruginosa* (brain abscess and

meningitis, respectively) were successfully treated with intravenous ceftazidime/avibactam and intravenous colistin.[66] Ceftaroline, a novel cephalosporin with affinity for PBP2a, the unique PBP or MRSA, has shown promise in a case series of *S. pneumoniae* meningitis ($n = 4$) and *S. aureus* meningitis ($n = 1$) as well as two other case reports of MRSA meningitis.[67–69] The pharmacokinetic properties of ceftaroline suggest it is probably reliable for CNS infections, particularly if using the off-label every 8 hour dosing, as often used for bacteremia.

Other Gram-negative organisms causing meningitis, excluding *P. aeruginosa* and *Acinetobacter* spp., most likely can be treated with a third- or fourth-generation cephalosporin, such as cefotaxime, ceftriaxone, ceftazidime, or cefepime. Ceftazidime, however, may not be the best choice of empirical monotherapy for situations where the offending organism is unknown initially due to lack of reliable Gram-positive activity. Cefotaxime should be used in place of ceftriaxone in the neonatal period because of the potential of ceftriaxone to displace bilirubin from its albumin-binding sites. Trimethoprim-sulfamethoxazole may offer utility for ventriculitis and meningitis caused by *Enterobacteriaceae* given that its penetration into the CSF does not depend on meningeal inflammation. Fluoroquinolones, such as ciprofloxacin, exhibit good penetration into the CSF and are recommended as alternative agents for the treatment of susceptible Gram-negative bacilli, including *P. aeruginosa*.

For patients with documented or suspected fungal meningitis or ventriculitis, empiric lipid formulation of liposomal amphotericin B in combination with flucytosine is recommended.[14] Once susceptibility is confirmed, fluconazole may be used for *Candida* spp. recovered from CSF.[70] Echinocandins are large molecules that penetrate into the CNS poorly and are not recommended for fungal meningitis or ventriculitis. For suspected of confirmed *Aspergillus* spp. the treatment of choice is voriconazole targeting a serum trough level of 2 to 5 mg/L (6 to 14 µmol/L).[14,71]

8 Some patients with meningitis or ventriculitis respond poorly to systemic antibiotic therapy. For these patients intraventricular therapy should be considered. Numerous antimicrobials can be given intraventricularly including: amikacin, amphotericin B deoxycholate, colistimethate sodium, daptomycin, gentamicin, polymyxin B, quinupristin/dalfopristin, tobramycin, and vancomycin. There is no consensus on the exact dose of intraventricular antimicrobial that should be used; however, some general recommendations are available.[14] If used, intraventricular antibiotic therapy requires vigilance in preparation and administration. Preservative-free product and diluents should be

used unless no preservative-free products exist. For patients receiving antimicrobial therapy through a ventricular drain, the drain should be clamped for 15 to 60 minutes to allow antimicrobial equilibration throughout the CSF.

CSF cultures may remain positive for several days or more with a regimen that eventually will be curative. Therapeutic efficacy can be monitored through bacterial colony counts every 2 or 3 days, which should decrease progressively over the period of therapy. Duration of therapy for healthcare-associated meningitis and ventriculitis is based on clinical response and the offending pathogen. For instance, for *P. acnes* and coagulase negative *Staphylococcal* spp. IDSA guidelines recommend 10 to 14 days. For *S. aureus* and Gram-negative pathogens 14 days or longer is recommended. For those with persistently positive CSF cultures therapy should continue for 10 to 14 days following the last positive culture.[14]

Finally, another important opportunity for antibiotic optimization exists for patients with external ventricular drains (EVDs). Patients with EVDs are often given systemic antibiotic therapy (eg, cefazolin) for infection prophylaxis for the duration of EVD placement to prevent ventriculostomy-related infections. However, the Neurocritical Care Society recommended against this practice citing the potential for harm (eg, *Clostridioides difficile* and antimicrobial-resistant pathogens) from the lack of efficacy attributable to antibiotic prophylaxis.[72] Instead the authors recommend administering one dose of antimicrobials prior to EVD insertion, avoiding routine CSF sampling, and using antibiotic-impregnated EVD catheters. Current IDSA guidelines also recommend against extended antibiotic prophylaxis following EVD insertion.[14]

BACTERIAL BRAIN ABSCESS

Brain abscess is a focal infection of the brain that begins as a localized area of cerebritis, and develops into a collection of pus surrounded by a well-vascularized capsule.[73] In immunocompetent patients, bacteria account for >95% of brain abscesses. Bacteria enter the brain either through contiguous spread (eg, following infection in the oropharynx, middle ear, paranasal sinuses, or neurosurgical procedures and cranial trauma), or hematogenous spread due to distant infections (eg, infective endocarditis, congenital heart disease, dental infection, pulmonary abscess).[73] Mortality rates have declined significantly in the past 50 years, with 70% of survivors expected to have no to minimal neurologic sequelae, although data on long-term functional and neuropsychological evaluation are lacking.[74]

2 The clinical presentation varies depending on the number, size, and location of the abscess. Headache, mental status changes, focal neurologic deficits, and fever are the most common symptoms of brain abscess. Brain imaging is the cornerstone for the diagnosis of brain abscess with MRI being the preferred modality over contrast-enhanced CT due to better resolution and differentiation of abscesses from tumors. Blood samples should be collected prior to initiation of antibacterial treatment for anaerobic and aerobic cultures, molecular biology, serology, and other diagnostic tests.

The etiology of brain abscess depends on the initial site of infection and the immune state of the host. Abscesses arising from spread of infection from oropharynx, middle ear, and paranasal sinuses are commonly caused by *Staphylococcus aureus*, streptococci, and oral anaerobes (eg, *Actinomyces* spp., *Bacteroides* spp., *Fusobacterium* spp., *Peptostreptococcus*). Staphylococci and Gram-negative bacilli are commonly involved in postoperative abscesses or those following head trauma. *Toxoplasma gondii, Mycobacterium tuberculosis*, and *Nocardia* spp. can also cause brain abscesses and are more commonly seen in immunocompromised patients.

5 All lesions equal or greater than 2.5 cm in diameter should be stereotactically aspirated or surgically excised and specimens should be sent to the microbiology and pathology laboratory.[73] Because brain abscesses are commonly polymicrobial, empiric antimicrobial therapy should include antibiotics with activity against Gram-positive, Gram-negative, and anaerobic organisms.[73,74] The antimicrobial agents should be able to penetrate into the abscess cavity and remain active in acidic environments. Most commonly the regimen includes a third- or fourth-generation cephalosporin plus metronidazole. Vancomycin should be added when infection caused by methicillin-resistant *Staphylococcus aureus* (MRSA) is suspected. Ceftazidime or cefepime can be used if *P. aeruginosa* is suspected. A carbapenem (such as meropenem) could replace the cephalosporin and metronidazole. In immunocompromised patients, the empiric regimen needs to be supplemented with voriconazole, and trimethoprim-sulfamethoxazole or sulfadiazine to cover fungi and *Nocardia* while awaiting definitive results. De-escalation of therapy should occur once a causative organism is identified. Repeated neuroimaging should be performed to monitor for abscess resolution or progression.

Prophylactic anticonvulsant therapy and corticosteroids are not routinely recommended.[74] Corticosteroids should be initiated in patients with edema causing increased intracranial pressure, brain shift, or increased risk of cerebral herniation. Intravenous antibiotics have traditionally been administered for 6 to 8

weeks, although shorter or longer durations may be used depending on the clinical and radiologic progress. Given the risk of neurotoxicity with prolonged courses of metronidazole, metronidazole may be discontinued once anaerobic pathogens have been ruled out. Oral options can consist of ciprofloxacin, metronidazole, trimethoprim-sulfamethoxazole, and amoxicillin but there is no consensus on when transition to oral agents can be safely done.

VIRAL ENCEPHALITIS

Encephalitis refers to inflammation of the brain parenchyma in association with clinical evidence of neurologic dysfunction. Meningoencephalitis is a term commonly used to describe meningeal inflammation along with encephalitis. Infectious encephalitis should be distinguished from those patients with encephalopathy (eg, due to metabolic disturbances, intoxications, hypoxia, systemic infections) or noninfectious encephalitis (eg, postimmunization encephalitis or encephalomyelitis), as they have similar clinical presentations.[16] While a confirmed or probable pathogen is identified in less than 50% of cases, viral etiologies are the most commonly diagnosed.[8,17] Collectively, about 20,000 encephalitis-associated hospitalizations are expected per year in the United States, with a case fatality rate of more than 5% and total health-care burden of nearly $2 billion. Of those 20,000 hospitalizations, approximately 20% are due to viral pathogens.[8,17]

The epidemiology of viral encephalitis in the United States has changed dramatically since the mid-1960s due to the introduction of large-scale polio, rubella, varicella-zoster virus, and mumps immunization programs. Worldwide, mumps remains a causative pathogen in countries with low vaccination rates. Common causes of viral encephalitis/meningoencephalitis in the United States include herpes simplex virus (HSV), West Nile virus (WNV), and the enteroviruses.[8,17]

Less common causes include arboviruses, adenoviruses, influenza, rotavirus, corona virus, cytomegalovirus (CMV), varicella-zoster virus, Epstein-Barr virus, and lymphocytic choriomeningitis. In recent years, Powassan, Chikungunya, and Zika viruses have emerged as increasing causes of encephalitis in North America. These arboviruses are transmitted via ticks (Powassan) or mosquitoes (Chikungunya and Zika) and have a diverse spectrum of disease. Of these, Powasan virus has seen the largest increase in incidence; between 1999 and 2005 there was an average of 1.3 cases per year reported in the United States, compared to 0.7 cases per year during the previous 40 years in the United States

and Canada. In 2003, the CDC included Powassan virus as a reportable disease, resulting in 64 cases reported between 2004 and 2013, with 16 cases reported in 2011 alone.[75]

Viral encephalitis is acquired primarily by hematogenous spread or, alternatively, by neuronal spread of the causative pathogen. After entry into the host, viral replication occurs, resulting in dissemination through the reticuloendothelial system or vasculature. Infection of the capillary endothelial cells and choroid plexus may provide a conduit for CNS infections. Viruses such as polio, HSV, and Varicella-zoster virus may also gain access to the CNS by axonal retrograde transmission from peripheral nerve endings. Once a virus gains access to the CNS, the course of infection depends on the virulence of the particular virus and the host immune response. Subsequent neuronal injury is caused by direct cell damage due to viral replication, but inflammatory and immune-mediated responses also contribute to neurological damage.

2 In contrast with purulent meningitis, host response to viral encephalitis is mediated primarily through cytotoxic T-lymphocytes. Increases in concentrations of IL-1, IL-6, and interferon (INF)-α, β and γ may occur. The clinical syndrome associated with viral encephalitis generally is independent of viral etiology and may vary depending on the patient's age. Common signs in adults include headache, mild fever, nuchal rigidity, malaise, drowsiness, nausea, vomiting, and photophobia. Only fever and irritability may be evident in the infant, and acute bacterial meningitis must be ruled out as a cause of fever when no other localized findings are observed in a child. Duration of symptoms generally is 1 to 2 weeks, and specific manifestations outside the meninges can also occur depending on the viral etiology.

Laboratory examination of the CSF usually reveals a pleocytosis with 100-1,000 WBC/mm^3 (0.1-1 $\times$ 10^9/L), which are primarily lymphocytic. However, 20% to 75% of patients with viral encephalitis may have a predominance of polymorphonuclear cells on initial examination of the CSF. On repeat lumbar puncture, 90% of patients presenting initially with a predominance of neutrophils experience a shift to a predominance of mononuclear cells. Other laboratory findings include normal to mildly elevated protein concentrations and normal or mildly reduced glucose concentrations (see Table 124-1).

3 As mentioned earlier, pathogens responsible for viral encephalitis are often unidentified. When clinical signs warrant pathogen identification, appropriate laboratory diagnostic techniques, including PCR and serologic testing, should be undertaken. Molecular methods are preferred to conventional laboratory tests, such as viral cultures and brain biopsy, in the diagnosis of viral

encephalitis owing to improved sensitivity and specificity, higher yield, and rapid results.[16,76]

Supportive and symptomatic treatments, including seizure control, hemodynamic management, venous thromboembolism prevention, ICP management, and secondary bacterial infection prevention, are of great importance in patients with viral encephalitis due to limited treatment options. Corticosteroid therapy is generally not recommended in most viral encephalitis cases; however, treatment should be considered for patients with cerebral edema and increased ICP.[16]

Although there are numerous pathogenic causes of viral encephalitis, much of the clinical presentation, diagnosis, and treatment are similar. The most commonly isolated viral etiologies are described here. HSV type 1 (HSV1) and type 2 (HSV2) are considered the most common treatable causes of viral encephalitis. Between 1998 and 2010, HSV encephalitis accounted for 74% of all viral encephalitis-associated hospitalizations.[8,17] HSV1 is associated with encephalitis in adults, whereas HSV2 is associated predominantly with encephalitis in newborns.[8,77] Sexually active adults acquire HSV meningitis during or after an attack of genital or rectal HSV, whereas neonates acquire the virus during passage through the vaginal canal of mothers with active HSV infection. HSV PCR on CSF specimens should be performed for all patients with presumed encephalitis. Repeat testing should be considered for patients with an initial negative test after 3 to 7 days.[16] Establishing the correct diagnosis early is paramount due to mortality rates approaching 70% without treatment and, unlike other viral etiologies, effective therapy is available. As a result, empiric therapy of suspected HSV encephalitis is recommended, while results are pending. Delaying antiviral therapy has been consistently associated with increased mortality. Additionally, a clinical decision to treat may need to be made regardless of test results.

Acyclovir is the drug of choice for HSV encephalitis. In adults with normal renal function, acyclovir is usually administered as 10 mg/kg intravenously every 8 hours for 2 to 3 weeks.[16,76] Higher doses of acyclovir (20 mg/kg intravenously every 8 hours) have been used in neonates and are associated with lower mortality rates.[78] HSV resistance to acyclovir has been reported with increasing incidence, particularly in immunocompromised patients with prior or chronic exposures to acyclovir, ranging from 3.5% to 10%.[79] The alternative treatment for acyclovir-resistant HSV is foscarnet. The dose for patients with normal renal function is 40 to 60 mg/kg infused over 1 hour every 8 to 12 hours for 3 weeks, with the higher dose typically reserved for HIV-infected

individuals.[76] Ensuring adequate hydration is imperative to decrease risk of acyclovir- and foscarnet-induced nephrotoxicity. In addition, patients receiving foscarnet should be monitored for seizures related to alterations in plasma electrolyte levels. Adult patients who completed standard initial HSV encephalitis treatment followed by long-term antiviral treatment (an additional 3-month course) of oral valacyclovir did not show improvements in neuropsychological testing 12 months later compared to placebo.[80]

Although mosquitoes primarily transmit WNV, transmissions via blood products, organ transplantation, transplacental transfer, and breast milk have been documented. Similar to other arboviruses, the incubation period for WNV ranges from 3 days to 2 weeks. Infection with WNV is asymptomatic in most adults or causes a mild flu-like syndrome characterized by fever, malaise, myalgia, and lymphadenopathy. Among 41,762 reported cases of WNV in the United States between 1999 and 2014, the overall mortality rate was approximately 4% (9% in patients with neuroinvasive disease).[81] CSF examination of WNV encephalitis typically shows pleocytosis and a slightly elevated CSF protein concentration. Several diagnostic methods have been developed for WNV, including a PCR assay and enzyme-linked immunosorbent assay (ELISA) tests. Treatment is typically supportive, including treatment for seizures and increased ICP, and in the majority of cases, the disease is self-limiting.[16]

CMV has emerged as a major cause of morbidity and mortality in immunocompromised patients, including HIV-infected individuals and transplant recipients on immunosuppressant therapy. CNS infections with CMV are often difficult to treat, with higher failure rates and poor outcomes. Combination therapy with ganciclovir and foscarnet is recommended for induction treatment due to higher failure rates and lack of survival benefits when monotherapy with either agent is utilized.[16] In adult patients, ganciclovir 5 mg/kg every 12 hours and foscarnet 60 mg/kg every 8 hours (or 90 mg/kg every 12 hours) for 3 weeks are recommended during the induction phase, followed by maintenance phase with either agent. Other interventions that may improve survival outcomes include the initiation of highly active antiretroviral therapy in untreated HIV-infected patients and reduction of immunosuppression intensity in transplant recipients.

HIV encephalitis is a common CNS complication associated with AIDS. Frequently, patients may complain of headache, photophobia, or stiff neck at the time of presumed seroconversion. As the disease progresses neurologic symptoms are frequently reported secondary to other opportunistic infections.

Diagnosis of viral encephalitis is difficult because mental status and neurologic examinations are not sensitive enough to detect early changes. Direct evidence of HIV encephalitis can be obtained through CSF culture, p24 antigen testing, and qualitative or quantitative PCR for HIV RNA. Diagnostic workup of coinfections, such as HSV, *Toxoplasma gondii*, *Mycobacterium tuberculosis*, *Aspergillus* spp., and *Cryptococcus*, should also be performed. See Chapter 143 "Human Immunodeficiency Virus" for a complete discussion of infectious complications in HIV-positive individuals.

CNS INFECTIONS IN SPECIAL POPULATIONS

This section discusses additional pathogens that can cause CNS infections. For discussion on CNS infections caused by *Cryptococcus, Histoplasma,* and *Aspergillous* species, the interested reader is referred to Chapter 139 "Invasive Fungal Infections." CNS infection due to *Treponema Pallidum* (neurosyphilis) is discussed in Chapter 135 "Sexually Transmitted Diseases."

Bacillus anthracis

Bacillus anthracis, the causative agent of anthrax, is a nonmotile spore-forming, Gram-positive, rod-shaped bacterium. The disease is common in wild and domestic animals and not uncommon among individuals who interact with animals in certain agricultural regions of the world. Biodefense experts place *Bacillus anthracis* at or near the top of the list for potential threat agents. It enters the host in the form of spores at the epidermis (cutaneous anthrax), the gastrointestinal epithelium (gastrointestinal anthrax), or the lung mucosa (inhalation anthrax). Anthrax meningitis has been reported with all three clinical forms of anthrax and likely results from hematogenous spread across the blood-brain barrier, generally presenting as hemorrhagic meningitis. Anthrax meningitis is characterized by a fulminant, rapidly progressive clinical course and is nearly always fatal even with treatment.[83] For diagnosis, blood and CSF exam for Gram stain, culture PCR and toxin assays are recommended.

For the general adult population, empiric treatment for suspected anthrax meningitis should include ≥3 antimicrobial drugs with activity against *B. anthracis*.[82–84] At least one antimicrobial agent should have bactericidal activity, ≥1 should be a protein synthesis inhibitor for suppression of exotoxin production, and all should have good CNS penetration. A higher percent survival has been observed for patients with anthrax meningitis receiving 3

antimicrobials than those receiving only 2 antimicrobial agents.[85]

5 Empiric regimens that include high doses of intravenous fluoroquinolones (ciprofloxacin preferably, levofloxacin, or moxifloxacin) along with a carbapenem (meropenem preferably, doripenem, or imipenem/cilastatin) and a protein synthesis inhibitor (eg, linezolid preferred, clindamycin) are recommended for ≥ 2 to 3 weeks until clinical criteria for stability are met. Once penicillin susceptibility is confirmed, the carbapenem can be de-escalated to intravenous penicillin G or ampicillin.[82] In addition, adjunctive corticosteroids should be considered for patients with suspected or confirmed anthrax meningitis. Doxycycline is not recommended for initial treatment of anthrax meningitis due to its poor CNS penetration, compared to MIC of most bacterial pathogens. *B. anthracis* is not susceptible to cephalosporins or trimehoprim-sulfamethoxazole.

Because disease can develop long after exposure to spores, once patients with systemic illness (including meningitis) who were exposed to aerosolized spores have completed initial combination treatment, they should be transitioned to single-agent oral treatment to prevent relapse from surviving *B. anthracis* spores. Antimicrobial drug options include ciprofloxacin (preferred), doxycycline (preferred), levofloxacin, moxifloxacin, clindamycin, and if penicillin sensitive, penicillin VK or amoxicillin. Additionally, guidelines recommend a three-dose subcutaneous series of Anthrax vaccine adsorbed administered at 0, 2, and 4 weeks postexposure for long-term protection[86] as well as one of the two available antitoxins, raxibacumab and Anthrax immune globulin intravenous.[82]

Borrelia burgdorferi (Lyme Disease)

Lyme disease (LD) is caused by the spirochete *Borrelia burgdorferi* and is the most common tick-borne infection in North America and Europe.[87] Lyme neuroborreliosis (LNB) is an infectious disorder of the nervous system caused by *B. burgdorferi* and has been reported in up to 15% of patients with untreated LD. CNS involvement may include meningitis, myelitis, cerebral vasculitis, or encephalitis. Clinical manifestations include fever, headache, fatigue, photosensitivity, confusion, hemiparesis, cerebellar ataxia, and Parkinson-like symptoms among others. Poliomyelitis-like syndromes and acute stroke-like symptoms caused by cerebral vasculitis have been documented but are considered rare. Unlike the European LD, the North American LD is also characterized by a skin rash called erythema migrans.[87,88] There is no international consensus for the diagnosis of Lyme neuroborreliosis (LNB).

Diagnosis is based on the presence of neurological symptoms without other obvious reasons, CSF analysis (lymphocytic pleocytosis, moderately elevated protein, normal glucose), intrathecal *B. burgdorferi* antibody production, blood and CSF serologic testing (ELISA plus Western blot), and MRI demonstrating areas of inflammation.[16,87,88] PCR testing for detection of *B. burgdorferi* in CSF has a sensitivity of <30% with an unknown specificity, therefore is not routinely recommended. Parenteral treatment with ceftriaxone once daily is recommended as first-line treatment of LNB.

5 Patients with cranial neuropathy without clinical signs of meningitis may be treated with oral amoxicillin, doxycycline, or cefuroxime axetil. The European Federation of Neurological Societies guidelines also recommend oral doxycycline as a first-line option for patients with symptoms confined to the meninges, cranial nerves, nerve roots, or peripheral nerves based on its CSF penetration, ability to achieve CSF concentrations above the MIC, and several studies showing similar short- and long-term efficacy to various parenteral regimens.[88] Alternative parenteral options to ceftriaxone include cefotaxime or penicillin G. For patients intolerant to β-lactams, doxycycline oral or intravenous is suggested.

Mycobacterium tuberculosis

5 *M. tuberculosis* is the primary cause of tuberculous meningitis and remains the most life-threatening form of extrapulmonary tuberculosis. The incidence of tuberculosis, in general, has decreased to 3 cases per 100,000 individuals in the United States in 2016.[89] The guidelines jointly sponsored by the CDC, IDSA, and the American Thoracic Society recommend an initial regimen of four drugs for empirical treatment of drug-susceptible *M. tuberculosis* in adults.[90] The recommended regimen consists of isoniazid, rifampin, pyrazinamide, and ethambutol for the first 2 months, followed by isoniazid plus rifampin for an additional 7 to 10 months, although the optimal duration of chemotherapy has not been defined. Furthermore, initial adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6 to 8 weeks is recommended, which provides mortality benefit. The recommended therapy for HIV-positive individuals is similar as for immunocompetent patients.[91] In HIV-infected patients with tuberculous meningitis, antiretroviral therapy should not be initiated in the first 8 weeks of antituberculosis therapy to reduce the risk of immune reconstitution syndrome (IRIS).[90] Therapy should be individualized based on susceptibility patterns and evidence-based guidelines including those

by the World Health Organization.[92]

Nocardia

Nocardia is an aerobic, Gram-positive bacterium. *Nocardia* species represent a ubiquitous group of environmental bacteria that commonly cause opportunistic infections in immunocompromised individuals. Nevertheless, about 30% of patients with nocardiosis are immunocompetent.[93] Pulmonary nocardiosis is the most common clinical presentation. However, CNS nocardiosis represents 40% of patients with extrapulmonary manifestation. The usual presentation of CNS infection is single or multiple brain abscesses. CNS symptoms appear gradually and are nonspecific including headache, nausea, vomiting, seizures, mental status changes.[94] MRI of the brain is the recommended imaging modality. Specific therapeutic recommendations on the basis of prospective controlled trials for nocardiosis are lacking. In addition, *Nocardia* has inconsistent antimicrobial susceptibility patterns *in vitro*. Thus, the management of nocardiosis must be individualized and isolates should undergo antimicrobial testing for treatment decisions.

5 Trimethoprim-sulfamethoxazole is active against most *Nocardia* species. Alternative therapies include amikacin, imipenem, minocycline, third generation cephalosporins, and linezolid.[93] For CNS nocardiosis empiric combination therapy that penetrates the blood brain barrier, such as trimethoprim-sulfamethoxazole plus imipenem or ceftriaxone, is recommended. Addition of a third agent like linezolid may be needed for severe disease. Combined treatment is required until there is evidence of clinical improvement and antimicrobial susceptibility is confirmed. Recommended duration of antimicrobial treatment for CNS nocardiosis is at least 12 months. Surgical resection is reserved for selected cases based on the location and extent of disease as well as response to therapy. Patients should be monitored for one year after completion of therapy for relapse.

Primary Amoebic Meningoencephalitis (PAM)

Naegleria fowleri is a thermophilic, unicellular parasite that lives in stagnant fresh or brackish waters and causes a very rare form of nearly fatal CNS infection known as Primary Amoebic Meningoencephalitis (PAM). Humans acquire PAM when water is insufflated through the nostrils usually while swimming in warm freshwater lakes and rivers.[95] The median age of infection is 11 years.[96] The time from exposure to *Naegleria fowleri* to the onset of

symptoms is approximately 5 days. Upon infection the patient may present with parosmia, anosmia, or ageusia. The pathogen attaches to the olfactory nerve and migrates through the cribriform plate into the brain. The disease becomes rapidly progressive as the parasite moves further into the brain and meninges causing fever, headache, neck rigidity, nausea, emesis, and possibly seizures.

TABLE 124-5 Dosing of Anti-infective Agents by Age Group[14,16,28,29]

Agent	Infants and Children	Adults	Monitoring/Comments
Antibacterial			
Ampicillin	75 mg/kg every 6 h	2 g every 4 h	
Aztreonam	—	2 g every 6-8 h	Alternative for penicillin allergy
Cefepime	50 mg/kg every 8 h	2 g every 8 h	Consider prolonged infusion
Cefotaxime	75 mg/kg every 6-8 h	2 g every 4-6 h	Preferred in neonates
Ceftazidime	50 mg/kg every 8 h	2 g every 8 h	
Ceftriaxone	100 mg/kg daily	2 g every 12 h	Avoid in neonates
Ciprofloxacin	10 mg/kg every 8 h	400 mg every 8-12 h	Consider higher doses for *P. aeruginosa*
Colistin	5 mg/kg/day	5 mg/kg/day	Consider intraventricular doses Only for MDR organisms Monitor renal function
Gentamicin	2.5 mg/kg every 8 h	2 mg/kg every 8 h *or* 5-7 mg/kg daily	TDM is recommended Monitor renal function
Levofloxacin	—	750 mg daily	May prolong QTc
Linezolid	10 mg/kg every 8 h	600 mg every 12 h	May cause thrombocytopenia and peripheral neuropathy
Meropenem	40 mg/kg every 8 h	2 g every 8 h	Consider prolonged infusion
Moxifloxacin	—	400 mg daily	May prolong QTc
Oxacillin/Nafcillin	50 mg/kg every 6 h	2 g every 4 h	Nafcillin preferred if renal dysfunction
Penicillin G	0.05 million Units/kg every 4 h	4 million Units every 4 h	
Polymyxin B	—	1.25-1.5 mg/kg every 12 h	Only for MDR organisms No data in pediatric patients
Tobramycin	2.5 mg/kg every 8 h	2.5 mg/kg every 8 h *or* 5-7 mg/kg daily	TDM is recommendedMonitor renal function
Trimethoprim-sulfmathoxazole	5 mg/kg every 6-12 h	5 mg/kg every 6-12 h	Dose based on trimethoprim
Vancomycin	15 mg/kg every 6 h	15-20 mg/kg every 8-12 h	TDM is recommended Monitor renal function
Antifungals			
Amphotericin B	1 mg/kg daily	0.7-1 mg/kg daily	Monitor renal function Maintain adequate hydration
Lipid amphotericin B	5 mg/kg once daily	3-5 mg/kg daily	Monitor renal function Maintain adequate hydration
Flucytosine	25 mg/kg every 6 h	25 mg/kg every 6 h	Consider TDM to avoid bone marrow suppression
Fluconazole	6-12 mg/kg daily	800-1,200 mg daily	Monitor liver function
Itraconazole			Consider TDM Suspension form is preferred
Posaconazole	—	400 mg every 12 h	Variable absorption No data in pediatric patients
Voriconazole	7 mg/kg every 12 h	6 mg/kg every 12 h × 2 doses then 4 mg/kg every 12 h	Consider TDM Many drug-drug interactions Monitor liver function
Antivirals			
Acyclovir	10-20 mg/kg every 8 h	10-20 mg/kg every 8 h	Monitor renal function Maintain adequate hydration
Ganciclovir	—	5 mg/kg every 12 h	Monitor renal function
Foscarnet	—	60 mg/kg every 8 h *or* 90 mg/kg every 12 h	Monitor renal function Maintain adequate hydration

TDM, therapeutic drug monitoring.

5 Even with early recognition of PAM, the clinical prognosis is poor. Most cases of PAM are misdiagnosed or the diagnosis is made at autopsy. In the past five decades, 132 cases of *Naegleria fowleri* PAM were reported to CDC and only 3 documented cases have survived in North America.[96] Treatment has included combination therapy with miltefosine (an oral drug used to treat breast cancer and leishmaniasis), azithromycin, rifampin, fluconazole, and amphotericin (intravenous and intrathecal). For patients weighing up to 45 kg, miltefosine should be administered at 50 mg two times a day. For patients with a body weight of 45 kg or higher, miltefosine should be administered at 50 mg three times a day.[96]

Toxoplasma gondii

5 Toxoplasmic encephalitis (TE) is caused by the protozoan *T. gondii*. Approximately 11% of the United States population 6 years and older have been infected with *T. gondii*. In other parts of the world, up to 95% of populations are infected. The primary routes of transmission are foodborne, animal-to-human (cats serving as the definitive host), and mother-to-child (congenital).[97] TE is typically caused by the reactivation of disease in immunocompromised patients, especially those with AIDS, or intrauterine infection in newborns. Clinical manifestations can range from asymptomatic in healthy, nonpregnant patient to headache, seizures, confusion, hemiparesis, cranial nerve abnormalities, or fever in immunocompromised patients.[97] In congenital toxoplasmosis, patients may also present with hydrocephalus, intracerebral calcification, microcephaly, convulsions, or chorioretinitis.[16,98] Definitive diagnosis of TE requires a clinical sample via a brain biopsy; therefore, TE is presumptively diagnosed on the basis of clinical symptoms, positive serology for antitoxoplasma IgG antibodies, and identification of space-occupying lesions on CT, MRI, or other radiologic imaging. In patients with AIDS, MRI typically shows multiple ring-enhancing lesions. *T. gondii* can also be detected by PCR in CSF. However, the sensitivity is low (50%) and the result is usually negative once treatment has started.[16,91,98] First-line treatment for TE in adults consists of pyrimethamine plus sulfadiazine plus leucovorin. Leucovorin is added to the treatment regimen to reduce the likelihood of hematologic toxicity associated with pyrimethamine. In patients who are unable to tolerate sulfadiazine, clindamycin may be used as an alternative. Other alternative treatment options are available, including trimethoprim-sulfamethoxazole, but have not been extensively studied. Treatment recommendations are the same in pediatric patients; however, several

of the alternative regimens have not been studied in children.[16,91,98] After completion of initial 6-week therapy, chronic maintenance therapy should be initiated.

EVALUATION OF THERAPEUTIC OUTCOMES

Because of the potential for rapid deterioration associated with CNS infections, the presence of fever, headache, meningismus (eg, nuchal rigidity, Brudzinski's, or Kernig's sign), and signs of cerebral dysfunction should be evaluated every 4 hours for the initial 3 days and then daily thereafter. The Glasgow Coma Scale should be used in severely ill patients. Trends in improvement and resolution rather than single evaluations in time are more important in monitoring the signs and symptoms of meningitis. Continued therapy should be based on the assessment of clinical improvement, culture, and susceptibility testing results. Once a pathogen is identified, anti-infective therapy should be tailored to the specific pathogen (Tables 124-4 and 124-5).[14,16,28,29] Throughout the course of treatment, efficacy parameters such as signs and symptoms, microbiologic findings, and CSF examination should be followed to evaluate the success of meeting the desired outcomes. If adjunctive dexamethasone is used, careful monitoring of signs and symptoms of gastrointestinal bleeding and hyperglycemia should be employed. Moreover, the use of dexamethasone may interfere with the interpretation of clinical response to treatment, such as resolution of fever.

Postclass Engaged Learning Activity

Perform a literature search to identify a primary article that evaluated a treatment regimen for CNS infection due to vancomycin-resistant methicillin-resistant *Staphylococcus aureus* (MRSA). Write a brief summary about the rationale of the antibiotic agent(s) used, along with dose(s), dosing interval(s), and duration of treatment. Discuss how the dosing compared to that listed in the package insert of the agent(s) used. This activity is intended to build your literature evaluation skills and ability to critically appraise primary literature.

ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices

AFB	acid fast bacillus
AIDS	acquired immunodeficiency syndrome
BBB	blood–brain barrier
BCSFB	blood–cerebrospinal fluid barrier
CBF	cerebral blood flow
CDC	United States Centers for Disease Control and Prevention
CFH	complement factor H
CFU	colony forming unit
CLSI	Clinical and Laboratory Standards Institute
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
CT	computed tomography
DIC	disseminated intravascular coagulation
EFNS	European Federation of Neurological Societies
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
EVD	external ventricular drains
FDA	US Food and Drug Administration
GBS	group B *Streptococcus*
Hib	*Haemophilus influenzae* type b
HIV	human immunodeficiency virus
HSV	herpes simplex virus
ICP	intracranial pressure
IDSA	Infectious Diseases Society of America
Ig	immunoglobulin
IL	interleukin
IPD	invasive pneumococcal disease
INF	interferon
IRIS	Immune reconstitution syndrome
LNB	Lyme neuroborreliosis
LPS	lipopolysaccharide
MenACWY	serogroup A, C, W, Y meningococcal vaccine

MenB	serogroup B meningococcal vaccine
MIC	minimum inhibitory concentration
MRI	magnetic resonance imaging
MRSA	methicillin-resistant *Staphylococcus aureus*
PAF	platelet-activating factor
PAM	primary amoebic meningoencephalitis
PCR	polymerase chain reaction
PCT	procalcitonin
PCV7	heptavalent pneumococcal conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PGE_2	prostaglandin E_2
PMN	polymorphonuclear neutrophil
PPV23	23-valent pneumococcal polysaccharide vaccine
rRNA	ribosomal ribonucleic acid
SNP	single-nucleotide polymorphism
TDM	therapeutic drug monitoring
TE	toxoplasmic encephalitis
TNF	tumor necrosis factor
WBC	white blood cell
WNV	West Nile virus

REFERENCES

1. Bijlsma MW, Brouwer MC, Kasanmoentalib ES, et al. Community-acquired bacterial meningitis in adults in the Netherlands, 2006-14: A prospective cohort study. *Lancet Infect Dis*. 2016;16:339–347.
2. Thigpen MC, Whitney CG, Messonnier NE, et al. Bacterial meningitis in the United States, 1998-2007. *N Engl J Med*. 2011;364:2016–2025.
3. Okike IO, Ribeiro S, Ramsay ME, et al. Trends in bacterial, mycobacterial, and fungal meningitis in England and Wales 2004-11: An observational study. *Lancet Infect Dis*. 2014;14:301–307.
4. Mcgill F, Heyderman RS, Panagiotou S, et al. Acute bacterial meningitis in adults. *Lancet*. 2016;388:3036–3047.
5. Brouwer MC, Coutinho JM, Van De Beek D. Clinical characteristics and

outcome of brain abscess: Systematic review and meta-analysis. *Neurology*. 2014;82:806–813.

6. Solomon T, Michael BD, Smith PE, et al. Management of suspected viral encephalitis in adults: Association of British Neurologists and British Infection Association National Guidelines. *J Infect*. 2012;64:347–373.
7. Granerod J, Cousens S, Davies NW, Crowcroft NS, Thomas SL. New estimates of incidence of encephalitis in England. *Emerg Infect Dis*. 2013;19:1455–1462.
8. Vora NM, Holman RC, Mehal JM, et al. Burden of encephalitis-associated hospitalizations in the United States, 1998-2010. *Neurology*. 2014;82:443–451.
9. Tack DM, Holman RC, Folkema AM, et al. Trends in encephalitis-associated deaths in the United States, 1999-2008. *Neuroepidemiology*. 2014;43:1–8.
10. Castelblanco RL, Lee M, Hasbun R. Epidemiology of bacterial meningitis in the USA from 1997 to 2010: A population-based observational study. *Lancet Infect Dis*. 2014;14:813–819.
11. Mcintyre, PB, O'brien, KL, Greenwood, B, et al. Effect of vaccines on bacterial meningitis worldwide. *Lancet* 2012;380:1703-1711.
12. Cohn AC, Macneil JR, Clark TA, et al. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2013;62:1–28.
13. Davila S, Wright VJ, Khor CC, et al. Genome-wide association study identifies variants in the CFH region associated with host susceptibility to meningococcal disease. *Nat Genet*. 2010;42:772–776.
14. Tunkel AR, Hasbun R, Bhimraj A, et al. 2017 Infectious Diseases Society of America's Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis. *Clin Infect Dis*. 2017;64:e34–e65.
15. Kneen R, Michael BD, Menson E, et al. Management of suspected viral encephalitis in children: Association of British Neurologists and British Paediatric Allergy, Immunology and Infection Group national guidelines. *J Infect*. 2012;64:449–477.
16. Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2008;47:303–327.
17. Bloch KC, Glaser CA. Encephalitis Surveillance through the Emerging Infections Program, 1997-2010. *Emerg Infect Dis*. 2015;21:1562–1567.

18. Franca GV, Schuler-Faccini L, Oliveira WK, et al. Congenital Zika virus syndrome in Brazil: A case series of the first 1501 livebirths with complete investigation. *Lancet*. 2016;388:891–897.
19. Garcez PP, Loiola EC, Madeiro Da Costa R, et al. Zika virus impairs growth in human neurospheres and brain organoids. *Science*. 2016;352:816–818.
20. Bleck T, Greenlee J. Anatomic considerations in central nervous system infections. 5th ed. New York: Churchill Livingstone; 2000.
21. Bennett JE, Dolin R, Blaser MA. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. Philadelphia, PA: Elsevier Saunders; 2015.
22. Kim, KS. Emerging molecular targets in the treatment of bacterial meningitis. *Expert Opin Ther Targets*. 2003;7:141–152.
23. Klein RS, Hunter CA. Protective and pathological immunity during central nervous system infections. *Immunity*. 2017;46:891–909.
24. Magnus T, Rother J, Simova O, et al. The neurological syndrome in adults during the 2011 northern German *E. coli* serotype O104:H4 outbreak. *Brain*. 2012;135:1850–1859.
25. Levin SN, Lyons JL. Infections of the nervous system. *Am J Med*. 2018;131:25–32.
26. Brouwer MC, Tunkel AR, Van De Beek D. Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. *Clin Microbiol Rev*. 2010;23:467–492.
27. Brouwer MC, Thwaites GE, Tunkel AR, et al. Dilemmas in the diagnosis of acute community-acquired bacterial meningitis. *Lancet*. 2012;380:1684–1692.
28. Tunkel, AR, Hartman, BJ, Kaplan, SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis* 2004;39:1267-1284.
29. Van De Beek D, Cabellos C, Dzupova O, et al. ESCMID guideline: Diagnosis and treatment of acute bacterial meningitis. *Clin Microbiol Infect*. 2016;22(Suppl 3):S37–62.
30. Sakushima, K, Hayashino Y, Kawaguchi T, et al. Diagnostic accuracy of cerebrospinal fluid lactate for differentiating bacterial meningitis from aseptic meningitis: A meta-analysis. *J Infect*. 2011;62:255–262.
31. Li Y, Zhang G, Ma R, et al. The diagnostic value of cerebrospinal fluids procalcitonin and lactate for the differential diagnosis of post-

neurosurgical bacterial meningitis and aseptic meningitis. *Clin Biochem*. 2015;48:50–54.

32. Leber AL, Everhart K, Balada-Llasat JM, et al. Multicenter evaluation of BioFire FilmArray meningitis/encephalitis panel for detection of bacteria, viruses, and yeast in cerebrospinal fluid specimens. *J Clin Microbiol*. 2016;54:2251–2261.
33. Srinivasan, L, Pisapia, JM, Shah, SS, et al. Can broad-range 16S ribosomal ribonucleic acid gene polymerase chain reactions improve the diagnosis of bacterial meningitis? A systematic review and meta-analysis. *Ann Emerg Med* 2012;60:609-620.
34. Wilson MR, O'donovan BD, Gelfand JM, et al. Chronic meningitis investigated via metagenomic next-generation sequencing. *JAMA Neurol*. 2018;75(8):947–955.
35. Nau R, Sorgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. *Clin Microbiol Rev*. 2010;23:858–883.
36. Costerus JM, Brouwer MC, Bijlsma MW, et al. Community-acquired bacterial meningitis. *Curr Opin Infect Dis*. 2017;30:135–141.
37. Mourvillier B, Tubach F, Van De Beek D, et al. Induced hypothermia in severe bacterial meningitis: A randomized clinical trial. *JAMA*. 2013;310:2174–2183.
38. Ajdukiewicz KM, Cartwright KE, Scarborough M, et al. Glycerol adjuvant therapy in adults with bacterial meningitis in a high HIV seroprevalence setting in Malawi: A double-blind, randomised controlled trial. *Lancet Infect Dis*. 2011;11:293–300.
39. Wall EC, Ajdukiewicz KM, Bergman H, et al. Osmotic therapies added to antibiotics for acute bacterial meningitis. *Cochrane Database Syst Rev*. 2018;2:CD008806.
40. Olarte L, Barson WJ, Barson RM, et al. Impact of the 13-valent pneumococcal conjugate vaccine on pneumococcal meningitis in US children. *Clin Infect Dis*. 2015;61:767–775.
41. Brouwer MC, Van De Beek D. Epidemiology of community-acquired bacterial meningitis. *Curr Opin Infect Dis*. 2018;31:78–84.
42. Pfaller MA, Mendes RE, Flamm RK, et al. Ceftaroline activity against multidrug-resistant Streptococcus pneumoniae from US Medical Centers (2014) and molecular characterization of a single ceftaroline nonsusceptible isolate. *Microb Drug Resist*. 2017;23: 571–579.

43. Hameed N, Tunkel AR. Treatment of drug-resistant pneumococcal meningitis. *Curr Infect Dis Rep*. 2010;12:274–281.
44. Faella F, Pagliano P, Fusco U, et al. Combined treatment with ceftriaxone and linezolid of pneumococcal meningitis: A case series including penicillin-resistant strains. *Clin Microbiol Infect*. 2006;12:391–394.
45. Vivas M, Force E, Garrigos C, et al. Experimental study of the efficacy of daptomycin for the treatment of cephalosporin-resistant pneumococcal meningitis. *J Antimicrob Chemother*. 2014;69:3020–3026.
46. Pilishvili T, Lexau C, Farley MM, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. *J Infect Dis*. 2010;201:32–41.
47. Moore MR, Link-Gelles R, Schaffner W, et al. Effect of use of 13- valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: Analysis of multisite, population-based surveillance. *Lancet Infect Dis*. 2015;15:301–309.
48. Ladhani SN, Collins S, Djennad A, et al. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000-17: A prospective national observational cohort study. *Lancet Infect Dis*. 2018;18:441–451.
49. Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. *Vaccine*. 2009;27(Suppl 2):B51–63.
50. Centers for Disease Control and Prevention. Enhanced Meningococcal Disease Surveillance Report. 2016. Available at:. https://www.cdc.gov/meningococcal/downloads/NCIRD-EMS-Report.pdf.
51. Brynildsrud OB, Eldholm V, Bohlin J, et al. Acquisition of virulence genes by a carrier strain gave rise to the ongoing epidemics of meningococcal disease in West Africa. *Proc Natl Acad Sci USA*. 2018;115:5510–5515.
52. Zalmanovici Trestioreanu A, Fraser A, Gafter-Gvili A, et al. Antibiotics for preventing meningococcal infections. *Cochrane Database Syst Rev*. 2013;CD004785.
53. Kimberlin DW, Brady MT, Jackson MA, Long SS. Red Book®: 2018 Report of the Committee on Infectious Diseases. 31st ed. Elk Grove Village, IL: American Academy of Pediatrics; 2018.
54. Thaver D, Zaidi AK. Burden of neonatal infections in developing countries: A review of evidence from community-based studies. *Pediatr Infect Dis J*. 2009;28:S3–9.
55. Weston EJ, Pondo T, Lewis MM, et al. The burden of invasive early-onset

neonatal sepsis in the United States, 2005-2008. *Pediatr Infect Dis J*. 2011;30:937–941.

56. Libster R, Edwards KM, Levent F, et al. Long-term outcomes of group B streptococcal meningitis. *Pediatrics*. 2012;130:e8–15.
57. Verani JR, Mcgee L, Schrag SJ, et al. Prevention of perinatal group B streptococcal disease: Revised guidelines from CDC, 2010. *MMWR Recomm Rep*. 2010;59:1–36.
58. Van De Beek D, Brouwer MC, Thwaites GE, et al. Advances in treatment of bacterial meningitis. *Lancet*. 2012;380:1693–1702.
59. Brouwer MC, Mcintyre P, Prasad K, et al. Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev*. 2015;(9):CD004405.
60. Ricard JD, Wolff M, Lacherade JC, et al. Levels of vancomycin in cerebrospinal fluid of adult patients receiving adjunctive corticosteroids to treat pneumococcal meningitis: A prospective multicenter observational study. *Clin Infect Dis*. 2007;44:250–255.
61. Smith RM, Schaefer MK, Kainer MA, et al. Fungal infections associated with contaminated methylprednisolone injections. *N Engl J Med*. 2013;369:1598–1609.
62. Lyons JL, Thakur KT, Lee R, et al. Utility of measuring (1,3)-beta-d-glucan in cerebrospinal fluid for diagnosis of fungal central nervous system infection. *J Clin Microbiol*. 2015;53:319–322.
63. Albanese J, Leone M, Bruguerolle B, et al. Cerebrospinal fluid penetration and pharmacokinetics of vancomycin administered by continuous infusion to mechanically ventilated patients in an intensive care unit. *Antimicrob Agents Chemother*. 2000;44:1356–1358.
64. Kullar R, Chin JN, Edwards DJ, et al. Pharmacokinetics of single-dose daptomycin in patients with suspected or confirmed neurological infections. *Antimicrob Agents Chemother*. 2011;55:3505–3509.
65. Samuel S, Edwards NJ, Rojas LJ. Ceftazidime-avibactam for the treatment of post-neurosurgical meningitis caused by a KPC-producing Klebsiella pneumoniae. ID Week 2016 Poster Presentation. Abstract # 1182. https://idsa.confex.com/idsa/2016/webprogram/Paper58791.html.
66. Xipell M, Bodro M, Marco F, et al. Clinical experience with ceftazidime/avibactam in patients with severe infections, including meningitis and lung abscesses, caused by extensively drug-resistant Pseudomonas aeruginosa. *Int J Antimicrob Agents*. 2017;49:266–268.
67. Sakoulas G, Nonejuie P, Kullar R, et al. Examining the use of ceftaroline

in the treatment of Streptococcus pneumoniae meningitis with reference to human cathelicidin LL-37. *Antimicrob Agents Chemother*. 2015;59:2428–2431.

68. Balouch, MA, Bajwa, RJ, Hassoun, A. Successful use of ceftaroline for the treatment of MRSA meningitis secondary to an infectious complication of lumbar spine surgery. *J Antimicrob Chemother* 2015;70:624-625.
69. Kuriakose SS, Rabbat M, Gallagher JC. Ceftaroline CSF concentrations in a patient with ventriculoperitoneal shunt-related meningitis. *J Antimicrob Chemother*. 2015;70:953–954.
70. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62:e1–50.
71. Patterson TF, Thompson GR 3rd, Denning DW, et al. Executive summary—Practice guidelines for the diagnosis and management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;63:433–442.
72. Fried HI, Nathan BR, Rowe AS, et al. The insertion and management of external ventricular drains—an evidence-based consensus statement: A statement for healthcare professionals from the Neurocritical Care Society. *Neurocrit Care*. 2016;24:61–81.
73. Sonneville R, Ruimy R, Benzonana N, et al. An update on bacterial brain abscess in immunocompetent patients. *Clin Microbiol Infect*. 2017;23:614–620.
74. Brouwer MC, Van De Beek D. Epidemiology, diagnosis, and treatment of brain abscesses. *Curr Opin Infect Dis*. 2017;30:129–134.
75. Doughty CT, Yawetz S, Lyons J. Emerging causes of Arbovirus ncephalitis in North America: Powassan, chikungunya, and Zika viruses. *Curr Neurol Neurosci Rep*. 2017;17:12.
76. Steiner I, Budka H, Chaudhuri A, et al. Viral meningoencephalitis: A review of diagnostic methods and guidelines for management. *Eur J Neurol*. 2010;17:999–e957.
77. Granerod J, Ambrose HE, Davies NW, et al. Causes of encephalitis and differences in their clinical presentations in England: A multicentre, population-based prospective study. *Lancet Infect Dis*. 2010;10:835–844.
78. Whitley R. Neonatal herpes simplex virus infection. *Curr Opin Infect Dis*. 2004;17:243–246.

79. Piret J, Boivin G. Resistance of herpes simplex viruses to nucleoside analogues: mechanisms, prevalence, and management. *Antimicrob Agents Chemother*. 2011;55:459–472.
80. Gnann JWJr., Skoldenberg B, Hart J, et al. Herpes simplex encephalitis: Lack of clinical benefit of long-term valacyclovir therapy. *Clin Infect Dis*. 2015;61:683–691.
81. ArboNET, Arboviral Diseases Branch, US Centers for Disease Control and Prevention (CDC). West Nile Virus Statistics, Surveillance, and Control. 2015.
82. Hendricks KA, Wright ME, Shadomy SV, et al. Centers for Disease Control and Prevention Expert Panel meetings on prevention and treatment of anthrax in adults. *Emerg Infect Dis*. 2014;20:e130687.
83. Bradley JS, Peacock G, Krug SE, et al. Pediatric anthrax clinical management. *Pediatrics*. 2014;133:e1411–1436.
84. Meaney-Delman, D, Zotti, ME, Creanga, AA, et al. Special considerations for prophylaxis for and treatment of anthrax in pregnant and postpartum women. *Emerg Infect Dis* [Internet]. 2014 Feb [accessed 9/8/2019]. http://dx.doi.org/10.3201/eid2002.130611
85. Pillai SK, Huang E, Guarnizo JT, et al. Antimicrobial treatment for systemic Anthrax: Analysis of cases from 1945 to 2014 identified through a systematic literature review. *Health Secur*. 2015;13:355–364.
86. Wright JG, Quinn CP, Shadomy S, et al. Use of anthrax vaccine in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. *MMWR Recomm Rep*. 2010;59:1–30.
87. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: Clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2006;43:1089–1134.
88. Mygland, A, Ljostad, U, Fingerle, V, et al. EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis. *Eur J Neurol* 2010;17:8-16, e11-14.
89. Centers for Disease Control and Prevention. Reported Tuberculosis in the United States. 2016. Available at: https://www.cdc.gov/tb/statistics/reports/2016/pdfs/2016_Surveillance_Ful
90. Nahid P, Dorman SE, Alipanah N, et al. Executive Summary: Official

American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. *Clin Infect Dis*. 2016;63:853–867.

91. Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf.
92. Falzon D, Schunemann HJ, Harausz E, et al. World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. *Eur Respir J*. 2017;49(3):pii: 1602308.
93. Wilson, JW. Nocardiosis: updates and clinical overview. *Mayo Clin Proc* 2012;87:403-407.
94. Brown-Elliott BA, Brown JM, Conville PS, et al. Clinical and laboratory features of the *Nocardia* spp. based on current molecular taxonomy. *Clin Microbiol Rev*. 2006;19:259–282.
95. Blair B, Sarkar P, Bright KR, et al. *Naegleria fowleri* in well water. *Emerg Infect Dis*. 2008;14:1499–1501.
96. Centers for Disease Control and Prevention. Naegleria Fowleri—Primary Amebic Meningoencephalitis (PAM). Last accessed April 30, 2018. www.cdc.gov/parasites/naegleria/infection-sources.html.
97. Centers for Disease Control and Prevention. Epidemiology & Risk Factors. Global Health—Division of Parasitic Diseases and Malaria. Parasites—Toxoplasmosis (Toxoplasma infection). Atlanta, GA: US Department of Health and Human Services. https://www.cdc.gov/parasites/toxoplasmosis/epi.html.
98. Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Department of Health and Human Services. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children. https://aidsinfo.nih.gov/guidelines/html/5/pediatric-opportunistic-infection/0.

125

Lower Respiratory Tract Infections

Evan J. Zasowski and Martha Blackford

KEY CONCEPTS

1. Respiratory infections remain a major cause of morbidity from acute illness in the United States and represent the most common reasons why patients seek medical attention.
2. The majority of pulmonary infections follow colonization of the upper respiratory tract with potential pathogens, whereas microbes less commonly gain access to the lungs via the bloodstream from an extrapulmonary source or by inhalation of infected aerosol particles. The competency of a patient's immune status is an important factor influencing the susceptibility to infection, etiologic cause, and disease severity.
3. An appropriate treatment regimen for a patient with uncomplicated lower respiratory tract infection can be established by evaluating the patient history, physical examination, chest radiograph, and properly collected sputum for culture interpreted in light of current knowledge of the most common lung pathogens and their antibiotic susceptibility patterns within the community.
4. Acute bronchitis is most commonly caused by respiratory viruses and is almost always self-limiting. Therapy targets associated symptoms such as lethargy, malaise, or fever and may include fluids for rehydration. Routine use of antibiotics should be avoided and medication to suppress cough is rarely indicated.
5. Chronic bronchitis is caused by several interacting factors, including inhalation of noxious agents (most prominent are cigarette smoke and exposure to occupational dusts, fumes, and environmental pollution) and host factors including genetic factors and bacterial (and possibly viral) infections. The hallmark of this disease is a chronic cough, accompanied by excessive production, and expectoration of sputum with a persistent

presence of microorganisms in the patient's sputum.

6. Treatment of acute exacerbations of chronic bronchitis includes attempts to mobilize and enhance sputum expectoration (chest physiotherapy, humidification of inspired air), oxygen if needed, aerosolized bronchodilators in select patients with demonstrated benefit, and possibly antibiotics.
7. Respiratory syncytial virus is the most common cause of acute bronchiolitis, an infection that mostly affects infants during their first year of life. In the well infant, bronchiolitis usually is a self-limiting viral illness.
8. The most prominent pathogen causing community-acquired bacterial pneumonia in otherwise healthy adults is *Streptococcus pneumoniae*, whereas the most common pathogens causing hospital-acquired pneumonia are *Staphylococcus aureus* and gram-negative aerobic bacilli.
9. Empiric antimicrobial therapy for pneumonia should consist of antibiotic regimens targeting presumed causative pathogens based on clinical presentation and patient-specific characteristics, local epidemiology, and resistance patterns.
10. Microbiologic tests for pneumonia etiology should be performed when clinically indicated and used along with patient clinical response to tailor antibiotic therapy using evidence-based pathogen-directed therapy when possible.

Preclass Engaged Learning Activity

Create a study chart of the following clinically important lower respiratory tract pathogens:

> *Streptococcus pneumoniae*, *Escherichia coli*, *Klebsiella pneumoniae*, respiratory syncytial virus, *Legionella pneumophila*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, methicillin-susceptible *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus*, and *Haemophilus influenzae*.

On the chart, include pathogen type and morphology (eg, bacteria, gram-positive cocci in pairs and chains), type of pneumonia most commonly associated with (ie CAP vs HAP/VAP), and three antibiotics that are active against the organism.

INTRODUCTION

1 Respiratory tract infections remain a major cause of morbidity from acute illness in the United States and most likely represent the single most common reason patients seek medical attention. This chapter focuses on bacterial and viral infections involving the lower respiratory tract, which includes the tracheobronchial tree and lung parenchyma.

2 The respiratory tract has an elaborate system of host defenses, including humoral immunity, cellular immunity, and anatomic mechanisms.[1] When functioning properly, respiratory tract host defenses are markedly effective in protecting against pathogen invasion and removing potentially infectious agents from the lungs. For the most part, infections in the lower respiratory tract occur only when these defense mechanisms are impaired, as in cases of dysgammaglobulinemia or compromised ciliary function, such as that caused by the chronic inflammation accompanying cigarette smoking. In addition, local defenses may be overwhelmed when a particularly virulent microorganism or excessive inoculum invades lung parenchyma. The majority of pulmonary infections follow colonization of the upper respiratory tract with potential pathogens, which, after achieving sufficiently high concentrations, gain access to the lung via aspiration of oropharyngeal secretions. Less commonly, microbes enter the lung via the blood from an extrapulmonary source or by inhalation of infected aerosolized particles. The specific type of pulmonary infection caused by an invading microorganism is determined by a variety of host factors, including age, anatomic features of the airway, and specific characteristics of the infecting agent.

The most common infections involving the lower respiratory tract are bronchitis, bronchiolitis, and pneumonia. Bronchitis and bronchiolitis are inflammatory conditions of the large and small airways, respectively, of the tracheobronchial tree. The inflammatory process does not extend to the alveoli. Bronchitis frequently is classified as acute or chronic; acute bronchitis occurs in individuals of all ages, whereas chronic bronchitis primarily affects adults. Bronchiolitis is a disease of infancy.

Lower respiratory tract infections in children and adults most commonly result from either viral or bacterial invasion of lung parenchyma. The diagnosis of viral infections rests primarily on the recognition of a characteristic constellation of clinical signs and symptoms. Because treatment of viral respiratory infections is largely supportive, only occasionally does the diagnosis require laboratory confirmation; this is achieved through serologic tests or

identification of the organism by culture or antigen detection in respiratory secretions.[2] Laboratory techniques using polymerase chain reaction (PCR), microarrays, and multiplex ligation-dependent probe amplification, to name a few, have emerged as a means to identify specific pathogens rapidly and accurately.[3]

In contrast, because bacterial pneumonia usually necessitates expedient, effective, and specific antibiotic therapy, its management depends, in large part, on an understanding of the risk factors for acquiring pneumonia, predominant pathogens within the community, and, if necessary, isolation of the etiologic agent by culture from lung tissue or secretions.[4–6] The pharynx is colonized with many organisms that can cause pneumonia; therefore, culture of expectorated sputum can be misleading unless the specimen is examined to ensure that it has originated from the lower respiratory tract. The Gram stain provides the easiest method for distinguishing lower from upper respiratory tract secretions; moreover, through determination of the shape and color of the bacteria, the Gram stain frequently narrows the microbiologic differential diagnosis sufficiently to allow accurate initial therapy. Scanned under low-power microscopy, Gram-stained expectorated upper respiratory tract secretions contain many irregularly shaped epithelial cells with little evidence of inflammation and may not reflect the pathogen. In contrast, a lower-tract specimen from a patient with bacterial pneumonia usually contains multiple neutrophils per high-powered field and a single or predominant bacterial species. More aggressive procedures can be performed in an attempt to more accurately identify responsible pathogens including respiratory secretion samples obtained via bronchoscopy or bronchoalveolar lavage (BAL). Culture of specimens confirmed to originate from the lower tract by Gram stain or collection via BAL provides valuable diagnostic information for the majority of patients with bacterial pneumonia. In addition, pneumonia promotes the release of inflammatory mediators and acute-phase proteins, such as C-reactive protein, which can be significantly elevated in serum in the presence of respiratory tract infections.[7] Unfortunately with the exception of pathogen identification by culture, elevations in C-reactive protein, changes in sputum color or peripheral white blood count, etc. are not specific for determining viral, bacterial, or fungal etiology. Newer genomic testing may aid tremendously in determining the identity of responsible pathogen(s) and then selection of optimal antimicrobial therapy.

3 An appropriate treatment regimen for the patient with an uncomplicated lower respiratory tract infection usually can be established by history, physical examination, chest radiograph, and properly collected sputum cultures

interpreted in light of the most common lung pathogens and their antibiotic susceptibility patterns within the community.[2,5] More sophisticated or invasive diagnostic methods (eg, computed tomography, bronchoscopy, and lung biopsy) are reserved for severely ill patients who are unable to expectorate sputum or who are not responding to empirical therapy or for pulmonary infections occurring in immunocompromised patients.[2]

BRONCHITIS

ACUTE BRONCHITIS

EPIDEMIOLOGY AND ETIOLOGY

Acute bronchitis occurs year-round, but more commonly during the winter months. Cough accounts for more than 6 million ambulatory visits annually, underscoring its major financial impact on the healthcare system.[8] Acute bronchitis is characterized by inflammation of the epithelium of the large airways resulting from infection or exposure to irritating environmental triggers (eg, air pollution and cigarette smoke). Acute (viral) infection and/or smoking are the most common precipitants of attacks, which usually manifest initially as a persistent cough.

4 Respiratory viruses are the predominant infectious agents associated with acute bronchitis, accounting for 85% to 95% of occurrences. The most common infecting agents include influenza A and B, respiratory syncytial virus (RSV), and parainfluenza virus, whereas the common cold viruses (rhinovirus and coronavirus) and adenovirus are encountered less frequently. Although far less common, bacterial pathogens are involved in a minority of cases and involve pathogens often associated with community-acquired pneumonia (CAP) including *Mycoplasma pneumoniae*, *Streptococcus pneumonia*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and less commonly *Chlamydophila pneumoniae* and *Bordetella pertussis*, the agent responsible for whooping cough. Although a primary bacterial etiology for acute bronchitis appears rare, secondary bacterial infection may be involved, particularly in patients with underlying disease(s).[8]

PATHOGENESIS

4 Since acute bronchitis is primarily a self-limiting illness and rarely a cause of

death, few data describing the pathology are available. In general, infection of the trachea and bronchi yields inflammation-induced hyperemic and edematous mucous membranes with an increase in bronchial secretions. Destruction of respiratory epithelium can range from mild to extensive and may affect bronchial mucociliary function. In addition, the increase in desquamated epithelial cells and bronchial secretions, which can become thick and tenacious, further impairs mucociliary activity. The probability of permanent damage to the airways as a result of acute bronchitis remains unclear but appears unlikely. However, epidemiologic evaluations support the belief that recurrent acute respiratory infections may be associated with increased airway hyperreactivity and possibly the pathogenesis of asthma, chronic obstructive pulmonary disease (COPD), or possibly the asthma-COPD syndrome.[9,10]

CLINICAL PRESENTATION

Acute bronchitis usually begins as an upper respiratory infection with nonspecific complaints.[8,11] Cough is the hallmark of acute bronchitis and occurs early. The onset of cough may be insidious or abrupt, and the symptoms persist despite resolution of nasal or nasopharyngeal complaints; cough may persist for up to 3 or more weeks. Frequently, the cough initially is nonproductive, but then progresses, yielding mucopurulent sputum. In older children and adults, the sputum is raised and expectorated; in the young child, sputum often is swallowed and can result in gagging and vomiting. Substantial discomfort may result from the coughing. Dyspnea, cyanosis, or signs of airway obstruction are observed rarely unless the patient has underlying pulmonary disease, such as emphysema or COPD. Fever, when present, rarely exceeds 39°C (102.2°F) and appears most commonly with adenovirus, influenza virus, and *M. pneumoniae* infections. The diagnosis typically is made on the basis of a characteristic history and physical examination, and should be differentiated from asthma or bronchiolitis as these latter diseases are usually associated with wheezing, shortness of breath, and hypoxemia. Bacterial cultures of expectorated sputum are of limited use because of the inability to avoid normal nasopharyngeal flora by the sampling technique. Similarly, viral cultures are unnecessary. In the absence of important risk factors, including COPD, congestive heart failure, or immune compromise, throat/sputum cultures have no role in the routine care of patients with acute bronchitis. For the vast majority of affected patients, an etiologic diagnosis is unnecessary and will not change the prescribing of routine supportive care for the management of these patients.

TREATMENT

Desired Outcome

In the absence of a complicating bacterial superinfection, acute bronchitis almost always is self-limiting. The goals of therapy are to provide comfort to the patient and, in the unusually severe case, to treat associated dehydration and respiratory compromise.[8]

General Approach to Treatment

4 Treatment of acute bronchitis is symptomatic and supportive in nature. Reassurance and antipyretics frequently are all that are needed. Bedrest for comfort may be instituted as desired. Patients should be encouraged to drink fluids to prevent dehydration and possibly to decrease the viscosity of respiratory secretions. Mist therapy (use of a vaporizer) may promote the thinning and loosening of respiratory secretions.

Pharmacologic Therapy

Mild analgesic–antipyretic therapy often is helpful in relieving the associated lethargy, malaise, and fever. Aspirin or acetaminophen (650 mg/dose in adults [maximum less than 4 g/day] or 10–15 mg/kg/dose in children [maximum 60 mg/kg/day]) administered every 4 to 6 hours or ibuprofen (200–800 mg/dose in adults [maximum 3.2 g/day] or 10 mg/kg/dose in children [maximum 40 mg/kg/day]) should be administered every 6 to 8 hours. Aspirin should be avoided in children less than 19 years of age with a fever-causing illness and acetaminophen or ibuprofen used as the preferred agents because of a possible, but unclear and unproven association between aspirin use and the possible development of Reye's syndrome.

Patients may present with mild-to-moderate wheezing. In otherwise healthy patients, no meaningful benefits have been described with the routine use of oral or aerosolized β_2-receptor agonists[15] and/or oral or aerosolized corticosteroids. Corticosteroids should be avoided in patients with acute bronchitis. A Cochrane review concluded (based on benefit vs potential for adverse effects) there is no evidence to support the routine use of β_2-receptor agonists in either pediatric or adult patients with acute bronchitis; however, adults with airflow obstruction may have a trend toward improvement in cough.[12] Some clinicians, despite no

data, may initiate a brief trial (eg, about 5–7 days) of β_2-receptor agonists and even oral or inhaled corticosteroid for patients with a persistent (more than 14–20 days), troublesome cough. This is rarely, if ever, necessary in patients with uncomplicated acute bronchitis and should be avoided. Cough may persist for 3+ weeks and airway hyperresponsiveness for 5 to 6 weeks in as many as 50% of affected patients. In contrast, COPD patients experiencing an acute exacerbation can (will) benefit from a short course of corticosteroid.

Patients suffering from acute bronchitis frequently medicate themselves with nonprescription cough and cold remedies containing various combinations of antihistamines, sympathomimetics, and antitussives despite the lack of definitive evidence supporting their effectiveness.[8] The tendency of these agents to dehydrate bronchial secretions could aggravate and prolong the recovery process. Although not recommended for routine use, persistent, mild cough, which may be bothersome, can be treated with dextromethorphan; more severe coughs may require intermittent codeine or other similar agents.[13] In severe cases, the cough may be persistent enough to disrupt sleep, and use of a mild sedative-hypnotic, concomitantly with a cough suppressant (eg, codeine), may be desirable. However, antitussives should be used cautiously when the cough is productive, and codeine is no longer recommended for use in pediatric patients. The primary or supplemental use of expectorants is questionable because their clinical effectiveness has not been well established.[8]

Routine use of antibiotics for treatment of acute bronchitis should be strongly discouraged due to limited benefit.[8,14] In previously healthy patients who exhibit persistent fever or respiratory symptoms for more than 5 to 7 days or for predisposed patients (eg, elderly/frail, COPD, and immune compromised), the possibility of a concurrent bacterial infection should be suspected. When possible, antibiotic therapy should be directed toward anticipated respiratory pathogen(s) (eg, *S. pneumoniae* and *H. influenzae*). *M. pneumoniae*, if suspected by history or if confirmed by culture serology or PCR, can be treated with azithromycin. Alternatively, a fluoroquinolone antibiotic with activity against these suspected pathogens (eg, levofloxacin or moxifloxacin) can be used empirically, but due to the increasing rate of pathogen resistance to current antimicrobial drugs, the use of antibiotics in patients with acute bronchitis should be reserved for only those patients not responding adequately to supportive care and deemed at risk of associated complications. During known epidemics involving the influenza A virus, amantadine or rimantadine may have been effective in minimizing associated symptoms if administered early in the course of the disease; however, treatment with these adamantanes is no longer

recommended by the Centers for Disease Control and Prevention due to increasing influenza resistance and associated adverse effects (see Chapter 127). The neuraminidase inhibitors (eg, zanamivir and oseltamivir) are active against both influenza A and B viral infections and may reduce the severity and duration of the influenza episode if administered promptly during the onset of the viral infection and are the preferred treatment (see Chapter 127).[15] Unfortunately, the incidence of influenza virus resistance to available antiviral drugs is increasing, necessitating reconsideration of how we administer antiviral drugs for prophylaxis and treatment.[16] The concept of antiviral drug combinations has emerged as a successful approach to effectively treat systemic viral infections.[17]

CHRONIC BRONCHITIS

EPIDEMIOLOGY AND ETIOLOGY

Chronic bronchitis, most often a component of COPD, is a clinical diagnosis for a nonspecific, heterogenic disease that primarily affects adults. An in-depth presentation of the spectrum and management of COPD is given in Chapter 44; this section focuses solely on chronic bronchitis. In developed countries, the prevalence of chronic bronchitis is slightly higher in men than in women. Depending on the definition used for chronic bronchitis, 3.4% to 22% of adults have chronic bronchitis and 14% to 74% of COPD patients suffer from chronic bronchitis.[18]

5 Chronic bronchitis is defined as the presence of a chronic cough productive of sputum lasting more than 3 consecutive months of the year for 2 consecutive years without an underlying etiology of bronchiectasis or tuberculosis. The disease is a result of several contributing factors; the most prominent factor is cigarette smoking; however, in nonsmokers who develop chronic bronchitis (4%–22%), other factors may be exposure to occupational dusts, fumes, and environmental pollution, and host factors (eg, genetic factors and bacterial [and possibly viral] infections).[18] The contribution of each of these factors and of others (either alone or in combination) to chronic bronchitis is unknown.[19] Cigarette smoke is a well-known airway irritant and is a predominant factor in the etiology of chronic bronchitis. Although previously assumed the most common etiologic cause of chronic bronchitis, more strict prohibition of public smoking and the resultant decrease in chronic tobacco smokers, particularly in developed countries, underscores the importance of other factors as causes of this chronic disease. Airway irritants including

occupational dust, chemicals, or air pollution, either alone or more likely in combination, are also responsible for the pathogenesis of chronic bronchitis and may explain the development in nonsmokers.[18,19] Furthermore, genomic studies have begun to expand our understanding of the molecular pathways that may have clinical relevance in this heterogeneous disease. Lastly, the influence of recurrent respiratory tract infections during childhood or young adult life on the later development of chronic bronchitis remains obscure, but recurrent respiratory infections may predispose individuals to the development of chronic bronchitis. Whether these recurrent respiratory tract infections are a result of unrecognized anatomic abnormalities of the airways or impaired pulmonary defense mechanisms is unclear.

Numerous consensus statements and published authoritative guidelines define chronic bronchitis and emphysema as the two main components of COPD/chronic obstructive lung disease.[20–22] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines document does not distinguish these two diagnoses (eg, emphysema or chronic bronchitis) in the definition of COPD, but it does define COPD as a disease characterized by airflow obstruction that is not fully reversible and progressive. The GOLD guidelines (www.goldcopd.com) provide a COPD classification scoring system according to severity that can be helpful in staging patients for intensity of therapy, acute/chronic therapy, and prognosis. Unfortunately, differences in definitions between authoritative organizations may cause confusion in the assignment of patients in clinical trials and thus in assessment and application of study results to clinical care.

PATHOGENESIS

Chronic inhalation of an irritating noxious substance compromises the normal secretory and mucociliary function of bronchial mucosa.[18] Bronchial biopsy specimens in bronchitic patients underscore the importance of T-cell-derived proinflammatory cytokines (eg, interleukins IL-4, IL-5, IL-13, and interferon gamma) in the pathogenesis and propagation of the observed inflammatory changes. In chronic bronchitis, the bronchial wall is thickened, and the number of mucus-secreting goblet cells on the surface epithelium of both larger and smaller bronchi is increased markedly. In contrast, goblet cells generally are absent from the smaller bronchi of normal individuals. In addition to the increased number of goblet cells, hypertrophy of the mucous glands and dilation of the mucous gland ducts are observed. As a result of these changes, chronic

bronchitis has substantially more mucus in the peripheral airways, further impairing normal lung defenses. This increased quantity (overproduction and hypersecretion) of tenacious secretions within the bronchial tree frequently causes mucous plugging of the smaller airways. Accompanying these changes is squamous cell metaplasia of the surface epithelium, edema, and increased vascularity of the basement membrane of larger airways and variable chronic inflammatory cell infiltration. In addition, the amounts of several proteases derived from inflammatory cells are increased and due to COPD-induced defective antiproteases lead to continued destruction of connective tissue. Continued progression of this pathology can result in residual scarring of small bronchi and peribronchial fibrosis augmenting airway obstruction and weakening of bronchial walls.[18]

CLINICAL PRESENTATION

5 The hallmark of chronic bronchitis is a cough that may range from a mild to a severe and incessant coughing productive of purulent sputum. Coughing may be precipitated by multiple stimuli, including simple, normal conversation. Expectoration of the largest quantity of sputum usually occurs on arising in the morning, although many patients expectorate sputum throughout the day. The expectorated sputum usually is tenacious and can vary in color from white to yellow-green. Patients with chronic bronchitis often expectorate as much as 100 mL/day more than normal. As a result, many patients complain of a frequent bad taste in their mouth and of halitosis. It is important to recognize that sputum color provides no prognostic indication of infection or cause of an infectious disease exacerbation, that is, viral versus bacterial cause. Although sputum color of more green and yellow can be a predictor of potentially pathogenic bacteria, this is unreliable clinically.[23] The diagnosis of an acute exacerbation requires consideration of a number of different factors all occurring within a discrete timeframe (eg, increased/worsening respiratory symptoms including dyspnea, sputum volume and/or clearance, cough, etc). The tracking of the number of acute exacerbations and their consequences (decline in forced expiratory volume in 1 second (FEV1), persistent/worsening of symptoms annually, is extremely important for prognostication and defining ongoing treatment strategies. Each acute exacerbation of chronic bronchitis results in continual declines in lung function.

The diagnosis of chronic bronchitis is based primarily on clinical assessment and history. Any patient who reports coughing sputum on most days for at least

3 consecutive months each year for 2 consecutive years presumptively has chronic bronchitis.[18] The diagnosis of chronic bronchitis is made only when the possibilities of bronchiectasis, cardiac failure, cystic fibrosis, and lung carcinoma, amongst others, have been effectively excluded. In an attempt to be more specific in the diagnosis, some investigators have added the criteria of lost wages for 3 or more weeks. In addition, many clinicians attempt to subdivide their patients based on severity of disease to guide therapeutic interventions. Two primary classification proposals are most often used in an attempt to determine the severity of the underlying disease as well as the occurrence/impending occurrence of an acute exacerbation of chronic bronchitis; for disease severity and acute exacerbations the prognostic tools advocated by GOLD are very helpful including classification based on spirometry ("mild" postbronchodilator FEV1 greater than or equal to 80% predicted to "very severe" postbronchodilator FEV1 less than 30% predicted: see Chapter 27); the COPD assessment test (eight-item measure of health status), the Clinical COPD Questionnaire (a measure of clinical control) and the Modified Medical Research Council Questionnaire to predict future mortality. The other simple classification system is that proposed by Anthonisen and colleagues in 1987 that is still used to categorize patients in many therapeutic clinical trials.[24] The use of patient symptom diaries can also be helpful in compliant patients. The importance of accurate classification for grouping patients of similar disease involvement cannot be overemphasized with respect to assessing publications outlining treatment strategies for these patients. These classifications attempt to capture specific phenotypes of chronic bronchitis patients. The typical clinical presentation of chronic bronchitis is listed in **Table 125-1**. Comparison of the trends in changes in a patient's physical activity, symptoms, and clinical/physical findings from the patient's "routine" is extremely helpful in determining the presence and severity of an acute exacerbation.

TABLE 125-1 Clinical Presentation of Chronic Bronchitis

Signs and symptoms
- Excessive sputum expectoration
- Cough
- Cyanosis (advanced disease)

Physical examination
- Chest auscultation usually reveals inspiratory and expiratory rales, rhonchi, and mild wheezing with an expiratory phase that is frequently prolonged
- Hyperresonance on percussion with obliteration of the area of cardiac dullness
- Normal vesicular breathing sounds are diminished
- Clubbing of digits (advanced disease)
- Obesity

Chest radiograph
- Increase in anteroposterior diameter of the thoracic cage (barrel chest)
- Depressed diaphragm with limited mobility

Laboratory tests
- Erythrocytosis (advanced disease), that is, increased hematocrit

Pulmonary function tests
- Decreased vital capacity
- Prolonged expiratory flow

In more advanced stages of chronic bronchitis, physical findings associated with cor pulmonale, including cardiac enlargement, hepatomegaly, and edema of the lower extremities, are observed. In general, chronic bronchitis tend to maintain at least normal body weight and commonly are obese. Radiographic studies are of limited value in either the diagnosis or follow-up of a patient. The microscopic and laboratory assessments of sputum are used in the overall evaluation of patients with chronic bronchitis. Gram staining of the sputum often reveals a mixture of both gram-positive and gram-negative bacteria, reflecting normal oropharyngeal flora and chronic tracheal colonization (in order of frequency) by nontypable *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*. **Table 125-2** lists the most common bacterial isolates identified from sputum culture for patients experiencing an acute exacerbation of chronic bronchitis. For patients with more severe airflow disease (eg., FEV_1 less than 40% predicted), enteric gram-negative bacilli, *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, and *Pseudomonas aeruginosa* may be significant pathogens during acute exacerbations.

TABLE 125-2 Common Bacterial Pathogens Isolated from Sputum of Patients with Acute Exacerbation of Chronic Bronchitis

Pathogen	Percent of Cultures
H. influenzae[a,b]	45
M. catarrhalis[a]	30
S. pneumoniae[c]	20
E. coli, *Enterobacter* species, *Klebsiella* species, *P. aeruginosa*	5

[a]Often β-lactamase positive.

[b]Vast majority are nontypable strains.

[c]More than 25% of strains may have intermediate or high resistance to penicillin.

TREATMENT

Desired Outcome

The goals of therapy for chronic bronchitis are twofold: to reduce the severity of chronic symptoms and to ameliorate acute exacerbations and achieve prolonged exacerbation-free intervals.

General Approach to Treatment

The approach to treatment of chronic bronchitis is multifactorial.[18] First and foremost, attempts must be made to reduce the patient's exposure to known bronchial irritants (eg, smoking and workplace pollution). A complete occupational and environmental history for determination of exposure to noxious, irritating gases as well as preference toward cigarette smoking must be assessed. Often easier to discuss than accomplish, honest, yet reasonable attempts should be made with the patient to reduce or eliminate the number of cigarettes smoked daily and to reduce exposure to secondhand smoke. An organized, coordinated, smoking cessation program, including counseling, possibly hypnotherapy, and the adjunctive use of nicotine substitutes (eg, nicotine gum or patch) or other pharmacotherapy (eg, bupropion and varenicline) may promote the reduction or complete withdrawal from cigarette smoking. Often just as difficult is modification of exposure to irritating substances within the home and workplace.

The importance of pulmonary rehabilitation has been realized in improving the quality of life for patients with chronic respiratory diseases.[25] Pulmonary rehabilitation is broadly defined as an interdisciplinary program individualized for patients with chronic respiratory impairment designed to optimize each

patient's physical and social performance and autonomy. A personalized exercise-training program including resistance and aerobic exercise is central to these programs. Pulmonary rehabilitation programs relieve dyspnea and fatigue, improve a patient's emotional function, and enhance their sense of control over their disease and life. These improvements are often moderately large and clinically relevant.[25] The challenge for the future is to determine what components of a comprehensive pulmonary rehabilitation program provide the greatest benefit.

6 Measures to provide chest physiotherapy (eg, pulmonary "toilet") can be instituted.[26] Clearly the cost-effectiveness of chest physiotherapy needs to be better described but their short-term effects have been demonstrated and may be of symptomatic value to many patients experiencing an acute exacerbation of the chronic bronchitis. During acute pulmonary exacerbations of the disease, the patient's ability to mobilize and expectorate sputum may be reduced dramatically. In these instances, attempts at postural drainage techniques, with instruction and or active participation from a respiratory therapist, may assist in promoting clearance of pulmonary secretions. In addition, humidification of inspired air may promote the hydration (liquefaction) of tenacious secretions, allowing for removal that is more productive. Use of aerosolized mucolytic aerosols, such as *N*-acetylcysteine (NAC) and DNAse, is of questionable therapeutic value, particularly considering their propensity to induce bronchospasm (NAC) and their excessive cost. NAC cleaves the disulfide bonds of Mucus, decreasing its elastic property that is important for upward mobility and then expectoration. A Cochrane meta-analysis in subjects with chronic bronchitis or COPD found that aerosol mucolytic therapy was associated with a small reduction in acute exacerbations and did not cause any harm, improve quality of life, or slow the decline of lung function.[27] The clinical benefit may be greater for chronic bronchitis/COPD patients who have frequent or prolonged exacerbations and are unable to utilize inhaled corticosteroids or long-acting β_2-agonists.[27] Although limited data are available, chronic use of oral or aerosolized bronchodilators may be of benefit by increasing mucociliary and cough clearance. For patients with moderate to severe COPD, combination therapy with a long-acting β_2-agonist and inhaled corticosteroid led to decreased exacerbations and rescue medication use, while it also improved quality of life, lung function, and symptom scores compared with long-acting β_2-agonist monotherapy.

Pharmacologic Therapy

Patients should be up to date with vaccinations, particularly pneumococcal and an annual influenza vaccine; however, the clinical utility of vaccination against haemophilus disease is questionable. For patients who consistently demonstrate clinical limitation in airflow, a therapeutic challenge of a short-acting β_2-agonist bronchodilator (eg, as albuterol aerosol) should be considered. Pulmonary function tests should be performed before and after β_2-agonist aerosol administration for more objective determination of a patient's propensity to benefit from supplemental aerosol therapy. Sufficient published experience supports the use of inhalation therapy with a β_2-agonist for patients with chronic bronchitis (COPD) to improve pulmonary function and exercise tolerance and to reduce the sense of breathlessness.[18] Regular use of a long-acting β-receptor agonist aerosol (eg, salmeterol and formoterol) in responsive patients are more effective and probably more convenient than short-acting β_2-receptor agonists.[28] The aerosol route for β_2-receptor agonist and/or corticosteroid administration is favored over systemic formulations for improved patient acceptance and compliance and to minimize the number and magnitude of associated adverse effects. Chronic inhalation of a combination long-acting β-receptor agonist (LABA) and a corticosteroid (eg, salmeterol-fluticasone and formoterol-mometasone) improved pulmonary function and quality of life.[29] Long-term use of aerosolized corticosteroid is associated with increased side effects including hoarseness, sore throat, thrush, pneumonia, and osteoporosis; however, caution should be exercised in withdrawing inhaled glucocorticoid administration in patients with severe COPD receiving triple inhalation therapy. A stepwise approach to withdrawing inhaled corticosteroids may minimize the risk for acute exacerbations but a decrease in lung function can still occur after discontinuation.[30]

Inhaled anticholinergic drugs, including ipratropium and tiotropium, have an important role in the chronic management of patients with chronic bronchitis and COPD.[31] Numerous studies are now available demonstrating the clinical effectiveness of inhaled long-acting muscarinic antagonists (LAMAs) alone or more frequently, when administered in combination with a LABA, in improving lung function and benefits in symptom control and reductions in the number of acute exacerbations. Triple combination inhalation therapy (eg, LABA + LAMA + an inhaled corticosteroid) is being evaluated in patients with more severe COPD with promising findings and its role remains to be defined.[32] Although

once prescribed extensively for patients with chronic bronchitis, chronic theophylline therapy is used with decreasing frequency in favor of aerosolized β_2-receptor agonists, LABA, LAMA, etc. Nevertheless, long-acting theophylline remains an effective “add on” therapy for many patients, particularly those with more severe chronic bronchitis/COPD due to the drug’s beneficial effects of bronchodilation, improved ciliary function and increased beat frequency, possibly increased mucus hydration, and low cost.[18]

Phosphodiesterase 4 inhibitors (PDE-4), compared with the nonselective phosphodiesterase inhibitor theophylline, only affect phosphodiesterase in the airway smooth muscle, immune cells (eosinophils, monocytes, and neutrophils), and proinflammatory cells. Roflumilast is a highly specific (second generation) PDE-4 inhibitor that is most often reserved for use in patients with moderate to severe COPD. Considering that many of the published studies assessing the viability of second-generation PDE-4 inhibitors in patients with COPD involved patients with chronic cough and increased sputum production, it is inferred that these drugs would be of value in patients with chronic bronchitis as well. The GOLD guidelines suggest roflumilast reduces exacerbations in COPD patients with chronic bronchitis treated with oral glucocorticosteroids. Roflumilast only provides a net benefit to patients at high risk of severe exacerbations.[33] A lower 30-day readmission rate in patients hospitalized for COPD with roflumilast therapy was reported.[34] PDE-4 inhibitors improved lung function over placebo and reduced the likelihood of exacerbations; they had little impact on a patient’s symptoms or quality of life. Nevertheless, the major limitation to the use of PDE-4 inhibitors is their side effect profiles. Patients receiving roflumilast often experience nausea, vomiting, headache, decreased appetite, sleep disturbances, and an increased risk of psychiatric events.[35] The exact role of roflumilast in chronic lung disease is evolving but many guidelines suggest its greatest use is in the more severely affected patients.

Use of antimicrobials for treatment of chronic bronchitis has been controversial, but is becoming more accepted in specific circumstances. Numerous comparative evaluations, including placebo-controlled studies of antibiotic administration for acute and chronic treatment of chronic bronchitis, have suggested clinical benefit. The antibiotics selected most frequently possess variable in vitro activity against the common sputum isolates *H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, and *M. pneumoniae*. Conflicting published results appear independent of the antibiotic used or the regimen compared. A wide disparity that existed in the published results from older studies served as the basis for the enormous controversy about the use of antibiotics for the treatment

of acute exacerbations of chronic bronchitis. Overall, good clinical results have been observed with the use of standard antibiotic regimens (eg, macrolides, azalides, oral cephalosporins, and the combination drug amoxicillin-clavulanate, trimethoprim-sulfamethoxazole, and tetracyclines) as well as with the use of fluoroquinolones.[36–39] The goal is to select the most effective antibiotic drug for the patient based on their history of previous exacerbations and response to drug therapy. The introduction of genome expression profiling of sputum and other biologic fluids can facilitate specific pathogen diagnosis and focused therapy.[40]

A useful paradigm for the assessment and treatment of acute exacerbations of chronic bronchitis and antibiotic decision making is shown in **Fig. 125-1**.[41] Many clinicians use the so-called Anthonisen criteria to determine if antibiotic therapy is indicated.[24] With the Anthonisen criteria, if a patient exhibits two of the following three criteria during an acute exacerbation of chronic bronchitis (AECB), the patient will most likely benefit from antibiotic therapy and, thus, should receive a treatment course: (a) increase in shortness of breath; (b) increase in sputum volume; and (c) production of purulent sputum. There are greater healthcare costs for patients who are noncompliant with their antibiotic regimen for their AECB.

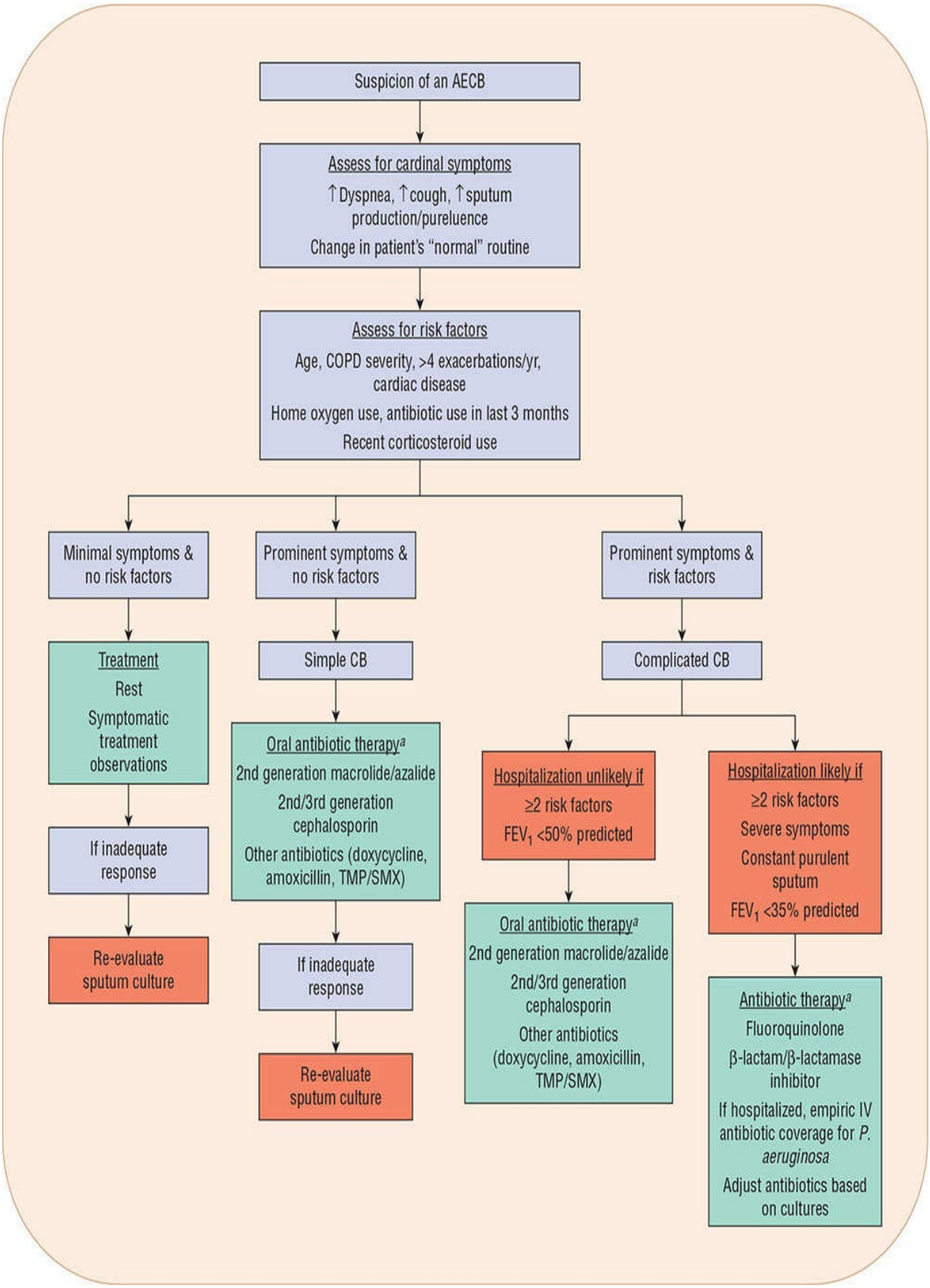

Suspicion of an AECB
Assess for cardinal symptoms
↑Dyspnea, ↑cough, ↑sputum production/pureluence
Change in patient's "normal" routine
Assess for risk factors
Age, COPD severity, >4 exacerbations/yr, cardiac disease
Home oxygen use, antibiotic use in last 3 months
Recent corticosteroid use
Minimal symptoms & no risk factors
Prominent symptoms & no risk factors
Prominent symptoms & risk factors
Treatment
Rest
Symptomatic treatment observations
If inadequate response
Re-evaluate sputum culture
Simple CB
Oral antibiotic therapy[a]
2nd generation macrolide/azalide
2nd/3rd generation cephalosporin
Other antibiotics (doxycycline, amoxicillin, TMP/SMX)
If inadequate response
Re-evaluate sputum culture
Complicated CB
Hospitalization unlikely if
≥2 risk factors
FEV1 <50% predicted
Oral antibiotic therapy[a]
2nd generation macrolide/azalide
2nd/3rd generation cephalosporin
Other antibiotics (doxycycline, amoxicillin, TMP/SMX)
Hospitalization likely if
≥2 risk factors
Severe symptoms
Constant purulent sputum
FEV1 <35% predicted
Antibiotic therapy[a]
Fluoroquinolone
β-lactam/β-lactamase inhibitor
If hospitalized, empiric IV antibiotic coverage for P. aeruginosa
Adjust antibiotics based on cultures

FIGURE 125-1 Clinical algorithm for the diagnosis and treatment of chronic bronchitis patients with an acute exacerbation incorporating the principles of the clinical classification system. (AECB, acute exacerbation of chronic bronchitis; CB, chronic bronchitis; COPD, chronic obstructive pulmonary disease; TMP/SMX, trimethoprim/sulfamethoxazole.)*a* See Table 125-3 for commonly used antibiotics and doses. (*Adapted, with permission, from Hayes DJ, Meyer K. Acute exacerbations of chronic bronchitis in elderly patients: Pathogenesis, diagnosis, and management. Drugs Aging 2007;24:555–572.*)

The increasing resistance of the common bacterial pathogens to first-line agents further complicates antibiotic selection. As many as 30% to 40% of *H. influenzae* isolates and 95% to 100% of *M. catarrhalis* isolates produce β-lactamases. Moreover, up to 40% of *S. pneumoniae* isolates demonstrate intermediate susceptibility (minimum inhibitory concentration [MIC] 0.125–1 mg/L) or resistance (MIC ≥ 2 mg/L) to oral penicillin, with approximately 20% of isolates being highly resistant (MIC > 2 mg/L). Concern regarding *S. pneumoniae* resistance is increasing, and resistance is now greater than or equal to 30% for macrolides. Despite these changes in bacterial susceptibility, the current recommendation is to initiate therapy with first-line antimicrobial agents in less severely affected patients (see Fig. 125-1). For patients with more moderate to severe disease, many clinicians will begin antibiotic therapy with the second-line agents, such as amoxicillin-clavulanate, a macrolide (such as azithromycin or clarithromycin, although they are being used less frequently), and more frequently with a fluoroquinolone, such as levofloxacin and moxifloxacin (see Fig. 125-1).

Regardless of the antibiotic selected, predetermined outcome measures should be monitored closely for each patient to determine the success or failure of the therapeutic intervention. Oral antibiotics with broader antibacterial spectra (eg, amoxicillin-clavulanate and fluoroquinolones) that possess potent in vitro activity against sputum isolates are increasingly becoming first-line antibiotics as initial therapy for treatment of acute exacerbations of chronic bronchitis.

An important clinical outcome variable directing drug selection and criteria for beginning antibiotics in individual patients is the infection-free period when chronic bronchitis are off antibiotics. The length of the infection-free time period and the change in the number of physician office visits and hospital admissions with a particular antibiotic regimen are extremely important to identify, whenever possible, for each patient. The antibiotic regimen that results in the longest infection-free period defines the “regimen of choice” for specific patients for future acute exacerbations of their disease. Long-term prophylactic antibiotic

use may provide a slight benefit in decreasing exacerbation rates, but do not appear to decrease mortality, and markedly increase the emergence and colonization of antibiotic-resistant pathogens. For this reason, most guidelines do not support this indication. However, chronic macrolide/azalide use reduces the incidence of acute exacerbations in COPD patients in a clinically significant manner (macrolide and anti-inflammatory activity addressed later).[41,42]

Antibiotics that are effective against responsible pathogens, demonstrate the least risk of drug interactions, and can be administered in a manner that promotes compliance should be selected. Antibiotics, commonly used for treatment of these patients with chronic bronchitis, and their respective adult starting doses are listed in **Table 125-3**. Doses of antibiotics should be adjusted as needed to the desired clinical effect and the lowest incidence of acceptable side effects. A frequently used clinical strategy to enhance the duration of symptom-free periods incorporates higher-dose antibiotic regimens using the upper limit of the recommended daily antibiotic dose for a period of 5 to 7 days. More clinicians are electing to limit their antibiotic treatment regimen to 5 days as compelling data continue to support equal efficacy, less exposure potentially reducing bacterial resistance development, and possibly less side effects with short-duration antibiotic therapy versus longer treatment regimens (greater than 7 days).

TABLE 125-3 Oral Antibiotics Commonly Used for the Treatment of Acute Respiratory Exacerbations in Chronic Bronchitis

Antibiotic	Brand Name	Usual Adult Oral Dose (mg)	Dose Schedule (Doses/Day)
Preferred Drugs			
Ampicillin	–	250–500	3–4
Amoxicillin	–	500–875	2–3
Amoxicillin-clavulanate	Augmentin®	500–875	2–3
Ciprofloxacin	Cipro®	500–750	2
Levofloxacin	Levaquin®	500–750	1
Moxifloxacin	Avelox®	400	1
Doxycycline	Monodox®	100	2
Minocycline	Minocin®	100	2
Tetracycline HCl	–	500	4
Trimethoprim-sulfamethoxazole	Bactrim DS®/Septra DS®	1 DS	2
Supplemental Drugs			
Azithromycin	Zithromax®	250–500	1
Erythromycin	Ery-Tab®/Erythrocin®	500	4
Clarithromycin	Biaxin®	250–500	2
Cephalexin	Keflex®	500	4

DS, double-strength tablet (160-mg trimethoprim/800-mg sulfamethoxazole).

With the exception of long-term macrolide/azalide administration, chronic antibiotic therapy is rarely indicated in the management of patients with chronic bronchitis. Such approaches lead to marked increase in cost and occurrence of multidrug resistant (MDR) pathogens. Conversely, long-term macrolide (erythromycin, clarithromycin, and roxithromycin) or azalide (azithromycin) administration has been associated with a clinically significant reduction in the incidence of acute exacerbations in patients with chronic bronchitis and COPD.[41–43] The benefit of these drugs is attributed to their antibacterial, anti-inflammatory, and immunomodulatory activity. These drugs reduce bacterial adherence and toxin production, inhibit biofilm function, and reduce the generation of oxygen free radicals, modulate mucin gene protein production controlling mucus hypersecretion, and improve mucociliary clearance. These drugs also decrease neutrophil chemotaxis, promote downregulation of adhesion molecule expression, and inhibit transcription factors leading to decreased production of pro-inflammatory cytokines.[43]

The importance of multifactorial cellular oxidative stress in the pathogenesis of chronic bronchitis and COPD has prompted the study of the efficacy of

antioxidants and particulary the oral administration of NAC, other mucolytic agents, and antioxidants.[27,44,45] Some guidelines suggest their use for more severely affected patients. Studies with oral NAC have suggested a dose-dependent response with 600 mg once to twice daily and it may slightly decrease the exacerbation rate in COPD patients not using inhaled steroids; however, there does not appear any effect on lung function. The exact role of antioxidant in the care of these patients remains to be defined—no specific recommendations can be provided until more data are available regarding which specific compound (as well as dose and duration of therapy) is optimal.

BRONCHIOLITIS

EPIDEMIOLOGY AND ETIOLOGY

Bronchiolitis is an acute viral infection of the lower respiratory tract that affects approximately 50% of children during the first year of life and 100% by age 2 years. The occurrence of bronchiolitis peaks during the winter months and persists through early spring. Bronchiolitis remains the major reason for hospital admission during the first year of life.[46]

Respiratory syncytial virus is the most common cause of bronchiolitis, accounting for up to 75% of all cases. During epidemic periods, the incidence of RSV-induced bronchiolitis may approach 90% of cases. Other detectable viruses include parainfluenza, adenovirus, and influenza. Bacteria serve as secondary pathogens in a minority of cases.[46,47]

CLINICAL PRESENTATION

The clinical presentation of bronchiolitis (Table 125-4) is often preceded by 1 to 4 days of symptoms (eg, nasal congestion, rhinorrhea, cough, and low-grade fever) indicative of an upper respiratory tract infection. Due to limited oral intake because of coughing combined with fever, vomiting, and diarrhea, infants frequently are dehydrated. The increased work of breathing and tachypnea most likely contribute to increased fluid loss. In most cases, bronchiolitis is self-limiting and typically symptoms improve within 7 to 10 days with resolution within 28 days without the need for hospitalization. In patients who require hospitalization, the average length of stay is approximately 3 days.[47]

TABLE 125-4 Clinical Presentation of Bronchiolitis

Signs and symptoms

- Prodrome with irritability, restlessness, and mild fever
- Cough and coryza
- Vomiting, diarrhea, noisy breathing, and increased respiratory rate as symptoms progress
- Labored breathing with retractions of the chest wall, nasal flaring, and grunting

Physical examination

- Tachycardia and respiratory rate of 40–80 per minute in hospitalized infants
- Wheezing and inspiratory rales
- Mild conjunctivitis in one-third of patients
- Otitis media in 5%–10% of patients

Laboratory tests

- Peripheral white blood cell count normal or slightly elevated
- Abnormal arterial blood gases (hypoxemia and, rarely, hypercarbia)

The diagnosis of bronchiolitis is based primarily on history and clinical findings. It is important for the clinician to attempt to differentiate between bronchiolitis and a host of other clinical entities affecting infants, which may produce a similar picture of dyspnea and wheezing. Asthma, congestive heart failure, anatomic airway abnormalities, cystic fibrosis, foreign bodies, and gastroesophageal reflux are the primary disease entities that may present with wheezing in children. Isolation of a viral pathogen in the respiratory secretions of a wheezing child establishes a presumptive diagnosis of infectious bronchiolitis. However, the ability to identify specific viral pathogens often is hindered by the limited availability of special virology laboratories. In addition, in the elderly and in immunocompromised patients, antigen detection lacks adequate sensitivity, and patients frequently seek medical care after the acute stage of the infection, thus compromising the ability of the available tests to diagnose RSV. However, the proliferation of commercial enzyme-linked immunosorbent assays and fluorescent antibody staining techniques of nasopharyngeal secretions has increased the ability to identify viral antigens within several hours. Identification of RSV by PCR should be available from most clinical laboratories, but its relevance to the clinical management of bronchiolitis remains obscure and therefore routine testing is not recommended.[47,48]

Multiple clinical laboratory determinations have been used to assist in the management of cases of bronchiolitis. Radiographic evaluation of the chest in children with bronchiolitis yields variable findings and rarely alters therapeutic decisions. Thus, the routine use of chest radiography is not recommended; however, in hospitalized patients who fail to demonstrate expected improvement,

they may help to distinguish bronchiolitis from other entities characterized by wheezing so that appropriate treatment may be initiated. In children requiring hospitalization, abnormalities in blood gas tensions are frequent and appear to relate to disease severity. Hypoxemia is common and increases the respiratory drive, whereas hypercarbia is seen in only the most severe cases. Despite the presence of moderate degrees of hypoxemia, clinical cyanosis is unusual.[46,47]

TREATMENT

Desired Outcome

7 In the well infant, bronchiolitis usually is a self-limiting illness, and reassurance, antipyretics, and adequate fluid intake usually are all that are necessary while waiting for resolution of the underlying viral infection. In-hospital support is necessary for the child suffering from respiratory failure or marked dehydration; underlying cardiac and pulmonary diseases potentiate these conditions.[47]

General Approach to Treatment

7 Almost all otherwise healthy babies with bronchiolitis can be followed as outpatients. Such infants are treated for fever, provided generous amounts of oral fluids, and observed closely for evidence of respiratory deterioration.[46] In severely affected children, the mainstays of therapy for bronchiolitis are oxygen therapy and IV fluids. In a subset of patients, aerosolized bronchodilators may have a role. For selected infants, particularly those with underlying pulmonary disease, cardiac disease, or both, therapy with the antiviral agent ribavirin can be considered.[47]

Pharmacologic Therapy

7 Aerosolized β_2-adrenergic therapy appears to offer little benefit for the majority of patients and may even be detrimental.[48–50] However, this therapy may offer some benefit to the child with a predisposition toward bronchospasm. In addition, although clinical trials have demonstrated varied results, nebulized epinephrine seems to be more efficacious than albuterol in hospitalized patients with bronchiolitis.[51] For such patients, bronchodilator therapy may be offered initially, but should not be pursued in the absence of a clear-cut clinical benefit.

Furthermore, given their overall ineffectiveness, neither aerosolized β_2-adrenergic nor nebulized epinephrine therapies are recommended by the American Academy of Pediatrics for the treatment of bronchiolitis.[50]

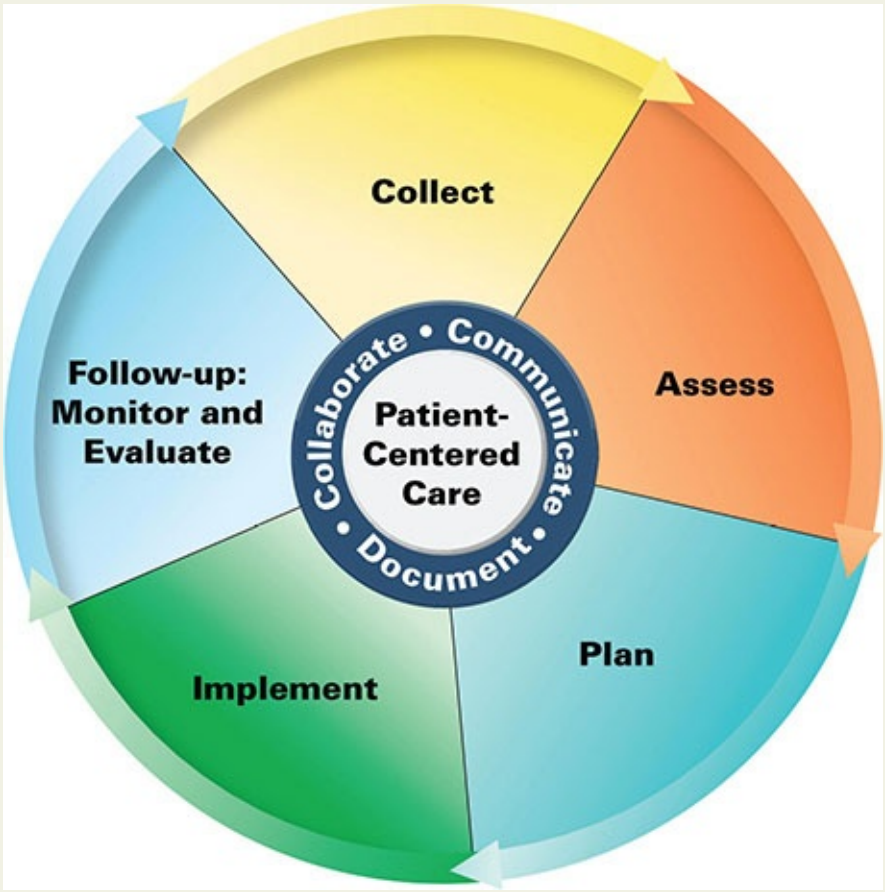
Similarly, controlled trials of corticosteroids in bronchiolitic infants have not shown therapeutic effects or significant harmful effects, though viral shedding may be prolonged.[47,50] As a result, the routine use of systemically administered corticosteroids is not recommended by the American Academy of Pediatrics and is therefore discouraged.[48,50] Combination therapy with oral dexamethasone and nebulized epinephrine may act synergistically to reduce hospital admissions and shorten the time to discharge and the duration of symptoms, but the overall clinical benefits is questionable based on study results.[51] Although placing children with bronchiolitis in mist tents has been common practice, no data have documented the effectiveness of this practice.

The American Academy of Pediatrics guidelines support the use of nebulized hypertonic saline (eg, 3% saline) for the treatment of bronchiolitis in hospitalized infants and children while other international guidelines do not recommend its use.[48,50] As such, although nebulized hypertonic saline has proven to be safe and effective for the symptomatic improvement in patients with bronchiolitis after 1 day of use, there continues to be debate on if it reduces the length of hospital stay.[52]

Ribavirin may offer benefit to a subset of infants with bronchiolitis. Ribavirin, a synthetic nucleoside, possesses in vitro antiviral properties against a variety of RNA and DNA viruses, including influenza A, influenza B, parainfluenza, and adenovirus; it is approved only in aerosolized form against RSV. Use of the aerosol drug formulation requires special equipment (small-particle aerosol generator) and specially trained personnel for administration via oxygen hood or mist tent. Special care must be taken to avoid drug particle deposition and the resulting clogging of respiratory tubing and valves in mechanical ventilators. Among hospital admissions for RSV infection, ribavirin therapy failed to decrease length of hospital stay, number of days in the intensive care unit, or number of days receiving mechanical ventilation. Consequently, the American Academy of Pediatrics does not recommend the routine use of ribavirin in children with bronchiolitis and most experts recommend reserving use of ribavirin for severely ill patients.[50]

For infants with underlying pulmonary or cardiovascular disease, prophylaxis against RSV may be warranted. When administered monthly during the RSV season, both RSV immune globulin and palivizumab (a monoclonal antibody for RSV) may decrease the number of RSV episodes and the need for

hospitalization. Between the two, palivizumab is preferred, given its ease of administration, lack of administration-related adverse effects, and noninterference with select immunizations.[53] Despite continuing research, there is no vaccine marketed for RSV.



Patient Care Process for Pneumonia

Collect

- Patient characteristics (eg, age, sex, pregnancy, drug allergies)
- Patient medical history including comorbid conditions, previous infections, previous hospitalization, and current or recent residence in a nursing facility
- Social history (including tobacco/ethanol/drug use)
- Current and past medications, particularly antimicrobials, immune suppressants, and chemotherapy
- Subjective data

    - Patient-reported risk factors for pneumonia (Table 125-5)
    - Patient-reported pneumonia signs/symptoms (Table 125-7)
    - Timing/location of symptom onset (ie, community vs hospital; time since onset)
- Objective data
    - Temperature, blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2-saturation, ventilator settings if applicable
    - Pertinent respiratory physical exam findings (Table 125-7)
    - Diagnostic procedures (such as chest imaging)
    - Labs including CBC and differential, basic metabolic panel, blood gasses and lactate (if sepsis suspected)
    - Current and previous microbiology results including antimicrobial susceptibility when available

Assess

- Likelihood of pneumonia based on history of present illness, physical exam, imaging, and laboratory and microbiologic data
- Severity of illness and mortality risk based on hemodynamics, respiratory status, presence of organ failure, severity score(s) if CAP
- Most likely pathogens and potential for antimicrobial resistance based on age, comorbidities, clinical presentation and diagnostics, pneumonia type (ie, CAP vs HAP vs VAP vs aspiration—Table 125-5), local epidemiology and antimicrobial resistance patterns, previous infections and antibiotic exposure

Plan

- Empiric antimicrobial regimen based on likely pathogen(s) and mortality risk
    - Include drug(s), route of administration, dose, frequency, and duration (Tables 125-8; 125-9; 125-10)
- Appropriate monitoring parameters for efficacy, toxicity, and potential modification of therapy (ie cultures or other tests for etiology when indicated)
    - Include timing (cultures preferably obtained before antimicrobials

administered) and frequency

- Provider education including rationale and evidence for recommendation
- Patient education including counseling points/monitoring for efficacy and safety

Implement*

- Clearly and professionally communicate recommendations to prescribers, healthcare team, and/or patient
- Determine consensus treatment plan as an interdisciplinary team
- Follow up to ensure accurate/appropriate implementation of consensus treatment plan (antimicrobial therapy, diagnostics, and monitoring)

Follow-up: Monitor and Evaluate

- Efficacy monitoring including improvement/resolution of signs/symptoms, physiologic and laboratory data with focus on indicators of infection (temperature, WBC, etc.), respiratory status (RR, oxygenation, ventilator settings), and organ failure/sepsis
- Safety monitoring (including SCr and urine output for nephroxiticy, etc.)
- Microbiologic cultures and diagnostic tests for etiology
- Assess whether therapy can be narrowed, should be broadened, or requires change based on above monitoring considerations
- When possible, change empiric therapy to pathogen-directed therapy (Table 125-11)
- Design and implement new plan and continual monitoring as needed/appropriate

*Collaborate with patient, caregivers, and other healthcare professionals.

PNEUMONIA

EPIDEMIOLOGY

Pneumonia remains one of the most common causes of severe sepsis and the leading infectious cause of death in children and adults in the United States, with a mortality rate as high as 50% depending on the severity of illness.[5,54] Pneumonia occurs throughout the year, with the relative incidence of disease

resulting from different etiologic entities varying with the seasons. It occurs in persons of all ages, although the clinical manifestations are most severe in the very young, the elderly, and the chronically ill.

PATHOGENESIS AND ETIOLOGY

Inspiration of ambient air constantly exposes the lungs to environmental and infectious particulate matter. Respiratory pathogens enter the lower respiratory tract by one of three routes: (1) direct inhalation of infectious droplets; (2) aspiration of oropharyngeal contents; or (3) hematogenous spread from another infection site. Respiratory host defenses comprise innate and adaptive immunity pathways. These defense mechanisms are preserved in healthy individuals and respiratory pathogens are effectively removed before infection occurs. Conversely, immunocompromised individuals (such as those with cystic fibrosis or prolonged neutropenia) lack robust defense mechanisms and are at higher risk of severe respiratory infections. Lung infections can also suppress the antibacterial activity of the lung by impairing alveolar macrophage function and mucociliary clearance, thus setting the stage for secondary bacterial pneumonia. Mucociliary transport is also depressed by ethanol and narcotics and by obstruction of bronchi by mucus, tumor, or extrinsic compression. All these factors can severely impair pulmonary clearance of aspirated bacteria. Any alteration of the normal lung microbiome by infection and/or disease can evolve to pneumonia requiring antimicrobial treatment.[55]

Pneumonia is caused by a variety of viral and bacterial pathogens. The causative organism(s) is highly dependent on how and/or where the pneumonia was contacted.[4–6,56] For epidemiologic and treatment purposes, pneumonia is often categorized as either community-acquired or hospital-acquired (**Table 125-5**).[6] Patients with pneumonia onset outside of the hospital or within 48 hours of hospital admission are considered to have community-acquired pneumonia (CAP). Those with pneumonia onset in the hospital after at least 48 hours of hospitalization are considered to have hospital-acquired pneumonia (HAP). Patients with pneumonia onset following 48 hours of endotracheal intubation are considerd to have ventilator-associated pneumonia (VAP).

TABLE 125-5 Pneumonia Classifications and Risk Factors

Type of Pneumonia	Definition	Risk Factors
Community-acquired pneumonia (CAP)	Pneumonia developing outside the hospital or<48 hours after hospital admission	• Age >65 years • Diabetes mellitus • Asplenia • Chronic cardiovascular, pulmonary, renal, and/or liver disease • Smoking and/or alcohol abuse
Hospital-acquired pneumonia (HAP)	Pneumonia developing >48 hours after hospital admission	• Witnessed aspiration • COPD, ARDS, or coma • Administration of antacids, H_2-antagonists, or proton pump inhibitor • Supine position • Enteral nutrition, nasogastric tube • Reintubation, tracheostomy, or patient transport • Head trauma, ICP monitoring • Age >60 years • MDR risk (eg, MRSA, MDR *Pseudomonas*) if IV antibiotic use within 90 days
Ventilator-associated pneumonia (VAP)	Pneumonia developing >48 hours after endotracheal intubation	• Same as hospital acquired • MDR risk with IV antibiotics in past 90 days, septic shock, ARDS preceding VAP, acute renal replacement therapy preceding VAP, or 5 + days of hospitalization preceding VAP

ARDS, acute respiratory distress syndrome; CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; HAP, hospital-acquired pneumonia; ICP, intracranial pressure; MDR, multidrug-resistant; MRSA, methicillin-resistant *S. aureus*; VAP, ventilator-associated pneumonia.

Community-Acquired Pneumonia

8 The causative pathogen in CAP in adult patients is most commonly viral, with human rhinovirus and influenza most common.[57] The most prominent bacterial pathogen causing CAP in otherwise healthy adults is *S. pneumoniae* accounting for up to 35% of all acute cases. It is particularly prevalent and severe for patients with splenic dysfunction, diabetes mellitus, chronic cardiopulmonary or renal disease, or HIV infection. Other common pathogens include *H. influenzae* (2.5%–45%) and the atypical pathogens *M. pneumoniae*, *Legionella* species, and *C. pneumoniae* (about 20%).[57–59] Although generally less common, *Staphylococcus aureus* is also an important CAP pathogen in children and adults and is often seen in patients with cystic fibrosis and those recovering from an antecedent viral respiratory infection such as influenza. Community-acquired pneumonia caused by enteric gram-negative bacteria, including *E. coli* and *K. pneumoniae*, is also uncommon but these pathogens are sometimes identified; most frequently among patients with chronic illness, especially alcoholism and diabetes mellitus.[4] Healthcare-associated pneumonia was a classification that had been previously used to distinguish nonhospitalized patients at risk for MDR pathogens from those likely infected with traditional

CAP pathogens; however, this has fallen out of use.[4,6]

Even more so than in adult patients, viral pathogens predominate in CAP among pediatric patients with a prevalence of up to 80% in those less than 2 years of age. Respiratory syncytial virus and human rhinovirus comprise the majority of these infections.[60] Other common viruses in children include parainfluenza, adenovirus, human metapneumovirus, and bocavirus.[5,60] Group B *Streptococcus*, although rare in adults, is the most common cause of bacterial pneumonia among neonates and typically causes a clinical and radiographic picture nearly indistinguishable from hyaline membrane disease.[61] The bacterial causes of CAP outside the neonatal period are generally similar to adults, with *S. pneumoniae* being the major bacterial pathogen in childhood pneumonia.[60] *M. pneumoniae* is also common, particularly among older children. *H. influenzae* type b, once a major childhood pathogen, has become an infrequent cause of pneumonia since the introduction of active vaccination against this organism in the late 1980s.

Hospital-Acquired Pneumonia

8 Hospital-acquired pneumonia (HAP) occurs most commonly in critically ill patients and is usually caused by bacteria.[6] Factors predisposing patients to the development of HAP include high severity of illness, longer duration of hospitalization, supine positioning, witnessed aspiration, coma, acute respiratory distress syndrome, patient transport, and prior antibiotic exposure (Table 125-5). The strongest predisposing factor, however, is mechanical ventilation (intubation). The length of stay for hospital admissions is increased by a mean of 7 to 9 days for patients who develop HAP.[6]

Hospital-acquired pneumonia is predominantly caused by gram-negative aerobic bacilli or *S. aureus* and is much more likely to be caused by a MDR isolate.[6] Collectively, the non-lactose fermenting gram-negative bacilli *P. aeruginosa* and *Acinetobacter* spp. are the most common cause of HAP (about 25%– 45%).[6] Enteric gram-negative bacilli such as *K. pneumoniae* and *E. coli* are also common (13%–20%).[6] *S. aureus* is also common (12%–21%) with approximately half of these isolates methicillin-resistant.[6] Patients with longer lengths of hospital admission or IV antibiotic use within the previous 90 days preceding HAP development are more likely to have MDR organisms.[6]

Hospital-acquired pneumonia can be subclassified as ventilator- associated pneumonia (VAP), which is pneumonia occurring after 48 or more hours of

endotracheal intubation.[6] The risk for developing pneumonia in the hospital increases by 6 to 21 times after a patient is intubated because the natural airway defenses against the migration of upper respiratory tract organisms into the lower tract are bypassed.[6] This situation is exacerbated by the wide use of acid-suppressing drugs (eg, H_2-receptor blocking agents and proton pump inhibitors) in the intensive care unit, which increases the pH of gastric secretions and may promote the proliferation of microorganisms in the upper GI tract. Subclinical microaspirations are events that occur routinely in intubated patients and result in the inoculation of bacteria-contaminated gastric contents into the lung and a higher incidence of nosocomial pneumonia.[62] Although generally similar in etiology to HAP, VAP is more likely to be caused by *S. aureus* (20%–30%) and multidrug resistance is more common.[6,63,64]

Aspiration pneumonia is classically treated as a separate entity from CAP or HAP. Early evidence suggested it was predominantly caused by anaerobic bacteria that commonly colonize the oropharynx. Recent epidemiologic evidence suggests a decreasing importance of anaerobic bacteria in aspiration pneumonia. Aspiration pneumonia has a bacteriology similar to CAP or HAP and anaerobic pathogens are less common and typically seen in patients with specific risk factors such as severe periodontal disease or those with specific clinical findings such as necrotizing pneumonia or lung abscess.[56]

Tuberculosis

The acid-fast bacillus *Mycobacterium tuberculosis* causes tuberculosis and is spread person to person by inhalation of droplets. After years of steady decline, the number of cases of pneumonia caused by *M. tuberculosis* in the United States began to increase in the mid to late 1980s. The new epidemic was a consequence of an increased incidence among prison inmates, IV drug abusers, immigrants, and, most prominently, HIV-infected patients. It is most prominent in urban neighborhoods afflicted with crowded living conditions and poor access to healthcare; thus, groups prone to tuberculosis include the homeless and patients in chronic care facilities and homes for the elderly. Unlike previous eras in which tuberculosis was seen most frequently in elderly men, infection currently is identified in increasing numbers of young adults. Multidrug-resistant strains of *M. tuberculosis* have become more common and treatment regimens for these patients should involve consultation with a specialist. (See Chapter 130 for a detailed discussion of tuberculosis pathophysiology, diagnosis, and treatment.)

Special Populations

Pneumonia in the HIV-Infected Patient

A broad range of pathogens can cause pneumonia in HIV infection (**Table 125-6**) including opportunistic infections such as *Pneumocystis jiroveci* and *Mycobacterium* species.[77] Patients may be afflicted with pneumonia multiple times, particularly in the advanced stages of the HIV and AIDS, and a given episode may be caused by more than one species. The clinical presentation of pneumonia in HIV-infected persons frequently is not helpful in distinguishing one pathogen from another. The pneumonia usually is subacute in onset and consists of fever, nonproductive cough, and dyspnea. Most pathogens produce a multilobular or diffuse radiographic pattern. Some practitioners initially treat the HIV-infected patient with pneumonia empirically; however, given the wide array of possible pathogens, more frequently a specific microbiologic diagnosis is aggressively pursued early in the patient's course through sputum induction or bronchoalveolar lavage to allow a rational choice of an antimicrobial regimen. The diagnosis and treatment of HIV-infected patients with pulmonary disease are discussed in detail in Chapter 143.

TABLE 125-6 Pulmonary Complications of Human Immunodeficiency Virus Infection

- Infections
  - Viruses
    - Cytomegalovirus
    - Herpes simplex virus
    - Varicella-zoster virus
    - Respiratory syncytial virus and other common respiratory pathogens (parainfluenza virus, adenovirus)
    - Measles virus
  - Bacteria
    - Pyogenic organisms (especially *S. pneumoniae, H. influenzae*; in late disease, *S. aureus* and gram-negative organisms)
    - *M. tuberculosis*
    - *M. avium* complex and other nontuberculous mycobacteria
  - Fungi
    - *Histoplasma capsulatum*
    - *Coccidioides immitis*
    - *Cryptococcus neoformans*
    - *Candida* species
    - *Aspergillus* species
  - Parasites
    - *Pneumocystis carinii*
    - *Toxoplasma gondii*
    - Cryptosporidia
    - *Strongyloides stercoralis*
  - Malignancies
    - Kaposi's sarcoma
    - Non-Hodgkin's lymphoma
    - Smooth muscle tumors
  - Lymphocytic interstitial pneumonitis
  - Nonspecific interstitial pneumonitis
  - Drug-induced pneumonitis

Pneumonia in the Neutropenic Host

Neutropenia in the cancer patient is a common complication of aggressive chemotherapy, but occasionally results from the cancer itself. The risk of infection for the cytopenic patient is increased significantly when the absolute neutrophil count falls to less than 500 cells/mm^3 (0.500×10^9/L) and the neutropenia persists for more than 7 days. For many patients, the duration of chemotherapy-induced cytopenia can be reduced by judicious application of colony-stimulating factors.[65]

The organisms that cause pneumonia in the cytopenic cancer patient include a broad range of bacteria and fungi. The most prominent among these are gram-positive bacteria (staphylococci and streptococci); others include enteric and nonenteric (particularly *P. aeruginosa*) gram-negative rods as well as the fungi

(*Candida*, *Aspergillus*). The chest radiograph may reveal the lobar pattern typical of bacterial infection in the normal host, or it may exhibit a diffuse pattern. The pneumonia may remain invisible by chest radiograph until the neutropenia resolves. Noninfectious entities that may cause pulmonary symptoms include toxicity from radiation or chemotherapy or infiltration of the lung parenchyma by the tumor itself.

CLINICAL PRESENTATION AND DIAGNOSIS

The common signs, symptoms, physical exam findings, and diagnostic features of patients with pneumonia are listed in **Table 125-7**. They are both constitutional (fever, chills, malaise) and respiratory (cough, increased sputum production, dyspnea). These signs and symptoms coupled with physical exam findings suggestive of a pulmonary infiltrate, with or without abnormal white blood cell (WBC) count or oxygen saturation, can form the basis of a presumed clinical diagnosis of pneumonia. The diagnosis of pneumonia is preferably further strengthened by radiographic evidence such as pulmonary infiltrate(s) on chest x-ray or other chest imaging. Clinical practice guidelines recommend a chest radiograph for all adult patients with suspected pneumonia but only in select pediatric patients with severe CAP (eg inpatient, signs of hypoxia/respiratory distress).[4–6]

TABLE 125-7 Clinical Presentation of Pneumonia

Signs and symptoms
Abrupt onset of fever, chills, dyspnea, and productive cough
Rust-colored sputum or hemoptysis
Pleuritic chest pain
Dyspnea
Physical examination
Tachypnea and tachycardia
Dullness to percussion
Increased tactile fremitus, whisper pectoriloquy, and egophony
Chest wall retractions and grunting respirations
Diminished breath sounds over affected area
Inspiratory crackles during lung expansion
Chest radiograph
Dense lobar or segmental infiltrate
Laboratory tests
Leukocytosis with predominance of polymorphonuclear cells
Low oxygen saturation on arterial blood gas or pulse oximetry

Clinical and radiographic data can begin to shape the differential diagnosis of suspected pneumonia pathogens. Pneumonia caused by the atypical pathogens, such as *M. pneumoniae* and *C. pneumoniae,* often has a more gradual onset and overall lower severity compared with other bacterial causes.[66,67] The exception to this is *Legionella pneumophila*, which is an atypical pathogen that often causes severe illness making it a common pathogen in patients with CAP who require ICU admission.[4,66,68] Patients with atypical pneumonia also commonly have extrapulmonary, constitutional symptoms.[66,67] Atypical pneumonias often demonstrate patchy infiltrates on chest x-ray that are more extensive that clinical symptoms suggest, hence the term "walking pneumonia."[69] Chest radiographs in patients with viral etiology are often diffuse, interstitial compared with the classic lobar or lobular consolidated infiltrates of bacterial pneumonia. Staphylococcal pneumonias often demonstrate cavitary or necrotizing lesions on imaging. Although these general clinical and diagnostic characteristics can be useful, there is considerable overlap in clinical presentation between pneumonia etiologies. These data alone are not sufficiently reliable to differentiate between bacterial, atypical bacterial, and viral etiology.[70]

10 Following a pneumonia diagnosis based on clinical and radiographic evidence, further diagnostic testing to confirm the diagnosis and determine the etiology may be warranted. Blood cultures and non-invasive sputum cultures (ie expectorated sputum, sputum induction, or nasotracheal suctioning) are recommended for all adult patients with suspected HAP or VAP.[6] Blood cultures often provide value in determining the causative pathogen, particularly in VAP where approximately 15% of patients have concomitant bacteremia.[71,72] Emphasis is placed on determining an etiology in HAP and VAP due to the high prevalence of MDR organisms and associated risk of ineffective empiric therapy. This allows adjustment of initial empiric therapy into optimal, pathogen-specific therapy.

Confirmation of etiology is less common in CAP, where a microbiologically confirmed etiology is identified in only 7% of cases in clinical practice.[73] As such, empiric treatment of CAP is often continued for the entire duration of therapy without ever determining the causative pathogen. Cultures are only routinely recommended in patients with more severe CAP where knowledge of the causative pathogen and whether the empiric antibiotic regimen is active are most important. In patients treated in the outpatient setting, sputum cultures are not routinely recommended. The exception to this is pediatric patients who have experienced failure of initial antibiotics.[4,5] Blood and/or sputum cultures are recommended in hospitalized adult patients with severe CAP. This includes, but

is not limited to, patients admitted to the ICU, those with failure of outpatient antibiotic therapy, and those with cavitary infiltrates on chest radiograph.[4] Sputum Gram stain and culture are recommended for hospitalized children who can produce a sputum sample along with blood cultures in those with moderate/severe CAP.[5] Urinary antigen tests are also available for *S. pneumoniae* and *L. pneumophila*, and are recommended in adults with severe CAP.[4] These tests are more rapid than traditional microbiologic methods and can detect pathogen antigen days (*S. pneumoniae*) to weeks (*L. pneumophila*) after initiation of antibiotic therapy.[74] These tests have a high specificity (90%–99%) but lower sensitivity (50%–80%). This translates to few false-positives and more false-negatives, making it a useful test to "rule in" these pathogens in adult patients.[75–77] Rapid diagnostic tests for viruses, including influenza, are also recommended in children with suspected CAP. A positive result in combination with an absence of clinical factors strongly suggestive of bacterial infection can be used to reduce unnecessary antibiotic use.[5]

TREATMENT

Treatment Goals

Eradication of the offending organism through selection of the appropriate antibiotic(s) and subsequent complete clinical cure is the primary goal of therapy of pneumonia. Secondary goals include minimization of the unintended consequences of therapy, including toxicities and selection for secondary infections such a *Clostridioides difficile* or antibiotic-resistant pathogens, and minimizing costs through outpatient and oral therapy when the patient's severity of illness and clinical considerations permit.

General Approach to Treatment

9 Achievement of the goals of therapy for pneumonia treatment requires the provider to follow the principles of good antimicrobial stewardship while ensuring adequate treatment of the potential infection. Comprehensive principles of optimal antimicrobial therapy and infectious diseases stewardship are discussed in detail in Chapter 123. In general, antimicrobial stewardship involves provision of the right antimicrobial(s) (or lack thereof when infection is not present); at the right time, at the right dose, for the right duration. This is often a balance between providing therapy broad enough to cover likely pathogens but not overly broad resulting in potentially unnecessary drug toxicity,

secondary infection, or antibiotic resistance. This also involves continual monitoring of patient clinical status and diagnostic data to support the decision to either continue empiric therapy, narrow or alter therapy, or discontinue therapy if infection is ruled out. This section discusses the selection of antimicrobial regimens in patients with a suspected or confirmed diagnosis of pneumonia.

Following diagnosis of the pneumonia, one of the first treatment decisions is what level of medical care is necessary (ie outpatient vs inpatient vs inpatient ICU). This decision is ultimately made by a physician and should be based on the patient's severity of illness and subsequent risk of mortality. However, it is important for pharmacists to be able to perform and understand this severity assessment because it should be used to recommend the appropriate diagnostic monitoring and empiric antimicrobial therapy. Multiple severity scores designed to estimate mortality risk in CAP are available for severity assessment. The most commonly used are the CURB-65 and CRB-65.[78,79] These short, simple point systems can easily be applied at the point of care using readily available clinical data. For CURB-65, patients receive 1 point for each criterion present: **C**onfusion, **U**remia (BUN > 20 mg/dL [7.1 mmol/L]), **R**espiratory rate ≥30 breaths/min, **B**lood pressure (systolic <90 mm Hg, diastolic ≤60 mm Hg), age ≥**65** years. CRB-65 is a simplified version of CURB-65 that does not require knowledge of serum BUN concentration. Patients with CURB-65 or CRB-65 scores <2 are generally candidates for outpatient treatment.[4] Patients with a score of 2 are typically admitted to the general ward of the hospital with ICU admission considered for patients with scores ≥3.[4] The Pneumonia Severity Index, also known as Pneumonia Outcomes Research Team (PORT) score, is more comprehensive but requires extensive laboratory and physiologic data not readily available upon patient presentation.[80] This coupled with a point system that varies widely across criteria makes it impractical to calculate without an electronic clinical decision support tool. It is commonly used for CAP severity assessment in clinical trials.

Empiric Antimicrobial Treatment

Treatment of bacterial pneumonia, like the treatment of most infectious diseases, initially involves the empirical use of a relatively broad-spectrum antibiotic therapy that is effective against probable pathogens after appropriate cultures and specimens for laboratory evaluation have been obtained as indicated.[58,81] Therapy should be narrowed to cover specific pathogens after the results of cultures are known in cases where cultures are obtained. Multiple factors can aid

in identifying the potential pathogens involved, including when and where the pneumonia was contracted, local pathogen epidemiology and susceptibility patterns, and individual patient factors. These individual patient factors include patient age, previous and current medication history, underlying disease(s), major organ function, and present clinical status. These factors must be evaluated to select an appropriate and effective empirical antibiotic regimen as well as the most appropriate route for drug administration (oral vs parenteral). (For a more detailed discussion on the principles of antibiotic selection, see Chapter 123.)

Because many antibiotics are effective in the treatment of bacterial pneumonia, and superiority of one antibiotic over another is often unclear or difficult to define, there are a variety of recommended empiric antimicrobial regimens for suspected bacterial pneumonia. For a list of potential empiric antimicrobial regimens, based on available clinical practice guidelines, primary literature, and antimicrobial susceptibility and PK/PD, refer to **Table 125-8** for adults and **Table 125-9** for children. A complete list of antimicrobial agents for specific pathogens is beyond the scope of this chapter and is presented in Chapter 123. **Table 125-10** lists dosages for selected antibiotics used for the treatment of bacterial pneumonia.

TABLE 125-8 Evidence-Based Empirical Antimicrobial Therapy for Pneumonia in Adults[a]

Clinical Setting and/or Patient Characteristics	Usual Pathogens	Empirical Therapy
Outpatient/Community-Acquired		
No at-risk comorbidity (diabetes, heart/lung/liver/ renal disease, alcoholism, malignancy, asplenia) AND no antimicrobial use in past 3 months	*S. pneumoniae, M. pneumoniae, H. influenzae, C. pneumoniae, M. catarrhalis*	Macrolide[b] OR doxycycline
At-risk comorbidity (diabetes, heart/lung/liver/ renal disease, alcoholism, malignancy, aspelnia) OR immunosuppressive condition/drugs OR antimicrobial use in past 3 months	*S. pneumoniae* (including drug-resistant), *M. pneumoniae, H. influenzae, C. pneumoniae, M. catarrhalis*	Antipneumococcal fluoroquinolone[c] OR β-lactam[d] + EITHER macrolide[b] OR doxycycline
Regions with more than 25% rate of macrolide-resistant *S. pneumoniae*	*S. pneumoniae* (including drug-resistant), *M. pneumoniae, H. influenzae, C. pneumoniae, M. catarrhalis*	Antipneumococcal fluoroquinolone[c] OR β-lactam[d] + EITHER macrolide[b] OR doxycyline
Inpatient/Community-Acquired		
Non-ICU	*S. pneumoniae* (including drug-resistant), *H. influenzae, M. pneumoniae, C. pneumoniae, Legionella* spp.	Antipneumococcal fluoroquinolone[c] OR β-lactam[e] + EITHER macrolide[b] OR doxycyline
ICU	*S. pneumoniae* (including drug-resistant), *S. aureus, Legionella* spp., gram-negative bacilli, *H. influenzae*	β-lactam[e] + EITHER azithromycin OR Antipneumococcal fluoroquinolone[c]
	If MRSA suspected	Add vancomycin or linezolid to above regimen
	If *P. aeruginosa* suspected	Antipseudomonal, antipneumococcal β-lactam[f] + EITHER (1) ciprofloxacin OR (2) levofloxacin OR (3) aminoglycoside + azithromycin OR (4) aminoglycoside + moxifloxacin
	If influenza suspected	Add oral oseltamivir or intravenous peramivir (when oral medications not possible)
Hospital-Acquired Pneumonia		
Low mortality risk[g] AND No MDR HAP[h] risk factors AND Local MRSA prevalence <20%	Non-fermenting gram-negative bacilli, enteric gram-negative bacilli, MSSA	Piperacillin-tazobactam, cefepime, levofloxacin, imipenem OR meropenem
Low mortality[g] risk AND No MDR HAP[h] risk factors AND Local MRSA ≥20% OR unknown	Non-fermenting gram-negative bacilli, enteric gram-negative bacilli, MRSA	Piperacillin-tazobactam, cefepime, levofloxacin, ciprofloxacin, imipenem, meropenem, OR aztreonam + vancomycin OR linezolid
High mortality risk[g] OR MDR risk factor(s)[h]	Non-fermenting gram-negative bacilli, enteric gram-negative bacilli, MRSA	Double cover *P. aeruginosa* with two of the following, avoiding two from the same class: piperacillin-tazobactam, cefepime, levofloxacin, ciprofloxacin, imipenem, meropenem, aztreonam, gentamicin, tobramycin, amikacin + vancomycin OR linezolid
Ventilator-Associated Pneumonia		
No MDR VAP risk factors[i] AND Local MRSA and gram-negative bacilli-resistance both <10%[j]	Non-fermenting gram-negative bacilli, enteric gram-negative bacilli, MSSA	Piperacillin-tazobactam, cefepime, levofloxacin, imipenem OR meropenem
No MDR VAP risk factors[i] AND Local MRSA ≥10% or unknown AND gram-negative bacilli-resistance <10%[j]	Non-fermenting gram-negative bacilli, enteric gram-negative bacilli, MRSA	Piperacillin-tazobactam, cefepime, levofloxacin, ciprofloxacin, imipenem, meropenem, OR aztreonam + vancomycin OR linezolid
MDR VAP risk factor(s)[i] OR local MRSA and gram-negative bacilli-resistance >10%[j] or unknown	MDR non-fermenting gram-negative bacilli, MDR enteric gram-negative bacilli, MRSA	Double cover *P. aeruginosa* with two of the following, avoiding two from the same class : piperacillin-tazobactam, cefepime, levofloxacin, ciprofloxacin, imipenem, meropenem, aztreonam, gentamicin, tobramycin, amikacin, colistin, polymyxin B + vancomycin OR linezolid
Aspiration Pneumonia		
Community-acquired	*S. pneumoniae, M. pneumoniae, H. influenzae, C. pneumoniae*	Treat as above for CAP
Hospital-acquired	*S. aureus, P. aeruginosa* enteric gram-negative bacilli	Treat as above for HAP
	If anaerobes suspected	Treat as above for CAP/HAP using antibiotic with anaerobic coverage OR add clindamycin OR metronidazole

[a]See the section Selection of Antimicrobial Agents.
[b]Macrolide: erythromycin, clarithromycin, and azithromycin.
[c]Antipneumococcal fluoroquinolone: levofloxacin and moxifloxacin.
[d]Infectious Diseases Society of America recommended outpatient β-lactams: high-dose amoxicillin or amoxicillin/clavulanate preferred, cefpodoxime, cefuroxime, ceftriaxone (intramuscular) alternatives.
[e]Infectious Diseases Society of America recommended inpatient β-lactams: ceftriaxone (intravenous), cefotaxime, ampicillin.
[f]Infectious Diseases Society of America recommended antipneumococcal, antipseudomonal β-lactams: piperacillin/tazobactam, cefepime, meropenem, imipenem.
[g]Indicators of high HAP mortality risk: need for ventilator support due to pneumonia; septic shock.
[h]MDR HAP risk factors: receipt of IV antibiotics in previous 90 days; structural lung disease (bronchiectasis or cystic fibrosis).
[i]MDR VAP risk factors: receipt of IV antibiotics in previous 90 days; septic shock; acute respiratory distress syndrome preceding VAP; ≥5 days hospitalization preceding VAP; acute renal replacement therapy preceding VAP.
[j]Resistance to antibiotic being considered for empiric gram-negative monotherapy.
MDR, multidrug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

TABLE 125-9 Empirical Antimicrobial Therapy for Pneumonia in Pediatric Patients[a]

Clinical Setting and/or Patient Characteristics	Usual Pathogen(s)	Empirical Therapy
Outpatient/Community-Acquired		
<1 month	Group B *Streptococcus*, *H. influenzae* (nontypable), *E. coli*, *S. aureus*, *Listeria* CMV, RSV, adenovirus	Ampicillin-sulbactam, cephalosporin,[b] carbapenem[c] Ribavirin for RSV[d]
1–3 months	*C. pneumoniae*, possibly *Ureaplasma*, CMV, *Pneumocystis carinii* (afebrile pneumonia syndrome) *S. pneumoniae*, *S. aureus*	Macrolide/azalide,[e] trimethoprim–sulfamethoxazole Semisynthetic penicillin[f] OR cephalosporin[g]
Preschool-aged children	Viral (rhinovirus, RSV, influenza A and B, parainfluenzae, adenovirus, human metapneumovirus, coronavirus)	Antimicrobial therapy not routinely required
Previously healthy, fully immunized infants and preschool children with suspected mild–moderate bacterial CAP	*S. pneumonia* *M. pneumoniae*, other atypical	Amoxicillin, cephalosporin[b,g] Macrolide/azalide or fluoroquinolone
Previously healthy, fully immunized school-aged children and adolescents with mild–moderate CAP	*S. pneumonia* *M. pneumoniae*, other atypical	Amoxicillin, cephalosporin,[b,g] or fluoroquinolone Macrolide/azalide, fluoroquinolone, or tetracycline
Moderate–severe CAP during influenza virus outbreak	Influenza A and B, other viruses	Oseltamivir or zanamivir
Inpatient/Community-Acquired		
Fully immunized infants and school-aged children	*S. pneumonia* CA-MRSA *M. pneumoniae*, *C. pneumoniae*	Ampicillin, penicillin G, cephalosporin[b] β-Lactam + vancomycin/clindamycin β-Lactam + macrolide/fluoroquinolone/ doxycycline
Not fully immunized infants and children; regions with invasive penicillin-resistant pneumococcal strains; patients with life-threatening infections	*S. pneumoniae*, PCN-resistant MRSA *M. pneumoniae*, other atypical pathogens	Cephalosporin[b] Add vancomycin/clindamycin Macrolide/azalide[e] + β-lactam/doxycycline/ fluoroquinolone

[a]See the section Selection of Antimicrobial Agents.

[b]Third-generation cephalosporin: ceftriaxone and cefotaxime. Note that cephalosporins are not active against *Listeria*.

[c]Carbapenem: imipenem–cilastatin and meropenem.

[d]See text for details regarding possible ribavirin treatment for RSV infection.

[e]Macrolide/azalide: erythromycin and clarithromycin/azithromycin.

[f]Semisynthetic penicillin: nafcillin and oxacillin.

[g]Second-generation cephalosporin: cefuroxime and cefprozil.

CAP, community-acquired pneumonia; CMV, cytomegalovirus; MRSA, methicillin resistant *Staphylococcus aureus*; RSV, respiratory syncytial virus.

Data from Reference 5.

TABLE 125-10 Antibiotic Doses for Treatment of Bacterial Pneumonia

Antibiotic Class	Antibiotic	Antibiotic Dose[a]	
		Pediatric	Usual Adult Dose
Penicillin	Ampicillin ± sulbactam	150–200 mg/kg/day IV	2 g IV every 4–6 h (6 h if ampicillin/sulbactam)
	Amoxicillin ± clavulanate[b]	45–100 mg/kg/day orally	875–2,000 mg orally twice daily
	Piperacillin-tazobactam	200–300 mg/kg/day IV	3.375–4.5 g IV every 6–8 h
	Penicillin	100,000–250,000 units/kg/day IV	12–24 million units/day in divided doses IV every 4–6 h
Extended-spectrum cephalosporins	Ceftriaxone	50–75 mg/kg/day IV	1–2 g IV daily
	Cefotaxime	150 mg/kg/day IV	1–2 g IV every 8 h
	Ceftazidime	90–150 mg/kg/day IV	1–2 g IV every 8 h
	Cefepime	100–150 mg/kg/day IV	1–2 g IV every 6–8 h
	Ceftolozane-tazobactam	–	3 g IV every 8 h
	Ceftazidime-avibactam	–	2.5 g IV every 8 h
Monobactam	Aztreonam	90–120 mg/kg/day IV	1–2 g IV every 8 h
Macrolide/azalide	Clarithromycin	15 orally mg/kg/day	0.5–1 g orally once or twice daily
	Erythromycin	30–50 IV or orally mg/kg/day	500 mg IV or orally every 6 to 8 h
	Azithromycin	10 mg/kg × 1 day (× 2 days if parenteral), and then 5 mg/kg days 2–5 IV or orally	500 mg × 1 day (× 2 days if parenteral), and then 250 mg days 2–5 IV or orally
Fluoroquinolones[c]	Moxifloxacin	–	400 mg IV or orally daily
	Levofloxacin	8–20 mg/kg/day IV or orally	750 mg IV or orally daily
	Ciprofloxacin	30 mg/kg/day IV or orally	400 mg IV every 8 h / 750 mg orally twice daily
Tetracycline[d]	Doxycycline	2–5 mg/kg/day IV or orally	100 mg IV or orally twice daily
	Tetracycline HCl	25–50 mg/kg/day orally	–
Aminoglycosides	Gentamicin	7.5–10 mg/kg/day IV	7.5 mg/kg IV daily
	Tobramycin	7.5–10 mg/kg/day IV	7.5 mg/kg IV daily
	Amikacin	15–20 mg/kg/day IV	15–20 mg/kg IV daily
Carbapenems	Imipenem	60–100 mg/kg/day IV	500–1000 mg IV every 6 to 8 h
	Meropenem	30–60 mg/kg/day IV	500–2000 mg IV every 6 to 8 h
	Meropenem-vaborbactam		2 g/2 g IV every 8 h
Polymyxins	Colistin	2.5–5 mg/kg/day IV	IV: 300 mg × 1, then 150 mg daily/ Neb: 150 mg every 8 h
	Polymyxin B	15,000–30,000 units/kg/day IV	IV: 2–2.5 mg/kg × 1, then 1.25–1.5 mg/kg every 12 h
Other	Vancomycin	45–60 mg/kg/day IV	15–20 mg/kg IV every 8–12 h
	Linezolid	20–30 mg/kg/day IV or orally	600 mg IV or orally every 12 h
	Clindamycin	30–40 mg/kg/day IV or orally	600 mg IV or orally every 8 h or 450 mg orally every 6 h

[a]Doses can be increased for more severe disease and may require modification for patients with organ dysfunction.

[b]Higher-dose amoxicillin and amoxicillin/clavulanate (eg, 90 mg/kg/day) are used for penicillin-resistant *S. pneumoniae*.

[c]Fluoroquinolones have been avoided for pediatric patients because of the potential for cartilage damage; however, they have been used for MDR bacterial infection safely and effectively in infants and children (see text).

[d]Tetracyclines are rarely used in pediatric patients, particularly in those younger than 8 years because of tetracycline-induced permanent tooth discoloration.

Community-Acquired Pneumonia

Tables 125-8 and 125-9 provide evidence-based guidelines for the treatment of CAP in adults[4] and children,[5] respectively. The bacterial causes are relatively constant, even across geographic areas and patient populations. Unfortunately, pathogen resistance to standard antimicrobials is increasing (penicillin-resistant *S. pneumoniae*, macrolide-resistant *S. pneumoniae*, etc.) and can vary geographically, necessitating careful attention by the clinician to local and regional bacterial susceptibility patterns.[82] Indiscriminate use of antimicrobials for treatment of pneumonia has contributed to the problem of antimicrobial resistance, underscoring the need for defining the optimal antibiotic regimen for each patient. Thus, initial therapy should be based on presumed antibacterial susceptibility.

Evidence-based empiric therapy for CAP in adults differs between outpatients, hospitalized patients, and hospitalized patients admitted to an intensive care unit (see Tables 125-8 and 125-9).[4,5] In adult outpatients, choice of therapy depends on the individual patient's risk for drug-resistant *S. pneumoniae*. Those at low risk (ie no at-risk comorbidities, no previous antibiotic use, infrequent local *S. pneumoniae* resistance) may be treated with a macrolide (such as azithromycin) or doxycycline monotherapy.[4] In patients at risk for drug-resistant *S. pneumoniae*, either anti-pneumococcal fluoroquinolone monotherapy (such as levofloxacin or moxifloxacin) or combination therapy consisting of a β-lactam (Table 125-8) plus either a macrolide or doxycycline is indicated to ensure coverage of resistant strains.[4] Empiric therapy of CAP for inpatients differs from that of outpatients in two ways: first, it is usually IV rather than oral route of administration; and second, coverage against drug-resistant *S. pneumoniae* is given to all patients. This reflects the desire to rapidly achieve adequate systemic antimicrobial exposures and increase the likelihood of providing *in vitro* active therapy in patients with a higher severity of illness where the importance of early appropriate therapy is increased. In patients with severe CAP admitted to the ICU, therapy should always consist of a combination regimen with a β-lactam backbone (Table 125-8), as these regimens are associated with reduced mortality in patients with bacteremic pneumococcal pneumonia.[83–85] In addition, coverage of less frequent CAP pathogens, such as MRSA and *P. aeruginosa*, may be considered in patients with risk factors for these pathogens.[4] Some risk factors for MRSA pneumonia include patients with preceding influenza infection, necrotizing/cavitary radiographic findings, and

structural lung disease. Risk factors for *P. aeruginosa* include severe COPD leading to repeated antibiotic exposures and structural lung disease.[4]

Similar to adult patients, empiric antibiotic regimens for CAP in pediatric patients differ between the outpatient and inpatient setting. However, in pediatric patients, choice of empiric therapy is more dependent on patient age group and immunization status rather than comorbidity. For outpatients, choice of therapy is predominantly based on age group and suspected etiology (ie, typical vs. atypical bacteria; viral). Among inpatients, those fully immunized against *S. pneumoniae* and *H. influenzae* type B may be treated with a penicillin antibiotic with or without macrolide for typical coverage as indicated based on clinical suspicion for atypical pneumonia.[5] Empiric regimens in unimmunized patients or in areas with a high prevalence of penicillin-resistant *S. pneumoniae* should consist of third-generation cephalosporin (such as ceftriaxone).[5] Similar to CAP in adults, MRSA is sometimes the causative pathogen. Addition of MRSA coverage (with vancomycin or linezolid) should be considered when clinical suspicion is high (post-viral pneumonia, necrotizing/cavitary radiographic findings).[5]

Hospital-Acquired and Ventilator-Associated Pneumonia

9 Because HAP and VAP have a distinctive epidemiology compared with CAP, empiric antimicrobial regimens for HAP and VAP differ greatly from those for CAP (Table 125-8). Despite this, selection of therapy is based on many of the same principles. As with CAP, knowledge of the local pathogen and antibiotic resistance distribution is important. Antibiotic resistance patterns can vary greatly between institutions in the same city and even within the same institution between hospital units. Because of this, use of institution-specific antibiograms is highly recommended. These antibiograms should ideally also contain separate susceptibility data specific to the ICU population.[6] Along with local susceptibility, patient-specific factors should weigh heavily in the choice of empiric therapy. Individual risk factors for infection with MRSA and MDR gram-negative bacilli are particularly important in HAP and VAP, as is severity of illness and mortality risk.

The vast majority of HAP cases are caused by gram-negative bacilli, predominantly *P. aeruginosa* and the Enterobacteriaceae, or *S. aureus*.[6] As such, all empiric HAP regimens should consist of at least one antibiotic with coverage against these pathogens, usually an antipseudomonal, antistaphylococcal β-

lactam (such as piperacillin/tazobactam or cefepime) or an antipseudomonal, antistaphylococcal fluoroquinolone (such as levofloxacin).[6] While aminoglycosides are useful in treating gram-negative pneumonia in combination with another gram-negative-active antibiotic, they should not be used as monotherapy in pneumonia given the lack of data supporting their use in this manner. Patients contracting the pneumonia in a hospital or hospital unit with an MRSA prevalence of 20% or greater should also receive MRSA coverage with either vancomycin or linezolid.[6] Patients with MDR HAP risk factors, such as receipt of IV antibiotics in the past 90 days or structural lung disease, should also receive MRSA coverage in addition to a second antipseudomonal agent to cover for MDR gram-negative bacilli. An empiric antibiotic regimen containing dual pseudomonal and MRSA coverage is also indicated in patients at high risk of mortality, such as those requiring mechanical ventilation as a result of their pneumonia and those in septic shock.[6] This approach is taken to maximize the likelihood of early effective therapy in those patients where the consequences of delayed appropriate therapy in the event the pathogen is resistant to the empiric regimen are greatest.

Empiric antibiotic regimens for patients with VAP are similar to patients with HAP. In patients with no MDR VAP risk factors, who contracted VAP in a unit with a low prevalence of both MRSA (less than 10%–20%) and of gram-negative bacilli resistance (<10% to an antibiotic being considered for use), monotherapy with an antipseudomonal antibiotic with staphylococcal coverage may be used.[6] Higher MRSA prevalence would indicate the addition of vancomycin or linezolid. Likewise, more than 10% resistance to all antibiotics being considered for gram-negative monotherapy would indicate the need for double antipseudomonal coverage (Table 125-8).[6] Patients at risk for MDR VAP, including those receiving IV antibiotics in previous 90 days, those in septic shock, those with VAP onset after 5 or more days of hospitalization, and those with acute respiratory distress syndrome or receiving renal replacement therapy preceding VAP onset should also receive double pseudomonal and MRSA coverage.[6]

Pathogen-Directed Antimicrobial Therapy

10 Tailoring antimicrobial therapy based on diagnostic test results and patient clinical status is an important aspect of the pharmacotherapy of pneumonia. Utilizing a pathogen-directed antimicrobial regimen can optimize patient outcome through the use of evidence-based antimicrobials for a particular

pathogen. It can also mitigate potential negative impacts of ongoing broad-spectrum antimicrobial use, including adverse drug reactions, *C. difficile* infection, and development of further MDR infection.[86–88] When tailoring antimicrobial therapy, it is important to take into account both diagnostic test results (chest imaging, Gram stain, respiratory cultures), and patient clinical factors (hemodynamics, temperature, respiratory status, white blood cell counts/differential). In patients who are clinically stable with signs of improving infection, narrowing of therapy should be considered, especially if culture results have identified a likely pathogen with associated susceptibility pattern.[6] Recommendations for directed therapy of common pneumonia pathogens can be found in **Table 125-11**.

TABLE 125-11 Directed Antimicrobial Therapy for Common Pneumonia Pathogens in Adult Patients

Pathogen	Preferred Antibiotic Therapy	Alternative Antibiotic Therapy
Penicillin-susceptible *S. pneumoniae* (MIC ≤ 2 mg/L)	Ampicillin, amoxicillin, penicillin G	Ceftriaxone, cefotaxime, macrolide, levofloxacin, moxifloxacin, doxycycline, clindamycin, vancomycin
Penicillin-resistant *S. pneumoniae* (MIC > 2 mg/L)	Ceftriaxone, cefotaxime, levofloxacin, moxifloxacin	High-dose amoxicillin (3 g/day), linezolid, clindamycin, vancomycin
Non-β-lactamase-producing *H. influenzae*	Ampicillin (IV), amoxicillin	Fluoroquinolone, doxycycline, azithromycin, clarithromycin
β-Lactamase-producing *H. influenzae*	Ceftriaxone, cefotaxime, ampicillin-sulbactam, amoxicillin-clavulanate	Fluoroquinolone, doxycycline, azithromycin, clarithromycin
Mycoplasma pneumoniae	Macrolide, doxycycline	Fluoroquinolone
Chlamydophila pneumoniae	Macrolide, doxycycline	Fluoroquinolone
Legionella pneumophila	Fluoroquinolone or azithromycin	Doxycycline
MSSA	Cefazolin, antistaphylococcal penicillin	Clindamycin, vancomycin
MRSA	Vancomycin, linezolid	Telavancin, ceftaroline, quinupristin/dalfopristin, clindamycin, sulfamethoxazole/trimethoprim
P. aeruginosa	Antipseudomonal β-lactam[a] or fluoroquinolone[b] based on antimicrobial susceptibility testing results. Can consider adding aminoglycoside if patient in septic shock or at high mortality risk	IV colistin or polymyxin B + inhaled colistin for isolates resistant to all preferred therapies
Acinetobacter spp.	Carbapenem OR ampicillin-sulbactam based on antimicrobial susceptibility testing results	IV colistin or polymyxin B + inhaled colistin for isolates resistant to all preferred therapies
Extended-spectrum β-lactamase-producing gram-negative bacilli	Carbapenem	Piperacillin-tazobactam or cefepime potential options depending on susceptibility/adequate dosing
Carbapenem-resistant organisms	New β-lactam/β-lactamase inhibitors[c] based on antimicrobial susceptibility testing OR IV colistin or polymyxin B + inhaled colistin	

[a]Antipseudomonal β-lactam: piperacillin/tazobactam, cefepime, ceftazidime, meropenem, imipenem/cilastatin, doripenem, aztreonam.

[b]Antipseudomonal fluoroquinolone: ciprofloxacin and levofloxacin

[c]New β-lactam/ β-lactamase inhibitors: ceftazidime/avibactam, meropenem/vaborbactam, ceftolozane/tazobactam.

MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; *PCN*, penicillin.

Directed Therapy of Important Gram-Positive Pathogens 10 Directed therapy for *S. pneumoniae*, the most common bacterial cause of CAP, primarily depends on penicillin susceptibility. For isolates considered susceptible to intravenous penicillin by the CLSI (MIC ≤ 2 mg/L), a narrow-spectrum penicillin such as penicillin, ampicillin, or amoxicillin is preferred.[4] Alternatively, a cephalosporin antibiotic may be used, or in the case of a severe β-lactam allergy, either a macrolide or antipneumococcal fluoroquinolone (Table

125-11).[4] For penicillin-resistant strains, a third-generation cephalosporin or fluoroquinolone is preferred Table 125-11. High-dose amoxicillin (3 g/day) may be used for penicillin-intermediate strains (MIC = 4 mg/L).[4] High-dose amoxicillin has efficacy in these situations because resistance of *S. pneumoniae* to penicillins is conferred through a change in penicillin-binding protein resulting in decreased affinity of the antibiotic for the binding site. In the case of penicillins and *S. pneumoniae*, this can be overcome by more aggressive dosing that maximizes achievement of adequate time drug concentration is in excess of the MIC (*t*>MIC) despite the elevated MIC.[89]

Treatment of *S. aureus* pneumonia is dependent on whether the strain exhibits methicillin resistance. Treatment with an antistaphylococcal penicillin, such as oxacillin, nafcillin, or dicloxacillin, is preferred by the community-acquired pneumonia guidelines for methicillin-susceptible strains.[4] Cefazolin is an alternative for methicillin-susceptible strains with fewer clinical data in pneumonia. However, it is generally considered an equivalent alternative to an antistaphylococcal penicillin on the basis of data from *S. aureus* bacteremia suggesting equivalence or even superiority.[90] Clindamycin or vancomycin may also be used, although these agents are not preferred for treatment of MSSA infections.[91] The treatment of choice for MRSA pneumonia is either vancomycin or linezolid, which are considered equivalent by infectious Diseases Society of America (IDSA) guidelines.[92–94] Telavancin, while FDA-approved for HAP/VAP caused by *S. aureus*, is often reserved for alternate therapy due to concerns of nephrotoxicity and potentially increased mortality in the subgroup of patients with a creatinine clearance less than 30 mL/min (0.5 mL/s). Additional alternatives for MRSA pneumonia include quinupristin-dalfopristin, ceftaroline, sulfamethoxazole-trimethoprim, and clindamycin. However, clinical evidence for these alternative options remains limited.[95–97]

Directed Therapy of Important Gram-Negative Pathogens 10 For *H. influenzae*, the most common gram-negative cause of CAP, the choice of directed therapy is dependent on whether the strain is β-lactamase producing. Non-β-lactamase-producing strains may be treated with ampicillin (IV) or amoxicillin (oral).[4] A third-generation cephalosporin (such as ceftriaxone) is the treatment of choice for β-lactamase-producing strains. Alternative therapy for *H. influenzae* includes Fluoroquinolone, doxycycline, azithromycin, or clarithromycin.[4] Azithromycin is generally preferred to clarithromycin. A larger proportion of *H. influenzae* strains are susceptible to azithromycin relative to clarithromycin and azithromycin has a more favorable drug interaction

profile.[98,99]

P. aeruginosa is a notoriously antibiotic-resistant pathogen that utilizes a variety of mechanisms of resistance, resulting in variable susceptibility patterns. Because of this, directed therapy against *P. aeruginosa* pneumonia is highly dependent on antimicrobial susceptibility results. When susceptible, all antipseudomonal agents recommended for empiric therapy are considered equivalent with respect to clinical outcomes in pneumonia.[6] The exception to this is the aminoglycosides, which are not recommended as monotherapy against *P. aeruginosa* pneumonia. Despite equivalence of most antibiotics in this setting, piperacillin-tazobactam, cefepime, and ceftazidime are generally preferred when susceptible. This is to preserve susceptibility of carbapenems, newer β-lactam/ β-lactamase inhibitors, and fluoroquinolones for use in more resistant infections. Another consideration in the directed therapy of *P. aeruginosa* is the utility of combination therapy. Patients receiving monotherapy and combination therapy generally have similar outcomes.[6] However, combination therapy may be associated with reduced mortality in patients with septic shock.[100] Directed combination therapy against *P. aeruginosa* only is recommended in patients in septic shock or at high risk of mortality at the time antimicrobial susceptibility testing results become available.[6]

The Enterobacteriaceae, particularly *K. pneumoniae* and *E. coli*, are common causes of both HAP and VAP. Although generally susceptible to the gram-negative active agents recommended for empiric therapy of HAP and VAP, Enterobacteriaceae-producing extended-spectrum β-lactamases (ESBL) capable of hydrolyzing many of the β-lactams commonly used for empiric therapy have become increasingly common.[101–103] Because this diverse family of β-lactamases each have variable affinity for different β-lactams, susceptibility to each β-lactam agent can vary depending on the enzyme (ie, CTX-M, TEM, SHV).[104] Further complicating this is the inoculum effect, whereby β-lactams seemingly susceptible in vitro, are hydrolyzed in vivo in the presence of a high-inoculum of ESBL-producing organism.[105] This variable susceptibility has resulted in debate regarding the treatment of choice for these infections. Although the limited evidence from observational studies did not demonstrate superiority of carbapenems over piperacillin/tazobactam or cefepime when the organism is susceptible to these agents, carbapenems are often considered the treatment of choice for serious ESBL infections such as pneumonia.[6] A randomized clinical trial failed to demonstrate non-inferiority of piperacillin/tazobactam compared to meropenem for ceftriaxone-resistant *E. coli* or *K. pneumoniae* bloodstream infections.[106] Based on this, carbapenems will

likely continue to be considered the treatment of choice for serious ESBL infections. If piperacillin/tazobactam or cefepime are utilized, it is important to ensure that the isolate is considered fully susceptible by the Clinical and Laboratory Standards Institute (CLSI) and that aggressive dosing strategies to ensure optimal $t >$ MIC are employed.

While initially thought of as reliable, last-line antibiotics for resistant gram-negative infections, resistance to carbapenems due to a variety of mechanisms has emerged. Until recently, few antibiotics retained activity against these organisms, resulting in a resurgence in the use of older, more toxic agents such as the polymyxins (colistin, polymyxin B). Availability of three new β-lactam/β-lactamase inhibitor combinations, ceftolozane-tazobactam, ceftazidime-avibactam, and meropenem-vaborbactam has provided hope for these infections. Ceftazidime/avibactam and meropenem/vaborbactam have in vitro activity against most carbapenem-resistant Enterobacteriaceae (CRE) acquiring resistance via carbapenemase enzymes.[107,108] Although ceftolozane-tazobactam does not have activity against carbapenemase-producing strains, it is active against many carbapenem-resistant *P. aeruginosa* strains.[109] Clinical experience with these agents against these highly resistant organisms is limited. Early data suggest they may be superior and less toxic relative to colistin-containing regimens.[110–112] Coupled with favorable in vitro susceptibility data it seems reasonable to prefer these novel agents to more toxic polymyxin-containing regimens when the isolate is susceptible. For infections that remain resistant to all other available antibiotics, treatment with inhaled polymyxins or aminoglycosides are recommended.[6] Inhaled antibiotics should be given with systemic antibiotics to which the pathogen is susceptible (ie if only susceptible to colistin, give both inhaled and IV colistin).

Directed Therapy of Important Atypical Pathogens 10 Treatment of pneumonia caused by atypical bacteria, including *C. pneumoniae, M. pneumoniae,* and *L. pneumophila,* generally consists of either a fluoroquinolone, macrolide, or doxycycline. For *C. pneumoniae* and *M. pneumoniae,* macrolides or doxycycline are preferred agents.[4] Fluoroquinolones or azithromycin are preferred over doxycycline for *Legionella* pneumonia due to the relative paucity of data involving doxycycline for this infection.[4]

Antimicrobial Pharmacokinetic/Pharmacodynamic Considerations

Antimicrobial pharmacokinetics/pharmacodynamics (PK/PD) is an important aspect of optimal antimicrobial therapy for pneumonia. Antibiotic concentrations in respiratory secretions in excess of the pathogen MIC are necessary for successful treatment of pulmonary infections.[113] Thus, ability of an antimicrobial to penetrate into pulmonary secretions is important and must be factored into antimicrobial selection and dosing for pneumonia. The ability of a drug to penetrate respiratory secretions depends on multiple physicochemical factors, including molecular size, lipid solubility, and degree of ionization at serum and biologic fluid pH and the extent of protein binding. Studies evaluating antibiotic concentrations in the pulmonary epithelial lining fluid (ELF) indicate that β-lactams, glycopeptide, and aminoglycosides tend to have ELF to plasma antibiotic concentration ratios less than 1. In contrast, macrolides, fluoroquinolones, and linezolid tend to have ELF to plasma antibiotic concentration ratios much greater than 1. Thus, the latter agents penetrate and concentrate into the ELF to a greater extent.[113]

Although β-lactams, glycopeptides, and aminoglycosides have less extensive ELF penetration, carefully constructed dosing schemes based on PK/PD principles allow these agents to be effective in treating lower respiratory tract infections. Although evidence is conflicting, most evidence suggests dosing guided by PK/PD principles reduces mortality and improves clinical outcome in patients with pneumonia.[6] The use of strategies maximizing antibiotic PK/PD to select antibiotic dosing for HAP and VAP is recommended by the Infectious Diseases Society of America guidelines.[6] This includes weight-based initial dosing of vancomycin and aminoglycosides followed by measurement of serum antibiotic concentrations to adjust doses through antibiotic therapeutic drug monitoring (TDM) and use of extended or continuous infusion of β-lactams. Dosing and TDM of vancomycin for pneumonia should target achievement of a vancomycin area under the concentration-time curve (AUC) > 400 mg*hr/L early in the course of therapy.[114,115] This is optimally achieved via AUC monitoring but may be achieved by targeting vancomycin trough concentrations of 15–20 mg/L [10.4-13.8 μmol/L] as surrogate for AUC > 400 mg*h/L.[114,115] This will maximize achievement of AUC/MIC ratios > 400 for *S. aureus* isolates with an MIC ≤ 1 mg/L. The preferred aminoglycoside dosing strategy for pneumonia, when patient renal function permits, is high-dose once-daily administration. This approach maximizes the AUC:MIC and peak:MIC ratios for efficacy while allowing undetectable serum trough concentrations for a period of time to minimize nephrotoxicity.[116,117] Aminoglycoside peak:MIC ratios ≥ 10 are typically targeted clinically for pneumonia. We refer the reader to Chapter

e122 and Chapter 123 for more in-depth discussion of antibiotic PK/PD concepts.

PATIENT MONITORING, THERAPY MODIFICATION, AND DURATION OF THERAPY

After therapy has been instituted, appropriate clinical parameters should be monitored to ensure the efficacy and safety of the therapeutic regimen. For patients with bacterial infections of the lower respiratory tract, the time to resolution of initial presenting symptoms and the lack of appearance of new associated symptomatology are important to determine.[118] For patients with pneumonia of mild to moderate clinical severity, the time to resolution of cough, decreasing sputum production, and fever, as well as other constitutional symptoms of malaise, nausea, vomiting, and lethargy, should be noted. If the patient requires supplemental oxygen therapy, the amount and need should be assessed regularly. A gradual and persistent improvement in the resolution of these symptoms and therapies should be observed. Initial resolution of infection should be observed within the first 2 days of therapy and progression to complete resolution within 5 to 7 days (usually no more than 10 days). Because cultures for causative organism are rarely obtained except for more severe CAP cases, empiric therapy is typically continued for the duration of therapy provided the patient is responding adequately. When cultures are obtained, tailoring therapy to be pathogen-directed as described above is recommended. The majority of hospitalized patients with CAP should be switched from IV to oral therapy when hemodynamically stable, improving clinically as described above, have normal gastrointestinal tract function, and be able to ingest oral medications.[4] The minimum duration of therapy for CAP is 5 days although CAP is commonly treated for 7 to 10 days.[4] When discontinuing therapy, patients should be afebrile for 48 to 72 hours and have no more than one CAP-related sign of clinical instability (ie, tachycardia, tachypnea, hypotension, hypoxia, altered mental status). Discontinuation of therapy using these criteria starting at day 5 of therapy decreases the duration of antibiotic therapy without reducing cure rates or increasing readmission in non-ICU CAP patients.[119]

For patients with HAP, substantial underlying diseases, or both, additional parameters can be followed, including the magnitude and character of the peripheral blood WBC count, chest radiograph, and blood gas determinations. Similar to patients with less severe disease, some resolution of symptoms should

be observed within 2 days of instituting antibiotic therapy. If no resolution of symptoms is observed within 2 days of starting seemingly appropriate antibiotic therapy or if the patient's clinical status is deteriorating, the appropriateness of initial antibiotic therapy should be critically reassessed. The patient should be evaluated carefully for deterioration of underlying concurrent disease(s). Additionally, the clinician should consider the possibility of changing the initial antibiotic therapy to expand antimicrobial coverage not included in the original regimen if the patient's clinical status is worsening or failing to improve after 48 to 72 hours of therapy. The results of initial and follow-up diagnostic tests, such as respiratory cultures, should also be used alongside clinical response to streamline therapy. De-escalation of antibiotic therapy to be more narrow spectrum in patients with HAP/VAP is strongly recommended. Evidence suggests this approach does not affect clinical outcomes while reducing excess antibiotic use.[6] The recommended duration of therapy for HAP/VAP is 7 days, as the clinical benefit of longer durations of therapy (≥10 days) is not clear based on available clinical evidence.[6] Serum procalcitonin concentrations in combination with clinical response criteria can be used in the decision to discontinue antibiotic therapy.[6]

Prevention of Pneumonia

Prevention of some cases of pneumonia is possible through the use of vaccines and medications against selected infectious agents. Polyvalent polysaccharide vaccines are available for two of the leading causes of bacterial pneumonia, *S. pneumoniae* and *H. influenzae* type b. Children should be vaccinated against *S. pneumoniae*, *H. influenzae* type b, pertussis, and influenza while caregivers for infants less than 6 months should also be vaccinated against influenza and pertussis. Immune prophylaxis for RSV is only recommended for high-risk infants during RSV season. To minimize the risk of developing VAP, healthcare providers should seek to minimize colonization of the aerodigestive tract, prevent aspiration (head raised 45 degrees), and limit the length of mechanical ventilation of patients.[62] (see Chapter 127 for a full discussion of influenza postexposure prophylaxis and Chapter 142 for vaccines.)[120]

Postclass Engaged Learning Activity

Create a study chart of the following antibiotics with potential utility in lower respiratory tract infections: ceftazidime-avibactam; ceftolozane-tazobactam;

meropenem-vaborbactam; plazomicin. On the chart include spectrum of activity, pharmacokinetics (ADME), dosing (including need for adjustment in special populations), adverse effects, FDA approved indication(s), level of evidence supporting use in lower respiratory tract infections (none, *in vitro/in vivo*, case report/series, observational study, randomized controlled trial), and potential place in therapy of lower respiratory tract infections.

ABBREVIATIONS

ADME	absorption, distribution, metabolism, and excretion
AECB	acute exacerbation of chronic bronchitis
AUC	area under the concentration-time curve
BAL	bronchoalveolar lavage
CAP	community-acquired pneumonia
CLSI	Clinical and Laboratory Standards Institute
Cmax	maximum concentration
COPD	chronic obstructive pulmonary disease
CRE	carbapenem-resistant Enterobacteriaceae
ELF	epithelial lining fluid
FEV_1	forced expiratory volume in the first second of expiration
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HAP	hospital-acquired pneumonia
HIV	human immunodeficiency virus
LABA	long-acting β-receptor agonist
LAMA	long-acting muscarinic antagonist
MDR	multidrug-resistant
MIC	minimum inhibitory concentration
MRSA	methicillin-resistant *Staphylococcus aureus*
NAC	*N*-acetyl cysteine
PCR	polymerase chain reaction
PDE4	phosphodiesterase 4
PK-PD	pharmacokinetics/pharmacodynamics
RSV	respiratory syncytial virus

SARS	severe acute respiratory syndrome
SARS-CoV	severe acute respiratory syndrome coronavirus
TDM	therapeutic drug monitoring
VAP	ventilator-associated pneumonia
WBC	white blood cell

REFERENCES

1. Eddens T, Kolls JK. Host defenses against bacterial lower respiratory tract infection. *Curr Opin Immunol*. 2012;24(4):424–430.
2. Jaroszewski DE, Webb BJ, Leslie KO. Diagnosis and management of lung infections. *Thorac Surg Clin*. 2012;22(3):301–324.
3. Yan Y, Zhang S, Tang YW. Molecular assays for the detection and characterization of respiratory viruses. *Semin Respir Crit Care Med*. 2011;32(4):512–526.
4. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(suppl 2):S27–S72.
5. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;53(7):e25–e76.
6. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016;63(5):e61–e111.
7. Lippi G, Meschi T, Cervellin G. Inflammatory biomarkers for the diagnosis, monitoring and follow-up of community-acquired pneumonia: clinical evidence and perspectives. *Eur J Intern Med*. 2011;22(5):460–465.
8. Kinkade S, Long NA. Acute bronchitis. *Am Fam Physician*. 2016;94(7):560–565.
9. Nielsen M, Barnes CB, Ulrik CS. Clinical characteristics of the asthma-COPD overlap syndrome—a systematic review. *Int J Chron Obstruct Pulmon Dis*. 2015;10:1443–1454.

10. Gibson PG, McDonald VM. Asthma-COPD overlap 2015: now we are six. *Thorax*. 2015;70(7):683–691.
11. Blush RR3rd. Acute bronchitis: evaluation and management. *Nurse Pract*. 2013;38(10):14–20.
12. Becker LA, Hom J, Villasis-Keever M, van der Wouden JC. Beta2-agonists for acute cough or a clinical diagnosis of acute bronchitis. *Cochrane Database Syst Rev*. 2015(9):Cd001726.
13. Martin MJ, Harrison TW. Causes of chronic productive cough: An approach to management. *Respir Med*. 2015;109(9):1105–1113.
14. Smith SM, Fahey T, Smucny J, Becker LA. Antibiotics for acute bronchitis. *Cochrane Database Syst Rev*. 2017;6:Cd000245.
15. Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev*. 2014;(4):Cd008965.
16. Spanakis N, Pitiriga V, Gennimata V, Tsakris A. A review of neuraminidase inhibitor susceptibility in influenza strains. *Expert Rev Anti Infect Ther*. 2014;12(11):1325–1336.
17. Dunning J, Baillie JK, Cao B, Hayden FG. Antiviral combinations for severe influenza. *Lancet Infect Dis*. 2014;14(12):1259–1270.
18. Kim V, Criner GJ. Chronic bronchitis and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2013;187(3):228–237.
19. Cai Y, Schikowski T, Adam M, et al. Cross-sectional associations between air pollution and chronic bronchitis: an ESCAPE meta-analysis across five cohorts. *Thorax*. 2014;69(11):1005–1014.
20. Celli BR, Decramer M, Wedzicha JA, et al. An official American Thoracic Society/European Respiratory Society statement: research questions in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2015;191(7):e4–e27.
21. Criner GJ, Bourbeau J, Diekemper RL, et al. Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society guideline. *Chest*. 2015;147(4):894–942.
22. Overington JD, Huang YC, Abramson MJ, et al. Implementing clinical guidelines for chronic obstructive pulmonary disease: barriers and solutions. *J Thorac Dis*. 2014;6(11):1586–1596.
23. Miravitlles M, Kruesmann F, Haverstock D, Perroncel R, Choudhri SH, Arvis P. Sputum colour and bacteria in chronic bronchitis exacerbations: a

pooled analysis. *Eur Respir J*. 2012;39(6):1354–1360.

24. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med*. 1987;106(2):196–204.
25. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2015;(2):Cd003793.
26. McIlwaine MP, Lee Son NM, Richmond ML. Physiotherapy and cystic fibrosis: what is the evidence base? *Curr Opin Pulm Med*. 2014;20(6):613–617.
27. Poole P, Chong J, Cates CJ. Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2015;(7):Cd001287.
28. Santus P, Radovanovic D, Paggiaro P, et al. Why use long acting bronchodilators in chronic obstructive lung diseases? An extensive review on formoterol and salmeterol. *Eur J Intern Med*. 2015;26(6):379–384.
29. Kew KM, Dias S, Cates CJ. Long-acting inhaled therapy (beta-agonists, anticholinergics and steroids) for COPD: a network meta-analysis. *Cochrane Database Syst Rev*. 2014;(3):Cd010844.
30. Magnussen H, Disse B, Rodriguez-Roisin R, et al. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. *N Engl J Med*. 2014;371(14):1285–1294.
31. Singh D. New combination bronchodilators for chronic obstructive pulmonary disease: current evidence and future perspectives. *Br J Clin Pharmacol*. 2015;79(5):695–708.
32. Cazzola M, Matera MG. Triple combinations in chronic obstructive pulmonary disease - is three better than two? *Expert Opin Pharmacother*. 2014;15(17):2475–2478.
33. Yu T, Fain K, Boyd CM, et al. Benefits and harms of roflumilast in moderate to severe COPD. *Thorax*. 2014;69(7):616–622.
34. Fu AZ, Sun SX, Huang X, Amin AN. Lower 30-day readmission rates with roflumilast treatment among patients hospitalized for chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2015;10:909–915.
35. Lipari M, Benipal H, Kale-Pradhan P. Roflumilast in the management of chronic obstructive pulmonary disease. *Am J Health Syst Pharm*. 2013;70(23):2087–2095.

36. Nicolau DP, Sutherland C, Winget D, Baughman RP. Bronchopulmonary pharmacokinetic and pharmacodynamic profiles of levofloxacin 750 mg once daily in adults undergoing treatment for acute exacerbation of chronic bronchitis. *Pulm Pharmacol Ther*. 2012;25(1):94–98.
37. Chuchalin A, Zakharova M, Dokic D, Tokic M, Marschall HP, Petri T. Efficacy and safety of moxifloxacin in acute exacerbations of chronic bronchitis: a prospective, multicenter, observational study (AVANTI). *BMC Pulm Med*. 2013;13:5.
38. Rohde GG, Koch A, Welte T. Randomized double blind placebo-controlled study to demonstrate that antibiotics are not needed in moderate acute exacerbations of COPD–the ABACOPD study. *BMC Pulm Med*. 2015;15:5.
39. Laopaiboon M, Panpanich R, Swa Mya K. Azithromycin for acute lower respiratory tract infections. *Cochrane Database Syst Rev*. 2015; (3):Cd001954.
40. Euba B, Moleres J, Segura V, et al. Genome expression profiling-based identification and administration efficacy of host-directed antimicrobial drugs against respiratory infection by nontypeable *Haemophilus influenzae*. *Antimicrob Agents Chemother*. 2015;59(12):7581–7592.
41. Hayes DJ, Meyer K. Acute exacerbations of chronic bronchitis in elderly patients: Pathogenesis, diagnosis, and management. *Drugs Aging*. 2007; (24):555–572.
42. Herath SC, Poole P. Prophylactic antibiotic therapy in chronic obstructive pulmonary disease. *JAMA*. 2014;311(21):2225–2226.
43. Spagnolo P, Fabbri LM, Bush A. Long-term macrolide treatment for chronic respiratory disease. *Eur Respir J*. 2013;42(1):239–251.
44. Tse HN, Tseng CZ. Update on the pathological processes, molecular biology, and clinical utility of N-acetylcysteine in chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2014;9:825–836.
45. Fischer BM, Voynow JA, Ghio AJ. COPD: balancing oxidants and antioxidants. *Int J Chron Obstruct Pulmon Dis*. 2015;10:261–276.
46. Meissner HC. Viral bronchiolitis in children. *N Engl J Med*. 2016;374(1):62–72.
47. Teshome G, Gattu R, Brown R. Acute bronchiolitis. *Pediatr Clin North Am*. 2013;60(5):1019–1034.
48. Cavaye D, Roberts DP, Saravanos GL, et al. Evaluation of national guidelines for bronchiolitis: AGREEments and controversies. *J Paediatr*

Child Health. 2018.

49. Schroeder AR, Mansbach JM. Recent evidence on the management of bronchiolitis. *Curr Opin Pediatr*. 2014;26(3):328–333.
50. Ralston SL, Lieberthal AS, Meissner HC, et al. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics*. 2014;134(5):e1474–e1502.
51. Kua KP, Lee SWH. Systematic review and meta-analysis of the efficacy and safety of combined epinephrine and corticosteroid therapy for acute bronchiolitis in infants. *Front Pharmacol*. 2017;8:396.
52. Auger KA, Parker MW, Huang B. New method, same answer: we do not know if hypertonic saline helps bronchiolitis. *Pediatrics*. 2018;142(3):e20181868. doi: 10.1542/peds.2018-1868.
53. Perrin KM, Begue RE. Use of palivizumab in primary practice. *Pediatrics*. 2012;129(1):55–61.
54. Nseir S, Mathieu D. Antibiotic treatment for severe community-acquired pneumonia: beyond antimicrobial susceptibility. *Crit Care Med*. 2012;40(8):2500–2502.
55. Segal LN, Rom WN, Weiden MD. Lung microbiome for clinicians. New discoveries about bugs in healthy and diseased lungs. *Ann Am Thorac Soc*. 2014;11(1):108–116.
56. DiBardino DM, Wunderink RG. Aspiration pneumonia: a review of modern trends. *J Crit Care*. 2015;30(1):40–48.
57. Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med*. 2015;373(5):415–427.
58. Musher DM, Thorner AR. Community-acquired pneumonia. *N Engl J Med*. 2014;371(17):1619–1628.
59. Prina E, Ranzani OT, Torres A. Community-acquired pneumonia. *Lancet*. 2015;386(9998):1097.
60. Jain S, Williams DJ, Arnold SR, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. *N Engl J Med*. 2015;372(9):835–845.
61. Pettersson K. Perinatal infection with Group B streptococci. *Semin Fetal Neonatal Med*. 2007;12(3):193–197.
62. Hunter JD. Ventilator-associated pneumonia. *BMJ*. 2012;344:e3325.
63. Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-resistant

pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011-2014. *Infect Control Hosp Epidemiol*. 2016;1–14.

64. Jones RN. Microbial etiologies of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. *Clin Infect Dis*. 2010;51(suppl 1):S81–S87.
65. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol*. 2006;24(19):3187–3205.
66. Cunha BA, Burillo A, Bouza E. Legionnaires' disease. *Lancet*. 2016;387(10016):376–385.
67. Phin N, Parry-Ford F, Harrison T, et al. Epidemiology and clinical management of Legionnaires' disease. *Lancet Infect Dis*. 2014;14(10):1011–1021.
68. Pereira JM, Paiva JA, Rello J. Assessing severity of patients with community-acquired pneumonia. *Semin Respir Crit Care Med*. 2012;33(3):272–283.
69. Saraya T, Kurai D, Nakagaki K, et al. Novel aspects on the pathogenesis of *Mycoplasma pneumoniae* pneumonia and therapeutic implications. *Front Microbiol*. 2014;5:410.
70. Huijskens EG, Koopmans M, Palmen FM, van Erkel AJ, Mulder PG, Rossen JW. The value of signs and symptoms in differentiating between bacterial, viral and mixed aetiology in patients with community-acquired pneumonia. *J Med Microbiol*. 2014;63 (pt 3):441–452.
71. Agbaht K, Diaz E, Munoz E, et al. Bacteremia in patients with ventilator-associated pneumonia is associated with increased mortality: a study comparing bacteremic vs. nonbacteremic ventilator-associated pneumonia. *Crit Care Med*. 2007;35(9):2064–2070.
72. Kunac A, Sifri ZC, Mohr AM, Horng H, Lavery RF, Livingston DH. Bacteremia and ventilator-associated pneumonia: a marker for contemporaneous extra-pulmonic infection. *Surg Infect (Larchmt)*. 2014;15(2):77–83.
73. Bartlett JG. Diagnostic tests for agents of community-acquired pneumonia. *Clin Infect Dis*. 2011;52(suppl 4):S296–S304.
74. Couturier MR, Graf EH, Griffin AT. Urine antigen tests for the diagnosis

of respiratory infections: legionellosis, histoplasmosis, pneumococcal pneumonia. *Clin Lab Med*. 2014;34(2):219–236.

75. Dominguez J, Gali N, Blanco S, et al. Detection of *Streptococcus pneumoniae* antigen by a rapid immunochromatographic assay in urine samples. *Chest*. 2001;119(1):243–249.
76. Helbig JH, Uldum SA, Luck PC, Harrison TG. Detection of *Legionella pneumophila* antigen in urine samples by the Binax NOW immunochromatographic assay and comparison with both Binax Legionella Urinary Enzyme Immunoassay (EIA) and Biotest Legionella Urin Antigen EIA. *J Med Microbiol*. 2001;50(6):509–516.
77. Murdoch DR, Laing RT, Mills GD, et al. Evaluation of a rapid immunochromatographic test for detection of *Streptococcus pneumoniae* antigen in urine samples from adults with community-acquired pneumonia. *J Clin Microbiol*. 2001;39(10):3495–3498.
78. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. 2003;58(5):377–382.
79. Bauer TT, Ewig S, Marre R, Suttorp N, Welte T. CRB-65 predicts death from community-acquired pneumonia. *J Intern Med*. 2006;260(1):93–101.
80. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997;336(4):243–250.
81. Ottosen J, Evans H. Pneumonia: challenges in the definition, diagnosis, and management of disease. *Surg Clin North Am*. 2014;94(6):1305–1317.
82. Feldman C, Anderson R. Antibiotic resistance of pathogens causing community-acquired pneumonia. *Semin Respir Crit Care Med*. 2012;33(3):232–243.
83. Martinez JA, Horcajada JP, Almela M, et al. Addition of a macrolide to a beta-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. *Clin Infect Dis*. 2003;36(4):389–395.
84. Waterer GW, Somes GW, Wunderink RG. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. *Arch Intern Med*. 2001;161(15):1837–1842.
85. Weiss K, Low DE, Cortes L, et al. Clinical characteristics at initial presentation and impact of dual therapy on the outcome of bacteremic *Streptococcus pneumoniae* pneumonia in adults. *Can Respir J*.

2004;11(8):589–593.

86. Davis ML, Sparrow HG, Ikwuagwu JO, Musick WL, Garey KW, Perez KK. Multicentre derivation and validation of a simple predictive index for healthcare-associated *Clostridium difficile* infection. *Clin Microbiol Infect*. 2018;24(11):1190–1194.
87. Johnson MT, Reichley R, Hoppe-Bauer J, Dunne WM, Micek S, Kollef M. Impact of previous antibiotic therapy on outcome of gram-negative severe sepsis. *Crit Care Med*. 2011;39(8):1859–1865.
88. Shehab N, Patel PR, Srinivasan A, Budnitz DS. Emergency department visits for antibiotic-associated adverse events. *Clin Infect Dis*. 2008;47(6):735–743.
89. Tomasz A. Antibiotic resistance in *Streptococcus pneumoniae*. *Clin Infect Dis*. 1997;24(suppl 1):S85–S88.
90. Bidell MR, Patel N, O'Donnell JN. Optimal treatment of MSSA bacteraemias: a meta-analysis of cefazolin versus antistaphylococcal penicillins. *J Antimicrob Chemother*. 2018;73(10):2643–2651.
91. McDanel JS, Perencevich EN, Diekema DJ, et al. Comparative effectiveness of beta-lactams versus vancomycin for treatment of methicillin-susceptible *Staphylococcus aureus* bloodstream infections among 122 hospitals. *Clin Infect Dis*. 2015;61(3):361–367.
92. Stevens DL, Herr D, Lampiris H, Hunt JL, Batts DH, Hafkin B. Linezolid versus vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* infections. *Clin Infect Dis*. 2002;34(11):1481–1490.
93. Wunderink RG, Mendelson MH, Somero MS, et al. Early microbiological response to linezolid vs vancomycin in ventilator-associated pneumonia due to methicillin-resistant *Staphylococcus aureus. Chest*. 2008;134(6):1200–1207.
94. Wunderink RG, Niederman MS, Kollef MH, et al. Linezolid in methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a randomized, controlled study. *Clin Infect Dis*. 2012;54(5):621–629.
95. Kaye KS, Udeani G, Cole P, Friedland HD. Ceftaroline fosamil for the treatment of hospital-acquired pneumonia and ventilator-associated pneumonia. *Hosp Pract (1995)*. 2015;43(3):144–149.
96. Markowitz N, Quinn EL, Saravolatz LD. Trimethoprim-sulfamethoxazole compared with vancomycin for the treatment of *Staphylococcus aureus i*nfection. *Ann Intern Med*. 1992;117(5):390–398.

97. Eliakim-Raz N, Hellerman M, Yahav D, et al. Trimethoprim/sulfamethoxazole versus vancomycin in the treatment of healthcare/ventilator-associated MRSA pneumonia: a case-control study. *J Antimicrob Chemother*. 2017;72(3):882–887.
98. Gordon KA, Biedenbach DJ, Jones RN. Comparison of *Streptococcus pneumoniae* and *Haemophilus influenzae* susceptibilities from community-acquired respiratory tract infections and hospitalized patients with pneumonia: five-year results for the SENTRY Antimicrobial Surveillance Program. *Diagn Microbiol Infect Dis*. 2003;46(4):285–289.
99. Hawser S, Morrissey I, Lemos B, Keedy K, Fernandes P. Surveillance of the activity of solithromycin (CEM-101) against bacteria from respiratory tract infections. *Int J Antimicrob Agents*. 2017;50(1):17–22.
100. Kumar A, Zarychanski R, Light B, et al. Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity-matched analysis. *Crit Care Med*. 2010;38(9):1773–1785.
101. Castanheira M, Farrell SE, Krause KM, Jones RN, Sader HS. Contemporary diversity of beta-lactamases among Enterobacteriaceae in the nine U.S. census regions and ceftazidime-avibactam activity tested against isolates producing the most prevalent beta-lactamase groups. *Antimicrob Agents Chemother*. 2014;58(2):833–838.
102. Coque TM, Baquero F, Canton R. Increasing prevalence of ESBL-producing Enterobacteriaceae in Europe. *Euro Surveill*. 2008;13(47):–pii=19044.
103. Lukac PJ, Bonomo RA, Logan LK. Extended-spectrum beta-lactamase-producing Enterobacteriaceae in children: old foe, emerging threat. *Clin Infect Dis*. 2015;60(9):1389–1397.
104. Bush K, Jacoby GA. Updated functional classification of beta-lactamases. *Antimicrob Agents Chemother*. 2010;54(3):969–976.
105. Wu N, Chen BY, Tian SF, Chu YZ. The inoculum effect of antibiotics against CTX-M-extended-spectrum beta-lactamase-producing *Escherichia coli*. *Ann Clin Microbiol Antimicrob*. 2014;13:45.
106. Harris PNA, Tambyah PA, Lye DC, et al. Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with *E. coli* or *Klebsiella pneumoniae* bloodstream infection and ceftriaxone resistance: a randomized clinical trial. *JAMA*. 2018;320(10):984–994.
107. Zasowski EJ, Rybak JM, Rybak MJ. The beta-lactams strike back:

ceftazidime-avibactam. *Pharmacotherapy*. 2015;35(8):755–770.

108. Petty LA, Henig O, Patel TS, Pogue JM, Kaye KS. Overview of meropenem-vaborbactam and newer antimicrobial agents for the treatment of carbapenem-resistant Enterobacteriaceae. *Infect Drug Resist*. 2018;11:1461–1472.
109. Zhanel GG, Chung P, Adam H, et al. Ceftolozane/tazobactam: a novel cephalosporin/beta-lactamase inhibitor combination with activity against multidrug-resistant gram-negative bacilli. *Drugs*. 2014;74(1):31–51.
110. Shields RK, Nguyen MH, Chen L, et al. Ceftazidime-avibactam is superior to other treatment regimens against carbapenem-resistant *Klebsiella pneumoniae* bacteremia. *Antimicrob Agents Chemother*. 2017;61(8):AAC.00883-1.
111. van Duin D, Lok JJ, Earley M, et al. Colistin versus ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant Enterobacteriaceae. *Clin Infect Dis*. 2018;66(2):163–171.
112. Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, et al. Effect and safety of meropenem-vaborbactam versus best-available therapy in patients with carbapenem-resistant Enterobacteriaceae infections: The TANGO II Randomized Clinical Trial. *Infect Dis Ther*. 2018;7(4):439–455.
113. Rodvold KA, George JM, Yoo L. Penetration of anti-infective agents into pulmonary epithelial lining fluid: focus on antibacterial agents. *Clin Pharmacokinet*. 2011;50(10):637–664.
114. Rybak MJ, Lomaestro BM, Rotschafer JC, et al. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the infectious diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. *Clin Infect Dis*. 2009;49(3):325–327.
115. Zasowski EJ, Lodise TP. The importance of individualized vancomycin dosing to ensure optimal exposure early in therapy. *J Clin Pharmacol*. 2018. doi: 10.1002/jcph.1281.
116. Drusano GL, Ambrose PG, Bhavnani SM, Bertino JS, Nafziger AN, Louie A. Back to the future: using aminoglycosides again and how to dose them optimally. *Clin Infect Dis*. 2007;45(6):753–760.
117. Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. *Antimicrob Agents Chemother*.

1995;39(3):650–655.

118. Zasowski E, Butterfield JM, McNutt LA, et al. Relationship between time to clinical response and outcomes among Pneumonia Outcomes Research Team (PORT) Risk Class III and IV hospitalized patients with community-acquired pneumonia who received ceftriaxone and azithromycin. *Antimicrob Agents Chemother*. 2014;58(7):3804–3813.
119. Uranga A, Espana PP, Bilbao A, et al. Duration of antibiotic treatment in community-acquired pneumonia: a multicenter randomized clinical trial. *JAMA Intern Med*. 2016;176(9):1257–1265.
120. Tablan OC, Anderson LJ, Besser R, Bridges C, Hajjeh R. Guidelines for preventing health-care–associated pneumonia, 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. *MMWR Recomm Rep*. 2004;53 (Rr-3):1–36.

126

Upper Respiratory Tract Infections

Christopher R. Frei and Bradi L. Frei

KEY CONCEPTS

1. Many upper respiratory tract infections will resolve spontaneously without pharmacologic therapy.
2. The most common bacterial causes are *Streptococcus pneumoniae* (acute otitis media and acute rhinosinusitis) and group A β-hemolytic *Streptococcus* (acute pharyngitis).
3. Vaccination against influenza and pneumococcus may decrease the risk of acute otitis media.
4. Because upper respiratory tract infections are so common, antibiotics used to treat them serve as catalysts for the emergence and spread of antibiotic resistance, thereby making prudent antibiotic use critically important.
5. When antibiotics are prescribed, the empirical medications of choice are amoxicillin or amoxicillin-clavulanate for acute otitis media, amoxicillin-clavulanate for acute rhinosinusitis, and amoxicillin or penicillin for acute pharyngitis.
6. For acute otitis media, high-dose amoxicillin (80-90 mg/kg/day in two divided doses) is recommended.

Preclass Engaged Learning Activity

Create a summary table of first-line drug treatment options, including recommended treatment if the patient has a penicillin allergy, for the upper respiratory tract infections discussed in this chapter: acute otitis media, rhinosinusitis, and pharyngitis. The table should include columns for type of upper respiratory tract infection, first-line treatment, dose, route, and duration

of treatment. The table should also include important counseling points and adverse effects.

INTRODUCTION

More patients present to physicians' offices and emergency departments for upper respiratory tract infections than any other infectious disease. There are over 25 million office visits per year for acute upper respiratory tract infections.[1] Otitis media, rhinosinusitis, and pharyngitis are the three most common upper respiratory tract infections. Because they are so common, community and emergency healthcare workers must be familiar with the diagnosis, assessment, and management of patients with these infections. Furthermore, antibiotics used for the treatment of upper respiratory tract infections serve as catalysts for the emergence and spread of antibiotic resistance, thereby making prudent antibiotic use critically important.

ACUTE OTITIS MEDIA

The term *otitis media* comes from the Latin *oto-* for "ear," *itis* for "inflammation," and *medi-* for "middle"; otitis media, then, is an inflammation of the middle ear. There are three subtypes of otitis media: acute otitis media, otitis media with effusion, and chronic otitis media. Acute otitis media is the subtype with the greatest role for antibiotics and will be discussed in detail.

Epidemiology

Otitis media is one of the leading reasons for physicians' office visits and emergency department visits in the United States. There are more than 709 million cases of otitis media worldwide each year; half of these cases occur in children under 5 years of age.[2] Many patients with otitis media will receive a prescription, and the costs associated with managing otitis media are several billion dollars annually in the United States. Fortunately, at least one study noted a downward trend in otitis media healthcare visits in children younger than 2 years of age from 2001 to 2011, coinciding with use of PCV-13, starting in 2010.[3]

Etiology

1 When comprehensive and sensitive microbiologic methods have been used in patients with a diagnosis of acute otitis media, bacteria have been found in more than 90% of cases; with standard diagnostic and microbiologic testing, bacteria have been found in approximately 70% of cases.[4]

2 Common bacterial pathogens include *Streptococcus pneumoniae* (*S. pneumoniae*), nontypeable *Haemophilus influenzae* (*H. influenzae*), and *Moraxella catarrhalis* (*M. catarrhalis*).[5] The microbial etiology has changed as a result of the introduction and widespread use of the pneumococcal conjugate vaccines.[6] Specifically, the proportion of *S. pneumoniae* cases has declined over time, and the proportion of *H. influenzae* cases has risen.[5] Today, these two pathogens occur in approximately equal proportions.[4]

S. pneumoniae, *H. influenzae*, and *M. catarrhalis* can all possess resistance to β-lactams. *S. pneumoniae* develops resistance through alteration of penicillin-binding proteins, whereas *H. influenzae* and *M. catarrhalis* produce β-lactamases. Many *S. pneumoniae* isolates in the United States are penicillin nonsusceptible, and most nonsusceptible strains have high-level penicillin resistance. Many *H. influenzae* isolates and nearly all *M. catarrhalis* isolates, from the upper respiratory tract, produce β-lactamases.

Pathophysiology

Acute otitis media usually follows a viral upper respiratory tract infection that impairs the mucociliary apparatus and causes Eustachian tube dysfunction in the middle ear. The middle ear is the space behind the tympanic membrane, or eardrum. A noninfected ear has a thin, clear tympanic membrane. In otitis media, this space becomes blocked with fluid, resulting in a bulging and erythematous tympanic membrane. Bacteria that colonize the nasopharynx enter the middle ear and are not cleared properly by the mucociliary system. The bacteria proliferate and cause infection. Children tend to be more susceptible to otitis media than adults because the anatomy of their Eustachian tube is shorter and more horizontal, facilitating bacterial entry into the middle ear.[7]

CLINICAL PRESENTATION Acute Otitis Media

General

- Cases of acute otitis media often follow viral upper respiratory tract infections. Nonverbal children with ear pain might hold, rub, or tug their

ear. Infants might cry, be irritable, or have difficulty sleeping.

Signs and Symptoms

- Bulging of the tympanic membrane
- Otorrhea
- Otalgia (considered to be moderate or severe if pain lasts at least 48 hours)
- Fever (considered to be severe if temperature is 39°C [102.2°F] or higher)

Data from Reference 4.

Clinical Presentation

Patients or caregivers frequently characterize acute otitis media as having an acute onset of otalgia (ear pain). For parents of young children, irritability and tugging on the ear are often the first clues that a child has acute otitis media.

The American Academy of Pediatrics (AAP) guidelines have stringent diagnostic criteria to ensure accurate diagnosis. Children should be diagnosed with acute otitis media if they have middle ear effusion *and* either (1) moderate-to-severe bulging of the tympanic membrane *or* new onset otorrhea not due to acute otitis externa or (2) mild bulging of the tympanic membrane *and* onset of ear pain within the last 48 hours or intense erythema of the tympanic membrane. Middle ear effusion should be identified based on pneumatic otoscopy and/or tympanometry.[4]

The diagnoses of acute otitis media and otitis media with effusion are easily confused, and careful attention to history, signs, and symptoms is important. Otitis media with effusion is characterized by fluid in the middle ear without signs and symptoms of acute ear infection, such as pain and a bulging eardrum.[8]

TREATMENT

Desired Outcomes

6 Treatment goals include pain management and prudent antibiotic use. It is important to consider primary prevention of acute otitis media through the use of

bacterial and viral vaccines.

3 Clinicians should recommend pneumococcal conjugate vaccine and annual influenza vaccine to all children according to the Advisory Committee on Immunization Practices (ACIP) schedule from the United States Centers for Disease Control and Prevention.[4] Also, because acute otitis media cases often follow influenza cases, influenza vaccination should be considered as a possible means to prevent acute otitis media.

General Approach to Treatment

The first step in treatment is to differentiate acute otitis media from otitis media with effusion or chronic otitis media, as the latter two types do not benefit substantially from antibiotic therapy. If the child has acute otitis media, then consider if the disease severity warrants antibiotic therapy. Recognize that amoxicillin is the mainstay of therapy and that penicillin resistance can be overcome, in many cases, with higher doses of amoxicillin. Address the child's pain as described below. The therapeutic strategy should be changed if complications develop or if symptoms fail to resolve within 3 days.

Nonpharmacologic Therapy

Children with acute otitis media should be assessed for pain. Those with pain should be offered treatment to reduce pain regardless of the decision to administer antibiotics.[4] This is largely because antibiotics do not reduce pain in the first 24 hours. Furthermore, some children may experience some pain up to 3 to 7 days even after antibiotics are started. Choice of pain treatment depends on possible benefits and risks to the individual patient. Acetaminophen and ibuprofen are mainstays of treatment, are effective analgesics for mild-to-moderate pain, and are readily available. Eardrops with a local anesthetic may offer additional, but brief, benefit over acetaminophen in patients at least 5 years of age.[4]

Pharmacologic Therapy

National clinical practice guidelines for diagnosis and management of acute otitis media (updated in 2013) are focused on children 6 months to 12 years of age with uncomplicated cases and without underlying conditions that may alter the natural course of the disease.[4] The decision to administer antibiotics depends

on patient age, symptom severity, laterality, and joint decision-making with parents/caregivers. Children 6 months to 12 years of age, with moderate-to-severe ear pain or temperature of 39°C (102.2°F) or higher should receive antibiotics. Children 6 to 23 months of age, with nonsevere bilateral acute otitis media should also receive antibiotics. Children 6 to 23 months, with nonsevere unilateral acute otitis media, and children 24 months to 12 years of age, with nonsevere acute otitis media, may receive antibiotics or observation without antibiotics (watchful waiting). Initial observation should be based on joint decision-making with parents/caregivers, and must include a plan to initiate antibiotics if the child's symptoms worsen or decline within 48 to 72 hours of symptom onset.[4] The central principle is to administer antibiotics quickly when the diagnosis is certain, but to withhold antibiotics, at least initially, when the diagnosis is uncertain.

4 Antibiotic therapy for upper respiratory diseases must be balanced with possible increases in adverse drug events and increased antibiotic pressure to cause bacterial resistance. Systematic reviews and randomized controlled trials suggest a moderate benefit of antibiotics for the treatment of acute otitis media, particularly in patients with severe symptoms.[9,10] On the other hand, rates of adverse effects, such as diarrhea and diaper rash are higher for children who receive antibiotics for acute otitis media.

5 If antibiotics are to be administered, then amoxicillin should be given to most children.[4] Exceptions include: children who have received amoxicillin in the last 30 days, have concurrent purulent conjunctivitis, or have a history of recurrent infection unresponsive to amoxicillin. These patients should receive amoxicillin-clavulanate instead of amoxicillin. Patients with otitis conjunctivitis syndrome are more likely to be infected with nontypeable *H. influenzae*, hence the need for a β-lactamase inhibitor (such as clavulanate).[4] Clinicians should reassess the plan if the child's symptoms worsen or decline within 48 to 72 hours of symptom onset.[4] **Table 126-1** lists antibiotic recommendations for acute otitis media.

TABLE 126-1 Antibiotics and Doses for Acute Otitis Media

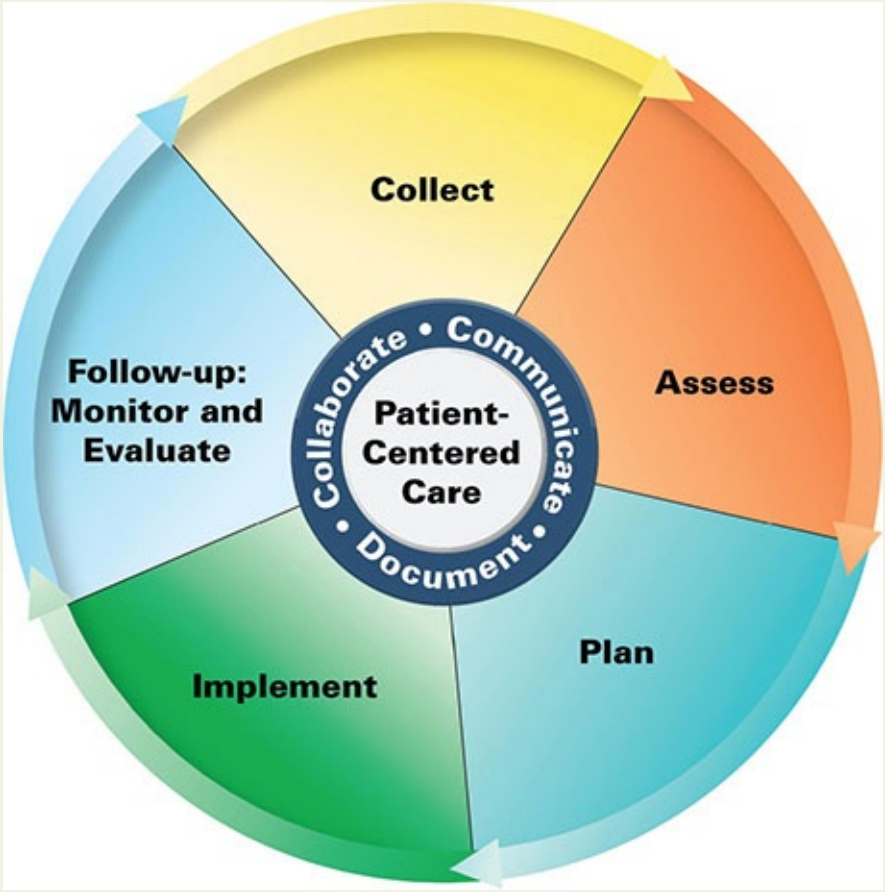
Antibiotic	Brand Name	Dose	Comments[a]
Initial Diagnosis			
Amoxicillin	Amoxil®	80-90 mg/kg/day orally divided twice daily	First line
Amoxicillin-clavulanate	Augmentin®	90 mg/kg/day orally of amoxicillin plus 6.4 mg/kg/day orally of clavulanate, divided twice daily	First line if certain criteria are present[b]
Cefdinir, cefuroxime, cefpodoxime	Omnicef®, Ceftin®, Vantin®	cefdinir (14 mg/kg/day orally in 1-2 doses), cefuroxime (30 mg/kg/day orally in two divided doses), cefpodoxime (10 mg/kg/day orally in two divided doses)	Second line or nonsevere penicillin allergy
Ceftriaxone (1-3 days)	Rocephin®	50 mg/kg/day IM or IV for 3 days	Second line or nonsevere penicillin allergy
Failure at 48-72 Hours			
Amoxicillin-clavulanate[b]	Augmentin®	90 mg/kg/day orally of amoxicillin plus 6.4 mg/kg/day orally of clavulanate, divided twice daily	First line
Ceftriaxone (1-3 days)	Rocephin®	50 mg/kg/day IM or IV for 3 days	First line or nonsevere penicillin allergy
Clindamycin	Cleocin®	30-40 mg/kg/day orally in three divided doses ± second- or third-generation cephalosporin	Second line or nonsevere penicillin allergy

IM, intramuscular; IV, intravenous; po, orally.

[a]Amoxicillin-clavulanate 90:6.4 or 14:1 ratio is available in the United States; 7:1 ratio is available in Canada (use amoxicillin 45 mg/kg for one dose, amoxicillin 45 mg/kg with clavulanate 6.4 mg/kg for second dose).

[b]If a patient has received amoxicillin in the last 30 days, has concurrent purulent conjunctivitis, or has a history of recurrent infection unresponsive to amoxicillin.

Data from Reference 5.



Patient Care Process for Acute Otitis Media

Collect

- Patient characteristics (eg, age, weight)
- Patient history (eg, past infections, current and past antibiotic/antiviral use noting previous failures, medication allergies)
- Determine whether patient has concurrent purulent conjunctivitis
- Objective data:
    - Temperature
    - Signs and symptoms (see Clinical Presentation)
    - Presence of congestion, fullness, purulent discharge, or pain in the ear
    - Presence of redness, fullness, bulging, or limited/absent mobility of the tympanic membrane

- Other diagnostic tests, when indicated (eg, procalcitonin)

Assess

- Infection status, including presence of signs and symptoms
- Determine which symptoms may need additional therapy (eg, ongoing ear pain)
- Use information collected, patient factors (eg, patient age, symptom severity, laterality), and joint decision-making with parents/caregivers to determine whether antibiotics are needed
- If antibiotics are appropriate, determine proper choice of antibiotic, dose, duration, and dosage form
  - Determine if the patient meets criteria for high-dose amoxicillin-clavulanate
  - Determine whether a short-course of therapy (5-7 days) may be appropriate

Plan*

- Select drug therapy regimen including specific antibiotic, dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Table 126-1)
- Monitor efficacy (eg, temperature, pain), safety (eg, medication-specific adverse effects), and time frame
- Educate patient and/or caregiver (eg, purpose of treatment, drug therapy) emphasizing adherence to treatment regimen
- Recommend self-monitoring of body temperature

Implement*

- Provide patient education regarding the infection and all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up, when indicated
- Recommend measures to reduce ear pain, if present

Follow-up: Monitor and Evaluate

- Improvement/resolution of signs and symptoms; reassess the plan if the child's symptoms worsen or decline within 48 to 72 hours of symptom onset
- Presence of adverse effects, particularly allergic reactions and diarrhea
- Patient adherence to treatment plan using multiple sources of information
- Recommend pneumococcal conjugate vaccine and annual influenza vaccination

**Collaborate with patient, caregiver(s), and other healthcare professionals.*

High-dose amoxicillin (80-90 mg/kg/day in two divided doses) is recommended for most patients with acute otitis media. Amoxicillin has the best pharmacodynamic profile against drug-resistant *S. pneumoniae* of all available oral antibiotics. In addition, amoxicillin has a long record of safety, possesses a narrow spectrum of activity, is inexpensive, and is more palatable than other options. Higher middle ear fluid concentrations of amoxicillin, as a result of higher dosing, overcome most drug-resistant *S. pneumoniae*.[4] Its excellent efficacy against *S. pneumoniae* outweighs the issue of β-lactamase-producing *H. influenzae* and *M. catarrhalis*, against which amoxicillin may not be effective. This is because both *H. influenzae* and *M. catarrhalis* are more likely than *S. pneumoniae* to lead to a spontaneous resolution of the infection.

A patient who has received amoxicillin in the last 30 days, has concurrent purulent conjunctivitis, or has a history of recurrent infection unresponsive to amoxicillin should receive high-dose amoxicillin- clavulanate (90 mg/kg/day of amoxicillin, with 6.4 mg/kg/day of clavulanate, in two divided doses) instead of amoxicillin. Amoxicillin-clavulanate has activity against β-lactamase-producing *H. influenzae* and *M. catarrhalis* as well as drug-resistant *S. pneumoniae*.[4] Other antibiotic choices include cefdinir, cefuroxime, cefpodoxime, and intramuscular or intravenous ceftriaxone.[4] Second-generation cephalosporins, though β-lactamase stable, are expensive, have an increased incidence of side effects, and may increase selective pressure for resistant bacteria. Furthermore, most cephalosporins do not achieve adequate middle ear fluid concentrations against drug-resistant *S. pneumoniae* for the desired duration of the dosing interval. Use of trimethoprim-sulfamethoxazole and erythromycin-sulfisoxazole is discouraged because of high rates of resistance. Intramuscular ceftriaxone and amoxicillin are the only antibiotics that achieve middle ear fluid concentrations above the minimal inhibitory concentration (MIC) for greater than 40% of the dosing interval. Although single doses of ceftriaxone have been used, daily

doses for 3 days are recommended to optimize clinical outcomes.[4] Ceftriaxone is more expensive than amoxicillin and the intramuscular injections are painful. Patients with a penicillin allergy can be treated with several alternative antibiotics, including a cephalosporin in patients without history of severe or type 1 penicillin allergy, or clindamycin. Notably, clindamycin lacks efficacy against *H. influenzae*, whereas macrolides lack efficacy against both *H. influenzae* and *S. pneumoniae*; therefore, macrolides are not recommended. Finally, tympanocentesis can also be considered for treatment failure or persistent acute otitis media. It has a therapeutic effect of relieving pain and pressure and can be used to collect fluid to identify the causative agent.

There is ongoing debate regarding the optimal duration of therapy for acute otitis media. Traditional recommendations call for 10 days of antibiotic therapy; however, some experts have speculated that patients can be treated for as little as 5 to 7 days. Unfortunately, evidence does not support this practice in children.[11] Short-course treatment is not recommended in children younger than 2 years of age. In children at least 6 years of age who have mild-to-moderate acute otitis media, a 5- to 7-day treatment course may be used.[4]

Recurrent acute otitis media is defined as at least three episodes in 6 months or four episodes in 1 year, with one episode in the preceding 6 months. Recurrent episodes are of concern because children younger than 3 years of age are at high risk for hearing loss and language and learning disabilities. Clinicians should not prescribe antibiotics as prophylaxis against recurrent episodes, but they may offer tympanostomy tubes (T tubes).[4]

Evaluation of Therapeutic Outcomes

Procalcitonin increases in response to bacterial infection and declines as the infection resolves. Clinicians are starting to use procalcitonin blood levels to decide when to initiate and discontinue antibiotics in patients with acute upper respiratory infections (URIs).[12] A Cochrane systematic review of 14 trials with 4,221 participants found that procalcitonin protocols significantly reduced antibiotic consumption without negatively impacting patient survival or treatment failure.[13] The finding was driven by lower prescription rates in primary care and shorter durations of antibiotic therapy in emergency departments and intensive care units.[13] Despite the enthusiasm for this approach, there are still several aspects of procalcitonin monitoring that need to be resolved, including the timing of levels, the procalcitonin cutoff values for different clinical decision points, and the cost-effectiveness of this technology.[14]

Patients with acute otitis media should be reassessed after 48 to 72 hours. By this time, there should be clinical improvement in the signs and symptoms of infection, including pain, fever, and erythema/bulging of the tympanic membrane. If the patient has not responded and antibiotics were withheld initially, they should be instituted now. If the patient initially received an antibiotic, then the antibiotic should be changed (Table 126-1). Most children will become asymptomatic at 7 days.

Early reevaluation of the eardrum when signs and symptoms are improving can be misleading because effusions persist. Over a period of 1 week, changes in the eardrum normalize, and the pus becomes serous fluid. Air-fluid levels are apparent behind the eardrum, at which point the stage is now referred to as *otitis media with effusion*. This does not represent ongoing infection, nor are additional antibiotics required.[4]

Immediate reevaluation is appropriate if hearing loss results from persistent middle ear effusions following infection. Complications of otitis media are infrequent but include mastoiditis, bacteremia, meningitis, and auditory sequelae with the potential for speech and language impairment.[4]

ACUTE BACTERIAL RHINOSINUSITIS

Sinusitis is an inflammation and/or infection of the paranasal sinuses, or membrane-lined air spaces, around the nose.[15] The term *rhinosinusitis* is now preferred because sinusitis typically also involves the nasal mucosa.[15] Even though the majority of rhinosinusitis infections are viral in origin, antibiotics are frequently prescribed. It is thus important to differentiate between viral and bacterial rhinosinusitis to avoid antibiotic overuse.

The most current clinical practice guidelines for acute bacterial rhinosinusitis were published in 2012 and 2015, by two different entities.[15,16] Several of the recommendations in these guidelines differ substantially from prior guidelines.

CLINICAL PRESENTATION Acute Bacterial Rhinosinusitis

General

- There are three clinical presentations that are most consistent with acute bacterial versus viral rhinosinusitis:
  - Onset with *persistent* signs or symptoms compatible with acute rhinosinusitis, lasting for ≥10 days without any evidence of clinical

improvement

- Onset with *severe* signs or symptoms of high fever (≥39°C [102.2°F]) and purulent nasal discharge or facial pain lasting for at least 3 to 4 consecutive days at the beginning of illness
- Onset with *worsening* signs or symptoms characterized by new-onset fever, headache, or increase in nasal discharge following a typical viral URI that lasted 5 to 6 days and were initially improving ("double sickening")

Signs and Symptoms

- Purulent anterior nasal discharge, purulent or discolored posterior nasal discharge, nasal congestion or obstruction, facial congestion or fullness, facial pain or pressure, fever, headache, ear pain/pressure/fullness, halitosis, dental pain, cough, and fatigue

Data from Reference 15.

Epidemiology

1 Nearly 30 million cases of rhinosinusitis are diagnosed annually in the United States.[17] Acute bacterial rhinosinusitis is overdiagnosed; thus, antibiotics are overprescribed. Most rhinosinusitis infections have a viral etiology, and yet, antibiotics are frequently prescribed. Adults with rhinosinusitis miss an average of 1 to 2 workdays/year with these infections and have significant activity, work, and social limitations.[16]

Etiology

2 Acute bacterial rhinosinusitis is caused, most often, by the same bacteria implicated in acute otitis media: *S. pneumoniae* and *H. influenzae*. These organisms are responsible for approximately 50% to 70% of bacterial causes of acute bacterial rhinosinusitis in both adults and children.[15] *M. catarrhalis* is also sometimes implicated in adults and children (approximately 8%-16%).[15] *Streptococcus pyogenes*, *Staphylococcus aureus*, gram-negative bacilli, and anaerobes are associated less frequently with acute bacterial rhinosinusitis.[15] Issues of bacterial resistance are similar to those found with acute otitis media.

Pathophysiology

Similar to acute otitis media, acute bacterial rhinosinusitis is often preceded by a viral respiratory tract infection that causes mucosal inflammation. This can lead to obstruction of the sinus ostia—the pathways that drain the sinuses. Mucosal secretions become trapped, local defenses are impaired, and bacteria from adjacent surfaces begin to proliferate. The maxillary and ethmoid sinuses are most frequently involved. The pathogenesis of chronic rhinosinusitis has not been well studied. Whether it is caused by more persistent pathogens or a subtle defect in the host's immune function, some patients develop chronic symptoms after their acute infection.

Clinical Presentation

The greatest barrier to efficient use of antibiotics in acute bacterial rhinosinusitis is the lack of a simple and accurate diagnostic test. The gold standard for diagnosis is sinus puncture with recovery of bacteria in high density (10^4 colony-forming units/mL [10^7 cfu/L] or greater)[15]; however, sinus puncture is invasive and costly, and can be painful, so it is not routinely done. Sinus radiography can help, but it is not routinely recommended. Because there is no simple and accurate office-based test for acute bacterial rhinosinusitis, clinicians rely on clinical findings to make the diagnosis.

TREATMENT

Desired Outcomes

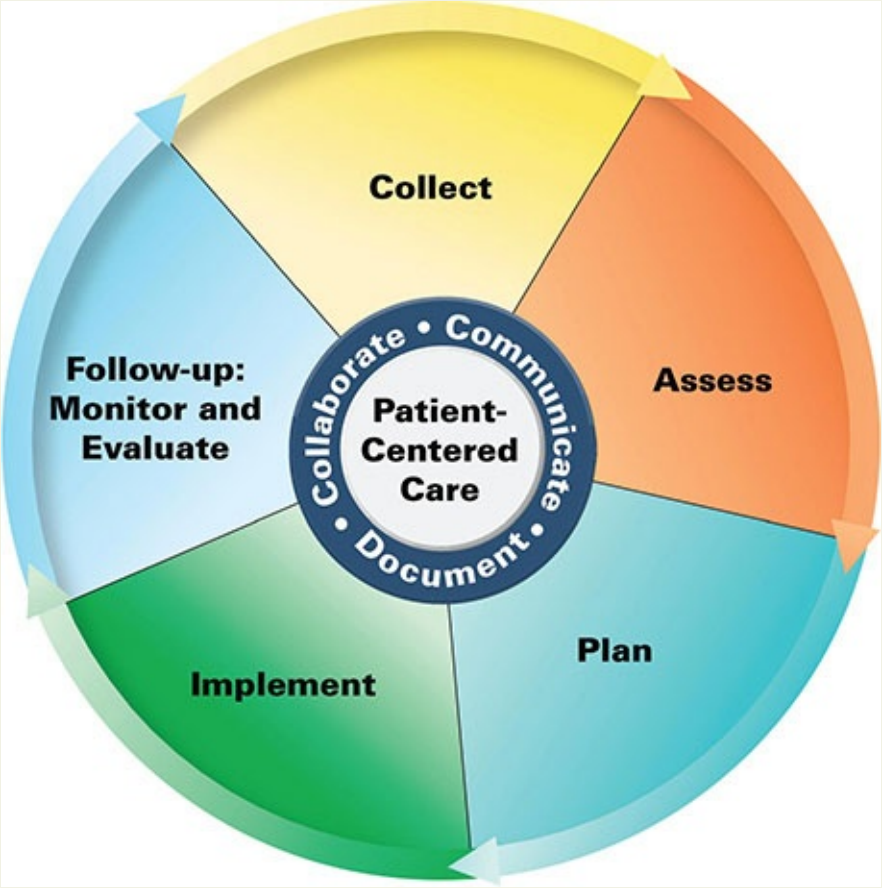
The goals of treatment for acute bacterial rhinosinusitis are to reduce signs and symptoms, achieve and maintain patency of the ostia, limit antibiotic treatment to those who may benefit, eradicate the bacterial infection with appropriate antibiotic therapy, minimize the duration of illness, prevent complications, and prevent progression from acute disease to chronic disease.

General Approach to Treatment

4 The first step is to differentiate viral and bacterial rhinosinusitis. This is based on disease duration, initial severity of illness, and worsening symptomatology. Viral rhinosinusitis typically improves in 7 to 10 days; therefore, a diagnosis of acute bacterial rhinosinusitis requires persistent symptoms (10 days or greater), worsening of symptoms after 10 days, or

worsening after initial improvement.[16] Acute bacterial rhinosinusitis may also be suspected if the patient has severe symptoms at the beginning of his/her illness. Amoxicillin-clavulanate is now recommended as the first-line antibiotic therapy for patients with acute bacterial rhinosinusitis.[15] Adjuvant, nonantibiotic therapies have a limited role.

The next step is to decide if the patient needs to be referred to a specialist. Potential reasons for referral include mental status changes, visual disturbances, immunosuppressive illness, nosocomial infections, anatomic defects causing obstruction and possibly requiring surgery, unusually severe symptoms, multiple recurrent episodes (3-4 times per year), unilateral findings, significant coexisting illnesses, risk factors for unusual or resistant pathogens, and history of antibiotic failure. The specialist may perform computed tomography to assess the severity and extent of disease and identify the underlying causes.



Patient Care Process for Acute Bacterial Rhinosinusitis

Collect

- Patient characteristics (eg, age, weight)
- Patient history (eg, past infections, current and past antibiotic/antiviral use noting previous failures, medication allergies, history of allergic rhinitis)
- Determine whether patient is in daycare, is a daycare worker, or has a child in daycare
- Objective data:
    - Temperature
    - Signs and symptoms (see Clinical Presentation)
    - Presence of congestion, fullness, or pain in the nose, face, or ear
    - Presence of purulent or discolored nasal discharge
    - Other diagnostic tests, when indicated (eg, CT, sinus puncture)

Assess

- Infection status, including presence of signs and symptoms
- Determine which symptoms may need additional therapy (eg, ongoing nose pain)
- Decide if referral is needed (eg, mental status changes, visual disturbances, immunosuppressive illness, nosocomial infections, anatomic defects, unilateral findings)
- Use information collected, patient factors (eg, patient age, symptom severity), and joint decision-making with parents/caregivers to determine whether antibiotics are needed
- If antibiotics are appropriate, determine proper choice of antibiotic, dose, duration, and dosage form
    - Determine if the patient meets criteria for high-dose amoxicillin-clavulanate

Plan*

- Select drug therapy regimen including specific antibiotic, dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Tables 126-2 and 126-3)
- Monitor efficacy (eg, temperature, pain), safety (eg, medication-specific adverse effects), and time frame
- Educate patient and/or caregiver (eg, purpose of treatment, drug therapy)

emphasizing adherence to treatment regimen
- Recommend self-monitoring of body temperature

Implement

- Provide patient education regarding the infection and all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up, when indicated
- Recommend measures to reduce nose pain and inflammation, if present

Follow-up: Monitor and Evaluate

- Improvement/resolution of signs and symptoms; reassess the plan if the patient's symptoms worsen or decline within 48 to 72 hours of symptom onset
- Use of nasal decongestant sprays and antihistamines; these are not recommended for treatment
- Presence of adverse effects, particularly allergic reactions and diarrhea
- Patient adherence to treatment plan using multiple sources of information

**Collaborate with patient, caregiver(s), and other healthcare professionals.*

Nonpharmacologic Therapy

Several nonprescription therapies are used in the management of *nonbacterial rhinosinusitis* for symptomatic relief. These include nasal decongestant sprays that reduce inflammation by vasoconstriction. Use should be limited to no more than 3 days to prevent the development of tolerance and/or rebound congestion. Oral decongestants may also aid in nasal/sinus patency. Irrigation of the nasal cavity with saline and steam inhalation may be used to increase mucosal moisture, and mucolytics (eg, guaifenesin) may be used to decrease the viscosity of nasal secretions.

In contrast, if a patient is suspected of having *acute bacterial rhinosinusitis*, then decongestants and antihistamines are not recommended.[15] These can dry mucosa and disturb clearance of mucosal secretions. Other therapies are recommended to be used as adjuncts to antibiotics for patients with acute bacterial rhinosinusitis. Intranasal saline irrigation with either physiologic or

hypertonic saline is recommended for adults.[15] Intranasal corticosteroids are recommended only for patients with a history of allergic rhinitis.

Pharmacologic Therapy

The Infectious Diseases Society of America (IDSA) published clinical practice guidelines in 2012 that are the primary source for many of the statements in this chapter.[15] Additional guidance and recommendations come from a 2015 update of the 2007 guidelines from the American Academy of Otolaryngology—Head and Neck Surgery Foundation (AAO-HNSF).[16] There are two major differences in the IDSA and AAO-HNSF guidelines. The AAO-HNSF guidelines endorse watchful waiting, without antibiotics, unless symptoms fail to improve within 7 days.[16] When antibiotics are given, the AAO-HNSF endorses amoxicillin as first-line treatment, instead of amoxicillin-clavulanate.[16] In contrast, the IDSA guidelines support amoxicillin-clavulanate as first-line treatment, without watchful waiting.[15]

5 Amoxicillin-clavulanate is considered the first-line treatment for acute bacterial rhinosinusitis in children and adults according to IDSA (**Tables 126-2** and **126-3**).[15] In contrast, prior guidelines, and the AAO-HNSF guidelines,[16] list amoxicillin as the first-line treatment option due to its safety, narrow spectrum of activity, good tolerability, and favorable cost. A randomized controlled trial questioned the value of amoxicillin in nonsevere cases of acute bacterial rhinosinusitis.[18] The IDSA guidelines support the choice of amoxicillin-clavulanate based on (a) the emergence of *H. influenzae* as a more common cause of upper respiratory tract infections in children than in the past,[5] and (b) the high prevalence of β-lactam-producing respiratory pathogens in acute bacterial rhinosinusitis (particularly *H. influenzae* and *M. catarrhalis*). The advantage of using amoxicillin-clavulanate, as compared with amoxicillin, is a greater spectrum of coverage. The disadvantages are increased cost, greater risk of adverse effects including diarrhea, and an added risk of hypersensitivity to the clavulanate component.[15] No other antibiotics are recommended as first-line for initial empirical therapy.

TABLE 126-2 Antibiotics and Doses for Acute Bacterial Rhinosinusitis in Children

Antibiotic	Brand Name	Dose	Comments
Initial Empirical Therapy			
Amoxicillin-clavulanate	Augmentin®	45 mg/kg/day orally twice daily	First line
Amoxicillin-clavulanate	Augmentin®	90 mg/kg/day orally twice daily	Second line
β-Lactam Allergy			
Clindamycin plus cefixime or cefpodoxime	Cleocin®, Suprax®, Vantin®	Clindamycin (30-40 mg/kg/day orally three times daily) plus cefixime (8 mg/kg/day orally twice daily) or cefpodoxime (10 mg/kg/day orally twice daily)	Non-type 1 allergy
Levofloxacin	Levaquin®	10-20 mg/kg/day orally every 12-24 hours	Type 1 allergy
Risk for Antibiotic Resistance or Failed Initial Therapy			
Amoxicillin-clavulanate	Augmentin®	90 mg/kg/day orally twice daily	
Clindamycin plus cefixime or cefpodoxime	Cleocin®, Suprax®, Vantin®	Clindamycin (30-40 mg/kg/day orally three times daily) plus cefixime (8 mg/kg/day orally twice daily) or cefpodoxime (10 mg/kg/day orally twice daily)	
Levofloxacin	Levaquin®	10-20 mg/kg/day orally every 12-24 hours	
Severe Infection Requiring Hospitalization			
Ampicillin-sulbactam	Unasyn®	200-400 mg/kg/day IV every 6 hours	
Ceftriaxone	Rocephin®	50 mg/kg/day IV every 12 hours	
Cefotaxime	Claforan®	100-200 mg/kg/day IV every 6 hours	
Levofloxacin	Levaquin®	10-20 mg/kg/day IV every 12-24 hours	

Data from Reference 15.

TABLE 126-3 Antibiotics and Doses for Acute Bacterial Rhinosinusitis in Adults

Antibiotic	Brand Name	Dose	Comments
Initial Empirical Therapy			
Amoxicillin-clavulanate	Augmentin®	500 mg/125 mg orally three times daily, or 875 mg/125 mg orally twice daily	First line
Amoxicillin-clavulanate	Augmentin®	2,000 mg/125 mg orally twice daily	Second line
Doxycycline		100 mg orally twice daily or 200 mg orally once daily	Second line
β-Lactam Allergy			
Doxycycline		100 mg orally twice daily or 200 mg orally once daily	
Levofloxacin	Levaquin®	500 mg orally once daily	
Moxifloxacin	Avelox®	400 mg orally once daily	
Risk for Antibiotic Resistance or Failed Initial Therapy			
Amoxicillin-clavulanate	Augmentin®	2,000 mg/125 mg orally twice daily	
Levofloxacin	Levaquin®	500 mg orally once daily	
Moxifloxacin	Avelox®	400 mg orally once daily	
Severe Infection Requiring Hospitalization			
Ampicillin-sulbactam	Unasyn®	1.5-3 g IV every 6 hours	
Levofloxacin	Levaquin®	500 mg orally once daily	
Moxifloxacin	Avelox®	400 mg orally once daily	
Ceftriaxone	Rocephin®	1-2 g IV every 12-24 hours	
Cefotaxime	Claforan®	2 g IV every 4-6 hours	

Data from Reference 15.

High-dose amoxicillin-clavulanate is recommended as second line for initial empirical therapy in children and adults; doxycycline is also second line for adults but should be avoided in children.[15] High-dose amoxicillin-clavulanate is preferred in the following situations: (a) geographic regions with high endemic rates (10% or greater) of invasive penicillin-nonsusceptible *S. pneumoniae*, (b) severe infection, (c) attendance at daycare, (d) age less than 2 or greater than 65 years, (e) recent hospitalization, (f) antibiotic use within the last month, and (g) immunocompromised persons.[15] Severe infections are those with "evidence of systemic toxicity with fever of 39°C (102.2°F) or higher, and threat of suppurative complications."[15]

If a child has a β-lactam allergy, he/she may receive levofloxacin monotherapy or clindamycin plus cefixime or cefpodoxime combination therapy.[15] Adults may receive doxycycline, levofloxacin, or moxifloxacin monotherapy.[15] The guidelines also provide several options for patients at risk

for antibiotic resistance, who failed initial therapy, or who have a severe infection requiring hospitalization (Tables 126-2 and 126-3).[15] Notably, cephalosporins are no longer recommended as monotherapy due to variable rates of resistance against *S. pneumoniae*.[15] Macrolides are no longer recommended because of high rates of *S. pneumoniae* resistance.[15] Trimethoprim-sulfamethoxazole has not been recommended for some time due to resistance among *S. pneumoniae* and *H. influenzae*.[15]

The duration of therapy for the treatment of acute bacterial rhinosinusitis is not well established. Most trials have used 10- to 14-day antibiotic courses for uncomplicated rhinosinusitis, and the guidelines support this treatment duration in children.[15] For adults, the recommended duration is only 5 to 7 days.[15]

It is important to consider patient weight and renal function when selecting antibiotic therapy for acute bacterial rhinosinusitis. Notice that all of the antibiotics recommended for children are dosed according to patient weight. Furthermore, most of the recommended antibiotics are excreted through the kidneys and should be adjusted for renal function as described in the package labeling. There is limited evidence to suggest that people with certain genetic polymorphisms may be at greater risk for chronic rhinosinusitis; however, no such link has been identified for acute bacterial rhinosinusitis. Furthermore, patient genetics are not currently used to guide selection of antibiotic therapy for this condition.

Evaluation of Therapeutic Outcomes

If symptoms persist or worsen after 48 to 72 hours of appropriate antibiotic therapy, then the patient should be reevaluated and alternative antibiotics should be considered.[15] Patients who do not respond to first- or second-line therapies should be referred to a specialist and evaluated more aggressively, potentially with direct sinus aspiration or contrast-enhanced computed tomography.[15]

ACUTE PHARYNGITIS

1 2 Pharyngitis is an acute infection of the oropharynx or nasopharynx.[19] It is responsible for 6% of visits by children to their primary care provider annually.[20] Although viral causes are most common, group A β-hemolytic *Streptococcus* (GABHS, also known as *S. pyogenes*) is the primary bacterial cause[19]; pharyngitis due to GABHS is commonly known as “strep throat.”

Epidemiology

Acute pharyngitis accounts for approximately 15 million healthcare visits per year, at a cost of up to $539 million for children alone.[19] Although viral causes are most common, GABHS is the primary bacterial cause and is associated with rare but severe sequelae if not treated appropriately.[19] Suppurative and nonsuppurative complications include acute rheumatic fever, acute glomerulonephritis, reactive arthritis, peritonsillar abscess, retropharyngeal abscess, cervical lymphadenitis, mastoiditis, otitis media, rhinosinusitis, and necrotizing fasciitis.

Although all age groups are susceptible, epidemiologic data demonstrate certain groups are at higher risk. Children 5 to 15 years of age are most susceptible; parents of school-age children and those who work with children are also at increased risk. Pharyngitis in a child younger than 3 years of age is rarely caused by GABHS.[19]

Seasonal outbreaks occur, and the incidence of GABHS is highest in winter and early spring.[19] The incubation period is 2 to 5 days, and the illness often occurs in clusters.[19] Spread occurs via direct contact (usually from hands) with droplets of saliva or nasal secretions, and transmission is thus worse in institutions, schools, families, and crowded areas.[19] Untreated, patients with streptococcal pharyngitis are infectious during the acute illness and for another week thereafter. Effective antibiotic therapy reduces the infectious period to about 24 hours.

Acute rheumatic fever is rarely seen in developed countries. In the United States, acute rheumatic fever secondary to GABHS infection was a cause of concern in the 1950s and was the major reason for penicillin therapy, but the annual incidence of this disease today is extremely rare (1 case or more per 1 million population); however, some risk does remain. Outbreaks have been reported in the United States as recently as the late 1980s and early 1990s. Furthermore, acute rheumatic fever is widespread in developing countries.

Etiology

1 Viruses cause the majority of acute pharyngitis cases. Specific etiologies include rhinovirus (20%), coronavirus (5%), adenovirus (5%), herpes simplex virus (4%), influenza virus (2%), parainfluenza virus (2%), and Epstein–Barr virus (1%).[19]

4 A bacterial etiology is far less likely. Of all the bacterial causes, GABHS

is the most common (10%-30% of persons of all ages with pharyngitis) and is the only commonly occurring form of acute pharyngitis for which antibiotic therapy is indicated.[19] In the pediatric population, GABHS causes 15% to 30% of pharyngitis cases. In adults, GABHS is responsible for 5% to 15% of all symptomatic episodes of pharyngitis.[19]

Other less common causes of acute pharyngitis are groups C and G *Streptococcus*, *Corynebacterium diphtheriae*, *Neisseria gonorrhoeae*, *Mycoplasma pneumoniae*, *Arcanobacterium haemolyticum*, *Yersinia enterocolitica*, and *Chlamydia pneumoniae*.[19] Treatment options for these organisms are not addressed in this chapter.

Pathophysiology

The mechanism by which GABHS causes pharyngitis is not well defined. Asymptomatic pharyngeal carriers of the organism may have an alteration in host immunity (eg, a breach in the pharyngeal mucosa) and the bacteria of the oropharynx may migrate to cause an infection. Pathogenic factors associated with the organism itself, pyrogenic toxins, hemolysins, streptokinase, and proteinase, may also play a role.

Clinical Presentation

Sore throat is the most common symptom of pharyngitis. Accurate differentiation of GABHS from pharyngitis caused by other agents is important for treatment decisions; however, this can be difficult even for experienced clinicians. Therefore, microbiologic testing is recommended for symptomatic patients unless they have symptoms suggestive of viral etiology or are younger than 3 years of age.[19]

In previous guidelines, clinical scoring systems, such as the Centor criteria or modifications of the Centor criteria, have been advocated for clinical diagnosis in adults as a way to overcome the lack of sensitivity and specificity of clinician judgment and to avoid laboratory testing of all patients; however, guidelines from Infectious Disease Society of America and the American Heart Association suggest testing be done in all patients with signs and symptoms of streptococcal pharyngitis.[19] Only those with a positive test for GABHS require antibiotic treatment.[19] Laboratory tests should not be performed unless the patient has symptoms consistent with GABHS pharyngitis. This is because a positive test does not necessarily indicate disease. A positive test may simply indicate that the

patient is a carrier for GABHS and is not actively infected.

Approximately 20% of children are carriers of GABHS; the prevalence is lower among adults.[19] There are several options to test for GABHS. A throat swab can be sent for culture or used for the rapid antigen-detection test (RADT). Cultures are the gold standard, but they require 24 to 48 hours for results. The RADT is more practical in that it provides results quickly, it can be performed at the bedside, and it is less expensive than culture. If RADT is positive, it does not require a follow-up throat culture.[19] If RADT yields negative test results, it is generally recommended to follow up with a throat culture to confirm the results for children and adolescents, but not necessary in adults.[19] Delaying therapy while awaiting culture results does not affect the risk of complications (although some argue that symptomatic benefit is postponed, and contagion remains), and patients must be educated as to the value of waiting, given the low false-negative rate of RADT.[19]

CLINICAL PRESENTATION Group A Streptococcal Pharyngitis

General

- A sore throat of sudden onset that is mostly self-limited
- Fever and constitutional symptoms resolving in about 3 to 5 days
- Clinical signs and symptoms are similar for viral causes and nonstreptococcal bacterial causes

Signs and Symptoms of GABHS Pharyngitis

- Sore throat
- Pain on swallowing
- Fever
- Headache, nausea, vomiting, and abdominal pain (especially in children)
- Erythema/inflammation of the tonsils and pharynx with or without patchy exudates
- Enlarged, tender lymph nodes
- Red swollen uvula, petechiae on the soft palate, and a scarlatiniform rash

Signs Suggestive of Viral Origin for Pharyngitis

- Conjunctivitis
- Coryza
- Cough

Laboratory Tests

- Throat swab and culture
- Rapid antigen-detection test (RADT)

Data from Reference 19.

TREATMENT

Desired Outcomes

The goals of treatment for pharyngitis are to improve clinical signs and symptoms, minimize adverse drug reactions, prevent transmission to close contacts, and prevent acute rheumatic fever and suppurative complications, such as peritonsillar abscess, cervical lymphadenitis, and mastoiditis.[19]

General Approach to Treatment

Once the diagnosis of GABHS pharyngitis has been made, the clinician must decide appropriate supportive care, when to initiate antibiotic therapy, the appropriate antibiotic, and the duration of therapy. The selection of appropriate antibiotic therapy will involve careful consideration of cost, safety, efficacy, potential for regimen adherence, and bacterial resistance rates. Clinicians should be aware of local resistance patterns, which may differ from the national patterns.

4 Antibiotic overuse has been well documented.[19] Antibiotics are prescribed for 60% of patients who visit their provider with a complaint of "sore throat."[21,22] This rate is well above the incidence of GABHS pharyngitis. Antibiotic therapy should be reserved for those patients with clinical and epidemiologic features of GABHS pharyngitis, preferably with a positive laboratory test. Empirical therapy is not recommended; however, if used while

results are pending, it is important to discontinue empirical antibiotics once laboratory results come back as negative.

Nonpharmacologic Therapy

Supportive care should be offered to all patients with acute pharyngitis. Little evidence is available for nonpharmacologic therapy for pharyngitis. However, pharmacologic supportive care interventions include antipyretic medications, analgesics, and nonprescription lozenges and sprays containing menthol and topical anesthetics for temporary relief of pain.[19] There are limited data for use of corticosteroids to reduce the symptoms of GABHS pharyngitis, and given the risk of adverse effects, their use is not recommended.[19] Because pain is often the primary reason for visiting a physician, emphasis on analgesics such as acetaminophen and nonsteroidal anti-inflammatory drugs to aid in pain relief is strongly recommended.

Pharmacologic Therapy

The clinical practice guidelines published by the IDSA in 2012 are the primary source for many of the recommendations in this chapter.[19] **Tables 126-4** and **126-5** outline dosing for acute GABHS pharyngitis and chronic carriers of GABHS.

TABLE 126-4 Antibiotics and Doses for Group A β-Hemolytic Streptococcal Pharyngitis

Antibiotic	Brand Name	Dose	Duration	Rating
Preferred Antibiotics				
Penicillin V	Pen-V®	Children: 250 mg twice daily or three times daily orally. Adult: 250 mg four times daily or 500 mg twice daily orally	10 days	IB
Penicillin G benzathine	Bicillin L-A®	<27 kg: 0.6 million units; 27 kg or greater: 1.2 million units intramuscularly	One dose	IB
Amoxicillin[a]	Amoxil®	50 mg/kg once daily (maximum 1,000 mg); 25 mg/kg (maximum 500 mg) twice daily	10 days	IB
Penicillin Allergy				
Cephalexin	Keflex®	20 mg/kg/dose orally twice daily (maximum 500 mg/dose)	10 days	IB
Cefadroxil	Duricef®	30 mg/kg orally once daily (maximum 1 g)	10 days	IB
Clindamycin	Cleocin®	7 mg/kg/dose orally thrice daily (maximum 300 mg/dose)	10 days	IIaB
Azithromycin[b]	Zithromax®	12 mg/kg orally once daily (maximum 500 mg) for one day, then 6 mg/kg orally once daily (maximum 250 mg) for four days	5 days	IIaB
Clarithromycin[b]	Biaxin®	15 mg/kg orally per day divided in two doses (maximum 250 mg twice daily)	10 days	IIaB

These guidelines provide a systematic weighting of the strength of the recommendation (Class I, conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective; Class II, conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment; Class IIa, weight of evidence/opinion is in favor of usefulness/efficacy; Class IIb, usefulness/efficacy is less well established by evidence/opinion; Class III, conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful) and quality of evidence (A, data derived from multiple randomized clinical trials or meta-analyses; B, data derived from a single-randomized trial or nonrandomized studies; C, only consensus opinion of experts, case studies, or standard of care).

[a]Standard formulation, not extended release.

[b]Resistance of group A β-hemolytic *Streptococcus* (GABHS) to these agents may vary and local susceptibilities should be considered with these agents.

Data from Reference 19.

TABLE 126-5 Antibiotics and Doses for Eradication of Group A β-Hemolytic Streptococcal Pharyngitis in Chronic Carriers

Antibiotic	Brand Name	Dose
Clindamycin	Cleocin®	20-30 mg/kg/day orally in three divided doses (maximum 300 mg/dose)
Amoxicillin-clavulanate	Augmentin®	40 mg/kg/day orally in three divided doses (maximum 2,000 mg/day of amoxicillin)
Penicillin V and rifampin	Pen-V®, Rifadin®	Penicillin V: 50 mg/kg/day orally in four doses for 10 days (maximum 2,000 mg/day); *and* rifampin: 20 mg/kg/day orally in one dose for the last 4 days of treatment (maximum 600 mg/day)
Penicillin G benzathine and rifampin	Bicillin L-A®, Rifadin®	Penicillin G benzathine: <27 kg—0.6 million units, 27 kg or greater—1.2 million units intramuscularly; *and* rifampin: 20 mg/kg/day orally in two doses during last 4 days of treatment with penicillin (maximum 600 mg/day)

Data from Reference 19.

5 For over 30 years, GABHS isolated in the United States have been susceptible to penicillin, with no reported cases of GABHS resistance to penicillin.[19] Because penicillin and amoxicillin have a narrow spectrum of activity and are readily available, safe, and inexpensive, they are considered to be the treatments of choice.[19] A study that demonstrated that antibiotic therapy prevents rheumatic fever following GABHS pharyngitis was done with procaine penicillin, which was later replaced with benzathine penicillin.[19] Penicillin given by other routes is assumed to be equally efficacious. The ability of other antibiotics to eradicate GABHS has led to extrapolation that these antibiotics will also prevent rheumatic fever.[19]

Amoxicillin may be preferable for children with GABHS pharyngitis because the suspension is more palatable than penicillin.[19] Gastrointestinal (GI) adverse effects and rash are more common with amoxicillin. A once-daily, extended-release formulation of amoxicillin has been approved for treatment of GABHS pharyngitis in adults and children aged 12 years and older.[19]

If patients are unable to take oral medications, intramuscular benzathine penicillin can be given, although it is painful.[19] In penicillin-allergic patients,

azithromycin, clarithromycin, clindamycin, or a first-generation cephalosporin such as cephalexin can be used if the reaction is nonimmunoglobulin E (IgE)–mediated.[19] Newer macrolides, such as azithromycin and clarithromycin, are equally effective as erythromycin and cause fewer GI adverse effects; therefore, these newer macrolides are preferred to erythromycin. GABHS resistance to macrolides is low (5%-8%) in the United States, but is higher in some other areas of the world.[19]

In previous pharyngitis treatment guidelines, clindamycin was only an alternative for erythromycin-resistant strains; however, it is now considered an acceptable alternative for penicillin-allergic patients due to the low GABHS resistance rate of 1%.[19] Tonsillectomy is not recommended.

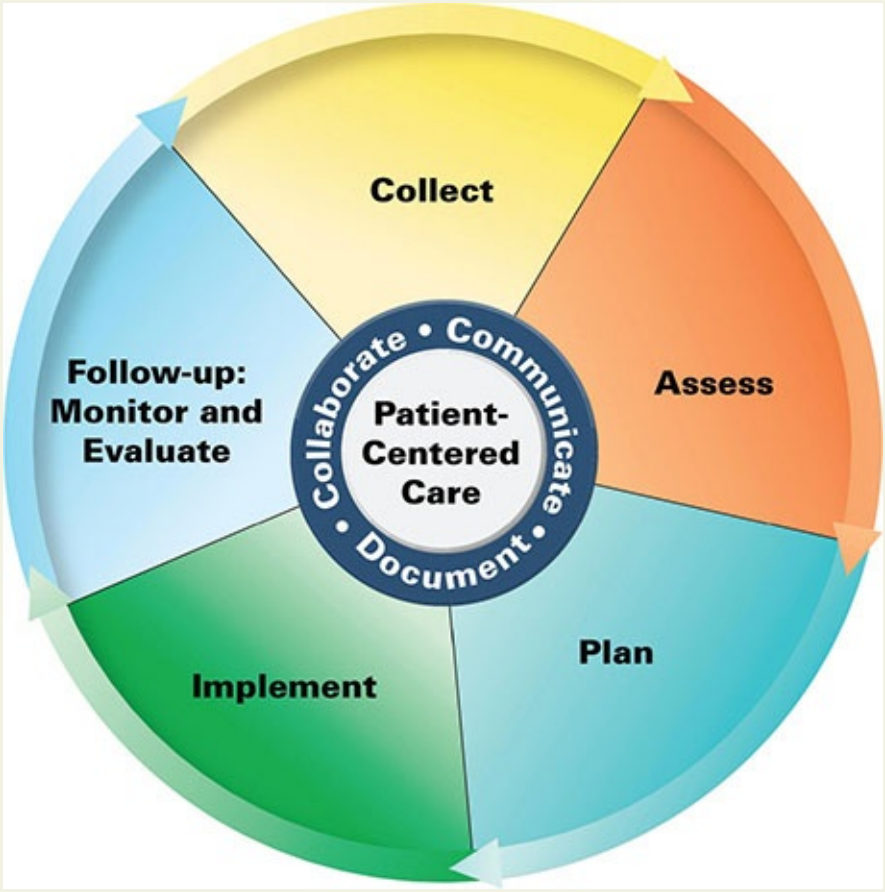
The ideal time to start antibiotics has not been established. The immediate therapy can be postponed up to 9 days without major nonsuppurative sequela.[19] Clinical guidelines recommend withholding antibiotics unless the patient has a positive laboratory result.[19]

GABHS resistance rates to tetracyclines are high. Sulfonamides and trimethoprim-sulfamethoxazole have poor eradication rates for GABHS; therefore, use of these antibiotics is no longer recommended.[19] Fluoroquinolones are not recommended due to poor activity of the older agents. The newer fluoroquinolones have activity against GABHS, but are expensive and have a broad spectrum of activity.[19]

The impact of appropriate antibiotic therapy is limited to decreasing the duration of signs and symptoms. The severity of pharyngitis symptoms and communicability of the disease is less after 24 hours of antibiotic therapy. The duration of therapy for GABHS pharyngitis is 10 days, except for benzathine penicillin and azithromycin, to maximize bacterial eradication.[19] A Cochrane review, published in 2012, examined short-course therapy and concluded that 3 to 6 days of oral antibiotics had comparable efficacy to oral penicillin for 10 days.[23] Although some clinicians have proposed shorter courses of treatment for pharyngitis, confounding factors from these studies, such as the lack of strict entry criteria or differentiation between new and failed infections, limit the widespread application of short-antibiotic courses at this time.[19]

Approximately 33% of household contacts of a person with acute GABHS pharyngitis harbor GABHS in their upper respiratory tracts.[19] Routine testing and/or treating of asymptomatic household contacts of an index patient is not recommended.[19] GABHS carriers do not need antimicrobial therapy due to low risk of spreading GABHS pharyngitis or developing suppurative or

nonsuppurative complications.[19] If tested, it is not necessary to treat these asymptomatic carriers. It is difficult to ascertain the cause of symptomatic pharyngitis in carriers of GABHS if they do develop symptoms. Providers should pay close attention to the symptoms to help differentiate viral versus bacteriologic cause of pharyngitis because laboratory tests will be positive in these patients.[19]



Patient Care Process for Acute Pharyngitis

Collect

- Patient characteristics (eg, age, weight)
- Patient history (eg, past infections including rheumatic fever and rheumatic heart disease, current and past antibiotic/antiviral use noting previous failures, medication allergies)
- Determine whether patient is a school-age child, parent/caregiver of a school-age child, or works with school-age children

- Objective data:
  - Temperature
  - Signs and symptoms (see Clinical Presentation)
  - Other diagnostic tests, when indicated (eg, rapid antigen-detection test [RADT], throat culture, microbiologic testing)

Assess

- Infection status, including presence of signs and symptoms
- Determine which symptoms may need additional therapy (eg, ongoing throat pain)
- Use information collected, patient factors (eg, patient age, symptom severity), and joint decision-making with parents/caregivers to determine whether antibiotics are needed
- If antibiotics are appropriate, determine proper choice of antibiotic, dose, duration, and dosage form

Plan*

- Select drug therapy regimen including specific antibiotic, dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Tables 126-4 and 126-5)
- Monitor efficacy (eg, temperature, pain), safety (eg, medication-specific adverse effects), and time frame
- Educate patient and/or caregiver (eg, purpose of treatment, drug therapy) emphasizing adherence to treatment regimen
- Recommend self-monitoring of body temperature

Implement*

- Provide patient education regarding the infection and all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up, when indicated
- Recommend measures to reduce throat pain, if present

Follow-up: Monitor and Evaluate

- Presence of adverse effects, particularly allergic reactions
- Patient adherence to treatment plan using multiple sources of information
- Inquire if there have been infections among household contacts

**Collaborate with patient, caregiver(s), and other healthcare professionals.*

When acute GABHS pharyngitis occurs in a carrier, a treatment course of appropriate antibiotics is recommended.[19] In the treatment of recurring episodes of culture-positive GABHS pharyngitis, there are limited data to support a particular antibiotic regimen. Several alternative antibiotics are preferred over penicillin or amoxicillin with GABHS carriers and recurrent pharyngitis. Amoxicillin-clavulanate, clindamycin, penicillin/rifampin combination, and benzathine penicillin G/rifampin combination may be considered for recurrent episodes of pharyngitis to maximize bacterial eradication in potential carriers and to counter copathogens that produce β-lactamases.[19] Table 126-5 outlines dosing for eradication of GABHS in chronic carriers and those who experience symptomatic episodes.

Patients with documented histories of rheumatic fever (including cases manifested solely by Sydenham's chorea) and those with definite evidence of rheumatic heart disease should receive continuous antibiotic prophylaxis initiated as soon as the patient is diagnosed and the initial infection has been treated. The duration of secondary prophylaxis is individualized based on patient risk of recurrence of rheumatic fever and/or rheumatic heart disease. Intramuscular benzathine penicillin G every 4 weeks is the recommended regimen for secondary prevention in the United States in most circumstances.[24] Additional options for secondary prophylaxis include oral penicillin V and sulfadiazine. Medication adherence is critical for successful secondary prevention with oral antibiotics. Sulfadiazine is an effective antibiotic for the prevention of infection and is appropriate if the patient is penicillin-allergic. Sulfonamides are not appropriate for treatment of GABHS pharyngitis because they are not effective for eradication of GABHS. If individuals are allergic to penicillin and sulfadiazine, a macrolide or azalide is recommended; however, this recommendation is based on expert opinion rather than clinical trial data.[25]

Factors that should be considered when personalizing therapy for a patient include allergy status, prior antibiotic use, and adherence. Those with a history of antibiotic use for acne may be at higher risk for resistant strains of GABHS. Short-course antibiotics or penicillin G benzathine may be considered in patients with a history of nonadherence.

Evaluation of Therapeutic Outcomes

Most pharyngitis cases are self-limited; however, antibiotics hasten resolution when given early for proven cases of GABHS pharyngitis.[19] Generally, fever and other symptoms resolve within 3 to 4 days of onset without antibiotics; however, symptoms will improve 0.5 to 2.5 days earlier with antibiotic therapy.[19] Follow-up testing is generally not necessary for index cases or asymptomatic contacts[19]; however, throat cultures 2 to 7 days after completion of antibiotics are warranted for patients who remain symptomatic or when symptoms recur despite completion of treatment.[19]

Postclass Engaged Learning Activity

Review the otitis media, rhinosinusitis, and acute pharyngitis case studies in the Pharmacotherapy Casebook, which can be obtained through Access Pharmacy. Prepare to answer questions related to each case. Compare and contrast what is described in the cases to the "classic" presentation, diagnosis, treatment, and prognosis described in this chapter.

ABBREVIATIONS

AAO-HNSF	American Academy of Otolaryngology—Head and Neck Surgery Foundation
AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
CFU	colony-forming unit
GABHS	group A β-hemolytic streptococci
GI	gastrointestinal
IDSA	Infectious Diseases Society of America
IgE	immunoglobulin E
MIC	minimal inhibitory concentration
PCV7	seven-valent pneumococcal conjugate vaccine
RADT	rapid antigen-detection test
T tube	tympanostomy tube
URI	upper respiratory infection

REFERENCES

1. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, National Ambulatory Medical Care Survey: 2015 State and National Summary Tables.
2. Monasta L, Ronfani L, Marchetti F, et al. Burden of disease caused by otitis media: Systematic review and global estimates. PLoS One. 2012;7:e36226.
3. Marom T, Tan A, Wilkinson GS, Pierson KS, Freeman JL, Chonmaitree T. Trends in otitis media-related health care use in the United States, 2001-2011. JAMA Pediatr 2014;168:68–75.
4. Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. Pediatrics. 2013;131:e964–999.
5. Casey JR, Kaur R, Friedel VC, Pichichero ME. Acute otitis media otopathogens during 2008 to 2010 in Rochester, New York. Pediatr Infect Dis J. 2013;32:805–809.
6. Jabarin B, Pitaro J, Lazarovitch T, et al. Decrease in pneumococcal otitis media cultures with concomitant increased antibiotic susceptibility in the pneumococcal conjugate vaccines era. Otol Neurotol. 2017;38:853–859.
7. Qureishi A, Lee Y, Belfield K, Birchall JP, Daniel M. Update on otitis media: Prevention and treatment. Infect Drug Resist. 2014;7:15–24.
8. Rosenfeld RM, Shin JJ, Schwartz SR, et al. Clinical practice guideline: Otitis media with effusion (update). Otolaryngol Head Neck Surg. 2016;154:S1–S41.
9. Tapiainen T, Kujala T, Renko M, et al. Effect of antimicrobial treatment of acute otitis media on the daily disappearance of middle ear effusion: A placebo-controlled trial. JAMA Pediatr. 2014;168:635–641.
10. Venekamp RP, Sanders SL, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. Cochrane Database Syst Rev 2015;6:CD000219.
11. Hoberman A, Paradise JL, Rockette HE, et al. Shortened antimicrobial treatment for acute otitis media in young children. N Engl J Med. 2016;375:2446–2456.
12. Schuetz P, Briel M, Christ-Crain M, et al. Procalcitonin to guide initiation and duration of antibiotic treatment in acute respiratory infections: An individual patient data meta-analysis. Clin Infect Dis. 2012;55:651–662.

13. Schuetz P, Muller B, Christ-Crain M, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Cochrane Database Syst Rev 2012;9:CD007498.
14. Schuetz P, Amin DN, Greenwald JL. Role of procalcitonin in managing adult patients with respiratory tract infections. Chest. 2012;141:1063–1073.
15. Chow AW, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis 2012;54:e72–e112.
16. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): Adult sinusitis. Otolaryngol Head Neck Surg. 2015;152:S1–S39.
17. Schiller JS, Lucas JW, Ward BW, Peregoy JA. Summary health statistics for U.S. adults: National Health Interview Survey, 2010. Vital Health Stat102012:1–207.
18. Garbutt JM, Banister C, Spitznagel E, Piccirillo JF. Amoxicillin for acute rhinosinusitis: A randomized controlled trial. JAMA. 2012;307:685–692.
19. Shulman ST, Bisno AL, Clegg HW, et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. Clin Infect Dis. 2012;55:1279–1282.
20. Cohen JF, Cohen R, Levy C, et al. Selective testing strategies for diagnosing group A streptococcal infection in children with pharyngitis: A systematic review and prospective multicentre external validation study. Can Med Assoc J. 2015;187:23–32.
21. Dooling KL, Shapiro DJ, Van Beneden C, Hersh AL, Hicks LA. Overprescribing and inappropriate antibiotic selection for children with pharyngitis in the United States, 1997-2010. JAMA Pediatr. 2014;168:1073–1074.
22. Barnett ML, Linder JA. Antibiotic prescribing to adults with sore throat in the United States, 1997-2010. JAMA Intern Med. 2014;174:138–140.
23. Altamimi S, Khalil A, Khalaiwi KA, Milner RA, Pusic MV, Al Othman MA. Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children. Cochrane Database Syst Rev 2012;8:CD004872.
24. Remond MG, Coyle ME, Mills JE, Maguire GP. Approaches to improving adherence to secondary prophylaxis for rheumatic fever and rheumatic

heart disease: A literature review with a global perspective. Cardiol Rev. 2016;24:94–98.

25. van Driel ML, De Sutter AI, Keber N, Habraken H, Christiaens T. Different antibiotic treatments for group A streptococcal pharyngitis. Cochrane Database Syst Rev 2013:CD004406.

Influenza

Jessica Njoku

KEY CONCEPTS

1. Influenza is a viral illness associated with high mortality and high hospitalization rates among persons older than 65 years of age. The aging of the population is contributing to an increased disease burden in the United States.
2. Seasonal influenza epidemics are the result of viral antigenic drift, which is why the influenza vaccine is changed on a yearly basis. Antigenic drift forms the foundation of the recommendation for annual influenza vaccination.
3. The acquisition of a new hemagglutinin and/or neuraminidase by the influenza virus is called *antigenic shift*, which results in a novel influenza virus that has the potential to cause a pandemic.
4. The primary route of influenza transmission is person-to-person via inhalation of respiratory droplets, and transmission can occur for as long as the infected person is shedding virus from the respiratory tract.
5. Clinical diagnosis of influenza is difficult. Classic signs and symptoms include abrupt onset of fever, muscle pain, headache, malaise, nonproductive cough, sore throat, and rhinitis. These signs and symptoms usually resolve within 1 week of presentation.
6. In the United States, the primary mechanism of influenza prevention is annual vaccination. Vaccination not only prevents influenza illness and influenza-related hospitalizations and deaths but may also decrease healthcare resource use and the overall cost to society.
7. The inactivated influenza vaccine (IIV) and the live-attenuated influenza vaccine (LAIV) are commercially available for prevention of seasonal influenza. Both vaccines contain influenza A subtypes H3N2 and H1N1,

and influenza B virus, which are initially grown in hens' eggs.

8. Antiviral drugs for prophylaxis of influenza should be considered adjuncts to vaccine and are not replacements for annual vaccination.
9. The sooner antiviral drugs are started after the onset of illness, within 48 hours of symptom onset, the more effective they are.
10. Neurominidase inhibitors (oseltamivir, zanamivir, and peramivir) and cap-dependent endonuclease inhibitor (baloxavir) that have activity against both influenza A and influenza B viruses. Although the adamantanes inherently have activity against influenza A H1N1 viruses, they are no longer used clinically due to overwhelming viral resistance.

Preclass Engaged Learning Activity

1. Complete the influenza vaccine table

Approved Influenza Vaccines for Different Age Groups—United States

Vaccine	Trade Name	Manufacturer	Dose/ Presentation	Thimerosal Mercury Content (mcg Hg/0.5-mL dose)	Age Group	Number of Doses
aIIV3						
IIV3 High Dose						
IIV4						
IIV4						
IIV4						
IIV4						
IIV4-High Dose						
ccIIV4						
RIV4						
LAIV4						

2. Complete the below treatment recommendation for influenza and duration of use. Please define appropriate ages for zanamivir use

	Treatment	Chemoprophylaxis
Oseltamivir		
Adults		
Children ≥12 months by Body Weight (kg)		
≤15 kg		
>15 kg to 23 kg		
>23 kg to 40 kg		
>40 kg		
Zanamivir		
Adults		
Children		
Peramivir		
Adult		
Children		
Baloxivir		
Adult		
Children		

INTRODUCTION

Influenza causes significant morbidity and mortality, particularly among young children and the elderly. Seasonal influenza epidemics result in 25 to 30 million cases, approximately 600,000 hospitalizations, and over 50,000 deaths each year in the United States.[1] Globally, influenza causes nearly 650,000 deaths each year, with the highest burden among children younger than 5 years and adults 75 years and older.[2] More people die of influenza than of any other vaccine-preventable illness. Significant societal consequences associated with influenza include visits to physicians' offices and emergency departments and days lost from school and/or work. The societal costs associated with influenza are more than $10 billion in healthcare costs and $16.3 billion in indirect costs.[3]

Vaccination is the primary mechanism of influenza prevention in the United States. The antiviral armamentarium for treatment and prophylaxis of influenza is limited, which further emphasizes the importance of prevention with vaccination and appropriate use of infection control measures during outbreaks.

Research toward the development of novel antivirals and vaccines is needed for effective control of seasonal epidemics and for pandemic preparedness.

ETIOLOGY AND EPIDEMIOLOGY

Influenza infection can occur at any time during the year with the highest rates of influenza-associated illness during the winter months. The highest rate of infection occurs in children, but the highest rates of severe illness, hospitalization, and death occur among those older than age 65 years, young children (younger than 2 years old), and those who have underlying medical conditions, including pregnancy and cardiopulmonary disorders, that increase their risk of complications from influenza. The seasonal influenza epidemics has resulted in an estimated 9.3 to 49 million influenza-related illnesses, 4.3 to 16.6 million healthcare visits, and between 12,000 and 79,000 deaths annually since 2010.[4] During 2018 to 2019 influenza season alone, influenza resulted in 37.4-42.9 million flu illnesses, 17.3-20.1 million flu medical visits, 531,000-647,000 flu hospitalizations, and 36,400-61,200 flu deaths.[5] Influenza-associated illness was three times higher among children aged 0 to 4 years compared with among those aged 5 to 17 years.[6] Similarly, influenza-associated illness rates were 8.9 times higher, and 2.8 times higher, among persons older than or equal to 65 years compared with among those aged 18 to 49 years, and 50 to 64 years, respectively.[1,6] Furthermore, influenza related hospitalization was highest among individuals age 65 years or older; 219.6 per 100,000 population. Vaccination coverage with ≥1 dose of flu vaccine was 62.6% among children 6 months through 17 years. Flu vaccination coverage among adults ≥18 years was 45.3%.[7] Vaccine coverage was highest among individuals 6 months to 4 years (73.4%) and age 65 years or older (68.1%), however, vaccine effectiveness was low, 12% among individuals 65 years or older compared to 49% for children less than 9 years of age.[8] Thus, the aging of the population is contributing to an increased disease burden. Deaths associated with influenza often result from secondary bacterial pneumonia, primary viral pneumonia, and/or exacerbation of underlying comorbidities.[9]

Influenza Viruses A, B, and C

Influenza virus types A, B, and C are members of the Orthomyxoviridae family and affect many species, including humans, pigs, horses, and birds. Influenza A and B viruses are the two types that cause disease in humans. Influenza A

viruses are responsible for the regular, seasonal epidemics of the flu, whereas influenza B viruses are typically associated with sporadic outbreaks, particularly among residents of long-term care facilities. Influenza A viruses are further categorized into different subtypes based on changes in two surface antigens—hemagglutinin and neuraminidase (NA). Influenza B viruses are not categorized into subtypes.

Hemagglutinin allows the influenza virus to enter host cells by attaching to sialic acid receptors and is the major antigen to which antibodies are directed on exposure.[10] NA allows the release of new viral particles from host cells by catalyzing the cleavage of linkages to sialic acid.[10]

Sixteen hemagglutinin subtypes (H1-H16) and nine NA subtypes (N1-N9) of influenza A have been isolated from birds. However, the only influenza A subtypes that have circulated among humans since the 1918 pandemic (see Antigenic Drift and Antigenic Shift in the following section) are H1 to H3 and N1 and N2.[10] The primary subtypes of influenza A that have been circulating among humans for the past three decades are H3N2 and H1N1.

Antigenic Drift and Antigenic Shift

2 Immunity to influenza virus occurs as a result of the development of antibody directed at the surface antigens, particularly hemagglutinin. However, immunity to one influenza subtype does not offer protection against other subtypes or types of influenza. Moreover, immunity to one antigenic variant of a subtype of influenza may not confer protection against other antigenic variants. Antigenic variants are created by point mutations in the surface antigens of a particular subtype, resulting in small changes in the hemagglutinin and/or NA molecules, which is called *antigenic drift*. Antigenic drift is the basis for seasonal epidemics of influenza, the reason for changes in the annual influenza vaccine, and the rationale behind the recommendation for annual vaccination.

3 Immunity to one subtype of influenza does not confer protection against other subtypes or types. Antigenic shift occurs when the influenza virus acquires a new hemagglutinin and/or NA via genetic reassortment rather than point mutations.[10] Most likely, the genetic reassortment occurs when an animal that supports the growth of multiple subtypes of influenza, such as a pig, is concurrently infected with two subtypes of the influenza virus. Conversely, antigenic shift may occur directly from avian strains that have gained competency in the human host. Antigenic shift results in the emergence of a novel influenza virus and carries the potential of causing a pandemic. However,

novelty alone is insufficient to cause an influenza pandemic; the virus must be able to replicate in humans, spread person-to-person, and affect a susceptible population.[10]

Spanish Influenza of 1918

The influenza pandemic of 1918 was the most significant infectious disease outbreak known to humans, causing approximately 40 to 50 million deaths in a year, with more than 500,000 deaths occurring in the United States.[11] The pandemic originated in China, but occurred almost concurrently in Europe, Asia, and North America.[11]

The 1918 pandemic was caused by a particularly virulent influenza A H1N1 virus, which was entirely of avian origin.[11] In contrast to the other pandemics of the 20th century, the 1918 pandemic resulted in an unusual mortality pattern. The mortality peaked for those younger than 4 years of age, those between the ages of 25 and 35 years, and those older than 65 years of age, which resulted in a W-shaped mortality curve, as opposed to the U- or J-shaped curve typically associated with influenza.[8] Over half of the deaths occurred in persons aged 20 to 40 years. The death toll associated with this pandemic culminated in an almost 10-year drop in the life expectancy of the population at the time.[11]

Asian Influenza of 1957

The Asian flu pandemic began when a new H2 subtype of influenza A surfaced in Hunan province in China in 1957.[10] The virus appeared to have formed from coinfection with an avian H2N2 virus and a human H1N1 virus in a common host, possibly a pig or a human. The H2N2 virus quickly spread to Japan, South America, the United States, New Zealand, and Europe, resulting in 1 to 2 million deaths worldwide, with 70,000 deaths occurring in the United States.[12] Unlike the Spanish flu of 1918, the mortality curve for the Asian flu pandemic was U- or J-shaped, with infants and elderly being most affected.

Hong Kong Influenza of 1968

The H2N2 virus of the Asian flu circulated in the human population until 1968, when a new H3 subtype emerged in China and Hong Kong following genetic reassortment with the H2N2 virus.[10] The H3N2 virus quickly spread to the United States and later to Europe. This pandemic caused more than 30,000

deaths in the United States and 0.5 to 2 million deaths worldwide. The lower morbidity and mortality associated with the Hong Kong flu may be explained by previous exposure of the population to the N2 subtype, and the availability of antibiotics for the management of secondary bacterial pneumonia. Similar to the Asian flu of 1957, the mortality curve for the Hong Kong flu pandemic was U- or J-shaped, primarily affecting infants and elderly.

Avian Influenza

Influenza viruses are in circulation in southern China during all months of the year.[10] Given this fact and the close proximity of dense populations of people, pigs, and wild and domestic birds, this area proves ideal for the development of new influenza viruses via genetic reassortment (antigenic shift), as demonstrated by the pandemics of 1957 and 1968 and, most recently, the emergence of what is known as avian influenza. Avian influenza infection have been reported with A(H5N1), A(H5N6), A(H7N9), A(H9N2), A(H6N1), and A(H7N4) in China.[13] Even though small clusters of cases have been reported, human-to-human transmission of the viruses have not been sustained.

The first report of human infection with the avian H5N1 virus occurred in 1997 in Hong Kong.[13] The virus reemerged in 2003 as an antigenically and genetically different virus that has spread widely through wild and domestic bird populations in Asia, Africa, and Europe as well as infecting humans in several countries.[14] From 2003 to June 24, 2019, 861 cases and 455 deaths caused by H5N1 infection have been reported. The current overall case fatality is 53%.

The novel avian influenza H7N9 virus infection was first reported in humans in March 2013, in China.[15] Since then, 1568 laboratory-confirmed cases of human infection have been reported, including 615 deaths.[14] The majority of avian H7N9 human infection cases have been among those with recent exposure to live poultry or potentially contaminated environments, especially markets where live birds are sold.[15] The current overall case fatality is 41%.

In December 2014, the first case of novel avian influenza H5N6 human infection, was reported in China,[14] and to date, 25 laboratory-confirmed human cases of avian influenza A(H5N6) virus infection, including 6 deaths, were reported to World Health Organization (WHO) from China.[10,16]

The spread of avian influenza viruses from person to person has been reported rarely, and has been limited, inefficient, and unsustained.[12–15] The precise mode of transmission is unknown, but most cases have occurred as a result of contact with poultry, contaminated environment, and prolonged person-

to-person contact.[12] Cases of transmission via aerosolization have not been reported.[12] Clinical presentation includes high fever and influenza-like illness, and watery diarrhea without blood may occur up to 1 week prior to respiratory symptoms.[12] Almost all patients have clinically apparent pneumonia. Progression to death, most commonly as a consequence of respiratory failure, occurs at a mean of 9 to 10 days after the onset of illness.[16] The NA inhibitors (oseltamivir, peramivir, and zanamivir) and cap-dependent endonuclease inhibitor (baloxavir marboxil) have activity against influenza A and B viruses (including H1N1), although higher doses of NA inhibitors may be needed.[16,17] Oseltamivir and peramivir resistance has been detected in several patients infected with A (H1N1)pdm09 and H5N1 viruses.[17–19] Amantadine and rimantadine are ineffective against avian influenza viruses. Two inactivated monovalent influenza vaccines, nonadjuvanted[20] and adjuvanted[21] influenza H5N1 vaccine and a H7N9[22] virus vaccine, are available for vaccination of persons 6 months and older. They are only available to government agencies and for stockpiles.[13] The recommended dose of the nonadjuvanted vaccine is two 1-mL injections given intramuscularly 28 days apart (range, 21-35 days) if 18 to 64 years old,[20] while the nonadjuvanted vaccine dose is two 0.5-mL injections given 21 days apart if adjuvanted vaccine if 18 to 64 years old, or two 0.25-mL injection given 21 days apart if 6 months to 17 years.[21] The vaccines are supplied in a 5-mL multidose vial, with ~50 mcg thimerosal per dose in the nonadjuvanted vaccine,[20] and 5 mcg thimerosal per dose in the adjuvanted vaccine,[21] added as a preservative. The monovalent adjuvanted vaccine is supplied in two separate vials, a vial of H5N1 antigen and a vial of AS03 adjuvant, that must be combined before use, for the final volume per vial that provides 10 doses at 0.5 mL per dose.[21] Individuals at high risk, for example, those who work with poultry and H5N1 poultry outbreak responders, are encouraged to receive annual seasonal influenza vaccine to minimize the risk of coinfection with human and avian influenza A viruses.

CLINICAL PRESENTATION Diagnosis of Influenza

General

- The clinical diagnosis of influenza can be difficult because the presentation is similar to a number of other respiratory illnesses. The sensitivity of clinical diagnosis ranges from 40% for children to 70% for adults and largely depends on the relative prevalence of influenza and

other respiratory viruses circulating in a community.[32–34]

- The clinical course and outcome are affected by age, immunocompetence, viral characteristics, smoking, comorbidities, pregnancy, and the degree of preexisting immunity.[34]
- Complications of influenza may include exacerbation of underlying comorbidities, primary viral pneumonia, secondary bacterial pneumonia or other respiratory illnesses (eg, sinusitis, bronchitis, otitis), encephalopathy, transverse myelitis, myositis, myocarditis, pericarditis, and Reye's syndrome.[31,34]

Signs and Symptoms

- 5 Classic signs and symptoms of influenza include rapid onset of fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis.[18,28,34]
- Nausea, vomiting, and otitis media are also commonly reported in children.[33]
- Signs and symptoms typically resolve in approximately 3 to 7 days, although cough and malaise may persist for more than 2 weeks.
- Primary viral pneumonia, occurring predominantly in pregnant women and in those with underlying cardiovascular disease, usually begins with fever and dry cough, which changes to a productive cough of bloody sputum. This rapidly progresses to dyspnea, hypoxemia, and cyanosis with radiologic evidence of bilateral interstitial infiltrates.[34]
- Secondary bacterial pneumonia is usually seen in individuals with underlying pulmonary disorders and presents during the early stages of defervescence from the influenza infection. These patients usually present with fever, productive cough, and radiologic evidence of consolidation.[34]

Laboratory Tests

- Complete blood count and chemistry panels should be obtained to assess the overall status of the patient.
- The gold standard for diagnosis of influenza are reverse-transcription polymerase chain reaction (RT-PCR) or viral culture, which can provide information on the specific strain and subtype. Viral culture has a high

sensitivity but can take as long as a week to develop, limiting the clinical relevance of the results.[34–35]

Other Diagnostic Tests

- Cultures of potential sites of infection should be obtained if coinfection, superinfection, or secondary infection is suspected.
- Chest radiograph should be obtained if pneumonia is suspected.

Influenza Diagnostics Tests

Influenza Molecular Assays;

Rapid influenza molecular assays (RIMAs): detect influenza viral RNA in upper respiratory tract specimens utilizing different nucleic acid amplification technologies (NAATs). Generally have high sensitivity (90%–95%) and high specificity (55%–99%), depending on the virus type, compared with RT-PCR assays.[36–37] FDA-cleared RIMAs are available for point of care (POC) use that produce results in approximately 15-30 minutes.

RT-PCR (real time or multiplex) is a nucleic acid amplification test that can identify the presence of influenza viral RNA or nucleic acids in respiratory specimens with very high sensitivity and specificity. It is the most sensitive, specific, and versatile diagnostic test for influenza.[35] Results are available in approximately 45 minutes to several hours (1 to 6 hours) depending upon the assay, and are frequently used as a confirmatory test.

Rapid influenza diagnostic tests (RIDTs)

RIDTs use enzyme immunoassay (EIA) technology to provide results within 10-15 minutes and may have utility in community- and hospital-based outpatient settings because of their rapid processing times. RIDTs allow for differentiation of influenza viruses A and B but none of the RIDTs provide any information about influenza A virus subtypes. Sensitivities for RIDTs range are low often yielding false-negative results, while specificities are high compared with RT-PCR or viral culture.[35–37] For this reason, RIDTs are not recommended for use in hospitalized patients with suspected influenza, and RIMAs are preferred in outpatient settings since CLIA-waived tests are available for POC use.

Immunofluorescence assays (IFAs)

IFAs are antigen detection assays that generally require use of a fluorescent microscope to produce results in approximately 2-4 hours with moderate

sensitivity and high specificity. One rapid IFA is an RIDT and utilizes an analyzer device to produce results in approximately 15 minutes.[35]

Viral Culture

Culture allows for extensive antigenic and genetic characterization of influenza viruses. However, viral culture results do not yield timely results to inform clinical management. Shell-vial tissue culture results may take 1-3 days, while traditional tissue-cell viral culture results may take 3-10 days.

Serologic Testing

Routine serological testing for influenza requires paired acute and convalescent sera, does not provide timely results to help with clinical decision-making, is only available at a limited number of public health or research laboratories and is not generally recommended, except for research and public health investigations.

Specimen collection

Upper respiratory tract specimens should be collected from outpatients for influenza testing as soon after illness onset as possible, preferably within 4 days of symptom on-set to increase detection of influenza viruses. Nasopharyngeal specimens are preferred over other upper respiratory tract specimens. If nasopharyngeal specimens are not available, nasal and throat swab specimens should be collected and combined together for influenza testing over single specimens from either site (particularly over throat swabs). Collect endotracheal aspirate or bronchoalveolar lavage fluid specimens from hospitalized patients with respiratory failure receiving mechanical ventilation, including patients with negative influenza testing results on upper respiratory tract specimens, for influenza testing.

The potential for avian viruses H5N1 and H7N9 to cause a pandemic is of concern as it could spread more quickly than pandemics of the past because of the mobility of people in today's world. In 2018 alone, international tourist travels worldwide was 1.5 billion, which was a 108% increase since 2000, and a 13.4% increase since 2016.[23] In 2018, U.S. residents made over 93 million travels outside the country, which was a 40% increase since 2009, and a 16% increase since 2016.[24] Likewise, in 2018 the U.S. was the third most frequent destination in international tourist travel arrivals with 80 million.[23] The wide spread of 2009 novel influenza was attributed to extensive global trade and travel, such that the virus was detected in 122 countries in 6 weeks as opposed to

6 months with previous pandemics.[25] A severe pandemic, like that of 1918, could cause more than 10 million hospitalizations and more than 2 million deaths, whereas a moderate pandemic, like those of 1957 and 1968, could result in more than 1 million hospitalizations and more than 650,000 deaths in the United States alone.[23–25]

Swine Influenza of 2009

An outbreak of a novel influenza A H1N1 (formerly swine origin influenza virus [SOIV]) was initially detected in Mexico in March 2009 and subsequently in the United States in April 2009 in California and Texas.[26] The virus then spread throughout North America, Europe, Asia, and subsequently worldwide, prompting the WHO on June 11, 2009 to declare phase 6, indicating widespread human infection, for the influenza pandemic.[27] Since 1998, triple reassortant swine influenza A (H1) viruses, containing genes from swine, avian, and human lineages, have circulated among swine in the United States.[12,26]

However, the novel influenza A H1N1 virus is unique in that although much of the genome is similar to the triple reassortant swine viruses previously seen in the United States, the genes encoding for NA and matrix (M) proteins are most similar to those circulating in the Eurasian swine population. This particular genetic combination has not been seen before.[26] The virus, now formally known as influenza A(H1N1) pdm09, has since become the predominant influenza A H1N1 in circulation, effectively replacing traditional seasonal influenza A (H1N1).

Several characteristics of the novel influenza A H1N1 outbreak differ from those of a typical seasonal influenza outbreak. Symptomatology associated with the novel influenza include fever (94%), cough (92%), sore throat (66%), diarrhea (25%), and vomiting (25%).[26,28] An estimated 43 to 89 million cases of 2009 H1N1 occurred between April 2009 and April 2010 with a median 274,000 hospitalizations. Globally, up to 575,000 H1N1-related deaths were reported; however, this may represent an underestimation of true disease burden.[25,27] The majority of the cases occurred in otherwise healthy children and young adults younger than 65 years of age including pregnant women, with the highest incidence reported among those aged 18 to 64 years.[27] Contrary to seasonal influenza where about 60% of hospitalizations and 90% of deaths occur in people older than or equal to 65 years, approximately 90% and 87% of 2009 H1N1-related hospitalizations and deaths, respectively, occurred in people younger than 65 years. However, like seasonal influenza, people with underlying

health conditions had greater risk of hospitalizations and death. Among those who were deceased due to novel H1N1 infection, the median age was ~40 years and 59% of deaths (respiratory and cardiovascular) occurred in Southeast Asia and Africa.[27]

Variant Influenza A (H3N2v) 2012

H3N2v is a nonhuman influenza virus that normally circulates in pigs and that has infected humans.[29] In August 2011, the US Centers for Disease Control and Prevention (CDC) reported the first case of an influenza infection due to influenza A H3N2 variant virus (H3N2v).[29] Since then, 430 cases have been documented from 17 states in the United States resulting in 34 hospitalizations and low mortality.[30] The H3N2v is considered a variant virus because it is different from influenza A viruses circulating among humans. The H3N2v virus contains genes from avian, swine, and human viruses and the M gene from the 2009 H1N1 pandemic virus (A[H1N1]pdm09).[29,30] The virus was originally detected in pigs in 2010 but human infection was first documented in July 2011. The virus appears to spread more readily from pigs to people than other variant viruses, but has limited person-to-person transmission. The main risk factor for infection with the virus based on evaluation of available cases is exposure to pigs, mostly at agricultural fairs.[30] Since the virus is related to human flu viruses from the 1990s, most adults have some immunity against it.[29] Hence, most cases to date have occurred in children, who have little immunity against this virus.[27,30]

The symptoms and severity of H3N2v have mostly been mild and similar to those of seasonal influenza (fever, cough, sore throat, body aches, etc.), but like seasonal influenza, serious illness with H3N2v infection is possible.[27] Vaccination remains key to preventing H3N2v infection. Additionally, the CDC has encouraged people at high risk of influenza complications to stay away from swine barns at fairs.[30] People who are at high risk of serious complications from influenza, including H3N2v virus infection, are: children younger than 5 years, people older than or equal to 65 years, pregnant women, body mass index of 40 or higher, age less than 19 years of age on long-term aspirin or salicylate containing drugs, chronic care facility residents, and people with certain chronic medical conditions (asthma, cystic fibrosis, chronic obstructive pulmonary disease, diabetes, heart disease, stroke, sickle cell, kidney and liver disorders, inherited metabolic disorders, immunocompromised, and neurologic or neurodevelopmental conditions).[31] The treatment of H3N2v virus infection is

similar to that of seasonal influenza. NA inhibitors and cap-dependent endonuclease inhibitor are the mainstay of treatment. The adamantanes should not be used due to high resistance.

PATHOGENESIS

4 The route of influenza transmission is person-to-person via inhalation of respiratory droplets, which can occur when an infected person coughs or sneezes.[28,32] Transmission may also occur if a person touches an object contaminated with respiratory secretions and then touches his or her mucus membranes. The incubation period for influenza ranges between 1 and 7 days, with an average incubation of 2 days.[32] Transmission can occur for as long as the infected person is shedding virus from the respiratory tract. Adults are considered infectious within 1 day before until 7 days after onset of illness. Children, especially younger children, might potentially be infectious for longer periods (more than 10 days).[33,34] Viral shedding can persist for weeks to months in severely immunocompromised people.

The pathogenesis of influenza in humans is not well understood. The severity of the infection is determined by the balance between viral replication and the host immune response. Severe illness is likely a result of both a lack of ability of host defense mechanisms to inhibit viral replication and an overproduction of cytokines leading to tissue damage in the host.[38]

PREVENTION

The best means to decrease the morbidity and mortality associated with influenza is to prevent infection through vaccination.[32-33] Appropriate infection control measures, such as hand hygiene, basic respiratory etiquette (eg, cover your cough, throw tissues away), and contact avoidance, are also important in preventing the spread of influenza. Additionally, chemoprophylaxis is useful in certain situations.

Vaccination

6 The primary means of influenza prevention used in the United States is annual vaccination. Vaccination can help prevent hospitalization and death among those at high risk, decrease influenza-like illness, decrease visits to

physicians' offices and emergency rooms, decrease otitis media in children, and prevent school and/or work absenteeism. Annual vaccination is recommended for all persons aged 6 months or older and caregivers (eg, parents, teachers, babysitters, nannies) of children younger than 6 months. Vaccination is also recommended for those who live with and/or care for people who are at high risk, including household contacts and healthcare workers.

The ideal time for all influenza vaccination is during October or November to allow for the development and maintenance of immunity during the peak of the influenza season.[32–33] **Table 127-1** lists the vaccination coverage rates and goals for various patient populations. Provider recommendation and offer of vaccination was associated with significantly higher vaccine uptake among adults 18 years and older (66.6%), compared to providers who only recommended but did not offer (48.4%), and those who neither recommended nor offered (32%).[39] If vaccination rates improved to the Healthy People goal of 70% for all age groups, another 4.6 million illnesses, 2.2 million medical visits, and 65,844 hospitalizations could have been prevented during the 2018 to 2019 influenza season.[5,38] Vaccine efficacy is highest when influenza virus in circulation is well matched with strains in the vaccine. Mismatched seasons have occurred, and were associated with reduced influenza vaccine uptake and severe influenza infection. A meta-analysis showed that TIV (vaccine efficacy 52% vs matched 65%) and LAIV (vaccine efficacy 54% vs matched 83%) provide cross protection against nonmatching circulating strains.[41]

TABLE 127-1 Influenza Vaccination Rates and Goals by Patient Population[38,39,40]

Patient Population	Vaccination Coverage (%) 2018–2019	Vaccination Coverage National Goal (2020)
Children aged 6 months to 17 years	63	70%
Persons aged 18 or greater	45.3	70%
Nursing home residents	68.1	90%
Pregnant women	53.7	80%
Healthcare workers	81.1 [hospital 95.2; ambulatory 79.8; Long-term care 67.9]	90%

7 The two vaccine types currently available for prevention of seasonal influenza are the inactivated influenza vaccine (IIV), and the live attenuated influenza vaccine (LAIV).[32] IIV is available as trivalent (IIV3) and quadrivalent (IIV4) formulations, while LAIV is a quadrivalent formulation. Both vaccines contain two influenza A subtypes (H3N2 and H1N1) and influenza B virus; the specific strains included in the vaccine each year change based on antigenic drift. The viruses used for both vaccines are initially grown in embryonated hens' eggs, which explains the precautionary measures for vaccination of persons with a severe allergic reaction to eggs.[32] Of the two vaccines produced using nonegg based technologies, recombinant quadrivalent vaccine [RIV4 (Flublok® Quadrivalent)] and cell-culture quadrivalent vaccine [ccIIV4 (Flucelvax Quadrivalent®)], only Flublok® is considered egg-free. Flucelvax® contains a maximum of 5×10^{-8} mcg/0.5-mL dose of total egg protein ovalbumin. The Advisory Committee on Immunization Practices (ACIP) has made the following recommendations regarding the vaccinations of persons with reports of egg allergy: (a) Vaccination with any age appropriate IIV, RIV4, or LAIV4 vaccine, for persons with a history of egg allergy that involves only hives. (b) Persons with severe allergic reactions (ie, symptoms other than hives) such as angioedema, respiratory distress, light-headedness, or recurrent emesis or required epinephrine after an egg exposure may be immunized with any licensed IIV, RIV4, or LAIV4 that is appropriate for age and health status. Vaccine should be administered in an inpatient or outpatient medical setting (including but not necessarily limited to hospitals, clinics, health departments, and physician offices), under the supervision of a healthcare provider who is able to recognize and manage severe allergic conditions. (c) Severe allergic reaction to influenza vaccine is a contraindication to receiving future vaccinations. (d) Vaccine providers should consider observing all patients for 15 minutes after vaccination to decrease the risk for injury should a patient experiences syncope.[30] The CDC encourages individuals to use the Vaccine Adverse Event Reporting System to aide in collecting and analyzing adverse events following influenza vaccinations.[32]

Trivalent and Quadrivalent Influenza Vaccine

7 Intramuscular IIV is FDA approved for use in people age 6 months and older regardless of their immune status. For adults and older children, the deltoid is the preferred injection site. Infants and younger children should be vaccinated in the anterolateral thigh. Several commercial products are available and are approved

for different age groups (Table 127-2). IIV is made with killed viruses, meaning it cannot cause signs and symptoms of influenza-like illness (Table 127-3). Age and immune status can affect the efficacy of IIV as can the similarity of the vaccine to the viruses in circulation. Fluzone quadrivalent may be given to children aged 6 through 35 months as either 0.25 mL per dose or 0.5 mL per dose. No preference is expressed for one or the other dose volume for this age group. Persons aged ≥3 years should receive 0.5-mL dose volume.[32] Afluria® quadrivalent vaccine use has been expanded to include people 6 months and older, and is contraindicated in patients with hypersensitivity to neomycin or polymyxin.[32]

TABLE 127-2 Approved Influenza Vaccines for Different Age Groups—United States, 2019–2020 Season[32,33]

Vaccine	Trade Name	Manufacturer	Dose/Presentation	Thimerosal Mercury Content (mcg Hg/0.5-mL dose)	Age Group	Number of Doses
Trivalent IIV (IIV3s) – adjuvanted and high dose						
aIIV3	Fluad	Seqirus	0.5-mL single dose prefilled syringe	0	≥65 years	1
IIV3 High Dose	Fluzone HD	Sanofi Pasteur	0.5-mL prefilled syringe	0	≥65 years	1
Quadrivalent IIVs (IIV4s)						
IIV4	Afluria	Seqirus	0.25-mL prefilled syringe	0	6-35 months	1 or 2[a]
			0.5-mL prefilled syringe	0	≥3 years	1 or 2[a]
			5-mL multidose vial	24.5	≥6 months via needle/ syringe or 18-64 years via jet injector	1 or 2[a]
IIV4	Fluarix Quadrivalent	GlaxoSmithKline	0.5-mL prefilled syringe	0	≥6 months	1 or 2[a]
IIV4	FluLaval Quadrivalent	GlaxoSmithKline	0.5-mL prefilled syringe	0	≥6 months	1 or 2[a]
			5-mL multidose vial	<25	≥6 months	
IIV4	Fluzone Quadrivalent[b]	Sanofi Pasteur	0.25-mL prefilled syringe	0	≥6-35 months	1 or 2[a]
				0	≥6 months	1 or 2[a]
			0.5-mL prefilled syringe	0	≥6 months	1 or 2[a]
			0.5-mL single-dose vial	25	≥6 months	1 or 2[a]
			5-mL multidose vial			
Quadrivalent IIV High Dose (IIV4-HD)						
IIV4 High Dose	Fluzone HD Quadrivalent	Sanofi Pasteur	0.7-mL prefilled syringe	0	≥65 years	1
Cell culture based quadrivalent IIVs (ccIIV4)						
ccIIV4	Flucelvax Quadrivalent	Seqirus	0.5-mL prefilled syringe	0	≥4 years	1 or 2[a]
			5-mL multidose vial	25	≥4 years	1 or 2[a]
Recombinant quadrivalent IIVs (RIV4)						
RIV4	Flublok Quadrivalent	Sanofi Pasteur	0.5-mL prefilled syringe	0	≥18 years	1
LAIV Quadrivalent (LAIV4)						
LAIV	FluMist Quadrivalent	AstraZeneca	0.2-mL sprayer	0	2-49 years	1 or 2[c]

[a]Two doses administered at least 4 weeks apart are recommended for children aged 6 months to less than 9 years who are receiving influenza vaccine for the first time or received one dose in first year of vaccination during the previous influenza season.

[b]Fluzone Quadrivalent may be given to children aged 6 through 35 months as either 0.25 mL per dose or 0.5 mL per dose. No preference is expressed for one or the other dose volume for this age group. Persons aged ≥3 years should receive 0.5-mL dose volume.

[c]Two doses administered.

IIV, inactivated influenza vaccine; IIV3, inactivated influenza trivalent vaccine; aIIV3, adjuvanted inactivated influenza vaccine, trivalent, standard dose; IIV4, inactivated influenza quadrivalent vaccine; IIV4-HD, inactivated influenza quadrivalent vaccine – high dose; ccIIV3, cell culture-based trivalent influenza vaccine; RIV4, recombinant quadrivalent influenza vaccine; LAIV, live-attenuated influenza vaccine.

Note: IIVs and RIV4 may be administered concomitantly or sequentially with other inactivated vaccines or live vaccines. LAIV4 may be administered simultaneously with other live or inactivated vaccines. However, after administration of a live vaccine (such as LAIV4), at least 4 weeks should elapse before another live vaccine is administered.

Influenza antiviral medications might reduce the effectiveness of LAIV4 if given within 48 hours before, to 14 days after administration of LAIV4. Persons who receive influenza antiviral medications within this period of LAIV4 vaccination can be revaccinated with another appropriate influenza vaccine (e.g., IIV or RIV4)..

TABLE 127-3 Comparison of Inactivated Influenza Vaccine (IIV) and Live-Attenuated Influenza Vaccine (LAIV)[32–34]

Characteristic	IIV (IIV3/IIV4)	LAIV
Age groups approved for use	≥6 months	2-49 years
Immune status requirements	Immunocompetent or immunocompromised	Immunocompetent
Viral properties	Inactivated (killed) influenza A (H3N2), A (H1N1), and B viruses	Live-attenuated influenza A (H3N2), A (H1N1), and B viruses
Route of administration	Intramuscular	Intranasal
Immune system response	High serum IgG antibody response	Lower IgG response and high serum IgA mucosal response

In children between 6 and 24 months of age, a 2-year randomized study of intramuscular IIV3 exhibited 89% seroconversion and efficacy of 66% in year 1 and 7% in year 2 versus culture-confirmed influenza.[42] In children between 2 and 15 years of age, the efficacy of IIV3 was 91.4% and 77.3% against culture-confirmed influenza A H1N1 and H3N2, respectively. A Cochrane review reported that IIVs reduced the risk of influenza and influenza-like illness (ILI) in children.[43] To prevent one case of influenza, five children would need to be vaccinated and to prevent one case of ILI, 12 children would need to be vaccinated. Therefore, vaccinating children could prevent influenza related mortality and may also lead to fewer parents taking time off work. Two doses of IIVs are important for children under the age of 9 years, supporting the rationale for the recommendation of a booster dose of IIV at least 4 weeks after the initial dose in children between 6 months and less than 9 years of age if no previous vaccination (see Table 127-2).[32]

IIV is also effective in adult populations under and older than the age of 65 years. A Cochrane analysis evaluating intramuscular IIVs in healthy adults 16 to 65 years demonstrated a reduction in influenza, ILI, hospitalization, and work absenteeism.[44] Seventy one adults would need to be vaccinated to prevent one influenza case, and 29 adults need to be vaccinated to prevent one ILI. In pregnant women, IIVs efficacy was 50% (number needed to vaccinate, NNV

55), and 49% in infants up to 24 weeks (NNV 56).

Adults older than the age of 65 years benefit from influenza vaccination, including prevention of complications, decreased risk of influenza-related hospitalization, and death.[46] However, people in this population may not generate a strong antibody response to the vaccine and may remain susceptible to infection. In patients older than the age of 60 years who do not reside in a long-term care facility, IIV efficacy was 58% against influenza illness.[45] Although the efficacy against influenza illness for those living in long-term care facilities is between 30% and 40%, the vaccine is 50% to 60% effective in preventing influenza-related hospitalization or pneumonia and 80% effective in preventing influenza-related death.[45]

A randomized controlled trial compared efficacy of Fluzone HD trivalent to standard IIV3 over two influenza seasons (2011-2013) among 31,989 persons aged ≥65 years.[46] Fluzone HD trivalent induced higher immune response and offered better protection than SD-IIV3 for this age group. Fluzone HD prevented 24% more cases of influenza caused by any circulating influenza strain and 51% more cases of influenza caused by strains similar to those contained in the vaccine compared to standard trivalent vaccine. Compared to IIV3, Fluzone HD trivalent would avert 195,958 cases of influenza, 22,567 influenza-related hospitalizations, 5423 influenza-related deaths, and generate 29,023 more Quality Adjusted Life Years among US seniors.[47] In November 2019, the FDA approved Fluzone HD quadrivalent vaccine for use in adult patients 65 years and older.[48] The vaccine will be available for use starting 2020-2021 influenza season to replace Fluzone HD trivalent vaccine.[48] For the 2019-2020 influenza season, the ACIP recommends that persons aged ≥65 years may receive any age-appropriate IIV (standard- or high-dose, trivalent or quadrivalent, adjuvanted or unadjuvanted) or RIV4.[32]

The most frequent adverse effect associated with IIV is soreness at the injection site that lasts for less than 48 hours. IIV may cause fever and malaise in those who have not previously been exposed to the viral antigens in the vaccine.[32] Allergic-type reactions (hives, systemic anaphylaxis) rarely occur after influenza vaccination and are likely a result of a reaction to residual egg protein in the vaccine.

The 1976 swine influenza vaccine was linked to a rise in the incidence of Guillain-Barré syndrome (GBS), and this has propagated the belief that IIV may cause GBS.[49] However, there is insufficient evidence to establish causality. Although several studies have failed to establish a relationship between

influenza vaccination and increased frequency of GBS, some studies have demonstrated a small but significant increase in GBS following influenza vaccination.[49] Therefore, vaccination should be avoided in persons who are not at high risk for influenza complications and who have experienced GBS within 6 weeks of receiving a previous influenza vaccine.[32] The potential benefits of influenza vaccination in terms of prevention of severe illness, hospitalization, and mortality significantly outweigh the risks of GBS, and vaccination is recommended for all groups previously discussed.

The multidose vials and a few of the single-dose preparations of intramuscular IIV contain trace to small amounts of a preservative, thimerosal, which is a mercury-containing compound (see Table 127-2). Some individuals are concerned about thimerosal exposure, particularly among children, because of the unfounded belief that thimerosal exposure is linked to the development of autism. No scientifically persuasive evidence exists to suggest harm from thimerosal exposure from a vaccine. Conversely, accumulating evidence reports the lack of harm from such exposure.[50,51] Thus, similar to GBS, the potential benefits of influenza vaccination in terms of prevention of severe illness, hospitalization, and mortality significantly outweigh the theoretical risk associated with thimerosal exposure, and vaccination is recommended for all groups previously discussed. However, to maximize the public health benefit and placate concerned individuals, thimerosal-free vaccine is available (see Table 127-2).

Live-Attenuated Influenza Vaccine

7 LAIV is made with live, attenuated viruses and is approved for intranasal administration in healthy people between 2 and 49 years of age (see Table 127-3). Advantages of LAIV include its ease of administration, intranasal rather than intramuscular administration, and the potential induction of broad mucosal and systemic immune response.[32] The mucosal response occurs at the site of viral entry and may prevent infection before viral replication occurs. LAIV is more expensive than IIV and is approved for use in a more limited population. Originally licensed as a trivalent vaccine, in February 2012, the FDA approved FluMist® Quadrivalent vaccine (LAIV4) for influenza prevention in people aged 2 to 49 years.[32] FluMist® Quadrivalent vaccine which has replaced the trivalent vaccine contains four strains of the influenza viruses, two influenza A strains and two influenza B strains.The inclusion of a second B strain in the vaccine is thought to increase the likelihood of adequate protection against circulating

influenza B strains.

Studies of FluMist® trivalent, in addition to three new clinical trials with the quadrivalent vaccine in 4,000 children (2-17 years) and adults (18-49 years) in the United States, provide supporting evidence on the efficacy and safety of FluMist® Quadrivalent.[52] Immune responses were similar between FluMist® Quadrivalent and FluMist® trivalent. LAIV4 recipients aged 2 to 5 years had 52.5% and 54.4% fewer cases of influenza illness against matched and mismatched strains, respectively, as compared with IIV3 recipients.[52]

Although LAIV4 is FDA approved for adults younger than the age of 49 years, LAIV is effective in healthy adults between 18 and 64 years old.[32] LAIV4 should not be used during pregnancy. Vaccination reduced the number of severe febrile illnesses by 18.8% and febrile upper respiratory tract illnesses by 23.6%.[52] Additionally, vaccination led to fewer days of illness, fewer days lost from work, fewer visits to healthcare providers, and decreased use of prescription antibiotics and nonprescription medications.[52]

Adverse reactions of LAIV are similar among those receiving FluMist® Quadrivalent and FluMist® trivalent. The adverse effects typically associated with LAIV administration include runny nose, congestion, sore throat, and headache. Because LAIV contains live, attenuated viruses, viral shedding may occur for several days following vaccination with LAIV, although this should not be equated with person-to-person transmission.[32] Additionally, because LAIV contains live, attenuated viruses, which carry a theoretical infection risk, LAIV should not be given to immunosuppressed patients or given by healthcare workers who are severely immunocompromised. Moreover, for the reasons discussed in IIV above, LAIV should not be administered to persons with a history of GBS or hypersensitivity to eggs. Research from the CDC showed vaccine effectiveness of LAIV was 45% against influenza A and B, with 25% protection against influenza A (H1N1)pdm09 compared with unvaccinated children.[32] LAIV is not recommended in several populations, including people older than 50 years and pregnant women, largely because the vaccine has not been studied extensively in these populations. However, many clinicians believe the use of LAIV in these populations is acceptable.[32,52]

Postexposure Prophylaxis

8 Antiviral drugs available for prophylaxis of influenza should be considered adjuncts but are not replacements for annual vaccination. Neuraminidase (NA)

inhibitor antiviral medications are approximately 70% to 90% effective in preventing influenza against susceptible influenza viruses and are useful adjuncts to influenza vaccination.[53] Historically, the adamantanes and NA inhibitors are two classes of antiviral drugs available for influenza prophylaxis and treatment. However, the adamantanes are no longer recommended for prophylaxis or treatment in the United States (because of widespread resistance among influenza viruses) until susceptibility is reestablished among influenza A virus.[33,53] Peramivir is not approved for chemoprophylaxis; however, oseltamivir and zanamivir are effective prophylactic agents against influenza in terms of preventing laboratory-confirmed influenza when used for seasonal prophylaxis (67% and 85% effective for zanamivir and oseltamivir, respectively) and preventing influenza illness among persons exposed to a household contact who was diagnosed with influenza (79%-81% and 68%-89% effective for zanamivir and oseltamivir, respectively).[32,53] Additionally, oseltamivir was 92% effective against influenza and also reduced associated complications when used as seasonal prophylaxis among immunized, institutionalized, elderly patients.[32,53] Oseltamivir is FDA approved for the treatment of influenza in individuals 14 days and older, and for chemoprophylaxis in individuals 1 year and older. However, the CDC, the American Academy of Pediatrics (AAP), and the Pediatric Infectious Diseases Society (PIDS) provide an expanded recommendation for treatment in those less than 14 days, and chemoprophylaxis in those 3 months and older.[33,53] All of these agents remain active against all influenza viruses, including influenza A H3N2v (**Tables 127-4** and **127-5**). **Table 127-6** gives dosing recommendations.

TABLE 127-4 Antiviral Susceptibilities of Circulating Viruses[53]

	Baloxavir	Oseltamivir	Zanamivir	Peramivir	Adamantanes
Variant influenza A (H3N2), 2015	Susceptible	Susceptible	Susceptible	Susceptible	Resistant
Novel influenza A (H1N1)	Susceptible	Susceptible[a]	Susceptible	Susceptible[a]	Resistant
Seasonal A (H3N2)	Susceptible	Susceptible	Susceptible	Susceptible	Resistant
Influenza B	Susceptible	Susceptible	Susceptible	Susceptible	Resistant
Avian influenza (H5N1)	Susceptible	Susceptible	Susceptible	Susceptible	Variable

[a]Small number of isolates shown to be resistant to oseltamivir and peramivir.

TABLE 127-5 Recommendations for the Selection of Antiviral Treatment Based on Confirmed Influenza Subtypes[33,34,53]

Laboratory Test	Preferred[a]	Alternative
Not performed or negative, but influenza suspected clinically[a]	Baloxavir or oseltamivir or zanamivir or peramivir	None
Positive variant H3N2v	Baloxavir or oseltamivir or zanamivir or peramivir	None
Positive novel H1N1	Baloxavir or oseltamivir or zanamivir or peramivir	None
Positive A (H3N2), or B	Baloxavir or oseltamivir or zanamivir or peramivir	None
Positive A + B	Baloxavir or oseltamivir or zanamivir or peramivir	None

[a]Viral surveillance data might help guide antiviral choices if oseltamivir resistance becomes more prevalent.

TABLE 127-6 Recommended Daily Dosage of Influenza Antiviral Medications for Treatment and Prophylaxis— United States[33,34,53]

Drug	Adult Treatment	Adult Prophylaxis[a]	Pediatric Treatment	Pediatric Prophylaxis[a]
		CAP-dependent endonuclease inhibitor		
Baloxavirb[b,c]	12 yrs and older: 40 to <80 kg: One 40 mg dose >80 kg: One 80 mg dose	None	FDA approved and recommended for use in children 12 yrs or older weighing at least 40 kg. See adult dosage	None
		Neurominidase inhibitors		
Oseltamivir[d,e,f]	75-mg capsule twice daily x 5 days	75-mg capsule daily x 10 days	Term infants 0–8 months: 3 mg/kg/dose twice daily 9–11 months[g]: 3.5 mg/kg/dose twice daily or 3 mg/kg/dose twice daily ≥1 year: ≤15 kg: 30 mg twice daily >15–23 kg: 45 mg twice daily >23–40 kg: 60 mg twice daily >40 kg: 75 mg twice daily Duration: All for 5 days	Not recommended if <3 months 3-< 12 months, 3 mg/kg/dose daily 9–11 months, 3.5 mg/kg/dose daily ≥1 year: ≤15 kg: 30 mg daily >15–23 kg: 45 mg daily >23–40 kg: 60 mg daily >40 kg: 75 mg daily Duration: All for 10 days
Zanamivir	10 mg (2 of 5 mg inhalations) twice daily × 5 days	10 mg (2 of 5 mg inhalations) daily x 10 days	10 mg (2 of 5 mg inhalations) twice daily × 5 days for ≥7 years old	10 mg (2 of 5 mg inhalations) daily for ≥ 5 years old x 10 days
Peramivir[c,f]	13 yrs and older: One 600 mg dose via intravenous infusion for 15-30 minutes	None	2 to 12 yrs of age: One 12 mg/kg dose, up to 600 mg maximum, via intravenous infusion for a minimum of 15–30 minutes	None

[a]If influenza vaccine is administered, prophylaxis can generally be stopped 14 days after vaccination for noninstitutionalized persons. When prophylaxis is being administered following an exposure, prophylaxis should be continued for 10 days after the last exposure. In persons at high risk for complications from influenza for whom vaccination is contraindicated or expected to be ineffective, chemoprophylaxis should be continued for the duration that influenza viruses are circulating in the community during influenza season.

[b]Time to peak = 4 hours. Food and cations (calcium, aluminum, magnesium, iron) can decrease peak concentration by 48%. Long half-life (79.1 hours) and is metabolized by UDP-glucuronosyltransferase (UGT1A3) and CYP3A4.

[c]For the treatment of uncomplicated influenza with oral baloxavir or intravenous peramivir, a single dose is recommended. Longer daily dosing (oral oseltamivir or intravenous peramivir) can be considered for patients who remain severely ill after 5 days of treatment.

[d]Oseltamivir dosing for preterm infants using their postmenstrual age (i.e., gestational age + chronological age): <38 weeks: 1.0 mg/kg/dose twice daily; 38–40 weeks: 1.5 mg/kg/dose twice daily; >40 weeks: 3.0 mg/kg/dose twice daily.[33]

[e]In patients with renal insufficiency, the dose should be adjusted on the basis of creatinine clearance. See https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm.[34,53]

[f]Some experts recommend 150 mg twice daily for severe illness in pregnant women. Optimal dosing for prophylaxis in pregnant women is unknown.[34]

[g]The American Academy of Pediatrics recommends 3.5 mg/kg per dose twice daily; CDC and US Food and Drug Administration (FDA)–approved dosing is 3 mg/kg per dose twice daily for children aged 9–11 months.[33,56]

Note: Although amantadine and rimantadine have been used historically for the treatment and prophylaxis of influenza A viruses, due to high resistance, the CDC no longer recommends the use of these agents for the treatment and/or prophylaxis of influenza.

In those patients who did not receive the influenza vaccination and are

receiving an antiviral drug for prevention of disease during the influenza season, the medication should optimally be taken for the entire duration of influenza activity in the community. The use of prophylaxis requires clinical judgment and depends on a variety of factors, but prophylaxis for seasonal influenza should be considered during influenza season for the following groups of patients after exposure to an infectious source:[33,34,53]

1. Persons at high risk of serious illness and/or complications who are exposed to an infectious person and cannot be vaccinated.
2. Persons at high risk of serious illness and/or complications who are vaccinated but exposed to an infectious person during the first 2 weeks following vaccination. The development of sufficient antibody titers after vaccination takes approximately 2 weeks.
3. Persons with severe immune deficiency or who may have an inadequate response to vaccination (e.g., advanced human immunodeficiency virus [HIV] disease, persons receiving immunosuppressive medications), after exposure to an infectious person.
4. Long-term care facility residents, regardless of vaccination status, when an outbreak has occurred in the institution.

LAIV should not be administered until 48 hours after influenza antiviral therapy has stopped, and influenza antiviral drugs should not be administered for 2 weeks after the administration of LAIV because the antiviral drugs inhibit influenza virus replication.[32,34] No contraindication exists for concomitant use of IIV and influenza antiviral drugs. If chemoprophylaxis is given, it should be administered as soon as possible after exposure, ideally no later than 48 hours after exposure.[34] Postexposure prophylaxis should not be given if >48 hours has elapsed since exposure, and full-dose empiric antiviral treatment should be initiated as soon as symptoms occur, if treatment is indicated. Duration of chemoprophylaxis in a non-outbreak setting is 7 days after the most recent exposure to a close contact with influenza.[34,53]

Pregnant Women and Immunocompromised Hosts

Pregnant women and immunocompromised hosts are special populations at increased risk of influenza complications and are also populations in whom careful consideration must be given in regard to prevention strategies.

Pregnant women, regardless of trimester, should receive annual influenza vaccination with IIV but not with LAIV.[32,34] No studies have demonstrated an

increased incidence of adverse effects in mothers or their infants related or potentially related to IIV, but no such data exist for LAIV.[32] A CDC study by Thompson and colleagues looked at pregnant mothers hospitalized with confirmed influenza across four countries, and found that getting a influenza vaccination reduced hospitalizations for influenza by about 40%.[54] Influenza vaccination of pregnant women reduced hospitalization of their infants by 92% during the first 6 months of life.[55] IIV is also safe for breast-feeding mothers. No data exist for LAIV and breast-feeding mothers, but caution is warranted because of the potential for viral shedding.[32]

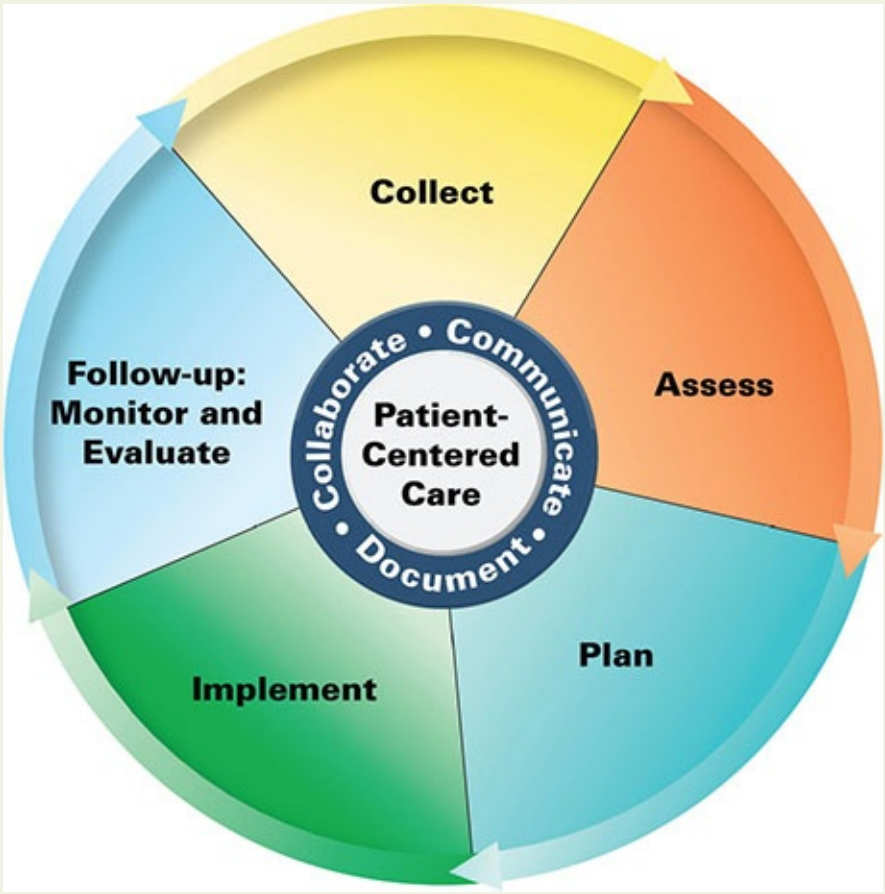
Immunocompromised hosts should receive annual influenza vaccination with IIV but not with LAIV. IIV was 100% effective against laboratory-confirmed influenza in HIV-positive patients with no significant effect on viral load or CD4 cell count.[56] HIV-infected persons may benefit from vaccination with high-dose IIV3 due to greater immunogenicity compared to standard-dose vaccine (H1N1, seroprotection rate; 96% vs 87%).[56] Similarly, a study comparing high-dose IIV3 to standard dose IIV in solid-organ transplant recipients reported higher immunogenicity with high-dose IIV3.[57] One study showed that two-dose vaccination strategy spaced 5 weeks apart in solid-organ transplant recipient elicited greater immune response compared to single dose.[58] Although this suggests a potential benefit from a two-dose regimen, such a regimen is not currently recommended for solid-organ transplant recipients. Yet annual influenza vaccination and early antiviral therapy was shown to reduce influenza-related morbidity in transplant recipients (solid and hematopoietic).[59] Immune responses in patients receiving chemotherapy for either solid or hematologic tumors are lower (fourfold rise, 17%-52%) than in those who had completed chemotherapy (50%-83%) and healthy patients (67%-100%).[60] However, a Cochrane analysis reported lower mortality and infection related outcomes with influenza vaccination of immunocompromised adults with cancer.[61]

Large clinical trials evaluating the use of influenza antivirals for prophylaxis are lacking in immunocompromised hosts. Viral shedding occurs for prolonged periods in this population and may promote the development of antiviral resistance, which has been documented with oseltamivir in immunocompromised patients.[33,34]

TREATMENT

When prevention efforts fail or are not used, clinicians must turn to the agents available for treatment of influenza. Currently, the antiviral treatment options are

limited, particularly in the face of resistance to the adamantanes and oseltamivir. The four primary goals of therapy of influenza are to control symptoms, prevent complications, decrease work and/or school absenteeism, and prevent the spread of infection.



Patient Care Process for Influenza Infection Treatment

Collect

- Patient characteristics: age, occupation, travel, lifestyle, immune status, present & past medical history, allergies
- Medication history (include prescription, nonprescription, and other substances); vaccination history; pregnancy status
- Microbiologic results from rapid respiratory viral panel and secondary bacterial infection. Bacterial susceptibility tests when available (see Clinical Presentation: Diagnosis of Influenza)
- Laboratory results, major organ function (particularly kidney and liver),

lactate

Assess

- Assess for medication contraindications and drug interactions
- Determine severity of illness based on vital signs, acute organ dysfunction, and source control (or lack thereof). (See Clinical Presentation: Diagnosis of Influenza)
- Determine at-risk patients for secondary bacterial infection of the respiratory tract, patient's microbiologic history, previous antibiotic exposure, and response to current therapy (see Clinical Presentation: Diagnosis of Influenza)
- Determine if other conditions are present such as chronic lung disease likely to affect outcomes of infection
- Estimate creatinine clearance for drug dosing

Plan*

- Strongly recommend future influenza vaccine if no contraindication is present (Tables 127-2 and 127-3)
- Initiate treatment neuraminidase therapy—oral or inhaled or IV based on severity of illness (Table 127-5 and 127-6)
- Determine influenza treatment goals of therapy with monitoring parameters for each goal (see Goals of Therapy)
- Determine appropriate antibiotic therapy for secondary bacterial infection and monitoring plan
- Establish antimicrobial monitoring goals for efficacy (eg, resolution of infection, clearance of bacteria from blood cultures) and drug toxicity
- Check for drug interactions and dose adjustments based on end-organ function

Implement

- Initiate a neuraminidase inhibitor and continue for ~7 days after identification of illness onset in the last patient (prophylaxis for community outbreak) or 5 days (treatment) or establish tentative stop date for severely ill patients
- If secondary bacterial infection suspected, initiate empiric antimicrobial regimen, and deescalate antimicrobial therapy to more narrow-spectrum

agents as appropriate based on response and microbiologic data

- Assess patient as needed for response to antiviral medications, and other treatments
- Use measures to minimize adverse events to medications and assess for occurrence of adverse events

Follow-up: Monitor and Evaluate

- Refer patient for other health, wellness, or follow-up services to their identified primary care provider or another provider (provide patient with documentation of referral)
- Determine if patient shows improvement in the signs and symptoms of infection within 48 hours after neuraminidase inhibitor is initiated
- Monitor for emergence of resistant virus. (Table 127-4)
- Monitor for occurrence of secondary bacterial pneumonia

**Collaborate with patient, caregiver(s), and other healthcare professionals.*

General Approach to Treatment

9 In the era of pandemic preparedness and increasing resistance, early and definitive diagnosis of influenza is crucial. The currently available antiviral drugs are most effective if started within 48 hours of the onset of illness. Moreover, the sooner the antiviral drugs are started after the onset of illness, the more effective they are. Antiviral drugs shorten the duration of illness and provide symptom control. Adjunct agents, such as acetaminophen for fever or an antihistamine for rhinitis, may be used concomitantly with the antiviral drugs.

Nonpharmacologic Therapy

Patients suffering from influenza should get adequate sleep and maintain a low level of activity. They should stay home from work and/or school in order to rest and prevent the spread of infection. Appropriate fluid intake should be maintained. Cough/throat lozenges, warm tea, or soup may help with symptom control (cough, sore throat).

Pharmacologic Therapy

The Cap-dependent endonuclease inhibitor, baloxavir and NA inhibitors, oseltamivir, zanamivir, and peramivir are the only antiviral drugs available for the treatment and prophylaxis of influenza.[53] Peramivir is the only intravenous formulation commercially available. The adamantanes (amantadine and rimantadine) are no longer recommended due to high resistance among influenza viruses. A limited discussion of adamantanes can be found in the following section, but the focus will be on oseltamivir, zanamivir, and peramivir.

Adamantanes

The adamantanes (amantadine and rimantadine) block the M2 ion channel, which is specific to influenza A viruses, and inhibit viral uncoating. Historically, the adamantanes were used for the treatment of seasonal influenza A H1N1, as they do not have activity against influenza A H3N2 or influenza B viruses. The novel influenza A H1N1 that emerged during the 2009 to 2010 influenza season, which has now replaced seasonal influenza A H1N1 as the predominant seasonal virus, was found to be discriminatorily resistant to the adamantanes. Data since 2009 influenza season showed that more than 99% of influenza A H3N2 and H1N1pdm09 were resistant to adamantanes.[53] As a result, the CDC only recommends the use of NA inhibitors for the treatment and prophylaxis of influenza A, until susceptibility of adamantanes is reestablished among influenza A viruses. Resistance to adamantanes is often conferred by a single-point mutation, and this is problematic because it results in crossresistance to the entire class.[34]

Cap-dependent Endonuclease Inhibitor

Oral baloxavir marboxil is a Cap-dependent polymerase acidic endonuclease inhibitor that interferes with viral RNA transcription and blocks virus replication.[62] It is approved for use within 48 hours of illness onset, in people 12 years and older, for the treatment of acute, uncomplicated influenza in patients who are at high risk for developing serious influenza-related complications - for example, those with chronic conditions like asthma, heart disease and diabetes. Avoid co-administration of baloxavir with dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives or antacids, or oral supplements (e.g., calcium, iron, magnesium, selenium, or zinc).[62] When administered within 48 hours of symptom onset, baloxavir decreased duration of illness by 2.5 days. The safety and efficacy of baloxavir in patients less than 12

years of age or weighing less than 40 kg have not been established. Baloxavir is not recommended for use in pregnant women or breastfeeding mothers. Commonly reported events for baloxavir were diarrhea, bronchitis, nausea, nasopharyngitis, and increased liver enzymes.[52] The recommended doses are listed on Table 127-6.

Neuraminidase Inhibitors

9 10 Oseltamivir, zanamivir, and peramivir are NA inhibitors that have activity against both influenza A and influenza B viruses.[53] Without NA, release of the virus from infected cells is impaired, and, thus, viral replication is decreased. Although no completed randomized, placebo-controlled trials of antiviral treatment have been conducted in hospitalized influenza patients to establish the efficacy NA inhibitors, a number of observational studies have reported clinical benefit of NA inhibitors in hospitalized patients, including reduction in duration of hospitalization and risk of death, including in ICU patients.[63,64] When administered within 48 hours of the onset of illness, NA inhibitors may reduce the duration of illness by approximately 1 day versus placebo. Neuroaminidase inhibitors shorten symptom duration in adults by 0.5 to 1 day, and improved survival in hospitalized patients.[64] In children NA inhibitor use resulted in shorter duration of illness and 34% lower risk of otitis media.[65] In this meta-analysis of 5 new randomized clinical trials that included 1598 children with laboratory confirmed influenza, treatment with oseltamivir significantly reduced the duration of illness in this population by 17.6 hours (95% CI, 234.7 to 20.62 hours), and when children with asthma were excluded, this difference was larger (-29.9 hours; 95% CI, -53.9 to -5.8 hours).[65] These reductions have a significant effect on not only the quality of life for the patient but also the societal costs associated with influenza. Of note, the benefits of treatment are highly dependent on the timing of the initiation of treatment, with the ideal initiation period being within 12 hours of illness onset, up to 48 hours after onset of illness.[33–34,53] Some debate still exists regarding the benefit of antiviral administration more than 48 hours after onset. Select observational studies have reported a lower risk for severe outcomes with oral oseltamivir started 4 and 5 days after onset of illness in critically ill patients with suspected or confirmed influenza.[66–68] A large meta-analysis of observational studies from 38 countries identified a 38% reduction in risk of mortality in critically ill adults and those aged ≥ 16 years old when comparing early NA inhibitor treatment (< 48 h) with later treatment (> 48 h), and a 69% reduction in mortality risk

between influenza patients receiving early NA inhibitor treatment and those who did not receive NAIs.[66] Also, there was a significantly reduced mortality risk reduction (35%) in critically ill patients aged ≥ 16 years old who received NAI treatment > 48 h after symptom onset compared with those who did not. Based upon available observational data in hospitalized patients with influenza, including ICU patients, initiation of NA inhibitor treatment is recommended as soon as possible for hospitalized patients with suspected or confirmed influenza.

Oseltamivir treatment in adults and adolescents with documented influenza illness resulted in a 26.7% reduction in overall antibiotic use, a 55% reduction in lower respiratory tract complications (bronchitis, pneumonia), and a 59% reduction in hospitalizations.[69] Zanamivir treatment in adults and adolescents with influenza-like illness resulted in a 28% reduction in antibiotic use and a 40% reduction in lower respiratory tract complications.[70] The data in these studies largely come from healthy individuals rather than those at highest risk for complications associated with influenza. The impact of appropriate treatment in high-risk populations may be even greater than that which has been documented to date.

Oseltamivir is approved for treatment in those 14 days and older, zanamivir for treatment in those older than the age of 7 years, and peramivir for those 2 years and older.[53] The recommended doses vary by agent and age (see Table 127-6). The recommended duration of treatment for both oseltamivir and zanamivir is 5 days, and one dose for 1 day for peramivir.

The FDA approved single-dose peramivir injection (Rapivab®) for intravenous use for the treatment of acute uncomplicated influenza in people 2 years and older.[34,53] Peramivir is as effective as oseltamivir, without severe adverse events.[71,72] Therefore, peramivir is an effective option in patients who are unable to tolerate or absorb oral or enterically administered oseltamivir due to gastric stasis, malabsorption, or gastrointestinal bleeding. A recent, multicenter randomized controlled trial of high-risk patients infected with seasonal influenza found similar clinical benefit between enteric oseltamivir and intravenous peramivir in hospitalized influenza patients.[71] Studies exploring the use of peramivir beyond 1 day have not shown a benefit. A randomized trial of influenza treatment in hospitalized patients younger than 6 years, with intravenous peramivir at a dosage of 600 mg once daily (10 mg/kg once daily in children) for 5 days plus standard of care compared with placebo plus standard of care did not demonstrate a clinical benefit.[73]

Neuropsychiatric complications consisting of delirium, seizures, hallucinations, and self-injury in pediatric patients (mostly from Japan) have

been reported following treatment with oseltamivir, and peramivir.[74,75] Since influenza itself can be associated with neuropsychiatric manifestations, a causal relationship between oseltamivir or peramivir and neuropsychiatric effects has not been delineated. However, the labels for oseltamivir and peramivir have been updated to include neuropsychiatric events as a precaution, and their occurrence with use of these agents should not be ignored.

Influenza resistance to the NA inhibitors has been documented but cross-resistance between the NA inhibitors has not been reported.[18,53] Antiviral resistance remains relatively low. During the 2018 to 2019 influenza season, 99% of the tested A(H1N1)pdm09 viruses were susceptible to oseltamivir and peramivir, and 100% of the 2009 H1N1 viruses tested were susceptible to zanamivir; 100% of influenza A (H3N2) tested were susceptible to both oseltamivir and zanamivir; and 100% of influenza B viruses tested were susceptible to both oseltamivir and zanamivir.[18,53] Antiviral susceptibility testing of circulating viruses confirmed that seasonal influenza A H3N2 and variant influenza H3N2 maintain susceptibility to oseltamivir, peramivir, and zanamivir.[18] The burden of surveillance rests on clinicians to identify local patterns of influenza circulation to guide antiviral therapy.

Special Populations

Inadequate data exist regarding the use of anti-influenza medications in special populations, such as immunocompromised hosts. Furthermore, limited data exist regarding use of influenza antivirals during pregnancy. The adamantanes are embryotoxic and teratogenic in rats, and limited case reports of adverse fetal outcomes following amantadine use in humans have been published. Oseltamivir and zanamivir have been used but lack solid safety clinical data in pregnant women. Pregnancy should not be considered a contraindication to oseltamivir or zanamivir use. Oseltamivir is preferred for the treatment of pregnant women because of its systemic activity; however, the drug of choice for chemoprophylaxis is not yet defined. Zanamivir may be preferred because of its limited systemic absorption, but respiratory complications need to be considered, especially in women with underlying respiratory diseases. Both the adamantanes and the NA inhibitors are excreted in breast milk and should be avoided by mothers who are breast-feeding their infants. More studies are needed in these populations who are at high risk for serious disease and complications from influenza.

PANDEMIC PREPAREDNESS

This chapter is not meant to provide an exhaustive review of the biology of influenza or pandemic preparedness. This topic is rapidly changing and interested readers are referred to the following Websites: www.flu.gov, www.who.int/influenza/human_animal_interface/en/, and www.cdc.gov/h1n1flu.

A vital component of pandemic preparedness is forethought—plans must be established for how to effectively triage large numbers of ill patients, prioritize and/or ration vaccine and antivirals, and communicate with the public through mass media during a period of severe labor shortage (a result of stress and illness among healthcare workers) and supply shortfall (a result of societal and economic disruption).

EVALUATION OF THERAPEUTIC OUTCOMES

Patients should be monitored daily for resolution of signs and symptoms associated with influenza, such as fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis. These signs and symptoms will typically resolve within approximately 1 week. If the patient continues to exhibit signs and symptoms of illness beyond 10 days or a worsening of symptoms after 7 days, a physician visit is warranted as this may be an indication of a secondary bacterial infection. Ideally, antiviral therapy should not be started until influenza is confirmed via the laboratory. However, therapy should be initiated within 48 hours of illness onset, emphasizing the need for rapid diagnosis. Repeat diagnostic tests to demonstrate clearance of the virus are not necessary.

Postclass Engaged Learning Activity

1. Outline how influenza virus included in the yearly influenza vaccine is determined and limitations of this process
2. Compare and Contrast antigenic drift with antigenic shift
3. Complete the following table of influenza pandemics. See also Reference 25

Name of pandemic	Date	Strain Suspected	Origin of Outbreak	Deaths (worldwide)	Deaths (United States)
1918 flu pandemic (Spanish flu)	1918-1920				
Asian Flu	1957-1958				
Hong Kong Flu	1968-1970				
Swine flu	2009-2010				

4. What class of antivirals is effective against influenza

ABBREVIATIONS

AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
CDC	US Centers for Disease Control and Prevention
DFA	direct fluorescence antibody
EIA	enzyme immunoassay
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
GMTs	geometric mean titers
HIV	human immunodeficiency virus
IFA	indirect fluorescence antibody
IIV	inactivated influenza vaccine
IIV3	trivalent influenza vaccine
IIV4	quadrivalent influenza vaccine
LAIV	live-attenuated influenza vaccine
M	matrix
NA	neuraminidase
PIDS	Pediatric Infectious Diseases Society
POC	point of care
PRs	protection rates
RIDTs	Rapid Influenza Diagnostic Tests
RIMAs	Rapid influenza molecular assays
RT-PCR	reverse-transcription polymerase chain reaction
SOIV	swine origin influenza virus

VE	Vaccine efficacy
WHO	World Health Organization

REFERENCES

1. Rolfes MA, Foppa IM, Garg S, et al. Annual estimates of the burden of seasonal influenza in the United States: A tool for strengthening influenza surveillance and preparedness. *Influenza Other Respir Viruses*. 2018;12(1):132–137. https://www.cdc.gov/flu/about/disease/2016-17.htm
2. Iuliano AD, Roguski KM, Chang HH, et al. Global Seasonal Influenza-associated Mortality Collaborator Network. Estimates of global seasonal influenza-associated respiratory mortality: A modelling study. *Lancet*. 31, 2018;391(10127):1285–1300.
3. Yan S, Weycker D, Sokolowski S. US healthcare costs attributable to type A and type B influenza. *Hum Vaccin Immunother*. 2017 2;13(9):2041–2047.
4. Centers for Disease Control and Prevention. Disease Burden of Influenza. Available at https://www.cdc.gov/flu/about/burden/index.html Accessed September 20, 2019
5. Centers for Disease Control and Prevention. 2018-2019 U.S. Flu Season: Preliminary Burden Estimates. Available at https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm Accessed September 20, 2019
6. Centers for Disease Control and Prevention. Laboratory-Confirmed Influenza Hospitalizations. Available at https://gis.cdc.gov/GRASP/Fluview/FluHospRates.html Accessed September 20, 2019
7. Centers for Disease Control and Prevention. Estimates of Flu Vaccination Coverage, United States, 2018–19 Influenza Season. Available at https://www.cdc.gov/flu/fluvaxview/coverage-1819estimates.htm Accessed September 20, 2019
8. Centers for Disease Control and Prevention. Preliminary Estimates of 2018–19 Seasonal Influenza Vaccine Effectiveness against Medically Attended Influenza from three U.S. Networks. Available at https://www.cdc.gov/flu/vaccines-work/2018-2019.html Accessed September 20, 2019
9. Reed C, Chaves SS, Perez A, et al. Complications among adults

hospitalized with influenza: A comparison of seasonal influenza and the 2009 H1N1 pandemic. *Clin Infect Dis*. 2014;59(2):166–174.

10. Lagacé-Wiens PR, Rubinstein E, Gumel A. Influenza epidemiology—past, present, and future. *Crit Care Med*. 2010;38(4 Suppl):e1–9.
11. Morens DM, Taubenberger JK, Harvey HA, et al. The 1918 influenza pandemic: Lessons for 2009 and the future. *Crit Care Med*. 2010;38 (4 Suppl):e10–20.
12. Trombetta C, Piccirella S, Perini D, et al. Emerging influenza strains in the last two decades: A threat of a new pandemic? *Vaccines (Basel)* 2015;3(1):172–185.
13. Centers for Disease Control and Prevention. Avian Influenza: Influenza Type A Viruses. Available at https://www.cdc.gov/flu/avianflu/influenza-a-virus-subtypes.htm Accessed October 10, 2019.
14. World Health Organization. Avian Influenza Weekly Update Number 631 (6 April 2018). Available at: http://www.wpro.who.int/emerging_diseases/AvianInfluenza/en/. http://www.wpro.who.int/emerging_diseases/AvianInfluenza/en/.
15. Anonymous. Avian influenza A(H7N9) virus. Available at: http://www.who.int/influenza/human_animal_interface/influenza_h7n9/en/ Accessed October 10, 2019
16. Nguyen HH. Brown T. Influenza Clinical Presentation. *Medscape News*. Available at https://emedicine.medscape.com/article/219557-clinical. April 23, 2019; Accessed October 12, 2019.
17. FluView. Weekly U.S. Influenza Surveillance Report 2019-2020 Influenza Season. Available at https://www.cdc.gov/flu/weekly/index.htm Accessed October 12, 2019
18. Centers for Disease Control and Prevention. Influenza Antiviral Drug Resistance. Available at https://www.cdc.gov/flu/treatment/antiviralresistance.htm Accessed October 10, 2019
19. Epperson S, Davis CT, Brammer L, et al. Update: Influenza Activity—United States and Worldwide, May 19–September 28, 2019, and Composition of the 2020 Southern Hemisphere Influenza Vaccine. *MMWR Morb Mortal Wkly Rep*. 2019;68:880–884.
20. Anonymous. Influenza virus vaccine, H5N1 [prescribing information]. Swiftwater, PA: Sanofi Pasteur; April 2007.
21. Anonymous. Influenza A (H5N1) virus monovalent vaccine, adjuvanted.

Research Triangle Park, NC: GlaxoSmithKline; September 2016.

22. World Health Organization. Summary of status of development and availability of avian influenza A(H7N9) candidate vaccine viruses and potency testing reagents. Available at https://www.who.int/influenza/vaccines/virus/candidates_reagents/summar ua=1 Accessed October 10, 2019
23. United Nations World Tourism Organization UNWTO Tourism Highlights: 2019. Available at https://www.e-unwto.org/doi/pdf/10.18111/9789284421152 Accessed October 12, 2019
24. U.S. Department of Commerce International Trade Administration/Industry and Analysis National Travel and Tourism Office (NTTO). U.S. Resident Travel to International Destinations Increased Six Percent in 2018. Available at: https://travel.trade.gov/tinews/archive/tinews2019/20190402.asp Accessed October 12, 2019
25. Saunders-Hastings PR, Krewski D. Reviewing the history of pandemic influenza: Understanding patterns of emergence and transmission. Pathogens. 6, 2016;5(4):pii: E66.
26. Centers for Disease Control and Prevention. Update: Novel influenza A (H1N1) virus infections—Worldwide, May 6, 2009. *MMWR Morb Mortal Wkly Rep.* 2009;58:453–458.
27. Dawood FS, Iuliano AD, Reed C, et al. Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: A modeling study. *Lancet Infect Dis*. 2012;12:687–695.
28. Uyeki TM. Influenza. Ann Intern Med. 2017;167(5):ITC33–ITC48.
29. Blanton L, Wentworth DE, Alabi N, et al. Update: Influenza Activity—United States and Worldwide, May 21–September 23, 2017. *MMWR Morb Mortal Wkly Rep*. 2017;66:1043–1051.
30. Centers for Disease Control and Prevention. Influenza A (H3N2) Variant Virus Outbreaks. Available at http://www.cdc.gov/flu/swineflu/h3n2v-case-count.htm Accessed October 12, 2019
31. Centers for Disease Control and Prevention. People at High Risk For Flu Complications. Available at https://www.cdc.gov/flu/highrisk/index.htm Accessed October 12, 2019
32. Grohskopf LA, Alyanak E, Broder KR, Walter EB, Fry AM, Jernigan DB. Prevention and control of seasonal influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices

—United States, 2019–20 Influenza Season. *MMWR Recomm Rep*. 2019;68(3):1–21.

33. Committee On Infectious Diseases. Recommendations for Prevention and Control of Influenza in Children, 2019-2020. *Pediatrics*. 2019;144(4). pii: e20192478.
34. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza. *Clin Infect Dis*. 2019;68(6):895–902
35. Centers for Disease Control and Prevention. Influenza testing and clinical algorithms. Available at https://www.cdc.gov/flu/professionals/diagnosis/index.htm Accessed October 12, 2019
36. Vos LM, Bruning AHL, Reitsma JB, et al. Rapid Molecular Tests for Influenza, Respiratory Syncytial Virus, and Other Respiratory Viruses: A Systematic Review of Diagnostic Accuracy and Clinical Impact Studies. *Clin Infect Dis*. 2019;69(7):1243–1253.
37. Merckx J, Wali R, Schiller I, et al. Diagnostic accuracy of novel and traditional rapid tests for influenza infection compared with reverse transcriptase polymerase chain reaction: a systematic review and meta-analysis. *Ann Intern Med.* 2017; 167:394–409.
38. Centers for Disease Control and Prevention. Flu Vaccination Coverage, United States, 2018–19 Influenza Season. Available at https://www.cdc.gov/flu/fluvaxview/nifs-estimates-nov2018.htm Accessed October 12, 2019
39. Lu PJ, Srivastav A, Amaya A, et al. Association of provider recommendation and offer and influenza vaccination among adults aged ≥18 years—United States. Vaccine. 2018;36(6):890–898.
40. Lindley MC, Kahn KE, Bardenheier BH, et al. Vital Signs: Burden and Prevention of Influenza and Pertussis Among Pregnant Women and Infants – United States. *MMWR Morb Mortal Wkly Rep*. 2019;68(40):885–892. doi: 10.15585/mmwr.mm6840e1.
41. Tricco AC, Chit A, Soobiah C, et al. Comparing influenza vaccine efficacy against mismatched and matched strains: A systematic review and meta-analysis. *BMC Med*. 2013;11:153.
42. Hoberman A, Greenberg DP, Paradise JL, et al. Effectiveness of inactivated influenza vaccine in preventing acute otitis media in young

children: A randomized controlled trial. *JAMA.* 2003;290(12):1608–1616.

43. Jefferson T, Rivetti A, Di Pietrantonj C, Demicheli V. Vaccines for preventing influenza in healthy children. *Cochrane Database Syst Rev*. 2018;2:CD004879.
44. Demicheli V, Jefferson T, Ferroni E, et al. Vaccines for preventing influenza in healthy adults. *Cochrane Database Syst Rev*. 2018;2:CD001269.
45. Demicheli V, Jefferson T, Di Pietrantonj C, et al. Vaccines for preventing influenza in the elderly. *Cochrane Database Syst Rev*. 2018;2:CD004876.
46. DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. *N Engl J Med.* 2014;371:635–645.
47. Chit A, Roiz J, Briquet B, Greenberg DP. Expected cost effectiveness of high-dose trivalent influenza vaccine in US seniors. *Vaccine*. 2015;33(5):734–741.
48. Fluzone High Dose Quadrivalent vaccine [Prescribing Information]. Swiftwater, PA: Sanofi Pasteur Inc, 2019.
49. Vellozzi C1, Iqbal S, Broder K. Guillain-Barré syndrome, influenza, and influenza vaccination: the epidemiologic evidence. *Clin Infect Dis*. 2014;58(8):1149–1155.
50. Price CS, Thompson WW, Goodson B, et al. Prenatal and infant exposure to thimerosal from vaccines and immunoglobulins and risk of autism. *Pediatrics.* 2010;126:656–664.
51. Taylor LE, Swerdfeger AL, Eslick GD. Vaccines are not associated with autism: an evidence-based meta-analysis of case-control and cohort studies. *Vaccine*. 2014 Jun 17;32(29):3623–3629. doi: 10.1016/j.vaccine.2014.04.085.
52. FluMist Quadrivalent Vaccine [prescribing information]. Gaithersburg, MD: MedImmune, LLC, 2019.
53. Centers for Diseases Control and Prevention. Influenza Antiviral Medications: Summary for Clinicians 2019-2020. https://www.cdc.gov/flu/professionals/antivirals/index.htm
54. Thompson MG, Kwong JC, Regan AK, et al. Influenza Vaccine Effectiveness in Preventing Influenza-associated Hospitalizations During Pregnancy: A Multi-country Retrospective Test Negative Design Study, 2010-2016. *Clin Infect Dis*. 2019;68(9):1444–1453.

55. Benowitz I, Esposito DB, Gracey KD, et al. Influenza vaccine given to pregnant women reduces hospitalization due to influenza in their infants. *Clin Infect Dis* 2010;51(12):1355–1361.
56. McKittrick N, Frank I, Jacobson JM, et al. Improved immunogenicity with high-dose seasonal influenza vaccine in HIV-infected persons: a single-center, parallel, randomized trial. *Ann Intern Med*. 2013;158(1):19–26.
57. Natori Y, Shiotsuka M, Slomovic J, et al. A Double Blind Randomized Trial of High Dose vs. Standard Dose Influenza Vaccine in Adult Solid Organ Transplant Recipients. *Clin Infect Dis*. 2018;66(11):1698–1704.
58. Cordero E, Roca-Oporto C, Bulnes-Ramos A, et al. TRANSGRIPE 1–2 Study Group. Two doses of inactivated influenza vaccine improve immune response in solid organ transplant recipients: Results of TRANSGRIPE 1-2, a randomized controlled clinical trial. *Clin Infect Dis*. 2017;64(7):829–838.
59. Kumar D, Ferreira VH, Blumberg E, et al. A five-year prospective multi-center evaluation of influenza infection in transplant recipients. *Clin Infect Dis*. 2018;67(9):1322–1329.
60. Shehata MA, Karim NA. Influenza vaccination in cancer patients undergoing systemic therapy. *Clin Med Insights Oncol.* 2014;8:57–64.
61. Bitterman R, Eliakim-Raz N, Vinograd I, et al. Influenza vaccines in immunosuppressed adults with cancer. *Cochrane Database Syst Rev*. 2018 Feb 1;2:CD008983.
62. XOFLUZA [Prescribing Information]. South San Francisco, CA: Genentech USA, Inc.; 2018.
63. Dominguez A, Romero-Tamarit A, Soldevila N, et al. Effectiveness of antiviral treatment in preventing death in severe hospitalised influenza cases over six seasons. *Epidemiol Infect*. 2018;146(7):799–808.
64. Doll MK, Winters N, Boikos C, et al. Safety and effectiveness of neuraminidase inhibitors for influenza treatment, prophylaxis, and outbreak control: A systematic review of systematic reviews and/or meta-analyses. *J Antimicrob Chemother*. 2017;72(11):2990–3007.
65. Malosh RE, Martin ET, Heikkinen T, et al. Efficacy and safety of oseltamivir in children: Systematic review and individual patient data meta-analysis of randomized controlled trials. *Clin Infect Dis*. 2018;66(10):1492–1500.
66. Muthuri SG, Venkatesan S, Myles PR, et al. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to

hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. *Lancet Respir Med*. 2014;2(5):395–404.

67. Katzen J, Kohn R, Houk JL, Ison MG. Early oseltamivir after hospital admission is associated with shortened hospitalization: a five-year analysis of oseltamivir timing and clinical outcomes. *Clin Infect Dis*. 2019;69(1):52–58.
68. Louie JK, Yang S, Acosta M, et al. Treatment with neuraminidase inhibitors for critically ill patients with influenza A (H1N1)pdm09. *Clin Infect Dis*. 2012;55(9):1198–1204.
69. Kaiser L, Wat C, Mills T, et al. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. *Arch Intern Med.* 2003;163(14):1667–1672.
70. Kaiser L, Keene ON, Hammond JM, et al. Impact of zanamivir on antibiotic use for respiratory events following acute influenza in adolescents and adults. *Arch Intern Med.* 2000;160(21):3234–3240.
71. Nakamura S, Miyazaki T, Izumikawa K, et al. Efficacy and safety of intravenous peramivir compared with oseltamivir in high-risk patients infected with influenza A and B viruses: a multicenter randomized controlled study. *Open Forum Infect Dis*. 2017;4(3):ofx129
72. Lee J, Park JH, Jwa H, Kim YH. Comparison of efficacy of intravenous Peramivir and Oral Oseltamivir for the treatment of influenza: systematic review and meta-analysis. *Yonsei Med J*. 2017;58(4):778–785
73. de Jong MD, Ison MG, Monto AS, et al. Evaluation of intravenous peramivir for treatment of influenza in hospitalized patients. *Clin Infect Dis.* 2014;59(12):172–185.
74. Peramivir (Rapivab)® [Package Insert]. Durham, NC 27703: BioCryst Pharmaceuticals, Inc; 2019.
75. Tamiflu [prescribing information]. San Francisco, CA: Genentech USA, Inc/Roche Group, October 2019, Available at: http://www.rocheusa.com/products/tamiflu/pi.pdf.

128

Skin and Soft-Tissue Infections

Douglas N. Fish

KEY CONCEPTS

1. Folliculitis, furuncles (boils), and carbuncles begin around hair follicles and are caused most often by *Staphylococcus aureus*. Folliculitis and small furuncles are generally treated with warm, moist heat to promote drainage; larger furuncles and carbuncles require incision and drainage. Purulent, moderately severe infections (eg, with fever or other systemic signs of infection) have a higher suspicion for community-associated methicillin-resistant *S. aureus* (MRSA) and empiric treatment should include trimethoprim-sulfamethoxazole or a tetracycline such as doxycycline.
2. Erysipelas, a superficial skin infection with extensive lymphatic involvement, is caused by *Streptococcus pyogenes*. The treatment of choice is penicillin, administered orally or parenterally, depending on the severity of the infection.
3. Impetigo is a superficial skin infection that occurs most commonly in children. It is characterized by fluid-filled vesicles that rapidly develop into pus-filled blisters that rupture to form golden-yellow crusts. Effective therapy includes penicillinase-resistant penicillins (dicloxacillin), first-generation cephalosporins (cephalexin), and topical mupirocin or retapamulin. *S. aureus* is the primary cause of impetigo, with MRSA becoming more common in recent years.
4. Lymphangitis, an infection of the subcutaneous lymphatic channels, is usually caused by *S. pyogenes*. Acute lymphangitis is characterized by the rapid development of fine, red, linear streaks extending from the initial infection site toward the regional lymph nodes, which are usually enlarged and tender. Penicillin is the drug of choice.
5. Cellulitis is an infection of the epidermis, dermis, and superficial fascia most commonly caused by *S. pyogenes* and *S. aureus*. Lesions generally are

hot, painful, and erythematous, with nonelevated, poorly defined margins. Oral trimethoprim-sulfamethoxazole, doxycycline, or minocycline is used for initial treatment of suspected MRSA in patients with purulent, moderately severe cellulitis (ie, lesion with purulent drainage or exudate, or nondrainable abscess plus systemic signs of infection). Treatment of nonpurulent cellulitis generally consists of penicillin VK, a penicillinase-resistant penicillin (dicloxacillin), first-generation cephalosporin (cephalexin), or clindamycin for 5 days, coverage for MRSA may be added in certain patients. More severe infections in hospitalized and/or immunocompromised patients should receive empiric therapy with parenteral agents active against streptococci (nonpurulent infections) or both streptococci and MRSA (purulent infections).

6. Necrotizing fasciitis is an uncommon but life-threatening infection of subcutaneous tissue that results in progressive destruction of superficial fascia and subcutaneous fat. Early and aggressive surgical debridement is an essential part of therapy for treatment of necrotizing fasciitis. Mixed infections are treated with broad-spectrum regimens that cover streptococci, gram-negative aerobes, and anaerobes. Infections caused by *S. pyogenes* or *Clostridium* species should be treated with the combination of penicillin and clindamycin.

7. Diabetic foot infections are managed with a comprehensive treatment approach that includes both proper wound care and antimicrobial therapy. Potential pathogens include staphylococci, streptococci, aerobic gram-negative bacilli, and obligate anaerobes. Antimicrobial regimens for diabetic foot infections are based on severity of the infection, expected treatment setting, and risk factors for infection with more resistant pathogens such as MRSA and *Pseudomonas aeruginosa*. Outpatient therapy with oral antimicrobials should be used whenever possible for less severe infections, while more severe infections initially require IV therapy.

8. Prevention is the single most important aspect in the management of pressure sores. After a sore develops, successful local care includes a comprehensive approach consisting of relief of pressure, proper cleaning (debridement), disinfection, and appropriate antimicrobial therapy if an infection is present. Good wound care is crucial to successful management.

9. All bite wounds (either animal or human) should be thoroughly irrigated with large volumes of sterile normal saline, and the injured area should be immobilized and elevated. Depending on the severity of the bite wound,

amoxicillin-clavulanic acid or ampicillin-sulbactam is often used for treatment of animal bites because of their coverage of *Pasteurella* species, streptococci, *S. aureus*, and anaerobes typically present in the oral flora of dogs and cats.

10 Antimicrobial prophylaxis (early preemptive therapy) of animal bites is not routinely recommended; however, patients at high risk of infection (eg, immunocompromised, moderate-to-severe bite injuries especially to the hands and face, penetration of the periosteum or joint capsule) should be given prophylactic antimicrobial therapy for 3 to 5 days. Infected bite wounds should be treated for 7 to 14 days with oral or IV antibiotics having activity against *Eikenella corrodens*, streptococci, *S. aureus*, and β-lactamase-producing anaerobes.

Preclass Engaged Learning Activity

Methicillin-resistant *Staphylococcus aureus* (MRSA) has become a prominent pathogen in a variety of skin and soft-tissue infections (SSTIs). Treatment decisions regarding SSTI often involve the decision of whether to empirically cover for MRSA with initial antibiotic therapy. Create a summary table of antibiotics with clinically useful activity against MRSA that could potentially be used in the treatment of SSTI. Include both oral and intravenous antibiotic options. Discuss pros, cons, and potential place in therapy of each specific treatment option. This activity is intended to enhance your drug information skills, apply knowledge regarding antibiotic pharmacology and spectra of activity to a specific disease state and pathogen, and anticipate the potential role of specific medications in clinical practice.

INTRODUCTION

Skin and soft-tissue infections (SSTIs) may involve any or all layers of the skin (epidermis, dermis, subcutaneous fat), fascia, and muscle. They may also spread far from the initial site of infection and lead to more severe complications, such as endocarditis, gram-negative sepsis, or streptococcal glomerulonephritis. Sometimes the treatment of SSTIs may necessitate both medical and surgical management. This chapter presents details of the pathogenesis and management of some of the most common infections involving the skin and soft tissues,

ranging in severity from superficial to life-threatening.

EPIDEMIOLOGY

Bacterial infections of the skin can be classified as primary or secondary (Table 128-1).[1-4] Primary bacterial infections usually involve areas of previously healthy skin and are caused by a single pathogen. In contrast, secondary infections occur in areas of previously damaged skin and are frequently polymicrobic. SSTIs are also classified as complicated or uncomplicated. Complicated infections are those that involve deeper skin structures (eg, fascia, muscle layers), require significant surgical intervention, and/or occur in patients with compromised immune function (eg, diabetes mellitus, human immunodeficiency virus [HIV] infection).[3-5] Other categories that are crucial for successful treatment are the differentiation of necrotizing versus non-necrotizing, as well as purulent versus nonpurulent, SSTIs.[3-6] Acute bacterial skin and skin structure infections (ABSSSIs) are a subset of SSTI and specifically denote those more severe bacterial infections of the skin with a lesion size area of at least 75 cm^2 and for which antibiotic therapy is generally considered to be required for successful resolution.[7] The subset of ABSSSI specifically includes cellulitis, erysipelas, wound infection, and major cutaneous abscess.[7]

TABLE 128-1 Bacterial Classification of Important Skin and Soft-Tissue Infections[1,2,8]

Primary Infections	
Erysipelas	Group A streptococci (*Streptococcus pyogenes*)
Impetigo	*Staphylococcus aureus* (including methicillin-resistant strains), group A streptococci
Lymphangitis	Group A streptococci; occasionally *S. aureus*
Cellulitis	Group A streptococci, *S. aureus* (potentially including methicillin-resistant strains); occasionally other gram-positive cocci, gram-negative bacilli, and/or anaerobes
Necrotizing fasciitis	
Type I	Anaerobes (*Bacteroides* spp., *Peptostreptococcus* spp.) and facultative bacteria (streptococci, Enterobacteriaceae)
Type II	Group A streptococci
Type III	*Clostridioides perfringens*
Secondary Infections	
Diabetic foot infections	*S. aureus*, streptococci, Enterobacteriaceae, *Bacteroides* spp., *Peptostreptococcus* spp., *Pseudomonas aeruginosa*
Pressure sores	*S. aureus* including methicillin-resistant strains, streptococci, Enterobacteriaceae, *Bacteroides* spp., *Peptostreptococcus* spp., *P. aeruginosa*
Bite wounds	
Animal	*Pasteurella* spp., *S. aureus*, streptococci, *Bacteroides* spp.
Human	*Eikenella corrodens*, *S. aureus*, streptococci, *Corynebacterium* spp., *Bacteroides* spp., *Peptostreptococcus* spp.
Burn wounds	*P. aeruginosa*, Enterobacteriaceae, *S. aureus*, streptococci

SSTIs are among the most common infections seen in community and hospital settings.[9,10] However, most infections are believed to be mild and are treated in an outpatient setting, making it difficult to accurately quantify community-acquired SSTIs. SSTIs occur in approximately 5 to 7 million persons each year, being more common among those 50 years of age and older.[8,9] Emergency room visits for SSTIs continue to increase each year, attributed primarily to an increase in community-associated methicillin-resistant

Staphylococcus aureus (CA-MRSA) cellulitis and abscesses.[3-5,11] Both inpatient admissions and outpatient office visits due to SSTIs increased by approximately 30% over a four-year period in the early 2000s; during this same period the prevalence of MRSA among SSTIs increased from 29% to 64% in one emergency department.[12] According to an Agency for Healthcare Research and Quality report, in 2009 SSTIs were responsible for nearly 600,000 hospitalizations and represented 2% of all admissions in males and 1.2% in females.[10] While the exact incidence of SSTIs is unknown, the frequency of infections caused by drug-resistant gram-positive cocci has been increasing.[3-6,11] The high incidence of healthcare-associated MRSA (HA-MRSA) has been a major concern for many years and the emergence of CA-MRSA is even more problematic.[3-6,13-20] CA-MRSA are characteristically isolated from patients lacking typical risk factors (eg, prior hospitalization, long-term care facility - residence) and are often susceptible to non-β-lactam antibiotics such as - trimethoprim-sulfamethoxazole, doxycycline, and clindamycin.[13-20] They also differ genetically from HA-MRSA with methicillin resistance carried on the type IV or type V staphylococcal chromosomal cassette *mec* (SCC*mec*) element of the *mecA* gene.[1,13,19] CA-MRSA strains often harbor genes for Panton-Valentine leukocidin (PVL), a cytotoxin responsible for leukocyte destruction and tissue necrosis. In contrast, HA-MRSA strains usually lack genes for PVL and are associated with SCC*mec* alleles I to III.[1,13,16,19] While the incidence of HA-MRSA has declined in recent years,[21] the incidence of CA-MRSA has dramatically increased; nearly half (46%) of all culture-positive SSTIs are caused by MRSA and nearly 50% of all CA-MRSA are isolated from SSTIs.[3-6,9,21] Clinicians should suspect CA-MRSA in geographic areas with a high prevalence of these strains, or in recurrent or persistent infections that are not responding to appropriate β-lactam therapy. In addition to the emergence of CA-MRSA, treatment choices for SSTIs have been further complicated by the increased incidence of macrolide-resistant strains of *S. aureus* and *Streptococcus pyogenes*.[22-24] There is concern about the use of clindamycin for CA-MRSA - infections due to the risk of inducible clindamycin resistance in *S. aureus* strains that are erythromycin-resistant, but clindamycin-susceptible.[8,16,19,23,24] A double-disk test (D-zone test) is recommended to identify erythromycin-resistant strains with inducible clindamycin resistance if treatment with clindamycin is desired.[4,6,13,16,19,23,24] A positive D-zone test, indicating the presence of inducible resistance conferred by the *erm* gene, suggests the possibility of the emergence of clindamycin resistance during therapy.[13,16,19,25]

ETIOLOGY

The majority of SSTIs are caused by gram-positive organisms present on the skin surface.[2,6,23,26] Gram-positive bacteria (coagulase-negative staphylococci, diphtheroids) are the predominant flora of the skin, with gram-negative organisms being relatively uncommon (Table 128-2).[1,2,8,23] *S. aureus*, as well as a variety of gram-negative bacteria, including *Acinetobacter* species, can be found in moist intertriginous areas (eg, axilla, groin, and toe webs) of the body.[1,2,23,24] Approximately 30% to 35% of healthy individuals are reported to be colonized with *S. aureus* on the skin or in the anterior nares.[1,8,23] Colonization, whether transient or permanent, provides a nidus for infection should the integrity of the epidermis be compromised.[1-3,5,6,8,23]

TABLE 128-2 Predominant Microorganisms of Normal Skin[1,2,8]

Bacteria
• Gram-positive
Coagulase-negative staphylococci
Micrococci (*Micrococcus luteus*)
Corynebacterium species (diphtheroids)
Propionibacterium species
• Gram-negative
Acinetobacter species
Fungi
• *Malassezia* species
• *Candida* species

S. aureus and *S. pyogenes* account for the majority of community-acquired SSTIs.[1,12,16,23,26] Data from large surveillance studies showed *S. aureus* to be the most common cause of SSTIs in hospitalized patients, with often 30% to 50% of these being caused by MRSA.[8,10,12-14,18,21] Other common nosocomial pathogens included *Pseudomonas aeruginosa* (11%), enterococci (9%), and *Escherichia coli* (7%).[8,6,10,13,14]

PATHOPHYSIOLOGY

The skin serves as a barrier between humans and their environment, therefore functioning as a primary defense mechanism against infections. The skin and subcutaneous tissues normally are extremely resistant to infection but may become susceptible under certain conditions. Even when high concentrations of

bacteria are applied topically or injected into the soft tissue, resulting infections are rare.[1-3,5,8,23,27] Although the human skin supports an abundant and diverse microbiome of bacteria and fungi,[1,2,23] several host factors act together to confer protection against skin infections. Continuous renewal of the epidermal layer results in the shedding of keratocytes, as well as skin bacteria.[2,23] In addition, sebaceous secretions are hydrolyzed to form free fatty acids that strongly inhibit the growth of many bacteria and fungi. A normal commensal skin microbiome itself serves a protective function by not allowing space or environmental conditions favorable to colonization with more pathogenic strains.[1,2,23] Conditions that may predispose a patient to the development of skin infections include (a) high concentrations of bacteria (more than 10^5 microorganisms), (b) excessive moisture of the skin, (c) inadequate blood supply, (d) availability of bacterial nutrients, and (e) damage to the corneal layer allowing for bacterial penetration.[2,3,5,8,23,24,27]

The best defense against SSTI is intact skin.[2,23,27] The majority of SSTIs result from the disruption of normal host defenses by processes such as skin puncture, abrasion, or underlying diseases (eg, diabetes).[1-3,5,8,23,27] The nature and severity of the infection depend on both the type of microorganism present and the site of inoculation.

FOLLICULITIS, FURUNCLES, AND CARBUNCLES

1 Folliculitis is inflammation of the hair follicle and is caused by physical injury, chemical irritation, or infection. Infection occurring at the base of the eyelid is referred to as a stye. While folliculitis is a superficial infection with pus present only in the epidermis,[4,16,24,26] furuncles and carbuncles occur when a follicular infection extends from around the hair shaft to involve deeper areas (subcutaneous tissue) of the skin.[4,16,24] A furuncle, commonly known as a *boil*, is a walled-off mass of purulent material arising from a hair follicle.[4,16,24] The lesions are called *carbuncles* when adjacent furuncles coalesce to form a single inflamed area.[4,16,24] This aggregate of infected hair follicles forms deep masses that generally open and drain through multiple sinus tracts.[16,24]
S. aureus is the most common cause of folliculitis, furuncles, and carbuncles.[4,14,16,24] Outbreaks of furunculosis caused by *S. aureus* and CA-MRSA have been reported in settings involving close contact (eg, families,

prisons), especially when skin injury was common (such as with athletes).[11,26] In addition, some individuals experience repeated episodes of furunculosis.[24,26] A major predisposing factor for recurrent infection is the presence of *S. aureus* in the anterior nares.[16,24,26]

CLINICAL PRESENTATION

Folliculitis

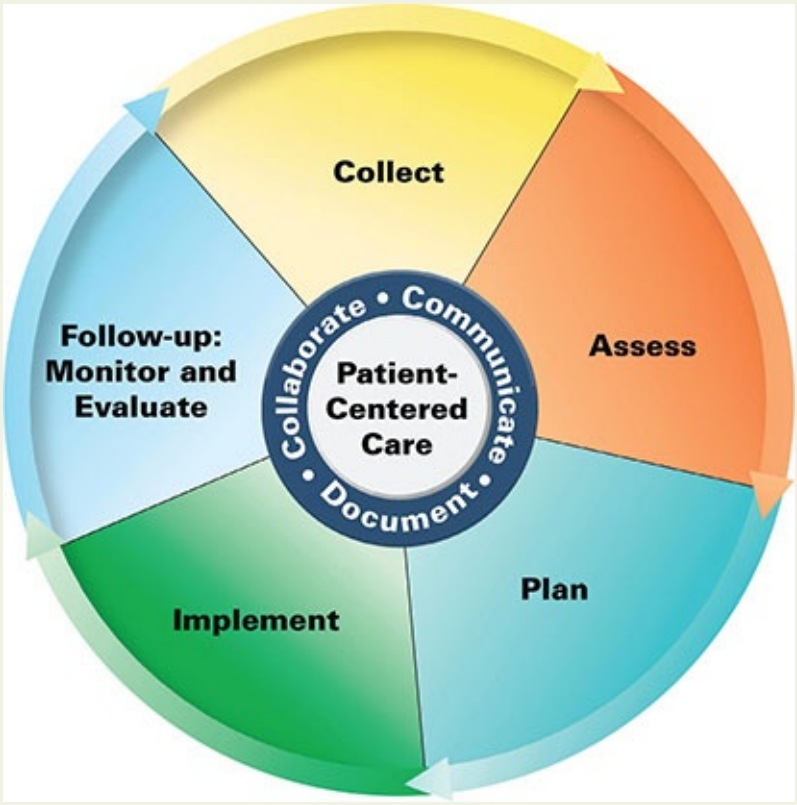
- Clustering, pruritic papules localized to hair follicles.
- Generally develop in areas subject to friction and perspiration.
- Papules are generally 5 mm or less in diameter and erythematous.
- Papules evolve into pustules that generally spontaneously rupture in several days.
- Systemic signs (fever, malaise) are uncommon.

Furuncles

- Inflammatory, draining nodule involving a hair follicle.
- Generally develop in areas subject to friction and perspiration.
- Lesions are discrete, whether occurring as singular or multiple nodules.
- Lesion starts as a firm, tender, red nodule that becomes painful and fluctuant.
- Lesions often drain spontaneously.
- Lesions caused by CA-MRSA often have necrotic centers
- Systemic signs are uncommon.

Carbuncles

- Formed when adjacent furuncles coalesce to form a single inflamed area.
- Form broad, swollen, erythematous, deep, and painful follicular masses.
- Commonly develop on the back of the neck
- Commonly associated with systemic signs (fever, chills, malaise).
- Bacteremia with secondary spread to other tissues is common.



Patient Care Process for The Treatment of Skin and Soft-Tissue Infections (SSTIS)

Collect

- Patient characteristics (eg, age, sex, pregnant)
- Patient medical history
- Social history (eg, drug/ethanol use), animal exposures (if bite injury)
- Current medications (eg, antimicrobials, immunosuppressive agents)
- Prior medications (eg, antimicrobials, immunosuppressive agents)
- Objective data
    - Weight, temperature, blood pressure (BP), heart rate (HR), respiratory rate (RR), altered mental status (AMS), urine output (UO), skin turgor/integrity
    - Labs including white blood cells (WBC) with differential, serum creatinine (SCr), liver function tests (LFT), blood glucose (especially for diabetic foot infection)

- Culture and antimicrobial susceptibility data
- Physical examination of skin lesions including location, size, appearance, presence of abscesses or ulcers, presence of purulence or drainage
- Imaging studies (if suspicion for osteomyelitis, necrotizing fasciitis)

Assess

- Evidence for specific type of infection (see Clinical Presentation boxes for various SSTIs)
- Classification of infection severity, especially for cellulitis, diabetic foot infection, and pressure sores (see Tables 128-8 and 128-10)
- Risk for infection with specific pathogens (see Tables 128-1 and 128-9)
- Ability/willingness to be treated as outpatient, including potential adherence barriers
- Hemodynamic/clinical stability (eg, SBP <90 mmHg, HR >100 bpm, RR>22, AMS, decreased UO)
- Contraindications to specific antibiotic therapy (eg, age, allergies, drug-drug/disease interactions)

Plan*

- Antibiotic regimen including specific antimicrobial(s), dose, route, frequency, and duration (see Figs. 128-1, 128-2, 128-3; Tables 128-3, 128-4, 128-5, 128-9)
- Monitoring parameters including efficacy (eg, improvement and/or healing of infectious lesions and other symptoms [depending on specific SSTI]), and safety (eg, antibiotic side effects, *Clostridioides difficile*); frequency and timing of follow-up
- Monitoring parameters for specific antibiotics administered to hospitalized patients (see Table 128-6)
- Patient education (eg, purpose of treatment, lifestyle modification, drug- and infection-specific information, medication administration)
- Self-monitoring for resolution of SSTI signs and symptoms, signs of worsening or unresponsive SSTI, when to seek additional medical attention
- Referrals to other providers when appropriate (eg, surgeon, diabetes

educator, wound care specialist)

Implement*

- Provide patient and caregiver education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence to outpatient antibiotics
- Schedule follow-up as needed for more severe infections (eg, cellulitis, diabetic foot infection, pressure sores, bite wounds)

Follow-up: Monitor and Evaluate*

- Resolution of infectious symptoms (depending on specific type of SSTI)
- Presence of adverse effects specific to the antibiotic regimen
- Patient adherence to treatment plan using multiple sources of information
- Presence of drug-drug interactions potentially requiring changes in drug regimens or monitoring plans
- Therapeutic drug levels for specific agents used in hospitalized patients (see Table 128-6)

**Collaborate with patient, caregivers, and other health professionals.*

TREATMENT

Folliculitis, Furuncles, and Carbuncles

Desired Outcomes

The goals of treatment include relieving discomfort, preventing further spread of the infection, and preventing recurrence. Controlling recurrent furunculosis is key due to the difficulty in treating chronic furunculosis.[26] Treatments should be effective and inexpensive and have minimal adverse effects.

Treatment

Table 128-3 summarizes evidence-based treatment recommendations from clinical guidelines for SSTIs.[3,4,8,16,28-30] Treatment of folliculitis generally requires only local measures, such as warm moist compresses or topical therapy (eg, clindamycin, erythromycin, mupirocin, or benzoyl peroxide).[8,24,26] Topical

agents are typically applied two to four times daily for 7 days. Small furuncles generally can be treated with moist heat, which promotes localization and drainage of pus.[4,8,24,26] Large and/or multiple furuncles and carbuncles require incision and drainage.[4,5,8,13,16,24,29] Systemic antibiotics are usually not necessary unless accompanied by fever or extensive cellulitis.[4,5,16,24] Treatment of more severe infections (eg, accompanied by systemic signs of infection) should include oral trimethoprim-sulfamethoxazole or a tetracycline (either doxycycline or minocycline) for 5 to 10 days due to a higher suspicion for MRSA (refer to Table 128-4 for adult and pediatric doses).[4,5,13,16,24,26,29] For individuals with nasal colonization, application of mupirocin ointment twice daily in the anterior nares for the first 5 days of each month decreases recurrent furunculosis by almost half.[13,16,26] Daily chlorhexidine washes and daily washing of personal items such as towels, bedding, and clothes may also be recommended.[16]

TABLE 128-3 Evidence-Based Recommendations for Treatment of Skin and Soft-Tissue Infections[3,4,8,16,28-31]

Recommendations	Recommendation Grade[a]
Folliculitis, Furuncles, Carbuncles	
Gram stain and culture of pus from carbuncles and abscesses are recommended, but treatment without cultures is reasonable in most patients	Strong, moderate
Carbuncles, abscesses and large furuncles of mild severity should be treated with incision and drainage	Strong, high
Administration of antibiotics with activity against *Staphylococcus aureus* as an adjunct to incision and drainage should be based on presence or absence of systemic signs of infection	Strong, low
Antibiotics with activity against MRSA are recommended for patients with carbuncles or abscesses of higher severity who have failed initial antibiotic therapy, have severe systemic signs of infection, or are immunocompromised	Strong, low
Erysipelas	
Most infections are caused by *Streptococcus pyogenes*. Penicillin (oral or IV depending on clinical severity) is the drug of choice	A-I
If *S. aureus* is suspected, a penicillinase-resistant penicillin or first-generation cephalosporin should be used	A-I
Impetigo	
Gram stain and culture of pus or exudates should be obtained to help identify causative pathogens	Strong, moderate
Bullous and nonbullous impetigo should be treated with either mupirocin or retapamulin for 5 days	Strong, high
Impetigo should be treated with oral antibiotics active against *S. aureus* unless cultures show streptococci alone. Dicloxacillin or cephalexin is recommended for 7 days. Doxycycline, clindamycin, or sulfamethoxazole-trimethoprim should be used when MRSA is suspected or confirmed	Strong, moderate
Cellulitis	
Cultures of blood or cutaneous aspirates, biopsies or swabs are not routinely recommended	Strong, moderate
Blood cultures are recommended, and cultures of cutaneous aspirates, biopsies, or swabs should be considered, in patients receiving chemotherapy for malignancies, neutropenia, severe cell-mediated immunodeficiency, immersion injuries, or animal bites	Strong, moderate (blood) Weak, moderate (other cultures)
Typical cases of mild nonpurulent cellulitis should be treated with antibiotics active against streptococci	Strong, moderate
Systemic antibiotics are recommended for moderate nonpurulent cellulitis with systemic signs of infection. Use of antibiotics active against methicillin-susceptible *S. aureus* could be considered	Weak, low
Patients with severe nonpurulent cellulitis associated with penetrating trauma, MRSA infection in another location, MRSA nasal colonization, injection drug use, or systemic signs of infection should be treated with vancomycin or other antibiotics active against both MRSA and streptococci	Strong, moderate
Broad-spectrum antibiotic therapy with vancomycin plus either piperacillin–tazobactam, imipenem, or meropenem may be considered for empiric treatment of severe nonpurulent cellulitis in severely immunocompromised patients	Weak, moderate (need for broad-spectrum therapy) Strong, moderate (recommended broad-spectrum antibiotic regimen if used)
A treatment duration of 5 days is recommended for cellulitis, but may be extended if lack of clinical response within that time	Strong, high
Elevation of the affected area and treatment of predisposing factors are recommended for cellulitis	Strong, moderate
Systemic corticosteroids for 7 days can be considered for adjunctive treatment of cellulitis in nondiabetic patients	Weak, moderate
Patients with mild nonpurulent cellulitis who do not have systemic signs of infection, altered mental status, or hemodynamic instability should be treated as outpatients	Strong, moderate
Hospitalization is recommended for patients with moderate-to-severe nonpurulent cellulitis who have failed outpatient therapy, have poor adherence to therapy, are immunocompromised, or in whom there is a concern for deeper or necrotizing infection	Strong, moderate
Empiric antibiotics for outpatients with purulent cellulitis should provide activity against community-associated MRSA; coverage of β-hemolytic streptococci is likely not required. Mild-to-moderate infections can generally be treated with oral agents (dicloxacillin, cephalexin, clindamycin) unless resistance is high in the community	A-II
Recommended antibiotics for empiric coverage of MRSA in outpatients include orally administered trimethoprim–sulfamethoxazole, doxycycline, minocycline, clindamycin, and linezolid	A-II for all listed options
If coverage of both β-hemolytic streptococci and community-associated MRSA is desired, empiric antibiotic regimens for outpatient therapy include orally administered clindamycin alone; linezolid alone; or trimethoprim–sulfamethoxazole, doxycycline, or minocycline in combination with amoxicillin	A-II for all listed options
Hospitalized patients with complicated or purulent cellulitis should receive IV antibiotics with activity against MRSA pending culture data. Antibiotic options include vancomycin, linezolid, daptomycin, telavancin, and clindamycin	A-I for all except clindamycin; clindamycin A-III
In the treatment of *S. aureus* infections, trough serum vancomycin concentrations should always be maintained >10 mg/L (7 μmol/L) to avoid development of resistance	B-III
Necrotizing Fasciitis	
Patients with severe nonpurulent cellulitis characterized by aggressive infection and associated with signs of systemic toxicity, necrotizing fasciitis, or gas gangrene should have prompt surgical consultation	Strong, low
Early and aggressive surgical debridement of all necrotic tissue is essential	A-III
Necrotizing fasciitis should be empirically treated with broad-spectrum antibiotics such as vancomycin or linezolid plus piperacillin–tazobactam or a carbapenem, or vancomycin or linezolid plus ceftriaxone and metronidazole	Strong, low
Necrotizing fasciitis caused by *S. pyogenes* should be treated with the combination of clindamycin and penicillin	Strong, low

In the treatment of necrotizing fasciitis caused by methicillin-resistant *S. aureus* infections, trough serum vancomycin concentrations of 15-20 mg/L (10-14 µmol/L) are recommended	B-II
Clostridial gas gangrene (myonecrosis) should be treated with clindamycin and penicillin	B-III
Diabetic Foot Infections	
Clinically uninfected wounds should not be treated with antibiotics	A-III
Empiric antibiotic regimens should be selected based on severity of infection and likely pathogens	A-III
Antibiotic therapy should target only aerobic gram-positive cocci in patients with mild-to-moderate infection who have not received antibiotics within the previous month	C-III
Broad-spectrum empiric antibiotic therapy should be initiated in most patients with severe infections, until culture and susceptibility data are available	A-III
Empiric antibiotics directed against *Pseudomonas aeruginosa* are usually unnecessary except in patients with specific risk factors for infection with this pathogen: patient has been soaking feet, patient has failed previous antibiotic therapy with nonpseudomonal agents, or clinically severe infection	A-III
Empiric antibiotics directed against MRSA should be considered in patients with specific risk factors, including prior history of infection or colonization with MRSA, high local prevalence of MRSA (eg, ≥50% for mild infections, ≥30% for severe infection), or clinically severe infection	C-III
Oral agents with high bioavailability may be used in the treatment of most mild, and many moderate, infections	A-II
Parenteral therapy is initially preferred for all severe, and some moderate, infections. After initial response, step-down therapy to oral agents can be considered	C-III
Definitive therapy should be based on results of appropriately collected cultures and sensitivities, as well as clinical response to empiric antimicrobial agents	A-III
Appropriate wound care, in addition to appropriate antimicrobial therapy, is often necessary for healing of infected wounds	A-III
Antibiotic therapy should only be continued until resolution of signs/symptoms of infection, but not necessarily until the wound is fully healed. The duration of therapy should initially be 1-2 weeks for mild infections and 2-3 weeks for moderate-to-severe infection	C-III
Pressure ulcers	
Optimize the host response by evaluating nutritional status and addressing deficits; stabilizing glycemic control; improving arterial blood flow; and/or reducing immunosuppressant therapy if possible.	A-III
Consider the use of topical antiseptics for pressure ulcers that are not expected to heal and are critically colonized/topically infected.	B-III
Consider use of silver sulfadiazine in heavily contaminated or infected pressure ulcers until definitive debridement is accomplished.	B-III
Consider the use of medical-grade honey in heavily contaminated or infected pressure ulcers until definitive debridement is accomplished.	C-III
Limit the use of topical antibiotics on infected pressure ulcers, except in special situations where the benefit to the patient outweighs the risk of antibiotic side effects and resistance.	B-III
Use systemic antibiotics for individuals with clinical evidence of systemic infection, such as positive blood cultures, cellulitis, fasciitis, osteomyelitis, systemic inflammatory response syndrome (SIRS), or sepsis.	B-III
Animal Bites	
Preemptive early antibiotics should be administered for 3-5 days in patients with any of the following: immunocompromised; asplenic; advanced liver disease; preexisting or resultant edema of the bitten area; moderate-to-severe bite-related injuries, especially to the hands or face; or bite injuries that have penetrated the periosteum or joint capsule	Strong, low
Amoxicillin–clavulanic acid or other antibiotics active against both aerobic and anaerobic bacteria should be used for treatment of infected animal bites	Strong, moderate
Serious infections requiring IV antimicrobial therapy can be treated with a β-lactam/β-lactamase inhibitor combination or second-generation cephalosporin with activity against anaerobes (eg, cefoxitin)	B-II
Penicillinase-resistant penicillins, first-generation cephalosporins, macrolides, and clindamycin should not be used for treatment of infected wounds because of their poor activity against *Pasteurella multocida*	D-III
Human Bites	
Antimicrobial therapy should provide coverage against *Eikenella corrodens*, *S. aureus*, and β-lactamase–producing anaerobes	B-III

[a]Cited evidence-based guidelines utilize different systems for grading the strengths of recommendation and quality of the associated evidence. Qualitative (descriptive) recommendations are from Reference 16; letter- and roman numeral–based recommendations are from the other cited guidelines. Readers are advised to consult the original documents for full explanations of the grading systems and definitions used in individual guidelines.

Strength of recommendation: A, good evidence for use; B, moderate evidence for use; C, poor evidence for use, optional; D, moderate evidence to support not using; E, good evidence to support not using. *Quality of evidence*: I, evidence from ≥1 properly randomized controlled trials; II, evidence from ≥1 well-designed clinical trials without randomization, case–control analytic studies, multiple time series, or dramatic results from uncontrolled experiments; III, evidence from expert opinion, clinical experience, descriptive studies, or reports of expert committees.

Qualitative (descriptive) recommendations: *Strong, high*: strong recommendation, high-quality evidence from well-performed randomized controlled trials (RCTs) or exceptionally strong evidence from unbiased observational studies; *Strong, moderate*: strong recommendation, moderate quality evidence from RCTs with important limitations or exceptionally strong evidence from unbiased observational studies; *Strong, low*: strong recommendation, low-quality evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws, or indirect evidence; *Weak, moderate*: weak recommendation, moderate quality evidence from RCTs with important limitations or exceptionally strong evidence from unbiased observational studies; *Weak, low*: weak recommendation, low-quality evidence for at least one critical outcome from observational studies, RCTs with serious flaws, or indirect evidence.

TABLE 128-4 Recommended Oral Drugs for Outpatient Treatment of Mild-to-Moderate Skin and Soft-Tissue Infections

Infection	Adults	Children
Folliculitis	None; warm saline compresses usually sufficient	
Furuncles and carbuncles	Trimethoprim–sulfamethoxazole[a,b] Doxycycline[a,b] Minocycline[a,b]	Trimethoprim–sulfamethoxazole[a,b] Clindamycin[a,b]
Erysipelas	Procaine penicillin G Penicillin VK Clindamycin[a] Erythromycin[a]	Penicillin VK Clindamycin[a] Erythromycin[a]
Impetigo	Mupirocin ointment[a] Retapamulin ointment[a] Dicloxacillin Cephalexin Trimethoprim–sulfamethoxazole[a,b] Clindamycin[a,b] Doxycycline[a,b]	Mupirocin ointment[a] Retapamulin ointment[a] Dicloxacillin Cephalexin Trimethoprim–sulfamethoxazole[a,b] Clindamycin[a,b]
Lymphangitis	Initial IV therapy, followed by penicillin VK Clindamycin[a]	Initial IV therapy, followed by penicillin VK Clindamycin[a]
Cellulitis	Penicillin VK[c] Cephalexin[c] Dicloxacillin[c] Clindamycin[b,c] Trimethoprim–sulfamethoxazole[b,d] Doxycycline[b,d] Minocycline[b,d] Linezolid[b]	Penicillin VK[c] Cephalexin[c] Dicloxacillin[c] Clindamycin[b,c] Trimethoprim–sulfamethoxazole[b,d] Linezolid[b]
Diabetic foot infections	Dicloxacillin Clindamycin Cephalexin Amoxicillin–clavulanate Levofloxacin ± metronidazole or clindamycin[a,e] Ciprofloxacin ± metronidazole or clindamycin[a,e] Moxifloxacin	
Bite wounds (animal or human)	Amoxicillin–clavulanate Doxycycline[a] Moxifloxacin[a] Trimethoprim–sulfamethoxazole + metronidazole or clindamycin[a] Levofloxacin or ciprofloxacin + metronidazole or clindamycin[a] Cefuroxime axetil + metronidazole or clindamycin Dicloxacillin + penicillin VK	Amoxicillin–clavulanate Trimethoprim–sulfamethoxazole + metronidazole or clindamycin[a] Cefuroxime axetil + metronidazole or clindamycin Dicloxacillin + penicillin VK

[a]May be used in patients with penicillin allergy.

[b]Recommended if CA-MRSA is suspected.

[c]For nonpurulent cellulitis when CA-MRSA is not suspected, or purulent cellulitis when CA-MRSA not documented (not penicillin VK).

[d]May be combined with amoxicillin if additional coverage for streptococci is desired.

[e]Fluoroquinolone alone may be suitable for mild infections, while addition of drugs with antianaerobic activity may be recommended for more severe infections.

Evaluation of Therapeutic Outcomes

Many follicular infections resolve spontaneously without medical or surgical intervention. Lesions should be incised if they do not respond to a few days of moist heat and nonprescription topical agents. Following drainage, most lesions begin to heal within several days without antimicrobial therapy. Any patient who is unresponsive to several days of systemic antibiotic therapy or suffers recurrent infection should have a culture and sensitivity test performed to guide continued antibiotic selection.

ERYSIPELAS

2 Erysipelas is a distinct form of cellulitis involving the more superficial layers of the skin and cutaneous lymphatics.[3,26,32,33] The intense red color and burning pain associated with erysipelas led to the common name of "St. Anthony's fire." The infection is almost always caused by β-hemolytic streptococci, with the organisms gaining access via small breaks in the skin. Group A streptococci (*S. pyogenes*) are responsible for most infections.[8,16,26,33] Infections are more common in infants, young children, the elderly, and patients with nephrotic syndrome or who are immunocompromised.[4,8,32,33] Erysipelas also commonly occurs in areas of preexisting lymphatic obstruction or edema.[8,13,32,33] Diagnosis is made on the basis of the characteristic lesion.

TREATMENT

Erysipelas

Desired Outcomes

The goal of treatment of erysipelas is rapid eradication of the infection, thereby providing relief of symptoms (pain, tenderness, fever).[32] Preventing recurrent infection is also important as recurrence is a common complication, occurring in approximately 20% of patients.[26,32] Treatments should be effective and inexpensive, and have minimal adverse effects.

Treatment

Mild-to-moderate cases of erysipelas are treated with intramuscular procaine penicillin G or penicillin VK for 7 to 10 days (see Table 128-4).[8,16,32] Recommended doses and monitoring parameters for selected antibiotics are given in **Tables 128-5** and **128-6**. Penicillin-allergic patients can be treated with clindamycin. For more serious infections, the patient should be hospitalized and aqueous penicillin G administered IV.[8,16] Marked improvement usually is seen within 48 hours, and the patient often may be switched to oral penicillin to complete the course of therapy.

TABLE 128-5 Drug Dosing Table[a]

Drug	Brand Name	Usual Dosing Range	Special Population Dose	Other
Oral Agents				
Amoxicillin–clavulanate	Augmentin®	875/125 mg orally every 12 hours	Pediatric: 40 mg/kg (of the amoxicillin component) orally in two divided doses	
Cefaclor	Ceclor®	500 mg orally every 8 hours	Pediatric: 20-40 mg/kg/day (not to exceed 1 g) orally in three divided doses	
Cefadroxil	Duricef®	250-500 mg orally every 12 hours	Pediatric: 30 mg/kg orally in two divided doses	
Cefuroxime axetil	Ceftin®	250-500 mg orally every 12 hours	Pediatric: 20-30 mg/kg orally in two divided doses	
Cephalexin	Keflex®	250-500 mg orally every 6 hours	Pediatric: 25-50 mg/kg orally in four divided doses	
Ciprofloxacin	Cipro®	500-750 mg orally every 12 hours		
Clindamycin	Cleocin®	300-600 mg orally every 6-8 hours	Pediatric: 10-30 mg/kg/day orally in three to four divided doses[3]	May be used for oral treatment of MRSA infection
Delafloxacin	Baxdela®	450 mg orally every 12 hours		May be used for oral treatment of MRSA infection
Dicloxacillin	Dynapen®	250-500 mg orally every 6 hours	Pediatric: 25-50 mg/kg orally in four divided doses	

Doxycycline	Vibramycin®	100-200 mg orally every 12 hours		May be used for oral treatment of MRSA infection
Erythromycin	E-Mycin® Erythrocin®	250-500 mg orally every 6 hours	Pediatric: 30-50 mg/kg orally in four divided doses®	
Levofloxacin	Levaquin®	500-750 mg orally once daily		
Linezolid	Zyvox®	600 mg orally every 12 hours	Pediatric: 20-30 mg/kg/day orally in two to three divided doses	For oral treatment of MRSA infection
Metronidazole	Flagyl®	250-500 mg orally every 8 hours	Pediatric: 30 mg/kg orally in three to four divided doses	
Moxifloxacin	Avelox®	400 mg orally once daily		
Mupirocin ointment	Bactroban®	Apply to affected areas every 8 hours	Pediatric: apply to affected areas every 8 hours	
Penicillin VK	Veetids® Pen-V®	250-500 mg orally every 6 hours	Pediatric: 25,000-90,000 units/kg orally in four divided doses	
Retapamulin ointment	Altabax®	Apply to affected area every 12 hours	Pediatric: apply to affected area every 12 hours	
Tedizolid	Sivextro®	200 mg orally once daily		For oral treatment of MRSA infection
Trimethoprim–sulfamethoxazole	Bactrim® Septra® Cotrimoxazole®	160/800 mg orally every 12 hours	Pediatric: 4-6 mg/kg (of the trimethoprim component) orally every 12 hours	Up to double the usual dose may be considered for oral treatment of MRSA infection
Parenteral Agents				
Ampicillin	Omnipen® Polycillin® Principen®	1-2 g IV every 6 hours	Pediatric: 200-300 mg/kg/day IV in four to six divided doses	
Aztreonam	Azactam®	1 g IV every 6 hours	Pediatric: 100-150 mg/kg/day IV in four divided doses	
Cefazolin	Ancef® Kefzol®	1 g IV every 6-8 hours	Pediatric: 75 mg/kg/dayIV in three divided doses	
Cefepime	Maxipime®	1-2 g IV every 12 hours	Pediatric: 100 mg/kg/day IV in two divided doses	
Cefotaxime	Claforan®	1-2 g IV every 6 hours	150-200 mg/kg/day in three to four divided doses	
Cefoxitin	Mefoxin®	1-2 g IV every 6 hours	Pediatric: 30-40 mg/kg/day IV in four divided doses	
Ceftazidime	Fortaz®	1-2 g IV every 8 hours	Pediatric: 150 mg/kg/day IV in three divided doses	
Ceftaroline	Teflaro®	600 mg IV every 12 hours		For MRSA infection
Ceftriaxone	Rocephin®	1 g IV once daily		
Cefuroxime	Zinacef®	0.75-1.5 g IV every 8 hours	Pediatric: 150 mg/kg/day IV in three divided doses	
Ciprofloxacin	Cipro®	400 mg IV every 8-12 hours		
Clindamycin	Cleocin®	300-600 mg IV every 6-8 hours; 600-900 mg IV every 6-8 hours for necrotizing fasciitis	Pediatric: 30-50 mg/kg/day IV in three to four divided doses	
Dalbavancin	Dalvance®	1,000 mg IV once on Day 1 of therapy, followed by 500 mg IV once on Day 8 of therapy; OR 1,500 mg IV once with no additional doses		For MRSA infection
Daptomycin	Cubicin®	4 mg/kg IV once daily		For MRSA infection
Delafloxacin	Baxdela®	300 mg IV every 12 hours		For MRSA infection
Doripenem	Doribax®	500 mg IV every 8 hours		
Ertapenem	Invanz®	1 g IV once daily	Pediatric: 30 mg/kg/day IV in one to two divided doses	
Gentamicin	Garamycin®	Traditional: 2 mg/kg loading dose, followed by 1.5 mg/kg IV every 8 hours and guided by measured serum concentrations. Alternative: 5-7 mg/kg IV once daily	Pediatric: 5-7 mg/kg/day IV in three divided doses; doses guided by serum concentrations	
Imipenem–cilastatin	Primaxin®	250-500 mg IV every 6-8 hours	Pediatric: 40-80 mg/kg/day IV in four divided doses	

Levofloxacin	Levaquin®	500-750 mg IV once daily		
Linezolid	Zyvox®	600 mg IV every 12 hours	Pediatric: 20-30 mg/kg/day IV in two to three divided doses	For MRSA infection
Meropenem	Merrem®	1 g IV every 8 hours	Pediatric: 60 mg/kg/day IV in three divided doses	
Metronidazole	Flagyl®	500 mg IV every 8 hours	Pediatric: 30-50 mg/kg/day IV in three divided doses	
Moxifloxacin	Avelox®	400 mg IV once daily		
Nafcillin	Nafcil®	1-2 g IV every 4-6 hours	Pediatric: 100-200 mg/kg/day IV in four to six equally divided doses	
Oritavancin	Orbactiv®	1,200 mg IV once with no additional doses		For MRSA infection
Penicillin G	Pfizerpen® Bicillin® Wycillin®	1-2 million units IV every 4-6 hours	Pediatric: 100,000-200,000 units/kg/day IV in four divided doses[a]	
Piperacillin–tazobactam	Zosyn®	3.375-4.5 g IV every 6 hours	Pediatric: 250-350 mg/kg/day IV in three to four divided doses	
Procaine penicillin G	Bicillin C-R®	0.6-1.2 million units IM every 12 hours	Pediatric: 25,000-50,000 units/kg (maximum 1.2 million units) IM once daily	
Tedizolid	Sivextro®	200 mg IV once daily		For MRSA infection
Telavancin	Vibativ®	10 mg/kg IV once daily		For MRSA infection
Tigecycline	Tigacil®	100 mg IV once, and then 50 mg IV every 12 hours		
Tobramycin	Nebcin®	Traditional: 2 mg/kg loading dose, followed by 1.5 mg/kg IV every 8 hours and guided by measured serum concentrations. Alternative: 5-7 mg/kg IV once daily	Pediatric: 5-7 mg/kg/day IV in three divided doses; doses guided by serum concentrations	
Vancomycin	Vancocin®	30-40 mg/kg/day IV in two divided doses; dosing guided by serum concentrations to achieve trough of 15-20 mg/L (10-14 µmol/L)	Pediatric: 40-60 mg/kg/day IV in three to four divided doses; doses guided by serum concentrations	For MRSA infection

[a]Dosing guidelines in patients with normal renal function.

IM, intramuscularly; MRSA, methicillin-resistant *S. aureus*.

TABLE 128-6 Drug Monitoring

Drug	Adverse Reaction	Monitoring Parameters	Comments
Aminoglycosides (tobramycin, gentamicin)	Nephrotoxicity	Serum creatinine, urine output, serum concentrations	Extended-interval ("once-daily") dosing potentially associated with less renal toxicity, similar efficacy to traditional dosing. Goal trough concentration <1 mcg/mL (mg/L; 2 µmol/L) during extended-interval dosing
Daptomycin	Myopathy	Serum creatine phosphokinase	Most creatinine phosphokinase elevations will be asymptomatic; risk of myopathy may be increased with concomitant use of HMG-coA reductase inhibitors
Imipenem–cilastatin	CNS toxicities, seizures	Serum creatinine, mental status, CNS function	Increased incidence with higher dose, failure to adjust dose/interval for reduced renal function. Increased risk compared with meropenem or doripenem
Linezolid	Myelosuppression, thrombocytopenia, optic/peripheral neuropathy, serotonin syndrome	CBC, vision changes, serum lactate, heart rate, blood pressure, temperature, myoclonus	Myelosuppression and neuropathy more common with prolonged use. Weak MAO inhibitor, serotonin syndrome possible with other serotonergic drugs such as SSRIs and SNRIs
Nafcillin	Interstitial nephritis	Serum creatinine, urine output	Reversible, requires switch to alternative β-lactam
Vancomycin	Nephrotoxicity, infusion reactions	Serum creatinine, urine output, blood pressure, heart rate, serum concentrations	Dose adjustment required for renal dysfunction. Pretreatment and slow infusion may decrease incidence of infusion reaction. Goal trough concentration 15-20 mcg/mL (mg/L; 10-14 µmol/L) for serious infections, including necrotizing fasciitis

CBC, complete blood count; MAO, monoamine oxidase; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Evaluation of Therapeutic Outcomes

Erysipelas generally responds quickly to appropriate antimicrobial therapy. Temperature and white blood cell count should return to normal within 48 to 72 hours. Erythema, edema, and pain also should resolve gradually.

IMPETIGO

3 Impetigo is a superficial skin infection that is seen most commonly in children.[5,24,26,32,34,35] The infection is generally classified as bullous or nonbullous based on clinical presentation.[5,26,32,34,35] Impetigo is most common during hot, humid weather, which facilitates microbial colonization of the skin.[8,4,26,32,34] Minor trauma, such as scratches or insect bites, allows entry of organisms into the superficial layers of skin, and infection ensues.[8,24,26,32,34] Impetigo is highly communicable and readily spreads through close contact,

especially among siblings and children in daycare centers and schools.[8,26,32,34]

CLINICAL PRESENTATION Erysipelas

General

- Lower extremities are the most common sites.

Symptoms

- Flu-like symptoms (fever, chills, malaise) common prior to the appearance of the lesion.
- Infected area described as very painful or as a burning pain.

Signs

- Lesion is intensely erythematous and edematous, often with lymphatic streaking.
- Lesion has raised border, which is sharply demarcated from uninfected skin.
- Temperature is often mildly elevated.

Laboratory Tests

- Causative organism usually cannot be cultured from the skin surface.
- Needle aspiration or punch biopsies occasionally identify organism.
- Cultures considered for more severe cases (eg, atypical clinical findings such as fluid-filled blisters).

Other Diagnostic Tests

- Complete blood cell count is often performed, leukocytosis is common.
- C-reactive protein is also generally elevated.

CLINICAL PRESENTATION Impetigo

General

- Exposed skin, especially the face, is the most common site.

Symptoms

- Pruritus is common.
- Systemic signs and symptoms of infection are minimal.
- Weakness, fever, and diarrhea occasionally seen with bullous form.

Signs

Nonbullous:

- Lesions start as small, fluid-filled vesicles.
- Vesicles rapidly develop into pustules that rupture readily.
- Purulent discharge dries to form characteristic golden yellow crusts.

Bullous:

- Lesions start as vesicles that rapidly progress into bullae containing clear yellow fluid.
- Bullae soon rupture, forming thin, light brown crusts.
- Regional lymph nodes may be enlarged.

Laboratory Tests

- Cultures should be collected for pathogen identification in more severe cases.
- Crusted tops of lesions should be raised to obtain purulent material at the base for culture.
- Open, draining pustules should not be cultured as they may be colonized with skin flora.

Other Diagnostic Tests

- Complete blood cell count often performed, leukocytosis is common.

Although historically caused by *S. pyogenes*, *S. aureus* has emerged as a principle cause of impetigo (either alone or in combination with *S. pyogenes*).[24,26,32,34,35] The bullous form is caused by strains of *S. aureus* capable of producing exfoliative toxins.[24,26,34,35] The bullous form most frequently affects neonates and children less than 5 years of age,[35,36] and accounts for

approximately 30% of all cases of impetigo.[8,34] Similar to other SSTIs, impetigo has been reported to be increasingly due to MRSA.[24,26,34,35]

TREATMENT

Impetigo

Desired Outcomes

The goals of treatment include relieving discomfort, improving the cosmetic appearance of lesions, preventing further spread of the infection, and preventing recurrence. Preventing transmission to others is also important.[26,34] Treatments should be effective and inexpensive and have minimal adverse effects.[32,34]

Treatment

Although impetigo may resolve spontaneously, antimicrobial treatment is indicated to relieve symptoms, prevent formation of new lesions, and prevent complications such as cellulitis. A review of interventions for impetigo by the Cochrane Collaboration found that topical mupirocin and oral antibiotics (except penicillin and erythromycin) were equally effective for the treatment of impetigo[36]; topical mupirocin ointment or retapamulin ointment for 5 days are now recommended as first-line treatment of mild cases of impetigo not involving multiple lesions or the face.[16,24,26,32,34,35] Penicillinase-resistant penicillins (such as dicloxacillin) are preferred for treatment because of the increased incidence of infections caused by *S. aureus*.[16,24,26,34,35] First-generation cephalosporins (eg, cephalexin) are also commonly used.[16,24,26,32,34,35] Penicillin, administered as a single intramuscular dose of benzathine penicillin G or as oral penicillin VK, is effective for infections known to be caused by *S. pyogenes* but should not be used for empiric therapy of unknown etiology.[24] Penicillin-allergic patients, or those known to be infected with MRSA, can be treated with clindamycin, doxycycline, or trimethoprim-sulfamethoxazole. The duration of therapy is 7 days.[16,32,35] With proper treatment, healing of skin lesions generally is rapid and occurs without residual scarring. Removal of crusts by soaking in soap and warm water also may be helpful in providing symptomatic relief.[8,26,32,34]

Evaluation of Therapeutic Outcomes

Clinical response should be seen within 5 to 7 days of initiating antimicrobial therapy for impetigo. Treatment failures could be a result of noncompliance or antimicrobial resistance. A follow-up culture of exudates should be collected for culture and sensitivity, with treatment modified accordingly.

LYMPHANGITIS

4 Acute lymphangitis is an inflammation involving the subcutaneous lymphatic channels. Lymphangitis usually occurs secondary to puncture wounds, infected blisters, or other skin lesions. Most infections are caused by *S. pyogenes*.[37]

TREATMENT

Lymphangitis

Desired Outcomes

The goal of treatment of lymphangitis is rapid eradication of the infection, thereby providing relief of symptoms (pain, tenderness, fever). Prevention of systemic complications is also an important goal as thrombophlebitis and abscess formation are possible. Treatments should be effective and inexpensive and have minimal adverse effects.

CLINICAL PRESENTATION Lymphangitis

General

- Lymphadenitis (acute or chronic inflammation of the lymph nodes) may occur when microorganisms reach the lymph nodes.

Symptoms

- Systemic signs and symptoms (ie, fever, chills, malaise, and headache) often develop rapidly before any sign of infection is evident at the initial site of inoculation, or after the initial lesion has subsided.
- Systemic signs and symptoms often are more profound than would be expected based on examination of the cutaneous lesion.

Signs

- Peripheral lesion associated with proximal red linear streaks directed toward the regional lymph nodes is diagnostic of acute lymphangitis.
- Lymph nodes usually are enlarged and tender.
- Peripheral edema of the involved extremity often is present.
- Thrombophlebitis and acute lymphangitis in the lower extremities may be confused because both are associated with red linear streaking and tender areas; however, in thrombophlebitis, no portal of entry is identifiable.

Laboratory Tests

- Cultures of the affected lesions often yield negative results.
- Pathogens often identified by Gram stain of the initial lesion if done early in the course of the disease.

Other Diagnostic Tests

- Complete blood cell count is often performed as leukocytosis is common.

Treatment

Penicillin is the antibiotic of choice. Because these infections are potentially serious and rapidly progressive, initial treatment should be with IV penicillin G 1 to 2 million units every 4 to 6 hours. Parenteral treatment should be continued for 48 to 72 hours, followed by oral penicillin VK for a total of 10 days.[37] Nondrug therapy includes immobilization and elevation of the affected extremity and warm-water soaks every 2 to 4 hours.[37] For penicillin-allergic patients, clindamycin may be used.

Evaluation of Therapeutic Outcomes

Lymphangitis usually responds rapidly to appropriate therapy; signs and symptoms often are decreased markedly or absent within 24 hours of starting antibiotics.

CELLULITIS

Cellulitis is an acute infectious process that initially affects the epidermis and dermis and may spread subsequently within the superficial fascia.[3,5,12] Cellulitis is considered a serious disease because of the propensity of the infection to spread through lymphatic tissue and to the bloodstream. *S. pyogenes* and *S. aureus* are the most frequent bacterial causes.[3-6,13,22,32] However, many bacteria have been implicated in various types of cellulitis (Table 128-1). Approximately 4 million patients were hospitalized for cellulitis between 1998 and 2006, representing 10% of all infection-related admissions.[3,10,38] Additionally, the hospitalization rate due to cellulitis and abscess increased by 73% between 1997 and 2011; the number of visits to ambulatory care clinics and emergency rooms doubled from 4.6 million in 1997 to 9.6 million in 2005.[3] The rising incidence of infections caused by methicillin-resistant *S. aureus* (MRSA) is a major concern in both the community and hospital settings and is thought to be the major factor contributing to the dramatic increases in both outpatient visits and hospitalizations.[3,5,14-19,39]

Injection drug users are predisposed to several infectious complications, including abscess formation and cellulitis at the site of injection.[3,5,16] These SSTIs are often polymicrobic in nature and are believed to originate from the skin and/or oropharynx, as well as from contaminated needles, syringes, and diluents.[3,5,16] *S. aureus*, including MRSA, is the most common pathogen isolated from injection drug users.[3-5,39] Anaerobic bacteria, especially oropharyngeal anaerobes, are also found commonly, particularly in polymicrobic infections.[3,5,16] Outbreaks caused by *Clostridium* species have also been reported in injection drug users.[16]

Acute cellulitis with mixed aerobic and anaerobic pathogens may occur in diabetics, following traumatic injuries, at sites of surgical incisions to the abdomen or perineum, or where host defenses have been otherwise compromised (vascular insufficiency).[3-5,24] In older patients, cellulitis of the lower extremities also may be complicated by thrombophlebitis. Other complications of cellulitis include local abscess, myositis, osteomyelitis, septic arthritis, bacteremia, endocarditis, and sepsis.[3,5,16,24,32] Such complications of cellulitis may occur in approximately 1% of outpatients but as many as 17% of hospitalized patients.[9]

TREATMENT

Desired Outcomes

The goals of therapy of acute bacterial cellulitis are rapid eradication of the infection and prevention of further complications. Effective treatment of cellulitis includes avoidance of unnecessary antimicrobials that contribute to increased resistance, and minimizing toxicities and cost of therapy.

Drug and Nondrug Management of Cellulitis

Local care of cellulitis includes elevation and immobilization of the involved area to decrease swelling.[3,5,16,24,32] Cool sterile saline dressings may decrease pain and can be followed later with moist heat to aid in localization of the cellulitis. Surgical intervention (incision and drainage) is rarely indicated in the treatment of uncomplicated cellulitis, but may play an important role in management of more severe or complicated cases. Antimicrobial therapy is directed against the type of bacteria either documented or suspected to be present based on the clinical presentation. Particular attention must be paid to patients with risk factors for more atypical or resistant bacterial pathogens when selecting antibiotics for treatment of cellulitis. Such organisms include particularly MRSA, but also aerobic gram-negative bacteria and anaerobes.

CLINICAL PRESENTATION Cellulitis

General

- A history of an antecedent wound from minor trauma, abrasion, ulcer, or surgery is often present.

Symptoms

- Patients often experience fever, chills, or malaise and complain that the affected area feels hot and painful.
- Systemic findings such as hypotension, dehydration, and altered mental status are common.

Signs

- Characterized by erythema and edema of the skin.

- Lesions are nonelevated and have poorly defined margins.
- Affected areas generally are warm to touch.
- Inflammation generally is present with little or no necrosis or suppuration of soft tissue.
- Lesions may be associated with purulent drainage, exudates, and/or abscesses.
- Tender lymphadenopathy associated with lymphatic involvement is common.

Laboratory Tests

- Cultures of fluid should be collected when purulent drainage, exudates, or abscesses are present.
- Gram stain of fluid obtained by injection and aspiration of 0.5 mL of saline (using a small 22-gauge needle) into the advancing edge of the lesion may aid the microbiologic diagnosis but often yields negative results.
- Diagnosis usually is made on clinical grounds rather than by culture.

Other Diagnostic Tests

- Complete blood cell count is often performed as leukocytosis is common.
- Blood cultures often useful because bacteremia may be present in up to 30% of cases.

Because staphylococcal and streptococcal cellulitis are indistinguishable clinically,[3-5,32] and because of concern regarding appropriate recognition and treatment of MRSA infections, guidelines from the Infectious Diseases Society of America (IDSA) provide detailed recommendations for empiric antibiotic therapy of cellulitis.[16,29] Antibiotic selection for treatment of cellulitis is chiefly determined by clinical findings such as appearance of the infected lesion and presence of more severe systemic illness. Cellulitis may be broadly classified as either purulent or nonpurulent for purposes of determining likely pathogens and appropriate empiric antibiotic therapy. Purulent cellulitis is defined as infection associated with purulent drainage or exudate in the absence of a simple drainable abscess; the presence of abscesses is also often associated with purulent cellulitis

but by definition is the only clinical feature.[4,16,29] Incision and drainage of any abscesses and good wound care are the primary therapies for mild purulent infections when no systemic findings of infection are present. Systemic antibiotic therapy is often unnecessary in such cases.[3-5,29] Antibiotic therapy is - recommended along with incision and drainage in patients with more - complicated abscesses and/or moderately severe purulent cellulitis including the following: those with systemic signs of infection; multiple sites of infection; rapidly progressive infection in the presence of associated cellulitis; - complicating factors such as extremes of age, comorbidities, or immunosuppression; abscesses in areas that are difficult to drain, such as hands, face, and genitalia; or lack of response to previous drainage alone.[3-5,16,24,29,40] Patients with complicated abscesses and/or moderately severe purulent cellulitis are usually treated as outpatients using orally administered antibiotics with activity against MRSA; infection due to streptococci is less likely in this situation and specific coverage is not required.[3-5,29] Oral agents recommended for moderate purulent cellulitis include trimethoprim-sulfamethoxazole and doxycycline (**Fig. 128-1**).[3-5,16] Oral linezolid is also recommended in such cases but is significantly more expensive and apparently no more efficacious than other treatment options.[3-5,29,39,41] Tedizolid, a new oxazolidinone, is also indicated for the treatment of complicated SSTI. Compared to linezolid, tedizolid may have advantages related to a more convenient dosing schedule and fewer adverse effects and drug interactions. However, tedizolid is likely no more effective than linezolid for SSTI and its role relative to linezolid has not been well established.[16,39,41,42]

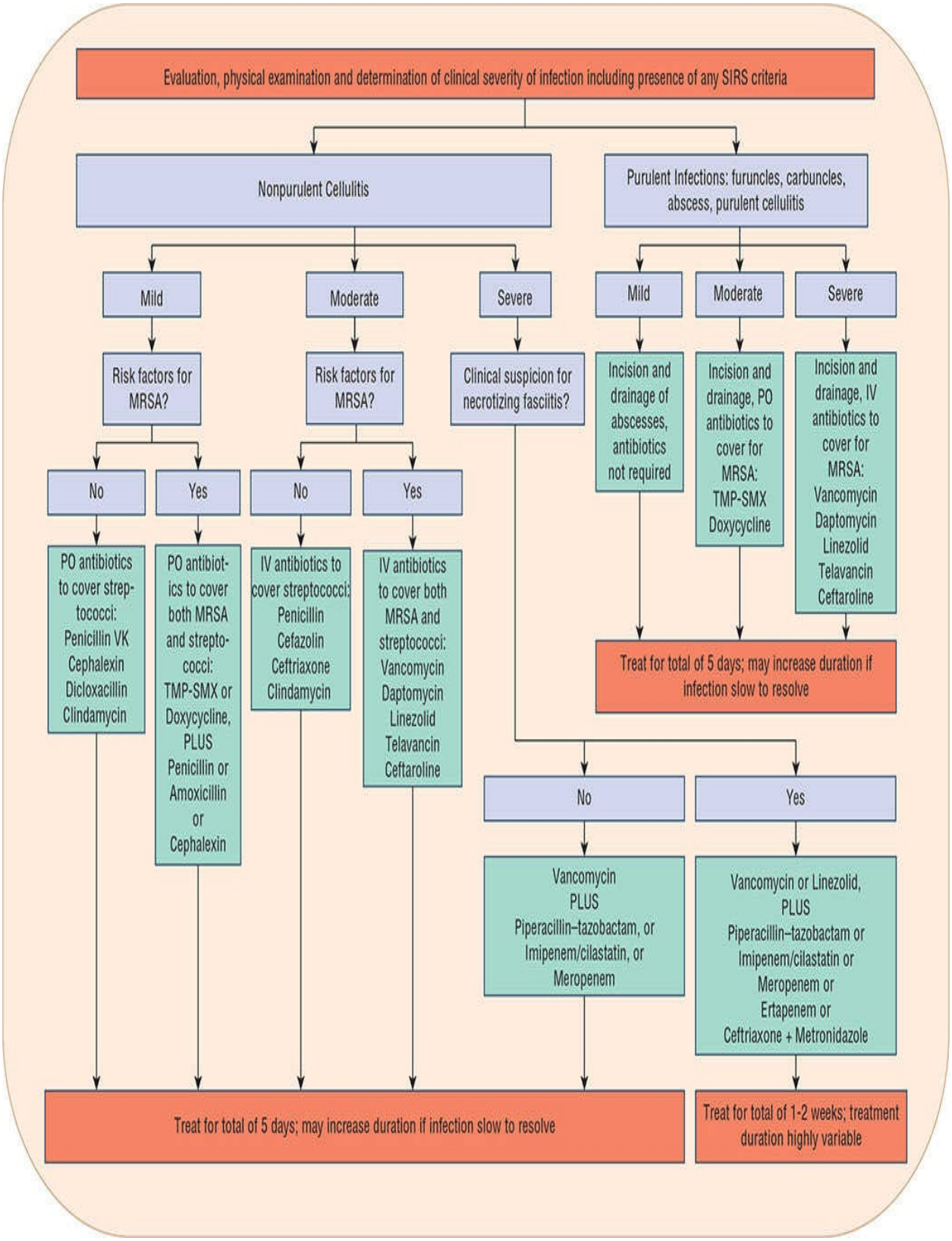


FIGURE 128-1 Recommended treatment algorithm for initial empiric management of selected purulent and nonpurulent skin and soft-tissue infections.

(GNR, aerobic gram-negative rods; GPC, aerobic gram-positive cocci; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; PO, oral; SIRS, systemic inflammatory response syndrome; TMP-SMX, trimethoprim-sulfamethoxazole.)

Severe purulent cellulitis is defined as purulent infections occurring in patients who have failed incision and drainage plus oral antibiotic therapy, patients with systemic signs of infection (defined as temperature greater than 38°C, heart rate greater than 90 beats/min, respiratory rate greater than 24 breaths/min, or white blood cell count greater than 12,000 [12×10^9/L] or less than 400 cells/μL[0.4×10^9/L]), or immunocompromised patients. Appropriate clinical specimens for culture and susceptibility testing should be collected whenever possible in such patients.[3-5,16,23,29] Patients with severe purulent cellulitis should be hospitalized for empiric treatment with parenteral antibiotics having activity against MRSA. Vancomycin, daptomycin, linezolid or tedizolid, televancin, and ceftaroline are all acceptable treatment options with comparable efficacy in adults (Fig. 128-1).[8,3-6,12-14,16,29,39,41] In children, vancomycin, linezolid, or clindamycin are the preferred treatment options.[3,16,35]

Linezolid, tedizolid, daptomycin, ceftaroline, and telavancin all exhibit excellent activity against resistant gram-positive pathogens.[6,12,14,39,40,41,42,43] However, significantly higher cost compared with vancomycin, as well as lack of demonstrated advantages in efficacy, makes them most appropriate for the treatment of complicated or refractory infections, or those documented as caused by multidrug-resistant pathogens, rather than as initial therapy. The availability of orally administered linezolid and tedizolid may provide cost-effective “step-down” options as alternatives to prolonged treatment with parenteral agents for many patients with more complicated infections and/or those patients who require initial hospitalization.[4,6,12-14,39,41,42]

The appropriate roles of dalbavancin and oritavancin, two newer glycopeptide drugs indicated for the treatment of complicated SSTI and with good activity against MRSA, are not well-defined for the routine management of SSTIs. Dalbavancin exhibits a terminal elimination half-life of approximately 14 days and is administered as a single large dose or two smaller doses given one week apart, while oritavancin has a half-life of approximately 10 days and is administered as a single one-time dose. The ability to provide an entire course of therapy with only one or two doses is attractive in terms of convenience, improved adherence compared to oral therapy, facilitation of early discharge of hospitalized patients, and potential for avoidance of inpatient hospitalization

costs through administration in the emergency department, infusion centers, or physician offices. However, drug acquisition costs are higher than other treatment options and there are concerns related to potential lack of patient follow-up for monitoring of severe infections. Although these agents should not be routinely used as first-line therapy, they may be considered for individual patients on a case-by-case basis in order to optimize their use.[3-6,12-14,16,24,39,41]

Delafloxacin is a newer fluoroquinolone with activity against staphylococci including MRSA, streptococci, and gram-negative bacteria including *P. aeruginosa*. Although IV followed by oral delafloxacin has been shown to be noninferior to vancomycin plus aztreonam in the treatment of ABSSSI, its role is not well-defined and delafloxacin is not routinely recommended for treatment of cellulitis. The ability to transition patients from IV to oral therapy and its broad spectrum of activity may make delafloxacin a potential treatment option for carefully selected patients, particularly those with severe polymicrobial infections.

Carbapenems (ie, imipenem, meropenem, ertapenem, and doripenem) and the penicillin-β-lactamase inhibitor combination antibiotics (ampicillin-sulbactam, piperacillin-tazobactam) appear to be equivalent to standard therapies in adults.[8,3,16] However, the greater cost of these agents without increased efficacy compared with other reliable regimens, particularly given the increasing problem of MRSA, makes them less desirable for empiric therapy except in serious polymicrobic infections.[3,16] Newer β-lactam-β-lactamase inhibitor combination agents such as ceftolozane-tazobactam, ceftazidime-avibactam, and meropenem-vaborbactam have few clinical data in the treatment of SSTIs and should not be used for empiric treatment of severe infections.

Nonpurulent cellulitis is defined as cellulitis without purulent drainage or exudate and no associated abscess. The role of MRSA in these types of infection is not clear, so empiric therapy of nonpurulent cellulitis is directed primarily against Group A β-hemolytic streptococci.[3-5,24] Recommended empiric therapy of mild nonpurulent cellulitis (ie, no focus of purulence or systemic signs of infection) consists of an orally administered β-lactam such as penicillin VK, cephalexin or dicloxacillin (Fig. 128-1).[3-5,16,22,29] Oral cephalosporins, such as cefadroxil, cefaclor, cefprozil, cefpodoxime proxetil, and cefdinir, are also effective in the treatment of cellulitis but are more expensive.[16,22,24] Oral clindamycin may be used in penicillin-allergic patients.[16,22,24,29] Alternatively, a first-generation cephalosporin may be used cautiously for patients without a history of immediate or anaphylactic reactions to penicillin. Patients with moderately severe nonpurulent cellulitis (ie, systemic evidence of infection) or

poor adherence to oral therapy should be hospitalized and treated with parenteral antibiotics directed against Group A streptococci. Recommended agents include penicillin VK, ceftriaxone, cefazolin, and clindamycin.[3-5,16,22,35] Hospitalization and treatment with parenteral antibiotics are also recommended for patients with severe nonpurulent cellulitis as indicated by the presence of systemic findings of infection (as previously defined for purulent cellulitis), failure of previous oral antibiotic therapy, immunocompromised states, or presence of clinical signs of deeper infection such as bullae, skin sloughing, hypotension, or organ dysfunction.[3,4,16,22,24] Empiric antibiotics for severe nonpurulent cellulitis should provide a broad spectrum of activity against MRSA and streptococci, as well as gram-negative and anaerobic bacteria. Recommended regimens include vancomycin plus piperacillin-tazobactam, and vancomycin plus imipenem-cilastatin or meropenem.[3,5,16,22,24]

Empiric treatment of MRSA should be considered for patients with either moderate or severe nonpurulent cellulitis that is associated with penetrating trauma, evidence of MRSA infection at another site or nasal colonization with MRSA, injection drug use, or in patients meeting SIRS criteria (fever, tachycardia, tachypnea, or leukocytosis or leukopenia as previously defined).[3,13,14,16,22,29] Recommended drugs for the coverage of MRSA in this setting are the same as those for purulent cellulitis. Clindamycin has reasonably good activity against β-hemolytic streptococci, but the activities of trimethoprim-sulfamethoxazole and the tetracyclines against this organism are not well-defined.[3,16,24,29] Therefore, if empiric coverage of both MRSA and β-hemolytic streptococci is desired for patients with nonpurulent cellulitis, they should receive clindamycin alone or amoxicillin in combination with trimethoprim-sulfamethoxazole, doxycycline, or minocycline.[3,13,14,16,24,29] Hospitalized patients with nonpurulent cellulitis who are not initially treated for MRSA should have their antibiotic changed to an agent with activity against MRSA if there is unsatisfactory clinical response.[3,17,24,29] Although often used for treatment of uncomplicated outpatient cellulitis, fluoroquinolones (eg, levofloxacin, moxifloxacin) are not recommended for routine use due to their unnecessarily broad spectrum of activity, concerns for resistance, and higher cost compared with other preferred options.

Patients in whom specific pathogens have been identified by culture should have empiric antibiotics narrowed according to susceptibility test results. If documented to be a mild cellulitis secondary to streptococci, oral penicillin VK or intramuscular procaine penicillin G may be administered. Since *S. aureus* susceptibilities are more variable, treatment of documented staphylococcal

infections will depend on test results for specific isolates. The usual duration of therapy for outpatient treatment of cellulitis, either purulent or nonpurulent, is 5 days; a longer duration should be considered if the infection has not sufficiently improved within that time.[8,3,16,24,32]

A 7 to 14 day course of antibiotics has been recommended for cellulitis in hospitalized patients, but shorter courses (5 to 7 days) are often as effective as longer courses and should be used whenever possible.[16] In all cases, duration of therapy should be individualized based on patient response.[3,4,16,29]

For cellulitis caused by gram-negative bacilli or a mixture of microorganisms, immediate antimicrobial therapy, as determined by Gram stain, is essential. Surgical debridement of necrotic tissue and drainage also may be appropriate. Gram-negative cellulitis may be treated appropriately with an aminoglycoside (such as gentamicin or tobramycin), or a first- or second-generation cephalosporin (eg, cephalexin, cefaclor, or cefuroxime). Ceftriaxone, ceftazidime, and the fluoroquinolones are also effective in the treatment of cellulitis caused by both gram-negative and gram-positive bacteria.[3,4,8,16] If gram-positive aerobic bacteria are also present on Gram stain, an additional agent such as penicillin G or a penicillinase-resistant penicillin may need to be added to provide coverage against staphylococci or streptococci as appropriate.[3,4,29] Addition of an agent active against MRSA (eg, vancomycin) may need to be considered for severe, complicated infections in hospitalized patients.[3,4,6,8,29] Ceftaroline is potentially advantageous in this setting since it has activity against MRSA and streptococci as well as gram-negative aerobic bacteria.

Because some polymicrobic infections may also involve anaerobic bacteria, antibiotic therapy may need to be broadened to include agents with good activity against these organisms. Many different treatment regimens are possible depending on the bacteriology of the lesion (Fig. 128-1). Orally administered antibiotics, as monotherapy or in combination regimens, may be appropriately used in the treatment of mild-to-moderate infections in outpatients. Monotherapy or combination regimens of IV antibiotics may be necessary for more severe infections in hospitalized patients. Therapy should be 5 to 7 days in duration, with longer durations potentially needed in patients who do not respond to therapy in that time.[8,3,4,16]

Because gram-negative and mixed aerobic-anaerobic cellulitis can progress quickly to serious tissue invasion, therapeutic intervention should be immediate.[8,3,16] If treated early, a rapid response can be seen. Unfortunately, because these infections often occur in patients with compromised immune

defenses, they may still progress, even with therapeutic intervention. If the infectious process is secondary to a systemic cause (eg, diabetes), the treatment course often is prolonged and may be associated with high morbidity and mortality.[8,3,4,24]

Infections in injection drug users generally are treated similarly to those in other types of patients.[8,16] It is important that blood cultures be obtained in these cases because 25% to 35% of patients may be bacteremic.[8,16,23] Also, patients should be assessed for the presence of abscesses; incision, drainage, and culture of these lesions are of extreme importance.[16] Initial antimicrobial therapy while awaiting culture results of abscesses should include broad coverage for gram-negative and anaerobic organisms, in addition to MRSA and streptococci.[8,16,23]

Evaluation of Therapeutic Outcomes

If treated promptly with appropriate antibiotics, the majority of patients with cellulitis are cured rapidly. Culture and sensitivity results should be evaluated carefully for both the adequacy of culture material and the presence of resistant organisms. Additional high-quality samples for culture may be needed for microbiologic analysis. Failure to respond to therapy also may be indicative of an underlying local or systemic problem or a misdiagnosis.

NECROTIZING SOFT-TISSUE INFECTIONS

Necrotizing soft-tissue infections consist of a group of extremely severe infections, associated with high morbidity and mortality, that require early and aggressive surgical debridement in addition to appropriate antibiotics and intensive supportive care.[4-6,24,44-48] Different terms have been used to classify necrotizing infections based on factors such as predisposing conditions, onset of symptoms, pain, skin appearance, etiologic agent, gas production, muscle involvement, and systemic toxicity.[3,4,24,45] However, while many types of necrotizing soft-tissue infections have been designated as unique infectious processes, they all share similar pathophysiologies, clinical features, and treatment approaches.[44-48] The major clinical entities of necrotizing infections are *necrotizing fasciitis* and *clostridial myonecrosis* (gas gangrene).[4,24,44-48]

6 Necrotizing fasciitis is a rare but severe infection of the subcutaneous tissue that may be caused by aerobic and/or anaerobic bacteria and results in progressive destruction of the superficial fascia and subcutaneous fat.[4,24,44-48]

Type I necrotizing fasciitis is the most common and accounts for approximately 80% of necrotizing soft-tissue infections.[4,24,44-48] It generally occurs after trauma or surgery and involves a mixture of anaerobes (*Bacteroides*, *Peptostreptococcus*) and facultative bacteria (streptococci and Enterobacteriaceae) that act synergistically to cause destruction of fat and fascia.[4,24,44,45] Type I necrotizing fasciitis is also reported more commonly among injection drug users.[44-47] In type I infections, the skin may be spared, and the speed at which the infection spreads
(3-5 days) is somewhat slower than that in type II.[24,45] Necrotizing fasciitis affecting the male genitalia is termed *Fournier's gangrene*.[4,44,45] Type II necrotizing fasciitis is caused by virulent strains of *S. pyogenes* and is commonly referred to as *streptococcal gangrene*.[4,24,44-48] This type of infection has often been called "flesh-eating bacteria" by the lay press. Type II infections may occur in young, previously healthy individuals as well as older individuals with underlying diseases.[4,24,44-48] It differs from type I infections in its clinical presentation. Type II infections have rapidly extending necrosis (ie, 24-72 hours) of subcutaneous tissues and skin, gangrene, severe local pain, and systemic toxicity.[44-48] They are also highly associated with an early onset of shock and organ failure and are present in approximately half the cases of streptococcal toxic shock-like syndrome.[44-48] Of note, MRSA is increasingly reported in type II infections, either as a single organism or in combination with streptococci.[4,24,44-46]

Clostridial myonecrosis (type III necrotizing fasciitis) is a necrotizing infection that involves the skeletal muscle.[4,24,44-48] Type III infections account for less than 5% of necrotizing infections.[45] Gas production and muscle necrosis are prominent features of this infection, which readily explains why this infection is commonly referred to as *gas gangrene*.[4,24,44-46] The infection advances rapidly, often over a matter of a few hours.[44-48] Most infections occur after surgery or trauma, with *Clostridium perfringens* identified as the most common etiologic agent.[4,24,44-48]

TREATMENT

Necrotizing Soft-Tissue Infections

Desired Outcomes

The goals of therapy of acute bacterial cellulitis are rapid eradication of the infection, prevention of further complications, and reduction in mortality. Effective treatment of necrotizing soft-tissue infections includes avoidance of unnecessary antimicrobials that contribute to increased resistance, and minimizing toxicities and cost of therapy.

Management of Necrotizing Infections

Immediate and aggressive surgical debridement of all necrotic tissues is essential in all patients with suspected or confirmed necrotizing fasciitis.[4,16,24,44-48] Initial surgical debridement performed greater than 14 hours after the diagnosis of necrotizing infection was independently associated with increased patient mortality, including a 34-fold increased risk of death in patients with septic shock.[44-48] Patients often require further surgical intervention following initial debridement to ensure that all necrotic tissue has been removed.[44-48] Type I necrotizing fasciitis must be empirically treated with broad-spectrum antibiotics that include coverage against streptococci, Enterobacteriaceae, and anaerobes. Piperacillin-tazobactam plus vancomycin is specifically recommended as appropriate empiric therapy of necrotizing fasciitis, although a number of antibiotic regimens are also appropriate to successfully treat necrotizing soft-tissue infections (see Fig. 128-1).[4,16] These antibiotic regimens are generally similar to regimens used for polymicrobic cellulitis.[4,8,24,44-48] Antibiotic therapy can be modified after Gram stain and culture reports are available.

CLINICAL PRESENTATION Necrotizing Soft-Tissue Infections

General

- Most frequently involve the abdomen, perineum, and lower extremities.
- Predisposing factors such as diabetes mellitus, local trauma or infection, or recent surgery often present.
- Rapid diagnosis is critical due to the aggressive nature and high associated mortality (20%-50%).

Symptoms

- Systemic symptoms generally are marked (eg, fever, chills, and leukocytosis) and may include shock and organ failure, especially in patients with type II infections.

- Pain in the affected area and systemic toxicity are characteristically more pronounced than with cellulitis.

Signs

- May be difficult to differentiate between necrotizing fasciitis and cellulitis early in infection.
- Affected area is initially hot, swollen, and erythematous without sharply demarcated margins.
- Affected area is often shiny, exquisitely tender, and very painful.
- Diffuse swelling of the area is followed by the appearance of bullae filled with clear fluid.
- Rapidly progressive infection with the frequent development of a maroon or violaceous color of the skin after several days.
- Infection may rapidly evolve into a cutaneous gangrene, sometimes with myonecrosis.

Laboratory Tests

- Tissue samples should be obtained for histologic examination, and culture and susceptibility testing.
- Clostridial myonecrosis shows little inflammation on histologic examination.

Other Diagnostic Tests

- Surgical exploration is the best and most rapid means of diagnosing necrotizing infections; computed tomography and magnetic resonance imaging may also be helpful.
- Blood samples should be collected for complete blood cell count and chemistry profile, as well as for bacterial culture.
- Laboratory tests that may aid in the diagnosis of necrotizing infections (LRINEC score) include C-reactive protein, white blood cell count, hemoglobin, sodium, creatinine, and glucose.

If a diagnosis of either type II (streptococcal) or type III (clostridial) necrotizing fasciitis is established, broad-spectrum empiric therapy should be

replaced with the combination of penicillin plus clindamycin.[4,16,24,44-48] Although *S. pyogenes* remains susceptible to penicillin, the combination with clindamycin is more effective.[44,46] Several factors have been postulated to explain the greater efficacy of clindamycin, including the mechanism of action (inhibition of protein synthesis) that may cause decreased production of bacterial exotoxins.[4,24,44-48] In addition, clindamycin has immunomodulatory properties that may account for the higher efficacy.[44-48] Clindamycin is also effective against some strains of MRSA.[4,24,45] Linezolid has also been suggested for necrotizing fasciitis due to mechanistic properties that are similar to those of clindamycin, but clinical data are fewer in comparison.[4,24,44,45] Hyperbaric oxygen is potentially beneficial for clostridial myonecrosis, but its use is not currently recommended due to lack of clear evidence of improved patient outcomes.[4,16,24,44-48] Likewise, the use of intravenous immunoglobulin (IVIG) has not yet been proven beneficial in the treatment of necrotizing streptococcal infections and its use is not routinely recommended.[4,16,24,44-48]

Evaluation of Therapeutic Outcomes

Because of the high mortality associated with necrotizing infections, rapid and complete debridement of all devitalized and necrotic tissue is essential. Surgical debridement, coupled with appropriate antimicrobial therapy and supportive measures for management of shock and organ failure, should stabilize the patient. Vital signs and laboratory tests should be monitored carefully for signs of resolution of the infection. Change in antimicrobial therapy or additional surgical debridement may be needed in patients who do not show signs of improvement.

DIABETIC FOOT INFECTIONS

Three major types of foot infections are seen in diabetic patients: deep abscesses, cellulitis of the dorsum, and mal perforans ulcers.[49,50] Most deep abscesses involve the central plantar space (arch) and are caused by minor penetrating trauma or by an extension of infection of a nail or web space of the toes. Infections of the dorsal area generally arise from infections in the toes that are related to routine care of the nails, nail beds, and calluses of the toes. Mal perforans ulcer is a chronic ulcer of the sole of the foot. The ulcer develops on thickened, hardened calluses over the first or fifth metatarsal. Mal perforans ulcers are associated with neuropathic changes, which are responsible for the

misalignment of the weight-bearing bones of the foot.[49,50] Osteomyelitis is one of the most serious complications of diabetic foot infection (DFI) and may occur in 30% to 40% of infections.[28,49]

Epidemiology

DFI is among the most common complications of diabetes, accounting for as many as 20% of all hospitalizations in diabetic patients at an annual cost of $200 to $350 million.[28,49,51] Approximately 25% of diabetic patients develop a foot ulcer during their lifetime; up to 60% of these ulcers involve significant soft-tissue infection and osteomyelitis is present in 20%.[49,51] Approximately 71,000 lower-extremity amputations, often sequelae of uncontrolled infection, are performed each year on diabetic patients; this represents up to 80% of all nontraumatic amputations in the United States.[28,49,51] Approximately 20% of diabetics will undergo additional surgery or amputation of a second limb within 12 months of the initial amputation.[28,49]

Etiology

Mild cases of DFI are often monomicrobial. However, more severe infections are typically polymicrobic; up to 60% of hospitalized patients have polymicrobial infections (Table 128-7).[28,49,50,52,53-57] Wide ranges in the frequency of various bacteria in DFI reflect differences in culture techniques as well as variation among different types and severity of infections. Staphylococci and streptococci are the most common pathogens, although gram-negative bacilli and/or anaerobes occur in up to 50% of cases.[52-57] Although *P. aeruginosa* is an important pathogen in DFI, it is usually reported in less than 10% of wounds and is most commonly associated with more severe infections.[28,53] Obligate anaerobes are also more commonly associated with severe infections in patients with chronic foot ischemia.[28,52,53] MRSA is increasingly important in DFI and has been reported in 10% to 30% of infected wounds.[28,53,54,57,58,59] The presence of MRSA in DFI has been associated with increased risk of treatment failure and worse patient outcomes, but these findings have not been consistent among studies and the clinical relevance of MRSA in this setting is still unclear.[28,50,58]

TABLE 128-7 Bacterial Isolates from Foot Infections in Diabetic Patients[28,49,50,52,53-58,60]

Organisms	Percentage of Isolates
Aerobes	63-100
Gram-positive	24-100
Staphylococcus aureus (all)	10-80
S. aureus (MRSA)	1-37
Streptococcus spp.	3-37
Enterococcus spp.	2-25
Coagulase-negative staphylococci	6-10
Other gram-positive aerobes	0-19
Gram-negative	16-73
Proteus spp.	3-7
Enterobacter spp.	1-9
Escherichia coli	3-10
Klebsiella spp.	1-6
Pseudomonas aeruginosa	1-48
Other gram-negative bacilli	3-13
Anaerobes	1-40
Peptostreptococcus spp.	4-28
Bacteroides fragilis group	2-9
Other *Bacteroides* spp.	3-6
Clostridium spp.	0-2
Other anaerobes	7-19

Identifying causative pathogens from cultures of diabetic wounds is often difficult. The chronic nature of DFI means that these wounds are often heavily colonized by organisms not playing a role in the infection. Superficial swab cultures are not as reliable as culture specimens obtained from deep tissues via biopsy, tissue scraping (curettage), or needle aspiration of drainage or abscess fluid.[23,54,57] Therefore, cultures and sensitivity tests should be done with specimens obtained from a deep culture of the wound base whenever possible. Before the wound is cultured, it should be scrubbed vigorously with saline-moistened sterile gauze to remove any overlying necrotic debris and further debrided as necessary.[23,28,54] Bone cultures should also be performed when there is diagnostic uncertainty regarding the presence of osteomyelitis or when therapeutic decisions are dependent on knowing the exact etiology of

infection.[23,28,54]

Pathophysiology

Three key factors are involved in the development of diabetic foot ulcers: neuropathy, angiopathy and ischemia, and immunologic defects. Any of these disorders can occur in isolation; however, they frequently occur together.[51]

Neuropathic changes to the autonomic nervous system as a consequence of diabetes may affect the motor nerve supply of small intrinsic muscles of the foot, resulting in muscular imbalance, abnormal stresses on tissues and bone, and repetitive injuries.[49,51] Diminished sensory perception causes an absence of pain and unawareness of minor injuries and ulceration. The sympathetic nerve supply may be damaged, resulting in an absence of sweating that may lead to dry cracked skin and secondary infection.[28,49,51]

Atherosclerosis is more common, appears at a younger age, and progresses more rapidly in the diabetic than in the nondiabetic. Diabetics may have problems with both small vessels (microangiopathy) and large vessels (macroangiopathy) that can result in varying degrees of ischemia, ultimately leading to skin breakdown and infection. Peripheral artery disease is present in up to 50% of diabetics and is strongly associated with impaired wound healing.[52]

Diabetic patients typically have normal humoral immunity, normal levels of immunoglobulins, and normal antibody responses. Patients with diabetes, however, have impaired phagocytosis and intracellular microbicidal function as compared with nondiabetics; this may be related to angiopathy and low tissue levels of oxygen.[28,49,51] These defects in cell-mediated immunity make patients with diabetes more susceptible to certain types of infection and impair the patients' ability to heal wounds adequately.[49-51]

TREATMENT

Diabetic Foot Infections

Desired Outcomes

7 The goals of therapy in the management of DFI include the following: (a) successfully treat infected wounds by using effective nondrug and antibiotic therapy; (b) prevent additional infectious complications; (c) preserve as much normal limb function as possible; (d) avoid unnecessary use of antimicrobials

that contribute to increased resistance; and (e) minimize toxicities and cost while increasing patient quality of life.

MANAGEMENT

Up to 90% of infections can be treated successfully with a comprehensive treatment approach that includes both wound care and antimicrobial therapy.[28,50,54,55] After carefully assessing the extent of the lesion and obtaining necessary cultures, necrotic tissue must be thoroughly debrided, with wound drainage and amputation as required. Wounds must be kept clean and dressings changed frequently (two to three times daily). Because of the relationship between hyperglycemia and immune system defects, glycemic control must be maximized to ensure optimal wound healing. In addition, the patient's activities should be restricted initially to bed rest for leg elevation and control of edema, if present. Adequate pressure relief from a foot wound (ie, off-loading) is crucial to the healing process.[28,51,54] Finally, appropriate antimicrobials must be initiated.[28,50,51,54,55] However, the optimal antimicrobial therapy for DFI has yet to be defined. Broad-spectrum empiric therapy that provides coverage of all possible pathogens is not recommended unless the infection is life- or limb-threatening, assuming that adequate wound care is also being performed.[49-52,54,58] This is particularly true regarding MRSA,
P. aeruginosa, and anaerobes; the perceived need for empiric coverage of these organisms often leads to use of excessively broad-spectrum drug regimens. Several studies have shown good antimicrobial treatment efficacy despite the fact that the regimens did not have consistently good activity against these particular organisms and no specific regimen has shown clear superiority over another.[49-56,58-60]

CLINICAL PRESENTATION Diabetic Foot Infections

General

- Infections are often much more extensive than they initially appear.

Symptoms

- Patients with peripheral neuropathy often do not experience pain; simple complaints of swelling or edema are common.

Signs

- Clinical signs of infection may not be present secondary to angiopathy and neuropathy.
- Lesions vary in size and clinical features (eg, erythema, edema, warmth, presence of pus, draining sinuses, pain, and tenderness).
- Foul-smelling odor suggests the presence of anaerobic organisms.
- Temperature may be mildly elevated or normal.

Laboratory Tests

- Specimens for culture and sensitivities should be collected.
- Deep-tissue samples obtained during surgical debridement are most useful for culture and susceptibility testing.
- Wounds must be cultured for both aerobic and anaerobic organisms.

Other Diagnostic Tests

- Possible presence of osteomyelitis also must be assessed via radiograph, bone scan, or both, as appropriate.

Proper selection of empiric antibiotics for DFI begins with thorough patient assessment and classification of the severity of the infection. Specific drug regimens, route of administration, and duration of therapy are all then largely dependent on the severity of infection. Although a number of classification systems are available, the most recent DFI treatment guidelines use those summarized in Table 128-8.[28,49,54] Wounds with no local signs of infection often do not require antibiotic therapy, and the majority of mild, uncomplicated infections can be managed successfully on an outpatient basis with highly bioavailable oral antimicrobials and good wound care (**Tables 128-8** and **128-9**).[49-52,57] Antibiotics for treatment of mild infections should be largely limited to those with activity against skin flora such as streptococci and methicillin-susceptible *S. aureus* (MSSA), except in those patients with risk factors for infection with other types of pathogens (**Fig. 128-2**).[49-51,54] Patients with specific risk factors for MRSA (Table 128-9) should empirically receive trimethoprim-sulfamethoxazole or doxycycline orally, while those who have received antibiotics within the past month should also receive empiric antibiotics that provide activity against gram-negative bacilli. Oral antimicrobials should be

used cautiously in DFI complicated by osteomyelitis, extensive ulceration, areas of necrosis, or a combination of these. The use of topical antimicrobials, including medical-grade honey, has been advocated for the treatment of DFI in an attempt to minimize the cost of therapy and systemic antibiotic exposure leading to adverse effects and resistance. Although the most recent guidelines allow for consideration of topical therapy in mild infection in selected patients, use of topical agents is quite controversial, inconsistent in proven benefits, and not routinely recommended.[28,50,54,61,62]

TABLE 128-8 Classifications and Treatment Strategies for Diabetic Foot Infections of Varying Severity[28]

Clinical Signs/Symptoms of Infection	Infection Severity	Treatment Setting
None	Uninfected	Outpatient management; nonantibiotic wound management only
Local infection present (≥2 of the following): local swelling or induration, erythema, local tenderness or pain, local warmth, purulent discharge		Outpatient or inpatient management according to severity (mild, moderate, or severe) as assessed by additional criteria
Local infection involving only skin and subcutaneous tissue, without involvement of deeper tissues or SIRS criteria present; if erythema is present, must be >0.5 and ≤2 cm around ulcer	Mild	Outpatient management; topical or oral antibiotics
Local infection with erythema >2 cm around ulcer, or involving structures deeper than skin and subcutaneous tissue (eg, abscess, osteomyelitis, septic arthritis, fasciitis); no SIRS criteria present	Moderate	Outpatient (or initial inpatient) management; oral (or initial parenteral) antibiotics
Local infection with ≥2 SIRS criteria: • Temperature >38°C (100.4°F) or <36°C (96.8°F) • HR >90 • RR >20 • WBC >12,000 (12 × 10^9/L) or <4,000 (4 × 10^9/L, or >10% (0.10) bands	Severe	Inpatient, followed by outpatient, management; initial parenteral antibiotics, followed by switch to oral when possible

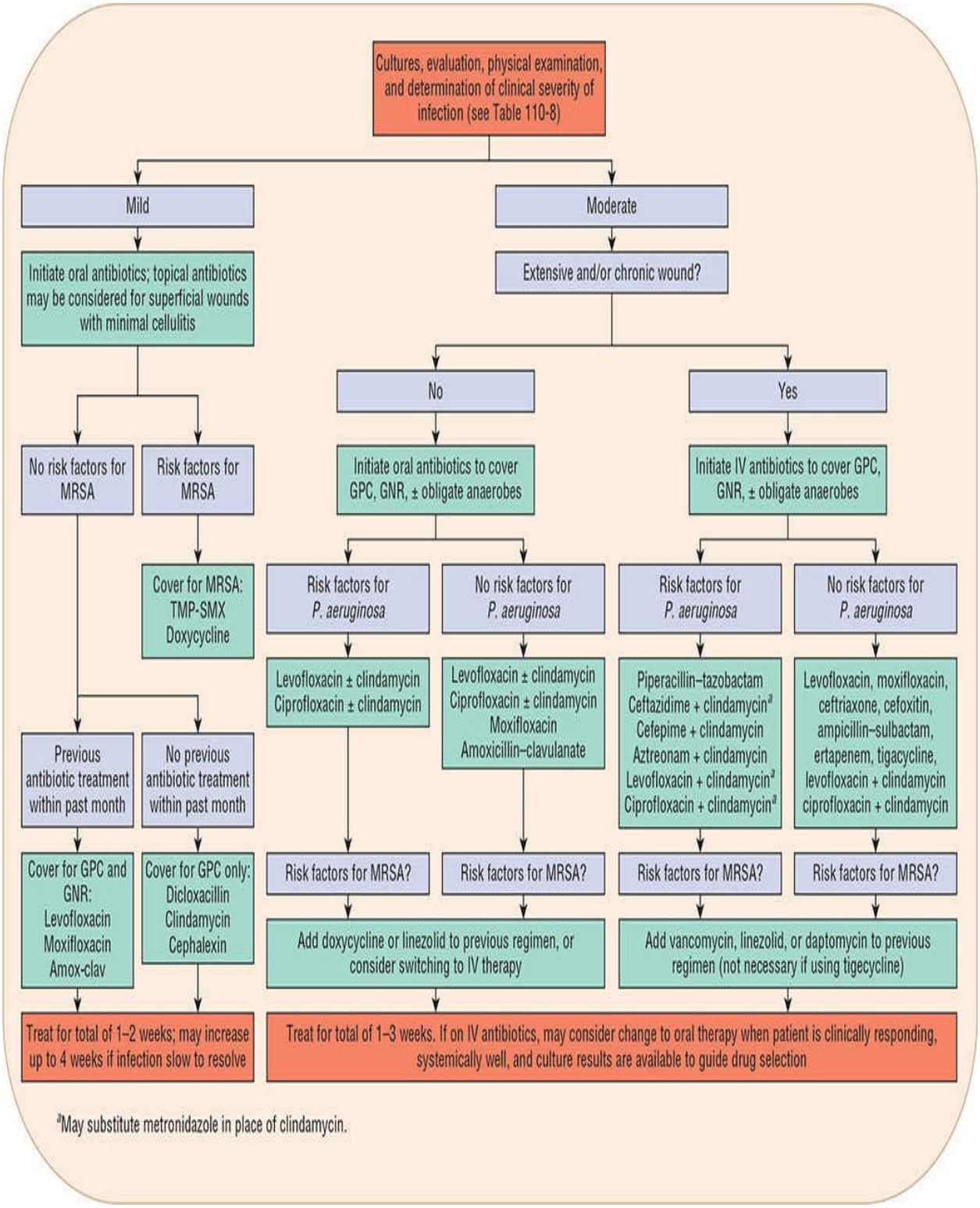


FIGURE 128-2 Recommended treatment algorithm for initial empiric management of mild-to-moderate diabetic foot infections. (GNR, aerobic gram-negative rods; GPC, aerobic gram-positive cocci; MRSA, methicillin-resistant *Staphylococcus aureus*; TMP-SMX, trimethoprim-sulfamethoxazole.)

TABLE 128-9 Suggested Antibiotic Regimens for Empiric Treatment of Diabetic Foot Infections[28]

Severity of Infection	Probable Pathogens	Drug(s)[a]	Duration of Therapy
Mild	*Staphylococcus aureus* (MSSA) *Streptococcus* spp. *S. aureus* (MRSA) • Patients with history of MRSA infection or colonization in past year • Prevalence of MRSA ≥50% in local geographic area • Recent hospitalization	Amoxicillin–clavulanate Cephalexin Dicloxacillin Clindamycin Levofloxacin Moxifloxacin[b]	1-2 weeks; may increase up to 4 weeks if infection slow to resolve
Moderate-to-severe (initially oral or IV antibiotics for moderately severe infections, IV antibiotics for severe infections)	MSSA *Streptococcus* spp. Enterobacteriaceae Obligate anaerobes	Ampicillin/Sulbactam Cefoxitin Ceftriaxone Imipenem/cilastatin Ertapenem Levofloxacin Moxifloxacin Tigecycline Levofloxacin or ciprofloxacin + clindamycin	Moderately severe infection: 1-3 weeks; severe infection: 2-4 weeks
	MRSA • Patients with history of MRSA infection or colonization in past year • Prevalence of MRSA ≥30% in local geographic area • Recent hospitalization • Infection severe enough that not empirically covering MRSA poses unacceptable risk of treatment failure	Add to one of the above regimens: • Vancomycin • Linezolid • Daptomycin	
	Pseudomonas aeruginosa • Patient has been soaking feet • Patient has previously failed therapy with nonpseudomonal antibiotic regimen • Severe infection	Piperacillin/tazobactam	
	Mixed infections potentially including all of the above	Cefepime, ceftazidime, or aztreonam + metronidazole or clindamycin + vancomycin[c] *Or* piperacillin–tazobactam or imipenem–cilastatin or meropenem[b] + vancomycin[c]	

MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

[a]Agents not shown in any particular order of preference.

[b]Not specifically recommended in IDSA guidelines but may be appropriate treatment option.

[c]Linezolid or daptomycin may be used in place of vancomycin.

Appropriate initial therapy for patients with moderate-to-severe infection is also dependent on the presence of specific risk factors that increase the likelihood of infection with more resistant pathogens such as *P. aeruginosa* and MRSA (Table 128-9).[28,49,51,54] Many moderate infections can be successfully treated with orally administered antibiotics that provide activity against MSSA, streptococci, and gram-negative aerobic bacilli; coverage of obligate anaerobes may also be considered in patients with chronic or previously treated wounds (Fig. 128-3).[28,49,51,54] The addition of orally administered agents with activity against MRSA is recommended in patients with moderate or severe infection and specific risk factors for MRSA; such patients may also be considered for hospitalization and initial treatment with parenteral antibiotics in order to ensure adequate antibiotics for potentially more complex infections.[28,49,51,53,54] Patients with more extensive or chronically unhealed wounds, even though assessed as moderate in severity, may also be more appropriately treated initially with parenteral antibiotics in the hospital setting.[50-56]

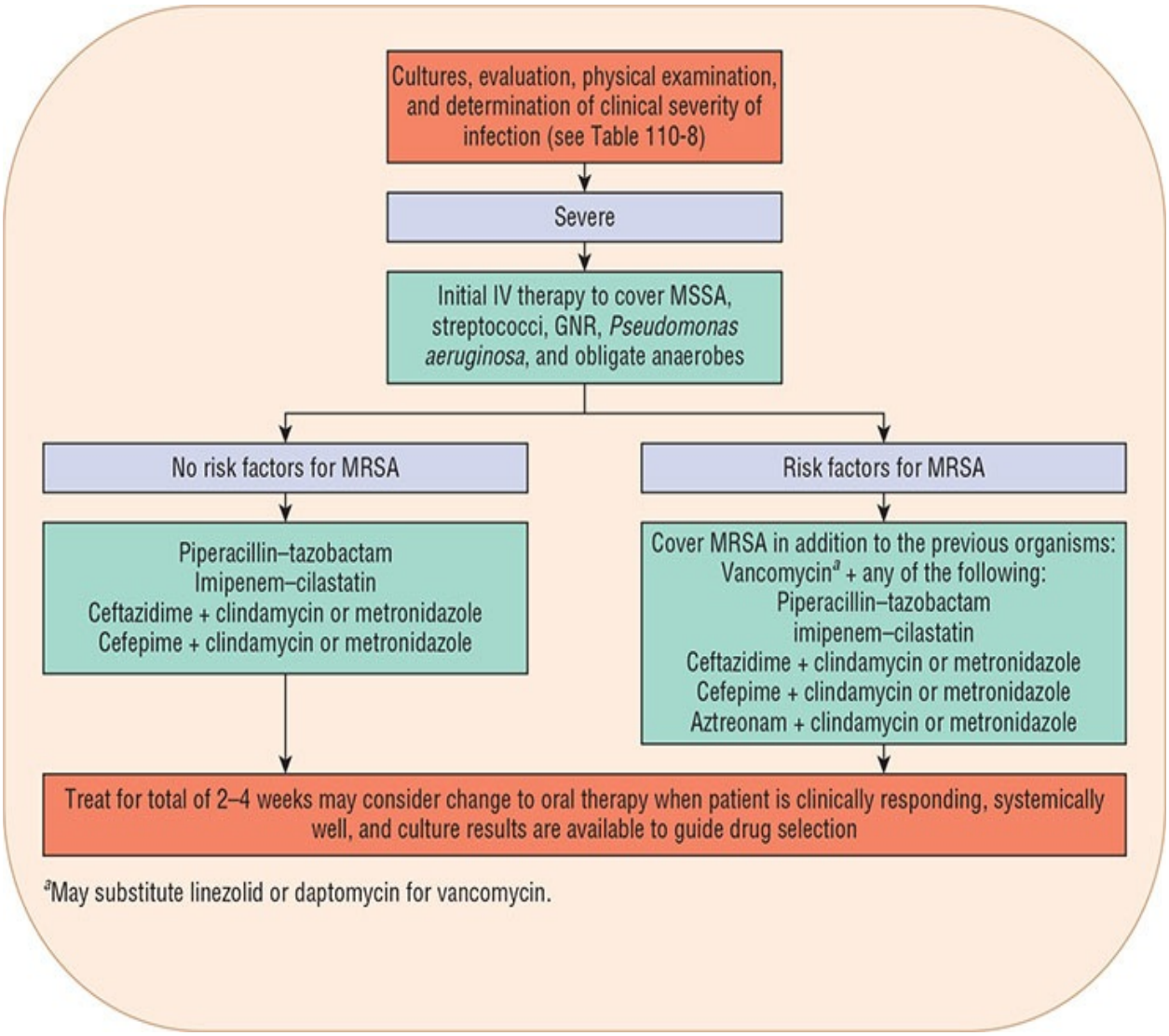


FIGURE 128-3 Recommended treatment algorithm for initial empiric management of severe diabetic foot infections. (GNR, aerobic gram-negative rods; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*.)

All patients with severe DFI should be hospitalized initially and treated with broad-spectrum IV antibiotics (Table 128-9 and Fig. 128-3).[49-56] Severe infection is considered a risk factor for *P. aeruginosa*, so most patients with severe DFI will be initially started on antipseudomonal antibiotics.[51-54] Many patients will also be initially started on antibiotics that provide activity against MRSA due to risk-versus-benefit considerations, but assessment of risk factors in individual patients is important in order to minimize the use of excessively broad-spectrum antibiotics when possible.

Guidelines for management of DFI include options for both monotherapy and combination regimens (Table 128-9).[28] Monotherapy, along with appropriate medical or surgical management, or both, is often effective in treating DFI, including those in which osteomyelitis is present.[49-56,60] Monotherapy is particularly attractive because of the potential advantages of convenience, cost, and avoidance of toxicities. Microbiologic and clinical cure rates ranging from 60% to 90% may be expected from any of these agents.[49-56,60] Selection of a specific regimen is determined by patient-specific factors including allergies, renal function, history of previous antibiotic use, and cost. In penicillin-allergic patients, metronidazole or clindamycin plus a fluoroquinolone, aztreonam, or possibly a third- or fourth-generation cephalosporin is appropriate.[49-56,60] Vancomycin also is used frequently in severe infections because of its excellent activity against gram-positive pathogens. Linezolid, daptomycin, and tigecycline are specifically recommended alternatives for the treatment of this pathogen.[49-56] Tigecycline may be particularly useful in this setting because of its activity against gram-negative aerobes and anaerobic bacteria, thus allowing it to be used as monotherapy for the treatment of mixed infections in patients where coverage of *P. aeruginosa* is not of great concern. Ceftaroline fosamil also has in vitro activity that is suitable for DFI but has not been studied for this indication. Because many patients already have some degree of diabetic nephropathy that may place them at higher risk of nephrotoxicity, strong recommendations have been made against the use of aminoglycoside antibiotics unless no alternative agents are available.[28,50] When an aminoglycoside is used, care must be taken to avoid further compromising renal function. All antibiotic regimens should be adjusted as necessary for renal dysfunction. There is currently no defined role for newer broad-spectrum agents such ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam, eravacycline, and delafloxacin; their use in DFI is not recommended.

Duration of therapy for DFI depends on the severity of the infection, ranging from 1 to 2 weeks for mild infections up to 2 to 4 weeks or more for severe infections.[49-56] In the cases of underlying osteomyelitis, treatment should continue for 6 to 12 weeks.[49-56] After healing of the infection has occurred, a well-designed program for the prevention of further infections should be instituted. The use of adjunctive agents such as colony-stimulating factors, growth factors, and hyperbaric oxygen for either prevention or treatment of DFIs is controversial and not widely recommended.[28,61]

Evaluation of Therapeutic Outcomes

Therapy should be reevaluated carefully after 48 to 72 hours to assess favorable response. Change in therapy (or route of administration, if oral) should be considered if clinical improvement is not observed at this time. For optimal results, drug therapy should be appropriately modified according to information from deep-tissue culture and the clinical condition of the patient. Infections in diabetic patients often require extended courses of therapy because of impaired host immunity and poor wound healing.

PRESSURE SORES

The terms *decubitus ulcer*, *bed sore*, and *pressure sore* are used interchangeably.[31,63-65] The decubitus ulcer and the bed sore are types of pressure sores. The term *decubitus ulcer* is derived from the Latin word *decumbere*, meaning "lying down." Pressure sores, however, can develop regardless of a patient's position.

Numerous systems for classification of pressure sores have been described. The 2016 recommendations of the National Pressure Ulcer Advisory Panel (NPUAP) are shown in Table 128-10. The NPUAP classification system is most commonly used and illustrates the various stages of progression through which a pressure sore may pass.[66]

TABLE 128-10 Pressure Injury Classification

Stage 1	Intact skin with a localized area of nonblanchable erythema. Presence of blanchable erythema or changes in sensation, temperature, or firmness may precede visual changes. Color changes do not include purple or maroon discoloration; these may indicate deep tissue pressure injury.
Stage 2	Partial-thickness loss of skin with exposed dermis. Wound bed is viable, pink or red, moist, and may also present as an intact or ruptured serum-filled blister. Adipose tissue is not visible and deeper tissues are not visible. Granulation tissue, slough, and eschar are not present.
Stage 3[a]	Full-thickness loss of skin, in which adipose tissue is visible in the ulcer and granulation tissue and epibole (rolled wound edges) are often present. Slough and/or eschar may be visible. Depth of tissue damage varies by anatomical location; areas of significant adiposity can develop deep wounds. Undermining and tunneling may occur. Fascia, muscle, tendon, ligament, cartilage and/or bone are not exposed.
Stage 4[a]	Full-thickness skin and tissue loss with exposed or directly palpable fascia, muscle, tendon, ligament, cartilage or bone in the ulcer. Slough and/or eschar may be visible. Epibole (rolled edges), undermining and/or tunneling often occur. Depth varies by anatomical location.
Unstageable[a]	Full-thickness skin and tissue loss in which the extent of tissue damage within the ulcer cannot be confirmed because it is obscured by slough or eschar. If slough or eschar is removed, a stage 3 or stage 4 pressure injury will be revealed.
Deep-tissue pressure injury	Intact or nonintact skin with localized area of persistent nonblanchable deep red, maroon, purple discoloration or epidermal separation revealing a dark wound bed or blood filled blister. Pain and temperature change often precede skin color changes. This injury results from intense and/or prolonged pressure and shear forces at the bone-muscle interface. The wound may evolve rapidly to reveal the actual extent of tissue injury, or may resolve without tissue loss.

[a]Stage 3, stage 4, and unstageable lesions are unlikely to resolve on their own and often require surgical intervention.

Adapted from Reference 66.

Complications of pressure sores are common and may be life-threatening. Infection is one of the most serious and most frequently encountered complications of pressure ulcers.[63,64] Although most pressure sore wounds are heavily colonized, the majority of these eventually heal.[63,64,67,68] When true infection is present, however, there is bacterial invasion of previously healthy tissue. Without treatment, an initial small, localized area of ulceration can rapidly progress to large ulcers within days. The visible ulcer is just a small portion of the actual wound[31]; up to 70% of the total wound is below the skin. A pressure-gradient phenomenon is created by which the wound takes on a conical nature; the smallest point is at the skin surface, and the largest portion of the defect is at the base of the ulcer (Fig. 128-4).

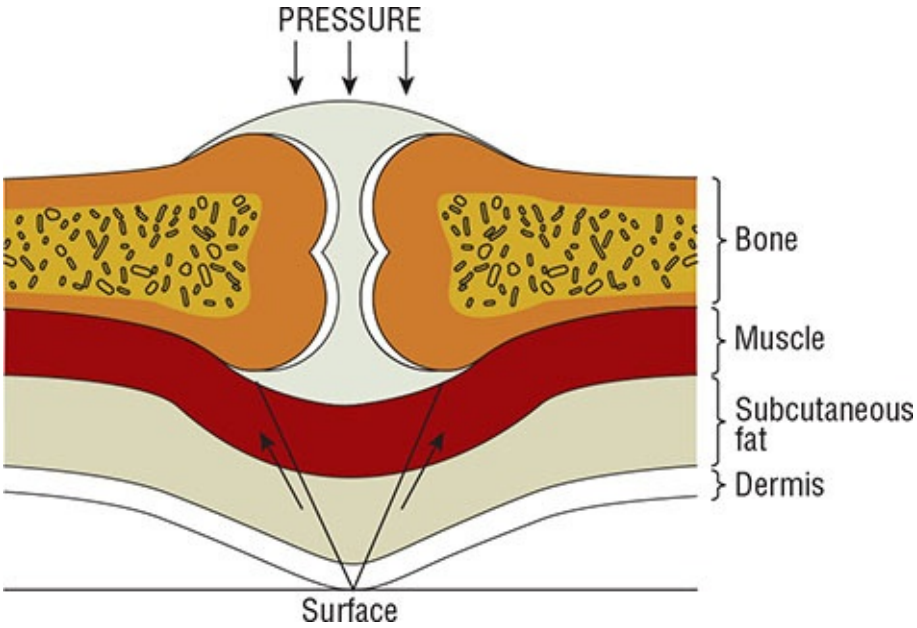


FIGURE 128-4 Distribution of forces involved with sore formation in a conical fashion.

Epidemiology

Pressure sores are most common among chronically debilitated persons, the elderly (70% involve persons greater than 70 years of age), and persons with serious spinal cord injury.[31,63,64] Generally, patients who are at risk for pressure sores are elderly or chronically ill young patients who are immobilized, in either bed or a wheelchair, and who may have altered mental status and/or incontinence.[63,64]

Etiology

Similar to DFIs, a large variety of aerobic gram-positive and gram-negative organisms, as well as anaerobes, frequently are isolated from wound cultures.[25,69] Most pressure sores are heavily colonized with microorganisms, making assessment for infection a clinical challenge.[25,69] Curettage of the ulcer base after debridement provides more reliable culture information than does needle aspiration.[67-69] Biopsy specimens give the most reliable data but may not be practical to obtain. Deep-tissue cultures from different sites may give different results. Cultures collected from pressure ulcers reveal polymicrobial growth. A culture collected by swab is likely to identify surface bacteria colonizing the wound rather than to diagnose the infection.[31,69]

Pathophysiology

Many factors apparently predispose patients to the formation of pressure sores: paralysis, paresis, immobilization, malnutrition, anemia, infection, and advanced age. Factors thought to be most critical to their formation are pressure, shearing forces, friction, and moisture[31,63,64]; however, there is still a debate as to the exact pathophysiology of pressure sore formation.[63,64,67]

Pressure is the essential element in the formation of pressure sores.[25,63,64,67] The areas of highest pressure are generated most often over the bony prominences.[25,63,64] Both the degree of pressure and the length of time that the pressure is applied are important.[63,64]

Shearing occurs when two surfaces move in opposite directions.[25,63,64,67] This situation can occur when the head of a bed is raised, causing the upper torso to slide downward, transmitting pressure to the sacrum and other areas. This effect results in occlusion or distortion of vessels, leading to compromise of the dermis. At the same time, sitting and gravity create shearing forces; the posterior sacral skin area can become fixed secondary to friction with the bed. The effects of friction and shearing forces combine, resulting in transmission of force to the deep portion of the superficial fascia and leading to further damage of soft-tissue structures.[25,63,64]

Compounding the problems of shearing and friction forces are the macerating effects of excessive moisture in the local environment, resulting from incontinence and perspiration. This factor is of critical importance because when combined with the other forces, it increases the risk of pressure sore formation fivefold.[31,63,64,67]

TREATMENT

Pressure Sores

Desired Outcomes

The primary goal for pressure sores is prevention. Once a pressure sore has developed, the goals of therapy are prevention of complications (ie, infections), preventing sores from growing larger, and preventing the development of sores in other locations.[63,64] Eradication of infection should include good wound care and topical therapies, and avoidance of broad-spectrum antimicrobials unless guided by results from appropriately collected cultures or in patients with -

bacteremia, sepsis, cellulitis, or osteomyelitis.

Drug and Nondrug Management

8 Prevention is the single most important aspect in the management of pressure sores. Skin surveillance and frequent repositioning (ie, pressure reduction) are key in preventing pressure sores.[31,63,64] Prevention is far easier and less costly than the intensive care necessary for the healing and eventual closure of pressure sores. Of primary importance, then, is the ability to identify patients who are at high risk so that preventive measures may be instituted. Relief of pressure through proper positioning, and periodic repositioning, is probably the single most important factor in preventing pressure sore formation. Relief for a period of only 5 minutes once every 2 hours gives protection against pressure sore formation.[31,63,64,68] Repositioning seated patients every 15 to 60 minutes is also recommended.[31,63,64] Pressure relief devices such as mattresses or overlays filled with air, water, gel, or foam are helpful in preventing pressure sores.[31,70] Cushions and ankle or heel protectors should also be encouraged.[31,64] Skin care and prevention of soilage are also important, with the intent being to keep the surface relatively free of moisture. Patients with problems of incontinence should be cleaned frequently, and efforts should be made to keep the involved areas dry.[31,63,64]

CLINICAL PRESENTATION Pressure Sores

General

- Most pressure sores are in the pelvic region and lower extremities; see Fig. 128-5.
- Most common sites: sacral and coccygeal areas, ischial tuberosities, and greater trochanter.

Symptoms

- Patients commonly have other medical problems that may mask signs and symptoms of infection.
- Pain may be present with or without infection; continuous pain may indicate infection.

Signs

- A dark red color on the surface of a pressure sore may indicate local infection.
- Surrounding erythema, swelling, and heat are commonly present with infection.
- Purulent discharge, foul odor, and systemic signs (eg, fever and leukocytosis) of infection may be present.

Laboratory Tests

- Cultures should be collected from either a biopsy or fluid obtained by needle aspiration.

Other Diagnostic Tests

- Complete blood cell count often performed for assessment of potential infection.
- Consider magnetic resonance imaging if suspicious of underlying osteomyelitis.

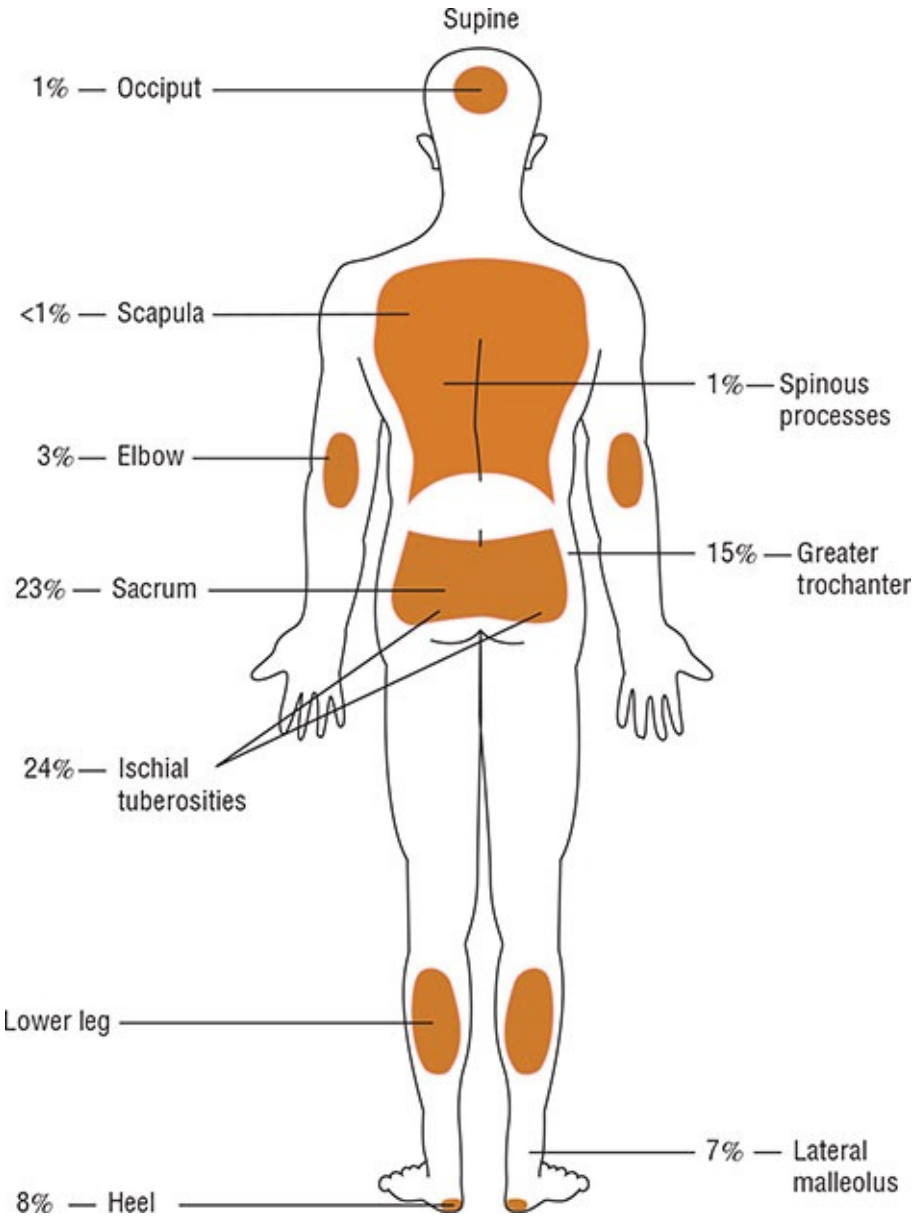


FIGURE 128-5 Supine view of areas where pressure sore formation tends to occur.

The medical approach to the treatment of pressure sores depends on the stage of the disease. Medical management generally is indicated for lesions that are of moderate size and relatively shallow depth (stage 1 or 2 lesions) and are not located over a bony prominence. Depending on their location and severity, from 30% to 80% of these ulcers will heal without an operation. Surgical intervention is almost always necessary for ulcers that extend through superficial layers or into bone (stage 3, stage 4, and unstageable lesions).[25,66]

The goal of therapy is to clean and decontaminate the ulcer in order to permit

formation of healthy granulation tissue that promotes wound healing or prepares the wound for an operative procedure. The main factors to be considered for successful topical therapy (local care) are (a) relief of pressure, (b) debridement of necrotic tissue as needed, (c) wound cleansing, (d) dressing selection, and (e) prevention, diagnosis, and treatment of infection.[31,63,64,68]

Relief of pressure is important once a pressure sore has developed. The same repositioning methods and pressure-reducing devices used for preventive care also apply to treatment.[31,63,64,68]

The goals of debridement and cleansing measures are removal of devitalized tissue and reduction of bacterial contamination, which can slow granulation time and impede healing.[31,63,64,68] Debridement can be accomplished by surgical, mechanical, or chemical means.[25,63,64,67,68] Surgical debridement rapidly removes necrotic material from the wound and is recommended for urgent situations (eg, cellulitis and sepsis).[31,63,64,68] Mechanical debridement generally involves wet-to-dry dressing changes. Saline-soaked gauze is applied to the wound; after drying, the gauze is removed and with it any adherent necrotic tissue. Other effective mechanical therapies include hydrotherapy (use of the whirlpool [Hubbard tank] to remove necrotic tissue and debris), wound irrigation, and dextranomers (beads placed in the wound to absorb exudate and bacteria).[25,63,64] Chemical debridement includes enzymatic and autolytic agents. Enzymatic debridement involves application of topical debriding agents to remove devitalized tissue. This method is recommended for patients who cannot tolerate surgery or are in a long-term care or home setting.[31,63,64,68] Autolytic debridement involves the use of synthetic dressings that allow devitalized tissue to self-digest via enzymes present in wound fluids. Autolytic debridement is contraindicated in the treatment of infected pressure sores.[31,63,64,68]

Pressure sore wounds should be cleaned with normal saline.[25,31,64,68] No cleansing solution or technique has demonstrated greater efficacy on healing.[70,71] Cleansing agents that are cytotoxic, such as povidone-iodine, iodophor, sodium hypochlorite solution, hydrogen peroxide, and acetic acid, should be avoided.[31,63,64,68] Many of these agents destroy granulation tissue and impair healing. Many different types of dressings are available for pressure sores.[25] Wound dressing materials should keep the wound moist, allow free exchange of air, act as a physical barrier to bacteria, and prevent physical damage.[25,31,64] Controlled studies of the various types of wound dressings have shown no significant differences in healing outcomes.[63,71] Occlusive dressings (hydrocolloid, such as DuoDERM™ or Tegaderm™) and transparent dressings

(eg, 3M Tegaderm™) are not recommended for infected wounds.[25,31,64] If occlusive dressings are used, any infection should be controlled or the dressing frequency increased.

Topical antibiotics (silver sulfadiazine, triple antibiotic) or medical grade honey may be considered for a clean ulcer that is not healing or is producing a moderate amount of exudate despite appropriate care.[31,63,64,67] When used, topical antibiotics should be limited to a 2-week trial or until additional definitive debridement can be performed, whichever comes first.[31,63,64,67] Systemic treatment of pressure ulcers is generally reserved for infections associated with bacteremia, sepsis, cellulitis, fasciitis, or osteomyelitis.[31,63,64,68] Empiric therapy for infected pressure sores or associated infectious complications should cover MRSA, anaerobes, enterococci, and more resistant gram-negative bacteria such as *Pseudomonas* (see Table 128-5).[63,64] Thereafter, antibiotics should be guided by results from appropriately collected cultures.

Other nonpharmacologic approaches to shorten the healing time have included the use of hyperbaric oxygenation, hydrotherapy, high-frequency/high-intensity sound waves, and electrotherapy.[31,67,68,70] Electrical stimulation is the only adjunctive therapy that is proven effective.[31,67,68] Various comorbid conditions (diabetes mellitus, smoking, peripheral vascular disease, malnutrition) may impair wound healing. Eliminating or optimizing these factors is recommended, although studies have not demonstrated benefit.[25,64]

Evaluation of Therapeutic Outcomes

With appropriate wound care and antimicrobial therapy, infected pressure sores can heal. A reduction in erythema, warmth, pain, and other signs and symptoms should be seen in 48 to 72 hours.

ANIMAL AND HUMAN BITE WOUNDS

Approximately half the population in the United States will be bitten by either an animal or another human sometime during their lifetimes.[72-74] Animal bites (typically from dogs or cats) are common causes of injury, particularly to children, and are associated with significant risk of infection without prompt attention and appropriate management. Likewise, human bite wounds are often deceptively severe and frequently require aggressive management to reduce the risk of infectious complications. If left untreated, severe soft-tissue infection and

osteomyelitis may occur, possibly requiring extensive debridement or amputation.

Epidemiology

Dog bites account for approximately 75% to 90% of all animal bite wounds requiring medical attention.[73] The Centers for Disease Control and Prevention reports that approximately 350,000 individuals seek emergency room attention for dog bites annually; rates of dog bite-related injuries are highest in children aged 5 to
9 years.[74] Most dog bites are to the extremities,[73] but the majority of bites to children less than 5 years of age are to the face and neck.[74] Cat bites are the second most common cause of bite wounds in the United States, accounting for up to 20% of all animal bites.[72] Cat bites occur most commonly on the upper extremities and face, with most injuries reported in women and the elderly.[72,75] Human bites are the third most frequent type of bites requiring medical attention.

Infection rates after dog and cat bites are estimated at 20% overall. However, infection may occur in up to 30% to 80% of serious cat bites, a rate more than double those seen with dog bites.[72,75] Also, bite wounds to the hands become infected in 30% to 40% of cases.[72] Patients at greatest risk of acquiring animal bite-related infection have had a puncture wound (usually to the hand), have not sought medical attention within 8 hours of the injury, and are older than 50 years of age.[72,73,75]

Infected human bites can occur as bites from the teeth or from blows to the mouth (clenched-fist injuries). Bites by others can occur to any part of the body, but most often involve the hands. Infectious complications occur in 10% to 50% of patients with human bites.[75]

Etiology

Infections in bite wounds are caused predominantly by mouth flora from the animal or human biter, and from the victim's own skin flora (Table 128-11).[72,73,75-79] Most infections are polymicrobial, with a median of three to nine bacterial isolates per culture.[75-79] *Pasteurella* is the most frequent isolate from both dog and cat bites. *Pasteurella multocida* is part of the normal oral flora of up to 90% of cats; dog bites more commonly involve *P. canis* (approximately 26% of infections).[72,73,75,77] Tularemia (*Pasteurella tularensis*) and cat scratch disease (*Bartonella henselae*) have also been transmitted by cat bites, while

rabies is associated with dog bites, particularly in developing countries.[72,73,77,78,80] Human bite wounds are notable for potential involvement of *Eikenella corrodens* in approximately 30% of infections.

TABLE 128-11 Bacterial Isolates from Infections in Animal and Human Bite Wounds[75-78]

Organisms	Percentage of Isolates	
	Dog and Cat	Human
Aerobes	74-90	44
Pasteurella spp.	50-75	—
Streptococcus spp.	46-50	52-84
S. anginosus	—	52
S. mitis	22	12
S. pyogenes	12	14
S. mutans	12	2
Staphylococcus spp.	35-46	54
S. aureus	20	30
S. epidermidis	18	22
Neisseria spp.	32-35	4
Moraxella spp.	10-35	2
Corynebacterium spp.	12-28	12
Enterococcus spp.	10-12	6
Bacillus spp.	8-11	—
Eikenella corrodens	2	30
Enterobacteriaceae	6-12	8-15
Anaerobes	50-70	40-90
Fusobacterium spp.	32-33	32-34
Porphyromonas spp.	28-30	2
Bacteroides spp.	18-28	4
Prevotella spp.	19-28	22-36
Propionibacterium spp.	18-20	4
Peptostreptococcus spp.	8-16	22
Veillonella spp.	2	24
Mixed aerobic and anaerobic	50-75	40-66

Pathophysiology

The potential for infection from an animal bite is great owing to the pressure that can be exerted during the bite and the vast number of potential pathogens that make up the normal oral flora.[72,73,75-78] Cats' teeth are slender and extremely sharp. Their teeth easily penetrate into bones and joints, resulting in a higher incidence of septic arthritis and osteomyelitis.[75-78] Although a dog's teeth may not be as sharp, they can exert a pressure of 200 to 450 lb/in.^{2} (~1,400-3,100 kPa) and therefore result in a serious crush injury with much devitalized tissue.[72,73,75-78] In addition, the polymicrobic (aerobic and anaerobic) nature of animal bites provides a synergistic relationship, thus making an infection harder to eradicate.[76]

Human bites generally are more serious and more prone to infection than animal bites, particularly clenched-fist injuries.[76] While the force of a punch may break a bone or sever a tendon or nerve, it most often causes a breach in the capsule of the metacarpophalangeal joint, leading to direct inoculation of bacteria into the joint or bone.[76,78] When the hand is relaxed, the tendons carry bacteria into deeper spaces of the hand, resulting in more extensive infection.[76,78]

CLINICAL PRESENTATION Bite Wounds

General

Animal bites:

- Only general wound care is required for most patients with dog bites who present early (<12 hours) after injury; infection is more likely in patients presenting late (≥12 hours) after injury.

Human bites:

- Most patients with clenched-fist injuries present for medical care after infection is already established.

Symptoms

- Patients often seek medical care for infection-related complaints (ie, pain, purulent discharge, and swelling) at the site of the injury.
- Wounds often have a purulent discharge, and decreased range of motion may be present.

Signs

- Erythema, swelling, and clear or purulent discharge at site of infected wound.

Animal bites:

- If *P. multocida* is present, a rapidly progressing cellulitis is observed within 24 to 48 hours of initial injury.
- Fever is often absent.
- Adenopathy or lymphangitis is uncommon.

Human bites:

- Lymphadenopathy is common.
- In clenched-fist injuries, edema may limit the ability of tendons to glide in their sheaths, thereby limiting a joint's range of motion.

Laboratory Tests

- Samples for bacterial cultures (aerobic and anaerobic) should be obtained from infected wounds.
- Wounds seen <8 hours or more than 24 hours after injury that show no signs of infection may not need to be cultured.
- White blood cell counts should be monitored for resolution of infection if initially elevated.

Other Diagnostic Tests

- Radiographic evaluation should be performed if damage to a bone or joint is suspected.

TREATMENT

Desired Outcomes

The goals of therapy of bite wounds, whether caused by animals or humans, are twofold: to provide effective prophylaxis against infection, when appropriate, and to achieve rapid eradication of established infection and prevent further complications. Effective treatment of bite wounds includes avoidance of unnecessary antimicrobials that contribute to increased resistance, and

minimizing toxicities and cost of therapy.

Management of Bite Wounds

9 Bite wounds should be irrigated thoroughly with a copious volume of sterile water or saline, and the wound washed vigorously with soap or povidone-iodine in order to reduce the bacterial count in the wound.[72,73,75,78] Surgical debridement and immobilization of the affected area is often required in dog and human bites associated with more extensive tissue injury. Clinical failures due to edema have occurred despite appropriate antibiotic therapy.[72] Therefore, it is important to stress to patients that the affected area should be elevated for several days or until edema has resolved. In the case of animal bites, an immunization history of the animal should be obtained. It is also important for the patient's tetanus immune status to be determined. Because transmission of viruses (HIV, herpes, hepatitis B and C) is a possibility with human bites, information about the biter is important. Although the possibility of acquiring HIV through saliva alone is believed to be unlikely, the presence of virus-containing blood in the saliva makes disease transmission possible.[81] Bite victims exposed to blood-tainted saliva may be offered antiretroviral chemoprophylaxis, but each case should be individually assessed based on the potential for significant exposure and potential risks and benefits of antiretroviral therapy.[81]

Patients with clenched-fist injuries should be seen by a specialist in hand care to evaluate for penetration into the synovium, joint capsule, and bone.[16,76] Primary closure for human bites generally is not recommended. Tetanus toxoid and antitoxin may be indicated.

10 All patients with human bite injuries should receive prophylactic antibiotic therapy ("early preemptive therapy") for 3 to 5 days due to high infection risk (Table 128-4).[78,79] Prophylactic antimicrobial agents should be given as soon as possible to all patients, regardless of the appearance of the wound, unless it can be documented that the wound does not involve hands, feet, or joints and penetrates no deeper than the epidermis.[16,67,78]

The role of prophylactic antimicrobial therapy for early, noninfected animal bite wounds remains controversial.[16,72,73,75,76,78] Recommendations from the IDSA suggest that prophylactic or early preemptive therapy seems to provide only marginal benefit for most patients in the absence of specific factors that increase the risk of infection.[16] The decision to administer prophylactic

antibiotics is therefore based on an assessment of wound severity and host immune competence. Specifically, prophylaxis is more strongly recommended in patients with the following factors associated with increased risk for infection: immunocompromised; asplenic; advanced liver disease; preexisting or resultant edema of the affected area; moderate-to-severe bite-related injuries, especially to the hands or face; deep puncture wounds that cannot be adequately irrigated; or bite injuries that have penetrated the periosteum or joint capsule.[16,73] A 3- to 5-day course of prophylactic antibiotics is recommended when such therapy is considered to be appropriate.[16,73,75,76,78]

Empiric antibiotics for the treatment of established infection of bite wounds should be directed at a variety of aerobic and anaerobic flora (Table 128-4). Amoxicillin-clavulanic acid is most commonly recommended for oral outpatient therapy due to excellent activity against all likely pathogens, including *Pasteurella* and *Eikenella*.[16,72,73,75,76,78] Alternative oral agents include moxifloxacin or doxycycline alone; or trimethoprim-sulfamethoxazole, levofloxacin, ciprofloxacin, or a second- or third-generation cephalosporin in combination with metronidazole or clindamycin to provide activity against oropharyngeal anaerobes.[16,72,73,75,76,78] Although the combination of penicillin VK plus dicloxacillin has been recommended traditionally for the treatment of bite wounds, its use has become less common in favor of other alternatives. Failure to provide adequate initial treatment of bite wounds results in treatment failures and increased need for hospitalization for parenteral antibiotics.[16,72,73,75,76-78]

Hospitalization for minor wounds is unnecessary if surgical repair of vital structures is not needed. Patients with clenched-fist or other serious bite injuries and severe resultant infection may be considered for IV antibiotics. Treatment options for patients requiring IV therapy include β-lactam-β-lactamase inhibitor combinations (ampicillin-sulbactam, piperacillin-tazobactam), second-generation cephalosporins with antianaerobic activity (eg, cefoxitin), and ertapenem.[16,78] The combination of doxycycline or a fluoroquinolone with metronidazole or clindamycin may be used in patients with severe β-lactam allergies. The length of antimicrobial therapy depends on the severity of the injury/infection. However, therapy should generally be continued for 7 to 14 days.[16,72,82-84]

Tetanus does not occur commonly after dog bites; however, it is possible. If the immunization history of a patient with anything other than a clean, minor wound is unknown, or if the last known vaccination was longer than 10 years ago, tetanus-diphtheria (TD) toxoids should be administered.[82] Both TD toxoids

and tetanus immune globulin should be administered to patients who have never been immunized.[78,83]

Because the rabies virus can be transmitted via saliva, rabies may be a potential complication of a bite. When the symptoms of rabies develop after a bite, the prognosis for survival is poor. Roughly 3% of rabies cases documented in animals were in dogs (the most frequent vectors are skunks, raccoons, and bats).[80,84] In the United States, recommendations for postexposure prophylaxis after a dog bite depend on the health of the dog. If the animal is healthy and able to be observed for a 10-day period, active prophylaxis is only required if the dog develops signs of rabies.[75,80] If the dog is known or suspected to be rabid, postexposure procedures should be initiated; current treatment guidelines should be consulted for appropriate management recommendations.[80,84] Outside of the United States, locally applicable guidelines such as those from the World Health Organization should be consulted.[85]

Evaluation of Therapeutic Outcomes

Evaluation of treatment for either animal or human bites should follow the same general guidelines. Bite victims treated on an outpatient basis with oral antimicrobials should be followed up within 24 hours by either phone or office visit.[16] Hospitalization or change to IV therapy should be considered if the infection has progressed. For hospitalized patients with no improvement in signs and symptoms following 24 hours of appropriate therapy, surgical debridement may be needed. Physical therapy may be needed to improve complications such as residual joint stiffness and loss of function, particularly after human bites involving clenched-fist injuries.

Postclass Engaged Learning Activity

In this chapter, several newer antibiotics are mentioned for which few clinical data in skin and soft-tissue infection (SSTI) exist or for which their appropriate role in the treatment of SSTI has not yet been well-defined. Select one of these previously mentioned medications, or some other antibiotic that has recently been approved for clinical use. Conduct a literature search on the selected antibiotic in order to identify mechanisms of action, pharmacokinetic properties, spectrum of antimicrobial activity, adverse effects, and currently available clinical data. Based on this search, write a brief summary describing in which type(s) of SSTI (impetigo, cellulitis, necrotizing fasciitis, diabetic

foot infection, etc.) this antibiotic would potentially have a role in therapy, and discuss one potential advantage or disadvantage of this new medication compared to the currently recommended agents for that type of SSTI. This activity is intended to increase your ability to critically evaluate new antibiotics, and ability to assess the potential impact of newer medications on disease states for which the role of those agents has not yet been well described.

ABBREVIATIONS

ABSSSI	acute bacterial skin and skin structure infection
AMS	Altered mental status
CA-MRSA	community-associated methicillin-resistant *S. aureus*
DFI	diabetic foot infection
HA-MRSA	healthcare-associated methicillin-resistant *Staphylococcus aureus*
HIV	human immunodeficiency virus
IDSA	Infectious Diseases Society of America
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *Staphylococcus aureus*
NPUAP	National Pressure Ulcer Advisory Panel
PVL	Panton-Valentine leukocidin
SCC*mec*	staphylococcal chromosomal cassette *mec*
SSTI	skin and soft-tissue infection
TD	tetanus-diphtheria

REFERENCES

1. Egert M, Simmering R. The microbiota of the human skin. *Adv Experiment Med Biol*. 2016;902:61-81.
2. Esposito S, Noviello S, Leone S. Epidemiology and microbiology of skin and soft tissue infections. *Curr Opin Infect Dis*. 2016;29:109-115.
3. Raff AB, Kroshinsky D. Cellulitis: A review. *JAMA*. 2016;316:325-337.
4. Esposito S, Bassetti M, Concia E, et al. Diagnosis and management of skin

and soft tissue infections (SSTI). A literature review and consensus statement: An update. *J Chemother*. 2017;29:197-214.

5. Cranendonk DR, Lavrijsen APM, Prins JM, Wiersinga WJ. Cellulitis: Current insights into pathophysiology and clinical management. *Netherlands J Med*. 2017;75:366-378.
6. Cardona AF, Wilson SE. Skin and soft tissue infections: A critical review and the role of telavancin in their treatment. *Clin Infect Dis*. 2015;61(Suppl2):S69-S78.
7. U.S. Food and Drug Administration, Department of Health and Human Services. Guidance for industry. Acute bacterial skin and skin structure infections: Developing drugs for treatment. Available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInf
8. Pasternak MS, Swartz MN. Cellulitis, necrotizing fasciitis, and subcutaneous tissue infections. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. Philadelphia, PA: Elsevier; 2015;1194-1215.
9. Miller LG, Eisenberg DF, Liu H, et al. Incidence of skin and soft tissue infections in ambulatory and inpatient settings, 2005-2010. *BMC Infect Dis*. 2015;15:362.
10. Suaya JA, Mera RM, Cassidy A, et al. Incidence and cost of hospitalizations associated with *Staphylococcus aureus* skin and soft infections in the United States from 2001 through 2009. *BMC Infect Dis*. 2014;14:296-303.
11. Poulakou G, Giannitsioti E, Tsiodras S. What is new in the management of skin and soft tissue infections in 2016? *Curr Opin Infect Dis*. 2017;30:158-171.
12. Pollack CV Jr, Amin A, Ford WT Jr, et al. Acute bacterial skin and skin structure infections (ABSSSI): Practice guidelines for management and care transitions in the emergency department and hospital. *J Emerg Med*. 2015;48:508-519.
13. Guillamet CV, Kollef MH. How to stratify patients at risk for resistant bugs in skin and soft tissue infections? *Curr Opin Infect Dis*. 2016;29:116-123.
14. Moran GJ, Abrahamian FM, LoVecchio F, Talan DA. Acute bacterial skin infections: developments since the 2005 Infectious Diseases Society of America (IDSA) guidelines. *J Emerg Med*. 2013;44:e397-e412.
15. Planet PJ. Life after USA300: The rise and fall of a superbug. *J Infect Dis*.

2017;215(S1):S71-S77.

16. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59:e10-e52.
17. Gupta AK, Lyons DCA, Rosen T. New and emerging concepts in managing and preventing community-associated methicillin-resistant *Staphylococcus aureus* infections. *Int J Dermatol*. 2015;54:1226-1232.
18. Bassetti M, Carnelutti A, Righi E. The role of methicillin-resistant *Staphylococcus aureus* in skin and soft tissue infections. *Curr Opin Infect Dis*. 2017;30:150-157.
19. Kale P, Dhawan B. The changing face of community-acquired methicillin-resistant *Staphylococcus aureus. Indian J Med Microbiol*. 2016;34:275-285.
20. Abetz JW, Adams NG, Mitra B. Skin and soft tissue infection management failure in the emergency department observation unit: A systematic review. *Emerg Med J*. 2018;35:56-61.
21. Centers for Disease Control and Prevention. Active Bacterial Core Surveillance Report, Emerging Infections Program Network, Methicillin-Resistant *Staphylococcus aureus*, 2015. Available at: https://www.cdc.gov/hai/eip/pdf/2015-MRSA-Report-P.pdf.
22. Gunderson CG. Overtreatment of nonpurulent cellulitis. *J Hosp Med*. 2016;11:587-590.
23. Moffarah AS, al Mohajer A, Hurwitz BL, Armstrong DG. Skin and soft tissue infections. *Microbiol Spectrum*. 2016;4:1-16.
24. Yamamoto LG. Treatment of skin and soft tissue infections. *Pediatr Emerg Care*. 2017;33:49-55.
25. Ricci JA, Bayer LR, Orgill DP. Evidence-based medicine: The evaluation and treatment of pressure injuries. *Plast Reconstr Surg*. 2017;139:275e-286e.
26. Napierkowski D. Uncovering common bacterial skin infections. *Nurs Pract*. 2013;38:30-37.
27. Quirke M, Ayoub F, McCabe A, et al. Risk factors for nonpurulent leg cellulitis: A systematic review and meta-analysis. *Br J Dermatol*. 2017;177:382-394.
28. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases

Society of America clinical practice guidelines for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis*. 2012;54:132-173.

29. Liu C, Bayer A, Cosgrive SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis*. 2011;52:1-38.
30. Rybak MJ, Lomaestro BM, Rotschafer JC, et al. Vancomycin therapeutic guidelines: A summary of consensus recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2009;66:82-98.
31. National Pressure Ulcer Advisory Panel, European Pressure Ulcer Advisory Panel and Pan Pacific Pressure Injury Alliance. Prevention and Treatment of Pressure Ulcers: Clinical Practice Guideline. Quick Reference Guide. Emily Haesler (Ed.). Cambridge Media: Osborne Park, Western Australia; 2014. Available at: http://www.npuap.org/wp-content/uploads/2014/08/Quick-Reference-Guide-DIGITAL-NPUAP-EPUAP-PPPIA-Jan2016.pdf.
32. Ibrahim F, Khan T, Pujalte GGA. Bacterial skin infections. *Prim Care Clin Office Pract*. 2015;42:485-499.
33. Blackberg A, Trell K, Rasmussen M. Erysipelas, a large retrospective study of aetiology and clinical presentation. *BMC Infect Dis*. 2015;15:402-407.
34. Kosar L, Laubscher T. Management of impetigo and cellulitis. *Canadian Fam Phys*. 2017;615-618.
35. Rush J, Dinulos JG. Childhood skin and soft tissue infections: New discoveries and guidelines regarding the management of bacterial soft tissue infections, molluscum contagiosum, and warts. *Curr Opin Pediatr*. 2016;28:250-257.
36. Koning S, Van der Sande R, Verhagen AP, et al. Interventions for impetigo. *Cochrane Database Syst Rev*. 2012;1:CD003261.
37. Pasternak MS, Swartz MN. Lymphadenitis and lymphangitis. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. Philadelphia, PA: Elsevier; 2015;1226-1237.
38. Seelang K, Manning ML, Saks M, Winstead Y. Skin and soft tissue infection management, outcomes, and follow-up in the emergency

department of an urban academic hospital. *Adv Emerg Nurs J*. 2014;36:348-359.

39. VanEperen A, Segreti J. Empirical therapy in methicillin-resistant *Staphylococcus aureus* infections: An up-to-date approach. *J Infect Chemother*. 2016;22:351-359.
40. Nathwani D, Morgan M, Masterton RG, et al. Guidelines for UK practice for the diagnosis and management of methicillin-resistant *Staphylococcus aureus* (MRSA) infections presenting in the community. *J Antimicrob Chemother*. 2008;61:976-994.
41. Bal AM, David MZ, Garau J, et al. Future trends in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infection: An in-depth review of newer antibiotics active against an enduring pathogen. *J Global Antimicrob Resist*. 2017;10:295-303.
42. McClain SL, Bohan JG, Stevens DL. Advances in the medical management of skin and soft tissue infections. *BMJ*. 2016;355:i6004.
43. Tong SYC, Davis JS, Eichenberger E, Holland TL, Fowler VGJr. *Staphylococcus aureus* infections: Epidemiology, pathophysiology, clinical manifestations, and management. *Clin Microbiol Rev*. 2015;28:603-661.
44. Kaafarani HMA, King DR. Necrotizing skin and soft tissue infections. *Surg Clin N Am*. 2014;94:155-163.
45. Stevens DL, Bryant AE. Necrotizing soft-tissue infections. *New Engl J Med*. 2017;377:2253-2265.
46. Bonne SL, Kadri SS. Evaluation and management of necrotizing soft tissue infections. *Infect Dis Clin N Am*. 2017;31:497-511.
47. Cocanour CS, Chang P, Huston JM, et al. Management and novel adjuncts of necrotizing soft tossie infections. *Surg Infect*. 2017;18:250-272.
48. Sun X, Xie T. Management of necrotizing fasciitis and its surgical aspects. *Int J Lower Extrem Wounds*. 2015;14:328-333.
49. Grigoropoulou P, Eleftheriadon I, Jude EB, Tentolouris N. Diabetic foot infections: An update in diagnosis and management. *Curr Diab Rep*. 2017;17:3.
50. Abbas M, Uckay I, Lipsky BA. In diabetic foot infections antibiotics are to treat infection, not to heal wounds. *Exp Opin Pharmacother*. 2015;16:821-832.
51. Uckay I, Aragon-Sanchez J, Lew D, Lipsky BA. Diabetic foot infections:

What have we learned in the last 30 years? *Int J Infect Dis*. 2015;40:81-91.

52. Markakis K, Bowling FL, Boulton AJM. The diabetic foot in 2015: An overview. *Diabetes Metab Res Rev*. 2016;32(Suppl 1):169-178.
53. Thurber EG, Kisuula F, Humbyrd C, Townsend J. Inpatient management of diabetic foot infections: A review of the guidelines for hospitalists. *J Hosp Med*. 2017;12:984-1000.
54. Lipsky BA. Diabetic foot infections: Current treatment and delaying the "post-antibiotic era". *Diabetes Metab Res Rev*. 2016;32(Suppl 1): 246-253.
55. Peters EJG, Lipsky BA. Diagnosis and management of infection in the diabetic foot. *Med Clin N Am*. 2013;97:911-946.
56. Kwon KT, Armstrong DG. Microbiology and antimicrobial therapy for diabetic foot infections. *Infect Chemother*. 2018;50:11-20.
57. Malone M, Bowling FL, Gannass A, Jude EB, Boulton AJM. Deep wound cultures correlate well with bone biopsy culture in diabetic foor osteomyelitis. *Diabetes Metab Res Rev*. 2013;29:546-550.
58. Noor S, Zubair M, Ahmad J. Understanding diabetic foot infection and its management. *Diabetes Metabol Syndr Clin Res Rev*. 2017;11:149-156.
59. Zenelaj B, Bouvet C, Lipsky BA, et al. Do diabetic foot infections with methicillin-resistant *Staphylococcus aureus* differ from those with other pathogens? *Int J Lower Extrem Wounds*. 2014;13:263-272.
60. Selva Olid A, Sola I, Barajas-Nava LA, Gianneo OD, Bonfill Cosp X, Lipsky BA. Systemic antibiotics for treating diabetic foot infections. *Cochrane Database Syst Rev*. 2015;9:CD009061.
61. Game FL, Jeffcoate WJ. Dressing and diabetic foot ulcers: A current review of the evidence. *Plast Reconstr Surg*. 2016;138:158S-164S.
62. Jull AB, Cullum N, Dumville JC, Westby MJ, Deshpande S, Walker N. Honey as a topical treatment for wounds. *Cochrane Database Syst Rev*. 2015;3:CD005083.
63. Atkinson RA, Cullum NA. Interventions for pressure ulcers: A summary of evidence for prevention and treatment. *Spinal Cord*. 2018;56:186-198.
64. Smith ME, Totten A, Hickam DH, et al. Pressure ulcer treatment strategies: A systematic comparative effectiveness review. *Ann Intern Med*. 2013;159:39-50.
65. National Pressure Ulcer Advisory Panel. NPUAP pressure injury stages. 2016. Available at http://www.npuap.org/resources/educational-and-

clinical-resources/npuap-pressure-injury-stages/.

66. Black J, Baharestani M, Cuddigan J, et al. National Pressure Ulcer Advisory Panel's updated pressure ulcer staging system. Dermatol Nurs. 2007;19:343-349.
67. Cushing CA, Phillips LG. Evidence-based medicine: Pressure sores. *Plast Recontruct Surg*. 2013;132:1720-1732.
68. Garwood CS, Steinberg JS. What's new in wound treatment: A critical appraisal. *Diabetes Metab Res Rev*. 2016;32(Suppl 1):268-274.
69. Dana AN, Bauman WA. Bacteriology of pressure ulcers in individuals with spinal cord injury: What we know and what we should know. *J Spinal Cord Med*. 2015;38:147-160.
70. Brolmann FE, Ubbink DT, Nelson EA, Munte K, van der Horst CM, Vermeulen H. Evidence-based decisions for local and systemic wound care. *Br J Surg*. 2012;99:1172-1183.
71. Westby MJ, Dumville JC, Soares MO, Stubbs N, Norman G. Dressings and topical agents for treating pressure ulcers. *Cochrane Database Syst Rev*. 2017;6:CD011947.
72. Goldstein EJC, Abrahamian FM. Diseases transmitted by cats. *Microbiol Spectrum*. 2015;3:IOL5-0013.
73. Jacob J, Lorber B. Diseases transmitted by man's best friend: The dog. *Microbiol Spectrum*. 2015;3(4):IOL5-002-2015.
74. Centers for Disease Control and Prevention. Leading causes of nonfatal injury reports, 2001-2016. Available at https://webappa.cdc.gov/sasweb/ncipc/nfilead.html.
75. Ellis R, Ellis C. Dog and cat bites. *Am Fam Physician*. 2014;90:239-243.
76. Aziz H, Rhee P, Pandit V, Tang A, Gries L, Joseph B. The current concepts in management of animal (dog, cat, snake, scorpion) and human bite wounds. *J Trauma Acute Care Surg*. 2015;78:641-648.
77. Raval P, Khan W, Haddad B, Mahapatra AN. Bite injuries to the hand: Review of the literature. *Open Orthopaed J*. 2014;8(Suppl 1:M11):204-208.
78. Goldstein EJC, Abrahamian FM. Bites. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. Philadelphia, PA: Elsevier; 2015;3510-3515.
79. Kennedy SA, Stoll LE, Lauder AS. Human and other mammalian bite injuries of the hand: Evaluation and management. *J Am Acad Ortho Surg*.

2015;23:47-57.

80. Rupprecht CE, Briggs D, Brown CM, et al. Use of a reduced (4-dose) vaccine schedule for postexposure prophylaxis to prevent human rabies: Recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep*. 2010;59(RR02):1-9.
81. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. Updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV—United States, 2016. Available at https://stacks.cdc.gov/view/cdc/38856.
82. Liang JL, Tiwari T, Moro P, et al. Prevention of pertussis, tetanus, and diphtheria with vaccines in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2018;67(No. RR-2):1-44.
83. Kroger AT, Pickering LK, Wharton M, Mawle A, Hinman AR, Orenstein WA. Immunization. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. Philadelphia, PA: Elsevier; 2015;3516-3553.
84. Willoughby RE Jr. Rabies: Rare human infection—common questions. *Infect Dis N Am*. 2015;29:637-650.
85. Rabies vaccines: WHO position paper—April 2018. World Health Organization Weekly epidemiological record 2018;93:201-220. Available at http://www.who.int/rabies/resources/who_wer9316/en/.

129

Infective Endocarditis

Daniel B. Chastain and Angie Veverka

KEY CONCEPTS

1. Infective endocarditis usually occurs in adult patients with specific risk factors (eg, injection drug use, heart failure, valvular disease, and healthcare exposure) and those with implanted cardiac material (eg, prosthetic heart valves).
2. Three groups of organisms cause most cases of infective endocarditis: staphylococci, streptococci, and enterococci.
3. The clinical presentation of infective endocarditis is highly variable and nonspecific, although a fever and murmur are usually present. Classic peripheral manifestations (eg, Osler's nodes) may or may not occur.
4. The diagnosis of infective endocarditis requires the integration of clinical, laboratory, and echocardiographic findings. The two major diagnostic criteria are bacteremia and echocardiographic changes (eg, valvular vegetation).
5. Treatment of infective endocarditis involves isolation of the infecting pathogen and determination of antimicrobial susceptibilities, followed by high-dose, parenteral, bactericidal antibiotics for an extended period.
6. Surgical replacement of the infected heart valve is an important adjunct to endocarditis treatment in certain situations (eg, patients with acute heart failure).
7. β-lactam antibiotics, such as penicillin G (or ceftriaxone), nafcillin, and ampicillin, remain the drugs of choice for streptococcal, staphylococcal, and enterococcal endocarditis, respectively.
8. Combination regimens, such as ampicillin plus an aminoglycoside antibiotic, are recommended to achieve a synergistic bactericidal effect in the treatment of enterococcal endocarditis. Adjunctive aminoglycosides

also may decrease the emergence of resistant organisms (eg, prosthetic valve endocarditis caused by coagulase-negative staphylococci) and hasten the pace of clinical and microbiologic response (eg, some streptococcal and staphylococcal infections).

9. Vancomycin is reserved for patients with immediate β-lactam allergies and the treatment of resistant organisms.
10. Antimicrobial prophylaxis is used to prevent infective endocarditis for patients who are at the highest risk before a bacteremia-causing procedure.

Preclass Engaged Learning Activity

Create a summary table of the primary treatment options, including recommended options for patients with immediate β-lactam allergies, for the most common organisms causing infective endocarditis (eg, *Staphylococcus* spp., *Streptococcus* spp., *Enterococcus* spp.). The table should include the risk factors for each organism, duration of treatment, as well as the dose, route, monitoring parameters, and potential adverse effects for each drug.

INTRODUCTION

Endocarditis is an inflammation of the endocardium, the membrane lining the chambers of the heart and covering the cusps of the heart valves.[1,2] More commonly, *endocarditis* refers to infection of the heart valves by various microorganisms. Although it typically affects native valves, it also may involve nonvalvular areas or implanted material (eg, prosthetic heart valves, cardiac defibrillators, pacemakers, and catheters). Bacteria primarily cause endocarditis, but fungi and a variety of other microorganisms can lead to the disease; hence, the more encompassing term *infective endocarditis* is preferred.[1,3]

Infective endocarditis is best classified based on the etiologic organism, anatomic site of infection, and pathogenic risk factors.[1,4,5] Endocarditis is often referred to as *acute* or *subacute* depending on the pace and severity of the clinical presentation. The acute, fulminating form is associated with high fevers and systemic toxicity. Virulent bacteria, such as *Staphylococcus aureus*, frequently cause this syndrome, and if untreated, death may occur within days to weeks. On the other hand, subacute infective endocarditis is more indolent,

caused by less virulent organisms, such as viridans group streptococci, and usually occurs in preexisting valvular heart disease. Infection may also occur following surgical insertion of a prosthetic heart valve, resulting in prosthetic valve endocarditis (PVE), or insertion of a cardiac implantable electronic device, resulting in cardiac device infective endocarditis (CDIE).[6,7]

EPIDEMIOLOGY AND ETIOLOGY

Although infective endocarditis is an uncommon infection, the prevalence in the United States has increased since 2000.[8,9] Population-based studies have reported annual incidence rates of 2 to 15 cases per 100,000 person-years.[8,10] The mean male-to-female ratio is approximately 2:1.[11] As the population ages and as valve replacement surgery becomes more common, the mean age of patients with infective endocarditis increases. Most cases occur in individuals older than 60 years of age, and it is less common in children.[11–13] Native valve infective (NVE) endocarditis occurs in 71% to 78% of cases, whereas PVE and CDIE account for 13% to 17% and 3% to 5% of cases, respectively.[5,9,14] Persons who inject drugs (PWID) are also at high risk and account for 5% to 13% of cases. Of note, the incidence of healthcare-associated infective endocarditis is rising, especially in the elderly population.[14] Other conditions associated with a higher incidence of infective endocarditis include diabetes mellitus, long-term hemodialysis, and poor dental hygiene.[5,11]

1 Most persons with infective endocarditis have risk factors, such as preexisting cardiac valvular abnormalities. Many types of structural heart disease result in turbulent blood flow that increases the risk for infective endocarditis. A predisposing risk factor, however, may be absent in up to 25% of cases. Some of the more important risk factors include:[4,5,7,11,14]

1. Presence of a prosthetic valve (highest risk)
2. Previous infective endocarditis (highest risk)
3. Healthcare-related exposure (high risk)
4. Congenital heart disease (CHD)
5. Advanced age
6. Chronic IV access
7. Diabetes mellitus
8. Acquired valvular dysfunction (eg, rheumatic heart disease)

9. Cardiac implantable device
10. Chronic heart failure
11. Mitral valve prolapse with regurgitation
12. PWID
13. HIV infection
14. Poor dentition and/or oral hygiene

Rheumatic heart disease was a prevalent risk factor for infective endocarditis, but the incidence of this disease continues to decline. The risk of infective endocarditis in persons with mitral valve prolapse and regurgitation is small; however, because the condition is prevalent, it is an important contributor to the overall number of infective endocarditis cases.[15] The risk of PVE is highest in the first 3 months after valve replacement and occurs in 1% to 3% of patients during the first postoperative year.[11,18]

2 Nearly every organism causing human disease may cause infective endocarditis, but three groups of organisms result in a majority of cases: staphylococci, streptococci, and enterococci (**Table 129-1**).[3–5,17] The incidence of staphylococci, particularly *S. aureus*, continues to increase primarily due to healthcare exposure, surpassing viridans group streptococci as the leading cause of infective endocarditis.[4,14,17] Staphylococci (*S. aureus* and coagulase-negative staphylococci) are the most common cause of PVE within the first year after valve surgery, and *S. aureus* is common in PWID. In general, streptococci cause infective endocarditis in patients with community-acquired disease and underlying cardiac abnormalities, such as mitral valve prolapse or rheumatic heart disease. Enterococcal endocarditis tends to follow genitourinary manipulations or obstetric procedures.[18] Although polymicrobial infective endocarditis is uncommon, it is encountered most often in PWID.[4] There are many exceptions to the preceding generalizations; thus, isolation of the causative pathogen and determination of its antimicrobial susceptibilities offer the best chance for successful therapy.

TABLE 129-1 Etiologic Organisms in Infective Endocarditis[a]

Agent	Percentage of Cases
Staphylococci	30-70
Coagulase positive 'S. aureus'	20-68
Coagulase negative	3-26
Streptococci	9-38
Viridans streptococci	10-28
Other streptococci	3-14
Enterococci	5-18
Gram negative aerobic bacilli	1.5-13
Fungi	1-9
Miscellaneous bacteria	<5
Polymicrobial infections	1-2
"Culture negative"	<5-17

[a]Values encompass community-acquired, healthcare-associated, native valve, and prosthetic valve infective endocarditis.

Data from References 3, 5, and 17.

The mitral and aortic valves are affected most commonly in cases involving a single valve. Subacute endocarditis tends to involve the mitral valve, whereas acute disease often involves the aortic valve. Up to 35% of cases involve concomitant infections of both the aortic and the mitral valves. Infection of the tricuspid valve is less common, with most of these cases occurring in PWID. It is rare for the pulmonary valve to be infected.[17,18]

Although outcomes for infective endocarditis have improved with rapid diagnosis, appropriate treatment (eg, antimicrobial therapy, surgery, or both), and prompt recognition of complications should they arise, in-hospital mortality remains approximately 20%, while 6-month mortality is 30%.[13] Factors associated with increased mortality include: (a) heart failure, (b) increasing age, (c) endocarditis caused by resistant organisms, such as gram negative bacteria, or fungi, (d) left-sided endocarditis caused by *S. aureus*, (e) paravalvular complications, (f) healthcare-acquired infection, and (g) PVE.[4,5,17] The presence of heart failure has the greatest negative impact on the short-term prognosis.[4] For left-sided native valve infective endocarditis, mortality rates range from 15% to 45%; lower rates (4%-16%) occur with community-acquired disease that is most commonly caused by viridans group streptococci. Higher rates (25%-45%) occur with healthcare-associated disease that is more commonly caused by enterococci and staphylococci. Even higher rates of mortality are seen with unusually

encountered organisms (eg, mortality >80% for fungi).[4,5] The mortality rate for right-sided infective endocarditis in PWID is generally low (eg, <10%).[4] For those who relapse after treatment for infective endocarditis, most will do so within the first 2 months after discontinuation of antimicrobials. Relapse rates for viridans group streptococcus are generally low (2%), whereas relapse is more likely in those with enterococcal infection (8%-20%) and PVE (10%-15%).[18] Despite appropriate treatment and recovery, the risk of morbidity and mortality following infective endocarditis persists for years, with a 5-year mortality rate of approximately 45%.[19] Morbidity remains elevated because of a greater likelihood of recurrent infective endocarditis, heart failure, and embolism or, if a valve is replaced, the risk of anticoagulation, valve thrombosis, or additional valve surgery.[20]

PATHOPHYSIOLOGY

The development of infective endocarditis via hematogenous spread, the most common route, requires the sequential occurrence of several factors. These components are complex and not fully elucidated.[21–23]

1. *The endothelial surface of the heart is damaged.* This injury occurs with turbulent blood flow associated with the valvular lesions previously described.
2. *Platelet and fibrin deposition occurs on the abnormal epithelial surface.* These platelet-fibrin deposits form a “sterile vegetation,” which is referred to as *nonbacterial thrombotic endocarditis*.
3. *Bacteremia gives organisms access to the endocardial surface.* Bacteremia is the result of trauma to a mucosal surface with a high concentration of resident bacteria such as the oral cavity and GI tract. Transient bacteremia commonly follows certain dental, GI, urologic, and gynecologic procedures. Staphylococci, viridans group streptococci, and enterococci are most likely to adhere to nonbacterial thrombotic endocarditis, probably because of production of specific adherence factors such as adhesins for staphylococci and dextran by some oral streptococci. Gram negative bacteria rarely adhere to heart valves and are uncommon causes of infective endocarditis.
4. *After colonization of the endothelial surface, a “vegetation” of fibrin, platelets, and bacteria forms.* As the vegetation matures, a protective

cover of fibrin and platelets protects bacteria from host immune response. This allows unimpeded bacterial growth to concentrations as high as 10^9 to 10^{11} organisms per gram of tissue, in addition to biofilm formation.

The pathogenesis of early PVE or CDIE differs from infective endocarditis acquired by the hematogenous route because surgery may directly inoculate prosthetic material with bacteria from the patient's skin or operating room personnel.[16,17] In the case of early PVE, a recently placed nonendothelialized valve is more susceptible to bacterial colonization than are native valves. Bacteria also may colonize the new valve from contaminated bypass pumps, cannulas, and pacemakers or from a nosocomial bacteremia subsequent to an intravascular catheter.[7,17,18] The mechanism of bacterial colonization and pathogenesis in late PVE is similar to NVE.[18]

One or more vegetations, varying in size from a few millimeters to centimeters, may be seen in a patient with infective endocarditis. Bacteria within the vegetation grow slowly and are protected from antibiotics and host defenses. The adverse effects of infective endocarditis and the resulting lesions can be far-reaching and include: (a) local perivalvular damage, (b) embolization of septic fragments with potential hematogenous seeding of remote sites, and (c) formation of antibody complexes.[18,22]

Formation of vegetations may destroy valvular tissue, and continued destruction can lead to acute heart failure in 50% to 60% of cases via perforation of the valve leaflet, rupture of the chordae tendineae or papillary muscle, or, for patients with PVE, valve dehiscence.[24,25] Occasionally, valvular stenosis may occur. Abscesses can develop in the valve ring or in myocardial tissue itself, potentially involving cardiac conduction tissue. Even with resolution of the process, fibrosis of tissue with some residual dysfunction is possible.

Vegetations may be friable, and fragments may be released downstream. These infected particles, termed *septic emboli*, can result in organ abscess or infarction. Septic emboli from right-sided endocarditis commonly lodge in the lungs, causing pulmonary abscesses. Emboli from left-sided vegetations commonly affect organs with high blood flow such as the kidneys, spleen, and brain.[4,18,22]

Circulating immune complexes consisting of antigen, antibody, and complement may deposit in organs, producing local inflammation, and damage (eg, glomerulonephritis in the kidneys). Other potential pathologic changes that result from immune-complex deposition or septic emboli include the development of "mycotic" aneurysms (although the aneurysm is usually

bacterial in origin, not fungal), cerebral infarction, splenic infarction and abscess, and skin manifestations such as petechiae, Osler's nodes, and Janeway lesions.[1,18,22]

CLINICAL PRESENTATION

Infective endocarditis

3 The clinical presentation of infective endocarditis is highly variable and nonspecific. Fever is the most common finding, in more than 90% of patients, and is often accompanied by other vague symptoms (Table 129-2).[24,25] Heart murmurs are found in most patients (approximately 85%), most often preexisting, with some documented as new or changing. Infective endocarditis usually begins insidiously and worsens gradually. Patients may present with nonspecific findings such as fever, chills, weakness, dyspnea, cough, night sweats, weight loss, or malaise. In contrast, patients with acute disease, such as PWID and those with *S. aureus* infective endocarditis, may appear with classic signs of sepsis.

TABLE 129-2 Clinical Presentation of Infective Endocarditis

General
The clinical presentation of infective endocarditis is highly variable and nonspecific

Symptoms
The patient may complain of fever, chills, weakness, dyspnea, cough, night sweats, weight loss, and/or malaise

Signs
Fever is common, as is a heart murmur (sometimes new or changing). The patient may have congestive heart failure, cardiac conduction abnormalities, cerebral manifestations, embolic phenomenon, splenomegaly, or skin manifestations (eg, Osler's nodes, Janeway lesions)

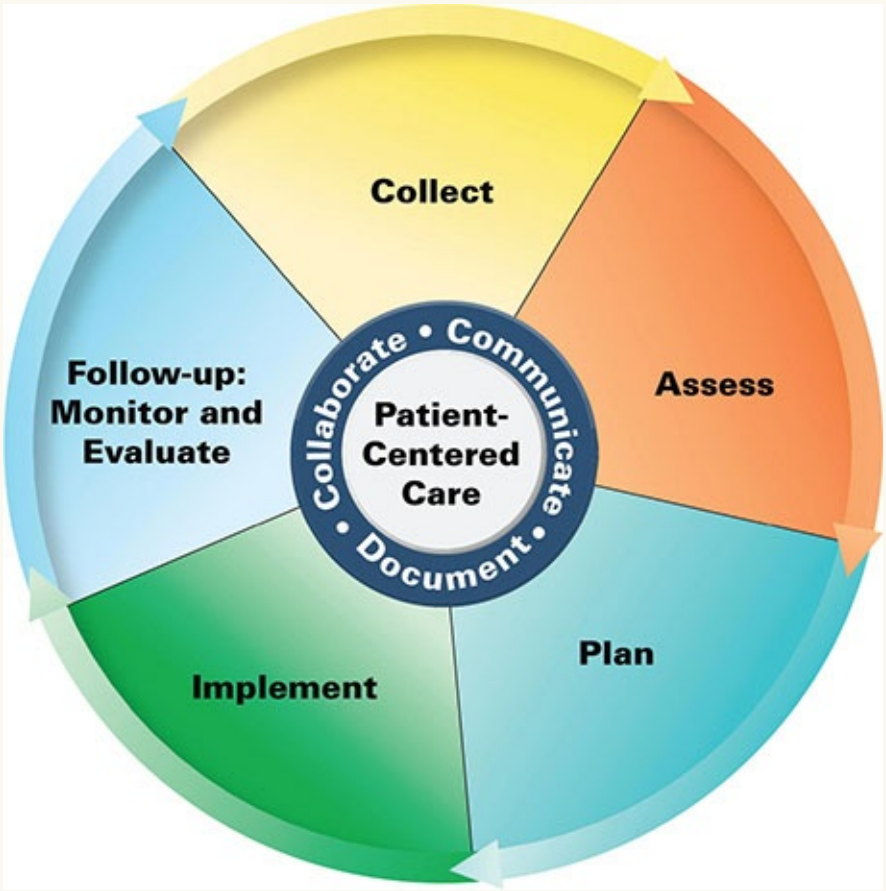
Laboratory tests
The patient's white blood cell count may be normal or only slightly elevated
Nonspecific findings include anemia (normochromic, normocytic), thrombocytopenia, an elevated erythrocyte sedimentation rate or C-reactive protein, and altered urinalysis (proteinuria/microscopic hematuria)
The hallmark laboratory finding is continuous bacteremia; three sets of blood cultures should be collected over 24 hours

Other diagnostic tests
An electrocardiogram, chest radiograph, and echocardiogram are commonly performed. Echocardiography to determine the presence of valvular vegetations plays a key role in the diagnosis of infective endocarditis; it should be performed in all suspected cases

Splenomegaly is an uncommon finding in acute infective endocarditis, due to improved diagnostics and antimicrobial therapy, but occurs more frequently in patients with subacute infective endocarditis. Other important clinical signs may include the following peripheral manifestations ("stigmata") of endocarditis[13,17,22]:

1. Osler's nodes: Purplish or erythematous subcutaneous papules or nodules on the pads of the fingers and toes occurring in less than 5% of cases. These lesions are 2 to 15 mm in size and are painful and tender. These nodes are not specific for infective endocarditis and may be the result of embolism, immunologic phenomena, or both.
2. Janeway lesions: Hemorrhagic, painless plaques on the palms of the hands or soles of the feet occurring in less than 5% of cases. These lesions are believed to be embolic in origin.

3. Splinter hemorrhages: Thin, linear hemorrhages found under the nail beds of the fingers or toes. These lesions are not specific for infective endocarditis and more commonly are the result of traumatic injuries. Distal lesions are more likely the result of trauma, whereas proximal lesions tend to be associated with infective endocarditis.
4. Petechiae: Small (usually 1-2 mm in diameter), erythematous, painless, hemorrhagic lesions. These lesions appear anywhere on the skin but more frequently on the anterior trunk, buccal mucosa and palate, and conjunctivae. Petechiae are nonblanching and resolve after a few days.
5. Clubbing of the fingers: Proliferative changes in the soft tissues about the terminal phalanges observed in long-standing endocarditis.
6. Roth's spots: Retinal infarct with central pallor and surrounding hemorrhage.
7. Emboli: Embolic phenomena occur in up to one-third of cases and may result in significant complications. Right-sided endocarditis may result in pulmonary emboli, causing pleuritic pain with hemoptysis. Left-sided endocarditis can result in renal artery emboli causing flank pain with hematuria, splenic artery emboli causing abdominal pain, and cerebral emboli, which may result in hemiplegia or alteration in mental status.



Patient Care Process for Infective Endocarditis

Collect

- Patient characteristics (eg, age, sex, height, weight, pregnancy status, allergies)
- Patient history (eg, past medical, surgical, family)
- Social history (eg, ethanol/IV drug abuse, recent travel, home residence, exposure to animals) and dietary habits, including intake of unpasteurized dairy products
- Current medication use, including prescription, nonprescription, and other substances, with emphasis on previous inpatient and outpatient antimicrobial use
- Objective data

- Temperature, blood pressure, respiratory rate, complete blood count (eg, white blood cell count, red blood cell count, hemoglobin, platelets), chemistry panel (eg, serum creatinine), urinalysis
- Results from blood and/or valve tissue cultures and specialized testing (eg, serology, polymerase chain reaction)
- Diagnostic testing (eg, electrocardiograph, chest radiograph, echocardiography)

Assess

- Identify risk factors (eg, immunocompromised status, recent dental procedure, central venous catheter, IV drug abuse, dietary habits)
- Assess signs and symptoms (eg, temperature >100.4 °F (38 °C), [see Table 129-2], radiographic evidence, pathogen identification, physical examination findings)
- Determine potential infectious etiologies based on patient history, current and previous antimicrobial use, risk factors, microbiologic data, and diagnostic testing
- Determine the need for surgical intervention (eg, heart failure, persistent bacteremia, persistent vegetation)
- Identify patients with underlying high-risk cardiac complications that would be candidates for antimicrobial prophylaxis

Plan*

- Determine the most appropriate empirical antimicrobial therapy, including dose, route, and frequency, based on patient characteristics, history, risk factors, and current and previous antimicrobial therapy
- Deescalate empirical therapy to an evidence-based regimen, including dose, route, frequency, and duration (see Tables 129-4 to 129-8), based on microbiologic and specialized testing results
- Develop monitoring parameters to assess efficacy and safety (eg, toxicities)
- Select evidence-based prophylaxis, including dose, route, and frequency (see Table 129-10)

Implement

- Provide patient education regarding all elements of treatment plan
- Initiate and deescalate antimicrobial therapy as appropriate
- Select an appropriate duration of therapy based on microbiologic and specialized testing results
- Develop an outpatient antimicrobial therapy (OPAT) plan at hospital discharge, including dose, route, frequency, and any necessary laboratory tests

Follow-up: Monitor and Evaluate

- Monitor for resolution of signs and symptoms of infective endocarditis
- Monitor results from blood and/or valve tissue cultures and specialized testing
- Monitor for the presence of antimicrobial related-adverse effects and toxicities
- Provide patient education regarding antimicrobial prophylaxis for infective endocarditis

**Collaborate with patient, caregivers, and other healthcare professionals.*

Patients with infective endocarditis typically have laboratory abnormalities; however, none of these changes is specific for the disease. Anemia (normochromic, normocytic), thrombocytopenia, and leukocytosis may be present. The white blood cell count is often normal or only slightly elevated, sometimes with a mild left shift. Acute bacterial endocarditis, however, may present with an elevated white blood cell count, consistent with a fulminant infection. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may be elevated in approximately 60% of patients. Often the urinalysis shows proteinuria and microscopic hematuria, which may occur in 50% to 65% and 30% to 60% of patients, respectively.[22]

DIAGNOSIS

4 The signs and symptoms of infective endocarditis are not specific, and the diagnosis is often unclear. The identification of infective endocarditis requires

the integration of clinical, laboratory, and echocardiographic findings. The modified Duke diagnostic criteria include major and minor variables (**Table 129-3**).[26,27] Based on the number of major and minor criteria that are fulfilled, patients suspected of infective endocarditis are categorized into three separate groups: definite infective endocarditis, possible infective endocarditis, or infective endocarditis rejected.[27]

TABLE 129-3 Diagnosis of Infective Endocarditis According to the Modified Duke Criteria

Definite IE

Pathological criteria
- Microorganisms demonstrated by culture or histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or pathological lesions; vegetation or intracardiac abscess confirmed by histological examination showing active endocarditis

Clinical criteria
- Two major criteria, or
- One major criteria and three Minor criteria, or
- Five Minor criteria

Possible IE

One major criterion and one minor criteria, or
Three minor criteria

Rejected IE

Firm alternative diagnosis explaining evidence of infective endocarditis, or
Resolution of infective endocarditis syndrome with antimicrobial therapy for four or fewer days, or
No pathological evidence of infective endocarditis at surgery or autopsy, with antimicrobial therapy for four or fewer days, or
Does not meet criteria for possible infective endocarditis, as above

Major Criteria

Blood culture positive for infective endocarditis

Typical microorganisms consistent with infective endocarditis from two separate blood cultures:
- Viridans streptococci, *S. gallolyticus*, HACEK group, *S. aureus*; or
- Community-acquired enterococci, in the absence of a primary focus; or

Microorganisms consistent with infective endocarditis from persistently positive blood cultures, defined as follows:
- At least two positive blood cultures drawn greater than 12 hours apart; or
- Three or a majority of four or more separate blood cultures (with first and last sample drawn at least 1 hour apart)

Single positive blood culture for *Coxiella burnetii* or antiphase I immunoglobulin G antibody titer >1:800

Evidence of endocardial involvement

Echocardiogram positive for infective endocarditis (transesophageal echocardiography recommended for patients with prosthetic valves, rated at least "possible infective endocarditis" by clinical criteria, or complicated infective endocarditis [paravalvular abscess]; transthoracic echocardiography as first test for other patients), defined as follows:
- Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets or on implanted material in the absence of an alternative anatomic explanation; or abscess; or
- New partial dehiscence of prosthetic valve
- New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)

Minor Criteria

Predisposition, predisposing heart condition, or injection drug use
Fever, temperature >38°C (100.4°F)
Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor
Microbiologic evidence: positive blood culture but does not meet a major criterion as noted above or serologic evidence of active infection with organism consistent with infective endocarditis
Echocardiographic minor criteria eliminated

HACEK, *Haemophilus* species (*H. parainfluenzae, H. aphrophilus, H. paraphrophilus*), *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*.

Data from References 26 and 27.

The hallmark of infective endocarditis is a continuous bacteremia caused by bacteria shedding from the vegetation into the bloodstream; 90% to 95% of patients with infective endocarditis have positive blood cultures.[1,4,18,28] In most cases, three sets of blood cultures, one aerobic and one anaerobic bottle per set, each from separate venipuncture sites, should be collected prior to starting antimicrobial therapy, with the first and last set drawn at least 1 hour apart. This allows expedient initiation of empirical antimicrobial therapy and can help guide early decisions regarding other potential interventions. Most cases of infective endocarditis are caused by easily cultivable pathogens that can be isolated from routine blood cultures within a 5-day incubation period. However, prolonged incubation of blood cultures or specialized testing may need to be performed (see "'culture-negative' endocarditis" below). In patients who undergo valve surgery, excised valve tissue should be submitted for microbiologic testing. Additionally, histopathologic evaluation should be performed to identify the presence of microorganisms and characteristics of inflammatory changes. Specialized testing may also be performed on valve tissue to improve the likelihood of identifying the infectious etiology.

"Culture-negative" endocarditis describes a patient in whom a clinical diagnosis of infective endocarditis is likely, but blood cultures do not yield a pathogen. This condition is often the consequence of previous antimicrobial therapy, improperly collected blood cultures, or unusual organisms.[4] When blood cultures from patients suspected of having infective endocarditis show no growth after 48 to 72 hours, cultures should be held for up to a month to detect growth of fastidious organisms.[4] Specialized testing, such as serology or polymerase chain reaction (PCR), may be required to identify less common pathogens (eg, *Coxiella burnetii*, *Bartonella* spp., *Brucella* spp.).

An electrocardiogram, chest radiograph, and echocardiogram are performed for patients suspected of endocarditis. The electrocardiogram rarely shows important diagnostic findings but may reveal heart block, suggesting extension of the infection. The chest radiograph may provide more diagnostic information, especially in a patient with right-sided endocarditis. Septic pulmonary emboli may occur, leading to multiple lung foci.

Echocardiography plays an important role in the diagnosis and management of infective endocarditis and should be performed for all patients suspected of this infection.[4,5] In addition to helping in the diagnosis of infective endocarditis, the echocardiogram allows the physician to evaluate hemodynamic stability and the need for urgent surgical intervention; it also provides a rough estimate of the

likelihood of embolism.[4,29] Typically, transthoracic echocardiography (TTE) is performed first due to the rapidity (eg, fasting state unnecessary) and accessibility (eg, 24-hour service available in most institutions) followed by transesophageal echocardiography (TEE). The TEE technique is more sensitive for detecting vegetations (90%-100%) as compared with TTE (40%-66%), and TEE maintains good specificity (90%-100%).[1,5,13] However, TTE may be the only evaluation needed for children or adults in whom the clinical suspicion of infective endocarditis is relatively low.[4,28] An initial or follow-up TEE is recommended in high-risk patients such as those with CHD, previous endocarditis, new murmur, heart failure, or other stigmata of endocarditis.[4,20,29] For those patients with suspected PVE or CDIE, TEE should be considered mandatory. The lack of vegetation on echocardiogram does not exclude infection even if the transesophageal approach is used. In these cases, there is an evolving role for advanced imaging modalities such as 3D TEE, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET), single-photon emission computed tomography, multidetector computed tomography, and cardiac computed tomographic angiography.[4,5,29]

TREATMENT

Desired Outcomes

The desired outcomes for treatment and prophylaxis of infective endocarditis are to:

1. Relieve the signs and symptoms of the disease
2. Decrease morbidity and mortality associated with the infection
3. Eradicate the causative organism with minimal drug exposure
4. Provide cost-effective antimicrobial therapy determined by the likely or identified pathogen, drug susceptibilities, hepatic and renal function, drug allergies, and anticipated drug toxicities
5. Prevent infective endocarditis from occurring or recurring in high-risk patients with appropriate prophylactic antimicrobials

General Approach to Treatment

Empirical antimicrobial therapy should usually be initiated in most patients after

presumptive or confirmed diagnosis of infective endocarditis.[4] However, in select patients, who are not acutely ill, empiric antimicrobial therapy can be withheld until the results of blood or tissue cultures or serologic tests are available. Due to the importance of identifying an infectious etiology, antimicrobial therapy should not be started until blood cultures have been obtained. Patient history, including past medical, surgical, social, and family, risk factors, and current and previous antimicrobial therapy should be considered when selecting empirical antimicrobial therapy. A consultation with an infectious diseases specialist should occur to assist in selecting an optimal empirical therapy. In most cases, vancomycin should be included in the empirical regimen to cover the most common causes of infective endocarditis, staphylococci, streptococci, and enterococci. Cefepime should be added to cover aerobic gram negative bacilli in patients with acute presentations. In patients with subacute presentations, ampicillin/sulbactam should be included in the empirical regimen to provide coverage against *S. aureus*, viridans group streptococci, enterococci, and HACEK organisms. Once an infectious etiology is identified from blood or tissue cultures or serologic tests, antimicrobial therapy should be deescalated to target that specific pathogen.

Specific treatment recommendations from the American Heart Association (AHA) provide guidance for the management of infective endocarditis, and these were last updated in 2015.[4] Guidelines published by the European Society of Cardiology (ESC) remain consistent, for the most part, with the AHA guidelines.[5] Both now provide important recommendations for the combination of early diagnosis, early antimicrobial therapy, and early surgery; but there are some subtle differences. The ESC guidelines recommend that an “endocarditis team,” consisting of cardiologists, cardiac surgeons, and specialists in infectious diseases, manage patients with infective endocarditis. The AHA guidelines place more emphasis on a team-based approach when assessing the timing and need for surgical intervention. The ESC guidelines also provide recommendations for specific situations, including infective endocarditis in the intensive care unit, in patients with cancer, and in patients with nonbacterial endocarditis.[5]

The AHA and ESC guidelines use an evidence-based scoring system where recommendations are given a classification as well as level of evidence. Class I recommendations are conditions for which there is evidence, general agreement, or both that a given procedure or treatment is useful and effective. Class II recommendations are conditions for which there is conflicting evidence, a divergence of opinion, or both about the usefulness/efficacy of a procedure or treatment (IIa implies that the weight of evidence/opinion is in favor of

usefulness/efficacy, whereas IIb implies that usefulness/efficacy is less well established by evidence/opinion). Class III recommendations are conditions for which there is evidence, general agreement, or both that the procedure/treatment is not useful/effective and in some cases may be harmful. Level of evidence is listed as A (data derived from multiple randomized clinical trials), B (data derived from a single randomized trial or nonrandomized studies), and C (consensus opinion of experts).

5 The most important approach in the treatment of infective endocarditis is isolation of the infecting pathogen and determination of antimicrobial susceptibilities, followed by high-dose, parenteral, and bactericidal antibiotics for an extended period.[4–6,22] Susceptibility testing is crucial given the increasing rate of antimicrobial resistance to commonly encountered pathogens. Treatment usually is started in the hospital, but for select patients it is often completed in the outpatient setting (termed outpatient antimicrobial therapy [OPAT]) so long as defervescence has occurred and follow-up blood cultures show no growth.[31] Large doses of parenteral antimicrobials, as opposed to oral antimicrobials, are currently recommended to achieve bactericidal concentrations within vegetations. An extended duration of therapy is required, even for susceptible pathogens, because microorganisms are enclosed within valvular vegetations and fibrin deposits. These barriers impair host defenses and protect microbes from phagocytic cells. In addition, high bacterial concentrations within vegetations may result in an inoculum effect that further resists killing (see Chapter e122 for additional discussion). Many bacteria are not actively dividing, further limiting the rate of bacterial death. For most patients, a minimum of 4 to 6 weeks of therapy is required.[4,5]

OPAT should be considered early in the treatment of infective endocarditis, after the patient is stable clinically and responds favorably to initial antibiotics. OPAT is safe and cost-effective in select situations.[31] Patients considered for home therapy must be hemodynamically stable, compliant with therapy, have careful medical monitoring, understand the potential complications of the disease, and have immediate access to medical care. Advances in technology allow for the outpatient administration of complex antimicrobial regimens that significantly reduce the cost of therapy. Simple regimens, such as single daily doses of ceftriaxone for streptococcal infective endocarditis, may improve patient convenience and potentially compliance. Although endocarditis is common in PWID and home healthcare would substantially reduce the cost of treatment, many clinicians are uncomfortable with outpatient IV therapy because central venous access is required. Sudden cardiac decompensation in an

outpatient setting is also of concern.[4]

In the Partial Oral Treatment of Endocarditis (POET) trial, changing to oral antimicrobial therapy after at least 10 days of IV therapy was noninferior to continuing IV antimicrobial therapy in patients with left-sided native or PVE caused by streptococci, *E. faecalis*, *S. aureus* (not MRSA), or coagulase-negative staphylococci.[32] The primary outcome, all-cause mortality, unplanned cardiac surgery, embolic events, or relapse of bacteremia within 6 months, was similar between groups (9.0% vs 12.1%, respectively). Oral antimicrobial regimens included a combination of at least two of the following antibiotics: moxifloxacin, amoxicillin, clindamycin, rifampicin, dicloxacillin, fusidic acid, and linezolid. Due to strict inclusion and exclusion criteria, frequent outpatient follow-up required, and use of oral antimicrobial agents that are unavailable or infrequently used in the United States, only a select group of patients with left-sided infective endocarditis with functioning GI tracts and a high likelihood for compliance may be candidates for combination oral antimicrobial therapy.

Nonpharmacologic Therapy

6 Surgical intervention to remove the infectious foci and repair valves and/or valvular structures is an important adjunct in the management of both NVE and PVE and is now performed in up to 50% of patients.[14] In most surgical cases, valvectomy and valve replacement are performed to remove infected tissue and to restore hemodynamic function. Indications for surgery include heart failure, persistent bacteremia, persistent vegetation, an increase in vegetation size, or recurrent emboli despite prolonged antimicrobial treatment, valve dysfunction, paravalvular extension (eg, abscess), or endocarditis caused by difficult to treat or resistant organisms (eg, fungi or gram negative bacteria).[4–6] More controversial is the appropriate timing of surgery as well as duration of antimicrobial therapy postsurgery. Additionally, studies evaluating postsurgical outcomes and associated mortality are limited such that a specific risk prediction system has not been established.[33–37] Early surgery (eg, within 48 hours) may be appropriate in patients with severe heart failure and large vegetations, whereas patients with septic shock, advanced age, or neurologic complications of infective endocarditis may have more detrimental outcomes.[33,34,38,39] The multiple factors that need to be considered in evaluating the need for and timing of surgery is why a multidisciplinary management approach (eg, “endocarditis team”) is critical.[4,5,22]

Pharmacologic Therapy

7 β-Lactam antibiotics, such as penicillin G (or ceftriaxone), nafcillin (or oxacillin), and ampicillin, remain the drugs of choice for streptococcal, staphylococcal, and enterococcal endocarditis, respectively. **Tables 129-4** to **129-7** summarize these recommendations, which are discussed in more detail in the following sections. **Tables 129-8** and **129-9** list drug dosing and monitoring recommendations for adult and pediatric patients. Because these guidelines focus on common causes of endocarditis, readers are referred to other references for more in-depth discussion of unusually encountered organisms.[4,5,40,41]

TABLE 129-4 Treatment Options for Native Valve Endocarditis by Causative Organism

Agent[a]	Duration	Strength of Recommendation	Comments
Highly Penicillin-Susceptible (MIC ≤0.12 mcg/mL [mg/L]) Viridans Group Streptococci and *S. gallolyticus*			
Aqueous crystalline penicillin G sodium[b]	4 weeks	IIaB	2-week regimens are not intended for the following patients: • Most patients >65 years of age • Children • Impairment of the eighth cranial nerve function • Renal function with a creatinine clearance <20 mL/min (0.33 mL/s) • Known cardiac or extracardiac abscess • Infection with *Abiotrophia, Granulicatella*, or *Gemalla* species
Ceftriaxone	4 weeks	IIaB	
Aqueous crystalline penicillin G sodium[b] plus gentamicin	2 weeks	IIaB	
Ceftriaxone plus gentamicin	2 weeks	IIaB	
Vancomycin	4 weeks	IIaB	Recommended only for patients unable to tolerate penicillin or ceftriaxone
Viridans Group Streptococci and *S. Gallolyticus* Relatively Resistant to Penicillin (MIC >0.12 to ≤0.5 mcg/mL [mg/L])			
Aqueous crystalline penicillin G sodium[b] plus gentamicin	4 weeks 2 weeks	IIaB	
Ceftriaxone	4 weeks	IIbC	
Plus gentamicin	2 weeks		
Vancomycin	4 weeks	IIaB	Recommended only for patients unable to tolerate penicillin or ceftriaxone
Oxacillin-Susceptible Staphylococci[c]			
Nafcillin or oxacillin	6 weeks	IC	
Cefazolin	6 weeks	IB	For use in patients with nonanaphylactoid-type penicillin allergies; patients with an unclear history of immediate-type hypersensitivity to penicillin should be considered for skin testing
Vancomycin	6 weeks	IB	For use in patients with anaphylactoid-type hypersensitivity to penicillin and/or cephalosporins
Daptomycin	6 weeks	IIaB	For use in patients with immediate-type hypersensitivity reactions to penicillin
Oxacillin-Resistant Staphylococci			
Vancomycin	6 weeks	IB	
Daptomycin	6 weeks	IIbB	

[a]See Tables 129-8 and 129-9 for appropriate dosing, administration, and monitoring information.

[b]May use ampicillin in the event of a penicillin shortage.

[c]Regimens indicate treatment for left-sided endocarditis or complicated right-sided endocarditis; uncomplicated right-sided endocarditis may be treated for shorter durations and is described in the text.

Please refer to Table 129-6 for treatment of NVE caused by enterococci.

Data from References 4 and 5.

TABLE 129-5 Treatment Options for Prosthetic Valve Endocarditis (PVE) by Causative Organism

Agent[a]	Duration	Strength of Recommendation	Comments
Highly Penicillin-Susceptible (MIC ≤0.12 mcg/mL [mg/L]) Viridans Group Streptococci and *S. gallolyticus*			
Aqueous crystalline penicillin G sodium[b] with or without gentamicin	6 weeks 2 weeks	IIaB	Combination therapy with gentamicin has not demonstrated superior cure rates compared with monotherapy with a penicillin or cephalosporin and should be avoided in patients with CrCl <30 mL/min (0.50 mL/s)
Ceftriaxone with or without gentamicin	6 weeks 2 weeks	IIaB	
Vancomycin	6 weeks	IIaB	Recommended only for patients unable to tolerate penicillin or ceftriaxone
Relatively Resistant or Fully Resistant (MIC >0.12 mcg/mL [mg/L]) Viridans Group Streptococci and *S. gallolyticus*			
Aqueous crystalline penicillin G sodium[b] plus gentamicin	6 weeks	IIaB	
Ceftriaxone plus gentamicin	6 weeks	IIaB	
Vancomycin[c]	6 weeks	IIaB	Recommended only for patients unable to tolerate penicillin or ceftriaxone
Oxacillin-Susceptible Staphylococci			
Nafcillin or oxacillin	≥6 weeks	IB	Cefazolin may be substituted for nafcillin or oxacillin in patients with nonimmediate-type hypersensitivity
plus rifampin	≥6 weeks		
plus gentamicin	2 weeks		
Vancomycin	≥6 weeks	IB	Recommended only for patients with anaphylactoid-type hypersensitivity to penicillin and/or cephalosporins
plus rifampin	≥6 weeks		
plus gentamicin	2 weeks		
Oxacillin-Resistant Staphylococci			
Vancomycin	≥6 weeks	IB	
plus rifampin	≥6 weeks		
plus gentamicin	2 weeks		

[a]See Tables 129-8 and 129-9 for appropriate dosing, administration, and monitoring information.

[b]May use ampicillin in the event of a penicillin shortage.

[c]The ESC 2015 guidelines recommend gentamicin (3 mg/kg/day) be administered with vancomycin for the initial 2 weeks of therapy in patients with relatively resistant strains to penicillin.

Please refer to Table 129-6 for treatment of PVE caused by enterococci.

Data from References 4 and 5.

TABLE 129-6 Treatment Options for Native or Prosthetic Valve Endocarditis Caused by Enterococci

Agent[a]	Duration[b]	Strength of Recommendation	Comments
Ampicillin-, Penicillin-, and Vancomycin-Susceptible Strains			
Ampicillin plus gentamicin	4-6 weeks	IIaB	Native valve plus symptoms present for <3 months: use 4-week regimen
Aqueous crystalline penicillin G sodium plus gentamicin	4-6 weeks	IIAB	Prosthetic valve or native valve plus symptoms present for >3 months: use 6-week regimen
Ampicillin plus ceftriaxone	6 weeks	IIaB	Recommended regimen if creatinine clearance is <50 mL/min (0.83 mL/s; at baseline or due to therapy with a gentamicin-containing regimen)
Vancomycin plus gentamicin	6 weeks	IIaB	Recommended only for patients unable to tolerate penicillin or ampicillin
Gentamicin-Resistant Strains			
If susceptible, use streptomycin in place of gentamicin in the regimens listed above if creatinine clearance is >50 mL/min (0.83 mL/s), cranial nerve VIII function is intact and there is laboratory capability for rapid streptomycin serum concentrations.			
Penicillin-Resistant Strains			
Ampicillin–sulbactam plus gentamicin (β-lactamase–producing strain)	6 weeks	IIbC	
Vancomycin plus gentamicin (intrinsic penicillin resistance[c])	6 weeks	IIbC	May also use in patients with β-lactamase–producing strains who have known intolerance to ampicillin–sulbactam
***Enterococcus faecium* Strains Resistant to Penicillin, Aminoglycosides, and Vancomycin[d]**			
Linezolid	>6 weeks	IIbC	Antimicrobial cure rates may be <50%; bacteriologic cure may only be achieved with cardiac valve replacement
Daptomycin	>6 weeks	IIbC	

[a]See Tables 129-8 and 129-9 for appropriate dosing, administration, and monitoring information.

[b]All patients with prosthetic valves should be treated for at least 6 weeks.

[c]Infectious diseases consult highly recommended.

[d]Patients should be managed by a multidisciplinary team that includes specialists in cardiology, cardiovascular surgery, infectious diseases, and clinical pharmacy.

Data from Reference 4.

TABLE 129-7 Treatment Options for Culture-Negative Endocarditis and Endocarditis Caused by Gram Negative Organismsa

Agent[b]	Duration[c]	Strength of Recommendation	Comments
HACEK[d] Microorganisms			
Ceftriaxone	4 weeks	IIaB	Other third- or fourth-generation cephalosporins may be used as an alternative
Ampicillin or Ampicillin–sulbactam	4 weeks	IIaB	Should only use if growth is adequate for in vitro susceptibility testing; otherwise, consider organism to be resistant
Ciprofloxacin	4 weeks	IIbC	Recommended for patients with known intolerance to cephalosporins or ampicillin; other fluoroquinolones may be used as an alternative
Culture-Negative Endocarditis, Native Valve[e]			
Vancomycin plus cefepime	4-6 weeks	IIaC	Recommended when onset is acute (days); *S. aureus*, β-hemolytic streptococci, and aerobic gram negative bacilli should be covered
Vancomycin plus ampicillin-sulbactam	4-6 weeks	IIaC	Recommended when onset is subacute (weeks); *S. aureus*, viridans group streptococci, HACEK, and enterococci should be covered
Culture-Negative Endocarditis, Early (<1 Year) Prosthetic Valve[e]			
Vancomycin plus cefepime plus rifampin plus gentamicin	6 weeks	IIaC	Staphylococci, enterococci, and aerobic gram negative bacilli should be covered
Culture-Negative Endocarditis, Late (>1 Year) Prosthetic Valve[e]			
Vancomycin plus ceftriaxone	6 weeks	IIaC	Staphylococci, viridans group streptococci, and enterococci should be covered
Suspected *Bartonella*, Culture-Negative			
Ceftriaxone	6 weeks	IIaB	
plus gentamicin	2 weeks		
with or without doxycycline	6 weeks		
Culture-Positive *Bartonella*			
Doxycycline plus gentamicin	6 weeks	IIaB	Rifampin is recommended as an alternative in patient who cannot be given gentamicin
	2 weeks		

[a]Infectious disease consult highly recommended.

[b]See Tables 129-8 and 129-9 for appropriate dosing, administration, and monitoring.

[c]All patients with prosthetic valves should be treated for 6 weeks.

[d]*Haemophilus* species (*H. parainfluenzae, H. aphrophilus*, and *H. paraphrophilus*), *Aggregatibacter* species, *Cardiobacterium hominis, Eikenella corrodens*, and *Kingella kingae.*

[e]Duration of therapy for culture-negative endocarditis may be variable and should be based on clinical course and recommendations from infectious diseases consult.

Data from References 4 and 5.

TABLE 129-8 Drug Dosing Table for Treatment of Infective Endocarditis[a]

Drug	Brand Name	Recommended Dose	Pediatric (Ped) Dose[b]	Additional Information
Ampicillin	NA	2 g IV every 4 hours	50 mg/kg every 4 hours or 75 mg/kg every 6 hours	24-hour total dose may be administered as a continuous infusion: 12 g IV every 24 hours
Ampicillin–sulbactam	Unasyn*	3 g IV every 6 hours	50 mg/kg every 4 hours or 75 mg/kg every 6 hours	
Aqueous crystalline penicillin G sodium	NA			
• MIC <0.12 mcg/mL (mg/L) (native valve only)		3 million units IV every 4 hours or every 6 hours	50,000 units/kg IV every 6 hours	24-hour total dose may be administered as a continuous infusion: 12-18 million units IV every 24 hours (Ped: 200,000 units/kg IV/24 hours)
• All other indications		4 million units IV every 4 hours or 6 million units IV every 6 hours	50,000 units/kg IV every 4 hours or 75,000 units/kg IV every 6 hours	24 million units IV every 24 hours (Ped: 300,000 units/kg IV every 24 hours)
Cefazolin	N/A	2 g IV every 8 hours	33 mg/kg IV every 8 hours	
Cefepime	Maxipime*	2 g IV every 8 hours	50 mg/kg IV every 8 hours	
Ceftriaxone sodium	N/A	2 g IV or IM every 24 hours 2 g IV or IM every 12 hours (*E. faecalis only*)	100 mg/kg IV or IM every 24 hours	

Ciprofloxacin	Cipro®	400 mg IV every 12 hours or 500 mg po every 12 hours	20-30 mg/kg IV or po every 12 hours	Avoid use if possible in patients <18 years of age
Daptomycin	Cubicin®	≥8 mg/kg IV every 24 hours	6 mg/kg IV every 24 hours	Doses as high as 10-12 mg/kg IV every 24 hours have been used in adults with enterococcus resistant to penicillin, aminoglycosides and vancomycin; doses should be calculated using actual body weight
Doxycycline	Vibramycin®	100 mg IV or po every 12 hours	1-2 mg/kg IV or po every 12 hours	
Gentamicin sulfate	NA	3 mg/kg IV or IM every 24 hours or 1 mg/kg IV or IM every 8 hoursc	1 mg/kg IV or IM every 8 hours	Once-daily dosing is only recommended for treatment of streptococcal infections.
Linezolid	Zyvox®	600 mg IV or po every 12 hours	10 mg/kg IV every 8 hours	
Nafcillin or oxacillin	NA	2 g IV every 4 hours	50 mg/kg IV every 6 hours	24-hour total dose may be administered as a continuous infusion: 12 g IV every 24 hours
Rifampin	Rifadin®	300 mg IV or po every 8 hours	5-7 mg/kg IV or po every 8 hours	
Streptomycin	NA	7.5 mg/kg IV or IM every 12 hours		
Vancomycin	Vancocin®	15-20 mg/kg IV every 8 hours or every 12 hours	15 mg/kg IV every 6 hours	A loading dose of 25-30 mg/kg may be administered in adults; doses should be calculated using actual body weight; single doses should not exceed 2 g

[a]All doses assume normal renal function.

[b]Should not exceed adult dosage.

[c]Actual body weight should be used when the full aminoglycoside dose is administered once daily; when administered in three divided doses, use ideal body weight or adjusted body weight when actual body weight is >120% ideal body weight.

TABLE 129-9 Drug Monitoring of Select Agents

Drug	Major Adverse Drug Reactions	Monitoring Parameters	Comments
Daptomycin	Myopathy, rhabdomyolysis	Creatinine phosphokinase (CPK) at least weekly; monitor for signs and symptoms of muscle pain	More frequent monitoring may be warranted in patients with renal dysfunction or receiving concomitant therapy with HMG-CoA reductase inhibitors; discontinue if symptomatic and CPK >5 times the upper limit of normal (ULN) or if CPK ≥10 times ULN
Gentamicin	Nephrotoxicity, ototoxicity, neuromuscular blockade	When dosed three times daily: • Target peak serum concentrations of 3-4 mcg/mL (mg/L; 6.3-8.4 µmol/L) and trough serum concentrations of <1 mcg/mL (mg/L; 2.1 µmol/L)	Avoid concomitant use of other nephrotoxic agents such as diuretics, nonsteroidal anti-inflammatory drugs, and radiocontrast media. Avoid rapid IV administration
Linezolid	Thrombocytopenia, optic, or peripheral neuropathy	Platelet counts at baseline and weekly, visual changes	More common with prolonged therapy (≥2 weeks for thrombocytopenia, >28 days for visual symptoms); avoid concomitant myelosuppressive agents
Rifampin	Hepatotoxicity	Baseline liver function tests, and then at least every 2-4 weeks during therapy	Avoid concomitant medications that cause hepatotoxicity; may cause red or orange discoloration of bodily secretions (urine, sweat, tears)
Vancomycin	Nephrotoxicity, red man syndrome	Target trough concentrations of 15-20 mcg/mL[a] (mg/L; 10-14 µmol/L)	Red man syndrome may be managed by prolonging the infusion time from 1 to 2 hours; administration of an antihistamine prior to loading or maintenance doses may also be considered

[a]Measuring peak serum vancomycin concentrations is no longer recommended.

8 For some pathogens, such as enterococci, the use of synergistic antimicrobial combinations (including an aminoglycoside) is essential to obtain a bactericidal effect. Combination antibiotics also may decrease the emergence of resistant organisms during treatment (eg, PVE caused by coagulase-negative staphylococci) and hasten the pace of clinical and microbiologic response (eg, some streptococcal and staphylococcal infections). Occasionally, combination treatment will result in a shorter treatment course.

Streptococcal Endocarditis

Streptococci are a common cause of infective endocarditis, with most isolates being viridans group streptococci. Viridans group streptococci refers to a large number of different species, such as *Streptococcus sanguinis, Streptococcus oralis, Streptococcus salivarius, Streptococcus mutans*, and *Gemella morbillorum*.[4] These bacteria are common inhabitants of the human mouth and gingiva, and they are especially common causes of endocarditis involving native

valves.[4,27] During dental surgery, and even when brushing the teeth, these organisms can cause a transient bacteremia. In susceptible individuals, this may result in infective endocarditis. Streptococcal endocarditis is usually subacute, and the response to medical treatment is very good. *Streptococcus gallolyticus* (formerly known as *Streptococcus bovis*) is not a viridans group streptococcus, but it is included in this treatment group because it is penicillin-susceptible and requires the same treatment. *S. gallolyticus* is a nonenterococcal group D streptococci that resides in the GI tract. Infective endocarditis caused by this organism is often associated with a GI pathology, especially colon carcinoma. Endocarditis caused by *Streptococcus pneumoniae, Streptococcus pyogenes*, and group B, C, and G streptococci are uncommon, and their treatment is not well defined.[4,5]

Antimicrobial regimens for viridans group streptococci are well studied, and in uncomplicated cases, the cure rate is expected to be more than 95%.[4,5] Viridans group streptococci are penicillin-susceptible, although some are more susceptible than others. Most are highly susceptible to penicillin G and have minimal inhibitory concentrations (MICs) of less than 0.12 mcg/mL (mg/L).[4] Approximately 10% to 20% are moderately susceptible (MIC 0.12-0.5 mcg/mL [mg/L]). This different in vitro susceptibility led to recommendations that the MIC be determined for all viridans group streptococci to guide therapy. Some streptococci are deemed tolerant to the killing effects of penicillin, where the minimal bactericidal concentration (MBC) exceeds the MIC by 32 times. A tolerant organism is inhibited but not killed by an antibiotic normally considered bactericidal.[4] Bactericidal activity is preferred for successful treatment of infective endocarditis; therefore, infections with a tolerant organism may relapse after treatment. Despite some animal studies of endocarditis suggesting that tolerant strains do not respond as readily to β-lactam therapy as nontolerant ones, this phenomenon is primarily a laboratory finding with little clinical significance.[4] Treatment for tolerant strains is identical to that for nontolerant organisms, and measurement of the MBC is not recommended.[4]

An assortment of regimens can be used to treat uncomplicated NVE caused by fully susceptible viridans group streptococci (see Table 129-4). Shorter-course antimicrobial regimens are advocated when possible. With susceptible streptococcal endocarditis (MIC ≤0.12 mcg/mL [mg/L]), a 2-week regimen of high-dose parenteral penicillin G or ceftriaxone in combination with an aminoglycoside is as effective as 4 weeks of penicillin alone.[4]

Two single-drug regimens consist of high-dose parenteral penicillin G or ceftriaxone for 4 weeks. If short-term, 2-week therapy is desired, the guidelines

suggest either high-dose parenteral penicillin G or ceftriaxone in combination with an aminoglycoside.[4] When used in select patients, this combination is as effective as 4 weeks of penicillin alone. Although streptomycin was listed in previous guidelines, gentamicin is the preferred aminoglycoside because serum drug concentrations are obtained easily, clinicians are more familiar with its use, and the few strains of streptococci resistant to the effects of streptomycin-penicillin remain susceptible to gentamicin–penicillin. Other aminoglycosides are not recommended. Whether extended-interval aminoglycoside dosing has a role in infective endocarditis continues to be debated. The combination of ceftriaxone (2 g daily) with gentamicin (3 mg/kg daily) for 2 weeks was compared with ceftriaxone (2 g daily) alone for 4 weeks for penicillin-susceptible streptococci and both regimens were safe and effective with similar clinical cure rates at 3 months following treatment.[42] Data support extended-interval dosing for the treatment of streptococcal infective endocarditis, and as compared with three-times-daily dosing this approach may have greater efficacy.[4]

The rationale for combination therapy against penicillin-susceptible viridans group streptococci is that enhanced activity against these organisms usually is observed in vitro when cell-wall-active agents are combined with aminoglycosides.[43] Combined treatment results in quicker sterilization of vegetations in animal models of endocarditis and probably explains the high response rates observed for patients treated for a total of 2 weeks.[4,42] The combined treatment, however, is not superior to penicillin alone.

The decision of which regimen to use depends on the perceived risk versus benefit. For example, a 2-week course of gentamicin in an elderly patient with renal impairment may be associated with ototoxicity, nephrotoxicity, or both. Furthermore, the 2-week regimen is not recommended for patients with known extracardiac infection. On the other hand, a 4-week course of penicillin alone generally entails greater expense, especially if the patient remains in the hospital. Monotherapy with once-daily ceftriaxone offers ease of administration, facilitates home healthcare treatment, and may be cost-effective.[4,5]

9 When a patient has a history of an immediate-type hypersensitivity to penicillin, vancomycin should be chosen for infective endocarditis caused by viridans group streptococci. When vancomycin is used, the addition of gentamicin is not recommended.[4] Most patients who report a penicillin allergy have a negative penicillin skin test and consequently are at low risk of anaphylaxis.[44] The published experience with penicillin is more extensive than with alternative regimens; consequently, a thorough allergy history must be

obtained before a second-line therapy is administered.

For patients with complicated infections (eg, extracardiac foci) or when the streptococcus has an MIC of 0.12 to less than or equal to 0.5 mcg/mL (mg/L), combination therapy with an aminoglycoside for the first 2 weeks and penicillin (higher dose) or ceftriaxone is recommended, followed by penicillin or ceftriaxone alone for an additional 2 weeks (see Table 129-4).[4] Some viridans group streptococci, previously referred to as nutritionally variant streptococci, have biologic characteristics that complicate diagnosis and treatment. *Abiotrophia defectiva* and *Granulicatella* species have nutritional deficiencies that hinder growth in routine culture media.[4] These organisms require special broth supplemented with pyridoxal hydrochloride or cysteine. For patients infected with nutritionally variant streptococci or when the *Streptococcus* spp. has an MIC of more than 0.5 mcg/mL (mg/L), treatment should follow the enterococcal endocarditis treatment guidelines.[4]

For patients with endocarditis of prosthetic valves or other prosthetic material caused by viridans group streptococci and *S. gallolyticus*, choices of treatment are similar to those without prosthetic material (eg, penicillin or ceftriaxone); however, treatment courses are extended to 6 weeks (see Table 129-5). For penicillin-susceptible isolates with an MIC of 0.12 mcg/mL (mg/L) or less, high-dose parenteral penicillin G or ceftriaxone should be administered for 6 weeks with or without an aminoglycoside for the first 2 weeks. On the contrary, for isolates with an MIC greater than 0.12 mcg/mL (mg/L), high-dose parenteral penicillin G or ceftriaxone combined with an aminoglycoside should be administered for the entire 6 weeks.

Staphylococcal Endocarditis

Endocarditis is most commonly caused by staphylococci, in particular *S. aureus*, mainly because of increased rates of injection drug use, more frequent use of peripheral and central venous catheters, and increased frequency of valve replacement surgery.[13] *S. aureus* is the most common organism causing infective endocarditis among PWID and persons with venous catheters. Coagulase-negative staphylococci (usually *Staphylococcus epidermidis*) and *S. aureus* are prominent causes of PVE.

Staphylococcal endocarditis is not a homogeneous disease; appropriate management requires consideration of several questions: Is the organism methicillin resistant? Should combination therapy be used? Is the infection on a native or prosthetic valve? Does the patient have a history of injection drug use?

Is the infection on the left or right side of the heart? Another consideration in staphylococcal endocarditis is that some organisms may exhibit tolerance to antibiotics. Similar to streptococci, however, the concern for tolerance among staphylococci should not affect antibiotic selection.[4]

Any patient who develops staphylococcal bacteremia is at risk for endocarditis. Echocardiography should be performed in all patients with *S. aureus* bacteremia as the prevalence of infective endocarditis is approximately 25%.[13,45] Many investigators have attempted to develop criteria that identify the bacteremic patient likely to have infective endocarditis. Patients with *S. aureus* bacteremia via nosocomial acquisition who have sterilization of blood cultures within 96 hours of the initial set without evidence of endocarditis, secondary foci of infection, a permanent intracardiac device or dependence on hemodialysis are at lower risk for infective endocarditis.[46] In hospitalized patients with *S. aureus* bacteremia and an identified focus of infection, such as a vascular catheter, the risk of concomitant infective endocarditis is low, and treatment of the bacteremia can be reduced to 2 weeks. This approach applies only if the patient does not have a prosthetic valve or additional clinical evidence for endocarditis.[46] Additionally, the following parameters predict higher risk of infective endocarditis for patients with *S. aureus* bacteremia: (a) the absence of a primary site of infection, (b) metastatic signs of infection, and (c) valvular vegetations detected by echocardiography.[13,45]

The recommended therapy for patients with left-sided, native valve infective endocarditis caused by methicillin-susceptible *S. aureus* (MSSA) is 6 weeks of nafcillin or oxacillin; a longer duration of therapy may be needed for complicated infections (eg, presence of perivalvular abscess or septic metastases). The AHA and ESC guidelines no longer recommend the addition of gentamicin because clinical benefit has not been demonstrated and there is an increased risk of toxicity (see Table 129-4). From in vitro studies, the combination of an aminoglycoside and penicillinase-resistant penicillin or vancomycin enhances the activity of these drugs for MSSA. In animal models of endocarditis, combinations of penicillin with an aminoglycoside eradicate organisms from vegetations more rapidly than penicillins alone.[5,47] In most human studies, the addition of an aminoglycoside to nafcillin hastens the resolution of fever and bacteremia, but it does not affect survival or relapse rates and can increase nephrotoxicity.[47] One small cohort study has demonstrated a decrease in recurrent bacteremia with combination therapy.[48]

9 If a patient has a mild, delayed allergy to penicillin, first-generation cephalosporins (such as cefazolin) are effective alternatives, but they should be

avoided for patients with a history of immediate-type hypersensitivity reactions to penicillins (see Table 129-4). The potential for a true immediate-type allergy should be assessed carefully. A penicillin skin test should be conducted before giving antibiotic treatment to any patient with infective endocarditis caused by MSSA if there is a questionable penicillin allergy.[44] For a patient with a positive skin test or a history of immediate hypersensitivity to penicillin, vancomycin is an option. Vancomycin, however, kills *S. aureus* slowly and is inferior to penicillinase-resistant penicillins for MSSA.[4] Alternatively, patients with immediate-type hypersensitivity reactions to penicillin can be considered for penicillin desensitization or daptomycin, a lipopeptide antibiotic approved for right sided infective endocarditis and *S. aureus* bacteremia.[4,5] Unfortunately, left-sided infective endocarditis caused by *S. aureus* continues to have a poor prognosis, with a mortality rate between 25% and 40%.[4] For reasons discussed in the following section, those with infective endocarditis associated with injection drug use have a more favorable response to therapy.

9 During the past decade, staphylococci more commonly have become resistant to penicillinase-resistant penicillins (eg, methicillin-resistant *S. aureus* [MRSA]). Although vancomycin is still the most commonly selected alternative in these cases (see Table 129-4), susceptibility reports with an MIC greater than 2 mcg/mL (mg/L) and reports of vancomycin-resistant *S. aureus* strains are increasing.[30] Success with daptomycin or linezolid has been demonstrated for these patients.[49–53] Based on available data, daptomycin (at a dose of 6 mg/kg/day) was approved by the FDA in 2006 for the treatment of *S. aureus* bacteremia associated with right-sided NVE and is now a recommended alternative.[30,50] Use of daptomycin in clinical practice may extend beyond the FDA-approved indication of right-sided NVE, and higher doses of daptomycin (greater than or equal to 8 mg/kg/day) should be used. Additionally, higher doses may be preferred by some experts due to favorable drug tolerability and potential for decreased treatment-emergent resistance, although prospective, randomized clinical trials are lacking.[54–57] To date, linezolid has not been approved by the FDA for use in endocarditis as most available data are based on case reports, and there is concern regarding use of a bacteriostatic agent for this condition.[30,49] The presence or lack of a prosthetic heart valve in patients with a methicillin-resistant organism guides therapy and determines whether vancomycin should be used alone or, if a prosthetic valve is present, combination therapy is necessary (see Table 129-5).[4]

Staphylococcus Endocarditis: PWID

Infective endocarditis in PWID is frequently (60%-70%) caused by *S. aureus*, although other organisms may be common in certain geographic locations.[5,13] In this setting, the tricuspid valve is frequently infected, resulting in right-sided infective endocarditis. Most patients have no history of valve abnormalities, are usually otherwise healthy, and have a good response to medical treatment. Nonetheless, surgery may be required.

As previously mentioned, an uncomplicated, left-sided MSSA endocarditis may be treated sufficiently with 6 weeks of monotherapy with penicillinase-resistant penicillin.[4] However, the clinical response with right-sided MSSA endocarditis in PWID is usually excellent and may be treated effectively (clinical and microbiologic cure exceeding 85%) with a 2-week course of nafcillin, oxacillin, or daptomycin.[4] Short 2-week courses of vancomycin for endocarditis in PWID are not recommended because of limited bactericidal activity, poor penetration into vegetations, and increased drug clearance in this population resulting in high rates of failure.[57] If vancomycin is selected, the standard 6-week regimen should be used. Selection of a 2-week treatment duration may be appropriate for patients with MSSA right-sided endocarditis if they do not have signs of renal failure, extrapulmonary septic emboli, aortic or mitral valve involvement, or CNS infection, otherwise a 6-week regimen is indicated.[4]

Although previous guidelines emphasized combination therapy with an aminoglycoside for the 2-week duration based on earlier studies, the current recommendation for monotherapy is based on data showing that a 2-week regimen of a penicillinase-resistant penicillin alone, without the addition of an aminoglycoside, is as effective as combined therapy in MSSA tricuspid valve endocarditis.[58–62] Additionally, a post-hoc analysis comparing daptomycin monotherapy with combination treatment (daptomycin plus 4 days of gentamicin) showed no difference in success rates but higher rates of renal toxicity.[46] Vancomycin and daptomycin are both options for native valve MRSA infective endocarditis in PWID.

An intriguing therapeutic approach for staphylococcal endocarditis in PWID is oral treatment.[63] One study indicated that short-course IV treatment (primarily nafcillin; mean: 16 days) followed by oral treatment (dicloxacillin or oxacillin; mean: 26 days) might be effective for tricuspid valve MSSA endocarditis.[64] The positive results of this trial can be explained by the relatively long duration of IV antibiotics (>2 weeks). Two other studies that predominantly used oral therapy (ciprofloxacin and rifampin) demonstrated efficacy (cure rates exceeding 90%)

in addicts with uncomplicated right-sided endocarditis caused by MSSA.[64,65] At this time, concerns with resistance (eg, ciprofloxacin), patient adherence, and limited published data preclude routine use of oral antibacterial regimens for the treatment of infective endocarditis in PWID.[4]

Staphylococcal Endocarditis: Prosthetic Valves

Prosthetic valve endocarditis accounts for 10% to 30% of all infective endocarditis cases.[5,8] Staphylococci (*S. aureus* and coagulase-negative staphylococci), gram negative bacilli, and fungi are the main causes of early PVE, while the microbiology of late PVE mirrors that of NVE. An episode of PVE occurring within 2 months of surgery strongly suggests that the cause is staphylococci implanted during the procedure. Yet the risk of staphylococcal endocarditis remains elevated for up to 12 months after valve replacement.[66] Because this type of infective endocarditis is typically a nosocomial infection, methicillin-resistant organisms are common, and vancomycin is the cornerstone of therapy. Combination antimicrobials are recommended because of the high morbidity and mortality associated with PVE and its refractoriness to therapy.[4,5,30] Although the addition of rifampin to a penicillinase-resistant penicillin or vancomycin does not result in predictable bacterial synergism, rifampin may have unique activity against staphylococcal infection that involves prosthetic material, where its addition results in a higher microbiologic cure rate.[4] Combination therapy also decreases the emergence of resistance to rifampin, which frequently occurs when it is used alone. For methicillin-resistant staphylococci (both MRSA and coagulase-negative staphylococci), vancomycin is recommended with rifampin for 6 weeks or more (see Table 129-5). Due to the risk of developing on therapy resistance, rifampin should not be started until blood cultures have cleared.[67] An aminoglycoside is added for the first 2 weeks if the organism is aminoglycoside susceptible; traditional dosing should be used as once-daily regimens have not been adequately evaluated in PVE and are not recommended.[4]

For MSSA, penicillinase-resistant penicillin is administered in place of vancomycin. PVE responds poorly to medical treatment and has a higher mortality compared with NVE. Valve dehiscence and incompetence can result in acute heart failure, and surgery is often a component of treatment.[4,38]

The use of anticoagulation is controversial in PVE. In general, those who require anticoagulation for a prosthetic valve should continue the anticoagulant cautiously during endocarditis therapy, unless a contraindication to therapy

exists. It is recommended to hold all anticoagulation for at least 2 weeks for patients with *S. aureus* PVE if a recent CNS embolic event has occurred.[4]

Enterococcal Endocarditis

Enterococci are normal inhabitants of the human GI tract and, occasionally, of the anterior urethra. These organisms are usually of low virulence but can become pathogens following healthcare intervention or in predisposed patients (most commonly elderly with comorbid conditions such as diabetes or need for hemodialysis).[68] Historically, enterococci were considered group D streptococci, but they have been reclassified into the genus *Enterococcus* spp. (*E. faecalis* and *E. faecium*). *E. faecalis* is the most common clinical isolate (approximately 97%) of the two species. Enterococci are the third leading cause of infective endocarditis, but they are more resistant to therapy than staphylococci and streptococci. Enterococci are noteworthy for the following reasons: (a) no single antibiotic is bactericidal, (b) MICs to penicillin are relatively high (1-25 mcg/mL [mg/L]), (c) intrinsic resistance occurs to all cephalosporins and relative resistance occurs to aminoglycosides (eg, “low-level” aminoglycoside resistance), (d) combinations of a cell-wall–active agent such as a penicillin or vancomycin and an aminoglycoside are necessary for killing, and (e) resistance to all available drugs is increasing.[69–71]

Monotherapy with penicillin for infective endocarditis caused by enterococci results in relapse rates of 50% to 80%. When used alone, penicillins are only bacteriostatic against enterococci, and thus combination therapy is always recommended for susceptible strains.[4,69,70] The killing of enterococci by the bactericidal combination of an aminoglycoside antibiotic and a penicillin is the best clinical example of antibiotic synergy. Because the aminoglycoside cannot penetrate the bacterial cell in the absence of the penicillin, enterococci usually will appear to be resistant to aminoglycosides by routine susceptibility testing (low-level resistance). However, in the presence of an agent that disrupts the cell wall such as penicillin, the aminoglycoside can gain entry, attach to bacterial ribosomes, and cause rapid cell death. An aminoglycoside–vancomycin combination is also synergistic against enterococci and is appropriate therapy for the penicillin-allergic patient.[70–72]

Enterococcal endocarditis ordinarily requires 4 to 6 weeks of ampicillin or high-dose penicillin G plus an aminoglycoside for cure (see Table 129-6). Recent literature suggests that ampicillin plus ceftriaxone is as effective and better tolerated as ampicillin plus gentamicin and should be considered as a

treatment option.[4,5] Use of two β-lactam antimicrobials results in saturation of the cell membrane penicillin binding proteins producing synergistic bactericidal activity.[73] Ampicillin has greater in vitro activity than penicillin G, although there are no clinical data to document differences in efficacy. A 6-week course is recommended for patients with symptoms lasting longer than 3 months and those with PVE. Streptomycin and gentamicin have similar efficacy, but gentamicin is preferred due to the inability to obtain streptomycin serum concentrations in most labs.[4,70] Because of resistance, other aminoglycosides, such as tobramycin and amikacin, cannot be substituted routinely. In the treatment of enterococcal endocarditis, relatively low serum concentrations of aminoglycosides appear adequate for successful therapy, such as a gentamicin peak concentration of approximately 3 to 4 mcg/mL (mg/L; 6.3-8.4 μmol/L).[4,70,72] Treatment of enterococcal endocarditis does not have the high success rate seen with infective endocarditis caused by viridans group streptococci, presumably because the organism is more resistant to killing.

Although some data support the use of extended-interval aminoglycoside dosing for other types of endocarditis (eg, streptococci), the data are more vague regarding this strategy in enterococcal infective endocarditis.[70] Some studies suggest that extended-interval aminoglycoside dosing and short-interval (traditional) dosing are clinically equivalent, discordant studies imply otherwise.[72–77] Newer evidence suggests that extended-interval dosing is appropriate in the setting of non-high-level aminoglycoside resistant (MIC <500 mcg/mL [mg/L]) *E. faecalis* infective endocarditis and this strategy has been adopted by the new ESC Guidelines.[5,74,75] As such, the duration of therapy can be shortened from 4 to 6 weeks to 2 weeks. This recommendation differs from the current AHA guidelines, which continue to support traditional dosing and a 4- to 6-week duration.[4]

Resistance among enterococci to penicillins and aminoglycosides is increasing.[4] Enterococci that exhibit high-level resistance to streptomycin (MIC >2,000 mcg/mL [mg/L]) are not synergistically killed by penicillin and streptomycin because the aminoglycoside either no longer binds to the ribosome or is inactivated by an aminoglycoside-modifying enzyme, streptomycin adenylase.[70] Because enterococci will appear resistant to aminoglycosides on routine susceptibility testing, the only way to distinguish high-level from low-level resistance is by performing special susceptibility tests using 500 to 2,000 mcg/mL (mg/L) of the aminoglycoside.[71] High-level streptomycin-resistant enterococci occur with a frequency approaching 60%, and high-level resistance to gentamicin is now found in 10% to 50% of isolates. Although most

gentamicin-resistant enterococci are resistant to all aminoglycosides (including amikacin), 30% to 50% remain susceptible to streptomycin.[70] High-level gentamicin resistance is mediated by a bifunctional aminoglycoside-modifying enzyme, 6-acetyltransferase/2-phosphotransferase, and most strains also possess streptomycin adenylase. The incidence of high-level aminoglycoside resistance is increasing; however, data on appropriate therapy are sparse, and therapeutic options are few.[70,72,77]

In addition to isolates with high-level aminoglycoside resistance, β-lactamase–producing enterococci (especially *E. faecium*) have been reported. If these organisms are discovered, use of vancomycin or ampicillin-sulbactam in combination with gentamicin should be considered. Vancomycin-resistant enterococci (VRE) are reported increasingly, primarily with *E. faecium*. Vancomycin resistance occurs when the bacterium replaces the normal vancomycin target with a peptidoglycan precursor that does not bind vancomycin.[71,77] Treating multidrug-resistant enterococci is difficult, and data on appropriate therapy are sparse. Guidelines suggest either linezolid or daptomycin (10-12 mg/kg/day), although use of either agent has produced conflicting results.[4,5,77] Surgery and replacement of the infected cardiac valve may be the only cure.

HACEK Group

Fastidious gram negative bacteria from the group of bacteria including *Haemophilus parainfluenzae*, *Haemophilus aphrophilus*, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae* (HACEK group) account for 0.8% to 6% of infective endocarditis cases.[78] Frequently, these types of infective endocarditis present as subacute illnesses with large vegetations and emboli.[78,79] These oropharyngeal organisms typically are slow growing and should be considered as possible causes of “culture-negative” endocarditis.[79] With proper treatment, infectious endocarditis caused by HACEK organisms has a low mortality rate.[78] β-lactamase–producing organisms are occurring more often; hence, HACEK organisms should be considered resistant to ampicillin alone and should not be used unless in vitro susceptibility testing is adequate. Ceftriaxone, or an alternate third- or fourth-generation cephalosporin, is the preferred treatment in most cases. Ciprofloxacin may be considered as an option if an allergy to cephalosporins is present (see Table 129-7).[4,5] Treatment is usually for 4 weeks, but it should be extended to 6 weeks in PVE caused by one of these organisms.

Less Common Types of Infective Endocarditis

Atypical Microorganisms

Endocarditis caused by organisms, such as *Bartonella* spp., *Coxiella burnetii*, *Brucella* spp., *Candida* spp., and *Aspergillus* spp., *Legionella* spp., and gram negative bacilli (eg, *Pseudomonas*), is relatively uncommon. Medical therapy for infective endocarditis caused by these organisms is usually unsuccessful.[4,5] Consultation with an infectious diseases expert is warranted when these microorganisms are identified.

In addition to *Pseudomonas* spp., other gram negative bacilli that have been implicated include *Salmonella* spp., *Escherichia coli, Citrobacter* spp., *Klebsiella* spp., *Enterobacter* spp., *Serratia marcescens, Proteus* spp., and *Providencia* spp. Generally, these infections have a poor prognosis, with mortality rates as high as 60% to 80%. Cardiac surgery in concert with an extended-course of combination antibacterial therapy is recommended (class IIa; level of evidence: B) for most patients with gram negative bacillary infective endocarditis. Readers are referred to the AHA guidelines for more extensive review of treatment regimens for infective endocarditis due to *Pseudomonas* spp. and unusual gram negative bacteria.[4]

Fungi cause less than 2% of endocarditis cases; most patients with fungal endocarditis have undergone recent cardiovascular surgery, are PWID, have received prolonged treatment with indwelling central venous catheters, or are immunocompromised.[80,81] *Candida* spp. and *Aspergillus* spp. are the most commonly involved, and the mortality rate is high (>80%) for the following reasons: (a) large, bulky vegetations that often form, (b) systemic septic embolization that may occur, (c) the tendency of fungi to invade the myocardium, (d) poor penetration of vegetations by antifungals, (e) the low toxic-to-therapeutic ratio of agents such as amphotericin B, and (f) the lack of consistent fungicidal activity of available antifungal agents.[3,5,81] When fungal infective endocarditis is identified, a combined medical–surgical approach is warranted. Because these infections occur infrequently, scant clinical data are available to make solid treatment recommendations. Amphotericin B with or without flucytosine or high dose echinocandin is the recommended pharmacologic approach for *Candida* spp. endocarditis while voriconazole is suggested for those with *Aspergillus* spp. endocarditis.[4,5,41,82] Greater than 6 weeks of therapy is usually recommended, followed by life-long suppressive therapy with an oral azole in most cases.

C. burnetii (Q fever), an obligate intracellular bacterium, is most likely to be

identified via serology or PCR testing since it cannot be isolated from routine blood cultures. It is a common cause of infective endocarditis in certain areas of the world where goat, cattle, and sheep farming are widespread. The most favorable therapy for Q fever is unknown but may include doxycycline with hydroxychloroquine, trimethoprim–sulfamethoxazole, rifampin, or fluoroquinolones for at least 18 months.[83] *Brucella* spp. are facultative intracellular gram negative bacilli. Humans are infected by this organism after ingesting infected unpasteurized dairy products or undercooked meat, inhaling infectious aerosols, or contacting infected tissues. This type of infective endocarditis is more common in veterinarians and livestock handlers. Cure requires valve replacement and antimicrobial agents including doxycycline with streptomycin or gentamicin or doxycycline with trimethoprim–sulfamethoxazole or rifampin for an extended period (6 weeks to months).[84]

Culture-Negative Endocarditis

Sterile blood cultures are reported in up to 40% of patients with infective endocarditis if strict diagnostic criteria are used.[1,5,26] This type of infective endocarditis may occur as a result of previous antimicrobial therapy (most common), unidentified subacute right-sided infective endocarditis, slow-growing fastidious organisms, nonbacterial etiologies (eg, fungi), noninfective endocarditis, and improperly collected blood cultures. When blood cultures from patients suspected of infective endocarditis show no growth after 48 to 72 hours, cultures should be held for up to a month and special testing techniques (eg, serological analysis, PCR) pursued to detect fastidious or nonbacterial organisms.[4,28,79]

The AHA guidelines provide very general recommendations for culture-negative infective endocarditis (see Table 129-7) and suggest that therapy should be guided based on the individual patient's past medical history and epidemiological risks identified. Selection of treatment can be difficult, balancing the need to cover all likely organisms against potential toxic drug effects (eg, aminoglycosides). Antimicrobial selection should involve consultation with an infectious diseases specialist. Irrespective of the chosen treatment, extended antimicrobial therapy is required. The empirical approaches for culture-negative infective endocarditis highlight the need for proper collection and monitoring of blood cultures and an extensive medication history.

EVALUATION OF THERAPEUTIC OUTCOMES

The evaluation of patients treated for infective endocarditis includes assessment of disease signs and symptoms, blood cultures, microbiologic tests, inflammatory markers, serum drug concentrations, and other tests to evaluate organ function.

Signs and Symptoms

Fever usually subsides within 1 week of initiating therapy.[18] Persistence of fever may indicate ineffective antimicrobial therapy, emboli, right-sided endocarditis, intravascular catheter infections, or drug reactions. For some patients, fever may persist even with appropriate antimicrobial therapy. With defervescence, the patient should begin to feel better, and other symptoms, such as lethargy or weakness, should subside. Echocardiography, typically a TTE, should be performed when antimicrobial therapy has been completed to determine new baseline cardiac function (eg, ventricular size and function).[4]

Blood Cultures

After initiation of appropriate therapy, blood should sterilize with negative cultures within a few days, although microbiologic response to vancomycin may be slower. If bacteria continue to be isolated from blood beyond the first few days of therapy, it may indicate that the antimicrobials are inactive against the pathogen or that the doses are not producing adequate concentrations at the site of infection. If this is the case, therapeutic adjustments should be made, and blood cultures should be rechecked until negative. In most situations, the duration of therapy should begin on the first day blood cultures were negative in patients with previously positive blood cultures. Alternatively, the duration of therapy should be counted from the first postoperative day in patients who undergo valve surgery with intraoperative findings of a paravalvular abscess or resultant positive culture from the valve tissue. During the remainder of therapy, frequent blood cultures are not necessary but should be obtained if fever recurs.[4]

Microbiologic Tests

For all isolates from blood cultures, MICs should be determined; MBCs are no longer recommended.[4] The agent currently being used should be tested, as well as alternatives that may be required if intolerance, allergy, or resistance occurs. Occasionally, it is useful to determine whether synergy exists for antimicrobial combinations, although synergistic regimens usually can be predicted from the

literature. Chapter e122 summarizes the methods for in vitro determinations of synergy.

Inflammatory Markers

Inflammatory markers are commonly used in infectious diseases processes for diagnosing, monitoring of clinical outcomes, as well as assisting clinicians with evaluating the efficacy of antimicrobial therapy. Currently only one inflammatory marker, rheumatoid factor (RF), is part of the modified Duke criteria for diagnosis. Other inflammatory markers, such as ESR, CRP, and procalcitonin (PCT), have all been investigated for evaluating the outcomes of patients with endocarditis.[85] High PCT levels (eg, >0.5 ng/mL [mcg/L]) indicate the need for surgical intervention and correlate with poor outcomes (eg, death or serious infectious complications).[85–87] While these markers may be beneficial in assessing clinical outcomes, further evidence is needed to establish routine use for infective endocarditis.

Serum Drug Concentrations

Of the agents used commonly for infective endocarditis, measurement of serum drug concentrations is routinely available for aminoglycosides (except streptomycin) and vancomycin.[88] Few data, however, support attaining any specific serum concentrations for patients with infective endocarditis. In general, serum concentrations of the antimicrobial should exceed the MIC of the organisms.

When aminoglycosides are administered for infective endocarditis caused by gram positive cocci with a traditional three-times-daily regimen, peak serum concentrations are recommended to be on the low side of the traditional ranges (3-4 mcg/mL [mg/L; 6.3-8.4 µmol/L] for gentamicin). If extended-interval dosing is used, which is only recommended in streptococcal infective endocarditis, the most appropriate method of monitoring has not been determined. When vancomycin is administered, the primary goal is to ensure adequate trough concentrations, in this case 15 to 20 mcg/mL (mg/L; 10-14 µmol/L), are achieved.[88]

PREVENTION

10 Antimicrobial prophylaxis is used as an attempt to prevent infective

endocarditis for patients who are at the highest risk.[4–6,21] The use of antimicrobials for this purpose requires consideration of (a) cardiac conditions associated with endocarditis, (b) procedures causing bacteremia, (c) organisms likely to cause endocarditis, and (d) pharmacokinetics, spectrum, cost, adverse effects, and ease of administration of available antimicrobial agents. The objective of prophylaxis is to diminish the likelihood of infective endocarditis in high-risk individuals from procedures that result in bacteremia. Although there are no prospective, controlled human trials demonstrating that prophylaxis in high-risk individuals protects against the development of endocarditis during bacteremia-inducing procedures, animal studies suggest possible benefit.[21] However, other studies have questioned the benefit of antimicrobial prophylaxis prior to invasive procedures.[89–91] Furthermore, many causes of infective endocarditis appear not to be secondary to an invasive procedure. Bacteremia as a consequence of daily activities may, in fact, be the major culprit, and the value of antimicrobial prophylaxis before bacteremia-causing procedures has been questioned.[90] The literature lacks adequate evidence to prove the effectiveness or ineffectiveness of antimicrobial prophylaxis, and the common practice of using antimicrobial therapy in this setting remains controversial.[91] The mechanism of a beneficial effect in humans is unclear, but antibiotics may decrease the number of bacteria at the surgical site, kill bacteria after they are introduced into the blood, and prevent adhesion of bacteria to the valve.

Regardless of the controversy about whether prophylactic antimicrobials should be used, infective endocarditis prophylaxis is recommended in select situations in those with underlying high-risk cardiac conditions. The AHA released updated guidelines that better define who should and should not receive infective endocarditis prophylaxis.[6,21]

Key points are that (a) only a small number of cases of infective endocarditis might be prevented with antimicrobial prophylaxis for dental procedures, even if 100% effective; (b) infective endocarditis prophylaxis should be recommended only for patients with underlying cardiac conditions associated with the highest risk, which includes presence of a prosthetic heart valve, prosthetic material used for cardiac valve repair, prior diagnosis of infective endocarditis, cardiac transplantation with subsequent valvulopathy, CHD, for dental procedures involving manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa, invasive respiratory procedures involving an incision or biopsy, or invasive procedures involving infected skin, skin structures, or musculoskeletal tissue; (c) prophylaxis is not recommended based solely on an increased lifetime risk of acquisition of infective endocarditis; and

(d) administration of antimicrobials solely to prevent endocarditis is not recommended for patients who undergo a GI tract or genitourinary procedure.

To determine whether a patient should receive prophylactic antibiotics, one needs to assess the patient's risk and whether he or she is undergoing a procedure resulting in bacteremia. When antimicrobial prophylaxis is appropriate, a single 2-g dose of amoxicillin is recommended for adult patients at risk, given 30 to 60 minutes before undergoing procedures associated with bacteremia. Because the duration of antimicrobial prophylaxis appears to be relatively short, guidelines do not advocate a second oral dose of amoxicillin, which was recommended previously. Alternative prophylaxis regimens for patients allergic to penicillins or those unable to take oral medications are also provided. A summary of guideline recommendations is available in **Table 129-10**. Consultation of the full AHA guideline is suggested for more detailed information.[6,21]

TABLE 129-10 Prophylaxis of Infective Endocarditis

Highest Risk Cardiac Conditions	Presence of a prosthetic heart valve Prosthetic material used for cardiac valve repair Prior diagnosis of infective endocarditis Cardiac transplantation with subsequent valvulopathy Congenital heart disease (CHD)[a]	
Types of procedures	Dental procedures that require perforation of the oral mucosa or manipulation of the periapical region of the teeth of gingival tissue Invasive respiratory procedures involving an incision or biopsy Invasive procedures involving infected skin, skin structures, or musculoskeletal tissue	
Antimicrobial Options	**Adult Doses[b]**	**Pediatric Doses[b] (mg/kg)**
Oral amoxicillin	2 g	50
IM or IV ampicillin[c]	2 g	50
IM or IV cefazolin or ceftriaxone[c,d,e]	1 g	50
Oral cephalexin[d,e,f]	2 g	50
Oral clindamycin[e]	600 mg	20
Oral azithromycin or clarithromycin[e]	500 mg	15
IV or IM clindamycin[c,e]	600 mg	20

[a]Includes only the following: unrepaired cyanotic CHD, prophylaxis within the first 6 months of implanting prosthetic material to repair a congenital heart defect, and repaired CHD with residual defects at or adjacent to prosthetic material.

[b]All one-time doses administered 30-60 minutes prior to initiation of the procedure.

[c]For patients unable to tolerate oral medication.

[d]Should be avoided in patients with immediate-type hypersensitivity reaction to penicillin or ampicillin (eg, anaphylaxis, urticaria, or angioedema).

[e]Option for patients with nonimmediate hypersensitivity reaction to penicillin or ampicillin.

[f]May substitute with an alternative first- or second-generation cephalosporin at an equivalent dose.

Data from References 6 and 21.

Postclass Engaged Learning Activity

Perform a literature search to identify one new primary literature report about infective endocarditis published in the last year. Write a brief summary comparing the new information in the epidemiology, diagnostic imagining modalities, treatment, and/or outcomes to current practice. Describe the potential impact on efficacy and safety. This activity will help develop skills in evaluating and applying primary literature to clinical practice.

ABBREVIATIONS

AHA	American Heart Association
CDIE	cardiac device infective endocarditis
CHD	congenital heart disease
CRP	clinical attachment loss
CCB	C-reactive protein
ESC	European Society of Cardiology
ESR	erythrocyte sedimentation rate
HACEK	the group of bacteria including Haemophilus parainfluenzae, *Haemophilus aphrophilus*, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*
IE	infective endocarditis
MBC	minimal bactericidal concentration
MIC	minimal inhibitory concentration
MRSA	methicillin-resistant Staphylococcus aureus
MSSA	methicillin-susceptible Staphylococcus aureus
NVE	native valve endocarditis
OPAT	outpatient antimicrobial therapy
PCR	polymerase chain reaction
PCT	procalcitonin
PVE	prosthetic valve endocarditis
PWID	persons who inject drugs
RF	rheumatoid factor
SBT	serum bactericidal titer
TEE	transesophageal echocardiography
TTE	transthoracic echocardiography
VRE	vancomycin resistant enterococcus

REFERENCES

1. Thuny F, Grisoli D, Cautela J, et al. Infective endocarditis: Prevention, diagnosis, and management. *Can J Cardiol*. 2014;30:1046–1057.
2. Sandoe JAT, Watkin RW, Elliott TSJ. Infective endocarditis in the adult patient. *Medicine*. 2013;41:689–692.
3. Fernandez Guerrero ML, Alvarez B, Manzarbeitia F, Renedo G. Infective endocarditis at autopsy: A review of pathologic manifestations and clinical correlates. *Medicine*. 2012;91:152–164.
4. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: Diagnosis, antimicrobial therapy, and management of complications: A scientific statement for healthcare professionals from the American Heart Association: Endorsed by the Infectious Diseases Society of America. *Circulation*. 2015;132(15):1435–86.
5. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J*. 2015;36(44):3075–3128.
6. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017;135(25):e1159–e1195.
7. Baddour LM, Epstein AE, Erickson CC, et al. On behalf of the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Nursing; Council on Clinical Cardiology; and the Interdisciplinary Council on Quality of Care and Outcomes Research. Update on cardiovascular implantable electronic device infections and their management: A scientific statement from the American Heart Association. *Circulation*. 2010;121:458–477.
8. Pant S, Patel NJ, Deshmukh A, et al. Trends in infective endocarditis incidence, microbiology, and valve replacement in the United States from 2000 to 2011. *J Am Coll Cardiol*. 2015;65:2070–2076.

9. Toyoda N, Chikwe J, Itagaki S, et al. Trends in infective endocarditis in California and New York State, 1998–2013 *JAMA*. 2017;317(16):1652–1660.
10. Bin Abdulhak AA, Baddour LM, Erwin PJ, et al. Global and regional burden of infective endocarditis, 1990–2010. *Glob Heart*. 2014;9:131–143.
11. Chirouze C, Hoen B, Duval X. Infective endocarditis epidemiology and consequences of prophylaxis guidelines modifications: The dialectical evolution. *Curr Infect Dis Rep*. 2014;16:440–448.
12. Elder RW, Baltimore RS. The changing epidemiology of pediatric endocarditis. *Infect Dis Clin N Am*. 2015;29:513–524.
13. Wang A, Gaca JG, Chu VH. Management considerations in infective endocarditis: A Review. *JAMA*. 2018;320(1):72–83.
14. Hoen B, Duval X. Infective endocarditis. *N Engl J Med*. 2013;369(8):785.
15. Katan O, Michelena HI, Avierinos JF, et al. Incidence and predictors of infective endocarditis in mitral valve prolapse: A population-based study. *Mayo Clin Proc*. 2016;91(3):336–42.
16. Athan E, Chu VH, Tattevin P, et al. Clinical characteristics and outcome of infective endocarditis involving implantable cardiac devices. *JAMA*. 2012;307:1727–1735.
17. Benito N, Miro JM, de Lazzari E, et al. Health care-associated native valve endocarditis: Importance of non-nosocomial acquisition. *Ann Intern Med*. 2009;150:586–594.
18. Hill EE, Herijgers P, Herregods MC, Peetermans WE. Evolving trends in infective endocarditis. *Clin Microbiol Infect*. 2006;12:5–12.
19. Bin Abdulhak AA, Tleyjeh IM. Indications of surgery in infective endocarditis. *Curr Infect Dis Rep*. 2017;19(3):10.
20. Thuny F, Grisoli D, Collart F, et al. Management of infective endocarditis: Challenges and perspectives. *Lancet*. 2012;379:965–975.
21. Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: Guidelines from the American Heart Association: A guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*. 2007;116:1736–1754.

22. Klein M, Wang A. Infective endocarditis. *J Intensive Care Med*. 2016;31(3):151–163.
23. Werdan K, Dietz S, Löffler B, et al. Mechanisms of infective endocarditis: Pathogen-host interaction and risk states. *Nat Rev Cardiol*. 2014;11(1):35–50.
24. Sexton DJ, Spelman D. Current best practices and guidelines. Assessment and management of complications in infective endocarditis. *Infect Dis Clin North Am*. 2002;16(2):507–521.
25. Habib G, Hoen B, Tornos P, et al. ESC Committee for Practice Guidelines. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. *Eur Heart J*. 2009;30(19):2369–413.
26. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: Utilization of specific echocardiographic findings. Duke Endocarditis Service. *Am J Med*. 1994;96:200–209.
27. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30:633–638.
28. Liesman RM, Pritt BS, Maleszewski JJ, Patel R. Laboratory diagnosis of infective endocarditis. *J Clin Microbiol*. 2017;55(9):2599–2608.
29. Bruun NE, Habib G, Thuny F, Sogaard P. Cardiac imaging in infectious endocarditis. *Eur Heart J*. 2014;35:624–632.
30. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis*. 2011;52(3):e18–e55.
31. Norris AH, Shrestha NK, Allison GM, et al. 2018 Infectious Diseases Society of America Clinical practice guideline for the management of outpatient parenteral antimicrobial therapy. *Clin Infect Dis*. 2019;68(1):e1–e35.
32. Iversen K, Ihlemann N, Gill SU, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. *N Engl J Med*. 2019;380(5):415–424.
33. Gelsomino S, Maessen JG, van der Veen F, et al. Emergency surgery for

native mitral valve endocarditis: The impact of septic and cardiogenic shock. *Ann Thorac Surg*. 2012;93:1469–1476.

34. Ramirez-Duque N, Garcia-Cabrera E, Ivanova-Georgieva R, et al. Surgical treatment for infective endocarditis in elderly patients. *J Infect*. 2011;63:131–138.
35. Manne MB, Shrestha NK, Lytle BW, et al. Outcomes after surgical treatment of native and prosthetic valve infective endocarditis. *Ann Thorac Surg*. 2012;93:489–494.
36. Kiefer T, Park L, Tribouilloy C, et al. Association between valvular surgery and mortality among patients with infective endocarditis complicated by heart failure. *JAMA*. 2011;306:2239–2247.
37. De Feo M, Cotrufo M, Carozza A, et al. The need for a specific risk prediction system in native valve infective endocarditis surgery. *Sci World J*. 2012;2012:307571. doi:10.1100/2102/307571.
38. Byrne JG, Rezai K, Sanchez JA, et al. Surgical management of endocarditis: The Society of Thoracic Surgeons clinical practice guideline. *Ann Thorac Surg*. 2011;91:2012–2019.
39. Kang DH, Kim YJ, Kim SH, et al. Early surgery versus conventional treatment for infective endocarditis. *N Engl J Med*. 2012;366:2466–2473.
40. Tattevin P, Revest M, Lefort A, Michelet C, Lortholary O. Fungal endocarditis: Current challenges. *Int J Antimicrob Agents*. 2014;44:290–294.
41. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62(4):e1–50.
42. Sexton DJ, Tenenbaum MJ, Wilson WR, et al. Ceftriaxone once daily for four weeks compared with ceftriaxone plus gentamicin once daily for two weeks for treatment of endocarditis due to penicillin-susceptible streptococci. Endocarditis Treatment Consortium Group. *Clin Infect Dis*. 1998;27:1470–1474.
43. Falagas ME, Matthaiou DK, Bliziotis IA. The role of aminoglycosides in combination with a beta-lactam for the treatment of bacterial endocarditis: A meta-analysis of comparative trials. *J Antimicrob Chemother*. 2006;57:639–647.
44. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and management of penicillin allergy: A Review. *JAMA*. 2019;321(2):188–199.

45. Holland TL, Arnold C, Fowler VG Jr. Clinical management of *Staphylococcus aureus* bacteremia: A review. *JAMA*. 2014;312(13):1330–1341.
46. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;49:1–45.
47. Cosgrove SE, Vigliani GA, Fowler VG Jr, et al. Initial low-dose gentamicin for *Staphylococcus aureus* bacteremia and endocarditis is nephrotoxic. *Clin Infect Dis*. 2009;48:713–721.
48. Lemonovich TL, Haynes K, Lautenbach E, et al. Combination therapy with an aminoglycoside for *Staphylococcus aureus* endocarditis and/or persistent bacteremia is associated with a decreased rate of recurrent bacteremia: A cohort study. *Infection*. 2011;39:549–554.
49. Falagas ME, Manta KG, Ntziora F, Vardakas KZ. Linezolid for the treatment of patients with endocarditis: A systematic review of the published evidence. *J Antimicrob Chemother*. 2006;58:273–280.
50. Fowler VG Jr, Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus. N Engl J Med*. 2006;355:653–665.
51. Levine DP, Lamp KC. Daptomycin in the treatment of patients with infective endocarditis: Experience from a registry. *Am J Med*. 2007;120(10 Suppl 1):S28–S33.
52. Rehm SJ, Boucher H, Levine D, et al. Daptomycin versus vancomycin plus gentamicin for treatment of bacteraemia and endocarditis due to *Staphylococcus aureus*: Subset analysis of patients infected with methicillin-resistant isolates. *J Antimicrob Chemother*. 2008;62: 1413–1421.
53. Segreti JA, Crank CW, Finney MS. Daptomycin for the treatment of gram-positive bacteremia and infective endocarditis: A retrospective case series of 31 patients. *Pharmacotherapy*. 2006;26:347–352.
54. Wu G, Abraham T, Rapp J, et al. Daptomycin: Evaluation of a high-dose treatment strategy. *Int J Antimicrob Agents*. 2011;38:192–196.
55. Dutante-Mangoni E, Casillo R, Bernardo M, et al. High-dose daptomycin for cardiac electronic device-related infective endocarditis. *Clin Infect Dis*. 2012;54:347–354.
56. Kullar R, Davis SL, Levine DP, et al. High-dose daptomycin for treatment

of complicated gram-positive infections: A large, multicenter, retrospective study. *Pharmacotherapy*. 2011;31:527–536.

57. Carugati M, Bayer AS, Miro JM, et al. High-dose daptomycin therapy for left-sided infective endocarditis: A prospective study from the International Collaboration on Endocarditis. *Antimicrob Agents Chemother*. 2013;57:6213–6222.
58. Fortún J, Pérez-Molina JA, Añón MT, Martínez-Beltrán J, Loza E, Guerrero A. Right-sided endocarditis caused by *Staphylococcus aureus* in drug abusers. *Antimicrob Agents Chemother*. 1995;39(2):525–8.
59. Chambers HF, Miller RT, Newman MD. Right-sided *Staphylococcus aureus* endocarditis in intravenous drug abusers: Two-week combination therapy. *Ann Intern Med*. 1988;109:619–624.
60. DiNubile MJ. Short-course antibiotic therapy for right-sided endocarditis caused by *Staphylococcus aureus* in injection drug users. *Ann Intern Med*. 1994;121:873–876.
61. Yung D, Kottachchi D, Neupane B, et al. Antimicrobials for right-sided endocarditis in intravenous drug users: A systematic review. *J Antimicrob Chemother*. 2007;60:921–928.
62. Ribera E, Gomez-Jimenez J, Cortes E, et al. Effectiveness of cloxacillin with and without gentamicin in short-term therapy for right-sided *Staphylococcus aureus* endocarditis. A randomized, controlled trial. *Ann Intern Med*. 1996;125:969–974.
63. Parker RH, Fossieck BE Jr. Intravenous followed by oral antimicrobial therapy for staphylococcal endocarditis. *Ann Intern Med*. 1980;93: 832–834.
64. Dworkin RJ, Lee BL, Sande MA, et al. Treatment of right-sided *Staphylococcus aureus* endocarditis in intravenous drug users with ciprofloxacin and rifampicin. *Lancet*. 1989;2:1071–1073.
65. Heldman AW, Hartert TV, Ray SC, et al. Oral antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users: Prospective randomized comparison with parenteral therapy. *Am J Med*. 1996;101:68–76.
66. Lopez J, Revilla A, Vilacosta I, et al. Definition, clinical profile, microbiological spectrum, and prognostic factors of early-onset prosthetic valve endocarditis. *Eur Heart J*. 2007;28:760–765.
67. Riedel DJ, Weekes E, Forrest GN. Addition of rifampin to standard therapy for treatment of native valve infective endocarditis caused by

Staphylococcus aureus. *Antimicrob Agents Chemother*. 2008;52(7):2463–2467.

68. Chirouze C, Athan E, Alla F, et al. Enterococcal endocarditis in the beginning of the 21st century: Analysis from the International Collaboration on Endocarditis-Prospective Cohort Study. *Clin Microbiol Infect*. 2013;19(12):1140–1147.
69. Reyes K, Zervos M. Endocarditis caused by resistant enterococcus: An overview. *Curr Infect Dis Rep*. 2013;15:320–328.
70. Pericás JM, Zboromyrska Y, Cervera C, et al. Enterococcal endocarditis revisited. *Future Microbiol*. 2015;10:1215–1240.
71. O'Driscoll T, Christopher CW. Vancomycin-resistant enterococcal infections: Epidemiology, clinical manifestations, and optimal management. *Infect Drug Resist*. 2015;8:217–230.
72. Arias CA, Contreras GA, Murray BE. Management of multidrug-resistant enterococcal infections. *Clin Microbiol Infect*. 2010;16(6): 555–562.
73. Mainardi JL, Gutmann L, Acar JF et al. Synergistic effect of amoxicillin and cefotaxime against Enterococcus faecalis. *Antimicrob Agents Chemother*. 1995;39:1984–1987.
74. Olaison L, Schadewitz K. Enterococcal endocarditis in Sweden, 1995–1999: Can shorter therapy with aminoglycosides be used? *Clin Infect Dis*. 2002;34:159–166.
75. Miro JM, Pericas JM, del Rio A. A new era for treating Enterococcus faecalis endocarditis: Ampicillin plus short-course gentamicin or ampicillin plus ceftriaxone: That is the question! *Circulation*. 2013;127:1763–1766.
76. Fernandez Guerrero ML, Goyenechea A, Verdejo C, et al. Enterococcal endocarditis on native and prosthetic valves: A review of clinical and prognostic factors with emphasis on hospital-acquired infections as a major determinant of outcome. *Medicine (Baltimore)*. 2007;86:363–377.
77. Sood S, Malhotra M, Das BK, et al. Enterococcal infections & antimicrobial resistance. *Indian J Med Res*. 2008;128:111–121.
78. Chambers ST, Murdoch D, Morris A, et al. HACEK infective endocarditis: Characteristics and outcomes from a large, multi-national cohort. *PLoS ONE*. 2013;8(5):e63181.
79. Katsouli A, Massa MG. Current issues in the diagnosis and management of blood culture-negative infective and non-infective endocarditis. *Ann Thorac Surg*. 2013;95:1467–1474.

80. Bor DH, Woolhandler S, Nardin R, Brusch J, Himmelstein DU. Infective endocarditis in the U.S., 1998–2009: A nationwide study *PLoS ONE*. 2013;8:e60033.
81. Pierrotti LC, Baddour LM. Fungal endocarditis, 1995–2000. *Chest*. 2002;122:302–310.
82. Patterson TF, Thompson GR 3rd, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;63(4):e1–e60.
83. Kersh GJ. Antimicrobial therapies for Q fever. *Expert Rev Anti Infect Ther*. 2013;11:1207–1214.
84. Solera J. Update on brucellosis: Therapeutic challenges. *Int J Antimicrob Agents*. 2010;36(Suppl 1):S18–S20.
85. Watkins RR, Lemonovich TL. Role of inflammatory markers in the diagnosis and management of infective endocarditis. *Infect Dis Clin Pract*. 2010;18:87–90.
86. Kocaxeybek B, Kucukoglu S, Oner YA. Procalcitonin and C-reactive protein in infective endocarditis: Correlation with etiology and prognosis. *Chemotherapy*. 2003;49:76–84.
87. Cornelissen CG, Frechen DA, Schreuner K, et al. Inflammatory parameters and prediction of prognosis in infective endocarditis. *BMC Infect Dis*. 2013;13:272–278.
88. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2009;66:82–98.
89. Duval X, Alla F, Hoen B, et al. Estimated risk of endocarditis in adults with predisposing cardiac conditions undergoing dental procedures with or without antibiotic prophylaxis. *Clin Infect Dis*. 2006;42(12): e102–e107.
90. Mougeot FK, Saunders SE, Brennan MT, Lockhart PB. Associations between bacteremia from oral sources and distant-site infections: Tooth brushing versus single tooth extraction. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2015;119(4):430–435.
91. Glenny AM, Oliver R, Roberts GJ, Hooper L, Worthington HV. Antibiotics for the prophylaxis of bacterial endocarditis in dentistry. *Cochrane Database Syst Rev*. 2013;10:CD003813.

130

Tuberculosis

Rocsanna Namdar and Charles Peloquin

KEY CONCEPTS

1. Tuberculosis (TB) is the most prevalent communicable infectious disease on earth; and it remains out of control in many developing nations. These nations require medical and financial assistance from developed nations in order to control the spread of TB globally.
2. In the United States, TB disproportionately affects the foreign born and other ethnic minorities, reflecting immigration patterns and greater ongoing transmission in these communities. Additional TB surveillance and preventive treatments are required within these communities.
3. TB is the leading cause of death in human immunodeficiency virus (HIV) infection worldwide. Coinfection with HIV and TB accelerates the progression of both diseases; thus, requiring rapid diagnosis and treatment of both diseases.
4. Mycobacteria are slow-growing organisms; in the laboratory, they require special stains, special growth media, and long periods of incubation to isolate and identify.
5. TB can produce atypical signs and symptoms in infants, the elderly, and immunocompromised hosts, and it can progress rapidly in these patients.
6. Latent TB infection (LTBI) can lead to reactivation disease years after the primary infection occurred.
7. The patient suspected of having active TB disease must be isolated until the diagnosis is confirmed and the patient is no longer contagious. Often, isolation takes place in specialized “negative-pressure” hospital rooms to prevent the spread of TB.
8. Isoniazid and rifampin are the two most important drugs in the treatment of TB. Organisms resistant to both these drugs (multidrug-resistant TB

[MDR-TB]) are much more difficult to treat.

9 Directly observed treatment (DOT) should be used whenever possible to reduce treatment failures and the selection of drug-resistant isolates.

10 To avoid the development of resistance, never add a single drug to a failing TB treatment regimen.

Preclass Engaged Learning Activity

Read and review the study questions in the Self-Study Module 6 on Tuberculosis: Managing Tuberculosis Patients and Improving Adherence located on the CDC website: https://tinyurl.com/y4dxogm6. This module is designed to teach healthcare providers about methods to improve medication adherence in different types patients with tuberculosis disease. Strategies to improve patient adherence are described including directly observed therapy, incentives, and education. The module is useful tool for students to enhance their understanding of assessment and implementation steps in the patient care process.

INTRODUCTION

1 Tuberculosis (TB) remains a leading infectious killer globally. TB is caused by *Mycobacterium tuberculosis*, which can produce either a silent, latent infection or a progressive, active disease.[1] Left untreated or improperly treated, TB causes progressive tissue destruction and, eventually, death. Because of renewed public health efforts, TB rates in the United States continue to decline. In contrast, TB remains out of control in many developing countries and one-third of the world's population currently is infected.[1] Given increasing drug resistance, it is critical that a major effort be made to control TB before the most potent drugs are no longer effective.

TB rates generally have risen with increasing urbanization and overcrowding because it is easier for an airborne disease to spread when people are living in closer proximity to each other. Hence, TB became a significant pathogen in Europe during the Middle Ages and peaked during the Industrial Revolution, when it caused significant mortality in Europe and in the United States.[1] This dire threat led to the rise of public health departments and to procedures such as

the isolation of infected patients. Thus, TB was directly responsible for many of the healthcare practices that are used today. Unfortunately, in developing nations, some of these practices are not widely available, and TB continues to rage unabated (**Fig. 130-1**).

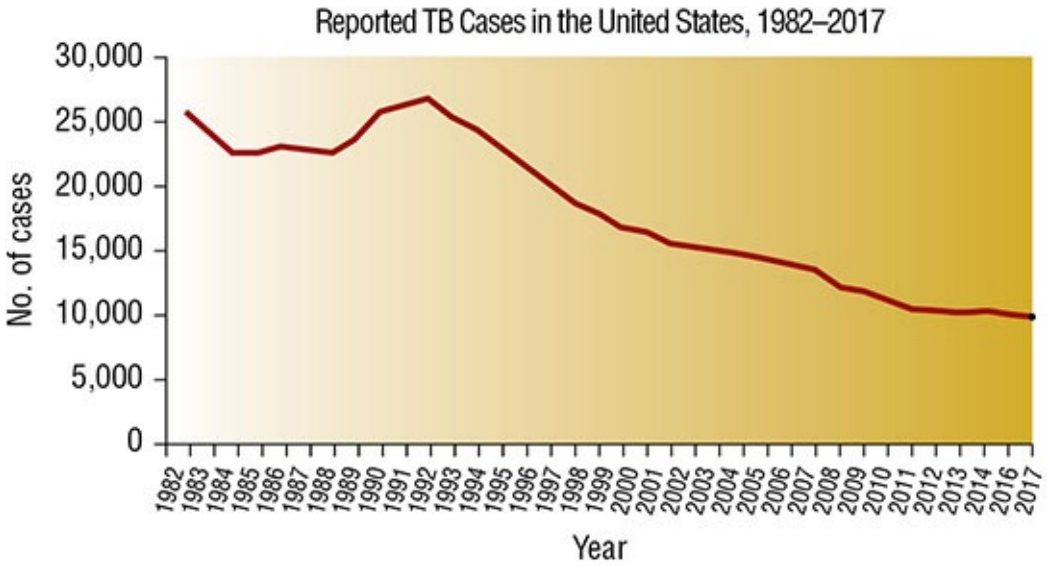


FIGURE 130-1 Reported tuberculosis cases in the United States. (*From the Centers for Disease Control and Prevention (CDC). Reported Tuberculosis in the United States, 2017. Atlanta, GA: US Department of Health and Human Services, CDC; 2018.*)

EPIDEMIOLOGY

Over one-fourth of the world's population is infected by *M. tuberculosis*, and roughly 1.3 million people died from active TB in 2017 despite the fact that it is curable.[1] In the United States, an estimated 9 million people are latently infected with *M. tuberculosis*, meaning that they are not currently sick but that they could fall ill with TB at any time.[2] In 2017, 9,105 new TB cases were reported in the United States, this is 1.6% lower than the cases reported in 2016.[2] The annual incidence of TB in the United States declined by approximately 5% per year from 1953 to 1983.[2] In 1984, this decline slowed, and then the incidence of TB rose from 1988 reaching its peak in 1992. Since 1993, more effective infection control practices and treatment protocols have reduced TB rates significantly as mentioned above. Despite this good news, the eradication of TB from the United States remains difficult. One reason is that TB among immigrants to the United States from high incidence countries remains a source of additional cases.[1,2]

Risk Factors for Infection

The following section will discuss the risk factors for infection including location, race, ethnicity, and human immunodeficiency virus (HIV) coinfection. Risk factors and likelihood of progression from infection to disease will also be discussed.

Location and Place of Birth

California, Florida, New York, and Texas accounted for just under half of the TB cases reported nationally in 2017.[2] Within these states, TB is most prevalent in large urban areas and among those born outside the United States in high TB incidence countries.[2]

The percentage of foreign-born TB patients in the United States has increased annually, reaching 70.1% in 2017.[2] In 2017, over half of foreign-born persons with TB originated from five countries: Mexico, the Philippines, Vietnam, India, and China.[2] Therefore, healthcare workers must consider TB when caring for patients from these countries who experience symptoms such as cough, fever, and weight loss. Furthermore, foreign-born persons account for greater than 90% of the multidrug-resistant (MDR) TB cases in the United States.[2]

The Tuberculosis Genotyping Information Management System (TB GIMS) was launched in 2010 by the CDC to support TB genotyping data and TB control.[2] During 2014 to 2016, the CDC identified genotype clusters among 20.8% of genotyped cases. Genotype clusters are defined as two or more cases with matching genotypes in the same county during a 3-year time period. The percentage of clustered cases among US-born persons with TB was 34.8% and 14.4% among non-US-born persons.[2] The CDC estimates about 13% of US TB cases with genotype data are attributed to recent transmission versus reactivation.[2]

Close contacts of pulmonary TB patients such as family members, coworkers, or coresidents in places such as prisons, shelters, or nursing homes are most likely to become infected. The more prolonged the contact, the greater is the risk, with infection rates as high as 30%.[2,3] TB patients frequently have limited access to healthcare, live in crowded conditions, or are homeless.[2,3] Many patients have histories of alcohol abuse or illicit drug use, and are coinfected with hepatitis B or HIV. These concurrent social and health problems make treating some TB patients particularly difficult.

Race, Ethnicity, Age

2 In the United States, TB disproportionately affects the foreign born and other ethnic minorities. In 2017, Asians had the largest percentage of total TB cases; the incidence rate among Asians was 17.7 per 100,000.[2,4] Since 2014, TB rates have slightly decreased among most ethnic groups.[2,4] The rate among whites have remained stable at 0.5 per 100,000. The TB rates reported in 2016 was 14.7 among foreign-born individuals versus 1.0 among US-born individuals.[2,4]

In 2016, TB was most commonly reported during adulthood at 31% in the 25- to 44-year-age group and the 45-to-64-year-age group. The case rates of TB declined from the previous years in all age groups except among persons aged 15 to 24, which increased from 2.1 to 2.2 per 100,000 from the previous year.[2]

Coinfection with Human Immunodeficiency Virus

3 In patients who have latent TB infection, HIV is the most important risk factor for progressing to active TB, especially among people between ages 25 and 44 years.[2,4,5] TB and HIV to act synergistically within patients and across populations, making each disease worse than it might otherwise be. In 2016, 5.6% of incident cases of TB in the United States (with test result information) were coinfected with HIV.[2,5] These numbers are estimates because laws and regulations in some states prohibit sharing HIV status of TB patients with the TB program. HIV coinfection may not increase the risk of acquiring *M. tuberculosis* infection, but it does increase the likelihood of progression to active disease.[1,5] There is evidence for higher mortality rates in HIV coinfected with MDR and extensively drug-resistant (XDR) TB.[5]

Risk Factors for Disease

Close contacts of pulmonary TB patients such as family members, coworkers, or coresidents in places such as prisons, shelters, or nursing homes are most likely to become infected. The more prolonged the contact, the greater is the risk, with infection rates as high as 30%.[2–4] TB patients frequently have limited access to healthcare, live in crowded conditions, or are homeless.[2–4] Many patients have histories of alcohol abuse or illicit drug use, and are coinfected with hepatitis B or HIV. These concurrent social and health problems make treating some TB patients particularly difficult.

Once infected with *M. tuberculosis*, a person's lifetime risk of active TB is

approximately 10%.[2–4] The greatest risk for active disease occurs during the first 2 years after infection. Children younger than 2 years and adults older than 65 years have two to five times greater risk for active disease compared with other age groups. Patients with underlying immune suppression (eg, renal failure, cancer, and immunosuppressive drug treatment) have 4 to 16 times greater risk than other patients.[2] HIV-infected patients with *M. tuberculosis* infection are 100 times more likely to develop active TB than normal hosts.[2–4] HIV-infected patients have an annual risk of active TB of approximately 10%, rather than a lifetime risk at that rate.[5] Therefore, all patients with HIV infection should be screened for tuberculosis infection, and those known to be infected with *M. tuberculosis* should be tested for HIV infection.

ETIOLOGY

M. tuberculosis is a slender bacillus with a waxy outer layer.[2,6] It is 1 to 4 μm in length, and under the microscope, it is either straight or slightly curved in shape.[6] It does not stain well with Gram stain, so the Ziehl-Neelsen stain or the fluorochrome stain must be used instead.[6] After Ziehl-Neelsen staining with carbol-fuchsin, mycobacteria retain the red color despite acid–alcohol washes. Hence, they are called *acid-fast bacilli* (AFB).[6] On culture, *M. tuberculosis* grows slowly, doubling about every 20 hours. This is slow compared with gram-positive and gram-negative bacteria, which double about every 30 minutes.

Culture and Susceptibility Testing

All clinical specimens suspected of containing mycobacteria should be cultured. Culture is required for species identification and for drug-susceptibility testing.

4 Direct susceptibility testing involves inoculating specialized media with organisms taken directly from a concentrated, smear-positive specimen.[1,6] This approach produces susceptibility results in 2 to 3 weeks. Culture-based phenotypic drug-susceptibility testing methods are currently the primary methods for drug-resistance detection. These methods are time consuming and require sophisticated laboratory infrastructure. Direct susceptibility testing uses critical concentrations of antituberculosis drugs to determine resistance of an isolate. A critical concentration previously established to define the lowest concentration that will inhibit the growth of the isolate. Indirect susceptibility testing involves inoculating the test media with organisms obtained from a pure

culture of the organisms, which can take several more weeks. The most common agar method, known as the *proportion method*, uses the ratio of colony counts on drug-containing agar to that on drug-free agar.[1,6] In the United States, the critical proportion for resistance is 1%. If a drug-containing plate shows 1% or more of the growth seen on a drug-free plate, some of the organisms from the specimen were resistant to that drug. Therefore, it is likely that many of the organisms in the patient also are resistant to that drug, and in general it should not be used to treat that patient.

The proportion method's limitations include many weeks to obtain results, drug degradation during the incubation, and a qualitative result (susceptible or resistant). The newer mycobacterial growth indicator tube (MGIT, Becton Dickson, Sparks, MD) systems use liquid media and detect live mycobacteria in as few as 9 to 14 days.[6,7]

Rapid-identification tests are now available, but cost and care of equipment remain an issue in many parts of the world. Nucleic acid amplifications tests use DNA probes to identify the presence of complementary ribosomal ribonucleic acid (rRNA) for several mycobacterial species.[6,7] Pyrosequencing and PCR is performed on specimens where nucleic acid amplification is positive and when rifampin susceptibility testing is unknown. DNA fingerprinting using restriction-fragment-length polymorphism analysis has been used to identify clusters of cases.[1,7,8] Amplification of the genetic material can be achieved through polymerase chain reaction (PCR), the amplified *M. tuberculosis* direct (MTD) test, and strand-displacement amplification.[7] Thin-layer chromatography, high-performance liquid chromatography for mycolic acid identification, and gas chromatography for short-chain fatty acids (methyl esters) have been used to speciate mycobacterial isolates.[6–9] The Enhanced Amplified *Mycobacterium Tuberculosis* Direct Test (E-MTD) has been approved for use by the US Food and Drug Administration in AFB smear-positive and smear-negative specimen in patients with fewer than 7 days of antimycobacterial therapy and the Gene X-pert MTB/RIF assay in patients with fewer than 3 days of treatment. The Amplicor *Mycobacterium Tuberculosis* Test has been approved for smear-positive samples.[9–12]

The Hain test, a line-probe assay that diagnoses resistance to isoniazid and rifampin by detecting several gene mutations responsible for drug resistance, has also entered into limited clinical use in the United States. The Gene X-pert MTB/RIF test simultaneously identifies *M. tuberculosis* and rapidly determines if resistance to rifampin is present.[9,13] The test has excellent performance in both smear-positive and -negative patients, and high accuracy for determination of

rifampicin resistance.[11] Colorimetric redox indicator and nitrate reduction assays for rapid detection of rifampicin and isoniazid resistance are both inexpensive and have rapid turnaround times of 1 week. Microscopic observation drug-susceptibility assay is simple test using sputum samples to detect characteristic patterns of growth of *M. tuberculosis* and resistance patterns. Time to diagnosis is 7 days and drug susceptibilities are available at the time of diagnosis.[11] Most patients with microscopic observation drug-susceptibility assays are diagnosed within 2 weeks and it is similarly efficient irrespective of bacterial burden.[12]

Other tests are designed to detect common genetic changes associated with drug resistance, such as changes in the *katG* gene associated with isoniazid resistance and the *rpoB* gene associated with rifampin resistance.[5,8,13] Mutations that affect the *rpoB* gene alter the protein structure of the target so that rifampin cannot bind; thus, conferring resistance. Similarly, isoniazid-resistant isolates can be detected by sequencing the *inhA* gene which leads to overproduction of the drug target and mutations in *katG* gene which inhibits activation of INH prodrug. Probe assays do not eliminate the need for conventional culture and susceptibility testing; conventional drug-susceptibility testing is needed to diagnose XDR TB. The decision to use nucleic acid amplification tests should be individualized.

Transmission

M. tuberculosis is transmitted from person to person by coughing or other activities that cause the organism to be aerosolized.[2,3] These particles, called *droplet nuclei*, contain one to three bacilli and are small enough (1-5 mm) to reach the alveolar surface. Approximately 30% of individuals who experience prolonged contact with an infectious TB patient will become infected.

A person with cavitary, pulmonary TB and a cough is considered infectious and may infect greater than 30% of contacts until that person is treated effectively, although this percentage and the absolute number can vary significantly. A person with the uncommon laryngeal form of TB can spread organisms even when talking, so the transmission rates can be even higher.

Beginning in 2018, the National TB Molecular Surveillance Center began performing whole genome sequencing on isolates of *Mycobacterium tuberculosis* gathered from newly diagnosed patients in the United States. Samples are submitted by contracted laboratories and then genotype results are loaded into the system to identify chains of transmission and outbreaks.[8] Public health interventions can be targeted and cases that are the same cluster are likely

to be related and treated similarly.[2]

PATHOPHYSIOLOGY

The following section will discuss the pathophysiology of primary infection, reactivation disease, and the influence of HIV on the pathogenesis of *M. tuberculosis* infections.

Immune Response

T-lymphocyte responses are essential to controlling *M. tuberculosis* infections.[2,3,14,15] In the mouse model, two different T-cell responses—the T-helper type 1 (TH_1) response and the T-helper type 2 (TH_2) response—have been described. The TH_1 response is the preferred response to TB, and the TH_2 response, including the potentially subversive influence of interleukin (IL) 4, is undesirable.[2,14,15] Some workers have argued that this dichotomy is clearer in the mouse model, and in many humans, the T-cell response may be classified as TH_0 (elements of both TH_1 and TH_2).[14] In either case, T lymphocytes activate macrophages that, in turn, engulf and kill mycobacteria. T lymphocytes also destroy immature macrophages that harbor *M. tuberculosis* but are unable to kill the invaders.[14,15] CD4+ cells are the primary T cells involved, with contributions by γ δ T cells and CD8+ T cells.[14] CD4+ T cells produce interferon-γ (INF-γ) and other cytokines, including IL-2 and IL-10, that coordinate the immune response to TB.[14] Because CD4+ cells are depleted in HIV-infected patients, these patients are unable to mount an adequate defense to TB.[14,15]

Although B-cell responses and antibody production can be demonstrated in TB-infected mammals, these humoral responses do not appear to contribute much to the control of TB within the host.[3,14] Tumor necrosis factor-α (TNF-α) and INF-γ are important cytokines involved in coordinating the host's cell-mediated response. Rheumatoid arthritis patients treated with TNF-α inhibitors (such as infliximab) have high rates of reactivation TB.[16] Therefore, patients known to be deficient in the activity of TNF-α or INF-γ should be screened for TB infection and offered appropriate treatment.

M. tuberculosis has several ways of evading or resisting the host immune response.[14,15] In particular, *M. tuberculosis* can inhibit the fusion of lysosomes to phagosomes inside macrophages. This prevents the destructive enzymes found in the lysosomes from getting to the bacilli captured in the phagosomes. This

inhibition of destructive mechanisms allows time for *M. tuberculosis* to escape into the cytoplasm. Virulent *M. tuberculosis* is able to multiply in the macrophage cytoplasm, thus perpetuating their spread. Finally, lipoarabinomannan (LAM), the principal structural polysaccharide of the mycobacterial cell wall, inhibits the host immune response.[14,15] LAM induces immunosuppressive cytokines, thus blocking macrophage activation; additionally, LAM scavenges O_2, thus preventing attack by superoxide anions, hydrogen peroxide, singlet oxygen, and hydroxyl radicals.[14,15] These survival mechanisms make *M. tuberculosis* a particularly difficult organism to control. Any defects in the host immune system make it likely that *M. tuberculosis* will not be controlled and that active disease will ensue.

Primary Infection

Primary infection usually results from inhaling airborne particles that contain *M. tuberculosis*.[3,15] The progression to clinical disease depends on three factors: (a) the number of *M. tuberculosis* organisms inhaled (infecting dose), (b) the virulence of these organisms, and (c) the host's cell-mediated immune response.[3,15,17] At the alveolar surface, the bacilli that were delivered by the droplet nuclei are ingested by pulmonary macrophages. If these macrophages inhibit or kill the bacilli, infection is aborted.[15] If the macrophages cannot do this, the organisms continue to multiply. The macrophages eventually rupture, releasing many bacilli, and these mycobacteria are then phagocytized by other macrophages. This cycle continues over several weeks until the host is able to mount a more coordinated response.[15] During this early phase of infection, *M. tuberculosis* multiplies logarithmically.[15]

Some of the intracellular organisms are transported by the macrophages to regional lymph nodes in the hilar, mediastinal, and retroperitoneal areas. The cycle of phagocytosis and cell rupture continues. During lymph node involvement, the mycobacteria may be held in check. More frequently, *M. tuberculosis* spreads throughout the body through the bloodstream.[3,15] When this intravascular dissemination occurs, *M. tuberculosis* can infect any tissue or organ in the body. Most commonly, *M. tuberculosis* infects the posterior apical region of the lungs. This may be so because of the high oxygen content, and it may be because of a less vigorous immune response in this area.

After about 3 weeks of infection, T lymphocytes are presented with *M. tuberculosis* antigens. These T cells become activated and begin to secrete INF-γ and the other cytokines noted earlier. The processes described in the Immune

Response section above then begin to occur. First, T lymphocytes stimulate macrophages to become bactericidal.[15] Large numbers of activated microbicidal macrophages surround the solid caseous (cheese-like) tuberculous foci (the necrotic area of infection).[15] This process of creating activated microbicidal macrophages is known as cell-mediated immunity (CMI).[15]

At the same time that CMI occurs, delayed-type hypersensitivity (DTH) also develops through the activation and multiplication of T lymphocytes. DTH refers to the cytotoxic immune process that kills nonactivated immature macrophages that are permitting intracellular bacillary replication.[15] These immature macrophages are killed when the T lymphocytes initiate Fas-mediated apoptosis (programmed cell death).[15] The bacilli released from the immature macrophages then are killed by the activated macrophages.[15]

By this time (more than 3 weeks), in most recently infected individuals, macrophages have begun to form granulomas to contain the organisms. In a typical tuberculous granuloma, activated macrophages accumulate around a caseous lesion and prevent its further extension.[15] At this point, the infection is largely under control, and bacillary replication falls off dramatically. Depending on the inflammatory response, tissue necrosis and calcification of the infection site plus the regional lymph nodes may occur.

Over 1 to 3 months, activated lymphocytes reach an adequate number, and tissue hypersensitivity results. In practical terms, this is the reason why tests to diagnose latent TB infection, purified protein derivative (PPD) skin test, and the INF-*γ* release assays take between 2 and 12 weeks to become positive. Any remaining mycobacteria are believed to reside primarily within granulomas or within macrophages that have avoided detection and lysis, although some residual bacilli have been found in various types of cells.[3,14]

Approximately 90% of infected patients have no further clinical manifestations. Most patients only show a positive skin test (70%), whereas some also have radiographic evidence of stable granulomas. This radiodense area on chest radiograph is called a *Ghon's complex*. Approximately 5% of patients (usually children, the elderly, and the immunocompromised) experience "progressive primary" disease that occurs before skin test conversion, which presents as a progressive pneumonia, usually in the lower lobes.[18] Disease frequently spreads, leading to meningitis and other severe forms of TB.[18] Because of this risk of severe disease, very young, elderly, and immunocompromised patients, including those with HIV, should be evaluated and treated for latent or active TB.

Reactivation Disease

6 Roughly 10% of infected patients develop reactivation disease at some point in their lives. Nearly half of these cases occur within 2 years of infection.[3,15] In the United States, most cases of TB are believed to result from reactivation. Reinfection is uncommon in the United States because of the low rate of exposure and because previously sensitized individuals possess some degree of immunity to reinfection.[3,15] Exceptions include patients coinfected with HIV who live in areas of higher exposure to *M. tuberculosis*.

The apices of the lungs are the most common sites for reactivation (85% of cases).[3] For reasons that are not entirely known (waning cellular immunity, loss of specific T-cell clones, blocking antibody), organisms within granulomas emerge and begin multiplying extracellularly.[15] The inflammatory response produces caseating granulomas, which eventually will liquefy and spread locally, leading to the formation of a hole (cavity) in the lungs.

The immune response contributes to the severity of the lung damage, and DTH allows for intracellular mycobacterial multiplication.[14,15] In addition, there is "innocent bystander" killing of host cells and locally thrombosed blood vessels.[15] The killing of mycobacteria, macrophages, and neutrophils that have entered the battle releases cytokines and lysozymes into the infectious foci. This toxic mixture can be too much for the surrounding alveoli and airway cells, causing regional necrosis and structural collapse.[3,15] These unstable foci liquefy, spreading the infection to neighboring areas of the lung, creating a cavity. Some of this necrotic material is coughed out, producing droplet nuclei. Bacterial counts in the cavities can be as high as 10^8 per milliliter (or 10^{11}/L) of cavitary fluid. Partial healing may result from fibrosis, but these lesions remain unstable and may continue to expand.[3,15] If left untreated, pulmonary TB continues to destroy the lungs, resulting in hypoxia, respiratory acidosis, and eventually death.

Extrapulmonary and Miliary Tuberculosis

Caseating granulomas at extrapulmonary sites can undergo liquefaction, releasing tubercle bacilli and causing symptomatic disease.[3] Extrapulmonary TB without concurrent pulmonary disease is uncommon in normal hosts but more common in HIV-infected patients. Because of these unusual presentations, the diagnosis of TB is difficult and often delayed in immunocompromised hosts.[3] Lymphatic and pleural diseases are the most common forms of extrapulmonary

TB, followed by bone, joint, genitourinary, meningeal, and other forms.[3] Occasionally, a massive inoculum of organisms enters the bloodstream, causing a widely disseminated form of the disease known as *miliary TB*. It is named for the millet seed appearance of the small granulomas seen on chest radiographs, and it can be rapidly fatal.[14] Miliary TB is a medical emergency requiring immediate treatment.

Influence of Human Immunodeficiency Virus Infection on Pathogenesis

3 HIV infection is the strongest single risk factor for progressing to active TB.[3,14] As CD4+ lymphocytes multiply in response to the mycobacterial infection, HIV multiplies within these cells and selectively destroys them. In turn, the TB-fighting lymphocytes are depleted.[14] This vicious cycle puts HIV-infected patients at 100 times the risk of active TB compared with HIV-negative people.[19,20] In addition, the combination of HIV infection and certain social behaviors increases the risk of newly acquired TB. In select areas of the United States during the resurgence of TB during the early 1990s, up to 50% of new TB cases were the result of recent infection, particularly among HIV-infected individuals.[1,19,20]

As mycobacteria spread throughout the body, HIV replication accelerates in lymphocytes and macrophages. This leads to progression of HIV disease.[14,19,20] HIV-infected patients who are infected with TB deteriorate more rapidly unless they receive antimycobacterial chemotherapy.[19,20] Most clinicians now recommend integrated antiretroviral therapy (ART) beginning TB treatment first, and then beginning HIV treatment within 2 to 12 weeks.[21–23] However, the timing needs to be individualized based on degree of immunosuppression from HIV and the patient's tolerance of the treatment regimen. Immune reconstitution inflammatory syndrome or a paradoxical worsening of TB can occur, especially in patients with more severe immunosuppression; this appears to result from a reinvigorated inflammatory response to TB.[21,23] HIV-positive patients should be screened for tuberculous infection or disease soon after they are shown to be HIV-positive.[21,22]

CLINICAL PRESENTATION

The classical presentation of TB is weight loss, fatigue, a productive cough,

fever, and night sweats. The onset of TB may be gradual, and the diagnosis may not be considered until a chest radiograph is performed. Unfortunately, many patients do not seek medical attention until more dramatic symptoms, such as hemoptysis, occur. At this point, patients typically have large cavitary lesions in the lungs. These cavities are loaded with *M. tuberculosis*. Expectoration or swallowing of infected sputum may spread the disease to other areas of the body.[1,3,17] Physical examination is nonspecific but suggestive of progressive pulmonary disease.

Human Immunodeficiency Virus

5 Patients coinfected with HIV may have atypical presentations.[1,3,17] As their CD4+ counts decline, HIV-positive patients are less likely to have positive skin tests, cavitary lesions, or fever. Pulmonary radiographic findings may be minimal or absent. HIV-positive patients have a higher incidence of extrapulmonary TB and are more likely to present with progressive primary disease. Because their symptoms are not specific to TB, a thorough workup for TB is essential.[3,14,15]

Extrapulmonary

Extrapulmonary TB typically presents as a slowly progressive decline in organ function.[3,17] Patients may have low-grade fever and other constitutional symptoms. Patients with genitourinary TB may present with sterile pyuria and hematuria. Lymphadenitis often involves the cervical and supraclavicular nodes and may appear as a neck mass with spontaneous drainage. Tuberculous arthritis and osteomyelitis occur most commonly in the elderly and usually affect the lower spine and weight-bearing joints. TB of the spine is known as *Pott's disease*.[3] Abnormal behavior, headaches, or convulsions suggest tuberculous meningitis. Involvement of the peritoneum, pericardium, larynx, and adrenal glands also occurs.[3,17]

CLINICAL PRESENTATION Tuberculosis

Signs and Symptoms

- Patients typically present with cough weight loss, fatigue, fever, and

night sweats.[3,14,15]

- Frank hemoptysis usually occurs late in the course of disease but may present earlier.

Physical Examination

- Dullness to chest percussion, rales, and increased vocal fremitus are observed frequently on auscultation but a normal lung examination is very common compared to the degree of radiological lung involvement.
- Patient is usually thin with evidence or recent weight loss.

Laboratory Tests

- Moderate elevations in the white blood cell (WBC) count with a lymphocyte predominance.
- High platelet count (thrombocytosis) and mild-to-moderate anemia are common.

Diagnostic Considerations

- Positive-sputum smear
- Fiber-optic bronchoscopy (if sputum tests are inconclusive and suspicion is high)

Chest Radiograph

- Patchy or nodular infiltrates in the apical areas of the upper lobes or the superior segment of the lower lobes.[3,14,15]
- Cavitation that may show air–fluid levels as the infection progresses.

The Elderly

5 TB in the elderly is easily confused with other respiratory diseases. Many clinical findings are muted or absent altogether. Compared with younger patients, TB in the elderly is far less likely to present with positive skin tests, fevers, night sweats, sputum production, or hemoptysis.[2,19,24] Weight loss may occur but is nonspecific. In contrast, mental status changes are twice as common

in the elderly, and mortality is six times higher.[3,17] TB is a preventable cause of death in the elderly that should not be overlooked.

Children

5 TB in children, especially those younger than 12 years, may present as a typical bacterial pneumonia and is called *progressive primary TB*.[17,18] Clinical disease often begins 1 to 2 months after exposure and precedes skin-test positivity. Unlike adults, pulmonary TB in children often involves the lower and middle lobes.[17,18] Dissemination to the lymph nodes, GI and genitourinary tracts, bone marrow, and meninges is common. Because of delays in recruitment of cellular immunity, cavitary disease is infrequent, and the number of organisms present typically is smaller than in an adult. Because cavitary lesions are uncommon, children do not spread TB readily. However, TB can be rapidly fatal in a child, and it requires prompt chemotherapy.

DIAGNOSIS

The following section focuses on diagnostic testing for infection with *M. tuberculosis*. If active disease is suspected based on clinical presentation, additional diagnostic tests are also reviewed to confirm active disease.

Diagnostic Testing

The key to stopping the spread of TB is early identification of infected individuals.[3,17] **Table 130-1** lists the populations most likely to benefit from testing (column 1 patients are at highest risk for TB, followed by those in column 2). Members of these high-risk groups should be tested for TB infection and educated about the disease.

TABLE 130-1 Criteria For Tuberculosis Positivity

Reaction ≥5 mm of Induration	Reaction ≥10 mm of Induration	Reaction ≥15 mm of Induration
HIV-infected persons	Recent immigrants (ie, within the last 5 years) from high-prevalence countries	Persons with no risk factors for TB
A recent contact of a person with TB disease	Injection drug users	
Fibrotic changes on chest radiograph consistent with prior TB	Residents and employees* of the following high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other healthcare facilities, residential facilities for patients with AIDS, and homeless shelters	
Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of 15 mg/day or more of prednisone for 1 month or longer, taking TNF-α antagonists)†	Mycobacteriology laboratory personnel, persons with the following clinical conditions that place them at high risk: silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders, other specific malignancies, gastrectomy, and jejunoileal bypass	
	Children younger than 5 years of age or infants, children, and adolescents exposed to adults at high risk	

Interpretation of IGRA Results

The interpretation of IGRAs is based on the amount of IFN-γ, in T-SPOT®.TB. An IGRA is recommended over a TST in persons at least 5 years of age who are likely to have *M. tuberculosis* infection; who are at low or moderate risk of the disease progressing; in whom it has been determined that LTBI testing is necessary; and who have been vaccinated against Calmette-Guerin or are not likely to return for follow up after a TST. The TST is a viable second option in certain circumstances, such as if an IGRA is unavailable. Laboratories should provide both the qualitative and quantitative results.

- Qualitative results are reported positive, negative, indeterminate, or borderline.
- Quantitative results are reported as numerical values that include a response to the TB antigen and two controls, nil and mitogen.
- Quantitative results may be useful for clinical decision making in individual cases, in combination with risk factors.

*For persons who are otherwise at low risk and who are tested at the start of employment, a reaction of ≥15 mm induration is considered positive.

†Risk of TB for patients treated with corticosteroids increases with higher dose and longer duration.

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; TB, tuberculosis.

Source: Centers for Disease Control and Prevention. Screening for tuberculosis and tuberculosis infection in high-risk populations: recommendations of the Advisory Council for the Elimination of Tuberculosis. M.M.W.R. 1995;44(No. RR-11):19–34.

The Mantoux test is a quantitative TB skin test that uses tuberculin PPD. The standard 5-tuberculin-unit PPD dose is placed intracutaneously on the volar aspect of the forearm with a 26- or 27-gauge needle.[3,17,24] This injection should produce a small, raised, blanched wheal. An experienced professional should read the test in 48 to 72 hours. The area of induration (the “bump”) is the important end point, not the area of redness. Table 130-1 lists the criteria for interpretation.[3,17,24] The Centers for Disease Control and Prevention (CDC) does not recommend the routine use of anergy panels.[24–26] Aplisol and Tubersol 5-tuberculin-unit products are available commercially and are similar in sensitivity, specificity, and reactivity. It is important, however, to use one product and notify appropriate users when switching between products.[27]

The “booster effect” occurs for patients who do not respond to an initial skin

test but show a positive reaction if retested about a week later or longer.[17,26] Patients with past *M. tuberculosis* infection and some patients with past immunization with bacillus Calmette-Guérin (BCG) vaccine or past infection with other mycobacteria may "boost" with a second skin test. Individuals who require periodic skin testing, such as healthcare workers, should receive a two-stage test initially.[17,26,28] Once they are shown to be skin-test negative, any positive skin test later shows recent infection, and this requires an evaluation to consider treatment.

The PPD skin test is an imperfect diagnostic tool. Up to 20% of patients with active TB are falsely skin-test negative, presumably because they may be immunocompromised.[14,26] False-positive results are more common in low-risk patients and those recently vaccinated with BCG. Despite BCG vaccination, one should not ignore a positive PPD result especially if the induration is more than 15 mm.[24] These patients require careful evaluation for active disease, and they may be offered preventive treatment because many come from areas where TB infection is common.

Interferon-*γ* release assays (IGRA) measure the release of INF-*γ* in blood in response to the TB antigens.[29] They may provide quick and specific results for identifying *M. tuberculosis*. IGRAs do not trigger a booster effect and are more specific for testing *M. tuberculosis* than the PPD. The QuantiFERON-TB Gold test (QFT-G) is an enzyme-linked immunosorbent assay (ELISA) and the T-SPOT.®TB is an enzyme-linked immunospot assay.[29,30] Both tests can be used for diagnosing latent TB infection (LTBI) and TB disease caused by *M. tuberculosis*. However, these are the tests designed to diagnose LTBI and are not to be used to confirm or reject a diagnosis of active TB disease. For active TB, the IGRAs provide supporting evidence for the diagnosis but need to be interpreted in light of other evidence of active TB disease such as epidemiological risk factors and other studies. The antigenic proteins are absent from BCG vaccine strains and from most non-TB mycobacteria. Therefore, QFT-G does not trigger a booster effect and is more specific for testing of *M. tuberculosis* than the PPD. Although these tests can provide results to diagnose both latent infection and disease, they cannot differentiate between the two. Results are available within 24 hours, instead of the 2 to 3 days required for the traditional PPD skin test; and the patient does not have to return to the clinic as required by the PPD skin test. The CDC has approved the use of these tests in all circumstances in which the PPD is currently used. IGRAs may be preferred for testing in patients who are suspected not to return for follow-up PPD reads or in patients who have received the BCG vaccine. Interferon-γ release assay (IGRA)

is recommended over a tuberculin skin test or PPD in individuals 5 years or older who meet the following criteria: (1) are likely to be infected with *M. tuberculosis*, (2) have a low-to-intermediate risk of disease progression, (3) testing for LTBI is warranted, (4) history of BCG vaccination, and (5) are unlikely to return to have their PPD read.[31] IGRA rather than PPD is also suggested in all other individuals who are likely to be infected with *M. tuberculosis*, who have a low-to-intermediate risk of disease progression, and in whom testing for LTBI is warranted.[31] There are insufficient data to recommend a preference for either a PPD or IGRA as the first-line diagnostic test in patients likely to be infected with *M. tuberculosis*, who have a high risk of progression to disease, and in whom it is determined that diagnostic testing is warranted.[31] **Figure 130-2** summarizes the recommendations for testing for latent tuberculosis infections.

Group	Testing Strategy	Considerations
Likely to be Infected **High** Risk of Progression (TST ≥ 5 mM)	**Adults** **Acceptable:** IGRA OR TST Consider dual testing where a positive result from either result would be considered **positive** **Children ≤ 5 years of age** **Acceptable:** TST **Acceptable:** IGRA OR TST Consider dual testing where a positive result from either result would be considered **positive**[1]	Prevalence of BCG vaccination Expertise of staff and/or laboratory Test availability Patient perceptions Staff perceptions Programmatic concerns
Likely to be Infected **Low** to **Intermediate** Risk of Progression (TST ≥ 10 mM)	**Preferred:** IGRA where available **Acceptable:** IGRA OR TST	
Unlikely to be Infected (TST > 15 mM)	**Testing for LTBI is not recommended** **If necessary:** **Preferred:** IGRA where available. **Acceptable:** Either IGRA OR TST **For serial testing:** **Acceptable:** Either IGRA OR TST Consider repeat or dual testing where a negative result from either would be considered **negative**[2]	

FIGURE 130-2 Summary of recommendations for testing for latent tuberculosis infection (LTBI)[1]. Performing a second diagnostic test when the initial test is a negative is a strategy to increase sensitivity. This may reduce specifically, but the panel decided that this is an acceptable trade off in situations in which the consequences of missing LTBI exceed the consequences of inappropriate therapy. [2]Performing a confirmatory test following an initial positive result is based upon both the evidence that false positive results are common among individuals who are unlikely to be infected with *Mycobacterium tuberculosis* and the committee's presumption that performing a second test on those patients whose initial test was positive will help identify initial false positive results. (*Adapted from Jamil SM, et al. Diagnosis of tuberculosis in adults and children. Ann Am Thorac Soc Vol 14, No 2, pp 275–278, Feb 2017.*)

The sensitivity for young children (younger than 5 years) and in immunocompromised patients has not clearly established.[29,30,32,33,34] A PPD test is recommended in healthy children (younger than 5 years) for who diagnostic testing is warranted. The American Academy of Pediatrics recommends IGRAs in place of PPD skin test in immunocompetent children aged 5 years or older who have received BCG vaccination to confirm TB infection.[32] However, an increasing number of experts are using the IGRAs in children 3 years or older.

IGRAs perform similarly to the PPD in detecting TB in HIV-infected patients with LTBI. Both PPD and IGRA have suboptimal sensitivity for active TB especially in the severely immunocompromised.[29,35]

Culture and Staining

When active TB is suspected, attempts should be made to isolate *M. tuberculosis* from the site of infection.[3,17,26] Sputum collected in the morning usually has the highest yield.[3,17] Daily sputum collection over three consecutive days is recommended. Microscopic examination is the most rapid and inexpensive TB diagnostic tool. After staining, microscopic examination ("smear") detects about 8,000 to 10,000 organisms per milliliter (8×10^6/L to 10×10^6/L) of specimen, so a patient can be "smear-negative" but still grow *M. tuberculosis* on culture. Microscopic examination also cannot determine which of the more than 100 mycobacterial species is present or whether the organisms in the original samples were alive or dead.[1,6]

For patients unable to expectorate, sputum induction with aerosolized hypertonic saline may produce a diagnostic sample. Bronchoscopy, in older children, or aspiration of gastric fluid via a nasogastric tube, in children (5 years or younger), may be attempted for select patients.[17] For patients with suspected extrapulmonary TB, samples of draining fluid, biopsies of the infected site, or both may be attempted. Blood cultures are positive occasionally, especially in acquired immunodeficiency syndrome (AIDS) patients.[17,36]

TREATMENT

Drugs used in the treatment of active disease are divided into first-line and second-line agents. First-line agents should be the preferred options unless susceptibility results dictate otherwise. Treatment in special populations is also addressed.

Desired Outcome

The primary desired outcomes during the treatment of TB are:

1. Rapid identification of a new TB case.
2. Initiation of specific anti-TB treatment.
3. Eradication of *M. tuberculosis* infection.
4. Achievement of a noninfectious state in the patient, thus ending isolation.
5. Prevention of the development of resistance.
6. Adherence to the treatment regimen by the patient.
7. Cure of the patient as quickly as possible (generally at least 6 months of treatment).

It is also important that patients with active disease are isolated to prevent spread of the disease and that appropriate samples for smears and cultures are collected. Secondary goals are identification of the index case that infected the patient, identification of all persons infected by both the index case and the new case of TB ("contact investigation"), and completion of appropriate treatments for those individuals.

General Approaches

Drug treatment is the cornerstone of TB management.[3,37] Monotherapy can be used only for infected patients who do not have active TB (latent infection, as shown by a positive skin test or positive IGRA). Once active disease is present, a minimum of two drugs, and generally three or four drugs, must be used simultaneously.[37] The duration of treatment depends on the condition of the host, extent of disease, presence of drug resistance, and tolerance of medications. The shortest duration of treatment generally is 6 months, and 18 to 24 months of treatment may be necessary for cases of MDR-TB.[37] Because the duration of treatment is so long and because many patients feel better after a few weeks of treatment, careful follow-up is required. Directly observed therapy (DOT) by a healthcare worker is a cost-effective way to ensure completion of treatment and is considered the standard of care.[37–39]

Principles for Treating Latent Infection and for Treating Disease

Asymptomatic patients with tuberculous infection have a bacillary load of about 10^3 organisms, compared with 10^{11} organisms in a patient with cavitary pulmonary TB.[3,7] As the number of organisms increases, the likelihood of naturally occurring drug-resistant mutants also increases. Naturally occurring resistant mutants are found at rates of 1 in 10^6 to 1 in 10^8 organisms for the anti-TB drugs.[3,7,37] When treating asymptomatic latent infection with isoniazid monotherapy, the risk of selecting out isoniazid-resistant organisms is low. The isoniazid mutation rate is about 1 in 10^6, but only about 10^3 organisms are present in the body. In contrast, the risk of selecting out isoniazid-resistant organisms is unacceptably high for patients with cavitary TB. One can prevent selection of these resistant mutants by adding more drugs because the rates for resistance mutations to multiple drugs are additive functions of the individual rates. For example, only 1 in 10^{13} organisms would be naturally resistant to both isoniazid (1 in 10^6) and rifampin (1 in 10^7).[3,7,37] It is unlikely that such rare organisms are present in a previously untreated patient.

Combination chemotherapy is required for treating active TB disease. The patient should receive at least two drugs to which the isolate is susceptible, and, generally, four drugs are given at the outset of treatment. Rifampin and isoniazid are the best drugs for preventing drug resistance, followed by ethambutol, streptomycin, and pyrazinamide.[3,7,37,40]

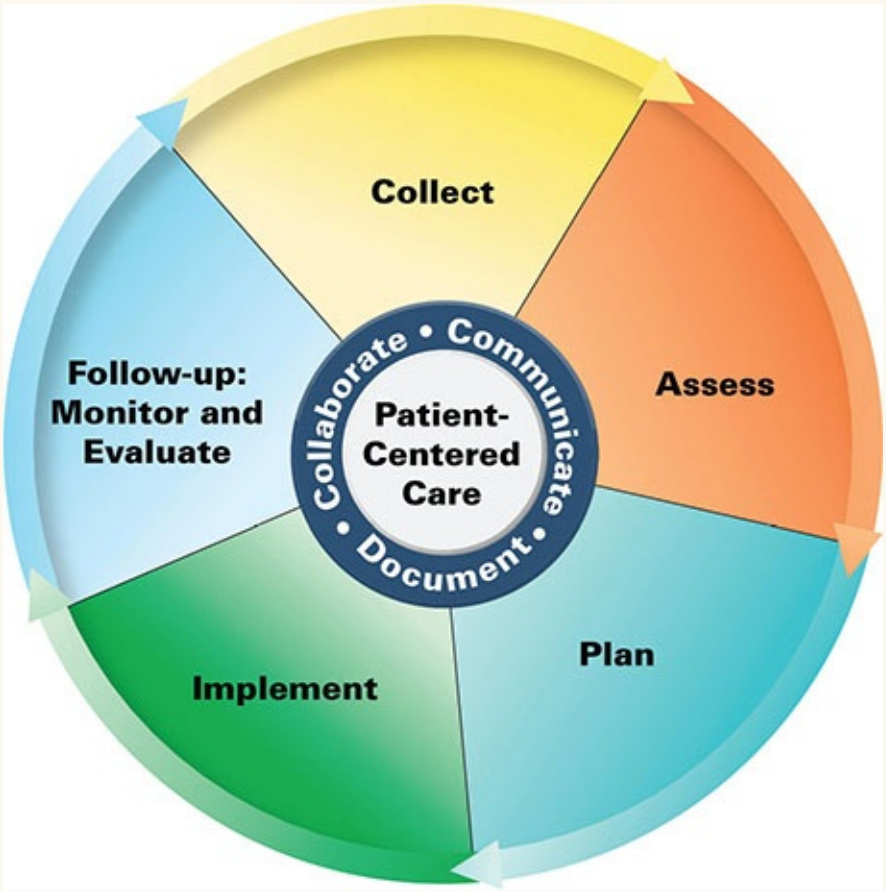
Three subpopulations of mycobacteria are proposed to exist within the body, and each appears to respond to certain drugs.[7,37] Most numerous are the extracellular, rapidly dividing bacteria, often found within cavities (about 10^7 to 10^9 organisms). These are killed most readily by isoniazid, followed by rifampin, streptomycin, and the other drugs. A second group resides within caseating granulomas (possibly 10^5 to 10^7 organisms). These organisms appear to be in a semidormant state, with occasional bursts of metabolic activity. Pyrazinamide, through its conversion within *M. tuberculosis* to pyrazinoic acid, appears most active against these organisms. Rifampin and isoniazid also may be active against this subpopulation. The third subset is the intracellular mycobacteria present within macrophages (10^4 to 10^6). Rifampin, isoniazid, and the quinolones appear to be most active against intracellular *M. tuberculosis*. While this appears to explain what happens during the treatment of TB, there is no practical way to quantitate these populations within a given patient.

Nonpharmacologic Therapy

7 Nonpharmacologic interventions aim to (a) prevent the spread of TB, (b) find where TB has already spread using contact investigation, and (c) replenish the weakened (consumptive) patient to a state of normal weight and well-being. The first two items are performed by public health departments. Clinicians involved in the treatment of TB should verify that the local health department has been notified of all new cases of TB.

Workers in hospitals and other institutions must prevent the spread of TB within their facilities.[7,24,27] All such workers should learn and follow each institution's infection control guidelines. This includes using personal protective equipment, including properly fitted respirators, and closing doors to "negative-pressure" rooms. These hospital isolation rooms draw air in from surrounding areas rather than blowing air (and *M. tuberculosis*) into these surrounding areas. The air from the isolation room may be treated with ultraviolet lights and then vented safely outside. However, these isolation rooms work properly only if the door is closed.

Debilitated TB patients may require therapy for other medical problems, including substance abuse and HIV infection, and some may need nutritional support. Therefore, clinicians involved in substance abuse rehabilitation and nutritional support services should be familiar with the needs of TB patients. Surgery may be needed to remove destroyed lung tissue, space-occupying infected lesions (*tuberculomas*), and certain extrapulmonary lesions.[37] BCG is the only clinically relevant vaccine for TB in use today. Although it is one of the most commonly administered vaccines in history, it is of limited value, and cannot prevent infection by *M. tuberculosis*. BCG (discussed further) may prevent extreme forms of TB in infants.[37]



Patient Care Process for Active Tuberculosis

Collect

- Patient characteristics (eg, age, sex, ethnicity)
- Patient medical history (medical risk factors, eg, immunocompromised, HIV, tobacco/ethanol/IV drug use)
- Social history (eg, living conditions, recent contacts)
- Current medications including prescription and nonprescription medicines, herbal products
- Information and history about patients adherence to medications
- History of clinical signs and symptoms (weight loss, cough, hemoptysis)
- Objective data

- Sputum smears/culture
- Chest x-ray
- Tuberculin skin test/Interferon-γ release assays
- Pertinent labs (WBC, platelets, serum creatinine, LFTs)

Assess

- Patient's potential for risk of transmission
- Risk of mycobacterial resistance
- Risk of drug malabsorption/drug interactions
- Need for therapeutic drug monitoring
- Immune status
- Ability/willingness to be adherent to prescribed regimen
- Psychological status to determine understanding and following instructions for adherence; need for directly observed therapy
- Ability/willingness to maintain follow-up

Plan*

- Devise a drug-therapy regimen with healthcare team to include most appropriate anti-tuberculosis agents, dose, route, frequency, and duration (see Tables 130-3 and 130-4)
- Monitoring parameters including efficacy (eg, sputum smears) and safety (eg, LFTs, neuropathy); frequency and timing of follow-up (see Table 130-7)
- Patient education (eg, purpose of treatment, infection control, drug-specific information, importance of compliance/legal ramifications and risk of noncompliance)

Implement

- Provide patient education regarding all elements of treatment plan and goals
- Ensure patient understanding of risk of transmission and importance of adherence

- Schedule follow-up (eg, adherence assessment, adverse effects, response to treatment)

Follow-up: Monitor and Evaluate

- Monthly clinic evaluation
- Objective data
  - Sputum smears
  - Chest x-ray results
  - Pertinent labs
- Determine response to therapy
  - Clinical response (cough, fever, night sweats)
  - Culture results
- Need for therapeutic drug monitoring
- Presence of adverse effects
- Patient adherence to treatment plan
  - Tablet/Capsule counts for compliance or attending directly observed treatment.

**Collaborate with patient, caregivers, and other healthcare professionals.*

Pharmacologic Therapy

Treating Latent Infection

Isoniazid is the traditional standard drug for treating LTBI.[24,37] Generally, isoniazid alone is given for 9 months. The treatment of LTBI reduces a person's lifetime risk of active TB from approximately 10% to approximately 1%. Because TB is spread easily through the air, each case prevented also prevents a second wave of cases that each prevented case would have produced. The treatment of LTBI has been called *prophylaxis*. **Table 130-2** lists the LTBI treatment options.

TABLE 130-2 Choosing the most effective treatment of LTBI

Drug	Duration	Dose	Frequency	Comments
Isoniazid	9 months	Adult: 5 mg/kg Children: 10-20 mg/kg*	Daily	In HIV-infected patients, isoniazid may be administered concurrently with nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors, or non-NRTIs (NNRTIs) Preferred regimen in children 2-11 years
	9 months	Adult: 15 mg/kg Children: 20-40 mg/kg*	Twice weekly†	Directly observed treatment (DOT) must be used with twice-weekly dosing
	6 months	Adult: 5 mg/kg Children: Not recommended	Daily	Treatment for LTBI for 6 months rather than 9 months may be more cost-effective and result in greater adherence by patients
	6 months	Adult: 15 mg/kg Children: Not recommended	Twice weekly†	Directly observed treatment (DOT) must be used with twice-weekly dosing
Isoniazid and Rifapentine	3 months	Rifapentine 10.0-14.0 kg: 300 mg 14.1-25.0 kg: 450 mg 25.1-32.0 kg: 600 mg 32.1-49.9 kg: 750 mg ≥50.0 kg: 900 mg	Once weekly†	Equal alternative to 9 months of daily isoniazid for otherwise healthy patients age >12 years DOT is recommended Not recommended for children <2 years; HIV-infected patients taking antiretroviral therapy, presumed resistance, pregnant women or women expecting to become pregnant during the treatment period Directly observed treatment (DOT) must be used
Rifampin	4 months	Adult: 10 mg/kg Children: 15-20 mg/kg‹	Daily	For persons who are contacts of patients with isoniazid-resistant rifampin-susceptible Can be considered for persons who cannot tolerate isoniazid or who have been ex-posed to isoniazid-resistant TB Rifampin should not be used to treat HIV-infected person taking some combinations of ART.

*The American Academy of Pediatrics recommends and INH dosage of 10-15 mg/kg for the daily regiment and 20-30 mg/kg for twice weekly regimen.

‹ In the United States, the recommended regimen for the treatment LTBI in children is a 9-month course of isoniazid. For the treatment of LTBI in infants, children, and adolescents when isoniazid could not be tolerated or the child has had contact with a case patient infected with an isoniazid resistant but rifamycin susceptible organism, the American Academy of Pediatrics recommends 6 months of daily rifampin (180 doses) at a dosage of 10 mg/kg.

†Intermittent regimens must be provided via directly observed therapy (DOT), ie, healthcare worker observes the ingestion of medication.

Source: Adapted from Latent tuberculosis infection: A guide for primary health care providers. US Department of Health and Human Services/CDC. Atlanta, GA, 2013.

Because young children, the elderly, and HIV-positive patients are at greater risk of active disease once infected with *M. tuberculosis*, they require careful evaluation. Once active TB is ruled out, they should receive treatment for latent infection.[24,37]

The keys to successful treatment of LTBI are (a) infection by an isoniazid-susceptible isolate, (b) adherence to the regimen, and (c) no exogenous reinfection.[24] Isoniazid adult doses are usually 300 mg daily (5-10 mg/kg of body weight)[37] (see Table 130-2). Lower doses are less effective.[24,41,42] Isoniazid should be given on an empty stomach, and antacids should be avoided within 2 hours of dosing. Rifampin 600 mg daily for 4 months can be used when isoniazid resistance is suspected or when the patient cannot tolerate

isoniazid.[24,37] There is a growing body of evidence that 4 months of rifampin may be a safer and more cost-effective alternative to 9 months of isoniazid. Four months of rifampin was significantly cheaper per patient completing treatment because of better completion and fewer adverse events.[43] The combination of pyrazinamide plus rifampin is no longer recommended because of higher than expected rates of hepatotoxicity. Rifabutin 300 mg daily might be substituted for rifampin for patients at high risk of drug interactions. When resistance to isoniazid and rifampin is suspected in the isolate causing infection, there are no randomized controlled trials to prove what regimen should be used to treat LTBI among contacts.[24,37] However, a course of 12-month regimen of a fluoroquinolone was effective in reducing the incidence of progression to active TB disease for MDR-TB contacts.[44] Regimens that *might* be effective include ethambutol plus levofloxacin, but data regarding efficacy are lacking.

A randomized controlled trial compared 12 weeks of once-weekly isoniazid and rifapentine by DOT with daily self-administered isoniazid for 9 months.[45] This study, with over 8,000 participants, showed that the 12 weeks of weekly isoniazid and rifapentine given by DOT was not inferior in efficacy to 9 months of self-administered isoniazid, had a significantly higher completion rate (82% vs 69%), and was associated with fewer grade 3 or 4 adverse reactions (1.6% vs 3%).[45] Hypersensitivity reactions were more common with the isoniazid/rifapentine regimen and close clinical follow-up should be undertaken while experience is gained with this new regimen for LTBI therapy. The CDC now recommends the 12-week isoniazid/rifapentine regimen as an equal alternative to 9 months of daily isoniazid for treating LTBI in otherwise healthy patients aged older than or 12 years who have a predictive factor for greater likelihood of TB developing, which included recent exposure to contagious TB, conversion from negative to positive on an indirect test for infection (ie, IGRA or tuberculin skin test), and radiographic findings of healed pulmonary TB.[46] HIV-infected patients who are otherwise healthy and are not taking antiretroviral medications are also included in this category. However, precautions should be taken as HIV-infected patients are more likely to have extrapulmonary TB or pulmonary TB with normal findings on chest radiograph. For recent skin-test converters of all ages, the risk of active TB outweighs the risk for drug toxicity.[24,37] Pregnant women, alcoholics, and patients with poor diets who are treated with isoniazid should receive pyridoxine (vitamin B_6) 10 to 50 mg daily to reduce the incidence of central nervous system (CNS) effects or peripheral neuropathies. All patients who receive treatment of LTBI should be monitored monthly for adverse drug reactions and for possible progression to active TB.

Treating Active Disease

8 The treatment of active TB requires the use of multiple drugs. There are two primary anti-TB drugs, isoniazid and rifampin, with the rest of the drugs having specific roles.[37,40] Isoniazid and rifampin should be used together whenever possible. Typically, *M. tuberculosis* is either very susceptible or very resistant to a given drug. Theoretically, minimal inhibitory concentration (MIC) results could be used to guide dosing in the treatment of moderately resistant *M. tuberculosis*, but this remains to be studied prospectively.[37,41]

Drug-susceptibility testing should be done on the initial isolate for all patients with active TB. These data should guide the selection of drugs over the course of treatment.[12,37] However, some patients are unable to provide a suitable specimen for laboratory testing. If susceptibility data are not available for a given patient, the drug-susceptibility data for the suspected source case or regional susceptibility data should be used.[12,37]

Drug resistance should be expected for patients presenting for the retreatment of TB. These patients require retesting of drug susceptibility using freshly collected specimens. It is imperative to learn what drugs the patient received and for how long the patient received them.[12,37] A treatment history, often called a *drug-o-gram*, shows the start and stop dates of all antimycobacterial drugs on a horizontal bar graph.[37] A drug-o-gram should be constructed for all retreatment patients.

9 The standard TB treatment regimen is isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by isoniazid and rifampin for 4 months, a total of 6 months of treatment.[37] If susceptibility to isoniazid, rifampin, and pyrazinamide is shown, ethambutol can be stopped at any time. Without pyrazinamide, a total of 9 months of isoniazid and rifampin treatment is required. **Table 130-3** shows the recommended treatment regimens. When intermittent therapy is used, DOT is essential. Doses missed during an intermittent TB regimen decrease its efficacy and increase the relapse rate. Note that Table 130-3 shows recommendations that differ for HIV-negative and HIV-positive patients. HIV-positive patients should not receive highly intermittent regimens. In general, regimens given daily five times each week or three times weekly can be used for HIV-positive patients. Less frequent dosing is associated with higher failure and relapse rates and the selection of rifampin-resistant organisms.[37]

TABLE 130-3 Drug Regimens for Microbiologically Confirmed Pulmonary

Tuberculosis Caused by Drug Susceptible Organisms

	Initial Phase		Continuation Phase		
Regimen	Drugs*	Interval and Doses† (Minimal Duration)	Drugs	Interval and Doses† (Minimal Duration)	Comments†,‖
1	Isoniazid Rifampin Pyrazinamide Ethambutol	7 days/week for 56 doses (8 weeks) or 5 days/ week for 40 doses (8 weeks)‡	Isoniazid/ Rifampin	7 days/week for 126 doses (18 weeks) or 5 days/week for 90 doses (18 weeks)‡	This is preferred regimen for patient with newly diagnosed pulmonary tuberculosis.
2	Isoniazid Rifampin Pyrazinamide Ethambutol	7 days/week for 56 doses or 5 days/week for 40 doses (8 weeks)	Isoniazid/ Rifampin	Three times weekly for 54 doses (18 weeks)§	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.
3	Isoniazid Rifampin Pyrazinamide Ethambutol	3 times weekly for 24 doses (8 weeks)	Isoniazid/ Rifampin	Three times weekly for 54 doses (18 weeks)	Use regimen with caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance.
4	Isoniazid Rifampin Ethambutol Pyrazinamide	7 days/week for 14 doses, then twice weekly for 12 doses‖	Isoniazid/ Rifampin	Twice weekly for 36 doses (18 weeks)	Do not use twice weekly regimens in HIV-infected patients or patients with smear positive and//or cavitary disease. If doses are missed, then therapy is equivalent to once weekly, which is inferior.

*Other combinations may be appropriate in certain circumstances.

†When DOT is used, drugs may be given 5 days/week and the necessary number of doses adjusted accordingly. Although there are no studies that compare 5 with 7 daily doses, extensive experience indicates this would be an effective practice. DOT should be used when drugs are administered <7 days/week.

‡Based on expert opinion, patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31-week) continuation phase.

§Pyridoxine (vitamin B_6), 25-50 mg/day, is given with INH to all persons at risk of neuropathy (eg, pregnant women; breastfeeding infants; persons with HIV; patients with diabetes, alcoholism, malnutrition, or chronic renal failure; or patients with advanced age). For patients with peripheral neuropathy, experts recommend increasing pyridoxine dose to 100 mg/day.

‖Alternatively, some US tuberculosis control programs have administered intensive-phase regimens 5 days/week for 15 doses (3 weeks), then twice weekly for 12 dose.

Abbreviations: DOT, directly observed therapy; EMB, ethambutol; HIV, human immunodeficiency virus; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin.

Source: Reprinted, with permission, from Nahid P, et al. Executive Summary: Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis, Clinical Infectious Diseases, Volume 63, Issue 7, 1 October 2016, Pages 853–867.

When a patient's sputum smears convert to a negative, the risk of the patient infecting others is greatly reduced, but it is not zero.[15,17,37] Such patients can be removed from respiratory isolation, but they must be careful not to cough on others and should meet with others only in well-ventilated places. Smear-negative patients still may be culture positive, so they still can transmit TB to others.

Patients who are slow to respond clinically, those who remain culture-positive at 2 months of treatment, those with cavitary lesions on chest radiograph, and

perhaps HIV-positive patients should be treated for a total of 9 months and for at least 6 months from the time that they convert to smear and culture negativity.[37] Some authors recommend therapeutic drug monitoring (TDM), the use of serum drug concentrations, to optimize therapy for such patients.[40,41,48] When isoniazid and rifampin cannot be used, treatment durations often become 2 years or more regardless of immune status.[37,40]

10 Adjustments to the regimen should be made once the susceptibility data are available.[37] If the organism is drug-resistant, careful consideration of the remaining therapeutic options must be made. Two or more drugs with in vitro activity against the patient's isolate and that the patient has not received previously should be added to the regimen, as needed.[37,40,47] In the United States, there is no standard regimen for MDR-TB.[37,47] Each patient's exposure history, treatment history (including toxicity and adherence issues), and current susceptibility data must be considered simultaneously. *It is critical to avoid monotherapy, and it is critical to never add a single drug to a failing regimen.*[37,40] Adding one drug at a time leads to the sequential selection of drug resistance until there are no drugs left. TB specialists should be consulted regarding cases of MDR-TB. It may take several months for a patient with MDR-TB to become culture-negative because the drugs used lack the potency of isoniazid and rifampin.[37,40] Consequently, prolonged respiratory isolation may be required.

Drug resistance should be considered in the following situations:

1. Patients who have received prior therapy for TB.
2. Patients from areas with a high prevalence of resistance (South Africa, Dominican Republic, Peru, Southeast Asia, the Baltic countries, and the former Soviet states).
3. Patients who are homeless, institutionalized, IV drug abusers, or infected with HIV.
4. Patients who still have AFB-positive sputum smears after 1 to 2 months of therapy.
5. Patients who still have positive cultures after 2 to 4 months of therapy.
6. Patients who fail treatment or relapse after treatment.
7. Patients known to be exposed to MDR-TB cases.

Empirical therapy with four or more drugs may be needed for acutely ill

patients.[37] These regimens may be altered when the susceptibility pattern becomes known. If the index case is known, then the same effective regimen should be employed for the new case. Again, MDR-TB cases should be referred to specialists. A new term in use, *XDR-TB*, refers to "extensively drug-resistant TB." Such organisms are resistant to at least isoniazid, rifampin, a fluoroquinolone, and one second-line injectable drug (amikacin, capreomycin, or kanamycin).[47–49]

Special Populations

Tuberculous Meningitis and Extrapulmonary Disease Patients with CNS TB usually are treated for longer periods (9-12 months instead of 6 months).[37] In general, isoniazid, pyrazinamide, ethionamide, and cycloserine penetrate the cerebrospinal fluid readily, but rifampin, ethambutol, and streptomycin have variable CNS penetration.[42] Of the quinolones, levofloxacin may be preferred based on current data. Extrapulmonary TB of the soft tissues can be treated with conventional regimens.[37] TB of the bone typically is treated for 9 months, occasionally with surgical debridement.[37]

Children TB in children may be treated with regimens similar to those used in adults, although some physicians still prefer to extend treatment to 9 months.[17,18,37] Pediatric doses of isoniazid and rifampin on a milligram-per-kilogram basis are higher than those used in adults (**Table 130-4**).[37]

TABLE 130-4 Antituberculosis Drugs for Adults and Children

Drug	Preparation	Adults/Children	Typical Doses*			
			Daily	1× Per Week	2× Per Week	3× Per Week
First-Line Drugs						
Isoniazid	Tablets (50, 100, 300 mg); elixir (50 mg/5 mL); aqueous solution (100 mg/mL) for IV or intramuscular injection	Adults Children	5 mg/kg 10-15 mg/kg	15 mg/kg —	15 mg/kg 20-30 mg/kg	15 mg/kg —
Rifampin[¥]	Capsule (150, 300 mg); powder may be suspended for oral administration; aqueous solution for IV injection	Adults[†] Children	10 mg/kg 10-20 mg/kg	— —	10 mg/kg 10-20 mg/kg	10 mg/kg —
Rifabutin	Capsule (150 mg)	Adult[†] Children	5 mg/kg Appropriate dosing for children is unknown	—		5 mg/kg
Rifapentine[¥]	Tablet (150 mg, film coated)	Adults Children	— The drug is not approved for use in children < 12 years old	10-20 mg/kg (continuation phase)	—	—
Pyrazinamide	Tablet (500 mg, scored)	Adults Children	40-55 kg: 1,000 mg 56-75 kg: 1,500 mg 76-90 kg: 2,000 mg 30-40 mg/kg	— — — —	40-55 kg: 2,000 mg 56-75 kg: 3,000 mg 76-90 kg: 4,000 mg 50 mg/kg	40-55 kg: 1,500 mg 56-75 kg: 2,500 mg 76-90 kg: 3,000 mg —
Ethambutol	Tablet (100, 400 mg)	Adults Children[†]	40-55 kg: 800 mg 56-75 kg: 1,200 mg 76-90 kg: 1,600 mg 30-40 mg/kg	— — — —	40-55 kg: 2,000 mg 56-75 kg: 2,800 mg 76-90 kg: 4,000 mg —	40-55 kg: 1,200 mg 56-75 kg: 2,000 mg 76-90 kg: 2,400 mg 50 mg/kg
Second-Line Drugs						
Cycloserine	Capsule (250 mg)	Adults Children	10-15 mg/kg/day, usually 500-750 mg/day in two doses[‡] 10-15 mg/kg/day	No data —	No data —	No data —
Ethionamide	Tablet (250 mg)	Adults[§] Children	15-20 mg/kg/day, usually 500-750 mg/day in a single daily dose or two divided doses[‖] 15-20 mg/kg/day	No data No data	No data No data	No data No data
Streptomycin	Aqueous solution (1-g vials) for IV or intramuscular administration	Adults Children[§]	15 mg/kg/day[‖] 15-20 mg/kg/day	— —	— 25-30 mg/kg	— 25 mg/kg
Amikacin/ kanamycin	Aqueous solution (500-mg and 1-g vials) for IV or intramuscular administration	Adults Children[§]	15 mg/kg/day[‖] 15-20 mg/kg/day IV or intramuscular as a single daily dose	— —	— 25-30 mg/kg	25 mg/kg —
Capreomycin	Aqueous solution (1-g vials) for IV or intramuscular administration	Adults Children[§]	15 mg/kg/day[#] 15-20 mg/kg/day as a single daily dose	[‖] —	 25-30 mg/kg	25 mg/kg 25-30 mg/kg
p-Aminosalicylic acid (PAS)	Granules (4-g packets) can be mixed with food; tablets (500 mg) are still available in some countries, but not in the United States; a solution for IV administration is available in Europe	Adults Children	8-12 g/day in two or three doses 200-300 mg/kg/day in two to four divided doses	No data No data	No data No data	No data No data
Levofloxacin	Tablets (250, 500, 750 mg); aqueous solution (500-mg vials) for IV injection	Adults Children	500-1,000 mg daily [¶]	No data [¶]	No data [¶]	No data [¶]

Moxifloxacin	Tablets (400 mg); aqueous solution (400 mg/250 mL) for IV injection	Adults Children	400 mg daily "	No data "	No data "	No data "
Bedaquiline		Adults Children	Weeks 1-2: 400 mg daily. Weeks 3-24: 200 mg three times weekly. The drug is not approved for use in children	No data	No data	No data

*The authors of this chapter do not agree with the use of maximum doses, since this arbitrarily caps doses for patients who otherwise might need larger doses. These maximum doses were not based on prospective studies in large or overweight individuals, and do not consider patients with documented malabsorption of their medications. Clinical judgment should be used in such circumstances.

†The drug can likely be used safely in older children but should be used with caution in children younger than 5 years, in whom visual acuity cannot be monitored. In younger children, ethambutol at the dose of 15 mg/kg/day can be used if there is suspected or proven resistance to isoniazid or rifampin.

‡Although this is the dose recommended generally, most clinicians with experience using cycloserine indicate that it is unusual for patients to be able to tolerate this amount. Serum concentration measurements are often useful in determining the optimal dose for a given patient.

§The single daily dose can be given at bedtime or with the main meal to reduce nausea.

‖Dose: 15 mg/kg/day (1 g), and 10 mg/kg in persons older than 59 years (750 mg). Usual dose: 750-1,000 mg administered intramuscularly or IV, given as a single dose 5-7 days/week and reduced to two or three times per week after the first 2-4 months or after culture conversion, depending on the efficacy of the other drugs in the regimen.

¶The long-term (more than several weeks) use of levofloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. However, most experts agree that the drug should be considered for children with tuberculosis caused by organisms resistant to both isoniazid and rifampin. The optimal dose is not known.

#The long-term (more than several weeks) use of moxifloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. The optimal dose is not known.

**Higher doses of rifampin and rifapentine are being studied. Rifabutin dose may need to be adjusted when there is concomitant use of protease inhibitors or non-nucleoside reverse transcriptase inhibitors.

§§Larger total body water content and faster clearance of injectable drugs in most children. Dosing can be guided by serum concentrations.

For purposes of this document, adult dosing begins at age 15 years.

Source: Reprinted, with permission, from Nahid P, et al. Executive Summary: Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis, Clinical Infectious Diseases, Volume 63, Issue 7, 1 October 2016, Pages 853–867.

Pregnancy Women with TB should be cautioned against becoming pregnant because the disease poses a risk to the fetus and to the mother. If already pregnant, the usual treatment is isoniazid, rifampin, and ethambutol for 9 months.[50] Isoniazid and ethambutol are relatively safe for use in pregnant women.[37,42,50] B vitamins are particularly important during pregnancy and should be provided to women being treated for TB. Rifampin is associated rarely with birth defects, including limb reduction and CNS lesions.[42] In general, rifampin is used in pregnant women with TB. Pyrazinamide has not been studied in large numbers of pregnant women, but anecdotal data suggest that it may be safe.[37]

Streptomycin use during pregnancy may lead to hearing loss in the newborn, including complete deafness. Streptomycin and the other aminoglycosides must be reserved for critical situations where alternatives do not exist.[37] Although the polypeptide capreomycin has not been studied, it probably carries the same risks.

Ethionamide may cause premature delivery and congenital deformities when used during pregnancy.[37,42] Down syndrome also has been reported with ethionamide, so it cannot be recommended in this setting. *p*-Aminosalicylic acid has been used safely in pregnancy, but specific data are lacking.[37,42] Cycloserine is known to cross the placenta, but the effects on the developing fetus are not known. Therefore, cycloserine generally cannot be recommended during pregnancy.[42]

Ciprofloxacin, levofloxacin, moxifloxacin, and the other quinolones are associated with permanent damage to cartilage in the weight-bearing joints of immature animals, especially dogs and rabbits.[37,42] Although these drugs do not frequently cause joint problems in humans, other anti-TB agents should be used during pregnancy.

Pregnant women with LTBI are not at the same level of risk compared with those with active disease. Therapy with isoniazid for LTBI may be delayed until after pregnancy. However in the case of recent infection documented by a skin-test conversion or a newly positive IGRA and in immunosuppressed women who are found to have LTBI while pregnant, treatment for LTBI is started during the second trimester of pregnancy.[37,42,50] Although most anti-TB drugs are excreted in breast milk, the amount of drug received by the infant through nursing is insufficient to cause toxicity. Quinolones should be avoided in nursing mothers, if possible.

HIV Infection For drug-susceptible strains of tuberculosis, patients with AIDS and other immunocompromised hosts may be managed with chemotherapeutic regimens similar to those used in immunocompetent individuals, although treatment is often extended to 9 months (see Table 130-3).[37] The precise duration to recommend remains a matter of debate. Highly intermittent regimens (twice or once weekly) are not recommended for HIV-positive TB patients. Rifamycin-based treatments are most effective; however, agents should be selected based on susceptibility and HIV drug interactions. Prognosis has been particularly poor for HIV-infected patients infected with MDR-TB, so all efforts should be made to reduce the time between clinical presentation, diagnosis of TB, and start of appropriate treatment. Recommendations for management of HIV and TB published by the World Health Organization and others have

provided guidance on monitoring of treatment, side effects, and drug interactions of HIV and TB, MDR, XDR-TB.[5,49,51,52] The timing for tuberculosis treatment antiretroviral treatment in patients with TB and HIV is unclear. In patients with CD4 cell counts <200/mm^3 (0.20 x 10^9/L) or <50 mm^3 (0.05 x 10^{69}/L)reductions in mortality have been seen when antiretroviral treatment was initiated within 2 weeks of anti-TB treatment.[53,31] Differentiation must be made between infection with *M. tuberculosis* and nontuberculous mycobacteria, such as *Mycobacterium avium* complex (MAC), because the drugs used are different. While awaiting laboratory results, the patient can be treated empirically for TB if there is any doubt about the causative organism. Some patients with AIDS malabsorb their oral medications; this is discussed in Therapeutic Drug Monitoring section below.[40,41,48]

Renal Failure For nearly all patients, isoniazid and rifampin do not require dose modification in renal failure. They are eliminated primarily by the liver.[40,42,54] In the unlikely event that peripheral neuropathies develop, the frequency of isoniazid dosing may be reduced. Pyrazinamide and ethambutol typically require a reduction in dosing frequency from daily to three times weekly (**Table 130-5**).[37,54]

TABLE 130-5 Dosing Recommendations for Adult Patients with Reduced Renal Function and for Adult Patients Receiving Hemodialysis

Drug	Change in Frequency?	Recommended Dose and Frequency for Patients with Creatinine Clearance <30 mL/min (0.50 mL/s) or for Patients Receiving Hemodialysis[*,†,‡,§]
Isoniazid	No change	300 mg once daily, or 900 mg three times per week
Rifampin	No change	600 mg once daily, or 600 mg three times per week
Pyrazinamide	Yes	25-35 mg/kg per dose three times per week (not daily)
Ethambutol	Yes	15-25 mg/kg per dose three times per week (not daily)
Levofloxacin	Yes	750-1,000 mg per dose three times per week (not daily)
Cycloserine	Yes	250 mg once daily, or 500 mg/dose three times per week[‖]
Ethionamide	No change	250-500 mg/dose daily
p-Aminosalicylic acid	No change	4 g/dose, twice daily
Streptomycin	Yes	12-15 mg/kg per dose two or three times per week (not daily)
Capreomycin	Yes	12-15 mg/kg per dose two or three times per week (not daily)
Kanamycin	Yes	12-15 mg/kg per dose two or three times per week (not daily)
Amikacin	Yes	12-15 mg/kg per dose two or three times per week (not daily)

*Standard doses are given unless there is intolerance.

†The medications should be given after hemodialysis on the day of hemodialysis.

‡Monitoring of serum drug concentrations should be considered to ensure adequate drug absorption, without excessive accumulation, and to assist in avoiding toxicity.

§Data currently are not available for patients receiving peritoneal dialysis. Until data become available, begin with doses recommended for patients receiving hemodialysis and verify adequacy of dosing, using serum concentration monitoring.

‖The appropriateness of 250-mg daily doses has not been established. There should be careful monitoring for evidence of neurotoxicity.

Source: Reprinted, with permission, from Nahid P, et al. Executive Summary: Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis, Clinical Infectious Diseases, Volume 63, Issue 7, 1 October 2016, Pages 853–867.

Renally cleared TB drugs include the aminoglycosides (amikacin, kanamycin, and streptomycin), capreomycin, ethambutol, cycloserine, and levofloxacin.[37,42,55] Dosing intervals need to be extended for these drugs (Table 130-5). Ciprofloxacin and moxifloxacin are approximately 50% cleared by the kidneys but may not require a change in dose from once daily, as used for TB. The metabolites of isoniazid, pyrazinamide, and *p*-aminosalicylic acid are cleared primarily by the kidneys. The role of these metabolites in causing toxicity is unknown, so their accumulation in renal failure may carry some risk.

Ethionamide and its sulfoxide metabolite are hepatically cleared, so dosing is unchanged.[37,55] *p*-Aminosalicylic acid is converted largely to metabolites prior to renal elimination; these metabolites may accumulate in renal failure.[55] For patients on hemodialysis, the usual 12-hour dosing interval for *p*-aminosalicylic acid granules seems to be safe. Dialysis will remove the metabolites. Serum

concentration monitoring must be performed for cycloserine to avoid dose-related toxicities in renal failure patients.[40,41,55]

Hepatic Failure Anti-TB drugs that rely on hepatic clearance for most of their elimination include isoniazid, rifampin, pyrazinamide, ethionamide, and *p*-aminosalicylic acid.[42] Ciprofloxacin and moxifloxacin are approximately 50% cleared by the liver. Elevations of serum transaminase concentrations generally are not correlated with the residual capacity of the liver to metabolize drugs, so these markers cannot be used as guides for drug dosing. Furthermore, isoniazid, rifampin, pyrazinamide, and, to a lesser degree, ethionamide, *p*-aminosalicylic acid, and, rarely, ethambutol may cause hepatotoxicity.[37,40,42] For some patients with drug-susceptible TB, a "liver-sparing" regimen of streptomycin, levofloxacin, and ethambutol may be used, at least temporarily.[37,40,42] Because this regimen requires 18 or more months of treatment to be successful, patients usually are switched to isoniazid- and rifampin-containing regimens as soon as they are able.

Morbid Obesity Data are not available for dosing the TB drugs for patients with morbid obesity.[42] Relatively hydrophilic drugs (isoniazid, pyrazinamide, the aminoglycosides, capreomycin, ethambutol, *p*-aminosalicylic acid, and cycloserine) can be dosed initially based on ideal body weight. Very low or very high serum concentrations can be avoided by checking the serum concentrations.[41]

The TB Drugs

The interested reader is referred to several other publications for more detailed information regarding these drugs (see Table 130-4).[37,40–42] The "maximum" dose for a given patient is the dose that produces the desired response with an acceptable level of toxicity.[40,41] This can only be determined on a case-by-case basis. Artificially capping doses may deprive patients of needed drug.

Primary Antituberculosis Drugs

Isoniazid Isoniazid is one of the two most important TB drugs. It is highly specific for mycobacteria, with a MIC against *M. tuberculosis* of 0.01 to 0.25 mcg/mL (mg/L; 0.07 to 1.82 μmol/L). It is bactericidal and is thought to inhibit mycolic acid synthesis and disruption of the cell wall in susceptible organisms. Most nontuberculous mycobacteria such as *M. avium* are resistant to isoniazid, although *Mycobacterium kansasii* and *Mycobacterium xenopi* are susceptible. The most common mechanisms of resistance result from mutations in the *katG*

or *inhA* genes.

Isoniazid is readily absorbed from the GI tract and from intramuscular injection sites. It also can be given as a short IV infusion over 5 minutes if diluted in about 20 mL of normal saline.[56] Isoniazid should be given on an empty stomach whenever possible.[57] *N*-Acetyltransferase 2 forms the principal metabolite acetylisoniazid, which lacks antimycobacterial activity. The rate at which humans acetylate isoniazid is determined genetically; slow acetylation is an autosomal recessive trait and reflects a relative lack of *N*-acetyltransferase 2. Fast acetylators have isoniazid half-lives of less than 2 hours. Approximately 50% of whites and blacks and 80% to 90% of Asians and Native Alaskans are rapid acetylators. Slow acetylators have isoniazid half-lives of 3 to 4 hours and may be at an increased risk of neurotoxicity. The association of acetylator status and risk of hepatotoxicity, however, appears to be weak.[58] Poor absorption and rapid clearance of isoniazid for patients receiving highly intermittent therapy are associated with poor clinical outcomes.[59,60]

Transient elevations of the serum transaminases occur in 12% to 15% of patients receiving isoniazid and usually occur within the first 8 to 12 weeks of therapy.[37] Overt hepatotoxicity, however, occurs in only 1% of cases. Risk factors for hepatotoxicity include patient age, preexisting liver disease, excessive alcohol intake, pregnancy, coadministration of other medications that are potentially hepatotoxic, and the postpartum state. Isoniazid also may result in neurotoxicity, most frequently presenting as peripheral neuropathy or, in overdose, as seizures and coma. Patients with pyridoxine deficiency, such as pregnant women, alcoholics, children, and the malnourished, are at increased risk. Isoniazid may inhibit the metabolism of phenytoin, carbamazepine, primidone, and warfarin.[40] Patients who are being treated with these agents should be monitored closely, and appropriate dose adjustments should be made when necessary.

Rifampin The introduction of rifampin into routine use during the 1970s allowed for true short-course treatment of TB (6-9 months).[37] Without rifampin, treatment is generally 18 months or longer. Drug resistance to rifampin is an ominous prognostic factor because it is frequently associated with isoniazid resistance and leaves the patient with few good therapeutic options. Clinicians *must* take care to protect susceptibility to rifampin by carefully treating their patients. Rifampin shows bactericidal activity against *M. tuberculosis* and several other mycobacterial species, including *Mycobacterium bovis* and *M. kansasii*.[61] It also is active against a broad array of other bacteria. Alteration of

the target site on RNA polymerase, primarily through changes in the *rpoB* gene, leads to most forms of rifampin resistance.[37,61]

Rifampin usually is given orally, but it also can be given as a 30-minute IV infusion.[61] Oral doses are best given on an empty stomach.[62] Patients with AIDS, diabetes, and other GI problems appear to have difficulty absorbing rifampin after oral doses, and this has been associated with therapeutic failures in some cases.[40,41,60,63] Rifampin is metabolized to 25-desacetyl rifampin, which retains some of rifampin's activity; most of rifampin and its metabolite are cleared in the bile. Rifampin generally is given at 600 mg daily or intermittently, although this dose does not take full advantage of rifampin's concentration-dependent killing.[40,41] Higher doses should be tested in humans within the context of clinical trials.

Elevations in hepatic enzymes have been attributed to rifampin in 10% to 15% of patients, with overt hepatotoxicity occurring in less than 1%.[37,61] More frequent adverse effects of rifampin include rash, fever, and GI distress. Allergic reactions to rifampin have been reported and occur more frequently with intermittent rifampin doses 900 mg or more twice weekly. These reactions may take the form of a flu-like syndrome with development of fever, chills, headache, arthralgias, and, rarely, hypotension and shock.[37] Alternatively, hemolytic anemia or acute renal failure may occur, requiring permanent discontinuation.

Rifampin's potent induction of hepatic enzymes, especially cytochrome P450 3A4, may enhance the elimination of many other drugs, most notably the protease inhibitors used to treat HIV (**Table 130-6**). HIV-positive patients may benefit from the use of rifabutin instead of rifampin.[25,37,51,64] Furthermore, women who use oral contraceptives must use another form of contraception during therapy because increased clearance of the hormones may lead to unexpected pregnancies. Patient records should be reviewed for potential drug interactions before dispensing rifampin. Rifampin may turn urine and other secretions orange-red and may permanently stain some types of contact lenses.

TABLE 130-6 Recommended Regimens for the Concomitant Treatment of TB and HIV Infection in Adults

Combined Regimen for Treatment of HIV and TB	Pharmacokinetic Effect of the Rifamycin	Tolerability/Toxicity	Antiviral Activity When Used with Rifamycin	Recommendations (Comments)
Efavirenz-based antiretroviral therapy* with rifampin-based TB treatment	Well-characterized, modest decrease in concentrations in some patients	Low rates of discontinuation	Excellent	Preferred (efavirenz should not be used during the first trimester of pregnancy)
PI-based antiretroviral therapy* with rifabutin-based TB treatment	Little effect of rifabutin on PI concentrations, but marked increases in rifabutin concentrations	Low rates of discontinuation (if rifabutin is appropriately dose-reduced)	Favorable, although published clinical experience is not extensive	Preferred for patients unable to take efavirenz† (caution to ensure patients who discontinue PI not to continue to receive reduced rifabutin dose)
Nevirapine-based antiretroviral therapy with rifampin-based TB treatment	Moderate decrease in concentrations	Concern about hepatotoxicity when used with isoniazid, rifampin, and pyrazinamide	Suboptimal when nevirapine is initiated using once-daily dosing largely favorable when nevirapine is given twice daily throughout cotreatment	Alternative for patients who cannot take efavirenz, though efavirenz is preferred (nevirapine should not be initiated among women with CD4 >250 [0.25 × 10^9/L] or men with CD4 >400 cells/μL [0.40 × 10^9/L])
Raltegravir-based antiretroviral therapy with rifampin-based TB treatment	Significant decrease in concentrations with standard dosing	Limited experience	Limited published clinical experience	Alternative at higher doses for patients who cannot take efavirenz and who have baseline viral load <100,000 copies/mL (100 × 10^6/L)
Dolutegravir-based antiretroviral therapy with rifampin-based TB-treatment	Coadministration with rifampicin results in decreases in dolutegravir plasma exposure requiring increased dose of dolutegravir	Limited experience	Limited published clinical experience	Alternative for patients who cannot take efavirenz
Zidovudine/lamivudine/abacavir/tenofovir with rifampin-based TB treatment	50% decrease in zidovudine, possible effect on abacavir not evaluated	Anemia	No published clinical experience, but this regimen is less effective than efavirenz or atazanavir based-regimens in person not taking rifampin	Alternative for patients who cannot take efavirenz or nevirapine and if rifabutin not available
Zidovudine/lamivudine/tenofovir with rifampin-based TB treatment	50% decrease in zidovudine, no other effects predicted	Anemia	Favorable, but not evaluated in a randomized trial	Alternative for patients who cannot take efavirenz and abacavir and if rifabutin not available
Zidovudine/lamivudine/abacavir with rifampin-based TB treatment	50% decrease in zidovudine, possible effect on abacavir not evaluated	Anemia	Early favorable experience, but this combination is less effective than efavirenz- or nevirapine-based regimens in persons not taking rifampin	Alternative for patients who cannot take efavirenz and tenofovir and if rifabutin not available
Superboosted‡ lopinavir-based antiretroviral therapy or double dose lopinavir/ritonavir-based therapy with rifampin-based TB treatment	Moderate decrease in concentrations	Hepatitis	Early favorable experience of super-boosting among young children and double dose among adults already on antiretroviral drugs at the time of rifampin initiation	Alternative if rifabutin not available; double dose an option among adults already taking lopinavir-based antiretroviral therapy and virologically suppressed at the time of tuberculosis treatment initiation; super boosting has not been adequately tested in adults but may be effective

*With two nucleoside analogues.

†Includes patients with NNRTI-resistant HIV, those unable to tolerate efavirenz, and women during the first one to two trimesters of pregnancy.

‡Super boosting of lopinavir is achieved by giving lopinavir 400 mg together with 400 mg ritonavir twice daily. Double dose lopinavir/ritonavir is lopinavir 800 mg plus ritonavir 200 mg twice daily.

ART, antiretroviral therapy; HIV, human immunodeficiency virus; TB, tuberculosis.

Source: CDC. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis [online]. 2013. Available at: http://www.cdc.gov/tb/TB_HIV_Drugs/default.htm

Other Rifamycins Rifabutin is used for disseminated *M. avium* infection in AIDS patients and is quite active against *M. tuberculosis*. Most rifampin-resistant organisms are resistant to rifabutin. Because rifabutin is a less potent enzyme inducer than rifampin, it may be used for patients who are receiving protease inhibitors.[37,51,64,65] For HIV-positive patients, the ATS/CDC recommends regimens with three or more doses of the TB drugs per week (see Table 130-3). Rifapentine is a long-acting rifamycin that can be used once weekly in the continuation phase of treatment (after the first 2 months) in carefully selected HIV-negative patients. It is approximately as potent an enzyme inducer as rifampin, so similar drug interactions are likely.[37,51,64,65]

Pyrazinamide Adding pyrazinamide to the first 2 months of treatment with isoniazid and rifampin shortens the duration to 6 months for most patients.[37] Pyrazinamide may be bacteriostatic or bactericidal depending on the concentration and the susceptibility of the organism. It is usually well absorbed and displays a fairly long half-life.[66,67] The most common toxicities of pyrazinamide are GI distress, arthralgias, and elevations in the serum uric acid concentrations.[37] Most patients do not experience true gout. Hepatotoxicity is the major limiting adverse effect and is dose-related when pyrazinamide is given daily.

A fixed-combination product (Rifater, Aventis) of rifampin 120 mg, isoniazid 50 mg, and pyrazinamide 300 mg is designed to prevent drug resistance by keeping the self-medicating patient from using only one drug at a time. If the patient is receiving DOT, there is no particular advantage to this product. The typical dose of Rifater will be five to six tablets daily. When pyrazinamide is discontinued after 2 months of treatment, the combination product Rifamate (isoniazid 150 mg and rifampin 300 mg) can be substituted.

Ethambutol Ethambutol replaced *p*-aminosalicylic acid as a first-line agent in the 1960s because it was better tolerated by patients.[37] It is used as a fourth drug for TB while awaiting susceptibility data.[37] If the organism is susceptible to isoniazid, rifampin, and pyrazinamide, ethambutol can be stopped. Ethambutol is active against most mycobacteria, by inhibiting synthesis of metabolites and impairing cell metabolism, and is generally bacteriostatic.

Ethambutol should not be given with antacids.[68] For patients with renal failure, the ethambutol dose should be reduced to three times per week.[54,69] Retrobulbar neuritis is the major adverse effect. Patients may complain of a change in visual acuity, the inability to see the color green, or both. They should

be monitored monthly while on the drug using Snellen wall charts for visual acuity and Ishihara red-green color discrimination cards.[30,37]

Second-Line Antituberculosis Drugs

Streptomycin Streptomycin is one of three aminoglycoside antibiotics (along with amikacin and kanamycin) that are active against mycobacteria. It is quite active against MAC and several other mycobacteria, enterococci, *Brucella*, *Yersinia*, and various other bacteria. Although labeled only for intramuscular dosing, streptomycin can be given safely as IV infusions (100 mL of 5% dextrose in water or normal saline) over 30 minutes, similar to the other aminoglycosides.[70] Streptomycin, like other aminoglycosides, is renally cleared by glomerular filtration and must be given less often to patients with renal dysfunction.[37,40]

Streptomycin occasionally causes nephrotoxicity, although it tends to be mild and reversible. It also is capable of causing ototoxicity (vestibular and cochlear), which may become permanent with continued use.[37] Older patients and those receiving long durations of treatment are most likely to experience hearing loss, whereas vestibular toxicity is highly unpredictable.

Resistance to amikacin and kanamycin is frequently linked but independent of resistance to streptomycin and independent of resistance to capreomycin. Therefore, susceptibility tests should guide the selection of these injectable drugs.

p-Aminosalicylic Acid In the United States, only the enteric-coated, sustained-release granule form (Paser) is available.[71–73] GI disturbances are the most common adverse effects from *p*-aminosalicylic acid. Diarrhea is usually self-limited, with symptoms improving after the first 1 to 2 weeks of therapy. Occasionally, a few doses of an opioid will resolve the problem. It also is important to tell the patient that the empty granules will appear in the stool. Although FDA-approved for three daily doses, pharmacokinetic data support twice-daily dosing.[72]

Various types of malabsorption, including steatorrhea, were reported with previous dosage forms of *p*-aminosalicylic acid. Hypersensitivity and, rarely, severe hepatitis may occur. *p*-Aminosalicylic acid is known to produce goiter, with or without myxedema, which seems to occur more frequently with concomitant ethionamide therapy.

Cycloserine Cycloserine is only used to treat MDR-TB. It is well absorbed orally and is best taken on an empty stomach.[74] It is cleared primarily through

the kidneys by glomerular filtration and requires dosage reduction in renal failure. Cycloserine can produce dose-related CNS toxicity, including lethargy, confusion, or unusual behavior. Seizures, although reported, are exceedingly rare in US patients.[37] Therapy is improved by maintaining 2-hour postdose serum concentrations between 20 and 35 mcg/mL (mg/L; 200 and 349 μmol/L).[40,41] Most patients reach a dose of 750 mg daily, divided unevenly into two doses. This can be achieved by starting with 250 mg daily for 2 days, followed by 250-mg increments over 2-day intervals. This dose of cycloserine can be maintained if the patient complains of only occasional mild CNS effects, such as difficulty concentrating. Serum concentrations can be checked 1 to 2 weeks into therapy. The addition of pyridoxine 50 mg daily may improve patient tolerance of cycloserine.

Ethionamide Ethionamide shares structural features with two other antimycobacterial agents, isoniazid and, more distantly, thiacetazone, a drug not used in the United States. Prothionamide, the *n*-propyl derivative of ethionamide, is used in Europe. Ethionamide is only active against organisms of the genus *Mycobacterium*, and it should be considered primarily bacteriostatic because it is difficult to achieve serum concentrations that would be bactericidal.[37,40,41]

GI toxicity is the dose-limiting adverse effect. The drug should be introduced gradually in 250-mg increments, as described earlier for cycloserine. Rarely will a patient tolerate more than 1,000 mg daily in divided oral doses. Ethionamide may be administered with a light snack or prior to bedtime to minimize GI intolerance. Food does not affect absorption significantly.[75] Little ethionamide is recovered in the urine, so doses remain the same in renal failure. Ethionamide may cause goiter with or without hypothyroidism (especially when given with *p*-aminosalicylic acid), gynecomastia, alopecia, impotence, menorrhagia, photodermatitis, and acne. The management of diabetes also may be more difficult for patients receiving ethionamide. Because of these problems, ethionamide only is used when necessary.

Clofazimine Clofazimine is a drug with good activity against *Mycobacterium leprae* and some activity against *M. tuberculosis* and *M. avium*. It is used in doses of 100 mg daily in advanced cases of MDR-TB or MAC, especially when therapeutic options are limited.[37,40] The drug has a terminal elimination half-life that is weeks long. GI distress and skin discoloration are the most important adverse reactions. Although uncommon, severe GI pain may occur because of deposition of clofazimine crystals within the intestines; this may require surgical

correction.

Quinolones Levofloxacin, moxifloxacin, and gatifloxacin (outside of the United States) are sometimes used to treat MDR-TB because of their excellent activity against *M. tuberculosis*. Several studies have suggested a potential role for moxifloxacin as a possible replacement for certain first-line agents.[40,76–78] Moxifloxacin has been compared with isoniazid and ethambutol during the first 8 weeks of therapy for pulmonary TB. It did not demonstrate a significant increase in 8-week culture negativity when compared with isoniazid. However, shorter time to culture conversion was seen when compared with ethambutol.[77] Quinolones are useful because most are available in oral and IV dosage forms, so they can be used in critically ill patients. However, resistance of MTB to the fluoroquinolones is a major concern. Resistance is attributed to mutations in the *gyrA* and *gyrB* genes and can develop in a relatively short period of time.[79]

Macrolides/Azalides The macrolide clarithromycin and azalide azithromycin represent substantial advances in the treatment of MAC but demonstrate limited activity against *M. tuberculosis* and are not used frequently for TB.[37,40]

Newer Drugs and Delivery Systems Bedaquiline is a diarylquinoline that operates by a new mechanism which targets the ATP synthase pump and depletes cellular energy stores. Bedaquiline does not demonstrate cross-resistance with existing TB drugs. The WHO and CDC have issued recommendations stating that bedaquiline may be used at a dose of 400 mg daily for 2 weeks and then 200 mg three times a week for 22 weeks of treatment in adults with pulmonary MDR-TB when an effective treatment regimen cannot otherwise be provided.[80] Bedaquiline may be used on a case-by-case basis in children, HIV-infected persons, pregnant women, and extrapulmonary TB. Patients treated with bedaquiline should be closely monitored every week for potential side effects and an electrocardiogram (QT monitoring) should be performed at baseline and at weeks 2, 12, and 24.[80] The QT monitoring is required due to a black box warning issued by the FDA as a result of increased rates of death due to QT prolongation in patients receiving bedaquiline.

Delamanid (OPC-67683) and Pretomanid (PA-824) are nitroimidazole derivatives that are chemically related to metronidazole and work through inhibiting mycolic acid synthesis. All of these agents have potent in vitro and in vivo activity with very low MICs against *M. tuberculosis*.[81–83] Delamanid has centralized marketing authorization by the European Medicines Agency for use in the European Union.[80,82,84] Due to less than promising results of a phase III

trial, the WHO is currently evaluating the data on delamanid. Delamanid can be added to a longer MDR-TB regimen in patients for extensively drug-resistant tuberculosis at high risk for poor outcomes. Delamanid has been shown to cause prolongation of QT interval. Therefore, patients with QTcF >500 ms should not receive the drug. Pretomanid is undergoing phase III studies and was shown to be safe, well tolerated, and efficacious among drug-sensitive, sputum smear positive adult patients. Combinations of pretomanid with other anti-TB drugs are also being investigated. Linezolid has also been used in some patients with MDR-TB.[85] Long-term use of linezolid requires careful monitoring of hematologic indices for potential anemia and thrombocytopenia. It may be possible to reduce the incidences of these toxicities by giving linezolid 600 mg daily for the slow-growing *M. tuberculosis* rather than the usual 600 mg twice-daily dose used for gram-positive organisms. Liposomes have been investigated as delivery systems for various agents against mycobacteria, including isoniazid, rifampin, and the aminoglycosides. By changing the pharmacokinetic profile of such agents, their use in the treatment of mycobacterial infections could be enhanced greatly. Currently, no such product is licensed for use against TB.

Other New Targets

Other new drugs currently in Phase II trials for treatment of TB include: Delpazolid (LCB01-0371) and Sutezolid (PNU-100480) that target protein synthesis. SQ-109 is a new chemical class that targets MmpL3, an essential membrane transporter involved in the building of the mycolic acids as part of the outer membrane of mycobacteria. Macozinone (PBTZ-169) targets the flavoenzyme DprE1, blocking the synthesis of the cell wall precursor decaprenyl phosphoarabinose and provoking lysis of the *Mycobacterium tuberculosis*.

Corticosteroids Adjunctive therapy with corticosteroids may be of benefit for some patients with tuberculous meningitis or pericarditis to relieve inflammation and pressure.[37] They should be avoided in most other circumstances because they detract from the immune response to TB.

Bacille Calmette-Guérin Vaccine The BCG vaccine is an attenuated, hybridized strain of *M. bovis*. It was developed in 1921 and is used as a prophylactic vaccine against TB. Administration of BCG vaccine is compulsory in many developing countries and is officially recommended in many others. Vaccination with BCG produces a subclinical infection resulting in sensitization of T lymphocytes and cross-immunity to *M. tuberculosis*, as well as cutaneous hypersensitivity and, in many cases, a positive tuberculin skin test.

The efficacy of several different BCG preparations ranged from negative 56%

(some patients did worse with the vaccine) to positive 80%.[37] Trials within the United States and Puerto Rico have shown efficacy rates of 6% to 29%. The primary benefit of BCG vaccination appears to be the prevention of severe forms of TB in children. Data from the BCG trials show that the incidence of tuberculous meningitis and miliary TB is 52% to 100% lower and that the incidence of pulmonary TB is 2% to 80% lower in vaccinated children younger than 15 years than it was in unvaccinated controls.

Unfortunately, BCG does not appear to be reliable in preventing disease by *M. tuberculosis* in other segments of the population. Side effects occur in 1% to 10% of vaccinated persons and usually include severe or prolonged ulceration at the vaccination site, lymphadenitis, and lupus vulgaris. Pregnant women and patients with impaired immune systems, including those with HIV infection, should avoid vaccination. The World Health Organization had recommended, however, that in populations where the risk of TB is high, HIV-infected infants who are asymptomatic should receive BCG vaccine at birth or as soon as possible thereafter. Because BCG infection has occurred in AIDS patients given the vaccine, individuals with symptomatic HIV infection should not be vaccinated.[37]

In the United States, BCG vaccination is recommended only for uninfected children who are at unavoidable risk of exposure to TB and for whom other methods of prevention and control have failed or are not feasible.[37] Its use is very limited.

THERAPEUTIC DRUG MONITORING

TDM, or applied pharmacokinetics, generally should be used if patients are failing appropriate treatment (no clinical improvement after 2-4 weeks or smear positive after 4-6 weeks).[40,41,86,87] Patients with AIDS, diabetes, obesity, cystic fibrosis, various GI disorders, or MDR-TB may be tested prospectively, before problems arise, to ensure adequate treatment. Blood samples collected at 2 and 6 hours after a dose have been used with some success, although they may not be the optimal sampling times for all the drugs. Finally, TDM of the TB and HIV drugs is perhaps the most logical way to untangle the complex drug interactions that take place.[88,89]

EVALUATION OF THERAPEUTIC OUTCOMES

Monitoring of the Pharmaceutical Care Plan

The most serious problem with TB therapy is patient nonadherence to the prescribed regimens.[90] Unfortunately, there is no reliable way to identify such patients a priori. Noncompliance rates of up to 89% have been reported with TB therapy.[90] It is critical to the control of TB that such adherence rates be improved dramatically. The most effective way to achieve this end is with DOT.[37] Despite criticisms that it will cost more money, it is far cheaper in the long run to prevent the further spread of disease with DOT than to track down and treat additional cases of TB continuously.

The homeless and other underprivileged individuals are assumed to constitute the group of patients considered “unreliable,” and DOT should be reserved for them; it is also assumed that “responsible” patients cared for by private physicians may be treated with daily, unsupervised therapy. A study conducted in Baltimore, however, compared outcomes (sputum culture conversion to negative at 3 months) for patients with pulmonary TB who were treated by private physicians with outcomes for patients treated via DOT in a city-run clinic. Surprisingly, 3-month culture conversion occurred in only 40% of the private-care patients, compared with 90% in the city clinic-care patients.[3] Clearly, expansion of the use of DOT to nearly all patients with TB may be of benefit.

Patients who are AFB-smear positive should have sputum samples sent for AFB stains every 1 to 2 weeks until two consecutive smears are negative. This provides early evidence of a response to treatment.[37] Once on maintenance therapy, sputum cultures can be performed monthly until two consecutive cultures are negative, which generally occurs over 2 to 3 months. If sputum cultures continue to be positive after 2 months, drug-susceptibility testing should be repeated, and serum concentrations of the drugs should be checked.

Serum chemistries, including blood urea nitrogen, creatinine, aspartate transaminase, and alanine transaminase, and a complete blood count with platelets should be performed at baseline and periodically thereafter, depending on the presence of other factors that may increase the likelihood of toxicity (eg, advanced age, alcohol abuse, pregnancy)[37] (**Table 130-7**). Hepatotoxicity should be suspected for patients whose serum transaminases exceed five times the upper limit of normal or whose total bilirubin concentration exceeds 3 mg/dL (51.3 μmol/L) and for patients with symptoms such as nausea, vomiting, or jaundice. At this point, the offending agent(s) should be discontinued. Sequential reintroduction of the drugs with frequent testing of liver enzymes is often successful in identifying the offending agent; other agents may be continued.

Alternative agents should be selected as needed. Audiometric testing should be performed at baseline and monthly for patients who must receive aminoglycosides for more than 1 to 2 months. Vision testing (Snellen visual acuity charts and Ishihara color discrimination plates) should be performed on all patients who receive ethambutol. All patients diagnosed with TB should be tested for HIV infection.

TABLE 130-7 Antituberculosis Drug Monitoring Table

Drug	Adverse Effects	Monitoring
Isoniazid	Asymptomatic elevation of aminotransferases, clinical hepatitis, fatal hepatitis, peripheral neurotoxicity, CNS effects, lupus-like syndrome, hypersensitivity, monoamine poisoning, diarrhea	LFT monthly in patients who have preexisting liver disease or who develop abnormal liver function that does not require discontinuation of drug; dosage adjustments may be necessary in patients receiving anticonvulsants or warfarin
Rifampin	Cutaneous reactions, GI reactions (nausea, anorexia, abdominal pain), flu-like syndrome, hepatotoxicity, severe immunologic reactions, orange discoloration of bodily fluids (sputum, urine, sweat, tears), drug interactions due to induction of hepatic microsomal enzymes	Liver enzymes and interacting drugs as needed (eg, warfarin)
Rifabutin	Hematologic toxicity, uveitis, GI symptoms, polyarthralgias, hepatotoxicity, pseudojaundice (skin discoloration with normal bilirubin), rash, flu-like syndrome, orange discoloration of bodily fluids (sputum, urine, sweat, tears)	Drug interactions are less problematic than rifampin
Rifapentine	Similar to those associated with rifampin	Drug interactions are being investigated and are likely similar to rifampin
Pyrazinamide	Hepatotoxicity, GI symptoms (nausea, vomiting), nongouty polyarthralgia, asymptomatic hyperuricemia, acute gouty arthritis, transient morbilliform rash, dermatitis	Serum uric acid can serve as a surrogate marker for adherence; LFTs in patients with underlying liver disease
Ethambutol	Retrobulbar neuritis, peripheral neuritis, cutaneous reactions	Baseline visual acuity testing and testing of color discrimination; monthly testing of visual acuity and color discrimination in patients taking >15-20 mg/kg, having renal insufficiency, or receiving the drug for >2 months
Streptomycin	Ototoxicity, neurotoxicity, nephrotoxicity	Baseline audiogram, vestibular testing, Romberg's testing, and SCr Monthly assessments of renal function and auditory or vestibular symptoms
Amikacin/ kanamycin	Ototoxicity, nephrotoxicity	Baseline audiogram, vestibular testing, Romberg's testing, and SCr; monthly assessments of renal function and auditory or vestibular symptoms
Capreomycin	Nephrotoxicity, ototoxicity	Baseline audiogram, vestibular testing, Romberg's testing, and SCr Monthly assessments of renal function and auditory or vestibular symptoms Baseline and monthly serum K^+ and Mg^{2+}
p-Aminosalicylic acid	Hepatotoxicity, GI distress, malabsorption syndrome, hypothyroidism, coagulopathy	Baseline LFTs and TSH TSH every 3 months
Moxifloxacin	GI disturbance, neurologic effects, cutaneous reactions	No specific monitoring recommended
Bedaquililne	GI disturbances, dizziness, headache, rash, arthralgia	Serum K, Ca, MgECG at baseline, weeks 2, 12, 24. Weekly ECG for persons taking other QTc prolonging drugs, history of arrhythmias, hypothyroidism, uncompensated heart failure, or have serum K, Ca, or Mg below normal

CNS, central nervous system; GI, gastrointestinal; LFT, liver function test; SCr, serum creatinine; TSH, thyroid-stimulating hormone.

Source: Data from Nahid P, et al. Executive Summary: Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis, Clinical Infectious Diseases, Volume 63, Issue 7, 1 October 2016, Pages 853–867.

Postclass Engaged Learning Activity

Role play the patient and healthcare provider using the Case Studies in Self-Study Module 6 on Tuberculosis: Managing Tuberculosis Patients and Improving Adherence located on the CDC website: https://tinyurl.com/y4dxogm6. Identify the barriers and challenges in each case and various approaches to overcome them. This active role play activity is intended to develop problem solving and communication skills in pharmacy students by providing examples of situations in which patient-centered approach to counseling and education is required. The activity will also provide an opportunity to heighten cultural competency.

ABBREVIATIONS

AFB	acid-fast bacillus
ATS	American Thoracic Society
BCG	bacillus Calmette-Guérin
CDC	Centers for Disease Control and Prevention
CMI	cell-mediated immunity
DOT	directly observed treatment
DTH	delayed-type hypersensitivity
ELISA	enzyme-linked immunosorbent assay
HIV	human immunodeficiency virus
IGRA	interferon-γ release assay
IL	interleukin
INF	interferon
LAM	lipoarabinomannan
LTBI	latent tuberculosis infection
MAC	*Mycobacterium avium* complex
MDR	multidrug resistant
MIC	minimal inhibitory concentration
MTD	*M. tuberculosis* direct

PCR	polymerase chain reaction
PPD	purified protein derivative
QFT-G	QuantiFERON-TB Gold test
rRNA	ribosomal ribonucleic acid
SDA	strand-displacement amplification
TB	tuberculosis
TDM	therapeutic drug monitoring
TH_1	T-helper type 1
TH_2	T-helper type 2
TNF	tumor necrosis factor
WBC	white blood cell
XDR	extensively drug-resistant

REFERENCES

1. WHO. Global Tuberculosis Report. France: World Health Organization; 2018.
2. Centers for Disease Control and Prevention (CDC). Reported Tuberculosis in the United States 2017. Atlanta, GA: US Department of Health and Human Services, CDC; 2017. http://www.cdc.gov/tb/statistics/reports/2017/default.htm.
3. Fitzgerald DW, Sterling TR. *Mycobacterium tuberculosis*. In: Mandell GL, Bennett JE, Dolin R,, eds. *Principles and Practice of Infectious Diseases*. 8th ed. New York, NY: Elsevier Health Sciences; 2015;3129–3164.
4. Stewart R, Tsang CA, Pratt R, et al. Tuberculosis trends. *MMWR*. 2018;67(11):317–323.
5. Global HIV/AIDS response. Epidemic update and health sector progress towards universal access. Geneva: World Health Organization; 2011.
6. Magee JG. *Mycobacterium tuberculosis*. In: Ollar RA., Connell ND,eds. *Molecular Mycobacteriology: Techniques and Clinical*. New York, NY: Marcel Dekker Inc., 1999.
7. Issa R, Mohd Hassan NA, Abdul H, et al. Detection and discrimination of *Mycobacterium tuberculosis* complex. *Diagn Microbiol Infect Dis* 2012;72:62–67.
8. France AM, Grant J, Kammerer JS, Navin TR. A field validated approach using surveillance and genotyping data to estimate tuberculosis attributable to recent transmission in the United States. Am J Epidemiol.

2015;182:799–807.

9. Boehme CC, Nabeta P, Hillemann D, Nicol MP, et al. Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med* 2010;363(11):1005.
10. Availability of an assay for detecting *Mycobacterium tuberculosis*, including rifampin-resistant strains, and considerations for its use—United States, 2013. Centers for Disease Control and Prevention. *MMWR Morb Mortal Wkly Rep*. 2013;62:821–827.
11. Helb D, Jones M, Boehme C, et al. Rapid detection of *Mycobacterium tuberculosis* and rifampin resistance by use of on-demand, near patient technology. *J Clin Microbiol* 2010; 48:229–237.
12. Wallis RS. Biomarkers and diagnostics for tuberculosis: Progress, needs, and translation into practice. *Lancet* 2010;375:1845–1938.
13. Somoskovi A, Parsons LM, Salfinger M. The molecular basis of resistance to isoniazid, rifampin, and pyrazinamide in *Mycobacterium tuberculosis.* *Respir Res* 2001;2:164–168.
14. Daniel TM, Boom WH, Ellner JJ. Immunology of tuberculosis. In: Reichman LB, Hershfield ES,eds. *Tuberculosis: A Comprehensive International Approach*. 2nd ed. New York, NY: Marcel Dekker, 2000:157–185.
15. Pathogenesis of tuberculosis. In: Heemskerk D, Caws M, Marais B, Farrar J, eds. *Tuberculosis in Adults and Children*. 1st ed. London: Springer; 2015;140.
16. Long, R, Gardam, M. Tumour necrosis factor-α inhibitors and the reactivation of latent tuberculosis infection. *Can Med Assoc J* 2003;168:1153–1156.
17. American Thoracic Society/Centers for Disease Control and Prevention. Diagnostic standards and classification of tuberculosis in adults and children. *Am J Respir Crit Care Med* 2000;161:1376–1395.
18. Cruz AT, Stark JR. Clinical manifestations of tuberculosis in children. *Paediatr Respir Rev* 2007;8:107–117.
19. Kwan CK, Ernst JD. HIV and tuberculosis: A deadly human syndemic. *Clin Microbiol Rev* 2011;24:351–376.
20. Getahun H, Gunneberg C, Granich R, Nunn P. HIV infection–associated tuberculosis: The epidemiology and the response. Clin Infect Dis. 15, 2010;50 Suppl 3:S201–S207. 10.1086/651492.

21. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed September 1, 2015.
22. Naidoo K, Yende-Zuma N, Padayatch N, et al. The immune reconstitution inflammatory syndrome after antiretroviral therapy initiation in patients with tuberculosis: Findings from the SAPiT trial. *Ann Intern Med* 2012;157:313.
23. Uthman OA, Okwundu C, Gbenga K, et al. Optimal timing of antiretroviral therapy initiation for HIV-infected adults with newly diagnosed pulmonary tuberculosis: A systematic review and meta-analysis. *Ann Intern Med* 2015;163:32–39.
24. American Thoracic Society/Centers for Disease Control and Prevention. Targeted tuberculin skin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med* 2000;161:S221–S247.
25. Akolo C, Adetifa I, Sheppard S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst Rev* 2010;(1):CD000171.
26. Anergy skin testing and preventive therapy for HIV-infected persons: Revised recommendations. Centers for Disease Control and Prevention. *MMWR Recomm Rep* 1997;46:1–0.
27. Jensen PA, Lambert LA, Iademarco MF, Ridzon R; Centers for Disease Control and Prevention. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health care settings. *MMWR Recomm Rep* 2005;54(RR-17):1–141.
28. Mandalakas AM, Kirchner HL, Zhu X, Yeo KT, Starke JR. Interpretation of repeat tuberculin skin testing in international adoptees: Conversions or boosting. Pediatr Infect Dis J. 2008;27(10):913–919. doi: 10.1097/INF.0b013e3181758187.
29. Mazurek GH, Jereb J, Varnon A, et al. Updated guidelines for interferon gamma release assay to detect *Mycobacterium tuberculosis* infection, United States. *MMWR Recomm Rep* 2010;59(RR-5):1–25.
30. Barnes PF. Weighing gold or counting spots. *Am J Respir Crit Care Med*

2006;174:731–735.

31. Lewinsohn David, Leonard Michael, LoBue Philip, Cohn David, Daley Charles, et al. Official American Thoracic Society/Infectious Diseases Society/Centers for Disease Control and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. 2017;64:e1–e11.
32. Starke JR, Committee on Infectious Diseases. Interferon-γ release assays for diagnosis of tuberculosis infection and disease in children. *Pediatrics* 2014;134:e1763.
33. Bergamini BM, Losi M, Vaienti F, et al. Performance of commercial blood tests for the diagnosis of latent tuberculosis infection in children and adolescents. *Pediatrics* 2009;123:e419–e424.
34. Lighter J, Rigaud M, Eduardo R, Peng CH, et al. Latent tuberculosis diagnosis in children by using the quantiferon-TB gold in tube test. *Pediatrics* 2009;123:30–37.
35. Richeldi L, Losi M, D'Amico R, et al. Performance of tests for latent tuberculosis in different groups of immunocompromised patients. *Chest* 2009;136:198–204.
36. Perry S, Catanzaro A. Use of clinical risk assessments in evaluation of nucleic acid amplification tests for HIV/tuberculosis. *Int J Tuberc Lung Dis* 2000;4:S34.
37. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, et al. ; American Thoracic Society/Centers for Disease Control/Infectious Disease Society of America. Treatment of drug susceptible tuberculosis. CID. 2016;1:1–49.
38. Fujiwara PI, Larkin C, Frieden TR. Directly observed therapy in New York City. *Clin Chest Med* 1997;18:135–148.
39. Cruz AT, Starke JR. Increasing adherence for latent tuberculosis infection therapy with health department-administered therapy. *Pediatr Infect Dis J* 2012;31:193.
40. Peloquin CA. Pharmacological issues in the treatment of tuberculosis. *Ann NY Acad Sci* 2001;953:157–164.
41. Alsultan A, Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis: An update. *Drugs* 2014;74:839–854.
42. Peloquin CA. Antituberculosis drugs: Pharmacokinetics. In: Heifets LB,ed. *Drug Susceptibility in the Chemotherapy of Mycobacterial Infections*. Boca Raton, FL: CRC Press, 1991:59–88.

43. Aspler A, Long R, Trajman A, et al. Impact of treatment completion, intolerance and adverse events on health system costs in a randomized trial of 4 months of rifampin or 9 months isoniazid for latent TB. *Thorax* 2010;65:582–587.
44. Bamrah S., Brostrom R. Dorina F. et al. Treatment for LTBI in contacts of MDR-TB patients, Federated States of Micronesia, 2009-2012. *Int J Tuberc Lung Dis* 2014;18(8):912–918.
45. Sterling TR, Villarino ME, Borisov AS, et al. Three months of once-weekly rifapentine and isoniazid for *M. tuberculosis* infection. *N Engl J Med* 2011;365:2155–2166.
46. Centers for Disease Control and Prevention. Recommendations for use of isoniazid–rifapentine regimen with direct observation to treat *Mycobacterium tuberculosis* infection. *MMWR Morb Mortal Wkly Rep* 2011;60:1650–1653.
47. Zumla A, Abubaker I, Raviglione M, et al. Drug resistant tuberculosis – current dilemmas, unanswered questions, challenges, and priority needs. *J Infect Dis* 2012;205:S228–S240.
48. Heysell SK, Moore JL, Keller SJ, Houpt ER. Therapeutic drug monitoring for slow response to tuberculosis in a state control program. *Emerg Infect Dis* 2010;16:1546–1553.
49. Lawn SD, Wilkinson R. Extensively drug resistant tuberculosis. *BMJ* 2006;333:559–560.
50. Mnyani CN, McIntyre JA. Tuberculosis in pregnancy. *Br J Obstet Gynecol* 2011;118:226–231.
51. WHO. Tuberculosis care with TB-HIV co-management: integrated management of adolescent and adult illness. Geneva: World Health Organization, 2007.
52. Centers for Disease Control and Prevention. Managing drug interactions in the treatment of HIV-related tuberculosis. 2013. Available at: http://www.cdc.gov/tb/TB_HIV_Drugs/default.htm. Accessed September 1, 2015.
53. Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. N Engl J Med. 25, 2010;362(8):697–706. doi: 10.1056/NEJMoa0905848.
54. Malone RS, Fish DN, Spiegel DM, et al. The effect of hemodialysis on isoniazid, rifampin, pyrazinamide, and ethambutol. *Am J Respir Crit Care Med* 1999;159:1580–1584.

55. Malone RS, Fish DN, Spiegel DM, et al. The effect of hemodialysis on cycloserine, ethionamide, *para*-aminosalicylate, and clofazimine. *Chest* 1999;116:984–990.
56. Crabbe SJ. Drug InfoSearch—Intravenous isoniazid. *P&T* 1990;15:1483–1484.
57. Peloquin CA, Namdar R, Dodge AA, Nix DE. Pharmacokinetics of isoniazid under fasting conditions, with food, and with antacids. *Int J Tuberc Lung Dis*. 1999;3:703–710.
58. Berning SE, Peloquin CA. Antimycobacterial agents: Isoniazid. In: Yu VL, Merigan TC, Barriere S, White NJ,eds. *Antimicrobial Chemotherapy and Vaccines*. Baltimore: Williams & Wilkins, 2010:654–663.
59. Weiner M, Burman W, Vernon A, et al. Low isoniazid concentration associated with outcome of tuberculosis treatment with once-weekly isoniazid and rifapentine. *Am J Respir Crit Care Med* 2003;167:1341–1347.
60. Weiner M, Benator D, Burman W, et al. Association between acquired rifamycin resistance and the pharmacokinetics of rifabutin and isoniazid among patients with HIV and tuberculosis. *Clin Infect Dis* 2005;40:1481–1491.
61. Morris AB, Kanyok TP, Scott J, et al. Rifamycins. In: Yu VL, Merigan TC, Barriere S, White NJ, eds. *Antimicrobial Chemotherapy and Vaccines*. Baltimore, MD: Williams & Wilkins; 1998;901–963.
62. Peloquin CA, Namdar R, Singleton MD, Nix DE. Pharmacokinetics of rifampin under fasting conditions, with food, and with antacids. *Chest* 1999;115:12–18.
63. Barroso EC, Pinheiro VG, Facanha MC, et al. Serum concentrations of rifampin, isoniazid, and intestinal absorption, permeability in patients with multidrug resistant tuberculosis. *Am J Trop Med Hyg* 2009;81:322–329.
64. Mofenson LM, Brady MT, Danner SP, et al. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children: Recommendations from the CDC, the National Institutes of Health, the HIV Medicine Association of Infectious Diseases Society of America, the Pediatric Infectious Disease Society and the American Academy of Pediatrics. *MMWR Recomm Rep* 2009;58:1–166.
65. Burman WJ, Gallicano K, Peloquin CA. Comparative pharmacokinetics and pharmacodynamics of the rifamycin antibiotics. *Clin Pharmacokinet* 2001;40:327–341.

66. Peloquin CA, Jaresko GS, Yong CL, et al. Population pharmacokinetic modeling of isoniazid, rifampin, and pyrazinamide. *Antimicrob Agents Chemother* 1997;41:2670–2679.
67. Peloquin CA, Bulpitt AE, Jaresko GS, et al. Pharmacokinetics of pyrazinamide under fasting conditions, with food, and with antacids. *Pharmacotherapy* 1998;18:1205–1211.
68. Peloquin CA, Bulpitt AE, Jaresko GS, et al. Pharmacokinetics of ethambutol under fasting conditions, with food, and with antacids. *Antimicrob Agents Chemother* 1999;43:568–572.
69. Summers KK, Hardin TC. Treatment of tuberculosis in hemodialysis patients. *J Infect Dis Pharmacother* 1996;2:37–55.
70. Peloquin CA, Berning SE. Comment: Intravenous streptomycin. *Ann Pharmacother* 1993;27:1546–1547.
71. Peloquin CA, Henshaw TL, Huitt GA, et al. Pharmacokinetic evaluation of *p*-aminosalicylic acid granules. *Pharmacotherapy*. 1994;14:40–46.
72. Peloquin CA, Berning SE, Huitt GA, et al. Once-daily and twice-daily dosing of *p*-aminosalicylic acid (PAS) granules. *Am J Respir Crit Care Med* 1999;159:932–934.
73. Peloquin CA, Zhu M, Adam RD, et al. Pharmacokinetics of *p*-aminosalicylate under fasting conditions, with orange juice, food, and antacids. *Ann Pharmacother* 2001;35:1332–1338.
74. Zhu M, Nix DE, Adam RD, et al. Pharmacokinetics of cycloserine under fasting conditions, with orange juice, food, and antacids. *Pharmacotherapy* 2001;21:891–897.
75. Zhu M, Namdar R, Stambaugh JJ, et al. Population pharmacokinetics of ethionamide in patients with tuberculosis. *Tuberculosis* 2002;82:91–96.
76. Burman WJ, Goldberg S, Johnson JL, et al. Moxifloxacin versus ethambutol in the first 2 months of treatment for pulmonary tuberculosis. *Am J Respir Crit Care Med* 2006;174:331–338.
77. Conde MB, Efron A, Loredo C, et al. Moxifloxacin versus ethambutol in the initial treatment of tuberculosis: A double blind, randomized, controlled phase II trial. *Lancet* 2009;373:1183–1189.
78. Dorman SE, Johnson JL, Goldberg S, et al. Substitution of moxifloxacin for isoniazid during intensive phase treatment of pulmonary tuberculosis. *Am J Respir Crit Care Med* 2009;180:273–280.
79. Devasia RA, Blackman A, Gebretsadik T, et al. Fluoroquinolone

resistance in *Mycobacterium tuberculosis*: The effect of duration and timing of fluoroquinolone exposure. *Am J Respir Crit Care Med* 2009;180:365–370.

80. Mase S, Chorba T, Lobue P, Castro K. Provisional CDC guidelines for the use and safety monitoring of bedaquiline fumarate for the treatment of multidrug resistant tuberculosis. *MMWR* 2013;62:1–9.
81. Diacon AH, Pym A, Grobusch M, et al. The diarylquinoline TMC207 for multidrug resistant tuberculosis. *N Engl J Med* 2009;360:2397–2405.
82. Diacon AH, Dawson R, Hanekom M, et al. Early bactericidal activity of delamanid (OPC-67683) in smear-positive pulmonary tuberculosis patients. *Int J Tuberc Lung Dis* 2011;15:949–954.
83. Hu Y, Coates AR, Mitchison DA. Comparison of the sterilizing activities of the nitroimidazopyran PA-824 and moxifloxacin against persisting *Mycobacterium tuberculosis. Int J Tuberc Lung Dis* 2008;12:69–73.
84. Gler MT, Skripconoka V, Sanchez-Garavito E, et al. Delamanid for multidrug resistant pulmonary tuberculosis. *N Engl J Med* 2012;366:2151–2160.
85. Forun J, Martin-Davila P, Navas E, et al. Linezolid for the treatment of multidrug resistant tuberculosis. *J Antimicrob Chemother* 2005;56:180–185.
86. Chaulk CP, Friedman M, Dunning R. Modeling the epidemiology and economics of directly observed therapy in Baltimore. *Int J Tuberc Lung Dis* 2000;4:201–207.
87. Tappero JW, Bradford WZ, Agerton TB, et al. Serum concentrations of antimycobacterial drugs in patients with pulmonary tuberculosis in Botswana. *Clin Infect Dis* 2005;41:461–469.
88. Perlman DC, Segal Y, Rosenkranz S, et al. The clinical pharmacokinetics of rifampin and ethambutol in HIV-infected persons with tuberculosis. *Clin Infect Dis* 2005;41:1638–1647.
89. Peloquin CA. Agents for tuberculosis. In: Piscitelli SC, Rodvold KA,eds. *Drug Interactions in Infectious Diseases*. Totowa, NJ: Humana Press, 2001:109–120.
90. Brudney K, Dobkin J. Resurgent tuberculosis in New York City: Human immunodeficiency virus, homelessness, and the decline of tuberculosis control programs. *Am Rev Respir Dis* 1991;144:745–749.

131

Gastrointestinal Infections and Enterotoxigenic Poisonings

Andrew M. Roecker and Brittany N. Bates

KEY CONCEPTS

1. Infectious diarrhea is a disease that causes significant morbidity and mortality worldwide. Its etiology includes various bacteria, viruses, and protozoans, with viral causes being most predominant globally.
2. Two types of infectious diarrhea include watery or enterotoxigenic diarrhea and dysentery or bloody diarrhea. Common pathogens responsible for watery diarrhea are viruses and enterotoxigenic *Escherichia coli*. Common pathogens responsible for dysentery diarrhea are *Shigella* spp., *Campylobacter jejuni*, nontyphoid *Salmonella*, and enterohemorrhagic *E. coli*.
3. Fluid and electrolyte replacement is the cornerstone of therapy for diarrheal illnesses. Oral rehydration therapy is preferred in most cases of mild and moderate diarrhea.
4. The use of antibacterial therapy for infectious diarrhea is not commonly indicated due to the mild and self-limited nature of the infection, or viral etiology. Antibiotic therapy is recommended in cases of severe diarrhea, moderate-to-severe cases of traveler's diarrhea, most cases of febrile dysenteric diarrhea, and culture-proven bacterial diarrhea in high-risk patients.
5. Loperamide and diphenoxylate/atropine may offer symptomatic relief in patients with moderate watery diarrhea; however, use of antimotility agents should be avoided in patients with watery and dysentery diarrhea.
6. Diarrheal illness can be largely prevented by procedures to prevent contaminated food or water supplies and with appropriate personal hygiene.

7. Oral vancomycin or fidaxomicin are recommended as the initial therapy for patients with *Clostridium difficile* infection.
8. Common traveler's diarrheal pathogens include enterotoxigenic *E. coli*, *Shigella* spp., *Campylobacter* spp., *Salmonella* spp., and viruses.
9. Patient education on prevention strategies and appropriate self-treatment of traveler's diarrhea is preferred, and prophylaxis with antibacterials is not recommended.
10. Pathogens commonly responsible for food poisoning include *Staphylococcus* spp., *Salmonella* spp., *Shigella* spp., and *Clostridium* spp.

Preclass Engaged Learning Activity

Watch the CDC expert commentary entitled, **Dying From *C. diff*: Who is most vulnerable?**, available from: http://tinyurl.com/yxthsmyk. This 6-minute video provides background information on risk factors, transmission, and prevention of *Clostridium difficile* infection.

INTRODUCTION

Gastrointestinal (GI) infections and enterotoxigenic poisonings encompass a wide variety of medical conditions characterized by inflammation of the GI tract. Inflammation-induced vomiting and diarrhea are responsible for much of the morbidity and mortality of these conditions. Diarrhea is defined as a decrease in consistency of bowel movements (ie, unformed stool) and an increase in frequency of stools to three or more per day.[1,2] Acute diarrheal disease is commonly associated with diarrhea lasting less than 7 days, prolonged diarrhea lasts 7 to 13 days, persistent diarrhea lasts 14 to 29 days, and chronic diarrhea lasts 30 days or longer.

This chapter focuses on infectious etiologies of acute GI infections and enterotoxigenic poisonings. A wide variety of viral, bacterial, and parasitic pathogens are responsible for these infections. Chapter e133 discusses the common protozoans that cause gastroenteritis. This chapter will focus on pathogenesis and management of common viral and bacterial etiologies. Because the clinical consequences of dysenteric diarrhea can be more severe compared with cases of watery diarrhea, the chapter is organized accordingly.

Epidemiology, clinical presentation, diagnosis, treatment, and prevention strategies are discussed for all GI infections generally, and further elaborated in subsequent sections for specific diseases such as *C. difficile* infection, traveler's diarrhea, and foodborne illnesses.

EPIDEMIOLOGY

Dehydration resulting from acute infectious diarrhea is the second leading cause of mortality in children younger than 5 years, killing 525,000 annually.[2] Globally, 1.7 billion cases of infectious diarrhea occur yearly and cause over 1.39 million deaths.[2,3] The incidence of diarrhea for all children younger than age 5 years is 2.9 episodes per child per year. The incidence of diarrhea is higher in younger children, with 4.5 episodes per child per year among children aged 6 to 11 months, compared with 2.3 episodes per child per year among children aged 24 to 59 months.[2,3] Younger children also have a higher risk of death from acute dehydrating diarrhea, and diarrheal disease is still the leading global cause of malnutrition in children younger than 5 years.[2] Although the incidence of childhood diarrhea has been declining, diarrhea remains a major health problem in children, especially in those younger than 1 year.

In the United States, 179 million episodes of acute gastroenteritis occur each year, resulting in nearly 500,000 hospitalizations and more than 5,000 deaths.[4–7] The highest mortality risk from infectious diarrhea in the United States occurs in the elderly, which contrasts to the developing world where the risk of death is highest among young children.[4] Twenty-five percent of all hospitalizations and 85% of all mortality associated with diarrhea involved the elderly (age 60 years and older).[4] In addition to children and the elderly, other groups at risk for GI infections include travelers and campers, patients in chronic care facilities, military personnel stationed abroad, and immunocompromised patients.

ETIOLOGY

1 The etiology of GI infections and enterotoxigenic poisonings includes a wide variety of viruses, bacteria, and parasites, although the specific incidence of each is difficult to quantify. Etiologic agents are rarely identified due to the infrequent collection of stool samples, or inability of many laboratories to detect the full range of pathogenic organisms. In this chapter, discussions of pathogens responsible for enterotoxigenic diarrhea focus on viral pathogens (rotavirus and

norovirus), enterotoxigenic *Escherichia coli* (ETEC), and cholera. Common pathogens associated with dysenteric diarrhea discussed will be *Shigella* spp., *Salmonella* spp., *Campylobacter* spp., enterohemorrhagic *E. coli* (EHEC), *Yersinia enterocolitica,* and *C. difficile*. Characteristics of watery and dysenteric diarrhea and common pathogens responsible for them are outlined in **Table 131-1**.

TABLE 131-1 Acute Infectious Diarrhea Clinical Syndromes: Watery Versus Dysentery

	Watery	Dysentery
Percentage of patients	90-95	5-10
Stools		
Appearance	Watery	Bloody
Volume	Increased: ++/+++	Increased: +/++
Number per day	<10	>10
Reducing substances	0 to +++	0
pH	5-7.5	6-7.5
Occult blood	Negative	Positive
Fecal polymorpho-nuclear cells	Absent or few	Many
Mechanisms	Toxins Reduced absorption	Toxins Mucosal invasion
Complications		
Dehydration	Could be severe	Mild
Others	Acidosis, shock, electrolyte imbalance	Tenesmus, rectal prolapse, seizures
Etiology	*Vibrio cholerae*	*Shigella* spp.
	Enterotoxigenic *Escherichia coli* (ETEC)	*Salmonella* spp.
	Rotaviruses	*Campylobacter* spp.
	Noroviruses	*Yersinia* spp.
		Enterohemorrhagic *E. coli* (EHEC)
		Clostridium difficile

Viruses are now the leading global cause of infectious diarrhea. Noroviruses, previously known as Norwalk-like viruses, account for greater than 90% of viral gastroenteritis among all age groups, and 50% of outbreaks worldwide. In the United States, noroviruses have been responsible for roughly 21% of all acute gastroenteritis cases in young children with outpatient visits, emergency department visits, and annual hospitalizations numbering, 627,000, 281,000, and 14,000, respectively.[8] Outbreaks occur throughout the year and have been

documented in families, healthcare systems, cruise ships, and college dormitories.

In infants and children, rotavirus, a double-stranded, wheel-shaped, RNA virus, is the most common cause of infectious diarrhea globally, and 1 million people die annually from the infection.[9] In the United States, approximately 3.5 million cases of diarrhea, 500,000 physician visits, 50,000 hospitalizations, and 20 deaths occur each year in children younger than 5 years.[7] Rotavirus is a ubiquitous contagion, infecting the vast majority of children younger than 5 years. After the initial infection, 40% of children are protected against subsequent rotavirus infection, 75% are protected against subsequent gastroenteritis, and up to 88% are protected against severe gastroenteritis. After more extensive vaccination coverage for rotavirus in recent years, hospitalizations from this infection have significantly decreased.[9] Other viral etiologies include astrovirus, enteric adenovirus, pestivirus, coronavirus, and enterovirus. These viruses are increasingly identified as causative etiologies of diarrhea. Characteristics of viral pathogens causing gastroenteritis are outlined in **Table 131-2**.

TABLE 131-2 Characteristics of Agents Responsible for Acute Viral Gastroenteritis

Virus	Peak Age of Onset	Time of Year	Duration	Mode of Transmission	Common Symptoms
Rotavirus	6 months to 2 years	October to April	3-7 days	Fecal–oral, water, food	Nausea, vomiting, diarrhea, fever, abdominal pain, lactose intolerance
Norovirus	All age groups	Peak in winter	2-3 days	Fecal–oral, food, water, environment	Nausea, vomiting, diarrhea, abdominal cramps, myalgia
Astrovirus	<7 years	Winter	1-4 days	Fecal–oral, water, shellfish	Diarrhea, headache, malaise, nausea
Enteric adenovirus	<2 years	Year-round	7-9 days	Fecal–oral	Diarrhea, respiratory symptoms, vomiting, fever
Pestivirus	<2 years	NR	3 days	NR	Mild
Coronavirus-like particles	<2 years	Fall and early winter	7 days	NR	Respiratory disease
Enterovirus	NR	NR	NR	NR	Mild diarrhea, secondary organ damage

NR, not reported.

2 In the United States, bacterial causes of acute gastroenteritis account for more than 5 million cases of diarrhea annually; however, these are vastly underreported and a causative pathogen is identified in less than 3% of cases.

FoodNet in 2015 identified 20,098 laboratory confirmed infections, resulting in 4,598 hospitalizations and 77 deaths from these infections.[4,10] Common pathogens responsible for watery diarrhea in the United States are norovirus and ETEC, while those most commonly associated with dysentery diarrhea are *Campylobacter* spp., EHEC, *Salmonella* spp., and *Shigella* spp. Other organisms that are responsible for dysentery include *Aeromonas* spp., noncholera *Vibrio*, and *Y. enterocolitica*. Characteristics of acute bacterial pathogens causing gastroenteritis are summarized in **Table 131-3**.

TABLE 131-3 Characteristics of Acute Bacterial Gastroenteritis

Bacteria	Incubation Period	Duration	Mode of Transmission	Common Symptoms
Watery Diarrhea				
Vibrio cholerae	2-3 days	1-3 days	Contaminated food or water with human feces usually in areas of inadequate treatment of sewage and drinking water	Profuse watery diarrhea, vomiting, and leg cramps Death can occur within hours without treatment
Enteroaggregative *E. coli*	NR	NR	Contaminated food or water with animal or human feces	Chronic, watery, mucoid, secretory diarrhea with low-grade fever in immunocompromised persons (HIV infections)
Enteroinvasive *E. coli*	10-18 hours	NR	Contaminated food or water with animal or human feces	Watery diarrhea in young children in the developing world
Enteropathogenic *E. coli*	9-12 hours	NR	Contaminated food or water with animal or human feces	Acute onset of profuse watery diarrhea, vomiting, and low-grade fever in young children (<2 years of age) in the developing world
Enterotoxigenic *E. coli*	1-3 days	3-4 days	Contaminated food or water with animal or human feces	Watery diarrhea and abdominal cramping
Dysentery Diarrhea				
Campylobacter jejuni	2-5 days	5-7 days	Contaminated food (particularly poultry), water, or contact with infected animals	Diarrhea (often bloody), cramping, abdominal pain, and fever
Enterohemorrhagic *E. coli*	3-4 days	5-7 days	Contaminated food (particularly cattle) or water with animal or human feces	Severe stomach cramps, diarrhea (often bloody), and vomiting Approximately 5%-10% develop hemolytic uremic syndrome
Nontyphoid Salmonella	12-36 hours	1-5 days	Contaminated food, water, or contact with infected animals	Diarrhea (sometimes bloody), fever, and abdominal cramps
Shigella	1-3 days	1-7 days	Fecal–oral Contaminated food or water with infected human feces	Watery or bloody diarrhea (8-10 stools/day), severe abdominal pain, fever, and malaise
Yersinia	4-7 days	1-3 weeks	Contaminated food or water	Fever, abdominal pain, and diarrhea (often bloody)

NR, not reported.

Cholera has been rare in the United States because of advanced water and sanitation systems, although slight increases in its incidence have occurred in recent years without clear causes. It is endemic on the Indian subcontinent and sub-Saharan Africa with five countries, Democratic Republic of the Congo,

Haiti, Somalia, the United Republic of Tanzania, and Yemen causing 80% of all cases.[11–13] *Vibrio cholerae* is a gram-negative bacillus sharing similar characteristics with the family Enterobacteriaceae. Cholera is caused by toxigenic *V. cholerae* serogroups O1 or O139. Infections due to *V. cholerae* result in severe and voluminous diarrhea that can quickly result in dehydration. Approximately half of those persons infected with *V. cholerae* O1 are symptomatic, whereas only 1% to 5% of those infected with *V. cholerae* O139 manifest symptoms.[12,13] Vaccination is available to affected areas and to people traveling to those areas that might help in reducing prevalence and severity of disease.[13]

E. coli is a gram-negative bacillus commonly found in the human GI tract, and *E. coli*–associated diarrhea may be differentiated into several distinct categories based on pathogenic features of diarrheal disease: enteroaggregative *E. coli* (EAEC), EHEC, enteroinvasive *E. coli* (EIEC), enteropathogenic *E. coli* (EPEC), and ETEC. ETEC occurs most commonly, and accounts for about half of all cases of *E. coli* diarrhea. There are an estimated 79,000 cases of ETEC in the United States each year.[4] ETEC is also the most common cause of traveler's diarrhea and a common cause of food- and water-associated outbreaks. Infections with EIEC and EPEC are primarily a disease of children in developing countries.[14] EAEC strains are implicated in persistent diarrhea (≥14 days) in human immunodeficiency virus (HIV)-infected patients.[15] EHEC, also known as Shiga toxin–producing *E. coli* (STEC), causes watery diarrhea that becomes bloody in 1 to 5 days in 80% of patients.[14]

EHEC is believed to be the major etiologic factor responsible for the development of hemorrhagic colitis and hemolytic uremic syndrome (HUS). The annual disease burden of STEC in the United States is more than 20,000 infections and as many as 250 deaths; however, the failure of many clinical laboratories to screen for this organism greatly complicates any estimates.[16] In the United States, STEC causes 50% to 60% of all EHEC infections, but in the southern hemisphere, including Argentina, Australia, Chile, and South Africa, non-STEC serotypes are often more prevalent. Non-STEC strains generally produce a lower frequency of dysentery than STEC-positive strains (62% vs 85%).

The *Campylobacter* spp. are flagellated, curved, gram-negative rods. Although there are 14 different species, *Campylobacter jejuni* is the species responsible for more than 99% of *Campylobacter*-associated gastroenteritis. Approximately 2.4 million persons are affected each year in the United States, involving almost 1% of the entire population.[4]

Salmonella enterica is a gram-negative bacilli belonging to the family Enterobacteriaceae. The most prevalent *S enterica* serotypes are Typhi and Paratyphi, which cause enteric fever. Gastroenteritis is caused by *S enterica* serotypes Typhimurium or Enteritidis. In the United States, the largest burden of *Salmonella* infection is due to nontyphoidal serotypes, causing approximately 1.4 million cases of salmonellosis, 16,000 hospitalizations, and 600 deaths, occurring annually.[17]

Approximately 165 million cases of shigellosis occur worldwide with 450,000 cases from the United States annually.[18,19] *Shigella* spp. are gram-negative bacilli belonging to the family Enterobacteriaceae. Four species most often associated with disease are *Shigella dysenteriae* type 1, *Shigella flexneri*, *Shigella boydii*, and *Shigella sonnei*.[18,19] *Shigella sonnei* and *S. flexneri* are the most common causes of gastroenteritis in the United States. The other two *Shigella* spp. are more commonly acquired during travel to developing countries. Poor sanitation or personal hygiene, inadequate water supply, malnutrition, and increased population density are associated with an increased risk of *Shigella* gastroenteritis epidemics.

Yersinia spp. are non–lactose-fermenting gram-negative coccobacilli that are widely distributed in nature. The genus *Yersinia* includes six species known to cause disease in humans. *Yersinia enterocolitica* and, to a lesser extent, *Y. pseudotuberculosis* are most likely associated with intestinal infection, but overall both are a relatively infrequent cause of diarrhea and abdominal pain. More than 50 serotypes of *Y. enterocolitica* exist; of these, serotypes 0:3, 0:8, and 0:9 are associated most frequently with enterocolitis.[20] Children are most likely to experience illness with *Y. enterocolitica* infection.

PATHOPHYSIOLOGY

Acute gastroenteritis and its resulting diarrhea are caused by altered movement of ions and water resulting in increased colonic secretion. Under normal conditions, the GI tract has tremendous capacity to absorb fluid and electrolytes, allowing only 100 to 200 mL of fluid to be excreted in the stool daily.[21] The classic enteric pathogen that causes secretary diarrhea is *V. cholerae*, but ETEC and rotavirus also cause watery diarrhea and are much more predominant etiologies in the United States.

V. cholerae is an enteric pathogen that causes classical secretory diarrhea due to changes in ion secretion and absorption. Among the toxins produced by *V.*

cholerae, the most important is cholera toxin.[11] Cholera toxin consists of two subunits, A and B. The B subunits are responsible for delivery of the A subunit into the cell. The A subunit stimulates adenylate cyclase, which increases intracellular cyclic adenosine monophosphate (cAMP) and results in protein kinase A-mediated activation of cystic fibrosis transmembrane conductance regulator. This leads to increased chloride secretion and decreased sodium absorption producing the severe watery diarrhea characteristic of the disease.[22] The toxin likely acts along the entire intestinal tract, but most fluid loss occurs in the duodenum. The net effect of the cholera toxin is isotonic fluid secretion early in the intestinal tract that exceeds the absorptive capacity of the latter intestinal tract.

ETEC also causes watery diarrhea characterized by severe intestinal water secretion by producing plasmid-mediated enterotoxins: heat-labile toxin and heat-stable toxin. The heat-labile toxin has two subunits (A and B) that have similar antigenic properties and action on the gut mucosa as cholera toxin. Heat-labile toxins increase chloride secretion via activation of cAMP. The net effect is luminal accumulation of electrolytes that draws water into the intestine, and production of a cholera-like secretory diarrhea.[23] Heat-stable toxin is thought to be nonantigenic and produces watery diarrhea by acting on the small intestine.

Rotavirus induces changes in transepithelial fluid balance, and causes malabsorption as a consequence of destruction of the epithelial lining of intestine, and vascular damage and ischemia in villi. Once rotavirus infects small intestinal villus cells, viroplasms are formed and its toxin, nonstructural protein 4, is released. The viral enterotoxin increases intracellular calcium, and the increase in calcium disrupts microvillus cytoskeleton, as well as barrier function. Changes to the villi include shortening of villus height, crypt hyperplasia, and mononuclear cell infiltration of the lamina propria.[24]

Inflammatory diarrhea is caused by two groups of organisms—enterotoxin-producing, noninvasive bacteria (eg, EAEC, EHEC) or invasive organisms (eg, *Campylobacter* spp., *Salmonella* spp., *Shigella* spp.). The enterotoxin-producing organisms adhere to the mucosa, activate cytokines, and stimulate the intestinal mucosa to release inflammatory mediators. Invasive organisms, which can also produce enterotoxin, invade the intestinal mucosa to induce an acute inflammatory reaction, involving the activation of local and systemic cytokines and inflammatory mediators.

Ingestion of as few as 10 to 200 viable organisms of the *Shigella* spp. causes disease in healthy adults.[18,19] *Shigella* multiply and spread within the submucosa of the small bowel, but they rarely extend beyond the mucosa. Inflammatory

diarrhea is caused by the pathogens invading the epithelial barrier through M cells where they encounter and eliminate macrophages. The destruction of macrophages after emergence from M cells causes an initial release of interleukin (IL)-1β. This initial inflammatory process is exacerbated by free bacteria binding to toll-like receptor that causes the production of IL-6 and IL-8. Both IL-1β and IL-8 attract polymorphonucleocytes.[25] Release of polymorphonucleocytes activates chloride secretion and subsequent diarrhea. Degranulation and release of toxic substances by neutrophils cause ulceration of the epithelium, distortion of the crypts, death to intestinal epithelium, sloughing of mucosal cells, bloody mucoid exudate into the gut lumen, and submucosal accumulation of inflammatory cells with microabscess formation.[26] Microabscesses eventually may coalesce, forming larger abscesses. *Shigella* will frequently affect the entire colon. In addition to the virulence characteristics of invasiveness, *S. dysenteriae* type 1 and, to a lesser degree, *S. flexneri* and *S. sonnei* produce a cytotoxin or Shiga toxin, which can lead to HUS.[14]

The pathogenicity of EHEC is related to the production of Shiga-like toxins, so named because of their resemblance to the Shiga toxin of *S. dysenteriae*.[21] The cytotoxic effect of Shiga-like toxins disrupts the mucosal integrity of the large intestine, causing diarrhea. In addition, the toxin is able to pass through the intestinal epithelium to reach the endothelial cells lining small blood vessels that supply the gut, kidney, and other viscera, causing the myriad metabolic events that could eventually lead to HUS.

CLINICAL PRESENTATION

Gastroenteritis is an illness characterized by diarrhea, which may be accompanied by nausea, vomiting, fever, and abdominal pain. For effective diagnosis and management, it is important to distinguish noninflammatory diarrhea that produces watery diarrhea from inflammatory diarrhea or dysentery. Most enteric pathogens produce acute diarrhea and pathogens associated with dysentery will often result in grossly bloody stools and mucus. Systemic symptoms of gastroenteritis, such as fever, are often associated with dysentery of infectious origin. Symptoms of enteric pathogens that cause watery and dysentery diarrhea are listed in Table 131-1.

A physical examination and careful history that includes information about symptoms and symptom duration, the number of individuals affected, and recent history of travel, diet, and medications are important factors in making a diagnosis. Infections with norovirus or ETEC will often result in mild, self-

limiting disease, whereas cholera will commonly produce severe dehydrating diarrhea. Infections with enteric pathogens such as *Campylobacter* spp., EHEC, *Salmonella* spp., *Shigella* spp., and *Y. enterocolitica* can result in severe symptomatology due to dysentery. The utilization of serum C-reactive protein (CRP) in young adult patients with infectious diarrhea may be able to help differentiate between noninflammatory and inflammatory causes.[27] Assessing CRP could assist with diagnosis, prognosis, and treatment selection. The clinical presentation of acute viral and bacterial gastroenteritis is summarized in Tables 131-2 and 131-3, respectively.

3 Stool culture is an important tool in making an organism-specific diagnosis and determining susceptibility to antimicrobial agents. Due to the low yield, stool cultures are not recommended in most mild-to-moderate watery diarrhea. Instead, indications for stool cultures include dysenteric diarrhea, persistent diarrhea in immunocompromised patients (ie, persons aged 65 years and older with comorbid diseases, neutropenia, or HIV infection), and diarrhea where an outbreak is suggested.[1] An appropriately obtained stool culture identifies the presence of *Campylobacter*, *Salmonella*, and *Shigella* spp. The yield of stool cultures for other pathogens is increased if the test is ordered specifically based on history and physical examination. For dysenteric diarrhea, the laboratory should be instructed to evaluate for EHEC including STEC (*E. coli* O157:H7). In hospitalized patients who develop diarrhea 3 days after hospitalization or in those with recent exposure to antimicrobials or chemotherapy, stool specimen should be sent for *C. difficile* toxins A and B. In addition to stool cultures, microscopic examination for fecal polymorphonuclear cells, or a simple immunoassay for the neutrophil marker lactoferrin, can further provide evidence of an inflammatory process and increase the yield of cultures in patients presenting with dysenteric diarrhea.[1]

Complications

Complications associated with acute diarrhea most likely result from dehydration so treatment focuses primarily on rehydration therapy, regardless the etiology. Dysenteric diarrhea is more likely to have severe complications, especially in children younger than 5 years and in elderly. Bacteremia is the most common complication of gastroenteritis and can be seen after infections with nontyphoid *Salmonella, C. jejuni* or *C. fetus*, and *Y. enterocolitica*.[16] Nontyphoid *Salmonella* is most common in children younger than 5 years, elderly, and patients with hemoglobinopathy, malaria, or immunosuppression. Bacteremia

due to *Campylobacter* spp. has been reported in patients with HIV infection, malignancy, transplantation, and hypogammaglobulinemia. *Y. enterocolitica* bacteremia has been rarely reported, but has an increased prevalence in patients with diabetes mellitus, severe anemia, hemochromatosis, iron overload (frequent transfusion), cirrhosis, malignancy, and in the elderly.[28] Persistent bacteremia with these pathogens will commonly result in prolonged intermittent fever with chills. Potentially complicating the diagnosis, stool cultures frequently are negative and leukocyte counts are often within the normal range. Vascular complications such as seeding of atherosclerotic plaques or aneurysms in arterial vessels occur in 10% to 25% of adults with bacteremia. Localized infections involving bone, cysts, heart, kidney, liver, lungs, pericardium, and spleen develop in 5% to 10% of patients with bacteremia.

A severe complication in patients infected with EHEC is HUS. HUS is defined by the triad of acute renal failure, thrombocytopenia, and microangiopathic hemolytic anemia and is more commonly observed in children younger than 5 years and in the elderly.[29] Approximately 2% to 7% of cases infected with STEC strains are complicated by development of HUS, which increases mortality associated with this infection. *S. dysenteriae* type 1 can also cause HUS, although more rarely than observed with EHEC.[18]

Shigella infection may also lead to complications such as generalized seizures, sepsis, toxic megacolon, perforated colon, arthritis, and protein-losing enteropathy. Mortality is rare, but it may be more likely with *S. dysenteriae* type I. Less than 3% of persons who are infected with *S. flexneri* will later develop Reiter syndrome, characterized by pains in the joints, irritation of the eyes, and painful urination. This can lead to chronic arthritis.[30]

Infection with *C. jejuni* has been associated with Guillain-Barré syndrome (GBS), but the relationship is not well understood.[31] The risk of developing GBS after *C. jejuni* infection appears to be low (approximately 1 case of GBS per 1,000 *C. jejuni* infections). The weakness associated with GBS usually starts in the legs, with difficulty in walking, and may progress to a complete paralysis of all extremities that lasts several weeks and usually requires intensive care.

Approximately 10% to 30% of adult patients develop a reactive arthritis 1 to 2 weeks after recovery from gastroenteritis secondary to *S. flexneri*, *Salmonella* spp., *C. jejuni*, and *Y. enterocolitica*. This arthritis, involving the knees, ankles, toes, fingers, and wrists, usually resolves in 1 to 4 months but may persist in approximately 10% of patients.[31] This complication is more common in persons with the HLA-B27 antigen.

A general complication that could occur long after an infectious

gastroenteritis, especially with dysentery and toxin-mediated dysentery, is postinfectious irritable bowel syndrome (IBS). This is classified as IBS symptoms for at least 3 months following an episode of gastroenteritis or traveler's diarrhea showing recurrent abdominal pain or discomfort.[32] Albeit rare, some long-term complications associated with these infections strengthen the need for appropriate diagnosis and treatment.

TREATMENT

Mortality associated with infectious diarrhea has declined substantially in the past 2 decades, especially among children younger than 1 year. Preventative measures including improved sanitation, breast-feeding and weaning practices, and increased use of oral rehydration therapy (ORT) for affected individuals are responsible for the decrease in case-fatality rates.

General Approach to Treatment

The cornerstone of management for all GI infections and enterotoxigenic poisonings is to prevent dehydration by correcting fluid and electrolyte imbalances. In mild, self-limiting acute gastroenteritis, a diet of oral fluids and easily digestible foods is recommended. In patients with severe dehydrating watery diarrhea and dysenteric diarrhea, IV rehydration therapy, antibiotics, and/or antimotility treatments are needed.

Rehydration Therapy

Initial assessment of fluid loss is essential for successful rehydration therapy and should include acute weight loss, as it is the most reliable means of determining the extent of water loss. However, if accurate baseline weight is not available, clinical signs are helpful in determining approximate deficits (**Table 131-4**). Physical assessment generally is more reliable in young children and infants than in adults.

TABLE 131-4 Clinical Assessment of Degree of Dehydration in Children Based on Percentage of Body Weight Loss[a]

Variable	Minimal or No Dehydration (<3% Loss of Body Weight)	Mild-to-Moderate (3%-9% Loss of Body Weight)	Severe (≥10% Loss of Body Weight)
Blood pressure	Normal	Normal	Normal to reduced
Quality of pulses	Normal	Normal or slightly decreased	Weak, thready, or not palpable
Heart rate	Normal	Normal to increased	Increased (bradycardia in severe cases)
Breathing	Normal	Normal to fast	Deep
Mental status	Normal	Normal to listless	Apathetic, lethargic, or comatose
Eyes	Normal	Sunken orbits/decreased tears	Deeply sunken orbits/absent tears
Mouth and tongue	Moist	Dry	Parched
Thirst	Normal	Eager to drink	Drinks poorly; too lethargic to drink
Skin fold	Normal	Recoil in <2 seconds	Recoil in >2 seconds
Extremities	Warm, normal capillary refill	Cool, prolonged capillary refill	Cold, mottled, cyanotic, prolonged capillary refill
Urine output	Normal to decreased	Decreased	Minimal
Hydration therapy	None	ORS 50-100 mL/kg over 3-4 hours	Lactated Ringer's solution or normal saline 20 mL/kg over 15-30 minutes IV until mental status or perfusion improves Followed by 5% dextrose/0.45% sodium chloride IV at higher maintenance rates or ORS 100 mL/kg over 4 hours.
Replacement of ongoing losses	For each diarrheal stool or emesis <10 kg body weight: 60-120 mL ORS >10 kg body weight: 120-240 mL ORS	Same as minimal dehydration	If unable to tolerate ORS, administer through nasogastric tube or administer 5% dextrose/0.45% sodium chloride with 20 mEq/L (mmol/L) potassium chloride IV

ORS, oral rehydration solution.

[a]Percentages vary among patients for each dehydration category; hemodynamic and perfusion status is most important; when unsure of category, therapy for more severe category is recommended.

3 Fluid replacement is the cornerstone of therapy for dehydration due to diarrhea regardless of etiology. For the treatment of mild-to-moderate dehydration, ORT is superior to administration of IV fluids. Oral replacement therapy reverses dehydration in nearly all patients with mild-to-moderate diarrhea with 94% to 97% efficacy.[1] It offers advantages of being inexpensive, noninvasive, and not requiring inpatient administration. Moreover, thirst drives use of ORT and provides a safeguard against overhydration. Replacement of ongoing losses as well as continuation of normal feeding should also be addressed.

The necessary components of oral rehydration solutions (ORS) include

carbohydrates (typically glucose), sodium, potassium, chloride, and water. Using both salt and glucose in the ORS takes advantage of glucose-coupled sodium transport in the small bowel and enhances sodium and subsequently water transport across intestinal walls. In 2002, the World Health Organization/United Nations Children's Fund (WHO/UNICEF) endorsed a reduced osmolarity solution (osmolarity ≤250 mOsm/L) as the use of these solutions reduced stool volume, shortened duration of diarrhea, and decreased need for unscheduled IV therapy when compared with previously used ORS more than or equal to 310 mOsm/L.[33] The newer formulation of ORS less than or equal to 250 mOsm/L was, however, more likely to cause hyponatremia (blood sodium levels <130 mmol/L).[34] If commercial ORS are unavailable, one can be roughly duplicated by mixing ½ teaspoon of salt with 6 teaspoons of sugar in 1 L of water.[35]

In restoring fluid and electrolyte balance in cholera infections, polymer-based ORS may be more efficacious than glucose-based ORS. Polymer-based ORS contains rice, wheat, sorghum, or maize. This polymer-based ORS releases glucose more slowly after digestion and, when absorbed in the small bowel, enhances the reabsorption of water and electrolyte secreted into the bowel lumen during diarrhea. Polymer-based ORS reduces the duration of diarrhea in adults with cholera when compared with glucose-based ORS more than or equal to 310 and less than or equal to 270 mOsm/L.[36]

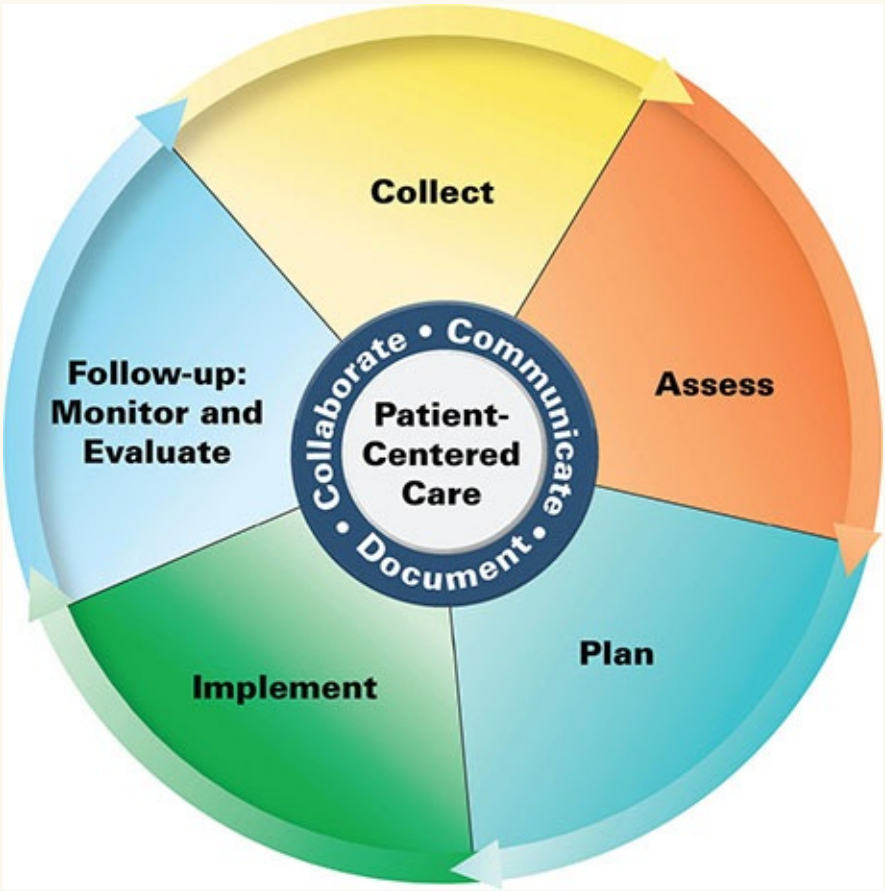
Guidelines for rehydration therapy based on the degree of dehydration and replacement of ongoing losses are outlined in Table 131-4. ORS should be given in small and frequent volumes (5 mL every 2-3 minutes in a teaspoon or oral syringe). Nasogastric administration of ORS is an alternative method of administration in a child with persistent vomiting. For breast-fed infants, nursing should be continued. The composition of commercial ORS and commonly consumed beverages is listed in **Table 131-5**. Clear fluids, such as soft drinks, sweetened fruit drinks, chicken broth, and sports drinks, should be avoided in the treatment of dehydration. These hyperosmolar solutions may cause an osmotic diarrhea.

TABLE 131-5 Comparison of Common Solutions Used in Oral Rehydration and Maintenance

Variable	Minimal or No Dehydration (<3% Loss of Body Weight)	Mild-to-Moderate (3%-9% Loss of Body Weight)	Severe (≥10% Loss of Body Weight)
Blood pressure	Normal	Normal	Normal to reduced
Quality of pulses	Normal	Normal or slightly decreased	Weak, thready, or not palpable
Heart rate	Normal	Normal to increased	Increased (bradycardia in severe cases)
Breathing	Normal	Normal to fast	Deep
Mental status	Normal	Normal to listless	Apathetic, lethargic, or comatose
Eyes	Normal	Sunken orbits/decreased tears	Deeply sunken orbits/absent tears
Mouth and tongue	Moist	Dry	Parched
Thirst	Normal	Eager to drink	Drinks poorly; too lethargic to drink
Skin fold	Normal	Recoil in <2 seconds	Recoil in >2 seconds
Extremities	Warm, normal capillary refill	Cool, prolonged capillary refill	Cold, mottled, cyanotic, prolonged capillary refill
Urine output	Normal to decreased	Decreased	Minimal
Hydration therapy	None	ORS 50-100 mL/kg over 3-4 hours	Lactated Ringer's solution or normal saline 20 mL/kg over 15-30 minutes IV until mental status or perfusion improves Followed by 5% dextrose/0.45% sodium chloride IV at higher maintenance rates or ORS 100 mL/kg over 4 hours.
Replacement of ongoing losses	For each diarrheal stool or emesis <10 kg body weight: 60-120 mL ORS >10 kg body weight: 120-240 mL ORS	Same as minimal dehydration	If unable to tolerate ORS, administer through nasogastric tube or administer 5% dextrose/0.45% sodium chloride with 20 mEq/L (mmol/L) potassium chloride IV

ORS, oral rehydration solution.

[a]Percentages vary among patients for each dehydration category; hemodynamic and perfusion status is most important; when unsure of category, therapy for more severe category is recommended.



Patient Care Process for *Clostridioides difficile* Infections (CDI)

Collect

- Patient characteristics (eg, age, sex)
- Patient medical history (personal and family), including any previous episodes of CDI
- Social history (eg, tobacco/ethanol use) and dietary habits
- Current medications including OTC, herbal products, dietary supplements, acid suppressive medication, and previous antibiotic use (within the past 3 months)
- Characteristics of diarrhea including onset, number of episodes per day, and presence of blood

- Objective data
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2-saturation
  - Labs including white blood cell count (WBC) and serum creatinine (SCr)
  - Stool sample to be tested for *Clostridim difficile* toxins
  - Radiographic abdominal imaging if concern for ileus or megacolon

Assess

- Hemodynamic stability (eg, systolic BP <90 mm Hg, HR >110 bpm, O_2-sat <90% [0.90], RR)
- Radiographic studies for the presence of ileus, megacolon, or perforation
- Presence of CDI risk factors (age, antibiotic use, recent healthcare exposure, chemotherapy, GI surgery, tube feeding, acid suppressive medications)
- Ability to stop offending antibiotic agent if applicable
- Ability/willingness to pay for first-line treatment options
- Ability/willingness to try investigational therapies such as fecal microbiota transplant (if applicable for recurrent disease)
- Ability/willingness to pay for adjunctive therapy with bezlotoxumab

Plan*

- Drug therapy regimen including specific antibiotic dose, route, frequency, and duration (see Table 131-7)
- Discontinuation of offending antibiotic agent if applicable
- Monitoring parameters, such as resolution of diarrhea; frequency and timing of follow-up
- Patient education (eg, purpose of treatment, drug-specific information, and prevention of disease transmission)
- Self-monitoring for resolution of diarrhea and when to seek emergency medical attention
- Referrals to other providers when appropriate (eg, infectious diseases,

gasteroenterology)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Resolution of diarrhea
- Presence of adverse effects (eg, CNS effects, metallic taste if metronidazole used; nausea, abdominal pain)
- Patient adherence to treatment plan using multiple sources of information
- Educate on limiting risk factors, such as antibiotic agents and acid suppressive medications

**Collaborate with patient, caregivers, and other healthcare professionals.*

In the treatment of severe dehydration, the primary goal of therapy is rapid restoration of fluid losses, correction of metabolic acidosis, and replacement of potassium deficiency. Severely dehydrated patients should be resuscitated initially with IV lactated Ringer solution or normal saline to restore hemodynamic stability. Lactated Ringer solution is preferred initially over normal saline because normal saline does not assist in correcting a metabolic acidosis. As GI and renal perfusion should be addressed aggressively, rapid IV administration is preferred over prolonged administration regimens for restoring extracellular fluids and electrolytes.[37] After rehydration, maintenance fluid is given based on accurate recording of intake and output volumes. ORT should be instituted as soon as it can be tolerated.

Early refeeding with age-appropriate unrestricted diet is recommended in children. Early refeeding during or immediately following the start of rehydration did not increase the risk of complications such as unscheduled IV fluids, vomiting, or development of persistent diarrhea compared with late refeeding that ranged from 20 to 48 hours after start of rehydration.[37] Initially,

easily digested foods such as bananas, applesauce, and cereal should be introduced and foods high in fiber, sodium, and sugar should be avoided. One caveat would be that lactase deficiency may be exacerbated among known lactase-deficient patients and may persist up to 10 days.

Antimicrobial Therapy

4 The indiscriminate use of antimicrobial therapy produces increases in antimicrobial resistance, side effects of antimicrobial agents, and the threat of superinfections owing to eradication of normal flora. Increasing fluoroquinolone resistance in *Campylobacter* and multidrug resistance in *Salmonella* spp. worldwide reinforces the importance of judicious use of antibiotics and prudent infection control measures.[38,39] Antibiotic therapy is recommended in severe cases of diarrhea, moderate-to-severe cases of traveler's diarrhea, most cases of febrile dysenteric diarrhea, and culture-proven bacterial diarrhea. Antimicrobial therapy is not recommended in EHEC diarrhea as it may increase HUS risk.

Antibiotic therapy is recommended in severe cases of cholera and ETEC diarrhea. In cases of cholera, antibiotics shorten the duration of diarrhea, decrease fluid loss, and shorten the duration of the carrier state.[1,12] It is important to consider local susceptibility patterns in the selection of the antimicrobial regimen. In areas of high fluoroquinolone resistance, azithromycin has been effective in patients with cholera. In patients with ETEC diarrhea, empiric antibiotics reduce severity and duration of diarrhea. A short course of therapy with fluoroquinolones is the most commonly recommended therapy due to increased resistance among other drug classes.[40] Rifaximin has been effective for ETEC for travel in Mexico.[41] Further discussions of antibiotic prophylaxis and treatment can be found in the section on traveler's diarrhea. **Table 131-6** summarizes antibiotic recommendations. Further details regarding treatment of *C. difficile*–associated diarrhea, traveler's diarrhea, and foodborne illnesses are discussed in respective sections.

TABLE 131-6 Recommendations for Antibiotic Therapy

Pathogen	Children	Adults
Watery Diarrhea		
Enterotoxigenic *Escherichia coli*	Azithromycin 10 mg/kg/day given orally once daily × 3 days; ceftriaxone 50 mg/kg/day given IV once daily × 3 days	Ciprofloxacin 750 mg orally once daily × 1-3 days. Alternatives: rifaximin 200 mg orally three times daily × 3 days; azithromycin 1,000 mg orally × 1 day *or* 500 mg orally daily × 3 days
Vibrio cholerae O1	Erythromycin 30 mg/kg/day divided every 8 hours orally × 3 days; azithromycin 10 mg/kg/day given orally once daily × 3 days	Doxycycline 300 mg orally × 1 day Alternatives: azithromycin 500 mg orally once daily × 3 days; ciprofloxacin 750 mg orally once daily × 3 days; ceftriaxone IV
Dysenteric Diarrhea		
Campylobacter species[a]	Azithromycin 10 mg/kg/day given orally once daily × 3-5 days; erythromycin 30 mg/kg/day divided into two to four doses orally × 3-5 days	Azithromycin 500 mg orally once daily × 3 days Alternatives: ciprofloxacin 750 mg orally once daily × 7 days
Salmonella Nontyphoidal[a]	Ceftriaxone 100 mg/kg/day divided IV every 12 hours × 7-10 days; azithromycin 20 mg/kg/day orally once daily × 7 days	Ceftriaxone 2 g IV/IM once; ciprofloxacin 750 mg orally once daily × 7-10 days; Alternatives: ampicillin 250-500 mg orally every 6 hours × 7 days; azithromycin 500 mg orally once daily × 7 days; Trimethoprim-sulfamethoxazole 160/800 mg twice daily × 7 days For immunocompromised patients, duration should be increased to 14 days for both fluoroquinolones and azithromycin
Shigella species[a]	Azithromycin 10 mg/kg/day given orally once daily × 3 days; ceftriaxone 50 mg/kg/day given IV once daily × 3 days	Azithromycin 500 mg orally once daily x 3 days; ceftriaxone 2 g IV/IM once; ciprofloxacin 750 mg orally once daily × 3 days; Alternatives: ampicillin 250-500 mg orally every 6 hours × 7 days; Trimethoprim–sulfamethoxazole 160/800 mg twice daily × 7 days
Yersinia species[a]	Treat as children with shigellosis	Trimethoprim-sulfamethoxazole160/800 mg twice daily × 7 days Alternatives: cefotaxime IV or ciprofloxacin 750 mg orally once daily × 7 days
Traveler's Diarrhea		
Prophylaxis[a]		Norfloxacin 400 mg or ciprofloxacin 750 mg orally daily; rifaximin 200 mg one to three times daily up to 2 weeks
Treatment		Ciprofloxacin 750 mg orally × 1 day or 500 mg orally every 12 hours × 3 days; levofloxacin 1,000 mg orally × 1 day or 500 mg orally daily × 3 days; rifaximin 200 mg three times daily × 3 days; azithromycin 1,000 mg orally × 1 day or 500 mg orally daily × 3 days

[a]For high-risk patients only. See the preceding text for the high-risk patients in each infection.

Antibiotic therapy is indicated in at-risk and febrile patients with dysenteric diarrhea. In shigellosis, antibiotics shorten the period of fecal shedding and attenuate the clinical illness. Antibiotic therapy is reserved for the elderly, those who are immunocompromised, children in daycare centers, malnourished children, and healthcare workers. In the United States, *Shigella* spp. remain

susceptible to fluoroquinolones. Fluoroquinolone resistance among *Shigella* spp. is of increasing concern in developing countries, and azithromycin may be a better choice in patients with a recent history of travel to a developing region.[1,18] Similar antibiotic regimens can be used for high-risk patients who develop *Yersinia* bacteremia (ie, infants younger than 3 months and patients with cirrhosis or iron overload) or in patients with bone and joint infections.[42] With Campylobacteriosis, antibiotics are not useful unless started within 4 days of the start of the illness because they do not shorten the duration or severity of diarrhea and only shorten the duration of bacterial excretion. Antibiotics are warranted in patients with high fevers, severe bloody diarrhea, prolonged illnesses (more than 1 week), pregnancy, and immunocompromised states, including HIV infection. Fluoroquinolone resistance among *Campylobacter* spp. has increased, and is now 10% to 13% in the United States and 41% to 88% in Europe and Asia. Resistance may be the result of the use of fluoroquinolone antibiotics in poultry and other animal feed, and the frequent use of these agents internationally in treating enteric infections. Macrolides like azithromycin are recommended especially in patients with a recent history of travel to Asia.[40]

Nontyphoid *Salmonella* infection leads to bacteremia in approximately 8% of otherwise healthy adults. However, patients with increased risk of bacteremia should be treated with antibiotics if appropriate diagnosis is made. High-risk patients include neonates or infants younger than 1 year, persons older than 50 years, and patients with primary or secondary immunodeficiency such as acquired immunodeficiency syndrome (AIDS) or chemotherapy-induced inflammatory bowel disease, sickle cell disease, vascular abnormalities (prostatic heart valve or abdominal aneurysm), or prosthetic joints.[18] If cultures are positive for Salmonellosis and antibacterial therapy is warranted, susceptibility testing should be done for appropriate targeted therapy due to concern of resistance.

Outcomes of some bacterial diarrheal illnesses may be worsened by the use of antibacterials, therefore precluding their use. In patients infected with EHEC, use of a fluoroquinolone or trimethoprim–sulfamethoxazole may increase the risk of HUS by increasing the production of Shiga-like toxin.[1,42] Empiric antimicrobial therapy should be withheld when clinical suspicion is high due to the high local prevalence EHEC, patient clinical presentation suggestive of EHEC infection, or a known foodborne outbreak of dysentery with an incubation period of longer than 2 days. Antibiotics should not be given to infants or children due to a higher incidence of HUS in this population. Treatment of EHEC infection is primarily limited to supportive care, which may include fluid

replacement therapy, hemodialysis, hemofiltration, transfusion red blood cells and/or platelets, and other interventions as indicated clinically. Severe disease may lead to chronic kidney failure and potential need of renal transplantation.

Antimotility Agents

5 Antimotility drugs such as diphenoxylate/atropine and loperamide offer symptomatic relief in patients with watery diarrhea by reducing the number of stools. However, in both enterotoxigenic and dysenteric diarrhea, slowing of fecal transit time with these agents is thought to result in extended toxin-associated damage, worsening symptomatology and leads to complications. Therefore, antimotility drugs should be avoided if possible and are not recommended in patients with toxin-mediated dysenteric diarrhea (ie, EHEC, pseudomembranous colitis, shigellosis). However, some evidence suggests that in adults with dysenteric diarrhea these agents do not appear to be harmful if given concomitantly with antibacterial therapy.[42]

Probiotics

Probiotics are preparations of microorganisms and most commercial products have been derived from food sources, particularly cultured milk products (ie, lactobacilli and bifidobacteria). When used in the treatment or prophylaxis of infectious diarrhea and antibiotic-associated diarrhea, efficacy is variable. Most individual studies have not shown significant benefit from the use of probiotics and meta-analyses have shown conflicting results, with one demonstrating efficacy when trials were assessed in aggregate[43] and another demonstrating no benefit.[44] No serious adverse effects have been reported in otherwise healthy persons; however, there are data suggesting a rare but increased incidence of fungemia or bacterial sepsis with probiotic use. With these potential adverse events and limited efficacy data, probiotics should not be recommended for prophylaxis or treatment of initial antibiotic-associated diarrhea.

Oral Zinc Supplementation

Zinc deficiency is largely due to inadequate dietary intake and is common in many developing countries where morbidity and mortality associated with acute diarrhea in children remains high. In children older than 6 months who demonstrate moderate signs of malnutrition, zinc supplementation may shorten the duration of diarrhea by approximately 27 hours (95% CI −14.62 to

−39.34).[45] Therefore, oral zinc supplementation of 20 mg/day for 1 to 2 weeks may have an additional benefit over ORS alone in reducing childhood mortality in developing countries. Common side effects include metallic taste and vomiting. At high doses, zinc supplementation may cause epigastric pain, lethargy, and fatigue.

PREVENTION OF GASTROINTESTINAL INFECTIONS

6 Public health measures of improved water supply and sanitation facilities and the quality control of commercial products are important for the control of the majority of GI infections. In addition, following simple rules of personal hygiene and safe food preparation can prevent many diarrheal diseases. Hand washing with soap and running water is instrumental in preventing the spread of illness and should be emphasized for caregivers and persons with diarrheal illnesses. Safe food handling and preparation practices can significantly decrease the incidence of certain enteric infections.

Reporting suspected outbreaks and cases of notifiable illness to local health authorities is vital to investigation of threats of enteric infection arising from increasingly global and industrialized food supplies. The reporting of specific infectious diseases to the appropriate public health authorities is the cornerstone of public health surveillance, outbreak detection, and prevention and control efforts.

Vaccines are used to boost specific immune processes directed against the bacteria themselves or against adherence appendages, cytotoxins, or enterotoxins. Unfortunately, there are only a few vaccines available for prevention of gastroenteritis. Vaccines for typhoid fever are the parenteral Vi capsular polysaccharide vaccine (ViCPS) and the oral live-attenuated Ty21a vaccine.[46] Efficacy rates for both vaccines range from 50% to 80%. The ViCPS is indicated for children who are 2 years of age or older, and a booster dose is administered 2 years after the first. The Ty21a vaccine is indicated for children 6 years or older; one capsule should be swallowed whole every other day for a total of four doses at least 1 week before the potential exposure. A booster should be taken every 5 years if continued protection is needed.

In the United States, routine rotavirus vaccination is recommended for all infants beginning at age 2 months. There are two vaccines, RotaTeq (RV5) and Rotarix (RV1), available for reducing rotaviral gastroenteritis.[47] The RV5

vaccine is a live, oral vaccine that offers 74% efficacy against gastroenteritis of any severity and 98% efficacy against severe disease. This vaccine also decreased office visits by 86%, emergency department visits by 94%, and hospitalizations by 96%. The RV1 vaccine is a live-attenuated human rotavirus vaccine. This vaccine has clinical efficacy of 79% against gastroenteritis of any severity and 96% efficacy against severe rotavirus disease. Rotarix reduced hospitalizations by 100% and medically attended visits by 92% in the first rotavirus season, and reduced hospitalizations by 96% through two seasons.[47] The RV5 vaccine is administered orally in a three-dose series at ages 2, 4, and 6 months while the RV1 vaccine is administered orally in a two-dose series at ages 2 and 4 months. The first dose may be given between 6 weeks and 14 weeks and 6 days of age and all doses should be given before 8 months of age. The vaccines are contraindicated in infants with severe allergic reactions to vaccine components, diagnosed with severe combined immunodeficiency, and with history of intussusception.[48]

Although not available in the United States, two oral vaccines against diarrheal pathogens are available in other countries. Dukoral consists of killed *V. cholerae* O1 organisms and the cholera B subunit, and is licensed in over 60 countries. Shanchol consists of killed whole cells from a mix of pathogenic strains of *V. cholerae* (O1 and O139) and is licensed in India.[11,13] Both vaccines are given in two doses (three doses of Dukoral are required for children aged 2-5 years) and administered about 7 to 14 days apart (up to 42 days apart for Dukoral). Dukoral must be administered with a buffer that requires 75 to 150 mL of clean water while Shanchol does not require the buffer. Both vaccines demonstrated protective efficacy of 47% to 87% after two doses but almost none after a single dose. Protection is achieved in approximately 1 week following the last dose and persists for approximately 2 years. The common side effects of the vaccines were considered mild and included abdominal pain, headache, fever, and nausea. The WHO does not require vaccination for international travel to or from endemic areas because vaccines require two doses and provide incomplete protection for a relatively short period of time.[13]

There are vaccines in development for common enteric pathogens including ETEC and *Shigella* spp. with the potential for combining them in a single vaccine. These are still in preliminary and animal-based studies, but could significantly affect global public health if they come to fruition for human administration, especially in the infants and children.[49]

EVALUATION OF THERAPEUTIC OUTCOMES

Appropriate follow-up care of patients with acute diarrhea is based on successful restoration of fluid losses. The clinical signs and symptoms that lead to the diagnosis also can assess adequate rehydration, and should be monitored frequently. With ORT preferred, routine laboratory testing often is unnecessary. Electrolytes should be measured in those receiving IV fluids, when oral replacement fails, or when signs of hypernatremia or hypokalemia are present. Follow-up stool samples to ensure complete evacuation of the infecting pathogen may be necessary only in patients who are at high risk to initiate or contribute to a community outbreak. All patients should be monitored for complications associated with the infecting pathogen, resolution of the diarrhea, and adverse reactions to the pharmacologic agents used. Prompt discharge of hospitalized patients is recommended when rehydration is achieved, IV fluids have not been required, oral intake equals or exceeds losses, or adequate education and medical follow-up are ensured. For most patients, discharge can occur in 16 to 24 hours.

CLOSTRIDIOIDES DIFFICILE

Epidemiology

C. difficile is the most commonly recognized cause of infectious diarrhea in healthcare settings with high rates of disease in the elderly and those exposed to antibiotic agents. While almost all antibiotics have been implicated in *C. difficile* infection (CDI), those most commonly associated include fluoroquinolones, clindamycin, carbapenems, and third-/fourth- generation cephalosporins. CDI often occurs during or shortly after completion of antimicrobial therapy; however, disease onset can be delayed for 3 or more months.[50] Other risk factors for acquisition of *C. difficile* include recent healthcare exposure, chemotherapy, patients undergoing gastrointestinal surgery or receiving tube feeding, and potentially those receiving acid suppressive medications. Although many studies have shown an association between *C. difficile* infection and acid suppressing medications, such as proton pump inhibitors (PPIs) and histamine-2 blockers, there is a need for prospective randomized trials to confirm this link.[50,51]

Incidence of CDI was steadily rising in the early 2000s, appearing to peak around 2010 in the United States and Europe. Since then rates of CDI have plateaued in the United States with an estimated 500,000 cases annually. While the epidemiology of CDI has remained steady, infection is becoming

increasingly common in the community setting, with an estimated 28% of cases being identified as community acquired, in addition to 37% classified as healthcare associated and 36% attributed to long-term care facilities.[50,52] Increased morbidity and mortality is associated with more severe disease, which may be linked to a hypervirulent strain, PCR ribotype 027 (also known as North American pulsed-field type [NAP-1]). Recurrent CDI poses up to a 33% higher risk of mortality compared to those who do not have a recurrence.[50]

Etiology and Pathophysiology

C. difficile is a gram-positive spore-forming bacterium that may colonize the large intestine of healthy patients, as well as those experiencing a symptomatic CDI. Two major toxins (toxin A [TcdA] and toxin B [TcdB]) are released that mediate the symptoms of CDI. Other virulence factors include production of binary toxin, mutations causing hyperproduction of toxins, antibiotic resistance, increased sporulation, and mutations that increase adherence to the intestinal epithelium.[52,53]

C. difficile is transmitted most commonly by the fecal-oral route through ingestion of *C. difficile* spores. Pathogenic CDI occurs when there is disruption of the bowel flora and/or an inadequate immune response. This leads to an inflammatory cascade mediated by toxins A and B that causes tissue damage and results in diarrhea. Initially, raised white and yellowish plaques form in the colon and the surrounding mucosa may be inflamed. With progression of disease, pseudomembranous plaques become enlarged and scatted over the colorectal mucosa resulting in pseudomembranous colitis.[50,53]

Clinical Presentation

Symptoms of CDI range from mild diarrhea to fulminant disease and toxic megacolon. The diarrhea is typically watery and nonbloody, and is often associated with abdominal discomfort, fever, and leukocytosis. CDI should be suspected in patients experiencing diarrhea with a recent history of antibiotic use (within the previous 3 months) or recent hospitalization. Clinical diagnosis is based on the presence of three unformed stools in 24 hours or radiographic evidence of ileus or toxic megacolon.

Diagnosis of CDI is confirmed by identification of *C. difficile* organisms/toxin in stool or pseudomembranous colitis visualized during endoscopy. However, due to risk of perforation or peritonitis endoscopy is not

routinely recommended. The optimal test for laboratory diagnosis remains controversial. Nucleic acid amplification tests (NAAT), such as PCR-based toxin testing, are very popular in the United States and have high sensitivity and specificity; however, they should only be used in patients with acute diarrhea due to the possibility of detecting the toxins in asymptomatic patients.[51,54] Alternatively, a stepwise approach uses screening for glutamate dehydrogenase (GDH) as the initial step. GDH assays detect a common antigen present in all isolates of *C. difficile*, including nontoxigenic strains, thus requiring combination with another test (typically a toxin test with or without NAAT). The stepwise approach may be preferred in institutions where there is no criteria for stool submission in order to minimize the false positive results that may result with NAAT alone. Utility of toxigenic culture or cell culture neutralization assays are limited due to delayed results and high cost. Use of toxin enzyme immunoassay (EIA) alone has a low sensitivity and has largely been replaced by NAAT testing or incorporated into multi-step algorithms along with GDH assays.[50]

Treatment

Supportive care of CDI includes fluid and electrolyte replacement therapy, in addition to discontinuation of the offending antimicrobial if possible. Empiric therapy for CDI may be considered if the patient has a strong pre-test suspicion for CDI and it severely ill, or if there is an expected substantial delay in laboratory confirmation. Antibiotic therapy is based on disease severity and may vary for first episode or recurrent infection.[50,51] **Table 131-7** outlines CDI disease severity and treatment regimens for initial episodes according to the IDSA/SHEA 2017 clinical practice guidelines. Differences exist among the available guidelines with regards to the definitions of nonsevere, severe, and fulminant or complicated CDI and slight treatment differences. There is a need for prospectively validated severity scores for patients with CDI.

TABLE 131-7 *Clostridioides difficile* Infection Severity and Treatment[50,51]

Severity	Markers of Disease Severity	Recommended Treatment
Nonsevere	WBC ≤15,000 cells/mm³ (15 × 10⁹/L) SCr <1.5 mg/dL (133 µmol/L)	Vancomycin 125 mg orally 4 times daily for 10 days, OR Fidaxomicin 200 mg orally twice daily for 10 days, OR *Metronidazole 500 mg orally every 8 hours for 10 days
Severe	WBC >15,000 cells/mm³(15 × 10⁹/L) SCr >1.5 mg/dL (133 µmol/L)	Vancomycin 125 mg orally 4 times daily for 10 days, OR Fidaxomicin 200 mg orally twice daily for 10 days
Fulminant	Hypotension or shock Ileus and/or megacolon	Metronidazole 500 mg IV every 8 hours *PLUS* vancomycin 500 mg every 6 hours via NG or orally (if ileus present use rectally)

NG, nasogastric; SCr, serum creatinine; WBC, white blood cell.

*Metronidazole is an alternative therapy if other agents are unavailable or too costly

7 In the United States, metronidazole, vancomycin, and fidaxomicin are the most commonly prescribed agents for CDI. Vancomycin and fidaxomicin are well tolerated given that they have minimal systemic absorption; the main adverse effects are nausea and abdominal pain. Metronidazole is commonly associated with a metallic taste and when used for prolonged or repeated courses it may lead to irreversible neurotoxicity.[50] The recommended treatment course is 10 days and repeat stool testing is not recommended as a test of cure.[50] For nearly 3 decades metronidazole was the drug of choice for mild-to-moderate CDI; however, it has fallen out of favor based on evidence showing it is significantly less effective than vancomycin or fidaxomicin. The IDSA/SHEA 2017 clinical practice guidelines recommended therapies for both nonsevere and severe CDI include oral vancomycin or fidaxomicin. When vancomycin has been compared to fidaxomicin, the rate of initial cure was not significantly different between treatment groups; however, fidaxomicin demonstrated a significant improvement in recurrence.[50] Because of the high cost of first line options, metronidazole may see continued use, but it should be restricted to initial episodes of nonsevere CDI. When used for CDI, vancomycin must be administered orally because IV vancomycin does not achieve adequate gut lumen concentrations for effective bacterial elimination. Vancomycin is available

for oral use in a capsule and a newly approved oral solution; the IV formulation has also been compounded and administered orally as a cost-effective option.

In patients with severe/complicated or fulminant CDI the preferred regimen is combination therapy with IV metronidazole and vancomycin.[55] The route of vancomycin administration is patient-dependent; oral is preferred, but if ileus is present, rectal administration via retention enema is recommended at a dose of 500 mg in 500 mL of saline administered four times daily. Fidaxomicin has not been studied in complicated or fulminant disease, therefore is not recommended.[50]

Recurrence of CDI may occur in up to 25% to 35% of cases and nearly doubles after two or more recurrences.[56] Risk factors for recurrent CDI include increasing age and severe underlying disease, use of additional antimicrobials, use of PPIs, and low antibody response to *C. difficile* toxins.[50,56] If metronidazole was used initially, then a standard vancomycin course can be utilized for the first recurrence. If vancomycin was used initially, then fidaxomicin can be used for the first recurrence. Alternatively, a tapered and pulsed dose of vancomycin can be used for the first recurrence and is the recommended treatment strategy for second or subsequent recurrences. An example of a tapered/pulsed course of vancomycin is 125 mg four times daily for 10 to 14 days, two times daily for 1 week, once daily for 1 week, and then every 2 to 3 days for 2 to 8 weeks.[50] Other regimens that have shown efficacy in recurrent disease include vancomycin followed by rifaximin or fecal microbiota transplantation (FMT).

Given the high rate of recurrences with standard therapy, microbiota of the gut may never fully recovers in some patients, thus the treatment strategy of FMT has gained popularity among many practitioners. Multiple randomized controlled trials have shown efficacy of FMT with resolution rates of 80% to 90% in most studies, yet the specific preparation and route of administration is not well established.[50,56,57] Protocols that have been studied include stool suspension administered to the lower bowel (through colonoscopy, rectal tube or enema) or the upper GI tract (through nasogastric or duodenal tube or gastroscope). Additionally, a frozen capsule formulation is commercially available for oral administration. Regarding the regulation of FMT, the FDA recommends appropriate informed consent from the patient indicating that FMT is an investigational therapy. The FDA has provided guidance regarding this process with continued updates.[56]

A monoclonal antibody, bezlotoxumab, that binds to and neutralizes toxin B was FDA approved in October 2016 as an adjunctive therapy to reduce the

recurrence of CDI. The approved dose is 10 mg/kg IV as a single dose during antibacterial treatment for CDI. Bezlotoxumab is not an antibiotic and should not be used as monotherapy. Its place in therapy is not well established; however, it represents a novel therapy for reducing problematic CDI recurrences.[58]

Alternative therapies with limited data include intravenous immunoglobulin (IVIG) and tigecycline. Intravenous immunoglobulin IVIG has been investigated in patients with intractable, recurrent CDI, and while case reports suggest promising results, high cost may preclude its use.[59] Data for tigecycline is limited to case reports and small case series and should be reserved for patients with severe, fulminant disease not responding to traditional therapy. Anti-motility agents (such as diphenoxylate/atropine and loperamide) and exchange resins (such as cholestyramine and colestipol) have been used in CDI; however, in general their use is discouraged.[50]

Prevention of CDI involves both preventing the acquisition of the infection and stopping transmission of *C. difficile* spores to other patients. CDI has become the focus of antimicrobial stewardship efforts aimed at eliminating unnecessary antibiotics and reducing durations of therapy, which may be responsible for the plateau of CDI rates in recent years. The use of probiotics to prevent CDI remains controversial; some studies and meta-analyses have shown no benefit, while other evidence supports probiotic safety and efficacy in preventing CDI.[60] There is insufficient evidence to recommend probiotics.[50,51] Hand washing and contact precautions are imperative measures in preventing the spread of the organism. Alcohol is less effective at eliminating *C. difficile* spores compared to use of soap and water; however, there is no association between alcohol-based hand hygiene and increased CDI incidence. Nonetheless, the use of soap and water to prevent disease transmission is the preferred strategy. Proper environmental disinfecting measures in healthcare settings include use of chloride-containing cleaning agents or other sporicidal agents.[50]

TRAVELER'S DIARRHEA

Traveler's diarrhea describes the clinical syndrome manifested by malaise, anorexia, and abdominal cramps followed by the sudden onset of diarrhea that incapacitates many travelers. It interferes with planned activities or work in 30% of those affected. In particular, an increased risk lies with North Americans and Northern Europeans traveling to Latin America, southern Europe, Africa, and Asia. The highest risk is observed with patients with immunocompromised conditions, achlorhydria, inflammatory bowel disease, and people with chronic

debilitating medical conditions. Overall, 30% to 70% of people traveling to high-risk areas will develop the illness.[40]

8 The onset of symptoms usually occurs during the first week of travel but can occur anytime during the visit or after returning home. Traveler's diarrhea is caused by contaminated food or water. The most common pathogens are bacterial and include ETEC, *Campylobacter* spp., *Shigella* spp., and *Salmonella* spp.[10] Viral causes occur in less than 10% of cases with 80% to 90% of cases resulting from bacterial etiologies.[40] Enterotoxigenic *E. coli* is predominantly pathogenic in Latin America, Africa, and South Asia. The invasive enteric pathogens (*Campylobacter* spp., *Salmonella* spp., and *Shigella* spp.) are more important causes of traveler's diarrhea in Asia.

The severity of the syndrome is determined by the number of stools per day and the presence of cramping, nausea, and vomiting. Mild diarrhea is defined as 1 to 3 loose stools per day that are associated with abdominal cramps lasting less than 14 days. Moderate diarrhea indicates more than 4 loose stools daily associated with dehydration, and severe diarrhea is defined as the presence of blood in stools or a fever. Traveler's diarrhea is rarely life-threatening and in most cases, symptoms resolve in several days without treatment. Travelers to high-risk areas should pack a kit that includes a thermometer, loperamide, antibiotics (3-day course) (see "Treatment" section below), ORS salts, and a water purification method.[40]

Prevention

9 Patient education in avoiding high-risk food and beverages should be the best method for minimizing the risk. High-risk foods and beverages include raw or undercooked meat and seafood, moist foods served at room temperature, fruits that cannot be peeled, vegetables, milk from a questionable source, hot sauces on the table, tap water, unsealed bottled water, iced drinks, and food from street vendors. Although education is readily available, the incidence of diarrhea was similar in travelers who followed advice and those who engaged in riskier eating habits.[61] Rationales for this include that cooking foods does not always kill pathogens and food should not be considered safe unless it is cooked until steaming hot. Nonetheless, advisement of avoidance measures regarding safe foods, beverages, and eating establishments is recommended to heighten awareness.

Bismuth subsalicylate 524 mg (2 chewable tablets or 2 ounces) orally four times daily for up to 3 weeks is a commonly recommended prophylactic

regimen.[40] Bismuth subsalicylate may inhibit enterotoxin activity and prevent diarrhea. Persons taking this regimen should be informed of adverse events, including temporary black discoloration of tongue and stools, and, rarely, tinnitus.

Although the efficacy of prophylactic antibiotics has been documented, their use is not recommended for most travelers due to the potential side effects of antibiotics (eg, photosensitivity), predisposition to other infections such as CDI or vaginal candidiasis, the increased risk of selection of drug-resistant organisms, cost, lack of data on the safety and efficacy of antibiotics given for more than 2 or 3 weeks, and availability of rapidly effective antibiotics for treatment. Prophylactic antibiotics are recommended only in high-risk individuals or in situations in which short-term illness could ruin the purpose of the trip, such as a military mission. A fluoroquinolone is the drug of choice when traveling to most areas of the world.[40] Due to fluoroquinolone resistance among *Campylobacter* spp., azithromycin can be considered when traveling to South and Southeast Asia.

Rifaximin is a nonabsorbed oral rifamycin that has activity against enteric pathogens and may have a role in the prevention of traveler's diarrhea in select populations. A randomized, double-blind trial of rifaximin 200 mg once, twice, or three times daily with meals for 2 weeks resulted in equal protection of 72% for each of the three dosing regimens compared with placebo.[41] Since rifaximin is effective against traveler's diarrhea due to noninvasive strains of *E. coli*, this agent should be reserved for travel regions where *E. coli* predominates, such as Latin America and Africa. Rifaximin has a tolerability and safety profile comparable to that of placebo. The concern with the class rifamycin is the emergence of resistance when used as monotherapy.

Treatment

The goals of treatment are to avoid dehydration, reduce the severity and duration of symptoms, and prevent interruption of planned activities. Fluid and electrolyte replacement should be initiated at the onset of diarrhea. ORT is generally not required in otherwise healthy individuals; flavored mineral water offers a good source of sodium and glucose. In infants and young children, elderly, and those with chronic debilitating medical conditions, ORT is recommended. For symptom relief, loperamide is preferred because of its quicker onset and longer duration of relief relative to bismuth. Standard dosing of loperamide is 4 mg orally initially and then 2 mg with each subsequent loose stool to a maximum of

16 mg/day in patients without bloody diarrhea and fever. Loperamide should be discontinued if symptoms persist for more than 48 hours. Other symptomatic therapy in mild diarrhea includes bismuth subsalicylate 524 mg every 30 minutes for up to eight doses.[40] As previously discussed, there is insufficient evidence to warrant the recommendation of probiotics.

Since behavioral modification has limited efficacy and chemoprophylaxis is not recommended in most travelers, the current recommendation relies on self-treatment. A single dose of antibiotic and up to 3 days of treatment will improve the condition within 24 to 36 hours, shortening the duration of diarrhea by 1 to 2 days.[40] A single dose of fluoroquinolone is recommended initially and if diarrhea is improved within 12 to 24 hours, antibiotics should be discontinued. Otherwise, it can be continued for up to 3 days. A fluoroquinolone is recommended when traveling to most areas of the world. Where fluoroquinolone-resistant *Campylobacter* is common, such as in South and Southeast Asia, azithromycin should be used.[40] Azithromycin can also be used in pregnant women and children younger than age 16 years. Empiric treatment of young children should be instituted with caution.

Rifaximin was as effective as a 3-day course of ciprofloxacin in shortening the duration of diarrhea in noninvasive traveler's diarrhea. However, rifaximin was not as effective in patients with fever and bloody diarrhea and in those with invasive pathogens. Therefore, a 3-day course of rifaximin has been approved for the treatment of traveler's diarrhea caused by noninvasive strains of *E. coli* in people 12 years or older and can be considered when traveling to areas where *E. coli*–associated traveler's diarrhea is common, such as Mexico and Jamaica.[40]

For rapid improvement in symptoms, antibiotic therapy with adjunctive treatment with loperamide has shown benefit.[62] All clinical trials concluded that the combination therapy was safe, and the worsening of the disease with the use of antimotility treatment has not been encountered.

FOOD POISONING

10 Foodborne illnesses result from the ingestion of food containing pathogenic microorganisms that cause GI infections or preformed toxins that were produced by microorganisms that cause enterotoxigenic poisonings. In the United States, foodborne diseases cause approximately 76 million illnesses, 325,000 hospitalizations, and 5,200 deaths each year.[4] Foodborne transmission may account for up to 80% of acute gastroenteritis. However, the incidence and

outbreaks of foodborne illness has declined in recent years.[63] Common enteric pathogens responsible for foodborne diseases have been discussed in the previous sections (*Campylobacter* spp., *E. coli*, norovirus, nontyphoidal *Salmonella*, *Shigella*). Common foodborne pathogens that cause enterotoxigenic poisonings include *Bacillus cereus*, *Clostridium botulinum*, *Clostridium perfringens*, and *Staphylococcus aureus*. Characteristics of pathogens responsible for foodborne illnesses are summarized in **Table 131-8**.

TABLE 131-8 Food Poisonings

Organism	Principal Foods	Peak Incidence (United States)	Time to Symptoms	Duration	Common Symptoms
Enterotoxigenic Poisonings					
Bacillus cereus	Fried rice, dairy products, spices, bean sprouts, vegetables	None	1-6 hours 6-24 hours	1 day 1 day	Nausea, vomiting Diarrhea
Clostridium botulinum	Home-canned fruits, vegetables, meats, honey	None	18-36 hours		Double vision, blurred vision, drooping eyelids, slurred speech, difficulty swallowing, dry mouth, and muscle weakness
Clostridium perfringens (type A)	Meats, poultry, gravies, dried or precooked foods	Fall, winter, spring	8-12 hours	1 day	Abdominal cramps, diarrhea
Staphylococcus aureus	Salad, pastries, ham, sandwiches, puddings, unpasteurized milk, cheese products	Summer	1-6 hours	1 day	Nausea, vomiting, abdominal cramps, diarrhea
GI Infections					
Campylobacter spp.	Poultry, dairy products, clams, water	Spring, summer	2-5 days	7 days	Diarrhea (may be bloody), cramping, abdominal pain, fever
Enteropathogenic *E. coli*	Water	None	1-3 days	5-7 days	Severe diarrhea, vomiting, dehydration
Enterotoxigenic *E. coli*	Water, ice, food	None	1-3 days	3-4 days	Profuse watery diarrhea, abdominal cramping
Salmonella spp.	Beef, poultry, water, eggs, dairy products	Summer	12-72 hours	4-7 days	Diarrhea (sometimes bloody), fever, abdominal cramps
Shigella spp.	Salad, water	Summer	1-2 days	5-7 days	Diarrhea (often bloody), fever, abdominal cramps
Vibrio cholerae	Water	None	2 hours to 5 days	2-3 days	Profuse watery diarrhea, vomiting, leg cramps
Vibrio parahemolyticus	Shellfish (oysters)	Spring, summer, fall	24 hours	3 days	Watery diarrhea, abdominal cramping, nausea, vomiting, fever, chills
Yersinia enterocolitica	Dairy products, raw or undercooked pork products	None	4-7 days	1-3 weeks	Fever, abdominal pain, diarrhea (often bloody)

Because foodborne disease can appear as sporadic cases or outbreaks, the diagnosis should be suspected whenever two or more people present with acute GI or neurologic manifestations after sharing a meal within the previous 72 hours. Important clues about etiologic agents can be gathered from demographic information (age, gender, etc.), the clinical syndrome, incubation period, and

medical history, type of foods consumed, seasonality, and geographic location of the outbreak.

Enterotoxigenic poisonings result from ingestion of food contaminated by preformed toxins. Therefore, symptoms are rapid in onset, but most cases of food poisoning are of short duration with recovery occurring within 1 to 2 days. *B. cereus* causes two different types of clinical syndromes. The first one is characterized by a short incubation period and vomiting. The second syndrome has a longer incubation period and is characterized by diarrhea. Foodborne *C. perfringens* infection may present as two distinct syndromes. Type A organisms are seen in Western Hemisphere nations and result in a 24-hour illness characterized by watery diarrhea and epigastric pain. Type C organisms can be found in undercooked pork and occur in underdeveloped tropical regions. They can produce a toxin-related syndrome called *enteritis necroticans,* which is a coagulative transmural necrosis of the intestinal wall.[64] This syndrome can result in intestinal perforation leading to sepsis and mortality in approximately 40% of victims.

Foodborne botulism results from the ingestion of food contaminated with preformed toxins or toxin-producing spores from *C. botulinum*. Poisoning from *C. botulinum* is rare; only 110 cases are reported per year in the United States.[64] Botulism is almost always associated with improper preparation or storage of food. Seven distinct toxins (A to G) have been described. The toxins prevent the release of acetylcholine at the peripheral cholinergic nerve terminal. Toxin activity has prompted the use of minute locally injected doses to treat select spastic disorders, such as blepharospasm, hemifacial spasm, and certain dystonias. Foodborne botulism is suspected when patients present with acute GI symptoms concurrently or just prior to the onset of a symmetric descending paralysis without sensory or central nervous system involvement. Diagnosis is made by culturing *C. botulinum* from the stool. The clinical presentation may resemble GBS associated with *C. jejuni* infection. The difference lies in the onset of neurologic symptoms, which typically occur 1 to 3 weeks after the onset of *C. jejuni* infection, and the condition usually is manifested by an ascending paralysis in *C. jejuni*–associated GBS.

Treatment consists primarily of respiratory support and use of botulinum antitoxin.[65] If evaluation is performed within several hours of ingestion, gastric lavage or induction of vomiting is suggested. Cathartics and enemas also can be used to remove residual toxin from the bowel, but they are contraindicated in cases of ileus. Botulinum antitoxin is a concentrated preparation of equine globulins obtained from horses immunized with toxins A, B, and E. Because

trivalent antitoxin is equine in origin, patients should be tested for hypersensitivity before receiving the product intravenously. Newer and more effective methods of treatment and prevention are under development, including a botulinum toxin vaccine consisting of nontoxic botulinum fragments. Prevention always should be stressed. Botulinum toxins are heat labile and readily destroyed by 10 minutes of boiling. All home-canned foods should be processed according to directions and boiled, not just warmed, prior to consumption.

In foodborne illnesses, the cornerstone of therapy remains supportive care. ORT is preferred in replenishing and maintaining fluid and electrolyte balance, and IV fluid therapy should be reserved for those who are severely ill and cannot tolerate oral therapy. Antiemetics and antimotility agents offer symptomatic relief, but the latter should not be given in patients who present with high fever, bloody diarrhea, or fecal leukocytes. Antimicrobial therapy is not effective in the management of *S. aureus*, *C. perfringens*, or *B. cereus* food poisonings. In developed countries, many of the foodborne illnesses can be prevented with proper food selection, preparation, and storage. However, in developing countries, sanitation and clean water supply are larger concerns.

Postclass Engaged Learning Activity

Perform a literature search on investigational drugs and therapies for *Clostridioides difficile* infection (CDI) not addressed in the book chapter. Create a document that describes the proposed mechanism of action for each agent and summarize the evidence available.

ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
cAMP	cyclic adenosine monophosphate
CDI	*Clostridioides difficile* infection
CRP	C-reactive protein
EAEC	enteroaggregative *Escherichia coli*
EHEC	enterohemorrhagic *Escherichia coli*
EIA	enzyme immunoassay
EIEC	enteroinvasive *Escherichia coli*
EPEC	enteropathogenic *Escherichia coli*
ETEC	enterotoxigenic *Escherichia coli*
FDA	Food and Drug Administration
FMT	fecal microbiota transplant
GBS	Guillain-Barré syndrome
GDH	glutamate dehydrogenase
HIV	human immunodeficiency virus
HUS	hemolytic uremic syndrome
IDSA	Infectious Diseases Society of America
IBS	irritable bowel syndrome
IL	Interleukin
IVIG	intravenous immune globulin
NAAT	nucleic acid amplification tests
NAP-1	North American pulsed-field type 1
ORS	oral rehydration solution
ORT	oral rehydration therapy
PKA	protein kinase A
PPI	proton pump inhibitor
SHEA	Society for Healthcare Epidemiology of America
STEC	Shiga toxin–producing *Escherichia coli*
UNICEF	United Nations Children's Fund
ViCPS	Vi capsular polysaccharide vaccine
WHO	World Health Organization

REFERENCES

1. Shane AL, Mody RK, Crump JA, et al. 2017 Infectious Diseases Society of America clinical practice guidelines for the diagnosis and management of infectious diarrhea. *Clin Infect Dis* 2017; 65(12): e45–e80.
2. World Health Organization: Diarrhoeal disease. Available at:

http://www.who.int/mediacentre/factsheets/fs330/en/. Accessed June 6, 2018.

3. GBD Diarrhoeal Diseases Collaborators. Estimates of global, regional, and national morbidity, mortality, and aetiologies of diarrhoeal diseases: A systematic analysis for the Global Burden of Disease Study 2015. *Lancet Infect Dis*. 2017;17:909–948.
4. CDC. *Foodborne Diseases Active Surveillance Network (FoodNet): FoodNet 2015 Surveillance Report (Final Data)*. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2017.
5. Scallan E, Griffin PM, Angulo FJ, Tauxe RV, Hoekstra RM. Foodborne illness acquired in the United States—Unspecified agents. *Emerg Infect Dis* 2011;17(1):16–22.
6. Scallan E, Hoekstra RM, Angulo FJ, et al. Foodborne illness acquired in the United States—Major pathogens. *Emerg Infect Dis* 2011;17(1):7–15.
7. Powell MR. Trends in reported foodborne illness in the United States; 1996-2013. *Risk Analysis*. 2016;36(8):1589–1598.
8. Payne DC, Vinje J, Szilagyi PG, et al. Norovirus and medically attended gastroenteritis in U.S. children. *N Eng J Med*. 2013;368:1121–1130.
9. Shah MP, Dahl RM, Parahar UD, et al. Annual changes in rotavirus hospitalization rates before and after rotavirus vaccine implementation in the United States. *PLoS ONE* 2018; 13(2): 1–13.
10. Marder EP, Griffin PM, Cieslak PR, et al. Preliminary incidence and trends of infection with pathogens transmitted commonly through food: Foodborne Diseases Active Surveillance Network, 10 U.S. Sites, 2006-2017. *MMWR*. 2018;67(11):324–328.
11. World Health Organization. Cholera, 2016. *Weekly Epidem Record*. 2017;92(36):521–536.
12. Leibovici-Weissman Y, Neuberger A, Bitterman R, et al. Antimicrobial drugs for treating cholera (review). *Cochrane Database Sys Rev*. 2014;6:1–181.
13. World Health Organization. Cholera vaccines: WHO position paper—August 2017. *Weekly Epidem Record*. 2017;92(34):477–500.
14. Fang FC, Patel R. 2017 Infectious Diseases Society of America infectious diarrhea guidelines: A view from the clinical laboratory. *Clin Infect Dis*. 2017;65(12):1974–1976.
15. Flores J, Okhuysen PC. Enteroaggregative *Escherichia coli* infection.

Curr Opin Gastroenterol 2009;25(1):8–11.

16. Pfeiffer ML, DuPont HL, Ochoa TJ. The patient presenting with acute dysentery—A systematic review. *J Infect* 2012;64(4):374–386.
17. Voetsch AC, Van Gilder TJ, Angulo FJ, et al. FoodNet estimate of the burden of illness caused by nontyphoidal *Salmonella* infections in the United States. *Clin Infect Dis* 2004;38(Suppl 3):S127–S134.
18. Toro C, Arroyo A, Sarria A et al. Shigellosis in subjects with traveler's diarrhea versus domestically acquired diarrhea: Implications for antimicrobial therapy and human immunodeficiency virus surveillance. *Am J Trop Med Hyg*. 2015;93(3):491–496.
19. Switaj TL, Winter KJ, Christensen SR. Diagnosis and management of foodborne illness. *Am Fam Physician*. 2015;92(5):358–365.
20. Sabina Y, Rahman A, Ray RC, Montet D. *Yersinia enterocolitica*: Mode of transmission, molecular insights of virulence, and pathogenesis of infection. *J Pathog* 2011;2011:429069.
21. Hodges K, Gill R. Infectious diarrhea: Cellular and molecular mechanisms. *Gut Microbes* 2010;1(1):4–21.
22. Date KA, Newton AE, Medalla F, et al. Changing patterns in enteric fever incidence and increasing antibiotic resistance of enteric fever isolates in the United States, 2008-2012. *Clin Infect Dis*. 2016;63(3):322–329.
23. Lucas ML. Enterocyte chloride and water secretion into the small intestine after enterotoxin challenge: Unifying hypothesis or intellectual dead end? *J Physiol Biochem* 2008;64(1):69–88.
24. Trivedi TK, Desai R, Hall AJ, et al. Clinical characteristics of norovirus-associated deaths: A systematic literature review. *Am J Infect Control*. 2013;41:654–657.
25. Rallabhandi P, Awomoyi A, Thomas KE, et al. Differential activation of human TLR4 by *Escherichia coli* and *Shigella flexneri* 2a lipopolysaccharide: Combined effects of lipid A acylation state and TLR4 polymorphisms on signaling. *J Immunol* 2008;180(2):1139–1147.
26. Fernandez MI, Sansonetti PJ. *Shigella* interaction with intestinal epithelial cells determines the innate immune response in shigellosis. *Int J Med Microbiol* 2003;293(1): 55–67.
27. Kim DH, Kang SH, Jeong WS, et al. Serum C-reactive protein (CRP) levels in young adults can be used to discriminate between inflammatory and non-inflammatory diarrhea. *Dig Dis Sci* 2013; 58: 504–8.

28. Haverly RM, Harrison CR, Dougherty TH. *Yersinia enterocolitica* bacteremia associated with red blood cell transfusion. *Arch Pathol Lab Med*. 1996;120(5):499–500.
29. Freedman SB, Xie J, Neufeld MS, et al. Shiga toxin-producing Escherichia coli infection, antibiotics, and risk of developing hemolytic uremic syndrome: A meta-analysis. *Clin Infect Dis*. 2016;62(10):1251–1258.
30. Garg AX, Pope JE, Thiessen-Philbrook H, Clark WF, Ouimet J. Arthritis risk after acute bacterial gastroenteritis. *Rheumatology (Oxford)* 2008;47(2):200–204.
31. Allos BM. *Campylobacter jejuni* infections: Update on emerging issues and trends. *Clin Infect Dis* 2001;32(8):1201–1206.
32. Connor BA, Riddle MS. Post-infectious sequelae of traveler's diarrhea. *J Travel Med*. 2013;20(5):303–312.
33. Hahn S, Kim S, Garner P. Reduced osmolarity oral rehydration solution for treating dehydration caused by acute diarrhoea in children. *Cochrane Database Syst Rev* 2002;(1):CD002847.
34. Musekiwa A, Volmink J. Oral rehydration salt solution for treating cholera: </= 270 mOsm/L solutions vs >/= 310 mOsm/L solutions. *Cochrane Database Syst Rev* 2011;(12):CD003754.
35. Barr W, and Smith A. Acute diarrhea. *Am Fam Physician*. 2014;89(3):180–189.
36. Gregorio GV, Gonzales ML, Dans LF, Martinez EG. Polymer-based oral rehydration solution for treating acute watery diarrhoea. *Cochrane Database Syst Rev* 2009;(2):CD006519.
37. Gregorio GV, Dans LF, Silvestre MA. Early versus delayed refeeding for children with acute diarrhoea. *Cochrane Database Syst Rev* 2011;(7):CD007296.
38. Payot S, Bolla JM, Corcoran D, Fanning S, Megraud F, Zhang Q. Mechanisms of fluoroquinolone and macrolide resistance in *Campylobacter* spp. *Microbes Infect* 2006;8(7):1967–1971.
39. Parry CM, Threlfall EJ. Antimicrobial resistance in typhoidal and nontyphoidal salmonellae. *Curr Opin Infect Dis* 2008;21(5):531–538.
40. Connor BA. Traveler's diarrhea. CDC Yellow Book. Available at: https://wwwnc.cdc.gov/travel/yellowbook/2018/the-pre-travel-consultation/travelers-diarrhea. Accessed June 6, 2018.

41. DuPont HL, Jiang ZD, Okhuysen PC, et al. A randomized, double-blind, placebo-controlled trial of rifaximin to prevent travelers' diarrhea. *Ann Intern Med* 2005;142(10):805–812.
42. Strand TA, Sharma PR, Gjessing HK, et al. Risk factors for extended duration of acute diarrhea in young children. *PLoS ONE*. 2012;7(5):1–6.
43. Hempel S, Newberry SJ, Maher AR, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: A systemic review and meta-analysis. *JAMA*. 2012;307(18):1959–1969.
44. Allen SJ, Wareham K, Wang D, et al. Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea and *Clostridium difficile* diarrhoea in older patients (PLACIDE): A randomised, double-blind, placebo-controlled, multicentre trial. *Lancet*. 2013;382(9900):1249–1257.
45. Lazzerini M, Ronfani L. Oral zinc for treating diarrhoea in children. *Cochrane Database Syst Rev* 2012;6:CD005436.
46. Steinberg EB, Bishop R, Haber P, et al. Typhoid fever in travelers: Who should be targeted for prevention? *Clin Infect Dis* 2004;39(2):186–191.
47. Cortese MM, Parashar UD. Prevention of rotavirus gastroenteritis among infants and children: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2009;58(RR-2):1–25.
48. Centers for Disease Control and Prevention. Addition of history of intussusception as a contraindication for rotavirus vaccination. *MMWR*. 2011;60(41):1427.
49. Walker RI. An assessment of enterotoxigenic *Escherichia coli* and *Shigella* vaccine candidates for infants and children. *Vaccine*. 2015;33:954–965.
50. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis* 2018; 66(00):e1–e48.
51. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for the diagnosis, treatment, and prevention of *Clostridium difficile* infections. *Am J Gastroenterol*. 2013;108:478–498.
52. DePestel DD, Aronoff DM. Epidemiology of *Clostridium difficile* infection. *J Pharm Pract*. 2013;26:464–475.
53. Burke KE, Lamont JT. *Clostridium difficile* infection: A worldwide

disease. *Gut Liver*. 2014;8:1–6.

54. Bagdasarian N, Rao K, Malani PN. Diagnosis and treatment of *Clostridium difficile* in adults: A systematic review. *JAMA*. 2015;313:398–408.
55. Rokas EE, Johnson JW, Beardsley JR, Ohl CA, Luther VP, Willaimson JC. The addition of intravenous metronidazole to oral vancomycin is associated with improved mortality in critically ill patients with Clostridium difficile infection. *Clin Infect Dis*. 2015;61(6):934–941.
56. Rao K, Higgins PDR. Epidemiology, diagnosis, and management of Clostridium difficile infection in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2016; 22(7): 1744–54.
57. Youngster I, Russell GH, Pindar C, Ziv-Baran T, Sauk J, Hohmann EL. Oral, capsulized, frozen fecal microbiota transplantation for relapsing *Clostridium difficile* infection. *JAMA* 2014;312(17): 1772–1778.
58. Kufel WD, Devanathan AS, Marx AH, et al. Bezlotoxumab: A novel agent for the prevention of recurrent *Clostridium difficile* infection. *Pharmacotherapy*. 2017;37(10):1298–1308.
59. Shah N, Shaaban H, Slim J, et al. Intravenous immunoglobulin in the treatment of severe *Clostridium difficile* colitis. *J Glob Infect Dis* 2014; 6(2): 82–5.
60. Goldenberg JZ, Yap C, Lytvyn L, et al. Probiotics for the prevention of Clostridium difficile–associated diarrhea in adults and children. *Cochrane Database Sys Rev*. 19, 2017;12:CD006095. doi: 10.1002/14651858.
61. Shlim D. Looking for evidence that personal hygiene precautions prevent traveler's diarrhea. *Clin Infect Dis* 2005;41(Suppl 8):S531–S535.
62. Riddle MS, Arnold S, Tribble DR. Effect of adjunctive loperamide in combination with antibiotics on treatment outcomes in traveler's diarrhea: A systematic review and meta-analysis. *Clin Infect Dis*. 2008;47(8):1007–1014.
63. Imanishi M, Manikonda K, Murthy BP, Gould LH. Factors contributing to decline in foodborne disease outbreak reports, United States. *Emerg Infect Dis*. 2014;20(9):1551–1553.
64. Sobel J, Tucker N, Sulka A, McLaughlin J, Maslanka S. Foodborne botulism in the United States, 1990-2000. *Emerg Infect Dis* 2004;10(9):1606–1611.
65. Sobel J. Botulism. *Clin Infect Dis*. 2005;41(8):1167–1173.

132

Intra-Abdominal Infections

Alan E. Gross and Keith M. Olsen

KEY CONCEPTS

1. Most intra-abdominal infections are "secondary" infections that are polymicrobial and are caused by a defect in the gastrointestinal (GI) tract that must be treated by surgical drainage, resection, and/or repair.
2. Primary peritonitis is generally caused by a single organism (*Staphylococcus aureus* in patients undergoing chronic ambulatory peritoneal dialysis [CAPD] or *Escherichia coli* in patients with cirrhosis).
3. Secondary intra-abdominal infections are usually caused by a mixture of bacteria, including enteric gram-negative bacilli and anaerobes, which enhance the pathogenic potential of the bacteria.
4. For peritonitis, early and effective IV fluid resuscitation and electrolyte replacement therapy are essential. A common cause of early death is tissue hypoperfusion precipitated by inadequate intravascular volume.
5. Treatment is generally initiated on a "presumptive" or empirical basis and should be based on the likely pathogen(s), local resistance patterns, and severity of illness.
6. Antimicrobial regimens for secondary intra-abdominal infections should include coverage for enteric gram-negative bacilli and anaerobes. Antimicrobials that may be used for the treatment of secondary intra-abdominal infections depending on severity of illness and microbiology data include: (a) third-generation cephalosporin (ceftriaxone) with metronidazole, (b) piperacillin–tazobactam, (c) a carbapenem (imipenem, meropenem, doripenem, or ertapenem), or (d) a quinolone (levofloxacin or ciprofloxacin) plus metronidazole or moxifloxacin alone.
7. Treatment of patients with peritoneal dialysis-associated peritonitis should include an antistaphylococcal antimicrobial such as a first-generation

cephalosporin (cefazolin) or vancomycin as well as an agent with significant gram-negative activity such as a third-generation cephalosporin or aminoglycoside; intraperitoneal administration is preferred.

8. The duration of antimicrobial treatment should be 4 days after achievement of source control for most secondary intra-abdominal infections.
9. Patients treated for intra-abdominal infections should be assessed for the occurrence of drug-related adverse effects, particularly hypersensitivity reactions (β-lactam antimicrobials), diarrhea (most agents), fungal infections (most agents), and nephrotoxicity (aminoglycosides).

Preclass Engaged Learning Activity

Find one published article that is a prospective study documenting an antimicrobial stewardship intervention and identify a potential intervention to impact the appropriate use of antimicrobial agents in intra-abdominal infections.

INTRODUCTION

Intra-abdominal infections are those contained within the peritoneal cavity or retroperitoneal space. The peritoneal cavity extends from the undersurface of the diaphragm to the floor of the pelvis and contains the stomach, small bowel, large bowel, liver, gallbladder, and spleen. The duodenum, pancreas, kidneys, adrenal glands, great vessels (aorta and vena cava), and most mesenteric vascular structures reside in the retroperitoneum. Intra-abdominal infections may be generalized or localized, complicated or uncomplicated, and community or healthcare-associated. Uncomplicated intra-abdominal infections are confined within visceral structures, such as the liver, gallbladder, spleen, pancreas, kidney, or female reproductive organs, while complicated intra-abdominal infections involve anatomical disruption, extend beyond a single organ, and yield peritonitis and/or abscess. *Peritonitis* is defined as the acute inflammatory response of the peritoneal lining to microorganisms, chemicals, or foreign-body injury. This chapter deals only with peritonitis of infectious origin.

An *abscess* is a purulent collection of fluid separated from surrounding tissue by a wall consisting of inflammatory cells and adjacent organs. It usually contains necrotic debris, bacteria, and inflammatory cells. These processes differ

considerably in presentation and approach to treatment.

EPIDEMIOLOGY

Peritonitis may be classified as primary, secondary, or tertiary.[1–5] Primary peritonitis, also called *spontaneous bacterial peritonitis*, is an infection of the peritoneal cavity without an evident source in the abdomen.[6] Bacteria may be transported from the bloodstream to the peritoneal cavity, where the inflammatory process begins. In secondary peritonitis, a focal disease process is evident within the abdomen. Secondary peritonitis may involve perforation of the gastrointestinal (GI) tract (possibly because of ulceration, ischemia, or obstruction), postoperative peritonitis, or posttraumatic peritonitis (blunt or penetrating trauma). Tertiary peritonitis occurs in critically ill patients and it persists or recurs at least 48 hours after apparently adequate management of primary or secondary peritonitis.[7,8]

1 Primary peritonitis occurs in both children and adults, although the incidence and mortality rates in both populations have been declining.[4] Primary peritonitis develops in up to 10% to 30% of patients with alcoholic cirrhosis.[4–6,10] Patients undergoing chronic ambulatory peritoneal dialysis (CAPD) average one episode of peritonitis every 20 to 33 months.[11,12] Secondary peritonitis may be caused by perforation of a peptic ulcer; traumatic perforation of the stomach, small or large bowel, uterus, or urinary bladder; appendicitis; pancreatitis; diverticulitis; bowel infarction; inflammatory bowel disease; cholecystitis; operative contamination of the peritoneum; or diseases of the female genital tract, such as septic abortion, postoperative uterine infection, endometritis, and salpingitis. Appendicitis is one of the most common causes of intra-abdominal infection. In 2010, 305,000 appendectomies were performed in the United States for suspected appendicitis.[13] Most healthcare-associated intra-abdominal infections occur as complications following intra-abdominal surgeries.

ETIOLOGY

Primary peritonitis in adults occurs most commonly in association with alcoholic cirrhosis, especially in its end stage, or with ascites caused by postnecrotic cirrhosis, chronic active hepatitis, acute viral hepatitis, congestive heart failure, malignancy, systemic lupus erythematosus, or nephritic syndrome. It may also result from the use of a peritoneal catheter for dialysis or CNS

ventriculoperitoneal shunting for hydrocephalus. Rarely, primary peritonitis occurs without apparent underlying disease.

Potential causes of bacterial peritonitis include inflammatory processes of the GI tract or abdominal organs, bowel obstruction, vascular occlusions that may lead to gangrene of the intestines, and neoplasia that may cause intestinal perforation or obstruction (**Table 132-1**). Other possible causes include those resulting from traumatic injuries, postoperative infections, or solid organ transplant in the abdomen.

TABLE 132-1 Causes of Bacterial Peritonitis

Primary (spontaneous) bacterial peritonitis
Cirrhosis with ascites
Nephrotic syndrome
Peritoneal dialysis (may be secondary to catheter site infection)
Secondary bacterial peritonitis
Miscellaneous causes
Diverticulitis
Appendicitis
Inflammatory bowel diseases
Salpingitis
Biliary tract infections
Necrotizing pancreatitis
Neoplasms
Intestinal obstruction
Perforation
Mechanical GI problems
Any cause of small bowel obstruction (adhesions, hernia)
Vascular causes
Mesenteric arterial or venous occlusion (atrial fibrillation)
Mesenteric ischemia without occlusion
Trauma
Blunt abdominal trauma with rupture of intestine
Penetrating abdominal trauma
Iatrogenic intestinal perforation (endoscopy)
Intraoperative events
Solid organ transplant in the abdomen
Peritoneal contamination during abdominal operation
Leakage from GI anastomosis

GI, gastrointestinal.

Abscesses are the result of chronic inflammation and may occur without preceding generalized peritonitis. They may be located within one of the spaces of the peritoneal cavity or within one of the visceral organs, and may range from a few milliliters to a liter or more in volume. These collections often have a

fibrinous capsule and may take from a few weeks to years to form.

The causes of intra-abdominal abscess overlap those of peritonitis and, in fact, may occur sequentially or simultaneously. Appendicitis is the most frequent cause of abscess. Other potential causes of intra-abdominal abscess include pancreatitis, diverticulitis, lesions of the biliary tract, genitourinary tract infections, perforation in the abdomen, trauma, and leaking intestinal anastomoses. In addition, pelvic inflammatory disease in women may lead to tubo-ovarian abscess. For some diseases, such as appendicitis and diverticulitis, abscesses occur more frequently than generalized peritonitis.

Microflora of the Gastrointestinal Tract and Female Genital Tract

A full appreciation of intra-abdominal infection requires an understanding of the normal microflora within the GI tract. There are striking differences in bacterial species and concentrations of flora within the various segments of the GI tract (**Table 132-2**), and this bacterial environment usually determines the severity of infectious processes in the abdomen. Generally, the low gastric pH eradicates bacteria that enter the stomach. With achlorhydria, bacterial counts may rise to 10^5 to 10^7 organisms/mL (10^8 to 10^{10}/L). The normally low bacterial count may also increase by 1,000- or 10,000-fold with gastric outlet obstruction, hemorrhage, gastric cancer, and in patients receiving histamine 2 (H_2)-receptor antagonists, proton pump inhibitors, or antacids.[14,15] A two to threefold increase in spontaneous bacterial peritonitis has been demonstrated with the use of proton pump inhibitors.

TABLE 132-2 Usual Microflora of the GI Tract

Site	Commonly Found Bacteria	Approximate Concentration (No. Organisms/mL [$\times 10^3$/L])	
		Aerobes	Anaerobes
Stomach[a]	*Streptococcus, Lactobacillus*	10–100	Rare
Biliary tract	Normally sterile (*Escherichia coli, Klebsiella*, or enterococci in some patients)	0	0
Proximal small bowel	*Streptococcus* (including enterococci), *E. coli, Klebsiella, Lactobacillus*, diphtheroids	100	Few
Distal ileum	*E. coli, Klebsiella, Enterobacter*, enterococci, *Bacteroides fragilis, Clostridium*, peptostreptococci	10^4–10^6	10^5–10^7
Colon	*Bacteroides* spp., peptostreptococci, *Clostridium, E. coli, Klebsiella*, enterococci, *Enterobacter, Candida*, and many others	10^5–10^8	10^9–10^{11}

[a]With achlorhydria, acid suppressive therapy, gastric cancer, or gastric outlet obstruction, bacterial counts may rise to 10^5/mL (10^8/L).

GI, gastrointestinal.

The biliary tract (gallbladder and bile ducts) is sterile in most healthy individuals, but in people older than 70 years, those with acute cholecystitis, jaundice, or common bile duct stones, it is likely to be colonized by aerobic gram-negative bacilli (particularly *E. coli* and *Klebsiella* spp.) and enterococci.[16,17] Patients with biliary tract bacterial colonization are at greater risk of intra-abdominal infection.

In the distal ileum, bacterial counts of aerobes and anaerobes are quite high. In the colon, there may be 500 to 600 different types of bacteria in stool, with concentrations often reaching 10^{11} organisms/mL (10^{14}/L) and anaerobic bacteria outnumbering aerobic bacteria by more than 1,000 to 1.[2,18] Fortunately, most colonic bacteria are not pathogens because they cannot survive in environments outside the colon. Perforation of the colon results in the release of large numbers of anaerobic and aerobic bacteria into the peritoneum.

The colonic flora generally remains the same unless exposed to a broad spectrum of antimicrobials or a GI infectious process. In either case, the flora may change due to the antibiotic or infectious process and is often replaced by more pathogenic bacteria. Depending on the type of antibiotic and spectrum, the duration of use, route of administration, and distribution to the GI tract, antibiotics can cause shifts in the normal GI microflora causing increased drug resistance.[19]

The lower female genital tract is generally colonized by a large number of aerobic and anaerobic bacteria. Anaerobes may number 10^9 organisms/mL (10^{12}/L) and often include lactobacilli, eubacteria, clostridia, anaerobic streptococci, and, less frequently, *Bacteroides fragilis.* Aerobic bacteria most often are streptococci and *Staphylococcus epidermidis*, and these may number 10^8 organisms/mL (10^{11}/L).

PATHOPHYSIOLOGY

Intra-abdominal infection results from bacterial entry into the peritoneal or retroperitoneal spaces or from bacterial collections within intra-abdominal organs. In primary peritonitis, bacteria may enter the abdomen via the bloodstream or the lymphatic system by transmigration through the bowel wall, through an indwelling peritoneal dialysis catheter, or via the fallopian tubes in females. Hematogenous bacterial spread (through the bloodstream) occurs more frequently with tuberculosis peritonitis or peritonitis associated with cirrhotic ascites. When peritonitis results from peritoneal dialysis, skin surface flora is introduced via the peritoneal catheter. In secondary peritonitis, bacteria most often enter the peritoneum or retroperitoneum as a result of perforation of the GI or female genital tracts caused by diseases or traumatic injuries. In addition, peritonitis or abscess may result from contamination of the peritoneum during a surgical procedure or from an anastomotic leak.

The physiologic characteristics of the peritoneal cavity determine the nature of the response to infection or inflammation within it.[1,4] The peritoneum is lined by a highly permeable serous membrane with a surface area approximately that of skin. The peritoneal cavity is lubricated with less than 100 mL of sterile, clear yellow fluid, normally with fewer than 250 WBC cells/µL, a specific gravity below 1.016, and protein content below 3 g/dL (30 g/L). These conditions change drastically with peritoneal infection or inflammation, as described below.

After bacteria are introduced into the peritoneal cavity, there is an immediate response to contain the insult. Humoral and cellular defenses respond first, then

the omentum adheres to the affected area. A limited bacterial inoculum is handled rapidly by defense mechanisms, including complement activation and a leukocyte response. Under certain conditions, the bacterial insult is not contained, and bacteria disseminate throughout the peritoneal cavity, resulting in peritonitis. This is more likely to occur in the presence of a foreign body, hematoma, dead tissue, a large bacterial inoculum, continuing bacterial contamination, and contamination involving a mixture of synergistic organisms. Protein–calorie malnutrition, antecedent steroid therapy, and diabetes mellitus may also contribute to the formation of an intra-abdominal abscess.

When bacteria become dispersed throughout the peritoneum, the inflammatory process involves most of the peritoneal lining. There is an outpouring into the peritoneum of fluid containing leukocytes, fibrin, and other proteins that form exudates on the inflamed peritoneal surfaces and begin to form adhesions between peritoneal structures. This process, combined with a paralysis of the intestines (ileus), may result in confinement of the contamination to one or more locations within the peritoneum. Fluid also begins to collect in the bowel lumen and wall, and distension may result.

The fluid and protein shift into the abdomen (called *third-spacing*) may be so dramatic that circulating blood volume is decreased, which may cause decreased cardiac output and hypovolemic shock. Accompanying fever, vomiting, or diarrhea may worsen the fluid imbalance. A reflex sympathetic response, manifested by perspiration, tachycardia, and vasoconstriction, may be evident. With an inflamed peritoneum, bacteria and endotoxins are absorbed easily into the bloodstream (translocation), and this may result in septic shock.[1,4,5] Other foreign substances present in the peritoneal cavity potentiate peritonitis. These adjuvants, notably feces, dead tissues, barium, mucus, bile, and blood, have detrimental effects on host defense mechanisms, particularly on bacterial phagocytosis.

Many of the manifestations of intra-abdominal infections, particularly peritonitis, result from cytokine activity. Inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL) 1, IL-6, IL-8, and interferon-γ (INF-γ), are produced by macrophages and neutrophils in response to bacteria and bacterial products or in response to tissue injury resulting from the surgical incision.[1,4] These cytokines produce wide-ranging effects on the vascular endothelium of organs, particularly the liver, lungs, kidneys, and heart. With uncontrolled activation of these mediators, sepsis may result (see Chapter 137 Sepsis and Septic Shock).[20–22]

Peritonitis may result in death because of the effects on major organ systems.

Fluid shifts, cytokines, and microorganism toxins may result in hypovolemia, hypoperfusion, and shock. Hypoalbuminemia may result from protein loss into the peritoneum exacerbating intravascular volume loss. Pulmonary function may be compromised by the inflamed peritoneum, producing splinting (muscle rigidity caused by pain) that inhibits adequate diaphragmatic movement leading to atelectasis and pneumonia. Increased lung vascular permeability and resulting shunting of blood may induce onset of the respiratory distress syndrome and associated hypoxemia and hypercarbia. With fluid loss and hypotension, renal and hepatic perfusion may be compromised, and acute renal and hepatic failures are potential threats.

If peritoneal contamination is localized but bacterial elimination is incomplete, an abscess results. This collection of necrotic tissue, bacteria, and white blood cells may be at single or multiple sites and may be within one of the spaces of the peritoneal cavity or in one of the visceral organs. The location of the abscess is often related to the site of primary disease. For example, abscesses resulting from appendicitis tend to appear in the right lower quadrant or the pelvis; those resulting from diverticulitis tend to appear in the left lower quadrant or pelvis.

An abscess begins by the combined action of inflammatory cells (such as neutrophils), bacteria, fibrin, and other inflammatory mediators. Bacteria may release heparinases that cause local thrombosis and tissue necrosis or fibrinolysins, collagenases, or other enzymes that allow extension of the process into surrounding tissues. Neutrophils gathered in the abscess cavity die in 3 to 5 days, releasing lysosomal enzymes that liquefy the core of the abscess. A mature abscess may have a fibrinous capsule that isolates bacteria and the liquid core from antimicrobials and immunologic defenses.

Within the abscess, the oxygen tension is low and anaerobic bacteria thrive; thus, the size of the abscess may increase because it is hypertonic, resulting in an additional influx of fluid. Hypertonicity promotes the formation of L-form bacteria, which are resistant to antimicrobial agents that disrupt cell walls. Abscess formation may continue and mature for long periods of time and may not be readily evident to either patient or physician. In some instances, the abscess may resolve spontaneously, and, infrequently, it may erode into adjacent organs or rupture and cause diffuse peritonitis. If the abscess erodes through the skin, it may result in an enterocutaneous fistula, connecting bowel to skin, or in a draining sinus tract.

The overall outcome of an intra-abdominal infection depends on key factors: patient-specific risk factors, inoculum size, virulence of the contaminating

organisms, the presence of adjuvants within the peritoneal cavity that facilitate infection, the adequacy of host defenses, source control, and the adequacy of initial treatment.[9,23,24]

Microbiology of Intra-Abdominal Infection

2 The prevalence of pathogens has not appreciably changed in community-onset intra-abdominal infection, although susceptibility to antibiotics has decreased over time. Primary bacterial peritonitis is often caused by a single organism. In children, the pathogen is usually group A *Streptococcus*, *E. coli*, *Streptococcus pneumoniae*, or *Bacteroides* species.[25–28] When peritonitis occurs in association with cirrhotic ascites, *E. coli* is isolated most frequently. Other potential pathogens are: *Haemophilus influenzae*, *Klebsiella* spp., *Pseudomonas* spp., anaerobes, and *S. pneumoniae*.[29] Occasionally, primary peritonitis may be caused by *Mycobacterium tuberculosis.* Peritonitis in patients undergoing peritoneal dialysis is caused most often by common skin organisms, such as coagulase-negative staphylococci, *S. aureus*, streptococci, and enterococci. Gram-negative bacteria associated with peritoneal dialysis infections include *E. coli*, *Klebsiella* spp., and *Pseudomonas* spp.[12] The mortality rate from primary peritonitis caused by gram-negative bacteria is much greater than that from gram-positive bacteria.[4,5]

3 Because of the diverse bacteria present in the GI tract, secondary intra-abdominal infections are often polymicrobial.[2] The mean number of different bacterial species isolated from infected intra-abdominal sites ranged from 2.9 to 3.7, including an average of 1.3 to 1.6 aerobes and 1.7 to 2.1 anaerobes.[29,30] With proper anaerobic specimen collection, anaerobic organisms are isolated in most patients. In one report of patients with gangrenous and perforated appendicitis, an average of 10.2 different organisms was isolated from each patient, including 2.7 aerobes and 7.5 anaerobes.[31] Purely aerobic or anaerobic infections are uncommon, as are infections caused by fungi. **Table 132-3** gives the frequencies with which specific bacteria were isolated from patients with peritonitis and other intra-abdominal infections.[3,32] Nosocomial infections tend to have a more diverse array of pathogens, are more likely to involve *Pseudomonas* spp., and have a higher likelihood of multidrug-resistance compared with isolates from community-acquired infections.[33]

TABLE 132-3 Pathogens Isolated from Patients with Intra-Abdominal Infection

	Secondary Peritonitis[3,33] (%)	Community-Acquired Infection[33] (%)	Nosocomial Infection[33] (%)
Gram-Negative Bacteria			
Escherichia coli	32–61	29	22.5
Enterobacter	8–26	5.2	8.0
Klebsiella	6–26	2.8	4.5
Proteus	4–23	1.7	2.4
Pseudomonas	5–13	5	13
Gram-Positive Bacteria			
Enterococcus	18–24	10.6	18
Streptococcus	6–55	13.7	10
Staphylococcus	6–16	3.1	4.8
Anaerobic Bacteria			
Bacteroides	25–80	13.7	10.3
Clostridium	5–18	3.5	3.4
Fungi	2–5	3	4

Visceral organ abscesses differ in character from the typical intra-abdominal abscess. Hepatic abscesses may be polymicrobial (involving *E. coli*, *Klebsiella* spp., and anaerobes) or occasionally may be caused by amoeba.[18] Pancreatic abscesses are often polymicrobial, involving enteric bacteria that ascend through the biliary system. Splenic abscesses usually result from hematogenous dissemination of bacteria, such as *E. coli*, *S. aureus*, *Proteus mirabilis*, *Enterococcus* spp., and *Klebsiella pneumoniae*, as well as anaerobes.[18] Pelvic inflammatory disease is associated initially with *Neisseria gonorrhoeae* or *Chlamydia trachomatis.* However, tubo-ovarian abscesses are usually polymicrobial, having a mix of gram-positive and gram-negative aerobes and anaerobes.

Bacterial Synergism

The size of the bacterial inoculum and the number and types of bacterial species present in intra-abdominal infections influence patient outcome. The combination of aerobic and anaerobic organisms appears to greatly increase the severity of infection. In animal studies, combinations of aerobic and anaerobic bacteria were much more lethal than infections caused by aerobes or anaerobes

alone.

Facultative bacteria may provide an environment conducive to the growth of anaerobic bacteria.[2] Although many bacteria isolated in mixed infections are nonpathogenic by themselves, their presence may be essential for the pathogenicity of the bacterial mixture.[9] The role of facultative bacteria in mixed infections can include (a) promotion of an appropriate environment for anaerobic bacterial growth through oxygen consumption, (b) production of nutrients necessary for anaerobes, and (c) production of extracellular enzymes that promote tissue invasion by anaerobes.

Rat models of intra-abdominal infection demonstrate that uncontrolled infection with an implanted mix of aerobes and anaerobes leads to a two-stage (biphasic) infectious process. There is an early peritonitis phase with a high mortality rate and isolation of *E. coli* from blood and a late abscess formation phase in all survivors with isolation of anaerobes such as *B. fragilis* and *Fusobacterium varium*. These experiments and others support the concept that aerobic enteric organisms and anaerobes are pathogens in intra-abdominal infection. Aerobic bacteria, particularly *E. coli*, appear responsible for the early mortality from peritonitis, whereas anaerobic bacteria are major pathogens in abscesses, with *B. fragilis* predominating.[34]

Enterococcus can be isolated from many intra-abdominal infections in humans, but its role as a pathogen is not clear. Enterococcal infection occurs more commonly in postoperative peritonitis, in the presence of specific risk factors indicating failure of the host's defenses (immunocompromised patients), or with the use of broad-spectrum antibiotics.[35,36]

CLINICAL PRESENTATION: INTRA-ABDOMINAL INFECTIONS

Intra-abdominal infections have a wide spectrum of clinical features often depending on the specific disease process, the location and magnitude of bacterial contamination, and concurrent host factors. Peritonitis is usually recognized easily, but intra-abdominal abscess may often continue for considerable periods of time, either going unrecognized or being attributed to an unrelated disease process. Patients with primary and secondary peritonitis present quite differently (**Table 132-4**).[1,4,5]

TABLE 132-4 Clinical Presentation of Peritonitis

Primary Peritonitis

General

The patient may not be in acute distress, particularly with peritoneal dialysis

Signs and symptoms

The patient may complain of loss of appetite, bloating, nausea, vomiting (sometimes with diarrhea), and abdominal tenderness

Temperature may be only mildly elevated or not elevated in patients undergoing peritoneal dialysis

Bowel sounds are hypoactive

The cirrhotic patient may have worsening encephalopathy

Cloudy dialysate fluid with peritoneal dialysis

Laboratory tests

The patient's WBC count may be only mildly elevated

Ascitic fluid usually contains greater than 250 leukocytes/mm^3 (0.25×10^9/L), and bacteria may be evident on Gram stain of a centrifuged specimen

In 60%–80% of patients with cirrhotic ascites, the Gram stain is negative

Other diagnostic tests

Culture of peritoneal dialysate or ascitic fluid should be positive, particularly if collected prior to initiation of antibiotics

Procalcitonin in conjunction with clinical findings is a sensitive test for bacterial peritonitis[37]

Secondary Peritonitis

Signs and symptoms

Generalized abdominal pain

Tachypnea

Tachycardia

Nausea and vomiting

Temperature is normal initially then increases to 37.8–38.9°C (100–102°F) within the first few hours and may continue to rise for the next several hours

Hypotension, hypoperfusion, and shock if volume is not restored

Decreased urine output due to vascular volume depletion

Physical examination

Voluntary abdominal guarding changing to involuntary guarding and a "board-like abdomen"

Abdominal tenderness and distension

Faint bowel sounds that cease over time

Laboratory tests

Leukocytosis (15,000–20,000 WBC/mm^3 [15×10^9 to 20×10^9/L]), with neutrophils predominating and an elevated percentage of immature neutrophils (bands)

Elevated hematocrit and blood urea nitrogen because of dehydration

Patient progresses from early alkalosis because of hyperventilation and vomiting to metabolic acidosis

Other diagnostic tests

Abdominal radiographs may be useful because free air in the abdomen (indicating intestinal perforation) or distension of the small or large bowel is often evident

WBC, white blood cell.

Primary peritonitis can develop over a period of days to weeks and is usually a more indolent process than secondary peritonitis. The first sign of peritonitis may be a cloudy dialysate in patients undergoing peritoneal dialysis or worsening encephalopathy in a cirrhotic patient.

The patient with generalized bacterial peritonitis presents most often in acute distress. The patient lies still, usually on his or her back, possibly with the hips slightly flexed. Any movement of the patient, including rocking the bed or breathing, worsens the generalized abdominal pain.

If peritonitis continues untreated, the patient may experience hypovolemic shock from third-space fluid loss into the peritoneum, bowel wall, and lumen. This may be accompanied by sepsis because the inflamed peritoneum absorbs bacteria and toxins into mesenteric blood vessels and lymph nodes, initiating production of inflammatory cytokines. Hypovolemic shock is the major factor contributing to mortality in the early stage of peritonitis.

Intra-abdominal abscess may pose a difficult diagnostic challenge because the symptoms are neither specific nor dramatic. The patient may complain of abdominal pain or discomfort, but these symptoms are not reliable. Fever is usually present; often it is low grade, but it may be high, with a spiking pattern. The patient may have a paralytic ileus and abdominal distension. The abdominal examination is unreliable; tenderness and pain may be present, and a mass may be palpated.

Peritonitis may result from an abscess that ruptures, spreading bacteria and toxins throughout the peritoneum. In other patients, the entry of bacterial toxins into the systemic circulation from the abscess may lead to sepsis and progressive multisystem organ failure (eg, renal, hepatic, pulmonary, or cardiovascular).

Laboratory studies are not generally helpful in the diagnosis of intra-abdominal abscess, although most patients will have leukocytosis. Some patients may have positive blood cultures, whereas others, particularly diabetics, may have hyperglycemia. The finding of *Bacteroides* or enteric bacteria in the bloodstream is often indicative of an intra-abdominal infectious process.

Radiographic methods are used to make the diagnosis of an intra-abdominal abscess. Plain radiographs may show air–fluid levels or a shift of normal intra-abdominal contents by the abscess mass. GI contrast studies may also demonstrate this displacement of abdominal structures. Both of these modalities provide indirect evidence of abscess presence but are not generally helpful in precisely locating the abscess.

Ultrasound is a frequent first diagnostic method used when an intra-

abdominal abscess is suspected. The procedure may be done at the bedside, which is particularly helpful when the patient is in the intensive care unit.

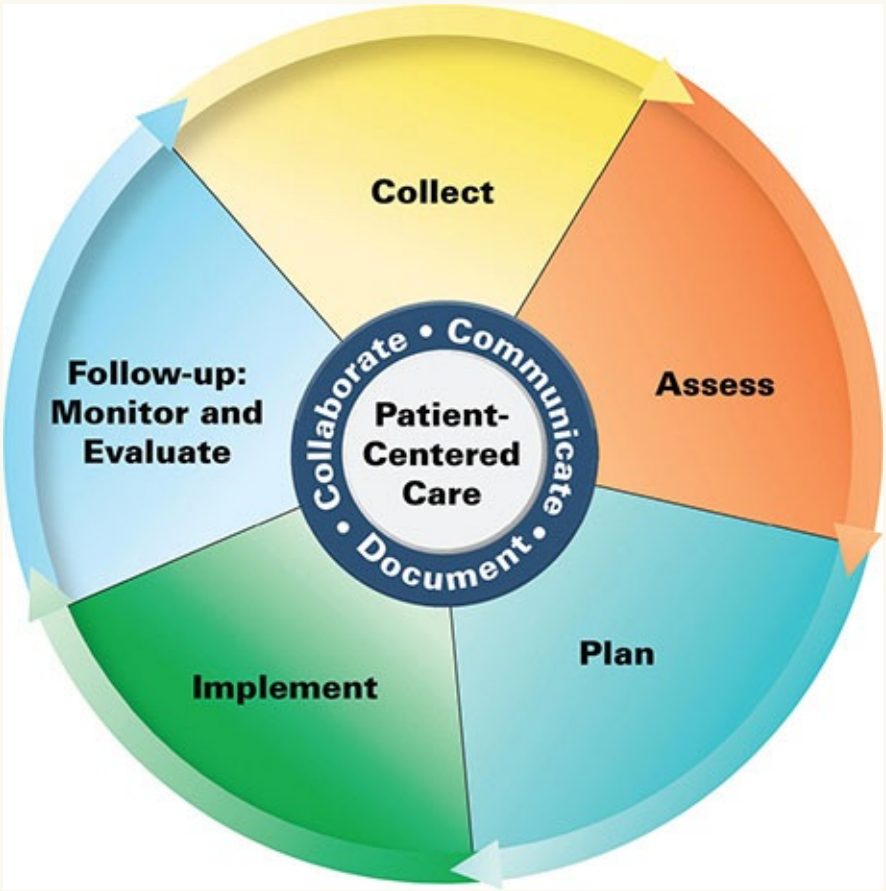
Computed tomographic (CT) scanning is the preferred modality used to evaluate the abdomen for the presence of an abscess and is the imaging study of greatest value. If not contraindicated, an oral radiocontrast agent should be given to allow differentiation of the abscess from the bowel. IV radiocontrast material will be taken up preferentially in the wall of the abscess, creating a unique radiographic appearance, so-called rim enhancement. Magnetic resonance imaging offers no significant advantage when compared with CT scanning.

Intra-abdominal infection caused by disease processes at specific sites often produces characteristic manifestations that are helpful in diagnosis. For example, a patient with diverticulitis may exhibit stabbing left-lower-quadrant abdominal pain and constipation. Fever and leukocytosis are frequently present, and a tender mass is sometimes palpable. With appendicitis, the findings may be inconsistent, but many patients have a sudden onset of periumbilical or epigastric pain that is usually colicky and later shifts to the right lower quadrant. The location of pain may vary because the appendix can be in many locations (eg, retrocecal or pelvic) in the abdomen. A mass may be palpable on abdominal, pelvic, or rectal examination. The patient's temperature is generally mildly elevated early and then increases. If perforation and peritonitis occur, findings would include diffuse abdominal pain, rigidity, and sustained fever. More often, however, appendiceal perforation results in a local abscess.

TREATMENT

Desired Outcome

The primary goals of treatment are correction of the intra-abdominal disease processes or injuries that have caused infection and the drainage of purulent collections (abscesses). A secondary objective is to achieve a resolution of infection without major organ system complications (pulmonary, hepatic, cardiovascular, or renal failure) or adverse drug effects. Ideally, the patient should be discharged from the hospital after treatment with full function for self-care and routine daily activities.



Patient Care Process for Treatment of Intra-Abdominal Infections

Collect

- Patient characteristics (eg, age, sex, weight, body mass index)
- Patient history (past medical, family, social—dietary habits, tobacco use, alcohol use, substance abuse) and surgical operations (site, date, procedure)
- Medication history at hospital admission (prescription and non-non-prescription medications and supplements), drug allergies, and intolerances; previous antibiotic use, inpatient and outpatient, dose and duration
- Microbiologic results from blood, intra-abdominal fluids, and other

sources, and obtain susceptibility results when they are available

- Laboratory results for infection, major organ function (particularly kidney and liver), and immune status

Assess

- Hemodynamic status (eg, MAP, HR)
- Estimate creatinine clearance for drug dosing
- Review all culture results and consider anaerobic bacteria may be causative agents but may not be isolated in cultures

Plan*

- Determine initial empiric treatment and monitoring plan
- Establish antimicrobial monitoring goals for microbiologic and clinical outcomes
- Consider other medications that may be needed during treatment or post-surgery (ie, analgesics, medications for nausea and vomiting, thrombosis prevention)
- Check for drug interactions and dose adjustments based on end-organ function

Implement

- Initiate an empiric antimicrobial regimen and continue until microbiologic data is available and establish tentative stop date
- De-escalate antimicrobial therapy as appropriate based on response and microbiologic data
- Discontinue adjunct medications when not needed or indicated
- Assess patient as needed for response to surgical control, medications, and other treatments
- Use measures to minimize adverse events to medications and assess for occurrence of adverse events
- Assess pain control and progress of gastrointestinal function
- Change to oral medications when appropriate after patient resumes oral feeding

Follow-up: Monitor and Evaluate

- Determine whether patient shows improvement with signs and symptoms of infection within 2 to 3 days after antimicrobials are initiated and surgical source control is completed
- The patient should be reassessed continually to determine the success or failure of therapies
- Monitor for emergence of resistant bacterial isolates in blood or other sources and change antimicrobials if needed
- Monitor for occurrence of secondary infections such as respiratory and urinary tract
- Upon hospital discharge, determine which medications the patient should be discharged with and provide counseling; discontinue unnecessary medications

**Collaborate with patient, caregiver(s), and other healthcare professionals.*

General Approach to Treatment

The treatment of intra-abdominal infection most often requires hospitalization and the coordinated use of three major modalities: (a) prompt surgical control and drainage of the infected site, (b) hemodynamic resuscitation and support of vital organ functions, and (c) early administration of appropriate antimicrobial therapy to treat infection not eradicated by surgery.[2]

Antimicrobials are an important adjunct to drainage procedures in the treatment of secondary intra-abdominal infections; however, the use of antimicrobial agents without surgical source control is usually inadequate. For most cases of primary peritonitis, drainage procedures may not be required, and antimicrobial agents become the mainstay of therapy.

4 In the early phase of serious intra-abdominal infections, attention should be given to the maintenance of organ system functions. With generalized peritonitis, initial large volumes of IV fluids are required to restore vascular volume, to improve cardiovascular function, and to maintain adequate tissue perfusion and oxygenation. Adequate urine output should be maintained to ensure adequate resuscitation and proper renal function. Respiratory function can be assisted by a variety of methods, including oxygen therapy, pulmonary physiotherapy, and ventilatory support in severely ill patients. Often the critically

ill patient with intra-abdominal infection will require intensive care management, particularly if there is cardiovascular or respiratory instability. In addition, isolation procedures may be required if the infectious process poses a threat to other hospitalized patients.

An important component of therapy is nutrition. Intra-abdominal infections often involve the GI tract or disrupt its function (paralytic ileus). The return of GI motility may take days, weeks, and, occasionally, months. In the interim, enteral or parenteral nutrition as indicated facilitates improved immune function and wound healing to ensure recovery.

Nonpharmacologic Treatment

Drainage Procedures

Primary peritonitis is treated with antimicrobials and rarely requires drainage. Secondary peritonitis requires surgical correction of the underlying pathology. The drainage of the purulent material is the critical component of management of an intra-abdominal abscess. Without adequate drainage of the abscess, antimicrobial therapy and fluid resuscitation can be expected to fail.

Secondary peritonitis is treated surgically; this is often called *source control*, which refers to all the physical measures undertaken to eradicate the focus of infection.[2,5] At the time of laparotomy (surgical opening and exploration of the abdomen), attempts are made to correct the cause of the peritonitis. This may include patching a perforated ulcer with omentum, removal of a segment of perforated colon, or excision of a portion of gangrenous small intestine. In addition, the surgeon may elect to leave the abdomen open after the laparotomy, plan a re-laparotomy at a later time regardless of the patient's condition, or perform re-laparotomy if the patient develops reinfection.[2,5] The goal of all these procedures is to repair or remove the inflamed or gangrenous viscus and to prevent further bacterial contamination. The presence of active inflammation increases the difficulty of the surgical procedure, which results in a higher morbidity and mortality rate than if the same procedures were performed in an elective setting without inflammation.

The presence of active inflammation may make it technically impossible to perform the definitive surgical procedure. In this situation, attempts are made to provide drainage of the infected or gangrenous structures. If an intra-abdominal abscess, separate from any intra-abdominal organ, is discovered during an exploratory laparotomy, it may be debrided, excised, or drained. If the intra-abdominal abscess involves an abdominal structure, then a resection of part or of

the entire organ may be required. An example of this situation is an abscess associated with diverticular disease of the colon. Management may include drainage of the abscess and resection of the involved part of the colon. All foreign material, necrotic tissue, feces, blood, or purulent material should be removed from the operative field, and the peritoneum should be copiously irrigated with 0.9% sodium chloride to decrease the concentrations of bacteria or other noxious substances.

After an abscess is located, it must be drained. This may be performed surgically or with percutaneous, image-guided techniques.[2,5,38] Typically, image-guided techniques use ultrasonography or CT scanning. The management of an intra-abdominal abscess with percutaneous catheter drainage may be sufficient to resolve the infection. Some patients may require a subsequent procedure to treat the underlying GI conditions; however, a significant advantage is obtained by first draining the abscess percutaneously. This allows the surgical procedure to be performed on a patient who is no longer suffering from the systemic manifestations of uncontrolled infection. Drainage techniques may be performed using endoscopy or laparoscopy. These minimal-access techniques may offer advantages when compared with traditional surgery but will probably be used less often than radiologically assisted percutaneous drainage techniques.

The most valuable microbiologic information may be obtained at the time of percutaneous or operative abscess drainage. If purulent material or presumably infected fluid is found, it is best to aspirate 2 to 3 mL into a syringe, remove any air, and tightly cap the syringe. The specimen should be promptly delivered to the microbiology laboratory, where a Gram stain should be performed immediately and cultures prepared for identification of aerobic and anaerobic bacteria. If no fluid is available for collection, culture swab devices may be applied to the infected area; however, anaerobic organisms often are not isolated from swabs.

Fluid Therapy

4 Patients should be evaluated for signs of hypovolemia, hypoperfusion, and shock. Initial effective fluid repletion and management are required for successful management of intra-abdominal infections. The Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock 2016 recommend that resuscitation should be guided by normalization of lactate (weak recommendation, low quality of evidence). Furthermore, in patients with septic shock requiring vasopressors, an initial mean arterial pressure (MAP) of 65 mmHg should be targeted (strong recommendation, moderate quality of

evidence).[39–41] Fluid therapy is instituted for the purposes of achieving or maintaining intravascular volume to ensure adequate cardiac output, tissue perfusion, and correction of acidosis. Loss of fluid through vomiting, diarrhea, or nasogastric suction contributes to fluid depletion. MAP is most representative of tissue perfusion and should be frequently monitored to guide therapy. When a contracted vascular volume is accompanied by hemorrhage, the initial hematocrit may be normal, but if there is no associated hemorrhage, the hematocrit is usually elevated as an indication of hemoconcentration. Urine output should be monitored continuously in severely ill patients by use of a urinary bladder catheter, quantitated hourly, and should equal or exceed 0.5 mL/kg of body weight per hour.

In patients with peritonitis, hypovolemia is often accompanied by metabolic acidosis. Although serum lactate is not a direct measure of tissue perfusion, it may serve as a surrogate marker representing tissue hypoxia and is therefore recommended by the Surviving Sepsis Campaign 2018 update to guide fluid administration. In those patients with sepsis hypoperfusion or septic shock, IV fluids should consist of a 30 mL/kg bolus of crystalloids with additional fluids targeting predefined therapeutic goals.[39–41] Initial fluid resuscitation should be completed within 3 hours of hypoperfusion recognition. Thereafter, fluids may be required at a rate of 1 L/h or higher. Once targeted therapeutic goals are reached, judicious use of fluids should be used as a sustained positive fluid balance after initial resuscitation may be harmful.[2,42] Maintenance fluids should be instituted with 0.9% sodium chloride and potassium chloride (20 mEq/L [mmol/L]) or 5% dextrose and 0.45% sodium chloride with potassium chloride (20 mEq/L [mmol/L]). The administration rate should be based on estimated daily fluid loss through urine and nasogastric suction, including 0.5 to 1 L for insensible fluid loss. Potassium would not be included routinely if the patient is hyperkalemic or has renal insufficiency. If appropriate fluid management fails to restore target goals of perfusion, vasopressor therapy should be initiated.[43] A more thorough discussion of fluid and vasopressor therapy is presented elsewhere in this book (Chapter 41 and 137).

In patients with significant blood loss, blood transfusion may be indicated. This is generally in the form of packed red blood cells. The criteria for blood transfusion are controversial, but a hematocrit of 25% is generally accepted. In the individual patient, the decision is often determined by the overall clinical status and the ability of the patient to compensate for the reduction in oxygen-carrying capacity associated with an acute anemia. Additional blood component therapy with fresh-frozen plasma or platelets is also based on the needs of the

individual patient. Aggressive fluid therapy must often be continued in the postoperative period because fluid will continue to sequester in the peritoneal cavity, bowel wall, and lumen.

Pharmacologic Treatment

Antimicrobial Therapy

The goals of antimicrobial therapy are: (a) to eliminate the intra-abdominal infection and prevent the establishment of metastatic foci of infection or bacteremia, (b) to reduce suppurative complications (eg, abscess formation) after bacterial contamination, and (c) to prevent local spread of existing infection. After suppuration has occurred, a cure by antibiotic therapy alone is very difficult to achieve; antimicrobials may serve to improve the results obtained with surgery.

5 An empirical antimicrobial regimen should be started as soon as the presence of intra-abdominal infection is suspected. The Surviving Sepsis Campaign Guidelines recommend that antimicrobial therapy is administered within 1 hour of the recognition of sepsis or septic shock (strong recommendation, moderate quality of evidence).[39] Therapy must be initiated based on the likely pathogens, potential resistance, and severity of patient illness. Resistance is common among gram-negative pathogens to fluoroquinolones and ampicillin–sulbactam; this emphasizes the importance of using local susceptibility data to guide empiric therapy and tailoring the antibiotic regimen based on susceptibility results.[43] Predominant pathogens, as discussed in the preceding section, vary depending on the site of intra-abdominal infection and the underlying disease process. **Table 132-5** lists the likely pathogens against which antimicrobial agents should be directed.

TABLE 132-5 Likely Intra-Abdominal Pathogens

Type of Infection	Aerobes	Anaerobes
Primary (Spontaneous) Bacterial Peritonitis		
Children	Group A *Streptococcus*, *E. coli*, pneumococci	—
Cirrhosis	*E. coli*, *Klebsiella*, pneumococci (many others)	—
Peritoneal dialysis	*Staphylococcus*, *Streptococcus*, *E. coli*, *Klebsiella*, *Pseudomonas*	—
Secondary Bacterial Peritonitis		
Gastroduodenal	*Streptococcus*, *E. coli*	—
Biliary tract	*E. coli*, *Klebsiella*, enterococci	*Clostridium* or *Bacteroides* (infrequent)
Small or large bowel	*E. coli*, *Klebsiella*, *Proteus*	*B. fragilis* and other *Bacteroides*, *Clostridium*
Appendicitis	*E. coli*, *Pseudomonas*	*Bacteroides*
Abscesses	*E. coli*, *Klebsiella*, *Streptococcus*, enterococci	*B. fragilis* and other *Bacteroides*, *Clostridium*, anaerobic cocci
Liver	*E. coli*, *Klebsiella*, *Streptococcus*, enterococci, *Staphylococcus*, amoeba	*Bacteroides* (infrequent)
Spleen	*Staphylococcus*, *Streptococcus*, *E. coli*, *Salmonella*	

Antimicrobial Experience Many studies have been conducted evaluating or comparing the effectiveness of antimicrobials for the treatment of intra-abdominal infections. Substantial differences in patient outcomes between specific agents have not generally been demonstrated.[44]

Important findings from over 20 years of clinical trials regarding selection of antimicrobials for intra-abdominal infections are the following:

1. Antimicrobial regimens used for secondary infections should cover a broad spectrum of aerobic and anaerobic bacteria from the GI tract. The local epidemiology of resistant pathogens, patient-specific risk factors for resistant pathogens, and patient severity of illness should guide empiric treatment.
2. Resistance is prevalent among *B. fragilis* to clindamycin and cefotetan and Enterobacteriaceae to ampicillin–sulbactam and quinolones, and therefore these agents should not be routinely used empirically for complicated intra-abdominal infections.[45,46]
3. If the causative pathogens are susceptible and the patient has clinically responded, antimicrobial treatment can be completed orally with amoxicillin–clavulanate, metronidazole with either ciprofloxacin or levofloxacin, or moxifloxacin.[47]
4. Four days of antimicrobial treatment after adequate source control is sufficient for most intra-abdominal infections.[2,48,49]

Intra-abdominal infections present in many different ways and with a wide spectrum of severity. The regimen employed and duration of treatment depends on the specific clinical circumstances (ie, the nature of the underlying disease process, severity of illness, and risk of resistant pathogens).

6 **Recommendations** For most intra-abdominal infections, the antimicrobial regimen should be effective against both aerobic and anaerobic bacteria.[49,50] When initial antimicrobial therapy is inactive, morbidity and mortality rates are higher than when initially active therapy is used.[49] Generally, agents with activity against enteric gram-negative bacilli such as *E. coli* and *Klebsiella* spp. and anaerobes including *B. fragilis* should be administered. If most of the organisms can be eliminated through drainage or antimicrobials, the synergistic effect may be removed, and the patient's defenses may be able to resolve the remaining infection.

Table 132-6 lists the agents recommended by the Infectious Diseases Society of America (IDSA) and the Surgical Infection Society (SIS) for the treatment of community-acquired complicated intra-abdominal infections.[2,49] These recommendations were formulated using an evidence-based approach. **Table 132-7** lists additional evidence-based recommendations for the treatment of complicated intra-abdominal infections. Choosing empiric antibiotic therapy based on these recommendations within the IDSA/SIS guidelines has been associated with a decreased time to active therapy for patients with community-

onset complicated intra-abdominal infection.[51] Although most community-acquired infections are of mild-to-moderate severity, healthcare-associated infections tend to be more severe, more difficult to treat, and more common due to resistant pathogens. **Table 132-8** presents guidelines for treatment and alternative regimens for specific situations. These are general guidelines; such a table cannot incorporate many factors including local resistance patterns to commonly used agents such as quinolones.

TABLE 132-6 Recommended Agents for the Treatment of Community-Acquired Complicated Intra-Abdominal Infections in Adults

Agents Recommended for Mild-to-Moderate Infections	Agents Recommended for High Severity Infections
Single Agent	
Cefoxitin[a]	Piperacillin–tazobactam
Moxifloxacin[b]	Imipenem–cilastatin,[c] meropenem,[c] doripenem[c]
Ertapenem[c]	
Combination Regimens	
Cefazolin,[a] cefuroxime,[a] ceftriaxone, or cefotaxime each in combination with metronidazole	Cefepime, ceftazidime, ceftazidime/avibactam,[d] or ceftolozane/tazobactam[e] each in combination with metronidazole
Ciprofloxacin[b] or levofloxacin[b] each in combination with metronidazole	Ciprofloxacin[b] or levofloxacin[b] each in combination with metronidazole

[a]Empiric first- and second-generation cephalosporin use should be avoided unless local antibiograms show >80% to 90% susceptibility of *E. coli* to these agents.

[b]Use of quinolones may be associated with treatment failure due to increasing resistance of enteric pathogens including *E. coli*. Empiric quinolone use should be avoided unless local antibiograms show >80% to 90% susceptibility of *E. coli* to quinolones.

[c]Carbapenems should be reserved for settings where there is a high risk of resistance to other agents (ie, extended-spectrum β-lactamase [ESBL]-producing pathogens).

[d]Ceftazidime/avibactam should be reserved for patients infected with Enterobacteriaceae that are resistant to all other β-lactams including carbapenems, and in particular, *Klebsiella pneumoniae* carbapenemase (KPC)-producing pathogens.

[e]Ceftolozane/tazobactam should be reserved for patients infected with gram-negative bacteria that are resistant to all other β-lactams. Ceftolozane/tazobactam may have activity against multidrug-resistant *Pseudomonas* however susceptibility must be confirmed.

Data from References 2 and 49.

TABLE 132-7 Evidence-Based Recommendations for Treatment of Complicated Intra-Abdominal Infections

	Grade of Recommendation[a]
Elements of Appropriate Intervention	
An appropriate source control procedure to drain infected foci, control ongoing peritoneal contamination by diversion or resection, and restore anatomic and physiological function to the extent feasible is recommended for nearly all patients with intra-abdominal infection	B-2
Community-Acquired Infections of Mild-to-Moderate Severity in Adults	
Antibiotics used for empiric treatment of community-acquired intra-abdominal infections should be active against enteric gram-negative aerobic and facultative bacilli and enteric gram-positive streptococci	A-1
For patients with mild-to-moderate community-acquired infections, regimens with substantial anti-pseudomonal activity are not required (**Table 132-6**)	A-1
Empiric coverage of *Enterococcus* is not necessary in patients with mild-to-moderate community-acquired intra-abdominal infection	A-1
The use of agents listed as appropriate for high-severity community-acquired infection and healthcare-associated infection is not recommended for patients with mild-to-moderate community-acquired infection, because such regimens may carry a greater risk of toxicity and facilitate acquisition of more resistant organisms	B-2
High-Severity Community-Acquired Infections in Adults[b]	
The empiric use of antimicrobial regimens with broad-spectrum activity against gram-negative organisms including *Pseudomonas* spp., such as meropenem, imipenem–cilastatin, doripenem, piperacillin–tazobactam, ciprofloxacin or levofloxacin in combination with metronidazole, or ceftazidime or cefepime in combination with metronidazole, is recommended for patients with high-severity community-acquired intra-abdominal infection (Table 132-6)	A-1
Aztreonam plus metronidazole is an alternative, but addition of an agent effective against gram-positive cocci is recommended	B-3
Healthcare-Associated Infections in Adults[c]	
Empiric antibiotic therapy for healthcare-associated intra-abdominal infection should be driven by local microbiologic results	A-2
To achieve empiric coverage of likely pathogens, multidrug regimens that include agents with expanded spectra of activity against gram-negative aerobic and facultative bacilli may be needed. These agents include meropenem, imipenem–cilastatin, doripenem, piperacillin–tazobactam, or metronidazole combined with either cefepime or ceftazidime. For multidrug-resistant aerobic gram-negative pathogens, aminoglycosides, colistin, polymyxin B, ceftazidime/avibactam, or ceftolozane/tazobactam may be required	B-3
Antimicrobial Agents Not Recommended	
Ampicillin–sulbactam is not recommended for use because of high rates of resistance to this agent among community-acquired *E. coli*	B-2
Quinolone-resistant *E. coli* have become common in some communities, and quinolones should not be used unless hospital surveys indicate 90% susceptibility of *E. coli* to quinolones	A-2
Cefotetan and clindamycin are not recommended for use because of increasing prevalence of resistance to these agents among *Bacteroides fragilis*	B-2
Because of the availability of less toxic agents demonstrated to be at least equally effective, aminoglycosides are not recommended for routine use in adults with community-acquired intra-abdominal infection	B-2
Oral Completion Therapy	
For adults recovering from intra-abdominal infection, completion of the antimicrobial course with oral forms of moxifloxacin, ciprofloxacin plus metronidazole, levofloxacin plus metronidazole, an oral cephalosporin with metronidazole, or amoxicillin–clavulanic acid is acceptable in patients able to tolerate an oral diet and in patients in whom susceptibility studies do not demonstrate resistance	B-2
Duration of Therapy	
Antimicrobial therapy of established infection should be limited to 4 days, unless it is difficult to achieve adequate source control. Longer durations of therapy have not been associated with improved outcome	A-1
For acute stomach and proximal jejunum perforations, in the absence of acid-reducing therapy or malignancy and when source control is achieved within 24 hours, prophylactic anti-infective therapy directed at aerobic gram-positive cocci for 24 hours is adequate	B-2
Bowel injuries attributable to penetrating, blunt, or iatrogenic trauma that are repaired within 12 hours and any other intraoperative contamination of the operative field by enteric contents should be treated with antibiotics for ≤24 hours	A-1
Acute appendicitis without evidence of perforation, abscess, or local peritonitis requires only prophylactic administration of narrow spectrum regimens active against aerobic and facultative and obligate anaerobes; treatment should be discontinued within 24 hours	A-1
The administration of prophylactic antibiotics to patients with severe necrotizing pancreatitis prior to the diagnosis of infection is not recommended	A-1
Anaerobic Coverage	
Coverage for obligate anaerobic bacilli should be provided for distal small bowel, appendiceal, and colon-derived infection and for more proximal GI perforations in the presence of obstruction or paralytic ileus	A-1
Antifungal Therapy	
Antifungal therapy for patients with high-severity community-acquired or healthcare-associated infection is recommended if *Candida* is grown from intra-abdominal cultures	B-2
Anti-MRSA Therapy	
Empiric antimicrobial coverage directed against MRSA should be provided to patients with healthcare-associated intra-abdominal infection who are known to be colonized with the organism or who are at risk of having an infection due to this organism because of prior treatment failure and significant antibiotic exposure	B-2

Vancomycin is recommended for treatment of suspected or proven intra-abdominal infection due to MRSA	A-3
Antienterococcal Therapy	
Antimicrobial therapy for enterococci should be given when enterococci are recovered from patients with high-severity community-acquired or healthcare-associated infection	B-III
Empiric antienterococcal therapy is recommended for patients with high-severity community-acquired infections and healthcare-associated intra-abdominal infections, particularly those with postoperative infection, those who have previously received cephalosporins or other antimicrobial agents selected for *Enterococcus* species, immunocompromised patients, and those with valvular heart disease or prosthetic intravascular materials	B-II
Initial empiric antienterococcal therapy should be directed against *Enterococcus faecalis*. Antibiotics that can potentially be used against this organism, on the basis of susceptibility testing of the individual isolate, include ampicillin, piperacillin/tazobactam, and vancomycin	B-III
Empiric therapy directed against vancomycin-resistant *Enterococcus faecium* is not recommended unless the patient is at very high risk for an infection due to this organism, such as a liver transplant recipient with an intra-abdominal infection originating in the hepatobiliary tree or a patient known to be colonized with vancomycin-resistant *E. faecium*	B-III

[a]Strength of recommendations: A, B, C = good, moderate, and poor evidence to support recommendation, respectively. Quality of evidence: 1 = Evidence from ≥1 properly randomized, controlled trial. 2 = Evidence from ≥1 well-designed clinical trial without randomization, from cohort or case-controlled analytic studies, from multiple time series, or from dramatic results from uncontrolled experiments. 3 = Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.

[b]Criteria for high-severity community-acquired infection: sepsis or septic shock, APACHE II score ≥15, delay in initial intervention >24 hours, advanced age, comorbidity and degree of organ dysfunction, low albumin level, poor nutritional status, degree of peritoneal involvement or diffuse peritonitis, inability to achieve adequate debridement or control of drainage, and presence of malignancy.

[c]Criteria for classification of intra-abdominal infections as healthcare-associated infection varies. However, patients who develop an infection after surgery, reside in a long-term care facility, who were recently hospitalized, or who have other significant healthcare exposure can be considered to have a healthcare-associated intra-abdominal infection.

MRSA, methicillin-resistant *Staphylococcus aureus*.

These recommendations have been adapted from References 2 and 49.

TABLE 132-8 Guidelines for Empiric Antimicrobial Agents for Intra-Abdominal Infections[49,71]

	Primary Agents	Alternatives
Primary (Spontaneous) Bacterial Peritonitis		
Cirrhosis	Ceftriaxone, cefotaxime	1. Piperacillin–tazobactam, carbapenems 2. Aztreonam combined with an agent active against *Streptococcus* spp. (eg, vancomycin) or quinolones with significant *Streptococcus* spp. activity (levofloxacin, moxifloxacin)
Peritoneal dialysis	Initial empiric regimens should be active against both gram-positive (including *S. aureus*) and gram-negative pathogens: gram-positive agent (first-generation cephalosporin or vancomycin) plus a gram-negative agent (third-generation cephalosporin or aminoglycoside)	1. Cefepime or carbapenems may be used alone 2. Aztreonam or an aminoglycoside may be used in place of ceftazidime or cefepime as long as combined with a gram-positive agent 3. Quinolones may be used in place of gram-negative agents if local susceptibilities allow
	1. *Staphylococcus* spp.: oxacillin/nafcillin or first-generation cephalosporin	1. Vancomycin should be used for methicillin-resistant *Staphylococcus* spp. 2. May consider addition of rifampin for 5-7 days with vancomycin for methicillin-resistant *S. aureus*
	2. *Streptococcus* or *Enterococcus*: ampicillin	1. Daptomycin or linezolid should ideally be used to treat vancomycin-resistant *Enterococcus* spp. not susceptible to ampicillin
	3. Aerobic gram-negative bacilli: ceftazidime or cefepime	1. The regimen should be based on in vitro sensitivity tests
	4. *Pseudomonas aeruginosa*: two agents with differing mechanisms of action, such as an intraperitoneal ceftazidime or cefepime each combined with either tobramycin or oral ciprofloxacin	
Secondary Bacterial Peritonitis		
Perforated peptic ulcer	First-generation cephalosporins	1. Ceftriaxone, cefotaxime, or antianaerobic cephalosporins[a]
Other	Third- or fourth-generation cephalosporin with metronidazole, piperacillin–tazobactam or carbapenem	1. Ciprofloxacin[b] or levofloxacin[b] each with metronidazole or *moxifloxacin*[b] alone 2. Aztreonam with vancomycin and metronidazole 3. Antianaerobic cephalosporins[a]
Abscess		
General	Third- or fourth-generation cephalosporin with metronidazole or piperacillin–tazobactam	1. Imipenem–cilastatin, meropenem, doripenem, or ertapenem 2. Ciprofloxacin[b] or levofloxacin[b] each with metronidazole or moxifloxacin alone
Liver	As above	Use metronidazole if amoebic liver abscess is suspected
Spleen	Ceftriaxone or cefotaxime	Moxifloxacin[b] or levofloxacin[b]
Other Intra-abdominal Infections		
Appendicitis	Same management as for community-acquired complicated intra-abdominal infections as listed in Table 132-6[39]	
Community-acquired acute cholecystitis	Ceftriaxone or cefotaxime	Severe infection, piperacillin/tazobactam, antipseudomonal carbapenem, aztreonam with metronidazole
Cholangitis	Ceftriaxone or cefotaxime each with or without metronidazole	Vancomycin with aztreonam with or without metronidazole
Acute contamination from abdominal trauma	Antianaerobic cephalosporins[a] or metronidazole with either ceftriaxone or cefotaxime	1. Piperacillin/tazobactam or a carbapenem 2. Ciprofloxacin[b] or levofloxacin[b] each with metronidazole or moxifloxacin alone

[a]Cefoxitin or ceftizoxime; these agents should be avoided empirically unless local antibiograms show >80% to 90% susceptibility of *E. coli* to these agents.

[b]Use of quinolones may be associated with treatment failure due to increasing resistance of enteric pathogens including *E. coli*. Empiric quinolone use should be avoided unless local antibiograms show >80% to 90% susceptibility of *E. coli* to quinolones.

Most patients with severe intra-abdominal infection, sepsis, or healthcare-associated infection should be placed on piperacillin–tazobactam, cefepime with metronidazole, or a carbapenem with *Pseudomonas* activity such as imipenem, doripenem, or meropenem. In patients with IgE-mediated allergic reactions to β-lactams (hives/urticaria, bronchospasm, angioedema, or anaphylaxis), a combination therapy with aztreonam, vancomycin and metronidazole may be used. The benefits of systemic preemptive antifungal therapy (with fluconazole or an echinocandin) as a means to prevent invasive candidiasis in patients with intra-abdominal infection have not been established.[52] However, patients with intra-abdominal infections are often at high risk for systemic candidiasis, given multiple risk factors may be present such as recent abdominal surgery, the presence of a central line, parenteral nutrition, and broad-spectrum antibiotic use.[2,49,53] When invasive candidiasis is suspected, generally an echinocandin should be used empirically because these patients are often severely ill and may be at risk for being infected with a fluconazole-resistant *Candida* species.[53] And as noted in Table 132-7, *Candida* should be treated if isolated from cultures in patients with high-severity community-acquired or healthcare-associated infection.[2,53] If the *Candida* spp. is fluconazole susceptible and the patient is clinically improving, it is reasonable to de-escalate from an echinocandin to fluconazole.

Aminoglycoside-based treatment regimens are not routinely recommended due to their narrow therapeutic index (nephrotoxicity, ototoxicity) relative to the recommended agents such as β-lactams.[54,55] Aminoglycosides are reserved primarily for infections due to presumed or proven multidrug-resistant pathogen(s).[44,49]

If an aminoglycoside is required, the initial dosage should be determined based on the patient's weight and renal function. Traditionally, gentamicin and tobramycin were administered multiple times daily with specific peak (6-10 mcg/mL [mg/L; 13-21 μmol/L]) and trough (less than 1-2 mcg/mL [mg/L; less than 2-4 μmol/L]) serum concentration targets. Because aminoglycosides have concentration-dependent killing and have a relatively long postantibiotic effect for aerobic gram-negative bacilli, extended-interval dosing of aminoglycosides is possible. For most patients and indications, extended-interval aminoglycoside dosing (ie, 5-7 mg/kg once daily for tobramycin or gentamicin, 15-20 mg/kg once daily for amikacin) has replaced traditional dosing, given equivalent efficacy and decreased nephrotoxicity.[56–58]

Antimicrobial resistance continues to increase worldwide.[59–61]

Enterobacteriaceae producing extended-spectrum β-lactamases (ESBL) have been increasingly isolated from intra-abdominal cultures.[43,45] For patients with ESBL-producing pathogens, carbapenems are typically the drugs of choice. With the increased use of carbapenems, pathogens have continued to evolve with the development of β-lactamases that hydrolyze carbapenems (eg, *Klebsiella pneumoniae* carbapenemase [KPC]), multidrug-resistant *Pseudomonas* spp., and carbapenem-resistant *Acinetobacter* spp. Especially in patients with healthcare-associated intra-abdominal infections, these multidrug-resistant pathogens have forced clinicians to use more toxic and potentially less effective agents such as the polymyxins, tigecycline, and aminoglycosides. For example, the product labeling for tigecycline carries a Black Box Warning, as it has been associated with an increased risk of mortality relative to comparator agents, which is based on pooled data collected from randomized controlled trials including patients with intra-abdominal infections, skin and skin structure infections, and ventilator-associated pneumonia.[62–64] Accordingly, the 2017 SIS guidelines recommend against the use of tigecycline except potentially as part of a combination regimen for multidrug-resistant pathogens.[2] Two potential therapeutic options for multidrug-resistant pathogens, ceftolozane/tazobactam and ceftazidime/avibactam, have been FDA-approved for the treatment of complicated intra-abdominal infections in combination with metronidazole.[65,66] Ceftolozane/tazobactam may be active against multidrug-resistant pathogens, particularly *Pseudomonas* spp., while ceftazidime/avibactam is active against KPC-producing Enterobacteriaceae. Ceftazidime/avibactam may be more effective than colistin-based regimens for infections due to KPC-producing Enterobacteriaceae.[67] Although not FDA-approved for complicated intra-abdominal infections, meropenem/vaborbactam, like ceftazidime/avibactam, may be active against KPC-producing Enterobacteriaceae. However, it is not uncommon for organisms that are resistant to all other beta-lactams to also be resistant to these three new agents, and so susceptibility must be confirmed. Despite this, these agents are highly valuable in terms of their activity against multidrug-resistant pathogens, and as such, their use should be reserved for patients with a suspected or confirmed infection due to a pathogen resistant to all other β-lactams. The limited safe-and-effective therapeutic options for resistant organisms highlight the need, from an individual patient and public health standpoint, for pharmacists and other clinicians to ensure that antimicrobials are selected appropriately, at the optimal dose, and for the correct duration.

With intra-abdominal contamination from the upper GI tract (perforation of a peptic ulcer or biliary tract disease), anaerobes such as *B. fragilis* are uncommon

pathogens, and therefore other empiric agents such as ampicillin, penicillin, or first-generation cephalosporins are reasonable. Anaerobic coverage is also not necessary for primary peritonitis associated with cirrhosis, and third-generation cephalosporins, such as cefotaxime or ceftriaxone, remain the treatments of choice.[68]

Empiric coverage of *Enterococcus* in mild-to-moderate community-acquired intra-abdominal infections is not recommended.[49] The failure of host defenses may be a critical factor in the pathogenicity of enterococci. In patients with high-severity community-acquired intra-abdominal infection or patients with healthcare-associated infection, coverage of *Enterococcus faecalis* should be included in the initial regimen.[2,49] Ampicillin remains the drug of choice for this indication because it is active against the vast majority of *E. faecalis.* Notably, piperacillin/tazobactam and imipenem/cilastin both have activity against ampicillin-susceptible *E. faecalis* and therefore these may be elegant choices for empiric therapy of high-severity community-acquired or healthcare-associated intra-abdominal infection. Vancomycin may also be active against enterococci; however, rates of vancomycin-resistant enterococci are increasing, especially in select patient populations (eg, liver transplantation, immunocompromised patients).[69] Agents including linezolid or daptomycin are commonly used for vancomycin-resistant *Enterococcus* infections. Table 132-7 lists additional evidence-based recommendations for *Enterococcus* spp. coverage.

7 Intraperitoneal administration of antibiotics is preferred over IV therapy in the treatment of peritonitis that occurs in patients undergoing CAPD.[70,71] The International Society of Peritoneal Dialysis guidelines for the diagnosis and pharmacotherapy of peritoneal dialysis-associated infections provide antimicrobial dosing recommendations based on the modality of dialysis (continuous or intermittent).[71]

Given the peritoneal catheter exit site and tunnel is frequently the source of peritoneal dialysis-related peritonitis, antimicrobial agents effective against both gram-positive skin flora (including *S. aureus*) and gram-negative organisms should be used for initial intraperitoneal empiric therapy. The most important factors to take into consideration for initial antimicrobial selection are the dialysis center’s and the patient’s history of infecting organisms and their sensitivities. For empiric intraperitoneal therapy, cefazolin or vancomycin in cases of high prevalence of methicillin-resistant *S. aureus* (MRSA) or β-lactam allergy may be used for gram-positive coverage. Glycopeptide-containing regimens (vancomycin or teicoplanin) were more likely to achieve complete cure compared to first-generation cephalosporins.[70,72] When vancomycin is used, it is

preferred that it be given intraperitoneally via intermittent dosing (15–30 mg/kg every 5-7 days) and serum concentrations should be maintained above 15 mcg/mL.[73] When administered via intermittent dosing, generally the antibiotic should dwell for at least 6 hours. One of these gram-positive agents should be combined with a gram-negative agent such as ceftazidime or an aminoglycoside. If an aminoglycoside is used, it is preferred that it be given intraperitoneally via intermittent dosing (eg, gentamicin 0.6 mg/kg/day). Long durations of aminoglycoside therapy should be avoided if possible to mitigate the risk of ototoxicity and loss of residual renal function. Another option is monotherapy with cefepime or imipenem–cilastatin. If patients have significant residual renal function, increased antimicrobial doses may not be necessary.[71,73] As with other intra-abdominal infections, source control should be prioritized; in patients with an ongoing catheter exit site or tunnel infection, catheter removal with reinsertion should be strongly considered. If peritonitis relapses or recurs, the catheter should be promptly removed. Antimicrobial therapy should typically be continued for 14 to 21 days. The reader is referred to recent guidelines for additional information.[71]

After acute bacterial contamination, such as with abdominal trauma where GI contents spill into the peritoneum, antibiotics should be administered. If the patient is seen soon after injury (within 2 hours) and surgical measures are instituted promptly, an antianaerobic cephalosporin (such as cefoxitin), a third-generation cephalosporin (such as ceftriaxone) with metronidazole, or piperacillin/tazobactam is effective in preventing most infectious complications. Antimicrobials should be administered as soon as possible after injury.[74]

8 For appendicitis, the antimicrobial regimen used should depend on the appearance of the appendix at the time of operation, which may be normal, inflamed, gangrenous, or perforated. It is advisable to begin antimicrobial agents before the appendectomy is performed. Reasonable regimens would be antianaerobic cephalosporins or, if the patient is seriously ill, piperacillin–tazobactam or an anti-pseudomonal carbapenem. If, at operation, the appendix is normal or inflamed, postoperative antimicrobials are not required. If the appendix is gangrenous or perforated, a treatment course of 3 to 4 days with the agents listed in Table 132-6 is appropriate.[75,76] For uncomplicated appendicitis (defined as the absence of perforation, abscess, appendicolith, CT consistent with possible tumor, peritonitis, severe systemic illness) confirmed by CT, a nonsurgical approach of antibiotic therapy alone may also be considered.[76,77] A 2015 randomized study found that patients who received initial appendectomy (mostly open procedures), instead of antibiotics alone, experienced greater pain,

a longer duration of sick leave from work, and more complications such as surgical site infections and delayed healing. In addition, 27% of patients managed nonsurgically required an appendectomy within 1 year of their index hospitalization. Despite these limitations, the risks and benefits of surgery versus antibiotics alone should be considered along with the patient's own preferences.

Acute intra-abdominal contamination, such as after a traumatic injury, may be treated with a short antimicrobial course (24 hours).[74] For established infections (ie, peritonitis or intra-abdominal abscess), an antimicrobial course limited to 4 days after source control is appropriate.[2,48] This allows eradication of bacteria remaining in the peritoneum after a surgical procedure that may enter the peritoneum through healing suture lines. Under certain conditions, therapy for longer than 4 days would be justified (eg, when the focus of infection in the abdomen is still present). For some abscesses, such as pyogenic liver abscess, antimicrobials may be required for a month or longer. If definitive source control is not possible, then a duration of 5 to 7 days of antibiotic therapy may be considered based on the patient's clinical stability including resolution or improvement in leukocytosis, fever, GI function.[2] These patients should be closely monitored for clinical worsening after cessation of antibiotics; a source control intervention may need to be reconsidered or antibiotics may need to be reinitiated.

Intraperitoneal irrigation of antimicrobial agents for the prevention of surgical site infection, abscess development, and other complications in patients with peritonitis has been studied; however, the quality of the data is limited and precludes a definitive determination of efficacy.[78,79] Possibly the most important aspect of peritoneal irrigation is the dilutional effect on bacteria and adjuvants that promote infection (intestinal contents and hemoglobin), and elimination of debris and gross contamination. Most systemically administered antimicrobials easily cross the peritoneal membrane so that peritoneal fluid concentrations are similar to serum. Confined areas, such as an abscess, can be expected to attain much lower antimicrobial concentrations. Given the unclear benefit of antibiotic irrigation, irrigation with crystalloid fluid alone is recommended.[2]

EVALUATION OF THERAPEUTIC OUTCOMES

Whichever antimicrobial regimen is chosen, the patient should be reassessed continually to determine the success or failure of therapies. The clinician should recognize that there are many reasons for poor patient outcomes with intra-abdominal infections, improper antimicrobial administration is only one. The

patient may be immunocompromised, which decreases the likelihood of successful outcome with any regimen. There may be surgical reasons for poor patient outcome. Failure to identify all intra-abdominal foci of infection or leaks from a GI anastomosis may cause continued infection. Finally, antimicrobial resistance may contribute to treatment failure as isolates from intra-abdominal infections are increasingly drug resistant.[43,80]

The outcome from intra-abdominal infection is not determined solely by what transpires in the abdomen. Unsatisfactory outcomes in patients with intra-abdominal infections may result from complications that arise in other organ systems, including renal or respiratory failure. Furthermore, pneumonia is a complication that is commonly associated with mortality after intra-abdominal infection.[81] Other nosocomial infections including catheter-related bacteremia and urinary tract infection are also independent predictors of mortality in patients with intra-abdominal infections.[82]

9 Once antimicrobials are initiated and the other important therapies described earlier are used, most patients should show improvement within 2 to 3 days. Usually, temperature will return to near normal, vital signs should stabilize, and the patient should not appear in distress, with the exception of recognized discomfort and pain from incisions, drains, and the nasogastric tube. Within 24 to 72 hours, aerobic bacterial culture results should return. If a suspected pathogen is not sensitive to the antimicrobial agents being given, the regimen should typically be changed to active therapy. If the isolated pathogen is susceptible to a narrower spectrum agent, therapy should be de-escalated.

With anaerobic culturing techniques and the slow growth of these organisms, anaerobes are often not identified until 4 to 7 days after culture. A report indicating that anaerobes were not isolated should not be the sole justification for discontinuing antianaerobic drugs because anaerobic bacteria that were present in the infectious process may not have been collected or maintained in anaerobic conditions which can lead to cell death in vitro.

Reasons for antimicrobial failure may not always be apparent. Even when antimicrobial susceptibility tests indicate that an organism is susceptible in vitro to the antimicrobial agent, therapeutic failures may occur. Possibly there is poor penetration of the antimicrobial agent into the focus of infection, or bacterial resistance may develop after initiation of antimicrobial therapy. In addition, it is possible that an antimicrobial regimen may encourage the development of infection by organisms not susceptible to the regimen being used. Superinfection in patients being treated for intra-abdominal infection can be caused by *Candida*; however, enterococci or opportunistic gram-negative bacilli such as

Pseudomonas may be involved.

Treatment regimens for intra-abdominal infection can be judged as successful if the patient recovers from the infection without recurrent peritonitis or intra-abdominal abscess and without the need for additional antimicrobials. A regimen can be considered unsuccessful if a significant adverse drug reaction occurs, reoperation or percutaneous drainage is necessary, or patient improvement is delayed beyond 1 or 2 weeks. The costs of treatment can be significantly reduced if parenteral antimicrobials can be switched to oral agents for completion of therapy.[83]

Postclass Engaged Learning Activity

Answer the questions for the case below on the basis of the information contained within the chapter and develop a treatment plan following the patient care process.

Case

A 59-year-old woman with history of cirrhosis secondary to alcohol abuse is admitted from an outside hospital for altered mental status and concern for hepatic encephalopathy. The patient lives at home and the day before admission the patient told her spouse that her stomach was hurting. The spouse expresses concern that patient was not receiving lactulose for past 1.5 weeks and missed her recent liver clinic appointment. The patient was initially admitted for less than 24 hours to an outside hospital and received unknown antibiotics before transfer to the current hospital. On exam, the patient is drowsy and not very responsive to questions. Patient appears jaundiced and is complaining of abdominal pain. No nausea, vomiting, or shortness of breath is observed.

Home medications:

Folic acid 1 mg orally every day

Lactulose 10 g orally twice a day

Magnesium oxide 400 mg orally every day

Pantoprazole 40 mg orally every day

Potassium chloride 20 mEq orally twice a day

Hydrochlorothiazide 25 mg orally every day

Spironolactone 25 mg orally every day

ALL: NKDA

Pertinent Labs:

Total bilirubin 11.5 mg/dL

Direct bilirubin 3.9 mg/dL

Alkaline phosphatase 68 U/L

AST/ALT 65/27 U/L

Albumin 2.3 g/dL

Creatinine 0.7 mg/dL

WBC 14.8 × 10^9 / L

Hemoglobin 8.9 × g/dL

Platelets 92 × 10^9 / L

INR 3.2

No significant culture history

Vitals:

Pulse 106 BPM, Respiratory rate 24 BPM, BP 145/65 mmHg, O_2 Saturation 96% on room air, T_{max} 38°C

Diagnostic paracentesis on admission:

Ascites fluid cell count/differential

Color: Yellow, cloudy

WBC: 8,080 cells/µL

RBC: 5,280 cells/µL

Neutrophil: 74%

Gram-stain negative

1. How do you classify this patient's infection?
   A. Cholecystitis
   B. Cholangitis
   C. Spontaneous bacterial peritonitis
   D. Secondary bacterial peritonitis
2. What laboratory data and patient symptoms support the diagnosis above?
3. What are the likely pathogens that could cause this syndrome?

4. What empiric therapy do you initiate?

A. Cefepime
B. Cefepime + metronidazole
C. Ceftriaxone
D. Ceftriaxone + metronidazole
E. Meropenem

Answers to Postclass exercise:

1. C

2. The patient has liver cirrhosis, which is a risk factor for spontaneous bacterial peritonitis (SBP). They present with fever, abdominal pain, and an ascitic fluid with >250 PMN which is suggestive of SBP. Although the Gram stain of the ascitic fluid was negative, the Gram stain is often negative with low inoculum infections and/or in patients who have received antibiotic therapy.

3. SBP is typically monomicrobial. The most common pathogens are Streptococcus *species and Enterobacteriaceae such as* E. coli *and* Klebsiella *spp. Notably, anaerobes are not a common cause of SBP.*

4. C, Ceftriaxone is the correct response, given it provides adequate empiric activity for the pathogens listed in question 3. Furthermore, it does not provide unnecessary broad coverage for anaerobes (responses B, D, E are incorrect) or Pseudomonas (responses A, B, E are incorrect).

ABBREVIATIONS

APACHE	acute physiology and chronic health evaluation
CAPD	chronic ambulatory peritoneal dialysis
CT	computed tomography
CVP	central venous pressure
ESBL	extended-spectrum β-lactamase
IDSA	Infectious Diseases Society of America
IL	interleukin
INF	interferon
KPC	*Klebsiella pneumoniae* carbapenemase
LD	loading dose
MAP	mean arterial pressure
MD	maintenance dose
MRSA	methicillin-resistant *Staphylococcus aureus*
SIS	Surgical Infection Society
TNF	tumor necrosis factor

REFERENCES

1. Shirah GR, O'Neill PJ. Intra-abdominal infections. *Surg Clin North Am*. 2014;94:1319–1333.
2. Mazuski JE, Tessler JM, May AK, et al. The Surgical Infection Society revised guidelines on the management of intra-abdominal infection. *Surg Infect (Larchmt)*. 2017;18(1):1–76.
3. Marshall JC, Innes M. Intensive care unit management of intra-abdominal infection. *Crit Care Med*. 2003;31:2228–2237.
4. Levison ME, Bush LM. Peritonitis and intraperitoneal abscesses. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. Philadelphia: Saunders; 2015:935–959[Chapter 76].
5. Sartelli M, Chichom-Mefire A, Labricciosa FM, et al. The management of intra-abdominal infections from a global perspective: 2017 WSES guidelines for management of intra-abdominal infections. *World J Emerg Surg*. 2017;12:29.
6. Wiest R, Krag A, Gerbes A. Spontaneous bacterial peritonitis: Recent guidelines and beyond. *Gut*. 2012;61:297–310.
7. Piericleous M, Sarnowski A, Moore A, Fijten R, Zaman M. The clinical management of abdominal ascites, spontaneous bacterial peritonitis and hepatorenal syndrome: A review of current guidelines and

recommendations. *Eur J Gastroenterol Hepatol*. 2016;28:e10–e18.

8. Jalan R, Fernandez J, Wiest R, et al. Bacterial infections in cirrhosis: A position statement based on the EASL Special Conference 2013. *J Hepatol*. 2014;60:1310–1324.
9. Dever JB, Sheikh MY. Spontaneous bacterial peritonitis—Diagnosis, treatment, and prevention. *Aliment Pharmacol Ther*. 2015;41:1116–1131.
10. Schmidt ML, Barritt AS, Orman ES, Hayashi PH. Decreasing mortality in patients hospitalized with cirrhosis in the United States from 2002 through 2010. *Gastroenterology*. 2015;148:967–977.
11. Niu B, Kim B, Limketkai BN, Sun J, Li Z, Woreta T, Chen PH. Mortality from spontaneous bacterial peritonitis among hospitalized patients in the USA. *Dig Dis Sci*. 2018;63(5):1327–1333.
12. Piraino B, Bernardini J. Catheter-related peritonitis. *Perit Dial Int*. 2013;33:592–595.
13. National Hospital Discharge Survey 2010. U.S. Department of Health and Human Services Centers for Disease Control and Prevention. National Center for Health Statistics. Available at http://www.cdc.gov/nchs/nhds.htm. Accessed August 18, 2016.
14. Min YW, Lim KS, Min BH, Gwak GY, Paik YH, Choi MS, et al. Proton pump inhibitor use significantly increases the risk of spontaneous bacterial peritonitis in 1965 patients with cirrhosis and ascites: a propensity score matched cohort study. *Aliment Pharmacol Ther*. 2014;40(6):695–704.
15. Ratelle M, Perreault S, Villeneuve JP, Tremblay L. Association between proton pump inhibitor use and spontaneous bacterial peritonitis in cirrhotic patients with ascites. *Can J Gastroenterol Hepatol*. 2014;28:330–334.
16. Toloza EM, Wilson SE. Cholecystitis and cholangitis. In: Fry DE, ed. *Surgical Infections*. Boston: Little, Brown; 1995:254–263.
17. Sartelli M, Catena F, Di Saverio S, et al. The challenge of antimicrobial resistance in managing intra-abdominal infections. *Surg Infect (Larchmt)*. 2015;16:213–220.
18. Brook I. Microbiology and management of abdominal infections. *Dig Dis Sci*. 2008;53:2585–2591.
19. Jernberg C, Lofmark S, Edlund C, Jansson JK. Long-term impacts of antibiotic exposure on the human intestinal microbiota. *Microbiology*. 2010;156:3216–3223.
20. Riche FC, Cholley BP, Panis YH, et al. Inflammatory cytokine response in

patients with septic shock secondary to generalized peritonitis. *Crit Care Med*. 2000;28:433–437.

21. Solomkin JS, Mazuski J. Intra-abdominal sepsis: Newer interventional and antimicrobial therapies. *Infect Dis Clin North Am*. 2009;23:593–608.
22. Schietroma M, Piccione F, Carlei F, Sista F, Cecilia EM, Amicucci G. Peritonitis from perforated peptic ulcer and immune response. *J Invest Surg*. 2013;26:294–304.
23. Sartelli M, Weber DG, Ruppé E, et al. Antimicrobials: A global alliance for optimizing their rational use in intra-abdominal infections (AGORA). *World J Emerg Surg*. 2016 Jul 15;11:33. doi:10.1186/s13017-016-0089-y.
24. Herzog T, Chromic AM, Uhl W. Treatment of complicated intra-abdominal infections in the era of multidrug resistant bacteria. *Eur J Med Res*. 2010;15:525–532.
25. Thompson AE, Marshall JC, Opal SM. Intra-abdominal infections in infants and children: Descriptions and definitions. *Pediatr Crit Care Med*. 2005;6:S30–S35.
26. Rangel SJ, Rice-Townsend SE, Karki M, Moss RL. Peritonitis. In: Long SS, Prober CG, Fischer M, eds. *Principles and Practice of Pediatric Infectious Diseases*. 5th ed. Elsevier, Inc; 2018.
27. Guillet-Caruba C, Cheikhelard A, Guillet M, et al. Bacteriologic epidemiology and empirical treatment of pediatric complicated appendicitis. *Diagn Microbiol Infect Dis*. 2011;69:376–381.
28. Lee SL, Islam S, Cassidy LD, et al. Antibiotics and appendicitis in the pediatric population: An American Pediatric Surgical Association outcomes and Clinical Trials Committee systematic review. *J Pediatr Surg*. 2010;45:2181–2185.
29. Nanchal RS, Ahmad S. Infections in liver disease. *Crit Care Clin*. 2016;32(3):411–424.
30. Brook I, Frazier EH. Aerobic and anaerobic microbiology of retroperitoneal abscesses. *Clin Infect Dis*. 1998;26:9384941.
31. Bennion RS, Baron EJ, Thompson JE, et al. The bacteriology of gangrenous and perforated appendicitis—Revisited. *Ann Surg.* 1990;211:165–171.
32. Sawyer RG, Rosenlof LK, Adams RB, et al. Peritonitis into the 1990s: Changing pathogens and changing strategies in the critically ill. *Am Surg.* 1992;58:82–87.

33. Montravers P, Lepape A, Dubreuil L, et al. Clinical and microbiological profiles of community-acquired and nosocomial infections: Results of the French prospective, observational EBIIA study. *J Antimicrob Chemother*. 2009;63:785–794.
34. Onderdonk AB, Bartlett JG, Louie T, et al. Microbial synergy in experimental intra-abdominal abscess. *Infect Immun.* 1997;13:22–26.
35. Donskey CJ, Chowdhry TK, Hecker MT, et al. Effect of antibiotic therapy on the density of vancomycin-resistant enterococci in the stool of colonized patients. *Ann Surg.* 2000;343:1925–1932.
36. Sitges-Serra A, Lopez MJ, Girvent M, et al. Postoperative enterococcal infection after treatment of complicated intra-abdominal sepsis. *Br J Surg*. 2002;89:361–367.
37. Yang SK, Xiao L, Zhang H, et al. Significance of serum procalcitonin as biomarker for detection of bacterial peritonitis: A systematic review and meta-analysis. *BMC Infect Dis*. 2014;14:452.
38. Leppäniemi A, Kimball EJ, De Laet I, et al. Management of abdominal sepsis: A paradigm shift. *Anesthesiol Inten Ther*. 2015;47:400–4008.
39. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock 2016. *Crit Care Med*. 2017;43:304–377.
40. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345:1368–1377.
41. Levy MM, Evans LE, Rhodes A. The Surviving Sepsis Campaign bundle: 2018 update. *Crit Care Med*. 2018;46:997–999.
42. Brotfain E, Koyman L, Toledan R, et al. Positive fluid balances as a major predictor of clinical outcomes with sepsis/septic shock after ICU discharge. *Am J Emerg Med*. 2016;34:2122–2126.
43. Hackel MA, Badal RE, Bouchillon SK, Biedenbach DJ, Hoban DJ. Resistance rates of intra-abdominal isolates from intensive care units and non-intensive care units in the United States: The Study for Monitoring Antimicrobial Resistance Trends 2010–2012. *Surg Infect (Larchmt)*. 2015 Jun;16(3):298–304.
44. Wong PF, Gilliam AD, Kumar S, et al. Antibiotic regimens for secondary peritonitis of gastrointestinal origin in adults. *Cochrane Database Syst Rev*. 2007;2:CD004539.
45. Hoban DJ, Bouchillon SK, Hawser SP, Badal RE, Labombardi VJ,

DiPersio J. Susceptibility of gram-negative pathogens isolated from patients with complicated intra-abdominal infections in the United States, 2007–2008: Results of the Study for Monitoring Antimicrobial Resistance Trends (SMART). *Antimicrob Agents Chemother*. 2010;54:3031–3034.

46. Snydman DR, Jacobus NV, McDermott LA, et al. Lessons learned from the anaerobe survey: Historical perspective and review of the most recent data (2005–2007). *Clin Infect Dis*. 2010;50(Suppl 1):S26–S33.
47. Hawser SP, Bouchillon SK, Hoban DJ, Badal RE. In vitro susceptibilities of aerobic and facultative anaerobic Gram-negative bacilli from patients with intra-abdominal infections worldwide from 2005–2007: Results from the SMART study. *Int J Antimicrob Agents*. 2009;34:585–588.
48. Sawyer RG, Claridge JA, Nathens AB, et al. Trial of short-course antimicrobial therapy for intra-abdominal infection. *N Engl J Med*. 2015;372:1996–2005.
49. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: Guidelines by the Surgical Infection Society and the Infectious Diseases society of America. *Clin Inf Dis*. 2010;50:133–164.
50. Gauzit R, Pean Y, Mistretta F, Lalaude O. Epidemiology, management, and prognosis of secondary non-postoperative peritonitis: A French prospective observational multicenter study. *Surg Infect*. 2009;10:119–127.
51. Huang LL, Van Schooneveld TC, Huang RD, et al. Guideline-concordant versus discordant antimicrobial therapy in patients with community-onset complicated intra-abdominal infections. *Infect Control and Hosp Epidemiol*. 2016; 37:855–8.
52. Knitsch W, Vincent J-L, Utzolino S, et al. A randomized, placebo-controlled trial of preemptive antifungal therapy for the prevention of invasive candidiasis following gastrointestinal surgery for intra-abdominal infections. *Clin Infect Dis*. 2015;61:1671–1678.
53. Pappas PG, Kauffman CA, Andes DR et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Inf Dis*. 2016;62(4): e1–e50.
54. Hooker KD, DiPiro JT, Wynn JJ. Aminoglycoside combinations versus single β-lactams for penetrating abdominal trauma: A meta-analysis. *J Trauma*. 1991;31:1155–1160.
55. Solomkin JS, Dellinger EP, Christou NV, et al. Results of a multicenter

trial comparing imipenem/cilastatin to tobramycin/clindamycin for intra-abdominal infections. *Ann Surg*. 1990;212:581–591.

56. Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R. Experience with a once-daily aminoglycoside program administered to 2184 adult patients. *Antimicrob Agents Chemother*. 1995;39:650–655.
57. Rybak MJ, Abate BJ, Kang SL, Ruffing MJ, Lerner SA, Drusano GL. Prospective evaluation of the effect of an aminoglycoside dosing regimen on rates of observed nephrotoxicity and ototoxicity. *Antimicrob Agents Chemother*. 1999;43:1549–1555.
58. Olsen KM, Rudis MA, Rebuck JA, Gelmont D, Mehdian R, Nelson C, Rupp ME. Effect of single daily dose vs. multiple daily dosing of tobramycin on alanine aminopeptidase and N-acetyl-β-d-glucosaminidase excretion. *Crit Care Med*. 2004;32:1678–1682.
59. Boucher HW, Talbot GH, Bradley JS, et al. Bad bugs, no drugs: No ESKAPE! An update from the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48:1–12.
60. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States; 2013. Available at: http://www.cdc.gov/drugresistance/threat-report-2013/. Accessed Accessed April 4, 2018.
61. World Health Organization. Antimicrobial resistance: Global report on surveillance. Geneva: Switzerland; 2014. Available at: http://www.who.int/drugresistance/documents/surveillancereport/en/. Accessed April 4, 2018.
62. Tasina E, Haidich AB, Kokkali S, Arvanitidou M. Efficacy and safety of tigecycline for the treatment of infectious diseases: A meta-analysis. *Lancet Infect Dis*. 2011 Nov;11(11):834–844.
63. Prasad P, Sun J, Danner R, Natanson C. Excess deaths associated with tigecycline after approval based on non-inferiority trials. *Clin Infect Dis*. 2012;54:1699–1709.
64. US Food and Drug Administration. FDA Drug Safety Communication: Increased risk of death with Tygacil (tigecycline) and approved new Boxed Warning. US Food and Drug Administration; September 27, 2013. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm369580.htm. Accessed April 4, 2018.
65. Ceftazidime/avibactam Package Insert. Cincinnati, OH: Forest

Pharmaceuticals; September 2015.
66. Ceftolozane/tazobactam Package Insert. Lexington, MA: Cubist; May 2015.
67. van Duin D, Lok JJ, Easley M, et al. Colistin versus ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant Enterobacteriaceae. *Clin Infect Dis*. 2018;66:163–171.
68. Runyon BA. Management of adult patients with ascites due to cirrhosis: Update 2012. Available at: http://www.aasld.org/publications/practice-guidelines-0. Accessed April 4, 2018.
69. Deshpande LM, Fritsche TR, Moet GJ, Biedenbach DJ, Jones RN. Antimicrobial resistance and molecular epidemiology of vancomycin-resistant enterococci from North America and Europe: A report from the SENTRY antimicrobial surveillance program. *Diagn Microbiol Infect Dis*. 2007;58:163–170.
70. Ballinger AE, Palmer SC, Wiggins KJ, et al. Treatment for peritoneal dialysis-associated peritonitis. *Cochrane Database Syst Rev*. 2014;(4): CD005284.
71. Li PK, Szeto CC, Piraino B, et al. ISPD peritonitis recommendations: 2016 update on prevention and treatment. *Perit Dial Int*. 2016 Sep;36(5):481–508.
72. Flanigan MJ, Lim VS. Initial treatment of dialysis associated peritonitis: A controlled trial of vancomycin versus cefazolin. *Perit Dial Int*. 1991;11:31–37.
73. Fish R, Nipah R, Jones C, Finney H, Fan SL. Intraperitoneal vancomycin concentrations during peritoneal dialysis-associated peritonitis: Correlation with serum levels. *Perit Dial Int*. 2012;32:332–8.
74. Bozorgzadeh A, Pizzi WF, Barie PS, et al. The duration of antibiotic administration in penetrating abdominal trauma. *Am J Surg*. 1999;172:125–135.
75. van Rossem CC, Schreinemacher MH, van Geloven AA, et al. Antibiotic duration after laparoscopic appendectomy for acute complicated appendicitis. *JAMA Surg*. 2016;151(4):323–9.
76. Salminen P, Paajanen H, Rautio T, et al. Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: The APPAC randomized clinical trial. *JAMA*. 2015;313(23):2340–8.
77. Sallinen V, Ak EA, You JJ, et al. Meta-analysis of antibiotics versus appendicectomy for non-perforated acute appendicitis. *Br J Surg*.

2016;103(6):656–667.

78. Schein M, Gecelter G, Freinkel W, et al. Peritoneal lavage in abdominal sepsis: A controlled clinical study. *Arch Surg*. 1990;125:1132–1135.
79. Norman G, Atkinson RA, Smith TA, et al. Intracavity lavage and wound irrigation for prevention of surgical site infection. *Cochrane Database Syst Rev*. 2017 Oct 30;10:CD012234. doi:10.1002/14651858.CD012234.pub2.
80. Baquero F, Hsueh P, Paterson DL, et al. In vitro susceptibilities of aerobic and facultatively anaerobic gram-negative bacilli isolated from patients with intra-abdominal infections worldwide: 2005 results from study for monitoring antimicrobial resistance trends. *Surg Infect*. 2009;10:99–104.
81. Merlino JI, Yowler CJ, Malangoni MA. Nosocomial infections adversely affect the outcomes of patients with serious intra-abdominal infections. *Surg Infect (Larchmt)*. 2004;5:21–27.
82. Christou NV, Barie PS, Dellinger EP, et al. Surgical infection society intra-abdominal infection study. *Arch Surg*. 1993;128:193–199.
83. Paladino JA, Gilliland-Johnson KK, Adelman MH, Coohn SM. Pharmacoeconomics of ciprofloxacin plus metronidazole vs. piperacillin–tazobactam for complicated intra-abdominal infections. *Surg Infect*. 2008;9:325.

Parasitic Diseases

Jason M. Cota

KEY CONCEPTS

1. Single-dose tinidazole is the preferred 5-nitroimidazole for giardiasis treatment.
2. HIV-infected patients with cryptosporidiosis must receive antiretroviral therapy as the mainstay of therapy in addition to antiparasitic therapy.
3. *Entamoeba histolytica*-specific immunoassays are required to diagnose amebiasis because stool sample microscopy does not distinguish between *E. histolytica* and the nonpathogenic *E. dispar*.
4. Metronidazole and tinidazole are tissue-acting agents against *Entamoeba*; whereas, paromomycin and iodoquinol are luminal amebicides.
5. Benznidazole is the only FDA-approved treatment for Chagas disease.
6. Chemoprophylaxis with non-chloroquine antimalarial drugs such as atovaquone-proguanil and doxycycline retain effectiveness in areas where chloroquine-resistant *P. falciparum* exposure is likely.
7. Patients with noncalcified parenchymal neurocysticercosis should initially receive symptomatic therapy with corticosteroids and antiepileptic drugs followed by antihelminthic therapy.
8. For head lice, either nonprescription 1% permethrin or pyrethrins plus piperonyl butoxide topical preparations are agents of choice unless local resistance to these agents is documented.
9. A single application of 5% permethrin results in cure rates in more than 90% of subjects with scabies at 14 and 28 days, but a second dose should be applied 1 week later because its ovicidal efficacy remains unclear.

Preclass Engaged Learning Activity

Review the figures depicting the life cycle of each of the following parasites on the CDC Website. Identify the primary way in which each parasite enters the human host and propose at least one strategy to prevent infection from that parasite. The parasites below are listed in order of least to most complex life cycle.

Head Lice (https://www.cdc.gov/parasites/lice/head/biology.html)
Giardiasis (https://www.cdc.gov/parasites/giardia/pathogen.html)
Cryptosporidiosis (https://www.cdc.gov/parasites/crypto/pathogen.html)
Cysticercosis (https://www.cdc.gov/parasites/cysticercosis/biology.html)
Chagas Disease (https://www.cdc.gov/parasites/chagas/biology.html)
Malaria (https://www.cdc.gov/dpdx/malaria/)

This activity is intended to help learners propose risk factors for parasitic infections and nonpharmacologic measures that can be implemented to prevent disease transmission.

INTRODUCTION

Parasitic diseases remain a significant global health problem causing approximately one million deaths per year and affecting more than 1.7 billion people worldwide.[1–4] In the United States, immunocompromised patients, ethnic/racial minorities, immigrants, those with recent travel to developing regions, individuals living in poor sanitary conditions, and people who lack access to basic healthcare services appear to be at highest risk for developing parasitic disease.[5,6] However, people in every income and social strata can become infected. In fact, the Centers for Disease Control and Prevention (CDC) has referred to five diseases as neglected parasitic infections and has prioritized these for increased public health action.[6] They include Chagas disease, cysticercosis, toxocariasis, toxoplasmosis, and trichomoniasis.

Host-Parasite Relationship

General prevention and treatment principles of parasitic infections are based on the host-parasite relationship. *Symbiosis* describes an essential biological relationship between two species. *Parasitism* is a symbiotic relationship in which one species (the host) is injured through the activities of the other (the

parasite). The life cycle of a parasite may occur solely in human hosts or in one or more hosts before it causes human disease. *Definitive hosts* are those in which parasites undergo sexual reproduction; whereas *intermediate hosts* allow larval or asexual stages of development to occur. Determining what part of a parasite's life cycle occurs in human hosts is important for antiparasitic drug development.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

134

Urinary Tract Infections and Prostatitis

Julianna M. Fernandez and Elizabeth A. Coyle

KEY CONCEPTS

1. Urinary tract infections (UTIs) can be classified as uncomplicated and complicated. *Uncomplicated* refers to an infection in an otherwise healthy, premenopausal female who lacks structural or functional abnormalities of the urinary tract. Most often complicated infections are associated with a predisposing lesion of the urinary tract; however, the term may be used to refer to all other infections, except for those in the otherwise healthy, premenopausal adult female.
2. Recurrent UTIs are considered either reinfections or relapses. Reinfection usually happens more than 2 weeks after the last UTI and is treated as a new uncomplicated UTI. Relapse usually happens within 2 weeks of the original infection, and is a relapse of the original infection either because of unsuccessful treatment of the original infection, a resistant organism, or anatomical abnormalities.
3. Majority (75%-90%) of uncomplicated UTIs are caused by Escherichia coli and the remainder are caused primarily by Staphylococcus saprophyticus, Proteus spp., and Klebsiella spp. Complicated infections may be associated with other gram-negative organisms and Enterococcus faecalis.
4. Symptoms of lower UTIs include dysuria, urgency, frequency, nocturia, and suprapubic heaviness, whereas upper UTIs involve more systemic symptoms such as fever, nausea, vomiting, and flank pain.
5. Significant bacteriuria has been defined as bacterial counts of greater than 10^5 organisms (colony-forming unit [CFU])/mL (10^8 CFU/L) of a midstream clean catch urine. However, this is too general and significant bacteriuria in patients with symptoms of a UTI may be defined as greater

than 10^2 organisms (CFU)/mL (10^5 CFU/L).

6. The goals of treatment of UTIs are to eradicate the invading organism(s), prevent or treat systemic consequences of infections, prevent the recurrence of infection, and prevent antimicrobial resistance.
7. Uncomplicated UTIs can be managed most effectively with short-course therapy (3 days) with either trimethoprim–sulfamethoxazole, one dose of fosfomycin, or 5 days of nitrofurantoin. Fluoroquinolones should be reserved for suspected pyelonephritis or complicated infections.
8. When choosing appropriate antibiotic therapy, practitioners need to be cognizant of antibiotic resistance patterns, particularly to E. coli. Trimethoprim–sulfamethoxazole has diminished activity against *E. coli* in some areas of the country, with reported resistance in some areas greater than 20%.
9. Acute bacterial prostatitis can be managed with many agents that have activity against the causative organism. Chronic prostatitis requires prolonged therapy with an agent that penetrates the prostatic tissue and secretions. Therapy with fluoroquinolone or trimethoprim–sulfamethoxazole is preferred for up to 6 weeks.

Preclass Engaged Learning Activity

Refer to the Infectious Diseases Society of America treatment guideline for acute, uncomplicated cystitis and pyelonephritis in female patients. Create a drug table that summarizes treatment options for the top five most common bacterial causes of urinary tract infections. Compare and contrast the drug choices, drug dosing, and duration of therapy for patient suffering from acute cystitis versus pyelonephritis.

INTRODUCTION

Infections of the urinary tract represent a wide variety of syndromes, including urethritis, cystitis, prostatitis, and pyelonephritis. Urinary tract infections (UTIs) are the most commonly occurring bacterial infections and one of the most common reasons for antibiotic exposure, especially in females of childbearing age.[1–3] Approximately 60% of females will develop a UTI during their lifetime

with about one-fourth having a recurrence within a year.[2] Infections in men occur much less frequently until the age of 65 years at which point the incidence rates in men and women are similar.

A UTI is defined as the presence of microorganisms in the urinary tract that cannot be accounted for by contamination. The organisms present have the potential to invade the tissues of the urinary tract and adjacent structures. Infection may be limited to the growth of bacteria in the urine, which frequently may not produce symptoms. A UTI can present as several syndromes associated with an inflammatory response to microbial invasion and can range from asymptomatic bacteriuria (ASB) to pyelonephritis with bacteremia or sepsis.

UTIs are classified by lower and upper UTIs. Typically, they have been described by anatomic site of involvement. Lower tract infections correspond to cystitis (bladder), and pyelonephritis (an infection involving the kidneys) represents upper tract infection.

1 Also, UTIs are designated as uncomplicated or complicated. Uncomplicated infections occur in individuals who lack structural or functional abnormalities of the urinary tract that interfere with the normal flow of urine or voiding mechanism. These infections occur in premenopausal females of childbearing age (15-45 years) who are otherwise normal, healthy individuals. Infections in males generally are not classified as uncomplicated because these infections are rare and most often represent a structural or neurologic abnormality.

Complicated UTIs are usually the result of a predisposing lesion of the urinary tract, such as a congenital abnormality or distortion of the urinary tract, a stone, indwelling catheter, prostatic hypertrophy, obstruction, or neurologic deficit that interferes with the normal flow of urine and urinary tract defenses. Complicated infections occur in both genders and frequently involve the upper and lower urinary tract.

2 Recurrent UTIs in healthy nonpregnant women—two or more UTIs occurring within 6 months or three or more UTIs within 1 year—are a common problem. They are characterized by multiple symptomatic infections with asymptomatic periods occurring between each episode and may be either reinfections or relapses. Reinfections are caused by a different organism than originally isolated and account for the majority of recurrent UTIs. Relapses are the development of repeated infections with the same initial organism and usually indicate a persistent infectious source.[2]

Asymptomatic bacteriuria is a common finding, particularly among those 65 years of age and older when there is significant bacteriuria (more than 10^5

bacteria/mL [10^8/L] of urine) in the absence of symptoms. Symptomatic abacteriuria or acute urethral syndrome consists of symptoms of frequency and dysuria in the absence of significant bacteriuria. This syndrome is commonly associated with *Chlamydia* infections.

Significant abacteriuria is a term used to distinguish the presence of microorganisms that represent true infection versus contamination of the urine as it passes through the distal urethra prior to collection. Historically, bacterial counts equal to or greater than 100,000 organisms/mL (10^8/L) of urine in a "clean-catch" specimen were judged to indicate true infection.[4–6] Counts less than 100,000 organisms/mL (10^8/L) of urine, however, may represent true infection in certain situations. For example, with concurrent antibacterial drug administration, rapid urine flow, low urinary pH, or upper tract obstruction.[6] **Table 134-1** lists the clinical definitions of significant bacteriuria, which are dependent on the clinical setting and the method of specimen collection.[6] These criteria allow for more appropriate specificity and sensitivity in documenting infection under differing clinical circumstances.

TABLE 134-1 Diagnostic Criteria for Significant Bacteriuria

≥10^2 CFU coliforms/mL (10^5 CFU/L) or ≥10^5 CFU noncoliforms/mL (10^8 CFU/L) in a symptomatic female
≥10^4 CFU bacteria/mL (10^7 CFU/L) in a symptomatic male
≥10^5 CFU bacteria/mL (10^8 CFU/L) in asymptomatic individuals on two consecutive specimens
Any growth of bacteria on suprapubic catheterization in a symptomatic patient
≥10^{2-5} CFU bacteria/mL (10^{5-8} CFU/L) in a catheterized patient

CFU, colony-forming unit.

EPIDEMIOLOGY

The prevalence of UTIs varies with age and gender. In newborns and infants up to 6 months of age, the prevalence of abacteriuria is approximately 1% and is more common in boys. Most of these infections are associated with structural or functional abnormalities of the urinary tract and also have been correlated with noncircumcision.[7] Between the ages of 1 and 6 years, UTIs occur more frequently in females. The prevalence of abacteriuria in females and males of this age group is 3% to 7% and 1% to 2%, respectively.[7,8] Infections occurring in preschool boys usually are associated with congenital abnormalities of the urinary tract. These infections are difficult to recognize because of the age of the

patient, but they often are symptomatic. In addition, the majority of renal damage associated with UTI develops at this age.[7,8]

Through grade school and before puberty, the prevalence of UTI is approximately 1%, with 5% of females reported to have significant bacteriuria prior to leaving high school. This percentage increases dramatically to 1% to 4% after puberty in nonpregnant females primarily as a result of sexual activity. Approximately one in five women will suffer a symptomatic UTI at some point in their lives. Many women have recurrent infections with a significant proportion of these women having a history of childhood infections. In contrast, the prevalence of bacteriuria in adult men is very low (less than 0.1%).[9]

In the elderly, the ratio of bacteriuria in women and men is dramatically altered and is approximately equal in persons older than 65 years.[10] The overall incidence of UTI increases substantially in this population with the majority of infections being asymptomatic. The rate of infection increases further for elderly persons who are residing in nursing homes, particularly those who are hospitalized frequently. The increase is probably the result of factors such as obstruction from prostatic hypertrophy in males, poor bladder emptying as a result of prolapse in females, fecal incontinence in demented patients, and neuromuscular disease including strokes and increased urinary instrumentation (catheterization).

ETIOLOGY

3 The bacteria causing UTIs usually originate from bowel flora of the host. Although virtually every organism is associated with UTIs, certain organisms predominate as a result of specific virulence factors. The most common cause of uncomplicated UTIs is *Escherichia coli*, which accounts for 80% to 90% of community-acquired infections. Additional causative organisms in uncomplicated infections include *Staphylococcus saprophyticus*, *Klebsiella pneumoniae*, *Proteus* spp., *Pseudomonas aeruginosa*, and *Enterococcus* spp.[11] Because *S. epidermidis* is frequently isolated from the urinary tract, it should be considered initially a contaminant. Repeat cultures should be performed to help confirm the organism as a real pathogen.

Organisms isolated from individuals with complicated infections are more varied and generally are more resistant than those found in uncomplicated infections. *E. coli* is a frequently isolated pathogen, but it accounts for less than 50% of infections. Other frequently isolated organisms include *Proteus* spp., *K. pneumoniae*, *Enterobacter* spp., *P. aeruginosa*, staphylococci, and enterococci.

Enterococci represent the second most frequently isolated organisms in hospitalized patients.[11–13] In part, this finding may be related to the extensive use of third-generation cephalosporin antibiotics, which are not active against the enterococci. Vancomycin-resistant *E. faecalis* and *E. faecium* (vancomycin-resistant enterococci) have become more widespread, especially in patients with long-term hospitalizations or underlying malignancies. Vancomycin-resistant enterococci are major therapeutic and infection control issues because these organisms are susceptible to few antimicrobials.[12,13] *S. aureus* infections may arise from the urinary tract, but they are more commonly a result of bacteremia producing metastatic abscesses in the kidney. *Candida* spp. are common causes of UTI in the critically ill and chronically catheterized patient. Most UTIs are caused by a single organism; however, in patients with stones, indwelling urinary catheters, or chronic renal abscesses, multiple organisms may be isolated. Depending on the clinical situation, the recovery of multiple organisms may represent contamination and a repeat evaluation should be done.

PATHOPHYSIOLOGY

Route of Infection

Organisms typically gain entry into the urinary tract via three routes: the ascending, hematogenous (descending), and lymphatic pathways. The female urethra usually is colonized by bacteria believed to originate from the fecal flora. The short length of the female urethra and its proximity to the perirectal area make colonization of the urethra likely. Other factors that promote urethral colonization include the use of spermicides and diaphragms as methods of contraception.[2,3] Although there is evidence in females that bladder infections follow colonization of the urethra, the mode of ascent of the microorganisms is incompletely understood. Massage of the female urethra and sexual intercourse allow bacteria to reach the bladder.[14] Once bacteria have reached the bladder, the organisms quickly multiply and can ascend the ureters to the kidneys. This sequence of events is more likely to occur if vesicoureteral reflux (reflux of urine into the ureters and kidneys while voiding) is present. UTIs are more common in females than in males because the anatomic differences in location and length of the urethra tend to support the ascending route of infections as the primary acquisition route.

Infection of the kidney by hematogenous spread of microorganisms usually occurs as the result of dissemination of organisms from a distant primary

infection in the body. Infections via the descending route are uncommon and involve a relatively small number of invasive pathogens. Bacteremia caused by *S. aureus* may produce renal abscesses. Additional organisms include *Candida* spp., *Mycobacterium tuberculosis*, *Salmonella* spp., and enterococci. Of particular interest, it is difficult to produce experimental pyelonephritis by IV administration of common gram-negative organisms such as *E. coli* and *P. aeruginosa*. Overall, less than 5% of documented UTIs result from hematogenous spread of microorganisms.

There appears to be little evidence supporting a significant role for renal lymphatics in the pathogenesis of UTIs. There are lymphatic communications between the bowel and kidney, as well as between the bladder and kidney. There is no evidence, however, that microorganisms are transferred to the kidney via this route. After bacteria reach the urinary tract, three factors determine the development of infection: the size of the inoculum, the virulence of the microorganism, and the competency of the natural host defense mechanisms. Most UTIs reflect a failure in host defense mechanisms.

Host Defense Mechanisms

The normal urinary tract generally is resistant to invasion by bacteria and is efficient in rapidly eliminating microorganisms that reach the bladder. The urine under normal circumstances is capable of inhibiting and killing microorganisms. The factors thought to be responsible include a low pH, extremes in osmolality, high urea concentration, and high organic acid concentration. Bacterial growth is further inhibited in males by the addition of prostatic secretions.[14,15]

The introduction of bacteria into the bladder stimulates micturition with increased diuresis and efficient emptying of the bladder. These factors are critical in preventing the initiation and maintenance of bladder infections. Patients who are unable to void urine completely are at greater risk of developing UTIs and frequently have recurrent infections. Also, patients with even small residual amounts of urine in their bladder respond less favorably to treatment than patients who are able to empty their bladders completely.[16]

An important virulence factor of bacteria is their ability to adhere to urinary epithelial cells resulting in colonization of the urinary tract, bladder infections, and pyelonephritis. Various factors that act as anti-adherence mechanisms are present in the bladder preventing bacterial colonization and infection. The epithelial cells of the bladder are coated with a urinary mucus or slime called *glycosaminoglycan*. This thin layer of surface mucopolysaccharide is

hydrophilic and strongly negatively charged. When bound to the uroepithelium, it attracts water molecules and forms a layer between the bladder and urine. The anti-adherence characteristics of the glycosaminoglycan layer are nonspecific and when the layer is removed by dilute acid solutions, rapid bacterial adherence results.[17]

In addition, the Tamm–Horsfall protein is a glycoprotein produced by the ascending limb of Henle and distal tubule that is secreted into the urine and contains mannose residues. These mannose residues bind *E. coli* that contain small surface-projecting organelle on their surfaces called *pili* or *fimbriae*. Type 1 fimbriae are mannose-sensitive and this interaction prevents the bacteria from binding to similar receptors present on the mucosal surface of the bladder. Other factors that possibly prevent adherence of bacteria include immunoglobulins (Ig) G and A. Investigators have documented both systemic and local kidney Ig synthesis in upper tract infections. The role of Igs in preventing bladder infection is less clear. Patients with reduced urinary levels of secretory IgA are, however, at increased risk of infections of the urinary tract.

After bacteria have invaded the bladder mucosa, an inflammatory response is stimulated with the mobilization of polymorphonuclear leukocytes (PMNs) and resulting phagocytosis. PMNs are primarily responsible for limiting the tissue invasion and controlling the spread of infection in the bladder and kidney. They do not play a role in preventing bladder colonization or infections and actually contribute to renal tissue damage.

Other host factors that may play a role in the prevention of UTIs are the presence of *Lactobacillus* in the vaginal flora and circulating estrogen levels. In premenopausal women, circulating estrogen supports the vaginal tract growth of lactobacilli, which produce lactic acid to help maintain a low vaginal pH, thereby preventing *E. coli* vaginal colonization.[18] Topical estrogens are used for the prevention of UTI in postmenopausal women who have more than three recurrent UTI episodes per year and are not on oral estrogens.[19]

Bacterial Virulence Factors

Pathogenic organisms have differing degrees of pathogenicity (virulence), which play a role in the development and severity of infection. Bacteria that adhere to the epithelium of the urinary tract are associated with colonization and infection. The mechanism of adhesion of gram-negative bacteria, particularly *E. coli*, is related to bacterial fimbriae that are rigid, hair-like appendages of the cell wall.[9] These fimbriae adhere to specific glycolipid components on epithelial cells. The

most common type of fimbriae is type 1, which binds to mannose residues present in glycoproteins. Glycosaminoglycan and Tamm–Horsfall protein are rich in mannose residues that readily trap those organisms that contain type 1 fimbriae, which are then washed out of the bladder.[20] Other fimbriae are mannose resistant and are associated more frequently with pyelonephritis, such as P fimbriae, which bind avidly to specific glycolipid receptors on uroepithelial cells. These bacteria are resistant to washout or removal by glycosaminoglycan and are able to multiply and invade tissue, especially the kidney. In addition, PMNs, as well as secretory IgA antibodies, contain receptors for type 1 fimbriae, which facilitate phagocytosis, but are lacking receptors for P fimbriae.

Other virulence factors include the production of hemolysin and aerobactin.[21] Hemolysin is a cytotoxic protein produced by bacteria that lyses a wide range of cells, including erythrocytes, PMNs, and monocytes. *E. coli* and other gram-negative bacteria require iron for aerobic metabolism and multiplication. Aerobactin facilitates the binding and uptake of iron by *E. coli*; however, the significance of this property in the pathogenesis of UTIs remains unknown.[22]

PREDISPOSING FACTORS TO INFECTION

The normal urinary tract typically is resistant to infection and colonization by pathogenic bacteria. In patients with underlying structural abnormalities of the urinary tract, the typical host defenses previously discussed usually are lacking or compromised. There are several known abnormalities of the urinary tract system that interfere with its natural defense mechanisms, the most important of which is obstruction. Obstruction can inhibit the normal flow of urine disrupting the natural flushing and voiding effect in removing bacteria from the bladder and resulting in incomplete emptying. Common conditions that result in residual urine volumes include prostatic hypertrophy, urethral strictures, calculi, tumors, bladder diverticula, and drugs such as anticholinergic agents. Additional causes of incomplete bladder emptying include neurologic malfunctions associated with stroke, diabetes, spinal cord injuries, tabes dorsalis, and other neuropathies. Vesicoureteral reflux represents a condition in which urine is forced up the ureters to the kidneys. Urinary reflux is associated not only with an increased incidence of UTIs and pyelonephritis, but also with renal damage.[8,16] Reflux may be the result of a congenital abnormality or, more commonly, bladder overdistension from obstruction. Other risk factors include urinary catheterization, mechanical instrumentation, pregnancy, and the use of spermicides and diaphragms.

CLINICAL PRESENTATION

4 The presenting signs and symptoms of UTIs in adults are recognized easily. Women frequently will report gross hematuria. Systemic symptoms, including fever, typically are absent in this setting. Unfortunately, large numbers of patients with significant bacteriuria are asymptomatic. These patients may be normal, healthy patients, elderly patients, children, pregnant patients, and patients with indwelling catheters. It is important to note that attempts at differentiating upper tract from lower tract infections on the basis of symptoms alone are not reliable.

Elderly patients frequently do not experience specific urinary symptoms, but they will present with altered mental status, change in eating habits, or gastrointestinal (GI) symptoms. In addition, patients with indwelling catheters or neurologic disorders commonly will not have lower tract symptoms. Instead, they may present with flank pain and fever. Many of the aforementioned patients, however, frequently will develop upper tract infections with bacteremia and no or minimal urinary tract symptoms.

Symptoms alone are unreliable for the diagnosis of bacterial UTIs. The key to the diagnosis of UTI is the ability to demonstrate significant numbers of microorganisms in an appropriate urine specimen to distinguish contamination from infection. The type and extent of laboratory examination required depends on the clinical situation.

Urine Collection

Examination of the urine is the cornerstone of laboratory evaluation for UTIs. There are three acceptable methods of urine collection. The first is the *midstream clean-catch method*. After cleaning the urethral opening area in both men and women, 20 to 30 mL of urine is voided and discarded. The next part of the urine flow is collected and should be processed immediately (refrigerated as soon as possible). Specimens that are allowed to sit at room temperature for several hours may result in falsely elevated bacterial counts. The midstream clean-catch is the preferred method for the routine collection of urine for culture. When a routine urine specimen cannot be collected or contamination occurs, alternative collection techniques must be used.

The two acceptable alternative methods include catheterization and suprapubic bladder aspiration. Catheterization may be necessary for patients who are uncooperative or who are unable to void urine. If catheterization is

performed carefully with aseptic technique, the method yields reliable results. Note, however, that introduction of bacteria into the bladder may result and the procedure is associated with infection in 1% to 2% of patients. Suprapubic bladder aspiration involves inserting a needle directly into the bladder and aspirating the urine. This procedure bypasses the contaminating organisms present in the urethra and any bacteria found using this technique generally are considered to represent significant bacteriuria.[23–26] Suprapubic aspiration is a safe and painless procedure that is most useful in newborns, infants, paraplegics, seriously ill patients, and others in whom infection is suspected and routine procedures have provided confusing or equivocal results.

Bacterial Count

5 The diagnosis of UTI is based on the isolation of significant numbers of bacteria from a urine specimen. Microscopic examination of a urine sample is an easy-to-perform and reliable method for the presumptive diagnosis of bacteriuria. The examination may be performed by preparing a Gram stain of unspun or centrifuged urine. The presence of at least one organism per oil-immersion field in a properly collected uncentrifuged specimen correlates well with more than 100,000 CFU/mL (10^5 CFU/mL or 10^8 CFU/L) of urine. For detecting smaller numbers of organisms, a centrifuged specimen is more sensitive. Such examinations detect more than 10^5 bacteria (CFU)/mL (10^8 CFU/L) with a sensitivity of greater than 90% and a specificity of greater than 70%.[23,24] A quantitative count of greater than or equal to 10^5 CFU/mL (10^8 CFU/L) is considered indicative of a UTI; however, up to 50% of women will present with clinical symptoms of a UTI with lower counts (10^3 CFU/mL) [10^6 CFU/L].[4]

CLINICAL PRESENTATION Urinary Tract Infections in Adults

Signs and Symptoms

- Lower UTI: Dysuria, urgency, frequency, nocturia, and suprapubic heaviness
- Gross hematuria

- Upper UTI: Flank pain, fever, nausea, vomiting, and malaise

Physical Examination

- Upper UTI: Costovertebral tenderness

Laboratory Tests

- Bacteriuria
- Pyuria (WBC count more than 10/mm^3 [10 × 10^6/L])
- Nitrite-positive urine (with nitrite reducers)
- Leukocyte esterase-positive urine
- Antibody-coated bacteria (upper UTI)

Pyuria, Hematuria, and Proteinuria

Microscopic examination of the urine for leukocytes is used to determine the presence of pyuria. The presence of pyuria in a symptomatic patient correlates with significant bacteriuria.[25] Pyuria is defined as a white blood cell (WBC) count of greater than 10 WBC/mm^3 (10 × 10^6/L) of urine. A count of 5 to 10 WBC/mm^3 (5 × 10^6 to 10 × 10^6/L) is accepted as the upper limit of normal. It should be emphasized that pyuria is nonspecific and signifies only the presence of inflammation and not necessarily infection. Thus patients with pyuria may or may not have infection. Sterile pyuria has long been associated with urinary tuberculosis, as well as chlamydial and fungal urinary infections. Hematuria, microscopic or gross, is frequently present in patients with UTI, but is nonspecific. Hematuria may indicate the presence of other disorders, such as renal calculi, tumors, or glomerulonephritis. Proteinuria is found commonly in the presence of infection.

Chemistry

Several biochemical tests have been developed for screening urine for the presence of bacteria. A common dipstick test detects the presence of nitrite in the urine, which is formed by bacteria that reduce nitrate normally present in the urine. False-positive tests are uncommon. False-negative tests are more common and are frequently caused by the presence of gram-positive organisms or *P.*

aeruginosa that do not reduce nitrate.[26] Other causes of false tests include low urinary pH, frequent voiding, and dilute urine.

The leukocyte esterase dipstick test is a rapid screening test for detecting the presence of pyuria. Leukocytes esterase is found in primary neutrophil granules and indicates the presence of WBCs. The leukocyte esterase test is a sensitive and highly specific test for detecting more than 10 WBC/mm^3 (10×10^6/L) of urine. When the leukocyte esterase test is used with the nitrite test, the reported positive predictive value and specificity is 79% and 82%, respectively, for the detection of bacteriuria.[27,28] These tests can be useful in the outpatient evaluation of uncomplicated UTIs. However, urine culture is still the "gold standard" test in determining the presence of UTIs.

Culture

The most reliable method of diagnosing UTI is by quantitative urine culture. Urine in the bladder is normally sterile making it possible to differentiate contamination of the urine from infection by quantifying the number of bacteria present in a urine sample. This criterion is based on a properly collected midstream clean-catch urine specimen. Patients with infection usually have greater than 10**5** bacteria/mL (10^8/L) of urine. However, as many as one-third of women with symptomatic infection have less than 10^5 bacteria/mL (10^8/L). Also, a significant portion of patients with UTIs, either symptomatic or asymptomatic, have less than 10^5 bacteria/mL (10^8/L) of urine.

Several laboratory methods are used to quantify bacteria present in the urine. The most accurate method is the pour-plate technique. This method is unsuitable for a high-volume laboratory because it is expensive and time-consuming. The streak-plate method is an alternative that involves using a calibrated-loop technique to streak a fixed amount of urine on an agar plate. This method is used most commonly in diagnostic laboratories because it is simple to perform and less costly.

After identification and quantification are complete, the next step is to determine the susceptibility of the organism. There are several methods by which bacterial susceptibility testing may be performed. Knowledge of bacterial susceptibility and achievable urine concentration of the antibiotics puts the clinician in a better position to select an appropriate agent for treatment.

Infection Site

History and physical examination are of little value in predicting the site of infection. The most direct method to determine the location of infection within the urinary system and differentiate upper tract from lower tract involvement is a ureteral catheterization procedure as described by Stamey and colleagues.[29] The method involves the passage of a catheter into the bladder and then into each ureter, where quantitative cultures are obtained. Although this method provides direct quantitative evidence for UTI, it is invasive, technically difficult, and expensive. The Fairley bladder washout technique is a modification of the Stamey procedure that involves Foley catheterization only.[30] After the catheter is passed into the bladder, bladder samples are obtained and the bladder is washed out with culture samples taken at 10, 20, and 30 minutes. The procedure shows that up to 50% of patients have renal involvement, regardless of signs and symptoms. Other investigators found 10% to 20% of tests to be equivocal.[30]

Noninvasive methods of localization may be more acceptable for routine use; however, they have limited clinical value. Patients with pyelonephritis can have abnormalities in urinary concentrating ability. The use of concentrating ability for localization of UTIs, however, is associated with high false-positive and false-negative responses and is not useful clinically.[26] The antibody-coated bacteria test is an immunofluorescent method that detects bacteria coated with Ig in freshly voided urine indicating upper UTI. The sensitivity and specificity of this test to localize the site of infection are reported to average 88% and 76%, respectively.[31] Because of the high incidence of false-positive and false-negative results, antibody-coated bacteria testing is not used routinely in the management of UTIs.

Virtually all patients with uncomplicated lower tract infections can be cured with a short course of antibiotic therapy and this assumption sometimes can be used to distinguish between patients with lower and upper tract infections. Patients who do not respond or who relapse may do so because of upper tract involvement. It is rarely necessary to localize the site of infection to direct the clinical management of such patients.

TREATMENT

Desired Outcomes

6 The goals of UTI treatments are (a) to eradicate the invading organism(s), (b) to prevent or to treat systemic consequences of infection, (c) to prevent the recurrence of infection, and (d) to decrease the potential for collateral

> damage with too broad of antimicrobial therapy.

Management

The management of a patient with a UTI includes initial evaluation, selection of an antibacterial agent, and duration of therapy and follow-up evaluation. The initial selection of an antimicrobial agent for the treatment of UTI is based primarily on the severity of the presenting signs and symptoms, the site of infection and whether the infection is determined to be uncomplicated or complicated. Other considerations include antibiotic susceptibility, side-effect potential, cost, current antimicrobial exposure, and the comparative inconvenience of different therapies.[1]

Various pharmacologic factors may affect the action of antibacterial agents. Certainly, the ability of the agent to achieve appropriate concentrations in the urine is of utmost importance. Factors that affect the rate and extent of excretion through the kidney include the patient's glomerular filtration rate and whether or not the agent is actively secreted. Filtration depends on the molecular size and degree of protein binding of the agent. Agents such as sulfonamides, tetracyclines, and aminoglycosides enter the urine via filtration. As the glomerular filtration rate is reduced, the amount of drug that enters the urine is reduced. Most β-lactam agents and quinolones are filtered and are actively secreted into the urine. For this reason, most of these agents achieve high urinary concentrations despite unfavorable protein-binding characteristics or the presence of renal dysfunction.

The ability to eradicate bacteria from the urine is related directly to the sensitivity of the microorganism and the achievable concentrations of the antimicrobial agent in the urine. Unfortunately, most susceptibility testing is directed at achievable concentrations in the blood. There is a poor correlation between achievable blood concentrations of antimicrobial agents and the eradication of bacteria from the urine.[32] In the treatment of lower tract infections, plasma concentrations of antibacterial agents may not be important, but achieving appropriate plasma concentrations appears critical in patients with bacteremia and renal abscesses.

Nonspecific therapies have been advocated in the treatment and prevention of UTIs. Fluid hydration has been used to produce rapid dilution of bacteria and removal of infected urine by increased voiding. A critical factor appears to be the amount of residual volume remaining after voiding. As little as 10 mL of residual urine can alter the eradication of infection significantly.[16] Paradoxically,

increased diuresis also may promote susceptibility to infection by diluting the normal antibacterial properties of the urine. Often in clinical practice the concentrations of antimicrobial agents in the urine are so high that dilution has little effect on efficacy.

The antibacterial activity of the urine is related to the low pH, which is the result of high concentrations of various organic acids. Large volumes of cranberry juice increase the antibacterial activity of the urine and prevent the development of UTIs.[3,33] Apparently, the fructose and other unknown substances (condensed tannins, proanthocyanidin) in cranberry juice may act to interfere with adherence mechanisms of some pathogens, thereby preventing infection or reinfection. Acidification of the urine by cranberry juice does not appear to play a significant role. Although there are a number of favorable studies, the benefit of ingested cranberry juice appears to be minimal and larger studies involving oral tablets or capsules needs to be done to prove effectivness.[35–38] With the current data available, women with repeated UTI's who receive the recommended 36 mg/d of proanthocyanidins (found in cranberry products) may gain some benefit but studies remain largely inconclusive.[36–38] The use of other agents (ascorbic acid) to acidify the urine to try to hinder bacterial growth does not achieve significant enough acidification. Consequently, attempts to acidify urine with systemic agents are not recommended. Lactobacillus potentially helps keep the vaginal pH in the normal range (pH 4-4.5); therefore, regulating genitourinary bacteria aiding in the prevention of UTIs.[41] In addition, *Lactobacillus* probiotics may aid in the prevention of female UTIs by decreasing the vaginal pH, thereby decreasing *E. coli* colonization.[19,33,34] In postmenopausal women, estrogen replacement may be of help in the prevention of recurrent UTIs. After 1 month of topical estrogen replacement, vaginal *Lactobacillus*, as well as vaginal pH and *E. coli* colonization decrease.[18,33]

Phenazopyridine hydrochloride is nonprescription urinary anesthetic/analgesic that can be used for symptom relief in UTIs. It is frequently used by patients as self-medication to alleviate the dysuria associated with UTIs. The use of phenazopyridine in the treatment of UTIs is controversial. It has no antimicrobial properties and has a number of adverse effects such as red-orange discoloration of body fluids, rash, anaphylaxis, and rare effects such as hemolytic anemia, methemoglobinemia, and acute renal failure. In addition, its use can mask the symptoms of an untreated or inappropriately treated UTI. Unfortunately, there are not any guidelines for its role in the treatment of UTIs; however, experts agree that if phenazopyridine is used, only use the recommended dose (maximum 200 mg three times a day) and limited to 1 to 2

days for symptomatic relief of the dysuria with UTIs.[41,42] In addition, it should be used with the combination of appropriate antibiotic therapy.

Pharmacologic Therapy

Ideally, the antimicrobial agent chosen should be well tolerated, well absorbed, achieve high urinary concentrations, and have a spectrum of activity limited to the known or suspected pathogen(s). **Table 134-2** lists the most common agents used in the treatment of UTIs along with comments concerning their general use. **Table 134-3** presents an overview of various therapeutic options for outpatient therapy of UTI. **Table 134-4** describes empirical treatment regimens for selected clinical situations.

TABLE 134-2 Commonly Used Antimicrobial Agents in the Treatment of UTIs

Drug	Adverse Drug Reactions	Monitoring Parameters	Comments
Oral Therapy			
Trimethoprim–sulfamethoxazole	Rash, Stevens–Johnson Syndrome, renal failure, photosensitivity, hematologic (neutropenia, anemia, etc.)	Serum creatinine, BUN, electrolytes, signs of rash, and CBC	This combination is highly effective against most aerobic enteric bacteria except *P. aeruginosa*. High urinary tract tissue concentrations and urine concentrations are achieved, which may be important in complicated infection treatment. Also effective as prophylaxis for recurrent infections
Nitrofurantoin	GI intolerance, neuropathies, and pulmonary reactions	Baseline serum creatinine and BUN	This agent is effective as both a therapeutic and prophylactic agent in patients with recurrent UTIs. Main advantage is the lack of resistance even after long courses of therapy
Fosfomycin trometamol	Diarrhea, headache, and angioedema	No routine tests recommended	Single-dose therapy for uncomplicated infections, low levels of resistance, use with caution in patients with hepatic dysfunction
Fluoroquinolones			
Ciprofloxacin Levofloxacin	Hypersensitivity, photosensitivity, GI symptoms, dizziness, confusion, and tendonitis (black box warning)	CBC, baseline serum creatinine, and BUN	The fluoroquinolones have a greater spectrum of activity, including *P. aeruginosa*. These agents are effective for pyelonephritis and prostatitis. Avoid in pregnancy and children. Moxifloxacin should not be used owing to inadequate urinary concentrations
Penicillins			
Amoxicillin–clavulanate	Hypersensitivity (rash, anaphylaxis), diarrhea, superinfections, and seizures	CBC, signs of rash, or hypersensitivity	Due to increasing *E. coli* resistance, amoxicillin–clavulanate is the preferred penicillin for uncomplicated cystitis
Cephalosporins			
Cefaclor Cefpodoxime-proxetil	Hypersensitivity (rash, anaphylaxis), diarrhea, superinfections, and seizures	CBC, signs of rash, or hypersensitivity	There are no major advantages of these agents over other agents in the treatment of UTIs, and they are more expensive. These agents are not active against enterococci
Parenteral Therapy			
Aminoglycosides			
Gentamicin Tobramycin Amikacin	Ototoxicity, nephrotoxicity	Serum creatinine and BUN, serum drug concentrations, and individual pharmacokinetic monitoring	These agents are renally excreted and achieve good concentrations in the urine. Amikacin generally is reserved for multidrug-resistant bacteria
Penicillins			
Ampicillin–sulbactam Piperacillin–tazobactam	Hypersensitivity (rash, anaphylaxis), diarrhea, superinfections, and seizures	CBC, signs of rash, or hypersensitivity	These agents generally are equally effective for susceptible bacteria. The extended-spectrum penicillins are more active against *P. aeruginosa* and enterococci and often are preferred over cephalosporins. They are very useful in renally impaired patients or when an aminoglycoside is to be avoided
Cephalosporins			
Ceftriaxone Ceftazidime Cefepime Ceftozolane/tazaobactam Ceftazidime/avabactam	Hypersensitivity (rash, anaphylaxis), diarrhea, superinfections, and seizures	CBC, signs of rash, or hypersensitivity	Second- and third-generation cephalosporins have a broad spectrum of activity against gram-negative bacteria, but are not active against enterococci and have limited activity against *P. aeruginosa*. Ceftazidime and cefepime are active against *P. aeruginosa*. They are useful for nosocomial infections and urosepsis due to susceptible pathogens
Carbapenems/monobactams			
Imipenem–cilistatin Meropenem Meropenem/vaborbactam Doripenem Ertapenem Aztreonam	Hypersensitivity (rash, anaphylaxis), diarrhea, superinfections, and seizures	CBC, signs of rash, or hypersensitivity	Carbapenems have a broad spectrum of activity, including gram-positive, gram-negative, and anaerobic bacteria. Imipenem, meropenem, and doripenem are active against *P. aeruginosa* and enterococci, but ertapenem is not. Aztreonam is a monobactam that is only active against gram-negative bacteria, including some strains of *P. aeruginosa*. Generally useful for nosocomial infections when aminoglycosides are to be avoided and in penicillin-sensitive patients
Fluoroquinolones			
Ciprofloxacin Levofloxacin	Hypersensitivity, photosensitivity, GI symptoms, dizziness, confusion, and tendonitis (black box warning)	CBC, baseline serum creatinine, and BUN	These agents have broad-spectrum activity against both gram-negative and gram-positive bacteria. They provide urine and high-tissue concentrations and are actively secreted in reduced renal function

BUN, blood urea nitrogen; CBC, complete blood count; GI, gastrointestinal; UTIs, urinary tract infections.

TABLE 134-3 Overview of Outpatient Antimicrobial Therapy for Lower Tract Infections in Adults

Indications	Antibiotic	Oral Dose	Interval*	Duration
Lower tract infections				
Uncomplicated	Trimethoprim–sulfamethoxazole	1 DS tablet	Twice a day	3 days
	Nitrofurantoin monohydrate	100 mg	Twice a day	5 days
	Fosfomycin trometamol	3 g	Single dose	1 day
	Ciprofloxacin	250 mg	Twice a day	3 days
	Levofloxacin	250 mg	Once a day	3 days
	Amoxicillin–clavulanate	500 mg	Every 8 hours	5-7 days
	Pivmecillinam	400 mg	Twice a day	3 days
Complicated	Trimethoprim–sulfamethoxazole	1 DS tablet	Twice a day	7-10 days
	Ciprofloxacin	250-500 mg	Twice a day	7-10 days
	Levofloxacin	250 mg	Once a day	10 days
		750 mg	Once a day	5 days
	Amoxicillin–clavulanate	500 mg	Every 8 hours	7-10 days
Recurrent infections	Nitrofurantoin	50 mg	Once a day	6 months
	Trimethoprim–sulfamethoxazole	1/2 SS tablet	Once a day	6 months
Acute pyelonephritis	Trimethoprim–sulfamethoxazole	1 DS tablet	Twice a day	14 days
	Ciprofloxacin	500 mg	Twice a day	14 days
		1,000 mg ER	Once a day	7 days
	Levofloxacin	250 mg	Once a day	10 days
		750 mg	Once a day	5 days
	Amoxicillin–clavulanate	500 mg	Every 8 hours	14 days

*Dosing intervals for normal renal function.

DS, double strength; SS, single strength.

TABLE 134-4 Evidence-Based Empirical Treatment of UTIs and Prostatitis

Diagnosis	Pathogens	Treatment Recommendation	Comments
Acute uncomplicated cystitis	*Escherichia coli*, *Staphylococcus saprophyticus*	1. Nitrofurantoin × 5 days (A,I)* 2. Trimethoprim–sulfamethoxazole × 3 days (A,I)* 3. Fosfomycin trometamol × 1 dose (A,I)* 4. Fluoroquinolone × 3 days (A,I)* 5. β-Lactams × 3-7 days (B,I)* 6. Pivmecillinam × 3-7 days (A,I)	Short-course therapy more effective than single dose Reserve fluoroquinolones as alternatives to development of resistance (A-III)* β-Lactams as a group are not as effective in acute cystitis then trimethoprim–sulfamethoxazole or the fluoroquinolones, do not use amoxicillin or ampicillin* Pivmecillinam not available in United States
Pregnancy	As above	1. Amoxicillin–clavulanate × 7 days 2. Cephalosporin × 7 days 3. Trimethoprim–sulfamethoxazole × 7 days	Avoid trimethoprim–sulfamethoxazole during the third trimester
Acute pyelonephritis			
Uncomplicated	*E. coli*	1. Quinolone × 7 days (A,I)* 2. Trimethoprim–sulfamethoxazole (if susceptible) × 14 days (A,I)*	Can be managed as outpatient
	Gram-positive bacteria	1. Amoxicillin or amoxicillin–clavulanic acid × 14 days	
Complicated	*E. coli* *P. mirabilis* *K. pneumoniae* *P. aeruginosa* *Enterococcus faecalis*	1. Quinolone × 14 days 2. Extended-spectrum penicillin plus aminoglycoside	Severity of illness will determine duration of IV therapy; culture results should direct therapy Oral therapy may complete 14 days of therapy
Prostatitis	*E. coli* *K. pneumoniae* *Proteus* spp. *P. aeruginosa*	1. Trimethoprim–sulfamethoxazole × 4-6 weeks 2. Quinolone × 4-6 weeks	Acute prostatitis may require IV therapy initially Chronic prostatitis may require longer treatment periods or surgery

*Strength of recommendations: A, good evidence for; B, moderate evidence for; C, poor evidence for and against; D, moderate against; E, good evidence against. Quality of evidence: I, at least one proper randomized, controlled study; II, one well-designed clinical trial; III, evidence from opinions, clinical experience, and expert committees.

UTI, urinary tract infection.

Data from Reference 1.

8 The therapeutic management of UTIs is best accomplished by first categorizing the type of infection: acute uncomplicated cystitis, symptomatic abacteriuria, ASB, complicated UTIs, recurrent infections, or prostatitis. In choosing the appropriate antibiotic therapy, it is important to be aware of the increasing resistance of *E. coli* and other pathogens to many frequently prescribed antimicrobials.[44] Resistance to *E. coli* is as high as 37% for amoxicillin and ampicillin.[1,45] Overall, most *E. coli* remain susceptible to trimethoprim–sulfamethoxazole, although resistance is continuing to increase

and has been reported as high as 27%.[46] Although resistance to the fluoroquinolones remains low, these agents are being used more frequently and the incidence of fluoroquinolone-resistant *E. coli* is increasingly being reported and is of great concern.[45–51] Current or recent antibiotic exposure is the most significant risk factor associated with *E. coli* resistance and with the extensive use of the fluoroquinolones and trimethoprim–sulfamethoxazole for various infections, including UTIs, resistance will continue to increase.[45–50] In addition, broad-spectrum antimicrobials such as fluoroquinolones and broad-spectrum cephalosporins have a high impact on GI flora, increasing the risk of collateral damage (term used to refer to ecological adverse effects of antibiotic therapy) or the selection of resistant *E. coli* pathogens.[45–48,51,52] In light of rising resistance and in order to decrease the overuse of broad-spectrum antimicrobials, agents such as nitrofurantoin and fosfomycin are now considered first-line treatments along with trimethoprim–sulfamethoxazole in acute uncomplicated cystitis. Both nitrofurantoin and fosfomycin have little effects on the gut flora and *E. coli* susceptibility still remains high.[52–56] With the increased use of nitrofurantoin and fosfomycin since the 2010 guidelines, clinicians are starting to evaluate the success rate of resolution of uncomplicated lower urinary tract infections in women when single-dose fosfomycin versus nitrofurantoin are used. More research will need to be done to establish that one therapy is more effective than the other.[57] Antibiotic therapy should be determined based on the geographic resistance patterns, as well as the patient's recent history of antibiotic exposure.

Acute Uncomplicated Cystitis

Acute uncomplicated cystitis is the most common form of UTI. These infections typically occur in women of childbearing age and often are related to sexual activity. Although the presence of dysuria, frequency, urgency, and suprapubic discomfort frequently is associated with lower tract infection, a significant number of patients have upper tract involvement as well.[3] Because these infections are predominantly caused by *E. coli*, antimicrobial therapy initially should be directed against this organism. Other common causes include *S. saprophyticus* and occasionally *K. pneumoniae* and *Proteus mirabilis*. Because the causative organisms and their susceptibility generally are known, many clinicians advocate a cost-effective approach to management. This approach includes a urinalysis and initiation of empirical therapy without a urine culture (**Fig. 134-1**).[1] Therefore, the susceptibility patterns of the geographic area drive the choice of empiric therapy.

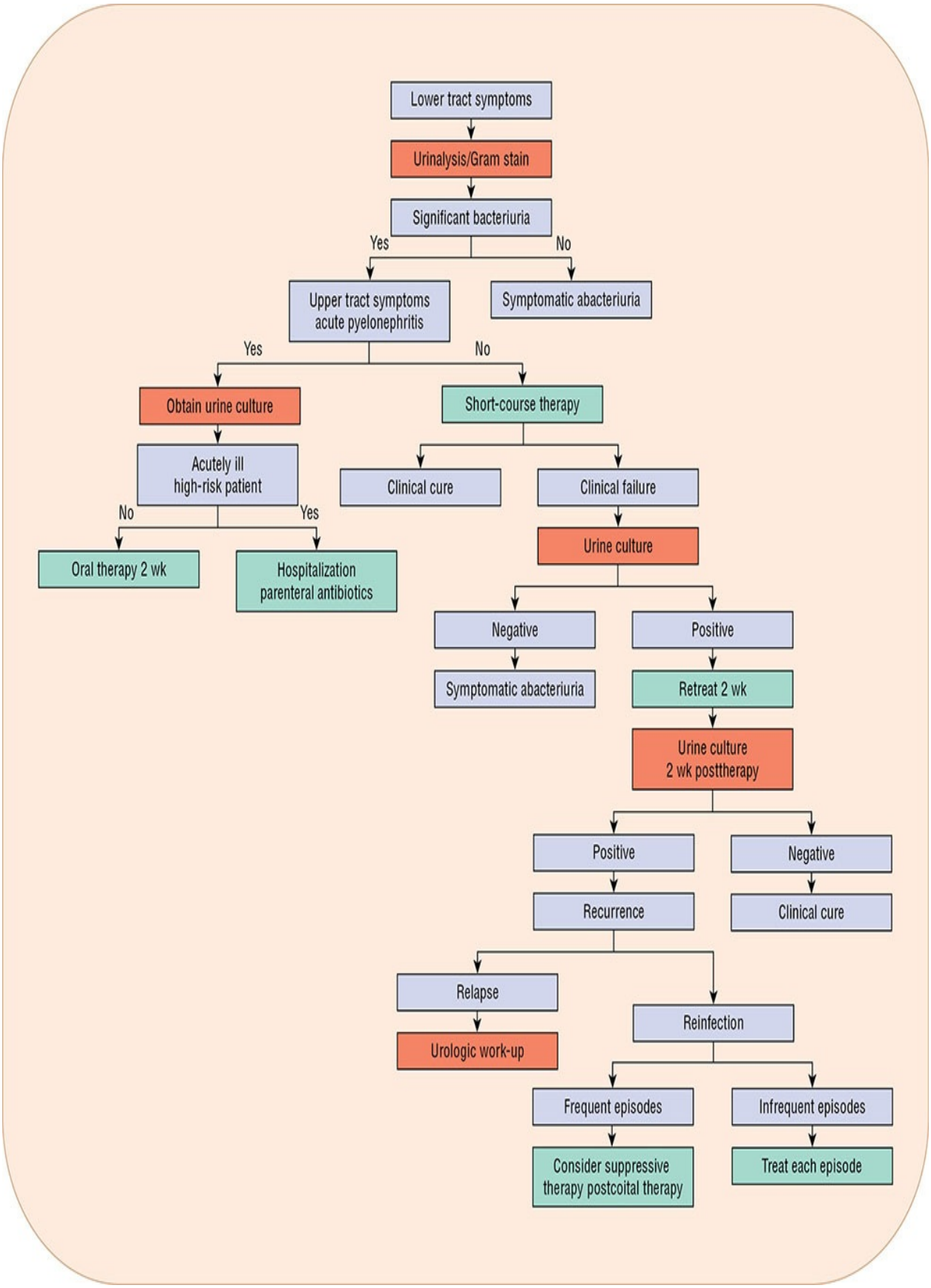

Lower tract symptoms
Urinalysis/Gram stain
Significant bacteriuria
Yes
No
Upper tract symptoms acute pyelonephritis
Symptomatic abacteriuria
Yes
No
Obtain urine culture
Short-course therapy
Acutely ill high-risk patient
Clinical cure
Clinical failure
No
Yes
Urine culture
Oral therapy 2 wk
Hospitalization parenteral antibiotics
Negative
Positive
Symptomatic abacteriuria
Retreat 2 wk
Urine culture 2 wk posttherapy
Positive
Negative
Recurrence
Clinical cure
Relapse
Reinfection
Urologic work-up
Frequent episodes
Infrequent episodes
Consider suppressive therapy postcoital therapy
Treat each episode

FIGURE 134-1 Management of urinary tract infections in females.

The goal of treatment for uncomplicated cystitis is to eradicate the causative organism and to reduce the incidence of recurrence caused by relapse or reinfection. The ability to reduce the chance of recurrence depends on the agent's efficacy in eradicating the uropathogenic bacteria from the vaginal and GI reservoir. In the past, conventional therapy consisted of an effective oral antibiotic administered for 7 to 14 days. However, acute cystitis is a superficial mucosal infection that can be eradicated with much shorter courses of therapy (3 days). Advantages of short-course therapy include increased adherence, fewer side effects, decreased cost, and less potential for the development of resistance.

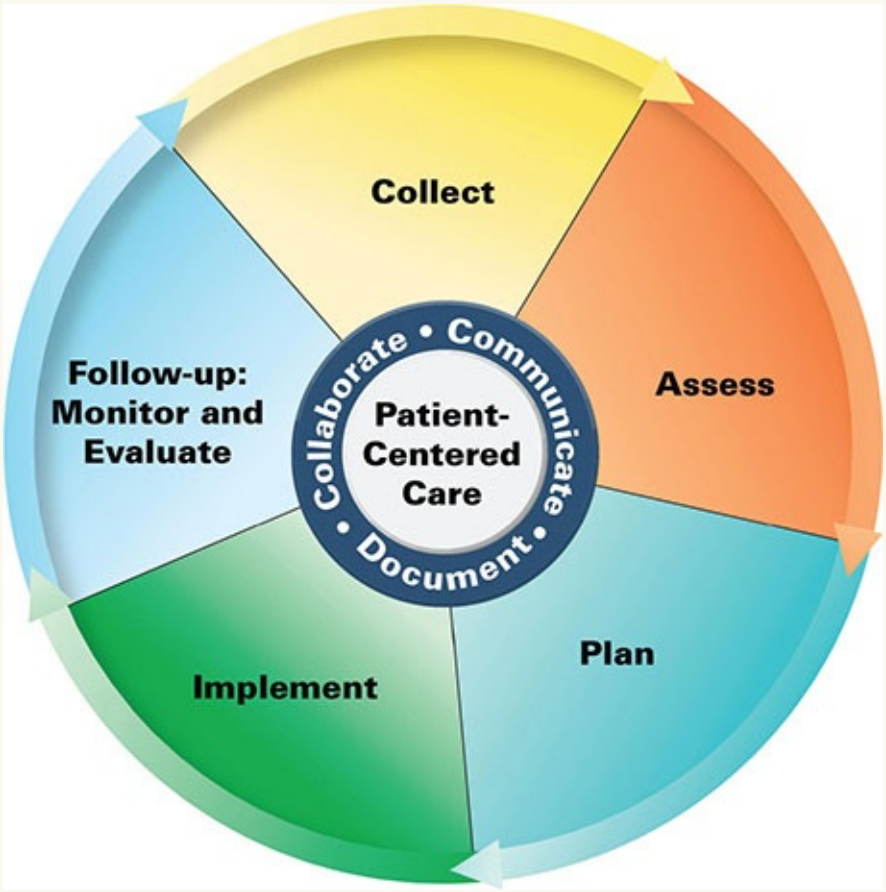
7 Three-day courses of trimethoprim–sulfamethoxazole or a fluoroquinolone (eg, ciprofloxacin or levofloxacin, not moxifloxacin) are superior to single-dose therapies.[55,58–60] Although the fluoroquinolones have shown excellent efficacy in acute cystitis, the newest guidelines recommend reserving these agents for patients with suspected or possible pyelonephritis due to the collateral damage risk. Instead, a 3-day course of trimethoprim–sulfamethoxazole, a 5-day course of nitrofurantoin, or a one-time dose of fosfomycin should be considered as first-line therapy[1,53–61] In areas where there is more than 20% resistance of *E. coli* to trimethoprim–sulfamethoxazole, nitrofurantoin or fosfomycin should be used. Amoxicillin or ampicillin should not be used due to the high incidence of resistant *E. coli*. Instead, if a β-lactam must be used, amoxicillin–clavulanate, cefdinir, cefaclor, or cefpodoxime proxetil for 3 to 7 days are the preferred choices. For most adult females, short-course therapy is the treatment of choice for uncomplicated lower UTIs. Short-course therapy is inappropriate for patients who have had previous infections caused by resistant bacteria, for male patients, and for patients with complicated UTIs. If symptoms recur or do not respond to therapy, a urine culture should be obtained and conventional therapy with a suitable agent instituted.[1]

Symptomatic Abacteriuria

Symptomatic abacteriuria or acute urethral syndrome represents a clinical syndrome in which females present with dysuria and pyuria, but the urine culture reveals less than 10^5 bacteria/mL (10^8/L) of urine. Acute urethral syndrome accounts for more than half the complaints of dysuria seen in the community today. These women most likely are infected with small numbers of coliform bacteria, including *E. coli*, *Staphylococcus* spp., or *Chlamydia trachomatis*.

Additional causes include *Neisseria gonorrhoeae*, *Gardnerella vaginalis*, and *Ureaplasma urealyticum.*

Most patients presenting with pyuria will, in fact, have infection that requires treatment. If antimicrobial therapy is ineffective, a culture should be obtained. If the patient reports recent sexual activity, therapy for *C. trachomatis* should be considered. Chlamydial treatment should consist of 1 g azithromycin or doxycycline 100 mg twice daily for 7 days. Often, concomitant treatment of all sexual partners is required to cure chlamydial infections and prevent reacquisition (see Chapter 135).



Patient Care Process for Urinary Tract Infection

Collect

- Patient characteristics (eg, age, sex, pregnant, immunocompetent)

- Patient symptoms (see Clinical Presentation box)
- Patient medical history (including history of past UTIs)
- Social history (eg, sexually active) and dietary habits
- Current medications including nonprescription and/or herbal products, dietary supplements
- Objective data
  - Vital signs: blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2 saturation, temperature
  - Labs including white blood cell count (WBC), serum creatinine (SCr)
  - Urinalysis (eg, nitrite or leukocyte esterase +) +/− culture and sensitivity data
  - Urine dipstick test
  - Physical exam (eg, abdominal tenderness, costovertebral tenderness)

Assess

- Hemodynamic stability (eg, systolic BP <90 mm Hg >110 bpm)
- Mental status
- Urinary catheter present

Plan

- Drug therapy regimen including drug name, dose, route, frequency, and duration (see Tables 134-2, 134-3, and 134-4)
- Monitoring parameters including efficacy (eg, afebrile, WBC, urinalysis, resolution of symptoms), decrease in urinary discomfort and safety (eg, signs and symptoms of antibiotic hypersensitivity, SCr, WBC, hemodynamics)
- Patient education (eg, purpose of treatment, personal hygiene, drug-specific information, medication administration instructions, when to follow-up if no improvement observed; see Table 134-3)
- Self-monitoring for resolution of symptoms (eg, urinary discomfort, flank pain, fever, mental status changes)
- Referrals to other providers when appropriate (eg, urologist)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up if necessary

Follow-up: Monitor and Evaluate

- Resolution of urinary symptoms (eg, burning, discomfort during urination, flank pain, tenderness)
- Normalization of labs (eg, WBC, SCr)
- Urinalysis Presence of adverse effects (eg, rash, diarrhea)
- Patient adherence to treatment plan using multiple sources of information
- Reevaluate if patient does not respond adequately to treatment

**Collaborate with patient, caregivers, and other healthcare professionals.*

Asymptomatic Bacteriuria

ASB is the finding of two consecutive urine cultures with more than 10^5 organisms/mL (10^8/L) of the same organism in the absence of urinary symptoms. Most patients with ASB are elderly and female. Also, pregnant women frequently present with ASB. Although this group of patients typically responds to treatment, relapse and reinfection are very common and chronic ASB is difficult to eradicate.

The management of ASB depends on the age of the patient and whether or not the patient is pregnant. In children, because of a greater risk of developing renal scarring and long-standing renal damage, treatment should consist of the same conventional courses of therapy as used for symptomatic infection. The greatest risk of renal damage occurs during the first 5 years of life.[62–63] In nonpregnant females, therapy is controversial; however, treatment has little effect on the natural course of infections. Two groups characterize ASB in the elderly: those with persistent bacteriuria and those with intermittent bacteriuria.

Several studies in hospitalized elderly subjects, however, have not found antimicrobial therapy to be efficacious for abacteruria.[64–67] A number of

questions remain unanswered. For example: What is the effect of eradication of bacteriuria on life expectancy? What are the cost-effectiveness and risk-to-benefit ratio of therapy? What is the effect on morbidity? Certainly with the information available and the high adverse reaction rate in the elderly, vigorous treatment and screening programs cannot be advocated.

Complicated Urinary Tract Infections

Acute Pyelonephritis

The presentation of high-grade fever (more than 38.3°C [100.9°F]) and severe flank pain should be treated as acute pyelonephritis and warrants aggressive management. Severely ill patients with pyelonephritis should be hospitalized and IV antimicrobials administered initially (see Table 134-4). However, milder cases may be managed with orally administered antibiotics in an outpatient setting. Signs and symptoms of nausea, vomiting, and dehydration may require hospitalization.

At the time of presentation, a Gram stain of the urine should be performed along with a urinalysis, culture, and sensitivity tests. The Gram stain should indicate the morphology of the infecting organism(s) and help direct the selection of an appropriate antibiotic. However, the precise identity and susceptibility of the infecting organism(s) will be unknown initially, warranting empirical therapy. The goals of treatment include the achievement of therapeutic concentrations of an antimicrobial agent in the bloodstream and urinary tract to which the invading organism is susceptible and sufficient therapy to eradicate residual infection in the tissues of the urinary tract.

In the mild-to-moderate symptomatic patient in whom oral therapy is considered, an effective agent should be administered for 7 to 14 days, depending on the agent used.[1,68–73] Oral antibiotics that are highly active against the probable pathogens and that are sufficiently bioavailable are preferred. Fluoroquinolones (ciprofloxacin or levofloxacin) orally for 7 to 10 days are the first-line choice in mild-to-moderate pyelonephritis. Other options include trimethoprim–sulfamethoxazole for 14 days. If amoxicillin–clavulanate or an oral cephalosporin is used, it is recommended to give an initial long-acting parenteral antimicrobial such as ceftriaxone first and continue the oral agent for 10 to 14 days. If a Gram stain reveals gram-positive cocci, *Enterococcus faecalis* should be considered and treatment directed against this potential pathogen (ampicillin). Close follow-up of outpatient treatment is mandatory to ensure success.

In the seriously ill patient, parenteral therapy should be administered initially. Therapy should provide a broad spectrum of coverage and should be directed toward bacteremia or sepsis, if present. A number of antibiotic regimens have been used as empirical therapy, including an IV fluoroquinolone, an aminoglycoside with or without ampicillin, and extended-spectrum cephalosporins with or without an aminoglycoside.[1,74] Other options include aztreonam, the β-lactamase inhibitor combinations (eg, ampicillin–sulbactam, ticarcillin–clavulanate, and piperacillin–tazobactam,cetazidime/avabactam and cefetolozone/tazobactam), carbapenems (eg, imipenem, meropenem, doripenem, or ertapenem), novel boronic acid-based beta-lactamase inhibitor (eg, meropenem-vaborbactam) and IV trimethoprim–sulfamethoxazole.[75–76] If the patient has been hospitalized within the past 6 months, has a urinary catheter, or is a nursing home resident, the possibility of *P. aeruginosa* and enterococci, as well as multiple resistant organisms, should be considered. In this setting, ceftazidime, ticarcillin–clavulanate, piperacillin, aztreonam, meropenem, or imipenem in combination with an aminoglycoside is recommended. Ertapenem should not be used in this situation owing to its inactivity against enterococci and *P. aeruginosa*.[72] The rationale for combination therapy is that in experimental animals 3 days of aminoglycoside combination therapy followed by nonaminoglycoside single-agent therapy for 7 days resulted in a 100% cure rate.[68,73] If the patient responds to initial combination therapy, the aminoglycoside may be discontinued after 3 days. Although the aminoglycoside therapy is stopped, renal tissue concentrations of the aminoglycoside will persist for days. Based on antimicrobial sensitivity data, the patient then can be maintained or switched to a less expensive single agent and ultimately, an appropriate oral agent may be used.

Effective therapy should stabilize the patient within 12 to 24 hours. A significant reduction in urine bacterial concentrations should occur in 48 hours. If bacteriologic response has not occurred, an alternative agent should be considered based on susceptibility testing. If the patient fails to respond clinically within 3 to 4 days or has persistently positive blood or urine cultures, further investigation is needed to exclude bacterial resistance, possible obstruction, papillary necrosis, intrarenal or perinephric abscess, or some other disease process. Usually by the third day of therapy, the patient is afebrile and significantly less symptomatic. In general, after the patient has been afebrile for 24 hours, parenteral therapy may be discontinued and oral therapy instituted to complete a 2-week course. Follow-up urine cultures should be obtained 2 weeks after completion of therapy to ensure a satisfactory response and detect possible

relapse.

Urinary Tract Infections in Males

The management of UTIs in males is distinctly different and often more difficult than in females. Infections in male patients are considered to be complicated because endogenous bacteria in the presence of functional and/or structural abnormalities that disrupt the normal defense mechanisms of the urinary tract cause them. The incidence of infections in males younger than 60 years is much less than the incidence in females. During the adult years, the occurrence of infection can be related directly to some manipulation of the urinary tract. The most common causes are instrumentation of the urinary tract, catheterization, and renal and urinary stones. Uncomplicated infections are rare, but they may occur in young males as a result of homosexual activity, noncircumcision, and having sex with partners who are colonized with uropathogenic bacteria. As the patient ages, the most common cause of infection is related to bladder outlet obstruction because of prostatic hypertrophy. In addition, the prostate gland may become infected and provide a nidus for recurrent infection in males.

The conventional view is that therapy in males requires prolonged treatment (**Fig. 134-2**). A urine culture should be obtained before treatment because the cause of infection in men is not as predictable as in women. Single-dose or short-course therapy is not recommended in males. Considerably fewer data are available comparing various antimicrobial agents in males as compared with females. If gram-negative bacteria are presumed, trimethoprim–sulfamethoxazole or the quinolone antimicrobials should be considered because these agents achieve high renal tissue, urine, and prostatic concentrations.[77]

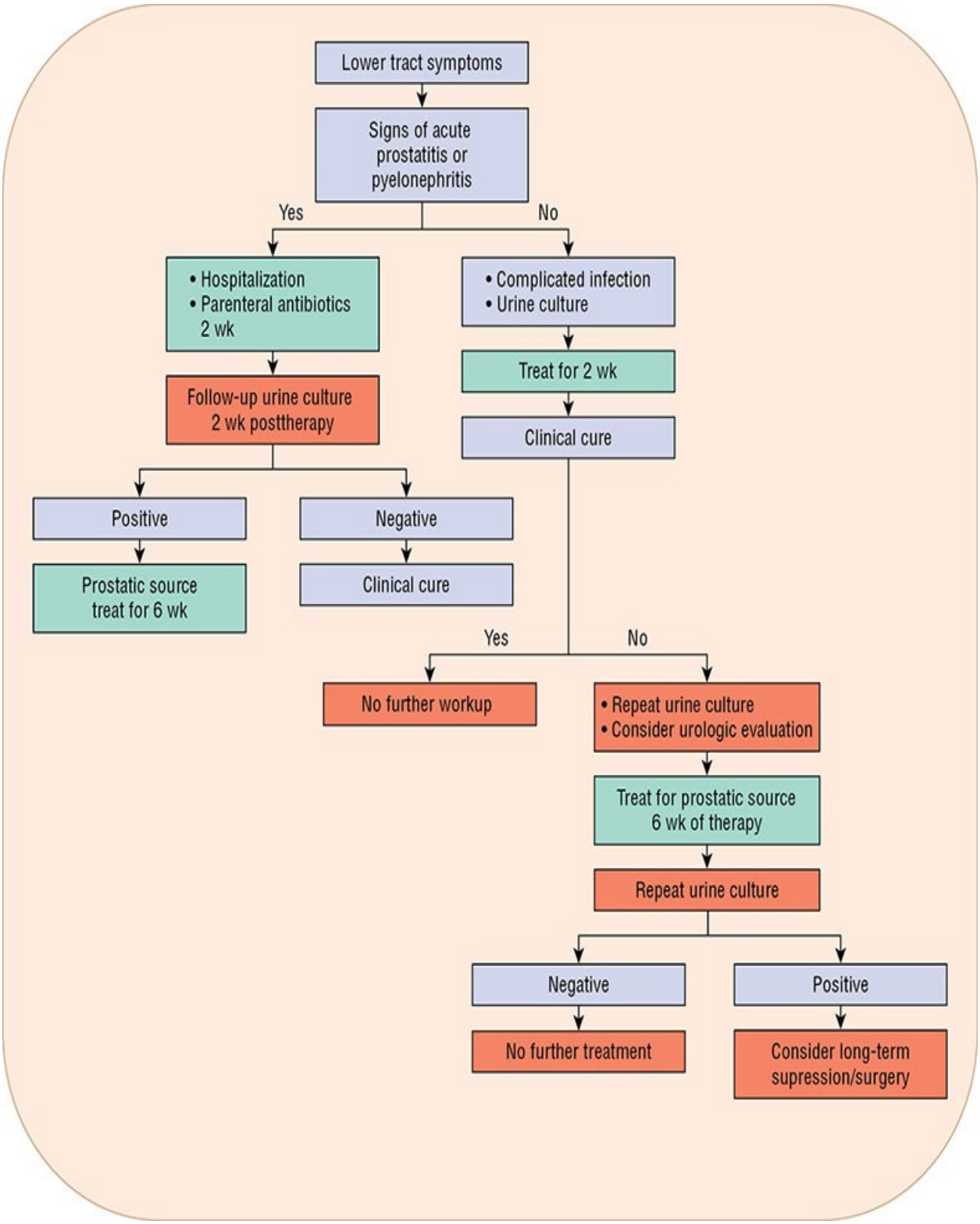


FIGURE 134-2 Management of urinary tract infections in males.

Initial therapy should be for 10 to 14 days. Factors associated with treatment

success are isolation of a single organism, the absence of significant obstruction or anatomic abnormalities, a normally functioning urinary tract, and the absence of prostatic involvement. Parenteral therapy may be required in certain situations, such as in severely ill patients, in the presence of acute prostatitis or epididymitis and in patients who cannot tolerate oral medications. A comparison of 2-week versus 6-week therapy in males with recurrent infections who were given trimethoprim–sulfamethoxazole had cure rates of 29% and 62%, respectively.[78] Other investigators advocate longer treatment periods in males, as well.[79] Follow-up cultures at 4 to 6 weeks after treatment are important in males to ensure bacteriologic cure. Many patients require longer periods of treatment and possible alterations in antibiotics, depending on culture and sensitivity results and clinical response.

Recurrent Infections

Recurrent episodes of UTI account for a significant portion of all UTIs. Of the patients suffering from recurrent infections, 80% can be considered reinfections, that is, the recurrence of infection by an organism different from the organism isolated from the preceding infection. These patients most commonly are female and recurrence develops in approximately 20% of females with cystitis. Reinfections can be divided into two groups: those with less than three episodes per year and those who develop more frequent infections. Treatment strategies are continuing to develop, as well as, an understanding of the role of the microbiome.[80,81] An excellent overview of the various treatment modalities for recurrent UTI in women has been published.[81]

Management strategies depend on predisposing factors, number of episodes per year, and the patient's preference. Factors commonly associated with recurrent infections include sexual intercourse and diaphragm or spermicide use for birth control. Therapeutic options include self-administered therapy, postcoital therapy, and continuous low-dose prophylaxis. In patients with infrequent infections (less than three infections per year), each episode may be treated as a separately occurring infection. Short-course therapy is appropriate in this setting. Many women have been treated successfully with self-administered short-course therapy at the onset of symptoms.[43,83]

In patients with more frequent symptomatic infections and no apparent precipitating event, long-term prophylactic antimicrobial therapy may be instituted. Prophylactic therapy reduces the frequency of symptomatic infections in elderly men, women, and children. In women, most studies show a reinfection rate of two to three per patient-year reduced to 0.1 to 0.2 per patient-year with

treatment.[83] Before prophylaxis is initiated, patients should be treated conventionally with an appropriate agent. Trimethoprim–sulfamethoxazole (one-half of a single-strength tablet), trimethoprim (100 mg daily), a fluoroquinolone (levofloxacin 500 mg daily), and nitrofurantoin (50 or 100 mg daily) all reduce the rate of reinfection as single-agent therapy.[83] Full-dose therapy with these agents is unnecessary and single daily doses can be used. Therapy generally is prescribed for a period of 6 months, during which time urine cultures are followed monthly. If symptomatic episodes develop, the patient should receive a full course of therapy with an effective agent and then resume prophylactic therapy. Therapy with methenamine hippurate for short-term use may be beneficial, but its overall utility is not well documented, especially for long-term prophylaxis.[84] In women who experience symptomatic reinfections in association with sexual activity, voiding after intercourse may help prevent infection. Also, single-dose prophylactic therapy with trimethoprim–sulfamethoxazole taken after intercourse reduces the incidence of recurrent infection significantly.[83]

In postmenopausal women with recurrent infections, the lack of estrogen results in changes in the bacterial flora of the vagina, resulting in increased colonization with uropathogenic *E. coli*. Topically administered estrogen cream reduces the incidence of infections in this population.[18,19]

The remaining 20% of recurrent UTIs are relapses, that is, persistence of infection with the same organism after therapy for an isolated UTI. The recurrence of symptomatic or ASB after therapy usually indicates that the patient has renal involvement, a structural abnormality of the urinary tract or chronic bacterial prostatitis. In the absence of structural abnormalities, relapse often is related to renal infection and requires a long duration of treatment. Women who relapse after short-course therapy should receive a 2-week course of therapy. In patients who relapse after 2 weeks of therapy, therapy should be continued for another 2 to 4 weeks. If relapse occurs after 6 weeks of therapy, urologic evaluation should be performed and any obstructive lesion should be corrected. If this is not possible, therapy for 6 months or longer may be considered. Asymptomatic adults who have no evidence of urinary obstruction should not receive long-term therapy.

In males, relapse usually indicates bacterial prostatitis, the most common cause of persistent bacteriuria. Although many agents have been used for long-term therapy of relapses, trimethoprim–sulfamethoxazole and the fluoroquinolones appear to be highly effective.

Special Conditions

Urinary Tract Infections in Pregnancy

During pregnancy, significant physiologic changes occur to the entire urinary tract that dramatically alter the prevalence of UTIs and pyelonephritis. Severe dilation of the renal pelvis and ureters, decreased ureteral peristalsis, and reduced bladder tone occur during pregnancy.[86] These changes result in urinary stasis and reduced defenses against reflux of bacteria to the kidneys. In addition, increased urine content of amino acids, vitamins, and nutrients encourages bacterial growth. All of these factors increase the incidence of bacteriuria resulting in symptomatic infections, especially during the third trimester.

ASB occurs in 4% to 7% of pregnant patients. Of these, 20% to 40% will develop acute symptomatic pyelonephritis during pregnancy. If untreated, ASB has the potential to cause significant adverse effects, including prematurity, low birth weight, and stillbirth.[86,87] Because pyelonephritis is associated with significant adverse events during pregnancy, routine screening tests for bacteriuria should be performed at the initial prenatal visit and again at 28 weeks gestation. In patients with significant bacteriuria, symptomatic or asymptomatic, treatment is recommended so as to avoid possible complications. Organisms associated with bacteriuria are the same as those seen in uncomplicated UTIs with *E. coli* isolated most frequently.

Therapy should consist of an agent administered for 7 days that has a relatively low adverse effect potential and is safe for the mother and baby. The administration of amoxicillin, amoxicillin–clavulanate, or cephalexin is effective in 70% to 80% of patients. Nitrofurantoin has been used in pregnancy; however, it must be used with caution as occurrences of birth defects have been reported. Tetracyclines should be avoided because of teratogenic effects and sulfonamides should not be administered during the third trimester because of the possible development of kernicterus and hyperbilirubinemia. In addition, fluoroquinolones should not be given because of their potential to inhibit cartilage and bone development in the newborn. A follow-up urine culture 1 to 2 weeks after completing therapy and then monthly until gestation is complete is recommended. Optimal treatment for preventing recurrent UTI and ASB has yet to be defined.[89]

Catheterized Patients

The use of an indwelling catheter frequently is associated with infection of the

urinary tract and represents the most common cause of hospital-acquired infection. The incidence of catheter-associated infection is related to a variety of factors, including method and duration of catheterization, the catheter system (open or closed), the care of the system, the susceptibility of the patient, and the technique of the healthcare personnel inserting the catheter. Catheter-related infections are reasonably preventable infections and are now considered one of the hospital-acquired complications chosen by the Centers for Medicare and Medicaid Services in which hospitals will no longer receive reimbursement for treatment.[90,91]

Bacteria may enter the bladder in a number of ways. During the catheterization, bacteria may be introduced directly into the bladder from the urethra. Once the catheter is in place, bacteria may pass up the lumen of the catheter via the movement of air bubbles, by motility of the bacteria, or by capillary action. In addition, bacteria may reach the bladder from around the exudative sheath that surrounds the catheter in the urethra. Cleaning the periurethral area thoroughly and applying an antiseptic (povidone-iodine) can minimize infection occurring during insertion of the catheter. The use of closed drainage systems has reduced significantly the ability of bacteria to pass up the lumen of the catheter and cause infection. A bacterium passing around the catheter sheath in the urethra is probably the most important pathway for infection. Avoiding manipulation of the catheter and trauma to the urethra and urethral meatus can minimize this path of acquisition.

Patients with indwelling catheters acquire UTIs at a rate of 5% per day.[90–92] The closed systems are capable of preventing bacteriuria in most patients for up to 10 days with appropriate care. After 30 days of catheterization, however, there is a 78% to 95% incidence of bacteriuria, despite use of a closed system.[91,93] Unfortunately, UTI symptoms in catheterized patient are not clearly defined. Fever, peripheral leukocytosis, and urinary signs and symptoms may be of little predictive value.[90,91] When bacteriuria occurs in the asymptomatic, short-term catheterized patient (less than 30 days), the use of systemic antibiotics should be withheld and the catheter removed as soon as possible. If the patient becomes symptomatic, the catheter should be removed and treatment as described for complicated infections started. The optimal duration of therapy is unknown. In the long-term catheterized patient (more than 30 days), bacteriuria is inevitable.[90,91] The administration of systemic antibiotics active against the infecting organism will sterilize the urine; however, reinfection occurs rapidly in more than 50% of patients. In addition, resistant organisms recolonize the urine. Symptomatic patients must be treated because they are at risk of developing

pyelonephritis and bacteremia. Bacteria adhere to the catheter and produce a biofilm consisting of bacterial glycocalyces, Tamm–Horsfall protein, as well as apatite and struvite salts, that act to protect the bacteria from antibiotics.[92] Biofilm mechanisms and their treatment continue to be examined and more fully understood.[93] Recatheterization with a new sterile unit should be performed in those symptomatic patients, if the existing catheter has been in place for more than 2 weeks.

Various methods have been proposed to prevent the development of bacteriuria and infection in the patient with an indwelling catheter (see Table 134-4). The success of these methods depends on the type of catheter and the length of time it is in place. The use of constant bladder irrigation with antiseptic or antibacterial solutions reduces the incidence of infection in those with open drainage systems, but this approach has no advantage in those with closed systems. The use of prophylactic systemic antibiotics in patients with short-term catheterization reduces the incidence of infection over the first 4 to 7 days.[91,93] In long-term catheterized patients, however, antibiotics only postpone the development of bacteriuria and lead to the emergence of resistant organisms. Therefore, antibiotic prophylaxis should not be utilized in short-term or long-term catheterized patients.

PROSTATITIS

Bacterial prostatitis is an inflammation of the prostate gland and surrounding tissue as a result of infection. It is classified as either acute or chronic. By definition, pathogenic bacteria and significant inflammatory cells must be present in prostatic secretions and urine to make the diagnosis of bacterial prostatitis. Prostatitis occurs rarely in young males, but it is commonly associated with recurrent infections in persons older than 30 years. As many as 50% of all males develop some form of prostatitis at some period in their life.[95–97] The acute form typically is an acute infectious disease characterized by a sudden onset of fever, tenderness, and urinary and constitutional symptoms. Chronic prostatitis presents with few symptoms related to the prostate but rather symptoms of urinating difficulty, low back pain, perineal pressure, or a combination of these. It represents a recurring infection with the same organism that results from incomplete eradication of bacteria from the prostate gland.

Pathogenesis and Etiology

The exact mechanism of bacterial infection of the prostate is not well understood. The possible routes of infection are the same as those for UTIs. Reflux of infected urine into the prostate gland is thought to play an important role in causing infection. Intraprostatic reflux of urine occurs commonly and results in direct inoculation of infected urine into the prostate.[95–97] In addition, intraprostatic reflux of sterile urine can result in a chemical prostatitis and may be the cause of nonbacterial prostatitis. Sexual intercourse may contribute to infection of the prostate gland because prostatic secretions from men with chronic prostatitis and vaginal cultures from their sexual partners grow identical organisms. Other known causes of bacterial prostatitis include indwelling urethral and condom catheterization, urethral instrumentation, and transurethral prostatectomy in patients with infected urine.

Physiologic factors are believed to contribute to the development of prostatitis. Functional abnormalities found in bacterial prostatitis include altered prostate secretory functions. Prostatic fluid obtained from normal males contains prostatic antibacterial factor. This heat-stable, low-molecular-weight cation is a zinc-complexed polypeptide that is bactericidal to most urinary tract pathogens.[98] The antibacterial activity of prostatic antibacterial factor is related directly to the zinc content of prostatic fluid. Prostate fluid zinc levels and prostatic antibacterial factor activity also appear diminished in patients with prostatitis, as well as in the elderly.[98] Whether these changes are a cause or effect of prostatitis remains to be determined.

The pH of prostatic secretions in patients with prostatitis is altered.[99] Normal prostatic secretions have a pH in the range of 6.6 to 7.6. With increasing age, the pH tends to become more alkaline. In patients with inflammation of the prostate, prostatic secretions may have an alkaline pH in the range of 7 to 9. These changes suggest a generalized secretory dysfunction of the prostate that not only can affect the pathogenesis of prostatitis but also can influence the mode of therapy.

Gram-negative enteric organisms are the most frequent pathogens in acute bacterial prostatitis.[95–97] *E. coli* is the predominant organism, occurring in 75% of cases. Other gram-negative organisms frequently isolated include *K. pneumoniae*, *P. mirabilis*, and less frequently, *P. aeruginosa*, *Enterobacter* spp., and *Serratia* spp. Infrequently, cases of gonococcal and staphylococcal prostatitis occur. *E. coli* most commonly causes chronic bacterial prostatitis with other gram-negative organisms isolated less frequently. The importance of gram-positive organisms in chronic bacterial prostatitis remains controversial. *S. epidermidis*, *S. aureus*, and diphtheroids have been isolated in some studies.

Clinical Presentation

Acute bacterial prostatitis presents similarly to other acute infections with fever, chills, myalgias, and other typical signs and symptoms. Massage of the prostate will express a purulent discharge that will readily grow the pathogenic organism. Prostatic massage is contraindicated in acute bacterial prostatitis, however, because of the risk of inducing bacteremia and the associated local pain. The diagnosis of acute bacterial prostatitis can be made from the patient's clinical presentation and the presence of significant bacteriuria. As with other UTIs, the infecting organism can be isolated from a midstream specimen.

In contrast, chronic bacterial prostatitis is more difficult to diagnose and treat. Chronic bacterial prostatitis typically is characterized by recurrent UTIs with the same pathogen and is the most common cause of recurrent UTI in males. The patient's clinical presentation can vary widely. Many adults, however, are asymptomatic.

Because physical examination of the prostate is often normal, urinary tract localization studies are critical to the diagnosis of chronic bacterial prostatitis. The method of quantitative localization culture, as described by Meares and Stamey,[15,100] remains the diagnostic standard (**Fig. 134-3**). The method compares the bacterial growth in sequential urine and prostatic fluid cultures obtained during micturition. The first 10 mL of voided urine is collected (voiding bladder 1, or VB_1) and constitutes urethral urine. After approximately 200 mL of urine has been voided, a 10-mL midstream sample is collected (VB_2). This specimen represents bladder urine. After the patient voids, the prostate is massaged and expressed prostatic secretions (EPS) are collected. After prostatic massage, the patient voids again and 10 mL of urine is collected (VB_3).

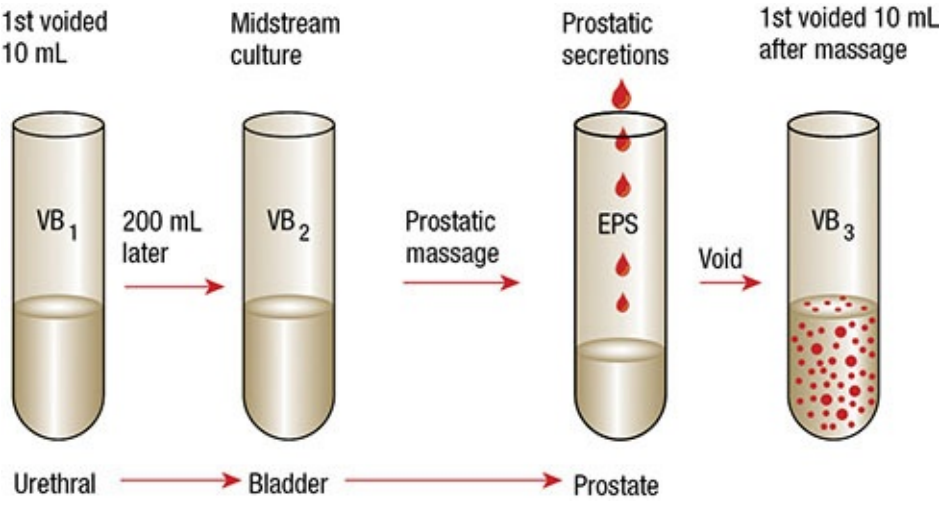


FIGURE 134-3 Segmented cultures of the lower tract in men. (EPS, expressed prostatic secretions; VB_1, voiding bladder 1; VB_2, voiding bladder 2; VB_3, voiding bladder 3.)

CLINICAL PRESENTATION Bacterial Prostatitis

Signs and Symptoms

- Acute bacterial prostatitis: High fever, chills, malaise, myalgia, localized pain (perineal, rectal, sacrococcygeal), frequency, urgency, dysuria, nocturia, and retention
- Chronic bacterial prostatitis: Voiding difficulties (frequency, urgency, dysuria), low back pain, and perineal and suprapubic discomfort

Physical Examination

- Acute bacterial prostatitis: Swollen, tender, tense, or indurated gland
- Chronic bacterial prostatitis: Boggy, indurated (enlarged) prostate in most patients

Laboratory Tests

- Bacteriuria
- Bacteria in EPSs

The diagnosis of bacterial prostatitis is made when the number of bacteria in EPS is 10 times that of the urethral sample (VB_1) and midstream sample (VB_2). If no EPS is available, the urine sample following massage (VB_3) should contain a bacterial count 10-fold greater than that of VB_1 or VB_2. If significant bacteriuria is present, ampicillin, cephalexin, or nitrofurantoin should be given for 2 to 3 days to sterilize the urine prior to performing the localization study.

Treatment

9 The goals for the management of bacterial prostatitis are the same as those

for UTIs. Acute bacterial prostatitis responds well to appropriate antimicrobial therapy that is directed at the most commonly isolated organisms. Prostatic penetration of antimicrobials occurs because the acute inflammatory reaction alters the cellular membrane barrier between the bloodstream and the prostate. Most patients can be managed with oral antimicrobial agents, such as trimethoprim–sulfamethoxazole and the fluoroquinolones (eg, ciprofloxacin, levofloxacin) (see Table 134-4). Other effective agents in this setting include cephalosporins and β-lactam–β-lactamase combinations. Although IV therapy is rarely necessary for total treatment, IV to oral sequential therapy with trimethoprim–sulfamethoxazole or the fluoroquinolones is appropriate. The conversion to an oral antibiotic can be considered after the patient is afebrile for 48 hours or after 3 to 5 days of IV therapy. The total course of antibiotic therapy should be 4 weeks in order to reduce the risk of development of chronic prostatitis, although in some cases 2 weeks may be sufficient. Therapy may be prolonged with chronic prostatitis (6-12 weeks). Long-term suppressive therapy also may be initiated for recurrent infections, such as three times weekly ciprofloxacin, trimethoprim–sulfamethoxazole regular-strength tablet daily, or nitrofurantoin 100 mg daily.[100]

Chronic bacterial prostatitis often presents a more vexing situation because cures are obtained rarely. Despite high serum concentrations of antibacterial drugs in excess of the minimal inhibitory concentrations of the infecting organisms, bacteria persist in prostatic fluid. Most likely the failure to eradicate sensitive bacteria is caused by the inability of antibiotics to reach sufficient concentrations in the prostatic fluid and cross the prostatic epithelium.

Several factors that determine antibiotic diffusion into prostatic secretions were delineated from the canine model. Lipid solubility is a major determinant in the ability of drugs to diffuse from plasma across epithelial membranes. The degree of ionization in plasma also affects the diffusion of drugs. Only unionized molecules can cross the lipid barrier of prostatic cells, and the drug's pK_a (negative logarithm of acid ionization constant) directly determines the fraction of unchanged drug.

The pH gradient across the membrane has an influence on tissue penetration, as well. A pH gradient of at least one pH unit between separate compartments allows for ion trapping. As the unionized drug crosses the epithelial barrier into prostatic fluid, it becomes ionized allowing less drug to diffuse back across the lipid barrier. In early studies with the canine model, the prostatic pH was reported to be acidic (6.4).[99] In humans, however, the pH of prostatic secretions from an inflamed prostate is actually basic (8.1-8.3).[99]

The choice of antibiotics in chronic bacterial prostatitis should include agents that are capable of reaching therapeutic concentrations in the prostatic fluid and which possess the spectrum of activity to be effective. Agents that achieve therapeutic prostatic concentrations include trimethoprim and the fluoroquinolones. Sulfamethoxazole penetrates poorly and probably contributes very little to trimethoprim activity when used in combination. The fluoroquinolones appear to provide the best therapeutic options in the management of chronic bacterial prostatitis. Therapy should be continued for 4 to 6 weeks initially. Longer treatment periods may be necessary in some cases. If therapy fails with these regimens, chronic suppressive therapy may be used or surgery considered.

Postclass Engaged Learning Activity

Since it has been several years since the last clinical guideline for acute cystitis and pyelonephritis was published, students should conduct a literature search and choose a manuscript that has been published within the last 12 months related to the treatment of acute cystitis or pyelonephritis. Select a manuscript that offers a new treatment option for patients with UTI. Write a brief summary of the manuscript findings and decide whether the findings of the manuscript lead to recommending something different than what is in current guidelines for treating urinary tract infections.

ABBREVIATIONS

ASB	asymptomatic bacteriuria
CFU	colony-forming unit
EPS	expressed prostatic secretions
GI	gastrointestinal
PMN	polymorphonuclear leukocyte
UTI	urinary tract infection
WBC	white blood cell

REFERENCES

1. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and

pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis*. 2011;52(5):e103–e120.

2. Naber KG, Cho YH, Matsumoto T, Schaeffer AJ. Immunoactive prophylaxis of recurrent urinary tract infections: A meta-analysis. *Int J Antimicrob Agents*. 2009;33(2):111–119.
3. Kallen AJ, Welch HG, Sirovich BE. Current antibiotic therapy for isolated urinary tract infections in women. *Arch Intern Med*. 2006;166(6):635–639.
4. Nicolle LE. Uncomplicated urinary tract infection in adults including uncomplicated pyelonephritis. *Urol Clin North Am* 2008;35(1):112,v.
5. Little P, Turner S, Rumsby K, et al. Developing clinical rules to predict urinary tract infection in primary care settings: Sensitivity and specificity of near patient tests (dipsticks) and clinical scores. *Br J Gen Pract* 2006;56(529):606–612.
6. Platt R. Quantitative definition of bacteriuria. *Am J Med* 1983;75(1b):44–52.
7. Alper BS, Curry SH. Urinary tract infection in children. *Am Fam Physician*. 2005;72(12):2483–2488.
8. Habib S. Highlights for management of a child with a urinary tract infection. *Int J Pediatr*. 2012;2012. doi: 10.1155/2012/943653.
9. Sobel J, Kaye D. *Urinary Tract Infections*. 7th ed. Philadelphia, PA: Churchill Livingstone/Elsevier; 2010.
10. Shortliffe LM, McCue JD. Urinary tract infection at the age extremes: Pediatrics and geriatrics. *Am J Med*. 2002;113(Suppl 1A):55s–66s.
11. Nicolle L, Anderson PA, Conly J, et al. Uncomplicated urinary tract infection in women. Current practice and the effect of antibiotic resistance on empiric treatment. *Can Fam Physician* 2006;52:612618.
12. Shigemura K, Arakawa S, Tanaka K, Fujisawa M. Clinical investigation of isolated bacteria from urinary tracts of hospitalized patients and their susceptibilities to antibiotics. *J Infect Chemother*. 2009;15(1):18–22.
13. Heintz BH, Halilovic J, Christensen CL. Vancomycin-resistant enterococcal urinary tract infections. *Pharmacotherapy*. 2010;30(11):1136–1149.
14. Stamatiou C, Bovis C, Panagopoulos P, et al. Sex-induced cystitis—patient burden and other epidemiological features. *Clin Exp Obstet Gynecol* 2005;32(3):180–182.

15. Stamey TA, Fair WR, Timothy MM, Chung HK. Antibacterial nature of prostatic fluid. *Nature*. 1968;218(5140):444–447.
16. Shand DG, Nimmon CC, O'Grady F, Cattell WR. Relation between residual urine volume and response to treatment of urinary infection. *Lancet*. 1970;760(1):1305–1306.
17. Parsons CL, Shrom SH, Hanno PM, Mulholland SG. Bladder surface mucin. Examination of possible mechanisms for its antibacterial effect. *Invest Urol*. 1978;16(3):196–200.
18. Raz R, Stamm WE. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. *N Engl J Med*. 1993;329(11):753–756.
19. Stamm WE. Estrogens and urinary-tract infection. *J Infect Dis* 2007;195(5):623–624.
20. Orskov I, Ferencz A, Orskov F. Tamm-horsfall protein or uromucoid is the normal urinary slime that traps type 1 fimbriated *Escherichia coli*. *Lancet*. 1980;1(8173):887.
21. Measley RE Jr, Levison ME. Host defense mechanisms in the pathogenesis of urinary tract infection. *Med Clin North Am*. 1991;75(2):275–286.
22. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: Epidemiology, mechanisms of infection and treatment options. *Nat Rev Microbiol*. 2015;13(5):269–284.
23. Jenkins RD, Fenn JP, Matsen JM. Review of urine microscopy for bacteriuria. *JAMA*. 1986;255(24):3397–3403.
24. Pezzlo M. Detection of urinary tract infections by rapid methods. *Clin Microbiol Rev* 1988;1(3):268–280.
25. Stamm WE. Measurement of pyuria and its relation to bacteriuria. *Am J Med* 1983;75(1b):5358.
26. Pappas PG. Laboratory in the diagnosis and management of urinary tract infections. *Med Clin North Am* 1991;75(2):313–325.
27. St John A, Boyd JC, Lowes AJ, Price CP. The use of urinary dipstick tests to exclude urinary tract infection: A systematic review of the literature. *Am J Clin Pathol*. 2006;126(3):428–436.
28. Nys S, van Merode T, Bartelds AI, Stobberingh EE. Urinary tract infections in general practice patients: Diagnostic tests versus bacteriological culture. *J Antimicrob Chemother*. 2006;57(5):955–958.

29. Stamey TA, Govan DE, Palmer JM. The localization and treatment of urinary tract infections: The role of bactericidal urine levels as opposed to serum levels. *Medicine (Baltimore)*. 1965;44:1–36.
30. Fairley KF, Bond AG, Brown RB, Habersberger P. Simple test to determine the site of urinary-tract infection. *Lancet*. 1967;2(7513):427–428.
31. Thomas VL, Forland M. Antibody-coated bacteria in urinary tract infections. *Kidney Int*. 1982;21(1):1–7.
32. Stamey TA, Fair WR, Timothy MM, et al. Serum versus urinary antimicrobial concentrations in cure of urinary-tract infections. *N Engl J Med* 1974;291(22):11591163.
33. Barrons R, Tassone D. Use of lactobacillus probiotics for bacterial genitourinary infections in women: A review. *Clin Ther*. 2008;30(3):453–468.
34. Zelenitsky SA, Zhanel GG. Phenazopyridine in urinary tract infections. *Ann Pharmacother*. 1996;30(7-8):866–868.
35. Stapleton AE, Dziura J, Hooton TM, et al. Recurrent urinary tract infection and urinary *Escherichia coli* in women ingesting cranberry juice daily: A randomized controlled trial. *Mayo Clin Proc*. 2012;87(2):143–150.
36. Jepson RG, Williams G, Craig JC. Cranberries for preventing urinary tract infections. *Cochrane Database Syst Rev*. 2012;10:CD001321.
37. Stapleton AE. Cranberry-containing products are associated with a protective effect against urinary tract infections. *Evid Based Med* 2013;18(3):110–111.
38. Singh I, Gautam LK, Kaur IR. Effect of oral cranberry extract (standardized proanthocyanidin-A) in patients with recurrent UTI by pathogenic *E. coli*: A randomized placebo-controlled clinical research study. Int Urol Nephrol. 2016;48(9):1379–1386.
39. Jepson R, Craig J, Williams G. Cranberry products and prevention of urinary tract infections. JAMA. 2013;310(13):1395–1396.
40. Howell AB, Botto H, Combescure C, et al. Dosage effect on uropathogenic *Escherichia coli* anti-adhesion activity in urine following consumption of cranberry powder standardized for proanthocyanidin content: A multicentric randomized double blind study. BMC Infect Dis. 2010;10:94.
41. Stapleton AE, Au-Yeung M, Hooton TM, et al.Randomized, placebo-

controlled phase 2 trial of a Lactobacillus crispatus probiotic given intravaginally for prevention of recurrent urinary tract infection. Clin Infect Dis. 2011;52(10):1212–1217.

42. Gaines KK. Phenazopyridine hydrochloride: The use and abuse of an old standby for UTI. *Urol Nurs* 2004;24(3):207–209.
43. Masson P, Matheson S, Webster AC and Craig JC. Meta-analyses in prevention and treatment of urinary tract infections. *Infect Dis Clin North Am*. 2009;23(2):355–385.
44. Chen YH, Ko WC, Hsueh PR. Emerging resistance problems and future perspectives in pharmacotherapy for complicated urinary tract infections. *Expert Opin Pharmacother*. 2013;14(5):587–596.
45. Olson RP, Harrell LJ, Kaye KS. Antibiotic resistance in urinary isolates of *Escherichia coli* from college women with urinary tract infections. *Antimicrob Agents Chemother*. 2009;53(3):1285–1286.
46. Colgan R, Johnson JR, Kuskowski M, Gupta K. Risk factors for trimethoprim-sulfamethoxazole resistance in patients with acute uncomplicated cystitis. *Antimicrob Agents Chemother*. 2008;52(3):846–851.
47. Bergman M, Nyberg ST, Huovinen P, et al. Association between antimicrobial consumption and resistance in *Escherichia coli*. *Antimicrob Agents Chemother*. 2009;53(3):912–917.
48. Talan DA, Krishnadasan A, Abrahamian FM, et al. Prevalence and risk factor analysis of trimethoprim-sulfamethoxazole- and fluoroquinolone-resistant *Escherichia coli* infection among emergency department patients with pyelonephritis. *Clin Infect Dis*. 2008;47(9):1150–1158.
49. Paterson DL. “Collateral damage” from cephalosporin or quinolone antibiotic therapy. *Clin Infect Dis* 2004;38(Suppl 4):S341–S345.
50. Karlowsky JA, Hoban DJ, Decorby MR, et al. Fluoroquinolone-resistant urinary isolates of *Escherichia coli* from outpatients are frequently multidrug resistant: Results from the north american urinary tract infection collaborative alliance-quinolone resistance study. *Antimicrob Agents Chemother*. 2006;50(6):2251–2254.
51. Johnson L, Sabel A, Burman WJ, et al. Emergence of fluoroquinolone resistance in outpatient urinary *Escherichia coli* isolates. *Am J Med*. 2008;121(10):876–884.
52. Wagenlehner FM, Weidner W, Naber KG. An update on uncomplicated urinary tract infections in women. *Curr Opin Urol*. 2009;19(4):368–374.

53. Kashanian J, Hakimian P, Blute M Jr, et al. Nitrofurantoin: The return of an old friend in the wake of growing resistance. *BJU Int* 2008;102(11):1634–1637.
54. Knottnerus BJ, Nys S, Ter Riet G, et al. Fosfomycin tromethamine as second agent for the treatment of acute, uncomplicated urinary tract infections in adult female patients in the netherlands? *J Antimicrob Chemother* 2008;62(2):356–359.
55. Tice AD. Short-course therapy of acute cystitis: A brief review of therapeutic strategies. *J Antimicrob Chemother* 1999;43(Suppl A):8593.
56. Stein GE. Comparison of single-dose fosfomycin and a 7-day course of nitrofurantoin in female patients with uncomplicated urinary tract infection. *Clin Ther* 1999;21(11):1864–1872.
57. Huttner A, Kowalczyk A, Turjeman A, et al. Effect of 5-day nitrofurantoin vs single-dose fosfomycin on clinical resolution of uncomplicated lower urinary tract infection in women: A randomized clinical trial. JAMA. 2018;319(17):1781–1789.
58. Cox CE, Marbury TC, Pittman WG, et al. A randomized, double-blind, multicenter comparison of gatifloxacin versus ciprofloxacin in the treatment of complicated urinary tract infection and pyelonephritis. *Clin Ther* 2002;24(2):223–236.
59. Iravani A, Klimberg I, Briefer C, et al. A trial comparing low-dose, short-course ciprofloxacin and standard 7 day therapy with co-trimoxazole or nitrofurantoin in the treatment of uncomplicated urinary tract infection. *J Antimicrob Chemother* 1999;43(Suppl A):67–75.
60. Stass H, Kubitza D. Pharmacokinetics and elimination of moxifloxacin after oral and intravenous administration in man. *J Antimicrob Chemother*. 1999;43(Suppl B):83–90.
61. Gupta K, Hooton TM, Roberts PL, Stamm WE. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. *Arch Intern Med*. 2007;167(20):2207–2212.
62. Chang SL, Shortliffe LD. Pediatric urinary tract infections. *Pediatr Clin North Am* 2006;53(3):379–400.
63. Korbel L, Howell M, Spencer JD. The clinical diagnosis and management of urinary tract infections in children and adolescents. Paediatr Int Child Health. 2017;37(4):273–279.
64. Nicolle LE, Bradley S, Colgan R, et al. Infectious diseases society of america guidelines for the diagnosis and treatment of asymptomatic

bacteriuria in adults. *Clin Infect Dis* 2005;40(5):643–654.

65. Lin K, Fajardo K; U.S. Preventive Services Task Force. Screening for asymptomatic bacteriuria in adults: U.S. Preventive services task force reaffirmation recommendation statement. *Ann Intern Med*. 2008;149(1):43–47.
66. Juthani-Mehta M, Quagliarello V, Perrelli E, et al. Clinical features to identify urinary tract infection in nursing home residents: A cohort study. *J Am Geriatr Soc* 2009;57(6):963–970.
67. Nicolle LE, Bjornson J, Harding GK, MacDonell JA. Bacteriuria in elderly institutionalized men. *N Engl J Med*. 1983;309(23):1420–1425.
68. Neal DE Jr. Complicated urinary tract infections. *Urol Clin North Am* 2008;35(1):13–22.
69. Talan DA, Stamm WE, Hooton TM, et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis pyelonephritis in women: A randomized trial. *JAMA* 2000;283(12):1583–1590.
70. van Nieuwkoop C, van't Wout JW, Assendelft WJ, et al. Treatment duration of febrile urinary tract infection (futirst trial): A randomized placebo-controlled multicenter trial comparing short (7 days) antibiotic treatment with conventional treatment (14 days). *BMC Infect Dis*. Aug 19, 2009;9:131.
71. Katchman EA, Milo G, Paul M, et al. Three-day vs longer duration of antibiotic treatment for cystitis in women: Systematic review and meta-analysis. *Am J Med* 2005;118(11):1196–1207.
72. Peterson J, Kaul S, Khashab M, et al. A double-blind, randomized comparison of levofloxacin 750 mg once-daily for five days with ciprofloxacin 400/500 mg twice-daily for 10 days for the treatment of complicated urinary tract infections and acute pyelonephritis. *Urology* 2008;71(1):17–22.
73. Brown P, Ki M, Foxman B. Acute pyelonephritis among adults: Cost of illness and considerations for the economic evaluation of therapy. *Pharmacoeconomics*. 2005;23(11):1123–1142.
74. Curran M, Simpson D, Perry C. Ertapenem: A review of its use in the management of bacterial infections. *Drugs*. 2003;63(17):1855–1878.
75. Wagenlehner FM, Wagenlehner C, Redman R, et al.Urinary bactericidal activity of doripenem versus that of levofloxacin in patients with complicated urinary tract infections or pyelonephritis. *Antimicrob Agents*

Chemother 2009;53(4):1567–1573.

76. van Duin D, Bonomo RACeftazidime/Avibactam and Ceftolozane/Tazobactam: Second-generation β-Lactam/β-Lactamase inhibitor combinations. Clin Infect Dis. 2016;63(2):234–241.
77. Naber KG. Management of bacterial prostatitis: What's new? *BJU Int* 2008;101(Suppl 3):710.
78. Gleckman R, Crowley M, Natsios GA. Therapy of recurrent invasive urinary-tract infections of men. *N Engl J Med*. 1979;301(16):878–880.
79. Lipsky BA. Urinary tract infections in men. Epidemiology, pathophysiology, diagnosis, and treatment. *Ann Intern Med* 1989;110(2):138–150.
80. Whiteside SA, Razvi H, Dave S, et al.The microbiome of the urinary tract: A role beyond infection. *Nat Rev Urol*. 2015;12(2):81–90.
81. O'Brien VP, Hannan TJ, Schaeffer AJ, Hultgren SJ. Are you experienced? Understanding bladder innate immunity in the context of recurrent urinary tract infection *Curr Opin Infect Dis*. 2015;28(1):97–105.
82. Geerlings SE, Beerepoot MA and Prins JM. Prevention of recurrent urinary tract infections in women: Antimicrobial and nonantimicrobial strategies. *Infect Dis Clin North Am* 2014;28(1):135–147.
83. Lichtenberger P, Hooton TM. Antimicrobial prophylaxis in women with recurrent urinary tract infections. *Int J Antimicrob Agents*. 2011;38(Suppl 36-41):doi: 10.1016/j.ijantimicag.2011.09.005.
84. Lee BS, Bhuta T, Simpson JM, Craig JC. Methenamine hippurate for preventing urinary tract infections. *Cochrane Database Syst Rev*. 2012;10:CD003265. doi: 10.1002/14651858.CD003265.pub3.
85. Renard J, Ballarini S, Mascarenhas T, et al. Recurrent lower urinary tract infections have a detrimental effect on patient quality of life: A prospective, observational study. *Infect Dis Ther.* 2015;Mar; 4(1):125–135.
86. Macejko AM, Schaeffer AJ. Asymptomatic bacteriuria and symptomatic urinary tract infections during pregnancy. *Urol Clin North Am*. 2007;34(1):35–42.
87. Christensen B. Which antibiotics are appropriate for treating bacteriuria in pregnancy? *J Antimicrob Chemother*. 2000;46(Suppl 1):29–34.
88. McDermott S, Daguise V, Mann H, et al. Perinatal risk for mortality and mental retardation associated with maternal urinary-tract infections. *J Fam Pract* 2001;50(5):433–437.

89. Schneeberger C, Geerlings SE, Middleton P, Crowther CA. Interventions for preventing recurrent urinary tract infection during pregnancy. *Cochrane Database Syst Rev*. 2012;11:CD009279. doi: 10.1002/14651858.CD009279.pub2.
90. Saint S, Meddings JA, Calfee D, et al. Catheter-associated urinary tract infection and the medicare rule changes. *Ann Intern Med* 2009;150(12):877–884.
91. Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 international clinical practice guidelines from the infectious diseases society of america. *Clin Infect Dis* 2010;50(5):625–663.
92. Ohkawa M, Sugata T, Sawaki M, et al.Bacterial and crystal adherence to the surfaces of indwelling urethral catheters. *J Urol* 1990;143(4):717–721.
93. Johnson JR, Kuskowski MA, Wilt TJ. Systematic review: Antimicrobial urinary catheters to prevent catheter-associated urinary tract infection in hospitalized patients. *Ann Intern Med*. 2006;144(2):116–126.
94. Kostakioti M, Hadjifrangiskou M, Hultgren SJ. Bacterial biofilms: Development, dispersal, and therapeutic strategies in the dawn of the postantibiotic era. *Cold Spring Harb Perspect Med*. 2013;3(4):a010306.
95. Murphy AB, Macejko A, Taylor A, Nadler RB. Chronic prostatitis: Management strategies. *Drugs*. 2009;69(1):71–84.
96. Sharp VJ, Takacs EB, Powell CR. Prostatitis: Diagnosis and treatment. *Am Fam Physician*. 2010;82(4):397–406.
97. Lipsky BA, Byren I, Hoey CT. Treatment of bacterial prostatitis. *Clin Infect Dis*. 2010;50(12):1641–1652.
98. Fair WR, Couch J, Wehner N. Prostatic antibacterial factor. Identity and significance. *Urology*. 1976;7(2):169–177.
99. Pfau A, Perlberg S, Shapira A. The pH of the prostatic fluid in health and disease: Implications of treatment in chronic bacterial prostatitis. *J Urol*. 1978;119(3):384–387.
100. Wagenlehner FM, Naber KG. Current challenges in the treatment of complicated urinary tract infections and prostatitis. *Clin Microbiol Infect*. 2006;12(Suppl 3):67–80.

135

Sexually Transmitted Infections

Bryson Duhon and Yvonne Burnett

KEY CONCEPTS

1. Due to drug resistance, gonococcal infections are becoming increasingly difficult to treat. Dual therapy, with ceftriaxone and azithromycin or doxycycline, is recommended to improve treatment efficacy and slow the emergence and spread of resistance. Coinfections with chlamydia are common, for which azithromycin and doxycycline are also effective.
2. Parenteral penicillin is the treatment of choice for all syphilis infections. For penicillin-allergic, few well-studied alternative agents are available, and most require prolonged courses of oral medications to be effective. Patient compliance, and thus efficacy, are a concern when alternative regimens must be used.
3. Chlamydia genital tract infections represent the most frequently reported communicable disease in the United States. In females, these infections are frequently asymptomatic or minimally symptomatic and, if left untreated, are associated with the development of pelvic inflammatory disease and attendant complications such as ectopic pregnancy and infertility. As a result, all sexually active females younger than 25 years and sexually active women with multiple sexual partners should be screened annually for this infection.
4. Oral acyclovir, famciclovir, and valacyclovir are effective in reducing viral shedding, duration of symptoms, and time to healing of first-episode genital herpes infections, with maximal benefits seen when therapy is initiated at the earliest stages of infection. Patient-initiated, episodic antiviral therapy started within 1 day of lesion onset or during the prodrome preceding an outbreak offers an alternative to continuous suppressive therapy of recurrent infection in some individuals.
5. Metronidazole and tinidazole are the only agents currently approved in the

United States to treat trichomoniasis. A single 2-g dose of either agent is recommended, but should be avoided for treating recurrent infections.

Preclass Engaged Learning Activity

View the following links that focus on the rise of STIs and importance of collecting a sexual history / understanding at-risk populations:

https://tinyurl.com/yyneho33
https://tinyurl.com/y35qgavq
https://tinyurl.com/l6nhyw2

INTRODUCTION

The spectrum of sexually transmitted infections (STIs) has broadened from the classic venereal diseases—gonorrhea, syphilis, chancroid, lymphogranuloma venereum, and granuloma inguinale—to include a variety of pathogens (**Table 135-1**). Because of the large number of infected individuals, diversity of clinical manifestations, changing drug-susceptibility patterns of some pathogens, and high frequency of multiple STIs occurring simultaneously in infected individuals, the diagnosis and management of patients with STIs are more complex than ever before.[3,4] Approximately 20 million new infections occur annually in the United States, with a total prevalence of 110 million infections resulting in a total medical cost of $16 billion to the US healthcare system.[1,2]

TABLE 135-1 Sexually Transmitted Diseases

Disease	Associated Pathogens
Bacterial	
Gonorrhea	*Neisseria gonorrhoeae*
Syphilis	*Treponema pallidum*
Chancroid	*Haemophilus ducreyi*
Granuloma inguinale	*Calymmatobacterium granulomatis*
Enteric disease	*Salmonella* spp., *Shigella* spp., *Campylobacter* fetus
Campylobacter infection	*Campylobacter jejuni*
Bacterial vaginosis	*Gardnerella vaginalis, Mycoplasma hominis, Bacteroides* spp., *Mobiluncus* spp.
Group B streptococcal infections	Group B *Streptococcus*
Chlamydial	
Nongonococcal urethritis	*Chlamydia trachomatis*
Lymphogranuloma venereum	*C. trachomatis*, type L
Viral	
Acquired immunodeficiency syndrome	Human immunodeficiency virus
Herpes genitalis	Herpes simplex virus, types I and II
Viral hepatitis	Hepatitis A, B, C, and D viruses
Condylomata acuminata	Human papillomavirus
Molluscum contagiosum	Poxvirus
Cytomegalovirus infection	Cytomegalovirus
Mycoplasmal	
Nongonococcal urethritis	*Mycoplasma genitalium*
Protozoal	
Trichomoniasis	*Trichomonas vaginalis*
Amebiasis	*Entamoeba histolytica*
Giardiasis	*Giardia lamblia*
Fungal	
Vaginal candidiasis	*Candida albicans*
Parasitic	
Scabies	*Sarcoptes scabiei*
Pediculosis pubis	*Phthirus pubis*
Enterobiasis	*Enterobius vermicularis*

Although the annual number of new infections is roughly equal between genders, STI complications generally are more frequent and severe in women.[1] In particular, serious effects on maternal and infant health during pregnancy are well documented including damage to reproductive organs, increased risk of cancer, complications associated with pregnancy, and transmission of disease to the fetus or newborn.[3] As a result of the physiologic, psychosocial, and economic consequences of STIs, and because of the increasing prevalence of some viral STIs, such as human immunodeficiency virus (HIV) and genital herpes, for which curative therapy is not available, there is continuing research into STIs and the primary prevention of these diseases.[4,5]

With the exception of HIV infection, which is reviewed in detail in Chapter 143, Human Immunodeficiency Virus, the most frequently occurring STIs in the United States are discussed in this chapter. For other less common STIs, only recommended treatment regimens are presented. The most current information on the epidemiology, diagnosis, and treatment of STIs provided by the US Centers for Disease Control and Prevention (CDC) can be obtained at the CDC Website (http://www.cdc.gov).

Numerous interrelated factors contribute to the epidemic nature of STIs. Sociocultural, demographic, and economic factors, together with patterns of sexual behavior, host susceptibility to infection, changing properties of the causative pathogens, disease transmission by asymptomatic individuals, and environmental factors, are important determinants of the frequency and distribution of STIs in the United States and worldwide.

Age is one of the most important demographic determinants of STI incidence. Approximately half of all new STI cases each year occur among persons in their teens and twenties, the peak years of sexual activity. With increasing age, the incidence of most STIs decreases exponentially. STI rates are highest in ages 20 to 24, likely correlated with a peak in casual sexual behaviour.[4,6]

Age-specific rates of STIs are historically higher in men than in women; however, reported rates may not represent true gender differences, but rather may reflect greater ease of detection in men. In recent years, the ratio of male-to-female cases for most STIs has declined, and in some cases reversed, possibly reflecting improvements in the diagnosis of STIs in asymptomatic women or changes in female sexual behavior following the availability of improved methods of contraception. Although some racial disparity exists for rates of STI infection, it is possible that this is a reflection of socioeconomic differences.[1,3,4]

The single greatest risk factor for contracting STIs is the number of sexual

partners. As the number of sexual partners increases, the risk of being exposed to someone infected with an STI increases. Sexual preference also plays a major role in STI transmission. For all major STIs, rates are disproportionately greater in men who have sex with men (MSM) than in heterosexuals. In addition, prostitution and illicit drug use are associated with a higher incidence of most STIs.[3,4]

Some of the most serious sequelae of STIs are associated with congenital or perinatal infections. Most neonatal infections are acquired at birth, after infant's passage through an infected cervix or vagina. Neonatal *Chlamydia trachomatis* (*C. trachomatis*), *Neisseria gonorrhoeae (N. gonorrhoeae),* and herpes simplex virus (HSV) infections are associated with this type of spread. For pregnant women with syphilis, infection is usually transmitted transplacentally, producing a congenital infection. Depending on the organism, neonatal infections can manifest in a variety of ways, produce significant morbidity, and in some cases result in infant death.[3,4]

Other than complete abstinence, the most effective way to prevent STI transmission is by maintaining a mutually monogamous sexual relationship between uninfected partners. Short of this, use of barrier contraceptive methods, such as the male and female condoms, diaphragm, cervical cap, vaginal sponges, and vaginal spermicides alone or in combination, provides varying degrees of protection from a number of STIs. When used correctly and consistently, male latex condoms with or without spermicide are more effective than natural skin condoms in protecting against STI transmission, including HIV, gonorrhea, chlamydia, trichomoniasis, HSV, and human papillomavirus (HPV). When lubrication is desired with latex condoms, water-based products, such as K-Y jelly, are recommended because oil-based agents (eg, petroleum jelly) can weaken latex condoms and reduce their effectiveness. For latex-allergic individuals, other synthetic condoms (eg, polyurethane) appear to possess efficacy against STI transmission similar to latex condoms. The female condom is a lubricated polyurethane sheath with a diaphragm-like ring on each end that can be used as a protective device for women with male sexual partners who do not desire to use a condom. Limited data suggest that the female condom blocks penetration of viruses, including HIV; for nonviral STIs, the female condom provides STI protection similar to the male condom.[3] Diaphragms may protect against cervical gonorrheal, chlamydial, and trichomonal infections. At one time, based in large part on in vitro and animal data, use of nonoxynol-9, a cytolytic vaginal spermicide, was advocated to reduce the transmissibility of several STIs. However, nonoxynol-9 does not reduce the risk of transmission of common

STIs, and may actually increase the risk of HIV transmission and development of bacterial urinary tract infections. Preexposure vaccination for HPV is recommended in specific adolescent age groups for prevention of transmission.[3,7]

The varied spectrum of clinical syndromes produced by common STIs is determined not only by the etiologic pathogen(s) but also by differences in male and female anatomy and reproductive physiology. For a number of STIs, the signs and symptoms overlap sufficiently to prevent accurate diagnosis without microbiologic confirmation. Frequently, symptoms are minimal or absent despite the presence of infection. **Table 135-2** lists common clinical syndromes associated with STIs.[3,4]

TABLE 135-2 Selected Syndromes Associated with Common Sexually Transmitted Pathogens

Syndrome	Commonly Implicated Pathogens	Common Clinical Manifestations[a]
Urethritis	*C. trachomatis*, herpes simplex virus, *N. gonorrhoeae*, *Trichomonas vaginalis*, *Ureaplasma Mycoplasma genitalium*	Urethral discharge, dysuria
Epididymitis	*C. trachomatis*, *N. gonorrhoeae*	Scrotal pain, inguinal pain, flank pain, urethral discharge
Cervicitis/ vulvovaginitis	*C. trachomatis*, *Gardnerella vaginalis*, herpes simplex virus, human papillomavirus, *N. gonorrhoeae*, *T. vaginalis*	Abnormal vaginal discharge, vulvar itching/irritation, dysuria, dyspareunia
Genital ulcers (painful)	*Haemophilus ducreyi*, herpes simplex virus	Usually multiple vesicular/ pustular (herpes) or papular/pustular (*H. ducreyi*) lesions that can coalesce; painful, tender lymphadenopathy[b]
Genital ulcers (painless)	*Treponema pallidum*	Usually single papular lesion
Genital/anal warts	Human papillomavirus	Multiple lesions ranging in size from small papular warts to large exophytic condylomas
Pharyngitis	*C. trachomatis*, herpes simplex virus, *N. gonorrhoeae*	Symptoms of acute pharyngitis, cervical lymphadenopathy, fever[c]
Proctitis	*C. trachomatis*, herpes simplex virus, *N. gonorrhoeae*, *T. pallidum*	Constipation, anorectal discomfort, tenesmus, mucopurulent rectal discharge
Salpingitis	*C. trachomatis*, *N. gonorrhoeae*	Lower abdominal pain, purulent cervical or vaginal discharge, adnexal swelling, fever[d]

[a]For some syndromes, clinical manifestations can be minimal or absent.

[b]Recurrent herpes infection can manifest as a single lesion.

[c]Most cases of pharyngeal gonococcal infection are asymptomatic.

[d]Salpingitis increases the risk of subsequent ectopic pregnancy and infertility.

GONORRHEA

Epidemiology and Etiology

Gonorrhea is the second commonly reported notifiable disease in the United States.[3,8] Since the mid-1990s, rates of reported cases in the United States remained relatively stable. However, in the past decade, rates of infection have increased. In 2016, 478,514 new cases of gonorrhea were reported at a rate of 146 cases per 100,000 persons, representing a 48.6% increase from the record low number of 98.1 cases per 100,000 persons in 2009.[8] Of growing concern are the substantial number of infections that remain undiagnosed and unreported, thereby perpetuating the spread of disease.[1,8] The highest rates of infections are seen in adolescents and young adults and have also been associated with Black race, lower socioeconomic status, lesser education, being unmarried, illicit drug use, and residence in the southeastern United States.[8]

The gram-negative diplococcus, *N. gonorrhoeae*, is the causative organism of gonorrhea infections. In 2013, the CDC identified drug-resistant *N. gonorrhoeae* as one of the top three pathogens presenting an urgent level threat, as it poses an immediate health threat requiring urgent and aggressive action.[9] Additionally the World Health Organization (WHO) listed drug-resistant *N. gonorrhoeae* as a high priority for new antibiotic development.[10] This is because *N. gonorrhoeae* has progressively developed resistance to all antibiotics used to treat it. Due to the increasing incidence of resistance, large numbers of infected individuals with asymptomatic disease, and ease of transmission, gonorrhea is difficult to control. Additionally, HIV infection is more easily transmitted in patients coinfected with gonorrhea.[3,9–12]

Pathophysiology

N. gonorrhoeae does not have any animal or environmental reservoirs and humans are the only known host. *N. gonorrhoeae* infects the mucosa of the urethra, endocervix, and, less commonly, the anorectum, pharynx, and conjunctiva. On contact with squamous epithelial cells, the gonococci attach to cell membranes via surface pili and are then pinocytosed. After mucosal damage is established, polymorphonuclear (PMN) leukocytes invade the tissue, submucosal abscesses form, and purulent exudates are secreted.[3,12,13]

Gonorrhea is highly transmissible via sexual contact. The risk of a female

acquiring a cervical infection after a single episode of vaginal intercourse with an infected male partner is 50% to 70%; however, the risk of female-to-male transmission following a single act of coitus is 20%.[14,15] With repeated exposure, the risk of female-to-male transmission increases to 60% to 80%.[14] No data are available on the rates of transmission after other types of sexual contact; however, transmission by anal intercourse is more efficient versus fellatio or cunnilingus.[12]

Clinical Presentation

Individuals infected with gonorrhea can be symptomatic or asymptomatic, have complicated or uncomplicated infections, and have infections involving several anatomic sites. Interestingly, most of the untreated symptomatic patients become asymptomatic within 6 months, with only a few becoming asymptomatic carriers of the disease.[3,11,12] In settings where sexually active women are routinely screened for subclinical infections, the majority of women diagnosed with gonorrhea are asymptomatic. Up to 50% of women experience nonspecific symptoms, including mucopurulent vaginal discharge and vaginal bleeding, especially following sexual intercourse. In comparison, 90% of males experience symptoms within 2 to 6 days following exposure, most commonly mucopurulent penile discharge and dysuria.[12,16] As such, the CDC recommends annual screening for those at highest risk of gonococcal infections, sexually active women under the age of 25.[3] The most common clinical features of gonococcal infections are presented in **Table 135-3**.

TABLE 135-3 Presentation of Gonorrhea Infections

	Males	Females
General	Incubation period: 1-14 days	Incubation period: 1-14 days
	Symptom onset in 2-8 days	Symptom onset in 10 days
Site of infection	Most common: urethra	Most common: endocervical canal
	Others: rectum (usually caused by rectal intercourse in MSM), oropharynx, eye	Others: urethra, rectum (usually caused by perineal contamination), oropharynx, eye
Symptoms	Commonly symptomatic, may be asymptomatic	Can be asymptomatic or minimally symptomatic
	Urethral infection: dysuria and urinary frequency	Endocervical infection: usually asymptomatic or mildly symptomatic
	Anorectal infection: asymptomatic to severe rectal pain	Urethral infection: dysuria, urinary frequency
	Pharyngeal infection: asymptomatic to mild pharyngitis	Anorectal and pharyngeal infection; symptoms same as for men
Signs	Purulent urethral or rectal discharge can be scant to profuse Anorectal: pruritus, mucopurulent discharge, bleeding	Abnormal vaginal discharge or uterine bleeding; purulent urethral or rectal discharge can be scant to profuse
Complications	Rare (epididymitis, prostatitis, inguinal lymphadenopathy, urethral stricture)	Pelvic inflammatory disease and associated complications (ie, ectopic pregnancy, infertility)
	Disseminated gonorrhea	Disseminated gonorrhea (three times more common than in men)

MSM, men who have sex with men.

Complications associated with untreated gonorrhea appear more pronounced in women, likely a result of a high percentage who experience nonspecific signs and symptoms or are minimally symptomatic. As a result, many women do not

seek treatment until after the development of serious complications, such as pelvic inflammatory disease (PID). Approximately 10% to 20% of women with gonorrhea develop PID.[12,17] Left untreated, PID can cause infertility and ectopic pregnancies. In 0.5% to 3% of patients with gonorrhea, the gonococci invade the bloodstream and result in disseminated disease.[12,18] Disseminated gonococcal infection (DGI) is three times more common in women than in men.[19] The usual clinical manifestations of DGI are tender necrotic skin lesions, tenosynovitis, and monoarticular arthritis. While very rare, DGI may also present as meningitis or endocarditis.[3,12,18,19]

Diagnosis

Obtaining a specific microbiologic diagnosis in all persons at risk for or are suspected to have gonorrhea is recommended to reduce complications, reinfections, and transmission.[3] Diagnosis of gonococcal infections can be made by Gram-stained smears, culture, or detection of cellular components (eg, enzymes, antigens, or DNA). Gram stains, the most widely used stain in clinical practice, are positive for gonococci when gram-negative diplococci are identified within PMN leukocytes.[3,12,20] In urethral specimens from men with symptomatic urethritis, a positive smear is diagnostic for infection. However, due to lower sensitivity, Gram-stained smears are not recommended in the diagnosis of endocervical, rectal, cutaneous, and asymptomatic male urethral infections. Because of the presence of nonpathogenic *Neisseria* spp. in the pharynx, the Gram stain is not useful in the diagnosis of pharyngeal infection.[3,12]

Although culture is highly sensitive and specific, limitations, including prolonged turnaround times and difficulty maintaining viable samples, preclude widespread usage. Additionally, culture requires invasive specimen collection for processing (endocervical or urethral swab). As a result, direct culture is primarily utilized in cases of suspected or documented treatment failures, as a test of cure (TOC) following use of alternative treatment regimens, or for detection of rectal, oropharyngeal, and conjunctival gonococcal infections.[3]

Nucleic acid amplification techniques (NAATs) have replaced culture in most settings as the primary diagnostic test for gonorrhea infections and when screening for asymptomatic infections. NAATs offer increased sensitivity and/or specificity over traditional diagnostic methods and provide a more rapid means of diagnosis than culture.[3,20,21] Of particular clinical importance is the high sensitivity of NAATs for detecting *N. gonorrhoeae* using noninvasive specimens (eg, self-collected urine specimens, vaginal swabs). NAAT is recommended by

the CDC for detection of gonorrhea in FDA-cleared specimen types specific to each NAAT manufacturer.[3] This technology is also being used to concurrently test for *C. trachomatis* using a single specimen.[20,21] A major drawback of NAATs is their inability to provide resistance data on isolated gonococcal strains. In cases of documented treatment failure, culture and antimicrobial susceptibility testing is recommended.[3,20]

TREATMENT

As mentioned previously, *N. gonorrhoeae* has developed resistance to all antibiotics previously used to treat it, including sulfonamides, penicillins, tetracyclines, fluoroquinolones, and early generation macrolides and cephalosporins.[22–28] In 2010, the CDC issued an update to their recommended treatment regimens for gonorrhea, eliminating oral cephalosporins due to increasing resistance. Single-dose intramuscular (IM) ceftriaxone remains the only recommended agent for treating gonorrhea as ceftriaxone-based regimens are the only regimens with well-documented efficacy in the treatment of urethral, cervical, rectal, and pharyngeal infections, curing 99.2% of uncomplicated cases and 98.9% of pharyngeal cases[3,22] (**Table 135-4**). Ceftriaxone 250 mg should be administered IM in combination with a 1,000-mg single dose of oral azithromycin. Dual antibiotic therapy with different mechanisms of action is recommended in an effort to delay further development of antimicrobial resistance and increase treatment efficacy.[3,26] Additionally, coexisting chlamydial infections, documented in up to 50% of women and 20% of men with gonorrhea, constitute a major cause of postgonococcal urethritis, cervicitis, and salpingitis in patients treated for gonorrhea for whom concurrent chlamydial infection has not been ruled out.[3,29] For presumed or diagnosed concurrent *C. trachomatis* infection, azithromycin, administered as a component of dual therapy for gonorrhea, is the preferred treatment.[3,12]

TABLE 135-4 Treatment of Gonorrhea

Type of Infection	Recommended Regimens[a]	Alternative Regimens[a]
Uncomplicated infections of the cervix, urethra, and rectum in adults	Ceftriaxone 250 mg IM once *plus* Azithromycin 1 g orally once	Cefixime 400 mg orally once *plus* Azithromycin 1 g orally once, or doxycycline 100 mg PO twice daily for 7 days[b,c] *or* Gemifloxacin 320 mg orally once or gentamicin 240 mg IM[d] *plus* Azithromycin 2 g orally once
Uncomplicated infections of the pharynx	Ceftriaxone 250 mg IM once *plus* Azithromycin 1 g orally once	Consult with infectious disease expert
Disseminated gonococcal infection in adults (>45 kg)	Ceftriaxone 1-2 g IM or IV every 12-24 hours[d] *plus* Azithromycin 1 g orally once	Cefotaxime 1 g IV every 8 hours[d] or ceftizoxime 1 g IV every 8 hours[d] *plus* Azithromycin 1 g orally once
Uncomplicated infections of the cervix, urethra, pharynx, and rectum in children (<45 kg)	Ceftriaxone 25-50 mg/kg IV or IM once (not to exceed 125 mg)	
Disseminated gonococcal infection in children (<45 kg)	Ceftriaxone 50 mg/kg IV or IM once daily (not to exceed 1 g)	
Gonococcal conjunctivitis in adults	Ceftriaxone 1 g IM once[e]	
Ophthalmia neonatorum	Ceftriaxone 25-50 mg/kg IV or IM once (not to exceed 125 mg)	
Disseminated gonococcal infection in neonates	Ceftriaxone 25-50 mg/kg/day IV or IM once daily or cefotaxime 25 mg/kg IV or IM twice daily for 7 days, or 10-14 days if meningitis is suspected[f]	
Infants born to mothers with gonococcal infection (prophylaxis)	Erythromycin (0.5%) ophthalmic ointment in a single application[g] Ceftriaxone 25-50 mg/kg IM or IV once (not to exceed 125 mg)	

[a]Recommendations are those of the CDC.

[b]Tetracyclines are contraindicated during pregnancy. Pregnant women should be treated with recommended cephalosporin-based combination therapy. In severe cephalosporin allergy, consultation with an infectious diseases expert is recommended.

[d]Parenteral treatment duration should be determined in consultation with an infectious diseases expert. Parenteral therapy for meningitis should be continued for at least 10-14 days and at least 4 weeks in endocarditis.

[e]A single lavage of the infected eye with normal saline should be considered; empiric therapy for *C. trachomatis* is recommended.

[g]Efficacy in preventing chlamydial ophthalmia is unclear.

CDC, Centers for Disease Control and Prevention; *C. trachomatis*, *Chlamydia trachomatis*; NAAT, Nucleic Acid Amplification Test; *N. gonorrhoeae*, *Neisseria gonorrhoeae*.

[h]Patients who are treatment failures with alternative regimens should be treated with ceftriaxone 250 mg IM once plus azithromycin 1 g PO once in consultation with an infectious disease expert.

[f]For patients with severe cephalosporin allergy.

[c]Caution should be taken when administering ceftriaxone to hyperbilirubinemic neonates.

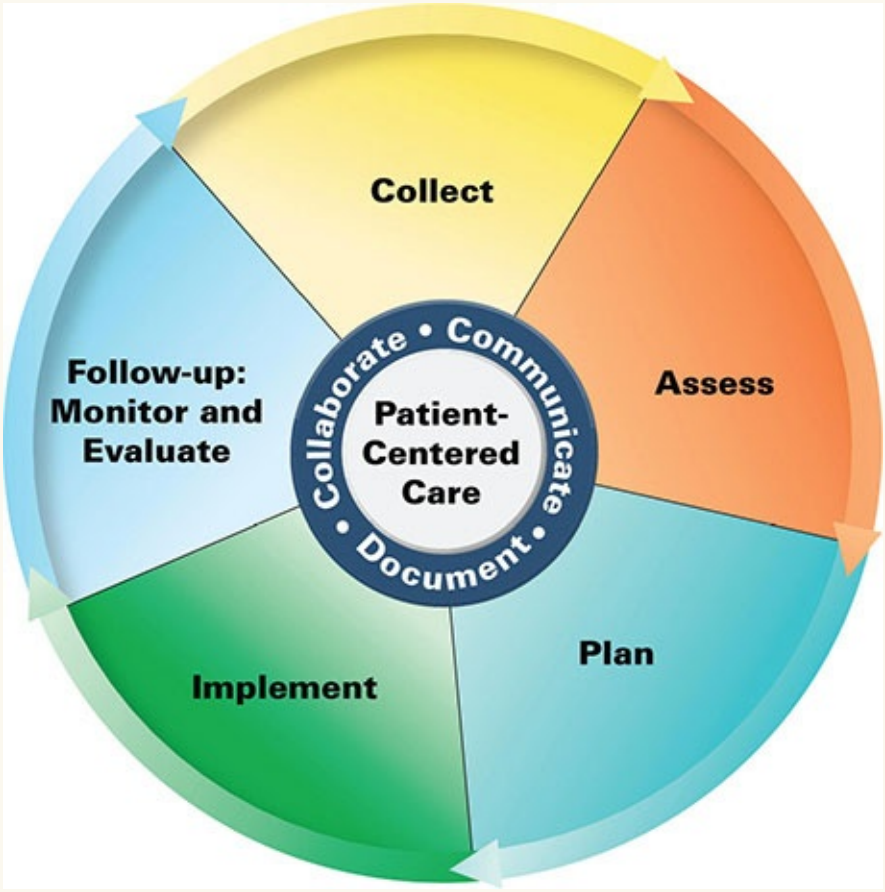
A 400-mg oral dose of cefixime may be substituted if ceftriaxone is unavailable, but due to reduced bactericidal levels and efficacy, 97.5% cure rate in uncomplicated cases and 92.3% in pharyngeal infections, compared to ceftriaxone, this regimen is not preferred. Additionally, only ceftriaxone is effective in treating pharyngeal gonorrhea as oral cephalosporins do not reliably cure these infections.[3,12,21]

Azithromycin 1,000 mg given orally as a one-time dose is preferred to doxycycline due to advantages of single-dose therapy and increased gonococcal resistance to tetracyclines. Doxycycline 100 mg orally twice a day may be used in cases of azithromycin allergy.[3] Alternative therapies can be used in cephalosporin-allergic individuals. While azithromycin (2 g) as a single dose appears highly effective in eradicating both gonorrhea and chlamydia, it is not recommended as a preferred alternative to ceftriaxone due to concerns regarding the development of resistance.[3,23–26] Single-dose regimens consisting of oral gemifloxacin or IM gentamicin, in combination with azithromycin, were associated with high cure rates (99.5% and 100%, respectively); however, high rates gastrointestinal (GI) side effects may limit their applicability.[3,12,30] More recently there are reports that increasing *N. gonorrhoeae* isolates with decreased ceftriaxone-susceptibility and azithromycin resistance may require higher doses of current antibiotics or utilization of alternate therapies.[24,25] Ongoing trials are investigating vaccine development and alternative agents, including aminoglycosides, eravacycline, tigecycline, and fosfomycin, to combat resistant gonococcal infections.[27,28,31]

Ceftriaxone is the recommended therapy for DGI, including meningitis and endocarditis, and any type of gonococcal infection in children. In cases of DGI, patients should be hospitalized and treated with ceftriaxone or one of the alternative parenteral cephalosporin antibiotics (see Table 135-4). Although marked improvement is usually noted within 48 hours of initiating therapy, treatment should be continued for at least 7 days, with longer durations necessary for serious infections, such as meningitis and endocarditis.[3,12] Gonococcal ophthalmia is highly contagious in adults and neonates and requires ceftriaxone therapy. Single, but higher, dose therapy is adequate for gonococcal conjunctivitis, although some physicians recommend continuing therapy until cultures are negative at 48 to 72 hours. Topical antibiotics are not effective when used alone for ocular infections and are unnecessary with appropriate systemic therapy. Infants with any evidence of ocular infection should be evaluated for signs of DGI.[3,12,32]

Treatment of gonorrhea during pregnancy is essential to prevent ophthalmia

neonatorum. Pregnant women infected with *N. gonorrhoeae* should be treated with ceftriaxone. Gonococcal infection in newborns results primarily from passage through an infected birth canal, but may be transmitted in utero. Conjunctival involvement, characterized by intense, bilateral conjunctival inflammation with chemosis, usually develops within 7 days of delivery. If not treated promptly, corneal ulceration and blindness can develop. Because the law in most states requires neonatal prophylaxis with topical ocular antimicrobials, gonococcal ophthalmia neonatorum is rare in the United States. The CDC recommends that erythromycin (0.5%) ophthalmic ointment be instilled in each conjunctival sac immediately postpartum.[3,12,32]



Patient Care Process for Genital Infection due to *Neisseria gonorrhoeae*

Collect

- Patient characteristics (eg, age, sex, pregnant)
- Patient medical history (personal and family)
- Social history, including sexual history
- Current medications
- Objective data
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight
  - Laboratory data including urine NAATs for gonorrhea and chlamydia, and/or urethral or vaginal cultures
  - Signs and symptoms consistent with gonorrhea (dysuria, mucopurulent urethral or vagina discharge)

Assess

- Presence of additional STIs (chlamydia, syphilis, HIV, etc.)
- Presence of extra-genital infection
- Ability/willingness to obtain follow-up testing as needed
- Ability/willingness to notify sexual partners
- Emotional status (eg, presence of anxiety, depression)

Plan

- Drug therapy regimen including, dose, route, frequency, and duration (Table 135-4)
- Monitoring parameters including efficacy (eg, retest 3 months after treatment) and safety, frequency and timing of follow-up
- Patient education (eg, purpose of treatment, notification of sexual partners, safe sexual practices, drug-specific information)
- Self-monitoring for resolution of gonorrhea symptoms, and if not resolved to seek follow-up for reevaluation
- Referrals to other providers when appropriate (eg, HIV care, behavioral health)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (eg, retest 3 months after treatment)
- Offer expedited partner therapy for patient's sexual partner(s) and partner education

Follow-up: Monitor and Evaluate

- Resolution of symptoms (eg, dysuria, mucopurulent urinary or vaginal discharge); in absence of symptom resolution after treatment, assess for resistance by obtaining culture and susceptibilities
- Presence of adverse effects (eg, rash or gastrointestinal upset)
- Patient adherence to treatment plan
- Reevaluation of laboratory tests in specific time frames (eg, retest 3 months for retest)

**Collaborate with patient, caregivers, and other healthcare professionals.*

Recent sex partners (within 60 days of preceding onset of symptoms or diagnosis) should be referred for evaluation and treatment. Unfortunately, less than half of partners present for evaluation. In order to reduce reinfection rates, the CDC supports expedited partner therapy (EPT), or the treatment of sexual partners of those infected with gonorrhea and chlamydial without first examining these partners.[3] This is particularly useful in cases when the patient's partner is unwilling to seek medical care. More information regarding participating states, laws, and regulations can be found at http://www.cdc.gov/std/ept. Patients, and sex partners, should abstain from unprotected sexual intercourse for 7 days after both have completed treatment and symptoms have resolved.[3]

Evaluation of Therapeutic Outcomes

Persistence of gonorrhea symptoms following treatment with a recommended regimen may indicate reinfection rather than treatment failure, reflecting the need for improved patient education and sex partner referral. However,

reinfection can no longer be assumed due to increased rates of drug resistance and subsequent treatment failure. As a result, the CDC recommends that all apparent treatment failures be assessed using culture and sensitivity testing. Persistence of symptoms may also be due to other infectious causes, such as *C. trachomatis*.[3,12]

While the CDC does not recommend a TOC for patients with uncomplicated urogenital or rectal gonorrhea treated with a recommended or alternative regimen, it is recommended that any patient treated for pharyngeal gonorrhea with an alternate regimen return 14 days after treatment for a TOC. The TOC test may be either culture or NAAT; however, if the NAAT is positive, a confirmatory culture should be obtained prior to retreatment. Antimicrobial susceptibilities should be obtained for all TOC positive cultures. Patients who require retreatment should be tested for cure 7 to 14 days following the second regimen. Additionally, all patients who have received treatment for gonorrhea should be retested 3 months after treatment, or when the patient next presents for medical care in the following 12 months.[3]

SYPHILIS

Epidemiology and Etiology

Although nearly eradicated in 2000, cases of syphilis have increased 18% in the United States from 2000 to 2016, with an annual total of primary and secondary syphilis diagnoses of around 16,000. Although the rise of newly diagnosed cases are primarily attributed to male cases, a majority of whom identified as MSM, a 36% increase was observed in women during the years 2015 to 2016. In addition to being highly contagious, syphilis is of major concern because, if left untreated, can progress to a fatal or seriously disabling chronic systemic disease. Syphilis is usually acquired by sexual contact with infected mucous membranes or cutaneous lesions, although on rare occasions it may be acquired by nonsexual personal contact, accidental inoculation, or blood transfusion. The causative organism of syphilis is *Treponema pallidum* (*T. pallidum*), a spirochete. The large majority of cases are acquired via sexual contact, with 30% to 50% of sexual contacts of persons with syphilis acquiring infection. After sexual contact, the organism penetrates the intact mucous membrane or a break in the cornified epithelium, and spirochetemia occurs.[3,33,34]

Rates of coinfection with HIV have remained high, particularly in MSM. Syphilis, similar to other sexually transmitted genital ulcer diseases, can increase

the risk of acquiring HIV in exposed individuals. In addition, immunologic defects in HIV-infected individuals can produce an atypical serologic response to syphilis. In particular, the possibility of delayed seroreactivity, markedly elevated serologic titers, and increased false-positive results could complicate the diagnosis, as well as assessment of treatment efficacy in HIV-positive individuals infected with syphilis. As a result of this association, the CDC recommends that all patients diagnosed with syphilis be tested for HIV infection.[3,34]

Clinical Presentation

The clinical presentation of syphilis is varied with progression through multiple stages possible in untreated or inadequately treated patients (**Table 135-5**).

TABLE 135-5 Presentation of Syphilis Infections

General	
Primary	Incubation period: 10-90 days (mean, 21 days)
Secondary	Develops 2-8 weeks after initial infection in untreated or inadequately treated individuals
Latent	Develops 4-10 weeks after secondary stage in untreated or inadequately treated individuals
Tertiary	Develops in approximately 30% of untreated or inadequately treated individuals 10-30 years after initial infection
Site of Infection	
Primary	External genitalia, perianal region, mouth, and throat
Secondary	Multisystem involvement secondary to hematogenous and lymphatic spread
Latent tertiary	Potentially multisystem involvement (dormant)
	CNS, heart, eyes, bones, and joints
Signs and Symptoms	
Primary	Single, painless, indurated lesion (chancre) that erodes, ulcerates, and eventually heals (typical); regional lymphadenopathy is common; multiple, painful, purulent lesions possible but uncommon
Secondary	Pruritic or nonpruritic rash, mucocutaneous lesions, flu-like symptoms, lymphadenopathy
Latent	Asymptomatic
Tertiary	Cardiovascular syphilis (aortitis or aortic insufficiency), neurosyphilis (meningitis, general paresis, dementia, tabes dorsalis, eighth cranial nerve deafness, blindness), gummatous lesions involving any organ or tissue

CNS, central nervous system.

Primary Syphilis

The primary stage, characterized by the appearance of a chancre on cutaneous or mucocutaneous tissue exposed to the organism, is highly infectious. Chancres heal within 4 to 6 weeks, although lymphadenopathy may persist longer. Because syphilitic chancres may be confused with other infectious etiologies, appropriate diagnostic testing is important.[34]

Secondary Syphilis

Often referred to as the “great imitator” due to its diverse differential diagnosis, the secondary stage of syphilis is characterized by a variety of mucocutaneous eruptions resulting from widespread hematogenous and lymphatic spread of *T. pallidum*. Skin lesions can be either generalized or localized to a small portion of the body. Additional nonspecific symptoms often accompany secondary syphilis, such as mild and transitory malaise, fever, pharyngitis, headache, anorexia, and lymphadenopathy. If untreated, secondary syphilis disappears spontaneously within 1 to 6 months.[34,35]

Latent Syphilis

By definition, persons with a positive serologic test for syphilis, but with no other evidence of disease, have latent syphilis. Latent syphilis is further divided into early and late latency. During early latency, due to a 25% risk of spontaneous mucocutaneous relapse, the patient is considered potentially infectious. The CDC defines early latency as 1 year from the onset of infection. With the exception of pregnancy, in which the mother can pass the disease to the fetus, late latency is considered noninfectious, although the patient remains a host.[3,34,35] Most untreated patients with late latent syphilis have no further sequelae; however, approximately 20% of patients progress either to neurosyphilis or to late syphilis with clinical manifestations other than neurosyphilis. Treatment of all patients with latent syphilis is essential as there is no way to predict which patients will experience disease progression.[3,34]

Tertiary Syphilis and Neurosyphilis

If left untreated, syphilis can slowly produce an inflammatory reaction in virtually any organ in the body. Manifestations of this disease progression were referred to previously as tertiary syphilis. These clinical manifestations now are differentiated into two subgroups based on the presence or absence of central nervous system (CNS) involvement: neurosyphilis or tertiary syphilis (ie, gumma and cardiovascular syphilis).[3,34] Currently, the term neurosyphilis encompasses any patient with cerebrospinal fluid (CSF) abnormalities consistent with CNS infection. Approximately 40% of patients with primary or secondary syphilis exhibit such abnormalities, although most remain asymptomatic. Manifestations of neurosyphilis can occur at any stage of infection, although symptoms vary depending on the timing of onset. Most investigators suggest that HIV-infected patients are at greater risk of developing symptomatic

neurosyphilis than patients with intact immune systems.[3,34] Rarely seen, the most common manifestations of disease progression from late latency are benign gumma formation and cardiovascular syphilis. The gumma, a nonspecific granulomatous lesion, is the classic lesion of late syphilis and can infiltrate any organ or tissue. Gummas of critical organs, such as the heart or brain, can be fatal.[3,34,35]

Congenital Syphilis

In pregnant women with syphilis, *T. pallidum* can cross the placenta at any time during pregnancy. The risk of fetal infection is greatest in pregnant women with primary and secondary syphilis and declines in pregnant women with late disease. Transmission of syphilis during pregnancy occurs primarily transplacentally and can result in fetal death, prematurity, or congenital syphilis. Symptoms vary based on onset, with early congenital manifestations appearing from 2 weeks to 2 years, and late syphilis symptoms appearing after two years throughout adolescence. Manifestations of early congenital syphilis resemble those of secondary syphilis, whereas those of late congenital syphilis correspond to the tertiary stage in adults.[34,35]

Diagnosis

Because *T. pallidum* is difficult to culture in vitro, diagnosis is based primarily on microscopic examination of serous material from a suspected syphilitic lesion or results from serologic testing. In primary syphilis, diagnosis is established by the presence of *T. pallidum* on dark-field microscopic examination of material from cutaneous lesions and enlarged lymph nodes in patients with secondary syphilis. In incubating syphilis, confirmation frequently is by dark-field microscopic examination because serologic tests may be unreactive early in the disease.[3,34,36]

Serologic tests are the mainstay in the diagnosis of syphilis and traditionally are categorized as nontreponemal or treponemal. Common nontreponemal tests include the Venereal Disease Research Laboratory (VDRL) slide test, rapid plasma reagin (RPR) card test, unheated serum reagin (USR) test, and the toluidine red unheated serum test (TRUST). Nontreponemal tests, which are inexpensive and easily performed, rely on detection of treponemal antibodies. A positive nontreponemal test can indicate the presence of any stage of syphilis or congenital syphilis, although incubating syphilis and very early primary syphilis produce a negative reaction; however, because they are nonspecific tests, false-

positive reactions occur, making them inappropriate to confirm the diagnosis alone. Transiently false-positive results can be seen in patients with acute febrile illnesses, after immunizations, and during pregnancy. Chronic false-positive results are commonly associated with intravenous drug abuse, aging, chronic infections, autoimmune diseases, and malignant disease. In some cases, false-positive reactions are familial and are related to abnormal serum globulin levels. As such, patients with a positive nontreponemal test should always receive a treponemal test for diagnosis confirmation.[3,34,36]

Nontreponemal tests are used primarily as screening tests; however, because *T. pallidum* antibody titers can also be quantitated by testing serial dilutions of the patient's serum for reactivity, they are useful in following the progression of the disease, recovery after therapy, and possible reinfection. Because antibody titers vary to some extent between tests, it is important that sequential serologic testing be performed using the same method each time. In patients treated successfully for primary and secondary syphilis, nontreponemal tests usually decline over time and may return to seronegativity. In addition to their use in serologic testing, nontreponemal tests often are used on CSF to diagnose neurosyphilis.[3,34,36]

For HIV-positive individuals with syphilis, the reactivity of nontreponemal tests can vary depending on the stage of the HIV infection, and atypical results may occur. As a result, the diagnosis of syphilis in HIV-infected individuals can be more difficult. Additionally, CSF results in HIV-coinfected patients demonstrate significant differences as compared to non-coinfected comparisons (higher leukocyte counts, lower glucose counts).[3,34,36]

Use of only one serologic test for diagnosis of syphilis is insufficient as false-positives can occur in those without syphilis and false-negatives in those with primary syphilis. In diagnosing all stages of syphilis, treponemal tests are more sensitive than nontreponemal tests. Because these tests are technically more demanding and are more expensive, they have been used as confirmatory rather than as screening tests. However, patients with a positive treponemal test should have a nontreponemal test with titer reflexively drawn in order to guide management decisions and to monitor response to therapy. If the nontreponemal test is negative, a different treponemal test should be used to confirm the initial positive result. If a second treponemal test is positive, previously untreated patients should be offered treatment. Those with a previous history of treatment require no further management unless sexual history indicates likelihood of reexposure, in which case a repeat nontreponemal test is recommended in 2 to 4 weeks.[3,34,36]

For many years, the fluorescent treponemal antibody absorption (FTA-ABS) test was the most frequently used treponemal test. The FTA-ABS test uses the *T. pallidum* antigen to detect specific antibodies to treponemal organisms. However, the FTA-ABS test has largely been replaced by card assays such as the *T. pallidum* hemagglutination assay (TPHA), the microhemagglutination assay for antibodies to *T. pallidum* (MHA-TP), and the *T. pallidum* particle agglutination assay (TPPA) that are automated and less expensive to perform. Despite adequate antibiotic therapy for any stage of syphilis, treponemal tests remain reactive for life and therefore are not useful in assessing serologic response to therapy, relapse, or reinfection, hence the need for a reflex nontreponemal test.[3,34,36]

Several EIAs for *T. pallidum* have become available and are gaining wide use as confirmatory tests. Polymerase chain reaction (PCR)–based tests are also being investigated, particularly in situations in which serologic testing has poor sensitivity and specificity (eg, congenital syphilis, early primary syphilis, and neurosyphilis). Additionally, multiplex PCR tests that can identify the presence of *T. pallidum*, HSV-1 and HSV-2, and *Haemophilus ducreyi* (*H. ducreyi*) from genital ulcer specimens are under study.[3,34,36]

TREATMENT

Table 135-6 presents the CDC's treatment recommendations.[3] Parenteral penicillin G is the treatment of choice for all stages of syphilis. Because *T. pallidum* multiplies slowly, single doses of short- or intermediate-acting penicillins do not provide the prolonged, low-level exposure to penicillin required for treponeme eradication. As a result, benzathine penicillin G is the only penicillin effective for single-dose therapy.[3,34,35]

TABLE 135-6 Drug Therapy and Follow-up of Syphilis

Stage/Type of Syphilis	Recommended Regimens[a,b]	Follow-up Serology
Primary, secondary, or early latent syphilis (<1 year's duration)	Adults: Benzathine penicillin G 2.4 million units IM in a single dose Children: Benzathine penicillin G 50,000 units/kg IM in a single dose, up to 2.4 million units	Quantitative nontreponemal tests at 6 and 12 months for primary and secondary syphilis; at 6, 12, and 24 months for early latent syphilis[c]
Late latent syphilis (>1 year's duration) or latent syphilis of unknown duration or tertiary syphilis or retreatment	Adults: Benzathine penicillin G 2.4 million units IM once a week for 3 successive weeks (7.2 million units total) Children: Benzathine penicillin G 50,000 units/kg IM once a week for 3 successive weeks, up to 7.2 million units total	Quantitative nontreponemal tests at 6, 12, and 24 months[d,e]
Neurosyphilis	Aqueous crystalline penicillin G 18-24 million units IV (3-4 million units every 4 hours or by continuous infusion) for 10-14 days[f] *or* Aqueous procaine penicillin G 2.4 million units IM daily plus probenecid 500 mg orally four times daily, both for 10-14 days[f]	CSF examination every 6 months until the cell count is normal; if it has not decreased at 6 months or is not normal by 2 years, retreatment should be considered
Congenital syphilis (infants with proven or highly probable disease)	Aqueous crystalline penicillin G 50,000 units/kg/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days *or* Procaine penicillin G 50,000 units/kg IM daily for 10 days	Serologic follow-up only recommended if antimicrobials other than penicillin are used
Penicillin-Allergic Patients[g]		
Primary, secondary, or early latent syphilis	Doxycycline 100 mg orally two times daily for 14 days[g,h] *or* Tetracycline 500 mg orally four times daily for 14 days[h] *or* Ceftriaxone 1-2 g IM or IV daily for 10-14 days	Same as for non–penicillin-allergic patients
Late latent syphilis (>1 year's duration) or syphilis of unknown duration	Doxycycline 100 mg orally twice a day for 28 days[h,i] *or* Tetracycline 500 mg orally four times daily for 28 days[h,i]	Same as for non–penicillin-allergic patients

[a]Recommendations are those of the CDC.

[b]The CDC recommends that all patients diagnosed with syphilis be tested for HIV infection.

[c]More frequent follow-up (ie, 3, 6, 9, 12, and 24 months) recommended for HIV-infected patients.

[d]More frequent follow-up (ie, 6, 12, 18, and 24 months) recommended for HIV-infected patients.

[e]No specific recommendations exist for tertiary syphilis because of the lack of available data.

[f]Some experts administer benzathine penicillin G 2.4 million units IM once per week for up to 3 weeks after completion of the neurosyphilis regimens to provide a total duration of therapy comparable to that used for late syphilis in the absence of neurosyphilis.

[g]For nonpregnant patients; pregnant patients should be treated with penicillin after desensitization.

[h]Pregnant patients allergic to penicillin should be desensitized and treated with penicillin.

[i]Limited data suggest that ceftriaxone may be effective, although the optimal dosage and treatment duration are unclear.

CDC, Centers for Disease Control and Prevention; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus.

The recommended treatment for syphilis of less than 1 year's duration is

benzathine penicillin G 2.4 million units as a single IM dose. Although the relapse rate for this regimen is less than 3%, some investigators advocate that 2.4 million units be administered once a week for two consecutive weeks. In patients with late latent syphilis and normal CSF examination, benzathine penicillin G is administered weekly for three successive doses. Although not specifically recommended by the CDC, this three-dose regimen is used by some experts to treat HIV-infected patients with syphilis of less than 1 year's duration based on data suggesting a greater risk of treatment failure with single-dose therapy.[3,34,35]

Patients with abnormal CSF findings should be treated as neurosyphilis. Preferred regimens for neurosyphilis provide treatment over 10 to 14 days with 18 to 24 million units per day of parenteral penicillin G administered as 3 to 4 million units every 4 hours or by continuous infusion. Benzathine penicillin G alone in standard weekly doses and procaine penicillin G in doses under 2.4 million units do not consistently provide treponemicidal levels in the CSF, resulting in treatment failures. Because *T. pallidum* penicillin resistance has not emerged, the primary need for alternative drugs in treating syphilis is for penicillin-allergic patients.[3,34,35]

2 Alternative regimens recommended for penicillin-allergic patients are doxycycline 100 mg orally twice daily or tetracycline 500 mg orally four times daily for 2 to 4 weeks depending on the duration of syphilis infection. These regimens should be used only in cases of documented penicillin allergy and, given concerns regarding patient compliance with these regimens, follow-up serologic testing is particularly important.[3,34,35]

Various other beta-lactams have successfully treated syphilis; however, none offers significant advantages over benzathine penicillin G. Even though ceftriaxone is considered effective in eradicating incubating syphilis when given as a single 125-mg dose, higher doses and more frequent administration (eg, 1-2 g daily for 10-14 days) appear necessary for more advanced syphilis and treatment failures have been reported in HIV-infected patients. Although azithromycin 2 g as a single dose produces good results in patients with early syphilis, treatment failures and resistance to azithromycin are reported.[3,34,35]

For pregnant patients, penicillin is the treatment of choice at the dosage recommended for that particular stage of syphilis. To ensure treatment success and prevent transmission to the fetus, some experts advocate an additional IM dose of benzathine penicillin G 2.4 million units 1 week after completion of the recommended regimen. In women allergic to penicillin, safe and effective alternatives are not available; therefore, skin testing should be performed to confirm a penicillin allergy. It is recommended that women with positive skin

tests undergo penicillin desensitization and receive the appropriate treatment regimen for their stage of disease.[3,34,35]

Patients treated for primary and secondary syphilis may experience the Jarisch-Herxheimer reaction after treatment. This benign, self-limiting reaction is characterized by flu-like symptoms, such as transient headache, fever, chills, malaise, arthralgia, myalgia, tachypnea, peripheral vasodilation, and aggravation of syphilitic lesions. The exact mechanism of the reaction is unknown, although proposed etiologies, including immunologic mechanisms and release of endotoxin or other toxic treponemal products, are not substantiated. The Jarisch-Herxheimer reaction is independent of the drug and dose used and should not be confused with penicillin allergy. It usually begins within 2 to 4 hours of initiating therapy, peaks at 8 hours, and is complete within 12 to 24 hours. Most reactions can be managed symptomatically with analgesics, antipyretics, and rest. Steroids and antihistamines have been administered prior to initiation of syphilitic therapy, but are of limited value.[3,34,35]

Evaluation of Therapeutic Outcomes

Table 135-6 lists the CDC recommendations for serologic follow-up of patients treated for syphilis.[3] Quantitative nontreponemal tests should be performed at 6 and 12 months in all patients treated for primary and secondary syphilis and at 6, 12, and 24 months for early and late latent disease. Patients indicated for retreatment should receive three weekly treatments of IM 2.4 million units of benzathine penicillin G, unless neurosyphilis is present. The CDC recommends more frequent monitoring of HIV-infected individuals (ie, 3, 6, 9, 12, and 24 months after therapy). In general, the time to reach seronegativity is proportional to the duration of the disease. Table 135-6 also includes specific testing recommendations for other stages of syphilis. Despite adequate therapy, some patients can remain seropositive based on nontreponemal test results. In these cases, stabilization of low antibody titers is indicative of adequate therapy. For women treated during pregnancy, monthly quantitative nontreponemal tests are recommended in those at high risk of reinfection.[3,34]

CHLAMYDIA TRACHOMATIS

Epidemiology and Etiology

Based on CDC data, over 1.58 million cases of chlamydia infection were

reported in 2016, making it the most frequently reported infectious disease in the United States since 1994.[3,37] Since 2000, chlamydia has been a notifiable condition in all 50 states and infection rates have been on the rise. However, due to the silent nature of many infections, it is estimated that more than double the number of cases actually reported occur annually.[1] Left untreated, chlamydia infections can cause PID, infertility, ectopic pregnancy, and chronic pelvic pain.[3,37]

Chlamydia is more commonly reported in females, approximately two times the rate in males, reflective of a greater number of women screened. Similar to gonorrhea, higher rates of chlamydia infection have also been associated with younger age, Black race, and residency in the southeastern United States.[37] Additional predictors of chlamydia infections in young women include having a new or multiple sex partners, smoking, gonorrhea or bacterial vaginosis, and presence of carcinogenic HPV. Chlamydia is also a primary cause of nongonococcal urethritis (NGU), accounting for up to 50% of cases.[3,38–41]

The risk of transmissibility of chlamydia after exposure is not well described, but is believed to be less than that following exposure to *N. gonorrhoeae*. One study that extrapolated data from partner notification programs from discordant couples, estimated 39% risk of male-to-female and 32% female-to-male transmission.[42] Another modeling study estimated the rate of transmission per-act to be 10%, increasing to 55% with multiple encounters between sexual partners.[43] Coinfection with chlamydia occurs in a substantial number of individuals with gonorrhea and all individuals diagnosed with *N. gonorrhoeae* should be assumed to have *C. trachomatis* present, until chlamydial infection has been ruled out.[3] Chlamydial infections are associated with a significantly increased risk of acquiring HIV infection. In addition to genital infections, ocular infections in adults (owing to autoinoculation) and infants (owing to vaginal delivery through an infected birth canal) are reported. Pharyngeal and rectal infections may develop secondary to orogenital or receptive anal intercourse, respectively, with an infected individual.[3,38–41]

Pathophysiology

C. trachomatis is an obligate intracellular bacterium that exclusively infects humans. Like viruses, chlamydiae require cellular material from host cells for replication; however, they maintain their cellular identity throughout development. *C. trachomatis* shares a similar outer membrane and ribosomes to gram-negative bacteria, but lacks cell-wall peptidoglycan, and cannot be seen via

Gram staining.[38–41]

C. trachomatis has a complex two-stage life cycle, existing as two forms, the infectious elementary body (EB), and the replicating reticulate body (RB). The EB attaches and enters a host epithelial cell and transforms into the RB. The RB multiplies by binary fission, within an inclusion, hijacking cell components and nutrients. The RBs then reorganize back to EBs and are released into the extracellular space, to infect surrounding cells.[38,44]

Clinical Presentation

In comparison with gonorrhea, chlamydial genital tract infections are more frequently asymptomatic, and when present, symptoms tend to be less noticeable. Urethral discharge is usually less profuse and more mucoid or watery than that associated with gonorrhea.[38–41] Many cases of chlamydia in asymptomatic or minimally symptomatic women are only diagnosed as a result of screening. **Table 135-7** summarizes the usual clinical presentation of chlamydial infections.

TABLE 135-7 Presentation of Chlamydia Infections

	Males	Females
General	Incubation period: 35 days Symptom onset: 7-21 days	Incubation period: 7-35 days Usual symptom onset: 7-21 days
Site of infection	Most common: urethra Others: rectum (receptive anal intercourse), oropharynx, eye	Most common: endocervical canal Others: urethra, rectum (usually caused by perineal contamination), oropharynx, eye
Symptoms	More than 50% of urethral and rectal infections are asymptomatic Urethral infection: mild dysuria, discharge Pharyngeal infection: asymptomatic to mild pharyngitis	More than 66% of cervical infections are asymptomatic Urethral infection: usually subclinical; dysuria and frequency uncommon Rectal and pharyngeal infection: symptoms same as for men
Signs	Scant to profuse, mucoid to purulent urethral or rectal discharge Rectal infection: pain, discharge, bleeding	Abnormal vaginal discharge or uterine bleeding, purulent urethral or rectal discharge can be scant to profuse
Complications	Epididymitis, Reiter's syndrome (rare)	Pelvic inflammatory disease and associated complications (ie, ectopic pregnancy, infertility) Reiter's syndrome (rare)

Similar to gonorrhea, chlamydia can be transmitted to an infant during contact with infected cervicovaginal secretions. Nearly two-thirds of infants acquire chlamydial infection after endocervical exposure, with the primary morbidity associated with seeding of the infant's eyes, nasopharynx, rectum, or vagina. In exposed infants, neonatal conjunctivitis develops in as many as 50%, and pneumonia develops in up to 16%. Inclusion conjunctivitis in newborns is usually self-limited, but can result in scarring and micropannus of the cornea. Interstitial pneumonitis occurring secondary to carriage in the nasopharynx typically is mild, but it can be severe and require hospitalization.[3,38–41,45]

Diagnosis

3 Because of the high rate of asymptomatic disease and the high prevalence of chlamydial infection in sexually active females 25 years of age or younger and sexually active women with new sex partners or multiple sex partners, the CDC recommends routine annual screening in these individuals. Additionally, the CDC recommends routine, at least annually, chlamydia screening of genital and rectal sites in MSM populations. Laboratory confirmation of chlamydial infection is important because of the relative lack of symptom specificity when present.[3]

Cell culture is the reference standard against which all other diagnostic tests are measured. Because chlamydiae are obligate intracellular organisms, specimens for culture must be obtained from endocervical (women) or urethral (men) epithelial cell scrapings rather than from urine or urethral discharges. Although tissue culture techniques have close to 100% specificity, the sensitivity is as low as 70%. Because of the technical demands of specimen collection, transport, processing, expense, and prolonged time until results (3-7 days), culture is not widely used for diagnostic purposes. However, culture remains the diagnostic standard in medicolegal cases, such as sexual assault and child abuse, because of its high specificity and ability to detect only viable organisms.[3,38–41]

Molecular tests that detect chlamydial nucleic acid provide more rapid results, are technically less demanding to perform, less costly, and, in some situations, have greater sensitivity than culture.[3] NAATs, which can detect small amounts of chlamydial DNA, are highly sensitive and specific for detecting infection in urogenital and anal specimens, as well as in urine. NAATs are the most sensitive tests for first-catch urine, endocervix and vaginal swab specimens in women, and urethral swab specimens in men, and are therefore the recommended tests for detecting chlamydia infection.[3] Use of self-collected vaginal or anal specimens or first-void urine samples offers greater patient acceptability. A further advantage of urine screening tests is that up to 30% of women are reported to have urethral infection only, which would be missed using a test on endocervical samples. Because of NAATs' ability to detect as little as a single gene copy in a specimen, whether it is live or a nonviable organism, nucleic acid residues that persist following successful antibiotic therapy of a chlamydial infection can result in a false-positive test for several weeks following cure. Molecular tests that do not use nucleic amplification, such as enzyme immunosorbent assays or DNA hybridization probes, are no longer recommended for diagnosis of *C. trachomatis* because of their poor sensitivity in

comparison to NAATs.[3,38]

TREATMENT

Many antimicrobials, including tetracyclines, macrolides, and some fluoroquinolones, display good in vitro and in vivo activity against *C. trachomatis*. In most clinical trials, cure rates exceed 90% for these agents.[3,38–41]

Azithromycin 1,000 mg orally as a single-dose and doxycycline 100 mg orally twice daily for 7 days are the regimens of choice for the treatment of uncomplicated urogenital chlamydia infections(**Table 135-8**).[3] Because of its prolonged serum and tissue half-life, azithromycin is the only single-dose therapy effective in treating *C. trachomatis*. Both therapies clear over 97% of infections, but single-dose therapy with azithromycin is more attractive from a medication adherence standpoint. Delayed-release doxycycline, 200 mg orally once daily for 7 days, may be considered as an alternative regimen for urogenital *C. trachomatis* infections as it was as effective as generic doxycycline, associated with less GI side effects, but may be more expensive.[46] Of the fluoroquinolones, ofloxacin and levofloxacin are included in the CDC recommendations, but do not offer an advantage over first-line or alternative therapies. Although ciprofloxacin and some other fluoroquinolones have activity against *C. trachomatis*, high dosages have not consistently eradicated chlamydial infections.[3,38–41]

TABLE 135-8 Treatment of Chlamydia Infections

Infection	Recommended Regimens[a]	Alternative Regimen
Uncomplicated urethral, endocervical, or rectal infection in adults	Azithromycin 1 g orally once, or doxycycline 100 mg orally twice daily for 7 days	Erythromycin base 500 mg orally four times daily for 7 days, or erythromycin ethylsuccinate 800 mg orally four times daily for 7 days, or levofloxacin 500 mg orally once daily for 7 days, or ofloxacin 300 mg orally twice daily for 7 days
Urogenital infections during pregnancy	Azithromycin 1 g orally as a single dose or amoxicillin 500 mg orally three times daily for 7 days	Amoxicillin 500 mg orally three times daily for 7 days, or erythromycin base 500 mg orally four times daily for 7 days, or erythromycin base 250 mg orally four times daily for 14 days, or erythromycin ethylsuccinate 800 mg orally four times daily for 7 days, or erythromycin ethylsuccinate 400 mg orally four times daily for 14 days
Conjunctivitis of the newborn or pneumonia in infants	Erythromycin base or ethylsuccinate 50 mg/kg/day orally in four divided doses for 14 days[b,c]	Azithromycin suspension 20 mg/kg/day orally once daily for 3 days[c]

[a]Recommendations are those of the CDC.

[b]Topical therapy alone is inadequate for ophthalmia neonatorum and is unnecessary when systemic therapy is administered. Effectiveness of erythromycin treatment is approximately 80%; therefore, a second course of therapy may be required.

[c]An association between oral erythromycin and azithromycin and IHPS has been reported in infants aged <6 weeks. Infants treated with either of these antimicrobials should be followed for signs and symptoms of IHPS.

CDC, Centers for Disease Control and Prevention; IHPS, infantile hypertrophic pyloric stenosis.

Clinical significance of oropharyngeal *C. trachomatis* infections is unclear, but as it may be transmitted to genital sites of sex partners, treatment with a single dose of azithromycin 1,000 mg orally or doxycycline 100 mg twice daily

for seven days is warranted. For patients with known or suspected anorectal chlamydia infections, the WHO suggests using doxycycline 100 mg orally twice daily over azithromycin 1,000 mg orally as a single-dose, but the CDC does not yet endorse this recommendation due to lack of prospective trials for this indication.[47] As mentioned in the treatment of gonorrhea, sex partners of patients with *C. trachomatis* infections should be examined, tested for other STIs, and counseled on prevention. EPT may also be offered. Patients, and sex partners, should abstain from unprotected sexual intercourse for 7 days after both have completed treatment and symptoms have resolved.[3]

For infected pregnant women, treatment can significantly reduce the risk of pregnancy complications and newborn transmission. Because tetracyclines and fluoroquinolones are contraindicated during pregnancy, azithromycin is the recommended treatment (see Table 135-8). Due to concerns regarding persistence of chlamydia infections after exposure to penicillin-class antibiotics, amoxicillin is an alternative therapy only in pregnant women. When compliance with a multiday regimen is a concern, azithromycin is the preferred treatment in women, regardless of pregnancy status, and directly observed single-dose administration ensures adherence. It is recommended that TOC 3 to 4 weeks after completion be obtained for pregnant patients treated for chlamydial infections.[3,38–40]

C. trachomatis transmission during perinatal exposure can result in neonatal or infant infections of the eye, oropharynx, lungs, urogenital tract, and rectum. Despite efficacy in preventing gonococcal ophthalmia, topical erythromycin ointment (0.5%) appears less effective in preventing chlamydial ophthalmia and has no effect on nasal carriage or colonization, so the potential for other infections, including pneumonia, remains. Because of the high percentage of treatment failures, topical therapy is not recommended to treat ophthalmia caused by *C. trachomatis*. Instead, an oral erythromycin regimen is recommended.[3,38–40]

Evaluation of Therapeutic Outcomes

Treatment of chlamydial infections with the recommended regimens is highly effective; therefore, posttreatment laboratory testing for therapeutic failure is not recommended unless symptoms persist or there are specific concerns (eg, regimen nonadherence or pregnancy). However, due to high risk of reinfection, all patients who have been treated for chlamydia should be retested approximately 3 months after treatment. Posttreatment tests should not be

performed for at least 3 weeks following completion of therapy due to false positives with continued presence of nonviable organisms.[3] When posttreatment tests are positive, they usually represent noncompliance, failure to treat sexual partners, or laboratory error rather than inadequate therapy or resistance. Infants with pneumonitis should receive follow-up testing, and sometimes subsequent courses of therapy, because erythromycin is only 80% effective.[3,38–40]

GENITAL HERPES

Epidemiology and Etiology

Genital herpes infections represent the most common cause of genital ulceration in the United States. More than 50 million Americans have genital herpes, a number increasing by at least 750,000 each year.[1,3] Because of its morbidity, recurrent nature, and potential for complications, as well as its ability to be transmitted asymptomatically, genital herpes is of major public health importance. Of note, the CDC does not recommend screening for HSV in the general population.[3] Similar to syphilis and other STDs, the presence of genital herpes lesions is associated with an increased risk of acquiring HIV following exposure.[3,48,49]

Pathophysiology

HSV-1 and 2 are two members of the Herpesvirus family. HSV-1 is associated most commonly with oropharyngeal disease, whereas HSV-2 is associated most closely with genital disease; however, each virus is capable of causing clinically indistinguishable infections in both anatomic areas. Humans are the sole known reservoir for HSV. Infection is transmitted via inoculation of virus from infected secretions onto mucosal surfaces (eg, urethra, oropharynx, cervix, and conjunctivae) or through abraded skin.[3,48,49]

The cycle of HSV infection occurs in five stages: primary mucocutaneous infection, ganglia infection, establishment of latency, reactivation, and recurrent infection. After gaining entry into the cell, transportation and replication occurs via viral spread from peripheral sensory nerves to contiguous cells and ganglia. Latency then is established in sensory or autonomic nerve root ganglia. Latency appears to be lifelong, interrupted only by reactivation of the viral infection. It is unclear what factors are important in maintaining latency, but immune responses and emotional and physical stress appear important in reactivating latent

virus.[48,50]

Clinical Presentation

The signs and symptoms of genital herpes infection are influenced by many factors, including previous exposure to HSV, viral type, and host factors, such as age and site of infection. Because a high percentage of initial and recurrent infections are asymptomatic, and because viral shedding can occur in the absence of apparent lesions or symptoms, identification and education of individuals with genital herpes are essential in controlling its transmission.[3,48–50] A summary of the clinical presentation of genital herpes is provided in **Table 135-9**.

TABLE 135-9 Presentation of Genital Herpes Infections

General	Incubation period: 2-14 days (mean, 4 days) Can be caused by either HSV-1 or HSV-2
Classification of infection	
First-episode primary	Initial genital infection in individuals lacking antibody to either HSV-1 or HSV-2
First-episode nonprimary	Initial genital infection in individuals with clinical or serologic evidence of prior HSV (usually HSV-1) infection
Recurrent	Appearance of genital lesions at some time following healing of first-episode infection
Signs and symptoms	
First-episode infections	Most primary infections are asymptomatic or minimally symptomatic Multiple painful pustular or ulcerative lesions on external genitalia developing over a period of 7-10 days; lesions heal in 2-4 weeks (mean, 21 days) Flu-like symptoms (eg, fever, headache, malaise) during first few days after appearance of lesions Others—local itching, pain, or discomfort; vaginal or urethral discharge, tender inguinal adenopathy, paresthesias, urinary retention Severity of symptoms greater in females than in males Symptoms are less severe (eg, fewer lesions, more rapid lesion healing, fewer or milder systemic symptoms) with nonprimary infections Symptoms more severe and prolonged in the immunocompromised On average viral shedding lasts approximately 11-12 days for primary infections and 7 days for nonprimary infections
Recurrent	Prodrome seen in approximately 50% of patients prior to appearance of recurrent lesions; mild burning, itching, or tingling are typical prodromal symptoms Compared to primary infections, recurrent infections associated with (1) fewer lesions that are more localized, (2) shorter duration of active infection (lesions heal within 7 days), and (3) milder symptoms Severity of symptoms greater in females than in males Symptoms more severe and prolonged in the immunocompromised On average viral shedding lasts approximately 4 days Asymptomatic viral shedding is more frequent during the first year after infection with HSV
Therapeutic implications of HSV-1 vs HSV-2 genital infection	Primary infections caused by HSV-1 and HSV-2 virtually indistinguishable Recurrent infections and subclinical viral shedding are less frequent with HSV-1 Recurrent infections with HSV-2 tend to be more severe
Complications	Secondary infection of lesions; extragenital infection because of autoinoculation; disseminated infection (primarily in immunocompromised patients); meningitis or encephalitis; neonatal transmission

HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2.

Complications

Complications from genital herpes infections result from both genital spread and autoinoculation of the virus and occur most commonly with primary first episodes. Lesions at extragenital sites, such as the eye, rectum, pharynx, and fingers, are not uncommon. CNS involvement is seen occasionally and can take several forms, including encephalitis, aseptic meningitis, and transverse myelitis.[48]

A major concern is the effect of genital herpes on neonates exposed during pregnancy. Neonatal herpes is associated with a high mortality and significant morbidity. It is transmitted to the newborn primarily through exposure to HSV in the birth canal but, in rare cases, also is transmitted transplacentally. The risk of transmission during birth appears much greater for first-episode primary infections than for recurrent infections. Neonatal herpes infection has a case-fatality rate of approximately 50%, with a large proportion of surviving infants experiencing significant morbidity, including permanent neurologic damage.[3,48,51]

Diagnosis

Confirmation of genital herpes infection can be made only with laboratory testing. Tissue culture is the most specific (100%) and sensitive method (80%-90%) of confirming the diagnosis of first-episode genital herpes; however, culture is relatively insensitive in detecting HSV in ulcers in the latter stages of healing and in recurrent infections, in part due to reduced viral load. Viral culture is expensive, time-consuming, and improper collection or transport of specimens can result in false-negative results. In most situations, HSV isolation from tissue culture takes 48 to 96 hours. Following isolation, it is recommended that typing of the virus be performed because of prognostic implications. HSV-1 is associated with a lower rate of asymptomatic and symptomatic recurrence, while HSV-2 is characterized by more frequent recurrences and subclinical shedding. Amplified culture techniques that combine cell culture for 24 hours and subsequent staining for HSV antigen have sensitivities and specificities only slightly less than those of culture.[3,49]

PCR assays that detect HSV DNA and differentiate HSV-1 and HSV-2 infections are more sensitive than culture and are considered the diagnostic test of choice for suspected CNS infections (ie, HSV encephalitis or meningitis). PCR assays are highly sensitive in detecting asymptomatic viral shedding.[3,48,50]

Several serologic tests capable of distinguishing HSV-1 and HSV-2 antibodies are available and detect antibodies to type-specific HSV-1 and HSV-2 proteins gG-1 and gG-2, respectively. Although antibody formation begins immediately following a primary herpes infection, complete seroconversion can take several months, resulting in false negatives during early stages of infection. Given the high prevalence of HSV-1 antibody in the adult population, accurate interpretation of positive results is not possible. Since nearly all HSV-2 infections are sexually acquired, presence of HSV-2 antibodies should direct

clinicians to provide STI education and counseling.[3,48]

Although the diagnosis of genital herpes can be confirmed only by laboratory tests, less stringent diagnostic criteria (eg, characteristic physical findings or clinical history) are frequently used in clinical practice. A presumptive diagnosis of genital herpes is commonly made based on the presence of dark-field-negative, vesicular, or ulcerative genital lesions. A history of similar lesions or recent sexual contact with an individual with similar lesions also is useful in making the diagnosis.

TREATMENT

Management goals for genital herpes include symptom relief and reducing the clinical course to prevent complications and recurrences and to minimize disease transmission. The CDC recommended treatments for genital herpes include the antiviral agents acyclovir, valacyclovir, and famciclovir (**Table 135-10**).[3] The overall efficacy of these agents is comparable, although patient compliance can be improved with less frequent dosing regimens.[3]

TABLE 135-10 Treatment of Genital Herpes

Type of Infection	Recommended Regimens[a,b]	Alternative Regimen
First clinical episode of genital herpes[c]	Acyclovir 400 mg orally three times daily for 7-10 days,[d] *or* Acyclovir 200 mg orally five times daily for 7-10 days,[d] *or* Famciclovir 250 mg orally three times daily for 7-10 days,[d] *or* Valacyclovir 1 g orally twice daily for 7-10 days[d]	Acyclovir 5-10 mg/kg IV every 8 hours for 2-7 days or until clinical improvement occurs, followed by oral therapy to complete at least 10 days of total therapy[e]
Recurrent infection		
Episodic therapy	Acyclovir 400 mg orally three times daily for 5 days,[f] *or* Acyclovir 800 mg orally twice daily for 5 days,[f] *or* Acyclovir 800 mg orally three times daily for 2 days,[f] *or* Famciclovir 125 mg orally twice daily for 5 days,[f] *or* Famciclovir 1 g orally twice daily for 1 day,[f] *or* Famciclovir 500 mg orally once, followed by 250 mg orally twice daily for 2 days,[f] *or* Valacyclovir 500 mg orally twice daily for 3 days,[f] *or* Valacyclovir 1 g orally once daily for 5 days[f]	
Suppressive therapy[g]	Acyclovir 400 mg orally twice daily, *or* Famciclovir 250 mg orally twice daily,[h] *or* Valacyclovir 500 mg or 1,000 mg orally once dailyi	

CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus; IV, intravenous.

[a]Recommendations are those of the CDC.

[b]HIV-infected patients can require more aggressive therapy.

[c]Primary or nonprimary first episode.

[d]Treatment duration can be extended if healing is incomplete after 10 days.

[e]Only for patients with severe symptoms or complications that necessitate hospitalization. HSV encephalitis requires 21 days of IV therapy.

[f]Requires initiation of therapy within 24 hours of lesion onset or during the prodrome that precedes some outbreaks.

[g]Consider discontinuation of treatment after one year to assess frequency of recurrence.

[h]Famcicolvir appears less effective for suppression of viral shedding.

[i]Valacyclovir 500 mg appears less effective than other valacyclovir and acyclovir regimens in patients with 10 or more recurrences per year.

First-Episode Infections

4 Oral formulations of acyclovir, famciclovir, and valacyclovir have demonstrated efficacy in reducing viral shedding, duration of symptoms, and time to healing of first-episode genital herpes infections, with maximal benefits seen when therapy is initiated at the earliest stages of infection. Table 135-10 lists the recommended regimens for first-episode infections. The CDC recommends that all patients with first episodes of genital herpes receive systemic antiviral therapy to prevent severe or prolonged symptoms associated

with newly acquired genital herpes. Additionally, topical antiviral therapy offers minimal clinical benefit and is not recommended. In immunocompromised patients, or those with severe symptoms or complications necessitating hospitalization, parenteral acyclovir is recommended, but has been associated with renal, GI, bone marrow, and CNS toxicity, particularly in patients with renal dysfunction receiving high doses. No antiviral regimen is known to prevent latency or alter the subsequent frequency and severity of recurrences in humans.[3,48–50]

Recurrent Infections

There are two approaches to management of recurrent episodes: episodic or chronic suppressive therapy. Episodic therapy is initiated early during the course of the recurrence, preferably within 6 to 12 hours of the onset of prodromal symptoms, but no more than 24 hours after the appearance of lesions. Patients should be instructed to initiate treatment immediately when symptoms begin. In most patients, appreciable effects on symptomatology are not seen. Patients with prolonged episodes of recurrent infection or severe symptomatology are most likely to benefit from episodic therapy. One concern with episodic therapy is that some patients continue to shed virus despite the absence of lesions or presence of prodromal symptoms. Because of the relative mildness and brevity of recurrent infections, parenteral administration of acyclovir usually is not justifiable.[3,48–50]

Table 135-10 lists the recommended suppressive regimens. Suppressive therapy with recommended antivirals reduces the frequency and severity of recurrences in 70% to 80% of patients experiencing frequent recurrences. Furthermore, many patients with frequent recurrences experience an improved quality of life with suppressive therapy as compared to episodic therapy. Asymptomatic viral shedding is markedly reduced in patients receiving suppressive therapy; however, the extent to which suppresive therapy decreases disease transmission to sexual partners remains to be determined. Despite antiviral suppressive therapy, low-level virus shedding still occurs. However, this virus shedding may be less than that seen in patients treated episodically for recurrences, and thus may be associated with a lower risk of disease transmission. Because the frequency of recurrences tends to diminish over time, periodic “drug holidays” are advocated to assess changes in the underlying recurrence rate and determine if continued suppressive therapy is warranted.[3,48–50]

Resistant HSV isolates have been identified in some patients experiencing breakthrough recurrences while taking acyclovir. Acyclovir-resistant strains are also resistant to valacyclovir, and, commonly, famciclovir as in vitro resistance to these three agents usually is mediated by alterations in viral thymidine kinase. Although there is concern about the development of resistant strains with suppressive therapy, clinical trials have found no evidence of cumulative toxicity or significant resistance in patients treated continuously with the recommended antivirals. Foscarnet or cidofovir are therapies reserved for treatment of acyclovir-resistant strains.[3,48–50]

Selected Populations

Immunocompromised patients are at greatest risk for severe and recurrent HSV infections. Acyclovir, valacyclovir, and famciclovir have been used to prevent reactivation of infection in patients seropositive for HSV who undergo transplantation procedures or induction chemotherapy for acute leukemia. Immunocompromised individuals, such as patients with acquired immunodeficiency syndrome (AIDS), who fail treatment or prophylaxis with recommended antiviral doses frequently demonstrate improved response with higher doses. If resistance is suspected or confirmed with recommended first-line antivirals, foscarnet is usually effective. However, foscarnet is associated with a greater risk of serious adverse effects. Intravenous cidofovir or topical imiquimod may be effective alternatives to forscarnet. Lesional application of an extemporaneous compounded cidofovir (1%) gel or trifluridine ophthalmic solution appears to offer some benefits.[3,50,51]

The safety of famciclovir and valacyclovir during pregnancy is not well established, although experience with both agents in animal studies suggests a low risk of fetal harm. Acyclovir has been used in pregnant patients and has produced no evidence of teratogenicity. However, levels in amniotic fluid are similar to infants treated with acyclovir, of which 20% develop neutropenia. Because of the high maternal and infant morbidity associated with first-episode primary genital infections or severe recurrent infections at or near term, many clinicians advocate the use of systemic acyclovir as the standard of care in such cases.[3,51,52]

Evaluation of Therapeutic Outcomes

Available antiviral compounds are of greatest benefit in patients with HSV

infections; however, these agents are palliative and not curative, and patients should be monitored closely for adverse drug effects. CDC guidelines suggest that discontinuation of suppressive therapy after 1 year should be considered to assess for possible changes in the patient's intrinsic pattern of recurrence. In many patients, decreases in recurrence rates and the severity of symptoms occur over time. However, some clinicians prefer to continue suppressive therapy indefinitely because it significantly reduces asymptomatic viral shedding, reducing the risk of disease transmission to uninfected sexual partners.[3]

TRICHOMONIASIS

Epidemiology and Etiology

Trichomonas vaginalis (*T. vaginalis*), a flagellated, motile protozoan, is responsible for 3 to 4 million cases of trichomoniasis annually in the United States, and represents the most prevalent nonviral sexually transmitted infection. Although infection by nonsexual contact is reported, it is rare. Contamination of inanimate objects and spread of infection via communal bathing or contact with infected bath or toilet articles is possible because *T. vaginalis* can survive for up to 3 hours in a wet environment. Neonatal infections also represent another possible nonvenereal route of disease transmission. Coinfection with other STIs is not unusual, and the inflammatory response produced by trichomoniasis may increase the risk of acquiring HIV by two- to threefold.[3,53,54]

Pathophysiology

Trichomonads typically infect the squamous epithelium of the genital tract. Extragenital sites are epidemiologically important because infection can persist and result in reinfection. After attachment to the vaginal or urethral mucosa, trichomonads usually elicit an inflammatory response that manifests as a discharge containing large numbers of PMNs.[54,55]

Clinical Presentation

Trichomonal infections are reported more commonly in women than in men. Most patients experience minimal or no symptoms, with untreated infections lasting years. If symptoms do occur, they typically manifest as urethral discharge and dysuria.[3,54] The clinical presentation of trichomoniasis in males and females

is presented in Table 135-11.

TABLE 135-11 Presentation of Trichomonas Infections

	Males	Females
General	Incubation period: 3-28 days Organism can be detectable within 48 hours after exposure to infected partner	Incubation period: 3-28 days
Site of infection	Most common: urethra Others: rectum (usually caused by rectal intercourse in MSM), oropharynx, eye	Most common: endocervical canal Others: urethra, rectum (usually caused by perineal contamination), oropharynx, eye
Symptoms	Can be asymptomatic (more common in males than females) or minimally symptomatic Urethral discharge (clear to mucopurulent) Dysuria, pruritus	Can be asymptomatic or minimally symptomatic Scant to copious, typically malodorous vaginal discharge (50%-75%) and pruritus (worse during menses) Dysuria, dyspareunia
Signs	Urethral discharge	Vaginal discharge Vaginal pH 4.5-6 Inflammation/erythema of vulva, vagina, and/or cervix Urethritis
Complications	Epididymitis and chronic prostatitis (uncommon) Male infertility (decreased sperm motility and viability)	Pelvic inflammatory disease and associated complications (ie, ectopic pregnancy, infertility) Premature labor, premature rupture of membranes, and low-birth-weight infants (risk of neonatal infections is low) Cervical neoplasia

MSM, men who have sex with men.

Diagnosis

T. vaginalis produces nonspecific symptoms consistent with bacterial vaginosis; as a result, laboratory diagnosis is required. Because *T. vaginalis* requires a pH range of 4.9 to 7.5 for survival, a vaginal discharge pH of greater than 5 usually indicates the presence of either *T. vaginalis* or *Gardnerella vaginalis*, a common cause of bacterial vaginosis. The simplest means of diagnosis is a wet-mount examination of the vaginal discharge. Trichomoniasis is confirmed if characteristic pear-shaped, flagellating organisms are observed. However, the wet mount is only 51% to 65% sensitive in detecting the presence of trichomonads, with lower sensitivities reported in men and in women with low-grade, subacute, or chronic infections.[3,53–55]

Presence of trichomonads may be reported on a Papanicolaou smear (Pap), but the sensitivity of this technique is less than for wet mount and also is associated with a high number of false-positive and false-negative results. Stained smears of cervical specimens have been used in diagnosis, but are less sensitive and more time-consuming than the wet mount and, therefore, not recommended. Culture techniques for trichomonads are highly specific up to 100% and more sensitive, 75% to 96% than the wet mount, but they are not useful in rapid diagnosis, as 48 hours or longer is necessary for growth. Cultures may be necessary, however, to confirm the diagnosis in the absence of a positive wet mount or to determine antimicrobial susceptibility in intractable cases.[3,53–55]

Newer diagnostic tests, such as monoclonal antibody or DNA probe techniques, as well as PCR tests that can detect small amounts of trichomonal DNA, are now available. These office-based tests are highly sensitive and specific for detecting infection in both vaginal specimens and urine and are now the CDC recommended tests for detecting *T. vaginalis*.[3,53–55]

In males, detection of trichomonads in urethral specimens or urine sediment by wet mount is difficult, and diagnosis depends largely on culture. Specimens from males should be taken prior to first voiding because the small number of trichomonads in males may be reduced by micturition.[3,53–55]

TREATMENT

5 Recommended and alternative treatment regimens for *T. vaginalis* include either metronidazole or tinidazole, both of which produce high cure rates. In only a few cases have *T. vaginalis* isolates been resistant to standard metronidazole or tinidazole doses. In these instances, longer courses of

therapy, or doses higher than those recommended routinely as initial therapy, usually produce a cure.[3,53–55]

Table 135-12 provides treatment recommendations for trichomonas infections.[3] The standard therapy for trichomoniasis is either metronidazole or tinidazole 2 g orally as a single-dose; cure rates are comparable with the recommended alternative regimen of metronidazole 500 mg twice daily for 7 days. When sexual partners are treated simultaneously, cure rates greater than 95% are reported. If sexual partners are not treated concurrently, cure rates are somewhat lower. In limited clinical testing, single metronidazole doses of less than 1.5 g are associated with high failure rates.[3,53–55]

TABLE 135-12 Treatment of Trichomoniasis

Type	Recommended Regimen[a]	Alternative Regimen
Symptomatic and asymptomatic infections	Metronidazole 2 g orally in a single dose *or* Tinidazole 2 g orally in a single dose[b]	Metronidazole 500 mg orally two times daily for 7 days[c,d]
Persistent or recurrent infections	Metronidazole 500 mg orally two times daily for 7 days[c]	Metronidazole 2 g orally for 7 days[e] *or* Tinidazole 2 g orally for 7 dayse
Treatment in pregnancy	Metronidazole 2 g orally in a single dose[e]	

CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus.

[a]Recommendations are those of the CDC.

[b]Randomized controlled trials comparing single 2 g doses of metronidazole and tinidazole suggest that tinidazole is equivalent to, or superior to, metronidazole in achieving parasitologic cure and resolution of symptoms.

[c]Metronidazole labeling approved by the FDA does not include this regimen. Dosage regimens for treatment of trichomoniasis included in the product labeling are the single 2 g dose; 250 mg three times daily for 7 days; and 375 mg twice daily for 7 days. The 250-mg and 375-mg dosage regimens are currently not included in the CDC recommendations.

[d]Recommended treatment regimen for women with HIV coinfection.

[e]For treatment failures with metronidazole 2 g as a single dose and metronidazole 500 mg orally two times daily for 7 days.

[f]Symptomatic pregnant women can be treated with this regimen at any stage of pregnancy.

Advantages of single-dose therapy over the multi-dose alternative regimen

include better patient compliance, lower total dose, lower cost, and shorter exposure of the patient's GI and urogenital anaerobic bacterial flora to the drug. GI complaints are more common with the single 2 g dose of either metronidazole or tinidazole and some patients also complain of a bitter metallic taste in the mouth with metronidazole. Patients intolerant of the single 2-g dose because of GI adverse effects usually tolerate the alternative metronidazole multi-dose regimen.[53,55]

To achieve maximal cure rates and prevent relapse, simultaneous treatment of infected sexual partners is necessary. Tinidazole is at least equivalent, or potentially superior, to metronidazole in achieving microbiologic and clinical cure.[56] In women treated with the alternative 7-day course, however, relapse rates are not appreciably different regardless of whether or not sexual partners are treated. It is speculated that in men, spontaneous resolution of trichomonal infection or a reduction in the number of trichomonads below the inoculum necessary to transmit disease may occur during the 7 days of a female's therapy. The 7-day metronidazole treatment regimen is also recommended in women coinfected with HIV and may be more effective than a single 2-g dose in these patients.[57] In patients who fail to respond to an initial course of metronidazole therapy, a second course of therapy with metronidazole 500 mg twice daily for 7 days or a single 2 g dose of tinidazole is recommended. Patients refractory to a second course of treatment usually respond to a 2 g daily 7 day regimen of either agent. Topical vaginal therapy alone is associated with low cure rates because infections involving the urethra or periurethral glands are unaffected and can serve as the source of reinfection. Sexual partners of all patients who require retreatment also should be treated or retreated because the majority of apparent treatment failures appear to be caused by reinfection or noncompliance.[53,55–57]

Concerns regarding the use of metronidazole in breast-feeding or pregnant women have been raised. Because metronidazole is secreted in breast milk, it is recommended that breast-feeding be interrupted for 12 to 24 hours after maternal ingestion of a single 2-g dose. Metronidazole (pregnancy category B) and tinidazole (pregnancy category C) are contraindicated during the first trimester of pregnancy based on FDA-approved labeling. Although some experts recommend avoiding use of either agent throughout pregnancy, others advocate the use of metronidazole during any stage of pregnancy because of the potential adverse pregnancy outcomes associated with trichomoniasis. The CDC now recommends that all symptomatic pregnant women, regardless of pregnancy stage, be tested and considered for treatment.[3,53]

EVALUATION OF THERAPEUTIC OUTCOMES

Follow-up was previously considered unnecessary in patients who become asymptomatic after treatment with recommended therapy; however, retesting is now recommended for all sexually active women within 3 months following initial treatment due to the high rates of reinfection. When patients remain symptomatic, it is important to determine if reinfection has occurred. In these cases, a repeat course of therapy, as well as identification and treatment or retreatment of infected sexual partners, is recommended. In situations where reinfection can be excluded, a relative resistance to metronidazole or tinidazole should be assumed, and an alternative regimen prescribed. Culture and sensitivity are warranted for infections unresponsive to alternative regimens.[3]

HUMAN PAPILLOMAVIRUS INFECTIONS

Epidemiology and Etiology

It is estimated that there are 14.1 million new genital HPV infections in the United States each year.[3,4] However, as HPV is not a reportable condition, the incidence is likely much higher. Over 40% of women have evidence of HPV infection, with incidence peaking in teens and early twenties, aligning with initiation of sexual activity.[58] Additionally, lifetime risk of acquiring an HPV infection is over 80%, and risk increases with number of sexual partners.[59] Since the introduction of the HPV vaccine, incidence of HPV infections in teen girls and women in their early twenties have decreased. Persistent infection with some HPV types can cause genital warts and cancer, and reinfection is common, especially in the young, sexually active population.[3,58–61]

More than 125 HPV types have been characterized by genomic makeup, over 40 of which are associated with genital tract lesions.[58,59] Of these, types 6 and 11 are associated most commonly with the development of low-grade dysplasia manifested as genital warts. Infection with several HPV types, particularly HPV-16 and HPV-18, have been associated with cervical neoplasma, the second most common cancer in women worldwide.[3,58] HPV-16 and 18 account for approximately 66% of cervical cancers in the United States.[58] The WHO estimates that 84% of HPV lesions are represented as cervical cancers worldwide.[62] Persistent carriers of oncogenic HPV strains, in combination with a variety of other factors including immunosuppression, smoking, chlamydial

infection, may all play a role in promotion of viral persistence and cancer.[60]

Pathophysiology

HPV is a double-stranded DNA virus that targets basal cells. It enters the cell through a break in the epithelium, and replicates within the basal cell as it differentiates and progresses to the surface of the epithelium. Complete virions are assembled and shed with the dead keratinocyte. Infection is then transmitted via contact with the virus, either within the dead keratinocyte or free virions. In a wart, viral replication is associated with excessive proliferation of all of the epidermal layers, except the basal layer, whereas malignant HPV disease is associated with proliferation of basal cells.[60,63] HPV is transmitted by sexual intercourse, including oral sex, and may also be spread by touching an infected partner's genitalia.

Clinical Presentation

In most individuals, genital infection with HPV is subclinical and self-limited, clearing within 6 to 9 months. HPV can infect genitalia of both women and men, as well as the perianal, anal, and oropharynx regions in both genders. Approximately 1% of all infected individuals will develop genital warts. When present, genital warts can be large and multifocal, producing variable degrees of discomfort. Appearance of genital warts may differ based on gender and anatomic site. For example, penile warts may be slightly raised with a rough pigmented surface, while vulvar warts are usually soft and whitish. Based on HPV DNA detection methods, most warts will regress spontaneously within 1 to 2 years of their initial appearance. HPV, while known for the link to cervical cancer, can also cause cancer of the anus, penis, vulva, vagina, and oropharynx, but are less common.[3,60]

Diagnosis

The Pap smear is the most frequently used and cost-effective diagnostic test for detecting clinical and subclinical HPV in women. However, Pap smears are neither specific for HPV nor useful in detecting latent infections. Various tests for detecting HPV DNA, RNA, or capsid protein also are available, and unlike the Pap smear do not require subjective interpretation of the results. The HPV-specific tests are only approved in women with abnormal Pap smears or women older than 30 years. However, use of HPV DNA testing as a routine screening

test in lieu of Pap smears is expected in the near future. In women identified to have high-risk HPV infections by these tests, follow-up cytology is performed. Annual screening is no longer recommended, but women should be screened every 3 years starting at age 21 until age 65.[63,64]

TREATMENT

No consensus exists regarding the best treatment approach for patients with genital HPV infection, particularly because most cases appear to be transient with spontaneous regression of lesions. A number of treatments are recommended (see **Table 135-13**), but none are clearly superior. Treatment generally is directed toward patients with manifestations of genital warts, with the goal of removing or destroying these lesions and grossly infected surrounding tissue. Because such treatment neither stops viral expression in surrounding tissue nor eliminates viral latency, recurrence of lesions is not uncommon.[3]

TABLE 135-13 Treatment Regimens for Miscellaneous Sexually Transmitted Infections

Infection	Recommended Regimen[a]	Alternative Regimen
Chancroid (*H. ducreyi*)	Azithromycin 1 g orally in a single dose, *or* Ceftriaxone 250 mg IM in a single dose, *or* Ciprofloxacin 500 mg orally twice daily for 3 days,[b] *or* Erythromycin base 500 mg orally four times daily for 7 days	
Lymphogranuloma venereum	Doxycycline 100 mg orally twice daily for 21 days[c]	Erythromycin base 500 mg orally four times daily for 21 days[d]
Nongonococcal urethritis (NGU)	Azithromycin 1 g orally in a single dose, or Doxycyline 100 mg orally twice daily for 7 days	Erythromycin base 500 mg orally four times daily for 7 days, or erythromycin ethylsuccinate 800 mg orally four times daily for 7 days, or levofloxacin 500 mg orally once daily for 7 days, or ofloxacin 300 mg orally twice daily for 7 days
NGU (Persistent or recurrent or due to *Mycoplasma genitalium*)	Azithromycin 1 g orally in a single dose	Fail initial regimen of azithromycin: Moxifloxacin 400 mg orally daily for 7 days
HPV infection		
External genital/perianal warts	*Provider-Administered Therapies:* Cryotherapy (eg, liquid nitrogen or cryoprobe); repeat weekly as necessary, *or* Podophyllin resin 10%-25% in compound tincture of benzoin applied to lesions; repeat weekly as necessary,[e,f] *or* TCA 80%-90% *or* BCA 80%-90% applied to warts; repeat weekly as necessary, *or* Surgical removal (tangential scissor excision, tangential shave excision, curettage, or electrosurgery) *Patient-Applied Therapies:* Podofilox 0.5% solution or gel applied twice daily for 3 days, followed by 4 days of no therapy; cycle is repeated as necessary for up to four cycles,[f] *or* Imiquimod 3.75% or 5% cream applied at bedtime three times weekly for up to 16 weeks,[f] *or* Sinecatechins 15% ointment applied three times daily for up to 16 weeks	Intralesional interferon *or* Photodynamic therapy *or* Topical cidofovir
Vaginal and anal warts	Cryotherapy with liquid nitrogen, or TCA or BCA 80%-90% as for external HPV warts; repeat weekly as necessary[g] Surgical removal (not for vaginal or urethral meatus warts)	
Urethral meatus warts	Cryotherapy with liquid nitrogen, or podophyllin resin 10%-25% in compound tincture of benzoin applied at weekly intervals[f,h]	
Prevention (ages 9-14 years)	Gardasil® (HPV quadrivalent [types 6, 11, 16, and 18]) recombinant vaccine 0.5 mL IM on day 1; a second dose administered 6 to 12 months following the first dose[i,k] Cervarix® (HPV bivalent [types 16 and 18]) recombinant vaccine 0.5 mL IM on day 1; a second dose are administered 6-12 months following the first dose[i,l] Gardasil9® (HPV 9-valent [types 6, 11, 16, 18, 31, 33, 45, 52, 58]) recombinant vaccine 0.5 mL IM on day 1; a second dose administered 6-12 months following the first dose[i]	
Prevention (age ≥15 years)	Gardasil® (HPV quadrivalent [types 6, 11, 16, and 18]) recombinant vaccine 0.5 mL IM on day 1; a second and third dose are administered 2 and 6 months following the first dose[i,k] Cervarix® (HPV bivalent [types 16 and 18]) recombinant vaccine 0.5 mL IM on day 1; a second and third dose are administered 1 and 6 months following the first dose[i,l] Gardasil9® (HPV 9-valent [types 6, 11, 16, 18, 31, 33, 45, 52, 58]) recombinant vaccine 0.5 mL IM on day 1; a second and third dose are administered 1 and 6 months following the first dose[i]	

BCA, bichloracetic acid; HPV, human papillomavirus; TCA, trichloroacetic acid.

[a]Recommendations are those of the Centers for Disease Control and Prevention (CDC).

[b]Ciprofloxacin is contraindicated for pregnant and lactating women and for persons aged <18 years.

[c]Azithromycin 1 g PO once weekly for 3 weeks can be effective.

[d]Pregnant patients should be treated with erythromycin.

[e]Some experts recommended washing podophyllin off after 1-4 hours to minimize local irritation.

[f]Safety during pregnancy is not established.

[g]Surgical removal of anal warts is also a recommended treatment.

[h]Some specialists recommend the use of podofilox and imiquimod for treating distal meatal warts.

[i]CDC recommendations: vaccination is recommended in girls 11-12 years of age, and in females aged 13-26 years who either were not previously vaccinated, or who did not complete the vaccination series.

[j]FDA-approved labeling for Gardasil®: indicated in girls and women 9 through 26 years of age for the prevention of cervical, vulvar, vaginal, and anal cancer caused by HPV types 16 and 18, genital warts (condyloma acuminata) caused by HPV types 6 and 11, and precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18.

[k]Vaccination is recommended in males aged 9-26 years to prevent genital warts and anal cancer.

[l]FDA-approved labeling for Cervarix®: indicated in females 9 through 25 years of age for the prevention of cervical cancer, cervical intraepithelial neoplasia grade 2 or worse, adenocarcinoma in situ, and cervical intraepithelial neoplasia grade 1 caused by HPV types 16 and 18.

Vaccination

As lesions are difficult to successfully treat, high incidence of reinfection, and concern for malignancy with persistent infections, the focus of HPV treatment is primarily on prevention. The only way to avoid acquiring HPV is to abstain from any type of sexual activity; however, barrier contraceptive methods may help decrease the risk of HPV transmission. Therefore, three HPV vaccines are licensed in the United States and endorsed by the CDC and Advisory Committee on Immunization Practices (ACIP). The vaccines cover the most common and virulent HPV strains. Cervarix (a bivalent vaccine for HPV-16 and 18), Gardasil (a quadrivalent vaccine for HPV-6, 11, 16, and 18), and Gardasil 9 (a 9-valent vaccine for HPV-6, 11, 16, 18, 31, 33, 45, 52, and 58) are all indicated for preventing cervical precancers and cervical cancer in females 9 to 26 years of age. In addition, Gardasil and Gardasil 9 are indicated in unvaccinated males 9 to 21 years of age. Specific populations (MSM, immunocompromised) are recommended to receive the vaccination up to the age of 26.[3] Although it is ideal to vaccinate patients prior to the onset of sexual activity, those infected with one or more HPV types may still receive protection from the vaccine.[3] Additionally, while the indication of the vaccine is to prevent cervical cancers, males are also included in the indication to reduce the spread of asymptomatic disease and reduce the risk of other HPV-related malignancies.

Previously, all vaccines were administered as a three-dose series over 6 months, but in 2016 the ACIP recommendation changed for patients less than 15 years of age to a two-dose schedule at 0 and 6 to 12 months. Data in women aged 16 to 26 years supports the use of a two-dose schedule in 9 to 14 year olds, instead of the three-dose schedule, as the 16 to 26 years old group studied had an antibody response with 2 doses non-inferior to three doses.[65–67] All three vaccines are equally recommended by the ACIP; however, since the end of 2016, only the 9-valent HPV vaccine has been available for sale within the United States.

The HPV vaccine was first introduced in 2006, and has since been the center of various controversies regarding safety and efficacy. Over 200,000,000 doses of the vaccine have been administered worldwide, and the safety profile of the HPV vaccines has been well established over the past decade.[59,65,68] The CDC and FDA continuously monitor the safety of vaccines via program such as Vaccine Adverse Event Reporting System (VAERS), Vaccine Safety Data link, and Clinical Immunization Safety Assessment Project.[68] The most common

adverse events are related to injection site reactions, including pain, redness, or swelling. Additionally, patients may also report fever, headache, asthenia, nausea, or muscle or joint pain. Early VAERS data showed high reported rates of syncope. Syncope is a known adverse event after any injectable vaccination, and adolescents are also more likely to experience syncope after a medical procedure, including vaccination. In response, the FDA, CDC, and ACIP recommend to observe all patients for 15 minutes after administration of the vaccine to monitor for syncope, taking appropriate precautions to prevent falls and injuries from fainting. CDC data from 2014 indicate that over 90% of health events reported to VAERS were classified as nonserious.[68] HPV vaccination has not been linked to new autoimmune diseases or neurologic disorders.[65,68]

The main goal of HPV vaccination is to prevent HPV-associated malignancies; however, time from HPV infection to cervical cancer may exceed 20 years, so effects of the vaccine may not be seen for some time.[60,65] Although the ability to measure effect of the vaccine on malignancies is currently impossible, introduction of the vaccines has substantially reduced HPV prevalence and HPV-related diseases.[58–60,65] There have also been concerns regarding the long-term effect of the vaccine given the young age at which it is recommended to be administered. Data from the bivalent vaccine demonstrate that antibody titers maintain appropriate levels for approximately 10 years and there is no evidence to suggest that protection decreases with time.[59] It is important that patients are vaccinated prior to onset of sexual activity to gain the greatest protection from the vaccine for the duration of time when they are at greatest risk. As mentioned, the vaccine may still be protective even after patients have become sexually active.

Despite CDC and ACIP recommendations for HPV vaccination in adolescent girls since 2006 and adolescent boys since 2011, the number of individuals receiving the vaccine is below the desired threshold of 80%.[69–71] Among girls aged 13 to 17, only 57% received at least one dose of the vaccine and only 38% received the entire series. The numbers are even lower for boys, with 35% receiving at least one dose and 14% receiving all three.[69] Rates of vaccine implementation may increase with interventions, such as patient education and reminders, but a barrier still exists introducing this vaccine into a nontraditional target population.[70,71]

OTHER SEXUALLY TRANSMITTED INFECTIONS

Several STIs other than those just discussed occur with varying frequency in the United States and throughout the world. Although an in-depth discussion of these diseases is beyond the scope of this chapter, Table 135-13 lists recommended treatment regimens.[3] Of notable importance among these other STIs, however, is *Mycoplasma genitalium* (*M. genitalium*) infection, one of the most common causes of nongonococcal urethritis (NGU). The CDC has identified *M. genitalium* infections as an emerging issue due to the increasing rates of resistance and lack of diagnostic assays.[72,73]

M. genitalium is a known colonizer of the genital tract in both males and females; however, it is an emerging cause of urogenital infections.[3,72–74] While *C. trachomatis* accounts for a majority of NGU cases, *M. genitalium* is the causative pathogen in up to 20% of NGU cases and 25% of nonchlamydial NGU. Rates are even higher in persistent or recurrent NGU, constituting approximately 30% of cases.[3] The relationship between *M. genitalium* and other male anogenital tract infections, like epididymitis or clinical proctitis, is not well defined. The pathogenic role is even less defined in women, as infections are commonly asymptomatic, but has been isolated in up to 30% of cervical infections. However, women infected with *M. genitalium* are at a 2- to 2.5-fold increased risk of cervicitis, PID, infertility, and preterm delivery.[72]

M. genitalium lacks a cell wall and is slow growing, fastidious organism. It is not readily cultured in a laboratory and, when able to grow, may take up to 6 months to isolate. NAATs are the preferred method to detect *M. genitalium*; however, these are only available in research settings, though some large academic medical centers and commercial laboratories have testing capabilities. There is currently no FDA-approved test to detect this organism in the United States. As such, many of these infections go undiagnosed, but *M. genitalium* should be suspected in persistent or recurrent urethritis and considered in persistent or recurrent cervicitis or PID.[3,72–74]

Treatment for *M. genitalium* infections has historically consisted of tetracyclines, macrolides, and fluoroquinolones. *M. genitalium* does not have a cell wall, rendering beta-lactam antibiotics ineffective. The 7-day doxycycline regimen, a primary treatment option for NGU is largely ineffective for treatment of *M. genitalium* urethritis, with a median cure rate of 31%.[3] The 1,000-mg single dose of azithromycin was significantly more effective than doxycycline, and has been the mainstay of therapy for *M. genitalium* infections.[3,72–74] Unfortunately, resistance to azithromycin is rapidly emerging, with 50% of all *M. genitalium* infections caused by organisms already resistant to azithromycin.

Providing a longer course of azithromycin has not been shown to increase cure rates if a patient has not responded to the 1,000 mg single-dose. It is hypothesized that the overuse of macrolides to treat respiratory tract infections, like community acquired pneumonia, may play a role in azithromycin resistance seen in *M. genitalium*.[72,73] Moxifloxacin, 400 mg daily for 7, 14, or 21 days, has been successfully used to eradicate *M. genitalium* infections, with cure rates up to 100%, but treatment failures have been reported with the 7-day regimen. For patients with PID, who are not responding to typical therapy within 7 to 10 days, moxifloxacin 400 mg daily for 14 days is recommended. If validated testing for *M. genitalium* is available, patient with persistent urethritis, cervicitis, or PID accompanied by persistent detection of *M. genitalium* could be treated with moxifloxacin.[3,72,73]

As with all STIs, patients are recommended to abstain from unprotected sexual activity until both partners have completed treatment and are asymptomatic. Additionally, patients and their sexual partners should be screened for other STIs and counseled on risk of transmission and consequences of untreated infections. If a patient's sexual partner is not tested, the same treatment may be offered to both. If testing method is available, TOC should be performed due to increased prevalence of macrolide resistance.[73]

Postclass Engaged Learning Activity

Conduct a literature search to identify novel strategies for treatment of drug-resistant gonorrhea. Focus on new therapies in development, and write a brief summary of the unique aspects of the therapy and its potential impact on the future treatment of drug-resistant gonorrhea. Also, list one advantage and disadvantage of this therapy compared to the current standard of care. This activity is intended to build your drug information skills and ability to critically appraise published research articles.

ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AIDS	acquired immunodeficiency syndrome
BCA	Bichloracetic acid
CDC	Centers for Disease Control and Prevention
CNS	central nervous system
CSF	cerebrospinal fluid
DFA-TP	direct fluorescent-antibody (test) for *T. pallidum*
DGI	disseminated gonococcal infection
DNA	deoxyribonucleic acid
EB	elementary body
EIA	enzyme immunoassay
EPT	expedited partner therapy
FDA	Food and Drug Administration
FTA-ABS	fluorescent treponemal antibody absorption
GI	gastrointestinal
HIV	human immunodeficiency virus
HPV	human papillomavirus
HSV	herpes simplex virus
HSV-1	herpes simplex virus type 1
HSV-2	herpes simplex virus type 2
IM	intramuscular
LPS	lipopolysaccharide
MHA-TP	microhemagglutination assay for antibodies to *T. pallidum*
MSM	men who have sex with men
NAATs	nucleic acid amplification tests
NGU	nongonococcal urethritis
Pap	Papanicolaou smear
PCR	polymerase chain reaction
PID	pelvic inflammatory disease
PMN	polymorphonuclear
RB	reticulate body
RPR	rapid plasma reagin
STI	sexually transmitted infection
TCA	Trichloroacetic acid
TOC	test of cure
TPHA	*T. pallidum* hemagglutination assay
TPPA	*T. pallidum* particle agglutination assay
TRUST	toluidine red unheated serum test
USR	unheated serum reagin
VAERS	Vaccine Adverse Event Reporting System
VDRL	Venereal Disease Research Laboratory
WHO	World Health Organization

REFERENCES

1. Satterwhite CL, Torrone E, Meites E, et al. Sexually transmitted infections among U.S. women and men: Prevalence and incidence estimates, 2008. *Sex Transm Dis*. 2013;40(3):187–193.
2. Owusu-Edusei K, Chesson HW, Gift TL, et al. The estimated direct medical cost of selected sexually transmitted infections in the United States, 2008. *Sex Transm Dis*. 2013;40(3):197–201.
3. Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep* 2015;64:1–135.
4. Marrazzo JM, Holmes KK. Sexually transmitted diseases: Overview and clinical approach. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York, NY: McGraw-Hill; 2012. http://www.accessmedicine.com.libproxy.uthscsa.edu/content.aspx?aID=9119937.
5. Obiero J, Mwethera PG, Wiysonge CS. Topical microbicides for prevention of sexually transmitted infections. *Cochrane Database Syst Rev* 2012;6:CD007961.
6. Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2016*. Atlanta, GA: U.S. Department of Health and Human Services; 2017. https://www.cdc.gov/std/stats16/Gonorrhea.htm. Accessed March 27, 2018.
7. Centers for Disease Control and Prevention. *Antibiotic Resistance Threats in the United States, 2013*. Atlanta, GA: U.S. Department of Health and Human Services; 2013.
8. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): Effectiveness results from the pilot phase of a pragmatic open-label randomized trial. *Lancet*. 2016;387:53–60.
9. Lyons HA, Longmore MA, Giordano PC. Gender and casual sexual activity from adolescence to emerging adulthood: Social and life course correlates. *J Sex Res*. 2015;52(5):543–557.
10. World Health Organization. *Prioritization of Pathogens to Guide Discovery, Research, and Development of New Antibiotics for Drug-Resistant Bacterial Infections, Including Tuberculosis*. Geneva, Switzerland: World Health Organization; 2017.

11. Newman LM, Moran JS, Workowski KA. Update on the management of gonorrhea in adults in the United States. *Clin Infect Dis*. 2007;44:S84–S101.
12. Marrazzo JM, Apicella MA. Neisseria gonorrhoeae. In: Bennett JE, Raphael D, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th ed. [electronic version]; Clinical Key, 2015*. Philadelphia, PA: Elsevier. https://www.clinicalkey.com/#!/content/book/3-s2.0-B978032340161600214X. Accessed March 28, 2018.
13. Criss AK, Seifert HS. A bacterial siren song: Intimate interactions between Neisseria and neutrophils. *Nat Rev Microbiol*. 2012;10:178–190.
14. Hooper RR, Renolds GH, Jones OG, et al. Cohort study of venereal disease, I: The risk of gonorrhea transmission from infected women to men. *Am J Epidemiol*. 1978;108:136–144.
15. Lin JS, Donegan Sp, Heeren TC, et al. Transmission of Chlamydia trachomatis and *Neisseria gonorrhoeae* among men with urethritis and their female sex partners. *J Infect Dis*. 1998;178:1707–1712.
16. McCormack WM, Stumacher RJ, Johnson K, et al. Clinical spectrum of gonococcal infection in women. *Lancet*. 1977;1:1182–1185.
17. Wiesenfeld HC, Hillier SL, Krohn MA, et al. Lower genital tract infection and endometritis: Insight into subclinical pelvic inflammatory disease. *Obstet Gynecol*. 2002;100:456–463.
18. Bleich AT, Sheffield JS, Wendel GD, et al. Disseminated gonococcal infections in women. *Obstet Gynecol*. 2012;119:597–602.
19. Barr J, Danielsson D. Septic gonococcal dermatitis. *Br Med J*. 1971;1:482–485.
20. Centers for Disease Control and Prevention. Recommendations for the laboratory-based detection of Chlamydia trachomatis and Neisseria gonorrhoeae-2014. *MMWR Morb Mortal Wkly Rep*. 2014;63:1–19.
21. Gaydos CA. Nucleic acid amplification tests for gonorrhea and chlamydia: Practice and applications. *Infect Dis Clin North Am*. 2005;19:367–386.
22. Centers for Disease Control and Prevention. Update to CDC's sexually transmitted diseases treatment guidelines, 2010: Oral cephalosporins no longer a recommended treatment for gonococcal infections. *MMWR Morb Mortal Wkly Rep*. 2012;61(31):590–594.
23. Unema M, Bradshaw CS, Hocking JS, et al. Sexually transmitted infections: Challenges ahead. *Lancet Infect Dis*. 2017;17:e235–279.

24. Wind CM, de Vries E, Schimm van der Loeff MF, et al. Decreased azithromycin susceptibilities of *Neisseria gonorrhoeae* isolates in patients recently treated with azithromycin. *Clin Infect Dis*. 2017;65:37–45.
25. Katz AR, Komeya AY, Kirkcaldy RD, et al. Cluster of Neisseria gonorrhoeae isolates with high-level azithromycin resistance and decreased ceftriaxone susceptibility, Hawaii, 2016. *Clin Infect Dis*. 2017;65:918–923.
26. Ison CA. Antimicrobial resistance in sexually transmitted infections in the developed world: Implications for rational treatment. *Curr Opin Infect Dis*. 2012;25:73–78.
27. Kahler CM. Multidrug-resistant *Neisseria gonorrhoeae*: Future therapeutic options. *Future Microbiol*. 2018;13:499–501.
28. Lagace-Wiens PRS, Adam HJ, Laing NM, et al. Antimicrobial susceptibility of clinical isolates of *Neisseria gonorrhoeae* to alternative antimicrobials with therapeutic potential. *J Antimicrob Chemother*. 2017;72:2273–2277.
29. Lyss SB, Kamb ML, Peterman TA, et al. Chlamydia trachomatis among patients infected with and treated for *Neisseria gonorrhoeae* in sexually transmitted disease clinics in the United States. *Ann Intern Med*. 2003;139:178–185.
30. Kirkcaldy RD, Weinstock HS, Moore PC, et al. The efficacy and safety of gentamicin plus azithromycin and gemifloxacin plus azithromycin as treatment of uncomplicated gonorrhea. *Clin Infect Dis*. 2014;59:1083–1091.
31. Russell MW. Could vaccination against *Neisseria gonorrhoeae* be on the horizon? *Future Microbiol*. 2018;(13):495–497.
32. Woods CR. Gonococcal infections in neonates and young children. *Semin Pediatr Infect Dis*. 2005;16:258–270.
33. Centers for Disease Control and Prevention. 2016 Sexually Transmitted Diseases Surveillance. Available at: https://www.cdc.gov/std/stats16/Syphilis.htm. Accessed April 12, 2018.
34. Lukehart SA. Syphilis.. In: Kasper D, Fauci A, Hauser S,, Longo D,, Jameson J,, Loscalzo J, eds.*Harrison's Principles of Internal Medicine, 19e*. New York, NY: McGraw-Hill; 2014. http://accesspharmacy.mhmedical.com/content.aspx?bookid=1130&sectionid=79737418. Accessed March 6, 2018.
35. Cohen SE, Klausner JD, Engelman J, Philip S. Syphilis in the modern era.

Infect Dis Clin N Am. 2013;27:705–722.

36. Morshed MG, Singh AE. Recent trends in the serologic diagnosis of syphilis. *Clin Vaccine Immunol*. 2015;22:137–147.
37. Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2016*. Atlanta, GA: U.S. Department of Health and Human Services; 2017. https://www.cdc.gov/std/stats16/chlamydia.htm. Accessed April 10, 2018.
38. Batteiger BE, Tan M. Chlamydia trachomatis (trachoma, genital infections, perinatal infections, lymphogranuloma venereum).. In: Bennett JE, Dolin R, Blaser MJ,, eds.*Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th ed. [electronic version]; Clinical Key, 2015*. Philadelphia, PA: Elsevier. https://www.clinicalkey.com/#!/content/book/3-s2.0-B9780323401616001820. Accessed April 5, 2018.
39. Gaydos CA, Quinn TC. Chlamydial infections.. In: Kasper DL, Fauci AS, Hauser SL,, Longo DL,, Jameson JL,, Loscalzo J, eds. *Harrison's Principles of Internal Medicine, 19th ed. [electronic version]*. New York, NY: McGraw-Hill; 2015. https://accessmedicine.mhmedical.com/content.aspx?bookid=1130&sectionid=79737875. Accessed April 5, 2018.
40. Geisler WM, Stamm WE. Genital chlamydial infections. In: Klausner JD, Hook EW, eds. *Current Diagnosis & Treatment of Sexually Transmitted Diseases [electronic version]*. 1st ed. New York, NY: McGraw-Hill; 2007. https://accessmedicine.mhmedical.com/content.aspx?bookid=369&sectionid=39914790. Accessed April 5, 2018.
41. O'Connell CM, Ferone ME. Chlamydia trachomatis genital infections. *Microbial Cell*. 2016;3:390–403.
42. Katz BP, Caine VA, Jones RB, et al. Estimation of transmission probabilities for chlamydial infections. In: Bowie WR, Caldwell HD, Jones RP, eds. *Chlamydial Infections*. Cambridge, UK: Cambridge University Press; 1990;567–570.
43. Althaus CL, Turner KM, Mercer CH, et al. Effectiveness and cost-effectiveness of traditional and new partner notification technologies for curable sexually transmitted infections: Observational study, systematic reviews and mathematical modelling. *Health Technol Assess*. 2014;18:1–100.
44. WitKin SS, Minis E, Athanaslou A, Leizer J, Linhares IM. Chlamydia

trachomatis: The persistent pathogen. *Clin Vaccine Immunol*. 2017;24:e00203–17.

45. Zar HJ. Neonatal chlamydial infections: Prevention and treatment. *Paediatr Drugs*. 2005;7:103–110.
46. Geisler WM, Koltun WD, Abdelsayed N, et al. Safety and efficacy of WC2031 versus vibramycin for the treatment of uncomplicated urogenital Chlamydia trachomatis infection: A randomized, double-blind, double-dummy, active-controlled, multicenter trial. *Clin Infect Dis*. 2012;55(1):82–88.
47. WHO. *World Health Organization guideline for the treatment of Chlamydia trachomatis [electronic reference]*. Geneva: World Health Organization; 2016. http://www.who.int/reproductivehealth/publications/rtis/chlamydia-treatment-guidelines/en/. Accessed April 4, 2018.
48. Corey L. Herpes simplex virus infections. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 19th ed. New York, NY: McGraw-Hill; 2014. http://accesspharmacy.mhmedical.com.ezproxy.lib.utexas.edu/content.aspx bookid=1130&sectionid=79738203. Accessed April 12, 2018.
49. Gnann JW, Whitley RJ. Genital herpes. *New Engl J Med*. 2016;375:666–674.
50. Erard V, Wald A, Corey L, et al. Use of long-term suppressive acyclovir after hematopoietic stem-cell transplantation: Impact on herpes simplex virus (HSV) disease and drug-resistant HSV disease. *J Infect Dis*. 2007;196:266–270.
51. Gupta R, Warren T, Wald A. Genital herpes. *Lancet*. 2007;370:2127–2137.
52. Corey L, Wald A. Maternal and neonatal herpes simplex virus infections. *N Engl J Med*. 2009;361:1375–1385.
53. Meites E, Gaydos CA, Hobbs MM, et al. A review of evidence-based care of symptomatic trichomoniasis and asymptomatic Trichomonas vaginalis infections. *Clin Infect Dis*. 2015;61(S8):S837–48.
54. Kissinger P. Trichomonas vaginalis: A review of epidemiologic, clinical and treatment issues. *BMC Infect Dis*. 2015;15(307):1–8.
55. Bouchemal K, Bories C, Loiseau PM. Strategies for prevention and treatment of Trichomonas vaginalis infections. *Clin Microbiol Rev*. 2017;30:811–825.
56. Forna F, Gulmezoglu AM. Interventions for treating trichomoniasis in

women. *Cochrane Database Syst Rev*. 2003;2:CD000218.

57. Kissinger P, Mena L, Levison J, et al. A randomized treatment trial: Single versus 7-day dose of metronidazole for the treatment of Trichomonas vaginalis among HIV-infected women. *J Aquir Immune Defic Syndr*. 2010;55:565–571.
58. Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2016*. Atlanta, GA: U.S. Department of Health and Human Services; 2017. https://www.cdc.gov/std/stats16/other.htm#foot-4. Accessed April 13, 2018.
59. Bogani G, Maggiore ULR, Signorelli M, Martinelli F, Sabatucci I, et al. The role of human papillomavirus vaccines in cervical cancer: prevention and treatment. *Crit Rev Oncol Hematol*. 2018;122:92–97.
60. Ermel AC, Brown DR. Human papillomavirus infections. In: Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine, [electronic version]*. 19th ed. New York, NY: McGraw-Hill; 2015. https://accessmedicine.mhmedical.com/content.aspx?bookid=1130&sectionid=79738493. Accessed April 13, 2018.
61. Hutchinson DJ, Klein KC. Human papillomavirus disease and vaccines. *Am J Health Syst Pharm*. 2008;65:2105–2112.
62. WHO. Human papillomavirus vaccines: WHO position paper, May 2017—Recommendations. *Vaccine*. 2017;35:5753–5755.
63. Bonnez W. Papillomaviruses. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases [electronic version]; Clinical Key, 2015*. 8th ed. Philadelphia, PA: Elsevier. https://www.clinicalkey.com/#!/content/book/3-s2.0-B9780323401616001467. Accessed April 5, 2018.
64. Yarbrough ML, Burnham CD. The ABCs of STIs: An update on sexually transmitted infections. *Clin Chem*. 2006;62:811–823.
65. Markowitz LE, Gee J, Chesson H, Stokley S. Ten years of human papillomavirus vaccination in the United States. *Acad Pediatr*. 2018;18:S3–S10.
66. Meites E, Kempe A, Markowitz LE. Use of a 2-dose schedule for human papillomavirus vaccination—updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2016;65:1405–1408.
67. Markowitz LE, Meites E, Unger ER. Two vs three doses of human

papillomavirus vaccine: New policy for the second decade of the vaccination program. *JAMA*. 2016;316:2370–2372.

68. Centers for Disease Control and Prevention. Human papillomavirus (HPV) vaccine safety. Available at: https://www.cdc.gov/vaccinesafety/vaccines/hpv-vaccine.html. Accessed April 13, 2018.
69. Stokley S, Jeyaraja J, Yankey D, Cano M, Gee J, Roark J, et al. Human papillomavirus vaccination coverage among adolescents, 2007-2013, and postlicensure vaccine safety monitoring, 2006-2014—United States. *MMWR Morb Mortal Wkly Rep*. 2014;63:620–624.
70. Kang HS, Gagne JC De, Son YD, Chae SM. Completeness of human papillomavirus vaccination: A systematic review. *J Pediatr Nurs*. 2018;38:7–14.
71. Bloom P, Ogbuanu I. Vaccination to prevent human papillomavirus infections: From promise to practice. *PLoS Med*. 2017;14:e1002325.
72. Sethi S, Zaman K, Jain N. Mycoplasma genitalium infections: Current treatment options and resistance issues. *Infect Drug Resist*. 2017;10:283–292.
73. Decker CF. Emerging sexually transmitted diseases: Hepatitis C, lymphogranuloma venereum (LGV), and Mycoplasma genitalium infections. *Dis Mon*. 2016;62:314–318.
74. Hardy RD. Infections due to mycoplasmas. In: Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine [electronic version]*. 19th ed. New York, NY: McGraw-Hill; 2015. https://accessmedicine.mhmedical.com/content.aspx?bookid=1130&sectionid=79737826. Accessed April 13, 2018.

136

Bone and Joint Infections

Scott J. Bergman and Edward P. Armstrong

KEY CONCEPTS

1. The most common cause of osteomyelitis (particularly that acquired by hematogenous spread) and infectious arthritis is *Staphylococcus aureus* (*S. aureus*).
2. Culture and susceptibility information are essential as a guide for antimicrobial treatment of osteomyelitis and infectious arthritis.
3. Joint aspiration and examination of synovial fluid are extremely important to evaluate the possibility of infectious arthritis.
4. The most important treatment modality of acute osteomyelitis is the administration of appropriate antibiotics in adequate doses for a sufficient length of time.
5. Antibiotics generally are given in high doses so that adequate antimicrobial concentrations are reached within the infected bone and joints.
6. Oral antimicrobial therapies can be used for osteomyelitis to follow a parenteral regimen in children who have a good clinical response to IV antibiotics and in adults without diabetes mellitus or peripheral vascular disease when the organism is susceptible to the oral antimicrobial, a suitable oral agent is available, and adherence is ensured.
7. The standard duration of antimicrobial treatment for acute osteomyelitis is 4 to 6 weeks.
8. The three most important therapeutic approaches to the management of infectious arthritis are appropriate antibiotics, joint drainage, and joint rest.
9. Monitoring of antibiotic therapy is important and typically involves noting clinical signs of inflammation, periodic white blood cell (WBC) counts, C-reactive protein, and erythrocyte sedimentation rate (ESR) determinations.

Preclass Engaged Learning Activity

Match the bone or joint infection subtype with the most common causative organism(s)—rank the order of bacteria in those that have multiple common causes.

Infections	Organism Choices
60-year-old adult with vertebral osteomyelitis from a hematogenous source	Beta-hemolytic Streptococci
50-year-old adult with diabetes and peripheral vascular disease having osteomyelitis of his plantar foot	*Staphylococcus aureus*
Intravenous drug user	Enteric gram-negative bacteria
Neonate	*Pseudomonas aeruginosa*
3-year-old child with infection of the femur	*Kingella kingae*
70-year-old woman with rheumatoid arthritis and septic arthritis	
65-year-old man with prosthetic joint infection from knee surgery 2 months ago	

INTRODUCTION

Bone and joint infections are comprised of two disease processes known, respectively, as *osteomyelitis* and *septic* or *infectious arthritis*. They are unique and separate infectious entities with different signs and symptoms and infecting organisms. Prosthetic joint infections, resulting from the advancement of modern technology, are distinct and blend attributes of each disease. Despite therapy, these infections all cause significant morbidity from residual damage with chronic or recurring infections. Emphasis on initiating antibiotic therapy, targeted to the most likely pathogens, as soon as possible is important in reducing long-term complications.

EPIDEMIOLOGY

Osteomyelitis

1 Osteomyelitis has historically been an uncommon disease. One classic publication reported that 247 patients had osteomyelitis in a prominent American teaching hospital during a 4-year period.[1] A more recent analysis in Spain showed more than 500 cases of osteoarticular infections per year over the course of a decade.[2] Over that time, the incidence increased from 11.4 to 24.4 cases per 100,000 person-years.[3] Acute osteomyelitis has an estimated annual incidence of 0.4 per 1,000 children. Osteomyelitis cases have been rising in adults due to an aging population having more cases of diabetic foot infections and prosthetic joint replacements. Osteomyelitis can be caused by contiguous spread, including postoperative contamination, direct puncture from trauma, or associated with adjacent soft tissue infections which is the most common source. *Hematogenous osteomyelitis* comprises 19% of infections, and osteomyelitis occurring in patients with significant peripheral vascular disease comprises 34% of infections.

The bacteriology of *hematogeous osteomyelitis* is unique in that one pathogen, *S. aureus*, is responsible for more than 80% of these infections. Streptococci and *Escherichia coli* (*E. coli*) make up the remainder in most of the population. One exception is in children 3 months to 4 years of age. With the advent of molecular diagnostics, *Kingella kingae* (*K. kingae*), an organism that is part of the oral microbiota, has been identified as a common cause of pre-school osteoarticular infections.[4] After children reach the age of 4 years, *S. aureus* again accounts for nearly 80% of infections. *Haemophilus influenzae* type b used to be an important pathogen but has been almost completely eliminated with the use of the conjugate vaccine. Osteomyelitis in neonates can result from organisms transferred from the mother at birth such as Group B Streptococcus, and *E. coli*, but is most commonly from infection with *S. aureus*.

Vertebral osteomyelitis occurs through hematogenous spread and has several unique features, being most common in adults over 50 years of age and often misdiagnosed initially. It typically presents with recalcitrant back pain unresponsive to usual symptomatic therapies, elevated inflammatory markers and sometimes fever.[5] The lumbar and thoracic regions are the locations of most infections. Infections are most likely to develop in the vascular areas near the subchondral plate region of the vertebral body. These infections are typically monomicrobial and are caused principally by Staphylococci.[5] Gram-negative

organisms can play a role, most commonly the Enterobacteriaceae, *E. coli*, and *Klebsiella pneumoniae*, that originate within the urinary tract or intra-abdominal cavity.[7] *Mycobacterium tuberculosis* and fungi also are known to cause infections in the spine, albeit rarely. Skin and respiratory tract infections are other sources of infection known to lead to vertebral infections.

Contiguous-spread disease has several important differences compared with *hematogeous osteomyelitis*. Although *S. aureus* is still the most common organism isolated, polymicrobial infections occur more often than with hematogenous osteomyelitis. Streptococcus, *Staphylococcus epidermidis*, *E. coli*, *Pseudomonas aeruginosa* (*P. aeruginosa*), and anaerobes can also be isolated.

Patients with diabetes mellitus frequently have infections that involve the foot. Cases extending to the bone may result in mixed infection, including with gram-negative bacilli. Puncture injuries to the foot, causing osteochondritis, are another reason for gram-negative infection, sometimes caused by *P. aeruginosa*. *S. aureus* remains a significant pathogen in these patients due to its prevalence on the skin. When anaerobes are grown from cultures, they usually are found in association with other organisms, including aerobic bacteria. *Bacteroides fragilis* comprises the majority of anaerobic isolates. Predisposing factors in patients who have anaerobic osteomyelitis include vascular disease, peripheral neuropathy, trauma, bites, or contiguous infections such as abscess.

Infectious Arthritis

Infectious or septic arthritis is an inflammatory reaction within the joint space. Septic arthritis is one of the most common causes of new cases of arthritis. The incidence of proven or likely septic arthritis is 4 to 10 cases per 100,000 patient-years. The incidence of septic arthritis increases 10-fold among patients that have rheumatoid arthritis.[8]

Although relatively infrequent, neonates can have infectious arthritis because of a broad range of organisms similar to osteomyelitis, with *S. aureus*, Group B Streptococcus, and *E. coli* being most common. *K. kingae* is now considered predominant in those 6 months to 4 years old while *S. aureus* is the most common pathogen in children 4 years of age and older.[9] Pneumococcal arthritis is decreasing in incidence as a result of conjugate pneumococcal vaccine administration to infants.[10] If the child has not been fully vaccinated or is immunocompromised, *S. pneumoniae* or *H. influenzae* type b may be a cause.

Some organisms, such as *S. aureus* and *Neisseria gonorrhoeae*, are especially

likely to infect a joint during bacteremia. Gonococcal arthritis is a common manifestation of disseminated gonococcal infection occurring in 42% to 85% of such patients.[11] Gonococcal arthritis is now uncommon in North America and Europe, although it remains an important concern in developing countries.

Within the adult population, *S. aureus* is responsible for the majority of arthritis cases.[12] Streptococcal infections are the second most common followed by gram-negative organisms. Among the latter, *E. coli* is the most common; however, *P. aeruginosa* can be seen in special situations such as in intravenous drug users or nosocomial infections.

Although rare, infectious arthritis can be caused by fungi, mycobacteria, or viruses such as varicella-zoster, rubella, or parvovirus.[13] Penetrating injury of the joint can result in an infection due to Pasteurella or Capnocytophaga from dog or cat bites, Eikanella in human bites or Pantoea when the injury is induced by a thorn.

ETIOLOGY

Osteomyelitis

The most common method of classifying osteomyelitis is based on the mode of acquisition of the bone infection. Disease that results from spread through the bloodstream is termed *hematogeous osteomyelitis*, while that reaching the bone from an adjoining soft tissue infection is termed *contiguous osteomyelitis*. Patients with peripheral vascular disease are at risk for the development of contiguous osteomyelitis, and they present unique management features so are sometimes classified separately. Osteomyelitis that results from direct inoculation, such as from trauma, puncture wounds, or surgery, generally is also classified as inoculation osteomyelitis.

Osteomyelitis also can be classified based on the duration of the disease. Acute osteomyelitis describes infections of recent onset, with symptoms usually present about a week, whereas chronic infections are those of a longer duration. Some authors describe chronic infections as those with symptoms for more than 1 month before therapy, while other authors define chronic infections as any relapse of an initial infection. *Hematogeous osteomyelitis* almost always involves one bone whereas contiguous osteomyelitis can present in multiple bones, especially when vascular insufficiency is an underlying risk factor.

Infectious Arthritis

Most infecting organisms produce an infection in a single joint, termed *monoarticular infection*; however, infections also can involve two or more joints, especially when associated with bacteremia. As with osteomyelitis, joint infections also can be classified according to the mechanisms by which the infecting organism reaches the joint. Infectious arthritis can result by spread from an adjacent bone infection, direct contamination of the joint space through trauma or surgery, or hematogenous dissemination. Hematogenous spread of the disease comprises the majority of infections; spread from osteomyelitis and direct inoculation is much less frequent. Septic arthritis is most prevalent in children and the elderly. Approximately, one-third of people with septic arthritis are children younger than 2 years of age.[8]

Unlike children, adults often have significant systemic diseases that predispose them to septic arthritis, such as diabetes mellitus, immunosuppressive states (eg, cancer or liver disease), or preexisting joint disease, particularly rheumatoid arthritis. Additional risk factors associated with adult septic arthritis (more than one factor may be present) are systemic corticosteroid use, arthrocentesis, distant infection, or trauma. Intravenous drug abusers and individuals with intravascular infections such as endocarditis also are prone to develop septic arthritis.

PATHOPHYSIOLOGY

Osteomyelitis

Hematogenous Osteomyelitis

Hematogeous osteomyelitis is typically a disease of the growing bone in children, but occurs primarily in vertebrae of adults. **Table 136-1** summarizes the primary characteristics of osteomyelitis.

TABLE 136-1 Types of Osteomyelitis, Age Distribution, Common Sites, and Risk Factors

Type of Osteomyelitis	Typical Age (years)	Site(s) Involved	Risk Factors
Hematogenous	<1	Long bones and joints	Prematurity, umbilical or other central venous catheter or venous cut-down, respiratory distress syndrome, and perinatal asphyxia
	1-20	Long bones (femur, tibia, and humerus)	Infection (pharyngitis, cellulitis, and respiratory infections), trauma, and sickle cell disease
	Older than 50	Vertebrae	Diabetes mellitus, blunt trauma to spine, and urinary tract infection
Contiguous	Older than 50	Femur, tibia, and mandible	Hip fractures and open fractures, soft tissue infections or abscesses
Direct Inoculation	<18	Foot	Puncture injury to foot or other trauma
Vascular insufficiency	Older than 50	Feet and toes	Diabetes mellitus, peripheral vascular disease, and pressure sores

Unique features of the anatomy and vascular supply of long bones appear to predispose them to become infected.[14] Bacteria are seeded within the metaphysis (**Fig. 136-1**) as the nutrient arteries of the long bones divide within the medullary canal of the bone into small arterioles. These end in hairpin turns near the growth plate and flow into veins, of much wider diameter, that drain the medullary cavity.[1] The infection is initiated within the bend of the arterioles where there is considerable slowing of blood flow in the hairpin capillary loops. This sludging of blood flow allows bacteria present within the bloodstream to settle and initiate an inflammatory response. They have access to the bone by gaps in the endothelium and the absence of a basement membrane. In addition to

these structural features, phagocytosis is less active within the metaphysis. After the bacteria settle in the bone, avascular necrosis can occur from occlusion of the nutrient vessels and release of bacterial enzymes. Once the infection is initiated, exudate begins to form within the bone marrow and the fluid accumulates under increased pressure. The age of the patient largely determines the next stage in the pathophysiology.

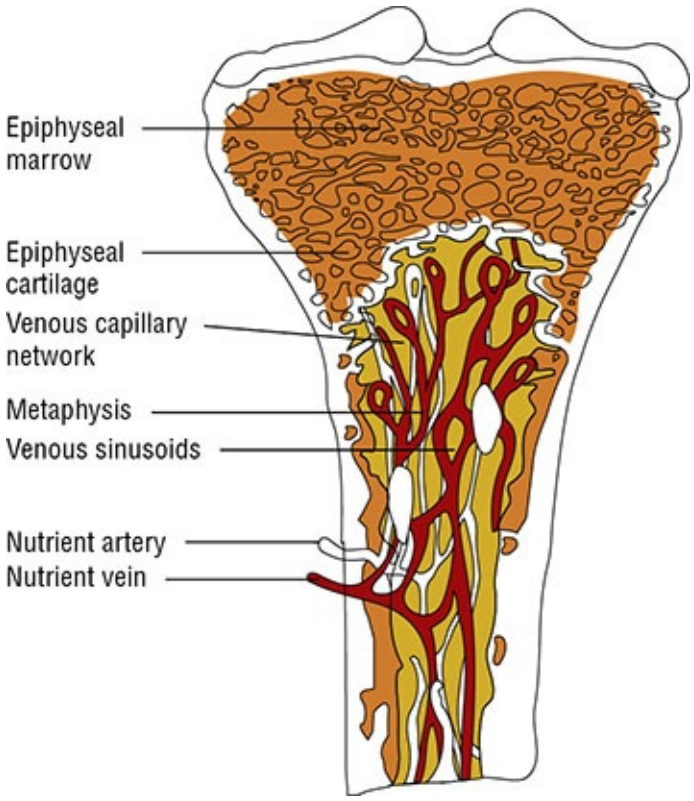


FIGURE 136-1 Cross-section of normal bone.

Neonatal infections commonly involve multiple bones. The vascular supply of long bones in neonates has unique anatomic characteristics that affect their clinical presentation. Bridging blood vessels go across the epiphyseal plate from the metaphysis into the epiphysis; thus, enabling an infection that started within the metaphyseal area to spread easily to involve the epiphyses and then break into the joint. Therefore, in infants, not only can the infection spread under the periosteum or break through the periosteum and the shaft as in older children, but the infection also can spread directly through the bridging blood vessels to involve the joint.

In children older than 12 to 18 months, *hematogeous osteomyelitis* typically involves a single bone and has a predilection for involvement of the long bones, such as the femur, tibia, humerus, and fibula. The infection that started in the

metaphysis of a long bone is prevented from spreading into the epiphysis and the adjacent joint space because of the epiphyseal growth plate which acts as a physical barrier; however, the exudate often dissects from the medulla through the soft cortex to the subperiosteal space as the periosteum in these children is loosely attached to the underlying cortex. The periosteum is thick and not easily ruptured; thus, containing the pus in the subperiosteal space, sometimes forming a subperiosteal abscess. If there is significant damage to the periosteum, the pus can decompress into a soft tissue abscess. The cortex obtains most of its blood supply from the periosteum and a subperiosteal abscess can impair the blood flow to the outer portion of the cortical bone resulting in a devitalized piece of dead bone termed a *sequestrum*. The elevated periosteum remains viable because its blood supply, derived from the overlying muscle, is unaffected. The raised periosteum will continue to produce bone; however, this new bone is now separated from the cortex because the periosteum has been raised from the infection. This new bone that is deposited under the periosteum is termed *involucrum*. In addition to these anatomic and functional features, there is some evidence that trauma is associated with developing an infection in specific bones. Children who develop *hematogeous osteomyelitis* may report some type of trauma before the onset of their symptoms and animal data indicate that traumatized bone is more likely to become infected than normal bone.

In adults, the periosteum is tightly bound to the cortex which is thick. These anatomic features generally cause the infections to remain intramedullary. As expected, subperiosteal abscess formation is less common in this population. The infection can spread to subperiosteal structures through the Haversian and Volkmann canals.

Osteomyelitis of the vertebrae is also acquired hematogenously and this occurs most frequently in patients older than 50 years of age.[5] Vertebral disease in younger adults and children usually involves the disk space and the two vertebral facets adjoining it because of the nature of the vascular supply of the vertebrae at that age. This syndrome is known as diskitis.

Direct Inoculation Osteomyelitis

This category of osteomyelitis includes infections caused by direct entrance of organisms from a source outside the body. Penetrating wounds (eg, trauma), open fractures, and various invasive orthopedic procedures can result in direct inoculation of organisms into the bone. More than 80% of cases of postoperative osteomyelitis are known to occur following open reduction of fractures. Specifically, these infections occur most commonly after internal fixation of a

hip fracture or femoral or tibial shaft fracture. Inoculation osteomyelitis can also occur as a result of penetrating foreign bodies, most commonly nail puncture injuries to the foot.

Contiguous Spread Osteomyelitis

Osteomyelitis secondary to spread from an adjacent soft tissue infection is called contiguous osteomyelitis. It can result from pressure ulcers (typically from laying in the decubitus position) or from adjacent soft tissue infections that most often involves the distal extremities (eg, diabetic foot infection). Less commonly, infections can spread from infected teeth to involve the mandible or occurs secondary to sinus infections by spreading through the mucosal lining of the sinuses into the vascular system surrounding the bone.

Contiguous-spread osteomyelitis occurs most commonly in patients older than age 50, likely because predisposing factors, such as diabetes mellitus, hip fractures or vascular disease, exist more often in this age group.

Patients with osteomyelitis in association with severe vascular insufficiency are extremely difficult to manage.[15] Frequently, patients with vascular disease develop osteomyelitis in their toes or even their fingers, and there is typically an adjacent area of infection, such as cellulitis or dermal ulcers. Importantly, infections in these patients can be polymicrobial, usually including staphylococcus and streptococcus, or a combination of those and Enterobacteriaceae. Enterococci and anaerobic organisms also can be involved, but not as often.

Chronic Osteomyelitis

Chronic osteomyelitis is more likely to occur if large segments of bone become avascular and necrotic. It is common in foot infections of patients with diabetes if proper surgery is not performed to debride a wound that goes to the bone. This results in a piece of devitalized bone to which antimicrobial delivery is impaired. As a result, the infection is prone to exacerbations and may lead to weakening of that bone or to the formation of draining sinuses to the skin.

Infectious Arthritis

Infectious arthritis usually is acquired by hematogenous spread. The synovial tissue is highly vascular and does not have a basement membrane, so organisms in the blood can easily reach the synovial fluid. **Table 136-2** summarizes the characteristics of acute infectious arthritis.

TABLE 136-2 Characteristics of Acute Infectious Arthritis

Feature	Finding
Peak incidence	Children younger than 16 years Adults older than 50 years
Clinical findings	Fever of 38-40°C (100.4-104°F) in children; painful swollen joint in the absence of trauma Physical examination: Effusion, restriction of joint motion, tenderness, redness, and warmth of joint
Most commonly affected joints	Knee, hip, ankle, elbow, wrist, and shoulder
Laboratory findings	
Erythrocyte sedimentation rate	Elevated in 90% of cases
White blood cell count	Elevated in 30%-60% of cases
Left shift	Seen in two-thirds of patients
Blood culture	Positive in 40% of cases
Needle aspiration of joint	Gram-stain diagnostic in 30%-50% of cases. Synovial fluid cultures are positive in 60%-80% of cases. Synovial fluid differential reveals 90% polymorphonuclear leukocytes. Synovial fluid glucose decreased relative to serum glucose. Lactic acid levels elevated in nongonococcal infectious arthritis, but not in gonococcal infectious arthritis

Preexisting abnormal joint architecture, joint trauma, and surgery are risk factors because chronic inflammation or trauma makes the joint more susceptible to infection. Individuals with rheumatoid arthritis can be prone to bacterial infection because of an inherent phagocytic defect, as well as concomitant corticosteroid therapy, biologic response modifier or other immunosuppressants. Patients infected with *N. gonorrhoeae* while sexually active are at risk of gonococcal arthritis.

In addition to hematogenous spread, organisms can gain access to the joint from a deep-penetrating wound injury, intra-articular steroid injections, arthroscopy, prosthetic joint surgery, or spread to the joint from a contiguous focus of osteomyelitis. After bacteria gain access to the joint, the organisms begin to multiply and produce a purulent exudate within the joint. If this joint effusion is present beyond 7 days, chronic, and sometimes irreversible, damage can occur to the bone and joint as a result of proteolytic enzymes and pressure

necrosis. Purulent effusions can promote cartilage destruction by increasing leukocyte enzyme activity. In conjunction with the development of the effusion, almost all patients will develop a hot, swollen, painful joint.

CLINICAL PRESENTATION

Osteomyelitis

The clinical presentation of acute *hematogeous osteomyelitis* is summarized in Table 136-3. Although neonatal *hematogeous osteomyelitis* can spread rapidly to involve the joint, often there are few associated systemic symptoms.[14] A joint effusion is present in 60% to 70% of neonatal infections. Decreased limb motion or edema over the affected area may be the only signs from which to suspect the diagnosis. While it is sometimes acute in onset, the disease is often insidious in children.

TABLE 136-3 Clinical Presentation of Hematogenous Osteomyelitis

Signs and symptoms
Significant tenderness of the affected area, pain, swelling, fever, chills, decreased motion, and malaise
Laboratory tests
Elevated erythrocyte sedimentation rate, C-reactive protein, and white blood cell count 50% of patients will have positive blood cultures
Diagnostic studies
Bone changes observed on radiographs 10-14 days after the onset of infection. Magnetic resonance imaging and technetium scans positive as early as 1 day after the onset of infection

Vertebral osteomyelitis produces nonspecific symptoms, such as constant back pain, fever or night sweats, and weight loss.[5] The pain typically is present at rest and increases in severity with movement. Serious neurologic complications can occur if the infection extends and compresses the spinal cord.

The presentation of osteomyelitis after surgery or trauma depends on the precipitating cause. If the infection follows surgery or bone trauma, the symptoms usually are noted within 1 month. The most frequent symptom is pain in the area of infection. Less commonly, patients also can develop a fever and elevated WBC count.

With contiguous-spread osteomyelitis there is often an area of localized tenderness, warmth, edema, and erythema over the infected site. Patients with

significant vascular insufficiency usually have local symptoms, such as pain, swelling, and redness. Less commonly, they also can have fever and elevated WBC count.

Infectious Arthritis

Patients with non-gonococcal bacterial arthritis almost always present with a fever, and 50% of patients have an elevated WBC count (see Table 136-2). The average initial synovial WBC count is $10 \times 10^3/mm^3$ ($10 \times 10^9/L$) or greater in non-gonococcal bacterial disease. Non-gonococcal bacterial arthritis is almost always monoarticular. The knee is the most commonly involved joint, but infections also can occur in the shoulder, wrist, hip, ankle, interphalangeal joints, and elbow joints. Sometimes, the initial focus of infection that acted as the portal of entry can be identified. Common routes for bacterial entrance include infections of the respiratory tract, skin, and urinary tract or previous bacteremia; often no specific source can be identified. Blood cultures are important in these patients because they can be positive in 50% of patients.

The most frequent initial sign of disseminated gonococcal infections is the triad of dermatitis, tenosynovitis (inflammation and swelling of a tendon), and migratory polyarthralgia or polyarthritis. Women are more prone to develop disseminated gonococcal infections than men by a ratio of 4:1. The second and third trimesters of pregnancy and the time of menses appear to be the times of greatest risk for developing gonococcal bacteremia, hypothesized to be associated with mucosal vascularity. Common joints involved include the knee, wrist, elbow, and ankle. Presentation varies slightly depending on whether or not the woman is pregnant. In nonpregnant women, duration of symptoms are longer, presence of joint effusion is more likely, and white blood cells are more often present within the synovial fluid.[16]

Another type of infectious arthritis occurs following prosthetic joint surgery. The most common symptom is pain. Local signs of inflammation and fever are common in acute infections but chronic infections present in a more subtle fashion, typically with pain alone and often loosening of the prosthesis. With these infections, the C-reactive protein typically is elevated, although a leukocytosis often is absent. Infections from intra-operative contamination usually become apparent within 1 year of surgery. Those that present early (<3 months) are usually *S. aureus,* occasionally gram-negative, anaerobic, or polymicrobial infections. Less virulent skin organisms such as *S. epidermidis,* Enterococcus, or the anaerobic gram-positive bacillus, *Cutibacterium* (formerly

Proprionibacterium) *acnes* present later, often 3 to 12 months from surgery. After 1 year, hematogenous spread becomes a risk factor for *S. aureus* infection again.

Radiologic and Laboratory Tests

Osteomyelitis

2 The evaluation of a patient who may have osteomyelitis has several unusual aspects. Radiographs of the involved area should be obtained to rule out other processes such as a fracture. Bone changes characteristic of osteomyelitis appear late and are not typically seen until at least 10 to 14 days after the onset of the infection as more than 50% of the bone matrix must be decalcified before the lesions can be detected radiologically. Magnetic resonance imaging (MRI) is the most sensitive and commonly used diagnostic imaging modality in those without metal hardware. It offers the advantage of better anatomic definition, especially of abscesses or joint effusions compared to plain radiograph or traditional computed topography (CT) scan. Radionuclide bone scanning (with technetium or gallium) CT or positron emission tomography (PET) scanning can be useful in identifying the focus of osteomyelitis in patients unable to have an MRI.[17]

Despite the seriousness of osteomyelitis, often there are few laboratory abnormalities. The erythrocyte sedimentation rate (ESR), C-reactive protein, and WBC count may be the only laboratory abnormalities. The degree of abnormality of these laboratory findings does not correlate with the disease outcome; however, these inflammatory markers are useful for monitoring therapy. C-reactive protein is generally the more sensitive marker of response to therapy and often increases and decreases before the ESR.

When a clinical assessment of osteomyelitis is suspected, it is important to establish a bacteriologic diagnosis by culture of the infected bone and blood. Accurate culture information is especially important as a guide for treatment of osteomyelitis in this era of increasing antimicrobial resistance. Bone aspiration or bone biopsy are valuable in determining an accurate bacteriologic diagnosis. In addition, they help determine whether or not there is an abscess present. If an abscess is identified, it must be drained and the pus cultured with a Gram stain performed. Aspirates of subperiosteal pus or metaphyseal fluid yield a pathogen in 70% of cases. Cultures should be done for both aerobic and anaerobic bacteria. A Gram-stain result from the aspirate can be useful in initiating appropriate empirical antibiotic therapy.

If a specimen is obtained from a previously undrained or unopened wound

abscess, the pathogen usually can be identified. In chronic osteomyelitis, however, identification can be more difficult. Open wounds and draining sinuses frequently are contaminated with other organisms and thus provide inaccurate culture information. They cannot be relied on to reflect the pathogen unless consecutive deep sinus tract cultures reveal the same pathogens.[15] Cultures of loculated pus aspirates in the area of orthopedic devices removed from infected bone can be trusted; however, to identify the infecting organism. The preferable time to obtain culture material in a patient with a chronic draining sinus is at the time of open surgical debridement.

In addition to performing cultures from the involved bone, it also is important to obtain cultures from any site believed to be the primary source of a bacteremia. Blood cultures should be obtained. Approximately 50% of patients with *hematogenous osteomyelitis* will have positive blood cultures and may obviate the need for bone aspiration in these patients.

Infectious Arthritis

3 Radiographs of infected joints often reveal distension of the joint capsule with soft tissue swelling in the adjacent space. MRI can be helpful in identifying an infected joint, especially the shoulder and hip. In patients who have developed an infected prosthetic joint, loosening of the prosthesis can be seen radiographically.

When evaluating the possibility of a patient having infectious arthritis, immediate joint aspiration with analysis of the synovial fluid is extremely important. The presence of purulent fluid usually indicates the presence of a septic joint. The synovial fluid WBC count is usually 50×10^3–$200 \times 10^3/mm^3$ (50×10^9–$200 \times 10^9/L$) when an infection is present. As with osteomyelitis, most patients will have an elevated C-reactive protein concentration and ESR. However, serum WBC, ESR, and C-reactive protein may not be useful acutely in septic arthritis.[18] Approximately half the patients with an infected joint have a low synovial glucose level, usually less than 40 mg/dL (2.2 mmol/L). Gram stains of joint fluid demonstrate bacteria in 50% of patients with septic arthritis; however, such stains are positive in only 25% of patients with gonococcal arthritis. Synovial fluid cultures usually are positive in patients with nongonococcal infections. Both blood and joint fluid should be cultured aerobically and anaerobically in a patient suspected of having an infected joint. Blood cultures are positive in one-half of patients with non-gonococcal infections but in only 20% of those with gonococcal infections. Pharyngeal, rectal, cervical, or urethral smears and cultures, as well as cultures of cutaneous

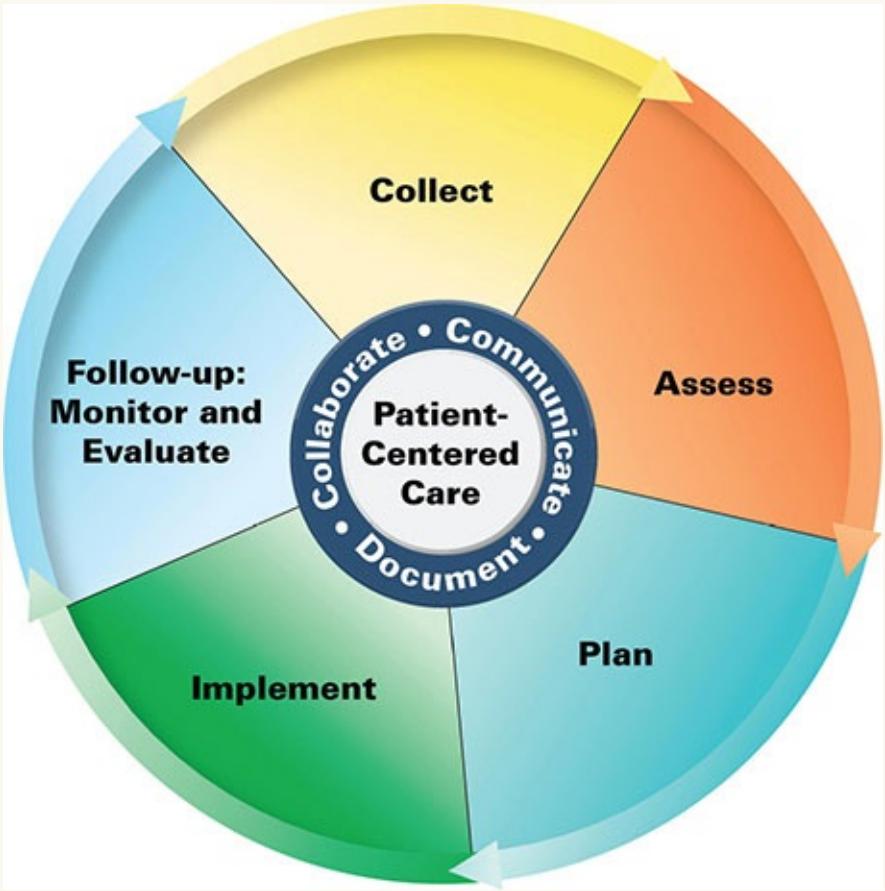
lesions, should be performed if a disseminated gonococcal infection is considered. Nucleic acid–based assays should also be used for the diagnosis of genital gonococcal infection.

TREATMENT

Desired Outcome

Osteomyelitis

The goals of treatment are resolution of the infection and prevention of long-term sequelae. The ultimate outcome of osteomyelitis depends on the acute or chronic nature of the disease and how rapidly appropriate therapy including surgical drainage where appropriate is initiated. Patients with acute osteomyelitis have the best prognosis. Cure rates exceeding 80% can be expected for patients with acute osteomyelitis who have surgery when indicated and receive appropriate antibiotics for 4 to 6 weeks. When the growth plate is involved in children, discrepancies in the growth of bones or angular bone deformities can result. The infection is almost never fatal.



Patient Care Process for Bone and Joint Infections

Collect

- Patient characteristics (eg, age, sex, pregnancy status)
- Patient medical history
- Social history (eg, ethanol or illicit drug use) and living conditions
- Current medications and recent antibiotic use
- Objective data
  - Culture of bone, synovial fluid, or deep tissue (not superficial)
  - Labs including white blood cells (WBC), serum creatinine (SCr), and C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)
  - Imaging for infection

Assess

- Risk factors for bone and joint infections (Table 136-1)
- Markers of infection (Tables 136-2 and 136-3)
- Culture results and antimicrobial susceptibilities
- Ability/willingness to adhere to treatment regimen, including self-administration of outpatient parenteral therapy or travel to infusion center
- Ability/willingness to pay for treatment options (eg, home health, infusion center visits, and/or prescriptions from pharmacy)
- Ability/willingness to obtain laboratory monitoring tests (eg, WBC, SCr, CRP, or ESR)
- Emotional status (eg, presence of anxiety, depression)

Plan*

- Drug therapy regimen including specific antibiotic dose, route, frequency, and duration (see Table 136-5)
- Monitoring parameters including efficacy (eg, WBC, CRP or ESR, pain, limb swelling) and safety (eg, complete blood count, SCr, diarrhea); frequency and timing of follow-up (Table 136-6)
- Patient education (eg, purpose of treatment, invasive procedures, drug-specific information, medication administration/injection technique)
- Self-monitoring for resolution of symptoms, occurrence of adverse effects, when to seek emergency medical attention
- Referrals to other providers when appropriate (eg, infectious diseases specialist, orthopedic surgeon, vascular surgeon, endocrine/diabetes specialist)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (2-4 weeks)

Follow-up: Monitor and Evaluate

- Resolution of symptoms (eg, pain, limb/joint swelling, instability)
- Presence of adverse effects (eg, cytopenias, diarrhea, hypersensitivity reactions)
- Patient adherence to treatment plan using multiple sources of information
- Reevaluate again at the end of therapy

**Collaborate with patient, caregivers, and other healthcare professionals.*

In contrast, patients with chronic osteomyelitis have a much poorer prognosis. Dead bone and other necrotic material from the infection act as a bacterial reservoir and make the infection very difficult to eliminate. Adequate surgical debridement to remove all the dead bone and necrotic material, combined with prolonged administration of antibiotics, provides the best chance to obtain a cure. The inability to remove all the dead bone can allow residual infection and require suppressive antibiotics to control the infection. Amputation, declines in quality of life, and recurrent infection are not uncommon with chronic osteomyelitis.

Infectious Arthritis

While many patients who develop infectious arthritis recover with no long-term sequelae, 50% are left with decreased joint function or mobility. Gonococcal arthritis usually resolves rapidly with antibiotics and has fewer sequelae. Individuals at greatest risk for long-term sequelae are those who have symptoms present for more than 7 days before starting therapy and those with infections occurring within the hip joint and infections caused by gram-negative organisms. Common long-term residual effects following infectious arthritis are limited joint motion and persistent pain.

During the initial phase of the infection, weight bearing such as walking on the joint should be avoided. Passive range-of-motion exercises should be initiated when the pain begins to subside to maintain joint mobility. Approximately one-third of patients with bacterial arthritis have a poor joint outcome, such as severe functional deterioration. Poor joint outcomes are associated with older patients, those with preexisting joint disease, and patients with an infected joint containing synthetic material.

General Approach to Treatment

Osteomyelitis

4 Following completion of the steps needed to determine the infecting organism, the most important treatment modality of acute osteomyelitis is the administration of appropriate antibiotics in adequate doses for a sufficient length of time. It is important to stress that early antibiotic therapy can mitigate the need for surgery, subsequent sepsis, chronic infection, disruption of longitudinal bone growth and angular deformity of the bone. A long delay in treatment can allow bone necrosis to occur and make eradication of the infection much more difficult. In these patients with chronic osteomyelitis, exacerbations of the infection can result if all necrotic tissue is not removed surgically and all microorganisms eliminated. Chronic suppressive antimicrobial therapy and adjunctive treatment with hyperbaric oxygen or antibiotic-impregnated implants during surgery also have been used.

If a patient with *hematogeous osteomyelitis* does not respond by having a decrease in fever, local swelling, redness, and pain following the initiation of adequate antibiotic therapy, the patient should undergo surgical debridement of the infected area. It is important to emphasize the priority of starting antibiotics immediately after the cultures have been obtained for best microbiological yield and outcomes.[19]

Infectious Arthritis

Patients with infectious arthritis are typically admitted to the hospital to obtain synovial fluid and blood cultures and initiate antimicrobial therapy. An attempt to decrease bacterial burden in the joint space is made by performing either open or arthroscopic debridement. Empiric antibiotics are started as soon as culture specimens are collected. As with osteomyelitis, it is important to stress early initiation of antibiotic therapy to avoid complications such as avascular necrosis, limb-length discrepancy, and pathologic fractures. Staphylococci and streptococci are the most common organisms found in septic arthritis, accounting for approximately 70% to 85% of all cases so treatment should be accordingly.[2,20,21]

In patients with prosthetic joint devices, it is imperative that orthopedic surgeons work alongside infectious disease practitioners to determine the best course of action.[22] The gold standard treatment method includes resection of the implant, placement of temporary antibiotic-impregnated cement spacer, and

delayed component re-implantation. Although it may be decided to retain the implant in certain cases for which patients will receive irrigation and debridement in addition to antibiotic therapy, or antibiotic therapy alone in patients unable to tolerate surgical procedures.[23]

Pharmacologic Therapy

Osteomyelitis

Antibiotic Selection A critical component in the management of osteomyelitis is the selection of appropriate antibiotics. Empiric therapy must be selected on the basis of the most likely infecting organism while the results of culture and susceptibility data are pending. Once culture and susceptibility results are obtained the antimicrobial therapy should be tailored. **Table 136-4** summarizes empiric therapy recommendations.

TABLE 136-4 Empiric Treatment of Osteomyelitis

Patient Subtype	Likely Infecting Organism	Antibiotic[a]	Recommendation Grades[b]
Newborn	*Staphylococcus aureus*, Group B *Streptococci*, *Escherichia coli*	Cefazolin 50-150 mg/kg/day IV	B-3
Children 3 years of age or younger	1. If vaccinated for *Haemophilus influenzae* type b: *K. kingae, S. aureus* or Streptococci 2. If not vaccinated against *H. influenzae* type b (*or Streptococcus pneumoniae*)	1. Cefazolin 100-150 mg/kg/day IV 2. Cefuroxime 150 mg/kg/day IV	B-3 B-3
Children 4 years of age and older	*S. aureus*	Vancomycin 60 mg/kg/day IV, clindamycin 40 mg/kg/day or cefazolin 100-150 mg/kg/day IV	A-3
Adults	*S. aureus*	Vancomycin 15 mg/kg every 12 hours or cefazolin 2 g IV every 8 hours	A-3
IV drug abusers	*S. aureus, Pseudomonas*	Vancomycin 15 mg/kg every 12 hours plus ciprofloxacin 750 mg orally twice daily, ceftazidime or cefepime 2 g IV every 8 hours	B-3
Postoperative or posttrauma patients	Gram-positive and gram-negative organisms	Vancomycin 15 mg/kg IV every 12 hours plus ceftazidime or cefepime 2 g IV every 8 hours	B-3
Patients with vascular insufficiency	Gram-positive and gram-negative organisms	Vancomycin 15mg/kg IV every 12 hours plus ceftriaxone 2 g every 24 hours	B-3
	If anaerobes suspected (necrosis)	Add metronidazole 500 mg every 8 hours or clindamycin 900 mg IV every 8 hours or substitute ertapenem for ceftriaxone	C-3

IV, intravenous.

[a]Dosage should be adjusted for some agents in patients with renal and/or hepatic dysfunction.

[b]Strength of recommendations: A, B, C = good, moderate, and poor evidence to support recommendation, respectively. Quality of evidence: 1 = Evidence from more than one properly randomized, controlled studies or multiple time series; or dramatic results from uncontrolled experiments. 2 = Evidence from more than one well-designed clinical trial with randomization, from cohort or case-controlled analytic studies. 3 = Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.

With staphylococcus being the most common bacteria in osteomyelitis, resistance patterns must be considered when deciding on an empiric agent. For communities showing low evidence of resistant strains of *S. aureus*, oxacillin, or nafcillin have historically been the drugs of choice, although cefazolin is now being used more often to treat susceptible strains due to ease of dosing, lower cost and fewer adverse effects compared to anti-staphylococcal penicillins.[22,23,24] Clindamycin can be used in less severe cases, in patients with severe beta-lactam allergies or where MRSA rates are unknown.[25,26] Clindamycin is used more commonly in children because MRSA is more likely to be community-acquired and susceptible to clindamycin in this population. If 10% or more of *S. aureus* isolates are methicillin resistant in the surrounding community, then an agent active more against MRSA should be selected

empirically. Vancomycin is the treatment of choice in this scenario and in adults since they often have risk factors for hospital-associated MRSA.[25,26] Daptomycin is an effective alternate in patients that are unable to tolerate the adverse effects associated with vancomycin.[27]

In the setting of vertebral osteomyelitis, empiric therapy should be initiated in conjunction with culture if the patient is hemodynamically unstable, septic or experiencing neurologic compromise; otherwise, it is recommended empiric therapy be held while awaiting culture results.[5] Vancomycin in combination with a fluoroquinolone or third/fourth generation cephalosporin such as ceftriaxone is a reasonable empiric regimen.

5 **Antibiotic Bone Concentration** Antibiotics used in the management of acute osteomyelitis generally are given in high doses (adjusted for weight, renal function, hepatic function, or both) so that adequate antimicrobial concentrations are reached within the infected bone and joint.[23,28] **Table 136-5** summarizes antibiotics doses that have been successful in the treatment of osteomyelitis.

TABLE 136-5 Antimicrobial Agents and Typical Doses for the Treatment of Bone and Joint Infections

Antimicrobial	Dose[a]	Comments
Amoxicillin	Adult: 1 g orally every 8 hours Children: 80-90 mg/kg/day divided every 12 hours	500-875 mg orally twice daily may be used for suppression in adults
Amoxicillin/Clavulanate	Adult: 2,000/125 mg orally every 12 hours Children: Children: 80-90 mg/kg/day of amoxicillin divided every 12 hours	875/125 mg orally twice daily or 500/125 mg three times daily may be used for suppression
Ampicillin	Adult: 2 g IV every 4 hours[21] Children: 150-200 mg/kg/day in 4 equal doses (max 8-12 g daily) VO: 12 g IV every 24 hours, continuous, or in 6 divided doses	May add IV aminoglycoside or ceftriaxone for treatment of *Enterococcus* spp. Continue adjunct therapy for 4-6 weeks in patients with infective endocarditis
Ampicillin/Sulbactam	Adult: 3 g IV every 6 hours	3 g dose equals 2 g ampicillin and 1 g sulbactam
Anti-staphylococcal (nafcillin, oxacillin, dicloxacillin) penicillins	Adult: Nafcillin or oxacillin 1-2 g IV every 4-6 hours Children: ≤200 mg/kg/day in 4 equal doses (max dose 8-12 g daily) VO: Nafcillin or oxacillin 1.5-2 g IV every 4-6 hours or continuous infusion	Adverse effects and cost are higher than cefazolin Dicloxicillin 500 mg four times daily may be used for suppression in adults
Aztreonam	Adult: 2 g IV every 8 hours	Use for patients with severe penicillin allergy and quinolone-resistant strains
Cefepime	Adult: 2 g IV every 8-12 hours	For Enterobacteriaceae, 2 g IV every 12 hours
Cefotetan	Adult: 2 g IV every 12 hours	
Ceftazidime	Adult: 2 g IV every 8 hours	
Ceftriaxone	Adult: 2 g IV every 24 hours Children: 80-100 mg/kg/dose every 12-24 hours	
Ciprofloxacin	Adult: 400 IV every 8-12 hours or 500-750 mg orally every 12 hours	Should not be used as monotherapy for Staphylococcus infection, but may be combined with rifampin. Higher dose for Pseudomonas
Clindamycin	Adult: 600 mg IV every 6 hours or 300-600 mg orally every 6 hours Children: 40 mg/kg/day in 4 equal doses (max dose 3 g daily) VO: 600-900 mg IV every 8 hours, or 300-450 mg orally four times daily	Recommended as second line for sensitive staphylococcal infection
Daptomycin	Adult: 6-8 mg/kg IV every 24 hours	
Doxycycline	Adult: 100 mg orally twice daily	Can be used in addition to rifampin for Brucella infection
Ertapenem	Adult: 1 g IV every 24 hours Children: 15 mg/kg every 12 hours	
First Generation Cephalosporin (Cefazolin, Cephalexin)	Adult: Cefazolin 2 g IV every 8 hours Children: 100-150 mg/kg/day in 3 equal doses (max dose 6 g daily)	Cephalexin 500 mg orally every 6 hours[21]
Imipenem/cilastatin	Adult: 500 mg IV every 6 hours	Can add IV aminoglycoside empirically for treatment of *P. aeruginosa*
Levofloxacin	Adult: 500-750 mg IV once daily or 750 mg orally once daily	Add rifampin for treatment of MRSA
Linezolid	Adult: 600 mg IV or orally every 12 hours Children: 30 mg/kg/day in 3 equal doses (max dose 1.2 g for no more than 28 days)	Long-term use can lead to cytopenias
Meropenem	Adult: 1 g IV every 8 hours	
Metronidazole	Adult: 500 mg orally or IV every 8 hours	Drug of choice for *Bacteroides* species and other susceptible anaerobes
Minocycline	Adult: 200 mg orally initially, then 100 mg orally twice daily	
Moxifloxacin	Adult: 400 mg orally once daily	For streptococci, enterobacteriaceae, and other susceptible gram-negative organisms. Not recommended for staphylococcal infection unless combined with rifampin
Penicillin G	Adult: 3-4 million units IV every 4 hours or 20 million units IV continuous every 24 hours	For enterococcus, add 4-6 weeks of aminoglycoside therapy in patients with infective endocarditis
Piperacillin/Tazobactam	Adult: 4.5 g IV every 6-8 hours	Every 6 hours or extended infusion (4 hour) for *P. aeruginosa*
Rifampin	Adult: 300 mg orally twice daily Children: 10 mg/kg/day orally divided twice daily	Only to be used in combination with another antimicrobial
Trimethoprim–Sulfamethoxazole	Adult: 1-2 double-strength tablets orally twice daily hours or 1 double-strength tablet orally three times a day	Second line agent for Enterobacteriaceae and other susceptible aerobic gram-negative organisms. May need to monitor sulfamethoxazole levels[5]
Vancomycin	Adult: 15 mg/kg IV every 12 hours Children: 60 mg/kg/day in 4 equal doses	Adjust based on patient and pharmacokinetic parameters. Target trough of 15 mcg per milliliter (mg/L; 10.4 µmol/L) or area under the concentration-curve of 400. Consider loading dose for MRSA and enterococcus. For enterococcus, add 4-6 weeks of aminoglycoside therapy in patients with infective endocarditis. For *S. aureus* or enterococcus, use only if patient is penicillin allergic or bacteria is penicillin resistant

IV, intravenous; MRSA, methicillin susceptible *Staphylococcus aureus*; VO, vertebral osteomyelitis.

[a]Dosage should be adjusted for some agents in patients with renal and/or hepatic dysfunction.

6 **Oral Antibiotic Therapy** Criteria for the use of oral outpatient antibiotic therapy for osteomyelitis includes all of the following:

- Confirmed osteomyelitis
- Initial positive clinical response to parenteral antibiotics
- A suitable oral agent available
- Adherence is ensured

Suitable candidates are children with good clinical response to intravenous therapy and adults without diabetes mellitus or peripheral vascular disease.

The use of oral antibiotics is well studied in children.[29–31] Typically, injectable antibiotics are used initially and then switched to oral antibiotics when the patient is afebrile and there is a decrease in the signs of inflammation and the ESR.[19] If pus is obtained on the initial needle aspirate, or if a reduction in fever, local swelling, and tenderness do not occur despite adequate rest, immobilization, and intensive antibiotic therapy, patients undergo surgical drainage. The patients enrolled in oral antibiotic trials generally had disease of recent onset, identification of a specific infecting organism, enforced adherence, and surgery as indicated. In patients who meet these criteria, oral antibiotics appear to offer a great advantage in the treatment of osteomyelitis. Patients not meeting these criteria may have a higher risk of developing chronic osteomyelitis if oral therapy is inappropriate or not strictly adhered to. In adults, oral antibiotics are used more conservatively due to more limited blood flow to the bones but evidence is emerging that oral therapy can be effective for adult osteomyelitis and septic arthritis.[32–34] Ciprofloxacin and levofloxacin are well-studied oral primary therapy due to their high bioavailability and great distribution into bone.[35] Flouroquinolones (with the exception of delafloxacin) are not reliably effective against Staphylococci on their own as resistance develops rapidly and should not be used alone empirically. They have successfully been combined with rifampin when isolates are susceptible to both classes of drugs.[36] Rifampin is particularly useful for treating infections with biofilms that have a propensity to grow on smooth surfaces such as bone, and especially prosthetic devices.[37]

Duration of Antibiotic Therapy

7 Following debridement, bone takes 3 to 4 weeks to revascularize, thus the

basis of treatment duration. The specific duration of antibiotic therapy needed in the management of osteomyelitis and septic arthritis has traditionally been 4 to 6 weeks and 3 to 4 weeks, respectively.[38] For adults, those durations of treatment are still recommended but newer studies in children have explored shorter durations along with more liberal transitions to oral antibiotics. For children with *septic arthritis*, a course as short as 10 days is sufficient as long as the C-reactive protein level normalizes.[39] French guidelines recommend treatment for a minimum of 3 weeks in children with osteomyelitis as failure rates approaching 20% have been observed with antibiotics for less than that.[40] This is based on studies showing that improvement in the patient's clinical signs and symptoms in addition to normalization of the C-reactive protein level or ESR are important parameters for predicting efficacy.[41,42] Treatment failures may be due to the presence of residual bacteria in necrotic bone or infected hardware (wires, plates, screws, and rods) that could not be removed.[35] If signs or symptoms are still present at the end of therapy, treatment should be extended. For adults, guidelines from the Infectious Diseases Society of America (IDSA) recommend therapy for 8 weeks in adults with osteomyelitis from MRSA,[43] particularly in patients with vertebral osteomyelitis at high-risk of relapse such as those with end-stage renal disease or undrained paravertebral/psoas abscesses.[44] In some cases of chronic osteomyelitis, lifelong suppressive therapy might be the most appropriate option, particularly when prosthetic devices remain.[45]

Duration of antibiotic administration for vertebral osteomyelitis can vary depending on the infecting organism, extent of bone destruction or abscesses. The IDSA guidelines recommend a minimum of 6 weeks of either parenteral therapy or highly bioavailable oral therapy.[3] This is necessary because of the outcomes in older patients with degenerative bone disease that have reduced blood flow to the site of infection and are most at risk of the disease. With gram-negative bacteria a longer duration (8 weeks or greater) is associated with less rates of recurrence compared to shorter durations (4-6 weeks).[7] One prospective trial compared 6 and 12 weeks of treatment for patients with pyogenic vertebral osteomyelitis (most commonly *S. aureus*) and found the longer duration to be no better.[46] For patients with retained hardware following prosthetic joint infection, 3 to 6 months of therapy is often necessary.[45] However, treatment durations of 6 to 8 weeks following debridement of retained implants can have similar outcomes to 12 weeks in that population.[47,48] Many questions remain on the optimal duration for bone infections in adults and whether it is safe to use shorter courses.[35]

Special Populations

Osteomyelitis in the intravenous drug user has unique features. More than 50% of such infections involve the vertebral column and up to 20% of infections are located in either the sternoarticular or pelvic girdle. Infections are much less frequent within the extremities. They also have an unusual spectrum of organisms. Although staphylococcus and streptococcus are sometimes cultured, with MRSA being more common than the general population, gram-negative bacteria are responsible for many infections. In one outbreak *P. aeruginosa*, either singly or in combination with other organisms, was cultured in 78% of all such infections. *Klebsiella*, *Enterobacter*, and *Serratia* species also can be found but less commonly. Spinal infections are caused predominately by *S. aureus.*[49]

Patients with sickle cell anemia and related hemoglobinopathies also represent a unique population in that two-thirds of bone infections in these patients are caused by *Salmonella* species, while the rest are usually caused by staphylococci and other gram-negative organisms.[50] Bowel infarctions from the sickle cell disease can facilitate the entry of salmonellae from the colon into the bloodstream with resultant hematogenous spread to the bone. Osteomyelitis in patients with sickle cell disease may occur in any bone, but it most commonly involves the medullary cavity of long or tubular bones. Because of the difficulty in separating bone pain during a sickle cell crisis from that of an infection, osteomyelitis can be relatively advanced in these patients by the time the diagnosis is made.

Infectious Arthritis

Antibiotic Selection

8 The three most important treatments of infectious arthritis are appropriate antibiotics, joint drainage, and joint rest. Smears of the synovial fluid can be useful to select appropriate antibiotic therapy initially.[8] If bacteria are not observed on the Gram stain in a patient who has a purulent joint effusion, antibiotics still should be initiated because of the low sensitivity of the Gram stain. A delay in initiating antibiotics significantly increases the likelihood for long-term complications. The specific antibiotic selected depends on the most likely infecting organism, but it should typically target *Staphylococcus* spp. (eg, vancomycin or clindamycin). When Staphylococci infect prosthetic hardware that cannot be removed, rifampin is recommended to be added to the therapy for its effects on biofilm, but drug–drug interactions should always be evaluated

with this agent.[45]

Antibiotic Joint Space Concentration

The antibiotics selected usually are administered parenterally to achieve sufficient concentrations within the synovial fluid, and thus intra-articular antibiotic injections are unnecessary.

In prosthetic joint infections, antimicrobial cement spacers are often used to aid in delivery of the antimicrobial to the site of infection. The most common antimicrobials used include vancomycin and aminoglycosides (tobramycin or gentamicin).[51] However, the doses of each agent are widely variable and it is uncertain whether the placement of antimicrobial cement spacers adds outcome benefit to systemic therapy.[51,52] The idea that antimicrobial cement spacers provide only beneficial local exposure of the antimicrobial agent without systemic consequences has been questioned.[53] The incidence of acute kidney injury in patients receiving treatment with antimicrobial cement spacers was 4.8%, with the incidence ranging from 2% to 17% based on the definition of acute kidney injury used.[54]

Similar to osteomyelitis, once the infection is confirmed and initial response to parenteral therapy is achieved, the culture susceptibilities have resulted, and adherence is ensured, then selected oral antibiotics can be used for the treatment of infectious arthritis.

Home Antibiotic Therapy

Because the management of bone and joint infections frequently requires prolonged parenteral antibiotics, administration of intravenous treatment in the home or a clinic is commonly performed. This is called outpatient parenteral antimicrobial therapy (OPAT). Although acute osteomyelitis is one of the more common infectious diseases that can be treated with long-term intravenous antibiotics outside the hospital, not all patients are acceptable candidates for home administration. Patients must be screened to include those who are receiving a stable treatment, are interested and motivated in participating, who have good venous access, and have support from family members or neighbors along with safe facilities for drug storage including refrigeration at home. Certain exclusion criteria also must be considered. Patients are not eligible if their eyesight or dexterity prevent them from attaching the admixture to their catheter when they do not have a caregiver that can help them daily. Many providers will not allow patients to receive parenteral antibiotics at home if they

have a recent history of alcoholism or of intravenous drug abuse. In addition to meeting these initial screening criteria, patients complete training before hospital discharge. Understanding of aseptic technique, proper catheter care, and correct administration techniques must be documented. Once a patient is receiving therapy in the home environment, continued monitoring of their antimicrobial therapy, and drug levels when indicated, is important. It is also vital to ensure compliance with the antimicrobial regimen. Complications in patients receiving outpatient courses of parenteral antibiotics are fairly common (18%), and often lead to readmission when they occur.[55] Patients without adequate insurance or the support at home necessary to administer intravenous antibiotics may choose to come to an infusion center each day for treatment. Others may need to be admitted to a skilled nursing facility for the duration of their therapy. Those with adequate vascular access can use a peripheral intravenous catheter, although these typically are only able to be accessed for a few days. A midline or central intravenous catheter is often required for long-term venous access. This is most commonly accomplished with a peripherally inserted central catheter (PICC).

The specific antibiotic regimen characteristics must also be considered when evaluating a patient for home antibiotics. After susceptibility of the microbiologic culture, the number of required daily antimicrobial doses is important. Some facilities are only able to accommodate infusions once each day. The stability of the antibiotic at room temperature is relevant when considering a continuous infusion (that can ideally be exchanged once daily), and shelf life can determine time of deliveries. Aminoglycosides and vancomycin have unique requirements for monitoring of the regimen, such as more frequent serum creatinine and drug-level monitoring. Although an organism can be susceptible to several antimicrobial agents, using one antibiotic can provide practical benefits over other agents or combinations.

Individualized Therapy

Individualized therapy is important in the treatment of osteomyelitis and infectious arthritis. Patient quality of life may be significantly diminished in the short-term from an inconvenient treatment regimen, but the long-term sequelae of inadequately treated infection can be much worse, such as impaired joint motion draining sinus tracts, or even amputation, if it is required. Patient demographics, infection characteristics (eg, infecting organism and its susceptibility patterns), treatment cost, and quality-of-life issues all play a major role in evaluating individualized treatment alternatives (oral therapy or OPAT) rather than requiring patients to remain hospitalized to receive 4 to 6 weeks of

intravenous antibiotics. Although serious adverse reactions are uncommon, in one study 85.7% of children receiving vancomycin had some form of adverse drug events and 42.9% of patients required the drug be discontinued.[56] Monitoring is important to ensure that personalized therapy is effective to both cure the infection as well as minimize the risk for complications.

EVALUATION OF THERAPEUTIC OUTCOMES

Monitoring of the Pharmaceutical Care Plan

9 Patients with bone and joint infections must be monitored closely. **Table 136-6** summarizes a pharmaceutical care monitoring protocol. An assessment of a therapy's success or failure is based on the patient's clinical findings and laboratory values. The clinical signs of inflammation, such as swelling, tenderness, pain, redness, and fever, should resolve relatively quickly with appropriate therapy. Initially, the clinical signs are assessed daily until improvement and then periodically thereafter. Elevations in WBC count also should decline gradually. The ESR usually is determined weekly. Elevations in the C-reactive protein or ESR may not return to normal until after several weeks of therapy. The WBC count usually is obtained once (or twice) per week until it returns to the normal range and then is monitored for myelosuppression along with other blood cells. If by the end of the 4- to 6-week antibiotic course the clinical findings of osteomyelitis are no longer present and the C-reactive protein and ESR are within normal limits, the patient can be considered a clinical cure. Patients can relapse, however, after initially appearing to be cured. No relapse for 1 year generally is considered a complete cure.

TABLE 136-6 Monitoring Protocol

Parameter	Frequency	Notes
Culture and susceptibility	At initiation of treatment	No need to repeat unless clinical failure or original was not from a deep culture site (surgical sample)
White blood cell count	One time per week until within normal range	
C-reactive protein or erythrocyte sedimentation rate	Weekly	May not decrease to normal range until several weeks of therapy
Clinical signs of inflammation (redness, pain, swelling, tenderness, and fever)	Daily during initiation of therapy	
Adherence of outpatient therapy	Reinforce before starting therapy and with each healthcare visit	Adherence is critical if treatment is to be successful
Complete blood count	Weekly	Certain antimicrobial agents may cause blood dyscrasias when used for long-term therapy (eg, linezolid, trimethoprim–sulfamethoxazole, even vancomycin and beta-lactams to a lesser extent)

If a patient fails to resolve the clinical signs and symptoms of inflammation after appropriate empirical antibiotics, suspicion for an abscess should be raised and imaging by MRI and surgical debridement may be needed. In addition, the patient might have a resistant or an atypical infecting organism that may require a modification of the antibiotic therapy. It is especially important to identify the infecting organism and its susceptibility pattern. Follow-up cultures at subsequent debridements can be useful to assess the antibiotic therapy in patients

with unresolved infection.

Despite apparently adequate surgery and antibiotics, some patients can fail therapy and have relapses in their infection. This scenario is more common in those having chronic osteomyelitis, especially with peripheral vascular disease. These patients can require long-term oral suppressive antimicrobial therapy to keep the infection under control.

Postclass Engaged Learning Activity

The long-acting lipoglycopeptide antibiotics, dalbavancin and oritavancin, are potentially useful treatments for bone and joint infections because of their infrequent dosing and gram-positive spectrum of activity. Conduct a literature search to identify one primary research report published on these agents in the last 2 years. If the manuscript provides data on the safety or effectiveness of these drugs in treating deep-seated infection for longer than 2 weeks, reflect on the advantages and disadvantages for this type of treatment strategy.

ABBREVIATIONS

CRP	C-reactive protein
CT	computerized tomography
ESR	erythrocyte sedimentation rate
IDSA	Infectious Diseases Society of America
MRI	magnetic resonance imaging
MRSA	methicillin-resistant *Staphylococcus aureus*
OPAT	outpatient parenteral antimicrobial therapy
PET	positron emission tomography
PICC	peripherally inserted central catheter
WBC	white blood cell
VO	vertebral osteomyelitis

REFERENCES

1. Waldvogel FA, Medoff G, Swartz MN. Osteomyelitis: A review of clinical features, therapeutic considerations and unusual aspects. *N Engl J Med*. 1970;282(4):198–206.
2. Titecat M, Senneville E, Wallet F, et al. Bacterial epidemiology of

osteoarticular infections in a referent center: 10-year study. *Orthop Traumatol Surg Res*. 2013;99(6):653–658.

3. Kremers HM, Nwojo ME, Ransom JE, Wood-Wentz CM, Melton LJ 3rd, Huddleston PM 3rd. Trends in the epidemiology of osteomyelitis: A population-based study, 1969 to 2009. *J Bone Joint Surg Am*. 2015;97(10):837–845.
4. Juchler C, Spyropoulou V, Wagner N, et al. The contemporary bacteriologic epidemiology of osteoarticular infections in children in Switzerland. *J Pediatr*. 2018;194:190–196.e1.
5. Berbari EF, Kanj SS, Kowalski TJ, et al. Executive summary: 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. *Clin Infect Dis*. 2015;61(6):859–863.
6. Desoutter S, Cottier JP, Ghout I, et al. Susceptibility pattern of microorganisms isolated by percutaneous needle biopsy in nonbacteremic pyogenic vertebral osteomyelitis. *Antimicrob Agents Chemother*. 2015;59(12):7700–7706.
7. Park KH, Cho OH, Jung M, et al. Clinical characteristics and outcomes of hematogenous vertebral osteomyelitis caused by gram-negative bacteria. *J Infect*. 2014;69(1):42–50.
8. Garcia-Arias M, Balsa A, Mola EM. Septic arthritis. *Best Pract Res Clin Rheumatol*. 2011;25(3):407–421.
9. Hernandez-Ruperez MB, Suarez-Arrabal MD, Villa-Garcia A, et al. *Kingella kingaeas* the main cause of septic arthritis: Importance of molecular diagnosis. *Pediatr Infect Dis J*. 2018;37(12):1211–1216.
10. Olarte L, Romero J, Barson W, et al. Osteoarticular infections caused by streptococcus pneumoniae in children in the post-pneumococcal conjugate vaccine era. *Pediatr Infect Dis J*. 2017;36(12):1201–1204.
11. Garcia-De La Torre I, Nava-Zavala A. Gonococcal and nongonococcal arthritis. *Rheum Dis Clin North Am*. 2009;35(1):63–73.
12. Mathews CJ, Weston VC, Jones A, Field M, Coakley G. Bacterial septic arthritis in adults. *Lancet*. 2010;375(9717):846–855.
13. Horowitz DL, Katzap E, Horowitz S, Barilla-LaBarca ML. Approach to septic arthritis. *Am Fam Physician*. 2011;84(6):653–660.
14. Funk SS, Copley LA. Acute hematogenous osteomyelitis in children: Pathogenesis, diagnosis, and treatment. *Orthop Clin North Am*. 2017;48(2):199–208.

15. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis*. 2012;54(12):e132–e173.
16. Bleich AT, Sheffield JS, Wendel GDJr, Sigman A, Cunningham FG. Disseminated gonococcal infection in women. *Obstet Gynecol*. 2012;119(3):597–602.
17. Manz N, Krieg AH, Heininger U, Ritz N. Evaluation of the current use of imaging modalities and pathogen detection in children with acute osteomyelitis and septic arthritis. *Eur J Pediatr*. 2018;177(7):1071–1080.
18. Carpenter CR, Schuur JD, Everett WW, Pines JM. Evidence-based diagnostics: Adult septic arthritis. *Acad Emerg Med*. 2011;18(8):781–796.
19. Spruiell MD, Searns JB, Heare TC, et al. Clinical care guideline for improving pediatric acute musculoskeletal infection outcomes. *J Pediatric Infect Dis Soc*. 2017;6(3):e86–e93.
20. Murillo O, Gomez-Junyent J, Grau I, et al. Clinical findings of bacteremic septic arthritis according to the site of acquisition: The overlap between health care-related and community- and nosocomial-acquired cases. *Eur J Intern Med*. 2016;28:38–42.
21. Ascione T, Pagliano P, Balato G, Mariconda M, Rotondo R, Esposito S. Oral therapy, microbiological findings, and comorbidity influence the outcome of prosthetic joint infections undergoing 2-stage exchange. *J Arthroplasty*. 2017;32(7):2239–2243.
22. Lee B, Tam I, Weigel B 4th, et al. Comparative outcomes of beta-lactam antibiotics in outpatient parenteral antibiotic therapy: Treatment success, readmissions and antibiotic switches. *J Antimicrob Chemother*. 2015;70(8):2389–2396.
23. DeRonde KJ, Girotto JE, Nicolau DP, et al. Management of pediatric acute hematogenous osteomyelitis, part I: Antimicrobial stewardship approach and review of therapies for methicillin-susceptible staphylococcus aureus, streptococcus pyogenes, and *Kingella kingae. Pharmacotheapy*. 2018;38(9):947–966.
24. Youngster I, Shenoy ES, Hooper DC, Nelson SB. Comparative evaluation of the tolerability of cefazolin and nafcillin for treatment of methicillin-susceptible staphylococcus aureus infections in the outpatient setting. *Clin Infect Dis*. 2014;59(3):369–375.
25. Kaplan SL. Recent lessons for the management of bone and joint

infections. *J Infect*. 2014;68(Suppl 1):S51–S56.

26. Pendleton A, Kocher MS. Methicillin-resistant *Staphylococcus aureus* bone and joint infections in children. *J Am Acad Orthop Surg*. 2015;23(1):29–37.
27. Byren I, Rege S, Campanaro E, et al. Randomized controlled trial of the safety and efficacy of daptomycin versus standard-of-care therapy for management of patients with osteomyelitis associated with prosthetic devices undergoing two-stage revision arthroplasty. *Antimicrob Agents Chemother*. 2012;56(11):5626–5632.
28. Pea F. Penetration of antibacterials into bone: What do we really need to know for optimal prophylaxis and treatment of bone and joint infections? *Clin Pharmacokinet*. 2009;48(2):125–127.
29. Zaoutis T, Localio AR, Leckerman K, Saddlemire S, Bertoch D, Keren R. Prolonged intravenous therapy versus early transition to oral antimicrobial therapy for acute osteomyelitis in children. *Pediatrics*. 2009;123(2):636–642.
30. Keren R, Shah SS, Srivastava R, et al. Comparative effectiveness of intravenous vs oral antibiotics for postdischarge treatment of acute osteomyelitis in children. *JAMA Pediatr*. 2015;169(2):120–128.
31. Alcobendas R, Remesal A, Murias S, Nunez E, Calvo C. Outpatients with acute osteoarticular infections had favourable outcomes when they received just oral antibiotics without intravenous antibiotics. *Acta Paediatr*. 2018;107(10):1792–1797.
32. Daver NG, Shelburne SA, Atmar RL, et al. Oral step-down therapy is comparable to intravenous therapy for staphylococcus aureus osteomyelitis. *J Infect*. 2007;54(6):539–544.
33. Babouee Flury B, Elzi L, Kolbe M, et al. Is switching to an oral antibiotic regimen safe after 2 weeks of intravenous treatment for primary bacterial vertebral osteomyelitis? *BMC Infect Dis*. 2014;14:226.
34. Li HK, Rombach I, Zambellas R, Walker AS, McNally MA, et al. Oral versus Intravenous Antibiotics for Bone and Joint Infection. *New Engl J Med*. 2019;380:425–36.
35. Spellberg B, Lipsky BA. Systemic antibiotic therapy for chronic osteomyelitis in adults. *Clin Infect Dis*. 2012;54(3):393–407.
36. Coiffier G, Albert JD, Arvieux C, Guggenbuhl P. Optimizing combination rifampin therapy for staphylococcal osteoarticular infections. *Joint Bone Spine*. 2013;80(1):11–17.

37. Zimmerli W, Sendi P. Orthopaedic biofilm infections. *APMIS*. 2017;125(4):353–364.
38. White CN, Rolston KV. Osteomyelitis: Drug bioavailability and bone penetration are key. *JAAPA*. 2012;25(7):21,27.
39. Peltola H, Paakkonen M, Kallio P, Kallio MJ, Osteomyelitis-Septic Arthritis (OM-SA) Study Group. Prospective, randomized trial of 10 days versus 30 days of antimicrobial treatment, including a short-term course of parenteral therapy, for childhood septic arthritis. *Clin Infect Dis*. 2009;48(9):1201–1210.
40. Lorrot M, Gillet Y, Gras Le Guen C, Launay E, Cohen R, Grimprel E. Antibiotic therapy of bone and joint infections in children: Proposals of the french pediatric infectious disease group. *Arch Pediatr*. 2017;24(12S):S36–S41.
41. Peltola H, Paakkonen M, Kallio P, Kallio MJ; Osteomyelitis-Septic Arthritis Study Group. Short- versus long-term antimicrobial treatment for acute hematogenous osteomyelitis of childhood: Prospective, randomized trial on 131 culture-positive cases. *Pediatr Infect Dis J*. 2010;29(12):1123–1128.
42. Paakkonen M, Peltola H. Simplifying the treatment of acute bacterial bone and joint infections in children. *Expert Rev Anti Infect Ther*. 2011;9(12):1125–1131.
43. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant staphylococcus aureus infections in adults and children. *Clin Infect Dis*. 2011;52(3):e18–55.
44. Park KH, Cho OH, Lee JH, et al. Optimal duration of antibiotic therapy in patients with hematogenous vertebral osteomyelitis at low risk and high risk of recurrence. *Clin Infect Dis*. 2016;62(10):1262–1269.
45. Osmon DR, Berbari EF, Berendt AR, et al. Diagnosis and management of prosthetic joint infection: Clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2013;56(1):e1–e25.
46. Bernard L, Dinh A, Ghout I, et al. Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: An open-label, non-inferiority, randomised, controlled trial. *Lancet*. 2015;385(9971):875–882.
47. Lora-Tamayo J, Euba G, Cobo J, et al. Short- versus long-duration levofloxacin plus rifampicin for acute staphylococcal prosthetic joint

infection managed with implant retention: A randomised clinical trial. *Int J Antimicrob Agents*. 2016;48(3):310–316.

48. Chaussade H, Uckay I, Vuagnat A, et al. Antibiotic therapy duration for prosthetic joint infections treated by debridement and implant retention (DAIR): Similar long-term remission for 6 weeks as compared to 12 weeks. *Int J Infect Dis*. 2017;63:37–42.
49. Ziu M, Dengler B, Cordell D, Bartanusz V. Diagnosis and management of primary pyogenic spinal infections in intravenous recreational drug users. *Neurosurg Focus*. 2014;37(2):E3.
50. Marti-Carvajal AJ, Agreda-Perez LH. Antibiotics for treating osteomyelitis in people with sickle cell disease. *Cochrane Database Syst Rev*. 2016;11:CD007175.
51. Iarikov D, Demian H, Rubin D, Alexander J, Nambiar S. Choice and doses of antibacterial agents for cement spacers in treatment of prosthetic joint infections: Review of published studies. *Clin Infect Dis*. 2012;55(11):1474–1480.
52. Athans V, Veve MP, Davis SL. Trowels and tribulations: Review of antimicrobial-impregnated bone cements in prosthetic joint surgery. *Pharmacotherapy*. 2017;37(12):1565–1577.
53. Edelstein AI, Okroj KT, Rogers T, Della Valle CJ, Sporer SM. Systemic absorption of antibiotics from antibiotic-loaded cement spacers for the treatment of periprosthetic joint infection. *J Arthroplasty*. 2018;33(3):835–839.
54. Luu A, Syed F, Raman G, et al. Two-stage arthroplasty for prosthetic joint infection: A systematic review of acute kidney injury, systemic toxicity and infection control. *J Arthroplasty*. 2013;28(9):1490–1498.e1.
55. Keller SC, Williams D, Gavgani M, et al. Rates of and risk factors for adverse drug events in outpatient parenteral antimicrobial therapy. *Clin Infect Dis*. 2018;66(1):11–19.
56. Faden D, Faden HS. The high rate of adverse drug events in children receiving prolonged outpatient parenteral antibiotic therapy for osteomyelitis. *Pediatr Infect Dis J*. 2009;28(6):539–541.

137

Sepsis and Septic Shock

S. Lena Kang-Birken and Sul R. Jung

KEY CONCEPTS

1. Gram-negative organisms are isolated in 44% to 59% in sepsis or septic shock, followed by gram-positive bacteria in 37% to 52%, and fungi in 4% to 10%. *Candida albicans* remains the most prevalent *Candida* species: however non-*albicans Candida* species collectively is more frequently isolated.
2. Pathogenesis of sepsis is complex and multifactorial consisting of causative pathogen, host characteristics, and the inflammatory responses during which the interactions between pro- and anti-inflammatory cytokines, procoagulant state, and decreased fibrinolysis occur simultaneously.
3. The highest mortality is reported in patients with complicated intra-abdominal infections, chronic kidney disease, renal replacement therapy, multiple organ dysfunction, candidemia, and septic shock.
4. Initial resuscitation from sepsis-induced hypoperfusion should begin with at least 30 mL/kg of IV crystalloid fluid. Dynamic fluid responsiveness assessment by examining cardiac output with fluid bolus is essential to avoid fluid overload.
5. Prompt initiation of empiric broad-spectrum IV antibiotics within 1 hour of recognition of sepsis or septic shock improves survival, and the regimen should be assessed daily for potential de-escalation.
6. Norepinephrine is the preferred vasopressor to achieve and maintain MAP goal of at least 65 mmHg in fluid-resuscitation refractory septic shock, and it should be titrated up carefully to an end point of adequate organ perfusion.
7. Implementation of a protocolized, performance improvement bundle including administration of fluid and broad-spectrum antibiotics and use of

vasopressor agents improves patient outcomes. The updated Sepsis-3 guidelines recommend 1-hour care for start of immediate treatment and possibly faster transition to vasopressors to meet MAP goal.

8. Intravenous hydrocortisone is recommended for adult patients with septic shock who are hemodynamically unstable after initial resuscitation with IV fluids and vasopressors.
9. A blood glucose level less than 180 mg/dL (10.0 mmol/L) is recommended for critically ill patients to reduce potential hypoglycemia and mortality associated with tighter blood glucose control (ie, blood glucose goal of 81-108 mg/dL [4.5-6.0 mmol/L]).

Preclass Engaged Learning Activity

Watch the video entitled “Sepsis: First Response” from Get Ahead of Sepsis, launched by the Centers for Disease Control and Prevention (CDC), at its website: https://tinyurl.com/y3tdturz. https://tinyurl.com/yxl7nlzr. This 15-minute video provides an overview of the initial presentation of sepsis as the patient is brought to the emergency department. It highlights the importance of recognizing the signs and symptoms of sepsis, assessing for sepsis-specific measurements, and initiating treatment with fluid resuscitation. This video will enhance the students’ understanding regarding the COLLECT and ASSESS steps in the patient care process.

INTRODUCTION

Sepsis is a medical emergency when left untreated, has high probability of death. It has a unique disease process where it may impact multiple organ systems. The inflammatory response with the release of numerous cytokines will directly affect the vasculature causing capillary leak, hypovolemia, decreased cardiac output, hypotension leading to renal failure, heart failure, brain failure, also puts stress on our endocrine system, etc. Due to the potential expansive downward spiral, sepsis requires a prompt recognition, efficient assessment, and aggressive treatment.

DEFINITIONS

The most recent sepsis guidelines published in 2016 (Sepsis-3) derived new categorization and definition of sepsis continuum. However, it is still important to recognize the old definitions related to the spectrum of sepsis and how they were utilized in the clinical trials and guidelines prior to 2016. Periods of bacteremia, systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock, or multiple-organ dysfunction syndrome often overlap, and they signify an important continuum of progressive physiologic decline. *Severe sepsis* was defined as patients with an acute organ dysfunction, such as acute renal failure or respiratory failure in 2012 guidelines (Sepsis-2).[1] Sepsis-induced hypotension is defined as a systolic blood pressure less than 90 mm Hg or mean arterial pressure (MAP) less than 70 mm Hg (**Table 137-1**).[1] *Septic shock* refers to sepsis patients with sepsis-induced hypotension that is refractory to adequate fluid resuscitation, thus requiring vasopressor administration. Sepsis-induced tissue hypoperfusion is defined as infection-induced hypotension, elevated lactate, or oliguria.[1,2] Sepsis-3 redefined sepsis by combining sepsis and severe sepsis from Sepsis-2 guideline as "life-threatening organ dysfunction caused by a dysregulated host response to infection."[3] The definition of septic shock is when a septic patient has persistent hypotension (MAP< 65 mm Hg) requiring vasopressor along with continued elevated serum lactate (≥2 mmol/L) post adequate fluid resuscitation defined as 30 mL/kg of crystalloids.

TABLE 137-1 Comparison of Definitions from Sepsis-2 and Sepsis-3 Guidelines

Sepsis-2 Guideline (2012)	Sepsis-3 Guideline (2016)
Systemic inflammatory response syndrome (SIRS) to infectious or noninfectious insults: Two or more of the following: • Temperature >38°C or <36°C • Heart rate >90 beats/minute • Respiratory rate >20 breaths/minute • WBC >12,000/mm³ (12 x 10⁹/L) or <4000 cells/mm³ (4 x 10⁹/L) or > 10% (0.10) immature bands **Sepsis**: SIRS + probable or documented infection **Severe sepsis**: Sepsis + one or more organ dysfunction or hypoperfusion **Septic shock**: Sepsis + refractory hypotension despite fluid resuscitation (30mL/kg) or serum lactate >1 mmol/L	**Sepsis**: Life-threatening organ dysfunction caused by a dysregulated host response to infection • Acute change in total SOFA score ≥2 points **Septic shock**: Sepsis + persistent hypotension requiring vasopressor use and serum lactate >2 mmol/L despite adequate fluid resuscitation

SOFA, sequential organ failure assessment; WBC, white blood cell.

Data from References 1 and 3.

EPIDEMIOLOGY

Sepsis continues to pose major healthcare burden. The US Nationwide Inpatient Sample reported a significant increase in the hospitalizations due to sepsis from 1.2% in 2005 to 2.7% in 2014.[4] Despite aggressive, prompt medical care and advances, overall in-hospital deaths remain approximately 15%, but the mortality rate may be as high as 50.7% in septic shock.[4–6] In addition, total cost of hospitalization due to sepsis increased from $22.2 to $38.1 billion between 2005 and 2014, making it the most expensive condition to be treated in the US hospitals.[4] Given the public health and financial burden, there is a vital need for the clinicians to comprehend the pathophysiology and the optimal management approaches for these acutely ill patients with sepsis or septic shock.

ETIOLOGY

Risk Factors for Infection

Pathogenesis of sepsis is multifactorial, which begins with the patient's specific predisposition to infection. Advanced or very young age, pre-existing conditions

including heart failure, diabetes, chronic obstructive pulmonary disease, cirrhosis, alcohol dependence, and end-stage renal disease, and other immunosuppressive diseases such as neoplasm and human immunodeficiency virus (HIV) disease predispose patients at risk for infection.[4,7] Male gender has been associated with higher incidence of sepsis in the past. However, the difference between the genders appears to be diminishing.[7,8] Once the infection occurs, the risk factors for developing sepsis and organ dysfunction have not been well described. However, multiple factors including patients' risk factors for infection, site of infection, etiologic microorganism, and a specific organ dysfunction as well as the number of organs contribute to poor prognosis.[7,9]

Pathogens

1 Among the microorganisms isolated from blood cultures, gram-negative organisms were isolated in 44% to 59% of patients with sepsis or septic shock, gram-positive bacteria in 37% to 52%, anaerobic organisms in 5%, and fungi in 4% to 10%.[8,10–12] However, in the majority (approximately 70%) of the sepsis cases, a specific causal microorganism was not documented.[8,10]

The most common anatomic source of infection that leads to sepsis is the lung (40%-42%), followed by intra-abdominal space (31%-34%), and genitourinary tract (11%-15%).[10,11]

Gram-Negative Bacteria

Escherichia coli is by far the most commonly isolated gram-negative microorganism in sepsis (55%-60%), followed by *Klebsiella* species, *Proteus* species, *Enterobacter* species, and *Pseudomonas aeruginosa*.[11,13,14] *P. aeruginosa* and *Acinetobacter* species are more likely to be associated with prior antibiotic exposure and usually exhibit multidrug resistance.[14,15]

Mortality increases significantly with increasing severity of sepsis (3.5% for sepsis, 9.9% in severe sepsis, and 29% in septic shock), especially in presence of *P. aeruginosa*.[14] Furthermore, severity of underlying conditions is a major factor associated with negative outcome of gram-negative sepsis. For example, patients with rapidly fatal conditions, such as acute leukemia, aplastic anemia, cirrhosis, or HIV, have a significantly worse prognosis than those patients with nonfatal underlying conditions such as diabetes mellitus or chronic renal insufficiency.[7]

Gram-Positive Bacteria

The most common gram-positive organisms are *Staphylococcus aureus*, followed by coagulase-negative *Staphylococci*, *Enterococcus* species, and *Streptococcus pneumoniae*.[11,13] *S. aureus* bacteremia is associated with an overall mortality rate ranging between 10% and 30%.[9] Factors related to a higher mortality include older age, shock, pre-existing renal failure, and the presence of a rapidly fatal underlying disease. *Staphylococcus epidermidis* is most often related to infected intravascular devices, artificial heart valves and stents, and the use of intravenous (IV) and intra-arterial catheters. Enterococci are most commonly isolated from blood cultures following a prolonged hospitalization and treatment with broad-spectrum cephalosporins.

Anaerobic Bacteria

Anaerobic bacteria, most commonly *Bacteroides fragilis* and *Clostridium* species, are usually considered low-risk organisms for the development of sepsis. If present, anaerobes are often found together with other pathogenic bacteria that are commonly found in sepsis. Polymicrobial infections accounted for 5% to 39% of sepsis, especially in cases of intra-abdominal infections.[7,11,13] Mortality rates associated with polymicrobial infections are similar to sepsis caused by a single organism.

Fungi

Candidemia is among the most common fungal etiologic causes of bloodstream infections. Of all the *Candida* species isolated from blood cultures, *Candida albicans* remains the most prevalent *Candida* species (38%-61%), but increasing incidences of invasive infections due to non-*albicans* species have been reported.[12,16–18] Non-*albicans Candida* species include *C. glabrata* (16%-28%), *C. parapsilosis* (14%-17%), *C. tropicalis* (7.5%-17%), and *C. krusei* (4.1%). Traditionally, risk factors for fungal infection include abdominal surgery, poorly controlled diabetes mellitus, prolonged granulocytopenia, use of broad-spectrum antibiotics or corticosteroids, prolonged hospitalization, central venous catheter, total parenteral nutrition, hematologic malignancy, and chronic indwelling bladder (Foley) catheter. Patients with candidemia and severe sepsis and septic shock were more likely to have been admitted from nursing homes or transferred from outside hospitals.[12]

Use of azoles in response to the rising incidences of *Candida* bloodstream

infection has led to fluconazole-resistant *Candida* species. Resistance to fluconazole has been reported in 17% of *C. albicans*, 58% of *C. parapsilosis*, 33% of *C. glabrata*, and 100% of *C. krusei* among critically ill patients with invasive candidiasis.[18]

A multicenter analysis of patients with septic shock due to candidemia between 2009 and 2011 reported overall 30-day mortality rate of 54%. A higher in-hospital mortality of 61% was reported among patients with healthcare-associated candidemia. The mortality rate was observed in upto 53% of patients with *C. krusei* candidemia; *C. parapsilosis* candidemia was associated with the lowest 12-week mortality rate of 24%.[19]

PATHOPHYSIOLOGY

2 The cascade leading to development of sepsis is complex and multifactorial, involving causative pathogen (virulence and organism load), host characteristics (comorbidities and immunosuppression), and the inflammatory responses (**Fig. 137-1**). The inflammatory responses lead to damage to host tissue, and the anti-inflammatory response causes leukocytes to activate. If the balance to control the local inflammatory process and to eradicate the invading pathogens is lost, systemic inflammatory response occurs which may lead to sepsis and septic shock.

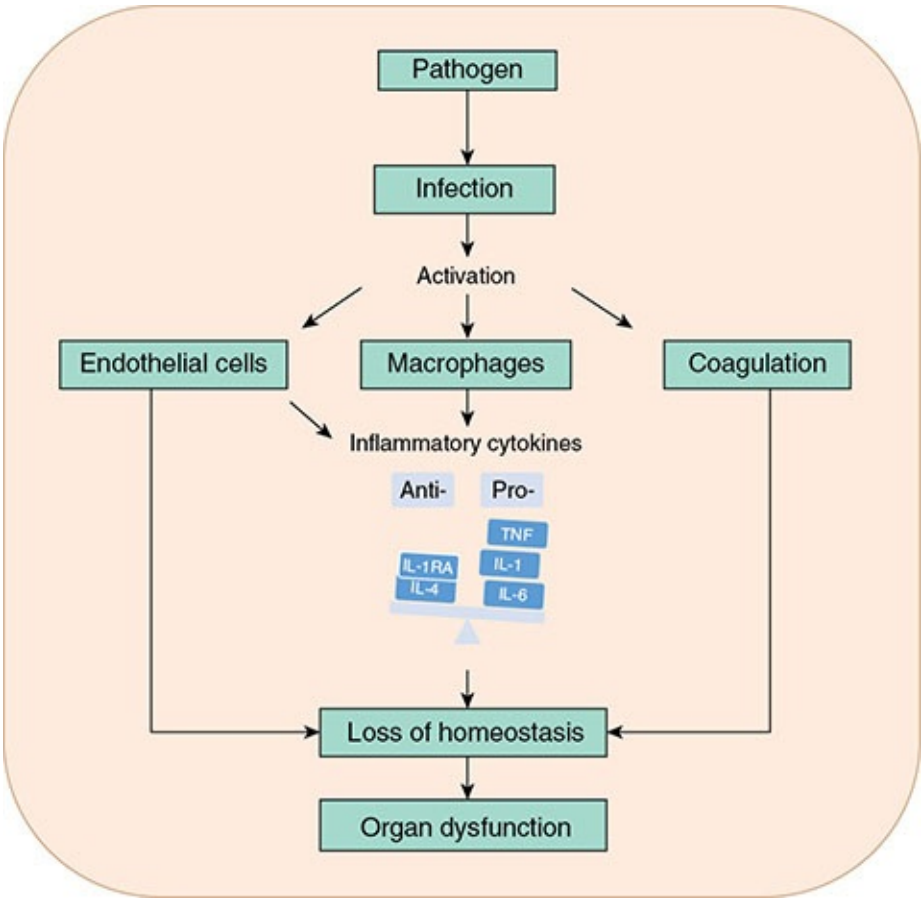


FIGURE 137-1 Pathophysiology of sepsis.

Cellular Components for Initiating the Inflammatory Process

The pathophysiologic focus of gram-negative sepsis has been on the lipopolysaccharide component of the gram-negative bacterial outer cell membrane. Commonly referred to as endotoxin, this substance is generally released with bacterial lysis. Upon its release, it forms a complex with an endogenous protein called a lipopolysaccharide-binding protein. Lipid A is the innermost region of the lipopolysaccharide and is highly immunoreactive. Its predominant effect is to activate macrophages through the CD14 receptor located on the macrophage. This endotoxin-lipopolysaccharide–binding protein complex is responsible for most of the toxic effects–the release of cytokine mediators which triggers the inflammatory cascade that is critical in the progression to sepsis and/or septic shock.[20]

In gram-positive sepsis, the exotoxin peptidoglycan on the cell wall surface appears to exhibit pro-inflammatory activity. It's similar to lipid A component of

gram-negative bacteria outer membrane for the similar binding site on the CD14 receptors of the macrophages. However, the potency of exotoxin peptidoglycan is less than that of endotoxin.[20] Clinically important exotoxins are those produced by *S. aureus* and *Streptococcus pyogenes* in septic shock.

Pro- and Anti-Inflammatory Mediators

A complex interaction between pro-inflammatory and anti-inflammatory mediators plays a major role in the pathogenesis of sepsis. In general, pro-inflammatory reactions are directed at eliminating invading pathogens and the anti-inflammatory reactions limit local and systemic tissue injury. The key pro-inflammatory mediators are tumor necrosis factor (TNF), and interleukin (IL)-1, IL-6, and IL-12, which are released by activated macrophages and endothelial cells. The TNF level is highly elevated early in the inflammatory response in majority of patients with sepsis, which leads to activation of other cytokines such as IL-1 and IL-6, associated with cellular damage. There is a correlation between the plasma TNF levels and the severity of sepsis and poor prognosis. In addition, higher levels of IL-6 have been reported in patients with septic shock than those with SIRS.[21] TNF also stimulates release of cyclooxygenase-derived arachidonic acid metabolites (thromboxane A_2 and prostaglandins) that contribute to vascular endothelial damage.

The significant anti-inflammatory mediators include interleukin-1 receptor antagonist (IL-1RA) IL-4, and IL-10. IL-1RA binds to IL-1, blocking its activity. Furthermore, anti-inflammatory cytokines inhibit the production of the pro-inflammatory cytokines and down-regulate some inflammatory cells. Levels of IL-10 and IL-1RA are higher in septic shock than in sepsis, and higher levels are found among non-surviving patients than in survivor.[21,22]

The activation and secretion of pro- and anti-inflammatory mediators in septic shock occur as a simultaneous immune response as early as the first 24 hours of diagnosis, but the balance between pro- and anti-inflammatory mechanisms determines the degree of inflammation, ranging from local antibacterial activity to systemic tissue toxicity, organ failure, shock, or death (Fig. 137-1).

Cascade of Sepsis

3 Macrophages and endothelial cells produce a variety of cytokines that mediate a primary mechanism of injury in sepsis. When injured, endothelial cells

allow circulating cells such as granulocytes and plasma constituents to enter inflamed tissues, which can result in organ damage.

The microcirculation is also affected by sepsis-induced inflammation. The arterioles become less responsive to either vasoconstrictors or vasodilators. The capillaries are less perfused even at the early phases of septic shock, and there is neutrophil infiltration and protein leakage into the venules.[23]

The inflammatory process in sepsis is also directly linked to the coagulation system. Pro-inflammatory mechanisms that promote sepsis are also procoagulant and antifibrinolytic, whereas fibrinolytic mechanisms can be anti-inflammatory.[24] A key endogenous substance involved in inflammation of sepsis is activated protein C, which enhances fibrinolysis and inhibits inflammation. Levels of protein C are generally reduced in patients with sepsis.[24]

COMPLICATIONS

Sepsis may lead to several complications including disseminated intravascular coagulation (DIC) and multiple organ dysfunctions, which are an important predictor of patient outcome. Among the patients admitted to academic US hospitals between 2009 and 2014 due to sepsis, approximately half had at least two acute organ dysfunctions.[5] National inpatient data between 2005 and 2014 reported approximately 20% of patients with sepsis having three-organ dysfunction, and increase in proportion of patients having four or more organ dysfunction from 16% to 24%.[4] The organ dysfunction occurred most frequently in kidneys (39%-49%), lungs (24%-43%), and heart (28%-40%).[4,5,8,25] Septic shock is the most ominous complication associated with sepsis. Among the patients who presented to the emergency department with sepsis 3.6% progressed to septic shock within the first 4 hours, and 8.4% progressed to septic shock between 4 and 48 hours.[26] The predictors for progression to septic shock in the latter group included female gender, nonpersistent hypotension, band neutrophils of at least 10% in blood, lactate of at least 4 mmol/L, and past medical history of coronary artery disease.[26] Mortality was reported in approximately half of the patients with septic shock.

Disseminated Intravascular Coagulation

The host inflammatory response to infection is a protective mechanism against the infecting pathogen. However, it also triggers disturbances in coagulation. A

dynamic process between procoagulant mechanisms and naturally occurring anticoagulants occurs nearly universally in septic patients.[27]

The initial procoagulant state is the interaction between the pro-inflammatory cytokines, such as TNF, IL-1, and IL-6, Tissue factor expression by endothelial cells and mononuclear phagocytes, and platelet-activating factor, which together contributes to hypercoagulopathy in the early inflammatory state.[28] Simultaneously, antithrombin synthesis is down-regulated, allowing ongoing thrombin formation. This acute phase interaction of the pro-inflammatory and hypercoagulative state is believed to sequester bacteria as part of compartmentalization.[28] Overall coagulation abnormalities consisting of excessive fibrin formation, compromised fibrin removal from a depressed fibrinolytic system, and endothelial injury may manifest as a small reduction in platelet count and subclinical clotting time prolongation or in more severe cases, disseminated intravascular coagulation (DIC).

Simultaneous widespread microvascular thrombosis and profuse bleeding from various sites characterize DIC. Consumption of clotting factors from ongoing thrombosis eventually leads to a hypocoagulable state. Various degrees of coagulation abnormalities may be present in 50% to 70% of septic patients. However, about 35% will progress to DIC.[28] Complications of DIC vary and depend on the affected organ and the severity of the coagulopathy. DIC can produce acute renal failure, hemorrhagic necrosis of the gastrointestinal (GI) mucosa, liver failure, acute pancreatitis, acute respiratory distress syndrome (ARDS), and pulmonary failure. Overall, as the procoagulant state appears to be the key to the ignition of the pathogenesis to DIC and multiple organ dysfunction, coagulation dysfunction and organ dysfunction often coexist in sepsis.

Acute Kidney Injury

The acute kidney injury (AKI), defined as an absolute increase in serum creatinine of 0.3 mg/dL (27 mmol/L) or more within a 48-hour period, not only affects survival, but also leads to worsening of chronic kidney disease or failure requiring renal replacement therapy. Sepsis-induced AKI has been reported up to 49%, and was associated with hypoperfusion, leading to renal ischemia. However, presence of normal or even increased renal blood flow in sepsis-induced AKI has been reported, providing an explanation for lack of beneficial evidence with the use of dopamine, a renal vasodilator in the treatment of AKI in septic patients. Rather, AKI develops from a complex relationship between the

activation of inflammation and pro-inflammatory molecules causing renal tubular injury and tubular epithelial dysfunction.[29] Subsequently, the injured kidney is unable to regulate the blood flow, making it more vulnerable to changes in blood flow as blood pressure varies and ultimately lead to progression to multiple organ dysfunction.

Acute Respiratory Distress Syndrome

ARDS is a serious and potentially fatal condition, characterized by severe hypoxemia that is resistant to oxygen. National Inpatient Sample reported increased incidence of ARDS in the United States from 2006 to 2014, and sepsis is one of the most common risk factors (46.8%), followed by pneumonia (44.9%) and shock (44.4%). Furthermore, sepsis-associated ARDS had a higher mortality rate in comparison to other risk factors.[30]

ARDS involves multifactorial processes which begin with activated neutrophils and platelets adhering to the pulmonary capillary endothelium which then initiates multiple inflammatory cascades with a release of a variety of toxic substances. There is diffuse pulmonary endothelial cell injury, increased capillary permeability, and alveolar epithelial cell injury. Consequently, interstitial pulmonary edema occurs that gradually progresses to alveolar flooding and collapse. The end result is loss of functional alveolar volume, impaired pulmonary compliance, and profound hypoxemia.[31]

Abnormalities of coagulation and fibrinolysis are also integral to the pathogenesis of ARDS. Coagulation is locally upregulated in the injured lung, whereas fibrinolytic activity is depressed. These abnormalities occur concurrently, but favor alveolar fibrin deposition, leading to local inflammation, macrophage migration, and increased vascular permeability.[27]

Hemodynamic Effects

Sepsis and septic shock are associated with excessive sympathetic outflow, high plasma catecholamine levels, myocardial depression, vascular hyporeactivity, and autonomic dysfunction. The hallmark of the hemodynamic effect of sepsis is the hyperdynamic state characterized by low systemic vascular resistance (SVR) and high cardiac output with tachycardia and arterial hypotension.[32,33]

Sepsis-induced myocardial dysfunction, defined as the intrinsic myocardial systolic and diastolic dysfunction of both the left and right sides of heart, occurs from excessive adrenergic stress.[34] Sepsis from overwhelming inflammation

may cause direct myocardial damage (eg, cardiomyopathy and tachyarrhythmia). Simultaneously, the heart as part of the circulatory system and responding to peripheral hemodynamics may be responding to alterations in preload, afterload, and microcirculation during sepsis. The microvasculature system, consisting of arterioles, capillaries, venules, and microlymphatics, is a functional system that responds promptly to the changes in blood flow to the tissues and the metabolic demand. It regulates adequate blood flow to tissues, ensuring adequate oxygen delivery and meet the oxygen demand. During sepsis and septic shock, massive pro-inflammatory cytokines are released, targeting the endothelium, the key component of this microvascular blood flow. Consequently, microvascular impairment leads to loss of ability to regulate oxygen distribution within the capillary network.[35] The severity of microcirculatory abnormalities and their persistence are associated with organ dysfunction. Overall, the combination of decreased preload, reduced afterload, myocardial dysfunction, microcirculatory impairments, and blood flow redistribution between organs lead to hemodynamic alterations during sepsis.

Septic Shock

There are four different types of shock syndrome: hypovolemic, cardiogenic, obstructive, and vasodilatory/distributive. Septic shock falls under the vasodilatory/distributive shock. Distributive shock results from overall systemic vasodilation leading to hypoperfusion. Hallmark signs and symptoms of distributive shock include decrease in blood pressure, increase in heart rate in response to decrease in SVR, and pulmonary capillary wedge pressure. The cardiac output is typically normal after adequate fluid resuscitation in vasodilatory shock unlike the other syndromes which are expected to have a low cardiac output. Details of the different shock syndromes are discussed in chapter titled “Shock Syndromes.”

CLINICAL PRESENTATION

The clinical presentation of sepsis varies significantly depending on the site of the infection (ie, pulmonary versus urinary tract), host response to the infection based on the patient’s underlying health status and risk factors, and organ dysfunction. The initial presentations may include general malaise or myalgia and nonspecific signs such as fever (or hypothermia), chills, tachycardia, tachypnea, or change in mental status. As uncontrolled sepsis progresses, the

presentation varies again depending on the specific organ system dysfunction. Arterial hypotension can be present which may compromise organ perfusion, leading to oliguria. Hyperventilation can occur, causing impaired gas exchange which can then lead to respiratory alkalosis. Altered glucose metabolism, including impaired gluconeogenesis and excessive insulin release, is evidenced by either hyperglycemia or hypoglycemia. Increased glycolysis with impaired clearance of lactate by the hypoperfused liver and kidneys result in elevated lactate levels which then contributes to metabolic acidosis.

Prognostic Factors

3 The highest mortality was reported in patients with intra-abdominal infection secondary to ischemic bowel (75%), whereas the obstructive uropathy-associated urinary tract infection was associated with the lowest hospital mortality (26%).[10] A worldwide multicenter evaluation of AKI in sepsis demonstrated in-hospital mortality rate of two- to threefold higher in patients with stage 3 kidney disease compared to those without kidney disease. Furthermore, the mortality rate was significantly higher in patients receiving renal replacement therapy than those without (40% vs 22%, respectively).[36] As the number of failing organs increased from one to four or more, the mortality rate increased from 15% to 40% (**Fig. 137-2**).[5] Patients with candidemia generally have septic shock, and the associated mortality is significantly higher in comparison to patients with bacteremia (47% vs 28%, respectively).[12]

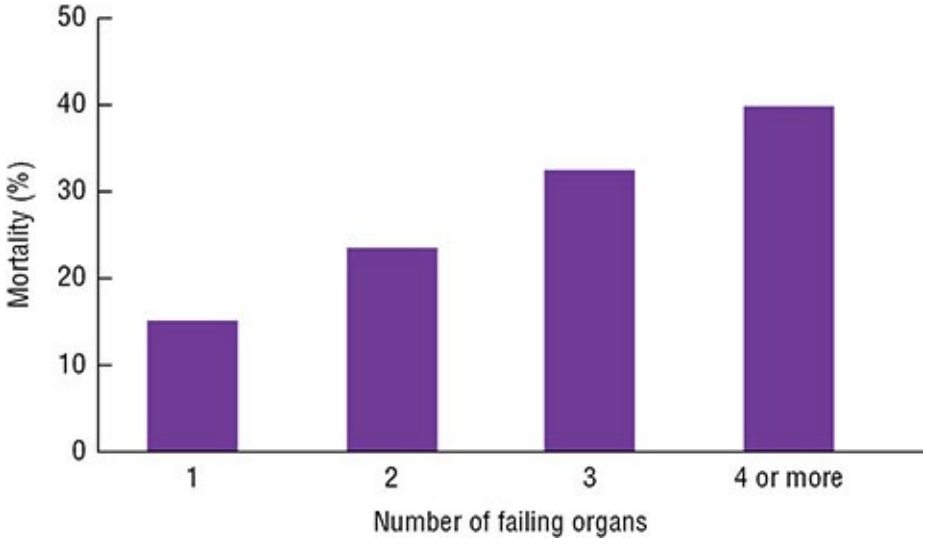


FIGURE 137-2 Mortality related to the number of failing organs.

An elevated serum lactate concentration of more than 4 mmol/L upon initial presentation and persistent elevation in lactate for more than 24 hours were associated with an increased mortality rate.[37] Furthermore, the 28-day mortality rate was the highest (45%) among patients with septic shock and hyperlactatemia of more than 2.5 mmol/L, followed by hyperlactatemia without vasopressor need (35%), and no hyperlactatemia with vasopressor need (28%). Hyperlactatemia increased the risk of 28-day mortality independent of vasopressor need.[38]

Diagnosis

Identification of Pathogens

The presence of clinical features suggesting sepsis should prompt further evaluation of the patient. In addition to obtaining a careful history of any underlying conditions and recent travel, injury, animal exposure, infection, or use of antibiotics, a complete physical examination should be performed to determine the source of the infection.

A collection of specimens should be sent for culture prior to initiating any antimicrobial therapy to increase the yield of cultures, making identification of a pathogen more likely. Minimally two sets of blood cultures (both aerobic and anaerobic bottles) should be collected without temporal separation between the sets.[1,39] Culturing of all body sites is not generally recommended, but the decision regarding which sites to culture requires careful consideration and should be based on the patient presentation and the likely site of infection. With suspected catheter-related infection, one set of blood culture should be drawn through every lumen of each vascular access device along with peripheral blood cultures.[39] In severe community-acquired pneumonia, respiratory secretions along with blood cultures must be obtained. Urinary antigen detection of *S. pneumoniae* and *Legionella* serogroup 1 is recommended to yield identification. To document a soft tissue infection, a Gram stain and bacterial culture of any obvious wound exudates should be performed. A needle aspiration of a closed infection such as cellulitis or abscess may be needed for Gram stain and bacterial culture. In abdominal infections, fluid collections identified by imaging studies should be aspirated for Gram stains and aerobic and anaerobic cultures. Implementation of accurate and rapid molecular diagnostic testing has demonstrated positive impact on prescribing appropriate therapy in bloodstream infections such as methicillin-resistant *S. aureus* (MRSA) and *Candida* species.[1,40,41]

A lumbar puncture is indicated with mental alteration, severe headache, or a seizure, assuming there are no focal cranial lesions identified by computed tomography scan. Further tests may be indicated to assess any systemic organ dysfunction caused by severe sepsis. The laboratory tests should include WBC with differential, hemoglobin, platelet count, complete chemistry profile, coagulation parameters, serum lactate, and arterial blood gases. The potential role of biomarkers such as procalcitonin (PCT) levels or C-reactive protein for diagnosis of infection in patients with sepsis remains undefined as there is no definitive way to discriminate the acute inflammatory pattern of sepsis from other generalized inflammation.[1]

Assessment of Acutely Ill, High-Risk Patients

Sepsis-3 redefined sepsis to "life-threatening organ dysfunction caused by a dysregulated host response to infection" based on the evidence of greater in-hospital mortality among patients with sequential sepsis-related organ failure.[3,42] As such, early recognition using a formal screening tool is critical. Organ dysfunction can be evaluated by using the SOFA scoring system. SOFA, developed for critical care setting, encompasses various organ systems such as pulmonary, hepatic, cardiovascular, renal, and neurological and gives a score ranging from 0 to 4 for each system (**Table 137-2**). Higher total score is associated with an increased probability of mortality. This scoring system is used to characterize a septic patient's prognosis, not to differentiate treatment options. A SOFA score of 2 or more is associated with an increased risk of mortality by 10% in hospitalized patients with presumed infection.[3] One of the difficulties in using the SOFA score is that clinicians need laboratory results such as platelets, bilirubin, and creatinine, which may not be available right away. Quick SOFA (qSOFA), on the other hand, can be useful in identifying adult patients with suspected infection who are likely to have poor outcome. This assessment includes three data elements: respiratory rate ≥22 breaths/min, altered mental status, and systolic blood pressure ≤ 100 mmHg. qSOFA of ≥2 or SOFA score change of ≥2 can serve as an indication for higher vigilance and potentially quicker escalation of care. If baseline SOFA score is unknown, then score of zero is used as baseline. If a patient has all three mentioned elements, in-hospital mortality can be as high as 40% to 50%.[3]

TABLE 137-2 Abbreviated Sepsis-Related Sequential Organ Failure Assessment

Organ System	Measured Variables for Scoring System
Pulmonary	PaO_2/FiO_2 (<200 to ≥400 mm Hg [26.6 kPa to 53.2 kPa])
Coagulation	Platelets (<50 to ≥ 150 × 10^3/mm^3 [50 to 150 × 10^9/L)
Liver	Bilirubin (<1.2 to 11.9 mg/dL [20.5 to 203.5 μmol/L])
Cardiovascular	MAP (<70 with or without vasopressor to ≥70 mm Hg)
Central nervous system	Glasgow Coma Scale (6 to 15)
Renal	Serum creatinine (<1.2 to 4.9 mg/dL [106 to 433 μmol/L]), urine output (<500 mL/d)

FiO2, fraction of inspired oxygen; MAP, mean arterial pressure pressure; PaO2, partial pressure ofoxygen.

Data from Reference 3.

TREATMENT

Since the Surviving Sepsis Campaign in 2003, the key concepts have changed the way we recognize and treat septic patients over the decades.[43] In 2001, the early goal-directed therapy (EGDT) with resuscitation targets was introduced, and it heavily influenced the Sepsis-2 guideline.[1,44] The most recent 2016 guideline (Sepsis-3) incorporated the data from the Protocolized Care for Early Septic Shock (ProCESS), Australasian Resuscitation in Sepsis Evaluation (ARISE), and Protocolized Management in Sepsis (ProMISe) trials which failed to confirm the survival advantage of protocolized EGDT.[45–47] In addition, Sepsis-3 not only changed the definition of classifying categories of sepsis, but it also emphasized the use of dynamic resuscitation markers.

It is important to discuss EGDT since the 2001 trial put the emphasis in early recognition of sepsis and a protocolized, quantitative approach to patient care for this disease state.[44] This was a single center, prospective, randomized study that included 263 patients who met the SIRS criteria and systolic blood pressure ≤ 90 mmHg or lactate ≥4 mmol/L. Specific resuscitation targets (ie, central venous pressure (CVP) of 8 to 12 mmHg, mean arterial pressure (MAP)≥ 65, hematocrit of ≥30% (0.30), and central venous oxygen saturation ($Scvo_2$)≥ 70% [0.70]) were evaluated for reducing mortality. When EGDT and standard therapy were

compared, the standard therapy led to significantly higher 28-day mortality rate. Subsequently, EGDT was quickly adopted and redefined the early, aggressive resuscitation of patients with sepsis and septic shock for the next decade. However, myriads of investigators attempted to reproduce the significant mortality benefit shown by the implementation of EGDT. Notably, the ProCESS (1341 subjects), ProMISe (1234 subjects), and ARISE (1588 subjects) investigators failed to confirm the survival benefits of protocolized targets for CVP and hemoglobin between EGDT and usual care.[45–47] However, these investigators were able to recognize the disease early allowing for quicker admission of patients from the emergency department to the inpatient care setting which may assist in overall mortality benefit in both standard therapy and EGDT.[48]

Desirable Outcomes

In addition to timely recognition and diagnosis of sepsis, other primary goals include prompt hemodynamic support, rapid identification of the pathogen and source control either medically and/or surgically, early initiation of appropriate broad-spectrum antimicrobial therapy, and avoidance complications such as organ failure and septic shock. Supportive care such as stress ulcer prophylaxis and venous thromboembolism prophylaxis is important to prevent complications during the stay in the ICU. **Table 137-3** describes the summary of the surviving sepsis campaign treatment recommendations.

TABLE 137-3 Evidence-Based Treatment Recommendations and Best Practice Statements

Recommendations	Recommendation Grades
Fluid therapy	
Initial resuscitation from sepsis-associated hypotension with at least 30 mL/kg of IV crystalloid fluid within 1 hour	Strong recommendation, low evidence
Either balanced crystalloids or saline for additional fluids guided by frequent assessment of dynamic variables	Weak recommendation, low evidence
Antimicrobial therapy	
IV broad-spectrum antibiotic within 1 hour of diagnosis of sepsis and septic shock against likely bacterial/fungal pathogens	Strong recommendation, moderate evidence
Reassess antibiotic therapy daily with microbiology and clinical data to narrow coverage (de-escalation)	BPS
Optimize dosing strategies based on pharmacokinetics/pharmacodynamics parameters in patients with sepsis or septic shock	BPS
Empiric combination therapy for patients with multidrug-resistant bacterial pathogens such as *Acinetobacter* and *Pseudomonas* species or septic shock	Weak recommendation, low evidence
Treatment duration of 7-10 days for most serious infections	Weak recommendation, low evidence
Vasopressors	
Initiate vasopressor therapy to maintain MAP ≥65 mm Hg	Strong recommendation, moderate evidence
Norepinephrine as the first-choice vasopressor	Strong recommendation, moderate evidence
Add vasopressin or epinephrine to norepinephrine to maintain adequate blood pressure	Weak recommendation, moderate evidence
Add vasopressin to norepinephrine to decrease norepinephrine dosage	Weak recommendation, moderate evidence
Corticosteroids	
IV hydrocortisone 200 mg per day for septic shock only when hemodynamically unstable after adequate fluid resuscitation and vasopressors	Weak recommendation, low evidence
Hydrocortisone should be tapered when vasopressors are no longer required	Weak recommendation, low evidence
Glucose control	
Use insulin dosing protocol when two consecutive blood glucose levels are >180 mg/dL (10 mmol/L), targeting an upper blood glucose <180 mg/dL (10 mmol/L)	Strong recommendation, high-level evidence
Monitor blood glucose every 1-2 hours until insulin infusion rates are stable, then every 4 hours thereafter	BPS
Venous thomboembolism prophylaxis	
Use daily low-molecular-weight heparin (LMWH) over unfractionated heparin	Strong recommendation, moderate evidence
Combination of LMWH and intermittent pneumatic compression, whenever possible	Weak recommendation, low evidence
If creatinine clearance is <30 mL/min (0.5 mL/s), use unfractionated heparin or dalteparin	Weak recommendation, low evidence
Stress ulcer prophylaxis	
Stress ulcer prophylaxis should be given to patients who have bleeding risk factors	Strong recommendation, low evidence
Either proton pump inhibitors or H2 receptor blockers	Weak recommendation, low evidence

BPS, best practice statement; MAP, mean arterial pressure.

Data from Reference 49.

Initial Resuscitation

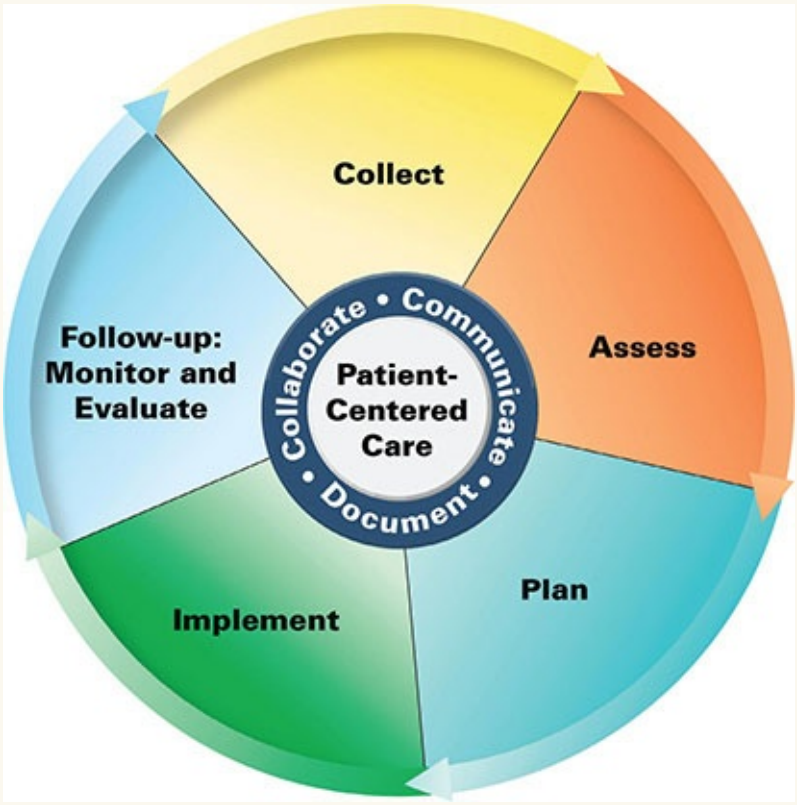
4 Once the patient is recognized for sepsis, early effective fluid resuscitation is crucial for preventing further sepsis-induced tissue hypoperfusion or septic shock. The Sepsis-3 guidelines recommend treating and resuscitating from sepsis-induced hypoperfusion immediately with at least 30 mL/kg of IV crystalloid fluid within the first 3 hours. The patient should be reassessed for hemodynamic status by measurements with better diagnostic accuracy at predicting those who are likely to respond to additional fluid.[49] The Sepsis-3 guidelines also recommend target MAP of 65 mg Hg to assess the need for vasopressors. While MAP indicates pressure of tissue perfusion, serum lactate represents tissue hypoxia. The Sepsis-3 guidelines recommend normalizing lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion.

Fluid Therapy

Initial resuscitation effort with fluid therapy on a septic patient with tissue hypoperfusion or in septic shock is a key ingredient.[50] The fluid therapy is closely related to the inflammatory cytokines that are released by the body in response to an infection. These pro-inflammatory cytokines lead to capillary leak. As the fluid travels more freely from intravascular to extravascular space, there is an overall increase in fluid in the extravascular space leading to intravascular hypovolemia. In turn, it causes end-organ edema, dysfunction, and ultimately organ failure. Therefore, understanding how the administered fluid will move within the body is essential. Often, IV fluids are not assessed during the management of a critically ill septic patient and may lead to fluid overload. However, it is important to consider both the indication and the contraindications of available IV fluids carefully, and as such, fluid therapy should be considered as a drug with potential benefits and risks.

There are few considerations regarding fluid therapy: initial amount, type of fluid, and duration of therapy.[51] First, the Sepsis-3 guidelines recommend administration of at least 30 mL/kg crystalloids within the first 3 hours. This 30 mL/kg dose is strongly recommended but with low quality of evidence. Despite the lack of a robust quality of evidence, this dose has been widely used in many landmark trials such as the ProCESS, ARISE, and ProMISe.[45–47] However, this amount of fluid is to be given judiciously within 3 hours. For example, if an 80-

kg patient requires 30 mL/kg fluid resuscitation, the complete 2.4 L should not be administered as a single bolus dose, but as needed based on the proper assessment of fluid status and fluid responsiveness. The Sepsis-2 guidelines promoted the use of CVP goal of ≥ 8 mmHg and $ScvO_2$ goal of ≥ 70% (0.70). However, this measurement not only requires an invasive line placement, central venous catheter, but is also considered to be a “static” measurement of fluid responsiveness that may lead to continued administration of fluid causing fluid overload.[1,44] Dynamic assessment of fluid responsiveness has been used with goal-directed therapy.[52] Dynamic assessment was defined as increase in stroke volume of more than 10% to 15% after a fluid challenge of 250 to 500 mL of crystalloids or from endogenous source by using the passive leg raise. Passive leg raise is performed by laying the patient in a supine position and raising both legs 45° at the same time. This will allow the blood from the leg to act as a bolus back to the heart. Using the passive leg raise test to check for fluid responsiveness intermittently leads to decreased use of IV fluids, especially for patients who are no longer responding adequately to IV fluid alone. Fluid therapy guided by dynamic assessment of fluid responsiveness by examining cardiac output was associated with decreased mortality compared to standard care.[52] Furthermore, the use of dynamic assessment also decreased the length of stay in the intensive care unit (ICU) and the duration of mechanical ventilation.



Patient Care Process for Sepsis and Septic Shock

Collect

- Patient characteristics (eg, age, sex)
- Patient medical history (including recent hospitalization and infection within last 6 months)
- Social history (eg, tobacco/ethanol use/IVDA/ place of residence)
- Current medications (prescription and nonprescription; including recent history of antibiotic usage within last 6 months)
- Subjective data (including general constitutional and infection-site specific, onset)
- Objective data
  - Temperature, blood pressure (BP), heart rate, respiratory rate, mean arterial pressure (MAP), O_2-saturation, height, and weight

- Labs including white blood cell (WBC) count with differential, hemoglobin, platelet count, complete serum chemistry including serum creatinine, and bilirubin, lactate, procalcitonin (PCT), coagulation panel including prothrombin time and activated partial thromboplastin time, and arterial blood gas including pH, $PaCO_2$, PaO_2, and HCO_3
- Objective parameters for sequential organ failure assessment (see sequential organ failure assessment [SOFA]; Table 137-2)
- Microbiology data (including gram stain, culture, rapid diagnostic testing)

Assess

- Mental status
- Systemic inflammatory response (SIRS) criteria (Table 137-1)
- Hemodynamic stability (eg, systolic BP> 100 mmHg, MAP> 65 mmHg)
- Presence of organ dysfunction (lactate > 2 mmol/L, baseline; SOFA/qSOFA; Table 137-2)
- Identification of pathogen and antibiotic susceptibility
- Risk of multidrug resistant bacterial pathogen (recent hospitalization, infection, antibiotic usage)
- Risk of fungal pathogen (recent usage of broad-spectrum antibiotics/corticosteroids/total parenteral nutrition, abdominal surgery, etc.)

Plan*

- Initiate 1-hour performance improvement bundle (Table 137-7)
- Initial fluid resuscitation with IV crystalloid for hypotension
- Begin antimicrobial therapy regimen based on site of infection (Table 137-5)
- Perform passive leg raise to assess response to fluid resuscitation (increase in stroke volume by 10%-15%)
- Initiate vasopressor if MAP< 65 mmHg with adequate fluid resuscitation (Table 137-6)
- Administer IV hydrocortisone if persistently hemodynamically unstable

and septic shock

- Initiate adjunct therapy including glucose control, venous thromboembolism prophylaxis, and stress ulcer prophylaxis
- Monitoring parameters: including efficacy (eg, signs and symptoms of infection, mental status, MAP, lactate, WBC with differential) and safety

Implement*

- Management of vasopressor selection after initial norepinephrine
- Daily assessment for opportunities to de-escalate antimicrobial therapy
- Design tapering schedule of IV hydrocortisone
- Coordination of treatment plan during transitioning from the ICU to a medicine unit

Follow-up: Monitor and Evaluate

- Resolution of symptoms of infection
- Procalcitonin levels to determine the antimicrobial treatment duration
- Normalization of lactate and MAP > 65 mmHg for discontinuation of vasopressors
- Presence of adverse effects of antimicrobial agents and vasopressors

**Collaborate with other healthcare professionals.*

The type of fluid administered (ie, crystalloids such as dextrose, sodium chloride, lactated ringer, and Plasma-Lyte) or colloid (ie, albumin) serves as an important factor in resuscitation. (**Table 137-4**). Ideally, the fluid should expand the intravascular volume without providing excess free water leading to tissue edema.[53] The Saline versus Albumin Fluid Evaluation (SAFE) trial showed similar safety and effectiveness between crystalloids and colloid. The 28-day mortality rates for crystalloids and colloid were similar (saline group 21.1%, albumin group 20.9%) as well as the length of stay in ICU (saline group 6.2 days, albumin group 6.5 days) or hospital (saline group 15.6 days, albumin group 15.3 days).[54] The Sepsis-3 guidelines recommend a crystalloid product (balanced solution such as lactated ringers and Plasma-Lyte or normal saline) based on accessibility and cost. Colloid (ie, albumin) can be utilized in patients

who have already received considerable amount of crystalloids and continue to require fluid.[49] Hetastarch products should be avoided at all times as they have been shown to increase risk of renal failure, requiring renal replacement therapy and death in multiple studies.[49]

TABLE 137-4 Comparison of IV Fluids–Crystalloids and Colloid

	Crystalloids					Colloid
	Human Plasma	Dextrose 5%	Sodium chloride 0.9%	Lactated ringers	Plasma-Lyte 148	Albumin 5%
pH	7.35-7.45	4	5	6.5	5.5	7.4
Osmolarity (mOsmol/L)	291	252	308	273	294	330
Sodium (mEq/L or mmol/L)	135-145	–	154	130	140	–
Chloride (mEq/L or mmol/L)	96-106	–	154	109	98	–
Potassium (mEq/L or mmol/L))	3.5-5	–	–	4	5	–
Bicarbonate (mEq/L or mmol/L)	23-27	–	–	28 (lactate)	27 (acetate)	–
Calcium (mg/dL) [mmol/L])	8.5-10.5 [2.13-2.63]	–	–	2.7	–	–
Magnesium (mEq/L [mmol/L])	1.8-2.4 [0.9-1.2]	–	–	–	3	–
Glucose (mg/dL [mmol/L])	70-100 [3.9-5.6]	50	–	–	–	–
Tonicity[a]		Isotonic[b]	Isotonic	Isotonic	Isotonic	Isotonic

[a]Tonicity is based on comparison of osmolarity of the product and human plasma. Hypotonic is defined as osmolarity < 250 mOsmol/L, Isotonic is between 250 and 375 mOsmol/L, and Hypertonic is > 375 mOsmol/L.

[b]Dextrose 5% acts as hypotonic solution in body. It can also increase CO_2 and lactate production.

Data from Reference 53.

The Sepsis-3 guidelines do not offer a specific recommendation on which crystalloid IV fluid should be used in septic shock, saline versus balance solution. However, there is increasing evidence of potential harm in developing hyperchloridemia metabolic acidosis from excessive administration of normal saline and subsequent increased renal failure and mortality in comparison to balanced salt solutions.[55–57] As such, judicious use of saline needs to be considered in practice.

Lastly, the total duration of fluid therapy is based on the four phases of septic shock: ROSE—resuscitation, optimization, stabilization, and evacuation.[51] *Resuscitation* phase occurs within minutes and the patient will most likely have a positive fluid balance especially after the 30 mL/kg bolus. During the second phase (within hours), optimization, the goal is to keep a neutral fluid balance between intake and output. During this time, the clinician should consider the

source of infection as well as any potential organ dysfunction when deciding volume and end point in fluid administration. For instance, a patient with peritonitis-related septic shock will most likely require more fluid than pneumonia-associated septic shock. Also, it is important to avoid fluid overload to decrease risk of acute respiratory distress syndrome and other consequences such as intra-abdominal hypertension. During the third phase, *stabilization*, which usually occurs in days, the focus should be on organ support and keeping fluid balance neutral to net negative. During this time, the patient would most likely need maintenance doses (30 mL/kg/day) of fluid only. Finally, the *evacuation* phase occurs in days to weeks and it is suggested to keep fluid balance negative. While attempting to achieve negative balance, careful deliberation to avoid excess fluid removal is crucial. Another hypotensive event in a recently recovering septic shock patient can lead to a further damage.

Infection Source Control

Once the source of infection is identified, prompt efforts to eradicate that source should be made as progression of sepsis was noted despite rapid initial resuscitation including fluid and appropriate antimicrobials in the absence of adequate source control. With sepsis shock, the infectious foci should be controlled once the patient is stabilized after initial resuscitation, but optimally no more than 6 to 12 hours after diagnosis. With an infected intravascular catheter, the catheter should be removed and cultured. However, infected central venous catheters without septic shock or fungemia may be able to be treated with prolonged antimicrobial therapy if the catheter removal is not practical. Urinary tract catheters should be removed if association with sepsis is suspected. Suspicion of soft tissue (cellulitis or wound infection) or bone involvement should lead to aggressive debridement of the affected area. Evidence of an abscess or sepsis associated with any intra-abdominal pathology (ie, GI perforation, ischemic bowel, cholecystitis, infected pancreatic necrosis) should prompt surgical intervention. Reduced survival with delayed surgical source control was reported in observational studies, and as such, the Surgical Infection Society guidelines on the management of intra-abdominal infections suggest earlier source control, allowing only a short delay for rapid resuscitation in patients who are hemodynamically unstable with sepsis.[49,58]

Antimicrobial Therapy

5 Administration of empiric broad-spectrum IV antibiotics immediately after

initial recognition of sepsis or septic shock is independently associated with lower hospital mortality, regardless of the number of organ failure.[49,50,59] Among the interventions in a 3-hour bundle of sepsis care, use of appropriate antibiotics in the first 3 hours was associated with an absolute reduction in mortality, not rapid administration of IV fluids.[37,60]

In addition to the timing of the empiric antibiotic, administration of appropriate antibiotic, especially for multidrug-resistant bacteria, has a great impact in reducing mortality.[14,15,37,61,62] Inappropriate initial antimicrobial therapy occurred in about 20% of patients with septic shock, and was associated with a fivefold reduction in survival in comparison to those who received appropriate therapy (52% vs 10%, respectively).[63] A critical analysis of 14 randomized controlled trials in adult patients concluded that early and appropriate antibiotic administration improves mortality in patients with sepsis and septic shock.[64] Therefore, the Sepsis-3 guidelines recommend administration of empiric broad-spectrum therapy with one or more IV antimicrobials within 1 hour of recognition of sepsis or septic shock to treat most likely pathogens.

Septic shock caused by *C. albicans* demonstrated 25% survival with initial appropriate therapy but only 4.6% survival without.[63] Among the patients with candidemia, delayed appropriate antifungal treatment, especially in presence of septic shock and failure to achieve timely source control, was independently associated with a greater risk of hospital mortality.[17,65,66] Hence, accurate and rapid identification of candidemia is critical in prompt initiation of appropriate therapy.[41,49]

Selection of Antimicrobial Agents

The selection of an optimal empiric regimen requires assessment of several factors. Key patient factors include age, concomitant underlying diseases, chronic organ dysfunction (ie, liver or renal failure), presence of immunosuppression (ie, active cancer, neutropenia, or uncontrolled HIV infection), or presence of indwelling devices (ie, central venous lines or urinary catheter). Interviewing the patient or the patient’s representative for recent hospitalization, recent history or colonization with specific pathogens, and the receipt of antimicrobials within the previous 3 months should assess risk for infection with multidrug-resistant pathogens. Infection factors include type or anatomic site of infection, the most likely pathogens, acquisition of the organism from the community or healthcare institution, and the usual antibiotic

susceptibility and resistance profile of the prevalent pathogens at the institution.

Table 137-5 lists specific empiric antimicrobial regimens for the anatomic site of infection based on the most likely pathogens.[49,58,67–70] However, general suggestions can be made when treating critically ill patients with sepsis or septic shock. All patients should be treated initially with parenteral broad-spectrum therapy with one or more antimicrobials for optimal drug concentrations in the presumed infection site after appropriate cultures have been taken.[1,49] Sepsis-3 guidelines suggest covering most pathogens isolated in healthcare-associated infections as the majority of patients with sepsis or septic shock have varying degrees of immunocompromised conditions.[49] A broad-spectrum carbapenem (eg, meropenem, imipenem/cilastatin or doripenem) or beta-lactam/beta-lactamase inhibitor combination such as piperacillin/tazobactam may be initiated.

TABLE 137-5 Empiric Antimicrobial Regimens in Sepsis

Infection (Site or Type)	Antimicrobial Regimen		
	Community-Acquired	Hospital-Acquired	
Urinary tract	Ceftriaxone or ciprofloxacin/levofloxacin	Ceftriaxone/ceftazidime or ciprofloxacin/levofloxacin	
Respiratory tract	Levofloxacin[a]/moxifloxacin or ceftriaxone + clarithromycin/azithromycin	Piperacillin/tazobactam or ceftazidime or cefepime or carbapenem[b] + levofloxacin/ciprofloxacin or aminoglycoside	± vancomycin or linezolid
Intra-abdominal	Ertapenem or ciprofloxacin/levofloxacin + metronidazole or Ceftriaxone + metronidazole	Carbapenem[b] or Piperacillin/tazobactam or Ceftazidime/cefepime + metronidazole	
Skin/soft tissue	Vancomycin or linezolid or daptomycin	Vancomycin + piperacillin/tazobactam	
Catheter-related		Vancomycin	
Unknown	Piperacillin/tazobactam or carbapenem[b]	Carbapenem[b]	

[a]750 mg once daily.

[b]Imipenem, meropenem, and doripenem.

Patients with nosocomial infections are at risk for sepsis with MRSA, and an anti-MRSA agent such as vancomycin should be initiated empirically in most cases. Vancomycin remains the mainstay of therapy for MRSA-associated infections.[71] However, vancomycin trough concentrations need to be monitored carefully for clinical efficacy, and the worldwide emergence of glycopeptide intermediately resistant *S. aureus* has been reported, albeit rare.[71] The 2016 Infectious Diseases Society of America (IDSA) guidelines recommended either vancomycin or linezolid for hospital acquired/ventilator associated pneumonia.[67]

Linezolid has better lung penetration into epithelial lining fluids than vancomycin. However, a systematic review of randomized controlled trials reported that linezolid was not superior to vancomycin in microbiological and clinical cure rates in patients with nosocomial pneumonia due to MRSA.[72] Telavancin, a bactericidal, lipoglycopeptide, was noninferior to vancomycin in treatment of hospital-acquired pneumonia due to gram-positive organisms in two randomized trials.[73] However, telavancin was associated with increased serum creatinine levels and higher mortality rates in patients with moderate to severe renal impairment at baseline. Inadequate empiric gram-negative antimicrobial therapy might have contributed to negative outcomes.[74] Telavancin resulted in higher cure rates in patients with *S. aureus* with a vancomycin minimum inhibitory concentration (MIC) of greater than 1 mg/L. However, vancomycin dosing and the subsequent serum trough levels were slightly lower than recommended. More data is warranted to define the role of telavancin.

Daptomycin is a cyclic lipopeptide that exhibits rapid bactericidal activity against gram-positive microorganisms including MRSA and vancomycin-resistant enterococci (VRE).[75] Daptomycin resulted in a 70% success rate for critically ill septic patients with bacteremia due to MRSA, VRE *E. faecium* or coagulase-negative staphylococci.[75] The daptomycin cohort had significantly lower clinical failure for MRSA bacteremia when matched with vancomycin cohort patients (29% vs 45%) and lower all-cause 30-day mortality (6.1% vs 15.3%).[76]

Bloodstream infections caused by extended-spectrum beta-lactamases (ESBL)-producing Enterobacteriaceae are associated with high rates of morbidity and mortality of up to 44% in patients with sepsis or septic shock.[77] Mortality was especially high with a delay in appropriate antimicrobial therapy.[77,78] Hence the appropriate empiric antibiotic therapy in critically ill patients with sepsis or septic shock is crucial. Carbapenems remain active and have been regarded as the treatment of choice for serious infections due to ESBL pathogens. However, increased use of carbapenems has led to emergence of carbapenem-resistant Enterobacteriaceae which represents a greater threat. Piperacillin/tazobactam has been evaluated in observational studies as carbapenem-sparing therapy with conflicting results.[78,79] In a meta-analysis of 25 observational studies describing 3824 participants who received either beta-lactam/beta-lactamase inhibitor or carbapenem as empiric or definitive therapy for ESBL-producing bacterial bloodstream infections, 30-day mortality was not significantly different.[78] However, a recent prospective noninferiority, parallel group, randomized trial reported all-cause 30-day mortality of 12.3% in the

piperacillin/tazobactam group and 3.7% in the meropenem group (absolute risk difference of 8.6%) in hospitalized patients who received definitive treatment for bloodstream infections due to ceftriaxone resistant *Escherichia coli* or *Klebsiella pneumoniae*.[80] As such, piperacillin/tazobactam should no longer be considered an alternative to meropenem for definitive treatment of bloodstream infection due to ESBL-producing gram-negative pathogens.

Combination therapy does not appear to be more effective than monotherapy in reducing organ failure or mortality in low-risk patients including sepsis without shock, and should not be used routinely.[13] However, multidrug resistance in sepsis due to gram-negative bacteremia was strongly associated with the receipt of inappropriate empiric therapy and a threefold increase in the risk of hospital mortality.[15] The greatest benefit of combination therapy appeared to be in patients with septic shock due to *Pseudomona*s or multidrug-resistant gram-negative bacteremia such as *Acinetobacter* and in neutropenic patients with sepsis or septic shock.[81–85] Combination therapy consisting of antibiotics from two different classes increases the probability of at least one active agent. For instance, if *P. aeruginosa* infection is suspected, beta-lactam antipseudomonal agents (ceftazidime or cefepime), antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin), or an aminoglycoside should be included in the regimen.[67]

Antifungal Therapy

Patients with candidemia are generally sicker based on their higher Acute Physiology and Chronic Health Evaluation (APACHE) II scores, and have a higher mortality rate than those with bacteremia.[12] As such, clinicians should consider empiric antifungal therapy based on the risk factors for invasive *Candida* infections and no other known cause of fever. The risk factors include immunocompromised status, dialysis, prolonged invasive vascular devices, total parental nutrition, necrotizing pancreatitis, major surgery especially abdominal, prolonged exposure to broad-spectrum antibiotics, corticosteroids, prolonged hospital/ICU stay, or fungal colonization.[86,87]

Empiric treatment of invasive candidiasis based on clinical assessment of risk factors, surrogate markers such as beta-D-glucan for invasive candidiasis, or culture includes echinocandins, triazoles, or a formulation of amphotericin B.[86,88] The selection depends on the clinical status of the patient, the local susceptibility of the most prevalent *Candida* species, recent exposure to antifungal agents, relative drug toxicity, and the presence of organ dysfunction or

shock that would affect drug clearance. Recent exposure to antibiotics and fluconazole has been associated with fluconazole-resistant *Candida* species.[89] Fluconazole resistance among *Candida* species from bloodstream infections ranges between 12% and 28% .[16,18] *C. glabrata* was the only species that may exhibit resistance to both triazoles and echinocandins. Among the 180 *C. glabrata* isolated from nosocomial bloodstream infections, 62% were non-susceptible to both caspofungin and fluconazole.[16]

Preferred empiric therapy for suspected invasive candidiasis in nonneutropenic patients in the ICU is an echinocandin (anidulafungin, micafungin, or caspofungin). They exhibit potent activity against all *Candida* species, including *C. krusei* that is typically resistant to an azole, as well as *Aspergillus* species. Empiric use of an echinocandin should be considered in most patients, despite the severity of illness including septic shock, who have recently been treated with other antifungal agents or suspected *C. glabrata* or *C. krusei* infection.[86]

Resistance to fluconazole, caspofungin, and amphotericin B was reported in 28%, 2.9%, and 3.1%, respectively, of adults admitted to ICUs with invasive candidiasis who received antifungal therapy empirically.[18] Approximately 20% of the antifungal agents were changed primarily based on *Candida* susceptibility, followed by inadequate clinical response. Overall, the hospital mortality was comparable between echinocandin (caspofungin/anidulafungin) and fluconazole (56% vs 58%, respectively). In a pooled, post hoc analysis of two Phase 3 trials, micafungin 100 mg daily was noninferior to liposomal amphotericin B 3 mg/kg daily or caspofungin 70 mg followed by 50 mg daily for the treatment of invasive candidiasis in patients with or without neutropenia. Overall treatment success was numerically lower in patients with neutropenia than those without (64% vs 73%).[90] All three echinocandins appear to be comparable in terms of efficacy, pharmacology, and adverse effects, and the guidelines do not make a distinction or recommend a preferred agent.[86]

Triazoles (fluconazole, voriconazole) are recommended in hemodynamically stable patients who have not had previous triazole exposure and not known to be colonized with azole-resistant *Candida* species.[86] The 2016 practice guidelines for candidiasis recommend fluconazole 800 mg loading dose, followed by 400 mg daily. However, the Sepsis-3 guidelines do not make a distinction between the triazoles. However, a recent publication of prospective randomized trial compared isavuconazole to caspofungin for treatment of invasive candidiasis, and overall response was 60% in the isavuconazole arm and 71% in caspofungin arm, not demonstrating non-inferiority of isavuconazole to caspofungin.[91]

A liposomal formulation of amphotericin B (3-5 mg/kg daily) is an alternative to echinocandins in patients with echinocandin intolerance or toxicity. There was no difference in treatment efficacy or mortality outcomes in critically ill patients with invasive candidiasis receiving an amphotericin B formulation compared with those receiving an echinocandin or voriconazole.[88] However, amphotericin B was poorly tolerated.

Pharmacokinetics and Pharmacodynamic Principles of Antimicrobial Agents

Physiologic changes during sepsis including unstable hemodynamics, increased cardiac output, variable kidney and hepatic perfusions, or hypoalbuminemia can dramatically alter antimicrobial pharmacokinetics.[92,93] Initially, high creatinine clearance can be seen in patients with normal serum creatinine because of increased renal preload. Reduced serum albumin leads to altered drug binding. Volume of distribution may be increased because of fluid accumulation from leaky capillaries into the extracellular space from aggressive fluid resuscitation. Consequently, some antimicrobial agents, especially for hydrophilic antimicrobials including aminoglycosides, beta-lactams, carbapenems, and vancomycin can result in suboptimal serum concentrations with standard doses.[94] Hence, dosage adjustments of antimicrobials may be required to optimize pharmacokinetic parameters and meet pharmacodynamic targets for optimal bacterial killing activity.

In cases of septic shock due to MRSA, inadequate vancomycin trough plasma concentrations in relation to the MIC of the pathogen has been associated with clinical failure.[95] A trough concentration target of 15 to 20 mg/L (10.4 to 13.8 µmol/L) is recommended to optimize the drug pharmacodynamics which will, in turn, improve clinical outcome. Vancomycin should be initiated with a loading dose of 25 to 30 mg/kg, based on actual body weight to rapidly achieve the target concentration.[49]

Daptomycin plasma concentrations after a dose of 6 to 8 mg/kg/day for primarily staphylococcal-related infections were lower in critically ill patients than healthy volunteers.[96] Daptomycin clearance did not change significantly in patients with or without sepsis. However, volume of distribution appeared to be larger. Consequently, weight-based daptomycin dose of at least 10 mg/kg/day was recommended as well as therapeutic drug monitoring, starting after the fourth dose of daptomycin.[96]

The time the plasma drug concentration remains above the pathogen MIC in relation to the dosing interval (T > MIC) best describes the pharmacodynamics of beta-actams. A minimum T > MIC of 60% generally provides a good clinical response. However, sepsis or septic shock may require longer duration of T > MIC.[97] Extended infusion of piperacillin/tazobactam over 4 hours rather than the standard 30 minutes achieved longer T > MIC and possibly may lead to better patient outcome in critically ill patients.[98]

Based on its concentration-depending killing activity, the Sepsis-3 guidelines recommend once daily dosing of 5-7 mg/kg daily gentamicin or an equivalent aminoglycoside. This high dosing strategy yielded comparable clinical efficacy but decreased renal toxicity compared to the multiple daily dosing regimens.[49] However, this dosing regimen should not be used for patients with severe renal function who may be clearing gentamicin for a prolonged period of time. However, suboptimal aminoglycoside concentrations have been reported in the early phase of therapy in critically ill patients, suggesting higher dosing of 8 mg/kg gentamicin may be required for optimal effect.[99] The target trough concentrations of below 2 mg/L (4.18 µmol/L) should be monitored to detect potential renal toxicity.

As sepsis progresses, organ perfusion decreases because of significant myocardial depression and leads to multiple organ dysfunction. Consequently, clearance of antimicrobial agents is decreased, prolonging the elimination half-life and accumulation of metabolites. Dosing strategies need to be assessed and modified continuously through the course of treatment for optimal efficacy.

De-escalation

Broad-spectrum-antibiotics should be initiated empirically due to the serious nature of the disease, but the antimicrobial regimen should be reassessed daily based on the microbiological and clinical data. This creates a potential de-escalation opportunity as part of good antibiotic stewardship to narrow down the spectrum once the pathogen has been identified to avoid unnecessary use of antimicrobials.[49,100] The de-escalation may also prevent drug toxicities and the development of nosocomial super infections with *Candida* species, *Clostridium difficile*, or VRE. Improved patient care outcomes have been demonstrated with such de-escalation of antibiotic therapy.[101] The hospital mortality rate among patients admitted to the ICU with severe sepsis or septic shock was 27% in whom therapy was de-escalated, 33% in the category of no change, and 43% in the escalation group.[102]

The data on when or precise criteria to de-escalate in case of negative cultures is lacking. However, antimicrobial regimen should still be assessed daily for opportunity for de-escalation in response to clinical improvement including shock resolution or decrease in vasopressor requirement and/or evidence of infection resolution by biomarkers, especially procalcitonin.[49]

EVALUATION OF THERAPEUTIC OUTCOMES

PCT is a serum biomarker that increases in response to endotoxins and inflammatory cytokines that are released during systemic bacterial infections, and it rises early in severe sepsis by pneumonia and bloodstream infections. Measurements of procalcitonin concentrations may assist in determining the duration of antimicrobial therapy in sepsis.[49] In a large randomized trial, using PCT concentration in critically ill patients was associated with reduced duration of antimicrobial treatment and daily doses of antimicrobials. Furthermore, the PCT group had a significant reduction in mortality.[103,104] Overall, PCT-guided therapy in critically ill patients as supplemental data to clinical assessment shortens the length of antimicrobial therapy, and a growing body of literature suggests survival advantage as well.

Duration of Therapy

The average duration of antimicrobial therapy in a patient with sepsis is 7 to 10 days in the absence of source control issues, and fungal infections can require 10 to 14 days.[49,86] However, the duration can be longer in patients with a slow clinical response, undrainable focus of infection, bacteremia with *S. aureus*, multidrug-resistant gram-negative pathogens, or neutropenia.

Treatment duration is based on a variety of factors including patient's immune status, infecting pathogen, and the site of infection such as large abscess in the abdomen. However, shorter courses of antibiotics for some serious infections, especially with successful source control, may be effective.[105,106] Current guidelines recommend a 7-day course of therapy for both hospital-acquired and ventilator-associated pneumonia.[67] A short course of antimicrobial treatment (median duration of 4 days) for patients with complicated intra-abdominal infection and adequate source control had similar surgical site infection, recurrent intra-abdominal infection, or death as the control group with a median of 8 days of antibiotics whose antibiotic duration was based on symptoms (ie, fever, leukocytosis, and ileus).[106] The Surgical Infection Society

recommends no more than four full days of antimicrobial therapy for patients with adequate source control and no more than 5 to 7 days in patients in whom a definitive source control was not performed.[58]

Hemodynamic Support with Vasopressors

The Sepsis-3 guidelines recommend a target MAP of at least 65 mm Hg [MAP = (SBP + 2*DBP)/3].[49] Achievement of a high (MAP of 80-85 mm Hg) or low (MAP of 65-70 mmHg) target did not result in significant difference in mortality at 28 and 90 days.[107] Among the patients with pre-existing hypertension, those in the high target group had less renal dysfunction and need for renal replacement therapy. However, the incidence of newly diagnosed atrial fibrillation was significantly higher in the high target group. The number needed to treat was 9.5 to prevent one patient from necessitating renal replacement therapy.[108]

Vasopressors should be used to achieve and maintain MAP goal in fluid-resuscitation refractory shock, and they are titrated up carefully to an end point of adequate organ perfusion. There are several adrenergic receptors that are the key to understanding the mechanism of action of various vasopressors (**Table 137-6**). Alpha adrenergic receptors are located in the vascular wall and in the heart, and the alpha receptor agonists induce peripheral vasoconstriction as well as increase the duration of contraction in the heart. Beta adrenergic receptors are primarily found in the heart. Stimulation of the beta receptors causes inotropic and chronotropic effect. Dopamine receptors are in the renal, splanchnic, coronary, and cerebral vascular beds. Dopamine receptor agonists cause vasodilation of the renal and splanchnic vessels. As dopamine is a precursor to epinephrine and norepinephrine, it affects both alpha-1 and beta-1 receptors, causing peripheral vasoconstriction and inotropy. There are three types of vasopressin receptors: V1, V2, and V3 receptors. Vasopressin works on the V1 and V2 receptors, which are in vascular smooth muscles and basolateral membrane of the collecting duck, respectively. Vasopressin contracts vascular smooth muscle mainly through the V1 receptor and retains water via V2 receptors.

TABLE 137-6 Mechanism of Action and Hemodynamic Effects of Vasopressors in Septic Shock

	Receptor Affinity				Physiologic Outcome			
Drug	Dopamine	Alpha-1	Beta-1	Beta-2	HR	SV	SVR	CO
Dopamine (0.5-2)[a]	+++	-	+	-	↔↑	↑	↔ or ↑	↑
Dopamine (5-10)[a]	++	+	+++	+	↑	↑	↔ or ↑	↑↑
Dopamine (10-20)[a]	++	+++	++	-	↑	↑	↑↑	↑
Epinephrine	-	++++	++++	+++	↑	↑	↑↑	↑↑
Norepinephrine	-	++++	++	+	↔ or ↑	↔	↑↑	↑
Phenylephrine	-	+++	-	-	↔ or ↓	-	↑↑	↔
Vasopressin	V1 receptor				↔ or ↓	-	↑↑	↔ or ↓
Angiotensin II	AT receptor				↑	-	↑	↑

CO, cardiac output; HR, heart rate; SV, stroke volume; SVR, systemic vascular resistance; V1, vasopressin receptor 1; V2, vasopressin receptor 2.

[a]mcg/kg/min.

Data from Reference 109.

6 Norepinephrine, a potent alpha-adrenergic agent with less pronounced beta-adrenergic activity than epinephrine is the preferred vasopressor to correct hypotension in fluid refractory septic shock[49,109] (Table 137-6). It increases MAP and SVR via vasoconstrictive effects on peripheral vascular beds. Doses of 0.01 to 3 mcg/kg/min can reliably increase MAP with little changes in heart rate, and less increase in stroke volume compared to dopamine. Norepinephrine is more potent than dopamine in refractory septic shock. Norepinephrine was associated with lower risk of mortality and lower risk of arrhythmia compared to dopamine.[110]

Dopamine may be considered as an alternative agent to norepinephrine in a small subset of patients who have bradycardia or are at low risk of developing arrhythmia.[49,108] Dopamine increases MAP and cardiac output by increasing the heart rate and cardiac contractility, making it potentially useful for patients with compromised systolic function. However, it is arrhythmogenic and can cause tachycardia.[110] Low-dose dopamine demonstrated no significant effect on enhancing urine output or need for renal replacement therapy in comparison to placebo. The guidelines do not recommend low-dose dopamine for renal protection.[49]

Epinephrine is a nonspecific alpha- and beta-adrenergic agonist (Table 137-6). It impairs blood flow to the splanchnic system and can increase lactate production via stimulation of the beta-adrenergic receptors located in the skeletal muscles. It may also induce or exacerbate tachycardia. It is unknown if this

process has any clinical implications. There was no significant difference in mortality between norepinephrine and epinephrine for septic shock.[110] The guidelines suggest adding epinephrine to norepinephrine to achieve target MAP in case of refractory hypotension.[49]

Phenylephrine, a selective alpha-1-agonist, has rapid onset, short duration, and primary vascular effects, and it is least likely to produce tachycardia. On the other hand, if the patient is hypovolemic, it can cause clinically significant bradycardia limiting its use in early sepsis for hemodynamic support. Based on the limited clinical trial data, phenylephrine should be restricted as a salvage therapy when all other vasopressors have failed to achieve target MAP or if arrhythmia makes norepinephrine intolerable.[49] Dobutamine may be considered in patients with persistent hypoperfusion despite adequate fluid resuscitation and the use of vasopressor agents.[49]

Multiple investigators have assessed the optimal dosing of norepinephrine among obese patients with septic shock. This is important to consider as many drug studies do not include obese patients in their patient cohort and therefore leave the clinicians to extrapolate pharmacokinetic parameters from nonobese patients at bedside. Several studies compared the clinical outcomes (ie, mortality, length of ICU and hospital stay, or duration of vasopressors) of weight-based dosing (WBD) versus non-weight-based dosing (non-WBD) of norepinephrine.[111–113] WBD of norepinephrine in obese adult patients (body mass index, BMI > 30 kg/m^2) did not achieve goal MAP earlier than the non-WBD group, and there was no difference in mortality (23.6% vs 23.1%, respectively).[112] However, the median cumulative dose of norepinephrine was higher in the WBD group compared to non-WBD group. When norepinephrine WBD was stratified by BMI, low (BMI <18.5 kg/m^2), control (BMI 19-25 kg/m^2), high (BMI > 40 kg/m^2) morbidly obese patients had significantly higher cumulative norepinephrine use.[111] Higher norepinephrine exposure was an independent risk factor for mortality during hospitalization and at 1 year. Increase in overall exposure to norepinephrine may have implications in higher mortality rates.[111]

Vasopressin, also known as antidiuretic hormone, is produced in the hypothalamus and released from pituitary. In a healthy individual, it controls osmolality by stimulating the V2 receptors in the kidneys, but has little effect on blood pressure. However, in a state of distributive shock, vasopressin binds to receptors in vascular smooth muscle, which leads to vasoconstriction, thereby increasing blood pressure. In contrast, decreased level of vasopressin is seen in

septic shock after an initial rise due to combination of depletion of vasopressin stores and inhibition of synthesis and release.[108] A synthetic formulation of vasopressin up to 0.03 U/min is recommended as a second agent added to norepinephrine to decrease norepinephrine dosage and/or to meet MAP goal. Higher doses of vasopressin have been associated with cardiac, digital, and splanchnic ischemia. A landmark study, the VASST trial comparing norepinephrine alone and norepinephrine with low-dose vasopressin in patients with septic shock showed similar mortality rates (39% vs 35%, respectively). When the investigators reevaluated the VASST trial, using the new definition of septic shock from the Sepsis-3 guidelines, the sample size decreased by half, and the 28-day mortality rates were increased by about 10% for both groups. However, vasopressin had more robust effectiveness in those patients with lactate of ≤2 mmol/L than in patients with lactate of >2 mmol/L.[114] While large studies evaluating the efficacy of vasopressin is lacking, addition to norepinephrine may decrease norepinephrine dosage to achieve target MAP.

The first synthetic angiotensin II was approved for the use in vasopressor refractory septic shock. In the setting of decreased renal perfusion, the angiotensinogen from liver and renin produced by the kidney come together to form angiotensin I which is then transformed to angiotensin II by angiotensin-converting enzyme. Angiotensin II ultimately increases blood pressure by increasing sympathetic activity that stimulates pituitary gland to increase antidiuretic hormone secretion to promote sodium, chloride, and water reabsorption in the kidneys. It also continues to promote aldosterone secretion from the adrenal gland, where aldosterone will carry on the sodium and water reabsorption in the distal tubule and collecting duct of the kidney via sodium-potassium pump. Angiotensin II was evaluated in adult patients with persistent hypotension despite adequate fluid resuscitation and received > 0.2 ng/kg/min norepinephrine equivalent vasopressor use (ATHOS-3 trial).[115] A greater response in MAP was reported in 321 patients who received angiotensin II versus placebo (69.9% vs 23.4%). Although there was a trend toward decrease in mortality, it was not statistically significant. Post hoc analysis of 105 patients from the ATHOS-3 trial, with AKI requiring renal replacement therapy (RRT) at initiation of angiotensin II, reported significantly higher 28-day survival and discontinuation of RRT in the angiotension II group, comparison to placebo (53% vs 30% and 38% vs 15%).[116] It is not clear where and how angiotensin II fits into treatment of septic shock. It is difficult to incorporate angiotensin II into a treatment algorithm for septic shock based on the small study population. Future large randomized trials comparing angiotensin II versus norepinephrine

or epinephrine and the treatment outcomes including survival rates are needed before defining its place in therapy can be made.

Performance Improvement Bundle

The Surviving Sepsis Campaign recommends implementation of hospital-based performance improvement efforts such as a core set of recommendation ("bundle") as they have been associated with improved patient outcomes.[1,49] While the details of each institution's performance improvement bundle may be different, there is a common theme of improved management of patients with sepsis and septic shock.[117] Hospital mortality rates dropped 0.7% per site for every 3 months of participation and the hospital and the ICU length of stay decreased by 4% for every 10% increase in site compliance in a 7.5-year study assessing the level of compliance to the performance bundle internationally.[118]

The 3-hour bundle based on the Sepsis-2 guidelines includes obtaining serum lactate, blood cultures prior to giving antibiotics, administration of a broad-spectrum antibiotics and 30 mL/kg of crystalloid fluid bolus for hypotension or lactate ≥ 4 mmol/L. Components that are recommended to be initiated before 6th hour (6-hour bundle) include vasopressors for persistent hypotension with goal MAP of ≥65 mm Hg, measurement of CVP with goal of ≥8 mm Hg, ScvO2 goal of ≥70% (0.70), and repeat of lactate if initial level was elevated.

7 The Sepsis-3 guidelines were recently updated to modify the 3-hour bundle with the use of a 1-hour care, putting the importance of beginning the initial treatment immediately (**Table 137-7**).[50] There are three major components of initial resuscitation after early recognition of sepsis: administration of fluid, administration of broad-spectrum antibiotics, and use of vasopressor agents. If the patient is hypotensive and not responding to initial fluid, a clinician should not be waiting until the third hour to consider the use of vasopressor as may be interpreted by the Sepsis-2 guideline. Resolution of serum lactate is desired to indicate adequate tissue perfusion and therefore should be repeated in 2 to 4 hours of initial level. The interpretation of repeat lactate requires careful consideration especially in patients with concomitant hepatic and/or renal failure as metabolism and elimination of lactate may be decreased in this setting.

TABLE 137-7 Sepsis-3 (2016) Performance Improvement Checklist for Bundle-Care Compliance

One-hour bundle

- Measure initial lactate
- Repeat in 2 hours if initial lactate > 2 mmol/L
- Obtain cultures (blood, urine, sputum, etc.) prior to administration of antibiotics
- Administer broad-spectrum IV antibiotics within 1 hour
- Initial fluid resuscitation of 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L
- Vasopressors if MAP < 65 mmHg during or after completion of fluid resuscitation

Outcome measurements:

- Length of stay in ICU and hospital
- Rate of organ dysfunction
- Mortality rate

CVP, central venous pressure; MAP, mean arterial pressure; $ScvO_2$, central venous oxygen saturation.

Data from References 49 and 50.

Adjunctive Therapies

Sepsis and septic shock present multitudes of complications in a relative short span of time. In addition to prompt initiation of a performance improvement bundle, numerous adjunctive therapies including transfusions of blood products, oxygen supplement, mechanical ventilation, or RRT may be required.

8 IV hydrocortisone is recommended for adult patients with septic shock who are hemodynamically unstable after initial resuscitation with IV fluids and vasopressors. Cortisol levels vary widely in patients with septic shock, and increased mortality has been associated with both low and high serum cortisol levels. The data on the benefits of corticosteroids as adjunct therapy in patients with sepsis and septic shock continues to demonstrate conflicting results in reduction of overall mortality.[119–125] A significant shock reversal and reduction in mortality were reported in patients with septic shock unresponsive to fluid resuscitation and vasopressors for more than an hour and had relative adrenal insufficiency who received prolonged courses (>5 days) of low-dose corticosteroid therapy compared to placebo (38% vs 44%; relative risk 0.84).[119] However, a large multicenter trial, the Corticosteroid Therapy of Septic Shock (CORTICUS), found no survival benefit among patients who were unresponsive to adequate fluid replacement and required vasopressors, with or without adrenal insufficiency.[120] The CORTICUS study included patients with septic shock regardless of their responsiveness to vasopressor therapy. Subsequent meta-

analyses and systematic reviews continue to present conflicting data. Low-dose corticosteroids reduced 28-day mortality, increased shock reversal, and reduced organ injury based on analysis of 22 randomized controlled trials.[121] In contrast, another systematic review of 35 trials of sepsis reported that while majority of trials had a high probability of bias and were unpowered, no statistically significant benefit on mortality was detected.[122]

Two large, randomized, blinded, multicenter, controlled trials of low-dose corticosteroids use in patients with septic shock did not confirm or refute the previously published data on reduction of mortality, unfortunately.[124,125] However, these landmark studies describing the largest comprehensive analysis in more than 5000 patients combined together offer practical benefits of low-dose corticosteroids. Both trials clearly defined adequate fluid resuscitation, vasopressor-dependent shock, and appropriate antimicrobial therapy. The 90-day mortality in the Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL) trial was 27.9% with continuous infusion of hydrocortisone 200 mg/day for maximum of 7 days and 28.8% with placebo.[123] There was no difference in mortality at 6 months after randomization.[125] The 90-day mortality in the Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) trial was 43.0% with hydrocortisone 50 mg IV bolus every 6 hours plus fludrocortisone 50 mcg tablet via a nasogastric tube once daily for 7 days and 49.1% with placebo.[124] The dramatic difference in the mortality data may rise from the patients' severity of illness. The patients from the APROCCHSS trial may have been more seriously ill based on their SOFA and APACHE II scores, and having higher rates requiring renal replacement therapy and bacteremia. Regardless, both trials showed significantly faster resolution of shock and more rapid cessation of mechanical ventilator, providing reassurance of short-term benefits of low-dose hydrocortisone in selected patients before assessing the 90-day mortality at patients' bedside.

The guidelines continue to recommend using IV hydrocortisone at a dose of 200 mg/day only if hemodynamic stability is not achieved after adequate fluid resuscitation and vasopressor therapy, regardless of the state of adrenal insufficiency.[1,49] Continuous infusion of hydrocortisone may prevent significant increase in blood glucose associated with repetitive bolus injections. The guidelines also recommend tapering steroids when vasopressors are no longer required as hemodynamic and immunologic rebound effects have been reported with abrupt cessation of corticosteroids.[49]

9 Blood glucose level of less than 180 mg/dL (10.0 mmol/L) is recommended along with frequent blood glucose monitoring to avoid

hypoglycemia. Hyperglycemia and insulin resistance are frequently associated with sepsis regardless of the presence of diabetes prior to sepsis, and more severe hyperglycemia is associated with higher morbidity and mortality.[1,49] However, in surgical and medical ICU patients receiving intensive insulin therapy, there was almost fourfold increase in risk of hypoglycemia, and it did not significantly decrease morality.[126] The NICE-SUGAR trial, the largest study to date on glucose control in ICU patients, reported a higher incidence of mortality at 90 days with the intensive insulin therapy (target glucose range of 81 to 108 mg/dL [4.5 to 6.0 mmol/L]) than the conventional therapy (target of < 180 mg/dL [10.0 mmol/L]). Furthermore, the highest rate of mortality was reported in the patients with severe hypoglycemia (≤40 mg/dL [2.2 mmol/L]) (35.4%).[127,128] Intensive insulin therapy in septic patients did not change the overall mortality and was associated with a higher incidence of hypoglycemia.[129]

The guidelines recommend using a protocolized approach to blood glucose management after two consecutive blood glucose levels of > 180 mg/dL (10 mmol/L). While it recommends targeting an upper blood glucose of < 180 mg/dL (10.0 mmol/L), a lower target is not specified as there is no evidence in differences in outcome between lower glucose target of 110 or 140 mg/dL (6.1 or 7.8 mmol/L). However, the guidelines recommend monitoring blood glucose every 1 to 2 hours until the glucose levels and insulin requirements are stable to avoid hypoglycemia.[49]

Venous thromboembolism (VTE) prophylaxis with daily subcutaneous LMWH should be initiated in all patients admitted to the ICU with sepsis and septic shock along with mechanical prophylaxis (intermittent pneumatic compression or graduated compression stockings) unless contraindicated.[49] Overall incidence of VTE in the ICU is approximately 10%. However, the incidence was much higher (37.2%) in patients with sepsis and septic shock which may increase the length of stay in ICU (18.2 vs 13.4 days).[130] Use of vasopressor was found to be an independent risk factor for VTE.[49]

There is limited data comparing LMWH to unfractionated heparin in VTE prophylaxis among septic patients. However, the overall rate of VTE and pulmonary embolism was lower in critically ill patients receiving LMWH in comparison to unfractionated heparin administered twice daily, and overall mortality was also reduced, albeit not significant.[131,132] In patients with renal impairment (creatinine clearance of less than 30 mL/min [0.50 mL/s]), dalteparin did not accumulate. LMWH may be an option for critically ill patients with acute renal injury based on limited data.[1,49] If pharmacologic prophylaxis is

contraindicated, mechanical prophylactic measures should be considered.[49]

An international prospective cohort study reported clinically important GI bleeding occurred in 2.6 % in critically ill adult patients.[133] Prophylaxis with either a proton pump inhibitor (PPI) or histamine 2 receptor antagonist (H2RA) reduced the risk of GI bleeding in comparison to no prophylaxis.[134] However, *Clostridium difficile* infection and pneumonia have been reported with both PPIs and H2RAs use.[49]

Stress ulcer prophylaxis should be initiated in all patients with sepsis and septic shock who have risk factors for GI bleeding.[1,49] Risk factors may include patients who are requiring mechanical ventilation for > 48 hours or experiencing coagulopathy (INR>1.5). Either a PPI or H2RA may be used. The selection of agent should also consider patient's renal, liver, hematologic dysfunction, as dose adjustments may be necessary. Although preventing clinically significant GI bleeding is important, it also must be balanced with potential adverse events from decreasing pH of the stomach such as possibility of developing *C. difficil*e infection or pneumonia.[49]

Postclass Engaged Learning Activity

Conduct a literature search on updates in pharmacological management of sepsis and septic shock since the publication of the Surviving Sepsis Campaign international guidelines in 2016. Select one publication from each area of fluid therapy, vasopressors and corticosteroids, and briefly summarize the study methods, the major findings, and how the new information might change current practice using a medication that is currently available or a new medication based on potential advantages and disadvantages. This activity will enhance the student's literature search and evaluation skills, and the PLAN step in the patient care process.

ABBREVIATIONS

AKI	acute kidney injury
APACHE	acute physiology and chronic health evaluation
ARDS	acute respiratory distress syndrome
BMI	body mass index
CVP	central venous pressure
DIC	disseminated intravascular coagulation
EGDT	early goal-directed therapy
ESBL	extended-spectrum beta-lactamases
GI	gastrointestinal
HIV	human immunodeficiency virus
H2RA	histamine 2 receptor antagonist
ICU	intensive care unit
IV	intravenous
IL	interleukin
IL-1RA	interleukin-1 receptor antagonist
LMWH	low-molecular-weight heparin
MAP	mean arterial pressure
MIC	minimum inhibitory concentration
MRSA	methicillin-resistant *Staphylococcus aureus*
PCT	procalcitonin
PPI	proton pump inhibitor
RRT	renal replacement therapy
$Scvo_2$	central venous oxygen saturation
SIRS	systemic inflammatory response syndrome
SOFA	sequential organ failure assessment
SVR	systemic vascular resistance
T>MIC	time above minimum inhibitory concentration
TNF	tumor necrosis factor
qSOFA	quick sequential organ failure assessment
VRE	vancomycin-resistant enterococci
VTE	venous thromboembolism
WBC	white blood cell
WBD	weight-based dosing

REFERENCES

1. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock.

Crit Care Med. 2013;41:580–637.

2. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med*. 2003;31:1250–1256.
3. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315:801–810.
4. Rubens M, Saxena A, Ramamoorthy V, *et al*. Increasing sepsis rates in the United States: results from national inpatient sample, 2005 to 2014. *J Intensiv Care Med*. 2018; September 2:885066618794136. doi:10.1177/0885066618794136. [Epub ahead of print].
5. Rhee C, Dantes R, Epstein L, et al. Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009-2014. *JAMA*. 2017;318:1241–1249.
6. Kadri SS, Rhee C, Strich JR, et al. Estimating ten-year trends in septic shock incidence and mortality in United States academic medical centers using clinical data. *Chest*. 2017;151:278–285.
7. Walkey AJ, Lagu T, Lindenauer PK. Trends in sepsis and infection sources in the United States. A population-based study. *Ann Am Thorac Soc*. 2015;12:216–220.
8. Paoli C, Reynolds M, Sinha M, et al. Epidemiology and costs of sepsis in the United States—an analysis based on timing of diagnosis and severity level. *Crit Care Med*. 2018;46:1889–1897.
9. van Hal SJ, Jensen SO, Vaska VL, et al. Predictors of mortality in *Staphylococcus aureus* bacteremia. *Clin Microbiol Rev*. 2012;25:362–386.
10. Leligdowicz A, Dodek PM, Norena M, et al. Association between source of infection and hospital mortality in patients who have septic shock. *Am J Resp Crit Care Med*. 2014;189:1204–1212.
11. Thomas-Ruddel DO, Poidinger B, Kott M, et al. Influence of pathogen and focus of infection on procalcitonin values in sepsis patients with bacteremia or candidemia. *Crit Care*. 2018;22:128. doi:10.1186/s13054-018-2050-9.
12. Guillamet CV, Vazquez R, Micek ST, et al. Development and validation of a clinical prediction rule for candidemia in hospitalized patients with severe sepsis and septic shock. *J Crit Care*. 2015;30:715–720.
13. Brunkhorst FM, Oppert M, Marx G, et al. Effect of empirical treatment with moxifloxacin and meropenem vs meropenem on sepsis-related organ

dysfunction in patients with severe sepsis. *JAMA*. 2012;307:2390–2399.

14. Burnham JP, Lane MA, Kollef MH. Impact of sepsis classification and multidrug-resistance status on outcome among patients treated with appropriate therapy. *Crit Care Med*. 2015;43:1580–1586.
15. Zilbergerg MD, Shorr AF, Micek ST, et al. Multi-drug resistance, inappropriate initial antibiotic therapy and mortality in Gram-negative severe sepsis and septic shock: A retrospective cohort study. *Crit Care*. 2014;18:596–608.
16. Wisplinghoff H, Ebbers J, Geurtz L, et al. Nosocomial bloodstream infections due to Candida spp. in the USA: species distribution, clinical features and antifungal susceptibilities. *Int J Antimicrob Agents*. 2014;43:78–81.
17. Bassetti M, Righi E, Ansaldi F, et al. A multicenter study of septic shock due to candidemia: outcomes and predictors of mortality. *Intensive Care Med*. 2014;40:839–845.
18. Al-Dorzi HM, Sakkijha H, Khan R, et al. Invasive candidiasis in critically ill patients: a prospective cohort study in two tertiary care centers. *J Intensive Care Med*. 2018. doi:10.1177/0885066618767835.
19. Diekema D, Arbefeville S, Boyken L, et al. The changing epidemiology of healthcare-associated candidemia over three decades. *Diagn Microb Infect Dis*. 2012;73:45–48.
20. Tamayo E, Fernandez A, Almansa R, et al. Pro- and anti-inflammatory responses are regulated simultaneously from the first moments of septic shock. *Eur Cytokine Network*. 2011;22:82–87.
21. Chousterman BG, Swirski FK, Weber GF. Cytokine storm and sepsis disease pathogenesis. *Semin Immunopathol*. 2017;39:517–528.
22. Carlyn C, Andersen N, Baltch A, et al. Analysis of septic biomarker patterns: prognostic value in predicting septic state. *Diagn Microb Infect Dis*. 2015;83:312–318.
23. Kanoore Edul VS, Enrico C, Laviolle B, et al. Quantitative assessment of the microcirculation in health volunteers and in patients with septic shock. *Crit Care Med*. 2012;40:1443–1448.
24. Fourrier F. Severe sepsis, coagulation, and fibrinolysis: dead end or one way? *Crit Care Med*. 2012;40:2704–2708.
25. Hatfield K, Dantes R, Baggs J, et al. Assessing variability in hospital-level mortality among U.S. Medicare beneficiaries with hospitalizations for severe sepsis and septic shock. *Crit Care Med*. 2018;46:1753–1760.

26. Capp R, Horton CL, Takhar SS, et al. Predictors of patients who present to the emergency department with sepsis and progress to septic shock between 4 and 48 hours of emergency department arrival. *Crit Care Med*. 2015;43:983–988.
27. Levi M, Schultz M, van der Poll T. Sepsis and thrombosis. *Semin Thromb Hemost*. 2013;39:559–566.
28. Simmons J, Pittet J. The coagulopathy of acute sepsis. *Curr Opin Anaesthesiol*. 2015;28:227–236.
29. Keir I, Kellum JA. Acute kidney injury in severe sepsis: pathophysiology, diagnosis, and treatment recommendations. *Vet Emerg Crit Care*. 2014;25:200–209.
30. Eworuke E, Major J, McClain L. National incidence rates for acute respiratory distress syndrome (ARDS) and ARDS cause-specific factors in the United States (2006–2014). *J Crit Care*. 2018;47:192–197.
31. Kim W, Hong S. Sepsis and acute respiratory distress syndrome: recent update. *Tuberc Respir Dis*. 2016;79:53–57.
32. Kanoore Edul VS, Enrico C, Laviolle B, et al. Quantitative assessment of the microcirculation in healthy volunteers and in patients with septic shock. *Crit Care Med*. 2012;40:1443–1448.
33. Pulido JN, Afessa B, Masaki M, et al. Clinical spectrum, frequency, and significance of myocardial dysfunction in severe sepsis and septic shock. *Mayo Clin Proc*. 2012;87:620–628.
34. Lv X, Wang H. Pathophysiology of sepsis-induced myocardial dysfunction. *Mil Med Res*. 2016;3:30–38.
35. Morelli A, Passariello M. Hemodynamic coherence in sepsis. *Best Pract Res Clin Anaesthesiol*. 2016;30:453–463.
36. Peters E, Antonelli M, Wittebole X, et al. A worldwide multicenter evaluation of the influence of deterioration or improvement of acute kidney injury on clinical outcome in critically ill patients with and without sepsis at ICU admission: results from the Intensive Care Over Nations audit. *Crit Care*. 2018;22:188–198.
37. Londoño J, Nino C, Arichila A, et al. Antibiotic has more impact on mortality than other early goal-directed therapy components in patients with sepsis: an instrumental variable analysis. *J Crit Care*. 2018;48:191–197.
38. Thomas-Rueddel D, Poidinger B, Weiss M, et al. Hyperlactatemia is an independent predictor of mortality and denotes distinct subtypes of severe

sepsis and septic shock. *J Crit Care*. 2015;30:439.e1–439.e6.

39. Coelho FR, Martins JO. Diagnostic methods in sepsis: the need of speed. *Rev Assoc Med Bras*. 2012;58:498–504.
40. Davies J, Gordon CL, Tong SY, et al. Impact of results of a rapid Staphylococcus aureus diagnostic test on prescribing of antibiotics for patients with clustered gram-positive cocci in blood cultures. *J Clin Microbiol*. 2012;50:2056–2058.
41. Aittakorpi A, Kuusela P, Koukila-Kahkola P, et al. Accurate and rapid identification of Candida spp. frequently associated with fungemia by using PCR and the microarray-based prove-it sepsis assay. *J Clin Microbiol*. 2012;50:3635–3640.
42. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis for the third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315:762–774.
43. Dellinger R, Carlet J, Masur H, et al. Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med*. 2004;32:858–873.
44. Rivers E, Nguyen B, Havastad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345:1368–1377.
45. The ProCESS Investigators. A randomized trial of protocol-based care for early septic shock. *N Engl J Med*. 2014;370:1683–1693.
46. The ARISE Investigators and the ANZICS Clinical Trials Group. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med*. 2014;371:1496–1506.
47. Mouncey PR, Osborn TM, Power GS, et al. Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med*. 2015;372:1301–1311.
48. Nguyen HB, Jaehne AK, Jayaprakash N, et al. Early goal-directed therapy in severe sepsis and septic shock: insights and comparison to ProCESS, ProMISe, and ARISE. *Crit Care*. 2016;20:160. doi:10.1186/s13054-016-1288-3.
49. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Crit Care Med*. 2017;45:486–552.
50. Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. *Crit Care Med*. 2018;46:997–1000.

51. Malbrain MLNG, van Regenmortel N, Saugel B, et al. Principles of fluid management and stewardship in septic shock: it is time to consider the four D's and the four phases of fluid therapy. *Ann Intensive Care*. 2018;8:66. doi:10.1186/s13613-018-0402-x.
52. Bednarczyk JM, Fridfinnson JA, Kumar A, et al. Incorporating dynamic assessment of fluid responsiveness into Goal-Directed Therapy: a systematic review and meta-analysis. *Crit Care Med*. 2017;45:1538–1545.
53. Brown RM, Semler MW. Fluid management in sepsis. *J Intensive Care Med*. 2018. doi:10.1177/0885066618784861.
54. Finfer S, Belloma R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350:2247–2256.
55. Semler MW, Self WH, Wanderer JP, et al. Balanced crystalloids versus saline in critically ill adults. *N Engl J Med*. 2018;378:829–839.
56. Self WH, Semler MW, Wanderer JP, et al. Balanced crystalloids versus saline in noncritically ill adults. *N Engl J Med*. 2018;378:819–828.
57. Filis C, Vasileiadis I, Koutsoukou A. Hyperchloraemia in sepsis. *Ann Intensive Care*. 2018;8:43. doi:10.1186/s13613-018-0388-4.
58. Mazuski JE, Tessier JM, May AK, et al. The surgical infection society revised guidelines on the management of intra-abdominal infection. *Surg Infect*. 2017;18:1–76.
59. Ferrer R, Martin-Loeches I, Phillips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. *Crit Care Med*. 2014;42:1749–1755.
60. Seymour C, Gesten F, Prescott H, et al. Time to treatment and mortality during mandated emergency care for sepsis. *N Engl J Med*. 2017;376:2235–2243.
61. Vazquez-Guillamet C, Scolari M, Zilberberg MD, et al. Using the number needed to treat as assess appropriate antimicrobial therapy as a determinant of outcome in severe sepsis and septic shock. *Crit Care Med*. 2014;42:2342–2349.
62. Liu VX, Fielding-Singh V, Greene JD, et al. The timing of early antibiotics and hospital mortality in sepsis. *Am J Respir Crit Care Med*. 2017;196:856–863.
63. Kumar A, Ellis P, Arabi Y, et al. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock.

Chest. 2009;136:1237–1248.

64. Sherwin R, Winters M, Vike G, et al. Does early and appropriate antibiotic administration improve mortality in emergency department patients with severe sepsis or septic shock? *J Emerg Med*. 2017;53:588–595.
65. Grim SA, Berger K, Teng C, et al. Timing of susceptibility-based antifungal drug administration in patients with Candida bloodstream infection: Correlation with outcomes. *J Antimicrob Chemother*. 2012;67:707–714.
66. Kollef M, Micek S, Hampton N, et al. Septic shock attributes to Candida infection: importance of empiric therapy and source control. *Clin Infect Dis*. 2012;54:1739–1746.
67. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016;63:e61–e111.
68. Musher DM, Thorner AR. Community-acquired pneumonia. *N Engl J Med*. 2014;371:1619–1628.
69. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Disease Society of America. *Clin Infect Dis*. 2014;59:147–159.
70. Wagenlehner FME, Tandogdu Z, Bjerklund Johansen TE. An update on classification and management of urosepsis. *Curr Opin Urol*. 2017;27:133–137.
71. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Disease Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis*. 2011;52:1–38.
72. Wang Y, Zou Y, Xie J, et al. Linezolid versus vancomycin for the treatment of suspected methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a systematic review employing meta-analysis. *Eur J Clin Pharmacol*. 2015;71:107–115.
73. Rubinstein E, Lalani T, Corey GR. Telavancin versus vancomycin for hospital-acquired pneumonia due to Gram-positive pathogens. *Clin Infect Dis*. 2011;52:31–40.
74. Shori A, Sandrock CE. The role of telavancin in hospital-acquired pneumonia and ventilator-associated pneumonia. *Clin Infect Dis*.

2015;61:S79–S86.

75. Brown JE, Fominaya C, Christensen KJ, et al. Daptomycin experience in critical care patients: results from a registry. *Ann Pharmacother*. 2012;46:495–502.
76. Claeys KC, Zasowski EJ, Casapao AM, et al. Daptomycin improves outcomes regardless of vancomycin MIC in a propensity-matched analysis of methicillin-resistant *Staphylococcus aureus* bloodstream infections. *Antimicro Agents Chemother*. 2016;60:5841–5848.
77. Russo A, Falcone M, Gutierrez-Gutierrez B, et al. Predictors of outcome in patients with severe sepsis or septic shock due to extended-spectrum beta-lactamase-producing Enterobacteriaceae. *Int J Antimicrob Agents*. 2018;52:577–585.
78. Sfeir MM, Askin G, Christos P. Beta-lactam/beta-lactamase inhibitors versus carbapenem for bloodstream infections due to extended-spectrum beta-lactamase-producing Enterobacteriaceae: systematic review and meta-analysis. *Int J Antimicrob Agents*. 2018;52:554–570.
79. Son S, Lee N, Ko J, et al. Clinical effectiveness of carbapenems versus alternative antibiotics for treating ESBL-producing Enterobacteriaceae bacteraemia: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2018;73:2631–2642.
80. Harris P, Tambyah P, Lye D, et al. Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with *E. coli* or *Klebsiella pneumoniae* bloodstream infection and ceftriaxone resistance. *JAMA*. 2018;320:984–994.
81. Tamma PD, Cosgrove SE, Maragakis LL. Combination therapy for treatment of infections with gram-negative bacteria. *Clin Microbiol Rev*. 2012;25:450–470.
82. Vasquez-Grande G, Kumar A. Optimizing antimicrobial therapy of sepsis and septic shock: focus on antibiotic combination therapy. *Semin Respir Crit Care Med*. 2015;36:154–166.
83. Qureshi ZA, Paterson DL, Potoski BA, et al. Treatment outcome of bacteremia due to KPC-producing *Klebsiella pneumoniae*: Superiority of combination antimicrobial regimens. *Antimicrob Agents Chemother*. 2012;56:2108–2113.
84. Bass SN, Bauer SR, Neuner EA, et al. Impact of combination antimicrobial therapy on mortality risk for critically ill patients with carbapenem-resistant bacteremia. *Antimicrob Agents Chemother*.

2015;59:3748–3753.

85. Poulikakos P, Tansarli GS, Falgas ME. Combination antibiotic treatment versus monotherapy for multidrug-resistant, extensively drug-resistant, and pandrug-resistant Acinetobacter infections: a systematic review. *Eur J Clin Microbiol Infect Dis*. 2014;33:1675–1685.
86. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of Candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62:e1–e50.
87. Antinori S, Milazzo L, Sollima S, et al. Candidemia and invasive candidiasis in adults: a narrative review. *Eur J Intern Med*. 2016;34:21–28.
88. Keane S, Geoghegan P, Povoa P, et al. Systematic review on the first line treatment of amphotericin B in critically ill adults with candidemia or invasive candidiasis. *Expert Rev Anti Infect Ther*. 2018;16:839–847.
89. Ben-Ami R, Olshtain-Pops K, Krieger M, et al. Antibiotic exposure as a risk factor for fluconazole-resistant Candida bloodstream infection. *Antimicrob Agents Chemother*. 2012;56:2518–2523.
90. Chandrasekar P, Sirohi B, Seibel N, et al. Efficacy of micafungin for the treatment of invasive candidiasis and candidaemia in patients with neutropenia. *Mycoses*. 2018;61:331–336.
91. Kullberg B, Viscoli C, Pappas PG, et al. Isavuconazole versus caspofungin in the treatment of candidemia and other invasive candida infections: The active trial.; *Int J Antimicrob Agents*. 2014;43:78–81.
92. Roberts J, Abdul-Aziz M, Lipman J, et al. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. *Lancet Infect Dis*. 2014;14:498–509.
93. Pea F. Plasma pharmacokinetics of antimicrobial agents in critically ill patients. *Curr Clin Pharmacol*. 2013;8:5–12.
94. Baptista JP, Sousa E, Martins PJ, et al. Augmented renal clearance in septic patients and implications for vancomycin optimization. *Int J Antimicrob Agents*. 2012;39:420–423.
95. Zelenitsky S, Rubinstein E, Ariano R, et al. Vancomycin pharmacodynamics and survival in patients with methicillin-resistant *Staphylococcus aureus*-associated septic shock. *Int J Antimicrob Agents*. 2013;41:255–260.
96. D'Avolio A, Pensi D, Baietto L, et al. Daptomycin pharmacokinetics and pharmacodynamics in septic and critically ill patients. *Drugs*.

2016;76:1161–1174.

97. Masich A, Heavner M, Gonzales J, et al. Pharmacokinetic/pharmacodynamic considerations of beta-lactam antibiotics in adult critically ill patients. *Curr Infect Dis Rep*. 2018;20:9. doi:10.1007/s11908-018-0613-1.
98. Yusuf E, Spapen H, Pierard D. Prolonged vs intermittent infusion of piperacillin/tazobactam in critically ill patients: a narrative and systematic review. *J Crit Care*. 2014;29:1089–1095.
99. Heavner M, Claeys K, Masich A, et al. Pharmacokinetic and pharmacodynamic considerations of antibiotics of last resort in treating gram-negative infections in adult critically ill patients. *Curr Infect Dis Rep*. 2018;20:10. doi:10.1007/s11908-018-0614-0.
100. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Disease Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis*. 2016;62:e51–e77.
101. Heenen S, Jacobs F, Vincent JL. Antibiotic strategies in severe nosocomial sepsis: Why do we not de-escalate more often? *Crit Care Med*. 2012;40:1404–1409.
102. Garnacho-Montero J, Gutierrez-Pizarraya A, Escoresc-Ortega A, et al. De-escalation of empirical therapy is associated with lower mortality in patients with severe sepsis and septic shock. *Intensive Care Med*. 2014;40:32–40.
103. de Jung E, van Oers JA, Beishuizen A, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. *Lancet Infect Dis*. 2016;16:819–827.
104. Huang HB, Peng JM, Weng L, et al. Procalcitonin-guided antibiotic therapy in intensive care unit patients: a systematic review and meta-analysis. *Ann Intensive Care*. 2017;7:114.
105. Chotiprasitsakul D, Han JH, Cosgrove SE, et al. Comparing the outcomes of adults with Enterobacteriaceae bacteremia receiving short-course versus prolonged-course antibiotic therapy in a multicenter, propensity score-matched cohort. *Clin Infect Dis*. 2018;66:172–177.
106. Sawyer RG, Claridge JA, Nathens AB, et al. Trial of short-course antimicrobial therapy for intra-abdominal infection. *N Engl J Med*. 2015;372:1996–2005.

107. Asfar P, Meziani F, Hamel JF, et al. High versus low blood-pressure target in patients with septic shock. *N Engl J Med*. 2014;370:1583–1593.
108. Gelinas JP, Russell JA. Vasopressors during sepsis: selection and targets. *Clin Chest Med*. 2016;37:251–262.
109. Van Diepen S, Katz JN, Albert JM, et al. Contemporary management of cardiogenic shock. *Circulation*. 2017;136:e232–e268.
110. Avni T, Lador A, Lev S, et al. Vasopressors for the treatment of septic shock: systematic review and meta-analysis. *PLoS One*. 2015;10:e0129305.
111. Kotecha AA, Vallabhajosyula S, Apala DR, et al. Clinical outcomes of weight-based norepinephrine dosing in underweight and morbidly obese patients: A propensity-matched analysis. *J Intensive Care Med*. 2018. doi:10.1177/0885066618768180.
112. Vadiei N, Daley MJ, Murthy MS, et al. Impact of norepinephrine weight-based dosing compared with non-weight based dosing in achieving time to goal mean arterial pressure in obese patients with septic shock. *Annals of Pharmacotherapy*. 2017;51:194–202.
113. Radosevish JJ, Patanwala AE, Erstad BL. Norepinephrine dosing in obese and nonobese patients with septic shock. *Am J Crit Care*. 2016;25:27–32.
114. Russell JA, Lee T, Singer J, et al. The septic shock 3.0 definition and trials: a vasopressin and septic shock trial experience. *Crit Care Med*. 2017;45:940–948.
115. Khanna A, English SW, Wang XS, et al. Angiotensin II for the treatment of vasodilatory shock. *N Engl J Med*. 2017;377:419–430.
116. Tumlin JA, Murugan R, Deane AM, et al. Outcomes in patients with vasodilatory shock and renal replacement therapy treated with intravenous angiotensin II. *Crit Care Med*. 2018;46:949.
117. Damiani E, Donati A, Serafini G, et al. Effect of performance improvement programs on compliance with sepsis bundles and mortality: a systematic review and meta-analysis of observational studies. *PLoS One*. 2015;10:e0125827.
118. Levy M, Thodes A, Phillips GS, et al. Surviving sepsis campaign: association between performance metrics and outcomes in a 7.5-year study. *Crit Care Med*. 2015;43:3–12.
119. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids in the treatment of severe sepsis and septic shock in adults: A systematic review. *JAMA*. 2009;301:2362–2375.

120. Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008;358:111–124.
121. Annane D, Ellissant E, Bollaert PE, et al. Corticosteroids for treating sepsis. *Cochrane Database Syst Rev*. 2015:CD002243. doi:10.1002/14651858.CD002243.
122. Volbeda M, Wetterslev J, Gluud C, et al. Glucocorticosteroids for sepsis: systematic review with meta-analysis and trial sequential analysis. *Intensive Care Med*. 2015;41:1220–1234.
123. Venkatesh B, Finfer S, Cohen J, et al. Adjunctive glucocorticoid therapy in patients with septic shock. *N Engl J Med*. 2018;378:797–808.
124. Annane D, Renault A, Brun-Buisson C, et al. Hydrocortisone plus fludrocortisone for adults with septic shock. *N Engl J Med*. 2018;378:809–818.
125. Venkatesh B, Finfer S, Myburgh J. Long term outcomes of the ADRENAL trial. *N Engl J Med*. 2018;378:1744–1745.
126. Fu Y, Sun Y, Zhang J, Cheng Y. Intensive glucose control for critically ill patients: an updated meta-analysis. *Endocr Connect*. 2018;7:1288–1298.
127. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360:1283–1297.
128. Finfer S, Liu B, Chittock DR, et al. Hypoglycemia and risk of death in critically ill patients. *N Engl J Med*. 2012;367:1108–1118.
129. Song F, Zhong LJ, Han L, et al. Intensive insulin therapy for septic patients: a meta-analysis of randomized controlled trials. *Biomed Res Int*. 2014. doi:10.1155/2014/698265.
130. Kaplan D, Casper C, Elliott G, et al. VTE incidence and risk factors in patients with severe sepsis and septic shock. *Chest*. 2015;148:1224–1230.
131. Alhazzani W, Lim W, Jaeschke RZ, et al. Heparin thromboprophylaxis in medical-surgical critically ill patients: a systematic review and meta-analysis of randomized trials. *Crit Care Med*. 2013;41:2088–2098.
132. Beitland S, Sandven I, Kjaervik LK, et al. Thromboprophylaxis with low molecular weight heparin versus unfractionated heparin in intensive care patients: a systematic review with meta-analysis and trial sequential analysis. *Intensive Care Med*. 2015;41:1209–1219.
133. Krag M, Perner A, Wetterslev J, et al. Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients. *Intensive Care Med*. 2015;41:833–845.

134. Krag M, Perner A, Wetterslev J, et al. Stress ulcer prophylaxis versus placebo or no prophylaxis in critically ill patients. A systematic review of randomised clinical trials with meta-analysis and trial sequential analysis. *Intensive Care Med*. 2014;40:11–22.

138

Superficial Fungal Infections

Thomas E. R. Brown and Linda Dresser

KEY CONCEPTS

1. Vulvovaginal candidiasis (VVC) is a fungal infection of the vagina that can be classified as uncomplicated or complicated. This classification is useful in determining appropriate pharmacotherapy.
2. *Candida albicans* is the major pathogen responsible for VVC. The number of cases of non–*C. albicans* species appears to be increasing.
3. Signs and symptoms of VVC are not pathognomonic, and reliable diagnosis must be made with laboratory tests including vaginal pH, saline microscopy, and 10% potassium hydroxide (KOH) microscopy.
4. *C. albicans* is the predominant species causing all forms of mucosal candidiasis. Important host and exogenous risk factors have been identified that predispose an individual to the development of mucosal candidiasis. In oropharyngeal and esophageal candidiasis, the key risk factor is impaired host immune system.
5. A topical antimycotic agent is the first choice for treating oropharyngeal candidiasis. Systemic therapy can be used in patients who are not responding to an adequate trial of topical treatment or are unable to tolerate topical agents and in those at high risk for systemic candidiasis. Fluconazole and itraconazole are the most effective azole antimycotic agents.
6. For esophageal candidiasis, topical agents are not of proven benefit; oral fluconazole or itraconazole solution is the first choice.
7. Optimal antiretroviral therapy is important for the prevention of recurrent and refractory candidiasis in patients with human immunodeficiency virus (HIV) infection.
8. Primary or secondary prophylaxis of fungal infection is not recommended

routinely for HIV-infected patients; use of secondary prophylaxis should be individualized for each patient.

9 Topical antimycotic agents are first-line treatment for fungal skin infections. Oral therapy is preferred for the treatment of extensive or severe infection and those with tinea capitis or onychomycosis.

10 Oral antimycotic agents such as terbinafine and itraconazole are first-line treatment for toenail and fingernail onychomycosis.

Preclass Engaged Learning Activity

Watch the YouTube video entitled “Watch and Learn KOH preparation” by Richard Usatine, MD. This 4-minute video demonstrates the quickest and most accurate way to diagnosis fungal skin infections. The video is useful in visualizing fungal elements such as hyphae and pseudohyphae.

INTRODUCTION

Superficial mycoses are among the most common infections in the world and the second most common vaginal infections in North America. Mucocutaneous candidiasis can occur in three forms—oropharyngeal, esophageal, and vulvovaginal disease—with oropharyngeal and vulvovaginal disease being the most common. Over the past 15 to 20 years, the occurrence rates of some fungal infections have increased dramatically. The prevalence of fungal skin infections varies throughout different parts of the world, from the most common causes of skin infections in the tropics to relatively rare disorders in the United States.

VULVOVAGINAL CANDIDIASIS

1 *Vulvovaginal candidiasis* (VVC) refers to infections in individuals with or without symptoms who have positive vaginal cultures for *Candida* species. Depending on episodic frequency, VVC can be classified as either sporadic or recurrent.[1] This classification is essential to understanding the pathophysiology, as well as the pharmacotherapy, of VVC. Furthermore, VVC may be defined as uncomplicated, which refers to sporadic infections that are susceptible to all forms of antifungal therapy regardless of the duration of treatment, or

complicated, in which consideration of factors affecting the host, microorganism, and pharmacotherapy all have an essential role in successful treatment.[1] Complicated VVC includes recurrent VVC, severe disease, non–*C. albicans* candidiasis, and host factors, including diabetes mellitus, immunosuppression, and pregnancy.[1]

EPIDEMIOLOGY

There is minimal information on the incidence and prevalence of VVC. Healthcare workers are not required to report cases of VVC; therefore, estimates are derived from self-reported histories. Epidemiologic data are limited because VVC usually is diagnosed without microscopy and/or cultures, and antifungal nonprescription preparations are available for self-treatment.[1] By 25 years of age, approximately 50% of college women will have had at least one episode of VVC.[1] It is rare before menarche and increases dramatically at about 20 years of age, with the peak incidence between age 30 and 40 years. It is associated with the initial act of sexual intercourse. As many as 75% of women experience one bout of symptomatic VVC in their lifetime. Between 40% and 50% of women who experience one episode of VVC experience a second episode, and 5% experience recurrent VVC.[2,3] Black women appear to be at higher risk than white women of developing VVC (62.8% vs 55%, respectively).[4] The incidence after menopause remains unknown. However, healthy postmenopausal women with vulvar conditions taking hormone replacement therapy (HRT) were more prone to developing VVC than those who were not taking HRT (culture-positive, clinical VVC in 49% on HRT vs 1% on those not on HRT).[5]

Costs from VVC can be direct (medical visits and self-treatment) and indirect (nonmedical expenses, eg, time losses from work, costs of travel, and time required in obtaining treatment). There are 6 million visits to healthcare providers each year, resulting in more than $1 billion spent annually on these medical visits and self-treatment.[6] Nonprescription sales for feminine itch and yeast treatments were $302 million in the United States in 2017.[7]

PATHOPHYSIOLOGY

2 *C. albicans* is the major pathogen responsible for VVC, accounting for 80% to 92% of symptomatic episodes. The remainder are caused by non–*C. albicans* species, with *Candida glabrata* dominating.[8] The number of cases of non–*C.*

albicans candidiasis appears to be increasing, possibly related to the use of nonprescription vaginal antifungal preparations and short-course therapy and/or the increased use of long-term maintenance therapy in preventing recurrent infections.[1]

Candida species can act as commensal members of the vaginal flora. Asymptomatic colonization with *Candida* species occurs in 10% to 20% of women of reproductive age.[8,9] *Candida* organisms are dimorphic; blastospores are believed to be responsible for colonization (transmission and spread), whereas germinated *Candida* forms are associated with tissue invasion and symptomatic infections.[10] To colonize the vagina, *Candida* species must be able to attach to the mucosa. The attachment process is complex. Not only are candidal surface structures important for attachment, but appropriate receptors for attachment must be present in the epithelial tissue. Not all women have the same range of receptors, which may explain variation in colonization.[9] Changes in the host's vaginal environment or response are necessary to induce a symptomatic infection. Unfortunately, in most cases of symptomatic VVC, no precipitating factor can be identified.[10]

RISK FACTORS

Several factors predispose a woman to VVC. VVC is not considered to be a sexually transmitted disease, although sexual factors can be important. There is a dramatic increase in the frequency of VVC when women become sexually active. In addition, oral-genital contact can increase the risk.[1] However, the treatment of asymptomatic partners is not recommended.[8] Contraceptive agents, including the diaphragm with spermicide, the contraceptive sponge, and the intrauterine device, increase the risk of VVC.[11] *Candida* species are capable of adhering to the contraceptive vaginal ring.[11] Oral contraceptive users demonstrated increased risk of candidiasis; however, these reports were with the higher-dose oral contraceptive pills, and the risk may not be as great with the lower-estrogen-dose oral contraceptives.[12]

Antibiotic use can increase the risk of VVC, but it is significant in only a small number of women. The mechanism by which antibiotics can increase the risk of VVC is unknown; colonization, however, is a prerequisite.[1] Three days of antibiotics increased the prevalence of asymptomatic vaginal colonization of *Candida* and the incidence of symptomatic VVC.[13] Diet (excess refined carbohydrates), douching, and tight-fitting clothing often are listed as important

risk factors; however, no association has been established between these factors and increased risk of VVC.[1]

CLINICAL PRESENTATION

3 The clinical presentation of VVC is given in **Table 138-1**.[1,8] These signs and symptoms are not pathognomonic, and a reliable diagnosis cannot be made without laboratory tests. The value of self-diagnosis and the success of self-treatment is limited. Self-diagnosis has a sensitivity of 35%, a specificity of 89%, and a positive predictive value of 62%.[4] More than 50% of women who had self-diagnosed VVC did not have yeast as the causative agent.[14] The American College of Obstetricians and Gynecologists (ACOG) recommends that whenever possible women requesting treatment for VVC should be examined and evaluated. They only recommend self-diagnosis in compliant women with multiple confirmed prior cases of VVC who report the same symptoms. They further recommend that if these individuals fail to improve on a short course of therapy, they be evaluated for a further diagnosis.[15] Therefore, in most instances the diagnosis should be based on both clinical presentation and investigations, including vaginal pH, saline microscopy, and 10% potassium hydroxide (KOH) microscopy of vaginal discharge. The vaginal pH remains normal in VVC, and microscopic investigations should detect blastospores or pseudohyphae. *Candida* cultures usually are not required in the diagnosis of uncomplicated VVC; however, they are recommended when an individual presents with classic signs and symptoms of VVC, has a normal vaginal pH, but microscopy is inconclusive or recurrence is suspected.[8]

TABLE 138-1 Clinical Presentation of Vulvovaginal Candidiasis

General	Often involves both the vulva and the vagina
Symptoms	Intense vulvar itching, soreness, irritation, burning on urination, and dyspareunia
Signs	Erythema, fissuring, curdy "cheese"-like discharge, satellite lesions, edema
Laboratory tests	Vaginal pH—normal, saline, and 10% KOH microscopy—blastospores or pseudohyphae
Other diagnostic tests	*Candida* cultures not recommended unless classic signs and symptoms with normal vaginal pH and microscopy are inconclusive or recurrence is suspected

KOH, potassium hydroxide.

TREATMENT

Goals of Therapy

The goal of therapy is complete resolution of symptoms in patients who have symptomatic VVC. A test of the cure is not necessary if symptoms resolve.[8] Antimycotic agents used in the treatment of VVC do not meet the definition of being fungicidal agents because of their slower killing rate. At the end of therapy, the number of viable organisms drops below the detectable range. However, by 6 weeks after a course of therapy, 25% to 40% of women will have positive yeast cultures and remain asymptomatic.[1] Asymptomatic colonization with *Candida* species does not require therapy.

General Approaches to Treatment

The approach to therapy is to remove or improve any predisposing factors if they can be identified. An effective antimycotic agent should have limited local and systemic side effects, a high cure rate, and easy administration. Additionally, it would be advantageous to use a treatment that resolves symptoms within 24 hours, has broad antimycotic activity (to cover increasing rates on non–*C. albicans* species), prevents recurrence, and that can be used over a shortened period of time, such as 1 to 3 days. Many topical azoles medications (such clotrimazole, miconazole, etc.) are available without a prescription, and although this may increase public access to these medications, there is concern that having them available without a prescription may lead to inappropriate use. A study

conducted using 10 actors as simulated patients who visited 60 pharmacies found that vaginal antimycotics were more likely to be appropriately provided to individuals as more information was exchanged, if interactions involved a pharmacist, and if questions regarding specific symptoms were used.[16]

Patients should be advised to avoid harsh soaps and perfumes that can cause or worsen vulvar irritation. The genital area must be kept clean and dry by avoiding constrictive clothing and frequent or prolonged exposure to hot tub use.[3] Douching is not recommended for either prevention or treatment.[14] Cool baths can soothe the skin.[3] The value of oral use of lactobacillus remains unclear. The addition of oral lactobacillus to a single dose of oral fluconazole augmented the cure rate compared to the use of fluconazole alone.[17] A trial of an oral mixture of bee-honey and yogurt showed some efficacy with mycotic cure rates of 76.9% compared to cure rates with antifungal agents of 91.5%.[18] Daily ingestion of 240 mL yogurt containing *Lactobacillus acidophilus* decreased colonization and symptomatic infections of VVC in women with recurrent infections.[19] However, the addition of oral lactobacillus to itraconazole therapy in the treatment of recurrent VVC did not confer any additional benefit and treatment using classic homeopathy was less effective than the use of itraconazole in recurrent VVC.[20]

Treatment of VVC will be considered to have positive outcomes if the symptoms of VVC are resolved within 24 to 48 hours and no adverse medication events are experienced. Self-assessment of symptom relief is appropriate for most cases of VVC. If symptoms remain unresolved or recur, then further testing and treatment can be required.

Pharmacologic Treatments

Uncomplicated Vulvovaginal Candidiasis

Cure rates for uncomplicated VVC are between 80% and 95% with topical or oral azoles and between 70% and 90% with nystatin preparations. **Table 138-2** lists many available topical and oral preparations for the treatment of uncomplicated VVC. There are no significant differences in in vitro activity or clinical efficacy among the topical azole agents.[1,3,8,15] The selection of a topical azole antimycotic agent should be based primarily on an individual patient's preference as to product formulation. Some topical products can cause vaginal burning, stinging, or irritation; conversely, the vehicle used in topical creams or gels can provide initial symptomatic relief.[1] Of note, most topical preparations

can decrease the efficacy of latex condoms and diaphragms.

TABLE 138-2 Treatment for Uncomplicated Vulvovaginal Candidiasis

Active Ingredient	Preparation	Regimen
Nonprescription/Topical Vaginal Products		
Butoconazole	2% cream	One applicator × 3 days
Clotrimazole	1% cream	One applicator × 1 day
	100 mg tablet	One 100 mg tablet × 7 days
	2% cream	One applicator × 1 day
	200 mg tablet	One 200 mg tablet × 3 days
	10% cream	One applicator × 1 day
	500 mg tablet	One 500 mg tablet × 1 day
Miconazole[a]	2% cream	One applicator × 1 day
	100 mg suppository	One 100 mg suppository × 7 days
	200 mg suppository	One 200 mg suppository × 3 days
	1,200 mg ovule	One ovule × 1 day
Ticonazole	2% cream	One applicator × 3 days
	6.5% cream	One applicator × 1 day
Prescription/Topical		
Nystatin	100,000 unit tablet	One tablet × 14 days
Terconazole	0.4% cream	One applicator × 7 days
	0.8% cream	One applicator × 3 days
Oral Products		
Fluconazole	150 mg	One tablet × 1 day

[a]The FDA warns of the possible increase in the anticoagulant effects of warfarin with concomitant use.

Oral azoles (such as fluconazole or itraconazole) have been used in the treatment of VVC and are therapeutically equivalent to topical therapies.[1] Patients may prefer oral therapy because of its convenience.[21] A Cochrane review of 19 trials analyzing 22 oral versus topical antifungal comparisons concluded that there were no differences between the routes in short-term mycologic cure rates. There was a significant difference between long-term cure rates in favor of long-term follow-up; however, the authors stated that the clinical significance of this finding is uncertain.[22]

In the treatment of uncomplicated VVC, the duration of therapy is not critical. Cure rates with different lengths of treatment have not demonstrated that one duration of therapy is significantly better.[21–23] Shorter-duration therapies (eg, clotrimazole 1-day therapy) consist of higher concentrations of azoles that maintain the local therapeutic effect for up to 72 hours and allow for resolution of signs and symptoms.[24] There was less than 7% difference in short-term cure rates or improvement between any two treatments in any two studies and no significant differences in short- or long-term clinical cure rates among 1-day regimens.[23]

Complicated Vulvovaginal Candidiasis

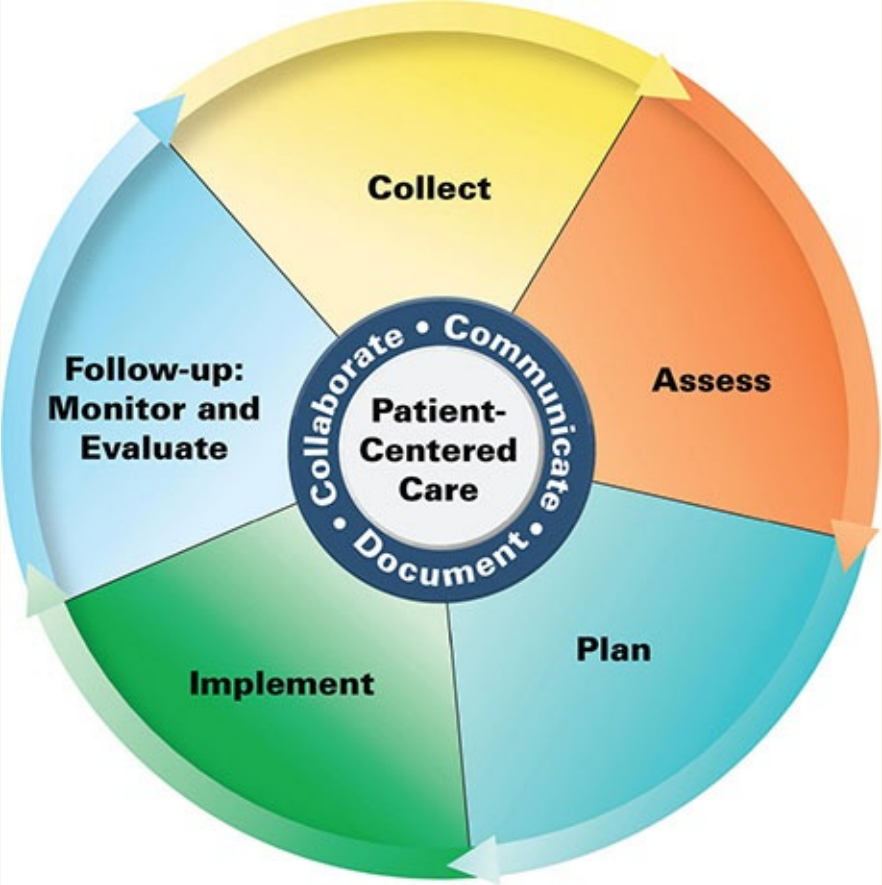
Complicated VVC occurs in patients who are immunocompromised or have uncontrolled diabetes mellitus.[1] These individuals need a more aggressive treatment plan and treatment should be lengthened to 10 to 14 days regardless of the route of administration.[15] Therapeutic options include those listed in Table 138-2; however, regimens should be continued for 10 to 14 days. Cure rates increased from 67% with single-dose oral fluconazole therapy in women with complicated VVC therapy to 80% when the 150 mg dose of fluconazole was repeated 72 hours after the initial dose.[25]

VVC during pregnancy can be considered complicated because consideration of host factors such as hormonal changes that can affect normal flora are essential in selecting therapeutic regimens. Topical agents are considered to be safe throughout pregnancy. Imidazole topical agents (such as fluconazole) were more effective than nystatin for VVC during pregnancy and treatment for 7 days was more effective than treatments of 4 days or less.[26] Oral agents are contraindicated in pregnancy because of the concern for fetal complications. A prospective assessment of pregnancy outcomes in 226 women exposed to fluconazole in the first trimester did not indicate increased risk of congenital abnormalities or other adverse outcomes.[27,28] However, the American College of Obstetricians and Gynecologists (ACOG) recommends avoiding oral therapy, as larger doses of fluconazole have been linked to birth defects.[28] Instead, the ACOG recommends a topical imidazole therapy for 7 days.[15]

Recurrent Vulvovaginal Candidiasis

Recurrent vulvovaginal candidiasis (RVVC) is defined as having more than four episodes of VVC within a 12-month period.[1,8] Fewer than 5% of women develop RVVC, and its pathogenesis is poorly understood. A proper diagnosis

should be obtained to rule out other infections or nonmycotic contact dermatitis. RVVC is best treated in two stages: an initial intensive stage followed by prolonged antifungal therapy to achieve mycologic remission (with 150 mg oral fluconazole daily for 10 days followed by 6 months of fluconazole 150 mg weekly). Ninety percent of women receiving 10-day initial and 6-month prolonged treatments were symptom free for the 6 months following initial treatment, and there were 50% fewer symptomatic episodes in the 6 months (compared with placebo treatment after the initial 10 days).[29] The Infectious Diseases Society of America recommends 10 to 14 days of induction therapy with a topical or oral azole, followed by 150 mg of fluconazole once weekly for 6 months for recurring *Candida* VVC.[30] A new immunotherapy vaccine (NDV-3A) containing a recombinant adhesion/invasion protein for candida is being investigated for RVVC. A Phase 1b/2a clinical trial reduced the frequency of episodes of VVC in women<40 years who suffer from RVVC.[31]



Patient Care Process for Vulcovaginal Candidiasis

Collect

- Patient Characteristics (age, pregnancy status)
- Patient medical history (previous vaginal infections, diabetes mellitus)
- Social history (sexual activity)
- Current Meds (oral contraceptives, antibiotics)

Assess

- Symptoms consistent with VVC (itching, clumpy white vaginal discharge)
- Absence of fever, pelvic pain, colored or foul smelling vaginal discharge
- Possibility of sexually transmitted disease
- Recurrence of symptoms from previous vaginal infection

Plan*

- Remove predisposing risk factors if possible
- Select a drug therapy regimen including specific antifungal(s) dose, route, frequency and duration (Table 138-2)
- Education of the patient regarding causes of VVC and the selected treatment
- Referral to other healthcare providers if complicated or recurrent VVC or risk factors for sexually transmitted disease

Implement

- Provide patient counselling (avoid harsh soaps, perfumes, hot tub use, contraceptive use)
- Keep vaginal area clean and dry, avoid constrictive clothing
- Self-assessment of symptom relief is appropriate

Follow-up: Monitor and Evaluate

- Monitor for complete resolution of symptoms within 24-48 hours of initiation of therapy (itching, clumpy white discharge)
- Determine the presence of adverse effects (nausea, abdominal discomfort, vaginal irritation)
- Refer to other healthcare provider if symptoms do not resolve despite adherence

**Collaborate with patient, caregivers, and other healthcare professionals.*

Antifungal-Resistant Vulvovaginal Candidiasis

Resistance to azole antimycotics should be considered in individuals who have persistently positive yeast cultures and fail to respond to therapy despite adherence to prescribed regimens.[1] These infections can be treated with boric acid or 5-flucytosine.[32,33] Boric acid is administered as a 600 mg intravaginal capsule daily for 14 days of induction therapy, followed by a maintenance regimen of one capsule intravaginally twice weekly. Boric acid should not be administered orally, as it is toxic. 5-Flucytosine cream is administered vaginally, 1,000 mg inserted nightly for 7 days. The prevalence of *C. glabrata* is higher in those with diabetes. In a study of diabetic patients with VVC, 68% had isolates for *C. glabrata* compared with 28.8% for *C. albicans.* Those with *C. glabrata* had significantly higher mycological cure rates with 600 mg of boric acid suppositories for 14 days compared with a single dose of fluconazole 150 mg.[34]

OROPHARYNGEAL AND ESOPHAGEAL CANDIDIASIS

Oropharyngeal and esophageal candidiasis are common and localized infections that occur in patients with HIV infection, diabetes, leukemia, and other malignancies. These infections are also associated with antimicrobial therapy, steroid use, radiation therapy and denture use.

Oropharyngeal candidiasis (OPC), often referred to as *thrush,* is caused by the yeast *Candida. C. albicans,* a common oral commensal organism, is the most frequent infecting species. OPC is also referred to as *candidiasis* (or the more correct but less commonly used term *candidosis*). The infection may extend into the esophagus, causing esophageal candidiasis.

EPIDEMIOLOGY AND ETIOLOGY

Candida is a commensal fungus found in the oral cavity in up to 65% of healthy individuals with higher prevalence in healthy children and young adults.[35,36] *Candida* carriage increases in immunocompromised and hospitalized patients.[36] Even in the era of highly active antiretroviral therapy (AART) up to 80% of human immunodeficiency virus (HIV)–infected persons may demonstrate oral yeast colonization.[37] The organism is capable of transition to a pathogen causing symptomatic mucosal infections in association with predisposing host factors.[36] *C. albicans* is the predominant colonizing *Candida* species (70%-80%), but any of the non–*C. albicans* species such as *C. glabrata* and *C. tropicalis,* which may account for 5% to 8% respectively, can be colonizers. Colonization rates are influenced by the severity and nature of the underlying medical illness and the duration of hospitalization, as well as age (highest in infants younger than 18 months of age and in adults older than 60 years of age). A variety of host and exogenous factors (**Table 138-3**) can lead to the transformation of asymptomatic colonization to symptomatic disease, such as oropharyngeal and esophageal candidiasis. *C. albicans* is the most common species causing all forms of mucosal candidiasis in humans. Less frequently, non–*C. albicans* species can be pathogenic and cause disease. These include *C. glabrata*, *C. tropicalis*, *C. krusei*, and *C. parapsilosis.*[37,38] *C. krusei,* although relatively uncommon, generally is recovered from mucosal surfaces of neutropenic patients with hematologic malignancies.[38] *Candida dubliniensis* has been identified in both HIV-infected and noninfected patients, and may cause ~15% of infections previously ascribed to *C. albicans.*[38] In patients with cancer, non–*C. albicans* species account for almost half of all *Candida* infections.

TABLE 138-3 Risk Factors for the Development of Oropharyngeal and/or Esophageal Candidiasis

Local Factors	Potential Mechanisms
Use of steroids and antibiotics	Suppression of cellular immunity and inhibition of phagocytosis by steroids, including chronic use of inhaled and topical steroids
	Alteration of endogenous oral flora by broad-spectrum antibiotics, especially when used with steroids, creates a milieu for proliferation of *Candida* species because of reduced environmental and nutritional competition
Dentures	Enhanced adherence of *Candida* species to the acrylic material of dentures, reduced saliva flow under surfaces of denture fittings, improperly fitted dentures, and poor oral hygiene provide a milieu conducive to the survival of microorganisms
Xerostomia caused by drugs (eg, tricyclic antidepressants and phenothiazine), chemotherapy, radiotherapy to the head/neck, and various diseases (eg, Sjögren's syndrome, HIV, and cancer of the head/neck), as well as bone marrow transplant recipients	Reduced dilutional and cleansing effect caused by low secretion rate and low pH in saliva: Saliva and mucosa secretions have defense factors, such as lactoferrin, sialoperoxidase, isozyme, histidine-rich polypeptide, secretory IgA antibodies, specific anti-*Candida* antibodies that help prevent adhesion and overgrowth of *Candida* species
Smoking	
Disruption of oral mucosa caused by chemotherapy and radiotherapy, ulcers, endotracheal intubation trauma, and burns	Oral mucositis induced by radiation and breaks in the physical barrier of the oral epithelium, which is protective against invasion by microorganisms; altered rate of mucosa regeneration by cancer chemotherapy, which increases vulnerability to infection
Systemic Factors	**Potential Mechanisms**
Drugs (eg, cytotoxic agents, corticosteroids, and immunosuppressants after organ transplant), omeprazole, and environmental chemicals (eg, benzene and pesticides)	Reduced immunity because of drug-induced neutropenia or cell-mediated immunity; potent inhibition of gastric acid by PPIs can facilitate the growth of *Candida* species; PPIs also can inhibit the cytotoxic effect of lymphocytes and reduce salivary secretion
Neonates or the elderly	Immature immune system of neonates who usually acquire infection during birth to a mother with vaginal candidiasis or from exposure to infected bottle nipples or to skin of adult caregiver
	Elderly—unclear if this is the direct effect of age per se or contribution from dentures or underlying comorbidity
HIV infection/AIDS	Depletion of CD4 T lymphocytes especially below 200-300 cells/mm^3 (0.2×10^9 – 0.3×10^9/L); anti-*Candida* protective mechanism of T lymphocytes at a mucosal level is unclear but can be caused by altered cytokines, especially interferon-γ, that inhibit transformation of *Candida* blastoconidia to the more invasive hyphal phase
Diabetes	Higher than normal numbers of *C. albicans* cultured from saliva of diabetic patients; can be related to the elevated glucose levels and reduced chemotactic factor in saliva, altered neutrophil function, and reduced saliva volume and flow
Malignancies (eg, leukemia and head/neck cancer)	Use of intensive radiotherapy and chemotherapy can disrupt oral mucosa and cause xerostomia; prolonged use of broad-spectrum antibiotics in neutropenic patients can alter the normal oral flora; because of the prolonged neutropenia, the principal immune defect, seen especially in leukemic patients, the initial oropharyngeal candidiasis can become systemic or invasive
Nutritional deficiencies (eg, iron, folate, and vitamins B1, B2, B6, B12, and C)	Can be related to dietary restriction or GI absorption problems; deficiencies can serve to enhance the pathogenic potential of the *Candida* inhabitants, alter host defense mechanisms, or change epithelial barrier integrity

AIDS, acquired immunodeficiency syndrome; GI, gastrointestinal; HIV, human immunodeficiency virus; IgA, immunoglobulin A; PPI, proton pump inhibitor.

Oropharyngeal candidiasis remains the most common opportunistic infection in patients with HIV disease, and it may be the first clinical manifestation of the HIV infection in the majority of untreated patients. OPC occurs in 50% to 90% of HIV-infected patients if the disease progresses to acquired immunodeficiency syndrome (AIDS).[35,37,38] The use of effective antiretroviral therapy has led to a significant reduction in the primary incidence and ultimately refractory disease. The absolute CD4 T-cell count is the primary risk factor for development of OPC with the greatest risk at CD4 T-cell levels <200 cells/mm^3 (<0.2 × 10^9/L). Also, the HIV viral load is a predictor of OPC development; OPC increases with HIV viral loads >10,000 copies/mL (>10 × 10^6/L). This finding correlates with the observation that initiation of antiretroviral therapy and subsequent increase in CD4 T-cell counts does not fully account for the decrease in OPC incidence.[37] Regardless of the CD4 T-cell count, or HIV viral load OPC is predictive for the development of AIDS-related illnesses if left untreated.[35,38]

In non-HIV diseases, such as cancer, the incidence of OPC varies depending on the type of malignant neoplastic disease, level of immune suppression, and type and duration of treatment, but it is less common than in HIV-infected patients. OPC was initially reported in ~25% of patients with solid tumors and up to 60% in those with hematologic malignancies or bone marrow transplant recipients.[39] Rates of OPC have decreased significantly in these patients because of widespread use of antifungal prophylaxis. Incidence in other patient populations predisposed to OPC such as the hospitalized patient administered broad-spectrum antibiotics or denture and other oral appliance users is not well quantified; however, it does represent at-risk individuals where the clinical pharmacist has an important patient-care role.[36,39]

OPC can predispose patients to develop more invasive disease, including esophageal candidiasis.[39] The esophagus is the second most common site of GI candidiasis. The prevalence of esophageal candidiasis increased mainly due to the emergence of AIDS, as well as the increased numbers of other severely immunocompromised patients, especially those with hematologic malignancies.[38] The mean incidence of esophageal candidiasis among HIV-infected patients is less than OPC and ranges from 15% to 20%.[38] The risk of esophageal candidiasis is increased in HIV-infected patients when the CD4 T-cell count has dropped below 100 to 200 cells/mm^3 (0.1 × 10^9 to 0.2 × 10^9/L), as well as in those with OPC.[39,40] However, the absence of OPC does not necessarily exclude the possibility of esophageal disease. Like OPC, the presence of esophageal candidiasis can help predict HIV disease progression and

prognosis.[39] The incidence of esophageal candidiasis in non-HIV-infected immunocompromised patients is not well established. *C. albicans* is the most common cause of esophageal candidiasis, accounting for ~80% of cases, with the rest being caused by non–*C. albicans* species.[37] However, the widespread use of the azole agents for treatment and prophylaxis has led to an emergence of refractory infections that are more challenging to treat.

PATHOGENESIS AND HOST DEFENSES

The pathogenesis of OPC is most clearly elucidated in the setting of HIV infection. There appear to be several levels of immune defense against the development of OPC in HIV-infected persons, and they involve both systemic and local immunity. The primary line of host defense against *C. albicans* is cell-mediated immunity (CMI) at the mucosal surfaces, which is mediated by CD4 T cells.[35] The efficacy of the CD4 T cells is reduced when the number of cells drops below a protective threshold, and protection against infection becomes dependent on secondary or local immune mechanisms.[35,37] When the number of CD4 T cells drops too low, recruitment of these cells to the oral cavity is impaired. The CD4 T-cell count is the hallmark predictor for development of OPC. However, HIV viral load may have a stronger association with OPC than CD4 cell number.[37,41] The possibility that HIV plays a strong role in susceptibility to infection is supported by the observation that OPC is more common in HIV-infected persons than in those with similar immunosuppression, such as lymphoma and bone marrow transplant. When the primary line of defense fails, the secondary host defenses become crucial. These include the CD8 T cells, salivary cytokines, and other innate immune cells, such as the neutrophils, macrophages, and epithelial cells (with anti-*Candida* activity). Deficiencies or dysfunction in any of these can result in increased susceptibility to OPC. The problem with the CD8 T cells is caused more by a dysfunction of the microenvironment, specifically, reduction in the E-cadherin adhesion molecule that promotes migration of the cells through mucosal tissues.[38] The role of humoral immunity by antibodies as a protective mechanism is unclear and controversial. The changeover of the role of *Candida* species from commensal to pathogenic in the human host usually occurs when breakdown in these host defenses occurs. The pathogenesis of OPC is still not completely understood. It is important to develop a better understanding of the pathogenesis and role of host defenses, including the mechanism of CD8 T-cell activity, reduced adhesion molecules, and whether other cofactors, such as HIV viral

load, AART, and injection drug use, play a role. Immunotherapeutic modalities can then be developed to eliminate the susceptibility factors and significantly reduce OPC in the at-risk populations.

Significant differences exist in the virulence among *Candida* species in mucosal candidiasis. One virulence factor is the ability of the organism to adapt and survive in response to changes in the host environment.[37] The genes required for virulence are regulated in response to the environmental signals indigenous to the host environment (eg, temperature, pH, osmotic pressure, iron and calcium ion concentrations, oxygenation, and carbon and nitrogen availability). The ability of *C. albicans* to undergo reversible morphologic transition between the budding pseudohyphal and the more invasive hyphal growth forms is also a determinant of virulence, and genes are recognized to play a role.[35] Other virulence factors are the adhesive ability of *C. albicans* to epithelial cells and proteins and its ability to invade host cells by means of phospholipase and proteinase enzymes. This may be one of the factors leading to OPC in non–HIV-infected individuals. Other components of the pathogenesis in the absence of HIV are the ability of the *Candida* species to adhere to buccal epithelial cells.[42] This is hypothesized to be a key element in the development of OPC in patients with altered microflora, including those receiving broad-spectrum antimicrobial therapy.

Risk Factors

4 Several host and exogenous factors contribute to the ability of *Candida* species to cause infection (see Table 138-3). Local and systemic factors, as well as characteristics of the organism itself, can increase the susceptibility of an individual to *Candida* infections.[35] Endocrine disorders besides diabetes mellitus, such as hypothyroidism, hypoparathyroidism, and hypoadrenalism, also can predispose patients to *Candida* species overgrowth. Patients with primary immune deficiencies such as lymphocytic abnormalities, phagocytic dysfunction, immunoglobulin A (IgA) deficiency, viral-induced immune paralysis, and severe congenital immunodeficiencies are also at risk for oropharyngeal candidiasis as well as disseminated candidiasis. Oral mucosal disease, such as lichen planus, can be preexistent causes of candidiasis. Smoking has been suggested as a predisposing risk factor. In many cases, multiple concurrent predisposing factors to candidiasis can exist, for example, xerostomia with mucositis and a break in the epithelial surface or immunosuppression, such as might occur in a leukemic patient receiving radiation and chemotherapy. The

severity and extent of *Candida* infections increase with the number and severity of predisposing risk factors.[36]

CLINICAL PRESENTATION AND DIAGNOSIS

Oropharyngeal candidiasis can manifest in several major forms (**Table 138-4**).[35,36] The clinical signs and symptoms of OPC and the locations of the lesions can be quite diverse (**Table 138-5**). A presumptive diagnosis of OPC usually is made by the characteristic appearance on the oral mucosa, with resolution of signs and symptoms after antifungal therapy. Pseudomembranous candidiasis, commonly known as *oral thrush,* is the classic and most common form seen in immunosuppressed and immunocompetent hosts. Erythematous and hyperplastic candidiasis and angular cheilitis occur less commonly in the HIV-infected population. Dysphagia, odynophagia, and retrosternal chest pain are common complaints of esophageal candidiasis, which is usually, but not always, accompanied by the presence of OPC. Clinical symptomatology, along with a therapeutic trial of antifungal, can provide a reliable presumptive diagnosis of esophageal candidiasis. If antifungal therapy does not lead to resolution, more invasive tests such as upper GI endoscopy can be undertaken.

TABLE 138-4 Clinical Classification of Oropharyngeal Candidiasis

Types	Population at Risk	Clinical Signs and Appearance
Pseudomembranous (thrush)	Neonates, patients with HIV or cancer, the debilitated elderly, patients on broad-spectrum antibiotics or steroid inhalers, patients with dry mouth from various causes, and smokers	Classic "cottage cheese" appearance, yellowish white, soft plaques (or milk curds) overlying areas of erythema on the buccal mucosa, tongue, gums, and throat; plaques are easily removed by vigorous rubbing but can leave red or bleeding sites when removed; lesions on the tongue dorsum give it a bald, depapillated appearance
Erythematous (atrophic)	Patients with HIV, patients on broad-spectrum antibiotics or steroid inhalers	Sensitive and painful erythematous mucosa with few, if any, white plaques; lesions are generally on the dorsal surface of the tongue or the hard palate, occasionally on the soft palate, but any part of the mucosa can be involved; appear as flat red patches on the palate or atrophic patches on the tongue dorsum with loss of papillae. Can be acute or chronic.
Hyperplastic (candidal leukoplakia)	Smokers; uncommon in patients with HIV	Thick white and adherent keratotic plaques commonly seen on the buccal mucosa and lateral border of the tongue; can also be seen on the lips and the bottom of the mouth; plaques cannot be easily scraped off or only partially removed; this condition is distinct from oral hairy leukoplakia, and it can progress to severe dysplasia or malignancy
Angular cheilitis	Patients with HIV, denture wearers	Painful red, ulcerative, cracking, or fissuring lesion at one or both comers of the mouth because of an inflammatory reaction; usually lesions are small and rather punctate, but occasionally they can extend in a linear fashion from the angles onto the facial skin
Denture stomatitis (chronic atrophic)	Denture wearers who tend to be elderly and have poor oral hygiene	Red, flat lesions on the mucosa beneath the denture and extend right up to the denture border; more commonly located beneath a maxillary denture, although they can be encountered beneath a mandibular denture
Central papillary atrophy (median rhomboid glossitis)	Uncommon (<1% prevalence), men more commonly infected than women (3:1)	Rhomboid-shaped hypertrophic or atrophic plaque in the mid-DORSAL tongue. Lesions may not resolve completely

HIV, human immunodeficiency virus.

TABLE 138-5 Clinical Presentation of Oropharyngeal and Esophageal Candidiasis

Oropharyngeal Candidiasis	Esophageal Candidiasis
General	**General**
The clinical features can be quite diverse (see Table 138-4)	This usually occurs as an extension of OPC; however, the esophagus can be the only site involved; the distal two-thirds, rather than the proximal one-third, is the most common site
Symptoms	**Symptoms**
Symptoms are diverse and range from none to a sore, painful mouth, burning tongue, metallic taste, and dysphagia and odynophagia with involvement of the hypopharynx	Typically, the symptoms are dysphagia, odynophagia, and retrosternal chest pain but can be asymptomatic in some patients; although rare, epigastric pain can be the dominant symptom
Signs	**Signs**
Signs are variable and can include diffuse erythema and white patches on the surfaces of the buccal mucosa, throat, tongue, or gums; constitutional signs are absent	Constitutional signs, including fever, occasionally occur; physical findings can range from a few to numerous white or beige plaques of variable size Plaques can be hyperemic or edematous, with ulceration in more severe cases Most advanced cases can occur with increased mucosal friability and narrowing of lumen Uncommon complications include perforation and aortic–esophageal fistula formation
Laboratory tests	**Laboratory tests**
Scraping of an active lesion for microscopic examination can help confirm the diagnosis (presence of pseudohyphae and budding yeast) but is usually not necessary Cultures are not necessary because isolation of *Candida* species does not distinguish between colonization and true infection; cultures can be taken in patients responding poorly to therapy to determine the infecting species and to predict likely drug resistance	The best test is upper GI endoscopy (more useful than barium swallow); helps exclude other causes of esophagitis (eg, viral, aphthous ulcers); diagnosis is confirmed by the histologic presence of *Candida* species in biopsy lesions taken during endoscopy Cultures to look for drug-resistant *Candida* species are warranted in patients who require endoscopy

GI, gastrointestinal; OPC, oropharyngeal candidiasis.

TREATMENT

Desired Outcomes

The primary desired outcome in the management of OPC is a clinical cure, that is, elimination of clinical signs and symptoms. Even when the patient is relatively asymptomatic, it is important to treat the initial episode of OPC to avoid progression to more extensive disease. In the most severe cases, the patient's quality of life can be impaired; this can result in decreased fluid and nutritional intake. Lack of appropriate treatment of OPC can lead to more extensive oral disease, especially in patients who are immunocompromised. The most serious complication of untreated OPC is extension of the infection to esophageal candidiasis which is more debilitating with greater impact on

> the patient's quality of life. Appropriate antifungal therapy should be initiated for both OPC and esophageal candidiasis. Preventing or minimizing the number of future recurrences of both types of candidiasis is an equally important outcome. The approach depends largely on the underlying predisposing conditions. Mycologic cure is not a necessary treatment outcome because it may not be feasible or realistic, given that *Candida* species exist commonly as part of the normal mouth flora.

Minimizing toxicities and drug–drug interactions of systemic antifungal agents, as well as maximizing adherence by ensuring that the patient understands the importance of therapy and the directions to take the medication appropriately, are important secondary outcomes of therapy.

General Approach to Treatment

The management of OPC should be individualized for each patient, taking into consideration the underlying immune status, other concurrent mucosal and medical diseases, concomitant medications, and exogenous infectious sources. In HIV-infected patients with inadequately controlled disease, antifungal treatment produces only a transient clinical response, and the relapse rates are higher than in other patient populations. These patients usually require frequent courses of antifungal treatment. Therefore, in patients with HIV disease, treatment with effective AART is paramount because this would provide the best prophylaxis against recolonization and recurrence of symptoms.[36,37,43]

Whenever feasible, it is desirable to minimize all predisposing factors, such as administration of corticosteroids, chemotherapeutic agents, and antimicrobials, as well as to institute proper oral hygiene and resolve concurrent conditions, such as denture stomatitis. Selection of an appropriate antifungal agent for treatment of candidiasis requires consideration of several factors, including the patient's drug adherence, adequate saliva for dissolution of solid topical medications, risk of caries from sucrose- or dextrose-containing preparations, potential drug interactions, coexisting medical conditions (eg, liver disease), location and severity of the infection, and the need for long-term maintenance therapy. Another factor that could affect drug selection is overuse of fluconazole, leading to the emergence of fluconazole-resistant species of *C. albicans*, and in some cases to all azoles, and other intrinsically more resistant species, such as *C. krusei*, *C. glabrata*, and *C. tropicalis*.

5 Topical antimycotic therapies should be the first choice for milder forms

of infections.[43] The efficacy of antimycotic agents for OPC varies in different patient populations. Until the polyene antimycotic agents became available in the 1950s, gentian violet, an aniline dye, was used to treat OPC. Problems with gentian violet include fungal resistance, skin irritation, and especially the unaesthetic staining of the oral mucosa. In resource limited areas gentian violet remains a therapeutic option. Gentian violet solution of 0.00165% does not stain the oral mucosa and has potent antifungal activity.[44] Topical agents, such as nystatin and clotrimazole, are the standard of treatment for uncomplicated OPC and generally are effective for treatment in otherwise healthy adults and infants with no underlying immunodeficiencies. Topical agents are available in an assortment of formulations, including oral rinses (suspension), troches, powder, vaginal tablets, creams and most recently as a mucoadhesive tablet[39,43,45] (**Table 138-6**).

TABLE 138-6 Therapeutic Options for Mucosal Candidiasis

Initial Episodes of OPC:[a] Treat for 7-14 Days	Common/Significant Side Effects
Clotrimazole 10 mg troche: hold 1 troche in mouth for 15-20 minutes for slow dissolution five times daily (B-2)	Altered taste, mild nausea, vomiting
Nystatin 100,000 units/mL suspension: 5 mL swish and swallow orally 4 times daily (B-2)	Mild nausea, vomiting, diarrhea
Miconazole 50 mg mucoadhesive buccal tablets 50 mg orally daily (A-1)	Diarrhea, headache, nausea, dysgeusia, upper abdominal pain, and vomiting
Fluconazole 100 mg tablets:[b] 100-200 mg orally daily (A-1)	GI upset, hepatitis not common
Itraconazole 10 mg/mL solution:[c] 200 mg orally daily (A-2)	GI upset, not common: hepatotoxicity, CHF, pulmonary edema with long-term use[d]
Posaconazole 40 mg/mL suspension: 400 mg orally daily with a full meal (A-2)	GI upset, fever, headache, increased hepatic transaminases not common
Fluconazole-Refractory OPC: Treat for ≥14 Days	
Itraconazole 10 mg/mL solution: 200 mg orally daily (A-3)	See above
Voriconazole 200 mg tablets: 200 mg orally twice daily (>40 kg), taken on empty stomach (A-3)	GI upset, rash, reversible visual disturbance (altered light perception, photopsia, chromatopsia, photophobia), increased hepatic transaminases, hallucinations, or confusion
Posaconazole 40 mg/mL suspension: 400 mg orally twice daily × 3 days, then 400 mg daily × 28 days (A-2)	See above
Amphotericin B 100 mg/mL suspension:[e] 1-5 mL swish and swallow orally four times daily (B-2)	Oral: nausea, vomiting, diarrhea with higher dose
Amphotericin B deoxycholate 50 mg injection: 0.3–0.7 mg/kg/day IV daily (B-2)	IV: fever, chills, sweats, nephrotoxicity, electrolyte disturbances, bone marrow suppression
Caspofungin 50 mg IV daily (B-2)	Fever, headache, infusion-related reactions (<5%) (eg, rash, facial swelling, pruritus, vasodilation), hypokalemia, increased hepatic transaminases, anemia, neutropenia
Micafungin 150 mg IV daily (B-2)	Similar to caspofungin
Anidulafungin 200 mg IV daily (B-2)	Similar to caspofungin
Esophageal Candidiasis:[a] Treat for 14-21 Days	
Fluconazole 100 mg tablets: 200-400 mg orally (3-6 mg/kg) daily (A-1)	See above
Echinocandin: see above (B-2)	See above
Amphotericin B deoxycholate 50 mg injection: 0.3-0.7 mg/kg/day IV daily (B-2)	See above
Posaconazole 40 mg/mL suspension: 400 mg orally twice daily (A-3)	See above
Itraconazole 10 mg/mL solution:[c] 200 mg orally daily (A-3)	See above
Voriconazole 200 mg tablets: 200 mg orally twice daily (>40 kg) (A-3)	See above
Voriconazole IV and echinocandins (A-1): generally reserved for refractory cases	See above
Fluconazole-Refractory EC: Treat for 21-28 Days	
Itraconazole 10 mg/mL solution: 200 mg orally daily (A-2)	See above
Posaconazole 40 mg/mL suspension: 400 mg orally twice daily (A-3)	See above
Voriconazole 200 mg tablets: 200 mg orally twice daily (>40 kg), taken on empty stomach (A-3)	See above
Caspofungin 50 mg IV daily (B-2)	See above
Micafungin 150 mg IV daily (B-2)	Similar to caspofungin
Anidulafungin 100 mg IV on day 1, then 50 mg IV daily (B-2)	Similar to caspofungin
Amphotericin B deoxycholate: 0.3-0.7 mg/kg/day IV, or lipid-based amphotericin 3-5 mg/kg/day IV (B-2)	See above

[a]Initial episodes of OPC can be adequately treated first with topical agents before resorting to systemic therapy (B-2), but systemic therapy is required for effective treatment of esophageal candidiasis. (A-2) Suppressive therapy is recommended for patients with frequent or severe recurrences (A-1).

[b]Fluconazole is more effective than ketoconazole (A-1).

[c]Solution is more effective than capsule (A-1); solution is better taken on an empty stomach.

[d]Suspension is not marketed; can be prepared extemporaneously by pharmacy.[59]

[e]See discussion under onychomycosis.

CHF, congestive heart failure; GI, gastrointestinal; OPC, oropharyngeal candidiasis.

Recommendation grades: Strength of recommendation: **A**—Both strong evidence for efficacy and substantial clinical benefit to support recommendation for use. *Should always be offered*. **B**—Moderate evidence for efficacy but only limited clinical benefit, to support recommendation for use. *Should generally be offered*. **C**—Evidence for efficacy is insufficient to support recommendation for or against use; or evidence for efficacy might not outweigh adverse consequences or cost of the treatment under consideration. *Optional*. **D**—Moderate evidence for lack of efficacy or adverse outcome supports a recommendation against use. *Should generally not be offered*. Quality of evidence: **1**—Evidence from at least one properly designed randomized, controlled trial. **2**—Evidence from at least one well-designed trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series studies, or dramatic results from uncontrolled experiments. **3**—Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees. (UR) Evidence currently unrated.

Topical agents require frequent applications because of the short contact time with the oral mucosa; the ideal contact time is 20 to 30 minutes. Sufficient saliva is needed to dissolve clotrimazole troches, and this can be problematic for patients with xerostomia. Also, the rough surface of the tablet can become irritating to the oral soft tissue. Troches also contain dextrose, which has cariogenic potential. Nystatin suspension might be a better choice for patients with xerostomia, but it is difficult to maintain adequate contact time with the oral mucosa. Some patients complain of the unpleasant taste of nystatin, which can cause nausea and vomiting; this is especially problematic in cancer patients experiencing chemotherapy-induced nausea. The high sucrose content of nystatin suspension is cariogenic in dentate patients, and it should be used with caution in diabetic patients.[36,39] Miconazole 50 mg mucoadhesive tablets are a buccal adherent miconazole product approved for the local treatment of OPC in adults and adolescents older than age 16 years.[46] This product offers the advantage of a once-daily formulation that is tasteless, odorless, and sugar free.[45] Topical creams, such as clotrimazole, ketoconazole, miconazole, and nystatin (usually mixed with a steroid), are more appropriate for application three times daily to the corners of the mouth in treating angular cheilitis, the inflammation, drying, and cracking of the corners of the mouth.[43]

Systemic therapy is necessary in patients with OPC that is refractory to topical treatment, those who cannot tolerate topical agents, have moderate-to-severe disease, and those at high risk for disseminated systemic or invasive candidiasis. Effective treatment of esophageal candidiasis generally requires the use of systemic antifungal agents. However, these agents have the disadvantage of producing more side effects (see Table 138-6) and drug–drug interactions (see Chapter 139). Fluconazole is inexpensive and generally well tolerated, and its absorption is unaffected by food or gastric acidity. Ketoconazole requires gastric acidity for absorption, which can be problematic and this agent is not recommended today with the availability of more effective triazoles. Itraconazole capsules also have the same absorption problem and are no longer recommended. In contrast, itraconazole solution has enhanced absorption and is best taken in a fasting state; in addition, the solution provides the benefit of both topical effects to the oral mucosa and systemic effects and is beneficial to patients with mucositis or swallowing problems. Whenever possible, it is generally beneficial to limit the use of systemic azole agents to prevent unnecessary drug exposure and to minimize the potential for occurrence of drug-resistant candidiasis, particularly from fluconazole resistance.

When patients become unresponsive to topical agents or fluconazole and itraconazole, alternative agents are available.[39,40,43,47,48] These include amphotericin B and other triazoles such as voriconazole and posaconazole and echinocandins (caspofungin, micafungin, and anidulafungin) (see discussion below). Although posaconazole is now available in three formulations, the original suspension as well as oral tablets and an intravenous product, only the suspension has an FDA indication for the treatment of OPC. The tablet formulation has stable bioavailability, one daily dosing and fewer challenges with absorption and may offer an attractive alternative.

Oropharyngeal Candidiasis: Human Immuodeficiency Virus–Infected Patients

Treatment for initial or recurrent episodes of OPC should be started with topical agents, provided that clinical symptoms are not severe and that there is minimal risk of esophageal involvement.[38,43] Clinical responses with the resolution of signs and symptoms generally occur within 5 to 7 days of initiating treatment. Clotrimazole appears to be the most effective topical agent and demonstrates comparable clinical response rates with both fluconazole and itraconazole.[38,43] However, topical therapy is associated with more frequent relapses than with fluconazole.[40,43] This may be of limited clinical significance in patients receiving effective AART because of their decreased susceptibility to opportunistic infection. In practice, nystatin suspension is still used frequently in initial episodes of OPC, although it is the least effective agent and is associated with frequent treatment failures and early relapses, especially in patients with advanced HIV disease or neutropenia.[36,39] Miconazole mucoadhesive tablets 50 mg once daily (MMT) were non-inferior to clotrimazole troches 10 mg five times daily for the treatment of OPC in HIV-infected patients. Safety and tolerability was also similar between treatment groups.[46]

Systemic oral azoles should be reserved for use in the more severe episodes of OPC unresponsive to topical agents or in patients with concurrent esophageal involvement.[39,43] In clinical practice, fluconazole usually is the systemic azole agent of choice because of its proven efficacy, favorable absorption, safety, and drug-interaction profiles, and it is relatively inexpensive. Fluconazole is superior to ketoconazole and itraconazole capsules.[39,43] Fluconazole should be given 100 to 200 mg/day for 7 to 14 days.[43] A single dose of fluconazole 750 mg orally was as effective as fluconazole 150 mg orally for 14 days, which warrants

further evaluation, given the potential advantages of adherence and cost-effectiveness.[47] Itraconazole oral solution with an improved absorption profile compared with the capsule formulation is as effective as fluconazole, with comparable clinical and mycologic response and relapse rates.[39,43] However, it carries a higher risk of drug interactions because it is a potent inhibitor of the cytochrome P450 enzymes, and it is associated with more nausea than fluconazole. Posaconazole is an extended-spectrum triazole with potent in vitro activity against both *C. albicans* and non–*C. albicans* species. It is equivalent to fluconazole in terms of efficacy, safety, and tolerability.[48] Posaconazole, itraconazole solution, and voriconazole are the azole alternatives to fluconazole in the management of moderate-to-severe OPC.[42] Other agents that are effective are amphotericin B and the echinocandins (caspofungin, micafungin, and anidulafungin). They are reserved for refractory OPC, however, because of their greater toxicity. They are also more expensive and are less convenient to use.

Oropharyngeal Candidiasis: Non-Human Immunodeficiency Virus–Infected Patients

This patient population includes patients with hematologic malignancy (eg, leukemias) or blood and bone marrow transplantation (BMT) with a long duration of neutropenia and chronic graft-versus-host disease, patients with solid tumors, patients with solid-organ transplants who are receiving immunosuppressive therapy, and patients with diabetes mellitus, as well as patients on prolonged courses of antibiotics or corticosteroids and the debilitated elderly. Factors to consider in deciding whether to use topical or systemic antifungal therapy include the severity and extent of mucosal involvement (oropharyngeal vs esophageal), predisposing risk factors, and risk for dissemination. Patients who develop neutropenia (eg, leukemic and BMT patients) are usually at high risk for disseminated and invasive fungal disease, and treatment of oral candidiasis is more aggressive. Patients with cell-mediated immune deficits but normal or near-normal granulocyte function and number (eg, solid tumors, solid-organ transplants, or diabetic patients) are at low risk for dissemination of infection.

Specific antifungal therapy can be unnecessary for asymptomatic patients at relatively low risk for disseminated candidiasis, such as those who are not granulocytopenic or who are expected to have a short duration of granulocytopenia.[43] Many of these infections will clear spontaneously after recovery of the granulocytes or discontinuation of antibiotic and/or

immunosuppressive therapy. However, antifungal therapy usually is required for patients who have persistent infection or significant symptoms, usually pain, or who are granulocytopenic with a relatively high risk of fungal dissemination. Topical agents first can be given a therapeutic trial depending on the severity of infection and the degree of immunosuppression. Although both nystatin and clotrimazole can be effective in treating OPC, nystatin suspension does not effectively reduce the incidence of either oropharyngeal or systemic *Candida* infections in immunocompromised patients receiving chemotherapy or radiation; its use often is associated with treatment failures and early relapses.[43] Clotrimazole appears to be more effective in reducing colonization and treating acute episodes in cancer patients who are immunocompromised. Miconazole mucoadhesive tablets were superior to miconazole oral gel in patients with head and neck cancer in achieving a complete response to therapy.[49] MMT has not been studied against clotrimazole in this patient population specifically but is approved for use in adults with OPC.

Systemic azole agents are used for treating OPC in patients who have failed or who are unable to take topical therapy.[39,43,48] The preceding discussion on the relative efficacy of fluconazole, itraconazole, and ketoconazole in HIV-infected patients can be extrapolated to the non-HIV-infected population. Oral fluconazole 100 to 200 mg daily is used more commonly because of more extensive experience with its use, and it is more effective and has a more favorable absorption and side-effect profile compared with other available azoles.[43] If the oral route is not feasible for reasons such as severe chemotherapy-induced mucositis, fluconazole can be administered IV. In patients unresponsive to azoles, IV amphotericin B in relatively low doses of 0.1 to 0.3 mg/kg/day can be tried.[43] Because of the higher risk for dissemination in patients who are severely neutropenic ($<0.1 \times 10^9$ neutrophils/L) or clinically unstable (hypotensive or febrile), some clinicians prefer to initiate therapy with IV amphotericin B at 0.6 mg/kg/day, with therapy continued until the neutropenia has resolved or an echinocandin.[43] The echinocandins caspofungin, micafungin, and anidulafungin are all effective for the treatment of OPC, thus offering other options, with fewer adverse effects in the patient with refractory disease.[43]

Topical therapy with clotrimazole or nystatin for 7 days is usually adequate for treating mucocutaneous candidiasis in most solid-organ transplant patients.[39] Use of topical therapy will reduce the number of systemic drugs that these patients receive and hence minimize the risk of drug–drug interactions. Failure to respond to topical agents warrants the use of fluconazole. Low-dose

amphotericin B solution as “swish and swallow” (100 mg/mL, 1 mL four times daily) for 7 to 10 days is reserved for the unusual cases of treatment failure as it is not readily available and requires compounding.

Patients who develop OPC because of prolonged antibiotic use or aerosolized corticosteroids use can be managed successfully by discontinuation of the offending agent, and the infection usually will resolve. If there is a strong desire to treat because of discomfort or need to hasten symptom resolution or an inability to stop the offending agent, therapy with a topical agent, either miconazole MT, clotrimazole or nystatin, is effective in most cases. The advantage of systemic azoles is the convenience of less frequent dosing. Symptoms usually improve in 3 or 4 days. Infants should be given smaller amounts more frequently (eg, nystatin 100,000 units every 2-3 hours) to ensure better contact time. For denture-related OPC, or candidal stomatitis, effective therapy requires treatment of both the mouth and the dentures to avoid relapse. The dentures must be brushed vigorously and disinfected every night by soaking in antiseptic solution, such as chlorhexidine gluconate 0.25% or a commercial denture disinfectant prodcut.[39,43] Topical antifungal therapy of the oral cavity is required. Consistent proper oral hygiene and care of the dentures can help prevent relapse.

Esophageal Candidiasis: Human Immunodeficiency Virus–Infected Patients

6 Treatment of esophageal candidiasis has not been as well studied as OPC. Because of the significant morbidity of esophageal candidiasis and the absence of evidence supporting the efficacy of topical antifungals, treatment requires systemic antifungal agents.[35,37] Fluconazole is superior to ketoconazole and itraconazole capsules with respect to endoscopic cure and clinical response and usually produces a more rapid onset of action and resolution of symptoms. Fluconazole is as effective as itraconazole solution, with reported response rates of >80% to 90%.[40,43] However, itraconazole solution causes more nausea and drug interactions because of inhibition of the cytochrome P450 enzymes. Amphotericin B, voriconazole, posaconazole, and the echinocandins are also effective in esophageal candidiasis, but they are generally reserved for patients with advanced or inadequately controlled HIV disease where the candidiasis tends to recur or becomes refractory to azole therapy.[50–53]

Esophageal Candidiasis: Non-Human Immunodeficiency Virus–Infected Patients

As in the case of HIV-infected patients, treatment of esophageal candidiasis requires systemic therapy. Patients can be started on oral fluconazole 200 to 400 mg/day for 14 to 21 days.[43] Higher fluconazole doses (up to 400 mg/day) have been suggested for patients with severe symptoms or those who are neutropenic.[54] Other agents currently recommended if fluconazole is not an option are an echinocandin or IV amphotericin B at 0.3 to 0.7 mg/kg. Itraconazole solution, posaconazole, and voriconazole are effective alternatives that may be considered for those not responding adequately to fluconazole. An echinocandin or IV amphotericin B may be selected over fluconazole for initial therapy in neutropenic patients who present with severe symptoms or who are at high risk for dissemination of *Candida* species, such as those receiving other aggressive immunosuppressive therapy (eg, corticosteroids, total-body irradiation, or antithymocyte globulin) and who have documented evidence of esophageal candidiasis or who have failed an initial empirical trial of oral nonabsorbable agents or systemic azoles.[43] Therapy should be continued at least until the neutropenia resolves. For patients whose symptoms have resolved and who are afebrile and clinically stable, therapy should be discontinued, and the patients should be monitored closely for infection recurrence. In high-risk patients, particularly those with persistent fever and neutropenia, the potential presence of clinically occult, diffuse GI or disseminated candidiasis should be considered. The echinocandins and newer azole agents (voriconazole and posaconazole) offer less toxic alternatives or oral agents and are preferred in patients who are intolerant of amphotericin B deoxycholate or who have preexisting renal impairment.[39,54,55]

Antifungal-Refractory Oral Mucosal Candidiasis

Treatment failure is generally defined as persistence of signs and symptoms of OPC or esophageal candidiasis after an appropriate trial of antifungal therapy.[38] Treatment of refractory oral mucosal candidiasis is frequently unsatisfactory, and clinical response is usually short-lived, with rapid and periodic recurrences. The key risk factors for occurrence of refractory candidiasis are advanced stage of AIDS with low CD4 cell counts (<50 cells/mm^3 [$<0.05 \times 10^9$/L]) and repeated or prolonged courses of various systemic antifungal agents, in particular systemic azoles.[39,43] Frequent or prolonged use of fluconazole can be associated

with fluconazole-refractory candidiasis because of selection of more resistant non–*C. albicans* species. An important initial management strategy is to assess and optimize the antiretroviral therapy of the patient with refractory OPC to help improve the immune function. With the widespread use of AART, fluconazole-refractory OPC is now less commonly encountered. It is also important to identify and rectify potentially correctable causes of clinical failures of mucosal candidiasis, such as poor drug adherence, adequate dosing, reduced drug absorption associated with hypochlorhydria, and drug–drug interactions.

There have been few controlled studies that assess the effectiveness of antifungal agents. Doubling of the fluconazole dosage to 400 or 800 mg/day can be effective in some patients with infection caused by *Candida* species of intermediate resistance, although the response may be only transient.[40] Fluconazole oral suspension can be beneficial in some patients because of increased salivary concentrations obtained when the suspension is taken with the swish and swallow technique.[43] Patients with fluconazole-refractory mucosal candidiasis can be treated with itraconazole oral suspension because it can be effective in 64% to 80% of patients; however, the benefit is short-lived if chronic suppressive therapy is not maintained.[38,43] Posaconazole suspension was successful in ~74% of patients with refractory oral or esophageal candidiasis; voriconazole may also be efficacious in these patients. Amphotericin B oral suspension is another alternative for azole-refractory patients.[40,43] It has broad-spectrum activity against many fungal species and low likelihood of *Candida* species resistance. Amphotericin B suspension is no longer available commercially in the United States, but it can be prepared extemporaneously by the pharmacy.[56]

Until recently, IV amphotericin B deoxycholate has been the alternative for patients with endoscopically proven disease who have failed fluconazole or itraconazole therapy. Patients with severe disease unresponsive to other agents require IV amphotericin B 0.3 to 0.7 mg/kg/day for 7 to 10 days to achieve clinical response; higher dose or longer treatment duration can be needed in more severe disease.[40,43] After response, suppressive therapy with amphotericin B is required to increase disease-free intervals. Patients who fail to respond to amphotericin B and require >1 mg/kg/day might be candidates for liposomal amphotericin B preparations because of renal and/or bone marrow toxicities, although at a markedly higher cost. Flucytosine usually is not used as monotherapy because of rapid development of resistance but can be used in combination with an azole or amphotericin B.[40] Less toxic agents that are also effective are voriconazole and the echinocandins.[54,55] Voriconazole, a triazole

antifungal available in both oral and IV preparations, is as effective as fluconazole for esophageal candidiasis, and has shown success in treatment of fluconazole-refractory disease.[53] However, voriconazole has more side effects and multiple pharmacokinetic drug interactions compared to fluconazole.[53] Caspofungin is the first of the echinocandins to be approved for esophageal candidiasis; recently, micafungin and anidulafungin have been approved for this indication. All three echinocandins have similar efficacy and tolerability profile as fluconazole, although higher relapse has been reported with caspofungin and anidulafungin compared with fluconazole.[43,55] Because the echinocandins require IV administration and are expensive, they are primarily used in patients who are refractory to the triazoles or have serious triazole-related adverse effects. As a class, the echinocandins have a favorable adverse effect profile. They are less toxic than amphotericin B (see Table 138-6) and have less impact on the cytochrome P450 enzymes than either itraconazole or voriconazole. Immunomodulation with adjunctive granulocyte-macrophage colony-stimulating factor and interferon have been used for refractory oral candidiasis in limited numbers of patients.[43]

Antifungal Prophylaxis

7 Ensuring that the HIV-infected patient is receiving appropriate antiretroviral therapy to enhance the immune system is perhaps the most important measure in preventing future episodes of mucosal candidiasis (oropharyngeal, esophageal, and vulvovaginal).[43] Initial success of treatment often is followed by symptomatic recurrences, especially in patients with advanced or poorly controlled HIV disease. Long-term suppressive therapy with fluconazole is effective in preventing recurrences or new infections of OPC in HIV disease and in patients with cancer.[43] However, the indications for antifungal prophylaxis and the best long-term management strategy still have not been well established. Fluconazole does not provide complete protection, and breakthrough infections can occur.[40] The reduced risk of recurrence of OPC also has not been demonstrated to improve survival. In addition, chronic exposure to azole therapy is a concern in that it might lead to the development of refractory disease or emergence of azole resistance.[43] However, in a randomized trial of continuous versus episodic fluconazole therapy, continuous therapy did not result in a higher rate of refractory OPC or esophageal disease.[57] HIV specialists do not recommend primary or secondary prophylaxis for OPC.[40] The rationale includes effectiveness of therapy for acute episodes of OPC, low incidence of serious

invasive fungal disease, low mortality associated with mucosal candidiasis, potential for drug interactions, potential for emergence of drug resistance, and the prohibitive long-term cost of prophylaxis.

8 The decision to use secondary prophylaxis should be individualized for each patient. Secondary prophylaxis can be considered in patients with multiple recurrent episodes of symptomatic OPC or when the disease is sufficiently severe and affecting the quality of life.[40] Patients with a history of one or more episodes of documented esophageal candidiasis and a CD4 T-cell count still <200 cells/mm^3 (<0.2 × 10^9/L) despite being on AART are candidates for secondary prophylaxis. Oral fluconazole 100 mg three times weekly is the regimen recommended by the Infectious Diseases Society of America for patients deemed in need of chronic suppressive therapy.[30] Itraconazole solution 200 mg daily orally is an alternative as suppressive therapy for OPC.[43]

Patients with malignant neoplastic diseases who are receiving irradiation, cytotoxic, and/or immunosuppressive therapy are at high risk for fungal infections in addition to bacterial and viral infections. Prophylaxis of *Candida* infection is controversial, and the results of studies have been conflicting and difficult to evaluate. In the hematopoietic stem cell transplant (HSCT) population, fluconazole prophylaxis is recommended prior to engraftment. Cross-resistance to other azoles may occur among *Candida* species; this should be a treatment consideration in a patient who develops a breakthrough fungal infection. Micafungin is an alternative to fluconazole prophylaxis of candidiasis.[58] The value of antifungal prophylaxis in these patients needs to be considered in the broader context of not only reducing colonization and the risk of superficial candidiasis but also, more importantly, reducing the risk for invasive candidiasis and improving survival. Management of these infections in this patient population is discussed further in Chapter 140.

Evaluation of Therapeutic Outcomes

Efficacy end points for oropharyngeal and esophageal candidiasis include rapid relief of symptoms and prevention of complications without early relapse after completion of the course of therapy.[40,43] Sterilization of the oral cavity is not a feasible end point because mycologic eradication is rarely achievable, especially in HIV-positive patients. Symptomatic relief of presenting signs and symptoms (see Table 138-5) generally occurs within 48 to 72 hours of starting therapy, with complete resolution by 7 to 10 days. Patients should be advised about the time course and told to return for reassessment when signs and symptoms recur. It is

usually unnecessary for the patient to be reassessed soon after finishing the treatment course. However, HIV patients should be questioned and examined for the occurrence of mucosal candidiasis as part of their regular follow-up. The frequency of monitoring can be more often in neutropenic patients because of concern for dissemination of candidiasis. During the period of neutropenia, temperature should be monitored daily, as well as signs of dissemination.

Efficacy of the antifungal agent is partly influenced by patient adherence to the medication regimen. Patients must be counseled on proper administration and dosing, in particular for topical agents (**Table 138-7**).[54] Safety end points include monitoring for occurrence of the relevant drug side effects and drug interactions (see Table 138-6). Mild GI intolerance can occur with topical therapy, but serious adverse effects are rare. It is prudent to monitor for hypersensitivity reactions, especially rash and pruritus that might occur with any medication. GI intolerance is more associated with the oral azoles. Hepatotoxicity can occur when azole therapy is prolonged beyond 7 to 10 days or high doses are used. Periodic monitoring of liver enzymes (alanine transaminase and aspartate amino-transferase) should be considered, especially if prolonged therapy (longer than 21 days) is anticipated. Patients who are receiving IV amphotericin B require daily monitoring by a pharmacist.

TABLE 138-7 Patient Counseling Tips for Managing Oropharyngeal Candidiasis

1. Clean the oral cavity prior to administering the topical antifungal agent. Daily fluoride rinses can help reduce the risk of caries when using an agent containing sucrose or dextrose.
2. Use the topical antifungal agent after meals, as saliva flow and mouth movements can reduce the contact time.
3. Troches should be slowly dissolved in the mouth, not chewed or swallowed whole, over 15-20 minutes, and the saliva swallowed.
4. Suspension should be swished around the mouth in the oral cavity to cover all areas for as long as possible, ideally at least 1 minute, then gargled and swallowed.
5. Remove dentures while medication is being applied to the oral tissues.
6. Use a suspension or buccal mucoadhesive tablet instead of a troche if xerostomia is present; if a troche is preferred, the patient should rinse or drink water prior to dosing. For xerostomia, suggest nonpharmacologic measures for symptomatic relief (eg, ice chips, sugarless gum or hard candy, citrus beverages).
7. Dentures should be removed and disinfected overnight using an antiseptic solution (eg, chlorhexidine 0.12%-0.2%). Disinfect oral tissues in addition to dental prosthesis.
8. Complete treatment course even though symptomatic improvement can occur in 48-72 hours.
9. Maintain good oral hygiene. Brush teeth daily (twice daily) and floss, rinse mouth, or brush teeth after eating sweets.
10. Stop smoking; avoid alcohol.

Data from reference 52.

MYCOTIC INFECTIONS OF THE SKIN, HAIR, AND NAILS

Superficial cutaneous mycoses affect up to 20%-25% of the population globally.[59] The usual pathogens are the dermatophytes classified by genera: *Trichophyton*, *Epidermophyton*, and *Microsporum*.[60] Less frequently infection is caused by nondermatophyte fungi (eg, *Malassezia furfur)* and *Candida* species. Dermatophytes have the ability to penetrate keratinous structures of the body and therefore infections are limited to hair, nails, and skin. These infections affect both male and female genders and all races. Reservoirs of mycotic infections include humans, animals, and soil.[60,61] Individuals can develop an infection if they come in contact with a reservoir in addition to having a conducive environment for mycotic growth (ie, moist conditions). Risk factors for the development of an infection include prolonged exposure to sweat or soaking in water, maceration, intertriginous folds, sharing personal belongings

such as combs, close living quarters (dormitories, barracks).[61]

Mycotic infections of the skin have a classic appearance that consists of a central clearing surrounded by an advancing red, scaly, elevated border, also referred to as an "active" border.[62] The central clearing of the lesion may distinguish dermatophytoses from other skin eruptions such as psoriasis or lichen planus that have a more uniform inflammatory presentation.[62] Infections of the nail can appear chalky and dull yellow or white and become brittle and crumbly.

Diagnosis usually is based on patient history, as well as the physical examination.[63,64] Diagnostic tests include direct microscopic examination of a specimen after the addition of KOH or fungal cultures. The KOH test is quick, inexpensive, and easy to perform, whereas cultures are more expensive and take longer to obtain results. Diagnostic tests are recommended when systemic therapy is likely to be prescribed.[63,64]

9 A general approach to treatment of superficial mycotic infections includes keeping the infected area dry and clean and limiting exposure to the infected reservoir. Topical agents generally are considered to be first-line therapy for infections of the skin. Oral therapy is preferred when the infection is extensive or severe or when treating tinea capitis or onychomycosis.[65–67] **Table 138-8** lists specific treatments for each mycotic infection. Superficial mycotic infections are categorized by the pattern and site of infection.[60] The most commonly occurring infections in North America are detailed in the following sections.

TABLE 138-8 Treatment of Mycoses of the Skin, Hair, and Nails

	Topical[a,b]	Oral regimen[c]
Tinea pedis	Butenafine, daily Sertaconazole, twice daily Luliconazole, daily Naftifine cream daily, gel daily	Fluconazole 150 mg 1 per week × 1-4 weeks
Tinea manuum	Ciclopirox, twice daily	Ketoconazole 200 mg daily × 4 weeks
Tinea cruris	Clotrimazole, twice daily Luliconazole, daily Naftifine cream, daily	Itraconazole 200-400 mg/day × 1 week
Tinea corporis	Econazole, daily	Terbinafine 250 mg/day × 2 weeks
	Haloprogin, twice daily	
	Ketoconazole cream, daily Luliconazole daily	
	Miconazole, twice daily	
	Naftifine cream, daily	
	Oxiconazole, twice daily	
	Sulconazole, twice daily	
	Terbinafine, twice daily	
	Tolnaftate, twice daily	
	Triacetin cream, solution, three times daily	
	Undecylenic acid, various preparations: apply as directed	
Tinea capitis	Shampoo only in conjunction with oral therapy **or** for treatment of asymptomatic carriers	Terbinafine 250 mg/day × 4-8 weeks
Tinea barbae	Ketoconazole twice weekly × 4 weeks	Ketoconazole 200 mg daily × 4 weeks
	Selenium sulfide daily × 2 weeks	Itraconazole 100–200 mg/day × 4-6 weeks
		Griseofulvin 500 mg/day × 4-6 weeks
Pityriasis versicolor	Clotrimazole, twice daily	Ketoconazole
	Econazole, daily	
	Haloprogin, twice daily	Fluconazole
	Ketoconazole, daily	
	Miconazole, twice daily	Itraconazole 200 mg daily × 3-7 days
	Oxiconazole cream only, twice daily	
	Sulconazole, twice daily	
	Tolnaftate, three times daily	
Onychomycosis	Ciclopirox 8% nail lacquer: apply solution at night for up to 48 weeks (fingernails and toenails) Efinaconazole 10% topical solution daily for 48 weeks (toenails) Tavaborole 5% topical solution daily for 48 weeks (toenails)	Terbinafine 250 mg/day × 6 weeks (fingernail), 12 weeks (toenail) Itraconazole 200 mg twice daily x 1 week/month for 2 months (fingernail); 200 mg daily x 12 weeks (toenail) Fluconazole 50 mg daily or 300 mg once weekly for ≥6 months (fingernail) or 12 months (toenail)

[a]Other products are available, including combination products.

[b]Length of therapy depends on mycotic sensitivity and severity of infection.

[c]Only capsule formulation studied; give with food for increased absorption.

Tinea Pedis

Tinea pedis is the most common dermatophytoses (affecting ~70% of adults). It is better known as “athlete’s foot” and occurs in hot weather, with exposure to surface reservoirs (locker room floors), and with use of occlusive footwear.[61] Tinea pedis has three common presentations. The most common is the interdigital form which is characterized by fissuring, maceration and scaling of the spaces between the toes (most frequently the fourth and fifth toes). Patients often complain of itching and burning. The “moccasin-like” distribution presentation is usually caused by *Trichophyton* rubrum. In this form the plantar surface becomes chronically scaly and thickened with accompanying erythema of the soles, heels and sides of the foot. The third presentation, vesiculobulous tinea pedis, is characterized by the formation of vesicles, pustules and occasionally bullae typically on the soles of the foot. Contact dermatitis, pustular psoriasis and eczema would be in the differential diagnosis. Disruption of skin integrity with tinea pedis is a risk factor for streptococcal cellulitis as a complication. Treatment with topical therapy for 2 to 4 weeks often is adequate for mild infections; however, severe infections or involvement of the nails require oral therapy[61] (see Table 138-8). Recurrence of infection occurs in up to 70% of individuals especially if there is concomitant onychomycosis. Prolonged treatment with either topical or systemic therapy may be required.[60,65] Other nonpharmacologic measures such as disinfecting footwear, avoidance of walking barefoot in public places, controlling hyperhidrosis, wearing absorbent socks and nonocclusive shoes should be advised.

Tinea Manuum

Tinea manuum is a superficial fungal infection of one or infrequently both hands, and can involve the feet (tinea pedis). The infection presents with dry and hyperkeratotic palmar surface of the hand. The fingernails, when involved, may present with vesicles and scaling. Contact dermatitis, eczema, psoriasis and callus formation should be in the differential diagnosis. Treatment of this infection is similar to tinea pedis (see Table 138-8). Emollients that contain lactic acid also can be useful.[61] Relapse or recurrence is frequent especially if tinea pedis or onychomycosis is present.

Tinea Cruris

Tinea cruris is an infection of the proximal thighs and buttocks.[66] It is referred to as “jock itch” and is more common in males. Tinea cruris and tinea pedis often occur concurrently. High humidity and warm temperatures along with wet or tight-fitting clothes contribute to the development of tinea cruris. The scrotum and penis often are spared from infection. The lesions are red, scaling with raised borders. Pustules or vesicles and maceration are usually found along the active border. Itching and burning are the most common patient complaint. The differential diagnosis would include candida infection, erythrasma, mechanical intertrigo, psoriasis, and seborrheic dermatitis.[62] Treatment with topical therapy is recommended and should continue for 1 to 2 weeks after symptom resolution. Severe infections can require oral therapy (see Table 138-8). Relief of pruritus and burning can be facilitated by the use of short-term (2 or 3 days) topical steroids (2.5% hydrocortisone).[61] The feet of the patient should also be examined as a source of infection. Nonpharmacological measures such as keeping the area dry or avoiding prolonged exposure to moisture are important patient counselling points.

Tinea Corporis

Tinea corporis, also known as ringworm, is an infection of the glabrous skin of the trunk, extremities, or face.[62] Lesions of tinea corporis may be singular or multiple and appear as round, scaly lesions with central clearing and a raised border with sharp margination. The border may exhibit pustules. The degree of pruritis is variable. The differential diagnosis includes nummular eczema, contact dermatitis, psoriasis, pityriasis rosea, tinea versicolor, granuloma annulare, and Lyme disease.[62] Prior use of topical corticosteroid preparations may alter the appearance such that the central clearing and raised borders are no longer apparent impacting diagnosis. Diagnosis should be confirmed with KOH examination of skin scrapings of the edge of the lesion. Therapy is similar to that for tinea pedis, tinea manuum, and tinea cruris (see Table 138-8). If the infection is widespread systemic antifungal therapy may be necessary.

Tinea Capitis

Tinea capitis is a mycotic infection involving the scalp, hair follicles, and adjacent skin that primarily affects children.[67,68] Treatment should consist of oral therapy, as well as the cleaning of combs and brushes, which can be contaminated (see Table 138-8). Daily shampooing is recommended for removal

of scales. Some children and adults can be asymptomatic carriers, thereby facilitating spread of the infection.[67] Family members who culture positive for Trichophyton tonsurans should be treated with an antifungal shampoo (eg, ketoconazole, selenium sulfide, or povidone-iodine).[67]

Tinea Barbae

Tinea barbae affects the hairs and follicles of beards and mustaches.[67] Treatment is similar to that for tinea capitis (see Table 138-8). Removal of the beard or mustache is recommended.[61]

Pityriasis Versicolor

Hyper- and hypopigmented scaly patches characterize pityriasis versicolor, which is also known as *tinea versicolor*. It is caused by yeasts of the *Malassezia* genus that, with the exception of *Malassezia pachydermatis*, are all lipophilic. The seborrheic areas (scalp, face, back and front of the trunk) of the human body are always colonized by one or more *Malassezia* spp., such as *M. globosa*, *M. sympodialis*, *M. sloffiae*, and *M. restricta* are the most common colonizers; *M. globosa* and *M. furfur* are most frequent clinical infection isolates. The lesions are found on the trunk, face and extremities.[60] It is more common in adults and in areas with tropical ambient temperatures. Topical treatment usually is adequate unless there is extensive involvement, recurrent infections, or failure of topical therapy.[69] Ketoconazole 2% shampoo was significantly more effective than selenium sulfide 2.5% shampoo (89% vs 35% cure rate).[69] Recurrence of infection after cessation of treatment may be as high as 60% in the first year and 80% the second year. Suppressive maintenance therapy either orally or topically may be used in these cases.[59]

Onychomycosis (Tinea Unguium)

Onychomycosis is a fungal infection of the nail apparatus and is the most common single cause of nail dystrophy, affecting up to 8% of the general population and accounting for up to 50% of all nail problems.[69–72] Onychomycosis more commonly affects the toenails (2% to 14% of adults), ~4 to 19 times more frequently than fingernails, with prevalence increasing with age.[71] This can be because of the slower growth of toenails (three times slower than fingernails), making it easier for fungi to establish infection.

Onychomycosis has a significant impact on quality of life, both functional and psychosocial. In addition, the affected nails can disrupt the integrity of the surrounding skin, potentially increasing the risk of secondary bacterial infections.[71]

Onychomycosis is due to infection by dermatophytes (tinea unguium), yeasts, and nondermatophyte fungi.[73] Dermatophytes are the most frequent causes of onychomycosis (~90% in toenail and ~50% in fingernail infections).[74] The dermatophytes responsible for causing >90% of cases of onychomycosis are *Trichophyton rubrum* (71%) and *Trichophyton mentagrophytes* (20%).[67,68] Less common fungi causing onychomycosis are the nondermatophytic molds (2.3%-11%) and yeasts (5.6%). *C. albicans* is the most commonly isolated yeast and typically affects fingernails rather than toenails.[69,75] Risk factors for dermatophytic onychomycosis are increasing age (especially older than 40 years), family history and genetic factors, immunodeficiency (eg, HIV, renal transplant, immunosuppressive therapy, and defective polymorphonuclear chemotaxis), diabetes mellitus, psoriasis, peripheral vascular disease, smoking, prevalence of tinea pedis, frequent nail trauma, and sporting activities such as swimming.[75,76] These risk factors also appear to apply to recurrence of onychomycosis. Mold onychomycosis does not seem to be associated with systemic or local predisposing factors, but there is a risk of systemic dissemination in immunosuppressed patients.[75] *Candida* onychomycosis seems to always occur in immunosuppressed patients.[75]

Onychomycosis can present in four or five different major clinical forms, of which lateral distal subungual onychomycosis is the most common type.[69,75,77] In distal subungual onychomycosis, the nail plate, the nail bed, and, in advanced cases, the matrix are all affected, and *T. rubrum* is the most common etiologic cause. The worst case of onychomycosis is progression of the infection to total dystrophic onychomycosis, characterized by almost complete destruction of the nail plate. White superficial onychomycosis is usually caused by *T. mentagrophytes*, where the infection is localized to the surface of the nail plate. In proximal subungual onychomycosis, the fungi (usually *T. rubrum*) invade the nail through the proximal nail fold and spread to the nail plate and matrix. Although proximal subungual onychomycosis is relatively uncommon in the general population, it occurs most frequently in severely immunocompromised patients and is often considered a marker for AIDS.[75,77] Because of the multifactorial etiology of onychomycosis, it is important to differentiate onychomycosis from other causes of nail dystrophies so that the patient receives appropriate therapy and is not subjected to prolonged treatment with unnecessary

drugs. Besides clinical history and physical examination, proper diagnosis of onychomycosis can include the combination of direct microscopy of scrapings from the appropriate nail area to look for fungal hyphae and fungal cultures, and, if necessary, histologic examination.[71,78,79] Table 138-9 provides a differential diagnosis for fungal nail diseases.[80]

TABLE 138-9 Differential Diagnosis of Fungal Nail Infections

Diagnosis	Features Consistent with Diagnosis
Psoriasis	Nail pitting, rash elsewhere on body, family history of psoriasis
Lichen planus	Nail atrophy, scarring at proximal aspect of the nail
Periungual squamous cell carcinoma	Single nail affected, pain, warty nail fold change, or ooze from the edge of nail
Yellow nail syndrome	Multiple nails turn yellow, grow slowly, increased longitudinal and transverse curvature, intermittent pain and shedding, associated with chronic sinusitis, bronchiectasis, lymphedema
Trauma	Single nail affected, homogeneous alteration of nail color and altered shape of nail

Reprinted, with permission, from de Berker D. Clinical practice. Fungal nail disease. N Engl J Med 2009; 360:2108-2116. Copyright © 2009 Massachusetts Medical Society. All rights reserved.

TREATMENT

General Approach

Onychomycosis merits proper assessment and treatment consideration because it is a debilitating disease and can exert a negative impact on quality of life (eg, cosmetic and psychosocial effects, pain, discomfort, and decreased ambulation).[71,73,75,81] It is reasonable to not treat persons with minimal toenail involvement and no associated symptoms.[80] Although definitive data are lacking regarding the risk of progression of untreated disease, it can lead to complications such as cellulitis or reduced mobility, which can further compromise peripheral circulation in those with diabetes or peripheral vascular disease; additionally, infected nails can serve as a source of transmission of fungi to other areas of the body, as well as to other people, such as close household contacts, or in communal bathing places.[72,73,75,81,82]

Treatment decisions should be made on an individual basis. The primary end point of treatment is eradication of the organism, with secondary end points being clinical cure and improvement.[72] Assessment of clinical success (cure or improvement) requires follow-up for several months after the end of treatment because of the slow growth rate of nails, especially toenails (1 mm/month).[71,75] Successful eradication of the fungus does not always result in normalization of the nails because they can have been dystrophic prior to infection. This can cause patient dissatisfaction, especially if this is not explained before starting treatment.[77] There are several factors that must be taken into account on a patient-by-patient basis to ensure appropriate treatment decisions (**Table 138-10**). The impact of patient adherence on the success of treatment cannot be overemphasized. Patients need to be educated about their disease, expectations of treatment, and prevention of recurrence, and various strategies have been suggested to improve treatment success.[79]

TABLE 138-10 Factors That May Impact Treatment Decisions and Outcomes

- Type and severity of onychomycosis
- Causative organism—dermatophyte vs molds or yeast
- Infection of the finger vs toenail
- Extent of disease—involvement of matrix, one or two lateral edges, number of nails
- Thickness of nail plate
- Other sites of mycotic infection (palms, soles, toe webs)
- Other nail alterations affecting outcome (onycholysis, paronychia, dermatophytoma, etc.)
- Other nail diseases and symptoms
- Age and underlying medical conditions (diabetes, poor perfusion, immunocompromised)
- Drug interactions and adverse effects
- Cost of therapy

Data from references 67, 76, 78, and 79.

In general, onychomycosis of the toenail is more difficult to treat than fingernails, requires longer treatment duration, and is associated with a higher recurrence. The treatment options for onychomycosis include oral and topical therapies, mechanical or chemical nail avulsion, or a combination of these. Mechanical or chemical nail avulsion is used primarily as adjunct to oral therapy in patients with total dystrophic onychomycosis, in whom there is severe onycholysis and extensive nail thickening or longitudinal spikes. This is to

enhance penetration of the antifungal agent to the entire nail plate and unit.[71,73,79,82]

Topical Therapy

10 Conventional topical antifungal products are available as creams, ointments, powders, and solutions. Because these formulations do not penetrate through the nail plate to the nail bed, they are most appropriately used when the nail plate has been removed.[73,82] Even then cure rates are still low and variable and are influenced by patient adherence.[73,75,82] Nail lacquer represents the latest advance in topical formulation. The volatile vehicle, used to deliver the drug, evaporates and leaves an occlusive film with a high-drug concentration on the nail surface.[75,82] There are only two marketed nail lacquers, amorolfine 5% and ciclopirox 8% solution (Penlac), the latter being the only one approved in the United States for the treatment of mild-to-moderate onychomycosis caused by *T. rubrum* without lunula involvement.[75,81,82] Ciclopirox, a hydroxypyridine, has a broad spectrum of antifungal activity (dermatophytes, *Candida* species, and some molds) and requires treatment for 1 year. Although ciclopirox was significantly better than vehicle alone, the mycologic cure rate was only 32% with ciclopirox versus 10% for vehicle alone after 48 weeks of treatment; the overall treatment cure (mycologic cure with 0%-10% involvement of the target nail) was 9% versus 0.9% for drug and vehicle, respectively.[75,82] However, higher mycologic cure rates of 45% to 65% have been reported in a variety of open-label trials involving 6 to 12 months of treatment.[75] Amorolfine appears to produce higher mycologic and treatment cure rates than ciclopirox.[73,81] Most experts consider topical therapy a feasible option when the infection is superficial involving the nail plate without matrix involvement, such as white superficial onychomycosis, involves a partial area of the nail plate not exceeding 50% (owing to difficulty of applying treatment to the margin of the nail), is limited to a few (three or four) nails, is in the early stages of distal subungual onychomycosis when infection is still confined to the distal edge of the nail, or when systemic therapy is contraindicated.[71,75,81] Combining topical therapy with debridement of the affected nail (thus diminishing the amount of nail requiring treatment) may increase the likelihood of successful treatment, although there is no strong supporting evidence.[80] Topical therapy is not associated with systemic adverse effects or drug interactions. Any adverse effect will be localized to the application site, such as mild erythema in the adjacent skin area.

Systemic Therapy

Oral antifungal therapy is considered to be more effective than topical for treating onychomycosis. Terbinafine and itraconazole (capsule), the current first-line agents for treatment, have yielded higher efficacy rates using shorter treatment periods (generally 3 months or shorter) for toenail and fingernail onychomycosis compared with the traditional agents, such as griseofulvin and ketoconazole, which are rarely used nowadays. Terbinafine, an allylamine, exerts fungicidal activity and demonstrates the greatest in vitro activity against dermatophytes compared with the other oral antifungals; it has good activity against nondermatophyte molds and only marginal activity against *Candida* species.[71,82] Like other azoles, itraconazole is fungistatic, has a broad antifungal spectrum, and is active against dermatophytes, nondermatophytes, and *Candida* species[71,82] Both agents have lipophilic and keratinophilic properties, which explains their excellent penetration (appearing in the nail plate within days of treatment initiation) and accumulation in the nails, achieving concentrations far exceeding the minimal inhibitory concentration (MIC) of most dermatophytes. Nail terbinafine concentrations are detected within 1 week of starting therapy, whereas itraconazole can be detected 1 (fingernails) to 2 weeks (toenails) after starting therapy.[75] Both drugs are slowly eliminated from the nail, with effective drug concentrations persisting in nails for 30 to 36 weeks after completion of treatment with terbinafine and for 27 weeks with itraconazole.[77] The persistence of drug in the nails explains in part the long-term protection against relapses after the end of treatment and also permits use of intermittent (pulse) dosing.

The treatment of toenail onychomycosis requires a 12-week course, whereas a 6-week course is adequate for fingernail onychomycosis with either drug (see Table 138-8).[72,77,83] In general, cure rates of 80% to 90% for fingernail infection and 70% to 80% for toenail infection can be expected.[71] Terbinafine is licensed for daily dosing. Various terbinafine pulse regimens have been evaluated;[73] in some trials, pulse dosing was less effective than continuous dosing, and it did not provide clear safety advantages.[78,79] One trial demonstrated similar efficacy of pulse terbinafine compared with continuous therapy and better outcomes compared with pulse itraconazole treatment.[84] Itraconazole pulse therapy is the preferred method over continuous dosing for fingernail infections, and it is licensed as twice-daily dosing for a 1-week cycle per month for two consecutive months (ie, two pulses), or as daily therapy for 6 weeks (see Table 138-8).[77,83] Although itraconazole pulse therapy is not approved by the US Food and Drug Administration (FDA), three or four pulses are effective for toenail infections;

otherwise, half the dose is taken daily for 3 months (see Table 138-8).[77,83] In addition to lower drug cost, the potential advantages of itraconazole pulse therapy compared with continuous therapy are a lower risk of adverse drug effects and improved patient adherence.

Terbinafine is the first-line agent for onychomycosis; itraconazole is the alternative. Direct comparative trials generally have shown that terbinafine is more effective than itraconazole either by continuous or pulse dosing.[71,81,82] Mycologic cure rates for terbinafine range from 77% to 100% depending on the study.[75,85,86] Continuous terbinafine was the most effective therapy for toenail onychomycosis.[87–89] In addition, terbinafine was reported to achieve high cure rates in high-risk immunosuppressed patients, such as diabetics and organ transplant recipients, comparable to the immunocompetent population, with no significant adverse effects or drug interactions. It also appears to be effective in HIV patients and nondermatophyte infections.[83,90] A pharmacoeconomic analysis of oral and topical (ciclopirox) therapies showed that terbinafine was the most cost-effective therapy in terms of highest success rate, lowest relapse rate, and highest number of disease-free days for both fingernail and toenail infections.[91] An analysis that looked only at oral therapy estimated that the cost per cure with the use of terbinafine (based on cure rates from clinical trials) ranged from $2,439 to $7,944, depending on disease severity.[92] Compared with the amount of money a patient would consider reasonable to spend on treatment, the current charges for a course of systemic therapy are considerably higher.[92,93]

Both terbinafine and itraconazole generally are well tolerated. The more common adverse effects reported with terbinafine are GI (eg, diarrhea, dyspepsia, nausea, and abdominal pain), dermatologic (eg, rash, urticaria, and pruritus), and headache; less common adverse effects are taste disturbances, fatigue, inability to concentrate, and asymptomatic liver enzyme abnormalities.[77,81,83] Terbinafine can cause transient decrease in absolute lymphocyte counts; hence, monitoring of complete blood counts can be useful, especially in immunocompromised patients.[83] Although uncommon, severe adverse effects have been reported with terbinafine, including erythema multiforme, Stevens-Johnson’s syndrome, toxic epidermal necrolysis, pancytopenia, lupus erythematosus, psoriasis, hair loss, and hepatotoxicity. Severe hepatotoxicity is rare.[94] Terbinafine thus is not recommended for patients with chronic or active liver disease, although hepatotoxicity can occur in patients with no preexisting liver disease or serious underlying medical condition. Prior to initiating terbinafine treatment, it is recommended to obtain appropriate nail specimens for laboratory testing to confirm the diagnosis of onychomycosis.

Liver function parameters (serum transaminases) should be assessed at baseline and periodically during treatment with terbinafine.[83,94]

The common adverse effects of itraconazole are similar to those of terbinafine, such as GI disturbance, dermatologic disorders, and headache; less common adverse effects include dizziness, fatigue, fever, decreased libido, and asymptomatic liver enzyme abnormalities (1%-5% with continuous dosing and ~2% with pulse dosing).[77,81,95] Although still considered rare, 24 serious cases of liver failure, including transplantation and death, have been reported with the use of itraconazole.[94] Some of these patients did not have preexisting liver disease or serious underlying medical conditions, and some developed within the first week of treatment. Itraconazole should be avoided in patients with elevated liver enzymes or active liver disease or in those who have experienced other drug-induced liver toxicity. Liver function parameters (serum transaminases) should be assessed prior to and periodically during treatment. However, some experts have suggested that frequent monitoring is not as necessary if pulse therapy is used because symptomatic hepatotoxicity has not been reported with pulse therapy.[95] In addition, there is risk of developing congestive heart failure (CHF) associated with the use of itraconazole, possibly related to its potential negative inotropic effect.[72,85] Therefore, itraconazole should not be used in patients with evidence of ventricular dysfunction, such as CHF. Symptomatic assessment for the development of CHF also should be included as part of therapy monitoring. Before a patient is subjected to several months of itraconazole treatment, it is important to confirm the diagnosis of onychomycosis.

In contrast to the azoles, terbinafine does not inhibit the cytochrome P450 (CYP)3A4 isoenzymes, but it is a potent inhibitor of the CYP2D6 isoenzymes, which are responsible for metabolism of tricyclic antidepressants and other psychotropic drugs.[72,77,83] The most significant drug interactions with terbinafine are decreased clearance of 33% by cimetidine and increased clearance of 100% by rifampin. Other drug interactions of variable clinical significance are tricyclic antidepressants, cyclosporine, caffeine, theophylline, and terfenadine. Itraconazole and its major metabolite can inhibit the CYP3A4 isoenzymes and result in numerous clinically significant drug interactions where coadministration with several drugs are contraindicated (eg, alprazolam, midazolam, triazolam, pimozide, lovastatin, simvastatin, cisapride, and terfenadine).[71,77,83]

Fluconazole is also active against dermatophytes, *Candida* species, and some nondermatophytes;[77,81] however, it does not have current FDA-approved

indication for treatment of onychomycosis. The overall mycologic cure rate of fluconazole is 48%, which is lowest compared with all other oral agents.[87] The most effective dose and treatment duration have not been clearly established, with a variety of dosing regimens used, ranging from 50 mg daily to 300 mg once weekly for 6 to 12 months (see Table 138-8).[77,83] The advantages of fluconazole include a relatively good safety profile and fewer drug interactions compared with itraconazole.[77,83]

These three oral antifungal agents have superseded the use of griseofulvin and ketoconazole as treatments of choice for onychomycosis.[71,81,82] Griseofulvin has a narrow antifungal spectrum, low clinical efficacy, especially for toenail infections, high relapse rates, and the need for prolonged treatment duration (up to 12-18 months for toenails). Use of ketoconazole is also associated with high relapse rates, and the prolonged treatment duration carries an increased risk of hepatotoxicity.

Treatment Response and Recurrence

Treatment failures and recurrence rates of infection following initial cure are high, ranging from 20% to 50%.[72,80] Recurrence could be either a relapse (original infection not completely cured) or reinfection (new infection after achieving a cure of the original). Factors associated with poor response to systemic therapy include a compromised immune system (AIDS), reduced blood flow (diabetes, peripheral vascular disease, vasculitis, connective tissue disease, and CHF), coexisting nail disease (psoriasis), nail factors (slow growth, thick nails, and severe disease), drug-resistant organisms because of extensive prior drug exposure, and reduced bioavailability (absorption problems, poor compliance, and drug interactions).[77,80] To improve treatment outcomes and reduce recurrence, patients should be counseled on the importance of proper foot hygiene, for example, wearing breathable footwear and 100% cotton socks with frequent changes, keeping the nails short and clean, keeping the feet dry, protecting the feet in shared bathing areas, treating tinea pedis, and controlling other predisposing medical conditions.[80]

The use of combination therapy (topical–oral or oral–oral agents) can improve cure rates and shorten treatment duration, as this approach provides complementary mechanisms of attack.[80,81] Favorable results were achieved with itraconazole or terbinafine combined with amorolfine.[80,81] To date, no specific combination has been approved or endorsed for use. Other novel approaches include giving supplemental therapy and use of boosted therapy.[80,81] The

efficacy and role of either approach remain to be defined.

Postclass Engaged Learning Activity

Review patient counselling information for nonprescription treatment of vulvovaginal candidiasis and develop a screening tool that can be used to determine if treatment with nonprescription antifungal agents is appropriate or whether the patient should be referred to a healthcare professional for a KOH preparation and further investigation. Be mindful when developing the screening tool to consider when it is useful to have closed-ended or open-ended questions (closed-ended questions can be answered by a simple "yes" or "no," while open-ended questions require more than a simple one-word answer).

ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
AIDS	acquired immune deficiency syndrome
BMT	bone marrow transplantation
CHF	congestive heart failure
CMI	cell-mediated immunity
CYP	cytochrome P450
FDA	Food and Drug Administration
GI	gastrointestinal
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
HSCT	hematopoietic stem cell transplant
IgA	immunoglobulin A
KOH	potassium hydroxide
MIC	minimum inhibitory concentration
MMT	miconazole mucoadhesive tablet
OPC	oropharyngeal candidiasis
RVVC	recurrent vulvovaginal candidiasis
VVC	vulvovaginal candidiasis

REFERENCES

1. Sobel JD, Faro S, Force R, et al. Vulvovaginal candidiasis: Epidemiologic, diagnostic and therapeutic considerations. *Am J Obstet Gynecol*. 1998;178:203–211.
2. Center for Disease Control and Prevention. Vaginal Discharge-STD Treatment Guidelines. 2006. Available at www.cdc.gov/std/treatment/2006/vaginaldischarge.htm.
3. Haefner HK. Current evaluation and management of vulvovaginitis. *Clin Obstet Gynecol*. 1999;42:184–195.
4. Foxman B, Barlow R, D'arcy H, et al. *Candida* vaginitis self-reported incidence and associated costs. *Sex Transm Dis*. 2000;27:230–235.
5. Fischer G, Bradford J. Vulvovaginal candidiasis in postmenopausal women: The role of hormone replacement therapy. *J Low Genit Tract Dis*. 2011;15:263–237.
6. Lipsky MS, Waters T, Sharp LK. Impact of vaginal antifungal products on utilization of health care services: Evidence from physician visits. *J Am Board Fam Pract*. 2000;13:178–182.
7. Consumers Healthcare Products Association. OTC sales by category 2014-2017. Available at www.chpa.org/OTCsCategory.aspx. Accessed May 2018.
8. Clinical Effectiveness Group. National guideline for the management of vulvovaginal candidiasis. *Sex Transm Infect*. 1999;75(suppl 1):S19–S20.
9. Larsen B. Vaginal flora in health and disease. *Clin Obstet Gynecol*. 1993;36:107–121.
10. Sobel JD. Clinical vulvovaginitis. *Clin Obstet Gynecol*. 1993;36:153–165.
11. Camacho DP, Consolaro ME, Patussi EV, Donatti L, Gasparetto A, Svidzinski TL. Vaginal yeast adherence to the combined contraceptive vaginal ring (CCVR). *Contraception*. 2007;76:439–443.
12. Barbone F, Austin H, Louv WC, Alexander WJ. A follow-up study of the methods of contraception, sexual activity, and rates of trichomoniasis, candidiasis, and bacterial vaginosis. *Am J Obstet Gynecol*. 1990;163:510–514.
13. Xu j, Schwartz k, Bartoces m, Monsur j, Severson RK, Sobel JD. Title Effect of Antibiotics on Vulvovaginal Candidiasis: A MetroNet Study. *J Am Board Fam Med*. 2008;21:261–268.
14. Ferris DG, Dekle C, Litaker MS. Women's use of over-the-counter antifungal pharmaceutical products for gynecologic symptoms. *J Fam*

Pract. 1996;42:595–600.

15. ACOG practice bulletin: Clinical management guidelines for obstetrician-gynecologists. *Obstet Gynecol*. 2006;107:1195–1206.
16. Watson MC, Bond CM, Grimshaw J, Johnston M. Factors predicting the guideline compliant supply (or non-supply) of non-prescription medicines in the community pharmacy setting. *Qual Saf Health Care*. 2006;15:53–57.
17. Martinez RC, Franceschini SA, Patta MC, et al. Improved treatment of vulvaovaginal candidiasis with fluconazole plus probiotic Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14. *Lett Appl Microbiol*. 2009;48:269–274.
18. Abdelmonem AW, Rasheed SM, Mohamed AS. Bee-honey and yogurt: A novel mixture for treating patients with vulvovaginal candidiasis during pregnancy. *Arch Gynecol Obstet*. 2012;8:109–114. doi: 10.1007/s00404-012-2242-5.
19. Hilton E, Isenberg HD, Alperstein P, et al. Ingestion of yogurt containing *Lactobacillus acidophilus* as prophylaxis for candidal vaginitis. *Ann Intern Med*. 1992;116:353–357.
20. Witt A, Kaufmann U, Bitschnau M, et al. Monthly itraconazole versus classic homeopathy for the treatment of recurrent vulvovaginal candidiasis: a randomized trial. *Br J Obstet Gynecol*. 2009;116:1499–1505.
21. Tooley PJ. Patient and doctor preferences in the treatment of vaginal candidiasis. *Practitioner*. 1985;229:655–662.
22. Nurbhai M, Grimshaw J, Watson M, Bond CM, Mollison JA, Ludbrook A. Oral versus intravaginal imidazole and triazole antifungal treatment of uncomplicated vulvovaginal candidiasis (thrush). *Cochrane Database Syst Rev*. 2007;4:CD002845. doi:10.1002/14651858.CD002845.pub2.
23. Edelman DA, Grant S. One-day therapy for vaginal candidiasis a review. *J Reprod Med*. 1999;44:543–547.
24. Mendling W, Plempel M. Vaginal secretion levels after 6 days, 3 days and 1 day of treatment with 100-, 200-, 500-mg vaginal tablets of clotrimazole and their therapeutic efficacy. *Chemotherapy*. 1982;28(suppl 1):43–47.
25. Sobel JD, Kapernick PS, Zervos M, et al. Treatment of complicated candida vaginitis: Comparison of single and sequential doses of fluconazole. *Am J Obstet Gynecol*. 2001;185:363–369.
26. Young G, Jewell D. Topical treatment for vaginal candidiasis (thrush) in

pregnancy. *Cochrane Database Syst Rev*. 2001;4:CD000225. doi:10.1002/14651858.CD000225.

27. Mastroiacovo P, Mazzone T, Botto L, et al. Prospective assessment of pregnancy outcomes after first-trimester exposure to fluconazole. *Am J Obstet Gynecol*. 1996;175:1645–1650.
28. Pursley TJ, Blomquist IK, Abraham J, Andersen HF, Bartley JA. Fluconazole-induced congenital anomalies in three infants. *Clin Infect Dis*. 1996;22:336–340.
29. Sobel JD, Wiesenfeld HC, Martens M, et al. Maintenance fluconazole therapy for recurrent vulvovaginal candidiasis. *N Engl J Med*. 2004;351:363–369.
30. Pappas PG, Kauffman CA, Andes DA, et al. Clinical practice guidelines for the management of candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62(4):e1–e50.
31. Edwards JEJr, Schwartz MM, Schmidt CS, et al. A fungal immunotherapeutic vaccine (NDV-3A) for treatment of recurrent vulvovaginal candidiasis – A phase 2 randomized, double-blind, placebo-controlled trial. *Clin Infect Dis*. 2018;66(12):1928–1936.
32. Sobel JD, Chiam W, Nagappan V, Leaman D. Treatment of vaginitis caused by *Candida glabrata*: Use of topical boric acid and flucytosine. *Am J Obstet Gynecol*. 2003;189:1297–1300.
33. Sobel JD, Chaim W. Treatment of *Torulopsis glabrata* vaginitis: Retrospective review of boric acid therapy. *Clin Infect Dis*. 1996;22:336–340.
34. Ray D, Goswami R, Banerjee U, Dadhawl V, et al. Prevalence of *Candida glabrata* and its response to boric acid vaginal suppositories in comparison with oral fluconazole in patients with diabetes and vulvovaginal candidiasis. *Diabetes Care*. 2007;30:312–317.
35. Leigh JE, Shetty K, Fidel PLJr. Oral opportunistic infections in HIV-positive individuals: Review and role of mucosal immunity. *AIDS Patient Care STDS*. 2004;18:443–456.
36. Farah CS, Lynch N, McCullough MJ. Oral fungal infections: An update for the general practitioner. *Aust Dent J*. 2010;55(1 suppl):48–54.
37. Thompson GRIII, Patel PK, Kirkpatrick WR, et al. Oropharyngeal candidiasis in the era of antiretroviral therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2010;109:488–495.
38. Delgado ACD, de Jesus PR, Aoki FH, et al. Clinical and microbiological

assessment of patients with long-term diagnosis of human immunodeficiency virus infection and *Candida* oral colonization. *Clin Microbiol Infect*. 2009;15:364–371.

39. Laudenbach JM, Epstein JB. Treatment strategies for oropharyngeal candidiasis. *Expert Opin Pharmaocother*. 2009;10(9):1413–1421.
40. Benson CA, Kaplan JE, Masur H, et al. Treating opportunistic infections among HIV-infected adults and adolescents: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. *Clin Infect Dis*. 2004;40:S131–S235.
41. Mercante DE, Leigh JE, Lilly EA, et al. Assessment of the association between HIV viral load and CD4 cell count on the occurrence of oropharyngeal candidiasis in HIV-infected patients. *J Acquir Immune Defic Syndr*. 2006;42:578–583.
42. Soysa NS, Samaranayake LP, Ellepola ANB. Antimicrobials as a contributory factor in oral candidosis: A brief overview. *Oral Dis*. 2008;14:138–143.
43. Pappas PG, Kauffman CA, Andes D, et al. Guidelines for management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48:503–535.
44. Jurevic RJ, Traboulsi RS, Mukherjee PK, et al. Identification of gentian violet concentration that does not stain oral mucosa, possesses anti-candidal activity and is well tolerated. *Eur J Clin Microbiol Infect Dis*. 2011;30(5):629–633.
45. Lalla RV, Bensadoun RJ. Miconazole mucoadhesive tablet for oropharyngeal candidiasis. *Expert Rev Anti Infect Ther*. 2011;9(1):13.
46. Vazquez JA, Patton LL, Epstein JB, et al. Randomized, comparative, double-blind, double-dummy, multicenter trial of miconazole buccal tablet and clotrimazole troches for the treatment of oropharyngeal candidiasis: Study of Miconazole Lauriad® Efficacy and Safety (SMiLES). *HIV Clin Trials*. 2010;11(4):186–196.
47. Hamza OJM, Matee MIN, Bruggemann RJM, et al. Single-dose fluconazole versus standard 2-week therapy for oropharyngeal candidiasis in HIV-infected patients: A randomized, double-blind, double-dummy trial. *Clin Infect Dis*. 2008;47:1270–1276.
48. Vasquez JA, Skiest DJ, Nieto L, et al. A multicenter randomized trial evaluating posaconazole versus fluconazole for the treatment of

oropharyngeal candidiasis in subjects with HIV/AIDS. *Clin Infect Dis*. 2006;42:1179–1186.

49. Bensadoun RJ, Daoud J, El Gueddari B, et al. Comparison of the efficacy and safety of miconazole 50 mg mucoadhesive buccal tablets with miconazole 500 mg gel in the treatment of oropharyngeal candidiasis: a prospective, randomized, single-blind, multicenter, comparative, phase III trial in patients treated with radiotherapy for head and neck cancer. *Cancer*. 2008;112(1):204–211.
50. Villanueva A, Arathoon EG, Gotuzzo E, et al. A randomized double-blind study of caspofungin versus amphotericin for the treatment of candidal esophagitis. *Clin Infect Dis*. 2001;33:1529–1535.
51. Arathoon EG, Gotuzzo E, Noriega LM, et al. Randomized, double-blind, multicenter study of caspofungin versus amphotericin B for treatment of oropharyngeal and esophageal candidiasis. *Antimicrob Agents Chemother*. 2002;46:451–457.
52. Villanueva A, Gotuzzo E, Arathoon EG, et al. A randomized, double-blind study of caspofungin versus fluconazole for the treatment of esophageal candidiasis. *Am J Med*. 2002;113:294–299.
53. Deresinski SC, Stevens DA. Caspofungin. *Clin Infect Dis*. 2003;36:1445–1457.
54. Akpan A, Morgan R. Oral candidiasis. *Postgrad Med J*. 2002;78:455–459.
55. Morris MI, Villmann M. Echinocandins in the management of invasive fungal infections, part 1. *Am J Health Syst Pharm*. 2006;63:1693–1703.
56. Grim SA, Smith KM, Romanelli F, Ofotokun I. Treatment of azole-resistant oropharyngeal candidiasis with topical amphotericin B. *Ann Pharmacother*. 2002;36:1383–1386.
57. Goldman M, Cloud GA, Wade KD, et al. A randomized study of the use of fluconazole in continuous versus episodic therapy in patients with advanced HIV infection and a history of oropharyngeal candidiasis: AIDS clinical trials group study 323/mycoses study group 40. *Clin Infect Dis*. 2005;41:1473–1480.
58. Marr KA, Bow E, Chiller T, et al. Fungal Infection prevention after hematopoietic cell transplantation. *Bone Marrow Transplant*. 2009;44:483–487.
59. Routt ET, Jim On SC, Zeichner JA, Kircik LH. What is new in fungal pharmacotherapeutics? *J Drugs Dermatol*. 2014;13(4) 391–395.
60. Schwartz RA. Superficial fungal infections. *Lancet*. 2004;364:1173–1182.

61. Mendez-Tovar LJ. Pathogenesis of dermatophytosis and tinea versicolor. *Clin Dermatol*. 2010;28:185–189.
62. Hainer BL. Dermatophyte Infections. *Am Fam Physician*. 2003;67:101–108.
63. Drake LA, Dinehart SM, Farmer ER, et al. Guidelines of care for superficial mycotic infections of the skin: Tinea corporis, tinea cruris, tinea faciei, tinea manuum, and tinea pedis. *J Am Acad Dermatol*. 1996;34:282–286.
64. Sahoo AK, Mahajan R. Management of tinea corporis, tinea cruris amd tinea pedis. A comprehensive review. *Dermatol Online J*. 2016;7:77–86.
65. Gupta AK, Chow M, Daniel CR, Aly R. Treatments of tinea pedis. *Dermatol Clin*. 2003;21:431–462.
66. Gupta AK, Chaudhry M, Elewski B. Tinea corporis, tinea cruris, tinea nigra, and piedra. *Dermatol Clin*. 2003;21:395–400.
67. Drake LA, Dinehart SM, Farmer ER, et al. Guidelines of care for superficial mycotic infections of the skin: Tinea capitis and tinea barbae. *J Am Acad Dermatol*. 1996;34:290–294.
68. Higgins EM, Fuller LC, Smith CH. Guidelines for the management of tinea capitis. *Br J Dermatol*. 2000;143:53–58.
69. Ansarun H, Ghaffarpour G. Comparison of effectiveness between ketoconazole 2% and selenium sulfide 2% shampoos in the treatment of tinea versicolor. *Iranian J Derm*. 2005;8:21–25.
70. Effendy I, Lecha M, Feuilhade de Chauvin M, et al. Epidemiology and clinical classification of onychomycosis. *J Eur Acad Dermatol Venereol*. 2005;19(supp11):8–12.
71. Roberts DT, Taylor WD, Boyle J. Guidelines for treatment of onychomycosis. *Br J Dermatol*. 2003;148:402–410.
72. Nunley KS, Cornelius L. Current management of onychomycosis. *J Hand Surg*. 2008;33A:1211–1214.
73. Welsh O, Vera-Cabrera L, Welsh E. Onychomycosis. *Clin Dermatol*. 2010;28:151–159.
74. Kaur R, Kashyap B, Bhalla P. Onychomycosis—Epidemiology, diagnosis and management. *Indian J Med Microbiol*. 2008;26(2):108–116.
75. Baran R, Kaoukhov A. Topical antifungal drugs for the treatment of onychomycosis: An overview of current strategies for monotherapy and combination therapy. *J Eur Acad Dermatol Venereol*. 2005;19:21–29.

76. Tosti A, Hay R, Arenas-Guzman R. Patients at risk of onychomycosis—Risk factor identification and active prevention. *J Eur Acad Dermatol Venereol*. 2005;19(suppl 1):13–16.
77. Iorizzo M, Piraccini BM, Rech G, Tosti A. Treatment of onychomycosis with oral antifungal agents. *Expert Opin Drug Deliv*. 2005;2:435–440.
78. Feuilhade de Chauvin M. New diagnostic techniques. *J Eur Acad Dermatol Venereol*. 2005;19(suppl 1):20–24.
79. Gupta AK, Tu LQ. Onychomycosis therapies: Strategies to improve efficacy. *Dermatol Clin*. 2006;24:381–386.
80. de Berker D. Fungal nail disease. *N Engl J Med*. 2009;360:2108–2116.
81. Lecha M, Effendy I, Feuilhade de Chauvin M, et al. Treatment options—Development of consensus guidelines. *J Eur Acad Dermatol Venereol*. 2005;19(suppl 1):25–33.
82. Gupta AK, Tu LQ. Therapies for onychomycosis: A review. *Dermatol Clin*. 2006;24:375–379.
83. Gupta AK, Ryder JE, Skinner AR. Treatment of onychomycosis: Pros and cons of antifungal agents. *J Cutan Med Surg*. 2004;8:25–30.
84. Gupta AK, Lynch LE, Kogan N, et al. The use of intermittent terbinafine for the treatment of dermatophyte toenail onychomycosis. *J Eur Acad Dermatol Venereol*. 2009;23:256–262.
85. Sigurgeirsson B, Elewski EE, Rich PA, et al. Intermittent versus continuous terbinafine in the treatment of toenail onychomycosis: A randomized, double-blind, comparison. *J Dermatol Treat*. 2006;17:38–44.
86. Warshaw EM, Fett DD, Bloomfield HE, et al. Pulse verus continuous terbinafine for onychomycosis: A randomized, double-blind, controlled trial. *J Am Acad Dermatol*. 2005;53:578–584.
87. Gupta AK, Ryder JE, Johnson AM. Cumulative meta-analysis of systemic antifungal agents for the treatment of onychomycosis. *Br J Dermatol*. 2004;150:537–544.
88. Haugh M, Helou S, Boissel JP, Cribier BJ. Terbinafine in fungal infections of the nails: A meta-analysis of randomized clinical trials. *Br J Dermatol*. 2002;147:118–121.
89. Crawford F, Young P, Godfrey C, et al. Oral treatments for toenail onychomycosis: A systematic review. *Arch Dermatol*. 2002;138:811–816.
90. Cribier BJ, Bakshi R. Terbinafine in the treatment of onychomycosis: A review of its efficacy in high-risk populations and in patients with

nondermatophyte infections. *Br J Dermatol*. 2004;150:414–420.

91. Casciano J, Amaya K, Doyle J, et al. Economic analysis of oral and topical therapies for onychomycosis of the toenails and fingernails. *Manag Care*. 2003;12:47–54.
92. Schram SE, Warshaw EM. Costs of pulse versus continuous terbinafine for onychomycosis. *J Am Acad Dermatol*. 2007;56:525–527.
93. Cham PM, Chen SC, Grill JP, et al. Reliability of self-reported willingness-to-pay and annual income in patients treated for toenail onychomycosis. *Br J Dermatol*. 2007;156:922–928.
94. Food and Drug Administration. FDA issues health advisory regarding the safety of Sporanox products and Lamisil tablets to treat finger nail infections. 2001. Available at www.fda.gov/cder/drug/advisory/sporanox-lamisil/advisory.htm.
95. Gupta AK, Chwetzoff, Del Rosso J, Baran R. Hepatic safety of itraconazole. *J Cutan Med Surg*. 2002;6:210–213.

Invasive Fungal Infections

Peggy L. Carver

KEY CONCEPTS

1. Systemic mycoses can be caused by pathogenic fungi and include histoplasmosis, coccidioidomycosis, cryptococcosis, blastomycosis, paracoccidioidomycosis, and sporotrichosis, or infections by opportunistic fungi such as *Candida albicans*, *Aspergillus* species, *Trichosporon*, *Candida glabrata*, *Fusarium*, *Alternaria*, and *Mucor*.
2. The diagnosis of fungal infection generally is accomplished by careful evaluation of clinical symptoms, results of serologic tests, and histopathologic examination and culture of clinical specimens. Rapid, accurate diagnostic laboratory tests are currently under development.
3. Histoplasmosis is caused by *Histoplasma capsulatum* and is endemic in parts of the central United States along the Ohio and Mississippi River valleys. Although most patients experience asymptomatic infection, some can experience chronic, disseminated disease.
4. Asymptomatic patients with histoplasmosis are not treated, although patients who do not have acquired immune deficiency syndrome (AIDS)—patients with evident disease—are treated with either oral ketoconazole or IV amphotericin B; AIDS patients are treated with amphotericin B and then receive lifelong suppression.
5. Blastomycosis is caused by *Blastomyces dermatitidis*. In the immunocompetent host, acute pulmonary blastomycosis can be mild and self-limited and may not require treatment. However, consideration should be given to treating all infected individuals to prevent extrapulmonary dissemination. All persons with moderate-to-severe pneumonia, disseminated infection, or those who are immunocompromised require antifungal therapy.
6. Coccidioidomycosis is caused by *Coccidioides immitis* and is endemic in

some parts of the southwestern United States. It can cause nonspecific symptoms, acute pneumonia, or chronic pulmonary or disseminated disease. Primary pulmonary disease (unless severe) frequently is not treated, whereas extrapulmonary disease is treated with amphotericin B, and meningitis is treated with fluconazole.

7. Cryptococcosis is caused by *Cryptococcus neoformans*, which occurs primarily in immunocompromised patients, and *Cryptococcus gattii*, which occurs primarily in nonimmunocompromised patients. Patients with acute meningitis are treated with amphotericin B with flucytosine. Patients infected with human immunodeficiency virus (HIV) often require long-term suppressive therapy with fluconazole or itraconazole.
8. A variety of *Candida* species (including *C. albicans*, *C. glabrata*, *Candida tropicalis*, *Candida parapsilosis*, and *Candida krusei*) can cause diseases such as mucocutaneous, oral, esophageal, vaginal, and hematogenous candidiasis, as well as candiduria. Candidema can be treated with a variety of antifungal agents; the optimal choice depends on previous patient exposure to antifungal agents, potential drug interactions and toxicities of each agent, and local epidemiology of intensive care unit (ICU) or hematology–oncology centers.
9. Aspergillosis can be caused by a variety of *Aspergillus* species that can cause superficial infections, pneumonia, allergic bronchopulmonary aspergillosis (BPA), or invasive infection. Voriconazole has emerged as the drug of choice of most clinicians for primary therapy of most patients with invasive aspergillosis (IA). Combination therapy, while widely used, lacks clinical trial data to support its use.

Preclass Engaged Learning Activity

Watch the following two videos, which provide a brief (9:48) overview of the epidemiology, diagnosis, and treatment of candidemia

Candida: Systemic Candidiasis Treatment & Prevention.
https://tinyurl.com/u22fqmt

INTRODUCTION

Advances in medical technology including organ and bone marrow transplantation, cytotoxic chemotherapy, the widespread use of indwelling IV catheters, and the increased use of potent broad-spectrum antimicrobial agents all have contributed to the dramatic increase in the incidence of fungal infections worldwide.[1–3] Problems remain in the diagnosis, prevention, and treatment of fungal infections.[1,4–6] The Infectious Diseases Society of America (IDSA) publishes guidelines regarding the prophylaxis and treatment of many commonly encountered fungal infections.[7–11,131]

MYCOLOGY

Fungi are eukaryotic organisms with a defined nucleus enclosed by a nuclear membrane; a cytoplasmic membrane containing lipids, glycoproteins, and sterols, mitochondria, golgi apparatus, and ribosomes bound to endoplasmic reticulum; and a cytoskeleton with microtubules, microfilaments, and intermediate filaments. Fungi have rigid cell walls composed of chitin, cellulose, or both that stain with Gomori methenamine silver or periodic acid–Schiff reagent. Most fungi, except *Candida* species, are too weakly gram-positive to be seen well on Gram stain. *Cryptococcus neoformans* has a polysaccharide capsule surrounding the cell wall.[1]

Morphologically, pathogenic fungi can be grouped as either filamentous molds or unicellular yeasts (**Fig. 139-1**). *Molds* grow as multicellular branching, threadlike filaments (hyphae) that are either septate (divided by transverse walls) or coenocytic (multinucleate without cross walls). Yeasts are oval or spherically shaped unicellular forms that generally produce pasty or mucoid colonies on agar medium similar to those observed with bacterial cultures. Yeasts have rigid cell walls and reproduce by budding, a process in which daughter cells arise from pinching off a portion of the parent cell.

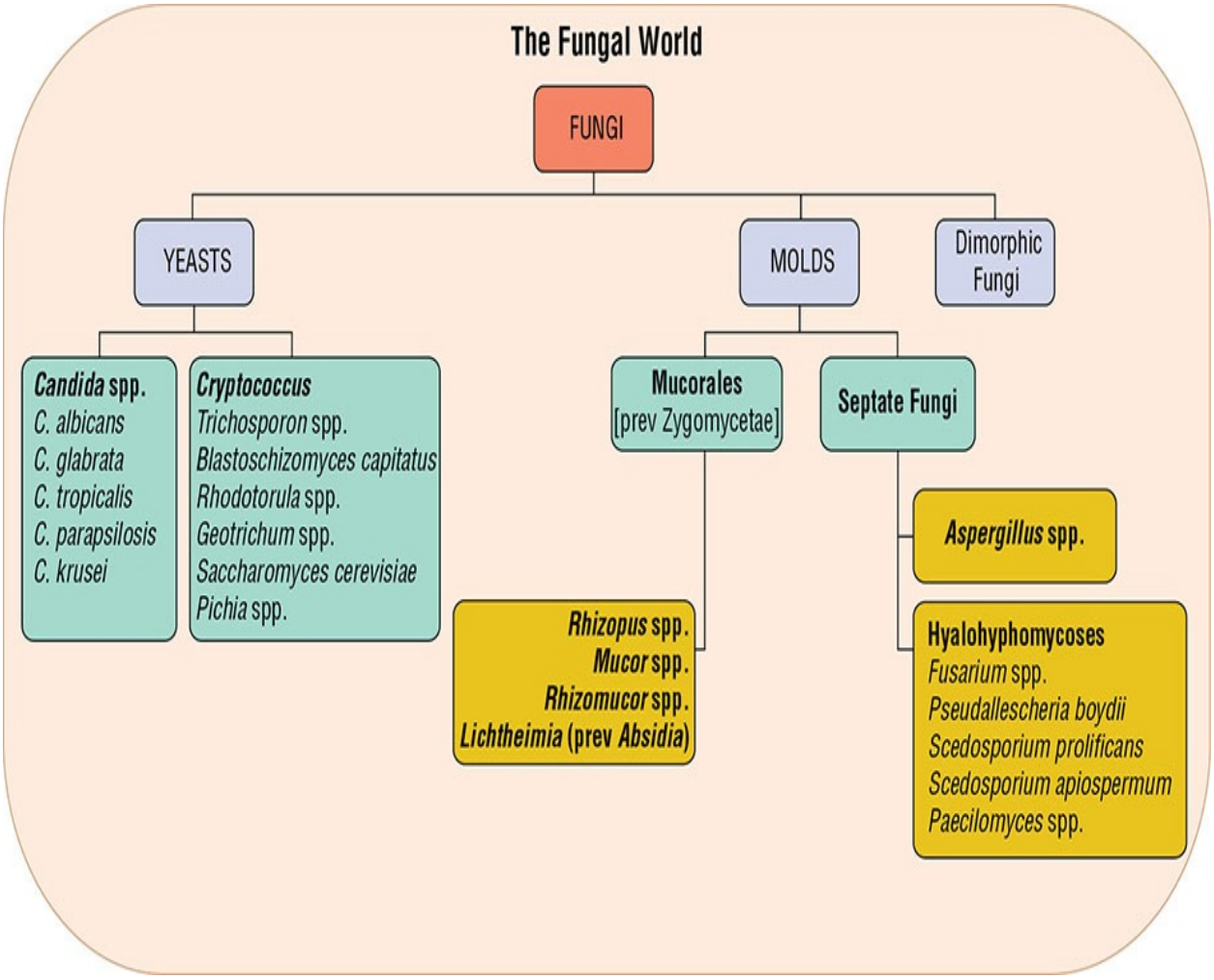


FIGURE 139-1 Morphologically, pathogenic fungi can be grouped as either filamentous molds or unicellular yeasts. Molds grow as multicellular branching, thread-like filaments (hyphae) that are either septate (divided by transverse walls) or coenocytic (multinucleate without crosswalls).

Many pathogenic fungi, termed *dimorphic fungi*, exist as either a yeast or a mold, depending on pathogen, site of growth (in the host or in the laboratory setting), and temperature. Usually yeasts are the parasitic form that invades human or animal host tissue, whereas molds are the free-living form found in the environment. For example, *Histoplasma capsulatum* exists as a yeast in humans and as a mold in the laboratory.[1]

Clinical Versus Microbial Resistance

Host factors contribute greatly to clinical outcome. A patient may respond clinically to treatment with an antifungal agent despite resistance to that agent in

vitro because the patient's own immune system may eradicate the infection, or the agent may reach the site of infection in high concentrations.[12] Thus, in vitro susceptibility does *not* necessarily equate with in vivo clinical success, and in vitro resistance might *not* always correlate with treatment failure.

It is important to distinguish between clinical resistance and microbial resistance. *Clinical resistance* refers to failure of an antifungal agent in the treatment of a fungal infection that arises from factors other than microbial resistance, such as failure of the antifungal agent to reach the site of infection or inability of a patient's immune system to eradicate a fungus whose growth is retarded by an antifungal agent.[12,13]

Microbial resistance can refer to *primary* or *secondary* resistance, as determined by in vitro susceptibility testing using standardized methodology. *Primary* or *intrinsic resistance* refers to resistance recorded prior to drug exposure in vitro or in vivo. *Secondary* or *acquired resistance* develops on exposure to an antifungal agent and can be either reversible, owing to transient adaptation, or acquired as a result of one or more genetic alterations. It is possible for a patient to respond clinically to treatment with an antifungal agent, despite resistance to that agent in vitro, because the patient's own immune system may eradicate the infection, or the agent reaches the site of infection in high concentrations.[6]

Susceptibility Testing of Antifungal Agents

Most laboratories do not routinely perform susceptibility tests on fungal isolates, but standardized methods for performing these tests are being developed and are now available for testing selected yeasts. As the prevalence of nosocomial and community-acquired fungal infections become more prominent, the need for in vitro susceptibility testing increases. Susceptibility testing occasionally is indicated, for example, in a patient with prolonged fungemia with a presumed susceptible isolate, and is most helpful in dealing with infections caused by non-*albicans* species of *Candida*.[5–7]

Clinical breakpoints (CBPs) are antimicrobial concentrations (MICs) obtained from susceptibility testing, which are used to define isolates as susceptible, intermediate, or resistant. No CBPs have been established for posaconazole, isavuconazole, or amphotericin B versus *Candida*, or for antifungal agents and filamentous fungi such as *Aspergillus*.[6] CBPs can be used to differentiate strains for which there is a high likelihood of treatment success (organisms that are clinically susceptible, or (S), from those for which treatment is more likely to

fail (clinically resistant [R]). (Tables 139-1–139-3). A clinically intermediate (I) or susceptible dose-dependent (SDD) category can be assigned to pathogens for which the level of antimicrobial agent activity is associated with uncertain therapeutic effect, implying that infections due to the isolate may be appropriately treated in body sites where the drugs are physically concentrated or when a high dosage of drug can be used. Although CBPs are designed to guide therapy, they do not distinguish between fungal isolates with or without resistance mechanisms, nor do they always allow for early detection of resistant isolates. Table 139-3 shows the currently approved interpretive CBPs for *Candida* species.

TABLE 139-1 General Patterns of Susceptibility and Interpretive Breakpoints of *Candida* Species[a]

Patterns of Susceptibility									
	Azoles					Echinocandins			Amphotericin
Candida Species	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Isavuconazole	Caspofungin	Micafungin	Anidulafungin	Amphotericin B
C. albicans	S	S	S	S	S	S	S	S	S
C. tropicalis	S	S	S	S	S	S	S	S	S
C. parapsilosis	S	S	S	S	S	S[b]	S[b]	S[b]	S
C. glabrata	S	S	S	S	S	S	S	S	S-I[c]
	S-DD to R[d]	S-DD to R[e]							
C. krusei	R	S-DD to R[e]	S	S	S	S	S	S	S-I[c]
C. lusitaniae	S	S	S	S	S	S	S	S	S to R[f]

[a]Except for amphotericin B, interpretations are based on the use of a broth sensitivity test.

[b]Most isolates of *C. parapsilosis* have reduced susceptibility to echinocandins.

[c]A significant proportion of *C. glabrata* and *C. krusei* isolates has reduced susceptibility to amphotericin B.

[d]Approximately 15% of *C. glabrata* isolates are resistant to fluconazole.

[e]Approximately 46% of *C. glabrata* isolates and 31% of *C. krusei* isolates are resistant to itraconazole.

[f]Although frank resistance to amphotericin B is not observed in all isolates, it is well described for isolates of *C. lusitaniae*

For antifungal drugs and pathogens for which susceptibility breakpoints have been established (fluconazole, itraconazole, voriconazole): S, susceptible; S-DD, susceptible-dose dependent (see the text); I, intermediate; R, resistant; NA, not applicable (has not been established for this antifungal against this pathogen).

Data from References 5, 6, 14 and 62.

TABLE 139-2 General Patterns of In Vitro Susceptibility of Non-*Candida* Fungal Pathogens[a]

Patterns of Susceptibility									
	Azoles						Echinocandins		Amphotericin B
Pathogen	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Isavuconazole	Caspofungin	Micafungin	Anidulafungin	Amphotericin B
Aspergillus									
A. fumigatus	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
A. flavus	No	Yes	Yes	Yes		Yes	Yes	Yes	Yes
A. terreus	No	Yes	Yes			Yes			No
Fusarium	No	No	Yes (but breakthrough infections are seen)	Conflicting data (species dependent)	Variable	No	No	No	Yes but occasional resistance
Scedosporium	No	No	Yes	Yes (*apiospermum*)	Variable	No	No	No	No
Zygomycetes[b]	No	No	No	Yes	Yes	No	No	No	Yes
Trichosporon	No	No	Yes	Yes	Yes	No	No	No	No
Cryptococcus	Yes	Yes	Yes	Yes	Yes	No	No	No	
Histoplasma	Yes	Yes	Yes	Yes	Yes	No[c]	No[c]	No[c]	Yes
Coccidioides	Yes	Yes	Yes	Yes	Yes	No[c]	No[c]	No[c]	Yes

[a]No = has minimal or no in vitro activity versus the pathogen; Yes = possesses adequate in vitro activity versus the pathogen.

[b]Includes *Rhizopus*, *Mucor*, and *Absidia* species.

[c]While the echinocandins display activity against the mycelial forms of endemic fungi such as *Histoplasma* spp., *Blastomyces* spp., and *Coccidioides* spp., they display significantly higher MIC values against the yeast forms of these organisms, and should not be used to treat these infections.

Data from References 5, 6, 15 and 67.

TABLE 139-3 Clinical Breakpoints for *Candida* Species and Azole Antifungals[5,6]

Drug*	Species	Interpretive Clinical Breakpoints (mg/L)			
		S	I	SDD	R
Fluconazole	*C. albicans*	≤2	---	4	≥8
	C. glabrata	---	---	≤32	≥64
	C. krusei	---	---	---	---
	C. parapsilosis	≤2	---	4	≥8
	C. tropicalis	≤2	---	4	≥8
Voriconazole	*C. albicans*	≤0.12	0.25-0.5	---	≥1
	C. glabrata	---	---	---	---
	C. krusei	≤0.5	1	---	≥2
	C. parapsilosis	≤0.12	0.25-0.5	---	≥1
	C. tropicalis	≤0.12	0.25-0.5	---	≥1
Posaconazole	*C. albicans*	---	---	---	---
	C. glabrata	---	---	---	---
	C. krusei	---	---	---	---
	C. parapsilosis	---	---	---	---
	C. tropicalis	---	---	---	---

*CBPs have not been established for isavuconazole by CLSI.

S, susceptible; I, intermediate; SDD, susceptible-dose dependent; R, resistant; ---, not defined or not applicable

Resistance to Antifungal Agents

Understanding mechanisms of resistance is an important process in the optimization of antifungal therapy. The most exhaustive and definitive accounts of antifungal resistance have been described in *Candida* species, in particular *Candida albicans* and, to a lesser extent, *Candida glabrata*, *Candida tropicalis*, and *Candida krusei*, as well as in a few *C. neoformans* isolates.[12,13] *C. glabrata* isolates are increasingly resistant to both azole and echinocandin antifungal agents.

There are four different mechanisms that result in azole resistance: (a) mutations or upregulation of *ERG11* (an enzyme involved in the ergosterol biosynthesis pathway), (b) expression of multidrug efflux transport pumps that decrease antifungal drug accumulation within the fungal cell, (c) alteration of the structure or concentration of antifungal drug target proteins, and (d) alteration of

membrane sterol proteins (Fig. 139-2). Although detailed analysis of each of the elucidated mechanism of resistance is beyond the scope of this chapter, interested readers are referred to several recent publications that have comprehensively summarized this topic.[12,13,16]

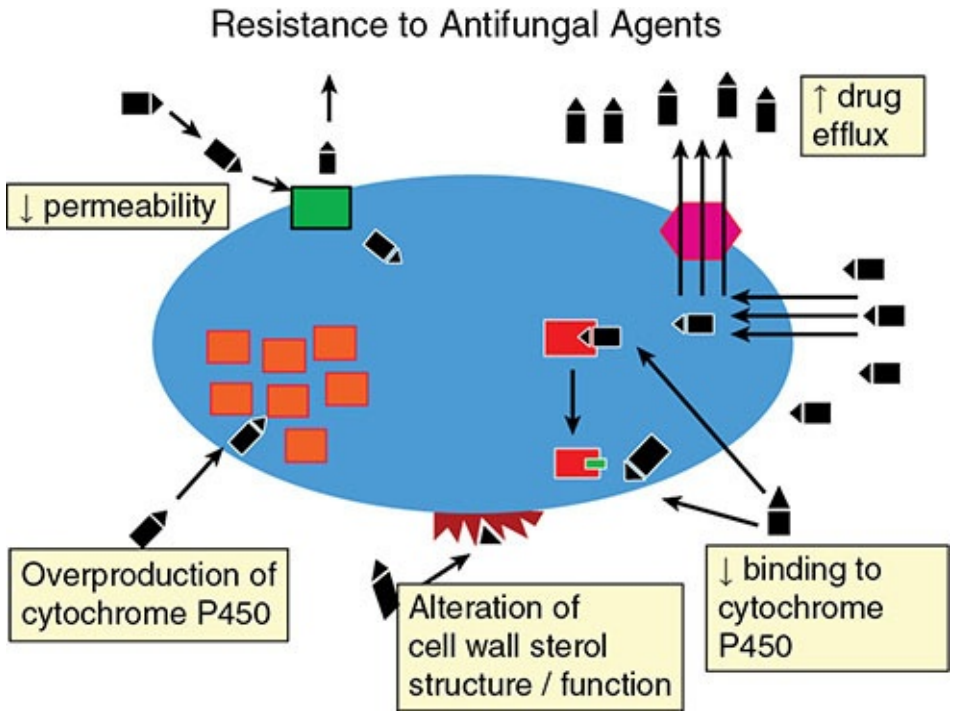


FIGURE 139-2 Mechanisms of azole resistance. Four different mechanisms result in azole resistance: (a) mutations or upregulation of *ERG11*, the target enzyme of azoles, (b) expression of multidrug efflux transport pumps that decrease antifungal drug accumulation within the fungal cell, (c) alteration of the structure or concentration of antifungal drug target proteins, and (d) alteration of membrane sterol proteins.

The most commonly reported mechanisms of azole resistance among *C. albicans* isolates include reduced permeability of the fungal cell membrane to azoles, modification or overproduction of the target fungal enzymes (cytochrome P450, CYP) resulting in decreased binding of the azole to the target site, alterations in sterol synthesis, and activation of efflux pumps capable of actively pumping azoles from the target pathogen.

Fluconazole resistance is observed most frequently in *C. glabrata*, which is often resistant, and in *C. krusei*, for which fluconazole resistance is universal.

With the increase in echinocandin use, there has been an increase in the number of reports of echinocandin-resistant isolates from patients failing therapy. Echinocandin exposure and previous episodes of *C. glabrata* are

predictors of FKS gene mutations in *Candida*.[17–19]

Although, to date, the rate of amphotericin B resistance remains low, the exact incidence remains difficult to quantify and the response to antifungal agents difficult to characterize. As such, no consensus for therapy has been formulated at this time, although clinicians should keep in mind that *C. glabrata*, *Candida guilliermondii*, *C. krusei*, and *Candida lusitaniae* may have a higher propensity to developing resistance than other species.

Acquired resistance of *Aspergillus* species during long-term azole exposure to azoles, while still relatively uncommon, is emerging, and varies widely between geographic centers. Acquisition of primary-resistant isolates is also increasing, due to the agricultural use of azoles.[127] Cross-resistance of azole-resistant strains of *Aspergillus* to amphotericin B has not been described. Azole resistance among *Aspergillus* spp. (specifically *A. fumigatus*) is predominantly mediated by specific point mutations in TR/L98H in the CYP51A gene promoter region, causing amino acid changes and tandem repeats, and often results in cross-resistance with azole antifungals.[83]

Epidemiology and Pathogenesis

Systemic mycoses caused by primary or pathogenic fungi include histoplasmosis, coccidioidomycosis, cryptococcosis, blastomycosis, paracoccidioidomycosis, and sporotrichosis. Primary pathogens can cause disease in both healthy and immunocompromised individuals, although disease generally is more severe or disseminated in the immunocompromised host. In contrast, mycoses caused by opportunistic fungi such as *C. albicans*, *Aspergillus* species, *Trichosporon*, *Torulopsis (Candida) glabrata*, *Fusarium*, *Alternaria*, and *Mucor* generally are found only in the immunocompromised host.[1]

Most fungal infections are acquired as a result of accidental inhalation of airborne conidia. For example, *H. capsulatum* is found in soil contaminated by bat, chicken, or starling excreta, and *C. neoformans* is associated with pigeon droppings. Although some fungi, including *C. albicans*, *C. neoformans*, and *Aspergillus* species, are ubiquitous pathogens with worldwide distribution, other fungi have regional distributions associated with specific geographic environments.[1]

Invasive fungal infections are a major cause of morbidity and mortality in the immunocompromised patient.[21,22] In patients with hematologic malignancies and following hematopoietic stem cell transplantation (HSCT), there has been a shift in the most commonly encountered IFIs from *Candida* spp. to *Aspergillus*

spp. *Candida* species (primarily *C. albicans*) are the fourth most commonly isolated bloodstream isolate and account for 78% of all nosocomial fungal infections.[15]

Nosocomially acquired fungal infections can arise from either exogenous or endogenous flora. Endogenous flora can include normal commensal organisms of the skin, GI, genitourinary, or respiratory tract. *C. albicans* is found as a normal commensal of the GI tract in 20% to 30% of humans. A complex interplay of host and pathogen factors influences the acquisition and development of fungal infections. Intact skin or mucosal surfaces serve as primary barriers to infection. Alterations in the balance of normal flora caused by the use of antibiotics or alterations in nutritional status can allow the proliferation of fungi such as *Candida*, increasing the likelihood of systemic invasion and infection.[1]

Patients with decreased neutrophil counts or decreased neutrophil function are at higher risk of infections, particularly infections caused by *Candida* and *Aspergillus* species. Fungal cells sometimes can persist within macrophages without being killed, perhaps because of resistance to the effects of lysosomal enzymes.[1]

Risk Factors for Fungal Infections

Increasing use of aggressive and intensive cancer chemotherapeutic regimens, immunosuppressive therapy for autoimmune disorders, and transplantation have led to an increase in the number of susceptible hosts, contributing to the changing epidemiology of fungal infections. Infection epidemiology can drastically vary depending on patients' underlying concomitant conditions, comorbidities, confounding risk factors, and geographical area.

A clinical indicator for a patient's immunologic status is the quantitation of absolute neutrophil count (ANC). Neutropenia, defined as an ANC $\leqq 500/mm^3$ ($0.5 \times 10^9/L$), dramatically escalates the risk of acquiring and opportunistic infection. However, the shift in fungemic pathogens occur in both neutropenic and non-neutropenic patients.

There is an increased prevalence of fungemia in the general in-patient setting and in critically-ill, neutropenic, and transplant patients.[25–27] Major risk factors for *Candida* blood stream infections (BSIs) in ICU patients include the use of central venous catheters (CVCs), receipt of multiple antibiotics or parenteral nutrition (PN), extensive surgery and burns, renal failure and hemodialysis, mechanical ventilation, and prior fungal colonization.[53]

Diagnosis and Rapid Diagnostic Tests

2 Traditionally, the diagnosis of invasive fungal infections (IFIs) is accomplished by careful evaluation of clinical symptoms, results of serologic tests, and histopathologic examination and culture of clinical specimens. While traditional direct microscopy, culture and histological techniques constitute the "gold standard" for diagnosis, obtaining biopsies from sterile body sites for these studies is a highly invasive approach that may not be possible in severely ill patients. Also, histopathology lacks sensitivity and selectivity, as several filamentous fungi may exhibit undistinguishable morphologies. Further, the finding of a positive culture from a sterile site may indicate transient colonization and not true infection, especially for opportunistic fungi. Fungi may require special laboratory conditions, with additional time (up to 4 days) required in order to obtain species identification and the results of susceptibility testing. Some species, such as *C. glabrata*, tend to grow more slowly; initial identification of yeast from blood averages 100 hours (~4 days) in most institutions.[28] Several rapid, accurate diagnostic laboratory tests, including matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF), peptide nucleic acid (PNA) in situ hybridization (PNA-FISH), PCR, galactomannan, and T2 magnetic resonance assays, have the potential to enhance sensitivity and speed of diagnosis of IFIs.[29,30]

New laboratory methods that allow for early differentiation of IFIs due to *Aspergillus* species versus zygomycetes and other moulds would be helpful in allowing clinicians in the earlier initiation of appropriate antifungal therapy. These underscore the need for rapid diagnosis and identification of clinically significant isolates to species level, and the need for susceptibility testing.[31]

TREATMENT

Invasive Mycoses

Strategies for the prevention or treatment of invasive mycoses can be classified broadly as prophylaxis, early empirical therapy, empirical therapy, and secondary prophylaxis or suppression.[1] In patients undergoing cytotoxic chemotherapy, antifungal therapy is directed primarily at the prevention or treatment of infections caused by *Candida* and *Aspergillus* species. Prophylactic therapy with topical, oral, or IV antifungal agents is administered prior to and throughout periods of granulocytopenia (absolute

> neutrophil count ≤ 1,000 cells/µL [1×10^9/L]). The potential benefits of prophylactic therapy must be weighed against the potential risks inherent in each regimen, including safety, efficacy, cost, the prevalence of infection, and the potential consequences (eg, resistance) of widespread use.

Early empirical therapy is the administration of systemic antifungal agents at the onset of fever and neutropenia. Empirical therapy with systemic antifungal agents is administered to granulocytopenic patients with persistent or recurrent fever despite the administration of appropriate antimicrobial therapy.

Secondary prophylaxis (or *suppressive therapy*) is the administration of systemic antifungal agents (generally prior to and throughout the period of granulocytopenia) to prevent relapse of a documented invasive fungal infection that was treated during a previous episode of granulocytopenia.

Although these treatment classifications also have been applied to the treatment of fungal infections in acquired immunodeficiency syndrome (AIDS), patients with AIDS rarely acquire systemic infections caused by *Candida* or *Aspergillus* species, unless they become granulocytopenic because of disease or drugs.

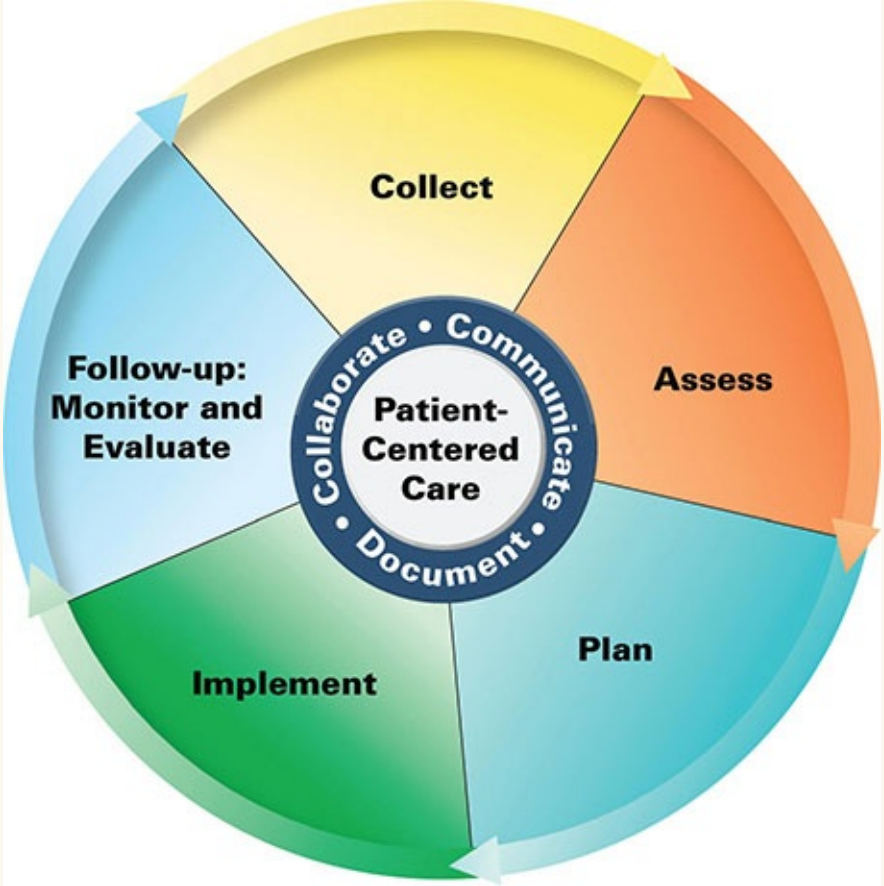
HISTOPLASMOSIS

In humans, histoplasmosis is caused by inhalation of dust-borne microconidia of the dimorphic fungus *H. capsulatum*. Although there exist two dimorphic varieties of *H. capsulatum*, the small-celled (2-5 microns) form (var. *capsulatum*) occurs globally, whereas the large-celled (8-15 microns) form (var. *duboisii*) is confined to the African continent and Madagascar. In tissues stained by conventional techniques, *H. capsulatum* appears as an oval or round, narrow-pore, budding, unencapsulated yeast.[32]

Epidemiology

3 Although histoplasmosis is found worldwide, certain areas of North and Central America are recognized as endemic areas. In the United States, most disease is localized along the Ohio and Mississippi River valleys, where more than 90% of residents may be affected. Precise reasons for this endemic distribution pattern are unknown but are thought to include moderate climate, humidity, and soil characteristics. *H. capsulatum* is found in nitrogen-enriched soils, particularly those heavily contaminated by avian or bat guano, which

accelerates sporulation. Blackbird or pigeon roosts, chicken coops, and sites frequented by bats, such as caves, attics, or old buildings, serve as “microfoci” of infections; once contaminated, soils yield *Histoplasma* for many years. Although birds are not infected because of their high body temperature, bats (mammals) may be infected and can pass yeast forms in their feces, allowing the spread of *H. capsulatum* to new habitats. Air currents carry the spores for great distances, exposing individuals who were unaware of contact with the contaminated site.[32]



Patient Care Process for Candidemia

Collect

- Patient characteristics (eg, age, sex, pregnant)
- Patient medical history (personal and family)

- Social history (eg, intravenous drug use)
- Current medications including OTC aspirin/NSAID use, herbal products, dietary supplements, and prior antifungal therapy
- Prior antifungal therapy (if applicable)
- Objective data
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2-saturation
  - Labs including white blood cells (WBC) with differential, hemoglobin (Hgb), platelets, serum creatinine (SCr), liver function tests (LFTs), blood cultures and susceptibility data
  - Objective confirmation of candidemia (+ blood cultures)

Assess

- Hemodynamic stability (eg, systolic BP 110 bpm, O_2-sat <90% [0.90], RR)
- Presence of
  - Ability/willingness to pay for antifungal agents
- Ability/willingness to obtain laboratory monitoring tests
- Emotional status (eg, presence of anxiety, depression)

Plan*

- Empiric drug therapy regimen including specific antifungal agent(s), dose, route, frequency, and duration; (see **Table 139-9**) and plan for step-down antifungal therapy, if appropriate, based upon blood culture results (*Candida* species) of susceptibility testing, patient specific factors (eg, LFTs, SCr, prior antifungal therapy, severity of illness)
- Monitoring parameters including efficacy including signs and symptoms of infection, temperature, BP, HR, WBC, daily blood cultures until negative cultures are obtained, transthoracic or transesophageal echocardiogram (TTE or TEE), ophthalmological exam) and safety (eg, LFTs, SCr, rash)
- Patient education (eg, purpose of treatment, drug-specific information)
- Referrals to other providers when appropriate (eg, ophthalmology)

Implement*

- Provide patient education regarding all elements of treatment plan
- Schedule follow-up (eg, labs, susceptibility data)

Follow-up: Monitor and Evaluate

- Resolution of symptoms (eg, shortness of breath, chest pain, limb swelling, redness, pain)
- Presence of adverse effects (three- to fivefold increase in LFTs, increased Scr, presence of rash)
- Patient adherence to treatment plan using multiple sources of information
- Re-evaluate antifungal agent(s) to assess need for specific therapy (pathogen-directed, based upon results of blood cultures) including step-down antifungal therapy, once final blood cultures and the results of susceptibility testing are available
- Re-evaluate duration of therapy as blood culture and other laboratory data becomes available after the start of therapy (see text)

**Collaborate with patient, caregivers, and other healthcare professionals.*

Pathophysiology

At ambient temperatures, *H. capsulatum* grows as a mold. The mycelial phase consists of septate branching hyphae with terminal micro- and macroconidia that range in size from 2 to 14 microns in diameter. When soil is disturbed, these conidia become aerosolized and reach the bronchioles or alveoli.[32]

Animal studies demonstrate that within 2 to 3 days after reaching lung tissue, the conidia germinate, releasing yeast forms that begin multiplying by binary fission. During the next 9 to 15 days, organisms are ingested but not destroyed by large numbers of macrophages that are recruited to the infected site, resulting in small infiltrates. Infected macrophages migrate to the mediastinal lymph nodes and other sites within the mononuclear phagocyte system, particularly the spleen and liver. At this time, the onset of specific T-cell immunity in the nonimmune host activates the macrophages, rendering them capable of fungicidal activity. Tissue granulomas form, many of which develop central caseation and necrosis over the next 2 to 4 months. Over a period of several

years, these foci become encapsulated and calcified, often with viable yeast trapped within the necrotic tissue.[32]

Cellular immunity, as measured by histoplasmin skin-test reactivity, wanes in the absence of occasional reexposure. Although exposure to heavy inocula can overcome these immune mechanisms, resulting in severe disease, reinfection occurs frequently in endemic areas. In the immune individual, the reactions of acquired immunity begin 24 to 48 hours after the appearance of yeast forms, resulting in milder forms of illness and little proliferation of organisms. Although viable organisms can be found within granulomas years after initial infection, the organisms appear to have little ability to proliferate within the fibrous capsules, except in immunocompromised patients.[32]

Clinical Presentation

The outcome of infection with *H. capsulatum* depends on a complex interplay of host, pathogen, and environmental factors.[10,32] Host factors include the degree of immunosuppression and the presence of immunity (from prior infection). Environmental factors include inoculum size, exposure within an enclosed area, and duration of exposure. Hematogenous dissemination from the lungs to other tissues probably occurs in all infected individuals during the first 2 weeks of infection before specific immunity has developed but is nonprogressive in most cases, which leads to the development of calcified granulomas of the liver and/or spleen. Progressive pulmonary infection is common in patients with underlying centrilobular emphysema.

Acute and chronic manifestations of histoplasmosis appear to result from unusual inflammatory or fibrotic responses to the pathogen, including pericarditis and rheumatologic syndromes during the first year after exposure, with chronic mediastinal inflammation or fibrosis, broncholithiasis, and enlarging parenchymal granulomas later in the course of disease.

In the vast majority of patients, low-inoculum exposure to *H. capsulatum* results in mild or asymptomatic pulmonary histoplasmosis. The course of disease generally is benign, and symptoms usually abate within a few weeks of onset. Patients exposed to a higher inoculum during an acute primary infection or reinfection can experience an acute, self-limited illness with flu-like pulmonary symptoms, including fever, chills, headache, myalgia, and a nonproductive cough. Patients with diffuse pulmonary histoplasmosis can have diffused radiographic involvement, become hypoxic, and require ventilatory support. A low percentage of patients present with arthritis, erythema nodosum,

pericarditis, or mediastinal granuloma.

Chronic pulmonary histoplasmosis generally presents as an opportunistic infection imposed on a preexisting structural abnormality, such as lesions resulting from emphysema. Patients demonstrate chronic pulmonary symptoms and apical lung lesions that progress with inflammation, calcified granulomas, and fibrosis. Patients with early, noncavitary disease often recover without treatment. Progression of disease over a period of years, seen in 25% to 30% of patients, is associated with cavitation, bronchopleural fistulas, extension to the other lung, pulmonary insufficiency, and often death.

In patients exposed to a large inoculum and in immunocompromised hosts, successful containment of the organism within macrophages may not occur, resulting in a progressive illness characterized by yeast-filled phagocytic cells and an inability to produce granulomas. This disease, termed *disseminated histoplasmosis*, is characterized by persistent parasitization of macrophages. The clinical severity of the diverse forms of disseminated histoplasmosis (**Table 139-4**) generally parallels the degree of macrophage parasitization observed.

TABLE 139-4 Clinical Manifestations and Therapy of Histoplasmosis

Type of Disease and Common Clinical Manifestations	Approximate Frequency (%)*	Therapy/Comments
Nonimmunosuppressed Host		
Acute pulmonary histoplasmosis		
Asymptomatic or mild-to-moderate disease	50-99	*Asymptomatic, mild, or symptoms <4 weeks:* No therapy generally required. Itraconazole (200 mg three times daily for 3 days and then 200 mg once or twice daily for 6-12 weeks) is recommended for patients who continue to have symptoms for 11 months *Symptoms >4 weeks:* Itraconazole 200 mg once daily × 6-12 weeks†
Self-limited disease	1-50	*Self-limited disease:* Amphotericin B‡ 0.3-0.5 mg/kg/day IV × 2-4 weeks (total dose 500 mg) or ketoconazole 400 mg orally daily × 3-6 months can be beneficial in patients with severe hypoxia following inhalation of large inocula; antifungal therapy generally not useful for arthritis or pericarditis; NSAIDs or corticosteroids can be useful in some cases
Mediastinal granulomas	1-50	Most lesions resolve spontaneously; surgery or antifungal therapy with amphotericin B 40-50 mg/day IV × 2-3 weeks or itraconazole 400 mg/day orally × 6-12 months can be beneficial in some severe cases; mild-to-moderate disease can be treated with itraconazole for 6-12 months
Moderately severe to severe diffuse pulmonary disease		Lipid amphotericin B 3-5 mg/kg/day IV followed by itraconazole 200 mg twice daily for 3 days then twice daily for a total of 12 weeks of therapy; alternatively, in patients at low risk for nephrotoxicity, amphotericin B deoxycholate 0.7-1 mg/kg/day IV can be utilized; methylprednisolone (0.5-1 mg/kg daily IV) during the first 1-2 weeks of antifungal therapy is recommended for patients who develop respiratory complications, including hypoxemia or significant respiratory distress
Inflammatory/fibrotic disease	0.02	*Fibrosing mediastinitis:* The benefit of antifungal therapy (itraconazole 200 mg orally twice daily × 3 months) is controversial but should be considered, especially in patients with elevated ESR or CF titers ≤1:32; surgery can be of benefit if disease is detected early; late disease cannot respond to therapy *Sarcoid-like:* NSAIDs or corticosteroids§ can be of benefit for some patients *Pericarditis:* Severe disease: Prednisone (0.5-1.0 mg/kg daily [maximum, 80 mg daily] in tapering doses over 1-2 weeks) or pericardial drainage procedure
Chronic cavitary pulmonary histoplasmosis	0.05	Antifungal therapy generally recommended for all patients to halt further lung destruction and reduce mortality *Mild–moderate disease:* Itraconazole 200 mg three times daily for 3 days and then one or two times daily for at least 1 year; some clinicians recommend therapy for 18-24 months due to the high rate of relapse; itraconazole plasma concentrations should be obtained after the patient has been receiving this agent for at least 2 weeks *Severe disease:* Amphotericin B 0.7 mg/kg/day for a minimum total dose of 25-35 mg/kg is effective in 59%-100% of cases and should be used in patients who require hospitalization or are unable to take itraconazole because of drug interactions, allergies, failure to absorb drug, or failure to improve clinically after a minimum of 12 weeks of itraconazole therapy
Histoplasma endocarditis		Amphotericin B (lipid formulations may be preferred, due to their lower rate of renal toxicity) plus a valve replacement is recommended; if the valve cannot be replaced, lifelong suppression with itraconazole is recommended
CNS histoplasmosis		Amphotericin B should be used as initial therapy (lipid formulations at 5 mg/kg/day IV, for a total dosage of 175 mg/kg may be preferred, due to their lower rate of renal toxicity) for 4-6 weeks, followed by an oral azole (fluconazole or itraconazole 200 mg two or three times daily) for at least a year; some patients may require lifelong therapy; response to therapy should be monitored by repeat lumbar punctures to assess *Histoplasma* antigen levels, WBC, and CF antibody titers; blood levels of itraconazole should be obtained to ensure adequate drug exposure
Immunosuppressed Host		
Disseminated histoplasmosis	0.02-0.05	*Disseminated histoplasmosis:* Untreated mortality 83%-93%; relapse 5%-23% in non-AIDS patients; therapy is recommended for all patients
Acute (Infantile)		*Nonimmunosuppressed patients:* Ketoconazole 400 mg/day orally × 6-12 months or amphotericin B 35 mg/kg IV
Subacute		*Immunosuppressed patients (non-AIDS) or endocarditis or CNS disease:* Amphotericin B >35 mg/kg IV × 3 months followed by fluconazole or itraconazole 200 mg orally twice daily × 12 months
Progressive histoplasmosis (immunocompetent patients and immunosuppressed patients without AIDS)		*Moderately severe to severe:* Liposomal amphotericin B (3 mg/kg daily) IV, amphotericin B lipid complex (ABLC, 5 mg/kg daily) IV, or deoxycholate amphotericin B (0.7-1 mg/kg daily) for 1-2 weeks IV, followed by itraconazole (200 mg twice daily for at least 12 months) *Mild to moderate:* Itraconazole (200 mg orally twice daily for at least 12 months)
Progressive disease of AIDS	25-50‖	Amphotericin B 15-30 mg/kg IV (1-2 g over 4-10 weeks)¶ or itraconazole 200 mg orally three times daily for 3 days then twice daily for 12 weeks, followed by lifelong suppressive therapy with itraconazole 200-400 mg orally daily; although patients receiving secondary prophylaxis (chronic maintenance therapy) might be at low risk for recurrence of systemic mycosis when their $CD4^+$ T-lymphocyte counts increase to >100 cells/μL (0.1×10^9/L) in response to HAART, the number of patients who have been evaluated is insufficient to warrant a recommendation to discontinue prophylaxis

*As a percentage of all patients presenting with histoplasmosis.

†Itraconazole plasma concentrations should be measured during the second week of therapy to ensure that detectable concentrations have been achieved. If the concentration is below 1 mcg/mL (mg/L; 1.4 μmol/L), the dose may be insufficient or drug interactions can be impairing absorption or accelerating metabolism, requiring a change in dosage. If plasma concentrations are greater than 10 mcg/mL (mg/L; 14 μmol/L), the dosage can be reduced.

‡Deoxycholate amphotericin B.

§Effectiveness of corticosteroids is controversial.

‖As a percentage of AIDS patients presenting with histoplasmosis as the initial manifestation of their disease.

¶Liposomal amphotericin B (AmBisome) may be more appropriate for disseminated disease.

AIDS, acquired immunodeficiency syndrome; CF, complement fixation; ESR, erythrocyte sedimentation rate; HAART, highly active antiretroviral therapy; NSAIDs, nonsteroidal anti-inflammatory drugs; PO, orally.

Data from References 10 and 33.

Acute (infantile) disseminated histoplasmosis is characterized by massive involvement of the mononuclear phagocyte system by yeast-engorged macrophages. Typically, this severe type of infection is seen in infants and young children and (rarely) in adults with Hodgkin's disease or other lymphoproliferative disorders. In infants or children, acute disseminated histoplasmosis is characterized by unrelenting fever, anemia, leukopenia or thrombocytopenia, enlargement of the liver, spleen, and visceral lymph nodes, and GI symptoms, particularly nausea, vomiting, and diarrhea. The chest roentgenogram often demonstrates remnants of the initiating acute pulmonary lesion. Untreated disease is uniformly fatal in 1 to 2 months. A less severe "subacute" form of the disease, which occurs in both infants and immunocompetent adults, is characterized by focal destructive lesions in various organs, weight loss, weakness, fever, and malaise. Untreated disease generally is fatal in approximately 10 months.

Most adults with disseminated histoplasmosis demonstrate a mild, chronic form of the disease. Untreated patients often are ill for 10 to 20 years, demonstrating long asymptomatic periods interrupted by relapses of clinical illness characterized primarily by weight loss, weakness, and fatigue. Chronic disseminated histoplasmosis can be seen in patients with lymphoreticular neoplasms (Hodgkin's disease) and patients undergoing immunosuppressant chemotherapy for organ transplantation or for rheumatic diseases. Although CNS involvement occurs in 10% to 20% of patients with severe underlying immunosuppressive conditions, focal organ involvement is uncommon. The disease is characterized by the development of focal granulomatous lesions, often with bone marrow involvement resulting in thrombocytopenia, anemia, and leukemia. Fever, hepatosplenomegaly, and GI ulceration are common.

Histoplasmosis in HIV-Infected Patients

Adult patients with AIDS demonstrate an acute form of disseminated disease that resembles the syndrome seen in infants and children. Progressive disseminated histoplasmosis (PDH), which is defined as a clinical illness that does not improve after at least 3 weeks of observation and that is associated with physical or radiographic findings and/or laboratory evidence of involvement of extrapulmonary tissues, can occur as the direct result of initial infection or because of the reactivation of dormant foci. In endemic areas, 50% of AIDS patients demonstrate PDH as the first manifestation of their disease. PDH is characterized by fever (75% of patients), weight loss, chills, night sweats,

enlargement of the spleen, liver, or lymph nodes, and anemia. Pulmonary symptoms occur in only one-third of patients and do not always correlate with the presence of infiltrates on chest roentgenogram. A clinical syndrome resembling septicemia is seen in approximately 25% to 50% of patients.[10]

Diagnosis

The diagnosis of histoplasmosis is made on the basis of histopathology, cultures, antigen detection, and serologic tests for *Histoplasma*-specific antibodies. Detection of single, ovoid cells 2 to 5 microns in diameter with narrow-based budding by direct examination or by histologic study of blood smears or tissues should raise strong suspicion of infection with *H. capsulatum* because colonization does not occur as with *Aspergillus* or *Candida* infection. In patients with acute self-limited histoplasmosis, extensive testing to verify the diagnosis may not be necessary.[32,33]

In most patients, serologic evidence (complement fixation test or immunodiffusion testing) remains the primary method in the diagnosis of histoplasmosis. Detection of *Histoplasma* antigen by enzyme immunoassay (EIA) in the urine, blood, or bronchoalveolar lavage fluid of infected patients provides rapid diagnostic information and is particularly useful in patients who are severely ill. The highest sensitivity is obtained by testing both urine and serum.[34] *Histoplasma* EIA has also been used to monitor the course of therapy and to detect relapses in patients with AIDS, and the clearance of antigen from serum and urine correlates with clinical efficacy during maintenance therapy.[35]

TREATMENT

Non-HIV-Infected Patient

4 **Table 139-4** summarizes the recommended therapy for the treatment of histoplasmosis. In general, asymptomatic or mildly ill patients and patients with sarcoid-like disease do not benefit from antifungal therapy. In the vast majority of patients, low-inoculum exposure to *H. capsulatum* results in *mild* or *asymptomatic* pulmonary histoplasmosis. The course of disease generally is benign, and symptoms usually abate within a few weeks of onset. Therapy can be helpful in symptomatic patients whose conditions have not improved during the first month of infection. Fever persisting more than 3 weeks can indicate that the patient is developing progressive disseminated disease,

> which can be aborted by antifungal therapy. Whether antifungal therapy hastens recovery or prevents complications is unknown because it has never been studied in prospective trials.

Fluconazole remains a second-line agent for the treatment of histoplasmosis. Clinical data regarding the use of newer azoles such as voriconazole and posaconazole are limited. While both have activity against *Histoplasma*, posaconazole appears to be more active than itraconazole in the immune compromised and nonimmune compromised mouse model of infection, while voriconazole has not been tested in animal models. Both agents have been used successfully in a few patients. Of note, the echinocandins have no activity against *Histoplasma*.

Patients with mild, self-limited disease, chronic disseminated disease, or chronic pulmonary histoplasmosis who have no underlying immunosuppression usually can be treated with either oral itraconazole or IV amphotericin B. The goals of therapy are resolution of clinical abnormalities, prevention of relapse, and eradication of infection whenever possible, although chronic suppression of infection can be adequate in immunosuppressed patients, including those with HIV disease.[10]

HIV-Infected Patient

In AIDS patients, intensive 12-week primary antifungal therapy (induction and consolidation therapy) is followed by lifelong suppressive (maintenance) therapy with itraconazole. Amphotericin B dosages of 50 mg/day (up to 1 mg/kg/day) should be administered IV to a cumulative dose of 15 to 35 mg/kg (1-2 g) in patients who require hospitalization. Amphotericin B can be replaced with itraconazole 200 mg orally twice daily when the patient no longer requires hospitalization or IV therapy to complete a 12-week total course of induction therapy. In patients who do not require hospitalization, itraconazole therapy for 12 weeks can be used.[10]

Fluconazole 800 mg/day orally as induction, followed by 400 mg/day, was effective in 88% of patients, but relapses occurred in approximately one-third of patients, and in vitro resistance developed in approximately 50% of patients who relapsed.[10]

In regions experiencing high rates of histoplasmosis (≥ 5 cases/100 patient-years), itraconazole 200 mg/day orally is recommended as prophylactic therapy in HIV-infected patients. Fluconazole is not an acceptable alternative because of its inferior activity against *H. capsulatum* and its lower efficacy for the treatment

of histoplasmosis.[10]

Although patients receiving secondary prophylaxis (chronic maintenance therapy) might be at low risk for recurrence of systemic mycosis when their $CD4^+$ T lymphocyte counts increase to greater than 100 cells/µL (0.1×10^9/L) in response to highly active antiretroviral therapy (HAART), the number of patients who have been evaluated is insufficient to warrant a recommendation to discontinue prophylaxis.

Evaluation of Therapeutic Outcomes

Response to therapy should be measured by resolution of radiologic, serologic, and microbiologic parameters and by improvement in signs and symptoms of infection. Although investigators are limited by the lack of standardized criteria to quantify the extent of infection, degree of immunosuppression, or treatment response, response rates (based on resolution or improvement in presenting signs and symptoms) of greater than 80% have been reported in case series in AIDS patients receiving varied dosages of amphotericin B. Rapid responses are reported, with the resolution of symptoms in 25% and 75% of patients by days 3 and 7 of therapy, respectively.

After the initial course of therapy for histoplasmosis is complete, lifelong suppressive therapy with oral azoles or amphotericin B (1-1.5 mg/kg IV weekly or biweekly) is recommended because of the frequent recurrence of infection. Relapse rates in AIDS patients not receiving maintenance therapy range from 50% to 90%.[10]

Antigen testing can be useful for monitoring therapy since concentrations decrease with therapy and increase with relapse.

BLASTOMYCOSIS

North American blastomycosis is a systemic fungal infection caused by *Blastomyces dermatitidis*, a dimorphic fungus that infects primarily the lungs. Patients, however, can present with a variety of pulmonary and extrapulmonary clinical manifestations. Pulmonary disease can be acute or chronic and can mimic infection with tuberculosis, pyogenic bacteria, other fungi, or malignancy. Blastomycosis can disseminate to virtually every other body organ, and approximately 40% of patients with blastomycosis present with skin, bone and joint, or genitourinary tract involvement without any evidence of pulmonary disease.[8,36]

Pulmonary infection probably occurs by inhalation of conidia, which convert to the yeast form in the lung. A vigorous inflammatory response ensues, with neutrophilic recruitment to the lungs followed by the development of cell-mediated immunity and the formation of noncaseating granulomas.

Epidemiology

Blastomycosis has been called *North American blastomycosis* because there is a similar fungus endemic to South America, *Blastomyces braziliensis*, that causes *South American blastomycosis*. Although North American blastomycosis is now recognized to be endemic to the southeastern and south central states of the United States (especially those bordering on the Mississippi and Ohio River basins) and the Midwestern states and Canadian provinces bordering the Great Lakes, numerous cases have been diagnosed in Africa, northern parts of South America, India, and Europe. Endemic areas have been defined primarily by analysis of sporadic cases and epidemics or clusters of disease because the lack of a dependable skin or laboratory test makes wide-scale epidemiologic testing to determine the incidence of infection unfeasible at present.[8,36] Although initial review of sporadic cases suggested that males with outdoor occupations that exposed them to soil were at greatest risk for blastomycosis, there is no sex, age, or occupational predilection for blastomycosis.[8,36]

Although *B. dermatitidis* generally is considered to be a soil inhabitant, attempts to isolate the organism in nature frequently have been unsuccessful. *B. dermatitidis* has been isolated from soil containing decayed vegetation, decomposed wood, and pigeon manure, frequently in association with warm, moist soil of wooded areas that is rich in organic debris.[8,36]

Pathophysiology and Clinical Presentation

Colonization does not occur with *Blastomyces*[8,36] *Acute pulmonary blastomycosis* generally is an asymptomatic or self-limited disease characterized by fever, shaking chills, and productive, purulent cough, with or without hemoptysis, in immunocompetent individuals. The clinical presentation can be difficult to differentiate from other respiratory infections, including bacterial pneumonia, on the basis of clinical symptoms alone.

Sporadic (nonepidemic) pulmonary blastomycosis can present as a more chronic or subacute disease, with low-grade fever, night sweats, weight loss, and productive cough that resembles tuberculosis rather than bacterial pneumonia.

Chronic pulmonary blastomycosis is characterized by fever, malaise, weight loss, night sweats, chest pain, and productive cough. Patients often are thought to have tuberculosis and frequently have evidence of disseminated disease that can appear 1 to 3 years after the primary pneumonia has resolved. Reactivation of disease can occur in the lungs or as the focus of new infection in other organs.

In approximately 40% of patients, dissemination is not accompanied by reactivation of pulmonary disease. The most common sites for disseminated disease include the skin and bony skeleton, although less commonly the prostate, oropharyngeal mucosa, and abdominal viscera are involved. CNS disease, while exceedingly uncommon, is associated with the highest mortality rate.

Laboratory and Diagnostic Tests

The simplest and most successful method of diagnosing blastomycosis is by direct microscopic visualization of the large, multinucleated yeast with single, broad-based buds in sputum or other respiratory specimens following digestion of cells and debris with 10% potassium hydroxide.[8,36] Histopathologic examination of tissue biopsies and culture of secretions also should be used to identify *B. dermatitidis*, although it can require up to 30 days to isolate and identify a small inoculum.

No reliable skin test exists to determine the incidence and prevalence of disease in endemic populations, and reliable serologic diagnosis of blastomycosis has long been hampered by the lack of specific and standardized reagents. Serologic response does not always correlate with clinical improvement, although some investigators have noted that a decline in the number of precipitins or CF titers can offer evidence of a favorable prognosis in patients with established disease.

TREATMENT

Non-HIV-Infected Patient

5 In the immunocompetent host, acute pulmonary blastomycosis can be mild and self-limited and may not require treatment. However, consideration should be given to treating all infected individuals to prevent extrapulmonary dissemination. All individuals with moderate-to-severe pneumonia, disseminated infection, or those who are immunocompromised require antifungal therapy.

In patients with mild-to-moderate pulmonary blastomycosis, itraconazole is effective; however, in patients with moderately severe to severe pulmonary disease, the clinical presentation of the patient, the immune competence of the patient, and the toxicity of the antifungal agents are the main determinants of the choice of antifungal therapy. All immunocompromised patients and patients with progressive pulmonary disease or with extrapulmonary disease should be treated (**Table 139-5**). In the case of disease limited to the lungs, cure might have occurred without treatment before the diagnosis is made. Regardless of whether or not the patient receives treatment, however, he or she must be followed carefully for many years for evidence of reactivation or progressive disease.[8,36]

TABLE 139-5 Therapy of Blastomycosis

Type of Disease	Preferred Treatment
Pulmonary[a]	
Moderately severe to severe disease	Lipid formulation of amphotericin B 3-5 mg/kg IV daily or amphotericin B[b] 0.7-1 mg/kg IV daily (total dose 1.5-2.5 g) × 1-2 weeks or until improvement is noted, followed by itraconazole[c,d] 200 mg orally three times daily for 3 days, then 200 mg twice daily, × total of 6-12 months
Mild-to-moderate disease	Itraconazole[b,d] 200 mg orally three times daily for 3 days, then 200 mg twice daily, for a total of 6 months[b]
CNS disease	*Induction:* Lipid formulation of amphotericin B 5 mg/kg IV daily × 4-6 weeks, followed by an oral azole as consolidation therapy *Consolidation:* Fluconazole[d] 800 mg orally daily, or itraconazole[d] 200 mg two or three times orally daily, or voriconazole[d] 200-400 mg orally twice daily, for ≥12 months and until resolution of CSF abnormalities
Disseminated or Extrapulmonary Disease	
Moderately severe to severe disease	Lipid formulation of amphotericin B 3-5 mg/kg IV daily or amphotericin B[b] 0.7-1 mg/kg IV daily × 1-2 weeks or until improvement is noted, followed by itraconazole[c,d] 200 mg orally three times daily for 3 days, then 200 mg twice daily × 6-12 months. Treat osteoarticular disease with 12 months of antifungal therapy Most clinicians prefer to step-down to itraconazole[d] therapy once the patient's condition improves
Mild to moderate	Itraconazole[c,d] 200 mg orally three times daily for 3 days, then 200 mg once or twice daily × ≥12 months. Treat osteoarticular disease with 12 months of antifungal therapy
Immunocompromised Host (Including Patients with AIDS, Transplants, or Receiving Chronic Glucocorticoid Therapy)	
Acute disease	Lipid formulation of amphotericin B 3-5 mg/kg IV daily or amphotericin B[a] 0.7-1 mg/kg IV daily × 1-2 weeks or until improvement is noted, then give suppressive therapy for a total of at least 12 months of therapy
Suppressive therapy	Itraconazole[c,d] 200 mg orally three times daily for 3 days, then 200 mg twice daily for a total of at least 12 months of therapy; lifelong suppressive therapy with oral itraconazole[d] 200 mg daily may be required for immunosuppressed patients in whom immunosuppression cannot be reversed, and in patients who experience relapse despite appropriate therapy

AIDS, acquired immunodeficiency syndrome.

[a]In the immunocompetent host, acute pulmonary blastomycosis can be mild and self-limited and may not require treatment.

[b]Desoxycholate amphotericin B.

[c]Serum levels of itraconazole should be determined after the patient has received itraconazole for ≥2 weeks, to ensure adequate drug exposure.

[d]Azoles should not be used during pregnancy.

Data from Reference 8.

Some authors recommend azole therapy for the treatment of self-limited pulmonary disease, with the hope of preventing late extrapulmonary disease; however, data supporting the efficacy of these regimens are lacking.[8,36] Itraconazole 200 to 400 mg/day demonstrated 90% efficacy as a first-line agent in the treatment of nonlife-threatening non-CNS blastomycosis, and for compliant patients who completed at least 2 months of therapy, a success rate of 95% was noted. No therapeutic advantage was noted with the higher (400 mg) dosage as compared with patients treated with 200 mg.

All patients with disseminated blastomycosis, as well as those with extrapulmonary disease, require therapy. Due to its adverse effects, variable oral absorption, and lack of CNS penetration, ketoconazole is now reserved as an alternative therapy for mild-to-moderate pulmonary and non-CNS disease. However, older studies demonstrate that ketoconazole 400 mg/day orally for 6 months cures more than 80% of patients with chronic pulmonary and nonmeningeal disseminated blastomycosis. Amphotericin B is more efficacious but more toxic and therefore is reserved for noncompliant patients and patients with overwhelming or life-threatening disease, CNS infection, and treatment failures.[8,36] Lipid preparations of amphotericin B have largely replaced conventional amphotericin B for treatment of blastomycosis, despite their higher cost, due to their decreased renal toxicity. Surgery has only a limited role in the treatment of blastomycosis.

HIV-Infected Patient

For unclear reasons, blastomycosis is an uncommon opportunistic disease among immunocompromised individuals, including AIDS patients; however, blastomycosis can occur as a late (CD4 lymphocytes $\leq$ 200 cells/mm^3 [0.2 $\times$ 10^9/L]) and frequently fatal complication of HIV infection. In this population, overwhelming disseminated disease with frequent involvement of the CNS is common.[8,36] Following induction therapy with amphotericin B (total cumulative dose of 1 g), HIV-infected patients should receive chronic suppressive therapy with an oral azole antifungal.[8,36]

COCCIDIOIDOMYCOSIS

Epidemiology

Coccidioidomycosis is caused by infection with *Coccidioides immitis*, a

dimorphic fungus found in the southwestern and western United States, as well as in parts of Mexico and South America. In North America, the endemic regions encompass the semiarid areas of the southwestern United States from California to Texas known as the Lower Sonoran Zone, where there is scant annual rainfall, hot summers, and sandy, alkaline soil. *C. immitis* grows in the soil as a mold, and mycelia proliferate during the rainy season. During the dry season, resistant arthroconidia form and become airborne when the soil is disturbed.

Although generally considered to be a regional disease, coccidioidomycosis has increased in importance in recent years because of the increased tourism and population in endemic areas, the increased use of immunosuppressive therapy in transplantation and oncology, and the AIDS epidemic. Although there is no racial, hormonal, or immunologic predisposition for acquiring primary disease, these factors affect the risk of subsequent dissemination of disease (**Table 139-6**).[37]

TABLE 139-6 Factors for Severe, Disseminated Infection with Coccidioidomycosis

Race (Filipinos > African Americans > Native Americans > Hispanics > Asians)
Pregnancy (especially when infection is acquired or reactivated in the second or third trimester)
Compromised cellular immune system, including
AIDS patients
Patients receiving
Corticosteroids
Immunosuppressive agents
Chemotherapy
Male gender
Neonates
Patients with B or AB blood types

AIDS, acquired immune deficiency syndrome.

Data from Reference 39.

Pathophysiology

When individuals come in contact with contaminated soil during ranching, dust storms, or proximity to construction sites or archaeological excavations, arthroconidia are inhaled into the respiratory tree, where they transform into spherules, which reproduce by cleavage of the cytoplasm to produce endospores. The endospores are released when the spherules reach maturity. Similar to

histoplasmosis, an acute inflammatory response in the tissue leads to infiltration of mononuclear cells, ultimately resulting in granuloma formation.[37]

Clinical Presentation

Coccidioidomycosis encompasses a spectrum of illnesses ranging from primary uncomplicated respiratory tract infection that resolves spontaneously to progressive pulmonary or disseminated infection.[37] Initial or primary infection with *C. immitis* almost always involves the lungs. Although approximately one-third of the population in endemic areas is infected, the average incidence of symptomatic disease is only approximately 0.43%.

Signs and Symptoms

Primary Coccidioidomycosis (“*Valley Fever*”): Approximately 60% of infected patients have an asymptomatic, self-limited infection without clinical or radiological manifestations. The remaining 40% of patients exhibit nonspecific symptoms that are often indistinguishable from ordinary upper respiratory infections, including fever, cough, headache, sore throat, myalgias, and fatigue that occur 1 to 3 weeks after exposure to the pathogen. More commonly, a diffuse, mild erythroderma or maculopapular rash is observed. Patients can have pleuritic chest pain and peripheral eosinophilia.

A fine, diffuse rash can appear during the first few days of the illness. Primary pneumonia can be the first manifestation of disease, characterized by a productive cough that can be blood-streaked, as well as single or multiple soft or dense homogeneous hilar or basal infiltrates on chest roentgenogram. *Chronic, persistent pneumonia or persistent pulmonary coccidioidomycosis* (primary disease lasting more than 6 weeks) is complicated by hemoptysis, pulmonary scarring, and the formation of cavities or bronchopleural fistulas.

Necrosis of pulmonary tissue with drainage and cavity formation occurs commonly. Most parenchymal cavities close spontaneously or form dense nodular scar tissue that can become superinfected with bacteria or spherules of *C. immitis*. These patients often have persistent cough, fevers, and weight loss.

Disseminated disease occurs in less than 1% of infected patients. The most common sites for dissemination are the skin, lymph nodes, bone, and meninges, although the spleen, liver, kidney, and adrenal gland also can be involved. Occasionally, miliary coccidioidomycosis occurs, with rapid, widespread dissemination, often in concert with positive blood cultures for *C. immitis*.

Patients with AIDS frequently present with miliary disease. Coccidioidomycosis in AIDS patients appears to be caused by reactivation of disease in most patients. Dissemination also is more likely if infection occurs during pregnancy, especially during the third trimester or in the immediate postpartum period.[37]

CNS infection occurs in approximately 16% of patients with disseminated coccidioidomycosis. Patients can present with meningeal disease without previous symptoms of primary pulmonary infection, although disease usually occurs within 6 months of the primary infection. The signs and symptoms are often subtle and nonspecific, including headache, weakness, changes in mental status (lethargy and confusion), neck stiffness, low-grade fever, weight loss, and occasionally, hydrocephalus. Space-occupying lesions are rare, and the main areas of involvement are the basilar meninges.

The diagnoses of coccidioidomycosis generally utilizes identification or recovery of *Coccidioides* spp. from clinical specimens and detection of specific anticoccidioidal antibodies in serum or other body fluids.

TREATMENT

General Guidelines

6 Therapy for coccidioidomycosis is difficult, and the results are unpredictable. Guidelines[11] are available for treatment of this disease; however, optimal treatment for many forms of this disease still generates debate. The efficacy of antifungal therapy for coccidioidomycosis often is less certain than that for other fungal etiologies, such as blastomycosis, histoplasmosis, or cryptococcus, even when in vitro susceptibilities and the sites of infections are similar. The refractoriness of coccidioidomycosis can relate to the ability of *C. immitis* spherules to release hundreds of endospores, maximally challenging host defenses.[37] Fortunately, only approximately 5% of infected patients require therapy.

Goals of Therapy

Desired outcomes of treatment are resolution of signs and symptoms of infection, reduction of serum concentrations of anticoccidioidal antibodies, and return of function of involved organs. It would also be desirable to prevent relapse of illness on discontinuation of therapy, although current therapy is often unable to achieve this goal.

Specific Agents Used for the Treatment of Coccidioidomycosis

Although there is continued disagreement among experts in endemic areas whether antifungal therapy in patients with uncomplicated early coccidioidal infection might shorten the course of illness or reduce the development of more serious complications, prospective randomized trials addressing this question are lacking. The excellent tolerability of oral azoles has lowered the threshold for deciding to treat primary infection, and clinicians should treat patients with significantly debilitating illness, those with extensive pulmonary disease, and with who are frail due to advanced age, concurrent diabetes or comorbidities.[11]

Azole antifungals, primarily fluconazole and itraconazole, have replaced amphotericin B as initial therapy for most chronic pulmonary or disseminated infections. Amphotericin B is now usually reserved for patients with respiratory failure because of infection with *Coccidioides* species, those with rapidly progressive coccidioidal infections, or women during pregnancy. Therapy often ranges from many months to years in duration, and in some patients, lifelong suppressive therapy is needed to prevent relapses. Specific antifungals (and their usual dosages) for the treatment of coccidioidomycosis include IV amphotericin B (0.5-1.5 mg/kg/day), ketoconazole (400 mg/day orally), IV or oral fluconazole (usually 400-800 mg/day, although dosages as high as 1,200 mg/day have been used without complications), and itraconazole (200-300 mg orally twice daily or three times daily, as either capsules or solution).[37] If itraconazole is used, measurement of serum concentrations can be helpful to ascertain whether oral bioavailability is adequate.

Amphotericin B generally is preferred as initial therapy in patients with rapidly progressive disease, whereas azoles generally are preferred in patients with subacute or chronic presentations. The lipid formulations of amphotericin B have not been studied extensively in coccidioidal infection but can offer a means of giving more drugs with less toxicity. Fluconazole probably is the most frequently used medicine given its tolerability, although high relapse rates have been reported in some studies. Relapse rates with itraconazole therapy can be lower than those with fluconazole.[37]

The usefulness of newly available antifungal agents of possible benefit for the treatment of refractory coccidioidal infections has not been adequately assessed and they are not yet FDA approved for use in this population. Case reports have suggested that voriconazole can be effective in selected patients. Caspofungin has been effective in treating experimental murine coccidioidomycosis, but in

vitro susceptibility of isolates varies widely, and there is only one report regarding its value. Posaconazole was effective treatment in patients with refractory infections. Its efficacy relative to other triazole antifungals is unknown.

Combination therapy with members of different classes of antifungal agents has not been evaluated in patients, and there is a hypothetical risk of antagonism. However, some clinicians feel that outcome in severe cases is improved when amphotericin B is combined with an azole antifungal. If the patient improves, the dosage of amphotericin B can be slowly decreased while the dosage of azole is maintained.[37]

Primary Respiratory Infection

Although most patients with symptomatic primary pulmonary disease recover without therapy, management should include follow-up visits for 1 to 2 years to document resolution of disease or to identify as early as possible evidence of pulmonary or extrapulmonary complications.

Patients with a large inoculum, severe infection, or concurrent risk factors (eg, HIV infection, organ transplant, pregnancy, or high doses of corticosteroids) probably should be treated, particularly those with high CF titers, in whom incipient or occult dissemination is likely. Because some racial or ethnic populations have a higher risk of dissemination, some clinicians advocate their inclusion in the high-risk group. Common indicators that are used to judge the severity of infection include weight loss (greater than 10%), intense night sweats persisting more than 3 weeks, infiltrates involving more than one-half of one lung or portions of both lungs, prominent or persistent hilar adenopathy, CF antibody titers of greater than 1:16, failure to develop dermal sensitivity to coccidial antigens, inability to work, or symptoms that persist for more than 2 months.[37]

Commonly prescribed therapies include currently available oral azole antifungals at their recommended doses for courses of therapy ranging from 3 to 6 months.[37] In patients with diffuse pneumonia with bilateral reticulonodular or miliary infiltrates, therapy usually is initiated with amphotericin B; several weeks of therapy generally are required to produce clear evidence of improvement. Consolidation therapy with oral azoles can be considered at that time. The total duration of therapy should be at least 1 year, and in patients with underlying immunodeficiency, oral azole therapy should be continued as secondary prophylaxis.

Infections of the Pulmonary Cavity

Many pulmonary infections that are caused by *C. immitis* are benign in their course and do not require intervention. In the absence of controlled clinical trials, evidence of the benefit of antifungal therapy is lacking, and asymptomatic infections generally are left untreated. Symptomatic patients can benefit from oral azole therapy, although recurrence of symptoms can be seen in some patients once therapy is discontinued. Surgical resection of localized cavities provides resolution of the problem in patients in whom the risks of surgery are not too high.[37]

Extrapulmonary (Disseminated) Disease

Nonmeningeal Disease

Almost all patients with disease located outside the lungs should receive antifungal therapy; therapy usually is initiated with 400 mg/day of an oral azole. Amphotericin B is an alternative therapy and can be necessary in patients with worsening lesions or with disease in particularly critical locations such as the vertebral column. Approximately 50% to 75% of patients treated with amphotericin B for nonmeningeal disease achieve a sustained remission, and therapy usually is curative in patients with infections localized strictly to skin and soft tissues without extensive abscess formation or tissue damage. The efficacy of local injection into joints or the peritoneum, as well as intra-articular or intradermal administration, remains poorly studied. Amphotericin B appears to be most efficacious when cell-mediated immunity is intact (as evidenced by a positive coccidioidin or spherulin skin test or low CF antibody titer). Controlled trials that document these clinical impressions are lacking, however.[37]

Meningeal Disease

Fluconazole has become the drug of choice for the treatment of coccidioidal meningitis. A minimum dose of 400 mg/day orally leads to a clinical response in most patients and obviates the need for intrathecal amphotericin B. Some clinicians will initiate therapy with 800 or 1,000 mg/day, and itraconazole dosages of 400 to 600 mg/day are comparably effective. It is also clear, however, that fluconazole only leads to remission rather than cure of the infections; thus suppressive therapy must be continued for life. Ketoconazole cannot be recommended routinely for the treatment of coccidioidal meningitis because of

its poor CNS penetration following oral administration. Patients who do not respond to fluconazole or itraconazole therapy are candidates for intrathecal amphotericin B therapy with or without continuation of azole therapy. The intrathecal dose of amphotericin B ranges from 0.01 to 1.5 mg given at intervals ranging from daily to weekly. Therapy is initiated with a low dosage and is titrated upward as patient tolerance develops.[37]

CRYPTOCOCCOSIS

Epidemiology

Cryptococcosis is a noncontagious, systemic mycotic infection caused by the ubiquitous encapsulated soil yeast *Cryptococcus*, which is found in soil, particularly in pigeon droppings, although disease occurs throughout the world, even in areas where pigeons are absent. Infections caused by *C. neoformans* var. *grubii* (serotype A) are seen worldwide among immunocompromised hosts, followed by *C. neoformans* var. *neoformans* (serotype D). On the other hand, *Cryptococcus gattii* (serotypes B and C) is geographically more restricted and in contrast to *C. neoformans*, rarely infects immunosuppressed patients, is not associated with HIV infection, and the infections are more difficult to treat. *C. gattii* is not associated with birds; its main reservoir was thought to be limited to certain species of eucalyptus tree. Until recently, it was most common in tropical and subtropical areas, such as Australia, South America, Southeast Asia, and central Africa, with the highest incidence in Papua New Guinea and Northern Australia, although infections occur in nontropical areas such as North America and Europe. *C. gattii* emerged on Vancouver Island, British Columbia, Canada, in 1999, and subsequently spread to the Vancouver lower mainland, Washington state, and Oregon.[38]

Infection is acquired by inhalation of the organism. The incidence of cryptococcosis has risen dramatically in recent years, reflecting the increased numbers of immunocompromised patients, including those with malignancies, diabetes mellitus, chronic renal failure, and organ transplants and those receiving immunosuppressive agents. In most developed countries, widespread use of HAART has significantly decreased the incidence of cryptococcosis; however, the incidence and mortality of this infection are still extremely high in areas with limited access to HAART and a high incidence of HIV.[39]

Disease can remain localized in the lungs or can disseminate to other tissues, particularly the CNS, although the skin also can be affected. Hematogenous

spread generally occurs in the immunocompromised host, although it also has been seen in individuals with intact immune systems.

Clinical Presentation

Primary cryptococcosis in humans almost always occurs in the lungs, although the pulmonary focus usually produces a subclinical infection.[38,39] Symptomatic infections usually are manifested by cough, rales, and shortness of breath that generally resolve spontaneously. Cryptococcus can present as part of an immune reconstitution inflammatory syndrome (IRIS), a paradoxical worsening of preexisting infectious processes following the initiation of HAART in HIV-infected individuals. In non-AIDS patients, the symptoms of cryptococcal meningitis are nonspecific. Headache, fever, nausea, vomiting, mental status changes, and neck stiffness generally are observed. Less common symptoms include visual disturbances (photophobia and blurred vision), papilledema, seizures, and aphasia. In AIDS patients, fever and headache are common, but meningismus and photophobia are much less common than in non-AIDS patients. Approximately 10% to 12% of AIDS patients have asymptomatic disease, similar to the rate observed in non-AIDS patients.[39,40] Intracerebral mass lesions (cryptococcomas) are more common in *C. gattii* than in *C. neoformans*, presumably due to their different host immune responses.[38]

Laboratory Tests

With cryptococcal meningitis, the CSF opening pressure generally is elevated. There is a CSF pleocytosis (usually lymphocytes), leukocytosis, a decreased glucose concentration, and an elevated CSF protein concentration. There is also a positive cryptococcal antigen (detected by LA). The test is rapid, specific, and extremely sensitive, but false-negative results can occur. False-positive tests can result from cross-reactivity with rheumatoid factor and *Trichosporon beigelii. C. neoformans* can be detected in approximately 60% of patients by India ink smear of CSF, and it can be cultured in more than 96% of patients. Occasionally, large volumes of CSF are required to confirm the diagnosis.

The CSF parameters in patients with AIDS are similar to those seen in non-AIDS patients, with the exception of a decreased inflammatory response to the pathogen, resulting in a strikingly low number of leukocytes in CSF and extraordinarily high cryptococcal antigen titers.

TREATMENT

The choice of treatment for disease caused by *C. neoformans* depends on both the anatomic sites of involvement and the host's immune status, and thus, treatment recommendations are divided into three specific risk groups: (a) HIV-infected individuals, (b) transplant recipients, and (c) non–HIV-infected and nontransplant hosts (**Table 139-7**).[9] The management of cryptococcosis includes systemic antifungal therapy, control of elevated intracranial pressure (ICP), and supportive care. When possible, immune defects should be addressed. Although no randomized clinical trials have been performed to address this, outcomes of treatment for CNS cryptococcosis (without mass lesions or hydrocephalus) appear to be similar for disease due to either *C. neoformans* or *C. gattii*.[38]

TABLE 139-7 Therapy of Cryptococcosis[a,b]

Type of Disease and Common Clinical Manifestations	Therapy/Comments
Nonimmunocompromised Patients (Non–HIV-Infected, Nontransplant)	
Meningoencephalitis *without* neurological complications, in patients in whom CSF yeast cultures are negative after 2 weeks of therapy	*Induction:* Amphotericin B[c] IV 0.7-1 mg/kg/day *plus* flucytosine 100 mg/kg/day orally in four divided doses × ≥4 weeks A lipid formulation of amphotericin B may be substituted for amphotericin B in the second 2 weeks
Follow all regimens with suppressive therapy	*Consolidation:* Fluconazole 400-800 mg orally daily × 8 weeks *Maintenance:* Fluconazole 200 mg orally daily × 6-12 months
Meningoencephalitis *with* neurological complications	*Induction:* Same as for patients without neurologic complications, but consider extending the induction therapy for a total of 6 weeks. A lipid formulation of amphotericin B may be given for the last 4 weeks of the prolonged induction period *Consolidation:* Fluconazole 400 mg orally daily × 8 weeks
Mild-to-moderate pulmonary disease (Nonmeningeal disease)	Fluconazole 400 mg orally daily × 6-12 months
Severe pulmonary cryptococcosis	*Same as CNS disease × 12 months*
Cryptococcemia (nonmeningeal, nonpulmonary disease)	*Same as CNS disease × 12 months*
Immunocompromised Patients	
Severe pulmonary cryptococcosis	*Same as CNS disease × 12 months*
HIV-infected Patients	
Primary therapy; induction and consolidation[d]	*Preferred regimen*: *Induction:* Amphotericin B[li] IV 0.7-1 mg/kg IV daily *plus* flucytosine 100 mg/kg/day orally in four divided doses for ≥2 weeks
Follow all regimens with suppressive therapy	*Consolidation:* Fluconazole 400 mg (6 mg/kg) orally daily × ≥8 weeks Liposomal amphotericin B 3-4 mg/kg IV daily, or amphotericin B lipid complex (ABLC) 5 mg/kg IV daily, for ≥2 weeks can be substituted for amphotericin B[e,i] in patients with or at risk for renal dysfunction *Alternative regimens, in order of preference:* Amphotericin B[e] IV 0.7-1 mg/kg IV daily × 4-6 weeks *or* liposomal amphotericin B 3-4 mg/kg IV daily[f] × 4-6 weeks *or* ABLC 5 mg/kg IV daily × 4-6 weeks *or* Amphotericin B[li] IV 0.7 mg/kg IV daily, *plus* fluconazole 800 mg (12 mg/kg) orally daily × 2 weeks, followed by fluconazole 800 mg (12 mg/kg) orally daily × ≥8weeks *or* Fluconazole ≥800 mg (1,200 mg/day is preferred) orally daily *plus* flucytosine 100 mg/kg/day orally in four divided doses × 6 weeks *or* Fluconazole 800-1,200 mg/day orally daily × 10-12 weeks (a dosage ≥1,200 mg/day is preferred when fluconazole is used alone)[g] *or* Itraconazole 200 mg orally twice daily × 10-12 weeks (use of itraconazole, which produces minimal concentrations of active drug in the CSF is discouraged)[h]

Suppressive/ maintenance therapy[i]	Preferred: Fluconazole 200 mg orally daily × ≥1 year *or* Itraconazole[h] 200 mg orally twice daily × ≥1 year *or* Amphotericin B[j] IV 1 mg/kg weekly × ≥1 year
Organ Transplant Recipients	
Mild-to-moderate non-CNS disease or mild-to-moderate symptoms without diffuse pulmonary infiltrates	Fluconazole 400 mg (6 mg/kg) orally daily × 6-12 months
CNS disease, moderately severe or severe CNS disease or disseminated disease without CNS disease, or severe pulmonary disease without evidence of extrapulmonary or disseminated disease	*Induction:* Liposomal amphotericin B 3-4 mg/kg IV daily,[f] or ABLC 5 mg/kg IV daily *plus* flucytosine 100 mg/kg/day orally in four divided doses × ≥2 weeks If induction therapy does not include flucytosine, consider a lipid formulation of amphotericin B for ≥4-6 weeks of induction therapy. Consider the use of a lipid formulation of amphotericin B[j] lipid formulation (6 mg/kg IV daily) in patients with a high-fungal burden disease or relapse of disease *Consolidation:* Fluconazole 400-800 mg (6-12 mg/kg) per day orally for 8 weeks *Maintenance:* Fluconazole 200-400 mg per day orally for 6-12 months

HIV, human immunodeficiency virus; IT, intrathecal.

[a]When more than one therapy is listed, they are listed in order of preference.

[b]See the text for definitions of induction, consolidation, suppressive/maintenance therapy, and prophylactic therapy.

[c]Deoxycholate amphotericin B.

[d]Initiate HAART therapy 2-10 weeks after commencement of initial antifungal treatment.

[e]In patients with significant renal disease, lipid formulations of amphotericin B can be substituted for deoxycholate amphotericin B during the induction.

[f]Liposomal amphotericin B has been given safely up to 6 mg/kg daily; could be considered in treatment failure or in patients with a high fungal burden.

[g]Or until cerebrospinal fluid (CSF) cultures are negative.

[h]Drug level monitoring is strongly advised.

[i]Consider discontinuing suppressive therapy during HAART in patients with a CD4 cell count ≥100 cells/μL (0.1×10^9/L) and an undetectable or very low HIV RNA level sustained for ≥3months (with a minimum of 12 months of antifungal therapy). Consider reinstitution of maintenance therapy if the CD4 cell count decreases to <100 cells/μL (0.1×10^9/L).

[j][j]Use is discouraged except in azole intolerant patients, since it is less effective than azole therapy, and is associated with a risk of IV catheter-related infections.

Data from Reference 9.

Nonimmunocompromised Patients

7 Prior to the introduction of amphotericin B, cryptococcal meningitis was an almost uniformly fatal disease; approximately 86% of patients died within 1 year. The use of large (1-1.5 mg/kg) daily doses of amphotericin B resulted in cure rates of approximately 64%. When amphotericin B is combined with flucytosine, a smaller dose of amphotericin B can be employed because of the in vitro and in vivo synergy between the two antifungal agents. Resistance develops to flucytosine in up to 30% of patients treated with flucytosine alone, limiting its usefulness as monotherapy.[41] Combination therapy with amphotericin B and flucytosine will sterilize the CSF within 2 weeks of treatment in 60% to 90% of patients, and most immunocompetent patients will be treated successfully with 6 weeks of combination therapy.[39] However, because of the need for prolonged IV therapy and the potential for renal and hematologic toxicity with this regimen, alternative regimens utilizing lipid formulations of amphotericin B and the use of shorter (2 weeks) courses of amphotericin B followed by consolidation therapy with fluconazole for 8 weeks, then maintenance therapy with a lower dosage of fluconazole for 6 to 12 months has been advocated.[9,40,42]

For asymptomatic, immunocompetent hosts with isolated mild-to-moderate pulmonary disease and no evidence of CNS disease, careful observation can be warranted; in the case of symptomatic infection, fluconazole for 6 to 12 months is warranted. In individuals with non-CNS cryptococcemia, a positive serum cryptococcal antigen titer (greater than 1:8), cutaneous infection, a positive urine culture, or prostatic disease, the clinician must decide whether to follow the regimen for isolated pulmonary disease or the more aggressive regimen for patients with CNS (disseminated) disease.[9]

Pilot studies evaluating combination therapy with fluconazole plus flucytosine as initial therapy yielded unsatisfactory results, and this approach is discouraged even in “low-risk” patients. Ketoconazole has been used successfully in the treatment of cutaneous cryptococcosis, but it is not useful in the treatment of CNS disease, probably because of its poor penetration into the CNS.[9]

Despite low CSF concentrations of amphotericin B (2%-3% of those observed in plasma), the use of intrathecal amphotericin B is not recommended for the treatment of cryptococcal meningitis except in very ill patients or in patients with recurrent or progressive disease despite aggressive therapy with IV

amphotericin B. The dosage of amphotericin B is usually 0.5 mg administered through the lumbar, cisternal, or intraventricular (through an Ommaya reservoir) route two or three times weekly. Side effects of intrathecal amphotericin B include arachnoiditis and paresthesias. Intrathecal amphotericin B therapy should be administered in combination with IV amphotericin B.[42]

The recommended management of raised ICP in cryptococcal meningitis (without hydrocephalus, a mass lesion, or a shift on computed tomography [CT] scan) has been repeated CSF removal by spinal tap. Those who do not respond and have ongoing raised ICP should have ophthalmologic monitoring for possible vision loss, and should be considered for ventriculoperitoneal shunt surgery. Neither corticosteroids (in the absence of IRIS) nor acetazolamide is recommended for management of raised ICP. Symptomatic, medically refractory mass lesions that may be compressing vital structures should be considered for surgical therapy.[38]

Immunocompromised Patients

Immunocompromised hosts with isolated severe pulmonary and extrapulmonary disease (including cryptococcemia) without CNS disease should be treated similarly to nonimmunocompromised patients with CNS disease. Immunocompromised patients with CNS infection require more prolonged therapy; treatment regimens are based on those used in the HIV-infected population and follow induction therapy with amphotericin B and consolidation therapy with 6 to 12 months of suppressive therapy with fluconazole.[9]

Organ Transplant Recipients

Cryptococcosis has been documented in an average of 2.8% of solid-organ transplant recipients. The median time to disease onset is 21 months after transplantation; 68.5% of the cases occur greater than 1 year after transplantation.

Induction therapy for solid organ transplant recipients with cryptococcal meningoencephalitis consists of liposomal amphotericin B or amphotericin B lipid complex (ABLC) plus flucytosine for at least 2 weeks. Fluconazole maintenance therapy should be continued for at least 6 to 12 months. Immunosuppressive management should include sequential or stepwise reduction of immunosuppressants, with consideration of lowering the corticosteroid dose first.[43] Amphotericin B should be used with caution in transplant recipients and is not recommended as first-line therapy in this patient

population due to the risk of nephrotoxicity in this population that frequently has reduced renal function. If used, the tolerated dosage of amphotericin B is uncertain, but 0.7 mg/kg daily is suggested with frequent renal function monitoring. Regardless of the agent utilized, all antifungal dosages need to be carefully monitored.[43]

HIV-Infected Patients

Primary antifungal prophylaxis for cryptococcosis is not routinely recommended in HIV-infected patients in the United States and Europe. However, in areas with limited HAART availability, high levels of antiretroviral drug resistance, and a high burden of disease, clinicians may wish to consider the use of either prophylactic therapy or a preemptive strategy with serum cryptococcal antigen testing for asymptomatic antigenemia.[9]

Early studies confirmed the benefit of early high-dose amphotericin B use, the usefulness of flucytosine added to amphotericin B for induction therapy, and the slight superiority of fluconazole over itraconazole for consolidation therapy.

Amphotericin B combined with flucytosine during the two-week induction phase of therapy is the initial treatment of choice, although 1 week of amphotericin B plus flucytosine and 2 weeks of fluconazole plus flucytosine were effective as induction therapy for cryptococcal meningitis in resource limited settings.[44] In patients who cannot tolerate flucytosine, amphotericin B alone is an acceptable alternative. After the initially successful 2-week induction period, consolidation therapy with fluconazole can be administered for 8 weeks or until CSF cultures are negative. In patients in whom fluconazole cannot be given, itraconazole is an acceptable, albeit less effective, alternative. Combination therapy with fluconazole plus flucytosine is effective; however, it is recommended as an alternative to the preceding therapies because of its potential for toxicity. Lipid formulations of amphotericin B are effective, but the optimal dosage is unknown.[9]

In HIV-infected patients, mortality is highly associated with elevated ICP (CSF opening pressure greater than 250 mm H_2O [2.5 kPa]). At the initiation of antifungal therapy, lumbar drainage should remove enough CSF to reduce the opening pressure by 50%. Patients initially should undergo daily lumbar punctures to maintain CSF opening pressure in the normal range. When the CSF pressure is normal for several days, the procedure can be suspended. Adjunctive steroid treatment is not recommended because therapy has resulted in mixed results and its impact on outcome is unclear. Similarly, neither mannitol nor

acetazolamide therapy provides any clear benefit in the management of elevated ICP.[9]

Suppressive (Maintenance) Therapy for Cryptococcal Meningitis in the HIV-Infected Patient

Relapse of *C. neoformans* meningitis occurs in approximately 50% of AIDS patients after completion of primary therapy. Persistence of asymptomatic urinary *C. neoformans* has been documented in a high percentage of AIDS patients despite seemingly adequate courses of therapy for primary meningeal disease. The prostate appears to act as a sequestered reservoir of infection in these patients, resulting in systemic relapse.

Patients appear to be at low risk for recurrence of cryptococcosis when they have successfully completed a course of initial therapy for cryptococcosis, remain asymptomatic with regard to signs and symptoms of cryptococcosis, have received antifungal therapy for greater than 3 of the previous 6 months, have a serum cryptococcal antigen titer less than 1:512, or have a sustained increase (eg, greater than 6 months) in their $CD4^+$ T-lymphocyte counts to greater than 100 to 200 cells/μL (0.1×10^9-0.2×10^9/L) and an HIV viral load of less than 50 copies/mL (50×10^3/L).[9,40,42]

After the completion of induction/consolidation phases of therapy, long-term chronic suppression with fluconazole (200 mg orally daily) should be continued for a minimum of one year. Maintenance therapy can be discontinued after one year in patients who have successfully completed primary therapy, are free of symptoms and signs of active cryptococcosis, and have been receiving HAART with a sustained CD4 cell count greater than 100 cells/mL (0.100×10^6/L) and an undetectable viral load.[9]

Evaluation of Therapeutic Outcomes

Once the CNS is involved, the usual course is weeks to months of progressive deterioration, with 80% of untreated patients dying within the first year. The prognosis of cryptococcal meningitis depends largely on the underlying predisposing factors of the host. Although cryptococcal antigen is positive in 90% of patients with cryptococcal meningitis, fewer than one half of the patients with cryptococcal meningitis develop antibody to capsular polysaccharide. Those who produce antibody have a slightly improved prognosis. In contrast, the presence of headache is a favorable symptom, presumably because it leads to an

earlier diagnosis. A favorable outcome is also associated with a normal mental status on diagnosis and a CSF white blood cell (WBC) count of less than 20 cells/mm^3 (0.020×10^9/L). A poor outcome is predicted, however, by the presence of one or more underlying diseases (including hematopoietic disorders and AIDS), corticosteroid or immunosuppressive therapy, pretreatment serum cryptococcal antigen titers of 1:32, and posttherapy serum antigen titers of 1:8. In non-AIDS patients, the cryptococcal antigen titer can be followed during therapy to assess response to antifungal therapy. In AIDS patients, decreasing titers are not necessarily predictive of success, and titers rarely become negative at the completion of therapy.[9]

CANDIDA INFECTIONS

Candida species are yeasts that exist primarily as small (4-6 microns), unicellular, thin-walled, ovoid cells that reproduce by budding. On agar medium, they form smooth, white, creamy colonies resembling staphylococci. Although there are more than 150 species of *Candida*, eight species—*C. albicans*, *C. tropicalis*, *Candida parapsilosis*, *C. krusei*, *Candida stellatoidea*, *C. guilliermondii*, *C. lusitaniae*, and *C. glabrata*—are regarded as clinically important pathogens in human disease. Yeast forms, hyphae, and pseudohyphae can be found in clinical specimens.[45]

Pathophysiology

8 *C. albicans* is a normal commensal of the skin, female genital tract, and entire GI tract of humans. Therefore, the mere presence of hyphae or pseudohyphae in a clinical specimen is insufficient for the diagnosis of invasive disease. The majority of infections with *C. albicans* are acquired endogenously, although human-to-human transmission also can occur. Although the term *fungemia* refers to the presence of fungi in the blood, the most commonly isolated organism is *Candida albicans*. Candidiasis can cause mucocutaneous or systemic infection, including endocarditis, peritonitis, arthritis, and infection of the CNS. (Mucocutaneous infections caused by *Candida* are discussed in further detail in Chapter 138.)

Adherence of *C. albicans* is important in the pathogenesis of oral candidiasis and subsequent colonization of the GI tract. Because evidence suggests that the GI tract is often the portal of entry for *Candida* in disseminated disease, factors that alter the adherence of *Candida* are crucial in the development of local and

systemic infection. *C. tropicalis* adheres to intravascular catheters at a higher rate than *C. albicans*, a factor that may help to account for the increased incidence of systemic infections caused by this pathogen.

CANDIDEMIA AND ACUTE HEMATOGENOUSLY DISSEMINATED CANDIDIASIS

Epidemiology

Candidemia has increased substantially in the past two decades, and the fourth most common bloodstream infection (BSI) in US hospitals.[46] It is associated with high mortality, increased length of hospital stay, and significant economic burden.[23,46,50] Although patients with neutropenia are at high risk for IFIs, the use of antifungal prophylaxis and prompt initiation of antifungal therapy in persistently febrile patients with neutropenia who do not respond to antibiotics has resulted in a reduction in the frequency of *Candida* BSIs in this population.[7] In fact, most BSIs due to *Candida* species now occur in non-neutropenic patients who have been hospitalized in adult and neonatal ICUs.[15,50,51,132]

The most commonly encountered clinical species of *Candida* include *C. albicans, C. glabrata, C. tropicalis, C. parapsilosis, C. lusitaniae, C. krusei, and C. guilliermondii.* While *C. albicans* is still the most common species of *Candida* causing candidemia, its relative frequency is decreasing, while the frequency of the other, non-*albicans* species, including *C. glabrata*, *C. tropicalis*, *C. krusei,* and *C. parapsilosis*, have increased. The change in species is of concern clinically, as certain pathogens, such as *C. krusei* and *C. glabrata*, are intrinsically more resistant to commonly used triazole drugs.[15,16] Although risk factors for the development of *Candida* BSIs in ICU patients can be identified, factors that lead to the acquisition of specific species are still unclear.[53] The recent emergence of infections caused by *Candida auris*, a novel, pathogenic *Candida* species associated with a high (40%-60%) mortality is concerning. Several outbreaks of *C. auris*, which first appeared in 2009, have been reported in the United Kingdom and Spain. Most infections appear in patients with previous exposure to antifungals and has high potential for interhuman transmission.

Patients' characteristics influence the distribution of *Candida* species: *C. krusei* in immunocompromised patients, while *C. parapsilosis* is most common in children and neonates. *C. lusitaniae* infections are a cause of breakthrough

fungemia in cancer patients; *C. parapsilosis* has emerged as the second most common pathogen, following *C. albicans*, in neonatal ICU patients, where it is often associated with central lines and PN, and fungemias in patients outside the United States, in particular in South America. Fungemia caused by *C. glabrata* is observed more commonly in adults older than 65 years of age, perhaps due to an increased rate of oral colonization with *C. glabrata* in the elderly, particularly those with dentures and those receiving psychotropic medications.[129]

Pathophysiology

Candida generally is acquired via the GI tract, although organisms also can enter the bloodstream via indwelling IV catheters. Immunosuppressed patients, including those with lymphoreticular or hematologic malignancies, diabetes, and immunodeficiency diseases and those receiving immunosuppressive therapy with high-dose corticosteroids, immunosuppressants, antineoplastic agents, or broad-spectrum antimicrobial agents, are at high risk for IFIs (**Table 139-8**). Major risk factors include the use of CVCs, total PN, receipt of multiple antibiotics, extensive surgery and burns, renal failure and hemodialysis, mechanical ventilation, and prior fungal colonization. Patients who have undergone surgery (particularly surgery of the GI tract) are increasingly susceptible to disseminated candidal infections.[54,58,60,134]

TABLE 139-8 Risk Factors for Invasive Candidiasis

Colonization
Corrected colonization index (CCI) ≥0.4*
Colonization index (CI) ≥0.8*
Candida spp. cultured from sites other than blood
Candiduria
Antibiotic use
Number of antibiotics prior to infection (per additional antibiotics)
Use of two or more antibiotics
Use of broad-spectrum antibiotics in previous 10 days
Surgery
Surgery on ICU admission
Gastro-abdominal surgery
Abdominal drainage
Elective surgery
Cardiopulmonary bypass time >120 minutes
Hickman catheter
Foreign devices
Central venous catheter
Triple lumen catheter in patients who have undergone surgery
Bladder catheter
Renal failure and dialysis
Prior hemodialysis
Hemofiltration procedures
Increased serum creatinine†
New-onset hemodialysis within 3 days of admission to ICU
Acute renal failure
Underlying disease/baseline characteristics
Total PN
Diabetes mellitus
Apache II (per point)
Signs of severe sepsis
Diarrhea at any time
Mechanical ventilation ≥10 days
Hospital-acquired bacterial infection
Bacterial peritonitis by ICU day 11
GI disease
ICU length of stay
Transferred from other hospital
Use of corticosteroids
Profound neutropenia (ANC <100/mm^3 [0.100 ×10^9/L])

*CI = the ratio of number of nonblood distinct body sites (dbs) heavily colonized with identical strains to the total number of dbs; CCI = the product of the CI and the ratio of the number of dbs showing heavy growth (≥10^5 CFU/mL [10^8 CFU/L]) to the total of dbs growing *Candida* spp.

†Serum creatinine >1.2 mg/dL (106 μmol/L) in females, >1.6 mg/dL (141 μmol/L) in males.

Data from Reference 53.

Clinical Presentation of Hematogenous Candidiasis

Dissemination of *C. albicans* can result in infection in single or multiple organs, particularly the kidney, brain, myocardium, skin, eye, liver, spleen, bone, and joints.[45] In most patients, multiple micro- and macroabscesses are formed.

Laboratory Tests

The interpretation of positive surveillance cultures of the skin, mouth, sputum, feces, or urine is hampered by their occurrence as commensal pathogens and in distinguishing colonization from invasive disease. A rapid presumptive identification of *C. albicans* can be made by incubation of *Candida* in serum; formation of a germ tube (the beginning of hyphae, which arise as perpendicular extensions from the yeast cell, with no constriction at their point of origin) within 1 to 2 hours offers a positive identification of *C. albicans*. Unfortunately, *C. dubliniensis* also can produce a germ tube, and a negative germ tube test does not rule out the possibility of *C. albicans*, but further biochemical tests must be performed to differentiate between other non-*albicans* species.

Several new rapid diagnostic methods are available at many hospitals, which can result in much more rapid identification of pathogens, including specific species, than with the use of traditional microbiological techniques. Matrix-assisted laser desorption/ionization time-of-flight intact cell mass spectrometry (MALDI-TOF-ICMS) and T2 Magnetic Resonance Assays, provide rapid detection and identification of pathogenic *Candida* species. The PNA fluorescence in situ hybridization (FISH) method uses fluorescein-labeled PNA probes that target *C. albicans* 26S rRNA for the identification of *C. albicans*. The test has excellent sensitivity (99%-100%) and specificity (100%) in the direct identification of *C. albicans* from blood cultures.[24,29,30]

Treatment

The list of risk factors for invasive candidiasis in critically ill patients is extensive, and trying to decipher which patients may benefit from antifungal prophylaxis or empirical therapy based on risk factors in an ICU is exceedingly difficult. In addition, the number of risk factors present in ICU patients changes over time, and the majority of ICU patients will have more than one risk factor. Clinically useful, practical predictive algorithms and “scoring systems” to identify high-risk patients early during their ICU admission have not proved

successful thus far. To maximize its clinical utility as a decision-making tool, the ideal algorithm would identify high-risk populations (ones with a rate of invasive candidiasis of 10%-15%), providing clinicians with a means of administering prophylaxis to a minimal number of patients, while preventing the maximal number of invasive candidiasis cases.[53,56,57]

Although it is common practice in today's standard of care to place indwelling catheters in patients for the administration of medications and parenteral nutrition (TPN), catheter-related infections are a common complication. These foreign bodies (especially triple lumen catheters) double as entry ports for normal skin flora or other nosocomial pathogens, and they provide a readily available site for the binding of pathogens via microbiotic biofilms. Their subsequent role as a source of BSIs is facilitated by frequent use, TPN, and the potential for contamination of catheters by medical staff who are colonized with *Candida* species. Most consensus recommendations urge removal of all existing tunneled CVCs and implantable devices, particularly in patients with fungemia caused by *C. parapsilosis*, which is frequently associated with catheters, as it has been associated with reduced mortality in adults, and a shorter duration of candidemia.[7] Arguments against the removal of all catheters in patients with candidemia include the prominent role of the gut as a source for disseminated candidiasis, the significant cost and potential for complications, and the problems that can be encountered in patients with difficult vascular access. However, in an individual patient it is often difficult to determine the relative contribution of gut versus catheter as the primary source of fungemia.[61] The evidence for this recommendation is weakest in cancer patients with severe neutropenia and mucositis (eg, acute leukemia, stem cell transplant), in whom candidemia is almost always primarily of gut origin, and removal of CVCs is least likely to have an impact on mortality.[7,48,54,55]

Hematogenous Candidiasis

There is a high rate of mortality in non-neutropenic patients with fungal blood cultures. Delays in the initiation of antifungal therapy significantly increase mortality.[68,69] Treatment of candidiasis should be guided by knowledge of the infecting species, the clinical status of the patient, and when available, the antifungal susceptibility of the infecting isolate. Therapy should be continued for 2 weeks after documented clearance of blood cultures, with resolution of all signs and symptoms of infection. All patients should undergo dilated fundiscopic exam within the first week of therapy. Susceptibility testing of the infecting isolate is a useful adjunct to species identification during selection of a

therapeutic approach, since it can be used to identify isolates that are unlikely to respond to fluconazole or amphotericin B.[7] However, this is not currently available at many institutions.

Nonimmunocompromised Patient

Prophylaxis In ICUs, the use of fluconazole for prophylaxis or empirical therapy has increased exponentially in the past decade. However, studies that demonstrated benefit in the prevention of invasive candidal BSIs did so either by using highly selective criteria or by studying patients in an unusually high-risk ICU setting, and the role of antifungal prophylaxis in the surgical ICU remains extremely controversial. For a study to demonstrate efficacy in clinical trials, the baseline rate of invasive candidiasis must be greater than 10%, and that prophylaxis must result in greater than fourfold reduction of disease.[7] Although ICU-specific, a greater than 10% rate of invasive candidiasis is generally found only in the setting of high-risk transplant patients (eg, patients undergoing liver transplantation), or in patients with one or more of the following risk factors by day 3 of their ICU stay: new-onset dialysis, receipt of broad-spectrum antibiotics, the presence of diabetes, and in patients receiving PN.[58,59] Prophylactic antifungals are indicated in patients with recurrent intestinal perforations and/or anastomotic leak as these patients are at extremely high risk for invasive candidiasis (35%) and the use of empiric fluconazole has been shown to significantly decrease the incidence of infection to 4%.[53]

"Empirical" Therapy (Also Known as Preemptive Therapy)

The term "preemptive" antifungal therapy is often used to describe early antifungal therapy given to high-risk patients with persistent signs and symptoms and clinical, laboratory, or radiologic surrogate markers of infection but without mycological evidence of infection, or those heavily colonized with *Candida*.[77] Few data are available for assessing the role of antifungals as empirical therapy for *suspected* fungemia in patients who do not yet exhibit a positive blood culture, or for isolates other than *C. albicans*. The empiric use of fluconazole did not significantly decrease the incidence of invasive candidiasis; thus, its use is not recommended at this time.[52,134]

Initial Antifungal Therapy in Non-Neutropenic

Patients with Documented Candidemia, in Whom the Species Is Not Yet Identified and Results of Antifungal Susceptibility Testing Are Not Known

Azoles (fluconazole or voriconazole), echinocandins, and deoxycholate amphotericin B are similarly effective for the therapy of documented candidemia in non-neutropenic patients; however, fewer adverse effects are observed with azole therapy.[65] Similarly, echinocandins are at least as effective as amphotericin B or fluconazole in (primarily non-neutropenic) adult patients with candidemia with fewer drug-related adverse events. Although the use of combination therapy (high-dose fluconazole plus amphotericin B) was superior to treatment with fluconazole alone, it was associated with a higher rate of nephrotoxicity, and the routine use of combination therapy in this patient population is not yet recommended.[7]

For empiric therapy in non-neutropenic adults, IDSA guidelines (**Table 139-9**) recommend use of an echinocandin or fluconazole as initial therapy. Echinocandins are recommended for patients with moderately severe to severe illness, and patients with recent azole exposure. Patients may be transitioned to fluconazole if their *Candida* isolates are known/likely to be susceptible to fluconazole (eg, *C. albicans*, *C. parapsilosis*) in patients who are clinically stable. Fluconazole may be used initially in patients who are less critically ill, with no recent azole exposure, who are not at high risk for *C. glabrata* or with central nervous system or endocardial disease.[7,65]

Among the lipid-associated formulations of amphotericin B, only liposomal amphotericin B (AmBisome) and ABLC (Abelcet) have been approved for use in proven cases of candidiasis; however, patients with invasive candidiasis also have been treated successfully with amphotericin B colloid dispersion (ABCD, Amphotec or Amphocil). The lipid-associated formulations are less toxic but as effective as amphotericin B deoxycholate.

Antifungal Therapy for Specific *Candida* Species

Since *C. glabrata* often demonstrate reduced susceptibility to fluconazole, treatment with echinocandins, or amphotericin B at a dosage of 0.7 mg/kg/day is often recommended as initial therapy (pending the results of susceptibility testing), although there are successful treatment outcomes reported in response to fluconazole therapy of 6 to 12 mg/kg/day, and may be suitable in less critically ill patients.[7,63,66–69]

Regardless of the species of *Candida*, in the absence of metastatic complications of disease, antifungal therapy should be continued for 2 weeks after the last positive blood culture, and until there is resolution of signs and symptoms of infection. It is important to note when counting days of therapy that the days of treatment "begin" on the first day of documented clearance of *Candida* species from bloodstream, with the use of an effective antifungal agent to which the species is susceptible. Existing central venous catheters should be removed when feasible, and all patients should undergo dilated retinal examination (preferably by an ophthalmologist) to rule out *Candida* endopthalmitis. Updated IDSA and European guidelines have recently been published.[7,31,98] The European Guidelines recommend daily blood cultures until negative, and that patients can be switched to oral therapy after 10 days of IV therapy. They also recommend the use of amphotericin or echinocandins preferentially if catheters cannot be removed.[31,98]

In non-neutropenic adults, once the species of *Candida* has been identified, amphotericin B, at a dosage of 1 mg/kg/day IV, is recommended for the management of systemic *C. krusei* infections. *C. tropicalis* and *C. parapsilosis* may be treated with either amphotericin B at 0.6 mg/kg/day or fluconazole at 6 mg/kg/day. Candidemia due to *C. parapsilosis* has increased in frequency among pediatric populations and appears to be associated with a lower mortality rate than other species of *Candida*. Since many, but not all isolates of *C. lusitaniae* are resistant to amphotericin B, fluconazole at 6 mg/kg/day is the preferred agent for treatment of this species. In patients with *C. parapsilosis* candidemia,[7] fluconazole is recommended, since MICs of echinocandins tend to be higher for *C. parapsilosis*. However, overall treatment success of candidemia or invasive candidiasis with echinocandins versus other agents was similar, and there was no difference in 30-day mortality between patients treated with fluconazole or an echinocandin.[71,72] The in vitro susceptibility of *C. auris* to antifungal agents is variable. However, while most isolates are susceptible to echinocandins, most are resistant to fluconazole, and ~40% of isolates are resistant to more than 2 classes of antifungal agents. An echinocandin is recommended as first-line therapy, with the addition of amphotericin B recommended in case of persistent fungemia or lack of clinical response.[73]

Expert opinion is divided regarding the optimal therapy of infections caused by *C. glabrata*. Guidelines recommend the use of an echinocandin.[7] The severity of illness and choice of antifungal predict response in patients with *C. glabrata* fungemia, and the choice of antifungal (fluconazole or an echinocandin) does not influence mortality.[49,63] Failure is associated with admission to an intensive care

unit. When fluconazole is dosed appropriately (**Table 139-9**), *C. glabrata* fluconazole susceptibility breakpoints are predictive of clinical and microbiological response. Echinocandin therapy is independently associated with treatment success, but not survival, in invasive candidiasis due to *C. glabrata*.[49,64]

TABLE 139-9 Antifungal Therapy of Invasive Candidiasis[7]

Type of Disease and Common Clinical Manifestations	Therapy/Comments
Prophylaxis of Candidemia	
Non-neutropenic patients[a]	Not recommended except for severely ill/high-risk patients in whom fluconazole IV/oral 400 mg daily should be used (see the text)
Neutropenic patients[a]	The optimal duration of therapy is unclear but at a minimum should include the period at risk for neutropenia: Fluconazole IV/oral 400 mg daily *or* itraconazole solution 2.5 mg/kg every 12 hours orally *or* micafungin 50 mg (1 mg/kg in patients under 50 kg) IV daily
Solid-organ transplantation, liver transplantation	*Patients with two or more key risk factors[b]:* Amphotericin B IV 10-20 mg daily *or* liposomal amphotericin B (AmBisome) 1 mg/kg/day *or* fluconazole 400 mg orally daily
Empirical (Preemptive) Antifungal Therapy	
Suspected disseminated candidiasis in febrile non-neutropenic patients	None recommended; data are lacking defining subsets of patients who are appropriate for therapy (see the text)
Initial Antifungal Therapy (Documented Candidemia with Unknown Candida Species)	
Febrile neutropenic patients with prolonged fever despite 4-6 days of empirical antibacterial therapy	*Treatment duration:* Until resolution of neutropenia An echinocandin[c] is a reasonable alternative; voriconazole can be used in selected situations (see the text)
Less critically ill patients with no recent azole exposure	An echinocandin[c] or fluconazole (loading dose of 800 mg [12 mg/kg], then 400 mg [6 mg/kg] daily)
Additional mold coverage is desired	Voriconazole
Antifungal Therapy of Documented Candidemia and Acute Hematogenously Disseminated Candidiasis, Unknown Species	
Nonimmunocompromised host[d]	*Treatment duration:* 2 weeks after the last positive blood culture and resolution of signs and symptoms of infection *Remove existing central venous catheters when feasible plus fluconazole (loading dose of 800 mg [12 mg/kg], then 400 mg [6 mg/kg] daily) or an echinocandin[d]*
Patients with recent azole exposure, moderately severe or severe illness, or who are at high risk of infection due to *C. glabrata* or *C. krusei*	An echinocandin[c] Transition from an echinocandin to fluconazole is recommended for patients who are clinically stable and have isolates (eg, *C. albicans*) likely to be susceptible to fluconazole
Patients who are less critically ill and who have had no recent azole exposure	Fluconazole
Antifungal Therapy of Specific Pathogens	
C. albicans, *C. tropicalis*, and *C. parapsilosis*	Fluconazole IV/oral 6 mg/kg/day *or* an echinocandin[c] or amphotericin B IV 0.7 mg/kg/day *plus* fluconazole IV/orally 800 mg/day; amphotericin B deoxycholate 0.5-1 mg/kg daily or a lipid formulation of amphotericin B (3-5 mg/kg daily) are alternatives in patients who are intolerant to other antifungals; transition from amphotericin B deoxycholate or a lipid formulation of amphotericin B to fluconazole is recommended in patients who are clinically stable and whose isolates are likely to be susceptible to fluconazole (eg, *C. albicans*); voriconazole (400 mg [6 mg/kg] twice daily × two doses then 200 mg [3 mg/kg] twice daily thereafter) is efficacious, but offers little advantage over fluconazole; it may be utilized as step-down oral therapy for selected cases of candidiasis due to *C. krusei* or voriconazole-susceptible *C. glabrata* *Patients intolerant or refractory to other therapy[e]:* Amphotericin B lipid complex IV 5 mg/kg/day Liposomal amphotericin B IV 3-5 mg/kg/day Amphotericin B colloid dispersion IV 2-6 mg/kg/day
C. krusei	Amphotericin B IV ≤1 mg/kg/day *or* an echinocandin[c]
C. lusitaniae	Fluconazole IV/orally 6 mg/kg/day
C. glabrata	An echinocandin[c] (transition to fluconazole or voriconazole therapy is not recommended without confirmation of isolate susceptibility)
Neutropenic host[f]	*Treatment duration:* Until resolution of neutropenia *Remove existing central venous catheters when feasible, plus:* Amphotericin B IV 0.7-1 mg/kg/day (total dosages 0.5-1 g) *or patients failing therapy with traditional amphotericin B:* Lipid formulation of amphotericin B IV 3-5 mg/kg/day

Chronic disseminated candidiasis (hepatosplenic candidiasis)	*Treatment duration:* Until calcification or resolution of lesions *Stable patients:* Fluconazole IV/orally 6 mg/kg/day *Acutely ill or refractory patients:* Amphotericin B IV 0.6-0.7 mg/kg/day
Urinary candidiasis	*Asymptomatic disease:* Generally no therapy is required *Symptomatic or high-risk patients*[g]: Removal of urinary tract instruments, stents, and Foley catheters, +7-14 days therapy with fluconazole 200 mg orally daily *or* amphotericin B IV 0.3-1 mg/kg/day

PO, orally.

[a]Patients at significant risk for invasive candidiasis include those receiving standard chemotherapy for acute myelogenous leukemia, allogeneic bone marrow transplants, or high-risk autologous bone marrow transplants. However, among these populations, chemotherapy or bone marrow transplant protocols do not all produce equivalent risk, and local experience should be used to determine the relevance of prophylaxis.

[b]Risk factors include retransplantation, creatinine of more than 2 mg/dL (177 µmol/L), choledochojejunostomy, intraoperative use of 40 units or more of blood products, and fungal colonization detected within the first 3 days after transplantation.

[c]Echinocandin = caspofungin 70 mg loading dose, then 50 mg IV daily maintenance dose, or micafungin 100 mg daily, or anidulafungin 200 mg loading dose, then 100 mg daily maintenance dose.

[d]Therapy is generally the same for acquired immunodeficiency syndrome (AIDS)/non-AIDS patients except where indicated and should be continued for 2 weeks after the last positive blood culture and resolution of signs and symptoms of infection. All patients should receive an ophthalmologic examination. Amphotericin B can be switched to fluconazole (IV or oral) for the completion of therapy. Susceptibility testing of the infecting isolate is a useful adjunct to species identification during selection of a therapeutic approach because it can be used to identify isolates that are unlikely to respond to fluconazole or amphotericin B. However, this is not currently available at most institutions.

[e]Often defined as failure of ≥500 mg amphotericin B, initial renal insufficiency (creatinine ≥2.5 mg/dL [221 µmol/L] or creatinine clearance <25 mL/min [0.42 mL/s]), a significant increase in creatinine (to 2.5 mg/dL [221 µmol/L] for adults or 1.5 mg/dL [133 µmol/L] for children), or severe acute administration-related toxicity.

[f]Patients who are neutropenic at the time of developing candidemia should receive a recombinant cytokine (granulocyte colony-stimulating factor or granulocyte–monocyte colony-stimulating factor) that accelerates recovery from neutropenia.

[g]Patients at high risk for dissemination include neutropenic patients, low-birth-weight infants, patients with renal allografts, and patients who will undergo urologic manipulation.

Data from Reference 7.

Immunocompromised Patients

In immunocompromised patients, the optimal agent, dose, and duration of therapy are unclear, and patients must be monitored carefully with serial blood cultures and careful physical examinations, particularly of the retina. Patients who experience prolonged neutropenia and persistent candidemia may benefit from administration of a recombinant cytokine (granulocyte colony-stimulating factor) that accelerates recovery from neutropenia.[7]

Prophylaxis Recognition of the role of the GI tract in invasive *Candida* infections has led to efforts to decrease infections by prophylactic administration of topical or systemically absorbed antifungal agents in immunocompromised patients. The use of systemically absorbable agents such as azole antifungal agents appears to decrease the risk of IFIs.[7,58,82]

Several antifungal agents, including fluconazole (400 mg/day), posaconazole (200 mg three times daily), micafungin or caspofungin (50 mg daily)

administered from the start of the conditioning regimen until day 75, can reduce the frequency of invasive *Candida* infections and decrease mortality in patients undergoing allogeneic bone marrow transplantation.[7,22,75,82]

Similarly, in less risk-selected patients with hematologic malignancies who are undergoing remission-induction chemotherapy, fluconazole, posaconazole, or caspofungin, during induction chemotherapy for the duration of neutropenia, are effective in preventing systemic infection and death caused by *Candida* species.[7]

For solid-organ transplant recipients, fluconazole or liposomal amphotericin B is recommended as postoperative antifungal prophylaxis for liver, pancreas, and small bowel transplant recipients at high risk of candidiasis.[7,21]

Widespread use of prophylactic fluconazole in all ICU patients is not warranted and may lead to an increase in resistance and adverse events. If utilized, prophylactic fluconazole should target high-risk patients with a presumed risk of invasive candidiasis of 10% to 15%.[7,53,82]

Empirical Therapy for Febrile Neutropenic Patients

In patients who have not been receiving antifungal prophylaxis, *Candida* spp. are the most likely cause of invasive fungal infection. In patients receiving fluconazole prophylaxis, fluconazole-resistant *Candida* spp. (eg, *C. glabrata* and *C. krusei*) and invasive mold infections, particularly *Aspergillus* spp., are the most likely causes. Amphotericin B deoxycholate, a lipid formulation of amphotericin B, caspofungin, voriconazole, or itraconazole are recommended as suitable options for empiric antifungal therapy in neutropenic patients.[76] Many clinicians advocate early institution of empirical IV amphotericin B in patients with neutropenia and persistent (greater than 5-7 days) fever. However, the potential toxicities (particularly nephrotoxicity) of this agent preclude its routine use in all patients. Suggested criteria for the empirical use of amphotericin B include: (a) fever of 5 to 7 days' duration that is unresponsive to antibacterial agents, (b) neutropenia of more than 7 days' duration, (c) no other obvious cause for fever, (d) progressive debilitation, (e) chronic adrenal corticosteroid therapy, and (f) indwelling intravascular catheters. In patients who fail therapy with amphotericin B, lipid formulations of amphotericin B can be used. Lipid formulations of amphotericin B can be used as alternatives to amphotericin B deoxycholate for empirical therapy. Although they do not appear to be substantially more effective, there is less drug-related toxicity.[76]

For persistently febrile patients who have been receiving anti-mold prophylaxis, a different class of antifungal agent with activity against molds

should be used for empiric therapy. The choice of the initial antifungal agent may vary based on an institution's experience (ie, epidemiology and susceptibility patterns) and patient risks for specific mold infections (eg, *Aspergillus* vs infections caused by the Mucorales). In patients with pulmonary nodules or nodular pulmonary infiltrates, invasive mold infection should be strongly suspected and treated.[82] As fluconazole lacks activity against filamentous fungi, its use in patients at high risk for these pathogens should be avoided. In addition, clinicians need to consider that echinocandins are not active against *Cryptococcus* spp., *Trichosporon* spp., and filamentous molds other than *Aspergillus* spp. (eg, *Fusarium* spp.), nor are they active against the endemic fungi (*Histoplasma, Blastomyces, Coccidioides* spp.).[105]

Specific Therapy

Amphotericin B, the azoles, and the echinocandins have roles in the treatment of hematogenous candidiasis, and the choice of therapy is guided by weighing the greater activity of amphotericin B for some non-*albicans* species (eg, *C. krusei*) against the lower toxicity and ease of administration of fluconazole and the echinocandins.[7]

Most clinicians recommend liposomal amphotericin B (3-5 mg/kg IV daily) for approximately 1 to 2 weeks in patients with *Candida* endophthalmitis and in all neutropenic patients with candidemia. Longer courses of therapy can be needed in some patients; patients who have vitreous involvement generally require a longer duration of therapy than those who have only chorioretinitis.[7] Fluconazole and amphotericin B appear similarly effective for the treatment of *C. albicans* BSIs in the neutropenic patient; controlled data, however, are lacking. In patients with uncomplicated *C. albicans* fungemia who have not received systemic prophylaxis with antifungal azoles, therapy with fluconazole 400 to 800 mg/day IV can be considered. However, in patients who have undergone allogeneic HSCT, the role of fluconazole is becoming more limited because of its widespread use for antifungal prophylaxis. In this setting, particularly if the patient has been treated previously with an azole antifungal agent, the possibility of microbiologic resistance must be considered. Infections with fluconazole-resistant *Candida* species, including *C. glabrata*, *C. krusei*, and fluconazole-resistant *C. albicans*, or with *Aspergillus* species are more likely.

CANDIDURIA

Within the urinary tract, most common lesions are either *Candida* cystitis or hematogenously disseminated renal abscesses. *Candida* cystitis often follows catheterization or therapy with broad-spectrum antimicrobial agents. The diagnosis of *Candida* cystitis can be problematic because of the frequent presence of *Candida* pseudohyphae and yeast cells in urine specimens secondary to urethral colonization. The usefulness of urine colony counts or antibody coating techniques is questionable. The recovery of 10,000 organisms or visualization of both yeast and pseudohyphae from fresh midstream urine or from bladder urine obtained by single catheterization (not indwelling) is suggestive of genitourinary candidiasis. In most patients, the infection is asymptomatic and clears spontaneously without specific antifungal therapy.[7]

Initial therapy of candidal cystitis should focus on removal of urinary catheters whenever possible. Changing the catheter will eliminate candiduria in only 20% of patients, whereas discontinuation will eradicate *Candida* in 40% of patients. Asymptomatic candiduria rarely requires therapy. Therapy should be used in symptomatic patients and in neutropenic patients, as well as in patients with renal allografts and those who will undergo urologic manipulation, because of the risk of dissemination.[74,78]

Oral fluconazole 200 mg/day for 14 days hastens the time to a negative urine culture as compared with placebo treatment, but 2 weeks after the end of therapy, the frequency of a negative urine culture remains the same with both treatments.[78] Short courses of therapy are not recommended; treatment should include removal of catheters and stents whenever possible plus 7 to 14 days of therapy. Bladder irrigation with amphotericin B (50 mg in 500 mL sterile water instilled twice daily into the bladder via a three-way catheter) is only transiently effective. Minimal quantities (less than 3%) of amphotericin B are absorbed systemically from the bladder.[78,81]

ASPERGILLOSIS

Saprophytic molds belonging to the *Aspergillus* spp. can be found around the world, of which, *Aspergillus fumigatus*[83] is the most commonly observed pathogen, followed by *Aspergillus flavus*. Guidelines for the prophylaxis and empiric treatment of invasive aspergillosis (IA) in neutropenic hosts can be referred to for more comprehensive details.[130,131]

IA is the second most common IFI, with increasing incidence over the last 20 years along with the advances in the treatment of hematological malignancies.

The infection most commonly affects immunocompromised patients and patients with acute myeloid leukemia (AML) and those who undergo allogeneic HSCT who have prolonged durations (more than 10 days) of neutropenia are at highest risk.[86] In the highest risk group, IA rates can reach 25%. The frequency of IA and infections caused by other molds has increased over the past 2 decades. Despite heightened awareness of the profiles of patients at risk, for *Aspergillus* infections, and despite the advent of liposomal formulations of amphotericin B, IA continues to be associated with extremely high mortality rates.[85,131] The crude mortality approaches 80% to 90% in patients with AIDS and bone marrow transplant patients. Major target sites for primary invasive disease include the lungs and sinuses; frequently, secondary infections involve the central nervous system. The appropriate duration of treatment is based on the extent of the infection, response to therapy, and host factors.[131]

Epidemiology

Aspergillus is a ubiquitous mold that grows well on a variety of substrates, including soil, water, decaying vegetation, moldy hay or straw, and organic debris. Although more than 300 species of *Aspergillus* have been characterized, three species are most commonly pathogenic: *A. fumigatus*, *A. flavus*, and *Aspergillus niger*. The varying degrees of pathogenicity of each species depend on their relative geographic prevalence, conidial size and shape, thermotolerance, and production of mycotoxins. For example, transport of *A. fumigatus* conidia into the lungs is facilitated by their smaller diameter in comparison with *A. flavus* and *A. niger*.

9 The term *aspergillosis* may be broadly defined as a spectrum of diseases attributed to allergy, colonization, or tissue invasion caused by members of the fungal genus *Aspergillus*. A single satisfactory classification system for these disease entities is difficult because different populations of patients can develop the same type of infection. For example, osteomyelitis can result from local trauma or hematogenous dissemination in an immunocompromised host. Colonization in normal hosts can lead to allergic diseases ranging from asthma to allergic BPA or, rarely, invasive disease.[79]

Pathophysiology

Aspergillosis generally is acquired by inhalation of airborne conidia that are small enough (2.5-3 microns) to reach alveoli or the paranasal sinuses. Each

conidiophore releases 10^4 conidia that remain suspended for long periods and are viable for months in dry locations. Although some authors advocate monitoring of hospital air for *Aspergillus* conidia, guidelines for interpreting results are not available. The use of high-efficiency particulate air (HEPA) filters in operating rooms and laminar flow rooms and removal of immunocompromised patients from hospital renovation sites can be helpful in preventing infection in this population.

Superficial or locally invasive infections of the ear, skin, or appendages often can be managed with topical antifungal therapy. Skin infections in patients with burn wounds, although uncommon, can progress to deep-tissue invasion despite the use of topical or parenteral antifungal agents. Risk factors for deep infection include extensive thermal injuries, malnutrition, cirrhosis, and previous infection with *Pseudomonas aeruginosa*.[79]

Allergic manifestations of *Aspergillus* range in severity from mild asthma to allergic BPA. BPA, which is almost always caused by *A. fumigatus*, is characterized by severe asthma with wheezing, fever, malaise, weight loss, chest pain, and a cough productive of blood-streaked sputum. Following recurrent episodes of severe asthma, the disease usually progresses to fibrosis and bronchiectasis with granuloma formation. When *Aspergillus* conidia become trapped in the viscous mucus of asthmatic patients, BPA develops. The fungus grows, releasing toxins and antigens. The resulting host sensitization results in a variety of immune reactions. Early in the course of disease, an immunoglobulin E (IgE)-mediated (type I) immune reaction results in bronchospasm, eosinophilia, and immediate skin reactivity. The ensuing fibrosis and pulmonary infiltrates appear to be mediated by circulating or precipitating antibody complexes of IgG antibody, followed by granuloma formation and mononuclear infiltration because of a type IV delayed hypersensitivity reaction. Therapy is aimed at minimizing the quantity of antigenic material released in the tracheobronchial tree. Management of acute asthma attacks minimizes trapping of *Aspergillus* by bronchial secretions, and administration of parenteral corticosteroids clears lung infiltrates.[79] Antifungal therapy generally is not indicated in the management of allergic manifestations of aspergillosis, although some patients have demonstrated a decrease in their corticosteroid dose following therapy with itraconazole.[84]

Aspergilloma

In the nonimmunocompromised host, *Aspergillus* infections of the sinuses most

commonly occur as saprophytic colonization (aspergillomas or “fungus balls”) of previously abnormal sinus tissue. An aspergilloma is composed of intertwined *Aspergillus* hyphae matted together with fibrin, mucus, and cellular debris. Infection usually is localized in the maxillary sinus and rarely is associated with local invasion of adjacent bone or brain tissue. Sinus aspergillosis also can present as allergic sinusitis with nasal drainage of brownish mucous plugs. Therapy with corticosteroids and surgery generally is successful. In the immunocompromised host, subacute, chronic, or fulminant invasive disease can be seen, and a combination of antifungal and surgical therapy generally is required.[131]

Pulmonary aspergillomas are fungus balls arising in preexisting cavities because of tuberculosis, histoplasmosis, lung tumors, or radiation fibrosis, although occasionally no previous pulmonary disease is present. The diagnosis of aspergilloma generally is made on the basis of chest radiographs, on which aspergillomas appear as a solid rounded mass, sometimes mobile, of water density within a spherical or ovoid cavity and separated from the wall of the cavity by an airspace of variable size and shape. Patients generally experience chest pain, dyspnea, and sputum production. Hemoptysis is observed in 50% to 80% of patients, probably because of ulceration of the epithelial lining of the cavity with formation of granulation tissue, and hemoptysis is the cause of death in up to 26% of patients with aspergilloma. A poor prognosis is associated with increasing size or number of aspergillomas, immunosuppression (including corticosteroids), increasing *Aspergillus*-specific titers, underlying sarcoidosis, and HIV infection. Although *Aspergillus* can be cultured in only 50% to 60% of patients, precipitating antibodies are positive in virtually 100% of patients.

Invasive disease occurs rarely, and therapy therefore is controversial. There are no controlled clinical trials with which to guide therapy, and recommendations for treatment have been generated from uncontrolled trials and case reports.[131] Concern regarding the risk of severe hemorrhage has led some clinicians to use aggressive surgical excision of aspergillomas or pulmonary resection in patients with hemoptysis. Complications, including bronchopulmonary fistulas, hemorrhage, empyema, and persistent airspace problems, have led to the recommendation that surgical intervention be reserved for patients with severe (greater than 500 mL per 24 hours) hemoptysis, however. Bronchial artery embolization has been used to occlude the vessel that supplies the bleeding site in patients experiencing hemoptysis. Unfortunately, bronchial artery embolization generally is unsuccessful or only temporarily effective. Collateral circulation eventually develops, supplying blood flow to the

affected area, and hemoptysis often recurs; consequently, reembolization is often unsuccessful. Bronchial artery embolization should be used as a temporizing procedure in a patient with life-threatening disease who might respond to more definitive therapy if hemoptysis is stabilized. Mild-to-moderate hemoptysis should be managed conservatively. Although IV amphotericin B generally is not useful in eradicating aspergillomas, inhaled or intracavitary instillation of amphotericin B has been employed successfully in a limited number of patients. Itraconazole has been efficacious in uncontrolled studies; however, the dose and duration of therapy have not been standardized. Hemoptysis generally ceases when the aspergilloma is eradicated.[131]

Invasive Aspergillosis

IA remains a disease of very high mortality: for example, in HSCT recipients with a diagnosis of invasive aspergillosis, the 3-month post HSCT mortality rate is 53.8% for autologous transplant recipients but approaches 90% for allogeneic HSCT recipients. However, the overall 1-year survival rate is only about 20% for autologous and allogeneic HSCT recipients with proven or probable invasive mold infections.[79]

Although exposure to *Aspergillus* conidia is nearly universal, impaired host defenses are required for the development of invasive disease. Phagocytes (neutrophils, monocytes, and macrophages) rather than antibodies or lymphocytes constitute the primary host defense system against invasive disease with aspergillosis. Macrophages prevent germination of conidia and also eradicate conidia, providing the first line of defense against invasive disease. Administration of corticosteroids appears to impair the killing of conidia by macrophages and to impair mobilization of neutrophils. Neutrophils halt hyphal growth and dissemination and kill mycelia, constituting a second line of defense. Prolonged neutropenia appears to be the most important predisposing factor to the development of IA, accounting for the high frequency of disease in patients with acute leukemia.[79]

Invasive disease with *Aspergillus* can arise de novo or from any of the allergic or colonizing forms of aspergillosis. Predisposing factors to the development of IA include glucocorticoid therapy, particularly following chronic administration or with higher dosages (30-200 mg/day of prednisone), cytotoxic agents, and recent or concurrent therapy with broad-spectrum antimicrobial agents. Patients with chronic hepatitis, alcoholism, diabetes mellitus, chronic granulomatous disease, leukopenia (less than 1,000 cells/mm^3 [1×10^9/L]), leukemia

(particularly acute lymphocytic or myelogenous leukemia), lymphoma, and acute rejection of an organ transplant are also at a higher risk of invasive disease. Although rare, IA has been reported in apparently normal hosts.[79] Aspergillosis is an uncommon fungal infection in patients with AIDS. AIDS patients may be at less risk for aspergillosis than other fungal infections because the primary cellular defect in AIDS patients is in the T-lymphocytes, whereas neutrophils and macrophages constitute the primary lines of defense to infection with aspergillosis.

Clinical Presentation

The lung is the most common site of invasive disease.[79] In the immunocompromised host, aspergillosis is characterized by vascular invasion leading to thrombosis, infarction, necrosis of tissue, and dissemination to other tissues and organs in the body. If bone marrow function returns, cavitation of the pulmonary lesion generally occurs, and the spread of infection can be halted. The progressive nature of the disease and its refractoriness to therapy are, in part, caused by the organism's rapid growth and its tendency to invade blood vessels.

CLINICAL PRESENTATION: ASPERGILLOSIS

Signs and Symptoms

Patients with IPA generally have blunted or nonspecific signs and symptoms of infection due to impaired inflammatory responses.[93] Patients often present with classic signs and symptoms of acute pulmonary embolus: pleuritic chest pain, fever, hemoptysis, and friction rubs. The CNS, liver, spleen, heart, GI tract, pericardium, and other body sites are involved in a substantial minority of cases. In neutropenic patients with *Aspergillus* pneumonia, hyphae invade the walls of bronchi and surrounding parenchyma, resulting in an acute necrotizing, pyogenic pneumonitis. As a result, patients often present with classic signs and symptoms of acute pulmonary embolus: pleuritic chest pain, fever, hemoptysis, and friction rubs.

Diagnosis

The diagnosis of aspergillosis is complicated by the presence of *Aspergillus* as a

normal commensal in the human GI tract and respiratory secretions, and establishment of a definitive diagnosis of disease is difficult. The likelihood of invasive fungal infections is assessed on a scale of probability (possible, probable, proven) based upon host factors, clinical and microbiological criteria. Demonstration of *Aspergillus* by repeated culture and microscopic examination of tissue provides the most firm diagnosis. A definitive diagnosis of invasive pulmonary aspergillosis (IPA) can be made by obtaining a biopsy of lung tissue; however, thrombocytopenia often limits clinicians' ability to perform this procedure. The appearance of *Aspergillus* in tissues varies with increasing host resistance from the normal vegetative hyphae found with necrotic tissue and exudate in the alveoli of immunocompromised hosts to the compact, tangled filaments (*granules*) observed in fungal balls. Identification of *Aspergillus* generally is based on the appearance of 2- to 4-micron-wide septate hyphae that are dichotomously branched at 45 degree angles. Sporulation is observed rarely in tissue. Although growth on Sabouraud dextrose or brain-heart infusion agar can be used for primary culture, bronchoscopy or bronchoalveolar lavage cultures are positive in only 40% of histopathologically identified specimens. Blood, CSF, and bone marrow cultures are rarely positive for *Aspergillus*.

The diagnosis is determined with the use of high resolution CT, in which IPA will manifest early on as "halo sign" (an area of low attenuation surrounding a nodular lung lesion, caused by edema or bleeding surrounding an ischemic area). In late IA nodular lesions, diffuse pulmonary infiltrates, consolidation, or ground glass opacities can be observed, and CT scans may demonstrate the crescent sign (an air crescent near the periphery of a lung nodule caused by contraction of infarcted tissue), while chest radiographs can demonstrate wedge-shaped, pleural-based infiltrates or cavities. These signs are not specific to IPA, however, as bacteria and other fungal infections may produce similar findings. CT abnormalities are best documented in neutropenic marrow transplant recipients and commonly precede plain chest radiograph abnormalities.[93,131]

Diagnostic Tests

The diagnosis of aspergillosis, and other invasive mold infections, remains difficult. New laboratory methods that allow for early differentiation of IFIs due to *Aspergillus* species versus zygomycetes and other moulds would be helpful in allowing clinicians in the earlier initiation of appropriate antifungal therapy. Although PCR-based testing is being performed in some centers, and appears promising, no FDA-approved method is commercially available.[47]

The galactomannan test is an enzyme-linked immunosorbent assay (ELISA) (Platelia *Aspergillus* EIA test; Bio-Rad Laboratories) that detects galactomannan, an antigen released from *Aspergillus* hyphae upon invasion of host tissue. The clinical utility of this assay has been assessed in the clinical setting by sampling serum, BAL fluid, cerebrospinal fluid (CSF), and pleural fluid; however, the currently approved test is performed on serum. Additionally, while FDA-approved for use in the diagnosis of IA in HSCT recipients and in patients with leukemia; its usefulness in solid-organ transplant and pediatric populations needs to be established. In most patients, circulating antigen can be detected at a mean of 8 days before diagnosis by other means. The test has a sensitivity ranging from 30% to 100% and a specificity of approximately 85%; however, the sensitivity of the assay is decreased in patients receiving mold-active drugs on the day of sampling.[20] False positives can occur, particularly in patients receiving cyclophosphamide, piperacillin–tazobactam and amoxicillin–clavulanate, those with bifidobacteria infections, and in neonates.[90,91] and there are differences in the cutoff values for a positive result in the United States versus Europe. False negatives can occur during the concomitant use of antifungals, presumably because the level of galactomannan is related to the fungal burden. In addition, it is important to note that the utility of galactomannan testing in the setting of prophylaxis has not been defined.[20]

1,3-β-d-glucan is a component of fungal cell walls that can be detected colorimetrically in clinical samples, including blood and bronchoalveolar lavage specimens, using a chromogenic variant of the limulus amoebocyte lysate assay. However, the current FDA-approved test (Fungitell; Associates of Cape Cod) is performed only on serum, and is nonspecific for *Aspergillus*. The 1,3-β-d-glucan test can be used to detect most fungi, including *Fusarium*, *Trichosporon*, *Saccharomyces*, and *Acremonium*, which are less common but important fungal pathogens, with a sensitivity of 55% to 100% and a specificity of 52% to 100%. In addition, the test does not detect the zygomycetes or cryptococci, and it can produce false positives in patients undergoing hemodialysis with cellulose membranes, and in other cases for unclear reasons.[20] Although a positive test6 result for the presence of (1,3)-β-d-glucan [BG] does not identify the infecting fungus, the practical application of this test includes its use as a screening assay (presumptive marker) for invasive fungal infection to allow the earlier initiation of antifungal therapy. Other tests are necessary for the confirmation and identification of the fungal pathogen.[20,47]

TREATMENT

Invasive Aspergillosis

Therapy for IA is far from optimal at this time in part because of the difficulties in establishing a diagnosis and in part because of a lack of truly effective antifungal agents. Administration of amphotericin B appears to decrease mortality from more than 90% to approximately 45%. These data, however, are difficult to interpret because many patients were diagnosed postmortem, or amphotericin B therapy was not administered until the patient had very advanced disease. Mortality from pulmonary aspergillosis in bone marrow transplant recipients exceeds 94% regardless of therapy.[79] Although early diagnosis and administration of antifungal therapy can result in higher response rates, correction of underlying immune deficits (in particular, return of neutrophil counts) is of paramount importance in eradication of infection.[79,92,93]

Until the diagnosis of aspergillosis can be determined more rapidly and definitively, empirical therapy must be instituted when invasive disease is suspected. In patients at highest risk for invasive disease (acute leukemia and bone marrow transplant recipients), the most important predisposing factors include prolonged severe neutropenia (less than 100 cell/μL [0.1×10^9/L] for more than 1 week), graft rejection, chronic administration of corticosteroids, and tissue damage from preexisting infection.[79]

Non-HIV-Infected Patient

Prophylaxis As noted above in the discussion of prophylaxis for *Candida* infections in immunocompromised hosts, prophylaxis with azoles or echinocandins can reduce the incidence of aspergillosis in select high-risk populations. The incidence of invasive fungal infections following solid organ transplantation varies with the organ being transplanted and the epidemiology at individual centers.[21,22] *Candida* and *Aspergillus* species are the leading causative agents, with the median time to onset following transplantation depending on the type of transplant. Several organizations have developed guidelines for the prevention of invasive fungal infections in patients with malignancies and in those undergoing solid organ or hematopoietic stem cell transplantation.[70,76,94]

Specific Therapy

The outcome of invasive aspergillosis (IA) continues to be associated with significant attributable mortality, especially in patients with hematological malignancies and in HSCT recipients. Older azole antifungal agents (miconazole, ketoconazole and fluconazole) possess poor in vitro activity against *Aspergillus* species; however, newer triazoles (itraconazole, voriconazole, posaconazole, and isavuconazole) demonstrate improved activity both in vitro and in animal models of infection. Antifungal agents with in vitro activity against *Aspergillus* species include amphotericin B, the echinocandins, and the azoles itraconazole, voriconazole, posaconazole, and isavuconazole. Historically, high dosages (1-1.5 mg/kg/day) of deoxycholate amphotericin B were utilized for the treatment of suspected or proven invasive aspergillosis. Lipid formulations of amphotericin B are overall less nephrotoxic and at least as effective as amphotericin B, and that they can be effective when amphotericin Bis not.[108] They are indicated when preexisting or arising nephrotoxicity or concomitant nephrotoxic agents preclude high-dose amphotericin B therapy or when treatment with amphotericin B appears to fail. Use of the highest approved dosages of the lipid formulations for treatment of suspected or documented infections is strongly advocated. However, randomized data from clinical trials are limited for most agents. Thus, while open-label trials support the potential of posaconazole and the echinocandins for treatment of invasive aspergillosis in immunocompromised patients, current guidelines from the United States and other countries consider voriconazole as the agent of choice for the primary treatment of aspergillus.[131]

Voriconazole has emerged as the drug of choice of most clinicians for primary therapy of most patients with IA, based on a pivotal study in which a randomized comparison of voriconazole and deoxycholate amphotericin B followed by other licensed antifungal agents for primary therapy for invasive aspergillosis demonstrated superior antifungal efficacy and improved survival at week 12 in the voriconazole arm.[109] Isavuconazole is approved for the primary treatment of aspergillosis, based upon the results of a double blind, randomized, multinational trial in subjects with proven or probable invasive fungal disease caused by *Aspergillus* spp. or other filamentous fungi. Isavuconazole was well tolerated, with fewer drug-related adverse effects than voriconazole.[87] In patients who are unable to tolerate voriconazole, amphotericin B can be used. Because *Aspergillus* is only moderately susceptible to amphotericin B, full doses (1-1.5 mg/kg/day) are generally recommended, with response measured by defervescence and radiographic clearing. To treat microfoci, therapy should be

continued after resolution of clinical and radiographic abnormalities until cultures (if they can be obtained) are negative, and reversible underlying predispositions have abated.

Clinical response rather than any arbitrary total dose should guide duration of therapy. The optimal dosage or duration of treatment of invasive disease is unknown and dependent on the extent of disease, the response to therapy, and the patient's underlying disease(s) and immune status. Response to therapy is largely related to the extent of aspergillosis at the time of diagnosis, and host factors, such as resolution of neutropenia and the return of neutrophil function, lessening immunosuppression, and the return of graft function from a bone marrow or organ transplant.[80]

Lipid formulations of amphotericin B can be indicated in patients with impaired renal function, and in those patients who develop nephrotoxicity while receiving deoxycholate amphotericin B. The lipid-based formulations may be preferred as initial therapy in patients with marginal renal function or in patients receiving other nephrotoxic drugs. Although these preparations appear less toxic than standard preparations, only limited data regarding their relative efficacy for IA are available at this time, as the studies with the lipid preparations have been open-label or with historical conventional amphotericin B controls.[101,108]

Although caspofungin (and other echinocandins) have in vitro activity against *Aspergillus* species, echinocandins are unable to completely kill or inhibit *Aspergillus* species. Caspofungin is approved by the FDA for use as salvage therapy in patients who are refractory to or intolerant of other therapies such as conventional amphotericin B, lipid formulations of amphotericin B, and/or itraconazole.[97,62] However, for primary therapy of aspergillosis, response rates are lower with caspofungin than those obtained with voriconazole and amphotericin B.[89]

The role of azoles in the management of azole-resistant aspergillosis remains unclear. In patients infected with azole-resistant strains of *Aspergillus*, combination therapy with liposomal amphotericin B or a combination of voriconazole or posaconazole with an echinocandin may be effective.[85]

Based on extensive experience in the management of bacterial, and more recently, retroviral infections, the use of combination agents for synergistic or additive effects is now common practice, particularly for the treatment of IA.[80] However, while the advantages of combination therapy include the possibility of more rapid, synergistic killing, disadvantages include the possibility of antagonism, as well as increased cost and the increased risk of drug interactions and adverse effects. A "proof of principle" study demonstrated that combination

antifungal therapy could provide superior outcomes versus single agent therapy in the treatment of candidemia. High-dose fluconazole, alone or in combination with amphotericin B, in non-immunocompromised patients with candidemia demonstrated no antagonism and a trend toward improved success and more rapid clearance of *Candida* from the bloodstream. However, renal toxicity (from amphotericin B) was higher in the combination therapy arm.[95] Whether these adverse effects would be similar, if lipid formulations were used instead of the deoxycholate formulation of amphotericin B, is not known. Combination therapy with voriconazole plus anidulafungin versus voriconazole alone in the subgroup of patients with invasive aspergillosis demonstrated only a trend toward increased 6 week survival.[96] Thus, there are as yet no firm recommendations regarding the use of such combinations in humans.[96,85]

Secondary Prophylaxis

The use of prophylactic antifungal therapy to prevent primary infection or reactivation of aspergillosis during subsequent courses of chemotherapy is controversial.[131] Studies assessing the utility of IV administration of amphotericin B in low doses (0.1 mg/kg/day) as prophylactic therapy or with higher dosages (0.5-0.6 mg/kg/day) as empirical therapy for IFIs in patients with granulocytopenia have not included sufficient numbers of patients to enable detection of differences in the number of *Aspergillus* infections.

In granulocytopenic patients who recover from an episode of IA, the risk of relapse of aspergillosis during subsequent courses of chemotherapy is greater than 50%. Secondary prophylaxis of aspergillosis with empirical administration of high-dose amphotericin B decreases the risk of relapse. Amphotericin B 1 mg/kg/day is started 24 to 48 hours prior to the start of chemotherapy and continued throughout the period of granulocytopenia.[80]

Treatment Options for Emerging Pathogens

The increased frequency of fungal pathogens that were once rare is gaining attention from the medical community. Mucormycosis, previously known zygomycosis, is a term describing infections caused by fungi belonging to the order Mucorales. Permissive environmental conditions, selective antifungal pressure, and increased numbers of immunosuppressed patients have led to increased numbers of infections caused by the Mucorales, which include *Rhizomucor* spp., *Absidia* spp. (now *Lichtheimia* spp.), *Rhizopus* spp., *Mucor* spp., and *Cunninghamella* spp. Prompt initiation of antifungal therapy is crucial,

as treatment delays are associated with increased mortality.[103]

Of currently available systemic antifungals, only amphotericin B (including the lipid formulations) and posaconazole exhibit good in vitro activity against the Mucorales. Isavuconazole displays variable in vitro activity against the Mucorales, with wide MIC ranges. Prompt initiation of antifungal therapy is crucial, as treatment delays are associated with increased mortality.[103]

Mucor Infections

European guidelines recommend surgical debridement, in addition to therapy with a liposomal or lipid-complex formulation of amphotericin B at a dosage of greater than equal to 5 mg/kg/day. Isavuconazole was approved for the primary treatment of invasive mold infections, and as salvage therapy of patients who were intolerant of or failing prior antifungal therapy.[14,88] The approval was based upon the results of an open-label, noncomparative trial of patients with IFIs caused by rare molds, including members of the order Mucorales and patients with invasive aspergillosis and renal impairment.[88]

Fusarium and *Scedosporium*

Unfortunately, the early presentation of *Fusarium* and *Scedosporium* infections often mimics that of aspergillosis. On histopathology, *Scedosporium* species resembles *Aspergillus* species with dichotomously branching, septate hyphae and has a tendency for invasion of vascular structures.[103] These pathogens often demonstrate intrinsic resistance to amphotericin B and are associated with high mortality rates. Interpretive CBPs for antifungal MICs and *Scedosporium* spp. are not available, and the optimal choice and duration of therapy is unknown.[99] Voriconazole is FDA approved for the treatment of serious fungal infections caused by *S. apiospermum* and *Fusarium* species, including *Fusarium solani*, in patients intolerant of or refractory to other therapy.[105]

Antifungal Therapy

Clinicians must have working knowledge of mechanism of action, spectrum of activity, dosing, and adverse effects of azole antifungals in order to provide appropriate recommendations for therapy. Dosing adjustments are needed for many antifungal agents in the setting of renal or hepatic dysfunction. A summary of the most common adverse effects of systemic antifungal agents are summarized in **Fig. 139-3** and described in the text below.[105,133]

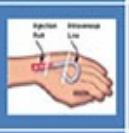
	Polyenes	Azoles					Echino-candins
Adverse Effect	AmB	Flucon	Itra	Vori	Posa	Isavu	Micafungin Anidulafungin caspofungin
Nephrotoxicity	✓	✗	✗ (possible with IV)	✗ (possible with IV)	✗	✗	✗
Abdominal Discomfort	✗	✓	✓	✓	✓	✓	✗
↑ Hepatic transaminases	✓	✓	✓	✓	✓	✓	✓
Rash, photosensitivity	✗	✓	✓	✓ Can lead to malignancy	✓	✓	✓
Infusion-related Reactions/ Histamine Release 	✓	✗	✗	✗	✗	✗	✓
CNS & Visual Disturbances	✗	✗	✗	✓	✗	✗	✗
Cardiomyopathy (itra), ↑ QT (azoles), ? echinos	✗	✓	✓	✓	✓	↓QT	?

FIGURE 139-3 Adverse effects of systemic antifungal agents.[105,133]

The antifungal armamentarium for the treatment of IFIs includes: (a) inhibitors of the fungal cell membrane such as polyenes (eg, amphotericin B) and azole antifungals, (b) inhibitors of DNA (5-flucytosine), and (c) inhibitors of cell wall biosynthesis (echinocandins).[105]

Antifungal therapy generally includes one or more antifungal agents, depending on the severity of infection and the patients' immune status. Rarely are the agents used in combination. Often therapy is initiated with an IV agent such as amphotericin B, and therapy is changed to an oral (azole) regimen as the patient's clinical status improves and oral therapy is tolerated. Controversy has arisen about whether single-drug therapy or combination therapy (eg, voriconazole plus an echinocandin or voriconazole plus a lipid formulation of amphotericin B) is optimum therapy. At present, the highest interest concerns combination therapy in the treatment of aspergillosis, given the continued high mortality of these infections. However, in vitro and animal data have produced conflicting results. Several retrospective studies have suggested an improvement

in mortality with combination therapy with two or three antifungal agents; however, prospective, controlled human studies are lacking. Thus, there are as yet no firm recommendations regarding the use of such combinations in humans.[85,96,105]

Antifungal stewardship, particularly with integration of real-time decision support for the results of rapid diagnostic testing methods such as MALDI-TOF, may improve diagnosis and quality of care, while decreasing mortality and the cost of antifungal therapy.[106]

Amphotericin B

Amphotericin B remains the therapy of choice for many systemic fungal infections despite a lack of controlled clinical trials documenting the optimal dosage, duration of therapy, or relative efficacy of this agent in comparison with newer azole antifungal agents. During pregnancy, amphotericin B remains the treatment of choice for most fungal infections because azole antifungals are teratogenic.[81,100] The side effects of amphotericin B generally are categorized as acute (infusion-related) or long term. Amphotericin B commonly causes renal functional impairment, including decreased glomerular filtration rate, hypokalemia, hypomagnesemia, metabolic acidosis due to distal (or type 1) renal tubular acidosis (RTA), and polyuria due to nephrogenic diabetes insipidus. The nephrotoxicity associated with amphotericin B is usually reversible with discontinuation of therapy. However, recurrent renal dysfunction can occur if treatment is reinstituted. The risk of amphotericin B nephrotoxicity is increased by higher daily doses and concurrent therapy with other nephrotoxins, such as an aminoglycoside or cyclosporine. The incidence and severity of nephrotoxicity can be minimized by administering amphotericin B in lipid-based formulations; liposomal amphotericin B may be less nephrotoxic than the ABLC.[101,105]

Lipid Formulations of Amphotericin B

The use of deoxycholate amphotericin B is frequently associated with the development of induced nephrotoxicity. In an attempt to decrease the incidence of nephrotoxicity, three lipid formulations of amphotericin B have been developed and approved for use in humans: ABLC (Abelcet; Enzon Pharmaceuticals), ABCD (Amphotec; Intermune Pharmaceuticals), and liposomal amphotericin B (AmBisome; Gilead Pharmaceuticals). In these preparations, amphotericin B is incorporated into the phospholipid bilayer membrane rather than in the enclosed aqueous phase.[101]

The various lipid formulations of amphotericin B exhibit markedly different pharmacokinetics; however, whether these differences result in different outcomes in the treatment of specific types of infections (eg, CNS infections) is unclear. Although larger doses of these preparations are required to achieve similar pharmacologic effects as the deoxycholate form of amphotericin B, the toxicity appears to be much lower. Although the FDA-approved dosages of these agents are 5 mg/kg/day (ABLC), 3 to 6 mg/kg/day (ABCD), and 3 to 5 mg/kg/day (liposomal amphotericin B), the agents appear generally equipotent. The optimal dose of these compounds for serious *Candida* infections is unknown; however, dosages of 3 to 5 mg/kg/day appear reasonable.[7]

Lipid formulations of amphotericin B are indicated for patients intolerant of, refractory to, or at high risk of being intolerant to conventional antifungal therapy.[7,101] Intolerance generally is defined as initial renal insufficiency (creatinine greater than 2.5 mg/dL [221 µmol/L] or creatinine clearance less than 25 mL/min [0.42 mL/s]), a significant increase in creatinine (to 2.5 mg/dL [221 µmol/L] for adults or 1.5 mg/dL [133 µmol/L] for children), or severe acute administration-related toxicity, whereas refractory infections are defined as therapeutic failure of more than 500 mg amphotericin B. Owing to the higher cost and paucity of randomized trials showing the efficacy of lipid-associated formulations of amphotericin B against proven invasive candidiasis, many clinicians limit their first-line use for the treatment of these infections to individuals who are intolerant to, at high risk of intolerance to, or refractory to amphotericin B deoxycholate. However, the data demonstrating up to a 6.6-fold increase in mortality in patients with amphotericin B–induced nephrotoxicity have convinced other clinicians that high-risk patients (eg, residence in an ICU care or intermediate care unit at the time of initiation of amphotericin B therapy) warrant first-line therapy with these agents.[7,101]

Flucytosine

Flucytosine (also known as 5-flucytosine) is a fluorinated pyrimidine analog that is highly water-soluble. Patients with creatinine clearances of less than 40 mL/min (0.67 mL/s) should receive careful dosage adjustments. Peak serum concentrations (2 hours after an oral dose) should be monitored in all patients (particularly those with a creatinine clearance of less than 10 mL/min [0.17 mL/s]) to maintain peak serum concentrations of more than 100 mg/L (775 µmol/L).[41]

Flucytosine generally is associated with few side effects in patients with normal renal, GI, and hematologic function, although rash, GI discomfort,

diarrhea (5%-10%), and reversible elevations in hepatic enzymes are observed occasionally. In patients with renal dysfunction or concomitant amphotericin B therapy, leukopenia, thrombocytopenia, and (rarely) enterocolitis can occur. Although studies have suggested that little or no conversion of flucytosine to fluorouracil occurs in vitro, serum concentrations of greater than 1,000 ng/mL (1 mg/L; ~7.7 μmol/L) (therapeutic for the treatment of malignancies) have been documented in some patients. Flucytosine may be secreted into the GI tract, deaminated by intestinal bacteria, and reabsorbed as 5-fluorouracil.[41]

Flucytosine is used in combination with amphotericin B or fluconazole in the treatment of cryptococcosis or (less commonly) candidiasis. The rapid development of resistance to flucytosine, however, precludes its use as single-agent therapy. Mechanisms for drug resistance can include loss of deaminase and decreased permeability to the drug.[41]

Echinocandins

The echinocandins (caspofungin, micafungin, and anidulafungin) are a new class of antifungal agents that act as concentration-dependent, noncompetitive inhibitors of BG synthase, an essential component of the cell wall of susceptible filamentous fungi that is absent in mammalian cells.[62,102]

All echinocandins display linear pharmacokinetics following administration of IV dosages, and are degraded primarily by the liver (also in the adrenals and spleen) by hydrolysis and *N*-acetylation. Following initial distribution, echinocandins are taken up by red blood cells (micafungin) and the liver (caspofungin and micafungin) where they undergo slow degradation to mainly inactive metabolites, although two uncommon metabolites of micafungin possess antifungal activity. Degradation products are excreted slowly over many days, primarily through the bile. Among the echinocandins, anidulafungin is unique in being eliminated almost exclusively by slow chemical degradation rather than undergoing hepatic metabolism.[62]

Echinocandins are available only as parenteral formulations, are not dialyzable, and do not require dosage adjustment in patients with renal insufficiency. They have minimal CSF penetration, largely because of their high protein binding and large molecular weights, although the clinical relevance of these findings can be disputed, given that several other antifungal agents (amphotericin B and itraconazole) are effective for the treatment of fungal meningitis despite low CSF concentrations.

Adverse effects of echinocandins include histamine release resulting in rash, facial swelling, and itchiness. Limited experience suggests that caspofungin and

micafungin are safe to use in pediatric patients; the safety and effectiveness of anidulafungin in pediatric patients has not been established. At the time of FDA approval, there were concerns regarding the safety of caspofungin when combined with cyclosporine. However, three retrospective analyses of the use of caspofungin and cyclosporine in patients do not support a risk of clinically relevant hepatotoxicity.[62,102]

Azole Antifungal Agents

Adverse effects of azoles include GI disturbances (primarily nausea, vomiting, epigastric pain, and diarrhea), which appear to be more common in patients receiving ketoconazole and the solution formulation of itraconazole. Although cyclodextrin is not absorbed following oral administration, use of the IV formulations of itraconazole and voriconazole is limited to 2 weeks because of concerns for potential nephrotoxicity secondary to accumulation of the cyclodextrin vehicle, although recent studies suggest that this is of less concern than previously thought.[104] Fluconazole is well tolerated; intestinal complaints are the most frequently reported, followed by headaches and rash.[133] Unlike ketoconazole, fluconazole does not inhibit testicular or adrenal steroidogenesis in healthy volunteers or hospitalized patients. Reversible alopecia occurs not infrequently and usually appears after several months of treatment with higher doses of fluconazole.[107,133] Azoles are potentially teratogenic and should be avoided in pregnant women.[100,105]

Azole antifungals have been implicated in idiosyncratic drug-induced liver injury with the incidence and pattern of injury varying between specific agents.[107,110,111] The exact mechanism of toxicity has not been elucidated and there is varying level of evidence with regards to the effect of dose on the development of the toxicity. It is recommended that baseline liver function tests (LFTs) be obtained for patients being started on therapy with these agents and periodically monitored. In general, hepatotoxicity can occur at any time after initiation of the antifungal with most cases occurring in the first month of therapy. The liver injury is usually reversible with discontinuation of the offending agent. Substitution of the offending azole antifungal with a different azole antifungal can occur without impacting resolution of the toxicity.

Itraconazole

Itraconazole is triazole antifungal with a broad spectrum of antifungal activity. Despite its marked structural similarity to ketoconazole, itraconazole differs in

several important respects. Itraconazole appears to have greater specificity against fungal versus mammalian CYP, resulting in greater potency and a decrease in CYP-mediated side effects. In addition, itraconazole possesses excellent in vitro activity against *Aspergillus* and *Sporothrix* species.[105,107]

Like ketoconazole, the capsule formulation of itraconazole depends on the availability of low gastric pH for dissolution and absorption. Administration with food appears to enhance significantly the bioavailability of itraconazole capsules, whereas it decreases the bioavailability of the oral solution. Because itraconazole exhibits pH-dependent dissolution and absorption, absorption of the capsule formulation is impaired in patients receiving antacids or H_2-receptor antagonists and in patients with achlorhydria.[104] Plasma concentrations of itraconazole following a single oral dose (capsules) in HIV-infected patients are approximately 50% lower than concentrations observed in healthy volunteers. The capsule formulation of itraconazole exhibits unpredictable oral bioavailability, particularly in subjects with hypochlorhydria and in patients with enteropathy caused by mucositis or graft versus host disease GVHD of the gut. An oral suspension formulation of itraconazole is available; that uses cyclodextrin as a solubilizing vehicle to increase the solubility of the drug. The oral bioavailability of the solution is unaffected by alterations in gastric pH or in patients with enteropathy.[104,105,107]

Fluconazole

Fluconazole is a triazole antifungal agent with markedly different pharmacologic features than other marketed azole antifungals. The small molecular weight, low protein binding, and increased water solubility of fluconazole result in rapid, essentially complete absorption of drug following oral administration. Because fluconazole is excreted primarily (greater than 80%) as unchanged drug in the urine, dosage adjustments are necessary in patients with renal dysfunction.[105]

Voriconazole

The hepatic biotransformation of voriconazole is fairly complex and involves CYP2C19, CYP3A4, and CYP2C9, with most metabolism mediated through CYP2C19. Two of the CYPs involved in voriconazole metabolism (CYP2C19 and CYP2C9) exhibit genetic polymorphism; variability in the CYP2C19 genotype accounts for approximately 30% of the overall between subject variability in voriconazole pharmacokinetics. About 3% to 5% of white and African human populations are poor metabolizers, while 15% to 20% of Asian

populations are poor metabolizers. Drug levels can be as much as fourfold greater in poor metabolizers than in individuals who are homozygous extensive metabolizers. Coadministration of voriconazole with drugs that are potent CYP450 enzyme inducers can significantly reduce voriconazole levels. Voriconazole drug interactions are dose-dependent, as they exhibit unpredictable nonlinear pharmacokinetics; thus, drug interactions are more difficult to predict and manage.[112]

The most common side effect of voriconazole is a reversible disturbance of vision (photopsia), which occurs in approximately 30% of patients but rarely leads to discontinuation of the drug. Symptoms tend to occur during the first week of therapy and decrease or disappear despite continued therapy.[133]

Patients experience altered color discrimination, blurred vision, the appearance of bright spots and wavy lines, and photophobia. Patients should be cautioned that driving can be hazardous because of the risk of visual disturbances. The visual effects are associated with changes in electroretinogram tracings, which revert to normal when treatment with the drug is stopped; no permanent damage to the retina has been demonstrated.[105,113–115]

Posaconazole

Posaconazole has a broad spectrum of antifungal activity, including *Aspergillus* and *Candida* species and zygomycetes. In vitro studies demonstrate that posaconazole is an inhibitor but not a substrate of hepatic (but not total) CYP3A4, and both a substrate and an inhibitor of P-glycoprotein (Pgp), suggesting that it may exhibit a drug interaction profile similar to other azoles. In addition, posaconazole undergoes glucuronidation by uridine diphosphate (UDP)-glucuronosyltransferase enzymes.[112]

Posaconazole was initially developed as an oral suspension for the prevention of IFIs in immunocompromised patients, including hematologic malignancy patients with prolonged neutropenia from chemotherapy as well as HSCT patients with GVHD.[116] However, to ensure adequate absorption, the suspension formulation had to be administered two to three times daily, with a high fat meal or a nutritional supplement. Most patients with GVHD, and many with chemotherapy-associated nausea or vomiting, mucositis or diarrhea, were unable to comply with the requirement for a fatty meal, resulting in decreased plasma concentrations of posaconazole and an increased risk of breakthrough fungal infection.[117–119] The development of IV and delayed-release tablet formulations of posaconazole have circumvented these absorption issues and allows once

daily oral administration of posaconazole following administration of a twice daily loading dose on the first day of therapy. However, in some patients, elevated serum concentrations of posaconazole are observed, and dosage reductions may be needed.[120]

Isavuconazole

Isavuconazole, is available both orally and IV, has a broad spectrum of activity against a number of clinically important yeasts and molds, including *Candida* spp., *Aspergillus* spp., *C. neoformans*, *Trichosporon* spp., and variable activity against the Mucorales. The most commonly reported adverse events, which are mild and limited in nature, include nausea, diarrhea, and elevated liver function tests. Its drug interaction potential appears similar to other azole antifungals, but less than those observed with voriconazole. The potential advantage of this agent over other currently available broad-spectrum azole antifungals is as a clinically useful alternative to voriconazole for the treatment of invasive aspergillosis, due to its lack of genetically determined variability in plasma levels, and more favorable and predictable drug interaction profile. Preliminary studies suggest that it may also prove useful for the treatment of invasive mold infections; however, these indications await the results of clinical trials.[14,88]

Drug Interactions with Antifungal Agents

Drug interactions with azole antifungals generally can be placed into three broad categories: (a) decreases in azole bioavailability because of chelation or secondary to increases in gastric pH, (b) interactions with other CYP-metabolized drugs, and (c) interactions caused by inhibition of Pgp. Drug interactions in the latter two categories can result in increases or decreases in the azole antifungal, in the interacting drug, or in both drugs.[112]

The interaction of azole antifungal agents with other CYP-metabolized drugs is well recognized. The azoles appear to be metabolized almost entirely via the CYP3A4 subfamily. As expected, they interact with other drugs metabolized partly or wholly through this enzyme pathway. In addition, fluconazole and voriconazole use the CYP2C19 pathway. Numerous clinically significant interactions have been documented with azole antifungals and a variety of other drugs. In most cases, the azole interferes with the metabolism of the other CYP-metabolized drug.[112]

Relative to ketoconazole and itraconazole, fluconazole appears to be intermediate in its ability to inhibit human cytochromes P450. The magnitude of

fluconazole-induced inhibition of cyclosporine metabolism appears, however, to depend on the dosage of fluconazole.[112]

Predictably, drugs such as rifampin, rifabutin, isoniazid, phenytoin, and carbamazepine, which are known to induce the activity of cytochromes P450, result in increased metabolism of the azole antifungals and can result in therapeutic failures. Increased dosages of azole antifungals can be required in patients receiving these combinations of drugs.[112]

Itraconazole is an inhibitor of intestinal Pgp. Significant increases in digoxin (a Pgp substrate) have been observed in patients receiving both agents concurrently. Interactions with other substrates of Pgp would be expected to occur.[112]

Echinocandins are not inducers of CYP enzymes, nor do they interact with Pgp, and are considered poor substrates of CYP3A4. Nevertheless, drug interactions are noted with caspofungin and cyclosporine and tacrolimus; the mechanism for these interactions is not yet known. Rifampin both inhibits (acutely) and induces (after chronic administration) caspofungin metabolism, and a dosage increase is recommended in patients receiving other enzyme inducers, such as efavirenz, nevirapine, phenytoin, dexamethasone, and carbamazepine. Although micafungin does not significantly affect the clearance (or area under the plasma-concentration vs time curve [AUC]) of tacrolimus, it increases the AUCs of sirolimus and nifedipine and decreases the clearance of cyclosporine.[62,121]

Therapeutic Drug Monitoring (TDM) of Antifungal Agents

There is insufficient data to justify the routine use of therapeutic drug monitoring for the prophylaxis or treatment of fungal infections with all antifungal agents. In addition, logistics, cost, and incorporation of therapeutic drug monitoring have yet to be worked out in modern prophylactic algorithms. However, under certain circumstances, serum or plasma concentration monitoring of select agents is warranted. Given the tremendous interpatient and intrapatient variability in voriconazole metabolism, TDM is warranted in most patients. Also, given the poor oral bioavailability of itraconazole capsules, and posaconazole solution, monitoring is recommended, particularly in patients with GVHD of the gut, mucositis, or diarrhea, or poor oral intake or those receiving concomitant therapy with proton-pump inhibitors.[123] Although the use of posaconazole tablets may result in a decreased need for TDM, patients with a

higher weight and those experiencing diarrhea are more likely to have lower levels.[120] Additional settings include patients susceptible to flucytosine toxicity, to document adequate oral absorption of poorly bioavailable azoles in cases of suspected treatment failure or concern about compliance or absorption, solubility and finally, when drug interactions that might reduce or accelerate the metabolism of azoles is suspected.[123] Recommendations regarding plasma concentration monitoring of antifungals are summarized in **Table 139-10**.

TABLE 139-10 Plasma Concentration Monitoring of Antifungal Agents[122–126,128]

	Serum Concentration Monitoring Necessary?	Target Concentration Range	Timing of Sample
Echinocandins	No	NA	NA
Amphotericin B (including lipids)	No	NA	NA
Fluconazole	No	NA	NA
Itraconazole	Yes, to ensure absorption and efficacy	*Efficacy:* Prophylaxis: >0.5 mcg/mL (mg/L; 0.7 µmol/L) Treatment: >1 mcg/mL (mg/L; 1.4 µmol/L) *Toxicity:* <5 mcg/mL (mg/L; 7 µmol/L)	Trough 7 days after initiation of therapy
Voriconazole	Probably yes—in all patients treated for IFI, altered liver function, potential drug–drug interactions, lack of response *Low* concentrations are associated with poor outcome; *high* concentrations are associated with adverse effects Variable metabolism due to nonlinear PK and genetic variability in CYP2C19 → unpredictable dose-exposure relationship	*Efficacy:* Prophylaxis: trough >0.5-2 mcg/mL (mg/L; 1.4-5.7 µmol/L) Treatment: trough >1-2 mcg/mL (mg/L; 2.9-5.7 µmol/L) Concentrations >2.05 mcg/mL (mg/L; 5.7 µmol/L) are associated with improved outcome; 2-5.5 mcg/mL (mg/L; 5.7-15.7 µmol/L) is probably the best target *Toxicity:* concentrations >5.5 mcg/mL (mg/L; 15.7 µmol/L) are associated with ↑ risk of visual and hepatic adverse events	Trough after 5-7 days therapy if no loading dose administered; 48 hours after administration of loading dose in critically ill patient (time to steady state is unpredictable due to nonlinear metabolism)
Posaconazole delayed release tablets	Maybe Outcomes (but not adverse events) correlate with higher plasma concentrations in prophylaxis and possibly treatment	*Efficacy:* Prophylaxis: >0.7 mcg/mL (mg/L; 1 µmol/L) Treatment: Not well studied; concentrations >1.25 mcg/mL (mg/L; 1.78 µmol/L) *Toxicity:* Correlation with toxicity poorly defined	Random level at SS (>7 days therapy). The long $t_{1/2}$ ensures little fluctuation in peaks and troughs at SS.
Flucytosine	Yes—high concentrations are associated with toxicity	*Toxicity:* "Peak" <80-100 mcg/mL (mg/L; 620-775 µmol/L) *Efficacy:* Trough >30 mcg/mL (mg/L; 232 µmol/L)	2 hours postdose "peak", 3-5 days after initiation of therapy

NA, not applicable.

Postclass Engaged Learning Activity

Conduct a literature search and identify a primary research manuscript that has been published in the past 18 months regarding the treatment of candidemia caused by *C. glabrata*.

ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
ABCD	amphotericin B colloid dispersion
ABLC	amphotericin B lipid complex
AUC	area under the plasma-concentration versus time curve
BG	(1,3)-β-d-glucan
BPA	bronchopulmonary aspergillosis
BSI	bloodstream infection
CBP	clinical breakpoint
CT	computed tomography
CVC	central venous catheter
CSF	cerebrospinal fluid
CYP	cytochrome P450
ELISA	enzyme-linked immunosorbent assay
FISH	fluorescence in situ hybridization
GVHD	graft-versus-host disease
HEPA	high-efficiency particulate air
HAART	highly active antiretroviral therapy
HSCT	hematopoietic stem cell transplantation
IA	invasive aspergillosis
ICP	intracranial pressure
ICUs	intensive care units

IDSA	Infectious Diseases Society of America
IPA	invasive pulmonary aspergillosis
IRIS	immune reconstitution inflammatory syndrome
LFT	liver function test
MALDI-TOF-ICMS	matrix-assisted laser desorption ionization time-of-flight mass spectrometry
NSAID	Non-steroidal antiinflammatory drug
PDH	progressive disseminated histoplasmosis
PN	parenteral nutrition
PNA	peptide nucleic acid
RR	respiratory rate
SDD	susceptible dose-dependent
TDM	therapeutic plasma drug concentration monitoring
TEE	transesophageal echocardiogram
TTE	transthoracic echocardiogram
WBC	white blood cell

REFERENCES

1. Bennett JE. Introduction to mycoses. In: Bennett JED, Raphael D, Blaser MJ, Martin J., eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. Philadelphia, PA: Elsevier/Saunders; 2015;2874–2878.
2. Pfaller MA, Jones RN, Messer SA, Edmond MB, Wenzel RP. National surveillance of nosocomial blood stream infection due to *Candida albicans*: Frequency of occurrence and antifungal susceptibility in the SCOPE Program. *Diagn Microbiol Infect Dis*. 1998;1:327–332.
3. Pfaller MA, Jones RN, Doern GV, et al. International surveillance of blood stream infections due to *Candida* species in the European SENTRY Program: Species distribution and antifungal susceptibility including the investigational triazole and echinocandin Agents. SENTRY Participant Group (Europe). *Diagn Microbiol Infect Dis*. 1999;1:19–25.
4. Pfaller MA, Diekema DJ. Progress in antifungal susceptibility testing of *Candida* spp. by use of clinical and laboratory standards institute broth microdilution methods, 2010 to 2012. *J Clin Microbiol*. 2012;9:2846–2856.

5. Pfaller MA, Andes D, Diekema DJ, Espinel-Ingroff A, Sheehan D, Testing CSfAS. Wild-type MIC distributions, epidemiological cutoff values and species-specific clinical breakpoints for fluconazole and Candida: Time for harmonization of CLSI and EUCAST broth microdilution methods. *Drug Resistance Updates: Reviews and Commentaries in Antimicrobial and Anticancer Chemotherapy* 2010;6:180–195.
6. Eschenauer GA, Carver PL. The evolving role of antifungal susceptibility testing. *Pharmacotherapy*. 2013;5:465–475.
7. Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;4:e1–e50.
8. Chapman SW, Dismukes WE, Proia LA, et al. Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2008;12:1801–1812.
9. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america. *Clin Infect Dis* 2010;3:291–322.
10. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2007;7:807–825.
11. Galgiani JN, Ampel NM, Blair JE, et al. Executive Summary: 2016 Infectious Diseases Society of America (IDSA) Clinical Practice Guideline for the Treatment of Coccidioidomycosis. Clin Infect Dis. 63(6):717–722.
12. Cowen LE, Sanglard D, Howard SJ, Rogers PD, Perlin DS. Mechanisms of antifungal drug resistance. *Cold Spring Harb Perspect Med*; 2015;5(7):a019752.
13. Perlin DS. Echinocandin resistance, susceptibility testing and prophylaxis: Implications for patient management. *Drugs* 2014;14:1573–1585.
14. Pettit NN, Carver PL. Isavuconazole: A new option for the management of invasive fungal infections. *Ann Pharmacother*. 2015;49(7):825–842.
15. Nguyen MH, Peacock JE Jr, Morris AJ, et al. The changing face of candidemia: emergence of non-Candida albicans species and antifungal resistance. *Am J Med*. 1996;100(6):617–623.
16. Maubon D, Garnaud C, Calandra T, Sanglard D, Cornet M. Resistance of *Candida* spp. to antifungal drugs in the ICU: Where are we now? *Intensive Care Med*. 2014;40(9):1241–1255.

17. Alexander BD, Johnson MD, Pfeiffer CD, et al. Increasing echinocandin resistance in Candida glabrata: Clinical failure correlates with presence of FKS mutations and elevated minimum inhibitory concentrations. *Clin Infect Dis* 2013;12:1724–1732.
18. Shields RK, Nguyen MH, Press EG, et al. The presence of an FKS mutation rather than MIC is an independent risk factor for failure of echinocandin therapy among patients with invasive candidiasis due to Candida glabrata. *Antimicrob Agents Chemother*. 2012;9:4862–4869.
19. Beyda ND, John J, Kilic A, Alam MJ, Lasco TM, Garey KW. FKS mutant *Candida glabrata*: Risk factors and outcomes in patients with candidemia. *Clin Infect Dis* 2014;6:819–825.
20. Miceli MH, Kauffman CA. Aspergillus Galactomannan for Diagnosing Invasive Aspergillosis. JAMA. 2017;318(12):1175–1176. 10.1001/jama.2017.10661.
21. Eschenauer GA, Lam SW, Carver PL. Antifungal prophylaxis in liver transplant recipients. *Liver Transpl*. 2009;8:842–858.
22. McCoy D, Depestel DD, Carver PL. Primary antifungal prophylaxis in adult hematopoietic stem cell transplant recipients: Current therapeutic concepts. Pharmacotherapy. 2009;11:1306–1325.
23. Morgan J, Meltzer MI, Plikaytis BD, et al. Excess mortality, hospital stay, and cost due to candidemia: A case-control study using data from population-based candidemia surveillance. *Infect Control Hosp Epidemiol*. 2005;26(6):540–547.
24. Kothari A, Morgan M, Haake DA. Emerging technologies for rapid identification of bloodstream pathogens. *Clin Infect Dis* 2014;2:272–278.
25. Rabin AS, Givertz MM, Couper GS, et al. Risk factors for invasive fungal disease in heart transplant recipients. *J Heart Lung Transplant*. 2015;2:227–232.
26. Barchiesi F, Mazzocato S, Mazzanti S, et al. Invasive aspergillosis in liver transplant recipients: Epidemiology, clinical characteristics, treatment, and outcomes in 116 cases. *Liver Transpl*. 2015;2:204–212.
27. Colombo AL, Guimaraes T, Sukienik T, et al. Prognostic factors and historical trends in the epidemiology of candidemia in critically ill patients: An analysis of five multicenter studies sequentially conducted over a 9-year period. *Intensive Care Med*. 2014;10:1489–1498.
28. Fernandez J, Erstad BL, Petty W, Nix DE. Time to positive culture and identification for Candida blood stream infections. *Diagn Microbiol Infect*

Dis. 2009;64(4):402–407.

29. Teles F, Seixas J. The future of novel diagnostics in medical mycology. *J Med Microbiol*. 2015;64:315–322.
30. Halliday CL, Kidd SE, Sorrell TC, Chen SC. Molecular diagnostic methods for invasive fungal disease: The horizon draws nearer? *Pathology* 2015;3:257–269.
31. Schelenz S, Barnes RA, Barton RC, et al. British Society for Medical Mycology best practice recommendations for the diagnosis of serious fungal diseases. *The Lancet Infectious Diseases* 2015;4:461–474.
32. Deepe GS. Histoplasma capsulatum. In: Bennett JED, Raphael D, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Philadelphia, PA: Elsevier/Saunders; 2015; 2949–2962: chap 265.
33. Riddell Jt, Kauffman CA, Smith JA, et al. *Histoplasma capsulatum* Endocarditis: Multicenter case series with review of current diagnostic techniques and treatment. *Medicine* 2014;5:186–193.
34. Hage CA, Ribes JA, Wengenack NL, et al. A multicenter evaluation of tests for diagnosis of histoplasmosis. *Clin Infect Dis* 2011;5:448–454.
35. Hage CA, Kirsch EJ, Stump TE, et al. Histoplasma antigen clearance during treatment of histoplasmosis in patients with AIDS determined by a quantitative antigen enzyme immunoassay. *Clinical and Vaccine Immunology: CVI* 2011;4:661–666.
36. Bradsher RW. Blastomycosis. In: Bennett JED, Raphael D, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. Philadelphia, PA: Elsevier/Saunders; 2015;2963–2973: chap 266.
37. Galgiani JN. Coccidioidomycosis (Coccidioides Species). In: Bennett JED, Raphael D, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. Philadelphia, PA: Elsevier/Saunders; 2015;2974–2984: chap 267.
38. Hoang LMN, Philips P, Galanis E. *Cryptococcus gattii*: A review of the epidemiology, clinical presentation, diagnosis, and management of this endemic yeast in the Pacific Northwest. *Clinical Microbiology Newsletter* 2011;24:187–195.
39. Bennett JE, Dismukes WE, Duma RJ, et al. A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptoccal meningitis. *N Engl J Med*. 1979;301(3):126–131.

40. Saag MS, Powderly WG, Cloud GA, et al. Comparison of amphotericin B with fluconazole in the treatment of acute AIDS-associated cryptococcal meningitis. The NIAID Mycoses Study Group and the AIDS Clinical Trials Group. *N Engl J Med*. 1992;326(2):83–89.
41. Francis P, Walsh TJ. Evolving role of flucytosine in immunocompromised patients: New insights into safety, pharmacokinetics, and antifungal therapy. *Clin Infect Dis* 1992;6:1003–1018.
42. van der Horst CM, Saag MS, Cloud GA, et al. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Clinical Trials Group. *N Engl J Med*. 1997;1:15–21.
43. Perfect JR. Cryptococcosis (*Cryptococcus neoformans* and *Cryptococcus gattii*). In: Bennett JED, Raphael D, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. Philadelphia, PA: Elsevier/Saunders; 2015;2934–2948: chap 264.
44. Molloy SF, Kanyama C, Heyderman RS, et al. Antifungal combinations for treatment of Cryptococcal Meningitis in Africa. N Engl J Med. 2018;378(11):1004–1017. 10.1056/NEJMoa1710922.
45. Edwards JE. *Candida* species. In: Bennett JED, Raphael D, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. Philadelphia, PA: Elsevier/Saunders; 2015;2879–2894: chap 258.
46. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: Analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis* 2004;3:309–317.
47. Lamoth F, Calandra T. Early diagnosis of invasive mould infections and disease. J Antimicrob Chemother. 2017;72(suppl 1):i19–i28. 10.1093/jac/dkx030.
48. Nucci M, Anaissie E. Should vascular catheters be removed from all patients with candidemia? An evidence-based review. *Clin Infect Dis* 2002;5:591–599.
49. Eschenauer GA, Carver PL, Patel TS, et al. Survival in patients with Candida glabrata bloodstream infection is associated with Fluconazole dose. Antimicrob Agents Chemother. 2018;62(6):10.1128/AAC.02566-17.
50. Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Hospital-acquired candidemia: The attributable mortality and excess length of stay. *Arch*

Intern Med. 1988;148(12):2642–2645.

51. Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Risk factors for hospital-acquired candidemia. A matched case-control study. *Arch Intern Med*. 1989;10:2349–2353.
52. Schuster MG, Edwards JE, Jr., Sobel JD, Darouiche RO, Karchmer AW, Hadley S, et al. Empirical fluconazole versus placebo for intensive care unit patients: a randomized trial. Annals of internal medicine. 2008 Jul 15;149(2):83–90.
53. Lam SW, Eschenauer GA, Carver PL. Evolving role of early antifungals in the adult intensive care unit. Critical Care Medicine. 2009;5:1580–1593.
54. Nucci M, Anaissie E. Revisiting the source of candidemia: Skin or gut? *Clin Infect Dis* 2001;12:1959–1967.
55. Rex JH, Bennett JE, Sugar AM, et al. Intravascular catheter exchange and duration of candidemia. NIAID Mycoses Study Group and the Candidemia Study Group. *Clin Infect Dis* 1995;4:994–996.
56. Quindos G. Epidemiology of candidaemia and invasive candidiasis: A changing face. Rev Iberoam Micol. 2014;31(1):42–48.
57. Paramythiotou E, Frantzeskaki F, Flevari A, Armaganidis A, Dimopoulos G. Invasive fungal infections in the ICU: How to approach, how to treat. *Molecules* 2014;1:1085–1119.
58. Eggimann P, Francioli P, Bille J, et al. Fluconazole prophylaxis prevents intra-abdominal candidiasis in high-risk surgical patients. *Critical Care Med*. 1999;6:1066–1072.
59. Rocco TR, Reinert SE, Simms HH. Effects of fluconazole administration in critically ill patients: Analysis of bacterial and fungal resistance. *Arch Surg*. 2000;135(2):160–165.
60. Cheng S, Clancy CJ, Hartman DJ, Hao B, Nguyen MH. *Candida glabrata* intra-abdominal candidiasis is characterized by persistence within the peritoneal cavity and abscesses. *Infect Immun*. 2014;82(7):3015–3022.
61. Clancy CJ, Nguyen MH. Finding the “missing 50%” of invasive candidiasis: How nonculture diagnostics will improve understanding of disease spectrum and transform patient care. *Clin Infect Dis* 2013;9:1284–1292.
62. Eschenauer G, Depestel DD, Carver PL. Comparison of echinocandin antifungals. Ther Clin Risk Manag. 2007;3(1):71–97.
63. Eschenauer GA, Carver PL, Lin SW, et al. Fluconazole versus an

echinocandin for *Candida glabrata fungaemia*: A retrospective cohort study. *The Journal of Antimicrobial Chemotherapy* 2013;4:922–926.

64. Andes DR, Safdar N, Baddley JW, et al. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: A patient-level quantitative review of randomized trials. *Clin Infect Dis* 2012;8:1110–1122.
65. Eschenauer GA, Nguyen MH, Clancy CJ. Is fluconazole or an echinocandin the agent of choice for candidemia. *Ann Pharmacother*. 2015;49(9):1068–1074.
66. Diekema DJ, Messer SA, Brueggemann AB, et al. Epidemiology of candidemia: 3-year results from the emerging infections and the epidemiology of Iowa organisms study. *J Clin Microbiol*. 2002;40(4):1298–1302.
67. Pfaller MA, Messer SA, Hollis RJ, et al. Trends in species distribution and susceptibility to fluconazole among blood stream isolates of *Candida* species in the United States. *Diagn Microbiol Infect Dis*. 1999;4:217–222.
68. Wisplinghoff H, Ebbers J, Geurtz L, et al. Nosocomial bloodstream infections due to *Candida* spp. in the USA: Species distribution, clinical features and antifungal susceptibilities. *Int J Antimicrob Agents*. 2014;43(1):78–81.
69. Garey KW, Rege M, Pai MP, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: A multi-institutional study. *Clin Infect Dis*. 2006;1:25–31.
70. Maertens J, Marchetti O, Herbrecht R, et al. European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3: 2009 update. Bone Marrow Transplant. 2011;46(5):709–718. 10.1038/bmt.2010.175.
71. Chiotos K, Vendetti N, Zaoutis TE, et al. Comparative effectiveness of echinocandins versus fluconazole therapy for the treatment of adult candidaemia due to Candida parapsilosis: a retrospective observational cohort study of the Mycoses Study Group (MSG-12). J Antimicrob Chemother. 2016;71(12):3536–3539. 10.1093/jac/dkw305.27494929.
72. Kale-Pradhan PB, Morgan G, Wilhelm SM, Johnson LB. Comparative efficacy of echinocandins and nonechinocandins for the treatment of *Candida parapsilosis* infections: A meta-analysis. Pharmacotherapy 2010;12:1207–13.
73. Lamoth F, Kontoyiannis DP. The Candida auris alert: Facts and

perspectives. J Infect Dis. 2018;217(4):516–520. 10.1093/infdis/jix597.

74. Kauffman CA, Vazquez JA, Sobel JD, et al. Prospective multicenter surveillance study of funguria in hospitalized patients. The National Institute for Allergy and Infectious Diseases (NIAID) Mycoses Study Group. *Clin Infect Dis* 2000;1:14–18.
75. Ullmann AJ, Lipton JH, Vesole DH, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med*. 2007;356(4):335–347.
76. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america.. Clin Infect Dis. 2011;52(4):e56–e93. 10.1093/cid/cir073.
77. Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of candida bloodstream infection until positive blood culture results are obtained: A potential risk factor for hospital mortality. *Antimicrob Agents Chemother*. 2005;49(9):3640–3645.
78. Sobel JD, Kauffman CA, McKinsey D, et al. Candiduria: A randomized, double-blind study of treatment with fluconazole and placebo. The National Institute of Allergy and Infectious Diseases (NIAID) Mycoses Study Group. *Clin Infect Dis* 2000;1:19–24.
79. Patterson TF. *Aspergillus* species. In: Bennett JED, Raphael D, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. Philadelphia, PA: Elsevier/Saunders; 2015; 2895–2908: chap 259.
80. Blyth CC, Gilroy NM, Guy SD, et al. Consensus guidelines for the treatment of invasive mould infections in haematological malignancy and haemopoietic stem cell transplantation, 2014. *Intern Med J*. 2014;44(12b):1333–1349.
81. Gallis HA, Drew RH, Pickard WW. Amphotericin B: 30 years of clinical experience. *Rev Infect Dis*. 1990;12(2):308–329.
82. Fleming S, Yannakou CK, Haeusler GM, et al. Consensus guidelines for antifungal prophylaxis in haematological malignancy and haemopoietic stem cell transplantation, 2014. *Intern Med J*. 2014;44(12b):1283–1297.
83. Vermeulen E, Lagrou K, Verweij PE. Azole resistance in *Aspergillus fumigatus*: A growing public health concern. *Current Opinion in Infectious Diseases* 2013;6:493–500.
84. Stevens DA, Schwartz HJ, Lee JY, et al. A randomized trial of

itraconazole in allergic bronchopulmonary aspergillosis. *N Engl J Med*. 2000;342(11):756–762.

85. Martin-Pena A, Aguilar-Guisado M, Espigado I, Cisneros JM. Antifungal combination therapy for invasive aspergillosis. *Clin Infect Dis* 2014;59(10):1437–1445.
86. Garcia-Vidal C, Upton A, Kirby KA, Marr KA. Epidemiology of invasive mold infections in allogeneic stem cell transplant recipients: Biological risk factors for infection according to time after transplantation. *Clin Infect Dis*. 2008;8:1041–1050.
87. Maertens JA, Raad II, Marr KA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): A phase 3, randomised-controlled, non-inferiority trial. Lancet. 2016;387(10020):760–769. 10.1016/S0140-6736(15)01159-9.
88. Miceli MH, Kauffman CA. Isavuconazole: A new broad-spectrum triazole antifungal agent. *Clin Infect Dis*. 2015;10:1558–1565.
89. Viscoli C, Herbrecht R, Akan H, et al. An EORTC Phase II study of caspofungin as first-line therapy of invasive aspergillosis in haematological patients. *J Antimicrob Chemother*. 2009;64(6):1274–1281.
90. Gerlinger MP, Rousselot P, Rigaudeau S, et al. False positive galactomannan Platelia due to piperacillin-tazobactam. *Medecine et Maladies Infectieuses*. 2012;1:10–14.
91. Alhambra A, Cuetara MS, Ortiz MC, et al. False positive galactomannan results in adult hematological patients treated with piperacillin-tazobactam. *Revista Iberoamericana de Micologia* 2007;2:106–112.
92. Nam HS, Jeon K, Um SW, et al. Clinical characteristics and treatment outcomes of chronic necrotizing pulmonary aspergillosis: A review of 43 cases. *Int J Infect Dis*. 2010;14(6):e479–482.
93. Reichenberger F, Habicht JM, Gratwohl A, Tamm M. Diagnosis and treatment of invasive pulmonary aspergillosis in neutropenic patients. *Eur Respir J*. 2002;19(4):743–755.
94. Cornely OA, Böhme A, Buchheidt D, et al. Primary prophylaxis of invasive fungal infections in patients with hematologic malignancies. Recommendations of the Infectious Diseases Working Party of the German Society for Haematology and Oncology. Haematologica. 2009;94(1):113–122.
95. Rex JH, Pappas PG, Karchmer AW, et al. A randomized and blinded

multicenter trial of high-dose fluconazole plus placebo versus fluconazole plus amphotericin B as therapy for candidemia and its consequences in nonneutropenic subjects. *Clin Infect Dis* 2003;10:1221–1228.

96. Marr KA, Schlamm HT, Herbrecht R, et al. Combination antifungal therapy for invasive aspergillosis: A randomized trial. *Ann Intern Med*. 2015;162(2):81–89.
97. Aigner M, Lass-Florl C. Treatment of drug-resistant Aspergillus infection. *Expert Opin Pharmacother*. 2015;16(15):1–4.
98. Cornely OA, Bassetti M, Calandra T, et al. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: Non-neutropenic adult patients. *Clin Microbiol Infect*. 2012;18(Suppl 7):19–37.
99. Tortorano AM, Richardson M, Roilides E, et al. ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: *Fusarium* spp., *Scedosporium* spp. and others. *Clin Microbiol Infect*. 2014;20(Suppl 3):27–46.
100. King CT, Rogers PD, Cleary JD, Chapman SW. Antifungal therapy during pregnancy. *Clin Infect Dis* 1998;5:1151–1160.
101. Ostrosky-Zeichner L, Marr KA, Rex JH, Cohen SH. Amphotericin B: Time for a new “gold standard”. *Clin Infect Dis* 2003;3:415–425.
102. Kauffman CA, Carver PL. Update on echinocandin antifungals. *Semin Respir Crit Care Med*. 2008;29(2):211–219.
103. Kontoyiannis DPL, Russell E. Agents of mucormycosis and entomophthoramycosis. In: Bennett JED, Raphael D, Blaser MJ, eds. *Mandell, Douglas, and Bennett’s Principles and Practice of Infectious Diseases*. Philadelphia, PA: Elsevier/Saunders; 2015;2909–2919: chap 260.
104. Stevens DA. Itraconazole in cyclodextrin solution. *Pharmacotherapy*. 1999;19(5):603–611.
105. Lewis RE. Current concepts in antifungal pharmacology. *Mayo Clin Proc*. 2011;86(8):805–817.
106. Muñoz P, Bouza E. The current treatment landscape: the need for antifungal stewardship programmes. J Antimicrob Chemother. 2016;71(Suppl 2):ii5–ii12. 10.1093/jac/dkw391.
107. Kauffman CA, Carver PL. Use of azoles for systemic antifungal therapy. *Adv Pharmacol*. 1997;39:143–189.
108. Walsh TJ, Hiemenz JW, Seibel NL, et al. Amphotericin B lipid complex

for invasive fungal infections: Analysis of safety and efficacy in 556 cases. *Clin Infect Dis* 1998;6:1383–1396.

109. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med*. 2002;347(6):408–415.
110. Song JC, Deresinski S. Hepatotoxicity of antifungal agents. *Curr Opin Investig Drugs*. 2005;6(2):170–177.
111. Leise MD, Poterucha JJ, Talwalkar JA. Drug-induced liver injury. Mayo Clin Proc. 2014;89(1):95–106.
112. Saad AH, DePestel DD, Carver PL. Factors influencing the magnitude and clinical significance of drug interactions between azole antifungals and select immunosuppressants. *Pharmacotherapy* 2006;12:1730–1744.
113. Zrenner E, Tomaszewski K, Hamlin J, Layton G, Wood N. Effects of multiple doses of voriconazole on the vision of healthy volunteers: A double-blind, placebo-controlled study. *Ophthalmic Research*. 2014;1:43–52.
114. Kinoshita J, Iwata N, Ohba M, Kimotsuki T, Yasuda M. Mechanism of voriconazole-induced transient visual disturbance: Reversible dysfunction of retinal ON-bipolar cells in monkeys. *Investigative Ophthalmology & Visual Science* 2011;8:5058–5063.
115. Gao H, Pennesi M, Shah K, et al. Safety of intravitreal voriconazole: Electroretinographic and histopathologic studies. *Trans Am Ophthalmol Soc*. 2003;101:183–189.discussion 89.
116. Frampton JE, Scott LJ. Posaconazole: A review of its use in the prophylaxis of invasive fungal infections. *Drugs* 2008;7: 993–1016.
117. Dolton MJ, Ray JE, Chen SC, Ng K, Pont L, McLachlan AJ. Multicenter study of posaconazole therapeutic drug monitoring: Exposure-response relationship and factors affecting concentration. *Antimicrob Agents Chemother*. 2012;56(11):5503–5510.
118. Dolton MJ, Ray JE, Marriott D, McLachlan AJ. Posaconazole exposure-response relationship: Evaluating the utility of therapeutic drug monitoring. *Antimicrob Agents Chemother*. 2012;56(6):2806–2813.
119. Kersemaekers WM, Dogterom P, Xu J, et al. Effect of a high-fat meal on the pharmacokinetics of 300-milligram posaconazole in a solid oral tablet formulation. *Antimicrob Agents Chemother*. 2015;6:3385–3389.
120. McKeage K. Posaconazole: A review of the gastro-resistant tablet and intravenous solution in invasive fungal infections. *Drugs* 2015;4:397–406.

121. Carver PL. Micafungin. *Ann Pharmacother*. 2004;10:1707–1721.
122. Laverdiere M, Bow EJ, Rotstein C, et al. Therapeutic drug monitoring for triazoles: A needs assessment review and recommendations from a Canadian perspective. *Can J Infect Dis Med Microbiol*. 2014;25(6):327–343.
123. Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW. Therapeutic drug monitoring (TDM) of antifungal agents: Guidelines from the British Society for Medical Mycology. *J Antimicrob Chemother*. 2014;69(5):1162–1176.
124. Seyedmousavi S, Mouton JW, Verweij PE, Bruggemann RJ. Therapeutic drug monitoring of voriconazole and posaconazole for invasive aspergillosis. *Expert Rev Anti Infect Ther*. 2013;11(9):931–941.
125. Heinz WJ, Einsele H, Helle-Beyersdorf A, et al. Posaconazole concentrations after allogeneic hematopoietic stem cell transplantation. *Transpl Infect Dis*. 2013;5:449–456.
126. Gross BN, Ihorst G, Jung M, Wasch R, Engelhardt M. Posaconazole therapeutic drug monitoring in the real-life setting: A single-center experience and review of the literature. *Pharmacotherapy*. 2013;33(10):1117–1125.
127. Verweij PE, Chowdhary A, Melchers WJ, Meis JF. Azole Resistance in Aspergillus fumigatus: Can We Retain the Clinical Use of Mold-Active Antifungal Azoles? Clin Infect Dis. 2016;62(3):362–368. 10.1093/cid/civ885.
128. Hussaini T, Ruping MJ, Farowski F, Vehreschild JJ, Cornely OA. Therapeutic drug monitoring of voriconazole and posaconazole. *Pharmacotherapy* 2011;2:214–225.
129. Malani AN, Psarros G, Malani PN, Kauffman CA. Is age a risk factor for Candida glabrata colonisation? Mycoses. 2011;54(6):531–537. 10.1111/j.1439-0507.2010.01941.x.
130. Ullmann AJ, Aguado JM, Arikan-Akdagli S, et al. Diagnosis and management of Aspergillus diseases: Executive summary of the 2017 ESCMID-ECMM-ERS guideline. Clin Microbiol Infect. 2018; 24(Suppl 1):e1–e38. 10.1016/j.cmi.2018.01.002.29544767.
131. Patterson TF, Thompson GR 3rd, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;63(4):e1–e60. 10.1093/cid/ciw326.27365388.

132. Lamoth F, Lockhart SR, Berkow EL, Calandra T. Changes in the epidemiological landscape of invasive candidiasis. J Antimicrob Chemother. 2018;73(Suppl_1):i4–i13. 10.1093/jac/dkx444.29304207.
133. Benitez LL, Carver PL. Adverse Effects Associated with Long-Term Administration of Azole Antifungal Agents. Drugs. 2019;79(8):833–853.
134. Segal BH, Almyroudis NG, Battiwalla M, et al. Prevention and early treatment of invasive fungal infection in patients with cancer and neutropenia and in stem cell transplant recipients in the era of newer broad-spectrum antifungal agents and diagnostic adjuncts. *Clin Infect Dis*. 2007;3:402–409.

140

Infections in Immunocompromised Patients

Scott W. Mueller and Douglas N. Fish

KEY CONCEPTS

1. An *immunocompromised host* is a patient with defects in host immune defenses that predispose to infection. Risk factors include neutropenia, immune system defects from disease or immunosuppressive drug therapy, compromise of natural host defenses, environmental contamination, and changes in normal flora of the host.
2. Immunocompromised patients are at high risk for a variety of bacterial, fungal, viral, and protozoal infections. Bacterial infections caused by gram-positive cocci (staphylococci and streptococci) occur most frequently, followed by gram-negative bacterial infections caused by Enterobacteriaceae and *Pseudomonas aeruginosa*. Fungal infections caused by *Candida* and *Aspergillus*, as well as certain viral infections (herpes simplex virus [HSV], cytomegalovirus [CMV]), are also important causes of morbidity and mortality.
3. Risk of infection in neutropenic patients is associated with both the severity and duration of neutropenia. Patients with severe neutropenia (absolute neutrophil count less than 500 cells/mm^3 [0.5×10^9/L]) for greater than 7 to 10 days are considered to be at high risk of infection.
4. Fever (single oral temperature of greater than or equal to 38.3°C [100.9°F], or a temperature of greater than or equal to 38°C [100.4°F] for greater than or equal to 1 hour) is the most important clinical finding in neutropenic patients and is usually the stimulus for further diagnostic workup and initiation of antimicrobial treatment. Infection should be considered as the cause of fever until proven otherwise. Usual signs and symptoms of infection may be altered or absent in neutropenic patients. Appropriate

empiric broad-spectrum antimicrobial therapy must be rapidly instituted to prevent excessive morbidity and mortality.

5. Empiric antimicrobial regimens for neutropenic infections should take into account patients' individual risk factors, as well as institutional infection and susceptibility patterns. The significant morbidity and mortality associated with gram-negative infections require that initial empiric regimens for treatment of febrile neutropenia have good activity against *P. aeruginosa* and Enterobacteriaceae. Parenteral regimens most commonly recommended for initial inpatient treatment include monotherapy with an antipseudomonal β-lactam, or a combination regimen consisting of an antipseudomonal β-lactam plus an aminoglycoside. Low-risk patients may be successfully treated with oral antibiotics (fluoroquinolone plus amoxicillin-clavulanate), with the treatment setting determined by the patient's clinical status.

6. Neutropenic patients who remain febrile after 3 to 5 days of initial antimicrobial therapy should be reevaluated to determine whether treatment modifications are necessary. Common regimen modifications include addition of vancomycin (if not already administered) and antifungal therapy (amphotericin B, an echinocandin, or fluconazole). Therapy should be directed at causative organisms, if identified, but broad-spectrum regimens should be maintained during neutropenia.

7. The optimal duration of therapy for febrile neutropenia is controversial. The decision to discontinue antimicrobials is based on resolution of neutropenia, defervescence, culture results, and clinical stability of the patient.

8. Prophylactic antimicrobials are administered to cancer patients expected to experience prolonged neutropenia, as well as to hematopoietic stem cell and solid-organ transplant recipients. Prophylactic regimens may include antibacterial, antifungal, antiviral, or antiprotozoal agents, or a combination of these, selected according to risk of infection with specific pathogens. Optimal prophylactic regimens should consider individual patient risk for infection and institutional infection and susceptibility patterns.

9. Patients undergoing hematopoietic stem cell transplantation (HSCT) are at an extremely high risk of infection because of prolonged neutropenia following intensive chemotherapy with or without irradiation, while solid-organ transplant recipients are at high risk because of prolonged administration of immunosuppressive drugs. Fungal (*Aspergillus*) and viral

(CMV) infections are particularly troublesome in these populations, and prophylactic regimens directed against these pathogens are commonly used. When documented, these infections must be treated aggressively in order to optimize patient outcomes. Nevertheless, mortality rates are often high despite appropriate and aggressive antimicrobial therapy.

10 Immunocompromised patients must be continuously assessed for evidence of infection and response to antimicrobial therapy. Because a large number of antimicrobials may potentially be used, the occurrence of drug-related adverse effects must also be carefully assessed. Efforts should be directed at designing cost-effective treatment strategies that promote optimal patient outcomes.

Preclass Engaged Learning Activity

Clostridioides difficile is a common and important infection that is difficult to treat in immunocompromised hosts. Frequent exposure to antimicrobials, contact with health care facilities and exposure to chemotherapy/immunosuppression add to the risk of recurrence. Create a summary table of drug and nondrug treatment options for *C. difficile* infection (CDI) in immunocompromised patient populations. Discuss pros, cons, place in therapy, and expected outcomes of each specific treatment option. This activity is intended to enhance your disease and drug information skills, apply knowledge regarding the treatment of CDI to specialized populations, and discuss the role of adjunctive (drug and nondrug) therapies in the treatment of CDI.

INTRODUCTION

An immunocompromised host is a patient with intrinsic or acquired defects in host immune defenses that predispose to infection. Advances in modern medicine have created more immunocompromised hosts than ever before. Historically, many of these patients died of their underlying diseases. Dramatic improvements in survival have been achieved by more aggressive therapy of underlying diseases and improved supportive care. However, because such aggressive therapy often renders patients profoundly immunosuppressed for long periods, opportunistic infections remain important causes of morbidity and

mortality. This chapter focuses on risk factors for infection, common pathogens and infection sites, and prevention and management of suspected or documented infections in cancer patients (including HSCT patients) and solid-organ transplant (SOT) recipients. Chapter 143 discusses infectious complications associated with human immunodeficiency virus (HIV) infection.

RISK FACTORS FOR INFECTION/EPIDEMIOLOGY

Numerous factors, such as underlying disease, immunosuppressive drug therapy, and antimicrobial administration, determine the immunocompromised host's risk of developing infection (see **Table 140-1**). These same factors may also influence the epidemiology of the associated infections. Multiple risk factors are present concomitantly in many patients.

TABLE 140-1 Risk Factors and Common Pathogens in Immunocompromised Patients

Risk Factor	Patient Conditions	Common Pathogens
Neutropenia	Acute leukemia Chemotherapy	Bacteria: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, streptococci, enterococci Fungi: *Candida*, *Aspergillus*, Mucorales (*Mucor*) Viruses: Herpes simplex
Impaired cell-mediated immunity	Lymphoma Immunosuppressive therapy (steroids, cyclosporine, chemotherapy)	Bacteria: *Listeria*, *Nocardia*, *Legionella*, Mycobacteria Fungi: *Cryptococcus neoformans*, *Candida*, *Aspergillus*, *Histoplasma capsulatum* Viruses: Cytomegalovirus, varicella-zoster, herpes simplex Protozo: *Pneumocystis jiroveci*
Impaired humoral immunity	Multiple myeloma Chronic lymphocytic leukemia Splenectomy Immunosuppressive therapy (steroids, chemotherapy)	Bacteria: *S. pneumoniae*, *H. influenzae*, *N. meningitidis*
Loss of protective skin barriers	Venipuncture, bone marrow aspiration, urinary catheterization, vascular access devices, radiation, biopsies	Bacteria: *S. aureus*, *S. epidermidis*, *Bacillus* spp., *Corynebacterium jeikeium* Fungi: *Candida*
Mucous membranes	Respiratory support equipment, endoscopy, chemotherapy, radiation	Bacteria: *S. aureus*, *S. epidermidis*, streptococci, Enterobacteriaceae, *P. aeruginosa*, *Bacteroides* spp., *Clostridioides difficile* Fungi: *Candida* Viruses: Herpes simplex
Surgery	Solid-organ transplantation	Bacteria: *S. aureus*, *S. epidermidis*, Enterobacteriaceae, *P. aeruginosa*, *Bacteroides* spp., *C. difficile* Fungi: *Candida* Viruses: Herpes simplex
Alteration of normal microbial flora	Antimicrobial therapy Chemotherapy Hospital environment	Bacteria: Enterobacteriaceae, *P. aeruginosa*, *Legionella*, *S. aureus*, *S. epidermidis*, *C. difficile* Fungi: *Candida*, *Aspergillus*
Blood products, donor organs	Bone marrow transplantation Solid-organ transplantation	Fungi: *Candida* Viruses: Cytomegalovirus, Epstein–Barr virus, hepatitis B, hepatitis C Protozo: *Toxoplasma gondii*

Neutropenia

[1] [2] [3] Neutropenia is defined as an abnormally reduced number of neutrophils circulating in peripheral blood. Although exact definitions of neutropenia can vary, an absolute neutrophil count (ANC) of less than 1,000 cells/mm^3 (1.0×10^9/L) indicates a reduction sufficient to predispose patients to infection.[1–3] ANC is the sum of the absolute numbers of both mature neutrophils (polymorphonuclear cells [PMNs], also called *polys* or *segs*) and immature neutrophils (*bands*). The absolute number of PMNs and bands is determined by dividing the total percentage of these cells (obtained from the white blood cell [WBC] differential) by 100 and then multiplying the quotient obtained by the total number of WBCs.

The degree or severity of neutropenia, rate of neutrophil decline, and duration of neutropenia are important risk factors for infection.[1–5] All neutropenic patients are considered to be at risk for infection, but those with ANC less than 500 cells/mm^3 (0.5×10^9/L) are at greater risk than those with ANCs of 500 to 1,000 cells/mm^3 (0.5×10^9 to 1.0×10^9/L). Most treatment guidelines use ANC less than 500 cells/mm^3 (0.5×10^9/L) as the critical value in making therapeutic decisions regarding the management of suspected or documented infections.[1–5] Risk of infection and death are greatest among patients with less than 100 neutrophils/mm^3 (0.1×10^9/L) ("profound neutropenia").[1–6] In patients with chemotherapy-induced neutropenia, the risk of infection is also increased according to both the rapidity of ANC decline and duration of neutropenia. Patients with severe neutropenia of more than 7 to 10 days' duration are considered to be at especially high risk for serious infections.[1–4,7] The duration of chemotherapy-induced neutropenia varies considerably among subsets of cancer patients according to the specific chemotherapeutic agents used and the intensity of treatment. Patients undergoing HSCT may have no detectable granulocytes in peripheral blood for up to 3 to 4 weeks and are at particular risk for severe infections with a variety of pathogens.[4–9]

Bacteria and fungi commonly cause infections in neutropenic patients. Gram-negative bacilli (*Escherichia coli*, *Klebsiella pneumoniae*, *P. aeruginosa*) historically were the most common causes of bacterial infection and remain frequent pathogens.[3,5,7–12] During the 1980s gram-positive cocci (*Staphylococcus aureus*, *Staphylococcus epidermidis* and other coagulase-negative staphylococci, streptococci, and enterococci) emerged as the most common cause of acute bacterial infections among neutropenic patients, accounting for up to 80% of all bloodstream infections.[5] This shift was likely due to widespread use of prophylaxis with fluoroquinolones, aggressive

chemotherapy regimens associated with severe mucositis, and more frequent use of central venous catheters.[5,7,9,10,13] However, the incidence of gram-negative infections is again increasing and now accounts for approximately half of bacterial infections.[4–7,10–12] Gram-negative infections are associated with significant morbidity and mortality, in large part due to increasing antibiotic resistance.[10–12,14] Patients who are neutropenic for extended periods and who receive broad-spectrum antibiotics are at high risk for fungal infections, usually due to *Candida* or *Aspergillus* spp.[1–7,15] Viral infections, although not as common as bacterial and fungal infections, also may cause severe infection in neutropenic patients.[1,4,6,7] Successful treatment of infections in neutropenic patients depends on resolution of neutropenia.[1–6,9]

Immune System Defects

Although not as readily quantifiable, abnormalities may exist in granulocyte function as well as in cell numbers. In addition to neutropenia, defects in T-lymphocyte and macrophage function (cell-mediated immunity), B-cell function (humoral immunity), or both predispose patients to infection.[3–5,8] Cellular immune dysfunction is the result of underlying disease or immunosuppressive drug therapy or radiation; these defects result in a reduced ability of the host to defend against intracellular pathogens. Patients with malignancies and transplant patients receiving a wide variety of immunosuppressive drugs, such as cyclosporine, tacrolimus, sirolimus, mycophenolate, corticosteroids, azathioprine, and antineoplastic agents, are at risk for a wide variety of infections (Table 140-1). Although some of these pathogens are associated with only asymptomatic or mild disease in normal hosts, they may cause disseminated, life-threatening infections in immunocompromised hosts.

Underlying disease also frequently causes defects in humoral immune function. Patients with multiple myeloma and chronic lymphocytic leukemia have progressive hypogammaglobulinemia that results in defective humoral immunity. Splenectomy performed as a part of the staging process for Hodgkin's disease places patients at risk for infectious complications. Disease states with humoral immune dysfunction predispose the patient to serious, life-threatening infection with encapsulated organisms such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*.

Destruction of Protective Barriers

Loss of protective barriers is a major factor predisposing immunocompromised patients to infection. Damage to skin and mucous membranes by surgery, venipuncture, IV and urinary catheters, radiation, and chemotherapy disrupts natural host defense systems, leaving patients at high risk for infection. Chemotherapy-induced mucositis may erode mucous membranes of the oropharynx and GI tract and establish a portal for subsequent infection by bacteria, HSV, and *Candida.*[1–6] Medical and surgical procedures, such as transplant surgery, indwelling IV catheter placement, bone marrow aspiration, biopsies, and endoscopy, further damage the integument and predispose patients to infection. Infections resulting from disruption of protective barriers usually are a result of skin flora, such as *S. aureus*, *S. epidermidis*, and streptococci.[3–5,7]

Environmental Contamination/Alteration of Microbial Flora

Infections in immunocompromised patients are caused by organisms either colonizing the host or acquired from the environment. Microorganisms may be transferred easily from patient to patient on the hands of hospital personnel unless strict infection prevention policies are followed. Contaminated equipment, such as nebulizers or ventilators, and contaminated water supplies have been responsible for outbreaks of *P. aeruginosa* and *Legionella pneumophila* infections, respectively. Foods, such as fruits and green leafy vegetables, which often are colonized with gram-negative bacteria and fungi, are sources of microbial contamination in immunocompromised hosts.[1,6]

Most infections in cancer patients are caused by organisms colonizing body sites, such as the skin, oropharynx, and GI tract and are therefore caused by the patient's own endogenous flora.[4–7] The GI tract is a common site from which infections in immunocompromised hosts originate. Periodontitis, pharyngitis, esophagitis, colitis, perirectal cellulitis, and bacteremias are caused predominantly by normal flora of the gut; bloodstream infections are thought to arise from microbial translocation across injured GI mucosa.[1,6,7] Normal flora may be significantly disrupted and altered; oropharyngeal flora rapidly change to primarily gram-negative bacilli in hospitalized patients. Many cancer patients may already be colonized with gram-negative bacilli on admission as a result of frequent prior hospitalizations and clinic visits. In hospitalized cancer patients, however, many infections are caused by colonizing organisms acquired after admission.[1]

Although hospitalization and severity of illness are important risk factors for

colonization by gram-negative bacilli, administration of broad-spectrum antimicrobial agents has the greatest impact on flora of immunocompromised hosts. Use of these agents disrupts GI tract flora and predisposes patients to infection with more virulent or resistant pathogens. Antineoplastic drugs (eg, cyclophosphamide, doxorubicin, and fluorouracil) and acid-suppressive therapy (eg, H_2-receptor antagonists, proton-pump inhibitors, and antacids) also may result in changes in GI flora and possibly predispose patients to infection.[1,4,5]

ETIOLOGY OF INFECTIONS IN NEUTROPENIC CANCER PATIENTS

2 Infection remains a significant cause of morbidity and mortality in neutropenic cancer patients. Febrile neutropenia occurs in 10% to 50% of patients with solid tumors and 80% to 100% of those with hematological malignancies.[1,2,5] More than 50% of febrile neutropenic patients have an established or occult infection, but these are microbiologically documented in only 30% to 40% of cases. Infections can be documented clinically (but not microbiologically) in another 30% to 40% of patients, with the remaining 20% to 40% of patients manifesting infection only by fever.[2–5,7] Bloodstream infections account for approximately 10% to 25% of all febrile episodes during neutropenia.[1,4,5,9] Patients with profound neutropenia are at greatest risk for systemic infection, with at least 20% of these individuals developing bacteremia.[1–6] Areas of impaired or damaged host defenses, such as the oropharynx, lungs, skin, sinuses, and GI tract, are common sites of infection. These local infections may progress to cause systemic infection and bacteremia.[4,5,9]

Table 140-1 lists organisms commonly infecting immunocompromised patients. Bacteremic episodes in cancer patients are caused by gram-positive organisms in 45% to 75% of cases, these rates being highly institution specific.[1,3,5,7,9–11,13] Important risk factors for these infections include frequent use of indwelling central and peripheral IV catheters, frequent use of broad-spectrum antibiotics with excellent gram-negative activity but often relatively poor gram-positive coverage, high rates of mucositis caused by aggressive cancer treatments, and prophylaxis with trimethoprim–sulfamethoxazole or fluoroquinolones.[1,3,5,7,9–11,14] Staphylococci (especially *S. epidermidis*) account for most infections, but *Bacillus* spp. and *Corynebacterium jeikeium* are also important pathogens.[1,4,5,7,13] Rates of infection due to methicillin-resistant *S.*

aureus (MRSA) have increased in the hospital and community settings.[4–6,13,14,16] Viridans streptococci, which may be resistant to β-lactams, also have emerged as important pathogens, particularly in patients with chemotherapy-induced mucositis of the oropharynx.[3–6,14] Enterococci, including vancomycin-resistant strains, also may be problematic in many institutions.[4,6,13,14,16] Bacteremia caused by vancomycin-resistant enterococci (VRE) in neutropenic patients is associated with a mortality rate up to 30%.[3,13,16,17]

Gram-positive infections are not always immediately life-threatening and are associated with somewhat lower mortality rates (approximately 5%-10%) compared with gram-negative infections.[1,4,10] However, increasing rates of antibiotic resistance have made treatment of gram-positive infections in immunocompromised patients more challenging.[4,7,10,13,14] MRSA infections are associated with increased morbidity, mortality, and hospital costs compared with susceptible organisms.[13,18] Methicillin resistance among coagulase-negative staphylococci, which may cause 40% to 80% of infections in certain populations, is common (70%-90% of isolates).[1,4,6,7,10,13,14] Vancomycin-resistant organisms such as VRE are increasing in importance.[1,3,4,10,13,17] Thus, prevention and timely diagnosis and treatment of gram-positive infections are clearly of great importance in the management of neutropenic cancer patients.

Gram-negative infections remain important causes of morbidity and mortality (approximately 10%-30%) in immunocompromised cancer patients.[5,10] However, the relative frequency of infection owing to specific pathogens has been shifting among gram-negative infections. *E. coli* and *Klebsiella* remain the most common isolates at many centers.[4,5,7] Strains of Enterobacteriaceae producing extended-spectrum β-lactamases that hydrolyze extended-spectrum cephalosporins, and carbapenemases that hydrolyze carbapenems, have emerged and are the cause for concern.[1,4,5,7,10,14] The global spread of carbapenem-resistant Enterobacteriaceae (CRE) is especially concerning. The frequency of infections resulting from other gram-negative organisms, such as *Enterobacter*, *Serratia*, and *Citrobacter*, has been increasing.[1,4,5] Infections with these particular organisms may be difficult to treat because of the ease of β-lactamase induction and the more frequent development of resistance to multiple antibiotics.[1,4,5,7,14]

P. aeruginosa has long been an important pathogen in cancer patients. *P. aeruginosa* infection rates are decreasing in patients with solid tumors but not in patients with hematologic malignancies.[3,7,10] Infections caused by *P. aeruginosa* are associated with significant morbidity and mortality in neutropenic patients,

with reported mortality rates of 31% to 75%.[1,5,10] The frequency of infection caused by difficult-to-treat organisms such as *Stenotrophomonas maltophilia* appears to be increasing at many centers, probably because of selective pressures of broad-spectrum antimicrobial use.[7,11] As with gram-positive organisms, antibiotic resistance among gram-negative organisms has continued to increase at alarming rates and has made appropriate antibiotic selection for treatment of febrile neutropenia more difficult.[1,5,14,16] Mortality rates of up to 40% to 70% have been reported in patients with infection caused by multidrug resistant gram-negative pathogens.[5,14] Although the GI tract is a common site of bacterial infection, severe infections caused by anaerobic organisms are relatively infrequent. Anaerobes are found most frequently in mixed infections, such as perirectal cellulitis and mucositis-associated oropharyngeal infections.[4,7]

In addition to bacterial infections, neutropenic cancer patients are at risk for invasive fungal infections. Patients with extended periods of profound neutropenia who have been receiving broad-spectrum antibiotics, corticosteroids, or both are at the highest risk for invasive fungal infection. Up to one-third of febrile neutropenic patients who do not respond to 1 week of broad-spectrum antibiotic therapy will have a systemic fungal infection.[1,4,11] Large autopsy studies have documented a change over time in invasive fungal infections. Whereas from 1989 to 2003 over 30% of autopsies of patients with hematologic malignancies found deep fungal infection (75% of which were undiagnosed prior to death), this number decreased to 19% from 2004 to 2008 (49% undiagnosed prior to death). These improvements may be due to improved awareness, diagnostic techniques and treatments. One single center estimated the average prevalence of invasive fungal infections was 30% in those autopsied over a 20-year period. Causative pathogens were usually either *Aspergillus* spp., *Candida* spp., or Mucorales fungi (such as *Mucor* spp.).[19] Mortality rates in patients with invasive fungal infections are highly dependent on pathogens and sites of infection, but often exceed 30% overall.[20]

Candida albicans is a common fungal pathogen in neutropenic cancer patients, especially those with solid tumors.[1,3,4,15,19,21] However, non-*albicans* species of *Candida* including *Candida glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei* are being isolated with increasing frequency and are more common than *C. albicans* infections in some studies.[15,21] Increased infections caused by pathogens such as *Trichosporon* spp., *Fusarium* spp., and *Curvularia* spp. have also been reported.[15,19,22] The shift toward more frequent infection with non-*albicans Candida* is important because of significantly decreased rates of azole

susceptibility among many of these strains.[23] Because *Candida* spp. are normal flora, alteration of body host defenses is an important risk factor for the development of these infections. Oral thrush is the most common clinical manifestation of fungal infection. Mucous membranes damaged from chemotherapy and radiation serve as areas of *Candida* surface colonization and subsequent entry into the bloodstream; disease then may disseminate throughout the body. Organs such as the liver, spleen, kidney, and lungs are commonly involved in disseminated disease.[1,4,19] Hepatosplenic candidiasis is a particularly important infection in patients with hematologic malignancies.[7,19,21] Diagnosis of *Candida* infections is difficult and often requires invasive tissue sampling.[7] In patients with invasive candidiasis, overall attributable mortality is as high as 35% to 50%.[3,15,21]

Invasive infections caused by *Aspergillus* spp. are a serious complication of neutropenia. Mortality rates have historically approached 80% in patients with prolonged neutropenia and/or patients undergoing allogeneic HSCT; however, mortality is now reported as low as 30%.[3,20,22,24] These infections are particularly prevalent and more common in patients with hematologic malignancies and in patients undergoing HSCT; invasive aspergillosis may occur in up to 10% of these patients.[3,15,19,22,24,25] Infections resulting from *Aspergillus* species (including *A. fumigatus*, *A. terreus*, *A. flavus*, and *A. niger*) usually are acquired via inhalation of airborne spores. After colonizing the lungs, *Aspergillus* invades the lung parenchyma and pulmonary vessels, resulting in hemorrhage, pulmonary infarcts, and a high mortality rate. Invasive pulmonary disease is the dominant manifestation of infection in patients with neutropenia. However, *Aspergillus* also may cause other infections, including sinusitis, cutaneous infection, and disseminated disease involving multiple organs, including the CNS.[19,25] Prolonged neutropenia is the primary risk factor for invasive pulmonary aspergillosis in patients with acute leukemia; use of corticosteroids also may predispose patients to disease.[25] Invasive aspergillosis should be suspected in neutropenic cancer patients colonized with *Aspergillus* (in sputum and/or nasal cultures) who remain persistently febrile despite at least 1 week of broad-spectrum antibiotic therapy.[1,4,25] Increased infections caused by other yeasts (such as *Trichosporon*) and molds (such as Mucorales, *Fusarium*, and *Curvularia*) have also been reported.[15,19,22]

Chemotherapy-induced mucous membrane damage may predispose neutropenic cancer patients to reactivation of HSV, manifesting as gingivostomatitis or recurrent genital infections. Untreated oropharyngeal HSV infections may spread to involve the esophagus and often coexist with *Candida*

infections. Clinical disease resulting from HSV occurs most often in patients with serologic evidence (eg, serum antibodies to HSV) of prior infection. Both HSV-seropositive HSCT patients and HSV-seropositive leukemics receiving intensive chemotherapy are at high risk for recurrent HSV disease during periods of immunosuppression.[3,4,6]

Pneumocystis jiroveci and *Toxoplasma gondii* are the most common parasitic pathogens found in immunocompromised cancer patients. Patients with hematologic malignancies and those receiving high-dose corticosteroids as part of chemotherapy regimens are at the greatest risk of infection.[3,4,6] Routine use of trimethoprim–sulfamethoxazole prophylaxis has substantially reduced the incidence of these infections.[1,4,6]

Because the majority of infecting organisms in cancer patients are from the host's own flora, some centers have used routine surveillance cultures in an attempt to prospectively identify causes of fever and suspected infection. In a typical surveillance culture program, cultures of the nose, mouth, axillae, and perirectal area are performed twice weekly, and culture results are correlated with the clinical status of the patient. Because these cultures are costly and have low diagnostic yield, the utility of surveillance culture programs is believed to be limited.[1,4] However, surveillance cultures are useful as research tools and in patients with prolonged profound neutropenia, and in institutions that have high rates of antimicrobial resistance or have problems with pathogens such as *P. aeruginosa* or *Aspergillus* spp. Surveillance cultures should be limited to the anterior nares for detecting colonization with MRSA, *Aspergillus*, and penicillin-resistant pneumococci and to the rectum for detecting VRE, *P. aeruginosa*, and multiple-antibiotic-resistant gram-negative bacilli (such as CRE).[1,4]

Knowledge of infection rates and local susceptibility patterns is essential for guiding optimal management of febrile neutropenia. These parameters must be monitored closely because the spectrum of infectious complications is related to multiple factors, including cancer chemotherapy regimens and antimicrobial therapy used for treatment and prophylaxis.

CLINICAL PRESENTATION

4 The most important clinical finding in the neutropenic cancer patient is fever. Because of the potential for significant morbidity and mortality associated with infection in these patients, fever should be considered to be the result of infection until proved otherwise.[1,2,4,5,7] At the appearance of fever, the patient

should be evaluated carefully for other signs and symptoms of infection. The use of biomarkers such as procalcitonin (PCT) has been extensively investigated for their utility in helping diagnose infections in febrile neutropenic patients. Although elevated PCT levels (typically ≥0.5 ng/mL [mcg/L]) have been associated with a significantly greater likelihood of bacterial infection in the febrile patient, lack of elevated PCT levels does not necessarily correspond to lack of infection and should not be used as the sole rationale for withholding or stopping initial antibiotic therapy.[26]

TREATMENT

Management of patients with febrile neutropenia, including both treatment and prophylaxis of infectious complications, can be extremely challenging. Although published guidelines are available, the most optimal clinical management of these patients remains unclear in many aspects.

Febrile Episodes in Neutropenic Cancer Patients

Desired Outcomes

4 5 The goals of therapy in neutropenic cancer patients with fever are the following: (a) protect the neutropenic patient from early death caused by undiagnosed infection; (b) prevent breakthrough bacterial, fungal, viral, and protozoal infections during periods of neutropenia; (c) effectively treat established infections; (d) reduce morbidity and allow for continued administration of optimal antineoplastic therapy; (e) avoid unnecessary use of antimicrobials that contribute to increased resistance; and (f) minimize toxicities and cost of antimicrobial therapy while increasing patient quality of life. Empirical broad-spectrum antibiotic therapy is effective at reducing early mortality.[1,2,4,10]

Approach to Treatment

General guidelines for management of febrile episodes and documented infections in neutropenic patients are shown in **Figs. 140-1** and **140-2**.[1] Although many controversies remain regarding optimal management of these patients, updated evidence-based guidelines from the Infectious Diseases Society of America (IDSA) for the management of febrile neutropenia were published in

2010 and, regarding outpatient management, in 2018.[1,2] Similarly, the National Comprehensive Cancer Network (NCCN) published updated clinical practice guidelines for the prevention and treatment of cancer-related infections in 2018.[4] Selected specific recommendations are discussed in the following sections of this chapter, and their associated evidence-based rankings are summarized in **Table 140-2**.

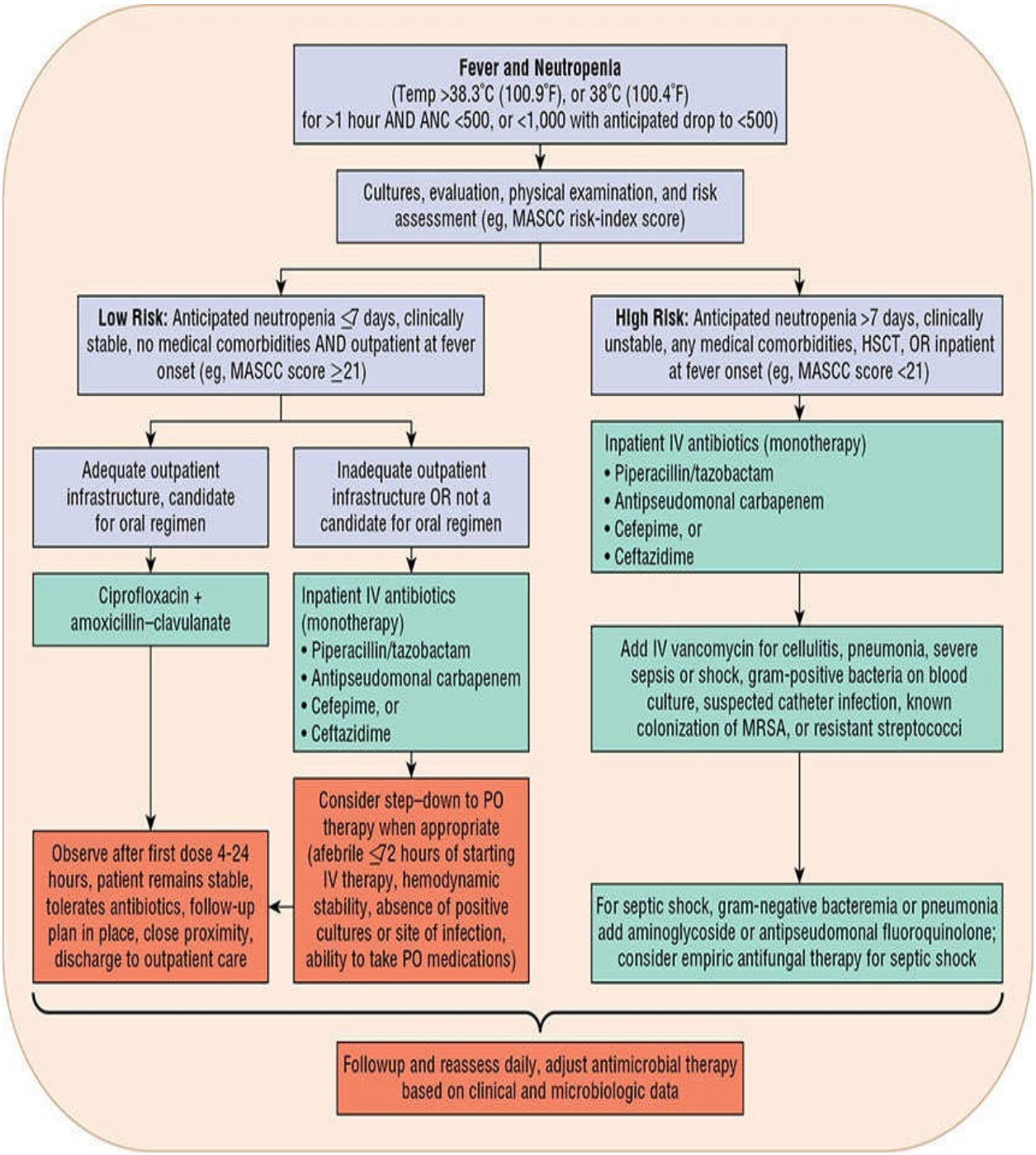


FIGURE 140-1 Initial management of febrile episodes in neutropenic patients. (ANC, absolute neutrophil count [expressed as cells/mm^3]; HSCT, hematopoietic stem cell transplantation; MASCC, Multinational Association for Supportive Care in Cancer; PO, oral.).

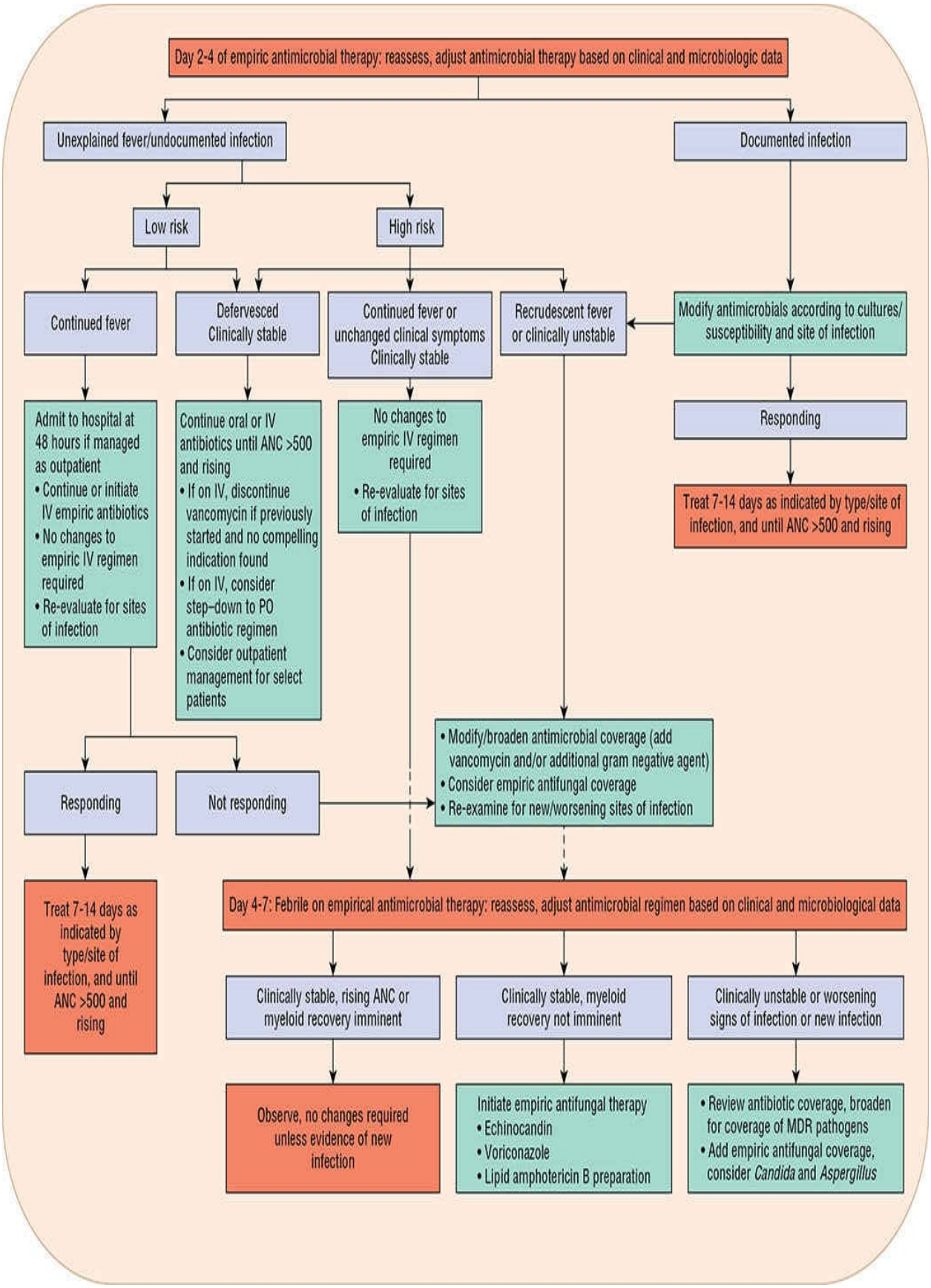

Day 2-4 of empiric antimicrobial therapy: reassess, adjust antimicrobial therapy based on clinical and microbiologic data
Unexplained fever/undocumented infection
Documented infection
Low risk
High risk
Continued fever
Defervesced Clinically stable
Continued fever or unchanged clinical symptoms Clinically stable
Recrudescent fever or clinically unstable
Modify antimicrobials according to cultures/ susceptibility and site of infection
Admit to hospital at 48 hours if managed as outpatient
• Continue or initiate IV empiric antibiotics
• No changes to empiric IV regimen required
• Re-evaluate for sites of infection
Continue oral or IV antibiotics until ANC >500 and rising
• If on IV, discontinue vancomycin if previously started and no compelling indication found
• If on IV, consider step–down to PO antibiotic regimen
• Consider outpatient management for select patients
No changes to empiric IV regimen required
• Re-evaluate for sites of infection
Responding
Treat 7-14 days as indicated by type/site of infection, and until ANC >500 and rising
Responding
Not responding
• Modify/broaden antimicrobial coverage (add vancomycin and/or additional gram negative agent)
• Consider empiric antifungal coverage
• Re-examine for new/worsening sites of infection
Treat 7-14 days as indicated by type/site of infection, and until ANC >500 and rising
Day 4-7: Febrile on empirical antimicrobial therapy: reassess, adjust antimicrobial regimen based on clinical and microbiological data
Clinically stable, rising ANC or myeloid recovery imminent
Clinically stable, myeloid recovery not imminent
Clinically unstable or worsening signs of infection or new infection
Observe, no changes required unless evidence of new infection
Initiate empiric antifungal therapy
• Echinocandin
• Voriconazole
• Lipid amphotericin B preparation
• Review antibiotic coverage, broaden for coverage of MDR pathogens
• Add empiric antifungal coverage, consider *Candida* and *Aspergillus*

FIGURE 140-2 Subsequent management of febrile episodes in neutropenic patients who have already received empirical antimicrobial therapy for 2-4 days. (ANC, absolute neutrophil count [expressed as cells/mm^3]; MDR, multidrug-resistant; PO, oral.).

TABLE 140-2 Summary of Evidence-Based Recommendations for Management of Febrile Episodes in Neutropenic Patients

Recommendations	Recommendation Grades[1]
The first dose of empirical antibiotic therapy should be administered within 1 hour after triage from initial presentation.	Strong, low
Oral antibiotics are feasible for treatment of carefully selected patients at low risk for complications	A-1
Clinical judgment and consideration of multiple patient factors should be used when selecting candidates for outpatient management.	Moderate, low
The MASCC index, Talcott's rules, and CISNE are recommended tools for identifying patients who may be candidates for outpatient management.	Moderate, intermediate
Patients who are eligible for outpatient management must meet appropriate psychosocial and logistical requirements.	Moderate, low
For outpatient management, first doses of antibiotics should be administered in the clinic, emergency department, or hospital.	Moderate, low
Monotherapy with appropriate antibiotics is as effective as combination regimens for initial empirical treatment of febrile neutropenic episodes	A-1
Patients at high risk for serious life-threatening infections must be initially treated with IV antibiotics. Patients at low risk can be treated with either IV or oral drugs (see text for risk stratification criteria)	A-2
Oral therapy with a fluoroquinolone (ciprofloxacin or levofloxacin) plus amoxicillin-clavulanate is appropriate for initial outpatient treatment.	Moderate, intermediate
Patients who become afebrile within 2-4 days of beginning initial empirical antibiotic therapy and in whom specific organisms have been identified should be treated for ≥7 days (until cultures are negative and patient has clinically recovered). Low-risk patients in whom no organism is identified can be switched to oral antibiotics if desired, whereas patients originally classified as high risk should continue on IV antibiotics	B-2

Management of Patients with Persistent Fever During First 2-4 Days of Treatment	
In patients initially receiving monotherapy or a two-drug regimen *not* including vancomycin, addition of vancomycin can be considered if any criteria for use of vancomycin are present (see the text for specific criteria)	B-3
In patients *already* receiving vancomycin as part of the initial empirical regimen, withdrawal of vancomycin should be considered after 2 days in the absence of a documented pathogen requiring continued therapy	A-2
Other initial antibiotics can be continued if the disease has not progressed, or switched to oral therapy if the patient was classified as low risk even in the presence of continued fever	A-1
Management of Patients with Fever Persisting for More Than 2-4 Days After Initial Treatment	
Reassess patient after 2 days of treatment. If still febrile by day 4, then: (a) continue the same antibiotics if clinically stable; (b) change antibiotics if any evidence of disease progression or antibiotic toxicities; or (c) add an antifungal drug if the duration of neutropenia is expected to be more than 5-7 additional days	Option a: A-1 Option b: A-3 Option c: A-3
Continuation of Antibiotics in Afebrile Patients with no Identified Infection	
Antibiotic therapy can be discontinued after 3 days of treatment if patient is afebrile for ≥48 hours and absolute neutrophil count (ANC) is ≥500 cells/mm^3 (0.5 × 10^9/L) for two consecutive days	A-2
If patient remains neutropenic, continue IV or oral antibiotics	A-2
Antibiotics should be continued in patients with profound neutropenia (ANC <100 cells/mm^3 [0.1 × 10^9/L]), mucous membrane lesions of mouth or GI tract, unstable vital signs, or other identified risk factors	A-2
Antibiotics can be stopped after 2 weeks in patients with prolonged neutropenia of unclear continued duration, no identified site of infection, and who can be closely observed	C-3
Alternatively, antibiotics can be discontinued after 4 days if no infection is documented and the patient shows no response to therapy	C-3
Management of Fungal Infections	
Suspected candidiasis:	
Lipid-associated amphotericin B (LAMB) or caspofungin[2]	A-1
Voriconazole	B-1
Fluconazole or itraconazole	B-1
Candidemia:	
An echinocandin[2] or LAMB	A-2
Fluconazole or voriconazole	B-3
Granulocyte Transfusions	
There are no specific indications for routine use of granulocyte transfusions	C-2
Colony-Stimulating Factors	
Colony-stimulating factors are not indicated for routine treatment of neutropenia in either febrile or afebrile patients	B-2
Prophylactic use of colony-stimulating factors should be considered for patients in whom the anticipated risk of fever and neutropenia is ≥20%	A-2
Antimicrobial Prophylaxis in Neutropenic Patients	
Fluoroquinolone prophylaxis should be considered for high-risk patients with profound neutropenia (ANC <100 cells/mm^3 [0.1 × 10^9/L]) expected to last 7-10 days	Moderate, high
Antibacterial prophylaxis is not required in routinely recommended in low-risk patients who are expected to be neutropenic <7 days	A-3
Prophylaxis with trimethoprim–sulfamethoxazole should be administered to all patients at high risk for *Pneumocystis jiroveci* pneumonia, regardless of whether they are neutropenic	Strong, high
Prophylaxis with an oral triazole or parenteral echinocandin is recommended in high-risk patients, starting with induction chemotherapy and continued for duration of neutropenia	Moderate, intermediate
In HSCT, prophylaxis with fluconazole, micafungin[2], posaconazole, itraconazole, voriconazole, or LAMB is recommended during the period of risk of neutropenia	A-1 for fluconazole and micafungin[2], all others B-2
In HSCT patients with graft-versus-host disease, or neutropenic patients with hematologic malignancies, prophylaxis with posaconazole is recommended for prevention of invasive fungal infections	A-1
HSV-seropositive patients undergoing HSCT or leukemia induction therapy should receive acyclovir prophylaxis during neutropenia, and for at least 30 days after HSCT	Strong-high for prophylaxis, A-2 for duration
In HSCT, prophylaxis with acyclovir should be administered during neutropenia and for at least 1 year afterward to prevent VZV infection or reactivation	A-2

[1]Cited evidence-based guidelines utilize different systems for grading the strengths of recommendation and quality of the associated evidence. Letter/number-based recommendations are from references 1 and 2; qualitative (descriptive) recommendations are from the other cited guidelines. Readers are advised to consult the original documents for full explanations of the grading systems and definitions used in individual guidelines.

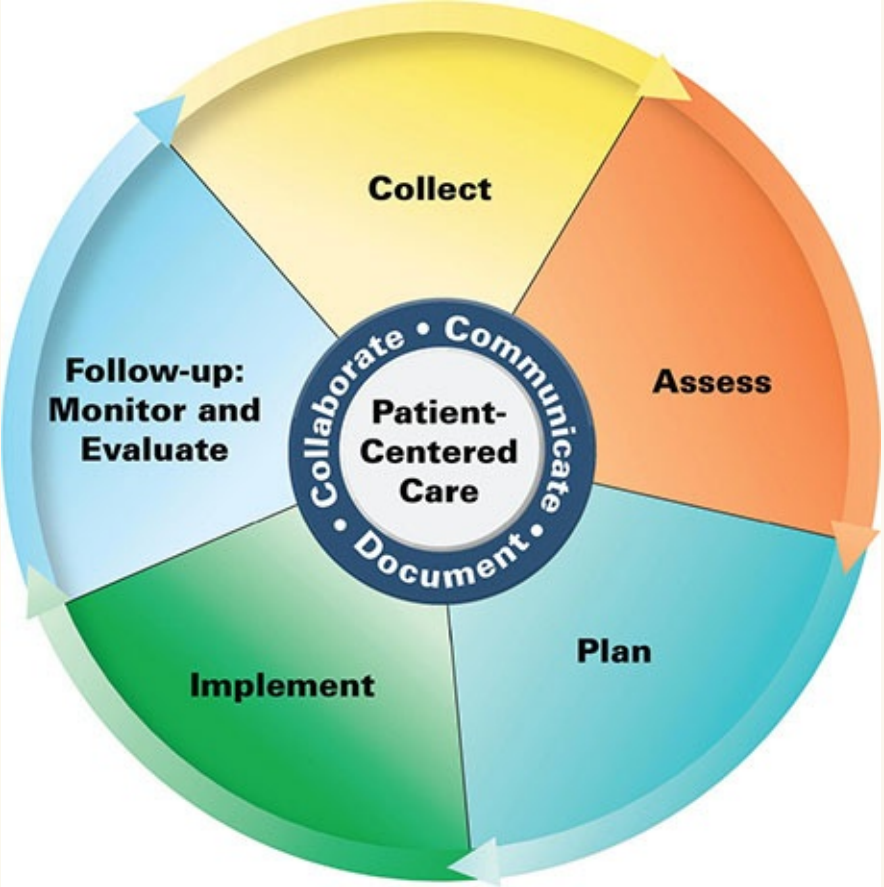
[2]Expert opinion indicates all echinocandins are likely interchangeable and equally effective.

Strength of recommendations: A, B, C = good, moderate, and poor evidence to support recommendation for use, respectively; D = moderate evidence to support a recommendation against use. *Quality of evidence*: 1 = evidence from ≥1 properly randomized, controlled trial; 2 = evidence from ≥1 well-designed clinical trial without randomization, from cohort or case–control analytic studies, from multiple time series, or from dramatic results from uncontrolled experiments; 3 = evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Qualitative (descriptive) recommendations: *Strong, high*: strong recommendation based on high-quality evidence; *Strong, moderate*: strong recommendation based on moderate-quality evidence; *Strong, low*: strong recommendation based on low-quality evidence; *Moderate, high*: moderate recommendation based on high-quality evidence; *Moderate, intermediate*: moderate recommendation based on intermediate-quality evidence; *Moderate, low*: moderate recommendation based on low-quality evidence; *Weak, moderate*: weak recommendation, moderate quality evidence from RCTs with important limitations or exceptionally strong evidence from unbiased observational studies; *Weak, low*: weak recommendation, low-quality evidence for at least one critical outcome from observational studies, RCTs with serious flaws, or indirect evidence.

Data from References 1, 2, 4, 6, 21, 25, and 27.

Fever in the neutropenic cancer patient is considered to be caused by infection until proved otherwise. High-dose broad-spectrum bactericidal, usually parenteral, empirical antibiotic therapy should be initiated at the onset of fever or at the first signs or symptoms of infection. Withholding antibiotic therapy until an organism is isolated results in unacceptably high mortality rates. Undiagnosed infection in immunocompromised patients can rapidly disseminate and result in death if left untreated or if treated improperly. Failure to initiate appropriate antibiotic therapy for *P. aeruginosa* bacteremia at the onset of fever in neutropenic cancer patients resulted in mortality rates of 15%, 48%, and 70% within 12, 24, and 48 hours, respectively.[1,4,28] Appropriate empirical antibiotic therapy is 70% to 90% effective at reducing early morbidity and mortality.[1,4,10] Therapy must be appropriate and initiated promptly, ideally within 1 hour after initial presentation. Antimicrobial therapy must also be initiated promptly in afebrile cancer patients with clinical signs and symptoms of infection.



Patient Care Process for the Treatment of Suspected Infection in an Immunocompromised Host

Collect

- Patient characteristics (eg, age, sex, height, weight)
- Patient medical history (oncologic, surgical, vaccines, previous infections, time since transplant/engraftment/last oncologic regimen)
- Social history (eg, drug/ethanol use), travel history (eg, endemic exposures)
- Current medications (eg, antimicrobial prophylaxis/treatment, immunomodulating agents [immunosuppressive or immunostimulatory])
- Prior medications (eg, antimicrobial, oncologic, immunomodulating) and future planned medications (eg, life-saving oncologic or immunomodulating regimens)

Objective data

- Mean arterial blood pressure (MAP), heart rate (HR), respiratory rate (RR), O_2-saturation, altered mental status (AMS), urine output (UO), skin turgor/integrity
- Labs including white blood cells (WBC) with differential, absolute neutrophil count (ANC) and trends, serum creatinine (SCr), lactate, liver function tests (LFT), blood glucose
- Culture data (eg, bacterial, fungal, viral), microbiologic diagnostic tests (eg, procalcitonin, galactomannan, β-D-glucan, viral polymerase chain reaction tests, infectious serologies)
- Presence of central, peripheral, urinary catheters and indwelling ports

Assess

- For febrile neutropenia: assess risk of infectious complications for possible outpatient management (see Table 140-3) including logistical barriers (eg, access to care, compliance, support)

- Hemodynamic/clinical stability and evidence of organ malperfusion (eg, MAP <65 mmHg, HR >100 bpm, RR>22, AMS, decreased UO, renal dysfunction)
- Evidence of infection at common sites (see Clinical Presentation boxes: Febrile Neutropenia and Infection in Solid Organ Transplant)
- Assess risk of infection based on duration/degree of neutropenia or magnitude of immunosuppression
- Assess need for colony-stimulating factors (CSF) (see Table 140-8)
- Assess risk for infection with specific pathogens (see Table 140-1)
- Assess contraindications to specific antimicrobial therapy (eg, allergies, drug–drug/disease interactions)
- Assess previous and current culture results and susceptibilities

Plan*

- Antimicrobial regimen including specific antimicrobial(s), dose, route, frequency, and duration (see Figs. 140-1, 140-2; Tables 140-4, 140-5, 140-7)
- Monitoring parameters including efficacy (eg, resolution of infectious symptoms, fever, ANC) and safety (eg, antimicrobial side effects, *Clostridioides difficile*, CNS toxicity)
- Patient education if treated outpatient (eg, self-monitoring, when/how to seek help, adherence)
- Referrals to other providers when appropriate (eg, infectious disease specialist)

Implement*

- Provide patient and caregiver education regarding when/how to seek advance medical attention
- Provide integrated health professionals, patient and family education (eg, expected outcomes/goals of therapy, therapeutic drug monitoring, avoidance of exposures)

Follow-up: Monitor and Evaluate*

- De-escalation of empiric antimicrobial regimens to targeted therapy (see

Table 140-7)

- Resolution of infectious symptoms (see also Figs. 140-1, 140-2)
- Presence of adverse effects specific to the antimicrobial regimen
- Presence of drug–drug interactions potentially requiring changes in drug regimens or additional therapeutic drug monitoring
- Patient adherence to outpatient antimicrobial plan
- Therapeutic drug levels to adjust antimicrobial therapy (see Table 140-6)

Collaborate with patient, caregivers, and other healthcare professionals.

CLINICAL PRESENTATION

Febrile Neutropenia[1–7,20]

General

- Due to high risk for serious infections, frequent (at least daily) careful clinical assessments must be performed to search for possible evidence of infection
- Physical assessment should include examination of all common sites of infection, including mouth/pharynx, nose and sinuses, respiratory tract, GI tract, urinary tract, skin, soft tissues, perineum, and intravascular catheter insertion sites

Symptoms

- Usual signs and symptoms of infection may be absent or altered in neutropenic patients owing to low numbers of leukocytes and an inability to mount an inflammatory response (eg, no infiltrate on chest x-ray film, urinary tract infection without pyuria)
- Pain may be present at the infection site(s)

Signs

- Fever in this setting is defined as a single oral temperature ≥38.3°C

(100.9°F) in the absence of other causes or temperature ≥38°C (100.4°F) for 1 hour or more. Other causes of fever unrelated to infection in this patient population include reactions to blood products, chemotherapeutic agents (and other drugs, including biologics), cell lysis, and underlying malignancy

- Usual signs of infection may be absent or altered; patients with bacteremia commonly exhibit no signs of infection other than fever

Laboratory Tests

- Neutropenia (ANC ≤1,000 cells/mm^3 [1.0×10^9/L])
- Blood cultures (two or more sets, including vascular access devices) for bacteria and fungi; cultures of other suspected infection sites (infection can be documented microbiologically in only about 30% of cases, about half of which are due to bacteremia)
- Other cultures should be obtained as indicated clinically according to the presence of signs or symptoms
- Recent surveillance cultures (nasal, rectal) should be reviewed, if available
- Complete blood count and blood chemistries should be obtained frequently to monitor neutropenia, plan supportive care, guide drug dosing, and assess patient's overall status

Other Diagnostic Tests

- Chest x-ray film
- Aspiration, biopsy of skin lesions
- Procalcitonin is indicative of bacterial infection when elevated, but negative test does not rule out infection
- Other diagnostic tests as indicated clinically on the basis of physical examination and other assessments

When designing optimal empirical antibiotic regimens, clinicians must consider infection patterns and antimicrobial susceptibility trends in their respective institutions. Patient factors such as risk for infection, drug allergies, concomitant nephrotoxins, and previous antimicrobial exposure (including

prophylaxis) must be considered.[1–4] Assessment of the patient's risk of infection will help determine the appropriate route and setting for antibiotic administration (Fig. 140-1). Neutropenic patients with fever can be divided into low- and high-risk groups for complications of severe infection. Risk stratification drives both type and setting of antimicrobial therapy. The Multinational Association for Supportive Care in Cancer (MASCC) risk-index score is recommended by many clinical guidelines to assess a patient's risk of complications.[1,2,4] Additional evaluation tools including Talcott groups and the Clinical Index of Stable Febrile Neutropenia (CISNE) score are also recommended.[2] These tools are provided in **Table 140-3**.

TABLE 140-3 Tools for Evaluating Febrile Neutropenia and Identifying Low-Risk Individuals for Outpatient Management[2,4]

	Patient Characteristic	Score or Group
MASCC		
	Burden of febrile neutropenia: no or mild symptoms *OR* moderate symptoms	5 points
		3 points
	No hypotension (systolic blood pressure >90 mm Hg	5 points
	No chronic obstructive pulmonary disease	4 points
	Solid tumor or hematologic malignancy with no previous fungal infection	4 points
	No dehydration requiring parenteral fluids	3 points
	Outpatient status	3 points
	Age <60 years	2 points
	Maximum total score = 26 points; score ≥21 points indicates low risk for medical complications.	
Talcott		
	Inpatients at time of fever onset	Group I
	Outpatients with acute comorbidity requiring, by itself, hospitalization	Group II
	Outpatients without comorbidity but with uncontrolled cancer	Group III
	Outpatients with cancer controlled and without comorbidity	Group IV
	Groups I-III = high risk; Group IV = low risk.	
CISNE		
	Eastern Cooperative Oncology Group performance status ≥2	2 points
	Stress-induced hyperglycemia	2 points
	Chronic obstructive pulmonary disease	1 point
	Chronic cardiovascular disease	1 point
	National Cancer Institute Common Toxicity Criteria mucositis of grade ≥2	1 point
	Monocytes <200/μL (0.2 x 10^9/L)	1 point

Maximum total score = 8 points; 0 points = low risk; 1-2 points = intermediate risk; ≥3 points = high risk. Suggested for use with patients with solid tumors who have undergone mild-to-moderate intensity chemotherapy and who appear to be clinically stable. Patients with CISNE score 0-2 would be considered candidates for outpatient management.

Most experts agree that, in general, low-risk patients have an anticipated duration of neutropenia less than or equal to 7 days, are clinically stable, and have no or few comorbidities and no bacterial focus or systemic signs of infection other than fever. In contrast, high-risk patients are those with an anticipated duration of neutropenia greater than 7 days or profound neutropenia, are clinically unstable or have comorbid medical problems (eg, focal or systemic signs of infection, GI symptoms, nausea, vomiting, diarrhea, hypoxemia, and chronic lung disease), or have a high-risk cancer (eg, acute leukemia) and/or

have undergone high intensity chemotherapy. High-risk patients (eg, MASCC less than 21, Talcott Groups I through III, CISNE ≥ 3) should be hospitalized for parenteral antibiotics whereas low-risk patients may be candidates for oral or outpatient antibiotics. Scoring tools such as MASCC must be used in conjunction with, not as a replacement for, careful clinical assessment of patients when selecting low-risk patients for oral outpatient management. Many additional patient factors (eg, worsening renal function, altered mental status, severe anemia, or thrombocytopenia) may increase risk of complications and potentially exclude patients from outpatient management of febrile neutropenia (see also "Oral Antibiotic Therapy for Management of Febrile Neutropenia" section below).[1,2,4,29]

The optimal antibiotic regimen for empirical therapy in febrile neutropenic cancer patients remains controversial, but it is clear that no single regimen can be recommended for all patients. Because of their frequency and relative pathogenicity, *P. aeruginosa* and other gram-negative bacilli and staphylococci remain the primary targets of empirical antimicrobial therapy.[1,2,4] Although *P. aeruginosa* may be documented in fewer than 5% of bloodstream infections in the population of hospitalized patients, adequate antipseudomonal antibiotic coverage still must be included in empirical regimens because of the significant morbidity and mortality associated with this pathogen.[1,3,16] All empirical regimens must be carefully monitored and appropriately revised on the basis of documented infections, susceptibilities of bacterial isolates, development of more defined clinical signs and symptoms of infection, or a combination of these factors.

Although there are some differences among them, consensus guidelines generally recognize three different types of empirical parenteral antibiotic regimens: (a) monotherapy with an antipseudomonal β-lactam such as a cephalosporin (cefepime or ceftazidime), a carbapenem (imipenem–cilastatin or meropenem), or piperacillin–tazobactam; (b) two-drug combination therapy with an antipseudomonal β-lactam plus either an aminoglycoside or an antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin); and (c) monotherapy or two-drug combination therapy as above, plus the addition of vancomycin (Fig. 140-1).[1,4] Each of these regimens has advantages and disadvantages, which are summarized in **Table 140-4**. There is no overwhelming evidence that any one of these regimens is superior to the others. The overall response to empirical antibiotic regimens in febrile neutropenic cancer patients is approximately 70% to 90% regardless of whether a pathogen is isolated or which antimicrobial regimen is used.[1,3,4,10] Additionally, other alternative regimens

may also be appropriate based on specific patient characteristics or susceptibilities of suspected pathogens.

TABLE 140-4 Comparative Advantages and Disadvantages of Various Antibiotic Regimens for Empiric Therapy of Febrile Neutropenic Cancer Patients

Regimen	Potential Advantages	Potential Disadvantages
β-Lactam monotherapy (ceftazidime, cefepime, piperacillin–tazobactam, imipenem–cilastatin, or meropenem)	Efficacy comparable to combination regimens; decreased drug toxicities; ease of administration; possibly less expensive	Possibly less efficacy in profound neutropenia or prolonged neutropenia; limited gram-positive activity; no potential for additive/synergistic effects; increased selection of resistant organisms; increased colonization and superinfection rates
Antipseudomonal β-lactam plus aminoglycoside (eg, gentamicin or tobramycin + cefepime, ceftazidime, or piperacillin–tazobactam)	Traditional regimen, broad-spectrum coverage; optimal therapy of *Pseudomonas aeruginosa*; rapidly bactericidal; synergistic activity; decreased bacterial resistance; reduction of superinfections	Limited gram-positive activity; potential for nephrotoxicity; need for therapeutic monitoring of aminoglycoside concentrations
Antipseudomonal β-lactam plus fluoroquinolone (ciprofloxacin or higher-dose levofloxacin + ceftazidime, cefepime, or piperacillin–tazobactam)	Efficacy similar to other regimens when used in combination therapy; no cross-resistance with β-lactams; possibility for oral administration; may be useful in patients with renal impairment in whom aminoglycosides are undesirable	Marginal gram-positive activity; fluoroquinolones not recommended as monotherapy; resistance may develop rapidly
Empirical regimens containing vancomycin (added to antipseudomonal β-lactam ± aminoglycoside or fluoroquinolone)	Early effective therapy of gram-positive infections	No demonstrated benefit of vancomycin empirical therapy versus addition of vancomycin if needed later; increased risk of selection for vancomycin-resistant enterococci; risk of toxicities; excessive cost; need for therapeutic monitoring of vancomycin concentrations
Oral antibiotic regimens (eg, ciprofloxacin or levofloxacin + amoxicillin–clavulanate or clindamycin)	Efficacy comparable with parenteral therapy in low-risk patients; less expensive; reduced exposure of patients to nosocomial pathogens	Least studied treatment approach; less potent than parenteral antibiotics; requires compliant patient with 24-hour access to medical care should clinical instability develop

Data from references 1-5, 10, 30, and 31.

β-Lactam Monotherapy

Monotherapy with an antipseudomonal β-lactam is recommended by IDSA 2010 and NCCN 2018 guidelines as initial parenteral therapy for management of febrile neutropenia without suspected or proven resistant organisms or complications (eg, pneumonia, hypotension, vascular access infection, etc.).[1,4] β-Lactam antibiotics that have been evaluated as monotherapy for management of

febrile episodes in neutropenic cancer patients, include antipseudomonal cephalosporins (ceftazidime and cefepime), piperacillin–tazobactam, and antipseudomonal carbapenems (imipenem–cilastatin and meropenem).[1,4] Three different meta-analyses assessing as many as 46 clinical trials involving more than 7,600 patients found no significant differences overall between monotherapy and combination therapy (β-lactam/aminoglycoside) in rates of survival, treatment response, and bacterial/fungal superinfections.[4] One study also found a higher rate of adverse effects in aminoglycoside-containing combination regimens.[30] Monotherapy with antipseudomonal β-lactams is therefore recommended by treatment guidelines and routinely used for initial treatment.[1,4] Institutional susceptibility patterns and patient characteristics should drive drug selection for the management of individual patients with febrile neutropenia.[1,4]

Ceftazidime-avibactam, ceftolozane-tazobactam, and meropenem-vaborbactam have appropriate overall spectrum of antibacterial activity with good activity against *P. aeruginosa* and other gram-negative organisms as well as many gram-positive pathogens. Neither the 2018 NCCN nor the 2010 IDSA consensus guidelines specifically recommend these agents as appropriate for monotherapy due to a lack of supportive clinical evidence at the time the guidelines were written.[1,4] These agents are also considered to be too broad-spectrum and expensive for routine empiric use. However, they may be considered reasonable treatment options in selected patients at high risk for, or with previous history of, infection with multidrug-resistant (MDR) pathogens or in institutions with high rates of infection with MDR pathogens in certain high-risk patients.

Use of monotherapy has several potential advantages and disadvantages (see Table 140-4). Perhaps the most common concerns are those regarding the selection of resistant strains of organisms, such as *P. aeruginosa*, *Enterobacter* spp., and *Serratia* spp., through expression of extended-spectrum β-lactamases and type 1 β-lactamases, especially with ceftazidime.[1,4,10,14] Activity against gram-positive organisms such as coagulase-negative staphylococci, MRSA, enterococci (including VRE), penicillin-resistant *S. pneumoniae*, and some strains of viridans streptococci is poor with some single β-lactams, but cefepime and antipseudomonal carbapenems have good activity against most viridans streptococci and pneumococci.[1,4] Although ceftazidime has been studied widely and used for treatment of febrile neutropenia, newer agents may be more effective owing to ceftazidime's susceptibility to β-lactamase induction and lower activity against gram-positive organisms.[1,4,10,14,32] Ertapenem, a

carbapenem, and ceftaroline, a cephalosporin active against MRSA, have excellent activity against many gram-negative organisms but should not be routinely used in the empirical treatment of febrile neutropenia due to their weak activity against *P. aeruginosa*. For the same reason, broad-spectrum tetracycline derivatives (eg, tigecycline, eravacycline, omadacycline) are not acceptable options for empiric monotherapy in most patients.

As with all empirical antibiotic regimens, patients receiving monotherapy should be monitored closely for treatment failure, secondary infections, and development of resistance. Use of monotherapy may not be appropriate in institutions with high rates of gram-positive infections or infections caused by relatively resistant gram-negative pathogens such as *P. aeruginosa* and *Enterobacter*. The carbapenems are less susceptible to inducible β-lactamases and often may be used effectively in these institutions. Overall, similar efficacy has been observed with monotherapy with antipseudomonal β-lactams compared to aminoglycoside combination therapy for treatment of *P. aeruginosa* infections.[1,4,30]

Aminoglycoside Plus Antipseudomonal β-Lactam

Regimens consisting of an aminoglycoside plus an antipseudomonal β-lactam traditionally have been the most commonly used for empirical treatment of febrile neutropenia, although many such regimens may lack adequate gram-positive activity (see Table 140-4).[1,4] This relative lack of activity remains a concern because of the increasing frequency of gram-positive infections. The choice of aminoglycoside and β-lactam for inclusion in empirical regimens should be based on institutional epidemiology and antimicrobial susceptibility patterns. Similar efficacy is observed with an antipseudomonal β-lactam in combination with an aminoglycoside.[1,4,30]

Combinations of broad-spectrum β-lactams and aminoglycosides may provide synergistic activity against bacteria commonly infecting neutropenic patients. The exact role of synergy in the outcome of febrile neutropenic patients treated with empirical antibiotic therapy is somewhat controversial, particularly in light of the efficacy of single-drug regimens and nephrotoxicity associated with aminoglycosides.[30] Nevertheless, combinations of antibiotics appear to be beneficial in patients with persistent profound neutropenia.

Aminoglycoside toxicity may be a concern in patients receiving these regimens who are already receiving other nephrotoxic drugs, such as cisplatin and cyclosporine. Administration of aminoglycosides in large single daily doses

(once-daily dosing) may be as effective, less costly, and no more toxic than conventional dosing methods. Although once-daily aminoglycoside dosing regimens appear to be safe and effective in these patients, standard dosing regimens are recommended for infections where data are not sufficient to recommend once-daily dosing (eg, endocarditis).[1,4]

Fluoroquinolones as a Component of Empirical Regimens

Because the fluoroquinolone antibiotics have broad-spectrum activity (particularly against gram-negative pathogens), rapid bactericidal activity, and favorable pharmacokinetic and toxicity profiles, these agents have been investigated as empirical therapy for febrile neutropenic patients. Ciprofloxacin is the preferred agent for use in this clinical setting because of its relatively better activity against *P. aeruginosa* and more extensive evidence-based support for its use.[1,4] Response rates to quinolone-containing combination regimens are comparable to those obtained with the other regimens described previously.[1,3,4] Ciprofloxacin is not recommended for monotherapy, however, because of its relatively poor activity against gram-positive pathogens, particularly streptococci, and variable response rates in clinical studies.[1,4] Fluoroquinolones should also not be used as empirical therapy in patients who have received quinolones as infection prophylaxis because of the risk of drug resistance.[1,4] Rates of fluoroquinolone resistance are increasing, and streptococcal treatment failures are a concern.[14,16] Although fluoroquinolones are not generally considered first-line empirical therapy for inpatient use, they may be useful as one component of combination regimens in patients with allergies or other contraindications to first-line agents.[1,4]

Empirical Regimens Containing Vancomycin

The inclusion of vancomycin in initial empirical therapy of febrile neutropenic cancer patients is not currently recommended by IDSA 2010 or NCCN 2018 guidelines unless the patient has specific risk factors; however, this remains an ongoing debate. This controversy continues because of the increasing incidence of gram-positive infections in this population, particularly MRSA. One approach is to include vancomycin in the initial empirical antibiotic regimen, thereby providing early effective treatment of possible gram-positive infections. Inclusion of vancomycin in initial empirical regimens may be more appropriate

today because of higher rates of MRSA infections as well as aggressive chemotherapy regimens causing significant mucosal damage that increases the risk for streptococcal infections. Decreased mortality from penicillin-resistant viridans streptococcal infections has been observed when vancomycin was included in initial therapy.[1,6,32] A second approach is to withhold vancomycin from initial empirical regimens, later adding the drug if gram-positive organisms are isolated from cultures or if there is clinical deterioration. Support for both these approaches can be found in the medical literature.[1,4,31,32] Prospective studies and multiple meta-analyses have failed to document increased response rates or decreased mortality with the routine addition of vancomycin to initial empirical regimens, provided that vancomycin can be added later as needed.[1,4,31,32] In addition to increased costs of therapy, vancomycin was also associated with increased adverse effects, including nephrotoxicity.[4] Finally, concerns remain regarding selection of resistant gram-positive bacteria such as VRE with excessive vancomycin use.[1,4,33]

Vancomycin is currently recommended for inclusion in initial empirical regimens only in patients at high risk for gram-positive infection, particularly due to MRSA and coagulase-negative staphylococci (including patients with evidence of infection of central venous catheters and other indwelling lines), high risk for viridans streptococcal infection due to severe mucositis, or pneumonitis or soft tissue infection in hospitals with high rates of MRSA infections.[1,4,10,32] Rates of β-lactam resistance among viridans streptococci range up to 25%.[1,4] Empirical vancomycin use may be justified in institutions using empirical or prophylactic antibiotic regimens without good activity against streptococci (eg, ciprofloxacin) and in patients known to be colonized with MRSA or β-lactam–resistant pneumococci. In patients with preliminary culture results indicating gram-positive infection, empirical vancomycin is appropriate while the susceptibility results are pending. Lastly, empirical use of vancomycin may be recommended in patients with hypotension or other evidence of cardiovascular impairment or sepsis without an identified pathogen.[1,4] If empirical vancomycin therapy is initiated and no evidence of gram-positive infection is found after 48 to 72 hours, the drug should be discontinued.[1,4] Continuing vancomycin when not warranted results in higher costs, more toxicities, and greater risk of development of VRE.[1,4,33] Of note, augmented renal clearance occurs with some frequency (approximately 16%) in patients with febrile neutropenia and has been associated with significantly higher rates of subtherapeutic vancomycin concentrations.[34] Clinicians should be alert to the need for therapeutic drug monitoring of vancomycin in patients with febrile

neutropenia and should carefully monitor patient response to therapy in those receiving vancomycin or other renally excreted antimicrobials.[34]

Other antimicrobial agents, such as quinupristin–dalfopristin, linezolid, daptomycin, telavancin, and ceftaroline, should be reserved for documented infections caused by multiresistant gram-positive pathogens that are not susceptible to, or are unresponsive to, vancomycin. The role of these drugs in the routine treatment of fever in neutropenic patients is undetermined, and linezolid is associated with risk of myelosuppression.[1,4]

Oral Antibiotic Therapy for Management of Febrile Neutropenia

An individual patient's risk for complications of severe infection determines appropriate antibiotic therapy and the proper setting for administration (see Table 140-4).[1–3,5] Risk stratification is based on several parameters (eg, MASCC score or other tools previously mentioned) as well as response to empirical antimicrobial therapy if IV therapy is initially given.[1] Benefits of oral therapy on an outpatient basis include increased convenience and quality of life for patients and caregivers and reduced exposure to multidrug-resistant institutional pathogens.[1,2,4] Outpatient therapy of low-risk patients now is common practice in most institutions. Careful patient selection obviously is required for such management strategies. Important criteria include patient and provider comfort, a history of protocol and medication compliance, caregiver support and transportation available 24 hours per day, and close proximity (less than one hour or less than 30 miles) to appropriate medical care in the event of failure to respond to outpatient antibiotic therapy.[2] If a patient qualifies for oral therapy based on social and clinical status, the first dose of oral regimen should be given in the clinic or hospital and the patient observed for at least 4 hours to ensure tolerance and clinical stability.

Because of the excellent spectrum of activity and favorable pharmacokinetics of currently available oral antibiotics, particularly the fluoroquinolones, oral antibiotics have an important role in the management of selected patients. In patients at low risk for severe or complicated bacterial infection, empirical therapy with broad-spectrum oral antibiotic agents achieves similar patient outcomes as parenteral antibiotics, with response rates of 77% to 95%.[1,3,4,29] This has made possible the treatment of febrile neutropenia in low-risk patients in the outpatient setting. Patients judged to be low risk with reliable follow-up may be appropriate candidates for oral antibiotic therapy administered on an

outpatient basis.[1–4,29] Ciprofloxacin or levofloxacin in combination with amoxicillin–clavulanate (or clindamycin for penicillin-allergic patients) for enhanced gram-positive coverage has been most commonly studied for outpatient therapy in low-risk patients and is recommended by IDSA and NCCN guidelines.[1,2,4] In general, monotherapy with ciprofloxacin should be avoided due to relatively poor gram-positive activity. Levofloxacin has been used as monotherapy for outpatient treatment of low-risk patients, due to enhanced gram-positive activity, and is formally recommended by NCCN guidelines although the IDSA guidelines recommend only combination therapy initially. If used, only the higher-dose levofloxacin 750 mg regimen should be administered in order to provide adequate activity against organisms such as *S. aureus* and *P. aeruginosa*.[1,4] Moxifloxacin has also been endorsed as a monotherapy option by NCCN guidelines; however, the lack of *P. aeruginosa* activity warrants special consideration.[4]

In patients at low risk for severe bacterial infection who were initiated on IV antibiotics, oral antibiotics may play a role in step-down therapy. Carefully selected neutropenic patients may be safely switched from broad-spectrum parenteral therapy to oral antibiotic regimens with response rates comparable to patients remaining on IV therapy.[1,2,4,29] Patient selection criteria generally include defervescence within 72 hours of initiation of parenteral therapy, hemodynamic stability, absence of positive cultures or a discernible site of infection, and ability to take oral medications. Many of these patients are able to complete their course of therapy at home.[1,2,4,29] Changing parenteral antimicrobials to oral regimens in carefully selected patients is an acceptable practice and allows for less expensive hospitalizations and earlier patient discharges.[2]

Antimicrobial Therapy After Initiation of Empirical Therapy

6 After initiation of empirical antimicrobial therapy (**Table 140-5**), judicious assessment of febrile neutropenic cancer patients is mandatory to evaluate response, clinical status, laboratory data, and potential need for therapy adjustments. After 2 to 4 days of empirical antimicrobial therapy, the clinical status and culture results of febrile neutropenic patients should be reevaluated to determine whether therapeutic modifications are necessary (Fig. 140-2). Modifications of antimicrobial therapy should be based on clinical and

laboratory data; antibiotic therapy should be optimized based on culture results. However, during periods of neutropenia, patients generally should continue to receive broad-spectrum therapy because of risk of secondary infections or breakthrough bacteremias when antimicrobial coverage is too narrow.[1,4] The treatment duration for a documented infection should be appropriate for the particular organism and site, and should continue for at least the duration of neutropenia (until ANC greater than or equal to 500 cells/mm^3 [0.5×10^9/L]) or longer if clinically necessary.

TABLE 140-5 Drug Dosing Table

Drug	Brand Name	Usual Dosing Regiman	Special Population Dose	Other
Amoxicillin–clavulanate	Augmentin®	875 mg orally every 12 hours		In combination with ciprofloxacin for outpatient treatment
Ceftazidime	Fortaz®	2 g IV every 8 hours		
Ceftazidime-avibactam	Avycaz®	2.5 g IV every 8 hours, administered over 2 hours		Not studied in febrile neutropenia, but spectrum is appropriate if high rates of MDR gram-negative bacteria (esp. CRE)
Cefepime	Maxipime®	2 g IV every 12 hours		
Ceftaroline	Teflaro®	600 mg IV every 12 hours		Activity against methicillin-resistant *S. aureus*
Ceftolozane-tazobactam	Zerbaxa®	1.5 g IV every 8 hours		Not studied in febrile neutropenia, but spectrum is appropriate if high rates of MDR gram-negative bacteria
Piperacillin–tazobactam	Zosyn®	3.375-4.5 g IV every 6 hours		
Imipenem–cilastatin	Primaxin®	500 mg IV every 6 hours		
Meropenem	Merrem®	1 g IV every 8 hours		
Meropenem/vaborbactam	Vabomere®	4 g IV every 8 hours, administered over 3 hours		Not studied in febrile neutropenia, but spectrum is appropriate if high rates of MDR gram-negative bacteria (esp. CRE)
Doripenem	Doribax®	500 mg IV every 8 hours		
Tobramycin	Nebcin®	Traditional: 2 mg/kg loading dose, followed by 1.5 mg/kg IV every 8 hours. Alternative: 5-7 mg/kg IV once daily		Traditional dosing: Guided by measured serum concentrations
Gentamicin	Garamycin®	Traditional: 2 mg/kg loading dose, followed by 1.5 mg/kg IV every 8 hours. Alternative: 5-7 mg/kg IV once daily		Traditional dosing: Guided by measured serum concentrations
Amikacin	Amikin®	Traditional: 7.5 mg/kg IV every 12 hours. Alternative: 15-20 mg/kg IV once daily		Traditional dosing: Guided by measured serum concentrations
Ciprofloxacin	Cipro®	400 mg IV every 8 hours	Outpatient treatment: 750 mg orally every 12 hours	May be given orally in low-risk patients in combination with amoxicillin-clavulanate
Levofloxacin	Levaquin®	750 mg IV once daily	Outpatient treatment: 750 mg orally once daily	May be given orally in low-risk patients
Moxifloxacin	Avelox®	400 mg IV/orally once daily	Outpatient treatment: 400 mg orally once daily	For select outpatient use, lacks *P. aeruginosa* activity
Delafloxacin	Baxdela®	300 mg IV or 450 mg orally every 12 hours		Activity includes methicillin-resistant *S. aureus* and *P. aeruginosa*; not studied in febrile neutropenia, but spectrum is appropriate
Vancomycin	Vancocin®	30-40 mg/kg/day IV in two divided doses administered every 12 hours		For methicillin-resistant *S. aureus* infection; dosing guided by serum concentrations to achieve trough of 15-20 mg/L (10-14 µmol/L)
Nafcillin	Nafcil®	1-2 g IV every 6 hours		For methicillin-susceptible *S. aureus* infection
Daptomycin	Cubicin®	Skin/soft tissue infections: 4 mg/kg IV once daily; bacteremia: 6 mg/kg IV once daily		For infection (esp. bacteremia) due to methicillin-resistant *S. aureus*, vancomycin-resistant enterococci
Linezolid	Zyvox®	600 mg IV or orally every 12 hours		For infection due to vancomycin-resistant enterococci
Ampicillin	Omnipen®, Polycillin®, Principen®	1-2 g IV every 4 hours		In combination with gentamicin for *Listeria* infection
Erythromycin	E-mycin®, Erythrocin®	1-2 g IV every 4-6 hours		For *Legionella* infection
Clotrimazole	Mycelex Troche®	10 mg orally five times daily		Administered as oral troche; dissolve in mouth
Nystatin	Nystatin Oral®	100,000 units orally every 4-6 hours		Administered as suspension; swish and swallow
Fluconazole	Diflucan®	800 mg IV or orally once, then 400-800 mg IV or orally once daily	Prophylaxis of *Candida* infection: 400 mg IV or orally once daily	

Itraconazole	Sporanox®	200-400 mg/day orally divided twice daily	Prophylaxis of *Candida* infection: 200 mg orally twice daily	Therapeutic drug monitoring recommended
Voriconazole	Vfend®	6 mg/kg IV every 12 hours for two doses, then 4 mg/kg IV or 200 mg orally every 12 hours	Prophylaxis in high-risk patients: 200 mg orally twice daily	Therapeutic drug monitoring recommended
Posaconazole	Noxafil®	Suspension: 800 mg/day orally in two to four divided doses Oral DR or IV: 300 mg every 12 hours × 2 doses, then 300 mg daily	Prophylaxis in high-risk patients: 200 mg orally three times daily	DR formulation has improved bioavailability, administered with food. Suspension: administer with full meal or enteral nutritional supplements Therapeutic drug monitoring recommended
Isavuconazonium	Cresemba®	372 mg IV/oral every 8 hours × 6 doses, then 372 mg daily		Limited clinical experience
Lipid-associated amphotericin B (LAMB)	AmBisome®, Abelcet®	3-5 mg/kg IV once daily	Prophylaxis in high-risk patients: 1 mg/kg IV once daily	
5-Flucytosine	Ancobon®	25 mg/kg/day orally every 6 hours		In combination with LAMB for cryptococcal meningitis. Therapeutic drug monitoring recommended
Caspofungin	Cancidas®	70 mg IV once, then 50 mg IV once daily		
Micafungin	Mycamine®	100 mg IV once daily	Prophylaxis in high-risk patients: 50 mg IV once daily	
Anidulafungin	Eraxis®	200 mg IV once, then 100 mg IV once daily		
Acyclovir	Zovirax®	5-10 mg/kg IV every 8 hours, or 800 mg orally two to five times daily	Prophylaxis of HSV or VZV: 800-1,600 mg orally twice daily; CMV prophylaxis in allogeneic HSCT: 800 mg orally four times daily; HSV or VZV encephalitis: 10 mg/kg IV every 8 hours	
Valacyclovir	Valtrex®	1 g orally every 8 hours	Prophylaxis of HSV or VZV: 500 mg orally two or three times daily; CMV prophylaxis in allogeneic HSCT: 2 g orally four times daily	
Ganciclovir	Cytovene®	CMV treatment or preemptive therapy: 5 mg/kg IV every 12 hours	CMV prophylaxis: 5-6 mg/kg IV daily 5 days/wk	
Valganciclovir	Valcyte®	CMV preemptive therapy: 900 mg orally every 12 hours for 2 weeks	CMV prophylaxis: 450-900 mg orally daily	
Foscarnet	Foscavir®	CMV treatment: 90 mg/kg IV every 12 hours for 2 weeks; CMV preemptive therapy: 60 mg/kg IV every 12 hours for 2 weeks	CMV prophylaxis: 60 mg/kg IV two or three times daily for 7 days, then 90-120 mg/kg IV daily	
Letermovir	Prevymis®	480 mg IV or PO once daily		For prophylaxis of CMV infection and disease in CMV-seropositive allogeneic HSCT recipients, used through day 100 post-transplant
CMV hyperimmune globulin	Cytogam®	400 mg/kg IV every other day for three to five doses		Consider as adjunct to ganciclovir or foscarnet for treatment of CMV pneumonia; IVIG considered equally effective
Trimethoprim–sulfamethoxazole	Bactrim®, Cotrimoxazole®	Treatment of *P. jiroveci*: 15-20 mg/kg/day IV divided every 6 hours[b]	Prophylaxis of *P. jiroveci*: 160 mg/800 mg orally daily or three times per week	
Atovaquone	Mepron®	Treatment of *P. jiroveci*: 750 mg orally every 12 hours	Prophylaxis of *P. jiroveci*: 1,500 mg/day orally in one or two divided doses every 12 hours	
Pentamidine	Pentam®	Treatment of *P. jiroveci*: 4 mg/kg IV once daily	Prophylaxis of *P. jiroveci*: 300 mg by inhalation once monthly	

Clindamycin	Cleocin®	450-600 mg orally every 6 hours	In combination with primaquine for *P. jiroveci*, or with pyrimethamine for toxoplasmosis
Primaquine	Aralen®, Primaquine®	15 mg orally once daily	In combination with clindamycin for *P. jiroveci*
Dapsone	Dapsone®	100 mg orally once daily	In combination with trimethoprim for *P. jiroveci*
Trimethoprim	Triprim®	15-20 mg/kg/day orally divided every 6 hours	In combination with dapsone for *P. jiroveci*
Pyrimethamine	Daraprim®	50-100 mg orally once daily[c]	In combination with sulfadiazine for toxoplasmosis
Sulfadiazine	Sulfadiazine®	1 g orally every 4-6 hours	In combination with pyrimethamine for toxoplasmosis
Thiabendazole	Mintezol®	25 mg/kg orally every 12 hours (maximum 3 g/day)	For *Strongyloides* and other intestinal worm infections

In patients who become afebrile after 2 to 4 days of therapy with no infection identified, it is generally optimal to continue antibiotic therapy until neutropenia has resolved (ANC greater than or equal to 500 cells/mm^3 [0.5 × 10^9/L]). Some clinicians switch therapy to an oral regimen (eg, ciprofloxacin plus amoxicillin–clavulanate) after 2 days of IV therapy in low-risk patients who become afebrile and have no evidence of infection. In high-risk patients, parenteral antibiotic regimens should be continued until resolution of neutropenia.[1,4] However, in afebrile patients with prolonged neutropenia but no signs or symptoms of infection, consideration can be given to discontinuing antibiotic therapy or switching to fluoroquinolone prophylaxis (discussed in “Prophylaxis of Infections in Neutropenic Cancer Patients” below), provided that patients can be observed carefully and have ready access to medical care.

The optimal management of patients who remain febrile in the absence of microbiologic or clinical documentation of infection remains highly controversial. Persistently febrile patients should be evaluated carefully, but modifications generally are not made to initial antimicrobial regimens within the first 2 to 4 days of therapy unless there is evidence of clinical deterioration (see Fig. 140-1).[1,3,4] It is important to note that the persistence of fever does not necessarily mean failure of a given antimicrobial regimen; up to 25% of neutropenic patients have fever due to noninfectious causes.[7] This is particularly true if patients are otherwise clinically stable. Fever after two or more days of antibiotic therapy can be due to a number of causes, including nonbacterial infection, resistant bacterial infection or infection slow to respond to therapy,

emergence of a secondary infection, inadequate drug concentrations, drug fever, infection at an avascular site (eg, catheter infection or abscess), or noninfectious causes such as tumor or administration of blood products.[1,3,4] Patients with documented infection who are receiving appropriate antimicrobial therapy (based on in vitro susceptibility tests) often remain febrile until resolution of neutropenia occurs. Therefore, the same antibiotic regimen can be continued in patients who remain febrile despite 2 to 4 days of antibiotic therapy but are otherwise clinically stable, especially if neutropenia is expected to resolve within 1 week. However, antibiotic regimens may require modification in patients experiencing toxicities (**Table 140-6**) as well as in patients with evidence of progressive disease, clinical instability, or documentation of an organism not covered by the initial regimen.[1,3,4] If not already part of the regimen, vancomycin should be considered as warranted by clinical and laboratory findings. However, if vancomycin was included in the initial empirical regimen and the patient is still febrile after 2 to 3 days of therapy without isolating a gram-positive pathogen, discontinuation of vancomycin should be considered to reduce the risk of toxicities or resistance.[1,4]

TABLE 140-6 Drug Monitoring of Selected Antimicrobials for Febrile Neutropenia, HSCT, and SOT

Drug	Adverse Reaction	Monitoring Parameters	Comments
Antibacterial Agents			
Aminoglycosides (Tobramycin, Gentamicin, Amikacin)	Nephrotoxicity	Serum creatinine, urine output, serum concentrations	Extended-interval ("once daily") dosing potentially associated with less renal toxicity, similar efficacy to traditional dosing. Goal trough concentration <1 mcg/mL (mg/L; 2 µmol/L) during extended-interval dosing
Imipenem–cilastatin	CNS toxicities, seizures	Serum creatinine, mental status, CNS function	Increased incidence with higher dose, failure to adjust dose/interval for reduced renal function. Increased risk compared to meropenem or doripenem
Linezolid	Myelosuppression, thrombocytopenia, optic/peripheral neuropathy, serotonin syndrome	CBC, vision changes, serum lactate, heart rate, blood pressure, temperature, myoclonus	Myelosuppression and neuropathy more common with prolonged use. Short course unlikely to affect marrow recovery in HSCT. Weak MAO inhibitor, serotonin syndrome possible with other serotonergic drugs such as SSRIs and SNRIs
Nafcillin	Interstitial nephritis	Serum creatinine, urine output	Reversible, requires switch to alternative β-lactam
Vancomycin	Nephrotoxicity, infusion reactions	Serum creatinine, urine output, blood pressure, heart rate, serum concentrations	Dose adjustment required for renal dysfunction. Pretreatment and slow infusion may decrease incidence of infusion reaction. Goal trough concentration 15-20 mcg/mL (mg/L; 10-14 µmol/L) for serious infections
Antifungal Agents			
Amphotericin B (lipid-associated)	Nephrotoxicity, hepatotoxicity, electrolyte disturbances, infusion reactions	Serum creatinine, electrolytes, LFTs, blood pressure, heart rate	Liposomal preparations associated with less renal toxicity, similar efficacy to standard preparation. Electrolyte disturbances occur before creatinine alterations. Pretreatment and slow infusion may decrease incidence of infusion reaction
5-Flucytosine	Myelosuppression, GI toxicities	CBC, GI symptoms, serum creatinine, 5-flucytosine serum concentrations	Dose adjustment required for renal dysfunction. Goal serum concentrations are peak <100 mcg/mL (mg/L; 775 µmol/L) and trough 20-40 mcg/mL (mg/L; 155-310 µmol/L)
Posaconazole	Hepatotoxicity, rash; interactions with CYP450 3A4	LFTs, skin, posaconazole serum concentrations	Poor absorption with suspension, goals of >1 mcg/mL (mg/L; 1.4 µmol/L) for treatment and >0.7 mcg/mL (mg/L; 1 µmol/L) for prophylaxis. Parenteral formulation contains SBECD, not recommended for patients with CrCL<50 mL/min (0.83 mL/s). Multiple interactions with drugs metabolized by CYP 3A4, including immunosuppressants; close monitoring needed.
Voriconazole	Mental status changes, headache, hallucinations, visual disturbances, hepatotoxicity, QTc prolongation; interactions with CYP450 2C9, 2C19, and 3A4	Mental status, visual function, LFTs, ECG, voriconazole serum concentrations	Mental status/visual changes associated with elevated troughs >5.5 mcg/mL (mg/L; 16 µmol/L); goal trough 1-5.5 mcg/mL (mg/L; 3-16 µmol/L) for treatment and prophylaxis, target trough of >2 mcg/mL (mg/L; 6 µmol/L) in disease with poor prognosis. Parenteral formulation contains SBECD, not recommended for patients with CrCL<50 mL/min (0.83 mL/s). Multiple interactions with drugs metabolized by CYP enzymes, including immunosuppressants; close monitoring needed
Antiviral Agents			
Foscarnet	Nephrotoxicity, hypocalcemia	Serum creatinine, electrolytes	IV hydration prior to administration. Dose adjustment required for renal dysfunction
Ganciclovir, valganciclovir	Myelosuppression, thrombocytopenia	CBC, serum creatinine	Dose adjustment required for renal dysfunction
Antiprotozoal/Antiparasitic Agents			
Dapsone	Hemolytic anemia, hypersensitivity (fever, jaundice, eosinophilia), peripheral neuropathy	CBC, bilirubin, LFTs, muscle strength, G6PD testing before use	Higher incidence of hemolytic anemia in G6PD-deficient patients
Pentamidine (IV)	Nephrotoxicity, leukopenia, hypotension, QTc prolongation, pancreatitis, hypo/hyperglycemia	Serum creatinine, serum blood glucose, blood urea nitrogen, CBC, blood pressure, heart rate; ECG	Adequate hydration recommended
Primaquine	Hemolytic anemia	CBC, bilirubin, G6PD testing before use	Avoid use in G6PD-deficient patients (hemolytic anemia)
Pyrimethamine	Bone marrow suppression	CBC	Folinic acid 5-10 mg/day often used for prevention of bone marrow toxicity
Trimethoprim–sulfamethoxazole	Myelosuppression, hyperkalemia, rash	Serum creatinine, electrolytes, CBC, skin	Dose adjustment required for renal dysfunction

CBC, complete blood count; ECG, electrocardiogram; G6PD, glucose-6-phosphate dehydrogenase; HSCT; hematopoietic stem cell transplantation; LFT, liver function test; MAO, monoamine oxidase; PFT, pulmonary function test; QTc, corrected Q-T interval; SBECD, sulfobutylether-β-cyclodextrin; SOT, solid-organ transplantation; SSNRI, selective serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Therapeutic drug monitoring recommendations from Reference 34.

Initiation of Antifungal Therapy

Neutropenic patients who remain febrile despite more than 4 to 7 days of broad-spectrum antibiotic therapy are candidates for antifungal therapy. A high percentage of febrile patients who die during prolonged neutropenia have evidence of invasive fungal infection on autopsy, even though many had no evidence of fungal disease before death.[19] Persistence of fever or development of a new fever during broad-spectrum antibiotic therapy may indicate the presence of a fungal infection, most commonly due to *Candida* or *Aspergillus* spp.[15,19,22] Blood cultures are positive in fewer than 50% of neutropenic patients with invasive fungal infections.[21,22] Rapid, sensitive diagnostic tests for fungi such as serum β–D-glucan, galactomannan, or fungal DNA assays are available and may be considered in higher-risk patients, however, delaying initiation of antifungal therapy pending results of these tests or isolation of fungal organisms may be associated with high morbidity and mortality. The empirical addition of antifungal therapy is thus justified in this clinical setting.[1,4] Therefore, empirical antifungal therapy should be initiated after 4 to 7 days of broad-spectrum antibiotic therapy in persistently febrile patients if the duration of neutropenia is expected to be greater than 1 week. Administered doses must be adequate to treat undiagnosed fungal infection and prevent fungal superinfection in high-risk febrile neutropenic patients.[1,4,21]

Evidence-based recommendations from published guidelines for management of suspected or documented fungal infections in neutropenic patients are summarized in Table 140-2.[21,25,35] Empirical coverage for both *Candida* spp. and *Aspergillus* should be considered because these organisms are responsible for more than 90% of fungal infections in neutropenic cancer patients.[6,15,19,22] *Aspergillus* is also particularly common in patients with hematologic malignancies and in patients undergoing HSCT. In the setting of febrile neutropenia, lipid-associated amphotericin B (LAMB) products are almost exclusively recommended over conventional amphotericin B due to reduced toxicities despite significantly higher cost without clear improvement in efficacy.[1,4,20,21,25,35] Although the use of higher doses of LAMB has been advocated in an effort to improve efficacy, lower doses (3 mg/kg) of liposomal amphotericin B may be as efficacious as higher doses (10 mg/kg) with lower cost and fewer toxicities.[4] Although LAMB products are recommended for empiric therapy of neutropenic fever when antifungal agents are desired, they are not preferred agents in patients with presumed or documented invasive fungal

infections.[4,21]

The azole compounds are also used in the management of febrile neutropenia.[1,4,21,25,35] The azoles have replaced LAMB as preferred antifungals for many patients with FN due to the increased cost and toxicities of LAMB.[4] However, concerns regarding the emergence of *Candida* strains with decreased azole susceptibility and unclear efficacy advantages have prevented these agents from replacing amphotericin B as the clear gold standard in persistently febrile neutropenic patients.[20,25,35] Fluconazole has good efficacy against *C. albicans* but lacks activity against molds such as *Aspergillus*. The use of fluconazole as an alternative to amphotericin B for empirical antifungal therapy is thus perhaps most appropriate in hospitals in which infections due to *Aspergillus* or non-*albicans* strains of *Candida* are not common.[1,4,20,35] If fluconazole is used as antifungal prophylaxis in cancer patients, it should not be included in empirical antifungal regimens. Voriconazole is the preferred agent in the treatment of documented invasive fungal infections and is recommended as a reliable option for febrile neutropenia.[1,4,35] Despite failing to meet noninferiority criteria when compared against LAMB for empiric therapy in febrile neutropenic patients, voriconazole is a preferred agent for invasive aspergillosis (especially pulmonary) due to improved survival and less toxicity when compared to amphotericin B.[1,4,20,25,35–37] Isavuconazonium, the prodrug of isavuconazole, is approved for the treatment of invasive aspergillosis and mucormycosis with overall activity generally comparable to voriconazole and posaconazole. Isavuconazonium has shown reductions in mortality and overall treatment success similar to voriconazole in a largely neutropenic patient population with hematologic malignancies and suspected invasive fungal infections including a subgroup of proven or probable aspergillosis.[38,39] The most recent guidelines recommend isavuconazonium as an alternative to voriconazole in the treatment of invasive aspergillosis, although there are few data related to use as empiric therapy of febrile neutropenia.[4,21,35] Posaconazole has extended activity against some Mucorales and rare molds in addition to *Candida* and *Aspergillus*, but is only approved for prophylaxis of fungal infections in neutropenic patients. The improved bioavailability of the delayed-release tablets and availability of a parenteral dosage form make posaconazole an attractive option; although clinical data are relatively limited, the most recent guidelines also recommend posaconazole as an alternative to voriconazole for presumed or documented invasive disease.[21,35] Itraconazole has similar efficacy as amphotericin B, with fewer toxicities. However, current lack of a parenteral dosage form, sometimes erratic oral absorption, numerous potential drug–drug interactions, and

availability of many other antifungal options limit the use of itraconazole for empiric therapy.[21,35,36] Therapeutic drug monitoring has been recommended for some azole antifungals given potential for interpatient variability, therapeutic failure associated with subtherapeutic concentrations, and toxicities associated with supratherapeutic concentrations (Table 140-6).[4,21,35,40]

The echinocandin antifungals (caspofungin, micafungin, and anidulafungin) are attractive agents for treatment of febrile neutropenia because of their broad spectrum of antifungal activity and favorable adverse effect profiles. Caspofungin is as effective as, and also generally better tolerated than, liposomal amphotericin B for empirical treatment of neutropenic patients with persistent fever.[1,4] Therefore, caspofungin is considered an appropriate alternative to LAMB and voriconazole.[1,4,20,21,25] Micafungin and anidulafungin have not been as well studied specifically in this capacity; however, most experts consider them likely as effective.[1,4,21,25] Micafungin is specifically recommended for empiric antifungal therapy in febrile neutropenia in the most recent NCCN guidelines.[4]

Initiation of Antiviral Therapy

Febrile neutropenic patients with vesicular or ulcerative skin or mucosal lesions should be evaluated carefully for infection due to HSV or varicella-zoster virus (VZV). Mucosal lesions from viral infections provide a portal of entry for bacteria and fungi during periods of immunosuppression. If viral infection is presumed or documented, neutropenic patients should receive aggressive antiviral therapy to aid healing of primary lesions and prevent disseminated disease. Acyclovir traditionally has been used in this population. However, the newer antivirals valacyclovir and famciclovir have better oral absorption and more convenient dosing schedules. Routine use of antiviral agents in the management of patients without mucosal lesions or other evidence of viral infection generally is not recommended.[1,4] Treatment recommendations for viral infections are given in **Table 140-7**.

TABLE 140-7 Infectious Complications During Neutropenia, and After Hematopoietic Stem Cell and Solid-Organ Transplantation: Syndromes of Disease and Treatment Guidelines

Pathogen	Syndromes of Disease	Recommended Treatment
Bacterial		
Gram-negative aerobic bacilli (Enterobacteriaceae, *Pseudomonas aeruginosa*, *Haemophilus influenzae*)	Blood, urinary tract, pulmonary, abdomen	*Empiric:* Ceftazidime ± aminoglycoside,[1,2] cefepime ± aminoglycoside[1,2]; piperacillin–tazobactam; imipenem–cilastatin ± aminoglycoside[1,2] *Definitive:* According to culture and sensitivity results
Gram-positive cocci (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Enterococcus faecalis*)	Skin, blood, urinary tract, pulmonary, abdomen	*Empiric:* Nafcillin; vancomycin *Definitive:* According to culture and sensitivity results
Legionella spp.	Pulmonary	Erythromycin; azithromycin; ciprofloxacin; levofloxacin
Listeria monocytogenes	CNS	Ampicillin with gentamicin1; trimethoprim–sulfamethoxazole
Nocardia spp.	Skin, pulmonary, CNS	Sulfadiazine; trimethoprim–sulfamethoxazole
Fungal		
Candida spp.3	Blood, urinary tract, mucous membranes, skin, disseminated disease	Clotrimazole; nystatin; fluconazole; itraconazole; amphotericin B ± 5-flucytosine; lipid-associated amphotericin B (LAMB); caspofungin; micafungin; anidulafungin
Aspergillus spp.4	Skin, pulmonary, CNS	Voriconazole; LAMB; caspofungin; micafungin; posaconazole; itraconazole; isavuconazole
Cryptococcus neoformans	Skin, pulmonary, CNS	LAMB + 5-flucytosine; fluconazole
Mucorales (*Mucor*)	Rhinocerebral disease	LAMB; posaconazole
Viral		
Herpes simplex virus	Skin, CNS, mucous membranes, pulmonary	Acyclovir; foscarnet
Human herpesvirus-6	CNS, hepatic, bone marrow	Ganciclovir; foscarnet
Cytomegalovirus	Pulmonary, blood, urinary tract, GI tract	Ganciclovir; foscarnet; immunoglobulin
Varicella-zoster virus	Skin, disseminated disease	Acyclovir; foscarnet
Epstein–Barr virus	Lymphoproliferative disease	Rituximab
Papovaviruses (BK, JC)	Skin, CNS	No effective treatment
Protozoal/Parasitic		
Pneumocystis jiroveci	Pulmonary	Trimethoprim–sulfamethoxazole; atovaquone; pentamidine; dapsone + trimethoprim; clindamycin + primaquine
Toxoplasma gondii	CNS	Pyrimethamine + sulfadiazine; pyrimethamine + clindamycin
Strongyloides stercoralis	Pulmonary, CNS	Thiabendazole

[1]Choice of specific agent determined according to institutional susceptibilities to individual drugs.

[2]For penicillin-allergic adults, use aztreonam or ciprofloxacin + an aminoglycoside.

[3]Refer to the Clinical Practice Guidelines of the Infectious Diseases Society of America (*Reference 21*) for selection and dosing of antifungal agents for specific infections.

[4]Refer to the Clinical Practice Guidelines by the Infectious Diseases Society of America (*Reference 25*) for selection and dosing of antifungal agents for specific infections.

Duration of Antimicrobial Therapy

7 The optimal duration of antimicrobial therapy in the neutropenic cancer patient remains controversial. Decisions regarding discontinuation of empirical antimicrobial therapy often are more difficult and complex than those regarding initiation of therapy (see Fig. 140-1). One point on which experts agree, however, is that the most important determinant of the total duration of antibiotic therapy is the patient's ANC.[1,4] If ANC is greater than or equal to 500 cells/mm^3 (0.5×10^9/L) for two consecutive days, if the patient is afebrile and clinically stable for 48 hours or more, and if no pathogen has been isolated, then antibiotics can be discontinued. Some clinicians advocate that patients with ANC less than 500 cells/mm^3 (0.5×10^9/L) be maintained on antibiotic therapy until resolution of neutropenia, even if they are afebrile. However, prolonged antibiotic use has been associated with superinfections resulting from resistant bacteria and fungi and increases the risk of antibiotic-related toxicities.[1,4] If low-risk patients are clinically stable with negative cultures but the ANC still is less than 500 cells/mm^3 (0.5×10^9/L) antibiotics may be discontinued after a total of 5 to 7 afebrile days. However, patients with profound neutropenia (ANC greater than 100 cells/mm^3 [0.1×10^9/L]), mucosal lesions, or unstable vital signs or other risk factors should continue to receive antibiotics until ANC has increased greater than or equal to 500 cells/mm^3 (0.5×10^9/L) and the patient is stable clinically.[1,4]

Patients who are persistently neutropenic and febrile, but who are stable clinically with no active site of infection, often can be successfully discontinued from antimicrobials after at least 2 weeks of therapy. However, these patients must be monitored carefully because reinstitution of antibiotics may be necessary.[1,4] An alternative approach is to place these patients on antimicrobial prophylaxis (discussed in "Prophylaxis of Infections in Neutropenic Cancer Patients" below). Patients with documented infections should receive antimicrobial therapy until the infecting organism is eradicated and signs and symptoms of infection have resolved (at least 10-14 days of therapy).

Consensus guidelines provide useful information regarding the management of febrile episodes in cancer patients with neutropenia.[1,4] However, therapy (including initial empirical regimens, modifications, and duration of treatment) must be individualized based on specific patient parameters and response to therapy.

Colony-Stimulating Factors

Because resolution of neutropenia is arguably the most important determinant of patient outcome from both febrile episodes and documented infections, numerous studies have evaluated hematopoietic colony-stimulating factors (CSFs) (sargramostim [granulocyte-macrophage colony-stimulating factor] and filgrastim [granulocyte colony-stimulating factor]) as adjunct therapy to antimicrobial treatment of febrile neutropenic cancer patients. A meta-analysis found that use of CSFs is associated with reduced total duration and severity of chemotherapy-related neutropenia, reduced duration of antibiotic use, fewer hospitalizations, and decreased hospital length of stay.[41] However, this meta-analysis failed to demonstrate a benefit of CSFs in relation to important outcomes such as decreased overall mortality or infection-related mortality.[41] Evidence-based guidelines from the IDSA, American Society of Clinical Oncology (ASCO), and the NCCN recommend that CSFs should not be routinely initiated in patients with uncomplicated fever and neutropenia.[1,4,42,43] However, CSFs should be considered in patients who are at high risk for infection-associated complications, or who have factors that are predictive of poor clinical outcomes.[4,42,43] These factors are summarized in **Table 140-8**. Patients with prolonged neutropenia and documented severe infections who are not responding to appropriate antimicrobial therapy may also benefit from treatment with CSFs.[42,43] Clinical judgment must be exercised in determining which patients may benefit from judicious use of these expensive agents.

TABLE 140-8 Recommendations for Use of Colony-Stimulating Factors in the Management of Neutropenic Cancer Patients and Those Undergoing Hematopoietic Stem Cell Transplantation

A. **Primary prophylaxis of febrile neutropenia**
   1. Colony-stimulating factors (CSFs) (filgrastim, pegfilgrastim, or sargramostim) may be considered in patients who have a high risk of febrile neutropenia (>20% incidence) based on myelotoxicity of the planned chemotherapy regimen.
   2. When risk of febrile neutropenia is 10%-20%, CSFs may be considered in the presence of certain patient and clinical factors predisposing to increased complications from prolonged neutropenia, including: patient age >65 years; poor performance status; extensive prior treatment including large radiation ports; administration of combined chemoradiotherapy; cytopenias due to bone marrow involvement by tumor; poor nutritional status; presence of open wounds or active infections; previous surgery; poor renal function; liver dysfunction, particularly when evidenced by increased bilirubin; and lack of antibiotic prophylaxis.

B. **Secondary prophylaxis of febrile neutropenia**
   1. CSFs (filgrastim, pegfilgrastim, or sargramostim) recommended for patients who experienced neutropenic complications from prior cycles of chemotherapy, and in which a reduced dose may compromise disease-free or overall survival or treatment outcome.

C. **Therapeutic use in febrile neutropenia**
   1. CSFs should not be routinely used for patients with neutropenia who are afebrile.
   2. CSFs (filgrastim or sargramostim only) may be considered in patients with febrile neutropenia who are at high risk for infection-associated complications, or who have prognostic factors that are predictive of poor clinical outcomes, including: profound neutropenia (absolute neutrophil count <100 cells/mm^3 [0.1 × 10^9/L]); expected prolonged period of neutropenia (>10 days); patient age >65 years; uncontrolled primary disease; sepsis syndrome, or severe infection manifest by hypotension and multiorgan dysfunction; pneumonia; invasive fungal infection; other clinically documented infection; hospitalized at the time of the development of fever; or severe complications during previous episode of febrile neutropenia.

D. **Reduction in duration of neutropenia in HSCT**
   1. CSFs are recommended to mobilize peripheral-blood progenitor cells (PBPC) prior to chemotherapy and to reduce the duration of neutropenia after autologous PBPC transplantation.

Data from References 4, 42, and 43.

Direct transfusion of neutrophils has also been studied for treatment of febrile neutropenia or documented infections.[5,44] Routine use of neutrophil transfusions is not generally supported by data demonstrating improved clinical outcomes.

However, use may be considered in patients with profound prolonged neutropenia with severe documented infections and in whom causative organisms have not been eradicated with appropriate antimicrobial therapy in combination with CSFs.[4] At present, the use of neutrophil transfusions is not recommended for routine management of febrile neutropenic patients.[4]

Prophylaxis of Infections in Neutropenic Cancer Patients

8 Owing to the potential morbidity and mortality of infections in neutropenic cancer patients, environmental modifications and prophylactic antimicrobial regimens have been implemented to prevent these complications. The overall goal of antimicrobial prophylaxis in cancer patients is to decrease the number and severity of systemic infections during prolonged periods of neutropenia. As with febrile neutropenia, patient risk factors for development of infection and complications should be assessed prior to initiation of prophylaxis (**Table 140-9**).

TABLE 140-9 Risk-Based Prophylactic Strategies for Patients with Neutropenia

Risk Group	Patient Characteristics	Prophylactic Strategies
High risk	*Neutropenia:* Severe (absolute neutrophil count <100/mm^3 [0.1 × 10^9/L]) and/or prolonged (≥10 days) *Malignancy/treatment:* Hematologic malignancy (acute leukemia), allogeneic HSCT, GVHD with high-dose steroids (≥20 mg prednisone equivalents daily for ≥1 month), or use of alemtuzumab or purine-containing regimens	Consider bacterial prophylaxis with fluoroquinolone for duration of neutropenia. Give fungal prophylaxis with product and duration based on patient-specific factors. Give/consider viral prophylaxis with product and duration based on patient-specific factors. Consider protozoal prophylaxis with product and duration based on patient-specific factors.
Moderate risk	*Neutropenia:* Moderate duration (7-10 days) *Malignancy/treatment:* Autologous HSCT, multiple myeloma, lymphoma, chronic lymphocytic leukemia, purine analog therapy	Consider bacterial prophylaxis with fluoroquinolone for duration of neutropenia. Consider fungal prophylaxis with product and duration based on patient-specific factors. Give/consider viral prophylaxis with product and duration based on patient-specific factors. Consider protozoal prophylaxis with product and duration based on patient-specific factors.
Low risk	*Neutropenia:* Short duration (≤7 days) *Malignancy/treatment:* Solid tumor treated with conventional chemotherapy	Antibacterial and antifungal prophylaxis not indicated. Viral prophylaxis considered during neutropenia if patient has prior HSV episode

GVHD, graft versus host disease; HSCT, hematopoietic stem cell transplant; HSV, herpes simplex virus.

Data from References 1,4,6,29,39 and 45.

General Measures

Because approximately 50% of pathogens infecting neutropenic cancer patients are acquired in the hospital, reducing acquisition of infectious organisms from the environment is a basic component in controlling nosocomial infections.[1,4,6] Neutropenic patients should be placed in reverse isolation (isolation to protect patients from contracting infections after exposure to others) with standard barrier precautions, and strict adherence to infection prevention guidelines by hospital personnel.[1,4,6] Plants and fresh or dried flowers are usually prohibited as part of standard neutropenic precautions in order to minimize risk of exposure to pathogenic bacteria. Proper handwashing and respiratory hygiene by hospital personnel are simple yet effective infection prevention measures.[27] Most neutropenic patients do not require specific room ventilation; however, HSCT recipients should be placed in a private positive-pressure room with greater than 12 air exchanges per hour and HEPA filtration.[1,4,6]

Bacterial Infections

Combinations of oral nonabsorbable antibiotics, such as gentamicin, nystatin, vancomycin, polymyxin B, and colistin, have been widely studied as a means of reducing colonization of the GI tract with virulent pathogens. Although selective intestinal decontamination with oral nonabsorbable antibiotics successfully reduces infections, these regimens are not routinely recommended for prophylaxis because of problems that include unpalatability, cost, frequent adverse effects (eg, nausea, vomiting, and diarrhea), and development of resistance.[1–6]

Prophylaxis with orally administered, systemically available antibiotics such as trimethoprim–sulfamethoxazole and fluoroquinolones is effective at reducing gram-negative infections.[1,4] Although trimethoprim–sulfamethoxazole is effective as prophylaxis against *P. jiroveci*, its lack of activity against *P. aeruginosa* is worrisome when used as prophylaxis against bacterial infection, particularly in institutions where pseudomonal infections are frequent.[1] Other concerns with trimethoprim–sulfamethoxazole prophylaxis include selection of resistant organisms, predisposition to development of oral fungal infections, and delay in bone marrow recovery resulting in prolonged neutropenic episodes.[1,4,6]

Fluoroquinolones are more effective than placebo in preventing febrile episodes and gram-negative infections in neutropenic cancer patients and, in some studies, have decreased all-cause mortality and infection-related

mortality.[1,4,6,45] However, there are several potential limitations to their use. In particular, ciprofloxacin may lack adequate gram-positive activity and may not be the preferred fluoroquinolone for this reason. Although fluoroquinolone prophylaxis has been associated with colonization and infection with fluoroquinolone-resistant gram-negative organisms, these findings have not been consistent in various studies.[1,4,11,45] The risk of colonization or infection with strains resistant to the prophylactic agent is also lower with fluoroquinolones compared to trimethoprim–sulfamethoxazole.[45] However, patients experiencing breakthrough infection during fluoroquinolone prophylaxis should not be subsequently placed on a fluoroquinolone-containing empirical antibiotic regimen.[1,4] Although studies have not consistently documented increased fluoroquinolone resistance in association with prophylaxis, other potentially unfavorable outcomes such as increased risk of *Clostridioides difficile* infection should also be considered in weighing the potential benefits of fluoroquinolone prophylaxis.[1,4,11,45]

Although the benefits of prophylaxis with fluoroquinolones outweigh the potential risks in neutropenic patients with intermediate to high risk for infection (Table 140-9), antibacterial prophylaxis in general remains somewhat controversial due to continued concerns regarding the potential for development of resistant bacteria, high cost, and lack of consistent benefits related to patient survival.[1,4,11] Therefore, antibacterial prophylaxis is not recommended routinely for all neutropenic patients. Prophylaxis with ciprofloxacin or levofloxacin generally is indicated for intermediate- to high-risk patients expected to be profoundly neutropenic for more than 1 week as shown in Table 140-9.[1,4,6,27] Fluoroquinolone prophylaxis is not routinely recommended for patients with solid tumors.[27] High-dose levofloxacin may be preferred by some clinicians due to enhanced gram-positive activity. An oral cephalosporin (cefpodoxime) may be considered for patients intolerant of fluoroquinolones.[27] Neutrophil recovery eliminates the need for continued prophylaxis, and recovery may be facilitated by use of CSFs.[42] CSFs have also been formally recommended by ASCO and NCCN for primary prevention of FN in high-risk patients (see Table 140-8).[1,4]

Fungal Infections

Because neutropenic patients are at risk for mucocutaneous and invasive fungal infections that are difficult to diagnose and treat in this population, antifungal prophylaxis can be considered in intermediate- to high-risk patients at institutions where fungal infections in cancer patients occur frequently.[1,4] The

goal of antifungal prophylaxis is to prevent development of invasive fungal infections during periods of risk, thereby reducing morbidity and mortality. Similar to antibacterial prophylaxis, prophylaxis against fungal infection is specifically recommended for patients who are at risk for profound, protracted neutropenia (Table 140-9).[4,6,27]

Antifungal prophylaxis with an oral triazole agent (fluconazole, itraconazole, voriconazole, posaconazole, isavoconazole), parenteral echinocandin, or LAMB is recommended for prophylaxis in select patients starting at the time of induction chemotherapy.[4,27] Fluconazole prophylaxis has been particularly well studied and reduces the incidence of both superficial and systemic fungal infections; it also significantly decreases mortality from fungal infections in patients with leukemia and HSCT recipients.[4,39] However, use of fluconazole prophylaxis has contributed to the emergence of infections caused by *C. krusei* and *C. glabrata*, pathogens that frequently are resistant to fluconazole and other azole-type antifungal agents.[4,23] When compared to prophylaxis with mold-active agents, patients on fluconazole have higher rate of aspergillosis and invasive fungal-related mortality but lower rate of adverse events leading to discontinuation.[46] The choice of a specific agent should be determined by the types of fungal isolates at individual institutions and risk for invasive mold infection compared to invasive candidiasis.[1,4,21,27,46] After initiation, antifungal prophylaxis should be continued until resolution of neutropenia or the need for institution of antifungal therapy for suspected/documented infection.[4,21,27]

Other Infections

Use of trimethoprim–sulfamethoxazole prophylaxis in cancer patients at risk for *P. jiroveci* pneumonia has substantially reduced the incidence of this protozoal infection. Trimethoprim–sulfamethoxazole is therefore recommended for use in patients receiving higher-risk chemotherapeutic regimens (see Table 140-9).[1,4,27] Antiviral prophylaxis with acyclovir, valacyclovir, or famciclovir is recommended to reduce the risk of HSV reactivation in patients with acute leukemia undergoing intensive chemotherapy.[4,27] Prophylaxis with a nucleoside reverse transcriptase inhibitor such as entacavir or tenofovir is recommended for patients at high risk of HBV reactivation.[4,27] Finally, patients should be assessed for indications for administration of vaccines such pneumococcal, influenza, varicella, and varicella zoster in order to provide protection from vaccine-preventable infections that commonly occur in patients with neutropenia and immunosuppression.[47] Many vaccines will be most effective when administered

to patients prior to beginning immunosuppressive chemotherapy regimens, while inactivated influenza vaccine may also be administered to already immunocompromised patients.[47]

When considering use of antimicrobial (antibacterial, antifungal, antiprotozoal, and antiviral) prophylaxis in neutropenic patients with cancer, the risks and benefits of prophylaxis must be weighed against issues with development of resistance, toxicities, and other concerns.

Evaluation of Therapeutic Outcomes

10 Close monitoring of febrile neutropenic patients, including both clinical and laboratory parameters, is essential for early detection and treatment of infectious complications. Three general therapeutic outcomes have been defined in the setting of febrile neutropenia: (a) success (survival during the febrile episode until resolution of neutropenia by judicious selection of empirical antimicrobial therapy), (b) success with modification (same as [a] but with additions/modifications to empirical therapy), and (c) failure (death during febrile neutropenia).[1] Because many of the drugs that can be used in this setting (eg, aminoglycosides and amphotericin B) have significant toxicity potential, careful attention must be paid to prevention and management of drug-related adverse effects. Evaluations of the parameters given in the Clinical Presentation are appropriate to help monitor and guide therapy. In addition, the NCCN guidelines for febrile neutropenia provide comprehensive recommendations on clinical/laboratory monitoring parameters, including schedules.[4] The reader is referred to individual chapters within this book for more detailed discussions of monitoring parameters related to specific types of infections (eg, pneumonia and urinary tract infections).

INFECTIONS IN PATIENTS UNDERGOING HSCT

1 Infection remains a major barrier to successful HSCT.[48–50] Recipients of HSCT are at enhanced risk for infection because of prolonged periods of neutropenia. In addition, patients receiving allogeneic transplants (related, matched unrelated, or cord blood) receive prolonged immunosuppressive drug therapy for prevention and treatment of graft-versus-host disease (GVHD) following engraftment. Allogeneic HSCT recipients are generally slower to engraft when compared to autologous HSCT recipients.[4] Intensive pretransplant conditioning regimens (high-dose chemotherapy and total-body irradiation), as

well as GVHD itself, often disrupt protective barriers, such as mucous membranes, skin, and the GI tract, placing patients at further risk of infection.[4,48,49] Although infectious complications are still associated with considerable morbidity and mortality, studies have documented significant reduction in mortality after HSCT in association with reductions in disease caused by bacterial, fungal, and viral infections.[4] As the number of HSCTs performed increases and patients live longer, the population of HSCT patients is expected to continue to grow exponentially.[51]

Etiology and Clinical Presentation of Infections

2 10 The timing with which specific types of infections typically occur following HSCT is shown in **Fig. 140-3**, but the relative incidence and importance of specific pathogens vary greatly according to the specific type of HSCT performed. Patients receiving allogeneic transplants are at greatest risk for infection after HSCT and are predisposed to earlier and more severe infections with opportunistic pathogens such as *Aspergillus*. The presence of GVHD also has an impact on the incidence and timing of various infections, including invasive fungal infections.

After administration of intensive conditioning regimens to eliminate malignant cells and prevent rejection of donor cells, patients may remain profoundly neutropenic for 3 to 4 weeks. During this pre-engraftment period, patients are at risk for the same types of infectious complications that occur in other granulocytopenic cancer patients (eg, bacterial and fungal infections) and should be managed accordingly (see Table 140-1).[4] Table 140-7 lists regimens for treatment of specific infections.

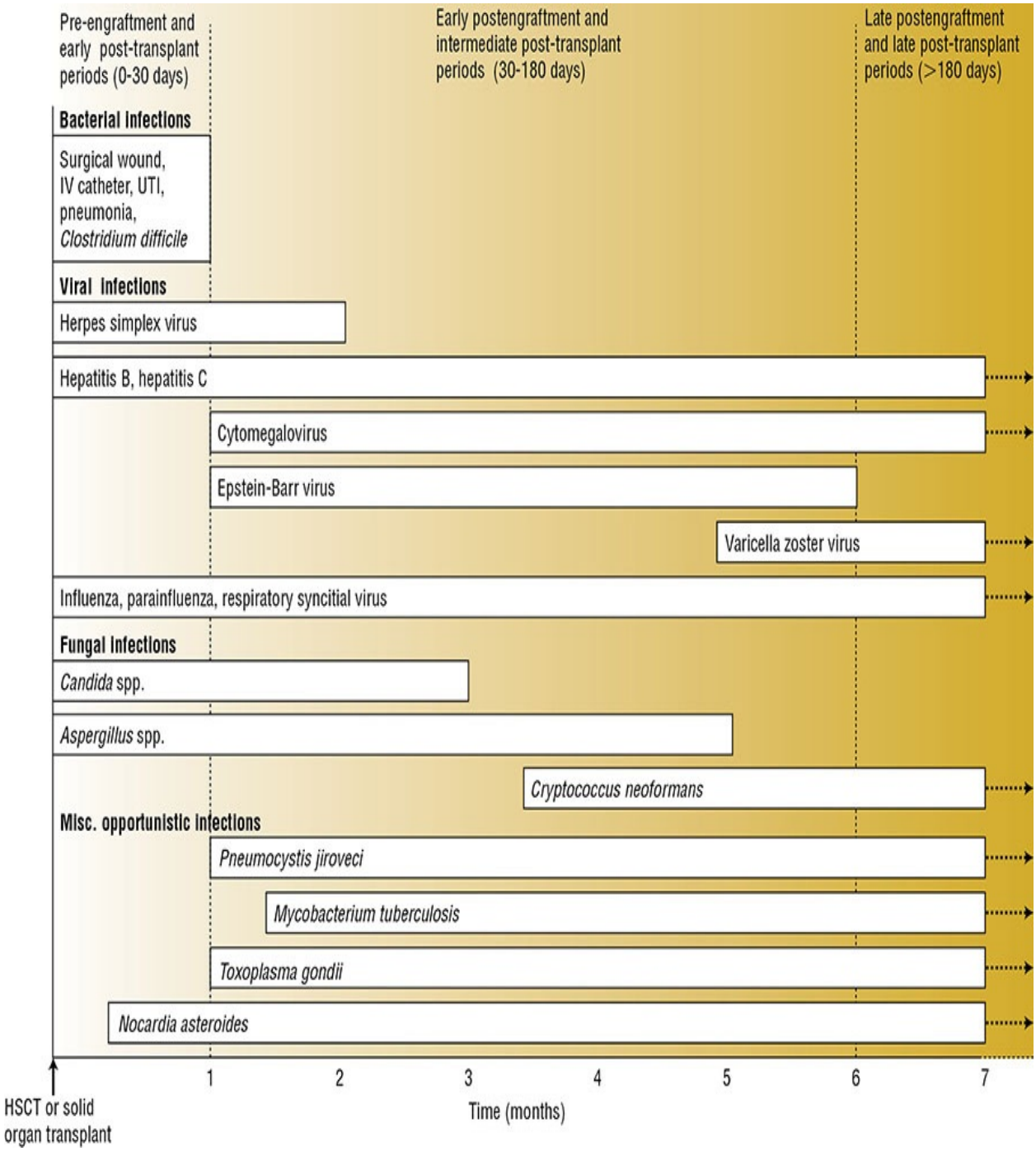


FIGURE 140-3 Timetable for the occurrence of infections in hematopoietic stem cell transplantation (HSCT) and solid-organ transplant patients. (UTI, urinary tract infection.).

HSCT recipients remain at high risk for infection after bone marrow engraftment has occurred.[4] Significant defects in neutrophil function and cell-mediated and humoral immunity, persisting for several months after

transplantation, predispose patients to infectious complications. Furthermore, specific medications, regimens and therapies utilized are associated with added risk or a prolong risk of various infections (alemtuzumab, anti-CD20 antibodies, fludarabine, steroids, asplenia, etc.).[4] Acute and chronic GVHD following allogeneic HSCT also results in prolonged periods of immunosuppression.[4,48,49] Those who experience acute GVHD had a 60% higher infection rate and higher risk of developing serious or fatal infections compared to allogeneic HSCT patients without acute GVHD.[49] Even in the absence of active GVHD, 10% to 20% of all deaths were attributable to infection after year two in allogeneic HSCT patients.[51]

HSCT recipients are at significant risk for serious bacterial infections at various sites.[4,50] Bacteremia is particularly concerning following allogeneic HSCT as those with GVHD have a three-fold increased risk.[48] Bacteremia has been reported in up to half of HSCT patients with gram-positive and gram-negative bacteremia occurring at similar rates.[48,50,52] However gram-negative bacteremia remains of significant clinical importance given mortality rates may reach 45% for increasingly common multidrug resistant strains.[53] *Clostridioides difficile* has become a common and important cause of gastrointestinal infections.[4,50]

Fungal infections, especially those caused by *Candida* and *Aspergillus* spp., are serious and often result in fatal complications. Fungi remain a serious cause of infection, particularly in allogeneic HSCT recipients, for up to 1 to 2 years following transplantation and may occur in as many as 20% of patients.[4,52,54] Significant mortality is associated with invasive aspergillosis (up to 60%) and mucormycosis infections.[4] HSCT recipients are also at risk for serious viral infections, particularly HSV and cytomegalovirus (CMV). HSV infections may include gingivostomatitis, esophagitis, genital lesions, and, rarely, pneumonia during the first month after transplant.[4,55] Clinical disease is more common in patients with serologic evidence of prior exposure and latent HSV infection pretransplant. Therefore, reactivation of latent disease during periods of immunosuppression is the most common etiology of HSV infection. Without prophylaxis, as many as 80% of HSV-seropositive patients experience mucocutaneous disease after intensive chemotherapy compared with less than 25% of seronegative patients.[4,55] HSV infections often coexist with *Candida* infection and mucositis secondary to chemotherapy, radiation, or both.[4,55] Painful swallowing associated with these conditions often makes it difficult for patients to take oral medications and maintain adequate nutritional intake.

Because of the considerable morbidity associated with HSV reactivation after transplantation, the HSV serologic status of patients should be determined prior to transplant.

HSCT recipients are at high risk for CMV infections during the early postengraftment period. Infections range in severity from asymptomatic infection with viral shedding (urine, throat, and lungs), to life-threatening disseminated disease and interstitial pneumonia.[4,55] As with HSV, patients seropositive for CMV before transplantation are at high risk for reactivation of infection during periods of immunosuppression; up to 60% of seropositive patients develop reactivation after transplantation compared with only 3% of seronegative patients.[4,55] Other risk factors for CMV infection in HSCT patients include advanced age, human lymphocyte antigen mismatch, total-body irradiation, multiagent conditioning regimens, and presence of GVHD.[4,55] Patients without evidence of latent CMV infection (CMV-seronegative) before transplantation may develop primary CMV infection after receiving bone marrow or blood products from CMV-seropositive donors. Although the typical onset of both primary and recurrent CMV infection is 1 to 2 months after transplantation, late-onset infections may occur more than 100 days after transplantation.[4,55,56] Patients receiving allogeneic transplants are at highest risk for CMV reactivation, with progression to clinical disease in approximately 10% to 30% of patients.[4,55] The most serious clinical manifestation of CMV disease is interstitial pneumonia, which is associated with a >50% mortality rate even when treated.[55] Interstitial pneumonia also may result from other infectious (*P. jiroveci*, VZV) and noninfectious causes (pulmonary damage by radiation and chemotherapy).[4,55] This clinical syndrome manifests as fever, dyspnea, hypoxia, nonproductive cough, and diffuse pulmonary infiltrates. As many as 40% of allogeneic HSCT patients will develop some form of interstitial pneumonia; a leading cause of infectious death in HSCT recipients and a significant proportion are viral in etiology.[55]

During the late postengraftment period (beginning approximately 180 days after transplantation), infections remain a major problem in patients suffering from chronic GVHD. Infections common during the late postengraftment period include those caused by encapsulated bacteria, such as *S. pneumoniae* and *H. influenza*, fungi, and viruses, including CMV and VZV.[4,54] Patients not undergoing allogeneic transplantation or suffering from chronic GVHD generally have few infections in this period.

Up to 60% of allogeneic patients with a history of VZV who survive up to 10 months after transplantation will develop VZV disease.[4,54,55] Infection with

VZV is most common in allogeneic HSCT recipients with acute or chronic GVHD.[54,55] Both primary (varicella) or recurrent disease (herpes zoster) usually present as skin lesions, most of which remain contained to local areas; however, 30% of these infections may disseminate to other cutaneous areas or body organs, causing severe morbidity or mortality.[4,55,57]

TREATMENT

Desired Outcomes

The goals of therapy in managing HSCT recipients from the neutropenic period through the late postengraftment period are: (a) protect the patient from early death caused by undiagnosed infection; (b) employ effective prophylactic therapy to prevent common bacterial, fungal, viral, and protozoal/parasitic infections; (c) effectively and aggressively treat established infections; (d) avoid unnecessary use of antimicrobials that contribute to increased resistance; and (e) minimize toxicities and cost while increasing patient quality of life.

Prophylaxis and Management of Infections in Recipients of HSCT

8 9 The overall goal of prophylaxis and treatment of infection in HSCT patients is prevention of infectious morbidity and mortality. Specific goals of antimicrobial use in HSCT patients include (a) prevention of bacterial, fungal, viral, and protozoal infections during pre-engraftment and postengraftment periods and (b) effective treatment of established infections. These goals must be achieved at the lowest possible toxicity and cost. Prophylactic therapy should be aimed specifically at pathogens known to cause a high incidence of infection within the HSCT population, the specific institution, or both. In addition, prophylactic therapy should be limited to regimens proved to be effective through well-designed clinical trials.

Appropriate immunizations should be a primary consideration in the prevention of infections in HSCT recipients. Immunizations against common bacterial and viral pathogens are timed to avoid periods of severe immunosuppression following HSCT when the protective response to vaccination potentially would be decreased.[4,58] Recommended vaccines for

immunization of HSCT patients include three doses each of diphtheria–pertussis–tetanus (or diphtheria–tetanus), inactivated polio, conjugated *H. influenzae* type b, and conjugated 13-valent pneumococcal; two doses each of hepatitis A and HBV; and one dose of meningococcal conjugate vaccine 6 to 12 months post-transplant. One dose of the 23-valent pneumococcal vaccine should follow after 12 months. The influenza vaccine should be resumed at least 4 to 6 months after transplantation, and continued annually for life. Family members, close contacts, and healthcare providers of HSCT patients also should be vaccinated annually against influenza. The injectable inactivated influenza vaccine is preferred both before and after HSCT due to severe underlying illnesses pretransplant and contraindication of the live-attenuated intranasal product post-transplant.[4,54,58] Finally, the live-attenuated measles–mumps–rubella vaccine should be administered no sooner than 24 months after HSCT if the patient is considered to be immunocompetent.[54,58]

The live-attenuated varicella vaccine may be considered on a case by case basis owing to the risk of VZV infection, but if administered should be given no sooner than 24 months after transplant.[4,54,58] Historically, the live attenuated zoster vaccine (Zostavax®) could be considered no earlier than 24 months after transplant, if given at all. However, this recommendation will likely be phased out as two inactivated zoster vaccines have shown promise in trials in autologous HSCT patients. Shingrix® (recombinant zoster vaccine) is currently FDA approved for immunocompetent adults and is effective at preventing herpes zoster, post-herpetic neuralgia, herpes zoster related complications and related hospitalizations.[59] Similarly, vaccine V212 was efficacious in lowering rates of herpes zoster disease, preventing moderate-to-severe zoster pain, post-herpetic neuralgia, and herpes zoster related complications.[60] V212 is not currently FDA approved as of late 2018. Although not yet fully adopted by clinical guidelines, one or both of these inactivated zoster vaccines will likely replace the live attenuated zoster vaccine in HSCT. However, efficacy specifically in allogeneic HSCT has not yet been demonstrated for either vaccine and updated vaccination guidelines should be consulted for these at-risk patients.

Bacterial Infections

Prophylaxis of infections in HSCT patients is similar in many ways to that used in other neutropenic patients. Oral antibacterial prophylaxis is used commonly; considerations are the same as those discussed in the “Prophylaxis of Infections in Neutropenic Cancer Patients” section. Although rates of bacteremia and other

bacterial infections after HSCT are decreased with prophylaxis, overall mortality rates have not been consistently reduced.[2,4,54,61] Therefore, routine use of prophylactic antibiotics in HSCT is somewhat controversial but should be considered in patients at moderate-to-high risk of infection (Table 140-9). Fluoroquinolones are the most frequently used agents, with levofloxacin preferred over ciprofloxacin due to enhanced gram-positive activity.[4] For those intolerant to a fluoroquinolone, cefpodoxime or trimethoprim–sulfamethoxazole may be considered.[2,4] These regimens usually are started either within 72 hours of beginning the chemotherapy conditioning regimens or on the day of hematopoietic stem cell infusion and continued throughout the neutropenic period. Patients who become febrile while receiving prophylaxis should be managed according to general guidelines for febrile neutropenic patients.

Antibiotic prophylaxis against bacterial infection is also recommended in the late postengraftment period (greater than 100 days after transplantation) in certain high-risk patients, specifically allogeneic HSCT recipients with chronic GVHD.[4] Antibiotics should be targeted against encapsulated bacteria, particularly *S. pneumonia*, and should be selected based on local susceptibility patterns for these organisms; penicillin is preferred in areas with low rates of penicillin-resistant pneumococci.[4] Patients receiving trimethoprim–sulfamethoxazole for prophylaxis of other opportunistic infections may be adequately protected and do not necessarily require an additional antibiotic, though the addition of penicillin may be considered.[4] Prophylaxis should be continued as long as the chronic GVHD is being actively treated.

Viral Infections

Prophylaxis of recurrent HSV infection is recommended for all HSV-seropositive patients undergoing HSCT.[2,4,55] Approximately 0% to 10% of HSV-seropositive patients receiving acyclovir experienced viral shedding, clinical symptoms of viral reactivation, or both compared with 60% to 80% of patients receiving placebo.[4,55] Many patients eventually require IV acyclovir because of the development of severe mucositis from conditioning regimens. However, oral acyclovir, valacyclovir, or famciclovir is effective and considerably less expensive in patients who can take oral medications. Valacyclovir has replaced acyclovir as first-line therapy in many institutions. The antiviral agent usually is started at the time of the conditioning regimen and continued until bone marrow engraftment or resolution of mucositis (approximately 30 days after HSCT), although longer durations of prophylaxis should be considered in allogeneic

HSCT recipients with GVHD or frequent HSV reactivations before transplantation.[2,4,55] In addition to preventing recurrence of HSV disease, acyclovir prophylaxis may reduce the incidence of CMV reactivation.[4,54] Patients receiving ganciclovir or foscarnet for prophylaxis or treatment of CMV infection do not need additional antiviral therapy for prevention of HSV or VZV.[4,55] Patients developing active HSV or VZV infection should be treated with high-dose acyclovir.[4,55,56]

Oral acyclovir or valacyclovir given for up to 12 months after transplantation also significantly reduces reactivation of VZV infections and prevents the occurrence of severe VZV disease.[2,4] Patients receiving either allogeneic or autologous HSCT may therefore be considered for long-term (up to 1 year after transplantation) prophylaxis against VZV.[2,4] Immunocompromised, nonimmune patients exposed to chickenpox or shingles should receive varicella-zoster immunoglobulin 625 units intramuscularly within 10 days (ideally as soon as possible) after close contact with persons with chickenpox or shingles for prevention of VZV-related disease.[62]

Acyclovir-resistant HSV has been reported occasionally in HSCT patients receiving acyclovir prophylaxis. Foscarnet is a drug of choice for treatment of documented infection with acyclovir-resistant HSV and should be reserved for this use.[4,55]

Prevention of CMV disease is a well-accepted indication for prophylaxis in HSCT patients because of the high associated infectious morbidity and mortality. If possible, CMV-seronegative patients should receive donor cells and supportive blood products from seronegative donors only; however, CMV-seropositive patients are not at significant additional risk by receiving blood or donor cells from seropositive donors.[56] Although acyclovir has relatively poor in vitro activity against CMV, a decrease in CMV infection and an improvement in overall survival were reported in HSV- and CMV-seropositive allogeneic HSCT recipients receiving IV acyclovir.[4,55]

Ganciclovir has been well studied for prophylaxis because of its superior activity against CMV compared with acyclovir.[4,54] Oral valganciclovir has also been studied in the setting of HSCT.[4,54] Valganciclovir has excellent pharmacokinetics, produces serum levels of ganciclovir that are at least similar to those achieved after IV administration, and is routinely used in many centers due to the convenience of oral dosing in certain patients.[4,55] Although administration of prophylactic valganciclovir to CMV-seropositive patients may significantly decrease the occurrence of CMV viremia, there is no clear survival

benefit compared to a preemptive approach (ie, initiating ganciclovir or valganciclovir only after detecting a specific threshold of CMV copies from blood or bronchoalveolar fluid), and ganciclovir-related bone marrow suppression is frequently problematic.[63] Therefore, a preemptive approach is generally preferred over a ganciclovir prophylaxis strategy.[4,54,55] Preemptive therapy with ganciclovir and valganciclovir remains a current standard of therapy.[4,54,55] Detection of CMV is typically done by quantitative polymerase chain reaction (PCR)-based tests. Preemptive therapy significantly reduces the occurrence of CMV disease (including CMV pneumonia) and improves survival significantly up to 180 days after transplantation.[4] Because CMV viremia and PCR-positive bronchoalveolar lavage are highly predictive of subsequent CMV disease, preemptive ganciclovir or valganciclovir therapy should be considered for autologous HSCT recipients within the first 100 days after transplantation or in allogeneic HSCT recipients at any time after transplantation.[4] The doses of ganciclovir or valganciclovir for preemptive therapy are the same as those used for prophylaxis. Foscarnet can also be used for either prophylaxis or preemptive therapy of CMV disease in patients intolerant of ganciclovir or in the setting of ganciclovir resistant CMV.

CMV prophylaxis remains of clinical interest, however, and may be considered for specific allogeneic HSCT recipients for the first 100 days after transplantation.[54] Letermovir is a highly active inhibitor of CMV replication approved for prophylaxis of CMV infection and disease in CMV-seropositive recipients undergoing allogeneic HSCT. In a study of allogeneic HSCT recipients assigned to letermovir or placebo, letermovir (taken until a median of 82 days posttransplant) showed a substantial reduction in significant CMV infections at week 24. Interestingly, rates of CMV infection increased at week 18 in the letermovir group when most patients were no longer receiving prophylaxis, indicating a prolonged risk for CMV following the withdrawal of active prophylaxis. Both CMV disease and viremia requiring preemptive treatment were most commonly treated with either ganciclovir or valganciclovir. Unlike ganciclovir, letermovir is not associated with bone marrow suppression and therefore may become an agent of choice for CMV prophylaxis in high risk HSCT patients.[56] Although FDA approved, letermovir is not addressed by current clinical practice guidelines.

Prophylaxis of CMV disease with either IV immunoglobulin (IVIG) or CMV hyperimmune globulin (CMVIG) has demonstrated variable and inconclusive benefits, and their use is not currently recommended.[4]

Ganciclovir or valganciclovir are the drugs of choice for treatment of active

CMV infection in HSCT patients (see Table 140-6). Foscarnet also may be used for treatment or prevention of infections in HSCT patients as an alternative to ganciclovir/valganciclovir because of its relative lack of bone marrow toxicity or in cases of resistant CMV. Foscarnet-related nephrotoxicity is often problematic, however, especially in the post-transplant period when patients may be receiving other nephrotoxic agents. Cidofovir has not been well studied in HSCT patients and is also associated with nephrotoxicity, but this agent may also be considered for preemptive therapy or treatment of active disease as a third-line option.[4]

Numerous combination treatments such as interferon plus ganciclovir have been used unsuccessfully for treatment for CMV pneumonitis. However, the combination of high-dose IVIG and ganciclovir may decrease the mortality of the syndrome from 85% to 30% to 50%.[4,64] Ganciclovir plus CMVIG also is considered effective for treatment of CMV disease, although this regimen has not been studied as extensively in the HSCT population in a controlled fashion. However, CMVIG was not more effective than IVIG, therefore ganciclovir plus IVIG is considered as the treatment regimen of choice for severe or life-threatening CMV disease based on benefit-versus-risk considerations rather than definitive clinical data.[4,55,64] The potential for ganciclovir-associated bone marrow suppression prior to marrow engraftment and in patients who are just recovering from granulocytopenia remains a concern, especially in patients with unstable renal function. CSFs are beneficial in this setting (Table 140-7), providing benefits similar to those noted in neutropenic patients with acquired immunodeficiency syndrome receiving ganciclovir therapy for CMV retinitis.[4]

Fungal Infections

Prophylaxis with antifungal agents is efficacious and generally recommended for prevention of mucocutaneous and disseminated fungal infections in high-risk HSCT patients (Tables 140-2 and 140-9).[2,4] Patients specifically recommended for prophylaxis with fluconazole or micafungin include all allogeneic recipients and autologous transplant recipients with extensive mucositis.[2,4] Fluconazole remains the most commonly used agent; it is started on the day of transplantation and continued until resolution of neutropenia or, in allogeneic HSCT, for at least 75 days after transplantation.[4] The variable activity of fluconazole against non-*albicans* species of *Candida* may be problematic in this population, as is lack of activity against *Aspergillus*.[4] Prophylaxis with fluconazole effectively reduced colonization, infection, and infection-related mortality due to *Candida* spp. in some HSCT populations, but has not consistently reduced overall mortality or

invasive infections such as aspergillosis in all types of HSCT recipients.[4] Micafungin was more efficacious than fluconazole in the prevention of early-onset *Candida* infections in HSCT patients with neutropenia prior to engraftment, and also showed a trend to fewer episodes of invasive aspergillosis.[4] Posaconazole was also more effective than fluconazole in the late prevention of invasive *Aspergillus* and other fungal infections in HSCT patients with GVHD receiving additional immunosuppressive therapy.[4] In a meta-analysis, prophylaxis with agents active against *Aspergillus* were associated with a 33% reduction in mortality related to invasive fungal infections compared to fluconazole.[46] Fluconazole and micafungin are both supported by a high level of evidence for fungal prophylaxis and either are appropriate following HSCT with local fungal ecology, risk factors and cost being appropriate determinants for specific populations.[4] Most experts consider caspofungin and anidulafungin reasonable alternatives to micafungin. Voriconazole, posaconazole, LAMB products, and to a lesser extent itraconazole may be used for prophylaxis of fungal infections in HSCT patients but do not carry the same strength of recommendation due to less favorable side-effect profiles or lack of positive comparative studies.[4] Posaconazole is the preferred agent in high-risk HSCT patients with severe GVHD due to the risk of invasive mold infections (Table 140-2).[2,4] When the risk of invasive aspergillosis infection is >6%, prophylaxis with a mold-active triazole such as posaconazole (voriconazole or isavuconazonium as alternatives) is appropriate.[2] Isavuconazonium has not been well studied for prophylaxis in HSCT patients and, although recommended as an option in some clinical guidelines, it has not been recommended in others.[2,4]

Therapeutic drug monitoring for azole antifungals remains important (Table 140-6). Furthermore, use of azole antifungals as prophylaxis introduces the potential for pharmacokinetic (CYP450 inhibition) and pharmacodynamic (eg, QTc prolongation with most azoles and fluoroquinolones) drug–drug interactions that vary in duration and severity. Drug half-lives, potential therapeutic benefit (eg, infection-free mortality), potential harm, and future oncologic plans must be assessed when initiating, continuing, adjusting or discontinuing a potentially interacting medication. An alternative prophylaxis regimen (echinocandin) may be preferred to an azole when the risk of a drug interaction is too great (eg, proteasome inhibitors, tyrosine kinase inhibitors, or vinca alkoliods). Consideration should be given to the mechanism of drug interaction and drug half-life before initiating therapy.[4]

Protozoal Infections

Pulmonary infection with *P. jiroveci* is a relatively infrequent complication of HSCT that is associated with high rates of mortality, especially in patients with GVHD.[4,50,54] Therefore, prophylaxis is recommended for a period of 3 to 6 months after autologous HSCT, and for at least 6 months and while receiving immunosuppressive therapy after allogeneic HSCT. Exposure to specific immunosuppressing medications (eg, >20 mg of prednisone daily for >4 weeks) also warrants prophylaxis. Prophylaxis with trimethoprim–sulfamethoxazole significantly reduces the incidence of *P. jiroveci* as well as *P. jiroveci*-related mortality so effectively that desensitization should be considered for intolerant reactions before switching to an alternative (eg, dapsone, atovaquone, or pentamidine).[4,54] Trimethoprim–sulfamethoxazole should also prevent *Toxoplasma gondii*, a rare but often fatal infection.[4,54]

Use of Colony-Stimulating Factors

Filgrastim, pegfilgrastim, and sargramostim have been studied in HSCT patients in an effort to speed bone marrow recovery, reduce the period of neutropenia, and decrease infectious complications. CSFs appear effective as well as safe following autologous HSCT and should be utilized. Although increased rates of GVHD and mortality with use of CSFs following allogeneic HSCT have been reported by retrospective studies, a meta-analysis found no increased risk and CSFs may be given to allogeneic HSCT patients to reduce the duration of severe neutorpenia.[42] The use of CSFs is now routinely recommended to mobilize blood progenitor cells and reduce the period of neutropenia in autologous transplants (Table 140-7).[42]

Evaluation of Therapeutic Outcomes

10 Close monitoring of HSCT patients, including clinical and laboratory data, is essential for early detection and treatment of infectious complications. In addition, because many of the drugs commonly used in this setting (eg, ganciclovir, amphotericin B, and trimethoprim–sulfamethoxazole) have significant toxicity potential in HSCT patients, careful attention must be paid to prevention and management of drug-related adverse effects as well as drug–drug interactions. Monitoring parameters related to specific types of infections (eg, pneumonia and urinary tract infections) should be applied as appropriate. The reader is referred to other chapters within this book for more specific

information.

INFECTIONS IN SOLID-ORGAN TRANSPLANT RECIPIENTS

Solid-organ transplantation (SOT) has become an established mode of treatment for end-stage diseases of the heart, lungs, kidney, liver, pancreas, and small bowel. Patient and allograft survival rates have greatly improved due to improvements in immunosuppressive drug therapy, candidate selection, and transplant surgery techniques as well as more experience in the management of complications (including infection) in these patients. Despite advances in diagnostic techniques and antimicrobial therapy, infectious complications remain important causes of morbidity and mortality after SOT.

Risk Factors

Many risk factors for infection are present in SOT patients (see Table 140-1). The most important risk factor in this population is immunosuppressive drug therapy for prevention and treatment of allograft rejection. Risk of infection depends on specific immunosuppressive drug regimens as well as the intensity (numbers and doses/exposure of drugs) and duration of immunosuppression. Most opportunistic infections in transplant patients occur during the first 6 months after transplantation, when the intensity and total cumulative exposures to immunosuppressive therapy are very high.[65,66]

Immunosuppressive drugs, often in escalated doses, are used to treat episodes of graft rejection and include immunoglobulins directed against T cells (eg, antithymocyte globulin), antibodies against interleukin 2 receptors (basiliximab), T-cell–depleting antibodies (alemtuzumab), B-lymphocyte depleting antibodies (rituximab), and high-dose corticosteroids. Rejection episodes often occur during the period 2 to 4 months post-transplant when the overall cumulative dose or net state of immunosuppression is high. Therefore, patients already at risk for infection are placed at even higher risk if additional immunosuppressive therapy is needed to treat one or more episodes of graft rejection.[65,67] Immunosuppressive drug therapy must be evaluated carefully when infections occur because, in many cases, immunosuppression may have to be reduced or altered to allow patients to survive the infectious episode, at the expense of increased risk of graft rejection. Risk of increased infectious complications from immunosuppressive therapy used to treat rejection episodes is determined, at

least in part, by the specific therapy used.[65,68]

The organ, organ donor status, surgical technique, recipient status and underlying illness of the recipients are also critical determinants of infection risk and possible etiologies. These considerations are extremely important within the first 3 months following SOT and may provide heightened suspicion leading to specific prophylaxis, preemptive strategies, and earlier appropriate and targeted treatment of infectious complications.[67–69]

Etiology

2 As with cancer patients, microorganisms infecting SOT patients are present before transplantation or are acquired from exogenous sources. Although opportunistic viral, fungal, and protozoal infections may occur commonly, bacterial infections remain the most frequent infectious complications after transplantation in all allograft recipients.[65,70,71] Liver, small bowel and lung transplant recipients are at high risk for serious gram-negative bacterial infections as a result of the technically difficult surgical procedures and precolonization.[70,72] All transplant recipients are at risk for mucocutaneous candidiasis from species colonizing body sites. Invasive fungal infection is less common following kidney and pancreas transplantation but may occur in up to 30% to 60% of heart, lung, liver, and small bowel transplant recipients. Rates are highest following lung, liver, and small bowel transplantation and are associated with mortality rates up to 60% to 80%.[73,74] *Candida* spp. is the most common of all systemic fungal infections in transplant recipients.[74–76] Abdominal surgery, especially the more complex procedures required for liver and small bowel transplantation, predispose patients to serious fungal disease, most likely as a consequence of entering an area of the body already colonized with *Candida* spp.[74] Lung and heart transplant recipients are particularly at risk for invasive aspergillosis; these infections may occur in up to 7% to 35% of patients and in lung transplant recipients may be more common than infections caused by *Candida* spp.[73,77]

Organisms present as latent tissue infections may reactivate and cause clinical disease with administration of immunosuppressive drug therapy. Disease resulting from infection reactivation has been noted with viruses (HSV, human herpesvirus-6, CMV, VZV, Epstein–Barr virus [EBV]), protozoa (*T. gondii*, *P. jiroveci*), and mycobacteria (*Mycobacterium tuberculosis*).[65–68,71] Serologic or immunologic tests are performed prior to transplantation to assess the risk for reactivation infection and identify other subclinical infections (eg, HBV,

hepatitis C virus [HCV], *Legionella*). Many patients with reactivated infection have no clinical symptoms; often the only evidence of active infection is a rise in antibody titer from the pretransplant baseline, positive culture, increasing viral replication, or histologic evidence. Reactivation of latent infection may result in severe life-threatening disease in immunosuppressed hosts.[65–67]

Exogenous sources of infection in transplant patients include environmental contamination and transmission of microorganisms via transplanted organs and blood products. Environmental sources of infection are similar to those noted in other immunocompromised hosts, such as cancer patients. Airborne pathogens, especially fungi such as *Aspergillus* and *Cryptococcus neoformans*, may cause infections in transplant patients; environmental exposure is an established risk factor for invasive mold infections among lung transplant patients.[73] Travel to areas of geographically endemic mycoses (eg, *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*) or animal exposures may broaden infectious risk.[65] SOT patients are at high risk for nosocomial infections (MRSA, *P. aeruginosa*, *Acinetobacter*). Optimal prevention and management of nosocomial infections in transplant patients require knowledge of the current epidemiology of infections and susceptibility patterns within an institution.[65,66,70,71]

Infections transmitted via donor organs or blood products are major causes of morbidity and mortality in transplant patients and may include HSV, *T. gondii*, HBV, and HCV. The most important infections transmitted from the donor, however, are caused by CMV.[78–80] These infections may cause serious disease, and predispose patients to other opportunistic infections, and contribute to acute and chronic allograft dysfunction or rejection, post-transplant lymphoproliferative disorders (particularly associated with EBV), and cardiac complications and atherosclerosis in heart transplant recipients.[78–80] In contrast to reactivation disease, transplant patients contracting primary CMV disease are at increased risk for serious life-threatening infections.[65,67,78–80] The most important source of primary CMV infection in transplant patients is the donor organ. Efforts are made to avoid transplanting organs from CMV-seropositive donors into CMV-seronegative recipients because of the potentially severe consequences. With the relative scarcity of suitable organs and the rapidity with which transplant decisions often must be made, however, this is not always possible. The consequences of transplanting an organ from a CMV-seropositive donor into an already CMV-seropositive recipient are less clear. CMV reinfection (as well as reactivation) syndromes may occur in these patients and antilymphocyte immunosuppression may increase the risk of

complications.[65,69,78] Alternatively, mammalian target of rapamycin (mTOR) inhibitors as part of a chronic immunosuppressive regimen may decrease the risk of CMV infection and related disease.[78] CMV serostatus, net immunosuppression and organ type (among others factors) inform the practitioner of risk to determine an appropriate preventative strategy.[65,69,78] Furthermore, primary CMV disease may be transmitted from seropositive blood products. The availability of leukoreduced and CMV-seronegative blood products has decreased the risk of transmission but has not eliminated it.

Organs from donors seropositive for *T. gondii* or HSV generally are not withheld from seronegative patients as effective prophylaxis is common. Organs from known HIV-infected donors may now be used for transplantation in HIV-infected recipients (the HIV Organ Policy Equity Act).[81] Center-specific and HIV-specific criteria often apply, but in general those stable on anti-retroviral therapy with well controlled disease may be considered for SOT (as well as HSCT) without prohibitively high risk for acceleration of HIV disease. The impact of protease inhibitors and highly active antiretroviral therapy on long-term outcome of HIV-infected patients following transplantation is believed to have improved the overall feasibility of transplanting these individuals.[82] Similarly, with highly effective therapies now available, organs from HCV-infected donors may be used for transplantation in HCV-infected recipients (and in some cases HCV-negative recipients).[83]

Timing of Infections After Transplantation

As with HSCT, the overall time course for infections can be divided into three general periods after transplantation (see Fig. 140-3).[65,66] Although risk of infection with specific pathogens varies with the type of transplant, the time course of infections is similar in all transplant recipients. During the early post-transplant period (within the first month after transplantation), patients are at risk for infections already present and brought forward from the pretransplant period (eg, HBV, HCV, HIV); postoperative infections, such as surgical wound and catheter infections; infection resulting from colonized donor organs (pneumonia following lung transplant); and reactivation of HSV.[65,66,78] In the intermediate post-transplant period (1-6 months after transplant), risk is highest for viral infections, including CMV, EBV, HBV, and HCV. The combination of these "immunomodulating" viruses plus sustained immunosuppressive therapy leads to a high risk for opportunistic infections with pathogens such as *P. jiroveci*, *Aspergillus*, and *Nocardia asteroides*.[65–68] In the late post-transplant period

(greater than 6 months after transplant), patients are at risk for persistent infections (particularly viral) from earlier post-transplant periods, reactivation of VZV and *C. neoformans*, and routine infections affecting the general population.[65,66,68] In addition, patients who required additional immunosuppression therapy for acute or chronic rejection are at continued high risk for opportunistic infections (*Aspergillus* and *P. jiroveci*).[65,66] Although Fig. 140-3 illustrates infection patterns common to all solid-organ transplants, the relative incidence and importance of a particular pathogen vary according to the type of transplant and prophylaxis measures.

Types of Infections and Clinical Presentation

10 Transplant patients are at risk for infections occurring at a variety of sites, including skin, surgical wound, urinary tract, lungs, blood, abdomen, and CNS. However, most infections occur at or near the site of the transplanted organ. For example, heart transplant and heart-lung transplant recipients most often are infected within the lungs or thoracic cavity. Urinary tract infections remain an important cause of morbidity in renal transplant patients, especially in the early post-transplant period. Administration of prophylactic antibiotics (eg, trimethoprim–sulfamethoxazole) to these patients has reduced the incidence and severity of urinary tract infections.[4,80] Serious bacterial and fungal infections originating from the abdomen and GI tract are most common after liver transplantation and are related to variables such as length of surgery and surgical procedures performed. Risk of bacteremia, usually originating from the gut, is high in liver transplant patients. Renal transplant recipients are at the lowest risk for infections and infectious deaths, whereas patients receiving heart, lung, and liver transplants are at the highest risk for infection-related morbidity and mortality.[71,84]

In contrast to febrile neutropenic patients, the threshold for initiating empirical antimicrobial therapy is higher in febrile transplant patients. Appropriate therapy for the large numbers of pathogens that may cause infections in transplant patients varies greatly from organism to organism (Table 140-6). Therefore, careful attempts at definitive diagnosis of suspected infections must be made. If comprehensive workup reveals no source of infection, careful observation of the febrile transplant patient (rather than empirical therapy) is common practice. Surveillance cultures and specifically weekly quantitative amplification nucleic acid testing of CMV may be useful during the first 3 to 4 months for detecting CMV infections if the patient is not

receiving prophylaxis.[65,78,80] Management and monitoring of documented infections are similar to that in other types of patients.

TREATMENT

Desired Outcomes

The goals of therapy in managing SOT recipients are similar to those in HSCT and include: (a) protect the patient from early death caused by undiagnosed infection, from the surgical procedure through the late postengraftment period; (b) prevent common bacterial, fungal, viral, and protozoal/parasitic infections; (c) effectively and aggressively treat established infections; (d) avoid unnecessary use of antimicrobials; and (e) minimize toxicities and cost while increasing patient quality of life and avoiding harm to the engrafted organ(s).

Prevention of Infection in Solid-Organ Transplantation

8 The goals of antimicrobial drug use in solid-organ transplant recipients are (a) prevention of infectious complications in the immediate postoperative period, (b) prevention of late infectious complications associated with prolonged periods of immunosuppression, and (c) effective treatment of established infections in order to prevent graft dysfunction and rejection and decrease patient morbidity and mortality. All of these goals must be achieved at the lowest possible toxicity and cost.

Prevention of infection in the transplant patient can be accomplished in a number of ways. First, risk of environmental contamination should be minimized.[65] Patients should be protected from institutional infectious outbreaks. Efforts should be made to vaccinate organ transplant candidates prior to transplantation whenever possible for vaccine preventable disease based on age and anticipated risk factors post-transplant. Live vaccines should be given more than 4 weeks in advance from the time of anticipated transplantation.[58] Transplant recipients should receive influenza vaccination annually, pneumococcal (PCV13 and/or PPSV23 separated by 8 weeks), hepatitis A and B vaccination series (if indicated, ideally started pretransplant), HPV series (if indicated) and Tdap generally 2 months or greater following transplantation;

however, their immunologic responses to these vaccines may be suboptimal due to immunosuppressive therapy.[58] Timing of reinstitution of regular vaccinations in relation to transplantation is not absolute, but live attenuated vaccines (varicella, zoster, MMR) should be avoided early post transplantation, if not altogether, similar to recommendations for HSCT.[58] An exception is made for varicella seronegative pediatric liver and kidney transplant recipients who are on low-levels of immunosuppression without recent graft rejection.[58] As with HSCT patients, inactivated zoster vaccines are anticipated to become preferred over the live zoster vaccine in all SOT patients; however, clinical evidence in this population is currently lacking.

Because the most important source of primary CMV infection is an infected donor organ, CMV serostatus should be evaluated in all recipients and donors. Two standard strategies to manage CMV in SOT patients have been recommended. Preemptive therapy is effective for some populations (eg, kidney transplant) but requires weekly monitoring, close follow-up and appropriate risk stratification of patients for CMV related complications. Prophylaxis is effective and easy to administer without the need for careful discrimination of suitable patients; but, universal prophylaxis results in unnecessary exposure (toxicities) and cost to low-risk patients (CMV serostatus donor negative, recipient negative).[78] The best approach to preventing CMV disease remains controversial and does require risk stratification as either preemptive or prophylaxis can be appropriate depending on patient specific factors (including immunosuppressive strategy). Most experts agree that CMV prophylaxis is not required in donor negative, recipient negative SOT patients. These patients may qualify for antiviral prophylaxis targeted against other herpes infections (eg, acyclovir) or preemptive therapy.[65,70]

CLINICAL PRESENTATION

Infections in Solid-Organ Transplant Patients

General

- Because transplant patients are at high risk for serious infections, frequent (at least daily), careful clinical assessments must be performed to search for evidence of infection
- Clinical presentation of infection is variable and depends on the type

and site of infection, type of transplant, time after transplantation, immune status of the host, and dose and duration of immunosuppressive therapy

- Primary viral disease usually is more symptomatic and severe than disease caused by reactivation
- Physical assessment should include examination of all common sites of infection, including mouth/pharynx, nose and sinuses, respiratory tract, GI tract, urinary tract, skin, soft tissues, perineum, and intravascular catheter insertion sites

Symptoms

- Usual signs and symptoms of infection may be absent or altered in patients receiving intensive immunosuppressive regimens owing to an inability to mount a typical inflammatory response (eg, no infiltrate on chest x-ray film, urinary tract infection without pyuria)
- Pain may be present at infection site(s)

Signs

- Fever is the single most important clinical sign indicating the presence of infection, though it may not be present in all infected patients. Other causes of fever unrelated to infection in this patient population include reactions to blood products, drugs, embolic events, and ischemic injury
- Usual signs of infection may be absent or altered
- Signs of allograft dysfunction may be related to infection. Distinguishing fever caused by allograft rejection from that caused by infection often is difficult and frequently requires allograft biopsy

Laboratory Tests

- Blood cultures (at least two sets, including vascular access devices) for bacteria and fungi; cultures of other suspected or potential infection sites (urine, lungs, surgical wounds, and soft tissue infections)
- Other cultures should be obtained as clinically indicated according to the presence of signs or symptoms
- Complete blood count and chemistries should be obtained frequently to

monitor allograft function, plan supportive care, guide drug dosing, and assess patient's overall status

- Surveillance testing for CMV and HSV may be useful during first 3 months after transplantation for early detection of infection

Other Diagnostic Tests

- Chest x-ray film
- Aspiration, biopsy of skin lesions
- Other diagnostic tests as indicated clinically on the basis of physical examination and other assessments

CMV prophylaxis is often recommended in high risk patients (ie, seronegative patients receiving seropositive organs). Oral valganciclovir and IV ganciclovir prophylaxis are effective for reducing the incidence of both primary and reactivated CMV infection in SOT.[78] Prophylaxis is recommended as a preferred strategy in many CMV seropositive SOT patients partly due to a lack of well-designed studies comparing prophylaxis to preemptive therapy in all SOT types.[78] Additional risk factors for CMV disease, the associated clinical impact of "indirect effects" of CMV, and logistical barriers should be considered on an individual basis when designing a strategy. For example, valganciclovir prophylaxis has been recommended for all CMV positive lung transplant recipients in part due to very high risk of CMV disease and associated severe consequences of direct and indirect effects on the graft.[65] The duration of CMV prophylaxis is typically 3 to 12 months depending on donor and recipient CMV serology status, immunosuppressive regimen, and type of organ transplanted.[65,78] Because CMV replication following prophylaxis occurs in up to one-third of donor-positive/recipient-negative SOT patients, surveillance after prophylaxis may be considered and is based on additional risk stratification.[65,78] Ganciclovir or valganciclovir prophylaxis also may significantly reduce reactivation of CMV infection in seropositive patients receiving antithymocyte globulin for treatment of acute rejection.[78]

Prophylactic high-dose oral acyclovir or valacyclovir effectively reduces the incidence of CMV infection and disease following renal transplantation. However, acyclovir is less active against CMV and may be less efficacious in some high-risk renal or other nonrenal transplant patients; therefore,

valganciclovir is generally preferred if prophylaxis is required.[65,78] Acyclovir prophylaxis may be recommended for targeting other herpes viruses when the risk of CMV is low and should not be used to treat active CMV replication.[85]

Preemptive IV ganciclovir or valganciclovir is an effective strategy in many SOT patients, but requires appropriate monitoring and a reliance on patient compliance. Additionally, no established thresholds have been clearly defined as a "cut-point" for initiation of preemptive valganciclovir when monitoring quantitative CMV copies (eg, absolute value, viral load kinetics, or viral doubling time).[78] Neither preemptive nor prophylaxis strategies are perfect for each situation. Therefore it is imperative that each SOT center develop a method based on patient risk, logistics, cost and continually assess patient risk with cumulative net immunosuppression in mind when prescribing a CMV preventative strategy.[78] Since ganciclovir-related bone marrow suppression is not as problematic in SOT recipients as in HSCT patients and valganciclovir is relatively well tolerated, many centers in the United States opt for a prophylactic strategy extending either duration or preemptive monitoring when additional risk factors (eg, intensified immunosuppression) are encountered.

The additional benefit of CMVIG compared to standard CMV prophylaxis in high risk heart, lung and small bowel transplant recipients is controversial. Cohort-level evidence suggests some possible benefit and therefore some experts will add monthly infusions in special circumstances; however, the optimal role of CMVIG has yet to be established.[65,78]

The use of mTOR inhibitors (sirolimus, everolimus) as part of an immunosuppressive regimen in SOT recipients may be useful in prevention of CMV disease. mTOR inhibitors exert a marked anti-CMV effect through reduction in viral replication and/or potent immunomodulating properties.[86] In a meta-analysis, patients receiving immunosuppressant regimens containing mTOR inhibitors (with or without a calcineurin inhibitor [CNI]) displayed a nearly threefold reduction in CMV infections compared to patients receiving CNI alone.[86] Although mTOR inhibitors are associated with significantly lower CMV infection rates in most SOT recipients, CMV disease and related complication is only one of many factors that must be considered when designing an immunosuppressive regimen.[78]

Although use of prophylactic acyclovir in HSV-seropositive patients undergoing HSCT is well accepted, prophylaxis in SOT recipients remains controversial. Reactivation disease caused by HSV occurs in approximately 25% of HSV-seropositive patients who are not receiving prophylaxis.[85] Mucocutaneous disease is the most common presentation, but

nonmucocutantious HSV disease also is seen occasionally and is associated with significant morbidity and high mortality (eg, HSV pneumonitis).[85] Acyclovir is therefore used at some centers because of the high incidence of clinical HSV infection after transplantation. Acyclovir prophylaxis of HSV infection may be considered in patients following a preemptive strategy for management of CMV infection, but would not be necessary in patients receiving ganciclovir or valganciclovir for CMV prophylaxis.[65,85]

Prophylactic antimicrobial agents are also of benefit to SOT patients in certain other clinical situations. Antibiotic prophylaxis, with agents such as cefazolin started perioperatively and continued for less than 24 hours, is considered to reduce wound infection rates effectively following renal transplantation.[72,84] Although the benefits of perioperative prophylaxis have not been well studied in other types of transplantation procedures, surgical prophylaxis usually is considered mandatory for pancreas, liver, heart, lung, or small bowel transplant patients because of the high risk of perioperative bacterial infections.[72,84] High rates of infection have been reported following liver and intestinal transplant often resulting from intra-abdominal pathogens (eg, gram-negative bacteria, *Enterococcus*, *Candida*, anaerobes, etc.) depending on patient, donor, and surgical risk factors. Broader surgical prophylaxis such as a third-generation cephalosporin plus ampicillin, ampicillin/sulbactam, or piperacillin/tazobactam have been recommended for liver transplant. An even broader approach with the addition of vancomycin and fluconazole has been suggested for intestinal transplant given the high risk of multidrug resistant and polymicrobial infection.[72] Pulmonary infections are particularly common in lung and heart-lung transplant recipients. They often are caused by bacteria colonizing the airways of the diseased organs prior to transplantation. Therefore, perioperative antibiotics for lung and heart-lung procedures often are selected based on pretransplant sputum cultures and/or known colonizations of the patient (including assist devices [eg, ventricular assist device or extracorporeal membrane oxygenation circuit]).[72]

Post-transplant antibiotic prophylaxis is effective in decreasing the number of bacterial infections in renal transplant patients. Prophylactic trimethoprim–sulfamethoxazole traditionally has been used because it is inexpensive and well tolerated; other antibiotics, such as the fluoroquinolones, also have been evaluated.[65] Administration of oral low-dose trimethoprim–sulfamethoxazole (one double-strength tablet, either daily or 3 times/week) for 6 to 12 months for prevention of *P. jiroveci* infection following heart and lung transplantation is common, although the efficacy and optimal duration are somewhat

controversial.[65] Selective bowel decontamination with nonabsorbable antibiotics in combination with a low-bacterial diet (no fresh fruits and vegetables) may reduce oropharyngeal and GI colonization with gram-negative aerobes and *Candida* in liver transplant patients; however, conclusive evidence of benefit is lacking and this practice is not recommended routinely.[72,84] Similarly, prebiotics and probiotics cannot be currently recommended.[72]

Because immunosuppressed transplant recipients are at risk for mucocutaneous fungal infections, prophylactic oral or topical antifungal agents may be indicated in these patients. Liver, pancreas, and small bowel transplant recipients are clearly at high risk for invasive fungal infections and should receive prophylaxis with fluconazole though the optimal duration remains unclear.[72,76] Antifungal prophylaxis has also been suggested for lung and heart-lung transplant recipients due to the high incidence of invasive fungal infections in these patients (up to 35% of patients, with mortality rates up to 60%).[77] Prophylaxis targeting *Aspergillus* spp. with inhaled amphotericin B or LAMB, or systemic regimens active against *Candida* and *Aspergillus* spp. such as itraconazole, voriconazole, posaconazole, and echinocandins have all been reported; however, data from well-designed trials supporting either the general recommendation for prophylaxis or choice of specific agent are largely lacking and center-to-center variability is great.[68,73,75,77,85] Oral voriconazole or inhaled LAMB for a period of 3 to 6 months post-transplant are most often recommended for prophylaxis of invasive fungal infection in lung and heart-lung transplant recipients.[73,77] However, prophylaxis out to a year or longer is not uncommon with oral triazole agents.[73,77] Concentrations of immunosuppressant drugs should be monitored closely in transplant patients receiving azole-type antifungal agents (fluconazole, itraconazole, and voriconazole).

Transplant patients, especially heart and heart-lung recipients, without serologic evidence of prior exposure to *T. gondii* who receive organs from seropositive donors are at high risk for toxoplasmosis.[65] Many of these patients will be receiving trimethoprim–sulfamethoxazole for prophylaxis of *P. jiroveci* infection; this agent will also provide effective prophylaxis against *T. gondii* as well as *N. asteroides*. Although prophylaxis specifically for *T. gondii* is not given routinely at all centers, this therapy for a period of up to 12 months may be justified in high-risk patients because of the delays in diagnosis and serious infections associated with toxoplasmosis.[65,82,87]

Postclass Engaged Learning Activity

Conduct a literature search and identify an article (either primary literature or review article) that has been published in the past 12 months regarding multidrug-resistant bacterial pathogens causing infections in immunocompromised patients. Write a brief summary regarding how increased antibiotic resistance may impact the initial therapy of suspected bacterial infections in immunocompromised patients and how these trends may potentially impact future recommendations from organizations such as the Infectious Diseases Society of American (IDSA) or the National Comprehensive Cancer Network (NCCN). Your summary should also include perspectives regarding the potential impact of antibiotic resistance on the use of monotherapy with newer agents (eg, ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam) compared to combination regimens including these or older antibiotics. This activity is intended to build your literature evaluation skills, ability to critically appraise current trends in clinical practice, and ability to evaluate the impact of newer medications on published clinical practice guidelines.

ABBREVIATIONS

ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
CDI	*Clostridioides difficile* infection
CISNE	Clinical Index of Stable Febrile Neutropenia
CMV	cytomegalovirus
CMVIG	cytomegalovirus hyperimmune globulin
CNT	calcineurin inhibitor
CRE	carbapenem-resistant Enterobacteriaceae
CSF	colony-stimulating factor
EBV	Epstein-Barr virus
GVHD	graft-versus-host disease
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplantation
HSV	herpes simplex virus
IDSA	Infectious Diseases Society of America
IVIG	intravenous immunoglobulin
LAMB	lipid-associated amphotericin B
MASCC	Multinational Association for Supportive Care in Cancer
MDR	multidrug resistant
MRSA	methicillin-resistant *Staphylococcus aureus*
NCCN	National Comprehensive Cancer Network
PCR	polymerase chain reaction
PCT	procalcitonin
PMN	polymorphonuclear leukocyte
SOT	solid-organ transplantation
VRE	vancomycin-resistant enterococci
VZV	varicella-zoster virus
WBC	white blood cell

REFERENCES

1. Freifeld AG, Bow EJ, Sepiowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious disease society of America. *Clin Infect Dis*. 2011;52(4):e56–e93.
2. Taplitz RA, Kennedy EB. Bow EJ, et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America clinical practice guideline update. *J Clin Oncol*. 2018;36:1443–1453.

3. Lyman GH, Abella E, Pettengell R. Risk factors for febrile neutropenia among patients with cancer receiving chemotherapy: A systematic review. *Clin Rev Oncol Hematol*. 2014;90:190–199.
4. National Comprehensive Cancer Network. Prevention and treatment of cancer-related infections. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), v.1.2018. December 1, 2017. Available at https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf.
5. Gustinetti G, Mikulska M. Bloodstream infections in neutropenic cancer patients: A practical update. *Viulence*. 2016;7:280–297.
6. Villafuerte-Gutierrez P, Villalon L, Losa JE, Henriquez-Camacho C. Treatment of febrile neutropenia and prophylaxis in hematologic malignancies: A critical review and update. *Adv Hematol*. 2014. Article ID 986938:1–9.
7. Nesher L, Rolston KVI. The current spectrum of infection in cancer patients with chemotherapy related neutropenia. *Infection*. 2014;42:5–13.
8. Marin M, Gudiol C, Ardanuy C, et al. Factors influencing mortality in neutropenic patients with haemotologic malignancies or solid tumours with bloodstream infection. *Clin Microbiol Infect*. 2015;21:583–590.
9. Cesar-Arce A, Volkow-Fernandez P, Valero-Saldana LM, et al. Infectious complications and multidrug-resistant bacteria in patients with hematopoietic stem cell transplantation in the first 12 months after transplant. *Transplant Proc*. 2017;49:1444–1448.
12. Feld R. Bloodstream infections in cancer patients with febrile neutropenia. *Int J Antimicrob Agents*. 2008;32(suppl):S30–S33.
13. Kosmidis CI, Chandrasekar PH. Management of gram-positive bacterial infection in patients with cancer. *Leuk Lymph*. 2012;53:8–18.
14. Zhang S, Wang Q, Ling Y, Hu X. Fluoroquinolone resistance in bacteremic and low risk febrile neutropenic patients with cancer. *BMC Cancer*. 2015;15:42–46.
15. Azie N, Neofytos D, Pfaller M, et al. The PATH (prospective antifungal therapy) alliance® registry and invasive fungal infections: Update 2012. *Diagn Microbiol Infect Dis*. 2012;73(4):293–300. doi:10.1016/j.diagmicrobio.2012.06.012.
16. Hidron A, Edwards JR, Patel J, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: Summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011-2014. *Infect Control Hosp*

Epidemiol. 2016;37:1288–1301.

17. Cho SY, Lee DG, Choi SM, et al. Impact of vancomycin resistance on mortality in neutropenic patients with enterococcal blood stream infection: A retrospective study. *BMC Infect Dis*. 2013;13:504. doi: 10.1186/1471-2334-13-504.
18. Nelson RE, Jones M, Lie CF, et al. The impact of healthcare-associated methicillin-resistant Staphylococcus aureus infections on post-discharge healthcare costs and utilization. *Infect Control Hosp Epidemiol*. 2015:36(5):534–542.
19. Lewis RE, Cahyame-Zuniga L, Leventakos K, et al. Epidemiology and site of involvement of invasive fungal infections in patients with haematological malignancies: A 20-year autopsy study. *Mycoses*. 2013;56:638–645.
20. Chen K, Wang Q, Pleasants RA, et al. Empiric treatment against invasive fungal diseases in febrile neutropenic patients: A systematic review and network meta-analysis. *BMC Infect Dis*. 2017;17:159–170.
21. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016:62:e1–e50.
22. Girmenia C, Raiola AM, Piciocchi A, et al. Incidence and outcome of invasive fungal diseases after allogeneic stem cell transplantation: A prospective study of the Gruppo Italiano Trapianto Midollo Osseo (GITMO). *Biol Blood Marrow Transplant*. 2014;20:872–880.
23. Wu P-F, Liu W-L, Hsieh M-H, et al. Epidemiology and antifungal susceptibility of candidemia isolates of non-*albicans Candida* species from cancer patients. *Emerg Microbes Infect*. 2017;6:e87.
24. van de Peppel RJ, Visser LG, Dekkers OM, de Boer MGJ. The burden of invasive aspergillosis in patients with haemotological malignancy: A meta-analysis and systematic review. *J Infect*. 2018;76:550–562.
25. Patterson TF, Thompson GR, Deming DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;63:e1–e60.
26. Wu C-W, Wu J-Y, Chen C-K, et al. Does procalcitonin, C-reactive protein, or interleukin-6 test have a role in the diagnosis of severe infection in patients with febrile neutropenia? A systematic review and meta-analysis. *Support Care Cancer*. 2015;23:2863–2872.
27. Taplitz RA, Kennedy EB. Bow EJ, et al. Antimicrobial prophylaxis for

adult patients with cancer-related immunosuppression: ASCO and IDSA clinical practice guideline update. *J Clin Oncol*. 2018; published online ahead of print on September 4, 2018. Available at https://www.asco.org/practice-guidelines/quality-guidelines/guidelines/supportive-care-and-treatment-related-issues#/32801.

28. Kim YJ, Jun YH, Kim YR, et al. Risk factors for mortality with *Pseudomonas aeruginosa* bacteremia; retrospective study of impact of combination antimicrobial therapy. *BMC Infect Dis*. 2014;14:161–167.
29. Carstensen M, Sorensen JB. Outpatient management of febrile neutropenia: Time to revise the present treatment strategy. *J Support Oncol*. 2008;6:199–208.
30. Paul M, Dickstein Y, Schlesinger A, et al. Beta-lactam versus beta-lactam-aminoglycoside combination therapy in cancer patients with neutropenia *Cochrane Database Syst Rev*. 2013;6:CD003038.
31. Paul M, Dickstein Y, Borok S, Vidal L. Empirical antibiotics targeting gram-positive bacteria for the treatment of febrile neutropenic patients with cancer. *Cochrane Database Syst Rev*. 2014;1:CD003914.
32. Gea-Banacloche J. Evidence-based approach to treatment of febrile neutropenia in hematologic malignancies. *Hematology Am Soc Hematol Educ Program*. 2013;2013:414–422.
33. Kang Y, Vicente M, Parsad S, et al. Evaluation of risk factors for vancomycin-resistant *Enterococcus* bacteremia among previously colonized hematopoietic stem cell transplant patients. *Transplant Infect Dis*. 2013;15:466–473.
34. Hirai K, Ishii H, Shimoshikiryo T, et al. Augmented renal clearance in patients with febrile neutropenia is associated with increased risk for subtherapeutic vancomycin concentrations. *Ther Drug Monit*. 2016;38:706–710.
35. Mousset S, Buchheidt D, Heinz W, et al. Treatment of invasive fungal infections in cancer patients: Updated recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Ann Hematol*. 2014;93:13–32.
36. Lass-Florl C. Triazole antifungal agents in invasive fungal infections: A comparative review. *Drugs*. 2011;71(18):2405–2419.
37. Blyth CC, Gilroy NM, Guy SD, et al. Consensus guidelines for the treatment of invasive mould infections in haematological malignancy and

haemopoietic stem cell transplantation, 2014. *Intern Med J*. 2014;44(12b):1333–1349.

38. McCormack PL. Isavuconazonium: First global approval. *Drugs*. 2015;75:817–822.
39. Omrani AS, Almaghrabi RS. Complications of hematopoietic stem cell transplantation: Fungal infections. *Hematol Oncol Stem Cell Ther*. 2017;10:239–244.
40. Ashbee HR, Barnes RA, Johnson EM, et al. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. *J Antimicrob Chemother*. 2014;69:1162–1176.
41. Mhaskar R, Clark OA, Lyman G, et al. Colony-stimulating factors for chemotherapy-induced febrile neutropenia. *Cochrane Database Syst Rev*. 2014;10:CD003039.
42. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2015;33:3199–3212.
43. National Comprehensive Cancer Network. Myeloid growth factors. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), v.2.2018; August 3, 2018. Available at http://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf.
44. Cugno C, Deola S, Filippini P, et al. Granulocyte transfusions in children and adults with hematological malignancies: Benefits and controversies. *J Transl Med*. 2015;13:362–378.
45. Gafter-Gvili A, Fraser A, Paul M, et al. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. *Cochrane Database Syst Rev*. 2014;1:CD004386.
46. Ethier MC, Science M, Beyene J, et al. Mould-active compared with fluconazole prophylaxis to prevent invasive fungal diseases in cancer patient receiving chemotherapy or haematopoietic stem-cell transplantation: A systematic review and meta-analysis of randomized controlled trials. *Br J Cancer*. 2012;106:1626–1637.
47. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guidelines for vaccination of the immunocompromised host. *Clin Infect Dis*. 2014;58:e44–e100.
48. Dandoy CE, Ardura MI, Papnicalaou GA, Auletta JJ. Bacterial bloodstream infections in the allogeneic hematopoietic cell transplant patient: New considerations for a persistent nemesis. *Bone Marrow*

Transpl. 2017;52:1091–1106. doi: 10.1038/bmt.2017.14.

49. Miller HK, Braun TM, Stillwell T, et al. Infectious risk after allogeneic hematopoietic cell transplantation complicated by acute graft-versus-host disease. *Biol Blood Marrow Transplant*. 2017;23:522–528.
50. Schuster MG, Cleveland AA, Dubberke ER, et al. Infections in Heamatopoietic cell transplant recipients: Results from the organ transplant infection project, a multicenter, prospective, cohort study. *Open Forum Infect Dis*. doi:10.1093/ofid/ofx050.
51. Battiwalla M, Tichelli A, Majhail NS. Long-term survivorship after hematopoietic cell transplantation: Roadmap for research and care. *Biol Blood Marrow Transplant*. 2017;23:184–192.
52. Mikulska M, Viscoli C, Orasch C, et al. Aetiology and resistance in bacteraemias among adult and paediatric haematology and cancer patients. *J Infect*. 2014;68:321–331.
53. Trecarichi EM, Tumbarello M. Antimicrobial-resistant gram-negative bacteria in febrile neutropenic patients with cancer: Current epidemiology and clinical impact. *Curr Opin Infect Dis*. 2014;27:200–210.
54. Ullmann AJ, Schmidt-Hieber M, Bertz H, et al. Infectious diseases in allogeneic haemotopoietic stem cell transplantation: Prevention and prophylaxis strategy guidelines 2016. *Ann Hematol*. 2016;95:1435–1455.
55. Lin R, Liu Q. Diagnosis and treatment of viral diseases in recipients of allogeneic hematopoietic stem cell transplantation. *J Hematol Oncol*. 2013;6:94. doi: 10.1186/1756-8722-6-94.
56. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell trans-plantation. *N Engl J Med*. 2017;377:2433–2444.
57. Umezawa Y, Kakihana K, Oshikawa G, et al. Clinical features and risk factors for developing varicella zoster virus dissemination following hematopoietic stem cell transplantation. *Transpl Infect Dis*. 2014;16:195–202.
58. Chong PP, Avery RK. A comprehensive review of immunization practices in solid organ transplant and hematopoietic stem cell transplant recipients. *Clin Ther*. 2017;39:1581–1598.
59. de la Serna J, Campora L, Chandrasekar P, et al. Abstract LBA2. Efficacy and safety of an adjuvanted herpes zoster subunit vaccine in autologous hematopoietic stem cell transplant recipients 18 years of age or older: First results of the phase 3 randomized, placebo-controlled ZOE-HSCT clinical

trial. Presented at: BMT Tandem Meetings; February 21-25, 2018; Salt Lake City.

60. Winston DJ, Mullane KM, Cornely OA, et al. Inactivated varicella zoster vaccine in autologous haemopoietic stem-cell transplant recipients: An international, multicentre, randomised, double-blind, placebo-controlled trial. *Lancet*. 2018; 391:2116.
61. Averbuch D, Tridello G, Hoek J, et al. Antimicrobial resistance in gram-negative rods causing bacteremia in hematopoietic stem cell transplant recipients: Intercontinental prospective study of the infectious diseases working party of the European Bone Marrow Transplantation Group. *Clin lnfect Dis*. 2017;65:1819–1828.
62. Centers for Disease Control and Prevention. Updated recommendations for use of VariZIG: United States, 2013. *MMWR*. 2013;62(28):574–576.
63. Boeckh M, Nichols WG, Chemaly RF, et al. Valganciclovir for the prevention of complications of late cytomegalovirus infection after allogeneic hematopoietic cell transplantation: A randomized trial. *Ann Intern Med*. 2015;162:1–10.
64. Crumpacker CS. Cytomegalovirus. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. Philadelphia, PA: Elsevier; 2015;1738–1753.
65. Fishman JA. Infection in organ transplantation. *Am J Transplant*. 2017;17: 856–879.
66. Green M. Introduction: Infections in solid organ transplantation. *Am J Transplant*. 2013;13:3–8.
67. Hosseini-Moghaddam SM, Shokoohi M, Singh G, et al. A Multi-center case-control study of the effect of acute rejection and cytomegalovirus infection on pneumocystis pneumonia (PCP) in solid organ transplant recipients. *Clin Infect Dis*. 2018; doi:10.1093/cid/ciy682.
68. Fishman JA. From the classic concepts to modern practice. *Clin Microbiol Infect*. 2014;20(suppl. 7):4–9.
69. Fischer SA, Lu K. AST Infectious Disease Community of Practice. Screening of donor and recipient in solid organ transplantation. *Am J Transplant*. 2013;13:9–21.
70. Gagliotti C, Morsillo F, Moro ML, et al. Infectious in liver and lung transplant recipients: A national prospective cohort. *Eur J Clin Microbiol Infect Dis*. 2018;37:399–407.
71. Hamandi B, Husain S, Grootendorst P, Papadimitropoulos EA. Clinical

and microbiological epidemiology of early and late infectious complications among solid-organ transplant recipients requiring hospitalization. *Transpl Int*. 2016;29:1029–1038.

72. Anesi JA, Blumberg EA, Abbo LM. Perioperative antibiotic prophylaxis to prevent surgical site infections in solid organ transplantation. *Transplantation*. 2018;102:21–34.
73. Kennedy CC, Razonable RR. Fungal infections after lung transplantation. *Clin Chest Med*. 2017;38:511–520.
74. Gavalda J, Meije Y, Fortún J, et al. Invasive fungal infections in solid organ transplant recipients. *Clin Microbiol Infect*. 2014;20(suppl. 7):27–48.
75. Schwartz IS, Patterson TF. The emerging threat of antifungal resistance in transplant infectious disease. *Curr Infect Dis Rep*. 2018;20:2.
76. Andes DR, Safdar N, Baddley JW, et al. The epidemiology and outcomes of invasive *Candida* infections among organ transplant recipients in the United States: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). *Transpl Infect Dis*. 2016;18:921–931.
77. Neoh CF, Snell G, Levvey B, et al. Antifungal prophylaxis in lung transplantation. *Int J Antimicrob Agents*. 2014;44(3):194–202.
78. Kotton CN, Kumar D, Caliendo AM, et al. The third international consensus guidelines on the management of cytomegalovirus in solid organ transplantation. *Transplantation*. 2018;102(6):900–931.
79. Stern M, Hirsch H, Cusini A, et al. Cytomegalovirus serology and replication remain associated with solid organ graft rejection and graft loss in the era of prophylactic treatment. *Transplantation*. 2014;98:1012–1018.
80. Martin-Gandul C, Mueller NJ, Pascual M, Manuel O. The impact of infection on chronic allograft dysfunction and allograft survival after solid organ transplantation. *Am J Transplant*. 2015;15:3024–3040
81. Durand CM, Segev D, Sugarman J. Realizing HOPE: The ethics of organ transplantation from HIV-positive donors. *Ann Intern Med*. 2016;165(2):138–142.
82. Muller E, Barday Z, Mendelson M, Kahn D. HIV-positive-to-HIV-positive kidney transplantation—results at 3 to 5 years. *N Engl J Med*. 2015;372(7):613–620.
83. Levitsky J, Formica RN, Bloom RD, et al. The American society of transplantation consensus conference on the user of hepatitis C viremic donors in solid organ transplantation. *Am J Transplant*. 2017;17:2790–

2802.

84. Kritkos A, Manuel O. Bloodstream infections after solid-organ transplantation. *Virulence*. 2016;7(3):329–340
85. Martin-Gandul C, Stampf S, Héquet D, et al. Preventive strategies against cytomegalovirus and incidence of α-herpesvirus infections in solid organ transplant recipients: A nationwide cohort study. *Am J Transplant*. 2017;17:1813–1822.
86. Andrassy J, Hoffmann VS, Rentsch M, et al. Is cytomegalovirus prophylaxis dispensable in patients receiving an mTOR inhibitor-based immunosuppression? A systematic review and meta-analysis. *Transplantation*. 2012;94:1208–1217.
87. Kittleson MM, Kobashigawa JA. Long-term care of the heart transplant patient. *Curr Opin Organ Transplant*. 2014;19:515–524.
88. Trecarichi E, Tumbarello M. Antimicrobial-resistant gram-negative bacteria in febrile neutropenic patients with cancer: Current epidemiology and clinical impact. *Curr Opin Infect Dis*. 2014;27:200–210.

141

Antimicrobial Prophylaxis in Surgery

Salmaan Kanji

KEY CONCEPTS

1. Prophylactic antibiotic therapy differs from presumptive and therapeutic antibiotic therapy in that the latter two involve treatment regimens for presumed or documented infections, whereas the goal of prophylactic therapy is to prevent infections in high-risk patients or procedures.
2. The risk of a surgical site infection (SSI) is determined from both the type of surgery and the patient-specific risk factors; however, most commonly used classification systems account for only procedure-related risk factors.
3. The timing of antimicrobial prophylaxis is of paramount importance. Antibiotics should be administered within 1 hour before surgery to ensure adequate drug levels at the surgical site prior to the initial incision.
4. Antimicrobial agents with short half-lives (eg, cefazolin) may require intraoperative redosing during procedures last more than 3 hours or 2.5 half-lives of the antimicrobial used.
5. The type of surgery, intrinsic patient risk factors, most commonly identified pathogenic organisms, institutional antimicrobial resistance patterns, and cost must be considered when choosing an antimicrobial agent for prophylaxis.
6. Single-dose prophylaxis is appropriate for many types of surgery. First-generation cephalosporins (eg, cefazolin) are the mainstay for prophylaxis in most surgical procedures because of their spectrum of activity, safety, and cost.
7. Vancomycin as a prophylactic agent should be limited to patients with a documented history of life-threatening β-lactam hypersensitivity or those in whom the incidence of infections with organisms resistant to cefazolin (eg, methicillin-resistant Staphylococcus aureus) is documented or high enough

to justify use.

Preclass Engaged Learning Activity

Watch the video entitled “WHO: Prevention of surgical site infections (WHO Global Guidelines 2016)” at https://tinyurl.com/yyocdygz. In 2017 the World Health Organization (WHO) published global recommendations for the prevention of surgical site infections and produced this promotional video. After viewing the video, read the official press release at https://tinyurl.com/zttj3s9. These two media releases highlight the global impact of surgical site infections and the need for a world-wide approach to prevention.

INTRODUCTION

According to the National Center for Health Statistics and the National Hospital Discharge Survey, nearly 57 million outpatient and 51 million inpatient surgical procedures are performed annually in the United States.[1,2] Infection is the most common complication of surgery.[3] Surgical site infections (SSIs) occur in approximately 3% to 6% of patients and prolong hospitalization by an average of 7 days at a direct annual cost of $5 billion to $10 billion.[4,5] SSIs that involve a prosthetic joint or antimicrobial-resistant organism can cost in excess of $90,000.[6] SSIs are now the most common cause of nosocomial infections among hospitalized patients (20% of all hospital-acquired infections).[7] Prophylactic administration of antibiotics decreases the risk of infection after many surgical procedures and represents an important component of care for this population.

Antibiotics administered prior to the contamination of previously sterile tissues or fluids are called prophylactic antibiotics. The goal of prophylaxis is to prevent an infection from developing. Although eradication of distal (preexisting, unrelated to surgery) infections lowers the risk for subsequent postoperative infections, it does not per se constitute a prophylactic regimen. In fact, surgical prophylaxis should be prescribed concurrently under these circumstances because of important antimicrobial spectrum- and timing-related concerns. Both SSIs and hospital-acquired infections not directly related to the surgical site (eg, urinary tract infections and pneumonia) are termed *nosocomial*. Prevention of hospital-acquired infections is a major goal of antibiotic

prophylaxis.

1 Presumptive antibiotic therapy is administered when an infection is suspected but not yet proven. Clinical scenarios where presumptive therapy is used commonly include acute cholecystitis, open compound fractures, and acute appendicitis of less than 24-hour duration. In these situations, if signs of perforation, contamination, or infection are absent during surgery, then routine prophylactic treatment rather than presumptive therapy is warranted. An operative finding of a gangrenous gallbladder or a perforated appendix, however, is suggestive of an established infectious process, and a therapeutic antibiotic regimen is required.[4]

According to the Centers for Disease Control and Prevention's (CDC) National Nosocomial Infections Surveillance System (NNIS),[4,7] SSIs can be categorized as either incisional (eg, cellulitis of the incision site) or organ/space (eg, meningitis; **Fig. 141-1**). Incisional SSIs are subcategorized into superficial (involving only the skin or subcutaneous tissue) and deep (fascial and muscle layers) infections. Organ/space SSIs can involve any anatomic area other than the incision site. For example, a patient who develops bacterial peritonitis after bowel surgery has an organ/space SSI. By definition, SSIs must occur within 30 days of surgery. If a prosthetic implant is involved, a deep incisional or organ/space SSI can be reported up to 1 year from the date of surgery. Although microbiologic testing of surgical drainage material or sites may help to guide care, the specificity of a negative culture is poor and generally does not rule out an SSI.[4,7]

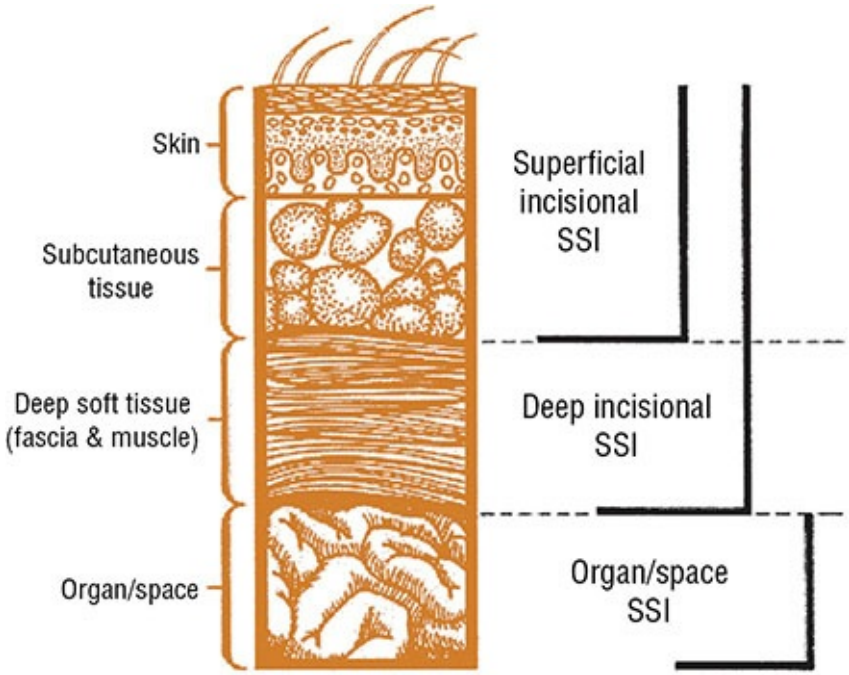


FIGURE 141-1 Cross-section of abdominal wall depicting Centers for Disease Control and Prevention classifications of surgical site infections (SSI). (*Reproduced, with permission, from Alexander JW, Solomkin JS, Edwards MJ. Updated recommendations for control of surgical site infections. Ann Surg 2011;253:1082-1093. Copyright {{#}}0169; 2011 with permission from Elsevier.*)

RISK FACTORS FOR SURGICAL SITE INFECTIONS

SSI incidence depends on both procedure- and patient-related factors. The risk for SSIs has been stratified by surgical procedure in a classification system developed by the National Research Council (NRC; **Table 141-1**).[8] The NRC classification system proposes that the risk of an SSI depends on the microbiology of the surgical site, the presence of a preexisting infection, the likelihood of contaminating previously sterile tissue during surgery, and the events during and after surgery.[8,9] A patient's NRC procedure classification is the primary determinant of whether antibiotic prophylaxis is warranted. However, because a patient's NRC wound classification is influenced by surgical findings (eg, gangrenous gallbladder) and perioperative events (eg, major technique breaks), categorization generally occurs intraoperatively.[10]

TABLE 141-1 National Research Council Wound Classification, Risk of Surgical Site Infection, and Indication for Antibiotics

	SSI Rate (%)			
Classification	Preoperative Antibiotics	No Preoperative Antibiotics	Criteria	Antibiotics
Clean	5.1	0.8	No acute inflammation or transection of GI, oropharyngeal, genitourinary, biliary, or respiratory tracts; elective case, no technique break	Not indicated unless high-risk procedure[a]
Clean–contaminated	10.1	1.3	Controlled opening of aforementioned tracts with minimal spillage/minor technique break; clean procedures performed emergently or with major technique breaks	Prophylactic antibiotics indicated
Contaminated	21.9	10.2	Acute, nonpurulent inflammation present; major spillage/technique break during clean–contaminated procedure	Prophylactic antibiotics indicated
Dirty	N/ A	N/ A	Obvious preexisting infection present (abscess, pus, or necrotic tissue present)	Therapeutic antibiotics required

N/ A, not applicable; SSI, surgical site infection.

[a]High-risk procedures include implantation of prosthetic materials and other procedures where surgical site infection is associated with high morbidity (see the text).

Data from references 5 and 11.

Inherent Patient Risk

The NRC classification system does not account for the influence of underlying patient risk factors for SSI development, instead categorizing the risks for SSIs simply based on a specific surgical procedure. Disease states and conditions known to increase SSI risk are listed in **Table 141-2**. Preexisting distal infections increase SSI rates and should be resolved prior to surgery whenever possible. Diabetic patients have an increased risk for SSIs, especially those with uncontrolled perioperative blood sugars. Preoperative smoking is an independent risk factor for SSI because of the deleterious effects of nicotine on wound healing. Preoperative immunosuppression, including corticosteroid use, may increase infection risk. Patients coinfected with human immunodeficiency virus (HIV) and hepatitis C are at approximately double the risk of SSI as the general population.[12] Malnutrition is a well-described risk factor for postoperative complications, including SSI, impaired wound and colonic anastomosis healing, and prolonged hospital stay. Although enteral feeding during the perioperative period can reduce bacterial translocation by maintaining the integrity of the intestinal mucosa, nutritional supplementation does not decrease the incidence of

infection.[13] Some patient-related risk factors are potentially modifiable (glycemic control, alcohol and smoking status, preoperative albumin and obesity). These represent opportunities for optimization prior to elective surgical procedures.[7]

TABLE 141-2 Patient and Operation Characteristics That May Influence the Risk of Surgical Site Infection

Patient	Operation
Age	Duration of surgical scrub
Nutritional status (preoperative albumin <3.5 g/dL [35 g/L])	Preoperative skin preparation
Diabetes and preoperative glycemic control	Preoperative shaving
Smoking and Alcohol use	Duration of operation
Obesity	Antimicrobial prophylaxis
Coexisting infections at distal body sites	Operating room ventilation
Colonization with resistant microorganisms	Sterilization of instruments
Altered immune response	Implantation of prosthetic materials
Length of preoperative stay	Surgical drains
	Surgical technique

Reproduced, with permission, from Alexander JW, Solomkin JS, Edwards MJ. Updated recommendations for control of surgical site infections. Ann Surg 2011;253:1082–1093.

Colonization of the nares with *S. aureus* is a well-described SSI risk factor.[4] A large multicenter study involving more than 38,000 patients undergoing more than 42,000 cardiac and orthopedic procedures showed that preoperative screening for carriers of *S. aureus* followed by intranasal mupirocin administration and chlorhexidine bathing for 5 days before surgery significantly reduced *S. aureus* SSI from 0.36% to 0.2%.[11] Although the absolute risk difference is small, this represents a 44% relative risk reduction. The potential impact on patient outcomes and health resource utilization is large given the number of surgeries performed annually. However, the logistics and cost of pre-screening and treatment of colonized patients represents a challenge. Other factors shown to increase the risk of SSI are age, length of preoperative hospital stay, and obesity.[4]

Identifying SSI Risk

Two large epidemiologic studies have objectively quantified SSI risk based on specific patient- and procedure-related factors. The Study on the Efficacy of Nosocomial Infection Control (SENIC) analyzed more than 100,000 surgery cases to identify and validate risk factors for SSI.[14] Abdominal operations, operations lasting longer than 2 hours, contaminated or "dirty" procedures (as per NRC classification), and more than three underlying medical diagnoses each was associated with an increased incidence of SSI. When NRC classification was stratified by number of SENIC risk factors present, SSI incidence varied by as much as a factor of 15 within the same NRC operative category (**Table 141-3**).[15]

TABLE 141-3 Surgical Site Infection Incidence (%) Stratified by NRC Wound Classification and SENIC Risk Factors[a]

Number of SENIC Risk Factors	Clean	Clean–Contaminated	Contaminated	Dirty
0	1.1	0.6	N/ A	N/ A
1	3.9	2.8	4.5	6.7
2	8.4	8.4	8.3	10.9
3	15.8	17.7	11.0	18.8
4	N/ A	N/ A	23.9	27.4

N/ A, not applicable; NRC, National Research Council; SENIC, Study on the Efficacy of Nosocomial Infection Control.

[a]Study on the Efficacy of Nosocomial Infection Control (SENIC) risk factors include abdominal operation, operations lasting >2 hours, contaminated or dirty procedures by National Research Council (NRC) classification, and more than three underlying medical diagnoses.

Reproduced, with permission, from Wilson AP, Hodgson B, Liu M, et al. Reduction in wound infection rates by wound surveillance with postdischarge follow-up and feedback. Br J Surg 2006;93:630-638.

In a subsequent analysis of more than 84,000 surgical cases, the NNIS attempted to simplify and refine the SENIC system by quantifying intrinsic patient risk using the American Society of Anesthesiologists' (ASA) preoperative assessment score (**Table 141-4**).[16,17] An ASA score greater than or equal to 3 was a strong predictor for the development of an SSI. Other factors associated with increased SSI incidence are contaminated or "dirty" operations (NRC criteria) and surgical procedures lasting longer than average. As in the SENIC study, the SSI rate was linked to the number of risk factors present and varied considerably within NRC class. The NNIS basic SSI risk index is

composed of the following criteria: ASA score = 3, 4, or 5; wound class; and duration of surgery. Overall, for 34 of the 44 NNIS procedure categories, SSI rates increased proportionally with the number of risk factors present.[18] The SSI rate was generally lower when the procedure was done laparoscopically.

TABLE 141-4 American Society of Anesthesiologists' Physical Status Classification

Class	Description
1	Normal healthy patient
2	Mild systemic disease
3	Severe systemic disease that is not incapacitating
4	Incapacitating systemic disease that is a constant threat to life
5	Not expected to survive 24 hours with or without operation

Data from reference 17.

Although evidence-based recommendations for antimicrobial prophylaxis during surgery are best established using the results of randomized clinical trials, many studies have small sample sizes and do not stratify patients according to overall SSI risk. Future studies, particularly those involving clean procedures, should be stratified by SSI risk so that the subset of high-risk patients who might benefit the most from prophylaxis is clearly established.

BACTERIOLOGY

The most important consideration when choosing antibiotic prophylaxis is the bacteriology of the surgical site. Organisms involved in an SSI are acquired by one of two ways: endogenously (from the patient's own normal flora) or exogenously (from contamination during the surgical procedure). Based on the type and anatomic location of the procedure and the NRC classification (see Table 141-1), resident flora can be predicted and appropriate antibiotic choices made. According to NNIS data, *S. aureus*, coagulase-negative staphylococci, enterococci, *Escherichia coli*, and *Pseudomonas aeruginosa* are the pathogens most commonly isolated (**Table 141-5**).[16] With the widespread use of broad-spectrum antibiotics, however, *Candida* species and methicillin-resistant *Staphylococcus aureus* (MRSA) are becoming more prevalent.[16]

TABLE 141-5 Major Pathogens in Surgical Wound Infections

Pathogen	Percent of Infections[a]
Staphylococcus aureus	20
Coagulase-negative staphylococci	14
Enterococci	12
Escherichia coli	8
Pseudomonas aeruginosa	8
Enterobacter species	7
Proteus mirabilis	3
Klebsiella pneumoniae	3
Other *Streptococcus* species	3
Candida albicans	3
Group D streptococci	2
Other gram-positive aerobes	2
Bacteroides fragilis	2

[a]Data reported by the National Nosocomial Infections Surveillance System from January 1992 through June 2004.

Data from reference 5.

Factors affecting the ability of an organism to induce an SSI depend on organism count, organism virulence, and host immunocompetency. Organisms in the commensal flora generally are not pathogenic. These organisms often serve the host as a form of protection against invasive organisms that otherwise would colonize the surgical site. Opportunistic organisms usually are kept in check by normal flora and rarely are problematic unless they are present in large numbers. The loss of normal flora through the use of broad-spectrum antibiotics can destabilize homeostasis, allowing pathogenic bacteria to proliferate and infection to occur.[5]

Normal flora translocated to a normally sterile tissue site or fluid during a surgical procedure can become pathogenic. For example, *S. aureus* or *Staphylococcus epidermidis* may be translocated from the surface of the skin to deeper tissues or *E. coli* from the colon to the peritoneal cavity, bloodstream, or urinary tract. Studies in animals and healthy volunteers have shown bacterial virulence to be an important determinant in the development of secondary infections.[19,20] Whereas more than one million *S. aureus* per square centimeter or gram of tissue are required to produce infection in animals, less than 100,000 *Streptococcus pyogenes* per square centimeter or gram of tissue are required at the same site.[20,21]

Impaired host defense reduces the number of bacteria required to establish an infection. A breach of normal host defenses through surgical intervention (eg, insertion of a prosthetic device) may enable organisms to cause infection. In addition, the loss of specific immune factors, such as complement activation, tissue-derived inhibitors (eg, proinflammatory cytokines), cell-mediated response (eg, T-cell function), and granulocytic or phagocytic function (eg, neutrophils or macrophages) can greatly increase the risk for SSI development.[22] Vascular occlusive states related to the surgical procedure or those occurring from hypovolemic shock can greatly affect blood flow to the surgical site, thus diminishing host defense mechanisms against microbial invasion. Traumatized tissue, hematomas, and the presence of foreign material also lead to more infections. When a foreign body is introduced during a surgical procedure, fewer than 100 bacterial colony-forming units are required to cause an SSI.[23] Studies examining *S. aureus*-contaminated wound infections on the skin of healthy volunteers demonstrate a 10,000-fold reduction in the number of organisms required to establish a wound infection if sutures are not present.[19]

ANTIMICROBIAL RESISTANCE AND STEWARDSHIP

Colonization of the host with antibiotic-resistant hospital flora prior to or during surgery may lead to an SSI that is unresponsive to routine antibiotic therapy. The most common cause of nosocomially acquired multiresistant organisms is transmission from hospital personnel.[24] Patients treated with broad-spectrum antibiotic therapy are at increased risk for colonization with hospital flora.

With cephalosporins established as first-line agents for prophylaxis, organisms resistant to cephalosporins represent the majority of pathogens causing SSIs. MRSA and coagulase-negative staphylococci have emerged as the most common pathogens in patients who develop SSIs despite prophylaxis with cephalosporins particularly in cardiothoracic, vascular, orthopedic, and neurologic surgery. Methicillin resistance not only limits the treatment/-prophylaxis options available, but it also is associated with increased mortality, longer hospital lengths of stay, and increased costs. Although the use of vancomycin for prophylaxis may be appropriate for some operations performed in hospitals with a high rate of infection due to MRSA, there is little guidance on what constitutes a “high rate” of MRSA infection and whether providing prophylaxis with vancomycin alone will result in fewer SSIs.[25] A more effective

strategy would be to screen elective surgical candidates for MRSA colonization preoperatively. MRSA colonization is predictive of MRSA SSI and thus effective prophylaxis with vancomycin is then reserved for carriers only. Some single center studies evaluating the decolonization of MRSA carriers preoperatively (ie, with intranasal mupirocin, chlorhexidine showers) yield mixed results and may not be cost-effective.[25]

The increase in frequency of fungal infections in surgical patients has drawn concern. In hospitalized patients, the incidence of nosocomial *Candida* infections nearly doubled from 1992 to 2004.[16,26] Overzealous use of broad-spectrum antibiotics is the most likely cause for this increase. A study of patients undergoing cardiovascular surgery identified female sex, length of stay in the ICU, and duration of central venous catheterization as risk factors for postoperative *Candida* infections. Although presurgical *Candida* colonization is associated with a higher risk of fungal SSIs, routine preoperative use of prophylactic antifungal agents is not being advocated at this time.[26]

Antimicrobial stewardship programs are typically run by multidisciplinary teams in hospitals to promote responsible antimicrobial use and optimize antimicrobial therapy through multimodal educational and clinical interventions with an aim to reduce antimicrobial resistance and infection related morbidity and mortality. Systematic reviews suggest that these programs are effective in reducing the development of antimicrobial resistance and hospital acquired infections.[27] Typically antimicrobial stewardship programs target areas of the hospital where there is high use of antimicrobials but surgical units and operating rooms are often overlooked. Given that approximately 15% of all antimicrobials prescribed in hospital are for surgical prophylaxis and the opportunity to improve the outcomes of surgical patients with respect to surgical site infections, surgical units would benefit from antimicrobial stewardship programs and surgeons should be part of the multidisciplinary team.[28]

SCHEDULING ANTIBIOTIC ADMINISTRATION

3 4 The following principles must be considered when providing antimicrobial surgical prophylaxis: (a) the agents should be delivered to the surgical site prior to the initial incision, and (b) bactericidal antibiotic concentrations should be maintained at the surgical site throughout the surgical procedure. Although animal and human models have demonstrated the efficacy of a single dose of an antibiotic administered just prior to bacterial contamination, long operations often require intraoperative doses of antibiotics

to maintain adequate concentrations at the surgical site for the duration of surgery.[29] Antibiotic administration should be completed within 60 minutes prior to the initial incision, preferably at the time of anesthetic induction. Since the administration duration varies between antimicrobials, this needs to be considered when determining when to start the infusion. Administration of antibiotics too early may result in concentrations below the MIC toward the end of the operation, and administration too late leaves the patient unprotected at the time of initial incision. In a study examining the timing of antibiotic administration to 2,847 patients receiving prophylaxis, Classen et al.[29] evaluated patients who received prophylaxis early (2-24 hours before surgery), preoperative prophylaxis (0-2 hours prior to surgery), perioperative prophylaxis (up to 3 hours after first incision), and postoperative prophylaxis (greater than 3 hours after the first incision). The risk of infection was lowest (0.6%) for patients who received preoperative prophylaxis, moderate (1.4%) for those who received perioperative antibiotics, and greatest for those who received postoperative antibiotics (3.3%) or preoperative antibiotics too early (3.8%). The risk for an SSI increases dramatically with each hour from the time of initial incision to the time when antibiotics are eventually administered. For these reasons, prophylactic antibiotics should not be prescribed to be given “on call to the operating room (OR),” which can occur two or more hours prior to the initial incision, nor should concurrent therapeutic antibiotics be relied on to provide adequate protection. In both situations, the chance for improperly timed doses is high. Although the landmark study by Classen et al.[29] confirmed that antimicrobial prophylaxis should be administered within 2 hours prior to the initial incision, administration immediately prior to the incision may not allow enough time for the drug to distribute throughout the tissues involved in the surgery.

In a large randomized controlled trial in Switzerland, hospitalized surgical patients were randomized to early (in the anesthesia room) or late (in the operating room) prophylactic antimicrobials.[30] 2589 patients in the early group received their antimicrobials a median of 42 minutes prior to the incision while 2586 patients in the late group received their antimicrobials a median of 16 minutes prior to the incision. All patients received cefuroxime (plus metronidazole for colorectal surgery) as a single dose except for long operations where the cefuroxime (and metronidazole for colorectal surgery) was readministered every 4 hours during the operation. SSIs were 5% in both groups suggesting that the current recommendation to administer surgical prophylaxis within 60 minutes prior to the incision is adequate.

Despite the importance of appropriately timed prophylactic antibiotic therapy, many patients receive antibiotics outside of the optimal time window in relation to surgery. Potential barriers include antibiotics ordered after the patient has arrived in the OR, delayed antibiotic preparation or delivery, and use of antibiotics that require long infusion times. One retrospective study assessed the timing of prophylactic antibiotics in more than 32,000 patients and found that 91.9% of patients received an antibiotic dose within 60 minutes of the initial surgical incision.[31]

Although most studies comparing single versus multiple doses of prophylactic antibiotics have failed to show a benefit of multidose regimens, the duration of operations in these studies may not be as long as that frequently observed in clinical practice. Proponents of administering a second antibiotic dose during lengthy operations suggest that the risk for SSI is just as great at the end of surgery (during wound closing) as it is during the initial incision. One study of patients undergoing clean–contaminated operations suggests that procedures longer than 3 hours require a second intraoperative dose of cefazolin or substitution of cefazolin with a longer-acting antimicrobial agent.[5] A second study of patients undergoing elective colorectal surgery suggests that low serum antimicrobial concentrations at the time of surgical closure is the strongest predictor of postoperative SSI.[32] Studies of patients undergoing cardiac surgery also have demonstrated a higher infection rate among patients with undetectable antibiotic serum concentrations at the conclusion of the procedure.[33] Ideally antibiotic prophylaxis should be repeated when surgeries last longer than two half-lives of chosen antibiotic (ie, 4 hours for cefazolin) or if intraoperative blood loss exceeds 1.5 L.[34]

One strategy to ensure appropriate redosing of prophylactic antibiotics during long operations is use of a visual or auditory reminder system. One hospital reported its experience with such a system, finding that an automated reminder improved compliance and reduced SSIs. However, even with the reminder system, intraoperative redosing was done in only 68% of eligible patients.[35]

ANTIMICROBIAL CHOICE

5 The choice of prophylactic antibiotic depends on the type of surgical procedure, the most frequent pathogens seen with this procedure, safety and efficacy profiles of the antimicrobial agent, current literature evidence supporting its use, and cost. Although most SSIs involve the patient’s normal

flora, antimicrobial selection also must take into account the susceptibility patterns of nosocomial pathogens within each institution. Typically, gram-positive coverage should be included in the choice of surgical prophylaxis because organisms such as *S. aureus* and *S. epidermidis* are encountered commonly as skin flora. The decision to broaden antibiotic prophylaxis to agents with gram-negative and anaerobic spectra of activity depends on both the surgical site (eg, upper respiratory, GI, or genitourinary tract) and whether the operation will transect a hollow viscous or mucous membrane that may contain resident flora.[4]

Although antimicrobial prophylaxis can be administered through a variety of routes (eg, oral, topical, or intramuscular), the parenteral route is favored because of the reliability by which adequate tissue concentrations may be acheived.[36] Cephalosporins are the most commonly prescribed agents for surgical prophylaxis because of their broad antimicrobial spectrum, favorable pharmacokinetic profile, low incidence of adverse side effects, and low cost. First-generation cephalosporins, such as cefazolin, are the preferred choice for surgical prophylaxis, particularly for clean surgical procedures.[4,5,10] In cases where broader gram-negative and anaerobic coverage is desired, antianaerobic cephalosporins, such as cefoxitin and cefotetan, are appropriate choices. Although third-generation cephalosporins (eg, ceftriaxone) have been advocated for prophylaxis because of their increased gram-negative coverage and prolonged half-lives, their inferior gram-positive and anaerobic activity and high cost have discouraged the widespread use of these agents.[4,5,10]

Allergic reactions are the most common side effects associated with cephalosporin use. Reactions can range from minor skin manifestations at the site of infusion to rash, pruritus, and rarely anaphylaxis (less than 0.02%). The structural similarity between penicillins and cephalosporins (each contains a β-lactam ring) has led to considerable confusion about the cross-allergenicity between these two classes of drugs. Twenty percent of the general population is labeled “penicillin allergic,” yet of these patients, only 10% to 20% have positive results of a penicillin skin test.[37] The rate of cross-reactivity with cephalosporins is approximately 2%, but as only 20% of all “penicillin-allergic” patients truly are penicillin allergic, the true incidence of cross-reactivity likely is less than 1%. Routine penicillin skin testing is not cost-effective.[37] The administration of cephalosporins is both safe and cost-effective for many patients who are labeled “penicillin allergic,” and they can be used by patients who have not experienced an immediate or type I penicillin allergy.

Vancomycin can be considered for prophylactic therapy in surgical

procedures involving implantation of a prosthetic device in which the rate of MRSA is high.[38] If the risk of MRSA is low, and a *β*-lactam hypersensitivity exists, clindamycin can be used for many procedures instead of cefazolin to limit vancomycin use. Infusion-related side effects, such as thrombophlebitis and hypotension, particularly with vancomycin, usually can be controlled by adequate dilution and slower administration rates.

Pseudomembranous colitis secondary to cephalosporins is uncommon and generally easily treated with a short course of oral metronidazole. Although infrequent, bleeding abnormalities related to cephalosporin use have been reported.[39] The primary hematologic effect appears to be inhibition of vitamin K-dependent clotting factors that results in prolongation of the prothrombin time. The mechanism for this effect, most commonly seen with cefotetan, is related to the methylthiotetrazole side chain of the *β*-lactam molecule. Patients at greatest risk for this hypoprothrombinemic effect have received a prolonged course of these agents and have underlying risk factors for vitamin K deficiency, such as malnutrition.

Because inappropriate prophylactic antibiotic use not only can induce antibiotic resistance but also can negatively affect an institution’s antibiotic budget, initiatives to curtail inappropriate antibiotic use have become the focus of many drug use evaluation efforts. Potential sources of inappropriate antibiotic prophylaxis include the use of broad-spectrum antimicrobials when a narrow-spectrum agent is warranted, extending prophylaxis for durations beyond that recommended in published guidelines, and using expensive antibiotics when equivalent, less expensive agents are available. Individualized institutional guidelines that take into account the best literature evidence, institution-based antibiotic susceptibility data, and surgeon preference are important tools for rationalizing antibiotic prophylaxis use.[40] This also highlights a potential role for antimicrobial stewardship.

RECOMMENDATIONS FOR SPECIFIC TYPES OF SURGERY

Guidelines for surgical prophylaxis usually are structured according to the tissues affected during an operation. Although many different surgical procedures may be performed at any one anatomic site, this method of categorization still is optimal because the factors related to the success of a prophylactic regimen, such as the endogenous flora that are expected and the

pharmacokinetics, pharmacodynamics, and spectrum of selected antimicrobials, generally are constant for a particular surgical site (see the discussion above). The choice of antimicrobial prophylaxis is always best evaluated using the results of properly conducted clinical trials. In the absence of studies specific to the procedure in question, extrapolation from data on regimens for different procedures in the same anatomic site in question usually can be made. Subsequent modifications to each prophylactic regimen should be based on intraoperative findings or events.

6 A comprehensive review of the surgical prophylaxis literature is beyond the scope of this chapter, but important factors are reviewed here for common types/sites of surgery. Specific recommendations are summarized in **Table 141-6**. The reader is referred to published guidelines and review articles.[3–5,10,36,41]

TABLE 141-6 Most Likely Pathogens and Specific Recommendations for Surgical Prophylaxis

Type of Operation	Likely Pathogens	Recommended Prophylaxis Regimen[a]	Comments	Grade of Recommendation[b]
GI Surgery				
Gastroduodenal	Enteric gram-negative bacilli, gram-positive cocci, oral anaerobes	Cefazolin 1 g × 1	High-risk patients only (obstruction, hemorrhage, malignancy, acid suppression therapy, morbid obesity)	IA
Bariatric Surgery	Enteric gram-negative bacilli, gram-positive cocci, oral anaerobes	Cefazolin 2 g x 1	Intraoperative redosing required for procedures longer than 4 hours	IB
Cholecystectomy	Enteric gram-negative bacilli, anaerobes	Cefazolin 1 g × 1 for high-risk patients; Laparoscopic: controversial	High-risk patients only (open biliary tract procedures, acute cholecystitis, common duct stones, previous biliary surgery, jaundice, age >60 years, obesity, diabetes mellitus)	IA
Transjugular intrahepatic portosystemic shunt (TIPS)	Enteric gram-negative bacilli, anaerobes	Ceftriaxone 1 g × 1	Longer-acting cephalosporins preferred	IA
Appendectomy	Enteric gram-negative bacilli, anaerobes	Cefoxitin or cefotetan 1 g × 1 or cefazolin 1 g plus metronidazole 1 g × 1	Second intraoperative dose of cefoxitin may be required if procedure lasts longer than 3 hours	IA
Colorectal	Enteric gram-negative bacilli, anaerobes	Orally: neomycin 1 g + erythromycin base 1 g at 1, 2, and 11 PM 1 day preoperatively plus mechanical bowel preparation IV: cefoxitin or cefotetan 1 g × 1	Role of mechanical bowel preparation is controversial. It is widely used despite evidence suggesting it may have no effect on SSI or other clinical outcomes	IA
GI endoscopy	Variable, depending on procedure, but typically enteric gram-negative bacilli, gram-positive cocci, oral anaerobes	Orally: amoxicillin 2 g × 1 IV: ampicillin 2 g × 1 or cefazolin 1 g × 1	Recommended only for high-risk patients undergoing high-risk procedures (see the text)	IA
Urologic Surgery				
Prostate resection, shock-wave lithotripsy, ureteroscopy	*E. coli*	Ciprofloxacin 500 mg orally or Trimethoprim-sulfamethoxazole 1 DS tablet	All patients with positive preoperative urine cultures should receive a course of antibiotic treatment	IA–IB
Removal of external urinary catheters, cystography, urodynamic studies, simple cystourethroscopy	*E. coli*	Ciprofloxacin 500 mg orally or Trimethoprim-sulfamethoxazole 1 DS tablet	Should be considered only in patients with risk factors (see the text)	IB
Gynecological Surgery				
Cesarean section	Enteric gram-negative bacilli, anaerobes, group B streptococci, enterococci	Cefazolin 2 g × 1 and azithromycin 500 mg IV x 1	Antimicrobial administration should be prior to the initial incision as opposed to after umbilical cord clamping	IA
Hysterectomy	Enteric gram-negative bacilli, anaerobes, group B streptococci, enterococci	Vaginal: cefazolin 1 g × 1 Abdominal: cefotetan 1 g × 1 or cefazolin 1 g × 1	Metronidazole 1 g IV × 1 is recommended alternative for penicillin allergy	IA
Head and Neck Surgery				
Maxillofacial surgery	*Staphylococcus aureus*, streptococci spp., oral anerobes	Cefazolin 2 g or clindamycin 600 mg	Repeat intraoperative dose for operations longer than 4 hours	IA
Head and neck cancer resection	*S. aureus*, streptococci spp., oral anerobes	Clindamycin 600 mg at induction and every 8 hours × 2 more doses	Add gentamicin for clean-contaminated procedures	IA

Cardiothoracic Surgery				
Cardiac surgery	*S. aureus*, *S. epidermidis*, *Corynebacterium*	Cefazolin 1 g every 8 hours × 48 hours Intranasal mupirocin twice daily for 5 days preoperatively for patients colonized with *S. aureus*	Patients >80 kg (>176 lb) should receive 2 g of cefazolin instead; in areas with high prevalence of *S. aureus* resistance, vancomycin should be considered	IA
Thoracic surgery	*S. aureus*, *S. epidermidis*, *Corynebacterium*, enteric gram-negative bacilli	Cefuroxime 750 mg IV every 8 hours × 48 hours	First-generation cephalosporins are deemed inadequate, and shorter durations of prophylaxis have not been adequately studied	IA
Vascular Surgery				
Abdominal aorta and lower extremity vascular surgery	*S. aureus*, *S. epidermidis*, enteric gram-negative bacilli	Cefazolin 1 g at induction and every 8 hours × 2 more doses	Although complications from infections may be infrequent, graft infections are associated with significant morbidity	IB
Orthopedic Surgery				
Joint replacement	*S. aureus*, *S. epidermidis*	Cefazolin 1 g × 1 preoperatively, then every 8 hours × 2 more doses Intranasal mupirocin twice daily for 5 days preoperatively for patients colonized with *S. aureus*	Vancomycin reserved for penicillin-allergic patients or where institutional prevalence of methicillin-resistant *S. aureus* warrants use	IA
Hip fracture repair	*S. aureus*, *S. epidermidis*	Cefazolin 1 g × 1 preoperatively, then every 8 hours for 48 hours	Compound fractures are treated as if infection is presumed	IA
Open/compound fractures	*S. aureus*, *S. epidermidis*, gram-negativebacilli, polymicrobial	Cefazolin 1 g × 1 preoperatively, then every 8 hours for a course of presumed infection	Gram-negative coverage (ie, gentamicin) often indicated for severe open fractures	IA
Neurosurgery				
CSF shunt procedures	*S. aureus*, *S. epidermidis*	Cefazolin 1 g every 8 hours × 3 doses or ceftriaxone 2 g × 1	No agents have been shown to be better than cefazolin in randomized comparative trials	IA
Spinal surgery	*S. aureus*, *S. epidermidis*	Cefazolin 1 g × 1	Limited number of clinical trials comparing different treatment regimens	IB
CSF shunt procedures	*S. aureus*, *S. epidermidis*	Cefazolin 1 g every 8 hours × 3 doses or ceftriaxone 2 g × 1	No agents have been shown to be better than cefazolin in randomized comparative trials	IA
Craniotomy	*S. aureus*, *S. epidermidis*	Cefazolin 1 g × 1 or cefotaxime 1 g × 1	Vancomycin 1 g IV × 1 can be substituted for patients with penicillin allergy	IA

CSF, cerebrospinal fluid; DS, double strength.

[a]One-time doses are optimally infused at induction of anesthesia except as noted. Repeat doses may be required for long procedures. See the text for references.

[b]Strength of recommendations:

Category IA: Strongly recommended and supported by well-designed experimental, clinical, or epidemiologic studies.

Category IB: Strongly recommended and supported by some experimental, clinical, or epidemiologic studies and strong theoretical rationale.

Category II: Suggested and supported by suggestive clinical or epidemiologic studies or theoretical rationale.

Gastrointestinal Surgery

GI surgery can be categorized according to surgical site and infectious risk.

Gastroduodenal surgery and hepatobiliary surgery generally are considered to be clean or clean–contaminated surgeries, with SSI rates generally less than 5%. Colorectal surgery, including appendectomies, is considered contaminated because of the large quantities and polymicrobial nature of bacterial flora within the colon. SSI rates for these types of surgeries generally range from 15% to 30%. Emergent abdominal surgery involving bowel perforation or peritonitis is considered a dirty surgical procedure, associated with a greater than 30% risk of SSI, and should be treated with therapeutic rather than prophylactic antibiotics.[4]

Gastroduodenal Surgery

Insignificant numbers of bacteria usually are found in the stomach and duodenum because of their acidity. The rate of SSIs in gastroduodenal surgery generally is low, so procedures in this region can be classified as clean. The risk for an SSI in this population increases with any condition that can lead to bacterial overgrowth, such as obstruction, hemorrhage, or malignancy, or increasing the pH of gastroduodenal secretions with concomitant acid suppression therapy. Antimicrobial prophylaxis is of clinical benefit only in this high-risk population. In most cases, a single IV dose of cefazolin will provide adequate prophylaxis.[10] Antimicrobial prophylaxis is indicated in esophageal surgery only in the presence of obstruction. Postoperative therapeutic antibiotics may be indicated if perforation is detected during surgery, depending on whether an established infection is present.

Use of antibiotic prophylaxis for percutaneous endoscopic gastrostomy placement is also warranted. Postoperative peristomal infection can occur in up to 30% of patients and a systematic review of 12 trials involving 1,271 patients found a significant reduction in peristomal infections with antimicrobial prophylaxis (OR 0.36, 95% CI 0.26-0.50).[42] A single dose of cefazolin given 30 minutes preoperatively is preferred over longer regimens.

There are no well-designed clinical trials of antimicrobial prophylaxis in bariatric surgery. However, given that obesity is a consistently identified risk factor for SSIs, guidelines do promote antimicrobial prophylaxis with cefazolin but at higher doses.[10] Pharmacokinetic studies suggest that 2 g of cefazolin provided adequate tissue levels for 4.8 hours.[43]

Hepatobiliary Surgery

Although bile normally is sterile, and the SSI rate after biliary surgery is low,

antibiotic prophylaxis is of benefit in this population. Bile contamination (bactobilia) can increase the frequency of SSIs and is present in many patients (eg, those with acute cholecystitis or biliary obstruction and those of advanced age).[41] In general, however, the correlation between bactobilia in surgical specimens and the subsequent pathogens implicated in an SSI is poor. The most frequently encountered organisms are *E. coli*, *Klebsiella* species, and enterococci. *Pseudomonas* is an uncommon finding in the absence of cholangitis. Most of the SSI literature on biliary tract surgery pertains to cholecystectomy while more recent trials pertain to laparoscopic procedures which have eclipsed the traditional open cholecystectomy because of a reduction in recovery time and hospital stay. The evidence in open cholecystectomy strongly supports the use of antimicrobial prophylaxis while the evidence for laparoscopic procedures is less impressive.[10] Trials comparing first-, second-, and third-generation cephalosporins have not demonstrated benefit over single-dose cefazolin prophylaxis even in high-risk patients (eg, age greater than 60 years, previous biliary surgery, acute cholecystitis, jaundice, obesity, diabetes, and common bile duct stones).[44] Ciprofloxacin and levofloxacin are effective alternatives for β-lactam-allergic patients undergoing open cholecystectomy.[45,46] In fact, oral levofloxacin appears to provide similar intraoperative gallbladder tissue concentrations.[46] For patients undergoing elective laparoscopic cholecystectomy, antibiotic prophylaxis has traditionally not been recommended but newer trials and systematic reviews are conflicting and assessments of current practice are reflective of this.[47,48] Detection of an active infection during surgery (eg, gangrenous gallbladder and suppurative cholangitis) is an indication for a course of postoperative therapeutic antibiotics. The risk for SSIs in cirrhotic patients undergoing transjugular intrahepatic portosystemic shunt surgery may be reduced with a single prophylactic dose of ceftriaxone,[49] but not with single doses of shorter-acting cephalosporins.[50]

Appendectomy

Acute appendicitis can be broadly categorized as complicated (evidence of perforation, gangrene, peritonitis, or abscess formation) or uncomplicated. Complicated appendicitis should be treated as an active intra-abdominal infection. While appendectomy for uncomplicated appendicitis is more common it has been associated with SSI rates of 9% to 30% in the absence of antimicrobial prophylaxis. Randomized controlled trials do suggest that preoperative antimicrobials are effective at reducing this risk and should be

administered in all cases.[51] Numerous antibiotic regimens, all with activity against gram-positive and gram-negative aerobes and anaerobic pathogens, are effective in reducing SSI incidence.[41] A cephalosporin with antianaerobic activity, such as cefoxitin or cefotetan, is recommended as first-line therapy; however, a comparative trial of cefoxitin and cefotetan suggests that cefotetan may be superior, possibly because of its longer duration of action.[52] Alternatively, cefazolin in combination with metronidazole is also effective. In patients with *β*-lactam allergy, metronidazole in combination with gentamicin is an effective regimen. Broad-spectrum antibiotics covering nosocomial pathogens (eg, *Pseudomonas*) do not further reduce SSI risk and instead may increase the cost of therapy and promote bacterial resistance.[53] Although single-dose therapy with cefotetan is adequate, prophylaxis with cefoxitin may require intraoperative redosing if the procedure extends beyond 3 hours.

Colorectal Surgery

In the absence of adequate prophylactic therapy, the risk for SSI after colorectal surgery is high because of the significant bacterial counts in fecal material present in the colon (frequently greater than 10^9 per gram). Anaerobes and gram-negative aerobes predominate, but gram-positive aerobes also may play an important role. Reducing this bacterial load with a thorough bowel preparation regimen (4 L of polyethylene glycol solution or 90 mL of sodium phosphate solution administered orally the day before surgery) is controversial; however, 99% of surgeons in a survey routinely use mechanical preparation.[54] A randomized trial of 380 patients undergoing elective colorectal surgery suggests that SSIs are not reduced by preoperative mechanical bowel preparation.[55] This finding was confirmed in two meta-analyses showing that mechanical bowel preparation does not reduce the risk of anastomotic leakage or other complications, including postoperative infection.[56,57] Despite this new evidence, mechanical bowel preparations continue to be a standard of practice prior to elective bowel surgery.

Risk factors for SSIs include age over 60 years, hypoalbuminemia, poor preoperative bowel preparation, corticosteroid therapy, malignancy, and operations lasting longer than 3.5 hours.[10] Antimicrobial prophylaxis reduced mortality from 11.2% to 4.5% in a pooled analysis of trials comparing antimicrobial prophylaxis with no prophylaxis for colon surgery.[58] Effective antibiotic prophylaxis consisting of an oral and IV regimen reduces even further the risk for an SSI. A Cochrane review comparing oral, IV, and combination

regimens found that while each one was more effective at reducing SSI than placebo, combination therapy (oral and IV) was superior to oral regimens alone (OR 0.52 [0.35, 0.76]) and IV regimens alone (OR 0.55 [0.43, 0.71]).[59]

Several oral regimens designed to reduce bacterial counts in the colon have been studied.[41] The combination of 1 g neomycin and 1 g erythromycin base given orally 19, 18, and 9 hours preoperatively is the regimen most commonly used in the United States.[60] Neomycin is poorly absorbed, but provides intraluminal concentrations that are high enough to effectively kill most gram-negative aerobes. Oral erythromycin is only partially absorbed but still produces concentrations in the colon that are sufficient to suppress common anaerobes. If surgery is postponed, the antibiotics must be readministered to maintain efficacy. Optimally, the bowel preparation regimen (if used) should be completed prior to starting the oral antibiotic regimen. This is of particular concern because most procedures now are performed electively on a “same-day surgery” basis. In this case, the bowel preparation regimen is self-administered by the patient at home on the day prior to hospital admission, and compliance cannot be monitored carefully.

Single dose cephalosporins are the most used and studied preoperative IV antimicrobial. Cefoxitin or cefotetan is used most commonly, but other second- and some third-generation cephalosporins also are effective.[61] The role of metronidazole in combination with cephalosporin therapy is unclear. Only retrospective evidence suggests that the addition of metronidazole to a cephalosporin or extended-spectrum penicillin provides additional benefit.[62] Until this finding is confirmed in prospective studies, metronidazole should be reserved for combination therapy with cephalosporins with poor anaerobic coverage (eg, cefazolin). At this time, the evidence recommending the addition of metronidazole to cephalosporins with anaerobic activity (eg, cefotaxime, cefoxitin, and ceftriaxone) is insufficient.[63] For β-lactam-allergic patients, perioperative doses of gentamicin and metronidazole have been used. Postoperative antibiotics generally are unnecessary in the absence of any untoward events or findings during surgery. IV antibiotics are required for colostomy reversal and rectal resection because enterally administered antibiotics will not reach the distal segment that is to be reanastomosed or resected.[64]

Gastrointestinal Endoscopy

Despite the large number of endoscopic procedures performed each year, the rate

of postprocedural infection is relatively low. The highest bacteremia rates have been reported in patients undergoing esophageal dilation for stricture or sclerotherapy for management of esophageal varices. Although postprocedural bacteremia can occur in as many as 22% of patients, the bacteremia usually is transient (less than 30 minutes) and rarely results in clinically significant infection. Therefore, antimicrobial prophylaxis is routinely recommended only for high-risk patients (eg, patients with prosthetic heart valves, a history of endocarditis, systemic-pulmonary shunt, synthetic vascular graft less than 1 year old, complex cyanotic congenital heart disease, obstructed bile duct, or liver cirrhosis, as well as immunocompromised patients) undergoing high-risk procedures (eg, stricture dilation, variceal sclerotherapy, and endoscopic retrograde cholangiopancreatography, ERCP).[65] Single-dose preprocedural regimens similar to those for endocarditis prophylaxis are most common (amoxicillin for patients who can tolerate oral premedication or either IV ampicillin or cefazolin). A meta-analysis of antimicrobial prophylaxis for endoscopic placement of percutaneous feeding tubes also suggests that a single preoperative dose of antibiotics reduces the risk of postoperative infection compared with no antibiotic (6.4% vs 24%).[66] Consensus guidelines have adopted this recommendation and suggest a single dose of cefazolin within 30 minutes prior to the procedure.[65]

Urologic Surgery

Preoperative bacteriuria is the most important risk factor for development of an SSI after urologic surgery. All patients should have a preoperative urinalysis and should receive therapeutic antibiotics if bacteriuria is detected. Patients undergoing clean urologic procedures with sterile urine preoperatively are at low risk for developing an SSI and antimicrobial prophylaxis is not recommended.[10] Antibiotic prophylaxis is recommended for all patients undergoing transurethral resection of the prostate or bladders tumors, shock-wave lithotripsy, percutaneous renal surgery, or ureteroscopy.[67] The exact incidence of SSIs in this population is obscured by the frequent use of postoperative urinary catheters and the subsequent risk of bacteriuria. *E. coli* is the most frequently encountered organism. Routine use of broad-spectrum antibiotics, such as third-generation cephalosporins and fluoroquinolones, does not decrease SSI rates more than cefazolin, but the ability to administer fluoroquinolones orally rather than IV makes antimicrobial prophylaxis with ciprofloxacin easier and less expensive.[68] First- or second-generation cephalosporins are considered the antimicrobial

agents of choice for patients undergoing open or laparoscopic procedures involving entry into the urinary tract and any urologic surgical procedures involving the intestine, rectum, vagina, or implanted prosthesis.[67] The evidence supporting antimicrobial prophylaxis for the removal of external urinary catheters, cystography, urodynamic studies, simple cystourethroscopy, and open or laparoscopic urologic procedures that do not involve entry into the urinary tract is not as evident. Only patients considered to have risk factors (patients of advanced age; those with anatomic anomalies, poor nutritional history, externalized catheters, colonized endogenous/exogenous material, or distant coexistent infection; smokers; immunocompromised patients; and those who are hospitalized for a prolonged stay) should receive antimicrobial prophylaxis.[67]

Obstetric and Gynecologic Surgeries

Cesarean Section

Cesarean section is the most frequently performed surgical procedure in the United States.[10] Prophylactic antibiotics are given to prevent endometritis, the most commonly occurring SSI. In the past, antibiotics were recommended for only high-risk patients, including those with premature membrane rupture or those not receiving prenatal care. Several large trials, as well as a meta-analysis of 81 trials, have shown benefit in administering prophylactic antibiotics to all women undergoing emergent or elective cesarean section regardless of their underlying risk factors.[69] Cefazolin remains the drug of choice despite the wide spectrum of potential pathogens, and a single 2 g dose appears to be superior to single or multiple 1 g doses.[70] For patients with a β-lactam allergy, preoperative metronidazole is an acceptable alternative.[69] In women undergoing cesarean section a composite outcome of endometritis, wound infection, or other infection occurring within 6 weeks was 6.1% in women who received extended spectrum coverage with azithromycin plus cefazolin versus 12% in those who received cefazolin alone.[71] This study makes a strong argument for extending the spectrum of coverage with azithromycin in addition to the standard cephalosporin regimen.

During a cesarean section, unlike other surgical procedures, the most appropriate timing of antibiotic administration has been a source of controversy. Traditionally, antimicrobials were administered after the initial incision and when the umbilical cord was clamped in an attempt to minimize infant drug exposure, which theoretically could mask the signs of infection and induce

antimicrobial resistance. The most recent CDC guidelines suggest that high-quality evidence supports antimicrobial administration at the time of the initial incision instead of at the time of umbilical cord clamping.[4] A meta-analysis of seven randomized controlled trials reports a 43% reduction in post-partum endometritis without an increase in neonatal sepsis or antimicrobial resistance.[4]

Hysterectomy

The most important factor affecting the incidence of SSI after hysterectomy is the type of procedure performed. Vaginal hysterectomies are associated with a high rate of postoperative infection when performed without the benefit of prophylactic antibiotics because of the polymicrobial flora normally present at the operative site.[72] As with cesarean sections, cefazolin is the drug of choice for vaginal hysterectomies despite the wide spectrum of possible pathogens.[72] The American College of Obstetricians and Gynecologists (ACOG) recommends a single dose of either cefazolin or cefoxitin.[73] For patients with a β-lactam allergy, a single preoperative dose of either metronidazole or doxycycline also is effective.[73]

Prophylactic antibiotics are recommended for abdominal hysterectomy despite the lack of bacterial contamination from the vaginal flora. Single-dose cefotetan was superior to single-dose cefazolin,[74] and the investigators suggested that cefotetan should be the drug of choice for abdominal hysterectomies. However, other investigators suggested that either agent is appropriate, provided 24 hours of antimicrobial coverage is not exceeded.[10] The ACOG guidelines suggest that first- (such as cefazolin), second- (such as cefotetan), or third-generation cephalosporins can be used for prophylaxis.[73] Metronidazole plus an aminoglycoside or fluoroquinolone is also effective and can be used if patients are allergic to β-lactam antibiotics. Antibiotic prophylaxis may not be required in laparoscopic gynecologic surgery or tubal microsurgery.[75] As with other surgical procedures, perioperative events and findings may require the use of therapeutic antibiotics after surgery.

Head and Neck Surgery

The use of prophylactic antibiotics during head and neck surgery depends on the procedure type. Clean procedures (per NRC definition), such as thyroidectomy, lymph node excision and simple tooth extraction, are associated with a low incidence of SSI. Antimicrobial prophylaxis is not recommended for these

procedures. Head and neck surgeries involving an incision through a mucosal layer are associated with a higher risk for SSI but antimicrobial prophylaxis is not always associated with a reduction in SSI (ie, adenoidectomy, tonsillectomy and septoplasty).[10] The normal flora of the mouth is polymicrobial; both anaerobes and gram-positive aerobes predominate. Although typical doses of cefazolin usually are ineffective for anaerobic infections, a 2 g dose produces concentrations high enough to inhibit these organisms. A single dose of clindamycin is adequate for prophylaxis in maxillofacial surgery unless the procedure lasts longer than 4 hours, when a second dose should be administered intraoperatively.[76] The greatest evidence for antimicrobial prophylaxis is in head and neck cancer resection surgeries. For most head and neck cancer resection surgeries, including free-flap reconstruction, 24 hours of clindamycin is appropriate, and no additional benefit of extending therapy beyond 24 hours is seen. A combination of clindamycin and gentamicin to cover aerobic, anaerobic, and gram-negative bacteria in clean–contaminated oncologic surgery is recommended.[77] Topical therapy with clindamycin, amoxicillin–clavulanate, and ticarcillin–clavulanate has been described in small trials, but the exact role of topical antibiotics is not defined.[78] Antimicrobial prophylaxis is not indicated for endoscopic sinus surgery without nasal packing.[36]

Cardiothoracic Surgery

Although cardiac surgery generally is considered a clean procedure, antibiotic prophylaxis lowers SSI incidence.[41] The substantial morbidity related to an SSI in this population, coupled with the routine implementation of prosthetic devices, further justifies the routine use of prophylaxis.[79] Patients who develop SSIs after coronary artery bypass graft surgery have a mortality rate of 22% at 1 year compared with 0.6% for those who do not develop an SSI.[80] Risk factors for developing an SSI after cardiac surgery include obesity, renal insufficiency, connective tissue disease, reexploration for bleeding, and poorly timed administration of antibiotics.[79] Skin flora pathogens predominate; gram-negative organisms are rare.

Cefazolin has been studied extensively and is considered the drug of choice. Although several studies and a meta-analysis advocate the use of second-generation cephalosporins (eg, cefuroxime) rather than cefazolin, various methodologic flaws in these studies have limited the extrapolation of these results to practice. Cefazolin was as effective as cefuroxime in a large randomized trial of 702 patients undergoing open heart surgery and thus remains

the standard of care.[81] Both patient weight and timing of cefazolin administration relative to surgery must be considered when developing a dosing strategy. Patients weighing greater than 80 kg (greater than 176 lb) should receive 2 g cefazolin rather than 1 g. Doses should be administered no earlier than 60 minutes before the first incision and no later than the beginning of induction.[77] Extending therapy beyond 48 hours does not further reduce SSI rates. Single-dose cefazolin therapy may be sufficient but is not recommended by the Society of Thoracic Surgeons at this time pending further study.[82]

7 Routine vancomycin administration may be justified in hospitals having a high incidence of MRSA or when sternal wounds are to be explored surgically for possible mediastinitis. However, a large comparative trial enrolling almost 900 patients in a single center with a high prevalence of MRSA infections found that both cefazolin and vancomycin had similar efficacy in preventing SSI in patients undergoing cardiac surgery that required sternotomy.[83] Mediastinitis constitutes a failure of a prior prophylactic regimen. Continued postoperative vancomycin should be guided by culture and sensitivity data.[37] Subsequent antibiotic therapy is guided by intraoperative findings.

Since *S. aureus* is routinely identified as the most common pathogen in SSIs after cardiac surgery, several studies have investigated alternative methods for preoperative eradication including nasal mupirocin administration (ie, twice daily for 5 days preoperatively) and chlorhexidine body wash (ie, daily preoperatively for up to 5 days). A bundled approach (ie, more than one intervention implemented together) in addition to preoperative antimicrobials appears to further reduce the risk of postoperative SSI in both cardiac and orthopedic surgeries.[11,84]

Pulmonary resection is associated with significant SSI risk, and prophylactic antibiotics have an established role in preventing postoperative infectious morbidity. Pleuropulmonary infections are much more common than wound infections, and pathogenic organisms likely migrate from the oral cavity or pharynx.[85] First-generation cephalosporins are inadequate; 48 hours of cefuroxime is preferred. A regimen of ampicillin–sulbactam is superior to first-generation cephalosporins, but further studies are required before this agent can be recommended as first-line prophylactic therapy.[86]

Vascular Surgery

Vascular surgery, like cardiac surgery, generally is considered clean by NRC criteria. Although vascular graft infections occur infrequently (3%-5%), the

associated morbidity and mortality are extensive because treatment often requires surgical graft removal along with therapeutic antibiotic therapy.[87] Prophylactic antibiotics are of benefit, particularly for procedures involving the abdominal aorta, lower extremities or the implantation of prosthetic devices. Cefazolin is regarded as the drug of choice. Twenty-four hours of prophylaxis with cefazolin is adequate; longer courses may lead to bacterial resistance.[88] For patients with β-lactam allergy, 24 hours of oral ciprofloxacin was effective.[87]

Orthopedic Surgery

Most orthopedic surgery is clean by definition; thus, prophylactic antibiotics generally are indicated only when prosthetic materials (eg, pins, plates, and artificial joints) are implanted.[23] A late-occurring infectious complication in this surgical population can result in substantial morbidity and may lead to prosthesis failure and subsequent removal. Staphylococci species are the most frequently encountered pathogens; gram-negative aerobes are infrequent. The use of cefazolin is supported by substantial evidence in the literature and therefore is the prophylactic agent of choice. Vancomycin, although effective, is not recommended for routine use unless a patient has a documented history of a serious allergy to β-lactams, or the propensity for MRSA infections at a particular institution necessitates its use. The current recommended duration of prophylaxis for joint replacement and hip fracture surgery is 24 hours.[10] Antibiotic-impregnated cement and beads have been used to lower SSI rates, but conclusive data regarding their efficacy are lacking.[23]

Duration of prophylaxis for the surgical repair of long bone fractures depends on the nature of the fracture. Multiple doses of prophylactic antibiotics offer no advantage over a single preoperative dose for repair of closed bone fractures and is more cost effective.[89,90] Patients suffering open (compound) fractures are particularly susceptible to infection because bacterial contamination almost always has occurred already. Under these circumstances, the use of antibiotics is presumptive. In this setting, cefazolin often is combined with an aminoglycoside, but controlled trials are lacking.[91] A clinical trial comparing clindamycin and cloxacillin suggests that clindamycin is superior and may be appropriate as monotherapy for Gustilo type I and II open fractures but not for type III fractures, for which added gram-negative activity is recommended.[92] Duration of antibiotic therapy is highly variable and depends on surgical findings during debridement, results of intraoperative cultures, and clinical status. A prospective trial and subsequent systematic review comparing short (less than 24

hours) and long (greater than 24 hours) courses of antimicrobial prophylaxis for severe trauma suggests that longer courses of antibiotics do not offer additional benefit and may be associated with the development of resistant infections.[93] However, established joint infections and osteomyelitis require an extended course of therapeutic antibiotics.

As in cardiac surgery, there is evidence to support the use of preoperative intranasal mupirocin and chlorhexidine body wash for patients colonized with *S. aureus*. For elective procedures patients would be instructed to administer these at home in the days prior to the surgery. This bundled approach appears to further reduce the risk of postoperative SSI in addition to preoperative antimicrobials.[11,84]

Neurosurgery

The rates of SSI after clean neurosurgical operations (ie, craniotomy, spinal procedures) are low, however, the morbidity and mortality of central nervous system SSI, should they occur, are high. Preoperative antibiotics are effective at reducing SSI rates and are recommended even in clean procedures.[94,95] While many antimicrobials have been studied, a single dose of cefazolin is what is recommended.[10]

Procedures involving cerebrospinal fluid (CSF) shunt placement should be considered separately because this procedure involves placement of a foreign body and is associated with higher infection rates. A study of 780 patients undergoing neurosurgical procedures that included shunt surgery reported that single doses of cefotaxime and trimethoprim–sulfamethoxazole were equally effective in preventing SSIs.[96] Most studies of procedures involving a shunt have been small in size and do not consistently show lower infection rates with antibiotic prophylaxis, although the results of a systematic review and meta-analysis suggest that a significant improvement in the incidence of shunt infection with 24 hours of systemic antibiotics (ie, cefazolin) and the use of antibiotic-impregnated catheters independently.[97]

SSIs associated with spinal surgery are rare but devastating when they occur. The use of antimicrobial prophylaxis in this setting is warranted and recommended.[93] Large randomized, controlled trials are lacking, but cefazolin is the antibiotic recommended most commonly. Cephalosporin penetration into the vertebral disk has been questioned. Some small studies suggest that the addition of gentamicin, which has better penetration, might be warranted; however, there is a paucity of clinical trials comparing these two regimens.[98]

NONPHARMACOLOGIC INTERVENTIONS

Strategies other than antimicrobial and aseptic technique for reducing postoperative infections have been investigated in different types of surgeries. The most commonly cited and practiced interventions include intraoperative maintenance of normothermia, provision of supplemental oxygen in the perioperative period, and aggressive perioperative glucose control. Although interventions to maintain normothermia intraoperatively, provide supplemental oxygen in the perioperative period, and aggressively control perioperative glucose show a significant reduction in SSI, they cannot be generalized to all types of surgeries. However, given the simplicity and low cost of these interventions, many clinicians consider applying these measures outside of the studied population(s).

Core body temperature can fall by 1°C to 1.5°C intraoperatively in patients under general anesthesia. Intraoperative hypothermia has been associated with impaired immune function, decreased blood flow to the surgical site, decreased tissue oxygen tension, and an increased risk of SSI. Efforts to maintain intraoperative normothermia should be exercised and may include the use of warming blankets and IV fluid warmers to maintain core body temperature between 36°C and 38°C. One prospective trial of 200 patients undergoing colorectal surgery found that maintenance of normothermia reduced postoperative infection rates along with other morbidity parameters, including length of stay.[99] CDC guidelines promote maintaining normothermia with strong recommendation based on moderate to high-quality evidence.[4]

Low oxygen tension in the tissues that make up the surgical site increases the risk of bacterial colonization and subsequent SSI by decreasing the efficiency of neutrophil activity. Administration of high concentrations of oxygen (80% via ventilator or 12 L/min via a nonrebreather mask) reduced postoperative infection rates significantly in a multicenter randomized trial of 500 patients undergoing colorectal surgery.[100] Supplemental oxygen during the intraoperative and immediate postoperative periods are recommended even in patients with normal pulmonary function.[4]

Diabetes and poor glucose control are well-known risk factors for SSI. The increased risk of infection is thought to be due to both macrovascular (vasculopathy and venoocclusive disease) and microvascular (subtle immunologic deficiencies, including neutrophil dysfunction and reduced complement and antibody activity) complications. Aggressive control of perioperative blood glucose level decreases the incidence of SSI in diabetics

undergoing cardiac surgery and is being evaluated in other types of surgery and in nondiabetic patients.[101] Perioperative blood glucose levels should be checked in all patients and conventional glucose targets (blood glucose less than 11.1 mmol/L [200 mg/dL]) should be encouraged.[4] Hypoglycemia is similarly associated with poor outcomes and thus blood glucose levels less than 4.1 mmol/L (74 mg/dL) should be avoided.[10]

Prophylactic antibiotics are only effective when therapeutic concentrations in the surgical field are maintained for the entire duration of the surgery. While consideration of drug half-life in the context of the duration of surgery has been discussed earlier in this chapter, other patient-related factors may influence the effectiveness of antibiotic prophylaxis and warrant consideration when choosing a prophylactic regimen (Table 141-7).

TABLE 141-7 Strategies for Implementing an Institutional Program to Ensure Appropriate Use of Antimicrobial Prophylaxis in Surgery

1. **Educate:** Develop an educational program that enforces the importance and rationale of timely antimicrobial prophylaxis. Make this educational program available to all healthcare practitioners involved in the patient's care.
2. **Standardize the ordering process**: Establish a protocol (eg, a preprinted order sheet) that standardizes antibiotic choice according to current published evidence, formulary availability, institutional resistance patterns, and cost.
3. **Standardize the delivery and administration process**: Use system that ensures antibiotics are prepared and delivered to the holding area in a timely fashion. Standardize the administration time to <1 hour preoperatively. Designate responsibility and accountability for antibiotic administration. Provide visible reminders to prescribe/administer prophylactic antibiotics (eg, checklists). Develop a system to remind surgeons/nurses to readminister antibiotics intraoperatively during long procedures.
4. **Provide feedback**: Follow up with regular reports of compliance and infection rates.

Obese patients require larger doses of prophylactic antibiotics to maintain therapeutic drug levels when compared to nonobese patients. Patients with a body mass index greater than 40 kg/m^2 are more likely to have subtherapeutic concentrations at the end of surgery with cefazolin 1 g preoperatively (and intraoperative for surgeries greater than 3 hours) and thus should receive 2 g doses.[102] Underlying disease states that may affect antibiotic metabolism and/or

elimination should be considered when developing a prophylactic regimen. For example, patients with thermal burn and spinal cord injuries eliminate certain classes of antibiotics, primarily the aminoglycosides and β-lactams, at unusually high rates compared with controls and will need more frequent intraoperative dosing. Conversely, individuals with renal failure may need less frequent dosing of renally cleared antibiotics. For example, while intraoperative dosing for cefazolin should be every 3 to 4 hours in patients with normal renal function, this interval should be extended to 8 hours for patients with creatinine clearances of less than 50 mL/min (0.83 mL/s). Individuals who are aggressively fluid resuscitated pre- or intraoperatively or those undergoing cardiac bypass may have altered antibiotic disposition related to increased volume of distribution and reduced total body clearance and may need larger doses (ie, 2 g cefazolin).

EVALUATION OF THERAPEUTIC OUTCOMES

When evaluating the outcome of surgical antibiotic prophylaxis, it is important to differentiate any potential SSI from other postoperative infection or complication. Although fever and leukocytosis are common in the immediate postoperative period, they typically resolve with prompt ambulation, timely removal of invasive devices, prevention and/or resolution of atelectasis through optimal respiratory care, and effective analgesia. It is important to remember that the emergence of distal infections, such as pneumonia, does not constitute a failure of surgical prophylaxis. Prophylaxis should be as short as possible because prolonged prophylactic regimens may contribute to the selection of resistant organisms and may make any infection more difficult to treat.

Surgical site appearance is the most important determinant of the presence of an infection. Drainage of pus from the incision accompanied by redness, warmth, and pain or tenderness is highly suggestive of an SSI. By definition, any surgical site that requires incision and drainage by the surgeon is considered infected regardless of appearance. Failure to heal and wound dehiscence also are seen with SSIs, although the surgical technique and nutritional status may be important contributing factors.

The presentation of signs and symptoms consistent with an SSI in relation to previous surgery is an important consideration when evaluating therapeutic outcomes after surgical prophylaxis. Many SSIs will not be evident during acute hospitalization. In fact, SSIs may not become evident until up to 30 days later or, in the case of prosthesis implantation, up to 1 year later. Thus, the true incidence of SSI can be determined only by completing comprehensive postdischarge

surveillance. All studies investigating the efficacy of surgical prophylaxis must include adequate postdischarge follow-up to be able to thoroughly assess the success of any prophylactic regimen.

Postclass Engaged Learning Activity

Perform a literature search to identify a randomized controlled trial published in the last 12 months that evaluates some aspect of antimicrobial prophylaxis for surgical procedure discussed in this chapter. Write a brief summary of the study methods and major findings. How do the study findings correlate with what you've learned in this chapter? Are the study findings consistent with recommendations in this chapter or do they represent new information that should change practice in some way? How, if at all, would the implementation of these study findings impact the prevalence of surgical site infections?

ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
ASA	American Society of Anesthesiologists
CDC	Centers for Disease Control and Prevention
CSF	cerebrospinal fluid
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-sensitive *Staphylococcus aureus*
NNIS	National Nosocomial Infections Surveillance System
NRC	National Research Council
SENIC	Study on the Efficacy of Nosocomial Infection Control
SSI	surgical site infection
WHO	World Health Organization

REFERENCES

1. Hollingsworth JM, Krein SL, Ye Z, et al. Opening of ambulatory surgery centers and procedure use in elderly patients: Data from Florida. *Arch Surg* 2011;146:187–193.
2. National Hospital Discharge Survey. Available at: ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Datset_Documentation/NHD Accessed October 19, 2015.

3. Alexander JW, Solomkin JS, Edwards MJ. Updated recommendations for control of surgical site infections. *Ann Surg*. 2011;253:1082–1093.
4. Berríos-Torres SI, Umscheid CA, Bratzler DW, et al. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. *JAMA Surg*. Aug 1, 2017;152(8):784–791. 10.1001/jamasurg.2017.0904.28467526.
5. Hendrick TL, Anastacio MM, Sawyer RG. Prevention of surgical site infection. *Expert Rev Anti Infect Ther*. 2006;4:223–233.
6. Kurtz SM, Lau E, Watson H, Schmier JK, Parvizi J. Economic burden of periprosthetic joint infection in the United States. J Arthroplasty. Sep 2012;27(8 Suppl):61–5.e1. 10.1016/j.arth.2012.02.022.22554729.
7. Ban KA, Minei JP, Laronga C, et al. American College of Surgeons and Surgical Infection Society: Surgical Site Infection Guidelines, 2016 Update. J Am Coll Surg. Jan 2017;224(1):59–74. 10.1016/j.jamcollsurg.2016.10.029.27915053.
8. National Academy of Sciences, National Research Council. Postoperative wound infections: The influence ofultraviolet irradiation of the operating room and of various other factors. *Ann Surg*. 1964;160:32–135.
9. Cruse PJE, Foord R. A five-year prospective study of 23,649 surgical wounds. *Arch Surg*. 1973;107:206–210.
10. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm*. 2013;70:195–283.
11. Schweizer ML, Chiang HY, Septimus E, et al. Association of a bundled intervention with surgical site infections among patients undergoing cardiac, hip or knee surgery. *JAMA*. 2015;313:2162–2171.
12. Drapeau CMJ, Pan A, Bellacosa C, et al. Surgical site infections in HIV-infected patients: Results from an Italian prospective multicenter observational study. *Infection*. 2009;37:455–460.
13. Dionigi R, Rovera F, Dionigi G, et al. Risk factors in surgery. *J Chemother*. 2001;13:6–11.
14. Haley RW, Culver DH, Morgan WM, et al. Identifying patients at high risk of surgical wound infection: A simple multivariate index of patient susceptibility and wound contamination. *Am J Epidemiol* 1985;127:206215.
15. Wilson AP, Hodgson B, Liu M, et al. Reduction in wound infection rates by wound surveillance with postdischarge follow-up and feedback. *Br J*

Surg. 2006;93:630–638.

16. NNIS.National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004 issued October 2004. *Am J Infect Control*. 2004;32:470–485.
17. Owens WD, Felts JA, Spitznagel EL. ASA physical status classifications: A study of consistency of ratings. *Anesthesiology*. 1978;49:239–243.
18. Gaynes RP, Culver DH, Horan TC, et al. Surgical site infection (SSI) rates in the United States, 1992-1998: The National Nosocomial Infections Surveillance System basic SSI risk index. *Clin Infect Dis*. 2001;33(Suppl 2):S69–S77.
19. Elek SD, Conen PE. The virulence of *Staphylococcus pyogenes* for man: A study of the problems of wound infection. *Br J Exp Pathol* 1958;38:573–586.
20. Burke JF. Identification of the sources of staphylococci contaminating the surgical wound during operation. *Ann Surg*. 1963;158:898–904.
21. Kaiser AB, Kernodle DS, Parker RA. Low-inoculum model of surgical wound infection. *J Infect Dis*. 1992;166:393–399.
22. Esposito S. Immune system and surgical site infection. *J Chemother*. 2001;13:12–16.
23. De Lalla F. Antibiotic prophylaxis in orthopedic prosthetic surgery. *J Chemother*. 2001;13:48–53.
24. Halwani M, Solaymani-Dodaran M, Grundman H, et al. Cross transmission of nosocomial pathogens in an adult intensive care unit: Incidence and risk factors. *J Hosp Infect*. 2006;63:39–46.
25. Kim DH, Spencer M, Davidson SM, et al. Institutional prescreening for detection and eradication of methicillin-resistant *Staphylococcus aureus* in patients undergoing elective orthopaedic surgery. *J Bone Joint Surg Am*. 2010;92:1820–1826.
26. Munoz P, Burrillo A, Bouza E. Criteria used when initiating antifungal therapy against *Candida* spp. in the intensive care unit. *Int J Antimicrob Agents*. 2000;15:83–90.
27. Davey P, Marwick CA, Scott CL, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. Feb 9, 2017;2:CD003543. 10.1002/14651858.CD003543.pub4.28178770.
28. Sartelli M, Duane TM, Catena F, et al. Antimicrobial Stewardship: A Call to Action for Surgeons. Surg Infect (Larchmt). Dec 2016;17(6):625–631.

10.1089/sur.2016.187.27828764.

29. Classen DC, Evans RS, Pestotnik SL, et al. The timing of prophylactic administration of antibiotics and the risk of surgical wound infection. *N Engl J Med*. 1992;326:281–286.
30. Weber WP, Mujagic E, Zwahlen M, et al. Timing of surgical antimicrobial prophylaxis: a phase 3 randomised controlled trial.. Lancet Infect Dis. Jun 2017;17(6):605–614. 10.1016/S1473-3099(17)30176-7.28385346.
31. Hawn MT, Richman JS, Vicks CC, et al. Timing of surgical antibiotic prophylaxis and the risk of surgical site infection. *JAMA Surg* 2013;148:649657.
32. Zelenitzky SA, Ariano RE, Harding GKM, et al. Antibiotic pharmacodynamics in surgical prophylaxis: An association between intraoperative antibiotic concentrations and efficacy. *Antimicrob Agents Chemother* 2002;46:30263030.
33. Goldman DA, Hopkins CC, Karchmer AW. Cephalothin prophylaxis in cardiac valve surgery: A prospective, double-blind comparison of two-day and six-day regimen. *J Thorac Cardiovasc Surg*. 1977;73:470–479.
34. Cataife G, Weinberg DA, Wong HH, et al. The effect of Surgical Care Improvement Project (SCIP) compliance on surgical site infection (SSI). *Med Care* 2014;52(Suppl 1):S66–S73.
35. Zanetti G, Flanagan HL Jr, Cohn LH, et al. Improvement of intraoperative antibiotic prophylaxis in prolonged cardiac surgery by automated alerts in the operating room. *Infect Control Hosp Epidemiol* 2003;24:79.
36. Weed HG. Antimicrobial prophylaxis in the surgical patient. *Med Clin North Am*. 2003;27:59–75.
37. Salkind AR, Cuddy PG, Foxworth JW. The rational clinical examination: Is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy *JAMA*. 2001;285:2498–2505.
38. Gemmel CG, Edwards DI, Fraise AP, et al. Guidelines for the prophylaxis and treatment of methicillin *Staphylococcus aureus* (MRSA) infections in the UK. *J Antimicrob Chemother*. 2006;57:589–608.
39. Wong RS, Cheng G, Chang NP, et al. Use of cefoperazone still needs a caution for bleeding from induced vitamin K deficiency. *Am J Hematol* 2006;81:76.
40. Frighetto L, Marra CA, Stiver HG, et al. Economic impact of standardized orders for antimicrobial prophylaxis program. *Ann Pharmacother*. 2000;34:154–160.

41. Bratzler DW, Houck PM. Antimicrobial prophylaxis for surgery: An advisory statement from the National Surgical Infection Prevention Project. *Clin Infect Dis*. 2004;38:1706–1715.
42. Lipp A, Lusardi G. Systemic antimicrobial prophylaxis for percutaneous endoscopic gastrostomy. *Cochrane Database Syst Rev* 2013;11:CD005571.
43. Chen X, Brathwaite CE, Barkan A, et al. Optimal cefazolin prophylactic dosing for bariatric surgery: No need for higher doses or intraoperative redosing. Obes Surg. Mar 2017;27(3):626–629. 10.1007/s11695-016-2331-9.27520693.
44. Jewesson PJ, Stiver G, Wai A, et al. Double-blind comparison of cefazolin and ceftizoxime for prophylaxis against infections following elective biliary tract surgery. *Antimicrob Agents Chemother*. 1996;40:70–74.
45. Agrawal CS, Sehgal R, Singh RK, Gupta AK. Antibiotic prophylaxis in elective cholecystectomy: A randomized, double-blinded study comparing ciprofloxacin and cefuroxime. *Ind J Physiol Pharmacol*. 1999;43:501–504.
46. Swoboda S, Oberdorfer K, Klee F, et al. Tissue and serum concentrations of levofloxacin 500 mg administered intravenously or orally for antibiotic prophylaxis in biliary surgery. *J Antimicrob Chemother* 2003;51:459–462.
47. Matsui Y, Satoi S, Hirooka S, Kosaka H, Kawaura T, Kitawaki T. Reappraisal of previously reported meta-analyses on antibiotic prophylaxis for low-risk laparoscopic cholecystectomy: an overview of systematic reviews. BMJ Open. Mar 16, 2018;8(3):e016666. 10.1136/bmjopen-2017-016666.29549197.
48. Gomez-Ospina JC, Zapata-Copete JA, Bejarano M, García-Perdomo HA. Antibiotic Prophylaxis in Elective Laparoscopic Cholecystectomy: a Systematic Review and Network Meta-Analysis. J Gastrointest Surg. Mar 19, 2018. 10.1007/s11605-018-3739-4.29556974.
49. Gulberg V, Deibert P, Ochs A, et al. Prevention of infectious complications after transjugular intrahepatic portosystemic shunt in cirrhotic patients with a single dose of ceftriaxone. *Hepatogastroenterology*. 1999;46:1126–1130.
50. Deibert P, Schwartz S, Olschewski M, et al. Risk factors and prevention of early infection after implantation or revision of transjugular intrahepatic portosystemic shunts: Results of a randomized study. *Dig Dis Sci*. 1998;43:1708–1713.

51. Andersen BR, Kallehave FL, Andersen HK. Antibiotics versus placebo for prevention of postoperative infection after appendicectomy. *Cochrane Database Syst Rev* 2005;3:CD001439.
52. Liberman MA, Greason KL, Frame S, Ragland JJ. Single-dose cefotetan or cefoxitin versus multiple-dose cefoxitin as prophylaxis in patients undergoing appendectomy for acute nonperforated appendicitis. *J Am Coll Surg*. 1995;180:77–80.
53. Colliza S, Rossi S. Antibiotic prophylaxis and treatment of surgical abdominal sepsis. *J Chemother*. 2001;13:193–201.
54. Zmora O, Wexner SD, Hajjar L, et al. Trend in preparation for colorectal surgery: Survey of the members of the American Society of Colon and Rectal Surgeons. *Am Surg*. 2003;69:150–154.
55. Zmora O, Mahajna A, Bar-Zakai B, et al. Colon and rectal surgery without mechanical bowel preparation: A randomized, prospective trial. *Ann Surg*. 2003;237:363–367.
56. Cao F, Li J, Li F. Mechanical bowel preparation for elective colorectal surgery: Updated systematic review and meta-analysis. *Int J Colorectal Dis*. 2012;27:803–810.
57. Dahabreh IJ, Steele DW, Shah N, Trikalinos TA. Oral Mechanical Bowel Preparation for Colo-rectal Surgery. Comparative Effectiveness Review No. 128. Rockville, MD: Agency for Healthcare Research and Quality; April 2014. AHRQ Publication No. 14-EHC018-EF. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed October 19, 2015.
58. Baum ML, Anish DS, Chalmers TC, et al. A survey of clinical trials of antibiotic prophylaxis in colon surgery: Evidence against further use of no-treatment controls. *N Engl J Med* 1981;305:795–799.
59. Nelson RL, Gladman E, Barbateskovic M. Antimicrobial prophylaxis for colorectal surgery. *Cochrane Database Syst* Rev 2014;5:CD001181.
60. Solla JA, Rothenberger DA. Preoperative bowel preparation: A survey of colon and rectal surgeons. *Dis Colon Rectum* 1990;33:154–159.
61. Fujita S, Saito N, Yamada T, et al. Randomized, multicenter trial of antibiotic prophylaxis in elective colorectal surgery: Single dose vs 3 doses of a second-generation cephalosporin without metronidazole and oral antibiotics. *Arch Surg* 2007;142:657–661.
62. Mittelkotter U. Antimicrobial prophylaxis for abdominal surgery: Is there a need for metronidazole? *J Chemother* 2001;13:27–34.

63. Kobayashi M, Mohri Y, Tonouchi H, et al. Randomized clinical trial comparing intravenous antimicrobial prophylaxis alone with oral and intravenous antimicrobial prophylaxis for the prevention of a surgical site infection in colorectal cancer surgery. *Surg Today* 2007;37:383–388.
64. Ghorra SG, Rzeczycki TP, Natarajan R, Pricolo VE. Colostomy closure: Impact of preoperative risk factors on morbidity. *Am Surg* 1999;65:266–269.
65. ASGE Standards of Practice Committee. Antibiotic prophylaxis for GI endoscopy. *Gastrointest Endosc* 2015;81:81–89.
66. Sharma VK, Howden CW. Meta-analysis of randomized, controlled trials of antibiotic prophylaxis before percutaneous endoscopic gastrostomy. *Am J Gastroenterol* 2001;96:1951–1952.
67. Wolf Jr JS, Bennett CJ, Dmochowski RR, Hollenbeck BK, Pearles MS, Schaeffer AJ. Best practice policy statement on urologic surgery antimicrobial prophylaxis. *J Urol* 2008;179:1379–1390.
68. Christiano AP, Hollowell CM, Kim H, et al. Double-blind, randomized comparison of single-dose ciprofloxacin versus intravenous cefazolin in patients undergoing outpatient endourologic surgery. *Urology* 2000;55:182–185.
69. Smaill F, Hofmeyr GJ. Antibiotic prophylaxis for cesarean section. *Cochrane Database Syst Rev* 2002;2:CD000933.
70. Rouzi AA, Khalifa F, Ba'aqeel H, et al. The routine use of cefazolin in cesarean section. *Int J Gynaecol Obstet* 2000;69:107–112.
71. Tita AT, Szychowski JM, Boggess K, Saade G, Longo S, Clark E, Esplin S, Cleary K, Wapner R, Letson K, Owens M, Abramovici A, Ambalavanan N, Cutter G, Andrews W. Adjunctive Azithromycin Prophylaxis for Cesarean Delivery.. N Engl J Med. Sep 29, 2016;375(13):1231–1241. 10.1056/NEJMoa1602044.27682034.
72. Guaschino S, De Santo D, De Seta F. New perspectives in antibiotic prophylaxis for obstetric and gynaecological surgery. *J Hosp Infect* 2002;50(Suppl A):S13–S16.
73. American College of Obstetricians and Gynecologists. Antibiotic prophylaxis for gynecologic procedures. *Obstet Gynecol* 2009;113:1180–1189.
74. Hemsell DL, Johnson ER, Hemsell PG, et al. Cefazolin is inferior to cefotetan as single dose prophylaxis for women undergoing elective total abdominal hysterectomy. *Clin Infect Dis* 1995;20:677–684.

75. Sturlese E, Retto G, Pulia A, et al. Benefits of antibiotic prophylaxis in laparoscopic gynaecological surgery. *Clin Exp Obstet Gynecol* 1999;26:217–218.
76. Meuller SC, Henkel KO, Neumann J, et al. Perioperative antibiotic prophylaxis in maxillofacial surgery: Penetration of clindamycin into various tissues. *J Craniomaxillofac Surg* 1999;27:172–176.
77. Simo R, French G. The use of prophylactic antibiotics in head and neck oncological surgery. *Curr Opin Otolaryngol Head Neck Surg* 2006;14:55–61.
78. Grandis JR, Vickers RM, Rihs JD, et al. Efficacy of topical amoxicillin plus clavulanate–ticarcillin plus clavulanate and clindamycin in contaminated head and neck surgery: Effect of antibiotic spectra and duration of therapy. *J Infect Dis* 1994;170:729–732.
79. Roy MC. Surgical-site infections after coronary artery bypass graft surgery: Discriminating site-specific risk factors to improve prevention efforts. *Infect Control Hosp Epidemiol* 1998;19:229–233.
80. Hollenbeak CS, Murphy DM, Koenig S, et al. The clinical and economic impact of deep chest surgical site infections following coronary artery bypass graft surgery. *Chest* 2000;118:397–402.
81. Curtis JJ, Boley TM, Walls JT, et al. Randomized, prospective comparison of first- and second-generation cephalosporins as infection prophylaxis for cardiac surgery. *Am J Surg* 1993;166:734–737.
82. Edwards FH, Egleman RM, Houck P, et al. The society of thoracic surgeons practice guidelines series: Antibiotic prophylaxis in cardiac surgery, part 1: Duration. *Ann Thorac Surg* 2006;81:397–404.
83. Finkelstein R, Rabino G, Masiah T, et al. Vancomycin versus cefazolin prophylaxis for cardiac surgery in the setting of a high prevalence of methicillin-resistant staphylococcal infections. *J Thorac Cardiovasc Surg* 2002;123:326–332.
84. Schweizer ML, Perencevich E, McDaniel J, et al. Effectiveness of a bundled intervention of decolonization and prophylaxis to decrease Gram positive surgical site infections after cardiac or orthopedic surgery: Systematic review and meta-analysis. *BMJ* 2013;346:f2743.
85. Sok M, Dragas AZ, Erzen J, et al. Sources of pathogens causing pleuropulmonary infections after lung cancer resection. *Eur J Cardiothorac Surg* 2002;22:23–27.
86. Boldt J, Piper S, Uphus D, et al. Preoperative microbiologic screening and

antibiotic prophylaxis in pulmonary resection operations. *Ann Thorac Surg* 1999;68:208–211.

87. Pratesi C, Russo D, Dorigo W, et al. Antibiotic prophylaxis in clean surgery: Vascular surgery. *J Chemother* 2001;13:123–128.
88. Terpstra S, Noorkhoek GT, Voesten HG, et al. Rapid emergence of resistant coagulase-negative staphylococci on the skin after antibiotic prophylaxis. *J Hosp Infect* 1999;43:195–202.
89. Slobogean GP, Kennedy SA, Davidson D, et al. Single- versus multiple-dose antibiotic prophylaxis in the surgical treatment of closed fractures: A meta-analysis. *J Orthop Trauma* 2008;22:264–269.
90. Slobogean PG, O'Brien PJ, Brauer CA. Single-dose versus multiple-dose antibiotic prophylaxis for the surgical treatment of closed fractures: A cost-effective analysis. *Acta Orthop* 2010;81:256–262.
91. Gillespie WJ, Walenkamp G. Antibiotic prophylaxis for surgery for proximal femoral and other closed long bone fractures. *Cochrane Database Syst Rev* 2001;1:CD000244.
92. Vasenius J, Tulikoura I, Vainionpaa S, Rokkanen P. Clindamycin versus cloxacillin in the treatment of 240 open fractures: A randomized, prospective study. *Ann Chir Gynaecol* 1998;87:224–228.
93. Shaffer WO, Baisden JL, Fernand R, Matz PG. An evidence-based clinical guideline for antibiotic prophylaxis in spine surgery. Spine J. Oct 2013;13(10):1387–1392. 10.1016/j.spinee.2013.06.030.23988461.
94. Barker FG II. Efficacy of prophylactic antibiotics against meningitis after craniotomy: A meta-analysis. *Neurosurgery* 2007;60:887–894.
95. Watters WC 3rd, Baisden J, Bono CM, et al. Antibiotic prophylaxis in spine surgery:an evidence-based clinical guideline for the sue of prophylactic antibiotics in spine surgery. *Spine J* 2009;9:142–146.
96. Whitby M, Johnson BC, Atkinson RL, et al. The comparative efficacy of intravenous cefotaxime and trimethoprim/sulfamethoxazole in preventing infection after neurosurgery: A prospective, randomized study. Brisbane Neurosurgical Infection Group. *Br J Neurosurg* 2000;14:13–18.
97. Ratilal B, Costa J, Sampaio C. Antibiotic prophylaxis for surgical introduction of intracranial ventricular shunts: A systematic review. *J Neurosurg Pediatr* 2008;1:48–56.
98. Riley LH 3rd. Prophylactic antibiotics for spine surgery: Description of a regimen and its rationale. *J South Orthop Assoc* 1998;7:212–217.

99. Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. *N Engl J Med* 1996;334:1209–1215.
100. Greif R, Akca O, Horn EP, et al. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. Outcomes Research Group. *N Engl J Med* 2000;342:161–167.
101. Kao LS, Meeks D, Moyer VA, Lally KP. Peri-operative glycaemic control regimens for preventing surgical site infections in adults. *Cochrane Database Syst Rev* 2009;3:CD006806.
102. Ho VP, Nicolau DP, Dakin GF, et al. Cefazolin dosing for surgical prophylaxis in morbidly obese patients. *Surg Infect (Larchmt)* 2012;13:33–37.

142

Vaccines and Immunoglobulins

Mary S. Hayney

KEY CONCEPTS

1. Live vaccines may confer life-long immunity but cannot be administered to immunosuppressed patients.
2. Inactivated and subunit vaccines and toxoids often require multiple doses to protect from infection, and generally booster doses are needed following the primary series.
3. Children less than 2 years of age are unable to mount T-cell–independent immune responses that are elicited by polysaccharide vaccines.
4. Severely immunocompromised individuals should not receive live vaccines, and their responses to inactivated, polysaccharide, toxoid, and recombinant vaccines may be poor.
5. The childhood and adult immunization schedules are updated frequently and published annually. These documents can be used to develop an immunization plan.
6. Immunoglobulin (Ig) provides short-term, rapid postexposure protection from measles, hepatitis A, varicella, and other infections.
7. Ig adverse effects are often secondary to infusion rate. Slowing the IV infusion rate ameliorate chills, nausea, and fever that may develop during administration.
8. Rh_o(D) Ig prevents Rh-negative mothers from mounting an immune response against the Rh(D) antigen on the red blood cells of the fetus that results in hemolytic disease of the newborn.

Preclass Engaged Learning Activity

Use the current childhood immunization schedule to recommend vaccines for the children in the following cases. The current immunization schedule can be found on the CDC's website.

A healthy 2-month-old infant who received hepatitis B vaccine dose #1 at hospital discharge. What vaccines are needed today?

A 4-month-old infant who received no vaccines except hepatitis B vaccine dose #1 at hospital discharge. Devise a vaccine schedule to catch up and to immunize him until age 12 months.

INTRODUCTION

Immunization is defined as rendering a person protected from an infectious agent. Immunity to an infectious agent can be acquired by exposure to the disease, by transfer of antibodies from mother to fetus, through administration of immunoglobulin (Ig), and from vaccination. Immunization is the process of introducing an antigen into the body to induce protection against the infectious agent without causing disease. An *antigen* is a substance that induces an immune response. An *antibody* produced by the humoral arm of the immune system usually is the response that is measured as evidence of successful vaccination. However, cellular immune responses, which are more difficult to measure, are also an important aspect of vaccine responses. This chapter introduces the clinical use of vaccines and immunoglobulins. Agents with a limited use, such as agents for bioterrorism or travel, are beyond the scope of this chapter.

PRODUCTS USED TO IMMUNIZE

1 2 3 Vaccines induce active immunity—that is, immunity generated by a natural immunologic response to an antigen. Vaccines can be live-attenuated or inactivated. Inactivated vaccines may consist of whole or a particle of the pathogen that induces a protective immune response. Live-attenuated vaccines induce an immunologic response more consistent with that occurring with natural infection. Because the organisms in live-attenuated vaccines undergo limited replication in the vaccinated individual after administration, they may confer lifelong immunity with one dose (as does a natural infection). Multiple doses of inactivated vaccines usually are needed to induce long-lasting, effective immunity. Additional doses at varying time intervals (booster doses) often are

required to maintain immunity. Booster doses of such vaccines elicit memory responses from the B cells that produce immunoglobulin G (IgG). The immune system already has developed an array of antibodies to the antigen. Upon restimulation with a booster dose, the B cells, which produce the most specific antibodies against the antigen, are selected and maintained in the "immunologic memory." Thus, the booster dose results in a rapid, intense antibody response that is long lasting. Inactivated vaccines can also differ in immunity potential, depending on their composition. For example, polysaccharide vaccines tend to be poorly immunogenic in infants, whereas protein–polysaccharide conjugated vaccines of the same antigen tend to be highly immunogenic (eg, pneumococcal polysaccharide vaccine vs pneumococcal conjugated vaccine). T-cell–independent immune response is made to polysaccharide antigens that stimulate B cells directly.[1] There is no maturation or booster response with a T-cell–independent immune response, and children younger than 2 years cannot make this type of response. Protein–polysaccharide conjugate vaccines stimulate T cells and promote interactions between T cells and B cells when producing the protective immune responses consisting of immunologic memory and high-affinity IgG.

Toxoids are inactivated bacterial toxins that generally are combined with aluminum salts to enhance their antigenicity by stimulating a strong, but short-lived inflammatory response. These adjuvants also increase local tissue irritation when injected. Toxoids stimulate the production of antibodies against the bacterial toxins rather than the infecting bacterial pathogens.

Immunoglobulins (Igs) are sterile solutions containing antibody derived from human (Ig) sources. Igs are derived from donor pools of blood plasma and are processed using cold ethanol fractionation in order to inactivate known potential pathogens. These products are indicated for induction of passive immunity (temporary immunity to infection as a result of administration of antibodies not produced by the host; see other immunoglobulins below).

In addition to the active component in a vaccine, other active and inert ingredients are often present. Suspending agents, such as water, saline, or complex fluids containing proteins (eg, albumin), are used as the vehicle for the vaccines. Preservatives, stabilizers, and antibiotics may be added to help maintain the integrity of the product. Immunized individuals may respond with allergic reactions not to the agent itself but to the other components of the pharmaceutical preparation. Different manufacturers of the vaccines have different active and inert ingredients or different quantities of these ingredients in their products.

Some vaccines manufactured by different companies are considered interchangeable. Hepatitis A, hepatitis B, and *Haemophilus influenzae* type b (Hib) conjugate vaccines from different manufacturers used for the primary series of three doses are considered interchangeable. It is preferable to use diphtheria, tetanus toxoids, and acellular pertussis (DTaP) vaccine from the same manufacturer to complete the entire primary series. However, immunization should not be delayed if the particular type of vaccine administered for the initial doses cannot be ascertained easily.[1]

FACTORS AFFECTING RESPONSE TO IMMUNIZATION

Various factors are known to affect response to vaccines. Viability of the live antigen is an important factor as discussed previously. Total dose also is important because there seems to exist a threshold dose above which no further increase in immune response is seen. The interval between immunization doses, number of doses given, or both may change immune response to an agent. Among hepatitis B vaccine nonresponders, a significant proportion of individuals mount a vaccine response when given additional doses of vaccine.[2] In contrast, additional doses of influenza vaccine are minimally effective in individuals with chronic illness.[3] Generally, intervals longer than those recommended between vaccine doses do not reduce immune response.[1]

The route and site of administration of the immunobiologic are important. This is best illustrated by the hepatitis B vaccine, which elicits a satisfactory antibody response when given in the deltoid muscle but not a consistent response when administered in the gluteal area. Injections should be administered at a site with little likelihood of site damage. Vaccines containing adjuvants should be given into a muscle mass because they can cause irritation when given subcutaneously or intradermally.[1]

Host factors influence vaccine response. Immunocompromise, increasing age, underlying disease, and genetic background have been associated with poor response rates.[1–4]

VACCINE ADMINISTRATION

Subcutaneous injections should be administered into the thigh of infants and in the upper arm area over the triceps of older children and adults. A ⅝-in., 25-

gauge needle (0.508 mm × 1.6 cm) should be used, taking care not to administer the dose intradermally or intramuscularly (IM). For IM injection, the anterolateral aspect of the upper thigh (infants and toddlers) or the deltoid muscle of the upper arm (children and adults) should be used. When giving an IM injection to an adult weighing less than 60 kg, a ⅝- or 1-in. needle (1.6 cm or 2.5 cm) can be used. If a ⅝-in. needle (1.6 cm) is used, the skin over the injection site must be stretched tight, and the needle must enter the skin at a 90° angle to assure that the needle reaches the muscle. A 1-in. needle (2.5 cm) should be used for adults who weigh 60 to 70 kg. Immunizers can choose either a 1- or 1½-in. needle (2.5 cm or 3.8 cm) for women who weigh 70 to 90 kg and for men who weigh 70 to 118 kg. For women weighing more than 90 kg and men who weigh more than 118 kg, a 1½-in. needle (3.8 cm) must be used.[1] The buttock should not be used because of the potential for inadequate immunologic response and the potential risk of injury to the sciatic nerve. When the buttock must be used (as for large doses of Ig), only the upper outer quadrant should be used with the needle inserted anteriorly. An influenza vaccine for intradermal administration over the deltoid is supplied in an injection device that reliably delivers the vaccine to the intradermal space.[5]

The rotavirus vaccines are administered orally. The tube of vaccine should be squeezed inside the infant's mouth toward the inner cheek until the dosing tube is empty. If the infant regurgitates or spits out the vaccine, readministration is not recommended.[6]

Live-attenuated influenza vaccine is administered intranasally.[5] A specially designed sprayer is inserted just inside the nostril, and the dose is sprayed by rapidly depressing the plunger of the sprayer. The clip is removed from the plunger so that the second half of the dose can be administered into the other nostril. The vaccinated individual should breathe normally. The dose does not need to be repeated if the individual sneezes during or shortly after administration.

Questions often arise concerning the simultaneous administration of vaccines. In general, inactivated and live-attenuated vaccines can be administered simultaneously at separate sites. If two or more inactivated vaccines cannot be administered simultaneously, they can be administered without regard to spacing between doses. Inactivated and live vaccines can be administered simultaneously or, if they cannot be administered simultaneously, at any interval between doses, except for cholera (killed) and yellow fever (live) vaccines, which should be given at least 3 weeks apart. If live vaccines are not administered simultaneously, their administration should be separated by at least 4 weeks.

Live viral vaccines may interfere with purified protein derivative response; thus, tuberculin testing should be postponed for 4 to 6 weeks after administration of live-virus vaccine.[1]

Simultaneous administration of Ig and live-attenuated vaccines may interfere with host antibody response. A dose relationship exists between administration of Ig and inhibition of immune response to a vaccine (**Table 142-1**). Whole blood and other blood products containing antibodies may interfere with the response to the measles, mumps, rubella, and varicella (MMRV) vaccines. In any individual, if vaccination with MMR or varicella is followed by emergency Ig administration, the vaccine can be repeated or seroconversion to viral antigens can be confirmed after sufficient time has elapsed (see Table 142-1). Ig does not interfere with the response to oral vaccines, live-attenuated zoster vaccine, or yellow fever vaccine. Inactivated vaccines and Igs may be administered simultaneously using separate anatomical sites.[1]

TABLE 142-1 Recommended Intervals Between Administration of Immunoglobulin and Measles- or Varicella-Containing Vaccine[a]

Product/Indication	Dose, Including mg Immunoglobulin G(IgG)/kg Body Weight	Recommended Interval Before Measles or Varicella-Containing[b] Vaccine Administration
RSV monoclonal antibody (Synagis®)[c]	15 mg/kg intramuscularly (IM)	None
TIG	250 units (10 mg IgG/kg) IM	3 months
Hepatitis A IG		
Contact prophylaxis	0.02 mL/kg (3.3 mg IgG/kg) IM	3 months
International travel	0.06 mL/kg (10 mg IgG/kg) IM	3 months
HBIG	0.06 mL/kg (10 mg IgG/kg) IM	3 months
RIG	20 IU/kg (22 mg IgG/kg) IM	4 months
Measles prophylaxis IG		
Standard (ie, nonimmunocompromised) contact	0.5 mL/kg (40 mg IgG/kg) IM	6 months
	0.5 mL/kg (80 mg IgG/kg) IM	6 months
Blood transfusion		
RBCs, washed	10 mL/kg negligible IgG/kg IV	None
RBCs, adenine-saline added	10 mL/kg (10 mg IgG/kg) IV	3 months
Packed RBCs (Hct 65%) [0.65][d]	10 mL/kg (60 mg IgG/kg) IV	6 months
Whole blood (Hct 35%–50%)[0.35-0.50][d]	10 mL/kg (80-100 mg IgG/kg) IV	6 months
Plasma/platelet products	10 mL/kg (160 mg IgG/kg) IV	7 months
Cytomegalovirus IV immunoglobulin (IGIV)	150 mg/kg maximum	6 months
IVIG		
Replacement therapy for immune deficiencies[e]	300-400 mg/kg Ivd	8 months
Immune thrombocytopenic purpura treatment	400 mg/kg IV	8 months
Immune thrombocytopenic purpura treatment	1 g/kg IV	10 months
Postexposure varicella prophylaxis[f]	400 mg/kg IV	8 months
Varicella IG	125 units/kg (60-200 mg IgG/kg) IM maximum 625 units	5 months

HBIG, Hepatitis B IG; RBCs, Red blood cells; RIG, Rabies IG; TIG, Tetanus IG.

[a]This table is not intended for determining the correct indications and dosages for using antibody-containing products. Unvaccinated persons might not be fully protected against measles during the entire recommended interval, and additional doses of Ig or measles vaccine might be indicated after measles exposure. Concentrations of measles antibody in an Ig preparation can vary by manufacturer's lot. Rates of antibody clearance after receipt of an Ig preparation also might vary. Recommended intervals are extrapolated from an estimated half-life of 30 days for passively acquired antibody and an observed interference with the immune response to measles vaccine for 5 months after a dose of 80 mg IgG/kg.

[b]Varicella-containing vaccine, as used here, does not include zoster vaccine. Zoster vaccine may be given without regard to antibody-containing blood products.

[c]Contains antibody only to respiratory syncytial virus (RSV).

[d]Assumes a serum IgG concentration of 16 mg/mL (g/L).

[e]Measles and varicella vaccinations are recommended for children with asymptomatic or mildly symptomatic human immunodeficiency virus (HIV) infection but are contraindicated for persons with severe immunosuppression from HIV or any other immunosuppressive disorder.

[f]The investigational product VariZIG, similar to licensed VZIG, is a purified human Ig preparation made from plasma-containing high levels of anti-varicella antibodies (immunoglobulin class G [IgG]). The interval between VariZIG and varicella vaccine is 5 months.

VACCINE STORAGE

Appropriate storage is critical to maintaining the integrity of vaccines because improperly stored vaccines can fail to protect the individuals to whom they are administered. Refrigerator temperature is defined as between 2°C and 8°C (36°F to 46°F) and freezer temperature as –50°C (–58°F) to –15°C (5°F). Inactivated vaccines are stored refrigerated. Varicella and live zoster vaccines must be stored frozen. MMR vaccine can be stored in either the freezer or refrigerator. Live-attenuated influenza vaccine is stored in the refrigerator. Specific storage conditions for individual vaccines can be found in the package insert.

IMMUNIZATION OF SPECIAL POPULATIONS

Groups of individuals may have precautions to vaccines. Many precautions are temporary, and vaccines can be administered later.

Infants

The age of the recipient is an important determining factor in vaccine response. In the first few months of life, passively transferred maternal antibodies acquired during the third trimester of gestation protect an infant. However, the maternal antibodies also inhibit the immune response to live vaccines because the circulating antibodies neutralize the vaccine before the infant has the opportunity to mount an immune response. For this reason, measles, mumps, rubella, and varicella vaccines are not administered until maternal antibodies have waned, generally by infant age 12 months.

Premature infants should be vaccinated at the same chronologic age using the same schedule and precautions for full-term infants. The full recommended doses of vaccines should be used, regardless of age or birth weight. Breastfed infants should be vaccinated according to standard pediatric schedules.

Pregnant Women and Postpartum Immunization

The benefit of most vaccines outweighs the risk for administration to pregnant females. As with most drugs, a lack of information regarding risks to the fetus exists rather than any actual known risk.[1] For example, no cases of congenital rubella syndrome from inadvertent administration of rubella vaccine to a

pregnant woman have ever been reported. Universal influenza immunization is recommended for women who will be or are pregnant during influenza season. Pregnant women should receive Tdap during the late second trimester or third trimester of pregnancy. Although live vaccines generally are avoided because of the theoretical risk of transmission of the vaccine organism to the fetus, inactivated vaccines may be administered to pregnant women when the benefits outweigh the risks.[1] Hepatitis B, hepatitis A, meningococcal, and inactivated polio vaccines should be administered to pregnant females if they are otherwise indicated. Insufficient evidence is available for the human papillomavirus (HPV) series during pregnancy, so it should be deferred.[1]

Administration of live vaccines, such as rubella or varicella, are deferred until pregnancy is completed and are routinely recommended for new mothers who do not have evidence of immunity prior to hospital discharge. These live vaccines can be administered without regard to administration of Rh_0(D) Ig in the postpartum period. Additionally, Tdap is recommended for all new mothers who have not received a Tdap before because household contacts are frequently implicated as the source of pertussis infection in a young infant.[7,8]

Immunocompromised Hosts

4 Immunization of individuals with chronic disease, such as immunocompromise, diabetes or connective tissue disease, alcoholism, or those with cancer or HIV disease, must be individualized based on the disease state and its treatment. In general, severely immunocompromised individuals should not receive live vaccines. Administration of other vaccines may be indicated, but responses may be lower than those mounted by healthy individuals, but may still confer protection.[6]

Patients with chronic pulmonary, renal, hepatic, or metabolic disease who are not receiving immunosuppressants can receive both live-attenuated and killed vaccines and toxoids to induce active immunity. These patients often need higher doses of vaccines or more frequent dosing to induce immunity. Generally, immunization should be considered early in the course of the disease in an attempt to induce immunity at a point when the disease is less severe.

Patients with active malignant disease can receive killed vaccines or toxoids but should not be given live vaccines. The MMR vaccine is not contraindicated for close contacts, however. Live-virus vaccines can be administered to persons with leukemia who have not received chemotherapy for at least 3 months. Vaccines should be timed so that they do not coincide with the start of

chemotherapy or radiation therapy.[3] Annual influenza vaccine should be administered 2 weeks prior to chemotherapy or between cycles.[3] If vaccines cannot be given at least 2 weeks before the start of these therapies, immunization should be postponed until 3 months after the therapy has been completed. Passive immunization with Ig can be used in place of active immunization regardless of the history of immunization.

Glucocorticoids may cause suppressed responses to vaccines. For the purposes of immunization, the immunosuppressing dose of corticosteroids is prednisone 20 mg or more daily or 2 mg/kg daily, or an equivalent dose of another steroid, for at least 2 weeks. Patients receiving long-term, alternate-day steroid therapy with short-acting agents, administration of maintenance physiologic doses of steroids (eg, 5-10 mg/day of prednisone) topical, aerosol, intra-articular, bursal, or tendon steroid injections require no special consideration for immunization. If patients have been receiving high-dose corticosteroids or have had a course lasting longer than 2 weeks, then at least 1 month should pass before immunization with live-virus vaccines.[1]

Patients with HIV infection require special consideration. Responses to live and inactivated vaccines generally are suboptimal and decrease as the disease progresses because HIV produces defects in cell-mediated and humoral immunity. The routinely recommended vaccines should be administered to children. MMR should be administered to anyone older than 12 months of age without evidence of immunity and who are not severely immunocompromised (CD4% greater than 15% [or CD4 fraction >0.15]and CD4 count greater than 200 lymphocytes/mm^3 [0.2×10^9/L] for at least 6 months).[9] Two doses of varicella vaccine separated by 3 months are recommended for those with no evidence of immunosuppression. Adults should receive routinely recommended vaccines. Zoster vaccine may be administered to individuals with HIV infection who do not have clinical manifestations of AIDS and have CD4 counts greater than 200/mm^3 (0.2×10^9/L).[1]

Solid Organ Transplant Patients

Organ transplantation has become routine treatment of end-stage organ disease of many causes. Solid organ transplant patients remain on immunosuppressive regimens for the rest of their lives. These immunosuppressive regimens result in a higher risk of infection and decrease the protection conferred by immunization.[10]

Whenever possible, transplant patients should be immunized prior to

transplantation. Live vaccines generally are not given after transplantation. Posttransplantation diphtheria, tetanus, pneumococcal, and influenza vaccine responses are unpredictable. Decreased immune response has been documented following hepatitis B vaccine.

Hematopoietic Stem Cell Transplant Patients

Reimmunization of patients with hematopoietic stem cell transplantation is necessary because antibody concentrations wane rapidly. Annual influenza immunization may begin as soon as 6 months after successful engraftment. Reimmunization with inactivated vaccines should begin approximately 6 months after hematopoietic stem cell transplantation. Hematopoietic stem cell transplant recipients are at increased risk for fulminant infection with encapsulated bacteria, so 13-valent pneumococcal vaccine (PCV13), the 23-valent pneumococcal polysaccharide vaccine (PPSV23), meningococcal vaccines, and Hib vaccines are recommended. MMR vaccine (MMR) can be administered at 24 months. Varicella vaccine is not routinely recommended but can be considered on a case-by-case basis. Immunization of household contacts and healthcare workers also is necessary.[1,11]

CONTRAINDICATIONS AND PRECAUTIONS

There are few contraindications to the use of vaccines except those outlined earlier. The contraindications include a history of anaphylactic reactions to the vaccine or a component of the vaccine. Unexplained encephalopathy occurring within 7 days of a dose of pertussis vaccine is a contraindication to future doses of pertussis vaccines. Immunosuppression and pregnancy are temporary contraindications to live vaccines. An interval of time must elapse based on the dose of Ig before a live vaccine can be administered (see Table 142-1). Precautions for DTaP administration include hypotonic hyporesponsive episode, fever of 40.5°C (104.9°F) or greater, crying lasting more than 3 hours within 48 hours of a previous dose, and seizures with or without fever within 3 days after a dose. A personal or family history of seizures is a precaution for receiving the combination MMR–varicella (MMRV) vaccine. Immunizers should use MMR and varicella vaccines separately.[1] Generally, mild-to-moderate local reactions, mild acute illnesses, concurrent antibiotic use, prematurity, family history of adverse events, diarrhea, and lactation or breastfeeding are not contraindications to immunization.

OBTAINING AN IMMUNIZATION HISTORY

An immunization history should be obtained from every patient, regardless of the reason for the healthcare visit. Ideally, any history provided by the patient from memory should be verified by reviewing the patient's personal written immunization record or a database that contains the complete immunization history. State-based or other public health jurisdiction-based immunization information systems, also called immunization registries, have been developed to improve immunization coverage by allowing healthcare providers access to records at any contact with the healthcare system. Registries are aimed primarily at facilitation of childhood immunization records.[10] If an official written record is not available, patient characteristics (eg, military service, travel history, and occupation) may provide clues to the immunization history. Serologic testing for immunity against certain diseases can provide specific information but is used routinely for only a few selected diseases (eg, measles, rubella, hepatitis A and B, and varicella) and selected circumstances (eg, employment in a healthcare facility). If a written record does not exist, one should be generated at the time of initiation of immunization. Patients without a written record should be considered susceptible, and an immunization program started and completed unless a serious adverse reaction occurs. As a general rule, the risks associated with overimmunization are minimal relative to the risks associated with contracting vaccine-preventable diseases.[1]

Every healthcare visit, regardless of its purpose, should be viewed as an opportunity to review a patient's immunization status and to administer needed vaccines. Immunization is perhaps the most cost-effective health intervention available. Each visit should include assessment of individuals' vaccine needs, administration of indicated vaccines, and documentation of immunization histories. The outcome measurement of what percentage of patients in a particular practice site is completely immunized is extremely important because the benefits of optimal vaccine use extend beyond the individual patient to the public as a whole.

NATIONAL VACCINE INJURY COMPENSATION PROGRAM

The National Childhood Vaccine Injury Act of 1986 was passed by the US Congress in response to reports of vaccine side effects and liability concerns of

vaccine manufacturers and healthcare providers. The National Vaccine Injury Compensation Program offers a no-fault alternative means to compensate individuals for injury following vaccination. The program offers liability protection to manufacturers and an efficient means of recovering damages for individuals potentially injured by vaccines. The types of vaccine-related injuries that are considered for compensation are outlined in the Health Resources and Services Administration's Vaccine Injury Table (https://vaers.hhs.gov/docs/VAERS_Table_of_Reportable_Events_Following_Va Healthcare providers must report all events requiring medical attention within 30 days of vaccination to the Vaccine Adverse Event Reporting System (VAERS), which serves as a central depot for vaccine-related adverse effects. Only a temporal association between the adverse event and vaccine administration is required. No adverse event rates can be determined because only the number of adverse events reported is known; the number of vaccines administered is not known. This database can be used to survey for changes in the frequencies of adverse events, to evaluate risk factors for adverse events, and to find rare adverse events.[11] VAERS report forms can be obtained by calling 1-800-822-7967, or reports can be made online at https://vaers.hhs.gov/reportevent.html.

USE OF VACCINES

The Advisory Committee on Immunization Practices (ACIP) makes recommendations for use of vaccines for the United States. Other professional organizations, for example, the American Academy of Pediatrics, the American Academy of Family Physicians, or the American College of Obstetrics and Gynecology, publish guidelines. Usually, these guidelines are the same as those issued by the ACIP or the groups try to reconcile their recommendations.

5 The latest vaccine schedules can be found at https://www.cdc.gov/vaccines/schedules/hcp/index.html. All states require children to be fully immunized prior to entering elementary school; however, optimal protection is achieved by immunizing at the recommended ages, which requires special attention to children younger than 2 years. Adults and adolescents also require vaccination and often are unaware of this need. An early adolescent preventive health visit at age 11 to 12 years is recommended. This visit is an opportunity to catch up on missed immunizations and to administer meningococcal conjugate, Tdap, and HPV vaccines. Additionally, another visit at age 16 is recommended during which time the second meningococcal conjugate vaccine can be administered and a discussion regarding the need for

meningococcal serogroup B vaccine series can occur. All individuals older than 6 months of age should receive an annual seasonal influenza vaccine. Adults should receive routine tetanus–diphtheria (Td) or Tdap boosters and be immune to measles, mumps, rubella, and varicella by either immunization or history of infection. Adults need zoster vaccine after age 50 years, and pneumococcal vaccines after age 65 years. Certain individuals with conditions or lifestyles that put them at high risk for vaccine-preventable diseases also should be immunized as described in the following text and outlined in the immunization schedules in the appendices.

VACCINES

Diphtheria Toxoid Adsorbed

Diphtheria is an acute illness caused by the toxin released by a *Corynebacterium diphtheriae* infection. The toxin inhibits cellular protein synthesis, and membranes form on mucosal surfaces. Systemic toxemia can result in myocarditis, neuritis, and thrombocytopenia. Membrane formation can cause respiratory obstruction, and significant toxin absorption can lead to severe illness and death.

Diphtheria toxoid adsorbed is a sterile suspension of modified toxins of *C. diphtheriae* that induces immunity against the exotoxin of this organism. Two strengths of diphtheria toxoid are available in the United States: pediatric strength (D) and adult strength (d), which contains less antigen. The widespread use of diphtheria toxoid essentially has eliminated diphtheria from the United States.

Primary immunization with diphtheria toxoid (D) is indicated for children older than 6 weeks. The toxoid is given in combination with tetanus toxoid and acellular pertussis vaccine (as DTaP or in combination with additional childhood vaccines that have been licensed to decrease the number of injections required to complete the childhood immunization recommendations) at age 2, 4, and 6 months. Additional doses are given at age 15 to 18 months and again at age 4 to 6 years.[12] Booster doses should be given every 10 years.

For unimmunized adults, a complete three-dose series of diphtheria toxoid should be administered, with the first two doses given at least 4 weeks apart and the third dose given 6 to 12 months after the second. One of the vaccine doses in this series should be Tdap. The combined Td preparation is used for adults because it contains less diphtheria toxoid than the pediatric dose and is

associated with fewer reactions to the diphtheria component. All adults should receive booster doses of Td every 10 years.[12] Adverse effects of diphtheria toxoid include mild-to-moderate tenderness, erythema, and induration at the injection site. Systemic reactions occur very rarely.

Haemophilus Influenzae Type b Vaccines

Before 1995, Hib was responsible for thousands of cases of serious illnesses (eg, meningitis, epiglottitis, pneumonia, sepsis, and septic arthritis). The incidence of Hib disease has declined more than 99% since the introduction of the conjugate vaccines based on the organism's capsular substance, polyribosylribitol phosphate (PRP).[15]

The Hib vaccines are conjugate products consisting of either a polysaccharide or an oligosaccharide of PRP covalently linked to a protein carrier. The protein carrier is important because it provides for T-lymphocyte–dependent immunologic response, whereas earlier Hib vaccines that consisted of only unconjugated PRP elicited a response that was T-cell independent. T-cell involvement in the response provides for (a) a greater antibody response regardless of the age of the patient receiving the vaccine, (b) immunologic response at an earlier age (including infants), and (c) a booster effect on subsequent exposure to the Hib capsule, whether through revaccination or natural exposure. The protein carrier is not considered a vaccine and should not be substituted for immunization against tetanus, diphtheria, or *Neisseria meningitidis.*

Hib conjugate vaccines are indicated for routine use in all infants and children younger than 5 years. Multiple products in various combinations are available for use in infants and children of different ages. The primary series of Hib vaccination consists of a 0.5-mL IM dose at ages 2, 4, and 6 months. If Hib PRP-OMP (outer membrane protein of *Neisseria meningitides* as the protein conjugate) is being used, the primary series consists of doses given at ages 2 and 4 months. The series should not be initiated in an infant younger than 6 weeks. Although use of one product for the entire primary series is desirable, adequate protection is achieved even when different products are used during the initial series. Following the primary series, a booster dose is recommended at age 12 to 15 months. Any of the Hib conjugate vaccines are suitable for the booster dose regardless of which conjugate was used for the primary series of doses.[13]

Schedules are more complex for infants who do not begin Hib immunization at the recommended age or who have fallen behind in the immunization

schedule. For infants 7 to 11 months of age who have not been vaccinated, three doses of Hib vaccine should be given: two doses spaced 4 weeks apart and then a booster dose at age 12 to 15 months (but at least 8 weeks since the second dose). For unvaccinated children ages 12 to 14 months, two doses should be given, with an interval of 2 months between doses. In a child older than 15 months, a single dose of any of the vaccine preparations is indicated.[13]

Vaccines for Hib are recommended for routine use only for children up to age 59 months; beyond this age, the incidence of invasive Hib disease is very low. Patients with certain underlying conditions (eg, children with HIV infection, sickle cell disease, splenectomy, and hematopoietic stem cell transplants and young children receiving chemotherapy for malignancies) are at higher than normal risk for Hib infection, and use of at least one dose of vaccine in these patients should be considered.[14] Adverse reactions to the Hib vaccine are uncommon. Erythema and induration at the injection site occur in approximately 5% to 30% of children and resolve within 12 to 24 hours. Fever, diarrhea, and vomiting are reported occasionally.[14]

Hepatitis Vaccines

Information on vaccination for viral hepatitis is given in Chapter 57.

Human Papillomavirus Vaccine

HPV infections are the most common sexually transmitted infections, with the highest prevalence of infection in sexually active young adults. Although more than 120 different HPV types have been identified, at least 40 different types of HPV infect the anogenital tract. These 40 different viruses are grouped into low-risk and high-risk types. Low-risk types can cause genital warts and mild abnormalities on Papanicolaou (Pap) tests. Ninety percent of all cases of genital warts and the majority of respiratory papillomatosis are caused by types 6 and 11. As many as 18 types are considered high risk as they have the ability to penetrate the nucleus of an epithelial cell to transform it to a precancerous cell. They cause abnormal Pap test results and may lead to cancer of the cervix, vulva, vagina, anus, penis, or oropharynx. Types 16 and 18 cause about 70% of all cervical cancers. Another 10% of HPV-related cancers are caused by types 31, 33, 45, 52, and 58. Men who have sex with men (MSM) are at a higher risk for infection with HPV, genital warts, and anal cancer.[15] The incidence of cancers associated with HPV is higher among MSM, and the rate of anal cancer

among MSM continues to rise. High-risk HPV infections are necessary but not sufficient for the development of cervical cancer and for the majority of other anogenital and oral squamous cell cancers.

A 9-valent HPV vaccine against types 6 and 11 and 16, 18, 31, 33, 45, 52, and 58 is licensed for the prevention of HPV. ACIP recommends HPV vaccine for the prevention of HPV-related disease in individuals aged 9 to 26 years. Individuals who start the HPV series between the ages of 9 and 14 years should receive two doses separated by 6 months. This vaccine is administered as a three-dose series using a schedule of 0, 1 to 2, and 6 months for individuals who start the series at age 15 years or older. The vaccines are recommended for adolescents aged 11 to 12 years and catch-up immunization for individuals aged 13 to 26 years. The ACIP recommended shared clinical decision-making for HPV vaccine for individuals aged 27 to 45 years.[15,16]

The vaccine is well tolerated, with injection-site reactions and systemic reactions (eg, headache and fatigue) occurring as commonly in immunized individuals as in the groups receiving placebo. Although syncope is possible with any immunization, the target population of adolescents and young adults has a higher incidence of syncope, including with administration of the HPV vaccine.[15]

The effective vaccine is an important advance, but the need for a Pap test for cervical cancer screening remains. Surveillance for the duration of protection conferred by the vaccine series is ongoing; the need for future booster doses is not yet known.

Influenza Virus Vaccine

Information on vaccination for influenza is given in Chapter 127.

Measles Vaccine

Measles (rubeola) is a highly contagious viral illness characterized by rash and high fever. Complications of measles infections include severe diarrhea, otitis media, pneumonia, and encephalitis. Measles results in one to two deaths per 1,000 cases, with a much higher death rate in developing countries. With widespread vaccination, measles is on the verge of elimination from the Western Hemisphere.

The measles vaccine is a live-attenuated viral vaccine that produces a subclinical, noncommunicable infection. Approximately 95% of vaccine

recipients mount a protective immune response after a single dose, and most individuals are protected for life.[9] Most persons who do not respond to the first dose of measles vaccine will respond after receiving a second dose, and this forms the basis for the two-dose vaccine strategy that was implemented in the United States in 1989.

The measles vaccine is administered subcutaneously as a 0.5-mL dose in the arm (or in the thigh if the patient is younger than 15 months). The vaccine is administered routinely for primary immunization to persons 12 to 15 months of age. Two combinations of measles containing vaccines are available: measles, mumps, rubella (MMR) or measles, mumps, rubella, varicella (MMRV). The measles vaccine is not administered earlier than 12 months (except in certain outbreak circumstances or for travel) because persisting maternal antibody that was acquired transplacentally late in gestation can neutralize the vaccine virus before the vaccinated person can mount an immune response. A second dose of measles-containing vaccine is recommended when children are 4 to 6 years old.[9] The second dose of vaccine results in seroconversion in 95% of individuals who were first-dose nonresponders.

Measles-containing vaccine should not be given to pregnant women or immunosuppressed patients. An exception is HIV-infected patients, who are at very high risk for severe complications if they develop measles. Adults with HIV infection who have no evidence of measles immunity should be immunized as long as they are not severely immunocompromised (CD4 greater than 200 lymphocytes/mm^3 [0.2×10^9/L] for at least 6 months). The second dose should be given 1 month later.[8] Children with HIV who are not severely immunocompromised can be immunized according to the childhood immunization schedule at 12 months and 4 to 6 years of age.[9]

Recent administration of Ig interferes with measles vaccine response, so the recommended interval between the Ig and vaccine is determined by the dose of Ig (see Table 142-1).[1] Live vaccines not administered during the same visit must be delayed for at least 30 days following measles or MMR vaccine.[1]

Measles vaccine is indicated in all persons born after 1956 or in those who lack documentation of wild-virus infection by either history or antibody titers. Two doses of a measles-containing vaccine separated by at least one month are required for children, college students, and healthcare workers who were born in 1957 or later.[9]

The measles vaccine has an excellent safety record. The most common side effect following vaccination is fever, which occurs in 5% to 15% of vaccinees. Transient generalized rash may occur in approximately 5% of vaccine recipients.

These reactions generally appear 5 to 12 days postvaccination and last 2 to 5 days. Other adverse effects, such as headache, cough, sore throat, eye pain, malaise, and transient thrombocytopenia, occur less frequently.[9]

Meningococcal Vaccines

N. meningitidis is a leading cause of meningitis and sepsis in children and young adults in the United States. Five serotypes, A, B, C, W-135, and Y, cause almost all infections in humans. The infection is transmitted by respiratory droplets from infected individuals and asymptomatic carriers. Symptoms include severe headache, sensitivity to light, stiff neck, nausea and vomiting, and high fever. Mortality occurs in 24 to 48 hours following onset of symptoms in 10% to 13% of infected individuals.[33] Immunization is recommended for high-risk populations, such as those exposed to the infection, those in the midst of uncontrolled outbreaks, travelers to areas with epidemic or hyperendemic meningococcal disease, and individuals who have terminal complement component deficiencies or asplenia.

MenACWY Conjugate

Two meningococcal conjugate vaccines combining the same serotypes are licensed for use in individuals aged 9 months to 55 years old (Menactra®, Sanofi-Pasteur) or 2 months to 55 years old (Menveo®, Novartis).

The meningococcal conjugate vaccine is recommended for adolescents at ages 11 to 12 years with a second dose at age 16 years. Reimmunization at 5-year interval is recommended for individuals who are at high risk.[34]

Injection-site reactions are the most common adverse effects following administration of either the meningococcal conjugate or polysaccharide vaccine.

MenB vaccines

Meningococcal serogroup B (MenB) vaccines use other antigens from the bacterial capsule, specifically factor H binding protein, Neisseria adhesin A, neisserial heparin binding antigen, and outer membrane vesicles. Two MenB vaccines have been licensed for the prevention of invasive disease caused by *N. meningitidis* serogroup B for individuals aged 10 to 25 years. The ACIP recommends either of the two MenB vaccines, Trumenba® and Bexsero®, for individuals at high risk for invasive meningococcal disease.[17] Additionally, MenB vaccine use is acceptable for adolescents and young adults. Trumenba®

requires two or three dose series administered at 0 and 6 months or 0, 2, and 6 month intervals. (The 3-dose series should be used for high-risk individuals and during an outbreak.) Bexsero® requires two doses with at least one month between doses. Both vaccines were licensed based upon antibody response studies.[17] The most common adverse events after MenB vaccines are pain at the injection site, fatigue, headache, myalgia, and chills.

Mumps Vaccine

Mumps is a viral illness that classically causes bilateral parotitis 16 to 18 days after exposure. Fever, headache, malaise, myalgia, and anorexia may precede the parotitis. Serious complications are rare but more common in adults.

The mumps vaccine is a lyophilized live-attenuated vaccine. The vaccine is available in combinations with measles, rubella (as MMR), and varicella (MMRV) vaccines.

The vaccine is administered as a 0.5-mL subcutaneous injection in the upper arm. Dosing recommendations coincide with those for measles vaccine, with the first dose administered at age 12 to 15 months and the second dose prior to the child's entry into elementary school. Two doses of mumps-containing vaccine are recommended for school-aged children, international travelers, students in post–high school educational institutions, and healthcare workers born after 1956.[18] A single dose of vaccine is acceptable documentation of immunity to mumps for other adults considered at lower risk of mumps infection, including adults born after 1956 and those with an uncertain history of wild-virus infection. Mumps vaccine should not be given to pregnant women or immunosuppressed patients.[1] A third dose of mumps vaccine should be considered for individuals at risk for infection during an outbreak.[18]

Serious adverse reactions to the vaccine are reported rarely. Fever, parotitis, rash, and lymphadenopathy occur rarely. Local reactions, including soreness, burning, and stinging, may occur at the injection site.[9]

Pertussis Vaccine

Pertussis is caused by a bacterial infection with *Bordetella pertussis*. The infection starts with signs and symptoms of an acute respiratory infection, called the catarrhal stage. The coughing spells manifest about a week later. Typically, young children will have the characteristic whoop as they struggle to inhale while coughing. Adolescents and adults are more likely to have prolonged

periods of coughing. Pertussis can affect any age group, but young infants are at much higher risk for pneumonia, seizures, brain damage, and death. Their rate of hospitalization is much higher than for other age groups. The individual is contagious during the catarrhal stage and the first two weeks of the cough.[19]

Acellular pertussis vaccines contain components of the *B. pertussis* organism. All acellular vaccines contain pertussis toxin, and some contain one or more additional bacterial components (eg, filamentous hemagglutinin, pertactin, and fimbriae types 2 and 3). Acellular pertussis vaccine is recommended for all doses of the pertussis schedule at 2, 4, 6, and 15 to 18 months of age. A fifth dose of pertussis vaccine is given to children 4 to 6 years of age.[20] Pertussis vaccine is administered in combination with diphtheria and tetanus (DTaP). Administration of an acellular pertussis-containing vaccine (Tdap) is also recommended for adolescents once between ages 11 and 18 years and a single dose of Tdap should be administered to all adults.[19] Special attention is warranted for the immunization of individuals who have close contact with young infants. Tdap should be administered to females in their late second or third trimester of pregnancy. Tdap should also be administered to all close contacts, including household contacts and out of home care providers.[8,21]

Local administration site reactions are relatively common. Systemic reactions, such as moderate fever, occur in 3% to 5% of vaccinees. Rarely, high fever, febrile seizures, persistent crying spells, and hypotonic hyporesponsive episodes occur following vaccination. Encephalopathy without known cause within 7 days of a pertussis vaccine are contraindications to future doses of this vaccine.[1]

Pneumococcal Vaccines

Streptococcus pneumoniae is a common pathogen with a range of manifestations, including asymptomatic upper respiratory tract colonization, sinusitis, acute otitis media, pharyngitis, pneumonia, meningitis, and bacteremia. Rates of invasive infections are highest in children younger than 2 years and in the elderly.[22,23] Invasive pneumococcal infections cause approximately 40,000 deaths annually. Most of the deaths occur in the elderly or in those with underlying medical conditions. Approximately half the deaths could be preventable by vaccine. Two pneumococcal vaccine preparations, PCV13 and 23-valent pneumococcal polysaccharide vaccine (PPSV23) are available. The vaccines have different indications and are not interchangeable.

Pneumococcal Polysaccharide Vaccine

Pneumococcal polysaccharide vaccine (Pneumovax 23) is a mixture of highly purified capsular polysaccharides from 23 of the most prevalent or invasive types of *S. pneumoniae* seen in the United States. Serotypes included are 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F. These 23 types represent 85% to 90% of all blood isolates and 85% of pneumococcal isolates from other generally sterile sites seen in the United States. The vaccine is administered IM or subcutaneously as a single 0.5-mL dose.

PPSV23 is recommended for the following individuals:[24]

1. Persons 65 years and older (if an individual received vaccine more than 5 years earlier and was younger than 65 years at the time of administration, revaccination should be given).
2. Persons aged 2 to 64 years with a chronic illness (congestive heart failure, cardiomyopathy, chronic pulmonary disease, diabetes, alcoholism, and liver disease).
3. Persons aged 2 to 64 years with functional or anatomic asplenia (when splenectomy is planned, PPSV23 should be given at least 2 weeks before surgery; a single revaccination is recommended at 5 years in subjects older than 10 years and at 3 years in subjects younger than 10 years).
4. Persons aged 19 to 64 years who smoke cigarettes or have asthma.
5. Persons with cochlear implants.

PPSV23 is recommended for immunocompromised persons 2 years and older with (a) HIV infection, (b) leukemia, (c) lymphoma, (d) Hodgkin disease, (e) multiple myeloma, (f) generalized malignancy, (g) chronic renal failure or nephrotic syndrome, (h) patients receiving immunosuppressive therapy including corticosteroids, and (i) organ and bone marrow transplant recipients. A single revaccination should be given if 5 years or more have passed since the first dose in subjects older than 10 years. In subjects 10 years of age and younger, revaccination should be given 3 years after the previous dose.

PPSV23 induces type-specific antibodies (T-cell-independent mechanisms) with a twofold rise within 2 to 3 weeks in 80% of young healthy adults. No correlation of antibody levels and protection has been determined. Antibody levels to these strains remain elevated for at least 5 years. In certain individuals, these levels decline within 10 years. Children may be protected for only 3 to 5

years. Elderly individuals and patients with chronic disease may have lower antibody levels produced with the vaccine. Children younger than 2 years do not respond adequately to the vaccine.

A number of other groups, including immunocompromised patients (eg, leukemia, lymphoma, and multiple myeloma), dialysis patients, and patients with acquired immune deficiency syndrome, have reduced antibody production with the vaccine. Asymptomatic HIV-infected patients respond sufficiently to the vaccine. Patients with Hodgkin disease respond to the vaccine better before splenectomy, chemotherapy, or radiation therapy.

PPSV23 vaccine efficacy has been debated in the literature. Study results generally point to a reduction in invasive pneumococcal disease in the general population and in the elderly. In immunosuppressed populations, the reduction in invasive disease is estimated at 50% to 80% with immunization.[25] Adults hospitalized with community-acquired pneumonia are significantly less likely to die if they have been immunized. In addition, immunized patients were less likely to have respiratory failure and had hospitalization stays that were shorter by 2 days.[26]

PPSV23 safety is well documented. Local reactions occur frequently within the first 48 hours and generally are mild. Local erythema and induration (30%), local discomfort (40%), and local swelling (3%) are the side effects observed most commonly. Revaccination has been associated with self-limited injection-site reactions more commonly than after the first dose. Severe systemic reactions occur rarely and consist of weakness, myalgia, headache, photophobia, chills, and fever.

Pneumococcal Conjugate Vaccine

Invasive pneumococcal disease occurs even more frequently in children younger than 2 years than in those older than 65 years. The infection ranges from nasopharyngeal carriage to bacteremia and meningitis. Because of the lack of immune responsiveness in children younger than 2 years when exposed to polysaccharide vaccines, a conjugate vaccine was developed to protect young children from certain strains of *S. pneumoniae*. However, the 13-valent vaccine is also licensed for individuals aged 50 years and older. The 13-valent vaccine (Prevnar-13) contains the conjugated capsular polysaccharides of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. In clinical use, the vaccine is associated with a dramatic decline in invasive disease not only in immunized young children but also in individuals in all age groups.[27]

Immunization of Children PCV13 is administered as a 0.5-mL IM injection at 2, 4, and 6 months of age and between 12 and 15 months of age. A single dose of PCV13 should be administered to children aged 6 to 18 years with sickle cell disease or splenic dysfunction, HIV infection, immunocompromising conditions, cochlear implant, or cerebral spinal fluid leak should be immunized.[28] PPSV23 can be used in conjunction with PCV13. PPSV23 should be administered after age 2 years and at least 2 months after the last dose of PCV13.[29]

Immunization of Adults The PCV13 offers additional protection over PPSV23 alone in adult high-risk populations. The ACIP recommended PCV13 for adults with immunocompromising conditions and for those 65 years of age and older (Table 142-2).[25,27] PCV13 should be administered prior to PPSV23 in adults who have not been immunized previously. PCV13 should be administered with at least a year interval in those adults for whom it has been recommended and have already received one or more doses of PPSV23.

TABLE 142-2 ACIP Recommendations for Use of PCV13 and PPSV23[25]

Vaccine naive adults
- PCV13 first with PPSV23 administered at least 8 weeks later
- Second dose of PPSV23 at 5-year interval and PPSV23 at age 65 years and at least 5 years after last dose

PPSV23-immunized adults
- PCV13 at least 1 year after last dose of PPSV23
- Second dose of PPSV23 at 5-year interval and PPSV23 at age 65 years and at least 5 years after last dose

Indications for PCV13 for adults 19 years and older
- Functional or anatomic asplenia
- Immunocompromising conditions
  - Congenital or acquired immunodeficiencies
  - HIV infection
  - Chronic renal failure or nephrotic syndrome
  - Leukemias, lymphomas, Hodgkin's lymphoma
  - Generalized malignancy
  - Diseases requiring treatment with immunosuppressive drugs, including long-term systemic corticosteroids or radiation therapy
  - Solid organ transplantation
  - Multiple myeloma
- Cerebral spinal fluid leaks or cochlear implants

PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

Poliovirus Vaccines

Poliomyelitis is a contagious viral infection that usually causes asymptomatic infection; however, in its serious form it causes acute flaccid paralysis. Poliovirus is spread via the fecal–oral route. The virus replicates in the upper respiratory tract, GI tract, and local lymphatics. The vast majority of polio infections are subclinical and asymptomatic. Polio has been eliminated from the United States since 1979, and the last case in Western Hemisphere was reported in 1991. Global eradication efforts are entering the final stages, and the eradication of polio should be accomplished in the next few years.

An inactivated trivalent vaccine developed by Jonas Salk was licensed for use in 1955. In 1987, an enhanced-potency inactivated polio vaccine (IPV) was introduced and that replaced the original inactivated vaccine. A live-attenuated oral polio vaccine (OPV) was developed by Albert Sabin in 1962. OPV was the primary immunizing agent for poliovirus infection. Widespread OPV use is responsible for the elimination of wild-type polio in most of the world. However, with no poliovirus circulation in the United States for years, IPV is the recommended vaccine for the primary series and booster dose for children.[30] OPV will continue to be used in areas of the world that have circulating poliovirus. The CDC maintains a stockpile of OPV to be used only in case of an outbreak.

The IPV series is administered routinely to children at ages 2, 4, and 6 to 18 months, and 4 to 6 years.[13] Primary poliomyelitis immunization is recommended for all children up to age 18 years. Primary immunization of adults over age 18 years is not recommended routinely because a high level of immunity already exists in this age group, and the risk of exposure in developed countries is exceedingly small. However, unimmunized adults who are at increased risk for exposure because of travel, residence, or occupation should receive IPV series. Incompletely immunized adults or children should complete the series of IPV regardless of the interval since initiation of primary immunization. Adults do not need a booster dose routinely unless they are at increased risk of exposure (travel), in which case a single dose of IPV can be given.[31]

No serious side effects are attributable to IPV. Pregnant women should be given IPV only if there is a clear need, such as women who will be traveling or living in an area with endemic or epidemic poliovirus.

Rabies Vaccine and Immunoglobulin

Rabies is a virtually universally fatal infection in humans. Although all

mammals are susceptible to rabies, carnivorous mammals are reservoirs of the virus and responsible for persistence of the virus in nature. In the United States, most human cases of rabies are from exposure to rabid bats, but raccoons, foxes, skunks, and coyotes are also associated with possible exposure. Worldwide, canines are the primary vectors. Transmission of rabies can occur via percutaneous, permucosal, or airborne exposure to the rabies virus. Circumstances favoring such transmission include animal bites and attacks and contamination of scratches, cuts, abrasions, and mucous membranes with saliva or other infectious material (brain tissue). Unprovoked attacks and daytime attacks by nocturnal animals are considered highly suspect. A few cases of person-to-person transmission have been reported.

Symptoms of rabies are nonspecific during the prodromal stage—fever, headache, malaise, irritability, nausea, and vomiting. The acute neurologic phase is characterized by hyperexcitability, hyperactivity, hallucinations, salivation, a fear of water, and air. A minority of patients present with limp paralysis. Patients die within 5 days of presentation with these neurologic symptoms.

Human diploid cell vaccine, and purified chick embryo cell rabies vaccine are killed vaccines used for preexposure and postexposure rabies virus prophylaxis. Preexposure indications for rabies vaccine include persons whose vocation or avocation place them at high risk for rabies exposure, such as veterinarians, animal handlers, laboratory workers in rabies research or diagnostic laboratories, cavers, wildlife officers where animal rabies is common, and anyone who handles bats. Travelers who will be in a country or area of a country where there is a constant threat of rabies, whose stay is likely to extend beyond 1 month, and who may not have readily available medical services (eg, Peace Corps workers and missionaries) should be considered for preexposure prophylaxis. Rabies immunization of immunocompromised individuals should be postponed until the immunosuppression has resolved, or activities should be modified to minimize the potential exposure to rabies. If the vaccine is used in immunocompromised persons, antibody titers should be checked postimmunization. Pregnancy is not a contraindication if the risk of rabies is great. Both vaccine preparations can be administered for preexposure prophylaxis as a three-dose series of 1 mL IM on days 0 and 7 and once between days 21 and 28.[32] Individuals with ongoing risk of exposure—either continuous risk (eg, research laboratory staff or those involved in rabies biologics production) or individuals with frequent exposures (eg, those involved with rabies diagnosis, spelunkers, veterinarians, animal control workers, and wildlife workers in rabies-enzootic areas)—should undergo serologic testing every 6 months and 2 years, respectively, to monitor rabies

antibody concentrations. A booster dose is recommended if the complete virus neutralization is less than 1:5 serum dilution by the rapid fluorescent focus inhibition test.

Preexposure prophylaxis does not eliminate the need for postexposure therapy. Persons previously immunized with rabies vaccine or those who previously received postexposure prophylaxis should receive two 1-mL IM doses of rabies vaccine on postexposure days 0 and 3.[32] Rabies Ig should not be given to this group.

Postexposure prophylaxis should be given after percutaneous or permucosal exposure to saliva or other infectious material from a high-risk source. Each case must be considered individually. Consideration needs to be given to the geographic area, species of animal, circumstances of the incident, and type of exposure. Local or state health departments should be contacted for assistance. Thorough cleansing of the wound with soap and water followed by irrigation with a virucidal agent such as povidone–iodine solution is an extremely important part of the management of rabies-prone wounds. Individuals who have not been immunized previously should receive the recommended regimen of rabies Ig (see Rabies Immunoglobulin below) and four doses of rabies vaccine 1 mL IM on days 0, 3, 7, and 14 after exposure. However, a fifth dose in a series should be considered if the exposed individual is immunocompromised. Vaccine response for these immunocompromised individuals should be checked.[31] Rabies vaccine must be administered in the deltoid muscle in adults and in the anterolateral thigh in children. The gluteal region should not be used.[1,32]

Adverse reactions to rabies biologicals are less common and less serious with the currently available vaccines compared with previously used preparations. Local or mild systemic symptoms can typically be managed with anti-inflammatory medications or antihistamines. Systemic allergic reactions ranging from hives to anaphylaxis occur in a very small number of subjects. Given the lack of alternative therapy and the fact that rabies infection is almost always fatal, persons exposed to rabies who do have adverse reactions should continue the vaccine series in a setting with medical support services.[32]

Human rabies Ig is used in conjunction with rabies vaccine as part of postexposure rabies management for previously unvaccinated individuals. The product is derived from plasma obtained from donors who have been hyperimmunized with rabies vaccine and have high titers of circulating antibody.

In persons who previously have not been immunized against rabies, rabies Ig is given simultaneously with rabies vaccine to provide optimal coverage in the interval before immune response to the vaccine occurs. The efficacy of this

regimen has been clearly demonstrated as it provides virtually complete protection from rabies when administered with the vaccine series promptly following exposure.[32] Rabies Ig does not interfere with vaccine-induced antibody formation. Its use is not recommended beyond 8 days after initiation of the vaccine series nor in persons previously immunized to rabies.

Human rabies Ig is administered in a dose of 20 international units/kg (0.133 mL/kg). If anatomically feasible, the entire dose should be infiltrated around the wound(s). Any remaining volume should be administered IM at a site distant from the rabies vaccination site. This product should never be administered by the IV route. Because other antibodies in the rabies Ig may interfere with the response to live-virus vaccines (MMR and varicella), it is recommended that these immunizations be delayed for 3 months.[1]

Side effects are rare but may include local soreness at the wound or IM injection site and mild temperature elevations. Pregnancy is not a contraindication to its use.

Rubella Vaccine

Rubella (German measles) is characterized by an erythematous rash, lymphadenopathy, arthralgia, and low-grade fever. The most important consequence of rubella infection occurs during pregnancy, particularly during the first trimester. Congenital rubella syndrome is associated with auditory, ophthalmic, cardiac, and neurologic defects. Rubella infection during pregnancy can also result in miscarriage or stillbirth. The primary goal of rubella immunization is to prevent congenital rubella syndrome. Rubella is no longer endemic in the United States, but high immunization rates are necessary to prevent rubella outbreaks from imported cases.[9]

Rubella vaccine contains lyophilized live-attenuated rubella virus grown in human diploid cell culture. The vaccine is available in combinations with measles and mumps (as MMR), or varicella (MMRV) vaccines.

Rubella vaccine induces antibodies that are protective against wild-virus infection. The duration of immunity has not been established. A second dose is recommended, however, at the same time measles vaccine is administered (as a second dose of MMR). The vaccine is indicated for children older than 1 year of age. Individuals born before 1957 are assumed to be immune to rubella except for females who could become pregnant. Therefore, all females of childbearing potential should have documentation of receiving at least one dose of a rubella-containing vaccine or laboratory evidence of immunity. The vaccine should not

be given to immunosuppressed individuals, although MMR vaccine should be administered to individuals with HIV infection without evidence of immunity (see Measles Vaccine section).[9] Adverse effects of the rubella virus vaccine tend to increase with the age of the recipient. Mild symptoms are similar to wild-virus infection and include lymphadenopathy, rash, urticaria, fever, malaise, sore throat, headache, myalgias, and paresthesias of the extremities. These symptoms occur 7 to 12 days after vaccination and last 1 to 5 days. Joint symptoms occur more often in susceptible postpubertal females. Arthralgia occurs in 25% of vaccinees, and 10% have arthritis-like symptoms. These symptoms usually begin 1 to 3 weeks after vaccination, persist for 1 day to 3 weeks, and rarely recur.[9] The vaccine may cause suppression of tuberculin skin tests for up to 6 weeks after vaccination.

The rubella vaccine has never been associated with congenital rubella syndrome, but its use during pregnancy is contraindicated. However, routine pregnancy testing prior to vaccination is not recommended. Females should be counseled not to become pregnant for 4 weeks following vaccination.[9] Termination of pregnancy is not indicated in women who are accidentally given the vaccine or who become pregnant during the month after vaccination.

Tetanus Toxoid Adsorbed and Tetanus Immunoglobulin

Tetanus is a severe acute illness caused by the exotoxin of *Clostridium tetani*. Tetanus is the only vaccine-preventable disease that is not contagious as it is acquired from the environment. Tetanus toxin interferes with neurotransmitters that promote muscle relaxation, leading to continuous muscle spasms that are characteristic of tetanus. Death can be due to the tetanus toxin itself or secondary to a complication such as aspiration pneumonia, dysregulation of the autonomic nervous system, or pulmonary embolism.

Tetanus toxoid adsorbed (adsorbed onto aluminum hydroxide, phosphate, or potassium sulfate to increase antigenicity) is a sterile suspension of the toxoid derived from *C. tetani.* A series of three 0.5-mL doses of tetanus toxoid elicits protection in virtually all individuals. Primary vaccination provides protection for at least 10 years.[33] Additional doses of tetanus toxoid (combined with diphtheria toxoid, ie, Td) are recommended as part of wound management if a patient has not received a dose of tetanus toxoid within the preceding 5 years. For minor or clean wounds, no dose is given (**Table 142-3**). Tetanus Ig should be given to individuals who have received fewer than three doses of tetanus toxoid

and have more serious wounds. It can be administered with tetanus toxoid, provided that separate syringes and separate injection sites are used.

TABLE 142-3 Tetanus Prophylaxis[35]

Vaccination History	Clean, Minor Wounds		All Other Wounds	
	Td[a]	TIG	Td[a]	TIG
Unknown or fewer than three doses	Yes	No	Yes	Yes
Three or more doses	No[a,b]	No	No[a,c]	No

[a]A single dose of Tdap should be used for the next dose of tetanus–diphtheria toxoid for individuals aged >10 years.

[b]Yes, if more than 10 years since last dose.

[c]Yes, if more than 5 years since last dose.

In children, primary immunization against tetanus usually is offered in conjunction with diphtheria and pertussis vaccination (using DTaP or a combination vaccine that includes other antigens used to decrease the number of injections to complete the childhood immunization schedule). A 0.5-mL dose is recommended at age 2, 4, 6, and 15 to 18 months.[34] In children 7 years and older and in adults who have not been immunized previously, a series of three 0.5-mL doses of a tetanus toxoid–containing vaccine is administered IM initially. The first two doses are given 1 to 2 months apart, and the third dose is recommended at 6 to 12 months after the second dose. Boosters are recommended every 10 years, and unless there is contraindication to diphtheria toxoid, Td should be used. Tetanus toxoid can be given simultaneously with other killed and live vaccines, and, if indicated, it can be given to immunosuppressed patients.[34]

Adverse reactions to tetanus toxoid include mild-to-moderate local reactions at the injection site, such as warmth, erythema, and induration. Occasionally, a nodule at the injection site develops and remains for a few weeks. This type of reaction is indicative of high preexisting antibody concentrations, and additional doses of toxoid should not be given any sooner than 10 years. Local reactions do not limit the use of the toxoid for further dosing.

Tetanus Ig is a sterile, concentrated, nonpyrogenic solution of Igs prepared from hyperimmunized humans. It is used to provide passive immunity to tetanus after the occurrence of traumatic wounds in nonimmunized or suboptimally immunized persons (see Table 142-3).[35] A dose of 250 to 500 units IM should be administered. When administered with tetanus toxoid, separate sites for administration should be used. Tetanus Ig also is used for treatment of tetanus. In

this setting, a single dose of 3,000 to 6,000 units IM is administered.

Adverse effects of tetanus Ig include pain, tenderness, erythema, and muscle stiffness at the injection site, which may persist for several hours. Systemic reactions occur rarely. IV administration has been associated with severe adverse reactions and is not recommended.

Varicella and Zoster Vaccines

Varicella is a highly contagious disease caused by varicella-zoster virus. The clinical illness is characterized by the appearance of successive waves of pruritic vesicles that rapidly crust over. Malaise and fever are common and last for 2 to 3 days. The virus remains dormant in the dorsal ganglia and reactivates as herpes zoster, also known as *shingles.* Although the exact stimulus for reactivation is unknown, a decrease in varicella-specific cell-mediated immunity associated with age or immunosuppression appears to be necessary but not sufficient for reactivation.

Varicella Vaccine

Live-attenuated varicella vaccine contains the Oka/Merck strain of varicella virus, which was attenuated by propagation through several different cell culture lines. Varicella vaccine is a lyophilized product that must be kept frozen and protected from light. Once reconstituted, it must be administered subcutaneously within 30 minutes.[36] The varicella vaccine is safe and immunogenic in healthy children and adults. In clinical studies, varicella vaccine has been 70% to more than 95% effective in preventing chickenpox. The varicella vaccine is recommended for all children at 12 to 18 months of age, with a second dose prior to entering school between ages 4 and 6 years.[36] Two doses separated by 4 to 8 weeks should be administered to anyone who lacks immunity to varicella. Because the varicella vaccine is a live vaccine, it is contraindicated in pregnant women and in immunocompromised individuals. An exception is children with asymptomatic or mildly symptomatic HIV infection, who should receive two doses of varicella vaccine 3 months apart. In addition, children with humoral immune deficiencies may be immunized. Varicella vaccination is contraindicated in individuals with a history of anaphylactic reaction to any component of the vaccine. Persons who have received blood, plasma, or Ig products in the recent past should not receive varicella vaccine because of concern that passively acquired antibody will interfere with response to the vaccine. The recommended time interval between antibody-containing products and varicella vaccine

depends on the dose of Ig (see Table 142-1).[1] Although no adverse events associated with salicylate use after vaccination have been reported, salicylates should be avoided for 6 weeks after vaccination because of the association of salicylate use and Reye syndrome following varicella infection.[36]

The varicella vaccine has an excellent safety record. Pain, local swelling, and erythema at the injection site occur in up to 32% of patients and fever in 10% to 15%. A varicella-like rash occurs in approximately 4% of vaccinees, accompanied by few, if any, systemic symptoms. The rash may be localized at the injection site or generalized. Lesions usually are few in number (2-10) and often papular rather than vesicular. Transmission of vaccine virus to susceptible close contacts has occurred but is rare and believed to occur only when the vaccinee develops a rash. Because the risk of vaccine virus transmission is very low and primary infection can be very severe, vaccination of household contacts of immunocompromised patients is recommended to prevent introduction of varicella into the household.[36]

Zoster Vaccine

After the primary infection with varicella-zoster virus manifested as chicken pox, the virus remains latent in the dorsal ganglia. Herpes zoster, more commonly known as *shingles*, occurs upon reactivation of varicella-zoster virus replication. Herpes zoster can occur at any age, but the incidence dramatically increases with increasing age. The rate of disease increases sharply after age 50 years. The disease rate in individuals older than 80 years of age is 15 cases per 1,000 person-years.[37] Patients with HIV, cancer, or other conditions associated with immunosuppression are at increased risk for disease.[38] The development of the disease is associated with waning cellular immunity to varicella-zoster virus.

The clinical presentation of herpes zoster usually is a vesicular eruption limited to one dermatome. The most common complication is postherpetic neuralgia, which is pain that persists after the skin lesions have healed. Postherpetic neuralgia can persist for weeks to years. The risk of postherpetic neuralgia increases with age. Virtually no risk of developing postherpetic neuralgia with herpes zoster exists prior to age 50 years, but the risk increases to 50% to 75% after ages 60 and 75 years, respectively. The pain can be so severe as to limit activities of daily living and quality of life.[39]

Two vaccines for the prevention of zoster are available. The live-attenuated zoster vaccine was licensed and used as a single-dose vaccine. A recombinant zoster vaccine (RZV) with an adjuvant is currently the preferred product for use

as recommended by the ACIP for use in immunocompetent individuals aged 50 years and older as a two-dose series at 0 and 2 to 6 months.[40] The vaccine is approximately 91% effective for the prevention of zoster.[41] Although the incidence of serious adverse effects were similar in the vaccine and placebo groups, the incidence of injection site and systemic adverse events were much higher in the vaccine group. Almost 80% of those who receive RZV report injection site pain with 9% of those reporting injection site reactions that interfere with their normal activities. No difference in the incidence of injection site reactions were found when comparing dose 1 to dose 2.[40]

Varicella-Zoster Immunoglobulin

Varicella-zoster Ig is used after exposure to varicella for passive immunization of susceptible immunodeficient patients or other susceptible individuals at particularly high risk for complications of varicella infection. Postexposure prophylaxis with varicella-zoster Ig is indicated for the following susceptible individuals: (a) immunocompromised patients without evidence of immunity, (b) neonates whose mothers develop varicella within 5 days before or 2 days after delivery, (c) hospitalized premature infants (more than 28 weeks of gestation) whose mothers have no evidence of immunity (d) hospitalized preterm infants (less than 28 weeks' gestation or weight less than 1,000 g), and (e) susceptible pregnant women.[42] If varicella is prevented, vaccination should be offered at a later date. Exposure to varicella is defined as direct indoor contact for more than 1 hour with an infectious person. A negative history of clinical disease is not a reliable indicator of varicella susceptibility. Most people with a negative clinical history will have detectable antibody on laboratory testing. Caution is warranted when interpreting a low-positive result in an immunosuppressed patient who has received blood products or Ig because the circulating antibody may be acquired passively.

For maximum effectiveness, varicella-zoster Ig must be given as soon as possible and not more than 10 days following exposure.[42] Because this agent may only attenuate infection, patients who receive varicella-zoster Ig still may have a period of communicability, and varicella-zoster Ig may prolong the incubation period to 28 days. Antiviral therapy can be initiated if signs and symptoms of varicella infection become apparent.

Administration of varicella-zoster Ig is by the IM route at doses of 125 plaque-forming units per 10 kg of body weight up to 625 units (five vials) for patients weighing more than 40 kg. The dose for newborn infants is 125 units.[42]

OTHER IMMUNOBIOLOGICS

Immunoglobulin

Ig is available as both intramuscular immunoglobulin (IMIG) and IV immunoglobulin (IVIG) preparations. The IMIG preparation, or the Cohn fraction II, is prepared from pooled plasma of several thousand donors by cold ethanol fractionation. It typically contains greater than 95% IgG and trace amounts of IgM, IgA, and other plasma proteins. Because Ig is harvested from a large donor pool, it contains a wide spectrum of IgG antibodies to the pathogens prevalent in the area from which the donors were obtained. In the fractionation process, high-molecular-weight IgG aggregates are formed, which can activate complement in the absence of antigen and precipitate anaphylactoid reactions. For this reason, IMIG is unsuitable for IV administration. IMIG typically contains 15% to 18% protein and not less than 90% IgG. A number of IVIG preparations are available commercially in the United States. Generally, these preparations contain greater than 90% IgG monomers and trace to small amounts of IgA.

When administered either IV or IM, Ig distributes in approximately 5% of the body weight of the recipient. The plasma half-life of Ig ranges from 18 to 32 days. This range of half-life probably is attributable to the variation in the half-life of IgG subclasses. Peak serum concentrations occur immediately with IVIG but within 2 days with IMIG. After the initial period of equilibration, circulating IgG levels are superimposable between IV and IM equivalent dosages. No dosage adjustment is necessary in patients with renal insufficiency, hepatic insufficiency, or both, dialysis patients, or geriatric patients.

6 Ig is indicated in a wide variety of circumstances to provide passive immunity to individuals. The indications for IMIG differ from those for IVIG. IMIG is indicated for providing passive immunity in patients with hepatitis A infections in those less than 1 year and older than 39 years, hepatitis B exposures (however, hepatitis B Ig is significantly more effective), measles, varicella, and primary immunodeficiency diseases. Although IMIG is indicated for the treatment of primary immunodeficiency, IVIG is better tolerated and is more effective. IMIG is not indicated for prevention of rubella, mumps, or poliomyelitis. **Table 142-4** lists the suggested dosages of IMIG for prevention or attenuation of various infectious diseases.

TABLE 142-4 Indications and Dosage of Intramuscular Immunoglobulin in Infectious Diseases

Primary immunodeficiency states	1.2 mL/kg IM then 0.6 mL/kg every 2-4 weeks
Hepatitis A exposure	0.02 mL/kg IM within 2 weeks if <1 year or >39 years of age
Hepatitis A prophylaxis	0.02 mL/kg IM for exposure <3 months' duration
	0.06 mL/kg IM for exposure up to 5 months' duration
Hepatitis B exposure	0.06 mL/kg (HBIG preferred in known exposures)
Measles exposure	0.5 mL/kg (maximum dose 15 mL) as soon as possible

There are many licensed indications, as well as off-label uses, for IVIG.[43] The therapeutic dose of IVIG is set empirically at 2 g/kg, often given as five daily doses of 400 mg/kg each. Mechanisms of IVIG action for treatment of these conditions have been hypothesized.

1. *Primary Immunodeficiency States.*[44,45] In primary immunodeficiency states, monthly doses of between 100 and 800 mg/kg are administered; the average dose is 200 to 400 mg/kg. The immunodeficiency states for which IVIG is indicated include both antibody deficiencies and combined immune deficiencies. Significant reactions can occur in patients with low intrinsic levels of IgA given IVIG with greater amounts of IgA. An IVIG product with very low amounts of IgA should be used for these patients.
2. *Immune Thrombocytopenia*.[45] For the treatment of hemorrhage associated with immune thrombocytopenia (ITP), doses of 1 g/kg daily for 2 to 3 days plus high-dose methylprednisolone are indicated. Adults tend to respond less well to IVIG than do children. IVIG is acceptable for treatment of both chronic and acute ITP, and IVIG has been used for ITP associated with pregnancy without adverse effects on the fetus. Corticosteroids remain the drugs of choice for adult ITP. In thrombotic thrombocytopenia purpura, IVIG is reported to be effective in patients who do not respond to plasmapheresis. Other platelet disorders in which IVIG may be useful include neonatal immune thrombocytopenia, perinatal autoimmune thrombocytopenia, drug-induced thrombocytopenia, thrombocytopenia secondary to infection, and transfusion-refractory thrombocytopenia; however, the data supporting these uses are minimal.

3. *Chronic Lymphocytic Leukemia.*[46] IVIG is used as a prophylactic measure in patients with chronic lympocytic leukemia who have had a serious bacterial infection.
4. *Kawasaki Disease.*[4,47] This disease, which generally occurs in children, carries the hallmark of development of coronary artery abnormalities. Generally, the American Academy of Pediatrics recommends that if the strict criteria for Kawasaki disease are met, an IVIG dose of 400 mg/kg/day for four consecutive days be used or, preferably, 2 g/kg as a single dose. The dose should be administered within 10 days of disease onset. Aspirin therapy also should be initiated.
5. *Pediatric HIV infection.*[47] IVIG prevents serious bacterial infections in children with HIV infection. However, in the era of highly active anti-retroviral therapy, its use has waned.
6. *Allogeneic bone marrow transplantation.*[48]
7. *Chronic inflammatory demyelinating polyneuropathy.*[49] This disabling neuropathy often responds to corticosteroids, IVIG, or plasmapheresis.
8. *Multifocal motor neuropathy*[50] IVIG is considered first-line therapy.
9. *Kidney transplantation involving a recipient with high antibody concentrations or an ABO-incompatible donor.*[51] Some transplant recipients have antibody concentrations that present an immunological barrier to transplantation. Desensitization can be accomplished using IVIG.

Many other proposed uses of IVIG have been identified. It is important to note that these uses are off-label but may be generally accepted in the medical community for routine treatment.[43,48]

7 Adverse effects of Ig vary with the route of administration. Following IMIG, pain, tenderness, and muscle stiffness persisting for hours or days are common. Repeat courses may cause sensitization with resulting allergic reactions. Chills, fever, nausea, and vomiting often are related to the rate of the infusion.[52] Infusion should be given at a rate of 0.01 to 0.02 mL/kg/min for 30 minutes. If no reactions occur, then the rate can be increased to 0.02 to 0.04 mL/kg/min. If reactions do occur, the infusion should be stopped for 30 minutes and restarted at a lower rate. Although recommendations for infusion rate vary slightly depending on the preparation, the guidelines presented can be followed for the various IV preparations.

Most adverse reactions are mild and transient. Arthralgia, myalgia, fever, pruritus, nausea, vomiting, chest tightness, palpitations, diaphoresis, dizziness, pallor, and respiratory distress have been reported. Rarely, aseptic meningitis has occurred from a few hours to 2 days after high-dose infusion. The syndrome resolves within days without sequelae. Acute renal failure has been reported, primarily in individuals with underlying renal dysfunction, diabetes, sepsis, volume depletion, or other nephrotoxic drugs or in patients older than 65 years. To minimize the risk, ensure adequate hydration prior to infusion and choose an IVIG product that does not contain high-sucrose concentrations for individuals at high risk.[52]

Ig products are derived from human blood. Precautions such as donor screening and fractionation procedures and solvent–detergent treatment during the manufacturing process render the IVIG products free of HIV and hepatitis B and C viruses. Although no manufacturing process can guarantee no viral contamination, the potential infection risk from Ig preparations is very small.

Rh_o(D) Immunoglobulin

8 Second only to the ABO blood group system, Rhesus antigen D [Rh_o(D)] is an important antigen in human blood. The Rh_o(D) locus encodes this antigen, but this locus is absent in approximately 15% of the population. Individuals lacking the Rh_o(D) locus are Rh_o(D) negative and have the potential to mount an antibody response to erythrocytes with the Rh_o(D) present. Rh_o(D) incompatibility during pregnancy can lead to sensitization of the mother. The maternal antibodies developed following normal fetal leakage of erythrocytes to the mother can cause hemolytic disease of the newborn during subsequent pregnancies.

Rh_o(D) Ig is a sterile solution of Igs prepared from human sera with high titers of Rh_o(D) antibody. Rh_o(D) Ig suppresses the antibody response and formation of anti-Rh_o(D) in Rh_o(D)-negative women exposed to Rh_o(D)-positive blood. Administration of Rh_o(D) Ig prevents hemolytic disease of the newborn in subsequent pregnancies with a Rh_o(D)-positive fetus. When administered within 72 hours of delivery of a full-term infant, Rh_o(D) Ig reduces active antibody formation from 1% to about 0.2%. The reduction in antibody formation is lower when Rh_o(D) Ig is given beyond 72 hours postpartum. Smaller doses of Rh_o(D) Ig are used after abortion, miscarriage, amniocentesis, or abdominal

trauma. In addition, Rh_o(D) Ig is used in the case of a premenopausal woman who is Rh_o(D) negative and has inadvertently received Rh_o(D)-positive blood or blood products.[53]

The dosage of Rh_o(D) Ig varies with the indication. A standard dose of 300 mcg is given within 72 hours of a term delivery. Occasionally, when the fetus is known to be Rh_o(D) positive, a 300-mcg dose is given at 28 weeks' gestation and within 72 hours after delivery. For postpregnancy termination occurring up to 13 weeks' gestation, one microdose (50 mcg) vial is given within 72 hours. For pregnancy termination after 13 weeks, one standard dose (300 mcg) is given within 72 hours. In other circumstances, such as in abdominal trauma, amniocentesis, or transfusion accidents, the dosage (number of standard dose vials) is based on the estimated packed red blood cell volume of fetal/maternal hemorrhage divided by 15. Rh_o(D) Ig is administered IM only.

Adverse reactions to Rh_o(D) Ig include injection-site tenderness and fever. Rh_o(D) may minimally interfere with response to rubella or varicella vaccine. Rubella- or varicella-seronegative women should be immunized with MMR or MMRV at hospital discharge even if they received Rh_o(D) Ig postpartum.[1]

VACCINE INFORMATION RESOURCES

The field of vaccinology is developing rapidly, with numerous changes in recommendations for vaccine use made each year. Keeping up to date with the current recommendations can be a challenge. The childhood and adult immunization schedules are updated frequently and published annually. Recommendations for the use of influenza vaccine are issued annually. Healthcare providers involved in primary care and immunization delivery must keep themselves abreast of these changes in a systematic way. Reading electronic newsletters and browsing reliable websites are efficient methods for obtaining information (**Table 142-5**). Although several excellent, reliable, and timely websites exist, hundreds of sites with misleading and incorrect information also exist. Many of these sites are targeted at parents.

TABLE 142-5 Web Resources for Vaccine Information

Recommended Internet Sites for Vaccine Information	
http://www.cdc.gov/vaccines/	Vaccines & Immunizations Centers for Disease Control and Prevention
www.immunize.org	Immunization Action Coalition
www.nfid.org/	National Foundation for Infectious Diseases
www.cdc.gov/mmwr/	Morbidity and Mortality Weekly Report
http://www.nationalacademies.org/hmd/	The National Academies of Sciences, Engineering, and Medicine. Health and Medicine Division
http://www.hrsa.gov/vaccinecompensation/	Vaccine Injury Compensation Program
http://www.chop.edu/centers-programs/vaccine-education-center/	Vaccine Education Center Children's Hospital of Philadelphia
https://vaers.hhs.gov/index.html	Vaccine Adverse Event Reporting System
Recommended Electronic Newsletters	
www.immunize.org/express	The Immunization Action Coalition's newsletter
www.cdc.gov/mmwr/	Morbidity and Mortality Weekly Report

Parents and patients often have questions regarding vaccine safety. The Vaccine Education Center at the Children's Hospital of Philadelphia has several documents that may answer those questions. http://www.chop.edu/centers-programs/vaccine-education-center. The CDC is another source of information for parents. https://www.cdc.gov/vaccines/parents/vaccine-decision/index.html. Vaccines are the only class of medications to which nearly every patient is exposed. Knowledge of these agents is critical to providing pharmaceutical care. Dramatic progress in public health has been made through the appropriate use of immunization. Additional improvements in quality of life and mortality can be made through continued increases in vaccination coverage with careful attention to this aspect of care by all healthcare providers.

Postclass Engaged Learning Activity

Devise immunization recommendations for below mentioned cases.

A 56-year-old male with newly diagnosed type 2 diabetes who has not received any vaccines in the past 12 years.

A 26-year-old patient who was fully immunized prior to kidney transplant 6 years ago.

A 52-year-old male who smokes a pack of cigarettes every day and has not received any vaccines as an adult.

ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
CDC	US Centers for Disease Control and Prevention
DTaP	diphtheria, tetanus toxoids, and acellular pertussis
HBIG	Hepatitis B immune globulin
Hib	*Haemophilus influenzae* type b
HPV	human papillomavirus
Ig	Immunoglobulin
IMIG	intramuscular immunoglobulin
IPV	inactivated polio vaccine
ITP	idiopathic (immune) thrombocytopenic purpura
IVIG	IV immunoglobulin
MenB	Meningococcal serogroup B
MMR	measles, mumps, rubella vaccine
MMRV	measles, mumps, rubella, varicella vaccine
MSM	men who have sex with men
OPV	oral polio vaccine
PCV	pneumococcal conjugate vaccine
PPSV23	23-valent pneumococcal polysaccharide vaccine
PRP	polyribosylribitol phosphate
RZV	recombinant zoster vaccine
Td	tetanus–diphtheria
Tdap	tetanus, diphtheria, acellular pertussis
TIG	Tetanus immune globulin
VAERS	Vaccine Adverse Event Reporting System

REFERENCES

1. Kroger A, Duchin J, Vazquez M. General best practice guidelines for

immunization. Best practices guidance of the Advisory Committee on Immunization Practices (ACIP). Available at: wwwcdcgov/vaccines/hcp/acip-recs/general-recs/downloads/general-recspdf2017.

2. Poland GA, Kennedy RB, McKinney BA, et al. Vaccinomics, adversomics, and the immune response network theory: Individualized vaccinology in the 21st century. *Seminars in Immunology*. 2013;25:89–103.
3. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis* 2013;58:309–18.
4. Weinberger B. Vaccines for the elderly: Current use and future challenges. *Immunity & Ageing*. 2018;15:3.
5. Centers for Disease Control and Prevention. Prevention and control of influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices, United States, 2017-18 influenza season. *MMWR Morb Mortal Wkly Rep*. 2017;66(2):1–20.
6. Centers for Disease Control and Prevention. Prevention of rotavirus gastroenteritis among infants and children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2009;58:1–24.
7. Centers for Disease Control and Prevention. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine in adults aged 65 years and older —Advisory Committee on Immunization Practices (ACIP), 2012. *MMWR Morb Mortal Wkly Rep* 2012;61:468–70.
8. Centers for Disease Control and Prevention. Updated recommendations for the use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women—ACIP, 2012. *MMWR Morb Mortal Wkly Rep*. 2013;62:131–135.
9. Centers for Disease Control and Prevention. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: Summary recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2013;62:1–33.
10. Danziger-Isakov L, Kumar D, the A. S. T. Infectious Diseases Community of Practice. Vaccination in solid organ transplantation. *Am J Transplant* 2013;13:311–7.

11. Chong PP, Avery RK. A comprehensive review of immunization practices in solid organ transplant and hematopoietic stem cell transplant recipients. *Clin Ther*. 2017;39:1581–1598.
12. Chapter 7 Diphtheria. In: Hamborsky J, Kroger A, Wolfe C, eds. Epidemiology and Prevention of Vaccine-Preventable Diseases. 13th ed. Washington, DC Public Health Foundation; 2015.
13. Chapter 8 *Haemophilus influenzae*. In: Hamborsky J, Kroger A, Wolfe C, eds. Epidemiology and Prevention of Vaccine-Preventable Diseases. 13th ed. Washington, DC Public Health Foundation; 2015.
14. Centers for Disease Control and Prevention. Prevention and control of *Haemophilus influenzae* type b disease. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2014;63:1–24.
15. Centers for Disease Control and Prevention. Use of 9-valent human papillomavirus (HPV) vaccine: Updated HPV vaccination recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2015;64:300–304.
16. Meites E, Szilgyi PG, Chesson HW, Unger ER, Romero JR Markowitz LE. Human papillomavirus vaccination for adults: Updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2019;68:698–702.
17. Centers for Disease Control and Prevention. Use of serogroup B meningococcal vaccines in persons aged >10 years at increased risk for serogroup B meningococcal disease: Recommendation of the Advisory Committee on Immunization Practices, 2015. *MMWR Morb Mortal Wkly Rep*. 2015;62:608–612.
18. Centers for Disease Control and Prevention. Recommendation of the Advisory Committee on Immunization Practices for use of a third dose of mumps virus-containing vaccine in persons at increased risk for mumps during an outbreak. *MMWR Morb Mortal Wkly Rep*. 2018;67:33–38.
19. Centers for Disease Control and Prevention. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine from the Advisory Committee on Immunization Practices, 2010. *MMWR Morb Mortal Wkly Rep*. 2011;60:13–15.
20. Chapter 16 Pertussis. In: Hamborsky J, Kroger A, Wolfe C, eds. Epidemiology and Prevention of Vaccine-Preventable Diseases. 13th ed. Washington, DC Public Health Foundation; 2015.

21. Centers for Disease Control and Prevention. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine in pregnant women and persons who have or anticipate having close contact with an infant aged <12 months-- Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR Morb Mortal Wkly Rep*. 2011;60:1424–1426.
22. Vila-Corcoles A, Aguirre-Chavarria C, Ochoa-Gondar O, et al. Influence of chronic illnesses and underlying risk conditions on the incidence of pneumococcal pneumonia in older adults. *Infection* 2015;43:699–706.
23. Jacobs DM, Yung F, Hart E, Nguyen MNH, Shaver A. Trends in pneumococcal meningitis hospitalizations following the introduction of the 13-valent pneumococcal conjugate vaccine in the United States. *Vaccine*. 2017;35:6160–6165.
24. Centers for Disease Control and Prevention. Updated recommendations for prevention of invasive pneumococcal disease among adults using the 23-valent pneumococcal polysaccharide vaccine (PPSV23). *MMWR Morb Mortal Wkly Rep*. 2010;59:1102–1106.
25. Centers for Disease Control and Prevention. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2012;61:816–819.
26. Fisman DN, Abrutyn E, Spaude KA, Kim A, Kirchner C, Daley J. Prior pneumococcal vaccination is associated with reduced death, complications, and length of stay among hospitalized adults with community-acquired pneumonia. *Clin Infect Dis*. 2006;42:1093–1101.
27. Centers for Disease Control and Prevention. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged >65 years: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2014;63:822–825.
28. Centers for Disease Control and Prevention. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among children aged 6-18 years with immunocompromising conditions: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2013;62:521–524.

29. Centers for Disease Control and Prevention. Prevention of pneumococcal disease among infants and children—Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2010;59:1–18.
30. Centers for Disease Control and Prevention. Updated recommendations of the Advisory Committee on Immunization Practices (ACIP) regarding routine poliovirus vaccination. *MMWR Morb Mortal Wkly Rep*. 2009;58:829–830.
31. Centers for Disease Control and Prevention. Poliomyelitis prevention in the United States: Updated recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2000;49:1–22.
32. Centers for Disease Control and Prevention. Use of a reduced (4-dose) vaccine schedule for postexposure prophylaxis to prevent human rabies. Recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep* 2010;59:1–9.
33. Centers for Disease Control and Prevention. Preventing tetanus, diphtheria, and pertussis among adults: Use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and Recommendation of ACIP, supported by the Healthcare Infection Control Practices Advisory Committee (HIPAC), for the Use of Tdap Among Health-Care Personnel. *MMWR Morb Mortal Wkly Rep*. 2006;55:1–37.
34. Chapter 21. Tetanus. In: Hamborsky J, Kroger A, Wolfe C, eds. Epidemiology and Prevention of Vaccine-Preventable Diseases. 13th ed. Washington, DC Public Health Foundation 2015.
35. Centers for Disease Control and Prevention. Preventing tetanus, diphtheria, and pertussis among adolescents: Use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2006;55:1–42.
36. Centers for Disease Control and Prevention. Prevention of varicella. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2007;56:1–39.
37. McLaughlin J, McGinnis J, Tan L, Mercatante A, Fortuna J. Estimated human and economic burden of four major adult vaccine-preventable

diseases in the United States, 2013. *J Primary Prevent*. 2015;36:259–273.

38. Zhang J, Xie F, Delzell E, et al. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. *JAMA*. 2012;308:43–49.
39. Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ, Sy LS. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. *Mayo Clin Proc*. 2007;82:1341–1349.
40. Centers for Disease Control and Prevention. Recommendations of the Advisory Committee on Immunization Practices for use of herpes zoster vaccines. *MMWR Morb Mortal Wkly Rep*. 2018;67(3):103–108.
41. Cunningham AL, Lal H, Kovac M, et al. Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. *N Engl J Med*. 2016;375:1019–1032.
42. Centers for Disease Control and Prevention. Updated recommendations for use of VariZIG—United States, 2013. *MMWR Morb Mortal Wkly Rep*. 2013;62:574–576.
43. Robert P, Hotchko M. Polyvalent immune globulin usage by indication in the United States, 2012: A quantitative analysis of the use of polyvalent immune globulin (intravenous and subcutaneous) by medical indication in the United States in 2012. *Transfusion*. 2015;55:S6–S12.
44. Krivan G, Jolles S, Granados EL, et al. New insights in the use of immunoglobulins for the management of immune deficiency (PID) patients. *American Journal of Clinical and Experimental Immunology* 2017;6:76–83.
45. Kistanguri G, McCrae KR. Immune Thrombocytopenia. *Hematology/oncology clinics of North America* 2013;27:495–520.
46. Kipps TJ, Stevenson FK, Wu CJ, et al. Chronic lymphocytic leukaemia. *Nature reviews Disease primers*. 2017;3:16096.
47. Wong PH, White KM. Impact of immunoglobulin therapy in pediatric disease: A review of immune mechanisms. *Clinical Reviews in Allergy and Immunology*. 2015;51:303–314.
48. Gelfand EW. Intravenous immune globulin in autoimmune and inflammatory diseases. *N Engl J Med*. 2012;367:2015–2025.
49. Mahdi-Rogers M, Brassington R, Gunn AA, van Doorn PA, Hughes RAC. Immunomodulatory treatment other than corticosteroids, immunoglobulin and plasma exchange for chronic inflammatory demyelinating

polyradiculoneuropathy. *Cochrane Database of Systematic Reviews*. 2017;5:CD003280. doi: 10.1002/14651858.CD003280.pub5.

50. Živković S. Intravenous immunoglobulin in the treatment of neurologic disorders. *Acta Neurologica Scandinavica* 2016;133:84–96.
51. Songsaroj P, Kahwaji J, Vo A, Jordan SC. Modern approaches to incompatible kidney transplantation. *World J Nephrol*. 2015;4:354–362.
52. Späth PJ, Granata G, La Marra F, Kuijpers TW, Quinti I. On the dark side of therapies with immunoglobulin concentrates: The adverse events. *Frontiers Immunol* 2015;6:11.
53. Committee on Practice Bulletins-Obstetrics. Practice Bulletin No. 181: Prevention of Rh D alloimmunization. *Obstet Gynecol*. 2017;130:e57–e70.

143

Human Immunodeficiency Virus Infection

Peter L. Anderson, Jenna Yager, and Courtney V. Fletcher

KEY CONCEPTS

1. Infection with human immunodeficiency virus (HIV) occurs through three primary routes: sexual, parenteral, and perinatal. Sexual intercourse, primarily receptive anal and vaginal intercourse, is the most common method for transmission.
2. HIV infects cells expressing cluster of differentiation 4 (CD4) receptors, such as T-helper lymphocytes, monocytes, macrophages, dendritic cells, and brain microglia. Infection occurs via an interaction between glycoprotein 160 (gp160) on HIV with CD4 (primary interaction) and chemokine coreceptors (secondary interactions) present on the surfaces of these cells.
3. The hallmark of untreated HIV infection is profound CD4 T-lymphocyte depletion and severe immunosuppression that puts patients at significant risk for infectious diseases caused by opportunistic pathogens. Opportunistic infections (OIs) in settings without access to antiretroviral drugs are the chief cause of morbidity and mortality associated with HIV infection.
4. The current goal of combination antiretroviral therapy (ART) is to achieve maximal and durable suppression of HIV replication, measured as the level of HIV-RNA in plasma (viral load) less than the lower limit of quantitation, usually 20 to 50 copies/mL (20×10^3 to 50×10^3/L). Another equally important outcome is an increase in CD4 lymphocytes because this closely correlates with the risk for developing OIs.
5. General principles for the management of OIs include preventing or reversing immunosuppression with ART, preventing exposure to pathogens,

vaccination, prospective immunologic monitoring, primary chemoprophylaxis, treatment of acute episodes, secondary chemoprophylaxis, and discontinuation of such prophylaxes following ART and subsequent immune recovery.

6. Clinical use of antiretroviral agents is complicated by drug–drug interactions. Some interactions are beneficial and used purposely; others may be harmful, leading to dangerously elevated or inadequate drug concentrations. For these reasons, clinicians involved in the pharmacotherapy of HIV infection must exercise constant vigilance and maintain a current knowledge of drug interactions.
7. Recommendations for the initial treatment of HIV advocate a minimum of three active antiretroviral agents from at least two drug classes. The typical regimen consists of two nucleoside/nucleotide analogs with an integrase strand transfer inhibitor (InSTI).
8. Inadequate suppression of viral replication allows HIV to select for antiretroviral-resistant HIV variants, a major factor limiting the ability of antiretroviral drugs to inhibit virus replication. Recommendations for treating drug-resistant HIV include choosing at least two drugs (preferably three) of different classes to which the patient's virus is susceptible. Susceptibility can be assessed using either genotypic or phenotypic resistance testing.
9. The reduction of viral load with ART lowers the risk of transmission to others. Additionally, prophylaxis with antiretroviral agents in at-risk persons lowers HIV acquisition risk.
10. The longer life span conferred by ART has given rise to other medical issues. A wide spectrum of complications associated with older age have become common, some of which overlap with adverse effects from antiretroviral drugs. Medical management of these contemporary HIV complications is constantly evolving.

Preclass Engaged Learning Activities

Create a chart of available antiretroviral drug classes. Include mechanism of action and class-specific distinguishing therapeutic considerations. Finally, identify first-line agents (as applicable) from these antiretroviral drug classes using the current DHHS guidelines (https://tinyurl.com/y32subbx). This

activity is intended to familiarize yourself with available antiretroviral drug classes and contemporary agents in these classes, as well as therapeutic considerations for selecting initial drug regimens.

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) was first recognized in a cohort of young, previously healthy homosexual men with new-onset profound immunologic deficits, *Pneumocystis carinii* (now *P. jirovecii*) pneumonia (PCP), and/or Kaposi's sarcoma. A retrovirus, human immunodeficiency virus type 1 (HIV-1), is the major cause of AIDS. A second retrovirus, HIV-2, also is recognized to cause AIDS, although it is less virulent, transmissible, and prevalent than HIV-1. These retroviruses are transmitted primarily by sexual contact and by contact with infected blood or blood products. Several risk behaviors for the acquisition of HIV infection have been identified in the United States, most notably the practice of anorectal intercourse and the sharing of blood-contaminated needles by injection-drug users. In many resource-limited countries, the majority of HIV transmission occurs via heterosexual intercourse and from childbearing women to their offspring. Initially, the medical management of HIV consisted of repeated treatments for opportunistic infections (OIs) and eventual palliative care. In the mid-1990s, a new era in the pharmacotherapy for HIV, known as *combination antiretroviral therapy* (ART), was born. ART consists of combinations of antiretroviral agents with different mechanisms of action that potently and durably suppress HIV replication, delay the onset of AIDS, reverse HIV-associated immunologic deficits, reduce HIV transmission, and significantly prolong survival. Modern antiretroviral drugs and ART regimens have improved tolerability and efficacy. Nevertheless, therapeutic challenges remain in the present ART era and include the need for continuous adherence to medications and care, drug–drug interactions, drug-resistant HIV, acute and long-term drug toxicities, and other complications associated with a prolonged life span. Despite progress in the treatment access for this disease, large numbers of HIV-infected persons remain outside of care, nationally and globally. Significant efforts to develop an HIV vaccine have not been fruitful. However, prophylactic use of antiretroviral drugs effectively prevents HIV infection in persons at high risk of exposure and those recently exposed to the virus.

EPIDEMIOLOGY

The epidemiologic characteristics of HIV infection differ according to geographic region and depend upon the mode of transmission, governmental prevention efforts and resources, and cultural factors.[1,2]

1 Infection with HIV occurs through three primary modes: sexual, parenteral, and perinatal. Sexual intercourse, primarily anal and vaginal intercourse, is the most common method for transmission. The probability of HIV transmission depends upon the type of sexual exposure. The highest risk appears to be from receptive anorectal intercourse at about 1.4 transmissions per 100 sexual acts.[3] Transmission risk is lower for receptive vaginal intercourse, and insertive sex acts have lower risk than receptive acts. Condom use reduces risk of transmission by approximately 80%.[3] Other factors that affect the probability of infection include the stage of HIV disease and viral load in the index partner. For example, transmission is significantly higher when the index partner has early or late HIV compared with asymptomatic HIV, as these disease stages are associated with higher viral loads.[3] Individuals with genital ulcers or sexually transmitted infections are at greater risk for contracting HIV. HIV incidence and prevalence are lower in cultures that advocate male circumcision, which is estimated to reduce risk of male acquisition of HIV approximately 50%.[3] Casual contact with patients with AIDS or HIV infection is not a significant risk factor for HIV transmission.

Prevention of sexual transmission has focused primarily on education that encourages safer sex practices such as use of condoms and reduction of high-risk behavior (eg, intercourse or promiscuity with partners of unknown HIV status).[4] A powerful tool for HIV prevention is combination ART for the infected individual, as this dramatically lowers viral replication and infectiousness, significantly reducing the risk of transmission to others.[3,5] In fact, the HIV scientific community has endorsed the notion that “U = U,” which means undetectable (plasma HIV-RNA) = untransmittable (no HIV transmissions).[6] Another effective prevention tool is chemoprophylaxis with antiretroviral drugs, as this significantly reduces HIV acquisition risk among uninfected individuals.[7–9] A combined approach has been advocated for optimal prevention.[4] Prevention strategies under investigation include HIV vaccines and topical vaginal/rectal microbicides, such as vaginal rings impregnated with antiretroviral drugs.[10,11]

Parenteral transmission of HIV broadly encompasses infections due to

infected blood exposure from needle sticks, IV injection with used needles, receipt of blood products, and organ transplants. Use of contaminated needles or other injection-related paraphernalia by drug abusers has been the main cause of parenteral transmissions. The risk of HIV transmission from sharing needles is approximately 0.67 per 100 episodes.[3,12] Prevention strategies include stopping drug abuse, obtaining needles from credible sources (eg, pharmacies), never reusing any paraphernalia, using sterile procedures in all injecting activities, and safely disposing of used paraphernalia.[4]

Before widespread screening, HIV was readily transmitted in blood products.[12] However, blood and tissue products in the healthcare system are now rigorously screened for HIV. The estimated risk for receiving tainted blood or blood products in the United States is well below 1:1,000,000 and that for receiving a tainted tissue transplant is 1:55,000.[13,14] Healthcare workers have a small but definite occupational risk of contracting HIV through accidental exposure. Most cases of occupationally acquired HIV have been the result of a percutaneous needle stick injury, which carries an estimated 0.3% risk of transmitting HIV.[3,15] Mucocutaneous exposures (eg, tainted blood splash in eyes, mouth, or nose) carries a transmission risk of approximately 0.09%.[15] Significant risk factors for seroconversion with a needle stick include deep injury, injury with a device visibly contaminated with blood, and advanced HIV disease in the index patient (high viral load). The risk of transmission from an HIV-infected healthcare worker to a patient is extremely remote. Comprehensive medical guidelines, including antiretroviral drug prophylaxis, have been developed to minimize the hazard of HIV transmission for healthcare workers and for persons exposed by rape or other means.[12,15]

Perinatal infection, or vertical transmission, is the most common cause of pediatric HIV infection. Most infections occur during or near to the time of birth, although a fraction can occur in utero.[2] The risk of mother-to-child transmission is approximately 25% in the absence of ART. Factors that increase the likelihood of vertical transmission include prolonged rupture of membranes, chorioamnionitis, genital infection during pregnancy, preterm delivery, vaginal delivery, birth weight less than 2.5 kg, illicit drug use and cigarette smoking during pregnancy, and high maternal viral load.[16] Breast-feeding also can transmit HIV. The frequency of breast milk transmission is approximately 5% to 10% in the first 6 months and 15% to 20% through 18 to 24 months.[17] High levels of virus in breast milk and in the mother are associated with higher risk of transmission. Formula feeding prevents breast milk transmission of HIV but may not improve mortality from other causes early in life in resource limited

settings.[17] In the United States, HIV-infected mothers are recommended not to breast-feed.[18] A separate and comprehensive set of medical guidelines including antiretroviral drug prophylaxis have been developed to minimize the risk of mother-to-child HIV transmission.[18]

Persons with HIV infection are broadly categorized as those living with HIV and those with an AIDS diagnosis (stage 3). An AIDS diagnosis is made when the presence of HIV is laboratory-confirmed and the cluster of differentiation 4 (CD4; T-helper cell) count drops below 200 cells/mm^3 (0.2×10^9/L) for those older than or equal to 6 years of age, or after an AIDS indicator condition is diagnosed.[19] Further distinctions regarding the stage of HIV and AIDS (stage 3) are given in the Revised Centers for Disease Control and Prevention (CDC) surveillance case definition (**Table 143-1**).[19] In the United States, the CDC estimates HIV epidemiology using models that rely on surveillance data from state and local health departments.[20] Using these models, it is estimated that about 1.1 million individuals are currently living with HIV (all stages) in the United States and that approximately 507,000 have died from complications of HIV infection.[20,21] Importantly, approximately 15% of persons with HIV are unaware of their infection and only approximately 45% of those who are aware of their infection are retained in care. Therefore, a majority of HIV-infected persons (~60%) are not receiving ART regularly, which significantly contributes to the ongoing transmission of HIV infection in the United States, totaling approximately 38,500 new infections per annum.[21,22]

TABLE 143-1 Surveillance Case Definition for HIV Infection Stage Based on CD4+ T-lymphocyte Counts, United States, 2014

	Age on Date of CD4+ T-lymphocyte Test					
	<1 year		1–5 years		≥6 years	
Stage	Cells/μL (×10⁶/L)	%	Cells/μL (×10⁶/L)	%	Cells/μL (×10⁶/L)	%
1	≥1,500	≥34	≥1,000	≥30	≥500	≥26
2	750–1,499	26–33	500–999	22–29	200–499	14–25
3 (AIDS)	<750	<26	<500	<22	<200	<14

AIDS Indicator Conditions

Bacterial infections, multiple or recurrent (specific to children <6 years)	
Candidiasis of bronchi, trachea, or lungs	Lymphoma, Burkitt
Candidiasis, esophageal	Lymphoma, immunoblastic
Cervical cancer, invasive (specific to adults, adolescents, children >6 years)	Lymphoma, primary, or brain
Coccidioidomycosis, disseminated or extrapulmonary	*Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary	*Mycobacterium tuberculosis*, any site (pulmonary or extrapulmonary)
Cryptosporidiosis, chronic intestinal (duration >1 month)	*Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month	*Pneumocystis jirovecii* pneumonia (PCP)
Cytomegalovirus retinitis (with loss of vision)	Pneumonia, recurrent (specific to adults, adolescents, children >6 years)
Encephalopathy, HIV-related	Progressive multifocal leukoencephalopathy
Herpes simplex: chronic ulcer(s) (duration >1 month); or bronchitis, pneumonitis, or esophagitis, onset at age >1 month	*Salmonella* septicemia, recurrent Toxoplasmosis of brain, onset at age >1 month Wasting syndrome due to HIV
Histoplasmosis, disseminated or extrapulmonary Isosporiasis, chronic intestinal (duration >1 month) Kaposi's sarcoma	

Data from Reference 19.

The epidemic in the United States initially was established in men who have sex with men (MSM), and this population continues to be prominently affected by HIV, accounting for approximately 65% of new cases.[21] Heterosexual transmissions accounted for approximately 25% of new cases and approximately 75% of these are women. Injection-drug use makes up about 10% of new cases. For women, the main risk factor for transmission is heterosexual intercourse (~87% of cases) and injection-drug use (~12% of cases). For men, the main risks are MSM (~78%), heterosexual sex (~10%), and injection-drug use (~10%).[21] African Americans and Hispanics are disproportionately affected by HIV infection. Of new infections in recent years, 44% were African American and

24% were Hispanic, although these populations only make up 12% and 18% of the US population, respectively. A relatively large proportion of these populations are not well linked to appropriate prevention, care, and treatment services, which represents a significant public health challenge.[20]

The number of individuals living with HIV/AIDS globally has risen to approximately 37 million persons.[1,2,23] Recent increases are due to a longer lifespan due to wider implementation of ART worldwide. This has reduced the death rate and new infection rate in recent years. For example, the peak number of new infections was 3.3 million per year in 2002 and this has declined to 1.8 million in 2017. New infections in children (mostly due to mother-to-child transmission) have declined by 35% between 2010 and 2017, and overall deaths have declined by approximately 50% since 2004. Nevertheless, approximately 940,000 people succumbed to HIV/AIDS in 2017 and HIV/AIDS is still a major contributor to the global burden of disease.[23,24] The highest concentration of HIV/AIDS cases in the world is in sub-Saharan Africa, where approximately 25 million people are infected. However, new infections have declined there by approximately 30% since 2010, albeit with regional differences.[1,23,24] Heterosexual transmission is the most common mode of transmission in sub-Saharan Africa and worldwide (~80% of cases). Women in sub-Saharan Africa and resource-limited countries are at disproportionately high risk for acquiring HIV because of biological and cultural factors that foster HIV transmission, such as limited ability to refuse sex.[23] Other important epidemiologic features of the HIV epidemic include growing incidence among injection-drug users in North Africa and the Middle East, as well as some regions of Eastern Europe and Central Asia (eg, Russia and Ukraine).[1]

ETIOLOGY

HIV is an enveloped single-stranded RNA virus and a member of the Lentivirinae (*lenti*, meaning “slow”) subfamily of retroviruses. Lentiviruses are characterized by their indolent infectious cycle. There are two related but distinct types of HIV: HIV-1 and HIV-2. HIV-2, found mostly in western Africa, consists of seven phylogenetic lineages designated as subtypes (clades) A through G. Four groups of HIV-1 are recognized: M (main or major), N (non-M, non-O), O (outlier), and P (pending the identification of further cases).[2] The nine subtypes of HIV-1 group M are identified as A through D, F through H, J, and K. Mixtures of subtypes are referred to as *circulating recombinant forms.* Group M, subtype B, is primarily responsible for the epidemic in North America and

western Europe.[25]

The accumulated evidence suggests that HIV in humans was the result of a cross-species transmission (zoonosis) from primates infected with simian immunodeficiency virus (SIV).[25] Phylogenetic and geographic relationships suggest that HIV-2 arose from SIV that infects sooty mangabeys, and HIV-1 groups M and N arose from SIVcpz, a virus that infects chimpanzees (*Pan troglodytes troglodytes*). Groups O and P may have arisen from an SIV variant that infects wild gorillas. Cultural practices, such as preparation and eating of bush meat or keeping animals as pets, may have allowed the virus to cross from primates to humans. The earliest known human infection with HIV has been traced to central Africa in 1959, but cross-species transmissions probably date back to the early 1900s.[25] Modern transportation, promiscuity, and drug abuse have caused the rapid spread of the virus within the United States and throughout the world. This chapter focuses on HIV-1 group M, which is the predominant strain likely to be encountered in the western world.

PATHOGENESIS

Understanding the life cycle of HIV (**Fig. 143-1**) is necessary because the current strategies used for treatment of HIV target points in this cycle. Once HIV enters the human body, the outer glycoprotein (gp160) on its surface, which is composed of two subunits (gp120 and gp41), has affinity for CD4 receptors, proteins present on the surface of T-helper lymphocytes, monocytes, macrophages, dendritic cells, and brain microglia. The gp120 subunit is responsible for CD4 binding. Once initial binding occurs, the intimate association of HIV with the cell is enhanced by further binding to chemokine coreceptors. The two major chemokine receptors used by HIV are chemokine (C–C motif) receptor 5 (CCR5) and chemokine (C–X–C motif) receptor 4 (CXCR4). HIV isolates may contain a mixture of viruses that target one or the other of these coreceptors, and some viral strains may be dual-tropic (ie, can use both coreceptors). The HIV strain that preferentially uses CCR5, R5 viruses, is macrophage-tropic and typically implicated in most cases of sexually transmitted HIV.[26] Individuals with a common 32-base-pair deletion in the CCR5 gene are protected from progression of HIV disease, and those who are homozygous for the 32-base-pair deletion have a degree of resistance to acquisition of HIV-1.[27] The HIV strain that targets CXCR4, designated X4 virus, is T-cell-tropic and often is predominant in the later stage of disease. CD4 and coreceptor attachment of HIV to the cell promotes membrane fusion, which is mediated by

gp41, and finally internalization of the viral genetic material and enzymes necessary for replication.

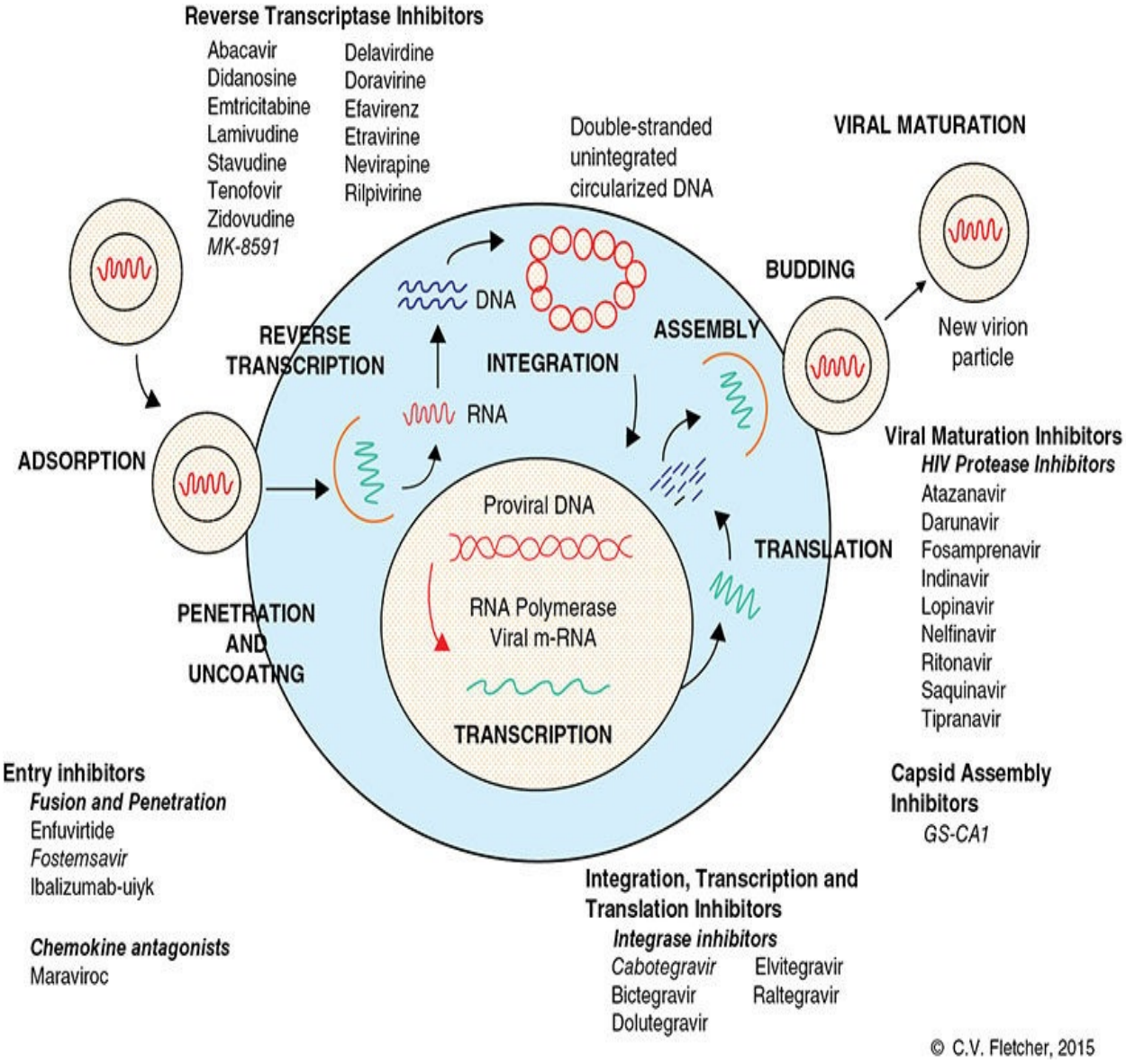


FIGURE 143-1 Life cycle of human immunodeficiency virus with potential targets where replication may be interrupted. Italicized compounds were in development at the time of this writing.

After internalization, the viral protein shell surrounding the nucleic acid (capsid) is uncoated in preparation for replication.[28] The genetic material of HIV is positive-sense single-stranded RNA; the virus must transcribe this RNA into DNA (transcription normally occurs from DNA to RNA; HIV works backward, hence the name *retrovirus*). To do so, HIV is equipped with the unique enzyme

RNA-dependent DNA polymerase (reverse transcriptase). HIV reverse transcriptase first synthesizes a complementary strand of DNA using the viral RNA as a template. The RNA portion of this DNA–RNA hybrid is then partially removed by ribonuclease H (RNase H), allowing HIV reverse transcriptase to complete the synthesis of a double-stranded DNA molecule. The fidelity of HIV reverse transcriptase is poor, and many mistakes are made during the process. These errors in the final DNA product contribute to the rapid mutation of the virus, which enables the virus to evade the immune response (thus complicating vaccine development), and promotes the evolution of drug resistance during partially suppressive therapy. Following reverse transcription, the final double-stranded DNA product migrates into the nucleus and is integrated into the host cell chromosome by integrase, another enzyme unique to HIV.

The integration of HIV into the host chromosome is critically important. Most notably, HIV can establish a persistent, latent infection, particularly in long-lived cells of the immune system such as memory T lymphocytes. The virus is effectively hidden in these cells, and this characteristic has greatly complicated efforts to cure HIV infection.[29] It also necessitates continuous ART therapy because virus reemerges from this reservoir if therapy is suspended.

After integration, HIV preferentially replicates in activated cells. Activation by antigens, cytokines, or other factors stimulates the cell to produce nuclear factor kappa B (NF-κB), an enhancer-binding protein. NF-κB normally regulates the expression of T-lymphocyte genes involved in growth but also can inadvertently activate replication of HIV.[29] HIV encodes six regulatory and accessory proteins: Tat, Nef, Rev, Vpu, Vif, and Vpr, which enhance replication and inhibit innate immunity. For example, the Tat protein is a potent amplifier of HIV gene expression; it binds to a specific RNA sequence of HIV that initiates and stabilizes transcription elongation.[29] Vif is a viral protein that binds human APOBEC 3G, a cytidine deaminase that disrupts the virus' genetic code by converting viral RNA cytosine to uracil, thereby providing innate cellular immunity.[30] Vpu inhibits tetherin, a human cellular membrane protein that prevents release of virus particles after budding from infected cells. Assembly of new viral particles occurs in a stepwise manner beginning with the coalescence of HIV proteins beneath the host cell lipid bilayer. The nucleocapsid subsequently is formed with viral single-stranded RNA and other components packaged inside. Once packaged, the virion then buds through the plasma membrane, acquiring the characteristics of the host lipid bilayer. After the virus buds, the maturation process begins. Within the virion, protease, another enzyme unique to HIV, cleaves a large precursor polypeptide (gag-pol) into functional

proteins that are necessary to produce a complete and infectious virus. Without this enzyme, the virion is immature and unable to infect other cells.

The natural history of HIV infection exhibits three general phases: acute, chronic, and terminal (AIDS). Initial rounds of HIV replication during acute infection take place largely in the mucosal CD4+, CCR5+ T-cell pools in the gut, resulting in a massive CD4 T-cell depletion in these tissues.[31] Cells are destroyed by various mechanisms, including cell lysis from newly budding virions, cytotoxic T-lymphocyte-induced cell killing, and induction of apoptosis. Following this destruction of the mucosal CD4 T-cell pool, which lasts for 2 to 3 weeks, a state of heightened immune activation ensues during the chronic infection phase, which can last for several years. The activated state is characterized by high levels of activation markers on circulating T cells (eg, HLA-DR and CD38) and proinflammatory cytokines, and may result from HIV antigen as well as translocation of microbial antigens from the T-cell-depleted gut mucosa. Heightened activation enables further HIV replication and ultimately leads to continued depletion of CD4+, CCR5+ T cells. HIV-1 exhibits a very high turnover rate during this chronic phase, with an estimated 10 billion new viruses produced each day.[32] More than 99% of these viruses are produced in newly infected activated cells. Nevertheless, for much of the chronic phase, the immune system is able to operate well enough to prevent overt OIs that herald AIDS. However, the depletion of CD4 cells and the continuous cellular activation eventually lead to a final collapse of the immune system, or AIDS. HIV may use the CXCR4 coreceptor during this last phase of infection, and these viruses infect a broader range of CD4 cells (naïve and central-memory) speeding the disease progression. It is this unrelenting destruction of CD4 cells that causes the profoundly compromised immune system and AIDS.

DIAGNOSIS

Detection of HIV and Surrogate Markers of Disease Progression

HIV is diagnosed through a multi-step process.[33] The presence of HIV infection is screened with an enzyme-linked immunosorbent assay (ELISA), which detects antibodies against HIV-1. Although ELISA has been the mainstay of HIV screening for decades, the technology has been evolving to detect infection earlier in the time course of the disease.[34] Older ELISA tests detected IgG (second-generation tests), but more modern tests detect IgG and IgM (third-

generation tests) and may further include detection of p24 antigen, an early marker of infection (fourth-generation tests). These technological advances enable earlier detection of HIV by as much as 15 to 20 days compared with older second-generation tests. ELISA tests are generally highly sensitive (greater than 99%) and highly specific (greater than 99%), but rare false-positive results can occur particularly in those with autoimmune disorders.[33] False-negative results also occur and may be attributed to the "window period" before adequate production of antibodies or antigen. This "window period" between HIV acquisition and detection of HIV with fourth- and third-generation tests is approximately 2 and 3 weeks, respectively.[33] Positive screening tests are confirmed with another enzyme immunoassay to specify if the antibodies are to HIV-1 versus HIV-2. (Although HIV-2 is rare in the United States, this step ensures proper diagnosis and treatment.) If this follow-up assay is indeterminant or negative, an HIV nucleic acid test is performed for definitive diagnosis. HIV-RNA is the earliest indicator of infection, detectable ~10 days from acquisition and about 1 week before fourth-generation tests.[34] Several point-of-care screening kits are available for serum, plasma, whole blood, or oral fluids. While oral fluid tests are convenient, they are not as sensitive as blood assays, which may result in false-negatives early in infections; this is a particular disadvantage in the setting of HIV testing prior to initiating or continuing preexposure prophylaxis (PrEP).[34]

HIV testing is recommended when HIV infection is suspected because of symptoms and/or high-risk behavior.[35] Additionally, the CDC recommends routine HIV screening at least once in all healthcare settings in all persons 13 to 64 years, a policy called "opt-out" testing.[36] A focus of the recommendations is to screen persons at high risk of HIV infection (eg, MSM) at least annually and to screen pregnant women while they are in care. The policy states that consent for medical care will imply consent for HIV testing; however, the person must be informed of the test and can opt out of taking it. Because states may have different HIV consent laws, the local requirements for HIV testing should be consulted. The rationale for the opt-out strategy is to diagnose those who unknowingly carry HIV so as to initiate ART early, leading to improved prognosis and reduced forward transmissions.

Once diagnosed, HIV disease is monitored primarily by two surrogate biomarkers, viral load and CD4 cell count.[37] The viral load test quantifies the degree of viremia by measuring the number of copies of viral RNA (HIV-RNA) in the plasma. Methods for determining HIV-RNA include reverse-transcription polymerase chain reaction (RT-PCR), branched-chain DNA, transcription-

mediated amplification, and nucleic acid sequence-based assay. RT-PCR is used more widely than the other techniques.[34] Irrespective of the method used, viral load is reported as the number of viral RNA copies per milliliter of plasma. Each assay has its own lower limit of quantitation, and results can vary from one assay method to the other; therefore, it is recommended that the same assay method be used consistently for each patient. Reductions in viral load often are reported in base 10 logarithm. For example, if a patient presents initially with a viral load of 100,000 copies/mL (10^5 copies/mL or 10^8 copies/L) and subsequently has a viral load of 10,000 copies/mL (10^4 copies/mL or 10^7 copies/L), the decrease is 1 $\log_{10}$. Given that HIV-RNA varies within a patient, a perceptible clinical response is generally considered when the decline in viral load is more than 0.5 $\log_{10}$.[37] Viral load is a major prognostic factor for disease progression, CD4 count decline, and death.[37,38] It is also the predominant way to assess the effectiveness of treatment.

Because HIV attacks and leads to the destruction of cells bearing the CD4 receptor, the number of CD4 lymphocytes (T-helper cells) in the blood is a critical surrogate marker of disease progression and immune system status.[37] The normal adult CD4 lymphocyte count ranges from 500 to 1,600 cells/mm^3 (0.5×10^9–1.6×10^9/L), or 40% to 70% (0.4 to 0.7) of total lymphocytes. CD4 counts in children are age dependent, with younger children having higher CD4 counts (see Table 143-1). The hallmark of HIV disease is depletion of CD4 cells and the associated development of OIs and malignancies, especially at lower CD4 cell counts.

CLINICAL PRESENTATION

3 Clinical presentation of primary HIV infection varies, but most patients (50%–90%) have an acute retroviral syndrome or mononucleosis-like illness, presumably due to the host immune response to the virus (ie, “cytokine storm”) (**Table 143-2**).[39] Although many of these symptoms are nonspecific, the presence of aseptic meningitis, oral or genital ulcers, rash, and leukopenia should raise suspicion of acute HIV infection in the setting of a potential exposure. Symptoms often last 2 weeks, and hospitalization may be required for a small fraction of patients. Primary infection is associated with a high viral load (more than 10^6 copies/mL [10^9/L]) and a precipitous drop in CD4 cells. After several weeks, an immune response is mounted, the amount of HIV-RNA in plasma falls substantially, CD4 cells rebound slightly, and symptoms resolve gradually.

However, as described above, this clinically latent period is not virologically latent because HIV replication is continuous (~10 billion viruses per day) and immune system destruction is ongoing. A steady decrease in CD4 cells (approximately 50 cells/μL [0.05×10^9/L] per year) is the most measurable aspect of this immune system deterioration during the asymptomatic phase. Plasma viral load, on the other hand, will appear to have stabilized at a particular level or "set point." The set point correlates strongly with the CD4 cell decline and time to AIDS and morbidity. For example, prior to ART, the Multicenter AIDS Cohort Study measured viral load in 1,604 HIV-positive men and followed them for as long as 11 years. The CD4 cell count decline was approximately twice as fast in those with HIV-RNA above 30,000 copies/mL (30×10^9/L) compared with those with HIV-RNA less than or equal to 500 copies/mL (500×10^3/L) and mortality rates (within 6 years) were 69.5% versus 0.9%, respectively.[38] Thus, a higher viral set point is associated with faster disease progression and poorer prognosis. Not all individuals infected with HIV progress to AIDS—these so-called "long-term nonprogressors" may be infected with a defective virus (eg, Nef-deficient HIV) or may have an intrinsic ability to resist infection (eg, CCR5 mutation).

TABLE 143-2 Clinical Presentation of Primary Human Immunodeficiency Virus Infection in Adults

Signs and Symptoms
Most common: Fever, headache, sore throat, fatigue, GI upset (diarrhea, nausea, vomiting), weight loss, myalgia, morbilliform or maculopapular rash usually involving the trunk, lymphadenopathy, night sweats
Less common: Aseptic meningitis, oral ulcers, leukopenia
Other
High viral load (may exceed 1,000,000 copies/mL or 10^9/L)
Persistent decrease in CD4 lymphocytes

Data from Reference 39.

Most children born with HIV are asymptomatic. On physical examination, children often present with nonspecific signs, such as lymphadenopathy, hepatomegaly, splenomegaly, failure to thrive, weight loss or unexplained low birth weight (in prenatally exposed infants), and fever of unknown origin.[40] Laboratory findings include anemia, hypergammaglobulinemia (primarily IgA and IgM), altered mononuclear cell function, and altered T-cell subset ratios. Of note, the normal range for CD4 cell counts in young children is much different

from the range in adults (Table 143-1). Children have different susceptibility and/or exposures to OIs compared with adults. Bacterial infections, including *Streptococcus pneumoniae*, *Salmonella* spp., and *Mycobacterium tuberculosis*, may be more prevalent in children with AIDS than in adults with the disease. Kaposi's sarcoma is rare in children. Children with HIV infection may develop lymphocytic interstitial pneumonitis without evidence of *P. jirovecii* or other pathogens on lung biopsy. Some children (~25%) will progress to AIDS rapidly within the first year of life. A presentation of serious OIs such as *P. jirovecii* pneumonia, encephalopathy, failure to thrive, and a precipitous drop in CD4 cells are common in these infants. General management of the HIV-infected child involves principles similar to those used for the adult: ART, treatment and prophylaxis of OIs, and supportive care.[41,42]

TREATMENT

Desired Outcomes

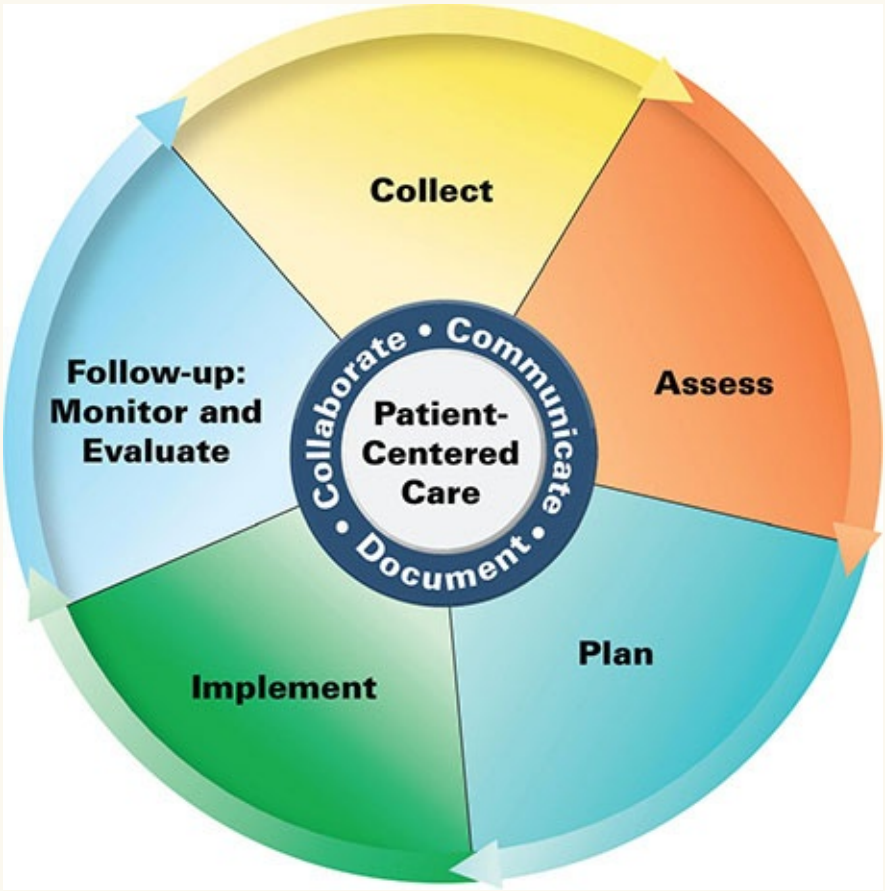
4 The central goals of ART are to decrease morbidity and mortality, improve quality of life, restore and preserve immune function, and prevent further transmission.[37] The most important and effective way to achieve these goals is maximal and durable suppression of HIV replication, which is interpreted as plasma HIV-RNA less than the lower limit of quantitation (ie, undetectable; usually less than 20 or 50 copies/mL [20 x 10^3 or 50 × 10^3/L]). Such a profound reduction in HIV-RNA is associated with reduced transmissions and long-term response to therapy (ie, durability), as well as increases in CD4 lymphocytes that closely correlates with a reduced risk for developing OIs. While undetectable HIV-RNA almost always corresponds with a rise in CD4 lymphocytes, some patients respond virologically or immunologically without the other.

General Approach to Treatment

5 Contemporary combinations of three active antiretroviral agents from two pharmacologic classes potently inhibit HIV replication to undetectable plasma levels, prevent and reverse immune deficiency, and substantially decrease morbidity and mortality—constituting the modern ART era.[43] Principles that serve as a guide for the clinical use of antiretroviral agents are still relevant

today[44]:

1. Ongoing HIV replication leads to immune system damage and progression to AIDS. HIV infection is always harmful, and true long-term survival free of clinically significant immune dysfunction is unusual.
2. Plasma HIV-RNA levels indicate the magnitude of HIV replication and its associated rate of CD4 cell destruction, whereas CD4 cell counts indicate the extent of HIV-induced immune damage already suffered.
3. Use of potent combination ART to suppress HIV replication to below the levels of detection of sensitive plasma HIV-RNA assays limits the potential for selection of antiretroviral-resistant HIV variants, the major factor limiting the ability of antiretroviral drugs to inhibit virus replication and delay disease progression. Therefore, maximum achievable suppression of HIV replication should be the goal of therapy.
4. The most effective means for accomplishing durable suppression of HIV replication is simultaneous initiation of combinations of effective anti-HIV drugs with which the patient has not been treated previously and that are not cross-resistant with antiretroviral agents with which the patient has been treated previously.
5. Each of the antiretroviral drugs used in combination therapy regimens always should be used according to optimal schedules and dosages.
6. The available effective antiretroviral drugs are limited in number and mechanism of action, and cross-resistance between specific drugs has been documented. Therefore, any change in ART increases future therapeutic constraints.
7. Women should receive optimal ART regardless of pregnancy status.
8. The same principles of ART apply to both HIV-infected children and adults, although treatment of HIV-infected children involves unique pharmacologic, virologic, and immunologic considerations.
9. Persons with acute primary HIV infections should be treated with combination ART to suppress virus replication to levels below the limit of detection of sensitive plasma HIV-RNA assays.



Patient Care Process for Human Immunodeficiency Virus (HIV)

Collect

- Patient characteristics (eg, age, sex, race, ethnicity, contraception methods or pregnancy intentions)
- Patient medical history (eg, HBV, HCV, STIs, other chronic/acute illnesses)
- Previous HIV/AIDS history (mode of transmission, date of diagnosis, nadir $CD4^+$ T-cell count, history of previous OIs, history of antiretroviral resistance)
- Social history (eg, drug use, sexual history, high-risk behaviors)
- Current prescription and nonprescription medications including herbal

products, dietary supplements, and any previous antiretroviral regimens

- Objective data
  - HIV screening and confirmatory tests
  - HIV-RNA and $CD4^+$ cell count
  - Baseline antiretroviral resistance testing
  - HLA B5701 testing
  - Complete blood count, basic metabolic panel, liver function panel, sexually transmitted infection screening

Assess

- Understanding of disease state and goals of treatment
- Access to ART (ie, insurance and co-pays)
- Willingness to start and adhere to ART
- Potential drug–drug interactions
- Any contraindications or concerns related to recommended ART regimens (eg, chronic kidney disease, ART resistance, HLA B5701 genotype, history of cardiovascular disease, hyperlipidemia, uncontrolled psychiatric illness, pregnancy or desire to become pregnant, history of multiple bone fractures or severe osteoporosis)
- Need for OI prophylaxis (ie, $CD4^+$ cell count)

Plan*

- ART regimen including specific agents, dose, frequency, administration (eg, food requirements), drug–drug interactions (see Tables 143-3 and 143-4)
- Monitoring parameters including efficacy (eg, HIV-RNA, $CD4^+$ cell count) and safety (eg, adverse effects, SCr, LFTs, CBC)
- Follow-up every 3 months until HIV-RNA is undetectable
- Patient education (eg, purpose of treatment, importance of adherence, transmission risk, drug-specific information; see Table 143-4)
- Referrals to other providers when appropriate (eg, behavioral health, social work)

Implement*

- Provide patient education regarding all elements of treatment plan
- Emphasize need for adherence to ART regimen and provide resources that can be used to maximize adherence
- Schedule follow-up for assessment of ART efficacy, safety, and adherence

Follow-up: Monitor and Evaluate

- Therapeutic efficacy (ie, reduction in HIV-RNA) and safety
- Restoration of immune function (ie, increasing $CD4^+$ cell count)
- Presence of adverse effects (eg, GI upset, headache, nausea)
- Renal and hepatic function
- Patient access and adherence to ART

**Collaborate with patient, caregivers, and other healthcare professionals.*

The extent to which these principles will continue to stand the test of time is unknown; new information on the pathogenesis and treatment of HIV accrues constantly. As of August 2018, 32 antiretroviral compounds have been approved by the FDA; two (amprenavir and zalcitabine) have since been removed from the market. **Table 143-3** presents the state of the art for treatment of HIV-infected individuals as of August 2018.[37] Treatment is recommended for all HIV-infected persons regardless of CD4 lymphocyte count, as long as the patient is ready to adhere to therapy. Urgent indications for therapy include pregnancy, history of AIDS-defining illness, CD4 counts below 200 cells/mm^3 (0.2 x 10^9/L), HIV-associated nephropathy, HIV/hepatitis C virus coinfection, and/or HIV/hepatitis B virus coinfection.

TABLE 143-3 Treatment of Human Immunodeficiency Virus Infection: Antiretroviral Regimens Recommended in Antiretroviral-Naïve Persons

	Preferred Regimens	Selected Limitations
InSTI-based	Bictegravir + tenofovir alafenamide fumarate + emtricitabine (coformulated) (AI)	Only if CrCl ≥ 30 mL/min (0.5 mL/s); interactions with polyvalent antacids; bictegravir inhibits creatinine secretion increasing serum creatinine (distinguish vs renal dysfunction)
	Raltegravir + tenofovir + emtricitabine (AI for tenofovir disoproxil fumarate; AII for tenofovir alafenamide fumarate)	Can be dosed once or twice daily; interactions with polyvalent antacids; creatine kinase increases
	Dolutegravir + abacavir + lamivudine (coformulated) (AI)	Only if HLA-B5701 negative; interactions with polyvalent antacids; possible increased risk of neural tube defects in infants if used at the time of conception; dolutegravir inhibits creatinine secretion increasing Scr—distinguish vs renal dysfunction
	Dolutegravir + tenofovir disoproxil fumarate (or tenofovir alafenamide fumarate) + emtricitabine (AI)	Same as above without HLA-B5701 negative requirement
Selected Alternative Regimens (Some Potential Disadvantages vs Preferred Regimens)		
InSTI-based	Elvitegravir + cobicistat + tenofovir disoproxil fumarate + emtricitabine (coformulated) (AI)	Only if CrCl ≥ 70 mL/min (1.17 mL/s); food requirement; interactions with polyvalent antacids; CYP3A4 drug interactions; cobicistat inhibits creatinine secretion increasing Scr - distinguish vs renal dysfunction
	Elvitegravir + cobicistat + tenofovir alafenamide fumarate + emtricitabine (coformulated) (AI)	Only if CrCl ≥ 30 mL/min (0.5 mL/s); same as above
	Raltegravir + abacavir + lamivudine (BI)	Only if HLA-B5701 negative and HIV-RNA < 100,000 copies/mL (100 x 10^6/L); can be dosed once or twice daily; interactions with polyvalent antacids; creatine kinase increases
HIV PI-based	Atazanavir + ritonavir (or cobicistat) + tenofovir disoproxil fumarate (or tenofovir alafenamide fumarate) + emtricitabine (BI)	GI; food requirement; CYP3A4 drug interactions; hyperbilirubinemia leading to drug discontinuation, especially in those with Gilbert's; only for CrCl ≥ 70 mL/min (1.17 mL/s) as cobicistat inhibits creatinine secretion increasing Scr—distinguish vs renal dysfunction
	Atazanavir + ritonavir (or cobicistat) + abacavir + lamivudine (CI for ritonavir and CIII for cobicistat)	Only if HLA-B5701 negative; see issues above
	Darunavir + ritonavir (or cobicistat) + tenofovir disoproxil fumarate (or tenofovir alafenamide fumarate) + emtricitabine (AI for ritonavir and AII for cobicistat)	Rash (darunavir has sulfonamide moiety); GI; food requirement; CYP3A4 drug interactions; only for CrCl ≥ 70 mL/min (1.17 mL/s) as cobicistat inhibits creatinine secretion increasing serum creatinine (distinguish vs renal dysfunction); see issues above
	Darunavir + ritonavir (or cobicistat) + abacavir + lamivudine (BII)	Only if HLA-B5701 negative; see issues above
NNRTI-based	Doravirine + tenofovir disoproxil fumarate + lamivudine (coformulated) (BI) Doravirine + tenofovir alafenamide + emtricitabine (BIII)	Only if CrCl ≥ 50 mL/min (0.83 mL/s)
	Efavirenz + tenofovir disoproxil fumarate + emtricitabine (coformulated) (BI) Efavirenz + tenofovir alafenamide fumarate + emtricitabine (BII)	CNS side effects with efavirenz; CYP450 drug interactions; empty stomach dosing; teratogenic in non-human primates—controversial in humans—consider avoiding in women planning to conceive
	Rilpivirine + tenofovir disoproxil fumarate (or tenofovir alafenamide fumarate) + emtricitabine (coformulated) (BI)	Not recommended when HIV-RNA >100,000 copies/mL (100 × 10^6/L) or CD4 <200 cells/μL (0.2 × 10^9/L); no proton-pump inhibitors (rilpivirine); food requirement; antacid interactions
If abacavir and tenofovir cannot be used	Dolutegravir + lamivudine (CI)	Only if HIV-RNA < 500,000 copies/mL (500 x 10^6/L); possible increased risk of neural tube defects in infants if used at the time of conception
	Darunavir + ritonavir + raltegravir (CI)	Only if HIV-RNA < 100,000 copies/mL (100 x 10^6/L)and CD4 > 200 cells/mm^3 (0.2 x 10^9/L); raltegravir must be dosed twice daily
	Darunavir + ritonavir + lamivudine (CI)	
Selected Regimens or Components that Should not be Used at Any Time		
Regimen or Component		**Comment**
Monotherapy with any single agent (AI)		Inferior virologic efficacy
Any NRTI regimen (AI)		Inferior virologic efficacy
Atazanavir + indinavir (AIII)		Additive adverse effects, including hyperbilirubinemia and jaundice
Didanosine + tenofovir (AII)		Inferior virologic efficacy, CD4 declines
Didanosine + Stavudine (AII)		Toxicity including subcutaneous fat loss, peripheral neuropathy, and lactic acidosis
2 NNRTI combinations (AI)		Higher adverse events, drug interactions

Regimen or Component	Comment
Emtricitabine + lamivudine or zidovudine + stavudine (AIII, AII)	Analogs of same nucleobase, no additive benefit (or antagonistic)
Unboosted PIs (ie, darunavir, saquinavir, tipranavir) (AII)	Inadequate bioavailability
Etravirine + selected boosted PIs (AII)	Possible induction of PI metabolism, doses not established
Nevirapine in ARV naïve with higher CD4 counts (>250 cells/μL [0.25 x 10^9/L] for women, >400 cells/μL [0.4 x 10^9/L] for men) (BI)	High incidence of symptomatic hepatotoxicity

Evidence-based rating definition. Rating strength of recommendation—A: Strong recommendation. B: Moderate recommendation. C: Optional recommendation. Rating Quality of Evidence Supporting the Recommendation—I: Evidence from at least one correctly randomized, controlled trial with clinical outcomes and/or validated laboratory. II: Evidence from at least one well-designed clinical trial without randomization or observational cohorts with long-term clinical outcomes. III: Expert opinion. Lamivudine and emtricitabine are considered interchangeable endpoints.

Data from Reference 37.

The optimal time to initiate therapy in chronic HIV infection has been a matter of debate for decades. The main arguments for postponing therapy were the concern for cumulative drug toxicity and trepidation for drug resistance and loss of therapeutic options. These concerns were well-founded when older drugs such as lopinavir/ritonavir, stavudine, zidovudine, indinavir, and efavirenz were the mainstay of therapy. Today, the availability of newer medications with different mechanisms of action (eg, InSTIs), significantly improved adverse event profiles, and the convenience of single tablet regimens help to mitigate these issues.

An additional issue, until recently, was the lack of high-quality evidence of clinical benefits for initiating therapy at higher versus lower CD4 counts (eg, 500 cells/μL [0.5 × 10^9/L] vs 350 cells/μL [0.35 × 10^9/L]). This issue was addressed in 2015 with results from two large randomized controlled trials.[45,46] The START trial randomized 4,685 patients with CD4 counts above 500 cells/μL (0.5 × 10^9/L) to either immediate ART or to delayed ART until the CD4 count reached 350 cells/μL (0.35 × 10^9/L). Immediate ART resulted in significantly fewer serious AIDS events (HR 0.28, 95% CI 0.15–0.50) and non-AIDS events (HR 0.61, 0.38–0.97) as compared with delaying ART. The TEMPRANO study was conducted in the Ivory Coast where HIV and tuberculosis (TB) coinfection is endemic. The trial randomized 2,056 patients with less than or equal to 800 CD4 cells/μL (0.8 × 10^9/L) to immediate ART, immediate ART with isoniazid

TB prophylaxis, delayed ART (based upon WHO guidelines), or delayed ART with isoniazid TB prophylaxis. Again, immediate ART resulted in fewer deaths or severe HIV-related illnesses as compared with deferred ART (HR among patients with a baseline CD4 greater than or equal to 500 cells/μL [0.5×10^9/L], 0.56; 95% CI, 0.33–0.94). In addition to these important studies, immediate ART and subsequent suppressed viral load is known to substantially prevent ongoing HIV transmissions compared with delayed ART.[5,47] Taken together, these studies provide high-quality evidence that untreated HIV is harmful even at high CD4 counts and immediate ART confers individual- and population-level benefit compared with delayed ART. Major policy-makers, including the WHO and US Department of Health and Human Services (DHHS), now recommend immediate ART regardless of CD4 count.[37,48] An excellent source of information on updated treatment guidelines is www.AIDSinfo.NIH.gov. Healthcare professionals involved in the care of HIV-infected persons are urged to consult the most current literature on the principles and strategies for ART therapy.

Pharmacologic Therapy

Several methods of therapeutic intervention have been evaluated against HIV, including systemic antiretroviral drugs (the focus of this chapter) for direct inhibition of chronic viral replication or prevention of HIV acquisition; vaccination; immunomodulators to help stimulate and restore the immune system; and topical antiretroviral drugs or virucides (chemicals that destroy intact viruses) to prevent HIV infection. The latter three approaches are investigational at this time. Several approaches for an HIV vaccine are in development, including whole killed virus, subunit and peptide vaccination, recombinant live vector, and naked DNA delivery. Historically, vaccine progress has been slow. Genetic variability in HIV and a nascent understanding of the role of the immune system in suppressing viral replication are significant barriers to the development of an effective HIV vaccine with long-lasting and protective immunity. A randomized placebo-controlled trial demonstrated a modest 30% reduction in HIV transmission in a modified intention-to-treat analysis of ALVAC-HIV plus AIDSVAX vaccine in 16,402 volunteers.[49] Efforts are now underway to understand the correlates of protection from this study to inform the vaccine field going forward.[50] Immunomodulators, such as aldesleukin (interleukin-2), provide mild benefits in terms of increased CD4 cells; however, aldesleukin is also associated with significant toxicities and no apparent clinical benefit.[51] Thus, the future is uncertain for immunomodulatory approaches.

Topical virucidal or antiretroviral drug formulations for use vaginally or rectally to prevent sexual transmission of HIV are in various phases of development.[10] For example, vaginal application of tenofovir 1% gel before and after intercourse reduced HIV acquisition by 39% in women.[52] However, daily tenofovir 1% gel administered vaginally did not reduce HIV acquisition, an outcome that was driven by poor adherence.[53] Microbicide research is now focusing on long-acting formulations (eg, vaginal rings and intra-uterine devices) to mitigate adherence challenges. Use of a dapivirine ring resulted in a ~30% reduction in HIV acquisition, leading to review by the European Medicines Agency (EMA) for HIV prevention in women.[54]

Antiretroviral Agents Systemic delivery of antiretroviral agents for direct inhibition of viral replication has been the most clinically successful strategy for both treatment and prophylaxis. Four general classes of drugs are used today: entry inhibitors, reverse transcriptase inhibitors, InSTIs, and HIV PIs (**Table 143-4**).[37] As a rule, newer agents exhibit significant advantages over first-generation drugs in terms of pharmacokinetics, tolerability, safety, and efficacy. This section will highlight specific advantages of newer agents over first-generation drugs and will focus the discussion on newer agents used most often today. Updated drug information is available in the DHHS guidelines including common adverse events and dosing recommendations for hepatic and renal insufficiency for all antiretroviral drugs.[37]

TABLE 143-4 Selected Pharmacologic Characteristics of Selected Antiretroviral Compounds

Drug	*F* (%)	$t_{1/2}$ (h)[1]	Adult Dose[2] (doses/day)	Plasma C_{max}/C_{min} (ng/mL)	Distinguishing Adverse Effect(s)
Integrase Inhibitors (InSTI)					
Bictegravir	?	17.3	50 mg (1)	6,150/2,610	Diarrhea, nausea, headache
Dolutegravir	?	14	50 mg (1)	3,670/1,110	Insomnia, headache, rash (can be severe)
			or		
			50 mg (2)	4,150/2,120	
Elvitegravir (coformulated with cobicistat)	?	13	150 mg (1)	2,100/290	Diarrhea, nausea
Raltegravir	?	9	400 mg (2)	2,171/68.5	Rash (can be severe), creatine phosphokinase increases
			or		
			1200 mg (1)	7,575/51.6	
Nucleoside (Nucleotide) Reverse Transcriptase Inhibitors (NRTIs)					
Abacavir	83	1.5/20	300 mg (2)	3,000/20	Hypersensitivity (HLA-B5701 test to predict)
			or		
			600 mg (1)	4,260[3]	
Didanosine	42	1.4/24	200 mg (2)	661/2.36	Peripheral neuropathy, pancreatitis
			or		
			400 mg (1)	1,320[3]	
Emtricitabine	93	10/39	200 mg (1)	1,800/90	Rarely pigmentation on soles and palms in nonwhites
Lamivudine	86	5/22	150 mg (2)	1,400/370	Headache
			or		
			300 mg (1)	2,410/110	
Stavudine	86	1.4/7	40 mg (2)	536/8	Lipoatrophy, peripheral neuropathy
Tenofovir alafenamide	?	35/150 (tenofovir component)	25 mg (1)	30/10	Increased lipids
			or		
			10 mg (1) (when combined with cobicistat)		
Tenofovir disoproxil fumarate	25	17/150 (tenofovir component)	300 mg (1)	299/115	Renal dysfunction (proximal tubulopathy), bone demineralization
Zidovudine	85	2/7	200 mg (3)	1,020/100	Anemia, neutropenia, myopathy
			or		
			300 mg (2)	2,290/20	
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)					
Delavirdine	85	5.8	400 mg (3)	19,344/8,290	Rash, elevated liver function tests
			or		
			600 mg (2)		
Doravirine	64	15	100 mg (1)	962/396	Abnormal dreams
Efavirenz	43	48	600 mg (1)	4,072/1,768	CNS disturbances and potential teratogenicity
Etravirine	?	41	200 mg (2)	736/161	Rash, nausea
Nevirapine	93	25	200 mg (2)[4]	5,400/3,730	Potentially serious rash and hepatotoxicity
			or		
			400 mg (1)	6,658/2,929	
Rilpivirine	?	50	25 mg (1)	280/120	Possibly depression
Protease Inhibitors (PIs)					
Atazanavir	68	7	400 mg (1)	2,298/120	Unconjugated hyperbilirubinemia
			or		
			300 mg (1)[5]	4,420/636	
Darunavir	82	15	800 mg (1)[5]	7,070/3,860	Hepatitis, rash
			or		
			600 mg (2)[5]		

Fosamprenavir[5]	?	8	1,400 mg (1)[5,6]	7,930/860	Rash
Indinavir	60	1.5	800 mg (3) *or* 400–800 mg (2)[5]	9,250/180	Nephrolithiasis
Lopinavir7	?	5.5	800 mg (1) *or* 400 mg (2)	9,800/7,100	Hyperlipidemia/GI intolerance
Nelfinavir	?	2.6	750 mg (3) *or* 1,250 mg (2)	3,000/1,400 4,700/1,500	Diarrhea
Ritonavir	60	3-5	600 mg (2)[4] *or* "Boosting doses"	11,535/3,605	GI intolerance
Saquinavir	4	3	1,000 mg (2)[5]	2,620/371	QT prolongation
Tipranavir	?	6	500 mg (2)[5]	46,770/21,456	Hepatotoxicity, intracranial hemorrhage
Entry Inhibitors					
Enfuvirtide	84	3.8	90 mg (2)	5,000/3,300	Injection-site reactions
Ibalizumab-uiyk	N/A	79	2,000 mg loading dose, then 800 mg (every 2 weeks)	567,000/230	Diarrhea, dizziness, nausea, rash
Maraviroc	33	15	300 mg (2)	618/33.6	Hepatitis, allergic reaction

[1]NtRTIs: Plasma NtRTI $t_{1/2}$/intracellular (peripheral blood mononuclear cells) NtRTI-triphosphate $t_{1/2}$; plasma $t_{1/2}$ only for other classes.

[2]Dose adjustment may be required for weight, renal or hepatic disease, and drug interactions.

[3]C_{min} concentration typically below the limit of quantification.

[4]Initial dose escalation recommended to minimize side effects.

[5]Fosamprenavir is a tablet phosphate pro-drug of amprenavir. Amprenavir is no longer available.

[6]Must be boosted with low doses of ritonavir (100–200 mg).

[7]Available as coformulation 4:1 lopinavir to ritonavir.

C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; *F*, bioavailability; $t_{1/2}$, elimination half-life.

Data from Reference 37.

Reverse transcriptase inhibitors consist of two classes: those that are chemical derivatives of purine- and pyrimidine-based nucleosides and nucleotides (nucleoside/nucleotide reverse transcriptase inhibitors [NRTIs]) and those that are not (nonnucleoside reverse transcriptase inhibitors [NNRTIs]). NRTIs include the thymidine analogs stavudine (d4T) and zidovudine (AZT or ZDV);

the deoxycytidine analogs emtricitabine (FTC) and lamivudine (3TC); the deoxyguanosine analog abacavir sulfate (ABC); and the deoxyadenosine analogs of which didanosine (ddI) is an inosine derivative and tenofovir is a deoxyadenosine-monophosphate nucleotide analog (a nucleotide is a nucleoside with one or more phosphates). **Note that drug abbreviations are provided here and below for reference, but their use is discouraged because they may lead to prescribing or administration errors.**

Tenofovir comes in two pro-drug formulations, tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF). Tenofovir disoproxil fumarate is an ester pro-drug that releases tenofovir upon absorption and first pass metabolism, producing relatively high systemic concentrations of tenofovir, which confers some risk of proximal tubulopathy and bone demineralization (both usually mild and reversible). Tenofovir alafenamide contains a different pro-drug configuration such that more of the intact pro-drug reaches the systemic circulation and penetrates lymphoid cells. Once in lymphoid cells, tenofovir is released via metabolism by cathepsin A or in hepatic cells via carboxylesterase 1. This strategy results in higher intracellular concentrations, but lower systemic tenofovir concentrations and less change in markers of proximal tubulopathy and bone demineralization.[55]

As a class, the NRTIs require phosphorylation in cells to the 5′-triphosphate moiety to become pharmacologically active. Intracellular phosphorylation occurs by cytoplasmic or mitochondrial kinases and phosphotransferases (not viral kinases). The 5′-triphosphate moiety acts in two ways: (1) it competes with endogenous deoxyribonucleotides for the catalytic site of reverse transcriptase, and (2) it prematurely terminates DNA elongation, if taken up and incorporated by reverse transcriptase, as it lacks the requisite 3′-hydroxyl for sugar-phosphate linking. NRTIs are active against both HIV-1 and HIV-2.[37] Emtricitabine, lamivudine, and tenofovir are also active against hepatitis B virus, and a combination of these agents should be used when possible in HIV–hepatitis B coinfected patients.

Although NRTI triphosphates (or diphosphate for tenofovir) are specific for HIV reverse transcriptase, their adverse effects may be caused in part by inhibition of mitochondrial DNA or RNA synthesis.[56] It is largely this problem that differentiates the first-generation drugs (didanosine, stavudine, and zidovudine) from the agents used most often at this time (tenofovir disoproxil fumarate, tenofovir alafenamide, emtricitabine, lamivudine, abacavir).[37,56] The mitochondrial toxicities include peripheral neuropathy, pancreatitis, lipoatrophy (subcutaneous fat loss), myopathy, anemia, and rarely life-threatening lactic

acidosis with fatty liver. The newer agents exhibit less potential to cause these toxicities, but they still have their own adverse event profiles to be considered (see Table 143-4).[37]

Most of the newer NRTIs are eliminated by the kidney, and dose adjustments are required for renal insufficiency; abacavir, however, is metabolized in the liver and it should not be used in advanced hepatic impairment. Resistance has been reported for all NRTIs, including cross-resistance within the class as multiple and/or specific mutations in the viral genome accrue.[57]

NNRTIs are a chemically heterogeneous group of agents that bind noncompetitively to reverse transcriptase adjacent to the catalytic site, forcing a conformation change to the enzyme. Unlike NRTIs, NNRTIs do not require intracellular activation, do not compete against endogenous deoxyribonucleotides, and do not have intrinsic antiviral activity against HIV-2. Available NNRTIs include delavirdine (DLV), doravirine (DOR), efavirenz (EFV), etravirine (ETR), nevirapine (NVP), and rilpivirine (RPV).[37] As a class, the NNRTIs are generally associated with rash and elevated liver function tests, including rare life-threatening cases, particularly for nevirapine.[56] The use of first-generation NNRTIs (delavirdine, nevirapine, efavirenz) are on the decline largely because of efficacy (delavirdine) or tolerability and/or safety concerns (nevirapine, efavirenz). However, some patients have remained on efavirenz-based therapy and it is still used in certain regions of the world. NNRTIs tend to have long plasma half-lives (except delavirdine) and they are mainly cleared by liver and/or gut-mediated metabolism through the cytochrome P450 (CYP) enzyme system. Caution should be used for those with advanced hepatic insufficiency (nevirapine should not be used in moderate or advanced hepatic insufficiency). NNRTIs can be perpetrators of drug–drug interactions, most often associated with induction of CYP metabolism. One exception to this is doravirine, which does not induce CYP metabolism. The older NNRTIs were unique, in that a single mutation is needed to confer high-level cross-resistance for the class (not including etravirine and doravirine), which has been termed a *low-genetic barrier* to resistance.[58]

The HIV PIs include atazanavir (ATV), darunavir (DRV), fosamprenavir (FPV), indinavir (IDV), lopinavir (LPV), nelfinavir (NFV), ritonavir (RTV), saquinavir (SQV), and tipranavir (TPV). HIV PIs competitively inhibit the cleavage of the gag-pol polyprotein, which is a crucial step in the viral maturation process, thereby resulting in the production of immature, noninfectious virions. HIV PIs have activity against HIV-1 and HIV-2 (particularly darunavir, lopinavir, and saquinavir).[37] HIV PIs are generally

associated with GI distress and metabolic changes, such as increased lipids, insulin insensitivity, and changes in body fat distribution. Some of these issues can be traced to formulation problems due to limited aqueous solubility, requiring high levels of excipients and large pill burdens. The first-generation HIV PIs (eg, indinavir, nelfinavir, saquinavir, lopinavir) exhibited poor solubility leading to erratic absorption (nelfinavir, saquinavir), crystallization of drug in urine (indinavir), gastrointestinal distress (nelfinavir, lopinavir), and hyperlipidemia (lopinavir). Generally, the newer HIV PIs, darunavir and atazanavir, improve upon (but do not eliminate) these issues. HIV PIs are cleared by liver- and gut-mediated metabolism (mainly CYP3A), and dose adjustments may be required in hepatic insufficiency (tipranavir/ritonavir should not be used in moderate-to-severe hepatic insufficiency). HIV PIs are almost always used with low doses of ritonavir or cobicistat, that is, CYP3A inhibitors, to increase the plasma concentrations of the HIV PI of interest. CYP3A-mediated drug interactions with concomitant medications are important considerations for PIs. Resistance to the HIV PIs generally requires the buildup of multiple mutations, termed a *high-genetic barrier* to resistance. Multiple mutations can lead to cross-resistance.[57]

There are three entry inhibitors. Enfuvirtide (T20) is the only fusion inhibitor available at this time. Enfuvirtide is a synthetic 36-amino-acid peptide that binds gp41, which inhibits envelope fusion of HIV-1 with the target cell, but does not have activity against HIV-2. Because of the peptide nature of enfuvirtide, oral delivery is impossible, and subcutaneous injection is the preferred route of administration. Injection-site reactions (pain, erythema, nodules) are the most common adverse effect, nearing 100% incidence. Enfuvirtide is cleared via protein catabolism and amino acid recycling.[37] Maraviroc is a CCR5 antagonist with activity against HIV-1 and HIV-2. Unlike the other available antiretrovirals that interact with a viral target, CCR5 antagonists block a human receptor. The long-term consequences of blocking CCR5 are unknown but may include increased susceptibility to disease by flaviviruses (eg, West Nile virus and tickborne encephalitis virus).[59] One advantage of targeting a human receptor is that resistance to CCR5 antagonists may be more difficult to develop. Because CCR5 antagonists are only effective against R5 virus and not X4 virus, a viral tropism assay must be performed prior to using a CCR5 antagonist. Maraviroc is a CYP3A and P-glycoprotein substrate and is therefore susceptible to drug–drug interactions and caution should be used in those with advanced hepatic insufficiency. Maraviroc has been associated with rash and hepatotoxicity. Resistance mutations have been identified for enfuvirtide, which has a low-

genetic barrier to resistance, but assays for maraviroc resistance have not been developed other than the R5 versus X4 tropism test.[37,57] The most recently approved entry inhibitor is ibalizumab-uiyk. It is a recombinant humanized monoclonal antibody with activity against HIV-1 that binds to domain 2 of the CD4 receptor on host cells. The binding of ibalizumab-uiyk to the CD4 receptor does not affect its ability to bind gp120 on viral particles. However, it interferes with the post-attachment steps necessary for the entry of HIV-1 viral particles into host cells. Ibalizumab-uiyk is administered by infusion and is indicated for heavily treatment-experienced adults with multidrug resistant HIV-1 infection who are failing their current antiretroviral regimen. It has activity against R5-tropic, X4-tropic, and dual-tropic viruses. The most common adverse effects associated with ibalizumab-uiyk seen in clinical trials were diarrhea, dizziness, nausea, and rash. Decreased susceptibility to ibalizumab-uiyk has been seen in some subjects, but the clinical significance of this is not well known. There is no evidence of cross-resistance between ibalizumab-uiyk and any other antiretroviral class.[60]

Among the newer classes of antiretroviral drugs are the InSTIs including, bictegravir (BIC), dolutegravir (DTG), elvitegravir (EVG), and raltegravir (RAL). InSTIs bind to HIV integrase while it is in a specific complex with viral DNA and inhibit the strand transfer that incorporates the proviral DNA into the chromosomal DNA. InSTIs are active against HIV-1 and HIV-2. Bictegravir, dolutegravir, and raltegravir are primarily glucuronidated by UGT1A1 and are not susceptible to major CYP-mediated drug interactions, although other kinds of interactions are important (Table 143-3). In particular, polyvalent cation containing antacids bind InSTIs leading to reduced bioavailability, so dosing should be separated temporally or an antacid with a different mechanism of action should be considered. Elvitegravir is extensively metabolized by CYP3A and is coformulated with cobicistat, a potent CYP3A inhibitor, to optimize drug exposure and enable once-daily dosing. InSTIs are relatively well-tolerated with adverse events that include rash, nausea, and headache. InSTIs should be used with caution in advanced hepatic insufficiency. Multiple mutations have been identified conferring resistance to InSTIs, including cross-resistance as mutations accrue. Bictegravir and dolutegravir appear to have a higher genetic barrier to resistance compared with elvitegravir and raltegravir.[61–63]

Novel antiviral agents in the classes listed above and novel agents in new drug classes that exploit other steps in the HIV life cycle (see Fig. 143-1) are in development, with a focus on long-lasting activity (eg, injectable nanosuspensions) and/or high activity against drug-resistant virus. In particular,

nanosuspensions of cabotegravir (an InSTI) and/or rilpivirine (an NNRTI) are currently in phase 3 clinical trials as intermittent injections (every 4–8 weeks) for treatment and prophylaxis.[64,65] Capsid inhibitors are another novel antiretroviral treatment approach currently in development. The capsid of HIV is the protein shell that contains the viral RNA and proteins. Upon viral entry into host cells, the capsid undergoes a disassembly process (uncoating) in order for reverse transcription to occur. Later in the replication cycle, the capsid must then assemble into its final structure. Capsid inhibitors are extremely potent and have the potential to interfere with multiple different steps in the HIV replication cycle.[66] The anti-herpes and anti-hepatitis B antivirals acyclovir, foscarnet, entecavir, and adefovir exhibit modest, non-suppressive anti-HIV activity. However, this is not a concern in the setting of suppressive ART.

6 **Drug Interactions** Medical use of antiretroviral agents is complicated by clinically significant drug–drug interactions that can occur with many of these agents.[37,67] Some interactions are beneficial and used purposely (eg, ritonavir and cobicistat as pharmacokinetic enhancers); others may be harmful, leading to dangerously elevated (eg, toxic) or inadequate drug concentrations (non-suppressive). Clinicians involved in the pharmacotherapy of HIV must understand the mechanistic basis for these interactions and maintain a current knowledge of drug interactions for these reasons.

Many clinically significant antiretroviral-associated drug interactions involve CYP3A-associated bioavailability, first-pass metabolism, and clearance. The HIV PIs (except nelfinavir), the NNRTIs delavirdine, etravirine, and rilpivirine, the CCR5 antagonist maraviroc, and the InSTI elvitegravir are extensively metabolized by CYP3A. In general, efavirenz, etravirine, and nevirapine are inducers of CYP3A, whereas delavirdine and the PIs inhibit CYP3A. Ritonavir is a potent mechanism-based inhibitor of CYP3A-mediated metabolism and is now used exclusively at lower doses as a pharmacokinetic enhancer of other HIV PIs. Similarly, cobicistat, which is an analog of ritonavir without antiretroviral activity, is also a potent mechanism-based inhibitor of CYP3A activity and is used in a similar fashion. Darunavir, lopinavir, saquinavir, and tipranavir must be taken with ritonavir or cobicistat to achieve optimal plasma concentrations. Atazanavir, fosamprenavir, and indinavir are also primarily used with ritonavir or cobicistat for the same reason. Nelfinavir is not effectively boosted by ritonavir, given its CYP2C19-mediated metabolism. Many potential concomitant drugs on the market are also metabolized by CYP3A and therefore susceptible to clinically relevant drug interactions with HIV PIs, NNRTIs, and cobicistat. Agents with narrow therapeutic indices and/or that exhibit major

changes in pharmacokinetics with CYP3A inhibition are most important in this regard. Examples include, but are not limited to, simvastatin, lovastatin, corticosteroids (including inhaled and intranasal), ergot derivatives, some antiarrhythmics, some erectile dysfunction drugs, some anticoagulants, and some anti-cancer agents.

The drug interaction potential of antimycobacterium agents, specifically the rifamycins, are particularly relevant, given the high potential for such infections in HIV-infected patients.[67] Rifampin, a potent inducer of CYP3A metabolism and conjugation enzymes, is contraindicated with use of most HIV PIs, etravirine, rilpivirine, and maraviroc because antiretroviral concentrations are reduced substantially even with ritonavir enhancement. Raltegravir or dolutegravir doses should be doubled in the presence of rifampin; efavirenz is an alternative agent. Ritonavir enhancement generally allows coadministration of HIV PIs with rifabutin.[38] In such cases, the rifabutin dose will require adjustment, given its CYP3A-mediated clearance. The herbal product St. John's wort (*Hypericum perforatum*) is a potent inducer of metabolism and is contraindicated with PIs, NNRTIs, and maraviroc.[37] It must be stressed that the pharmacology of CYP3A interactions may be complicated by simultaneous induction/inhibition of drug transporter–mediated (eg, P-glycoprotein) bioavailability or clearance and/or other phase I (eg, CYP 2B6 for RTV) or phase II enzymes.

Some antiretroviral drugs require acidic environments for optimal absorption leading to interactions with antacids, particularly proton-pump inhibitors (eg, atazanavir, rilpivirine). On the other hand, some antiretroviral agents chelate polyvalent cations in antacids, reducing absorption following concomitant dosing (eg, InSTIs); dosing can be temporally separated for these cases. Other potential mechanisms for drug interactions include inhibition of renal tubule secretion (eg, tenofovir and OAT inhibitors), and antagonistic phosphorylation for NRTIs of the same nucleobase (eg, lamivudine and emtricitabine). This list of drug interactions and mechanisms for drug interactions is not complete. Clinicians who treat HIV must stay abreast of antiretroviral drug interaction data. Websites are available that catalog and regularly update HIV drug-interaction information (http://www.hiv-druginteractions.org/), and the DHHS guidelines for antiretroviral use provide, and regularly update, excellent summaries of known clinically relevant drug interactions.[37]

7 **Landmarks in the Evolution of Antiretroviral Therapy** ART has undergone major changes over the past decades. Illustrating these changes is

important for a thorough understanding of current treatment strategies. The first landmark in this evolution was the availability of zidovudine, the first antiretroviral agent, which conferred a survival benefit in persons with AIDS, when given as monotherapy. A combination of two NRTIs was then found to be superior to zidovudine monotherapy in immunologic and virologic parameters, as well as survival benefit. Later, triple therapy (two NRTIs with an HIV PI or NNRTI) was associated with reduced incidence of OIs and improved survival, establishing the current paradigm of ART. Triple drug therapy has since evolved to include new drug classes, coformulations, and better tolerated agents. This has in turn led to improvements in convenience, tolerability, safety, and virologic efficacy.

Taken together, these landmarks established that HIV should not be treated with single or dual NRTIs. Recommendations for initial treatment of HIV infection advocate a minimum of three active antiretroviral agents: tenofovir (as either tenofovir disoproxil fumarate or tenofovir alafenamide) plus emtricitabine with an InSTI (bictegravir, dolutegravir, or raltegravir). Abacavir/lamivudine plus dolutegravir is another first-line option (abacavir can only be used in patients who are HLA-B5701 negative). Multiple alternative regimens are also safe and effective, but have one or two disadvantages compared with the preferred regimens such as weaker virologic responses with high viral loads, lower tolerability, or greater risk of long-term toxicities (eg, subcutaneous fat loss). Preferred antiretroviral regimens are listed in Table 143-3. Recommended first-line ART regimens constantly evolve (as described above) and clinical controversies emerge as data and clinical experience accrue and new strategies come under consideration.

Adherence The simplest definition of adherence is the patient's follow-through on taking medication as directed. As with any chronic therapy, variable adherence to ART is common, and significantly impacts virologic response. Factors associated with poor adherence include major psychiatric illnesses, active substance abuse, unstable social circumstances, adverse events, and poor adherence with clinic visits.[37] Most, but not all, modern ART regimens consist of coformulations and long half-life drugs allowing for once-daily dosing (sometimes without food restrictions), which facilitates improved adherence compared with multiple dose units, multiple doses per day, and food restrictions with dosing. Average adherence rates range from 60% to 80% for both HIV PI and NNRTI-based regimens, including 30% of subjects who miss less than 7 consecutive days of dosing.[74,75] The odds of persistent or breakthrough viremia are several-fold higher in patients with adherence below 60% to 80%, and the

risk mounts with longer dosing "holidays."[76] As clinicians, it is critical to establish a relationship of trust with the patient and to communicate to the patient the importance of proper medication taking. Education should be aimed at understanding the disease process, monitoring, goals of therapy, and consequences of poor adherence. An individual's "readiness" to take medications should be clearly established before treatment is initiated.[37] Help from caregivers, friends, and/or family members should be leveraged by the patient because social and psychological support are among the most important factors that influence adherence in this patient population.

Efficacy Based on clinical trial data, approximately 90% of patients will achieve undetectable viral loads with modern ART regimens.[63,72,73] The preferred NRTI combination, tenofovir (as tenofovir disoproxil fumarate or tenofovir alafenamide) plus emtricitabine, has demonstrated virologic and safety/tolerability advantages compared with zidovudine/lamivudine and abacavir/lamivudine (when combined with atazanavir/ritonavir or efavirenz).[77,78] Its main drawback is renal tubulopathy risk for tenofovir disoproxil fumarate, especially in persons with pre-existing renal dysfunction. When combined with dolutegravir, abacavir–lamivudine exhibited superior efficacy rates regardless of baseline viral load compared with efavirenz–tenofovir disoproxil fumarate–emtricitabine.[73] This finding was mainly due to fewer discontinuations arising from adverse events for the abacavir–lamivudine–dolutegravir regimen (most in the other arm were associated with efavirenz). Tenofovir alafenamide was compared with tenofovir disoproxil fumarate both given with emtricitabine–elvitegravir–cobicistat.[72] Similar efficacy was observed but changes in creatinine clearance and bone demineralization was more favorable for tenofovir alafenamide compared with tenofovir disoproxil fumarate. Together, these studies established recommendations for tenofovir disoproxil fumarate–emtricitabine, tenofovir alafenamide–emtricitabine, or abacavir–lamivudine as initial NRTI therapy. As mentioned above, if abacavir is to be used in any regimen, a test for the presence of human leukocyte antigen (HLA)-B*5701 must be done as its presence has been strongly correlated with the development of abacavir hypersensitivity. Should this test be positive, an abacavir allergy should be added to the patient's medical record and abacavir should not be used in the patient, as the hypersensitivity reaction can be life-threatening.

The third active agent of ART regimens has also evolved based on large, randomized, controlled trials. Efavirenz maintained a long history as the

recommended third active agent until recently, when comparative trials demonstrated poorer tolerability and more therapy discontinuations for efavirenz versus InSTIs.[73,79] CNS perturbations such as somnolence, vivid dreams, and depressive symptoms are troublesome issues for efavirenz. Similarly, atazanavir–ritonavir was a recommended third active agent until it showed higher rates of treatment discontinuations compared with raltegravir and darunavir-ritonavir.[80] Atazanavir inhibits the bilirubin-conjugating enzyme resulting in asymptomatic hyperbilirubinemia, but in those with Gilbert's disease, the hyperbilirubinemia can be more pronounced leading to drug discontinuation.[81] More recently, improved tolerability and increased potency of InSTIs have been demonstrated compared to PIs, including darunavir.[82] Together, these studies support recommendations for InSTIs as third active agents for preferred initial ART regimens. Many agents are available for inclusion in alternative regimens, including efavirenz, darunavir–ritonavir, and atazanavir–ritonavir, among others. Patients with sustained undetectable HIV-RNA taking out-of-date drug regimens may be candidates for simplification to one of the preferred regimens or a more desirable alternative regimen based on past treatment history and other variables. Dual ART therapy may be considered in situations where the use of tenofovir disoproxil fumarate, tenofovir alafenamide, and abacavir are not optimal choices. Dual ART regimens including more potent agents (dolutegravir plus lamivudine and darunavir/ritonavir plus either lamivudine or raltegravir) have evidence supporting their use in patients who are not ideal candidates for recommended ART regimens. Clinicians are urged to consult the most recent recommended preferred and alternative regimens, as they are continuously updated wiith new studies and as longer-term follow-up data accrue.

8 **Resistance** Regimen failure may be associated with antiretroviral resistance, and testing for such resistance is a useful clinical tool.[57,58] The two types of resistance tests available are phenotype and genotype. A phenotype test determines the concentration of antiretroviral agent necessary to inhibit replication of the patient's viral isolate by 50% (inhibitory concentration of 50% [IC_{50}]) in a recombinant in vitro viral assay. Results usually are expressed as a fold change in susceptibility (IC_{50}) compared with a wild-type laboratory strain virus. Generally, the fold-change in IC_{50} increases as HIV accumulates additional mutations that confer resistance to a particular drug. However, a single mutation may confer a very high fold-change in IC_{50} for some drugs (eg, lamivudine, emtricitabine, efavirenz, nevirapine), rendering them ineffective

after a single mutation. Although small-to-moderate increases in the fold change suggest reduced susceptibility to that antiretroviral agent, resistance may not be absolute, and partial susceptibility may remain. Theoretically, drug concentrations may be increased to overcome reduced susceptibility. The strength of phenotypic testing is to provide resistance information for complex mutation patterns, but it is also associated with higher cost, limited number of commercial providers, and slower turnaround time for results. Genotyping assesses genetic mutations and associated codon changes in gp41, reverse transcriptase, integrase, or protease in the patient's virus and compares it with the wild-type sequence. Certain mutations are known to confer resistance to specific drugs. An updated list of drug resistance mutations can be found at http://www.iasusa.org/resistance_mutations. Mutations are listed by the wild-type amino acid followed by the position in the protein or enzyme and end with the mutation found in the patient's virus. For example, a common mutation caused by lamivudine and emtricitabine is the M184V mutation: a substitution of valine (V) for methionine (M) at the 184 position of reverse transcriptase. Mutations can confer varying degrees of antiretroviral drug resistance and in some cases, weighting algorithms have been developed to predict the relative impact of mutation combinations on antiretroviral activity. Algorithms have also been developed to predict a phenotype from a genotype test (ie, virtual phenotype). Not all mutations, however, are only detrimental—for example, while M184V confers significant resistance to lamivudine and emtricitabine, it is also associated with a less fit virus. Interpretation of genotype resistance tests is complex; therefore, the reader is encouraged to obtain expert advice and consult the most recent guidelines on HIV resistance testing.

Treatment of Special Populations

Pregnancy Several considerations are relevant to the treatment of pregnant women, including the health of the mother, prevention of HIV transmission to the fetus, potential for teratogenicity, and drug dosing issues based on pharmacokinetic changes during pregnancy. Treatment recommendations should be consulted to address the specific requirements for HIV-infected pregnant women and the prevention of vertical transmission.[18] Generally, pregnant women should be treated as would nonpregnant women, with the goal of maximally suppressing HIV-RNA. Prior to modern ART, efavirenz was avoided in women planning to become pregnant or who are not using effective contraception as it was associated with neural tube defects in some, but not all studies.[79] Recently, dolutegravir use at the time of conception was associated

with neural tube defects in infants. Neural tube defects occur in the first 4 weeks from conception, or 6 weeks from last menstrual period.[83] Until more is known, dolutegravir should be avoided if possible in women who are planning to become pregnant or are not using effective contraception. In women who are at least 8 weeks from their last menstrual period, dolutegravir may be initiated or continued.[84]

Zidovudine is recommended intrapartum depending on the mother's viral load (more than 1,000 copies/mL [1×10^6/L] or unknown), based on early studies demonstrating clear prophylactic effectiveness as well as extensive familiarity with the side effect profile.[18] Infants born to HIV-infected mothers should also receive zidovudine (± several doses of nevirapine) prophylaxis for 4 to 6 weeks after birth. HIV transmission rates to their infants have been reduced to less than 0.5% for women who are treated with ART and when zidovudine prophylaxis is used. Breastfeeding is not recommended in the United States, but in resource-limited settings where lack of clean water makes breastfeeding a more favorable option, infants receive 6 weeks of once-daily nevirapine for prophylaxis.[18]

Chemoprophylaxis

9 In addition to fetal and infant chemoprophylaxis, protection of healthcare workers from accidental exposure to HIV and protection in cases of rape or high-risk postcoital and postinjection drug-use episodes are important concerns. The CDC has issued guidelines governing antiretroviral postexposure prophylaxis (PEP) of occupational and other high-risk HIV exposures that should be consulted for updates as the knowledge in this field evolves.[12,15] The principles of the guidelines are to assess the exposure risk and treat as soon as possible after high-risk exposures to prevent HIV infection. Assessing the exposure risk requires knowledge of the HIV-infection status of the source individual, which may be difficult to ascertain. The HIV status of the source should be determined as soon as possible with a rapid HIV test, whenever feasible. However, providers may have to rely on reasonable suspicion when this is not possible, so provider expertise is essential. PEP should not be delayed while waiting on the HIV status of the source, if reasonable suspicion is present. PEP should be considered an urgent medical situation. The guidelines recommend conventional ART regimens (eg, tenofovir disoproxil fumarate–emtricitabine–raltegravir), initiated as soon as possible, ideally within 1 to 2 hours of exposure. Animal studies show reduced PEP efficacy when initiated 72 hours or more after the exposure.[15] The

optimal duration of treatment is unknown, but at least 4 weeks of therapy is advocated. Expert consultation is needed when exposure to drug-resistant virus is suspected or confirmed, but this should not delay initial initiation of PEP.

Preexposure prophylaxis (PrEP) involves daily tenofovir disoproxil fumarate–emtricitabine in HIV-negative persons at high risk of HIV acquisition to prevent infection should an HIV-exposure occur.[85] PrEP is effective in MSM, serodiscordant couples, and at-risk heterosexual men and women, including those who inject drugs. The key considerations for PrEP are to assess HIV risk for the individual (ie, risk should be elevated) and to document a negative HIV test prior to initiating PrEP, including negative symptoms of acute HIV infection. Reports of drug resistance from PrEP failures were mostly among individuals who initiated PrEP during acute HIV infection, in the window period before the rapid HIV test could detect infection.[81] HIV testing should be repeated at least every 3 months and renal function should be assessed every 6 months while on PrEP.[85] Promotion of adherence is critical for PrEP effectiveness. The most up-to-date PrEP guidelines should be consulted, as new PrEP strategies are currently under evaluation including dosing with tenofovir alafenamide–emtricitabine.

EVALUATION OF THERAPEUTIC OUTCOMES

Two laboratory tests are used to evaluate response to ART: the plasma HIV-RNA and the CD4 count.[37] These tests should be performed at baseline, along with a medical history and physical, urinalysis, hematology, chemistries, serologies for coinfections, and patient education about HIV infection. An HIV resistance test is recommended upon initiation of care. After therapy is initiated, patients are generally monitored at 3-month intervals until HIV-RNA reaches undetectable levels. An assessment at 2 to 8 weeks is warranted to document early response. Monitoring may be increased to every 6 months in stabilized patients.

The two main indications for a change in therapy are significant toxicity and treatment failure. Should a single agent be responsible for an intolerable side effect that agent often can be singly changed out of the regimen. For example, the patient who experiences intolerable CNS disturbances during initiation of efavirenz can switch to a boosted PI or InSTI without changing the dual NRTI backbone. Maintaining virologic suppression is an important goal for switching therapy due to adverse events. Caution must be exercised when drugs in the regimen have overlapping toxicities, which makes changing a single agent problematic. Serious and life-threatening toxicities warrant cessation of the whole regimen before deciding upon a subsequent therapy.

As a general guide, the inability to achieve and maintain less than 200 copies/mL (200×10^3/L) of HIV-RNA represents treatment failure and should prompt consideration for changing therapy. This includes the inability to achieve less than 200 copies/mL (200×10^3/L) by 24 weeks of therapy initiation (repeat testing is suggested to confirm), or, after HIV-RNA suppression, repeated detection of greater than 200 copies/mL (200×10^3/L) of HIV-RNA.

Therapeutic Failure

8 The most important measure of therapeutic failure is suboptimal suppression of viral replication. Many reasons may underlie suboptimal suppression of viral replication such as pre-ART disease factors (eg, high viral load or pre-existing drug resistance), nonadherence to medication, development of new drug resistance, intolerance to one or more medications, adverse drug–drug or drug–food interactions, or pharmacokinetic–pharmacodynamic variability.[37] In cases of suboptimal suppression of viral replication, these potential causes should be investigated and addressed, if possible. As a general rule, drug resistance develops for regimens that do not maximally suppress HIV replication. Drug resistance testing is recommended while the patient is undergoing the failing regimen or within 4 weeks after stopping the regimen as long as the HIV-RNA count is greater than 500 copies/mL (500×10^3/L), which is the threshold for most resistance assays (~500–1,000 copies/mL [$\sim 500 \times 10^3$–1.0×10^6/L]). Virus may revert to wild-type if more than 4 to 6 weeks has elapsed between regimen discontinuation and the resistance test. Most clinicians use the genotype assay because it is less expensive and results typically are available sooner compared with the phenotype assay. Resistance results usually require expert interpretation. Treating patients who have drug-resistant HIV utilizes the same general treatment approaches described for initial therapy above. Patients should be treated with at least two (preferably three) fully active antiretroviral drugs from different mechanistic classes based on medication history and resistance tests. The goal of therapy is to suppress HIV-RNA to undetectable levels. In cases when undetectable HIV-RNA cannot be attained, maintenance on the regimen is preferred over drug discontinuation so as to prevent rapid immunological and clinical decline.

Several antiretroviral drugs are well-suited for drug-resistant HIV. The drugs in the newer classes (ie, InSTIs, entry inhibitors) are also active against NRTI-, NNRTI-, and PI-resistant viruses in highly treatment-experienced patients in controlled trials.[37,60]

Prior to the availability of new drugs and drug classes, other strategies were studied to help manage therapeutic failure including drug holidays, structured or strategic treatment interruptions, and structured intermittent therapy. The overall premise of these strategies was similar: stop all antiretrovirals to spare the patient from drug toxicities and to allow the virus to revert to wild-type. Reinitiation of therapy was intended to reestablish control of viral replication, as wild-type virus would be expected to predominate, although it was known that resistant virus was archived in long-lived cells, so viral suppression was short-lived. A landmark clinical trial showed that patients randomized to episodic therapy (drug-sparing) guided by the CD4 experienced significantly increased risk of opportunistic disease or death from any cause, including non-AIDS causes.[86,87] This and other studies have established that viral replication is damaging to the immune system and end organs and drug-sparing approaches are not advocated.

HIV CURE RESEARCH

In 2007, the “Berlin patient,” an HIV+ patient with new-onset acute myeloid leukemia, underwent an allogeneic bone marrow transplant with homozygous CCR5delta32 stem cells. Following a complicated clinical course, including graft versus host disease and second transplant, he was found to be free of HIV infection, as no virus could be detected in any sample tested. This was deemed a sterilizing cure and his case gave hope to researchers and patients alike for curing HIV infection. However, replicating the Berlin patient’s treatment and clinical course is impractical. Developing a cure will be particularly challenging because HIV integrates its genome into host cells, creating a latent reservoir. Thus, researchers have begun focusing on creating “functional cures,” where new treatments might allow patients to stop ART without disease progression. Ongoing clinical trials are evaluating such approaches.

COMPLICATIONS OF HIV INFECTION AND AIDS

3 In the pre-ART era, the major therapeutic focus was prevention and treatment of OIs associated with uncontrolled HIV replication and the steady decline in CD4 cells.[43] Uncontrolled HIV is an insidious disease; persons often present with OIs, a consequence of the weakened immune system rather than

HIV per se. Most OIs are caused by organisms that are common in the environment and often represent the reactivation of quiescent, hidden infections common in the population. The probability of developing specific OIs is closely related to CD4 count thresholds (**Fig. 143-2**). These CD4 thresholds serve as a basis for initiating primary OI chemoprevention.

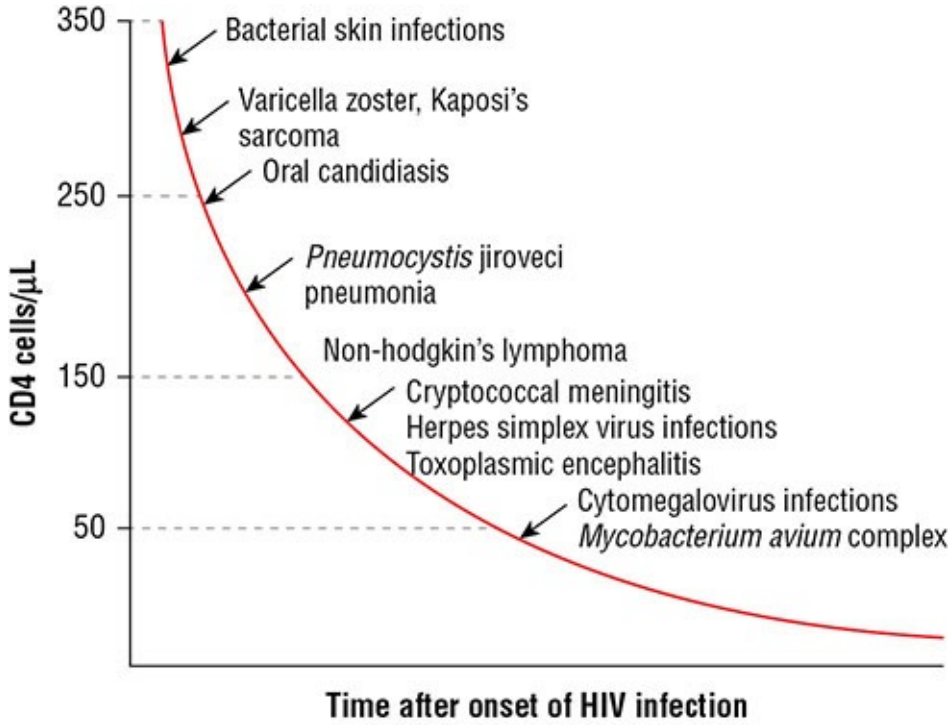


FIGURE 143-2 Natural history of opportunistic infections associated with human immunodeficiency virus infection. CD4 counts expressed as cells/μL can be converted into SI units by multiplying by 10^6/L. Reprinted with permission, © Courtney V. Fletcher, 2009.

5 In the ART era, the main principle in the management of OIs is treating HIV infection to enable CD4 cell recovery and maintenance above protective levels.[67] Additional important principles regarding management of OIs are as follows:

1. Prevent exposure to opportunistic pathogens
2. Vaccinate to prevent first-episode disease (consult HIV-specific guidelines)
3. Use primary chemoprophylaxis at certain CD4 thresholds to prevent first-episode disease
4. Treat emergent OI

5. Use secondary chemoprophylaxis to prevent disease recurrence
6. Discontinue prophylaxes with sustained ART-associated immune recovery

Several considerations are required for the patient who presents with an OI and is simultaneously diagnosed with HIV and who thus needs both OI and ART treatment. Immediate initiation of ART is indicated for OIs that respond to CD4 recovery, such as cryptosporidiosis, progressive multifocal leukoencephalopathy (JC virus), and mild-to-moderate Kaposi's sarcoma (HHV8 virus). Rapid initiation of ART (within days to weeks) is also indicated in the setting of other OIs such as tuberculosis, *Mycobacterium avium* complex (MAC), and PCP, but several potential issues need consideration. First, drug–drug interactions and the complexity of adhering to concomitant ART and OI regimens can be daunting. Careful review of potential interactions and adherence support should be provided. Second, clinicians must be cognizant of potentially overlapping drug toxicities (eg, rash) that create problems when attempting to stop the perceived culprit drug. Third, an immune reconstitution inflammatory syndrome (IRIS) has been associated with initiation of ART in the presence of underlying OIs. IRIS is generally characterized by fever and worsening of OI manifestations in the first few weeks to months after initiating ART despite evidence of treatment efficacy.[88] Risk factors for IRIS are a low CD4 count (eg, less than 50 cells/μL [0.050×10^9/L]) and a high antigenic burden. An ART-associated rapid-onset immune reconstitution against the smoldering OI infection, and resulting proinflammatory cytokine cascade, is thought to be the mechanism of IRIS. The most serious IRIS reactions involve neurological OIs such as cryptococcal meningitis, where IRIS can lead to increased morbidity and mortality. For cryptococcal meningitis, it may be prudent to delay ART until completion of the induction or induction/consolidation phase of antifungal therapy (up to 10 weeks).[63] Generally, treatment of IRIS is supportive and may include corticosteroids and/or NSAIDs, depending on the OI. Expert consultation should be used in the management of ART initiation in patients with advanced HIV infection and OIs, and the most up-to-date guidelines should be consulted.[67]

The epidemiology of specific OIs can depend upon geographical region. For instance, TB is particularly endemic on the Africa continent and is considered a major OI in that region, but the incidence of TB is relatively uncommon in the United States.[89] Major OIs in the United States include PCP, toxoplasmosis, MAC, cytomegalovirus retinitis, and cryptococcal meningitis. All have decreased substantially in incidence with the advent of ART.[43,67,71] Furthermore, primary and secondary chemoprophylaxis for specific OIs have contributed to

the same decreases.[43] Nevertheless, opportunistic diseases continue to be complications of HIV disease and occur at low CD4 lymphocyte counts in patients who are unaware of their HIV infection, or who have not responded to ART therapy or OI prophylaxis because of adherence issues or inadequate engagement with the healthcare system.[67]

Selected OIs and example recommended first-line regimens for OI treatment are given in **Table 143-5**. Example recommended therapies for primary OI prophylaxis are given in **Table 143-6**.[67] These recommendations are representative and not as extensive as in the published guidelines, which include multiple additional treatment considerations and alternatives, as well as coverage of less common OIs. The following brief discussion of PCP provides a more in-depth overview of the epidemiology, diagnosis, clinical manifestations, and results of treatment and serves as an illustration for the principles discussed above.

TABLE 143-5 Selected Therapies for Common Opportunistic Pathogens in HIV-Infected Individuals

Clinical Disease	Preferred Initial Therapies for Acute Infection in Adults (Strength of Recommendation in Parentheses)	Common Drug- or Dose-Limiting Adverse Reactions
Fungi		
Candidiasis, oral	Fluconazole 100 mg orally for 7–14 days (AI)	Elevated liver function tests, hepatotoxicity, nausea, and vomiting
	or	
	Nystatin 500,000 units oral swish (~5 mL) four times daily for 7–14 days (BII)	Taste, patient acceptance
Candidiasis, esophageal	Fluconazole 100–400 mg orally or IV daily for 14–21 days (AI)	Same as above
	or	
	Itraconazole 200 mg/day orally for 14–21 days (AI)	Elevated liver function tests, hepatotoxicity, nausea, and vomiting
Pneumocystis jirovecii pneumonia	*Moderate-to-severe episodes*	
	Trimethoprim–sulfamethoxazole IV or orally 15–20 mg/kg/day as trimethoprim component in three to four divided doses for 21 days[1] (AI) moderate or severe therapy should be started IV	Skin rash, fever, leucopenia, thrombocytopenia
	Mild-to-moderate episodes	
	Trimethoprim–sulfamethoxazole 15–20 mg/kg/day as trimethoprim component orally in three divided doses or trimethoprim–sulfamethoxazole double strength tablets, two tablets three times daily	
Cryptococcal meningitis	Liposomal amphotericin B 3–4 mg/kg/day IV with flucytosine 100 mg/kg/day orally in four divided doses for a minimum of 2 weeks (AI) *followed by*	Nephrotoxicity, hypokalemia, anemia, fever, chills Bone marrow suppression
	Fluconazole 400 mg/day, orally for 8 weeks or until CSF cultures are negative (AI)[1]	Same as above
Histoplasmosis	Liposomal amphotericin B 3 mg/kg/day IV for 2 weeks (AI) *followed by*	Same as above
	Itraconazole 200 mg orally thrice daily for 3 days then twice daily, for 12 months (AII)[1]	
Coccidioidomycosis	Liposomal amphotericin B 3–5 mg/kg/day IV until clinical improvement (usually after 500–1,000 mg) then switch to azole (AIII)[1]	Same as above
	or	
	Fluconazole 400–800 mg once daily (meningeal disease) (AII)[1]	Same as above
Protozoa		
Toxoplasmic encephalitis	Pyrimethamine 200 mg orally once, then 50–75 mg/day	Bone marrow suppression
	plus	
	Sulfadiazine 1–1.5 g orally four times daily	Rash, drug fever
	and	
	Leucovorin 10–25 mg orally daily for 6 weeks (AI)[1]	
Isosporiasis	Trimethoprim and sulfamethoxazole: 160 mg trimethoprim and 800 mg sulfamethoxazole orally or IV four times daily for 10 days (AII)[1]	Same as above
Bacteria		
Mycobacterium avium complex	Clarithromycin 500 mg orally twice daily, *plus* ethambutol 15 mg/kg/day orally (AI) for at least 12 months	GI intolerance, optic neuritis, peripheral neuritis, elevated liver tests
Salmonella enterocolitis or bacteremia	Ciprofloxacin 500–750 mg orally (or 400 mg IV) twice daily for 14 days (longer duration for bacteremia or advanced HIV) (AIII)	GI intolerance, headache, dizziness
Campylobacter enterocolitis (mild-to-moderate)	Ciprofloxacin 500–750 mg orally (or 400 mg IV) twice daily for 7–10 days (or longer with bacteremia) (BIII)	Same as above
Shigella enterocolitis	Ciprofloxacin 500–750 mg orally (or 400 mg IV) twice daily for 7–10 days (or 14 days for bacteremia) (AIII)	Same as above
Viruses		
Mucocutaneous herpes simplex	Acyclovir 5 mg/kg IV every 8 hours until lesions regress, then acyclovir 400 mg orally three times daily until complete healing (famciclovir or valacyclovir is alternative) (AIII)	GI intolerance, crystalluria
Primary varicella-zoster	Acyclovir 10–15 mg/kg every 8 hours IV for 7–10 days (severe cases), then switch to oral valacyclovir 1 g three times daily after defervescence (famciclovir or acyclovir is alternative) (AIII)	Obstructive nephropathy, CNS symptoms

Cytomegalovirus (retinitis)	Intravitreal ganciclovir (2 mg) or foscarnet (2.4 mg) for 1–4 doses over 7–10 days (for sight threatening lesions) *plus* valganciclovir 900 mg twice daily for 14–21 days then once daily until immune recovery from ART (AIII)[1]	Neutropenia, thrombocytopenia
Cytomegalovirus esophagitis or colitis	Ganciclovir 5 mg/kg IV every 12 hours for 21–42 days; may switch to valganciclovir 900 mg orally every 12 hours when oral therapy can be tolerated (BI)	Same as above

[1]Maintenance therapy is recommended.

ART, antiretroviral therapy; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus.

See Table 143-3 for levels of evidence-based recommendations.

Data from Reference 67.

TABLE 143-6 Therapies for Prophylaxis of Select First-Episode Opportunistic Diseases in Adults and Adolescents

Pathogen	Indication	First Choice (Strength of Recommendation in Parentheses)
Standard of care		
Pneumocystis jirovecii	$CD4^+$ count <200/mm³ (0.2 × 10⁹/L) *or* oropharyngeal candidiasis	Trimethoprim–sulfamethoxazole, one double-strength tablet orally once daily (AI) or one single-strength tablet orally once daily (AI)
Histoplasma capsulatum	$CD4^+$ count <150/mm³ (0.15 × 10⁹/L) endemic geographic area and high risk for exposures	Intraconazole 200 mg orally once daily (BI)
Mycobacterium tuberculosis		
Isoniazid-sensitive	(Active TB should be ruled out): + test for latent TB infection with no prior TB treatment history (AI) *or* – test for latent TB infection, but close contact with case of active tuberculosis (AII)	Isoniazid 300 mg orally plus pyridoxine, 25 mg orally once daily for 9 months (AII) *or* Isoniazid 900 mg orally twice weekly by directly observed therapy (BII) plus pyridoxine 25 mg orally daily for 9 months (BII)
For exposure to drug-resistant TB	Consult public health authorities	
Toxoplasma gondii	Immunoglobulin G antibody to *Toxoplasma* and $CD4^+$ count <100/mm³ (0.1 × 10⁹/L)	Trimethoprim–sulfamethoxazole one double-strength tablet orally once daily (AII)
Mycobacterium avium complex	$CD4^+$ count <50/mm³ (0.05 × 10⁹/L)	Azithromycin 1,200 mg orally once weekly (AI) or 600 mg orally twice weekly (BIII) or clarithromycin 500 mg orally twice daily (AI)
Varicella zoster virus (VZV)	Preexposure: CD4 ≥200/mm³ (0.2 × 10⁹/L), no history of varicella vaccination or infection, or, if available, negative antibody to VZV Postexposure: Significant exposure to chicken pox or shingles for patients who have no history of vaccination or either condition or, if available, negative antibody to VZV	Varicella vaccination; two doses, 3 months apart (CIII) Varicella-zoster immune globulin, 125 IU per 10 kg (maximum of 625 IU) IM, as soon as possible and within 10 days after exposure (AIII)
Streptococcus pneumoniae	Any individual regardless of CD4 count	13-valent polysaccharide vaccine, 0.5 mL intramuscularly once (AI) followed by 23-valent polysaccharide vaccine 0.5 mL 8 weeks later (CIII) Re-vaccinate with 23-valent polysaccharide vaccine every 5 years
Hepatitis B virus	All susceptible patients	HBV vaccine IM (Engerix-B 20 mcg/mL or Recombivax HB 10 mcg/mL), 0, 1, and 6 months (AII) Anti-HBs should be obtained 1 month after the vaccine series completion (BIII)
Influenza virus	All patients (annually, before influenza season)	Inactivated trivalent influenza virus vaccine (annual): 0.5 mL intramuscularly (AIII) (live-attenuated vaccine is contraindicated in all HIV-infected patients)
Hepatitis A virus	All susceptible (anti-hepatitis A virus–negative) patients at increased risk for hepatitis A infection (eg, chronic liver disease, injection-drug users, men who have sex with men)	Hepatitis A vaccine: two doses (AII) antibody response should be assessed 1 month after vaccination, with revaccination as needed when CD4 >200 cells/μL (0.2 × 10⁹/L)(BIII)
Human papillomavirus (HPV) infection	13- to 26-year-old males and females	HPV recombinant vaccine 9 valent intramuscularly at months 0, 1–2, and 6 (BIII)

See Table 143-3 for levels of evidence-based recommendations.

Data from Reference 67.

Pneumocystis jirovecii Pneumonia

5 *Pneumocystis jirovecii* (*carinii*) pneumonia (PCP) has been and continues to be the most common life-threatening OI in patients with AIDS.[90] *P. jirovecii* was formerly named *P. carinii*; the name change was made to distinguish the organism that infects humans (*P. jirovecii*) from the strain that infects rodents (*P. carinii*). Nevertheless, the acronym PCP is still used today. Early in the AIDS epidemic 80% of patients experienced PCP at some point during their lifetime.[91] Although the incidence of PCP has fallen markedly since the advent of ART and effective prophylaxis for PCP, it still occurs in persons unaware of their HIV infection, and breakthrough PCP can occur in those with variable adherence to ART and/or prophylaxis.

P. jirovecii is a fungus that has protozoan characteristics as well.[90,91] Exposure to *P. jirovecii* is widespread; two-thirds of the population have developed serum antibodies by age 2 to 4 years. The organism appears to reside without consequence in humans unless the host becomes immunologically impaired.[90,91] Disease associated with immunosuppression probably occurs from both new acquisition and reactivation. Ninety percent of PCP cases in AIDS patients occurred in those with CD4 counts less than 200 cells/mm^3 (0.2×10^9/L).[67] Other risk factors include oral thrush, recurrent bacterial pneumonia, unintentional weight loss, and high-plasma HIV-RNA. Past episodes of PCP increase risk for future episodes, which provides the basis for secondary chemoprophylaxis, as described below.

The presentation of PCP in AIDS often is insidious.[90] Characteristic symptoms include fever and dyspnea. Clinical signs are tachypnea with or without rales or rhonchi and a nonproductive or mildly productive cough occurring over a period of weeks, although more fulminant presentations can occur. Chest radiographs may show florid or subtle interstitial and bilateral infiltrates but occasionally are normal. Arterial blood gases may show minimal hypoxia (PaO_2 80 to 95 mm Hg [10.6–12.6 kPa]) but in more advanced disease may be markedly abnormal. The diagnosis of PCP usually is made by identification of the organism in induced sputum or in specimens obtained from bronchoalveolar lavage. Less commonly, transbronchial or open lung biopsy is used to locate the organism. The stain used for organism identification affects the sensitivity and specificity of the respiratory samples. Many laboratories prefer direct immunofluorescent staining using monoclonal antibodies. PCR is an alternative diagnostic method that is highly sensitive and specific for

detecting *Pneumocystis.* Unfortunately, PCR does not distinguish whether the presence of the organism is due to colonization or disease. 1,3β-D-glucan is a component of *Pneumocystis* cell walls that is elevated in patients with PCP. The assay for 1,3β-D-glucan has a high sensitivity for those with PCP and can therefore be used to rule out PCP, but it is non-specific because elevation may also be due to various causes, including other fungal infections.[67]

Untreated PCP has a mortality rate of nearly 100%. Several potential treatments are available for PCP, but the treatment of choice is trimethoprim–sulfamethoxazole (also called cotrimoxazole), which is associated with a response rate of 60% to 100%.[67] Parenteral pentamidine is equally efficacious but significantly more toxic. Trimethoprim–sulfamethoxazole is also the regimen of choice for primary and secondary prophylaxis of PCP in patients with and without HIV.[67,90]

When used for treatment of PCP, the dose of trimethoprim–sulfamethoxazole is 15 to 20 mg/kg/day (based on the trimethoprim component) as three to four divided doses. Treatment duration typically is 21 days but also must be based on clinical response. Trimethoprim–sulfamethoxazole usually is initiated by the IV route, although oral therapy may suffice in mildly ill and reliable outpatients or for completion of a course of therapy after a response has been achieved with IV administration.[67,90] Patients with moderate-to-severe PCP (eg, PaO_2 more than 70 mm Hg [9.3 kPa]) should be treated with corticosteroids as soon as possible after starting PCP therapy and certainly within 72 hours, in order to blunt the deterioration seen just after initiation of PCP therapy. Alternative regimens include pentamidine for moderate-to-severe disease and dapsone with trimethoprim, primaquine with clindamycin, and atovaquone for mild-to-moderate PCP.[67] Early initiation of ART (within 2 weeks) is recommended, keeping in mind the potential issues described earlier.

Adverse reactions to trimethoprim–sulfamethoxazole and pentamidine are common, occurring in 20% to 85% of patients in this setting.[67] The more common adverse reactions seen with trimethoprim–sulfamethoxazole are rash (rarely including Stevens–Johnson syndrome), fever, leukopenia, elevated serum transaminase levels, and thrombocytopenia. The incidence of these adverse reactions is higher in HIV-infected individuals than in those not infected with HIV. Mild rashes should be watched closely for progression to more severe reactions but are not an absolute contraindication to continuing therapy.[67] This highlights the need for thoughtful consideration of ART components because of overlapping toxicities with some antiretrovirals such as NNRTIs, which also are associated with rash and hypersensitivity, including life-threatening cases. For

pentamidine, side effects are pronounced and include hypotension, tachycardia, nausea, vomiting, severe hypoglycemia or hyperglycemia, pancreatitis, irreversible diabetes mellitus, elevated serum transaminase levels, nephrotoxicity, leukopenia, and cardiac arrhythmias. Some of these reactions appear to be related to the infusion rate (eg, hypotension and tachycardia) and can be minimized by infusing pentamidine over 1 hour or more.[91] Dosage modification or pharmacokinetic monitoring can reduce the toxicity of both pentamidine and trimethoprim–sulfamethoxazole. Dose reduction of pentamidine from 4 to 3 mg/kg/day appears to be successful in minimizing further rises in serum creatinine levels.[91] As mentioned previously, early addition of adjunctive corticosteroid therapy to anti-PCP regimens decreases the risk of respiratory failure and improves survival.[67] The adverse effects associated with corticosteroid use for this scenario are minimal, primarily an increased incidence of herpetic lesions, although some concerns exist about the potential for reactivation of tuberculosis or cytomegalovirus and/or long-term effects on bones.[91,92]

Prevention of PCP is clearly a preferable treatment strategy. Primary prophylaxis is recommended for any HIV-infected person who has a CD4 lymphocyte count less than 200 cells/mm^3 (0.2×10^9/L) (or CD4 percentage of total lymphocytes less than 14% [0.14]) or a history of oropharyngeal candidiasis.[67,90] Secondary PCP prophylaxis is recommended for all HIV-infected individuals who have had a previous episode of PCP.

Trimethoprim–sulfamethoxazole is the most effective and least expensive agent and is the preferred therapy for both primary and secondary prophylaxis of PCP in adults and adolescents.[67,90] It also confers cross-protection against toxoplasmosis and many bacterial infections. The recommended dose in adults and adolescents is one double-strength tablet daily, although other regimens, such as one double-strength tablet thrice weekly or one single-strength tablet daily and gradual dose escalation using liquid trimethoprim–sulfamethoxazole, have been used in an attempt to reduce the incidence of adverse reactions and improve adherence. Alternative prophylactic regimens are available if trimethoprim–sulfamethoxazole cannot be tolerated.[67]

In the ART era, the profound reduction in HIV replication and restoration in CD4 cell count to levels rarely associated with the development of OIs provides a basis for the discontinuation of primary and secondary prophylaxis.[67] For PCP, primary prophylaxis should be discontinued in patients receiving and responding to ART who have a CD4 cell count greater than 200 cells/mm^3 (0.2×10^9/L) sustained for at least 3 months, but should be reinstated if the CD4 count drops

to less than 200 cells/mm^3 (0.2 × 10^9/L). The same criteria apply for both discontinuation and reinitiation of secondary prophylaxis of PCP. However, continued secondary prophylaxis should be considered when the original PCP episode occurred at a CD4 count greater than 200 cells/mm^3 (0.2 × 10^9/L).[67]

Comprehensive recommendations are available for management of PCP and other OIs in the context of HIV infection, including prophylaxis, treatment, and removal of prophylaxis with the control of HIV infection.[67] Readers are advised that data continue to emerge on new OI therapies, the safety of stopping primary and secondary prophylaxis, as well as criteria for when to restart secondary prophylaxis. The most current guidelines should always be consulted. Similar OI guidelines specific to children have been developed and are updated regularly.[42]

Complications in the ART Era

10 As with any medication, adverse reactions occur with antiretroviral agents that can range from minor intolerances to life-threatening events. Representative side effects for each antiretroviral agent are listed in Table 143-4. A comprehensive discussion of all the adverse effects during ART is beyond the scope of this chapter, but can be found in various other sources.[37] The purpose of this section is to highlight certain medical issues that have emerged in the modern ART era as HIV-infected patients live longer and are exposed to antiretroviral drugs for many years.

Given the life-prolonging effects of ART, as many as half of the HIV-infected population is over 50 years old in resource-rich countries.[93] Along with older age come higher rates of well-known chronic and acute illnesses such as osteoporosis and osteopenia, renal and hepatic insufficiency, metabolic syndrome, neurocognitive decline, atherosclerotic disease, frailty, and non-AIDS malignancies. Many of these illnesses occur at higher than expected rates in older HIV-infected patients in the ART era.[94] The cause(s) of these higher rates is the focus of intense study. Initially, adverse events from antiretroviral medications were thought to contribute significantly to these conditions but evidence now suggests that ongoing inflammation and viral persistence play a critical role.[87] Therefore, a theme that emerges in this section is that ART generally protects against non-AIDS events and it is universally recommended to manage these emerging complications.

One-third of deaths in people living with HIV are attributed to cancer.[95] While contemporary ART has reduced the incidence of HIV-related cancers such as Kaposi’s sarcoma and non-Hodgkin’s lymphoma, other non-AIDS-related

malignancies impact HIV-infected individuals at significantly elevated rates such as Hodgkin's lymphoma and anal, lung, skin, and hepato-carcinoma.[95] Part of this risk may be attributed to elevated exposures to, or susceptibilities to human papillomavirus (oral and anal cancer), smoking (lung carcinoma), and chronic hepatitis B and/or C coinfection (liver cancer), which are modifiable risk factors. For example, primary care guidelines advocate HPV vaccination for younger HIV-infected individuals, as well as increased screening for anal cancer in those with existing genital or anal warts.[35] Concern has been raised that antiretroviral drugs may contribute directly to these increased cancer rates, as some agents have been associated with cancers in observational studies.[96] However, there are similar elevated cancer rates in organ transplant recipients with medication-induced immunosuppression, suggesting it is the impairment to the immune system and/or inflammation associated with HIV-infection that is driving much of these higher cancer rates.[97] While the approach to treatment of non-AIDS-related malignancies in HIV-infected patients is similar to that in non-HIV-infected patients, treatment is complicated by drug–drug interactions that may exist between the antiretrovirals and the oncolytics.[98]

Cardiovascular disease has also emerged as a major concern for HIV-infected patients. Patients with HIV infection exhibit an approximately 1.5-fold higher risk of cardiovascular disease compared with matched HIV-negative individuals.[93] This increased risk is similar in magnitude to other well-established risk factors such as hypertension and hyperlipidemia. Elevated systemic inflammation and its impact on endothelial structure and function and the clotting cascade is thought to underlie much of this risk, as elevations in circulating IL-6 and D-dimer correlate with clinical outcomes.[99] Statins are thought to be beneficial in persons living with HIV and dyslipidemia, in part because of their anti-inflammatory effects. In this population, pitavastatin reduced markers of arterial inflammation and immune system activation.[100] Antiretroviral drugs may contribute to risk, given the well-known relationships between PIs, efavirenz, and the thymidine analog NRTIs and dyslipidemia (increased triglycerides and low-density lipoproteins [LDL] and decreased high-density lipoproteins [HDL]), abnormal glucose homeostasis (insulin resistance and impaired glucose tolerance), body fat abnormalities (lipoatrophy of the face and extremities and central lipoaccumulation), and lactic acidosis with hepatosteatosis (all the NRTIs).[101] Many agents within these drug classes are less associated with these complications, including atazanavir and darunavir for the PIs, rilpivirine for NNRTIs, and lamivudine, emtricitabine, tenofovir, and abacavir for the NRTIs.[101,102] The same appears to be true for InSTIs and

maraviroc.[102] Retrospective studies have found an association between myocardial infarction and abacavir and didanosine use, but other studies have not, so this association is controversial.[103,104] This controversy highlights the difficulty in using observational and retrospective data to attribute risk to these emerging medical conditions. Metabolic abnormalities such as hyperlipidemia and hyperglycemia should be treated according to national guidelines for those conditions with the caveat to intensively screen for potential drug–drug interactions.[35]

A relevant problem for HIV-infected individuals with years of ART experience is body fat abnormalities, as older ART was associated with changes in body fat distribution.[105] The thymidine analogs, particularly stavudine, were associated with lipoatrophy of the subcutaneous fat in the extremities and face, and these agents and older PIs were associated with hypertrophy of the deep abdominal fat depot. Collectively these fat abnormalities were termed HIV lipodystrophy. Newer agents such as abacavir, tenofovir, emtricitabine, darunavir, and InSTIs appear to be less associated with lipodystrophy compared with older agents such as stavudine, zidovudine, and indinavir. In patients still taking older ART regimens, this provides a basis for switching therapy to newer regimens, which may result in small gains in subcutaneous fat in those with existing lipoatrophy. Small controlled studies have demonstrated modest but inconsistent gains in subcutaneous fat with thiazolidinedione therapy. Central fat accumulation is difficult to treat. Lifestyle changes, such as reducing calorie intake and increasing aerobic exercise, should be the first-line approach. Metformin reduces central fat accumulation, but lean body mass and subcutaneous fat may exhibit unwanted declines. Tesamorelin, a growth hormone-releasing analog was approved to safely reduce central adiposity, although a drawback is that visceral fat returns within months of discontinuation.[105] Unfortunately, both lipoatrophy and fat accumulation eventually may lead to reconstructive surgery strategies in severe or refractory cases. The best management of body fat changes is prevention through initiation of preferred regimens less likely to cause such changes (see current recommendations for initial therapy, Table 143-3).[37]

Functional declines of end organs such as kidney, liver, and brain (cognition) are another important problem for older HIV-infected patients. Like above, these declines appear to be related with HIV infection itself, and some improvement may be seen with therapy, particularly for neurocognitive function.[106,107] However, certain drugs may also exacerbate these issues.[108] The NNRTI efavirenz, for instance, is commonly associated with central nervous system

perturbations including somnolence, attention deficits, and psychiatric issues. These effects exacerbate neurocognitive impairment, although this is controversial and difficult to disentangle from the effects of HIV.[109] The most important defense against HIV-associated neurocognitive decline is durable suppression of viral replication.[108]

HIV also causes a nephropathy (termed HIV-associated nephropathy, or HIVAN), most commonly a glomerulopathy that can lead to end-stage renal disease in the absence of ART.[110] The incidence of this condition has declined by approximately 60% in the ART era, demonstrating that ART is the most important intervention against HIVAN. African Americans are more likely to experience HIVAN compared with those of European ancestry. Some antiretroviral drugs impact renal health and these may exacerbate the effects of HIV. For example, atazanavir and lopinavir may crystallize in urine leading to obstruction, whereas tenofovir may injure the proximal tubule leading to Fanconi syndrome in rare cases.[111] The newer tenofovir alafenamide pro-drug appears to be less likely to cause proximal tubulopathy because plasma concentrations of tenofovir are lower compared with tenofovir disoproxil.[55] Renal function should be monitored routinely in all HIV-infected patients, including consideration for more frequent monitoring for patients receiving the drugs mentioned above.[37]

HIV-infected patients experience coinfection with hepatitis B (HBV) and hepatitis C virus (HCV) relatively commonly, and this can drive declines in hepatic function in this population.[112] For example, up to 30% of HIV-infected patients in the United States have HIV-HCV (approximately 300,000 individuals) including as many as 90% of injection–drug users and 90% of hemophiliacs. HIV worsens the prognosis of HCV by reducing the chance of HCV clearance and accelerating HCV progression. With chronic HCV infection, progression to fibrosis, cirrhosis, and liver failure is several-fold faster in HIV-HCV patients versus HCV-monoinfected patients. ART reduces progression to hepatic decompensation and, among HIV-HCV coinfected population on ART, progression is faster in those who do not fully suppress HIV replication.[112,113] For these reasons, ART is recommended for HIV-HCV coinfected patients and HCV therapy should be offered according to HCV guidelines.[114] The most important consideration for co-treatment is potential drug–drug interactions between ART and HCV therapies. Again, the most recent information should be consulted in reviewing potential interactions.[37,114]

The same general principles extend to HIV-HBV coinfected patients, who

comprise approximately 10% of the HIV-infected population.[115] However, two unique considerations are relevant for HIV-HBV coinfection. First, the ART regimen should include tenofovir plus either lamivudine or emtricitabine, given the HBV activity of these agents. Second, hepatic flares and decompensation has been reported when tenofovir-based therapy was interrupted or discontinued. If discontinuation is necessary, close monitoring of hepatic function is indicated.

Despite these issues in the contemporary ART era, the pharmacotherapy of HIV infection has steadily improved over the past 30 years, such that HIV is now a chronic but manageable condition. Whether the patient will ultimately mount a durable response to ART depends upon adherence, convenience/tolerability, and pharmacologic effectiveness. As discussed throughout this chapter, a large number of considerations go into choosing the optimal ART for a given patient. These factors include: pre-ART disease characteristics (eg, resistance testing, viral load, and CD4 count), ART characteristics (eg, coformulations, food requirements, drug–drug interactions, etc.), comorbid conditions (eg, pre-existing renal dysfunction), potential for pregnancy (eg, efavirenz and dolutegravir may be excluded), HLA-B5701 and/or tropism testing (if abacavir or maraviroc are being considered), and co infections (eg, TB infection). Thus, the clinician's knowledge and application of HIV pathophysiology and pharmacologic principles of ART will ultimately guide therapeutic success.

ACKNOWLEDGEMENTS

The authors wish to thank Dr. Thomas Kakuda for his invaluable contributions and efforts on previous editions of this chapter. This work was supported by Grants R01 AI122298, UM1 AI06701, R01 HD085887, and R01 AI124965 from the National Institute of Allergy and Infectious Disease.

Postclass Engaged Learning Activities

Identify a medication that was recently approved (i.e. within the last year) or is currently in late clinical trials for the treatment of HIV infection. Describe its mechanism of action and discuss its potential role in treatment as well as advantages/disadvantages of the new medication compared to the current standard of care. This activity is intended to build skills in primary literature evaluation and interpretation for clinical practice.

ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
CCR5	chemokine (C–C motif) receptor 5
CD	cluster of differentiation
CDC	Centers for Disease Control and Prevention
CXCR4	Chemokine (C–X–C motif) receptor 4
CYP	cytochrome P450
DHHS	Department of Health and Human Services
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
gp	glycoprotein
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HIVAN	HIV-associated nephropathy
HLA	human leukocyte antigen
IC_{50}	concentration of antiretroviral agent necessary to inhibit 50% of viral replication
Ig	immunoglobulin
InSTI	integrase strand transfer inhibitor
IRIS	immune reconstitution inflammatory syndrome
LDL	low-density lipoprotein
LTR	long-terminal repeat
MAC	*Mycobacterium avium* complex
MSM	men who have sex with men
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
OI	opportunistic infection
PCP	*Pneumocystis jirovecii* (*carinii*) pneumonia
PCR	polymerase chain reaction
PI	protease inhibitor
PEP	postexposure prophylaxis
PrEP	preexposure prophylaxis
RT-PCR	reverse-transcription polymerase chain reaction
SIV	simian immunodeficiency virus
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
WHO	World Health Organization

REFERENCES

1. Henry J Kaiser Family Foundation. The Global HIV/AIDS epidemic. Available at: https://www.kff.org/global-health-policy/fact-sheet/the-global-hivaids-epidemic/.
2. Maartens G, Celum C, Lewin SR. HIV infection: Epidemiology, pathogenesis, treatment, and prevention. *Lancet*. 2014;384:258–271.
3. Patel P, Borkowf CB, Brooks JT, et al. Estimating per-act HIV transmission risk: A systematic review. *AIDS*. 2014;28:1509–1519.
4. Centers for Disease Control, Health Resources and Services Administration, National Institutes of Health, American Academy of HIV Medicine, Association of Nurses in AIDS Care, International Association of Providers of AIDS Care, National Minority AIDS Council, and Urban Coalition for HIV/AIDS Prevention Services. Recommendations for HIV prevention with adults and adolescents with HIV in the United States. Available at: http://stacks.cdc.gov/view/cdc/26063.
5. Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral therapy for the prevention of HIV-1 transmission. *N Engl J Med*. 2016;375:830–839.
6. Science validates undetectable = untransmittable HIV prevention message. Available at: https://www.niaid.nih.gov/news-events/undetectable-equals-untransmittable. Accessed November 6, 2018.
7. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med*. 2012;367:399–410.
8. Chasela CS, Hudgens MG, Jamieson DJ, et al. Maternal or infant antiretroviral drugs to reduce HIV-1 transmission. *N Engl J Med*. 2010;362:2271–2281.
9. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. 2010;363:2587–2599.
10. Friend DR, Kiser PF. Assessment of topical microbicides to prevent HIV-1 transmission: Concepts, testing, lessons learned. *Antiviral Res*. 2013;99:391–400.
11. Esparza J. A brief history of the global effort to develop a preventive HIV vaccine. *Vaccine*. 2013;31:3502–3518.

12. Domiguez KL, Smith DK, Thomas V, et al. Updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection drug use, or other nonoccupational exposure to HIV—United States: Recommendations from the U.S. Department of Health and Human Services. Available at: https://stacks.cdc.gov/view/cdc/38856.
13. Zou S, Dodd RY, Stramer SL, et al. Probability of viremia with HBV, HCV, HIV, and HTLV among tissue donors in the United States. *N Engl J Med*. 2004;351:751–759.
14. Zou S, Stramer SL, Dodd RY. Donor testing and risk: Current prevalence, incidence, and residual risk of transfusion-transmissible agents in US allogeneic donations. *Transfus Med Rev*. 2012;26:119–128.
15. Kuhar DT, Henderson DK, Struble KA, et al. Updated US Public Health Service Guidelines for the management of occupational exposures to human immunodeficiency virus and recommendations for postexposure prophylaxis. *Infect Cont Hosp Epidemiol*. 2013;34:875–892.
16. Magder LS, Mofenson L, Paul ME, et al. Risk factors for in utero and intrapartum transmission of HIV. *J Acquir Immune Defic Syndr*. 2005;38:87–95.
17. World Health Organization. HIV transmission through breastfeeding. Available at: http://apps.who.int/iris/bitstream/10665/43879/1/9789241596596_eng.pdf.
18. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf.
19. Revised surveillance case definition for HIV infection–United States, 2014. *MMWR Recomm Rep*. 2014;63:1–10.
20. Centers for Disease Control and Prevention. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 dependent areas, 2016. *HIV Surveillance Supplemental Report*. 2018;23(4).
21. Centers for Disease Control and Prevention. HIV/AIDS basic statistics. Available at: http://www.cdc.gov/hiv/basics/statistics.html.
22. Skarbinski J, Rosenberg E, Paz-Bailey G, et al. Human immunodeficiency virus transmission at each step of the care continuum in the United States. *JAMA Intern Med*. 2015;175:588–596.

23. UNAIDS. 2017 Global HIV Statistics. Available at: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_
24. Ortblad KF, Lozano R, Murray CJ. The burden of HIV: Insights from the global burden of disease study. *AIDS*. 2010;27:2003–2017.
25. Sharp PM, Hahn BH. Origins of HIV and the AIDS pandemic. *Cold Spring Harb Perspect Med*. 2011;1.
26. Shaw GM, Hunter E. HIV transmission. *Cold Spring Harbor Perspect Med*. 2012;2.
27. Huang Y, Paxton WA, Wolinsky SM, et al. The role of a mutant CCR5 allele in HIV-1 transmission and disease progression. *Nat Med*. 1996;2:1240–1243.
28. Tang H, Kuhen KL, Wong-Staal F. Lentivirus replication and regulation. *Annu Rev Genet*. 1999;33:133–170.
29. Chan JK, Greene WC. Dynamic roles for NF-κB in HTLV-I and HIV-1 retroviral pathogenesis. *Immunol Rev*. 2012;246:286–310.
30. Cullen BR. Role and mechanism of action of the APOBEC3 family of antiretroviral resistance factors. *J Virol*. 2006;80:1067–1076.
31. Siewe B, Landay A. Key concepts in the early immunology of HIV-1 infection. *Curr Infect Dis Rep*. 2012;14:102–109.
32. Ho DD, Neumann AU, Perelson AS, et al. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. *Nature*. 1995;373:123–126.
33. Centers for Disease Control and Prevention. Laboratory testing for the diagnosis of HIV infection: Updated recommendations. Available at: http://www.cdc.gov/hiv/pdf/hivtestingalgorithmrecommendation-final.pdf.
34. Branson BM. HIV testing updates and challenges: When regulatory caution and public health imperatives collide. *Curr HIV/AIDS Rep*. 2015;12:117–1126.
35. Aberg JA, Gallant JE, Ghanem KG, et al. Primary care guidelines for the management of persons infected with HIV: 2013 Update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;58:e1–e34.
36. Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep*. 2006;55:1–17.
37. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines

for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

38. Mellors JW, Munoz A, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med*. 1997;126:946–954.
39. Richey LE, Halperin J. Acute human immunodeficiency virus infection. *Am J Med Sci*. 2013;345:136–142.
40. Khoury M, Kovacs A. Pediatric HIV infection. *Clin Obstet Gynecol*. 2001;44:243–275.
41. Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf.
42. Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/OI_guidelines_pediatrics.p
43. Walensky RP, Paltiel AD, Losina E, et al. The survival benefits of AIDS treatment in the United States. *J Infect Dis*. 2006;194:11–19.
44. NIH Panel to Define Principles of Therapy of HIV Infection. Report of the NIH panel to define principles of therapy of HIV infection. 1997.
45. The INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. 2015; *N Engl J Med*. 9.
46. The TEMPRANO ANRS 12136 Study Group. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med*. 2015;373:808–822.
47. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. 2011;365:493–505.
48. World Health Oganization. Guideline on when to start antiretroviral therapy and pre-exposure prophylaxis for HIV. Available at: http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/.
49. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *N Engl J Med*. 2009.
50. Kim JH, Excler J-L, Michael NL. Lessons from the RV144 Thai Phase III

HIV-1 vaccine trial and the search for correlates of protection. *Ann Rev Med*. 2015;66:423–437.

51. Abrams D, Levy Y, Losso MH, et al. Interleukin-2 therapy in patients with HIV infection. *N Engl J Med*. 2009;361:1548–1559.
52. Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science*. 2010;329:1168–1174.
53. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *N Engl J Med*. 2015;372:509–518.
54. Baeten JM, Palanee-Phillips T, Brown ER, et al. Use of a vaginal ring containing dapavirine for HIV-1 prevention in women. *N Engl J Med*. 2016;375:2121–2132.
55. Mills A, Crofoot GJ, McDonald C, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate in the first protease inhibitor–based single-tablet regimen for initial HIV-1 therapy: A randomized phase 2 study. *J Acquir Immune Defic Syndr*. 2015;69:439–445.
56. Fernandez-Montero JV, Eugenia E, Barreiro P, et al. Antiretroviral drug-related toxicities: Clinical spectrum, prevention, and management. *Expert Opin Drug Saf*. 2013;12:697–707.
57. Hirsch MS, Gunthard HF, Schapiro JM, et al. Antiretroviral drug resistance testing in adult HIV-1 infection: 2008 recommendations of an International AIDS Society-USA panel. *Clin Infect Dis*. 2008;47:266–285.
58. Vandamme AM, Camacho RJ, Ceccherini-Silberstein F, et al. European recommendations for the clinical use of HIV drug resistance testing: 2011 update. *AIDS Rev*. 2011;13:77–108.
59. Telenti A. Safety concerns about CCR5 as an antiviral target. *Curr Opin HIV AIDS*. 2009;4:131–135.
60. Emu B, Fessel J, Schrader S, et al. Phase 3 study of Ibalizumab for multidrug-resistant HIV-1. *N Engl J Med*. 2018;379:645–654.
61. Park TE, Mohamed A, Kalabalik J, et al. Review of integrase strand transfer inhibitors for the treatment of human immunodeficiency virus infection. *Expert Revi Anti-infect Ther*. 2015;13:1195–1212.
62. Panel on Antiretroviral Guidelines for Adults and Adolescents. Department of Health and Human Services Adults and Adolescents Guidelines Panel classifies a fixed-dose combination product of bictegravir/tenofovir alafenamide/emtricitabine as one of the

recommended initial regimens for most people with HIV. Available at: https://aidsinfo.nih.gov/news/2044/adult-arv-panel-classifies-bic-taf-ftc-as-recommended-initial-regimen-for-hiv.

63. Sax PE, Pozniak A, Montes ML, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): A randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet*. 2017;390:2073–2082.
64. Margolis DA, Gonzalez-Garcia J, Stellbrink HJ, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomized, open-label, phase 2b, non-inferiority trial. *Lancet*. 2017;390:1499–1510.
65. Markowitz M, Frank I, Grant RM, et al. Safety and tolerability of long-acting cabotegravir injections in HIV-uninfected men (ÉCLAIR): A multicenter, double-blind, randomized, placebo-controlled, phase 2a trial. *Lancet HIV*. 2017;4:e331–e340.
66. Carnes SK, Sheehan JH, Aiken C. Inhibitors of the HIV-1 capsid, a target of opportunity. *Curr Opin HIV AIDS*. 2018;13:359–365.
67. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf.
68. Fischl MA, Richman DD, Grieco MH, et al. The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. *N Engl J Med*. 1987;317:185–191.
69. Hammer SM, Katzenstein DA, Hughes MD, et al. A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500 per cubic millimeter. *N Engl J Med*. 1996;335:1081–1090.
70. Hammer S, Squires K, Hughes M, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. *N Engl J Med*. 1997;337:725–733.

71. Palella FJJr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med*. 1998;338:853–860.
72. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: Two randomised, double-blind, phase 3, non-inferiority trials. *Lancet*. 2015;385:2606–2615.
73. Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med*. 2013;369:1807–1818.
74. Genberg BL, Wilson IB, Bangsberg D, et al. Patterns of ART adherence and impact on HIV RNA among patients from the MACH14 study. *AIDS*. 2012.
75. Parienti J-J, Das-Douglas M, Massari V, et al. Not all missed doses are the same: Sustained NNRTI treatment interruptions predict HIV rebound at low-to-moderate adherence levels. *PLoS ONE*. 2008;3:e2783.
76. Haberer JE, Musinguzi N, Boum Y 2nd, et al. Duration of antiretroviral therapy adherence interruption is associated with risk of virologic rebound as determined by real-time adherence monitoring in rural Uganda. *J Acquir Immune Defic Syndr*. 2015;70:386–392.
77. Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med*. 2006;354:251–260.
78. Sax PE, Tierney C, Collier AC, et al. Abacavir/Lamivudine versus tenofovir DF/emtricitabine as part of combination regimens for initial treatment of HIV: Final results. *J Infect Dis*. 2011;204:1191–1201.
79. Rockstroh JK, DeJesus E, Lennox JL, et al. Durable efficacy and safety of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: Final 5-year results from STARTMRK. *J Acquir Immune Defic Syndr*. 2013;63:77–85.
80. Lennox JL, Landovitz RJ, Ribaudo HJ, et al. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naive volunteers infected with HIV-1: A randomized, controlled equivalence trial. *Annals of Internal Medicine*. 2014;161:461–471.
81. Gammal RS, Court MH, Haidar CE, et al. Clinical Pharmacogenetics

Implementation Consortium (CPIC) guideline for UGT1A1 and atazanavir prescribing. *Clin Pharmacol Ther*. 2015.

82. Molina JM, Clotet B, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naïve adults with HIV-1 infection (FLAMINGO): 96 week results from a randomized, open-label, phase 3b study. *Lancet HIV*. 2015;2:e127–e136.
83. Zash R, Holmes L, Makhema J, et al. Surveillance for neural tube defects following antiretroviral exposure from conception, the Tsepamo study (Botswana). *The 22nd International AIDS Conference*. Amsterdam, The Netherlands, 2018.
84. Department of Health and Human Services Antiretroviral Guidelines Panels. Recommendations regarding the use of dolutegravir in adults and adolescents with HIV who are pregnant or of child-bearing potential. Available at: https://aidsinfo.nih.gov/news/2109/recommendations-regarding-the-use-of-dolutegravir-in-adults-and-adolescents-with-hiv-who-are-pregnant-or-of-child-bearing-potential.
85. US Public Health Service. Preexposure prophylaxis for the prevention of HIV infection in the United States – 2017 update: a clinical practice guideline. Available at: https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf.
86. El-Sadr WM, Lundgren J, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med*. 2006;355:2283–2296.
87. Phillips AN, Neaton J, Lundgren JD. The role of HIV in serious diseases other than AIDS. *AIDS*. 2008;22:2409–2418.
88. Walker NF, Scriven J, Meintjes G, et al. Immune reconstitution inflammatory syndrome in HIV-infected patients. *HIV AIDS (Auckl)*. 2015;7:49–64.
89. Bruchfeld J, Correia-Neves M, Källenius G. Tuberculosis and HIV coinfection. *Cold Spring Harbor Perspect Med*. 2015;5.
90. Krajicek BJ, Thomas CF Jr, Limper AH. *Pneumocystis pneumonia*: Current concepts in pathogenesis, diagnosis, and treatment. *Clin Chest Med*. 2009;30:265–278.
91. Santamauro J, Stover D. *Pneumocystis carinii* pneumonia. *Med Clin North Am*. 1977;81:299–318.
92. Morse CG, Kovacs JA. Metabolic and skeletal complications of HIV infection: The price of success. *JAMA*. 2006;296:844–854.

93. Martin-Iguacel R, Llibre JM, Friis-Moller N. Risk of cardiovascular disease in an aging HIV population: Where are we now? *Curr HIV/AIDS Rep*. 2015;12:375–387.
94. Hunt PW. HIV and aging: Emerging research issues. *Curr Opin HIV AIDS*. 2014;9:302–308.
95. Brickman C, Palefsky J. Cancer in the HIV-infected host: Epidemiology and pathogenesis in the antiretroviral era. *Curr HIV/AIDS Rep*. 2015;12:388–396.
96. Bruyand M, Ryom L, Shepherd L, et al. Cancer risk and use of protease inhibitor or nonnucleoside reverse transcriptase inhibitor-based combination antiretroviral therapy: The D:A:D study. *J Acquir Immune Defic Syndr*. 2015;68:568–577.
97. Grulich AE, van Leeuwen MT, Falster MO, et al. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: A meta-analysis. *Lancet*. 2007;370:59–67.
98. Mounier N, Katlama C, Costagliola D, et al. Drug interactions between antineoplastic and antiretroviral therapies: Implications and management for clinical practice. *Crit Rev Oncol/Hematol*. 2009;72:10–20.
99. Deeks SG, Tracy R, Douek DC. Systemic effects of inflammation on health during chronic HIV infection. *Immunity*. 2013;39:633–645.
100. Toribio M, Fitch KV, Sanchez L, et al. Effects of pitavastatin and pravastatin on markers of immune activation and arterial inflammation in HIV. *AIDS*. 2017;31:797–806.
101. Kotler DP. HIV and antiretroviral therapy: Lipid abnormalities and associated cardiovascular risk in HIV-infected patients. *J Acquir Immune Defic Syndr*. 2008;49:S79–S85.
102. da Cunha J, Maselli LM, Stern AC, et al. Impact of antiretroviral therapy on lipid metabolism of human immunodeficiency virus-infected patients: Old and new drugs. *World J Virol*. 2015;4:56–77.
103. Ding X, Andraca-Carrera E, Cooper C, et al. No association of abacavir use with myocardial infarction: Findings of an FDA meta-analysis. *J Acquir Immune Defic Syndr*. 2012.
104. Marcus JL, Neugebauer RS, Leyden WA, et al. Use of abacavir and risk of cardiovascular disease among HIV-infected individuals. *J Acquir Immune Defic Syndr*. 2015.
105. Stanley TL, Grinspoon SK. Body composition and metabolic changes in HIV-infected patients. *J Infect Dis*. 2012;205:S383–S390.

106. Peluso MJ, Spudich S. Treatment of HIV in the CNS: Effects of antiretroviral therapy and the promise of non-antiretroviral therapeutics. *Curr HIV/AIDS Rep*. 2014;11:353–362.
107. Kalayjian RC, Franceschini N, Gupta SK, et al. Suppression of HIV-1 replication by antiretroviral therapy improves renal function in persons with low CD4 cell counts and chronic kidney disease. *AIDS*. 2008;22:481–487.
108. Zayyad Z, Spudich S. Neuropathogenesis of HIV: From initial neuroinvasion to HIV-associated neurocognitive disorder (HAND). *Curr HIV/AIDS Rep*. 2015;12:16–24.
109. Apostolova N, Funes HA, Blas-Garcia A, et al. Efavirenz and the CNS: What we already know and questions that need to be answered. *J Antimicrob Chemother*. 2015;70:2693–2708.
110. Rosenberg AZ, Naicker S, Winkler CA, et al. HIV-associated nephropathies: Epidemiology, pathology, mechanisms and treatment. *Nature Rev Nephrol*. 2015;11:150–160.
111. Bagnis CI, Stellbrink HJ. Protease inhibitors and renal function in patients with HIV infection: A systematic review. *Infect Dis Ther*. 2015.
112. Lo Re V, Kallan MJ, Tate JP, et al. Hepatic decompensation in antiretroviral-treated patients co-infected with HIV and hepatitis C virus compared with hepatitis C virus–monoinfected patients: A cohort study. *Ann Intern Med*. 2014;160:369–379.
113. Anderson JP, Tchetgen Tchetgen EJ, Lo Re V 3rd, et al. Antiretroviral therapy reduces the rate of hepatic decompensation among HIV- and hepatitis C virus-coinfected veterans. *Clin Infect Dis*. 2014;25:719–727.
114. AASLD and IDSA. HCV Guidance: Recommendations for testing, managing, and treating hepatitis C. Available at: http://www.hcvguidelines.org/.
115. Soriano V, Labarga P, de Mendoza C, et al. Emerging challenges in managing hepatitis B in HIV patients. *Curr HIV/AIDS Rep*. 2015;12:344–352.

SECTION 19 ONCOLOGIC DISORDERS

144

Cancer Treatment and Chemotherapy

Lisa M. Cordes and Stacy S. Shord

KEY CONCEPTS

1. Carcinogenesis is a multistep process that includes initiation, promotion, conversion, and progression.
2. Cancer cells demonstrate unique traits that distinguish them from normal cells. Cancer cells can stimulate their own growth, resist inhibitory signals, avoid programmed cell death, grow new blood vessels (angiogenesis), invade local tissues, and spread to distant sites (ie, metastases).
3. Screening programs are designed to detect cancers in asymptomatic people who are at risk of a specific cancer.
4. Diagnosis and staging informs the treatment goals and helps select the most appropriate anticancer therapy. The treatment goal may be cure, control, or palliation. The therapy may include a combination of surgery, radiation therapy, or systemic anticancer agents. Systemic anticancer agents include chemotherapy, targeted agents, and immunotherapy.
5. Chemotherapy inhibits cancer growth by killing rapidly proliferating cells. These agents can be categorized as either cell-cycle phase-specific, targeting one specific phase of the cell cycle, or cell-cycle phase-nonspecific, targeting all proliferating cells regardless of their place in the cell cycle. Cell-cycle phase-specific chemotherapy is generally given more frequently or as a continuous infusion and cell-cycle phase-nonspecific chemotherapy is usually given less frequently.
6. Small molecule targeted agents inhibit kinases or enzymes responsible for the activation of various proteins that form intracellular signaling cascades. These agents treat cancer by correcting a dysregulated signaling pathway.

7. Biologic therapies include cytokines, vaccines, growth factors, and monoclonal antibodies (mAbs) with most biologic therapies classified as mAbs. A mAb recognizes an antigen that is expressed preferentially on cancer cells or immune cells or targets growth factors responsible for cancer growth. These antibodies can also be used to deliver drugs, radioisotopes, or toxins to the antigen-expressing cells.
8. Various factors can affect the response and toxicities a patient may experience with anticancer therapy. When determining the optimal therapy, the health professional should carefully consider patient-specific factors, tumor-specific factors, and treatment goals.
9. Myelosuppression is a common acute dose-limiting toxicity for chemotherapy agents. Common toxicities associated with small molecular and mAb-targeted agents are typically related to the interference with an intracellular signaling pathway or the alteration of the immune system and may occur several months after starting therapy.

Preclass Engaged Learning Activity

Instructions

Fill in the blanks of the Cytotoxic Chemotherapy Table from the list of chemotherapy agents.

Chemotherapy Agents: cabazitaxel, bleomycin, gemcitabine, cisplatin, pemetrexed, ifosfamide, lenalidomide, topotecan, vinblastine, bortezomib, capecitabine, etoposide phosphate, temozolomide, doxorubicin, etoposide, pomalidomide, mercaptopurine, docetaxel, belinostat, oxaliplatin, epirubicin, carmustine, fluorouracil, vorinostat, vinorelbine, pentostatin, carfilzomib

CYTOTOXIC CHEMOTHERAPY TABLE

Alkylating and Alkylating-Like Agents

Nitrogen Mustards	Nitrosoureas	Platinum Analogues	Triazenes	Misc
Bendamustine	_____	Carboplatin	Dacarbazine	Altretamine
Chlorambucil	Lomustine	_____	_____	Busulfan
Cyclophosphamide	Streptozocin	_____		Procarbazine
_____				Thiotepa
Mechlorethamine				
Melphalan				

Antimetabolites

DNA Methylation Inhibitors	Folate Antagonists	Purine Analogues	Pyrimidine Analogues
Azacitadine	Methotrexate	Cladribine	_____
Decitabine	_____	Clofarabine	Cytarabine
	Pralatrexate	Fludarabine	Floxuridine
		_____	_____
		Nelarabine	_____
		_____	Trifluridine and Tipiracil
		Thioguanine	

Antimicrotubule Agents

Taxanes	Vinca Alkaloids	Misc
_____	_____	Eribulin
_____	Vincristine, Conventional	Ixabepilone
Paclitaxel, Conventional	Vincristine, Liposomal	
Paclitaxel, Protein Bound	_____	

Topoisomerase Inhibitors

Topoisomerase I Inhibitors

Camptothecins
Irinotecan, Conventional
Irinotecan, Liposomal
_____

Topoisomerase II Inhibitors

Epipodophyllotoxins	Anthracyclines	Misc
_____	Daunorubicin, Conventional	Mitoxantrone
_____	Daunorubicin, Liposomal	
Teniposide	_____	
	_____	
	Idarubicin	
	Valrubicin	

Misc

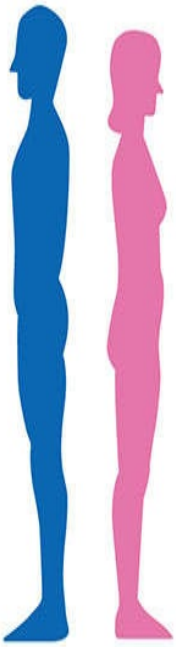
Antitumor Antibiotics	HDAC Inhibitors	Proteasome Inhibitors	Retinoids	Angiogenesis Inhibitors/ Immunomodulators	Misc Agents
_____	_____	_____	Bexarotene	_____	Arsenic trioxide
Dactinomycin	Panobinostat	_____	Tretinoin	_____	Asparaginase
Mitomycin	Romidepsin	Ixazomib		Thalidomide	Hydroxyurea
	_____				Mitotane
					Omecetaxine
					Pegaspargase
					Porfimer
					Trabectedin

INTRODUCTION

Cancer is a group of many different diseases that are characterized by uncontrolled cellular growth, local tissue invasion, and distant metastases. It is the second leading cause of death in Americans. Nearly 1.8 million cases of cancer were diagnosed in 2019 with an estimated 600,000 deaths in the United States.[1] **Figure 144-1** shows the estimated incidence of common cancers and cancer-related deaths. The most common cancers are prostate, breast, and lung cancer. The most common cause of cancer-related deaths in the United States is lung cancer, which accounts for nearly 150,000 deaths each year. These cancers are discussed in further detail in subsequent chapters.

Estimated new cases

Males			Females		
Prostate	174,650	20%	Breast	268,600	30%
Lung & bronchus	116,920	13%	Lung & bronchus	111,710	13%
Colon & rectum	78,500	9%	Colon & rectum	67,100	8%
Urinary bladder	61,700	7%	Uterine corpus	61,880	7%
Melanoma of the skin	57,220	7%	Melanoma of the skin	39,260	4%
Kidney & renal pelvis	44,120	5%	Thyroid	37,810	4%
Non-Hodgkin lymphoma	41,090	5%	Non-Hodgkin lymphoma	33,110	3%
Oral cavity & pharynx	38,140	4%	Kidney & renal pelvis	29,700	3%
Leukemia	35,920	4%	Pancreas	26,830	3%
Pancreas	29,940	3%	Leukemia	25,860	3%
All sites	**870,970**	**100%**	**All sites**	**891,480**	**100%**



Estimated deaths

Males			Females		
Lung and bronchus	76,650	24%	Lung and bronchus	66,020	23%
Prostate	31,620	10%	Breast	41,760	15%
Colon and rectum	27,640	9%	Colon and rectum	23,380	8%
Pancreas	23,800	7%	Pancreas	21,950	8%
Liver and intrahepatic bile duct	21,600	7%	Ovary	13,980	5%
Leukemia	13,150	4%	Uterine corpus	12,160	4%
Esophagus	13,020	4%	Liver and intrahepatic bile duct	10,180	4%
Urinary bladder	12,870	4%	Leukemia	9,690	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,460	3%
Brain & other nervous system	9,910	3%	Brain and other nervous system	7,850	3%
All sites	**321,670**	**100%**	**All sites**	**285,210**	**100%**

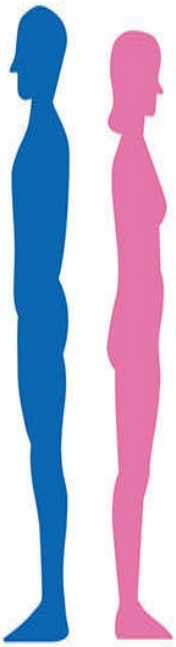


FIGURE 144-1 Estimated 2019 cancer incidences (top) and deaths (bottom) in the United States for males and females. *Estimates are rounded to the nearest 10 and exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. (*Reproduced with permission from Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;68:7–34.*)

Health professionals treating patients with cancer should have a thorough understanding of the pharmacokinetic, pharmacodynamic, and pharmacogenomic properties of all available anticancer agents, in addition to the reported safety and efficacy of each agent in each cancer population. Health professionals should be able to critically evaluate, summarize, and communicate the essential information to other health professionals, patients, and caregivers. This chapter defines the etiology, pathology, diagnosis, staging, and screening; introduces anticancer therapies; provides general information on how to safely administer systemic anticancer agents; and presents an overview of common supportive care measures for patients with cancer undergoing anticancer treatment.

ETIOLOGY OF CANCER

Normal healthy cells are strictly regulated, with stimulatory and inhibitory signals in a delicate balance. For normal cells to become cancer cells, it is believed that a physical, chemical, or biological agent must damage the cell and cause a genetic or epigenetic alteration that is subsequently propagated during cell division. Cancer cells eventually acquire multiple alterations and these alterations lead to unlimited growth, invasion, and metastases.

Carcinogenesis

The mechanisms by which cancers occur are incompletely understood. A cancer is thought to develop from a cell in which the normal mechanisms that control cell growth and proliferation are altered. Current evidence supports the concept of carcinogenesis as a multistage process that is genetically regulated.[2,3] The first step in this process is *initiation*, which requires exposure of normal cells to carcinogens. These carcinogens produce genetic alterations that, if not repaired, result in irreversible cellular changes. The changed cell may subsequently have an altered response to their environment that provides a selective growth advantage and permits the development of a clonal population

of cancer cells. During the second step, known as *promotion*, carcinogens or other factors alter the environment to favor growth of the altered cell population compared to normal cells. Promotion could be affected by chemoprevention strategies (strategies to lower cancer risk), including changes in lifestyle and diet. At some point, the altered cell becomes cancerous (*conversion* or *transformation*). Depending on the cancer, 5 to 20 years may elapse between the initiation and the development of a clinically detectable cancer. The final stage, called *progression*, involves further genetic alterations that lead to increased cell proliferation. The critical elements of this phase include invasion into local tissues and the development of metastases.

Substances that may act as carcinogens include a myriad of chemical, physical, and biologic agents.[2] Chemical exposures may occur by occupational and environmental means or by lifestyle habits. Some chemicals associated with cancer include aniline dye, asbestos, and benzene. Aniline dye is a known cause of bladder cancer; benzene is a known cause of leukemia and asbestos is a known cause of mesothelioma. Some medications and hormones used for therapeutic purposes are also classified as carcinogens (see **Table 144-1**). Physical agents that act as carcinogens include ionizing radiation and ultraviolet light; radiation induces mutations by forming free radicals that damage deoxyribonucleic acid (DNA) and other cellular components. Biologic agents that are associated with certain cancers include natural compounds (ie, viruses) or pollutants. The Epstein-Barr virus (EBV) may be an important factor in the initiation of Burkitt lymphoma. Similarly, infection with human papilloma virus (HPV) is a cause of cervical and head and neck cancers. Hereditary factors, age, and gender may also contribute to the development of cancer.

TABLE 144-1 Selected Drugs and Hormones Known to Cause Cancer in Humans

Drug or Hormone	Type of Cancer
Alkylating agents (eg, chlorambucil, mechlorethamine, melphalan, and nitrosoureas)	Leukemia
Anabolic steroids	Liver
Analgesics containing phenacetin	Renal, urinary bladder
Anthracyclines (eg, doxorubicin)	Leukemia
Antiestrogens (tamoxifen)	Endometrium
Coal tars (topical)	Skin
Nonsteroidal estrogens (diethylstilbestrol)	Vagina or cervix, endometrium, breast, testes
Steroidal estrogens (estrogen replacement therapy, oral contraceptives)	Endometrium, breast, liver
Epipodophyllotoxins (etoposide, teniposide)	Leukemia
Immunosuppressive drugs (cyclosporine, azathioprine)	Lymphoma, skin
Oxazaphosphorines (cyclophosphamide, ifosfamide)	Urinary bladder, leukemia

Source: Data from Compagni A, Christofori G. Recent advances in research on multistage tumorigenesis. Br J Cancer 2000;83:1-5; and Stricker TP, et al. In: Kumar V, et al., eds. Robbins and Cotran Pathologic Basis of Disease. 8th ed. Philadelphia, PA: Saunders; 2010;259–330.

Genetic Alterations

In recent years, there has been marked progress in our understanding of the genetic changes that lead to the development of cancer.[2,3] Two types of genes play an important role in the development of cancer: oncogenes and tumor suppressor genes. **Figure 144-2** illustrates the acquired capabilities of cancer cells that differ from normal cellular function.[4]

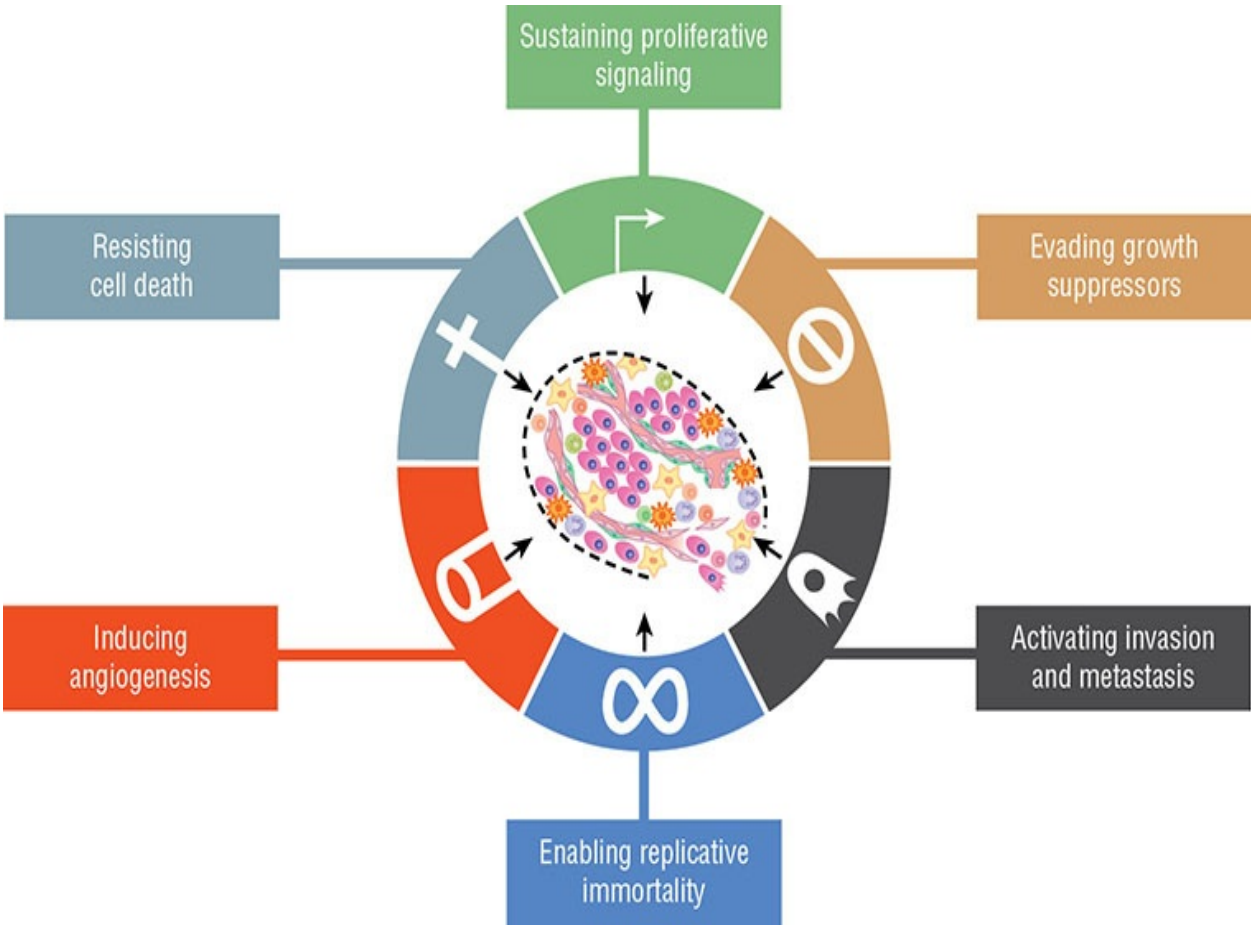


FIGURE 144-2 Functional capabilities acquired by cancer cells, including angiogenesis, self-proliferation, insensitivity to antigrowth signals and limitless growth potential, metastasis, and antiapoptotic effects. It is thought that most, if not all, cancer cells acquire these functions through a variety of mechanisms, including activation of oncogenes and mutations in tumor suppressor genes. (*Reprinted from Reference 4.*)

Oncogenes

Oncogenes develop from normal genes, called proto-oncogenes. Proto-oncogenes are present in all cells and are essential regulators of normal cellular functions. Genetic alterations of the proto-oncogene through point mutation, chromosomal rearrangement, or gene amplification can activate the oncogene. Carcinogens may cause these genetic alterations (somatic mutations) or these alterations may be inherited (germline mutations). After activation, the oncogene produces either excessive amounts of the normal gene product or an abnormal gene product. The result is dysregulation of normal cell growth and proliferation, which imparts a distinct growth advantage to the cell and increases the

probability of transformation. For example, the erythroblastic leukemia viral oncogene (ErbB) family members are oncogenes that mediate cell proliferation and differentiation through activation of intracellular signaling pathways. As an oncogene, the ErbB gene product is typically mutated, overexpressed, or amplified, resulting in excessive cellular proliferation, invasion, and metastasis and increased cell survival in several cancers. **Table 144-2** lists examples of oncogenes by their cellular function.

TABLE 144-2 Examples of Oncogenes and Tumor Suppressor Genes

Gene	Associated Human Cancer
Oncogenes	
ALK	Lung cancer, lymphomas, neuroblastoma, and ovarian cancer
BCR-ABL	Acute lymphoblastic leukemia, chronic myeloid leukemia
BCL-2	B-cell lymphomas
BRAF	Colon cancer, lung cancer, melanoma, ovarian cancer, thyroid cancer
ERBB1	Colon cancer, glioblastoma multiforme, lung cancer
ERBB2	Breast cancer, gastric cancer, lung cancer
FLT3	Acute myeloid leukemia, colorectal cancer
KIT (CD117)	Acute leukemia, gastrointestinal stromal tumor, and gastrointestinal stromal tumor
MYC	Acute myeloid leukemia, breast cancer, lung cancer, pancreatic cancer, retinoblastoma, T-cell lymphomas
PI3KCA	Lung cancer, ovarian cancer
RAS (NRAS, HRAS, KRAS)	Colon cancer, melanoma, ovarian cancer, thyroid cancer
ROS1	Lung cancer, cholangiocarcinoma
RET	Lung cancer, thyroid cancer
Tumor Suppressor Genes	
APC	Colon cancer, thymus cancers
BRCA1, BRCA2	Breast cancer, ovarian cancers
MSH2, MLH1, PMS1, PMS2, MSH6	Colon cancer
NF1, NF2	Leukemias, melanoma
TP53	Multiple cancers
PTEN	Lung cancer, ovarian cancer
RB1	Bladder cancer, retinoblastoma, sarcoma
VHL	Renal cell cancer

Data collated from My Cancer Genome, http://www.mycancergenome.org/.

Tumor Suppressor Genes

Tumor suppressor genes regulate and inhibit inappropriate cellular growth and proliferation.[3] Genetic alterations result in loss of control over normal cell growth. *Retinoblastoma* (Rb) 1 and *TP53* are examples of tumor suppressor genes. Mutation of *TP53* is one of the most common genetic alterations associated with cancer. The normal gene product of *TP53* is responsible for negative regulation of the cell cycle (ie, a series of cellular events that lead to the division and duplication of a cell), allowing the cell cycle to halt for repairs, corrections, and responses to other external signals. Inactivation of *TP53* following a genetic alteration removes this checkpoint, allowing genetic alterations to accumulate within a cell. Mutation of *TP53* is linked to a variety of cancers. For example, a germline mutation in which an individual has only one functional copy of *TP53* is associated with Li-Fraumeni syndrome, a syndrome characterized by multiple cancers by early adulthood. Another important function of *TP53* may be modulation of cytotoxic drug effects; loss of *TP53* is associated with anticancer drug resistance.

DNA Repair Genes

Another important type of gene that plays a role in the development of cancer is the DNA repair genes. Their normal function is to repair DNA that is damaged by environmental factors or errors in DNA that occur during replication.[3] If not corrected, these errors can result in alterations that activate oncogenes or inactivate tumor suppressor genes. Subsequently, more genetic alterations accumulate within a cell and the risk for transformation increases for the altered cell population. Specifically, DNA repair genes can affect mismatch repair, single-strand break repair, and double-strand break repair. For example, poly ADP ribose polymerase (PARP) is a family of proteins that is responsible for DNA repair and programmed cell death by affecting multiple repair mechanisms.[5] PARP1 is a member of the PARP family that plays a role in repairing single-strand DNA breaks. Deficiencies in DNA repair genes have been discovered in breast, colon, and ovarian cancers.

Accumulation of Genetic Alterations

It has become evident that a single genetic alteration is probably insufficient to initiate cancer.[2,3] Most cancers acquire multiple somatic genetic alterations; some alterations may make no contribution to the development of the cancer (eg, passenger mutations), while other alterations likely support the ongoing survival

of the cancer (eg, driver mutations). Scientists postulate that combinations of alterations are required for carcinogenesis and that each alteration is inherited by the next generation of cells. Thus, several detectable genetic alterations may be present in a cancer. Although early alterations are found in both premalignant lesions and established cancers, later alterations are found only in an established cancer. This theory of sequential genetic alteration has been demonstrated in colon cancer. In colon cancer, the initial genetic alteration is believed to be loss of the *adenomatous polyposis coli (APC)* gene, which results in formation of a small benign polyp (ie, abnormal tissue growth in a mucus membrane). An oncogenic mutation of ras genes is often the next step, leading to enlargement of the polyp. Loss of function of DNA mismatch repair enzymes may occur at many points during the transformation. Loss of *TP53* and another gene, believed to be the *deleted in colorectal cancer (DCC)* gene, completes the transformation. Loss of *TP53* may be a late event in the development and progression of colon cancer, as well as other cancers.

Four genes have been associated with DNA mismatch repair: *mutL homologue 1*, *mutS homologue 2*, *mutS homologue 6*, and *postmeiotic segregation increased 2*. When one or more of these proteins is mutated or missing, the tumor is characterized as mismatch repair deficient (dMMR). Tumors with a defective mismatch repair system may contain thousands of somatic mutations.[6,7] When a high number of these mutations accumulate within microsatellites (short repeating sequences of DNA), the tumor is characterized as microsatellite instability-high (MSI-H). As discussed later in the chapter, dMMR and MSI-H tumors are more susceptible to immune checkpoint inhibitors.

Epigenetic Alterations

Epigenetics refers to changes in gene expression that occur without altering the DNA sequence.[8] The two most common mechanisms of epigenetic regulation include methylation and histone modification. DNA methylation commonly occurs at CpG dinucleotides (or islands) and is catalyzed by DNA methyltransferases (DNMTs). Histones are basic proteins associated with DNA in the nucleosome. These proteins may be modified by acetylation, methylation, or phosphorylation on their N-terminal tail. These modifications play a role in transcriptional regulation. For example, histone deacetylases (HDAC) repress transcription and histone acetylases activate transcription. Epigenetic changes may be involved in the development of cancer by either priming the cell or making it susceptible to genetic alterations associated with the development of

cancer. As an example, hypermethylation at CpG dinucleotides found near tumor suppressor genes can switch these genes off and promote the development of cancer. Anticancer agents, identified as inhibitors of DNMT or HDAC, target these modifications. **Figure 144-3** shows the effects of these inhibitors on methylation, chromatin formation, and transcription.

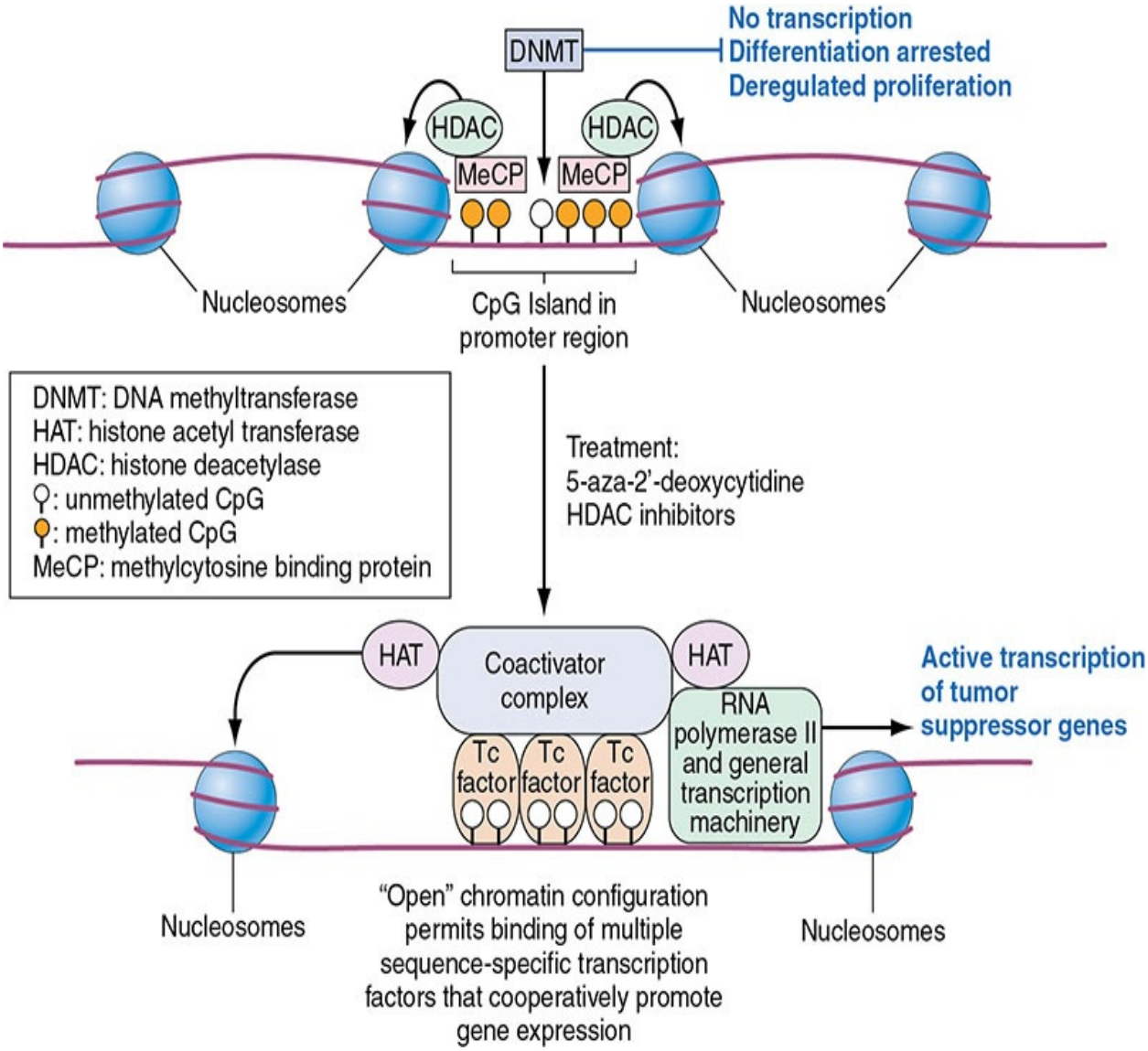


FIGURE 144-3 Epigenetic regulation of gene expression in cancer cells. CpG islands within the promoter and enhancer regions of the gene are methylated, resulting in the complexes with HDAC activity. Chromatin is in a condensed conformation that inhibits transcription (upper figure). Inhibitors of DNMT with inhibitors of HDAC confer a chromatin structure that allows transcription (lower figure). (*Reproduced with permission from Longo DL. Cancer Cell Biology and Angiogenesis. In: Longo DL, Fauci AS, Kasper DL, et al. eds. Harrison's*

Principles of Internal Medicine, 18th ed. New York, NY: McGraw-Hill, 2012.)

An oncometabolite is a metabolite whose abnormal accumulation may result in epigenetic dysregulation and carcinogenesis. Isocitrate dehydrogenase (IDH) 1 and 2 are enzymes involved in cellular metabolism through the conversion of isocitrate to alpha-ketoglutarate (αKG).[9] Mutations in *IDH1* and *IDH2* have been identified in gliomas and acute myeloid leukemia (AML) and result in the conversion of αKG to D-2-hydroxyglutarate (2-HG). Elevated levels of 2-HG, an oncometabolite, inhibit αKG-dependent histone and DNA demethylases which has been associated with impaired cellular differentiation. Anticancer agents have been developed to inhibit the mutant variants of IDH1 and 2 enzymes thereby restoring myeloid differentiation.

PATHOLOGY OF CANCER

2 Cancer cells demonstrate several characteristics that differentiate them from normal cells. These traits include unlimited growth in which the cell cycle is no longer strictly regulated. Genetic alterations permit activation of multiple oncogenes and suppression of various tumor suppressor genes, releasing the cancer cells from the strict regulation observed with healthy cells. The cancer cells subsequently undergo multiple cell divisions, allowing the tumor size to increase exponentially. Cancer cells also resist programmed cell death by inhibiting apoptosis and senescence (aging). Lastly, cancer cells grow new blood vessels, invade new local tissue, and spread to distant sites.

Cell Cycle

The cell cycle incorporates a series of events by which normal and cancer cells divide and make new cells. This process is strictly regulated in healthy cells. Oncogenes and tumor suppressor genes provide the stimulatory and inhibitory signals that regulate the cell cycle. These signals converge on a molecular system in the nucleus known as the cell-cycle clock. The function of the clock in healthy cells is to integrate the signal input and to determine if the cell cycle should proceed. The clock is composed of a series of interacting proteins, the most important of which are cyclins and cyclin-dependent kinases (CDKs). Cyclins and CDKs promote entry into the cell cycle and are overexpressed in several cancers. CDK inhibitors have been identified as important negative regulators of the cell cycle.

The cell cycle proceeds from one cell division to the next. The cycle involves five phases: DNA replication (S phase), cell division (M phase), two resting phases (G_1 and G_2), and a nondividing state (G_0 phase). In the first resting phase G_1, the cell grows in size and decides to commit to the cell cycle or remain in a resting state. If the cell is normal, the cell will move into the S phase to synthesize its DNA. Next, the cell enters the second resting phase G_2, in which the cell prepares to divide. In the M phase, the cell enters mitosis and yields two daughter cells. If the cell is not healthy, the cell can stop dividing and initiate apoptosis. **Figure 144-4** depicts the cell cycle and the phases of activity for some chemotherapy agents.

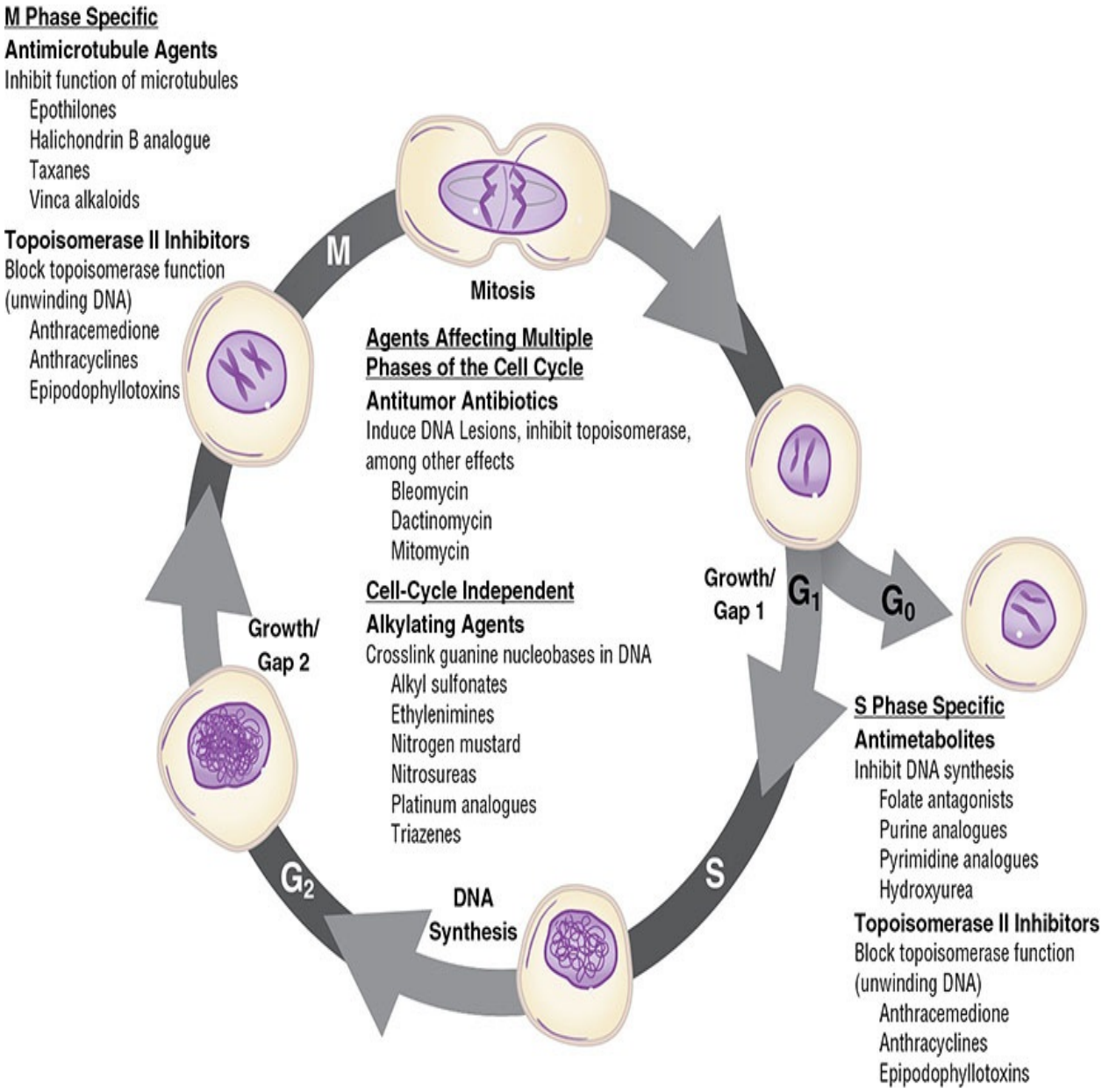


FIGURE 144-4 Cell-cycle activity for chemotherapy. Cell-cycle phase-specific chemotherapy are most active during a particular phase. Cell-cycle phase-nonspecific chemotherapy may have activity in more than one phase. In many cases, it is likely that chemotherapy cytotoxicity involves multiple intracellular sites of action and may not be linked to specific cell-cycle events.

Four checkpoints exist within the cell cycle, one in each phase of the cell cycle, and these checkpoints serve as quality control checkpoints. The cell will not proceed to the next phase unless all requirements for the current phase are met. Complexes of cyclin and CDK regulate these checkpoints. These complexes lead to the activation of other proteins that are responsible for the

specific events of each phase of the cell cycle. The first checkpoint is called the restriction site. Rb complexed to a transcription factor called E2F controls the restriction site. The presence of this complex prevents cell cycle progression. A cell can proceed beyond the G_1 restriction site and continue into the S phase when cyclin–CDK complexes phosphorylate Rb and target it for degradation. A cell may alternatively withdraw into the G_0 phase in the presence of antimitogenic or the absence of mitogenic factors.

Defense Systems

When the normal regulatory mechanisms for cell growth fail, backup defense systems may be activated. The secondary defenses include apoptosis (programmed cell death or suicide) and cellular senescence. Apoptosis is a normal mechanism of cell death required for tissue homeostasis. This process is regulated by oncogenes and tumor suppressor genes and is also a mechanism of cell death after exposure to cytotoxins. Overexpression of oncogenes responsible for apoptosis may produce an "immortal" cell, which has increased potential for malignancy. For example, the *B-cell lymphoma 2* (*BCL-2*) is normally located on chromosome 18, but it may be translocated to chromosome 14 in proximity to the immunoglobulin heavy chain gene. This translocation leads to overexpression of *BCL-2* in lymphoid malignancies, which decreases apoptosis and confers a survival advantage. As another example, loss of *TP53* disrupts normal apoptotic pathways, imparting a survival advantage. Apoptosis may also play an important role as a mechanism of inherent resistance to some chemotherapy agents.

Cellular senescence is another important defense mechanism.[3] Laboratory studies demonstrate that after a cell population has undergone a preset number of doublings, growth stops, and the cells die. This is known as senescence, a process that is regulated by telomeres. Telomeres are the DNA segments or caps at the ends of chromosomes. They are responsible for protecting the end of the DNA from damage. With each replication, the length of the telomeres is shortened. After the telomeres are shortened to a critical length, senescence is triggered. In this way, telomeres tally and limit the number of cell doublings. In cancer cells, the function of telomeres is overcome by overexpression of an enzyme known as telomerase. Telomerase replaces the portion of the telomeres that is lost with each cell division, thereby avoiding senescence and permitting an infinite number of cell doublings.

Immune Evasion

Immunosurveillance, a key feature of the host immune system, is the recognition and elimination of abnormal cells including malignant cells. Antitumor immunity depends on T-cell identification of tumor antigens: a process regulated in part by various receptor-ligand interactions. Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and programmed death-1 (PD-1) are inhibitory receptors expressed on activated T-cells that serve as immune checkpoints. Checkpoints are critical in maintaining self-tolerance and preventing autoimmunity. When these T-cell receptors bind to their respective ligands on tumor cells, B7-1 and PD-ligand-1 (PD-L1), T-cell down-regulation occurs and the tumor is able to evade immunosurveillance. These ligands are overexpressed on multiple types of tumors and this process represents one of the multiple mechanisms that tumors evade immune elimination. Immune checkpoint inhibitors block the receptor-ligand interactions, reverse the immune down-regulation, and allow for tumor cell elimination.

Cancer Growth

The study of cancer growth forms the foundation for many of the basic principles of modern chemotherapy. The growth of most cancers is illustrated by the Gompertzian growth curve (see **Fig. 144-5**).[3] Gompertz was an insurance actuary who described the relationship between age and expected death. This mathematical model also approximates cancer cell proliferation. In the early stages, cancer growth is exponential, which means that the cancer takes a constant amount of time to double its size. During this early phase, most cancer cells are actively dividing. This population of cells is called the growth fraction. The doubling time, or time required for the cancer to double in size, is very short. Because cytotoxic chemotherapy agents typically have a greater effect on rapidly dividing cells, cancers are most sensitive to their effects when the cancer is small and the growth fraction is high. As the cancer grows, the doubling time is slowed. The growth fraction decreases, probably owing to the cancer outgrowing its blood and nutrient supply or the inability of blood and nutrients to diffuse throughout the mass. Wide variability exists in measured doubling times for different cancers. The doubling time of most solid tumors is about 2 to 3 months, but some cancers have doubling times of only days (eg, aggressive non-Hodgkin lymphoma [NHL]).[3]

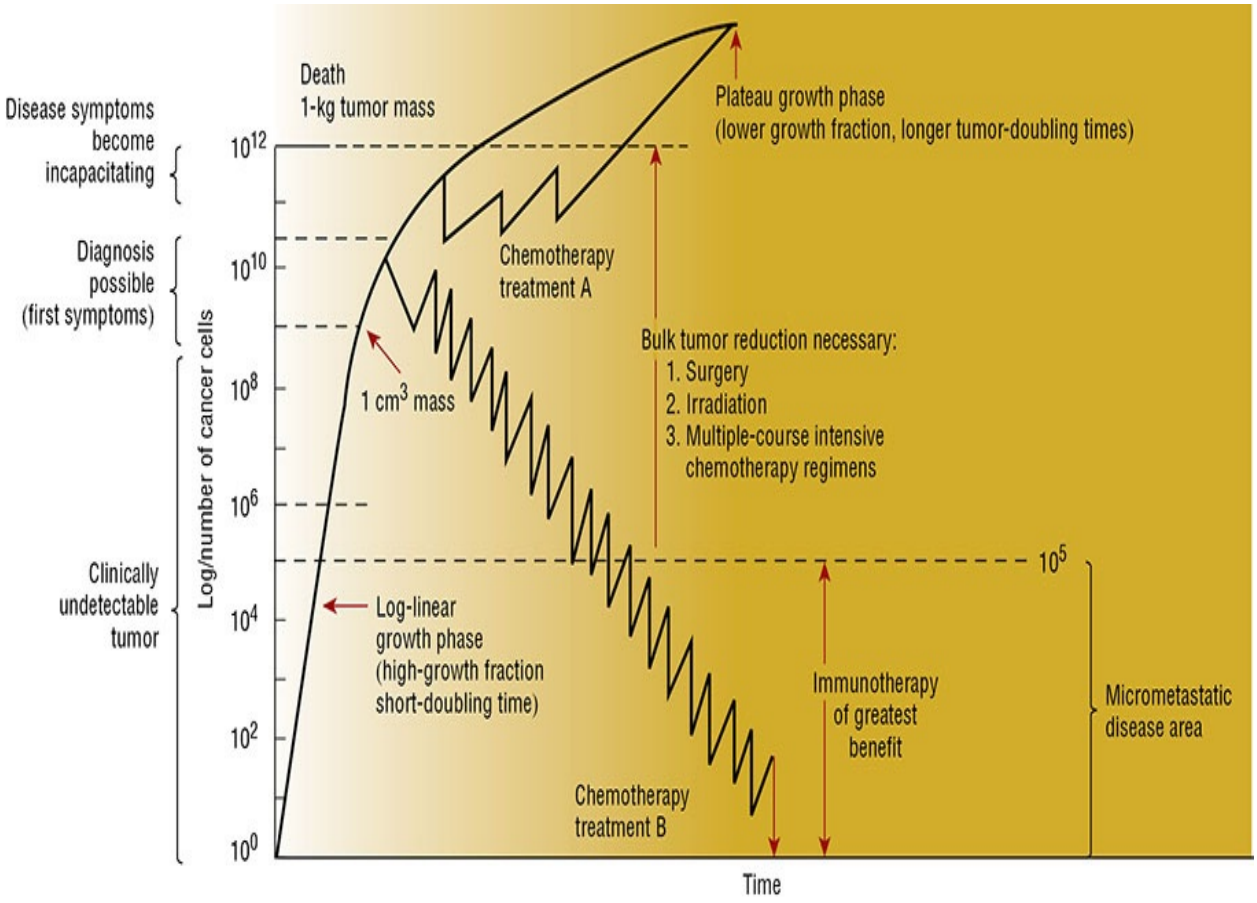


FIGURE 144-5 Gompertzian kinetics tumor-growth curve: relationship to symptoms, diagnosis, and various treatment regimens. (*Reproduced with permission from Buick RN. Cellular basis of chemotherapy. In: Dorr RT, Von Hoff DD, eds. Cancer Chemotherapy Handbook, 2nd ed. New York: Appleton & Lange/McGraw-Hill, 1994:3-14.*)

Tumor burden impacts diagnosis and treatment (see Fig. 144-5). It takes about 10^9 cancer cells (1 g mass, 1 cm in diameter) for a cancer to be clinically detectable by palpation or radiography. A cancer of this size has likely undergone about 30 doublings in cell number. It only takes 10 additional doublings for this 1 g mass to reach 1 kg in size. A cancer possessing 10^{12} cells (1 kg mass) is considered lethal. Thus, a cancer is clinically undetectable for most of its life span. Tumor burden also impacts treatment. The cell kill hypothesis states that a certain percentage of cells will be killed with each course of cytotoxic chemotherapy. For example, if a cancer consists of 1,000 cells and the first treatment kills 90% of the cells, then 10% or 100 cells remain. The second treatment kills another 90% of cells, and again only 10% or 10 cells remain. According to this hypothesis, the tumor burden will never reach zero.

Cancers consisting of less than 10^4 cells are believed to be small enough for elimination by host factors, including immunosurveillance. The limitations of this theory are that it assumes all cancers are equally responsive to treatment and that resistance to anticancer agents and the development of metastases do not occur.[3]

Invasion and Metastasis

As the cancer grows, cancer cells break away or shed from the primary site to invade surrounding tissue and metastasize to distant sites.[2,10] Metastatic disease is associated with a poorer prognosis and shortened survival compared to earlier disease. The cancer cells invade adjacent tissue or metastasize to distant sites by hematogenous or lymphatic spread but not all of the shed cells result in a metastatic lesion. The shed cells must first find an environment suitable for growth.[10] The onset and time course for the development of metastasis depends largely on the individual cancer, as illustrated by the diverse patterns of metastasis observed for different cancers. Breast cancer, for example, tends to metastasize very early. Prostate cancer commonly metastasizes to bone and colon cancer commonly metastasizes to the liver. Other less common modes of disease spread include dissemination via cerebrospinal fluid and transabdominal spread within the peritoneal cavity.

For a cancer cell to break away from the primary tumor site, the shed cell and surrounding host tissue must first secrete substances that stimulate angiogenesis.[11] The shed cells must then detach from the primary tumor by expressing proteins that degrade the extracellular matrix, such as matrix metalloproteases, and invade surrounding blood and lymph vessels. The cells must then attach to the vascular endothelium. The cells may proliferate within the lumen of the vessel, but most commonly extravasate into the surrounding tissue. The local microenvironment may provide growth factors that can serve as fertilizer to potentiate the development of a metastatic site. At every step, the potential metastatic cell must fight the host immune system. Finally, the metastasis must again initiate angiogenesis to ensure continued growth and proliferation.

Angiogenesis is the development of new blood vessels. This process becomes unregulated in several cancers and supports growth, invasion, and metastasis. Angiogenesis is regulated by pro- and antiangiogenic growth factors, which are released in response to hypoxia and other stresses to the cell. Proangiogenic growth factors include vascular endothelial growth factor (VEGF), fibroblast

growth factor, platelet-derived growth factor (PDGF), and tumor necrosis factor-alpha (TNF-α). Antiangiogenic growth factors include interleukin-12 (IL-12), interferon (IFN), and tissue inhibitors of metalloproteinases. The best studied proangiogenic factor is VEGF, whose elevated levels have been associated with a poor prognosis and an increased risk of metastases in many cancers, including breast cancer, non-small cell lung cancer (NSCLC), ovarian cancer, and colon cancer. Similar to other growth factors, VEGF binds to specific receptors located on the extracellular domain: VEGFR1, 2, and 3. VEGFR1 and VEGFR2 are expressed primarily in endothelial cells and in some cancer cells and mediate the biologic effects of VEGF. Each of the receptors induces a different signal transduction pathway. These pathways eventually result in the generation of proteases that are necessary for the breakdown of the extracellular matrix. Inhibiting the development of new blood vessels can limit or prevent tumor growth.

DIAGNOSIS OF CANCER

Tumors may be either benign or malignant. Benign tumors are noncancerous growths that are often encapsulated, localized, and indolent. Benign tumors are named for the cell or tissue of origin followed by the suffix-oma. The tumor cells resemble the cells from which they developed. These masses seldom metastasize and rarely recur after being removed. In contrast to benign tumors, malignant tumors invade and destroy the surrounding tissue. The cancer cells are genetically unstable and loss of normal cell architecture results in cells that are atypical of their tissue or cell of origin. These cells lose the ability to perform their usual functions. This loss of structure and function is called anaplasia. Cancers tend to metastasize and consequently, recurrences are common after removal or destruction of the primary tumor. Cancers arising from epithelial cells are called carcinomas and those arising from muscle or connective tissue are called sarcomas. **Table 144-3** lists common nomenclature by tissue type.[3]

TABLE 144-3 Tumor Classification by Tissue Type

Tissue of Origin	Benign	Malignant
Epithelium		
Surface epithelium	Papilloma	Carcinoma (squamous, epidermoid)
Glandular tissue	Adenoma	Adenocarcinoma
Connective tissue		
Fibrous tissue	Fibroma	Fibrosarcoma
Bone	Osteoma	Osteosarcoma
Smooth muscle	Leiomyoma	Leiomyosarcoma
Striated muscle	Rhabdomyoma	Rhabdomyosarcoma
Fat	Lipoma	Liposarcoma
Lymphoid tissue and hematopoietic cells		
Hematopoietic cells		Leukemias
Lymphoid tissue		Hodgkin and non-Hodgkin lymphoma
Plasma cell		Multiple myeloma
Neural tissue		
Glial tissue	"Benign" gliomas	Glioblastoma multiforme; astrocytoma
Nerve sheath	Neurofibroma	Neurofibrosarcoma
Melanocytes	Pigmented nevus	Melanoma
Mixed tumors		
Gonadal tissue	Teratoma	Teratocarcinoma

Adapted from Stricker TP, Kumar V. Neoplasia. In: Kumar V, Abbas AK, Aster JC, Fausto N, eds. Robbins and Cotran Pathologic Basis of Disease. 8th ed. Philadelphia, PA: Saunders; 2010;259–330.

Screening

3 Because cancers are most curable before they metastasize, early detection and treatment have obvious potential benefits. Cancer screening programs are designed to detect cancers in individuals who have not yet developed symptoms, but screening is only available for a few cancers, such as colon, prostate, breast, and cervical cancers. Available screening tools include the Papanicolaou (Pap) smear test for cervical cancer and mammography for breast cancer. Limitations of the available screening tests include false-negative test results (related to the sensitivity of the test), false-positive test results (related to the specificity), and

overdiagnosis (true positives not likely to become clinically significant). For example, most abnormal test results identified by a screening mammography are false-positive, although the specificity of a mammogram exceeds 90%. For most cancers, lack of effective screening methods and inaccessible anatomic sites limit the potential impact of a screening program. Public education on the early warning signs of common cancers is therefore extremely important for facilitating early detection. The American Cancer Society and other organizations publish guidelines for routine screening examinations (see **Table 144-4**).[12]

TABLE 144-4 Screening Guidelines for Early Detection of Cancer in Average-Risk, Asymptomatic Individuals

Cancer	Test or Procedure	Age (y)	Frequency
Breast	Mammography	40-44	Every year, optional
		45-54	Every year
		≥55	Every 1-2 years; depending on life expectancy
Cervical	Pap test (conventional or liquid based)	21-29	Every 3 years
		30-65	Every 3 years (acceptable)
	Pap test and HPV DNA test	30-65	Every 5 years (preferred)
	Pap test and HPV DNA test	≥65	Stop if ≥3 consecutive negative Pap tests or ≥2 consecutive negative Pap and HPV tests within last 10 years with the most recent test in the last 5 years
Colorectal	One of the following examination schedules should be followed:	45-75	
	Guaic-based fecal occult blood test (FOBT) or fecal immunochemical test (FIT)[d]		Every year
	Multitarget stool DNA test (high-sensitivity)		Every 3 years
	Flexible sigmoidoscopy		Every 5 years
	Colonoscopy		Every 10 years
	Computed tomography colonography		Every 5 years
		76-85	Individualized based on patient preference, life expectancy, prior screening history
		>85	Discourage from screening
Endometrial	Information on risks and symptoms	Menopause	Once
Lung	Low-dose helical computed tomography	Current or former smokers 55-74 years in good health with at least a 30-pack-year history of smoking	Annually[a]
Prostate	Prostate-specific antigen (PSA) with or without digital rectal examination	≥50	Option if at least a 10-year life expectancy to make informed decision with their healthcare provider whether to be screened after receiving information about the potential benefits, risks and uncertainties associated with screening

[a]In adults who currently smoke or have quit within the past 15 years and have at least a 30-pack-year history and receive evidence-based smoking cessation counseling if they are current smokers and have undergone a process of informed/shared decision making that included information about the potential benefits, limitations and harms of screening with low-dose computed tomography and have access to a high volume, high-quality lung cancer screening and treatment center.

Adapted from Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2018: A review of current American Cancer Society guidelines and issues in cancer screening. CA Cancer J Clin. 2018;68:297–316.

Clinical Presentation

4 The presenting signs and symptoms vary widely and depend on the type of cancer. The presentation in adults may include any of the seven warning signs listed in **Table 144-5**, as well as headaches, weight loss, chronic pain, fatigue, or anorexia.[13] The warning signs of cancer in pediatrics are different and reflect the cancers more common in this population (see **Table 144-6**). The definitive diagnosis of cancer relies on the procurement of a tissue sample and pathologic assessment of this sample. This sample can be obtained by numerous methods, including an excisional, core, or needle aspiration biopsy. A tissue diagnosis is essential because many benign tumors can masquerade as cancers and most tumors are not cancer. Depending on the tumor type, the diagnosis may include evaluation for genetic alterations such as hormone receptor status in breast cancer or epidermal growth factor receptor (EGFR) status in NSCLC. Multiple companion or complementary tests are available and are indicated to either detect a select mutation associated with a specific tumor type or identify hundreds of genetic mutations in any solid tumor.

TABLE 144-5 Cancer's Seven Warning Signs

Change in bowel or bladder habits
A sore that does not heal
Unusual bleeding or discharge
Thickening or lump in the breast or elsewhere
Indigestion or difficulty in swallowing
Obvious change in wart or mole
Nagging cough or hoarseness
If YOU have a warning signal, see your doctor!

Adapted from American Cancer Society study communicating cancer information through mass distribution leaflets: An American Cancer Society study. CA Cancer J Clin. 1967;17:291–293.

TABLE 144-6 Cancer's Warning Signs in Children

Continued, unexplained weight loss
Headaches with vomiting in the morning
Increased swelling or persistent pain in bones or joints
Lump or mass in abdomen, neck, or elsewhere
Development of a whitish appearance in the pupil of the eye
Recurrent fevers not caused by infections
Excessive bruising or bleeding
Noticeable paleness or prolonged tiredness

Staging

Following a pathologic diagnosis, cancers should be staged to determine the extent of disease (ie, tumor location and size) before starting treatment. Staging provides information on prognosis and guides treatment selection. A staging workup may involve physical examination, biopsy, imaging tests (ie, computed tomography scans, magnetic resonance imaging, and positron emission tomography scans), and laboratory tests. The laboratory tests may include tumor markers, antigens, or other substances produced by the cancer. However, tumor markers are often nonspecific and may be elevated in many different cancers or in patients with nonmalignant conditions. As a result, tumor markers are generally more useful for monitoring response and detecting recurrence than as diagnostic tools. For example, human chorionic gonadotropin (hCG) and alpha-fetoprotein (AFP) in testicular cancer or prostate-specific antigen (PSA) in prostate cancer are useful markers to monitor response or recurrence. After starting treatment, the staging workup is usually repeated at regular intervals to evaluate the effectiveness of the treatment.

The most common staging system for solid tumors is the TNM system that describes the tumor (T), nodes (N), and metastases (M). A numerical value is assigned to each letter to indicate the size or extent of disease. The T describes the size of the primary tumor and spread to adjacent tissues; the N specifies the size, location, and number of regional lymph nodes affected by the cancer; and the M describes the presence or absence of metastases. Each letter is followed by an Arabic number that uniquely describes that tumor, node, or metastases. After the individual T, N, and M are determined, their values are combined to provide an overall stage that is identified using Roman numerals ranging from stage I to stage IV. For example, stage $T_3N_1M_0$, which describes a moderate-to-large primary mass with regional lymph node involvement and no distant metastases, is typically a stage III cancer. This simplified staging system allows healthcare professionals to easily identify the extent of disease. For example, stage I usually indicates localized cancer, stages II and III typically indicate local and regional disease, and stage IV typically indicates distant metastases. The criteria for classifying disease extent are quite specific for each different cancer. Alternative staging systems are used in clinical practice for leukemias and lymphomas as discussed in subsequent chapters.

TREATMENT MODALITIES

Three main modalities are used to treat cancer: surgery, radiation, and systemic anticancer agents. These modalities may be used alone but are typically given sequentially or concurrently to treat a specific cancer. The timing of the different modalities relative to one another is based on the outcomes of a clinical trial.

Surgery is the oldest treatment modality and it plays a major role in diagnosis and treatment. It may be curative if the primary cancer has not metastasized. Surgery remains the treatment of choice for most early stage cancers, such as breast and colon cancers. Surgery typically involves removal of the primary tumor and adjacent lymph nodes. This modality may also be used to remove isolated metastases and relieve symptoms associated with metastatic disease. For example, hepatic metastases may be removed for patients with colon cancer.

Radiation therapy can be used alone for localized cancer or for cancer that may encompass a single radiation field. It was first used to treat cancer in the late 1800s and remains a mainstay of treatment for some cancers. Radiation therapy may also be used to alleviate symptoms associated with vena cava syndrome, bone metastases, spinal cord compression, and brain tumors. This modality typically damages normal tissue surrounding the cancer, but the normal tissue typically repairs itself more readily than the cancer cells. Several different types of radiation therapy are available including external beam radiation therapy, stereotactic radiation, brachytherapy, and radioisotopes. Both early and late toxicities associated with radiation therapy are dependent on the organs within the radiation field. For example, mucositis is commonly observed in patients receiving radiation for head and neck cancer. Secondary cancers are a devastating late toxicity that can occur following radiation therapy.

Systemic anticancer agents include chemotherapy, targeted therapy, and immunotherapy. Multiple radiopharmaceuticals are also now available. In general, systemic anticancer agents are developed to destroy cancer cells while minimizing effects to healthy cells. Specific agents will be discussed later in this chapter.

Combined Modality Treatment

As stated earlier in the chapter, a cancer may be treated with multiple modalities. For example, systemic anticancer agents are often administered to patients with local disease (ie, early stage) following surgery or radiation therapy, because most patients with local disease have undetectable metastatic disease (ie, micrometastases) at diagnosis. Localized anticancer treatment alone would likely fail to completely eliminate the cancer. *Adjuvant* therapy is systemic therapy

administered to eradicate micrometastatic disease after surgery or radiation. The goal of adjuvant therapy is to reduce recurrence rates and prolong long-term survival. Thus, adjuvant therapy is given to patients with potentially curable cancers who have no clinically detectable disease after surgery or radiation. Because adjuvant therapy is given at a time when the cancer is undetectable (ie, no measurable disease), its effectiveness is evaluated by recurrence rates and survival. *Neoadjuvant* (ie, preoperative or preradiation) therapy may be given to patients before surgery or radiation therapy to reduce tumor burden and destroy micrometastases. For example, neoadjuvant therapy has been given to women with breast cancer to reduce the size of the primary tumor and allow for a less invasive surgical procedure.

The management of hematologic malignancies typically involves the use of systemic anticancer therapies and radiation therapy since these cancers are systemic diseases that cannot be effectively treated with localized modalities. Systemic therapy that is administered to eradicate the cancer cells is called *induction* therapy. When a complete remission (the disappearance of all signs of cancer) is documented, postremission, or *consolidation,* therapy is administered. These therapies are designed to eradicate any remaining disease, similar to adjuvant therapy for solid tumors, and can include systemic therapy, a hematopoietic stem cell transplant, or radiation therapy. *Maintenance* therapy is sometimes administered after consolidation therapy. This therapy is given to prevent the cancer from recurring and may include combination chemotherapy. Not all treatment phases are employed for all hematologic malignancies.

Goals of Treatment

The goals of treatment depend on the cancer stage and patient factors, such as comorbidities. When an anticancer agent is administered to patients with local or regional disease, the treatment (eg, adjuvant therapy) is often administered to cure the patient and may be labeled as *curative* therapy. When the cancer has metastasized to distant sites, a cure is usually not possible with rare exceptions including testicular cancer. Anticancer therapy may be administered to patients with metastatic disease to slow the progression of cancer and prolong survival by months to years. If anticancer therapy is given to patients with the goal of reducing symptoms, the treatment is often called *palliative* therapy.

SYSTEMIC THERAPY

Chemotherapy

5 Chemotherapy was first administered in 1941 when Goodman and Gilman gave nitrogen mustard to patients with lymphoma. As discussed later in the chapter, a chemotherapy agent is typically given as part of a combination regimen, in which multiple anticancer agents with different mechanisms of action and toxicities are given together. Most chemotherapy agents target rapidly proliferating cells (both normal and cancer cells) and these agents might act at one or more phases of the cell cycle. A chemotherapy agent that demonstrates major activity in a particular phase of the cell cycle is known as a cell-cycle phase-specific agent. For example, antimetabolites exert their effect during the S phase. Cell-cycle phase-specific agents may be less active in other phases of the cell cycle. A cell-cycle phase-nonspecific agent has significant activity in multiple phases. Alkylating agents, such as nitrogen mustards, are examples of cell-cycle phase-nonspecific agents. Despite this classification, it is believed that most chemotherapy agents provide cytotoxic effects following interactions with other intracellular activities, not just specific cell-cycle events. Knowledge of cell-cycle specificity has been used to optimize treatment schedules. For example, a cell-cycle phase-specific chemotherapy agent is typically administered as a continuous infusion or in multiple repeated fractions to maximize the number of cancer cells in the sensitive cell-cycle phase. Thus, a cell-cycle phase-specific chemotherapy agent is also termed schedule dependent. In contrast, cell-cycle phase-nonspecific chemotherapy is active in many phases and consequently these agents are not schedule dependent. The activity of these chemotherapy agents depends on the dose, so these chemotherapies are termed dose-dependent. Chemotherapy agents are typically given in a defined repeating schedule called a cycle. The cycle length typically depends on the toxicities associated with the chemotherapy agent, such that sufficient time elapses between doses to allow a patient to adequately recover from a serious adverse reaction (eg, neutropenia). The number of cycles depends, in part, on the treatment goals. The number of cycles is typically defined by prior clinical trials for early stage disease, while the number of cycles is typically defined by individualized treatment response and tolerability for locally advanced or metastatic disease.

Targeted Agents

Targeted anticancer agents, including small molecule inhibitors and mAbs, stop cancer progression by blocking aberrant intracellular signaling pathways that

govern cell responses, movement, and division. Some of these agents can cause cancer cell death by inducing apoptosis or stimulating the immune system to destroy the cancer cells.

The first small molecular targeted agent was developed in the late 1980s. Small molecule targeted agents have a low-molecular weight (less than 1,000 daltons) and have been specifically designed to interfere with intracellular signaling pathways. These agents are typically given orally once or twice daily until disease progression or unacceptable toxicity. Since resistance commonly develops with small molecule targeted agents, they may be administered concurrently with other anticancer agents.

Similar to small molecule targeted agents, most mAbs are administered with other anticancer treatments. Both mAbs and targeted agents have been developed to interfere with intracellular signaling. Although small molecule targeted agents typically inhibit intracellular kinases, mAbs target the extracellular receptors or their natural ligands and prevent ligand binding to the receptor. The net effect of both strategies is to interfere with intracellular signal transduction and decrease cell proliferation (see **Fig. 144-6**). Some common receptors and pathways affected by available small molecule targeted agents and mAbs include ErbB2 family, mitogen-activated protein kinase (MAPK) pathway, and phosphatidylinositide 3-kinase (PI3K) pathway.

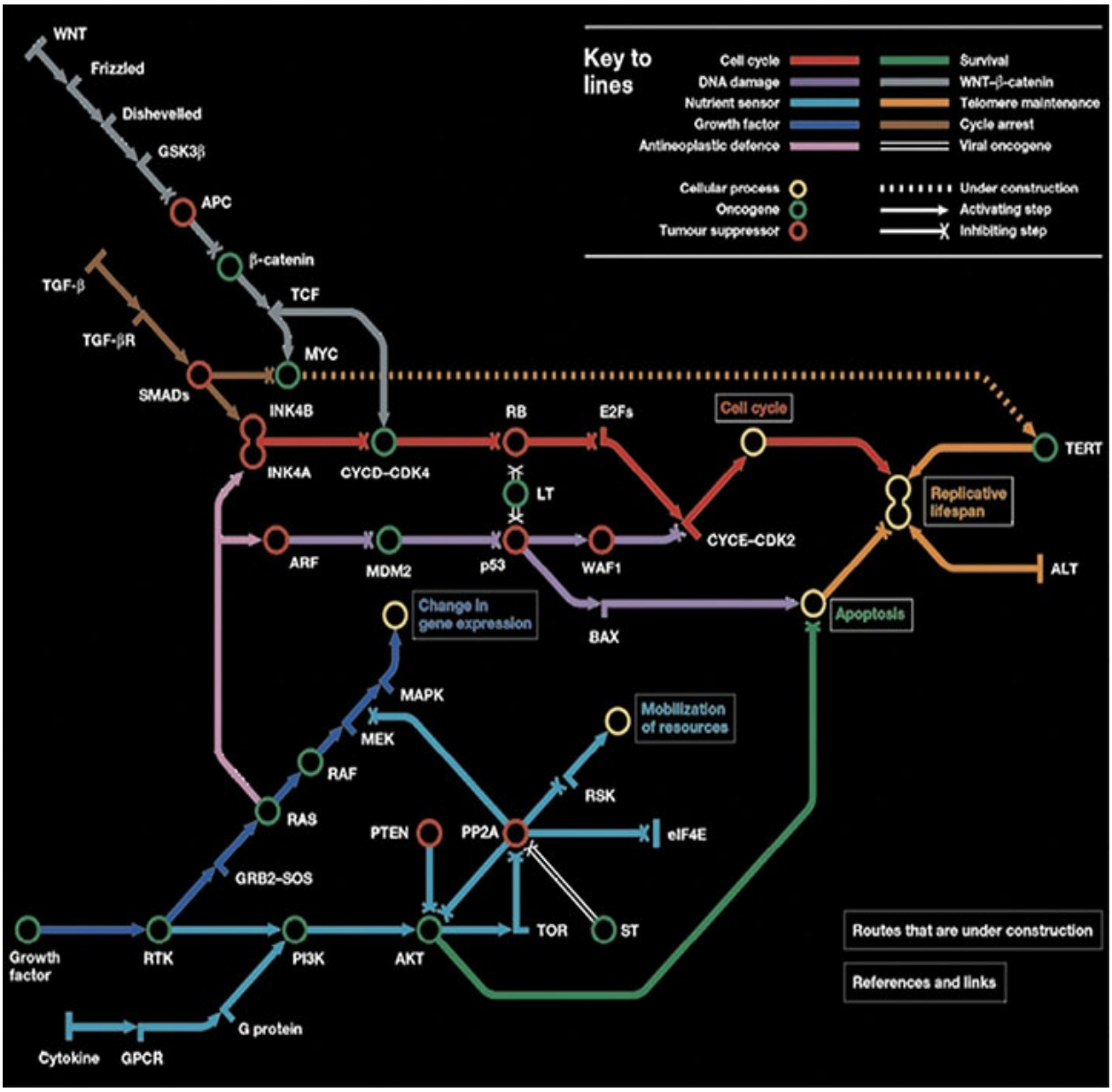


FIGURE 144-6 Common elements of intracellular signaling pathways and targeted strategies that inhibit these pathways, such as (1) mAb against the growth factor receptor, (2) mAb against a growth factor, (3) targeted drugs that inhibit intracellular kinases and prevent subsequent activation of downstream signals, and (4) targeting downstream signals. All targeted drugs have the same goal of decreasing cell proliferation and increasing cancer cell death. (MAPK, mitogen-activated protein kinase.)

The ErbB family of receptors contains four known members: ErbB1 (EGFR), ErbB2 (human epidermal growth factor receptor 2 [HER2]), ErbB3, and ErbB4. EGFR and HER2 are overexpressed in several cancers, including breast, lung,

gastric, and colon cancers. The roles of the other receptors in cancer growth and proliferation are still under investigation. Members of this family are inactive by themselves and must form a dimer (a molecule composed of two subunits) either with a member of the same family (homodimer) or with a member of a different ErbB family (heterodimer). Dimerization of the receptor leads to kinase phosphorylation and subsequent activation of downstream pathways required to activate signal transduction and cell growth.

Well-described intracellular signaling pathways include PI3K, JAK-STAT (Janus kinase–signal transducers and activators of transcription), and MAPK. When these pathways are activated, they promote cell proliferation and survival. These pathways consist of a chain of proteins that ultimately communicate a signal from a cell surface receptor to the DNA found in the nucleus. A protein within a signaling pathway communicates by adding a phosphate group to its neighboring protein; the phosphate groups act as an “on” or “off” switch for the pathway. In cancer, a mutated protein permits the pathway to remain in the “on” or “off” position. The downstream effectors of these pathways also initiate cell cycle progression by promoting the expression of cyclins and repressing the expression of CDK inhibitors.

The MAPK signaling pathway regulates many fundamental cellular processes, including cell differentiation, proliferation, and senescence. These pathways relay the intracellular signals through a series of ras, raf, MEK (mitogen-activated protein kinase-extracellular signal-regulated kinase), and ERK (extracellular signal-regulated kinase) proteins that subsequently phosphorylate and regulate nuclear and cytoplasmic structures. Some of these proteins are commonly altered in pancreatic, melanoma, colorectal, hepatocellular, and other solid tumors.[14]

The PI3K signaling pathway also regulates cell proliferation, growth, survival, and mobility. PI3K becomes activated in response to growth hormones, and it ultimately activates protein kinase B (as known as AKT), a serine–threonine kinase that serves as a master switch for the cell cycle progression. Fully activated AKT translocates to the nucleus, where it can inhibit proapoptotic signals and activate antiapoptotic substrates. It can also phosphorylate mammalian target of rapamycin (mTOR). After being activated, mTOR stimulates protein synthesis by phosphorylating translation regulators. mTOR also contributes to protein degradation and angiogenesis. Phosphatase and tensin homolog (PTEN) is a tumor suppressor gene that blocks intracellular signaling through this pathway and is frequently inactivated in several solid tumors.

The JAK-STAT signaling pathway helps regulate the immune system. This pathway contains three main components: extracellular receptors, JAKs, and STAT. The pathway is initiated when cytokines or growth factors bind to the receptor, activate JAK, and subsequently recruit STAT. The STAT proteins then translocate to the nucleus and modify gene expression. Altered JAK signaling has been associated with JAK mutations in patients with myelofibrosis.

Immunotherapy

Immunotherapy works by boosting the natural defenses of host immune system to eradicate tumor cells. These agents work in two main ways: by training the individual's immune system to attack the cancer directly or by administering immune components that results in a more general stimulation of the immune system. Agents classified as immunotherapies include cytokines, chimeric antigen receptor (CAR) T-cell therapies, immune checkpoint inhibitors, and therapeutic vaccines.

Combination Therapy

Although a single anticancer agent may be administered to a patient, the more common approach to systemic therapy is to administer multiple agents known as a regimen. Initially, this approach was based on the Goldie-Coldman hypothesis, which addresses the issue of cancer cell heterogeneity and the inevitable development of drug resistance. The individual agents selected for combination therapy should have different mechanisms of action and adverse event profiles. For example, myelosuppressive agents are typically combined with nonmyelosuppressive agents to minimize myelosuppression. The individual agents should each have significant activity against the cancer and the combination therapy should have known clinical benefit in the cancer to be treated. Combination regimens that include multiple chemotherapy agents with or without a targeted agent or immunotherapy have been used to successfully manage many cancers for decades. Predictive biomarkers, such as HER2 and BRAF, may be used to identify which patients may benefit from targeted therapy.

CHEMOTHERAPY

Since all chemotherapy agents interfere with the cellular synthesis of DNA,

ribonucleic acid (RNA), or proteins, chemotherapy agents are commonly categorized by their mechanism of action. For example, alkylators exert their effects on DNA and protein synthesis by binding to DNA and preventing the unwinding of the DNA molecule. As another example, antimetabolites resemble nucleotide bases or inhibit enzymes involved in the synthesis of DNA and proteins. **Figure 144-7** shows the sites of action of common categories of anticancer agents.

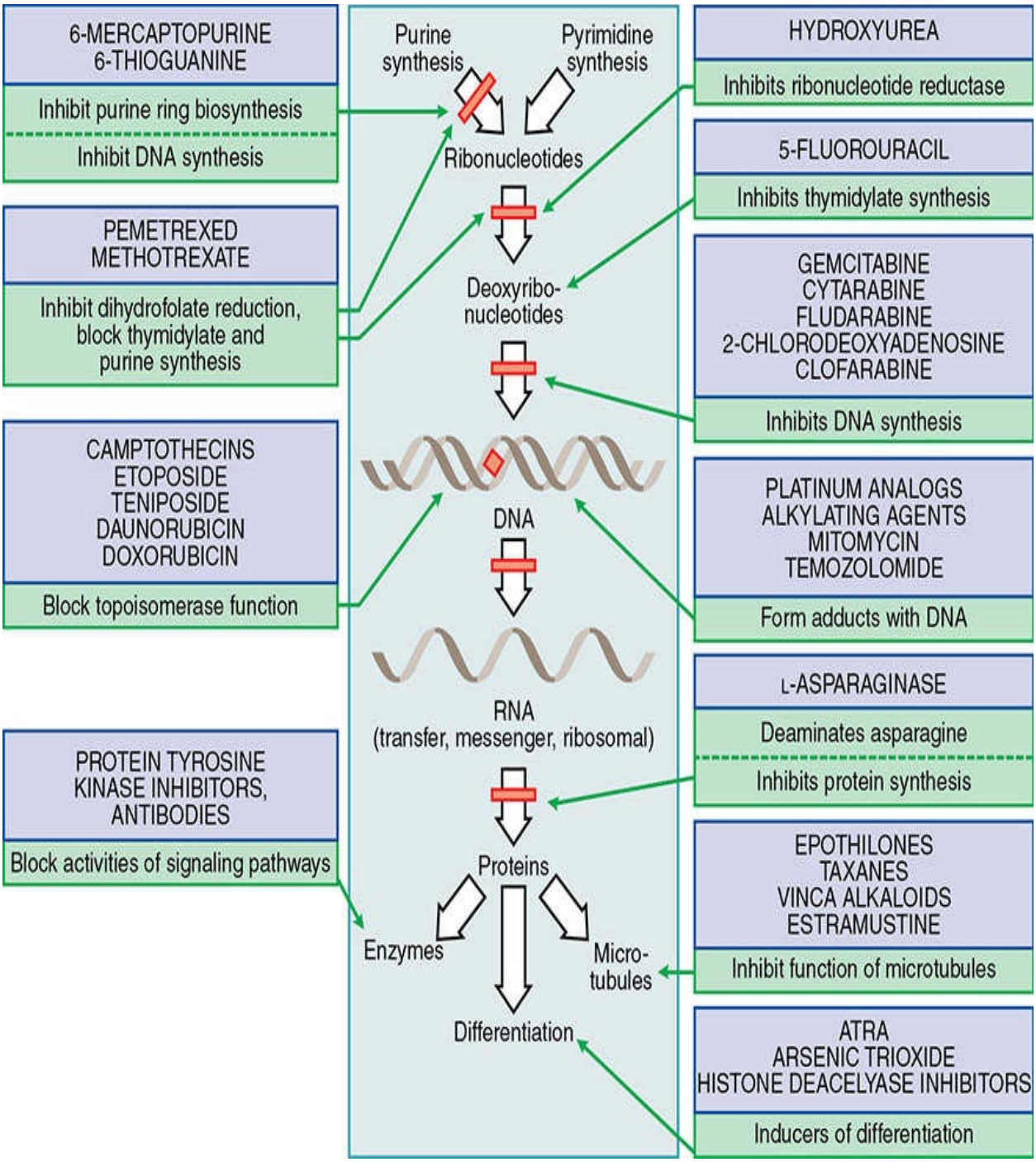


FIGURE 144-7 Mechanisms of action of commonly used anticancer agents. (ATRA, all-trans-retinoic acid.) (*Reproduced with permission from Chabner BA. General Principles of Chemotherapy. In: Brunton LL, Chabner BA, Knollman BC (eds). Goodman & Gilman's The Pharmacologic Basis of Therapeutics, 12th ed. New York: McGraw-Hill, 2010.*)

The following sections discuss the biochemical classification system and the

individual agents within each classification. The clinical uses, mechanisms of action, common toxicities, and practical patient management for most available chemotherapy agents are detailed below. **Table 144-7** summarizes dose modifications of individual chemotherapy agents.

TABLE 144-7 Monitoring of Anticancer Drugs[a]

Agent	Major Adverse Effects	Monitoring Parameters	Comments
Antimetabolites			
Capecitabine	Diarrhea, hand-foot syndrome (palmar–plantar erythema), mild nausea and vomiting, mucositis	Stool count, hands and feet for early signs of skin breakdown	Adjust dose for renal impairment Oral prodrug of 5-FU Warfarin results in increased anticoagulant effects; may require phenytoin dose reduction
Cladribine	Myelosuppression, fever (onset by day 6, persisting for about 3 days), immunosuppressive, severe opportunistic infections occur	CBC, signs of infection	Risk of opportunistic infections necessitate prophylactic antibiotics for PJP and other infections
Clofarabine	Myelosuppression, elevated liver enzymes, nausea and vomiting, TLS	CBC, liver function, uric acid	
Cytarabine and liposomal cytarabine for intrathecal use	Myelosuppression, nausea and vomiting, diarrhea, mucositis, TLS, flu-like syndrome, rash high-dose toxicities: worsening of above and cerebellar toxicity, conjunctivitis	CBC, signs of infection, renal function, neurologic examinations (signs of confusion)	High-dose infusions should be administered over 2-3 hours to decrease risk of CNS toxicity, use eye drops during treatment and for 48 hours after treatment to prevent conjunctivitis with high dose Increased high-dose neurotoxicity with impaired renal function
Fludarabine	Myelosuppression, including decreased T cells; diarrhea; rare CNS toxicity; somnolence; peripheral neuropathy; hearing and visual changes; altered mental status; seizures; pulmonary toxicity; TLS	CBC, signs of infection, renal function, neurologic examinations	Adjust dose for renal impairment Risk of opportunistic infections necessitate prophylactic antibiotics for PJP and HSV
Fluorouracil	Mucositis, diarrhea, hand-foot syndrome, myelosuppression, nausea and vomiting, hyperpigmentation, photosensitivity, ocular toxicity, myocardial ischemic symptoms	CBC, stool count, hands and feet for early signs of skin breakdown	Deficiency of DPD correlates with increased toxicity Drug interaction with warfarin: increased anticoagulant effect
Gemcitabine	Myelosuppression, flu-like syndrome, rash, elevations in liver transaminases, nausea and vomiting	CBC, liver function	Rash may respond to topical steroids, fevers may respond to acetaminophen
6-Mercaptopurine	Myelosuppression, dry skin, rash, photosensitivity, hepatotoxicity, jaundice and hyperbilirubinemia, nausea and vomiting	CBC, liver function	Allopurinol increases the toxicity of mercaptopurine by interfering with metabolism Mercaptopurine reduces anticoagulant effects of warfarin
Methotrexate	Myelosuppression, mucositis, renal failure at high doses, nausea and vomiting, CNS toxicity (more severe with IT administration), hepatotoxicity	CBC, liver function, renal function, urine pH and methotrexate drug levels with high-dose therapy	Adjust dose or avoid use with renal impairment, avoid drugs that decrease renal excretion of methotrexate (eg, NSAIDs, PPIs, sulfas, and penicillins) Distributes readily into third-space fluids (ascites, pleural effusions), prolonging exposure and increasing toxicity; may be contraindication for use Monitor methotrexate levels with high-dose administration; these must include leucovorin rescue to prevent excessive myelosuppression; sodium bicarbonate also given for high-dose therapy to prevent nephrotoxicity (maintain urine pH >7) Use preservative-free preparations for IT and high-dose administration
Pemetrexed	Myelosuppression, stomatitis, pharyngitis, rash, desquamation	CBC, renal function, skin examinations	Avoid with renal impairment Avoid NSAIDs during administration Supplement with folic acid (400 mcg daily starting 1 week before first dose, continued days after last dose) and vitamin B_{12} (1,000 mcg IM during week before first dose and even cycles thereafter) to decrease myelosuppression Premedicate with dexamethasone (day before, the day of, and day after) to decrease incidence of rash
Trifluridineand tipiracil	Anemia, neutropenia, thrombocytopenia, asthenia/fatigue, decreased appetite, diarrhea, nausea and vomiting, abdominal pain, pyrexia	CBC, renal function	Consider dose modifications for moderate renal impairment
Microtubule-Targeting Drugs			
Cabazitaxel	Myelosuppression, infection, hypersensitivity reactions, diarrhea, asthenia, renal failure, nausea and vomiting	CBC, signs of infection, stool count, renal function, signs of hypersensitivity reactions, liver function	Avoid with hepatic impairment Premedicate with H_1 and H_2 antagonist plus dexamethasone to decrease risk of hypersensitivity

Docetaxel	Myelosuppression, fluid retention and edema, pleural effusions, ascites, alopecia, rash, peripheral neuropathy, hypersensitivity reactions	CBC, fluid status, liver function	Contraindicated with hepatic impairment (hyperbilirubinemia, elevated transaminases, or elevated alkaline phosphatase) Premedicate with dexamethasone to lower risk of fluid retention
Paclitaxel and nab-paclitaxel	Myelosuppression, infection, hypersensitivity reactions, peripheral neuropathy, myalgias or arthralgias, mucositis, cardiac arrhythmias, alopecia	CBC, signs of infection, signs of hypersensitivity reactions, liver function	Avoid or adjust dose with hepatic impairment Premedicate with dexamethasone, diphenhydramine, and ranitidine 30 minutes before paclitaxel; nab-paclitaxel is associated with minimal risk of hypersensitivity reactions and does not require premedication Neurotoxicity may require discontinuation Products are not interchangeable
Vinblastine and vinorelbine	Myelosuppression, mucositis, neurotoxicity (less common than with vincristine), myalgias, SIADH (rarely), vesicant	CBC, liver function	Adjust dose with elevated bilirubin Treat extravasation injury with warm soaks and injection of hyaluronidase
Vincristine	Peripheral neuropathy (highest of vinca alkaloids); motor, sensory, autonomic, and cranial nerves may be affected (paresthesias, ileus, urinary retention, facial palsies) and can be irreversible; SIADH; vesicant	Signs of neurotoxicity (tingling in extremities, constipation, CNS toxicity); liver function	Adjust dose with elevated bilirubin Treat constipation aggressively to prevent ileus Doses are commonly capped at 2 mg to minimize neurotoxicity LETHAL if administered IT Treat extravasation similar to vinblastine
Eribulin	Myelosuppression, peripheral neuropathy, asthenia, alopecia, nausea, constipation	CBC, liver function, renal function, potassium and magnesium levels	Dose reduce for Child-Pugh class A or B hepatic impairment and moderate renal impairment May cause QT prolongation in patients with electrolyte or congenital abnormalities (avoid other drugs that may prolong QT interval)
Ixabepilone	Myelosuppression, peripheral neuropathy, hypersensitivity reactions, asthenia, arthralgias, alopecia	CBC, signs of infection, signs of hypersensitivity reactions, liver function	Avoid or adjust dose with hepatic impairment CYP3A4 substrate, levels may be effected by inducers or inhibitors, avoid use or dose adjustment to ixabepilone may be necessary Premedicate with H_1 and H_2 antagonist
Topoisomerase Inhibitors			
Irinotecan and liposomal irinotecan	Diarrhea: acute (during or immediately after infusion, related to cholinergic effects) and delayed (>24 hours after administration, usually after the second or third dose), nausea and vomiting, myelosuppression (neutropenia), alopecia, fatigue, increased liver enzymes, pulmonary toxicity: diffuse infiltrates, fever, dyspnea	CBC, GI symptoms (bowel movements), fluid and electrolytes	Acute diarrhea is best treated or prevented with atropine, delayed diarrhea is managed with antimotility agents Consider dose adjustment with elevated total bilirubin or UGT1A1 deficiency Products are not interchangeable and have different indications
Topotecan	Myelosuppression (neutropenia and thrombocytopenia), mucositis, reversible increased liver enzymes	CBC, liver function, renal function	Adjust dose for renal impairment
Daunorubicin and liposomal daunorubicin	Myelosuppression (dose related); mucositis; nausea and vomiting; alopecia; vesicant: severe extravasation injury; cardiac toxicities: acute—not related to cumulative dose, arrhythmias, pericarditis; chronic—cumulative injury to myocardium (total dose >550 mg/m^2)	CBC, LVEF, liver function	Adjust dose for elevated bilirubin LVEF should be >50% to administer safely Liposomal form: decreased risk of cardiac and vesicant toxicity
Doxorubicin and liposomal doxorubicin	Similar to daunorubicin, cardiac toxicity associated with cumulative doses >450-550 mg/m^2, radiation recall reactions	CBC, LVEF, liver function	Adjust dose for elevated bilirubin LVEF should be >50% to administer safely May discolor urine (red-orange) Liposomal form: decreased risk of cardiac and vesicant toxicities
Epirubicin	Similar to daunorubicin, cardiac toxicity associated with cumulative doses >900 mg/m^2	CBC, LVEF, liver function	Adjust dose for elevated bilirubin LVEF should be >50% to administer safely
Etoposide	Myelosuppression; nausea and vomiting: may be worse with oral and high-dose regimens; alopecia; mucositis; hypotension (infusion rate–related); hypersensitivity reactions	CBC, blood pressure	Adjust dose for renal impairment Requires large volumes of fluid for IV administration because of limited solubility (maximum concentration 0.4 mg/mL) Available orally in liquid-filled gelatin capsules; ~50% bioavailability but absorption is variable and greater at lower oral doses

Idarubicin	Similar to daunorubicin Total cumulative dose not well established; >150 mg/m² reported to be associated with decreased LVEF	CBC, LVEF, liver function	Adjust dose for elevated bilirubin LVEF should be >50% to administer safely
Mitoxantrone	Myelosuppression, nausea and vomiting, mucositis, alopecia, less cardiotoxic than the anthracyclines	CBC, LVEF, liver function	Not a vesicant (may cause vein irritation but not associated with severe tissue injury such as anthracyclines) May discolor urine blue-green
Alkylating Agents			
Bendamustine	Myelosuppression, infection, dermatologic reactions including Stevens-Johnson syndrome, TLS, infusion reactions	CBC, signs of infection, signs of dermatologic toxicity, uric acid	Not studied in renal impairment Allopurinol may increase risk for Stevens-Johnson syndrome
Busulfan	Myelosuppression, skin hyperpigmentation, pulmonary fibrosis, gynecomastia, adrenal insufficiency High (HSCT) dose toxicities: seizures; hepatic venoocclusive disease; severe nausea and vomiting	CBC, pulmonary status, liver function, signs of edema (weight gain, fluid status)	Bone marrow recovery may be delayed (3-6 weeks), pulmonary fibrosis associated with >3-year exposure, prior chest radiation Seizure prophylaxis with HSCT doses Pharmacokinetic monitoring is required with IV busulfan IV and oral preparations are not interchangeable, put tablets in gelatin capsules for easier administration with high-dose administration
Carboplatin	Myelosuppression (thrombocytopenia), nausea and vomiting (acute and delayed), risk of hypersensitivity reactions at higher cumulative doses (frequently results in cross-hypersensitivity to cisplatin)	CBC, renal function	Calvert formula used to dose carboplatin Lower incidence of nephrotoxicity, neurotoxicity, nausea and vomiting than cisplatin
Chlorambucil	Myelosuppression, increased liver enzymes, skin rash, menstrual irregularities, pulmonary toxicity, risk of secondary malignancies, causes infertility and sterility, teratogenic	CBC, liver function, pulmonary function	Administer on an empty stomach, food decreases absorption May be dosed in low daily-dosing regimens or in higher dose, "pulse," or intermittent dosing schedules administered biweekly or monthly; pulse dosing may require patients to take several tablets (eg, 10-20 tablets) per dose
Cisplatin	Nephrotoxicity, potassium and magnesium wasting, severe nausea and vomiting (acute or delayed onset), peripheral neuropathy that is cumulative and dose related, ototoxicity, anemia seen with chronic dosing	Renal function, potassium and magnesium levels, GI symptoms (nausea and vomiting)	Avoid with renal impairment IV hydration required before and after administration; ensure good urine output; potassium and magnesium sulfate in IV fluid to replace losses; consider carboplatin with impaired renal function Aggressive antiemetics required pretreatment and for 3-5 days after to prevent delayed nausea and vomiting Doses should not exceed 100 mg/m² (maximum single dose and per-cycle dose)
Cyclophosphamide	Hemorrhagic cystitis; nausea and vomiting (acute and delayed); myelosuppression; alopecia; SIADH: typically with high doses (>2 g/m²); risk of secondary malignancies; causes infertility and sterility	CBC, renal function, urinalysis	Adjust dose for renal impairment Hydration needed to prevent hemorrhagic cystitis (oral or IV); mesna may be required with high-dose regimens (see ifosfamide) Instruct patients to take oral tablets in the morning to allow for elimination of toxic metabolite; absorbed through skin: avoid spills Drug interactions: CYP450 inducers (eg, barbiturates) may increase formation of toxic metabolites; CYP450 inhibitors (eg, cimetidine) may increase myelosuppression
Ifosfamide	Hemorrhagic cystitis; nephrotoxicity; myelosuppression; CNS effects: somnolence, confusion, disorientation, cerebellar symptoms that are dose-related; nausea and vomiting (acute and delayed); alopecia	CBC, urinalysis, renal function	Adjust dose for renal impairment 3-4 L/day fluid for hydration; potassium, magnesium, and phosphate may be required to replace losses Mesna is always given (typically 60%-100% of ifosfamide dose); may be delivered in same IV bag CNS toxicity, nausea, and vomiting may be more severe with rapid infusion Methylene blue is controversial for CNS toxicity
Mechlorethamine	Myelosuppression, severe nausea and vomiting, vesicant, secondary malignancies, sterility and infertility	CBC, GI symptoms (nausea and vomiting)	Antidote for extravasation is sodium thiosulfate

Nitrosoureas (carmustine and lomustine)	Myelosuppression, severe nausea and vomiting, cumulative nephrotoxicity, pulmonary fibrosis, facial flushing during infusion	CBC, renal function, pulmonary function	Bone marrow recovery may require 6-8 weeks Carmustine is a vein irritatant; facial flushing may be related to alcohol vehicle; also available in wafer form for implantation into brain tumor cavities after resection Lomustine is administered orally
Oxaliplatin	Pharyngolaryngeal dysesthesias; peripheral neuropathy >50% patients: acute form: <14 days, rapid onset, reversible, exacerbated by cold; chronic form: onset >14 days and may be permanent; nausea and vomiting; anaphylaxis risk	CBC, renal function, acute and chronic neuropathies	Adjust dose for renal impairment Magnesium and calcium controversial for prevention of neuropathies Avoid exposure to cold
Procarbazine	Myelosuppression, diarrhea, neurotoxicity, neuropathy, flu-like syndrome, infertility and sterility, secondary malignancies	CBC	Administer as a single daily dose on an empty stomach MAOIs that interact with tyramine-rich foods and may precipitate hypertensive crisis; drug interactions: TCAs and SSRIs, sympathomimetics, disulfiram-like reaction with alcohol
Thiotepa	Myelosuppression, nausea and vomiting, mucositis, pruritus and dermatitis	CBC, dermatologic toxicities	Most commonly used in HSCT preparative regimens
Trabectedin	Myelosuppression, rhabdomyolysis, hepatotoxicity, nausea and vomiting, diarrhea or constipation, cardiomyopathy	CBC, CPK, liver function	Extravasation may lead to tissue necrosis
Triazenes (dacarbazine and temozolamide)	Myelosuppression, severe nausea and vomiting, increased liver enzymes, flu-like syndrome (may last for several days after dacarbazine administration), facial flushing, photosensitivity	CBC, liver function	Dispense in a light-proof bags Temozolamide crosses the blood–brain barrier, may cause lymphosuppression and requires PJP prophylaxis when given with radiation therapy
Miscellaneous Agents			
Arsenic trioxide	Differentiation syndrome (pulmonary infiltrates, respiratory distress, fever, and hypotension); QT prolongation; electrolyte abnormalities (hypokalemia, hyperkalemia, hypomagnesemia); hyperglycemia; rash; lightheadedness; fatigue; musculoskeletal pain	ECG and serum electrolytes (calcium, magnesium, potassium) before each course; renal function	Differentiation syndrome must be treated promptly with corticosteroids Do not give if QTc >500 msec Replace electrolytes before therapy
Bleomycin	Anaphylaxis and hypersensitivity reactions, fever and flu-like symptoms, mucositis, pulmonary fibrosis	Obtain PFTs before use and if signs of pulmonary toxicity develop; monitor for anaphylactic reactions	Adjust dose for renal impairment Test dose (1 unit) is recommended but controversial; premedicate for subsequent doses with acetaminophen Pulmonary toxicity associated with cumulative dose >400 units and pre-existing pulmonary disease
Hydroxyurea	Myelosuppression, rash, skin hyperpigmentation, TLS, secondary leukemias	CBC, uric acid	Dose may need to be adjusted with renal impairment (use with caution) Used to decrease white blood cell counts rapidly to prevent adverse effects of leukocytosis
Mitomycin C	Myelosuppression (delayed and prolonged), mucositis, nausea and vomiting, vesicant, pulmonary fibrosis, hemolytic anemia and uremic syndrome	CBC, renal function, pulmonary function	Apply ice or cold packs to site for extravasation
Omacetaxine	Myelosuppression (thrombocytopenia including increased risk of hemorrhage, anemia, neutropenia); diarrhea; nausea; fatigue; asthenia; injection site reaction; pyrexia; infection; lymphopenia; hyperglycemia	CBC, blood glucose	
Retinoids			
Bexarotene	Peripheral edema, insomnia, headache, fever, increased triglycerides and cholesterol, hypothyroidism, leukopenia and anemia, dry skin, increased liver enzymes, pancreatitis, photosensitivity	CBC, liver function, cholesterol and triglyceride levels, thyroid function	Avoid gemfibrozil to treat elevated triglycerides Limit vitamin A supplements May cause hypoglycemia in patients receiving insulin, sulfonylureas, or metformin Teratogenic, contraindicated in pregnancy, female patients should be educated about proper contraceptive measures

Tretinoin (ATRA)	Headache; differentiation syndrome; "ATRA syndrome" consisting of pulmonary symptoms, fever, hypotension, and pleural effusions; dry skin and mucous membranes; mucositis; increases in liver enzymes and bilirubin	CBC, liver function, signs of differentiation syndrome	Differentiation syndrome must be treated promptly with corticosteroids Teratogenic, contraindicated in pregnancy, female patients should be educated about proper contraceptive measures
ALK Inhibitors			
Alectinib	Fatigue, bradycardia, hepatotoxicty, anemia, constipation, edema, myalgia, visual disturbances	CBC, liver function, heart rate, CPK	Administer with food
Brigatinib	ILD and pneumonitits, hypertension, bradycardia, visual disturbances, creatinine phosphokinase elevation, pancreatic enzyme elevation, hyperglycemia	HR, BP, pulmonary symptoms, CPK, pancreatic enzymes	Dose escalation required to decrease early-onset pulmonary symptoms Avoid strong CYP3A inhibitors and inducers; may affect hormonal contraceptives
Ceritinib	Gastrointestinal toxicity, increases in liver enzymes, fatigue, visual disturbances, QT prolongation, bradycardia, hyperglycemia	CBC, renal function, liver function, blood glucose, pancreatic enzymes, cardiac monitoring, electrolytes	Administer on an empty stomach
Crizotinib	Nausea and vomiting, diarrhea, constipation, fatigue, increases in liver enzymes, visual disorders, edema, ILD, QT prolongation, bradycardia	CBC, renal function, liver function, HR, BP, cardiac monitoring, electrolytes, pulmonary symptoms	Visual disorders (visual impairment, blurred vision, and photopsia) occur in approximately half of patients
Lorlatinib	Hepatotoxicity, CNS toxicity, hyperlipidemia, atrioventricular block, ILD and pneumonitits	Liver function, lipids, ECG	Strong CYP3A inducers contraindicated, avoid strong CYP3A4 inhibitors and certain CYP3A4 substrates
B-Cell Lymphoma-2 Inhibitor			
Venetoclax	TLS, myelsosuppression, diarrhea, upper respiratory tract infection	CBC, chemistries	Ramp-up dose required Premedicate with antihyperuricemics and ensure adequate hydration Contraindicated with strong CYP3A inhibitors during initiation and ramp-up Avoid strong and moderate CYP3A inhibitors, strong or moderate CYP3A inducers, P-gp inhibitors, or narrow therapeutic Avoid live-attenuated vaccines Administer with a meal
BCR-ABL Inhibitors			
Bosutinib	Nausea and vomitin, edema, pleural effusions and ascites, myelosuppression, CHF, arthralgias, rash, diarrhea, increased liver enzymes, hypophosphatemia	CBC, liver function, electrolytes, Philadelphia chromosome levels, signs of edema	Adjust dose for hepatic impairment Avoid antacids and PPIs Maintenance dose based on CBC Administer with food
Dasatinib	Nausea and vomiting, edema, pleural effusions and ascites, myelosuppression, CHF, arthralgias, fatigue, rash, diarrhea, increased liver enzymes, QT prolongation, hypophosphatemia and hypocalcemia	CBC, liver function, electrolytes, signs of edema, Philadelphia chromosome levels	Avoid antacids, H_2 antagonists, and PPIs Maintenance dose based on CBC
Imatinib	Nausea and vomiting, edema, pleural effusions and ascites, myelosuppression, CHF, arthralgias, rash, diarrhea, increased liver enzymes, hypophosphatemia	CBC, liver function, electrolytes, Philadelphia chromosome levels, signs of edema	Dose adjustments should be considered with severe liver and moderate renal impairment May increase warfarin effects Maintenance dose based on CBC Take with meals and a full glass of water
Nilotinib	Nausea and vomiting, edema, myelosuppression, increased lipase, hyperglycemia, arthralgias, rash, diarrhea, increased liver enzymes, QT prolongation	CBC, liver function, serum lipase, serum glucose, electrolytes, Philadelphia chromosome levels	Adjust dose for hepatic impairment Take on an empty stomach CYP3A4 substrate: avoid inhibitors Maintenance dose based on CBC Avoid PPIs, stagger administration with H_2 antagonists and antacids if use is necessary
Ponatinib	Myelosuppression, hypertension, rash, abdominal pain, fatigue, headache, dry skin, constipation, arthralgia, nausea, pyrexia, thromboembolic events, hepatotoxicity, congestive heart failure, pancreatitis, hemorrhage (secondary to thrombocytopenia), fluid retention	Cardiac monitoring (CHF, arrhythmias), BP, pancreatic enzymes, fluid retention, CBC, liver function	May need to decrease or hold therapy if hepatotoxicity develops Avoid antacids and drugs that decrease gastric pH

BRAF Inhibitors			
Dabrafenib	Papilloma, arthralgia, alopecia, fatigue, headache, HFSR, pyrexia	CBC, serum glucose, electrolytes, renal function, dermatologic evaluations	Take on an empty stomach
Encorafenib	Cutaneous and noncutaneous malignancies, tumor promotion, hemorrhage, uvetis, QT prolongation	Visual symptoms, opthamalogic evaluations, ECG, electrolytes	Avoid strong and moderate CYP3A inhibitors, strong inducers, and sensitive CYP3A substrates Use nonhormonal contraceptives
Vemurafenib	Papilloma, arthralgia, alopecia, fatigue, headache, photosensitivity reaction, hypersensitivity reactions, QT prolongation	Liver function, electrolytes, cardiac monitoring, dermatologic evaluations	Radiation sensitization/recall
BTK Inhibitor			
Acalabrutinib	Infections (including opportunistic and hepatitis reactivation), secondary primary malignancies, atrial flutter and fibrillation	CBC, cardiac monitoring	Avoid strong CYP3A inhibitors, strong CYP3A inducers Avoid PPIs, stagger administration with H_2 antagonists and antacids if use is necessary
Ibrutinib	Diarrhea, fatigue, musculoskeletal pain, nausea, rash, atrial fibrillation, hemorrhage, TLS, bone marrow suppression	CBC, renal function, liver function, uric acid levels, electrolytes, cardiac monitoring	Reduce dose with hepatic impairment
CDK Inhibitor			
Abemaciclib	Diarrhea, neutropenia, hepatotoxicity, venous thromboembolism	CBC, electrolytes, liver function	Avoid moderate and strong CY3A inducers Dose reduce with moderate and strong CYP3A inhibitors Reduce dose with severe hepatic impairment
Palbociclib	Thromboembolic events, infection, bone marrow suppression, gastrointestinal toxicity	CBC, infection	Administer with food
Ribociclib	QT prolongation, hepatobiliary toxicity, neutropenia	ECG, electrolytes, liver function, CBC	Avoid drugs known to prolong QT interval; strong CYP3A inhibitors; strong CYP3A inducers; sensitive CYP3A substrates
DNA Methyltransferase Inhibitors			
Azacitidine and decitabine	Myelosuppression and infection, constitutional symptoms, musculoskeletal symptoms (arthralgias), cough, dyspnea	CBC, infection	
EGFR Inhibitors			
Afatinib	Rash, diarrhea, ILD, keratitis	Liver function, renal function, dermatologic evaluations, electrolytes, LVEF in patients with cardiac risk factors, pulmonary symptoms	Administer on an empty stomach
Dacominitinb	ILD, diarrhea, dermatologic toxicity	Pulmonary symptoms, skin	Avoid PPIs and sensitive CYP2D6 inhibitors Initiate use of moisturizers and appropriate measures to limit sun exposure
Erlotinib	Rash, diarrhea, ILD, hepatic and renal failure reported	Liver function, renal function, electrolytes, pulmonary symptoms, dermatologic evaluations	Dose reductions or delays may be required for rash but supportive care should be attempted first Major interaction with warfarin (may lead to increased bleeding risk) H_2 antagonists, PPIs, and antacids may decrease drug levels Administer on an empty stomach as food increases absorption and possibly toxicity
Gefitinib	Similar to erlotinib	Liver function, renal function, electrolytes, pulmonary symptoms, dermatologic evaluations	Similar precautions and drug interactions as with erlotinib
Lapatinib	Diarrhea, rash, nausea, vomiting, fatigue, decreases in LVEF, hepatotoxicity, QT prolongation, ILD	Liver function, cardiac monitoring (LVEF, QT, MUGA), electrolytes, pulmonary symptoms	Adjust dose for severe hepatic impairment Administer on empty stomach Avoid strong CYP3A4 inhibitors (if unavoidable, consider dose reduction); avoid strong CYP3A4 inducers (if unavoidable, consider gradual dose increases)

Neratinib	Diarrhea, hepatotoxicity	Liver function, electrolytes	Use prophylactic antidiarrheal Lower starting dose for hepatic impairment Avoid PPIs, strong and moderate CYP3A inhibitors, strong and moderate CYP3A inducers, and sensitive P-gp substrates
Osimertinib	Gastrointestinal toxicity, dermatologic toxicity, ILD/pneumonitis, pneumonia, pulmonary embolism, cardiomyopathy, QT prolongation	Cardiac monitoring (LVEF, QT), pulmonary symptoms, dermatologic evaluations	Avoid strong CYP3A4 inhibitors and inducers
Fibroblast Growth Factor Receptor (FGFR) Inhibitor			
Erdafitinib	Ocular disorders, hyperphosphatemia, stomatitis, creatinine increased, HFSR, elevated liver enzymes	Ophthalmological exams, phosphate levels	Avoid strong CYP2C9 or CYP3A4 inhibitors and inducers Increased phosphate levels are a pharmacodynamic effect
FMS-Like Tyrosine Kinase-3 (FLT3) Inhibitors			
Gilteritinib	PRES, QT prolongation, pancreatitis, hypersensitivity	ECG, electrolytes	Avoid dual P-gp and CYP3A inducers and strong CYP3A inhibitors
Midostaurin	Pulmonary toxicity	ECG	Administer with food Avoid strong CYP3A inducers
Hedgehog Inhibitors			
Glasdegib	QT prolongation, teratogenic effects	Pregnancy status, ECG	Boxed warning for severe birth defects and embryo-fetal death; advise females to use contraception during treatment and for 20 months after the last dose; advise males to use condoms during treatment and for at least 8 months after the last dose; do not donate blood during treatment and for 30 months after the last dose; do not donate sperm during treatment and for 8 months after the last dose
Sonidegib	Fatigue, alopecia, amenorrhea, musculoskeletal toxicity, teratogenic effects	Pregnancy status, CPK, renal function, liver function	Boxed warning for severe birth defects and embryo-fetal death; advise females to use contraception during treatment and for 20 months after the last dose; advise males to use condoms during treatment and for at least 8 months after the last dose; do not donate blood during treatment and for 20 months after the last dose; do not donate sperm during treatment and for 8 months after the last dose Avoid strong and moderate CYP3A modulators; moderate CYP3A inhibitors may be used for short term
Vismodegib	Muscle spasms, alopecia, dysgeusia, fatigue, nausea and vomiting, diarrhea, decreased appetite, constipation, arthralgias, teratogenic effects	Pregnancy status	Boxed warning for severe birth defects and embryo-fetal death; patients should not donate blood or blood products while receiving vismodegib and for at least 7 months after the last dose; verify pregnancy status within 7 days prior to treatment initiation; do not donate sperm during treatment and for 3 months after the last dose
Histone Deacetylase Inhibitors			
Belinostat	Pyrexia, nausea, fatigue, anemia, hepatotoxicity, infection, TLS	Liver function, renal function, CBC, electrolytes, uric acid levels	
Panobinostat	Cardiotoxicity, nausea, vomiting, diarrhea, hemorrhage, infection, hepatotoxicity	Cardiac monitoring, electrolytes, CBC, liver function, pregnancy status	Boxed warnings for cardiovascular events and gastrointestinal events
Romidepsin	Neutropenia, lymphopenia, thrombocytopenia, infection, nausea and vomiting, fatigue, anorexia, anemia, ECG T-wave changes	CBC, cardiac monitoring (ECG), electrolytes	Monitor INR with concurrent use of warfarin
Vorinostat	Diarrhea, fatigue, nausea, thrombocytopenia, anorexia, dysgeusia, thromboembolic events, hyperglycemia	CBC, electrolytes, serum glucose, renal function	Avoid or adjust dose for hepatic impairment Increase in INR with concomitant warfarin Severe thrombocytopenia and GI bleeding have been reported with concomitant use with vorinostat and other HDAC inhibitors (eg, valproic acid)

Isocitrate Dehydrogenase (IDH) Inhibitors			
Enasidenib	Differentiations syndrome, TLS, myelosuppression, hepatotoxicity, nausea and vomiting	CBC, electolytes	
Ivosidenib	Differentiation syndrome, QT prolongation, Guillain-Barré Syndrome, TLS	CBC, chemistries, CPK, ECG, electrolytes	Reduce ivosidenib dose with strong CYP3A4 inhibitor Avoid strong CYP3A inducers; sensitive CYP3A substrates; drugs that prolong QT interval
JAK Inhibitor			
Ruxolitinib	Thrombocytopenia, anemia, bruising, dizziness, headache, infections, cardiovascular abnormalities	CBC, renal function, liver function, cardiac monitoring	Consider dose adjustment for renal and hepatic impairment
MEK Inhibitor			
Binimetinib	Cardiomyopathy, venous thromboembolism, ILD, hepatotoxicity, rhabdomyolysis, hemorrhage, ophthalmic events	LVEF, ophthalmologic evaluation, liver function, CPK, renal function	Reduce dose for moderate and severe hepatic impairment
Cobimetinib	Dermatologic toxicity, nausea and vomiting, pyrexia, hemorrhage, new primary malignancies, cardiomyopathy, ophthalmic events, hepatotoxicity, rhabdomyolysis	CBC, liver function, dermatologic evaluation, ophthalmologic evaluation, LVEF, CPK, electrolytes	Avoid coadministration with strong or moderate CYP3A inducers or inhibitors
Trametinib	Diarrhea, lymphedema, hemorrhage, venous thromboembolism, febrile reactions, cardiomyopathy, dermatologic toxicity, hyperglycemia, hypertension, ophthalmic events	CBC, liver function, LVEF, ophthalmologic evaluation, dermatologic evaluation, BP	Capsules are stored refrigerated Administer on an empty stomach
mTOR Inhibitors			
Everolimus	Rash, asthenia, stomatitis, nausea, edema, anorexia, anemia, pneumonitis, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypophosphatemia, elevated liver enzymes, elevated Scr, lymphopenia, thrombocytopenia, leukopenia, infection	Metabolic toxicities, CBC, renal function, liver function, electrolytes, pulmonary symptoms	Adjust dose for hepatic impairment Initiation or increase in cholesterol or diabetic medications often needed CYP3A4 and Pgp substrate; may require dose adjustment based on concurrent medication
Temsirolimus	Similar to everolimus with addition of infusion-related reactions	Similar to everolimus, infusion reactions	Adjust dose for hepatic impairment Requires diphenhydramine premedication
Multikinase Inhibitors			
Axitinib	Diarrhea, rash, HFSR, bleeding, thrombotic events, hypertension, hepatotoxicity, hypothyroidism, proteinuria, GI perforation, fatigue, rare reports of progressive multifocal leukoencephalopathy	CBC, liver function, BP, thyroid function, urine protein, neurologic evaluation, dermatologic evaluation	Adjust dose for hepatic impairment Substrate of CYP3A4, may require dose adjustment based on concurrent medication administered
Cabozantinib	Diarrhea, stomatitis, HFSR, decreased weight, decreased appetite, nausea, fatigue, oral pain, hair color changes, dysgeusia, hypertension, abdominal pain, constipation, increased liver enzymes, proteinuria, lymphopenia, neutropenia, thrombocytopenia, hypocalcemia, hypophosphatemia, GI perforations and fistulas and hemorrhage have been reported	BP; urine protein, CBC, liver function, thyroid function; electrolytes; dermatologic evaluation	Administer on an empty stomach CYP3A4 substrate, monitor for drug interactions
Lenvatinib	Hypertension, fatigue, diarrhea, proteinuria, stomatitis, HFSR, hypothyroidism, hepatotoxicity, thromboembolic events, renal toxicity, hypocalcemia	Liver function, renal function, thyroid function, BP, electrolytes	Adjust dose for severe hepatic and renal impairment
Pazopanib	Diarrhea, hypertension, hair/skin hypopigmentation, nausea, anorexia, vomiting, decreased weight, fatigue, musculoskeletal pain, dysguesia, dyspnea, hypothyroidism, proteinuria, fatal hepatotoxicity, thromboembolic events	Liver function, cardiac monitoring (ECG), BP, thyroid function, urine protein, dermatologic evaluation	Adjust dose for hepatic impairment Take on empty stomach Reduce dose when administered with strong CYP3A4 inhibitors, avoid CYP3A4 inducers, concomitant use with simvastatin increases liver enzymes

Regorafenib	Asthenia, fatigue, decreased appetite, HFSR, diarrhea, mucositis, weight loss, infection, hypertension, dysphonia, hepatotoxicity, hemorrhage	Liver function, BP, dermatologic evaluation	Administer with food (low-fat breakfast that contains <30% fat) Monitor INR closely with concomitant warfarin because of an increased risk of hemorrhage
Sorafenib	Diarrhea, rash, HFSR, fatigue, hypertension, prolonged QT interval, cardiac events (including MI), hepatitis	BP, liver function, cardiac monitoring, electrolytes, dermatologic evaluation	Administer on an empty stomach May increase the anticoagulation effects of warfarin
Sunitinib	Diarrhea, rash, bleeding, CHF and cardiac effects, QT prolongation, fatigue, hypertension, hepatotoxicity, thyroid dysfunction	CBC, liver function, BP, thyroid function, cardiac monitoring (CHF, ECG), electrolytes	CYP3A4 substrate, may require dose adjustment based on concurrent medication administered
Vandetanib	Diarrhea, rash, acne, nausea, hypertension, headache, fatigue, upper respiratory tract infections, decreased appetite, abdominal pain, QT prolongation, torsades de pointes and sudden death, ILD, hemorrhage, increased liver enzymes	Liver function, electrolytes, cardiac monitoring (ECG), BP, pulmonary symptoms, dermatologic evaluation	REMS program for QT prolongation/sudden death; avoid other medications that prolong the QT interval Adjust dose for renal impairment Advise patients to wear sunscreen and protective clothing when exposed to sun
Neurotrophic receptor tyrosine kinase (NTRK) Inhibitor			
Larotrectinib	Neurotoxicity; hepatotoxicity	Liver function	Avoid strong CYP3A inhibitors and inducers; avoid sensitive CYP3A substrates Reduce starting dose in moderate-to-severe hepatic impairment
PARP Inhibitor			
Niraparib	Myelodysplastic syndrome, acute myeloid leukemia, myelosuppression, cardiovascular toxicity	CBC, BP, HR	
Olaparib	Fatigue, musculoskeletal pain, dermatitis, nausea and vomiting, upper respiratory infections, anemia, pneumonitis, secondary malignancies (MDS/AML)	CBC, pulmonary symptoms	Tablets and capsules are not bioequivalent Reduce dose for renal impairment
Rucaparib	Myelodysplastic syndrome, acute myeloid leukemia, nausea and vomiting	CBC	
Talazoparib	Myelodysplastic syndrome/acutem myeloid leukemia, myelosuppression	CBC	Reduce starting dose for renal impairment Reduce dose for certain P-gp inhibitors
PI3K Inhibitor			
Alpelisib	Dermatologic reactions, severe diarrhea, pneumonitis, hyperglycemia, severe hypersensitivity reactions	Blood glucose, dermatologic evaluation, pulmonary symptoms	Avoid strong CYP3A inducers, closely monitor with concurrent CYP2C9 substrates (eg, warfarin)
Copanlisib	Infections, hyperglycemia, hypertension, pneumonitis, neutropenia, dermatologic reactions	CBC, blood glucose, BP	Reduce dose with strong CYP3A inhibitors Avoid strong CYP3A inducers Consider PJP prophylaxis
Duvelisib	Infections, neutropenia, fatal/serious diarrhea, dermatologic reactions, pneumonitis, hepatotoxicity	CBC, liver function, dermatologic evaluation, pulmonary symptoms	Avoid strong CYP3A inducers Reduce moderate and strong CYP3A inhibitors PJP prophylaxis required; considered antiviral prophylaxis for cytomegalovirus
Idelalisib	Fatal/serious diarrhea, intestinal perforation, hepatotoxicity, pneumonitis, infections, neutropenia, dermatologic reactions, anaphylaxis	Liver function, CBC, dermatologic evaluation, pulmonary symptoms	PJP prophylaxis required
Proteasome Inhibitors			
Bortezomib	Fatigue or malaise, nausea and vomiting, diarrhea, anorexia, constipation, myelosuppression (especially thrombocytopenia), hyponatremia, hypokalemia, peripheral neuropathy (cumulative and dose-related), fever	CBC, thyroid function, symptoms of neuropathy, electrolytes	Adjust dose for hepatic impairment Administer IV or subcutaneous (subcutaneous administration has been shown to decrease neuropathies) Increased risk of severe neuropathy with pre-existing neuropathy Coadministration with strong CYP3A4 inhibitors can increase bortezomib concentrations
Carfilzomib	Fatigue, anemia, thrombocytopenia, nausea, diarrhea, dyspnea, pyrexia, infusion-related reactions, rare reports of cardiac arrest, CHF, and MI	Pulmonary symptoms, CBC, liver function, cardiac monitoring, infusion reactions	Premedicate with dexamethasone before all cycle 1 doses then as needed for future cycles to reduce the incidence of infusion reactions

Ixazomib	Gastrointestinal toxicity, thrombocytopenia, peripheral neuropathy, edema, cutaneous reactions, hepatotoxicity	CBC, liver function, dermatologic evaluation	Administer on an empty stomach Reduce starting dose for hepatic or renal impairment Avoid use with strong CYP3A4 inducers Consider antiviral prophylaxis
Radiopharmaceuticals			
Ibritumomab tiuxetan	Prolonged hematologic toxicity, infusion-related reactions, cutaneous and mucocutaneous reactions, development of leukemia and myelodysplastic syndrome	Infusion-related reactions, CBC, extravasation	Must consider toxicities of rutiximab Radiopharmaceutical; prepared and administered only by personnel trained in radiopharmaceuticals; patients must be trained in precautions to decrease radiation exposure
Iobenguane I 131	Radiation exposure, myelosuppression, secondary malignancies, hypothyroidism, hypertension, renal toxicity, pneumonititis	CBC, thyroid function, BP, renal function	Radiopharmaceutical; prepared and administered only by personnel trained in radiopharmaceuticals; patients must be trained in precautions to decrease radiation exposure Premedications include antiemetics, hydration, and thyroid blockade Administer dosimetric and therapeutic dose Avoid drugs that affect catecholamine uptake or stores
Lutetium Lu 177 dotatate	Myelosuppresion, renal toxicity, hepatotoxicity, secondary malignancies, neuroendocrine hormonal crisis	CBC, renal function, liver function	Radiopharmaceutical; prepared and administered only by personnel trained in radiopharmaceuticals; patients must be trained in precautions to decrease radiation exposure Administer with short- and long-acting octreotide and amino acid solution
Radium Ra 223 dichloride	Myelosuppresion, increased fractures	CBC	Radiopharmaceutical; prepared and administered only by personnel trained in radiopharmaceuticals; patients must be trained in precautions to decrease radiation exposure
Miscellaneous Small Molecule Inhibitors			
Lanreotide	Abdominal pain, musculoskeletal pain, vomiting, headache, injection site reaction, hypertension, hypo- and/or hyperglycemia, gallstones, hypothyroidism (mild)	HR, BP, blood glucose, thyroid function, gall bladder ultrasonography	
Lenalidomide	Teratogen, fatigue, peripheral neuropathy, neutropenia and thrombocytopenia, thromboembolic events	CBC, signs of thrombosis, signs of peripheral neuropathies, pregnancy status	REMS program for fetal toxicity Adjust dose for renal impairment Prophylactic anticoagulation may be required
Pomalidomide	Teratogen, neutropenia, hepatotoxicity, thromboembolic events	Same as for lenalidomide	REMS program for fetal toxicity Adjust dose for renal and hepatic impairment Prophylactic anticoagulation may be required
Thalidomide	Teratogen, somnolence, constipation, dizziness or orthostatic hypotension, rash, peripheral neuropathy, thromboembolic events, increased HIV viral load	Same as for lenalidomide; HIV viral load	REMS program for fetal toxicity Prophylactic anticoagulation may be required
Monoclonal Antibodies that Target CD20			
Obinutuzumab	Infusion reactions, myelosuppression, nausea, diarrhea, Progressive Multifocal Leukoencaphalopathy, HBV reactivation	CBC, hepatitis B screening at baseline, renal function, electrolytes, infusion reaction, fluid status	Antimicrobial, antiviral, and antifungal prophylaxis in select patients Antihyperuricemic prophylaxis and hydration if risk for TLS Premedicate with acetaminophen, an antihistamine, and a glucocorticoid
Ofatumumab	Neutropenia, pneumonia, pyrexia, cough, diarrhea, anemia, fatigue, dyspnea, rash, nausea, bronchitis, upper respiratory infection	Infusion-related reactions, CBC, hepatitis B screening at baseline	Premedicate with acetaminophen, antihistamine, and corticosteroid Infusion rate-escalation required
Rituximab	Hypersensitivity reactions and infusion-related reactions, TLS (especially with large tumor burden), myelosuppression and infection, rare reports of progressive multifocal leukoencephalopathy, severe skin reactions, myalgias, tachycardia	Infusion-related reactions, CBC, neurologic examination, hepatitis B screening at baseline, electrolytes, HR, BP	Patients should be screened for Hepatitis B before therapy initiation Infusion-related reactions may be severe; increase rate of infusion gradually and premedicate with acetaminophen and diphenhydramine; rituximab and hyaluronidase available for subcutaneous injection

Monoclonal Antibodies that Target CD52			
Alemtuzumab	Myelosuppression and immunosuppression, autoimmune conditions, infection, infusion-related reactions, nausea and vomiting, fever, hypotension, rash, headache, fatigue, secondary malignancies	CBC, infusion-related reactions, CMV, $CD4^+$counts, HR, BP, autoimmune symptoms, symptoms of infection	Restricted distribution through REMS program to mitigate risks of autoimmune conditions, infusion reactions, and secondary malignancies Patients should be started on antiviral and PJP prophylaxis during and 6 months posttreatment
Monoclonal Antibodies that Target CD38			
Daratumumab	Infusion-related reactions, pyrexia, fatigue, upper respiratory tract infection, nausea, myelosuppression	CBC, acute or delayed infusion-related reactions	Type and screen patients prior to starting treatment as daratumumab may interfere with cross-matching and red blood cell antibody screening Premedicate with corticosteroids, antipyretics, and antihistamines; administer postinfusion medications
Monoclonal Antibodies that Target Chemokine Receptor			
Mogamulizumab-kpkc	Dermatologic reactions, infusion reactions, infections, autoimmune complications, complications of allogeneic HSCT	Infusion reactions	Administer diphenhydramine and acetaminophen for the first infusion
Monoclonal Antibodies that Target GD2 Receptor			
Dinutuximab	Infections, infusion reactions, hypokalemia, hypotension, capillary leak syndrome, neurological ocular toxicity, pain, bone marrow suppression, hemolytic uremic syndrome	CBC, electrolytes, renal function, BP, infusion reaction	Premedicate with IV analgesics (such as morphine), an antihistamine, acetaminophen, antiemetics, and IV hydration
Monoclonal Antibodies that Target PDGFR-α			
Olaratumab	Infusion-related reactions	Infusion reactions	Premedicate with diphenhydramine and dexamethasone prior to the first dose
Monoclonal Antibodies that Target SLAMF7			
Elotuzumab	Fatigue, pyrexia, diarrhea or constipation, respiratory infections, peripherial neuropathy, hepatotoxicity, infusion-related reactions, second primary malignancies	Liver function, infusion-related reactions, infections	May interfere with the assay used to monitor M-protein which can impact the determination of complete response Premedicate with dexamethasone, diphenhydramine, ranitidine, and acetaminophen
Monoclonal Antibodies that Target EGFR			
Cetuximab, necitumumab, and panitumumab	Rash, paronychial cracking in fingers or toes, asthenia, abdominal pain, nausea, constipation, diarrhea, infusion and hypersensitivity reactions, electrolyte wasting, cardiopulmonary arrest	Electrolytes, infusion reactions, dermatologic evaluation	Dose reductions or delays may be required for rash but supportive care should be attempted first Decreased risk of infusion-related reactions to panitumumab and does not appear to be cross-reactive (ie, a patient may receive panitumumab if they react to cetuximab)
Monoclonal Antibodies that Target HER2			
Pertuzumab	Diarrhea, nausea, alopecia, rash, neutropenia, fatigue, peripheral neuropathy, embryo and fetal toxicity, left ventricular dysfunction, infusion-related reactions	LVEF, infusion reactions, pregnancy status	
Trastuzumab	Cardiac toxicity: congestive cardiomyopathy (usually reversible with medical management); infusion-related reactions; pulmonary toxicity; embryo and fetal toxicity	Infusion-related reactions, cardiac monitoring (LVEF)	Do not administer with anthracyclines because of increased cardiotoxicity Trastuzumab and ado-trastuzumab ematansine are NOT interchangeable; trastuzumab and hyaluronidase available for subcutaneous injection
Monoclonal Antibodies that Target VEGFR			
Bevacizumab	GI bleeding or perforation, impaired wound healing, hypertension, proteinuria, thrombotic events, rare severe pulmonary hemorrhage, rare reports of progressive multifocal leukoencephalopathy	BP, urine protein, neurologic examination, signs of GI perforation, symptoms of thromboembolism	
Ramucirumab	GI bleeding or perforation, impaired wound healing; hypertension, proteinuria, thyroid dysfunction, thromboembolic events, hemorrhage	BP, urine protein, thyroid function, liver function	

Bispecific T-Cell Engagers			
Blinatumomab	Infusion reactions, cytokine release syndrome, neurologic toxicities, infections, fever, headache, peripheral edema, rash, TLS, hepatotoxicity, bone marrow suppression	CBC, liver function, neurological examination, uric acid levels, electrolytes	Premedicate with dexamethasone prior to the first dose of each cycle; prior to a step dose or when restarting therapy after an interruption >4 hours Administered as a continuous intravenous infusion over 28 days
Antibody-Drug Conjugates			
Ado-Trastuzumab ematansine	Cardiac toxicity, thrombocytopenia, hemorrhage, hepatotoxicity, infusion reactions, peripheral neuropathy, ILD, embryo-fetal toxicity	CBC, liver function, pregnancy status, cardiac monitoring (LVEF), pulmonary symptoms	Ado-Trastuzumab Ematansine and Trastuzumab are NOT interchangeable
Brentuximab vedotin	Neutropenia, peripheral neuropathy, fatigue, nausea or vomiting, anemia, diarrhea, rash, thrombocytopenia, infusion-related reactions, TLS, rare reports of progressive multifocal leukoencephalopathy	CBC, symptoms of neuropathy, infusion-related reactions, uric acid levels, electrolytes	Adjust dose for renal and hepatic impairment
Gemtuzumab ozogamicin	Hypersensitivity, infusion-related reactions, hemorrhage	Infusion reactions	Premedicate with a corticosteroid, antihistamine, and acetaminophen
Inotuzumab ozogamicin	Myelosuppression, infusion-related reactions, QT interval prolongation, hepatotoxicity	CBC, ECG, infusion reactions, liver function	Premedicate with a corticosteroid, antipyretic, and antihistamine
Polatuzumab vedotin	Peripheral neuropathy, infusion-related reactions, myelosuppression, infections, TLS, hepatotoxicity	CBC, symptoms of neuropathy, infusion-related reactions, uric acid levels, electrolytes, liver function	Premedicate with an antihistamine and antipyretic
Immune Checkpoint Inhibitors			
Ipilimumab	Fatigue, diarrhea, pruritus, rash, immune-mediated reactions (eg, enterocolitis, dermatitis, neuropathy, endocrinopathy, hepatitis)	Thyroid function, electrolytes; liver function; renal function; dermatologic evaluations; gastrointestinal symptoms	Treat severe immune-related adverse events with corticosteroids
Atezolizumab; avelumab; cemiplimab; durvalumab, nivolumab, and pembrolizumab	Fatigue, immune-mediated toxicities (eg, pneumonitis, colitis, hepatitis, nephritis, thyroid dysfunction)	Liver function, renal function, thyroid function, GI symptoms	Treat severe immune-related adverse events with corticosteroids For avelumab, premedicate with an antihistamine and acetaminophen prior to the first 4 infusions
Miscellaneous Monoclonal Antibodies			
Denosumab	Arthralgia, headache, nausea, hypocalcemia, hypophosphatemia, osteonecrosis of the jaw	Dental evaluations, electrolytes	A dental examination prior to initiation of therapy
Siltuximab	Pruritis, weight gain, hyperuricemia, infection, GI perforation	CBC, uric acid levels, cytokine release reactions	Do not administer live vaccines while being treated with siltuximab HIV-positive and HHV-8-positive patients excluded from the clinical trials
Cytokines			
Interferon-alfa	Flu-like symptoms; fatigue; serious or fatal neuropsychiatric (eg, depression and suicide); autoimmune, ischemic, and infectious complications; pulmonary symptoms; thyroid disorders; hyperglycemia	Neurological evaluation, infection, pulmonary and cardiac monitoring, blood glucose, thyroid function	Fatigue and flu-like symptoms tend to decrease with duration of therapy Exists in a pegylated form that has a prolonged half-life
Interleukin-2	Flu-like syndrome: fevers, chills, malaise; vascular or capillary leak syndrome: hypotension, pulmonary and peripheral edema; nausea and vomiting; diarrhea; nephrotoxicity; myelosuppression (thrombocytopenia and leukopenia); bacterial infections; CNS: somnolence and confusion; arrhythmias; rash; itching	Intense monitoring required, electrolytes, liver function, renal function, CBC, thallium stress test, pulmonary function tests, cardiac monitoring during interleukin-2 administration, BP, HR	Vasopressor support and fluid resuscitation may be necessary during treatment because of hypotension Pulmonary edema can be managed with cautious use of diuretics; short courses of albumin may also be beneficial Itching may respond to treatment with antihistamines; emollient skin creams or occlusive agents are effective for dry, peeling skin Avoid corticosteroids because they may counteract the antitumor effects of interleukin-2 Patients on beta-blockers will need to be tapered off before initiation of aldesleukin

Enzymes			
L-asparaginase	Hypersensitivity reactions (fever, hypotension, rash, dyspnea in 25%); much lower risk with polyethylene glycol form and asparaginase *E. chrysanthemi;* pancreatitis; decreased synthesis of proteins, clotting factors; lethargy	Pancreatic enzymes; liver function; coagulation parameters (fibrinogen, PT, PTT); hypersensitivity reactions; blood glucose; CBC	Skin test before administration of *E. coli*–derived asparaginase; anaphylaxis precautions Pegaspargase complexes with polyethylene glycol to decrease immunogenicity and prolong duration of action Asparaginase *E. chrysanthemi*was developed for patients who have developed hypersensitivity to *E. coli*–derived asparaginase
Fusion Proteins			
Denileukin diftitox	Pyrexia, nausea, fatigue, rigors, vomiting, diarrhea, headache, peripheral edema, cough, dyspnea, pruritus, infusion reactions, capillary leak syndrome, loss of visual acuity	Infusion reactions, fluid status, BP, serum albumin, ophthalmologic evaluation	Serum albumin should be ≥3 g/dL (30 g/L) before initiating therapy Premedicate with an antihistamine and acetaminophen
Moxetumomab pasudotox	Renal toxicity, infusion-related reactions, electrolyte abnormalities, hemolytic uremic syndrome	Renal function, electrolytes, infusion reactions	Premedicate with acetaminophen, an antihistamine, and an H_2 antagonist Consider low-dose aspirin on days 1-8 of each cycle
Ziv-aflibercept	Neutropenia, diarrhea, proteinuria, increases in liver enzymes, stomatitis, fatigue, thrombocytopenia, hypertension, weight decreased, decreased appetite, epistaxis, abdominal pain, dysphonia, increased serum creatinine, headache, hemorrhage, GI perforation, compromised wound healing, arterial thromboembolic events, fistula formation	BP, urine protein, signs and symptoms of hemorrhage, CBC, liver function, renal function	Should be held at least 4 weeks before elective surgery and restarted at least 4 weeks after major surgery and until the surgical wound is fully healed
Vaccines			
Sipuleucel-T	Infusion reactions; chills; fatigue; back pain; nausea; joint ache; headache; thromboembolic events have occurred	Infusion reaction	Physicians and patients must be registered Premedicate with an antihistamine and acetaminophen For autologous use only
Talimogene laherparepvec	Fatigue, chills, pyrexia, nausea, influenza-like illness, injection-site pain, cellulitis, risk of herpetic infection	Herpetic infections, injection-site complications, immune-mediated events	Administered directly into the cutaneous, subcutaneous, and/or nodal lesion(s) Precautions for accidental exposure of healthcare works and close contacts Acyclovir and other antiviral medications may interfere with the efficacy of talimogene leherparepvec
Chimeric Antigen Receptor Therapies			
Axicabtagene ciloleucel and tisagenlecleucel	Hypersensitivity, myelosuppression, hypogammaglobulinemia, secondary malignancies, neurologic toxicities, cytokine release syndrome	CBC, infection, cytokine release syndrome	For autologous use only REMS program to mitigate the risk of cytokine release syndrome and neurological toxicities

[a]Only approximate guidelines can be given. Consult current references before dispensing as not all dose adjustments and monitoring parameters are provided in the table.

5-FU, fluorouracil; AML, acute myeloid leukemia; ATRA, all-trans-retinoic acid; BP, blood pressure; CBC, complete blood count; CHF, congestive heart failure; CMV, cytomegalovirus; CNS, central nervous system; CPK, creatinine phosphokinase; CYP, cytochrome P450 isoenzyme; DPD, dihydropyrimidine dehydrogenase; ECG, electrocardiogram; GI, gastrointestinal; H_1 and H_2, histamine 1 and 2; HBV, hepatitis B virus; HDAC, histone deacetylase; HFSR, hand-foot skin reaction; HHV-8, human herpesvirus 8; HIV, human immunodeficiency virus; HR, heart rate; HSCT, hematopoietic stem cell transplantation; HSV, herpes simplex virus; ILD, interstitial lung disease; IM, intramuscular; INR, international normalized ration; IT, intrathecal; IV, intravenous; LVEF, left ventricular ejection fraction; MAOI, monoamine oxidase inhibitor; MDS, myelodysplastic syndrome; MI, myocardial infarction; mTOR, mammalian target of rapamycin; MUGA, multigated acquisition scan; NSAID, nonsteroidal anti-inflammatory drug; PFT, pulmonary function tests; Pgp, P-glycoprotein; PJP, Pneumocystis jiroveci pneumonia; PPI, proton pump inhibitor; PRES, posterior reversible encephalopathy syndrome; PT, prothrombin time; PTT, partial thromboplastin time; REMS, risk evaluation and mitigation strategy; Scr, serum creatinine; SIADH, syndrome of inappropriate secretion of antidiuretic hormone; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TLS, tumor lysis syndrome; UGT1A1, Uridine 5'-diphospho-glucuronosyltransferase (UDP-glucuronosyltransferase).

Data from Chabner BA, Longo DL ed. Cancer Chemotherapy and Biotherapy: Principles and Practice, 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2010 and prescribing information package inserts.

Antimetabolites

Antimetabolites are similar to the nucleotides that make up DNA and RNA. The body mistakes these chemotherapy agents for the naturally occurring nucleotide bases and metabolizes these agents as the natural nucleotides. These chemotherapy agents ultimately disrupt replication and cell division by interfering with the production of nucleic acids, DNA, and RNA. Unfortunately, these compounds are not selective for cancer cells and rapidly dividing normal cells may be affected by an antimetabolite. The most common toxicities associated with the antimetabolites are secondary to their effect on rapidly dividing normal cells, such as cells of the bone marrow and gastrointestinal tract. The three major classes of antimetabolites include pyrimidine analogues, purine analogues, and folate antagonists.

Pyrimidine Analogues

Cytarabine Cytarabine is a cytidine analogue commonly used to treat AML, acute lymphoblastic leukemia (ALL), and NHL. It is phosphorylated to its active phosphates within cancer cells and inhibits DNA polymerase, an enzyme responsible for strand elongation. It is also incorporated directly into DNA, where it inhibits the replication of DNA and acts as a chain terminator to prevent DNA elongation. Deaminase enzymes, particularly cytidine deaminase, degrade cytarabine.

Cytarabine may be given intravenously or intrathecally. Intrathecal administration allows for cytotoxic concentrations of cytarabine to be maintained in the central nervous system (CNS) for several hours. It may be given to patients with leukemia.

The dose-limiting toxicities are leukopenia and thrombocytopenia. Other common toxicities include nausea, vomiting, mucositis, and diarrhea. Following administration of high-dose cytarabine (greater than 1 g/m^2 per dose), cerebellar syndrome may occur presenting with dysarthria, nystagmus, and ataxia. The risk of cerebellar syndrome is strongly correlated with advanced age and renal dysfunction. Renal dysfunction permits accumulation of high levels of the triphosphate, which is believed to be neurotoxic. Hepatic dysfunction, high cumulative doses, and bolus dosing may also increase the risk of neurotoxicity. Conjunctivitis or keratitis is another common toxicity associated with high-dose cytarabine. Prophylactic steroid or saline eye drops should be administered with high-dose cytarabine to minimize irritation as discussed later in this chapter.

Allopurinol may be given with high-dose cytarabine to minimize the risk of tumor lysis syndrome (TLS), a group of metabolic complications that can occur following the breakdown of dying cancer cells.

Fluoropyrimidines Fluorouracil (5-FU) is a fluorinated uracil analogue that was originally synthesized in the late 1950s. It acts as a false pyrimidine and undergoes sequential phosphorylation to a mono-, di-, and triphosphate similar to natural nucleotide bases. In the presence of folates, the monophosphate binds tightly to and interferes with the function of thymidylate synthase. The triphosphate metabolite is incorporated into RNA as a false base and interferes with its function. The interference with both thymidine formation and RNA function both contribute to its cytotoxic effects. 5-FU is commonly used to treat gastrointestinal tract and head and neck cancers.

The dosage and administration influences both the mechanism of action and toxicity profile. With continuous-infusion regimens, thymidylate synthesis inhibition plays a greater role and dose-limiting toxicities are hand-foot syndrome and diarrhea. Comparatively, the incorporation into RNA plays a greater role with intermittent bolus schedules. The dose-limiting toxicity commonly associated with a bolus administration is myelosuppression.

Several pharmacologic strategies have been attempted to increase its cytotoxicity against cancer cells and decrease its toxicity to normal cells. The most common strategy combines 5-FU with the reduced folate leucovorin. Folates increase the reduced folate pool, stabilize the monophosphate–thymidylate synthase complex and prolong the inhibition of thymidylate synthase. Clinical trials suggest that combining reduced folates with 5-FU provides greater anticancer activity and improves tolerability.

Dihydropyrimidine dehydrogenase (DPD) is a pyrimidine catabolic enzyme that is responsible for about 80% of the catabolism of 5-FU. Reduced expression of this enzyme has been associated with drug accumulation and serious adverse events.[15] DPD deficiency is an autosomal recessive genetic disorder, with genetic variation in the *DYPD* gene associated with reduced enzyme activity. DPD deficiency occurs in up to 5% of the overall population. 5-FU is contraindicated in patients with known DPD deficiency.

Capecitabine is an oral pyrimidine uracil analogue used to treat breast and colon cancers. Because capecitabine is enzymatically converted to 5-FU, it shares the same mechanisms of action. Capecitabine is typically taken twice daily with food for the first 14 days of a 21-day treatment cycle. Since chronic twice-daily oral dosing produces sustained 5-FU levels similar to those observed with continuous infusions, hand-foot syndrome and diarrhea are the dose-

limiting toxicities.

Uridine triacetate is approved for the emergency treatment of adult and pediatric patients following a 5-FU or capecitabine overdose regardless of the presence of symptoms, or who exhibit early-onset, severe or life-threatening toxicity affecting the cardiac or CNS, and/or early-onset unusually severe adverse reactions within 96 hours following the 5-FU or capecitabine exposure. It is not recommended for nonemergent treatment of adverse reactions. The safety and efficacy has not been established when more than 96 hours have elapsed following the end of 5-FU or capecitabine administration. Few adverse events have been reported, but the most common adverse reactions are vomiting, nausea, and diarrhea.

Gemcitabine Gemcitabine is a fluorine-substituted deoxycytidine analogue that is related structurally to cytarabine and is used to treat pancreatic cancer, NSCLC, breast cancer, and urothelial cancer. Its activation and mechanism of action are similar to those of cytarabine. Gemcitabine is incorporated into DNA, where it inhibits DNA polymerase activity. It also inhibits ribonucleotide reductase, which is the enzyme required to convert ribonucleotides into the deoxyribonucleotides that are needed for both DNA synthesis and repair. Compared with cytarabine, gemcitabine achieves intracellular concentrations about 20 times higher, secondary to increased penetration of cell membranes and greater affinity for the activating enzyme deoxycytidine kinase. Gemcitabine that is incorporated into DNA has a prolonged intracellular half-life. Its stereoconfiguration causes another normal base pair to be added next to the fraudulent gemcitabine base pair in the DNA strand. This “masked chain termination” protects the gemcitabine from excision and elimination. Flu-like symptoms are commonly associated with gemcitabine.

Trifluridine and Tipiracil Trifluridine and tipiracil are combined in a molar ration of 1:0.5 in one tablet that is approved for the treatment of metastatic colorectal cancer. Trifluridine is a thymidine-based nucleoside analogue and tipiracil is a thymidine phosphorylase inhibitor. Following uptake into cancer cells, trifluridine is incorporated into DNA, interferes with DNA synthesis and inhibits cell proliferation. Inclusion of tipiracil increases trifluridine exposure by inhibiting its metabolism by thymidine phosphorylase. The dose-limiting toxicity is myelosuppression; patients older than 65 years of age may be at greater risk. Other common toxicities include asthenia/fatigue, nausea, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia.

Purine Analogues

Cladribine and Pentostatin Cladribine and pentostatin are purine nucleoside analogues with slightly different mechanisms of action. Both agents are used to treat hairy cell leukemia. Cladribine is resistant to inactivation by adenosine deaminase and is triphosphorylated to an active form that is incorporated into DNA that inhibits DNA synthesis and early chain termination. Its anticancer activity is unusual for an antimetabolite in that it affects both actively dividing and resting cancer cells. Pentostatin is a potent inhibitor of adenosine deaminase. Adenosine deaminase is an enzyme critical in purine base metabolism and is found in high concentrations in lymphatic tissue. Both agents have immunosuppressive effects that place patients at risk for serious opportunistic infections and require the administration of prophylactic antibiotics.

Fludarabine Fludarabine is an adenine analogue used to treat chronic lymphocytic leukemia (CLL) and indolent NHL. Similar to cytarabine, fludarabine interferes with DNA polymerase, causing chain termination. Fludarabine also incorporates into RNA, resulting in inhibition of transcription. Fludarabine is immunosuppressive; it has been associated with the development of opportunistic infections, secondary to its effect on T cells and subsequent decrease in CD4 counts. Prophylactic antibiotics and antiviral medications are recommended and should continue until CD4 counts normalize.

Mercaptopurine and Thioguanine 6-Mercaptopurine (6-MP) and its analogue thioguanine are oral antimetabolites used for the treatment of ALL. These antimetabolites are rapidly converted to ribonucleotides that inhibit purine biosynthesis or undergo purine interconversion reactions needed to supply purine precursors for synthesis of nucleic acids. Clinical cross-resistance is generally observed. Both antimetabolites are metabolized by thiopurine methyltransferase (TPMT) and hypoxanthine phosphoribosyl transferase to produce multiple metabolites that contribute to the observed anticancer activity, hepatotoxicity, and myelosuppression. Certain genetic alterations within the *TPMT* gene can lead to a reduction of loss of TPMT enzyme activity. Therefore, patients who are homozygous or heterozygous for a genetic alteration that affects TPMT enzyme activity may experience an accumulation of toxic metabolites and an increased risk of severe myelosuppression. The Clinical Pharmacogenetics Implementation Consortium (CPIC) provides primary dosing recommendations for patients with TPMT alterations.

6-MP depends on xanthine oxidase for an initial oxidation step. Its metabolism is markedly decreased by coadministration with a xanthine oxidase

inhibitor (eg, allopurinol), which may lead to the development of serious adverse events. If allopurinol is given concurrently with 6-MP to minimize TLS, the dose of 6-MP must be reduced.

Folate Antagonists

Methotrexate Methotrexate is commonly used to treat ALL and some lymphomas. It inhibits dihydrofolate reductase (DHFR), which results in the depletion of intracellular pools of reduced folates (tetrahydrofolates) essential for thymidylate and purine synthesis. Folates are essential cofactors for DNA and RNA synthesis and, thus, lack of either thymidine or purines prevents DNA or RNA synthesis.

Chemotherapy regimens may contain low-, intermediate- or high-dose methotrexate and may incorporate methotrexate given orally, intravenously, or intrathecally. High-dose methotrexate defined as doses greater than 500 mg/m^2 given intravenously as prophylaxis or treatment of CNS disease can cause severe myelosuppression and gastrointestinal toxicity. The development of these toxicities is related to both the maximal concentrations and the time that concentrations remain above 0.02 mg/L (50 nmol/L). These effects may be neutralized by exogenously supplying reduced folates, such as leucovorin (folinic acid), which bypasses the metabolic block induced by DHFR inhibitors. Leucovorin should be administered until methotrexate levels fall below the threshold and various dosing algorithms are available. Vigorous hydration and sodium bicarbonate to alkalinize the urine should be given to decrease the risk of renal failure. Patients with third space fluids may require prolonged leucovorin rescue, since these fluids influence methotrexate volume of distribution and elimination half-life.

Glucarpidase is approved for the treatment of toxic plasma methotrexate concentrations in patients with delayed methotrexate clearance because of impaired renal function. It is important to note that methotrexate concentrations within 48 hours after glucarpidase administration can only be reliably measured by chromatographic methods. Immunoassays can overestimate methotrexate concentration because of interference from metabolites.

Methotrexate is highly protein bound and drugs such as sulfonamides, salicylates, phenytoin, and tetracyclines may displace methotrexate from albumin. Increased toxicity may be observed. Nonsteroidal anti-inflammatory drugs (NSAIDs) and vitamin C may also affect methotrexate disposition and prolong methotrexate elimination half-life. Although the exact mechanism is uncertain, proton pump inhibitors are thought to inhibit methotrexate elimination

and thereby potentially increase methotrexate toxicity.

Pemetrexed Pemetrexed is a multi-targeted antifolate that is used to treat nonsquamous NSCLC and mesothelioma. It inhibits at least three biosynthetic pathways in thymidine and purine synthesis. In addition to inhibiting DHFR, it also inhibits thymidine synthase and glycinamide ribonucleotide formyltransferase, decreasing the risk of the development of drug resistance. Severe hematologic toxicity and deaths associated with neutropenic sepsis have been reported in clinical trials. Elevated baseline cystathionine or homocysteine concentrations correlated with this unexpected toxicity. Routine supplementation of folic acid and vitamin B_{12} prior to the initiation of pemetrexed and throughout the duration of treatment lowers levels of these substances and lowers the risk of mortality related to neutropenic sepsis. Dexamethasone should be given with pemetrexed to minimize the risk of dermatologic toxicities.

Pralatrexate Pralatrexate is an antifolate drug approved for patients with relapsed or refractory peripheral T-cell leukemias. It competitively inhibits DHFR and polyglutamylation by the enzyme folylpolyglutamyl synthetase. This inhibition results in the depletion of thymidine and other synthesis of biological molecules that depends on single carbon transfer.[16] The most common adverse events resulting in dose reductions are pyrexia, mucositis, febrile neutropenia, sepsis, and thrombocytopenia.

Microtubule-Targeting Drugs

Microtubules are an integral part of the cytoskeleton and help maintain the shape of a cell. These structures are also involved in chromosome separation during mitosis and form the mitotic spindle responsible for separating chromosomes during cell replication. Several chemotherapy agents affect microtubule function, including epipodophyllotoxins, taxanes, vinca alkaloids, epitholones, and macrolides.

Eribulin

Eribulin is a fully synthetic antimicrotubule analogue of the macrolide halichondrin B. Eribulin inhibits tubulin polymerization by inhibiting microtubule growth, but it does not shorten or promote depolymerization of microtubules. Additionally, eribulin only binds to the β-tubulin subunit and has demonstrated the ability to overcome taxane resistance conferred by β-tubulin mutations.[17] The most common toxicities are similar to other microtubule

inhibitors, but eribulin demonstrates a decreased incidence of neuropathy compared with vincristine and taxanes. Eribulin is approved for the treatment of metastatic breast cancer and unresectable or metastatic liposarcoma.

Estramustine

Estramustine is indicated for the treatment of metastatic prostate cancer. It structurally combines the alkylating agent nornitrogen mustard with estradiol. It was designed with the intent that the estradiol portion of the molecule would facilitate uptake of the alkylating agent into hormone-sensitive prostate cancer cells. Despite the inclusion of an alkylator, estramustine does not function as an alkylating agent. The estradiol is released after its administration and it is responsible for most of the toxicity associated with estramustine; the estradiol is not believed to contribute to its anticancer activity. In the mid-1980s, estramustine was redefined as an antimicrotubule agent. It binds covalently to microtubule-associated proteins that are part of the structural support for microtubules. The binding causes the separation of microtubule-associated proteins from the microtubules, inhibiting microtubule assembly and eventually causing their disassembly. Observed toxicities include gastrointestinal disorders, edema, gynecomastia, thromboembolic events, and cardiovascular events.

Ixabepilone

Ixabepilone is a synthetic epothilone approved for the treatment of metastatic breast cancer. Its binding to microtubules appears distinct from other microtubule inhibitors, such as the taxanes. Dose-limiting toxicities are leukopenia and neuropathy, consistent with other microtubule inhibitors. Other toxicities include anemia, thrombocytopenia, diarrhea, myalgia, and alopecia. Premedication with antihistamines must be administered to reduce the risk of hypersensitivity reactions.

Taxanes

Paclitaxel and docetaxel are taxane plant alkaloids with antimitotic activity used to treat many different solid tumors. Paclitaxel and docetaxel both act by binding to tubulin, but they do not interfere with tubulin assembly. Instead, the taxanes promote microtubule assembly and interfere with microtubule disassembly. They induce tubulin polymerization, resulting in formation of inappropriately stable, nonfunctional microtubules. The stability of the microtubules damages cells by disrupting the dynamics of microtubule-dependent structures required for mitosis

and other cellular functions. Taxanes also have some nonmitotic actions that can promote cancer cell death, such as inhibition of angiogenesis.

Resistance to the antitumor effects of the taxanes is attributable to alterations in tubulin or tubulin-binding sites or to P-glycoprotein (Pgp)-mediated multidrug resistance. Although paclitaxel and docetaxel have very similar mechanisms of action, cross-resistance between the two chemotherapy agents is incomplete.

Myelosuppression and peripheral neuropathy frequently occur with both docetaxel and paclitaxel. Fluid retention is more common with docetaxel and hypersensitivity reactions may be more frequent with conventional paclitaxel. Both require premedication to decrease the likelihood of hypersensitivity reactions.

Two paclitaxel formulations are available. The original product (ie, conventional paclitaxel) contains Cremophor and ethanol. The subsequent product (nab-paclitaxel) contains paclitaxel bound to albumin and does not contain the Cremophor excipient believed to contribute to hypersensitivity reactions. In clinical trials, nab-paclitaxel has shown comparable activity to conventional paclitaxel with a lower incidence of hypersensitivity reactions. Peripheral neuropathy remains a common adverse event with nab-paclitaxel. Nab-paclitaxel is approved for the treatment of metastatic breast cancer, NSCLC, and pancreatic cancer. Of note, the products are not interchangeable and the doses are not comparable on a mg to mg basis.

Cabazitaxel is a semisynthetic derivative of docetaxel that has demonstrated anticancer activity in hormone refractory prostate cancer that has progressed following treatment with docetaxel-based chemotherapy. Despite having the same mechanism of action, the lack of affinity for Pgp allows cabazitaxel to remain inside the cancer cells, partially accounting for its benefit in the refractory setting. Toxicities and premedications are similar to docetaxel.[18]

Vinca Alkaloids

Vincristine, vinblastine, and vinorelbine are natural alkaloids derived from the periwinkle (vinca) plant. These agents act as mitotic inhibitors or spindle poisons. Although these alkaloids have a very similar structure, they have different activities and patterns of toxicity. These agents are used to treat different cancers. For example, vinblastine may be used to treat testicular cancer and Hodgkin lymphoma, vincristine may be used to treat NHL and Hodgkin lymphoma, and vinorelbine may be used to treat NSCLC and breast cancer. Vinorelbine and vinblastine are associated with dose-limiting myelosuppression, while vincristine is associated with dose-limiting neurotoxicity, including

constipation and paralytic ileus. All vinca alkaloids are vesicants upon extravasation; the application of local heat allows dispersal or dilution of the alkaloid to minimize the tissue damage. Vinca alkaloids should never be administered intrathecally and accidental overdose is associated with a very high mortality rate.

Vinca alkaloids bind to tubulin and disrupt the normal balance between polymerization and depolymerization of microtubules, which inhibits assembly of microtubules and disrupts microtubule dynamics. This interferes with formation of the mitotic spindle and causes cells to accumulate in mitosis. These agents also disturb a variety of microtubule-related processes in cells and induce apoptosis. Resistance to the vinca alkaloids develops primarily from Pgp-mediated multidrug resistance, which decreases drug accumulation and retention within cancer cells.

Topoisomerase Inhibitors

Topoisomerases (I and II) are essential enzymes involved in maintaining DNA topologic structure during replication. During replication, these enzymes cleave DNA strands and form intermediates with the strands, producing a gap through which DNA strands can pass, and then reseal the strand breaks. Topoisomerase I produces single-strand breaks and topoisomerase II produces double-strand breaks. Several important anticancer agents interact with topoisomerase enzymes: anthracyclines, camptothecins, and podophyllotoxins.

Anthracyclines

The anthracyclines include doxorubicin, daunorubicin (daunomycin), idarubicin, and epirubicin. These agents share a common, four-membered anthracene ring complex with an attached aglycone or sugar portion. The ring complex is a chromophore and accounts for the intense colors of these derivatives.[19] Anthracyclines are sometimes classified as antitumor antibiotics, but they have multiple mechanisms of action, including intercalation into DNA and inhibition of topoisomerase II.[19] The production of free radicals following their metabolism may also contribute to their anticancer activity. These agents are used to treat many cancers, including leukemias, lymphomas, and multiple solid tumors.

Although the dose-limiting toxicity is myelosuppression, development of cardiomyopathy is a significant concern with these agents. All patients should have a baseline study to evaluate left ventricular ejection fraction. Since the

probability of congestive heart failure increases with the cumulative dose, a maximum cumulative dose has been suggested for each anthracycline. The relatively low level of defensive enzymes found in cardiac muscle that scavenge against oxygen free radicals may account for the relative risk of cardiomyopathy compared to toxicity in other organs. Oxygen free-radical formation likely contributes to extravasation injury associated with these agents, as well. Other common toxicities include nausea, vomiting, and alopecia. Doxorubicin also causes a red discoloration of the urine. Resistance to anthracyclines is usually secondary to Pgp-mediated multidrug resistance but altered topoisomerase II activity may also contribute to the development of resistance.

A liposomal combination product with daunorubicin is also available. This agent contains daunorubicin and cytarabine in a fixed 1:5 molar ratio and is approved for the treatment of AML.

Mitoxantrone has been identified as an anthracendione. It was synthesized in an attempt to develop a chemotherapy agent with comparable antitumor activity to doxorubicin but with an improved safety profile. Similar to the anthracyclines, mitoxantrone is an intercalating topoisomerase II inhibitor, but its potential for free-radical formation is much less than that of the anthracyclines. This decreased tendency for free-radical formation may explain the reduced risks of cardiac toxicity and ulceration after extravasation. Mitoxantrone may be used with other anticancer agents to treat leukemias and lymphomas. Common toxicities include nausea, vomiting, alopecia, and blue discolored urine.

Camptothecins

Topotecan and irinotecan, through an active metabolite SN-38, inhibit topoisomerase I enzyme activity. Topoisomerase I enzymes stabilize DNA single-strand breaks and inhibit strand resealing. Topotecan is available for oral and intravenous administration and it is used to treat ovarian cancer and small cell lung cancer. Irinotecan is used for the treatment of colorectal cancer. SN-38 undergoes metabolism in part by uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1). Although variant tandem repeats in the promoter of this gene have been associated with a higher risk of diarrhea and neutropenia, genotyping has not been widely adopted in clinical practice. All patients receiving irinotecan are at risk of developing early and/or late diarrhea. Early diarrhea is a cholinergic effect and may be prevented with atropine, whereas late diarrhea is typically treated with loperamide.

Liposomal irinotecan is approved for the treatment of patients with metastatic adenocarcinoma of the pancreas whose disease has progressed following

gemcitabine-based therapy with 5-FU and leucovorin. The common toxicities associated with irinotecan have been observed with liposomal irinotecan, including gastrointestinal toxicity and myelosuppression. The recommended dose is lower for patients homozygous for the UGT1A1*28 allele.

Etoposide and Teniposide

Etoposide and teniposide are semisynthetic podophyllotoxin derivatives that bind to tubulin and interfere with microtubule formation. Etoposide and teniposide also damage cancer cells by causing strand breakage through inhibition of topoisomerase II. Resistance may be caused by differences in topoisomerase II levels, increased cell ability to repair strand breaks, or increased levels of Pgp. Etoposide and teniposide are usually clinically cross-resistant. They are cell-cycle phase-specific and arrest cells in the S or early G_2 phase. As a result, activity is much greater when they are administered in divided doses over several days rather than in large single doses. Etoposide may be used to treat testicular cancer and small cell lung cancer and teniposide is used to treat pediatric ALL. Both agents are associated with dose-limiting myelosuppression, as well as nausea, vomiting and alopecia.

Alkylating Agents

The alkylating agents are among the oldest and most widely used class of chemotherapy agents. Their clinical use evolved from the observation of myelosuppression and lymph node shrinkage in soldiers exposed to sulfur mustard gas warfare during World War I. In an effort to develop similar agents that might be useful in treating lymphomas, less reactive derivatives were synthesized. Their anticancer activity was confirmed by clinical trials in the mid-1940s.

All alkylating agents work by covalently bonding to highly reactive alkyl groups or substituted alkyl groups with nucleophilic groups of proteins and nucleic acids. Some agents react directly with biologic molecules, but others form an intermediate compound that reacts with these molecules. The most common binding site for alkylating agents is the seven-nitrogen group of the DNA base guanine. These covalent interactions result in cross-linking between two DNA strands or between two bases in the same strand of DNA and prevent the separation of DNA strands that needs to occur during replication. Reactions between DNA and RNA and between drug and proteins may also occur. Alkylating agents are cell-cycle phase-nonspecific, but their greatest effect is

seen in rapidly dividing cells.

As a class, alkylators are cytotoxic, mutagenic, teratogenic, carcinogenic, and myelosuppressive. Resistance to these chemotherapies can occur from increased DNA repair capabilities, decreased entry into or accelerated exit from cells, increased inactivation inside cells, or lack of cellular mechanisms to result in cell death after DNA damage. They are inactivated by hydrolysis, making spontaneous degradation an important component of their elimination.[20]

Nitrogen Mustards

Bendamustine Bendamustine is an alkylating agent with a benzimidazole ring that demonstrates only partial cross-resistance in vitro with other alkylating agents.[21] It is used primarily to treat lymphoid malignancies, such as CLL and NHL. Bendamustine is incompatible with polycarbonate or acrylonitrile-butadiene-styrene found in syringes and adapters and has been shown to minimize the integrity of these supplies. Typical adverse events associated with alkylating agents have been observed with bendamustine, but it appears to cause less alopecia.

Cyclophosphamide and Ifosfamide Cyclophosphamide and ifosfamide are nitrogen mustard derivatives and are widely used in the treatment of solid tumors and hematologic malignancies. These mustards are closely related in structure, clinical use, and toxicity. Neither agent is active in its parent form and must be activated by cytochrome P450 enzymes. The cytochrome P450-mediated metabolites 4-hydroxycyclophosphamide and 4-hydroxyifosfamide are also cytotoxic compounds. Acrolein, a metabolite of both cyclophosphamide and ifosfamide, has little anticancer activity, but is responsible for the hemorrhagic cystitis associated with ifosfamide and high-dose cyclophosphamide. Encephalopathy after ifosfamide can occur within 48 to 72 hours after the infusion and is generally reversible once the infusion is stopped. Methylene blue has been suggested to manage neuropathy but data is lacking to support its routine use. The increased production of dechloroethylated metabolites after administration of ifosfamide compared with cyclophosphamide may explain the increased risk of CNS toxicity associated with ifosfamide.

Nitrosoureas

Carmustine and Lomustine Carmustine (BCNU) and lomustine (CCNU) are characterized by their lipophilicity and their ability to cross the blood–brain barrier; both agents are used to treat brain cancers. Carmustine is also used to

treat multiple myeloma and lymphoma and in preparation for a bone marrow transplant. It is available as an intravenous preparation and as a drug-impregnated biodegradable wafer for direct application to residual tumor tissue after surgical resection of brain tumors. Both agents cause dose-limiting myelosuppression, but the nadir is typically delayed to 4 to 6 weeks after administration. The nitrosoureas decompose to reactive alkylating metabolites and to isocyanate compounds that have several effects on reproducing cells.[20]

Nonclassic Alkylating Agents

Several other chemotherapy agents appear to act as alkylators, although their structures do not include the classic alkylating groups. These agents are capable of binding covalently to cellular components and include procarbazine, dacarbazine, temozolomide, and platinum analogues.[20]

Dacarbazine and Temozolomide Dacarbazine and temozolomide are commonly classified as triazenes and undergo demethylation to the same active intermediate (monomethyl triazeno-imidazole-carboxamide [MTIC]) that interrupts DNA replication by causing methylation of guanine. Unlike dacarbazine, temozolomide does not require the liver for activation and is chemically degraded to MTIC at physiologic pH. Both agents inhibit DNA, RNA, and protein synthesis.[20]

Important pharmacokinetic differences exist between these two agents. Dacarbazine is poorly absorbed and must be administered by intravenous infusion. Temozolomide is rapidly absorbed after oral administration; it demonstrates nearly 100% bioavailability when given under fasted conditions. Dacarbazine penetrates the CNS poorly, but temozolomide readily crosses the blood–brain barrier, achieving therapeutically active concentrations in cerebrospinal fluid and brain tumor tissues.[20] Temozolomide is approved for the treatment of glioblastoma multiforme and dacarbazine was commonly used to treat melanoma. Common adverse events include nausea and vomiting, alopecia, and myelosuppression.

Platinum Analogues The platinum derivatives—cisplatin, carboplatin, and oxaliplatin—are chemotherapy agents with remarkable usefulness in cancer treatment. Recognition of cisplatin's cytotoxic activity was the result of a serendipitous observation that bacterial growth in culture was altered when an electric current was delivered to the media through platinum electrodes. The growth change was noted to be similar to that produced by alkylating agents and radiation. It was found that a platinum–chloride complex, now known as

cisplatin, generated by the current was responsible for the changes. Carboplatin is a structural analogue of cisplatin in which the chloride groups of the parent compound are replaced by a carboxycyclobutane moiety. It shares a similar spectrum of clinical activity with cisplatin and cross-resistance is common. Oxaliplatin is an organoplatinum compound in which the platinum is complexed with an oxalate ligand as the leaving group and to diaminocyclohexane. Its spectrum of activity differs substantially from the other platinum compounds and includes notable activity against colorectal cancers.

The cytotoxicity of the platinum derivatives depends on platinum binding to DNA and the formation of intrastrand cross-links or adducts between neighboring guanines. These intrastrand links cause a major bending of the DNA. These agents may cause cellular damage by distorting the normal DNA conformation and preventing bases that are normally paired from lining up with each other. Interstrand cross-links also occur.

The aquated species differ among these platinum compounds, but all of these species contribute to the anticancer activity. The cytotoxic form of cisplatin is the aquated species in which hydroxyl groups or water molecules replace the two chloride groups. This reaction occurs readily in low concentrations of chloride, such as the concentrations present within cells, and produces a positively charged compound that can react with DNA. The aquated species is responsible for both the efficacy and toxicity of cisplatin. Carboplatin also undergoes aquation but at a slower rate. Oxaliplatin becomes active when the oxalate ligand is displaced in physiologic solutions.[20]

Resistance to the therapeutic effects of platinum compounds may occur through several mechanisms. The ability to repair platinum-induced DNA damage may be increased or the compounds may be inactivated by increased levels of intracellular glutathione, metallothioneins, or other thiol-containing proteins. Altered uptake into cells may also affect sensitivity to platinum compounds.[20]

The dose-limiting toxicities differ substantially among these compounds. Cisplatin can cause serious nephrotoxicity, ototoxicity, peripheral neuropathy, emesis, and anemia, but its significant anticancer activity in many tumors makes it a valuable agent despite these toxicities. Most of these toxicities can be prevented or managed with aggressive supportive care measures. Intravenous hydration, mannitol and diuretics have been used to minimize the risk of nephrotoxicity, but it appears intravenous hydration alone is adequate. In contrast, carboplatin administration is limited by hematologic toxicity. Patients with compromised renal function require dose reductions to limit

myelosuppressive toxicity. The most widely used dosage schema, the Calvert formula, uses a target area-under-the-curve and renal and nonrenal parameters to estimate the carboplatin dose. Carboplatin's potential to cause renal damage, peripheral neuropathy, and ototoxicity is much less than that of comparable cisplatin doses. Oxaliplatin is not nephrotoxic or ototoxic, but it can cause peripheral neuropathies and unique cold-induced neuropathies. Intravenous calcium and magnesium were commonly used to minimize the risk of neuropathy, but these measures do not appear to decrease the risk of acute neurotoxicity or cumulative sensory neurotoxicity based on the results of a controlled trial.[22] All of the platinum derivatives have potential to cause hypersensitivity reactions, including anaphylaxis, after a threshold exposure is reached. De-sensitization protocols may be successful in reestablishing tolerance to these agents.

Trabectedin Trabectedin is an alkylating drug that binds guanine residues in the minor groove of DNA. Subsequently, adducts form and cause a bending of the DNA helix toward the major groove. It is approved for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who have received a prior anthracycline-containing regimen. Possible risks associated with trabectedin include neutropenic sepsis, rhabdomyolysis, cardiomyopathy, hepatotoxicity, anaphylaxis, and extravasation leading to tissue necrosis.

Endocrine Therapies

Endocrine therapies are perhaps the earliest successful approach to target the growth processes of cancer cells. Endocrine manipulation is an option for management of cancers in which its growth is under gonadal hormonal control, such as breast, prostate, and endometrial cancers. These cancers may regress if the feeding hormone is eliminated or antagonized. Major organ system toxicity is uncommon from endocrine therapies. Specific anticancer agents such as the selective estrogen receptor modulators (SERM) and aromatase inhibitors (AI) have increased the utility of endocrine therapies in the treatment of cancer. These therapies are discussed in detail in Chapters 145, "Breast Cancer," and 148, "Prostate Cancer."

Corticosteroids

Corticosteroids are also useful anticancer therapies because of their lymphotoxic effects. These agents are primarily used to treat hematologic malignancies and

are also given in combination with chemotherapy for prostate cancer. In addition to their cytotoxic effects, corticosteroids have many other applications as part of supportive care measures and in the management of oncologic emergencies. Short-term corticosteroid regimens are generally well tolerated.

Therapeutic Radiopharmaceuticals

An oncology therapeutic radiopharmaceutical is an agent that contains a radionuclide and is used for the treatment of cancer or for palliation of tumor-associated symptoms. Radioisotopes can emit either alpha or beta particles as their payload.[23] Alpha emitters have high energy and travel only the length of a few cell diameters resulting in double strand DNA breaks of adjacent cells. In contrast, beta emitters have lower energy and travel the length of hundreds of cell diameters. As a result, these agents not only affect the cancer cells they bind but also other cells that are within the path length of the radioisotope's emissions (ie, bystander effect). Additionally, some radioisotopes emit gamma radiation which has no mass or charge and can travel further than alpha or beta particles.

Ibritumomab Tiuxetan

Ibritumomab tiuxetan is a radioimmunoconjugate that consists of the murine anti-CD20 antibody ibritumomab and a linker chelator tiuxetan that allows the attachment of yttrium-90 (active radiotherapy). This therapeutic radiation isotope selectively delivers beta particles to B-cells that express the CD20 antigen. Consequently, ibritumomab tiuxetan can induce cell death in CD20-positive and -negative cancer cells while also inducing antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and apoptosis. These processes are described later in the chapter. Ibritumomab tiuxetan is indicated for the treatment of low-grade or follicular B-cell NHL. The therapeutic regimen consists of two steps: rituximab is administered on day 1 and about one week later (day 7, 8, or 9), an additional dose of rituximab is administered followed by yttrium-90-ibritumomab within 4 hours after completion of the rituximab infusion.

Adverse effects include severe infusion-related reactions. Myelosuppression is common with ibritumomab tiuxetan as a consequence of the radioisotope. Ibritumomab tiuxetan results in prolonged thrombocytopenia and neutropenia and dose modifications are necessary based on baseline neutrophil and platelet blood counts. The median durations of thrombocytopenia and neutropenia were 24 and 22 days, respectively. Monitoring and management of cytopenias, along

with their complications is necessary for up to 3 months after completing treatment.

Iobenguane I 131

Iobenguane is a molecule structurally similar to norepinephrine and is therefore involved in the same uptake pathways. Labeled with I 131, this agent targets the norepinephrine transporter and is a beta emitter. Two rare tumors, pheochromocytoma and paraganglioma, express high levels of norepinephrine on their cell surfaces. When iobenguane I 131 is administered, it accumulates in these tumor cells allowing the radioisotope to cause cell death and tumor necrosis. Of note, this agent is only approved for patients with an iobenguane positive scan.

Prior to administration of iobenguane I 131, patients should receive thyroid-blocking medication. Additionally, medications that reduce catecholamine uptake or deplete stores should not be administered concurrently with iobenguane I 131 as they may interfere with the efficacy. The most common toxicities include myelosuppression, fatigue, hypertension, nausea, and vomiting.

Lutetium Lu 177 Dotatate

Lutetium Lu 177 dotatate is a radiolabeled somatostatin analogue that emits beta and gamma radiation and is approved for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NET). After binding to somatostatin receptor expressing cells, such as GEP-NET cells, lutetium Lu 177 is taken up into the cell where the beta emission induces cellular damage.

Special precautions should be taken with the administration of somatostatin analogues prior to lutetium Lu 177. An amino acid solution must be administered before, during, and after lutetium Lu 177 to decrease reabsorption of the radiopharmaceutical through the proximal tubules, thereby reducing the radiation exposure to the kidneys. Patients must be advised on minimizing exposure to contacts. Reported adverse effects include increased hepatic enzymes, hyperglycemia, hypokalemia, nausea, and vomiting. Patients should also be monitored for neuroendocrine hormonal crisis.

Radium Ra 223 dichloride

Radium Ra 223 dichloride (ie, radium-223) is an alpha emitter, which is

indicated for the treatment of patients with castration-resistant prostate cancer who have symptomatic bone metastases and no known visceral metastatic disease. Radium-223 mimics calcium and forms complexes with hydroxyapatite at areas of increased bone turnover, such as bone metastases. Alpha particles are then emitted resulting in DNA breaks and an antitumor effect. Toxicities of radium-223 include bone marrow suppression, gastrointestinal adverse reactions, dehydration, and potentially an increased risk of fractures in select patients.

Miscellaneous Agents

Arsenic Trioxide

Arsenic is an organic element and a well-known poison that is an effective treatment for acute promyelocytic leukemia (APL). As an anticancer agent, arsenic trioxide acts as a differentiating agent, inducing the growth progression of cancer cells into mature, more normal cells. It also induces apoptosis. This anticancer agent is discussed in more detail in Chapter 151, “Acute Leukemias.”

Asparaginase

L-Asparaginase is unique among anticancer agents in its unusual mechanism of action, patterns of toxicity, and source. It is an enzyme produced by *Escherichia coli* or Erwinia chrysanthemi. L-Asparagine is a nonessential amino acid that can be synthesized by most mammalian cells except cells with certain lymphoid malignancies, which have no or limited synthetase levels required for L-asparagine formation. L-Asparagine is degraded by the enzyme L-asparaginase, which depletes existing supplies and inhibits protein synthesis. Increased L-asparagine synthetase activity within cancer cells causes resistance to L-asparaginase treatment. L-Asparaginase is a component of combination chemotherapy regimen used for the treatment of ALL and multiple products are available.

Bleomycin

Bleomycin is an antitumor antibiotic used with other anticancer agents to treat Hodgkin lymphoma and testicular cancer and for pleurodesis to prevent recurrence of a pleural effusion. It is a mixture of peptides from fungal *Streptomyces* species. Its strength is expressed in units of drug activity and one unit is roughly equal to 1 mg of polypeptide protein. The predominant peptide is bleomycin A2, which makes up about 70% of the commercial drug product. Its

cytotoxicity is secondary to DNA strand breakage, which it produces via free-radical formation. Cytotoxicity depends on binding of the bleomycin–iron complex to DNA. The bleomycin–iron complex then reduces molecular oxygen to free oxygen radicals that cause primarily single-strand breaks in DNA. Bleomycin has greatest effect on cells in the G2 and M phases of the cell cycle.

Bleomycin is inactivated within cells by the enzyme aminohydrolase. This enzyme is widely distributed but is present in only low concentrations in the skin and the lungs, explaining the predominant toxicities of bleomycin to those sites. Baseline pulmonary function tests and monitoring for pulmonary toxicity are necessary. The presence of hydrolase enzymes in cancer cells is the primary mechanism of resistance to bleomycin. Cells can also become resistant by repairing the DNA breaks produced by bleomycin.

Hydroxyurea

Hydroxyurea is a unique drug that inhibits ribonucleotide reductase. Cells accumulate in the S phase because DNA synthesis is inhibited and only abnormally short DNA strands are produced. This anticancer agent was used to treat chronic myeloid leukemia (CML) because of its ability to cause a rapid decline in white blood cells.

Lanreotide

As an octapeptide analogue of somatostatin, the mechanism of lanreotide is believed to be similar to that of natural somatostatin through the inhibition of neuroendocrine functions. Somatostatin analogues are commonly used to treat hypersecretion syndromes associated with neuroendocrine tumors, but only recently have been proven to have an antitumor effect associated with prolonged progression-free survival. Lanreotide is approved for the treatment of unresectable, well or moderately differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors. Common toxicities include abdominal pain, musculoskeletal pain, vomiting, headache, injection site reaction, and hypertension. Patients should be monitored for hypoglycemia, hyperglycemia, and gallstones.

Mitomycin C

Mitomycin C is a natural product that is sometimes classified as an antitumor antibiotic. It has similarities to nitrogen mustards and may function as an alkylating agent, although its toxicity pattern differs from conventional

alkylating agents. It is used to treat bladder cancer. Mitomycin C may be given intravenously or as an instillation directly into the bladder (ie, intravesical instillation). Mitomycin C causes delayed myelosuppression, so treatment is typically given every 6 weeks.

Omacetaxine Mepesuccinate

Omacetaxine mepesuccinate is a natural ester of the alkaloid cephalotaxine. It inhibits protein translation and thus prevents the initial elongation step of protein synthesis. It is given subcutaneously for treatment of patients with CML who have failed two or more approved therapies for this disease. Additionally, synergy with these approved therapies has been demonstrated in a few clinical studies and additional combination trials are ongoing.[24] Adverse reactions include myelosuppression, hemorrhage, and hyperglycemia.

Retinoids

Three retinoids are available to treat patients with cancer. Tretinoin (all-trans-retinoic acid), a naturally occurring derivative of vitamin A (retinol), is used to treat APL. Other retinoids indicated for the treatment of cancers include alitretinoin (9-cis-retinoic acid) gel for topical management of Kaposi's sarcoma lesions and bexarotene gel or capsules for treatment of cutaneous T-cell lymphoma.

Retinoids are classified as morphogens, small molecules released from one type of cell that can affect the growth and differentiation of neighboring cells. Their normal roles in the human body are to induce differentiation of some cells, stop the differentiation of others, and both suppress and induce apoptosis in different cell types. Their diverse actions come from the diversity of their receptors. The two classes of retinoid receptors are retinoid X receptors (RXR) and retinoic acid receptors (RAR). RXR are versatile; they bind to RAR and to other nuclear receptors, such as thyroid hormone receptors. After being activated, the receptors act as transcription factors that in turn regulate the expression of genes that control cellular growth and differentiation.

Tretinoin binds primarily to the RAR-α receptors. Alitretinoin is considered a pan-agonist, which means that it binds to all known retinoid receptors, producing diverse regulatory effects. Bexarotene is synthetic and is classed as a rexinoid. It is the first RXR-selective retinoid agonist.

The common adverse events differ for these three agents. Tretinoin may be associated with retinoic acid syndrome. This syndrome manifests with dyspnea,

fever, weight gain, or peripheral edema following cytokine release from the differentiating promyelocytes. Corticosteroids should be administered to manage this syndrome. Aliretinoin is associated with pain, itching and rash and bexarotene is associated with skin reactions, thyroid disorders, hypercholesterolemia, and hyperlipidemia.

Thalidomide, Lenalidomide, and Pomalidomide

Thalidomide, the infamous drug that caused severe limb deformities when used by pregnant women as a nonprescription sedative in the 1960s, is approved for treatment of leprosy and multiple myeloma. Thalidomide is a glutamic acid derivative and is broadly classified as an immunomodulatory drug. Lenalidomide and pomalidomide are analogues of thalidomide with similar therapeutic activity but different adverse event profiles. Lenalidomide is approved for the treatment of multiple myeloma, transfusion-dependent anemia caused by MDS with a specific mutation, follicular lymphoma, marginal zone lymphoma, and mantle cell lymphoma. Pomalidomide is also approved for the treatment of multiple myeloma.

These drugs have many potential mechanisms of action, but the most important is thought to be angiogenesis inhibition, an action also linked to their teratogenic effects. Other possible mechanisms include direct inhibition of cancer cells, free radical oxidative damage to DNA, interference with adhesion of cancer cells, inhibition of TNF-α production, or alteration of cytokine secretion that affects the growth of cancer cells.

The most common toxicities for thalidomide include somnolence, constipation, dizziness, orthostatic hypotension, rash, and peripheral neuropathies. In contrast, lenalidomide is associated with much less somnolence and neuropathies compared with thalidomide. Neutropenia, thrombocytopenia, and thrombotic events are common with thalidomide, lenalidomide, and pomalidomide. To avoid embryo-fetal exposure and to inform healthcare professionals and patients of the teratogenic potential, these agents are only available through a risk evaluation and mitigation strategy (REMS) program.

TARGETED AGENTS: SMALL MOLECULES

6 Small molecule targeted agents (molecular weight less than 1,000 daltons) are typically identified as kinase inhibitors. Kinases are enzymatic proteins that constitute the intracellular signaling pathways, such as the JAK-STAT and MAPK/ERK pathways described earlier. Following ligand binding to an

extracellular receptor, kinases transmit signals to the cell interior that stimulates activation of the pathway. The small molecule targeted agents turn off or inhibit these pathways by inhibiting the adenosine triphosphate (ATP) binding domain of the kinases.[25] Most of the approved kinase inhibitors inhibit more than one kinase. The binding to multiple kinases typically leads to off-target effects or toxicities; some toxicities are attributed to specific kinase families. For example, the VEGF family is associated with hypertension, poor wound healing, and proteinuria. Although most inhibitors are given orally continuously for months to years, their anticancer activity is typically limited by the development of resistance. Before initiation of therapy, some targeted drugs require identification of the target within the cancer with a companion or complementary diagnostic test.

ALK Inhibitors

Crizotinib

Crizotinib binds to the ATP intracellular domain of activated anaplastic lymphoma kinase (ALK), thereby inhibiting phosphorylation and subsequent downstream signaling. ALK rearrangements were first identified in large cell lymphomas and later in NSCLC. In NSCLC, the most common rearrangement involves inversion of chromosome 2p that is primarily fused to the echinoderm microtubule-like protein 4 (EML4), which forms the ALK-EML4 oncogene fusion protein. This rearrangement leads to the activation of downstream signaling pathways and inhibition of apoptosis.[26] ALK-EML4 has a higher prevalence in younger patients, never or light smokers, and adenocarcinoma histology. Crizotinib also inhibits other kinases, such as ROS1, RON, and MET. Crizotinib is approved for the treatment of patients with locally advanced or metastatic NSCLC that is ALK- or ROS1-positive as detected by an FDA-approved test.

The most common toxicities reported in patients taking crizotinib include nausea, vomiting, diarrhea, constipation, fatigue, and elevated transaminases. Visual disorders occur in about half of patients and usually occur within the first weeks of therapy. Edema is also commonly seen and is most likely attributed to the inhibition of MET. Crizotinib has been associated with interstitial lung disease/pneumonitis, hepatotoxicity, QT interval prolongation, and bradycardia.

Many patients with ALK-positive NSCLC initially respond to crizotinib, but most patients will develop resistance possibly related to the development of brain metastases or the development of genetic alterations in ALK. The L1196M

mutation has been recently identified as a mechanism of crizotinib resistance.

Alectinib, Brigatinib, and Ceritinib

Alectinib, brigatinib, and ceritinib are second-generation ALK inhibitors that are approved for the treatment of patients with metastatic ALK-positive NSCLC. Similar to crizotinib, these agents inhibit autophosphorylation of ALK and subsequent downstream signaling. In addition to ALK, ceritinib also inhibits insulin-like growth factor 1 receptor (IGF-1R), although to a lesser extent.[27]

Toxicities that are seen with both alectinib and ceritinib include fatigue, bradycardia, and hepatotoxicity. Additional adverse effects seen in patients taking alectinib include anemia, constipation, edema, and myalgia. Brigatinib has been associated with pulmonary toxicities and bradycardia. Patients taking ceritinib should be monitored for QT interval prolongation, gastrointestinal toxicity, pancreatitis, and hyperglycemia. Visual disturbances have been reported with second-generation ALK inhibitors, although to a much lesser extent. While crizotinib and brigatinib may be taken without regard to food, alectinib should be taken with food. Of note, ceritinib was previously recommended at a higher dose administered on an empty stomach but the currently approved dose is lower and is to be taken with food to improve gastrointestinal tolerability. To decrease the risk of early onset pulmonary toxicities, a dose escalation approach must be used for brigatinib.

Lorlatinib

A third-generation ALK- and ROS1-inhibitor, lorlatinib, has demonstrated activity following progression on one or more ALK inhibitors.[28] Lorlatinib is approved for ALK-positive NSCLC. Similar to other agents in this category, lorlatinib is associated with hepatotoxicity and interstitial lung disease/pneumonitis. CNS toxicities, hyperlipidemia, and atrioventricular block have also been reported.

BCL-2 Inhibitor

Venetoclax is a selective inhibitor of B-cell lymphoma-2 (BCL-2), an antiapoptotic protein overexpressed in CLL. Permeabilization of the mitochondrial membrane, with the help of mediators BAX and BAK, is last step in the apoptosis pathway. BCL2 constrains BAX and BAK resulting in CLL cells resistant to apoptosis.[29] Venetoclax binds directly to the BCL-2 protein restoring the apoptotic process. It is approved for the treatment of patients with CLL,

small lymphocytic lymphoma, and newly diagnosed AML in adults who are age 75 years or older. Reported toxicities associated with venetoclax include myelosuppression, fatigue, diarrhea, cough, and upper respiratory tract infection. To reduce the risk of TLS, a weekly dose escalation over the first 5 weeks is required and patients should receive antihyperuricemic agents and hydration. Oral administration of venetoclax should be with food.

BCR-ABL Inhibitors

Imatinib

Imatinib is a selective inhibitor of the Breakpoint Cluster Region-Abelson (BCR-ABL) fusion gene, the product of the Philadelphia chromosome. The Philadelphia chromosome is the hallmark finding of CML and it is a translocation of genetic material between chromosomes 9 and 22. Imatinib binds to the kinase-binding site of the BCR-ABL gene, competitively blocking access to ATP. This prevents tyrosine-kinase phosphorylation of the gene and downstream activation of cellular proliferation. An additional effect of imatinib is its ability to inhibit stem-cell factor receptor (KIT) and platelet-derived growth factor receptor (PDGFR).

Imatinib is a standard treatment option for newly diagnosed Philadelphia chromosome–positive (Ph^+) CML and for gastrointestinal stromal tumors (GIST). A major advantage of imatinib is that it can eliminate the Philadelphia chromosome, resulting in cytogenetic responses (ie, elimination of the genetic defect). Imatinib and other BCR-ABL inhibitors are further discussed in Chapter 152, “Chronic Leukemias.” Imatinib is also approved for the treatment of Ph^+ALL and other rare diseases.

Potential serious adverse events observed with imatinib include fluid retention and rash. Severe fluid retention (ie, pleural effusion, pericardial effusion, and ascites) occurs in fewer than 10% of patients taking imatinib, but patients should be monitored regularly for early signs and symptoms of fluid retention and instructed to call their health professionals when symptoms first develop. A rash may require early intervention because Stevens-Johnson syndrome has been reported.

Dasatinib, Nilotinib, and Bosutinib

These targeted drugs are next-generation kinase inhibitors that share the same binding site on the BCR-ABL kinase ATP-binding domain with imatinib. These

inhibitors maintain clinical activity in patients with CML with some mutations in the BCR-ABL binding site that confer imatinib resistance, but none of these inhibitors are active against the genetic alteration identified as T315I. Dasatinib is approved for the treatment of Ph^+CML and Ph^+ALL. Nilotinib and bosutinib are approved for the treatment of Ph^+CML. Both bosutinib and dasatinib also inhibit a family of kinases called sarcoma (Src) kinases that are believed to mediate cellular differentiation, proliferation, and survival; Src kinases have been implicated in modulating multiple oncogenic signal transduction pathways.[30]

These inhibitors have a toxicity profile similar to that of imatinib with myelosuppression, nausea, vomiting, headache, and fluid retention being commonly reported. Bosutinib does not inhibit KIT or PDGFR, which may account for its reported decrease in the incidence of myelosuppression.[30]

Ponatinib

As mentioned earlier, the T315I mutation, often referred to as the gatekeeper mutation, confers resistance to the above BCR-ABL inhibitors. Ponatinib was developed with a computational chemistry-based approach to inhibit this mutated conformation of BCR-ABL and provide an effective treatment for this traditionally resistant tumor.[31] Ponatinib is also approved for the treatment of Ph^+ALL that is resistant or intolerant to prior therapy. Common toxicities are similar to other BCL-ABL inhibitors, such as hypertension, rash, headache, constipation, fever, and nausea. Arterial thrombosis and hepatotoxicity have also been observed.

BRAF Inhibitors

BRAF is mutated in a variety of solid tumors with most mutations occurring at codon 600. This codon is in the activation loop of BRAF and increases downstream activity at MEK then ERK, which results in proliferation and survival of cancer cells. BRAF mutations occur in up to 50% of melanomas. The most common mutations are the V600E mutation, which replaces valine with glutamic acid at codon 600 and is seen in about 80% of BRAF mutated melanomas and the V600K mutation, which replaces valine with lysine at this codon and occurs in about 8% of BRAF mutated melanomas. Dabrafenib, encorafenib, and vemurafenib inhibit BRAF V600, thereby blocking the MAPK pathway in BRAF-mutated cells. Combination therapy with a BRAF and MEK inhibitor has been associated with improved outcomes in melanoma so doublet

therapy is given in clinical practice: dabrafenib with trametinib, encorafenib with binimetinib, and vemurafenib with cobimetinib. Dabrafenib is approved for V600E and V600K mutated melanoma, V600E NSCLC, and V600E anaplastic thyroid cancer. Vemurafenib is approved for V600E melanoma and V600 mutated Erdheim-Chester disease. Encorafenib is approved for V600E and V600K melanoma. Toxicities associated with all BRAF inhibitors either as monotherapy or in combination with a MEK inhibitor include uveitis, arthralgia, fatigue, and nausea. Patients should be monitored for the development of new cutaneous malignancies and noncutaneous squamous cell carcinoma that have been associated with dabrafenib-, encorafenib- and vemurafenib-induced paradoxical activation of the MAPK pathway.[32] Hand-foot skin reaction (HFSR) and pyrexia are commonly seen with dabrafenib, whereas QT prolongation is more commonly reported with encorafenib and vemurafenib. Vemurafenib is also associated with severe dermatologic reactions and photosensitivity.

BTK Inhibitors

Bruton's tyrosine kinase (BTK) is involved in the B-cell receptor (BCR) signaling pathway that leads to B-cell proliferation and differentiation upon its activation. In B-cell malignancies, the BCR signaling pathway is thought to promote disease progression, although the exact mechanism of BCR stimulation has not been determined. Ibrutinib forms an irreversible covalent bond with a cysteine residue of BTK resulting in the inhibition of malignant B-cell proliferation and survival.[33] Ibrutinib is approved for the treatment of the following B-cell malignancies: Waldenstrom's macroglobulinemia; mantle cell lymphoma; marginal zone lymphoma; and CLL. Patients should be monitored for hemorrhage, infections, cytopenias, atrial fibrillation, and TLS. Additional common toxicities include diarrhea, fatigue, musculoskeletal pain, nausea, and rash. Acalabrutinib is a second generation, irreversible BTK inhibitor that is approved for mantle cell lymphoma. Compared to ibrutinib, acalabrutinib is more selective and does not inhibit off targets such as EGFR.

CDK Inhibitors

As discussed earlier in this chapter, CDKs play an important role in cell cycle progression. Specifically, CDK 4/6 and cyclin D1 regulate transition from the G_1 phase to the S phase by phosphorylating the retinoblastoma protein (pRb). Palbociclib, ribociclib, and abemaciclib inhibit CDK 4/6, resulting in the

blockade of pRb hyperphosphorylation and ultimately G_1 arrest.[34] In breast cancer, it has been demonstrated that cyclin D1 expression and subsequent pRb phosphorylation can be maintained despite estrogen receptor (ER) antagonism. Therefore, inhibiting CDK 4/6 may overcome acquired resistance to hormonal therapy observed in ER-positive breast cancer.[35]

Palbociclib, ribociclib, and abemaciclib are approved for use in ER-positive, HER2-negative advanced or metastatic breast cancer in combination with an AI in postmenopausal women. Palbociclib and abemaciclib are also approved in combination with fulvestrant after failure of endocrine therapy. Patients receiving these agents should be monitored for hematologic toxicities, infections, and pulmonary embolisms. Additionally, ribociclib has been associated with concentration-dependent QT prolongation so electrocardiographs (ECGs) and electrolytes should be regularly monitored.

DNA Methyltransferase Inhibitors

Azacitidine and decitabine are approved for the treatment of patients with myelodysplastic syndrome (MDS), a disorder of hematopoietic cell maturation that can progress to AML. These inhibitors are nucleoside analogues that demonstrate dose-dependent effects. At lower doses, these analogues exert their effects by directly incorporating into DNA and inhibiting DNMT, which leads to cellular differentiation and apoptosis.[8]At higher doses, these agents might cause the formation of covalent adducts between DNMT and active drug being incorporated into DNA, particularly in cells actively dividing. Hypomethylation also appears to normalize the function of genes that control cell differentiation and proliferation, promoting normal cell maturation.[36]

These inhibitors slow the progression of MDS to AML, reduce transfusion requirements, and allow for the improvement of normal hematopoiesis over time. The primary toxicity is myelosuppression, particularly during early phases of treatment as the malignant clone driving the MDS is cleared from the bone marrow and normal hematopoiesis is slowly restored. As a result, infections occur frequently.

EGFR Inhibitors

Erlotinib

Erlotinib is an oral first-generation selective EGFR kinase inhibitor. By

competing with ATP for its binding site on the EGFR kinase cytosolic domain, it blocks intracellular downstream signaling and ultimately interferes with the proliferation and growth of cancer cells. Erlotinib is approved for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. Erlotinib is also approved for use in pancreatic cancer in combination with gemcitabine.

The most common adverse events that occur with erlotinib result from the abundance of EGFR in skin and mucosa and include acneiform rash and diarrhea.[37] Some studies suggest that the development of a rash may be predictive of a response to therapy and correlates with clinical benefit.[38] Interstitial lung disease is a rare adverse event reported in patients taking erlotinib.

Afatinib and Dacomitinib

Unlike erlotinib which reversibly binds to EGFR, afatinib and dacomitinib irreversibly block all kinases of the ErbB family by covalently binding to the intracellular kinase domain, which subsequently inhibits tumor growth. Afatinib is approved for the treatment of patients with EGFR mutation-positive NSCLC and previously treated squamous NSCLC and dacomitinib is approved for the first-line treatment of patients with EGFR-positive metastatic NSCLC. Adverse events observed with afatinib and dacomitinib are similar to those seen with erlotinib.

Gefitinib

Gefitinib similarly blocks the promotion of the development of lung cancer cells with specific EGFR mutations (exon 19 deletions and exon 21 substitution). This inhibitor was initially approved in 2003, but it was subsequently restricted in 2005 when a confirmatory clinical trial failed to demonstrate survival advantages in an unselected population. In 2015, gefitinib was approved for the first-line treatment of metastatic NSCLC whose tumors harbor specific EGFR gene mutations. This approval was based on a clinical trial that demonstrated an improvement in response in this specific population, which was supported by a retrospective analysis of another trial.[39] Gefitinib has similar adverse events compared to other EGFR inhibitors, including diarrhea and skin reactions.

Lapatinib and Neratinib

Lapatinib is a 4-anilinoquinazoline kinase inhibitor that inhibits the intracellular

kinase domains of both EGFR (ErbB1) and HER2 (ErbB2). It has demonstrated clinical activity with capecitabine in patients with previously treated breast cancer whose tumors overexpress HER2. Lapatinib is also approved for use with letrozole in postmenopausal women for the treatment of hormone receptor–positive metastatic breast cancer that overexpresses HER2. Common adverse events include diarrhea, hepatotoxicity, rash, and QT interval prolongation. Two specific mutations observed in the HLA-DQA and HLA-DRB genes have been associated with an increased risk of hepatotoxicity.[40,41]

In addition to EGFR and HER2, neratinib irreversibly inhibits HER4 and is approved for HER2-positive breast cancer. Diarrhea is the most common toxicity associated with neratinib and antidiarrheal prophylaxis is recommended during the first two treatment cycles. Patients should be monitored for gastrointestinal toxicities, fatigue, dehydration, and hepatotoxicity.

Osimertinib

Osimertinib is approved for the treatment of patients with metastatic NSCLC whose tumors harbor EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test. It is also indicated for EGFR T790M mutation-positive NSCLC after disease progression on or after an EGFR inhibitor. The T790M mutation, referred to as the EGFR gatekeeper mutation, occurs in about 50% of patients who develop acquired resistance to first-line therapy with erlotinib or gefitinib.[31] Gastrointestinal and dermatologic toxicities are commonly reported with osimertinib. Serious adverse events include interstitial lung disease/pneumonitis, pneumonia, and pulmonary embolism.

FGFR Inhibitor

The fibroblast growth factor receptor (FGFR) pathway regulates numerous physiological processes including embryogenesis, wound healing, inflammation, and angiogenesis.[42] Alterations occur in approximately 7% of solid tumors, including urothelial carcinoma. Erdafitinib is an oral pan-FGFR inhibitor (FGFR1-4) that is approved for the treatment of patients with urothelial carcinoma and a susceptible FGFR3 or FGFR2 alteration. Serious ocular disorders have been reported with erdafitinib. Interestingly, elevated phosphate levels are a pharmacodynamic effect associated with erdafitinib and doses should be adjusted accordingly.

FLT3 Inhibitors

FMS-like tyrosine kinase-3 (FLT3) is one of the most common mutations in AML and is known to play a role in the normal growth and differentiation of hematopoietic precursor cells. FLT3 mutations can be divided into internal tandem duplications (ITD mutations) or point mutations of the activation loop of the tyrosine kinase domain (TKD mutations).

Midostaurin inhibits multiple receptors including FLT3 mutant kinases ITD and TKD resulting in apoptosis of leukemic cells. It is indicated in combination with cytotoxic chemotherapy for the treatment of FLT3-positive AML. Other indications include mast cell leukemia and systemic mastocytosis. Adverse events reported with midostaurin include pulmonary toxicity, febrile neutropenia, gastrointestinal toxicities, fatigue, and hyperglycemia.

Similarly, gilteritinib inhibits multiple receptors including FLT3. It is indicated for the treatment of adult patients who have relapsed or refractory AML with a FLT-3 mutation. Adverse events reported with gilteritinib include hepatotoxicity, fatigue, gastrointestinal toxicities, pneumonia, and rash. Both midostaurin and gilteritinib are oral agents; midostaurin should be administered with food, whereas gilteritinib may be administered without regard to food.

HDAC Inhibitors

Belinostat

The mechanism of HDAC inhibitors was discussed earlier in the chapter. Belinostat is an HDAC inhibitor that is approved for the treatment of relapsed or refractory peripheral T-cell lymphoma. The most common toxicities reported with belinostat include pyrexia, nausea, fatigue, and anemia.

Panobinostat

Panobinostat is an HDAC inhibitor that has been shown to improve progression-free survival with bortezomib and dexamethasone in patients with multiple myeloma who have received at least two prior regimens, including bortezomib and an immunomodulatory agent.[43] Since severe cardiac toxicities have been reported with panobinostat, an ECG and electrolytes should be monitored at baseline and during treatment. Nausea, vomiting, and severe diarrhea are often seen with panobinostat.

Romidepsin and Vorinostat

Similar to belinostat and panobinostat, romidepsin and vorinostat inhibit HDAC. Romidepsin is approved for the treatment of cutaneous or peripheral T-cell lymphoma who have received at least one prior therapy and vorinostat is approved for patients with cutaneous T-cell lymphoma who have received at least two prior therapies. Patients receiving romidepsin should be monitored for myelosuppression, ECG changes, and infections. Reactivation of DNA viruses, including EBV and hepatitis B virus (HBV), have been reported with romidepsin. Additional serious adverse events reported with vorinostat include venous thromboembolism (VTE), dose-related thrombocytopenia, and anemia.

Hedgehog Inhibitors

Sonidegib, vismodegib, and glasdegib are oral inhibitors of the Hedgehog signaling pathway that is abnormally activated in basal cell carcinoma, medulloblastoma, and leukemias. Through binding to smoothened (SMO) receptor, these agents prevent downstream signaling and activation of the Hedgehog pathway leading to the inhibition of tumor growth.

The Hedgehog pathway is essential for early embryogenesis. Therefore, sonidegib, vismodegib, and glasdegib can cause embryotoxicity, fetotoxicity, and teratogenicity in animals. The approved labeling for these drugs contains specific recommendations regarding contraception for women of child-bearing potential and for men with a pregnant partner or a female partner of child-bearing potential, as well as limitations regarding blood and sperm donation during treatment and for several months following the last dose.

Vismodegib is approved for metastatic or locally advanced basal cell carcinoma, while sonidegib is approved only for locally advanced disease. Vismodegib is generally well tolerated and toxicities include muscle spasm, alopecia, dysgeusia, fatigue, and nausea. Sonidegib is associated with an increased risk of serious musculoskeletal toxicities and the probability of developing this adverse event appears to rise with increasing sonidegib exposure. Grades 3 and 4 serum lipase and creatine kinase elevations have also been reported. Sonidegib uniquely has a very long elimination half-life of 28 days compared to vismodegib and other small molecular targeted agents.

Glasdegib is indicated for the treatment of newly diagnosed AML in patients 75 years of age or older in combination with low-dose cytarabine. Similar to vismodegib and sonidegib, muscle spasms and fatigue have been reported with glasdegib. QT prolongation may occur so ECGs and electrolytes should be monitored while on treatment.

IDH Inhibitors

As discussed earlier in the chapter, IDH mutations are associated with impaired cellular differentiation in about 15% to 20% of patients with AML. Ivosidenib and enasidenib are approved for the treatment of AML with a susceptible IDH1 or IDH2 mutation, respectively. Nausea, vomiting, diarrhea, and elevated serum bilirubin have been reported with enasidenib. Common toxicities associated with ivosidenib include nausea, mucositis, rash, and leukocytosis. Warnings for ivosidenib include QT prolongation and Guillian-Barré syndrome. Differentiation syndrome, a type of cytokine release syndrome (CRS) previously known as retinoic acid syndrome, is a potentially fatal complication associated with both IDH inhibitors. Symptoms including fever, respiratory complications, edema, and multi-organ dysfunction require corticosteroids and hemodynamic monitoring.

JAK Inhibitor

Ruxolitinib is an oral inhibitor of JAK1 and JAK2 of the JAK-STAT signaling pathway; these kinases are involved in the regulation of blood and immunologic functioning. In myelofibrosis and polycythemia vera (PCV), JAK1 and JAK2 activity is dysregulated. Ruxolitinib has been shown to modulate the affected JAK1 and JAK2 activity resulting in clinical responses and symptomatic improvement.[44] Approved indications for ruxolitinib include the treatment of intermediate- or high-risk myelofibrosis and the treatment of PCV in patients who have had an inadequate response to or are intolerant of hydroxyurea. The most common toxicities include thrombocytopenia, anemia, bruising, dizziness, and headache.

MEK Inhibitors

Reported resistance mechanisms of the BRAF inhibitors dabrafenib, encorafenib, and vemurafenib include reactivation of the MAPK pathway. The combination of BRAF and MEK inhibition has demonstrated delayed resistance and decreased incidence of secondary cancers. MEK inhibitors, including binimetinib, cobimetinib, and trametinib, are given in combination with a BRAF inhibitor and their indications in BRAF V600 mutated tumors are discussed above. Severe toxicities associated with MEK inhibitors include cardiomyopathy and hemorrhage. Rhabdomyolysis and hepatotoxicity have been reported with binimetinib and cobimetinib. Additionally, VTE and interstitial lung disease

have been associated with binimetinib and trametinib.

mTOR Inhibitors

Temsirolimus

Temsirolimus and its primary active metabolite, sirolimus, bind to the intracellular protein 12-kilodalton FK506 binding protein (FKBP-12) and this protein–drug complex inhibits mTOR by blocking its kinase activity.[45] mTOR inhibition suppresses the production of proteins that regulate progression through the cell cycle resulting in G_1-phase arrest. Temsirolimus is approved for the treatment of advanced renal cell carcinoma.

The most common adverse reactions with temsirolimus are rash, asthenia, mucositis, nausea, edema, and anorexia. Infusion reactions may occur and pretreatment with an antihistamine is recommended. Metabolic abnormalities are common with temsirolimus including hyperglycemia and hyperlipidemia. Rare but potentially serious adverse events include interstitial lung disease, immunosuppression, and renal failure.

Everolimus

Similar to temsirolimus, everolimus is an mTOR inhibitor that reduces protein synthesis and cell proliferation by binding to FKBP-12. Everolimus has the following indications: advanced renal cell carcinoma; hormone receptor–positive, HER2-negative breast cancer with exemestane in postmenopausal women; subependymal giant cell astrocytoma with tubular sclerosis complex (TSC); renal angiomyolipoma with TSC; and pancreatic, gastrointestinal, and lung neuroendocrine tumors. Dosage forms for everolimus include traditional oral tablets and tablets for oral suspension, but it is important to note that the indications differ depending on formulation. Stomatitis is one of the most common toxicities with everolimus while other adverse reactions are similar to those of temsirolimus.

Multikinase Inhibitors

Axitinib, Pazopanib, Sorafenib, and Sunitinib

Several kinase inhibitors such as axitinib, pazopanib, sorafenib, and sunitinib block multiple kinases. Sunitinib and sorafenib inhibit multiple growth factor receptors (VEGFR2 and PDGFR), cell surface proteins (KIT), and cytokine

receptors (FLT3) and, thus, disrupt multiple aberrant intracellular signaling pathways. In addition, sorafenib inhibits Raf, which is part of the MAPK signaling pathway. Sunitinib is approved for GIST, pancreatic neuroendocrine tumors, and renal cell carcinoma and sorafenib is approved for unresectable hepatocellular carcinoma, advanced renal cell carcinoma, and differentiated thyroid carcinoma refractory to radioactive iodine treatment.

Pazopanib and axitinib are second-generation inhibitors. Pazopanib inhibits all VEGFR kinases with additional activity against KIT and PDGFR. Axitinib has enhanced potency and selectivity to all VEGFR kinases with minor activity against PDGFR and KIT. Pazopanib is approved for the treatment of advanced renal cell carcinoma and axitinib is approved for the same indication after failure of one prior systemic therapy. Pazopanib has an additional indication for patients with advanced soft tissue sarcoma who have received prior chemotherapy.

Gastrointestinal toxicities such as diarrhea are common with these agents, as are rash and fatigue. Patients should also be monitored for the development of thyroid dysfunction and hepatotoxicity. All of the multikinase agents inhibit VEGFR and are therefore associated with class toxicities including hypertension, proteinuria, wound healing complications, bleeding, VTE, and gastrointestinal perforation.

Cabozantinib

Cabozantinib is a small molecule inhibitor of numerous receptor kinases, most importantly RET (rearranged during transfection), VEGFR2, and MET membrane receptor. MET is required for several important processes during embryogenesis (eg, angiogenesis) and leads to abnormal growth and proliferation of several tumors. Medullary thyroid cancers express mutated RET as well as VEGFR2 and MET. Cabozantinib is approved for the treatment of metastatic medullary thyroid cancer, renal cell carcinoma, and hepatocellular carcinoma. Toxicities reported in clinical trials included diarrhea, HFSR, electrolyte abnormalities, transaminitis, and stomatitis. Of note, cabozantinib is available as both an oral capsule and tablet which are not bioequivalent and therefore not interchangeable.

Lenvatinib

Lenvatinib primarily inhibits VEGFR1, -2, and -3, but it can also inhibit other kinases including FGFR, PDGFR, KIT, and RET. Lenvatinib is approved as a single agent for the treatment of radioactive iodine-refractory differentiated thyroid cancer, unresectable hepatocellular carcinoma, and in combination with

everolimus for the treatment of renal cell carcinoma. Common toxicities seen with lenvatinib include fatigue, diarrhea, stomatitis, and HFSR.

Regorafenib

Regorafenib is a multikinase inhibitor that blocks the activity of several protein kinases, including those involved in the regulation of tumor angiogenesis (VEGFR1, -2, and -3), oncogenes and downstream targets (KIT, RET, RAF1, and BRAF), as well as PDGFR and FGFR. Because many of these targets are important in colon cancer and GIST, regorafenib has demonstrated activity in these settings. FDA-approved indications include colorectal cancer, GIST, and hepatocellular carcinoma. Serious adverse events reported with regorafenib include hepatotoxicity and reversible posterior leukoencephalopathy syndrome. Common adverse reactions with regorafenib include asthenia, mucositis, gastrointestinal toxicities, and HFSR. Regorafenib should be given orally with a low-fat evening meal, as the toxicities appear minimized when given at night.

Vandetanib

Vandetanib is a small molecule inhibitor of RET, VEGFR2 and -3, and EGFR.[46] It is approved for the treatment of metastatic medullary thyroid cancer. Toxicities observed with vandetanib include diarrhea and rash. Vandetanib can prolong the QT interval and cases of Torsades de pointes and sudden death have been reported. Because of this risk, vandetanib is only available through a REMS program where prescribers and pharmacies must be certified through the program prior to prescribing or dispensing vandetanib.

TRK Inhibitor

Chromosomal rearrangements involving in-frame fusions of NTRK (neurotrophic receptor tyrosine kinase) genes with various partners can result in constitutively activated chimeric tropomyosin receptor kinase (TRK) fusion proteins that can act as oncogenic drivers, promoting cell proliferation and survival in tumor cell lines. Larotrectinib is an inhibitor of TRK proteins. It is indicated for the treatment of adult and pediatric patients with solid tumors that have a NTRK-gene fusion. Adverse reactions include fatigue, nausea, dizziness, vomiting, transaminitis, cough, constipation, and diarrhea. Warnings with larotrectinib include neurotoxicity and hepatotoxicity.

PARP Inhibitors

PARP is essential for the repair of single-stranded DNA breaks through the base-excision-repair pathway. Tumors with breast cancer gene 1 (BRCA1) or BRCA2 mutations are highly sensitive to the blockade of single-strand DNA breaks (through PARP inhibition), because they exhibit a compromised ability to repair double-strand DNA breaks. This concept is known as *synthetic lethality* and occurs when there is a lethal synergy between two nonlethal events. PARP inhibitors induce synthetic lethality in BRCA1 and BRCA2 deficient tumor cells.[47,48] Four PARP inhibitors are currently available and their corresponding FDA-approved indications are as follows: niraparib is approved for ovarian, fallopian tube, or primary peritoneal cancers; olaparib is approved for BRCA-mutated, HER2-negative breast cancer, and BRCA-mutated ovarian cancer; rucaparib is approved for BRCA-mutated ovarian cancer; and talazoparib is approved for BRCA-mutated, HER2-negative locally advanced or metastatic breast cancer.

As a class, these agents are commonly associated with anemia, fatigue, and nausea. Secondary malignancies of MDS/AML have been reported. Olaparib and rucaparib are commonly associated with a serum creatinine increase which does not appear to have clinical significance. Niraparib is more often associated with thrombocytopenia and hypertension, whereas transaminase elevation is most commonly seen with rucaparib and talazoparib. Talazoparib is also associated with myelosuppression. Of note, olaparib is available as both an oral capsule and tablet which are not bioequivalent and therefore not interchangeable.

PI3K Inhibitors

Malignant B-cell proliferation and survival depend on PI3K signaling. The p110δ isoform is highly expressed in malignant lymphoid B-cells and plays a direct role in activation of the PI3K pathway. Idelalisib inhibits p110δ*;* duvelisisb inhibits p110δ and p110γ; and copanlisib preferentially targets p110α and p110δ.[49] Idelalisib is an oral agent with the following indications: the treatment of relapsed CLL in combination with rituximab; follicular B-cell NHL; and small lymphocytic lymphoma. Duvelisib is an oral agent indicated for relapsed or refractory CLL and small lymphocytic lymphoma and copanlisib is an intravenous agent indicated for relapsed follicular lymphoma. In solid tumors, mutations in the p110α subunit of PI3K result in dysregulation of the PI3K/mTOR pathway.[50] Alpelisib, an oral PI3Kα-selective inhibitor, is indicated in combination with fulvestrant for PIK3CA-mutated, hormone receptor–

positive, HER2-negative breast cancer.

Serious adverse effects associated with these agents include infections, pneumonitis, and diarrhea/colitis. Hepatotoxicity has been reported with idelalisib and duvelisib, whereas cutaneous reactions are more common with alpelisib, copanlisib, and duvelisib. Both alpelisib and copanlisib have been associated with hyperglycemia but hypertension is unique to copanlisib.

Proteasome Inhibitors

The proteasome is an enzyme complex that is responsible for degrading proteins that control the cell cycle. Some of the proteins degraded by proteasomes regulate critical functions for cancer growth, such as regulation of the cell cycle, transcription factors, apoptosis, angiogenesis, and cell adhesion.

Bortezomib

Bortezomib reversibly inhibits the 26S proteasome resulting in accumulation of IκB, an inhibitor of the major transcription factor nuclear factor κB (NF-κB). NF-κB induces transcription of genes that block cell death pathways and promote cell proliferation. Its activity depends on its release from its inhibitory partner protein, IκB, in the cytoplasm and its move to the nucleus. When IκB fails to degrade, through the actions of bortezomib, NF-κB remains in the cytoplasm, preventing it from transcribing the genes that promote cancer growth. Bortezomib is approved for the treatment of multiple myeloma and mantle cell lymphoma.

The most commonly reported toxicities with bortezomib include fatigue, nausea, diarrhea, thrombocytopenia, and fever. Peripheral neuropathy may develop or worsen with the use of bortezomib. Subcutaneous administration of bortezomib has been associated with a lower incidence of severe peripheral neuropathy when compared with intravenous administration. Caution should be used when treating patients with existing heart disease as cardiac failure has been reported. Patients should also be monitored for hypotension and acute respiratory syndrome. At least 72 hours should elapse between consecutive doses of bortezomib to minimize cumulative toxicity by permitting the restoration of proteasome function between doses. Proteasome inhibitors are associated with herpes reactivation so antiviral prophylaxis should be considered.

Carfilzomib

Carfilzomib is a second-generation, irreversible inhibitor of the 20S proteasome and is approved for relapsed or refractory multiple myeloma. As a result of its irreversible inhibition, carfilzomib produces more sustained inhibition of the proteasome. Carfilzomib is a more potent and selective inhibitor of the chymotrypsin-like activity of the proteasome and immunoproteasome and has been demonstrated to overcome bortezomib resistance in cell lines.[51]

Ixazomib

Ixazomib is an oral 20S proteasome inhibitor approved with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma. Common adverse reactions are gastrointestinal toxicity, thrombocytopenia, peripheral neuropathy, peripheral edema, and back pain. Ixazomib has a unique administration schedule for an oral agent (given on days 1, 8, and 15 of a 28-day cycle) and should be taken on an empty stomach.

TARGETED AGENTS: MONOCLONAL ANTIBODIES

7 Biologic therapies are a diverse group of agents that include cytokines, mAbs, and growth factors. Biologics are generally large and complex molecules that are manufactured in a microorganism or other living system. The mAb is the most common biologic therapy available to treat patients with solid tumors and hematologic malignancies.

Biosimilars

Due to the complex process associated with manufacturing biologics, “generic” biologic products are not approved in the same manner as small molecule pharmaceuticals. Unlike generic small molecule agents that must demonstrate bioequivalence to a branded product, biosimilars must be “highly similar” to the reference product. Biosimilars must demonstrate that no clinically meaningful differences in safety, purity, and potency exist between it and the reference product. Some biosimilar agents undergo additional evaluation and testing to meet the requirements of an “interchangeable product.” An interchangeable product is expected to produce the same clinical result as the reference product and can generally be substituted without consulting the prescriber.[52]

Monoclonal Antibodies

A mAb is designed to target a pathway critical for the survival and growth of cancer cells resulting in improved outcomes and minimal toxicities. The mAb can bind to either the extracellular receptor or its natural ligand and prevent the activation of downstream intracellular signaling. mAbs are also considered targeted agents (eg, mAbs against EGFR or HER2) or immunotherapies (eg, immune checkpoint inhibitors).

Each mAb consists of immunoglobulin sequences that are known to recognize a specific antigen or protein on the surface of cells. There are five classes of immunoglobulins, but IgG is the most commonly used therapeutically. Similar to endogenous antibodies, the Fab portion is composed of heavy and light chains that are responsible for binding to antigens and the constant region determines the effector function of the antibody. The mAb may be naked (unconjugated) or conjugated to a toxin (immunotoxin), chemotherapy agent (antibody-drug conjugate), or radioactive particle (radioimmunoconjugate).

In 2017, the standard nomenclature for mAbs was revised. As before, mAbs receive a random prefix, an infix indicating the target, and the suffix “-mab.” However, the prior requirement to include the source (ie, -o-, -u-, -xi-, and -zu- to indicate murine, human, chimeric, and humanized, respectively) has been removed. If the product is conjugated, a separate word is added to identify the toxin, chemotherapy, or radioactive particle. For example, the antibody-drug conjugate (ADC) of trastuzumab and mertansine is named ado-trastuzumab emtansine. The nonproprietary name of a monoclonal antibody consists of a core name (eg, bevacizumab or trastuzumab) and a distinguishing suffix composed of four lowercase letters (eg, trastuzumab-dkst).

The first mAbs used in humans were murine, but most of the antibodies used today are humanized or human. These agents differ in the amount of foreign component. Hypersensitivity and infusion-related reactions, with or without the development of antiproduct antibodies (APA), are generally greatest with murine antibodies and least with humanized antibodies. The severity of these reactions can range from mild (eg, fever, chills, nausea, and rash) to severe, life-threatening anaphylaxis with cardiopulmonary collapse. Patients with a hypersensitivity or infusion-related reaction may also experience chest or back pain during the infusion. Patients with circulating cancer cells in the bloodstream are at highest risk for more severe reactions. Patients must be monitored closely during infusion. The reactions tend to be more severe with the initial few treatments and subside with subsequent infusions. Some mAbs require premedication, including antihistamines, acetaminophen, or steroids, to

minimize hypersensitivity reactions. Recommended infusion rates may be longer for the initial dose, with incremental increases as tolerated. For patients experiencing signs or symptoms of infusion-related reactions, the infusion should be interrupted and prompt treatment with antihistamines, corticosteroids, and other supportive measures should be initiated. Other adverse events are typically determined by the selectivity of the target antigen. mAbs against antigens found on normal and cancer cells are expected to have increased toxicity compared with tumor-specific antigens found only on tumor tissues.

Unconjugated mAbs that target antigens on the cell surface of cancer cells may induce death of cancer cells by several mechanisms. These mAbs could directly mediate cell killing through CDC, ADCC, or inhibiting intracellular signaling. CDC occurs when the Fc portion of the antibody activates the complement system, leading to tumor cell lysis. ADCC occurs when effector cells that contain Fc receptors bind to the Fc portion of the antibody and either lyses or phagocytizes the antibody-containing cell. Natural killer cells, monocytes, and macrophages are all capable of mediating ADCC. Finally, antibody binding may result in the transmission of signals that induce apoptosis or programmed cell death in the targeted cell.

Immunoconjugates deliver a payload, typically a chemotherapy agent, toxin, or radioactive particle to a cell targeted by the antibody. After the antibody binds the target antigen, the payload is internalized by the target cell and kills cancer cells through traditional mechanisms of action. In addition to killing the target cell, radioimmunoconjugates are capable of killing antigen-negative cancer cells, sometimes termed the bystander effect. Theoretically, immunoconjugates deliver therapy to specific sites of disease while limiting systemic exposure to the chemotherapy, radiation, or toxin. The mAb might also contribute to the observed anticancer effects.

Monoclonal Antibodies That Target CD20

Rituximab

Rituximab is a chimeric antibody directed against the cluster of differentiation (CD) 20 antigen found on the surface of normal and cancerous B-cells. The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes and the Fc domain recruits immune effector functions to mediate B-cell lysis. Possible explanations for its anticancer effect include CDC and ADCC of malignant B-cells and possibly a direct apoptotic effect.

Rituximab is approved for the treatment of low-grade or follicular, CD20-

positive, B-cell NHL in multiple settings and for the treatment of CD20-positive CLL with standard chemotherapy. Rituximab is also indicated for the treatment of a variety of immune-mediated diseases, including rheumatoid arthritis, granulomatosis with polyangiitis, and microscopic polyangiitis. In combination with hyaluronidase, rituximab is indicated for follicular lymphoma, diffuse large B-cell lymphoma, and CLL. Rituximab is administered as an intravenous infusion but rituximab with hyaluronidase is administered as a subcutaneous injection. All patients must first receive at least one full dose of a rituximab product by intravenous infusion without experiencing severe adverse reactions before starting treatment with rituximab and hyaluronidase.

Most of the infusion-related reactions associated with rituximab occur during the first infusion and are components of an infusion-related complex secondary to the amount of circulating B-cells. After the first infusion, the incidence and the severity of these reactions decrease dramatically. Premedication and additional supportive care medications may be required depending on indication. The most common events with the infusion-related complex are transient fever, chills, nausea, asthenia, and headache. Additionally, rituximab may cause HBV reactivation and should not be administered in patients with severe, active infections.

Obinutuzumab

Obinutuzumab is a type II humanized anti-CD20 mAb approved for CLL and follicular lymphoma. When compared with the type I anti-CD20 antibodies such as rituximab, type II agents exhibit a different elbow hinge angle and therefore bind CD20 in a different orientation. Furthermore, the Fc portion of obinutuzumab has been glycoengineered to reduce fucosylation resulting in improved receptor affinity and enhanced ADCC potency.[53,54]

Adverse events associated with obinutuzumab include infusion reactions, myelosuppression, nausea, and diarrhea. HBV reactivation and Progressive Multifocal Leukoencephalopathy (PML) have also been reported with obinutuzumab.

Ofatumumab

Ofatumumab is a type I human mAb that also targets the CD20 antigen. Its mechanism of action is similar to that of rituximab, but ofatumumab targets a different epitope than rituximab, has greater affinity for the antigen, and dissociates from the epitope slower than rituximab.[55] Specifically, ofatumumab

binds to two regions of the CD20 antigen, the small extracellular loop and the N-terminal region of the large extracellular loop. As a result, anticancer activity has been demonstrated in patients who have progressed on rituximab in a variety of B-cell cancers.[55]

Ofatumumab is approved for the treatment of CLL. Adverse reactions are similar to rituximab with fewer infusion-related reactions and a higher rate of infectious complications.

Monoclonal Antibodies That Target CD52

Alemtuzumab is a recombinant humanized mAb that is directed against CD52. CD52 is expressed on the surface of B and T lymphocytes, natural killer cells, monocytes, and macrophages. Its anticancer activity comes from binding to the CD52 antigen present on leukemic lymphocytes and inducing cell lysis and death. Alemtuzumab is indicated as a single agent for the treatment of B-cell CLL.

Alemtuzumab is associated with severe infusion-related reactions, hematologic toxicity, and opportunistic infections. Hematologic toxicity consisting of severe prolonged neutropenia and thrombocytopenia occurs in most patients. Health professionals should monitor complete blood counts prior to each dose to determine the need for dose modification. Since CD52 is expressed on lymphocytes, alemtuzumab can induce profound lymphopenia including a decrease in CD4 and CD8 counts. Patients should receive prophylaxis for *Pneumocystis jiroveci* pneumonia and herpes virus, which should be continued for a minimum of 2 months after completing alemtuzumab therapy or until recovery of CD4 counts. Alemtuzumab is only available through a restricted distribution REMS program to mitigate the risks of autoimmune conditions, infusion reactions, and malignancies associated with the use of alemtuzumab.

Monoclonal Antibodies That Target CD38

Daratumumab is a mAb that inhibits CD38 expressing tumor cells by inducing apoptosis directly through Fc-mediated cross-linking and immune-mediated tumor cell lysis through CDC, ADCC, and antibody dependent cellular phagocytosis. Myeloid-derived suppressor cells and a subset of regulatory T-cells express CD38. Daratumumab is approved for the treatment of patients with multiple myeloma.

The most frequently reported adverse effects are infusion reactions, fatigue, nausea, back pain, pyrexia, cough, upper respiratory tract infection, and myelosuppression. Premedications (corticosteroid, antipyretic, and an antihistamine) and a postinfusion medication (corticosteroid) are recommended to prevent acute and delayed infusion reactions. Since daratumumab interferes with blood bank cross-matching, specifically with indirect antiglobulin tests, it is recommended that a type and screen be performed prior to treatment initiation. If a blood transfusion is necessary, inform the blood bank that the patient has received daratumumab.

Monoclonal Antibodies That Target Chemokine Receptor

Mogamulizumab-kpkc is a recombinant humanized IgG1 kappa mAb that targets CC chemokine receptor 4 (CCR4)–expressing cells. CC chemokine receptors are a subfamily of chemokine receptors that possess four cysteine residues; chemokines are chemoattractants that facilitate the migration of cells. CCR4 is involved in the trafficking of lymphocytes to various organs. Mogamulizumab-kpkc is indicated for relapsed or refractory mycosis fungoides or Sézary syndrome. The most common adverse reactions are rash, infusion-related reactions, fatigue, diarrhea, musculoskeletal pain, and upper respiratory tract infection.

Monoclonal Antibodies That Target GD2

Glycolipid GD2 is expressed primarily on the cell surface of neuroblastoma cells and on normal tissues including neurons and peripheral sensory nerve fibers.[56,57] The function of the GD2 carbohydrate antigen is not completely understood but is thought to play a role in the attachment of tumor cells to extracellular matrix proteins.[56] Dinutuximab is a chimeric mAb that binds GD2-inducing cell lysis through ADCC and CDC. This activity is thought to be enhanced when dinutuximab is given with granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-2.[57] Dinutuximab is approved to be given with GM-CSF, IL-2, and 13-cis-retinoic acid for the treatment of pediatric patients with high-risk neuroblastoma. Serious toxicities associated with dinutuximab include infections, infusion reactions, hypokalemia, hypotension, and capillary leak syndrome. Severe neuropathic pain occurs in most patients and intravenous opioids are required prior to, during, and immediately following administration.

Monoclonal Antibodies That Target PDGFR-α

PDGFR-α is overexpressed on cells of mesenchymal origin and on some tumor cells, including sarcomas. Binding of PDGF-AA and -BB ligands results in downstream signaling associated with cell differentiation, growth, and angiogenesis. Olaratumab binds to the PDGFR-α receptor, thereby preventing activation and signaling. Although approved for the treatment of patients with soft tissue sarcoma in combination with doxorubicin, a confirmatory study failed to demonstrate improved efficacy. Therefore, no new patients should be started on olaratumab outside of a clinical trial. Common toxicities associated with the combination include gastrointestinal adverse effects, neuropathy, pain, headache, and laboratory abnormalities. Infusion-related reactions are also reported so premedications are required.

Monoclonal Antibodies That Target SLAMF7

Elotuzumab is an IgG mAb directed against Signaling Lymphocytic Activation Molecule Family 7 (SLAMF7). SLAMF7 is expressed on multiple myeloma cells, natural killer cells, and other immune cells. The antitumor effects of elotuzumab are a result of ADCC and through blocking multiple myeloma and stromal cell interaction but it is not thought to induce CDC.[58] Elotuzumab is approved in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma. The most common adverse reactions reported include fatigue, diarrhea, constipation, pyrexia, peripheral neuropathy, decreased appetite, cough, and respiratory infections. Patients should also be monitored for infusion reactions, infections, second primary malignancies, and hepatotoxicity. Of note, elotuzumab can be detected in the serum protein electrophoresis and immunofixation assays of M-protein, which may interfere with the ability to assess complete response.

Monoclonal Antibodies That Target EGFR

Cetuximab

Cetuximab is a chimeric mAb that binds specifically to the extracellular domain of EGFR on both normal and cancer cells and competitively inhibits the binding of epidermal growth factor and other ligands, such as transforming growth factor-α. Binding of cetuximab to the EGFR inhibits cell growth, induces apoptosis, and inhibits VEGF production. Cetuximab is indicated for the

treatment of metastatic KRAS wild-type (ie, without mutation) colorectal cancer and for squamous cell head and neck cancer. Acneiform rash and skin reactions occur in most patients receiving cetuximab, as observed with other agents that inhibit EGFR.[38] Multiple follicular or pustular lesions generally appear within the first 2 weeks of therapy and usually resolve after cessation of treatment. Resolution can be slow, continuing beyond 28 days in nearly half of cases. In patients who develop a severe rash, dose modifications may be necessary. Interestingly, a trend for improved responses with increasing severity of skin reactions has been suggested but additional research is required to confirm this association.[38]

Panitumumab

Panitumumab, the first human mAb approved to treat cancer, is an IgG2 antibody that binds to the cell surface EGFR. It is approved to treat RAS wild-type metastatic colon cancer. Adverse reactions are similar to cetuximab, although severe reactions appear to be less common because panitumumab does not have a murine component.

Both cetuximab and panitumumab appear to be more effective in patients with tumors that are RAS wild-type compared to tumors that are RAS mutation-positive. Therefore, patients with metastatic colorectal cancer should not receive anti-EGFR antibody therapy if a RAS mutation is detected.[59] Genetic testing of colorectal cancers is discussed in further detail in Chapter 147, “Colorectal Cancer.”

Necitumumab

Necitumumab is a next-generation mAb that binds to the human EGFR and blocks the binding of EGFR to its ligands. It is approved for the treatment of patients with metastatic *squamous* NSCLC in combination with gemcitabine and cisplatin. Serious and clinically significant adverse events include cardiopulmonary arrest, hypomagnesemia, thromboembolic events, dermatologic toxicities, and infusion reactions. Since increased toxicity and mortality was observed when necitumumab was given with pemetrexed and cisplatin for the treatment of nonsquamous NSCLC, patients with metastatic nonsquamous NSCLC should not receive necitumumab.

Monoclonal Antibodies That Target HER2

Trastuzumab

Trastuzumab is a humanized mAb that selectively binds to HER2. HER2 is overexpressed in about 33% of breast cancers, in about 22% of gastroesophageal junction and gastric cancers, and to varying degrees in other malignancies.[60] Trastuzumab inhibits cell cycle progression by decreasing cells entering the S phase of the cell cycle, which leads to downregulation of HER2 receptors on cancer cells and decreased cell proliferation.[59] Trastuzumab also leads to ADCC and CDC and directly induces apoptosis in cells overexpressing HER2. In addition, synergy between trastuzumab and chemotherapy has been demonstrated, resulting in trastuzumab often being used in combination regimens. Trastuzumab is administered via intravenous infusion and is approved for the treatment of HER2-positive breast cancer and metastatic gastric or gastroesophageal junction adenocarcinoma. The tumor should overexpress HER2 as measured by diagnostic tests that can quantify gene amplification or protein expression. Additionally, a trastuzumab and hyaluronidase subcutaneous injection has been approved for the treatment of HER2-positive breast cancer.

The most serious adverse events associated with trastuzumab include cardiomyopathy, hypersensitivity reactions, and increased myelosuppression. An evaluation of cardiac function should be performed before administration and extreme caution should be exercised in patients with pre-existing cardiac dysfunction and in those who have received prior anthracyclines. In patients who develop a clinically significant decrease in left ventricular function (defined as greater than 16% decrease in ejection fraction from pretreatment levels or an ejection fraction below normal limits and greater than 10% decrease from baseline), discontinuation of therapy should be considered. Myelosuppression is infrequent with trastuzumab alone, but the incidence of neutropenia and febrile neutropenia is higher when trastuzumab is given with myelosuppressive chemotherapy.

Pertuzumab

Pertuzumab is a humanized mAb that targets the HER2 receptor. It is synergistic with trastuzumab and is effective in tumors that have developed resistance to trastuzumab. Pertuzumab binds to extracellular domain II of HER2, a site distinct from trastuzumab, and inhibits ligand-dependent HER2–HER3 dimerization, which subsequently decreases tumor proliferation and resistance pathways.[61] Dual targeting of the HER2 receptor allows for increased efficacy against variant forms of the HER2 receptor, including truncated HER2 receptors.

Similar to trastuzumab, it appears to induce ADCC in cancer cells. Pertuzumab is approved to treat HER2-overexpressed breast cancer in combination with trastuzumab and chemotherapy.

Monoclonal Antibodies That Target VEGF

Bevacizumab

Bevacizumab is a humanized mAb directed against circulating VEGF. It binds to all biologically active circulating isoforms of VEGF and prevents the activation and promotion of angiogenesis. Bevacizumab is approved for the treatment of patients with multiple types of solid tumors including the following: cervical cancer; colorectal cancer; glioblastoma; nonsquamous NSCLC; ovarian, fallopian tube, or primary peritoneal cancer; and renal cell carcinoma. A bevacizumab biosimilar, bevacizumab-awwb, was the first biosimilar approved for the treatment of cancer.

Several serious adverse events have been associated with bevacizumab including hypertension, bleeding, and thrombotic events. Hypertension is more common in patients with a history of hypertension and it responds to oral antihypertensive medications. Although the most common bleeding episodes are transient epistaxis, fatal CNS and gastrointestinal hemorrhages have been reported. The product labeling includes a boxed warning regarding the risk of gastrointestinal perforation, wound dehiscence, and hemorrhage. Bevacizumab is not recommended for use within 28 days of major surgery and patients should be instructed to report abdominal pain (an initial sign of gastrointestinal hemorrhage) to their health professionals immediately. Paradoxically, bevacizumab also has been associated with thrombotic events, including deep vein thrombosis, pulmonary embolism, and myocardial infarction, especially in elderly patients with a history of cardiac events. Another potentially serious adverse event associated with bevacizumab is proteinuria/nephrotic syndrome, and patients should be monitored for the development or worsening of proteinuria with serial urine dipsticks.

Ramucirumab

Ramucirumab is a human mAb that binds to VEGFR2 resulting in the inhibition of ligand-induced proliferation. While bevacizumab binds the circulating ligand (ie, VEGF), ramucirumab inhibits angiogenesis through the specific blockade of VEGFR2.[62] Ramucirumab is approved for the treatment of advanced gastric or

gastroesophageal junction adenocarcinoma as a single agent or with paclitaxel. Other indications include the following: treatment of metastatic NSCLC with docetaxel after progression with platinum-based chemotherapy; treatment of hepatocellular carcinoma in patients who have an AFP of ≥400 ng/mL (mcg/L) following treatment with sorafenib; and for the treatment of metastatic colorectal cancer in the second-line setting. When administered as a single agent, the most common toxicities associated with ramucirumab are hypertension and diarrhea. Patients should also be monitored for thromboembolic events, hypertension, proteinuria, and thyroid dysfunction.

Bispecific T-Cell Engagers

Blinatumomab is a bispecific T-cell engaging antibody against a B-lymphocyte-specific molecule CD19. Through the formation of a synapse, blinatumomab serves as a linker between CD19 on malignant B-cells and CD3 on T-cell receptors, thereby potentiating T-cell–induced cytotoxic cell killing. Blinatumomab is indicated for the treatment of B-cell precursor ALL.[63]

Due to its short half-life (~2 hours) and mechanism of action, blinatumomab is administered as a continuous intravenous infusion over 28 days. In addition to possible decreased efficacy, early trials that utilized shorter infusion durations also reported a higher rate of neurologic toxicities and cytokine-release syndrome.[63] Patients receiving blinatumomab are usually hospitalized for initiation of cycles 1 and 2 to monitor for infusion reactions. Patients should also be monitored for CRS, neurological toxicities, and infections. Other common adverse events include fever, headache, peripheral edema, and rash.

Antibody-Drug Conjugates

ADCs were developed to exploit the selectivity and binding properties of mAbs to deliver cytotoxic chemotherapy.[64] These agents consist of three components: the antibody, the linker, and the cytotoxic payload. To cause cancer cell death, the antibody must first bind to the target antigen and the complex must then be internalized into the cell through receptor-mediated endocytosis. The antibody-drug complex is then degraded, the cytotoxic payload is released, and cancer cell death occurs. Theoretical benefits of conjugates are a result of the delivery of cytotoxic chemotherapy directly to the target site resulting in decreased toxicity.

Ado-Trastuzumab Emtansine

Ado-trastuzumab emtansine, also known as T-DM1, is indicated for the treatment of HER2-positive breast cancer. Ado-trastuzumab emtansine is an ADC that consists of the humanized anti-HER2 mAb trastuzumab covalently linked to the microtubule inhibitory drug DM1 (derivative of maytansine 1).[65] Ematansine refers to the linker-payload complex. It is important to note that ado-trastuzumab ematansine and trastuzumab are not interchangeable and should not be substituted for one another. The adverse events associated with ado-trastuzumab emtansine are similar to those reported with trastuzumab and microtubule inhibitors.

Brentuximab Vedotin

Brentuximab vedotin is an ADC that targets the CD30 antigen found on cancer cells. Upon binding to the CD30 antigen, brentuximab vedotin is internalized by endocytosis and the dipeptide bond that links the naked mAb to the chemotherapy monomethylauristatin E (MMAE) is cleaved.[66] MMAE then binds to microtubules and acts as an inhibitor of microtubule polymerization. It may also induce apoptosis by inhibiting NF-κB. Brentuximab vedotin is indicated for Hodgkin lymphoma, anaplastic large cell lymphoma, peripheral T-cell lymphoma, and mycosis fungoides. Infusion reactions, peripheral neuropathy, and neutropenia are common toxicities seen with brentuximab vedotin administration; these toxicities are common with other microtubule inhibitors.

Gemtuzumab Ozogamicin

Consisting of an IgG4 kappa antibody linked to a calicheamicin derivative, gemtuzumab ozogamicin is an ADC targeting CD33 which is expressed on leukemic cells in AML. Gemtuzumab ozogamicin has a unique approval history. In 2000, gemtuzumab ozogamicin received an accelerated approval for the treatment of patients with AML but was removed from the market soon thereafter due to lack of benefit and excessive toxicity. However, since then, multiple studies have been completed using a modified dosing scheme resulting in the reapproval of gemtuzumab ozogamicin for the treatment of CD33-positive AML. Warnings associated with the use of this agent include hepatotoxicity (including veno-occlusive disease), infusion-related reactions, and hemorrhage. Other common toxicities are infection, fever, nausea, vomiting, constipation, headache, rash, and mucositis.

Inotuzumab Ozogamicin

Inotuzumab ozogamicin is an ADC targeting CD22 on B-cells. This agent consists of an IgG4 antibody linked to calicheamicin and is approved for the treatment of B-cell precursor ALL. Prescribing information for inotuzumab ozogamicin warns about the risk of increased posthematopoietic stem cell transplant nonrelapse mortality rate. Potentially severe toxicities include hepatotoxicity, myelosuppression, infusion-related reactions, and QT prolongation.

Polatuzumab Vedotin

While CD79B is present on the surface of most malignant B-cells, its expression on mature B cells is restricted, thus making it an attractive target.[67] Polatuzumab vedotin is an ADC consisting of MMAE conjugated to an anti-CD79B mAb. It is given in combination with bendamustine and rituximab for the treatment of diffuse large B-cell lymphoma. Toxicities include peripheral neuropathy, infusion-related reactions requiring premedications, myelosuppression, infections, multifocal leukoencephalopathy, TLS, and hepatotoxicity.

Fusion Proteins

Moxetumomab Pasudotox

Moxetumomab pasudotox-tdfk is a CD-22 directed cytotoxin that is composed of a recombinant murine immunoglobulin variable domain fused to a truncated form of *Psuedomonas* exotoxin. It is approved for the treatment of relapsed or refractory hairy cell leukemia. The most common adverse reactions include infusion-related reactions, edema, nausea, headache, pyrexia, constipation, anemia, and diarrhea. Most patients develop anti-moxetumomab binding and neutralizing antibodies, which decreases the systemic moxetumomab pasudotox-tdfk antibodies.

Ziv-Aflibercept

Ziv-aflibercept is a soluble recombinant fusion protein that was designed to block multiple signals that stimulate the angiogenic process. It was developed by fusing sections of the VEGFR1 and VEGFR2 immunoglobulin domains to the Fc portion of human IgG1. Ziv-aflibercept blocks VEGFA, VEGFB, and phosphatidylinositol-glycan biosynthesis class F by “trapping” the ligands before

they get to the native transmembrane receptors and thus decreasing proangiogenic signaling and tumor growth. It is approved with chemotherapy for resistant or progressive metastatic colorectal cancer and has toxicities similar to other anti-VEGF therapies.

IMMUNOTHERAPY

Immune Checkpoint Inhibitors

As discussed earlier in the chapter, immune checkpoint inhibitors (including PD-1, PD-L1, and CTLA-4 inhibitors) reverse immune down-regulation, thereby unleashing T-cells to eliminate malignant cells. PD-L1 is overexpressed on multiple types of tumors and it has been suggested that PD-L1 expression is associated with increased tumor aggressiveness. Unlike cytotoxic chemotherapy, which can elicit cell death immediately after administration, immune checkpoint inhibitors may have a slower onset based on their inherent mechanism of action. Furthermore, durable responses are common with checkpoint inhibitors as tumor suppression may continue months after administration.

CTLA-4 Inhibitor

Ipilimumab is a human mAb that blocks CTLA-4 and was the first FDA-approved immune checkpoint inhibitor. CTLA-4 acts as a negative regulator of T-cell function, decreasing the ability of the immune system to mount an antitumor response. By binding to CTLA-4, ipilimumab allows for enhanced T-cell stimulation, proliferation, and antitumor activity. Based on its ability to produce an enhanced immune response, ipilimumab has been associated with several severe and fatal immune-related adverse events (irAEs) including enterocolitis, hepatitis, dermatitis, neuropathies, and endocrinopathies. Ipilimumab is often administered in combination with nivolumab and is indicated for the treatment of MSI-H or dMMR colorectal cancer, melanoma, and renal cell carcinoma.

PD-1 Inhibitors

Cemiplimab Cemiplimab-rwlc is a recombinant human IgG4 mAb that binds to PD-1 and blocks its interaction with PD-L1 and PD-L2. It is approved for the treatment of advanced cutaneous squamous cell carcinoma. Patients receiving cemiplimab-rwlc must be monitored for irAEs including pneumonitis, colitis, dermatologic conditions, hepatitis, nephritis, and endocrine dysfunction.

Nivolumab Nivolumab, a fully human IgG4 mAb, binds to and blocks PD-1 from interacting with its receptor resulting in the restoration of T-cell activity. Nivolumab is approved for the treatment of MSI-H or dMMR colorectal cancer, squamous cell cancer of the head and neck, hepatocellular carcinoma, Hodgkin lymphoma, urothelial carcinoma, SCLC, NSCLC, melanoma, and renal cell carcinoma. Nivolumab is also approved in combination with ipilimumab for a variety of solid tumor indications. Patients receiving nivolumab must be monitored for irAEs similar to cemiplimab.

Pembrolizumab Pembrolizumab is a highly selective humanized IgG4 mAb. Similar to cemiplimab and nivolumab, pembrolizumab binds to the PD-1 receptor, thereby reversing T-cell suppression. Pembrolizumab is approved for the following indications: cervical cancer, gastric cancer, squamous cell cancer of the head and neck, Hodgkin lymphoma, melanoma, SCLC, NSCLC, primary mediastinal large B-cell lymphoma, hepatocellular carcinoma, renal cell carcinoma, and urothelial carcinoma. Additionally, pembrolizumab received the FDA's first tissue/site agnostic approval for the treatment of MSI-H solid tumors. Given its similar mechanism of action, toxicities reported with pembrolizumab are consistent with other PD-1 inhibitor-related toxicities.

PD-L1 Inhibitors

Atezolizumab Unlike the PD-1 inhibitors which bind to the receptor, PD-L1 inhibitors bind to the associated ligand resulting in immune activation. Atezolizumab is an IgG1 mAb indicated for the treatment of SCLC, triple-negative breast cancer, NSCLC, and urothelial carcinoma. Toxicities of PD-L1 inhibitors are similar to those of PD-1 inhibitors.

Avelumab The mechanism and toxicity profile of avelumab are similar to atezolizumab. Infusion-related reactions are more common with avelumab and premedications are required prior to the first four infusions at minimum. Avelumab is a human IgG1 mAb approved for the treatment of Merkel cell carcinoma, urothelial carcinoma, and in combination with axitinib for renal cell carcinoma. The development of antidrug antibodies (ADAs) has been shown to reduce avelumab exposure and exploratory analyses suggest that the development of these ADAs may reduce the effectiveness in some populations. The development of ADAs does not appear to affect the incidence or severity of adverse reactions.

Durvalumab Durvalumab, a human IgG1 mAb, shares the same mechanism of

action and similar toxicity profile as other agents in this class. Indications include NSCLC and urothelial carcinoma.

Cytokines

Interferons

Recombinant IFN-alfa is approved for hairy cell leukemia, melanoma, Kaposi's sarcoma, and CML. A pegylated IFN-alpha (identified as peginterferon-alfa) has been approved for adjuvant treatment of metastatic melanoma. The exact mechanisms by which IFNs exert their anticancer effects is unknown, but it is thought IFNs bind specific membrane receptors and initiate various intracellular signaling pathways. The most frequent toxicities are flu-like symptoms and elevated transaminases. Potentially serious toxicities include neuropsychiatric, autoimmune, ischemic, and infectious disorders.

Interleukin-2 (aldesleukin)

IL-2 is a cytokine produced by recombinant DNA technology that promotes B- and T-cell proliferation and differentiation and initiates a cytokine cascade with multiple interacting immunologic effects. The IL-2 receptor is expressed in increased amounts on activated T-cells and mediates most of the effects of aldesleukin. Anticancer activity depends on proliferation of cytotoxic immune cells that can recognize and destroy cancer cells without damaging normal cells. Some of these cytotoxic cells are natural killer cells, lymphokine-activated killer cells, and tumor-infiltrating lymphocytes.[68] Aldesleukin is approved for the treatment of metastatic renal cell carcinoma and melanoma.

Aldesleukin is a toxic therapy that requires vigorous supportive care under the supervision of experienced healthcare professionals. The most common dose-limiting toxicities are hypotension, fluid retention, and renal dysfunction. Aldesleukin decreases peripheral vascular resistance, producing peripheral vasodilation, tachycardia, and hypotension. A characteristic vascular or capillary leak syndrome produces fluid retention, which in turn can cause respiratory compromise. These toxicities require administration of vasopressors in most patients, judicious use of fluid support and diuretics, and supplemental oxygen. Patients with underlying cardiovascular or renal abnormalities are more susceptible to these toxicities, making careful patient selection important. Most patients treated with aldesleukin experience thrombocytopenia, anemia, eosinophilia, reversible cholestasis, and skin erythema with burning and pruritus;

some patients have neuropsychiatric changes, hypothyroidism, and bacterial infections.[68] In general, the toxicities from aldesleukin reverse quickly after therapy is stopped and can be managed or prevented by careful monitoring and supportive care.

Therapeutic Vaccines

Sipuleucel-T

Sipuleucel-T was the first therapeutic vaccine approved by the FDA. It is classified as an autologous cellular immunotherapy and is indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer. Through leukapheresis, a patient's dendritic cells are collected and isolated, then cultured ex-vivo. The fusion protein (PAP-GM-CSF) is composed of prostate acid phosphatase (PAP) and GM-CSF. PAP is selectively expressed on prostatic tissues and GM-CSF is included to enhance the immune response. Antigen-presenting cells take up this antigen and are then reinfused into the donor patient to stimulate a T-cell response.[69]

Treatment with sipuleucel-T consists of three infusions separated by approximately 2 weeks. Due to the leukapheresis, ex-vivo cell manipulation, and reinfusion, treatment with sipuleucel-T can be logistically challenging. Premedication consisting of acetaminophen and an antihistamine should be given prior to each infusion to decrease the risk of an infusion reaction. Common toxicities include chills, fatigue, back pain, nausea, joint ache, and headache.

Talimogene Laherparepvec

Talimogene laherparepvec (T-VEC) is an oncolytic viral therapy based on a modified herpes simplex virus (HSV) type 1. T-VEC is modified through the deletion of two HSV genes, ICP34.5 and ICP47, and is designed to lyse tumor cells and promote antitumor immunity. It is indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery and is injected directly into the lesion. The most common toxicities are fatigue, chills, pyrexia, nausea, influenza-like illness, and injection site pain. Pyrexia, chills, and influenza-like illness can occur any time during treatment but were more frequent during the first 3 months. Cellulitis is the most commonly reported serious adverse event.

Chimeric Antigen Receptor T-Cell Therapies

CAR T-cell therapies were the first FDA-approved genetically modified autologous T-cell immunotherapies and are also known as adoptive T-cell therapies. Peripheral blood mononuclear cells are harvested from a patient via apheresis. The T-cells are then reprogrammed with a transgene encoding a CAR, which consists of a binding domain and signaling domains. Following lymphodepletion with a conditioning regimen (often fludarabine and cyclophosphamide), the CAR T-cells are then reinfused into the patient.

Axicabtagene Ciloleucel and Tisagenlecleucel

The axicabtagene ciloleucel CAR consists of a CD19 binding domain, which recognizes CD19-expressing cells such as select lymphoma cells. Binding of the CD19-expressing cell activates downstream signaling through the CD28 and CD3 zeta signaling domains resulting in cytokine and chemokine secretion and ultimate destruction of the B-cell. Tisagenlecleucel has a similar structure and mechanism but contains a different signaling domain (4-1BB substituted for CD28).

Toxicities associated with CAR T-cell therapies can be severe and life threatening. As a result, a REMS program has been implemented which, among other requirements, mandates hospitals and clinics be certified before administering these agents. Cytokine-associated toxicities are common and include CRS which manifests with hypotension, organ toxicity, fever, and hypoxia. CAR T-cell related encephalopathy (CRES) has also been reported and is associated with seizures, neurologic changes, motor weakness, and raised intracranial pressure.

RESPONSE CRITERIA

The response to anticancer agents and other treatment modalities could be described as a cure, complete response (CR), partial response (PR), stable disease, or progression. A cure implies that the patient is entirely free of disease and has the same life expectancy as a cancer-free individual. Because of our inability to detect small numbers of cancer cells, we can never be absolutely certain that an individual patient is cured. Cancers that are curable with treatment are characterized by a stable plateau in the survival curve where the risk of relapse is very low. For most curable cancers, the survival curve has plateaued by about 5 years. Therefore, patients with a curable cancer who are alive 5 years from the time of diagnosis without disease recurrence are often considered “cured,” but patients with some malignancies, such as breast cancer and

melanoma, are still at significant risk for relapse after 5 years.

Response Criteria for Solid Tumors

In an attempt to simplify and unify response definitions in clinical practice, clinical trials, and published reports, the response evaluation criteria in solid tumors (RECIST) criteria were developed in 2000 and revised in 2009 (RECIST 1.1).[70] At baseline, overall tumor burden and measurable disease is assessed. Target lesions are identified and measured at baseline and are later reevaluated to determine objective tumor response. Nontarget lesions are also assessed. A CR means disappearance of all target lesions and any pathological lymph nodes must be reduced in short axis to less than 10 mm. A PR is defined as a 30% or greater decrease in the sum of diameters of target lesions from baseline. Overall objective response rates for a given treatment are calculated by adding the CR and PR rates. Progressive disease is defined as a 20% or greater increase in the sum of diameters of target lesions when compared to the smallest sum since treatment initiation. The development of one or more new lesions while receiving treatment is also considered progressive disease. A patient whose tumor size neither grows nor shrinks by the above criteria is termed to have stable disease.[70] Some patients may experience subjective improvement in cancer-related symptoms without a defined response. Although clinically important, this does not indicate an objective response. RECIST 1.1 is the most widely accepted criteria for the assessment of tumor response in solid tumors but it does not come without shortcomings. The modified RECIST (mRECIST) assessment may be more accurate for the evaluation of tumor burden in some cancers.[71]

Furthermore, the emergence of immunotherapy in oncology has led to the need for revised response criteria that accounts for the mechanism of immunotherapeutic agents. RECIST neglects to take into account pseudoprogression (ie, “flare”) associated with these agents which may result in the premature discontinuation of an effective therapy. Pseudoprogression refers to apparent tumor growth on imaging which is the result of an immunotherapy treatment-related effect rather than malignant cell proliferation. The apparent progression is thought to be a result of immune infiltrates and is followed by tumor regression. Immune-related response criteria (irRC) and immune-related RECIST (irRECIST) have been proposed to overcome the challenges of RECIST 1.1 with immunotherapy.[72,73]

Response Criteria for Hematologic Malignancies

The response definitions described above are applicable to solid tumors, but leukemias and multiple myeloma are not characterized by discrete, measurable masses. Responses in these cancers are measured by elimination of abnormal cells (eg, return to normal hematology parameters and normal bone marrow in leukemia), return of tumor markers to normal levels (eg, normal serum protein electrophoresis in multiple myeloma), or improved function of affected organs (eg, improved renal function after obstructive uropathy). Cytogenetic markers and molecular techniques have an increasingly important role in determining whether all cancer has been truly eliminated. For example, in CML, the Philadelphia chromosome can be detected by polymerase chain reaction techniques even when no leukemia is evident in the bone marrow or bloodstream. Patients without evidence of the Philadelphia chromosome are classified as having a complete cytogenetic response. Measuring cytogenetic responses is increasingly common in patients with known cytogenetic abnormalities and the absence of a complete cytogenetic response may be predictive of disease relapse. Minimal residual disease (MRD) is a prognostic factor used to guide treatment in ALL and AML. Data regarding MRD is still emerging but it is now recommended that MRD be monitored in patients with AML as MRD positivity is associated with higher relapse rates and shorter survival.[74]

FACTORS AFFECTING TREATMENT RESPONSE

8 Factors affecting response include tumor burden, cancer cell heterogeneity, drug resistance, dose intensity, and patient-specific factors such as pharmacogenomics. The significance of tumor burden was discussed earlier in the chapter. Tumors consist of a heterogeneous population of cells. Because of the genetic instability of cancer cells compared with normal cells, genetic alterations commonly occur during cell division. Large tumors have therefore undergone many cell divisions and express multiple genetic alterations, resulting in genetically varied populations.[3] In 1979, Goldie and Coldman proposed that these cytogenetic changes were not completely random and were highly associated with the development of the ability of tumors to develop drug resistance. The probability of developing resistant cell populations increases as tumor size increases. It is believed that a small percentage of resistant cancer cells may survive initial therapy. Resistant populations later proliferate and

eventually become the dominant population, which could explain the common pattern of an initial response to therapy followed by progressive tumor regrowth despite continuing the same treatment.

Drug Resistance

Drug resistance may be either acquired or inherited. Mechanisms of drug resistance include altered drug transport systems, metabolism, and target enzymes; inability to repair drug-induced damage; and insensitivity to drug-induced apoptosis.[3] For example, multidrug resistance has been observed with natural chemotherapies (eg, anthracyclines, vinca alkaloids, epipodophyllotoxins, and taxanes), and it occurs when some cancer cells are exposed to increasing concentrations of a specific chemotherapy. Surprisingly, these same cells also become resistant to other structurally unrelated chemotherapies and are therefore considered multidrug resistant. The resistant cancer cells may overexpress the drug transporter Pgp, which enhances the export of these chemotherapies. Other potential mechanisms of drug resistance include inactivation of chemotherapy by glutathione metabolism, upregulation of drug targets, alternative intracellular signaling pathways, and decreased apoptosis. The last mechanism can be mediated by overexpression of BCL-2 or loss of TP53, as discussed earlier in the chapter.

Dose Intensity

The relationship between dose and response has been extensively explored for chemotherapy agents,[1] because dose is believed to be a critical factor in determining response for many cancers. Dose intensity is defined as the dose delivered to the patient over a specified period of time. The three main variables that determine delivered dose intensity are the dose per course, the interval between doses, and the total cumulative dose. Dose density refers to shortening of the usual interval between doses (eg, every 2 weeks instead of every 3 weeks) and is designed to maximize the effects of therapy on tumor growth kinetics. This strategy has been extensively studied in breast cancer. The delivery of optimal dose intensity is often compromised by the toxicities of the anticancer agent. Treatment cycles are commonly delayed because of inadequate recovery from toxicity, especially myelosuppression. Subsequent doses of the anticancer agents are often reduced to prevent or minimize the severity of these toxicities. The impact on patient outcome has been proven in studies showing reduced rates of response and survival in individuals receiving less-than-optimal doses.

Understanding the pathophysiology of toxicities has led to the development of more effective agents to prevent and manage these toxicities. The development of chemoprotective agents has facilitated application of dose-intensity principles. For example, colony-stimulating factors minimize neutropenia and permit delivery of dose-intensive or dose-dense regimens that are myelosuppressive. The concept of dose intensity is particularly important in the setting of high-dose chemotherapy with autologous hematopoietic stem cell support. Although lethal myelosuppression is avoided through hematopoietic stem cell transplant, other severe end-organ toxicities emerge as doses of the anticancer agents are increased.

Molecular Biomarkers

A molecular biomarker is a molecular characteristic of the tumor that influences prognosis or predicts response to a specific therapy. Many of these molecular biomarkers are somatic mutations that contribute to the development of the cancer. Prognostic biomarkers inform the risk of clinical outcomes such as disease progression or recurrence. Numerous tests are currently available that measure tumor gene expression and may provide information on a patient's risk of recurrence. For example, the Oncotype Dx® Breast Cancer Assay measures 21 genes associated with breast cancer recurrence and chemotherapy benefit in select women with breast cancer. A predictive biomarker predicts response to a specific therapeutic intervention. For example, EGFR and ALK mutations predict response to EGFR and ALK inhibitors in NSCLC. Similarly, HER2 overexpression predicts response to trastuzumab in breast cancer. Molecular testing of cancer at the time of diagnosis allows for personalized therapy with targeted agents.

Patient-Specific Factors

Patient-specific factors create unpredictable variability in response to anticancer therapy. For example, interindividual variations in absorption, distribution, or elimination could lead to sub- or supratherapeutic levels of anticancer agents and their metabolites. The genetic alterations that resulted in the cancer can also affect response. For example, breast cancers that overexpress HER2 are often sensitive to anthracycline-based regimens. As a result, both efficacy and tolerability can be affected. Healthcare professionals in oncology may preemptively modify doses based on variations in body size, blood counts, and organ function to optimize the effectiveness of therapy and minimize toxicity.

However, more specific tools are becoming available as we learn how to identify and apply genetic differences. Pharmacogenomics is the study of the role of inheritance in individual variation of drug response. In oncology, several clinically relevant genetic polymorphisms or variations have been identified that can affect pharmacokinetics and pharmacodynamics. Examples include polymorphisms in genes responsible for the activity of the enzymes DPD (responsible for 5-FU metabolism), TPMT (responsible for thiopurine metabolism), UGT1A1 (responsible for irinotecan metabolism), and CYP2D6 (responsible for tamoxifen metabolism). Patients with deficiencies in these enzymes can experience significant and possibly life-threatening toxicity. Identifying these genetic variants could permit individualization of regimens to reduce toxicity. Furthermore, pharmacokinetic and pharmacodynamic modeling is associated with improved responses and decreased toxicity in children with ALL.

The presence of other disease states (eg, comorbidities) may also affect response to treatment by limiting treatment options. The overall functional status of a patient may be assessed using performance status scales, such as the Karnofsky Performance Status (KPS) and the Eastern Cooperative Oncology Group (ECOG) scales. These scales can be used to predict patient tolerance of anticancer therapy and to assess the effects of therapy on the patient's level of activity and quality of life. For many cancers, performance status at diagnosis is the most important prognostic indicator.

Today's oncology healthcare professionals have a wealth of information to consider when designing a personalized treatment approach. Patient-specific factors (eg, performance status, comorbidities, organ function, and pharmacogenomics), tumor-specific factors (eg, pathology, stage, and biomarkers), and treatment goals (eg, palliation and cure) are all considered when determining the best treatment option. Treatment cost can also be an important consideration.

DRUG ADMINISTRATION

Dosage and Administration

Healthcare professionals should monitor all clinical and laboratory values that are affected by a specific anticancer agent at baseline and periodically during treatment. For example, a complete blood count should be evaluated weekly or prior to each cycle while receiving anticancer agents associated with

myelosuppression. In general, an absolute neutrophil count (ANC) of 1,500 cells/mm^3 (1.5×10^9/L) or above and a platelet count of 100,000 cells/mm^3 (100×10^9/L) or above are usually required before administering myelosuppressive agents. In addition, a chemistry panel is drawn to assess organ function, especially for agents eliminated or metabolized via those routes. Table 144-7 lists agents that require dosing adjustments and require specific laboratory tests before administration.

Anticancer agents might be dosed based on body size (such as body weight or body surface area [BSA]) or as a fixed (ie, flat) dose. Cytotoxic chemotherapy is generally dosed based on BSA. BSA is commonly used as an estimate of cardiac output and subsequent distribution to the liver and kidneys, the primary determinants of drug elimination. The most common methods used to determine BSA are the Mosteller and DuBois formulas. Traditionally, body-sized dosing has been used for mAbs but some agents, such as some immune checkpoint inhibitors, may use a flat dose. In contrast, most oral targeted agents are based on a fixed-dose approach.

Other dosing methods are being used to improve tolerability and anticancer activity. For example, carboplatin is dosed based on the patient's estimated glomerular filtration rate (GFR). This method is known as the Calvert formula and has been demonstrated to achieve adequate levels of carboplatin while minimizing excessive toxicity.

Molecular diagnostic tests are required prior to administration of some targeted agents (eg, trastuzumab, vemurafenib, and crizotinib), which are indicated only for patients whose tumors express a specific protein or gene. Additionally, health professionals must know how to interpret the findings from the various diagnostic tests. For example, some tests may identify if a tumor is mutation positive or negative, whereas other tests may identify the specific genetic alteration present in the tumor.

Safety and Handling

All anticancer agents regardless of the route of administration should be handled with care to avoid inadvertent exposure to healthcare professionals and caregivers. Consequently, all healthcare facilities should have written procedures for safely handling these agents and all personnel should be oriented to these procedures. Healthcare professionals should provide information about safe handling and disposal to patients and their families when a patient is prescribed an oral anticancer agent. Patients should be informed of proper methods for

disposing of potentially contaminated body excreta and cytotoxic waste. Safe handling includes avoiding skin contact and inhalation, but patient-centered guidelines regarding safe handling of oral anticancer agents have not been developed.[75]

The United States Pharmacopeia regulates the preparation of extemporaneously compounded sterile preparations and should be used by healthcare professionals that prepare intravenous chemotherapy. Chapter 800 provides standards for the safe handling of hazardous agents in the healthcare setting. The most common avenue of exposure is via inhalation or skin absorption. Individuals preparing intravenous chemotherapy should work in an International Organization for Standardization (ISO) Class 5 biologic safety cabinet and wear appropriate personal protective equipment including a gown, face mask, eye protection, hair covers, shoe covers, and double sterile chemo-type gloves. Closed-system vial-transfer devices should be used when possible. Negative-pressure techniques should be used in drug preparation to minimize aerosolization. Health professionals administering chemotherapy should take similar precautions to avoid exposure. Double chemotherapy-tested gloves, protective gowns, and protective eyewear (if there is potential for splashing) should be worn whenever handling or administering hazardous drugs. Kits for cleaning up chemotherapy spills should be located in all areas where chemotherapy is handled and cytotoxic waste should be disposed of properly.

SUPPORTIVE CARE

9 The treatment of cancer is complicated by the risk of multiple serious adverse reactions, many of which may be life-threatening. Adverse reactions (or toxicities) are commonly graded on a scale from no toxicity (grade 0) to death (grade 5) with the Common Terminology Criteria for Adverse Events (CTCAE) developed by the National Cancer Institute (NCI). Specific toxicities observed with individual anticancer agents were listed earlier in the chapter. Toxicities such as myelosuppression, mucositis, nausea and vomiting, and alopecia are commonly observed with chemotherapy, because these agents target rapidly dividing normal and cancer cells. Other toxicities associated with chemotherapy are infertility and carcinogenesis. The safety profile with biologic therapies and small molecular targeted agents typically differ from chemotherapy. The adverse reactions observed with these anticancer agents depend on the altered intracellular signaling. For example, rash has been observed with EGFR inhibitors and hemorrhage and thrombosis have been observed with VEGF or

VEGFR inhibitors. Immunotherapies also have a unique adverse event profile including autoimmune toxicities. The management of chemotherapy-induced nausea and vomiting and the basic principles of nutritional support and pain management are discussed in detail in other chapters. The basic principles for the management of some common adverse reactions are described below.

Hematologic

Myelosuppression has been reported with chemotherapy and small molecule tyrosine kinase inhibitors. It is the most common dose-limiting toxicity observed with chemotherapy and the risk of myelosuppression increases with concurrent radiation to the chest or pelvic region. Myelosuppresion has also been commonly observed with several small molecule kinase inhibitors, including anticancer agents that target BCR-ABL, EGFR, VEGFR, FLT-3, ALK, and HER2.

The effects of myelosuppression are usually not observed immediately after administration, because the currently circulating blood cells must first be consumed. For example, neutropenia is typically observed before thrombocytopenia, because white blood cells have a short life span of 6 to 12 hours compared to platelets with a life span of 5 to 10 days. Anemia typically occurs a few months after the first dose, since erythrocytes have a relatively long life span of 120 days. The lowest blood cell count (or nadir) typically occurs 10 to 14 days after chemotherapy administration, with a recovery in cell counts by 3 to 4 weeks after administration, but the nadir commonly occurs later following administration of nitrosoureas, mitomycin C, and radiolabeled antibodies (about 4-6 weeks). Subsequent doses should be delayed until the minimum suggested blood counts are achieved to minimize additional toxicity and morbidity. Patients with leukemia or receiving a hematopoietic stem cell transplant may have a more rapid nadir of about 5 to 7 days.

A dose reduction should be considered if a patient develops severe myelosuppression, such as anemia necessitating a transfusion or neutropenia with a fever. A dose reduction may be considered empirically before the first dose if the patient has a low baseline neutrophil or platelet count, has diminished bone marrow reserve, has impaired drug elimination, or is to receive a combination of several myelosuppressive agents; these patients may be at an increased risk of developing severe myelosuppression. A decreased bone marrow reserve has been observed in patients who have received multiple prior courses of myelosuppressive chemotherapy or extensive radiation therapy.

A dose reduction should be carefully balanced with the treatment goals, since

reduced dose can compromise anticancer activity in select tumors (eg, breast cancer and lymphoma).[1] Some myelosuppression is accepted by most health professionals if it is not compromising the patient's quality of life and the cancer is responding to therapy. In these patients, empiric use of hematopoietic growth factors provides an alternative to dose reduction.

Anemia

Anemia is a common complication associated with chemotherapy agents, but anemia has also been reported with tyrosine kinase inhibitors, including anticancer agents that target EGFR, HER2, and VEGFR. The incidence of anemia following the administration of chemotherapy agents depends on several factors, including the type and duration of therapy and the type and stage of the underlying malignancy. Multiple conditions can also contribute the risk of developing anemia, including gastrointestinal blood loss, nutrient deficiency (eg, iron and folate), radiation therapy, bone marrow invasion, hemolysis, renal dysfunction, and anemia of chronic disease. Of all the signs and symptoms of anemia, fatigue is most common in patients with cancer. In fact, fatigue is the most commonly reported symptom overall in patients undergoing anticancer therapy. Of note, other common causes of fatigue include insomnia, depression, unrelieved pain, and the underlying malignancy.

The underlying cause of the anemia should be identified before treatment for anemia is started. Red blood cell transfusions are the mainstay of treatment, but erythropoiesis-stimulating agents (epoetin alfa and darbepoetin alfa) may be considered for patients with underlying kidney disease and for patients receiving palliative treatment. Serious adverse reactions related to erythropoiesis-stimulating agents include thrombosis and myocardial infarction. These events have generally occurred when the target hemoglobin of 12 g/dL (120 g/L; 7.45 mmol/L) is exceeded or the hemoglobin rises too quickly. Various studies have demonstrated an increased risk of mortality with the use of erythropoiesis-stimulating agents in patients with cancer so patients and healthcare professionals must weigh the benefits and risks of treatment. Other rare and generally mild toxicities include pain at injection site, rash, flu-like symptoms, seizures, and hypertension. The presence of functional iron deficiency should be determined before administering these products. If the functional iron deficiency is identified, supplemental iron should be administered. Clinical practice guidelines for the treatment of cancer- and chemotherapy-related anemia are available.

Neutropenia

Neutropenia in patients with cancer is associated with an increased risk of infection. The probability of developing an infection increases when ANC falls below 500 cells/mm^3 (0.5×10^9/L) or when the duration of neutropenia is prolonged. Other risk factors for infection include alteration in the integrity of physical defense barriers and the functional integrity of the leukocytes. Neutrophil function can be affected by the underlying cancer, anticancer agent, or radiation therapy.

In the neutropenic patient, it can be difficult to identify an infection, as the usual signs and symptoms of infection, such as pus, abscesses, and infiltrates on chest radiography, are often absent. Subsequently, healthcare professionals must rely on fever as an indicator of infection in these patients. Definitive culture results may take days and a septic neutropenic cancer patient can die within hours if not treated. Therefore, empiric antibiotics are promptly initiated based on reliable coverage of the most likely organisms, antibiotic sensitivities at the institution, and the patient's signs and symptoms (if present). The most common source of infection in these patients is self-infection with body flora, which includes both gram-positive and gram-negative bacteria. Specific treatment of infections in immunocompromised hosts is discussed in Chapter 140, "Infections in Immunocompromised Patients."

Colony-stimulating factors may minimize the severity of neutropenia and subsequently, reduce the risk of infection. These factors are naturally occurring proteins that are essential for the normal growth and maturation of blood cell components (see **Fig. 144-8**). For example, filgrastim specifically stimulates the production of neutrophilic granulocytes and sargramostim promotes the proliferation of granulocytes (neutrophils and eosinophils), monocytes and macrophages. Although sargramostim stimulates megakaryocytes, no consistent effect on platelet production has been observed in clinical trials and this agent is not commonly used in clinical practice. Both factors initially enhance demargination and mobilization of mature cells from the marrow and then provide constant stimulation of stem cell progenitors. Pegfilgrastim is a peglyated form of filgrastim that has a substantially longer half-life compared to filgrastim. While multiple daily doses of filgrastim are typically needed to increase neutrophil count, only a single dose of pegfilgrastim per cycle is needed to similarly increase neutrophil counts.

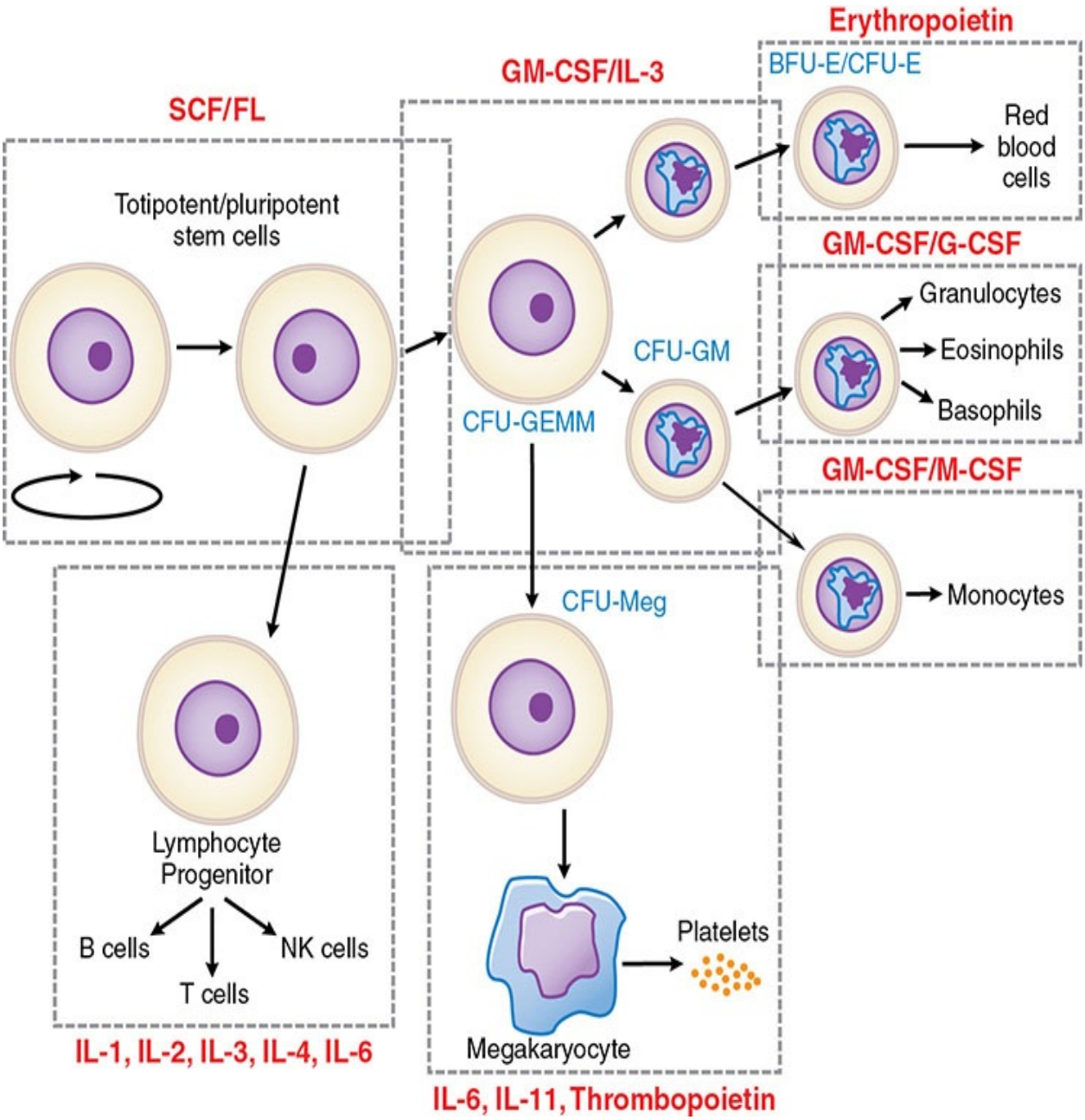


FIGURE 144-8 Sites of action of hematopoietic growth factors in the differentiation and maturation of marrow cell lines. A self-sustaining pool of marrow stem cells differentiates under the influence of specific hematopoietic growth factors to form a variety of hematopoietic and lymphopoietic cells. Stem cell factor (SCF), FTL-3 ligand (FL), interleukin-3 (IL-3), and granulocyte-macrophage colony-stimulating factor (GM-CSF), together with cell–cell interactions in the bone marrow, stimulate stem cells to form a series of burst-forming units (BFU) and colony-forming units (CFUs): CFU-GEMM, CFU-GM, CFU-Meg, BFU-E, and CFU-E (GEMM, granulocyte, erythrocyte, monocyte,

and megakaryocytes; GM, granulocyte and macrophage; Meg, megakaryocyte; E, erythrocyte). After considerable proliferation, further differentiation is stimulated by synergistic interactions with growth factors for each of the major cell lines—granulocyte colony-stimulating factor (G-CSF), monocyte/macrophage-stimulating factor (M-CSF), thrombopoietin, and erythropoietin. Each of these factors also influences the proliferation, maturation, and, in some cases, the function of the derivative cell line (NK, natural killer). (*Reproduced with permission from Kaushansky K, Kipps TJ. Hematopoietic agents: Growth factors, minerals and vitamins. In: Brunton LL, Chabner BA, Knollman BC (eds). Goodman & Gilman's The Pharmacologic Basis of Therapeutics, 12th ed. New York: McGraw-Hill, 2010.*)

Growth factors may be used as primary or secondary prophylaxis of neutropenia. Primary prophylaxis refers to the use of these factors to prevent neutropenia with the first cycle of chemotherapy. The National Comprehensive Cancer Network (NCCN) recommends this strategy for patients who are receiving a chemotherapy regimen with a 20% or higher risk of febrile neutropenia.[76] These guidelines also recommend primary prophylaxis for patients with risk factors receiving a chemotherapy regimen with a 10% to 20% risk of febrile neutropenia. Patient risk factors include age 65 years or older receiving full chemotherapy dose intensity, previous chemotherapy or radiation, persistent neutropenia, bone marrow involvement of tumor cells, recent surgery and/or open wounds, liver dysfunction, and renal dysfunction. Secondary prophylaxis refers to the use of growth factors to prevent recurrent neutropenia in patients who had experienced neutropenia with the prior cycle of chemotherapy. It is recommended that secondary prophylaxis be reserved for patients with chemosensitive cancers when a dose reduction may affect survival. The role of these factors in the treatment of established neutropenia is less well defined and is generally based on clinical judgment and patient-specific risk factors as there is no consensus among published guidelines.

Both filgrastim and sargramostim have also proven effective in accelerating hematopoietic engraftment and in treating graft failure after hematopoietic stem cell transplantation. Other uses for the factors include peripheral blood stem cell mobilization and congenital or idiopathic neutropenia. Growth factors should be used with caution in patients receiving concomitant chemotherapy and radiotherapy, especially if the radiation involves the mediastinum. These patients appear to experience more significant thrombocytopenia.

At currently recommended doses, these factors are well tolerated. Toxicities are more commonly seen with sargramostim and may be related to its ability to

enhance binding of neutrophils to endothelial cells or to activation of monocytes or macrophages, which may stimulate the release of cytokines such as IL-1 and TNF-α.[77] The most common adverse event with these factors is bone pain. Other toxicities include constitutional symptoms, such as low-grade fever, myalgia, arthralgia, lethargy, and mild headache. At higher sargramostim doses, pleural and pericardial effusions, capillary leak syndrome, and thrombus formation may occur. Both factors may produce mild erythema at subcutaneous injection sites, as well as a generalized maculopapular rash. The toxicities observed with pegfilgrastim are similar to those of filgrastim.

Growth factors should be started between 24 and 72 hours after chemotherapy. Filgrastim and sargramostim can be stopped the day before chemotherapy, but pegfilgrastim should be administered at least 14 days before the next dose of chemotherapy due to its extended half-life. Both sargramostim and filgrastim may be given intravenously, but subcutaneous administration is preferred. Because of the high cost of these agents, doses are commonly rounded to the nearest product vial size to minimize waste.

Thrombocytopenia

Thrombocytopenia associated with chemotherapy increases the risk for significant bleeding. To date, platelet transfusions remain the mainstay of management. At most centers, platelet transfusions are reserved for patients with a platelet count of less than 10,000 cells/mm^3 (10×10^9/L) unless the patient is actively bleeding, must undergo a surgical procedure, or has documented infections or fever. Oprelvekin (IL-11) was previously available for the treatment of thrombocytopenia but was associated with significant toxicities and is no longer available in the United States.

Gastrointestinal

Nausea and vomiting are common toxicities observed with chemotherapies and some small molecular targeted agents. Medications to minimize the risk of nausea and vomiting are typically given before administration of anticancer agents with emetic risk. The antiemetic medications selected depends on the underlying emetogenic potential of the anticancer regimen and patient-specific risk factors. In addition to scheduled medications to prevent nausea and vomiting, patients should be given an as-needed medication to take if nausea/vomiting develop. The underlying pathophysiology and available antiemetic regimens are discussed further in Chapter 52, “Nausea and

Vomiting."

The gastrointestinal mucosa is a common site of toxicity associated with anticancer therapy. The subsequent inflammation (mucositis) can lead to painful ulcerations, local infection, and an inability to eat, drink, or swallow. Disruption of the gastrointestinal mucosal barrier may also provide an avenue for systemic microbial invasion. Anticancer agents most commonly associated with mucositis include 5-FU, doxorubicin, methotrexate, multikinase inhibitors, and mTOR inhibitors. Currently, the most effective means of preventing mucositis is through good oral hygiene. Patients who are at high risk for this toxicity (those with poor dentition, high-dose chemotherapy, or radiation therapy involving the oropharynx) should be evaluated by a dentist before starting therapy and should be instructed to rinse their mouths frequently with baking soda and salt water or plain saline rinses during therapy. Clinical practice guidelines for the prevention and treatment of anticancer therapy-induced mucositis are available.

A better understanding of the pathophysiology of mucositis has resulted in identification of promising new agents that may minimize the risk of developing mucositis. The keratinocyte growth factor palifermin is approved for use in patients receiving hematopoietic stem cell transplant conditioning regimens. Palifermin is administered intravenously for three consecutive days immediately before the initiation of myelotoxic therapy and then again for 3 days after the completion of the myelotoxic regimen. The effect of palifermin on solid tumor growth is unknown, and its use in nonhematologic cancers is not recommended.

After mucositis has developed, treatment is mainly supportive, including use of topical or systemic analgesics and oral hygiene. Numerous formulations of "magic mouthwash" are commercially available or compounded and often include viscous lidocaine, diphenhydramine, and liquid antacid. These mouthwashes are commonly used in clinical practice despite insufficient data. Severe cases of mucositis may lead to dehydration and require intravenous hydration and opioid analgesics. Local infections caused by *Candida* species and HSV are common in these patients. Suspicious lesions should be cultured and appropriate antifungal or antiviral treatment should then be initiated. Antifungal therapy may be delivered topically for mild infections (thrush) with clotrimazole troches or nystatin oral suspension. For more severe oral or esophageal fungal infections, systemic treatment with oral or intravenous antifungals is indicated.

Mucosal damage can occur at any point along the entire length of the gastrointestinal tract. In the lower portion of the gastrointestinal tract, this damage is usually manifested as diarrhea and abdominal pain. Intravenous fluids and electrolyte supplementation should be initiated promptly in severe cases.

After infectious causes have been ruled out, diarrhea can safely be treated with agents such as diphenoxylate/atropine or loperamide. The somatostatin analogue octreotide has also been used successfully to treat severe cases of chemotherapy-induced refractory diarrhea; guidelines for the treatment of chemotherapy-induced diarrhea are available.

It is important to note that patients receiving immunotherapy may experience diarrhea that is immune-mediated, and corticosteroids should be administered in prolonged or severe cases. Irinotecan can cause an acute or delayed diarrhea. Acute diarrhea occurs within the first 24 hours after administration and should be managed with atropine to counteract the underlying cholinergic mechanism, whereas delayed diarrhea occurs after the initial 24 hours and should be managed as described for chemotherapy-induced diarrhea.

Dermatologic

A multitude of dermatologic adverse reactions have been reported with chemotherapy, targeted agents, and immunotherapy.

Alopecia

Many patients find alopecia to be one of the most distressing toxicities associated with anticancer therapy. Alopecia from chemotherapy is usually temporary and the degree of hair loss varies widely. Hair loss is not limited to the scalp; any area of the body may be affected. Patients receiving a taxane as part of their chemotherapy regimen are especially prone to total body alopecia. Hair loss usually begins 1 to 2 weeks after chemotherapy and regrowth may begin before completing treatment. Cryotherapy (local application of ice) and scalp tourniquets have both been investigated as methods of preventing alopecia. Both techniques produce vasoconstriction, resulting in decreased exposure of hair follicles to the chemotherapy. Notably, the FDA has granted marketing authorization for the DigniCap Cooling System® to reduce alopecia in patients with solid tumors. Long-term effects of scalp-cooling and the risk of scalp metastasis has not been determined. These techniques are contraindicated in patients whose cancer can metastasize to the scalp, such as leukemia and lymphoma.

In addition to alopecia, other hair changes may occur that may be distressing to patients. Notably, some kinase inhibitors (eg, pazopanib) have been associated with hair depigmentation. This loss of pigmentation (white color) is thought to be the result of the inhibition of KIT signaling which decreases melatonin

synthesis.

Extravasation

Vesicants are agents that may cause severe tissue damage if they escape from the vasculature. These agents include the anthracyclines, the vinca alkaloids, the taxanes, and others. The anthracyclines are the most notorious agents and the most extensively investigated. The tissue damage may result in prolonged pain, tissue sloughing, infection, and loss of mobility. Prompt initiation of the appropriate interventions is important to minimize morbidity. Unfortunately, most information on extravasation management is anecdotal and few controlled clinical trials have been conducted to determine optimal intervention strategies. Consequently, prevention is the focus of extravasation management. The most important method of prevention is good administration technique, but extravasations may occur despite optimal administration.[78] The vein selected for administration should be on the distal portion of the arm. The large veins of the forearm are desirable because if a drug does extravasate, there is adequate soft tissue coverage to protect crucial structures such as nerves and tendons and joint function is not put at risk. The healthcare provider administering the vesicant should verify needle stability and adequate blood return regularly throughout the administration. A central venous catheter is highly recommended for the intravenous infusion of vesicants of longer duration. For extravasation of anthracyclines, antitumor antibiotics, and alkylating agents, apply ice packs to the affected area. Only a few antidotes to vesicant agents are used clinically. Topical dimethyl sulfoxide (DMSO) or intravenous dexrazoxane are recommended as antidotes for anthracycline extravasation. Topical DMSO may also be given for mitomycin C extravasation. Dry, warm compresses and hyaluronidase are recommended for the extravasation of vinca alkaloids and taxanes. Clinical practice guidelines for the management of extravasation are available.[79]

HFSR and Hand-Foot Syndrome

Although the terms HFSR and hand-foot syndrome are commonly interchanged, it is important to note that these adverse reactions are distinct in both cause and presentation. HFSR is associated with multikinase inhibitors and characteristically localizes to areas of pressure or friction on the hands and feet. Hand-foot syndrome, also known as palmar-plantar erythrodysesthesia, is associated with chemotherapy including 5-FU, capecitabine, and liposomal doxorubicin. Hand-foot syndrome typically presents with diffuse edema and

redness on the palms and soles of the feet. Both HFSR and hand-foot syndrome can be uncomfortable and interfere with daily activities. Topical moisturizers may aid in prevention. Urea cream, topical steroids, and pain medication (such as gabapentin or an NSAID) may be beneficial for treatment.

Rash

Rash has been observed with some targeted agents. For example, rash is one of the most common toxicities associated with therapy that inhibits EGFR signaling pathways. Some studies suggest that the rash may be a surrogate marker of response to these agents. Therefore, extensive patient counseling is required to prevent premature drug discontinuation. Patients should also be instructed to prophylactically apply sunscreen and avoid alcohol-containing skin products. Rash occurs in up to two-thirds of patients taking EGFR inhibitors, most commonly in the first month of treatment with the typical site of presentation being the face and upper torso. Anecdotal reports indicate that emollients help if patients present with dry skin, topical and systemic antibiotics may help if the rash becomes infected, and steroids may help prevent itching and inflammation.

Endocrine

Blood Glucose Dysregulation

Both hyper- and hypoglycemia have been reported with numerous small molecular and mAb targeted agents. Hyperglycemia is most commonly associated with mTOR inhibitors. Fasting blood glucose and hemoglobin A1C should be monitored closely especially in diabetic patients. Standard guidelines should be used to adjust antidiabetic medications as necessary. Hypoglycemia has been commonly reported with multikinase inhibitors and bexarotene. Fasting blood glucose should be closely monitored and doses of antidiabetic medications reduced as required. Although rare, immune checkpoint inhibitors have been associated with new-onset diabetes.

Hypothyroidism

Hypothyroidism is a common adverse event that is seen with multikinase inhibitors and immunotherapies. Thyroid stimulating hormone (TSH) and free T4 should be measured at baseline and periodically throughout treatment. Most symptoms are mild and can be reversed with thyroid supplementation. Bexarotene has also been associated with hypothyroidism. It rapidly suppresses

TSH levels and affects thyroid hormone metabolism. Free T4 levels should be monitored closely and supplementation is usually required.

Immune-Related Adverse Events

Immune checkpoint inhibitors (ie, CTLA-4, PD-1, and PD-L1 inhibitors) work by activating the immune response but this activation can enable the immune system to attack healthy cells. These irAEs can affect multiple organs; most commonly the lung, skin, liver, gastrointestinal tract, and kidney. Patients with pre-existing autoimmune disease or prior organ transplant appear to be at a higher risk of developing these adverse reactions and the benefit-risk ratio should be carefully explored in these patients. Depending on the severity of the irAE, the immunotherapy may be withheld or permanently discontinued. Early detection is vital in optimizing patient outcomes and corticosteroids and other immunosuppressive agents may be needed to adequately manage moderate-to-severe irAEs. Several clinical practice guidelines to manage irAEs have been published by various professional organizations including the Society for Immunotherapy of Cancer, the European Society for Medical Oncology, the NCCN, and the American Society of Clinical Oncology.

Cytokine Release Syndrome

CRS is a potentially life-threatening systemic inflammatory reaction that may be observed after administration of CAR T-cell therapies. Additionally, blinatumomab has been associated with a dose-dependent CRS and the incidence has been reduced with modification of the administration schedule. The development of CRS occurs following by an increase of inflammatory cytokines (such as IL-6), which are released after the activation and destruction of monocytes, macrophages, and lymphocytes by the CAR therapies. Presentation of CRS may include various constitutional symptoms, organ-related disorders, and laboratory abnormalities such as fever, chills, headache, myalgia, arthralgia, bronchospasm, dyspnea, hypotension, tachycardia, arrhythmia, confusion, dermatologic reactions, hypokalemia, decreased renal function, and coagulopathies. Treatment options include supportive care and tocilizumab for severe CRS. By neutralizing the key mediator (IL-6), tocilizumab interrupts the inflammatory process.

Miscellaneous

Numerous other toxicities are seen with both targeted therapies and chemotherapy agents and many of these are discussed in other chapters. A few common toxicities including hypertension and ocular toxicities are discussed here.

Hypertension

Many anticancer agents, especially those that inhibit the VEGF signaling pathway, are associated with hypertension. Although the exact mechanism has yet to be established, it is thought that VEGF inhibition leads to a decrease in nitric oxide and prostacyclin production, resulting in an increase in vascular resistance and blood pressure.[80] Prior to treatment initiation, blood pressure should be well-controlled according to standard guidelines. If hypertension develops, antihypertensive therapy should be initiated or adjusted. Anticancer treatment should be held with persistent or severe hypertension.

Ocular

A broad spectrum of ocular toxicities are seen with kinase inhibitors, immunotherapies, and chemotherapy agents. Common ocular toxicities seen with a variety of anticancer agents include blurred vision, photophobia, conjunctivitis, cataracts, abnormal lacrimation, dry eye, keratitis, optic neuropathy, and retinopathy.

Thrombosis

Patients with cancer have a higher risk of developing a VTE compared to the general population. The factors that may affect a patient's risk of developing a thromboembolism include the specific cancer (ie, lung cancer, pancreatic cancer, gastric cancer), tumor burden, anticancer treatment (ie, antiangiogenic agents and endocrine therapies), and surgical interventions. Other risk factors might include familial thrombophilia, previous VTE, immobilization, age, and indwelling catheters. Thromboembolism increases morbidity and mortality, with thromboembolic events a leading cause of death in patients with cancer.

Routine primary prophylaxis is not recommended for most patients, but it should be considered for patients undergoing major surgery or for immobilized hospitalized patients. Unfractionated heparin or a low-molecular-weight heparin is recommended for patients undergoing major surgery. As discussed earlier in the chapter, thromboprophylaxis is recommended with thalidomide and its analogues.

For patients who develop a VTE, treatment goals include preventing a pulmonary embolus, reducing risk of recurrence, and avoiding long-term complications. In ambulatory patients, current guidelines prefer a low-molecular-weight heparin, although new data with direct oral anticoagulants in this population is emerging. For patients with severe renal impairment, anti-Xa activity monitoring or unfractionated heparin is recommended and dose modifications may be necessary. Treatment with oral vitamin K antagonists, such as warfarin, is not currently recommended as first-line treatment. The optimal duration of antithrombotic therapy for the prevention of recurrence has not been specifically studied and is often determined based on patient-specific factors including the underlying disease and anticancer treatment. Treatment duration may be a minimum of 3 to 6 months or indefinite.

Survivorship

Advances in the treatment of some cancers, such as ALL, Hodgkin lymphoma and testicular cancer, have produced long-term survivors and the opportunity to examine the late consequences of chemotherapy. Survivors should be assessed for long-term psychosocial and physical effects and survivorship guidelines are available for health professionals through the NCCN.[81] Infertility and secondary cancers have emerged as important late effects.

Infertility

The gonadal toxicities of chemotherapy have not received much attention in the past because they are not life threatening. High rates of fertility deficits and sexual dysfunction have been noted for both men and women. In men, chemotherapy can produce severe oligospermia or azoospermia, as well as infertility. Serum testosterone levels are rarely altered. The recovery of spermatogenesis after completing therapy is unpredictable. Men receiving combination chemotherapy appear to sustain more long-lasting toxicities on fertility than do men receiving single-agent chemotherapy. Age, total dose, duration of therapy, and the chemotherapy mechanism are other important variables. In women, toxic effects on the ovaries result clinically in amenorrhea, vaginal epithelial atrophy, and menopausal symptoms. These effects are related to dose and age. Younger patients are more resistant to the effects on the ovaries. As with men, the recovery of fertility is unpredictable, but women younger than 25 years of age appear to have the best outcomes. The effects of the alkylating agents on fertility have been extensively studied. These agents exert profound

and consistently detrimental effects on reproductive function. The impact of this drug-induced amenorrhea on patient survival has been less clear with some trials demonstrating a benefit to patients who achieve chemotherapy-induced amenorrhea. Trial results have been mixed, however, and conclusive statements cannot be made at this time.

The risk of infertility with other anticancer agents, such as tyrosine kinase inhibitors, is unknown. The risk of infertility should be discussed with all patients before they receive anticancer agents, and they should be informed about options for fertility preservation.

Secondary Malignancies

Secondary cancers induced by chemotherapy and radiation are serious long-term complications.[82] Some targeted drugs may also be associated with development of secondary cancers. Although many solid tumors have been reported as chemotherapy-induced malignancies, AML and MDS are the most common secondary cancers and have been reported after successful treatment of Hodgkin lymphoma, NHL, acute leukemias, multiple myeloma, breast cancer, and advanced ovarian cancer. For curable cancers, the relatively small risk for occurrence of secondary malignancies is far outweighed by the benefits of survival in large numbers of patients. The risk of secondary malignancies is of particular concern in patients receiving adjuvant chemotherapy. As with the late complication of infertility, the anticancer agents primarily associated with secondary cancers are the alkylating agents. Etoposide, teniposide, radioimmunoconjugates, and the anthracyclines also are linked to secondary leukemias. Solid tumors as secondary malignancies occur more commonly after treatment with radiation than with chemotherapy.

Postclass Engaged Learning Activity

Immune checkpoint inhibitors have revolutionized the treatment of patients with cancer. However, their unique toxicity profile brings a new challenge to the health professional. Multiple guidelines have been published by oncologic societies to aid in the management of immune-related adverse events (irAEs). Please review the joint ASCO/NCCN “Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy” published in 2018. Based on these guidelines, please provide your recommendations on the case below.

Patient Case

AD is a 64-year-old female with metastatic urothelial carcinoma who presents to clinic for cycle 5 day 1 of pembrolizumab. She complains of a 3-day history of severe abdominal pain and “profuse diarrhea” which she estimates to be about 10 bowel movements per day (baseline = 1 bowel movement/day). On exam, there is tenderness to palpation but overall you feel her symptoms are not life-threatening. Based on vital signs and laboratory assessments, you admit the patient. Work-up suggests an inflammatory process in the colon which you attribute to pembrolizumab.

PMH: HTN diagnosed 3 years ago, metastatic urothelial carcinoma diagnosed 5 months ago

Vitals: 0_2sat: 98% RA; HR 82 bpm; BP 99/51 mm Hg; 37.4°C

Labs: sodium 138 mmol/L (136-145 mmol/L); potassium 2.9 mmol/L (3.4-5.1 mmol/L); chloride 99 mmol/L (98-107 mmol/L); glucose 98 mg/dL (74-99 mg/dL) or 5.4 mmol/L (4.1-5.5 mmol/L); albumin 3.6 g/dL (3.5-5.2 g/dL) or 36 g/L (35-52 g/L); calcium 9.28 mg/dL (8.60-10.2 mg/dL) or 2.32 mmol/L (2.15-2.55 mmol/L); magnesium 1.34 mg/dL (1.61- 2.60 mg/dL) or 0.55 mmol/L (0.66-1.07 mmol/L); phosphorous 2.0 mg/dL (2.5-4.5 mg/dL) or 0.65 mmol/L (0.81-1.45 mmol/L); creatinine 0.94 mg/dL or 83 µmol/L (CrCl ~80 mL/min or 1.33 mL/s); ALT 28 U/L (0-33 U/L) or 0.47 µkat/L (0-0.55 µkat/L); ALT 23 U/L (0-32 U/L) or 0.38 µkat/L (0-0.53 µkat/L); T Bili 0.02 mg/dL (0-1.2 mg/dL) or 0.3 µmol/L (0-20.5 µmol/L)
Allergies: NKDA

Medication List: lisinopril 10 mg PO once daily; pembrolizumab 200 mg IV every 3 weeks

Q1. Using NCI CTCAE v5.0, what grade of colitis is AD experiencing?

Q2. Based on the ASCO/NCCN guidelines, what is your initial treatment recommendation for this patient?

Q3. After 72 hours of treatment with your initial recommendation, AD’s symptoms have not improved. What is your recommendation for refractory colitis?

ABBREVIATIONS

2-HG	D-2-hydroxyglutarate
5-FU	fluorouracil
6-MP	6-mercaptopurine
ADA	antidrug antibodies
ADC	antibody-drug conjugate
ADCC	antibody-dependent cell-mediated cytotoxicity
AFP	alpha-fetoprotein
AI	aromatase inhibitor
ALL	acute lymphoblastic leukemia
ALK	anaplastic lymphoma kinase
αKG	alpha-ketoglutarate
AML	acute myeloid leukemia
ANC	absolute neutrophil count
APA	antiproduct antibodies
APC	adenomatous polyposis coli
APL	acute promyelocytic leukemia
ATP	adenosine triphosphate
BCNU	carmustine
BCL-2	B-cell lymphoma 2
BCR	B-cell receptor
BCR-ABL	breakpoint cluster region-Abelson
BRCA	breast cancer gene
BSA	body surface area
BTK	Bruton's tyrosine kinase
CAR	chimeric antigen receptor
CCNU	lomustine
CCR4	CC chemokine receptor 4
CD	cluster of differentiation
CDC	complement-dependent cytotoxicity
CDK	cyclin-dependent kinase
CLL	chronic lymphocytic leukemia
CML	chronic myeloid leukemia
CNS	central nervous system

CPIC	Clinical Pharmacogenetics Implementation Consortium
CR	complete response
CRS	cytokine release syndrome
CRES	CAR T-cell related encephalopathy
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte antigen 4
DCC	deleted in colorectal cancer
DHFR	dihydrofolate reductase
DM1	derivative of maytansine 1
dMMR	mismatch repair deficient
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DNMT	DNA methyltransferase
DPD	dihydropyrimidine dehydrogenase
EBV	Epstein-Barr virus
ECG	electrocardiograph
ECOG	Eastern cooperative oncology group
EGFR	epidermal growth factor receptor
EML4	echinoderm microtubule-like protein 4
ER	estrogen receptor
ErbB	erythroblastic leukemia viral oncogene
ERK	extracellular signal-regulated kinase
FDA	Food and Drug Administration
FGFR	fibroblast growth factor receptor
FKBP-12	12-kilodalton FK506 binding protein
FLT3	FMS-like tyrosine kinase 3
GEP-NET	gastroenteropancreatic neuroendocrine tumors
GFR	glomerular filtration rate
GIST	gastrointestinal stromal tumor
GM-CSF	granulocyte-macrophage colony stimulating factor
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HDAC	histone deacetylase
HER2	human epidermal growth factor receptor 2
HFSR	hand-foot skin reaction
HHV	human herpes virus
HIV	human immunodeficiency virus
HPV	human papilloma virus
HSV	herpes simplex virus
IDH	isocitrate dehydrogenase
IFN	interferon
IGF-1R	insulin-like growth factor 1 receptor
IL	interleukin
irAE	immune-related adverse event
irRC	immune-related response criteria
irRECIST	immune-related RECIST
ISO	International Organization for Standardization
ITD	internal tandem duplications
JAK	Janus kinase
JAK-STAT	Janus kinase–signal transducers and activators of transcription
KPS	karnofsky performance status
mAb	monoclonal antibody
MAPK	mitogen-activated protein kinase
MCD	multicentric Castleman's Disease
MDS	myelodysplastic syndrome
MEK	mitogen-activated protein kinase- extracellular signal-regulated kinase
MMAE	monomethylauristatin E
MRD	measurable residual disease
mRECIST	modified RECIST
MSI-H	microsatellite instability-high
MTIC	monomethyl triazeno-imidazole-carboxamide

mTOR	mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NF-κB	nuclear factor-κB
NHL	non-Hodgkin lymphoma
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
NTRK	neurotrophic receptor tyrosine kinase
Pap	Papanicolaou
PAP	prostate acid phosphatase
PARP	poly ADP ribose polymerase
PCV	polycythemia vera
PD-1	programmed death-1
PD-L1	programmed death ligand-1
PDGF	platelet-derived growth factor
PDGFR	platelet-derived growth factor receptor
Pgp	p-glycoprotein
Ph^+	Philadelphia chromosome-positive
PI3K	phosphatidylinositide 3-kinases
PML	progressive multifocal leukoencephalopathy
PR	partial response
pRb	retinoblastoma protein
PSA	prostate-specific antigen
PTEN	phosphatase and tensin homolog
RANK	receptor activator of nuclear factor kappa-B
RANKL	receptor activator of nuclear factor kappa-B ligand
RAR	retinoic acid receptor
Rb	retinoblastoma
RECIST	response evaluation criteria in solid tumors
REMS	risk evaluation and mitigation strategy
RET	rearranged during transfection
RNA	ribonucleic acid
RXR	retinoid X receptor
SERM	selective estrogen receptor modulator
SLAMF7	signaling lymphocytic activation molecule family 7
SMO	smoothened
STAT	signal transducers and activators of transcription
T-VEC	talimogene laherparepvec
TKD	tyrosine kinase domain
TLS	tumor lysis syndrome
TNF-α	tumor necrosis factor-alpha
TPMT	thiopurine methyltransferase
TRK	tropomyosin receptor kinase
TSC	tubular sclerosis complex
TSH	thyroid stimulating hormone
UGT1A1	uridine diphosphate-glucuronosyl transferase 1A1
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VTE	venous thromboembolism

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;68:7–34.
2. Weston A, Harris CC, et al. Chemical carcinogenesis. In: Waun KH, Bast RC, Hait WN, et al., eds. *Cancer Medicine*. 8th ed. Shelton, CT: People's Medical Publishing House-USA; 2010;225–236.
3. Stricker TP, Kumar V. Neoplasia. In: Kumar V, Abbas AK, Aster JC, Fausto N, eds. *Robbins and Cotran Pathologic Basis of Disease*. 8th ed. Philadelphia, PA: Saunders; 2010;259–330.
4. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. *Cell*. 2011;144:646–674.
5. Davar D, Beumer JH, Hamieh L, Tawbi H. Role of PARP inhibitors in cancer biology and therapy. *Curr Med Chem*. 2012;19:3907–3921.
6. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med*. 2015;372:2509–2520.
7. Richman S. Deficient mismatch repair: Read all about it (review). *Int J Oncol*. 2015;47:1189–1202.
8. Duarte JD. Epigenetics primer: Why the clinician should care about epigenetics. *Pharmacotherapy*. 2013;33:1362–1368.
9. Clark O, Yen K, Mellinghoff IK. Molecular pathways: Isocitrate dehydrogenase mutations in cancer. *Clin Cancer Res*. 2016;22:1837–1842.
10. Minn AJ, Massave J. Invasion and metastases. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.
11. Heymach JV, Sledge GW, Jain RK, et al. Tumor angiogenesis. In: Waun KH, Bast RC, Hait WN, et al., eds. *Cancer Medicine*. 8th ed. Shelton, CT: People's Medical Publishing House-USA; 2010;149–169.
12. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2018: A review of current American Cancer Society guidelines and issues in cancer screening. *CA Cancer J Clin*. 2018;68:297–316.
13. American Cancer Society study communicating cancer information through mass distribution leaflets: An American Cancer Society study. *Ca Cancer J Clin*. 1967;17:291–293.
14. Santarpia L, Lippman SM, El-Naggar AK. Targeting the MAPK-RAS-

RAF signaling pathway in cancer therapy. *Expert Opin Ther Targets*. 2012;16:103–119.

15. Amstutz U, Froehlich TK, Largiadèr CR. Dihydropyrimidine dehydrogenase gene as a major predictor of severe 5-fluorouracil toxicity. *Pharmacogenomics*. 2011;12:1321–1336.
16. Hui J, Przespo E, Elefante A. Pralatrexate: A novel synthetic antifolate for relapsed or refractory peripheral T-cell lymphoma and other potential uses. *J Oncol Pharm Pract*. 2012;18:275–283.
17. Jain S,Vahdat LT. Eribulin mesylate.*Clin Cancer Res*.2011;17:6615–6622.
18. Mita AC, Figlin R, Mita MM. Cabazitaxel: More than a new taxane for metastatic castrate-resistant prostate cancer? *Clin Cancer Res*. 2012;18:6574–6579.
19. Rubin EH, Hait WN, et al. Drugs that target DNA topoisomerase. In: Waun KH, Bast RC, Hait WN, et al., eds. *Cancer Medicine*. 8th ed. Shelton, CT: People's Medical Publishing House-USA; 2010;645–654.
20. Colvin M, et al. Alkylating agents and platinum antitumor compounds. In: Waun KH, Bast RC, Hait WN, et al., eds. *Cancer Medicine*. 8th ed. Shelton, CT: People's Medical Publishing House-USA; 2010;633–644.
21. Cheson BD,Rummel MJ. Bendamustine: Rebirth of an old drug.*J Clin Oncol*.2009;27:1492–1501.
22. Loprinzi CL, Qin R, Dakhil SR, et al. Phase III randomized, placebo-controlled, double-blind study of intravenous calcium and magnesium to prevent oxaliplatin-induced sensory neurotoxicity. *J Clin Oncol*. 2014;32:997–1005.
23. Turck R. Radio-pharmaceuticals for cancer treatment: Are they ready for prime time yet? *Ann Oncol*. 2018;29:1594–1597.
24. Wetzler M, Segal D. Omacetaxine as an anticancer therapeutic: What is old is new again. *Curr Pharm Res*. 2011;17:59–64.
25. Busse D,Yakes FM,Lenferink AE,Arteaga CL. Tyrosine kinase inhibitors: Rationale, mechanisms of action, and implications for drug resistance.*Semin Oncol*.2001;28(suppl 16):47–55.
26. Camidge DR, Bang YJ, Kwak EL, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: Updated results from a phase 1 study. *Lancet Oncol*. 2012;13:1011–1019.
27. Shaw AT, Kim D, Mehra R, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. *N Engl J Med*. 2014;370:1189–1197.

28. Solomon BJ, Besse B, Bauer TM, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: Results from a global phase 2 study. *Lancet Oncol*. 2018;19:1654–1667.
29. Anderson MA, Deng J, Seymour JF, et al. The BCL2 selective inhibitor venetoclax induces rapid onset apoptosis of CLL cells in patients via a TP53-independent mechanism. *Blood*. 2016;127:3215–3224.
30. Keller-V Amsberg G, Brummendorf TH. Novel aspects of therapy with the dual Src and Abl kinase inhibitor bosutinib in chronic myeloid leukemia. *Expert Rev Anticancer Ther*. 2012;12:1121–1127.
31. Gibbons DL, Pricl S, Kantarjian H, Cortes J, Quintas-Cardama A. The rise and fall of gatekeeper mutations? The BCR-ABL1 T315I paradigm *Cancer*. 2012;118:293–299.
32. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N Engl J Med*. 2014;371:1877–1888.
33. Burger JA,Buggy JJ. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765).*Leuk Lymphoma*.2013;54:2385–2391.
34. Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2 negative, advanced breast cancer (PALOMA-1/TRIO-18): A randomised phase 2 study. *Lancet Oncol*. 2015;16:25–35.
35. Cadoo KA, Gucalp A, Traina TA. Palbociclib: An evidence-based review of its potential in the treatment of breast cancer. *Breast Cancer: Targets and Therapy*. 2014;6:123–133.
36. Fandy TE. Development of DNA methyltransferase inhibitors for the treatment of neo-plastidiseases.*Curr Med Chem*.2009;16:2075–2085.
37. Pallis AG,Syrigos KN. Epidermal growth factor receptor tyrosine kinase inhibitors in the treatment of NSCLC.*Lung Cancer*.2013;80:120–130.
38. Li T,Perez-Soler R,Saltz L. Skin toxicities associated with epidermal growth factor inhibitors.*Target Oncol*.2009;4:107–119.
39. Iressa (gefintinib) tablets for oral use. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206995s000lbl. Accessed 7 September 2015.
40. Spraggs CF, Budde LR, Briley LP, et al. HLA-DQA1*02:01 is a major risk factor for lapatinib-induced hepatotoxicity in women with advanced breast cancer. *J Clin Oncol*. 2011;29:667–673.

41. Schaid DJ, Spraggs CF, McDonnell SK, et al. Prospective validation of HLA-DRB1*07:01 allele carriage as a predictive risk factor for lapatinib-induced liver injury. *J Clin Oncol*. 2014;32:2296–2303.
42. Patani H, Bunney TD, Thiyagarajan N, et al. Landscape of activating cancer mutations in FGFR kinases and their differential responses to inhibitors in clinical use. *Oncotarget*. 26, 2016;7(17):24252–24268. doi: 10.18632/oncotarget.8132.26992226.
43. San-Miguel JF, Hungria V, Yoon S, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: A multicenter, randomised, double-blind phase 3 trial. *Lancet Oncol*. 2014;15:1195–1206.
44. Verstovsek S, Kantarjian H, Mesa R, et al. Safety and efficacy of INCB018424, a JAK1 and JAK2 inhibitor, in myelofibrosis. *N Engl J Med*. 2010;363:1117–1127.
45. Klümpen H, Beijnen JH, Gurney H, Schellens J. Inhibitors of mTOR. *The Oncologist*. 2010;15:1262–1269.
46. Chau NG,Haddad RI. Vandetanib for the treatment of medullary thyroid cancer.*Clin Cancer Res*.2013;19:524–529.
47. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med*. 2012;366:1382–1392.
48. Audeh MW, Carmichael J, Penson RT, et al. Oral poly (ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: A proof-of-concept trial. *Lancet*. 2010;376:245–251.
49. Paul J, Soujon M, Wengner AM, et al. Simultaneous inhibition of PI3Kδ and PI3Kα induces ABC-DLBCL regression by blocking BCR-dependent and independent activation of NF-κB and AKT. *Cancer Cell*. 2017;31:64–78.
50. Juric D, Rodon J, Tabernero J, et al. Phosphatidylinositol 3-Kinase α-Selective Inhibition with Alpelisib (BYL719) in PIK3CA-Altered Solid Tumors: Results from the First-in-Human Study. *J Clin Oncol*. 2018;36(13):1291–1299. doi: 10.1200/JCO.2017.72.7107.
51. Ruschak AM,Slassi M,Kay LE,Schimmer AD. Novel proteasome inhibitors to overcome bortezomib resistance.*J Natl Cancer Inst*.2011;103:1–11.

52. U.S. Food and Drug Administration. Biosimilars and interchangeable products. Available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareD Accessed, December 18, 2018.
53. Mössner E, Brünker P, Moser S, et al. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated b-cell cytotoxicity. *Blood*. 2010;115:4393–4402.
54. Sehn LH, Assouline SE, Stewart DA, et al. A phase 1 study of obinutuzumab induction followed by 2 years of maintenance in patients with relapsed CD20-positive b-cell malignancies. *Blood*. 2012;119:5118–5125.
55. Cheson BD. Ofatumumab, a novel anti-CD20 monoclonal antibody for the treatment of B-cell malignancies.*J Clin Oncol*.2010;28:3525–3530.
56. Navid F,Santana VM,Barfield RC. Anti-GD2 antibody therapy for GD2-expressing tumors.*Curr Cancer Drug Targets*.2010;10:200–209.
57. Yu AL, Gilman AL, Ozkaynak MF, et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. *N Engl J Med*. 2010;363:1324–1334.
58. van de Donk NW, Moreau P, Plesner T, et al. Clinical efficacy and management of monoclonal antibodies targeting CD38 and SLAMF7 in multiple myeloma. *Blood*. 2016;127:681–695.
59. Allegra CJ, Jessup JM, Somerfield MR, et al. American Society of Clinical Oncology pro-visional clinical opinion: Testing for KRAS gene mutations in patients with metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor mono-clonal antibody therapy. *J Clin Oncol*. 2009;27:2091–2096.
60. Okines AF, Cunningham D. Trastuzumab in gastric cancer. *Eur J Cancer*. 2010;46:1949–1959.
61. Capelan M, Pugliano L, De Azambuja E, et al. Pertuzumab: New hope for patients with HER2-positive breast cancer. *Ann Oncol*. 2013;24:273–282.
62. Clarke JM,Hurwitz HI. Targeted inhibition of VEGF receptor 2: An update on ramucirumab.*Expert Opin Biol Ther*.2013;13:1187–1196.
63. Portell CA, Wenzell CM, Advani AS. Clinical and pharmacologic aspects of blinatumomab in the treatment of b-cell acute lymphoblastic leukemia. *Clin Pharmacol*. 2013;5(suppl 1):5–11.
64. Panowski S, Bhakta S, Raab H, et al. Site-specific antibody drug

conjugates for cancer therapy. *MAbs*. 2014;6:34–45.

65. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med*. 2012;367:1783–1791.
66. Katz J,Janik JE,Younes A. Brentuximab vedotin (SGN-35).*Clin Cancer Res*.2011;17:6428–6436.
67. Palanca-Wessels MC, Czuczman M, Salles G, et al. Safety and activity of the anti-CD79B antibody-drug conjugate polatuzumab vedotin in relapsed or refractory B-cell non-Hodgkin lymphoma and chronic lymphocytic leukaemia: A phase 1 study. *Lancet Oncol*. 2015;16(6):704–715. doi: 10.1016/S1470-2045(15)70128-2.
68. Ekmekcioglu S, Grimm EA, Kurzrock R, et al. Cytokines and hematopoietic growth factors. In: Waun KH, Bast RC, Hait WN, et al., eds. *Cancer Medicine*. 8th ed. Shelton, CT: People's Medical Publishing House-USA; 2010;686–709.
69. Di Lorenzo G,Buonerba C,Kantoff PW. Immunotherapy for the treatment of prostate cancer.*Nat Rev Clin Oncol*.2011;8:551–561.
70. Eisenhauer EA,Therasse P,Bogaerts J,et al. New response evaluation criteria in solid tumours: Revised RECIST guidelines (version 1.1).*Eur J Cancer*.2009;45:228–247.
71. Lencioni R,Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma.*Semin Liver Dis*.2010;30:52–60.
72. Wolchok JD,Hoos A,O'Day S,et al. Guidelines for the evaluation of immune therapy activity in solid tumors: Immune-related response criteria.*Clin Cancer Res*.2009;15:7412–7420.
73. Bohnsack O, Hoos A, Ludajic K. Adaptation of the immune related response criteria: irRECIST. Abstract presented at: ESMO 2014 Congress; 2014 September 26-30; Madrid, Spain.
74. Schuurhuis GJ, Heuser M, Freeman S, et al. Minimal/measurable residual disease in AML: A consensus document from the European LeukemiaNet MRD Working Party. *Blood*. 2018;131:1275–1291.
75. Goodin S, Griffith N, Chen B, et al. Safe Handling of oral chemotherapeutic agents in clinical practice: Recommendations from an international pharmacy panel.*J Oncol Pract*.2011;7:7–12.
76. The NCCN Myeloid Growth Factor Clinical Practice Guidelines in Oncology (version 2.2019). National Comprehensive Cancer Network, Inc. 2019. Available at: http://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf.

Accessed October 15, 2019.

77. Metcalf D. The colony-stimulating factors and cancer.*Nat Rev Cancer*.2010;10:425–434.
78. McCurdy MT, Shanholtz CB. Oncologic emergencies. *Crit Care Med*. 2012;40:2212–2222.
79. Pérez Fidalgo JA, García Fabregat L, Cervantes A, et al. Management of chemotherapy extravasation: ESMO-EONS clinical practice guidelines. *Ann Oncol*. 2012;23(suppl 7):167–173.
80. Bhargava P. VEGF kinase inhibitors: How do they cause hypertension?*Am J Physiol Regul Integr Comp Physiol*.2009;297:R1–R5.
81. The NCCN Survivorship Clinical Practice Guidelines in Oncology (version 2.2019). National Comprehensive Cancer Network, Inc. 2019. Available at http://www.nccn.org/professionals/physician_gls/pdf/survivorship.pdf. Accessed October 15, 2019.
82. Travis LB, Bhatia S, Allan JM, Oeffinger KC, Ng A. Second primary cancers. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer Principles and Practice of Oncology*. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.

145

Breast Cancer

Bonnie Lin Boster, Neelam K. Patel, and Laura Boehnke Michaud

KEY CONCEPTS

1. Breast cancer is usually diagnosed in the early stages when it is highly curable.
2. Although controversial, regular screening mammography in women younger than 50 years of age is beneficial, and many studies demonstrate that annual or biennial screening mammography in women ages 50 to 74 years reduces the breast cancer mortality rate.
3. Local therapy of early-stage breast cancer consists of modified radical mastectomy or lumpectomy plus external-beam radiation therapy. The surgical approach to the ipsilateral axilla may consist of a lymph node mapping procedure with sentinel lymph node biopsy or a full level I/II axillary lymph node dissection.
4. Adjuvant endocrine therapy reduces the rates of relapse and death in patients with hormone receptor–positive early breast cancer. Adjuvant chemotherapy reduces the rates of relapse and death in all patients with early-stage breast cancer.
5. The choice of the most appropriate chemotherapy, endocrine therapy, and anti-*HER2* therapy regimen is complex and rapidly changes as results from ongoing randomized clinical trials are reported.
6. Neoadjuvant chemotherapy and biotherapy are appropriate for selected patients with early breast cancer and most patients with locally advanced and inflammatory breast cancer followed by local therapy and further adjuvant systemic therapy as indicated.
7. The goal of adjuvant and neoadjuvant chemotherapy is cure while the goal of chemotherapy in the metastatic setting is palliation.
8. Anti-*HER2* therapies and other biologic or targeted agents (eg, everolimus,

cyclin-dependent kinase [CDK] inhibitors) in combination with chemotherapy or endocrine therapy have significantly improved outcomes for patients with metastatic breast cancer (MBC).

9. Initial therapy of MBC in most women with hormone receptor–positive tumors should include endocrine therapy.
10. About 60% of women with MBC will respond to chemotherapy regimens; anthracycline- and taxane-containing regimens are the most active.

Preclass Engaged Learning Activity

Create a summary table of anti-*HER2* treatment options for patients treated in the adjuvant setting with *HER2*-positive breast cancer. Conduct a literature search and discuss their impact on treatment.

INTRODUCTION

Breast cancer is the most common cancer and is second only to lung cancer as a cause of cancer death in American women. It is estimated that 271,270 new cases of breast cancer were diagnosed and that 42,260 people died of breast cancer in 2019.[1] In addition to invasive breast cancers, it is estimated that 62,930 cases of noninvasive, or *in situ*, cancer were diagnosed among women in the United States in 2019.[1]

Female breast cancer incidence rates have increased for women since 1980, although the rate of increase slowed in the 1990s and decreased starting in 2000. The decreased incidence of about 7% from 2002 to 2003 is thought to be related to decreased use of menopausal hormone therapy, also known as hormone replacement therapy (HRT), in postmenopausal women.[2] The incidence of carcinoma *in situ* also increased rapidly in the 1980s and continues to increase; the increase is attributed to the increased use of screening mammography.[2]

Female breast cancer incidence rates vary considerably across racial and ethnic groups. The average annual age-adjusted incidence rate from 2010 to 2014 was 128.7 cases per 100,000 among non-Hispanic whites, 125.5 cases among non-Hispanic African Americans, 91.9 cases in Hispanics, 100.7 cases in American Indians/Alaska Natives, and 90.8 cases among Asian Americans/Pacific Islanders.[3] The higher incidence rates in whites than in other

racial and ethnic groups may be related to differences in reproductive and lifestyle factors and access to and use of screening.

1 For all racial and ethnic groups, most breast cancers are diagnosed at an early stage when tumors are small and localized. Unfortunately, breast cancer mortality is higher among African American women compared to white women despite the lower incidence. The cause of this disparity between white and African American women is widely debated and multifactorial, and proposed explanations include differences in stage at diagnosis, tumor characteristics, obesity, comorbidities, access to care, adherence to therapy, and response to treatment.[2] Overall breast cancer mortality rates in the United States have declined since 1990; this decline has been attributed to improvements in early detection and treatment.[2]

The median age at diagnosis for breast cancer is 62 years of age.[2] Although lung cancer is the leading cause of cancer deaths for women regardless of age, breast cancer is the leading cause of cancer deaths for females between the ages of 20 and 59 years.[3]

EPIDEMIOLOGY AND ETIOLOGY

The two variables most strongly associated with the occurrence of breast cancer are gender and age. Although one commonly thinks of breast cancer as a disease confined to women, about 2,670 cases of male breast cancer are estimated to be diagnosed in the United States in 2019.[2] Men are more likely to have more advanced disease at the time of diagnosis. Men also have lower unadjusted rates of overall survival than women with breast cancer. This difference is not only due to advanced disease at diagnosis but also older age at diagnosis as well as shorter life expectancy in general.[4] Treatment of breast cancer in men is similar to treatment in women.

The incidence of breast cancer increases with advancing age. A frequently quoted breast cancer statistic is that one in eight women will develop breast cancer during her lifetime. It should be emphasized that this is a cumulative lifetime risk of developing the disease from birth to death. The one-in-eight women figure is often misinterpreted by women who assume that it translates into one in eight women being diagnosed with breast cancer each year. A more useful method of presenting the risk data is based on age intervals (see **Table 145-1**).

TABLE 145-1 Age-specific Ten-year Probability of Breast Cancer Diagnosis or Death for US Women

Current Age	Diagnosed with invasive Breast Cancer	Dying from Breast Cancer
20	0.1% (1 in 1,479)	<0.1% (1 in 18,503)
30	0.5% (1 in 209)	<0.1% (1 in 2,016)
40	1.5% (1 in 65)	0.2% (1 in 645)
50	2.4% (1 in 42)	0.3% (1 in 310)
60	3.5% (1 in 28)	0.5% (1 in 193)
70	4.1% (1 in 25)	0.8% (1 in 132)
80	3.0% (1 in 33)	1.0% (1 in 101)
Lifetime risk	**12.8% (1 in 8)**	**2.6% (1 in 39)**

Note: Probability is among those who have not been previously diagnosed with cancer. Percentages and "1 in" numbers may not be numerically equivalent due to rounding.

Data from Reference 2.

A number of calculators are available to estimate a woman's risk of developing breast cancer. The National Cancer Institute (NCI) has an online version of the Breast Cancer Risk Assessment Tool (https://bcrisktool.cancer.gov/calculator.html). This tool is based on a statistical model known as the Gail model, derived from a mammography screening project conducted in the 1970s. It was designed for healthcare professionals to project a woman's individualized risk for invasive breast cancer over a 5-year period and over her lifetime. This model has been shown to provide accurate estimates in several racial and ethnic groups, but it has not been validated for those with genetic risk factors, a previous history of *in situ* or invasive breast cancer, or for certain subgroups. Other risk assessment models also exist, each taking into account different risk factors.

Endocrine Factors

Many endocrine factors have been associated with the risk of breast cancer. Many of these relate to the total duration of menstrual life. Early menarche, generally defined as menstruation beginning before age 12 years, increases the cumulative lifetime risk of breast cancer development. Similarly, a late age of natural menopause (age 55 years or later) increases the risk of breast cancer development.[2] Conversely, bilateral oophorectomy before age 45 years reduces the risk of developing breast cancer.[5]

Nulliparity and a late age at first birth (greater than or equal to 30 years) are reported to increase the lifetime risk of developing breast cancer. It is suggested that the period between the onset of menses and the age of first pregnancy provides a “window of initiation” for the development of breast cancer. This is a time when an unbalanced hormonal environment reacts with the abundant and highly responsive breast tissue. Investigators postulate that international differences in age of menarche, age at menopause, and childbearing may account for a substantial part of the international differences in the incidence of breast cancer.

Many studies have evaluated the relationship between exogenous hormones and the development of breast cancer. The Women’s Health Initiative (WHI) is a series of clinical trials designed to investigate the risks and benefits of treatment strategies that could affect women’s health issues, such as breast cancer. The estrogen plus progestin trial, in which women took either estrogen with medroxyprogesterone or a placebo, reported an increased risk of breast cancer in women taking combined estrogen and progestin. In the estrogen alone trial, which included postmenopausal women with prior hysterectomy, the incidence of breast cancer was lower in those who received estrogen alone compared with those who received placebo.[6] Unresolved issues remain as to whether lower doses or short-term use of estrogen or estrogen–progestin for menopausal symptoms can be safe and effective. A longer duration of HRT and concurrent use of progestins appear to contribute to breast cancer risk. In addition, the impact of HRT use on breast cancer risk also varies according to race, body mass index (BMI), and breast density.[2] The use of postmenopausal HRT in women with a history of breast cancer is generally contraindicated. Women who are considering HRT should carefully consider the risks versus benefits (see Chapter 98 for a detailed discussion of HRT).

Epidemiologic studies of oral contraceptives do not show a consistent relationship between the use of birth control pills and breast cancer risk. Results are conflicting, and assessment of the studies should consider the particular oral contraceptive products involved, daily and cumulative doses of the hormones administered, and latency period for development of breast cancer. It is also important to note that oral contraceptives are known to reduce the risk of ovarian and endometrial cancers. Most experts believe that the safety and benefits of low-dose oral contraceptives currently outweigh the potential risks.

Genetic Factors

Both personal and family histories influence a woman's risk of developing breast cancer. A personal history of breast cancer is associated with an increased risk of developing contralateral breast cancer. Cancers of the uterus and ovary are also associated with an increased risk of developing breast cancer. Several cancer family syndromes include breast cancer in association with other types of cancers.

Many women have "lumpy breasts" or have a clinical diagnosis of fibrocystic breast disease or benign breast disease. Nonproliferative lesions, such as cysts or simple fibroadenomas, do not increase the risk of breast cancer. Proliferative lesions without atypia, such as intraductal papillomatosis, are associated with a mildly elevated breast cancer risk of about 1.5 to 2.0 times that of the general population. Atypical hyperplasias are classified as either ductal or lobular units, and these lesions may increase a woman's risk for breast cancer to about 4.0 times that of the general population.[7]

Dense breast tissue reduces the sensitivity of mammography in detecting breast cancer and is associated with an increased risk of breast cancer. The risk of breast cancer in women with dense breasts (defined by mammography) has been estimated to be between four to five times that of women of the same age with little density.[8] Many variables, including age, BMI, menopausal status, HRT, parity, and the ratio of fibroglandular to fatty tissue, can influence mammographic breast density. Genetic factors may also play a role in this finding because mammographic breast density has been shown to have high heritability and is also strongly associated with a positive family history of breast cancer.

About 10% of all breast cancers in the United States population can be attributed to family history. Empirical estimates of the risks associated with particular patterns of family history of breast cancer indicate the following[2,5]:

1. Having any first-degree relative with breast cancer increases a woman's risk of breast cancer about 50%. Risk increases with increasing numbers of affected first-degree relatives.
2. The risk is affected by both the woman's age and the age of the relative when diagnosed. A higher risk is seen when a woman and her relative at diagnosis are younger than 50 years.
3. The risk associated with having any second-degree relative with breast cancer is complex and depends on other family history patterns. The risk is generally lower than that of first-degree relatives.

4. Affected family members on both the maternal and the paternal sides are important to consider in the evaluation of risk.

Although women with a family history of breast cancer are at increased risk for the disease, the diagnosis of breast cancer is still uncommon in young women even with a positive family history.

Germline mutations in either *BRCA1* or *BRCA2* are associated with an increased risk for breast and ovarian cancer. These genes function as tumor suppressor genes, maintaining genomic integrity and DNA repair. Compared with an average woman's 10% lifetime risk of developing breast cancer, the probability of developing breast cancer by the age of 80 years in women with a *BRCA1* or *BRCA2* mutation is estimated to be 70%.[2]

The probability of being a *BRCA* gene mutation carrier is related to ethnicity and family history. Ashkenazi (Eastern European) Jewish descents have an unusually high (2.1%) carrier rate of germline mutations in *BRCA1* and *BRCA2* compared with the rest of the US population. Conversely, it is estimated that clinically significant *BRCA* mutations occur at a frequency of about one in 300 to 500 persons in the general, non-Jewish US population.[9] Testing for *BRCA1* and *BRCA2* mutations is now widely available, but it is generally recommended only when there is personal or family history suggestive of hereditary cancer, when the test results can be adequately interpreted, and when results will assist with diagnosis and management. The decision to test an individual for a genetic mutation related to breast cancer risk is complex, and several organizations have published recommendations on genetic susceptibility testing for individuals who meet the criteria for increased risk.[9,10]

Although most genetic causes of breast cancer are attributed to *BRCA1* and *BRCA2*, other genes that have been associated with hereditary breast cancer include *TP53*, *CHEK2*, *PALB2*, *PTEN*, *ATM*, and others.[10]

Environmental and Lifestyle Factors

Breast cancer incidence rates vary considerably among countries, which suggests that environmental and lifestyle factors play an important role.

Diet is an important and modifiable environmental risk factor. Possible relationships between fat intake and steroid hormone metabolism have led to an emphasis on dietary fat as a possible risk factor for breast cancer. To confirm the hypothesis that low dietary fat intake reduces breast cancer risk, the WHI Randomized Controlled Dietary Modification Trial compared groups of women

given different diets. Over an 8-year mean follow-up period, the incidence of invasive breast cancer was not significantly different between the group that consumed a diet with reduced fat, several servings of fruits and vegetables and several servings of grains daily versus the group without any dietary intervention.[11] Although the effects of diet on the risk of developing breast cancer are not fully understood, a low-fat diet is a reasonable approach to potentially reduce the risk of breast cancer.

Another dietary factor that deserves mention is the possible effect of phytoestrogens on breast cancer risk. Phytoestrogens are natural plant estrogens found in soybean products, seeds, berries, and nuts. Because these compounds exhibit weak estrogenic properties, some experts believe that they may function as relative antiestrogens by displacing natural estradiol. However, studies have also reported a potential stimulatory effect on breast tissue. Nonetheless, the effect of phytoestrogens on breast cancer is very controversial, and further research is needed.[12]

Both body weight and height are associated with the risk of breast cancer. Most studies of premenopausal women show either no relationship with body weight or slightly declining breast cancer risks with increasing body weight. Most studies in postmenopausal women show increasing breast cancer risks with increasing body weight. An increase in circulating estrogen is postulated to be the most likely explanation.[2] Although height is not a modifiable risk factor, weight and body composition are modifiable. Maintaining a healthy weight and body composition appear to be beneficial and promote many different health benefits. Many studies report an association between physical activity and breast cancer risk. Exercise may provide modest protection against breast cancer, but the relationship is complex. Possible explanations include the effects of physical activity on systemic inflammation, hormones, and energy balance.[2] Making healthy choices appears to be the best health advice for women.

Many studies have reported that alcohol increases the risk of breast cancer. Although the exact mechanism is unknown, the most plausible biologic explanation relates to increased levels of estrogen or other reproductive steroid hormones caused by impaired liver function.[2] Because alcohol consumption is a modifiable risk factor, use in moderation appears to be a sensible approach.

Radiation to the breast tissue is associated with an increased risk of breast cancer, particularly with exposure between 10 and 30 years of age.[2] Women treated with chest irradiation for Hodgkin lymphoma in childhood or adolescence and survivors of other childhood cancers (in which radiation is used as a mainstay of therapy) are among the populations at greater risk for secondary

breast cancers. The risk increases linearly with radiation dose. Exposure to diagnostic x-rays, including annual screening mammography, does not impart a sufficient dose of radiation for clinical concern in the general population. However, the risk of breast cancer after radiation exposure even in low levels in those with genetic risk factors is unclear and is an ongoing area of research.

Tobacco smoke exposure has not been previously associated with an increased risk of breast cancer. In recent years, however, research shows that smoking may slightly increase breast cancer risk. Women with long-term, heavy smoking and women who started smoking before their first pregnancy are at higher risk. The 2014 US Surgeon General's report on smoking concluded that there is "suggestive but not sufficient" evidence that smoking increases the risk of breast cancer.[2]

In conclusion, several endocrine, genetic, environmental, and lifestyle factors are associated with the development of breast cancer to varying degrees. Some factors are modifiable, but others are not. The impact of individual risk factors may vary depending on other confounding variables such as age, family history, estrogen use, and menopausal status. Further studies are needed to confirm the importance of factors that are associated with the risk of developing breast cancer.

PREVENTION AND EARLY DETECTION

Current efforts at breast cancer prevention are directed toward the identification and removal of risk factors often referred to as risk-reducing strategies. Unfortunately, a number of risk factors, such as family history of breast cancer or personal history of breast or other gynecologic malignancies, cannot be modified. Isolation and cloning of breast cancer susceptibility genes now allow screening of women with histories suggestive of "breast cancer families" and identification of appropriate candidates for prophylactic bilateral mastectomies or bilateral salpingo-oophorectomy. These surgeries are considered for women who are at very high risk for the development of breast or ovarian cancer, particularly if her breasts are difficult to evaluate by both physical examination and mammography and if the women have persistent disabling fears that they will be diagnosed with cancer. Guidelines for the incorporation of surgical risk-reducing strategies are largely based on genetics and other known risk factors for the development of breast (or ovarian) cancer.

There is an increasing interest in pharmacologic risk reduction for breast cancer. The drugs with the most clinical information as risk-reducing agents for

breast cancer are the selective estrogen receptor modulators (SERMs), tamoxifen and raloxifene. Tamoxifen is useful as an adjunct after treatment of primary breast cancer (see section “Adjuvant Endocrine Therapy” for details). The National Surgical Adjuvant Breast and Bowel Project (NSABP) was first to demonstrate significant reductions in risk of invasive and noninvasive breast cancers with 5 years of tamoxifen therapy (20 mg/day) in high-risk women without a diagnosis of breast cancer. This study (also known as P-1) and other studies from around the world have investigated the role of tamoxifen as a risk-reducing strategy. A meta-analysis of these trials indicates a consistent benefit with tamoxifen in reducing the risk of ER (estrogen receptor)-positive breast cancers by about 50%. Tamoxifen has been shown to be a relatively safe drug with an acceptable toxicity profile when used to treat patients with breast cancer. However, its estrogenic effects on the uterus and the coagulation system increase the risk of serious adverse effects which are critical for patients taking this agent as a risk-reducing strategy where the threshold for acceptable risk is lower. Toxicities associated with tamoxifen are described in the section “Adjuvant Endocrine Therapy.” Any decision to use tamoxifen for risk reduction should be made after a thorough discussion of the woman’s risk of breast cancer, the potential benefits of tamoxifen, and the potential serious adverse events associated with tamoxifen.

A second trial, Study of Tamoxifen and Raloxifene (STAR or P2), compared tamoxifen to raloxifene in high-risk postmenopausal women. Although a similar rate of invasive breast cancers was shown with the two drugs, the rates of noninvasive breast cancer were numerically higher in the raloxifene arm. Both agents increased thromboembolic events while only tamoxifen increased endometrial cancer.[6] Based on these results, the Food and Drug Administration (FDA) approved raloxifene for breast cancer risk reduction in high-risk women.

A similar reduction in the risk of contralateral primary breast cancers was demonstrated in the adjuvant clinical trials with the aromatase inhibitors (AIs), leading to the hypothesis that AIs may also reduce the risk of breast cancer. The AIs studied include exemestane and anastrozole. Both have been studied separately (not compared to each other) in randomized, placebo-controlled, phase III trials. Each AI was compared with placebo for 5 years in high-risk postmenopausal women. Significant reductions were seen in the rates of invasive breast cancers with both exemestane and anastrozole when each was compared to placebo. In both studies, adverse events were tolerable. Based on these data, AIs are reasonable options for breast cancer risk reduction in postmenopausal women. In this setting, AIs were not compared to SERMs and both classes of

agents are appropriate options.[6] Although neither exemestane nor anastrozole is FDA approved for breast cancer risk reduction, the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines include AIs as acceptable options for risk reduction in postmenopausal women.[5,13]

The rationale for early detection of breast cancer is based on the relationship between the stage of breast cancer at diagnosis and the probability of cure. If all breast cancer cases could be detected at a very early stage of the disease (ie, small primary tumor and negative lymph nodes), then more patients theoretically could be cured of their disease. Screening guidelines for early detection of breast cancer in women at average risk have been developed by several organizations, including but not limited to the American Cancer Society (ACS), the United States Preventive Services Task Force (USPSTF), and the NCCN (See **Table 145-2**).[14–16] The ACS guidelines are most commonly cited. However, it is important to note that the expert panels developing these guidelines often differ in their approach and analysis of the available data, as is evident in the different recommendations in the guidelines.

TABLE 145-2 Breast Cancer Screening Guidelines

Risk Category	ACS	USPSTF	NCCN
Average Risk			
BSE	Age ≥20 years: optional (discuss benefits and limitations)	Not recommended	Age ≥25 years: breast awareness
CBE	Evidence does not support	Insufficient evidence	Age ≥25-39 years: every 1-3 years Age ≥40 years: annually
Mammography	Age 40-44 years: opportunity annually	Age 40-50 years: individualized decision Age 50-74 years: biennial Age >75 years: insufficient evidence	Age ≥40 years: annually; consider tomosynthesis
	Age 45-54 years: annually		
	Age ≥55 years: biennially or opportunity annually (as long as in good health and at least 10-year life expectancy)		
High Risk[a,b]			
BSE	NA	NA	All ages: breast awareness
CBE	NA	NA	All ages: every 6-12 months
Mammography	Age ≥30 years: annually with MRI	NA	Prior RT or strong family history or genetic predisposition, age ≥25 years: annually (+ CBE); consider tomosynthesis All other categories: annually (+ CBE); consider tomosynthesis
Breast MRI	Age ≥30 years: annually with mammogram	NA	Annually with mammogram + CBE for (a) prior RT, age ≥25 years; (b) lifetime risk >20%; (c) consider MRI if history of LCIS or ADH/ALH and lifetime risk >20%

ACS, American Cancer Society; ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; BSE, breast self-examination; CBE, clinical breast examination by a healthcare professional; LCIS, lobular carcinoma in situ; MRI, magnetic resonance imaging; NA, not addressed; NCCN, National Comprehensive Cancer Network; RT, thoracic radiation therapy; USPSTF, United States Preventive Services Task Force.

[a]High risk is defined by the ACS as women with (1) a known *BRCA1/2* gene mutation; (2) untested woman with first-degree relative with a known *BRCA1/2* gene mutation; (3) lifetime risk of breast cancer of 20%-25% or greater using a risk-assessment tool based largely on family history; (4) radiation therapy to the chest between the ages of 10 and 30 years; (5) LiFraumeni syndrome, Cowden syndrome, or Bannayan-Riley-Ruvalcaba syndrome or have first-degree relatives with one of these syndromes.

[b]High risk is defined by the NCCN as women with (1) prior thoracic radiation therapy before age 30 years, (2) 5-year risk of ≥1.7% of invasive breast cancer in women ≥35 years old, (3) lifetime risk of >20% as defined by models that are largely based on family history, (4) strong family history or genetic predisposition, (5) LCIS or ADH/ALH and lifetime risk of >20%, (6) prior history of breast cancer.

Data from References 14–16.

2 The most controversial screening recommendation for breast cancer is annual mammography. Although screening mammography clearly decreases mortality from breast cancer, the controversies surround the balance of benefits

and harms associated with a less than perfect screening test in women of different ages at average risk of developing breast cancer. The Cancer Intervention and Surveillance Modeling Network (CISNET) was commissioned by the USPSTF to estimate the number-needed-to-screen (NNS) to prevent one breast cancer death. The estimated NNS for women aged 50 to 59 years was 351. The estimated NNS for women aged 40 to 49 years was 746, and in women aged 70 to 79 years, the estimated NNS was 377. The largest benefit was found in women aged 60 to 69 years with an estimated NNS of 233.[17] Incorporation of this information into national guidelines differs with each organization (see Table 145-2).

Other radiologic methods of breast imaging are also being investigated (eg, digital mammography [two-dimensional, 2D], digital breast tomosynthesis [DBT also known as tomosynthesis or three-dimensional mammography], ultrasonography, and magnetic resonance imaging [MRI]). Tomosynthesis appears to improve cancer detection and reduce false-positive call back rates (rates of return visits to have further testing/imaging after screening mammogram). Tomosynthesis combined with 2D doubles the radiation exposure compared to mammography alone, but this increase in radiation dose falls below the dose limits of radiation set by the FDA for standard mammography.[16] Recommendations regarding these other radiologic methods vary among the national guidelines and definitions of “high risk” also vary among the guidelines (see Table 145-2). It should also be noted that any screening procedure has risks and they should be discussed with patients so they are able to make an informed decision regarding these procedures. The risks involved with screening mammograms include false-negative results, false-positive results, overdiagnosis (true positives that will not become clinically significant), and radiation risk. The rate of false-negative results with the current technology is about 20%, which explains why clinical breast examination (CBE) is an important adjunct to screening for many women. Although the specificity of mammography is quite high (90%), most abnormal examinations are false-positive results, leading to additional biopsies and psychological distress. The term “overdiagnosis” refers primarily to the increased detection of ductal carcinoma *in situ* (DCIS) from screening mammography (see “Noninvasive Carcinoma” section for a detailed discussion of DCIS). The biologic significance of these tumors is unknown because only some of them would become invasive if left in place. So the question remains: Are we treating women who do not require treatment? Experts in the field continue to debate this issue. Radiation exposure also has been discussed in the context of screening mammography, but the small doses of

radiation exposure with mammograms (2-4 mGy [0.2-0.4 Rad] per standard two-view examination) appears to be overshadowed by other benefits in terms of reduction in mortality as a consequence of early cancer detection.[15]

CLINICAL PRESENTATION

A painless lump is the initial sign of breast cancer in most women. The typical malignant mass is solitary, unilateral, solid, hard, irregular, and nonmobile. In small numbers of cases, stabbing or aching pain is the first symptom. Less commonly, nipple discharge, retraction, or dimpling may herald the onset of the disease. In more advanced cases, prominent skin edema, redness, warmth, and induration of the underlying tissue may be observed.

The breast is a complex organ composed of skin, subcutaneous tissue, fatty tissue, and branching ductal and glandular structures (see **Fig. 145-1**). Various diseases that affect these structures can produce a palpable mass. In addition, the physiologic changes associated with the menstrual cycle can cause normal breast changes. Common causes of breast masses in young women are fibroadenoma, fibrocystic disease, carcinoma, and fat necrosis.

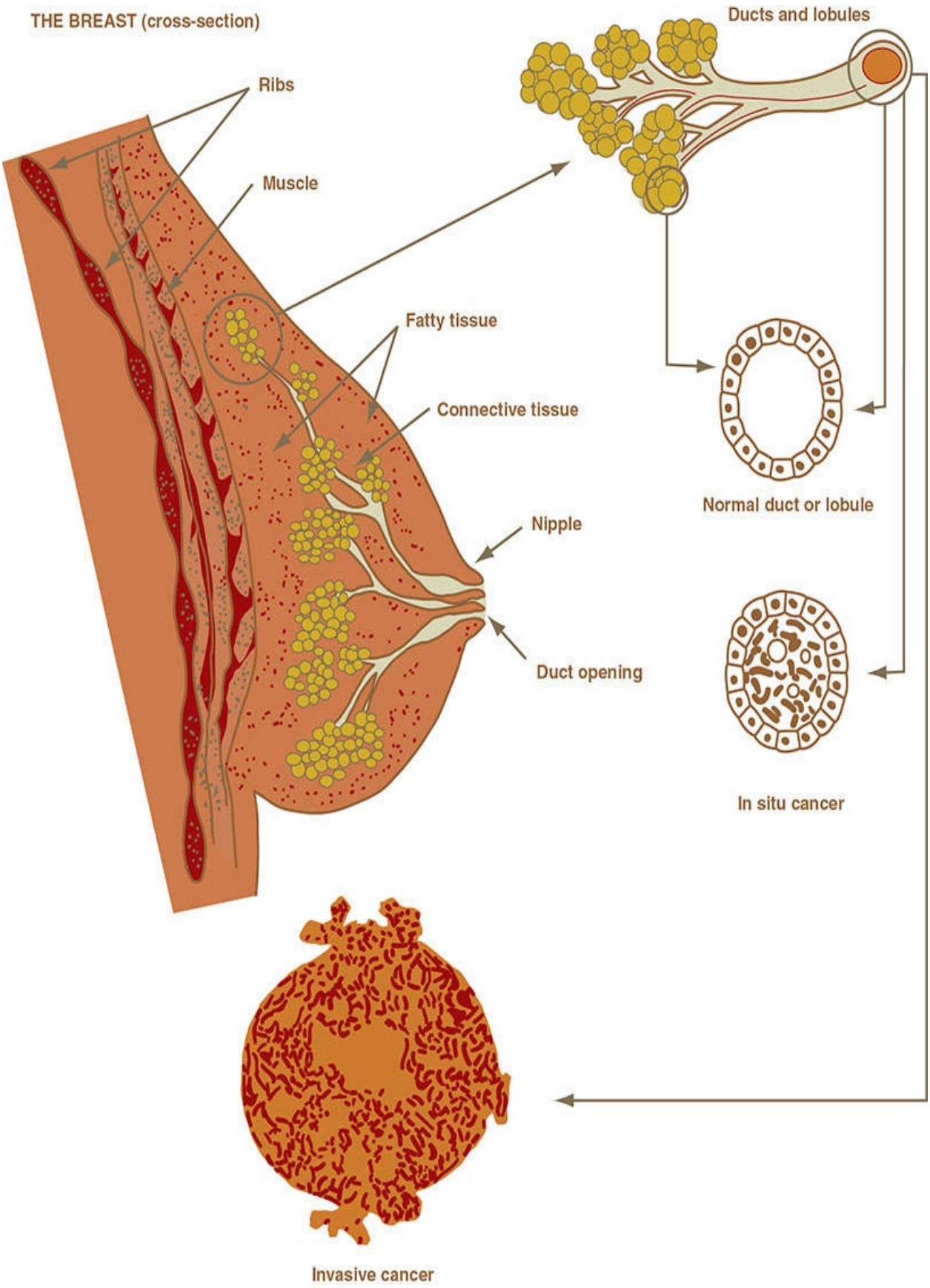

THE BREAST (cross-section)
Ribs
Muscle
Fatty tissue
Connective tissue
Nipple
Duct opening
Ducts and lobules
Normal duct or lobule
In situ cancer
Invasive cancer

FIGURE 145-1 Breast anatomy.

Breast cancer that is confined to a localized breast lesion is often referred to as *early*, *primary*, *localized*, or *curable*. Breast cancer that has spread to local–regional lymph nodes is still considered early stage (see **Fig. 145-2**). Unfortunately, breast cancer cells often spread by contiguity, through lymph channels, and through the blood to distant sites. When breast cancer cells can be detected clinically or radiologically in sites distant from the breast, the disease is referred to as *advanced* or *metastatic* breast cancer (MBC). Tissues most commonly involved with distant metastases are lymph nodes (other than local–regional lymph nodes), skin, bone, liver, lungs, and brain. Symptoms of bone pain, difficulty breathing, abdominal enlargement, jaundice, and mental status changes may herald the clinical presentation of MBC. A small percentage of women have signs and symptoms of distant metastases when they first seek treatment. In virtually all of them, a neglected breast mass has been present for several months to years. In addition, 10% to 50% of all patients who initially are treated for localized disease eventually develop signs and symptoms of MBC.[18]

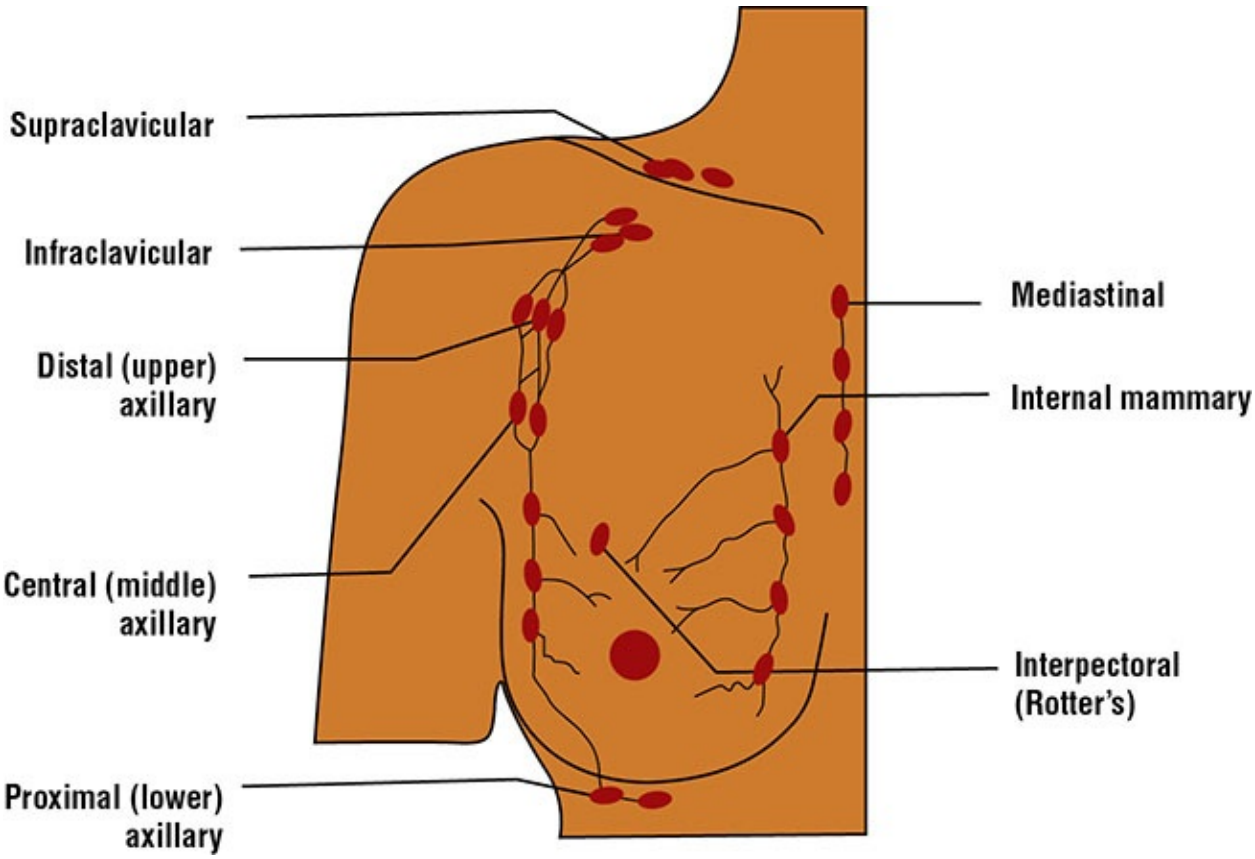


FIGURE 145-2 Lymph node anatomy.

DIAGNOSIS

The initial workup for a woman presenting with a breast mass or symptoms suggestive of breast cancer should include a careful history, physical examination of the breast, three-dimensional diagnostic mammography, and possibly other breast imaging techniques such as ultrasonography or MRI. Most breast cancers can be visualized on a mammogram as a mass, a cluster of calcifications, or a combination of these findings. One major factor that affects the ability of mammography to detect cancer includes breast density, which may be affected by age, menopausal status, and HRT use. Ultrasonography, MRI, digital mammography, and tomosynthesis are alternate breast imaging methods that are being investigated for women with dense breasts or other specific subsets of patients with breast cancer (eg, MRI in patients with inflammatory breast cancer).[16] The technical quality of the examination and the expertise of the radiologist are also important factors affecting reliability.

Breast biopsy is indicated for a mammographic abnormality that suggests malignancy or for a palpable mass on physical examination. Three techniques are available: fine-needle aspiration, core-needle biopsy, and excisional biopsy.[16] Excisional biopsy completely removes the abnormal tissue. Needle biopsies are performed percutaneously and include both core-needle biopsy (which removes a core of tissue) and fine-needle aspiration (which removes cells from the suspicious site). Core-needle biopsy is the preferred biopsy method for mammographically detected, nonpalpable abnormalities.[16] Core-needle biopsy offers a more definitive histologic diagnosis, avoids inadequate samples, and can distinguish invasive from *in situ* breast cancer (which fine-needle biopsy cannot). After confirmation of malignancy via core-needle biopsy, subsequent surgical procedures are performed (either before or after systemic therapy) to assure complete removal of the abnormal tissue.

PATHOLOGY

The pathologic evaluation of breast tissue serves to establish the histologic diagnosis and to confirm the presence or absence of other factors believed to influence prognosis.

Invasive Carcinoma

Invasive breast cancers are a histologically heterogeneous group of lesions. Most

breast cancers are adenocarcinomas and are classified on the basis of their microscopic appearance as ductal or lobular, corresponding to the ducts and lobules of the normal breast (see Fig. 145-1). The various histologic types of breast cancer have different prognoses, but it is unknown whether their response to therapy differs because patients in therapeutic trials are not typically stratified according to histologic type. The five most common types of invasive breast cancer are briefly described below.

Invasive or *infiltrating ductal carcinoma* is the most common histology, accounting for about 75% of all invasive breast cancers. These tumors commonly spread to the axillary lymph nodes, and their prognosis is poorer than for some other histologic types. *Invasive or infiltrating lobular carcinoma* accounts for 5% to 10% of breast tumors. Both clinical and radiologic findings for these tumors may be quite subtle. The typical presentation is an area of ill-defined thickening in the breast in contrast to a prominent lump characteristic of infiltrating ductal carcinoma. *Infiltrating lobular carcinoma* can also be more difficult to detect by mammography. Overall, *infiltrating lobular carcinoma* and *infiltrating ductal carcinoma* have similar likelihoods of axillary node involvement and disease recurrence and death, but the sites of metastases may differ. While *infiltrating ductal carcinoma* more frequently metastasizes to the bone or to the liver, lung, or brain, *infiltrating lobular carcinoma* tends to metastasize to the leptomeninges, peritoneal surfaces, retroperitoneum, gastrointestinal tract, reproductive organs, and other unusual sites.

CLINICAL PRESENTATION Breast Cancer

General

- The patient may not have any symptoms because breast cancer may be detected in asymptomatic patients through routine screening mammography.

Local Signs and Symptoms

- A painless, palpable lump is most common.
- Less common: pain; nipple discharge, retraction, or dimpling; skin edema, redness, or warmth.

- Palpable local–regional lymph nodes may also be present.

Signs and Symptoms of Systemic Metastases

- Varies depending on the site of metastases, but may include bone pain, difficulty breathing, abdominal pain or enlargement, jaundice, or mental status changes.

Laboratory Tests

- Tumor markers such as cancer antigen (CA 15-3) or carcinoembryonic antigen (CEA) may be elevated.
- Alkaline phosphatase or liver function test results may be elevated in patients with metastatic disease.

Other Diagnostic Tests

- Mammography (with or without ultrasonography, breast MRI, or both).
- Biopsy for pathology review and determination of tumor estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (*HER2*) status.
- Systemic staging tests may include chest radiography, chest computed tomography (CT), bone scan, abdominal CT or ultrasonography, or MRI.

The three most common special types of invasive cancer are *medullary*, *mucinous*, and *tubular*. The prognosis may be more favorable with these unusual histologies. *Medullary carcinoma* accounts for fewer than 7% of all breast carcinomas, *mucinous (or colloid) carcinoma* constitutes about 3%, *and tubular carcinoma* accounts for about 2% of all breast cancers.

Special situations seen clinically and histologically include Paget's disease of the breast, phyllodes tumors, and inflammatory breast cancer (IBC). Paget's disease of the breast is characterized by neoplastic cells in the nipple areolar complex. The patient presents clinically with eczematous changes in the nipple with itching, burning, oozing, bleeding, or some combination of these. Phyllodes tumors of the breast are rare tumors with subtypes that range from benign to

malignant. These tumors often enlarge rapidly, are painless, and can appear as fibroadenomas.[19] IBC is rare, aggressive, and characterized clinically by prominent skin edema, redness and warmth, and induration of the underlying tissue. Biopsies of the involved skin reveal cancer cells in the dermal lymphatics. IBC typically has a very rapid onset and is often mistaken for infectious cellulitis or mastitis. Although it may look somewhat similar to a neglected mass, its presentation with rapid onset and progression of local symptoms distinguishes it from other cases of locally advanced breast cancer. The prognosis of patients with IBC is poor even if the disease is apparently localized.[19]

Noninvasive Carcinoma

As with invasive carcinoma, the noninvasive lesions may be divided broadly into ductal and lobular categories. Evidence supports that the development of malignancy is a multistep process and that invasive breast cancer has a pre-invasive (ie, *in situ*) phase. During the carcinoma *in situ* phase, normal epithelial cells undergo genetic alterations that result in malignant transformation. Transformed epithelial cells proliferate and pile up within lobules or ducts but lack the required genetic alterations that enable the cells to penetrate the basement membrane. Carcinoma *in situ* is diagnosed when malignant transformation of cells has occurred, but the basement membrane is intact.

The widespread use of screening mammography with subsequent biopsy and greater recognition of noninvasive breast carcinoma by pathologists has resulted in a significant increase in the diagnosis of *in situ* breast cancer. An estimated 62,930 new cases of female noninvasive (*in situ*) breast cancer were diagnosed in 2019.[1] The natural history of these disorders is not well described, and thus the debate continues whether carcinoma *in situ* is a pre-invasive cancer or simply a marker of unstable epithelium that represents an increased risk for the development of subsequent aggressive cancer. Ductal carcinoma *in situ* (DCIS) is more frequently diagnosed than lobular carcinoma *in situ* (LCIS). Most cases of DCIS today are found by biopsies performed for clustered microcalcifications seen on screening mammography, a hallmark of this disorder.

The ultimate goal of treatment for noninvasive carcinomas is to prevent the development of invasive disease. If left untreated, it is estimated that 14% to 50% of DCIS lesions will progress to invasive breast cancer.[20] Therefore, more than 50% of these tumors do not progress to invasive disease, but identifying this group of patients is not yet possible and all diagnoses should be treated. Locoregional treatment of DCIS depends on its location, size, and pathology.[19]

Treatment options include (a) local excision alone with negative margins, (b) local excision (with negative margins) followed by breast irradiation, and (c) traditional total mastectomy with or without reconstruction. Whole-breast irradiation is recommended after excision to significantly decrease the risk of local recurrence, although there is no evidence that survival differs between the previously mentioned options.[19] Excision with negative margins alone without radiation may be considered in patients with small and low-grade DCIS. If more than one area of the breast is involved with DCIS, a mastectomy is the preferred option. Axillary lymph node dissection (ALND) is generally not indicated, although sentinel lymph node biopsy (SLNB) (see the "Early Breast Cancer" section) may be considered in selected patients.[19] Cytotoxic chemotherapy has no role in the treatment of patients with pure DCIS. It is important to determine hormone receptor status on the cancer cells. Tamoxifen treatment for 5 years may be considered in premenopausal and postmenopausal women with hormone receptor–positive DCIS. Anastrozole for 5 years may be considered in postmenopausal women with hormone receptor–positive DCIS, particularly if they are less than 60 years old.[19] These decisions are often difficult to discuss with patients because these treatments have toxicities that are worrisome. Nonetheless, an open and honest conversation regarding the risks and benefits is warranted.

LCIS is a microscopic diagnosis; there is generally no palpable mass and no specific clinical abnormality. Unlike DCIS, LCIS does not generally demonstrate calcifications on mammography and is usually undetectable by mammography. The diagnosis of LCIS is usually an incidental finding in biopsy specimens obtained because of symptoms or mammography findings consistent with benign lesions. It is unclear whether LCIS is a precursor lesion to invasive carcinoma or serves as a marker of risk for invasive carcinoma developing somewhere in the breast. The risk for developing invasive carcinoma is about 0.5% to 1% per year, and both invasive ductal carcinoma and invasive lobular carcinoma can occur. In about 50% to 70% of patients, there are multiple foci of LCIS in the ipsilateral breast, and the contralateral breast is also affected. Thus, the risk for the development of breast cancer is equally high in either breast, which makes the management of LCIS very controversial.[21] Some experts favor a program of observation, with physical examination every 6 to 12 months, annual mammography, and consideration of annual breast MRI or ultrasound.[16] In selected patients with high-risk genetic mutations or strong family history and in women who are particularly anxious about the development of cancer, bilateral mastectomies with or without reconstruction may be considered.[5] Radiation and

systemic chemotherapy have no role in the management of LCIS. The use of chemoprevention with tamoxifen in premenopausal women or tamoxifen, raloxifene, anastrozole, or exemestane in postmenopausal women may also be considered for risk reduction in these patients (see the “Prevention and Early Detection” section for details).[5]

PROGNOSTIC AND PREDICTIVE FACTORS

The natural history of breast cancer varies among patients, with some having extremely aggressive disease that progresses rapidly and others following a more indolent course. The ability to predict prognosis is extremely important in designing personalized treatment recommendations. Several pathologic prognostic and predictive factors have been identified. Prognostic factors are characteristics or measurements available at diagnosis or time of surgery that in the absence of neoadjuvant or adjuvant systemic therapy are associated with recurrence rate, death rate, or other clinical outcomes. Predictive factors are measurements available at diagnosis that are associated with response to a specific therapy. Prognostic and predictive factors fall into three general categories: (a) patient characteristics that are independent of the disease such as age; (b) cancer characteristics such as tumor size or histologic type; (c) other biomarkers that are measurable parameters in tissues, cells, or fluids, such as hormone-receptor status; and (d) genetic variables. The use of prognostic and predictive factors can personalize treatment to patients, increase the likelihood of clinical benefit, and reduce the risk of unnecessary toxicities.

Age at diagnosis and ethnicity can affect prognosis. Some younger patients, particularly those younger than 35 years of age, have more aggressive forms of breast cancer and a worse prognosis. Younger patients are more likely to present with poor prognostic features, such as affected lymph nodes, large tumor size, and tumors negative for hormone receptors. African American women have decreased survival compared with white women. The cause of this racial disparity is widely debated, with possible explanations including access to care, socioeconomic status, cultural differences, higher stage at diagnosis, and more aggressive biologic features.

Potentially modifiable prognostic factors include alcohol use, dietary factors, weight, and exercise. The association between alcohol use and breast cancer prognosis is not as strong as with alcohol and breast cancer risk. A review of seven observational studies showed that postdiagnosis alcohol consumption was not associated with breast cancer outcomes.[22] Randomized controlled studies of

diet on the risk of breast cancer have reported conflicting results. One study found decreased recurrence and death with the incorporation of a low-fat diet, but two other studies did not.[23] Most clinicians recommend that breast cancer survivors eat a low-fat, high-fiber diet and maintain a healthy weight. Obesity at the time of a breast cancer diagnosis is associated with increased risk of breast cancer–specific and overall mortality compared with nonobese breast cancer patients, although the impact of weight loss in this population is unclear.[22] Observational studies have reported that exercise in women after a diagnosis of breast cancer may decrease the risk of breast cancer recurrence and breast cancer–related death.[22] Based on these data, agencies such as the ACS have recognized that physical activity, weight control, and diet are potentially modifiable risk factors for reducing the risk of recurrent breast cancer and other comorbidities (eg, heart disease, diabetes).[23]

Disease characteristics that can provide important prognostic information include lymph node status, tumor size, histologic subtype, nuclear or histologic grade, lymphatic and vascular invasion, and proliferation indices.

Tumor size and the number of involved lymph nodes are established independent factors that influence the risk for breast cancer recurrence and subsequent metastatic disease. The number of affected lymph nodes is directly related to the risk of disease recurrence. The staging system for breast cancer recognizes the absolute number of positive nodes as a prognostic factor: N1 represents one to three positive nodes, N2 represents four to nine positive nodes, and N3 represents 10 or more positive nodes in its pathologic staging system (see **Table 145-3** for further details).[24] The relationship between tumor size and lymph node status is complex and is not a simple grouping.

TABLE 145-3 Definitions for Tumor, Node, Metastasis

TX	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
Tis (DCIS)	Ductal carcinoma *in situ*	
Tis (Paget)	Paget's disease of the nipple NOT associated with invasive carcinoma or carcinoma *in situ*	
T1	Tumor ≤2 cm in greatest dimension	
	T1mi	<0.1 cm; microinvasion
	T1a	>0.1 cm ≤0.5 cm
	T1b	>0.5 cm ≤1 cm
	T1c	>1 cm ≤2 cm
T2	Tumor >2 cm ≤5 cm	
T3	Tumor >5 cm	
T4	Tumor of any size with direct extension to the chest wall and/or to the skin	
	T4a	Extension to the chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures
	T4b	Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria of inflammatory carcinoma
	T4c	Both T4a and T4b present
	T4d	Inflammatory carcinoma
Regional Lymph Nodes: Clinical (cN)		
cNX	Regional lymph nodes cannot be assessed	
cN0	No regional lymph node metastases	
cN1	Metastases to movable ipsilateral Level 1, II axillary lymph node(s)	
	cN1mi	Micrometastases (approximately 200 cells, >0.02 cm <0.2 cm)
cN2	Metastases in ipsilateral Level I, II axillary lymph nodes that are clinically fixed or matted; or in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases	
	cN2a	Metastases in ipsilateral Level I, II axillary lymph nodes fixed to one another (matted) or to other structures
	cN2b	Metastases only in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN3	Metastases in ipsilateral infraclavicular (Level III axillary) lymph node(s) with or without Level I, II axillary lymph node involvement; or in ipsilateral internal mammary lymph node(s) with Level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement	
	cN3a	Metastases in ipsilateral infraclavicular lymph node(s)
	cN3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
	cN3c	Metastases in ipsilateral supraclavicular lymph node(s)
Regional Lymph Nodes: Pathologic (pN)		
pNX	Regional lymph nodes cannot be assessed	
pN0	No regional lymph node metastasis identified or ITCs only	
	pN0(i+)	ITCs only, no larger than 0.02 cm in regional lymph nodes
	pN0(mol+)	Positive molecular findings by reverse transcriptase polymerase chain reaction; no ITCs detected

pN1	Micrometastases; or metastases in 1-3 axillary lymph nodes; and/or clinically negative internal mammary nodes with micrometastases or macrometastases by sentinel lymph node biopsy	
	pN1mi	Micrometastases, (approximately 200 cells, >0.02 cm <0.2 cm)
	pN1a	Metastases in ipsilateral internal mammary sentinel nodes, excluding ITCs
	pN1c	pN1a and pN1b combined
pN2	Metastases in 4-9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases	
	pN2a	Metastases in 4-9 lymph nodes (at least one deposit >0.2 cm)
	pN2b	Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary nodes
pN3	Metastases ≥10 or more axillary lymph nodes; or in infra-clavicular (Level III axillary) lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the presence ≥1 positive Level I, II axillary lymph nodes; or in >3 axillary lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes; or in ipsilateral mammary lymph nodes	
	pN3a	Metastases in ≥10 axillary lymph nodes (at least one tumor deposit >0.2 cm)
	pN3b	pN1a or pN2a in the presence of cN2b (positive internal mammary nodes by imaging)
	pN3c	Metastases in ipsilateral supraclavicular lymph nodes
Distant Metastasis (M)		
M0	No clinical or radiographic evidence of distant metastases	
	cM0(i+)	No clinical or radiographic evidence of distant metastases in the presence of tumor cells or deposits <0.02 cm detected microscopically or by molecular techniques in circulating blood, bone marrow, or other nonregional nodal tissue in a patient without symptoms or signs of metastases
cM1	Distant metastases detected by clinical and radiographic means	
pM1	Any histologically proven metastases in distant organs; or if in nonregional nodes, metastases >0.02 cm	

ITCs, isolated tumor cells.

Reproduced, with permission, from AJCC Cancer Staging Manual, 8th ed. (2017) published by Springer Science and Business Media LLC, www.springer.com.

Certain histologic subtypes and clinical presentation of breast cancer have prognostic importance. As mentioned earlier, treatment recommendations may differ because women with pure *tubular* or *mucinous* tumors have more favorable outcomes than those with *invasive ductal carcinomas*.[19] IBC, a clinical designation and not a distinct histologic subtype, is associated with a poor prognosis.[19]

Nuclear grade and tumor (histologic) differentiation are also independent prognostic indicators. Several histologic grading systems have been developed, most of which grade tumors with a score from 1 to 3: grade 1, well differentiated; grade 2, moderately differentiated; and grade 3, poorly differentiated. Grading has been incorporated as part of the updated staging system (see **Table 145-4** for details regarding grading).[24] Higher grade tumors are associated with higher rates of distant metastasis and poorer survival. This factor aids in making treatment decisions, particularly for patients with small tumors and negative lymph nodes.

TABLE 145-4 Invasive Cancer Histologic Grading

Grade	Grade Definition
GX	Grade cannot be assessed
G1	Low combined histologic grade (favorable)
	SBR score of 3-5 points
G2	Intermediate combined histologic grade (moderately favorable)
	SBR score of 6-7 points
G3	High combined histologic grade (unfavorable)
	SBR score of 8-9 points

SBR, Scarf-Bloom Richardson grading system, Nottingham Modification.

Reproduced, with permission, from AJCC Cancer Staging Manual, 8th ed. (2017) published by Springer Science and Business Media LLC, www.springer.com.

Hormone receptors are not strong prognostic markers but are used clinically to predict responses to endocrine therapy. Determination of both estrogen receptor (ER) and progesterone (PR) status are established procedures that are important in the management of breast cancer. About 60% to 70% of patients with ER-positive and PR-positive tumors will respond to hormonal manipulation. Most patients with primary or MBC have hormone receptor–positive tumors. Hormone receptor positivity, more common in postmenopausal

women, is associated with a higher response to endocrine therapy and longer disease-free survival.

The *HER2* gene is located on chromosome 17q21 and encodes a 185-kDa transmembrane tyrosine kinase growth factor receptor. The *HER2* protein is normally expressed at low levels in the epithelial cells of normal breast tissue. *HER2* overexpression occurs in about 20% to 30% of breast cancers and is associated with increased tumor aggressiveness, increased rates of recurrence, and increased mortality rates. *HER2* gene amplification is measured by fluorescence in situ hybridization (FISH) and levels of protein expression are measured by immunohistochemistry (IHC). Both amplification and overexpression are associated with poor prognosis. Tumors that are either IHC 3+ or FISH positive are considered to be positive for *HER2*.[19] *HER2*-positive status clearly predicts response to anti-*HER2* therapy. However, patients with *HER2*-positive MBC treated with trastuzumab, a MoAB directed against the extracellular domain of the *HER2* receptor, have improved survival rates compared to patients with *HER2*-negative MBC or patients with *HER2*-positive MBC who do not receive trastuzumab.[25]

Genetic profiling is also being used to provide prognostic and predictive information on clinical outcomes of breast cancer.[19] Commercially available multigene expression assays include Oncotype DX®, MammaPrint®, and Prosigna®. Further details on these assays are available in the “Systemic Adjuvant Therapy” section.

In summary, lymph node status and tumor size are two significant prognostic factors that are used by clinicians to estimate prognosis and personalize treatment recommendations for breast cancer patients (see “Systemic Adjuvant Therapy” section later). Although the risk of recurrence is clearly higher in patients with large primary tumors or lymph node–positive disease, patients with small primary tumors and lymph node–negative disease can still develop metastases. Evaluation of additional prognostic factors can help identify which patients will have a good outcome with local therapy alone and which patients with aggressive features would benefit from more aggressive, multimodality treatment. Despite these markers, many patients will likely be treated unnecessarily with systemic adjuvant therapy, and better prognostic and predictive tools are needed to better select patients to undergo these potentially toxic and costly treatments and procedures.

STAGING AND PROGNOSIS

Breast cancer stage is based on the primary tumor extent and size, presence and extent of lymph node involvement, and presence or absence of distant metastases (Fig. 145-2, Tables 145-3 and 145-5). Although many possible combinations of T and N are possible within a given stage, simplistically, stage 0 represents carcinoma *in situ* (Tis) or disease that has not invaded the basement membrane of the breast tissue. Stage I represents a small primary invasive tumor without lymph node involvement or with micrometastatic nodal involvement, and stage II disease usually involves regional lymph nodes. Stages I and II are often referred to as *early breast cancer*. It is in these early stages that the disease is highly curable (98.7% 5-year survival in patients with disease confined to the breast, node negative).[26] Stage III, also referred to as *locally advanced disease*, usually represents a large tumor with extensive nodal involvement in which either node or tumor is fixed to the chest wall. Stage IV disease is characterized by the presence of metastases to organs distant from the primary tumor and is often referred to as *advanced or metastatic disease* as described earlier (27% 5-year survival rate in patients with distant metastases).[26] Most women with breast cancer in the United States present in early stages where the prognosis is favorable (93% of newly diagnosed patients have disease confined to the breast or local lymph nodes).[26]

TABLE 145-5 Clinical Staging System

TNM	Grade	*HER2*	ER	PR	Stage	TNM	Grade	*HER2*	ER	PR	Stage
Tis N0 M0	Any	Any	Any	Any	0						
T1[a] N0 M0	G1	Positive	Positive	Positive	IA	T0 N1[b] M0	G1	Positive	Positive	Positive	IB
T0 N1mi M0				Negative		T1[a] N1[b] M0				Negative	IIA
T1[a] N1mi M0			Negative	Positive		T2 N0 M0			Negative	Positive	
				Negative						Negative	
		Negative	Positive	Positive				Negative	Positive	Positive	IB
				Negative						Negative	IIA
			Negative	Positive					Negative	Positive	
				Negative	IB					Negative	
	G2	Positive	Positive	Positive	IA		G2	Positive	Positive	Positive	IB
				Negative						Negative	IIA
			Negative	Positive					Negative	Positive	
				Negative						Negative	
		Negative	Positive	Positive				Negative	Positive	Positive	IB
				Negative						Negative	IIA
			Negative	Positive					Negative	Positive	
				Negative	IB					Negative	IIB
	G3	Positive	Positive	Positive	IA		G3	Positive	Positive	Positive	IB
				Negative						Negative	IIA
			Negative	Positive					Negative	Positive	
				Negative						Negative	
		Negative	Positive	Positive				Negative	Positive	Positive	
				Negative	IB					Negative	IIB
			Negative	Positive					Negative	Positive	
				Negative						Negative	
TNM	**Grade**	***HER2***	**ER**	**PR**	**Stage**	**TNM**	**Grade**	***HER2***	**ER**	**PR**	**Stage**
T2 N1[c] M0	G1	Positive	Positive	Positive	IB	T0 N2 M0	G1	Positive	Positive	Positive	IIA
T3 N0 M0				Negative	IA	T1[a] N2 M0				Negative	IIIA
			Negative	Positive		T2 N2 M0			Negative	Positive	
				Negative	IIB	T3 N1[c] M0				Negative	
		Negative	Positive	Positive	IIA	T3 N2 M0		Negative	Positive	Positive	IIA
				Negative	IIB					Negative	IIIA
			Negative	Positive					Negative	Positive	
				Negative						Negative	IIIB
	G2	Positive	Positive	Positive	IB		G2	Positive	Positive	Positive	IIA
				Negative	IIA					Negative	IIIA
			Negative	Positive					Negative	Positive	
				Negative	IIB					Negative	
		Negative	Positive	Positive	IIA			Negative	Positive	Positive	IIA
				Negative	IIB					Negative	IIIA
			Negative	Positive					Negative	Positive	
				Negative	IIIB					Negative	IIIB
	G3	Positive	Positive	Positive	IB		G3	Positive	Positive	Positive	IIB
				Negative	IIB					Negative	IIIA
			Negative	Positive					Negative	Positive	
				Negative						Negative	
		Negative	Positive	Positive				Negative	Positive	Positive	
				Negative	IIIA					Negative	IIIB
			Negative	Positive					Negative	Positive	
				Negative	IIIB					Negative	IIIC

TNM	Grade	*HER2*	ER	PR	Stage	TNM	Grade	*HER2*	ER	PR	Stage
T4 N0 M0	G1	Positive	Positive	Positive	IIIA	Any T Any N M1	Any	Any	Any	Any	IV
T4 N1[c] M0				Negative	IIIB						
T4 N2 M0			Negative	Positive							
Any T N3 M0				Negative							
		Negative	Positive	Positive							
				Negative							
			Negative	Positive							
				Negative	IIIC						
	G2	Positive	Positive	Positive	IIIA						
				Negative	IIIB						
			Negative	Positive							
				Negative							
		Negative	Positive	Positive							
				Negative							
			Negative	Positive							
				Negative	IIIC						
	G3	Positive	Positive	Positive	IIIB						
				Negative							
			Negative	Positive							
				Negative							
		Negative	Positive	Positive							
				Negative	IIIC						
			Negative	Positive							
				Negative							

[a]T1 includes T1mi.

[b]N1 does not include N1mi. T1N1miM0 and T0N1miM0 are included for prognostic staging with T1N0M0 cancers of the same prognostic factor status.

[c]N1 includes N1mi, T2, T3, and T4 cancers and N1mi are included for prognostic staging with T2N1, T3N1, and T4N1, respectively.

Reproduced, with permission, from AJCC Cancer Staging Manual, 8th ed. (2017) published by Springer Science and Business Media LLC,www.springer.com.

Staging for breast cancer is separated into clinical and pathologic staging. Clinical stage is assigned before surgery and is based on physical examination

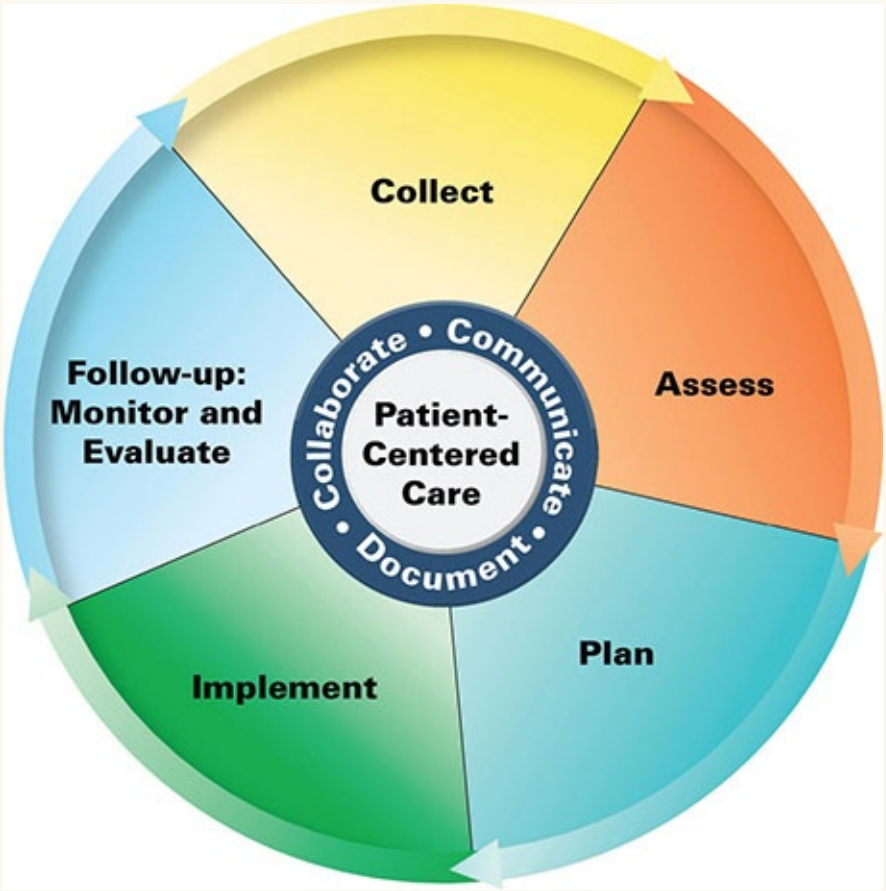
(assessment of tumor size and presence of axillary lymph nodes), imaging (eg, mammography, ultrasonography), and pathologic examination of tissues (eg, biopsy results). Pathologic staging occurs after surgery and adds data from surgical exploration and resection. The American Joint Committee for Cancer (AJCC) publishes staging criteria for cancers, and the breast cancer criteria were most recently updated in 2017 with the eighth edition.[24] The update includes not only TNM (tumor, nodes, metastasis) but also includes ER/PR status, *HER2* receptor status, and grade in order to estimate prognosis and personalize therapy. The update also includes the ability to lower the stage of patients with low-risk genomic profiling, allowing for less aggressive adjuvant therapy. This staging system is widely accepted and used to determine prognosis and assist with treatment decisions.

TREATMENT

Early Breast Cancer (Stage I and II)

Desired Outcomes

The desired therapeutic outcome of adjuvant therapy of breast cancer differs significantly from that of metastatic disease. Adjuvant therapy—chemotherapy, biologic or targeted therapy, and hormonal therapy—is administered with curative intent. The rationale for adjuvant therapy is that breast cancer, even when diagnosed in early stages when clinical evidence of distant spread is not apparent, is a systemic disease that spreads early to distant sites. Adjuvant therapy is intended to eradicate micrometastases and thus cure the patient. A predetermined number of cycles or duration of adjuvant therapy is administered. The goals of neoadjuvant therapy are to eradicate micrometastatic disease, determine prognosis, and potentially conserve the breast tissue for a better cosmetic result. Adjuvant and neoadjuvant chemotherapy is often associated with significant toxicity. Clinicians and patients must weigh the short- and long-term risks of chemotherapy, biologic or targeted therapy, and endocrine therapy against the benefits of lowering the risk of breast cancer recurrence.



Patient Care Process for Breast Cancer

Collect

- Patient characteristics (eg, age, sex)
- Physical exam
- Patient medical history (personal and family history for breast and ovarian cancers, start of menstruation, time of menopause, surgical history [eg, hysterectomy, oophorectomy])
- Social history (eg, tobacco/ethanol use) and dietary habits
- Current medications including OTC use, herbal products, birth control, and dietary supplements
- Objective data

- Height, weight
- Labs including complete blood count with differential, serum creatinine (SCr), total bilirubin, AST, ALT, Alkaline phosphatase
- For other details, see section “Clinical Presentation”

Assess

- History of diabetes, hypertension, overall cardiac health and history, complete with current medications
- Ability/willingness to pay for treatment options, insurance coverage
- Emotional status (eg, presence of anxiety, depression)
- For other details, see section “Clinical Presentation”

Plan*

- Drug therapy regimen including specific chemotherapy, endocrine therapy or targeted therapy and include dose, route, frequency, and duration (see Fig. 145-3, Tables 145-7 through 145-10 and Table 145-12 in sections “Systemic Adjuvant Therapy” and “Metastatic Breast Cancer (Stage IV)”)
- Monitoring parameters including efficacy (eg, staging studies such as CT chest/abdomen/pelvis, bone scan, CT/MRI brain in the cases of metastatic disease; ultrasound in the cases of neoadjuvant therapy), side effect management (eg, nausea/vomiting, mucositis, neutropenia, hot flashes, myalgias) and safety (eg, CBC with differential, SCr, total bilirubin, AST/ALT, DEXA scan for bone health); frequency and timing of follow-up
- Patient education (eg, goal of treatment, dietary and lifestyle modification, drug-specific information; see section “Systemic Adjuvant Therapy,” Table 145-11)
- Self-monitoring for resolution of nausea/vomiting, mucositis, fever, when to seek emergency medical attention
- Referrals to other providers when appropriate (eg, dietician, supportive care services, psychiatry, bone health, cardiology, genetics)

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (eg, labs, staging scans, monitoring tests [eg, Echo/MUGA, DEXA scan])

Follow-up: Monitor and Evaluate

- Resolution of nausea/vomiting, mucositis, myalgia
- Presence of adverse effects (eg, constipation, diarrhea)
- Patient adherence to treatment plan using multiple sources of information
- Re-evaluate duration of therapy, depending on specific regimen

**Collaborate with patient, caregivers, and other healthcare professionals.*

Locoregional Therapy

3 Most patients presenting with breast cancer have an *in situ* tumor (stage 0), a small invasive tumor with negative lymph nodes (stage I), or a small invasive tumor with axillary lymph node involvement (stage II). Surgery alone can cure most, if not all, patients with *in situ* cancers: 70% to 80% of patients with stage I and about half of patients with stage II cancers. The choice of surgical procedures has changed drastically over the past 50 years, which is related to an increased understanding of the biology of breast cancer and the results of a series of well-conducted clinical trials performed over this time period.

Over the years, many trials have investigated less extensive surgery required to maintain acceptable cosmetic results and rates of local and distant recurrence and mortality. Breast-conserving therapy (BCT) includes removal of part of the breast, surgical evaluation of the axillary lymph node basin, and radiation therapy to the breast. The amount of breast tissue removed as a part of BCT varies from just removing the cancerous “lump” (ie, lumpectomy) with a small margin of adjacent normal-appearing tissue to removing the “lump” with a wider excision of adjacent normal-appearing tissue (ie, wide local excision) to removing the entire quadrant of the breast that includes the cancerous “lump” (ie, quadrantectomy). All of these techniques are referred to as *segmental or partial mastectomy*. A meta-analysis of 18 clinical trials in almost 10,000 women found no difference in overall survival for patients who received BCT

compared with mastectomy, which involves complete removal of the breast.[27] However, this and other meta-analyses have suggested the potential for a small increase in the risk of locoregional recurrence with BCT.[27,28]

Most patients diagnosed with breast cancer can be treated with BCT. Several factors should be considered in selecting patients for BCT, including any additional risk the remaining breast tissue poses despite the local effects of radiation therapy. The NCCN recommends that women who carry a known *BRCA1* or *BRCA2* mutation undergo mastectomy and consider additional risk reduction strategies (eg, bilateral mastectomies).[10] Bilateral total mastectomy and oophorectomy reduce the risk of breast cancer recurrence in patients with *BRCA1* or *BRCA2* mutations. Multiple sites of cancer within the breast and the inability to attain negative pathologic margins on the excised breast specimen are indications for mastectomy. Some collagen vascular diseases (eg, scleroderma, systemic lupus erythematosus) are relative contraindications for BCT because of an increased risk of radiation-related adverse effects. Local recurrence after BCT has not been consistently associated with an increased mortality rate, but it is distressing to the patient and requires surgical removal of the remaining breast tissue. In addition, reconstructive therapy is often not feasible in a breast that has previously received irradiation. Another major consideration in selecting patients for BCT is the expected cosmetic result. For some patients, the preservation of a limited amount of breast tissue may not justify the inconvenience of radiation therapy. Another approach to therapy for these patients is primary (neoadjuvant) systemic therapy to potentially shrink the tumor and minimize surgery (see "Systemic Adjuvant Therapy" and "Locally Advanced Breast Cancer" sections for further details). The availability of an external-beam radiation facility and the patient's willingness to comply with the prescribed course of radiotherapy must also be considered. A meta-analysis of 10,801 patients in 17 randomized controlled trials showed that radiotherapy after BCT reduces the 10-year risk of first recurrence by 15.7% and the 15-year risk of breast cancer death by 3.8% as compared with no radiotherapy.[29] External-beam radiation therapy after BCT usually involves 3 to 5 weeks of radiation therapy directed to the entire breast tissue (total of 40-50 Gy [4000-5000 rad] administered in 15-25 daily doses Mondays through Fridays with an optional boost of radiation to the tumor bed) to eradicate residual disease. Local tumor control is similar with shorter courses versus longer courses of radiation, and toxicities such as breast shrinkage, telangiectasias, and breast edema are less common with shorter regimens. The recommended radiation course by the NCCN is 40 to 42.5 Gy (4000-4250 rad) in 15 to 16 fractions or 45 to 50.4 Gy (4500-5040 rad) in 25 to 28 fractions.[19]

Complications associated with radiation therapy to the breast are generally minor and include reddening and erythema of the breast tissue and subsequent shrinkage of the total breast mass beyond that predicted on the basis of breast tissue removal.

Clinical trials are investigating the use of accelerated partial breast irradiation, intraoperative radiotherapy, or no radiation after segmental mastectomy for certain patient populations with a very low risk of recurrence.[30] Until the results of these studies are available, the standard approach to BCT includes whole-breast radiation therapy for most patients.

Postmastectomy radiation therapy to the chest wall and regional lymph nodes (if indicated) may also be required in certain situations when tumors are large or the number of positive axillary lymph nodes is high (see the "Locally Advanced Breast Cancer" section). The NCCN guideline recommends that women with four or more positive axillary lymph nodes should undergo postmastectomy radiation therapy. Patients with one to three positive ipsilateral axillary lymph nodes should strongly consider postmastectomy radiation, although conflicting data exist in this patient population. Patients with positive surgical margins, tumors larger than 5 cm, or tumors less than 5 cm with close margins (less than 1 mm of normal adjacent tissue) should consider postmastectomy chest wall radiation therapy. Patients with surgical margins of at least 1 mm, tumor size of 5 cm or less, and negative axillary lymph nodes do not require postmastectomy chest wall radiation therapy.[19]

The optimal sequence of radiation therapy and chemotherapy is somewhat controversial, but it is common to begin radiation after completion of chemotherapy when chemotherapy is recommended. If chemotherapy is not indicated, radiation is administered after surgery (see the "Adjuvant Biologic or Targeted Therapy" section for a discussion of sequencing trastuzumab).

Accurate assessment of the spread of breast cancer cells to the axillary lymph nodes is critical for prognosis and personalizing local and systemic treatments. ALND with histopathologic study of the full axillary specimen, including level I and II lymph nodes, was the gold standard for detecting axillary nodal involvement and determining the number of lymph nodes containing tumor for many years. The number of positive axillary lymph nodes remains the most powerful predictor of breast cancer recurrence and survival, but other benefits may include a therapeutic effect of removing the lymph nodes and obtaining information to guide treatment selection. However, axillary dissection is associated with significant morbidity, including lymphedema, arm pain or numbness, and reduced quality of life.[31] Recent studies indicate that about 60%

of patients with early-stage breast cancer (ESBC) present with lymph node–negative disease, which indicates that many women would derive no therapeutic benefit but would be exposed to the complications from the full ALND.

For these reasons, a procedure involving lymphatic mapping and SLNB is now recommended for patients with clinically negative lymph nodes.[32] The sentinel lymph node(s) is the first lymph node(s) that receives lymph drainage from the primary tumor. Injection of a vital blue dye, a radiocolloid, or both, around the primary breast tumor identifies the sentinel lymph node(s) in most patients, and the status of this lymph node(s) predicts the status of the remaining nodes in the nodal basin. Patients with lymph nodes that are suspicious for cancer involvement either by physical examination or imaging should have a biopsy performed to exclude lymph node involvement. SLNB is the standard of care for patients with clinically negative axillary lymph nodes.[19] Historically, patients with positive sentinel nodes have proceeded to a level I and II ALND, although this practice has recently been questioned. Results from a randomized trial showed that ALND after SLNB in women with clinically node-negative tumors smaller than 5 cm, fewer than three involved sentinel lymph nodes, and undergoing BCT with subsequent breast irradiation resulted in higher morbidity, no improvement in local recurrence, and no difference in disease-free or overall survival as compared with SLNB alone.[33] Therefore, the ASCO guidelines do not recommend ALND for women with ESBC with one or two positive sentinel lymph nodes who will receive BCT followed by radiation.[32] Women undergoing mastectomy with positive sentinel lymph nodes should be offered ALND.

Women with large tumors (greater than 5 cm) or locally advanced disease, IBC, or DCIS when BCT is planned should not receive SLNB.[32] Patients with multifocal or multicentric breast tumors, DCIS when mastectomy is planned, prior neoadjuvant (preoperative) chemotherapy, or prior surgery involving the breast or axilla may be offered SLNB.[32] Patients who are pregnant or lactating are not considered candidates for this procedure because of concerns regarding the effects of the blue dye or the radiocolloid on the fetus. The decision of whether to undergo the SLNB procedure or a full axillary dissection is complex, and readers are referred to an excellent review for further information.[31]

Early trials of less extensive surgical approaches to breast cancer show that BCT is an appropriate primary therapy for most women with stages I and II disease and is preferable because it provides survival rates equivalent to those of modified radical mastectomy. These historical trials provided valuable information regarding the natural history of the disease and identified pathologic prognostic factors associated with early cancer spread. Most of the information

available regarding the selection of women most likely to benefit from systemic adjuvant therapy was derived from pathologic evaluation of tissues archived from these early trials. Further trials of less extensive local therapy (now focused on the surgical approach to the axilla and radiation therapy) should also provide valuable information for future patients.

Systemic Adjuvant Therapy

4 *Systemic adjuvant therapy* is defined as the administration of systemic therapy after definitive local therapy (surgery, radiation, or both) when there is no evidence of metastatic disease but a high likelihood of disease recurrence. By the time breast cancers become clinically detectable, they have likely been present for a number of years and have had an opportunity to establish distant micrometastases. Micrometastatic disease can travel from the primary breast tumor and spread to distant organs through several different routes (eg, hematogenous spread through blood vessels, lymphangitic spread through lymph channels, local extension to surrounding structures). Local therapies such as breast surgery and irradiation do not eradicate distant micrometastases; therefore, systemic therapy is required to target these tumor cells that may have escaped the local area of the breast. The risk of micrometastatic disease is one factor used to identify patients with a high risk of recurrence who would require systemic adjuvant therapy. Many collaborative research groups have conducted several stepwise series of studies designed to identify appropriate candidates for systemic adjuvant therapy and the optimal regimens and duration of therapy. Several hundred randomized clinical trials of various systemic adjuvant modalities have been conducted. The results of these trials show that chemotherapy, endocrine therapy, targeted therapy, or some combination of these agents improves disease-free and/or overall survival for high-risk patients in specific prognostic subgroups (eg, nodal involvement, menopausal status, hormone-receptor status, or *HER2* status). The huge amounts of data generated by these trials have resulted in a great deal of controversy, with different conclusions being reached by various experts.

5 Interpretation of results of systemic adjuvant therapy trials is difficult because of differences in the patient populations studied, the variation in the natural history of breast cancer, the absence of information regarding pathologic prognostic factors in many studies, and differences in treatment approach and methods of analysis. Several international groups have conducted meta-analyses of similar breast cancer trials to summarize the results of adjuvant systemic therapy. One such effort, organized by the Early Breast Cancer Trialists'

Collaborative Group (EBCTCG), is based on a worldwide collaboration involving multiple randomized trials and is continually updated with results from new clinical trials. The EBCTCG's overview analyses are updated periodically as new data become available. The most recent updates reflect the long-term effects on breast cancer recurrence and survival for adjuvant endocrine therapy and chemotherapy.[18,34,35] Many important questions regarding the optimal way to administer adjuvant chemotherapy and endocrine therapy and the magnitude of benefit as measured by disease-free and/or overall survival in clinically relevant subsets of patients have been answered by these overview analyses. Simply stated, the results of these analyses support the use of adjuvant endocrine therapy in all patients with positive hormone-receptor status regardless of age, menopausal status, involvement of axillary lymph nodes, or tumor size.[34] The results of these overviews also support the use of adjuvant chemotherapy in most women with lymph node metastases or with primary breast cancers larger than 1 cm in diameter (both node-negative and node-positive).[18] It is important to note that data from clinical trials incorporating anti-*HER2* therapy into adjuvant regimens are not included in these analyses because sufficient long-term follow-up had not been reached at the time of publication. Results from these more recent clinical trials are discussed later.

Table 145-6 uses data from the EBCTCG overview analyses to show the absolute benefits of adjuvant chemotherapy in terms of age and nodal status. In the highest risk group, node-positive women younger than 50 years of age, only 44.8% were alive and disease-free at 5 years with no polychemotherapy as compared with 59.4% with polychemotherapy, which translates into an absolute 5-year disease-free survival benefit of 14.6%. However, in the node-negative group, patients younger than 50 years old in whom disease-free survival with no polychemotherapy was highest (ie, 72.6%), the addition of polychemotherapy produced an absolute benefit of only 9.9%.[36] It should be pointed out that all of these differences in disease-free survival are statistically significant and form the basis for national and international guidelines that recommend offering cytotoxic chemotherapy to most women with ESBC.[19,37,38] However, the absolute survival benefit in node-positive women 50 to 69 years old is quite small (3%) and patients may decide to not pursue treatment, depending on other disease characteristics and comorbid conditions.

TABLE 145-6 Absolute Benefits of Adjuvant Chemotherapy by Age and Nodal Status

	With Polychemotherapy (%)	With No Polychemotherapy (%)	Absolute Benefit (%)
Disease-Free Survival			
Age <50 years			
Node negative	82.5	72.6	9.9
Node positive	59.4	44.8	14.6
Age 50-69 years			
Node negative	85.7	80.4	5.3
Node positive	63.3	57.4	5.9
Survival[a]			
Age <50 years	67.6	57.6	10
Age 50-69 years	52.6	49.6	3

[a]Younger women, 35% node-positive; older women, 70% node-positive.

Data from Reference 36.

Several international and national groups have developed guidelines for the treatment of ESBC based on specific patient and disease characteristics and the results of the EBCTCG overview analyses. The three most commonly referenced guidelines are the St. Gallen International Expert Consensus Conference, European Society of Medical Oncology (ESMO), and the NCCN guidelines.[19,37,38] The St. Gallen guidelines are updated every two years by an international group of researchers that meets in St. Gallen, Switzerland to review available evidence and create consensus recommendations for selection of adjuvant systemic therapies in specific patient populations outside of the framework of clinical trials. The NCCN and ESMO have also developed practice guidelines for the treatment of breast cancer that are updated annually or more often based on the available evidence. Recommendations from the NCCN for patients with tumors 1 cm or larger or positive lymph nodes are summarized in **Fig. 145-3**. For patients with tumors smaller than 1 cm, micrometastatic lymph node involvement, or negative lymph nodes, treatment is highly individualized and based on multiple patient- and tumor-related factors, including hormone-

receptor status, *HER2* status, comorbidities, and patient preferences. Specific treatment recommendations are complex and readers are referred to the guidelines for further details.

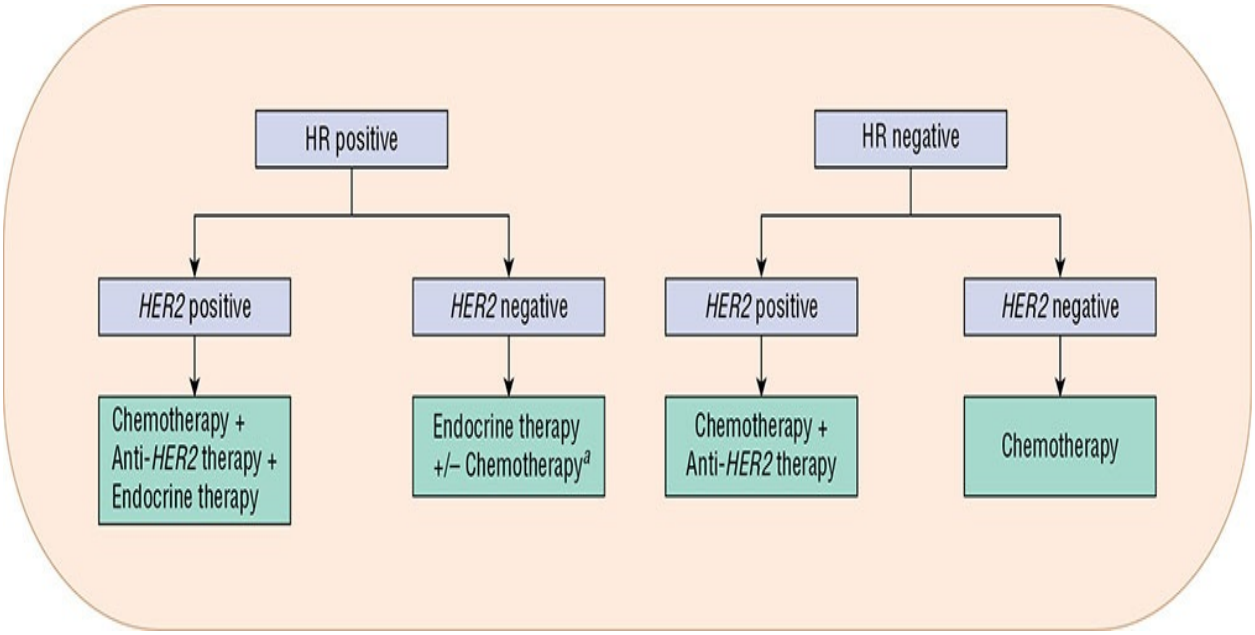


FIGURE 145-3 Treatment of patients with breast cancers larger than 1 cm or with positive lymph nodes. Refer to the text for definitions of HR and *HER2* positivity. Refer to the text for the management of patients with tumors smaller than 1 cm, micrometastatic lymph node involvement, or negative lymph nodes. *a*Oncotype DX® may identify patients who derive little benefit from chemotherapy (lymph node–negative patients only) (see "Systemic Adjuvant Therapy" section for details). (HR, hormone receptor; *HER2*, human epidermal growth factor receptor-2.)

6 The use of preoperative systemic therapy is the standard of care for patients with locally advanced breast cancer and represents an important treatment option for patients with ESBC. This approach to therapy, referred to as *neoadjuvant* or *primary systemic therapy*, usually consists of chemotherapy, either alone or combined with biologic or targeted therapy, but in special circumstances may also include endocrine therapy (eg, in inoperable patients with significant comorbidities or in tumors with high sensitivity to endocrine therapy). Advantages of preoperative systemic therapy include a decrease in tumor size to minimize surgery, determination of response to chemotherapy or hormone therapy in vivo (an important prognostic indicator), and other theoretical advantages (eg, delivery of chemotherapy through an intact vascular

system). In a pivotal NSABP (B18) trial, preoperative chemotherapy was compared with traditional chemotherapy given after surgery (the same chemotherapy and the same number of cycles).[39,40] Although no difference was found in disease-free or overall survival, rates of BCT were higher in the group receiving preoperative chemotherapy.[40] This study also identified a small subset of patients (13%) who had a pathologic complete response (defined as no tumor left at surgery [pCR]) after chemotherapy. Patients who achieved a pCR had a significantly longer disease-free survival compared to patients who did not achieve a pCR.[40] Importantly, even after 16 years of follow-up, patients who achieved a pCR continued to have superior disease-free and overall survival as compared with patients who did not achieve a pCR.[41] Although this approach to therapy was historically reserved for patients with inoperable tumors (locally advanced), the use of preoperative systemic therapy in patients with ESBC is increasing in popularity because of the ability to assess the response to therapy in vivo as well as the potential to decrease the size of the tumor, allowing for less radical surgery and better cosmetic results.

Intensive research efforts are directed toward identifying characteristics of the primary tumor (eg, pathologic or molecular prognostic factors) that may predict for a higher or lower likelihood of distant metastases and death in node-negative patients. Although many prognostic factors are being investigated, no single factor or combination of factors sufficiently identifies those at risk of metastases or is sufficiently standardized to be reproducibly applicable to all patients. Several multigene expression assays are commercially available as decision-support tools for adjuvant chemotherapy.[42] Oncotype DX® is one test that screens for expression of 21 genes with RT-PCR and reports a recurrence score that correlates with the risk of distant recurrence or death from breast cancer in women with ER-positive, node-negative, invasive breast cancer. A low recurrence score (less than 18) indicates a low risk of recurrence with endocrine therapy alone indicating that perhaps adjuvant chemotherapy could be avoided. A high recurrence score (greater than or equal to 31) indicates a high risk of recurrence despite endocrine therapy, suggesting a need for adjuvant chemotherapy followed by endocrine therapy. The utility of chemotherapy in patients with an intermediate score (18-30) is unclear and was the subject of the prospective TAILORx clinical trial. In that trial, patients with an Oncotype DX® score of 11 to 25 were randomized to receive adjuvant endocrine therapy alone or chemotherapy followed by endocrine therapy. The results of the study indicate that patients with an Oncotype DX® score of 18 to 25 may be spared chemotherapy.[43] Retrospective data suggest that Oncotype DX® testing may

also be beneficial in selecting patients with positive lymph nodes who would derive little benefit from chemotherapy, and an ongoing clinical trial is underway to further elucidate the role of Oncotype DX® in patients with one to three positive lymph nodes after surgery. Other commercially available multigene assays include MammaPrint® and Prosigna®. MammaPrint® screens the tumor for 70 genes with microarray technology in breast cancer patients with ESBC, regardless of hormone-receptor status. The assay reports the predicted rates of recurrence as high or low. The Microarray In Node-negative Disease may Avoid ChemoTherapy (MINDACT) trial compared the predictive capabilities of MammaPrint® against standard prognostic factors to assess which patients with node-negative, ER-positive breast cancer would benefit from adjuvant chemotherapy. The results showed that patients with high clinical risk (based on Adjuvant! online) and low genomic risk who did not receive adjuvant chemotherapy had a similar 5-year survival without distant metastases of 94.7% compared to 95.9% for those patients who did receive adjuvant chemotherapy.[44] PAM50 (Prosigna®) is a multigene test that screens the tumor for 50 genes (plus 5 control genes) to predict distant relapse-free survival and likelihood of recurrence at 10 years in postmenopausal women with ER-positive breast cancer treated with endocrine therapy regardless of nodal status.[42] An internet-based tool that has been adopted for clinical use called Adjuvant! (www.adjuvantonline.com) helps clinicians make informed decisions regarding adjuvant therapy for breast, colon, and lung cancers. The tool allows healthcare professionals to estimate the risks of negative outcomes (eg, cancer recurrence, death) and the potential benefits of therapy (eg, reductions in risks of recurrence and death) and then discuss these estimates with the patient. This is a validated, evidence-based tool that incorporates multiple prognostic and predictive factors into a mathematical model in which each factor is weighted based on established evidence from clinical trials and is placed in the background of the SEER database for patients living in the United States.[45] Several characteristics and tumor features are entered by the clinician, and the tool will estimate the breast cancer mortality and recurrence risk at 10 years and determine the impact of chemotherapy, hormone therapy, or both on these risks. The results are projected in a graphic format that is easy to understand and explain to patients.

Adjuvant Chemotherapy The basic principle of adjuvant therapy for any cancer type is that the regimen with the highest response rate in advanced disease should be the optimal regimen for use in the adjuvant setting. However, results from individual clinical trials investigating specific regimens in the adjuvant setting are required to identify the benefits and risks in a specific

patient population. Early administration of effective combination chemotherapy at a time when the tumor burden is low should increase the likelihood of cure and minimize the emergence of drug-resistant tumor cell clones. Historically, combination chemotherapy regimens (polychemotherapy) have been more effective than single-agent chemotherapy. The most common cytotoxic drugs that have been used alone and in combination as adjuvant therapy for breast cancer include doxorubicin, epirubicin, cyclophosphamide, methotrexate, fluorouracil, carboplatin, paclitaxel, and docetaxel. **Table 145-7** lists the most common combination chemotherapy regimens used in the adjuvant setting.

TABLE 145-7 Selected Neo/Adjuvant Chemotherapy Regimens for Breast Cancer

Dose-Dense AC → Paclitaxel[a]	AC → Paclitaxel
Doxorubicin 60 mg/m² IV bolus, day 1	Doxorubicin 60 mg/m² IV, day 1
Cyclophosphamide 600 mg/m² IV, day 1	Cyclophosphamide 600 mg/m² IV, day 1
Repeat cycles every 14 days for 4 cycles (must be given with growth factor support)	Repeat cycles every 21 days for 4 cycles
Followed by:	Followed by:
Paclitaxel 80 mg/m² IV weekly	Paclitaxel 80 mg/m² IV weekly
Repeat cycles every 7 days for 12 cycles	Repeat cycles every 7 days for 12 cycles
TC[a]	**TAC**
Docetaxel 75 mg/m² IV, day 1	Docetaxel 75 mg/m² IV, day 1
Cyclophosphamide 600 mg/m² IV, day 1	Doxorubicin 50 mg/m² IV bolus, day 1
Repeat cycles every 21 days for 4 cycles	Cyclophosphamide 500 mg/m² IV, day 1 (doxorubicin should be given first)
	Repeat cycles every 21 days for 6 cycles (must be given with growth factor support)
Dose-Dense AC → Dose Dense Paclitaxel[a]	**CMF**
Doxorubicin 60 mg/m² IV bolus, day 1	Cyclophosphamide 100 mg/m² per day orally, days 1-14
Cyclophosphamide 600 mg/m² IV, day 1	Methotrexate 40 mg/m² IV, days 1 and 8
Repeat cycles every 14 days for 4 cycles (must be given with growth factor support)	5-fluorouracil 600 mg/m² IV, days 1 and 8
Followed by:	Repeat cycles every 28 days for 6 cycles
Paclitaxel 175 mg/m² IV over 3 hours	
Repeat cycles every 14 days for 4 cycles (must be given with growth factor support)	

[a]Designated as a preferred regimen in the NCCN Breast Cancer Guidelines.

AC, Adriamycin (doxorubicin), Cytoxan (cyclophosphamide); CMF, cyclophosphamide, methotrexate, 5-fluorouracil; TAC, Taxotere (docetaxel), Adriamycin (doxorubicin), cyclophosphamide; TC, Taxotere (docetaxel), cyclophosphamide.

Data from Reference 19.

Anthracyclines (doxorubicin or epirubicin) and more recently taxanes (paclitaxel or docetaxel) have become the cornerstones of modern chemotherapy for the adjuvant treatment of breast cancer. The EBCTCG overview analysis of adjuvant chemotherapy analyzed the use of CMF- or anthracycline-based chemotherapy regimens compared with no chemotherapy. Patients who received polychemotherapy had a 23% ± 2% reduction in annual odds of recurrence and a 14% ± 2% reduction in annual odds of death as compared with patients who did not receive chemotherapy, establishing adjuvant chemotherapy as a powerful option for reducing breast cancer recurrence. The authors also analyzed results from 20 trials that directly compared an anthracycline-containing regimen with a CMF-type regimen and demonstrated a significant advantage with the anthracycline regimens.[18] In that meta-analysis, anthracycline-containing regimens were modestly superior in reducing recurrence and death as compared with regimens without anthracyclines. In the 2012 update, anthracycline-containing regimens reduced the annual odds of recurrence (7% ± 3%) and death (9% ± 3%). The 2012 update also reported data from an additional 33 clinical trials and showed that the addition of a taxane reduced the risk of distant recurrence (13% ± 3%), any recurrence (14% ± 2%), and overall mortality (11% ± 3%) as compared with a nontaxane regimen.[18] These trials included both sequential and concurrent taxane therapy (paclitaxel or docetaxel) in conjunction with anthracyclines (with or without cyclophosphamide, fluorouracil, or methotrexate). Proportional reductions in recurrence and breast cancer mortality were largely independent of age, nodal status, tumor size, tumor differentiation, or ER status. Most of these trials enrolled node-positive patients only, but some high-risk node-negative patients were also included. There is no apparent biologic reason why patients with node-negative disease should respond differently to the taxanes than those with node-positive disease, but the absolute benefits for this population may not be large enough to require that all patients with node-negative disease receive an anthracycline- and taxane-based chemotherapy regimen. Toxicities such as peripheral neuropathy, myelosuppression, and alopecia should also be considered. Taxane-containing, non-anthracycline regimens were not included in the meta-analysis but may be appropriate for some patients with a low risk of disease recurrence based on the results from a single randomized clinical trial.[45] However, this subject remains widely debated, and no single adjuvant chemotherapy regimen is preferred.

Cytotoxic chemotherapy is a particularly important treatment modality for patients with tumors that do not express ER or PR and do not overexpress *HER2*

(triple-negative breast cancer [TNBC]).[46] Patients with TNBC treated with anthracycline- and taxane-based chemotherapy have significantly decreased survival compared to patients with other breast cancer subtypes. Ironically, this patient subgroup is more likely to respond to neoadjuvant chemotherapy. Furthermore, patients with TNBC who achieve a pCR have excellent long-term survival, but those who have residual disease at the time of surgery have a worse prognosis than non-TNBC patients. The optimal type and duration of chemotherapy for patients with TNBC is unknown. More recently, the addition of carboplatin to a neoadjuvant anthracycline- and taxane-based chemotherapy regimen resulted in a higher pCR rate as compared to chemotherapy without carboplatin, but at the cost of increased toxicity.[46] Identification of actionable molecular targets for this aggressive breast cancer subtype is needed and research is ongoing. Molecular targets of interest include epidermal growth factor receptor (EGFR), mammalian target of rapamycin (mTOR), poly-ADP ribose polymerase (PARP), and immunotherapy. Based on a recent study in patients with *HER2*-negative ESBC that detected residual disease after neoadjuvant chemotherapy, some clinicians may offer adjuvant capecitabine for 6 to 8 cycles.[47] Patients in the Capecitabine for Residual Cancer as Adjuvant Therapy (CREATE-X) study who received capecitabine in the adjuvant setting had longer disease-free and overall survival as compared to those who did not receive additional chemotherapy.[47]

Although the optimal duration of adjuvant chemotherapy administration is unknown, it appears to be between 12 and 24 weeks and depends on the regimen being used. Optimally, chemotherapy should be initiated within 12 weeks of surgical removal of the primary tumor.[48] “Dose intensity” and “dose density” appear to be critical factors in achieving optimal outcomes in adjuvant breast cancer therapy. *Dose intensity* is defined as the amount of drug administered per unit of time and is typically reported in milligrams per square meter of body surface area per week (mg/m^2/week). Increasing dose, decreasing time between doses, or both can increase dose intensity. *Dose density* is one way of achieving dose intensity but not by increasing the amount of drug given, as occurs with dose escalation, but instead by decreasing the time between treatment cycles. Dose reductions for standard treatment regimens should be avoided unless necessitated by severe toxicity. Increasing doses beyond those contained in standard treatment regimens does not appear to be beneficial and may be harmful.

Several studies investigating the impact of *dose density* have now been reported. Interest in this approach to adjuvant therapy was stimulated when the

Cancer and Leukemia Group B (CALGB) reported results from their trial 9741, which tested not only dose density but also sequential versus combination chemotherapy regimens. Investigators randomized node-positive breast cancer patients after surgery to sequential versus concurrent chemotherapy (with doxorubicin, cyclophosphamide, and paclitaxel) and standard dose versus dose density.[49] After a median follow-up period of 36 months, the patients who received chemotherapy every 2 weeks (dose-dense) had a significantly prolonged disease-free survival (85% vs 81%) and overall survival (92% vs 90%) at 3 years compared with chemotherapy every 3 weeks.[49] The use of sequential versus concurrent chemotherapy did not show a difference in disease-free or overall survival, but sequential therapy did appear to be less toxic. Patients in the concurrent every 2 week group (group 4) had significantly more regimen-related toxicity, including a very high rate of red blood cell transfusions for anemia (13% of cycles).[49] Red blood cell transfusions are rarely required with most other standard adjuvant chemotherapy regimens used for breast cancer.

Dose intensity appears to be important for some drugs but not for others. Many studies with anthracyclines (without taxanes) show no benefit from a dose-dense approach to drug administration. These data seem to contradict the CALGB 9741 data. However, data with the taxanes, especially paclitaxel, appear to support a dose-dense (not intense) approach, with weekly therapy producing optimal outcomes.[50] Data with paclitaxel given weekly versus every 3 weeks indicate that this drug is more effective when given weekly in the adjuvant, neoadjuvant, and metastatic settings.[50–52] Thus, some experts suggest that the different paclitaxel schedule is the primary reason for the success with this approach to therapy in the CALGB 9741 study.

Although other trials have attempted to investigate dose-dense regimens, they also have other variables that could potentially impact the outcomes. A meta-analysis by Bonilla et al. evaluated four trials of chemotherapy given in a dose-dense fashion as compared with conventional administration.[53] In these studies, patients who received dose-dense chemotherapy had statistically improved disease-free and overall survival compared with patients who received conventionally administered chemotherapy. Unfortunately, none of the trials, with the exception of the CALGB 9741 study, adequately evaluated the true impact of dose density.

The short-term toxic effects of chemotherapy used in the adjuvant setting are generally well tolerated. Although a number of investigators have reported reduced quality of life, most patients are able to maintain a reasonable level of

function and emotional and social well-being during treatment.[54] Supportive therapy of patients receiving systemic adjuvant chemotherapy has improved over the past decades. More effective antiemetics have become available to manage chemotherapy-induced nausea and vomiting, and myeloid growth factors can prevent febrile neutropenia, particularly in elderly patients and patients receiving dose-dense chemotherapy regimens. Standard anti-nausea medications for anthracycline-based chemotherapy include olanzapine, serotonin receptor antagonists, dexamethasone, and neurokinin-1 antagonists.[55] The use of myeloid growth factors to support some adjuvant chemotherapy regimens may be required (eg, with dose-dense regimens), but these are not routinely used with adjuvant chemotherapy regimens. Many other side effects are common with the chemotherapy regimens used for the treatment of ESBC, and patients should be appropriately counseled regarding the likelihood of alopecia, weight gain, and fatigue. Patients who are menstruating often experience a cessation of menses that may not return; cessation of menses may be accompanied by signs and symptoms of menopause. Deep vein thrombosis has been reported in women receiving combination chemotherapy regimens.[56] Leukemia and other hematologic disorders have long been associated with the alkylating agents (eg, cyclophosphamide) and the topoisomerase II inhibitors (eg, doxorubicin and epirubicin). Several studies have reported a 0% to 1.5% cumulative incidence of leukemia or myelodysplasia after adjuvant chemotherapy with median follow-up periods of 3 to 11 years.[57] To date, the dose-dense regimens have not been associated with an excess rate of leukemias, but the follow-up periods for these trials are relatively short.

Cardiomyopathy induced by doxorubicin occurs in fewer than 1% of women whose total dose of anthracycline is less than 320 mg/m^2 of doxorubicin equivalents.[58] This risk may be further decreased by the use of continuous infusion or weekly doxorubicin. It should be noted that epirubicin in the adjuvant setting is usually given at a dose of 100 mg/m^2.[19] At this dose, epirubicin has an equal risk of cardiomyopathy as standard doxorubicin doses when both agents are given as bolus or short infusions. Taxanes are often associated with hypersensitivity reactions, peripheral neuropathy, or myalgias and arthralgias for a few days after the infusion.

It is important to note that the magnitude of survival benefit for adjuvant chemotherapy in stages I and II breast cancer is modest, with an absolute reduction in 10-year mortality rate of only 5% for patients with negative axillary lymph nodes and 10% for patients with positive axillary lymph nodes. In addition, it is currently not possible to accurately predict who will attain this

survival benefit. Genetic prognostic tools, such as Oncotype DX®, can help to identify patients who may derive little or no benefit from chemotherapy. However, these tests are only appropriate in specific subsets of patients. Many patients with breast cancer would accept toxicity from treatment to achieve as little as a 1% to 5% absolute improvement in survival. Therefore, most patients with stage I and stage II breast cancer will likely choose adjuvant chemotherapy.

The optimal chemotherapy regimen for use in the adjuvant setting has yet to be identified, and the choice of chemotherapy regimen for a specific patient is complex. Many adjuvant chemotherapy regimens are available, but most of these regimens have not been directly compared in randomized clinical trials. In some cases, the choice of chemotherapy regimen may be geographic, particularly if a regimen has been developed and studied by a specific institution. Based on data from clinical trials and the previously mentioned meta-analysis, the concomitant or sequential addition of a taxane to an anthracycline-based chemotherapy regimen has become the standard of care for women with node-positive breast cancer. Data from meta-analyses and randomized trials specifically in patients with high-risk node-negative disease support the use of anthracycline- and taxane-based chemotherapy regimens in this patient population.[18,45] Results from a single trial that evaluated a taxane-containing (non-anthracycline) regimen suggest that this regimen may be an appropriate treatment in selected patients at low risk of disease recurrence. NCCN recommendations are purposefully vague, and they do not differentiate between patients with node-positive or -negative breast cancer. The NCCN has designated preferred chemotherapy regimens, as listed in Table 145-7, although detailed information is not provided regarding the rationale behind these designations.

Adjuvant Biologic or Targeted Therapy Therapies directed at molecular targets through novel mechanisms are often referred to as targeted therapy. Many of the targeted therapies are also biologic therapies because they are MoABs. Trastuzumab is a MoAB targeted against the *HER2*-receptor protein. It has demonstrated significant survival benefits when administered with chemotherapy in women with metastatic, *HER2*-positive breast cancer. Several published trials support the use of trastuzumab in combination with or sequentially after adjuvant chemotherapy for patients with early-stage, *HER2*-positive breast cancer (**Table 145-8**).[59] Results from these trials report up to a 50% reduction in the risk of recurrence with the addition of trastuzumab to an adjuvant chemotherapy regimen. A meta-analysis of the six available clinical trials investigating the addition of trastuzumab to chemotherapy involving almost 14,000 women reported superior disease-free and overall survival in

patients with *HER2*-positive breast cancer who received trastuzumab with chemotherapy as compared with those that received chemotherapy alone.[60] Although the benefit of adding trastuzumab to these regimens is clear, the optimal trastuzumab-based regimen is less clear because the type of chemotherapy, sequence of administration, and duration of trastuzumab differed among the trials.

TABLE 145-8 Selected Regimens for *HER2*-Positive Early-Stage Breast Cancer

Regimen	Drugs	Doses	Frequency	Cycles
Adjuvant				
AC ⇒ PH ⇒ H + pertuzumab[a]	Doxorubicin	60 mg/m² IV	Every 21 days	4
	Cyclophosphamide	600 mg/m² IV	Every 21 days	4
	followed by			
	Paclitaxel	80 mg/m² IV over 1 hour	Every 7 days	12 weeks
	with Trastuzumab	8 mg/kg IV → 6 mg/kg IV	Every 21 days	4
	plus Pertuzumab	840 mg IV → 420 mg IV	Every 21 days	4
	followed by			
	Trastuzumab	6 mg/kg IV	Every 21 days	Complete 1 year
	plus Pertuzumab	420 mg IV	Every 21 days	Complete 1 year
TCH[a]	Docetaxel	75 mg/m² IV	Every 21 days	6
	Carboplatin	AUC 6 IV	Every 21 days	6
	Trastuzumab	4 mg/kg IV → 2 mg/kg IV	Every 7 days	18 weeks
	followed by			
	Trastuzumab	6 mg/kg IV	Every 21 days	Complete 1 year
AC ⇒ TH	Doxorubicin	60 mg/m² IV	Every 21 days	4
	Cyclophosphamide	600 mg/m² IV	Every 21 days	4
	followed by			
	Docetaxel	100 mg/m² IV	Every 21 days	4
	Trastuzumab	4 mg/kg IV → 2 mg/kg IV	Every 7 days	12 weeks
	followed by			
	Trastuzumab	6 mg/kg IV	Every 21 days	Complete 1 year
TCHP[a,b]	Docetaxel	75 mg/m² IV	Every 21 days	6
	Carboplatin	AUC 6 IV	Every 21 days	6
	Trastuzumab	8 mg/kg IV → 6 mg/kg IV	Every 21 days	6
	Pertuzumab	840 mg IV → 420 mg IV	Every 21 days	6
	followed by			
	Trastuzumab	6 mg/kg IV	Every 21 days	Complete 1 year
	Pertuzumab	420 mg IV	Every 21 days	Complete 1 year
AC ⇒ THP	Doxorubicin	60 mg/m² IV	Every 21 days	4
	Cyclophosphamide	600 mg/m² IV	Every 21 days	4
	followed by			
	Docetaxel	75 mg/m² IV	Every 21 days	4
	Trastuzumab	8 mg/kg IV → 6 mg/kg IV	Every 21 days	4
	Pertuzumab	840 mg IV → 420 mg IV	Every 21 days	4
	followed by			
	Trastuzumab	6 mg/kg IV	Every 21 days	Complete 1 year
	Pertuzumab	420 mg IV	Every 21 days	Complete 1 year

AC, Adriamycin (doxorubicin), Cytoxan (cyclophosphamide); FEC, fluorouracil, epirubicin, cyclophosphamide; H, Herceptin (trastuzumab); PH, paclitaxel, Herceptin (trastuzumab); TCH, Taxotere (docetaxel), carboplatin, Herceptin (trastuzumab); TCHP, Taxotere (docetaxel), carboplatin, Herceptin (trastuzumab), pertuzumab; TH, Taxotere (docetaxel), Herceptin (trastuzumab); THP, Taxotere (docetaxel), Herceptin (trastuzumab), pertuzumab.

[a]Designated as a preferred regimen in the NCCN Breast Cancer Guidelines.

[b]From Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with *HER2*-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol* 2013;24:2278-84.

Data from Reference 19.

Most of the regimens investigated in these adjuvant trials included an anthracycline and a taxane given concurrently with trastuzumab or sequentially before trastuzumab. Administration of a taxane with trastuzumab may be more effective than trastuzumab administered after chemotherapy. In the meta-analysis, sequential and concomitant use of trastuzumab with chemotherapy prolonged disease-free survival as compared with chemotherapy alone. Concomitant trastuzumab also improved overall survival, but sequential trastuzumab did not.[60] The adjuvant use of trastuzumab without an anthracycline has been reported in one trial (Breast Cancer International Research Group 006 also known as BCIRG 006) and appears to provide similar benefit with diminished cardiac adverse effects as compared with traditional anthracycline-containing adjuvant trastuzumab regimens.[61] The duration of trastuzumab therapy in these adjuvant trials ranges from 9 to 104 weeks in the published studies. The optimal duration of trastuzumab therapy is unknown, although the majority of data support the use of trastuzumab for a total of 52 weeks. The most commonly used trastuzumab-based adjuvant chemotherapy regimens are listed in Table 145-8.

The addition of MoAB pertuzumab is another important treatment option for patients with *HER2*-positive breast cancer in the neoadjuvant setting.[62] Two clinical trials have reported high rates of pCR at the time of surgery following chemotherapy in combination with trastuzumab and pertuzumab (see Table 145-8 for details regarding the most commonly used regimens). Patients included in these trials were required to have tumors larger than 2 cm or positive lymph nodes. A large clinical trial with pertuzumab in combination with trastuzumab and chemotherapy in the adjuvant setting for *HER2*-positive breast cancer recently showed about a 1% absolute benefit in invasive disease-free survival at 3 years. The FDA added an indication for pertuzumab in combination with trastuzumab in the adjuvant setting for high-risk *HER2*-positive breast cancer based on this trial.[63] The incidence of adverse cardiac effects associated with the addition of trastuzumab appears to increase when an anthracycline is included in the regimen before administration of trastuzumab. The risk of symptomatic heart failure with adjuvant trastuzumab ranges from 0.5% to 4% in highly selected patients who participated in the clinical trials.[61,64] The higher risk of cardiac complications may be acceptable in many patients, given the significant reductions in breast cancer recurrence and death. Sequential administration of trastuzumab after chemotherapy (as in the HERA trial) appears to produce a lower incidence of cardiac toxicity. Also, the use of a non-anthracycline–based

regimen in the BCIRG 006 trial (see Table 145-8) was associated with a low incidence of symptomatic heart failure as compared with other regimens.[61] However, cross-trial comparisons are difficult because the definition of cardiac events in each trial was different. Concurrent administration of trastuzumab with an anthracycline is very controversial because of potentially higher rates of cardiac dysfunction (see the "*HER2*-Targeted Agents of MBC" section) and not generally recommended outside of a clinical trial. Similar to many MoABs, trastuzumab is associated with infusion-related reactions such as fever, chills, and rigors.[65] Postmarketing surveillance data have identified pulmonary toxicity and anaphylaxis as rare but potentially life-threatening reactions associated with trastuzumab. Chemotherapy-related adverse effects, including neutropenia, infection, and diarrhea, are slightly more frequent with the addition of concurrent trastuzumab and pertuzumab therapy, but these toxicities are easily managed and do not preclude the use of trastuzumab in patients with ESBC.

Most of these trials continued trastuzumab administration during adjuvant radiation therapy and endocrine therapy. The administration of trastuzumab during radiation therapy was evaluated in patients that participated in the N9831 clinical trial. Patients who received concurrent radiation therapy with adjuvant trastuzumab did not experience a significant increase in cardiac events or acute radiation-related adverse events with the exception of transient leukopenia.[66] Therefore, if radiation therapy is clinically indicated, trastuzumab is typically administered concomitantly with radiation.

Many questions remain regarding the optimal use of trastuzumab in the adjuvant or neoadjuvant therapy of ESBC. The use of trastuzumab with chemotherapy in the adjuvant or neoadjuvant setting is now considered to be the standard of care for patients with node-positive and high-risk node-negative *HER2*-positive breast cancer.[19] The use of anti-*HER2* therapy in patients with small, *HER2*-positive, node-negative tumors is controversial. Several retrospective analyses of patients with *HER2*-positive tumors smaller than 1 cm who did not receive trastuzumab appear to indicate a poor prognosis, suggesting that these patients may also benefit from trastuzumab-based adjuvant chemotherapy.[67] A single arm, nonrandomized clinical trial demonstrated an excellent 3-year disease-free survival (98.7%) in patients who received weekly paclitaxel and trastuzumab for 12 weeks, followed by trastuzumab every 3 weeks for a total of one year in patients with lymph-node negative, *HER2*-positive, breast cancers smaller than 3 cm.[68] Neratinib, an oral tyrosine kinase inhibitor, is indicated for extended adjuvant therapy after completion of trastuzumab in the adjuvant setting. Its approval was based on a clinical trial in

which patients with *HER2*-positive breast cancer who had completed adjuvant trastuzumab within the previous 2 years were randomized to receive neratinib 240 mg by mouth daily for 1 year versus placebo. Patients in the neratinib group had a small benefit in disease-free survival. The most common side effects of neratinib include diarrhea, which requires aggressive management, as well as nausea, fatigue, and vomiting.[69] Neratinib may be an option for extended adjuvant therapy in some patients at higher risk of recurrence who meet the same eligibility requirements of the phase III trial.

Adjuvant Endocrine Therapy Endocrine therapies that have been studied in the treatment of primary or early-stage breast cancer include tamoxifen, toremifene, oophorectomy, ovarian irradiation, luteinizing hormone–releasing hormone (LHRH) agonists, and AIs. The choice of agent(s) depends on menopausal status and is based on many clinical trials that establish different roles for different therapies.

Tamoxifen is historically considered as the gold standard adjuvant endocrine therapy and has been used in this setting for several decades. Tamoxifen is antiestrogenic in breast cancer cells, but it appears to have estrogenic properties in other tissues and organs.[70,71] More recent studies show that tamoxifen, and other similar drugs, have many estrogenic and antiestrogenic effects that depend on the tissue and the gene in question, and they are more appropriately considered SERMs. Women receiving adjuvant tamoxifen therapy have reduced risk of recurrence and mortality compared with women not receiving adjuvant tamoxifen therapy.[34] In the United States, tamoxifen is generally considered the adjuvant endocrine therapy of choice for premenopausal women, although newer data also support the use of LHRH agonists or oophorectomy in combination with AIs.

If chemotherapy and radiation therapy are not indicated, adjuvant endocrine therapy is generally initiated shortly after surgery or as soon as pathology results are known. When adjuvant chemotherapy is also indicated, endocrine therapy should be administered after chemotherapy is completed because tamoxifen administered concurrently with chemotherapy may antagonize the beneficial effect of chemotherapy.[72] Some clinicians also recommend the initiation of endocrine therapy after completion of radiation therapy, but this recommendation is controversial because few trials have addressed the issue of concurrent versus sequential endocrine therapy and radiation therapy.

Historically, the duration of tamoxifen therapy in the adjuvant setting has been 5 years. However, the results of more recent studies suggest that a longer

duration of tamoxifen may be more effective in some patients. In the ATLAS trial, patients with ER-positive breast cancer who had 10 years of tamoxifen had improved disease-free and overall survival compared to those with 5 years of treatment.[73] In the aTTom trial, patients with ER-positive breast cancer who received 10 years of tamoxifen had improved disease-free survival, but not breast cancer mortality, compared with those who received 5 years of treatment.[74] Previous randomized trials comparing 5 years of tamoxifen treatment with longer than 5 years of tamoxifen treatment have shown opposite results and, in fact, were stopped early because of detrimental outcomes.[75] Patients in the ATLAS and aTTom trials who received 10 years of tamoxifen had increased toxicities, including an increased risk of developing endometrial cancer (ATLAS and aTTom trials) and pulmonary embolism (ATLAS trial only) compared with those receiving tamoxifen for 5 years.[73,74] Based on these data, the administration of tamoxifen for 10 years can be considered in women with a higher risk of breast cancer recurrence.

The most reliable information regarding the adverse effects of tamoxifen comes from the NSABP Breast Cancer Prevention Trial (P-1).[76] This trial randomized 13,388 women 35 years of age or older who were at increased risk for breast cancer to placebo or to 20 mg/day of tamoxifen for 5 years. Although the primary finding of this study is that tamoxifen reduces the risk of invasive breast cancer by 49%, this study also provides comprehensive data on the risk of adverse effects associated with tamoxifen. Information on hot flashes, vaginal discharge, irregular menses, fluid retention, nausea, skin changes, diarrhea, and weight gain or loss was prospectively collected. The self-administered depression scale, a global quality-of-life and a sexual function scale were administered at each follow-up visit. The only symptomatic differences noted between the placebo and tamoxifen group were related to hot flashes and vaginal discharge, both of which occurred more often in the tamoxifen group. No important differences between the two groups were observed in the various self-reported instruments. Tamoxifen did not increase the risk of ischemic heart disease but did reduce the risk of hip radius and spine fractures. Of note, the risks of stroke, pulmonary embolism, and deep vein thrombosis were higher in the tamoxifen group, particularly in women age 50 years or older. The rate of endometrial cancer was increased in the tamoxifen group, and this increased risk occurred primarily in women age 50 years or older. The increased risk of endometrial carcinoma is similar in magnitude to that associated with postmenopausal estrogen replacement therapy and is likely related to an estrogenic effect of tamoxifen on the endometrium. Some experts argue that this

risk is acceptable because endometrial cancer induced by tamoxifen is low stage, low grade, easily treated with surgery and does not pose a life-threatening risk to women. Tamoxifen was also associated with an increased risk of uterine sarcomas (a more aggressive form of endometrial cancer), but this risk appears to be lower than the more common endometrial cancers identified in the study. Routine endometrial biopsy is not currently recommended for women receiving tamoxifen therapy. However, women receiving tamoxifen therapy should be counseled to have regular gynecologic examinations and immediately report unusual vaginal bleeding to their primary clinicians for further evaluation.[77]

In premenopausal women, the use of LHRH agonists (ovarian suppression) or ovarian ablation provides benefit in the adjuvant setting. In the EBCTCG overview analysis published in 2005, the overall benefit of ovarian ablation or suppression was significant compared with no treatment.[36] Many of the trials with the LHRH agonists were not yet included in this analysis due to timing, and most of the clinical trials analyzed included all patients regardless of hormone-receptor status. In an update of this analysis, study inclusion was restricted to patients treated with ovarian suppression with LHRH agonists (not ovarian oblation or oophorectomy) and patients with tumors known to be hormone receptor–positive.[78] The addition of an LHRH agonist reduced the rates of recurrence by 25%, deaths after recurrence by 28%, and all deaths by 27% in women younger than 40 years; no significant reductions in recurrence or death were noted in patients older than 40 years. Also, a similar benefit was observed with goserelin as compared with CMF chemotherapy in hormone-sensitive premenopausal breast cancer patients but not in patients with hormone-receptor–negative tumors.[78] It is not clear whether the benefit of chemotherapy in this population is a result of the antitumor activity of chemotherapy or the endocrine effects of chemotherapy-induced amenorrhea. Consequently, some studies have investigated the benefits of adding ovarian ablation or suppression to chemotherapy either with or without tamoxifen. Results from these studies clearly indicate a benefit from ceasing menses regardless of whether this is caused by chemotherapy or ovarian ablation or suppression.[78] The optimal duration of adjuvant LHRH agonist use is unknown, with trials ranging from 18 months to 5 years of treatment. Two recently published clinical trials evaluated an LHRH agonist combined with tamoxifen or an AI in premenopausal women. In the Tamoxifen and Exemestane Trial (TEXT), premenopausal patients with hormone receptor–positive ESBC were randomized to receive 5 years of tamoxifen or exemestane, both concomitantly with triptorelin for ovarian suppression. In the Suppression of Ovarian Function Trial (SOFT),

premenopausal patients with hormone receptor–positive ESBC were randomized to receive 5 years of tamoxifen alone, tamoxifen with triptorelin, or exemestane with triptorelin. Combined results of the tamoxifen/triptorelin arms and exemestane/triptorelin arms from SOFT and TEXT showed significantly prolonged 5-year disease-free survival with exemestane as compared to tamoxifen.[79] In a subsequent analysis of SOFT, the estimated 5-year disease-free survival rate was similar with tamoxifen alone versus tamoxifen with ovarian suppression.[80] As expected, patients who received tamoxifen with ovarian suppression experienced more menopausal symptoms such as hot flushes, sweating, and vaginal dryness as compared to patients who received tamoxifen alone. Based on these data, the combination of ovarian suppression and an AI is recommended in premenopausal women with hormone receptor–positive ESBC.

In postmenopausal women, AIs are the standard of care in the adjuvant setting. Four different approaches to therapy have been undertaken with these agents: single-agent use for adjuvant endocrine therapy, sequential use after 5 years of adjuvant tamoxifen therapy, sequential use after 2 to 3 years of adjuvant tamoxifen, and 2 years of treatment with an AI followed by 3 years of adjuvant tamoxifen. In an analysis of two trials that compared 5 years of adjuvant tamoxifen to 5 years of an AI, the risk of recurrence at 10 years was significantly reduced in women who received an AI.[35] In a separate analysis of trials investigating a switch to an AI, 12,799 patients who had completed 2 to 3 years of adjuvant tamoxifen therapy were randomized to continue tamoxifen or crossover to an AI for the remainder of 5 years.[35] The results of this analysis show a decreased risk of recurrence at 7 years after randomization in patients who switched to an AI as compared with those who continued with tamoxifen alone. The Breast International Group (BIG) 1-98 trial, which compared letrozole with tamoxifen, also included two separate arms that investigated the benefit of switching from tamoxifen to an AI or vice versa. With 71 months of follow-up, the sequential arms did not improve estimated 5-year disease-free survival as compared with letrozole alone in either comparison.[19]

Most national and international guidelines currently recommend incorporation of an AI into the adjuvant endocrine therapy regimen for all postmenopausal, hormone-sensitive breast cancers.[19] The current NCCN guideline for breast cancer management states that any of the following are acceptable endocrine therapy regimens for postmenopausal women: (a) an AI for at least 5 years; (b) tamoxifen for 2 to 3 years followed by an AI for a total of 5 years of endocrine therapy; or (c) tamoxifen for 5 years followed by an AI for another 5 years (total of 10 years of endocrine therapy).[19] The NCCN panel

believes that the three available AIs (anastrozole, letrozole, and exemestane) have similar antitumor efficacy and toxicity profiles. AIs are generally well tolerated. Adverse effects include bone loss or osteoporosis, hot flashes, myalgias or arthralgias, vaginal dryness or atrophy, mild headaches, and diarrhea. Bone modifying agents, which are often coadministered with AIs in the metastatic setting, may also be beneficial in patients treated with AIs in the adjuvant setting. Other worrisome adverse events include questionable effects on the cardiovascular system (eg, hypercholesterolemia), cognitive functioning, and joint health. Longer follow-up from these trials will continue to provide valuable information to guide treatment decisions and management of adverse effects.

In summary, tamoxifen has been used in the adjuvant setting for nearly 30 years and has a very well-defined safety and efficacy profile in this setting. The roles of other agents such as AIs in postmenopausal women and LHRH agonists in premenopausal women have changed the landscape of adjuvant endocrine therapy, and incorporation of other biologic or targeted therapies may further impact outcomes.

The pharmacologic disposition of tamoxifen in humans is very complex and has only recently been elucidated (see **Fig. 145-4**). Tamoxifen is considered a prodrug. Although the parent compound has significant clinical activity, tamoxifen is metabolized through multiple enzymes, including CYP3A4, CYP2C19, CYP2D6, and others, to metabolites that appear to be more active than the parent compound.[81] The active metabolites 4-hydroxytamoxifen (4OH-TAM) and 4-hydroxy-*N*-desmethyltamoxifen (endoxifen) have nearly a 100-fold higher affinity for the ER as compared with tamoxifen. Endoxifen is present in the serum at a 6- to 12-fold higher concentrations as compared with 4OH-TAM, and is considered to be the most important metabolite for the clinical activity of tamoxifen. The formation of endoxifen depends on the enzymatic activity of CYP2D6, but other pathways may be important (eg, SULT-1-A1, UGT). Polymorphisms in CYP2D6 can increase or decrease the formation of endoxifen and may improve or diminish clinical outcomes, respectively. Although some studies have reported an association between certain CYP2D6 polymorphisms and poorer disease-free or relapse-free survival in patients receiving tamoxifen, other studies report either no relationship or the opposite effect between clinical outcomes and CYP2D6 polymorphisms. Multiple commercially available CYP2D6 assays are available, but widespread testing for patients receiving tamoxifen is not currently recommended based on available evidence.[19,37] Excellent reviews on this subject are available.[81] Potent inhibitors of CYP2D6, such as paroxetine and fluoxetine, may decrease endoxifen levels in patients

receiving tamoxifen.[81] The clinical outcomes related to such drug–drug interactions in an individual patient are largely unknown and may depend on their underlying CYP2D6 genetic status (eg, poor metabolizer, extensive metabolizer). In one population-based cohort study, concomitant use of tamoxifen and paroxetine (but not other antidepressants) was associated with an increased risk of breast cancer death.[82] Although high-quality evidence on strong CYP2D6 inhibitors and breast cancer outcomes in patients receiving tamoxifen is limited, many experts recommend avoidance of known strong inhibitors of CYP2D6, if possible, in patients receiving tamoxifen.

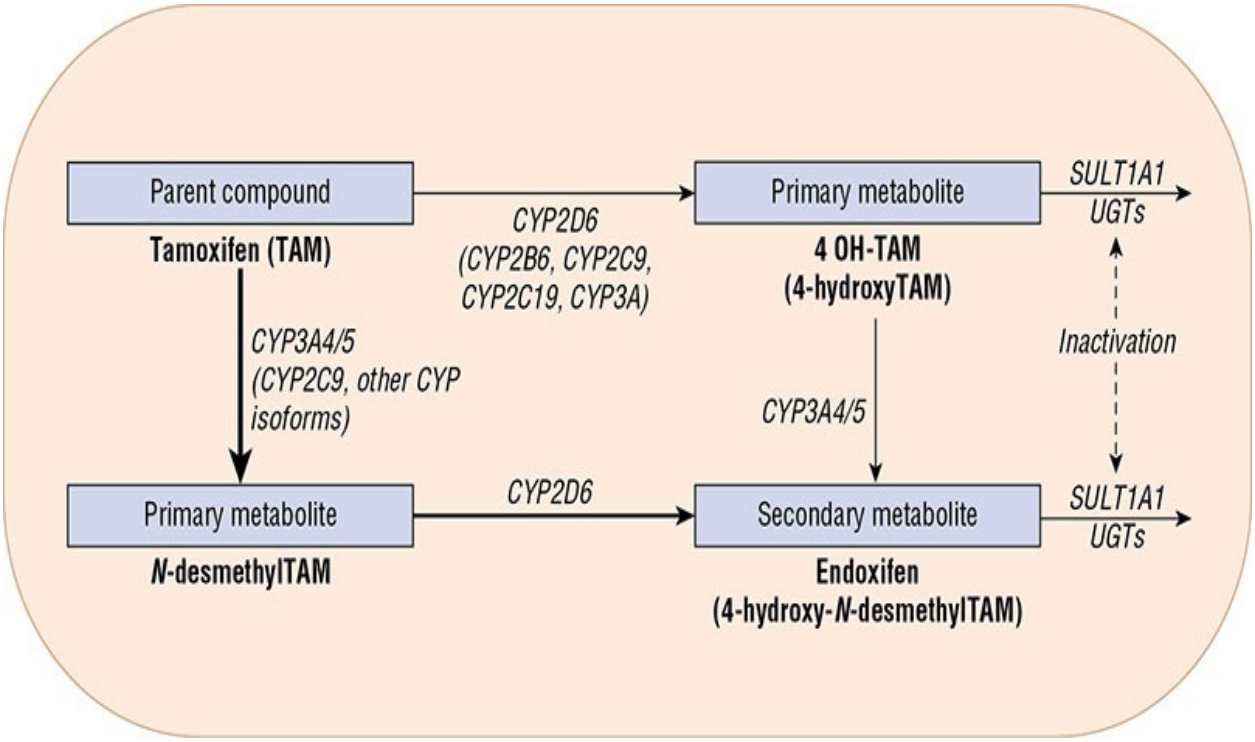


FIGURE 145-4 Tamoxifen metabolism. Widths of the arrows approximate the allocation of parent compound to various metabolites.

Locally Advanced Breast Cancer (Stage III)

6 *Locally advanced breast cancer* generally refers to breast carcinomas with significant primary tumor and nodal disease but in which distant metastases cannot be documented. A wide variety of clinical scenarios can be seen within this group of patients, including neglected tumors that have spread locally to IBCs that are a unique clinical entity. IBC is associated with similar clinical findings compared with neglected, locally advanced breast tumors (eg, erythema representing skin involvement). The distinction between the two diagnoses lies

in the rapidity of onset of symptoms. Many locally advanced breast cancers are diagnosed in patients who have had symptoms for months to years and have neglected to seek medical attention. Although these women have a poor prognosis because of the delay in diagnosis, they are not classified as IBC.

The natural history of locally advanced breast cancer shows that even when local–regional control is accomplished, systemic relapse and death from breast cancer eventually occur in most patients if systemic therapy is not used.[83] That observation led to interest in the use of neoadjuvant or primary chemotherapy in locally advanced breast cancer, which renders inoperable tumors resectable and can increase rates of BCT. Other potential benefits related to early initiation of systemic therapy include the delivery of drugs through an intact vasculature, in vivo assessment of response to therapy, and the opportunity to study the biologic effects of the systemic treatment. For patients with inoperable breast cancer, including IBC, the initial approach to therapy should be chemotherapy with the goal of achieving resectability. The NCCN guideline addressing the management of locally advanced disease recommends primary chemotherapy with an anthracycline- and taxane-containing regimen, either alone or combined with *HER2*-targeted agents as appropriate.[19]

After neoadjuvant chemotherapy, most tumors respond with more than a 50% decrease in tumor size; about 70% of patients experience a reduction in their stage of disease. The chemotherapy regimens used in this setting are similar to those used in the adjuvant setting, and generally include an anthracycline and incorporate a taxane. For patients with *HER2*-positive tumors, the incorporation of trastuzumab and pertuzumab with chemotherapy is appropriate.[62] Less commonly, neoadjuvant endocrine therapy may be an option for patients who have unresectable hormone receptor–positive tumors who are unable to receive chemotherapy (eg, multiple comorbid conditions).[84] Local therapy usually follows chemotherapy, and the extent of surgery is determined by response to chemotherapy, the preferences of the patient, and the cosmetic results likely to be achieved. However, many patients may be able to have BCT if an acceptable response to chemotherapy is accomplished. Adjuvant radiation therapy should be administered to all locally advanced breast cancer patients to minimize local recurrences regardless of the type of surgery used for that individual patient (eg, mastectomy or segmental mastectomy). Inoperable tumors that are unresponsive to systemic chemotherapy may require radiation therapy for local management and may not be eligible for surgical resection after radiation. These patients are not commonly encountered but have a very poor prognosis. For most patients with locally advanced breast cancer, cure is still the primary goal of therapy and

can be achieved in most patients when all treatment modalities are used.

Metastatic Breast Cancer (Stage IV)

7 Treatment of MBC with cytotoxic, endocrine, or targeted therapy often results in regression of disease and improvements in quality of life. More recent advances have also improved overall survival with the addition of some biologic or targeted therapies. The choice of therapy for metastatic disease is based on the presence or absence of certain tumor characteristics. The most important predictive factors are *HER2*, estrogen, and progesterone receptors in the primary or metastatic tumor tissue. Tumors overexpressing *HER2* receptor protein are more likely to benefit from *HER2*-targeted therapy. Tumors expressing high levels of ER, PR, or both are more likely to respond to endocrine therapy. The addition of therapies that target endocrine resistance is also an option in combination with some endocrine therapies. For TNBC, investigators are diligently searching for biologic targets that may predict response to a number of agents (eg, *BRCA1* mutations with the PARP inhibitors). For cases where hormone receptors and *HER2* receptors are over-expressed, an endocrine agent combined with a *HER2*-targeting agent should be considered. Data with biologic or targeted therapies, which appear to target endocrine resistance, have changed the approach in patients with *HER2*-negative, hormone receptor–positive MBC. Patients with symptomatic visceral or central nervous system involvement generally have more rapidly growing cancers that require initial chemotherapy, either alone or with *HER2*-targeted therapy. For tumors that overexpress *HER2*, regimens that combine *HER2*-targeted therapy with chemotherapy are preferred.[85]

Patients who respond to initial therapy often respond to a second- (or even third-) line of therapy. But the response rate is lower and the duration of response is shorter with second- (and third-) line therapy. Little information is known about subsequent response to therapy after targeted/endocrine therapy combinations in this setting. Patients typically are sequentially treated with endocrine therapy (alone or with a targeted agent) until their tumors cease to respond or the patient ceases to benefit from endocrine therapy, at which time cytotoxic chemotherapy can be administered. Subsequent chemotherapy after endocrine/targeted therapy combinations is recommended for patients who can tolerate chemotherapy. Concurrent administration of more than one endocrine therapy or combining chemotherapy plus endocrine therapy is generally avoided in the setting of MBC because of increased toxicity and no substantial

improvement in overall survival. Women with hormone receptor–negative tumors; rapidly progressive or symptomatic lung, liver, or bone marrow involvement (a visceral crisis); or progressive disease while on initial endocrine therapy (with or without a targeted agent) are usually treated with cytotoxic chemotherapy.[19]

All breast cancer patients with bone metastases should be considered for treatment with a bone-modifying agent (eg, pamidronate, zoledronic acid, or denosumab) because these agents decrease the risk of skeletal-related events, such as fractures, spinal cord compression, and pain, and the need for radiation to the bones or surgery.[86] These agents do not act as anticancer agents and should be coadministered with other therapies targeting the cancer cells.

Desired Outcomes

After advancing beyond local–regional disease, MBC is currently incurable. However, some patients live for many years with metastatic disease, making this a chronic disease requiring long-term management strategies that improve or maintain quality of life. Palliation is the desired therapeutic outcome in the treatment of MBC. Optimizing benefits and minimizing toxicity are general therapeutic goals of any therapy administered in this setting. Therefore, sequential single-agent chemotherapy is often chosen over combination chemotherapy regimens, but specific clinical situations may require more rapid responses in which combination chemotherapy may be indicated. Endocrine therapy is generally better tolerated than chemotherapy and may be a more appropriate option for patients with hormone receptor–positive breast cancer. Tumor response to a particular treatment regimen may be measured by changes in laboratory tests, diagnostic imaging, and physical signs and symptoms. The patient usually continues treatment with the regimen, unless the patient clearly cannot tolerate the regimen or the cancer is clearly progressing at a rate that will cause symptoms (or is causing symptoms already). Optimizing quality of life is an important therapeutic end point in the treatment of patients with MBC and eventually requires discontinuation of active cancer therapy and a shift to supportive care with hospice services. Oncology clinicians, in close collaboration with their patients, consider these tradeoffs between quantity and quality of life when making treatment decisions.

Biologic or Targeted Therapy

As mentioned previously, therapies directed at molecular targets through novel mechanisms are often referred to as targeted therapy. Many of the targeted

therapies are also biologic therapies because they are MoABs. For breast cancer, several agents are directed at several targets that are differentially expressed in breast cancer cells and play a critical role in their proliferation and survival.

8 **HER2-Targeted Agents** *HER2* is a very important protein for maintenance of breast cancer cell proliferation and survival. Five anti-*HER2* agents are currently available in the United States, trastuzumab, pertuzumab, ado-trastuzumab emtansine, lapatinib, and neratinib.

As mentioned previously, trastuzumab is a MoAB targeted against the *HER2*-receptor protein. Pertuzumab is also a MoAB but binds to a different epitope on *HER2* and prevents protein dimerization and subsequent cell signaling. Ado-trastuzumab emtansine (also called T-DM1) is a MoAB-drug conjugate with a trastuzumab backbone linked to a potent tubulin inhibitor, emtansine (DM1). Lapatinib is a small-molecule tyrosine kinase inhibitor targeted against the *HER2* and *HER1* (EGFR) protein, leading to dual signaling blockade. Neratinib is also a small molecule tyrosine kinase inhibitor which inhibits all receptors in the HER family (ie, pan-inhibitor) and is currently reserved for use in the extended adjuvant setting.

First-line therapy with a pertuzumab-trastuzumab-taxane combination is the preferred option for *HER2*-overexpressing MBC in patients who have not received pertuzumab in the neoadjuvant or adjuvant setting. Docetaxel administered every 3 weeks in combination with trastuzumab and pertuzumab (both administered every 3 weeks) has the most evidence to support its use in this setting. Substitution of docetaxel with weekly paclitaxel may be used if patients cannot tolerate docetaxel.[87] Other acceptable options include ado-trastuzumab emtansine, trastuzumab plus chemotherapy (eg, vinorelbine, capecitabine, gemcitabine) or other *HER2*-targeted regimens (eg, lapatinib plus capecitabine, trastuzumab plus lapatinib).

Second-line *HER2*-targeted therapy for MBC depends on the specific agent given as first-line therapy. Continuation of *HER2*-targeted therapy beyond progression is warranted when concurrent therapies are changed to renew antitumor efficacy. Subsequent therapy (third-line) for *HER2*-positive MBC is controversial. If a patient has not yet received pertuzumab or T-DM1, then these agents can be administered. If a patient has been treated with pertuzumab and T-DM1, then the use of another *HER2*-targeted regimen may be considered (see **Table 145-9** for details on *HER2*-targeted regimens).[87] Possible options include lapatinib plus capecitabine, a chemotherapy-trastuzumab combination, or trastuzumab plus lapatinib. For patients with tumors that are ER/PR positive,

endocrine therapy, either alone or with trastuzumab or lapatinib, is an option.

TABLE 145-9 Selected Regimens for *HER2*-Positive Metastatic Breast Cancer

Selected Chemotherapy/Biologic Therapy Regimens

Docetaxel + Trastuzumab + Pertuzumab

Docetaxel 75 mg/m² IV day 1
Trastuzumab 8 mg/kg IV day 1 followed 21 days later by 6 mg/kg IV
Pertuzumab 840 mg IV day 1 followed 21 days later by 420 mg IV
Repeat cycle every 21 days

Ado-Trastuzumab Emtansine (T-DM1)

Ado-Trastuzumab Emtansine 3.6 mg/kg IV day 1
Repeat cycle every 21 days

Paclitaxel + Trastuzumab + Pertuzumab

Paclitaxel 80 mg/m² IV days 1, 8, 15
Trastuzumab 8 mg/kg IV day 1 followed 21 days later by 6 mg/kg IV
Pertuzumab 840 mg IV day 1 followed 21 days later by 420 mg IV
Repeat cycle every 21 days

Trastuzumab + chemotherapy

Trastuzumab 8 mg/kg IV day 1 followed 21 days later by 6 mg/kg IV day 1
Repeat cycle every 21 days (for every 21 day chemotherapy)
OR
Trastuzumab 4 mg/kg IV day 1 followed 7 days later by 2 mg/kg IV day 1
Repeat cycle weekly (for weekly chemotherapy)
Chemotherapy may include any one of the following:
Paclitaxel, docetaxel, protein-bound paclitaxel, capecitabine, vinorelbine, gemcitabine

Selected Endocrine Therapy/Biologic Therapy Regimens

Trastuzumab + Lapatinib (± Aromatase inhibitor)
Lapatinib 1,000 mg orally daily continuously
Trastuzumab 8 mg/kg IV day 1 followed 21 days later by 6 mg/kg IV
Repeat cycle every 21 days
(aromatase inhibitor dosed per Table 145-10*)*

Trastuzumab (± Aromatase inhibitor or fulvestrant or tamoxifen)
Trastuzumab 8 mg/kg IV day 1 followed 21 days later by 6 mg/kg IV day 1
Repeat cycle every 21 days
(aromatase inhibitor, fulvestrant and tamoxifen dosed per Table 145-10*)*

Lapatinib + Capecitabine
Lapatinib 1,250 mg orally daily continuously
Capecitabine 1,000 mg/m² twice daily × 14 days
Repeat cycle every 21 days

Lapatinib + Aromatase inhibitor
Lapatinib 1,500 mg orally daily continuously
(aromatase inhibitor dosed daily continuously per Table 145-10*)*

Data from References 1–4, 19, 87, 89, and 92.

Brain metastases are very common in patients with *HER2*-positive MBC, with over 50% of patients experiencing brain metastases over their lifetime. This statistic is somewhat misleading because the brain is an uncommon site of first recurrence in patients with ESBC (1%-3%); this observation appears to be related to the overall success of *HER2*-targeted therapy at extracranial sites and the ability of the blood-brain barrier to prevent *HER2*-targeted MoAB from accessing these tissues, creating a sanctuary site for breast cancer cells. Nonetheless, responses in the brain have been reported with the large, *HER2*-targeted antibodies and are likely due to disruptions in the blood-brain barrier from disease or prior local therapy (surgery or radiation). The small molecule tyrosine kinase inhibitor, lapatinib, may also be effective in this setting, but local therapies tend to offer the best approach in combination with systemic therapy. Local therapy including surgery, whole-brain radiation, stereotactic radiosurgery or some combination of these approaches is considered as initial therapy. Systemic therapy is continued if the other metastatic sites are stable. If extracranial metastases are progressing, a change in the *HER2*-targeted therapy according to guidelines is appropriate. If local therapy fails to control disease in the brain, best supportive or palliative care may be indicated, depending on the status of their extracranial sites of disease and their overall performance status.[88]

Adverse effects of *HER2*-targeted therapies are primarily related to the heart. All therapies in this class, regardless of their exact mechanism of receptor blockade, have some degree of cardiotoxicity. The type of cardiotoxicity differs depending on the agent. Trastuzumab, T-DM1, and likely pertuzumab are associated with myocardial damage leading to heart failure, which is clinically similar to anthracycline-associated cardiomyopathy. The incidence of heart failure is about 5% with single-agent trastuzumab and the risk is unacceptably high when trastuzumab is given concurrently with an anthracycline.[89] Heart failure associated with trastuzumab is somewhat reversible with pharmacologic management, and some patients have continued therapy with trastuzumab after their left ventricular ejection fraction has returned to normal with medical management. Close monitoring for clinical signs and symptoms of heart failure and routine echocardiography are recommended in order to intervene with appropriate cardiac treatments. The risk of cardiotoxicity with pertuzumab administered in combination with trastuzumab appears to be similar to that seen with either agent. The risk of cardiotoxicity with T-DM1 is similar to that seen with trastuzumab.

The risk of cardiac dysfunction with lapatinib has been carefully evaluated

because of concerns regarding the role of *HER2* in normal cardiac functioning. In a review of more than 3,689 patients who received lapatinib in clinical trials, cardiotoxicity occurred in only 1.6% of patients.[90] Although these data are reassuring, it does not rule out the possibility of expanded toxicity when this agent is used in patient populations not included in the clinical trials such as those with underlying cardiac risks. Rare QT prolongation has also been reported with lapatinib, but the clinical significance of this effect is unclear. Concurrent administration of drugs that increase systemic exposure to lapatinib or have similar effects on QT interval may predispose patients to this rare complication and warrant closer monitoring.

Adverse events associated with MoABs are seen with trastuzumab, pertuzumab, and T-DM1 and include infusion-related reactions (primarily fever and chills). These reactions occur in about 40% of patients receiving trastuzumab during the initial infusion and generally go unrecognized by patients. Other infusion-related reactions with trastuzumab include mild nausea, pain at tumor sites, rigors, headaches, dizziness, hypotension, rash, and asthenia, which are much less common.[89] A rare but more serious reaction consisting of severe hypersensitivity or pulmonary reactions has been reported in postmarketing surveillance with trastuzumab. It is important to educate patients regarding the pulmonary reactions because they may occur up to 24 hours after the infusion and can be fatal if not promptly treated. Trastuzumab may slightly increase the risk of infection, diarrhea, and other adverse events when given with chemotherapy, but these increased risks are not clinically significant for an individual patient. The adverse effects of pertuzumab appear to be similar, with increased risk of febrile neutropenia and grade 3 diarrhea when given in combination with docetaxel.[91] While relatively uncommon, some patients require discontinuation due to severe diarrhea while on pertuzumab.

Other adverse events associated with lapatinib include primarily rash and diarrhea. These adverse effects appear to be more significant when combined with chemotherapy (eg, capecitabine, paclitaxel) but are generally manageable with aggressive antidiarrheal therapy or dose reductions. Other rare effects have been reported (QT prolongation, hepatotoxicity, and interstitial lung disease), and patients should be counseled regarding these effects. Drug–drug and drug–food interactions are particularly important with lapatinib because of its metabolism through CYP 3A4 and other pharmacokinetic and pharmacodynamic issues.[92] Many of the adverse effects listed previously may be exacerbated by drug or food interactions, and careful review of patients' medication lists and education regarding these issues is extremely important.

It should be noted that only 15% to 20% of patients with MBC overexpress *HER2*. To date, no benefit has been observed with the administration of trastuzumab to patients with *HER2*-negative tumors (IHC score of 0-1+, or FISH negative) and a very questionable benefit has been observed with administration of trastuzumab to women with tumors that are 2+ for *HER2* by IHC staining alone.

Cyclin-Dependent Kinase (CDK) Inhibitors Cyclin-dependent kinases (CDK), in coordination with their regulatory cyclin partners, form CDK-cyclin heterodimer complexes that control cell cycling. CDK-4 and -6 are critical components of this process. In some breast cancer cell lines, these complexes are responsible for phosphorylating the retinoblastoma tumor suppressor gene product (RB), thus inactivating the suppression of cell division and allowing unregulated progression through the cell cycle. Three CDK-inhibitors have an FDA-approved indication for MBC (abemaciclib, palbociclib, and ribociclib). These agents selectively inhibit CDK-4 and -6, effectively preventing RB phosphorylation and leaving it in an active state that is able to appropriately regulate cell division. To date, CDK inhibitors have improved progression-free survival in combination with AIs (as first-line therapy), fulvestrant (as first- and second-line therapy), and tamoxifen (as first-line therapy) (see **Table 145-10**). A CDK inhibitor-containing regimen should be considered in newly diagnosed patients with *HER2*-negative, hormone receptor–positive MBC. The addition of the CDK inhibitor increases the toxicity of the regimen. Neutropenia (all grades) is the dose-limiting toxicity of palbociclib and ribociclib and is also fairly common with abemaciclib. However, very low rates of neutropenic fever and other infections have been reported. The dose-limiting adverse effect with abemaciclib is diarrhea and occurs in nearly all patients. Diarrhea in these trials is typically managed with dose reductions and medical interventions, allowing most patients to continue therapy. Ribociclib also has a warning in its labeling for QT prolongation and requires electrocardiogram monitoring for the first two cycles.[93]

TABLE 145-10 Therapies Used for Hormone Receptor–Positive Metastatic Breast Cancer

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Comments
Aromatase Inhibitors: Nonsteroidal					
Anastrozole	Arimidex, generic	1 mg orally daily			
Letrozole	Femara, generic	2.5 mg orally daily		Caution in severe liver impairment[a]	
Aromatase Inhibitor: Steroidal					
Exemestane	Aromasin, generic	25 mg orally daily			Take after meals
Antiestrogens: SERMs					
Tamoxifen	Nolvadex, generic	20 mg orally daily		See text regarding *CYP2D6*	
Toremifene	Fareston	60 mg orally daily			
Antiestrogen: SERD					
Fulvestrant	Faslodex	500 mg IM every 28 days (after loading days 1, 15, 29)	250-500 mg (see text for details)	Moderate liver impairment[a] administer 250 mg IM every 28 days (after loading days 1, 15, 29)	
LHRH Agonists					
Goserelin	Zoladex	3.6 mg SC every 28 days		Premenopausal women only	
Leuprolide	Lupron (IM), generic	3.75 mg IM every 28 days	Other formulations and doses are not used for breast cancer	Premenopausal women only	Not FDA approved for breast cancer; other formulations are administered differently
Triptorelin	Trelstar	3.75 mg IM every 28 days		Premenopausal women only	Not FDA-approved for breast cancer
Progestins					
Megestrol acetate	Megace, generic	40 mg orally 4 times a day	80 mg twice daily also appropriate		Absorption may be increased when taken with food
Medroxyprogesterone	DepoProvera, generic	400 mg IM every week	400-1,000 mg IM every week	May need to decrease dose in severe liver impairment[a]	
Androgens					
Fluoxymesterone	Androxy, generic	10 mg orally twice a day	10-20/day in divided doses	Avoid in severe renal or liver impairment[a]	
Estrogens					
Ethinyl estradiol	Multiple generics	1 mg orally 3 times a day	Lower doses not effective	Avoid in jaundice or "marked" liver disease	Take with food
Conjugated estrogens	Premarin	2.5 mg orally 3 times a day	Lower doses not effective	Avoid in jaundice or "marked" liver disease	Take with food
Biologic/Targeted Therapies					
Abemaciclib (+/– Letrozole or Fulvestrant)	Verzenio	Single agent 200mg orally twice a day continuously OR Combination 150 mg orally twice a day continuously	50-200 mg twice a day	Adjust dose for diarrhea, myelosuppression, and/or severe hepatic impairment. Monitor for hepatotoxicity and thromboembolism. Avoid concomitant strong inhibitors of *CYP3A4* and moderate/strong inducers of *CYP3A4*	Do not split tablets
Palbociclib (+ Letrozole or Fulvestrant)	Ibrance	125 mg orally daily × 21 days, followed by 7 days off, repeated every 28 days	75-125 mg daily	Adjust dose for myelosuppression and severe hepatic impairment. Monitor for nausea, diarrhea, and hepatotoxicity. Avoid concomitant strong inhibitors of *CYP3A4* and moderate/strong inducers of *CYP3A4*	Do not open capsules
Ribociclib (+ Letrozole or Fulvestrant)	Kisqali	600 mg orally daily × 21 days, followed by 7 days off, repeated every 28 days	200-600 mg daily	Adjust dose for myelosuppression and/or severe hepatic or renal impairment. Monitor for hepatotoxicity and QT prolongation. Avoid concomitant strong inhibitors of *CYP3A4* and moderate/strong inducers of *CYP3A4*	Do not split tablets

Everolimus (+ Exemestane or Fulvestrant or Tamoxifen)	Afinitor	10 mg orally daily	2.5-10 mg daily	Adjust dose in mild, moderate and severe liver impairment; also monitor for myelosuppression, hyperglycemia, dyslipidemia, renal dysfunction. May need to adjust dose with concomitant CYP3A4 inhibitors/inducers	Do not split tablets

[a]Severe liver impairment: Child-Pugh class C; moderate liver impairment: Child-Pugh class B; minor liver impairment: Child-Pugh class A.

IM, intramuscular; LHRH, luteinizing hormone-releasing hormone; SC, subcutaneous; SERD, selective estrogen receptor downregulator; SERM, selective estrogen receptor modulator.

Preclinical data combining CDK inhibitors with other therapies (eg, chemotherapy, anti-*HER2* therapy) are promising but remain investigational until further information on optimal timing and sequencing with specific agents is available.

Mammalian Target of Rapamycin (mTOR) Inhibitors The PI3K/protein kinase-B (also called Akt) pathway includes many different proteins, of which one of the most important is the mTOR tyrosine kinase. mTOR is an important mediator for cell proliferation and regulation of apoptosis, angiogenesis, and cellular metabolism. Everolimus, an oral mTOR inhibitor, improved progression-free survival when given in combination with either exemestane, fulvestrant, or tamoxifen and should be considered in patients with hormone receptor–positive MBC whose disease has progressed within a year of or while receiving endocrine therapy (see Table 145-10). The choice of endocrine therapy depends on what endocrine therapy the patient received previously.

The most common serious (grade 3 or 4) adverse events reported in the combination everolimus/exemestane trial were stomatitis, anemia, dyspnea, and pneumonitis. Subsequent trials reported a high rate of stomatitis (51.3%) with no improvement in overall survival. Other PI3K inhibitors are also being investigated with promising results (eg, alpelisib, buparlisib, taselisib).[94]

Poly (ADP-Ribose) Polymerase (PARP) Inhibitors Poly (ADP-ribose) polymerase (PARP) is a family of enzymes partially responsible for repairing single-strand DNA breaks. Patients who harbor a germline mutation in *BRCA1* or *BRCA2* have impaired ability to repair double-strand DNA breaks. PARP inhibitors may be effective in this setting, based on preclinical data showing that cells without functional *BRCA1* or *BRCA2* are sensitive to PARP inhibition. Olaparib and talazoparib are two PARP inhibitors that have demonstrated activity in this setting. Olaparib and talazoparib, given as single agents, improved progression-free survival compared with single-agent chemotherapy in

patients with *HER2*-negative MBC who had a germline mutation in *BRCA1* or *BRCA2*. Rates of severe adverse events (grade 3 or higher) are less common with the PARP inhibitor arms compared with chemotherapy. Commonly reported adverse effects of PARP inhibitors include anemia, nausea, vomiting, diarrhea, and fatigue.[95,96]

Endocrine Therapy

Endocrine therapy should be considered in combination with a targeted agent (as noted previously) when feasible. The choice of endocrine therapy is based on the menopausal status of the patient, prior therapies and previous response, duration of response, or disease-free interval. Combinations of targeted therapies with endocrine agents may not be appropriate for all patients, and individual decisions should consider other comorbidities, the complexity of the regimen, expected adverse events, and drug or disease interactions.

9 The pharmacologic goal of endocrine therapy for breast cancer is to either (a) decrease circulating levels of estrogen or (b) prevent the effects of estrogen on breast cancer cells by blocking the hormone receptors or downregulating the presence of these receptors. The first goal depends on the menopausal status of the patient while the second goal is independent of menopausal status. Many endocrine therapies are available to target either pathway, and combinations of drugs with differing mechanisms of action have also been investigated. Unfortunately, most combinations of endocrine therapy have not demonstrated significant benefits over single-agent hormone therapy but have increased toxicity. Therefore, combinations of endocrine agents for MBC are generally not recommended outside the context of a clinical trial.

With the approval of lapatinib, everolimus, and the CDK inhibitors for MBC, we now have combination regimens that are quite effective, but they often increase the risk of adverse events that require supportive management strategies. These combinations address *de novo* or acquired resistance with endocrine therapy and have demonstrated efficacy over single agents in specific patient populations. Optimal subsequent therapy after progression on targeted-endocrine treatment is largely unknown and the subject of many ongoing clinical trials.

Historically, sequential use of single endocrine agents was common in the metastatic setting when a patient progressed on one agent after experiencing an initial response. Responsive patients were often treated with a sequence of endocrine agents, usually over several years, before chemotherapy was considered. In combination with targeted therapies, such sequential approaches

are currently untested but are rational given the indolent nature of these hormone-sensitive metastases.

Outside of regimens that include novel targeted agents, there is little evidence that the survival benefit from one endocrine therapy is clearly superior to that achieved with other therapies in women with MBC. Prior to the availability of targeted agents, randomized controlled trials comparing different endocrine therapies (eg, antiestrogens, AIs, progestins, estrogens, androgens) and surgical procedures (eg, oophorectomy, adrenalectomy, and hypophysectomy) showed similar overall survival in patients with MBC. Therefore, the choice of a particular endocrine therapy was based primarily on the mechanism of action, toxicity, and patient preference (see Tables 145-10 and 145-11). Based on these criteria, AIs, tamoxifen or toremifene, and fulvestrant were the preferred initial agents in MBC except when the patient's cancer recurs during or within one year of adjuvant therapy with the same class of agent. In these cases, therapies from a different pharmacologic class were indicated. For postmenopausal women, the AIs are generally used first followed by other endocrine therapies upon progression.

TABLE 145-11 Drug Monitoring for Endocrine Therapies

Drug	Adverse Drug Reaction	Monitoring Parameters	Comments
Aromatase inhibitors	Hot flashes Arthralgias or myalgias Osteoporosis Hypercholesterolemia	Patient assessment BMD Lipid panel	Interval of monitoring controversial
Antiestrogens: SERMs[a]	Hot flashes Endometrial hyperplasia or cancer Venous thromboembolism Osteopenia (premenopausal women only)	Patient assessment Annual gynecologic assessment Consider BMD for premenopausal women	Routine transvaginal ultrasonography and endometrial biopsies are not recommended in the absence of symptoms
Antiestrogens: SERDs[a]	Hot flashes Injection-site reactions	Patient assessment	
LHRH agonists	Hot flashes Injection-site reactions Osteoporosis	Patient assessment BMD	
Progestins[a]	Weight gain Vaginal bleeding or spotting Nausea Venous thromboembolism	Patient assessment Periodic weights	
Androgens[a]	Hirsutism Acne Masculinization Increased hemoglobin Nausea Venous thromboembolism	Patient assessment Complete blood counts	
Estrogens[a]	Nausea or vomiting Venous and arterial thromboembolism Fluid retention Breast tenderness Endometrial hyperplasia or cancer	Patient assessment Annual gynecologic assessment	Routine transvaginal ultrasonography and endometrial biopsies are not recommended in the absence of symptoms

[a]Liver function tests obtained periodically to screen for changes in hepatic elimination, hepatotoxicity, and the presence of hepatic metastases.

BMD, bone mineral density; LHRH, luteinizing hormone-releasing hormone; SERD, selective estrogen receptor downregulator; SERM, selective estrogen receptor modulator.

In premenopausal women, ovarian suppression or ablation (eg, LHRH agonists or oophorectomy, respectively) is generally considered first, followed by tamoxifen or toremifene. Although AIs can be combined with ovarian suppression or ablation in premenopausal women, the use of AIs in a woman with functioning ovaries is not appropriate in any setting of breast cancer treatment. Fulvestrant is generally considered second-line because of its route of administration (intramuscular injections) and the data supporting its use. With the advent of many clinical trials of fulvestrant in combination with targeted therapies in the first- and second-line settings, its use has increased and it is

being used earlier in the course of the disease. Other endocrine therapies are generally reserved for subsequent lines of therapy because they are associated with more significant adverse effects that may negatively impact quality of life and have little to no data in combination with targeted agents. However, these agents are better tolerated than many chemotherapies and may be clinically useful in certain situations (eg, elderly patients with comorbidities).

In postmenopausal women, the main source of estrogen is derived from the peripheral conversion of androstenedione produced by the adrenal gland into estrone and estradiol. This conversion requires the enzyme aromatase. Aromatase also catalyzes the conversion of androgens to estrogens in the ovary in premenopausal women and in extraglandular tissues (eg, the breast and breast cancer cells) in postmenopausal women. Therefore, AIs effectively reduce the levels of estrogens in circulation and in the target organ. Third-generation AIs include anastrozole, letrozole, and exemestane. A major advantage of these specific compounds is their toxicity profile, which consists mainly of bone loss and osteoporosis, mild nausea, hot flashes, arthralgias/myalgias, and mild fatigue. Anastrozole and letrozole are nonsteroidal triazole compounds that reversibly and competitively inhibit aromatase; they have no intrinsic hormonal activity. Exemestane is a steroidal compound that binds irreversibly to aromatase, forming a covalent bond. Although this mechanism may have theoretical advantages to the reversible binding of the nonsteroidal agents, there is no clinical evidence that this drug is superior to other agents in this class. Exemestane does possess some androgenic properties at doses that are much higher than those used clinically and may have unique toxicities.[97] AIs should only be used in postmenopausal women. Pre- or perimenopausal women, whose ovaries are functioning, are not appropriate candidates for these therapies, but the use of AIs in addition to ovarian ablation or suppression (eg, oophorectomy or LHRH agonists) is appropriate and acceptable.

Antiestrogens bind to ERs, which inhibit receptor-mediated gene transcription and therefore block the effect of estrogen on the end target. This class of agents is subdivided into two pharmacologic categories, SERMs, and pure antiestrogens. SERMs include tamoxifen and toremifene (and raloxifene for breast cancer–risk reduction in high-risk women) and demonstrate tissue-specific activity, both estrogenic and antiestrogenic, as described previously. The agonist activity is thought to be responsible for many of the adverse reactions seen with these agents, including the increased risk of endometrial cancer, and has led to the development of pure ER antagonists that lack estrogen agonist activity. Pure antiestrogens are also referred to as selective estrogen receptor downregulators

(SERDs). These molecules bind to ER, inhibit estrogen binding, and degrade the drug–ER complex, thus decreasing the amount of ER expressed. Fulvestrant is currently the only pure antiestrogen commercially available in the United States.

Tamoxifen is generally considered to be the antiestrogen of choice in premenopausal women with MBC who have hormone receptor–positive tumors. Figure 145-4 shows important role of CYP2D6 in the metabolism of tamoxifen (as described earlier). Results from clinical studies of CYP2D6 genotyping in patients receiving tamoxifen have been mixed and genotyping is not routinely recommended (see section "Adjuvant Endocrine Therapy"). The toxicities of tamoxifen are described in the "Adjuvant Endocrine Therapy" section. The only additional toxicity that may be observed in the setting of MBC (specifically bone metastases) is a tumor flare or hypercalcemia, which occurs in about 5% of patients after the initiation of any SERM therapy and is not an indication to discontinue the drug. It is generally accepted that this reaction is associated with response to endocrine therapy, but patients who do not experience such a reaction may still respond. This reaction is seen less frequently with the concurrent use of bisphosphonates as a result of their inhibition of osteoclasts, subsequently preventing the release of calcium from the bone.

Toremifene is another commercially available SERM for the treatment of breast cancer. It exhibits similar efficacy and tolerability compared with tamoxifen in the metastatic setting. Cross-resistance to toremifene has been demonstrated in patients with tamoxifen-refractory disease. Toremifene is an alternative to tamoxifen in postmenopausal patients with positive or unknown hormone-receptor status with MBC, but it is unlikely to be beneficial after tamoxifen exposure. Details regarding its metabolism are available and indicate it may be an alternative to tamoxifen in settings where there are concerns regarding drug interactions. However, compared to the amount of data available with tamoxifen, toremifene use in the United States is minimal.[98] Raloxifene, another SERM, was originally approved for the prevention of osteoporosis in postmenopausal women. Available data with raloxifene as a treatment for breast cancer show very low response rates and no significant clinical benefit. Consequently, the use of this agent for breast cancer treatment should be discouraged. The clinical benefits of raloxifene for breast cancer risk reduction in high-risk postmenopausal women have been discussed (see "Prevention and Early Detection" section).

Fulvestrant is approved for the second-line therapy of postmenopausal patients with hormone receptor–positive tumors. Fulvestrant should produce similar outcomes in premenopausal women, but limited data exist to confirm the

safety or efficacy in premenopausal women with active ovarian function. When combined with ovarian suppression or ablation, fulvestrant is an appropriate therapy in young women. It is unique, in that it is given as an intramuscular injection. The dosing of fulvestrant is controversial. The dose used in early studies is now considered to be insufficient. The use of an aggressive loading dose schedule has improved efficacy and led to further testing in combination with targeted therapies as mentioned previously.

The combination of anastrozole and fulvestrant has been investigated in three randomized phase III trials with conflicting results. Although the combination does appear to be well tolerated, the overall benefits (if any) appear to be modest, and sequential single agents are most commonly administered in the palliative setting of metastatic disease.[19] Adverse events related to fulvestrant include injection-site reactions, hot flashes, asthenia, and headaches.

Another goal of endocrine therapy in premenopausal women is to reduce estrogen production with surgery, radiation, or medication. Ovarian ablation or suppression alone is still commonly used in the United States and is considered by many specialists to be the endocrine therapy of choice in premenopausal women. The management of patients as postmenopausal after successful ablation/suppression is standard of care according to most national and international guidelines.[19] The mortality rate with surgical oophorectomy is low, usually less than 3% in appropriately selected patients. While radiotherapeutic ablation of the ovaries is effective, this approach is typically not used in the United States because of its morbidity. Medical ovarian suppression with LHRH analogs is increasingly used instead of oophorectomy in premenopausal women. Because the effects of the LHRH analogs are reversible, the administration of these agents may also determine how a patient will tolerate estrogen deprivation. If the patient tolerates this therapy, then an oophorectomy may be recommended as a permanent therapeutic intervention.

Medical ovarian suppression or ablation with LHRH analogs alone induces responses in about one-third of unselected premenopausal patients with MBC. The activity of LHRH analogs is related to its ability to downregulate LHRH receptors in the pituitary and decrease LH levels, which subsequently decreases circulating estrogen to suppressed/ablated levels. Therefore, the effect of LHRH analogs on circulating estrogen levels in premenopausal breast cancer is similar to an oophorectomy. The three agents available in the United States are leuprolide, goserelin, and triptorelin, but only goserelin is FDA-approved for the treatment of MBC. These agents are administered as an injection every 4 weeks (all products have extended formulations, lasting 3 months to 1 year, but they are

not recommended for the initial treatment of breast cancer) and are associated with minimal side effects, including amenorrhea, bone loss or osteoporosis, hot flashes, and occasional nausea (see Table 145-11). LHRH analogs may also produce a flare response because of an initial surge in LH and estrogen production lasting 2 to 4 weeks. This flare response is similar to that seen with tamoxifen, and patients with high-volume, bulky disease should be monitored for increasing pain and hypercalcemia during the initiation period. LHRH analogs combined with tamoxifen or an AI have been investigated with varying results. In order to safely administer AIs to premenopausal women, ovarian function must be suppressed or ablated. The question remains as to whether the combination of an LHRH analog and an AI is superior to tamoxifen alone. Combining an LHRH analog with tamoxifen is also controversial, but it can be considered in young premenopausal women with MBC based on some data in ESBC.[19]

Other endocrine therapies in MBC include the progestins (such as megestrol acetate and medroxyprogesterone acetate), high-dose estrogens (such as ethinyl estradiol) and high-dose androgens (fluoxymesterone). These agents are usually less well tolerated than first-line options discussed previously. The most common side effect of megestrol acetate is weight gain, occurring in 20% to 50% of patients. Other side effects associated with progestins include vaginal bleeding in 5% to 10% of patients, either while taking the progestational agent or when it is discontinued, and less than a 10% incidence of hot flashes. Thromboembolic complications are also associated with these agents.[99] About one-third of patients placed on high-dose estrogens will discontinue them because of side effects, the most important of which are thromboembolic events, vomiting, and fluid retention. Less common side effects include areolar hyperpigmentation, breast tenderness and engorgement, vaginal discharge, incontinence, hot flashes, and phlebitis. Androgens cause masculinizing effects, including hirsutism and acne, in more than 50% of patients. The mechanism by which these agents exert a therapeutic effect in breast cancer is unknown. However, these agents may inhibit aromatase, among other pharmacologic effects that antagonize estrogen.

Chemotherapy

10 Most patients with MBC have tumors that lack *HER2*-overexpression and represent one of the most prevalent cancer problems facing the developing world. Investigators continue to look for acceptable targets and innovative approaches to treating this group of cancers. Hormone receptor–positive tumors

that fail to respond to initial endocrine/targeted therapy regimens or become refractory to endocrine therapy require chemotherapy. Patients with TNBC require chemotherapy as initial therapy of metastases. TNBC represents an uncommon subtype (10%-15%) and has a relatively poor prognosis. Therefore, cytotoxic chemotherapy is eventually required in most patients with MBC.[100]

Combination chemotherapy results in an objective response in about 50% to 60% of unselected, chemotherapy-naive patients. The clinical use of biomarkers and genetic panels to assist treatment decisions is relatively new. In the absence of predictive biomarkers, chemotherapy is chosen based on overall efficacy, the risk of toxicity, performance status and presence of comorbidities in the patient, aggressiveness of disease (eg, indolent vs visceral crisis), and patient preferences related to schedules, dosing route (eg, oral vs intravenous), and frequency (eg, weekly vs every 3 weeks) of the chemotherapy.

While response rates are high with combination chemotherapy, sequential use of single-agent therapies is also an effective strategy that may be preferred due to decreased rates of adverse events. In the palliative setting, when efficacy is similar, the least toxic approach is preferred. In clinical practice, patients who require a rapid response (eg, those with symptomatic bulky metastases or a visceral crisis) should receive combination chemotherapy despite the added toxicity. This decision is complex and should be made on an individual patient basis.

Most patients experience partial responses to chemotherapy, but complete disappearance of disease occurs in fewer than 10% of patients. The median duration of response is highly variable, ranging from 5 to 18 months. Some patients with small volume metastatic disease will have an excellent response to an initial course of chemotherapy and may live 5 to 10 years or longer without evidence of disease. The median overall survival for patients after commonly used chemotherapy combinations ranges between 14 and 33 months. The median time to response ranges from 2 to 3 months in most studies, but this period depends on the site of metastatic disease and can range from 3 weeks (skin and lymph node metastases) to 18 weeks (bone metastases). After a chemotherapy regimen has been initiated, it is usually continued until progressive disease or intolerable adverse effects occur. **Table 145-12** lists some selected chemotherapy agents used in the metastatic setting.[101]

TABLE 145-12 Selected Chemotherapy Regimens for *HER2*-Negative Metastatic Breast Cancer

Single-Agent Chemotherapy

Paclitaxel
Paclitaxel 175 mg/m² IV over 3 hours
Repeat cycles every 21 days
or
Paclitaxel 80 mg/m²/week IV over 1 hour
Repeat dose every 7 days

Docetaxel
Docetaxel 60-100 mg/m² IV over 1 hour
Repeat cycles every 21 days

Protein-Bound Paclitaxel
Protein-bound Paclitaxel 260 mg/m² IV over 30 minutes
Repeat cycles every 21 days

or
Protein-bound paclitaxel 100-125 mg/m² IV over 30 minutes on days 1, 8, and 15
Repeat cycle every 28 days

Capecitabine
Capecitabine 1,000-1,250 mg/m² orally twice daily for 14 days
Repeat cycles every 21 days

Olaparib
Olaparib tablet 300 mg orally twice daily
Repeat cycles every 28 days

Vinorelbine
Vinorelbine 25 mg/m²/week IV
Repeat cycles every 7 days (adjust dose based on absolute neutrophil count; see product information)

Gemcitabine
Gemcitabine 800-1,200 mg/m²/week IV, days 1, 8, and 15
Repeat cycles every 28 days (may need to hold day 15 dose based on blood counts)

Ixabepilone
Ixabepilone 40 mg/m² IV over 3 hours
Repeat cycles every 21 days

Eribulin
Eribulin 1.4 mg/m²/dose IV over 2-5 minutes on days 1 and 8
Repeat dose every 21 days

Liposomal Doxorubicin
Liposomal doxorubicin 50 mg/m² IV over variable duration
Repeat cycles every 28 days

Talazoparib
Talazoparib tablet 1 mg orally daily
Repeat cycles every 28 days

Combination Chemotherapy Regimens

Gemcitabine + Carboplatin
Gemcitabine 1,000 mg/m² IV, days 1 & 8
Carboplatin AUC 2 IV, days 1 & 8
Repeat cycles every 21 days

Docetaxel + Capecitabine
Docetaxel 75 mg/m² IV over 1 hour, day 1
Capecitabine 950 mg/m² orally twice daily for 14 days
Repeat cycles every 21 days

Paclitaxel + Gemcitabine
Paclitaxel 175 mg/m² IV over 3 hours, day 1
Gemcitabine 1,250 mg/m² IV days 1 and 8
Repeat cycles every 21 days

Paclitaxel + Bevacizumab
Paclitaxel 90 mg/m² IV over 1 hour, days 1, 8, and 15
Bevacizumab 10 mg/kg IV over 30-90 minutes, days 1 and 15
Repeat cycles every 28 days

Adapted from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Breast Cancer V.3.2019. National Comprehensive Cancer Network, Inc. Accessed September 20, 2019.

Factors associated with an increased likelihood of response to chemotherapy include good performance status, a limited number (one to two) of disease sites (or involved organ systems), and prolonged previous response to chemotherapy or hormonal therapy (ie, long disease-free interval). Patients who develop progressive disease during chemotherapy have a lower likelihood of response to subsequent chemotherapy. However, this is not necessarily true for patients who are given chemotherapy after a treatment-free interval of substantial duration (eg, more than 1 year). Treatments may be repeated if some time has passed between therapies, but this is rarely done because of the large number of agents now available to treat breast cancer. Hormone receptor–positive tumors that are resistant to endocrine therapy are as likely to respond to chemotherapy as patients who receive upfront chemotherapy. Age, menopausal status, and receptor status do not appear to be directly associated with response to chemotherapy. However, the association between hormone-receptor status and response to chemotherapy (eg, ER status and anthracyclines) is unclear. Most clinical decisions regarding chemotherapy are not currently influenced by hormone-receptor status. Molecular tumor subtypes (eg, luminal A, luminal B, etc.) have not been helpful in selecting an optimal chemotherapy regimen. TNBC is an aggressive phenotype associated with a poor prognosis. TNBCs have variable responses to chemotherapy, a high risk of brain metastases, and shorter survival after a first metastatic event as compared with other subtypes. TNBC is strongly associated with germline mutations in the *BRCA-1* gene, which can increase sensitivity to platinum agents due to impaired DNA repair mechanisms. Therefore, many clinicians will add a platinum agent to the chemotherapy regimen in some patients with a *BRCA-1* germline mutation.[100] As mentioned previously, these patients are also candidates for therapy with the PARP inhibitors and prior exposure to platinum agents may limit response to PARP inhibitors.

Many chemotherapeutic agents have demonstrated activity in the treatment of breast cancer, including doxorubicin (conventional and liposomal), epirubicin, paclitaxel (conventional and protein-bound), docetaxel, capecitabine, fluorouracil, cyclophosphamide, methotrexate, vinblastine, vinorelbine, gemcitabine, ixabepilone, eribulin, carboplatin, cisplatin, mitoxantrone, mitomycin C, thiotepa, and melphalan. The most active classes of chemotherapy in MBC are the anthracyclines and the taxanes, producing response rates as high as 50% to 60% in patients who have not received prior chemotherapy for metastatic disease.[101] Doxorubicin (conventional and liposomal) and epirubicin have significant antitumor activity in the metastatic setting and are generally

considered therapeutically equivalent when dosed appropriately. Administration of these agents is limited by their cumulative cardiotoxicity. Paclitaxel, docetaxel, and protein-bound paclitaxel are also FDA-approved for the treatment of MBC and are generally considered therapeutically equivalent, but lack complete cross-resistance. Taxane administration is limited by cumulative peripheral neuropathy. Most patients will likely receive each of these agents at some point in the course of their MBC.

Many patients with MBC have been exposed to adjuvant chemotherapy consisting of an anthracycline and a taxane. If metastases are found within 6 to 12 months of completing treatment with these agents, many clinicians will choose a treatment from a different chemotherapy class. If it has been a long time since their adjuvant therapy, then retreating with the same agents may be considered. However, given the cardiotoxicity associated with the anthracyclines, the use of these agents in the metastatic setting has been generally avoided until the availability of liposomal anthracyclines. Pegylated liposomal doxorubicin is associated with less cardiotoxicity and similar efficacy compared with conventional doxorubicin and is a viable option for women who recur more than 1 year after their adjuvant anthracycline-containing chemotherapy regimen.[101]

Weekly administration of paclitaxel and protein-bound paclitaxel results in higher response rates, time-to-progression, and survival and a more favorable side effect profile compared with administration every 3 weeks.[101] The most useful weekly dose of conventional paclitaxel in the metastatic setting is 80 mg/m^2/week with no breaks in therapy. With this dose schedule, the toxicity profile of paclitaxel changes with less myelosuppression and delayed onset of peripheral neuropathy but slightly more fluid retention and skin and nail changes. Although the risk of hypersensitivity reactions is also slightly less at these lower doses (requiring fewer premedications), it remains at about 3% despite the incorporation of all available preventive measures. The most appropriate weekly dose of protein-bound paclitaxel in the metastatic setting is not clear. Doses of 100 to 150 mg/m^2/week administered on days 1, 8, and 15 of a 28-day cycle have been investigated, demonstrating some evidence of a dose–response relationship. In the metastatic palliative setting, a lower dose is generally given to minimize toxicity while not significantly compromising efficacy. Docetaxel is most appropriately dosed on an every 3-week schedule for MBC. Weekly dosing did not produce improvements in disease response and was associated with significantly more toxicities than the every 3-week dosing strategy.

After patients have been treated with an anthracycline and a taxane, single-agent capecitabine, vinorelbine, or gemcitabine have resulted in response rates of 20% to 25%.[101] Of these agents, only capecitabine is FDA approved as a single agent for MBC. Gemcitabine is only FDA-approved in combination with paclitaxel for MBC. However, all of these are included in most national and international guidelines as appropriate therapy for MBC. Decisions regarding which agent to choose are based on patient characteristics, expected toxicities, and previous exposure to chemotherapy.

Other antimicrotubule agents have also been approved for the management of MBC, demonstrating significant benefits in patients who have had prior exposure to multiple other chemotherapy agents. Ixabepilone is an epothilone compound with a similar but distinct mechanism of action from the taxanes, binding to β-microtubulin in a unique manner but ultimately leading to microtubule stabilization and cell death in a similar manner compared with the taxanes. It is approved for use in combination with capecitabine and as a single agent for the management of MBC. Eribulin is another antimicrotubule agent with a unique mechanism of action. The first synthetic analogue of halochondrin B, eribulin effectively inhibits polymerization of tubulin into microtubules and suppresses the microtubule growth phase similar to the vinca alkaloids. The mechanism of action for eribulin differs from the vinca alkaloids, in that eribulin does not appear to have any effect on the microtubule shortening phase. These subtle differences may be important for eribulin's efficacy in patients who have been exposed to multiple therapies, including other antimicrotubule agents. It is approved for use as a single agent for the management of patients with MBC who have received at least two prior chemotherapies for their metastatic disease.[101] Both of these agents are associated with similar toxicities compared with the taxanes and vinca alkaloids, respectively (eg, myelosuppression, neuropathy, myalgias or arthralgias, alopecia, and skin and nail changes with ixabepilone and myelosuppression and neuropathy with eribulin). Hypersensitivity is occasionally seen with ixabepilone because it is also solubilized in Cremophor-EL, the likely causative agent in paclitaxel-associated hypersensitivity. However, eribulin has not been associated with hypersensitivity reactions and is not formulated in a complex solvent system that may predispose patients to allergic-type reactions. Neuropathy may become problematic in patients who have received numerous sequential neurotoxic chemotherapy agents. Ongoing clinical trials are investigating these agents in other combinations and in earlier stages of the disease.[101]

Ongoing clinical trials are investigating the combination of chemotherapy and

biologic or targeted therapies in MBC, especially in the TNBC population. Recent data with immunotherapy combined with traditional chemotherapy are encouraging. While MoABs against programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) have failed to demonstrate antitumor activity as single agents in MBC, combining these agents with traditional chemotherapy may improve efficacy in patients with TNBC. The combination of pembrolizumab (MoAB against PD-1) and eribulin demonstrated a modest response rate of 33% with some durable responses. Atezolizumab (MoAB against PD-L1) has also shown some activity when given in combination with nab-paclitaxel (response rates of 42%). Adverse effects reported with the addition of immune therapies to traditional chemotherapy are substantial with nearly two-thirds of patients experiencing grade 3 or 4 adverse events (about 13% possibly immune-related including rash, hyperglycemia, pneumonitis, and renal failure) in the pembrolizumab study. Many ongoing clinical trials will determine the optimal role of these agents in the management of MBC. However, their largest impact may be seen in earlier stages of the disease where the tumor volume is low and tumor cell sensitivity to immune mechanisms is high.[102]

Radiation Therapy

Radiation is an important modality in the treatment of symptomatic metastatic disease. The most common indication for treatment with radiation therapy is painful bone metastases or other localized sites of disease refractory to systemic therapy. Radiation therapy provides significant pain relief to about 90% of patients who are treated for painful bone metastases. Radiation is also an important modality in the palliative treatment of metastatic brain lesions and spinal cord lesions, which respond poorly to systemic therapy, as well as eye or orbit lesions and other sites where significant accumulation of tumor cells occurs. Skin and lymph node metastases confined to the chest wall area may also be treated with radiation therapy for palliation (eg, open wounds or painful lesions). Chemotherapy may also be added to radiation for sensitization purposes.

EVALUATION OF THERAPEUTIC OUTCOMES

The desired therapeutic outcome of adjuvant therapy of ESBC differs significantly from that of MBC. Adjuvant therapy—chemotherapy, biologic or targeted therapy, and endocrine therapy—is administered with curative intent.

The rationale for adjuvant therapy is that breast cancer, even when diagnosed in early stages when clinical evidence of distant spread is not apparent, is a systemic disease that spreads early to distant sites. Adjuvant therapy is intended to eradicate micrometastases and thus cure the patient of breast cancer. Therefore, the overall goal of adjuvant therapy is to cure the disease, which cannot be fully evaluated for years after initial diagnosis and treatment. In addition, because disease cannot be detected at the time adjuvant therapy is started, an assessment of disease response is not possible. Instead, a predetermined number of cycles of adjuvant therapy or years of targeted or hormonal therapy are administered. Adjuvant chemotherapy is often associated with significant toxicity. Maintaining dose intensity has been demonstrated to be important and therefore optimizing supportive care measures such as antiemetics and growth factors is highly recommended. The use of dose-dense regimens, which require growth factors to maintain blood counts while decreasing the interval between chemotherapy administrations, is very controversial in the management of ESBC. Multiple studies investigating this approach to adjuvant chemotherapy have been conducted with conflicting results and many more trials continue to be analyzed to determine the long-term outcomes related to this approach. The goals of therapy with neoadjuvant chemotherapy are slightly different. These goals focus on earlier end points of tumor response to minimize surgery, determine prognosis, and potentially conserve the breast tissue for a better cosmetic result. The other outcomes discussed with adjuvant therapy also apply to this scenario in terms of improving survival and decreasing recurrences compared with no systemic therapy.

Palliation is the therapeutic outcome in the treatment of MBC. Optimizing benefits and minimizing toxicity are general therapeutic goals of any therapy administered in this setting. The addition of targeted therapies is considered in some patients. Careful consideration of quality of life is important in this setting. Tumor response to a particular treatment regimen may be measured by changes in laboratory tests, diagnostic imaging, or physical signs or symptoms. The patient usually continues treatment with the regimen, unless the patient clearly cannot tolerate the regimen or the cancer is clearly progressing at a rate that will cause symptoms (or is causing symptoms already). Optimizing quality of life is an important therapeutic end point in the treatment of patients with MBC and eventually requires discontinuation of active cancer therapy and a shift to supportive care with hospice services.

Postclass Engaged Learning Activity

Conduct a literature search and identify a primary research manuscript regarding the treatment of metastatic breast cancer in ER/PR-positive patients. If the manuscript is regarding a medication that is discussed in the book chapter, write a brief summary of the study methods, the major findings, and how this new information might change current practice. If the manuscript is regarding a new medication that is not described in the chapter, write a brief summary of the medication's mechanisms of action, how it is administered, and one potential advantage or disadvantage of this new medication compared to the current standard of care. This activity is intended to build your literature evaluation skills and the ability to critically appraise research manuscripts.

ABBREVIATIONS

ACS	American Cancer Society
AI	aromatase inhibitor

AJCC	American Joint Committee for Cancer
ALND	axillary lymph node dissection
ASCO	American Society of Clinical Oncology
BCT	breast-conserving therapy
BIG	Breast International Group
BMI	body mass index
BSE	breast self-examination
CALGB	Cancer and Leukemia Group B
CBE	clinical breast examination
CDK	cyclin-dependent kinases
CI	confidence interval
CMF	cyclophosphamide, methotrexate, fluorouracil (regimen)
CREATE-X	Capecitabine for Residual Cancer as Adjuvant Therapy
CYP	cytochrome P450 enzyme
DCIS	ductal carcinoma in situ
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
EGFR	epidermal growth factor receptor; also known as HER1
ER	estrogen receptor
ESBC	early-stage breast cancer
ESMO	European Society of Medical Oncology
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
HER2	human epidermal growth factor receptor-2
HR	hazard ratio
HRT	hormone replacement therapy
IBC	inflammatory breast cancer
IHC	immunohistochemistry
LCIS	lobular carcinoma in situ
LH	luteinizing hormone
LHRH	luteinizing hormone–releasing hormone
MBC	metastatic breast cancer
MINDACT	Microarray In Node-negative Disease may Avoid ChemoTherapy
MoAB	Monoclonal antibody
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NNS	number needed to screen to prevent one breast cancer death
NSABP	National Surgical Adjuvant Breast and Bowel Project
OR	odds ratio
PARP	poly-ADP ribose polymerase
pCR	pathologic complete response
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PI3K	phosphatidylinositol 3-kinase
PR	progesterone receptor
RR	relative risk
RT-PCR	Reverse transcription polymerase chain reaction
SEER	Surveillance, Epidemiology, and End Results
SERD	selective estrogen receptor downregulator
SERM	selective estrogen receptor modulators
SLNB	sentinel lymph node biopsy
STAR	Study of Tamoxifen and Raloxifene
TNBC	triple negative breast cancer
USPSTF	United States Preventive Services Task Force
VEGF	vascular endothelial growth factor
WHI	Women's Health Initiative

REFERENCES

1. American Cancer Society. *Cancer Facts & Figures 2019*. Atlanta: American Cancer Society; 2019.
2. American Cancer Society. *Breast Cancer Facts & Figures 2019–2020*. Atlanta: American Cancer Society, Inc.; 2019.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;68:7–34.
4. Giordano SH. Breast cancer in men. *N Engl J Med*. 2018;378:2311–2320.
5. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer Risk Reduction V.1.2019. National Comprehensive Cancer Network, Inc 2019. All rights reserved. Last accessed, September 20, 2019.
6. Chlebowski RT. Current concepts in breast cancer chemoprevention. *Pol Arch Med Wewn*. 2014;124:191–199.
7. Hartmann LC, Degnim AC, Santen RJ, et al. Atypical hyperplasia of the breast: Risk assessment and management options. *N Engl J Med*. 2015;372:78–89.
8. Pettersson A, Graff RE, Ursin G, et al. Mammographic density phenotypes and risk of breast cancer: A meta-analysis. *J Natl Cancer Inst*. 2014;106:1–11.
9. Moyer VA. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;160:271–281.
10. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Genetic/Familial High-Risk Assessment: Breast and Ovarian V.3.2019. National Comprehensive Cancer Network, Inc 2019. All rights reserved. Last accessed, September 20, 2019.
11. Prentice RL, Caan B, Chlebowski RT, et al. Low-fat dietary pattern and risk of invasive breast cancer: The women’s health initiative randomized controlled dietary modification trial. *JAMA*. 2006;295:629–642.
12. Bilal I, Chowdhury A, Davidson J, Whitehead S. Phytoestrogens and prevention of breast cancer: The contentious debate. *World J Clin Oncol*. 2014;5:705–712.
13. Visvanathan K, Hurley P, Bantug E, et al. Use of pharmacologic

interventions for breast cancer risk reduction: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2013;31:2942–2962.

14. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2018: A review of current American Cancer Society guidelines and current issues in cancer screening. *CA Cancer J Clin*. 2018;68:297–316.
15. Siu AL. Screening for breast cancer: U.S. preventive services task force recommendation statement. *Ann Intern Med*. 2016;164:279–296.
16. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer Screening and Diagnosis V.1.2019. National Comprehensive Cancer Network, Inc 2019. All rights reserved. Last accessed, September 20, 2019.
17. Hendrick RE, Helvie MA. Mammography screening: A new estimate of number needed to screen to prevent one breast cancer death. *AJR Am J Roentgenol*. 2012;198:723–728.
18. Peto R, Davies C, Godwin J, et al. Comparisons between different polychemotherapy regimens for early breast cancer: Meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet*. 2012;379:432–444.
19. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer V.3.2019. National Comprehensive Cancer Network, Inc 2019. All rights reserved. Last accessed, September 20, 2019.
20. Kuerer HM, Albarracin CT, Yang WT, et al. Ductal carcinoma in situ: State of the science and roadmap to advance the field. *J Clin Oncol*. 2009;27:279–288.
21. Venkitaraman R. Lobular neoplasia of the breast. *Breast J*. 2010;16:519–528.
22. Ligibel J. Lifestyle factors in cancer survivorship. *J Clin Oncol*. 2012;30:3697–3704.
23. Demark-Wahnefried W, Rogers LQ, Alfano CM, et al. Practical clinical interventions for diet, physical activity, and weight control in cancer survivors. *CA Cancer J Clin*. 2015;65:167–189.
24. Hortobagyi GN, Connolly JL, D'Orsi CJ, et al. Breast. In: Amin EB, Edge SB, Gress DM, et al., eds. *AJCC Cancer Staging Manual*. 8th ed. Chicago, IL: Springer; 2017;589–638.
25. Dawood S, Broglio K, Buzdar AU, et al. Prognosis of women with metastatic breast cancer by HER2 status and trastuzumab treatment: an

institutional-based review. *J Clin Oncol*. 2010;28:92–98.

26. SEER Cancer Statistics Review: Female Breast Cancer. Available at: https://seer.cancer.gov/statfacts/html/breast.html. Accessed October 8, 2018.
27. Yang SH, Yang KH, Li YP, et al. Breast conservation therapy for stage I or stage II breast cancer: A meta-analysis of randomized controlled trials. *Ann Oncol*. 2008;19:1039–1044.
28. Jatoi I, Proschan MA. Randomized trials of breast-conserving therapy versus mastectomy for primary breast cancer: A pooled analysis of updated results. *Am J Clin Oncol*. 2005;28:289–294.
29. Darby S, McGale P, Correa C, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: Meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet*. 2011;378:1707–1716.
30. Fisher CM, Rabinovitch R. Frontiers in radiotherapy for early-stage invasive breast cancer. *J Clin Oncol*. 2014;32:2894–2901.
31. Rao R, Euhus D, Mayo HG, Balch C. Axillary node interventions in breast cancer: A systematic review. *JAMA*. 2013;310:1385–1394.
32. Lyman GH, Temin S, Edge SB, et al. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2014;32:1365–1383.
33. Giuliano AE, Ballman KV, McCall L, et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: The ACOSOG Z0011 (Alliance) randomized clinical trial. *JAMA*. 2017;318:918–926.
34. Davies C, Godwin J, Gray R, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: Patient-level meta-analysis of randomised trials. *Lancet*. 2011;378:771–784.
35. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: Patient-level meta-analysis of the randomised trials. *Lancet*. 2015;386:1341–1352.
36. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. *Lancet*. 2005;365:1687–1717.
37. Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies-improving

the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. *Ann Oncol*. 2015;26:1533–1546.

38. Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26(suppl 5):v8–v30.
39. Fisher B, Brown A, Mamounas E, et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J Clin Oncol*. 1997;15:2483–2493.
40. Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol*. 1998;16:2672–2685.
41. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: Updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. *J Clin Oncol*. 2008;26:778–785.
42. Adaniel C, Jhaveri K, Heguy A, Esteva FJ. Genome-based risk prediction for early stage breast cancer. *Oncologist*. 2014;19:1019–1027.
43. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med*. 2018;379:111–121.
44. Cardoso F, van't Veer LJ, Bogaerts J, et al.70-gene signature as an aid to treatment decisions in early-stage breast cancer. *N Engl J Med*. 2016;375:717–729.
45. Anampa J, Makower D, Sparano JA. Progress in adjuvant chemotherapy for breast cancer: An overview. *BMC Med*. 2015;13:195.
46. Kumar P, Aggarwal R. An overview of triple-negative breast cancer. *Arch Gynecol Obstet*. 2015;293:247–269.
47. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *N Engl J Med*. 2017;376:2147–2159.
48. Lohrisch C, Paltiel C, Gelmon K, et al. Impact on survival of time from definitive surgery to initiation of adjuvant chemotherapy for early-stage breast cancer. *J Clin Oncol*. 2006;24:4888–4894.
49. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of Intergroup Trial

C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol*. 2003;21:1431–1439.

50. Sparano JA, Zhao F, Martino S, et al. Long-term follow-up of the E1199 phase III trial evaluating the role of taxane and schedule in operable breast cancer. *J Clin Oncol*. 2015;33:2353–2360.
51. Seidman AD, Berry D, Cirrincione C, et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: Final results of Cancer and Leukemia Group B protocol 9840. *J Clin Oncol*. 2008;26:1642–1649.
52. Green MC, Buzdar AU, Smith T, et al. Weekly paclitaxel improves pathologic complete remission in operable breast cancer when compared with paclitaxel once every 3 weeks. *J Clin Oncol*. 2005;23:5983–5992.
53. Bonilla L, Ben-Aharon I, Vidal L, et al. Dose-dense chemotherapy in nonmetastatic breast cancer: A systematic review and meta-analysis of randomized controlled trials. *J Natl Cancer Inst*. 2010;102:1845–1854.
54. Moore HC. Impact on quality of life of adjuvant therapy for breast cancer. *Curr Oncol Rep*. 2007;9:42–46.
55. Hesketh PJ, Bohlke K, Kris MG. Antiemetics: American Society of Clinical Oncology clinical practice guideline update summary. *J Oncol Pract*. 2017;13:825–830.
56. Levine MN, Gent M, Hirsh J, et al. The thrombogenic effect of anticancer drug therapy in women with stage II breast cancer. *N Engl J Med*. 1988;318:404–407.
57. Matesich SM, Shapiro CL. Second cancers after breast cancer treatment. *Semin Oncol*. 2003;30:740–748.
58. Henderson IC, Sloss LJ, Jaffe N, et al. Serial studies of cardiac function in patients receiving adriamycin. *Cancer Treat Rep*. 1978;62:923–929.
59. Costa RB, Kurra G, Greenberg L, Geyer CE. Efficacy and cardiac safety of adjuvant trastuzumab-based chemotherapy regimens for HER2-positive early breast cancer. *Ann Oncol*. 2010;21:2153–2160.
60. Yin W, Jiang Y, Shen Z, et al. Trastuzumab in the adjuvant treatment of HER2-positive early breast cancer patients: A meta-analysis of published randomized controlled trials. *PloS One*. 2011;6:e21030.
61. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*. 2011;365:1273–1283.

62. Jhaveri K, Esteva FJ. Pertuzumab in the treatment of HER2+ breast cancer. *J Natl Compr Canc Netw*. 2014;12:591–598.
63. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med*. 2017;377:122–131.
64. Telli ML, Witteles RM. Trastuzumab-related cardiac dysfunction. *J Natl Compr Canc Netw*. 2011;9:243–249.
65. Thompson LM, Eckmann K, Boster BL, et al. Incidence, risk factors, and management of infusion-related reactions in breast cancer patients receiving trastuzumab. *Oncologist*. 2014;19:228–234.
66. Halyard MY, Pisansky TM, Dueck AC, et al. Radiotherapy and adjuvant trastuzumab in operable breast cancer: Tolerability and adverse event data from the NCCTG Phase III Trial N9831. *J Clin Oncol*. 2009;27:2638–2644.
67. Reeder-Hayes KE, Carey LA. How low should we go? The search for balance in management of small human epidermal growth factor receptor 2-positive breast cancers. *J Clin Oncol*. 2014;32:2122–2124.
68. Tolaney SM, Barry WT, Dang CT, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. *N Engl J Med*. 2015;372:134–141.
69. Chan A, Delaloge S, Holmes FA, et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): A multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2016;17:367–377.
70. Love RR, Mazess RB, Barden HS, et al. Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. *N Engl J Med*. 1992;326:852–856.
71. Love RR, Wiebe DA, Newcomb PA, et al. Effects of tamoxifen on cardiovascular risk factors in postmenopausal women. *Ann Intern Med*. 1991;115:860–864.
72. Albain KS, Barlow WE, Ravdin PM, et al. Adjuvant chemotherapy and timing of tamoxifen in postmenopausal patients with endocrine-responsive, node-positive breast cancer: A phase 3, open-label, randomised controlled trial. *Lancet*. 2009;374:2055–2063.
73. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial.

Lancet. 2013;381:805–816.

74. Gray RG, Rea D, Handley K, et al. aTTom: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer. *J Clin Oncol*. 2013;31(suppl 5):, abstract.
75. Fisher B, Dignam J, Bryant J, Wolmark N. Five versus more than five years of tamoxifen for lymph node-negative breast cancer: Updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. *J Natl Cancer Inst*. 2001;93:684–690.
76. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst*. 1998;90:1371–1388.
77. Khatcheressian JL, Hurley P, Bantug E, et al. Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2013;31:961–965.
78. Cuzick J, Ambroisine L, Davidson N, et al. Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: A meta-analysis of individual patient data from randomised adjuvant trials. *Lancet*. 2007;369:1711–1723.
79. Pagani O, Regan MM, Walley BA, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med*. 2014;371:107–118.
80. Francis PA, Regan MM, Fleming GF, et al. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med*. 2015;372:436–446.
81. Hertz DL, McLeod HL, Irvin WJ Jr. Tamoxifen and CYP2D6: A contradiction of data. *Oncologist*. 2012;17:620–630.
82. Kelly CM, Juurlink DN, Gomes T, et al. Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: A population based cohort study. *BMJ*. 2010;340:c693.
83. Tryfonidis K, Senkus E, Cardoso MJ, Cardoso F. Management of locally advanced breast cancer-perspectives and future directions. *Nat Rev Clin Oncol*. 2015;12:147–162.
84. Charehbili A, Fontein DB, Kroep JR, et al. Neoadjuvant hormonal therapy for endocrine sensitive breast cancer: A systematic review. *Cancer Treat Rev*. 2014;40:86–92.

85. Giordano SH, Temin S, Davidson NE. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: ASCO clinical practice guideline update summary. *J Oncol Pract*. 2018;14:501–504.
86. Van Poznak C, Somerfield MR, Barlow WE, et al. Role of bone-modifying agents in metastatic breast cancer: An American Society of Clinical Oncology-Cancer Care Ontario focused guideline update. *J Clin Oncol*. 2017;35:3978–3986.
87. Giordano SH, Temin S, Chandarlapaty S, et al. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: ASCO clinical practice guideline update. *J Clin Oncol*. 2018;36:2736–2740.
88. Ramakrishna N, Temin S, Chandarlapaty S, et al. Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2-positive breast cancer and brain metastases: ASCO clinical practice guideline update. *J Clin Oncol*. 2018;36:2804–2807.
89. Herceptin (trastuzumab) product information. Available at: https://www.gene.com/download/pdf/herceptin_prescribing.pdf. Accessed October 28, 2018.
90. Perez EA, Koehler M, Byrne J, et al. Cardiac safety of lapatinib: Pooled analysis of 3689 patients enrolled in clinical trials. *Mayo Clin Proc*. 2008;83:679–686.
91. Pernas S, Barroso-Sousa R, Tolaney SM. Optimal treatment of early stage HER2-positive breast cancer. *Cancer*. 2018;124:4455–4466.
92. Tykerb (lapatinib) product information. Available at: https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/fil Accessed October 28, 2018.
93. Hecht KA, Selby C. Review of cyclin-dependent kinase 4/6 inhibitors for the treatment of hormone receptor-positive advanced breast cancer. *Ann Pharmacother*. 2019;53:195–203.
94. Ballinger TJ, Meier JB, Jansen VM. Current landscape of targeted therapies for hormone-receptor positive, HER2 negative metastatic breast cancer. *Front Oncol*. 2018;8:308.
95. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *N Engl J Med*. 2018;379:753–763.
96. Turk AA, Wisinski KB. PARP inhibitors in breast cancer: Bringing

synthetic lethality to the bedside. *Cancer*. 2018;124:2498–2506.

97. Sainsbury R. The development of endocrine therapy for women with breast cancer. *Cancer Treat Rev*. 2013;39:507–517.
98. Vogel CL, Johnston MA, Capers C, Braccia D. Toremifene for breast cancer: A review of 20 years of data. *Clin Breast Cancer*. 2014;14:1–9.
99. Cardoso F, Bischoff J, Brain E, et al. A review of the treatment of endocrine responsive metastatic breast cancer in postmenopausal women. *Cancer Treat Rev*. 2013;39:457–465.
100. Tong CWS, Wu M, Cho WCS, To KKW. Recent advances in the treatment of breast cancer. *Front Oncol*. 2018;8:227.
101. Partridge AH, Rumble RB, Carey LA, et al. Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2014;32:3307–3329.
102. Wein L, Luen SJ, Savas P, et al. Checkpoint blockade in the treatment of breast cancer: Current status and future directions. *Br J Cancer*. 2018;119:4–11.

146

Lung Cancer

Val R. Adams and Keith A. Hecht

KEY CONCEPTS

1. Lung cancer is the leading cause of cancer deaths in both men and women in the United States. The overall 5-year survival rate for all types of lung cancer is about 18%.
2. Cigarette smoking is responsible for most lung cancers. Smoking cessation should be encouraged, particularly in those receiving curative treatment (ie, Stages I to IIIA nonsmall cell lung cancer [NSCLC] and limited-stage small cell lung cancer [SCLC]).
3. NSCLC is the most commonly diagnosed type of lung cancer (about 80%). NSCLC typically has a slower growth rate and doubling time than SCLC.
4. Annual screening with low-dose computed tomography (LDCT) imaging is currently recommended to identify lung cancer in high-risk individuals. However, ongoing studies are evaluating the optimal frequency and duration, and the effects of false-positive tests.
5. Treatment decisions for NSCLC are guided by the stage of disease, histology (squamous or nonsquamous), and molecular features (PD-L1, EGFR, ALK, BRAF, NTRK, and ROS1) of the tumor. Patient-specific factors (eg, performance status, comorbid conditions) must also be considered when developing a treatment plan.
6. The treatment goals for SCLC lung cancer are cure (early-stage disease), prolonged survival, and maintenance of or improved quality of life through alleviation of symptoms.
7. Early-stage lung cancer has the highest cure rates, following surgical resection of the tumor with or without chemotherapy for NSCLC and chemoradiotherapy for SCLC.
8. Immunotherapy with anti-programmed-death 1 (PD-1) targeting

monoclonal antibody is recommended as first-line treatment of metastatic NSCLC that is PD-L1 positive. Immunotherapy can be added to a platinum doublet in patients with tumors that do not have a targetable genetic mutation and are PD-L1 negative. Patients with extensive-stage SCLC may receive immunotherapy either with a platinum doublet as first-line therapy or alone as second-line therapy.

9 Targeted therapies for advanced-stage NSCLC are preferred over platinum-based doublets or immunotherapy as first-line therapy in patients whose tumors harbor targetable genetic mutations such as EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, or mutations in ALK, BRAF, NTRK, or ROS1.

10 Optimal patient care includes the management of adverse events from drug therapy. Adverse events may cause delays in treatment administration, increase morbidity, and contribute to treatment failure.

Preclass Engaged Learning Activity

View the video "Lung Cancer Screening" from the American Cancer Society regarding the use of low-dose CT scans for early detection in patients at an increased risk of lung cancer. What are some consequences of lung cancer screening in patients who are not at high risk for the disease? Consider the process for low-dose CT scan and the characteristics of appropriate candidates for screening. What are some difficulties patients may have while undergoing this exam?

INTRODUCTION AND EPIDEMIOLOGY

Lung cancer is a major cause of morbidity and mortality. It has reached epidemic proportions in many industrialized countries and is the most common cause of cancer-related death in the world. It is estimated that 238,150 new cases of lung cancer were diagnosed in the United States in 2019.[1]

1 Despite major advances in the understanding and management of lung cancer, the overall 5-year survival rate for all types of lung cancer remains a dismal 18%. In the United States, lung cancer accounts for about 13% of all newly diagnosed cancers and is the leading cause of cancer death in both adult

men and women, with about 142,670 deaths in 2019.[1] The incidence and death rate related to lung cancer are declining, which has been attributed to decreased tobacco use over the last 50 years. The incidence of lung cancer increases with age, with about 58% of deaths occurring between 60 and 79 years.[1] In comparison to whites, the lung cancer incidence and mortality are higher in African American men and slightly lower in African American women.[1] The cure rate is highest with early-stage disease treated with surgical resection, but most patients present with metastatic disease.[1]

Further reductions in mortality related to lung cancer will require ongoing smoking cessation programs, screening of high-risk patients to diagnose the disease early when it is potentially curable, and better treatment. This chapter discusses screening but is focused on the care and treatment of patients diagnosed with lung cancer. Two leading oncology groups in the United States have published clinical practice guidelines for the treatment of lung cancer. The National Comprehensive Cancer Network (NCCN) has developed consensus-based guidelines that provide recommendations regarding the screening, staging, and treatment of both nonsmall cell lung cancer (NSCLC) and small cell lung cancer (SCLC).[2,3] The American Society of Clinical Oncology (ASCO) published evidence-based guidelines that were updated in 2017.[4,5] ASCO also endorsed the guidelines of other organizations related to the treatment of SCLC[6] and the use of molecular testing for NSCLC.[7]

ETIOLOGY

Lung carcinomas arise from normal bronchial epithelial cells that have acquired multiple genetic lesions and express a variety of phenotypes.[8] Important advances have been made recently in our understanding of the molecular genetic changes involved in lung cancer pathogenesis.[8] A large variety of molecular lesions result in the abrogation of key cellular regulatory and growth control pathways. Activation of proto-oncogenes, inhibition or mutation of tumor suppressor genes, and production of autocrine (self-stimulatory) growth factors contribute to cellular proliferation and malignant transformation.[8] Many of these molecular alterations are common to both SCLC and NSCLC, but certain mutations are found more frequently in specific subtypes of lung cancer and can be potentially treated with more targeted interventions. In autocrine loop abnormalities, SCLC frequently overexpresses C-KIT, a protein tyrosine kinase receptor that is specific for stem cell factor (CD117), while NSCLC frequently

overexpresses epidermal growth factor receptor (EGFR). EGFR inhibitors, such as erlotinib, gefitinib, afatinib, dacometinib, and osimertinib, are used clinically to treat NSCLC and offer a potential method of lung cancer chemoprevention.[8–10] Crizotinib, ceritinib, alectinib, and brigatinib, drugs that target the EML4-ALK gene rearrangement protein, demonstrate the importance of this pathway in patients with a specific type of NSCLC (ie, adenocarcinoma).[11] Although less common, mutations in BRAF, NTRK, and ROS1 can also drive tumor growth and be targeted with TKIs.

2 Smoking is a major cause of lung cancer, with about 80% of lung cancer deaths in the United States directly attributed to tobacco use. Tobacco smoke contains many substances, including tumor promoters, carcinogens, and cocarcinogens.[12] The association between environmental tobacco smoke (ETS; also referred to as passive smoking) and lung cancer risk in nonsmokers is clear. Most studies show that spouses of smokers have higher rates of lung cancer than spouses of nonsmokers (about 25% higher risk). In addition, workplace exposure to environmental smoke increases the risk of lung cancer by about 17%. It is currently estimated that ETS contributes to about 3,000 lung cancers annually. Although these studies are observational studies, they consistently show a dose-risk relationship, with no safe level of exposure.[12] Smoking cessation is associated with a gradual decrease in the risk, but more than 5 years is necessary before an appreciable decline in risk occurs and the risk never returns to that of a nonsmoker.[12] Because of the public health implications, the United States has several, mainly state-led, tobacco control efforts, including antismoking campaigns, increased tobacco taxes, and smoke-free areas in many public areas. Although the prevalence of cigarette smoking has slowly decreased, it remains at about 15% in 2016.[13]

Although most cases of lung cancer are attributable to cigarette smoking, less than 20% of smokers develop lung cancer, which suggests that other risk factors are relevant. An increased risk of lung cancer has been associated with exposure to other environmental respiratory carcinogens (eg, asbestos, benzene, and arsenic). Genetic risk factors are also important, with an increased risk of lung cancer observed in those with first-degree relatives diagnosed with the disease. Lung cancer risk is associated with polymorphisms that affect the expression and/or function of enzymes regulating the metabolism of tobacco carcinogens, DNA repair, or inflammation. Patients with a history of chronic obstructive airway disease and adults with asthma are at an increased risk for lung cancer.[8,9] Further studies to better identify which patients are at the highest risk of developing lung cancer will be key for new lung cancer screening trials and in

chemoprevention trials.

HISTOLOGIC CLASSIFICATION

Before treatment begins, it is critical that an experienced lung cancer pathologist reviews the pathologic material to confirm malignancy, characterize the tumor histology, and identify targetable molecular characteristics of the tumor.

3 NSCLC is diagnosed in most (80%) lung cancer patients. NSCLC typically has a slower growth rate and doubling time than SCLC. The histologic classification of NSCLC is well defined and widely accepted (**Table 146-1**).[14] In the most recent classification, the histologic types, subtypes, and identifiable variants provide information about the prognosis and can influence therapeutic decisions.[14,15]

TABLE 146-1 Histologic Classification of Nonsmall Cell Lung Carcinomas

1. Squamous cell carcinoma
   - Papillary
   - Clear cell
   - Small cell
   - Basaloid
2. Adenocarcinoma
   - Minimally invasive adenocarcinoma (MIA)
   - Invasive adenocarcinoma
   - Lepidic predominant (previously classified as bronchioalveolar carcinoma [BAC])
   - Acinar predominant
   - Papillary predominant
   - Micropapillary predominant
   - Solid predominant with mucin
   - Variants of invasive adenocarcinoma
   - Invasive mucinous adenocarcinoma (previously classified as BAC)
   - Colloid
   - Fetal (low and high grade)
   - Enteric
3. Large cell carcinoma
   - Large cell neuroendocrine carcinoma
   - Combined large cell neuroendocrine carcinoma
   - Basaloid carcinoma
   - Lymphoepithelioma-like carcinoma
   - Clear cell carcinoma
   - Large cell carcinoma with rhabdoid phenotype
4. Adenosquamous carcinoma
5. Sarcomatoid carcinomas
   - Pleomorphic carcinoma
   - Spindle cell carcinoma
   - Giant cell carcinoma
   - Carcinosarcoma
   - Pulmonary blastoma
   - Other
6. Carcinoid tumor
   - Typical carcinoid (TC)
   - Atypical carcinoid (AC)
7. Carcinomas of salivary gland type
   - Mucoepidermoid carcinoma
   - Adenoid cystic carcinoma
   - Epimyoepithelial carcinoma

Source: Adapted from 2004 WHO classification and the 2011 IASCL/ATS/ERS classification.

Four major cell types of carcinomas (squamous cell, adenocarcinoma, large cell, and small cell) account for more than 90% of lung tumors. Early studies

with localized disease demonstrated that radiation could cure small cell histology, while surgery could not. Studies with the other histologic types demonstrated better outcomes with surgery than with radiation, which provided the basis for the general classification of SCLC and NSCLC. Historically, systemic treatment for NSCLC histologies was the same and resulted in a similar overall prognosis, which supported a general classification of SCLC and NSCLC. Incorporation of genetics in NSCLC and the availability of targeted therapies have led to personalized treatment. Optimal therapy requires knowledge of histology, immunotherapy marker expression, and genetic mutational status.[7,8]

Squamous cell carcinoma was once the most common histology, but it now represents less than 30% of all lung cancers. Squamous cell carcinomas have a much higher incidence in smokers and among males and appear to have a strong dose-response relationship to tobacco exposure. Studies of the natural history of lung cancer in the era of screening with low-dose computed tomography imaging (LDCT) show a relatively constant tumor volume doubling time (104-122 days) for squamous tumors.[16] Squamous cell tumors are slower to metastasize, but they eventually spread to the hilar and mediastinal lymph nodes, liver, adrenal glands, kidneys, bone, and GI tract.

The other histologies that can occur in NSCLC are collectively referred to as nonsquamous NSCLC. Adenocarcinoma accounts for about one-half of lung cancers and is increasing in frequency. It is the most common histology in nonsmoking lung cancer patients. The natural history of adenocarcinoma in the lung shows that small tumors discovered with CT screening are relatively slow growing and the tumor doubling time increases as they get larger. Doubling time of tumors discovered with CT screening is about 576 days, while those found only with routine patient care grew more rapidly, doubling in size every 169 days.[16] This information is most important when considering screening frequency and efficacy. Patients with adenocarcinoma can present with a single nodule, multifocal nodules, or rapidly progressing, bilateral, diffuse processes. This histology is likely to metastasize from a relatively small tumor (often before the diagnosis of the primary tumor) and spread widely to distant sites, including the contralateral lung, liver, bone, adrenal glands, kidneys, and CNS. As a result, adenocarcinoma has a worse prognosis than squamous cell carcinoma, but the prognosis is similar when controlled for stage.[2,9] Table 146-1 shows several subclassifications and variants of adenocarcinoma. Large cell carcinomas occur infrequently. They are undifferentiated epithelial tumors, which tend to be large and bulky tumors arising in the periphery of the lung. Large cell carcinomas

have a propensity to metastasize in a pattern quite similar to adenocarcinomas and are associated with a similar poor prognosis.[2,9]

SCLCs account for about 15% of all lung tumors. They are distinguished by their appearance as small neoplastic cells with round to oval nuclei. Historically, SCLC was referred to as “oat cell” carcinoma due to the unique appearance. These tumors occur in both the major bronchi and the periphery of the lung. SCLC is a very aggressive and rapidly growing tumor, with about 60% to 70% of patients initially presenting with disseminated disease outside of the hemithorax. These tumors commonly express neuroendocrine differentiation, which may account for some of the paraneoplastic syndromes frequently associated with this disease. SCLC secretes gastrin-releasing peptide that acts as an autocrine growth factor. The secretion of other peptide hormones, cytogenetic abnormalities, and amplification and increased expression of oncogenes are also common. SCLC has a propensity to metastasize to the lymph nodes, opposite lung, liver, adrenal glands and other endocrine organs, bone, bone marrow, and CNS.[3,10] Unlike NSCLC, SCLC treatment is not guided by specific biomarkers due to their lack of clinical data demonstrating efficacy with targeted agents. However, genetic studies may be performed should new targeted therapies be developed.

Lung tumors can exhibit more than one histologic cell type (eg, adenosquamous) and mixed histology tumors should also undergo genetic testing.[7,8] Patients can also occasionally have multiple lung nodules arising in different lobes or the contralateral lung. This is referred to as synchronous tumors, and the nodules can be the same or different cell types. Synchronous tumors worsen the patient’s overall prognosis.[2]

CLINICAL PRESENTATION

At the time of diagnosis, 16% of lung cancers are localized, 22% have regional spread, and 57% have distant metastases (some patients were not staged). The location and extent of the tumor determine the presenting signs and symptoms. A lesion in the central portion of the bronchial tree is more likely to cause symptoms at an earlier stage as compared with a lesion in the periphery of the lung, which may remain asymptomatic until the lesion is large or has spread to other areas. The most common initial signs and symptoms include cough, dyspnea, and chest pain or discomfort, with or without hemoptysis.[9] Unfortunately, many patients with lung cancer also have chronic pulmonary and/or cardiovascular diseases (usually related to smoking), and such symptoms

may go unnoticed or be attributed to the concomitant disease. Many patients also exhibit systemic symptoms of malignancy such as anorexia, weight loss, and fatigue. Disseminated disease can cause extrapulmonary signs and symptoms such as neurologic deficits resulting from CNS metastases, bone pain or pathological fractures secondary to bone metastases, or liver dysfunction resulting from tumor involvement in the liver.[9]

CLINICAL PRESENTATION | Lung Cancer

Local signs and symptoms

- Cough
- Hemoptysis
- Dyspnea
- Rust-streaked or purulent sputum
- Chest, shoulder, or arm pain
- Wheeze and stridor
- Superior vena cava obstruction
- Pleural effusion or pneumonitis
- Dysphagia (secondary to esophageal compression)
- Hoarseness (secondary to laryngeal nerve paralysis)
- Horner's syndrome
- Phrenic nerve paralysis
- Pericardial effusion/tamponade
- Tracheal obstruction

Extrapulmonary signs and symptoms

- Bone pain and/or pathologic fractures
- Liver dysfunction
- Neurologic deficits
- Spinal cord compression

Paraneoplastic syndromes

- Weight loss
- Cushing's syndrome
- Hypercalcemia (most commonly in squamous cell lung cancer)
- Syndrome of inappropriate secretion of antidiuretic hormone (most commonly in SCLC)
- Pulmonary hypertrophic osteoarthropathy
- Clubbing
- Anemia
- Eaton-Lambert myasthenic syndrome
- Hypercoagulable state

Paraneoplastic syndromes are signs and symptoms that occur at sites away from the primary tumor or its metastases and are not associated with direct tumor involvement. They may be caused by the production of biologically active substances (eg, peptide hormones) or antibodies, or by other undefined mechanisms. Paraneoplastic syndromes occur more frequently with lung cancer than with any other tumor, and more frequently with SCLC than with NSCLC. These syndromes may be the first signs of a tumor and may prompt the search for an underlying malignancy.[10]

SCREENING AND PREVENTION

4 Most lung cancer patients have advanced disease at the time of diagnosis, which explains the poor prognosis associated with this disease. Surgery and radiation are the most effective treatment modalities in NSCLC and SCLC, respectively, and only patients diagnosed at an early clinical stage can be cured with these treatment modalities.[2,3,6,17] Therefore, it is important to diagnose lung cancer earlier and provides the rationale for screening. The current screening recommendation is based on the National Lung Cancer Screening Trial, which enrolled more than 54,000 high-risk smokers. In that trial, screening discovered 70% of tumors at stage I or II, when they were potentially curable with surgical resection. The study reported a decrease in overall (7% vs 7.5%) and lung cancer-specific (1.3% vs 1.7%) mortality with LDCT versus control,

respectively.[18] Based on these results, annual LDCT screening should be offered to high-risk individuals, defined as aged 55 to 74 years with a 30-pack-year history who are still smoking or have quit for less than 15 years.[19] This recommendation comes with a few caveats, including the fact that the most important step is for current smokers to quit. The optimal frequency and duration of screening are unknown, and the harm from screening, including frequent false-positive findings, is unknown.[20] The cost-effectiveness of screening is also a concern.[21] Consequently, patients interested in screening are encouraged to enroll in a clinical trial to address these important questions.

The term *chemoprevention* refers to the use of prophylactic medications to prevent the development of cancer. Many studies of potential chemopreventive agents, including nonsteroidal anti-inflammatory drugs (NSAIDs), retinoids, inhaled glucocorticoids, vitamin E, selenium, and green tea extracts, have been conducted, but none have been successful.[22] Large randomized clinical trials have evaluated β-carotene as a lung cancer chemopreventive agent in high-risk patients (older smokers). Rather than prevent lung cancer, the trials clearly show that older people who smoke have a higher risk of developing and dying of lung cancer if they take a β-carotene supplement. Nonsmokers do not appear to have an altered risk of lung cancer with β-carotene consumption.[22]

In summary, the most effective prevention/early intervention approach is to avoid tobacco, maintain a healthy diet with high amounts of fruits and vegetables, and offer screening to high-risk individuals.[23]

DIAGNOSIS

A patient suspected of having lung cancer should undergo a diagnostic evaluation. Diagnosis of lung cancer requires both visualization of the cancerous lesion and tissue sampling for pathologic assessment. All patients must have a thorough history and physical examination with an emphasis on detecting signs and symptoms of the primary tumor, regional spread of the tumor, distant metastases, and paraneoplastic syndromes. The patient's performance status should be assessed to determine whether or not a patient may be able to tolerate surgery or chemotherapy.[2,3,9,10]

Visualization of the suspected tumor provides the clinician with the information necessary to choose the most appropriate sampling technique. A chest and upper abdomen CT scan is the most common initial staging radiologic evaluation. The staging workup can include an endobronchial ultrasound, PET

scan, or other tests.[9,10] Most recently, the use of integrated CT-PET technology has been reported to improve the diagnostic accuracy in the staging of NSCLC over either CT or PET technology alone.[9]

Once the tumor has been located, pathologic examination of tumor tissue is necessary to establish the diagnosis of lung cancer. Tissue is usually obtained through the least invasive method most likely to result in an adequate sample; methods include sputum cytology, tumor biopsy by bronchoscopy, mediastinoscopy, percutaneous needle biopsy, or open lung biopsy. The tissue sample not only confirms malignancy but is also necessary to determine the histology (ie, squamous cell, adenocarcinoma, large cell, or small cell) and to provide adequate tissue for molecular analysis. Additionally, it is essential for patients with NSCLC that the tissue sample be submitted for PD-L1 testing as well as tested for genetic mutations that drive tumor growth, such as EFGR, ALK, ROS1, NTRK, and $BRAF^{V600E}$.[5] Once the diagnosis is established, additional radiologic tests may be required to evaluate lymph nodes and potential metastatic sites for accurate staging.[2,3,9,10]

STAGING

5 Once the diagnosis of lung cancer is confirmed, the extent of disease must be determined to estimate prognosis and guide therapy. For NSCLC, tumor growth and spread are staged with the American Joint Committee on Cancer (AJCC) tumor, node, and metastasis (TNM) staging system. SCLC is typically staged with the Veterans Administration Lung Cancer Study Group method.[14,24]

Nonsmall Cell Lung Cancer

Clinical staging of NSCLC with the TNM system evaluates the size of the tumor, extent of nodal involvement, and presence of metastatic sites. The TNM criteria were last updated in 2017.[14] Clinical stages and associated survival rates are described in **Table 146-2**. For comparison of various therapeutic modalities, a simpler stage grouping system is used in which stage I refers to tumors confined to the lung without lymphatic spread, stage II refers to large tumors with ipsilateral peribronchial or hilar lymph node involvement, stage III includes other lymph node and regional involvement that may or may not involve both lungs, and stage IV includes tumor with distant metastases. Local disease is associated with the highest cure and survival rates, while those with advanced disease have a 5-year survival rate of less than 5%. Once evidence of metastatic

disease has been found, further evaluation is not necessary.

TABLE 146-2 Tumor (T), Node (N), Metastasis (M) Staging for Nonsmall Cell Lung Cancer

Primary Tumor (T	Description
T_1	Tumor ≤3 cm in diameter, surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus
T_{1mi}	Minimally invasive adenocarcinoma: adenocarcinoma (≤3 cm in diameter) with a predominately lepidic pattern
T_{1a}	Tumor ≤1cm in diameter
T_{1b}	Tumor >1 cm but ≤2 cm in diameter
T_{1c}	Tumor >2 cm but ≤3 cm in diameter
T_2	Tumor >3 cm but ≤5 cm, or tumor with any of the following features: - Involves main bronchus, without involvement of the carina - Invades visceral pleura - Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung
T_{2a}	Tumor >3 cm but ≤4 cm
T_{2b}	Tumor >4 cm but ≤5 cm
T_3	Tumor >5 cm but ≤7 cm or directly invading the parietal pleura, chest wall, phrenic nerve, parietal pericardium, or with separate tumor nodule(s) in the same lobe as the primary tumor
T_4	Tumor >7 cm or tumor of any size that invades the diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or with separate tumor nodules in a different ipsilateral lobe
Regional Lymph Nodes (N)	
N_0	No regional lymph node metastases
N_1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N_2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N_3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
Distant Metastasis (M)	
M_0	No distant metastasis
M_1	Distant metastasis
M_{1a}	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodules, or malignant pleural or pericardial effusion
M_{1b}	Single extrathoracic metastasis in a single organ (including involvement of a single nonregional node)
M_{1c}	Multiple extrathoracic metastases

Stage	T	N	M	5-Year Survival (%)
IA1	T_{mi}-T_{1a}	N_0	M_0	92%
IA2	T_{1b}	N_0	M_0	83%
IA3	T_{1c}	N_0	M_0	77%
IB	T_{2a}	N_0	M_0	68%
IIA	T_{2b}	N_0	M_0	60%
IIB	T_{1a}, T_{1b}, T_{1c}, T_{2a}, T_{2b}	N_1	M_0	53% (All IIB)
	T_3	N_0	M_0	
IIIA	T_{1a}, T_{1b}, T_{1c}, T_{2a}, T_{2b}	N_2	M_0	36% (all IIIA)
	T_3	N_1	M_0	
	T_4	N_0, N_1	M_0	
IIIB	T_{1a}, T_{1b}, T_{1c}, T_{2a}, T_{2b}	N_3	M_0	26% (all IIIB)
	T_3, T_4	N_2	M_0	
IIIC	T_3, T_4	N_3	M_0	13%
IVA	Any T	Any N	M_{1a} or M_{1b}	10%
IVB	Any T	Any N	M_{1c}	<1%

Small Cell Lung Cancer

The most commonly used system of staging SCLC was developed originally by the Veterans Administration Lung Cancer Study Group.[24] This system categorizes SCLC into two stages: limited and extensive disease. When evidence of the tumor is confined to a single hemithorax and can be encompassed by a single radiation port, the disease is considered limited. Any progression beyond this point is extensive disease. About 60% to 70% of patients initially present with extensive-stage disease. The initial pretreatment evaluation of an SCLC patient should include a medical history, a clinical examination, and laboratory survey, as well as a CT scan of the chest, abdomen, and head. The typical approach is to identify tumor spread that would demonstrate extensive stage, at which time the workup can stop. For patients without extrathoracic disease identified by typical radiology scans, a bone scan and bone marrow biopsy should be performed to confirm limited-stage disease.[3,10]

TREATMENT

Desired Outcomes

6 The desired outcomes of lung cancer treatment depend on tumor histology, extent of disease, and patient characteristics such as age, history, and performance status.[2,3] These aspects must be assessed before appropriate treatment can be recommended. In the development of a patient care plan, the ultimate goals of therapy should be considered. Stage I and II (NSCLC) or limited-stage (SCLC) diseases are commonly referred to as early-stage disease, while stages III and IV (NSCLC) or extensive-stage (SCLC) diseases are referred to as advanced-stage disease. In patients with early-stage disease who can tolerate aggressive treatment, a definitive cure is the desired outcome of treatment. In patients with advanced-stage disease who can tolerate aggressive therapy, the desired outcome is prolongation of survival. Regardless of treatment goals, all therapies should ultimately improve quality of life through the alleviation of symptoms. Patients should carefully consider whether to receive aggressive treatment that may prolong survival by a few months but includes a high potential for toxicity that could significantly decrease quality of life. Treatment decisions must include both the healthcare team and an informed and well-counseled patient.

Nonsmall Cell Lung Cancer

If left untreated, patients with advanced NSCLC will die within months.[9] Surgery, radiation therapy, and systemic therapy with cytotoxic chemotherapy, immunotherapy, or targeted therapies are used in the management of NSCLC patients. The applications of these treatment modalities are determined by stage and other patient-specific factors (eg, performance status).[2,9]

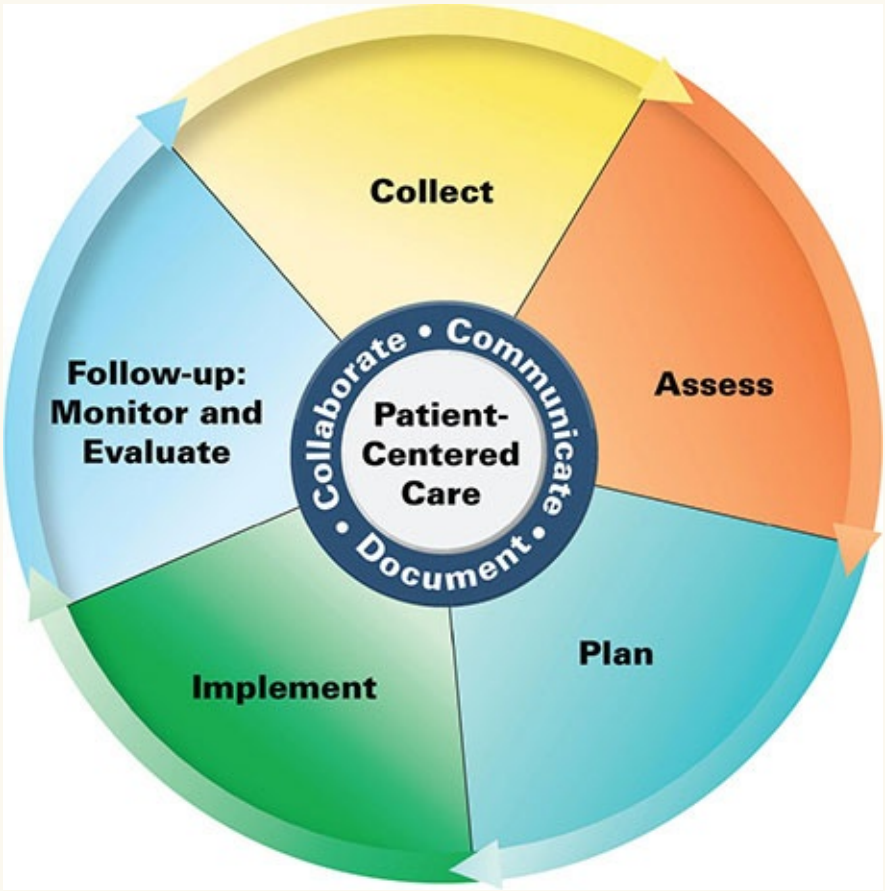
Local Disease (Stage I-II)

7 Local disease is associated with a favorable prognosis and the goal of therapy is cure. Surgery is the mainstay of treatment and may be used alone or in some situations with radiation and/or chemotherapy. Patients who are not surgical candidates can be treated with radiation with curative intent, although the cure rates are lower. Stage IA and IB tumors are treated with surgery alone; when complete resection is achieved, adjuvant therapy is not routinely recommended.[2,4] If surgical margins are positive, re-resection is recommended. Alternatively, patients may receive radiotherapy with or without chemotherapy. Although controversial, patients with IB tumors and high-risk features (poorly differentiated tumors, vascular invasion, wedge resection, minimal margins, tumors more than 4 cm, or visceral pleural involvement) may also receive adjuvant chemotherapy.[2,4] Postoperative radiation therapy with older techniques may be detrimental and is not recommended.[2,4]

Stage IIA and IIB diseases are primarily treated with surgery, which should be followed by adjuvant chemotherapy. The optimal adjuvant chemotherapy regimen is not clear, but the positive clinical trials used platinum-based regimens, with arguably the best clinical trial data coming from cisplatin–vinorelbine (see **Table 146-3**).[15] The absolute benefit in 5-year overall survival in large randomized trials ranges from no benefit to 15%, with a recent systematic review reporting an absolute difference of 4%. The analysis suggested little effect of the chemotherapy regimen.[15] Although genetics and histology influence systemic treatment and outcomes in advanced disease, this approach has not been tested in large randomized trials of adjuvant chemotherapy.

TABLE 146-3 Common Chemotherapy Regimens used in the Adjuvant Treatment of Nonsmall Cell Lung Cancer

Regimen	Drugs and Doses	Frequency and Number of Cycles
Cisplatin/ etoposide	Cisplatin 100 mg/m² IV day 1 Etoposide 100 mg/m² IV daily on days 1, 2, and 3	Every 28 days for 4 cycles
Cisplatin/ vinorelbine	Cisplatin 50 mg/m² IV days 1 and 8 Vinorelbine 25 mg/m² IV days 1, 8, 15, and 22	Every 28 days for 4 cycles
	Cisplatin 100 mg/m² IV day 1 Vinorelbine 30 mg/m² IV days 1, 8, 15, and 22	Every 28 days for 4 cycles
Carboplatin/ paclitaxel	Carboplatin AUC 6 IV day 1 Paclitaxel 200 mg/m² IV day 1	Every 21 days for 4 cycles
Cisplatin/ pemetrexed	Cisplatin 75 mg/m² IV day 1 Pemetrexed 500 mg/m² IV day 1	Every 21 days for 4 cycles (for nonsquamous histology only)



Patient Care Process for Lung Cancer

Collect

- Patient characteristics (eg, age, gender, ancestry)
- Patient history (past medical, family, social—dietary habits, tobacco use)
- Current medications and any prior anticancer therapy
- Symptoms of pain, pain score, pain management
- Clinical and objective evaluation of tumor status
- Objective data
  - BP, heart rate (HR), height, weight, respiratory rate
  - Labs (eg, serum electrolytes, complete blood count, Scr, BUN)
  - Imaging scans (CT scan, endobrachial ultrasound)

- Biopsy to obtain histology (NSCLC or SCLC, squamous or nonsquamous [Table 146-1])
- Tumor expressed biomarkers (PD-1, EGFR, ALK, ROS1, $BRAF^{V600E}$, NTRK)

Assess

- Type of and response to any prior treatments
- Stage of tumor (Table 146-2)
- Drug therapy options based on the cancer's histology, stage, and presence/absence of biomarkers
- Need for any dose adjustments based on renal or hepatic function or potential drug interactions
- Adverse effects from current anticancer regimen if this is second dose or second cycle
- Barriers to adherence for oral anticancer regimens
- Emotional status (eg, presence of anxiety, depression)

Plan*

- Goals of treatment (curative or palliative)
- Drug therapy regimen including drugs, dose, route, frequency, and duration (Tables 146-3 to 146-5)
- Supportive care plan (eg, antiemetics, premedications, infection prophylaxis, and medications for specific drugs [folic acid and vitamin B_{12} for pemetrexed])
- Patient education (eg, treatment plan and schedule, side effects and how to manage them)
- Provide tools to support adherence to oral anticancer agents and supportive care medications
- Encourage use of a diary to track pain medication and diarrhea/constipation medication use
- Referrals to other providers when appropriate (eg, physician, dietician, spiritual and/or psychological support, social work, nursing, palliative care or hospice)

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up for assessment of adverse effects and timing of next cycle of chemotherapy

Follow-up: Monitor and Evaluate

- Presence of adverse effects
- Measure complete blood count, renal/hepatic function, and electrolytes to determine the presence of serious adverse effects that warrant dose adjustments, delays, or discontinuation at the next cycle
- Assess for signs/symptoms of infection
- Inquire about pain symptoms
- Verify patient adherence to the treatment plan

**Collaborate with patient, caregivers, and other healthcare professionals.*

Adjuvant radiation should generally be avoided in patients with stage I or II disease who have complete resection and clean margins as it does not improve survival and can be detrimental. However, radiation, or more commonly chemoradiotherapy, can be indicated in specific situations. Patients who are medically inoperable should receive chemoradiotherapy if they can tolerate the combined modality therapy. Patients who have positive margins after resection should ideally undergo “re-resection”; if that is not possible, then radiation to the positive margin(s) with or without chemotherapy can be given. Concurrent rather than sequential administration of chemotherapy and radiation therapy is preferred when both treatment modalities are used. Platinum-based chemotherapy is usually given concurrently with radiotherapy; recommended regimens include cisplatin with either etoposide, vinblastine, or pemetrexed (only for nonsquamous histology) or carboplatin with either paclitaxel or pemetrexed (only for nonsquamous histology).[2] Neoadjuvant chemotherapy can be used in patients with early-stage disease. The trials and meta-analysis include stages I to III and are discussed below in the treatment of stage III disease.

Locally Advanced Disease (Stage III)

Patients with more advanced local disease have large tumors, multiple tumors, and/or nodal involvement—particularly mediastinal nodal involvement (N_2 or N_3 disease). This group of patients is heterogeneous and few large clinical trials are available to guide treatment. Therefore, treatment is best planned by a multidisciplinary team where individual features and the patient's preferences are considered. Optimal outcomes are achieved with multimodality therapy that typically includes systemic chemotherapy. For patients with stage III disease (large tumor [T_3 or T_4] or mediastinal node positive [N_2 or N_3]), radiation in the adjuvant or neoadjuvant setting with or without chemotherapy is recommended. Patients with operable disease should be considered for surgery preceded or followed by systemic chemotherapy. Adjuvant chemotherapy after surgery in selected patients improves overall survival (see Table 146-3).[2,15] The primary adjuvant trials included patients with stage IIIA disease and early-stage disease; 5-year survival in these studies improved by about 5%. Chemotherapy administration prior to surgery (ie, neoadjuvant) should also be considered to treat micrometastatic disease (if present) prior to surgery and reduce tumor size, making surgery easier and better tolerated. Two meta-analyses have reported that neoadjuvant chemotherapy improves 5-year survival by about 5% as compared with surgery alone.[25,26] The meta-analysis did not analyze what stage is most likely to benefit, what regimen is best, or how it would compare to surgery followed by adjuvant therapy. The potential benefit of reducing tumor size to make the surgery easier and, in some cases, feasible is most attractive for patients with larger tumors. Although a randomized controlled trial of neoadjuvant versus adjuvant therapy has not been reported, it appears that both approaches are equivalent and superior to surgery alone.

Radiation may be given in place of surgery as the local treatment modality combined with chemotherapy. Although a large definitive trial has not been performed to compare radiation and surgery in this subset of patients, this research question has been evaluated in small randomized trials. The largest trial randomized 333 stage IIIA (N_2) patients who responded to three cycles of induction chemotherapy to radiation or surgery. No significant difference in median overall survival (17.5 vs 16.3 months for radiation and surgery, respectively) or overall 5-year survival was observed.[27] These results suggest that surgery could be avoided by administering chemoradiotherapy because it does not improve survival. A few trials have evaluated the role of radiation therapy in patients receiving neoadjuvant chemotherapy and surgery. The only

phase III randomized trial (SAKK-16/00) compared neoadjuvant chemotherapy followed by surgery with sequential neoadjuvant chemoradiotherapy followed by surgery.[28] Event-free survival, overall survival, and local failure rate did not differ between groups. It is currently recommended that patients with resectable stage IIIA NSCLC be treated with chemotherapy followed by surgery or radiation, depending on individual patient and tumor features.[2,4]

Patients with stage IIIA disease who are not surgical candidates or have a tumor that cannot be resected, and nearly all stage IIIB patients, are typically treated with both an active platinum-containing regimen and concurrent radiotherapy. Patients with tumors that cannot fit safely in a radiation port may receive induction chemotherapy followed by chemoradiotherapy. Responding patients may then become surgical candidates. Patients who are not surgical candidates should receive concurrent chemotherapy and radiation. Patients who respond to chemotherapy (CR+PR+SD, about 80% of patients) should then receive maintenance therapy with durvalumab, a PD-L1 inhibitor. The recommendation for durvalumab maintenance is based on a phase III trial of 12 months of durvalumab therapy versus placebo in patients with unresectable stage III NSCLC whose disease had not progressed following chemoradiotherapy. Patients receiving durvalumab had significantly improved 2-year survival (66.3% vs 55.6%) and median progression-free survival (17.2 vs 5.6 months) as compared to placebo. Median overall survival was 28.7 months in the placebo group and had not yet been reached in the durvalumab group at the time of publication.[29] Patients with stage III disease who are not candidates for radiation are treated like those with stage IV disease.[2,4,5]

Advanced (Stage IV) and Relapsed Disease

About 55% of NSCLC patients have advanced disease (stage IV) at the time of diagnosis.[1,2,9] These advanced tumors are generally not surgically resectable. A few patients with single metastatic sites may undergo surgical resection of both the primary tumor and the metastatic site.[2,5] For patients who have a tumor that will fit in a tolerable radiation port, chemoradiotherapy can be considered, but systemic therapy is the primary treatment modality for most of these patients.

The treatment approach for NSCLC that has relapsed after initial treatment of localized disease is similar to the approach used for patients who have stage IV disease at the time of diagnosis. The goal of initial therapy in this setting is to palliate symptoms, improve quality of life, and increase the duration of survival. Therapy for advanced-stage NSCLC depends on patient-specific factors and tumor characteristics.

The most important patient-specific factor is performance status, as described in Chapter 144. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 are most likely to derive benefit from intensive treatment. Patients with an ECOG performance status of 2 or significant comorbidities should be considered for less intensive therapy (eg, single-agent therapy). Patients with poor ECOG performance status (3 or 4) do not respond well to chemotherapy and have a high likelihood of toxicity and should receive best supportive care and palliative radiation when necessary.[2,5]

Three pathways have been identified for advanced NSCLC: (1) immune sensitive (PD-L1+), (2) targetable genetic mutation-driven, which is further divided based on the mutation (EGFR, ALK, BRAF, NTRK, and ROS1), and (3) nonbiomarker-driven therapy treatment, which is further classified as squamous histology or nonsquamous histology due to drug toxicity and efficacy (see **Fig. 146-1**). Unlike tumors of nonsquamous histology, tumors of squamous histology did not usually harbor a targetable genetic mutation. Testing for these mutations in squamous tumors is encouraged, but optional for this patient population. However, like other histologies of NSCLC, squamous histology tumors should have PD-L1 testing to determine sensitivity to first-line immunotherapy.[2,8,9]

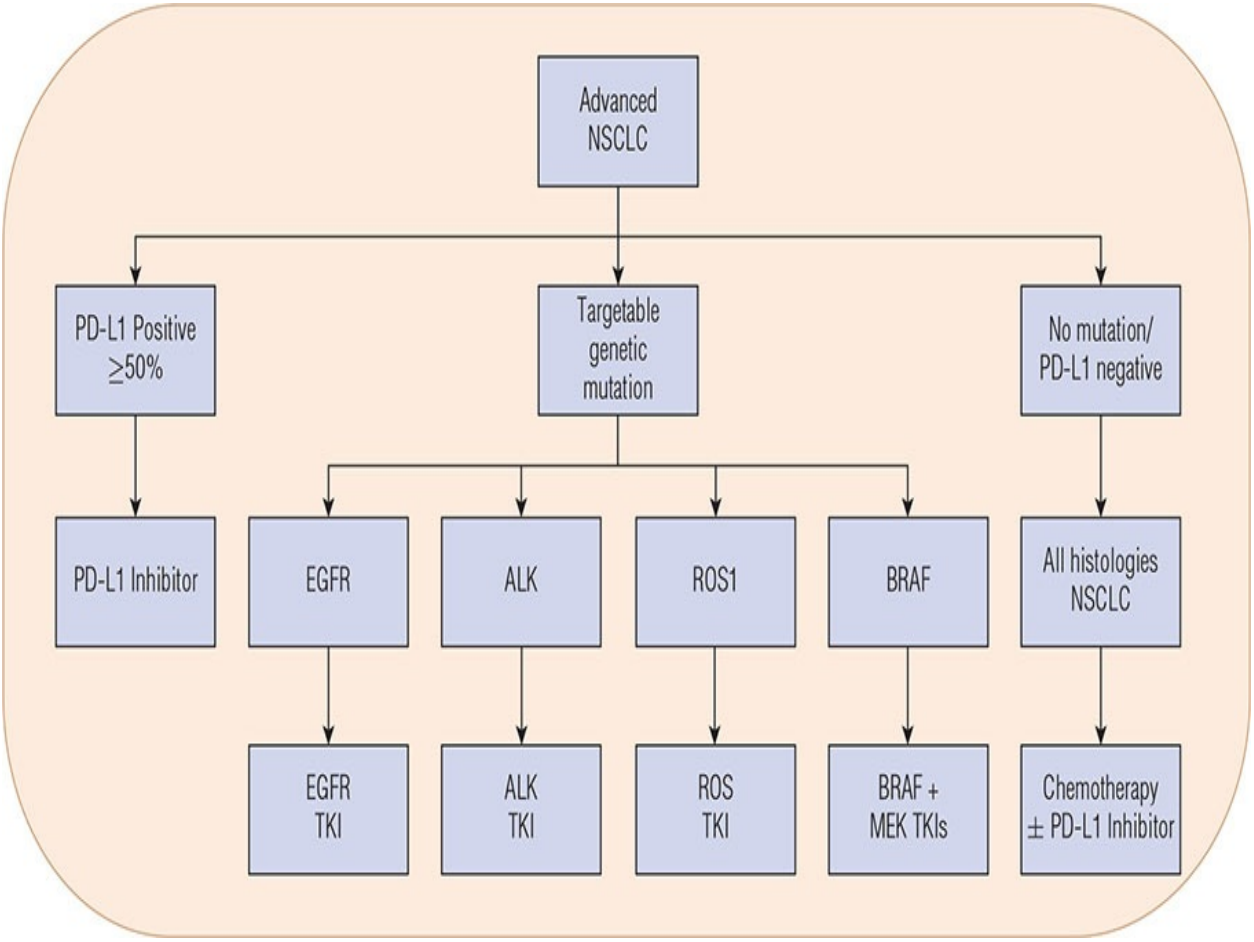


FIGURE 146-1 Treatment algorithm for advanced-stage NSCLC.

PD-L1 expression is currently tested with an immunohistochemistry assay; as it relates to treatment selection, a tumor is considered to be PD-L1+ if 1% or more of the viable tumor cells stain positive for PD-L1 expression (TPS ≥1%). Testing for targetable genetic mutations identifies tumors that harbor mutations in EGFR, ALK, ROS1, BRAF, or NTRK. Tumors that are negative for PD-L1 and do not harbor a targetable genetic mutation are further categorized as squamous or nonsquamous histology to guide treatment. Selected treatments for each group are listed in **Table 146-4**.

TABLE 146-4 Selected Regimens Used to Treat Advanced-Stage Nonsmall Cell Lung Cancer

	Nonbiomarker Driven							
	Nonsquamous		Squamous Cell		EGFR Mutation Positive		ALK Rearrangement Positive	
Place in Therapy	Regimen	Drugs, Doses, Frequency	Regimen	Drugs, Doses, Frequency	Regimen	Drugs, Doses, Frequency	Regimen	Drugs, Doses, Frequency
First line	Carboplatin/ paclitaxel/ bevacizumab	Carboplatin AUC 6 IV on day 1 Paclitaxel 200 mg/m² IV on day 1 Bevacizumab 15 mg/kg IV on day 1 Repeat cycle every 3 weeks × 6 cycles—bevacizumab maintenance until progression	Gemcitabine/ cisplatin	Gemcitabine 1,250 mg/m² IV on days 1 and 8 Cisplatin 75 mg/m² IV on day 1 Repeat cycle every 21 days × 6 cycles	Erlotinib	Erlotinib 150 mg (one 150 mg capsule) daily on an empty stomach	Crizotinib	Crizotinib 250 mg (one 250 mg capsule) twice daily without regard to meals
	Carboplatin/ pemetrexed	Carboplatin AUC 5 IV on day 1 Pemetrexed 500 mg/m² IV on day 1 Repeat cycle every 3 weeks	Carboplatin/ Paclitaxel/ Pembrolizumab	Carboplatin AUC 6 IV on day 1 Paclitaxel 200 mg/m² IV on day 1 or nab-paclitaxel 100 mg/m² IV on day 1, 8, 15 Pembrolizumab 200 mg IV on day 1 Repeat cycle every 3 weeks × 4 cycles—Pembrolizumab maintenance up to 31 additional doses or until progression	Afatinib	Afatinib 40 mg (one 40 mg tablet) daily on an empty stomach	Alectinib	Alectinib 600 mg (four 150 mg capsules) twice daily with food
	Platinum/ Pemetrexed/ Pembrolizumab	Cisplatin 75 mg/m² or Carboplatin AUC 5 IV on day 1 Pemetrexed 500 mg/m² IV on day 1 Pembrolizumab 200 mg IV on day 1 Repeat cycle every 3 weeks × 4 cycles—Pembrolizumab maintenance up to 31 additional doses or until progression			Osimertinib	Osimertinib 80 mg (one 80 mg tablet) daily without regard to meals		
	Carboplatin/ Paclitaxel/ Bevacizumab/ Atezolizumab	Carboplatin AUC 6 IV on day 1 Paclitaxel 200 mg/m² IV on day 1 Bevacizumab 15 mg/kg IV on day 1 Atezolizumab 1,200 mg IV on day 1 Repeat cycle every 3 weeks × 4 or 6 cycles—atezolizumab and bevacizumab maintenance until progression						
Second line	Docetaxel/ Ramucirumab	Docetaxel 75 mg/m² IV day 1 Ramucirumab 10 mg/kg IV day 1 Repeat every 21 days	Docetaxel/ Ramucirumab	Docetaxel 75 mg/m² IV day 1 Ramucirumab 10 mg/kg IV day 1 Repeat every 21 days	Osimertinib (if patient has not previously received)	Osimertinib 80 mg (one 80 mg tablet) daily without regard to meals	Brigatinib	Brigatinib 90 mg (one 90 mg tablet) daily for 7 days, then 180 mg (one 180 mg tablet) daily. Take without regards to meals
	Nivolumab	Nivolumab 3 mg/kg IV day 1 Repeat every 2 weeks	Nivolumab	Nivolumab 3 mg/kg IV day 1 Repeat every 2 weeks				
	Pembrolizumab	Pembrolizumab 2 mg/kg IV day 1 Repeat every 3 weeks	Pembrolizumab	Pembrolizumab 2 mg/kg IV day 1 Repeat every 3 weeks				

PD-L1+ Tumors 8 First-line therapy for patients with NSCLC with PD-L1+ tumors is pembrolizumab, an immune checkpoint inhibitor that binds to the PD1 receptor on T cells. A pivotal phase III trial that compared first-line pembrolizumab monotherapy to chemotherapy was published in 2016 and changed the standard of care.[30] That trial randomized 305 patients with newly diagnosed NSCLC with PD-L1+ tumors, defined as an expression threshold of 50% (TPS ≥50%) to pembrolizumab or a platinum doublet. The median progression-free survival was 10.3 months in the pembrolizumab arm versus 6.0 months in the chemotherapy arm (hazard ratio [HR] 0.50, $P < 0.001$), with a preliminary analysis demonstrating improved overall survival. Results of a larger randomized phase III trial comparing first-line pembrolizumab to chemotherapy in patients with NSCLC with a PD-L1 expression of 1% or more (TPS of ≥1%) confirmed the survival benefit of pembrolizumab.[31] After 24 months of follow-up, patients with tumors with the highest level of PDL-1 expression (TPS ≥50%) had a median overall survival of 20 months and 12 months in the pembrolizumab and chemotherapy arms, respectively. The survival benefit decreased as PD-L1 expression decreased, but survival was higher for the pembrolizumab in all groups. Although PD-L1+ tumors generally do not express a targetable genetic mutation, patients with a genetic mutation were excluded. In the second-line setting, PD-L1-based therapy has not been shown to prolong survival as compared to chemotherapy with docetaxel in patients with tumors with EGFR mutation.[32] If the tumor has high PD-L1 expression and a targetable genetic mutation, targeted therapy based on the genetic mutation is given because of its impressive activity.

Second-line therapy after failing first-line pembrolizumab therapy would be chemotherapy. It is not clear if a platinum doublet should be used or a single cytotoxic agent. If a platinum doublet is selected, then the regimen would be selected based on histology (as described below for tumors that are PD-L1 negative and have no targetable genetic mutations). If single-agent chemotherapy is selected, pemetrexed is preferred for non-squamous cell tumors and docetaxel with or without ramucirumab for squamous cell tumors (see Table 146-4)

Targetable Genetic Mutation 9 Patients with advanced lung cancer and a targetable genetic driver mutation have several treatment options based on the specific mutation: EGFR-positive, ALK-positive, ROS1-positive, $BRAF^{V600E}$-positive, or NTRK-positive. These mutations are most common in patients with

nonsquamous NSCLC. Genetic testing of tumors should be performed at the time of diagnosis in all patients, including those with localized disease.[2,5] Adverse events and monitoring parameters of select oral targeted therapies used in NSCLC are included in **Table 146-5**.

TABLE 146-5 Monitoring of Selected Oral Targeted Therapies for NSCLC

Drug	Adverse Reactions	Monitoring Parameters	Comments
EGFR Targeting			
Erlotinib	Common: • Rash • Diarrhea • Anorexia • Fatigue • Dyspnea • Cough • Nausea and vomiting Rare but serious: • Interstitial lung disease • Hepatotoxicity including hepatorenal syndrome • Gastrointestinal perforation • Severe rash, including Stevens-Johnson Syndrome and toxic epidermal necrolysis • Cerebrovascular accident • Hemolytic anemia with thrombocytopenia • Ocular disorders including corneal perforation, ulceration, or severe keratitis	• Skin exam to monitor development and progression of rash • CMP at baseline and periodically for renal failure, electrolyte loss, and hepatoxicity • Evaluate for signs and symptoms of interstitial lung disease including dyspnea, cough, and fever • Ophthalmic examinations periodically and at the onset of any changes in vision • Evaluate for signs and symptoms of hemorrhage if patients are receiving warfarin.	• Should be taken 1 hour before or 2 hours after meals • Increased risk of hemorrhage when taken with warfarin • Cytochrome P450 3A4 substrate, use with caution with 3A4 inducers/inhibitors • Best absorbed in acidic gastric environment • Resistance caused by T790M mutation
Afatinib	Common: • Diarrhea • Dermatologic reactions including dry skin and rash • Stomatitis • Paronychia • Anorexia • Nausea and vomiting • Pruritus Rare but serious: • Renal impairment from dehydration due to diarrhea • Interstitial lung disease • Severe rash, including Stevens-Johnson syndrome and toxic epidermal necrolysis • Hepatotoxicity • Keratitis	• Skin exam to monitor development and progression of rash • CMP at baseline and periodically for renal failure, electrolyte loss, and hepatoxicity • Evaluate for signs and symptoms of interstitial lung disease including dyspnea, cough, and fever • Ophthalmic examinations periodically and at the onset of any changes in vision	• Should be taken 1 hour before or 2 hours after meals • Diarrhea can be severe and require dose reduction of afatinib • Patients with reduced ejection fraction excluded from clinical trials • Pharmacokinetics may be affected by P-glycoprotein inhibitors (eg, verapamil, cyclosporine, amiodarone) and inducers (eg, carbamazepine, phenytoin) • Resistance caused by T790M mutation
Osimertinib	Common: • Diarrhea • Dermatologic reactions including dry skin and rash • Stomatitis • Paronychia • Anorexia • Fatigue • Myelosuppression Rare but serious: • Interstitial lung disease • QTc Interval prolongation • Cardiomyopathy • Keratitis	• Skin exam to monitor development and progression of rash • BMP at baseline and periodically for electrolyte loss, due to diarrhea • Evaluate for signs and symptoms of interstitial lung disease including dyspnea, cough, and fever • Ophthalmic examinations periodically and at the onset of any vision changes • CBC at baseline and periodically for myelosuppression • ECG should be monitored periodically in patients with congenital long QTc syndrome, heart failure, electrolyte abnormalities, or concomitantly receiving other QT prolonging agents • Ejection fraction should be monitored at baseline and periodically in patients at risk for developing heart failure or if patients develop cardiac symptoms	• Activity not effected by T790M mutation • Improved CNS activity compared to other EGFR targeting agents • Dose should be increased by 50% if patient is also taking strong cytochrome P450 3A4 inducer (eg, phenytoin, carbamazepine, topiramate, rifampin)
ALK Targeting			
Crizotinib	Common: • Vision disorders • Nausea and vomiting • Diarrhea • Edema • Constipation • Hepatotoxicity • Fatigue • Anorexia • Dizziness • Neuropathy • Lymphopenia and neutropenia • Upper respiratory infection, including possible pneumonia Rare but serious: • Interstitial lung disease • QTc Interval prolongation • Bradycardia • Pulmonary embolism	• Evaluate for signs and symptoms of interstitial lung disease including dyspnea, cough, and fever • BMP periodically to monitor electrolytes in patients at risk for QT-prolongation • Ophthalmic evaluation in patients with new-onset vision changes • CBC with differential monthly for leukopenia and neutropenia • Liver function tests every 2 weeks for the first 2 months, then monthly • ECG should be monitored periodically in patients with heart failure, bradyarrhythmias, electrolyte abnormalities, or concomitantly receiving other QT prolonging agents • Heart rate and blood pressure should be monitored regularly due to bradycardia	• Also used for ROS-1 positive NSCLC • Fatal hepatoxicity has occurred • Ocular toxicity can lead to severe vision loss • Cytochrome P450 3A4 substrate, should not be used with strong inhibitors or inducers of 3A4.

Alectinib	Common: • Edema • Constipation • Anemia • Leukopenia • Hepatotoxicity • Myalgia • Fatigue Rare but serious: • Interstitial lung disease • Bradycardia • Endocarditis • Gastrointestinal perforation • Increased creatine kinase • Renal impairment • Pulmonary embolism	• Evaluate for signs and symptoms of interstitial lung disease including dyspnea, cough and fever • BMP periodically to monitor renal function • CBC with differential monthly for leukopenia and neutropenia • Liver function tests every 2 weeks for the first 3 months of treatment then monthly • Heart rate and blood pressure should be monitored regularly due to bradycardia • CPK every 2 weeks for the first month of treatment and with patient reports of unexplained muscle pain, tenderness, or weakness.	• Should be taken with meals
Brigatinib	Common: • Hyperglycemia • Diarrhea • Increased serum lipase and amylase • Nausea • Increased creatine kinase • Cough • Fatigue Rare but serious: • Interstitial lung disease • Hypertension • Bradycardia • Pneumonitis, including pneumonia • Visual disturbances	• Evaluate for signs and symptoms of interstitial lung disease including dyspnea, cough and fever • Ophthalmic evaluation in patients with new-onset vision changes • Blood pressure should be monitored after 2 weeks then monthly • Heart rate and blood pressure should be monitored regularly due to bradycardia • CPK levels should be monitored regularly during treatment • Fasting serum glucose at baseline and regularly during treatment • Lipase and amylase levels should be monitored regularly during treatment.	• Start dose at 90 mg daily for 7 days, then increase to 180 mg daily if tolerated • Cytochrome P450 3A4 substrate, should not be used with moderate-to-strong inhibitors or inducers of 3A4

Tumors should be tested for mutations in the kinase domain of EGFR (exon 18–exon 24). Deletion mutations in exon 19 and point mutations in exon 21 are the most common, comprising about 90% of EGFR mutations. The only mutation associated with resistance to EGFR inhibitors is an insertion mutation in exon 20, which results in steric hindrance that prevents the drug from binding to the kinase. The prevalence of EGFR mutations varies depending on tumor histology, ethnicity, gender, and smoking history. The highest prevalence occurs in adenocarcinomas, patients of Asian descent, female gender, and nonsmokers. The overall prevalence is 32% of NSCLC patients worldwide.[33]

Patients with a tumor that harbors an activating mutation in the EGFR receptor should receive a first-line EGFR tyrosine kinase inhibitor.[5] In prospective randomized trials, first-generation EGFR inhibitors (erlotinib and

gefitinib) provide superior progression-free survival as compared to traditional chemotherapy regimens. The second-generation inhibitor afatinib has also been shown to be better than chemotherapy as first-line therapy. A meta-analysis compared the EGFR inhibitors (erlotinib, gefitinib, and afatinib) to chemotherapy in patients with the two most common EGFR mutation types (exon 19 deletion and exon 21 L858R mutation) and subgroup comparisons by EGFR inhibitor type (reversible binding vs irreversible binding).[34] The analysis showed that patients with an exon 19 deletion had improved overall survival (HR 0.72, 95% CI: 0.60-0.88). The analysis was not able to account for cross over from chemotherapy to an EGFR tyrosine kinase inhibitor.[34] The meta-analysis suggested that these three agents have similar overall progression-free survival results (about 11 months) and response rates that are about two times higher than chemotherapy. The meta-analysis also showed that prognosis with exon 19 deletion is better than exon 21 L858R mutation.[34] Dacomitinib, another second-generation irreversible inhibitor has been compared to gefitinib in this population. In the ARCHER 1050 trial, patients were randomized to dacomitinib or gefitinib in a study that enrolled predominantly Asian patients. The study reported improved median progression-free survival (14.7 vs 9.2 mo; HR 0.59, $P < 0.0001$) and median overall survival (34.1 vs 26.8 mo; HR 0.76, $P = 0.043$) in patients treated with dacomitinib as compared with gefinitib.[35,36]

Osimertinib, a third-generation EGFR tyrosine kinase inhibitor, shows the most impressive activity in patients with EGFR-positive tumors. The FLAURA trial randomized 556 patients with EGFR-positive NSCLC receive first-line osimertinib or either gefitinib or erlotinib (prescriber choice). Patients receiving osimertinib had significantly longer progression-free survival (18.9 vs 10.2 mo; HR 0.46, $P < 0.001$). At the time of publication, median overall survival had not been reached, but the survival rate at 18 months favored osimertinib (83% vs 71%; HR 0.63, $P = 0.007$). Two other endpoints in this trial that favored osimertinib were the improved CNS response rate and lower rate of CNS disease defining progression, which is consistent with the improved CNS penetration of osimertinib versus first-generation agents. This finding is important for NSCLC patients because more than half will develop CNS metastasis during their disease course.[37] Osimertinib is also better tolerated than the first-generation agents, which is consistent with the lower affinity for wild-type EGFR. These characteristics make osimertinib the preferred agent to target EGFR-mutation positive tumors.[2]

Subsequent therapy after progression during treatment with an EGFR inhibitor depends on initial treatment and further genetic evaluation of the tumor.

No specific mutation-driven treatment approach is recommended but participation in a clinical trial is recommended. However, many clinicians will repeat tumor genetic testing to identify targetable mutations before starting standard therapy with a platinum doublet with or without immunotherapy. If patients received initial therapy with a first- or second-generation agent, testing for the acquired T790M mutation should be conducted. If the tumor tests positive for T790M, osimertinib is the drug of choice. If the patient received initial therapy with osimertinib, evaluation should be performed to screen for the C797S mutation. This mutation confers resistance to osimertinib, but the tumor may respond to a first-generation agent. Regardless of the initial therapy, cMET amplification should be assessed. If this mutation is present, a combination of an EGFR inhibitor with a drug that inhibits cMET, such as crizotinib, may be effective.

In summary, patients with advanced NSCLC that harbors an EGFR mutation should be treated with first-line osimertinib. Upon progression, patients can be retested for an additional targetable mutation/amplification, but most patients will proceed to a platinum doublet with or without an immunotherapy agent.

The presence of an ALK rearrangement represents another therapeutic target for patients with advanced NSCLC. The ALK mutation is less common than EGFR mutations, occurring in 2% to 5% of lung cancer patients.[38] Several ALK inhibitors have been approved for use in these patients. Crizotinib, the first approved ALK inhibitor, is superior to chemotherapy as initial therapy for ALK-positive advanced NSCLC. The median progression-free survival was 10.9 months versus 7 months ($P < 0.001$) favoring crizotinib.[39] Ceritinib is the first of the second-generation ALK inhibitors, and it improved median progression-free survival from 8.1 to 16.6 months (HR 0.55, $P < 0.00001$).[40] Both agents are approved as first-line therapy in ALK-positive advanced NSCLC. Alectinib and brigatinib are second-generation ALK inhibitors that have been compared to crizotinib in this population.[41,42] In the ALEX trial, 303 patients with advanced ALK-positive NSCLC were randomized to first-line alectinib or crizotinib. A recent update of this trial reported the significantly longer median progression-free survival in the alectinib group (34.8 vs 10.9 months; HR 0.43).[41] In the ALTA-1L trial, brigatinib also improved 12-month progression-free survival as compared to crizotinib (67% vs 43%; HR 0.49, $P < 0.001$). The median follow-up in ALTA-1L was significantly shorter (10 months) than in the ALEX trial (about 25 months).[42] Based on these results, alectinib received FDA approval for first-line therapy. While brigatinib results are promising, the data are immature and it has not received FDA approval for first-line therapy. Based on this

evidence, patients with ALK-positive advanced NSCLC should receive initial treatment with an ALK inhibitor, with a preference for alectinib.[2]

Patients who relapse while receiving initial ALK-targeted therapy may be treated with lorlatinib, a third-generation ALK inhibitor. Lorlatinib was recently approved as second-line therapy after failure on a first-line ALK inhibitor (crizotinib, ceritinib, or alectinib). FDA approval was based on a global phase II expansion cohort study that reported a progression-free survival of 5.5 months after prior alectinib, ceritinib, or brigatinib therapy.[43] In that trial, 62 subjects were treated with lorlatinib after prior alectinib treatment and 37% of these patients responded and 3% had a complete response. Among the 37 patients previously treated with alectinib who had intracranial disease, 16 (43%) achieved a CNS response, including 9 (24%) who had a complete remission. Although these data and approval are new, lorlatinib is becoming the standard second-line therapy for patients with ALK-mutated NSCLC.

Mutation in ROS1 is a rare genetic driver of NSCLC that occurs in about 1% of patients. It has proven to be a highly active target for drug therapy with crizotinib. In a study of 50 patients with metastatic, ROS1-positive NSCLC, regardless of prior chemotherapy for metastatic disease, crizotinib had a 72% response rate, including a 6% complete response rate.[44] The median progression-free survival was 19.2 months. Although this study did not have a comparison group, crizotinib is recommended as treatment for metastatic ROS1-positive NSCLC based on these positive results.[2] The global expansion cohort study with lorlatinib had a ROS1 arm that enrolled 47 patients; 13 were crizotinib naïve and 34 had prior crizotinib. The overall response rate was 36%. Among the 25 patients with CNS disease, 14 had a CNS response. The median progression-free survival was 9.9 months.[45] Crizotinib remains the standard of care for this population, with lorlatinib as second-line therapy.

For the 1% to 2% of patients with metastatic adenocarcinoma who have the $BRAF^{V600E}$ mutation, the combined use of trametinib, a MEK inhibitor, and dabrafenib, an inhibitor of some mutated BRAF kinases, has been shown to be beneficial. In a phase II study, 36 patients with metastatic NSCLC positive for $BRAF^{V600E}$ mutation who had not received prior treatment for metastatic disease were enrolled. The combination of trametinib and dabrafenib was active, with a response rate of 64%, including complete responses in 6% of patients. The median progression-free survival was 10.9 months.[46] This combination also showed benefit in a separate study of 57 patients who had received prior chemotherapy for metastatic disease. The results of that study were similar, with a response rate of 63% including some complete responses. The median

progression-free survival was 9.7 months.[47] Based on these data, this combination of kinase inhibitors is approved for the treatment of patients with metastatic $BRAF^{V600E}$-positive lung cancer, regardless of prior chemotherapy use.[2]

Larotrectinib is a novel agent that is approved for the treatment of adult and pediatric patients with a metastatic solid tumor that is positive for a neurotrophic receptor kinases (NTRK) gene fusion. It is estimated that 0.2% of patients with NSCLC have this genetic driver of tumor growth. Larotrectinib's approval is based on a study of patients with a variety of solid tumors, including NSCLC. The study had a limited sample size of 55 patients, 4 of whom had NSCLC. The study demonstrated an overall response rate of 75% and a 1-year survival rate of 90%. Side effects were generally mild, including primarily grade 1/2 increased liver function tests, fatigue, nausea, and diarrhea. The most common grade 3 side effect was anemia (11%).[2,48]

After options targeting genetic mutations have been exhausted, other systemic therapies may be considered. In the uncommon situation where the patient's tumor is PD-L1 positive, pembrolizumab as monotherapy should be considered, but most patients will start down the "nonbiomarker-driven" pathway.

Nonbiomarker Driven For patients with metastatic NSCLC who are not candidates for targeted therapies or have progressed despite targeted therapies and are candidates for further therapy, combination chemotherapy is the preferred treatment option. Historically, platinum-based doublets consisting of cisplatin or carboplatin combined with paclitaxel (or nab-paclitaxel), docetaxel, gemcitabine, pemetrexed, or vinorelbine are considered the standard and are equally effective in this population.[2,5] Based on an intergroup study that compared four regimens, carboplatin and paclitaxel had slightly less toxicity and was considered by ECOG to be the standard of care.[49] Another chemotherapy option for patients with nonsquamous NSCLC is platinum with pemetrexed. A phase III trial of NSCLC patients compared six cycles of cisplatin and either gemcitabine or pemetrexed. When overall survival was analyzed by histology, cisplatin and pemetrexed was superior to cisplatin and gemcitabine in patients with nonsquamous NSCLC, but cisplatin and pemetrexed had lower progression-free survival and similar overall survival as compared to the gemcitabine arm in patients with squamous NSCLC. The cisplatin and pemetrexed had less neutropenia, anemia, and thrombocytopenia but more nausea than cisplatin and gemcitabine.[50] The benefit of pemetrexed for nonsquamous NSCLC and its limited activity in squamous NSCLC was confirmed in other studies of its use as

a second-line agent and as maintenance therapy.

To evaluate the addition of a targeted agent, ECOG performed a prospective randomized trial that compared carboplatin and paclitaxel for six cycles with or without bevacizumab 15 mg/kg every 3 weeks.[51] The bevacizumab was continued until progression or unacceptable toxicity. As a result of bleeding complications seen in the phase II trial, patients with squamous cell carcinoma or brain metastases were excluded. The addition of bevacizumab led to longer median progression-free survival (6.2 vs 4.5 months, $P < 0.001$), median overall survival (12.3 vs 10.3 months, $P = 0.003$), and 1-year survival (51% vs 44%).[51] The NCCN guideline recommends the addition of bevacizumab to chemotherapy for patients with advanced NSCLC of nonsquamous cell histology, no history of recent significant hemoptysis, no CNS metastasis, and not receiving therapeutic anticoagulation.[2] Cisplatin and pemetrexed have not been directly compared with carboplatin, paclitaxel, and bevacizumab and both regimens are listed as treatment options in nonsquamous NSCLC.

The most recent treatment advance for metastatic NSCLC is the addition of PD-1 or PD-L1 inhibitors, regardless of the level of PD-L1 expression. The KEYNOTE-407 study evaluated the addition of pembrolizumab to chemotherapy that contained carboplatin and paclitaxel or nab-paclitaxel (prescriber's choice) in the treatment of metastatic squamous NSCLC.[52] Patients treated with the pembrolizumab-containing regimen had improved median progression-free survival (6.4 vs 4.8 months; HR 0.56, $P < 0.001$) and overall survival (15.9 vs 11.3 months; HR 0.64, $P < 0.001$). The KEYNOTE-189 study evaluated the addition of pembrolizumab to chemotherapy that contained a platinum agent and pemetrexed in the treatment of metastatic nonsquamous NSCLC.[53] Similar to the results of the KEYNOTE-407, pembrolizumab prolonged median progression-free survival (8.8 vs 4.9 mo; HR 0.52, $P < 0.001$) and 12-month overall survival (69.2% vs 49.4%; HR 0.49, $P < 0.001$) in these patients with nonsquamous disease. The IMpower150 study evaluated the addition of atezolizumab, a PD-L1 inhibitor, to treatment with carboplatin, pemetrexed, and bevacizumab in patients with nonsquamous NSCLC.[54] A third arm of the trial included the combination of carboplatin, pemetrexed, and atezolizumab, but the results for this arm have not been reported. Unlike the pembrolizumab-chemotherapy studies, the IMpower150 study enrolled patients with EGFR and ALK mutations if they had failed at least one prior therapy targeting the mutation. The data were analyzed in multiple groups with each favoring the group receiving the atezolizumab-containing regimen. The addition of atezolizumab resulted in significantly longer median progression-free survival

for all patients (8.3 vs 6.8 months, HR 0.61), patients without EGFR or ALK mutations (8.3 vs 6.8 months, HR 0.62), and patients with an EGFR or ALK mutation (9.7 vs 6.1 months, HR 0.59). This is the first study to show benefit in progression-free survival from the addition of immunotherapy to a chemotherapy-based regimen in patients with EGFR or ALK mutation. Median overall survival was longer in patients without a mutation (19.2 vs 14.7 months; HR 0.78, $P = 0.02$), but was not reported for other patient groups. Based on these trials, the addition of anti-PD-L1 directed therapy is clearly beneficial for patients with all types of NSCLC. With longer follow-up of these trials, including comparative data from IMpower150 for the arm not containing bevacizumab, the true magnitude of benefit will be observed. Clinical guidelines recommend the combination of PD-1 or PD-L1 directed therapy and chemotherapy as first-line therapy for patients with nonbiomarker-driven NSCLC.[2]

Maintenance therapy is the ongoing use of one or more agents after a positive tumor response to four to six cycles of an initial chemotherapy regimen until disease progression.[2] Several studies show that continuation or switch maintenance therapy improves survival of NSCLC patients with nonsquamous histology.[5] In continuation maintenance therapy, patients receive ongoing treatment with at least one of the agents used in the initial chemotherapy regimen. Alternatively, switch maintenance therapy starts a new agent not included in the initial regimen. Pemetrexed is the most established maintenance chemotherapy option. A meta-analysis showed that pemetrexed, given as maintenance therapy, provided a consistent overall survival benefit.[55] This benefit, however, was limited to patients with nonsquamous NSCLC. Neither docetaxel nor gemcitabine was shown to improve overall survival. Erlotinb was also evaluated, but the benefit seen in erlotinib was limited to patients with EGFR mutation. Bevacizumab has also been evaluated as continuation maintenance in patients with nonsquamous NSCLC.[56] A retrospective study reported improved progression-free and overall survival in patients who continued bevacizumab after completing initial chemotherapy with bevacizumab. The use of pemetrexed and bevacizumab maintenance has been evaluated. A meta-analysis of trials of combined pemetrexed and bevacizumab maintenance therapy showed improved progression-free survival. However, no difference in overall survival was observed and the combination resulted in more toxicity.[57] Because of concerns about efficacy (pemetrexed) and safety (bevacizumab), maintenance with these agents is not recommended for patients with squamous NSCLC. Based on the benefit of maintenance therapy, the

pembrolizumab and chemotherapy (KEYNOTE-189 and -407) and atezolizumab, bevacizumab, and chemotherapy (IMpower150) trials included maintenance therapy with the monoclonal antibody components of their regimens.

Relapsed Disease Monotherapy with nivolumab, pembrolizumab, atezolizumab, docetaxel, or pemetrexed is the most commonly considered options for second-line therapy in patients with a good performance status who progress during or after first-line chemotherapy.[2,5] The PD-1 inhibitors, nivolumab and pembrolizumab, and PD-L1 inhibitor, atezolizumab, are options in the second-line setting for patients who have not previously received one of the drugs in the class. A meta-analysis of randomized trials of PD-1 inhibitors found that these agents significantly improved overall survival, progression-free survival, and duration of response as compared to single-agent chemotherapy.[58] This benefit was seen in both squamous and nonsquamous NSCLC. Clinical benefit from PD-1 inhibitors is superior compared to docetaxel regardless of the level of PD-1 expression. However, patients with higher levels of PD-1 expression received an even greater benefit than those patients with low-level expression.

Docetaxel was the first chemotherapy to receive FDA approval for the treatment of advanced NSCLC after failure of a platinum-based chemotherapy regimen. Docetaxel, at the 75 mg/m^2 dose, was superior to best supportive care in terms of time-to-disease progression (10.6 vs 6.7 weeks, $P = 0.001$), median survival (7.5 vs 4.6 months, $P = 0.047$), and 1-year survival (37% vs 11%, $P = 0.003$).[59] Docetaxel also significantly improved 1-year survival when compared with a control regimen of vinorelbine or ifosfamide (21% and 19%, respectively).[60] The efficacy of docetaxel has recently been improved with the addition of ramucirumab. A large randomized trial of docetaxel with or without ramucirumab reported longer progression-free survival (4.5 vs 3 months, $P < 0.0001$) and overall survival (10.5 vs 9.1 months, $P = 0.023$) favoring the ramucirumab arm.[61] Response by histology was not analyzed, but ramucirumab appeared to be active in all histologies. Due to the relatively modest improvement in survival, clinicians must decide if the benefit outweighs the risks in adverse effects and cost. Although ramucirumab binds to the VEGF receptor, it is important to note that safety concerns (serious and fatal bleeding) like those seen with bevacizumab and chemotherapy in squamous histology were not reported.

The second chemotherapy agent approved as second-line treatment is pemetrexed. The approval was based on results of a phase III trial that

randomized 571 patients to receive either pemetrexed 500 mg/m^2 with folate and cyanocobalamin supplementation or docetaxel 75 mg/m^2. No significant differences in overall response rate, stable disease, or median survival between the pemetrexed and docetaxel arms were observed. Docetaxel had significantly more hematologic toxicities as compared with pemetrexed, leading to more hospitalizations and use of hematopoietic growth factors and erythropoiesis-stimulating agents. Patients receiving docetaxel had a significantly higher incidence of alopecia, while patients receiving pemetrexed had a significantly higher elevation of alanine aminotransferase.[62] Pemetrexed is a preferred chemotherapy option based on this study, but it is not appropriate as second-line therapy when it is used as maintenance therapy. It is also important to note that pemetrexed should not be used for patients with squamous NSCLC.

The comparative trials indicate that pemetrexed and docetaxel are equally effective,[62] and docetaxel plus ramucirumab is superior to docetaxel alone.[61] Similarly, nivolumab, pembrolizumab, and atezolizumab are superior to docetaxel alone.[63] All five monotherapies and ramucirumab-docetaxel are acceptable regimens, but guidelines list nivolumab, pembrolizumab, or atezolizumab as preferred.[2] This recommendation is likely attributed to the impressive durability of response. However, docetaxel with or without ramucirumab has emerged as a standard second-line option because immunotherapy and pemetrexed are commonly used first line and as maintenance.

Third-line therapy (and beyond) is reasonable for patients who have a good performance status and can tolerate another agent. Monotherapy with an active agent would typically be used in this setting. For patients who received a PD-L1 guided therapy, docetaxel would be an option with or without ramucirumab. For those who received second-line docetaxel with or without ramucirumab, an immune checkpoint inhibitor would be an option. For patients who want treatment beyond third-line, a single agent could be used.[2,5] The best agent(s) has not been determined in clinical trials. Therapeutic decisions are based on patient-specific factors including prior therapies and potential contraindications to specific agents. The most common treatment option is monotherapy with an agent known to have activity in clinical trials.[2]

In summary, patients with advanced-stage NSCLC should have their tumor tested for histology and those with a nonsquamous histology should be tested for an EGFR mutation or ALK rearrangement. Based on these findings, patients can be categorized into one of four distinct groups with different treatment pathways and prognosis. A better understanding of tumor biology has resulted in the

development of targeted drugs and personalized therapy, which will hopefully improve the prognosis for most patients.

Elderly and Poor-Performance Status Single-agent chemotherapy is an alternative in elderly patients or those with an ECOG performance status of 2.[64] First-line, single-agent chemotherapy has objective response rates of 5% to 25% with no significant effect on overall survival. Complete responses are rare and responses that do occur are of brief duration (ie, 2-4 months).[65,66] Among the most active cytotoxic chemotherapy agents in NSCLC are cisplatin, carboplatin, docetaxel, paclitaxel, etoposide, gemcitabine, ifosfamide, irinotecan, topotecan, mitomycin, vinblastine, vinorelbine, and pemetrexed.[2] Targeted therapies are also active as a single agent and should be considered in patients with a mutation-positive tumor.

Historically, patients with an ECOG performance status 2 were excluded from NSCLC trials because of excessive toxicity with minimal benefit from combination cytotoxic therapy. A recent randomized phase III trial comparing single-agent weekly docetaxel with docetaxel and gemcitabine in elderly or poor performance status (35% of patients) had disappointing results.[67] No survival differences were observed between the two treatment arms in the 122 poor-performance status patients (3.8 vs 2.9 months, respectively) and the median survival is short compared with patients with good performance status.[67] Another randomized phase III trial compared single-agent gemcitabine with gemcitabine/carboplatin in patients with ECOG performance status 2.[68] The median overall survival was not different between gemcitabine and gemcitabine/carboplatin (5.1 vs 6.7 months, respectively). The authors concluded that single-agent therapy is still the standard in this setting.[69] The updated ASCO guidelines state that available data support the use of single-agent and combination chemotherapy, but are relatively weak and incorporate elderly and poor performance status patients. They emphasize the need to individualize this decision.[5] A recent meta-analysis shows that patients with performance status 2 benefit from treatment.[70] The NCCN guidelines list both single agents and combinations for patients with a performance status of 2, and best supportive care for patients with a performance status of 3 or 4 unless they have an EGFR mutation or ALK rearrangement where they can receive a tyrosine kinase inhibitor.[2]

Evaluation of Therapeutic Outcomes

For patients who have undergone surgical resection with or without

chemotherapy, radiation, or both, a physical examination and chest radiography are recommended every 3 to 4 months for the first 2 years, then every 6 months for 3 years, and then annually. In addition, a low-dose spiral chest CT scan is recommended annually to monitor for evidence of local recurrence. Suspicious symptoms or physical findings (eg, bone pain, visual abnormalities, headache, or elevated liver function tests) should prompt an evaluation to rule out distant metastases.[2,5]

Tumor response to chemotherapy is generally evaluated at the end of the second or third cycle and at the end of every second cycle thereafter. Patients with stable disease, with an objective response, or with a measurable decrease in tumor size (complete or partial response) should continue until four to six cycles have been administered. Patients with nonsquamous histology tumors who respond (ie, nonprogressive disease) should be considered for maintenance therapy with pemetrexed. Following initial therapy for NSCLC, patients must be monitored for evidence of disease progression.[2,5] Second-line therapy and beyond is traditionally given until progression. The immune checkpoint inhibitors can display a different response pattern than traditional chemotherapy or targeted therapy. It can take some time for the immune system to become activated and then the tumor will initially be infiltrated with cytotoxic lymphocytes that can appear radiographically as progression prior to a response. The median time-to-response for immune checkpoint inhibitors is 10 to 12 weeks. Although the registry trials continue to assess response based on RECIST criteria, an immune response criterion has been proposed where progression needs to be documented on two consecutive assessments at least 4 weeks apart.[71]

Small Cell Lung Cancer

Small cell lung cancer is a rapidly dividing malignancy that spreads early in the disease course. Consequently, about 60% to 70% of patients present with extensive-stage disease. When patients with SCLC are not treated, the disease quickly becomes fatal. Fortunately, SCLCs are very responsive to chemotherapy and radiation. Chemotherapy with or without radiotherapy is the treatment of choice for most patients. Even after a complete response to therapy, the cancer usually recurs within 6 to 8 months, and survival time following recurrence is typically short (about 4 months). With treatment, median survival rates for patients with limited and extensive disease are 14 to 20 and 9 to 11 months, respectively. Treatment planning starts with stage of disease (ie, limited vs extensive stage), but must also consider other factors, including performance

status (treatment usually restricted to performance status 0 or 1), patient age, comorbid conditions (eg, renal failure), and patient desire to receive treatment.[3,6]

Limited Disease

7 When a single SCLC mass is found, local therapy with radiation or surgery is considered, although the use of surgery in SCLC is limited to solitary nodules, without evidence of metastasis to lymph nodes. One of the differences between SCLC and NSCLC is that radiation is preferred for treatment of local disease over surgery. Radiation is always combined with chemotherapy in limited-stage SCLC, and the regimen of choice is etoposide and cisplatin (ie, EP regimen). Carboplatin may be substituted for cisplatin to reduce nausea and vomiting, nephrotoxicity, or neurotoxicity,[72] although increased myelosuppression in the form of thrombocytopenia may result. Alternative regimens have failed to demonstrate improved outcomes compared to EP plus concurrent radiation and typically have more toxicity.[73] Guidelines recommend that the EP regimen be used with concurrent radiotherapy.[3,6] Regimens used in the treatment of SCLC can be found in **Table 146-6**. Because patients with SCLC commonly have a recurrence in the CNS, trials have been performed to evaluate the benefit of prophylactic cranial irradiation (PCI). A pivotal study showed that PCI reduces the incidence of brain metastasis and increases 3-year survival from 15% to 21%.[74,69] Therefore, patients who achieve a complete response with treatment should be offered PCI.

TABLE 146-6 Chemotherapy Regimens Used in the Treatment of SCLC

	Regimen	Drugs and Doses
First Line	Etoposide/ cisplatin (EP)	Cisplatin 75 mg/m² IV on day 1 Etoposide 100 mg/m² IV on days 1-3; repeat cycle every 3 weeks for 4-6 cycles or Cisplatin 60 mg/m² IV on day 1 Etoposide 120 mg/m² IV on days 1-3; repeat cycle every 3 weeks for 4-6 cycles
	Etoposide/ carboplatin (EC)	Carboplatin AUC 5-6 IV on day 1 Etoposide 120 mg/m² IV on days 1-3; repeat cycle every 3 weeks for 4-6 cycles
	Cisplatin/ irinotecan (IP)	Cisplatin 60 mg/m² IV on day 1 Irinotecan 60 mg/m² IV on days 1, 8, 15; repeat cycle every 4 weeks for 4-6 cycles or Cisplatin 30 mg/m IV on day 1 Irinotecan 65 mg/m IV on days 1 and 8; repeat cycle every 3 weeks for 4-6 cycles
	EC + atezolizumab[a]	Carboplatin AUC 5 IV on day 1 Etoposide 100 mg/m IV on days 1-3 Atezolizumab 1,200 mg IV on day 1; repeat cycle every 3 weeks for 4 cycles followed by Atezolizumab 1,200 mg every 3 weeks as maintenance
Second Line	Topotecan	Topotecan 1.5 mg/m²/day IV days 1-5; repeat every 3 weeks
	Nivolumab	Nivolumab 3 mg/kg IV; repeat every 2 weeks

[a]Extensive stage only.

Extensive Disease

Historically, platinum regimens have been the treatment of choice in extensive disease as studies have failed to show superiority to the EP regimen as first-line treatment. A combination of irinotecan and cisplatin in one Japanese study demonstrated an increased median survival time by about 3 months over the EP regimen. This regimen showed a lower incidence of severe neutropenia but exhibited higher rates of moderate-to-high grade diarrhea in an Asian population.[75] However, irinotecan and cisplatin failed to improve survival as compared with EP in a study conducted in the United States.[76] Therefore, EP

remains the regimen of choice for treating extensive-stage SCLC in the United States, with irinotecan and cisplatin reserved as an acceptable alternative. As in limited disease, carboplatin is an acceptable substitute for cisplatin in EP.[72]

8 The addition of a PD-L1 inhibitor to chemotherapy may be beneficial in this patient population. The IMpower133 study randomized 403 patients with extensive disease SCLC to receive carboplatin (AUC = 5, day 1) with etoposide (100 mg/m^2, days 1-3) with or without atezolizumab (1,200 mg, day 1) every 3 weeks for 4 cycles. Patients were enrolled without regard to PD-1 expression on tumors. Patients randomized to atezolizumab continued atezolizumab maintenance every 3 weeks until disease progression. Patients randomized to atezolizumab and chemotherapy had an improved median progression-free survival (5.2 vs 4.3 months, HR 0.77, *P* = 0.02) and overall survival (12.3 vs 10.3 months, HR 0.70, *P* = 0.007) as compared to chemotherapy alone. This new combination represents the first significant improvement over standard platinum plus etoposide chemotherapy.

Concurrent radiotherapy is not used routinely in extensive disease. However, a randomized study of extensive-stage patients responding to chemotherapy comparing observation or PCI reported that PCI decreased the 1-year risk of brain metastasis (14.6% vs 40.4%), and prolonged 1-year survival (27.1% vs 13.3%).[77] A more recent Japanese study reported that PCI reduced the risk of brain metastases, but did not improve overall survival. The results of these studies led to guideline revisions recommending PCI for patients with limited disease responding to chemotherapy.[3,6]

Relapsed Disease

Patients with SCLC who relapse or progress after first-line chemotherapy have a median survival of 4 to 5 months. Unfortunately, when the disease recurs, it is usually less sensitive to chemotherapy. The decision of how to approach patients who experience relapsed SCLC often depends on the length of time between completion of the initial chemotherapy regimen and relapse. If this interval is less than 3 months, the patient has refractory SCLC and is unlikely to respond to second-line therapy, and should receive best supportive care or be enrolled in a clinical trial. For those with greater than a 3-month time interval between first-line chemotherapy and relapse, the expected response rate to treatment is about 25%, and second-line therapy should be considered.[3,6] Based on limited evidence, if the interval between completion of initial chemotherapy and relapse is 6 months or greater, retreating the patient with the initial chemotherapy

regimen is appropriate.[3,78,79] Topotecan (IV and oral) is approved as second-line therapy for SCLC, based on a trial that randomized patients to IV topotecan or to cyclophosphamide, doxorubicin, and vincristine (CAV) regimen.[80] The response rates, time-to-disease progression, and overall survival were not different between groups. Interestingly, the proportion of patients experiencing symptom improvement was higher in the topotecan arm. The hematologic toxicity was similar between arms, but there was slightly more neutropenia in the CAV arm and more anemia and thrombocytopenia in the topotecan arm. Nonhematologic toxicity appears to be higher in the CAV arm; 11% of patients required a dose reduction compared with 1% in the topotecan arm.[80] Oral topotecan appears to be equally effective and similar in terms of dosing, toxicity, and effectiveness as IV topotecan.[81] Based on these studies, topotecan should be considered as the second-line treatment of choice, but other agents should be considered because of its modest efficacy. Other agents recommended in national guidelines include single-agent topotecan (oral or IV), irinotecan, gemcitabine, paclitaxel, docetaxel, oral etoposide, temozolomide, and vinorelbine; CAV regimen; and participation in a clinical trial.[3,6] Nivolumab was recently approved under accelerated approval based on CHECKMATE-032, a phase I/II study in patients with various malignancies, including 214 with SCLC, who received nivolumab with or without ipilimumab. The FDA approval is based on the 109 patients receiving nivolumab monotherapy who achieved a response rate of 12%, with the duration of response ranging from 3 to 42 months.[68,82] It is important to note that the patients in CHECKMATE-032 had not received any prior immunotherapy, such as atezolizumab.

Evaluation of Therapeutic Outcomes

The effectiveness of first-line therapy is evaluated after two to three cycles of treatment. If the patient achieves a complete or partial response, therapy is continued for four to six cycles of therapy. If the patient has evidence of progressive disease, therapy is discontinued or changed to a non–cross-resistant regimen. In the case of SCLC, responding patients benefit from the addition of PCI following initial therapy. After recovery from first-line therapy, follow-up visits should occur every 3 months for years 1, 2, and 3, then every 4 to 6 months for years 4 and 5, and then annually for patients with either a partial or complete response.[2,6]

Complications and Supportive Care

Patients with lung cancer frequently have numerous concurrent medical problems. Such problems may be related to invasion of the primary tumor and its metastases, paraneoplastic syndromes (see Clinical Presentation earlier), chemotherapy and radiotherapy toxicity, or concomitant disease states (eg, cardiac disease, renal dysfunction, chronic obstructive pulmonary disease, asthma, or diabetes). Depression is also common and sometimes persistent in patients with SCLC and NSCLC and should be treated. Identification, diagnosis, and treatment of the patient as a whole may improve the patient's overall quality of life and tolerance to cancer treatments.

10 The chemotherapy regimens used in the management of lung cancer are intensive and are associated with a wide variety of toxic effects. Nausea and vomiting may be severe. Cisplatin-containing regimens require the use of aggressive acute and delayed antiemetic regimens containing agents such as serotonin antagonists, dexamethasone, and neurokinin-1 receptor antagonist, and olanzapine.[83] Patients experiencing protracted nausea and vomiting may require IV hydration and nutritional support. Myelosuppression is often the dose-limiting toxicity associated with chemotherapy. Granulocytopenia places patients at high risk for serious infections. Other toxic effects associated with these chemotherapy regimens include mucositis, anemia, nephrotoxicity, peripheral neuropathies, and ototoxicity.

About 30% to 65% of advanced-stage NSCLC patients will develop bone metastases, which may lead to significant bone pain, pathologic fractures, spinal cord compression, and hypercalcemia.[84] Zoledronic acid, an IV administered bisphosphonate, has been shown to reduce skeletal-related events in patients with bone metastases at a dose of 4 mg over 15 minutes infused every 3 weeks. Although the data do not show a significant reduction in skeletal-related events, the time-to-first event is significantly increased (230 vs 163 days, $P = 0.023$), thereby making zoledronic acid a viable therapy for patients with bone metastases. Denosumab has been compared to zoledronic acid in solid tumor patients including lung cancer and found to be noninferior in preventing or delaying first on-study skeletal-related events.[85] A subgroup exploratory analysis of lung cancer patients suggests that denosumab may prolong survival by just over a month.[86] Since they are equally effective for the primary endpoint, the potential benefit in survival might be considered when selecting therapy.

Patients receiving radiation therapy may experience complications including severe esophagitis, fatigue, radiation pneumonitis, and cardiac toxicity. These toxicities are usually more common and severe when radiation is combined with chemotherapy. The patient's baseline performance status and the degree of

pulmonary dysfunction (eg, chronic obstructive pulmonary disease from years of tobacco use) must be considered in decisions concerning radiation dosage and fractionation.

Patients who receive an immune checkpoint inhibitor can develop immune-related adverse events, which frequently include the GI tract, skin, and pneumonitis. Holding therapy and intervening with steroids can blunt the progression of these toxicities. The other key point is that responses to immune checkpoint inhibitors can be delayed in onset.[87] A new response criterion has been developed for immunotherapies, which differs from RECIST criteria by requiring documentation of significant tumor grown on two occasions at least 4 weeks apart to be defined as progression.

It is readily apparent that many lung cancer patients receive complex pharmacologic regimens that include chemotherapeutic agents, immune checkpoint inhibitors, antiemetics, antibiotics, analgesics, anticoagulants, bronchodilators, corticosteroids, anticonvulsants, and cardiovascular agents. Such regimens necessitate intensive therapeutic monitoring in order to avoid drug-related and radiotherapy-related toxic effects and to optimize therapeutic outcomes for individual patients.

Postclass Engaged Learning Activity

The PD-1/PD-L1 inhibitors are growing in importance in the treatment of many cancers, including lung cancer. Immunotherapies (also called immune checkpoint inhibitors) such as the PD-1/PD-L1 inhibitors cause significant immune-mediated adverse effects. Perform a literature search to identify guidelines for the management of these adverse effects published by major oncology organizations such as ASCO, NCCN, and ESMO. Create a list of the different types of immune-mediated adverse effects and summarize the management of each.

ABBREVIATIONS

AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ASCO	American Society of Clinical Oncology
AT	atypical carcinoid
AUC	area under the curve
BAC	bronchioalveolar carcinoma
CAV	cyclophosphamide, doxorubicin, and vincristine
CI	confidence interval
CNS	central nervous system
CR	complete response
CT	computed tomography
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EC	etoposide and carboplatin
EML4	echinoderm microtubule-associated protein-like 4
EP	etoposide and cisplatin
ESMO	European Society of Medical Oncology
ETS	environmental tobacco smoke
GI	gastrointestinal
HR	hazard ratio
IP	irinotecan and cisplatin
LDCT	low-dose computed tomography
MEK	mitogen-activated extracellular signal-regulated kinase
MIA	minimally invasive adenocarcinoma
NCCN	National Comprehensive Cancer Network
NSAIDs	nonsteroidal anti-inflammatory drugs
NSCLC	nonsmall cell lung cancer
NTRK	neutrotrophic receptor kinase
PD-1	programmed death-1
PD-L1	programmed death ligand-1
PCI	prophylactic cranial irradiation
PET	positron emission tomography
PR	partial response
RECIST	response evaluation criteria in solid tumors
SCLC	small cell lung cancer
SD	stable disease
TNM	tumor, node, and metastasis
TKI	tyrosine kinase inhibitor
TPS	tumor proportion score
TC	typical carcinoid

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;68:7–34.
2. National Comprehensive Cancer Network. NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology, v5.2019; 2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nsclc.pdf. Accessed July 29, 2019.
3. National Comprehensive Cancer Network. NCCN Small Cell Lung Cancer Clinical Practice Guidelines in Oncology, v1.2019; 2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf. Accessed July 29, 2019.
4. Kris MG, Gaspar LE, Chaft JE, et al. Adjuvant systemic therapy and adjuvant radiation therapy for stage I to IIIA completely resected non-small-cell lung cancers: American Society of Clinical Oncology/Cancer Care Ontario clinical practice guideline update. *J Clin Oncol*. 2017;35:2960–2974.
5. Hanna N, Johnson D, Temin S, et al. Systemic therapy for stage IV non–small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2017;35:3484–3515.
6. Rudin CM, Ismaila N, Hann CL, et al. Treatment of small-cell lung cancer: American Society of Clinical Oncology endorsement of the American College of Chest Physicians guideline. *J Clin Oncol*. 2015;33:4106–4111. doi:10.1200/JCO.2015.63.7918.
7. Kalemkerian GP, Narula N, Kennedy EB, et al. Molecular testing guideline for the selection of patients with lung cancer for treatment with targeted tyrosine kinase inhibitors: American Society of Clinical Oncology Endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology clinical practice guideline update. *J Clin Oncol*. 2018;36:911–919.
8. Horn L, de Lima Arauo LH, Nana-Sinkam P, Al E. Molecular biology of lung cancer. In: Devita VT, Lawrence TS, Rosenberg SA, eds. *Devita, Helma, and Rosenberg's Cancer: Principles and Practice of Oncology*.

10th ed. Philadelphia, PA: Wolters Kluwer; 2014;482–494.

9. Detterbeck FC, Decker RH, Tanoue L, Lilenbaum RC. Non-small cell lung cancer. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *Devita, Helma, and Rosenberg's Cancer: Principles and Practice of Oncology*. 10th ed. Philadelphia: Wolters Kluwer; 2014;495–535.
10. Pietanza MC, Krug LM, Wu AJ, Al E. Small cell and neuroendocrine tumors of the lung. In: Devita VT, Lawrence TS, Rosenberg SA, eds. *Devita, Helma, and Rosenberg's Cancer: Principles and Practice of Oncology*. 10th ed. Philadelphia, PA: Wolters Kluwer; 2014;536–559.
11. Awad MM, Shaw AT. ALK Inhibitors in non-small cell lung cancer: Crizotinib and beyond. *Clin Adv Hematol Oncol*. 2014;12:429–439.
12. US Department of Health and Human Services. *The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General*. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.
13. Centers for Disease Control and Prevention. Current cigarette smoking among adults—United States, 2016. *Morb Mortal Wkly Rep*. 2018;67:53–59.
14. Amin MB, Edge SB, Greene F, et al. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017.
15. Burdett S, Pignon J, Tierney J, et al. Adjuvant chemotherapy for resected non-small cell lung cancer. *Cochran Database Syst Rev*. 2015;3. CD011430.
16. Couraud S, Cortot AB, Greillier L, et al. From randomized trials to the clinic: Is it time to implement individual lung-cancer screening in clinical practice? A multidisciplinary statement from French experts on behalf of the French Intergroup (IFCT) and the Groupe d'Oncologie de Langue Française (GOLF) on behalf of the French lung cancer screening statement taskforce reviews *Ann Oncol*. 2013;24:586–597.
17. Bezjak A, Temin S, Franklin G, et al. Definitive and adjuvant radiotherapy in locally advanced non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline endorsement of the American Society for Radiation Oncology evidence-based clinical practice guideline. *J Clin Oncol*. 2015;33:2100–2105. doi:10.1200/JCO.2014.59.2360.
18. The National Lung Screening Trial Research Team. Reduced lung-cancer

mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365:395–409.

19. U.S. Preventive Services Task Force. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;160:330–338.
20. Bach PB, Mirkin JN, Oliver TK, et al. Benefits and harms of CT screening for lung Cancer. *JAMA*. 2012;307:2418–2429.
21. Black WC, Gareen IF, Soneji SS, et al. Cost-effectiveness of CT screening in the National Lung Screening Trial. *N Engl J Med*. 2014;371:1793–1802.
22. Keith RL, Miller YE. Lung cancer chemoprevention: Current status and future prospects. *Nat Rev Clin Oncol*. 2013;10:334–343.
23. Kushi LH, Doyle C, McCullough M, et al. American Cancer Society guidelines on nutrition and physical activity for cancer prevention: Reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin*. 2012;62:30–67.
24. Micke P, Faldum A, Metz T, et al. Staging small cell lung cancer: Veterans Administration Lung Study Group versus International Association for the Study of Lung Cancer--what limits limited disease? *Lung Cancer*. 2002;37:271–276.
25. Felip E, Rosell R, Maestre JA, et al. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non–small-cell lung cancer. *J Clin Oncol*. 2010;28:3138–3145.
26. Westeel V, Quoix E, Puyraveau M, et al. A randomised trial comparing preoperative to perioperative chemotherapy in early-stage non-small-cell lung cancer (IFCT 0002 trial). *Eur J Cancer*. 2013;49:2654–2664.
27. van Meerbeeck JP, Kramer GWPM, Van Schil PEY, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. *JNCI J Natl Cancer Inst*. 2007;99:442–450.
28. Pless M, Stupp R, Ris H-B, et al. Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: A phase 3 randomised trial. *Lancet*. 2015;386:1049–1056.
29. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med*. 2018;379:2342–2350.

30. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. *N Engl J Med*. 2016;375:1823–1833.
31. Mok TSK, Wu Y-L, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): A randomised, open-label, controlled, phase 3 trial. *The Lancet*. 2019;393:1819–1830.
32. Lee CK, Man J, Lord S, et al. Clinical and molecular characteristics associated with survival among patients treated with checkpoint inhibitors for advanced non–small cell lung carcinoma. *JAMA Oncol*. 2018;4:210–216.
33. Zhang Y-L, Yuan J-Q, Wang K-F, et al. The prevalence of EGFR mutation in patients with non-small cell lung cancer: A systematic review and meta-analysis. *Oncotarget*. 2016;7:78985–78993.
34. Kuan F-C, Kuo L-T, Chen M-C, et al. Overall survival benefits of first-line EGFR tyrosine kinase inhibitors in EGFR-mutated non-small-cell lung cancers: A systematic review and meta-analysis. *Br J Cancer*. 2015;113:1519–1528.
35. Wu Y-L, Cheng Y, Zhou X, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR -mutation-positive non-small-cell lung cancer (ARCHER 1050): A randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18:1454–1466.
36. Mok TS, Cheng Y, Zhou X, et al. Improvement in overall survival in a randomized study that compared dacomitinib with gefitinib in patients with advanced non–small-cell lung cancer and EGFR-activating mutations. *J Clin Oncol*. 2018;36:2244–2250.
37. Shin D-Y, Na I Il, Kim CH, Park S, Baek H, Yang SH. EGFR mutation and brain metastasis in pulmonary adenocarcinomas. *J Thorac Oncol*. 2014;9:195–199.
38. Chia PL, Mitchell P, Dobrovic A, John T. Prevalence and natural history of ALK positive non-small-cell lung cancer and the clinical impact of targeted therapy with ALK inhibitors. *Clin Epidemiol*. 2014;6:423–432.
39. Solomon BJ, Mok T, Kim D-W, et al. First-line crizotinib versus chemotherapy in ALK -positive lung cancer. *N Engl J Med*. 2014;371:2167–2177.
40. Soria J-C, Tan DSW, Chiari R, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK -rearranged non-small-cell lung

cancer (ASCEND-4): A randomised, open-label, phase 3 study. *Lancet*. 2017;389:917–929.

41. Camidge DR, Peters S, Mok T, et al. Updated efficacy and safety data from the global phase III ALEX study of alectinib (ALC) vs crizotinib (CZ) in untreated advanced ALK+ NSCLC. *J Clin Oncol*. 2018;36(15 suppl):9043–9043.
42. Camidge DR, Kim HR, Ahn M-J, et al. Brigatinib versus crizotinib in ALK-positive non–small-cell lung cancer. *N Engl J Med*. 2018;379:2027–2039.
43. Solomon BJ, Besse B, Bauer TM, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: Results from a global phase 2 study. *Lancet Oncol*. 2018;19:1654–1667.
44. Shaw AT, Ou S-HI, Bang Y-J, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med*. 2014;371:1963–1971.
45. Ou S, Shaw A, Riely G, et al. Clinical activity of lorlatinib in patients with ROS1+ advanced non-small cell lung cancer: Phase 2 study cohort EXP-6. *J Thorac Oncol*. 2018;13:S322–S323.
46. Planchard D, Smit EF, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously untreated BRAF V600E -mutant metastatic non-small-cell lung cancer: An open-label, phase 2 trial. *Lancet Oncol*. 2017;18:1307–1316.
47. Planchard D, Besse B, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: An open-label, multicentre phase 2 trial. *Lancet Oncol*. 2016;17:984–993.
48. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of Larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med*. Feb 22, 2018;378:731–739. doi:10.1056/NEJMoa1714448.
49. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non–small-cell lung cancer. *N Engl J Med*. 2002;346:92–98.
50. Scagliotti G, Brodowicz T, Shepherd FA, et al. Treatment-by-histology interaction analyses in three phase III trials show superiority of pemetrexed in nonsquamous non-small cell lung cancer. *J Thorac Oncol*. 2011;6:64–70.
51. Sandler A, Gray R, Perry MC, et al. Paclitaxel–carboplatin alone or with bevacizumab for non–small-cell lung cancer. *N Engl J Med*.

2006;355:2542–2550.

52. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non–small-cell lung cancer. *N Engl J Med*. 2018;379:2040–2051.
53. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. *N Engl J Med*. 2018;378:2078–2092.
54. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*. 2018;378:2288–2301.
55. Kulkarni S, Vella ET, Coakley N, et al. The use of systemic treatment in the maintenance of patients with non–small cell lung cancer: A systematic review. *J Thorac Oncol*. 2016;11:989–1002.
56. Nadler E, Yu E, Ravelo A, Sing A, Forsyth M, Gruschkus S. Bevacizumab treatment to progression after chemotherapy: Outcomes from a U.S. community practice network. *Oncologist*. 2011;16:486–496.
57. Shan F, Zhang B, Sun L, Xie L, Shen M, Ruan S. The role of combination maintenance with pemetrexed and bevacizumab for advanced stage nonsquamous non-small cell lung cancer: A Systematic Review and Meta-Analysis. *Biomed Res Int*. 2018;2018:1–14.
58. Ramos-Esquivel A, van der Laat A, Rojas-Vigott R, Juárez M, Corrales-Rodríguez L. Anti-PD-1/anti-PD-L1 immunotherapy versus docetaxel for previously treated advanced non-small cell lung cancer: A systematic review and meta-analysis of randomised clinical trials. *ESMO open*. 2017;2:e000236.
59. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol*. 2000;18:2095–2103.
60. Fossella F V, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol*. 2000;18:2354–2362.
61. Garon EB, Ciuleanu T-E, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy

(REVEL): A multicentre, double-blind, randomised phase 3 trial. *Lancet*. 2014;384:665–673.

62. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol*. 2004;22:1589–1597.
63. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. *N Engl J Med*. 2015;373:1627–1639.
64. Shepherd FA, Pereira JR, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med*. 2005;353:123–132.
65. Lilenbaum RC, Herndon JE, List MA, et al. Single-agent versus combination chemotherapy in advanced non-small-cell lung cancer: The Cancer and Leukemia Group B (study 9730). *J Clin Oncol*. 2005;23:190–196.
66. Ramalingam SS, Dahlberg SE, Langer CJ, et al. Outcomes for elderly, advanced-stage non-small-cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: Analysis of Eastern Cooperative Oncology Group Trial 4599. *J Clin Oncol*. 2008;26:60–65.
67. Hainsworth JD, Spigel DR, Farley C, et al. Weekly docetaxel versus docetaxel/gemcitabine in the treatment of elderly or poor performance status patients with advanced nonsmall cell lung cancer: A randomized phase 3 trial of the Minnie Pearl Cancer Research Network. *Cancer*. 2007;110:2027–2034.
68. Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): A multicentre, open-label, phase 1/2 trial. *Lancet Oncol*. 2016;17:883–895.
69. Christodoulou C, Skarlos D V. Treatment of small cell lung cancer. *Semin Respir Crit Care Med*. 2005;26:333–341.
70. Goffin J, Lacchetti C, Ellis PM, Ung YC, Evans WK. First-line systemic chemotherapy in the treatment of advanced non-small cell lung cancer: A systematic review. *J Thorac Oncol*. 2010;5:260–274.
71. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: Immune-related response criteria. *Clin Cancer Res*. 2009;15:7412–7420.
72. Rossi A, Di Maio M, Chiodini P, et al. Carboplatin- or cisplatin-based

chemotherapy in first-line treatment of small-cell lung cancer: The COCIS meta-analysis of individual patient data. *J Clin Oncol*. 2012;30:1692–1698.

73. Sundstrøm S, Bremnes RM, Kaasa S, et al. Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: Results from a randomized phase III trial with 5 years' follow-Up. *J Clin Oncol*. 2002;20:4665–4672.
74. Aupérin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med*. 1999;341:476–484.
75. Noda K, Nishiwaki Y, Kawahara M, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med*. 2002;346:85–91.
76. Hanna N, Bunn PA, Langer C, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lime cancer. *J Clin Oncol*. 2006;24:2038–2043.
77. Slotman BJ, Mauer ME, Bottomley A, et al. Prophylactic cranial irradiation in extensive disease small-cell lung cancer: Short-term health-related quality of life and patient reported symptoms-results of an international phase III randomized controlled trial by the EORTC radiation oncology and Lung Cancer Groups. *J Clin Oncol*. 2009;27:78–84.
78. Postmus PE, Berendsen HH, van Zandwijk N, Splinter TA, Burghouts JT, Bakker W. Retreatment with the induction regimen in small cell lung cancer relapsing after an initial response to short term chemotherapy. *Eur J Cancer Clin Oncol*. 1987;23:1409–1411.
79. Giaccone G, Ferrati P, Donadio M, Testore F, Calciati A. Reinduction chemotherapy in small cell lung cancer. *Eur J Cancer Clin Oncol*. 1987;23:1697–1699.
80. von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. *J Clin Oncol*. 1999;17:658–667.
81. Eckardt JR, von Pawel J, Pujol J-L, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. *J Clin Oncol*. 2007;25:2086–2092.
82. Hellmann M, Antonia S, Ponce S, et al. Nivolumab alone or with

ipilimumab in recurrent small cell lung cancer (SCLC): 2-Year survival and updated analyses from the CheckMate 032 Trial. *J Thorac Oncol*. 2017;12(1s):s393–394.

83. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2017;35:3240–3261.
84. Rosen LS, Gordon D, Tchekmedyian S, et al. Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: A phase III, double-blind, randomized trial—The Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *J Clin Oncol*. 2003;21:3150–3157.
85. Henry DH, Costa L, Goldwasser F, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J Clin Oncol*. 2011;29:1125–1132.
86. Scagliotti GV, Hirsh V, Siena S, et al. Overall survival improvement in patients with lung cancer and bone metastases treated with denosumab versus zoledronic acid: Subgroup analysis from a randomized phase 3 Study. *J Thorac Oncol*. 2012;7:1823–1829.
87. Dolan DE, Gupta S. PD-1 pathway inhibitors: Changing the landscape of cancer immunotherapy. *Cancer Control*. 2014;21:231–237.

147

Colorectal Cancer

Lisa M. Holle, Jessica M. Clement, and Lisa E. Davis

KEY CONCEPTS

1. Advancing age, high-risk adenomatous polyps, inherited and acquired genetic susceptibilities, inflammatory bowel disease, diabetes mellitus, and lifestyle factors are associated with colorectal cancer risk.
1. Regular use of aspirin and other nonsteroidal anti-inflammatory drugs reduces risk of colorectal cancer, but is not currently recommended for routine cancer prevention.
3. Effective colorectal cancer detection programs incorporate routine screening starting at age 50 years for average-risk individuals. Colorectal adenomas can progress to cancer and should be removed.
4. The treatment goal for stages I, II, and III colon cancer is cure; surgery should be offered to all eligible patients for this purpose. Six months of fluoropyrimidine-based adjuvant systemic therapy reduces the risk of cancer recurrence and overall mortality in patients with stage III and select patients with stage II colon cancer. An oxaliplatin-containing regimen further reduces risk as compared with fluoropyrimidine alone in stage III patients.
5. Combined modality neoadjuvant therapy consists of fluoropyrimidine-based chemosensitized radiation therapy and surgery for patients with stage II or III cancer of the rectum and is considered standard of care to decrease risk of local and distant disease recurrence.
6. Preoperative chemotherapy may reduce tumor size and convert unresectable disease to resectable disease in selected patients with metastatic colorectal cancer. This strategy offers the potential for prolonging overall survival and cure for metastatic disease.
7. Chemotherapy is palliative for metastatic disease. A fluoropyrimidine with

oxaliplatin or irinotecan improves survival compared to fluoropyrimidine monotherapy and should be offered to patients who are candidates for aggressive treatment. The ability for patients to receive all active cytotoxic agents (eg, fluoropyrimidine, oxaliplatin, and irinotecan) during the course of their disease improves their overall survival.

8. Bevacizumab plus fluoropyrimidine-based chemotherapy as initial therapy for metastatic disease is considered standard of care and provides a survival benefit as compared with combination chemotherapy alone.

9. The addition of an epidermal growth factor receptor (EGFR) inhibitor (cetuximab or panitumumab) to initial treatment for *RAS* and *BRAF* wild-type, left-sided advanced or metastatic disease may improve tumor response rates (RRs) and survival. Individuals who have disease progression after initial therapy not containing an EGFR inhibitor may benefit from cetuximab or panitumumab, combined with other drugs. However, patients with *RAS* gene mutations or those with right-sided tumors should not receive cetuximab or panitumumab as these tumor features predict lack of treatment response.

10. Immune checkpoint inhibitors are effective in metastatic colorectal cancer patients with deficient DNA mismatch-repair (MMR) genes or high microsatellite instability (MSI-H) and who have progressed after two or more regimens.

Preclass Engaged Learning Activity

For each of the available antiangiogenic inhibitor and epidermal growth factor receptor (EGFR) inhibitors, describe when in the treatment of colorectal cancer (ie, neoadjuvant, adjuvant, first-line metastasic, second- or greater-line metastatic treatment) it is appropriate to use the drug, including the rationale and whether the drugs within a class are interchangeable. This activity is useful to enhance student understanding of the ASSESS, PLAN, and FOLLOW-UP steps in the patient care process.

INTRODUCTION

Colorectal cancer involves the colon, rectum, and anal canal. It is one of the

three most common cancers in adult men and women in the United States.[1] In 2019, an estimated 145,600 new cases were diagnosed, of which 101,420 will involve the colon and 44,180 the rectum. An additional 8,580 new cases of cancer involve the anus, anal canal, or anorectum. For both adult men and women, colorectal cancer is the third leading cause of cancer-related death in the United States. An estimated 51,020 deaths occurred during 2019.

Overall colorectal cancer mortality and incidence rates in the United States have decreased steadily over the past two decades. Incidence rates vary worldwide, with the highest incidence rates in economically developed countries.[2] The decline in colorectal cancer mortality rates is likely due to increased screening and/or improved treatments, but mortality rates continue to increase in low-income and middle-income countries in eastern Europe, Asia, and South America.[2]

Multiple factors are associated with the development of colorectal cancer, including inherited susceptibility, lifestyle factors, and certain disease states. Overall, about 74% of affected individuals are diagnosed at an early stage of disease that can potentially be cured with surgery alone or surgery followed by adjuvant radiation therapy (XRT), chemotherapy, or both. Five-year survival rates are about 90% for persons with early stages of colon and rectal cancer.[3] After the tumor has spread regionally to adjacent lymph nodes or tissues, the 5-year survival rate drops to 71% for both colon and rectal cancer. Five-year survival for individuals with metastatic disease is about 14%.

Treatment modalities for colorectal cancer include surgery, XRT, chemotherapy, targeted molecular therapies (eg, angiogenesis inhibitors and epidermal growth factor receptor [EGFR] inhibitors), and immune checkpoint inhibitors. Surgery is the definitive procedure associated with cure. XRT can improve curability following surgical resection in rectal cancer and can reduce symptoms and complications associated with advanced disease. Chemotherapy is used in the adjuvant setting to increase cure rates and in treatment for advanced stages of disease to prolong survival. Some patients with metastatic disease who receive aggressive preoperative chemotherapy and targeted therapies experience higher resection rates and can be potentially cured. Much progress has been made in the treatment of advanced disease and the availability of active drug regimens that improve patients' survival.

EPIDEMIOLOGY

Colorectal cancer is the third most common diagnosed malignancy worldwide

and the fourth most common cause of cancer-related deaths, accounting for about 1.4 million new cases and 700,000 deaths annually.[2] Although the highest incidence and mortality rates are found in economically developed countries, such as the United States, Australia, New Zealand, and Western Europe where the human development index is highest, rates have stabilized or are decreasing.[2] This is in contrast to countries with a medium-to-high human development index, such as Eastern Europe, Asia, and South America, where colorectal cancer incidence and mortality rates are increasing rapidly.[2] These increases are believed to be associated with an increased prevalence of risk factors associated with westernization, such as unhealthy diet, obesity, and smoking. The lowest incidence rates are observed in less-developed areas such as sub-Saharan Africa and South Central Asia.

The incidence of invasive colon cancer is greatest among males, who have an age-adjusted incidence rate of 42.7 per 100,000, as compared with females for whom the rate is 34.35 per 100,000.[4] Invasive cancer of the rectum occurs less frequently, with an incidence rate of 18.90 and 11.60 per 100,000 for males and females, respectively. Differences in colorectal cancer incidence exist among ethnic groups in the United States, where incidence is highest among non-Hispanic blacks followed by American Indian/Alaska Native, non-Hispanic whites, Hispanic/Latinos, and Asian/Pacific Islanders.[3] Cultural and genetic factors as well as disparities in access to healthcare services may influence risk among population groups.

The overall incidence of colon and rectal cancers in the United States has steadily decreased since the mid-1980s, with an annual decline by 4.6% among individuals 65 years and older from 2009 to 2013.[3] However, the incidence rate decreased by only 1.4% per year in adults between 50 and 64 years of age and in adults younger than 50, the incidence of colorectal cancer increased by 1.6% per year. The incidence of colorectal cancer in adults younger than 55 has been increasing since the mid-1990s, with the most rapid increase in metastatic disease.[5]

Cancer incidence rates have been declining among every broadly defined racial/ethnic group since the mid-1990s, except in American Indian/Alaska Natives, for whom cancer incidence rates remain stable.[3] **Figure 147-1** displays trends for incidence and mortality rates among non-Hispanic white and black males and females in the United States.[4]

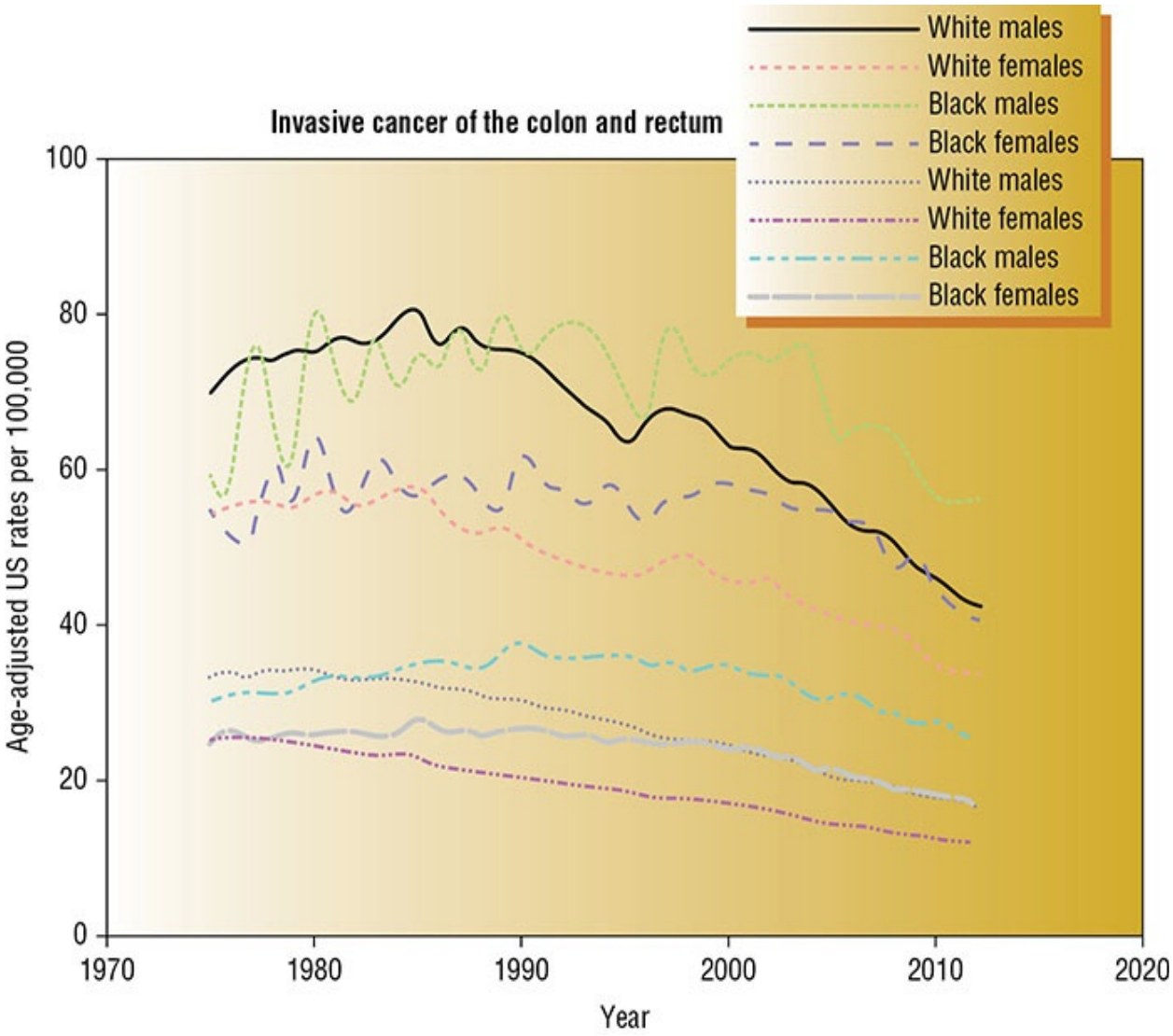


FIGURE 147-1 National Cancer Institute, Surveillance Epidemiology, and End Results (SEER) incidence and mortality rates for invasive colon and rectum cancer, 1975-2015. SEER 9 areas and US Mortality Files (National Center for Health Statistics, CDC). Rates are age-adjusted to the 2000 US standard population (19 age groups—Census P25-1130). (*Data from Reference 4.*)

Cancer of the colon and rectum accounts for about 8% of all cancer deaths in the United States.[4] The median age for death from cancer of the colon or rectum is 67 years.[4] An estimated 51,020 individuals died of colorectal cancer in the United States in 2019, which represents a continued decline in overall combined mortality for both colon and rectal cancer.[1] Overall mortality rates are highest among non-Hispanic black males and females, although a steep rate of decline began in the late 1990s.[3] Colorectal cancer death rates are decreasing among all

ethnic groups, but mortality rates are not statistically lower in American Indian/Alaska Natives.[4] Factors contributing to the overall decline in colorectal cancer mortality include decreasing incidence rates, screening programs with early polyp removal, and more effective and better tolerated treatments. Differences among different world geographic regions, and in population groups in the United States, may also reflect more unfavorable tumor characteristics, later state at diagnosis, decreased access to screening programs, comorbidities, and lower availability or utilization of effective treatments.[3]

ETIOLOGY AND RISK FACTORS

The development of colorectal cancer is related to both uncontrollable and modifiable risk factors. Age, family history, clinical and genetic susceptibilities cannot be controlled by individuals. Modifiable lifestyle factors are responsible for an estimated 16% to 71% of colorectal cancers.[6]

Personal Medical History

Age

1 An individual's risk of developing cancer of the colon or rectum increases with advancing age, rising progressively after age 50.[4] The median age at colon cancer diagnosis is 67 years in men and 71 years in women and 62 years in men and 63 years in women for rectal cancer.[4] The proportion of individuals diagnosed with colorectal cancer who were younger than 50 increased from 6% to 11% between 1990 and 2013, with the majority of cases diagnosed in adults in their 40s.[3] The increase in colorectal cancer incidence in younger adults may reflect trends in obesity and detrimental lifestyle factors.

Adenomatous Polyps or Colorectal Cancer

A prior history of high-risk adenomatous polyps, particularly multiple adenomas or size 10 mm or more, is associated with an increased risk of colorectal cancer.[6] Individuals with a prior diagnosis of colon or rectal cancer have a greater risk of developing a new malignancy at another area in their colon or rectum as compared to individuals without a prior history of colorectal cancer.

Inflammatory Bowel Disease

Individuals with chronic inflammatory bowel disease, such as ulcerative colitis or Crohn's disease, have about a twofold greater risk of developing colorectal cancer than the average individual.[3,7] This risk rises with increasing extent, duration, and severity of disease, a familial history of colorectal cancer, and coexistent primary sclerosing cholangitis. Overall, persons diagnosed with chronic inflammatory bowel disease constitute about 1% to 2% of all new cases of colorectal cancer each year.

Diabetes Mellitus

Individuals with type 2 diabetes mellitus have an increased risk of developing colorectal cancer, independent of body mass size and physical activity level. Epidemiologic studies show that diabetes is associated with a 27% to 40% increase in risk of colorectal cancer, as well as a higher risk of colorectal cancer-related and all-cause mortality.[8] Metformin use may improve survival outcomes in patients with colorectal cancer and diabetes, but further study is needed.[8]

Family History and Inherited Genetic Risk

Colorectal Cancer or Adenomatous Polyps

Three specific patterns of colon cancer occurrence are generally observed: sporadic, familial, and recognized hereditary syndromes. Although most cases of colorectal cancer are sporadic in nature, about 30% of patients who develop colorectal cancer will have a family history of colorectal cancer that is not associated with an inherited syndrome.[9] First-degree relatives of patients diagnosed with colorectal cancer have an increased risk of the disease (2 times the risk), which is higher if the relative was diagnosed at age 45 or younger (3-6 times higher). Similarly, parents and siblings of relatives diagnosed with adenomatous polyps are at increased risk for developing colorectal cancer.

Hereditary Syndromes

Colorectal cancer is a consequence of several well-defined genetic syndromes.[9] The two most common forms of hereditary colon cancer are familial adenomatous polyposis (FAP) and Lynch syndrome, historically known as *hereditary nonpolyposis colorectal cancer* (HNPCC). Both forms result from a specific germline mutation. FAP is a rare autosomal dominant trait caused by inactivating mutations of the adenomatous polyposis coli (*APC*) gene and accounts for about 1% of all colorectal cancers. The disease is manifested by

hundreds to thousands of tiny sessile adenomatous polyps that carpet the colon and rectum, typically arising during adolescence. The polyps continue to proliferate throughout the colon, with eventual transformation to malignancy. The risk of developing colorectal cancer for individuals with untreated FAP is virtually 100%; most will develop colorectal cancer by the fourth and fifth decades of life.

Lynch syndrome is an autosomal dominant inherited syndrome and is the most common hereditary predisposition for colorectal cancer.[10] Patients with Lynch syndrome are predisposed to many types of cancer (eg, endometrial, stomach, and ovarian), but the risk of colorectal cancer is the highest.[4] Germline mutations in one of the DNA mismatch-repair (MMR) genes, most commonly *MLH1*, *MSH2*, *MSH6*, or *PMS2*, or epithelial cell adhesion molecule *(EpCAM)*, are responsible for Lynch syndrome, which accounts for 2% to 4% of overall colorectal cancer cases.[9,11] The estimated lifetime risk of developing colorectal cancer is about 60% for carriers of germline MMR mutations. Multiple generations within a family are affected, and colorectal cancer develops early in life, with a mean age at time of diagnosis of about 45 years of age.[3] If Lynch syndrome is suspected in a patient diagnosed with colorectal cancer, typically due to early age at diagnosis or family cancer history, the tumor is examined for evidence of deficient MMR to distinguish between sporadic or germline genetic mutations. It is important to identify carriers of these MMR mutations so that they can be counseled and followed appropriately.[9,11]

Enzyme Polymorphisms

Increasing evidence suggests that genetic polymorphisms in drug-metabolizing enzymes, such as *N*-acetyltransferases (NAT1 and NAT2), cytochrome P450 (CYP) isoenzymes, glutathione-*S*-transferase enzymes, methylenetetrahydrofolate reductase (MTHFR), and hemochromatosis gene mutations, may confer genetic susceptibility to colorectal cancer.[10] Certain variations in drug-metabolizing enzyme genotypes may confer greater susceptibility to dietary or environmental carcinogens.

Lifestyle Factors

Nonsteroidal Anti-inflammatory Drug and Aspirin Use

2 Several lifestyle factors influence affect colorectal cancer risk (Table 147-1). Regular (at least 2 doses/week) nonsteroidal anti-inflammatory drug (NSAID) and aspirin use is associated with a reduced risk of colorectal cancer. In an average-risk individual, regular aspirin use is associated with a 20% to 40% reduction in the risk of colorectal adenoma and colorectal cancer.[12]

TABLE 147-1 Lifestyle Factors Associated with Colorectal Cancer Risk

Factor	Comments
Elevated Risk	
Physical inactivity	Sedentary lifestyle associated with a 25%-50% increased risk of colorectal cancer compared with the risk in physically active individuals
Overweight and obesity	Elevated BMI, waist circumference, and waist-to-hip ratio directly associated with increased cancer risk
Alcohol intake	Moderate and heavy alcohol consumption associated with 20% or greater cancer risk compared to light drinking (<1 drink/day)
Smoking	Prolonged tobacco smoking increases risk of large adenomas and carcinoma; higher colorectal cancer mortality in current smokers; risk persists after smoking cessation
Western diet	High red meat, processed meat, and saturated fat dietary consumption increases cancer risk; cancer risk lower with diets high in whole fiber grains and cereals, fruits, and vegetables
Reduced Risk	
Aspirin and nonaspirin NSAID use	Regular aspirin or NSAID use associated with a 20% to 45% reduction in adenoma recurrence and colorectal cancer risk. Benefit in risk reduction may require at least 5-10 years of use
Postmenopausal hormone use	Exogenous hormone intake decreases the risk of adenomas, colon, and rectal cancer by about 35%
Calcium and vitamin D intake	Vitamin D 400 international units and calcium intake of 1,000 mg/day (adults <50 years) or 1,200 mg/day (adults >50 years) may help reduce colorectal cancer risk but data remains unclear

BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drug.

Benefit is also seen with NSAID and cyclooxygenase-2 inhibitor (COX-2) use. NSAID use over a 10- to 15-year period is associated with protection against adenomas and colorectal cancer, with a 30% to 45% reduction in the risk of colorectal cancer.[12] The protective effects of these agents appear to be related to their inhibition of COX-2, which is overexpressed and elevated in up to 50% of colorectal adenomas and 85% of sporadic colon carcinomas.[13] Inhibition of COX-2 also downregulates the phosphatidylinositol 3-kinase (PI3K) signaling pathway, which plays an important role in carcinogenesis and cancer cell resistance to apoptosis.[14]

Postmenopausal Hormone Replacement Therapy

Exogenous postmenopausal oral hormone replacement therapy is associated with a significant reduction in colorectal cancer risk.[12,15] Risk reduction is seen in postmenopausal women receiving combined estrogen and progestin therapy and persists for about 10 years after therapy is discontinued. However, because of the harmful risks associated with postmenopausal hormone replacement therapy, its use is not recommended to prevent colorectal cancer.

Obesity and Physical Inactivity

1 Physical inactivity and elevated body mass index (BMI) are associated with an elevated risk of colon adenoma, colon cancer, and rectal cancer.[6,12,16,17] Individuals with a higher level of activity throughout life have the lowest risk, which may be 54% lower than that of physically inactive individuals.

Elevated BMI, and higher general and abdominal body fatness are risk factors for colorectal cancer in adults, although the associations are weaker and less consistent for women.[17] Obesity promotes insulin resistance, chronic inflammation, and elevated insulin-like growth factor-1 (IGF-1) levels, which can stimulate cell proliferation.[17,18]

Alcohol and Tobacco Use

1 Moderate and heavy alcohol consumption is a major risk factor for colorectal adenomas and colorectal cancer.[6,19,20] Individuals with an intake of 2 to 3 alcoholic beverages per day have a 21% higher risk of developing colorectal cancer, and heavier drinking further increases cancer risk.[3,19] This association is stronger in men than in women, perhaps due to differences in drinking patterns or alcohol metabolism.

Cigarette smoking is associated with an increased risk of colorectal cancer (about 38% and 18% in current and former smokers, respectively) and mortality than in nonsmokers.[3,20] The risk of colorectal cancer development increases with longer duration of smoking and number of cigarettes consumed daily, and persists after smoking cessation.[20]

Dietary Intake and Nutrients

1 Epidemiologic studies of worldwide incidence of colorectal cancer suggest that economic development and dietary habits strongly influence its development. Dietary characteristics of economically developed countries and increased colorectal cancer risk include higher intake of red and processed meat,

fat, and refined grains, and a lower intake of fruit, vegetables, and whole grains.

Many large epidemiologic studies have identified a positive association of a high consumption of red and processed meat with the risk of developing colorectal cancer.[3,21,22] Potential underlying mechanisms for this association include carcinogenic chemicals formed during the cooking process or the presence of specific fatty acids in red meat.[3,21,22] Processed meat products may increase exposure to carcinogenic nitrates and *N*-nitroso compounds.[21]

Worldwide, high-fiber dietary patterns have been associated with a low incidence of colorectal cancer.[6,12] Foods that are high in fiber include fruit, vegetables, whole grains, and cereals. Fruit and vegetables are rich in soluble fiber, vitamins, minerals, flavonoids, and other micronutrients that may be protective for colorectal cancer risk. However, the role of dietary fiber with regard to amount, source, and type and colorectal cancer risk has not been defined.

Dietary and supplemental calcium consumption is associated with a decreased risk of adenomas and colorectal cancer.[4,6,21] The protective effects of calcium may be due to antiproliferative, proapoptotic actions, and reduced colonic epithelial cell exposure to mutagens.[12,21] High levels of circulating 25-hydroxyvitamin D_3 are also associated with a reduced risk of colorectal cancer.[3,6,21,23] Vitamin D has antiproliferative, anti-inflammatory, and immune regulatory effects.[12,21] Vitamin D and calcium appear to interact synergistically to protect against adenoma recurrence and colorectal cancer, but large clinical trials have yet to confirm that supplementation with calcium and vitamin D in individuals with adequate dietary calcium and vitamin D intake reduces colorectal cancer risk.[12,21]

An association between folate intake through diet or supplements and colorectal cancer is complex, as data has shown both protective and tumor promoting effects.[3,12,21] However, the underlying basis for this is complex, particularly because alcohol use, smoking, genetic variants of the *MTHFR* gene, and other factors can interfere with folate metabolism. Thus, an adequate dietary folate intake may be enough to lower the risk of colorectal cancer, and exceeding normal intake may not be beneficial.

Deficiencies in other dietary micronutrients and antioxidants, including vitamin B_6, selenium, vitamin C, vitamin E, and carotenoids, may increase colorectal cancer risk, but there is no convincing evidence that the risk of colorectal cancer is greater in patients with low serum levels than in patients with adequate levels.[21]

PATHOPHYSIOLOGY

Anatomy and Bowel Function

The large intestine consists of the cecum; the ascending, transverse, descending, and sigmoid colon; and the rectum (**Fig. 147-2**). In adults, it extends about 1.5 m and has a diameter ranging from 8 cm in the cecum to 2 cm in the sigmoid colon. Absorption of fluid and solutes occurs in the right colon or the segments proximal to the middle of the transverse colon, with movement and storage of fecal material in the left colon and distal segments of the colon. Mucus secretion from goblet cells into the intestinal lumen lubricates the mucosal surface and facilitates movement of the dehydrated feces. It also serves to protect the luminal wall from bacteria and colonic irritants such as bile acids.

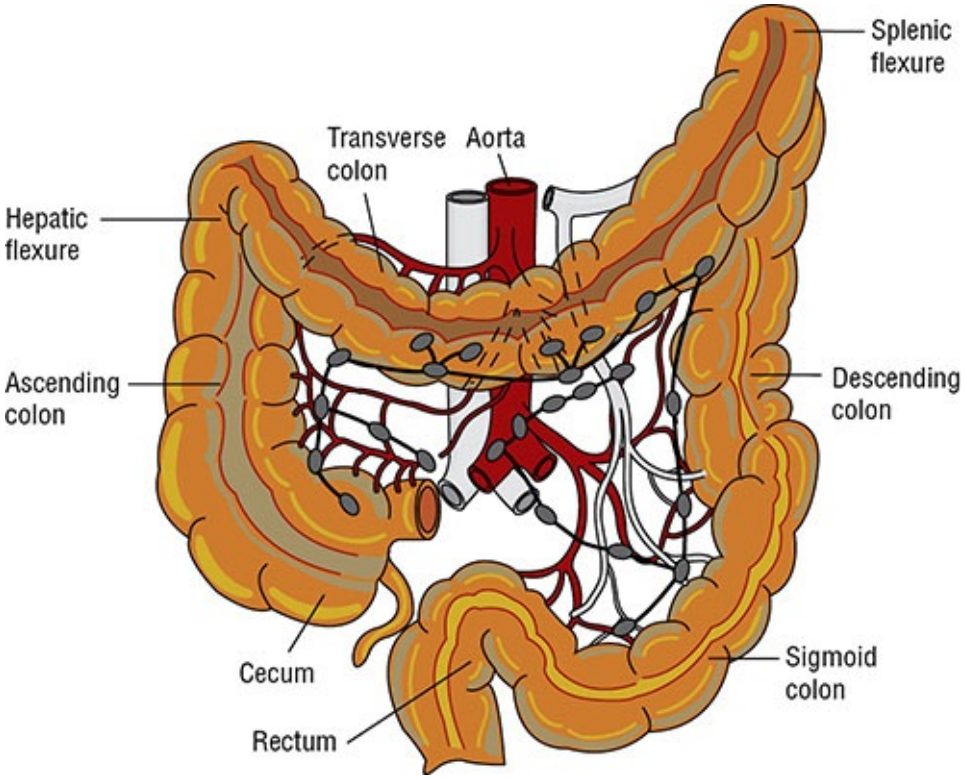


FIGURE 147-2 Colon and rectum anatomy.

Four major tissue layers, from the lumen outward, form the large intestine: the mucosa, submucosa, muscularis propria, and serosa (**Fig. 147-3**). Embedded in the submucosa and muscularis propria is a rich lymphatic capillary system. Lymphatic channels do not extend into the mucosa. The muscularis propria consists of circular smooth muscle and outer longitudinal smooth muscle bands. Contraction of these muscle groups moves colonic material toward the anal

canal. The outermost layer of the colon, the serosa, secretes a fluid that allows the colon to slide easily over nearby structures within the peritoneum. The serosa covers only the anterior and lateral aspects of the upper third of the rectum. The lower third lies completely extraperitoneal and is surrounded by fibrofatty tissue as well as adjacent organs and structures.

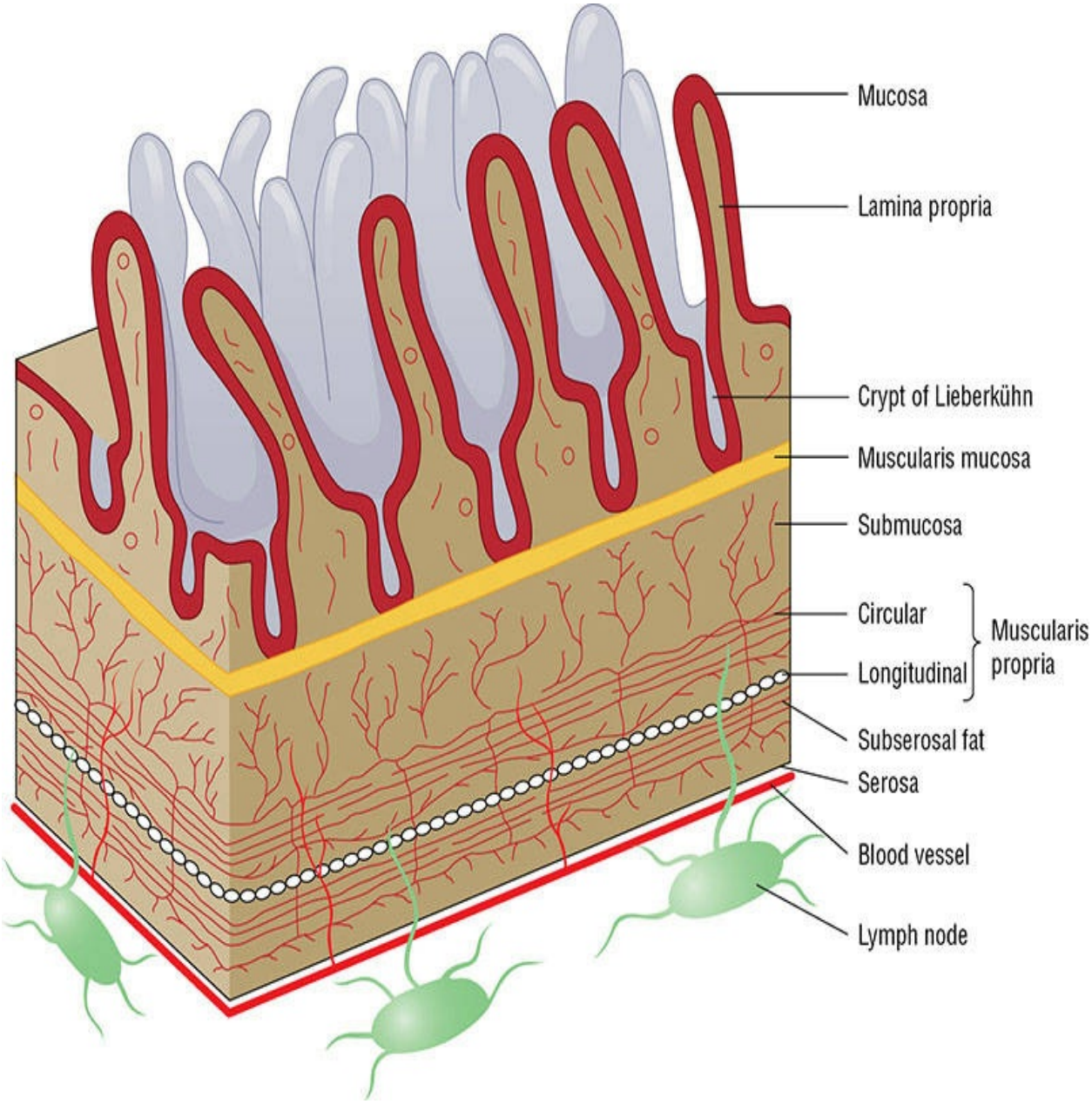


FIGURE 147-3 Cross-section of bowel wall.

The surface epithelium of the colonic mucosa undergoes continual renewal, and complete replacement of epithelial cells occurs every 4 to 8 days. Cell

replication normally takes place within the lower third of the crypts, the tubular glands located within the intestinal mucosa. The cells then mature and differentiate to either goblet or absorptive cells as they migrate toward the bowel lumen. The total number of epithelial cells remains relatively constant as the number of cells migrating from the crypts is balanced by the rate of exfoliation of cells from the mucosal surface. This two-phase process is critical to the malignant transformation of the epithelial cells. The number of dysplastic and hyperplastic aberrant crypt foci increases with increasing age; as the mass of abnormal cells accumulates at the top of the crypt and starts to protrude into the stream of fecal matter, their contact with fecal mutagens can lead to further cell mutations and eventual adenoma formation.

Colorectal Tumorigenesis

The development of a colorectal neoplasm is a multistep process involving several genetic and phenotypic alterations of normal bowel epithelium structure and function, leading to dysregulated cell growth, proliferation, and tumor development. Because most colorectal cancers develop sporadically, with no inherited or familial disposition, efforts have been directed toward identifying these alterations and learning whether detection of such changes may lead to improved cancer detection or treatment outcomes.

Features of colorectal tumorigenesis include genomic instability, activation of oncogene pathways, mutational inactivation or silencing of tumor-suppressor genes, DNA mismatch repairs, and activation of growth factor pathways.[10] During the early stages of tumorigenesis, emerging tumor cells expressing tumor antigens are eliminated by the immune system, which serves as an initial barrier to cancer progression.[24] These cells eventually escape immune surveillance as the tumor microenvironment becomes progressively immunosuppressive.

Genetic models have been proposed for colorectal tumorigenesis that describe a process of transformation from adenoma to carcinoma (**Fig. 147-4**).[24–27] The adenoma to carcinoma sequence of tumor development reflects an accumulation of mutations within colonic epithelium that confers a selective growth advantage to the affected cells. Key elements of this process include hyperproliferation of epithelial cells to form a small benign neoplasm or adenoma in conjunction with acquisition of various genetic mutations and epigenetic alterations.[11,26] Two discrete adenoma to carcinoma progression sequences have been described.[6,26] Although both pathways share several genetic alterations, each has unique molecular and phenotypic characteristics. **Table 147-2** lists important genetic

mutations that are associated with colorectal cancers.[6,10,26]

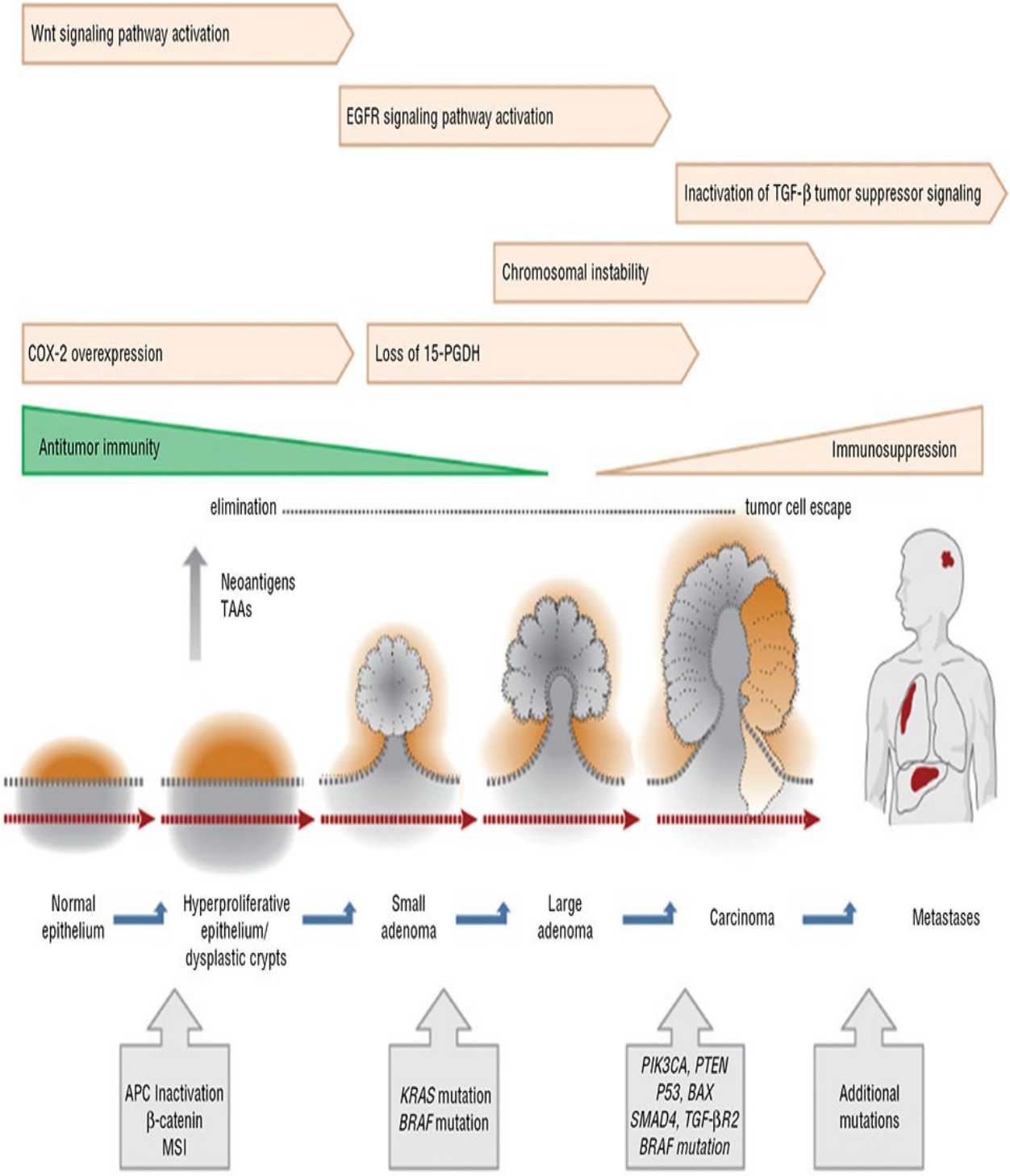


FIGURE 147-4 Genetic changes associated with the adenoma–carcinoma sequence in colorectal cancer. The accumulation of genetic changes in the pathogenesis of colorectal cancer includes microsatellite instability (MSI) initiated by aberrant DNA methylation or mismatch repair (MMR) gene

mutation with subsequent disruption in transforming growth factor-β receptor type II (TGF-β2R) and BAX signaling; mutation in the adenomatous polyposis coli (*APC*) gene or abnormalities in β-catenin leading to inappropriate activation of the Wnt signaling pathway; mutational activation of cyclooxygenase-2 (COX-2) and impaired prostaglandin degradation from loss of 15-prostaglandin dehydrogenase (15-PGDH); *KRAS*, *PIK3CA*, or *BRAF* oncogene activation; increased epidermal growth factor receptor (EGFR) signaling; and deletions or mutations of tumor suppressor genes *SMAD4*, *PTEN*, *P53*. Chromosomal instability (CIN) is a common feature of sporadic disease, but causative factors are not defined. Tumor-associated antigens (TAAs) expressed by emerging tumor cells are eliminated by the immune system during early tumorgenesis but eventually escape immune surveillance. The sequence of molecular events may differ between somatic and inherited genetic alterations. (*Data from References* 10,24–27.)

TABLE 147-2 Genetic Mutations Associated with Colorectal Cancer

Type of Mutation	Disease	Genes	Comments
Germline	Familial adenomatous polyposis (FAP)	*APC*	Multiple adenomas and carcinomas in colon and rectum
	MYH-associated polyposis	*MYH*	Autosomal recessive syndrome; wide spectrum of degree of polyposis; frequent *KRAS* mutations
	Lynch syndrome	DNA MMR genes: *MSH2, MLH1, MSH6, PMS2, EpCAM*	Colorectal cancer in absence of extensive polyposis; predisposition for endometrial, ovarian, gastric, hepatobiliary, urothelial, pancreatic, brain, and skin cancers
Somatic	Sporadic colorectal cancer	Oncogenes	
		KRAS	Mutations found in about 40% of cancers
		NRAS	Mutations found in <5% of cancers
		BRAF	*BRAF* V600E mutation found in 8%-25% of cancers
		PIK3CA	Mutations found in 15%-25% of cancers
		EGFR	Gene amplification in 5%-15% of cancers
		c-MYC	Gene amplification in 70%-80% of cancers
		ERBB2 (known as HER2)	Gene amplification in 35% of cancers
		SRC	Gene deregulated in up to 80% of cancers
		Tumor suppressor genes	
		P53	Loss or mutation in 50% of cancers
		SMAD4	Mutations in 10%-15% of cancers
		APC	Inactivated in 40%-70% of sporadic cancers
		TGF-βR2	Inactivating mutations present in 20% of cancers; mutations in more than 90% of cancers with MSI
		PTEN	Frequency of inactivating mutations about 10% but loss of PTEN protein expression evident in 15%-20% of cancers

APC, adenomatous polyposis coli; *EGFR*, epidermal growth factor receptor; *EpCAM*, epithelial cell adhesion molecule; *HER-2*, human epidermal growth factor receptor 2; MMR, mismatch repair; MSI, microsatellite instability; TGF-βR2, transforming growth factor-β receptor type II.

Data from References 6, 10, and 26.

Genomic Instability

Genomic instability plays an integral role in normal colonic or rectal mucosal transformation to carcinoma.[10] Three molecular pathways that lead to genomic instability are the microsatellite instability (MSI), CpG island methylator phenotype (CIMP), and chromosomal instability (CIN) pathways. The most common type is CIN, which leads to alterations in chromosomal structure and copy number. Important consequences of CIN include imbalanced chromosome

number (aneuploidy), chromosomal gene amplification, and loss of a wild-type allele of a tumor-suppressor gene, also referred to as loss of heterozygosity (LOH). More than 50% of sporadic colorectal cancers exhibit CIN and involve tumor suppressor genes *APC* and *P53*, loss of 18q allele, and aneuploid DNA content.

Microsatellites are a series of repeat nucleotide sequences that are spread out across the entire genome.[10] Microsatellite replication errors within tumor DNA occur frequently, and mutations of the MMR genes that recognize and regulate DNA MMR errors contribute to MSI and colorectal tumorigenesis. Germline mutation of MMR genes is an important characteristic of Lynch syndrome, but somatic mutations are also present in about 15% of sporadic colorectal cancers.

Alterations in gene expression or function in the absence of DNA sequence alterations are referred to as epigenetic changes, and these are usually due to methylation of DNA gene promoter regions or histone modifications.[10] CIMP is characterized by hypermethylation of a panel of multiple genes that are associated with gene silencing and subsequent loss of tumor suppressor gene function.[26] About 15% of sporadic colorectal cancers arise as a consequence of CIMP.

Oncogene and Tumor Suppressor Gene Alterations

Mutation or loss of the *APC* tumor suppressor gene is a key factor involved in tumor formation through constitutive activation of the Wnt signaling pathway, a mediator of cell-cycle progression, cell proliferation, differentiation, and apoptosis.[10] The *APC* gene encodes for APC protein that binds to and degrades cytoplasmic β-catenin, a downstream component of the Wnt signaling pathway. Inactivation of the *APC* gene is the single gene defect responsible for FAP, and is frequently an initiating event in sporadic colorectal cancer.[10]

Mutational inactivation of *P53* represents a frequent and key step in colorectal tumorigenesis, occurring in about 50% to 75% of colorectal cancers.[10] Normal *P53* gene expression is important for G_1 cell-cycle arrest to facilitate DNA repair during replication and to induce apoptosis. An additional step in tumor progression is the mutational inactivation of the transforming growth factor-β (TGF-β) signaling pathway, which facilitates adenoma transition to high-grade dysplasia or carcinoma and also inactivates *SMAD4*. In normal epithelium, TGF-β has an antiproliferative role and induces growth arrest and apoptosis. Alterations in *SMAD4* or TGF-β receptors lead to a loss of the normal growth inhibitory response to TGF-β.

Several oncogene-activating mutations play an important role in promoting colorectal cancer.[10] Mutations in members of the *RAS* gene family—*KRAS*, *HRAS*, and *NRAS*—in addition to *BRAF*, activate the mitogen-activated protein kinase (MAPK) signaling pathway, which stimulates cell proliferation and other activities that promote carcinogenesis. Mutations of *PIK3CA*, which encodes the catalytic subunit of a PI3K survival pathway, increase production of phosphatidylinositol-3,4,5-triphosphate, which influences cell growth, proliferation, and survival. Mutation or loss of *PTEN*, a tumor suppressor gene that antagonizes PI3K signaling, produces similar effects. Multiple additional genetic alterations contribute to carcinoma formation and metastases by altering cellular growth, metabolism, migration, and invasive capabilities, and angiogenesis.[27]

Growth Factor Signaling Pathways

Aberrant signaling of growth factor pathways plays an important role in colorectal tumorigenesis. Activation of prostaglandin signaling is an early step in the adenoma to carcinoma transformation process and is induced by upregulated expression of COX-2 and inflammation.[10] COX-2 mediates the synthesis of prostaglandin E_2, which stimulates cancer growth.[10] Furthermore, 80% of colorectal cancers have loss of 15-prostaglandin dehydrogenase (15-PGDH), the rate-limiting enzyme responsible for prostaglandin degradation. EGFR, a transmembrane glycoprotein involved in signaling pathways that affect cell growth, differentiation, proliferation, and angiogenesis, plays a key role in colorectal cancer pathogenesis. EGFR activation enables downstream signaling of the MAPK, PI3K, and Akt pathways that influence colorectal tumorigenesis. EGFR is overexpressed in up to 82% of colorectal cancers and high tumor EGFR overexpression is associated with a worse prognosis.[10] These mechanisms are relevant because of the availability of pharmacologic agents that can influence these signaling pathways and affect cell growth.

Histology

Adenocarcinomas account for about 92% of tumors of the large intestine and about 7% are classified mucinous adenocarcinoma.[4] The other histologic types, such as signet-ring adenocarcinoma, squamous cell carcinoma, and neuroendocrine carcinomas, are rare. Adenocarcinomas are assigned one of three tumor grade designations based on the degree of cellular differentiation, the

degree to which the tumor resembles the structure, and the function of its cell of origin. The most differentiated adenocarcinomas are low-grade tumors, whereas high-grade tumors are the most undifferentiated, and have frequently lost the characteristics of mature normal cells. Poorly differentiated tumors are associated with a worse prognosis than those that are relatively better differentiated.

Mucinous adenocarcinomas possess the same basic structure as adenocarcinomas but differ in that they secrete an abundant quantity of extracellular mucus. They tend to be frequent in patients with MMR mutations. Signet-ring adenocarcinomas also have a characteristic appearance but are uncommon. Signet-ring histology occurs more frequently in individuals younger than 50 years of age, patients with ulcerative colitis, and tends to present at a more advanced stage of disease at diagnosis. Both mucinous and signet-ring adenocarcinoma histologies confer a poor prognosis. Patients with neuroendocrine tumors and squamous cell carcinoma often present with distant metastases and also have a poor prognosis.

PREVENTION AND SCREENING

Cancer prevention efforts can be either primary or secondary. Primary prevention strategies aim to prevent the development of colorectal cancer in a population at risk. Secondary prevention approaches are undertaken to prevent malignancy in a population that has already manifested an initial disease process.

Chemoprevention

2 Several agents have been evaluated as chemoprevention strategies for colorectal cancer, including prospective population-based screening trials of dietary fiber intake, and randomized controlled trials of calcium, vitamin D, and folate supplementation.[28–30] However, findings do not support their use at this time. Additional intervention trials of various micronutrients, epigenetic modulators, and other chemopreventive agents have been completed or are ongoing.[12,23,24,29,31–38] The most widely studied agents for the chemoprevention of colorectal cancer are aspirin, nonaspirin NSAIDs, and COX-2 selective inhibitors, but only aspirin is recommended for chemoprevention in some patients.[13,30,39] The effectiveness of these agents has been studied in high-risk individuals and within the general population.

In individuals with FAP, celecoxib, NSAIDs, and aspirin have been studied to

delay the development of adenomatous polyps and to reduce polyp recurrence following colectomy with a retained rectum, but they are not viewed as alternatives to surgery.[28,29] In randomized controlled trials, celecoxib 400 mg orally twice daily as an adjunct to usual care significantly reduced the mean size and number of colorectal polyps after 6 to 9 months of treatment. However, the US Food and Drug Administration (FDA) approval for celecoxib was withdrawn because of lack of data showing long-term benefit. Sulindac induces adenoma regression but does not appear to delay or prevent malignancy. The benefits of these agents are transient because polyps increase in size and number within a few months after discontinuing treatment. These agents may be useful to reduce adenoma recurrence following surgery, but they are not recommended for chemoprevention.

2 Nonaspirin NSAIDs and COX-2 inhibitors reduce the risk of sporadic and recurrent colorectal adenomas in cohort and case-control studies, and COX-2 inhibitors were also effective in controlled trials.[40] Celecoxib is associated with a 34% relative risk reduction in adenoma recurrence and 55% risk reduction in the incidence of advanced adenomas.[28,40] Optimal dosing, agents, and duration of treatment remain to be determined, and cardiovascular events in addition to the risk of gastric ulceration and bleeding with these agents are of concern. Although NSAIDs may be appropriate for selected individuals at high risk for colorectal cancer but low risk for cardiovascular disorders, the United States Preventive Services Task Force (USPSTF) has concluded that potential harms associated with NSAID use (other than aspirin) outweigh benefits for prevention of colorectal cancer in the general population.[39]

The use of aspirin as both a primary and a secondary chemopreventive agent remains controversial. In patients with prior adenomas or diagnosis of colorectal cancer, regular daily aspirin use reduces colorectal adenoma recurrence, and colorectal cancer incidence and mortality.[12,30]

Aspirin reduces of risk of sporadic and recurrent adenomas by about 17% and advanced adenomas by 28%.[28,30,40] Higher aspirin doses reduced the risk of colorectal cancer over a 23-year follow-up period by 26% among the general population, but lower doses (75-300 mg) of daily aspirin for 5 years were also associated with a reduction in risk of colorectal cancer and in 20-year mortality from colorectal cancer by 34%.[40,41] Individuals with Lynch syndrome who received aspirin 600 mg daily for at least 2 years experienced a 59% reduction in colorectal cancer risk that became evident 5 years after the aspirin was first started and had been discontinued.[30] Although the optimal aspirin dose and treatment durations are unknown, increasing evidence supports a

chemoprotective effect of aspirin in select high-risk individuals and in the general population. The extent of risk reduction appears to be inversely related to the duration of therapy and the chemopreventive effects of aspirin may be delayed by 5 to 10 years. However, the balance of risks and benefits with long-term aspirin use is currently unclear, and aspirin is only recommended for chemoprevention in some patients. USPSTF guidelines endorse daily low-dose aspirin for at least 10 years in adults ages 50 to 59 years with a ≥10% 10-year cardiovascular disease risk, a life expectancy of at least 10 years, and who are not at risk for bleeding, for primary prevention of both cardiovascular disease and colorectal cancer.[42] Adults ages 60 to 69 years may also receive low-dose-daily aspirin for at least 10 years if the benefits outweigh the risks. *PIK3CA* mutations, which are present in up to 20% of colorectal cancers, and polymorphisms in genes that regulate pro-inflammatory processes may serve as biomarkers to identify patients who may benefit from prophylactic or adjuvant aspirin therapy.[42]

Randomized controlled trials of calcium, vitamin D, and folate supplementation as chemoprevention have also been conducted, but findings do not support their use at this time.[28–30] Individuals at high risk of colorectal cancer may experience a moderate reduction in risk of recurrent colorectal adenomas with 5 years of calcium supplementation.[20] However, individuals with adequate vitamin D levels and no known increased risk of colorectal cancer do not appear to benefit from calcium or vitamin D supplementation.[41] In two trials, folate supplementation was associated with a nonsignificant increase in adenoma recurrence. Based on these results, the use of folate supplementation to reduce colorectal cancer risk is not recommended at this time.[29]

Surgical Resection

Surgical resection remains an option to prevent colon cancer in individuals at extremely high risk for its development.[43] Despite the effects of NSAIDs and COX-2 selective inhibitors on adenoma development and recurrence in individuals with FAP, their effects are incomplete and surgical resection is necessary for cancer prevention for these high-risk individuals. Individuals with FAP who have polyposis on lower endoscopy screening examinations should undergo colectomy or proctocolectomy, typically starting around age 20 years. Because of the high incidence of metachronous (ie, consecutive development) cancers (45%) in patients with Lynch syndrome, prophylactic subtotal colectomy is recommended for individuals who are not candidates for routine close follow-

up. Colonoscopic polypectomy, removal of polyps detected during screening colonoscopy, is considered the standard of care for all individuals to prevent the progression of premalignant adenomatous polyps to adenocarcinomas.

Screening

Colorectal cancer screening decreases mortality by detecting cancers at an early, curable stage, and by detecting and removing adenomatous polyps. Multiple screening recommendations for early detection of colorectal cancer have been established; differences exist in specific screening guidelines published by various organizations.[3,28,44–47] Structural (visual) tests detect colorectal polyps and cancer while fecal-based tests detect early cancer. This section reviews available screening techniques for colon and rectal cancer.

Colonoscopy

Colonoscopy facilitates examination of the entire large bowel to the cecum in most patients and allows for simultaneous removal of premalignant lesions. Although no randomized trials show that colonoscopy decreases colorectal cancer mortality, observational studies show screening colonoscopy and polypectomy reduces the incidence in colorectal cancer by about 80%, with a 50% to 60% reduction in colorectal mortality.[6,28,47] Colonoscopy allows for greater visualization of the colon, but it involves sedation, complete bowel preparation, and is associated with greater risk and inconvenience to patients. Colonoscopy is considered the gold standard for colorectal screening because of its ability to detect and remove lesions in the proximal as well as distal colon.[6,28,47]

Flexible Sigmoidoscopy

Flexible sigmoidoscopy (FSIG) uses a 60-cm flexible sigmoidoscope to examine the lower half of the bowel to the splenic flexure for most patients and is thus capable of detecting 50% to 60% of cancers.[47] Randomized trials show that FSIG decreases colorectal cancer incidence and mortality by 27% and 31%, respectively.[3,44,47] The combination of FSIG and a fecal-based test appears to improve sensitivity for lesions that will be missed by sigmoidoscopy alone, but the true benefit of this approach to general practice has not been established.[47] FSIG offers the advantage of not requiring sedation or extensive bowel preparation, but the entire colon cannot be examined with FSIG and suspicious

lesions must be evaluated by colonoscopy.

Computed Tomography Colonography

Computed tomography colonography, also referred to as *virtual colonoscopy*, is an imaging procedure that creates two- or three-dimensional images of the colon by combining multiple helical computed tomography (CT) scans.[3,44] Sedation is not required and initial tests show high sensitivity and specificity for detecting adenomas at least 6 mm in size. However, the procedure requires complete bowel preparation, is associated with radiation exposure, and colonoscopy will still be necessary to remove detected lesions.[44,47] Individuals may find this method as a more acceptable option to colonoscopy or sigmoidoscopy.

Fecal Occult Blood Tests

Fecal occult blood tests (FOBTs) detect occult blood in the stool that may be associated with bleeding adenomas or cancer. Results from randomized controlled trials of annual FOBT screening show a reduction in colorectal cancer mortality by 33%.[47] Unlike structural tests, FOBTs are noninvasive and do not require bowel preparation. However, they will not detect most polyps and may produce false-positive or false-negative results.[3] Two main methods are available to detect occult blood in the feces: guaiac-based FOBT (gFOBT) and fecal immunochemical tests (FITs), also known as immunochemical fecal occult blood test (iFOBT). gFOBTs detect pseudoperoxidase activity of heme in human blood. Because gFOBTs detect blood from any sources and some foods affect peroxidase activity, patients are instructed to avoid NSAIDs, red meat, vitamin C, and large amounts of citrus for at least 3 days before and through the testing period.

Several limitations associated with gFOBT screening are of concern. Many early-stage tumors do not bleed, and therefore the false-negative rates can be high and are variable depending on the gFOBT product used. In addition, the test results may not be valid because the test is often poorly performed both in the home and in physician office settings.[3,44,47] However, these concerns are addressed by testing three successive stool samples. False-positive results can prove to be very expensive and inconvenient for a patient because of the follow-up tests required to confirm a positive result. Annual screening, preferably using a high-sensitivity gFOBT (eg, Hemoccult SENSA), is an acceptable option for individuals at average risk for colorectal cancer. It should be noted that FOBT conducted in conjunction with a digital rectal exam during an office visit is not

considered adequate colorectal screening.

FITs (iFOBTs) were developed to reduce false-positive and false-negative test results associated with the gFOBT. FIT uses antibodies to detect the globin protein portion of human hemoglobin. Since globin is degraded by enzymes in the upper gastrointestinal tract, FIT is more specific for lower gastrointestinal bleeding. Also, no diet or medication restrictions are necessary and testing involves a single stool sample collection annually.[46] Comparative studies report that FIT is more accurate than gFOBT for detecting cancer and advanced adenomas, although colonoscopy identifies more adenomas.[44,47]

Stool DNA Screening Tests

Molecular screening strategies analyze stool samples for the presence of potential markers of malignancy in cells that are shed from premalignant polyps or adenocarcinomas in the bowel.[44,46] Adenoma and carcinomas can contain certain DNA mutations and markers of MSI that can be detected using multi-target stool DNA (mt-sDNA) testing. A combined FIT and mt-sDNA test is available that has improved sensitivity for advanced adenomas and sessile serrated polyps, but lower specificity compared to FIT.[44,47] The appropriate screening interval is unclear, although it may be less frequent than annual FIT.[47] However, it is not routinely recommended as a screening option by all screening guidelines.

Capsule Colonography

Capsule colonography (CapC) is not approved for screening average-risk patients, but it is approved for colorectal imaging in patients who are not candidates for sedation or colonoscopy or who had a previous incomplete colonoscopy.[45] This procedure uses a wireless capsule device that is swallowed by the patient to examine the gastrointestinal tract, thereby avoiding risks associated with sedation and colonoscopy.

Serology Test

A *SEPT9* DNA methylated blood test is approved for colorectal cancer screening but is not recommended in US cancer screening guidelines. Methylated *SEPT9* DNA is a form of the *SEPT9* gene that distinguishes colorectal cancer from normal tissue and is found in circulating plasma with some colorectal cancers.[46] Although the test has low sensitivity for detecting colorectal cancer, it may be an alternative for individuals who refuse to undergo other screening tests.[47]

Screening Summary

3 **Table 147-3** shows current US screening guidelines for early detection of colorectal cancer with the goal of cancer prevention.[44–48] Men and women who are at average risk for colorectal cancer (their only risk factor is age greater than or equal to 50 years) should begin regular screening starting at age 50 years with a colonoscopy every 10 years, annually with a sensitive gFOBT or FIT, or undergo FSIG every 5 years. Limited evidence supports starting screening at age 45 years for all individuals, or for African Americans, as recommended by the American Cancer Society and United States Multi-Society Task Force on Colorectal Cancer, respectively.[44,45] Several screening methods are available that all have the potential to reduce colorectal cancer mortality, and because each method is associated with different benefits and potential harms, patient preferences and available resources should be considered for individual patients.[6,44] More aggressive (usually starting at an earlier age) screening recommendations are given for moderate-to-high risk individuals and colonoscopy is generally preferred for initial screening and surveillance following polyp removal in this population.[6,9,11,47] Most organizations recommend discontinuing screening and surveillance in populations when risk may outweigh benefit.[6] Routine colorectal cancer screening is recommended for individuals age 50 to 75 years with a life expectancy ≥10 years, with individualized screening decisions made for individuals aged 76 through 85 years and discontinuing screening in adults older than 85 years.[44–48]

TABLE 147-3 Guidelines for Colorectal Cancer Screening in the United States for Individuals at Average Risk, 50 Years of Age and Older[a,b]

	ACS	USPSTF	USMSTF	NCCN	ACP
Fecal-based Tests					
FIT	Annually	Annually	Annually	Annually	Annually
gFOBT[c]	Annually	Annually	Not recommended	Annually	Annually
mt-sDNA	Every 3 years	Annually or every 3 years	Every 3 years	Interval uncertain but every 3 years suggested	Not recommended
Structural (visual) Tests					
Colonoscopy	Every 10 years	Every 10 years	Every 10 years	Every 10 years	Every 10 years
CTC	Every 5 years	Every 5 years	Every 5 years	Every 5 years	Not recommended
FSIG	Every 5 years	Every 5 years	Every 5-10 years	Every 5-10 years	Every 5 years
Other	----------	FSIG every 10 years + FIT *annually*	CapC every 5 years if patient declines other options	----------	FSIG every 5 years + gFOBT[c] *or* FIT every 3 years

[a]*Starting at age 45 years (ACS)*

[b]*Starting at age 45 years if African American (USMSTF)*

[c]If high-sensitivity test.

ACP, American College of Physicians; ACS, American Cancer Society; CapC, capsule colonography; CTC, CT colonography; FIT, fecal immunochemical test; FSIG, flexible sigmoidoscopy; gFOBT, guaiac-based fecal occult blood test; mt-sDNA, multi-targeted stool DNA; NCCN, National Comprehensive Cancer Network; USMSTF, US Multi-Society Task Force on Colorectal Cancer; USPSTF, US Preventive Services Task Force.

Data from References 44–48.

CLINICAL PRESENTATION AND DIAGNOSIS

Signs and Symptoms

The signs and symptoms associated with colorectal cancer can be extremely varied and nonspecific. Patients with early-stage colorectal cancer are often asymptomatic, and lesions are usually found through screening studies. Any change in bowel habits (eg, constipation, diarrhea, alteration in size or shape of stool), abdominal pain or distension may be warning signs of a malignant process. Obstructive symptoms and changes in bowel habits frequently develop with tumors located in the transverse and descending colon. Rectal cancer may be associated with tenesmus, though bleeding is the most common symptom. Bleeding may be acute or chronic and can appear as bright red blood mixed with stool or melena. Iron-deficiency anemia, presenting as weakness and fatigue, can develop from chronic occult blood loss.

About 20% of patients with colorectal cancer present with metastatic

disease.[1] Metastatic spread occurs in the setting of direct tumor invasion of the peritoneum or by lymphatic or hematogenous spread. The venous drainage of the colon and rectum influences the pattern of metastases most commonly seen. The most common site of metastasis is the liver followed by the lungs, and then bones, specifically the sacrum, coccyx, pelvis, and lumbar vertebrae. Liver metastases are present in 25% of patients at presentation, with another 25% to 30% of patients developing liver metastases in the following 2 to 3 years from diagnosis.[49]

Workup

When a patient is suspected of having colorectal carcinoma, a complete history and physical examination should be performed. The patient history should include a past medical history and family history, especially noting the presence of inflammatory bowel disease, colorectal cancer, polyps, and familial clustering of cancers to assess risk for an inherited colorectal cancer syndrome, as well as a full medication history, including prescription, over-the-counter and complementary or alternative therapies. A complete physical examination includes careful abdominal examination for the presence of masses or ascites, a rectal examination, and an assessment for possible hepatomegaly and lymphadenopathy. A breast and pelvic examination is recommended in all women.

Evaluation of the entire large bowel requires a total colonoscopy, which allows for tissue collection for histologic evaluation to provide a tissue diagnosis following the procedure. Patients with invasive cancer of the colon or rectum require a complete staging workup, which includes laboratory testing and imaging of the abdomen, pelvis, and chest. Baseline laboratory tests should be obtained and include a complete blood cell count, platelet count, international normalized ratio, prothrombin time, activated partial thromboplastin time, liver chemistries, renal function tests, and carcinoembryonic antigen (CEA) level. Abnormal liver chemistry test results may suggest liver involvement with tumor, though normal levels do not preclude metastatic involvement. Iron studies (eg, serum ferritin, serum iron, and total iron-binding capacity) may identify iron deficiency in patients with anemia.

General

- Patient symptoms are usually nonspecific and can vary drastically among patients.
- Most patients are asymptomatic.

Symptoms

- Change in bowel habits (generally an increase in frequency) or rectal bleeding.
- Constipation, depending on the location of the tumor.
- Nausea, vomiting, and abdominal discomfort.
- Fatigue may be present if anemia is severe.

Signs

- Blood in the stool is the most common sign in symptomatic patients.
- Hepatomegaly and jaundice in advanced disease.
- Leg edema is a consequence of lymph node involvement, thrombophlebitis, fistula formation, weight loss, and pain in the lower back or radiating down the legs may be indicative of widespread disease.

Laboratory Tests

- Positive guaiac stool test and anemia (iron deficiency) from blood loss.
- Elevated carcinoembryonic antigen (more likely in patients with higher stages at presentation).
- Elevated liver enzymes may be present with metastatic disease.

CEA belongs to a group of cell-surface glycoproteins termed *oncofetal proteins*, which are expressed during embryonic development and re-expressed on the cell surfaces of many carcinomas, particularly those originating from the gastrointestinal tract. CEA concentrations can be measured in the blood and can, therefore, potentially serve as a marker for colorectal cancer. Elevated CEA

levels are more frequent in patients with metastatic disease, but not all colorectal cancers produce CEA. It is important to recognize that several concomitant disease states are associated with an elevated CEA: liver diseases, gastritis, peptic ulcer disease, diverticulitis, chronic obstructive pulmonary disease, chronic or acute inflammatory conditions, and diabetes.[50] Most commercially available assays list a value of less than 5 ng/mL (mcg/L) as the upper limit of normal. Although CEA measurement is too insensitive and nonspecific to be used as a screening test for early-stage colorectal cancer, it is the surrogate marker of choice for monitoring colorectal cancer response to treatment, particularly if the pretreatment concentration is elevated.[50] The CEA test may have preoperative prognostic implications because it has been shown to correlate with the size and degree of differentiation of the carcinoma. Elevated preoperative CEA levels correlate with poor survival and may predict the likelihood of recurrence, regardless of tumor stage at diagnosis. However, it should not be used as an indication for adjuvant therapy. After a potentially curative resection, CEA levels should return to normal within 4 to 6 weeks. Persistently elevated CEA levels may indicate residual disease, while elevations after normalization may indicate relapsed disease.

Radiographic imaging studies are used to evaluate the extent of disease involvement for initial staging, and subsequently to monitor disease response to therapy. Contrast dye-enhanced CT scans of the chest, abdomen, and pelvis are performed to evaluate for pulmonary, hepatic, and retroperitoneal involvement as well as occult abdominal and pelvic disease. In certain cases, such as patients with contrast dye allergies, magnetic resonance imaging (MRI) of the abdomen and pelvis may be substituted. A glucose analog [^{18}F]-fluorodeoxyglucose-positron emission tomography (PET) scan may also be performed as the primary imaging modality or to confirm metastatic disease if findings from CT or MRI scans are not conclusive. PET imaging may provide functional information to assist in discriminating between benign and malignant disease by detecting tumor-related metabolic alterations in affected tissues. PET scans are commonly used for the detection of recurrent colorectal cancer in patients with rising CEA levels and inconclusive findings on standard imaging studies. A PET scan is often performed in conjunction with a CT scan for anatomical localization of a lesion(s). For initial rectal cancer staging, assessment of the extent of tumor spread into the surrounding mesorectum and depth of invasion within the bowel wall may be performed using MRI or endorectal ultrasound.

Because of the increased likelihood of HNPCC in patients diagnosed with colorectal cancer younger than the age of 50 years, MMR protein testing on the

cancer specimen is recommended.[48] The level of MMR protein expression can be determined by immunohistochemistry, which is decreased with MMR gene mutations. Gene sequencing can also be performed to detect MSI. If immunohistochemical analysis of the tumor reveals the absence of MLHI protein expression, *BRAF* gene mutation testing is recommended to distinguish between somatic and germline *MLH1* gene mutation.[48] Individuals with abnormal MMR protein expression or MSI should be referred for genetic counseling as additional testing and cancer susceptibility risk assessment may be appropriate for themselves and family members.

Staging

The purpose of staging examinations is to determine the extent of disease, which allows the oncologist to develop treatment plans and estimate overall prognosis. The same TNM classification system is used for both cancers of the colon and rectum since the categories reflect similar survival outcomes.[50,51] This classification assesses three aspects of cancer growth: T (tumor size or penetration), N (lymph node involvement), and M (presence or absence of metastases). The TNM classification also allows for various subdivisions within each of the three categories, which is then used to determine the disease stage. **Table 147-4** summarizes the staging definitions used in the TNM system and corresponding 5-year survival rates.[50–52] **Figure 147-5** shows the various stages of cancer based on cancer penetration through the bowel wall and extension to regional lymph nodes. Of note, an individual patient's stage is determined at the time of the initial diagnosis and does not change with progression of disease or recurrence. For example, if a patient is diagnosed with stage II colon cancer and later recurs with metastases to the liver, that patient is stage II now with metastatic disease to the liver, not stage IV.

TABLE 147-4 Colon Cancer by TNM Classification and Associated 5-Year Survival Rate

Stage	T	N	M	Survival (%)
0	T_{is}	N_0	M_0	95.6
I	T_1	N_0	M_0	97.4
	T_2	N_0	M_0	96.8
IIA	T_3	N_0	M_0	87.5
IIB	T_{4a}	N_0	M_0	79.6
IIC	T_{4b}	N_0	M_0	58.4
IIIA	T_1-T_2	N_1/N_{1c}	M_0	71.1
	T_1	N_{2a}	M_0	68.5
IIIB	T_3-T_{4a}	N_1/N_{1c}	M_0	60.6-68.7
	T_2-T_3	N_{2a}	M_0	53.4-81.7
	T_1-T_2	N_{2b}	M_0	62.4
IIIC	T_{4a}	N_{2a}	M_0	40.9
	T_3-T_{4a}	N_{2b}	M_0	21.8-37.3
	T_{4b}	N_1-N_2	M_0	15.7
IVA	Any T	Any N	M_{1a}	11.5[a]
IVB	Any T	Any N	M_{1b}	11.5[a]
IVC	Any T	Any N	M_{1c}	11.5[a]

Primary Tumor (T)

T_{is}, Carcinoma in situ: intraepithelial or invasion of lamina propia with no extension through muscularis mucosae.

T_1, Tumor invades submucosa through the muscularis mucosa but not into the muscularis propria.

T_2, Tumor invades muscularis propria.

T_3, Tumor invades through the muscularis propria into pericolorectal tissues.

T_{4a}, Tumor invades through the visceral peritoneum, including bowel perforation through tumor and invasion of tumor through inflammatory surface of visceral peritoneum.

T_{4b}, Tumor directly invades or is adherent to other organs or structures.

Lymph Nodes (N)

N_0, no regional lymph node metastasis.

N_1, metastasis in 1-3 lymph nodes.

N_{1a}, metastasis in 1 lymph node.

N_{1b}, metastasis in 2-3 lymph nodes.

N_{1c}, tissue tumor deposits without lymph node metastasis.

N_2, metastasis in more than 4 lymph nodes.

N_{2a}, metastasis in 4-6 lymph nodes.

N_{2b}, metastasis in more than 7 lymph nodes.

Distant Metastasis (M)

M_0, no distant metastasis

M_{1a}, metastasis confined to one site or organ without peritoneal metastasis.

M_{1b}, metastasis in 2 or more sites or organs without peritoneal metastasis.

M_{1c}, metastasis to the peritoneal surface with/without metastasis to another site or organ.

[a]Survival for Stage IVA-C.

Data from References 50–52.

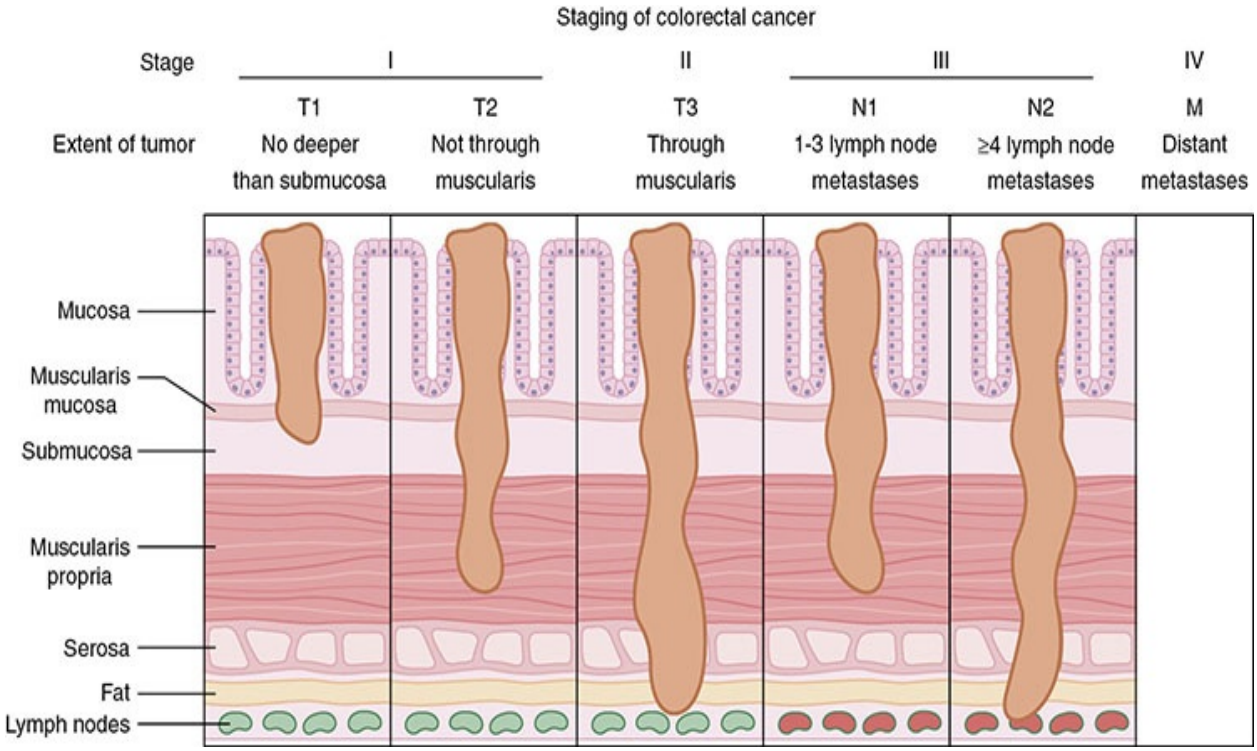


FIGURE 147-5 TNM staging for colorectal cancer. (*Reproduced with permission from Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: Harrison's Principles of Internal Medicine, 18th ed. New York: McGraw-Hill; 2011.*)

PROGNOSIS

The stage of colorectal cancer upon diagnosis is the most important independent prognostic factor for survival and disease recurrence. Five-year survival is about 90% for individuals who present with a localized tumor stage at diagnosis as compared with about 14% for individuals with metastatic disease at diagnosis.[1]

Clinical factors present at the time of diagnosis that are associated with a poor prognosis and decreased survival include bowel obstruction or perforation, high preoperative CEA level, distant metastases, and location of the primary tumor in the rectum or rectosigmoid area.[53] Along with resection of the primary tumor, a minimum of 12 lymph nodes must be examined to accurately determine regional lymph node involvement and predict lymph node-negative disease.[53] The pathologic assessment also includes determination of TNM stage, tumor type, and histologic grade, presence of venous, and lymphatic invasion, and whether the resected margins are free of tumor.[50] Consideration of these factors plays an important role in determining optimal strategies for treatment and appropriate

follow-up. Additional morphologic tumor features that have been associated with adverse clinical outcome include infiltrative tumor border configuration, evidence of perineural invasion, extranodal tumor deposits, and presence of tumor budding, characterized by clusters of cells that possess properties of malignant stem cells and are associated with increased risk of local and distant spread.

Certain molecular markers, particularly MSI, 18q/*DCC* mutation or LOH, *BRAF V600E* mutation, and *RAS* mutations, are also associated with colorectal cancer prognosis, although the pathologic stage of disease remains the primary prognostic assessment.[50,54] Colorectal cancers with allelic LOH on chromosome 18q or absent DCC protein are associated with a worse prognosis within stages II and III disease, but data are insufficient to warrant use of this test in practice at this time.[55] MSI can be determined through DNA sequencing or by immunohistochemistry staining for protein products of the MMR genes. Colorectal cancers that demonstrate MSI-H appear to be associated with a more favorable outcome and appear to predict the benefit of adjuvant fluoropyrimidines for early-stage disease.[55] Tumor DNA *BRAF* and *RAS* mutation status appear to be associated with overall survival but are not used to determine prognosis.

Although multiple prognostic biomarkers for colorectal cancer have been identified, single molecular tests other than MSI are not used routinely in clinical practice. However, several multigene assays have been developed that provide prognostic information to assist in identifying individuals at high risk for cancer recurrence from early-stage disease.[50,54] The Onco*type* DX colon cancer assay is commercially available and has been validated in several trials as a prognostic test for stage II and III colon cancer.[56,57] Gene expression profiles classify risk of recurrence as low, intermediate, or high, and these scores are prognostic for recurrence, disease-free survival, and overall survival. The ColoPrint gene expression assay characterizes the risk of recurrence as low or high, and is undergoing further validation in clinical trials.[50] The ability for these and other gene signature assays in development to predict which patients may benefit from adjuvant chemotherapy has not been well established.

TREATMENT

Desired Outcomes

Treatment goals for cancer of the colon or rectum are based on the stage of

> disease at presentation. Stages I, II, and III disease are considered potentially curable and the goal of management is to eradicate potential micrometastases after surgical resection. Based on the numbers and site(s) of metastases, about 20% to 30% of patients with metastatic colorectal cancer may be cured, if their metastases are considered resectable.[50] Most patients with stage IV disease are not curable, and treatments for metastatic disease are considered palliative to reduce symptoms, avoid disease-related complications, and prolong survival. However, special attention should be given to those with oligo-lesions in the liver or lung since potential cure is still possible for some of these patients.

General Approach

Performance status, concomitant disease states, lifestyle factors, patient preferences, and patient age (although advanced age is not an absolute contraindication for aggressive therapies) must be considered in the treatment planning process. Special or emergent conditions, such as bowel obstruction or perforation, severe pain, anemia, or other symptomatic problems, need to be addressed acutely, after which time a more long-term disease-specific plan can be developed. The treatment approaches for cancer of the colon or rectum reflect two primary treatment goals: curative therapy for localized disease and palliative therapy for metastatic cancer.

For patients for whom treatment intent is curative, surgical resection of the primary tumor is the most important component of therapy. Depending on the extent of disease and whether the tumor originated in the colon or rectum, further adjuvant chemotherapy or chemotherapy plus XRT (chemoradiation) may be appropriate. For selected patients with resectable metastases, surgical resection may be an option. However, for most patients with metastases, systemic chemotherapy is the mainstay of treatment; XRT may also be useful for disease palliation of localized symptoms. Patients with metastatic disease who are asymptomatic may benefit from initiation of therapy and continuous treatment should be considered.

Operable Disease

Surgery

4 Individuals with operable—stages I, II, and III—cancer of the colon or

rectum should undergo complete surgical resection of the primary tumor mass with regional lymphadenectomy as a curative approach for their disease.[58] The surgical approach for colon cancer generally involves complete resection of the tumor with at least a 5-cm margin of tumor-free bowel and regional lymphadenectomy.

The preferred surgical procedure for rectal cancer is total excision of the mesorectum, the surrounding tissue containing perirectal fat and draining lymph nodes.[51,58] If the distal margin clear of tumor is at least 1 cm, sphincter-preserving surgery may be possible for patients with cancers in the middle and lower portion of the rectum. Individuals who are not candidates for sphincter-sparing resections or have extensive local spread of tumor will require an abdominoperineal resection. This involves removal of the distal sigmoid, rectosigmoid, rectum, and anus with the establishment of a permanent sigmoid colostomy.

Colectomies for colon cancer can be performed as open procedures or laparoscopically. Laparoscopic colectomy has become an accepted procedure for colon cancer.[50] This technique appears to produce similar results to conventional surgery, with the benefits of a smaller surgical incision, shorter hospital stay, shorter duration of ileus, and reduced pain. Complications associated with colorectal surgery include infection, anastomotic leakage, obstruction, adhesion formation, sexual dysfunction, and malabsorption syndromes, depending on the site and extent of resection. Complications affecting bowel function associated with surgery for rectal cancer increase as the level of anastomosis approaches the anus.

Adjuvant Radiation Therapy for Colon Cancer

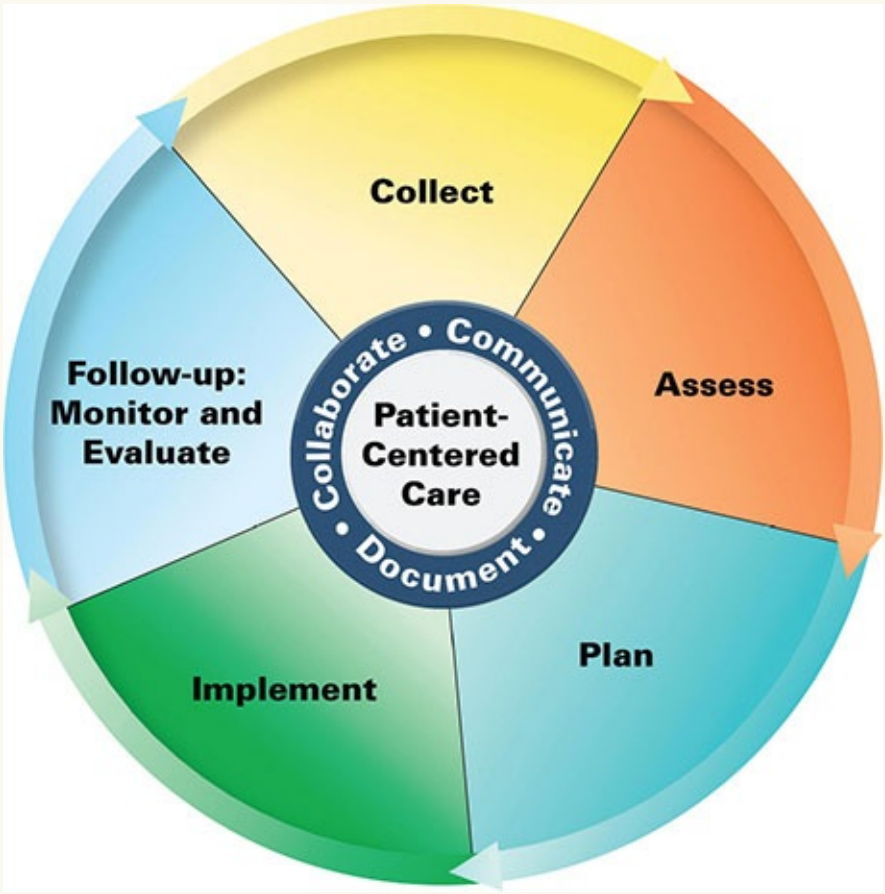
Adjuvant XRT has a limited role in colon cancer because most recurrences are extrapelvic and occur in the abdomen. A subset of patients with recurrent disease or with T_4 tumors that have penetrated fixed structures may benefit from adjuvant fluorouracil-based chemoradiation, with consideration of intraoperative radiation.[50] Selected candidates may also be considered for preoperative fluoropyrimidine-based chemoradiation to improve resectability. Adverse effects associated with XRT in colorectal cancer can be acute or chronic. Acute effects primarily include hematologic depression, dysuria, diarrhea, abdominal cramping, and proctitis. Chronic symptoms that sometimes persist for months following discontinuation of XRT include persistent diarrhea, proctitis or enteritis, small bowel obstruction, perineal tenderness, sexual dysfunction, and impaired wound healing.

Adjuvant Chemotherapy for Colon Cancer

Adjuvant therapy in colorectal cancer is administered after complete tumor resection in an attempt to eliminate residual micrometastatic disease, thereby decreasing tumor recurrence and improving survival rates. Patients should start adjuvant therapy as soon as they are medically stable following surgery because each 4-week delay results in a 14% decrease in overall survival.[50] Because more than 90% of patients with stage I colon cancer are cured by surgical resection alone, adjuvant therapy is not indicated.[50]

Patients with stage II disease who are at higher risk for relapse should be offered adjuvant therapy, with a detailed discussion regarding the potential benefits versus treatment-related toxicities.[50] High-risk features include those with inadequate lymph node sampling, perforation of the bowel at presentation, poorly differentiated tumors, lymphovascular invasion, perineural invasion, inadequately sampled lymph nodes (<12 evaluated), T_4 lesions (stage IIB/IIC), and lesions with localized perforation or close or indeterminate margins. Individuals with MSI-H tumors have a better prognosis compared to those with MSI-L and may not benefit or even be harmed from adjuvant chemotherapy.

The presence of lymph node involvement with tumor places patients with stage III colon cancer at high risk for recurrence, and the risk of death within 5 years of surgical resection alone is as high as 70%, depending on the number of lymph nodes involved.[3] In this group of patients, adjuvant chemotherapy significantly decreases risk of cancer recurrence and death and is standard of care.



Patient Care Process for Colorectal Cancer

Collect

- Patient characteristics (eg, age, race, sex)
- Patient history (lifestyle factors—alcohol use, tobacco use, physical activity)
- Patient characteristics (eg, social history/situation, insurance coverage) and treatment preferences
- Patient medical and family history (eg, performance status, concurrent disease states [inflammatory bowel disease, colorectal cancer, polyps])
- Clinical presentation signs and symptoms (see Clinical Presentation Box)
- Current signs and symptoms and evaluation of tumor growth (for follow-up visits)

- Current medications (prescription, over-the-counter, and complementary alternative)
- Objective data
  - BP, heart rate (HR), height, weight, and BSA
  - Labs (eg, serum electrolytes, renal function, liver chemistries, complete blood count, coagulation studies, carcinoembryonic antigen [CEA] level—see Workup)
  - Physical examination data (eg, hepatomegaly, lymphadenopathy, ascites)
  - Colorectal cancer staging (see Table 147-4)
  - Colorectal tumor genomics (eg, *KRAS*, *NRAS*, MMR/MSI, *BRAF*, *PIK3CA*)

Assess

- Risk factors for treatment-related toxicities (eg, *UGT1A1*28* genotype, poor nutritional intake, uncontrolled blood pressure or hypertension, baseline peripheral neuropathy)
- Type of and response to prior treatments
- Potential for disease responsiveness to specific agents and risk factors for disease recurrence
- Potential problems with medication adherence to oral treatment regimens
- Need for drug dose reductions or supportive care

Plan*

- Goals of treatment
- Drug therapy regimen including specific anticancer agent(s), dose, route, frequency, and duration (see Tables 147-5 to 147-7)
- Supportive care plan (eg, antiemetics, prophylactic antidiarrheals, infusion reaction prophylaxis)
- Monitoring parameters including efficacy (eg, cancer imaging studies-chest, abdominal, and/or pelvic CT scans and radiographs, CEA if previously elevated, symptoms of recurrence), safety (medication-specific adverse effects, including major-dose limiting toxicities), and time frame

(see Tables 147-5 to 147-7)

- Patient education (eg, goals of treatment, expected and potential serious toxicities, drug therapy, monitoring and management plan)

Implement*

- Provide patient education regarding all elements of treatment plan
- Survivorship care plan (eg, primary prevention of other diseases, such as infections, and other cancers; support systems for maintaining healthy lifestyle choices and BMI)

Follow-up: Monitor and Evaluate

- Determine disease response to treatment (see section "Evaluation of Therapeutic Outcomes") and occurrence of disease progression or recurrence (cancer imaging studies, CEA if previously elevated)
- Presence of adverse effects (see section "Evaluation of Therapeutic Outcomes" and Tables 147-5 to 147-7)
- Patient adherence to treatment plan using multiple sources of information (eg, patient self-report, medication administration records or refill data)
- Patient's satisfaction with treatment, including understanding of adherence

**Collaborate with patient, caregivers, and other healthcare professionals.*

4 Standard adjuvant chemotherapy regimens include a fluoropyrimidine (fluorouracil [with leucovorin] or capecitabine) in combination with oxaliplatin (FOLFOX or CapeOx) or administered alone (**Table 147-5**).[59–61] The addition of oxaliplatin is superior to fluoropyrimidines alone in stage III colon cancer, but this benefit has not been observed in stage II colon cancer.[50]

TABLE 147-5 Chemotherapy Regimens for the Adjuvant Treatment of Colorectal Cancer

Regimen	Agents	Comments
FOLFOX[62]	Oxaliplatin 85 mg/m² IV on day 1 Leucovorin 400 mg/m² IV on day 1 Fluorouracil 400 mg/m² IV bolus, after leucovorin on day 1, then 1,200 mg/m²/day × 2 days CIV (total 2,400 mg/m² over 46-48 hours) Repeat every 2 weeks × 24 weeks[a]	Preferred regimen for stage III colon and rectal cancer high-risk stage colon cancer; common toxicities: sensory neuropathy, neutropenia.
CapeOx[63]	Oxaliplatin 130 mg/m² IV day 1 Capecitabine 1,000 mg/m² twice daily orally days 1 through 14 Each cycle lasts 3 weeks × 24 weeks[a]	Improved DFS in patients with stage III colon cancer compared to capecitabine alone or Roswell Park Regimen; common dose-limiting toxicities: neuropathies and hand-foot syndrome. A preferred regimen for adjuvant rectal therapy.
Capecitabine[64]	Capecitabine 1,000 mg/m² to 1,250 mg/m² PO twice daily on days 1 through 14 Each cycle lasts 14 days and is repeated every 3 weeks × 24 weeks	Equivalent DFS as compared with the Mayo Clinic regimen with improved tolerability; hand-foot syndrome common, useful for patients without vascular access or who have difficulties with travel to infusion center
Roswell Park Regimen[65]	Leucovorin 500 mg/m² IV day 1 over 2 hours Fluorouracil 500 mg/m² IV bolus 1 hour after leucovorin Repeat weekly for 6 of 8 weeks × 4 cycles	Leukopenia common dose-limiting toxicity, diarrhea, and stomatitis common
Simplified Biweekly[62]	Leucovorin 400 mg/m² per day IV Fluorouracil 400 mg IV bolus, after leucovorin, then 1,200 mg/m²/day days 1 and 2 (total 2,400 mg/m² over 46-48 hours) for 2 consecutive days Repeat every 2 weeks × 12 cycles	Hand-foot syndrome common

[a]Known as mFOLFOX6; survival benefit has not been demonstrated for patients 70 years and older.

[b]In patients with low-risk stage III (T1-3, any N), 3 months of CapeOX is noninferior to 6 months of CapeOX for DFS but this has not been proven for FOLFOX. In patients with high-risk stage III disease (T4, N1-2, or any T, N2), 3 months of FOLFOX is inferior to 6 months of FOLFOX for DFS, but this has not been proven with CapeOX. Grade 3 neuropathy is lower with 3 months of CapeOX or FOLFOX.

CIV, continuous intravenous infusion; DFS, disease-free survival; OS, overall survival; PO, by mouth.

Data from References 50, 59–61.

4 **Fluorouracil Plus Oxaliplatin Regimens** Current National Comprehensive Cancer Network (NCCN) guidelines recommend the FOLFOX (fluorouracil/leucovorin and oxaliplatin) regimen as the preferred treatment for patients with stage III colon cancer who can tolerate combination therapy.[50] These recommendations are based on results from the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial, where the addition of oxaliplatin resulted in a 20% risk reduction in disease recurrence and increased 5-year disease-free survival (73% vs 67%) as compared with fluorouracil plus leucovorin alone.[66] With a median follow-up of 82 months, the addition of oxaliplatin resulted in a statistically significant absolute 6-year overall survival difference of 2.5%.

FOLFOX was associated with increased risk of paresthesia, neutropenia, and gastrointestinal toxicity (nausea, vomiting, and diarrhea) but were manageable with supportive care. This initial trial was performed with FOLFOX4 dosing schedule, more recent studies have further modified the regimen to improve tolerability and the most current standard is the mFOLFOX6 regimen.[50] A survival benefit has not been demonstrated for FOLFOX in patients with stage II colon cancer, but it is often used in stage II patients with multiple high-risk factors.[59]

Toxicity associated with fluorouracil differs based on the dose, route, and schedule of administration. Leukopenia is the primary dose-limiting toxicity of IV bolus fluorouracil, although diarrhea, stomatitis, and nausea and vomiting can also occur.[62] The incidence and severity of stomatitis can be significantly reduced with the use of oral cryotherapy. In this approach, the patient is instructed to chew and hold ice chips in the mouth during the period between 5 minutes prior to and 30 minutes following the bolus injection of fluorouracil. The protective effects of this procedure are probably related to the local vasoconstriction caused by the ice chips, which temporarily reduces blood flow to the oral mucosa, thereby reducing drug exposure to the oral mucosa.

Although continuous IV infusion fluorouracil is generally well tolerated, dose-limiting toxicities can be substantial. A distinct toxicity, palmar–plantar erythrodysesthesia (“hand-foot syndrome” or PPE), and stomatitis occur most frequently with this route of administration.[62] Hand-foot syndrome occurs in 24% to 40% of patients receiving extended continuous IV infusions and is characterized by painful swelling and erythroderma of the soles of the feet, palms of the hands, and distal fingers. The skin toxicity is fully reversible on interruption of therapy or dose reduction and is not life threatening, but it can be significant and acutely disabling. The risk of stomatitis, diarrhea, and hematologic toxicity is not substantial at standard doses, but it increases with increasing fluorouracil doses. No significant difference is noted in the incidence of mucositis, diarrhea, nausea and vomiting, or alopecia between continuous and bolus IV fluorouracil administration.[62]

An additional determinant of fluorouracil toxicity, regardless of the method of administration, is related to its catabolism and pharmacogenomic factors. Dihydropyrimidine dehydrogenase (DPD) is the main enzyme responsible for the catabolism of fluorouracil to inactive metabolites. A rare pharmacogenetic disorder characterized by complete or near-complete deficiency of this enzyme has been identified in patients with cancer. Patients with this enzyme deficiency develop severe toxicity, including death, after fluorouracil administration.

Molecular studies have identified a relationship between allelic variants in the *DPYD* gene (the gene that encodes DPD) and a deficiency in DPD activity.[50] An approved genetic test for *DPYD* polymorphisms is available to identify patients who would require lower fluorouracil doses to avoid severe toxicity, but pretreatment DPYD genotyping is not recommended.

Because of the wide inter- and intrapatient variability in fluorouracil pharmacokinetics and a narrow therapeutic range, pharmacokinetic optimization of fluorouracil represents a potential strategy to individualize dosing and optimize efficacy and minimize adverse effects. Results from controlled clinical trials suggest that therapeutic drug monitoring reduces variability in fluorouracil exposure and reduces risk of grade 3/4 toxicities in patients with colorectal cancer.[64] Compared to conventional body surface area (BSA)–based fluorouracil dosing, therapeutic dose monitoring with pharmacokinetic-guided dosing improved overall response rates from 18% to 33%. An improvement in overall survival, however, was not statistically significant. Valid assay methods that facilitate therapeutic drug monitoring are available and are being used in some centers. Algorithms are available for specific treatment protocols that enable practitioners to determine doses based on patient physiological and pathophysiological characteristics, and therapeutic drug monitoring with adaptive dosing has been recommended.[64] Implementation of this dosing strategy in practice settings will be required to determine if it will indeed improve therapeutic outcomes for patients with colorectal cancer.

The addition of leucovorin to fluorouracil regimens increases the binding affinity of the active fluorouracil metabolite to thymidylate synthase (TS), thus enhancing its cytotoxic activity. Leucovorin administration prior to fluorouracil is the most effective approach to enable intracellular-reduced folates to accumulate prior to fluorouracil administration. When leucovorin is unavailable, levoleucovorin, the active isomer of racemic leucovorin, can be substituted as an alternative. The recommended levoleucovorin dose is 50% of the leucovorin dose.[63]

Oxaliplatin has minimal renal toxicity, myelosuppression, and nausea and vomiting when compared with other platinum-based drugs. Oxaliplatin is associated with both acute and persistent neuropathies.[67] The acute neuropathies occur within 1 to 2 days of dosing and resolve within 2 weeks. The neuropathies usually occur peripherally, but may also occur in the jaw and tongue. A rare acute syndrome of pharyngolaryngeal dysesthesia (1%-2% of patients) is characterized by subjective sensations of difficulty in swallowing and shortness of breath. Overall, acute neuropathies occur in about 90% of patients, and are

precipitated or exacerbated by exposure to cold temperatures or cold objects. Thus, patients should be instructed to avoid cold drinks and use of ice, and to cover skin before exposure to cold or cold objects. Several prophylactic and treatment strategies have been studied with varying degrees of success. Persistent neuropathy is typically a cumulative adverse effect, occurring after 8 to 10 cycles. The neuropathy is characterized by paresthesia, dysesthesia, and hypoesthesia, but may also include deficits in proprioception that can interfere with daily activities (eg, writing, buttoning, swallowing, and difficulty walking as a result of impaired proprioception). Persistent neuropathy occurs in about one-half of patients receiving oxaliplatin but usually resolves with dosage reductions or cessation of oxaliplatin therapy.[50,67] Prophylaxis with calcium and magnesium infusions has not been proven effective. A “stop-and-go” approach where oxaliplatin is temporarily discontinued after 3 months of therapy (or sooner with significant neuropathic symptoms) with the other drugs continued reduces neurotoxicity without compromising antitumor activity and has been advocated.[50] Oxaliplatin can be reinitiated at disease progression in those patients that experience near complete resolution of neurotoxicity. Anticonvulsant and antidepressant agents are potentially useful to treat symptoms.

Fluorouracil/Leucovorin Regimens Clinical studies comparing the efficacy of bolus and continuous infusion schedules generally favor continuous infusion of fluorouracil, which is probably related to its short plasma half-life and S-phase specificity for optimal TS inhibition. Continuous IV infusions also permit increased fluorouracil dose intensity, which may account for the higher response rates observed with prolonged infusions of fluorouracil. Most commonly, fluorouracil is administered by both IV bolus injection and continuous IV infusion (eg, FOLFOX and simplified biweekly regimens; see Table 147-5).

4 **Capecitabine Regimens** Capecitabine has been evaluated as a replacement for fluorouracil in an attempt to improve the safety and ease of administration of the chemotherapy regimen. Capecitabine is converted to fluorouracil through a three-step activation process, the final step being activation by thymidine phosphorylase, which is present in greatest concentrations at the tumor site. These activation steps lead to about a threefold increase in tumor fluorouracil levels. CapeOx (capecitabine plus oxaliplatin) has been demonstrated to prolong 3-year disease-free survival (71% vs 67%) as compared to bolus fluorouracil alone in patients with stage III disease, but no difference in overall survival was observed.[68] The toxicities differed for the two regimens, with increased risks of

neuropathies and hand-foot syndrome with CapeOx and increased risk of neutropenia/neutropenic fever with fluorouracil. Capecitabine has been shown to be noninferior to bolus fluorouracil and leucovorin in patients with stage III colon cancer. Both regimens were given for 6 months.[69] Disease-free survival between the groups was found to be equivalent. Secondary endpoints of relapse-free survival (hazard ratio [HR] 0.86; $P = 0.04$) and safety were improved with capecitabine. In particular, the incidence of diarrhea, stomatitis, and neutropenia was decreased with capecitabine, but the incidence of hand-foot syndrome was increased with capecitabine. Doses may need to be reduced in patients who experience side effects. Patients with renal dysfunction can accumulate drug and often require dose modification. This regimen is recommended when patients are unable to tolerate combination therapy.[50]

Selection of an Adjuvant Regimen Selecting a specific regimen from those listed in Table 147-5 requires an assessment of several patient-specific factors, including the performance status of the patient, comorbid conditions that may exist, and patient preferences for treatment based on lifestyle factors that are important to the patient. If a clinical trial is not an option, most patients with a good performance status will receive FOLFOX. Some patients prefer to not receive IV chemotherapy and may choose CapeOX. Single-agent capecitabine may be the preferred option for patients with preexisting neuropathies, such as diabetic patients, or those patients wishing not to receive IV chemotherapy for any other reason. Fluorouracil and leucovorin has limited use at this time but is an acceptable option for patients, with low risk or average-risk stage II disease or those who cannot receive oxaliplatin and are unable to tolerate or take oral capecitabine. For example, patients who develop severe hand-foot syndrome may tolerate IV bolus fluorouracil/leucovorin because the risk of this toxicity is minimal with this administration method.

Patient age should also be considered when selecting an appropriate regimen. Subset analysis of the MOSAIC and National Surgical Adjuvant Breast and Bowel Project (NSABP)-C07 trials have demonstrated no overall survival benefit from adding oxaliplatin to patients older than the age of 70 years and these patients may be appropriate for fluoropyrimidine-based therapy.[59,65]

The usual length of adjuvant therapy is 6 months. Recently noninferiority studies have compared 3 versus 6 months of therapy in an effort to minimize long-term toxicities, particularly neuropathy associated with FOLFOX and CapeOX. The results of two meta-analyses found that 3 months of CapeOX is noninferior to 6 months of CapeOX in terms of disease-free survival in patients with low-risk stage III disease, but the same results have not been proven for

FOLFOX and overall survival results were not evaluated.[61] In patients with high-risk stage III disease, a randomized controlled trial showed that 6 months of FOLFOX is superior to 3 months (3-year disease-free survival 76% vs 72% [HR 1.27; 95% CI, 1.07-1.51]), but this has not been evaluated with CapeOX.[60] The incidence of grade 3 neuropathy is lower with 3 months of CAPEOX or FOLFOX. Therefore, it remains controversial whether 3 months of adjuvant therapy is appropriate.

Adjuvant and Neoadjuvant Therapy for Rectal Cancer

5 Rectal cancer involves those tumors found below the peritoneal reflection in the most distal 15 cm of the large bowel, and as such is distinct from colon cancer in that it has a propensity for both local and distant recurrence. The higher incidence of local failure and overall poorer prognosis associated with rectal cancer is a result of anatomic limitations in excising adequate radial margins around the rectal tumor. Most patients with stage II or stage III rectal cancer should receive combined-modality therapy consisting of XRT and fluoropyrimidine-based chemotherapy perioperatively.[51]

5 Neoadjuvant (preoperative) chemoradiation is considered standard of care for most patients with stage II or III rectal cancer because of the significant reduction in local recurrence, fewer toxicities, and improved sphincter-preserving surgeries as compared to postoperative chemoradiation.[51,58] However, some patients are unable to tolerate a typical 5- to 6-week chemoradiation regimen and may be more appropriate candidates for a short course of preoperative radiation therapy alone.[51] Chemotherapy combined with XRT typically involves continuous infusion fluorouracil, oral capecitabine, or bolus fluorouracil and leucovorin; the addition of oxaliplatin to either fluoropyrimidine was associated with increased toxicities without clear improvements in complete remission rates or survival benefit. Although oxaliplatin and other agents continue to be evaluated in this setting, the addition of oxaliplatin, irinotecan, or biologic agents (eg, cetuximab, panitumumab, and bevacizumab) is currently not recommended.

5 Current NCCN guidelines for rectal cancer indicate that preoperative fluoropyrimidine-based chemotherapy plus XRT is the preferred initial treatment for resectable stage IIA (T_3 N_0), stage III (any T, N_{1-2}, or T_4/locally unresectable lesions).[51] This should be followed by additional adjuvant chemotherapy after surgery to a total 6 months of chemotherapy (combined total from preoperative

and postoperative regimens). Postoperative treatment regimens include fluoropyrimidine-based chemotherapy. FOLFOX or CapeOx are preferred regimens, but fluorouracil and leucovorin combination regimens and capecitabine can be used. Combined chemoradiation is preferred for patients that do not receive preoperative radiation therapy.[51,58]

Metastatic Disease: Initial Therapy

Patients are generally classified as having resectable, potentially resectable, or unresectable metastatic disease. Surgery and XRT are used to manage isolated sites of tumor. Chemotherapy is used for disseminated disease and the primary treatment modality for unresectable metastatic colorectal cancer. Patients with resectable or potentially resectable metastases are candidates for multimodality therapy.[70] Tumor *RAS* (*KRAS* exon 2 and nonexon 2 and *NRAS*) and *BRAF* genotyping for mutation status and determination of tumor MMR or MSI status (if not previously done) are recommended for patients at the time when metastatic disease is diagnosed to identify appropriate treatment options.[50,51] Testing can also be performed on archived tissue samples obtained when the cancer was initially diagnosed.

Resectable (or Potentially Resectable) Metastatic Colorectal Cancer

6 Patients that present with metastatic disease isolated to the liver or lung and who undergo resection of all metastatic and primary lesions (metastasectomy) have an increased probability of survival compared with those whose metastatic lesions remain unresected.[70] Therefore, strategies to increase the success rate of these resections (or convert unresectable lesions to resectable) is the primary goal in these patients. Neoadjuvant chemotherapy, also referred to as conversional chemotherapy, is the primary method to increase complete resection rates in both patients with resectable or potentially resectable liver or lung lesions. In some cases, individuals with metastatic disease initially deemed unresectable may achieve significant tumor regression following neoadjuvant chemotherapy to then be considered for surgery.[50]

The optimal sequencing of chemotherapy for patients with initially resectable metastatic disease is controversial, as treatment options include surgery followed by chemotherapy or perioperative (pre- and postoperative) chemotherapy with surgery.[50,51] Because of the high risk of recurrence following resection of

metastases, postoperative chemotherapy is always recommended. Administration of both pre- and postoperative chemotherapy is common practice, but the risk of hepatotoxicity associated with preoperative chemotherapy should be considered. Irinotecan-containing regimens can cause steatohepatitis and oxaliplatin-containing regimens can cause vascular sinusoidal obstructive liver injury.[50] Therefore, surgery is performed as soon as possible after the disease becomes resectable and preoperative chemotherapy is limited to a 2- to 3-month time period while patients undergo close monitoring.

Regimens are the same for neoadjuvant and adjuvant therapy. The choice of agents depends on patient-specific factors and includes regimens such as FOLFOX, CapeOX, FOLFIRI (infusional fluorouracil and leucovorin, oxaliplatin, and irinotecan). Bevacizumab can be added to these regimens. If patients receive bevacizumab, surgery should not occur within 6 weeks of the last dose of therapy, and bevacizumab should not be restarted until 6 to 8 weeks after surgery due to the risk of bleeding or wound healing complications. Postoperative chemotherapy should be administered to patients to complete a total of 6 months of chemotherapy (pre- and postoperative).[50]

Patients with unresectable lesions are eligible for the same chemotherapy regimens. However, because the primary goal is surgical resection whenever possible, patients should be evaluated for possible resection after every 2 months of therapy. If resection occurs, adjuvant chemotherapy should be administered to complete a total of 6 months of chemotherapy.

6 **Hepatic-Directed Therapies** Hepatic-directed therapy, in addition to or as an alternative to surgical resection, can be considered in individuals with liver-only or liver-predominant metastatic disease. Hepatic artery infusion (HAI) involves the placement of a permanent access catheter to the hepatic artery through which chemotherapy can be infused directly into the liver.[50] This approach offers the advantage of delivering high drug concentrations to tumors locally, thereby limiting systemic toxicities. Floxuridine with dexamethasone and fluorouracil with or without leucovorin are the most commonly used agents. HAI is associated with potential biliary toxicity and the technical expertise required warrants use in selected patients by experienced practitioners.[50] Another option is hepatic transarterial chemoembolization, which delivers high concentrations of cytotoxic agents directly to the tumor and results in the embolization or devascularization of the liver, blocking perfusion of the tumor and eliminating its blood supply. This procedure involves the instillation of a mixture that incorporates chemotherapeutic agents, radioactive contrast dye,

and/or an embolic agent directly into the hepatic artery. Agents most commonly used include doxorubicin, mitomycin, and cisplatin, which are usually dissolved in about 10 to 15 mL of a radiographic contrast dye. The addition of an embolic agent to the mixture results in either a temporary or permanent occlusion of the hepatic artery. Alternatively, drug-eluding beads of doxorubicin or irinotecan mixed with an embolic agent have been used. Local tumor response rates with these strategies are high and most patients will experience partial or complete relief of symptoms. Toxicities include postembolization syndrome characterized by nausea, fatigue, and transient elevations in hepatic enzymes and bilirubin, gastrointestinal ulcerations, and biliary toxicity. Although various hepatic-directed therapies offer potential disease palliation in select patients with unresectable, yet limited hepatic metastases, no survival advantage has been demonstrated. XRT can also be given to sites of hepatic tumor with external beam radiation therapy or percutaneous arterial injection of micron-sized embolic particles loaded with a radioisotope (radioembolization). Other less common methods include tumor ablation procedures using radiofrequency ablation or microwave energy to generate heat that destroys localized tumor cells. Cryoablation can also be used, which includes placement of a cryoprobe into the tumor, either percutaneously or intraoperatively, and then lowering the probe temperature to −20°C to −40°C and rewarming it in cycles, resulting in formation of an ice ball that causes tumor destruction. These strategies may be useful for patients who have very small hepatic lesions and are unable to undergo liver resection surgery, but they are less successful than surgical interventions.[50]

Unresectable Metastatic Colorectal Cancer

Unless the primary tumor is causing an obstruction, surgery in patients with established unresectable disease is rarely indicated. XRT may be useful to control localized symptoms in patients with metastatic colorectal cancer. Systemic chemotherapy palliates symptoms and improves survival in patients with unresectable disease. Common treatment regimens include combinations of cytotoxic and biologic agents.

7 **Chemotherapy** Several chemotherapy regimens are acceptable for initial treatment of metastatic colorectal cancer.[50] The goals of therapy, history of prior chemotherapy, tumor *RAS* and MMR/MSI mutation status, performance status/comorbidities, and risk of drug-related toxicities should be considered when an appropriate management strategy is defined for each individual.

Treatment regimens are the same for metastatic cancer of the colon and rectum. **Table 147-6** lists common initial chemotherapeutic regimens for metastatic disease.[50,51]

TABLE 147-6 Initial Chemotherapeutic Regimens for Metastatic Colorectal Cancer[a]

Regimen	Agents	Major-Dose Limiting Toxicities	Comments
Patients Appropriate for Intensive Therapy with *RAS* Mutations			
FOLFOX+/− bevacizumab	Oxaliplatin 85 mg/m² IV day 1 Leucovorin 400 mg/m² IV day 1 Fluorouracil 400 mg/m² IV bolus, after leucovorin day 1, then 1,200 mg/m²/day × 2 days CIV (total 2,400 mg/m² over 46-48 hours) Repeat every 2 weeks +/− Bevacizumab 5 mg/kg IV day 1 before FOLFOX Repeat cycle every 2 weeks	FOLFOX: Sensory neuropathy, neutropenia Bevacizumab: hypertension, thrombosis, proteinuria	Most commonly used first-line regimen
CapeOx +/− bevacizumab	Oxaliplatin 130 mg/m² IV day 1 Capecitabine 1,000 mg/m² orally twice a day, days 1-14 Repeat cycle every 3 weeks +/− Bevacizumab 7.5 mg/kg IV day 1 Repeat cycle every 3 weeks	CapeOx: Diarrhea, hand-foot syndrome, neuropathies Bevacizumab: hypertension, thrombosis, proteinuria	Reduced capecitabine dose better tolerated; patient must be able to be adherent and report side effects in a timely fashion
FOLFIRI+/− bevacizumab	Irinotecan 180 mg/m² IV day 1 Leucovorin 400 mg/m² IV day 1 Fluorouracil 400 mg/m² IV bolus, after leucovorin day 1, then 1,200 mg/m²/day × 2 days CIV (total 2,400 mg/m² over 46-48 hours) +/− Bevacizumab 5 mg/kg IV day prior to FOLFIRI Repeat cycle every 2 weeks	FOLFIRI: Diarrhea, mucositis, neutropenia Bevacizumab: hypertension, thrombosis, proteinuria	May be preferred in patients who have preexisting neuropathy or those in which neuropathy may be debilitating to their line of work (eg, musician)
Fluorouracil/ leucovorin +/− bevacizumab	See Table 147-5 for fluorouracil/leucovorin regimen options +/− Bevacizumab 5 mg/kg IV day prior to fluorouracil and leucovorin Repeat cycle every 2 weeks	Fluorouracil/Leucovorin: diarrhea, hand-foot syndrome, mucositis, neutropenia Bevacizumab: hypertension, thrombosis, proteinuria	Infusional fluorouracil/leucovorin regimen preferred to bolus fluorouracil regimen. Infusional regimens tend to have more hand-foot syndrome and stomatitis and bolus regimens more neutropenia; weekly or bimonthly schedule of leucovorin plus fluorouracil (either bolus or continuous infusion) may be more convenient for the patient in terms of fewer scheduled clinic appointments, less interference with work schedules, and ease of dose adjustments based on toxicity
Capecitabine +/− bevacizumab	Capecitabine 850-1,250 mg/m² orally twice a day, days 1-14 +/− Bevacizumab 7.5 mg/kg IV day 1 Repeat cycle every 3 weeks	Capecitabine: Hand-foot syndrome, diarrhea, hyperbilirubinemia Bevacizumab: hypertension, thrombosis, proteinuria	May be preferred in those without a port or limited venous access; patient must be able to be adherent and report side effects in a timely fashion
FOLFOXIRI +/− bevacizumab	Irinotecan 165 mg/m² IV day 1 prior to oxaliplatin Oxaliplatin 85 mg/m² IV prior to leucovorin day 1 Leucovorin 400 mg/m² IV day 1 prior to fluorouracil Fluorouracil 1,200 mg/m²/day × 2 days CIV (total 2,400 mg/m² over 48 hours)[b] Repeat cycle every 2 weeks +/− Bevacizumab 5 mg/kg IV day 1 before FOLFOXIRI Repeat cycle every 2 weeks	FOLFOXFIRI: Neutropenia, diarrhea, stomatitis, peripheral neurotoxicity, thrombocytopenia Bevacizumab: hypertension, thrombosis, proteinuria	More neutropenia and peripheral neurotoxicity compared to FOLFIRI; often used in medically fit individuals with diffuse aggressive disease to palliate symptoms and as potential conversion therapy

Patients Appropriate for Intensive Therapy with *RAS* or *BRAF* Wild-Type and Left-Sided Tumors			
FOLFOX + cetuximab or panitumumab	FOLFOX regimen + cetuximab (400 mg/m² IV loading dose, then cetuximab 250 mg/m² IV weekly thereafter OR cetuximab 500 mg/m² IV every 2 weeks) IV before FOLFOX OR FOLFOX regimen + panitumumab 6 mg/kg IV day 1 before FOLFOX Repeat cycle every 2 weeks	FOLFOX: Sensory neuropathy, neutropenia Cetuximab: Papulopustular and follicular rash, asthenia, constipation, diarrhea, allergic reactions, hypomagnesemia Panitumumab: rash, diarrhea, hypomagnesemia	Only *RAS* wild-type tumor
FOLFIRI + cetuximab or panitumumab	FOLFIRI + cetuximab (400 mg/m² IV loading dose, then cetuximab 250 mg/m² IV weekly thereafter OR cetuximab 500 mg/m² IV every 2 weeks) IV before FOLFIRI OR FOLFIRI + panitumumab 6 mg/kg IV day 1 before FOLFIRI Repeat cycle every 2 weeks	FOLFIRI: Diarrhea, mucositis, neutropenia Cetuximab: papulopustular and follicular rash, asthenia, constipation, diarrhea, allergic reactions, hypomagnesemia Panitumumab: Rash, diarrhea, hypomagnesemia	Only *RAS* wild-type tumor; preferred for patients with preexisting neuropathy or those in which neuropathy may be debilitating to their line of work (eg, musician)
Patients NOT Appropriate for Intensive Therapy with *RAS* Mutations			
Infusional fluorouracil + leucovorin +/− bevacizumab	Fluorouracil 400 mg/m² IV bolus, after leucovorin on day 1, then 1,200 mg/m²/day × 2 days CIV (total 2,400 mg/m² over 46-48 hours) Repeat cycle every 2 weeks +/− Bevacizumab 5 mg/kg IV day 1 prior to fluorouracil and leucovorin Repeat cycle every 2 weeks	Infusional fluorouracil/leucovorin: neutropenia, diarrhea Bevacizumab: hypertension, bleeding, proteinuria	Infusional fluorouracil/leucovorin regimen preferred to bolus fluorouracil regimen
Capecitabine +/− bevacizumab	Capecitabine 850-1,250 mg/m² orally twice a day, days 1-14 +/− Bevacizumab 7.5 mg/kg IV day 1 Repeat cycle every 3 weeks	Capecitabine: Hand-foot syndrome, diarrhea, hyperbilirubinemia Bevacizumab: hypertension, thrombosis, proteinuria	
Patients NOT Appropriate for Intensive Therapy with *RAS* or *BRAF* Wild-Type and Left-Sided Tumors			
Cetuximab[c]	Cetuximab 400 mg/m² IV loading dose, then cetuximab 250 mg/m² IV weekly thereafter Or Cetuximab 500 mg/m² IV every 2 weeks	Papulopustular and follicular rash, asthenia, constipation, diarrhea, allergic reactions, hypomagnesemia	Only *RAS* wild-type tumor
Panitumumab[c]	6 mg/kg IV over 60 minutes every 2 weeks	Rash, hypomagnesemia, rare allergic reactions	Only *RAS* wild-type tumor
Patients NOT Appropriate for Intensive Therapy with dMMR or MSI-H			
Nivolumab	3 mg/kg IV every 2 weeks or 240 mg IV every 2 weeks[d]	Immune-mediated side effects (most common: skin, liver, kidney, gastrointestinal tract, lung and endocrine systems)	Only in MMR-d or MSI-H tumors. Patients should be closely monitored for side effects and report any side effects immediately as interruption of treatment or initiation of corticosteroids may be needed
Pembrolizumab	2 mg/kg IV every 2 weeks or 200 mg IV every 3 weeks[d]	Immune-mediated side effects (most common: skin, liver, kidney, gastrointestinal tract, lung and endocrine systems)	Only in MMR-d or MSI-H tumors. Patients should be closely monitored for side effects and report any side effects immediately as interruption of treatment or initiation of corticosteroids may be needed
Nivolumab + ipilimumab[c]	Nivolumab 3 mg/kg IV over 30 minutes and ipilimumab 1 mg/kg IV over 30 minutes every 3 weeks × 4 doses, then nivolumab 3 mg/kg IV or nivolumab 240 mg IV every 2 weeks[d]	Immune-mediated side effects (most common: skin, liver, kidney, gastrointestinal tract, lung and endocrine systems)	Only in MMR-d or MSI-H tumors. Patients should be closely monitored for side effects and report any side effects immediately as interruption of treatment or initiation of corticosteroids may be needed

[a]National Comprehensive Cancer Network (NCCN) Guideline recommendations for initial therapy. All recommendations are category 2A unless otherwise noted. Category 2A: based upon lower-evidence, there is uniform NCCN consensus that the intervention is appropriate.

[b]Original dosing was 1600 mg/m²/day but it is recommended that US patients use this dose as they don't tolerate fluorouracil as well.

[c]NCCN Category 2B: based upon lower-evidence, there is NCCN consensus that the intervention is appropriate.

[d]Flat dosing is preferred.

Data from References 50, 51.

Currently, most metastatic colorectal cancers are incurable, and treatment goals are to control cancer growth, reduce patient symptoms, improve quality of life, and extend survival. The benefit of palliative chemotherapy for metastatic colorectal cancer as compared to observation or supportive care alone with regard to these treatment goals has been established. Results from multiple randomized trials and meta-analyses demonstrate that chemotherapy prolongs life and improves quality of life of patients with metastatic colorectal cancer.[71]

Most first-line chemotherapy regimens for metastatic colorectal cancer incorporate a fluoropyrimidine. Irinotecan or oxaliplatin added to a fluoropyrimidine-based regimen significantly improves response rates, progression-free survival, and median survival.[50,51] The addition of the targeted anti-angiogenesis agent bevacizumab further improves response rate and survival. Patients considered appropriate for initial intensive chemotherapy usually receive an oxaliplatin or irinotecan-containing regimen with infusional fluorouracil plus leucovorin and bevacizumab (unless contraindicated) or an EGFR inhibitor (if their tumors are left-sided and express *RAS* and *BRAF* wild type). Capecitabine can be substituted for fluorouracil and leucovorin. Patients who are not appropriate candidates for initial intensive therapy may be treated with fluoropyrimidine monotherapy with or without bevacizumab, EGFR inhibitor monotherapy (if their tumors are left-sided and express *RAS* and *BRAF* wild type) or immunotherapy if they have dMMR or MSI-H, as appropriate.[50] Patients may receive multiple different regimens; the sequence of drugs used appears less important than exposure to all active agents during the course of cancer treatments. Please refer back to the *Adjuvant Systemic Chemotherapy Section* for more information on the toxicities of the regimens used in both the adjuvant and metastatic settings.

Fluorouracil can be administered as an IV bolus, a continuous infusion, or a combination of the two in the metastatic setting. Continuous IV infusion fluorouracil regimens increase the duration of drug exposure during the S-phase of the cell cycle, increase cytotoxicity, and are better tolerated than bolus administration. When combined with irinotecan or oxaliplatin, infusional fluorouracil is recommended because of improved efficacy.[50]

Unlike in the adjuvant setting, irinotecan added to fluorouracil plus leucovorin as initial therapy for metastatic disease improves tumor response rates, time-to-progression, and overall survival.[72] The most common adverse effects of irinotecan in these regimens are diarrhea, neutropenia, nausea and vomiting, dehydration, asthenia, abdominal pain, and alopecia; diarrhea and

neutropenia are dose limiting. Two distinct patterns of diarrhea have been described. Early-onset diarrhea occurs during or within 2 to 6 hours after irinotecan administration and is characterized by lacrimation, diaphoresis, abdominal cramping, flushing, and/or diarrhea. These cholinergic symptoms, thought to be caused by inhibition of acetylcholinesterase, respond to atropine 0.25 to 1 mg given IV or subcutaneously. About 10% of patients experience acute symptoms during or shortly following the irinotecan. More commonly, late-onset diarrhea occurs 1 to 12 days after irinotecan administration and may last for 3 to 5 days. Late-onset diarrhea may require hospitalization or discontinuation of therapy, and fatalities have been reported. The risk of late-onset diarrhea can be decreased with aggressive antidiarrheal intervention. Aggressive intervention with high-dose loperamide therapy should consist of 4 mg taken at the first sign of soft or watery stools, followed by 2 mg orally every 2 hours until symptom-free for 12 hours; this regimen can be modified to 4 mg taken orally every 4 hours during the night.

The severity of delayed diarrhea is correlated with the systemic exposure (ie, area under the concentration-vs-time curve) of irinotecan and SN-38 (irinotecan's active metabolite) and with genetic polymorphisms in the enzyme uridine diphosphate-glucuronosyltransferase (UGT1A1), which is responsible for the glucuronidation of SN-38 to inactive metabolites. Reduced or deficient levels of the UGT1A1 enzyme are observed in Gilbert syndrome, a familial hyperbilirubinemia disorder, and correlate with irinotecan-induced diarrhea and neutropenia.[103] FDA-approved testing to determine *UGT1A1* genotype is commercially available. Although some individuals advocate testing *UGT1A1* genotype prior to starting irinotecan, widespread testing has not been adopted.[50,73] The prescribing information recommends an initial reduced dose of irinotecan in patients with *UGT1A1*28* genotype.

Oxaliplatin, in combination with infusional fluorouracil plus leucovorin, is FDA-approved for use in first-line and salvage regimens for metastatic colorectal cancer. Oxaliplatin incorporation into fluorouracil-based regimens as first-line therapy for metastatic colorectal cancer is associated with higher response rates and prolonged progression-free survival, with variable effects on overall survival.[74] Oxaliplatin is not effective as a single agent in colorectal cancer and is therefore only used in combination regimens.

To further improve survival rates achieved with FOLFOX and FOLFIRI regimens, a four-drug regimen (FOLFOXIRI) was developed and has been compared with FOLFIRI. FOLFOXIRI improved progression-free survival and overall survival compared to FOLFIRI, and a higher proportion of patients

receiving FOLFOXIRI were able to undergo radical resection of metastases.[50] As expected, FOLFOXIRI causes more neutropenia, neurotoxicity, diarrhea, and alopecia, but may be appropriate for medically fit individuals with diffuse aggressive disease to palliate symptoms and as potential conversion therapy.[50]

Capecitabine is an oral, tumor-activated, and tumor-selective fluoropyrimidine carbamate. Capecitabine can be administered alone or in combination with oxaliplatin (CapeOx also known as XELOX). When administered alone, it has higher response rates but comparable time-to-progression and median survival to fluorouracil/leucovorin.[75] CapeOx has similar progression-free and overall survival when compared with FOLFOX.[50] Hand-foot syndrome is common with capecitabine, while grades 3 or 4 neutropenia and stomatitis are more common with fluorouracil plus leucovorin. The convenience of oral administration and different toxicity profile make capecitabine a useful substitute for infusional fluorouracil in regimens for metastatic disease.

7 **Targeted Therapy** Current guidelines and clinical practice recommend the addition of targeted therapy to one of the chemotherapy backbones mentioned earlier.[50]

8 Bevacizumab is a recombinant, humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF). Results from randomized trials show a modest increased progression-free and overall survival benefit when combined with chemotherapy regimens as compared with chemotherapy alone.[50] Results of a meta-analysis of randomized controlled trials showed that the addition of bevacizumab results in higher treatment-related mortality than chemotherapy alone (relative risk 1.33; 95% CI, 1.02-1.73, $P = 0.04$) because of hemorrhage (24%), neutropenia (12%), and gastrointestinal perforation (7%).[76]

Hypertension is also common with bevacizumab.[50] The hypertension is easily managed with oral antihypertensive agents. Bleeding, thromboembolism and proteinuria also can occur with bevacizumab. Proteinuria is monitored with urine dipsticks regularly during therapy, and therapy is withheld in patients with 2+ protein or more, confirmed with a 24-hour urine collection. The risk of gastrointestinal perforation is increased by the addition of bevacizumab and extensive prior intra-abdominal surgery. Patients complaining of abdominal pain associated with vomiting or constipation should be evaluated for this rare but potentially fatal complication. Bevacizumab is also associated with a twofold increased risk of arterial thrombotic events, with patients who are older than age 65 or who have a prior history of arterial thrombotic events at greatest risk.

Since bevacizumab can also interfere with wound healing, it is recommended there be at least a 6 to 8 week interval between the last dose of bevacizumab and elective surgery and wait at least 6 to 8 weeks to reinitiate bevacizumab after surgery. Necrotizing fasciitis can occur following wound healing or gastrointestinal perforation.

9 Cetuximab and panitumumab are monoclonal antibodies directed against EGFR. EGFR inhibitors may be used in combination with first-line chemotherapy regimens FOLFOX or FOLFIRI or administered as single agents, but should not be combined with bevacizumab because of increased toxicity and no efficacy benefit.[50] The benefit of EGFR inhibitors, however, is limited to patients with wild-type *RAS* and wild-type *BRAF* tumors and they should not be used in patients with tumor *RAS* or *BRAF* mutations.[50] Furthermore, patients with left-sided primary tumors have improved overall survival when treated with EGFR inhibitors while those with right-sided tumors (cecum to hepatic flexure) do not. Because fewer than 60% of patients with *KRAS* wild-type tumors respond to cetuximab or panitumumab, additional factors downstream of *RAS* signaling have been explored for their ability to predict response to EGFR inhibitors, including *BRAF* V600E mutation, and mutation or loss of *PTEN* or *PIK3CA*.[50,77] Tumors with wild-type *KRAS*/*NRAS* and *BRAF* V600E mutation do not respond to anti-EGFR antibodies.[50] The only situation where this might be beneficial is if the EGFR is administered in combination with a BRAF inhibitor, but at this time this has only been recommended after failure of the first-line setting (see section “Metastatic Disease: Second-Line and Subsequent Therapy”).[78]

Severe infusion reactions, including anaphylaxis, can occur with cetuximab (3%) and panitumumab (1%).[50] Administration of panitumumab seems feasible in those who experienced a reaction with cetuximab.[79] Skin toxicity is also a common side effect with these drugs and is not part of the infusion reaction. The presence of papulopustular skin rash has been shown to correlate with response and survival. It most commonly occurs within 2 to 4 weeks of therapy initiation and preventative therapy with topical corticosteroids with moisturizer, sunscreen, and oral doxycycline is recommended unless contraindications exist.[80] Both of these agents have also been associated with an increased risk for venous thromboembolism.[50]

10 **Immunotherapy** Immunotherapy is effective in dMMR tumors because these tumors encode mutant proteins and have the potential to be recognized and targeted by the immune system. Because the immune system can become

suppressed when programmed death-ligands 1 and 2 (PD-L1 and PD-L2) on tumor cells bind to programmed cell death protein (PD-1) receptors on T cells, the use of PD-1 inhibitor drug therapy is reasonable in these tumors. The PD-1 inhibitor nivolumab has also been evaluated in combination with ipilimumab, a cytotoxic-T-lymphocyte-associated protein 4 (CTLA4) inhibitor; these drugs act synergistically to promote T-cell antitumor activity.[81] Studies evaluating PD-1 inhibitor nivolumab with or without ipilimumab and pembrolizumab have focused on their use as subsequent-line therapy. However, in patients who may not tolerate first-line therapies, the use of immunotherapy is reasonable. For more information about these therapies, see section “Metastatic Disease: Second-Line and Subsequent Therapy” below.

Selection of an Initial Metastatic Regimen Several factors should be considered when selecting first-line therapy for metastatic colorectal cancer when disease palliation is the primary treatment goal. The first consideration is whether intensive therapy is appropriate for the patient. Those with multiple comorbidities or low performance status would likely better tolerate less-intensive therapy. The second consideration is *RAS* and *BRAF* status and side of tumor involvement. Those with *RAS* and *BRAF* wild-type and left-sided tumors can receive an EGFR inhibitor therapy. Also, patients with dMMR or MSI-H tumors who are not appropriate for intensive therapy could receive immunotherapy as first-line therapy. Once these factors are known, the selection of the appropriate regimen is based on the toxicity profile and convenience of administration for the patient. Based on the comparable results of FOLFIRI versus FOLFOX, either of these regimens is considered the reference standard in metastatic colorectal cancer. Most patients will receive first- and second-line regimens and patient preference for either sequence of treatments based on their different toxicity profiles is important. FOLFIRI may be chosen initially in patients with preexisting neuropathies, whereas FOLFOX may be chosen in patients with increased bilirubin or known UGT1A1 deficiency (known risk factors for delayed diarrhea). Alopecia occurs much more frequently with irinotecan compared to oxaliplatin combinations. Because FOLFOX can cause persistent neuropathy, a rationale for starting with FOLFIRI is that time-to-progression is longer with first-line treatment than in second line. Therefore, the time to death during which some patients will have to live with neuropathy may be shorter. Capecitabine is an appropriate substitute for IV fluorouracil in oxaliplatin combination regimens. Because of a higher response rate and modest survival benefit with FOLFOXIRI, this four-drug combination may be useful for patients with initially aggressive and symptomatic disease. Select patients who

are candidates for FOLFOXIRI may benefit from the addition of bevacizumab, but the incidence of moderate or severe toxicities is increased.

Metastatic Disease: Second-Line and Subsequent Therapy

Systemic chemotherapy represents the mainstay of therapy for patients who have progressive disease following initial treatment for metastatic disease. **Table 147-7** lists treatment options for refractory metastatic disease.[50,51] Treatment options are based on the type of and response to prior treatments, the site and extent of disease, and patient factors and treatment preferences.

TABLE 147-7 Second-line and Salvage Chemotherapy Regimens for Metastatic Colorectal Cancer[a]

Disease Progression with First-Line Regimen	Comments
First-Line Therapy: Oxaliplatin-Based Regimen ± Bevacizumab (ie, FOLFOX, CapeOX)	
Second-line options	
1. FOLFIRI or irinotecan	Use with caution in patients with elevated bilirubin
2. FOLFIRI + bevacizumab or ziv-aflibercept or ramucirumab	Use with caution in patients with elevated bilirubin; bevacizumab is preferred antiangiogenic agent based on toxicity and cost
3. Irinotecan + bevacizumab or ziv-aflibercept or ramucirumab	Use with caution in patients with elevated bilirubin; bevacizumab is preferred antiangiogenic agent based on toxicity and cost
4. FOLFIRI + cetuximab or panitumumab	Only if *RAS* wild-type and *BRAF* wild-type; if neither previously given; use with caution in patients with elevated bilirubin
5. Irinotecan ± cetuximab or panitumumab	Only if *RAS* wild-type and *BRAF* wild-type; if neither previously given; use with caution in patients with elevated bilirubin
6. Irinotecan ± (cetuximab or panitumumab) + vemurafenib	Only if *RAS* wild-type and *BRAF V600E* mutation positive; use with caution in patients with elevated bilirubin
7. Dabrafenib + trametinib + (cetuximab or panitumumab)	Only if *BRAF V600E* mutation positive
8. Encorafenib + binimetinib + (cetuximab or panitumumab)	Only if *BRAF V600E* mutation positive
9. Nivolumab ± ipilimumab	Only if dMMR/MSI-H
10. Pembrolizumab	Only if dMMR/MSI-H
11. Trastuzumab + (pertuzumab or lapatinib)	Only if *HER2*-amplified and *RAS* wild-type
First-Line Therapy: Irinotecan-Based Regimen ± Bevacizumab (ie, FOLFIRI)	
Second-line options	
1. FOLFOX or CapeOx ± bevacizumab	Bevacizumab FDA-approved to continue with second-line options
2. FOLFOX + cetuximab or panitumumab	Only if *RAS* wild-type and *BRAF* wild-type
3. Irinotecan + cetuximab or panitumumab	Only if *RAS* wild-type and *BRAF* wild-type; if neither previously given; use with caution in patients with elevated bilirubin
4. Irinotecan + (cetuximab or panitumumab) + vemurafenib	Only if *RAS* wild-type and *BRAF V600E* mutation positive; use with caution in patients with elevated bilirubin
5. Dabrafenib + trametinib + (cetuximab or panitumumab)	Only if *BRAF V600E* mutation positive
6. Encorafenib + binimetinib + (cetuximab or panitumumab)	Only if *BRAF V600E* mutation positive
7. Nivolumab ± ipilimumab	Only if dMMR/MSI-H
8. Pembrolizumab	Only if dMMR/MSI-H
9. Trastuzumab + (pertuzumab or lapatinib)	Only if *HER2*-amplified and *RAS* wild-type
First-Line Therapy: Fluorouracil-Based Regimen ± Bevacizumab (ie, Fluorouracil/Leucovorin, Capecitabine)	
Second-line options	
1. FOLFOX or CapeOx ± bevacizumab	
2. FOLFIRI or irinotecan ± bevacizumab or ziv-aflibercept or ramucirumab	Bevacizumab has least toxicity and lower cost of antiangiogenic agents
3. Irinotecan + oxaliplatin (IROX) ± bevacizumab	Use with caution in patients with elevated bilirubin
4. Nivolumab ± ipilimumab	Only if dMMR/MSI-H
5. Pembrolizumab	Only if dMMR/MSI-H
6. Trastuzumab + (pertuzumab or lapatinib)	Only if *HER2*-amplified and *RAS* wild-type
Therapy After Second Progression or Third Progression	
1. Regorafenib	Used after progressed through all available regimens
2. Irinotecan ± cetuximab or panitumumab	Only if *RAS* wild type and neither previously given; use with caution in patients with elevated bilirubin
3. Trifluridine/tipiracil	Used after progressed through all available regimens
4. Nivolumab ± ipilimumab	Only if dMMR/MSI-H and not previously given
5. Pembrolizumab	Only if dMMR/MSI-H and not previously given
6. Trastuzumab + (pertuzumab or lapatinib)	Only if *HER2*-amplified and *RAS* wild-type
7. Clinical trial	If available and only if patient eligible
8. Best supportive care	Appropriate for patients who do not want to pursue treatment or quality of life is expected to decrease

[a]National Comprehensive Cancer Network (NCCN) Guideline recommendations for initial therapy. All recommendations are category 2A unless otherwise noted. Category 2A: based upon lower-evidence, there is uniform NCCN consensus that the intervention is appropriate.

CapeOx, capecitabine plus oxaliplatin; dMMR, DNA mismatch repair deficiency; FOLFIRI, fluorouracil plus leucovorin plus irinotecan; FOLFOX, fluorouracil plus leucovorin plus oxaliplatin; MSI-H, high microsatellite instability.

Data from References 50, 51.

Systemic Chemotherapy

On disease progression following standard initial therapy, appropriate treatment options depend primarily on the type of prior therapy received (see Table 147-7). Because most patients will have received a combination of a fluoropyrimidine with either irinotecan or oxaliplatin, second-line therapy with the alternate regimen should be considered. Patient survival can exceed 2 years with this approach and it is important for patients to receive all traditional chemotherapy options if possible. Targeted agents can either be added to the regimens or used as single agents.

Irinotecan Two phase III trials compared irinotecan to either best supportive care or continuous-infusion fluorouracil in patients who had progressed within 6 months of treatment with fluorouracil.[50] Both trials demonstrated an improvement in overall survival with irinotecan as compared to the control arms. However, this approach is rarely used since single-agent fluorouracil is rarely given as first-line therapy.

The use of the FOLFIRI regimen after progression with first-line FOLFOX demonstrated an objective response rate of 4% with a median progression-free survival of 2.5 months.[50] These results are consistent with observations that demonstrate improved outcomes in those patients who are able to receive all active cytotoxic agents during the course of their disease.

Based on these results, irinotecan should be considered standard second-line therapy for patients with disease progression with first-line treatment with oxaliplatin-containing regimens. Continuous-infusion fluorouracil (FOLFIRI), with or without targeted therapy, is most commonly given.

Oxaliplatin Oxaliplatin plus fluorouracil and leucovorin should be considered for patients who received primary treatment with irinotecan plus fluorouracil. When oxaliplatin is administered in a bimonthly regimen with high-dose leucovorin and continuous fluorouracil infusion, a 21% response rate with a median survival in excess of 10 months has been reported.[71] The combination of oxaliplatin plus fluorouracil and leucovorin is also effective as salvage therapy after initial treatment with irinotecan plus fluorouracil and leucovorin, with a similar response rate.[82] Although irinotecan can be used effectively as a single agent in colorectal cancer, it should be noted that oxaliplatin does not have substantial activity alone, and should only be given in combination with a fluoropyrimidine.

Trifluridine/Tipiracil Trifluridine is a thymidine-based nucleoside analog that is incorporated into DNA and inhibits cell proliferation. The addition of tipiracil increases trifluridine exposure by inhibiting its metabolism by thymidine phosphorylase. This combination chemotherapy product has activity in *RAS* wild-type tumors. Trifluridine/tipiracil is FDA approved for treatment of metastatic colorectal cancer patients who have been previously treated with an fluoropyrimidine-, oxaliplatin-, and irinotecan-containing regimens, an anti-VEGF targeted therapy, and an anti-EGFR monoclonal antibody if *RAS* wild type.[83] In a double-blind, randomized controlled trial of trifluridine/tipiracil and placebo, an improvement in overall survival was observed (7.1 vs 5.3 months; HR 0.68; $P < 0.01$). This chemotherapy product is administered 35 mg/m^2 orally twice daily within 1 hour of completing morning and evening meals on days 1 through 5 and days 8 through 12 of a 28-day cycle. Common adverse effects include myelosuppression, fatigue, diarrhea, nausea/vomiting, abdominal pain, and pyrexia.

Targeted Therapy

The addition of targeted therapy to chemotherapy in second and subsequent therapies does improve outcomes, but typically also increases toxicity. EGFR inhibitors may be administered in combination with irinotecan-containing regimens. Angiogenesis inhibitors can also be used in second-line and subsequent therapy in combination with other regimens, even when they were used in first-line therapy.

EGFR Inhibitors Patients wild-type *RAS* and wild-type *BRAF* tumors who experience progression on therapies that do not contain an EGFR inhibitor may benefit from the combination of cetuximab or panitumumab and irinotecan or FOLFIRI.[50] However, further treatment is not recommended in those who had progressed while receiving an EGFR inhibitor. The combination of cetuximab and irinotecan significantly improves response rates (16% vs 4%, $P < 0.001$) and progression-free survival (4 vs 2.6 months, $P < 0.001$) but not overall survival when compared with irinotecan alone.[84] Panitumumab in combination with FOLFIRI also improves response rates (35% vs 10%) and progression-free survival (5.9 vs 3.9 months, $P = 0.004$), but did not improve overall survival.[85]

BRAF and Mitogen-Activated Protein Kinases (MEK) Inhibitors In patients with *BRAF V600E* mutations, several options exist to improve overall outcomes in second- and subsequent-line therapy for metastatic disease. The results of a

phase II study of patients with metastatic colorectal cancer with *RAS* wild-type and *BRAF V600* mutations receiving irinotecan and cetuximab with or without vemurafenib (a second-generation, select BRAF inhibitor) showed an improved median progression-free survival of 4.4 versus 2 months (HR 0.42; $P = 0.002$) and disease control rates of 67% versus 22% ($P = 0.001$) in the vemurafenib group.[78] The addition of vemurafenib increased the risk of myelosuppression, nausea, and arthralgias.

Preclinical data have suggested that the combined inhibition of the EGFR and MAPK pathways is needed to maximally inhibit BRAF in metastatic disease. The three-drug combination of encorafenib (a BRAF inhibitor), binimetinib (a MEK inhibitor that inhibits the MAPK pathway), and cetuximab (an EGFR inhibitor) significantly improves overall survival in *BRAF V600* mutated metastatic colorectal cancer (9 vs 5.4 months; $P < 0.001$).[86] Overall response rates were also improved (26 vs 2%). Fatigue is the most common side effect of this regimen. Anemia, increases in creatine kinase and aspartate aminotransferase, and urinary tract infections were also reported. However, skin toxicities are less common than when cetuximab is used alone. Similarly, the three-drug combination of dabrafenib (a BRAF inhibitor), trametinib (a MEK inhibitor), and panitumumab (an EGFR inhibitor) produces response rates of 26%.[87] Most common side effects with this triplet regimen are acniform rashes and diarrhea.

Angiogenesis Inhibitors Angiogenesis inhibitors including VEGF inhibitors bevacizumab, ramucirumab, and ziv-aflibercept and the multikinase inhibitor regorafenib may be used in patients who have progressed on other therapies (see Table 147-7). VEGF inhibitors may be used as second- or subsequent-line therapies, whereas regorafenib is limited to third- or subsequent-line use. The 2019 NCCN guidelines recommend bevacizumab over ramucirumab and ziv-aflibercept based on toxicity and cost. Continuation of bevacizumab as second-line therapy provides a modest improvement in overall survival based on several clinical trials.[50] Bevacizumab may also be added to another second-line therapy in patients who did not receive it as part of their initial therapy, also resulting in a modest improvement in overall survival (12.1 vs 10.8 months, $P = 0.001$).[88] Single-agent bevacizumab is not recommended because it is inferior to combination therapy.[50]

Ziv-aflibercept is a soluble recombinant fusion protein designed to block the angiogenic process. The agent was developed by fusing sections of the VEGFR-1 and VEGFR-2 immunoglobulin domains to the F_c portion of human

immunoglobulin G1 (IgG1) and blocks VEGF-A, VEGF-B, and placental growth factor (PIGF) by "trapping" the ligands before they get to the native transmembrane receptors. In a phase III randomized trial, FOLFIRI plus ziv-aflibercept was compared to FOLFIRI after progression on an oxaliplatin-based regimen. The trial met its primary end point with a modest improvement in overall survival (13.5 vs 12.06 months; HR 0.817; $P = 0.003$).[89] It is dosed at 4 mg/kg as an IV infusion over 1 hour every 2 weeks and is associated with similar adverse effects as bevacizumab.

Ramucirumab is a human monoclonal antibody that binds directly to the ligand-binding pocket of VEGFR-2 to block binding of VEGF-A, VEGF-C, and VEGF-D. A phase III randomized placebo-controlled trial of patients who had failed an oxaliplatin-based regimen and bevacizumab were randomized to receive FOLFIRI with or without ramuciumab.[90] A modest improvement in overall survival (13.3 vs 11.7 months; HR 0.84; $P = 0.02$) and progression-free survival (5.7 vs 4.5 months; HR 0.79; $P < 0.0005$) were observed. Ramucirumab is administered as 8 mg/kg IV over 1 hour every 2 weeks and is associated with similar adverse effects as bevacizumab.

The addition of ziv-aflibercept or ramucirumab to oxaliplatin regimens has not been evaluated and therefore is not recommended. Additionally, the use of either of these drugs following failure of a bevacizumab-containing regimen has not been evaluated. Therefore, ziv-aflibercept and ramucirumab should only be used in patients naïve to antiangiogenic regimens and only with irinotecan-containing regimens.

Regorafenib, a small-molecule inhibitor of tumor angiogenesis (VEGFR-1, VEGFR-2, and VEGFR-3) and other downstream targets (FGF receptors, PDGF receptors, BRAF, KIT, and RET), is approved for the third- or fourth-line treatment of metastatic colorectal cancer. This oral agent is dosed 160 mg once daily for the first 21 days of each 28-day cycle; although it is common to start at a lower dose (80 or 120 mg) and titrate as tolerated.[50] In a phase III trial of patients with metastatic colorectal cancer and progression during or within 3 months of last chemotherapy, regorafenib demonstrated a 1.4-month improvement in overall survival when compared to placebo.[91] Patients with mutant or wild-type *RAS* may receive this therapy. Because this is an oral-only regimen, patients must be counseled on its use and potential toxicity. Regorafenib should be taken with a low-fat breakfast and may interact with CYP450 3A4 inducers and inhibitors. Toxicities include hypertension, hand-foot syndrome, diarrhea, and hepatotoxicity.

Human Epidermal Growth Factor Receptor-2 (*HER2*) Inhibitors *HER2*, a member of the same kinase family as EGFR, is rarely overexpressed in colorectal cancer.[50] However, it is more common in those with *RAS* and *BRAF* wild-type tumors. The HERACLES study found that trastuzumab (a *HER2* monoclonal antibody) and lapatinib (a *HER2* inhibitor) in treatment refractory colorectal cancer patients with *RAS* wild-type produce responses in patients who typically are refractory to therapy, producing a 30% response rate.[92] Side effects of *HER2* inhibitors include fatigue, skin rash, and bilirubin increases. Initial results from an ongoing basket trial show that the combination of two *HER2* monoclonal antibodies, trastuzumab and pertuzumab, also produce similar results.[93] The most common side effects are diarrhea, fatigue, and nausea. *HER2* inhibitor therapy can be an option for those with *HER2* overexpression when other options have failed.

Immunotherapy

10 Pembrolizumab, a humanized, IgG4 monoclonal antibody that binds to PD-L1 with high affinity is effective in metastatic colorectal cancer patients with dMMR who have progressed through 2 to 4 other regimens. The immune-related objective response rate was 40% in those with dMMR versus 0% in those with proficient MMR. Both the median progression-free survival and overall survival were not reached in those with dMMR and were 2.2 and 5.5 months, respectively in those MMR proficient patients (HR 0.10; $P < 0.001$).[94]

Nivolumab, another humanized IgG4 monoclonal antibody PD-1 inhibitor has also been evaluated with or without ipilimumab in patients with metastatic colorectal cancer who have dMMR/MSI-H tumors. In patients who progressed after at least two other therapies, the overall response rate with monotherapy was 31% and with combination therapy is 55%.[81,95] The median progression-free survival was 14.3 months with monotherapy and was not reached with the combination therapy. Although the risk of grade 3/4 adverse effects was higher with the combination (32% vs 20%), it was considered manageable. This study was not designed to formally compare the two arms, thus statistical comparisons have not been done.

PD-1 immune checkpoint inhibitors are generally well tolerated. The adverse effects are typically immune-mediated and commonly affect the skin, liver, kidneys, gastrointestinal tract, lung, and endocrine systems. Immune-mediated pneumonitis is an uncommon but serious adverse effect. Close monitoring for these adverse effects is important to allow for prompt identification and

treatment to minimize morbidity and mortality. Treatment includes temporary treatment suspension and corticosteroid treatment. Refractory cases may require infliximab or immunotherapies. The American Society of Clinical Oncology has published practice guidelines for management.[96]

EVALUATION OF THERAPEUTIC OUTCOMES

The goal of monitoring is to either evaluate whether the patient is receiving any benefit from the management of the disease or to detect recurrence for those who have completed curative intent therapy. During treatment for active disease, patients should undergo monitoring for measurable tumor response, progression, or new metastases; these tests may include chest, abdominal or pelvic CT scans, or other imaging modalities, depending on known sites of disease and previous imaging results, and CEA measurements every 3 months if the CEA is or was previously elevated. These radiologic tests and other selected laboratories should also be evaluated with the development of any new symptoms or significant change in disease status. Patients should be evaluated during every treatment visit for the presence of anticipated side effects, which generally include loose stools or diarrhea, nausea or vomiting, mouth sores, fatigue, and fever, as well as other adverse effects such as neuropathy (oxaliplatin) and skin rash (EGFR inhibitors). In addition, a complete blood cell count should be obtained prior to each course of chemotherapy administration to ensure that hematologic indices are adequate. Baseline liver function tests and an assessment of renal function should be evaluated prior to and periodically during therapy. Hepatotoxicity may be seen with regorafenib, and in addition to neuropathy, oxaliplatin may cause renal injury. Serum electrolytes, including magnesium, should be monitored during treatment with EGFR inhibitors. Patients receiving bevacizumab, ziv-aflibercept, or regorafenib should be evaluated for hypertension and proteinuria.

Symptoms of recurrence such as pain syndromes, changes in bowel habits, rectal or vaginal bleeding, pelvic masses, anorexia, and weight loss develop in less than 50% of patients. Recurrences can be detected in asymptomatic patients because of increased serum CEA levels that lead to further examination. Although the value of CEA monitoring for disease recurrence is controversial because of its cost and emotional stress associated with false-positive elevations, CEA monitoring plays an important role in postoperative follow-up studies. A PET scan can identify localized sites of metastatic disease when a rising CEA level suggests metastatic disease but CT scans and other imaging studies are negative.

Patients who undergo curative surgical resection, with or without adjuvant therapy, require close follow-up based on the premise that early detection and treatment of recurrence could still render them cured. In addition, early treatment for asymptomatic metastatic colorectal cancer appears to be superior to delayed therapy. Specific practice guidelines for postoperative surveillance examinations following successful treatment for stage II or III disease were developed by NCCN and include history, physical examination, and CEA test every 3 to 6 months for the first 2 years, then every 6 months for a total of 5 years; chest and abdominal and pelvic CT scans every 6 to 12 months for up to 5 years following primary therapy; and colonoscopy at about 1 year after surgery. If an obstructing lesion prevented preoperative colonoscopy, it should be done within 3 to 6 months. Repeat colonoscopies are recommended at 3 years, unless findings of polyps warrant closer follow-up. PET/CT is not indicated. Less intensive surveillance is recommended for patients treated for stage I disease because of low risk of recurrence.[50]

Posttreatment surveillance should also include a survivorship care plan with immunizations for vaccine-preventable diseases, early detection of second primary cancers, and support systems that encourage smoking cessation, establish regular exercise and maintain a healthy BMI, and encourage healthy lifestyle and dietary choices.[50] In addition, if there is a strong family history of colorectal cancer or related malignancies or clinicopathologic findings in an individual consistent with a hereditary syndrome, a consultation with a geneticist is indicated. Recent advances in the treatment for colorectal cancer now offer the potential to improve patient survival, but for many patients, improved disease-free and progression-free survival represent equally important therapeutic outcomes. Although treatment approaches for metastatic colorectal cancer have been historically assessed by their ability to produce a measurable objective tumor response, which is generally believed necessary for any treatment to improve survival, the effects of therapies on survival are clinically more meaningful than their ability to induce a tumor response. However, with the availability of multiple active treatments for metastatic disease, and the likelihood that patients will receive more than one during the course of their treatment, improvements in overall survival with new therapies will be increasingly difficult to determine.

In the absence of the ability of a specific treatment to demonstrate improved overall survival, important outcome measures should include the effects of the treatment on patient symptoms, daily activities, performance status and other quality-of-life indicators, progression-free survival, and time-to-treatment

failure. Because most metastatic colorectal cancers are incurable, a specific decision regarding an individual patient's care will ultimately be required. This decision should be based on a careful assessment of the balance between risks associated with treatment (or lack thereof) and benefits of treatment. Efforts should also be made to ensure that the costs of screening, diagnostic tests, treatments, and procedures for colorectal cancer are consistent with their value in improving patient outcomes.

Postclass Engaged Learning Activity

Create a table that includes the adverse effects, including major dose-limiting toxicities and time frame, and potential preventative or management of side effects for each of the regimens in the treatment of metastatic colorectal cancer. This activity is useful to enhance student understanding of the PLAN, IMPLEMENT and FOLLOW-UP steps in the patient care process.

ABBREVIATIONS

APC	adenomatous polyposis coli (gene)
BMI	body mass index
BSA	body surface area
CapC	capsule colonography
CapeOx	capecitabine plus oxaliplatin
CEA	carcinoembryonic antigen
CI	confidence interval
CIN	chromosomal instability
CIMP	CpG island methylator phenotype
COX-2	cyclooxygenase-2
CT	computed tomography
CTLA-4	cytotoxic-T-lymphocyte-associated protein 4
CYP	cytochrome P450 isoenzyme
DPD	dihydropyrimidine dehydrogenase
EGFR	epidermal growth factor receptor
EPCAM	epithelial cell adhesion molecule
FAP	familial adenomatous polyposis
FDA	Food and Drug Administration
FIT	fecal immunochemical test
FLOX	fluorouracil, leucovorin, oxaliplatin
FOBT	fecal occult blood test
FOLFIRI	fluorouracil, leucovorin, and irinotecan
FOLFOX	fluorouracil, leucovorin, and oxaliplatin
FOLFOXIRI	fluorouracil and leucovorin, oxaliplatin, irinotecan
FSIG	flexible sigmoidoscopy
gFOBT	guaiac-based fecal occult blood test
HAI	hepatic artery infusion
HbA_{1c}	glycosylated hemoglobin
HNPCC	hereditary nonpolyposis colorectal cancer
HR	hazard ratio
iFOBT	immunochemical fecal occult blood test
IGF-1	insulin-like growth factor-1
IgG1	immunoglobulin G1
LOH	loss of heterozygosity
MAPK	mitogen-activated protein kinase
MMR	mismatch-repair
MOSAIC	Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer
MRI	magnetic resonance imaging
MSI	microsatellite instability
MTHFR	methylenetetrahydrofolate reductase
mt-sDNA	multi-target stool DNA
NAT1	*N*-acetyltransferase 1
NAT2	*N*-acetyltransferase 2
NCCN	National Comprehensive Cancer Network
NSAID	nonsteroidal anti-inflammatory drug
PD-1	programmed cell death protein
PD-L1	programmed cell death ligand-1
PD-L2	programmed cell death ligand-2
PET	positron emission tomography

15-PGDH	15-prostaglandin dehydrogenase
PIGF	placental growth factor
PI3K	phosphatidylinositol 3-kinase
PPE	palmar–plantar erythrodysesthesia
RR	relative risk
TGF-β	transforming growth factor-β
TS	thymidylate synthase
UGT1A1	uridine diphosphate-glucuronosyltransferase
USPSTF	United States Preventive Services Task Force
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
XELOX	capecitabine plus oxaliplatin
XRT	radiation therapy

REFERENCES

1. American Cancer Society. *Cancer Facts & Figures 2019*. Atlanta: American Cancer Society; 2019.
2. Arnold M, Sierra MS, Laversanne M, et al. Global patterns and trends in colorectal cancer incidence and mortality. *Gut*. 2017;66:683–691.
3. American Cancer Society. *Colorectal Cancer Facts & Figures 2017–2019*. Atlanta, GA: American Cancer Society; 2019.
4. Noone AM, Howlader N, Krapcho M eds, et al. SEER Cancer Statistics Review, 1975-2015. Bethesda, MD: National Cancer Institute; 2017. https://seer.cancer.gov/csr/1975_2015/.
5. Siegel RL, Miller KD, Jemal A. Colorectal cancer mortality rates in adults aged 20 to 54 years in the United States, 1970-2014. *JAMA*. 2017;318:572–574.
6. Kuipers EJ, Grady WM, Lieberman D, et al. Colorectal cancer. *Nat Rev Dis Primers*. 2015;1:15065. doi:10.1038/nrdp.2015.65.
7. Kim E, Change DK. Colorectal cancer in inflammatory bowel disease: The risk, pathogenesis, prevention and diagnosis. *World J Gasteroenterol*. 2014;20:9872–9881.
8. Gonzalez N, Priety I, del Puerto-Nevado L, et al. 2017 Update on the relationship between diabetes and colorectal cancer: Epidemiology, potential molecular mechanisms and therapeutic implications. *Oncotarget*. 2017;8:18456–18485.

9. Samadder NJ, Japerson K, Burt RW. Hereditary and common familial colorectal cancer evidence for colorectal screening. *Dig Dis Sci*. 2015;60:734–747.
10. Rassol S, Rasool V, Naqvi T, Ganai BA, Shah BA. Genetic unraveling of colorectal cancer. *Tumor Biol*. 2014;35:5067–5082.
11. Sinicrope FA. Lynch syndrome-associated colorectal cancer. *N Engl J Med*. 2018;379:764–773.
12. Teixeria MC, Braghiroli MI, Sabbaga J, Hoff PM. Primary prevention of colorectal cancer myth or reality. *World J Gastoenterol*. 2014;20:15060–15069.
13. Thun MJ, Jacobs EJ, Patrono C. The role of aspirin in cancer prevention. *Nat Rev Clin Oncol*. 2012;9:259–267.
14. Liao X, Lochhead P, Nishihara R, et al. Aspirin use, tumor *PIK3CA* mutation, and colorectal-cancer survival. *N Engl J Med*. 2012;367:1596–1606.
15. Gartlehner G, Patel SV, Feltner C, et al. Hormone therapy for the primary prevention of chronic conditions in postmenopausal women: Evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2017;318:2234–2249.
16. Kerr J, Anderson C, Lippman SM. Physical activity, sedentary behaviour, diet, and cancer: An update and emerging new evidence. *Lancet Oncol*. 2017;18:e457–e471.
17. Ma Y, Yang Y, Wang F, et al. Obesity and risk of colorectal cancer risk: A systematic review of prospective studies. *PLoS One*. 2013;8:e53916.
18. Abar L, Vieira AR, Aune D, et al. Height and body fatness and colorectal cancer risk: An update of the WCRF-AICR systematic review of published prospective studies. *Eur J Nutr*. 2018;57:1701–1720.
19. Rossi M, Anwar MJ, Usman A, et al. Colorectal cancer and alcohol consumption-populations to molecules. *Cancers (Basel)*. 2018;10:38.
20. Fagunwa IO, Loughrey MB, Coleman HG. Alcohol, smoking and the risk of premalignant and malignant colorectal neoplasms. *Best Pract Res Clin Gastroenterol*. 2017;31:561–568.
21. Song M, Garrett WS, Chan AT. Nutrients, foods, and colorectal cancer prevention. *Gastroenterology*. 2015;148:1244–1260.e16.
22. Pan P, Yu J, Want LS. Colon cancer. *Surg Onc Clin North Am*. 2018;27(2):243–267.

23. McCullough ML, Zoltick ES, Weinstein SJ, et al. Circulating vitamin D and colorectal cancer risk: An international pooling project of 17 cohorts. *J Natl Cancer Inst*. 2019;111:158–169.
24. Fletcher R, Wang YJ, Schoen RE, et al. Colorectal cancer prevention: Immune modulation taking the stage. *Biochimica et Biophysica Acta (BBA) – Reviews on Cancer*. 2018;1869:138–148.
25. Nguyen HT, Duong HQ. The molecular characteristics of colorectal cancer: Implications for diagnosis and therapy. *Oncol Lett*. 2018;16:9–18.
26. Testa U, Pelosi E, Castelli G. Colorectal cancer: Genetic abnormalities, tumor progression, tumor heterogeneity, clonal evolution and tumor-initiating cells. *Med Sci*. 2018;6:31.
27. Grady WM, Markowitz SD. The molecular pathogenesis of colorectal cancer and its potential application to colorectal cancer screening. *Dig Dis Sci*. 2015;60:762–772.
28. Stoffel EM. Updates on translational research on prevention of polyps and colorectal cancer. *Clin Colon Rectal Surg*. 2018;31:153–160.
29. Waluga M, Zorniak M, Fichina J, et al. Pharmacological and dietary factors in prevention of colorectal cancer. *J Physiol Pharmacol*. 2018;69:325–336.
30. Kunzmann AT, Coleman HG, Huang WY, et al. Dietary fiber intake and risk of colorectal cancer and incident and recurrent adenoma in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Am J Clin Nutr*. 2015;102:881–890.
31. Elshaer M, Chen Y, Wang XJ, Tang X. Resveratrol: An overview of its anti-cancer mechanisms. *Life Sciences*. 2018;207:340–349.
32. Mohammed A, Yarla NS, Madka V, et al. Clinically relevant anti-inflammatory agents for chemoprevention of colorectal cancer: New perspectives. *Int J Mol Sci*. 2018;29:2332.
33. Weinberg DS, Lin JE, Foster NR, et al. Bioactivity of oral linaclotide in human colorectum for cancer chemoprevention. *Cancer Prev Res (Phila)*. 2017;10:345–354.
34. Yin TF, Wang M, Qing Y, Lin YM, Wu D. Research progress on chemopreventive effects of phytochemicals on colorectal cancers and their mechanisms. *World J Gastroenterol*. 2016;22:7058–7068.
35. Shin CM, Lee DH, Seo AY, et al. Green tea extracts for the prevention of metachronous colorectal polyps among patients who underwent endoscopic removal of colorectal adenomas: A randomized clinical trial.

Clin Nutr. 2018;37:452–458.

36. Talero E, Ávila-Roman J, Motilva V. Chemoprevention with phytonutrients and microalgae products in chronic inflammation and colon cancer. *Curr Pharm Des*. 2012;18:3939–3965.
37. Dos Reis SA, da Conceicão LL, Sigueira NP, et al. Review of the mechanisms of probiotic actions in the prevention of colorectal cancer. *Nutr Res*. 2017;37:1–19.
38. Farjardo AM, Piazza GA. Chemoprevention in gastrointestinal physiology and disease. Anti-inflammatory approaches for colorectal cancer chemoprevention. *Am J Physiol Gastrointest Liver Physiol*. 2015;309:G59–G70.
39. Bibbins-Domingo K; U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. 2016;164:836–845.
40. Veettil SK, Lim KG, Ching SM, et al. Effects of aspirin and non-aspirin nonsteroidal anti-inflammatory drugs on the incidence of recurrent colorectal adenomas: A systematic review with meta-analysis and trial sequential analysis of randomized clinical trials. *BMC Cancer*. 2017;17(1):763. doi:10.1186/s12885-017-3757-8.
41. Rothwell PM. Aspirin in prevention of sporadic colorectal cancer: Current clinical evidence and overall balance of risks and benefits. *Recent Results Cancer Res*. 2013;191:121–142.
42. Nan H, Huytter CM, Lin Y, et al. Association of aspirin and NSAID use with risk of colorectal cancer according to genetic variants. *JAMA*. 2015;313:1133–1142.
43. NCCN Clinical Practice Guidelines in Oncology—Genetic/Familial High-Risk Assessment: Colorectal v1.2018. 2018. Available at http://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf.
44. Wolf AMD, Fontham ETH, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 Guideline update from the American Cancer Society. *CA Cancer J Clin*. 2018;68:250–281.
45. Rex DK, Boland CR, Dominitz JA, et al. Colorectal cancer screening: Recommendations for physicians and patients from the U.S. Multi-Society Task Force on Colorectal Cancer. *Gastroenterology*. 2017;153:307–323.
46. US Preventive Services Task Force. Screening for colorectal cancer. US Preventive Services Task Force Recommendation Statement. *JAMA*.

2016;315:2564–2575.

47. NCCN Clinical Practice Guidelines In Oncology—Colorectal Cancer Screening v.1.2019. 2019, Available at http://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.
48. Wilt TJ, Harris RP, Qaseem A, et al. Screening for cancer: Advice for high-value care from the American College of Physicians. *Ann Intern Med*. 2015;162:718–725.
49. Hadden WJ, de Reuver PR, Brown K, et al. Resection of colorectal liver metastases and extra-hepatic disease: A systematic review and proportional meta-analysis of survival outcomes. *HPB (Oxford)*. 2016;18:209–220.
50. NCCN Clinical Practice Guidelines In Oncology—Colon Cancer v.2.2019. 2019. Available at http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
51. NCCN Clinical Practice Guidelines In Oncology—Rectal Cancer v.2.2019. 2019. Available at http://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf.
52. Amin MB, Greene FL, Edge SB, et al. Colon and rectum. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017.
53. Libutti KS, Saltz LB, Willett CG. Cancers of the gastrointestinal tract: Cancer of the colon. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2015;1084–1126.
54. Sepulveda AR, Hamilton SR, Allegra CJ. Molecular biomarkers for the evaluation of colorectal cancer: Guideline summary from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology. *J Oncol Pract*. 2017;13:333–337.
55. Bockelman C, Engelmann BE, Kaprio T, et al. Risk of recurrence in patients with colon cancer stage II and III: A systematic review and meta-analysis of recent literature. *Acta Oncol*. 2015;54:5–16.
56. Venook AP, Niedzwiecki D, Lopatin M, et al. Biologic determinants of tumor recurrence in stage II colon cancer: Validation study of the 12-gene recurrence score in cancer and leukemia group B (CALGB) 9581. *J Clin Oncol*. 2013;31:1775–1781.
57. Yamanaka T, Oki E, Yamazaki K, et al. 12-Gene recurrence score assay stratifies the recurrence risk in stage II/III colon cancer with surgery alone:

The SUNRISE study. *J Clin Oncol*. 2016;34:2906–2913.

58. Phillips JG, Hong TS, Ryan DP. Multidisciplinary management of early-stage rectal cancer. *J Natl Compr Canc Netw*. 2012;10:1577–1585.
59. Touringand C, Andre T, Bonnetain F, et al. Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly patients (between ages 70-75 years) with colon cancer: Subgroup analyses of the multicenter international study of oxaliplatin, fluorouracil, and leucovorin in the adjuvant treatment of colon cancer trial. *J Clin Oncol*. 2012;30:3353–3360.
60. Andre T, Vernerey D, Mineur L, et al. Three versus six months of oxaliplatin-based adjuvant chemotherapy for patients with stage III colon cancer: Disease-free survival results from a randomized, open-label, international duration evaluation of adjuvant (IDEA) France, phase III trial. *J Clin Oncol*. 2018;36:1469–1477.
61. Grothey A, Sobrero AF, Shields AF, et al. Duration of adjuvant chemotherapy for stage III colon cancer. *N Engl J Med*. 2018;378:1177–1188.
62. Meta-Analysis Group in Cancer. Toxicity of fluorouracil in patients with advanced colorectal cancer: Effect of administration schedule and prognostic factors. *J Clin Oncol*. 1998;16:3537–3541.
63. Chuang VTG, Suno M. Levoleucovorin as replacement for leucovorin in cancer treatment. *Ann Pharmacother*. 2012;46:1349–1357.
64. Beumer JH, Chu E, Allegra C, et al. Therapeutic drug monitoring in oncology: International Association of Therapeutic Drug Monitoring and Clinical Toxicology recommendations for 5-fluorouracil therapy. *Clin Pharmacol Ther*. 2018 June 20.
65. Yothers G, O'Connell MJ, Allegra CJ, et al. Oxaliplatin as adjuvant therapy for colon cancer: Updated results of NSABP C-07 trial, including survival and subset analyses. *J Clin Oncol*. 2011;29:3768–3774.
66. Andre T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol*. 2009;27:3109–3116.
67. Weikhardt A, Wells K, Messersmith W. Oxaliplatin-induced neuropathy in colorectal cancer. *J Oncol*. 2011. doi:10.1155/2011/201593.
68. Haller DG, Tabernero J, Maroun J, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage

III colon cancer. *J Clin Oncol*. 2011;29:1465–1471.

69. Twelves C, Scheithauer W, McKendrick J, et al. Capecitabine versus 5-fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: Final results from the X-ACT trial with analysis by age and preliminary evidence of a pharmacodynamic marker of efficacy. *Ann Oncol*. 2012;23:1190–1197.
70. Cai GX, Cai SJ. Multi-modality treatment of colorectal liver metastases. *World J Gastroenterol*. 2012;18:16–24.
71. Glimelius B, Cavalli-Björkman N. Metastatic colorectal cancer: Current treatment and future options for improved survival. *Scand J Gastroenterol*. 2012;47:296–314.
72. Douillard J, Cunningham D, Roth A, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: A multicentre randomised trial. *Lancet*. 2000;355:1041–1047.
73. Lin PS, Semrad TJ. Molecular testing for the treatment of advanced colorectal cancer: An overview. *Methods Mol Bio*. 2018;1765:281–297.
74. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol*. 2000;18:2938–2947.
75. Twelves C. Capecitabine as first-line treatment in colorectal cancer. *Eur J Cancer*. 2002;38:15–20.
76. Ranpura V, Hapani S, Wu S. Treatment-related mortality with bevacizumab in cancer patients: A meta-analysis. *JAMA*. 2011;305:487–494.
77. Silvestri A, Calvert V, Belluco C, et al. Protein pathway activation mapping of colorectal metastatic progression reveals metastasis-specific network alterations. *Clin Exp Metastasis*. 2013;30:309–316.
78. Kopetz S, McDonough SL, Lenz H-J, et al. Randomized trial of irinotecan and cetuximab with or with vemurafenib in BRAF-mutant metastatic colorectal cancer (SWOG S1406). *J Clin Oncol*. 2017;35(suppl; abstr 3505).
79. Resch G, Schaberl-Moser R, Kier P, et al. Infusion reactions to the chimeric EGFR inhibitor cetuximab—change to the fully human anti-EGFR monoclonal antibody panitumumab is safe. *Ann Oncol*. 2011;22:486–487.
80. Lacotoure ME, Anadkat MJ, Bensadoun RJ, et al. Clinical practice

guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. *Support Care Cancer*. 2011;19:1079–1095.

81. Overman MJ, Lonardi S, Wong WYM, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. *J Clin Oncol*. 2018;36:773–779.
82. Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol*. 2004;22:23–30.
83. Mayer RJ, Van Cutsem E., Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med*. 2015;372:1909–1919.
84. Sobrero AF, Maurel J, Fehrenbacher L, et al. EPIC: Phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. *J Clin Oncol*. 2008;26:2311–2319.
85. Peeters M, Price TJ, Cervantes A, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. *J Clin Oncol*. 2010;23:4706–4713.
86. Kopetz S, Grothey A, Yaeger R, Cuyle AR, Huijberts S, Schllens HM. Updated results of the BEACON CRC safety lead-in: Encorafenib (ENCO) + binimetinib (BINI) + cetuximab (CETUX) for BRAFV600E-mutant metastatic colorectal cancer (mCRC). J Clin Oncol. 2019;37(4 (suppl)):688.
87. Atreya CE, Van Cutsem E, Bendell JC, Andre T, Schellens HM, Gordon MS. Updated efficacy of the MEK inhibitor trametinib (T), BRAF inhibitor dabrafenib (D), and anti-EGFR antibody panitumumab (P) in patients (pts) with BRAF V600E mutated (BRAFm) metastatic colorectal cancer (mCRC). J Clin Oncol. 2015;(15 (suppl)):103.
88. Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: Results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol*. 2007;25:1539–1544.
89. Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of afilbercept to

fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol*. 2012;30:3499–3506.

90. Tabernero J, Yoshino T, Cohn AL, et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): A randomised, double-blind, multicentre, phase 3 study. *Lancet Oncol*. 2015;16:499–508.
91. Grothey A, Van Cutsem E, Sobreror A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): An international, multicenter, randomized, placebo-controlled, phase 3 trial. *Lancet*. 2013;381:303–312.
92. Sartore-Bianchi A, Trusolino L, Martino C, Bencardino K, Lonardi S, Bergamo F. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): A proof-of-concept, multicentre, open-label, phase 2 trial. Lancet Oncol. 2016;17:1470.
93. Meric-Bernstam F, Hurwitz H, Raghav KPS, McWilliams RR, Fakih M, VancerWalde A. Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): An updated report from a multicentre, open-label, phase 2a, multiple basket study. Lancet Oncol. 2019;20:518.
94. Le DT, Uram JN, Want H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med*. 2015;372:2509–2520.
95. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): An open-label, multicentre, phase 2 study. *Lancet Oncol*. 2017;18:1182–1191.
96. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2018;36:1714–1768.

148

Prostate Cancer

LeAnn B. Norris

KEY CONCEPTS

1. Prostate cancer is the most frequent cancer in men in the United States. African American ancestry, family history, and increased age are the primary risk factors for prostate cancer.
2. Screening recommendations for prostate cancer have changed and digital rectal examination (DRE) and prostate-specific antigen (PSA) are no longer recommended for patients without a discussion with their clinician on the risks versus benefits of screening.
3. The prognosis for prostate cancer patients depends on the histologic grade, the tumor size, and the disease stage. More than 85% of patients with localized disease but less than 1% of those with metastatic disease can be cured.
4. Androgen deprivation therapy (ADT) with a luteinizing hormone-releasing hormone (LHRH) agonist plus an antiandrogen should be used prior to radiation therapy for patients with locally advanced prostate cancer to improve outcomes over radiation therapy alone.
5. Systemic therapy for nonmetastatic castration-naive disease, whereby the disease has not yet become resistant to ADT therapy, may include either orchiectomy, LHRH agonist with or without an antiandrogen, LHRH antagonist, or observation.
6. Antiandrogen withdrawal for patients having progressive disease while receiving combined hormonal blockade with an LHRH agonist plus an antiandrogen can provide additional symptomatic relief. Mutations in the androgen receptor can cause antiandrogen compounds to act like receptor agonists.
7. Chemotherapy with docetaxel and prednisone improves survival in patients

with castrate-resistant prostate cancer and is considered a first-line therapy option for these patients. Other effective agents include apalutamide, enzalutamide and abiraterone.

Preclass Engaged Learning Activity

Conduct a brief literature search and retrieve the most recent prostate cancer screening guidelines from the American Urological Association, the American Cancer Society, and the US Preventive Services Task Force. Compare and contrast the different prostate cancer recommendations. Review the data behind the recommendations from these consensus guidelines and be prepared to discuss them in class. This activity is intended to help you to become familiar with the updated screening recommendations and understand how these recommendations were made. What are the potential benefits and harms of screening patients?

INTRODUCTION

Prostate cancer is the most commonly diagnosed cancer in American men.[1] For most men, prostate cancer has an indolent course, and treatment options for early disease include expectant management, surgery, or radiation. With expectant management, patients are monitored for disease progression or development of symptoms. Localized prostate cancer can be cured by surgery or radiation therapy, but advanced prostate cancer is not yet curable. Treatment for advanced prostate cancer can provide significant disease palliation for many patients for several years after diagnosis. The endocrine dependence of this tumor is well documented, and hormonal manipulation to decrease circulating androgens remains the basis for the treatment of advanced disease.

EPIDEMIOLOGY

1 Prostate cancer is the most frequent cancer among American men and represents the second leading cause of cancer-related deaths in males.[1] In the United States alone, it is estimated that 174,650 new cases of prostate carcinoma were diagnosed and more than 31,620 men died from this disease in 2019.[1] Although the incidence of prostate cancer increased during the late 1980s and

early 1990s related to widespread PSA screening, deaths from prostate cancer declined from 1993 to 2013.[1] Prostate cancer mortality stabilized between 2013 and 2016 as a result of the decrease in PSA screening and an increase in advanced stage diagnoses.[1]

ETIOLOGY

Table 148-1 summarizes the possible risk factors associated with prostate cancer.[2–4] The widely accepted risk factors for prostate cancer are age, race-ethnicity, and family history of prostate cancer. The disease is rare in those younger than 40 years, but the incidence sharply increases with each subsequent decade, most likely because of increased lifetime exposure to testosterone, a known growth signal for the prostate.

TABLE 148-1 Risk Factors Associated with Prostate Cancer

Factor	Possible Relationship
Probable Risk Factors	
Age	More than 70% of cases are diagnosed in men older than 65 years old
Race	African Americans have higher incidence and death rate
Genetic	Familial prostate cancer inherited in an autosomal dominant manner
	Mutations *BRCA, BRCA2, ATM, CHEK2, BRCA1, FH, RAD51D, PALB2, ATR, NBN, PMS2, GEN1, MSH2, MSH6, RAD51C, MRE11A, BRIP1, or FAM175A* are associated with an increased risk of prostate cancer
Possible Risk Factors	
Environmental	Clinical carcinoma incidence varies worldwide
	Latent carcinoma similar between regions
	Nationalized males adopt intermediate incidence rates between those of the United States and their native country
Occupational	Increased risk associated with cadmium exposure
Diet	Mediterranean diet associated with reduced risk. Increased risk associated with high-meat and high-fat diets
	Decreased intake of 25-dihydroxyvitamin D, lycopene, and β-carotene increases risk
Hormonal	Does not occur in castrated men
	Low incidence in cirrhotic patients
	Up to 80% are hormone-dependent; African Americans have 15% increased testosterone
	Japanese have decreased 5-α-reductase activities
	Polymorphic expression of the androgen receptor

Race and Ethnicity

The incidence of clinical prostate cancer varies across geographic regions. Scandinavian countries and the United States report the highest incidence of prostate cancer, while the disease is relatively rare in Japan and other Asian countries.[5] African American men have the highest rate of prostate cancer in the world, and prostate cancer mortality in African Americans is more than twice that seen in white populations in the United States.[1] Hormonal, dietary, and genetic differences, and differences in access to healthcare may contribute to the altered susceptibility to prostate cancer in these populations.[2,3] Testosterone, commonly implicated in the pathogenesis of prostate cancer, is about 15% higher in African American men compared with white males. Activity of 5-α-reductase, the enzyme that converts testosterone to its more active form, dihydrotestosterone (DHT), in the prostate, is decreased in Japanese men as compared with African Americans and whites.[2,3]

In addition, genetic variations in the androgen receptor exist. Activation of the androgen receptor is inversely correlated with CAG repeat length. Shorter CAG repeat sequences have been found in African Americans, and a meta-analysis demonstrated that carriers of a short CAG repeat were at increased risk of prostate cancer (odds ratio 1.21, 95% confidence interval [CI] 1.10-1.51) when compared to individuals with long CAG repeats.[3] Therefore the combination of increased testosterone and increased androgen receptor activation may account for the increased risk of prostate cancer for African American men.[2,3] The Asian diet is generally considered to be low in fat and high in fiber with a high concentration of phytoestrogens, potentially explaining the decreased risk in Asians.[5]

Family History

Men with a brother or father with prostate cancer have twice the risk for prostate cancer as compared with the rest of the population and 5% to 10% of prostate cancers are thought to be inherited.[6] Familial clustering of prostate cancer syndrome has been reported, and genome-wide scans have identified potential prostate cancer susceptibility candidate genes. Carriers of germline mutations in one of 16 DNA repair genes (eg, *BRCA1*, *BRCA2*, and *CHEK2*) are known to have an increased risk of developing prostate cancer, although they are not routinely tested.[4,5] Other genes implicated in hereditary prostate cancer are *MSH2* and *HOXB13*.[6] Mutations in DNA repair genes may be predictive of

clinical benefit of poly-ADP ribose polymerase (PARP) inhibitors.[5] Common exposure to environmental and other risk factors may also contribute to increased risk among patients with first-degree relatives with prostate cancer.[5]

Diet

The overall dietary factor associated with the lowest risk of developing prostate cancer appears to be adherence to a Mediterranean diet.[7] The typical Mediterranean diet is high in fruits, vegetables, legumes, fish, olive oil and red wine, with low-to-moderate amounts of red meat, poultry and dairy. In a meta-analysis of studies including about 1.5 million individuals, adherence to a Mediterranean diet was associated with a small, but significantly reduced risk of prostate cancer (relative risk [RR] 0.96, 95% CI 0.92-0.99).[7]

Many individual dietary factors have been assessed to ascertain their role in the development or prevention of prostate cancer.[8] Green tea and lycopene are currently considered the most useful, and at least not harmful. Green tea consumption was associated with a reduced risk of prostate cancer in a small case-control study. Lycopene, obtained primarily from tomatoes, was shown to decrease the risk of prostate cancer in small cohort studies, although a meta-analysis failed to show benefit for high-tomato consumption.[8]

Consistent with the beneficial effects of the Mediterranean diet, red meat and high-milk intake have been clearly and consistently associated with an increased risk of prostate cancer in epidemiological studies.[8]

Other Factors

Benign prostatic hyperplasia (BPH) is a common problem among elderly men, affecting more than 40% of men older than 70 years (see Chapter 100). BPH results in the urinary symptoms of hesitancy and frequency. Because prostate cancer affects a similar age group and often has similar presenting symptoms, the presence of BPH often complicates the diagnosis of prostate cancer, although it does not appear to increase the risk of developing prostate cancer.[2]

Smoking has not been associated with an increased risk of prostate cancer, but smokers with prostate cancer have an increased mortality resulting from the disease when compared with nonsmokers with prostate cancer (RR 1.5-2).[2] In addition, the results of an observational study showed that alcohol consumption was not associated with the development of prostate cancer.

CHEMOPREVENTION

The use of 5-α-reductase inhibitors, finasteride, and dutasteride to prevent prostate cancer has been debated for more than a decade.[9–12] These drugs inhibit 5-α-reductase, an enzyme that converts testosterone to its more active form, DHT, which is involved in prostate epithelial proliferation. 5-α-Reductase exists as two types, type I and type II, and both are implicated in the development of prostate cancer. Finasteride selectively inhibits the 5-α-reductase type II isoenzyme, while dutasteride inhibits both isoenzymes.[10] Both finasteride and dutasteride can falsely lower the PSA by about 50% in patients, and this must be considered when one interprets PSA in patients on these medications.[13]

The efficacy of 5-α-reductase inhibitors in reducing the risk of prostate cancer was evaluated in a Cochrane review.[9] Eight randomized studies involving 41,638 men were included, including the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study, which compared dutasteride to placebo in more than 8,000 subjects, and the Prostate Cancer Prevention Trial (PCPT) study, which compared finasteride to placebo in more than 18,000 subjects. Compared with placebo, 5-α-reductase inhibitors reduced the risk of prostate cancers detected by 25% (RR 0.75, 95% CI 0.67-0.83; absolute risk reduction 1.4%, [3.5% vs 4.9%]). Although the incidence of prostate cancers was reduced in both the PCPT[10] and REDUCE[11] trials, the prostate tumors that were diagnosed were significantly more aggressive grades (Gleason 7-10) than those diagnosed in the placebo arm. The studies were not designed to evaluate prostate cancer mortality and 5-α-reductase inhibitors did not reduce mortality in the combined analysis. Adverse effects, including gynecomastia, decreased libido, and erectile dysfunction, were more common in patients treated with 5-α-reductase inhibitors than in placebo.[9] In a recent follow-up (median 18.4 years), the PCPT study reported that 42 of 3,048 deaths in the 9,423 men randomized to finasteride were due to prostate cancer, as compared to 56 of 2979 deaths in the 9457 men randomized to placebo. The 25% lower risk of death due to prostate cancer in patients who received finasteride was not statistically significant because of the small number of deaths due to prostate cancer.[14,15]

Based on the concern for the development of more aggressive tumors, lack of survival benefit and increased risk of adverse effects, neither finasteride nor dutasteride is approved for preventing prostate cancer.[12] The American Society of Clinical Oncology and the American Urological Association published a joint practice guideline for prostate cancer chemoprevention.[16] The guideline recommends that asymptomatic men with a PSA less than or equal to 3.0 ng/mL

(mcg/L) who are regularly screened with PSA for early detection of prostate cancer may benefit from a discussion of both the benefits and the potential risks of dutasteride or finasteride for 7 years for the prevention of prostate cancer.[16] Notably, the guideline does not recommend either chemoprevention or prostate cancer screening. The data from PCPT and REDUCE have been criticized for both selection bias and altered differential sensitivity in diagnosis.[12,13] Additional post-hoc analyses that account for these potential biases have generally reported that the inherent biases in the trials were most likely responsible for the increased risk of high-grade prostate cancer observed in the treatment arms. However, in the current environment where overdiagnosis and overtreatment of prostate cancer are of concern, these analyses have not generated sufficient interest in 5-α-reductase inhibitors as chemoprevention agents. Current research focuses on the ability of the 5-α-reductase inhibitors to reduce the risk of progression in patients with low-grade prostate cancers and in those who fail initial therapy.

Selenium and vitamin E, either alone or in combination, were evaluated as possible chemopreventive agents in the *Sel*enium and Vitamin *E C*ancer Prevention *T*rial (SELECT), a clinical trial of healthy men. The data and safety monitoring committee found that, after 5 years, selenium or vitamin E taken alone or together did not prevent prostate cancer. Based on these data and safety concerns, the trial was halted. With longer follow-up of that trial, dietary supplementation with vitamin E significantly increased the risk of prostate cancer by 17% ($P = 0.008$).[17] Other agents, including lycopene, green tea, nonsteroidal anti-inflammatory agents, isoflavones, and statins, are under investigation for prostate cancer and show some promise, but none are currently recommended for routine use outside of a clinical trial.[18]

SCREENING

2 Screening recommendations for prostate cancer have changed and DRE and PSA are no longer recommended for patients without a discussion with their clinician about risks versus benefits. If prostate cancer screening is performed, PSA is the method of choice, although low specificity is a major limitation.[19,20] PSA may be elevated in men with acute urinary retention, acute prostatitis, and prostatic ischemia or infarction, as well as BPH, a nearly universal condition in men at risk for prostate cancer. PSA elevations between 4.1 and 10 ng/mL (mcg/L) cannot distinguish between BPH and prostate cancer, limiting the utility of PSA alone for the early detection of prostate cancer. Additionally, many men

with clinically significant prostate cancer do not have a serum PSA outside the reference range.[21]

Early detection of potentially curable prostate cancers is the goal of prostate cancer screening. For cancer screening to be beneficial, it must reliably detect cancer at an early stage, when intervention would decrease mortality. Whether prostate cancer screening fits these criteria is debatable.[20,22–24] The European Randomized Study of Screening for Prostate Cancer (ERSPC) evaluated the effect of PSA screening on prostate cancer mortality.[25] More than 182,000 men from seven different European countries were randomized between being offered screening with PSA and no screening. The frequency of screening and PSA threshold for a biopsy varied by country. Most centers used a PSA cutoff of 3 ng/mL (mcg/L), but Belgium allowed up to 10 ng/mL (mcg/L). Most centers screened every 4 years, although Sweden screened every 2 years. Most (82%) of the men in the screening group had at least one PSA performed. With a median follow-up of 11 years, the cumulative incidence of prostate cancer was 9.6% in the screening group and 6.0% in the control group.[25] The rate ratio for death from prostate cancer in the screening group, as compared with the control group, was 0.79 (95% CI 0.68-0.91, adjusted $P = 0.001$), which corresponds to about one death from prostate cancer per 1,000 men (at a median follow-up of 11 years) prevented in the screened group as compared with the unscreened group. Of the 136,689 PSA tests performed, 16.6% of the tests were positive; biopsies were performed for 86% of men with elevated PSAs. Overall mortality was similar in the two study groups.[25]

In the United States, the Prostate, Lung, Colon and Ovarian Screening (PLCO) study randomized 76,693 men to receive either annual screening (38,343 subjects) or usual care as the control (38,350 subjects).[26] In the screening group, men were offered annual PSA testing for 6 years and DRE for 4 years. Compliance with screening was 85%. Men in the usual care group were able to receive screening, with the rate of PSA testing ranging from 40% to 52% and DRE from 41% to 46%. After 13 years of follow-up, the incidence of death per 10,000 person-years was not significantly different between the two groups with 3.7 (158 deaths total) in the screening group and 3.4 (145 deaths total) in the control group (RR 1.09, 95% CI 0.87-1.36).[26]

The ERSPC demonstrated that PSA testing every 4 years was better than no PSA testing and decreased prostate cancer deaths in the screened group by about 1 per 1,000 men screened as compared with the unscreened group, but the false-positive rate was 76%, which resulted in more than 13,000 unnecessary biopsies.[25] The PLCO screening study showed no reduction in prostate cancer

death between the annual (PSA and DRE) screening group and the usual care group, which is not surprising given the small reduction in death expected and that about one-half of the patients in the usual care groups had PSA and/or DRE screening performed.[26] An updated systemic review found similar results in that PSA screening for prostate cancer may reduce risk of prostate cancer mortality but is associated with harms including false-positive results, biopsy complications, and overdiagnosis in 20% to 50% of screen-detected prostate cancers. Early, active treatment for screen-detected prostate cancer may reduce the risk of metastatic disease, although the long-term impact of early, active treatment on prostate cancer mortality remains unclear. Active treatments for prostate cancer are frequently associated with sexual and urinary difficulties.[27]

Based on this evidence, the US Preventive Task Force recommended that men age 55 to 69 make an individual decision about prostate cancer screening with their clinician (recommendation grade C), and recommended against routine screening for men age 70 and older (recommendation grade D).[27] The American Urologic Association (AUA) does not recommend routine screening in men between the ages of 40 and 54 years of average risk. In men aged 55 to 69 years, the AUA recommends that the risks and benefits of prostate cancer screening are discussed.[20] For men who elect to be screened, the frequency should be no more than 2 years, and a recent study suggests that screening every 5 years may be adequate. The American Cancer Society recommends that asymptomatic men who have at least a 10-year life expectancy have an opportunity to make an informed decision about prostate cancer screening, including discussion of the uncertainties, risks, and potential benefits associated with screening.[23]

PATHOPHYSIOLOGY

The prostate gland is a solid, rounded, heart-shaped organ positioned between the neck of the bladder and the urogenital diaphragm (see **Fig. 148-1**). The normal prostate is composed of acinar secretory cells arranged in a radial shape and surrounded by a foundation of supporting tissue. The size, shape, or presence of acini is almost always altered in the gland that has been invaded by prostatic carcinoma. Adenocarcinoma, the major pathologic cell type, accounts for more than 95% of prostate cancer cases.[28,29] Much rarer tumor types include small cell neuroendocrine cancers, sarcomas, and transitional cell carcinomas.

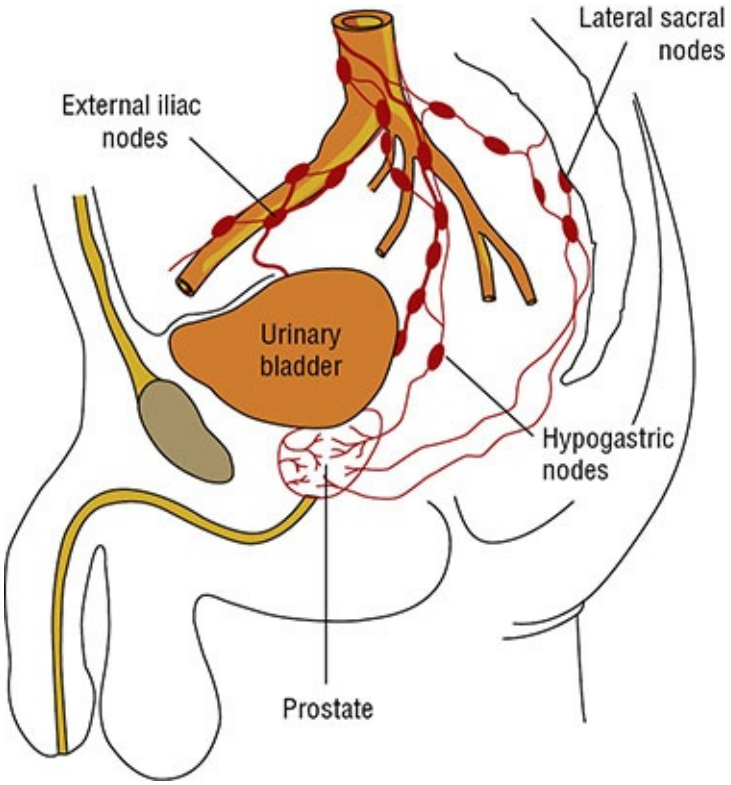


FIGURE 148-1 The prostate gland.

Prostate cancer can be graded systematically according to the histologic appearance of the malignant cell and then grouped into well, moderately, or poorly differentiated grades.[29,30] Gland architecture is examined and then rated on a scale of 1 (well differentiated) to 5 (poorly differentiated). Two different specimens are examined, and the score for each specimen is added. Groupings for total Gleason score are 2 to 4 for well differentiated, 5 or 6 for moderately differentiated, and 7 to 10 for poorly differentiated tumors. Poorly differentiated tumors grow rapidly (poor prognosis), while well-differentiated tumors grow slowly (better prognosis).

Metastatic spread can occur by local extension, lymphatic drainage, or hematogenous dissemination.[30,31] Lymph node metastases are more common in patients with large, undifferentiated tumors that invade the seminal vesicles. The pelvic and abdominal lymph node groups are the most common sites of lymph node involvement (see Fig.148-1). Skeletal metastases from hematogenous spread are the most common sites of distant spread. Typically, the bone lesions are osteoblastic or a combination of osteoblastic and osteolytic. The most common site of bone involvement is the lumbar spine. Other sites of bone involvement include the proximal femur pelvis, thoracic spine, ribs, sternum, skull, and humerus. The lung, liver, brain, and adrenal glands are the most

common sites of visceral involvement, although these organs are not usually initially involved. About 25% to 35% of patients will have evidence of lymphangitic or nodular pulmonary infiltrates at autopsy. The prostate is rarely a site for metastatic involvement from other solid tumors.

Normal growth and differentiation of the prostate depend on the presence of androgens, specifically DHT.[31,32] The testes and the adrenal glands are the major sources of circulating androgens. Hormonal regulation of androgen synthesis is mediated through a series of biochemical interactions between the hypothalamus, pituitary, adrenal glands, and testes (see **Fig. 148-2**). Luteinizing hormone-releasing hormone (LHRH) released from the hypothalamus stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland. LH complexes with receptors on the Leydig cell testicular membrane and stimulates the production of testosterone and small amounts of estrogen. FSH acts on the Sertoli cells within the testes to promote the maturation of LH receptors and to produce an androgen-binding protein. Circulating testosterone and estradiol influence the synthesis of LHRH, LH, and FSH by a negative feedback loop operating at the hypothalamic and pituitary level.[33] Prolactin, growth hormone and estradiol appear to be important accessory regulators for prostatic tissue permeability, receptor binding, and testosterone synthesis.

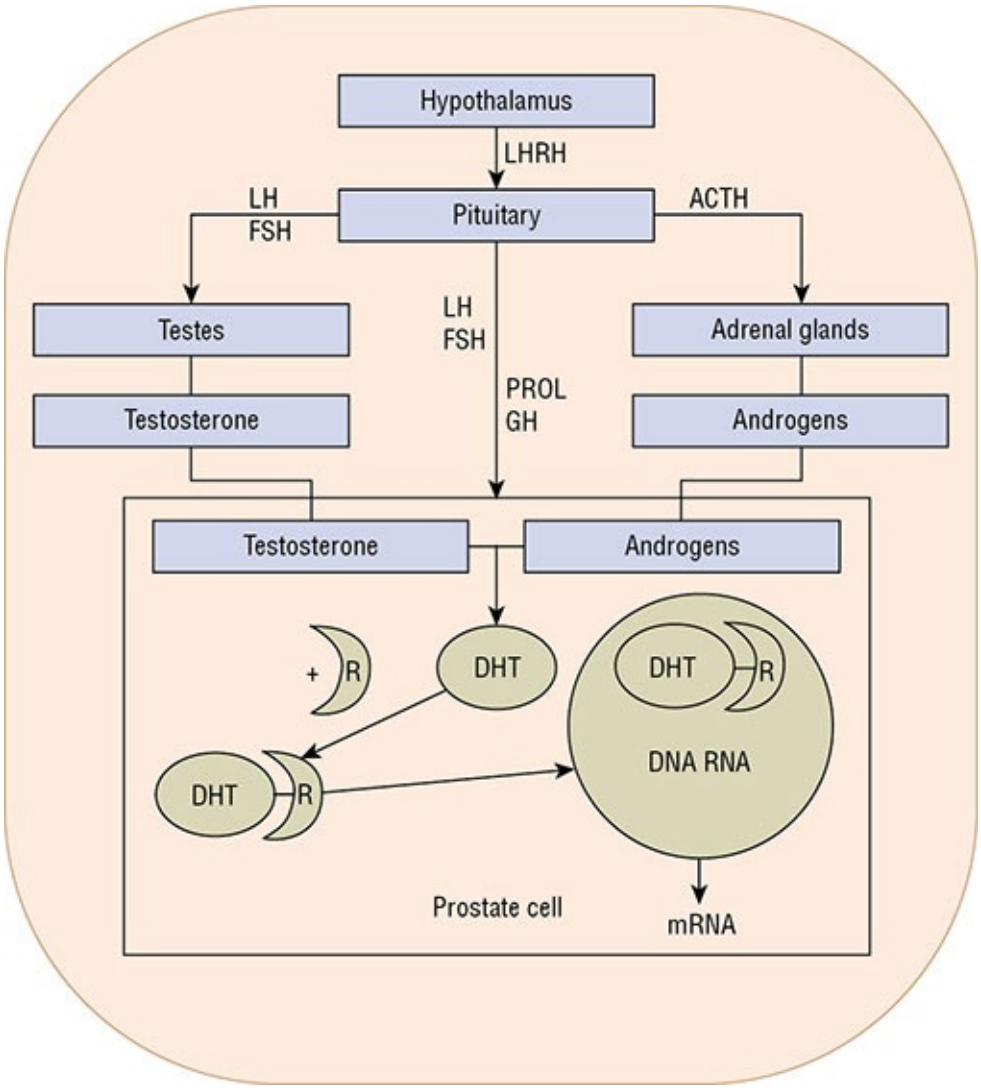


FIGURE 148-2 Hormonal regulation of the prostate gland. (ACTH, adrenocorticotropic hormone; DHT, dihydrotestosterone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; LHRH, luteinizing hormone-releasing hormone; PROL, prolactin; R, receptor.)

Testosterone, the major androgenic hormone, accounts for 95% of the androgen concentration. The primary source of testosterone is the testes, but 3% to 5% of the testosterone concentration is derived from direct adrenal cortical secretion of testosterone or C19 steroids such as androstenedione.[30–32]

In early-stage prostate cancers, aberrant tumor cell proliferation is promoted by the presence of androgens. For these tumors, blockade of androgens induces tumor regression in most patients. Hormonal manipulations to ablate or reduce circulating androgens can occur through several mechanisms[31,32] (**Table 148-2**). The organs responsible for androgen production can be removed surgically

(orchiectomy, hypophysectomy, or adrenalectomy). Hormonal pathways that modulate prostatic growth can be interrupted at several steps (see Fig. 148-2). Interference with LHRH or LH can reduce testosterone secretion by the testes (estrogens, LHRH agonists, progestogens, and cyproterone acetate). Estrogen administration reduces androgens by directly inhibiting LH release, by acting directly on the prostate cell, or by decreasing free androgens by increasing steroid-binding globulin levels.[30–32]

TABLE 148-2 Hormonal Manipulations in Prostate Cancer

Androgen source ablation	**First-generation antiandrogens**
Orchiectomy	Bicalutamide
Adrenalectomy	Flutamide
Hypophysectomy	Nilutamide
LHRH or LH inhibition	Cyproterone acetate[b]
Estrogens	Progesterones
LHRH agonists	**Second-generation antiandrogens**
Progesterones[a]	Apalutamide
Cyproterone acetate[b]	Enzalutamide
Androgen synthesis inhibition	Darolutamide
Aminoglutethimide	**5-α-reductase inhibition**
Ketoconazole	Dutasteride
Abiraterone Acetate	Finasteride[b]
Progesterones[a]	

[a]Minor mechanisms of action.

[b]Investigational compounds or use.

LH, luteinizing hormone; LHRH, luteinizing hormone-releasing hormone.

Isolation of the naturally occurring hypothalamic decapeptide hormone, LHRH has provided another group of effective agents for advanced prostate cancer treatment. The physiologic response to LHRH depends on both the dose and the mode of administration. Intermittent pulsed LHRH administration, which mimics the endogenous release pattern, causes sustained release of both LH and FSH, whereas high-dose or continuous IV administration of LHRH inhibits gonadotropin release due to receptor downregulation.[25] Structural modification of the naturally occurring LHRH and innovative delivery have produced a series of LHRH agonists that cause a similar downregulation of pituitary receptors and a decrease in testosterone production.[33]

Androgen synthesis can also be inhibited in the testes or in the adrenal gland. Aminoglutethimide inhibits the desmolase-enzyme complex in the adrenal gland, thereby preventing the conversion of cholesterol to pregnenolone.

Pregnenolone is the precursor substrate for all adrenal-derived steroids, including androgens, glucocorticoids, and mineralocorticoids. Ketoconazole, an imidazole antifungal agent, causes a dose-related reversible reduction in serum cortisol and testosterone concentration by inhibiting both adrenal and testicular steroidogenesis.[33] Megestrol is a synthetic derivative of progesterone that exhibits a secondary mechanism of action by inhibiting androgen synthesis. This inhibition appears to occur at the adrenal level, but circulating levels of testosterone are also reduced, suggesting that inhibition at the testicular level may also occur.[33]

Antiandrogens inhibit the formation of the DHT-receptor complex and therefore interfere with androgen activity at the cellular level.[33] The conversion of testosterone to DHT may be inhibited by 5-α-reductase inhibitors.[8]

In advanced stages of disease, prostate cancer cells may be able to survive and proliferate without the signals normally provided by circulating androgens.[33] When this occurs, the tumor is no longer sensitive to therapies that depend on androgen blockade. These tumors are often referred to as hormone refractory or androgen independent.

CLINICAL PRESENTATION

Prior to the implementation of routine screening, prostate cancers were frequently diagnosed after the onset of symptoms, including urinary hesitancy, retention, painful urination, hematuria, and erectile dysfunction. With the introduction of screening techniques, most prostate cancers are now identified prior to the development of symptoms, although this may change as routine screening is no longer the norm.

CLINICAL PRESENTATION — Prostate Cancer

Localized Disease

- Asymptomatic

Locally Invasive Disease

- Ureteral dysfunction, frequency, hesitancy, and dribbling

- Impotence

Advanced Disease

- Back pain
- Cord compression
- Lower extremity edema
- Pathologic fractures
- Anemia
- Weight loss

DIAGNOSIS AND STAGING

The information obtained from the diagnostic tests is used to stage the patient (**Table 148-3**). The formal international classification system is the AJCC-UICC System (tumor, node, metastases [TNM]), adopted by the International Union Against Cancer in 1974, was last updated in 2017 (**Table 148-4**).

TABLE 148-3 Diagnostic and Staging Workup for Prostate Cancer

Initial tests	DRE PSA TRUS if either DRE is positive or PSA is elevated Biopsy
Staging tests	Gleason score on biopsy specimen Bone scan Complete blood count Liver function tests Serum phosphatases (acid/alkaline) Excretory urogram Chest x-ray
Additional staging tests (depends on tumor classification, PSA, and Gleason score)	Skeletal films Lymph node evaluation Pelvic computed tomography ^{111}In-labeled capromab pendetide scan Bipedal lymphangiogram Transrectal magnetic resonance imaging

DRE, Digital rectal examination; PSA, Prostate-specific antigen; TRUS, transrectal ultrasonography.

TABLE 148-4 Staging and Classification System for Prostate Cancer

AJCC-UICC[a] Classification (TNM)

$T_xN_xM_x$ (cannot be assessed)

$T_0N_0M_0$ (nonpalpable)

T: Tumor

T_0: No evidence of primary tumor

T_1 Clinically inapparent tumor not palpable

T_{1a}: Tumor incidental histologic finding in 5% or less of tissue resected

T_{1b}: Tumor incidental histologic finding in 5% or more of tissue resected

T_{1c}: Tumor identified by needle biopsy found in one or both sides, but not palpable

T_2: Tumor is palpable confined within the prostate

T_{2a}: Tumor involves one-half of one side or less

T_{2b}: Tumor involves more than one-half of one side, but not both sides

T_3: Extraprostatic tumor that is not fixed or does not invade adjacent structures

T_{3a}: Extraprostatic extension (unilateral or bilateral)

T_{3b}: Tumor invades seminar vesical(s)

T_{3c}: Tumor invades the seminal vesicle(s)

T_4: Tumor is fixed or invades adjacent structures other than the seminal vesicles such as external sphincter, rectum, bladder

T_{4a}: Tumor invades any of bladder neck, external sphincter, or rectum, levator muscles, and/or pelvic wall

T_{4b}: Tumor invades levator muscles and/or is fixed to the pelvic wall

N: Regional Lymph Nodes

N_1: Metastasis in a single lymph node, 2 cm or less in greatest dimension

N_2: Metastasis in single lymph node more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph node metastases, none more than 5 cm in greatest dimension

N_3: Metastasis in lymph node more than 5 cm in greatest dimension

M: Distant Metastasis

M_0: No distant metastasis

M_{1a}: Nonnetregional lymph node(s)

M_{1b}: Bone(s)

M_{1c}: Other site(s) with or without bone disease

[a]American Joint Committee on Cancer–International Union Against Cancer.

PSA, prostate-specific antigen.

3 The prognosis for patients with prostate cancer depends on the histologic grade, the tumor size, and the local extent of the primary tumor.[29] The most important prognostic criterion appears to be the histologic grade because the degree of differentiation ultimately determines the stage of disease. Poorly differentiated tumors are highly associated with both regional lymph node involvement and distant metastases.[29]

From 2008 to 2014, 5-year overall survival rates were estimated at 98% in white males and 96% in African American males.[1] For almost the same period, the survival rates for localized or regional disease and distant disease were about the same in white and African American males.[1]

TREATMENT

Desired Outcomes

The desired outcome in early-stage prostate cancer is to minimize morbidity and mortality caused by prostate cancer.[34,35] The most appropriate therapy of early-stage prostate cancer is controversial. Early-stage disease may be treated with surgery, radiation, or expectant management. While surgery and radiation are curative, they are associated with significant morbidity and mortality. Because the overall goal is to minimize morbidity and mortality associated with the disease, watchful waiting is appropriate in selected individuals. Advanced prostate cancer is not currently curable, and treatment should provide symptom relief and maintain quality of life. The mainstay of treatment for advanced prostate cancer is ADT, with a goal of reducing testosterone to castrate levels, with either an orchiectomy or an LHRH agonist.

General Approach to Treatment

The initial treatment for prostate cancer depends primarily on the disease stage, the Gleason score, the presence of symptoms, and the life expectancy of the patient.[34] Prostate cancer is usually initially diagnosed by PSA and DRE and confirmed by a biopsy, where the Gleason score is assigned. Asymptomatic patients with a low risk of recurrence, those with a T_1 or T_{2a}, with a Gleason score of less than 6, and a PSA of less than 10 ng/mL (mcg/L) may be managed

by observation, radiation, or radical prostatectomy (Table 148-5). As patients with asymptomatic early-stage disease generally have an excellent 10-year survival, immediate morbidities of treatment must be balanced with the lower likelihood of dying from prostate cancer. More aggressive treatment of early-stage prostate cancer is generally reserved for younger men, although patient preference is a major consideration in all treatment decisions. In a patient with a normal life expectancy of less than 10 years, observation or radiation therapy may be offered. In those with a normal life expectancy of equal to or greater than 10 years, either observation, radiation (external beam or brachytherapy), or radical prostatectomy with a pelvic lymph node dissection may be offered. Radiation therapy and radical prostatectomy are generally considered therapeutically equivalent for localized prostate cancer, although neither has been proven to be better than observation alone.[36]

TABLE 148-5 Initial Management of Prostate Cancer Based on Expected Survival and Recurrence Risk

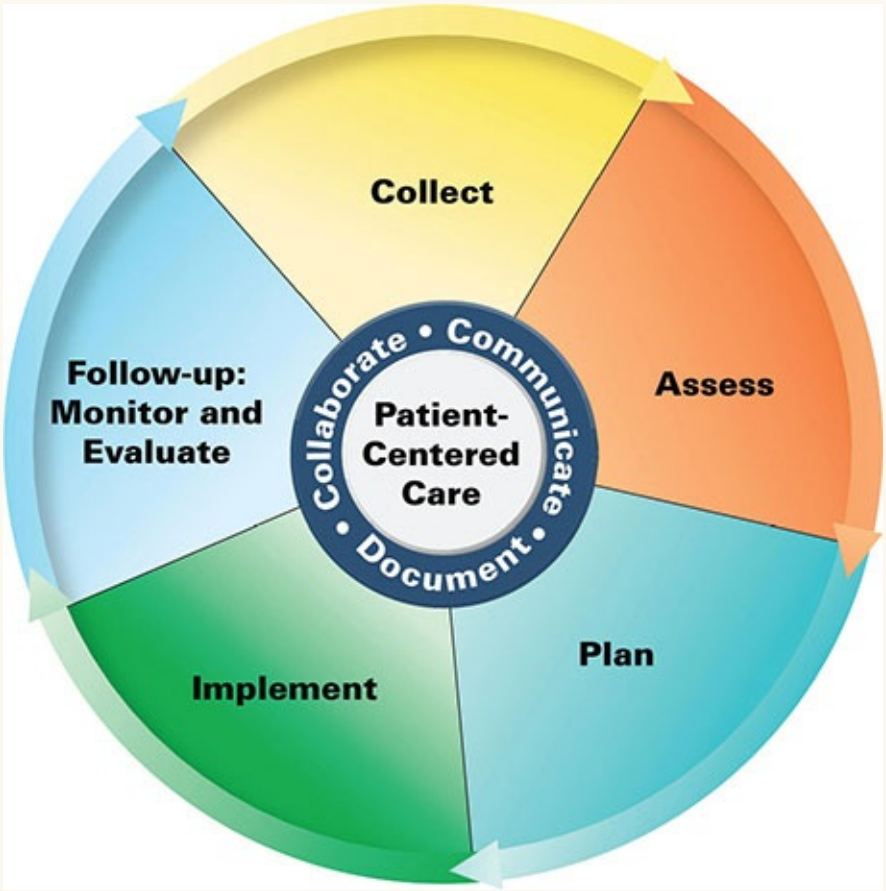
Recurrence Risk	Expected Survival (Years)	Initial Therapy
Very Low		
T_{1c}, Gleason score less than 6 and PSA less than 10 ng/mL (mcg/L)	<20	Observation
T_{1c}, Gleason score less than 6 and PSA less than 10 ng/mL (mcg/L)	20 or more	Observation or Radical prostatectomy with or without pelvic lymph node dissection or Radiation therapy
Low		
T_1–T_{2a} and Gleason and PSA less than 10 ng/mL (mcg/L) and <5% tumor in the specimen	10 or more	Observation or Radical prostatectomy with or without pelvic lymph node dissection or radiation therapy
	<10	Observation
Intermediate		
T_{2b}–T_{2c} or Gleason 7 or PSA 10-20 ng/mL (mcg/L)	10 or more	Observation or Radical prostatectomy with pelvic lymph node dissection or Radiation therapy with or without 4-6 months of neoadjuvant ADT with or without brachytherapy
T_{2b}–T_{2c} or Gleason 7 or PSA 10-20 ng/mL (mcg/L)	10 or more	Radical prostatectomy with pelvic lymph node dissection or Radiation therapy with or without 4-6 months of neoadjuvant ADT with or without brachytherapy
High		
T_{3a}, Gleason 8-10, PSA >20 ng/mL (mcg/L)	5 years or more	Radiation therapy and ADT[a] (2-3 years) with or without brachytherapy or Radical prostatectomy and pelvic lymph node dissection
Very High		
T_{3b}-T_4 or Gleason pattern 5 or >4 cores with Gleason score 8-10		Radiation therapy and ADT (2-3 years) with or without brachytherapy or Radical prostatectomy and pelvic lymph node dissection or ADT
Very High		
Any T, N_1		ADT (2-3 years) with or without abiraterone and prednisone or Radiation therapy and ADT (2-3 years) with or without abiraterone and prednisone (or methylprednisolone)
Any T, Any N, M_1		Orchiectomy or LHRH agonist[b] with or without an antiandrogen or LHRH antagonist or Observation

[a]Androgen deprivation therapy to achieve serum testosterone levels <50 ng/dL (1.7 nmol/L).

[b]LHRH agonist, medical castration, or surgical castration are equivalent.

ADT, androgen-deprivation therapy; LHRH, luteinizing hormone-releasing hormone; PSA, prostate-specific antigen.

Wilt and colleagues conducted a systematic review of 18 randomized trials and 473 observational studies to compare the effectiveness and potential complications from treatment options from prostate cancer. This study showed that the effectiveness of radiation, radical prostatectomy, and ADT could not be compared because of the paucity of high-quality evidence available for analysis. Adverse effect profiles were similar, although severity varied among the treatments.[37] Complications from radical prostatectomy include blood loss, stricture formation, incontinence, lymphocele, fistula formation, anesthetic risk, and impotence. Nerve-sparing radical prostatectomy can be performed in many patients; 50% to 80% regain sexual potency within the first year. However, even in patients with good preoperative sexual health, many do not return to baseline after surgery even with the assistance of erectile dysfunction treatments.[38] Acute complications from radiation therapy include cystitis, proctitis, hematuria, urinary retention, penoscrotal edema, and impotence (30% incidence).[29] Chronic complications include proctitis, diarrhea, cystitis, enteritis, impotence, urethral stricture, and incontinence.[29] In addition, ADT can cause cognitive impairment, mood disturbances, and lack of initiative.[37] Because radiation and prostatectomy have significant and immediate mortality when compared with expectant management alone, many patients may elect to postpone therapy until symptoms develop.



Patient Care Process for Prostate Cancer

Collect

- Patient characteristics (eg, age, race, sex)
- Patient history (past medical, family, social, dietary habits, tobacco use)
- Current signs and symptoms (frequency of urination, dribbling, hesitancy, etc.)
- Thorough medication history (including prescription, nonprescription medications, and other substances), drug allergies, and intolerances
- Testing including laboratory, staging scans, and biopsy (see Table 148-3)

Assess

- Determine the severity of illness based on symptoms, laboratory testing, scans, and biopsy information to appropriately stage patient (Table 148-4)
- Evaluate current medication regimen and past medical history for potential drug-drug interactions or treatment contraindications
- Assess if metastatic lesions are present that may require additional treatment including radiation therapy or Radium-223

Plan*

- Drug therapy regimen including dose, route, frequency, and duration (see Table 148-5)
- Monitoring parameters including efficacy and time frame
- Patient education for potential side effects or complication
- Self-monitoring of symptoms
- Referrals to other providers when appropriate (eg, dietician, palliative care)

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Presence of adverse effects
- Monitoring laboratory testing including CBC, CMP, and PSA
- Patient adherence to treatment plan using multiple sources of information

**Collaborate with patient, caregivers, and other healthcare professionals.*

Individuals with T_{2b} and T_{2c} disease or a Gleason score of 7 or a PSA ranging from 10 to 20 ng/mL (mcg/L) are considered at intermediate risk for prostate cancer recurrence.[34] Individuals with less than a 10-year expected survival may be offered observation or radical prostatectomy with pelvic lymph node

dissection or radiation therapy with or without 4 to 6 months of neoadjuvant ADT with or without brachytherapy, and those with a greater than or equal to 10-year life expectancy may be offered either radical prostatectomy with or without a pelvic lymph node dissection or radiation therapy with or without 4 to 6 months of neoadjuvant ADT with or without brachytherapy (see Table 148-5).

The treatment of patients at high risk of recurrence (stage T_3, a Gleason score ranging from 8 to 9, or a PSA value greater than 20 ng/mL [mcg/L]) should be treated with androgen ablation for 2 to 3 years combined with radiation therapy with or without brachytherapy (Table 148-5). Selected individuals with a low-tumor volume may receive a radical prostatectomy with or without a pelvic lymph node dissection.

4 Patients with T_{3b} and T_4 disease have a very high risk of recurrence and are usually not candidates for radical prostatectomy because of extensive local spread of disease, although it may be possible for some individuals.[34] ADT with a LHRH agonist plus an antiandrogen should be used prior to radiation therapy for patients with locally advanced prostate cancer to improve outcomes over radiation therapy alone. Recent evidence suggests that androgen ablation should be instituted at diagnosis rather than waiting for symptomatic disease or progression to occur. In a randomized clinical trial of 500 men with locally advanced prostate cancer who were randomized to either immediate initiation of androgen ablation (either orchiectomy or androgen ablation) or deferred hormonal therapy, patients who received immediate therapy had a median actuarial cause-specific survival of 7.5 years for immediate treatment as compared with 5.8 years for deferred treatment.[39]

5 Systemic therapy for nonmetastatic castration-naive disease, where the disease has not yet become resistant to ADT therapy, may include either orchiectomy, LHRH agonist with or without an antiandrogen, LHRH antagonist, or observation. ADT in addition to one of the following: docetaxel (6 cycles), abiraterone/prednisone, enzalutamide, or apalutamide are recommended options for patients with metastatic castration-naive disease. Systemic therapy for nonmetastatic (M_0) castration-resistant disease include ADT to maintain serum levels of testosterone <50 ng/dL (1.7 nmol/L), a second-generation antiandrogen, or another secondary hormone therapy. Patients who develop metastatic disease often have tumor progression and develop castration-resistant prostate cancer (CRPC).[34] CRPC is described clinically by a rising PSA while on optimal ADT, or the development of symptoms, typically related to bone metastases, including bone pain and fractures. Importantly, further therapy is determined by the

presence of symptomatic disease or whether the metastatic progression is manifested as only a rising PSA. In CRPC, tumor testing for MSI-H or dMMR should be considered. Positive tests indicate eligibility for pembrolizumab, a PD-1 inhibitor, in later lines of treatment for CRPC. Patients with metastatic disease may be continued on ADT and denosumab or an IV bisphosphonate is added in patients with bone metastases. For clinically asymptomatic patients with metastatic CRPC who have a rising PSA, sipuleucel-T is another option. Palliative radiation therapy to bony metastases and best supportive care are also options that may be utilized in these patients.[34]

For those with symptoms or disease involving internal organs (eg, liver), docetaxel, enzalutamide, or abiraterone are all category 1 treatment recommendations.[34] Radium-223, an alpha emitter, is also recommended for patients with bony metastases. Other first-line treatment options are a clinical trial or other secondary hormone manipulations (see **Fig. 148-3**).

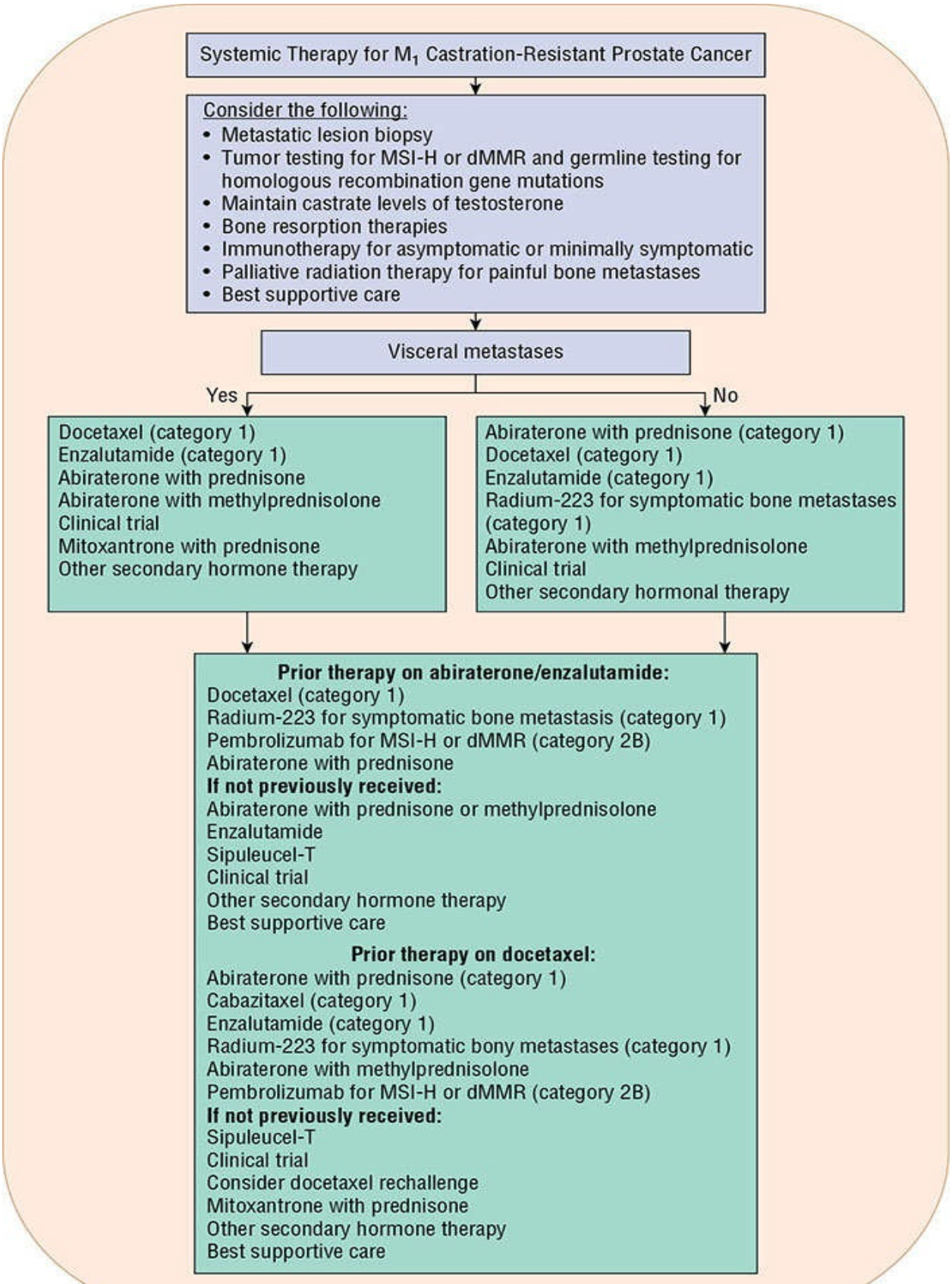

Systemic Therapy for M1 Castration-Resistant Prostate Cancer
Consider the following:
• Metastatic lesion biopsy
• Tumor testing for MSI-H or dMMR and germline testing for homologous recombination gene mutations
• Maintain castrate levels of testosterone
• Bone resorption therapies
• Immunotherapy for asymptomatic or minimally symptomatic
• Palliative radiation therapy for painful bone metastases
• Best supportive care
Visceral metastases
Yes
No
Docetaxel (category 1)
Enzalutamide (category 1)
Abiraterone with prednisone
Abiraterone with methylprednisolone
Clinical trial
Mitoxantrone with prednisone
Other secondary hormone therapy
Abiraterone with prednisone (category 1)
Docetaxel (category 1)
Enzalutamide (category 1)
Radium-223 for symptomatic bone metastases (category 1)
Abiraterone with methylprednisolone
Clinical trial
Other secondary hormonal therapy
Prior therapy on abiraterone/enzalutamide:
Docetaxel (category 1)
Radium-223 for symptomatic bone metastasis (category 1)
Pembrolizumab for MSI-H or dMMR (category 2B)
Abiraterone with prednisone
If not previously received:
Abiraterone with prednisone or methylprednisolone
Enzalutamide
Sipuleucel-T
Clinical trial
Other secondary hormone therapy
Best supportive care
Prior therapy on docetaxel:
Abiraterone with prednisone (category 1)
Cabazitaxel (category 1)
Enzalutamide (category 1)
Radium-223 for symptomatic bony metastases (category 1)
Abiraterone with methylprednisolone
Pembrolizumab for MSI-H or dMMR (category 2B)
If not previously received:
Sipuleucel-T
Clinical trial
Consider docetaxel rechallenge
Mitoxantrone with prednisone
Other secondary hormone therapy
Best supportive care

FIGURE 148-3 Treatment of metastatic castration-resistant prostate cancer.

Nonpharmacologic Therapy

Observation

Observation is often referred to as expectant management, active surveillance, or watchful waiting. Observation involves monitoring the course of disease and initiating treatment if the cancer progresses. It is estimated that only about 10% of men who are eligible for observation choose this option.[36] A PSA and DRE are performed every 6 months, with a repeat biopsy at any sign of disease progression. The advantages of observation are avoiding the adverse effects associated with definitive therapies such as radiation and radical prostatectomy and minimizing the risk of unnecessary therapies. The major disadvantage of observation is the risk that cancer progresses and requires more intensive therapy.

Orchiectomy

Bilateral orchiectomy, or removal of the testes, is a form of ADT that rapidly reduces circulating androgens to castrate levels (less than 50 ng/dL [1.7 nmol/L]).[24] However, many patients are not surgical candidates because of advanced age, and other patients find this procedure psychologically unacceptable.[28] Orchiectomy is the preferred initial treatment in patients with impending spinal cord compression or ureteral obstruction.

Radiation

The two commonly used methods for radiation therapy are external beam radiotherapy and brachytherapy.[34] In external beam radiotherapy, doses of 70 to 75 Gy (7,000-7,500 rad) are delivered in 35 to 41 fractions in patients with low-grade prostate cancer and 75 to 80 Gy (7,500-8,000 rad) for those with intermediate- or high-grade prostate cancer. Brachytherapy involves the permanent implantation of radioactive beads of 145 Gy (14,500 rad) ^{125}iodine or 124 Gy (12,400 rad) ^{103}palladium and is generally reserved for individuals with low-risk cancers. Radiation therapy may also be given after surgery in patients with localized disease. Acute complications from radiation therapy include cystitis, proctitis, hematuria, urinary retention, penoscrotal edema, and impotence.[19] Chronic complications include proctitis, diarrhea, cystitis, enteritis,

impotence, urethral stricture, and incontinence.[28] Because radiation therapy and radical prostatectomy have significant and immediate mortality when compared with observation alone, many patients elect to postpone therapy until symptoms develop.

Radical Prostatectomy

Complications from radical prostatectomy include blood loss, stricture formation, incontinence, lymphocele, fistula formation, anesthetic risk, and impotence. Nerve-sparing radical prostatectomy can be performed in many patients; 50% to 80% regain sexual potency within the first year.

Pharmacotherapy

Drug Treatments of First Choice

Luteinizing Hormone-Releasing Hormone Agonists LHRH agonists are a reversible method of androgen ablation and are as effective as orchiectomy in treating prostate cancer.[40] Currently available LHRH agonists include leuprolide, leuprolide depot, leuprolide implant, triptorelin depot, triptorelin implant, and goserelin acetate implant (**Table 148-6**). The leuprolide depot formulation contains leuprolide acetate in coated pellets. The dose is administered intramuscularly, and the coating dissolves at different rates to allow sustained leuprolide levels throughout the dosing interval. Goserelin acetate implant contains goserelin acetate dispersed in a plastic matrix of D, L-lactic, and glycolic acid copolymer and is administered subcutaneously. Hydrolysis of the copolymer material provides continuous release of goserelin over the dosing period. A leuprolide implant is a mini-osmotic pump that delivers 120 mcg of leuprolide daily for 12 months. After 12 months the implant is removed, and a different implant can be placed.

TABLE 148-6 Hormonal Therapies for Prostate Cancer[55–66,68,84]

Drug (Brand Name)	Usual Dose	Toxicities	Hepatic/Renal Adjustments	Monitoring Parameters	Drug Interactions	Administration
First-Generation Antiandrogens						
Flutamide (Eulexin)	750 mg/day	Gynecomastia Hot flashes Gastrointestinal disturbances (diarrhea) Loss of libido LFT abnormalities Breast tenderness Methemoglobinemia	Contraindicated in patients with hepatic impairment No dosage adjustment necessary in chronic renal impairment	Serum transaminases should be monitored prior to start of therapy and monthly for the first 4 months, then periodically thereafter Monitor for tumor reduction, testosterone/estrogen, and phosphatase serum levels	Substrate of CYP1A2 and CYP3A4	Administered orally in three divided doses; capsule may be opened into applesauce, pudding, or other soft foods
Bicalutamide (Casodex)	50 mg/day (up to 150 mg/day—unlabeled use)	Gynecomastia Hot flashes Gastrointestinal disturbances (diarrhea) Decrease libido LFT abnormalities Breast tenderness	Discontinue if ALT >2 times upper limit of normal or patient develops jaundice	Serum transaminases should be monitored prior to start of therapy and monthly for the first 4 months, then periodically thereafter Periodic monitoring of CBC, EKG, echocardiograms, serum testosterone, luteinizing hormone, and PSA	Inhibits CYP3A4 May increase the concentration of vitamin K antagonists	May be taken with or without food
Nilutamide (Nilandron)	300 mg/day for first month then 150 mg/day	Gynecomastia Hot flashes Gastrointestinal Disturbances (constipation) LFT abnormalities Breast tenderness Visual disturbances (impaired dark adaptation) Alcohol intolerance Interstitial pneumonitis	Contraindicated in patients with hepatic impairment Discontinue if ALT >2 times upper limit of normal or patient develops jaundice	Serum transaminases should be monitored prior to start of therapy and monthly for the first 4 months, then periodically thereafter Chest x-ray at baseline and consideration of pulmonary function testing (at baseline)	Substrate of CYP2C19 and weak inhibitor of CYP2C19	May be taken with or without food
Second-Generation Antiandrogens						
Apalutamide (Erleada)	240 mg/day	Gastrointestinal disturbances (diarrhea, nausea) Hot flashes Fatigue Hypertension Rash Decreased weight Falls and fractures Peripheral edema Seizures	No adjustment necessary for renal or hepatic impairment	Complete blood counts baseline and periodically LFTs baseline and periodically	Strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9	May be taken with or without food
Enzalutamide (Xtandi)	160 mg/day	Gastrointestinal disturbances (diarrhea) Musculoskeletal disorders (back pain, arthralgias, muscle pain, weakness) Asthenia Peripheral edema CNS (headache, dizziness) Seizures LFT abnormalities	No adjustment necessary for renal or hepatic impairment	Complete blood counts baseline and periodically LFTs baseline and periodically	Strong CYP3A4 and moderate CYP2C9 and CYP2C19 inducer; avoid CYP3A4, CYP2C9, and CYP2C19 sensitive substrates. CYP2C8 substrate, avoid strong inducers and inhibitors of CYP2C8. If vitamin K antagonists are necessary, conduct additional INR monitoring	May be taken with or without food

Darolutamide (Nubeqa)	1,200 mg/day	Fatigue Gastrointestinal disturbances (diarrhea, constipation, nausea) Rash Musculoskeletal disorders (back pain, arthralgias, pain in an extremity) Falls, including accidents/bone fractures Hypertension Seizures	For moderate hepatic impairment or severe renal impairment (not on dialysis): dose should be reduced to 600 mg/day	Complete blood counts baseline and periodically LFTs baseline and periodically	Breast Cancer Resistance Protein (BCRP) transporter Inhibitor Darolutamide inhibits OATP1B1 and OATP1B3	Take with food
Androgen Synthesis Inhibitor						
Abiraterone acetate (Zytiga)	1,000 mg/day + prednisone 5 mg BID	Gastrointestinal disturbances (diarrhea) Edema Hypokalemia Hypophosphatemia LFT abnormalities Hypertriglyceridemia	250 mg daily for Child Pugh Class B; avoid use in Child Pugh Class C Withhold treatment if LFTs >5 times the ULN or bilirubin >3 ULN	Serum transaminases should be monitored prior to start of therapy, every 2 weeks for 3 months, then monthly thereafter Monitor for signs and symptoms of adrenocorticoid insufficiency; monthly for hypertension, hypokalemia, and fluid retention	Substrate of CYP3A4. Use with caution with CYP3A4 inhibitors and inducers. Inhibits CYP1A2, CYP2C19, CYP2C8, CYP2C9, CYP2D6, CYP3A4, and P-glycoprotein Use sensitive substrates with caution	Administer on an empty stomach, at least 1 hour before and 2 hours after food
Luteinizing-Hormone Agonists						
Leuprolide (Lupron)	7.5 mg IM every month 22.5 mg IM every 3 months 30 mg IM every 4 months 45 mg IM every 6 months	Hot flashes Decreased libido Gynecomastia Osteoporosis Fatigue Weight gain	No adjustment necessary for renal or hepatic impairment	Serum testosterone ~4 weeks after initiation, PSA, blood glucose, and $HgbA_{1c}$ prior to initiation and periodically thereafter	May diminish the effects of antidiabetic agents	Vary injection site
Goserelin (Zoladex)	3.6 mg SQ implant every month 10.8 mg SQ implant every 3 months	Hot flashes Decreased libido Gynecomastia Osteoporosis Fatigue Weight gain	No adjustment necessary for renal or hepatic impairment	Monitor bone mineral density, serum calcium, and cholesterol/lipids	May diminish the effects of antidiabetic agents	Vary injection site
Triptorelin (Trelstar)	3.75 mg IM every month 11.25 mg IM every 3 months 22.5 mg IM every 6 months	Hot flashes Decreased libido Gynecomastia Osteoporosis Fatigue Weight gain	No adjustment necessary for renal or hepatic impairment	Monitor serum testosterone levels and prostate-specific antigen	May diminish the effects of antidiabetic agents	Vary injection site
Gonadotropin-Releasing Hormone Antagonists						
Degarelix (Firmagon)	240 mg SQ loading dose 80 mg SQ every 28 days (following 28 days after loading dose)	Hot flashes Decreased libido Gynecomastia Osteoporosis Fatigue Weight gain	Use with caution with CL_{cr} <50 mL/min (0.83 mL/s) Do not use in patients with severe hepatic impairment	Prostate-specific antigen periodically, serum testosterone monthly until castration achieved then every other month, LFTs at baseline in addition to serum electrolytes and bone mineral density	Use with caution with agents that may increase QTC interval	Vary injection site

ALT, alanine aminotransferase; BID, twice daily; CBC, complete blood count; CL_{cr}, creatinine clearance; CNS, central nervous system; CYP, cytochrome P450; EKG, electrocardiogram; $HgbA_{1c}$, hemoglobin A1c; IM, intramuscular injection; INR, international normalized ratio; LFT, liver function test; PSA, prostate-specific antigen; SQ, subcutaneous injection; ULN, upper limit of normal.

Several randomized trials have demonstrated that leuprolide, goserelin, and triptorelin are effective agents when used alone in patients with advanced prostate cancer.[32] Response rates around 80% have been reported, with a lower incidence of adverse effects as compared with estrogens.[32] The currently available LHRH agonists or the dosage formulations have not been directly compared in clinical trials, but a meta-analysis showed no significant differences in efficacy or toxicity between leuprolide, goserelin, and orchiectomy.[41] Triptorelin is a more recent addition that is generally considered to be equally effective. Therefore, the choice between the three agents is usually made based on cost and patient and physician preference for a dosing schedule.

The most common adverse effects reported with LHRH agonist therapy include a disease flare during the first week of therapy, hot flashes, erectile impotence, decreased libido, and injection-site reactions.[32] The disease flare is caused by an initial induction of LH and FSH by the LHRH agonist leading to an initial phase of increased testosterone production, and manifests clinically as either increased bone pain or increased urinary symptoms.[32] This flare reaction usually resolves after 2 weeks and has a similar onset and duration pattern for the depot LHRH products.[42,43] Tumor flare can be minimized by initiating an antiandrogen prior to the administration of the LHRH agonist and continuing for 2 to 4 weeks.[33]

LHRH agonist monotherapy can be used as initial therapy, with response rates similar to those for orchiectomy. The risk of cardiovascular-related adverse effects is lower with LHRH therapy than with estrogen administration. Patients should be counseled to expect worsening symptoms during the first week of therapy. Appropriate pain and symptom management is required during this period, and a short course of concomitant antiandrogen therapy may need to be considered prior to initiating the LHRH agonist. Caution should be exercised if initiating LHRH agonist therapy in patients with widely metastatic disease involving the spinal cord or having the potential for ureteral obstruction because irreversible complications may occur.

Another potentially serious complication of ADT is a decrease in bone mineral density leading to an increased risk for osteoporosis, osteopenia, and skeletal fractures. During initial therapy, bone mineral density of the hip and spine decreases by 2% to 3%.[44] Additionally, ADT has been associated with a 21% to 45% relative increase in fracture risk.[45–47] Therefore, most clinicians recommend that men starting long-term ADT should have a baseline bone mineral density and be initiated on a calcium and vitamin D supplement.[33,34]

In addition, an antiresorptive agent, either zoledronic acid or denosumab should be considered. A meta-analysis combined data from three identically designed double-blind randomized controlled trials that compared the efficacy and safety of denosumab at a dose of 120 mg with that of zoledronic acid at a dose of 4 mg administered IV.[48] Almost 6,000 patients with breast and prostate cancer and multiple myeloma were included in the meta-analysis. Denosumab reduced the risk of first skeletal-related event (SRE) by 17% (hazard ratio 0.83, 95% CI 0.76-0.90, $P < 0.001$ for both noninferiority and superiority tests) as compared with zoledronic acid and the median time-to-first SRE was 27.66 months for denosumab versus 19.45 months for zoledronic acid. The benefits were consistent across tumor types evaluated and the incidence of adverse effects was not significantly different between the denosumab and zoledronic acid groups.

ADT has also been associated with a higher incidence of metabolic effects. In a landmark population-based trial, patients treated with an ADT and a gonadotropin-releasing hormone (GnRH) agonist had a greater risk of new-onset diabetes, coronary artery disease, and myocardial infarctions.[49] However, it is not clear whether ADT increases the risk of cardiovascular death. A published meta-analysis of eight trials with 4,141 patients treated with ADT evaluated prostate cancer-specific mortality and all-cause mortality.[50] The trials included patients with nonmetastatic disease who were treated with immediate predominantly GnRH-agonist–based ADT versus no immediate ADT (control group). The risk of cardiovascular death for ADT versus control was not significantly different (RR 0.93, 95% CI 0.79-1.10, $P = 0.41$) and these results suggest that ADT does not increase cardiovascular mortality.[34] Patients receiving ADT should be screened for cardiovascular disease and diabetes and appropriate interventions to prevent and treat these complications should be initiated.[34]

Gonadotropin-Releasing Hormone Antagonists An alternative to LHRH agonists is the approved GnRH antagonist, degarelix. Degarelix works by binding reversibly to GnRH receptors in the pituitary gland, reducing the production of testosterone to castrate levels. The major advantage of degarelix over LHRH agonists is the rapidity at which it reduces testosterone levels. Castration levels are achieved in 7 days or less with degarelix, as compared with 28 days with leuprolide. Tumor flare does not occur and antiandrogens are not required.

In a trial of 610 men with advanced prostate cancer, degarelix was shown to be equivalent to leuprolide in lowering testosterone levels for up to 1 year.

Degarelix is available as 40 mg/mL and 20 mg/mL vials for subcutaneous injection, and the starting dose is 240 mg followed by 80 mg every 28 days. The starting dose should be divided into two 120-mg injections.[51] Degarelix has not been studied in combination with antiandrogens, and routine use of the combination is not recommended.

The most frequently reported adverse reactions were injection site reactions, including pain (28%), erythema (17%), swelling (6%), induration (4%), and nodules (3%). Most reactions were transient and mild to moderate, leading to discontinuation in less than 1% of study subjects. Other adverse effects included elevations in liver function tests, which occurred in about 10% of study subjects. Osteoporosis may develop, and calcium and vitamin D supplementation should be considered.[51]

Antiandrogens The first-generation antiandrogens include flutamide, bicalutamide, and nilutamide. Three second-generation antiandrogens, apalutamide, enzalutamide, and darolutamide, are currently available (see Table 148-6).[52–63] Cyproterone is another agent with antiandrogen activity, but it is not available in the United States. Antiandrogens have been used as monotherapy in previously untreated patients, but a meta-analysis showed that monotherapy with antiandrogens is less effective than LHRH agonists.[43] Therefore, for advanced prostate cancer, flutamide, bicalutamide, and nilutamide are indicated only in combination with androgen-ablation therapy. Flutamide and bicalutamide are indicated in combination with an LHRH agonist, and nilutamide is indicated in combination with orchiectomy.[64] Antiandrogens can reduce the symptoms from the flare phenomenon associated with LHRH agonist therapy.[33] Enzalutamide, also known as MDV3100, is currently approved as a single agent for patients with metastatic CRPC.[65] As with the other antiandrogens, enzalutamide does not lower androgen levels but inhibits androgen receptor signaling by competitively inhibiting androgen binding without stimulation of the androgen receptor. Enzalutamide may have an advantage over the currently available first-generation antiandrogen agents in that it inhibits nuclear translocation of the androgen receptor, DNA binding, and coactivator recruitment. It also has a greater affinity for the androgen receptor and has shown activity in patients resistant to other antiandrogens. Initially approved in docetaxel failure only, enzalutamide may be used in the first-line setting to delay the initiation of chemotherapy in both nonmetastatic and metastatic disease.[66] Apalutamide and darolutamide are also second-generation antiandrogens. Apalalutamide was initially approved in the nonmetastatic castration naive patient population based

on the results of a clinical trial that demonstrated increased median metastasis-free survival as compared to placebo (40.5 vs 16.2 months).[67] Apalutamide has since been approved for the use in castrate-resistant prostate cancer. Darolutamide is structurally distinct, consisting of two pharmacologically active diastereomers.[82,83] Lower penetration of the blood-brain barrier and low-binding affinity for γ-aminobutyric acid type A receptors offers a potential for fewer and less severe toxic effects than enzalutamide and apalutamide despite similar metastasis-free survival rates.

The most common antiandrogen-related adverse effects are listed in Table 148-6. In the only randomized comparison of bicalutamide plus an LHRH agonist versus flutamide plus an LHRH agonist, diarrhea was more common in flutamide-treated patients. The adverse effects of apalutamide and enzalutamide are similar to those of the other antiandrogens, but they both have an increased risk of seizures.

Combined Androgen Blockade Although up to 80% of patients with advanced prostate cancer will respond to initial hormonal manipulation, almost all patients will progress within 2 to 4 years after initiating therapy.[28] Two mechanisms have been proposed to explain this tumor resistance. The tumor could be heterogeneously composed of cells that are hormone-dependent and hormone-independent, or the tumor could be stimulated by extratesticular androgens that are converted intracellularly to DHT. The rationale for combination hormonal therapy is to interfere with multiple hormonal pathways to completely eliminate androgen action. In clinical trials, combination hormonal therapy, sometimes also referred to as maximal androgen deprivation or total androgen blockade, or *combined androgen blockade* (CAB), has been used. The combination of LHRH agonists or orchiectomy with antiandrogens is the most extensively studied CAB approach.

A systematic review of six meta-analyses concluded that the best evidence for CAB came from the largest meta-analysis, conducted by the Prostate Cancer Trialists Collaborative Group including 8,725 patients from 27 trials.[69] That analysis found no difference in overall survival between CAB and castration alone at 2 or 5 years, but a subgroup analysis showed that CAB with nonsteroidal antiandrogens, including flutamide, bicalutamide, or nilutamide was associated with a statistically significant improvement in 5-year survival over castration alone (27.6% vs 24.7%, $P = 0.005$). As expected, antiandrogens increased toxicity over placebo.

Although some clinicians consider CAB to be the initial hormonal therapy of

choice for newly diagnosed patients, the clinician must weigh the costs of combined therapy against the modest survival benefit.[69] It is appropriate to use either LHRH agonist monotherapy or CAB as initial therapy for metastatic prostate cancer. CAB may be most beneficial in patients with minimal disease and prevents tumor flare, particularly in those with advanced metastatic disease. All other patients may be started on LHRH monotherapy, and an antiandrogen may be added after several months if androgen ablation is incomplete.

It is not clear when to start hormonal-deprivation therapy in patients with advanced prostate cancer.[32] The original recommendation to start therapy when symptoms appeared was based on the Veterans Administration Cooperative Urologic Research Group (VACURG) trials, in which no overall survival difference was demonstrated in patients who either started diethylstilbestrol (DES) initially or crossed over to active treatment when symptoms appeared; the excess mortality was attributed to estrogen administration.[70] Because LHRH agonists and antiandrogens are viable therapies with less cardiovascular toxicity, it is not clear whether delaying therapy is justified with these agents. Reanalysis of the original VACURG data[71] and recent combined ADT trials[70] demonstrate a survival advantage for young, good performance status, minimal disease patients treated initially with hormonal therapy, suggesting that early intervention before symptoms appear may be appropriate.[71]

Alternative Drug Treatments

Secondary or salvage therapies for patients who progress after their initial therapy depend on what was used for initial management.[34] For patients initially diagnosed with localized prostate cancer, radiotherapy can be used in the case of failed radical prostatectomy. Alternatively, androgen ablation can be used in patients who progress after either radiation therapy or radical prostatectomy.

Secondary Hormonal Manipulations In patients treated initially with one hormonal modality, secondary hormonal manipulations may be attempted. This may include adding an antiandrogen to a patient with incomplete suppression of testosterone secretion with an LHRH agonist. In patients that have progression while receiving CAB, withdrawing antiandrogens, or using agents that inhibit androgen synthesis may be attempted. For patients who initially received an LHRH agonist alone, castration testosterone levels should be documented. Patients with inadequate testosterone suppression (greater than 20 ng/dL [0.7 nmol/L]) can be treated by adding an antiandrogen or performing an orchiectomy. If castration testosterone levels have been achieved, the patient is

considered to have androgen-independent disease, and palliative androgen-independent salvage therapy can be used.

6 If the patient initially received CAB with an LHRH agonist and an antiandrogen, then androgen withdrawal is the first salvage manipulation.[34] Objective and subjective responses have been noted following the discontinuation of flutamide,[72] bicalutamide,[73] or nilutamide[74] in patients receiving these agents as part of combined androgen ablation with an LHRH agonist. Mutations in the androgen receptor can allow antiandrogens such as flutamide, bicalutamide, and nilutamide (or their metabolites) to become agonists and activate the androgen receptor.[75] Patient responses to androgen withdrawal manifest as significant PSA reductions and improved clinical symptoms. Androgen withdrawal responses lasting 3 to 14 months have been observed in up to 35% of patients, and responses appear to be most closely related to longer androgen exposure times. Incomplete cross-resistance has been noted in some patients who received bicalutamide after they had progressed while receiving flutamide.[76] The addition of an agent that blocks adrenal androgen synthesis, such as aminoglutethimide, at the time that androgens are withdrawn may produce a better response than androgen withdrawal alone.[75] Because of the potential for a response immediately after antiandrogen withdrawal, a sufficient observation and assessment period (usually 4-6 weeks) is usually required before a patient can be enrolled on a clinical trial evaluating a new agent or therapy for advanced prostate cancer.

Androgen synthesis inhibitors, such as aminoglutethimide or ketoconazole, can provide symptomatic relief for a short time in about 50% of patients with progressive disease despite previous androgen-ablation therapy.[34] Adverse effects during aminoglutethimide therapy occur in about 50% of patients.[34] Central nervous system effects that include lethargy, ataxia, and dizziness are the major adverse reactions. A generalized morbilliform, pruritic rash has been reported in up to 30% of patients treated. The rash is usually self-limiting and resolves within 5 to 8 days with continued therapy. Adverse effects from ketoconazole include gastrointestinal intolerance, transient rises in liver and renal function tests, and hypoadrenalism. Ketoconazole is combined with replacement doses of hydrocortisone to prevent symptomatic hypoadrenalism.[34]

Abiraterone is the newest androgen synthesis inhibitor that targets cytochrome P450 (CYP)17A1, which results in a decrease in circulating levels of testosterone.[77] Abiraterone is indicated in patients with metastatic CRPC, either before or after docetaxel-based chemotherapy. The initial approval was

based on the results of a phase III study of patients previously treated with a docetaxel-containing regimen. The combination of abiraterone and prednisone increased median overall survival by 3.9 months in comparison to placebo. Hypertension, hypokalemia, and edema may occur due to hypoadrenalism. Abiraterone is available as the prodrug, abiraterone acetate, and should be taken on an empty stomach as food increases bioavailability by up to 10-fold. Monitoring of liver function tests is recommended at baseline, every 2 weeks for the first 3 months, and then monthly thereafter. Since abiraterone is an inhibitor of CYP2D6, medication profiles should be reviewed for potential drug interactions prior to initiation of abiraterone therapy.[77]

7 **Chemotherapy** Chemotherapy with docetaxel and prednisone improves survival in patients with CRPC and is considered a first-line therapy option. Docetaxel 75 mg/m^2 every 3 weeks combined with prednisone 5 mg twice a day improves survival in CRPC.[78] The most common adverse events with this regimen are nausea, alopecia, and bone marrow suppression. Other adverse effects of docetaxel include fluid retention and peripheral neuropathy. Docetaxel is metabolized in the liver; patients with hepatic impairment may not be eligible for treatment with docetaxel because of an increased risk for toxicity (see **Table 148-7**).

TABLE 148-7 Chemotherapy and Immunotherapy for Prostate Cancer[62-64]

Drug (Brand Name)	Usual Dose	Toxicities	Hepatic/Renal Adjustments	Monitoring Parameters	Drug Interactions	Administration
Antimicrotubule Agents						
Docetaxel (Taxotere)	75 mg/m² IV every 3 weeks	Fluid retention, alopecia, mucositis, myelosuppression, hypersensitivity	Aspartate transaminase/ alanine transaminase >1.5 times the upper limit of normal and alkaline phosphatase >2.5 times the upper limit of normal do not administer	CBC with differential, LFTs, bilirubin, alkaline phosphatase, renal function Monitor for hypersensitivity reactions	Avoid concomitant use of CYP3A4 inhibitors	Administer IV infusion over 1 hour. Premedication with corticosteroids for 3 days beginning the day before
Cabazitaxel (Jevtana)	25 mg/m² IV every 3 weeks	Fluid retention, constipation, mucositis, myelosuppression, hypersensitivity	Discontinue if ALT >2 times upper limit of normal or patient develops jaundice	CBC weekly during the first cycle, then prior to each treatment Monitor for hypersensitivity	Avoid concomitant use of CYP3A4 inducers and inhibitors	Administer IV infusion over 1 hour
Immunotherapy						
Sipuleucel-T (Provenge)	Each injection contains >50 million autologous CD54+ cells (obtained through leukapheresis) activated with PAP-GM-CSF Dose is given ~ every 2 weeks for 3 total doses	Hypersensitivity, chills, fatigue, fever, headache, myalgias	No dosage adjustment necessary for renal or hepatic dysfunction	No specific laboratory monitoring recommended	Immunosuppressants may decrease the therapeutic effects of sipuleucel-T	Administer IV infusion over 1 hour. Observe the patient for 30 minutes after the completion of the infusion Premedicate with acetaminophen and an antihistamine 30 minutes prior to administration

ALT, alanine aminotransferase; CBC, complete blood count; CYP, cytochrome P450; LFT, liver function test; PAP-GM-CSF, prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor.

Cabazitaxel is a taxane with demonstrated activity in docetaxel resistant cell lines and animal models of human cancer.[79] Cabazitaxel has a lower affinity for P-glycoprotein multidrug resistance transporter than docetaxel, which may explain why cabazitaxel is active in the setting of docetaxel resistance. In

patients previously treated with docetaxel and prednisone, treatment with cabazitaxel 25 mg/m^2 every 3 weeks with prednisone 10 mg daily significantly improved progression-free and overall survival as compared to mitoxantrone and prednisone. Neutropenia, febrile neutropenia, neuropathy, and diarrhea are the most significant toxicities. Hypersensitivity reactions may occur and premedication with an antihistamine, a corticosteroid, and an H_2 antagonist is recommended. Cabazitaxel is extensively metabolized in the liver and should be avoided in patients with hepatic dysfunction (see Table 148-7). Mitoxantrone plus prednisone has not demonstrated a survival improvement after failure of docetaxel, but remains a palliative therapeutic option, specifically in men who are not candidates for cabazitaxel or radium-223 therapy.[34]

Immunotherapy Sipuleucel-T is a novel autologous cellular immunotherapy that was FDA-approved in April 2010 for the treatment of asymptomatic or minimally symptomatic metastatic CRPC.[80] Alternative treatment options for this patient population are secondary hormonal therapy, including antiandrogen therapy, withdrawal of antiandrogen therapy, ketoconazole, abiraterone acetate, enzalutamide, steroids, estrogen, or enrollment on a clinical trial, although none of these options has been shown to improve overall survival. No clinical trials have compared sipuleucel-T to secondary hormonal therapies. Patients treated with sipuleucel-T undergo leukapheresis on day 1 to collect peripheral blood mononuclear cells, the cellular fraction that includes immune effector cells. These cells are incubated with a prostatic acid phosphatase (PAP)–granulocyte-macrophage colony-stimulating factor (GM-CSF) fusion protein; PAP is the specific tumor antigen, and GM-CSF is the immune cell activator. The cellular product is then infused IV into the patient on day 3 or 4, providing an autologous infusion of activated cells. Each course of sipuleucel-T consists of three infusions of activated cells, given every 2 weeks. In the pivotal trial, sipuleucel-T prolonged median survival by 4.1 months and reduced the risk of death by 22% (HR 0.78, 95% CI 0.61-0.98, $P = 0.03$).[80] Adverse effects related to sipuleucel-T were generally mild and nearly all patients were able to receive the entire course (ie, 3 infusions). A course of sipuleucel-T costs about $93,000, and some insurers have questioned the value of the therapy.

Nuclear Medicine Radium-223, an alpha emitter, can be administered to target specific bone metastases with alpha particles in patients with metastatic CRPC. Radium-223 administered every 4 weeks improved overall survival by 2.8 months in patients who had received, were not eligible for, or had declined docetaxel therapy. Improvements in skeletal pain, pain-related outcomes, and

quality of life were also significant. Opioid needs were decreased in patients who received radium-223 (36% vs 50%). The most common adverse effects of radium-223 include nausea, diarrhea, vomiting, peripheral edema, and bone marrow suppression.[81] Radium-223 is a category 1 recommendation and may be used in first-, second-, or third-line therapy in patients with metastatic castrate-resistant prostate cancer with symptomatic primary bone metastases. Radium-223 has not been approved for use with concomitant chemotherapy.

EVALUATION OF THERAPEUTIC OUTCOMES

Monitoring of prostate cancer depends on the stage of the cancer.[34] When definitive, curative therapy is attempted, objective parameters to assess tumor response include assessment of the primary tumor size, evaluation of involved lymph nodes, and the response of tumor markers such as PSA to treatment. Following definitive therapy, the PSA level is checked every 6 months for the first 5 years, then annually. Local recurrence in the absence of a rising PSA may occur, so a DRE is also performed. In the metastatic setting, chemotherapy and novel hormonal manipulations have been shown to prolong overall survival. In addition, clinical benefit responses can be documented by evaluating performance status, body weight, quality of life, and analgesic requirements, in addition to the PSA or DRE at 3-month intervals.

Postclass Engaged Learning Activity

Conduct a literature search and identify a primary research article that has been published in the past 12 months regarding the use of a poly-ADP ribose polymerase (PARP) inhibitor in patients with DNA repair defects. Write a brief summary of the study methods, major findings and how this new information might change current practice. This activity is intended to build your literature evaluation skills and the ability to critically appraise research articles.

ABBREVIATIONS

ADT	androgen deprivation therapy
BPH	benign prostatic hyperplasia

CAB	combined androgen blockade
CI	confidence interval
CRPC	castrate-resistant prostate cancer
CYP	cytochrome P450
DES	diethylstilbestrol
DHT	dihydrotestosterone
DRE	digital rectal examination
ERSPC	European Randomized Study of Screening for Prostate Cancer
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GM-CSF	granulocyte-macrophage colony-stimulating factor
GnRH	gonadotropin-releasing hormone
LH	luteinizing hormone
LHRH	luteinizing hormone–releasing hormone
PAP	prostatic acid phosphatase
PCPT	Prostate Cancer Prevention Trial
PLCO	Prostate, Lung, Colon, and Ovarian Screening (study)
PSA	prostate-specific antigen
RANK	receptor activator of nuclear factor k B
REDUCE	Reduction by Dutasteride of Prostate Cancer Events
RR	relative risk
SELECT	Selenium and Vitamin E Cancer Prevention Trial
SRE	skeletal-related event
TNM	tumor, node, metastases
USPSTF	United States Preventative Services Task Force
VACURG	Veterans Administration Cooperative Urologic Research Group

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69:7–34.
2. Hsieh K, Albertsen PC. Populations at high risk for prostate cancer. *Urol Clin North Am*. 2003;30:669–676.
3. Sun JH, Lee SA. Association between CAG repeat polymorphisms and the

risk of prostate cancer: A meta-analysis by race, study design and the number of (CAG)n repeat polymorphisms. *Int J Mol Med*. 2013;32:1195–1203.

4. Abida W1, Armenia J2, Gopalan A. Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making. *JCO Precis Oncol*. 2017;2017. doi:10.1200/PO.17.00029.
5. Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with prostate cancer. *New Engl J Med*. 2016;375:443–453.
6. Maia S, Cardoso M, Paulo P, et al. The role of germline mutations in the BRCA1/2 and mismatch repair genes in men ascertained for early-onset and/or familial prostate cancer. *Fam Cancer*. 2015;15(1):111–121.
7. Schwingshackl L, Hoffmann G. Adherence to Mediterranean diet and risk of cancer: A systematic review and meta-analysis of observational studies. *Int J Cancer* 2014;135:1884–1897.
8. Mandair D, Rossi RE, Pericleous M, Whyand T, Caplin ME. Prostate cancer and the influence of dietary factors and supplements: A systematic review. *Nutr Metab (Lond)* 2014;11:30.
9. Wilt TJ, Macdonald R, Hagerty K, et al. 5-alpha-Reductase inhibitors for prostate cancer chemoprevention: An updated Cochrane systematic review. *BJU Int*. 2010;106:1444–1451.
10. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003;349:215–224.
11. Andriole GL, Bostwick DG, Brawley OW, et al. Effect of dutasteride on the risk of prostate cancer. *N Engl J Med* 2010;362:1192–1202.
12. Lacy JM, Kyprianou N. A tale of two trials: The impact of 5α-reductase inhibition on prostate cancer. *Oncol Lett* 2014;8:1391–1396.
13. Redman MW, Tangen CM, Goodman PJ, Lucia MS, Coltman CA Jr, Thompson IM. Finasteride does not increase the risk of high-grade prostate cancer: A bias-adjusted modeling approach. *Cancer Prev Res (Phila)* 2008;1:174–181.
14. Thompson IMJr, Goodman PJ, Tangen CM, et al. Long-term survival of participants in the prostate cancer prevention trial. *N Engl J Med*. 15, 2013;10(7):369–603.
15. Goodman PJ, Tangen CM, Darke AK, et al. Long-term effects of

finasteride on prostate cancer mortality. *N Engl J Med*. 24, 2019;380(4):393–394.

16. Kramer BS, Hagerty KL, Justman S, et al. Use of 5 alpha-reductase inhibitors for prostate cancer chemoprevention: American Society of Clinical Oncology/American Urological Association 2008 Clinical Practice Guideline. *J Urol* 2009;181:1642–1657.
17. Klein EA, Thompson IM Jr, Tangen CM, et al. Vitamin E and the risk of prostate cancer: The Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA*. 2011;306:1549–1556.
18. Thompson IM, Tangen CM, Goodman PJ, Lucia MS, Klein EA. Chemoprevention of prostate cancer. *J Urol* 2009;182:499–507.
19. Cuzick J, Thorat MA, Andriole G, et al. Prevention and early detection of prostate cancer. *Lancet Oncol* 2014;15:e484–e492.
20. Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA Guideline. *J Urol* 2013;190(2):419–426.
21. Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. *N Engl J Med* 2004;350:2239–2246.
22. Shteynshlyuger A, Andriole GL. Prostate cancer: To screen or not to screen? *Urol Clin North Am*. 2010;37:1–9.
23. Wolf AM, Wender RC, Etzioni RB, et al. American Cancer Society guideline for the early detection of prostate cancer: Update 2010. *CA Cancer J Clin*. 2010;60:70–98.
24. Sammon JD, Abdollah F, Choueiri TK, et al. Prostate-specific antigen screening after 2012 US Preventive Services Task Force recommendations. *JAMA*. 17;314:2077–2079.
25. Schroder FH, Hugosson J, Roobol MJ, et al. Prostate-cancer mortality at 11 years of follow-up. *N Engl J Med* 2012;366:981–990.
26. Andriole GL, Crawford ED, Grubb RL 3rd, et al. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: Mortality results after 13 years of follow-up. *J Natl Cancer Inst*. 2012;104:125–132.
27. Fenton JJ, Weyrich MS, Durbin S, Liu Y, Bang H, Melnikow J, et al. Prostate-specific antigen-based screening for prostate cancer: Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*. 8, 2018;319(18):1914–1931. doi:10.1001/jama.2018.3712.

28. Khauli RB. Prostate cancer: Diagnostic and therapeutic strategies with emphasis on the role of PSA. *J Med Liban*. 2005;53:95–102.
29. Iczkowski KA. Current prostate biopsy interpretation: Criteria for cancer, atypical small acinar proliferation, high-grade prostatic intraepithelial neoplasia, and use of immunostains. *Arch Pathol Lab Med*. 2006;130:835–843.
30. De Marzo AM, Meeker AK, Zha S, et al. Human prostate cancer precursors and pathobiology. *Urology* 2003;62(5 Suppl 1):55–62.
31. Culig Z. Role of the androgen receptor axis in prostate cancer. *Urology* 2003;62(5 Suppl 1):21–26.
32. Marks LS. Luteinizing hormone-releasing hormone agonists in the treatment of men with prostate cancer: Timing, alternatives, and the 1-year implant. *Urology*. 2003;62(6 Suppl 1):36–42.
33. Sharifi N, Gulley JL, Dahut WL. Androgen deprivation therapy for prostate cancer. *JAMA* 2005;294:238–244.
34. National Comprehensive Cancer Network. National Comprehensive Cancer Network guidelines for the management of prostate cancer. v4.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.
35. Scher HI. Prostate carcinoma: Defining therapeutic objectives and improving overall outcomes. *Cancer*. 2003;97(3 Suppl):758–771.
36. Ganz PA, Barry JM, Burke W, et al. National Institutes of Health State-of-the-Science Conference: Role of active surveillance in the management of men with localized prostate cancer. *Ann Intern Med* 2012;156:591–595.
37. Wilt TJ, MacDonald R, Rutks I, Shamliyan TA, Taylor BC, Kane RL. Systematic review: Comparative effectiveness and harms of treatments for clinically localized prostate cancer. *Ann Intern Med*. 2008;148:435–448.
38. Dalkin BL, Christopher BA. Potent men undergoing radical prostatectomy: A prospective study measuring sexual health outcomes and the impact of erectile dysfunction treatments. *Urol Oncol*. 2008;26(3):281–285.
39. Immediate versus deferred treatment for advanced prostatic cancer: Initial results of the Medical Research Council Trial. The Medical Research Council Prostate Cancer Working Party Investigators Group. *Br J Urol* 1997;79:235–246.
40. Novara G, Galfano A, Secco S, Ficarra V, Artibani W. Impact of surgical and medical castration on serum testosterone level in prostate cancer

patients. *Urol Int* 2009;82:249–255.

41. Seidenfeld J, Samson DJ, Aronson N, et al. Relative effectiveness and cost-effectiveness of methods of androgen suppression in the treatment of advanced prostate cancer. *Evid Rep Technol Assess (Summ)* 1999(4):i–x, 1246, I241236,passim.
42. Hedlund PO, Henriksson P. Parenteral estrogen versus total androgen ablation in the treatment of advanced prostate carcinoma: Effects on overall survival and cardiovascular mortality. The Scandinavian Prostatic Cancer Group (SPCG)-5 Trial Study. *Urology*. 2000;55:328–333.
43. Seidenfeld J, Samson DJ, Hasselblad V, et al. Single-therapy androgen suppression in men with advanced prostate cancer: A systematic review and meta-analysis. *Ann Intern Med* 2000;132:566–577.
44. Smith MR, Finkelstein JS, McGovern FJ, et al. Changes in body composition during androgen deprivation therapy for prostate cancer. *J Clin Endocrinol Metab* 2002;87:599–603.
45. Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med* 2005;352:154–164.
46. Smith MR, Boyce SP, Moyneur E, Duh MS, Raut MK, Brandman J. Risk of clinical fractures after gonadotropin-releasing hormone agonist therapy for prostate cancer. *J Urol* 2006;175:136–139.
47. Smith MR, Lee WC, Brandman J, Wang Q, Botteman M, Pashos CL. Gonadotropin-releasing hormone agonists and fracture risk: A claims-based cohort study of men with nonmetastatic prostate cancer. *J Clin Oncol*. 2005;23:7897–7903.
48. Lipton A, Fizazi K, Stopeck AT, et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: A combined analysis of 3 pivotal, randomised, phase 3 trials. *Eur J Cancer* 2012;48:3082–3092.
49. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol* 2006;24:4448–4456.
50. Nguyen PL, Je Y, Schutz FA, et al. Association of androgen deprivation therapy with cardiovascular death in patients with prostate cancer: A meta-analysis of randomized trials. *JAMA* 2011;306:2359–2366.
51. Klotz L, Boccon-Gibod L, Shore ND, et al. The efficacy and safety of degarelix: A 12-month, comparative, randomized, open-label, parallel-

group phase III study in patients with prostate cancer. *BJU In*. 2008;102:1531–1538.
52. Flutamide [package insert]. Kenilworth, NJ: Schering Corporation, 2000.
53. Bicalutamide [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP, 2000.
54. Nilutamide [package insert]. Bridgewater, NJ: Sanofi-Aventis, 2006.
55. Enzalutamide [package insert]. Northbrook, IL: Astellas Pharma, 2015.
56. Abiraterone [package insert]. Horsham, PA: Janssen Biotech, 2015.
57. Leuprolide [package insert]. Irvine, CA: SICOR Pharmaceuticals, 2005.
58. Goserelin [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP, 2012.
59. Triptorelin [package insert]. Kalamazoo, MI: Pharmacia & Upjohn Company, 2001.
60. Degarelix [package insert]. Parsippany, NJ: Ferring Pharmaceuticals, 2012.
61. Docetaxel [package insert]. Bridgewater, NJ: Sanofi-Aventis, 2011.
62. Cabazitaxel [package insert]. Bridgewater, NJ: Sanofi-Aventis, 2012.
63. Sipuleucel-T [package insert]. Seattle, WA: Dendreon Corporation, 2011.
64. Akaza H. Combined androgen blockade for prostate cancer: Review of efficacy, safety and cost-effectiveness. *Cancer Sci* 2011;102:51–56.
65. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012;367:1187–1197.
66. Beer TM, Armstrong AJ, Rahkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371:424–433.
67. Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. 2018;378(15):1408–1418.
68. Erleada [package insert}]. Horsham, PA: Janssen Pharmaceuticals; 2018.
69. Lukka H, Waldron T, Klotz L, Winquist E, Trachtenberg J. Maximal androgen blockade for the treatment of metastatic prostate cancer: A systematic review. *Curr Oncol*. 2006;13:81–93.
70. The Veterans Administration Cooperative Urological Research Group. Carcinoma of the prostate: Treatment comparisons. *J Urol*. 1967;98:516–522.
71. Ryan CJ, Small EJ. Early versus delayed androgen deprivation for prostate cancer: New fuel for an old debate. *J Clin Oncol* 2005;23:8225–8231.

72. Scher HI, Kelly WK. Flutamide withdrawal syndrome: Its impact on clinical trials in hormone-refractory prostate cancer. *J Clin Oncol* 1993;11:1566–1572.
73. Small EJ, Srinivas S. The antiandrogen withdrawal syndrome. Experience in a large cohort of unselected patients with advanced prostate cancer. *Cancer* 1995;76:1428–1434.
74. Huan SD, Gerridzen RG, Yau JC, Stewart DJ. Antiandrogen withdrawal syndrome with nilutamide. *Urology* 1997;49:632–634.
75. Sartor O, Cooper M, Weinberger M, et al. Surprising activity of flutamide withdrawal, when combined with aminoglutethimide, in treatment of "hormone-refractory" prostate cancer. *J Natl Cancer Inst* 1994;86:222–227.
76. Scher HI, Liebertz C, Kelly WK, et al. Bicalutamide for advanced prostate cancer: The natural versus treated history of disease. *J Clin Oncol*. 1997;15:2928–2938.
77. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011;364:1995–2005.
78. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004;351:1502–1512.
79. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: A randomised open-label trial. *Lancet*. 2010;376:1147–1154.
80. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010;363:411–422.
81. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med* 2013;369:213–223.
82. AM Moilanen, R Riikonen, R Oksala, et al. Discovery of ODM-201, a new-generation androgen receptor inhibitor targeting resistance mechanisms to androgen signaling-directed prostate cancer therapies. *Sci Rep*. 2015;5:12007.
83. K Fizazi, N Shore, TL Tammela, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*. 2019;380(13):1235–1246.
84. Nubeqa (darolutamide) [package insert]. Whippany, NJ: Bayer Healthcare Pharmaceuticals; 2019.

149

Lymphomas

Alexandre Chan, Chia Jie Tan, and Jolynn Sessions

KEY CONCEPTS

1. With all stages and risk groups of Hodgkin lymphoma, restaging PET-CT following 8 to 12 weeks of chemotherapy will further guide the patient-specific treatment plan.
2. Patients with early stage Hodgkin lymphoma should be treated with combination chemotherapy with or without involved-site radiation.
3. Combination chemotherapy with doxorubicin (Adriamycin®), Bleomycin, Vinblastine, and Dacarbazine (ABVD) is the primary treatment for patients with advanced stage Hodgkin lymphoma. Patients with advanced unfavorable disease may be treated with more aggressive regimens, which are associated with a higher risk of secondary malignancies.
4. Some patients with Hodgkin lymphoma will be refractory to initial therapy or will have a recurrence following a complete remission. Response to salvage therapy depends on the extent and site of recurrence, previous therapy, and duration of initial remission. High-dose chemotherapy and autologous hematopoietic stem cell transplantation (HSCT) should be considered in patients with refractory or relapsed disease.
5. The current classification system for non-Hodgkin lymphoma (NHL) is the World Health Organization (WHO) classification system, which is based on the principle that NHLs can be classified into specific disease entities, defined by a combination of morphology, immunophenotype, genetic features, and clinical features.
6. As compared with Hodgkin lymphoma, the clinical presentation of NHL is more variable because of disease heterogeneity and more frequent extranodal involvement.
7. The Ann Arbor staging system correlates poorly with prognosis in NHL

because the disease does not spread through contiguous lymph nodes and often involves extranodal sites.

8. Several prognostic models have been developed to estimate prognosis in patients with NHL. The International Prognostic Index (IPI) score is a well-established model for patients with aggressive NHL. The Follicular Lymphoma International Prognostic Index (FLIPI) is a similar model used for patients with follicular and other indolent lymphomas.

9. The clinical behavior and degree of aggressiveness can be used to categorize NHL into indolent and aggressive lymphomas. Patients with an indolent lymphoma usually have a relatively long survival, with or without aggressive chemotherapy. Although these lymphomas respond to a wide range of therapeutic approaches, few if any of these patients are cured of their disease. In contrast, aggressive lymphomas are rapidly growing tumors and patients have a short survival if appropriate therapy is not initiated. Most patients with aggressive lymphomas respond to intensive chemotherapy and many are cured of their disease.

10. Patients with localized follicular lymphoma can be cured with radiation therapy alone. Advanced follicular lymphoma is not curable, and many treatment options are available, including watchful waiting, extended-field radiation therapy, single-agent alkylating agents, anthracycline-containing combination chemotherapy, anti-CD20 monoclonal antibodies, fludarabine, lenalidomide, PI3K inhibitors, and high-dose chemotherapy with HSCT.

11. Patients with localized aggressive lymphomas can be cured with several cycles of R-CHOP (rituximab, Cyclophosphamide, doxorubicin [Hydroxydaunorubicin], vincristine [Oncovin®], Prednisone) chemotherapy and involved-field irradiation. Patients with bulky stage II, stage III, or stage IV aggressive lymphomas can be cured of their disease with R-CHOP chemotherapy.

12. Conventional-dose salvage therapy can induce responses in patients with aggressive lymphomas who relapse, but long-term survival and cure are uncommon. Some patients with aggressive lymphoma who relapse and respond to salvage therapy can be cured with high-dose chemotherapy and autologous HSCT.

Preclass Engaged Learning Activity

Read the patient information sheets from the American Society of Clinical Oncology at Cancer. Net on the diagnosis of Hodgkin and non-Hodgkin lymphoma (https://tinyurl.com/y2rr48nq and https://tinyurl.com/wm8emum). These information sheets briefly describe the various procedures used to diagnose lymphoma and will help students to understand how lymphoma is diagnosed.

INTRODUCTION

Lymphomas are a heterogeneous group of malignancies that arise from malignant transformation of immune cells that reside predominantly in lymphoid tissues. They most commonly present as a solid tumor, but can sometimes present as circulating tumor cells in peripheral blood. The differing histology of lymphoma cells has led to classification of Hodgkin lymphoma (Reed–Sternberg cells) or non-Hodgkin lymphoma (NHL) (B- or T-cell lymphocyte markers). NHLs are further classified into distinct clinical entities, which are defined by a combination of morphology, immunophenotype, genetic features, and clinical features. Chemotherapy is the mainstay of treatment in patients with lymphoma, especially those with widespread disease. Overall cure rates are high for many subtypes of lymphomas, even when patients present with advanced disease.

HODGKIN LYMPHOMA

Hodgkin lymphoma is one of the most curable forms of cancer. Although initial reports of Hodgkin lymphoma demonstrated the disease to be uniformly fatal, an impressive 80% of patients can be cured today with recommended treatments.[1] Some of the keys to the success of the treatments for Hodgkin lymphoma include the appropriate use of multidrug chemotherapy regimens with differing mechanisms of action and toxicities, and treatment with full doses of chemotherapy and on schedule whenever possible. It is also common to use radiation therapy in the treatment schema. However, the success of treatment has not been without cost. The treatment programs are intense, technically demanding, and associated with considerable acute toxicity and long-term complications. The long-term effects, particularly secondary malignancies, account for a higher cumulative mortality than Hodgkin lymphoma 15 to 20 years after treatment. Long-term toxicities with standard chemotherapy regimens have been more fully documented in recent years and are shaping future

therapies.[2–4]

Hodgkin lymphoma is named after Thomas Hodgkin, who first described seven cases of a mysterious disease of the lymph system in 1832. Although Hodgkin lymphoma was not the first cancer to be described, it was one of the first cancers to have methodical investigational treatments that ultimately lead to successful outcomes.[4]

Since many factors influence prognosis of patients with Hodgkin lymphoma, treatment plans must be personalized for each patient. The staging for Hodgkin lymphoma uses the Ann Arbor Staging Classification where the "A" refers to the absence of B symptoms, and "B" refers to the presence of B symptoms. Beyond the stage of the disease, certain factors have been associated with a poor prognosis (unfavorable risk). Several research groups have defined these unfavorable factors, and the International Prognostic Score (IPS) is used clinically to predict an individual's risk of recurrence.

Epidemiology and Etiology

Hodgkin lymphoma represents less than 1% of all known cancers in the United States. It is estimated that 8,110 new cases of Hodgkin lymphoma were diagnosed in the United States in 2019, and 1,000 deaths associated with Hodgkin lymphoma will occur during this same period.[5] Hodgkin lymphoma occurs slightly more frequently in males than in females. It exhibits bimodal distribution in industrialized countries; the first peak occurs in young adults and the second smaller peak occurs after age 50.[2,4] The 5-year overall survival for all stages of Hodgkin lymphoma is about 85%.[1] Death as a consequence of recurrent Hodgkin lymphoma is less than those from all other causes 15 years after treatment.

The etiology of Hodgkin lymphoma is currently unknown, but laboratory and epidemiologic evidence support infectious exposure as a potential cause.[2,4] Studies suggest an increased risk of Hodgkin lymphoma in patients who have been infected with the Epstein-Barr virus (EBV) and many patients experience EBV activation even before the onset of Hodgkin lymphoma. EBV is found in about 40% of all classical Hodgkin lymphoma cases, and it is frequently observed in cases of mixed cellularity and lymphocyte-depleted Hodgkin lymphoma. Reed–Sternberg cells (large, bilobate, multinuclear cells looking like "owl eyes"), the malignant cells in Hodgkin lymphoma, are linked to EBV. Individuals who are immunosuppressed, such as patients with congenital immunosuppression, solid-organ transplant recipients, and human

immunodeficiency virus (HIV)-infection, are also at much higher risk to develop Hodgkin lymphoma. Although the risk of developing Hodgkin lymphoma is up to 25-fold greater in patients with HIV, the CD4 level may be very low or within the normal range at diagnosis. Almost all cases of Hodgkin lymphoma in HIV-infected individuals are EBV positive and are most commonly the lymphocyte-deplete subtype of Hodgkin lymphoma. Hodgkin lymphoma is not an AIDS-defining illness.

Genetic factors are also associated with an increased risk of Hodgkin lymphoma. The strongest evidence comes from identical twin studies, which show that the unaffected identical twin has almost a 100-fold increase in risk.

Pathophysiology

Hodgkin lymphoma is a clonal malignant lymphoid disease of transformed B-lymphocytes. The malignant cell in Hodgkin lymphoma is known as the Reed–Sternberg cell named after Dorothy Reed and Carl Sternberg, who were credited with the first definitive microscopic description of Hodgkin lymphoma.[2] Single-cell polymerase chain reaction and DNA microarray analyses indicate that nearly all classic Hodgkin lymphoma cases and all nodular lymphocyte-predominant Hodgkin lymphomas (NLPHLs) have immunoglobulin gene rearrangements, which indicates a germinal center or postgerminal center of B-cell origin. Interestingly, nearly all Reed–Sternberg cells of classical Hodgkin lymphoma fail to express B-cell specific cell surface proteins.

B-cell transcriptional processes are disrupted during malignant transformation, which prevents B-cell surface marker expression and production of immunoglobulin messenger ribonucleic acid. The normal cellular consequence of failure to express immunoglobulin is apoptosis, but because of alterations in the normal apoptotic pathways, cell survival and proliferation are favored. Reed–Sternberg cells overexpress nuclear factor-κB, which is associated with cell proliferation and antiapoptotic signals. Infections with viral and bacterial pathogens upregulate nuclear factor-κB and consequently are hypothesized to be involved with the etiology of Hodgkin lymphoma.[2] This hypothesis is supported by the presence of EBV in many Hodgkin lymphoma tumors, but it is important to note that not all tumors are associated with EBV. Another signaling pathway, Janus kinase–signal transduction and transcription (JAK–STAT), has also been found to be active in Hodgkin lymphoma.[2] As molecular techniques continue to improve, our understanding of the pathophysiology of Hodgkin lymphoma will also improve.

The histopathologic classification of Hodgkin lymphoma has undergone numerous changes over the past three decades. The current classification system is the 2016 World Health Organization (WHO) classification (**Table 149-1**).[6] This classification divides Hodgkin lymphoma into two major groups: classical Hodgkin lymphoma and NLPHL, which constitute about 95% and 5% of cases, respectively. Classic Hodgkin lymphoma is further divided into four subtypes: nodular sclerosis, mixed cellularity, lymphocyte-depleted, and lymphocyte-rich. The subtypes in these classifications are based on characteristics of the Reed–Sternberg cell, the surrounding cells, and the tissue. Nodular sclerosis has features that make it distinct from the other three subtypes, which represent a continuum of background cellularity, with lymphocyte-predominance being the most cellular and lymphocyte-depletion being the least cellular. Typical immunophenotype for classical Hodgkin lymphoma includes $CD15^+$, $CD30^+$, PAX-5^+ (weak), $CD3^-$, $CD20^-$, $CD45^-$, $CD79a^-$. NLPHL is separated because of its distinct immunophenotype: $CD15^-$, $CD20^+$, $CD30^-$, and $CD45^+$ (the opposite of classical Hodgkin lymphoma). With the introduction of extensive staging, sophisticated radiotherapy, and effective combination chemotherapy, the prognostic value of these subtypes is becoming less clear. The true value of understanding these subtypes is likely tied to the pathogenesis of the disease and its potential prevention in the future.

TABLE 149-1 WHO Classification of the Mature B-Cell, T-Cell, and NK-Cell Neoplasms (2016)

B Cell	NK cells	Hodgkin Lymphoma
B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma	T-cell prolymphocytic leukemia	Nodular lymphocyte-predominant Hodgkin lymphoma
B-cell prolymphocytic leukemia	T-cell granular lymphocytic leukemia	Classical Hodgkin lymphoma
Lymphoplasmacytic lymphoma	Aggressive NK-cell leukemia	Nodular sclerosis classical Hodgkin lymphoma
Splenic marginal zone B-cell lymphoma (± villous lymphocytes)	Adult T-cell leukemia/lymphoma (HTLV-I+)	Lymphocyte-rich classical Hodgkin lymphoma
Hairy cell leukemia	Extranodal NK/T-cell lymphoma, nasal type	Mixed cellularity classical Hodgkin lymphoma
Plasma cell myeloma/plasmacytoma	Enteropathy-associated T-cell lymphoma	Lymphocyte-depleted classical Hodgkin lymphoma
Extranodal marginal zone B-cell lymphoma of MALT type	Hepatosplenic γδ T-cell lymphoma	
Mantle cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma	
Follicular lymphoma	**Mycosis fungoides/Sézary syndrome**	
Nodal marginal zone B-cell lymphoma (± monocytoid B cells)	Anaplastic large cell lymphoma, primary cutaneous type	
Diffuse large B-cell lymphoma (DLBCL)	**Peripheral T-cell lymphoma, not otherwise specified (NOS)**	
Germinal center B-cell type	**Angioimmunoblastic T-cell lymphoma**	
Activated B-cell type	**Anaplastic large cell lymphoma, primary systemic type**	
Burkitt lymphoma		

HTLV, human T-cell lymphotropic virus; MALT, mucosa-associated lymphoid tissue; NK, natural killer; WHO, World Health Organization.

Note: Not all subtypes are listed. **Malignancies in bold occur in at least 1% of patients.**

Adapted from SH Swerdlow et al: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th ed. World Health Organization, 2008.

Clinical Presentation

Most patients with Hodgkin lymphoma present with a painless, rubbery, enlarged lymph node in the supradiaphragmatic area and commonly have mediastinal nodal involvement. Lymphadenopathy may come and go, but persistence of lymphadenopathy more than 2 months warrants evaluation. Hodgkin lymphoma is occasionally diagnosed in an asymptomatic patient who has a mediastinal mass found with chest radiography or another imaging procedure. Asymptomatic adenopathy of the inguinal and axillary regions may be present at diagnosis but is less common (**Fig. 149-1**).[2,4] Patients can also present with constitutional symptoms (B symptoms) before the discovery of lymph node enlargement, and these symptoms include fever greater than 38°C (100.4°F), drenching night sweats, and weight loss greater than 10% within 6 months of diagnosis. At diagnosis, these symptoms may appear in about 25% of all patients and up to 50% of patients with advanced disease. Patients may also experience other nonspecific symptoms including pruritus, fatigue, and development of pain after alcohol consumption at sites where nodes are involved.[4] Extranodal manifestations, such as bowel or hepatic involvements,

are much less common in Hodgkin lymphoma than NHL.[2]

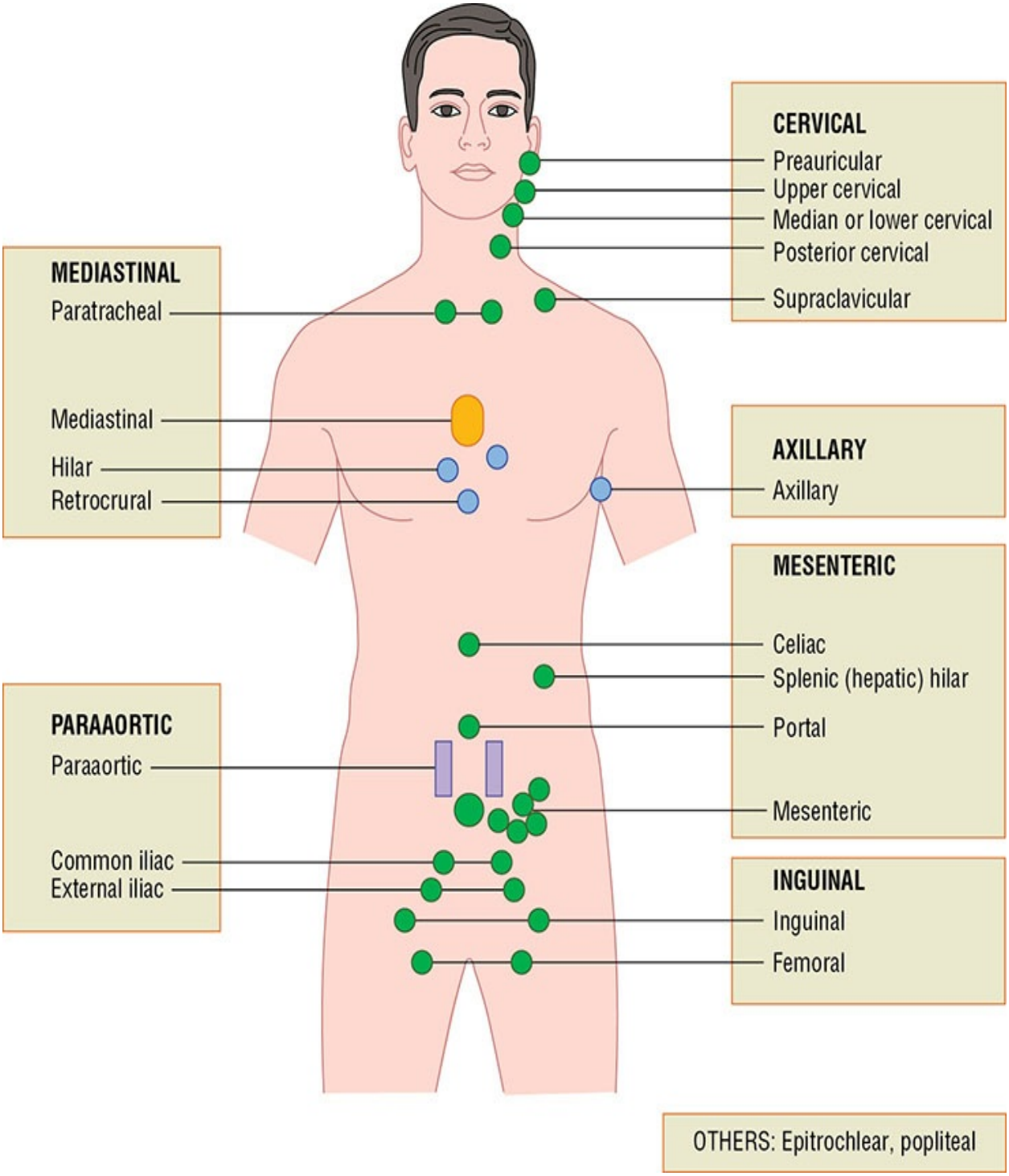


FIGURE 149-1 Areas of lymph nodes used in the staging of Hodgkin and non-Hodgkin lymphoma. Each rectangle corresponds to a nodal area.

Diagnosis, Staging, and Prognostic Factors

Diagnostic and staging procedures are based on recommendations made at the Ann Arbor and Cotswolds conferences and new scientific advances. The diagnosis and pathologic classification of Hodgkin lymphoma can only be made by review of a biopsy (preferably an excisional biopsy) of the enlarged node by an expert hematopathologist.

In addition to a careful physical examination, routine laboratory tests including a complete blood count, complete metabolic panel to assess renal and hepatic function, lactate dehydrogenase (LDH), and erythrocyte sedimentation rate (ESR) will be helpful in treatment planning and aid in prognosis. Pregnancy test and HIV status should be assessed. Computed tomography (CT) scans of the chest, abdomen, and pelvis are routinely performed. Furthermore, positron emission tomography (PET) plays an important role in the initial staging of Hodgkin lymphoma, as it has shown high sensitivity and specificity in the staging of the disease response to treatment.[7] The use of integrated PET-CT has further improved the staging of Hodgkin lymphoma given that it can provide more sensitive and specific imaging as compared with each imaging alone. Bone marrow biopsy is now only recommended in patients with cytopenias and a negative PET.

Staging can be based on clinical or pathologic findings. The clinical stage is based on all noninvasive procedures (history, physical examination, laboratory tests, and radiologic findings), whereas the pathologic stage is based on the biopsy findings of strategic sites (bone marrow, spleen, and abdominal nodes). Patients with extranodal disease (bone marrow, bone, or Waldeyer ring) contiguous to involved nodes are classified with the subscript “E” in the Cotswolds staging system.

CLINICAL PRESENTATION Hodgkin Lymphoma

General

- Most patients with Hodgkin lymphoma have lymph node involvement in the supradiaphragmatic and mediastinal areas.

Symptoms

- Fatigue, malaise, and pruritus.
- About 25% of all patients present with fever, night sweats, and weight loss (ie, B symptoms), and up to 50% of patients with advanced disease.

Signs

- Enlarged lymph node, which may present as painless and rubbery.

The Ann Arbor staging classification, which was developed at the 1970 Ann Arbor conference, has proven to be a good schema. At the Cotswolds meeting in 1989, the Ann Arbor classification was modified to incorporate new diagnostic techniques (eg, CT and magnetic resonance imaging), and the understanding that prognosis is associated with the bulk of the disease and the number of involved nodal sites (Table 149-2).[4] After careful staging, about one-half of patients have localized disease (stages I, II, and II_E) and the remainder have advanced disease (stage III or IV). About 10% to 15% present with metastatic disease (stage IV). It is important to note that Hodgkin lymphoma appears to follow a predictable pattern of nodal spread that is not seen with the NHLs.[4,8]

TABLE 149-2 The Ann Arbor Staging Classification of Hodgkin Lymphoma

Stage I	Involvement of a single lymph node region or structure (I) or of a single extralymphatic organ or site (I_E)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (II_E). The number of nodal regions involved should be indicated by a subscript (eg, II_2)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of an extralymphatic organ or site (III_E) or by involvement of the spleen (IIIS) or both ($IIIS_E$). III_1: with or without splenic, hilar, celiac, or portal node involvement. III_2: with paraaortic, iliac, or mesenteric node involvement
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement A—No symptoms B—Fever, night sweats, weight loss (>10%) X—Bulky disease >One-third of the width of the mediastinum >10-cm maximal dimension of nodal mass E—Involvement of extralymphatic tissue on one side of the diaphragm by limited direct extension from an adjacent, involved lymph node region S—Involvement of the spleen CS—Clinical stage PS—Pathologic stage

Patient prognosis is predominately driven by age and amount of disease. Patients older than ages 65 to 70 have a lower cure rate than younger patients. The difference in cure rates may be related to the higher prevalence of comorbid diseases and decreased organ function in older patients, which impairs their ability to tolerate intensive chemotherapy. Stage is a dominant factor in predicting survival; patients with limited-stage disease (stages I-II) have a 90% to 95% cure rate, while those with advanced disease (stages III-IV) have only a 60% to 80% cure rate.[2,4]

Seven adverse prognostic factors with similar impact on survival (each factor reduced survival by 7%-8% per year) have been identified through an international collaborative effort. These factors can be combined to generate an IPS that can be used to predict progression-free and overall survival (**Table 149-**

3).[9]

TABLE 149-3 The International Prognostic Factors Project Score for Advanced Hodgkin Lymphoma

Risk Factors		
Serum albumin (<4 g/dL [40 g/L])		
Hemoglobin (<10.5 g/dL [105 g/L; 6.52 mmol/L])		
Male gender		
Stage IV disease		
Age (≥45 years)		
White blood cell (WBC) count (≥15,000 cells/mm³ [15 × 10⁹/L])		
Lymphocytopenia (<600 cells/mm³ [0.6 × 10⁹/L] or <8% of WBC count)		
Number of Factors	**Freedom from Progression***	**Overall Survival***
0	84 ± 4	89 ± 2
1	77 ± 3	90 ± 2
2	67 ± 2	81 ± 2
3	60 ± 3	78 ± 3
4	51 ± 4	61 ± 4
≥5	42 ± 5	56 ± 5

*Percentage of patients at 5 years.

Data from Reference 10.

TREATMENT

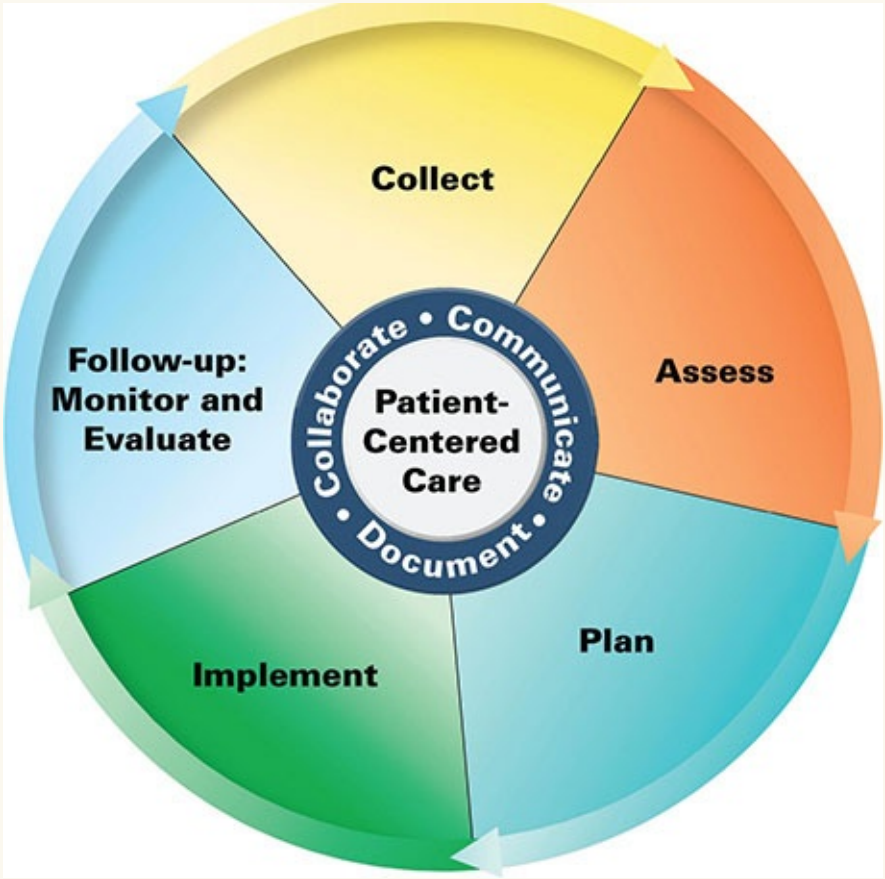
Hodgkin Lymphoma

Desired Outcomes

The current goal in the treatment of Hodgkin lymphoma is to maximize curability while minimizing short- and long-term treatment-related complications. According to the Surveillance, Epidemiology, and End Results (SEER) database, the 5-year age-adjusted relative survival is greater than 80%.[1] Therefore, the initial treatment goal for all stages of Hodgkin lymphoma is cure.

General Approach

Combination chemotherapy is the primary treatment modality for most patients with Hodgkin lymphoma. In general, patients of all stages are initially treated with combination chemotherapy for about 8 to 12 weeks (depending on the regimen) and then restaged with PET-CT. Three combination chemotherapy regimens are primarily used for the initial treatment of classical Hodgkin lymphoma: ABVD, Stanford V, and some version of BEACOPP (bleomycin, etoposide, doxorubicin (Adriamycin®), cyclophosphamide, vincristine (Oncovin®), procarbazine, and prednisone). Depending on the initial radiographic response from the restaging, further chemotherapy with or without radiation is planned. For patients with refractory or recurrent disease, salvage therapy consists of multi-agent chemotherapy with or without high-dose chemotherapy and autologous hematopoietic stem cell transplantation (HSCT).[2,4]



Patient Care Process

Collect

- Patient characteristics (eg, age, sex, pregnant, smoking history)
- Patient medical history (personal and family)
- Current medications including OTC aspirin/NSAID use, herbal products, dietary supplements
- Objective data
  - Height and weight to calculate body surface area (BSA)
  - Labs including complete blood count (CBC), complete metabolic panel which includes liver function tests, LDH, pregnancy test for women with reproductive potential
  - Baseline assessment of cardiac ejection fraction by ECHO or MUGA if treatment with anthracycline is planned
  - Baseline assessment of pulmonary function (pulmonary function test including diffusing capacity of lungs for carbon monoxide—DLCO) if treatment with bleomycin is planned
  - Lymphoma-specific immunophenotyping, cytogenetics (such as CD20, CD30, t(11:14), t(14;18))
  - Stage and prognostic score (eg, IPS, IPI, FLIPI)

Assess

- Comorbid illnesses that may affect drug therapy selection (baseline neuropathy, CHF, renal or hepatic dysfunction)
- Potential for drug–drug interactions (particularly with oral agents such as idelalisib or ibrutinib)
- Patient's risk of tumor lysis syndrome based on disease, planned therapy, tumor burden, and renal function
- Ability to self-care, family/social support
- Financial challenges—copays, coinsurance, specialty pharmacy medication access
- Birth control and fertility options if the patient is child bearing age (male

and female)
- Emotional status (eg, anxiety, depression)
- Need for central venous access
- Access and availability of eligible clinical trials

Plan*

- Logistics of treatment plan (inpatient, outpatient, daily oral medication) and monitoring plan
- Patient education (eg., goals and purpose of treatment, treatment schedule, duration/number of treatment cycles, drug-specific information, medication administration)
- Self-monitoring for toxicities, when to seek emergency medical attention
- Referrals to other providers when appropriate (eg, dietician, navigator, behavioral health, integrative health, palliative/supportive care)

Implement*

- Provide patient education regarding all elements of treatment plan
- Obtain consent for planned treatment
- Use motivational interviewing and coaching strategies to maximize adherence
- Write, order, or review therapy orders to ensure appropriate dosing, supportive-care therapies (eg, nausea/vomiting, infection prevention, prevention of hypersensitivity reactions)
- Schedule follow-up (eg, oral therapy medication therapy management, adherence assessment, symptom management)
- Connect patient to resources such as support groups, educational websites, community resources, social worker

Follow-up: Monitor and Evaluate

- Survivorship teaching and follow-up with focus on monitoring for long-term toxicities
- Patient adherence to treatment plan using multiple sources of information

- Imaging studies to be ordered for appropriate follow-up
- Necessary vaccines following stem-cell transplant

Collaborate with patient, caregivers, and other healthcare professionals.

Radiation is often an integral part of the treatment plan. Selected patients with early stage disease (usually nodular lymphocyte-predominant histology) can receive radiation as the only treatment modality, whereas most other patients with early stage disease may receive chemotherapy and radiation depending on the initial bulk of disease and the response to chemotherapy alone. Although radiation is a local therapy, many patients with advanced disease will also receive radiation therapy to residual or bulky disease sites after chemotherapy. Many different radiation techniques targeting different radiation fields have been used over the last few decades, including involved-field radiation (IFRT), extended-field radiation, subtotal nodal irradiation, and total nodal irradiation. The major concern with radiation therapy is its long-term effects, particularly on organs at risk, such as cardiovascular disease and secondary malignancies that commonly occur in the lung, breast, gastrointestinal tract and connective tissue.[11] Involved-site radiation therapy (ISRT) and involved-node radiation therapy are now being used as alternatives to the classic IFRT, and both define a smaller field than IFRT. ISRT targets the nodal sites and extranodal extensions that were involved at diagnosis but spares adjacent uninvolved organs when lymphadenopathy regresses after chemotherapy and ISRT. Additional techniques help to refine the volume of radiation delivered to the intended sites such as 4D-CT simulation planning, intensity modulated radiation therapy, image-guided RT, and respiratory gating.[12–14]

Although multiple treatment modalities are used to treat Hodgkin lymphoma, surgery has a limited role regardless of stage. Surgery is important for an accurate diagnosis via excisional biopsy, and on certain other occasions, such as placement of a central line. The following sections will review treatment of early stage favorable disease, early stage unfavorable disease, advanced stage disease, and salvage therapy.

Chemotherapy Regimens

Prior to the 1960s, the outcome for patients with Hodgkin lymphoma was dismal. Treatment with single-agent therapies or broad radiation fields provided excessive toxicities and few durable responses with advanced disease. The

mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) regimen was introduced in the early 1960s and was the initial combination chemotherapy regimen shown to cure advanced Hodgkin lymphoma (**Table 149-4**). This was a tremendous advance in oncology at that time. MOPP chemotherapy was a mainstay of treatment for patients with stages III and IV advanced Hodgkin lymphoma for years to come. However, investigators later learned that MOPP is associated with high rates of sterility and secondary malignancies. The young cohort of Hodgkin survivors would live long enough to endure these consequences. The research focus was then shifted to maintain the high cure rates obtained with MOPP while decrease the long-term toxicities.

TABLE 149-4 Combination Chemotherapy Regimens for Hodgkin Lymphoma

Drug	Dosage (mg/m²)	Route	Days
MOPP			
Mechlorethamine	6	IV	1, 8
Vincristine	1.4	IV	1, 8
Procarbazine	100	Oral	1-14
Prednisone	40	Oral	1-14
Repeat every 21 days			
ABVD			
Doxorubicin (Adriamycin®)	25	IV	1, 15
Bleomycin	10	IV	1, 15
Vinblastine	6	IV	1, 15
Dacarbazine	375	IV	1, 15
Repeat every 28 days			
MOPP/ABVD			
Alternating months of MOPP and ABVD			
MOPP/ABV hybrid			
Mechlorethamine	6	IV	1
Vincristine	1.4	IV	1
Procarbazine	100	Oral	1-7
Prednisone	40	Oral	1-14
Doxorubicin	35	IV	8
Bleomycin	10	IV	8
Vinblastine	6	IV	8
Repeat every 28 days			
Stanford V			
Doxorubicin	25	IV	Weeks 1, 3, 5, 7, 9, 11
Vinblastine	6	IV	Weeks 1, 3, 5, 7, 9, 11
Mechlorethamine	6	IV	Weeks 1, 5, 9
Etoposide	60	IV	Weeks 3, 7, 11
Vincristine	1.4*	IV	Weeks 2, 4, 6, 8, 10, 12
Bleomycin	5	IV	Weeks 2, 4, 6, 8
Prednisone	40	Oral	Every other day for 12 weeks; begin tapering at week 10
One course (12 weeks)			
BEACOPP (standard-dose)			
Bleomycin	10	IV	8
Etoposide	100	IV	1-3
Adriamycin (doxorubicin)	25	IV	1
Cyclophosphamide	650	IV	1
Oncovin® (vincristine)	1.4*	IV	8
Procarbazine	100	Oral	1-7
Prednisone	40	Oral	1-14
Repeat every 21 days			
BEACOPP (escalated-dose)			
Bleomycin	10	IV	8
Etoposide	200	IV	1-3
Adriamycin (doxorubicin)	35	IV	1
Cyclophosphamide	1250	IV	1
Oncovin® (vincristine)	1.4*	IV	8
Procarbazine	100	Oral	1-7
Prednisone	40	Oral	1-14
Granulocyte colony-stimulating factor		Subcutaneously	8+
Repeat every 21 days			
A-AVD			
Brentuximab vedotin	1.2 mg/kg	IV	1,15
Doxorubicin	25	IV	1,15
Vinblastine	6	IV	1,15
Dacarbazine	375	IV	1,15

*Vincristine dose capped at 2 mg.

The development of ABVD by Bonadonna and colleagues at the Milan Cancer Institute about a decade later represents the next important step in the evolution of therapy for Hodgkin lymphoma (see Table 149-4).[15] ABVD was initially shown to be effective in treating MOPP failures and was later compared directly to MOPP in advanced disease, where it produced an 82% complete response rate, as compared to a 67% complete response rate with MOPP. Improved failure-free survival was demonstrated with ABVD, but no significant differences in 5-year overall survival were noted.[10] Because ABVD was less toxic and provided similar or better outcomes than MOPP, it eventually replaced MOPP as the standard regimen for advanced stage Hodgkin lymphoma.

In the early 1980s, the Goldie–Coldman hypothesis proposed that chemotherapy resistance was related to spontaneous mutation rates and the development of resistant clones. To test that hypothesis, researchers designed several clinical trials to evaluate the efficacy of alternating non–cross-resistant drug combinations in patients with Hodgkin lymphoma.[16] The initial approach adopted by investigators was to alternate or combine the MOPP and ABVD regimens. When MOPP and ABVD (or doxorubicin [Adriamycin®], bleomycin, vinblastine [ABV]) are combined in a monthly cycle, it is referred to as a hybrid regimen. Besides a potential benefit in efficacy, another potential benefit of alternating or hybrid regimens is the decreased risk of long-term toxicities. In the alternating MOPP/ABVD regimen, the cumulative doses of procarbazine and mechlorethamine are reduced by 50%, and the cumulative doxorubicin dose is reduced by 50%. In the hybrid regimen, the cumulative doxorubicin dose is reduced by 33%, and the cumulative bleomycin dose is reduced by 50%.

Several clinical trials have been performed to evaluate the efficacy of alternating or hybrid MOPP/ABVD regimens. The results of these trials show that alternating and hybrid regimens are superior to MOPP but not to ABVD.[16,17] Another approach evaluated by researchers was the administration of sequential cycles of MOPP and ABVD (MOPP/ABVD). Results of an intergroup trial showed sequential MOPP and ABVD to be inferior to the MOPP/ABV hybrid regimen in terms of response and survival.[17] In another randomized comparison trial of the MOPP/ABV hybrid regimen and ABVD, the complete remission rate, failure-free survival, and overall survival were similar between the two regimens.[18] The latter trial was closed prematurely because of an increased number of treatment-related deaths and secondary malignancies in the patients who received the MOPP/ABV hybrid regimen.

More complex regimens, such as Stanford V and BEACOPP, have been

evaluated as alternatives to MOPP or ABVD. It is important to note that radiation therapy is an integral part of the Stanford V regimen for all patients. The Stanford V regimen generated considerable interest based on the results of phase II trials.[19] Stanford V, ABVD, and an MOPP/ABV hybrid-like regimen (mechlorethamine, vincristine, procarbazine, prednisone, epidoxorubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine [MOPPEBVCAD]) were then compared in a randomized trial to determine the best regimen to support a reduced radiotherapy program.[20] Five-year failure-free and progression-free survival were significantly worse for the Stanford V regimen as compared to the other two regimens. However, no significant differences in overall response rate or 5-year overall or failure-free survival were observed between Stanford V and ABVD in a published randomized trial of patients with advanced Hodgkin lymphoma (E2496).[21] Investigators have speculated that differences in the application of radiotherapy may explain the divergent results in the randomized trials. More pulmonary toxicity occurred in the ABVD group, but other toxicities occurred more frequently in the Stanford V group.

The German Hodgkin Study Group (GHSG) developed the BEACOPP regimens based on the principles of dose density, dose intensity, and mathematical modeling. BEACOPP uses similar drugs as in the cyclophosphamide, vincristine, procarbazine, and prednisone (COPP)/ABVD regimen, but rearranges the drugs in a shorter 3-week cycle. Several different versions of BEACOPP have been developed: standard-dose BEACOPP, escalated-dose BEACOPP, and dose-dense BEACOPP (BEACOPP-14). Granulocyte colony-stimulating factor support is required for the escalated-dose BEACOPP and BEACOPP-14 regimens.

It is important to note that the initial evidence for these regimens focused on patients with advanced or metastatic disease as described in this section, but subsequent trials have focused on the use of these regimens in early stage disease.

1 With all stages and risk-groups of Hodgkin lymphoma, it is current practice to treat with chemotherapy for 8 to 12 weeks and then obtain a restaging PET-CT.[22] This scan is assessed on a PET 5-point scale, also known as Deauville Criteria. Score 1 indicates no uptake, and can be called a complete response, or no measurable disease.[7] For all stages of Hodgkin lymphoma, further treatment is based on the restaging PET/CT results such that residual uptake at the end of chemotherapy would likely indicate the need for ISRT. If a Deauville score of 5 exists after completion of chemotherapy, then a biopsy of the involved area is

indicated. With an interval PET/CT scan, every patient's treatment plan is personalized based on the response to treatment.

Classical Hodgkin Lymphoma

Hodgkin lymphoma can initially be divided into two broad classifications: classical Hodgkin lymphoma and NLPHL. Although classical Hodgkin lymphoma can be further divided into pathologic subtypes, the treatments are based on risk factors and presence of bulky disease regardless of the subtype of classical Hodgkin lymphoma.

Treatment of Early Stage Favorable Disease

Patients with early stage favorable disease have stage IA or IIA disease and no adverse risk factors (B symptoms, extranodal disease, bulky disease, three or more sites of nodal involvement, or an ESR of >50 mm/hr [13.9 μm/s]). Extended-field radiation was previously considered to be the treatment of choice for stages IA and IIA disease. Although most patients were cured of their disease, the radiation is associated with long-term toxicities due to large radiation fields such as heart disease, pulmonary dysfunction, and secondary malignancies.[4,11]

Combined modality therapy (chemotherapy and radiation therapy) has replaced radiation therapy alone in patients with early stage favorable disease. With combined modality therapy, both a shorter duration of chemotherapy and newer, more focused radiation techniques (ISRT, others) are used to decrease the long-term toxicities of both.

Clinical trials comparing radiation alone to radiation plus chemotherapy show lower relapse rates in patients treated with combined modality therapy (radiation and chemotherapy), but no change in overall survival because of the availability of effective salvage therapy. Ongoing trials focus on questions such as the optimal number of chemotherapy cycles, the volume of radiation that must be used to obtain optimal patient outcomes, and the role of PET scanning to individualize therapy. Long-term results of clinical trials also suggest that as few as two cycles of Stanford V or ABVD chemotherapy followed by IFRT is sufficient in favorable, early stage disease patients.[23,24] Different combination chemotherapy regimens have been used in these studies and no one regimen is clearly superior to another.

Clinical trials have also investigated the use of chemotherapy alone to treat low-risk early stage Hodgkin lymphoma. Long-term results of clinical trials

show a lower rate of disease control versus combined modality therapy. Selected patients can be treated with chemotherapy alone if they achieve a complete response following two cycles of chemotherapy, with a total treatment of four cycles of chemotherapy.

Patients with early stage favorable disease can be treated with two cycles of ABVD alone or plus ISRT or two to four cycles of the Stanford V regimen (doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone), followed by a restaging PET-CT scan.[23,24] Depending on the response to the initial chemotherapy, consolidative ISRT is recommended if anything less than a complete response is achieved. With this approach, 5-year progression-free and overall survival rates of more than 90% can be achieved in early stage favorable disease.

Treatment of Early Stage Unfavorable Disease

Patients with early stage disease who have certain features associated with a poor prognosis (B symptoms, extranodal disease, bulky disease, three or more sites of nodal involvement, or an ESR >50 mm/hr [13.9 μm/s]) are defined as having unfavorable disease. Different research groups or clinical trials have different definitions for unfavorable disease. Most groups consider an ESR >50 mm/hr (13.9 μm/s), presence of B symptoms, large mediastinal mass, and more than three affected nodal sites to be unfavorable risk factors. Current guidelines recommend combined modality therapy (combination chemotherapy and ISRT) to reduce the relapse rate and avoid the toxicity associated with extended-field radiation.[22]

Randomized trials show that combined modality therapy reduces the relapse rate in patients with early stage unfavorable disease. Different chemotherapy regimens and number of chemotherapy cycles have been compared in clinical trials. In most studies involving early stage unfavorable disease, ABVD is the comparator arm. ABVD plus 30 Gy [3,000 rad] ISRT remains the standard of care for patients with early stage unfavorable disease, but the Stanford V regimen plus radiation or BEACOPP for two cycles followed by ABVD for two cycles are both alternatives in select patients. The Stanford V regimen has been studied in several single arm trials[19,25] and comparative trials versus ABVD[21,26] report overall response rates in the 90% range and 5-year overall survival from 88% to 94%. All of these trials included radiation therapy as part of the treatment schema. The GHSG studied the use of a more aggressive regimen of escalated-dose BEACOPP for two cycles followed by ABVD for two cycles versus ABVD for four cycles. Both treatment arms received 30 Gy [3,000 rad]

of IFRT. Patients treated with BEACOPP had longer progression-free survival but similar 5-year overall survival as compared with ABVD.[27] BEACOPP is associated with more toxicities than ABVD in early stage unfavorable Hodgkin lymphoma.[28]

2 In summary, most patients with early stage disease will be treated with two to four cycles of ABVD chemotherapy and involved-site radiation. The number of cycles initially administered is based on the classification of favorable versus unfavorable disease. Restaging with a PET-CT after 4 to 12 weeks of chemotherapy further guides the need for more chemotherapy or radiation (ISRT), but most patients with unfavorable disease will require radiation. Clinical trials have demonstrated the utility of PET scans as biomarkers to individualize therapy and minimize the amount of therapy necessary for cure.[7] Although ABVD is the preferred initial regimen (NCCN category 1 recommendation), evidence supports the use of Stanford V in favorable and unfavorable early stage patients and escalated BEACOPP-ABVD in unfavorable early stage patients.[22] Despite excellent results from treatment with ABVD and radiation, about 5% of patients do not respond to initial treatment and another 15% of patients will relapse following an initial response.

Treatment of Advanced Stage Disease

Advanced stage disease consists of stages III and IV disease. In some studies, stage IIB with a large mediastinal mass or extranodal disease is also considered advanced stage disease (see Table 149-2). By definition, patients with stages III and IV disease have tumors on both sides of the diaphragm, which almost always precludes the use of radiation alone as a therapeutic modality. Intensive combination chemotherapy is the mainstay of treatment, although some patients will benefit from radiation following chemotherapy. The prognosis of advanced stage disease is excellent with 5-year overall survival rates ranging from 56% to 90%. Most patients obtain a complete response from their initial treatment. Prognostic factors have been identified and standardized to predict an individual's prognosis, according to the IPS (see Table 149-3).[9]

Patients with advanced stage Hodgkin lymphoma can be classified into two groups based on the number of prognostic factors present from the IPS (see Table 149-3). Advanced stage patients with three or fewer poor prognostic factors are considered to have favorable disease and have about a 60% likelihood of being failure-free at 5 years with traditional combination chemotherapy. Advanced stage patients with four or more poor prognostic factors are

considered to have unfavorable disease and a less than 50% likelihood of being failure-free at 5 years with traditional combination chemotherapy. Cures are possible in patients with high-risk disease, but long-term disease control is a more realistic goal for most patients.

Doxorubicin (Adriamycin®), bleomycin, vinblastine, and dacarbazine for (ABVD) decades have continued to be the standard initial regimens utilized for advanced Hodgkin lymphoma in many cancer programs. As discussed in section "Chemotherapy Regimens," many multinational, randomized large trials have demonstrated ABVD's sustained positive outcomes and lower toxicity profile as compared to other regimens.

The activity of the Stanford V regimen with ISRT in advanced Hodgkin lymphoma has been demonstrated in prospective trials. In a phase III intergroup trial (E2496) comparing ABVD to Stanford V with radiation therapy in either arm, no significant differences in the 5-year overall or failure-free survival were observed.[21]

The BEACOPP regimens were designed to provide a more aggressive treatment for advanced disease. Several randomized trials have compared BEACOPP to other regimens.[4,29] The GHSG conducted a large randomized comparison of COPP/ABVD (alternating), BEACOPP, or an escalated-dose BEACOPP regimen (HD9 trial).[29] Escalated-dose BEACOPP was the most active regimen in this study, with 10-year freedom from treatment failure at 82% and overall survival at 86%, but this regimen was also associated with more toxicities including secondary leukemias, and was particularly toxic in the elderly.[30] In the HD2000 study, patients with advanced Hodgkin lymphoma were randomized to receive six cycles of ABVD, four cycles of escalated-dose BEACOPP with two cycles of standard-dose BEACOPP, or a third chemotherapy regimen that is not a current standard of care.[31] BEACOPP was superior to ABVD for 5-year failure-free survival (78% vs 65%, $P = 0.036$) and progression-free survival (81% vs 68%, $P = 0.038$), but 5-year overall survival was not significantly different between ABVD and BEACOPP. It appears that BEACOPP may be superior to ABVD in patients with high-risk advanced Hodgkin lymphoma (IPS ≥3). Higher rates of neutropenia and severe infections were observed with BEACOPP as compared with ABVD. The HD2000 trial also demonstrated a higher risk of secondary malignancy in the BEACOPP versus ABVD arm (6.7% vs 0.9%, $P = 0.027$) at 10 years.[32] Finally, GHSG has conducted several trials to evaluate the optimal number and intensity of BEACOPP. The HD12 and HD15 trials are two examples of this research.[33,34] The results of these studies suggest that escalated-dose BEACOPP is superior to

ABVD in the treatment of advanced Hodgkin lymphoma, but at the cost of more treatment-related toxicity.

Current treatment options for patients with advanced disease are ABVD, Stanford V or escalated-dose BEACOPP. Stanford V may be considered in patients with IPS less than 3 and escalated-dose BEACOPP may be considered in patients less than 60 years old with an IPS of greater than or equal to 4.[34] As with earlier stage disease, combination chemotherapy should be administered for 4 to 18 weeks, depending on the regimen chosen, followed by a restaging PET scan. Based on the residual Deauville score, additional chemotherapy and/or radiation may be administered.

Brentuximab vedotin is an antibody-drug conjugate (ADC) comprising an anti-CD30 antibody conjugated by a protease cleavable linker to a potent antimicrotubule agent, monomethyl auristatin E (MMAE). After binding of the ADC to CD30 on the cell surface, the ADC-CD30 complex is internalized. This leads to the release of MMAE via proteolytic cleavage in the lysosomal compartment. Tubulin binding by MMAE disrupts the microtubule network, which can lead to apoptotic death of the cancer cells. The A-AVD regimen incorporates brentuximab vedotin instead of bleomycin into the “AVD” backbone (doxorubicin, vinblastine and dacarbazine). In a large phase III, multicenter, international trial, A-AVD was compared to ABVD in patients with newly diagnosed stage III or IV Hodgkin lymphoma. The modified 2-year progression-free survival rates were 82.1% in the A-AVD arm and 77.2% in the ABVD arm (P = 0.04). Toxicities varied in the two arms, where neutropenia, neutropenic fever, and peripheral neuropathy were more common in the A-AVD arm as compared to ABVD. Grade 3 or higher pulmonary toxicity was more common in patients receiving ABVD arm compared to A-AVD (1%). Of the deaths that occurred in this trial, 11 of the 13 receiving ABVD were associated with pulmonary toxicities, and 7 of the 9 receiving A-AVD were associated with neutropenia. The authors concluded that A-AVD was superior to ABVD, based on the absolute difference of 4.9% in the combined risk of death, progressive disease or incomplete response. Possible candidates for the A-AVD regimen are patients with newly diagnosed disease, no preexisting neuropathy, and a contraindication to bleomycin.[35]

3 In summary, there are several approaches to the initial treatment of stages III and IV Hodgkin lymphoma. A standard treatment of advanced stage favorable Hodgkin lymphoma is to administer two cycles of ABVD chemotherapy followed by a restaging PET-CT. If minimal disease is found (Deauville score 1-3), four additional courses of ABVD should be given (total of

six cycles). If residual disease is suspected (Deauville score 4-5), a switch to escalated-BEACOPP for four cycles should be considered. If the Stanford V regimen is selected for initial therapy, then the full 12 weeks of planned chemotherapy would be given before the restaging PET-CT. Escalated-dose BEACOPP for six cycles should be considered for patients with unfavorable disease. This risk-adapted approach should result in 70% to more than 90% of patients achieving a complete remission and 60% to 80% of patients being cured of their disease. No further treatment is needed for patients who achieve a complete remission (Deauville 1-2) with chemotherapy alone. Patients who achieve a partial remission (Deauville 3-5) should be considered for consolidative radiation to residual sites of disease. As with all stages and risk-groups of Hodgkin lymphoma, if a Deauville score of 5 remains after completion of initial chemotherapy, a biopsy is recommended to determine if refractory disease is present.

Nodular Lymphocyte-Predominant Hodgkin Lymphoma

Nodular lymphocyte-predominant Hodgkin lymphoma has been described as more indolent in nature, and has a better prognosis as compared with classical Hodgkin lymphoma. The use of radiation alone for stages I and II NLPHL patients who choose to omit chemotherapy or who cannot tolerate chemotherapy does not appear to adversely affect survival.[22] The disadvantage of radiation therapy alone as compared with combination chemotherapy plus radiation is the higher relapse rate. Patients who relapse after radiation alone (20%-25%) can be successfully salvaged with chemotherapy. If the decision is made to use radiation alone, ISRT is the preferred method. Patients with advanced stage disease can be treated with combined chemotherapy and radiation therapy. Historically, MOPP and MOPP/ABVD have been used, but these regimens have fallen out of favor much like classical Hodgkin lymphoma. ABVD is frequently used in these patients due to the available evidence to support its use for classical Hodgkin lymphoma, although other regimens, such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), and CVP (cyclophosphamide, vincristine, and prednisone), have been studied. No randomized clinical trials of different chemotherapy regimens have been conducted in NLPHL. NLPHL reliably expresses CD20, and therefore rituximab has demonstrated efficacy in both newly diagnosed and progressive NLPHL. Several phase II trials have reported overall response rates of 90% to 100% with single agent rituximab.[36,37]

Current NCCN guidelines recommend that patients with stage IA or IIA nonbulky disease preferentially be treated with ISRT alone. In very select patients with stage IA disease that was completely resected with the excisional biopsy, observation may be an option. Patients with IB, IIB, or advanced disease should receive chemotherapy with or without rituximab and with or without ISRT.[22]

Treatment of Refractory or Relapsed Disease

4 Refractory disease is defined as disease that persists following initial therapy, including any response less than a complete response. Relapsed disease suggests tumor recurrence following attainment of a complete response. Patients who experience relapsed disease less than 12 months after the completion of therapy have a poor prognosis. The goal of second-line or salvage therapy is still cure. With the increasing use of chemotherapy with or without radiation, regardless of disease extent, the rate of primary refractory disease is decreasing. Many therapeutic options are available for treatment of refractory or relapsed disease, so each patient's treatment should be personalized. The highest survival and cure rates are reported for patients with chemosensitive disease who are medically able to undergo high-dose therapy and autologous HSCT.[38] Since most patients are initially treated with ABVD, doxorubicin should be avoided in salvage chemotherapy regimens if the cumulative dose has reached between 300 and 400 mg/m^2, particularly in those patients who have received mediastinal radiotherapy, because of the higher risk of cardiotoxicity.

The response to salvage therapy depends on the extent and site of recurrence, previous therapy, and duration of initial remission. Patients who relapse after radiation therapy alone have a good chance of being cured with combination chemotherapy, although fewer patients are being treated with radiation alone. High response rates (60%-87%) have been reported with salvage chemotherapy regimens.[2,4] Other patient groups who have a favorable prognosis following salvage therapy include patients who experience a local recurrence in a nonirradiated location and those who relapse more than 1 year after completion of their initial chemotherapy. Patients who experience late relapses can be cured with retreatment with the same chemotherapy regimen, treatment with a different, potentially non–cross-resistant regimen, or high-dose chemotherapy and autologous HSCT.

Patients who have an early relapse (<1 year after treatment) generally respond poorly to standard-dose salvage chemotherapy. High-dose chemotherapy and

autologous HSCT is more effective, but also produces a higher risk of treatment-related mortality. Therefore, the choice of salvage treatment should consider the patient's tolerance for a particular set of chemotherapeutic agents and treatment approach (standard-dose chemotherapy vs high-dose chemotherapy and autologous HSCT).

High-dose therapy should be considered in patients who relapse within 12 months of initial remission and in those who are refractory to first-line chemotherapy. Although no single preparative regimen has been shown to be superior to another, most regimens do not include total-body irradiation because of its potential pulmonary toxicity. Most patients are already at higher risk for pulmonary toxicity because of previous exposure to one or more of the following: bleomycin, thoracic radiation, and nitrosoureas.

Brentuximab vedotin is effective in the relapse or refractory setting. In a pivotal multicenter phase II study of 102 patients with relapsed or refractory Hodgkin lymphoma after HSCT, 75% and 34% of patients treated with brentuximab vedotin had an objective response and complete remission, respectively.[39] End-of-study results showed that response to brentuximab was durable; patients who achieved complete remission had an overall survival rate of 64% at 5 years and 26% remained in remission with no further anti-cancer therapy after receiving brentuximab.[40] Brentuximab vedotin has also been evaluated as posttransplant consolidation therapy in a phase III trial in 329 patients undergoing autologous HSCT. All patients had a high risk of relapse, defined as disease refractory to initial therapy or relapsed disease less than 12 months from completion of initial therapy with extranodal disease. Patients randomized to receive 16 cycles of brentuximab had significantly longer median progression-free survival (42.9 vs 24.1 months) as compared with placebo.[41] Common toxicities associated with brentuximab vedotin include neuropathy, neutropenia, nausea, and fatigue.[39] Based on these results, brentuximab vedotin (Adcetris®) received FDA approval for the treatment of classical Hodgkin lymphoma after failure of autologous HSCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not candidates for autologous HSCT, and also for patients with classical Hodgkin lymphoma at high risk of relapse or progression as consolidation therapy after autologous HSCT.

Many single-agent and combination regimens can be used as salvage therapy. In this setting, the goal of therapy is disease control and cures are unlikely. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), ifosfamide, carboplatin, and etoposide (ICE) and ifosfamide, gemcitabine and

vinorelbine are examples of chemotherapy regimens that include drugs with different mechanisms of action and toxicity profiles than regimens used earlier in therapy. Bendamustine, lenalidomide, and everolimus have shown activity in patients with refractory or relapsed Hodgkin lymphoma.

Immune checkpoint inhibitors, specifically PD-1 (programmed death 1 pathway) inhibitors, are treatment options in refractory Hodgkin lymphoma. Promising results have been reported from phase II trials of heavily pretreated patients. One trial with single-agent nivolumab reported an objective response rate of 87%, with some complete responses; progression-free survival at 24 weeks was 86%.[42] In another phase II trial of nivolumab in 80 patients with classical Hodgkin lymphoma after failure to both HSCT and brentuximab (median of 4 previous therapies), objective responses were achieved in two-thirds of patients.[43] Pembrolizumab, another PD-1 inhibitor, has also been studied in patients with relapsed or refractory disease. In a trial of 31 heavily pretreated patients, a complete response rate of 16% and a partial remission rate of 48% was observed, and the 52-week progression-free survival rate was 46%.[44] A large phase II trial of 210 patients treated with pembrolizumab 200 mg IV every 3 weeks also reported an overall response rate of 69.0% and a complete response rate of 22.4%.[45] Based on these results, both nivolumab and pembrolizumab received FDA approval for relapsed Hodgkin lymphoma. Potentially severe graft-versus-host disease has been described in patients who received a checkpoint inhibitor following allogeneic HSCT.[46]

Long-Term Complications

A variety of acute and chronic toxicities may occur as a result of treatment for Hodgkin lymphoma. Long-term complications of radiation therapy, chemotherapy, and combined modality therapy have become more evident as the curability and long-term survival of Hodgkin lymphoma patients has improved.[2,4,11,22] Gonadal dysfunction (including sterility and hypothyroidism), secondary malignancies, and cardiopulmonary diseases have become important considerations in the treatment of this malignancy. Almost all men and up to 50% of premenopausal women treated with six cycles of regimens containing alkylating agents become sterile. This appears to be a dose-related phenomenon. For men, even a single dose of nitrogen mustard or chlorambucil can cause sterility, so if fertility is a major concern, ABVD is the best alternative.

The risk of secondary malignancies is increased about threefold in long-term survivors of Hodgkin lymphoma. The risk of developing leukemia carries the

highest increase in risk and is seen with radiotherapy, chemotherapy, and chemoradiotherapy. Solid tumors, including breast cancers, gastrointestinal cancers, and lung cancers, are also likely to develop more than 10 years after the completion of treatment. A recently published British cohort study suggested that unlike radiotherapy, which may increase the occurrence of cancer at almost all anatomic sites, chemotherapy is associated with an increased risk of leukemia, NHL, and lung cancer. However, studies that evaluate the risk of secondary malignancies (and other complications) must be interpreted cautiously because many factors probably contribute to the development of secondary malignancies. In addition, much of the long-term complication data are derived from patients who were treated with older regimens and extensive field radiotherapy, which are no longer commonly used in clinical practice. As the field of cancer survivorship continues to grow, more specific recommendations for long-term follow-up are developed. Regular mammograms and breast MRI are recommended starting 10 years following the completion of therapy or at age 40 (whichever is earlier) for females. Patients are at increased risk of lung cancer if they have a smoking history, chest irradiation, and/or alkylating agent exposure. These patients should be considered for low-dose screening chest CT. For cardiovascular monitoring, annual blood pressure monitoring and aggressive management of cardiovascular risk factors are strongly encouraged. Hypothyroidism is reported in about 50% of long-term survivors who received irradiation to this area. Thyroid function tests should be performed annually. Monitoring and follow-up should be personalized and patient-specific, after assessing a patient's risks for long-term complications.[22]

NON-HODGKIN LYMPHOMA

The NHLs are a heterogeneous group of lymphoproliferative disorders that affect individuals from early childhood to late adulthood. Advances in molecular biology techniques and our understanding of the human immune system have led to major progress in understanding the pathogenesis and treatment of the lymphomas. NHLs are classified into distinct clinical entities that are defined by a combination of morphology, immunophenotype, genetic features, and clinical features. These differences influence the natural history, and approach and response to treatment. The use of extensive combination chemotherapeutic regimens shows dramatic improvement in survival and cure in patients with a disease that was once considered incurable. The 5-year survival rate for patients with NHL has increased from 48% to 74% over the past 30 years, and the

mortality rate actually *declined* from 1997 to 2015.[1,5] Further improvement in survival is anticipated with the continued expansion of our therapeutic armamentarium, including high-dose chemotherapy and targeted therapy.

Epidemiology and Etiology

NHL is the fifth most common cause of newly diagnosed cancer in the United States and accounts for about 4% of all cancers. An estimated 74,200 new cases were diagnosed in 2019, and it is estimated that 19,970 people will die from NHL during this same period.[5] Although the average age of patients at the time of diagnosis is about 67 years, NHL can occur at any age. The incidence rate generally increases with age, and is higher in men than in women and in whites than in blacks.[5] The age-adjusted incidence rate of NHL increased by more than 80% in the United States since the early 1970s, from about 11 cases per 100,000 in 1975 to about 20 cases per 100,000 in 2011 and 2012.[1] The incidence of NHL increased by 3% to 4% from 1975 to 1991, but appears to have stabilized since reaching its peak in 1994. The increased incidence of NHL over the past three decades is second only to melanoma and has been referred to as an epidemic of NHL. Although the increase has been noted particularly among the elderly and patients with acquired immune deficiency syndrome (AIDS), much of it cannot be explained by known risk factors.

The etiology of NHL is unknown, although several genetic diseases, environmental agents, and infectious agents are associated with the development of NHL.[47] An increased incidence of NHL is seen in many congenital and acquired immunodeficiency states, supporting the role of immune dysregulation in the etiology of NHL.[47] Patients with congenital immunodeficiency disorders such as Wiskott-Aldrich's syndrome and ataxia telangiectasia, acquired immunodeficiency disorders such as AIDS, and those receiving chronic pharmacologic immunosuppression in the setting of solid-organ transplantation are predisposed to the development of NHL. Autoimmune diseases (Hashimoto's thyroiditis and Sjögren's syndrome) cause chronic inflammation in the mucosa-associated lymphoid tissue (MALT), which predisposes patients to subsequent lymphoid malignancies. Other autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis, are also associated with the development of NHL, but the use of immunosuppressive agents in these diseases makes the pathologic cause less clear.

Certain infections are associated with the development of lymphoma.[47] EBV was discovered in cell lines from tumors of patients with African (endemic)

Burkitt lymphoma, and EBV DNA is associated with nearly all cases of endemic Burkitt lymphoma. However, EBV is associated with sporadic Burkitt lymphoma in 15% to 85% of cases. EBV is also associated with posttransplant lymphoproliferative disorders and some lymphomas in patients with AIDS or congenital immunodeficiencies. Extranodal NK-T cell lymphoma is also strongly associated with EBV infection. The nasal-type extranodal NK-T cell lymphoma is more common in east Asia, and less common in Central and South America, than in other regions. The human T-cell lymphotropic virus type 1 was the first human retrovirus associated with a malignancy. Infection with human T-cell lymphotropic virus type 1, especially in early childhood, is strongly associated with an aggressive form of T-cell lymphoma, known as adult T-cell leukemia/lymphoma. Human T-cell lymphotropic virus type 1 is endemic in parts of southern Japan, Africa, South America, and the Caribbean. In endemic areas, more than 50% of all NHL cases are adult T-cell leukemia/lymphoma. A third virus associated with NHL is human herpes virus 8 (also referred as Kaposi sarcoma–associated herpesvirus [KSHV]). This virus was originally isolated from Kaposi sarcoma lesions in AIDS patients. Gastric infection with *Helicobacter pylori*, a gram-negative bacteria that leads to chronic gastritis, is associated with gastric MALT lymphomas. Finally, hepatitis C virus has been associated with splenic and nodal marginal zone lymphomas.

A number of physical agents are also associated with the development of NHL.[47] Exposure to herbicides, particularly phenoxyl herbicides, is associated with the development of NHL. These observations may explain why certain occupations, such as farmers, forestry workers, and agricultural workers, are associated with a higher risk of NHL. Exposure to lawn-care pesticides is also increasing in the general population. A higher risk of NHL is also associated with exposure to other chemical solvents and dyes, exposure to radiation from nuclear explosions, and high intake of meats and dietary fats. Smoking or alcohol consumption is not strongly associated with an increased risk of NHL.

Molecular Abnormalities

Chromosomal translocations are a hallmark of many lymphoid malignancies.[47,48] The presence of these specific translocations can be helpful in the diagnosis and classification of lymphoid malignancies. The mechanisms leading to the translocations are unknown, but they usually involve the antigen receptor loci. In contrast to most myeloid and some lymphoid leukemias, NHLs usually place a structurally intact cellular proto-oncogene under the regulatory

influence of highly expressed immunoglobulin or T-cell receptor genes, leading to effects on cell growth, cellular differentiation, or apoptosis. The most common chromosomal translocations involve t(8;14), t(14;18), and t(11;14); each translocation involves the immunoglobulin heavy-chain gene locus on chromosome 14 at 14q32. The translocation t(8;14) that involves c-*MYC*, a well-characterized oncogene clearly associated with malignancy, is implicated in nearly all cases of Burkitt lymphoma. The translocation t(14;18) that involves *BCL*-2, one of several putative B-cell lymphoma-associated oncogenes, is found in about 90% of cases of follicular B-cell lymphomas. The translocation t(11;14) that involves *BCL*-1 is found in about 70% of patients with mantle cell lymphoma (MCL). Another putative B-cell lymphoma-associated oncogene, *BCL*-6, is found in about one-third of diffuse large B-cell lymphomas (DLBCLs).

Although mutations in the *p53* tumor suppressor gene are found in many human neoplasms, such mutations have not been consistently found in patients with lymphoma, which suggests that it may occur late in malignant evolution. Because of their role in the pathogenesis of lymphoma, oncogenes are attractive molecular targets for the development of new and novel therapies.

Pathology and Classification

NHLs are neoplasms derived from the monoclonal proliferation of malignant B or T lymphocytes and their precursors. About 85% to 90% of NHLs in the United States are of B-cell origin.[47] Proliferation of malignant cells results in the replacement of the normal cells and architecture of lymph nodes or bone marrow with a relatively uniform population of lymphoid cells. The classification of NHLs has evolved over the past five decades, as advances in immunology and genetics have allowed scientists to recognize a number of previously unrecognized subtypes of NHLs (**Table 149-5**).[49] The current classification schemes characterize the NHLs according to the cell of origin (B cell vs T cell), clinical features, and morphologic features. Additional immunohistochemical markers, cytogenetic features, and genotypic characteristics may further classify NHL into subtypes.

TABLE 149-5 Evolution in the Classification of Non-Hodgkin Lymphomas

Time	Classification System	Basis for Classification
1950s-1960s	Rappaport	Morphology
1970s-1980s	Luke–Collins	Morphology and immunophenotype
1970s-1980s	Kiel	Morphology and immunophenotype
1980s-1990s	International Working Formulation	Morphology and clinical behavior
1990s	REAL	Disease entities
2001-present (revised in 2008, 2016)	WHO	Disease entities

REAL, revised European–American Classification of Lymphoid Neoplasms developed by the International Lymphoma Study Group; WHO, World Health Organization.

Morphology

The macroscopic and microscopic appearance of the involved tissue remains one of the most important factors in the diagnosis and classification of NHLs.[49] In the 1950s, Rappaport et al proposed a morphologic classification of malignant lymphomas based on two features: that the malignant cell would disrupt the nodal architecture in a *nodular* or *diffuse* manner, and that lymphomas of histiocytic origin existed. The Rappaport classification gained rapid acceptance in the United States because of its precision, simplicity, and prognostic significance. Application of the system divided NHLs into those with large (ie, incorrectly called “histiocytes”) or small cells, with or without a nodular (ie, follicular) growth pattern.

Immunology

In the 1970s, it became apparent that NHLs were tumors of the immune system and were derived from B or T lymphocytes. With the availability of techniques using antibodies to antigens on the surface of lymphoid cells (ie, immunophenotype) and cytochemical assays, expert pathologists independently developed new classification schemes for NHL in the 1970s and 1980s.[49] The Kiel classification was based primarily on the work of Lennert in Germany and became widely used in Europe. In North America, the Lukes and Collins classification scheme was used briefly, but was soon superseded by the Working Formulation. Like the Rappaport classification, divisions within the Working

Formulation were based largely on cell size (large [histiocytic] vs small [lymphocytic]), cell shape (round vs not round), and growth pattern (follicular [nodular] vs diffuse). Both the Kiel and Working Formulation classification schemes considered the histologic grade of the tumor, but only the Working Formulation considered actual survival curves of patients with the various subtypes of NHL. *Low-grade* indicated longer median survival (ie, indolent) while *intermediate-grade* and *high-grade* indicated shorter median survival (ie, aggressive). In the 1980s and early 1990s, the Working Formulation became the most widely used classification scheme in North America. It was based on the premise that NHL was a single disease with a range of histologic grades and clinical aggressiveness.

Disease Entities

In the 1980s and early 1990s, rapid advances in immunology and genetics allowed scientists to recognize a number of previously unrecognized subtypes of NHLs. Cytogenetic and molecular genetic analyses identified the presence of many chromosomal translocations, oncogenes, and their gene products in patients with NHL (see section “Molecular Abnormalities” earlier in this Chapter). In addition, diseases that would have been lumped together as low-grade or intermediate/high grade in the Working Formulation showed marked differences in survival, which prompted scientists to reevaluate lymphoma classification schemes.

Information from these studies allowed scientists to further classify B-cell lymphomas as malignant expansions of cells from the germinal center, mantle zone, or marginal zone of normal lymph nodes.[49] Germinal centers are complex structures that form in the spleen and lymph nodes in response to antigenic challenge. In addition to B cells, germinal centers contain antigen-presenting cells and helper T cells that cooperate in mediating the B-cell changes that result in a more potent secondary immune response. Malignant transformation often occurs or is initiated in germinal center B cells. Follicular, Burkitt, and most large cell lymphomas are believed to be tumors of germinal center B cells. Three histologically distinct microenvironments have been described within the germinal center: a mantle zone surrounding interior, dark, and light zones. The mantle zone contains small resting B cells that have not been exposed to antigens (naïve). Tumors of cells from the mantle zone are usually clinically indolent and histologically low grade. Antigen-triggered activation of the densely packed B cells of the dark zone causes cells to proliferate and subjects genomic DNA to somatic hypermutation. Surviving clones from within the dark

zone then enter the light zone where proliferation slows and affinity selection occurs. During affinity selection, only cells with surface immunoglobulin receptors with high affinity for the antigen survive. Antigen-specific B cells generated in the germinal center reaction leave the follicle and reappear in the outer mantle zone, to form a marginal zone. Marginal zones are particularly prominent in mesenteric lymph nodes, Peyer's patches, and the spleen. These postgerminal center B cells include memory B cells of the marginal zone and plasma cells. Marginal zone B-cell lymphomas tend to be indolent and may be either extranodal or nodal; extranodal marginal zone B-cell lymphomas are also referred to as MALT lymphomas.

T-cell lymphomas can be classified based on antigen expression as either precursor (thymic) or mature (peripheral) in origin. These classifications clinically translate to precursor lymphoblastic lymphomas or to a heterogeneous group of peripheral T-cell lymphomas. Tumors of natural killer or natural killer-like T cells are uncommon.

The International Lymphoma Study Group, an informal group of 19 hematopathologists from the United States, Europe, and Asia adopted a new approach to lymphoma classification in 1993. Because it represented a revision of current or prior European and American lymphoma classifications, it was called the Revised European-American Classification of Lymphoid Neoplasms (REAL). The REAL classification system is based on the principle that a classification is a list of "real" disease entities, which are defined by a combination of morphology, immunophenotype, genetic features, and clinical features.[49] The relative importance of each of these criteria for both definition and diagnosis differs among different diseases. Morphology is always important, and some diseases are primarily defined by morphology alone (eg, follicular lymphoma), although immunophenotype can be helpful in difficult cases. Some diseases have a specific immunophenotype (eg, MCL, small lymphocytic lymphoma) that is virtually diagnostic of that disease. A specific genetic abnormality is important in some lymphomas—t(11;14) in MCL, t(8;14) in Burkitt lymphoma, and t(14;18) in follicular lymphoma—whereas other lymphomas lack specific genetic abnormalities (eg, MALT lymphoma, DLBCL). Finally, other lymphomas consider clinical features (eg, extranodal vs nodal presentation in marginal zone lymphoma and peripheral T-cell lymphoma).

Since 1995, members of the European and American Hematopathology societies have worked to develop a new WHO classification of hematologic malignancies. The final classification was published in 2001, and revised in 2008 and 2016.[6,49] The WHO classification uses an updated version of the

REAL classification and expands the principles of the REAL classification to the classification of myeloid and lymphoid malignancies.

5 The 2016 WHO classification categorizes lymphoid malignancies into two major categories: B-cell lymphomas and T-cell (and natural killer cell) lymphomas (see Table 149-1).[6,49] B-cell lymphomas represent about 85% to 90% of all NHLs. Lymphomas within each category can be divided into malignancies of precursor or mature cells. Hodgkin lymphoma and multiple myeloma are recognized as mature B-cell neoplasms. The WHO classification uses the term *grade* to refer to histologic parameters such as cell and nuclear size, density of chromatin, and proliferation fraction, and the term *aggressiveness* to denote clinical behavior of a tumor. This classification scheme includes both lymphomas and lymphoid leukemias because there is no distinction between the solid and circulating forms of these diseases. The WHO classification includes several previously unrecognized types of lymphomas, and new entities not specifically recognized in the Working Formulation account for about 20% to 25% of the cases.

The WHO classification has broad clinical implications. The WHO Clinical Advisory Committee has agreed that clinical groupings of lymphoid neoplasms into prognostic categories are neither necessary nor desirable because such arbitrary groupings are of no practical value and may be misleading.[50]

Clinical Presentation

6 Patients with NHL present with a wide variety of symptoms, depending on the site of involvement and whether tumor involvement is nodal or extranodal. Sites of involvement and dissemination of the malignant cells can sometimes be predicted based on the cell of origin and the tendency of tumors to frequently disseminate to areas where the normal counterparts of the lymphoma cells are located. For example, B-cell lymphomas involve areas of the lymphoid system normally populated by B-lymphocytes such as lymph nodes, spleen, and bone marrow. T-cell lymphomas commonly disseminate to various extranodal sites such as the skin and lungs.[48]

Most patients present with peripheral lymphadenopathy. The lymphadenopathy may be either localized or generalized, and the involved nodes are often painless, rubbery, and discrete, and usually located in the cervical and supraclavicular regions as in Hodgkin lymphoma (see Fig. 149-1). Rapid and progressive lymphadenopathy is more characteristic of aggressive lymphomas. Waxing and waning of lymph nodes, including their complete disappearance and

reappearance, is more characteristic of indolent lymphomas. Massive lymphadenopathy can sometimes lead to organ dysfunction. For example, patients with NHL may present with acute renal failure from retroperitoneal adenopathy causing ureteral obstruction or from metabolic abnormalities such as hyperuricemia with uric acid nephropathy.

CLINICAL PRESENTATION Non-Hodgkin Lymphoma

General

- Patients with NHL present with a wide variety of symptoms, depending on the site of involvement and whether tumor involvement is nodal or extranodal.

Symptoms

- About 40% of patients present with fever, night sweats, and weight loss (ie, B symptoms).
- Fatigue, malaise, and pruritus.

Signs

- More than two-thirds of patients present with peripheral lymphadenopathy.

Laboratory Tests

- A complete blood count, tests of renal and liver function, and serum electrolytes should be obtained.
- Serum β_2-microglobulin and LDH levels may be useful as prognostic factors and for monitoring response to therapy.

Other Diagnostic Tests

- Varies depending on sites of involvement.

About 40% of patients with NHL present with fever (temperature >38°C [100.4°F]), weight loss (unexplained weight loss of 10% of body weight over the past 6 months), or night sweats (drenching night sweats). If one or more of these symptoms is present, the patient is noted to have B symptoms, and a B is added to the stage of disease (discussed in section “Diagnosis, Staging, and Prognostic Factors” under Hodgkin Lymphoma earlier in this chapter). B symptoms are more commonly observed in patients with aggressive NHLs.

Patients with Hodgkin lymphoma rarely present with extranodal (ie, extralymphatic) disease, but 10% to 35% of patients with NHL have primary extranodal disease at the time of diagnosis. The frequency of extranodal presentation varies dramatically among different subtypes. The most common extranodal sites are the gastrointestinal tract followed by the skin. The liver or spleen may be enlarged in patients with generalized adenopathy. Patients with mesenteric or gastrointestinal involvement may present with signs and symptoms of nausea, vomiting, obstruction, abdominal pain, a palpable abdominal mass, or gastrointestinal bleeding. Patients with bone marrow involvement may have symptoms related to anemia, neutropenia, or thrombocytopenia. Other sites of extranodal disease include the testes and bone. The incidence of solitary brain lymphoma is increasing, especially in patients with AIDS.

Diagnosis, Staging, and Prognostic Factors

As with Hodgkin lymphoma, the diagnosis of NHL must be established by pathologic review of tissue obtained by biopsy.[48,51,52] The preferred procedure is an excisional biopsy, where the entire involved lymph node is removed for review by an experienced hematopathologist. This procedure should be done carefully to prevent distortional artifact of the architecture, which could lead to an inaccurate diagnosis. Needle biopsy of the node can sometimes provide adequate tissue for pathologic diagnosis, if an excisional biopsy cannot be performed. When adenopathy is not present, diagnosis may be established by biopsy of cutaneous lesions, bone marrow biopsy and aspiration in patients with unexplained myelosuppression, liver biopsy in patients with hepatomegaly or elevated liver function tests, or biopsy of involved extranodal organs such as bone, Waldeyer’s ring, lung, and testis.

After the diagnosis is established, further workup is required to determine the extent of involvement.[48,51,52] Clinical staging always begins with a thorough

history and physical examination. Patients should be questioned about the presence or absence and extent of fever, night sweats, and weight loss. A detailed history of lymphadenopathy should also be obtained, including when and where the lymph nodes were first noted, and their rate of growth. A complete physical examination is performed to assess the extent of disease involvement, with special attention given to all nodal areas (see Fig. 149-1). All patients should have a complete blood count, serum chemistries including liver and renal profiles. Lumbar puncture to evaluate the cerebrospinal fluid is recommended in patients who have histologic types of lymphoma that often spread to the CNS.

Imaging studies are important in the staging workup. In the most recent recommendations, PET-CT is the gold standard for assessment of essentially all lymphoma histologies, except chronic lymphocytic leukemia/small lymphocytic lymphoma, lymphoplasmacytic lymphoma/Waldenstrom's macroglobulinemia, mycosis fungoides, and marginal zone NHLs, unless there is a suspicion of aggressive transformation.[52] Magnetic resonance imaging is of limited usefulness in the staging of NHL. Gallium scans are sometimes used as part of the staging workup. Other tests, such as liver-spleen scan, bone scan, upper gastrointestinal series, and IV pyelogram, are sometimes useful in patients with organ symptomatology or serum chemistry abnormalities.

The likelihood of bone marrow involvement varies among the different histologic types of lymphoma (**Table 149-6**). In the NCCN guidelines, bone marrow biopsy with or without aspirate is included as part of essential workup for all lymphomas. Although PET-CT scans appear to be as sensitive as bone marrow biopsy in the identification of bone marrow involvement in certain subtypes of NHL including DLBCL, bone marrow biopsy remains preferable for identifying bone marrow involvement in indolent lymphomas such as follicular lymphoma.

TABLE 149-6 Clinical Characteristics of Patients with Common Types of Non-Hodgkin Lymphomas

Disease	Median Age (Years)	Frequency in Children	% Male	Stage I/II vs III/IV (%)	B Symptoms (%)	BM Involvement (%)	GI Tract Involvement (%)	% Surviving 5 Years
B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma	65	Rare	53	9 vs 91	33	72	3	51
Mantle cell lymphoma	63	Rare	74	20 vs 80	28	64	9	27
Extranodal marginal zone B-cell lymphoma of MALT type	60	Rare	48	67 vs 33	19	14	50	74
Follicular lymphoma	59	Rare	42	33 vs 67	28	42	4	72
Diffuse large B-cell lymphoma	64	≈25% of childhood NHL	55	54 vs 46	33	16	18	46
Burkitt lymphoma	31	≈30% of childhood NHL	89	62 vs 38	22	33	11	45
Precursor T-cell lymphoblastic lymphoma	28	≈40% of childhood NHL	64	11 vs 89	21	50	4	26
Anaplastic large T-/null cell lymphoma	34	Common	69	51 vs 49	53	13	9	77
Peripheral T-cell non-Hodgkin lymphoma	61	≈5% of childhood NHL	55	20 vs 80	50	36	15	25

BM, bone marrow; GI, gastrointestinal; MALT, mucosa-associated lymphoid tissue; NHL, non-Hodgkin lymphoma.

Reproduced with permission from Longo DL. Malignancies of lymphoid cells. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 19th ed. New York, NY: McGraw-Hill; 2015.

The Ann Arbor staging classification developed for the clinical staging of Hodgkin lymphoma is also used to stage patients with NHL (see Table 149-2). After completion of the staging workup, most patients will be found to have advanced disease (stages III and IV). The frequency of localized disease at the time of diagnosis varies depending on the histologic type of lymphoma (see Table 149-6). Stage is a more important prognostic factor in Hodgkin lymphoma than in NHL.

7 The Ann Arbor system emphasizes the distribution of nodal disease sites because Hodgkin lymphoma usually spreads through contiguous lymph nodes and does not involve extranodal sites. But NHL is a disease with tremendous heterogeneity that does not spread through contiguous lymph nodes and that often involves extranodal sites. As a result of these clinical differences between Hodgkin lymphoma and NHL, Ann Arbor stage correlates poorly with prognosis.

8 This lack of accuracy with the Ann Arbor staging system in NHL has led

to several international projects to develop prognostic models for the most common types of NHLs—DLBCLs and follicular lymphomas. The International Non-Hodgkin Lymphoma Prognostic Factors Project was based on more than 2,000 patients with diffuse aggressive lymphomas treated with an anthracycline-containing combination chemotherapy regimen in the United States, Europe, and Canada.[53] The Project identified five risk factors that correlated with low complete response rate to chemotherapy and poor survival, and a subgroup analysis found three specific risk factors correlated with low complete response rate to chemotherapy and poor survival in patients 60 years old and above (**Table 149-7**). It is unclear whether the effect of serum LDH level is related to a tumor or a host event. LDH likely measures cellular catabolism (the enzyme is released from injured cells) or the product of tumor burden and proliferation. Because each of the factors has about the same impact (eg, relative risk) on prognosis, the number of adverse risk factors is summed to provide the IPI. Patients could therefore have a score of 0 to 5. For patients older than or equal to 60 years old, a simplified IPI score can be determined based on Ann Arbor stage, serum LDH level, and performance status.

TABLE 149-7 Risk Factors According to the International Non-Hodgkin Lymphoma Prognostic Factors Project

All Patients	Patients ≤60 Years of Age
Age >60 years	Abnormal LDH level
Abnormal LDH level	Performance status ≥2
Performance status ≥2	Ann Arbor stage III or IV
Ann Arbor stage III or IV	
Extranodal involvement ≥2 sites	

LDH, lactic dehydrogenase.

Data from Reference 54.

It is important to periodically reevaluate prognostic factors as prognosis improves as a result of more effective therapy. The IPI was based on patients treated from 1982 to 1987 with anthracycline-based combination chemotherapy; none of the patients received rituximab. Hence, an enhanced IPI (NCCN-IPI) was developed to stratify newly diagnosed DLBCL patients based on their clinical features (age, normalized LDH, sites of involvement, Ann Arbor and ECOG performance status) in the rituximab era.[55] Through an independent validation, the NCCN-IPI was shown to discriminate patients in the low- and high-risk subgroups better than the IPI.

Although the IPI is often used to predict prognosis in patients with other NHL subtypes, the IPI has several shortcomings when applied to patients with indolent lymphomas. Because only patients with diffuse aggressive lymphomas were used to develop the IPI system, some important prognostic factors may have been missed. Furthermore, the IPI system has limited discriminating power in follicular lymphoma because only about 10% of patients are categorized as high-risk in the IPI system. To address these concerns, an international cooperative study was designed to develop a prognostic model similar to the IPI in patients with follicular lymphoma. The results of that study, which was based on more than 4,000 patients with follicular lymphoma diagnosed between 1985 and 1992, identified five factors that were correlated with poor survival (**Table 149-8**).[56] Analogous to the IPI, the number of adverse risk factors is summed to provide the Follicular Lymphoma International Prognostic Index (FLIPI). FLIPI appeared to have higher discriminating power among groups as compared with the IPI system. Table 149-8 shows the number of risk factors stratified using FLIPI. The survival data from FLIPI, however, may not reflect current treatment results because none of the patients in the cohort used to derive the FLIPI were treated with rituximab. In an updated prognostic model (FLIPI-2) derived from patients with newly diagnosed follicular lymphoma treated with rituximab-containing chemoimmunotherapy regimens, age older than 60 years, low hemoglobin level (<12 g/dL [120 g/L; 7.45 mmol/L]), longest diameter of the largest lymph node more than 6 cm, abnormal β_2-microglobulin levels and bone marrow involvement were identified as adverse risk factors. FLIPI-2 was highly predictive of treatment outcomes and separated patients into three distinct risk groups: low-risk (0 factors), intermediate-risk (1 or 2 factors), and high-risk (≥3 factors). Three-year progression-free survival was 91%, 69%, and 51% and overall survival was 99%, 96%, and 84% in low-, intermediate-, and high-risk patients, respectively.[57]

TABLE 149-8 Risk Factors According to the Follicular Lymphoma International Prognostic Index

All Patients	
Age >60 years	
Ann Arbor stage III or IV	
Number of nodal sites ≥5	
Abnormal lactate dehydrogenase level	
Hemoglobin <12 g/dL (120 g/L; 7.45 mmol/L)	
Risk Group (% of Patients)	**Number of Risk Factors**
Low (36)	0-1
Intermediate (37)	2
High (27)	≥3

Although IPI and FLIPI are clinically useful tools to estimate prognosis, the factors used to calculate these scores probably represent clinical surrogates for the biologic heterogeneity among NHLs and many researchers are interested in determining the prognostic importance of certain phenotypic and molecular characteristics of NHLs. For example, molecular markers of apoptosis, cell-cycle regulation, cell lineage, and cell proliferation are being evaluated as potentially clinically useful prognostic factors.[58]

Gene expression profiling with microarrays may also correlate with survival. Using gene expression profiling, investigators identified at least two molecularly distinct forms of DLBCLs based on gene expression patterns indicative of different stages of B-cell differentiation: germinal center B-cell–like (GCB) and activated B-cell–like (ABC).[58,59] The GCB subtype of DLBCL probably arises from normal germinal center B-cells while the ABC subtype may arise from postgerminal center B-cells. Many oncogenic pathways are different for the GCB and ABC subtypes, and these differences may lead to the development of targeted therapies for each subtype.[58] Patients with the germinal center B-cell profile had significantly better overall survival independent of IPI score after treatment with cyclophosphamide, doxorubicin [hydroxydaunorubicin], vincristine (Oncovin®), prednisone (CHOP) or CHOP-like chemotherapy. In a published study of patients with DLBCL treated with either CHOP or rituximab and CHOP (R-CHOP), Lenz et al identified several gene expressions signatures that predicted survival in both CHOP and R-CHOP cohorts: GCB, stromal-1, and stromal-2.[60] The GCB and stromal-1 signatures were associated with a favorable prognosis while the stromal-2 signature was associated with an unfavorable prognosis. The stromal-1 signature reflects extracellular matrix deposition and

histiocytic infiltration whereas the stromal-2 signature reflects tumor blood vessel density. It is speculated that DLBCLs that express the stromal-2 signature may respond to antiangiogenic agents.

Another important but rare molecular subtype is double-hit NHL, defined as the existence of both MYC gene arrangement and t(14;18) BCL2 translocation.[61] Patients with double-hit NHL have very poor prognosis, with a median overall survival that is 4 to 6 months even with highly aggressive chemotherapy.[62] Some lymphoma experts suggest that patients with double-hit NHL should be treated with regimens that are more dose-intensive.[58] Besides double-hit NHL, a more commonly observed (accounts for 20%-30% of DLBCL cases) molecular subtype is double-expressor NHL is recently being recognized as an adverse prognostic indicator. Unlike double-hit NHL, patients with double-expressor lymphoma co-express MYC and BCL2 proteins without underlying chromosomal rearrangements. Double-expressor NHL is associated with a worse prognosis than other DLBCLs, but it has slightly better outcomes than double-hit NHLs. More intensive treatment regimens are also being evaluated in patients with double-expressor NHL.[54]

Two molecularly distinct profiles of follicular lymphoma have been identified. The first included genes encoding for T-cell markers and genes highly expressed in macrophages, and the second included genes that are preferentially expressed in macrophages, dendritic cells, or both.[63] Patients with the first molecular signature had a more favorable outcome than those with the second signature. These results suggest that molecular classification of NHL on the basis of gene expression may allow identification of clinically significant subtypes.

TREATMENT

Non-Hodgkin Lymphoma

Desired Outcomes

The primary goals in the treatment of NHL are to relieve symptoms, cure the patient of the disease whenever possible, and minimize the risk of serious toxicities. The treatment strategy depends on many factors, including the patient’s age, concomitant disease, disease type, stage of disease, site of disease, and patient preference.

General Approach

9 Historically, both the clinical behavior and degree of aggressiveness are used to describe NHLs. Indolent lymphomas, which make up about 25% to 40% of all NHLs, are characterized by their slow-growth behavior. Patients with an indolent lymphoma usually have a relatively long survival (measured in years), with or without aggressive chemotherapy. Although these lymphomas respond to a wide range of therapeutic approaches, there is no convincing evidence of a survival plateau, which indicates that patients are rarely cured of their disease. In contrast, aggressive lymphomas, which make up about 60% to 75% of all NHLs, are characterized by rapid growth rate and short survival (measured in weeks to months), if appropriate therapy is not initiated. Despite their more aggressive nature, many patients with aggressive lymphomas who respond to chemotherapy can experience prolonged disease-free survival and some are cured of their disease. Therefore, the terminology for the NHLs represents a paradox, where "indolent" is bad and "aggressive" is good in terms of the likelihood for cure.

Therapeutic approaches to NHL include radiation therapy, chemotherapy, and biologic or targeted agents. The role of radiation therapy in the treatment of NHL differs from its role in the treatment of Hodgkin lymphoma. Although the disease responds to radiation therapy, only a small percentage of patients with NHL present with truly localized disease that can be treated with local or regional radiation therapy. Radiation therapy is used more commonly in advanced disease, primarily as a palliative measure to control local bulky disease.

Effective chemotherapy for NHL ranges from single-agent therapy in indolent lymphomas to aggressive, complex chemotherapy regimens in aggressive lymphomas. The most active agents used in the treatment of NHL include the alkylating agents (eg, cyclophosphamide, chlorambucil), bleomycin, doxorubicin, purine analogs, etoposide, methotrexate, vincristine, and corticosteroids (eg, prednisone, dexamethasone). The most aggressive chemotherapy approaches are dose-dense chemotherapy or high-dose chemotherapy followed by autologous or allogeneic HSCT.

B-cell lymphomas have served as a model for immunotherapy with monoclonal antibodies for more than 20 years, beginning with the successful use of custom-made monoclonal antibodies targeted against the idiotype present on the patient's cancer cells.[64] These encouraging results lead to the development of monoclonal antibodies against a more generic target, a molecule on the surface of B cells that would be present on tumor cells. One potential target, the CD20

molecule, is present only on cells in the B-lymphocyte lineage. It is expressed on the surface of both normal and malignant B cells, but not on other normal tissues. Rituximab (Rituxan®) is a chimeric monoclonal antibody directed at the CD20 molecule. Its antitumor activity is mediated through complement-dependent cytotoxicity, antibody-dependent cytotoxicity, and induction of apoptosis.[64] With the availability of monoclonal antibodies and radioimmunoconjugates for the therapy of lymphoma, nearly all patients with NHL will receive one or more biologic agents during the course of their disease.

Objective response to therapy for NHL should be defined according to the Lugano classification. The Lugano classification was established in the 12th International Conference on Malignant Lymphoma 2013 where the previous International Working Group Guidelines for assessing response to lymphoma treatment was revised. The revised guidelines describe criteria for response (eg, complete response, partial response, and stable disease) and emphasize the role of PET-CT and CT in the assessment of response in lymphoma treatment. PET-CT is recommended in FDG-avid histologies such as Hodgkin lymphoma, DLBCL and follicular lymphoma while CT is advised for other lymphomas with low or variable FDG-avidity.[52]

Appropriate therapy for NHL depends on the patient's age, histologic type, stage of disease, site of disease, presence of adverse prognostic factors (as measured by IPI or FLIPI score), and patient preferences. In general, treatment of lymphoma can be divided into limited disease and advanced disease. Limited disease includes those patients with localized disease (Ann Arbor stages I and II). Advanced disease is defined as all Ann Arbor stage III or IV patients, and also frequently includes Ann Arbor stage II patients with poor prognostic features (see Tables 149-6 and 149-7).[53,56]

The following section discusses the clinical characteristics and therapy of the most common disease entities.

Follicular Lymphomas

The combined group of follicular lymphomas makes up the second most common histologic type of NHL in the United States, comprising about 20% of all NHLs worldwide and up to 70% of indolent lymphomas reported in American and European clinical trials.[47] The WHO classification includes criteria for grading follicular lymphoma based on the number of centroblasts per high-power field: grade 1 to 2 (0-15 centroblasts/high-power field) and grade 3 (>15 centroblasts/high-power field).[6] The clinical behavior and treatment

outcome of grades 1 and 2 follicular lymphoma are similar, and they are usually treated as indolent lymphomas. The current WHO classification subdivides grade 3 follicular lymphoma into grades 3A and 3B. The WHO recommends that grade 3A follicular lymphoma should be treated in the same way as low-grade follicular lymphoma, whereas grade 3B should be treated in the same way as an aggressive lymphoma.

Follicular lymphomas tend to occur in older adults, with a slight female predominance (see Table 149-6). Most patients have advanced disease at diagnosis, but about 25% to 33% of patients have localized disease (clinical stage I or II) at diagnosis.[65] Extranodal disease, bulky disease, and B symptoms are uncommon features at diagnosis. Most patients with follicular lymphoma have the chromosomal translocation t(14;18) at the time of diagnosis.

The clinical course is generally indolent, with median survivals of 8 to 10 years. But the natural history of follicular lymphoma can be unpredictable. Spontaneous regression of objective disease has been noted in as many as 20% to 30% of patients.[66] There is also a high conversion rate of follicular lymphoma to a more aggressive histology over time that steadily increases after diagnosis and reaches about 30% at 10 years.[67] At autopsy, most patients with follicular lymphoma have some evidence of DLBCL. Patients with transformed indolent lymphoma should be treated in the same way as patients with an aggressive lymphoma.

Most patients have dramatic responses to initial therapy, and their disease course is characterized by multiple relapses, with responses to salvage therapy becoming progressively shorter after every relapse, eventually leading to death from disease-related causes. This pattern of constant relapses over time without evidence of a survival plateau and the failure of randomized controlled trials to show a survival benefit with aggressive chemotherapy led to the conclusion that therapy does not prolong overall survival and patients are not cured of their disease. However, the use of biologic agents, particularly rituximab, has changed the natural history of the follicular lymphoma. In a study of patients enrolled in Southwest Oncology Group (SWOG) trials over a period of more than 20 years, patients treated with CHOP and a monoclonal antibody had a significantly longer 4-year overall survival than those treated with CHOP alone (91% vs 69%).[68] Similar results were reported in patients treated over a 30-year period at the MD Anderson Cancer Center.[69] That study also showed an apparent plateau in the failure-free survival curve.

Certain subsets of patients with follicular lymphoma have a much better or worse prognosis. Some studies suggest that the natural history of follicular large

cell lymphoma (ie, grade 3 follicular lymphoma) is similar to that of other aggressive lymphomas and that treatment with intensive combination chemotherapy regimens may result in long-term disease-free survival, including a possible plateau in the survival curve.[47] The recent development of the FLIPI prognostic model should help clinicians to identify patients in different prognostic groups based on disease characteristics at the time of diagnosis.[56] Patients who are predicted to have a poor prognosis (ie, high-risk) could then be offered aggressive or experimental therapy, while those who are predicted to have a good prognosis (ie, low-risk) would be treated with standard therapy, avoiding unnecessary toxicity.

Treatment of Localized Disease (Stages I and II)

Radiation therapy is the standard treatment for early stage follicular lymphoma. Involved-field, extended-field, and total nodal irradiation have been used. Carefully staged patients with either stage I or contiguous stage II disease treated with radiation therapy alone can achieve disease-free survival rates of 40% to 50% and overall survival rates of 60% to 70% at 10 years.[47] Late relapses are uncommon; only 10% of patients who reached 10 years without relapse subsequently experienced a recurrence.

Chemotherapy is not usually given in most patients with localized follicular lymphoma, but it may be helpful in some patients with high-risk stage II disease (eg, multiple sites of involvement or bulky disease).[70]

10 About 40% to 60% of patients with clinical stage I or II follicular lymphoma are cured of their disease with radiation therapy alone.[51] Most centers use radiation at a dose of 30 to 40 Gy (3,000-4,000 rad) to either involved (ie, local) or regional fields, which would consist of irradiation to the involved nodal region plus one additional uninvolved region on each side of the involved nodes. Extended-field irradiation is not usually used because of the absence of a survival benefit and possible increased risk of secondary malignancies. In addition, previous use of extended-field irradiation compromises the ability of that patient to receive subsequent chemotherapy. The current NCCN guideline states that locoregional radiation therapy is preferred for most patients with early stage follicular lymphoma.[51] Anti-CD20 antibodies, in combination with chemotherapy, is also listed as an option.

Treatment of Advanced Disease (Stages II Bulky, III, and IV)

The management of stages II Bulky, III, and IV indolent lymphomas remains controversial because until recently, no therapeutic approaches had been shown to prolong overall survival despite the high complete remission rates to initial therapy. However, the results of recently published studies suggest that the initial use of biologic therapy such as rituximab is associated with longer overall survival.[68,69] More than 80% of patients with stage III or IV follicular lymphoma are alive at 5 years, and the median survival ranges between 7 and 10 years.

Therapeutic options for these patients are diverse and include watchful waiting, radiation therapy, single-agent chemotherapy, combination chemotherapy, biologic or targeted therapy, radioimmunotherapy, and combined-modality therapy.[51] Although complete remission can be achieved in 50% to 80% of patients with various treatments, the median time to relapse is usually only 18 to 36 months. About 20% of patients who have a complete response remain in remission for longer than 10 years. After relapse, patients are retreated, and high remission rates can be achieved. Unfortunately, response rates and duration of response both decrease with each retreatment.

Several different approaches can be used to treat follicular lymphoma. Carefully selected patients may receive no initial therapy followed by single-agent chemotherapy, anti-CD20 therapy, or radiation therapy when treatment is needed. Candidates for the conservative approach are usually older, asymptomatic, and have minimal tumor burden. Patients with symptoms, extensive extranodal involvement, bulky disease, cytopenia due to bone marrow involvement, or impaired end-organ function at the time of diagnosis are not candidates for conservative treatment. Alternatively, patients can be treated aggressively with combination chemotherapy with anti-CD20 therapy early in the disease course. Both conservative and aggressive approaches are listed as possible options in the current NCCN guideline, but the guideline recommends that initial therapy should include anti-CD20 therapy unless contraindicated.[51] Patients who respond to induction therapy may receive maintenance therapy with single-agent anti-CD20 therapy.

At the time of relapse, many of the same treatment options are available, and the following factors must be considered: age, symptomatic status of the patient, tumor burden, rate of regrowth (based on previous assessment of active disease sites), presence or absence of characteristics suggesting transformation or biologic progression, prior therapy, degree and duration of response to prior therapy, availability of clinical trials, and patient preferences.[51]

Watch-and-Wait Because there are no convincing data that standard treatment

approaches have improved survival, some clinicians have adopted a “watch-and-wait” approach for asymptomatic patients where therapy is delayed until the patient experiences systemic symptoms or disease progression such as rapidly progressive or bulky adenopathy, anemia, thrombocytopenia, or disease in threatening sites such as the orbit or spinal cord.[70] In a randomized study of asymptomatic patients with indolent lymphomas (mostly follicular), patients who underwent watchful waiting had similar cause-specific and overall survival as compared with those who received immediate chlorambucil.[71] With a median length of follow-up of 16 years, about 17% of patients who were randomized to the watchful waiting group died of other causes without receiving chemotherapy and an additional 9% are alive and have not yet had chemotherapy. Due to the frequent use of rituximab in current clinical practice, a recent study has evaluated whether the use of the “watch-and-wait” approach is more effective than the use of rituximab to delay the need for chemotherapy or radiotherapy in patients with advanced stage, low tumor burden follicular lymphoma. Immediate treatment with rituximab significantly delays disease progression and the time until chemotherapy or radiotherapy compared with a watchful waiting approach.[71] However, an overall survival advantage has not been demonstrated with this approach.

As described above, patients with follicular lymphoma who are followed without therapy sometimes have spontaneous regressions that can be complete while the disease in other patients can convert to a more aggressive histology. Current guidelines suggest that “watch and wait” is an acceptable initial management approach for patients with low-grade follicular lymphoma who are asymptomatic, have no threatened end-organ function, do not have cytopenias secondary to lymphoma, or lack bulky disease, and in whom the disease is not steadily progressing. If the watchful waiting approach is chosen, the patient should be evaluated at least every 3 to 6 months for 5 years and then annually, so that intervention can occur before serious problems occur.[51]

Chemotherapy Oral alkylating agents, given either alone or combined with prednisone, have been the mainstay of treatment for follicular lymphoma. More intensive chemotherapy has not been shown to improve patient outcome. In a randomized trial of oral chlorambucil, oral cyclophosphamide, or CVP in patients with indolent lymphoma, no significant difference in overall survival or freedom-from-relapse between the three groups was observed.[66] The dosage of single-agent chlorambucil or cyclophosphamide is usually adjusted to maintain a platelet count above 100,000 cells/mm^3 (100×10^9/L) and a white blood cell

count above 3,000 cells/mm^3 (3×10^9/L). Although single-agent alkylating agents have a high initial complete remission rate, the time required to achieve a complete response is slow (median time is 9-12 months). Complete responses occur more rapidly with combination chemotherapy, particularly with doxorubicin-containing regimens. Many clinicians will therefore give CHOP or CHOP-like chemotherapy when a rapid response is necessary. The development of the CHOP regimen is described in more detail later in this chapter. **Table 149-9** shows the CHOP regimen that is widely used in the treatment of NHL. In those who achieve a complete response, the duration of response is relatively short (about 2.5 years). Maintenance therapy with chemotherapy provides no additional benefit. After the "best" response is achieved, many experts will discontinue therapy and observe.

TABLE 149-9 CHOP Regimen

Drug	Dose	Route	Treatment Days
Cyclophosphamide	750 mg/m^2	IV	1
Doxorubicin	50 mg/m^2	IV	1
Vincristine*	1.4 mg/m^2	IV	1
Prednisone	100 mg	Oral	1-5
One cycle is 21 days			

*Vincristine dose is typically capped at 2 mg.

Another name for doxorubicin is hydroxydaunorubicin.

The advantages of oral chlorambucil are no hair loss, little or no nausea, and minimal myelosuppression. Because of its mild side effects profile, oral chlorambucil is usually recommended for older patients who are minimally symptomatic or who have other comorbidities. There are some concerns with the risk of secondary acute leukemia in patients receiving continuous exposure to alkylating agents.

Rituximab The approval of rituximab is arguably the most important recent development in the treatment of NHL. Its initial approval in 1997 was based on an open-label multicenter study that enrolled 166 patients with relapsed or recurrent indolent lymphoma.[72] Rituximab, given IV at a dose of 375 mg/m^2 weekly for 4 weeks, resulted in an overall response of 48% (complete response: 6%, partial response: 42%). Median time to progression for responders was 13.2 months and median duration of response was 11.6 months. Other studies of single-agent rituximab in patients with relapsed or refractory indolent NHL have

reported overall response rates of 40% to 60% and complete response rates of 5% to 10%.[73]

Based on the activity of rituximab in relapsed or refractory patients, it is currently being used as first-line therapy, either alone or in combination with chemotherapy.[73] When given as a single agent to patients with previously untreated indolent NHL, the overall response rate is 60% to 70% and the complete response rate is 20% to 30%. It is interesting to note that many of these patients remain in molecular remission (ie, polymerase chain reaction—negative) at 12 months. Single-agent rituximab is listed as an acceptable option for first-line therapy of follicular lymphoma, particularly for patients who cannot tolerate more intensive chemotherapy regimens.[51]

The rationale for the use of rituximab in combination with conventional agents is based on clinical activity of both agents/regimens, non–cross-resistant mechanisms of action, non-overlapping toxicities, and synergistic antitumor activity in vitro. In a meta-analysis of all randomized controlled trials, patients with indolent lymphoma treated with rituximab and chemotherapy had a significantly higher overall response rate and reduced risk of treatment failure (hazard ratio [HR] 0.62) and death (HR 0.65).[74] Rituximab is FDA approved for first-line therapy for follicular lymphoma in combination with chemotherapy.

In patients who respond to rituximab, either alone or combined with chemotherapy, maintenance therapy with single-agent rituximab is often given to prolong the duration of remission. Rituximab is FDA approved as single-agent maintenance therapy in patients achieving a complete or partial response following induction chemotherapy. The FDA approval was based on a randomized controlled trial in previously untreated patients with advanced stage follicular lymphoma treated with maintenance rituximab after CVP chemotherapy.[75] After a median follow-up of 11.5 years in the E1496 study, patients with indolent lymphoma receiving maintenance rituximab had longer median progression-free survival than patients on observation (4.8 vs 1.3 year; HR 0.49, $P < 0.0001$). However, no significant difference in 10-year overall survival between maintenance rituximab and the observation group was observed (67% vs 59%; HR 0.91, $P = 0.69$).[76] Maintenance rituximab is expensive and may be associated with adverse effects, including an increased risk of grades 3 or 4 infections. The NCCN guideline lists maintenance therapy with rituximab (one dose every 8 weeks for up to 2 years) as an option following first-line therapy for patients initially presenting with high tumor burden.[51]

Rituximab maintenance following second-line therapy has also been evaluated in patients with relapsed or refractory disease. Two randomized trials

have demonstrated a progression-free survival advantage with rituximab maintenance over observation for patients treated with induction chemotherapy.[77,78] It is important to note that patients who develop progressive disease during or within 6 months of first-line maintenance rituximab will likely experience little, if any, benefit from maintenance therapy in the second-line setting. The NCCN guideline recommends optional maintenance therapy with rituximab (one dose every 12 weeks for 2 years) for patients who are in remission after second-line therapy.[51]

Most of the adverse effects of rituximab are infusion-related, particularly after the first intravenous infusion, and consist of fever, chills, respiratory symptoms, fatigue, headache, pruritus, and angioedema. Premedication with oral acetaminophen 650 mg and diphenhydramine 50 mg is usually given 30 minutes before rituximab infusion. Duration of infusions may take up to 5 hours. The package insert recommends a step-up infusion rate of rituximab to decrease the risk of infusion-related infusion. Studies have demonstrated that rapid infusion of rituximab (infused over 90 minutes) is feasible in patients who tolerate their first cycle of rituximab without increasing the risk of infusion-related reactions.[79,80] The FDA has approved rapid infusions of rituximab, but they are not recommended in patients with clinically significant cardiovascular disease and high circulating lymphocyte counts (>5,000 cells/mm^3 [5×10^9/L]). Reactivation of hepatitis B has been reported in patients receiving chemotherapy, either alone or combined with rituximab.[81] Hepatitis B testing is recommended in patients who are considering rituximab therapy.[51]

In addition to the intravenous formulation of rituximab, a subcutaneous formulation of rituximab was recently approved. In this formulation, rituximab is combined with recombinant human hyaluronidase, which allows rituximab to be rapidly dispersed and absorbed after subcutaneous administration. Subcutaneous administration shortens the administration time to 5 to 7 minutes as compared to several hours for the intravenous infusion. FDA approval for the subcutaneous rituximab was based on multiple randomized clinical trials that demonstrated non-inferior rituximab blood concentrations and comparable efficacy and safety for the two formulations.[82,83] Premedication with acetaminophen and antihistamine is still required before each dose of subcutaneous rituximab, and subcutaneous administration should only be considered after patients receive at least one full dose of a rituximab product by intravenous infusion with no severe adverse reactions.

Obinutuzumab Obinutuzumab is a humanized anti-CD20 monoclonal antibody

developed to have lower complement-dependent cytotoxicity, but greater antibody-dependent cellular cytotoxicity, phagocytosis and direct B-cell killing than rituximab. Obinutuzumab has been evaluated in both first- and second-line settings. In the first-line trial, patients with previously untreated advanced stage follicular lymphoma were randomized to receive chemotherapy combined with either obinutuzumab or rituximab.[84,85] Patients who achieved a complete or partial remission received maintenance therapy with the same antibody. Although progression-free survival at 3 years favored patients receiving obinutuzumab, overall survival was similar in the two groups. Serious adverse events such as infusion-related events occurred more frequently in patients receiving obinutuzumab. In the second-line setting, patients with indolent lymphoma (majority being follicular lymphoma) refractory to rituximab were randomized to bendamustine, either alone or combined with obinutuzumab for 6 cycles, followed by maintenance obinutuzumab therapy for 2 years.[86,87] Patients in the obinutuzumab arm had increased progression-free and overall survival as compared to bendamustine monotherapy.

The NCCN guidelines list obinutuzumab, combined with chemotherapy, as first-line, second-line and subsequent therapy options for treatment of follicular lymphoma.[51] To reduce the risk of infusion reactions associated with obinutuzumab, patients should receive premedication including glucocorticoids, acetaminophen and antihistamines, as well as a step-up infusion rate. In addition, patients receiving obinutuzumab and bendamustine should receive prophylaxis for *Pneumocystis jiroveci* pneumonia and varicella zoster virus.

Radioimmunotherapy ^{90}Y-ibritumomab tiuxetan (Zevalin®) is an anti-CD20 radioimmunoconjugate which is currently available for patients with indolent NHLs.[88] It is a mouse antibody linked to yttrium-90$^{(90Y)}$, a radioisotope. Indolent lymphomas are known to be responsive to radiation therapy (ie, radiosensitive), and the rationale for radioimmunotherapy is that the antibody will act as a guided missile to deliver its payload (ie, radiation) to its target (ie, lymphoma cells that express the CD20 antigen). The specificity of the monoclonal antibody allows delivery of the radiation selectively to the tumor (and adjacent normal tissues).

^{90}Y-ibritumomab tiuxetan has shown activity in relapsed and refractory patients with indolent or transformed lymphomas.[88] In patients who respond to radioimmunotherapy, the duration of remission can be more than several years. Radioimmunotherapy is generally well-tolerated. The major acute toxicities with both radioimmunoconjugates are infusion-related reactions and

myelosuppression. The primary concern with radioimmunotherapy is the development of treatment-related myelodysplastic syndrome or acute myelogenous leukemia.

The decision to use radioimmunotherapy must be made carefully because of the complexity, risks, and costs of the treatment regimen. Because of safety concerns related to delivery of radiation to bone marrow, candidates for radioimmunotherapy usually have limited bone marrow involvement and adequate absolute neutrophil and platelet counts. Although medical oncologists usually select patients for therapy, the radioimmunotherapy regimen must be administered at a radiation oncology or nuclear medicine facility.

Bendamustine Bendamustine is an alkylating agent with structural similarities to both alkylating agents and purine analogs. The mechanism of action of bendamustine appears to be different from other alkylating agents and it does not show cross-resistance to other alkylating agents. When used as a single agent, bendamustine shows antitumor activity in relapsed or refractory indolent lymphomas. Overall and complete response rates of 70% to 80% and 30% to 35% have been reported, respectively, in phase II trials.[89] Two randomized, noninferiority studies have reported that bendamustine and rituximab (BR) is noninferior to R-CHOP for indolent lymphomas. In a randomized noninferiority phase III study of patients with advanced indolent lymphoma (with slightly over half follicular lymphoma patients), patients randomized to receive BR had longer median progression-free survival as compared to those in the R-CHOP group. In the subgroup analysis of patients with follicular lymphoma subtype, a significant benefit for progression-free survival was observed with BR versus R-CHOP.[90] In another study, BR was demonstrated to be noninferior to standard therapies (R-CHOP or R-CVP) for both overall (97% vs 91%) and complete response rate (31% vs 25%).[91] Both studies also reported that BR was associated with fewer infectious episodes and fewer hematological toxicities such as grade 3 to 4 leukopenia and neutropenia. BR was also associated with less peripheral neuropathy and alopecia.[90,91] However, dermatological toxicities, drug-related hypersensitivities and vomiting were more common with BR. Based on these results, BR, R-CHOP, and R-CVP are all listed as first-line therapy of follicular lymphoma (category 1).[51]

Fludarabine Fludarabine phosphate shows encouraging results in previously untreated and relapsed advanced follicular lymphoma. The mechanism of action is not well understood, but it accumulates in lymphocytes and is resistant to adenosine deaminase. In patients with relapsed or refractory indolent lymphoma,

single-agent fludarabine has an overall response rate of almost 50% and a complete response rate of 10% to 15%. Response rates are higher in previously untreated patients, with overall and complete response rates of 70% and almost 40%, respectively. The median time-to-progression is less than 6 months for relapsed disease and more than 12 months for previously untreated patients. Combination regimens with fludarabine have also been investigated. Fludarabine, cyclophosphamide, and mitoxantrone, given with or without rituximab, are examples of fludarabine-containing regimens that show encouraging results in patients with indolent lymphoma.[92]

Fludarabine does not usually cause nausea and vomiting or hair loss, but it is associated with cumulative and prolonged myelosuppression and profound immunosuppression, which increases the risk of opportunistic infections, such as fungal infections, Pneumocystis jiroveci pneumonia, and viral infections. Because the use of fludarabine-based regimens may impair stem cell mobilization and collection, some experts avoid fludarabine-based regimens for patients who are potential candidates for autologous HSCT.

Lenalidomide Lenalidomide is an immunomodulating agent that is currently indicated for the treatment of multiple myeloma and myelodysplastic syndromes. Emerging data suggest it has activity in indolent NHL that is comparable to chemotherapy. In the first-line setting, one phase III study compared rituximab and lenalidomide or rituximab and chemotherapy (R-CHOP, BR or R-CVP) in advanced stage follicular lymphoma. Patients received different lenalidomide doses and treatment duration (maximum duration of 18 cycles) depending on their response. Maintenance rituximab was given to all patients. Complete response rates at 120 weeks and 3-year progression-free survival were similar in both arms. Safety profiles, however, differed between the two treatment arms, with more patients in the chemotherapy and rituximab group experiencing grade 3 or 4 neutropenia. Patients receiving lenalidomide and rituximab experienced more grade 3 or 4 cutaneous reactions.[93]

The combination of rituximab and lenalidomide was compared to lenalidomide monotherapy in patients with recurrent follicular lymphoma. Compared to lenalidomide monotherapy, the combination had higher overall (53% vs 76%) and complete response rates (20% vs 39%, $P = 0.029$). The time-to-progression was also longer in the rituximab and lenalidomide group (2.0 vs 1.1 year, $P = 0.0023$). Commonly reported toxicities of lenalidomide include neutropenia, fatigue, and thrombosis.[94] The NCCN guidelines list rituximab-lenalidomide as a treatment option for first-line, second-line and subsequent therapy for treatment of follicular lymphoma.[51]

Phosphatidylinositol-3-Kinase (PI3K) Inhibitor PI3K inhibition reduces phosphatidylinositol 3,4,5-triphosphate (PIP_3), a messenger that affects pivotal cell function including cell proliferation, survival, and metabolism. Among the four isoforms of PI3K, PI3Kδ mediates B-cell receptor signaling and microenvironment support signals that promote the growth and survival of malignant B lymphocytes. Several PI3K inhibitors (idelalisib, copanlisib and duvelisib) are approved for treatment of relapsed and refractory follicular lymphoma. Idelalisib is an isoform-selective PI3K inhibitor and targets specifically at PI3Kδ, whereas copalisinb is a pan-class I PI3K inhibitor, predominantly targeting PI3Kα and PI3Kδ. On the other hand, duvelisib targets PIK3Kδ and PI3Kγ.

The use of PI3K inhibitors for follicular lymphoma is based on three Phase II studies. In one study, patients with relapsed or refractory indolent NHL received oral idelalisib 150 mg twice daily until disease progression. The overall response rate was 57% in patients with follicular lymphoma who had relapsed within 24 months of chemoimmunotherapy, with a median duration of response of 11.8 months.[95,96] Similar results were reported with copanlisib and duvelisib in patients with relapsed or refractory follicular lymphoma.[97,98] All of the PI3K inhibitors can cause severe neutropenia, diarrhea, infection, and pneumonia. Idelalisib is also associated with severe hepatotoxicity, severe diarrhea, colitis, and lung infection. Hypertension and hyperglycemia are more prominent with copanlisib because of its potent inhibition of PI3Kα. Severe skin infections have also been observed with copanlisib while duvelisib is associated with serious adverse events including infection and death. The NCCN guidelines list idealisib and copanlisib as treatment options for second-line therapy for patients with relapsed or refractory follicular lymphoma.[51]

Hematopoietic Stem Cell Transplantation High-dose chemotherapy, followed by autologous or allogeneic HSCT, is another option for patients with relapsed follicular lymphoma.[99] In patients who are transplanted at the time of initial treatment failure, 5-year event-free survival is about 40% to 50%. Although the rate of recurrence is lower after allogeneic HSCT as compared with autologous HSCT, that benefit is offset by increased treatment-related mortality after allogeneic HSCT. The presence of a survival plateau after allogeneic HSCT suggests that some patients may be cured of their disease.

A recent study has evaluated the role of HSCT in relapsed/refractory follicular lymphoma following disease relapse after prior rituximab-based therapy. Allogeneic HSCT was associated with increased risk of death on

analysis. Autologous HSCT, on the other hand, was associated with a 3-year overall survival rates of 87%.[100] The current NCCN guideline lists the use of autologous HSCT as an appropriate consolidative therapy for patients achieving second or third remission.[51] However, emerging data suggest that patients transplanted after their first or second relapse could achieve better outcomes than those who receive transplant later in their course of illness.[101]

Diffuse Large B-Cell Lymphoma

DLBCLs are the most common lymphoma in the International NHL Classification Project, accounting for about 30% of all NHLs.[65] DLBCLs are characterized by the presence of large cells, which are similar in size to or larger than tissue macrophages and usually more than twice the size of normal lymphocytes. The median age at the time of diagnosis is in the seventh decade, but DLBCL can affect individuals of all ages, from children to the elderly. Patients often present with a rapidly enlarging symptomatic mass, with B symptoms in about 30% to 40% of cases.[47] About 30% to 40% of patients with DLBCL present with extranodal disease; common sites include the head and neck, gastrointestinal tract, skin, bone, testis, and CNS. DLBCL is the most common type of diffuse aggressive lymphomas, which are characterized by an aggressive clinical behavior that leads to death within weeks to months if the tumor is not treated. Diffuse aggressive lymphomas are also sensitive to many chemotherapeutic agents, and some patients treated with chemotherapy can be cured of their disease.

Several factors correlate with response to chemotherapy and survival in patients with aggressive lymphoma. Because the IPI was originally developed based on patients with aggressive lymphoma, IPI score correlates with prognosis (see Table 149-7).[53] As described above, the revised NCCN-IPI score may more accurately predict prognosis in patients receiving rituximab-containing combination chemotherapy.[55]

Therapy of DLBCL is based on the Ann Arbor stage, IPI (or revised IPI) score, and other prognostic factors.[47] About one-half of patients present with localized (stage I or II) disease. However, many patients present with large bulky masses (ie, larger than 10 cm), and patients with bulky stage II disease are treated with the same approach used for patients with advanced disease (stage III or IV).

Treatment of Localized Disease (Stages I and II)

Before 1980, radiation therapy was the primary treatment for patients with localized DLBCL. Five-year disease-free survival with radiation therapy alone was about 50% and 20% in patients with stage I and stage II disease, respectively.[47] Randomized trials in the 1980s showed that radiation therapy followed by chemotherapy resulted in significantly longer disease-free and overall survival as compared with radiation therapy alone. Other studies reported excellent results with a short course of chemotherapy (three cycles) followed by involved-field radiotherapy or six to eight cycles of CHOP chemotherapy, with or without consolidation radiotherapy. With either of these approaches, 5-year progression-free survival was more than 90% for patients with stage I disease and about 70% for patients with stage II disease.[47]

Because the most effective approach was not clear, the SWOG performed a randomized trial that compared three cycles of CHOP and involved-field radiotherapy or six cycles of CHOP in patients with stage I and nonbulky stage II aggressive lymphoma.[102] Patients treated with three cycles of CHOP plus radiotherapy had significantly better 5-year progression-free (77% vs 64%) and overall (82% vs 72%) survival with a lower incidence of life-threatening toxicity than did patients treated with CHOP alone. However, with longer follow-up, the differences in progression-free or overall survival were no longer significant between the two arms.

In the rituximab era, most patients with localized disease are treated with either three to four cycles of R-CHOP followed by radiotherapy or six to eight cycles of R-CHOP with no radiotherapy. Although these two treatment options have not been directly compared in a randomized controlled trial, observational data shows similar 5-year overall survival in patients with stage I and II DLBCL. Patients who received the abbreviated course of R-CHOP plus radiotherapy experienced less acute toxicity and a lower risk of requiring second-line therapy.[103]

Based on these findings, three cycles of R-CHOP followed by locoregional radiation is recommended for patients with localized, nonbulky DLBCL. Alternatively, if the disease presents at sites where radiotherapy may lead to significant morbidity, six cycles of R-CHOP without radiation can be considered.[51]

Treatment of Advanced Disease (Bulky Stage II, Stages III and IV)

It has been known since the late 1970s that intensive combination chemotherapy

can cure some patients with disseminated DLBCL.[4] Initial studies with cyclophosphamide, vincristine (Oncovin®), and prednisone or prednisolone (COP; same as CVP) produced a plateau on the survival curve of just 10%, with a median survival of less than 1 year. Based on the activity of single-agent doxorubicin, McKelvey et al developed the CHOP regimen (see Table 149-9).[104] A few years later, a SWOG study showed that CHOP was more active than COP, and CHOP chemotherapy rapidly became the treatment of choice for patients with aggressive lymphomas.[105] Studies in larger numbers of patients showed that about 50% of patients had a complete remission to CHOP chemotherapy, and 50% to 75% of the patients who had a complete response (about one-third of all patients) experienced long-term disease-free survival and cure of their disease.

In an effort to improve these results, many investigators used several general approaches to develop second- and third-generation regimens in the 1980s.[47] Results of phase II trials suggested that these second- and third-generation regimens were more active than CHOP, with slightly higher complete response rates and improved disease-free survival rates. However, they were also more difficult to administer, more toxic, and more expensive. Based on these results, many oncologists adopted one of these second- or third-generation combination regimens as their standard regimen for patients with advanced aggressive lymphomas.

Many randomized studies have compared different combination regimens in patients with aggressive lymphoma. Although the results of these studies show that no one regimen is clearly superior to another, they demonstrate the superiority of anthracycline-containing regimens over those that do not contain an anthracycline. In the largest and most widely quoted study, the SWOG initiated a randomized trial in 1986 that compared CHOP to three of the most commonly used third-generation regimens in nearly 900 patients with bulky stage II, stage III, or stage IV aggressive NHL. At the time of the initial publication (median follow-up: 35 months), no differences in disease-free and overall survival were observed between the four groups.[106] Furthermore, no significant differences in disease-free or overall survival were observed in any subgroup of patients. But the risk of treatment-related mortality was higher in patients receiving one of the third-generation regimens. Extended follow-up of that trial shows that about 35% of patients who participated in that trial are probably cured of their disease, regardless of the initial combination chemotherapy regimen. Interestingly, the overall survival is about 10% higher than the disease-free survival, which probably reflects the effectiveness of

salvage high-dose chemotherapy with autologous HSCT (see section “Treatment of Refractory or Relapsed Disease” later in this chapter).

Based on the lack of survival benefit with the newer combination chemotherapy regimens, the less complicated and less expensive CHOP regimen was considered as the treatment of choice for most patients with DLBCL and other aggressive NHLs for many years. Even with CHOP chemotherapy, however, less than 50% of patients with DLBCL were cured of their disease and most patients who relapse after an initial response do so in the first 2 years. New treatment approaches were clearly needed.

Based on the encouraging results of R-CHOP in indolent lymphomas, several studies evaluated this combination in aggressive lymphomas. The first randomized controlled trial that established the efficacy of R-CHOP in advanced stage DLBCL showed that R-CHOP significantly increased complete response rates and overall survival in elderly (≥60 years old) patients as compared with CHOP alone (discussed in section “Treatment of Elderly Patients with Advanced Disease” later in this chapter).[107] Although the results of that study established R-CHOP as standard therapy in older patients, the role of R-CHOP in the treatment of younger patients was not clear. That issue was addressed in the MabThera International Trial, which enrolled younger (18-60 years old) patients with good-prognosis DLBCL.[108] Patients randomized to receive rituximab plus CHOP-like chemotherapy had significantly higher complete response rates (86% vs 68%) and longer 3-year event-free and overall survival (79% vs 59%; HR 0.44 and 93% vs 84%; HR 0.40, respectively). Recent updates from the study cohort indicate that the survival benefits of adding rituximab are sustained at 6 years with no increase in the incidence of secondary malignancies.[109] Based on these trial results, rituximab received FDA approval for first-line treatment in combination with CHOP or CHOP-like chemotherapy and R-CHOP is recommended for all patients with advanced stage DLBCL in the current NCCN guideline.[51]

Several studies attempted to improve treatment results by increasing chemotherapy dose (ie, dose-intensity), shortening the interval between chemotherapy cycles (ie, dose-density), or both. Because of the increased risk of severe neutropenia, these treatment approaches require growth factor support. Dose-dense chemotherapy, where the interval between cycles is shortened from 3 to 2 weeks, has been evaluated in randomized trials. Before the rituximab era, event-free and overall survival rates had been found to be longer with biweekly CHOP-14 compared to standard CHOP-21 every 21 days.[110] However, recent data shows that with the addition of rituximab, the survival benefit associated

with a dose-dense schedule is not superior to that of R-CHOP-21.[111,112] In one of the trials, which was conducted in elderly patients, the incidence of severe neutropenia was significantly higher despite an increased use of granulocyte colony-stimulating factor.[112]

Treatment outcomes for high-risk patients according to the IPI (or revised IPI) score are unsatisfactory. High-risk groups generally include all patients older than 60 years and those with an IPI score of 3 or more (or an age-adjusted IPI score of ≥2). Since progression-free survival is only about 50% in these high-risk patients treated with R-CHOP, other more aggressive treatments, preferably as part of a clinical trial, should be considered in these patients.

One approach is to give high-dose chemotherapy with autologous HSCT as intensive consolidation in high-risk patients with DLBCL who achieve a remission with standard chemotherapy. A recent published study suggested that this approach improves progression-free survival among patients with high-to-intermediate-risk or high-risk disease who had a response to CHOP-based chemotherapy.[113]

11 In summary, all patients with bulky stage II, stage III, or stage IV disease should be treated with R-CHOP or rituximab and CHOP-like chemotherapy until a complete response is achieved (usually four to six cycles).[51] The use of long-term maintenance therapy following a complete response has not been shown to improve overall survival. Treatment outcomes for high-risk patients according to the IPI (or revised IPI) score are unsatisfactory and alternative treatment approaches, preferably as part of a clinical trial, should be considered in these patients. High-dose chemotherapy with autologous HSCT should be considered in high-risk patients who respond to standard chemotherapy and are candidates for autologous HSCT.[51]

Treatment of Elderly Patients with Advanced Disease

More than one-half of patients with NHL are older than 60 years of age at diagnosis, and about one-third are older than age 70 years. The International Non-Hodgkin Lymphoma Prognostic Factors Project showed that patients older than 60 years of age had a significantly lower complete response rate and overall survival.[53] The reasons for the poorer outcome in elderly patients are not clear. Older patients do not tolerate intensive chemotherapy as well as younger patients, and some studies report that older patients have a higher risk of treatment-related mortality. As a result, many clinicians treat elderly patients with reduced dose or less-aggressive chemotherapy regimens. In general, these

less-intensive regimens have used anthracyclines with less cardiotoxicity than doxorubicin, have substituted mitoxantrone for doxorubicin, or have used short-duration weekly therapy.[114]

Over the past few years, several nonrandomized and randomized trials have evaluated different treatment approaches in older patients with aggressive NHL. The results of these studies suggest that carefully selected elderly patients with good performance status and without significant comorbidities can tolerate aggressive anthracycline-containing regimens as well as younger patients. These patients should be treated initially with full-dose R-CHOP or similar regimens; dosages can be reduced later if severe toxicity occurs. Hematopoietic growth factors may allow elderly patients to maintain dose intensity.[114]

The combination therapy, R-CHOP, has replaced CHOP as standard treatment for elderly patients with aggressive lymphoma, based on the results of the Groupe d'Etude des Lymphomes de l'Adulte (GELA) study.[107] In that study of 399 elderly patients with DLBCL, patients who were randomized to receive R-CHOP had a significantly higher complete response rate (76% vs 63%) and longer event-free and overall survival as compared with those who received CHOP. After 10 years of follow-up, progression-free survival was significantly longer among those who received R-CHOP than CHOP (36.5% vs 20.1%).[107] A higher risk of death or secondary cancer was not observed with the addition of rituximab to CHOP after 10 years of follow-up. In another randomized controlled trial conducted primarily in the United States (Eastern Cooperative Oncology Group 4494), elderly (≥60 years old) patients who received rituximab, either as induction or maintenance with CHOP chemotherapy, had significantly longer failure-free survival as compared with those not given rituximab during their treatment course.[115] Maintenance therapy with single-agent rituximab did not provide any additional benefit in patients who received R-CHOP as induction therapy. It is important to note that rituximab is given differently in the two studies. In the GELA study, rituximab is given on day 1 (the same day that cyclophosphamide, doxorubicin, and vincristine are administered) with each cycle of CHOP chemotherapy.[107] In the Eastern Cooperative Oncology Group 4494 study,[115] R-CHOP was modeled after the regimen developed by Czuczman et al: two doses of rituximab are given before cycle 1, and one dose is given before cycles 3, 5, and 7 (if administered).[116] In most NHL protocols and in clinical practice, rituximab is given on day 1 of each cycle of CHOP chemotherapy.

Previous trials have evaluated different drugs, including rituximab, as maintenance treatment in DLBCL but have failed to show survival benefits.

Lenalidomide as maintenance in elderly patients (60-80 years old) who had responded to R-CHOP was recently evaluated in the REMARC trial. Maintenance lenalidomide for 24 months extended progression-free survival, but did not improve overall survival and was associated with a higher premature discontinuation rate.[117] Based on these results, lenalidomide is an option if maintenance therapy is considered in elderly patients who have responded to treatment.[51]

Treatment of Refractory or Relapsed Disease

12 Although many patients with aggressive NHL experience long-term survival and cure with intensive chemotherapy, about 10% to 20% of patients fail to achieve a complete remission and about 20% to 30% of patients who do achieve a complete remission will subsequently relapse. Therefore, about 30% to 40% of all patients with aggressive NHL will require salvage therapy at some point during their disease course. Response to salvage therapy depends on the initial responsiveness of the tumor to chemotherapy. Patients who achieve an initial complete remission and then relapse generally have a better response to salvage therapy than those who are primarily or partially resistant to chemotherapy.[118]

Many conventional-dose salvage chemotherapy regimens have been used in patients with relapsed or refractory NHL. Many patients who respond to salvage therapy (ie, chemosensitive relapse) will then receive high-dose chemotherapy with autologous HSCT. In an effort to avoid cross-resistance, most salvage regimens incorporate drugs not used in the initial therapy. Some of the more commonly used salvage regimens include ICE, dexamethasone, cytarabine, cisplatin (DHAP), etoposide, methylprednisolone, cytarabine, cisplatin (ESHAP), and mesna, ifosfamide, mitoxantrone, etoposide (MINE), gemcitabine, dexamethasone, cisplatin (GDP) and no one regimen appears to be clearly superior to any other regimen.[119] With these salvage regimens, about 30% to 50% of patients achieve a complete response, with a median duration of remission of 1 to 2 years. Only about 5% to 10% of patients will have long-term disease-free survival.[118]

Rituximab is sometimes added to these salvage regimens. It is recommended, however, to exclude rituximab in second-line therapy if the patient’s disease is refractory or if the duration of remission is less than 6 months. One study (CORAL study) compared two salvage regimens (R-ICE and R-DHAP) in patients with relapsed or refractory DLBCL, followed by autologous HSCT.[120] No significant difference in 3-year event-free survival or overall survival was

observed between R-ICE and R-DHAP. However, patients who had received prior rituximab and experienced early relapse (defined as less than 12 months after diagnosis) had a poor prognosis. New treatment strategies are needed to improve the response rates of salvage regimens.

To improve the cure rate, many studies have evaluated high-dose chemotherapy with autologous HSCT as intensive consolidation therapy in patients who respond to salvage therapy. In the PARMA study, 215 patients with relapsed aggressive NHL who had a response to DHAP salvage therapy were randomized to receive either high-dose chemotherapy or continued DHAP therapy.[121] Patients who received high-dose chemotherapy had significantly longer 5-year disease-free survival (46% vs 12%) and overall survival (53% vs 32%) than those treated with conventional salvage therapy. Further analysis of that study showed that patients who relapsed within 12 months of their initial diagnosis were less likely to benefit from high-dose chemotherapy than patients who relapsed after 12 months. Based on a review of the available evidence, including the PARMA study, high-dose chemotherapy with autologous HSCT is considered to be the treatment of choice in younger patients with chemotherapy-sensitive relapse.[51] High-dose chemotherapy with autologous HSCT is not recommended in patients with untested or chemotherapy-refractory relapse.

In patients who have failed multiple lines of treatment, chimeric antigen receptor (CAR) T-cell therapy can be considered. CAR T-cell therapy is a type of adoptive immunotherapy where the patient’s own T-lymphocytes are collected, modified genetically in the laboratory to target antigens on malignant cells and then administered back to the patient by infusion.[122] Recently, two CAR T-cell therapies, tisagenlecleucel and axicabtagene ciloleucel, have been approved by the FDA for relapsed and refractory DLBCL after two or more lines of systemic treatment have failed. The approval of tisagenlecleucel and axicabtagene ciloleucel was based on high response rates reported in phase II trials JULIET and ZUMA-1 respectively, which compared favorably to historical data. In the JULIET trial, an overall best response rate of 53.1% was reported in 81 patients with refractory disease treated with tisagenlecleucel. In the ZUMA-1 trial, a response rate of 82% and 18-month overall survival of 52% was reported in 101 patients with refractory disease. Ongoing randomized trials are investigating the role of CAR-T cell therapy as first-line therapy or in combination with other immunotherapy agents in relapsed and refractory DLBCL.[123,124]

Both tisagenlecleucel and axicabtagene ciloleucel are associated with a high incidence of cytokine release syndrome, which is characterized by fever, hypoxia, and hypotension, and may require the use of vasopressors in severe

cases. Severe neurological toxicities such as encephalopathy and seizures can also occur, usually within days of T-cell infusion. While mild episodes can be symptomatically managed, moderate-to-severe grades of cytokine release syndrome and neurological toxicities may require immunosuppressants including tocilizumab and corticosteroids.[51,122,125]

Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is found in 6% of cases in the International Lymphoma Classification Project.[76] The chromosomal translocation t(11;14) occurs in most cases of MCL. MCL usually occurs in older adults, particularly in men, and most patients have advanced disease at the time of diagnosis (see Table 149-6). Extranodal involvement is found in about 90% of cases. The course of the disease is moderately aggressive; the median overall survival is about 3 years, with no evidence of a survival plateau.

Both aggressive and less-aggressive chemotherapy regimens have been evaluated in patients with disseminated MCL. One widely used aggressive combination regimen is cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with methotrexate and cytarabine (hyperCVAD) with or without rituximab. Overall response rates to these regimens is about 90%, with about two-thirds of patients achieving a complete response. Because MCL usually expresses CD20, rituximab, either alone or combined with CHOP and bendamustine, has been used with some success in patients with newly diagnosed and relapsed MCL.[90,126] In a phase III study, BR was compared to R-CHOP for first-line therapy in patients with advanced follicular, indolent and MCL. In the MCL subgroup, progression-free survival was higher with BR compared to R-CHOP, and it is associated with less hematological toxicities.[90,91]

Bortezomib (Velcade®), in combination with rituximab, cyclophosphamide, doxorubicin, and prednisolone, (VR-CAP, similar to R-CHOP regimen but with bortezomib replacing vincristine) is also indicated for newly-diagnosed MCL.[127] In a phase III randomized study, patients with newly diagnosed mantle-cell lymphoma who were ineligible or not considered for HSCT received R-CHOP or VR-CAP. After a median follow-up of 40 months, median progression-free survival was longer in the VR-CAP arm compared to R-CHOP (24.7 vs 14.4 mo; $P < 0.001$). Rates of neutropenia and thrombocytopenia were higher in the VR-CAP group.[127]

Despite the high response rates, MCL is not considered curable with standard chemotherapy. Consequently, younger patients who have an initial response to

chemotherapy often undergo autologous or allogeneic HSCT as consolidation therapy. The NCCN guidelines recommend that patients with advanced stage MCL be treated initially with rituximab and combination chemotherapy, followed by autologous HSCT as first-line consolidation therapy.[51] In patients who respond to autologous HSCT, maintenance rituximab can prolong both progression-free and overall survival.[128,129] Findings from a prospective study suggest that similar survival benefits are also associated with the use of maintenance rituximab after R-CHOP in elderly patients who are not candidates for autologous HSCT.[130]

Unfortunately, most patients with MCL eventually relapse and are treated with salvage therapy or enrolled in trials of investigational agents, some of which are directed at molecular targets. First-line regimens such as R-CHOP, VR-CAP, and bendamustine can be considered if they have not been previously given.[51] Bortezomib with or without rituximab is also approved for the treatment of MCL that has relapsed after at least one prior therapy.

Other agents approved for the treatment of relapsed or refractory MCL are the Bruton tyrosine kinase (BTK) inhibitors ibrutinib and acalabrutinib. In a phase III randomized trial, ibrutinib, compared to standard of care, had a higher response rate (72% vs 40%) and longer median duration of response (23.1 vs 6.3 mo) with a more tolerable side effect profile.[131] Addition of rituximab to ibrutinib was further evaluated in a phase II trial that reported a response rate of 88%, with a median duration of response of 46 months.[132] Based on these findings, current recommendations list ibrutinib with or without rituximab as a treatment option for relapsed MCL. Another recommended treatment for relapsed MCL is the new oral BTK inhibitor acalabrutinib, which was recently approved for relapsed and refractory MCL based on an overall response rate of 81% reported in a phase II trial.[133] The most common adverse effects of ibrutinib and acalabrutinib include diarrhea and fatigue. Since cytopenias are also common, complete blood counts should be monitored monthly while patients are on treatment. Bleeding may rarely occur during the first 6 months of BTK inhibitor therapy. Cases of new onset atrial fibrillation have also been reported.

Non-Hodgkin Lymphoma in Acquired Immune Deficiency Syndrome

The risk of NHL for patients with AIDS is increased more than 100-fold as

compared with the general population.[47] AIDS-related lymphoma arises as a consequence of long-term stimulation and proliferation of B lymphocytes from HIV and the reactivation of prior EBV infection as a consequence of HIV-induced immunosuppression. AIDS-related lymphoma usually occurs late in the course of HIV infection and is the cause of death in about 15% of HIV-infected individuals. Although HIV infects T cells, more than 95% of AIDS-related lymphomas are B-cell neoplasms. Most cases of AIDS-related lymphomas are classified as Burkitt or DLBCL.

The clinical presentation is similar to that observed in other immunocompromised states. Most patients with AIDS-related lymphoma present with B symptoms and have advanced stage (III or IV) disease at the time of diagnosis.[47] Involvement of extranodal sites is common. The clinical course of AIDS-related lymphoma is usually aggressive and has improved with the availability of highly active antiretroviral therapy (HAART). Improved survival has been observed, primarily in patients with DLBCL. Patients with AIDS-related lymphoma treated with intensive therapy have a median survival that is similar to the survival of patients with HIV-negative NHLs.[47] In the post-HAART era, many of the prognostic factors have also changed and only lymphoma-related factors such as the IPI remain as independent predictors of prognosis.

The treatment of patients with AIDS-associated lymphomas is difficult because the immunocompromised state of these patients increases their risk of significant toxicity as a consequence of myelosuppressive therapy. Except for primary CNS lymphoma, AIDS-related lymphoma is never considered truly localized and systemic chemotherapy is indicated. For patients with adequate immune function and without a history of an opportunistic infection, chemotherapy regimens similar to that used for aggressive lymphomas may be used.[51] However, many patients with AIDS-related lymphoma were previously treated with less-intensive regimens because of the increased risk of treatment-related toxicity. In the post-HAART era, however, most clinicians believe that standard doses of chemotherapy can be safely administered to patients who achieve a virologic response to HAART.

The results of treatment with standard chemotherapy regimens have been disappointing, particularly in patients with Burkitt lymphoma. In patients with DLBCL, the complete response rate with combination chemotherapy is about 40% to 50%, with 5-year overall survival rates of about 20% to 30%. Newer approaches, such as the dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) regimen developed at the

National Cancer Institute, appear promising. In a published pooled analysis that included patients with HIV-associated NHL treated in the R-CHOP or R-EPOCH, patients receiving R-EPOCH achieved an improvement of response and survival when compared against R-CHOP.[134] Treatment-associated deaths were more prominent among patients with very low $CD4^+$ counts.

The role of rituximab in the treatment of AIDS-related DLBCL is not clear. In a randomized trial of CHOP versus R-CHOP, no significant differences in progression-free and overall survival were observed. However, 14% of patients treated with R-CHOP died of treatment-related infection as compared with only 2% of those in the CHOP group. NCCN guidelines suggest omission of rituximab in patients at high risk for serious infectious complications (eg, patients on HAART with persistently low $CD4^+$ count).[51]

The optimal timing for HAART is not clear in patients with AIDS-related lymphoma. Current NCCN guidelines recommend the use of HAART and growth factor support along with full-dose chemotherapy regimen.[51] If HAART is given concurrently with chemotherapy, patients should be monitored closely for possible pharmacokinetic interactions between HAART and chemotherapy. Prophylactic antibiotics should be continued during chemotherapy and intrathecal chemotherapy should be administered to prevent CNS relapses.

EVALUATION OF THERAPEUTIC OUTCOMES

Hodgkin lymphoma and NHLs tend to respond well to radiation, chemotherapy, and biologic therapy. The goal of therapy for patients with Hodgkin lymphoma and aggressive NHL is long-term survival and cure. The therapeutic goal in patients with indolent NHLs is less clear because of the indolent nature of the disease and the lack of convincing evidence showing that therapy prolongs survival. Therapeutic responses should be evaluated based on physical examination, radiologic evidence, PET/CT scanning, and other positive findings at baseline. The current standard of care to evaluate response to treatment in Hodgkin lymphoma, follicular lymphoma, and DLBCL is PET imaging. As described earlier, the five-point scale is recommended for PET-CT interpretation where a Deauville score of 1, 2, or 3 (uptake less than or equivalent to liver) indicates complete response, even in the presence of a persistent mass. If salvage treatment is considered on the basis of a metabolically active residual mass, a biopsy or follow-up scan should be considered.[52] CT is advised for other lymphomas with low or variable FDG avidity. The rapidity of response to therapy in patients with indolent NHL depends on the choice of therapy.

Responses occur slowly with therapy with oral alkylating agents but occur much more rapidly with aggressive therapies such as combination chemotherapy with or without rituximab. Recent studies have also shown that early interim PET-CT scans may possess prognostic value in patients with advanced Hodgkin lymphoma.[51] In NHL, the prognostic value of interim PET-CT scans is less established and is currently not recommended to guide changes in therapy.[51] Surveillance scans after disease remission has been achieved are currently not advised, especially in Hodgkin lymphoma and DLBCL, but they can be considered in the event of equivocal findings at the end of treatment or in indolent lymphomas with residual disease.[52]

Postclass Engaged Learning Activity

Search the database of FDA-approved drug products and identify drugs that have been newly approved by the FDA in the last 12 months for lymphoma. Select one drug and compare the mechanism of action and its role in therapy with existing treatments that carry the same indication. Discuss advantages of this new drug over current therapies and challenges posed when using this new medication.

ABBREVIATIONS

ABC	activated B-cell–like
ABV	doxorubicin (Adriamycin®), bleomycin, vinblastine
ABVD	doxorubicin (Adriamycin®), bleomycin, vinblastine, and dacarbazine
ADC	antibody-drug conjugate
AIDS	acquired immune deficiency syndrome
BEACOPP	bleomycin, etoposide, doxorubicin (Adriamycin®), cyclophosphamide, vincristine (Oncovin®), procarbazine, and prednisone
BR	bendamustine and rituximab
BTK	Bruton tyrosine kinase
BVR	bendamustine, rituximab, and bortezomib
CEC	cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epirubicin, vincristine, procarbazine, vinblastine, bleomycin
CHOP	cyclophosphamide, doxorubicin, vincristine (Oncovin®), prednisone
COP	cyclophosphamide, vincristine (Oncovin®), and prednisone or prednisolone
COPP	cyclophosphamide, vincristine, procarbazine, and prednisone

CT	computed tomography
CVP	cyclophosphamide, vincristine, and prednisone
DHAP	dexamethasone, cytarabine, cisplatin
DLBCL	diffuse large B-cell lymphoma
EBV	Epstein-Barr virus
EPOCH	etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin
ESHAP	etoposide, methylprednisolone, cytarabine, cisplatin
ESR	erythrocyte sedimentation rate
FDA	Food and Drug Administration
FLIPI	Follicular Lymphoma International Prognostic Index
FN	fludarabine and mitoxantrone
FND	fludarabine, mitoxantrone, and dexamethasone
GCB	germinal center B-cell–like
GDP	gemcitabine, dexamethasone, cisplatin
GELA	Groupe d'Etude des Lymphomes de l'Adulte
GHSG	German Hodgkin Study Group
GVD	gemcitabine, vinorelbine, and pegylated liposomal doxorubicin
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	hazard ratio
HSCT	hematopoietic stem cell transplantationhyper
CVAD	cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with methotrexate and cytarabine
ICE	ifosfamide, carboplatin, and etoposide
IFRT	involved-field radiation
IPI	International Prognostic Index
IPS	International Prognostic Score
ISRT	involved-site radiation therapy
JAK–STAT	Janus kinase–signal transduction and transcription
KSHV	Kaposi sarcoma–associated herpesvirus
LDH	lactate dehydrogenase
MALT	mucosa-associated lymphoid tissue
MCL	mantle cell lymphoma
MINE	mesna, ifosfamide, mitoxantrone, etoposide
MMAE	monomethyl auristatin
EMOPP	mechlorethamine, vincristine, procarbazine, and prednisone
MOPPEBVCAD	mechlorethamine, vincristine, procarbazine, prednisone, epidoxorubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine
NCCN	National Comprehensive Cancer Network
NHL	non-Hodgkin lymphoma
NLPHL	nodular lymphocyte-predominant Hodgkin lymphoma
PET	positron emission tomography
PJP	Pneumocystis jiroveci pneumonia
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine (Oncovin®), prednisone
R-FCM	rituximab, fludarabine, cyclophosphamide, and mitoxantrone
REAL	Revised European-American Classification of Lymphoid Neoplasms
RICE	rituximab, ifosfamide, carboplatin, and etoposide
SEER	surveillance, epidemiology, and end results
SWOG	Southwest Oncology Group
WHO	World Health Organization

REFERENCES

1. Noone AM, Howlader N, Krapcho M, et al. SEER Cancer Statistics Review, 1975–2015. 2018. Available at: https://seer.cancer.gov/csr/1975_2015/. Accessed October 1, 2018.
2. Diehl V, Re D, Harris NL, Mauch PM. *Hodgkin's Lymphoma*. 10th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2015.
3. Townsend W, Linch D. Hodgkin's lymphoma in adults. *Lancet*. 2012;380:836–847.
4. Bartlett NL, Foyil KV. Hodgkin's lymphoma. In: Niederhuber JE, Armitage JO, Doroshow JH, Kastan MB, Tepper JE, eds. *Abeloff's Clinical Oncology*. 5th ed. New York: Churchill Livingstone; 2014.
5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69:7–34.
6. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127:2375–2390.
7. Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group. *J Clin Oncol*. 2014;32:3048–3058.
8. Mauch PM, Kalish LA, Kadin M, Coleman CN, Osteen R, Hellman S. Patterns of presentation of Hodgkin disease. Implications for etiology and pathogenesis. *Cancer*. 1993;71:2062–2071.
9. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. *N Engl J Med*. 1998;339:1506–1514.
10. Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. *N Engl J Med*. 1992;327:1478–1484.
11. Hodgson DC. Late effects in the era of modern therapy for Hodgkin lymphoma. *Hematology American Society of Hematology Education Program*. 2011;2011:323–329.
12. Hoppe BS, Flampouri S, Su Z, et al. Effective dose reduction to cardiac structures using protons compared with 3DCRT and IMRT in mediastinal

Hodgkin Lymphoma. *Int J Radiat Oncol Biol Phys*. 2012;84:449–455.

13. Paumier A, Ghalibafian M, Gilmore J, et al. Dosimetric benefits of intensity-modulated radiotherapy combined with the deep-inspiration breath-hold technique in patients with mediastinal Hodgkin's lymphoma. *Int J Radiat Oncol Biol Phys*. 2012;82:1522–1527.
14. Filippi AR, Ragona R, Fusella M, Botticella A, Fiandra C, Ricardi U. Changes in breast cancer risk associated with different volumes, doses, and techniques in female Hodgkin lymphoma patients treated with supra-diaphragmatic radiation therapy. *Pract Radiat Oncol*. 2013;3:216–222.
15. Bonadonna G, Zucali R, Monfardini S, De Lena M, Uslenghi C. Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, vinblastine, and imidazole carboxamide versus MOPP. *Cancer*. 1975;36:252–259.
16. Goldie JH, Coldman AJ, Gudauskas GA. Rationale for the use of alternating non-cross-resistant chemotherapy. *Cancer Treat Rep*. 1982;66:439–449.
17. Glick JH, Young ML, Harrington D, et al. MOPP/ABV hybrid chemotherapy for advanced Hodgkin's disease significantly improves failure-free and overall survival: The 8-year results of the intergroup trial. *J Clin Oncol*. 1998;16:19–26.
18. Duggan DB, Petroni GR, Johnson JL, et al. Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: Report of an intergroup trial. *J Clin Oncol*. 2003;21:607–614.
19. Horning SJ, Hoppe RT, Breslin S, Bartlett NL, Brown BW, Rosenberg SA. Stanford V and radiotherapy for locally extensive and advanced Hodgkin's disease: Mature results of a prospective clinical trial. *J Clin Oncol*. 2002;20:630–637.
20. Gobbi PG, Levis A, Chisesi T, et al. ABVD versus modified Stanford V versus MOPPEBVCAD with optional and limited radiotherapy in intermediate- and advanced-stage Hodgkin's lymphoma: Final results of a multicenter randomized trial by the Intergruppo Italiano Linfomi. *J Clin Oncol*. 2005;23:9198–9207.
21. Gordon LI, Hong F, Fisher RI, et al. Randomized phase III trial of ABVD versus Stanford V with or without radiation therapy in locally extensive and advanced-stage Hodgkin lymphoma: An intergroup study coordinated by the Eastern Cooperative Oncology Group (E2496). *J Clin Oncol*. 2013;31:684–691.

22. National Comprehensive Cancer Network. Hodgkin's Lymphoma (Version 2.2019). 2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf. Accessed July 30, 2019.
23. Advani RH, Hoppe RT, Baer D, et al. Efficacy of abbreviated Stanford V chemotherapy and involved-field radiotherapy in early-stage Hodgkin lymphoma: Mature results of the G4 trial. *Ann Oncol*. 2013;24:1044–1048.
24. Engert A, Plutschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med*. 2010;363:640–652.
25. Edwards-Bennett SM, Jacks LM, Moskowitz CH, et al. Stanford V program for locally extensive and advanced Hodgkin lymphoma: The Memorial Sloan-Kettering Cancer Center experience. *Ann Oncol*. 2010;21:574–581.
26. Hoskin PJ, Lowry L, Horwich A, et al. Randomized comparison of the Stanford V regimen and ABVD in the treatment of advanced Hodgkin's Lymphoma: United Kingdom National Cancer Research Institute Lymphoma Group Study ISRCTN 64141244. *J Clin Oncol*. 2009;27:5390–5396.
27. von Tresckow B, Plutschow A, Fuchs M, et al. Dose-intensification in early unfavorable Hodgkin's lymphoma: Final analysis of the German Hodgkin Study Group HD14 trial. *J Clin Oncol*. 2012;30:907–913.
28. Eich HT, Diehl V, Gorgen H, et al. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: Final analysis of the German Hodgkin Study Group HD11 trial. *J Clin Oncol*. 2010;28:4199–4206.
29. Diehl V, Franklin J, Pfreundschuh M, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. *N Engl J Med*. 2003;348:2386–2395.
30. Engert A, Diehl V, Franklin J, et al. Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 Years of follow-up of the GHSG HD9 study. *J Clin Oncol*. 2009;27:4548–4554.
31. Federico M, Luminari S, Iannitto E, et al. ABVD compared with BEACOPP compared with CEC for the initial treatment of patients with advanced Hodgkin's lymphoma: Results from the HD2000 Gruppo Italiano per lo Studio dei Linfomi Trial. *J Clin Oncol*. 2009;27:805–811.

32. Merli F, Luminari S, Gobbi PG, et al. Long-term results of the HD2000 trial comparing ABVD versus BEACOPP versus COPP-EBV-CAD in untreated patients with advanced Hodgkin lymphoma: A study by Fondazione Italiana Linfomi. *J Clin Oncol*. 2016;34:1175–1181.
33. Borchmann P, Haverkamp H, Diehl V, et al. Eight cycles of escalated-dose BEACOPP compared with four cycles of escalated-dose BEACOPP followed by four cycles of baseline-dose BEACOPP with or without radiotherapy in patients with advanced-stage Hodgkin's lymphoma: Final analysis of the HD12 trial of the German Hodgkin Study Group. *J Clin Oncol*. 2011;29:4234–4242.
34. Engert A, Haverkamp H, Kobe C, et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): A randomised, open-label, phase 3 non-inferiority trial. *Lancet*. 2012;379:1791–1799.
35. Connors JM, Jurczak W, Straus DJ, et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's Lymphoma. *N Engl J Med*. 2018;378:331–344.
36. Schulz H, Rehwald U, Morschhauser F, et al. Rituximab in relapsed lymphocyte-predominant Hodgkin lymphoma: Long-term results of a phase 2 trial by the German Hodgkin Lymphoma Study Group (GHSG). *Blood*. 2008;111:109–111.
37. Advani RH, Horning SJ, Hoppe RT, et al. Mature results of a phase II study of rituximab therapy for nodular lymphocyte-predominant Hodgkin lymphoma. *J Clin Oncol*. 2014;32:912–918.
38. Majhail NS, Weisdorf DJ, Defor TE, et al. Long-term results of autologous stem cell transplantation for primary refractory or relapsed Hodgkin's lymphoma. *Biol Blood Marrow Transplant*. 2006;12:1065–1072.
39. Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol*. 2012;30:2183–2189.
40. Chen R, Gopal AK, Smith SE, et al. Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma. *Blood*. 2016;128:1562–1566.
41. Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*.

2015;385:1853–1862.

42. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med*. 2015;372:311–319.
43. Younes A, Santoro A, Shipp M, et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: A multicentre, multicohort, single-arm phase 2 trial. *Lancet Oncol*. 2016;17:1283–1294.
44. Armand P, Shipp MA, Ribrag V, et al. Programmed death-1 blockade with pembrolizumab in patients with classical Hodgkin lymphoma after brentuximab vedotin failure. *J Clin Oncol*. 2016;34:3733–3739.
45. Chen R, Zinzani PL, Fanale MA, et al. Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. *J Clin Oncol*. 2017;35:2125–2132.
46. Herbaux C, Gauthier J, Brice P, et al. Efficacy and tolerability of nivolumab after allogeneic transplantation for relapsed Hodgkin lymphoma. *Blood*. 2017;129:2471–2478.
47. Armitage JO, Mauch PM, Harris NL, Coiggier B, Dalla-Favera R. *Non-Hodgkin Lymphomas*. 2nd ed. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins Health; 2010.
48. Roschewski MJ, Wilson WH, et al. Non-Hodgkin's lymphoma. In: Niederhuber JE, Armitage JO, Doroshow JH, eds., et al. *Abeloff's Clinical Oncology*. 5th ed. New York: Churchill Livingstone; 2014.
49. International Agency for Research on Cancer. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon: International Agency for Research on Cancer; 2008;Vol 2.
50. Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: Report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. *J Clin Oncol*. 1999;17:3835–3849.
51. National Comprehensive Cancer Network. B-Cell Lymphomas (Version 4.2019). 2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed July 30, 2019.
52. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano classification. *J Clin Oncol*.

2014;32:3059–3067.

53. International Non-Hodgkin's Lymphoma Prognostic Factors P. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med*. 1993;329:987–994.
54. Riedell PA, Smith SM. Double hit and double expressors in lymphoma: Definition and treatment. *Cancer*. 2018;124:4622–4632.
55. Zhou Z, Sehn LH, Rademaker AW, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. *Blood*. 2013;123:837–842.
56. Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. *Blood*. 2004;104:1258–1265.
57. Federico M, Bellei M, Marcheselli L, et al. Follicular lymphoma international prognostic index 2: A new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. *J Clin Oncol*. 2009;27:4555–4562.
58. Nowakowski GS, Czuczman MS. ABC, GCB, and double-hit diffuse large B-Cell lymphoma: Does subtype make a difference in therapy selection? *Am Soc Clin Oncol Educ Book*. 2015;35:e449–e457.
59. Rosenwald A, Wright G, Chan WC, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large B-cell lymphoma. *N Engl J Med*. 2002;346:1937–1947.
60. Lenz G, Wright G, Dave SS, et al. Stromal gene signatures in large B-cell lymphomas. *N Engl J Med*. 2008;359:2313–2323.
61. Aukema SM, Siebert R, Schuuring E, et al. Double-hit B-cell lymphomas. *Blood*. 2010;117:2319–2331.
62. Green TM, Young KH, Visco C, et al. Immunohistochemical double-hit score is a strong predictor of outcome in patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J Clin Oncol*. 2012;30:3460–3467.
63. Dave SS, Wright G, Tan B, et al. Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells. *N Engl J Med*. 2004;351:2159–2169.
64. Maloney DG. Anti-CD20 antibody therapy for B-cell lymphomas. *N Engl J Med*. 2012;366:2008–2016.
65. The Non-Hodgkin's Lymphoma Classification Project. A clinical evaluation of the International Lymphoma Study Group classification of

non-Hodgkin's lymphoma. *Blood*. 1997;89:3909–3918.

66. Horning SJ. Natural history of and therapy for the indolent non-Hodgkin's lymphomas. *Semin Oncol*. 1993;20(5 Suppl 5):75–88.
67. Bernstein SH, Burack WR. The incidence, natural history, biology, and treatment of transformed lymphomas. *Hematology American Society of Hematology Education Program*. 2009:532–541.
68. Fisher RI, LeBlanc M, Press OW, Maloney DG, Unger JM, Miller TP. New treatment options have changed the survival of patients with follicular lymphoma. *J Clin Oncol*. 2005;23:8447–8452.
69. Liu Q, Fayad L, Cabanillas F, et al. Improvement of overall and failure-free survival in stage IV follicular lymphoma: 25 Years of treatment experience at The University of Texas M.D. Anderson Cancer Center. *J Clin Oncol*. 2006;24:1582–1589.
70. Armitage JO, Longo DL. Is watch and wait still acceptable for patients with low-grade follicular lymphoma? *Blood*. 2016;127:2804–2808.
71. Ardeshna KM, Qian W, Smith P, et al. Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: An open-label randomised phase 3 trial. *Lancet Oncol*. 2014;15:424–435.
72. McLaughlin P, Grillo-López AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: Half of patients respond to a four-dose treatment program. *J Clin Oncol*. 1998;16:2825–2833.
73. Friedberg JW, Taylor MD, Cerhan JR, et al. Follicular lymphoma in the United States: First report of the national LymphoCare study. *J Clin Oncol*. 2009;27:1202–1208.
74. Schulz H, Bohlius JF, Trelle S, et al. Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: A systematic review and meta-analysis. *J Natl Cancer Inst*. 2007;99:706–714.
75. Hochster H, Weller E, Gascoyne RD, et al. Maintenance rituximab after cyclophosphamide, vincristine, and prednisone prolongs progression-free survival in advanced indolent lymphoma: Results of the randomized phase III ECOG1496 Study. *J Clin Oncol*. 2009;27:1607–1614.
76. Barta SK, Li H, Hochster HS, et al. Randomized phase 3 study in low-grade lymphoma comparing maintenance anti-CD20 antibody with observation after induction therapy: A trial of the ECOG-ACRIN Cancer

Research Group (E1496). *Cancer*. 2016;122:2996–3004.

77. Forstpointner R, Unterhalt M, Dreyling M, et al. Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). *Blood*. 2006;108:4003–4008.
78. van Oers MH, Van Glabbeke M, Giurgea L, et al. Rituximab maintenance treatment of relapsed/resistant follicular non-Hodgkin's lymphoma: Long-term outcome of the EORTC 20981 phase III randomized intergroup study. *J Clin Oncol*. 2010;28:2853–2858.
79. Al Zahrani A, Ibrahim N, Al Eid A. Rapid infusion rituximab changing practice for patient care. *J Oncol Pharm Pract*. 2009;15:183–186.
80. Chiang J, Chan A, Shih V, Hee SW, Tao M, Lim ST. A prospective study to evaluate the feasibility and economic benefits of rapid infusion rituximab at an Asian cancer center. *Int J Hematol*. 2010;91:826–830.
81. Yeo W, Chan TC, Leung NWY, et al. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. *J Clin Oncol*. 2009;27:605–611.
82. Davies A, Merli F, Mihaljević B, et al. Efficacy and safety of subcutaneous rituximab versus intravenous rituximab for first-line treatment of follicular lymphoma (SABRINA): A randomised, open-label, phase 3 trial. *Lancet Haematol*. 2017;4:e272–e282.
83. Lugtenburg P, Avivi I, Berenschot H, et al. Efficacy and safety of subcutaneous and intravenous rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in first-line diffuse large B-cell lymphoma: The randomized MabEase study. *Haematologica*. 2017;102:1913–1922.
84. Hiddemann W, Barbui AM, Canales MA, et al. Immunochemotherapy with obinutuzumab or rituximab for previously untreated follicular lymphoma in the GALLIUM study: Influence of chemotherapy on efficacy and safety. *J Clin Oncol*. 2018;36:2395–2404.
85. Marcus R, Davies A, Ando K, et al. Obinutuzumab for the first-line treatment of follicular lymphoma. *N Engl J Med*. 2017;377:1331–1344.
86. Cheson BD, Chua N, Mayer J, et al. Overall survival benefit in patients with rituximab-refractory indolent non-Hodgkin lymphoma who received

obinutuzumab plus bendamustine induction and obinutuzumab maintenance in the GADOLIN Study. *J Clin Oncol*. 2018;36:2259–2266.

87. Sehn LH, Chua N, Mayer J, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): A randomised, controlled, open-label, multicentre, phase 3 trial. *Lancet Oncol*. 2016;17:1081–1093.
88. Hohloch K. Radioimmunotherapy of lymphoma: An underestimated therapy option. *The Lancet Haematol*. 2017;4:e6–e7.
89. Rummel MJ, Gregory SA. Bendamustine's emerging role in the management of lymphoid malignancies. *Semin Hematol*. 2011;48 (Suppl 1):S24–36.
90. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*. 2013;381:1203–1210.
91. Flinn IW, van der Jagt R, Kahl BS, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: The BRIGHT study. *Blood*. 2014;123:2944–2952.
92. Magnano L, Montoto S, Gonzalez-Barca E, et al. Long-term safety and outcome of fludarabine, cyclophosphamide and mitoxantrone (FCM) regimen in previously untreated patients with advanced follicular lymphoma: 12 Years follow-up of a phase 2 trial. *Ann Hematol*. 2017;96:639–646.
93. Morschhauser F, Fowler NH, Feugier P, et al. Rituximab plus lenalidomide in advanced untreated follicular lymphoma. *N Engl J Med*. 2018;379:934–947.
94. Leonard JP, Jung S-H, Johnson J, et al. Randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma: CALGB 50401 (Alliance). *J Clin Oncol*. 2015;33:3635–3640.
95. Gopal AK, Kahl BS, de Vos S, et al. PI3Kdelta inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med*. 2014;370:1008–1018.
96. Gopal AK, Kahl BS, Flowers CR, et al. Idelalisib is effective in patients with high-risk follicular lymphoma and early relapse after initial chemoimmunotherapy. *Blood*. 2017;129:3037–3039.
97. Dreyling M, Santoro A, Mollica L, et al. Phosphatidylinositol 3-kinase

inhibition by copanlisib in relapsed or refractory indolent lymphoma. *J Clin Oncol*. 2017;35:3898–3905.

98. Zinzani P, Wagner-Johnston N, Miller C, et al. DYNAMO: A phase II study demonstrating the clinical activity of duvelisib in patients with double-refractory indolent non-Hodgkin lymphoma. *Hematol Oncol*. 2017;35:69–70.
99. Kuruvilla J. The role of autologous and allogeneic stem cell transplantation in the management of indolent B-cell lymphoma. *Blood*. 2016;127:2093–2100.
100. Evens AM, Vanderplas A, LaCasce AS, et al. Stem cell transplantation for follicular lymphoma relapsed/refractory after prior rituximab: A comprehensive analysis from the NCCN lymphoma outcomes project. *Cancer*. 2013;119:3662–3671.
101. Oh DH, Li H, Duan Q, et al. Quantifying benefit of autologous transplantation for relapsed follicular lymphoma patients via instrumental variable analysis. *Biol Blood Marrow Transplant*. 2016;22:941–948.
102. Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. *N Engl J Med*. 1998;339:21–26.
103. Odejide OO, Cronin AM, Davidoff AJ, LaCasce AS, Abel GA. Limited stage diffuse large B-cell lymphoma: Comparative effectiveness of treatment strategies in a large cohort of elderly patients. *Leukemia Lymphoma*. 2014;56:716–724.
104. McKelvey EM, Gottlieb JA, Wilson HE, et al. Hydroxyldaunomycin (Adriamycin) combination chemotherapy in malignant lymphoma. *Cancer*. 1976;38:1484–1493.
105. Jones SE, Grozea PN, Metz EN, et al. Superiority of adriamycin-containing combination chemotherapy in the treatment of diffuse lymphoma: A Southwest Oncology Group study. *Cancer*. 1979;43:417–425.
106. Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a standard Regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N Engl J Med*. 1993;328:1002–1006.
107. Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: A study by the Groupe d'Etudes des Lymphomes de l'Adulte. *Blood*.

2010;116:2040–2045.

108. Pfreundschuh M, Trümper L, Österborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: A randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol*. 2006;7:379–391.
109. Pfreundschuh M, Kuhnt E, Trümper L, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-Year results of an open-label randomised study of the MabThera International Trial (MInT) Group. *Lancet Oncol*. 2011;12:1013–1022.
110. Pfreundschuh M. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: Results of the NHL-B1 trial of the DSHNHL. *Blood*. 2004;104:626–633.
111. Cunningham D, Hawkes EA, Jack A, et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: A phase 3 comparison of dose intensification with 14-day versus 21-day cycles. *Lancet*. 2013;381:1817–1826.
112. Delarue R, Tilly H, Mounier N, et al. Dose-dense rituximab-CHOP compared with standard rituximab-CHOP in elderly patients with diffuse large B-cell lymphoma (the LNH03-6B study): A randomised phase 3 trial. *Lancet Oncol*. 2013;14:525–533.
113. Stiff PJ, Unger JM, Cook JR, et al. Autologous transplantation as consolidation for aggressive non-Hodgkin’s lymphoma. *N Engl J Med*. 2013;369:1681–1690.
114. Morrison VA, Hamlin P, Soubeyran P, et al. Approach to therapy of diffuse large B-cell lymphoma in the elderly: The International Society of Geriatric Oncology (SIOG) expert position commentary. *Ann Oncol*. 2015;26:1058–1068.
115. Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. *J Clin Oncol*. 2006;24:3121–3127.
116. Czuczman MS, Grillo-Lopez AJ, White CA, et al. Treatment of patients with low-grade B-cell lymphoma with the combination of chimeric anti-CD20 monoclonal antibody and CHOP chemotherapy. *J Clin Oncol*.

1999;17:268–276.

117. Thieblemont C, Tilly H, Gomes da Silva M, et al. Lenalidomide maintenance compared with placebo in responding elderly patients with diffuse large B-cell lymphoma treated with first-line rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J Clin Oncol*. 2017;35:2473–2481.
118. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: Results from the international SCHOLAR-1 study. *Blood*. 2017;130:1800–1808.
119. Crump M, Kuruvilla J, Couban S, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. *J Clin Oncol*. 2014;32:3490–3496.
120. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol*. 2010;28:4184–4190.
121. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med*. 1995;333:1540–1545.
122. Dai H, Wang Y, Lu X, Han W. Chimeric antigen receptors modified T-cells for cancer therapy. *J Natl Cancer Inst*. 2016;108:djv439.
123. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med*. 2017;377:2531–2544.
124. Schuster SJ, Bishop MR, Tam CS, et al. Primary analysis of Juliet: A global, pivotal, phase 2 trial of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma. *Blood*. 2017;130(suppl 1):577.
125. Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy: Assessment and management of toxicities. *Nat Rev Clin Oncol*. 2018;15:47–62.
126. Delarue R, Haioun C, Ribrag V, et al. CHOP and DHAP plus rituximab followed by autologous stem cell transplantation in mantle cell lymphoma: A phase 2 study from the Groupe d'Etude des Lymphomes de l'Adulte. *Blood*. 2013;121:48–53.
127. Robak T, Huang H, Jin J, et al. Bortezomib-based therapy for newly

diagnosed mantle-cell lymphoma. *N Engl J Med*. 2015;372:944–953.

128. Graf SA, Stevenson PA, Holmberg LA, et al. Maintenance rituximab after autologous stem cell transplantation in patients with mantle cell lymphoma. *Ann Oncol*. 2015;26:2323–2328.
129. Le Gouill S, Thieblemont C, Oberic L, et al. Rituximab after autologous stem-cell transplantation in mantle-cell lymphoma. *N Engl J Med*. 2017;377:1250–1260.
130. Hoster E, Kluin-Nelemans H, Hermine O, et al. Rituximab maintenance after first-line immunochemotherapy in mantle cell lymphoma: Long-term follow-up of the randomized European MCL elderly trial. *Blood*. 2017;130(suppl 1):153.
131. Rule S, Jurczak W, Jerkeman M, et al. Ibrutinib versus temsirolimus: 3-Year follow-up of patients with previously treated mantle cell lymphoma from the phase 3, international, randomized, open-label RAY study. *Leukemia*. 2018;32:1799–1803.
132. Jain P, Romaguera J, Srour SA, et al. Four-year follow-up of a single arm, phase II clinical trial of ibrutinib with rituximab (IR) in patients with relapsed/refractory mantle cell lymphoma (MCL). *Br J Haematol*. 2018;182:404–411.
133. Wang M, Rule S, Zinzani PL, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): A single-arm, multicentre, phase 2 trial. *Lancet*. 2018;391:659–667.
134. Barta SK, Lee JY, Kaplan LD, Noy A, Sparano JA. Pooled analysis of AIDS malignancy consortium trials evaluating rituximab plus CHOP or infusional EPOCH chemotherapy in HIV-associated non-Hodgkin lymphoma. *Cancer*. 2012;118:3977–3983.

150

Ovarian Cancer

Emily B. Borders and Judith A. Smith

KEY CONCEPTS

1. Ovarian cancer is denoted “the silent killer” because of the nonspecific signs and symptoms that contribute to the delay in diagnosis. The few patients who present with disease still confined to the ovary will have a 5-year survival rate greater than 90%, but most patients present with advanced disease and have a 5-year survival rate of 10% to 30%.
2. Ovarian cancer is a sporadic disease with less than 10% of cases of ovarian cancer attributed to heredity. However, a history of two or more first-degree relatives with ovarian cancer increases a woman’s risk of developing ovarian cancer by greater than 50%.
3. Considerable education efforts have been made to identify patients with the persistence, greater than 2 weeks, of nonspecific presenting symptoms of ovarian cancer including: abdominal pressure/pain, difficulty eating or feeling full quickly, urinary urgency/frequency, change in bowel habits, or unexplained vaginal bleeding.
4. CA-125 is a nonspecific antigen used as a tumor marker for diagnosis and monitoring epithelial ovarian carcinoma. If CA-125 is positive at the time of diagnosis, changes in CA-125 levels correlate with disease response and progression.
5. Although most patients will achieve a complete response to initial treatment, more than 50% of patients will have recurrence within the first 2 years. If recurrence occurs less than 6 months after completion of chemotherapy, the tumor is defined to be platinum-resistant. The antitumor activity of second-line chemotherapy regimens is similar, and the choice of treatment for recurrent platinum-resistant ovarian cancer depends on residual toxicities, physician preference, and patient convenience. Participation in a clinical trial is also a reasonable option for these patients.

6 Ovarian cancer is staged surgically with the International Federation of Gynecology and Obstetrics (FIGO) staging algorithm. Tumor-debulking and total abdominal hysterectomy–bilateral oophorectomy surgery are the primary surgical interventions for ovarian cancer. After the completion of the staging and primary surgical treatment, the current standard of care is six cycles of a taxane/platinum-containing chemotherapy regimen.

7 The intraperitoneal (IP) route of chemotherapy administration has significantly improved progression-free and overall survival, but patients must be carefully selected.

8 A platinum-containing doublet chemotherapy regimen is the standard of care for the first recurrence of platinum-sensitive ovarian cancer.

9 Despite recent advances, enrollment in an investigational study is still the primary treatment recommendation for patients with recurrent platinum-resistant ovarian cancer.

10 The activity of the new class of the poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors in the maintenance treatment of recurrent or refractory advanced ovarian cancer depends on BCRA status or "BRCAness" of the tumor.

Preclass Engaged Learning Activity

Create a summary table of the chemotherapy agents used in the initial treatment of ovarian cancer (refer to Table 150-1). Identify each agent's drug class, mechanism of action, main adverse event profile, and important patient counseling information. This table will enhance the student's ability to appropriately utilize the patient care process with particular emphasis on the *Implement* and *Follow-up* steps.

INTRODUCTION

1 Ovarian cancer is a gynecologic cancer that usually arises from disruption or mutations in the espithelium of the ovary. It is associated with the highest mortality among the gynecologic cancers, primarily because most patients present with advanced disease. Ovarian cancer is denoted "the silent killer" because of the nonspecific signs and symptoms that often lead to a delayed

diagnosis. Ovarian cancers often metastasize via the lymphatic and blood systems to the liver or lungs. Common complications of advanced and progressive ovarian cancer include ascites and small bowel obstruction. Patients who present with disease still confined to the ovary will have a 5-year survival rate greater than 90%, but most patients present with advanced disease and have a 5-year survival rate of 10% to 30%. Primary treatment includes tumor-debulking surgery followed by six cycles of a taxane-platinum chemotherapy regimen. Although 70% of patients achieve an initial complete response to chemotherapy, most of these patients will have recurrence within the first 2 years from diagnosis.[1]

EPIDEMIOLOGY

It is estimated that 22,530 new cases of ovarian cancer were diagnosed and 13,980 women died of the disease in 2019.[2] Unfortunately, despite clinical advances over the past two decades, the overall mortality rate for ovarian cancer is an estimated 60% and has not changed over the past two decades. Ovarian cancer is still associated with the highest mortality rate among the gynecologic cancers and is the fifth leading cause of cancer-related deaths in women. The high mortality rate is related to the insidious onset of nonspecific symptoms and the lack of adequate screening tools, which allows the disease to go undiagnosed until it has progressed beyond the pelvic cavity.

ETIOLOGY

As with many other cancers, the risk of ovarian cancer increases with increasing age. A woman's risk increases from 15.2 to 56.7 per 100,000 as her age advances from 40 to 79 years, and the median age at diagnosis is 63.[2] Most cases of ovarian cancer are diagnosed during the peri- and postmenopausal phase of women's reproductive life span.

Heredity accounts for less than 10% of all ovarian cancer cases. Family history is an important risk factor in the development of ovarian cancer. If one family member has a diagnosis of ovarian cancer, the associated lifetime risk is 9%, but this risk increases to greater than 50% if two or more first-degree relatives (eg, her mother and sister) have a diagnosis of ovarian cancer or multiple cases of ovarian and breast cancer within the same family.[1] Risk is greatest in women with family members diagnosed at an early age.

BRCA1 and *BRCA2* are the tumor suppressor genes thought to be involved in one or more pathways of DNA damage recognition and repair. The *BRCA1* gene is located on chromosome 17q12–21 and the *BRCA2* gene is located on chromosome 13q12–13. Both *BRCA1* and *BRCA2* mutations are associated with ovarian cancer. However, *BRCA1* is more prevalent and is associated with 90% of inherited and 10% of sporadic cases of ovarian cancer.[3] Patients with *BRCA1*-associated ovarian cancer are usually considerably younger than patients with *BRCA2* mutations, with a mean age of 54 years.[3] Patients usually present with advanced stage at diagnosis, and the *BRCA1*-linked ovarian cancers are more aggressive tumors that typically are serous histology, moderate-to-high grade. As *BRCA1* and *BRCA2* are thought to be involved in DNA damage or repair, their mutations may be associated with an increased resistance of ovarian cancer cells to cytotoxic agents.

Hereditary breast and ovarian cancer syndrome is one of the two different forms of hereditary ovarian cancer that are associated with germline mutations in *BRCA1* and *BRCA2*.[3] The hereditary nonpolyposis colorectal cancer or Lynch syndrome is a familial syndrome with germline mutations causing defects in enzymes involved in DNA mismatch repair, which is associated with up to 12% of hereditary ovarian cancer cases.[3] This syndrome is associated with mutations in DNA mismatch repair genes such as *MSH2, MLH1, PMS1*, and *PMS2* and leads to microsatellite instability.

Hormone exposure, specifically estrogen, and reproductive history is also associated with the risk of developing ovarian cancer. Conditions that increase the total number of ovulations in women's reproductive history, such as nulliparity, early menarche, or late menopause, are associated with an increased risk for epithelial ovarian cancers.[4] Conversely, those conditions that limit ovulations are associated with a protective effect. Each time ovulation occurs, the ovarian epithelium is broken, followed by cellular repair. According to the *incessant ovulation hypothesis*, the risk of mutations and, ultimately, cancer increases each time the ovarian epithelium undergoes cell repair.

Finally, ovarian cancer is associated with certain dietary, lifestyle, and environmental factors. A diet that is high in galactose, animal fat, and meat may increase the risk of ovarian cancer, whereas a vegetable-rich diet may decrease the risk of ovarian cancer.[5] Although controversial, exogenous factors such as asbestos and talcum powder use in the perineal area are also associated with an increased risk of ovarian cancer.[5] Obesity has also been associated with an increased risk of low-grade ovarian cancer in some studies.[6,7]

PATHOPHYSIOLOGY

Ovarian carcinomas can be separated into three major entities: epithelial carcinomas, germ cell tumors, and stromal carcinomas. Most ovarian tumors (85%-90%) are derived from the epithelial surface of the ovary.[8] The classification of common epithelial tumors has been developed by the World Health Organization and FIGO.[8] The nomenclature considers cell type, location of the tumor, and the degree of the malignancy, which ranges from benign tumors to tumors of low malignancy to invasive carcinomas. Epithelial tumors classified as low malignancy ("borderline malignancy") are characterized by epithelial papillae with atypical cell clusters, cellular stratification, nuclear atypia, and increased mitotic activity, and have a much better prognosis than those classified as invasive carcinomas. Malignant tumors are characterized by an infiltrative destructive growth pattern with malignant cells growing in a disorganized manner and dissection into stromal planes.

Invasive epithelial adenocarcinomas are characterized by histologic subtype and grade, which measures the degree of cellular differentiation. Although the histologic type of the tumor is not a significant prognostic factor, with the exception of clear cell, the histopathologic grade is an important prognostic factor. Undifferentiated tumors are associated with a poorer prognosis than those lesions that are considered to be well or moderately differentiated. A universal grading system for ovarian cancer was developed that combines mitotic score, nuclear atypia score, and architectural score based on the histologic pattern.[9]

The histologic subtypes of adenocarcinomas include papillary serous, mucinous, endometrioid, clear cell, mixed epithelial, transition-cell, and undifferentiated adenocarcinomas.[1,10] Papillary serous adenocarcinoma is the most common type of epithelial ovarian cancer and accounts for about 46% of cases. The peak age of diagnosis ranges from 45 to 65 years with 63 years as the median age of diagnosis.[8] Serous carcinomas typically display complex papillary and solid patterns and qualify as high-grade carcinomas. Endometrioid carcinomas are seen in women 40 to 50 years of age and comprise about 8% of ovarian carcinomas, of which about 6% are surface epithelial neoplasms.[10] Endometrioid tumors are usually diagnosed as stage I disease and have a better prognosis than tumors with serous histology. Mucinous carcinomas occur in women between 40 and 70 years of age and account for about 36% of all ovarian cancers. The overall prognosis for mucinous carcinoma is better than for serous carcinoma because most patients present with stage I disease. Clear cell carcinoma comprises about 3% of ovarian carcinomas in women, with a mean

age of 57 years. Although clear cell carcinoma is the least common ovarian neoplasm, it is most commonly associated with paraneoplastic-related hypercalcemia.[10]

Germ cell tumors of the ovary, including malignant teratoma and dysgerminomas, are rare, comprising about 2% to 3% of all ovarian cancers in Western countries with an increased incidence in black and Asian women.[8] These tumors are highly curable and affect primarily young women. In contrast to epithelial tumors, about 60% to 70% of germ cell tumors are stage I at diagnosis, which is related to earlier detection and response to symptoms in this younger patient population.[8] Serum markers (human β-chorionic gonadotropin and α-fetoprotein) are helpful to confirm the diagnosis and monitor response to treatment.

Finally, ovarian sex cord-stromal tumors account for 7% of all ovarian cancers and tend to be diagnosed at an early stage.[8] Sex cord-stromal tumors are associated with hormonal effects, such as precocious puberty, amenorrhea, and postmenopausal bleeding. Because these tumors are rare, the optimal treatment of ovarian sex cord-stromal tumors is not clear. The current recommended standard of care is surgery followed by treatment with a platinum-based chemotherapy regimen.

Ovarian cancer is usually confined to the abdominal cavity, but can spread to the lung, liver, and, less commonly, the bone or brain. Disease is spread by direct extension, peritoneal seeding, lymphatic dissemination, or bloodborne metastasis. Lymphatic seeding is the most common pathway and frequently causes ascites.

SCREENING AND PREVENTION

Screening

3 Ovarian cancer is an uncommon disease with no known preinvasive component, which has made it difficult to detect early disease. In addition, the risk factors for developing ovarian cancer are not well understood, which also makes it difficult to identify a high-risk group of individuals. At the present time, there are no effective screening tools for early detection of ovarian cancer. However, considerable education efforts have been made to identify patients with the persistence of nonspecific presenting symptoms of ovarian cancer including: abdominal pressure/pain, difficulty eating or feeling full quickly, urinary urgency/frequency, change in bowel habits, or unexplained vaginal

bleeding.

Pelvic examinations are noninvasive and well accepted and can detect large tumors with a sensitivity of 67% for detecting all tumors.[11] However, routine pelvic examinations are not an effective screening tool and do not decrease overall mortality because pelvic examinations cannot detect minimal or microscopic disease.[11]

Transvaginal ultrasound (TVUS) creates an image of the ovary by releasing sound waves. It can be used to evaluate the size and shape and to detect the presence of cystic or solid masses or abdominal fluid. Transvaginal ultrasound can also evaluate blood flow within an ovarian mass. Transvaginal ultrasound is sensitive in identifying ovarian lesions and abnormalities, but its use as a routine screening test is limited by a lack of specificity and an inability to detect peritoneal cancer or cancer in normal-size ovaries.[11]

Serum cancer antigen-125 (CA-125) is a nonspecific inflammatory antigen that can be elevated in numerous conditions associated with inflammation in the abdominal cavity. CA-125 has been extensively studied as a potential tumor marker for ovarian cancer based on the observation that CA-125 levels in a woman without ovarian cancer tend to stay the same or decrease over time, whereas levels associated with malignancy tend to gradually increase over time.[11] However, CA-125 is a nonspecific test that can be elevated in a number of benign conditions, including other gynecologic conditions, such as endometriosis, and many nongynecologic conditions, such as diverticulitis and peptic ulcer disease. Because of these limitations, CA-125 levels are not recommended as a routine screening test for detection of ovarian cancer. Numerous other serologic markers such as carcinoembryonic antigen and lipid-associated sialic acid have been evaluated but cannot be recommended for routine screening for ovarian cancer.

The United States Preventive Services Task Force found fair evidence to support screening with CA-125 or TVUS and concluded that earlier detection would likely have a small effect, at best, on mortality from ovarian cancer.[12] Unfortunately, because of the low prevalence of ovarian cancer and the invasive nature of diagnostic testing after a positive screening test, the Task Force also found fair evidence that screening could likely lead to important harms. The United States Preventive Services Task Force concluded that the potential harms outweigh the potential benefits and recommended against any form of routine screening with CA-125 or TVUS for ovarian cancer for asymptomatic women who do not have a high-risk hereditary cancer syndrome.

In high-risk women, as defined by family history, most clinicians use a

multimodality approach for ovarian cancer screening that includes an annual TVUS in combination with a CA-125 blood test every 6 months. Changes in CA-125 are monitored over time, and changes such as a persistent elevation or consistent increases in CA-125 levels in conjunction with TVUS abnormalities are evaluated further.

Prevention

It is difficult to make recommendations for prevention for the general population because ovarian cancer is a sporadic disease with no established risk factors. Noninvasive measures, such as chemoprevention, can decrease the risk of developing ovarian cancer. Ovulation itself is considered a potential insult to the ovarian epithelium, increasing its susceptibility to damage and, ultimately, to cancer. Interventions or reproductive conditions associated with decreasing the number of ovulations, including multiparity, may have a protective effect for the prevention of ovarian cancer. However, the more invasive prevention interventions, such as prophylactic surgery and genetic screening, should be reserved for those women identified to be at high risk based on their inherited risk for developing ovarian cancer.

Chemoprevention

Although a number of agents have been investigated as chemoprevention of ovarian cancer, including oral contraceptives, aspirin, nonsteroidal anti-inflammatory agents, and retinoids, none of these agents is currently accepted as standard treatment for the prevention of ovarian cancer. Oral contraceptives inhibit ovulation, which reduces the potential for damage to the ovarian epithelium. When taken for longer than 10 years, oral contraceptives decrease the relative risk to less than 0.4.[13] Because oral contraceptive use is associated with an increased risk of breast cancer, women with a family history of breast cancer are not candidates for the use of oral contraceptives as chemoprevention of ovarian cancer.[13]

Nonsteroidal anti-inflammatory drugs, aspirin, and acetaminophen also have been suggested for use in the chemoprevention of different cancers, especially hereditary nonpolyposis colon cancer.[124] Although the results of observational studies show that the use of nonsteroidal anti-inflammatory drugs, aspirin, and acetaminophen reduces the risk of ovarian cancer, these findings have not been confirmed in prospective clinical studies. The proposed mechanism of these

agents is the anti-inflammatory effect on normal ovulation and inhibition of ovulation.[14]

Prophylactic Surgery

Prophylactic surgical interventions for the prevention of ovarian cancer are reserved for patients with a significant family history or known genetic mutations such as *BRCA1* and should be postponed until after childbearing is completed, preferably between the ages of 35 to 40 years.[15] The goal is to remove healthy, at-risk organs before any carcinogenic activity is initiated, ultimately reducing the risk of developing cancer. These surgeries include prophylactic oophorectomy or bilateral salpingo-oophorectomy and tubal ligation. These procedures cause surgical menopause, which can be associated with severe hot flashes, vaginal dryness, sexual dysfunction, and increased risk for development of osteoporosis and heart disease in these women. Because of the potential impact on quality of life and increased health risks, prophylactic surgery is not recommended as a general prevention intervention.

Although prophylactic surgical interventions are the most effective way to reduce the risk of developing ovarian cancer in high-risk populations, patients who choose to have a prophylactic oophorectomy/bilateral salpingo-oophorectomy need to be informed that complete protection is not guaranteed.[13,15,16] Although a 67% risk reduction has been shown, a potential 2% to 5% risk of primary peritoneal cancer remains.[16] Primary peritoneal cancers have identical histology of ovarian tumors with diffuse involvement of peritoneal surfaces. Primary peritoneal cancers can often result from “seeding” during the prophylactic surgery. It is recommended for peritoneal washings to be completed during the prophylactic surgery to check for the presence of tumor cells on peritoneal surfaces. If positive, then prophylactic surgery would change to staging and treatment surgery to determine extent of disease and remove any other possible lesions.

Tubal ligation is another procedure that can reduce the risk for developing ovarian cancer. In a case-control study, Narod et al. reported that tubal ligation in *BRCA*-positive women was associated with a 63% reduction in risk of developing ovarian cancer.[17] However, it is not recommended as a sole procedure in prophylaxis. The mechanism for its protective effect is not clear, but it has been proposed that tubal ligation may limit exposure of the ovary to environmental carcinogens.

Genetic Screening

Genetic screening should be considered for all women who are suspected of carrying a BRCA mutation, based on family history or young age (less than 50 years old) at diagnosis and a high-grade serous tumor. Patients should be evaluated for the presence of genes such as *BRCA1*, *BRCA2*, or other genes such as those associated with hereditary nonpolyposis colorectal cancer or the hereditary breast ovarian cancer (hereditary breast and ovarian cancer syndrome) syndrome.[17] Prior to genetic screening, appropriate patient/family counseling and genetic counseling should be available to help women prepare and deal with the health and psychosocial implications of the genetic screening results.

CLINICAL PRESENTATION

Patients with early ovarian cancer are often asymptomatic and the ovarian mass is detected incidentally during their annual pelvic examinations. Patients with ovarian cancer often present with nonspecific, vague symptoms such as abdominal bloating, pressure or pain, indigestion, or change in bowel movements.[1] These symptoms can easily be confused with symptoms of common benign gastrointestinal disorders. Patients will often not seek medical attention until these symptoms become unrelenting and bothersome, which allows the disease to progress undetected. Patients with advanced disease may report symptoms such as pain, abdominal distension, and ascites.[1]

Several groups have partnered together to educate women about early signs and symptoms of ovarian cancer. Goff et al. recently developed a symptom index, based on a comparison of symptoms experienced in patients with ovarian cancer and a matched control group.[18] Symptoms that were correlated with ovarian cancer include persistent or recurrent bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, and urinary symptoms (either urgency or frequency). The Gynecologic Cancer Foundation, Society of Gynecologic Oncologists, and American Cancer Society recommend that women who have any of those problems nearly every day for more than 2 weeks should see a gynecologist, especially if the symptoms are new and quite different from her usual state of health. Furthermore, healthcare professionals should keep ovarian cancer in the differential for women presenting with these persistent symptoms.

The diagnostic workup for suspected ovarian cancer includes a careful physical examination including a Papanicolaou (Pap) smear and a pelvic and rectovaginal examination.[19] The presence of a pelvic mass that is unilateral or

bilateral, solid, irregular, fixed, or nodular is highly suggestive of ovarian cancer. Unfortunately, by the time a pelvic mass can be palpated on physical exam, the disease is already advanced beyond the pelvic cavity. A detailed family history should be taken, especially noting the number and pattern of first-degree relatives with malignancies. All patients with suspected ovarian malignancies should be referred to a gynecologic oncologist for evaluation as survival is increased when primary assessment and surgery is performed by a specialist.[20]

4 A complete blood count, chemistry profile (including liver and renal function tests), and CA-125, carcinoembryonic antigen, and CA19-9 levels should be performed. Although CA-125 is a nonspecific antigen, it is the best current tumor marker for epithelial ovarian carcinoma.[19] A normal CA-125 value is less than 35 units/mL (kU/L). If the CA-125 is elevated at the time of diagnosis, changes in CA-125 levels correlate with tumor burden. Rising CA-125 levels are often associated with disease progression, but CA-125 can be elevated in various other conditions such as different phases of the menstrual cycle, diverticulitis, endometriosis, as well as other nongynecologic cancers. When a patient presents with an abdominal mass, it is important to rule out other cancers in the abdominal cavity. Carcinoembryonic antigen and CA19–9 are markers for other gastrointestinal cancers and may be helpful in the differential diagnosis.

Other diagnostic tests should include a transvaginal or abdominal ultrasonography, chest radiography, computed tomography, magnetic resonance imaging, or positron emission tomography scan. An upper GI series, IV pyelogram, cystoscopy, proctoscopy, or barium enema is sometimes indicated to confirm diagnosis and extent of disease.

CLINICAL PRESENTATION Ovarian Cancer

General

- Ovarian cancer is sometimes referred to as “the silent killer” because of the vague nonspecific signs and symptoms that contribute to the delay in diagnosis.

Symptoms

- The patient may complain of abdominal discomfort, nausea, dyspepsia,

flatulence, bloating, fullness, early satiety, urinary frequency, change in bowel function (diarrhea or constipation), weight change, and digestive disturbances.

Signs

- Abdominal or pelvic mass may be palpable.
- Lymphadenopathy may be present.
- Vaginal bleeding may be irregular.
- Patient may have signs of ascites (abdominal distension, shifting, and dullness to percussion—may present like "pregnant abdomen").

Laboratory Tests

- CA-125 may be elevated (normal level is <35 units/mL [kU/L]).
- Abnormalities in liver function tests may suggest hepatic involvement.
- Abnormalities in renal function tests may suggest compression of the renal system by the tumor.

TREATMENT

Desired Outcomes

5 The goals of treatment of ovarian cancer depend upon the FIGO stage at diagnosis. While ideally "treatment for cure" is desired, it is important to set realistic expectations for the patient. Most patients will achieve a complete response to the initial multimodality treatment, but over 50% of these patients will present with recurrent disease within the first 2 years after completion of treatment.[1,20] Although overall survival has not significantly changed for ovarian cancer patients, progression-free survival has improved, which translates to less time on chemotherapy and overall improvement in quality of life for these patients.

In patients who present with metastatic disease or are not surgical candidates, the goal of treatment is to alleviate symptoms and prolong survival as long as quality of life is acceptable. In the setting of recurrent platinum-resistant ovarian

cancer, the treatment goal is also to alleviate symptoms and prolong survival as long as quality of life is acceptable.

General Approach

5 A multimodality approach that includes comprehensive surgery and chemotherapy is used for the initial treatment of ovarian cancer with curative intent. Although most patients will initially achieve a complete response, more than 50% will recur within the first 2 years.[120] A clinical complete response to treatment is defined as no evidence of disease by physical examination or diagnostic tests and a normal CA-125 level.

Chemotherapy regimens for ovarian cancer have evolved over the past several decades. Treatment regimens began with single-agent melphalan followed by single-agent cyclophosphamide. Shortly after cisplatin was introduced into clinical practice, it was added to cyclophosphamide, and this combination was the “standard of care” for more than a decade until the introduction of paclitaxel in the 1980s. Paclitaxel soon replaced cyclophosphamide, and paclitaxel plus cisplatin became the standard of care. Carboplatin was then substituted for cisplatin because of its improved toxicity profile, and paclitaxel plus carboplatin was adopted. During this same period, many researchers conducted numerous clinical trials of intraperitoneal (IP) chemotherapy. In 2006, Armstrong and colleagues published the first clinical trial to demonstrate a survival advantage of IP therapy over the standard IV regimen.[21] Long-term follow-up of that trial suggests IP therapy significantly improves overall survival.[22] However, these advances in chemotherapy for the treatment of ovarian cancer have not yet translated into major changes in overall 5-year survival for women with advanced ovarian cancer, which remains less than 20%.

Certain subgroups of patients have a better or worse response to chemotherapy. The histologic subtype of the tumor is a prognostic factor; clear cell histology is more likely to be poorly differentiated, faster growing, and have intrinsic drug resistance.[1,8] However, the extent of residual disease, size larger than 1 cm, and tumor grade are better predictors of response to chemotherapy and overall survival.[1]

In general, younger patients have a better performance status and tolerate chemotherapy better than elderly patients. For unknown reasons, white women tend to have a worse prognosis and response to therapy as compared with women of other ethnic backgrounds.[1]

In patients with recurrent ovarian cancer, the goals of treatment are to relieve symptoms such as pain or discomfort from ascites, slow disease progression, and prevent serious complications such as small bowel obstructions.

Surgery

Surgery is the primary treatment intervention for ovarian cancer.[23–25] Surgery may be curative for selected patients with limited stage IA disease. Primary surgical treatment includes a total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH/BSO), omentectomy, and lymph node dissection (**Fig. 150-1**).[23–25] The primary objective of the surgery is to optimally debulk the tumor to less than 1 cm of residual disease.[19] Long-term follow-up studies confirm that residual disease smaller than 1 cm correlates with higher complete response rates to chemotherapy and longer overall survival as compared to patients with bulky residual disease (>1 cm).[25]

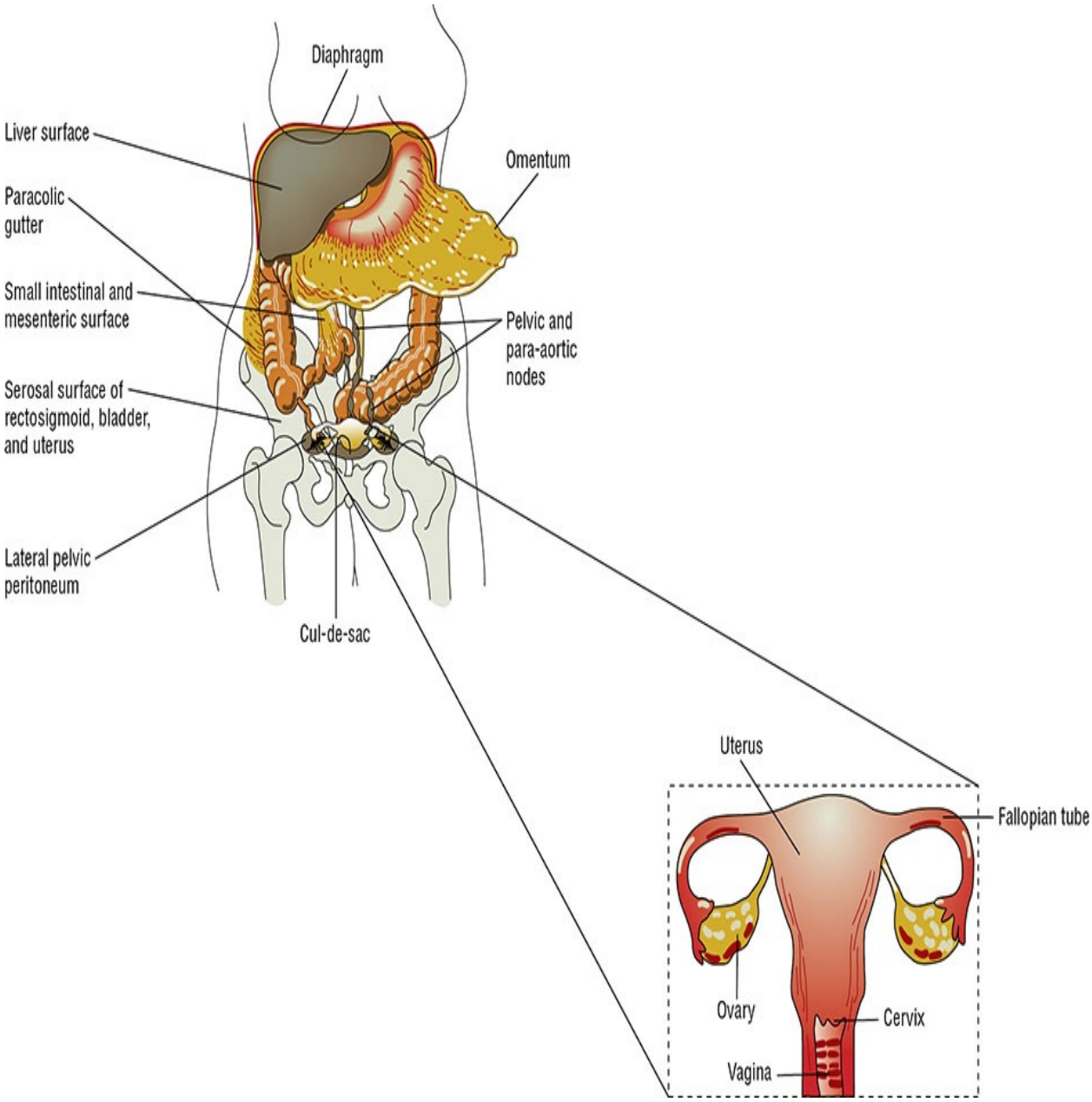
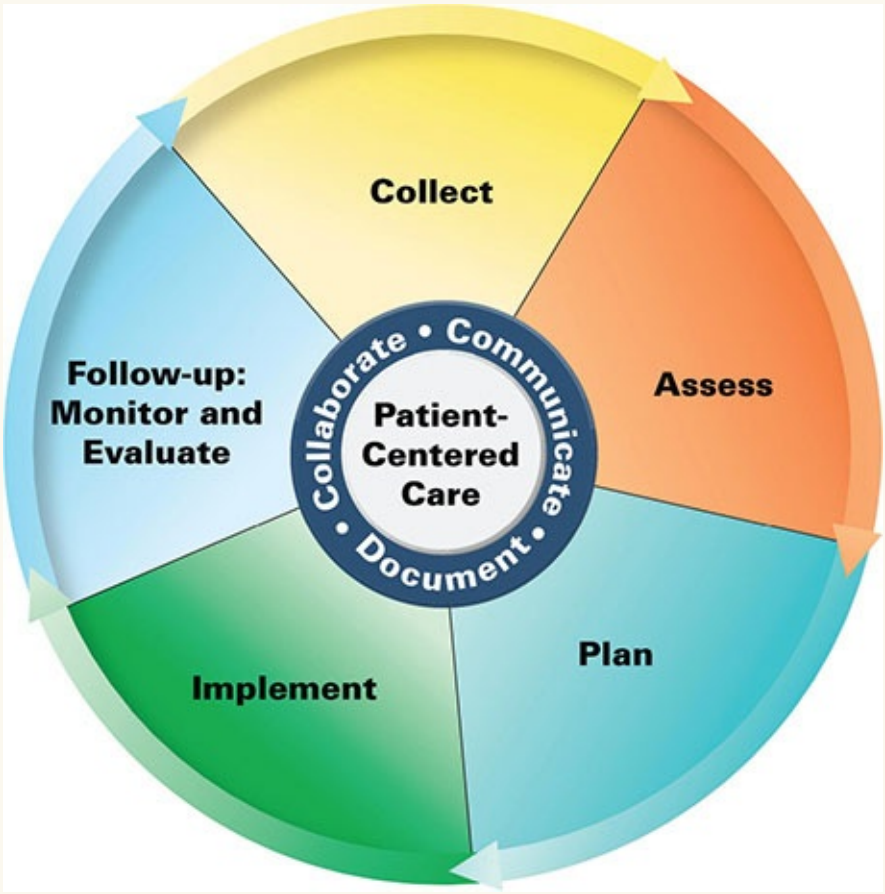


FIGURE 150-1 Staging laparotomy for ovarian cancer with diagram of female reproductive tract (uterus, fallopian tubes, ovaries, and vagina). *Dashed line box* outlines what is removed during the total abdominal hysterectomy with bilateral salpingo-oophorectomy.



Patient Care Process for Ovarian Cancer

Collect

- Patient characteristics and medication history, including any allergies
- Medical history, family cancer history and physical assessment findings
- Patient-specific factors, tumor-specific factors, and laboratory information that may influence chemotherapy selection and drug dosing
- Lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care

Assess

- Goal of therapy defined by prognosis-based stage of disease and patient

preferences

- Medication profile to identify agents that may worsen the patient's symptoms, potential interactions, duplicate therapies, or unnecessary medications. Determine need for symptomatic supportive care medications including antiemetics or pain medications
- Medical and family history to determine whether the patient has compelling indications or contraindications for specific chemotherapy and if additional genetic testing is recommended
- Relevant laboratory tests (eg, complete blood count, electrolytes, complete metabolic panel to determine liver and hepatic function, tumor markers [CA-125, CEA, and CA-19 as part of differential], tumor genetic profile) that may impact drug selection or dosing
- Potential appropriate chemotherapy regimens and the related toxicities; review chemotherapy history to determine potential for platinum sensitivity/resistance and consider genetic mutation status in selection of treatment options

Plan*

- Recommendations for any medications or supplements that need to be held temporarily before surgery (eg, anticoagulants nonsteroidal anti-inflammatory agents, omega 3 fatty acids, etc.).
- Chemotherapy order with dosages based on organ function and patient characteristics (calculate body surface area), list of drug-interactions and possible adverse effects from the regimen
- Determine whether patient has insurance coverage for planned chemotherapy regimen and supportive care medications as indicated; consider institution's formulary if applicable
- Recommendations for lifestyle modifications that may assist in symptom and disease management and supportive care options
- Counseling for potential adverse effects of the regimen and management strategies

Implement

- Patient education treatment plan

- Surgery patients: use of low-molecular weight heparin for postoperative clot prevention, list of medication to stop prior to surgery and when to resume, plan for postoperative pain
- Chemotherapy patients: chemotherapy agents including timing of administration, expected adverse effects and prevention and management of these toxicities (nausea, infection, neuropathy, alopecia, electrolyte disturbances), necessary laboratory monitoring and follow-up visits; help patient set realistic expectations during treatment

Follow-up: Monitor and Evaluate

- Surgical patients (2-3 weeks postoperation): evaluate symptom management including nausea, pain control, and determine if adjuvant chemotherapy is required
- Chemotherapy patients:
  - CBC with differential should be obtained prior to each chemotherapy dose
  - Complete laboratory values should be obtained with each cycle
- Adjust doses based on unacceptable toxicity or organ dysfunction when indicated.
  - Tumor markers obtained with each cycle

  Consider reevaluating therapy if a 50% increase or consistent trend upwards
  - Radiographic scan (CT scan/MRI/PET) once every 3 months

  Assess tumor response

  Follow current RECIST criteria to determine disease status

**Collaborate with patient, caregivers, and other healthcare professionals.*

6 A comprehensive exploratory laparotomy is vital for the accurate confirmation of diagnosis and staging of ovarian cancer.[23,24] Unlike other cancers that are typically diagnosed by biopsy or laboratory results and clinically staged by results from imaging tests, gynecologic cancers are surgically diagnosed and then staged according to the FIGO staging algorithm (**Fig. 150-2**).

The FIGO staging system requires a fairly extensive surgery by an experienced gynecologic oncologist. The training and skill of the surgeon has a significant effect on prognosis, with definitive benefit of a trained gynecologic oncologist performing surgery as compared with a gynecologist or general surgeon.[20,26] The reasons for this approach include (a) pelvic tumors cannot be readily biopsied without risk of “tumor seeding,” which can increase the risk of recurrence, and (b) surgical staging takes into account the presence of microscopic disease in samples obtained by pelvic washing and lymph node dissection and read by a pathologist during the surgical procedure. It is recommended that the initial surgical staging and tumor-debulking surgery be completed by a trained gynecologic oncology surgeon when ovarian cancer is suspected to prevent understaging and to optimize overall outcome.[19,20,23,27]

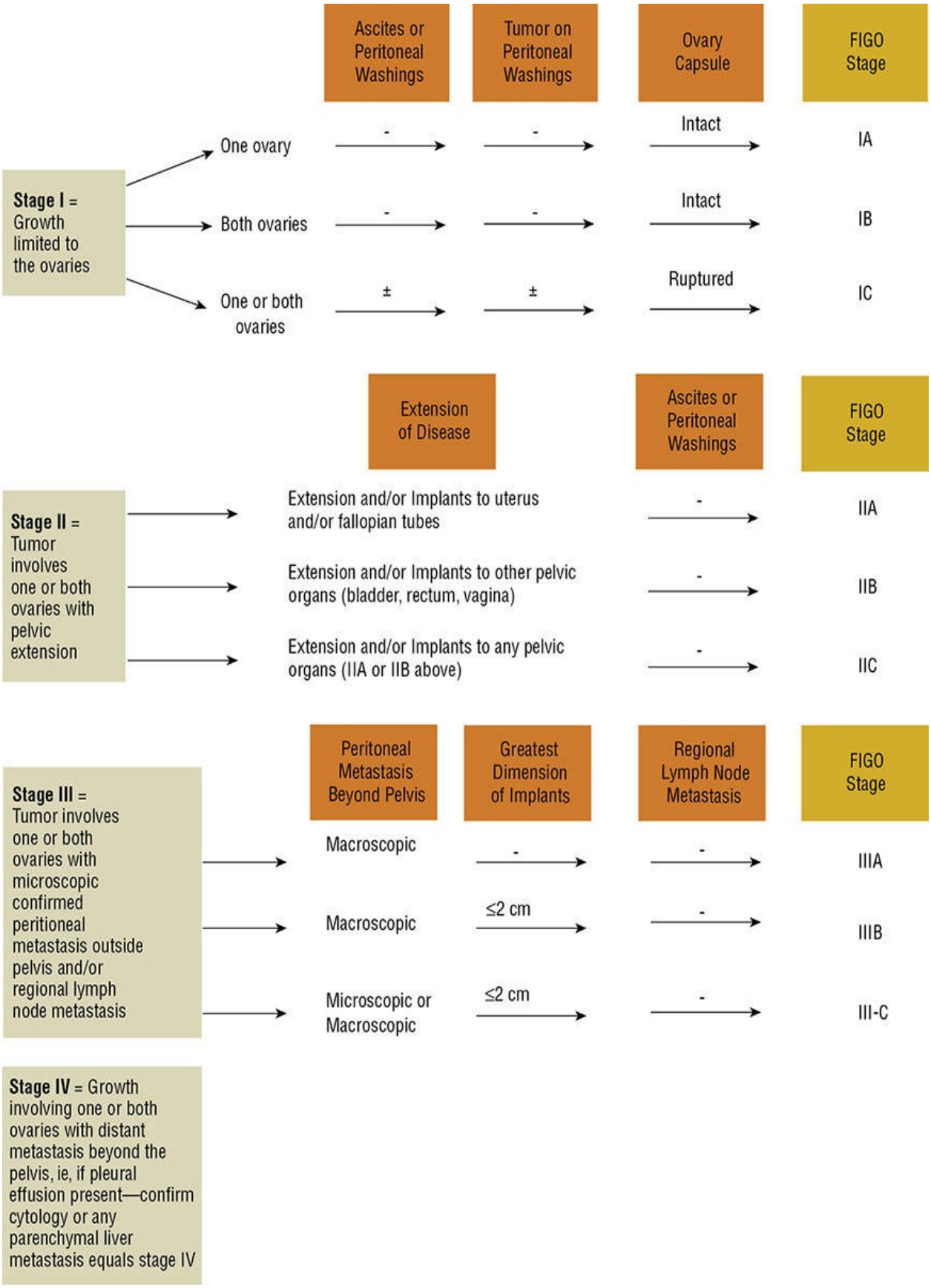

Ascites or Peritoneal Washings
Tumor on Peritoneal Washings
Ovary Capsule
FIGO Stage
Stage I = Growth limited to the ovaries
One ovary
Both ovaries
One or both ovaries
-
-
Intact
IA
-
-
Intact
IB
±
±
Ruptured
IC
Extension of Disease
Ascites or Peritoneal Washings
FIGO Stage
Stage II = Tumor involves one or both ovaries with pelvic extension
Extension and/or Implants to uterus and/or fallopian tubes
Extension and/or Implants to other pelvic organs (bladder, rectum, vagina)
Extension and/or Implants to any pelvic organs (IIA or IIB above)
-
IIA
-
IIB
-
IIC
Peritoneal Metastasis Beyond Pelvis
Greatest Dimension of Implants
Regional Lymph Node Metastasis
FIGO Stage
Stage III = Tumor involves one or both ovaries with microscopic confirmed peritioneal metastasis outside pelvis and/or regional lymph node metastasis
Macroscopic
Macroscopic
Microscopic or Macroscopic
-
≤2 cm
≤2 cm
-
-
-
IIIA
IIIB
III-C
Stage IV = Growth involving one or both ovaries with distant metastasis beyond the pelvis, ie, if pleural effusion present—confirm cytology or any parenchymal liver metastasis equals stage IV

FIGURE 150-2 International Federation of Gynecology and Obstetrics (FIGO) staging algorithm.

Secondary cytoreduction or interval debulking is when surgery is performed after completion of some or all chemotherapy to remove residual disease. Some protocols include additional cycles of chemotherapy after the surgical procedure. The importance of cytoreduction before, during, or after chemotherapy is still controversial, but it has been recommended to facilitate response to chemotherapy and improve overall survival.[19] Randomized trials of secondary surgical cytoreduction have reported conflicting results. In a study of 550 women with stage III or IV disease treated with primary cytoreductive surgery and three cycles of paclitaxel and cisplatin, patients randomized to receive secondary cytoreductive surgery followed by three more cycles of chemotherapy had similar progression-free survival and overall survival as compared with those randomized to receive three more cycles of chemotherapy alone.[28]

The overall effect of interval debulking is influenced by several factors, including initial response to chemotherapy, the amount of residual disease before and after second-look surgery, and the presence of microscopic residual disease. The results of recent trials suggest that secondary surgical cytoreduction does not prolong survival in patients who are treated with maximal primary cytoreductive surgery followed by appropriate postoperative chemotherapy.

"Second-look surgery" is an elective surgical procedure performed in patients who achieve a clinical complete response after primary chemotherapy to determine if any visible or microscopic disease is present in the peritoneal cavity. The benefit of "second-look laparotomy" to evaluate residual disease after completing chemotherapy remains controversial because it has been difficult to establish any impact on overall survival. It has questionable benefit because about 50% of those with a negative second look still relapsed.[28] If visible or microscopic disease is detected during second look, then the clinician may decide to give additional chemotherapy. But if no visible or microscopic disease is detected during second look, the clinician may decide to observe and monitor the patient. Use of laparoscopic surgical techniques is controversial for initial surgery but is sometimes considered in debulking of recurrent or advanced disease when the intent is palliative rather than curative.[25] In patients with recurrent disease, the goal of debulking surgery is to relieve symptoms associated with complications such as small bowel obstructions and to improve the patient's quality of life.

Radiation

Radiation has a limited role in the management of ovarian cancer. Use of radiation for treatment of early stage disease has no impact on overall survival.[29] Radiation therapy is most beneficial for palliation of symptoms in patients with recurrent pelvic disease, often associated with small bowel obstructions. The two forms of radiation therapy used in ovarian cancer are external beam whole-abdominal irradiation and intraperitoneal isotopes such as phosphorus-32 (^{32}P). Alleviation of symptoms with external beam whole-abdominal irradiation is associated with a significant improvement in the patient's quality of life. The recommended dose ranges from 35 to 45 Gy (3,500-4,500 rad), depending on the treatment history and ability to tolerate radiation treatments.

First-Line Chemotherapy

The mainstay of ovarian cancer treatment is chemotherapy. It is used as a component of first-line treatment after completion of surgery and is the primary modality of treatment for recurrent ovarian cancer. Systemic chemotherapy with a taxane and platinum regimen following optimal surgical debulking is the standard of care for treatment of epithelial ovarian cancer (**Fig. 150-3**).[19] **Table 150-1** summarizes the chemotherapeutic regimens used as the initial treatment of newly diagnosed epithelial ovarian cancer. More than 60 randomized controlled clinical trials have evaluated combination chemotherapy regimens for the treatment of advanced ovarian cancer, and a meta-analysis of these trials confirms the efficacy of platinum and taxane regimens over other regimens.[30]

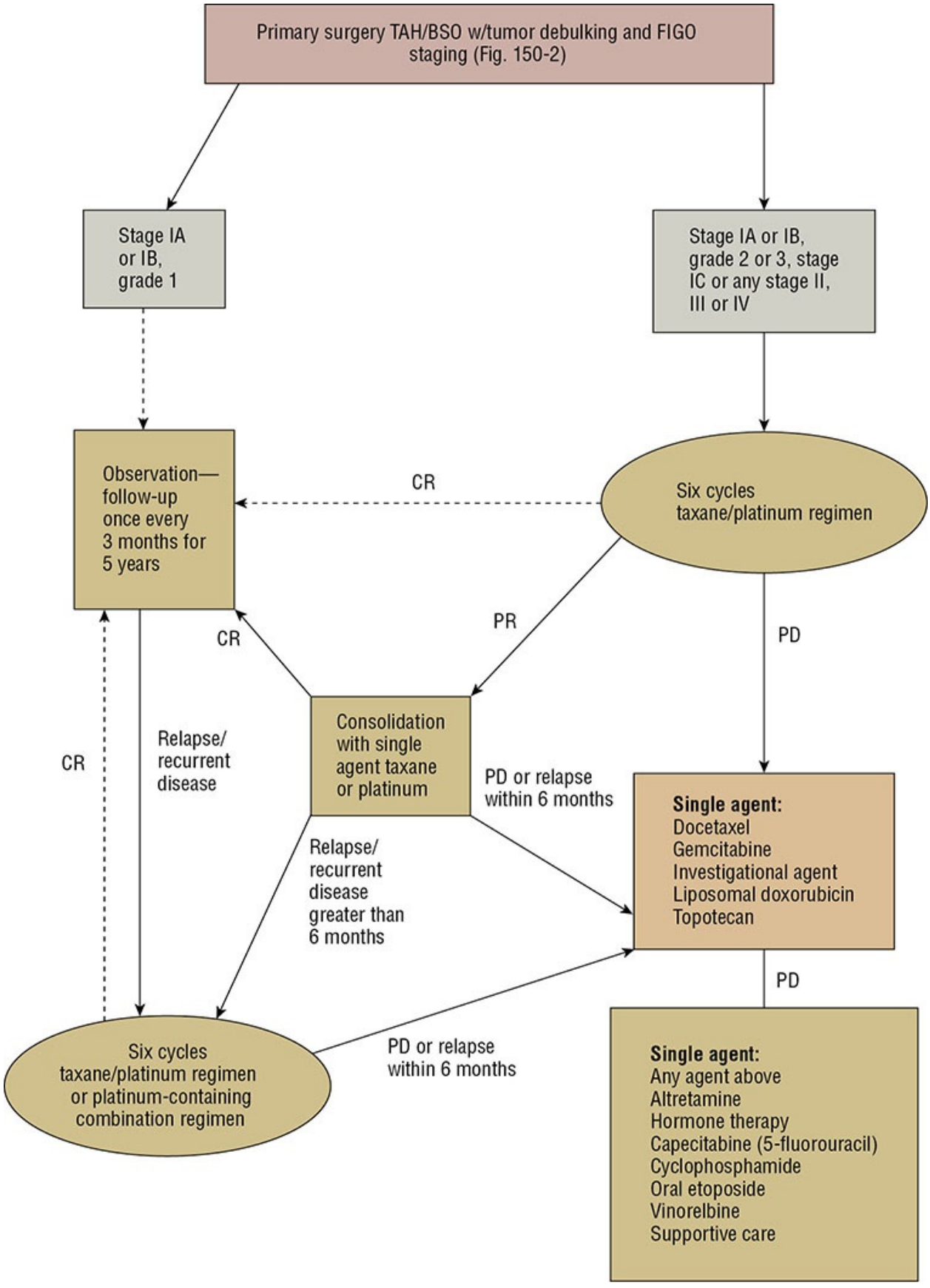

Primary surgery TAH/BSO w/tumor debulking and FIGO staging (Fig. 150-2)
Stage IA or IB, grade 1
Stage IA or IB, grade 2 or 3, stage IC or any stage II, III or IV
Observation—follow-up once every 3 months for 5 years
CR
Six cycles taxane/platinum regimen
CR
PR
PD
CR
Relapse/ recurrent disease
Consolidation with single agent taxane or platinum
PD or relapse within 6 months
Relapse/ recurrent disease greater than 6 months
Single agent:
Docetaxel
Gemcitabine
Investigational agent
Liposomal doxorubicin
Topotecan
PD
Six cycles taxane/platinum regimen or platinum-containing combination regimen
PD or relapse within 6 months
Single agent:
Any agent above
Altretamine
Hormone therapy
Capecitabine (5-fluorouracil)
Cyclophosphamide
Oral etoposide
Vinorelbine
Supportive care

FIGURE 150-3 Management of newly diagnosed, refractory, and progressive epithelial ovarian cancer. All recommendations are category 2A unless otherwise indicated. (CR, complete response; PD, progression of disease; PR, partial response; TAH/BSO, total abdominal hysterectomy/bilateral salpingo-oophorectomy; USO, unilateral salpingo-oophorectomy.)

TABLE 150-1 Initial Chemotherapeutic Regimens of Epithelial Ovarian Cancer

Drug(s)	Brand Name	Initial Dose(s)/Usual Range	Cycle Frequency
Paclitaxel + carboplatin	Taxol/Paraplatin	175 mg/m² IV (3-hour infusion) day 1 Dosed to AUC 5–6 IV day 1	Every 21 days
Paclitaxel + carboplatin (dose-dense)	Taxol/Paraplatin	80 mg/m² IV (1-hour infusion) days 1, 8, 15 Dosed to AUC 5-6 IV day 1	Every 21 days
Paclitaxel + cisplatin (IV)	Taxol/Platinol	135 mg/m² IV (24-hour infusion) day 1 75 mg/m² IV day 1	Every 21 days
Paclitaxel + cisplatin (IP)	Taxol/Platinol	Day 1: Paclitaxel 135 mg/m² IV infused over 24 hours Day 2: Cisplatin 100 mg/m² IP infused over 1 hour Day 8: Paclitaxel 60 mg/m² IP infused over 1 hour.	Every 21 days
Carboplatin + peglylated liposomal doxorubicin	Paraplatin/Doxil	Dosed to AUC 5 IV day 1 30 mg/m² IV day 1	Every 28 days
Paclitaxel + carboplatin + bevacizumab	Taxol/Paraplatin/Avastin	175 mg/m² IV (3-hour infusion) day 1 Dosed to AUC 5-6 IV day 1 7.5-15 mg/kg IV on day 1	Every 21 days
Cisplatin + cyclophosphamide	Platinol/Cytoxan	Dosed to AUC 5-6 IV day 1 500-1,000 mg/m² IV day 1	Every 21-28 days
Docetaxel + carboplatin	Taxotere/Paraplatin	75 mg/m² IV day 1 Dosed to AUC 5-6 IV day 1	Every 21 days

AUC, area under the curve; IP, intraperitoneal.

Historically, single-agent alkylating agents such as melphalan, and later cyclophosphamide, were used for the treatment of advanced ovarian cancer until cisplatin was introduced in the 1970s. Combination chemotherapy regimens containing cisplatin and cyclophosphamide achieved higher response rates and overall survival than regimens without cisplatin in patients with advanced ovarian cancer.[20] Based on the results of these trials, the combination of cisplatin plus cyclophosphamide remained the standard of care for the treatment of ovarian cancer until the early 1990s.

The next major advance in the therapy of advanced ovarian cancer occurred

with the introduction of paclitaxel into chemotherapy regimens. McGuire et al. reported the results of a Gynecologic Oncology Group (GOG)-111 study that found the combination of paclitaxel 135 mg/m^2 over 24 hours and cisplatin 75 mg/m^2 achieved higher response rates and longer survival than did cyclophosphamide 750 mg/m^2 and cisplatin 75 mg/m^2 in patients with newly diagnosed, suboptimally debulked, stages III and IV ovarian cancer.[31] Survival improved significantly in the paclitaxel arm, with an increase in median progression-free survival (18 vs 13 months) and overall survival (38 vs 24 months). Neutropenia, alopecia, and peripheral neuropathy were more severe in the paclitaxel plus cisplatin group. Similar results were reported in a large European-Canadian Intergroup Phase III randomized trial study (OV10) that also confirmed superior response rates with the paclitaxel 135 mg/m^2 over 24 hours and cisplatin 75 mg/m^2 regimen as compared with the cyclophosphamide 750 mg/m^2 and cisplatin 75 mg/m^2 regimen.[32] Based on the results of these studies, paclitaxel plus cisplatin was widely adopted and became the accepted standard of care.

The availability of carboplatin led to clinical trials to evaluate whether carboplatin could be substituted for cisplatin, which would spare patients from the significant neurotoxicity and nephrotoxicity associated with cisplatin. Several prospective randomized comparisons of carboplatin plus paclitaxel versus cisplatin plus paclitaxel in patients with advanced ovarian cancer have been conducted.[33–36] The results of these trials show that carboplatin plus paclitaxel is equally efficacious and better tolerated than cisplatin and paclitaxel. In the GOG-158 study, 840 previously untreated patients with optimally resected stage III disease (no residual tumor nodule >1 cm) were randomized to carboplatin (area under the curve [AUC] = 7.5) plus paclitaxel 175 mg/m^2 over 3 hours, or cisplatin 75 mg/m^2 plus paclitaxel 135 mg/m^2 over 24 hours administered every 21 days for six cycles.[33] The results of that trial showed no difference in progression-free survival between the two treatment arms with a median time-to-progression of 19.4 months in the paclitaxel plus cisplatin arm versus 20.7 months in the paclitaxel plus carboplatin arm. As expected, the incidence of leukopenia, fever, gastrointestinal toxicity, and metabolic toxicity was higher in patients in the cisplatin arm, while patients in the carboplatin arm experienced more thrombocytopenia and pain. Although the incidence of neurotoxicity was similar in the two treatment arms, it was more severe in the paclitaxel plus cisplatin arm. The results of this study showed that the substitution of carboplatin for cisplatin in the regimen does not compromise efficacy and improves tolerability. These findings were confirmed in two other

large randomized controlled studies.[35,36] Based on these results, paclitaxel plus carboplatin became the accepted standard of care.

While most chemotherapy drugs used to treat ovarian cancer are dosed according to body surface area (BSA), carboplatin dosing is personalized based on each individual's renal function with the Calvert formula: carboplatin dose = AUC × (glomerular filtration rate [GFR] + 25).[37] When it was originally developed and validated, measured GFR was used in the Calvert equation. However, estimated creatinine clearance (CL_{CR}) is now used in clinical practice in place of measured GFR. Despite more than 30 years of clinical use, it is still not clear which equation to use to estimate CL_{CR} and the best method to estimate CL_{CR} in certain patient subgroups. The use of personalized carboplatin dose has reduced potential toxicity such as thrombocytopenia, neuropathy, and nephrotoxicity.[37] Personalized dosing of carboplatin is one of the reasons why it is the preferred platinum agent over cisplatin for primary treatment for ovarian cancer.[36]

Other clinical trials have evaluated the use of docetaxel as a substitute for paclitaxel. In the Scottish Randomized Trial in Ovarian Cancer (SCOTROC), Vasey et al. compared carboplatin (AUC = 5) combined with either docetaxel (75 mg/m^2 over 1 hour) or paclitaxel (175 mg/m^2 over 3 hours) administered every 21 days for six cycles as first-line chemotherapy for stages I to IV epithelial ovarian cancer.[38] The results of this study showed that the substitution of docetaxel for paclitaxel does not compromise efficacy and improves tolerability, particularly neurotoxicity. These findings were not confirmed in another randomized controlled trial. However, based on the results of this study, the combination of docetaxel plus carboplatin is considered a reasonable treatment option for patients with advanced ovarian cancer. Six cycles of paclitaxel plus carboplatin following tumor-debulking surgery remain the current standard of care for treatment of advanced ovarian cancer.

Although the choice of taxane or platinum agent does not appear to have a major effect on antitumor activity, the impact of paclitaxel dose and frequency of administration is controversial.[39–41] In a phase III trial conducted in Japan, Katsumata et al. reported that patients randomized to six cycles of dose-dense weekly paclitaxel plus carboplatin every 3 weeks had longer progression-free survival as compared to the standard paclitaxel plus carboplatin every 3 weeks.[41] Overall survival at 3 years was also significantly longer in patients who received the dose-dense regimen (72% vs 65%, $P = 0.03$). However, over 42% of the patients who received the dose-dense regimen dropped out of the study before

completing six cycles because of treatment-related toxicities. Two recently completed phase III trials were not able to confirm these efficacy results of "dose-dense" paclitaxel plus carboplatin. In the overall patient population of GOG-262, progression-free survival was not prolonged in patients with advanced ovarian cancer randomized to receive carboplatin plus dose-dense weekly paclitaxel compared to carboplatin plus paclitaxel every 3 weeks. Patients were also stratified according to whether they received bevacizumab in addition to the carboplatin and taxane regimen. The lack of progression-free survival benefit was limited to patients who received bevacizumab.[42] A second trial, ICON8, also failed to show a difference in progression-free survival between dose-dense paclitaxel and administration every 3 weeks in 1,566 European women with advanced ovarian cancer.[43] Due to less favorable treatment-related toxicities and questionable benefit on progression-free survival, dose-dense weekly paclitaxel regimens are not widely used.

IP chemotherapy was initially employed as palliative care in the management of ascites and uncontrolled intra-abdominal tumors. In the late 1970s, IP chemotherapy as a primary treatment intervention was initiated based on the rationale that exposure of the tumor to high drug concentrations would increase tumor drug uptake by passive diffusion and ultimately cancer cell death.[44] The increase in AUC exposure in the peritoneal cavity was demonstrated, but the correlative increase in drug uptake in tumor tissue has yet to be validated in any preclinical or clinical study.

7 IP chemotherapy has demonstrated benefit in the first-line treatment of patients with optimally debulked advanced-stage ovarian cancer.[45,46] In a landmark trial, Armstrong et al. reported the results of the GOG-172 study, which evaluated 415 patients randomized to receive either the combination regimen of paclitaxel 135 mg/m^2 over 24 hours and cisplatin 75 mg/m^2 or a new combination regimen that included paclitaxel 135 mg/m^2 IV infused over 24 hours followed by cisplatin 100 mg/m^2 IP infused over 1 hour on day 2, and then paclitaxel 60 mg/m^2 IP infused over 1 hour on day 8.[21] Both treatment regimens were given once every 21 days for a total of six cycles. Patients randomized to the IP chemotherapy arm had a 5.5-month increase in median progression-free survival and a 15.9-month increase in overall survival.[21] A secondary analysis by Tewari et al. of patients from GOG-172 and GOG-114 IP therapy studies reported a 10.4 month improvement in the median overall survival and 23% decreased risk of death in those patients that had received IP chemotherapy compared to IV chemotherapy.[22] Contributing factors that negatively impacted

survival included gross residual disease, clear cell or mucinous histology, and not completing all six cycles of IP chemotherapy.

A limitation of IP therapy is significantly more toxicity, including pain, fatigue, myelosuppression, gastrointestinal, metabolic, and neurotoxicity.[19,21,47,48] Despite its potential benefits, IP therapy has been slowly adopted into routine clinical use. In a cohort study of 823 women with advanced ovarian cancer from six National Comprehensive Cancer Network (NCCN) institutions, Burger et al. found that less than 50% of eligible patients had received IP chemotherapy as part of their primary treatment.[49] The significant increase in systemic toxicity, primarily neurotoxicity, has led to the question of whether IP carboplatin could be substituted for IP cisplatin. Although these platinum agents have demonstrated equal efficacy when administered IV to ovarian cancer patients, it is difficult to extrapolate the IP activity of cisplatin to carboplatin because of the difference in molecular size of cisplatin versus carboplatin and the importance of passive diffusion of drug into the tumor. The use of IP chemotherapy as first-line treatment of advanced ovarian cancer is recommended by the NCCN guidelines but is not without clinical controversy. Most clinical trials have used platinum agents given IP until the GOG-172 trial that incorporated IP paclitaxel. Many clinicians are concerned about how to manage hypersensitivity reactions to either platinum or taxane agents when administered IP.

7 The 2019 NCCN guidelines recommend that IP chemotherapy be considered and offered to appropriate patients as first-line treatment of stage II-III, optimally debulked, <1 cm residual disease, ovarian cancer.[19] Because of the significant toxicities associated with IP therapy, only carefully selected patients should receive IP therapy. Ideal candidates for IP therapy are younger patients with good performance status, minimal comorbidities, adequate renal and liver function, and optimally debulked disease without significant bowel resection.[19,48]

In patients who are poor surgical candidates because of comorbidities or bulky tumors, neoadjuvant chemotherapy can be given prior to any surgical interventions.[50] In patients with bulky disease, the goal of neoadjuvant chemotherapy is to reduce tumor burden to make surgery more feasible and optimal tumor debulking more likely. The typical regimen used in neoadjuvant chemotherapy is three cycles of a taxane combined with a platinum agent, followed by surgery. After surgery, patients usually receive another three to six cycles (IV or IP/IV), depending on their response to chemotherapy.[19,51] In patients who are poor candidates for surgery because of comorbidities, the

primary intent of neoadjuvant chemotherapy is to relieve symptoms and slow disease progression. In this setting, palliative chemotherapy alone has not been curative for patients with advanced ovarian cancer.[50] If tolerated, these patients will receive the standard taxane plus platinum chemotherapy regimen once every 3 to 4 weeks. Another option for palliative neoadjuvant chemotherapy, especially in elderly patients, is single-agent carboplatin once every 4 weeks.

Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy is first-line treatment for patients who are poor surgical candidates or patients with bulky or significant tumor burden.[50] The neoadjuvant chemotherapy regimen typically includes a combination of taxane with platinum agent and is administered every 21 to 28 days as tolerated with intent to reduce tumor burden to where it potentially could be surgically resected and ideally optimally debulked during surgery.[50] After surgery, patients receive another three to six cycles depending on response to chemotherapy. The role of neoadjuvant chemotherapy for all patients presenting with advanced ovarian cancer is being revisited in ongoing GOG clinical trials.

Consolidation Therapy

If patients do not achieve a clinical complete response after completion of six cycles of a taxane-platinum regimen, then consolidation chemotherapy should be considered in an attempt to achieve a complete response (Fig. 150-3). If the patient has a partial response to first-line chemotherapy, as measured by a greater than 50% decline in CA-125 (as compared with the presurgery level) or tumor regression, the cancer is still considered sensitive to the regimen. The typical regimens for consolidation chemotherapy are the taxane plus platinum regimen or single-agent therapy with either a taxane or platinum agent.[19] If the patient had a poor response to taxane and platinum, then alternative second-line agents can be considered.[19] Additional cycles of chemotherapy are given until complete response is achieved. Another alternative in the setting of no or minimal measurable disease after completion of primary chemotherapy is to just observe the patient and provide supportive care as indicated until disease progresses, then reinitiate chemotherapy at that time.[19]

Since the initial clinical complete response observed in first-line treatment is not durable, optimization of first-line therapy is under investigation. Numerous options have been evaluated, including the use of additional cycles or

maintenance chemotherapy and dose intensity.

Maintenance Chemotherapy

Maintenance chemotherapy is given to those patients who have achieved a clinical complete response to first-line chemotherapy. The primary differences between consolidation and maintenance chemotherapy are the types of agents used and duration of therapy. Consolidation therapy usually consists of more aggressive combination regimens, while maintenance chemotherapy usually consists of single intravenous agents given less frequently (ie, once monthly) to minimize adverse effects. Oral targeted agents are alternatives to intravenous therapy in a subset of patients with specific gene mutations and allow for increased dosing convenience in the outpatient setting. The goal of maintenance chemotherapy is to eliminate any residual microscopic disease that may be present to extend progression-free and overall survival.

Maintenance chemotherapy has gained popularity after the results of the collaborative Southwest Oncology Group (SWOG) and GOG 178 study that compared single-agent paclitaxel 175 mg/m^2 over 3 hours once every 21 days for three additional cycles versus an additional 12 cycles.[52] Eligible patients had to have been in complete clinical remission after at least five to six cycles of a taxane-platinum regimen. This study was closed after the interim analysis by the SWOG Safety Monitoring Committee because patients receiving the additional 12 cycles had longer progression-free survival than those receiving three cycles of single-agent paclitaxel (28 vs 21 months). After the results were reported, many patients randomized to the three-cycle arm chose to receive nine additional cycles of paclitaxel, which reduced the ability of the trial to show a difference in overall survival.[53] Because this study was closed early and did not demonstrate an overall survival benefit, another randomized, controlled GOG trial was initiated to confirm the improvement in progression-free survival and to attempt to determine the impact on overall survival. Until these confirmatory trials are completed, the role of maintenance taxane-based chemotherapy is controversial in the management of advanced ovarian cancer patients. Olaparib, an oral poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor, should be considered as maintenance therapy in women with a germline mutation in BRCA1 or BRCA2 and a response to frontline platinum-based therapy. Continuous twice-daily oral dosing of olaparib provided substantial clinical benefit in progression-free survival when compared to placebo in this patient population in the phase III SOLO1 trial.[54] The use of maintenance therapy with

olaparib resulted in a 70% lower risk of disease progression or death. The publication of this trial immediately impacted the treatment paradigm for women with newly diagnosed, advanced ovarian cancer and a BRCA 1/2 mutation.

Maintenance chemotherapy is listed as an option in the 2019 NCCN guidelines (category 1 recommendation for germline mutations; category 2A recommendation for somatic mutations).[19]

Treatment of Recurrent Disease

Although most patients will achieve a complete response to initial treatment, most patients will eventually have recurrence of their disease within the first 2 years. When a patient relapses, the prognostic factors are similar to the factors after initial surgery except that the disease-free interval—defined as the length of time that has lapsed since the completion of chemotherapy—should be considered to determine if the tumor is likely to be drug resistant to agents used in first-line treatment (ie, platinum and taxanes). If recurrence occurs less than 6 months after completion of chemotherapy or if the patient progresses during platinum-based chemotherapy, the tumor is defined as platinum-resistant. Patients with platinum-sensitive disease generally have a better prognosis than platinum-resistant patients.

8 9 If the patient had a clinical complete response to first-line chemotherapy and the recurrence occurred more than 6 months after chemotherapy is completed, the tumor is considered platinum-sensitive. In patients with platinum-sensitive ovarian cancer, the standard of care is to treat the first recurrence with a doublet, platinum-containing chemotherapy regimen. **Table 150-2** summarizes some of the chemotherapeutic regimens used in the treatment of recurrent or refractory ovarian cancer. Because the chemotherapy agents used for second-line treatment of recurrent or refractory platinum-resistant disease have similar response rates that average less than 30%, the selection of the agent depends on the toxicity profile of the agent, physician preference, patient performance status, residual toxicities, and patient convenience (Fig. 150-3). In this setting, the intent of treatment is to prolong survival and alleviate symptoms, not necessarily to achieve another “complete response” to chemotherapy. Because of poor response rates of the available agents, participation in a clinical trial of an investigational agent is often recommended for patients with recurrent platinum-resistant ovarian cancer.

TABLE 150-2 Single-Agent Chemotherapeutic Regimens for Recurrent or

Refractory Ovarian Cancer

Drug(s)	Brand Name(s)	Initial Dose(s)/Usual Range	Cycle Frequency
Docetaxel	Taxotere	75 mg/m² IV day 1	Every 21 days
Pegylated-liposomal doxorubicin	Doxil	40 mg/m² IV day 1	Every 28 days
Gemcitabine	Gemzar	800-1,000 mg/m² IV days 1, 8, and 15	Every 28 days
Paclitaxel	Taxol	60-80 mg/m² IV (1-hour infusion) day 1	Every week
Paclitaxel	Taxol	135-175 mg/m² IV day 1	Every 21 days
Carboplatin	Paraplatin	AUC 5 IV day 1	Every 21-28 days
Cisplatin	Platinol	75 mg/m² IV day 1	Every 21-28 days
Topotecan	Hycamtin	1.3-1.5 mg/m² IV once daily for 5 days	Every 21 days
Topotecan	Hycamtin	4 mg/m² IV once a week × 3 weeks, then 1 week off	Every 21 days
Etoposide	Vepesid	50 mg/m² orally once daily days 1-10 repeat every 21 days	Every 28 days
Capecitabine	Xeloda	1,800-2,000 mg/m² in divided dose twice a day for 2 weeks on, 1 week off	Every 21 days
Altretamine	Hexalen	260 mg/m² orally (total daily dose divided in four doses) for 14-21 days	Every 28 days
Olaparib	Lynparza	300 mg orally twice daily	Continuous
Rucaparib	Rubraca	600 mg orally twice daily	Continuous
Tamoxifen	Nolvadex	20 mg orally twice a day	Continuous
Letrozole	Femara	2.5 mg orally once daily	Continuous

AUC, area under the curve.

Current research efforts are focused on identifying biomarkers that are predictive of response in ovarian cancer. The primary focus has been on response to first-line treatment agents, paclitaxel and platinum and the multidrug resistance (MDR) pathway, specifically ABC-transport protein p-glycoprotein (Pgp).[55] Epigenetic changes are heritable changes outside of the “traditional” DNA coding sequence that could potentially account for drug resistance. Aberrant DNA methylation and histone acetylation are epigenetic events that can silence tumor suppression genes required for apoptosis or DNA repair and therefore lead to resistance. The acetylation of histones is required for active genes and deacetylation occurs in silenced genes. Histone acetyltransferases (HATs) add acetyl groups and histone deacetylases (HDACs) remove acetyl groups.[56]

Ovarian cancers upregulate a variety of factors involved in DNA repair, angiogenesis, proliferation, and migration; they also downregulate mismatch-repair (MMR), cell adhesion, and apoptotic genes.[56] Tumorigenesis can induce hypermethylation or hypomethylation, which leads to chromosomal instability.

Hypermethylation or deacetylation can silence specific genes such as *hMLH1*, which leads to tumor formation and progression in the ovaries. Deacetylation of p21, a cell cycle regulator, can occur in ovarian carcinomas. Epigenetics may downregulate Apaf-1 and p16 while potentially upregulating MDR1. Finally, resistance to a platinum and taxane regimen may be associated with *hMLH1* methylation.[56]

Genomic information such as amplified or deleted sequences or single nucleotide polymorphisms (SNPs) is being evaluated for their possible role in resistance. Proteomics can also be used to identify mechanisms of resistance by finding over- or underexpressed proteins. These methods could optimize pharmacotherapy if any of these biomarkers are predictive of drug response or resistance.[57]

Platinum-Sensitive Disease

9 Retreatment with a platinum-containing regimen should be considered in patients with platinum-sensitive disease. The International Collaborative Ovarian Neoplasm 4 and Arbeitsgemeinschaft Gynaekologische randomized 802 patients with recurrent platinum-sensitive ovarian cancer to either single-agent platinum, a non–taxane-platinum combination, or a taxane plus platinum combination.[58] Patients treated with the paclitaxel plus platinum regimen had significantly longer progression-free (29 vs 24 months) and overall survival (hazard ratio 0.82; 95% CI 0.69–0.97) as compared with the other two treatment arms.[58,59] Although the taxane-platinum combination was clearly superior in this European study, it is difficult to extrapolate these results to patients treated in the United States because of differences in first-line treatment. At the time that International Collaborative Ovarian Neoplasm 4 (ICON4) was conducted, the standard of care in Europe for first-line treatment was single-agent carboplatin, so most patients enrolled in this study had no prior exposure to a taxane agent.[58] However, the standard of care in the United States has been a taxane-platinum combination since the early 1990s. Confirmatory data are needed to evaluate whether combination regimens would also be more beneficial in these patients for treatment of recurrent ovarian cancer.

Biologic and targeted agents play an important role in the treatment of recurrent disease. Bevacizumab is a recombinant humanized monoclonal antibody that targets vascular endothelial growth factor (VEGF), a key mediator of angiogenesis. The phase 3 randomized trial (OCEANS) randomized women with platinum-sensitive recurrent disease to carboplatin/gemcitabine with and

without bevacizumab.[60] Progression-free survival was significantly longer in patients receiving bevacizumab (12.4 vs 8.4 months), but no difference in overall survival was observed. The addition of bevacizumab to the combination of carboplatin and paclitaxel did show a modest increase in overall survival in GOG-213 compared to chemotherapy alone (42.2 vs 37.3 months, hazard ratio 0.83; 95% CI, 0.68-1.00; $P = 0.056$).[61] Due to the toxicity profile of bevacizumab, patients considered for bevacizumab therapy must be carefully selected. Further details regarding the role of bevacizumab and other targeted and biologic agents in the treatment of ovarian cancer will be discussed in the following section.

The preferred regimen for platinum-sensitive recurrent disease varies by clinician. Some clinicians will recommend retreatment with a chemotherapy regimen including a platinum agent. Other clinicians suggest that the platinum-free interval for these patients should be extended and recommend that recurrent disease first be treated with a nonplatinum regimen (ie, liposomal doxorubicin) and reserve the platinum agent until the next relapse.

The 2019 NCCN guidelines recommend the combination of platinum agent with gemcitabine, liposomal doxorubicin, or paclitaxel for treatment of platinum-sensitive recurrent ovarian cancer (**Table 150-3**).[19] In addition, the combination of gemcitabine plus cisplatin, gemcitabine plus carboplatin and bevacizumab and carboplatin plus paclitaxel and bevacizumab has demonstrated improvement in progression-free survival.[59–61] Carboplatin alone or any of the second-line agents is recommended for patients with platinum-sensitive disease who are unable to tolerate additional combination chemotherapy regimens because of residual toxicity or poor performance status.

TABLE 150-3 Combination Chemotherapy Regimens for Platinum-Sensitive Recurrent Ovarian Cancer

Drug(s)	Brand Name	Initial Dose(s)/Usual Range	Cycle Frequency
Gemcitabine + carboplatin	Gemzar/Paraplatin	800 mg/m² IV day 1 & 8	Every 21 days
Gemcitabine + cisplatin	Gemzar/Platinol	Dosed to AUC 5 IV day 1	Every 21 days
Liposomal doxorubicin + carboplatin	Doxil/Paraplatin	Day 1 & day 8: gemcitabine 800 mg/m² & cisplatin 40 mg/m²	Every 28 days
Gemcitabine + carboplatin + bevacizumab	Gemzar/Paraplatin/ Avastin	1000 mg/m² IV day 1 & 8 Dosed to AUC 4 IV day 1 15 mg/kg IV on day 1	
Cyclophosphamide + bevacizumab	Cytoxan/Avastin	30 mg/m² IV over 1-3 hours & carboplatin AUC 5 50 mg PO once daily + bevacizumab 15 mg/kg q3 weeks	Every 28 days

AUC, area under the curve; PO, by mouth.

Platinum-Resistant Disease

Patients frequently present with recurrent drug-resistant disease after initial platinum-based therapy and cytoreductive surgery.[20] Patients who progress on a platinum agent or have no response are considered “platinum-refractory,” while those patients who have recurrence within 6 months of completing a platinum-containing regimen are considered “platinum-resistant.”[19] The 2019 NCCN guidelines list many possible treatment options for recurrent platinum-resistant or refractory ovarian carcinoma.[19] The optimal chemotherapeutic agent or regimen in the treatment of platinum-resistant disease is unclear. Ideally, the agent should be active in ovarian cancer and non–cross-resistant with taxanes or platinum agents. Unfortunately, the response rate is low for all of the agents in platinum-refractory or resistant ovarian cancer.[20] Patients should typically be evaluated for response after treatment with at least three cycles of the chemotherapy agent or regimen. Because partial responses are rare, stable disease with relief of symptoms is considered a treatment success. If no response is observed, then an alternative chemotherapy regimen may be selected. Because all the potential agents have similar efficacy, the selection of agents and sequence used for treatment as the patient progresses will vary based on residual toxicity, dosing schedule, patient convenience, and physician preference.

Topotecan, an analog of the plant alkaloid 20(S)-camptothecin, is active in patients with metastatic ovarian cancer and is non–cross-resistant with platinum-based chemotherapy.[20] Preclinical studies suggest that protracted schedules of administration with low doses achieve the greatest antitumor response.[20] Topotecan has demonstrated activity in phase II trials as second-line and salvage therapy in patients who have relapsed after, or progressed during, platinum-

based therapy.[62] A randomized phase III trial compared topotecan and paclitaxel in patients with advanced ovarian cancer who had failed one platinum-based regimen.[63] Patients were randomized to receive topotecan 1.5 mg/m^2 per day as a 30-minute infusion for 5 days repeated every 21 days or paclitaxel 175 mg/m^2 as a 3-hour infusion every 21 days. The overall response rate was 21% and 13% for the topotecan- and paclitaxel-treated groups, respectively. The median time-to-progression for topotecan-treated patients (32 weeks) was not significantly different from that for paclitaxel-treated patients (20 weeks). Median survival was 61 weeks in the topotecan-treated group and 43 weeks in the paclitaxel-treated group. Topotecan was well tolerated with minimal nonhematologic toxicities.[62,63]

Pegylated liposomal doxorubicin is one of the primary agents used for second-line therapy of recurrent ovarian cancer.[64–66] The drug tends to be better tolerated than topotecan, which is important for heavily pretreated patients with advanced disease. A large, randomized phase III study compared pegylated liposomal doxorubicin 50 mg/m^2 every 4 weeks to topotecan 1.5 mg/m^2 per day for 5 days repeated every 21 days in patients who failed first-line platinum therapy.[66] A total of 474 patients were randomized, 239 to pegylated liposomal doxorubicin and 235 to topotecan. The overall response rates for the pegylated liposomal doxorubicin and topotecan groups were 20% and 17%, respectively. Overall survival tended to favor pegylated liposomal doxorubicin, with a median of 108 weeks versus 71 weeks for topotecan. Differences in toxicity were observed between the arms, with more hematologic toxicity occurring in the topotecan arm and more palmar–plantar erythrodysesthesia (PPE) in the pegylated liposomal doxorubicin arm. However, the incidence of PPE in current clinical practice has decreased because the standard dose of pegylated liposomal doxorubicin used currently (40 mg/m^2) is less than the dose that was used in the initial clinical trials and approved by the FDA.[67,68]

Gemcitabine, a novel pyrimidine antimetabolite, is also widely used in the treatment of recurrent platinum-resistant ovarian cancer. Although the overall response rate is only about 13% to 22% with single-agent gemcitabine in patients with platinum-refractory recurrent ovarian cancer, an additional 16% to 50% of patients have stable disease for a median of 7 months.[69] The main toxicities include myelosuppression, fatigue, myalgia, and skin rash. Because of its non–cross-resistant activity and in vivo synergy with platinum agents, gemcitabine is being evaluated in doublet regimens in patients with refractory disease and with carboplatin/taxane regimens in previously untreated patients.[69] The combination of gemcitabine with taxanes has demonstrated response rates

from 36% to 90%, which if confirmed are extremely encouraging.[20]

Other agents that have shown an overall response rate of 10% to 25% in patients with recurrent ovarian cancer include altretamine, etoposide, capecitabine, tamoxifen, letrozole, vinorelbine, and oxaliplatin.[20] Response rates tend to be higher in the platinum-sensitive subgroups. Most of these agents are available in oral formulations, which allows for outpatient administration in the palliative care setting.

The three most commonly used agents in clinical practice are pegylated liposomal doxorubicin, gemcitabine, and topotecan. These agents have demonstrated efficacy when used as a single agent and in combination with other agents. Selection of chemotherapy for treatment of recurrent disease is based on the patient's residual toxicities, scheduling and convenience, and physician preference.

Additional research continues to identify new agents and new targets for the treatment of ovarian cancer. Because platinum agents and taxanes have been identified as the most active classes of agents for treatment of ovarian cancer, drug development has focused on new platinum derivatives, taxanes and taxane analogs, and agents that exert cytotoxic activity by interacting with DNA directly. Specifically, new cytotoxic agents such as trabectedin, pemetrexed, and epothilones are currently being evaluated in clinical trials.

Biologic and Targeted Agents

Monoclonal antibodies such as bevacizumab and cetuximab and small molecule tyrosine kinase inhibitors such as pazopanib, sunitinib, gefitinib, or sorafenib are being evaluated to be incorporated into first-line, recurrent and maintenance treatment regimens for ovarian cancer.[20] Although the biologic agents as single agents have not demonstrated significant activity, the results of several clinical trials show that the addition of agents such as bevacizumab into first-line and maintenance regimens improves progression-free survival. However, the impact on overall survival is controversial.

Anti-Angiogenesis Agents

Bevacizumab is a recombinant humanized monoclonal antibody that targets VEGF, a key mediator of angiogenesis. In the setting of recurrent disease, single-agent bevacizumab produces a response rate similar to other therapies of 16% to 21%.[70,71] Response rates with combinations of bevacizumab range from 15% to 80%.[70–74] However, these phase II trials have also reported a higher risk of

bowel perforation in patients treated with bevacizumab-containing regimens.[70,71] Bevacizumab should therefore not be given to patients who have had recent bowel surgery or a history of significant bowel resections. In an open label phase III study (AURELIA Study) that evaluated the combination of bevacizumab in combination with chemotherapy (pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan), the addition of bevacizumab to chemotherapy had no significant impact on overall survival but did improve median progression-free survival (6.4 vs 3.7 months).[75] Based on this study, bevacizumab was approved for use in combination with pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan for treatment of recurrent ovarian cancer.

Recent efforts have focused on the use of bevacizumab in first-line treatment regimens. Perren et al. conducted an international multi-institutional phase III randomized study (ICON-7) that demonstrated a 7.8 month improvement in overall survival in women who had bevacizumab added to first-line treatment.[76] Based on these encouraging preliminary results, the GOG initiated a confirmatory phase III (GOG-218) study comparing six cycles of standard paclitaxel plus carboplatin to six cycles of the same regimen with bevacizumab to determine whether bevacizumab improves the efficacy of paclitaxel plus carboplatin.[77] A third arm evaluated the benefit of maintenance bevacizumab for an additional 10 months. At the conclusion of the study, no difference in overall survival was observed between the three study arms. However, a four-month increase in median progression-free survival was observed in the group that received an additional 10 months of maintenance bevacizumab. Cohn et al. completed a cost utility analysis that incorporated quality of life scores to estimate the cost effectiveness of bevacizumab with paclitaxel/carboplatin for first-line treatment of advanced ovarian cancer.[78] In that analysis, the incremental cost effectiveness ratio of the addition of bevacizumab 15 mg/kg once every 3 weeks to paclitaxel/carboplatin regimen was $632,571 per progression-free year and $792,380 per quality-adjusted progression-free year. Incorporation of quality-of-life scores resulted in a less favorable incremental cost effectiveness ratio. Although bevacizumab has demonstrated some progression-free survival advantages when used in combination, its effect on overall survival is not clear. Furthermore, the benefits do not appear to justify the high cost of bevacizumab. As a result, health insurance companies do not consistently reimburse for bevacizumab when used for the primary treatment of ovarian cancer.

Pazopanib, an oral anti-angiogenesis agent, is an alternative treatment regimen for platinum-refractory recurrence.[79] A phase 2 trial assessed oral

pazopanib in patients with low-volume recurrent disease who had achieved complete response to initial therapy. Overall response rate was 18% (n=36). Single agent pazopanib is listed as an alternative option for the treatment of platinum-resistant disease in the 2019 NCCN guidelines (category 2B recommendation).[19]

PARP Inhibitors

10 Poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) plays a critical role in the repair of single-strand DNA breaks via the base-excision repair pathway. Specifically PARP keeps the low-fidelity nonhomologous-end-joining DNA repair machinery functioning. PARP inhibition results in double-stranded DNA breaks that cannot be repaired in cancer cells with homologous recombinant deficiency such as those with BRCA1/2 mutations. The activity of the new class of the PARP inhibitors may depend on BCRA status or "BRCAness" of the tumor. Three oral PARP inhibitors are commercially available—olaparib, rucaparib and niraparib—with drug specific FDA-labeled approvals as maintenance therapy. Both olaparib and rucaparib also have FDA-approved indications for treatment of recurrent platinum-sensitive ovarian cancers.

In 2015, olaparib, the first PARP inhibitor was approved for treatment of recurrent, platinum-sensitive BRCA1/2 positive ovarian cancer after failure of at least three prior treatments.[80] The second agent to gain approval in the treatment of recurrent disease was rucaparib. Progression-free survival was increased in patients with BRCA mutations in a recent phase 2 trial (ARIEL2) of rucaparib for patients with platinum-sensitive ovarian cancer following failure of two or more lines of chemotherapy.[81] Patients with platinum-sensitive disease have a higher response rate to PARP inhibitors compared to those with platinum-resistant disease (66% vs 20%-30%).[82] However, PARP inhibitors are considered a preferred option in this setting because of the lack of active agents in platinum-resistant disease.[19]

Olaparib is FDA-labeled for use as first-line maintenance treatment in advanced disease patients with BRCA 1/2 mutations who are in complete or partial response to first-line platinum-based chemotherapy. At a median follow-up of 41 months, olaparib resulted in a decreased 3-year rate of disease progression or death compared with placebo (60% vs 27%; hazard ratio for disease progression or death 0.30, 95% CI 0.23-0.41).[54] All three PARP inhibitors have FDA-labeled indications as maintenance therapy options in

patients with recurrent disease. The approval for these agents was based on improvements in progression-free survival ranging from 9 to 14 months.[83,84] Niraparib was specifically approved for maintenance treatment regardless of platinum-sensitivity and BRCA status.

The common adverse effects associated with PARP inhibitors include nausea and vomiting and significant anemia with associated fatigue. Patients often require antiemetics and some require transfusion support due to drug-induced anemia. Additional serious but infrequent toxicities include thrombocytopenia, neutropenia, and rarely progression of malignant neoplasms. The challenge of combining PARP inhibitors with chemotherapy has been the fatigue, nausea and significant hematological toxicity, primarily anemia, thrombocytopenia and neutropenia.

Other Targeted Agents

Tyrosine kinase inhibitors such as sorafenib, sunitinib, pazopanib, and cediranib inhibit angiogenesis by specifically targeting the VEGF receptor (VEGFR). When given as single agents, tyrosine kinase inhibitors have demonstrated some antitumor activity in ovarian cancer.[85,86] Ongoing trials have focused on combination regimens with cytotoxic agents for first-line treatment and also treatment of recurrent ovarian cancer. Another interesting targeted agent is VEGF Trap (aflibercept), a fusion protein that targets VEGF-A. Aflibercept has been beneficial in the treatment of malignant ascites and is currently being incorporated into first-line regimens. Epidermal growth factor receptor (EGFR) inhibitors such as erlotinib have not demonstrated activity either alone or combined with chemotherapy or bevacizumab for the treatment of ovarian cancer.[87] Newer classes of targeted therapies such as platelet-derived growth factor (PDGF) inhibitors are being investigated in ongoing clinical trials.[88]

Immunotherapy

Many clinical trials are evaluating the role of immunotherapy in the treatment of ovarian cancer based on changes in chromosomal instability and epigenetic silencing. Improved survival has been correlated with the increased presence of CD3+ tumor-infiltrating lymphocytes (TIL) and a high CD8+/regulatory T-cell ratio in ovarian cancer patients provides evidence for the immunogenicity of this tumor.[89,90] Increased TILs are linked to tumors with high chromosomal instability such as those with *BRCA* mutation or epigenetic loss. Immunotherapy is currently not indicated for ovarian cancer except for those who have high

microsatellite-instability tumors, which are only seen in 2% of ovarian cancers.

EVALUATION OF THERAPEUTIC OUTCOMES

During chemotherapy, patients may experience numerous side effects such as nausea and vomiting, myelosuppression, neuropathy, and changes in organ function. Patients receiving a taxane or platinum chemotherapy regimen should be monitored for signs of hypersensitivity or infusion-related reactions. Patients treated with paclitaxel often experience infusion-related reactions, which have been attributed to the polyethoxylated castor oil (Cremophor) diluent. Premedications including an H_1-blocker, H_2-blocker, and steroid should be administered prior to each chemotherapy administration to prevent hypersensitivity reactions. If a patient has a reaction, increasing the duration of the infusion from 3 to 6 hours may help with infusion-related reactions. For patients with a true taxane allergy, paclitaxel desensitization can be attempted with 24 hours of premedications (H_1-blocker, H_2-blocker, and steroids) followed by paclitaxel given as a titrated infusion (1:1000 → 1:100 → 1:10 → full dose) over 8 hours. With repeated exposure (ie, seven cycles or more) to carboplatin, patients can develop a delayed hypersensitivity reaction. A similar protocol can be used for carboplatin desensitization.

Ovarian cancer patients receive multiple courses of chemotherapy that can have varying effects on kidney and liver function, often with a delayed onset. Appropriate laboratory tests should be ordered to assess organ function so that chemotherapy doses can be adjusted as indicated. Patients on platinum-containing regimens can often experience electrolyte wasting, so patients should be monitored for electrolyte replacement, IV or oral, as indicated. The use of myeloid growth factors should be considered to prevent treatment delays or dose reductions. Prevention of nausea and vomiting, both acute and delayed, is critical for patients receiving emetogenic chemotherapy regimens.

During initial taxane plus platinum chemotherapy, a CA-125 level should be obtained with each cycle and monitored for at least a 50% reduction in CA-125 after completion of four cycles, which is related to an improved prognosis. Patients who achieve a complete response after completion of first-line treatment should have follow-up once every 3 months, including CA-125, physical examination, pelvic examination, and appropriate diagnostic scans (eg, computed tomography, magnetic resonance imaging, or positron emission tomography), which should be evaluated for presence of disease. In addition to routine follow-up examinations, clinicians should monitor for resolution of any

residual chemotherapy-related side effects, including neuropathies, nephrotoxicity, ototoxicity, myelosuppression, and nausea and vomiting.

In the progressive disease or recurrent setting, CA-125 levels can be used to monitor for response and should be checked with each cycle, although no change in therapy is recommended until after completion of at least three cycles of the second-line chemotherapy. In addition to laboratory monitoring, appropriate diagnostic scans (eg, computed tomography, magnetic resonance imaging, or positron emission tomography) should be done once every three cycles. Patients need to be monitored with each cycle of chemotherapy to evaluate for new or persistent toxicities such as neuropathies, fluid retention, PPE, myelosuppression, and nausea and vomiting. Another precaution to keep in mind for patients with significant ascites, the "dry weight" or an adjusted body weight should be used for dosing chemotherapy.

Most patients with ovarian cancer will eventually progress through all chemotherapy regimens and investigational treatment options, after which the best supportive care measures should be provided to maintain patient comfort and quality of life. A plan to treat common complications of progressive ovarian cancer, including thrombosis, ascites, uncontrollable pain, and small bowel obstruction, should be developed. This plan should include an opioid-based pain regimen with both long-acting agents and short-acting opioids for breakthrough or progressive pain; it should also include a bowel regimen to prevent opioid-induced constipation. Nausea can be a problem in women with advanced ovarian cancer when disease progression causes ascites or partial/complete bowel obstruction. Both antiemetic medications and nonpharmacotherapy interventions with nutrition and hydration can be helpful. Management of partial or complete small bowel obstruction focuses on controlling symptoms of pain and nausea. Bowel rest with best supportive care may lead to spontaneous resolution of the small bowel obstruction but most often it is a complication associated with rapidly progressive disease.[91] Palliative surgery may be considered in selected patients to relieve symptoms.

Postclass Engaged Learning Activity

Perform a primary literature search and identify a pivotal research study that led to the approval or additional indication for any of the FDA-approved PARP inhibitors. Write a brief summary describing the rationale for the study, the study methodology, major findings, and impact on the treatment of ovarian cancer. This activity is intended to build your drug literature evaluation skills

and ability to critically appraise research manuscripts.

ABBREVIATIONS

AUC	area under the curve
BRCA1	breast cancer activator gene 1
BRCA2	breast cancer activator gene 2
BSA	body surface area
CA-125	cancer antigen 125
CI	confidence index
CL_{cr}	creatinine clearance
EGFR	epidermal growth factor receptor
FDA	Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
GFR	glomerular filtration rate
GI	gastrointestinal
GOG	Gynecologic Oncology Group
HAT	histone acetyltransferase
HDAC	histone deacetylase
HSCT	hematopoietic stem cell transplantation
ICON4	International Collaborative Ovarian Neoplasm 4
IP	intraperitoneal
MDR	multidrug resistance

MMR	mismatch-repair
NCCN	National Comprehensive Cancer Network
^{32}P	phosphorus-32
Pap	Papanicolaou
PARP	poly-ADP-ribose polymerase
PDGF	platelet-derived growth factor
Pgp	p-glycoprotein
PPE	palmar–plantar erythrodysesthesia
QOL	quality of life
SBO	small bowel obstruction
SCOTROC	Scottish Randomized Trial in Ovarian Cancer
SNP	single nucleotide polymorphism
SWOG	Southwest Oncology Group
TAH/BSO	total abdominal hysterectomy/bilateral salpingo-oophorectomy
TVUS	transvaginal ultrasound
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

REFERENCES

1. Berek JS, Crum C, Friedlander M. Cancer of the ovary, fallopian tube and peritoneum. *Int J Gynaecol Obstet*. 2015;131(Suppl):S111–S122.
2. Siegel R, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69:7–34.
3. Bai H, Cao D, Yang J, et al. Genetic and epigenetic heterogeneity of epithelial ovarian cancer and the clinical implications for molecular targeted therapy. *J Cell Mol Med*. 2016. doi: doi:10.1111/jcmm.12771.
4. RimMertens-Waler I, Baxter RC, Marsh DJ. Gonadotropin signaling in epithelial ovarian cancer. *Cancer Lett*. 2012;324:152–159.
5. Reid BM, Permuth JB, Sellers TA, et al. Epidemiology of ovarian cancer: A review. *Cancer Biol Med*. 2017;14:9–32.
6. Olsen CM, Nagle CM, Whiteman DC, et al. Obesity and risk of ovarian cancer subtypes: Evidence from the Ovarian Cancer Association Consortium. *Endocr Relat Cancer*. 2013;20:251–262.
7. Beral V, Doll R, Hermon C, Peto R, Reeves G; Collaborative Group on Epidemiological Studies of Ovarian Cancer. Ovarian cancer and oral

contraceptives: Collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. *Lancet*. 2008;371:303–314.

8. Sundar S, Neal RD, Kehoe S. Diagnosis of Ovarian Cancer. *BMJ*. 2015;351:h4443.
9. Silverberg SG. Histopathologic grading of ovarian carcinoma: A review and proposal. *Int J Gynecol Pathol*. 2000;19:7–15.
10. Longuespee R, Boyon C, Desmons A, et al. Ovarian cancer molecular pathology. *Cancer Metastat Rev*. 2012;31:713–732.
11. Buys SS, Partridge E, Black A, et al. Effect of screening on ovarian cancer mortality: The prostate, lung, colorectal, and ovarian (PLCO) cancer screening randomized controlled trial. *JAMA*. 2011;305: 2295–2303.
12. Grossman DC, Curry SJ, Owens DK, et al. U.S. Preventive Services Task Force. Screening for ovarian cancer. *JAMA*. 2018;319:588–594.
13. Walker JL, Powell CB, Chen LM, et al. Society of Gynecologic Oncology recommendations for the prevention of ovarian cancer. *Cancer*. 2015;121:2108–2120.
14. Harris RE, Beebe-Donk J, Doss H, et al. Aspirin, ibuprofen, and other non-steroidal anti-inflammatory drugs in cancer prevention: A critical review of non-selective COX-2 blockade. *Oncol Rep*. 2005;13:559–583.
15. Lancaster JM, Powell CB, Chen L, Richardson DL; SGO Clinical Practice Committee. Society of Gynecologic Oncology statement on risk assessment for inherited gynecologic cancer predispositions. *Gynecol Oncol*. 2015;136:3–7.
16. Hartmann LC, Lindo NM. The role of risk-reducing surgery in hereditary breast and ovarian cancer. *N Engl J Med*. 2016;374:454–468.
17. Narod SA, Sun P, Ghadirian P, et al. Tubal ligation and risk of ovarian cancer in carriers of *BRCA1* and *BRCA2* mutations: A case control study. *Lancet*. 2001;357:1467–1470.
18. Goff BA, Mandel LS, Drescher CW, et al. Development of an ovarian cancer symptom index. *Cancer*. 2007;109:221–227.
19. National Comprehensive Cancer Network (NCCN) Practice Guidelines in Oncology—Ovarian Cancer, V1. 2019. Available at: http://www.nccn.org. Accessed July 29, 2019.
20. Earle CC, Schrag D, Neville BA, et al. Effect of surgeon specialty on processes of care and outcomes for ovarian cancer patients. *J Natl Cancer*

Inst. 2006;98:172–180.

21. Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med*. 2006;354:34–43.
22. Tewari D, Java JJ, Salani R, et al. Long-term survival advantage and prognostic factors associated with intraperitoneal chemotherapy treatment in advanced ovarian cancer: A gynecology oncology group study. *J Clin Oncol*. 2015;33(13):1460–1466. doi: doi:10.1200/JCO.2014.55.9898.
23. Chang SJ, Bristow RE, Chi DS, Cliby WA. Role of aggressive surgical cytoreduction in advance ovarian cancer. *J Gynecol Oncol*. 2015;26:336–342.
24. Schorge JO, McCann C, Del Carmen M. Surgical debulking of ovarian cancer: What difference does it make? *Rev Obstet Gynecol*. 2010;3:111–117.
25. Ibeanu OA, Bristow RW. Predicting the outcome of cytoreductive surgery for advanced ovarian cancer: A review. *Int J Gynecol Cancer*. 2010;20(Suppl 1):S1–S11.
26. Mayer AR, Chambers SK, Graves E, et al. Ovarian cancer staging: Does it require a gynecologic oncologist? *Gynecol Oncol*. 1992;47:223–227.
27. Nguyen HN, Averette HE, Hoskins W, et al. National survey of ovarian carcinoma, V: The impact of physician's specialty on patients' survival. *Cancer*. 1993;72:3663–3670.
28. Martinek IE, Kehoe S. When should surgical cytoreduction in advanced ovarian cancer take place? *J Oncol*. 2010;2010:8520–8528.
29. Lorusso D, Mancini M, Di Rocco R, Fontanelli R, Raspagliesi F. The role of secondary surgery in recurrent ovarian cancer. *Int J Surg Oncol*. 2012;2012:613890. doi: 10.1155/2012/613980.
30. Bohra U. Recent advances in management of epithelial ovarian cancer. *Apollo Med*. 2012;9:212–218.
31. McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med*. 1996;334:1–6.
32. Piccart MJ, Bertelsen K, Stuart G, et al. Long-term follow-up confirms a survival advantage of the paclitaxel-cisplatin regimen over the cyclophosphamide-cisplatin combination in advanced ovarian cancer. *Int J Gynecol Cancer*. 2003;13(Suppl 2):144–148.
33. Bookman MA, Greer BE, Ozols RF. Optimal therapy of advanced ovarian

cancer: Carboplatin and paclitaxel vs. cisplatin and paclitaxel (GOG 158) and an update on GOG0 182-ICON5. *Int J Gynecol Cancer*. 2003;136:735–740.

34. Ozols RF, Bundy BN, Green BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: A Gynecologic Oncology Group Study. *J Clin Oncol*. 2003;21:3194–3200.
35. du Bois A, Luck HJ, Meier W, et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. *J Natl Cancer Inst*. 2003;95:1320–1329.
36. Neijt JP, Engelholm SA, Tuxen MK, et al. Exploratory phase III study of paclitaxel and cisplatin versus paclitaxel and carboplatin in advanced ovarian cancer. *J Clin Oncol*. 2000;18:3084–3092.
37. Calvert AH, Newell DR, Gumbrell LA, et al. Carboplatin dosage: Prospective evaluation of a simple formula based on renal function. *J Clin Oncol*. 1989;7:1748–1756.
38. Vasey PA, Jayson GC, Gordon A, et al. Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. *J Natl Cancer Inst*. 2004;96:1682–1691.
39. Fennelly D, Aghajanian C, Shapiro F, et al. Phase I and pharmacologic study of paclitaxel administered weekly in patients with relapsed ovarian cancer. *J Clin Oncol*. 1997;15:187–192.
40. Markman M, Blessing J, Rubin SC, et al. Phase II trial of weekly paclitaxel (80 mg/m^2) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: A Gynecologic Group Study. *Gynecol Oncol*. 2006;101:436–440.
41. Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: A phase 3, open-label, randomized controlled trial. *Lancet*. 2009;374:1331–1338.
42. Chan JK, Brady MF, Penson RT, et al. Weekly vs. every-3-week Paclitaxel and Carboplatin for ovarian cancer. *N Engl J Med*. 2016;374:738–748.
43. Abstract 929O_PR ’ICON8: A GCIG Phase III randomised trial evaluating weekly dose- dense chemotherapy integration in first-line Epithelial Ovarian/Fallopian Tube/Primary Peritoneal Carcinoma (EOC) treatment: Results of Primary Progression- Free Survival (PFS) analysis.

ESMO 2017.

44. Fujiwara K, Armstrong D, Morgan M, Markman M. Principles and practice of intraperitoneal chemotherapy for ovarian cancer. *Int J Gynecol Cancer*. 2007;17:1–20.
45. Jaaback K, Johnson N. Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. *Cochrane Database Syst Rev*. 2006;3:1–28.
46. Markman M, Bundy BN, Alberts DS, et al. Phase III trial of standard-dose intravenous cisplatin in small-volume stage III ovarian carcinoma: An intergroup study of the gynecologic oncology group, southwestern oncology group, and eastern cooperative oncology group. *J Clin Oncol*. 2001;19:1001–1007.
47. Alberts DS, Liu PY, Hannigan EV, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *N Engl J Med*. 1996;335:1950–1955.
48. Walker JL, Armstrong DK, Huang HQ, et al. Intraperitoneal catheter outcomes in a phase III trial of intravenous versus intraperitoneal chemotherapy in optimal stage III ovarian and primary peritoneal cancer: A Gynecologic Oncology Group Study. *Gynecol Oncol*. 2006;100:27-
49. Wright AA, Cronin A, Milne DE, et al. Use and effectiveness of intraperitoneal chemotherapy for treatment of ovarian cancer. *J Clin Oncol*. 2015;33:2841–2847.
50. Seward SM, Winer I. Primary debulking surgery and neoadjuvant chemotherapy in the treatment of advanced epithelial ovarian carcinoma. *Cancer Metastasis Rev*. 2015;34:5–10.
51. Provencher DM, Gallagher CJ, Parulekar WR, et al. OV21/PETROC: A randomized Gynecologic Cancer Intergroup phase II study of intraperitoneal versus intravenous chemotherapy following neoadjuvant chemotherapy and optimal debulking surgery in epithelial ovarian cancer. *Ann Oncol*. 2018;29:431–438.
52. Markman M, Liu PY, Wilczynski S, et al. Phase III randomized trial of 12 versus 3 months of maintenance paclitaxel in patients with advanced ovarian cancer who attained a clinically-defined complete response to platinum/paclitaxel-based chemotherapy: A Southwest Oncology Group and Gynecology Oncology Group trial. *J Clin Oncol*. 2003;21:2460–2465.
53. Markman M. Unresolved issues in the chemotherapeutic management of

gynecologic malignancies. *Semin Oncol*. 2006;33(Suppl 6):S33–S38.

54. Moore K, Colombo N, Scambia G, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2018;379:2495–2505.
55. Glasspool RM, Teodoridis JM, Brown R. Epigenetics as a mechanism driving polygenic clinical drug resistance. *Br J Cancer*. 2006;94:1087–1092.
56. Kanai Y. Alterations of DNA methylation and clinicopathological diversity of human cancers. *Pathol Int*. 2008;58:544–558.
57. Schiavone MB, Bashir S, Herzog TJ. Biologic therapies and personalized medicine in gynecologic malignancies. *Obstet Gynecol Clin North Am*. 2012;39:131–144.
58. ICON and AGO Collaborators. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: The ICON4/AGO-OVAR-2.2 trial. *Lancet*. 2003;361:2099–2106.
59. Bozas G, Bamias A, Koutsoukou, et al. Biweekly gemcitabine and cisplatin in platinum resistant/refractory, paclitaxel pre-treated, ovarian and peritoneal carcinoma. *Gynecol Oncol*. 2007;104:580–585.
60. Aghajanian C, Blank SV, Goff BA, et al. OCEANS: A randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol*. 2012;30:2039–2045.
61. Coleman RL, Brady MF, Herzog TJ, et al. Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): A multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2017;18:779–791.
62. ten Bokkel Huinink W, Gore M, Carmichael J, et al. Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. *J Clin Oncol*. 1997;15:2183–2193.
63. Creemers GJ, Bolis G, Gore M, et al. Topotecan, an active drug in the second-line treatment of epithelial ovarian cancer: Results of a large European phase II study. *J Clin Oncol*. 1996;14:3056–3061.
64. Muggia FM, Hainsworth JD, Jeffers S, et al. Phase II study of liposomal doxorubicin in refractory ovarian cancer: Antitumor activity and toxicity

modification by liposomal encapsulation. *J Clin Oncol*. 1997;15: 987–993.

65. Gordon AN, Cranai CO, Rose PG, et al. Phase II study of liposomal doxorubicin in platinum- and paclitaxel refractory epithelial ovarian cancer. *J Clin Oncol*. 2000;18:3093–3100.
66. Gordon AN, Fleagle JT, Guthrie D, et al. Recurrent epithelial ovarian carcinoma: A randomized phase III trial of pegylated liposomal doxorubicin versus topotecan. *J Clin Oncol*. 2001;19:3312–3322.
67. Wilailk S, Linasmita V. A study of pegylated liposomal doxorubicin in platinum-refractory epithelial ovarian cancer. *Oncology*. 2004;67: 183–186.
68. Drake RD, Lin WM, King M, et al. Oral dexamethasone attenuates Doxil-induced palmer-plantar erythrodysesthesias in patients with recurrent gynecologic malignancies. *Gynecol Oncol*. 2004;94:320–324.
69. Lund B, Hansen P, Theilade K, et al. Phase II study of gemcitabine (2′,2′-difluorodeoxycytidine) in previously treated ovarian cancer patients. *J Natl Cancer Inst*. 1994;6:1530–1533.
70. Cannistra SA, Matulonis UA, Penson RT, et al. Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. *J Clin Oncol*. 2007;25:5180–5186.
71. Burger RA, Sill MW, Monk BJ, Greer BE, Sorvosky JI. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: A gynecologic oncology group study. *J Clin Oncol*. 2007;25:5165–5171.
72. Garcia AA, Hirte H, Fleming G, et al. Phase II clinical trial of bevacizumab and low-dose metronomic oral cyclophosphamide in recurrent ovarian cancer: A trial of the California, Chicago, and Princess Margaret Hospital phase II consortia. *J Clin Oncol*. 2008;26: 76–82.
73. McGonigle KF, Muntz HG, Vuky J, et al. Combined weekly topotecan and biweekly bevacizumab in women with platinum-resistant ovarian, peritoneal, or fallopian tube cancer: Results of a phase 2 study. *Cancer*. 2011;117:3731–3740.
74. Penson RT, Dizon DS, Cannistra SA, et al. Phase II study of carboplatin, paclitaxel, and bevacizumab with maintenance bevacizumab as first-line chemotherapy for advanced müllerian tumors. *J Clin Oncol*. 2009;28:154–159.
75. Pujade-Lauraine E, Hilpert F, Weber F. Bevacizumab combined with chemotherapy for platinum resistant recurrent ovarian cancer: The

AUREILIA open label randomized phase III trial. *J Clin Oncol*. 2014;32.

76. Perren TJ, Swart AM, Pfisterer J. A phase 2 trial of bevacizumab in ovarian cancer. *N Engl J Med*. 2011;365:2482–2496.
77. Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med*. 2011;365:2473–2483.
78. Cohn DE, Barnett JC, Wenzel L. A cost-utility analysis of NRG Oncology/Gynecologic Oncology Group Protocol 218: Incorporating prospectively collected quality-of-life scores in an economic model of treatment of ovarian cancer. *Gynecol Oncol*. 2015;136:293–299.
79. Friedlander M, Hancock KC, Rischin D, et al. A Phase II, open-label study evaluating pazopanib in patients with recurrent ovarian cancer.. *Gynecol Oncol*. Oct 2010;119:32–37.
80. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol*. 2015;33:244–250.
81. Swisher EM, Lin KK, Oza AM. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): An international, multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2017;18:75–87.
82. Kristeleit R, Shapiro GI, Burris HA, et al. A phase I-II study of the oral PARP inhibitor rucaparib in patients with germline BRCA1/2-mutated ovarian carcinoma or other solid tumors. *Clin Cancer Res*. 2017;23:4095–4106.
83. Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): A double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2017;18:1274–1284.
84. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N Engl J Med*. 2016;375:2154–2164.
85. Matulonis UA, Berlin S, Ivy P, et al. Cediranib, an inhibitor of vascular endothelial growth factor receptor kinases, in an active drug in recurrent epithelial ovarian, fallopian tube and peritoneal cancer. *J Clin Oncol*. 2009;27:5601–5606.
86. Biagi JJ, Oza AM, Chalchal HI, et al. A phase II study of sunitinib in patients with recurrent epithelial ovarian and primary peritoneal

carcinoma: An NCIC Clinical Trials Group Study. *Ann Oncol*. 2011;22: 335–340.

87. Banerjee S, Kaye S. The role of targeted therapy in ovarian cancer. *Eur J Cancer*. 2011;47(Suppl 3):S116–S130.
88. Marsh S, Paul J, King CR, Gifford G, McLeod H, Brown R. Pharmacogenetic assessment of toxicity and outcome after platinum plus taxane chemotherapy in ovarian cancer: The Scottish Randomized Trial in Ovarian Cancer. *J Clin Oncol*. 2007;25:4528–4535.
89. Zhang L, Conejo-Garcia JR, Katsaros D, et al. Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. *N Engl J Med*. 2003;348:203–213.
90. Sato E, Olson SH, Ahn J, et al. Intraepithelial CD8+ tumor-infiltrating lymphocytes and a high CD8+/regulatory T cell ratio are associated with favorable prognosis in ovarian cancer. *Proc Natl Acad Sci USA*. 2005;102:18538–18543.
91. Tuca A, Guell E, Martinez-Losada, Cordorniu N. Malignant bowel obstruction in advanced cancer patients: Epidemiology, management, and factors influencing spontaneous resolution. *Cancer Manag Res*. 2012;4:159–169.

Acute Leukemias

David DeRemer and Tara Higgins

KEY CONCEPTS

1. Acute leukemias are the most common malignancies in children and the leading cause of cancer-related death in patients younger than age 20 years.
2. Several risk factors correlate with prognosis for acute lymphoblastic leukemia (ALL). Poor prognostic factors include high–white blood cell (WBC) count at presentation, very young or very old age at diagnosis, delayed remission induction and presence of certain cytogenetic abnormalities (eg, Philadelphia chromosome positive [Ph^+]).
3. For children with ALL, remission induction therapy includes vincristine, a corticosteroid, and asparaginase, with or without an anthracycline. For adults with ALL, vincristine, prednisone, an anthracycline, and asparaginase are used.
4. All patients with ALL require prophylactic therapy to prevent CNS disease because of the high risk of central nervous system (CNS) relapse. The choice for therapy includes a combination of the following: cranial irradiation, intrathecal chemotherapy, or high-dose systemic chemotherapy with drugs that cross the blood-brain barrier.
5. Long-term maintenance therapy for 2 to 3 years is essential to eradicate residual leukemia cells and prolong the duration of remission. Maintenance therapy consists of oral methotrexate and mercaptopurine, with or without monthly pulses of vincristine and a corticosteroid.
6. Disease-free survival is lower in adults with ALL and has been attributed to greater drug resistance, poor side effect tolerance with subsequent nonadherence, and possibly less effective therapy. This population is also more likely to have Ph^+ ALL, which is associated with a worse outcome, but the use of tyrosine kinase inhibitors (TKIs) has improved treatment results.

7. Several poor prognostic factors for adult acute myeloid leukemia (AML) include older age, organ impairment, presence of extramedullary disease, and presence of certain cytogenetic and molecular abnormalities.
8. Treatment of AML usually includes therapy with an anthracycline and cytarabine. Postremission therapy is required in all patients and can include either consolidation chemotherapy with or without maintenance therapy, or hematopoietic stem cell transplantation (HSCT). Novel oral therapies that inhibit FMS-related tyrosine kinase (FLT-3), isocitrate dehydrogenase (IDH1 and IDH2), and B-cell leukemia/lymphoma (BCL-2) have emerged in the AML treatment landscape.
9. Treatment of acute promyelocytic leukemia (APL) consists of induction therapy, followed by consolidation and maintenance therapy. Induction includes tretinoin and an anthracycline; consolidation therapy consists of two to three cycles of anthracycline-based therapy; maintenance consists of pulse doses of tretinoin, mercaptopurine, and methotrexate for 2 years.
10. Hematopoietic growth factors can be safely and effectively used with myelosuppressive chemotherapy for acute leukemias. They reduce the incidence of serious infections, hospital length of stay, and treatment delays, but do not prolong disease-free survival or overall survival.

Preclass Engaged Learning Activity

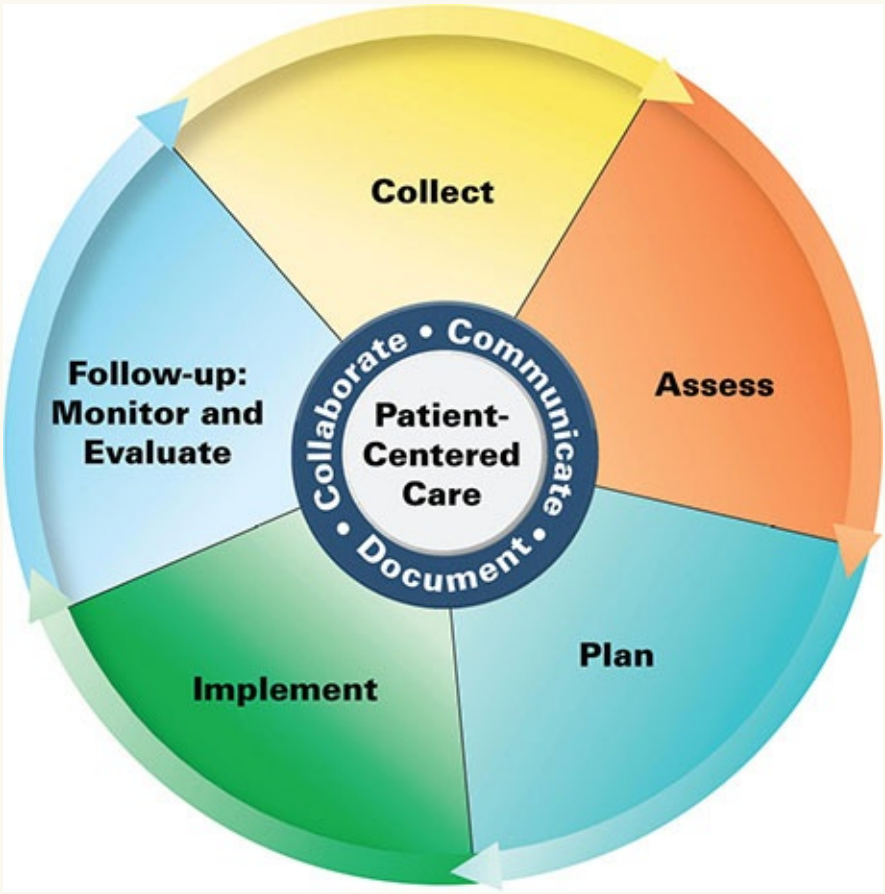
Faculty Instructions

1. Divide students into two teams. One team will assume the role of a chief medical officer (CMO) who has been asked by clinicians in the institution to initiate a CAR-T program at their institution. The other team will assume the role of the chief financial officer (CFO) who will debate the argument not to initiate a CAR-T program.
2. Ask students to prepare briefs for each position as a team effort. Each team should prepare arguments supportive of their position.
3. Create a scoring checklist for the actual debate. Rubric could include: (1) presentation style, (2) organization of statements, (3) reputable sources, (4) rebuttal statements, (5) summary statement.

INTRODUCTION

The leukemias are heterogeneous hematologic malignancies characterized by unregulated proliferation of the blood-forming cells in the bone marrow. These immature proliferating leukemia cells (blasts) physically “crowd out” or inhibit normal cellular maturation in bone marrow, resulting in anemia, granulocytopenia, including neutropenia, and thrombocytopenia. Leukemic blasts may also infiltrate a variety of tissues such as lymph nodes, skin, liver, spleen, kidney, testes, and the central nervous system (CNS).

Leukemia is historically classified based on the cell of origin and cell line maturation, and as acute or chronic based on differences in clinical presentation, rapidity of progression of the untreated disease, and response to therapy. The four major leukemias are acute lymphoblastic (or lymphocytic) leukemia (ALL), acute myeloid (or myelogenous) leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML). Undifferentiated immature cells that proliferate autonomously characterize acute leukemias. Chronic leukemias also proliferate autonomously, but the cells are more differentiated and mature. Untreated, acute leukemia is fatal within weeks to months.



Patient Care Process for Ph+ Adult Lymphoblastic Leukemia

Collect

- Patient characteristics (eg, age, gender, pregnancy status)
- Patient medical history (personal and family)
- Social history (eg, tobacco/marijuana, ethanol use)
- Current medications including OTCs and herbal products
- Confirmation of histological diagnosis
- Objective data

  Complete blood count (CBC) with differential, platelets

  Hepatic function tests

Basic chemistry panel

DIC panel: D-dimer, fibrinogen, PT, PTT

Tumor lysis panel (uric acid, potassium, calcium, phosphate)

Hepatitis B/C serologies, HIV, CMV status

ABO blood typing

Human leukocyte antigen (HLA) typing

- Molecular/cytogenetic information

Assess

- Tumor lysis syndrome risk
- Risk for Hepatitis B reactivation (CD20+ monoclonal antibody)
- Central venous access device
- Echocardiogram or MUGA scan (anthracyclines component in ALL therapy)
- Chemotherapy consent (willingness for intrathecal chemotherapy)
- Chemotherapy-induced nausea/vomiting risk
- Hemodynamic stability (eg, systolic blood pressure <90 mm Hg, heart rate >110 bpm, O_2 sat <90%, respiratory rate)
- Presence of active bleeding and/or bleeding risk factors
- Testicular disease (males)
- Dental evaluation
- Presence of Ph^+ disease
- Emotional status (eg, presence of anxiety, depression)
- Health insurance/prescription drug coverage (eg, hospitalization, BCR-ABL inhibitor)

Plan

- Comprehensive patient education regarding treatment plan
- Drug therapy regimen including multiagent chemotherapy (IV, IT) with corticosteroids and TKI (eg, Hyper-CVAD + rituximab + dasatinib)
- Monitoring parameters including efficacy (eg, circulating blasts, platelets,

trilineage hematopoiesis) and safety (eg, sign and symptoms of bleeding, serum creatinine); frequency and timing of follow-up
- Implement supportive care measures (transfusions, hematopoietic growth factors)
- Infection prophylaxis (antifungal, antiviral, *Pneumocystis jirovecii*)
- Referrals to other providers when appropriate
- Initiate donor search for future allogeneic HSCT
- Provide and document discharge summary and patient education

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence with tyrosine kinase inhibitor (ie, dasatinib)
- Schedule clinic follow-up visits

Follow-up: Monitor and Evaluate

- Response assessment (monitor for minimal residual disease-> RT-PCR or next generation sequencing to detect BCR-ABL1) after completion of induction
- PET scans for extramedullary disease if applicable
- Repeat echocardiogram or MUGA scan if applicable
- Physical exam every 1-2 months within first year following completion of therapy
- Referral to Cancer Survivorship clinic

** Collaborate with patient, caregivers, and other healthcare professionals.*

EPIDEMIOLOGY

1 It is estimated that 27,380 new cases of acute leukemia—21,450 cases of AML and 5,930 cases of ALL were diagnosed in the United States in 2019, accounting for about 1.5% of the total number of cancers diagnosed.[1] The incidence has been relatively stable for two decades. An estimated 12,420 deaths

per year, representing about 2% of all cancer deaths, are caused by acute leukemias.[1]

Leukemia is the leading cause of cancer-related deaths in persons younger than age 20 years.[2] It is now the leading cause of cancer death for males 20 to 39 years old, but it continues to be an uncommon cause of cancer-related death for both genders after age 40 years. Among adults, acute and chronic leukemias occur at equal rates. More than 90% of the cases of acute and chronic leukemia occur in adults. AML accounts for most cases of acute leukemia in adults and occurs with increasing frequency in elderly patients.[1]

Despite the low incidence, acute leukemias are the most common malignancy in persons younger than 20 years of age, accounting for 27% of all childhood malignancies. About 75% of children with leukemia have ALL and most of the remaining cases are AML.[1] Conversely, AML represents about 80% of acute leukemias in adults while only 20% of cases are ALL. Pediatric ALL is about 30% more common in males than in females, peaks at 1 to 4 years of age, and is almost twice as likely to affect Caucasian children than African American children.[2] Geographically, the highest rates of ALL have been identified in the Western portion of the US region.[3] Acute leukemia during the first year of life (infant leukemia) slightly favors ALL over AML.

ETIOLOGY

The exact cause of acute leukemias is unknown. A multifactorial process involving genetics, environmental and socioeconomic factors, toxins, immunologic status, and viral exposures is likely. **Table 151-1** summarizes the major factors that have been linked to acute leukemias. Infectious and genetic factors have the strongest associations. In pediatric ALL, a number of environmental factors are inconsistently linked to the disease: exposure to ionizing radiation, toxic chemicals, herbicides and pesticides; maternal use of contraceptives, diethylstilbestrol, or cigarettes; parental exposure to drugs, diagnostic radiographs, alcohol consumption, coffee and cola consumption, or chemicals before and during pregnancy; and chemical contamination of groundwater.[4,5] A growing body of evidence indicates that high birth weight is a risk for ALL. Ionizing radiation and benzene exposure are the only environmental risk factors strongly associated with ALL or AML. A few studies have reported a possible link between electromagnetic fields of high-voltage power lines and the development of leukemia, but larger studies could not

confirm this association. In most patients who develop leukemia, a cause cannot be identified.

TABLE 151-1 Factors Associated with the Development of Acute Leukemias

Drugs	**Chemicals**
Alkylating agents	Benzene
Anthracyclines	Pesticides
Epipodophyllotoxins	Pyrethroid-based shampoo
Genetic conditions	**Radiation**
Amegakaryocytic thrombocytopenia	Ionizing radiation
Ataxia telangiectasia	**Viruses**
Bloom syndrome	Epstein-Barr virus
Diamond-Blackfan anemia	Human T-lymphocyte virus (HTLV-1 and HTLV-2)
Down syndrome	**Social habits**
Dyskeratosis congenita	Cigarette smoking
Familial monosomy 7	Maternal marijuana use
Fanconi anemia	Maternal ethanol use
Klinefelter syndrome	Maternal caffeine consumption
Kostmann syndrome	
Langerhans cell histocytosis	
Li Fraumeni syndrome	
Neurofibromatosis type 1	
Noonan syndrome	
Shwachman syndrome	
Severe combined immunodeficiency syndrome	
Wiskott-Aldrich syndrome	

PATHOPHYSIOLOGY

Normal hematopoiesis consists of multiple well-orchestrated steps of cellular development. Pluripotent stem cells undergo differentiation, proliferation, and maturation, to form the mature blood cells seen in the peripheral circulation.

These pluripotent stem cells initially differentiate to form two distinct stem cell pools. The myeloid stem cell gives rise to six types of blood cells (erythrocytes, platelets, monocytes, basophils, neutrophils, and eosinophils). Lymphoid stem cells differentiate to form natural killer cells, B-lymphocytes, and T-lymphocytes. Leukemia may develop at any stage and within any cell line.

Two features are common to both AML and ALL. First, both arise from a single leukemic cell that expands and acquires additional mutations, culminating in a monoclonal population of leukemia cells. Second, there is a failure to maintain a relative balance between proliferation and differentiation, so that the cells do not differentiate past a particular stage of hematopoiesis. Cells (lymphoblasts or myeloblasts) then proliferate uncontrollably. Proliferation, differentiation, and apoptosis are under genetic control, and leukemia can occur when the balance between these processes is altered.

AML likely arises from a defect in the pluripotent stem cell or a more committed myeloid precursor, resulting in partial differentiation and proliferation of immature precursors of the myeloid blood-forming cells. In older patients, trilineage leukemia occurs suggesting that the cell of origin is probably a stem or very early progenitor cell. In younger patients, a more differentiated progenitor becomes malignant, allowing maturation of some granulocytic and erythroid populations. These two forms of AML exhibit different patterns of resistance to chemotherapy, with resistance more evident in older adults with AML. ALL is a disease characterized by the proliferation of immature lymphoblasts. In this type of acute leukemia, the defect is probably at the level of the lymphopoietic stem cell or an early lymphoid precursor.

Leukemic cells have growth and/or survival advantages over normal cells, leading to a “crowding out” phenomenon in the bone marrow. This growth advantage is not caused by more rapid proliferation as compared with normal cells. Some studies suggest that it is caused by factors produced by leukemic cells that either inhibit normal cellular proliferation and differentiation or reduce apoptosis as compared with normal blood cells.

Specific genetic alterations that lead to leukemia continue to be elucidated. Genetic defects may include (a) activation of a normally suppressed gene (protooncogene) to create an oncogene that produces a protein product that signals increased proliferation; (b) loss of signals for the blood cell to differentiate; (c) loss of tumor suppressor genes that control normal proliferation; and (d) loss of signals for apoptosis. Most normal cells are programmed to die eventually through apoptosis, but the appropriate programmed signal is often interrupted in cancer cells, leading to continued

survival, replication, and drug resistance. Signal transduction, RNA transcription, cell-cycle control factors, cell differentiation, and programmed cell death may all be affected.[6,7]

LEUKEMIA CLASSIFICATION

In 2016, the World Health Organization (WHO) revised the current classification system for myeloid neoplasms (Table 151-2).[8] This classification system incorporates not only morphologic findings, but also genetic, immunophenotypic, cytochemical, and clinical features. With the recent discoveries of mutations involved in AML, the revised classification system expanded the prognostic significance of mutations such as c-KIT, FLT-3, CEBPA, NPM1, IDH, WT1, and TET2 in AML subtypes.

TABLE 151-2 World Health Organization Classification of Acute Myeloid Leukemia and Related Neoplasms

Acute myeloid leukemia (AML) with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1); RUNX1-RUNX1T1
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);CBFB-MYH11
APL with PML-RARA
AML with t(9;11)(p21.3;q23.3);MLLT3-KMT2A
AML with t(6;9)(p23;q34.1);DEK-NUP214
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);RBM15-MKL1
AML with BCR-ABL1
AML with biallelic mutations of CEBPA
AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, not otherwise specified
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis
Myeloid leukemia associated with Down syndrome

PML, promyelocytic leukemia, RARα, retinoic acid receptor-α

ALL is classified based on lymphoblast analysis. Immunophenotype is determined by flow cytometry that analyzes specific antigens, known as clusters of differentiation (often abbreviated “CD”), present on the cell surface. Although no leukemia-specific antigens have been identified, the pattern of cell-surface antigen expression reliably distinguishes between lymphoid and myeloid leukemia. The immunophenotype defines the cell of origin. The major

phenotypes are mature B-cell, precursor B-cell, and T-cell disease, but the WHO classifies ALL as either B lymphoblastic or T lymphoblastic. About 80% of childhood ALL derives from precursor B cells and about 15% from T cells; the remainder is either mixed lineage or from mature B cells. T-cell ALL is more common in teenage males. In adults, about 75% of ALL is B-cell lineage and 25% are T-cell lineage ALL.

Leukemias may also be described by cytogenetic abnormalities. Chromosome alterations include numerical (hyperdiploidy and hypodiploidy) and structural abnormalities due to exchanges of genetic information within (inversion) or between (translocation) chromosomes. Unique translocations can identify specific subtypes of acute leukemia. The most common translocation in adult ALL, occurring in 25% of patients, is the t(9;22) or Philadelphia chromosome positive (Ph^+), which causes fusion of the BCR signaling protein to the ABL nonreceptor tyrosine kinase, resulting in constitutive tyrosine kinase activity. Acute promyelocytic leukemia (APL) is characterized by a specific translocation between chromosomes 15 and 17: t(15;17). Molecular tests may be used to identify products of specific translocations, such as promyelocytic leukemia (PML) retinoic acid receptor-α (RARα) in APL and *AML1-ETO* and *CBFβ/MYH 11* in other subtypes of AML.

Several factors can affect the cytogenetics of AML in adults. First, in about 5% of patients, simultaneous blood and marrow samples demonstrate normal cytogenetics versus abnormal cytogenetics, respectively. Second, central cytogenetic analysis is done in multicenter trials because of variability in specimen examination. Some patients may have a normal karyotype on standard review, but carry fusion genes, which are identical to those of translocations or inversions.[8] These insertions of very small chromosome segments do not alter chromosome morphology but may affect outcome.

CLINICAL PRESENTATION

Common signs and symptoms at presentation result from malignant cells that replace and suppress normal hematopoietic progenitor cells and infiltrate into extramedullary spaces. Patients with acute leukemia often present with symptoms related to complications of pancytopenia (eg, anemia, neutropenia, and thrombocytopenia) which include fatigue, infections, gingival bleeding, ecchymoses, and epistaxis.

In addition to clinical presentation, laboratory and pathology evaluations are required for a definitive diagnosis of leukemia. An abnormal complete blood

count (CBC) is usually the diagnostic test that initiates a leukemia workup. Although leukemic blast cells may be present on the peripheral blood smear, they are not diagnostic of leukemia because there are other causes in which immature blast cells may be present in peripheral blood. The most important diagnostic test is a bone marrow biopsy and aspirate, which is submitted to hematopathology for numerous evaluations, including flow cytometry, cytogenetics, and immunophenotyping. A lumbar puncture is performed to determine if there are blasts in the CNS. Unlike ALL, AML is less commonly associated with CNS involvement. A chest radiograph or computed tomography is performed to screen for a mediastinal mass (most common in T-cell disease). The results of these evaluations help to determine the patient's prognosis and therapeutic plan.[9]

ACUTE LYMPHOBLASTIC LEUKEMIA

Risk Classification

2 Several clinical and biologic features at diagnosis are associated with response to treatment, as measured by the complete remission rate, duration of remission, and long-term survival. The patient's response to initial therapy is strongly associated with response to treatment. Identification of these risk factors allows the clinician to better understand the disease and to personalize treatment according to the risk of disease recurrence (ie, risk-adapted therapy). For example, if a patient has many clinical and laboratory features that are associated with a favorable response to antineoplastic therapy (standard risk), then the clinician may choose to give less-intensive therapy to reduce the risk of long-term adverse effects. Conversely, if a patient is unlikely to respond well to standard therapy (high-risk or very-high-risk disease), then the clinician may choose to give more intensive antineoplastic therapy. The factors can be grouped as follows: patient characteristics at diagnosis, leukemic cell features at diagnosis, and patient response to initial therapy.

CLINICAL PRESENTATION

Acute Leukemias

General

- Recent history of vague symptoms such as tiredness, lack of exercise

tolerance, weight loss, and “feeling unwell,” but in no obvious distress.

Signs and Symptoms

- Common: Patients with anemia present with pallor, malaise, palpitations, and fatigue. Patients with low platelet counts present with bruising, ecchymoses, and petechiae. Temperature is often elevated and may be caused by disease or infection. Patients may have bone pain from a hyperactive bone marrow.
- Other possible symptoms include epistaxis, dyspnea on exertion, seizures, or headache. Splenomegaly, hepatomegaly, and/or lymphadenopathy are common in patients presenting with ALL, but may also have painless testicular enlargement and rarely, small, blue-green collections of leukemia cells under the skin (chloromas). Patients with AML may present with gum hypertrophy and bleeding.

Laboratory Tests

- Complete blood count with differential. Anemia (<7 g/dL [70 g/L; 4.34 mmol/L]) is normochromic and normocytic (without a compensatory increase in reticulocytes). Thrombocytopenia (severe, <20,000 cells/mm^3 [20×10^9/L]) is present in 28% of ALL and 50% of AML cases. Patients can present with leukopenia or leukocytosis; about 20% of patients will present with a WBC count ≥50,000 cells/mm^3 (50×10^9/L) and 53% of ALL and 20% of AML cases with a WBC <10,000 cells/mm^3 (10×10^9/L). Even patients with elevated counts can be considered functionally neutropenic.
- Uric acid may be elevated because of rapid cellular turnover and is more common in patients presenting with elevated WBC count and with ALL.
- Electrolytes: potassium and phosphate may be elevated with a compensatory decrease in calcium, more common with ALL.
- Coagulation (more common with AML): elevated prothrombin time, partial thromboplastin time, D-dimers; hypofibrinogenemia.

Other Diagnostic Tests

- Bone marrow aspirate and biopsy: send for morphologic examination,

cytochemical staining, immunophenotyping, and cytogenetic (chromosome) analysis. Molecular testing for FMS-like tyrosine kinase 3 (FLT3), nucleophosmin (NPM1), and CCAAT/enhancer binding-protein α (CEBPA), mutations is warranted for suspected AML.

- All adults with ALL should have a screening lumbar puncture performed to assess CNS involvement. Screening in patients with AML is not routine and depends on multiple factors at presentation including symptoms, WBC count, and morphology that includes monocytic disease.
- All pediatric patients with acute leukemias will receive a diagnostic lumbar puncture and will receive intrathecal chemotherapy at that time (usually performed on day 1 of induction chemotherapy).

The National Cancer Institute (NCI) developed an ALL-risk stratification to create a standard for comparison in children.[10] Induction therapy is initially selected based on this classification, which divides children into standard- or high-risk categories based on age and initial WBC count (**Table 151-3a**). Age remains an independent predictor of outcome with children aged 1 to 9 years having the best event-free survival which is possibly due to a more frequent favorable cytogenetics in this age group.[11] Age and WBC count has limited prognostic importance in T-cell ALL.[10] The presence of CNS disease at diagnosis is associated with a higher relapse rate. About 2% of males have testicular disease at diagnosis, but not all cooperative groups classify this as an adverse prognostic factor. The incidence of ALL varies according to race and ethnicity with Hispanics having the highest incidence with 40.9 cases per million and African Americans having the lowest with 14.8 cases per million. ALL develops more frequently in males (55%) versus females (45%).[10] Male ALL patients have a slightly worse prognosis.[12]

TABLE 151-3a National Cancer Institute (NCI) Risk Classification for Pediatric Acute Lymphoblastic Leukemia

Risk Group	Standard Risk	High Risk
Age (years)	1– <10	<1 or ≥10
WBC count (× 10^3 cells/mm^3 or × 10^9/L)	<50	≥50
Karyotype	No t(9;22) or t(4;11)	t(9;22) or t(4;11)

WBC, white blood cell

Data from Smith M, Arthur D, Camitta B, et al. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. J Clin Oncol. 1996;14:18-24.

Cell surface and immunophenotype classify childhood ALL into B-cell (85%) or T-cell (15%). T-cell ALL patients are often male, African American, older and less likely to be Hispanic than B-cell ALL. T-cell ALL generally presents with higher WBC counts and have mediastinal lymph node and CNS involvement. Survival for T-cell ALL historically was inferior to B-cell ALL but with more intensive therapy this difference has narrowed.[10] Several cytogenetic abnormalities are associated with prognosis. Favorable outcomes are associated with the presence of trisomy of chromosome 4 and 10, high hyperdiploidy (chromosome number >50 and DNA index >1.16), and the *ETV6-RUNX1* cryptic translocation, t(12;21).[13] Unfavorable or poor prognostic genetic factors are hypodiploidy (chromosome number <44), MLL rearrangement, BCR-ABL1, Ph-like ALL, CRLF2 rearrangement, intrachromosomal amplification of chromosome 21, and IKZF1 alterations, this is common in Ph-positive and Ph-like ALL.[10] Ph-like ALL can have translocations similar to BCR/ABL (ie, fusions including ABL1 (non-BCR), ABL2, CSF1R, and PDGFRB) or defects in the Janus kinase (JAK) pathway. The most common cytogenetic abnormalities in B-cell ALL are hyperdiploidy (25%), ETV6-RUNX1 (25%), MLL (5%), hypodiploidy (1%-5%) and Ph-positive (4%).[13]

The strongest prognostic factor for outcome for ALL is response to therapy. Previous indicators for early response to treatment were response to the first week of glucocorticoid therapy and evaluation of marrow blasts following 1 to 2 weeks of induction therapy. Minimal residual disease (MRD) quantification at end of induction has become the most important prognostic factor. Molecular measurement of subclinical MRD by either flow cytometry or polymerase chain reaction detects leukemic cells not visible on morphologic examination to assess treatment response and detect relapse. This technique detects 1 leukemia cell per 10^4 to 10^5 normal cells. The goal is to have MRD less than 0.01% at the end of

remission induction therapy. Children with higher levels have a 3 to 5 times greater risk of treatment failure and death.[10]

The Children's Oncology Group uses a risk- and response-based classification of childhood ALL (**Fig. 151-1**). This classification system uses the NCI-risk assignment to initially categorize patients into standard- or high-risk groups (see Table 151-3a). Following induction therapy, risk is reclassified based on completeness of response to therapy, the presence or absence of cytogenetic abnormalities, and CNS involvement (**Table 151-3b**). Patients are then reclassified as low risk, standard risk, high risk, or very-high risk (see Fig. 151-1). Patients who are initially high risk do not have therapy reduced, but may have it intensified to very high risk.

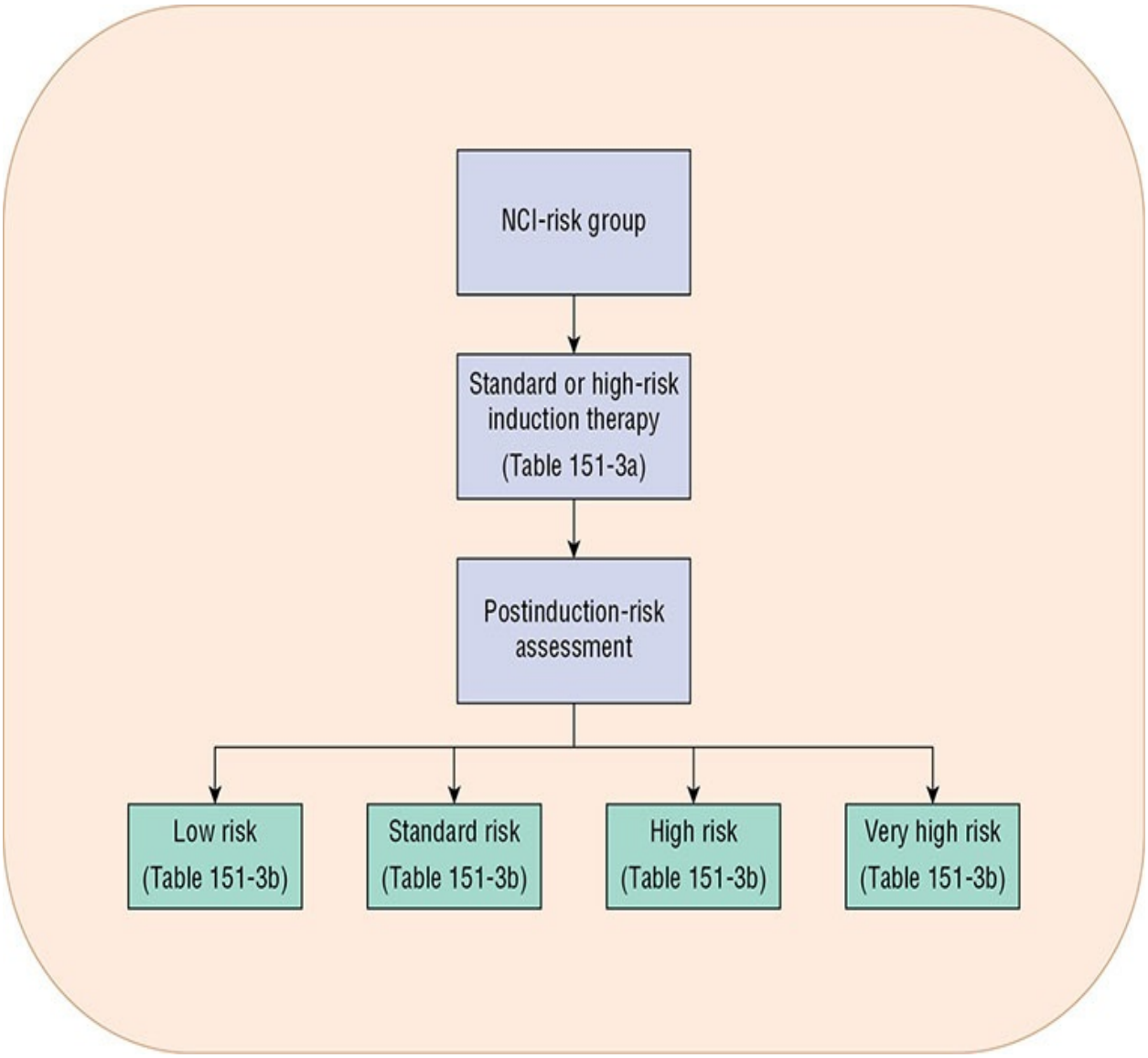


FIGURE 151-1 Risk and response classification of childhood acute

lymphoblastic leukemia.

TABLE 151-3b Pediatric Precursor B-Cell Acute Lymphoblastic Leukemia Risk Classification

	Low	Standard			High Risk			Very High Risk		
NCI Risk	SR	SR	SR	SR	SR	HR (age <13)	SR	HR	HR (age >13)	Any
Favorable Genetics	Yes	Yes	No	Yes	No	Any	No	Any	Any	Any
Unfavorable Characteristics	None	None	None	None	None	None	None	None	None	Yes
Day 29 Marrow MRD	<0.01%	<0.01%	<0.01%	>0.01%	<0.01%	>0.01%	<0.01%	>0.01%	<0.01%	Any

HR, high risk, MRD, minimal residual disease, NCI, National Cancer Institute, SR, standard risk.

Note: See Table 151-3a for criteria used to categorize patients into risk categories.

Data from Schultz KR, Pullen DJ, Sather HN, et al. Blood. 2007;109:926-935.

Children are classified as low risk and will have therapy reduced if they have trisomy 4 and 10 or the *ETV6-RUNX1* cryptic translocation with less than 0.01% MRD on day 29 bone marrow samples and do not have CNS or testicular disease. Children with testicular disease, MRD greater than or equal to 0.01% on day 29, or who received steroids prior to diagnosis have postinduction therapy intensified and are classified as high risk. Childhood precursor B-ALL with more than five WBCs and blasts present in the cerebrospinal fluid (CSF), Ph^+ disease, hypodiploidy, $iAMP_{21}$, induction failure, or *MLL* gene rearrangement have therapy intensified and are considered very high risk. Infant ALL, trisomy 21, or childhood T-cell ALL have unique risk classification schemas.[13] Relapse occurs in 15% to 20% of children with ALL. Factors contributing to prognosis include time to relapse (ie, shorter time), immunophenotype (ie, T cell), and site of relapse (ie, bone marrow disease). If relapse occurs following the completion of primary treatment, the likelihood for cure is about 50%. If a patient relapses during therapy, only 20 to 30% are cured.[10]

Treatment—Acute Lymphoblastic Leukemia

Desired Outcomes

The short-term goal for ALL treatment is to rapidly achieve a complete clinical and hematologic remission. A complete remission (CR) is defined as the disappearance of all physical and bone marrow evidence (normal cellularity with less than 5% blasts) of leukemia, with restoration of normal hematopoiesis. After a CR is achieved, the goal is to maintain the patient in continuous CR. In

general, a child is considered cured after being in continuous CR for 5 years.

Successful treatment of ALL was first developed in children. Cure rates in children have risen from less than 10% with treatments used in the 1960s to current rates of about 90%.[10] The reason for this improvement lies largely in improved scheduling of existing drugs, as relatively few new drugs have come to the market since the 1960s. MRD is a strong predictor of relapse in ALL. Children with low-risk disease have a 5-year event-free survival of more than 95%. The 5-year event-free survival for average-risk disease is 90% to 95%. The 5-year event-free survival is nearly 90% for high-risk childhood B-precursor and T-cell ALL. Children with very-high-risk disease have a 5-year event-free survival of less than 80%.[14] Response to treatment is determined by intrinsic drug sensitivity and the patient's pharmacogenomics and pharmacodynamics, treatment received, and treatment adherence.

Although treatment response with adult ALL is worse than those with childhood ALL, recent use of aggressive chemotherapy in adult ALL has increased the initial CR rate after induction therapy from 60% to 85%. Long-term event-free survival in this population, however, remains low (between 30% and 40%) because a higher proportion of adults present with poor-risk disease. CR rates and event-free survival depend on a number of poor prognostic factors and certain types of ALL are associated with a very poor outcome.

Treatment Phases

Therapy for childhood ALL is divided into five or six phases: (a) induction, (b) consolidation therapy, (c) interim maintenance, (d) delayed intensification, (e) interim maintenance II and (f) maintenance therapy (**Fig. 151-2**). CNS prophylaxis is a mandatory component of ALL treatment regimens and is administered longitudinally during all phases of treatment. The total duration of treatment is 2 to 3 years.[12]

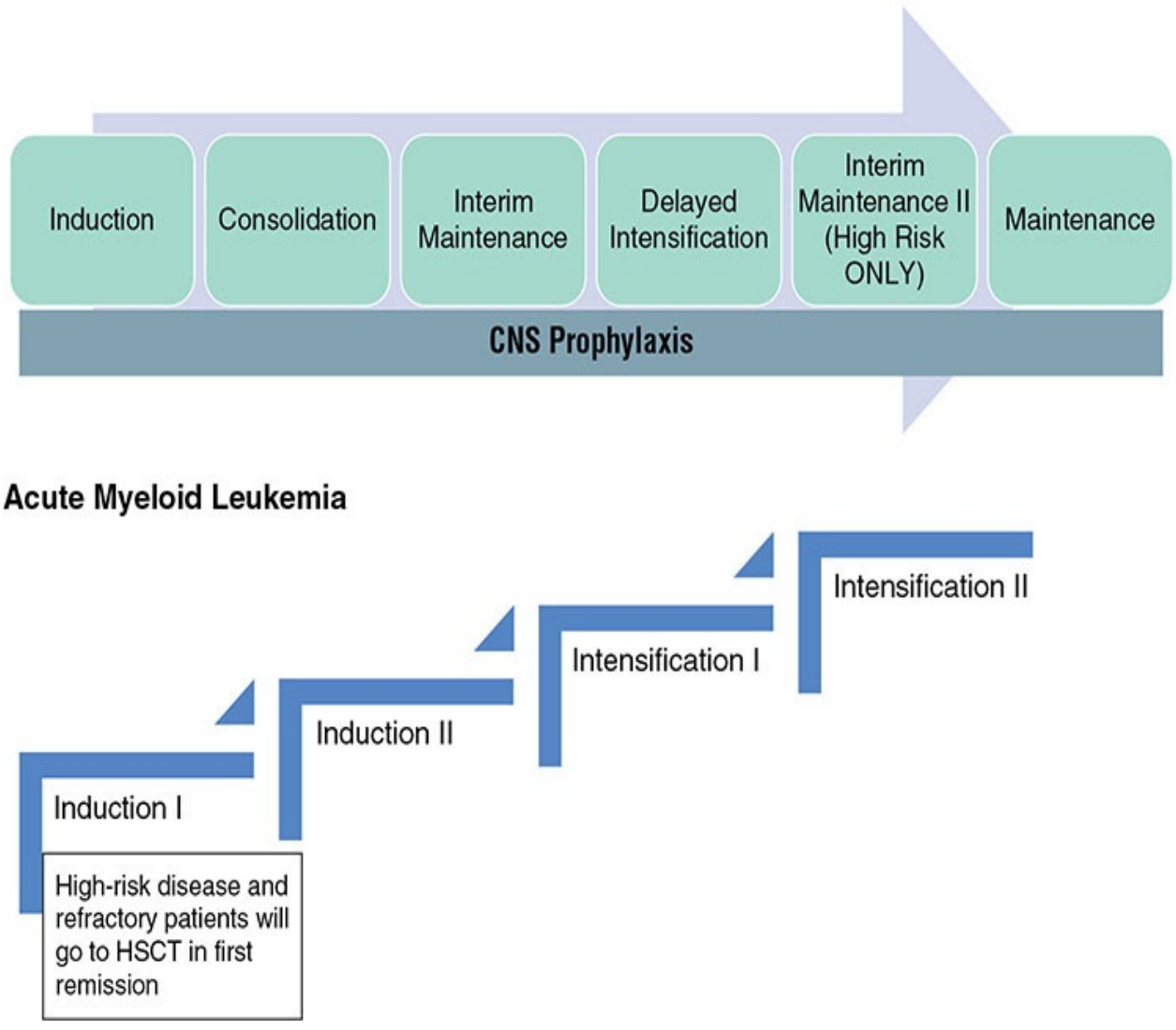


FIGURE 151-2 Treatment phases for acute leukemias.

Induction The goal of induction is to rapidly induce a complete clinical and hematologic remission. The CR rate is about 98% for standard-risk children treated with vincristine, a glucocorticoid (dexamethasone or prednisone), and pegaspargase.[10] Many treatment protocols include daunorubicin in induction (four-drug induction) for high-risk or very-high-risk ALL. Most children achieve a CR in 4 weeks. Those who have positive MRD at day 29 receive intensified therapy. About 2% to 3% of children fail induction therapy and have a 10-year survival rate of 32%.

Historically, prednisone has been the primary glucocorticoid used in pediatric ALL regimen but has been replaced with dexamethasone in most standard-risk protocols due to longer duration of action and higher CSF penetration.[15]

Dexamethasone improves event-free survival and decreases the risk of CNS relapse, but increases the risk of osteonecrosis, mood alteration, steroid myopathy, hyperglycemia, and infections.[15,16] Adolescents (older than 10 years of age) are particularly prone to osteonecrosis and receive prednisone instead of dexamethasone to minimize this adverse event.[12] Since patients with Down syndrome have increased infections and mortality with dexamethasone, these patients receive prednisone.[17]

Asparaginase has historically been available in three forms. L-asparaginase (no longer manufactured in the United States) and pegaspargase are isolated from *Escherichia coli* while *Erwinia* asparaginase is isolated from *Erwinia chrysanthemi*. Erwinia asparaginase is generally utilized in the setting of an allergic reaction to *E. coli* asparaginase. Erwinia asparaginase is given intramuscularly or intravenously. Erwinia asparaginase intravenously may require more frequent administration every 48 hours or the need for nadir serum asparaginase activity if every 72 hour dosing is required (ie, Monday, Wednesday, and Friday administration).[18] A recombinant *E. coli* asparaginase and a pegylated form of recombinant *Erwinia* asparaginase are currently in clinical trials.[19,20] Pegaspargase is pegylated *E. coli* asparaginase; pegylation prolongs its duration of activity and allows it to be given less frequently. Pegaspargase is used in most protocols and is preferred over L-asparaginase because of fewer intramuscular injections, decreased antibody formation, and superior response rates. Pegaspargase is also approved for IV administration.[21] The addition of asparaginase and an anthracycline to vincristine and prednisone improves remission rates from 85% to 95%.[13]

Asparaginase products are the antineoplastic agents used in ALL which are most likely to cause hypersensitivity reactions. Depending on the type of asparaginase used and the presence of a coadministered steroid, 8% to 42% of patients may develop hypersensitivity reactions to asparaginase.[22] Hypersensitivity reactions to pegaspargase may be delayed in onset (when administered intramuscularly) and prolonged in duration, sometimes requiring hospitalization.[23] *Erwinia* asparaginase is currently only utilized for patients who are allergic to pegaspargase. Because *Erwinia* asparaginase has a short half-life, administration must occur more frequently. A single dose of pegaspargase is replaced by six doses of *Erwinia* asparaginase, given three times per week.[22]

Patients may develop silent inactivation, also known as subclinical hypersensitivity, in which they develop neutralizing antibodies that can rapidly inactivate asparaginase, but without developing a clinical hypersensitivity reaction. Silent inactivation can be detected by therapeutic monitoring of

asparaginase activity. If inadequate asparaginase activity is detected, a therapeutic switch from pegaspargase to *Erwinia* asparaginase can be made to optimize activity and outcomes.[24,25] The use of therapeutic drug monitoring to optimize the dosing of asparaginase has also been demonstrated in clinical trials.[18]

4 **Central Nervous System Prophylaxis** Central nervous system prophylaxis is incorporated throughout all phases of therapy. The rationale for CNS prophylaxis is based on two observations. First, many antineoplastic agents do not readily cross the blood-brain barrier. Second, results from early clinical trials of ALL showed that the majority of patients with ALL experienced CNS relapse.[10] These observations indicate that the CNS is a potential sanctuary for leukemic cells and undetectable leukemic cells are present in the CNS in many patients at the time of diagnosis, while only 3% of children have detectable CNS involvement at diagnosis.[11]

The goal of CNS prophylaxis is to eradicate undetectable leukemic cells from the CNS while minimizing neurotoxicity and late effects. Once CNS relapse has occurred, patients are at increased risk of bone marrow relapse and death from refractory leukemia. Initial trials of childhood ALL in the 1960s established craniospinal irradiation as the standard for prevention of CNS relapse. However, this approach is associated with long-term sequelae including neuropsychological deficits, precocious puberty, osteoporosis, decreased intellect, thyroid dysfunction, brain tumors, short stature, and obesity. Subsequent trials have demonstrated that irradiation may be replaced by frequent administration of intrathecal chemotherapy in children with ALL. Some centers may treat children with CNS disease at diagnosis or very-high-risk disease with cranial radiation. The use of CNS irradiation and early intensified intrathecal chemotherapy has decreased the rate of CNS relapse to less than 5%.[12]

The CNS prophylaxis regimen is selected based on efficacy, toxicity, and risk of CNS disease. Intrathecal chemotherapy, cranial irradiation, dexamethasone, and high-dose IV methotrexate or cytarabine can be used to treat or prevent CNS disease. At least 80% of children with newly diagnosed ALL are treated without the use of cranial radiation.[10] Risk factors for CNS relapse include male sex, hepatomegaly, T-cell phenotype, CNS2 disease (the presence of leukemic blasts in a CSF sample that contains less than 5 WBC/mm^3 [5×10^6/L]), age younger than 2 years or older than 6 years, and a bloody diagnostic lumbar puncture.[26,27] Intrathecal therapy consists of methotrexate and cytarabine, given either alone or in combination. When given together, hydrocortisone is commonly added (triple

intrathecal therapy) to decrease the incidence of arachnoiditis. Triple intrathecal therapy is typically reserved for children with refractory CNS disease. For standard-risk ALL, triple intrathecal therapy decreased CNS relapse rates by 30% in comparison to intrathecal methotrexate but had no effect on event-free survival and worsened overall survival.[26] Liposomal cytarabine given intrathecally can induce remission of CNS disease but is associated with arachnoiditis and other CNS-related adverse effects.[28]

Patients with T-cell leukemia have an increased incidence of CNS disease and usually receive systemic therapy that penetrates the CNS such as high-dose methotrexate. Patients with T-cell disease have lower methotrexate polyglutamate accumulation in leukemic blasts and therefore were expected to require higher doses of methotrexate intravenously. The Capizzi methotrexate regimen, which consists of low escalating doses of methotrexate without leucovorin rescue plus pegaspargase, was reported to be superior to high-dose methotrexate with leucovorin rescue in 90% of patients receiving cranial radiation therapy.[29]

Consolidation Therapy Consolidation therapy is initiated after a CR has been achieved and refers to continued intensive-antineoplastic therapy in an attempt to eradicate clinically undetectable disease in order to secure (consolidate) the remission. Regimens usually incorporate either non–cross-resistant drugs that are different from the induction regimen, or more dose-intensive use of the same drugs.

Randomized trials show that consolidation therapy clearly improves patient outcomes in children, but its benefit in adults is less clear. The relative benefit of individual components of treatment regimens is difficult to demonstrate because of the overall complexity of therapy in ALL. Standard consolidation lasts 4 weeks and usually consists of vincristine, mercaptopurine, and intrathecal methotrexate. In children, the intensity of consolidation therapy is personalized based on the child's initial risk classification and response to induction therapy. Children who have high-risk disease receive intensified consolidation that includes the addition of pegaspargase, cyclophosphamide, and low-dose cytarabine to standard therapy.[10] Children with testicular disease usually receive radiation during this phase of therapy if a complete clinical response in the testes is not achieved by the end of induction. Patients with T-cell leukemia also receive nelarabine, a prodrug of ara-G that preferentially accumulates in T-lymphoblasts as ara-guanosine triphosphate (GTP), during consolidation and throughout the remainder of their treatment course given the improved event-

free survival when it is added to an intensified-therapeutic backbone.[30]

Reinduction (Interim Maintenance and Delayed Intensification) One or two interim maintenance phases separated by a high-intensity delayed intensification cycle can be added to maintain remission and to decrease cumulative toxicity. Interim maintenance is given to both standard-risk and high-risk ALL patients. Standard-risk patients receive one interim maintenance cycle that includes IV methotrexate (low dose that escalates over the course of the cycle) and vincristine while high-risk patients receive interim maintenance which includes vincristine, high-dose methotrexate and mercaptopurine. High-risk patients will receive a second interim maintenance after delayed intensification which is similar to standard-risk interim maintenance but adds asparaginase. Delayed intensification is similar for both standard- and high-risk patients and includes vincristine, glucocorticoid, doxorubicin, asparaginase, cyclophosphamide, cytarabine and thioguanine.[12] ALL patients previously received one interim maintenance and two delayed intensification cycles. Delayed intensification with dose intensification improved event-free survival and decreased late relapses for high-risk childhood ALL, but there was no additional benefit for the second delayed intensification cycle. Children on the intensified arms of the study received significantly more antimicrobial drugs, blood products, and parenteral nutrition but had no increase in treatment-related mortality.[31] These phases use an augmented schedule and chemotherapy dose that reduces tumor burden and prevents the emergence of drug resistant clones.[12]

5 **Maintenance Therapy** Maintenance therapy provides long-term drug exposure to slowly dividing cells, allows the immune system time to eradicate leukemia cells, and promotes apoptosis (programmed cell death). The goal of maintenance therapy is to further eradicate residual leukemic cells and prolong remission duration. Although maintenance therapy is clearly beneficial in childhood ALL, the benefit in adults has only recently been demonstrated.

Maintenance therapy usually consists of daily mercaptopurine and weekly methotrexate for 12-week courses, at doses that produce mild myelosuppression, with monthly pulses of vincristine and a steroid.[32] Based on the results of studies that show a trend toward an increase in late relapse (excluding isolated testicular relapse) among male children treated for 2 years versus 3 years, some centers treat female children for 2 years while males receive maintenance for a total of 3 years of therapy.[11]

Mercaptopurine and oral methotrexate are available as tablets and recently as an FDA-approved commercially available oral suspension. It was previously

recommended that mercaptopurine be taken at night and administered on an empty stomach without concomitant milk products. It was thought xanthine oxidase in milk products would inactivate the drug and circadian rhythm would affect absorption. However, recent studies show that red cell thioguanine levels are not influenced by coadministration of food or dairy, timing of administration or whether the tablet is swallowed whole, crushed, or chewed. Therefore, previous recommendations may hinder drug adherence.[33] Interpatient variability in the adherence and systemic exposure to oral methotrexate and mercaptopurine is an important determinant of the effectiveness and toxicity of maintenance therapy. Children with an adherence rate less than 95% with mercaptopurine have a 2.7-fold higher risk of suffering a relapse.[34] Factors associated with nonadherence include single-parent household, adolescence, lower socioeconomic status, and Hispanic ethnicity.[35] To account for the interpatient variability, most clinicians will titrate the dose of these agents to achieve adequate myelosuppression.[11] Some protocols overcome bioavailability and poor adherence issues by administering methotrexate IV or intramuscularly. The importance of these pharmacokinetic issues in adults is not well defined.

Genetic polymorphisms may affect drug metabolism, receptor expression, drug transport, drug disposition, and pharmacologic response. Pharmacogenomic polymorphisms are an important determinant of mercaptopurine toxicity. Thiopurine methyltransferase (TPMT) is the predominant inactivating enzyme for thiopurines in hematopoietic tissues. About 10% of the population has intermediate TPMT activity as a result of heterozygous polymorphisms in the gene encoding for TPMT, and 1 in 300 has extremely low activity as a result of homozygous presence of this TPMT polymorphism. Patients with low activity (homozygous mutant TPMT genotype) require 85% to 90% dose reductions.[36] About 50% of the heterozygous patients will require dose reductions. TPMT testing is now a standard of care at many institutions and treatment dosing is adjusted to minimize toxicity without compromising anti-leukemic outcomes. A recently identified coding variant in nudix hydrolase 15 (NUDT15) has emerged as another important determinant of thiopurine toxicity. NUDT15 encodes a nucleoside diphosphatase that dephosphorylates active thiopurine metabolites, which prevents them from incorporating into DNA and minimizes their cytotoxicity. If a patient has defective NUDT15 alleles, active thiopurine metabolites can accumulate and cause toxicity.[37]

Philadelphia Chromosome Positive Acute

Lymphoblastic Leukemia

Ph^+ ALL has historically been treated as very-high-risk disease, which includes the use of a four-drug induction regimen with the addition of continuous imatinib mesylate, a tyrosine kinase inhibitor that inhibits BCR-ABL kinase, throughout all phases of treatment. This targeted therapeutic approach has resulted in a 5-year overall survival of 70%. The results for patients receiving chemotherapy with imatinib were equivalent to those receiving hematopoietic stem cell transplantation (HSCT).[38] Imatinib is currently incorporated into childhood treatment trials for Ph^+ ALL in Europe and the United States. Trials are ongoing with the more potent second-generation tyrosine kinase inhibitors (TKIs), nilotinib and dasatinib, and with ponatinib, which is effective in imatinib-resistant leukemia.[39] Ph-like ALL is more common in the adolescent and young adult age group (ie, 15-39 years). TKIs (dasatinib), JAK inhibitor (ruxolitinib) and mTOR inhibitors (sirolimus and everolimus) are being investigated for Ph-like ALL.[12]

Acute Lymphoblastic Leukemia in Adolescents and Young Adults

Although ALL is relatively uncommon in adolescents and young adults (AYA) (15-39 years old), the outcomes are generally worse than for childhood ALL.[40] The number of AYA patients with ALL has doubled since 1975 and it is estimated to be a total average of 1,200 new diagnoses per year since 2006. In the last decade, about 50% of AYA patients with ALL survived 10 years. ALL in AYA has a higher frequency of T-cell immunophenotype and a lower frequency of the t(12;21)(p13;q22) cryptic translocation responsible for hyperdiploidy and the *ETV6-RUNX1* fusion gene; and increased incidence of Ph^+ ALL, intrachromosomal amplification of chromosome 21, and Ph-like ALL which occurs most frequently in the AYA population. Thirteen studies have compared outcomes of AYA patients treated with either pediatric or adult regimens. Pediatric-inspired regimens had better outcomes reported in twelve of the thirteen studies. Event-free survival rates ranged from 60% to 77% with pediatric regimens versus 32% to 72% with adult regimens, with an overall survival rate of 27% to 80% versus 10% to 74% for pediatric and adult regimens, respectively. Treatment outcomes for AYA patients undergoing related or unrelated HSCT were compared to similar patients treated with pediatric chemotherapy regimen. Patients treated with chemotherapy alone had a similar

rate of relapse but significantly less treatment-related mortality. The AYA patients treated with chemotherapy had a significantly higher 4-year survival rate.

The toxicity of chemotherapy regimens is a vital consideration when treating the AYA population. Pediatric regimens do not usually require hospitalization and have a low potential for cardiotoxicity, infertility and carcinogenesis while adult regimens often require hospitalization for neutropenic fever and other infectious complications. Pediatric chemotherapy regimens are associated with an overall increase in both life years and quality-associated life years (QALYs) following the initial stages of treatment. Based on mental health and quality-of-life surveys, depression, anxiety and posttraumatic stress disorder were present in one-third of AYA patients. Adherence is more problematic in the AYA population due to education, employment, various relationships and insurance. Oral chemotherapy agents are a large portion of treatment in pediatric regimens while adult regimens often require inpatient therapy, thus affecting school or employment. Both require reliable access to transportation.[41]

Acute Lymphoblastic Leukemia in Adults

6 Treatment-risk stratification for adult patients differs depending on age and Philadelphia chromosome status. The National Comprehensive Cancer Network (NCCN) guidelines recommend different strategies for AYA (15-39 years), adults (40-65 years), and ≥65 years with substantial comorbidities.[42] The most common treatment regimens use a four-drug induction regimen consisting of an anthracycline, vincristine, an asparaginase formulation, and a corticosteroid. These regimens produce high CR rates (>70%), but the long-term event-free survival is unsatisfactory.[43] Poorer outcomes in adults have been attributed to differences in cytogenetic abnormalities, greater drug resistance, higher risk of treatment-related adverse effects with subsequent nonadherence, and possibly less effective therapy. Several different regimens are considered appropriate first-line therapies in adults including the Cancer and Leukemia Group B (CALGB) 8811 (Larson regimen), Eastern Cooperative Oncology Group (ECOG) 2903, or Linker regimen.[42] Some studies suggest that high-dose methotrexate and cytarabine alternating with fractionated cyclophosphamide plus vincristine, doxorubicin, and dexamethasone (hyper-CVAD) may improve response and survival in adults with ALL. A considerable number of ALL cases occur in patients older than age 65 years, and the response to therapy and durability of response in this subgroup is less than in other populations. Treatment-related mortality rates during remission induction therapy are also

higher in this population.[43]

While the overall incidence of Ph^+ positive disease is 25% in adults, the incidence rises with increasing age to over 40% in adults older than the age of 50 years. Historically patients with Ph^+ ALL had a poor prognosis, with 1-year survival of about 10% without an allogeneic HSCT.[43] As compared with historical control patients treated with standard chemotherapy alone, the addition of BCR-ABL TKI-based therapy to chemotherapy is associated with an increased CR rate and overall survival.[44–47] TKIs should be incorporated early in the Ph^+ ALL patient and continuous dosing has demonstrated superior outcomes compared to pulse or intermittent dosing strategies.[48] For patients older than 65 years of age or for those with poor performance status, remission induction regimens may include a TKI (imatinib, dasatinib, or nilotinib) combined with corticosteroids.[43]

The emergence of resistance to BCR-ABL TKIs provides a challenge in patients relapsing after treatment. Point mutations within the ABL kinase domain and the activation of alternative signaling pathways due to SRC kinase have been identified. A patient's specific mutation analysis should be considered in the selection of a specific TKI in the relapsed or refractory setting. Second- and third-generation TKIs have demonstrated activity in patients with imatinib-resistant Ph^+ ALL, but ABL mutations such as T315I, V299L, and F317L have demonstrated resistance to dasatinib. Ponatinib is the only BCR-ABL TKI available with known activity against T315I mutations. With the emergence of more potent inhibitors that are capable of inducing sustained remissions, studies evaluating the need for intensive chemotherapy are ongoing.[49]

In adults with B-cell ALL, about 50% have leukemic cells that express CD20. CD20 expression is associated with decreased CR rates, higher risk of relapse, and shorter overall survival.[50] A Phase 2 study has evaluated hyper-CVAD and rituximab versus hyper-CVAD alone and reported a higher CR rate (70% vs 38%) and longer overall survival (75% vs 47%) in patients treated with hyper-CVAD and rituximab.[42] Ofatumumab, a more potent second-generation anti-CD20 monoclonal antibody, was also combined with hyper-CVAD and produced CR and MRD negativity rates of 98% and 93%, respectively.[51]

HSCT plays an important role in the treatment of adult patients with ALL. For patients with Ph^+ ALL or Ph^- ALL who have a CR after induction therapy, consolidation with allogeneic HSCT should be considered if a human leukocyte antigen (HLA)-matched sibling or matched unrelated donor is available. After HSCT, patients with Ph^+ ALL should continue with standard maintenance

therapy that includes a tyrosine kinase inhibitor. For patients with Philadelphia chromosome negative (Ph^-) disease who have MRD after induction therapy, an allogeneic HSCT should be considered if a matched donor is available. Allogenic HSCT is preferred over autologous HSCT because of lower disease relapse rates.[52,53]

Relapsed Acute Lymphoblastic Leukemia

About 20% of children with ALL will relapse, but about 40% will experience long-term overall survival following relapsed treatment regimens.[10] In adults, about 30% to 60% of patients will relapse despite aggressive consolidation and maintenance chemotherapy.[54] The most common site for relapse is isolated to the bone marrow, although isolated relapses can occur in the CNS or testicles, in addition to combined sites of involvement. Patients who have completed treatment and remained in remission for longer periods are more likely to achieve remission again.[11,42]

Clofarabine, a purine antimetabolite, is an option for patients with second or later relapses, but the duration of response is short. Single-agent clofarabine is associated with hepatotoxicity, prolonged myelosuppression, and febrile neutropenia.[55] Nelarabine, a T-cell specific purine nucleoside analogue, is approved for the treatment of T-cell ALL who have relapsed disease following at least two prior therapies.[56] Data continues to emerge with the use of nelarabine in a frontline setting.[57] Toxicities such as severe peripheral and sensory neurotoxicity, severe somnolence, and seizures are associated with nelarabine.[56]

Blinatumomab is approved for relapsed or refractory B-cell precursor ALL and in first or second CR with minimal residual disease (MRD) greater than or equal to 0.1%. As a bispecific T-cell engager (BiTE), blinatumomab binds to both CD19, an antigen that is present throughout B cell development, and CD3, a T-cell receptor. By linking CD19 and CD3, blinatumomab enables a cascade of events resulting in lysis of CD19 cells.[58] Blintumomab can induce a CR and achieve MRD negativity in adult and pediatric patients with relapsed or refractory ALL. In a randomized Phase 3 clinical trial, patients receiving blinatumomab had improved overall survival as compared to standard chemotherapy.[59] Blinatumomab has a short half-life and therefore must be administered as a continuous infusion for 28 days of a 6-week cycle. Adverse reactions occur in most patients, ranging from mild, reversible symptoms such as fever and rigors to more severe toxicities including neurotoxicity, infections, and cytokine release syndrome.[58]

Inotuzumab ozogamicin, an antibody-drug conjugate targeting CD22, received FDA approval in 2017 for relapsed or refractory B-cell ALL.[60] In a Phase 3 clinical trial, inotuzumab ozogamicin demonstrated significantly higher CR rates (80.7% vs 29.4%) compared to a standard chemotherapy group (FLAG, fludarabine, cytarabine; cytarabine and mitoxantrone; HIDAC, high-dose cytarabine) in patients with relapsed or refractory ALL. Positive responses were identified in patients with heavy disease burden and Ph^+ disease.[61] In a pediatric study, inotuzumab ozogamicin was evaluated in 51 children who received therapy in a compassionate use program. A CR was achieved in 67% of patients with overt marrow disease with most responders having MRD negativity.[62] Inotuzumab ozogamicin is associated with hepatotoxicity (including veno-occlusive disease [ie, sinusoidal obstruction syndrome]) and increased nonrelapse mortality for patients who proceed to HSCT.[60]

Chimeric antigen receptor (CAR) T-cell therapy is a therapeutic option for ALL patients without other curative options. This novel therapeutic modality involves genetically engineered T cells designed to express CARs directed against CD19, resulting in T cells targeting leukemic cells that express CD19. In August 2017, the FDA-approved tisagenlecleucel, a CD19-directed autologous T-cell immunotherapy, for treatment of patients up to 25 years of age with B-cell ALL that is refractory or in second or later relapse.[63] An impressive 81% of children and young adults had a CR, many of which were durable.[64] The enthusiasm over CAR T-cell therapy based on its activity must be balanced by its significant adverse events and cost. Serious adverse events of CAR T-cell therapy include hypogammaglobulinemia, encephalopathy, seizures, and cytokine release syndrome, ranging from mild, flu-like symptoms to multiorgan system failure.[65] A single infusion of tisagenlecleucel is estimated to cost $475,000.[66]

Allogeneic HSCT has traditionally been the treatment of choice for early bone marrow relapse (continuous CR less than 36 months) while children who relapse more than 36 months after completion of initial therapy have traditionally received chemotherapy alone.[10] The American Society for Blood and Marrow Transplantation (ASBMT) guidelines recommend allogeneic HSCT for both standard- and high-risk ALL patients in first CR (CR1).[53] This recommendation is based on a systematic review and meta-analysis of randomized trials which reported significantly reduced all-cause mortality with allogeneic HSCT in CR1 when compared to autologous HSCT.[67] For elderly patients, reduced-intensity conditioning (RIC) nonmyeloablative transplants may

produce similar outcomes with less treatment-related morbidity and mortality.[68]

ACUTE MYELOID LEUKEMIA

Risk Classification

7 Risk stratification for AML is divided into patient-related and disease-related factors that can contribute to a patient's likelihood of responding to drug therapy.[6] Early identification of these risk factors allows clinicians to personalize treatment according to the risk of disease recurrence. A key prognostic factor for AML is age. Patients 60 years of age and older have significantly worse outcomes than their younger counterparts. Older patients have differences in tumor biology which confers resistance and patient characteristics (eg, impaired performance status) that reduces treatment tolerance.[69] Other unfavorable prognostic factors in adult AML include multidrug-resistance gene expression, WBC greater than 100,000 cells/mm^3 (100×10^9/L) and therapy-related AML.[70] Patients who develop a "secondary" leukemia after treatment of another malignancy usually have a very poor response to antileukemic chemotherapy (ie, therapy-related AML). Patient factors such as where patients received treatment, educational level, and cohabitation status may also affect treatment-related mortality.[70,71]

Genetic analysis which includes karyotyping and molecular mutational profiling provides important prognostic information (**Table 151-4**). For example, patients with core-binding factor with t(8;21)(q22;q22) or inv (16)(p13;q22)/t(16;16)(p13;q22) treated with a cytarabine-based regimen have a relatively favorable prognosis. Adults and children with chromosomal deletions such as 3q[abn(3q)] or 5q[del(5q)], monosomies of chromosome 5 and/or 7(−5/−7) have a poor prognosis with standard chemotherapy for AML and may be candidates for experimental treatments. About 40% of cases have a normal karyotype.[70] Molecular markers such as FMS-like tyrosine kinase 3 (FLT3), NPM1, c-KIT, DNA (cytosine-5)-methyltransferase (DNMT3), CEBPA, and isocitrate dehydrogenase 1 and 2 (IDH 1/2) can provide prognostic information and guide postremission therapy.[72]

TABLE 151-4 AML-Risk Status According to Cytogenetics and Molecular Abnormalities

Risk	Cytogenetics	Molecular
Favorable	Inv(16) t(8;21) t(15;17)	NPM1 mutation in the absence of FLT3-ITD or presence of FLT3-ITD^{low} Biallelic CEBPA mutation
Intermediate	Normal cytogenetics t(9;11)	Core binding factor with KIT mutation Mutated NPM1 and FLT3-ITD^{high} WT-NPM1 without FLT3-ITD^{low}
Poor-risk	Complex (≥3 clonal chromosomal abnormalities Monosomal karyotype -5, 5q, -7, 7q- 11q23 Inv(3) t(6;9) t(9;22)	Normal cytogenetics with FLT3-ITD TP53 Mutated RUNX1 Mutated ASXL WT-NPM1 and FLT3-ITD^{high}

AML, acute myeloid leukemia; NPM1, nucleophosmin; FLT-3-ITD, Fms-like tyrosine kinase 3 internal tandem duplication; TP53, tumor protein; RUNX1, Runt-related transcription factor 1; ASXL, additional sex combs.

Data from Dohner H, Estey E, Grimwade D, et al. Blood. 2017;129:424-447. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Acute Myeloid Leukemia. Version 2.2018. Accessed October 1, 2018.

Two classes of FLT3 mutations have been identified—internal tandem duplications (ITD) and tyrosine kinase domain (TKD) point mutations. Patients with FLT3-ITD mutations have shorter remission durations and worse survival outcomes.[73] FLT3-ITD mutations occur in about 15% of older patients and 25% of patients younger than 60 years old.[74] *NPM1* mutations occur in about 30% of patients with AML, even in patients with normal karyotype, and commonly coexists with FLT3. They are associated with a higher CR and reduced relapse risk as compared to patients without the mutation. c-KIT mutations have been observed in about 20% of patients with core-binding factor AML and are associated with decreased duration of CR and overall survival.[70,75] CEBPA mutations occur in about 10% of patients with AML. The most common CEBPA mutation, a biallelic (double) mutation, is associated with improved prognosis.[8] IDH1/2 mutations occur in <10% of patients and its effect on prognosis is

unclear.[70]

Prognostic factors associated with pediatric AML include response to the first course of remission induction therapy, cytogenetics, and molecular genetics. Poor prognostic factors include monosomy 7, age older than 10 years, black race, internal tandem duplications of FLT3, *MLL* gene rearrangements, and a diagnosis of AML secondary to prior chemotherapy or radiation therapy. Conversely, inversion of chromosome 16, trisomy 21, CBF-AML, *PML-RARA*, *NPM1*, biallelic CEBPA, and *RUNX1-RUNX1T1* fusion transcript t(8;21) are associated with a favorable outcome.[76]

Treatment—Acute Myeloid Leukemia

Desired Outcomes

The short-term goal of treatment for AML is to rapidly achieve a complete clinical and hematologic remission. In the absence of a CR, a rapid and fatal outcome is inevitable. CR is defined as the disappearance of all clinical and bone marrow evidence (normal cellularity more than 20% with less than 5% blasts) of leukemia, with restoration of normal hematopoiesis (neutrophils more than or equal to 1,000 cells/mm^3 [1×10^9/L] and platelets more than 100,000 cells/mm^3 [100×10^9/L]). Partial remission is a significant response to treatment (a decrease of at least 50% of blasts), but evidence of residual disease in the bone marrow remains (5%-25% blasts) and is considered a treatment failure requiring additional therapy. The definition of CR has several categories including CR (morphologic CR with restoration of normal hematopoiesis), CR with complete remission with incomplete hematological recovery (CRi), cytogenetic CR ([CRc] patient with normal cytogenetics in which cytogenetics were previously abnormal), and molecular CR ([CRm] molecular studies negative). If there is a question of residual leukemia on bone marrow biopsy in adults, a bone marrow aspirate/biopsy should be repeated in 7 to 14 days.[73]

A CR is achieved in 60 to 85% of adults who are 60 years of age or younger. After a CR is achieved, the goal is to maintain the patient in continuous CR.[75] The occurrence of leukemic relapse in the bone marrow significantly reduces the likelihood of cure. Upon relapse, available clinical trials, additional chemotherapy, or best supportive care should be pursued depending on the patient's clinical status.[73] Most patients who will die from acute leukemia die within the first 6 years; survival curves tend to plateau after that time and patients are considered to be cured of their leukemia.

With recent advances in antineoplastic therapy and supportive care, 20% to 40% become long-term survivors. Overall, the median duration of remission is 1 to 2 years.[75] In contrast to ALL, effective therapies utilized in AML result in severe and often prolonged myelosuppression. As a result, patients with AML, particularly patients older than 60 years of age, are at greater risk for treatment-related fatal infectious and bleeding complications.

Treatment Phases

Therapy for AML is divided into two phases: (a) induction and (b) postremission therapy (eg, consolidation, intensification) (Fig. 151-2).

Induction As with ALL, the goal of remission induction for AML is to rapidly induce a CR with associated restoration of normal hematopoiesis. Compared to ALL, however, fewer patients with AML achieve CR. Because the CR rate in AML is related to the intensity of the remission induction regimen, the drugs used in AML are given at doses that uniformly cause severe myelosuppression (except tretinoin). One reason for the lower CR rate in AML as compared to ALL is the inability to give optimal doses of chemotherapy because of marrow toxicity. With continued improvement of supportive care, more intensive treatment regimens are given in an effort to reduce the high rate of leukemic relapse and increase the proportion of long-term survivors. Most patients achieve a CR after 1 or 2 courses of chemotherapy. Patients who require additional chemotherapy to achieve a CR have been reported to have a poor prognosis, even if remission is ultimately achieved.

The most active single agents in AML are the anthracycline antibiotics (daunorubicin, doxorubicin, and idarubicin), mitoxantrone, and the antimetabolite cytarabine. The standard therapy for the treatment of adult AML has not changed in several decades. The most common regimen (“7+3”) combines daunorubicin administered as a short infusion of 45 to 60 mg/m^2/day on days 1 to 3, along with cytarabine administered as a continuous 24-hour infusion of 100 to 200 mg/m^2/day on days 1 to 7.[6] The CR rate with the 7+3 regimen is 65% to 75% in patients 18 to 60 years old. Several trials have attempted to improve on conventional 7+3 therapy, but have shown no improvement by (a) increasing cytarabine to 10 days, (b) shortening cytarabine to 5 days, (c) substituting doxorubicin, idarubicin, or mitoxantrone for daunorubicin, (d) adding other agents such as etoposide, thioguanine, or topotecan, or (e) increasing cytarabine to higher doses (2 g/m^2 every 12 hours for 8-12 doses).[73] The most recent change to the standard 7+3 regimen is to

increase the daunorubicin dose. Adults younger than 60 years old with AML who were randomized to receive higher daunorubicin dosages (90 mg/m^2/day on days 1-3) in combination with 7 days of standard-dose cytarabine (100 mg/m^2/day) had a significantly higher CR rate (71% vs 57%) and longer median overall survival (23.7 vs 15.7 months) as compared with those who received the standard 7+3 regimen of daunorubicin (45 mg/m^2/day on days 1-3) and cytarabine. However, on subgroup analysis, the survival benefit with high-dose daunorubicin was restricted to patients with favorable or intermediate-risk cytogenetics and those younger than 50 years of age.[77]

Idarubicin and mitoxantrone have been evaluated as alternatives to daunorubicin in combination with standard-dose continuous infusion cytarabine. Trials in younger patients reported improved CR rates with these newer anthracyclines (idarubicin) or anthracenediones (mitoxantrone), and one trial reported prolonged survival. Among older adults, the CR rate and overall survival do not appear to be different among the different anthracyclines or anthracenediones.[75] Therefore, the anthracycline of choice for the standard 7+3 regimen is daunorubicin or idarubicin with many centers adopting idarubicin or higher doses of daunorubicin into the induction regimen in younger AML patients.

Based on experimental tumor models that showed a steep dose-response curve for cytarabine, higher cytarabine doses have been evaluated to increase the antileukemic activity of induction therapy. The decision to give high-dose cytarabine in induction depends on the treatment plan for postremission or consolidation therapy. A study specifically in younger patients compared conventional dose cytarabine to high-dose cytarabine (with both cohorts receiving daunorubicin and etoposide) demonstrated improved overall survival in patients aged 15 through 45 years of age.[78] A retrospective study conducted by the European Group for Blood and Marrow Transplantation demonstrated that the cytarabine dose administered during induction and/or consolidation did not influence the outcome in patients who ultimately went on to receive allogeneic or autologous HSCT.[79] These data suggest that high doses of cytarabine during induction may not be needed in patients who receive HSCT as postremission therapy. In summary, the role of high-dose cytarabine during induction remains controversial. If used during induction, high-dose cytarabine is more appropriate in younger patients than in elderly patients because of poor tolerance by elderly patients. In addition, it may be an option in patients unable to tolerate anthracyclines.

A novel induction option has emerged for patients with poor prognosis AML.

In August 2017, the FDA granted regular approval to a liposome-encapsulated combination of daunorubicin and cytarabine (CPX-351) for the treatment of adults with newly-diagnosed therapy-related AML or AML with myelodysplasia-related changes.[80] In an open-label phase 3 trial, newly diagnosed high-risk AML patients between 60 to 75 years old were randomized to receive the standard 7+3 regimen or CPX-351 for 1 to 2 cycles of induction followed by similar consolidation. The CPX-351 induction course consisted of 100 units/m^2 (100 mg/m^2 cytarabine and 44 mg/m^2 daunorubicin) administered as a 90-minute infusion on days 1, 3, and 5. Patients who received CPX-351 had significantly higher CR rates (37.3% vs 25.6%) and overall remission rates (47.7% vs 33.3%) as compared to those receiving the standard 7+3 regimen.[81] Adverse events associated with CPX-351 include hemorrhagic events, febrile neutropenia, rash, fatigue, and increased risk of infections. Since CPX-351 includes daunorubicin, cardiotoxicity is still a concern and clinicians should monitor cardiac function.[80]

Another recent addition to induction therapy is gemtuzumab ozogamicin, which was withdrawn from the United States market in 2010 due to increased deaths and lack of survival benefit in the pivotal trial. Subsequent trials have evaluated lower doses of gemtuzumab ozogamicin.[82] In a Phase 3 trial, patients were randomized to receive daunorubicin (60 mg/m^2 days 1-3) and cytarabine (200 mg/m^2 days 1-7) with or without gemtuzumab ozogamicin (3 mg/m^2 on days 1, 4, and 7) for the treatment of adults with newly diagnosed *de novo* AML. Patients in the gemtuzumab ozogamicin group had significantly longer median event-free survival (17.3 vs 9.5 months) as compared with those in the daunorubicin and cytarabine group, but also a higher risk of grade 3 or higher adverse events (infection, hemorrhage, veno-occlusive disease, and thrombocytopenia).[83]

Several small molecule FLT3 inhibitors have been developed and are changing the AML treatment landscape.[84] Midostaurin is an oral multitargeted TKI that is active against FLT3. In a large phase 3 trial, patients less than 60 years old with AML and an *FLT3* mutation were randomly assigned to receive standard induction with daunorubicin and cytarabine plus either midostaurin or placebo. Patients who remained in remission after consolidation therapy received either midostaurin or placebo as maintenance therapy. Patients randomized to the midostaurin arm had a significant improvement in overall survival (74.7 vs 25.6 months, hazard ratio 0.78, $P = 0.009$).[85] Midostaurin is administered days 8 to 21 of each cycle of induction with chemotherapy and during each consolidation cycle.[86]

The NCCN guidelines recommend the standard 7+3 regimen for AML patients less than 60 years of age. Younger patients with intermediate-risk disease cytogenetics with *FLT3*-mutant disease should receive 7+3 therapy combined with midostaurin. Patients with therapy-related AML should receive standard 7+3 as treatment induction, but CPX-351 administered on days 1,3, and 5 for 1 cycle is a recommended alternative option.[73]

Older patients (more than or equal to 60 years) who are not candidates for intensive remission induction therapy should be offered a low-intensity therapy with low-dose subcutaneous cytarabine, a hypomethylating agent such as azacitidine or decitabine, a clinical trial or best supportive care because of the dismal outcomes and toxicity risks associated with conventional chemotherapy.[73] Azacitidine and decitabine are pyrimidine nucleoside analogs of cytidine that inhibit DNA methylation. While each agent has shown promising results versus conventional chemotherapy and best supportive care, the agents have not been compared to each other in trials.[87,88] Azacitidine is usually given 75 mg/m^2/dose IV or subcutaneously for 7 days while decitabine is given 20 mg/m^2/dose IV for 5 days. Patients with unfavorable cytogenetics or TP53 mutations should receive 10 days of decitabine therapy.[89] Cycles are repeated every 28 days. A minimum of 4 to 6 cycles of therapy must be given before the evaluation of response. Azacitidine has resulted in OS rates of 50% as compared to 16% in those treated with usual care (chemotherapy, low-dose cytarabine, or best supportive care).[73] These agents are generally well-tolerated with the most significant adverse effect being myelosuppression. Best supportive care includes the use of blood product transfusion support.

Other options for older patients who are not candidates for intensive remission induction therapy include gemtuzumab ozogamicin in CD33-positive patients and IDH inhibitors for patients with IDH1/2 mutations.[73] A single induction course of gemtuzumab of 6 mg/m^2 on day 1 and 3 mg/m^2 on day 8 improves overall survival as compared to best supportive care.[90] Ivosidenib (IDH1 inhibitor) and enasidenib (IDH2 inhibitor) are both FDA approved in the setting of relapsed/refractory AML.[91] These agents are currently being evaluated in combination with hypomethylating agents in a frontline setting. A novel oral hedgehog pathway inhibitor, glasdegib, is approved in combination with low-dose cytarabine for patients ≥75 years old who are unable to tolerate intensive induction therapy.[92]

All adult patients who present with CNS symptoms or asymptomatic monocytic disease should have a diagnostic lumbar puncture, and, if it is

positive, should be treated for disease. Methotrexate or cytarabine should be administered intrathecally twice a week until clearance of leukemic blasts from the CSF, and then weekly for 4 to 6 weeks. Continued secondary prophylaxis is recommended following treatment for CNS disease.[73]

8 **Postremission Therapy** Although most adults with AML achieve a CR, the duration of remission is short (6-9 months) if no further treatment is given. Relapse is presumably a consequence of the presence of residual, but clinically undetectable, leukemic cells after remission induction therapy. The goal of intensive postremission therapy is to eradicate these residual leukemic cells and prevent the emergence of drug-resistant disease. The need for postremission therapy is based on postmortem analysis and cell kinetic data suggesting that nearly 10^9 residual leukemic cells remain after effective remission induction therapy. Strategies evaluated as postremission therapy include (a) low-dose, prolonged maintenance therapy, (b) short-course intensive chemotherapy-alone regimens, and (c) high-dose chemotherapy with or without radiation therapy followed by allogeneic or autologous HSCT.

In the treatment of AML, intensive-postremission therapy is referred to as consolidation therapy. Results of randomized controlled trials in adults clearly show that intensive-postremission therapy following remission induction therapy prolongs survival versus no therapy, although the exact duration of postremission therapy is controversial.[6,75]

The intensity of postremission therapy is important. In a large CALGB trial, all patients who achieved a CR after standard 7+3 induction were randomized to receive one of three cytarabine-based consolidation regimens: 100 mg/m^2/day or 400 mg/m^2/day as a continuous 24-hour infusion, or 3,000 mg/m^2 every 12 hours on days 1, 3, and 5. For adults younger than age 60 years, the probability of remaining in CR after 4 years was significantly higher in patients who received high-dose cytarabine (25% vs 29% vs 44%, respectively). Elderly patients had lower response rates in all arms and did not benefit from the administration of higher cytarabine doses, probably because they were unable to tolerate the high-dose regimen. Dose-limiting neurotoxicity in the high-dose arm was more common in elderly patients and those patients with impaired renal function.[93]

High-dose cytarabine appears to be an important component of postremission therapy, particularly if it is not used in induction therapy. However, many questions remain, such as the optimal dose (g/m^2), number of doses per cycle, and number of cycles of high-dose cytarabine. Among patients with core-

binding factor AML, defined as the presence of either t(8;21) or inv(16), multiple cycles are clearly beneficial. The NCCN guideline recommends 3 to 4 cycles of high-dose cytarabine for adults younger than 60 years of age and with favorable cytogenetics. Patients with intermediate-risk cytogenetics should receive 3 to 4 cycles of high-dose cytarabine, or proceed directly to a matched allogeneic HSCT.[73] For those patients with FLT3 positive AML, midostaurin 50 mg every 12 hours on days 8 to 21 should be added to high-dose cytarabine.[85,86] Daunorubicin, in addition to gemtuzumab ozogamicin and cytarabine, is an option for CD33-positive, intermediate-risk cytogenetics AML patients.

Patients with treatment-related or poor-risk disease should continue directly to a matched allogenic HSCT or receive high-dose cytarabine (1.5-3 g/m^2) for 3 to 4 cycles.[73]

If a patient is 60 years of age or older, standard-dose cytarabine with or without an anthracycline for one to two cycles, a reduced-dose high-dose cytarabine regimen (1-1.5 g/m^2/day for 4-6 doses) for one to two cycles, continuation of low-intensity therapy such as azacitidine or decitabine, or enrollment in a clinical trial is recommended. Patients with high-risk cytogenetics, underlying MDS, or secondary AML should either be enrolled in a clinical trial or be referred for either a matched sibling or alternative donor allogeneic HSCT.[73]

Allogeneic Hematopoietic Stem Cell Transplantation Allogeneic HSCT is the most aggressive postremission therapy in the management of AML. Controversy surrounds this treatment approach, specifically the appropriateness, timing, treatment design, and donor selection.

The antileukemic activity of allogeneic HSCT is based on the administration of pretransplant high-dose chemotherapy (or chemoradiotherapy) and the development of a posttransplant immune-based antileukemic response. The immune-based response, referred to as a graft-versus-leukemia (GVL) effect, often accompanies the graft-versus-host disease (GVHD) reaction. Evidence for the immune-based benefit of allogeneic HSCT is based on the observation of consistently lower relapse rates with allogeneic HSCT as compared to autologous or syngeneic HSCT. This potential benefit of allogeneic HSCT can be offset by the risk of posttransplant complications such as GVHD, sinusoidal obstruction syndrome, graft failure, and infections.

Allogeneic HSCT was first evaluated as a treatment modality for AML in refractory patients, but because of initial success in small numbers of patients, it has also been evaluated as intensive-postremission therapy in AML patients in

first or subsequent remission.[94] Nonrandomized trials of HLA-identical sibling allogeneic HSCT performed in AML patients in first complete remission (CR1) reported 5-year survival rates of 45% to 60% with relapse rates of 10% to 20%.[75,95,96] Transplant-related mortality following HLA-matched sibling allogeneic HSCT ranges from 10% to 25%.[96] However, this data is based on traditional trials that consisted of HLA-identical sibling donors. With increasing use of matched unrelated donors and umbilical cord blood as donor sources, transplant-related mortality of allogeneic transplants continues to be evaluated. With the availability of more effective immunosuppressive and antibiotic regimens, transplant-related mortality has decreased and survival has increased.

Allogeneic HSCT from an HLA-matched sibling donor for AML patients in CR1 results in long-term event-free survival in 43% to 55% of patients. Although the results vary, some of the studies show longer event-free survival and lower relapse rates with allogeneic HSCT in AML in CR1 as compared to chemotherapy-alone postremission regimens. Single center prospective trials have not shown an overall survival advantage for allogeneic HSCT in all patients with AML CR1. Meta-analyses of clinical trials comparing allogeneic HSCT to other consolidation strategies in CR1 show that allogeneic HSCT does provide an overall survival advantage for patients with intermediate- and high-risk AML[97] The ASBMT recommends allogeneic HSCT for AML patients who are in CR1 with intermediate- or high-risk disease and CR2 patients.[53]

Myeloablative allogeneic HSCT is generally restricted to patients younger than 60 years of age, which limits the number of patients eligible for treatment of a disease that primarily affects older adults. Non-myeloablative transplantation (NMT) uses reduced-intensity preparative regimens and is now being utilized in AML patients, particularly in older patients and those with comorbid illnesses that would limit their eligibility for conventional allogeneic HSCT.[97] NMT is designed to provide enough immunosuppression in the preparative regimen to allow for engraftment of donor cells, and depends heavily on the development of a GVL effect as a means to treat and prevent relapse of AML. The procedure is well tolerated in a wide age range of patients, with low rates of regimen-related toxicity. In a large study of 1,637 patients who received NMT, age was not associated with outcome.[98] Registry data of patients aged 70 years or older (89% received NMT) reported that 2-year overall survival significantly improved between 2000-2007 and 2008-2013 (26% vs 39%, $P < 0.001$).[99]

Given that only 30% of patients have an HLA matched sibling donor, matched unrelated donor HSCT is also an option for children and younger adults

with AML. This approach is associated with improved survival, but the risk of transplant-related mortality is higher than in patients undergoing HLA-matched sibling allogeneic HSCT. A multivariable analysis of clinical outcomes of matched unrelated donor transplants indicates that overall survival, nonrelapse mortality, and relapse rate has improved over the last two decades.[100]

Autologous Hematopoietic Stem Cell Transplantation Compared to allogeneic HSCT, autologous HSCT has the advantages of a lower risk of posttransplant complications because of lack of immunosuppression and GVHD, and more broad applicability because of a lack of donor limitations and fewer age restrictions. Although the preparative regimen still provides antileukemic activity, autologous HSCT is associated with a higher risk of relapse because of a lack of a GVL effect and potential tumor contamination with autologous stem cells. The ASBMT does not recommend autologous HSCT in pediatric patients.[53] In adults, autologous HSCT is an alternative option particularly in low-risk patients but should not be pursued in patients with high-risk cytogenetics.[94]

Postremission Therapies Several randomized trials in AML patients in CR1 have compared outcomes following allogeneic HSCT, autologous HSCT, and/or intensive consolidation chemotherapy.[94] In most trials, eligible patients based on age and donor availability received an allogeneic HSCT and the remaining patients were randomized between autologous HSCT and chemotherapy alone. The effect of stem cell source on event-free survival and overall survival is controversial. Several comparative trials of bone marrow versus peripheral blood have been completed in patients with hematologic malignancies, and a meta-analysis of nine randomized trials showed a lower relapse rate and similar overall survival for those patients receiving peripheral blood stem cells.[101]

The decision to transplant is often based upon cytogenetic-risk category.[70] Patients with high-risk cytogenetics do poorly with conventional chemotherapy or autologous HSCT, thus allogeneic HSCT is the treatment of choice in this population. Patients with favorable-risk cytogenetics should not proceed to transplant in CR1, as neither autologous nor allogeneic HSCT is superior to conventional chemotherapy. The optimal treatment of choice in patients with intermediate-risk cytogenetics is not clear and is based on the availability of matched-related donor and clinician preference. Despite recommendations that patients with intermediate-risk cytogenetics should receive HSCT in CR1, a recent study reported only 27% of patients in a European study proceeded to transplant at CR1.[102]

For younger patients (<60 years) with favorable-risk cytogenetics, 3 to 4 cycles of high-dose cytarabine therapy or cytarabine in combination with daunorubicin and gemtuzumab ozogamicin if disease is CD33 positive is recommended. The NCCN guideline recommends that patients with favorable-risk cytogenetics who have c-KIT mutations are similar to intermediate-risk patients and should pursue clinical trials or other therapies for consolidation. The NCCN guideline does not recommend autologous HSCT outside the setting of a clinical trial.[73]

Patients with intermediate-risk and high-risk cytogenetics with molecular abnormalities typically receive high-dose cytarabine for several cycles while a donor search (sibling, unrelated, cord) is initiated.[73] For FLT3-positive patients, midostaurin should be continued during consolidation with high-dose cytarabine.[85] The optimal dose of cytarabine administered during consolidation in this patient subgroup is not clear. There is no evidence to show that high-dose cytarabine (2-3 g/m^2) provides improved outcomes as compared to intermediate-dose cytarabine (1.5 g/m^2) in intermediate-risk cytogenetics patients.

For patients 60 years and older, additional consolidative chemotherapy or immediately proceeding to a HSCT is recommended if the patient has achieved a CR1 and is deemed a suitable transplant candidate. The NCCN guideline recommends NMT rather than a myeloablative transplant in this patient population. For the AML patient who relapses early after induction therapy, if a sibling or matched unrelated donor is available, then allogeneic HSCT is the primary reinduction therapy because conventional chemotherapy offers little benefit. If the relapse occurs late, then HSCT may be used as postremission consolidation after reinduction therapy. In those patients who achieve remission with an intensive regimen but experience significant toxicities, the use of maintenance hypomethylating agents (eg, decitabine or azacytidine) every 4 to 6 weeks until progression is an option.[73]

Acute Myeloid Leukemia in Children

AML comprises about 20% of leukemias in children and adolescents. Most cases of AML in children arise *de novo* but AML is associated with trisomy 21, Fanconi's anemia, dyskeratosis congenital, Schwachman-Diamond's syndrome and Kostmann's syndrome. Secondary AML is extremely rare in children but is classically associated with alkylating agents, topoisomerase inhibitors and radiation therapy.[12] AML patients are stratified to low risk or high risk based on molecular and cytogenetic markers and response to therapy. Examples of low-

risk cytogenetic and molecular markers are PML-RARA, inv(16), RUNX1, CEBPα, and NPM1 and examples of high-risk markers are monosomy 5, monosomy 7, FLT3/ITD, and c-KIT.[103] Low-risk patients have a 5-year overall survival of 83% and event-free survival of 72% while high-risk patients have a lower overall survival and event-free survival of 46% and 15 to 35%, respectively. Patients with therapy-related AML have the worst survival rate of about 20%.[12] Therapy for AML in children includes 1 to 2 cycles of induction therapy followed by 2 to 3 cycles of consolidation therapy. The number of cycles varies by protocol.[76] Induction therapy with cytarabine and an anthracycline is standard. Etoposide is often included in induction but its contribution to efficacy has been debated.[76] Consolidation therapy or intensification phases of treatment involve the use of high-dose cytarabine in combination with an anthracycline and etoposide.[103] Maintenance therapy has no role in pediatric AML (see Fig. 151-2). Intrathecal chemotherapy for CNS prophylaxis is routinely used, but the optimal regimen is unknown and varies by protocol.[76] Cranial radiation is only used for patients with refractory CNS disease.

Certain patients may be eligible to receive an HSCT as consolidation therapy instead of continued chemotherapy. The use of HSCT in CR1 rather than waiting until relapse/CR2 is controversial. Most trials recommend consolidation with chemotherapy for favorable-risk patients; the role of HSCT in unfavorable-risk patients may be considered on an individual basis after carefully weighing the risks and benefits.[103]

Relapsed or Refractory Acute Myeloid Leukemia

Treatment of relapsed or refractory AML is a therapeutic challenge despite the emergence of novel agents and the increasing number of available donor pools for bone marrow transplantation. The most common cause of treatment failure in AML patients receiving chemotherapy alone or undergoing HSCT is relapse. In addition, many patients, particularly elderly patients, have refractory disease as defined by the inability to achieve a CR after two courses of induction therapy. In most cases, the preferred method of treatment for relapsed or refractory disease is HSCT if patients are able to tolerate it. Unfortunately, most patients receive salvage chemotherapy because only a small percentage of relapsed or refractory adult patients will be eligible for HSCT, particularly allogeneic HSCT, because of age and donor restrictions.

Commonly used salvage chemotherapy regimens include FLAG-IDA (fludarabine, cytarabine, idarubicin, and granulocyte colony stimulating factor),

MEC (mitoxantrone, etoposide, cytarabine), and GCLAC (clofarabine, high-dose cytarabine, and priming granulocyte colony stimulating factor). These regimens are associated with CR rates of 40% to 65% in younger patients and significant toxicity.[104,105] Patients who achieve a CR2 should pursue an allogeneic HSCT since this modality is the only potential curative therapy. Allogeneic HSCT should be performed when a patient is in CR to allow for a robust GVL effect.

In patients unfit to receive intensive-salvage chemotherapy, less aggressive therapies such as hypomethylating agents (azacitidine, decitabine) are options.[73] In patients older than 50 years old with relapsed or refractory AML, 17% had a CR to azacitidine, with an overall survival of 8.4 months. Notably, 42% of patients were unable to receive four cycles of azacitidine, primarily due to death and toxicities.[106] Given these poor outcomes with current options, patients with relapsed or refractory AML who are elderly or unfit are encouraged to pursue clinical trials.[73]

Several novel classes of agents have emerged as treatment options for relapsed or refractory AML including FLT-3 (eg, midastaurin, gilteritinib), IDH (eg, enasidenib, ivosidenib), murine double minute 2 (MDM2) and BCL-2 inhibitors (venetoclax). These agents are given either as single agents or combined with other agents such as low-dose cytarabine and hypomethylating agents. Immunotherapy approaches such as CAR T-cells, BiTEs, antibody-drug conjugates, and cell-based vaccines are being investigated in clinical trials.[105]

Treatment—Acute Promyelocytic Leukemia

Acute promyelocytic leukemia (APL) is a subclass of AML that accounts for about 10% of all cases. APL is the most curable of the AML subtypes, but its clinical presentation is associated with a high early death rate secondary to coagulopathy.[107] Most patients are diagnosed between the ages of 15 and 60 years, and the average age is 44 years.[1] Although the management of APL is complex, remission induction regimens produce CR rates exceeding 90% with 5-year event-free survival rates of 70% to 80%.[108] APL is clinically unique from the other subclasses because of the common occurrence of severe coagulopathy (characterized by disseminated intravascular coagulation) at diagnosis and during induction therapy, which frequently results in intracerebral hemorrhage. In APL, differentiation and maturation arrest are caused by alterations in the retinoic acid receptor (RAR) because of the translocation of chromosomes 15 and 17. The discovery of t(15;17) provides a cytogenetic marker of the disease

and is predictive of response to differentiation therapy with tretinoin (commonly referred to as all-*trans* retinoic acid or ATRA). This translocation leads to a fusion protein of the *PML* gene on chromosome 15 and the RARα on chromosome 17.

Prior to the availability of tretinoin in the late 1980s, treatment of APL consisted of the same combination chemotherapy regimens used in the treatment of other subclasses of AML. Such standard regimens produced CR rates of 50% to 60% but were associated with high-treatment–related mortality rates caused by hemorrhagic complications. The introduction of targeted therapy with tretinoin results in high-CR rates with a significant reduction in life-threatening bleeding complications. Arsenic trioxide targets the PML moiety, resulting in apoptosis, and appears to be synergistic with tretinoin.[109]

The initial WBC count at presentation is the most important prognostic factor in patients with APL. Risk stratification of patients at diagnosis based on WBC count has improved outcomes. Abnormal creatinine, increased peripheral blast count, and presence of coagulopathy are prognostic factors that predict for early death due to hemorrhage.[110]

Treatment Phases

9 **Induction Therapy** Tretinoin, an oral vitamin A analog, is given orally in a dose of 45 mg/m^2/day, as a single dose or divided into two doses, after a meal. Tretinoin-based regimens achieve CR rates as high as 95% in APL patients within 1 to 3 months. Because tretinoin does not cross the blood-brain barrier, leukemic meningitis should be treated with conventional intrathecal chemotherapy.

Although it is not myelosuppressive, tretinoin therapy is associated with headache, skin and mucous membrane reactions, bone pain, nausea, and retinoic acid syndrome. When tretinoin is started, rapid onset of differentiation of promyelocytes occurs, which can lead to leukocytosis and retinoic acid syndrome. The retinoic acid syndrome (unexplained fever, acute respiratory distress, interstitial pulmonary infiltrates, pleural effusions, and weight gain) is now referred to as APL differentiation syndrome (or APL hyperleukocytosis syndrome) because it is associated with other treatment modalities in the management of APL. The syndrome is fatal in 5% to 29% of cases. A combination of chemotherapy with tretinoin induction decreases the risk of APL differentiation syndrome, and rapid initiation of dexamethasone 10 mg (0.2 mg/kg per dose in children) twice daily on development of symptoms decreases

associated mortality.[110]

For newly diagnosed low-risk APL patients (WBC ≤10,000/mm^3 [10 × 10^9/L]), induction therapy should consist of tretinoin 45 mg/m^2 in two divided doses daily in addition to arsenic trioxide (ATO) 0.15 mg/kg IV daily until hematologic complete remission.[73] This "chemotherapy free" strategy achieved an impressive 100% CR rate in a Phase 3 clinical trial. Furthermore, early mortality and hematological toxicities were significantly less with patients who received tretinoin + ATO compared to those who received tretinoin+chemotherapy.[110] For patients with adequate cardiac function, the combination of daily tretinoin and idarubicin 12 mg/m^2 on days 2, 4, 6, and 8 is also a recommended alternative regimen. Assessment of response to treatment of APL is completed at the time of count recovery after induction therapy. A day 10 to 14 day bone marrow biopsy, which is completed for monitoring the effect of induction chemotherapy for other types of AML, is not a long enough time from initiation of therapy because leukemic promyelocytes need more time for differentiation.

High-risk patients (WBC >10,000/mm^3 [10 × 10^9/L]) represent about 30% of APL patients. They should proceed with induction therapy that consists of tretinoin in addition to an anthracycline. All of these regimens include tretinoin 45 mg/m^2 per day until a CR is achieved, in combination with an anthracycline (either daunorubicin 50-60 mg/m^2 per dose for 3 or 4 days, or idarubicin 6-12 mg/m^2 per dose every other day for four doses) or tretinoin plus ATO for patients unable to tolerate anthracycline therapy. Several of the induction regimens also contain cytarabine 200 mg/m^2 per dose for 7 days; similar CR rates are observed with daunorubicin or idarubicin.[76] APL cells appear to be more sensitive to anthracyclines, possibly because of decreased P-glycoprotein expression. Gemtuzumab ozogamicin 6 to 9 mg/m^2 has been added to tretinoin and anthracycline combinations for high-risk patients but does not increase event-free or overall survival.[111]

Consolidation Therapy Both low-risk and high-risk APL patients should receive consolidation therapy due to a high relapse rate. Consolidation therapy typically consists of an idarubicin or daunorubicin-based regimen in combination with tretinoin. ATO is included in some regimens for low-risk and high-risk patient populations; ATO is administered 5 days/week for 4 weeks every 8 weeks for a total of four cycles.[73]

Maintenance Therapy Unlike other subtypes of AML, maintenance therapy is

an important but controversial component of therapy for APL. Before the development of tretinoin, nonrandomized trials suggested a benefit of continuous low-dose methotrexate and mercaptopurine as maintenance therapy. Larger prospective randomized trials have demonstrated decreased relapse rates in patients who received maintenance therapy (either tretinoin or combination chemotherapy) and some trials have demonstrated increased event-free survival and overall survival.[108] However, several large APL study (APL0406, UK AML17, and MD Anderson) protocols do not include maintenance therapy for patients in molecular remission at the end of consolidation.[111] The AIDA 0493 study evaluated four maintenance cohorts (intramuscular methotrexate and mercaptopurine, tretinoin, alternating chemotherapy with tretinoin, and observation) and reported a 12-year event-free survival of 69%, with no significant differences between cohorts.[73] Some experts do not recommend the use of maintenance therapy, particularly in low-risk patients.[111] NCCN guidelines currently recommend that APL patients who achieve molecular remission after consolidation should receive maintenance therapy if indicated by treatment protocol.[73]

Relapsed Acute Promyelocytic Leukemia

The overall incidence of relapsed APL is 10% to 15%, with rates as high as 20% to 30% in high-risk disease. Most relapses occur in the first 3 years following induction therapy. ATO is the agent of choice for relapsed APL, and this agent serves as a backbone for treatment regimens. Multiple studies have reported CR rates of about 85%.[108]

ATO induces clinical remissions in relapsed APL through its induction of apoptosis and differentiation. The recommended dose is 0.15 mg/kg/day IV until bone marrow remission, not to exceed 60 doses, followed by consolidation beginning 3 to 6 weeks after completion of induction at the same dose for a total of 25 doses over a period up to 5 weeks. ATO therapy is associated with two specific toxicities. First, it can cause the APL differentiation syndrome, similar to that seen with tretinoin. Management is similar: corticosteroids at first signs of pulmonary distress or a rapidly rising WBC count. The second toxicity is a prolongation of the QT_c interval. Consequently, it is important to obtain a baseline 12-lead electrocardiogram prior to starting therapy with ATO and correct any electrolyte abnormalities, including potassium, calcium, and magnesium. Other medications known to prolong the QT_c interval should be avoided, if possible, during arsenic trioxide therapy. The QT_c interval should not

exceed 500 ms at baseline, and if it increases to more than 500 ms during therapy, the patient should be reevaluated. ATO should not be restarted until the QT_c is less than 460 ms. Following induction of a CR2 with arsenic trioxide in relapsed patients, postremission therapy with combination ATO and chemotherapy can result in molecular remissions and improved event-free survival, as compared to chemotherapy or ATO alone following remission.

It is recommended for patients to proceed to autologous HSCT following hematologic and molecular remission after arsenic therapy.[73] Outcomes with autologous HSCT depend on the disease status of the patient at the time of transplant. Autologous HSCT in CR2 (vs CR1) is associated with lower overall survival, leukemia-free survival, and increased treatment-related mortality. Autologous HSCT have shown increased disease-free and overall survival as compared to allogeneic HSCT.[112]

Patient Monitoring

In comparison to non-APL AML, molecular and cytogenetic testing at the end of remission induction therapy in APL has no prognostic value. Clinicians should therefore not make decisions based on the presence or absence of any genetic abnormalities. Since terminal differentiation of blasts in APL requires more than 40 days, results of a bone marrow biopsy obtained at the end of remission induction can be misleading because insufficient time has elapsed to determine response. Molecular and cytogenetic response assessment should occur after the completion of consolidation treatment.

Detection of residual PML/RARα transcripts in the bone marrow at the end of consolidation therapy is strongly associated with subsequent hematologic relapse. Achievement of PML/RARα-negative status is associated with a higher probability of cure. The use of this molecular technique allows the clinician to assess response to therapy and also detect relapse earlier, which might prevent the development of overt disease recurrence and is associated with improved outcome compared with delaying treatment until overt morphologic relapse. Most experts recommend that APL patients should be routinely evaluated with polymerase chain reaction for PML/RARα every 3 to 6 months for 2 years, and then every 6 months for 2 years.[73,108]

ROLE OF HEMATOPOIETIC GROWTH FACTORS IN ACUTE MYELOID LEUKEMIA

10 Hematopoietic growth factors have been evaluated in AML patients to enhance chemotherapy cytotoxicity, shorten the duration of neutropenia, and reduce the incidence and severity of infection following induction and consolidation chemotherapy. Most studies show limited benefit with the use of colony-stimulating factors as “priming” agents administered during remission induction therapy in an effort to recruit leukemia cells into the cycle to enhance susceptibility to cell-cycle–specific chemotherapy agents, leading to increased cell kill. Use of hematopoietic growth factors concurrently during chemotherapy administration is discouraged outside the setting of a clinical trial and is not recommended in the American Society of Clinical Oncology (ASCO) guidelines.[113]

Both filgrastim and sargramostim are FDA approved to prevent neutropenic complications in adult AML patients receiving intensive chemotherapy. Since myeloid blast cells have receptors for granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor, some experts were initially concerned that the use of these factors would stimulate regrowth of leukemia. Although subsequent studies have addressed these concerns, many clinicians do not initiate filgrastim until an initial remission is achieved. Growth factors are not recommended in APL patients during induction therapy because they can increase the risk of differentiation syndrome.[73]

Several randomized trials, primarily in elderly patients, show that filgrastim or sargramostim reduces the duration of neutropenia following AML-induction chemotherapy. The ASCO Guidelines for the Use of White Blood Cell Growth Factors considers the use of hematopoietic growth factors after initial induction therapy reasonable, with the understanding that the effects on length of hospitalization and incidence of severe infection are modest. Patients older than age 55 years appear to derive the greatest benefit, and use is appropriate in this population where more rapid marrow recovery might decrease the duration of hospitalization.[113] A review of 19 trials including 5,256 patients reported no difference in the risk of bacteremias or invasive fungal infections with the use of hematopoietic growth factors.[114] This study concluded the use of hematopoietic growth factors after consolidation did not affect CR duration, relapse rates or overall survival. Further pharmacoeconomic data are required in this setting, but the body of evidence supports their use following consolidation therapy in adults. Other controversial issues surrounding hematopoietic growth factor use in AML include which growth factor to use, what dose, which day to start after chemotherapy, how long to continue, and should the marrow be examined for leukemia prior to starting a colony-stimulating factor. All hematopoietic growth

factors have been evaluated in patients with AML, including sargramostim, filgrastim, and pegfilgrastim. Although pegfilgrastim is not FDA approved for this indication, research supports its use in this setting. Two biosimilar products are available. Filgrastim-sndz was the first FDA-approved growth factor and is indicated in patients with AML receiving induction and consolidation therapy.[115] Filgrastim-aafi was recently approved to reduce the time of neutrophil recovery and duration of fever in AML patients.[116] The use of hematopoietic growth factors can also interfere with the interpretation of the day 14 bone marrow examination. Hematopoietic growth factors should be discontinued at least 7 days prior to a bone marrow aspirate and biopsy to avoid interfering with the interpretation of the results (ie, may see immature myeloid forms that would suggest residual disease).[117]

SUPPORTIVE CARE

The most common and significant adverse effect of antileukemic agents is marrow suppression. With the exception of corticosteroids, tretinoin, asparaginase/pegaspargase, and vincristine, antineoplastic agents used to treat acute leukemia cause myelosuppression. During AML remission and postremission therapy, daily monitoring of the complete blood count and the absolute neutrophil count is necessary to determine when red cell and platelet transfusions are needed and when neutropenia occurs and resolves. Marrow hypoplasia from the myelosuppressive regimens usually reaches its lowest point (nadir) after 1 to 2 weeks of therapy and lasts for another 1 to 2 weeks. During this period of hypoplasia, infectious and bleeding complications are major causes of death in leukemic patients.

Typical signs and symptoms of infection may be absent in the neutropenic host, frequent monitoring of vital signs (particularly fever) and daily assessment are essential. Infection control strategies often include routine hand washing; dietary restrictions; reverse isolation and laminar-air flow rooms; fungal, *Pneumocystis*, and bacterial prophylaxis; and the empiric use of broad-spectrum antibiotics when fever occurs. A recent joint ASCO/IDSA guideline recommends antibacterial and antifungal prophylaxis in high-risk neutropenic patients (<100 cells/mm^3 [0.1 × 10^9/L] for 7 days). Furthermore, *Pneumocystis jirovecii* prophylaxis is recommended in patients receiving chemotherapy that is associated with >3.5% risk for pneumonia. Leukemia patients who are herpes simplex virus seropositive undergoing induction therapy should receive antiviral prophylaxis.[118]

In children, short-term levofloxacin prophylaxis is recommended during intensive chemotherapy for acute leukemias (ie, *de novo* AML, relapsed AML, secondary AML, ambiguous lineage leukemia treated on AML therapy and relapsed ALL) to reduce the risk of bacteremias. However, pediatric HSCT patients have not shown a significant reduction in bacteremia with levofloxacin prophylaxis. Levofloxacin prophylaxis in pediatric leukemia patients decreases the risk of febrile episodes but does not reduce the risk of severe infection or invasive fungal disease.[119] Infectious complications, especially fungi, are a major cause of morbidity and mortality; therefore, primary antifungal prophylaxis is strongly recommended for pediatric AML and HSCT patients.[120]

Acute leukemia patients, particularly those patients with an initial elevated WBC count, are at risk for tumor lysis syndrome. Measures to prevent the development of urate nephropathy from the rapid destruction of WBCs include allopurinol or rasburicase, and adequate hydration prior to and during chemotherapy. Rasburicase, a recombinant urate oxidase enzyme produced by genetic modification of *Saccharomyces cerevisiae,* catalyzes the enzymatic oxidation of uric acid into the inactive soluble metabolite, allantoin. In children, rasburicase more rapidly reduces uric acid levels in patients with aggressive malignancies as compared to allopurinol, and reduces the need for dialysis. Rasburicase has been evaluated in adults, and some studies in adults show that fixed dosing produces equivalent outcomes to a weight-based, mg/kg dosing strategy. Due to its high cost, rasburicase is usually limited to patients with ALL who have a high-WBC count or bulky extramedullary disease, aggressive lymphoma, or patients with AML with a high-presenting WBC. Most institutions also include an elevated uric acid as part of the criteria for use. Rasburicase has a rapid onset of action and long duration of action, so many institutions also limit its use to a single dose and allow repeat doses as needed. Rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to an increased risk of methemoglobinemia. Tumor lysis syndrome may result in hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and subsequent renal insufficiency.[121]

Hematologic support consists primarily of platelet and packed red blood cell transfusions. Platelet transfusions are often given for peripheral counts below 10,000 cells/mm^3 (10×10^9/L) or clinical signs of bleeding. Transfusions of packed red cells may also be indicated for a hemoglobin less than 8 g/dL (80 g/L; 4.96 mmol/L), fatigue, dyspnea, tachycardia, or chest pain. APL can release procoagulants that can cause disseminated intravascular coagulation, necessitating close monitoring and replacement of coagulation factors with

cryoprecipitate.

EVALUATION OF THERAPEUTIC OUTCOMES

Development of a pharmaceutical care plan for the acute leukemia patient begins with information about the patient's diagnosis and prognosis. Long-term therapeutic goals for the patient may include long-term event-free survival, although palliative care is a possibility in some patients. The desired short-term outcome is the achievement of remission. Restoration of normal hematopoiesis and a repeat bone marrow biopsy that demonstrates no evidence of disease serve as documentation that remission has been achieved. After the appropriate postremission therapy has been completed, the patient may return monthly for 1 year, and then every 3 months, to check hematologic values. If no evidence of disease exists after 5 years from the diagnosis and the patient has been in continuous CR, the patient is considered cured.

Frequent monitoring of fevers, hematologic and chemistry laboratory values, microbiology reports, and the patient's physical condition are necessary to identify infection, risk of bleeding, and tumor lysis syndrome early. A coagulation screening panel will identify patients with ongoing disseminated intravascular coagulation, a particular risk with APL.

Clinicians should provide patient education on acute and chronic toxicities of the chemotherapy administered and information regarding antibiotics, antiemetics, nutritional support, hematopoietic growth factors, and other supportive care issues. With the emergence of novel oral agents in the treatment landscape of AML, patients should receive institutional assistance to prevent financial toxicity given potential out-of-pocket expenses that can occur. Financial distress can impact drug therapy adherence, which could potentially impact clinical outcomes. Clinicians need to be actively engaged in assessing drug doses and any dose modifications for organ dysfunction.

Numerous late sequelae from leukemia therapy have been recognized and should be included in the monitoring plan after therapy is completed. Chapter 157 discusses the long-term consequences of HSCT. The Children's Oncology Group (COG) Long-Term Follow-Up guidelines provide an additional resource for assessment and monitoring.[122]

Postclass Engaged Learning Activity

CMO TEAM potential statements

- Across several studies, there have been impressive overall response rates from 53% to 82% in refractory disease patients (ALL/NHL)
- Serve the needs of patient catchment area
- Enhance the cancer treatment reputation of institution
- Supplement recruitment efforts of required staffing expertise
- YouTube videos of CAR-T survivors (Emily Whitehead)

CFO TEAM potential statements

- Present findings of ICER: Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value
- Financial burden to institution
- Pharmacy drug cost impact (conditioning regimens, tocilizumab for CRS management, IVIG-hypogammaglobulinemia)
- Significant adverse events, impact on ICU staffing models
- New hires—pharmacists, nurses, blood bank, oncologists, immunotherapists, social workers
- Education of emergency department staff—recognize needs of CAR-T recipients

ABBREVIATIONS

ASBMT	American Society for Blood and Marrow Transplantation
ASCO	American Society of Clinical Oncology
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
APL	acute promyelocytic leukemia
ATRA	all-*trans* retinoic acid
AYA	adolescents and young adults
BCR-ABL	breakpoint cluster region-Abelson protooncogene
BiTE	bi-specific T-cell engager

BMI	body mass index
CALGB	Cancer and Leukemia Group B
CAR	chimeric antigen receptor
CD	cluster of differentiation
CEBPA	CCAAT/enhancer binding-protein α
CNS	central nervous system
COG	Children's Oncology Group
CR	complete remission
CR1	first complete remission
CR2	second complete remission
CRi	complete remission with incomplete hematological recovery
CRc	cytogenetic complete remission
CRm	molecular complete remission
CSF	cerebrospinal fluid
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FLT3	FMS-like tyrosine kinase 3
GTP	guanosine triphosphate
GVHD	graft-versus-host disease
GVL	graft-versus-leukemia
HLA	human leukocyte antigen
HSCT	hematopoietic stem cell transplantation
hyper-CVAD	high-dose methotrexate and cytarabine alternating with fractionated cyclophosphamide plus vincristine, doxorubicin, and dexamethasone
JAK	Janus kinase
iAMLP$_{21}$	intrachromosomal amplification of chromosome 21
IDH	isocitrate dehydrogenase
ITD	internal tandem duplication
MDS	myelodysplastic syndrome
MLL	mixed lineage leukemia
MRD	minimal residual disease
m-TOR	mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NMT	nonmyeloablative transplant
NPM1	nucleophosmin
PETHEMA	Programa para el Estudio de la Terapeutica en Hemopatıa Maligna
Ph$^-$	Philadelphia chromosome negative
Ph$^+$	Philadelphia chromosome positive
PML	promyelocytic leukemia
QALYs	quality adjusted life years
RARα	retinoic acid receptor-α
TET	Tet methylcytosine dioxygenase
TKD	tyrosine kinase domain
TKI	tyrosine kinase inhibitor
TPMT	thiopurine *S*-methyltransferase
WBC	white blood cell
WHO	World Health Organization
WT1	Wilms tumor 1

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69:7–34.
2. Noone A, Howlader N, Krapcho M, Miller D. *SEER Cancer Statistics Review, 1975-2015*. Bethesda, MD: National Cancer Institute; 2017.
3. Siegel DA, Henley SJ, Li J, Pollack LA, Van Dyne EA, White A. Rates and trends of pediatric acute lymphoblastic leukemia—United States, 2001-2014. *MMWR Morb Mortal Wkly Rep*. 2017;66:950–954.
4. Wiemels J. New insights into childhood leukemia etiology. *Eur J Epidemiol*. 2015;30:1225–1227.
5. Thomopoulos TP, Ntouvelis E, Diamantaras AA, et al. Maternal and childhood consumption of coffee, tea and cola beverages in association with childhood leukemia: A meta-analysis. *Cancer Epidemiol*. 2015;39:1047–1059.
6. Short NJ, Rytting ME, Cortes JE. Acute myeloid leukaemia. *Lancet*. 2018;392:593–606.
7. Rose-Inman H, Kuehl D. Acute Leukemia. *Hematol Oncol Clin North Am*. 2017;31:1011–1028.
8. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127:2391–2405.
9. Arber DA, Borowitz MJ, Cessna M, et al. Initial diagnostic workup of acute leukemia: Guideline from the College of American Pathologists and the American Society of Hematology. *Arch Pathol Lab Med*. 2017;141:1342–1393.
10. Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children. *N Engl J Med*. 2015;373:1541–1552.
11. Cooper SL, Brown PA. Treatment of pediatric acute lymphoblastic leukemia. *Pediatr Clin North Am*. 2015;62:61–73.
12. Madhusoodhan PP, Carroll WL, Bhatla T. Progress and prospects in pediatric leukemia. *Curr Probl Pediatr Adolesc Health Care*. 2016;46:229–241.
13. Seth R, Singh A. Leukemias in children. *Indian J Pediatr*. 2015;82:817–824.

14. Hunger SP, Loh ML, Whitlock JA, et al. Children's Oncology Group's 2013 blueprint for research: Acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2013;60:957–963.
15. Inaba H, Pui CH. Glucocorticoid use in acute lymphoblastic leukaemia. *Lancet Oncol*. 2010;11:1096–1106.
16. Mitchell CD, Richards SM, Kinsey SE, et al. Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukaemia: Results of the UK Medical Research Council ALL97 randomized trial. *Br J Haematol*. 2005;129:734–745.
17. Izraeli S, Vora A, Zwaan CM, Whitlock J. How I treat ALL in Down's syndrome: Pathobiology and management. *Blood*. 2014;123:35–40.
18. Vrooman LM, Kirov II, Dreyer ZE, et al. Activity and toxicity of intravenous Erwinia asparaginase following allergy to E. coli-derived asparaginase in children and adolescents with acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2016;63:228–233.
19. Rau RE, Dreyer Z, Choi MR, et al. Outcome of pediatric patients with acute lymphoblastic leukemia/lymphoblastic lymphoma with hypersensitivity to pegaspargase treated with PEGylated Erwinia asparaginase, pegcrisantaspase: A report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2018;65.
20. van der Sluis IM, de Groot-Kruseman H, Te Loo M, et al. Efficacy and safety of recombinant E. coli asparaginase in children with previously untreated acute lymphoblastic leukemia: A randomized multicenter study of the Dutch Childhood Oncology Group. *Pediatr Blood Cancer*. 2018;65:e27083.
21. Place AE, Stevenson KE, Vrooman LM, et al. Intravenous pegylated asparaginase versus intramuscular native Escherichia coli L-asparaginase in newly diagnosed childhood acute lymphoblastic leukaemia (DFCI 05-001): A randomised, open-label phase 3 trial. *Lancet Oncol*. 2015;16:1677–1690.
22. Salzer WL, Asselin B, Supko JG, et al. Erwinia asparaginase achieves therapeutic activity after pegaspargase allergy: A report from the Children's Oncology Group. *Blood*. 2013;122:507–514.
23. Petersen WCJr, Clark D, Senn SL, et al. Comparison of allergic reactions to intravenous and intramuscular pegaspargase in children with acute lymphoblastic leukemia. *Pediatr Hematol Oncol*. 2014;31:311–317.
24. Asselin B, Rizzari C. Asparaginase pharmacokinetics and implications of

therapeutic drug monitoring. *Leuk Lymphoma*. 2015;56:2273–2280.

25. Bleyer A, Asselin BL, Koontz SE, Hunger SP. Clinical application of asparaginase activity levels following treatment with pegaspargase. *Pediatr Blood Cancer*. 2015;62:1102–1105.
26. Matloub Y, Lindemulder S, Gaynon PS, et al. Intrathecal triple therapy decreases central nervous system relapse but fails to improve event-free survival when compared with intrathecal methotrexate: results of the Children's Cancer Group (CCG) 1952 study for standard-risk acute lymphoblastic leukemia, reported by the Children's Oncology Group. *Blood*. 2006;108:1165–1173.
27. Bhojwani D, Pui CH. Relapsed childhood acute lymphoblastic leukaemia. *Lancet Oncol*. 2013;14:e205–e217.
28. Levinsen M, Harila-Saari A, Grell K, et al. Efficacy and toxicity of intrathecal liposomal cytarabine in first-line therapy of childhood acute lymphoblastic leukemia. *J Pediatr Hematol Oncol*. 2016;38:602–609.
29. Sison EA, Silverman LB. CNS prophylaxis in pediatric acute lymphoblastic leukemia. *Hematology Am Soc Hematol Educ Program*. 2014;2014:198–201.
30. Winter SS, Dunsmore KP, Devidas M, et al. Safe integration of nelarabine into intensive chemotherapy in newly diagnosed T-cell acute lymphoblastic leukemia: Children's Oncology Group Study AALL0434. *Pediatr Blood Cancer*. 2015;62:1176–1183.
31. Seibel NL, Steinherz PG, Sather HN, et al. Early postinduction intensification therapy improves survival for children and adolescents with high-risk acute lymphoblastic leukemia: A report from the Children's Oncology Group. *Blood*. 2008;111:2548–2555.
32. De Moerloose B, Suciu S, Bertrand Y, et al. Improved outcome with pulses of vincristine and corticosteroids in continuation therapy of children with average risk acute lymphoblastic leukemia (ALL) and lymphoblastic non-Hodgkin lymphoma (NHL): Report of the EORTC randomized phase 3 trial 58951. *Blood*. 2010;116:36–44.
33. Landier W, Hageman L, Chen Y, et al. Mercaptopurine ingestion habits, red cell thioguanine nucleotide levels, and relapse risk in children with acute lymphoblastic leukemia: A report from the children's oncology group study AALL03N1. *J Clin Oncol*. 2017;35:1730–1736.
34. Bhatia S, Landier W, Hageman L, et al. Systemic exposure to thiopurines and risk of relapse in children with acute lymphoblastic leukemia: A

Children's Oncology Group Study. *JAMA Oncol*. 2015;1:287–295.

35. Bhatia S, Landier W, Shangguan M, et al. Nonadherence to oral mercaptopurine and risk of relapse in Hispanic and non-Hispanic white children with acute lymphoblastic leukemia: A report from the children's oncology group. *J Clin Oncol*. 2012;30:2094–2101.
36. Relling MV, Gardner EE, Sandborn WJ, et al. Clinical pharmacogenetics implementation consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing: 2013 Update. *Clin Pharmacol Ther*. 2013;93:324–325.
37. Lee SHR, Yang JJ. Pharmacogenomics in acute lymphoblastic leukemia. *Best Pract Res Clin Haematol*. 2017;30:229–236.
38. Schultz KR, Carroll A, Heerema NA, et al. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group study AALL0031. *Leukemia*. 2014;28:1467–1471.
39. Bernt KM, Hunger SP. Current concepts in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia. *Front Oncol*. 2014;4:54.
40. Curran E, Stock W. How I treat acute lymphoblastic leukemia in older adolescents and young adults. *Blood*. 2015;125:3702–3710.
41. McNeer JL, Bleyer A. Acute lymphoblastic leukemia and lymphoblastic lymphoma in adolescents and young adults. *Pediatr Blood Cancer*. 2018;65:e26989.
42. National Comprehensive Cancer Center Network Pracicce Guidelines in Oncology. Acute lymphoblastic leukemia. Version 2.2019. Accessed October 7, 2019.
43. Paul S, Kantarjian H, Jabbour EJ. Adult acute lymphoblastic leukemia. *Mayo Clin Proc*. 2016;91:1645–1666.
44. Ravandi F, O'Brien SM, Cortes JE, et al. Long-term follow-up of a phase 2 study of chemotherapy plus dasatinib for the initial treatment of patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Cancer*. 2015;121:4158–4164.
45. Lim SN, Joo YD, Lee KH, et al. Long-term follow-up of imatinib plus combination chemotherapy in patients with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. *Am J Hematol*. 2015;90:1013–1020.
46. Kim DY, Joo YD, Lim SN, et al. Nilotinib combined with multiagent

chemotherapy for newly diagnosed Philadelphia-positive acute lymphoblastic leukemia. *Blood*. 2015;126:746–756.

47. Jabbour E, Kantarjian H, Ravandi F, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: A single-centre, phase 2 study. *Lancet Oncol*. 2015;16:1547–1555.
48. Jabbour E, O'Brien S, Konopleva M, Kantarjian H. New insights into the pathophysiology and therapy of adult acute lymphoblastic leukemia. *Cancer*. 2015;121:2517–2528.
49. Short NJ, Kantarjian H, Jabbour E, Ravandi F. Which tyrosine kinase inhibitor should we use to treat Philadelphia chromosome-positive acute lymphoblastic leukemia? *Best Pract Res Clin Haematol*. 2017;30:193–200.
50. Maury S, Huguet F, Leguay T, et al. Adverse prognostic significance of CD20 expression in adults with Philadelphia chromosome-negative B-cell precursor acute lymphoblastic leukemia. *Haematologica*. 2010;95:324–328.
51. Bazarbachi A, Yilmaz M, Ravandi F, Thomas D, Khouri M. A phase 2 study of hyper-CVAD plus ofatumumab as frontline therapy in CD20+ acute lymphoblastic leukemia (ALL): Updated results. *J Clin Oncol*. 2018;36:7041.
52. Oliansky DM, Larson RA, Weisdorf D, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of adult acute lymphoblastic leukemia: Update of the 2006 evidence-based review. *Biol Blood Marrow Transplant*. 2012;18:16–17.
53. Majhail NS, Farnia SH, Carpenter PA, et al. Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2015;21:1863–1869.
54. Frey NV, Luger SM. How I treat adults with relapsed or refractory Philadelphia chromosome-negative acute lymphoblastic leukemia. *Blood*. 2015;126:589–596.
55. Clolar (clofarabine) [package insert]. Cambridge. MA: Genzyme; 2014.
56. Arranon (nelarabine) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals; 2018.
57. Jain P, Kantarjian H, Ravandi F, et al. The combination of hyper-CVAD plus nelarabine as frontline therapy in adult T-cell acute lymphoblastic

leukemia and T-lymphoblastic lymphoma: MD Anderson Cancer Center experience. *Leukemia*. 2014;28:973–975.

58. Buie LW, Pecoraro JJ, Horvat TZ, Daley RJ. Blinatumomab: A first-in-class bispecific t-cell engager for precursor b-cell acute lymphoblastic leukemia. *Ann Pharmacother*. 2015;49:1057–1067.
59. Kantarjian H, Stein A, Gokbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. *N Engl J Med*. 2017;376:836–847.
60. Besponsa (inotuzumab ozogamicin) [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals; 2017.
61. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. *N Engl J Med*. 2016;375:740–753.
62. Bhojwani D, Sposto R, Shah NN, et al. Inotuzumab ozogamicin in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. *Leukemia*. 2019;33(4):884–892.
63. O'Leary MC, Lu X, Huang Y, et al. FDA approval summary: Tisagenlecleucel for treatment of patients with relapsed or refractory B-Cell precursor acute lymphoblastic leukemia. *Clin Cancer Res*. 2019;25:1142–1146.
64. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-Cell lymphoblastic leukemia. *N Engl J Med*. 2018;378:439–448.
65. Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy: Assessment and management of toxicities. *Nat Rev Clin Oncol*. 2018;15:47–62.
66. Bach PB, Giralt SA, Saltz LB. FDA approval of tisagenlecleucel: Promise and complexities of a $475000 cancer drug. *JAMA*. 2017;318:1861–1862.
67. Ram R, Gafter-Gvili A, Vidal L, et al. Management of adult patients with acute lymphoblastic leukemia in first complete remission: Systematic review and meta-analysis. *Cancer*. 2010;116:3447–3457.
68. Marks DI, Wang T, Perez WS, et al. The outcome of full-intensity and reduced-intensity conditioning matched sibling or unrelated donor transplantation in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia in first and second complete remission. *Blood*. 2010;116:366–374.
69. Klepin HD, Rao AV, Pardee TS. Acute myeloid leukemia and

myelodysplastic syndromes in older adults. *J Clin Oncol*. 2014;32:2541–2552.

70. Estey EH. Acute myeloid leukemia: 2019 Update on risk-stratification and management. *Am J Hematol*. 2018;93:1267–1291.
71. Sorror ML, Storer BE, Fathi AT, et al. Development and validation of a novel acute myeloid leukemia-composite model to estimate risks of mortality. *JAMA Oncol*. 2017;3:1675–1682.
72. Papaemmanuil E, Dohner H, Campbell PJ. Genomic classification in acute myeloid leukemia. *N Engl J Med*. 2016;375:900–901.
73. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Acute Myeloid Leukemia. Version 2.2019. Accessed October 7, 2019.
74. Lazenby M, Gilkes AF, Marrin C, Evans A, Hills RK, Burnett AK. The prognostic relevance of flt3 and npm1 mutations on older patients treated intensively or non-intensively: A study of 1312 patients in the UK NCRI AML16 trial. *Leukemia*. 2014;28:1953–1959.
75. Dohner H, Weisdorf DJ, Bloomfield CD. Acute Myeloid Leukemia. *N Engl J Med*. 2015;373:1136–1152.
76. Zwaan CM, Kolb EA, Reinhardt D, et al. Collaborative efforts driving progress in pediatric acute myeloid leukemia. *J Clin Oncol*. 2015;33:2949–2962.
77. Pophali P, Litzow M. What is the best daunorubicin dose and schedule for acute myeloid leukemia induction? *Curr Treat Options Oncol*. 2017;18:3.
78. Willemze R, Suciu S, Meloni G, et al. High-dose cytarabine in induction treatment improves the outcome of adult patients younger than age 46 years with acute myeloid leukemia: Results of the EORTC-GIMEMA AML-12 trial. *J Clin Oncol*. 2014;32:219–228.
79. Cahn JY, Labopin M, Sierra J, et al. No impact of high-dose cytarabine on the outcome of patients transplanted for acute myeloblastic leukaemia in first remission. Acute Leukaemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). *Br J Haematol*. 2000;110:308–314.
80. Vyexos (daunorubicin and cytarabine; liposome) [package insert]. Palo Alto, CA: Jazz Pharmaceuticals; 2017.
81. Lancet JE, Uy GL, Cortes JE, et al. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute

myeloid leukemia. *J Clin Oncol*. 2018;36:2684–2692.

82. Jen EY, Ko CW, Lee JE, et al. FDA Approval: Gemtuzumab ozogamicin for the treatment of adults with newly diagnosed CD33-positive acute myeloid leukemia. *Clin Cancer Res*. 2018;24:3242–3246.
83. Lambert J, Pautas C, Terre C, et al. Gemtuzumab ozogamicin for de novo acute myeloid leukemia: Final efficacy and safety updates from the open-label, phase III ALFA-0701 trial. *Haematologica*. 2019;104:113–119.
84. Assi R, Ravandi F. FLT3 inhibitors in acute myeloid leukemia: Choosing the best when the optimal does not exist. *Am J Hematol*. 2018;93:553–563.
85. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *N Engl J Med*. 2017;377:454–464.
86. Rydapt (midostaurin) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals; 2017.
87. Kantarjian HM, Thomas XG, Dmoszynska A, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. *J Clin Oncol*. 2012;30:2670–2677.
88. Dombret H, Seymour JF, Butrym A, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. *Blood*. 2015;126:291–299.
89. Welch JS, Petti AA, Miller CA, et al. TP53 and decitabine in acute myeloid leukemia and myelodysplastic syndromes. *N Engl J Med*. 2016;375:2023–2036.
90. Amadori S, Suciu S, Selleslag D, et al. Gemtuzumab ozogamicin versus best supportive care in older patients with newly diagnosed acute myeloid leukemia unsuitable for intensive chemotherapy: Results of the randomized Phase III EORTC-GIMEMA AML-19 Trial. *J Clin Oncol*. 2016;34:972–979.
91. Talati C, Sweet K. Recently approved therapies in acute myeloid leukemia: A complex treatment landscape. *Leuk Res*. 2018;73:58–66.
92. Daurismo (glasdegib) [package insert]. New York, NY: Pfizer; 2018.
93. Li W, Gong X, Sun M, et al. High-dose cytarabine in acute myeloid leukemia treatment: A systematic review and meta-analysis. *PLoS One*. 2014;9:e110153.

94. Cornelissen JJ, Blaise D. Hematopoietic stem cell transplantation for patients with AML in first complete remission. *Blood*. 2016;127:62–70.
95. Dohner H, Estey EH, Amadori S, et al. Diagnosis and management of acute myeloid leukemia in adults: Recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood*. 2010;115:453–474.
96. Ferrara F, Schiffer CA. Acute myeloid leukaemia in adults. *Lancet*. 2013;381:484–495.
97. Appelbaum FR. Impact of allogeneic hematopoietic cell transplantation on the outcome of older patients with acute myeloid leukemia. *Best Pract Res Clin Haematol*. 2017;30:320–326.
98. Sorror ML, Sandmaier BM, Storer BE, et al. Allogeneic hematopoietic cell transplantation (HCT) in the eighth decade of life: How much does age matter. *Biol Blood Marrow Transplant*. 2017;23:S98–S99.
99. Muffly L, Pasquini MC, Martens M, et al. Increasing use of allogeneic hematopoietic cell transplantation in patients aged 70 years and older in the United States. *Blood*. 2017;130:1156–1164.
100. Canaani J, Beohou E, Labopin M, et al. Trends in patient outcome over the past two decades following allogeneic stem cell transplantation for acute myeloid leukaemia: An ALWP/EBMT analysis. *J Intern Med*. 2019; (4):407–418.
101. Holtick U, Albrecht M, Chemnitz JM, et al. Bone marrow versus peripheral blood allogeneic haematopoietic stem cell transplantation for haematological malignancies in adults. *Cochrane Database Syst Rev*. 2014. CD010189.
102. Ostgard LSG, Lund JL, Norgaard JM, et al. Impact of allogeneic stem cell transplantation in first complete remission in acute myeloid leukemia: A national population-based cohort study. *Biol Blood Marrow Transplant*. 2018;24:314–323.
103. Faulk K, Gore L, Cooper T. Overview of therapy and strategies for optimizing outcomes in de novo pediatric acute myeloid leukemia. *Paediatr Drugs*. 2014;16:213–227.
104. Becker PS, Medeiros BC, Stein AS, et al. G-CSF priming, clofarabine, and high dose cytarabine (GCLAC) for upfront treatment of acute myeloid leukemia, advanced myelodysplastic syndrome or advanced myeloproliferative neoplasm. *Am J Hematol*. 2015;90:295–300.
105. Rashidi A, Weisdorf DJ, Bejanyan N. Treatment of relapsed/refractory

acute myeloid leukaemia in adults. *Br J Haematol*. 2018;181:27–37.

106. Itzykson R, Thepot S, Berthon C, et al. Azacitidine for the treatment of relapsed and refractory AML in older patients. *Leuk Res*. 2015;39:124–130.
107. Mantha S, Tallman MS, Devlin SM, Soff GA. Predictive factors of fatal bleeding in acute promyelocytic leukemia. *Thromb Res*. 2018;164(Suppl 1):S98–S102.
108. Coombs CC, Tavakkoli M, Tallman MS. Acute promyelocytic leukemia: Where did we start, where are we now, and the future. *Blood Cancer J*. 2015;5:e304.
109. McCulloch D, Brown C, Iland H. Retinoic acid and arsenic trioxide in the treatment of acute promyelocytic leukemia: Current perspectives. *Onco Targets Ther*. 2017;10:1585–1601.
110. Kayser S, Schlenk RF, Platzbecker U. Management of patients with acute promyelocytic leukemia. *Leukemia*. 2018;32:1277–1294.
111. Osman AEG, Anderson J, Churpek JE, et al. Treatment of acute promyelocytic leukemia in adults. *J Oncol Pract*. 2018;14:649–657.
112. Holter Chakrabarty JL, Rubinger M, Le-Rademacher J, et al. Autologous is superior to allogeneic hematopoietic cell transplantation for acute promyelocytic leukemia in second complete remission. *Biol Blood Marrow Transplant*. 2014;20:1021–1025.
113. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2015;33:3199–3212.
114. Gurion R, Belnik-Plitman Y, Gafter-Gvili A, et al. Colony-stimulating factors for prevention and treatment of infectious complications in patients with acute myelogenous leukemia. *Cochrane Database Syst Rev*. 2012;2012(6):CD008238.
115. Zarxio (filgrastim-sndz) [package insert]. Princeton, NJ: Sandoz; 2018.
116. Nivestym (filgrastim-aafi) [package insert]. New York, NY: Pfizer; 2018.
117. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Myeloid Growth Factors. Version 2.2019. Accessed October 7, 2019.
118. Taplitz RA, Kennedy EB, Bow EJ, et al. Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA clinical practice guideline update. *J Clin Oncol*. 2018;36:3043–3054.

119. Alexander S, Fisher BT, Gaur AH, et al. Effect of levofloxacin prophylaxis on bacteremia in children with acute leukemia or undergoing hematopoietic stem cell transplantation: A randomized clinical trial. *JAMA*. 2018;320:995–1004.
120. Science M, Robinson PD, MacDonald T, Rassekh SR, Dupuis LL, Sung L. Guideline for primary antifungal prophylaxis for pediatric patients with cancer or hematopoietic stem cell transplant recipients. *Pediatr Blood Cancer*. 2014;61:393–400.
121. Howard SC, Trifilio S, Gregory TK, Baxter N, McBride A. Tumor lysis syndrome in the era of novel and targeted agents in patients with hematologic malignancies: A systematic review. *Ann Hematol*. 2016;95:563–573.
122. Children's Oncology Group. Long-Term Follow-Up Guidelines. V 4.0. 2013. Available at: http://www.survivorshipguidelines.org.

152

Chronic Leukemias

Patrick J. Kiel and Meagan Grove

KEY CONCEPTS

1. Chronic myeloid leukemia (CML) is defined by the presence of the Philadelphia chromosome (Ph), a translocation between chromosomes 9 and 22. The resulting abnormal fusion protein, p210 *BCR-ABL*, phosphorylates tyrosine kinase residues and is constitutively active, resulting in uncontrolled hematopoietic cell proliferation.
2. Without treatment, the disease course of CML is characterized by a progressive increase in white blood cells over a period of years that ultimately transforms into acute leukemia.
3. The commercially available tyrosine kinase inhibitors, imatinib, dasatinib, nilotinib, bosutinib, and ponatinib have demonstrated efficacy in the treatment of newly diagnosed CML patients and in patients with either accelerated phase or blast crisis.
4. CML monitoring requires the assessment of milestones throughout the therapy such as hematologic, cytogenetic, and molecular responses, the ideal of which is a molecular response.
5. Allogeneic hematopoietic stem cell transplant (HSCT) is the only known curative treatment option for CML and is reserved for patients with a suitable donor and progression after treatment with tyrosine kinase-based therapy.
6. The management of chronic lymphocytic leukemia (CLL) is highly individualized and includes observation in patients with early-stage disease and treatment with targeted therapy, chemotherapy, biologic therapy, or both in patients with more advanced disease.
7. Alemtuzumab, ofatumumab, obinutuzumab, and rituximab are monoclonal antibodies that are indicated for the treatment of CLL.

8. Regimens such as fludarabine, cyclophosphamide, and rituximab are considered as first-line therapy for patients with CLL who are younger or have more aggressive disease.
9. Novel agents such as ibrutinib, idelalisib, duvelisib, venetoclax, and acalabrutinib provide an orally administered option for the treatment of CLL. Ibrutinib is approved for treatment of previously untreated patients and for patients with relapsed disease who have received at least one prior therapy. Oral agents such as venetoclax and idelalisib in combination with monoclonal antibodies are now first-line treatment options in patients with comorbidities.

Preclass Engaged Learning Activity—Chronic Myeloid Leukemia (CML)

Watch the video entitled "What is chronic myelogenous leukemia?" by the Khan Academy

This 10-minute video provides a brief overview of CML as well as how to identify its signs, symptoms, diagnosis, and basic treatment overview. This video is useful to enhance student understanding regarding COLLECT and ASSESS steps in the patient care process.

Preclass Engaged Learning Activity—Chronic Lymphocytic Leukemia (CLL)

Watch the video: "Chronic Lymphocytic Leukemia with Bruce D. Cheson, MD-Everything You Need to Know". This 12-minute video by the Lymphoma Research Foundation briefly reviews CLL, diagnosis, and treatment options. This video is designed to aid in the student's patient care process, particularly the COLLECT and ASSESS steps.

INTRODUCTION

The chronic leukemias include chronic myeloid leukemia (CML), chronic

lymphocytic leukemia (CLL), hairy cell leukemia, and prolymphocytic leukemia. The typical clinical presentation of the chronic leukemias is an indolent course in contrast to patients with acute leukemia who will die of their disease within weeks to months if not treated. This chapter focuses on the two most common types of chronic leukemia, CML, and CLL.

CHRONIC MYELOID LEUKEMIA

CML is a myeloproliferative disease that results from malignant transformation of a subpopulation of pluripotent hematopoietic stem cells. Bone marrow hyperplasia and the accumulation of differentiated myeloid cells in the peripheral blood are the initial presenting features of the disease. The terminal stage of CML is characterized by the rapid accumulation of blast cells in the bone marrow and suppression of normal hematopoiesis that ultimately leads to death. CML was the first malignant disease identified with a consistent cytogenetic abnormality, namely the Philadelphia Chromosome (Ph) that contains the BCR-ABL oncogene. This dominant cytogenetic abnormality has allowed CML to become the template for the development of molecular targeted drug therapies.

Epidemiology and Etiology

It is estimated that 8,990 new cases of CML were diagnosed in the United States in 2019.[1] The median age of diagnosis is 67. The development of CML is not associated with hereditary, familial, geographic, ethnic, or economic status. An increased risk of CML has been noted with ionizing radiation exposure and in atomic bomb survivors from Hiroshima and Nagasaki.[2,3]

Pathophysiology

CML was first described in 1845, but extensive research into the genetic and molecular characteristics of the disease began with the discovery of the Ph in 1960 by Nowell and Hungerford.[4] Research in the 1980s identified the molecular changes that occur as a result of the Ph when an oncogenic protein was identified and implicated in the pathophysiology of CML.[4,5]

Ph is the first karyotypic abnormality specifically implicated in the pathogenesis of cancer, and its discovery has resulted in extensive research into the molecular biology of CML.[6] This chromosomal abnormality is characteristic

of CML and is present in about 95% of patients with the disease.[4–6]

1 Ph, identified as a shortened long arm of chromosome 22, is found in granulocyte and erythrocyte progenitors, macrophages, megakaryocytes, and lymphocytes. The Ph is the consequence of breaks in chromosomes 9 and 22 resulting in a transposition that relocates the 3′ end of *ABL* (Abelson proto-oncogene) from its normal site on chromosome 9 at band 34 to the 5′ end of *BCR* (breakpoint cluster region) on chromosome 22 at band 11 (symbolized as *t*[9;22][q34;q11]).[6,7] This results in the formation of the hybrid *BCR-ABL* fusion gene (**Fig. 152-1**). Through this chromosomal translocation, the *ABL* proto-oncogene is able to escape the normal genetic controls on its senescence and is activated into a functional oncogene, directing the transcription of an 8.5-kilobase messenger ribonucleic acid (mRNA) molecule. The mRNA is translated into a 210-kDa protein—p210 BCR-ABL—that is constitutively (ie, constantly) activated compared to the 145-kDa protein translated by the normal *ABL* gene.[5–7] Although p210 BCR-ABL is the most common tyrosine kinase found in CML, variations in the breakpoints in the *ABL* gene encode different size proteins. For example, a smaller protein, p190 BCR-ABL, is involved in two-thirds of adults with Ph-positive acute lymphoblastic leukemia (ALL) but is rarely found in patients with CML.[6]

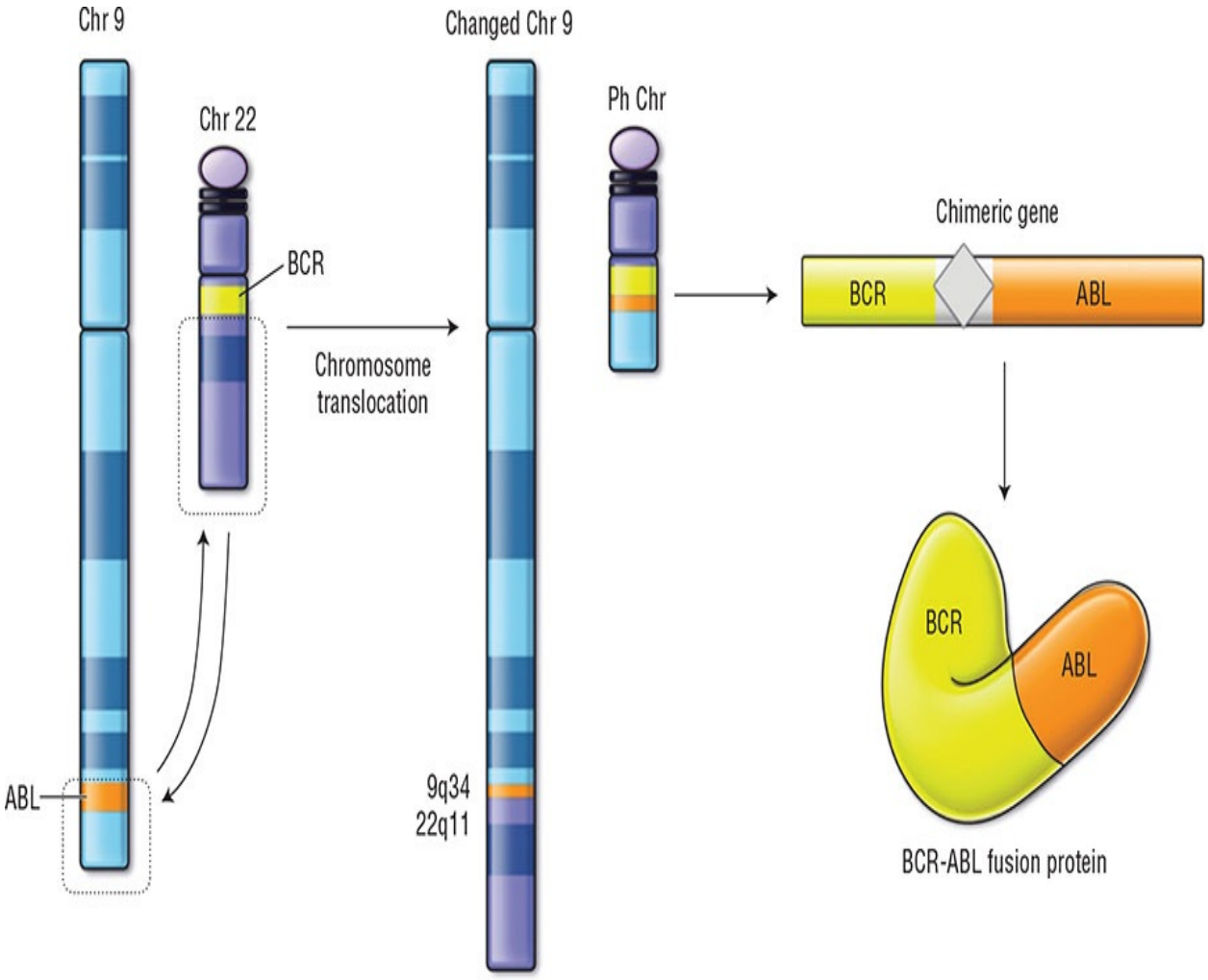


FIGURE 152-1 Specific chromosomal translocation that results in the Philadelphia chromosome. The fusion of these DNA sequences allows the generation of a constitutively activated fusion protein. (*Reproduced, with permission, from Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 20th ed. New York, NY: McGraw-Hill; 2019.*)

CML is considered a clonal disease because it begins with the malignant transformation of a single cell. The progeny from this transformed primitive hematopoietic stem cell results in a proliferative advantage over normal hematopoietic cells that displaces normal hematopoiesis. The Ph is found in both myeloid and lymphoid cells, which suggests that the transformed cell of CML is a pluripotent stem cell.[7] This alteration gives the transformed progenitor cell an inheritable growth advantage, leading to the proliferation of a neoplastic, monoclonal population of cells.[8] Disrupted maturation leads to additional divisions by CML progenitor cells before reaching a nonproliferative stage; the

resulting number of circulating granulocytes may be many times higher than normal. In the advanced stages of CML, cytopenias may occur in association with fibrotic changes in the bone marrow.

The *BCR-ABL* fusion gene encodes for a constitutively active tyrosine kinase that is involved in both the increased proliferation of the CML clone and the reduction in Fas-mediated apoptosis. Characterization of the adenosine triphosphate binding site on the BCR-ABL tyrosine kinase has provided a target for inhibition of tyrosine kinase activity. The first FDA-approved tyrosine kinase inhibitor (TKI), imatinib mesylate (Gleevec®), was indicated for patients in chronic phase who had failed interferon alfa (IFN-α) or for those with advanced disease. Imatinib received additional FDA approval in 2002 for first-line treatment in newly diagnosed CML. Second-generation TKIs with a higher binding affinity and selectivity for BCR-ABL kinase are approved as both frontline agents and salvage for patients with resistance or intolerance to imatinib.

Clinical Presentation

2 The three clinical phases of CML are chronic phase (CP), accelerated phase (AP), and blast crisis (BC) (**Table 152-1**). Nearly 90% of patients present with CP at the time of diagnosis. Often the diagnosis of CML is found incidentally during a routine examination or if a complete blood count is obtained for unrelated reasons because patients are often asymptomatic upon presentation. Signs and symptoms include fatigue, sweating, bone pain, weight loss, abdominal discomfort, and early satiety secondary to splenomegaly. Leukocytosis is the hallmark of CP and the white blood cell count can be as high as 1,000,000 cells/mm^3 (1,000 × 10^9/L), placing patients at risk for complications of leukostasis. Symptoms secondary to leukostasis include acute abdominal pain resulting from splenic infarctions, priapism, retinal hemorrhage, cerebrovascular accidents, confusion, hyperuricemia, and gouty arthritis.[6] Patients can survive several years in CP without treatment.

TABLE 152-1 Criteria for Different Phases of Chronic Myeloid Leukemia

Chronic Phase	Accelerated Phase	Blast Crisis
• <10% blasts in peripheral blood or bone marrow	• 10%-19% blasts in peripheral blood or bone marrow • Platelets <100,000 cells/mm^3 (100×10^9/L) unrelated to therapy or >1,000,000 cells/mm^3 ($1,000 \times 10^9$/L) unresponsive to therapy • Persistent or increasing white blood cells >10,000 cells/mm^3 (10×10^9/L), unresponsive to therapy • 20% or more basophils in the peripheral blood • Any new clonal chromosomal abnormalities in Ph+ cells that occur during therapy Additional findings • Cytogenetic evolution • Progressive splenomegaly, unresponsive to therapy	• >20% blasts in peripheral blood or bone marrow • Large clusters of blasts on bone marrow biopsy • Presence of extramedullary infiltrates

Data from Reference 6.

Initial laboratory workup includes complete blood count with differential, complete metabolic panel, and serum uric acid. A bone marrow aspiration and biopsy is required to confirm the diagnosis of CML. The differential diagnosis of CML includes infection, myeloproliferative disorders (ie, polycythemia vera, essential thrombocythemia, myelofibrosis), and chronic myelomonocytic leukemia. Bone marrow is markedly hypercellular (75%-90%) with increased granulocyte/erythroid ratio increased (10-30:1), erythropoiesis increased megakaryocytes normal. Karyotyping (ie, cytogenetic analysis) is required for a diagnosis. The bone marrow aspiration is analyzed with fluorescence in situ hybridization (FISH) to determine the presence of the Ph chromosome. Quantitative RT-PCR is also performed to assess the baseline *BCR-ABL* transcript levels and monitored with the International Scale (IS). In the IS, the standardized baseline, defined as the mean expression of *BCR-ABL1* transcripts observed from previous study patients, is set to 100%.[12] Levels measured by individual laboratories may need to be converted to the IS by a conversion

factor.

AP is characterized by progressive myeloid maturation arrest and loss of efficacy of drug therapy directed to attenuate the increase in white blood cells. Clinical findings of AP include anemia, increasing peripheral blood and bone marrow blasts and basophils, clonal cytogenetic evolution, extramedullary disease sites (eg, bone, breast, CNS, mucosal tissue, lymph nodes, and skin), exacerbation of splenomegaly, and either thrombocytosis or thrombocytopenia. Nonspecific findings such as bone pain, fever, night sweats, and weight loss may occur. The most commonly observed cytogenetic changes with disease progression are an additional Ph chromosome, trisomy 8, and isochromosome 17q. Survival typically will not exceed several months. The World Health Organization (WHO) classification[6] defines AP CML as one or more of the following changes: 10% to 19% of blasts in the peripheral blood or bone marrow, persistent thrombocytopenia less than 100,000 cells/mm^3 (100×10^9/L) (not related to drug therapy), thrombocytosis greater than 1,000,000 cells/mm^3 ($1{,}000 \times 10^9$/L) despite drug therapy, peripheral basophilia >20%, increasing spleen size and white blood cell count despite drug therapy, bone marrow evidence of progression of the leukemic clone or new cytogenetic abnormalities.

CLINICAL PRESENTATION Chronic Myeloid Leukemia[1,6]

General

- 90% of patients are diagnosed in CP
- 50% are asymptomatic in CP and often diagnosed following abnormal complete blood count

Signs and Symptoms

- Fatigue
- Left upper quadrant pain
- Abdominal pain or distension
- Weight loss
- Night sweats

Physical Examination

- Splenomegaly
- Hepatomegaly

Laboratory Tests

Peripheral blood

- Leukocytosis
- Thrombocytosis
- Basophilia
- Low or undetectable leukocyte alkaline phosphatase
- Elevated uric acid and lactate dehydrogenase

Molecular testing

- Presence of *BCR-ABL* by reverse-transcription polymerase chain reaction (RT-PCR)

Bone marrow

- Hypercellular
- Fully mature myeloid cells
- Increased megakaryocytes
- <10% blasts in CP

Cytogenetics

- Presence of Ph
- Additional abnormalities

BC is the terminal stage of the disease and clinically resembles acute leukemia where the leukemic clone overwhelmingly dominates the bone marrow at the expense of normal hematopoiesis. The WHO classification defines BC CML as the presence of one or more of the following: greater than 20% blasts in the peripheral blood or bone marrow, extramedullary disease, or large clusters of blasts in the bone marrow.[6] Patients can present occasionally with BC without an apparent AP. One-third of patients present with BC of lymphoid lineage, while

two-thirds present with BC of myeloid lineage or undifferentiated like phenotype. The increased proliferative rate in BC CML is the consequence of several factors in addition to *BCR-ABL*, such as the activation of the oncogene signaling pathways and loss of tumor suppressors such as p53. Duration of BC is typically days to weeks before death.

Prognosis

Several models have been proposed to estimate prognosis in patients with CML, but the one by Sokal et al. has become the most widely used.[8] The Sokal algorithm uses spleen size, percentage of circulating blasts, platelet count, and age as prognostic factors for patients in CP. However, this scoring system was developed prior to the advent of TKI therapy and may have limited predictive value in the era of imatinib. The median overall survival for patients diagnosed with CP, AP, and BC CML was reported to be 47 months, 12 to 24 months, and 3 to 6 months, respectively, in the era prior to the introduction of TKIs.[9,10]

TREATMENT

Chronic Myeloid Leukemia

Desired Outcomes

Without effective treatment, CML disease progression leads inexorably to a fatal outcome within 5 years. The overriding treatment goals for CML include the eradication of the leukemic clone from the bone marrow and maintenance of CP with minimal toxicity from treatment. The only proven therapy to eradicate the malignant clone from the bone marrow is allogeneic hematopoietic stem cell transplantation (HSCT). Both immunotherapy with IFN-α and TKI-based therapies have demonstrated the ability to extend CP beyond the expected period of several years. The introduction of TKI therapy has dramatically changed the clinical course of CML where patients can now expect to maintain disease control for many years.[10] The current standard of practice is to initiate TKI therapy for newly diagnosed CML patients. Long-term follow-up from phase III trials have documented response rates in excess of 85% of patients who received imatinib as primary treatment.[11–13]

Clinical response in CML is measured by hematologic, cytogenetic, and molecular indices, all of which have standardized criteria.[6,13] *Hematologic response* is defined as the normalization of peripheral blood counts and is the

earliest type of response observed in CML patients. *Cytogenetic responses* are based on the percentage of cells positive for Ph in a bone marrow biopsy. A *complete cytogenetic response* is defined as the elimination of Ph from all cells in the marrow sample and a *major cytogenetic response* is defined as fewer than 35% Ph-positive cells. Patients who have a major or complete cytogenetic response have improved survival compared to those who fail to achieve a cytogenetic response.[13]

More sensitive tests to monitor disease status are now used because most patients on imatinib achieve a complete cytogenetic response. *Molecular responses* are determined by RT-PCR (based on IS), which are several logs more sensitive than methods used to measure cytogenetic responses. An early molecular response is the observation of <10% *BCR-ABL* (IS) at 3 and 6 months. A major molecular response is a >3 log reduction in *BCR-ABL* mRNA from the baseline or a BCR-ABL (IS) of <0.1%. A *complete molecular response* is the absence of *BCR-ABL* transcripts by RT-PCR. RT-PCR assays should be interpreted carefully because they have varying sensitivities and may show a complete molecular remission even when low levels of *BCR-ABL* transcripts are present.[17] Quantitative RT-PCR should be performed prior to initiating therapy and throughout therapy to monitor residual disease. Peripheral blood can often be used for this analysis because bone marrow and peripheral blood *BCR-ABL* mRNA levels are correlated.[12,13]

Conventional Chemotherapy

Conventional cytotoxic chemotherapy is used in CP CML to reduce and temporarily control high peripheral white blood cell (WBC) counts. Historically, the two agents used for leukoreduction are busulfan (Myleran®) and hydroxyurea (Hydrea®). Busulfan is no longer used because randomized trials have shown that hydroxyurea treatment provides a modest survival advantage, and busulfan has a risk of potentially life-threatening pulmonary fibrosis.[14]

Hydroxyurea rapidly lowers high circulating WBCs in CP CML by inhibiting ribonucleotide reductase, which inhibits DNA synthesis, eliminating cells in the S phase of the cell cycle, and synchronizing cells in the G_1 or pre-DNA synthesis phase. Hydroxyurea is initiated at 40 to 50 mg/kg/day in divided doses until the WBC count falls to about 10,000 cells/mm^3 (10×10^9/L). Hydroxyurea may be discontinued once adequate control of the WBC count is achieved and a TKI has been initiated. Hydroxyurea does not change the natural progression of the disease to BC.

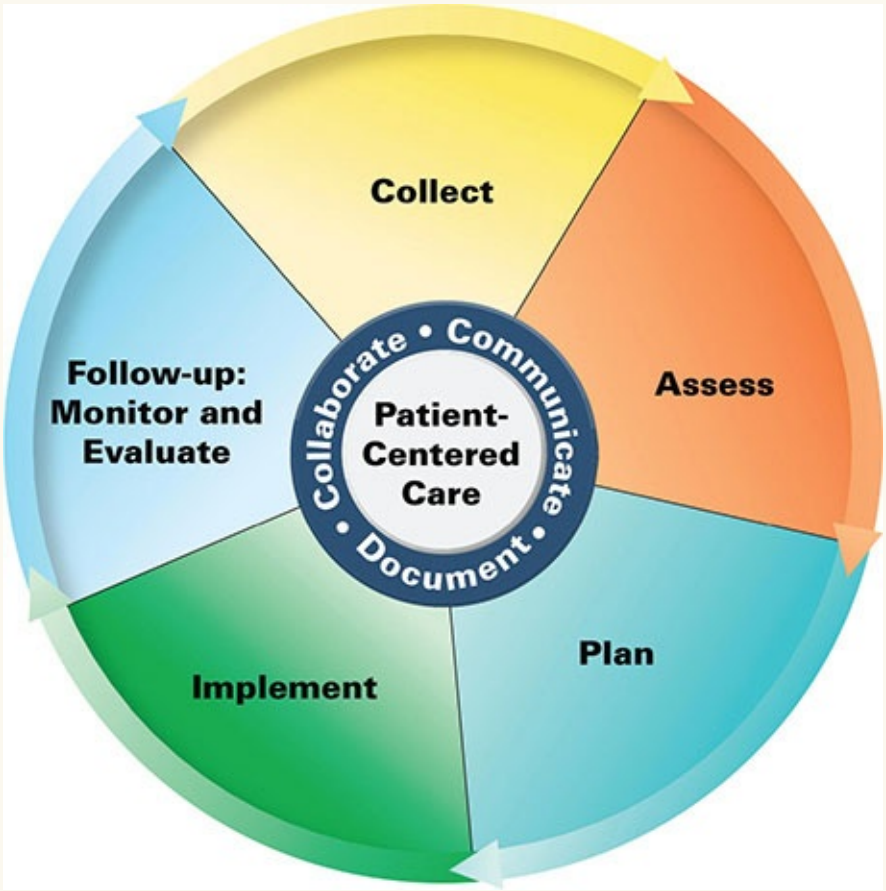
Interferon Alfa

The interferons are a family of glycoproteins involved in many of the functional aspects of the hematopoietic system. Prior to the introduction of imatinib, IFN-α was the preferred agent in the treatment of CML. IFN-α is currently reserved for patients who fail TKIs and are not candidates for allogeneic HSCT.

3 The use of IFN-α in the treatment of CP CML was based on reports that 20% to 50% of patients achieve a major cytogenetic response, which led to prolonged survival.[5,9] In the 10% to 15% of patients achieving a complete cytogenetic response, the median survival was more than 10 years. Patients enrolled on the IFN-α arm in the International Randomized Interferon versus STI571 (IRIS) trial had a complete cytogenetic response of 14%, as compared with 76% of patients treated with imatinib.[11] The National Comprehensive Cancer Network (NCCN) guidelines recommend IFN-α only for posttransplant relapse.[12]

IFN-α use is limited by its toxicity profile because it is associated with both short-term constitutional toxicities and potentially dose-limiting long-term toxicities. In the IRIS trial, 26% of patients discontinued IFN-α as a result of intolerable side effects.[15] The most predictable early toxicity is a flu-like syndrome characterized by fever, chills, myalgia, headache, and anorexia. These dose-dependent effects may be a result of IFN-α–induced leukocytosis and the release of inflammatory cytokines. Cardiovascular toxicities (eg, tachycardia, hypotension) are seen in about 15% of patients in the first few weeks. Long-term adverse effects include weight loss, alopecia, neurologic effects (eg, paresthesia, cognitive impairment, and depression), and immune-mediated complications (eg, hemolysis, thrombocytopenia, nephrotic syndrome, systemic lupus erythematosus, and hypothyroidism), which occur in about 5% to 20% of patients.

Despite falling out of clinical favor, IFN-α still remains a disease-modifying agent and ongoing clinical trials are investigating the use of imatinib and IFN-α in combination for the treatment of CML. Imatinib has been combined with pegylated IFN-α_{2A} in newly diagnosed CP CML yielding improved major molecular response rate at 12 months compared with imatinib 400 mg daily alone (57% vs 38%), but the 12-month complete cytogenetic response rate was similar (66% vs 58%).[15]



Patient Care Process for Chronic Myeloid Leukemia (CML)

Collect

- Patient characteristics (eg, age, sex)
- Patient medical history (personal and family)
- Social history (eg, tobacco/ethanol use)
- Current medications including acid-suppressing agents, herbal products, dietary supplements, and inhibitors/inducers of CYP3A4
- Objective data

  Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2-saturation

Labs including Complete Blood Counts (CBC) with differential, comprehensive metabolic panel

Objective confirmation of CML via bone marrow biopsy with chromosomal and molecular analysis

Assess

- Bone marrow biopsy morphology, cytogenetics, molecular mRNA transcripts
- CBC and presence of active bleeding due to potential thrombocytopenia
- Presence of VTE provoking factors (eg, recent surgery, plaster casting of lower extremity, indwelling catheter)
- Ability/willingness to obtain laboratory monitoring tests (eg, CBC, CMP, BCR-ABL assessments)
- Emotional status (eg, presence of anxiety, depression)

Plan

- Drug therapy regimen including tyrosine kinase inhibitor dose, route, frequency, and duration (see Tables 152-3 and 152-4)
- Monitoring parameters including efficacy (eg, cytogenetic response, BCR-ABL mRNA) and safety (eg, sign and symptoms of bleeding, anemia, fluid retention, ECG); frequency and timing of follow-up
- Patient education (eg, goal of treatment, drug-specific information, oral medication adherence, drug-drug interaction)

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence to oral therapy

Follow-up: Monitor and Evaluate

- Monitor for assessment of hematologic, cytogenetic, and molecular milestones
- Presence of adverse effects (eg, bleeding, fluid retention, QTc evaluation)

- Patient adherence to treatment plan using multiple sources of information
- Re-evaluate duration of therapy every 3 months

**Collaborate with patient, caregivers, and other healthcare professionals.*

Imatinib Mesylate (Gleevec®)

A transformative discovery in cancer therapeutics was the characterization of the adenosine triphosphate binding site on the BCR-ABL tyrosine kinase. This specific receptor established a novel drug discovery platform for molecular targeted therapy in CML. Numerous TKIs were in development in the 1990s and STI571 (STI stands for *signal transduction inhibitor*), subsequently named imatinib (Gleevec®), emerged as the drug with the best oral bioavailability and high binding affinity for the BCR-ABL tyrosine kinase.[16,17] In 2001, imatinib mesylate received FDA approval for patients in CP CML who had failed IFN-α treatment and in patients with AP or BC CML based on phase II studies. In 2002, it received FDA approval for first-line treatment in newly diagnosed CML based on data from the IRIS phase III trial.[18]

Imatinib inhibits several other tyrosine kinases including BCR-ABL, C-Kit, and platelet-derived growth factor receptor (PDGFR). Imatinib competitively binds to the adenosine triphosphate (ATP)-binding site on BCR-ABL, which inhibits the phosphorylation of proteins involved with CML clone proliferation.[16–18] **Table 152-2** summarizes the clinical results of imatinib in CML patients in CP, AP, and BC CML. **Table 152-3** summarizes the dosing, food–drug interactions, and drug–drug interactions of TKIs. Early phase I and phase II studies of imatinib, designed to determine the maximum tolerated dose and safety, showed higher than expected response rates in all stages of CML.[19]

TABLE 152-2 Cytogenetic and Molecular Response Rate Associated with Tyrosine Kinase Inhibitor Therapy in Chronic Myeloid Leukemia

Drug (Disease Status)	Daily Dose (mg)	CCyR (%)	MMR	Median Follow-up
Imatinib (CP)	400	82	57%	70 months
	800	90	NR	30 months
Imatinib (AP)	600	43	NR	12 months
	400	11	NR	
Imatinib (BC)	400-800	7.40	NR	—
Dasatinib (CP)	100	83	76%	60 months
Dasatinib (AP)	140	32	NR	15 months
Nilotinib (CP)	600	87	77%	36 months
Nilotinib (AP)	800	16	NR	24 months
Bosutinib (CP–3rd line)	500	24	15%	28.5 months
Bosutinib (CP–1st line)	500	79	59%	12 months
Omacetaxine (CP–2nd line, T315I mutation)	2.5	16	NR	19.1 months
Ponatinib (CP-resistant/ intolerant disease)	45	37	NR	10 months
Ponatinib (CP-T315I mutation)	45	66	NR	10 months

AP, accelerated phase; BC, blast crisis; CCyR, complete cytogenetic response; CP, chronic phase; MCyR, major cytogenetic response; MMR, major molecular response; NR, no response.

TABLE 152-3 Dosing of Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia

Drug	Brand Name	Dose Range	Food–Drug Interactions	Drug–Drug Interactions
Imatinib	Gleevec	400 mg/day (CP) 600 mg/day (AP/BC) 400 mg/day (moderate hepatic impairment) 300 mg/day (severe hepatic impairment)	Take with food and a large glass of water	CYP3A4 inducers may decrease C_{max} and AUC CYP3A4 inhibitors may increase C_{max} and AUC Imatinib inhibits CYP3A4 and 2D6 Package labeling recommendations against using warfarin concurrently
Dasatinib	Sprycel	100 mg/day (CP) 140 mg/day (AP/BC)	With or without meals; do not crush tablets	CYP3A4 inhibitors may increase dasatinib drug levels CYP3A4 inducers may decrease dasatinib drug levels H_2 antagonists/PPIs decrease dasatinib drug levels
Nilotinib	Tasigna	300 mg BID (CP) 400 mg BID (AP/BC)	Take with water; avoid food 2 hours prior to a dose or 1 hour after	Avoid drugs concurrently known to prolong QT interval CYP inducers may decrease nilotinib serum concentrations CYP inhibitors may increase nilotinib serum concentrations Nilotinib is an inhibitor of CYP3A4, CYP2C8, CYP2C9, and CYP2D6 Nilotinib is an inducer of CYP2B6, CYP2C8, and CYP2C9
Bosutinib	Bosulif	500 mg/day; may increase to 600 mg/day in patients who do not clinically respond by weeks 8-12	Take with food; PPIs may decrease absorption	Concurrent use with CYP3A or Pgp inhibitors increase bosutinib plasma concentrations Concurrent use with CYP3A inducers reduces bosutinib plasma concentrations
Ponatinib	Iclusig	45 mg/day (lower dosing may be required as the optimal dose is not defined)	With or without food	Concurrent use with CYP3A or Pgp inhibitors increase ponatinib plasma concentrations Concurrent use with CYP3A inducers reduces ponatinib plasma concentrations

AP, accelerated phase; AUC, area under the curve; BC, blast crisis; BID, twice daily; C_{max}, maximum concentration; CP, chronic phase; CYP, cytochrome P450; Pgp, P-glycoprotein; PPI, proton pump inhibitor.

Chronic Phase The IRIS study compared imatinib 400 mg orally daily to IFN-α plus low-dose subcutaneous cytarabine in 1,106 patients with newly diagnosed CP CML.[18] After a median follow-up of 19 months, patients who received imatinib achieved a complete hematologic response of 96%, major cytogenetic response of 85%, and complete cytogenetic response of 69%. Six percent of patients had progressed to AP or BC and only 4% discontinued imatinib because of an adverse event. The study was designed to allow crossover to the opposite treatment arm for lack of response or intolerance. After 5 years of follow-up, only 3% of patients randomized initially to receive IFN-α remained on their initial regimen compared with 69% of patients in the imatinib arm. The estimated 10-year overall survival of the 553 patients who were originally randomized to receive imatinib is 83.3% with 47% alive and still on initial imatinib treatment. At 10 years, estimated event-free survival was 79.6%.[20]

Cytogenetic and molecular responses secondary to imatinib are associated with event-free survival and risk of progression to AP or BC. Patients who do not achieve a hematologic response by 3 months, cytogenetic response by 6 months, or a major cytogenetic response by 12 months fare significantly worse compared to responders. In addition, patients with a complete cytogenetic response and at least a 3-log reduction in *BCR-ABL* levels via RT-PCR correlated with a 100% survival without disease progression at 18 months. The risk of disease progression according to the Sokal scoring system predicted the rates of disease progression to be 3%, 8%, and 17% in low-risk, intermediate-risk, and high-risk patients, respectively. However, the Sokal score was not associated with disease progression in patients who achieved a complete cytogenetic response.[11]

4 Although most patients attain a complete cytogenetic response on imatinib, very few patients achieve a complete molecular response. In a study of patients enrolled in the IRIS study, Hughes et al. reported that less than 5% of patients on imatinib have undetectable levels of *BCR-ABL* when analyzed by RT-PCR.[21] Recent data suggest that the level of residual disease is predictive of progression-free survival. A 3-log decline in *BCR-ABL* mRNA within 3 months after achieving a complete cytogenetic response may be a predictor of longer progression-free survival.[22] Careful monitoring of *BCR-ABL* levels by RT-PCR is necessary to guide clinician decision making for therapy modification. The NCCN guidelines recommend imatinib 400 mg orally daily as one of several options for patients in CP CML (see Table 152-2).[12]

Higher imatinib doses have been evaluated in clinical trials. The European Leukemia Net conducted a randomized phase II trial in high-risk patients defined by the Sokal scoring system to imatinib 400 mg versus 800 mg daily and evaluated the proportion of patients achieving a complete cytogenetic response at 12 months.[23] Patients receiving the higher dose of imatinib achieved a 64% complete cytogenetic response compared to 58% of patients receiving standard dose with a median follow-up period of 12 months ($P = 0.435$). These study results do not justify the routine use of imatinib 800 mg daily as frontline therapy in high-risk patients with CP CML. A phase II trial evaluated imatinib 400 mg daily for 2 weeks, then titrated to 400 mg twice daily in patients with an intermediate-risk Sokal score appeared to show benefit with 88% and 91% of patients achieving a complete cytogenetic response at 12 and 24 months.[24]

Accelerated Phase/Blast Crisis Response rates for patients with AP or BC CML are lower as compared with those in CP CML. A phase II study evaluating

imatinib 600 mg daily in patients with AP CML reported complete hematologic and complete cytogenetic response rates of 71% and 19%, respectively.[25] Prior to protocol amendments, patients were able to receive imatinib 400 mg daily, but the rates of hematologic response, cytogenetic response, disease progression, and overall survival were inferior to imatinib 600 mg. The toxicity profile between imatinib 400 mg and 600 mg daily was similar.

Traditional therapy for BC CML has focused on administering cytotoxic chemotherapy in treatment programs similar to acute leukemia induction. Etoposide (VP-16), cytarabine (Ara-C), and carboplatin (VAC-regimen) has demonstrated efficacy in patients with BC CML with a median overall survival of 7 months.[26] Imatinib has demonstrated modest activity in BC CML. An open-label, nonrandomized trial evaluated imatinib 400 mg daily with dose escalation to 600 mg daily and 400 mg twice daily for patients not achieving a hematologic response after one month.[27] Fifteen percent had a complete hematologic response, 7.4% achieved a complete cytogenetic response, and 18% achieved a second CP. Imatinib 600 mg was associated with sustained hematologic response. The median overall survival was 6.9 months.

Imatinib Resistance Despite having high cytogenetic response rates, some patients treated with imatinib will not respond to therapy or will relapse after an initial response.[28] The most prominent mechanism of imatinib resistance is the presence of point mutations in one or more areas on the ABL kinase. More than 100 different mutations have been discovered thus far. Many of these mutations can cause a conformational change in the ATP binding site, which greatly decreases the ability of imatinib to bind and inhibit kinase activity.[13,28] Imatinib binds to BCR-ABL by establishing a series of hydrogen bonds with side chains of amino acids within the kinase domain. Mutations that alter this surface can decrease the affinity of imatinib for BCR-ABL, potentially preventing binding entirely. The kinase domain of BCR-ABL, which encompasses amino acids 225 to 400, can be subdivided into ATP and imatinib binding site (P loop), the catalytic site where the phosphate from ATP is transferred to the substrate protein, and the activation domain that determines the state of the kinase (open or closed). The imatinib binding site is located in the region of amino acids 300 to 325. Resistance is caused by point mutations in one or more areas on the ABL kinase. The T315I mutation occurs directly within the imatinib binding site and completely disrupts imatinib binding.[13,28] This mutation is important because it confers resistance not only to imatinib but also to second-generation BCR-ABL kinase inhibitors.

The other known clinically relevant mechanism of resistance is *BCR-ABL* gene amplification. The *BCR-ABL* gene is overexpressed to such an extent that the typical 400 mg daily dose of imatinib is insufficient to inhibit the activity of the kinase. Reports of clinically significant resistance have been related to *BCR-ABL* gene amplification, multiple copies of Ph, or both. The largest series published this far included 66 patients, in whom only 2 patients had confirmed *BCR-ABL* genomic amplification.[28] Other proposed mechanisms of resistance to imatinib include differential binding to α_1-acid glycoprotein in serum, overexpression of P-glycoprotein-induced drug efflux, and clonal evolution to acquisition of additional cytogenetic abnormalities.[12,13,28]

Monitoring Response to Imatinib Imatinib therapy should be frequently monitored to assess response or disease progression. Recommendations for monitoring include baseline molecular and cytogenetic assessment. Patients with CP CML who have an optimal response have a complete hematologic response within 3 months, partial cytogenetic response within 6 months, complete cytogenetic response within 12 months and major molecular response within 18 months of starting imatinib. *BCR-ABL* transcripts should be evaluated by RT-PCR every 3 months and bone marrow cytogenetics performed at 3 months if RT-PCR is unavailable or 12 months if neither complete cytogenetic response nor major molecular response is achieved. Bone marrow cytogenetics are repeated at 18 months if the patient is not in major molecular response or did not have a complete cytogenetic response at 12 months.[12,13] The loss of hematologic or cytogenetic responses or clonal evolution at any time should be considered a treatment failure warranting a change in therapy. *BCR-ABL* kinase domain mutation analysis is performed for patients who have an inadequate initial response at 3, 12, or 18 months, have any sign of loss of response or demonstrate disease progression to AP or BC.[12,13]

Adverse Effects and Drug Interactions Tables 152-3 and **152-4** summarize drug–drug interactions, adverse drug reactions, and monitoring of imatinib. Imatinib-induced myelosuppression is one of the most common adverse events. Moderate-to-severe myelosuppression occurs in about 5% to 10% of patients with CP CML and in 50% to 60% of patients in AP or BC.[11–13] The myelosuppression typically occurs within the first 4 weeks of therapy and is more common in patients with advanced disease (ie, high blastic involvement of the bone marrow) and those with a low hemoglobin. Hematopoiesis in patients with CML depends on the amount of Ph-positive progenitors, although some degree of myelosuppression should be expected when the malignant clone is

suppressed. However, imatinib also suppresses normal hematopoiesis, which suggests that myelosuppression associated with imatinib is probably related to effects on the Ph clone and normal hematopoietic cells. When imatinib is initiated, patients should have complete blood counts drawn every 1 to 2 weeks to assess for myelosuppression until they have stabilized.[12] Appropriate initial management of myelosuppression is to interrupt imatinib treatment rather than dose reduce because dose reductions below 300 mg daily do not fully inhibit BCR-ABL and may lead to the emergence of imatinib resistance.[12]

TABLE 152-4 Monitoring of Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia

Drug	Adverse Reactions	Monitoring Parameters	Comments
Imatinib	Common: • Myelosuppression • Fluid retention (pleural/pericardial effusion, ascites, periorbital, and peripheral edema) • Nausea/vomiting • Rash • Fatigue • Hepatotoxicity • Hypothyroidism • Myalgias Rare but serious: • Congestive heart failure/left ventricular dysfunction • Hemorrhage • Bullous dermatologic reactions	• CBC for myelosuppression • CMP for hepatotoxicity • Consider baseline echocardiogram if preexisting cardiac dysfunction or risk factors for cardiac dysfunction, repeat if experiencing symptoms of cardiac dysfunction • Thyroid-stimulating hormone	Nausea and vomiting improved when the drug is administered with food
Dasatinib	Common: • Myelosuppression • Myalgia • Fluid retention • Cardiotoxicity • Rash • Gastrointestinal toxicity • Hypophosphatemia • Hepatotoxicity Rare but serious: • Pleural effusion • QT prolongation • Congestive heart failure/left ventricular dysfunction • Pulmonary arterial hypertension • Hemorrhage	• CBC for myelosuppression • CMP for hypophosphatemia and hepatotoxicity • ECG if risk factors for QTc prolongation • Chest radiograph for signs and symptoms of pleural effusion • Evaluate for signs/symptoms of underlying cardiopulmonary disease for pulmonary arterial hypertension	Gastrointestinal hemorrhage reported to be fatal; severe pleural effusions requiring thoracentesis; fatal myocardial infarction are reported
Nilotinib	Common: • Myelosuppression • Rash • Gastrointestinal toxicity • Peripheral edema • Liver function abnormalities • Elevated serum lipase/amylase • Electrolyte abnormalities (hypophosphatemia, hypokalemia, hypocalcemia, and hyponatremia) Rare but serious: • Tumor lysis syndrome • Cardiotoxicity (QTc prolongation/sudden cardiac death/ left ventricular dysfunction)	• CBC for myelosuppression • CMP for hypophosphatemia and hepatotoxicity • Serum amylase/lipase • ECG if risk factors for QTc prolongation at baseline, 7 days thereafter and then as clinically indicated	Sudden deaths reported with nilotinib; ventricular repolarization abnormalities may have been contributory
Bosutinib	Common: • Myelosuppression • Gastrointestinal toxicity • Fluid retention • Hepatotoxicity • Hypophosphatemia • Rash Rare but serious: • Embryofetal toxicity	• CBC for myelosuppression • CMP for hypophosphatemia and hepatotoxicity • Serum amylase/lipase • ECG if risk factors for QTc prolongation at baseline, 7 days thereafter and then as clinically indicated	Potential for additive risk of hepatotoxicity when given concurrently with letrozole
Ponatinib	Common: • Myelosuppression • Arthralgia • Headache • Fatigue • Fever • Pancreatitis • Elevated lipase • Hypertension • Gastrointestinal toxicity • Dermatologic toxicity • Electrolyte abnormalities • Fluid retention Rare but serious: • Arterial thrombosis • Hepatotoxicity • Cardiotoxicity (arrhythmia/congestive heart failure) • Embryofetal toxicity • Hemorrhage • Tumor lysis syndrome • Impaired wound healing / GI perforation	• CBC for myelosuppression • Serum lipase • CMP for hepatotoxicity, at baseline for tumor lysis syndrome • Blood pressure as clinically indicated	Deaths reported from hepatotoxicity, thrombosis including myocardial infarction and hemorrhage

CBC, complete blood count; CMP, comprehensive metabolic panel; ECG, electrocardiogram; GI, gastrointestinal.

Nonhematologic toxicities associated with imatinib include gastrointestinal complications, fluid retention, myalgias and arthralgias, rash, and hepatotoxicity. Drug rash frequently occurs but is usually mild and can be managed with antihistamines or topical steroids. Severe rash, while uncommon, can be an important cause for discontinuation of therapy. Algorithms for desensitization for patients that have experienced serious imatinib-associated rash have been published.[29] Hepatotoxicity can occur with imatinib, and the drug should be withheld if liver function tests exceed five times the upper limits of normal. After the liver function tests normalize, imatinib can be restarted at a reduced dose of not less than 300 mg/day. Imatinib dose is then escalated to the initial dose if liver function tests do not rise during 6 to 12 weeks of treatment. Death as a consequence of liver failure has been reported in a patient receiving large doses of acetaminophen concomitantly with imatinib. It is recommended that patients on imatinib limit their use of acetaminophen to 1,300 mg daily.[12] Other medications that are known to be hepatotoxic should be used with caution while patients are treated with imatinib.

Advanced-Generation Tyrosine Kinase Inhibitors

Dasatinib (Sprycel®) and nilotinib (Tasigna®) are approved second-generation TKIs used for the treatment of CML in patients who are resistant or intolerant to imatinib therapy; both drugs are also approved for first-line treatment of CP CML. Dasatinib is an oral BCR-ABL TKI that was FDA approved in 2006 for the treatment of imatinib-resistant CML. Dasatinib is an oral TKI of BCR-ABL, the SRC family, c-KIT, EPHA2, and PDGFR. Preclinical data show that dasatinib is 300 times more potent than imatinib and inhibits the growth of imatinib-resistant clones, except for the T315I mutation.[30] Dasatinib received accelerated approval based on hematologic and cytogenetic responses seen in imatinib-resistant or imatinib-intolerant patients.

Dasatinib has been evaluated in patients with imatinib-resistant or intolerant CP, AP, and BC CML. In a phase II trial of 186 patients in CP CML receiving dasatinib 70 mg orally twice daily, a hematologic response and major cytogenetic response were noted in 90% and 52% of patients, respectively.[31] Kantarjian et al. evaluated imatinib 400 mg twice daily compared to dasatinib 70 mg twice daily in patients who developed resistance or were intolerant to imatinib 400 mg daily. Patients receiving dasatinib had a higher complete hematologic response rate (93% vs 82%), major cytogenetic response rate (53% vs 33%), and estimated progression-free survival at 2 years, which suggests that

dasatinib is superior to imatinib dose escalation in disease progression.[32] A trial evaluating different dosing strategies of dasatinib showed that 100 mg once daily was as efficacious as dasatinib 70 mg twice daily, 50 mg twice daily or 140 mg once daily but with decreased adverse events such as pleural effusions.[33] The standard dose of dasatinib for patients with CP CML is now accepted to be 100 mg daily.

Dasatinib induces responses in patients who are resistant or intolerant to imatinib with advanced disease CML. In a phase II trial of dasatinib 70 mg twice daily in patients with AP CML, 45% achieved a complete hematologic response and 39% achieved a complete cytogenetic response. At 12 months, 66% had progression-free survival and 82% were alive.[34] A phase III trial comparing dasatinib 70 mg twice daily to 140 mg once daily reported similar efficacy at 15 months follow-up, but an improved safety profile that established dasatinib 140 mg once daily as the preferred dosing in AP CML.[35] In patients with BC CML, dasatinib induced a hematologic response in 35% and a major cytogenetic response in 33% of patients. Median overall survival for patients receiving dasatinib in BC CML is 11.8 months.[36]

Dasatinib has been evaluated as first-line therapy in a phase III trial of 519 patients with CP CML.[37] Patients were randomized to dasatinib 100 mg once daily or imatinib 400 mg once daily. The rate of complete cytogenetic response at 5 years was higher with dasatinib as compared with imatinib (83% vs 78%). The rate of major molecular response was significantly higher in the dasatinib group (76% vs 64%). Five-year overall survival was similar in the two groups. Adverse effects were similar between the two treatment groups, with the exception that 28% of dasatinib-treated patients developed grade 1 or 2 pleural effusions.

Nilotinib has 20 to 30 times the inhibitory activity of the BCR-ABL tyrosine kinase than imatinib, with activity against c-Kit and PDGFR (but not SRC kinases) due to a modification of the methylpiperazinyl structure of imatinib. Nilotinib has inhibitory activity against imatinib-resistant mutants with the exception of T315I. In a phase II trial of 280 patients with imatinib-resistant or intolerant CP CML, 59% of patients treated with nilotinib 400 mg twice daily achieved a major cytogenetic response, with an estimated 4-year progression-free and overall survival of 57% and 78%, respectively.[38] In patients with AP CML treated with nilotinib 400 or 600 mg twice daily, 26% achieved a complete hematologic response and 29% achieved a major cytogenetic response.[39] For first-line treatment of CML, results of a randomized trial in 846 patients comparing nilotinib at two doses (300 or 400 mg twice daily) to imatinib 400 mg

once daily have been published.[40] The primary end point of the trial was major molecular response. In the final 5 year analysis, both nilotinib arms had a significantly higher major molecular response rate at 12 months (77% for nilotinib 300 and 400 mg twice daily) as compared to imatinib (60%, $P < 0.0001$ for both comparisons). The nilotinib arms also had significantly improved time-to-progression to AP or BC, as compared to the imatinib arm. The number of patients who discontinued treatment was similar in the three treatment arms. Nilotinib provides an alternative to dasatinib in patients with imatinib-resistant or intolerant CP or AP CML and is one of several options in the initial treatment of CP CML.[12] The phase III trial results for both dasatinib and nilotinib have made them viable alternatives to imatinib for first-line treatment for newly diagnosed CP CML.

Two other TKIs were approved for the treatment of CML in 2012, bosutinib and ponatinib. Bosutinib has 15 to 100 times the inhibitory activity of the BCR-ABL tyrosine kinase as imatinib with activity against SRC kinases with minimal activity against c-Kit and PDGFR. Among 288 patients previously treated with imatinib, 34% achieved a major cytogenetic response at 24 weeks. Among patients previously treated with imatinib followed by dasatinib or nilotinib, 27% achieved a major cytogenetic response at 24 weeks. Grade 3 or 4 nonhematologic adverse events included diarrhea (9%), rash (9%), and vomiting (3%). Based on this study, the bosutinib dose recommended for phase II trials was 500 mg daily. A major cytogenetic response was observed in 32% of patients and a complete cytogenetic response was observed in 24% of patients in the phase II trials.[42] Bosutinib 400 mg daily was compared to imatinib 400 mg daily in a phase III randomized trial of 487 patients in newly diagnosed CP CML.[43] The primary endpoint of major molecular response rate at 12 months was significantly higher in patients treated with bosutinib (47.2% vs 36.9%). The incidence of adverse events was similar between the groups with the exception that bosutinib had a higher incidence of diarrhea (68% vs 21%) and imatinib had a higher incidence of edema (70% vs 33%).

Ponatinib is considered a third-generation TKI which contains a novel triple-bond linkage in its chemical structure that avoids the steric hindrance caused by the bulky isoleucine residue at position 315 in T315I BCR-ABL binding site cleft, providing clinical activity against this resistance phenotype.[44] In the combined phase I and II trials of 147 patients with T315I mutated BCR-ABL CML in either CP, AP, BC or Ph positive ALL, the maximum tolerated daily dose of ponatinib was 45 mg and the dose-limiting toxicities were pancreatitis and myelosuppression.[44,45] Of the 76 patients with CP CML, 72% achieved a

complete cytogenetic response and 61% a major molecular response. Of the 45 patients with AP or BC CML, the rate of major hematologic response was 58% and 27%, respectively.[44,45] Hepatotoxicity including reports of liver failure, vascular occlusion, heart failure, and death are also included in the black box warning, several of which occurred within 1 week of starting therapy. The manufacturer recommends specific dose modifications for myelosuppression, hepatotoxicity, and elevated lipase. Due to these toxicities, ponatinib is generally reserved for patients with a documented T315I mutation or for patients in whom no other TKI therapy is indicated.[46]

Tables 152-3 and 152-4 summarize dosing, drug interactions, adverse drug reactions, and monitoring of advanced-generation TKIs. Dasatinib can cause edema and pleural effusions, which can be managed by drug holiday, diuretics, or short courses of steroids. Nilotinib can be associated with indirect bilirubin elevations in 10% to 15% of patients.[38,39] Nilotinib may prolong the QTc interval (black box warning) and patients should have an electrocardiogram at baseline, at 7 days following initiation of therapy, and periodically thereafter. Based on early clinical trial data, bosutinib appears to have similar rates of adverse events of diarrhea, nausea and vomiting, rash, and abdominal discomfort.[41] Similar to imatinib, advanced-generation TKIs are metabolized by cytochrome P450 (CYP) 3A4. Clinicians need to be aware of possible drug interactions with inducers and inhibitors of the CYP3A4 pathway such as phenytoin, azole antifungals, or macrolide antibiotics.

Omacetaxine

Omacetaxine was approved by the FDA in October 2012 for the treatment of CP or AP CML with resistance or intolerance to two or more TKIs. Omacetaxine is a first-in-class cephalotaxine ester that inhibits protein synthesis independent of direct BCR-ABL binding. The putative mechanism is the reduction of BCR-ABL oncoproteins and Mcl-1, an anti-apoptotic Bcl-2 family member, via binding to A-site cleft in the peptidyl-transferase center of the large ribosomal subunits. Efficacy with omacetaxine has been demonstrated in two patient groups: CP or AP CML resistant to two or more TKIs and patients previously treated with imatinib harboring the T315I mutation. The former group was evaluated in a combined analysis of two phase II studies for CP and AP CML. Omacetaxine was administered at 1.25 mg/m^2 subcutaneously twice daily for 14 consecutive days every 28 days then for 7 days every 28 days as maintenance.[47] Of the 122 patients enrolled, 81 had CP CML of which 20% achieved a major cytogenetic response, 10% achieved a complete cytogenetic response, with a median overall

survival of 34 months.

A phase II trial of omacetaxine was conducted in 62 CP CML patients with a history of the T315I mutation.[48] Patients were treated with the induction regimen as above and transitioned to maintenance when the patient achieved a hematologic response. Hematologic response was achieved in 77%, complete cytogenetic response in 16%, and major cytogenetic response in 23% of patients. The median duration of complete hematologic response was 9.1 months, and major cytogenetic response was 6.6 months. Most of the grade 3/4 toxicities reported in these trials were myelosuppression with occasional reports of myalgias and arthralgias and gastrointestinal toxicity.

Discontinuation of Tyrosine Kinase Therapy

Discontinuation of TKI therapy with close monitoring has recently emerged as a possibility in carefully selected patients. Candidates for discontinuation include those who achieved and maintained a major molecular response, or what is referred to as a deep molecular response (>4 log decrease in *BCR-ABL* RT-PCR or <0.01% *BCR-ABL* (IS) detection), for at least two years. The discontinuation of imatinib was evaluated in 100 patients to assess the possibility of treatment-free remission in patients with a deep and sustained molecular response.[49] Following imatinib discontinuation, the risk of molecular recurrence, defined as a significant *BCR-ABL* increase at two assessment points, was 43% at six months and 38% at 5 years without any patients experiencing progression of disease. At the time of increasing *BCR-ABL* PCR transcripts, imatinib therapy was reinitiated and molecular responses were achieved once again. Careful patient selection for discontinuation of TKI therapy, followed by close monitoring of *BCR-ABL* transcripts and restarting therapy if *BCR-ABL* levels rise may become standard management in the future. Results with dasatinib, nilotinib, and additional data on imatinib were similar, with a molecular relapse-free survival of 61% at 6 months and 50% at 2 years.[50]

Hematopoietic Stem Cell Transplantation

5 Allogeneic HSCT remains the only therapy proven to cure patients with CML, with many patients alive and disease-free decades after transplant. Patients undergoing allogeneic HSCT from a human leukocyte antigen (HLA)-matched sibling donor have 5-year survival rates ranging from 60% to 80% and long-term survival of about 50%.[51,52] In most long-term survivors, the *BCR-ABL* translocation is absent in all diagnostic tests including RT-PCR. Prognostic risk

factors associated with survival outcomes include age, phase of disease, and disease duration. Increasing age is associated with poorer prognosis, with higher transplant-related mortality in patients older than age 50 years. Patients with CP who receive allogeneic HSCT have better outcomes than those in AP or BC. The time from diagnosis to transplantation also affects outcomes. Patients who undergo matched-sibling allogeneic HSCT within the first year of diagnosis have a better 5-year survival rate than those who undergo transplantation more than 1 year after their diagnosis (70%-80% vs 50%-60%).[51] These data were reported prior to the use of imatinib as first-line therapy for CML.

The major limitation for the application of HSCT is that fewer than 30% of patients who are transplant-eligible will have an HLA-matched sibling donor. The most practical approach is to use an HLA-matched unrelated donor, if available. Matched unrelated donor HSCT has an overall 5-year survival reported to be 40% to 70%, which approaches overall survival data results reported for matched-sibling donor HSCT.[7,12,51,52] The advent of TKI therapy has resulted in fewer transplants for CML. Data collected to date appear to show that imatinib use prior to transplantation does not adversely affect transplant-related mortality.[53]

Treatment options in patients who relapse after HSCT are limited. Graft-versus-leukemia (GVL) effect, TKIs, omacetaxine, IFN-α, or a clinical trial are reasonable options. The infusion of donor lymphocytes functions as a form of adoptive immunotherapy that can induce a GVL effect. In relapsed CML, donor lymphocytes induce durable responses and these responses strongly correlate with the development of graft-versus-host disease (GVHD).[54] Tumor burden also predicts the likelihood of response to donor lymphocyte infusion in relapsed CML. The optimal method of administering donor lymphocytes remains unclear, but these data suggest it may be possible to partially separate the GVL effect from GVHD.

Evaluation of Therapeutic Outcomes

The current standard of care is for patients with newly diagnosed CP CML to receive imatinib or one of the second-generation TKIs.[12] The goal of disease monitoring in CML is to differentiate patients who have optimally responded to an initial course of TKI therapy from those at high risk for treatment failure. With imatinib, nilotinib, dasatinib, and bosutinib as appropriate options for initial therapy for newly diagnosed CP CML, and ponatinib and omacetaxine approved for salvage therapy, clinicians have many treatment options before

allogeneic HSCT. Future research opportunities will focus on how to select second-, third-, and fourth-line therapies and whether combination therapy provides additional long-term benefit.

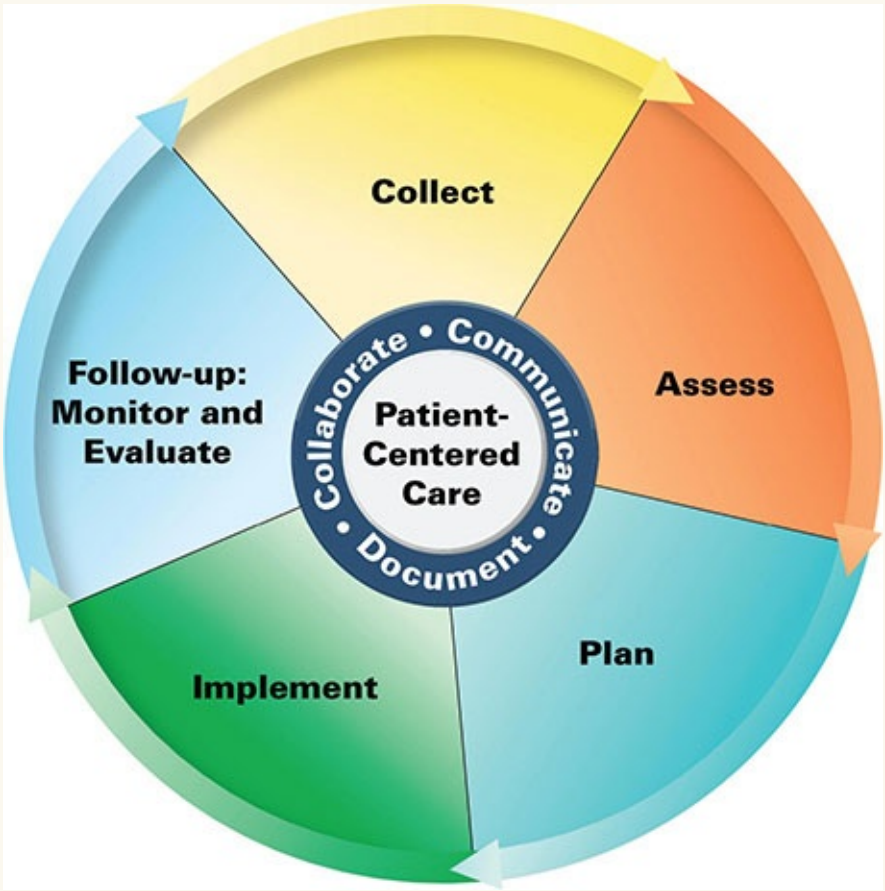
CHRONIC LYMPHOCYTIC LEUKEMIA

Epidemiology and Etiology

CLL is a lymphoproliferative disorder characterized by the accumulation of functionally incompetent clonal B lymphocytes.[55] CLL is the most common form of leukemia in the United States but is rare in other countries, such as Japan and China. It is estimated that 20,720 new cases of CLL were diagnosed in the United States in 2019.[1] Occasional family clusters have been recognized, and first-degree relatives of patients with CLL are at three times the risk of developing a lymphoid malignancy as compared with the general population. CLL is a disease of the elderly, with a median age of 71 years, although 20% to 30% of CLL occurs in patients who are younger than 55 years of age. Male sex, white race, family history, and advanced age are known risk factors for the disease.

Pathophysiology

CLL cells are comprised of a neoplastic clone of $CD5^+$ cells, which express low levels of surface-membrane immunoglobulin M (IgM) and immunoglobulin D (IgD) compared to normal peripheral blood B cells. Normal $CD5^+$ B lymphocytes are present in the lymph nodes and in the blood. Neoplastic $CD5^+$ cells accumulate in the lymph nodes and spleen because of the loss of apoptosis by either the overexpression of an oncogene, such as *BCL-1* or *2*, or loss of a tumor suppressor gene, such as *RB1*.[55] The BCL-2 protein is a major regulator of apoptosis or programmed cell death. Evidence is emerging that antigenic stimulation and cytokines drive the proliferation of the CLL cells.



Patient Care Process for Chronic Lymphocytic Leukemia (CLL)

Collect

- Patient characteristics (eg, age, sex)
- Medical history (personal and family)
- Social history (eg, tobacco, alcohol, chemical exposure)
- Current medications (eg, complementary or alternative medicines, inducers or inhibitors of CYP3A4, QT prolonging medications, over-the-counter medications includes aspirin/NSAID use)
- Objective data:

  Vital signs: height, weight, blood pressure, heart rate, respiratory rate,

oxygen status
Laboratory data: CBC with differential, CMP
Flow cytometry (chromosomal and molecular markers of CLL) and bone marrow analysis if performed
Imaging studies (PET or CT scan, if performed)
Immune system function including immunoglobulin status

Assess

- Cytogenetic and molecular markers of CLL (eg, high-risk disease with del(17p) or *TP53* mutation)
- Infection risk (eg, IgG <500 mg/dL (5 g/L) or absolute neutrophil count <500 cells/mm^3 [0.5 × 10^9/L])
- Performance status (ie, to determine if the patient is fit enough to receive chemotherapy)
- Comorbidities
- Symptoms of disease
- Patient's and family's goals of care

Plan*

- Watch and wait versus treatment
- Drug therapy based on high-risk CLL features, patient age, and comorbidities
- Monitoring parameters of efficacy (ie, disease response criteria) and safety (eg, myelosuppression, nausea, vomiting)
- Patient education (eg, goal of treatment, drug-specific education, medication adherence, food-drug and drug-drug interactions)

Implement*

- Educate patient on all aspects of the treatment plan
- Patient compliance (intravenous vs oral)

Follow-up: Monitor and Evaluation of Response*

- Evaluate efficacy using disease response criteria

- Assess safety and adverse effects of treatment regimen
- Assess adherence to treatment plan (eg, patient-initiated delays versus toxicity-related delays)

**Collaborate with patient, caregivers, and other healthcare professionals.*

Although CLL lacks a common genetic target as observed in CML, B-cell-receptor signaling has emerged as a driving factor for CLL tumor survival. Bruton's tyrosine kinase (BTK), a member of the Tec family of kinases, is essential for the activation of several constitutively active pathways for CLL cell survival. BTK leads to activation of the Akt, extracellular signal-regulated kinase (ERK), and nuclear factor kappa light-chain enhancer of active B-cells (NF-κβ) pathways.[56] Additionally, BTK is required for B-cell chemokine-mediated homing and adhesion. Phosphatidylinositol 3-Kinase (PI3K) is a lipid kinase that has a catalytic subunit with four different isoforms: α, β, γ, and δ. When PI3K is activated, it generates phospholipid messengers on the cell membrane that recruit and activate various intracellular enzymes that regulate cell motility, survival, and proliferation.[57] The δ isoform plays a critical role in normal B-cell development, function, and transducing signals from receptors. The PI3Kδ signaling pathway is hyperactive in CLL and other B-cell cancers.

A monoclonal population of B cells with a similar surface antigen phenotype as CLL cells has been recently identified in patients up to several years prior to diagnosis of the disease.[58] This phenomenon, termed monoclonal B-cell lymphocytosis (MBL), appears to predict whether a patient is at risk for developing CLL over time. In a cohort of 77,000 patients enrolled in a cancer screening trial, 45 patients were diagnosed with CLL throughout the duration of the study. Baseline blood samples collected on enrollment of the screening trial were analyzed for the patients who developed CLL. MBL was present in 44 of 45 of the patients by either flow cytometric or molecular analysis (ie, RT-PCR assay) and confirmed in 41 of 45 of these patients by both methods. Samples predated the diagnosis of CLL in a time period ranging from 6 months to 6.4 years. This finding could lead to potentially earlier diagnosis and intervention for CLL.

Cytogenetic abnormalities correlate with disease progression in CLL. About 80% of patients with CLL have a karyotypic abnormality. The chromosomes that are most frequently involved include chromosomes 11, 12, 13, and 17.[59] Additional cytogenetic abnormalities may be acquired during therapy,

particularly with deletions of chromosome 17, which have an adverse effect on survival.[60] Somatic point mutations have been identified in a cohort of 91 patients yielding nine mutated genes: *TP53*, *ATM*, *MYD88*, *NOTCH1*, *SF3B1*, *ZMYM3*, *MAPK1*, *FBXW7*, and *DDX3X*.[61] These mutations were associated with cell-cycle and DNA repair pathways, intracellular signaling, inflammatory pathways, and RNA splicing and processing. A correlation was identified with *SF3B1* and chromosome 11 deletions providing insight into how these mutations may impact clinical outcomes.

About 4% to 10% of patients with CLL will undergo transformation of their disease to an aggressive lymphoma, most commonly non-Hodgkin lymphoma (diffuse large B cell), which is termed as *Richter's syndrome*.[62] Richter's syndrome may be triggered by accumulation of additional cytogenetic abnormalities in the malignant clone of lymphocytes or by viral infections, such as Epstein-Barr virus.[63]

Staging and Prognosis

Survival times for patients with CLL are widely variable, with some patients succumbing to the disease within 3 years and others living into a second decade from the time of diagnosis. The Rai and the Binet staging systems are commonly used in CLL with the Rai being favored in the United States and the Binet in Europe. The Rai staging system has been combined into a risk classification scheme: low risk (stage 0), intermediate risk (stages I and II), and high risk (stages III and IV) with median survivals of greater than 10 years, 7 years, and 2 to 4 years, respectively.[55,64]

The disease course for CLL varies within each stage such that one patient may have an indolent course with long survival time, while another patient may have more aggressive disease and a relatively short survival time. The Rai and Binet staging systems incompletely predict for individual patients who may experience more rapid disease progression. Patients with Richter's syndrome will have a rapidly advancing disease course that mimics diffuse large B-cell non-Hodgkin lymphoma. However, successful treatment of the diffuse large B-cell non-Hodgkin lymphoma with combination chemotherapy will not eradicate the underlying clone of CLL cells and patients will ultimately relapse.[63]

Biomarkers, such as CD38 expression and ζ-associated protein 70 (ZAP-70) expression, have been explored as prognostic factors for CLL. CD38 is a cell-surface antigen that is associated with early progression, significantly shorter overall survival, and a poor response to fludarabine.[55,65,66] ZAP-70 is an

intracellular protein with tyrosine kinase activity. Once considered as simply a surrogate marker for the unmutated variable region of the immunoglobulin heavy chain gene (IGHV), elevated ZAP-70 expression appears to predict for rapid CLL disease progression and independently correlates with prognosis.[64,66]

CLINICAL PRESENTATION Chronic Lymphocytic Leukemia

Constitutional Symptoms

- Fever, fatigue, weight loss

Physical Examination

- Lymphadenopathy (87%)
- Splenomegaly (54%)
- Hepatomegaly (14%)

Laboratory Tests

Peripheral blood

- Lymphocytosis
- Coombs-positive autoimmune hemolytic anemia
- Hyper- or hypogammaglobulinemia
- Monoclonal gammopathy
- Anemia
- Thrombocytopenia

Bone marrow

- Hypercellular
- Increased mature lymphocytes
- Increased megakaryocytes

Molecular markers

- Cytogenetics (11q, del(13p), del (17p))
- IGHV status
- CD38+ Status

Cytogenetic changes such as deletion of the short arm of chromosome 17 (del[17p]), which corresponds to p53 silencing, can be biomarkers of poor response to therapy. A study showed that newly diagnosed patients with del(17p) had a median time-to-progression following first-line therapy with either fludarabine or combination fludarabine and cyclophosphamide of 10 to 12 months.[60] Patients with chromosomal abnormalities of 11, 12, 13, and 17 have reported median survivals of 133 months, 114 months, 79 months, and 32 months, respectively.[59] Mutations in the p53 gene (ie, *TP53*) can occur separately from del(17p) and are associated with uncontrolled cell proliferation.[62] Unmutated IGHV is also an independent indicator of poor prognosis.

TREATMENT

Chronic Lymphocytic Leukemia

Desired Outcomes

The primary goals of treatment for CLL are to achieve and maintain a prolonged remission with minimal treatment-related toxicity. The management of patients with CLL is highly personalized with some patients receiving therapy on diagnosis, while other patients, particularly with early-stage disease, are managed expectantly. Indications for starting treatment include disease-related symptoms (fatigue, night sweats, weight loss, and fever), threatened end-organ function, bulky disease, doubling of lymphocyte doubling time in less than 6 months, progressive anemia, and platelet count less than 100,000/mm^3 (100×10^9/L).[62,71] Consideration of initial treatment options is based on several factors including patient age, disease stage, and high-risk prognostic factors, such as del(17p) or *TP53* mutation.

Most stage 0 patients do not require treatment and can be managed with observation. In patients with stage I disease, treatment is controversial. A consistent survival benefit from early therapy has not been reported in asymptomatic patients.[62,71] Cytotoxic chemotherapy in early-stage CLL is

usually reserved for patients who have disease characteristics consistent with a more aggressive course, such as short lymphocyte doubling times and presence of biologic markers such as ZAP-70 or high-risk cytogenetics. In stages II through IV disease, treatment is required, with the goal of achieving a partial or complete remission. Response definition varies based on the sites of involvement: resolution of lymphadenopathy and organomegaly, reduction of blood or marrow lymphocytes, and restoration of normal hematopoiesis.[62] **Figure 152-2** shows the molecular targets of the various chemotherapy, targeted, and biologic agents used to treat CLL. **Table 152-5** shows the response rates of regimens used to treat newly diagnosed and previously treated CLL.[62,67–71]

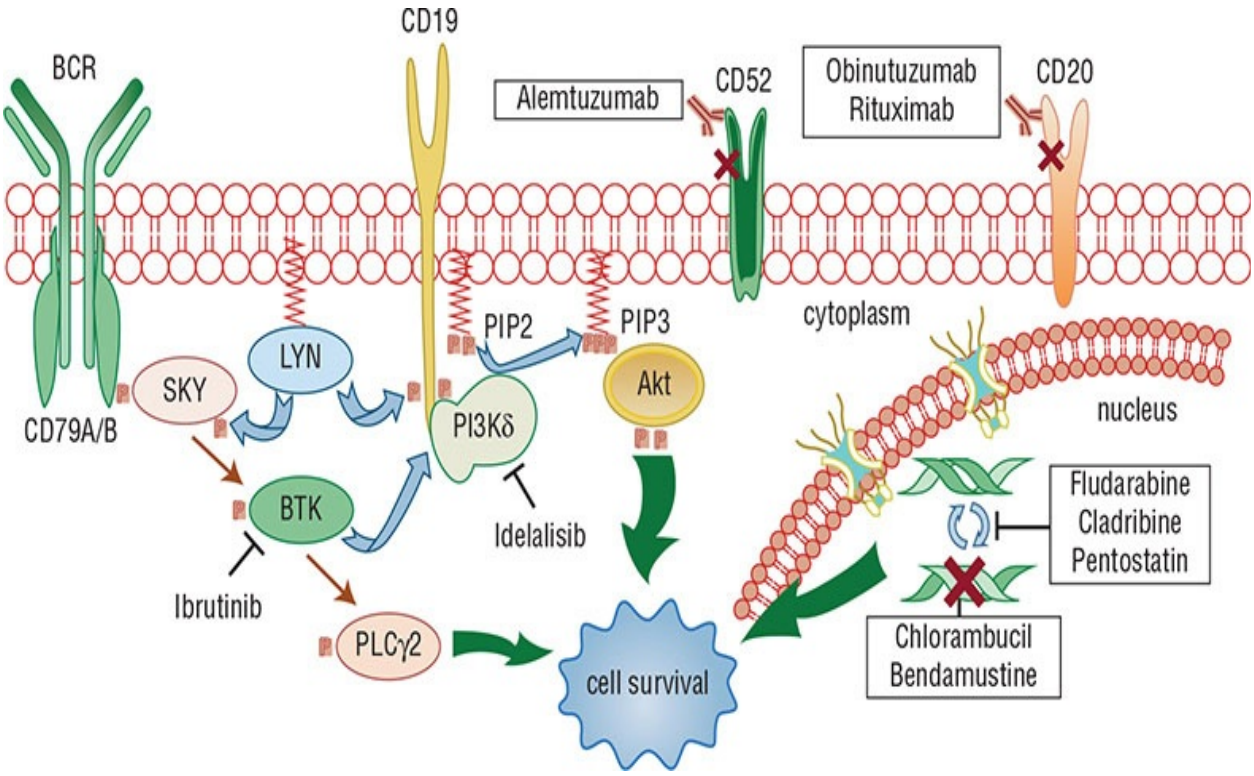


FIGURE 152-2 Current treatments and their molecular targets in chronic lymphocytic leukemia (*Reprinted with permission from Manman W, Wang X, Song Z, et al. Targeting PI3Kδ: Emerging Therapy for Chronic Lymphocytic Leukemia and Beyond. Med Res Rev 2015;35:720-752. Copyright © 2015 John Wiley and Sons. All rights reserved.*)

TABLE 152-5 Treatment for Newly Diagnosed and Previously Treated Chronic Lymphocytic Leukemia

Treatment	Overall Response (%)	Complete Response (%)
Chlorambucil		
Untreated	37	4
Fludarabine alone		
Untreated	60-80	20-30
Previously treated	13-59	3-37
Fludarabine + cyclophosphamide		
Untreated	80-90	25-40
Previously treated	60-70	10-15
Rituximab alone		
Untreated	50-60	10-20
Previously treated	80-90	20-40
Fludarabine + rituximab		
Untreated	80-100	30-50
Previously treated	80-90	20-40
Fludarabine + cyclophosphamide + rituximab		
Untreated	95	70
Previously treated	73	25
Alemtuzumab alone		
Untreated	80-90	20-30
Previously treated	30-50	0-20
Alemtuzumab + fludarabine		
Previously treated	83	17-30
Bendamustine + rituximab		
Untreated	97	38
Previously treated	60	9
Ofatumumab + chlorambucil		
Untreated	82	12
Obinutuzumab		
Previously treated	30-62	0-5
Obinutuzumab + chlorambucil		
Untreated	78	20
Obinutuzumab + ibrutinib		
Untreated	88	19
Ibrutinib		
Untreated	86	4
Previously treated	71	5
Idelalisib + rituximab		
Previously treated	81	0
Venetoclax		
Previously treated	79	20
Venetoclax + rituximab		
Previously treated	79	8
Venetoclax + obinutuzumab		
Untreated	85	35
Duvelisib		
Previously treated	74	1
Acalabrutinib		
Previously treated	81	

Cytotoxic Chemotherapy

Alkylating Agents Historically, orally administered alkylating agents, such as chlorambucil and cyclophosphamide, given either alone or with corticosteroids have been used as the primary treatment for CLL.

A meta-analysis of 2,048 patients from six randomized controlled studies evaluated low-dose alkylating agents in patients with CLL.[69] Results showed that delayed treatment with alkylating agents in asymptomatic patients did not adversely affect 10-year survival. More importantly, if only deaths caused by CLL were considered, significantly longer survival was observed when treatment was deferred. Chlorambucil has been used in elderly, symptomatic patients as initial treatment for CLL, but its use is based on a small number of studies with no demonstrable survival advantage.[68,69] Commonly used dosing schedules for chlorambucil are intermittent pulse dosing of 15 to 40 mg/m^2 orally every 28 days or daily doses of 4 to 8 mg/m^2/day.[71] The dose of chlorambucil is often titrated to circumvent myelosuppression.

Cyclophosphamide produces a similar response rate as chlorambucil (overall response rate: 40%-60%; complete response: 4%) and can be used in patients who cannot tolerate chlorambucil or in whom response is not optimal. Some patients who do not respond to chlorambucil will respond to single-agent cyclophosphamide. Cyclophosphamide is typically given orally at a daily dose of 1 to 3 mg/kg. Oral cyclophosphamide is less commonly used than chlorambucil because of the risk of hemorrhagic cystitis and bladder cancer with prolonged treatment.

Purine Analogs Purine analogs, fludarabine, 2-chlorodeoxyadenosine (cladribine) and 2-deoxycoformycin (pentostatin), are highly active in CLL, and fludarabine is the most widely studied agent in CLL[67–70] and fludarabine-based regimens are commonly used as initial treatment. Fludarabine is particularly useful in younger patients and in those patients who can tolerate immunosuppressive chemotherapy.[67–70] Most patients receive fludarabine 25 to 30 mg/m^2 IV daily for 5 days when used as a single agent. Cladribine and pentostatin have similar activity, although head-to-head trials comparing these three nucleosides have not been conducted.[70–72]

Fludarabine was initially studied in CLL patients who were refractory to chlorambucil. Several trials reported overall response rates to fludarabine in previously treated patients ranging from 13% to 59% and complete response

rates of 3% to 37%.[71–74] Fludarabine has higher overall response and complete remission rates than alkylating-based therapies in the frontline setting. In one of the randomized studies that compared fludarabine to chlorambucil in chemotherapy-naïve patients, fludarabine-treated patients had a higher complete remission rate as compared with chlorambucil (20% vs 5%).[72] However, the higher complete remission rate did not translate into a significant difference in overall survival and patients treated with fludarabine had a higher rate of severe neutropenia and infection. The study allowed chlorambucil failures to cross over to fludarabine, which may have hampered the ability to show a survival advantage in the fludarabine arm. A recent review of younger patients enrolled in a large phase III trial showed that 33% of patients receiving fludarabine or fludarabine-based therapy had infectious complications.[73] An increase in *Pneumocystis* infections was not observed, but a 6% increase in herpes and varicella zoster infection was documented. Dose reductions occurred frequently as a result of the infectious episodes. Based on the increased risk of infectious complications, some practitioners recommend antiviral and antibacterial prophylaxis with treatment.[69,73,74]

Bendamustine is an alkylating agent that contains a purine-derivative benzimidazole ring in its chemical structure that yields a compound that is non–cross-resistant with other alkylating agents. Bendamustine induces cell death via single- and double-stranded cross-links.[75] The efficacy of bendamustine was established as first-line therapy in Binet stage B or C CLL in a phase III trial that randomized 319 patients to bendamustine or chlorambucil.[76,77] Complete response rates of 31% versus 2% and an overall response rate for 68% versus 31% were observed for bendamustine and chlorambucil, respectively. The median progression-free survival was longer in patients receiving bendamustine (21.2 vs 8.8 months, $P < 0.0001$). The median overall survival was not reached in the bendamustine group and was 78.8 months in the chlorambucil group. Adverse events reported for bendamustine include hematologic toxicity in about 25% of patients, and gastrointestinal and cutaneous toxicity.

Biologic Therapy

Monoclonal antibodies are a mainstay in the treatment of CLL. Rituximab is a chimeric monoclonal antibody that targets the CD20 antigen expressed on B lymphocytes. Rituximab was initially approved for patients with indolent non-Hodgkin lymphoma and later for aggressive non-Hodgkin lymphoma. Rituximab received FDA approval for the treatment of CD20-positive CLL in 2010. CLL cells have less prominent CD20 expression on their surface as compared to non-

Hodgkin lymphoma, which may explain the lower clinical response. Rituximab as a single agent has moderate activity in CLL, with a 58% overall response rate reported with 9% complete responses.[67,71] Subsequent studies have used higher rituximab doses (up to 500 mg/m^2 per cycle) when given in combination with other agents.

Alemtuzumab is a monoclonal antibody that targets the CD52 antigen found on both B and T lymphocytes. This agent was initially FDA approved in 2001 for the treatment of patients with CLL who had been treated with alkylating agents and had failed fludarabine therapy and is now approved as a single agent for both frontline and salvage treatment of CLL. Alemtuzumab is titrated to a maintenance dose of 30 mg IV or subcutaneously given three times a week for 12 weeks. As a single agent, alemtuzumab has produced response rates from 33% to 53% in patients with refractory disease, but complete responses are infrequent.[78–80] Results from a randomized phase III trial comparing alemtuzumab to chlorambucil in chemotherapy-naïve patients with symptomatic CLL showed higher complete response rates with alemtuzumab than with chlorambucil (24% vs 2%).[78] Alemtuzumab therapy is complicated by infusion-related reactions, pancytopenia, and opportunistic infections.[79]

Ofatumumab is a fully human monoclonal antibody to CD20 that was approved as single-agent therapy in 2009 for patients with CLL that is refractory to fludarabine and alemtuzumab. Ofatumumab is administered as an IV infusion with an initial dose of 300 mg then four weekly doses followed by four monthly doses of 2,000 mg. An overall response rate of 58% in patients with fludarabine and alemtuzumab refractory disease and 47% in bulky fludarabine refractory disease was reported.[80] Median time-to-progression was 5.7 and 5.9 months and median overall survival was 13.7 and 15.4 months in the fludarabine and alemtuzumab refractory patients and bulky fludarabine refractory disease patients, respectively. Adverse events reported in greater than 10% of patients included infection and neutropenia. Infusion-related events were reported in about 60% of patients, 40% during the first infusion and 25% with the second infusion. Serious toxicities such as fatal infections, progressive multifocal leukoencephalopathy, and hepatitis B reactivation have been reported.

The efficacy of first-line ofatumumab was studied in a phase III trial of 447 patients with previously untreated CLL.[91] Median progression-free survival was significantly longer in the ofatumumab and chlorambucil group versus the chlorambucil alone group (23.4 vs 14.7 months) at the 5-year follow-up assessment[104]. Grade III toxicity including neutropenia and infusion-related events were reported more frequently in the combination arm, although the

overall infection rate was similar in both treatment arms. These results led to the approval of ofatumumab in combination with chlorambucil in patients with previously untreated CLL who are not candidates for fludarabine-based therapy.

Targeted Therapy

Ibrutinib is an orally administered compound that covalently binds to the cysteine-481 amino acid of the BTK enzyme and inhibits signaling of ERK, NF-κB, and cytosine phosphate-guanine–mediated tumor cell proliferation and migration.[56] Ibrutinib was FDA approved in 2014 for the treatment of CLL. In the phase Ib/II trial, 85 patients with relapsed or refractory CLL received oral ibrutinib at 420 mg or 840 mg daily. The overall response rate was 71% for both groups with a partial response observed in 20% and 15%, respectively. In a phase III trial, ibrutinib was compared to ofatumumab in patients with relapsed or refractory CLL with a primary endpoint of progression-free survival.[81] Median progression-free survival in the ibrutinib groups was not reached as compared to 8.1 months in the ofatumumab group (hazard ratio 0.22, $P < 0.001$). The overall response rate was significantly higher in the ibrutinib group (42.6% vs 4.1%). At 12 months, overall survival also favored ibrutinib (90% vs 81%). At 4 years of follow-up, the median progression-free survival was still not reached in patients who had received ibrutinib as compared to 8 months with ofatumumab, and 3-year overall survival continued to favor ibrutinib (59% vs 3%).[82] In the subgroup of CLL patients with del(17p), the response rate was 68%, including one complete response. In a follow-up study of relapsed and refractory CLL patients with del(17p), the overall response rate was 83% with an estimated 24-month progression-free survival of 63%.[83] Ibrutinib has also been studied in treatment-naïve elderly CLL patients who did not have del(17p). Patients randomized to ibrutinib had statistically longer 24-month progression-free survival (89% vs 34%, hazard ratio 0.12, $P < 0.0001$) as compared to single-agent chlorambucil.[84] The most frequent nonhematologic adverse events were diarrhea, fatigue, fever, and nausea. A common toxicity unique to ibrutinib is lymphocytosis secondary to tumor cell mobilization to the peripheral blood. This lymphocytosis is not an indicator of disease progression and ibrutinib should be continued at the standard dose. New onset atrial fibrillation has been reported with ibrutinib use. Although ibrutinib has antileukemic activity, even in CLL refractory to purine analogues and alkylating agents, resistance can develop. The substitution of cysteine at base pair 481 for serine of BTK (BTK C481S) prevents the covalent binding of ibrutinib resulting in ibrutinib resistance. The gain of function mutation of phospholipase C gamma 2 (PLCG2), a protein

downstream from BTK, activates PLCγ2 and is another mechanism of resistance to ibrutinib.[85,86]

Acalabrutinib is a second-generation BTK inhibitor that is FDA approved for mantle cell lymphoma but has also been studied in patients with relapsed CLL.[87] The phase III trial comparing acalabrutinib monotherapy to investigator choice (idelalisb plus rituximab or bendamustine plus rituximab) reported a significantly improved median progression-free survival with acalabrutinib (not reached vs 16.5 months; hazard ratio 0.31, $P < 0.001$).[105] Improvement in progression-free survival was seen in patients with deletion 17p, TP53 mutation, and across all Rai stages. Acalabrutinib does not have activity in patients with BTK C481S and should not be used in patients with this resistance mutation. Acalabrutinib is not recommended in patients who have ibrutinib-refractory disease.[62]

Idelalisib is a small-molecule inhibitor of PI3Kδ and interferes with the PI3Kδ-AKT signaling pathway leading to increased apoptosis.[57] In a randomized phase III trial, patients with relapsed CLL who had comorbidities that precluded them from being treated with standard chemotherapy were randomized to receive rituximab with either placebo or idelalisib.[57] The primary endpoint of progression-free survival was not reached in the idelalisib group as compared to 5.5 months in the rituximab monotherapy group ($P < 0.001$). Patients in the idelalisib group had a higher overall response rate (81% vs 13%) and longer 12-month overall survival (92% vs 80%, $P = 0.02$). Black box warnings include hepatic dysfunction, severe diarrhea, colitis, intestinal perforation, and pneumonitis. Patients should have complete blood counts and hepatic function monitored prior to initiation and throughout treatment.

Duvelisib is a dual small-molecule inhibitor of both PI3Kδ and PI3Kγ.[102] While PI3Kδ is involved in the survival and proliferation of B-cells, PI3Kγ is a mediator in the migration and differentiation of T-cells and macrophages. Inhibition of both the delta and gamma kinases results in a blockade of malignant B-cell survival and proliferation and disruption of the malignant microenvironment. In an open-label, phase III clinical trial of previously treated patients, duvelisib showed improved progression-free survival over ofatumumab, 13.3 versus 9.9 months respectively (hazard ratio 0.52, $P < 0.0001$). The improvement in progression-free survival was also observed in patients with high-risk cytogenetic markers. Like Idelalisib, black box warnings include hepatic dysfunction, diarrhea and colitis, and pneumonitis. Patients receiving idelalisib or duvelisib should receive *Pneumocystis jiroveci* pneumonia prophylaxis and monitoring for CMV reactivation.

Venetoclax is an orally administered selective BCL-2 inhibitor. BCL-2 is an antiapoptotic protein which regulates the intrinsic apoptosis pathway.[88–90] It is overexpressed in CLL cells resulting in lymphocyte accumulation. BCL-2 inhibition with venetoclax results in apoptosis. Venetoclax was FDA approved in 2016 based on a phase I/IIb trial of venetoclax in 116 patients with relapsed CLL.[89] The overall response rate was 79%, with a complete response rate of 20%. In patients with del(17p) had a similar overall and complete response rate. In a follow-up phase II study of venetoclax in patients with del(17p) relapsed or refractory CLL, the overall response rate was 85%.[90] Patients treated with venetoclax can develop tumor lysis syndrome when therapy is initiated. The manufacturer recommends slow dose titration from 20 mg daily to the target dose of 400 mg daily weekly over 5 weeks to minimize the risk of tumor lysis. Specific recommendations regarding inpatient versus outpatient initiation, dose escalation, and tumor lysis syndrome prophylaxis are based on disease burden and the patient's clinical status.

Tables 152-6 and **152-7** summarize dosing, drug interactions, adverse drug reactions, and monitoring of oral targeted agents used to treat CLL.

TABLE 152-6 Dosing of Oral Targeted Agents in Chronic Lymphocytic Leukemia

Drug	Brand Name	Dosing	Food–Drug Interactions	Drug–Drug Interactions
Ibrutinib	Imbruvica	420 mg/day 140 mg/day with mild hepatic impairment or voriconazole 70 mg/day with moderate hepatic impairment or posaconazole	Avoid grapefruit and seville oranges	Strong CYP 3A4 inhibitors increase C_{max} 6.7-fold to 29-fold and AUC 5.7-fold to 24-fold Strong CYP 3A4 inducers decrease C_{max} >13-fold and AUC >10-fold
Idelalisib	Zydelig	150 mg twice daily Moderate or severe hepatic impairment, reduce dose to 150 mg daily	None	Idelalisib is a CYP 3A4, 2C8, 2C19, UGT1A1, and P-gp inhibitor Strong CYP 3A4 inducers decrease C_{max} by 58% and AUC by 75% Strong CYP 3A4 inhibitors increase AUC 1.8-fold (no change C_{max})
Venetoclax	Venetoclax	Week 1: 20 mg once daily Week 2: 50 mg once daily Week 3: 100 mg once daily Week 4: 200 mg once daily Week 5: 400 mg once daily Concomitant strong 3A4 inhibitors, reduce dose to 100 mg Concomitant moderate 3A4 inhibitors, reduce dose to 200 mg	Take with a meal and a water Avoid grapefruit, Seville oranges, Star Fruit	Substrate of CYP 3A, P-gp, and BRCP Inhibits CYP 2C8, 2C9, UGT1A1, P-gp, BCRP, and OATP1B1
Duvelisib	Copiktra	25 mg orally twice daily	None	Substrate of CYP 3A4, P-gp, and BCRP Strong CYP 3A4 inhibitors increase C_{max} 1.7-fold and AUC 4-fold Strong CYP 3A4 inducers decrease C_{max} by 66% and AUC by 82% Moderate inhibitor of CYP 3A4
Acalabrutinib	Calquence	100 mg orally twice daily	Avoid taking with proton pump inhibitors Take 2 hours prior to taking an H_2-receptor antagonist Separate from antacids by at least 2 hours Avoid grapefruit, Seville oranges, Star Fruit	Substrate of CYP 3A4 to an active metabolite (ACP-5862), 50% less potent than the parent compound Strong CYP 3A4 inhibitors increase C_{max} by 3.9-fold and AUC by 5.1-fold Strong CYP 3A4 inducers decrease C_{max} by 68% and AUC by 77% Weak inhibitor of CYP 3A4/5, 2C8, and 2C9 Weak inducer of CYP1A2, 2B6, and 3A4

AUC, area under the curve; C_{max}, maximum concentration; CYP, cytochrome P450; Pgp, P-glycoprotein; UGT, uridine 5'-diphospho-glucuronosyltransferase; BRCP, breast cancer resistance protein; OATP, organic-anion-transporting polypeptide.

TABLE 152-7 Monitoring of Oral Targeted Agents in Chronic Lymphocytic Leukemia

Drug	Adverse Reactions	Monitoring Parameters	Comments
Ibrutinib	Common: • Edema • Hypertension • Fatigue • Dizziness • Dermatologic toxicity • Myalagias and arthralgias • Fever • Myelosuppression • Renal toxicity Rare but Serious: • Hemorrhage • Cardiovascular effects: atrial fibrillation, atrial flutter, ventricular tachyarrhythmias • Nonmelanoma skin carcinoma • Tumor lysis syndrome	• CBC for myelosuppression • CMP for renal function and liver function • ECG at baseline if cardiac risk factors	Ibrutinib increases bleeding risk; hold 3-7 days prior to and after procedures Upon initiation, transient increase in lymphocyte count (not progression)
Idelalisib	Common • Myelosuppression • Hepatotoxicity • Diarrhea/Colitis • Fatigue • Edema Rare but serious • Dermatologic toxicity • Gastrointestinal perforation • Pneumonitis	• CBC for myelosuppression • CMP for renal function and liver function • Signs and symptoms of diarrhea/colitis, intestinal perforation • Signs and symptoms of pneumonitis • CMV reactivation	Upon initiation, transient increase in lymphocyte count (not progression) PJP prophylaxis needed
Duvelisib	Common • Edema • Skin rash • Fatigue • Dizziness • Electrolyte abnormalities (hypophosphatemia, hyponatremia, hyperkalemia, hypocalcemia) • Colitis • Diarrhea • Hepatotoxicity • Myelosuppression Rare but serious • Pneumonitis • *Pneumocystis jiroveci* pneumonia • Cytomegalovirus disease	• CBC for myelosuppression • CMP for liver function • Signs and symptoms of CMV reactivation or PJP • Signs and symptoms of diarrhea/colitis, intestinal perforation • Signs and symptoms of pneumonitis	PJP prophylaxis needed
Venetoclax	Common • Myelosuppression • Tumor lysis syndrome • Edema • Dermatologic toxicity • Fatigue • Dizziness • Electrolyte abnormalities (hypocalcemia, hyperkalemia, hypophosphatemia, hyponatremia) • Diarrhea • Nausea • Hepatotoxicity • Myalgias, arthralgias	• CBC for myelosuppression • CMP and uric acid for tumor lysis syndrome, renal toxicity, hepatoxicity	Risk for tumor lysis is based on patients disease burden and rate of dose escalation
Acalabrutinib	Common • Dermatologic toxicity • Diarrhea • Myalgias • Headaches • Fatigue • Infections • Myelosuppression Rare but Serious • Atrial fibrillation and flutter • Hemorrhage	• CBC for myelosuppression • CMP for renal function and liver function • ECG at baseline if cardiac risk factors	Acalabrutinib increases the risk of bleeding; therapy may be held from 3 to 7 days prior to and after surgery.

CBC, complete blood count; CMP, comprehensive metabolic panel; ECG, electrocardiogram; PJP, *Pneumocystis jiroveci* pneumonia.

Combination Therapy

The single-agent activity of fludarabine has led to the incorporation of fludarabine in combination regimens in patients with CLL. The most widely studied combination is fludarabine with cyclophosphamide, which produces complete response rates between 25% and 40% in treatment-naïve patients as compared with 20% to 30% for single-agent fludarabine.[67–72] Although improved response rates and progression-free survival have been reported with fludarabine and cyclophosphamide combinations compared with fludarabine alone, no benefit in overall survival has been observed.

The combination of fludarabine and rituximab has promising activity. Based on in vitro studies that suggested that rituximab is synergistic with fludarabine and cyclophosphamide, investigators evaluated this combination in clinical trials. An uncontrolled trial of fludarabine, cyclophosphamide, and rituximab (FCR) in previously untreated CLL patients reported a complete remission rate of 70%.[92] FCR is also active in previously treated patients, with a complete remission rate of 25%. Results of two phase III trials that compared FCR with fludarabine and cyclophosphamide showed a progression-free survival benefit (30 vs 20 months) in patients treated with FCR in patients with refractory disease and an overall survival benefit (87.2% vs 82.5%) in patients with newly diagnosed disease.[93,94] The results of these phase III trials led to FDA approval of rituximab with fludarabine and cyclophosphamide in CLL. The FDA recently approved subcutaneous rituximab and hyaluronidase (1,600 mg/26,800 units) in combination with fludarabine and cyclophosphamide.[95] Subcutaneous administration of rituximab greatly reduces the time patients spend in an infusion center during their therapy by decreasing rituximab infusion from several hours to 15 minutes. Because the volume of rituximab needed is large, hyaluronidase is a component of the viscous, subcutaneous solution. The hyaluronidase breaks down collagen, increasing the subcutaneous space for rituximab solution and facilitating absorption. A phase Ib study showed that serum concentrations following subcutaneous rituximab were at least as high as following intravenous rituximab. Injection site reactions (injection site swelling, injection site pain), erythema, and rash were more common following subcutaneous administration.

Bendamustine and rituximab (BR) have been combined in two phase II studies in patients with CLL, in the frontline and relapsed setting.[96,97] In the frontline setting, 117 patients were treated with bendamustine 90 mg/m^2 days 1

and 2 and rituximab 375 mg/m^2 IV on day 0 for cycle 1 and then 500 mg/m^2 IV on day 1 for subsequent cycles.[96] Overall, 88% of patients had a clinical response with 23% being complete responses. The median event-free survival was 34 months, with 90% of patients alive at the median follow-up time of 27 months. Patients with del (17p) responded less well, with a 37.5% overall response rate. Grade 3/4 myelosuppression was observed in about 20% of patients. BR is currently being compared to FCR in previously untreated fit patients with CLL. An interim analysis showed overall response rates of 97.8% for both regimens, but the FCR group had a higher complete response rate (47.4% vs 38.1%) and 2-year progression-free survival (85% vs 78.2%, P = 0.041).[97] The advantages of FCR need to be balanced by its higher risk of severe adverse events, particularly neutropenia (81.7% vs 56.8%) and infections (39% vs 25.4%). The risks and benefits of FCR and BR should be discussed with the patient because no overall survival advantage has been reported.

In the relapsed setting, BR was administered as above, with the exception of a lower bendamustine dose of 70 mg/m^2 in 78 patients who had received a median of two prior treatments.[98] The overall response rate was 59%, with 9% of patients having a complete response. With a median follow-up of 24 months, the event-free survival was 14.7 months with a median overall survival of 34 months. About 25% of patients experienced grade 3/4 myelosuppression with three treatment-related deaths related to infection.

Obinutuzumab is a glycoengineered type II anti-CD20 monoclonal antibody that does not induce translocation of CD20 monoclonal antibody complexes or complement-dependent cytotoxicity, but rather stimulates direct cell death via actin reorganization and homotypic adhesion.[98] Obinutuzumab, in combination with chlorambucil, was initially FDA approved in 2013 for patients with previously untreated CLL. A Phase III trial randomized 781 patients to one of three groups: single-agent chlorambucil, obinutuzumab and chlorambucil, or rituximab and chlorambucil. Progression-free survival was increased with obinutuzumab and chlorambucil (26.7 months) as compared to rituximab and chlorambucil (16.3 months) or chlorambucil (11.1 months).[99] Overall survival favored obinutuzumab and chlorambucil compared to chlorambucil monotherapy (hazard ratio 0.41, P = 0.002). Treatment with obinutuzumab and chlorambucil versus rituximab and chlorambucil resulted in longer progression-free survival (hazard ratio 0.39, $P < 0.001$) and higher rates of complete response (70% vs 20.7%). Infusion-related reactions and neutropenia were more common with the obinutuzumab group than rituximab, but the risk of infection was similar.

The combination of ibrutinib and obinutuzumab was FDA approved for patients with previously untreated CLL in January 2019. In a phase III, randomized, open-label study, patients with CLL received obinutuzumab and either ibrutinib or obinutuzumab.[100] Patients in the obinutuzumab and ibrutinib group had significantly longer median progression-free survival as compared to obinutuzumab and chlorambucil (not reached vs 19 months, hazard ratio 0.23, $P < 0.0001$).

Venetoclax in combination with rituximab (VR) has shown advantages in patients with relapsed or refractory CLL.[88] Rituximab helps to mitigate the microenvironment of the CLL cells to promote increased susceptibility to venetoclax. The combination was studied in a phase III trial with 389 patients with relapsed or refractory CLL. Venetoclax dose was escalated over 5 weeks from 20 mg to 400 mg orally once daily and continuing for up to two years. Rituximab was given on day 1 as 375 mg/m^2 with cycle 1 of a 28 day cycle and the 500 mg/m^2 day 1 of cycles 2 through 6. Venetoclax and rituximab was compared to BR. Patients in the VR group had longer 2-year progression-free survival as compared to BR (84.9% vs 36.3%, hazard ratio 0.17, $P < 0.001$). The risk of any grade 3 or 4 toxicity was higher in the VR group (82% vs 70.2%), with an increased risk of neutropenia and tumor lysis. However, BR had a higher risk of febrile neutropenia and infections compared to VR.

In June 2019, the combination of venetoclax and obinutuzumab (VO) was FDA approved for treatment naïve patients.[89] In an open-label, phase III clinical trial comparing VO with chlorambucil plus obinutuzumab (CO), patients treated with VO had a statistically significant improvement in progression-free survival over CO (hazard ratio 0.23-0.53, $P < 0.001$) after a median follow-up of 28.1 months.[103] Obinutuzumab was given in both arms for 6 cycles, with cycle 1 consisting of 100 mg on day 1, 900 mg on day 2, and 1,000 mg on day 15 and cycles 2 through 6 consisting of 1,000 mg on day 1. Each cycle was 28 days. The VO arm initiated venetoclax via standard dose titration starting cycle 1 day 22 and was continued at 400 mg orally daily for 12 cycles. The chlorambucil was given orally at a dose of 0.5 mg/kg on days 1 and 15 for 12 cycles. The risk of grade 3 or 4 adverse events, including tumor lysis syndrome, was similar in the two groups.

Hematopoietic Stem Cell Transplantation

The experience with the use of HSCT in CLL is limited. Patients treated with allogeneic HSCT achieve higher remission rates and appear to have a longer disease-free survival, but is associated with high treatment-related mortality,

which approaches 40%. Contrary to the high mortality reported in most studies, a randomized phase II study of high-risk CLL patients comparing allogeneic and autologous HSCT reported 100-day mortality of 4% in both arms. After 6 years of follow-up, no difference in overall survival (58% autologous and 55% allogeneic) was observed.[91] This low early mortality must be interpreted carefully, given that only 25 carefully selected patients received allogeneic HSCT as compared with 137 who received autologous HSCT. T-cell depletion was performed on the allogeneic grafts, which may reduce 100-day mortality at the cost of increased relapse, infectious complications, or posttransplant lymphoproliferative disorders as a consequence of reduced GVL effect.[101]

Although allogeneic HSCT may offer the potential of cure in CLL, the advanced age of most patients, limited donor availability, and high treatment-related mortality precludes the routine application in the management of this disease. Additionally, the new, target therapies provide additional options for disease control and overall survival advantages, so the role of allogeneic HSCT is further limited. Allogeneic HSCT is a more viable option for younger patients with aggressive disease. Older patients who are not candidates for full-intensity allogeneic HSCT may be candidates for nonmyeloablative allogeneic HSCT.

Summary of Treatment Options

The NCCN guidelines recommend first-line treatment options based on the presence of deletion 17p or *TP53* mutation, age (older or younger than 65) and the presence of significant comorbidities.[62]

Without del(17p) or *TP53* mutation The preferred first-line therapy options for patients younger than 65 years of age with or without significant comorbidities and for patients who are 65 years of age or older with significant comorbidities are ibrutinib (category 1) or venetoclax in combination with obinutuzumab (VO). In patients younger than 65 years of age without significant comorbidities, other first-line treatment options include bendamustine plus an anti-CD20 monoclonal antibody, the combination of fludarabine, cyclophosphamide, and rituximab in patients with IGV-mutated CLL, or fludarabine plus rituximab. In patients with significant comorbidities regardless of age, other first-line treatment options include bendamustine (70 mg/m^2 with potential dose escalation to 90 mg/m^2) or chlorambucil in combination with an anti CD20 monoclonal antibody. In relapsed or refractory disease, therapies include acalabrutinib, ibrutinib, or venetoclax with rituximab (all category 1 recommendations). Many other treatment options, including several novel

targeted therapies (eg, duvelisib, idelalisib), are available for the relapsed or refractory disease setting.

With del(17p) or *TP53* mutations Ibrutinib monotherapy or venetoclax with obinutuzumab (VO) are recommended as first-line treatment options regardless of patient age or comorbidities. For patients with relapsed or refractory disease, preferred treatment options include ibrutinib (if not previously received), acalabrutinib, and venetoclax with rituximab (all category 1 recommendations). Many other treatment options, including several novel targeted therapies (eg, duvelisib, idelalisib), are available for the relapsed or refractory disease setting.

Evaluation of Therapeutic Outcomes

CLL is an incurable disease and the goal of therapy is to achieve and maintain disease remission while minimizing the burden of treatment-related adverse effects. Therefore, patients should not be initiated on therapy unless symptomatic and treatment depends on cytogenetics, age, and comorbidities. Historically, FCR has been the preferred first-line therapy for symptomatic CLL in younger patients without significant comorbidities. With the development of the novel targeted agents, such as ibrutinib, the preferred treatment regimens are shifting to include oral agents. Oral therapy has an expanded role in the second-line setting with agents such as venetoclax and idelalisib. Treatment selection should be based on patient comorbidities, risk for cardiac toxicity, organ function, and side effect profile.

Postclass Engaged Learning Activity—Chronic Myeloid Leukemia (CML)

Conduct a literature search and identify a recently published primary research manuscript and a review/commentary perspective article on the discontinuation of TKI treatment in patients with CML who have developed a sustained and durable response. Provide a brief summary of the process of discontinuing a TKI, how you would monitor a patient, how feasible you believe the process would be to implement in practice, and how you would re-institute treatment if needed. Write a brief summary of the study methods, the major findings, and how this new information might change current practice. This activity is intended to build your literature evaluation skills and ability to critically appraise research manuscripts.

Postclass Engaged Learning Activity—Chronic Lymphocytic Leukemia (CLL)

Conduct a literature search and find a recently published primary research manuscript on the treatment of CLL with venetoclax either as monotherapy or combination therapy. After reading the clinical trial, write a summary of the study methods, major findings, and how this study may change current treatment strategies. This activity is designed to enhance your primary literature searching and literature evaluation skills.

ABBREVIATIONS

ABL	Abelson proto-oncogene
ALL	acute lymphoblastic leukemia
AP	accelerated phase
ATP	adenosine triphosphate
BC	blast crisis

BCR	breakpoint cluster region
BTK	Bruton's tyrosine kinase
CHOP	cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone
CLL	chronic lymphocytic leukemia
CML	chronic myeloid leukemia
CMV	Cytomegalovirus
CNS	central nervous system
CP	chronic phase
CYP	cytochrome P450
Del(17p)	deletion 17p
ERK	extracellular signal-regulated kinase
FCR	fludarabine, cyclophosphamide, rituximab
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
GVHD	graft-versus-host disease
GVL	graft-versus-leukemia (effect)
HLA	human leukocyte antigen
HSCT	hematopoietic stem cell transplantation
Ig	immunoglobulin M
IGHV	immunoglobulin heavy chain gene
IFN-α	interferon alfa
IRIS	International Randomized study of Interferon vs STI571 trial
IS	International scale
MBL	monoclonal B-cell lymphocytosis
mRNA	messenger ribonucleic acid
NCCN	National Comprehensive Cancer Network
PDGFR	platelet-derived growth factor receptor
Ph	Philadelphia chromosome
PI3K	phosphatidylinositol 3-kinase
REMS	Risk Evaluation and Mitigation Strategy
RT-PCR	reverse-transcription polymerase chain reaction
STI	signal transduction inhibitor
TKI	tyrosine kinase inhibitor
WBC	white blood cell
WHO	World Health Organization
ZAP-70	ζ-associated protein 70

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin.* 2019;69:7–34.
2. Corso A, Lazzarino M, Morra E, et al. Chronic myelogenous leukemia and exposure to ionizing radiation—a retrospective study of 443 patients. *Ann Hematol.* 1995;70:79–82.
3. Ichimaru M, Ishimaru T, Belsky JL. Incidence of leukemia in atomic bomb survivors belonging to a fixed cohort in Hiroshima and Nagasaki, 1950-71. Radiation dose, years after exposure, age at exposure, and type of leukemia. *J Radiat Res.* 1978;19:262–282.
4. Borgaonkar DS. Philadelphia-chromosome translocation and chronic myeloid leukaemia. *Lancet.* 1973;1:1250.
5. Stam K, Heisterkamp N, Grosveld G, et al. Evidence of a new chimeric bcr/c-abl mRNA in patients with chronic myelocytic leukemia and the Philadelphia chromosome. *N Engl J Med.* 1985;313:1429–1433.
6. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127:2391–2405.
7. Fialkow PJ, Jacobson RJ, Papayannopoulou T. Chronic myelocytic leukemia: Clonal origin in a stem cell common to the granulocyte, erythrocyte, platelet, and monocyte/macrophage. *Am J Med.* 1977;63:125–130.
8. Sokal JE, Cox EB, Baccarani M, et al. Prognostic discrimination in “good-risk” chronic granulocytic leukemia. *Blood*. 1984;63:789–799.
9. Cortes JE, Kantargian HM. How I treat newly diagnosed chronic phase CML. *Blood*. 2012;120:1390–1397.
10. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2012 Update on diagnosis, monitoring and management. *Am J Hematol.* 2012;87: 1038–1045.
11. Druker BJ, Guilhot F, O’Brien S, et al. Five-year follow-up of patients receiving imatinib for chronic myelogenous leukemia. *N Engl J Med.* 2006;355:2408–2417.
12. National Comprehensive Cancer Network. The NCCN Chronic Myelogenous Leukemia Clinical Practice Guideline (Version 1.2020). 2019. Available at: http://www.nccn.org. Accessed September 24, 2019.

13. Mathisen MS, Kantarjian HM, Cortes J, et al. Practical issues surrounding the explosion of tyrosine kinase inhibitors for the management of chronic myeloid leukemia. *Blood Rev.* 2014;28:179–187.
14. Hehlmann R, Heimpel H, Hasford J, et al. Randomized comparison of busulfan and hydroxyurea in chronic myelogenous leukemia: Prolongation of survival by hydroxyurea. The German CML Study Group. *Blood*. 1993;82:398–407.
15. Preudhamme C, Guillhot J, Nicolini FE, et al. Imatinib plus peginterferon alfa-2a in chronic myeloid leukemia. *N Engl J Med.* 2010;363:2511–2521.
16. Deininger MWN, Druker BJ. Specific targeted therapy at chronic myelogenous leukemia with imatinib. *Pharmacol Rev.* 2003;55:401–423.
17. Deininger M, Buchdunger E, Druker BJ. The development of imatinib as a therapeutic agent for chronic myeloid leukemia. *Blood*. 2005;105:2640–2653.
18. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med.* 2003;348:994–1004.
19. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med.* 2001;344:1031–1037.
20. Hochhaus A, Larson RA, Guilhot F, et al. Long-term outcomes of imatinib treatment for chronic myeloid leukemia. *N Engl J Med.* 2017;376:917–927.
21. Hughes TP, Kaeda J, Branford S, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. *N Engl J Med.* 2003;349:1423–1432.
22. Press RD, Love Z, Tronnes AA, et al. BCR-ABL mRNA levels at and after the time of a complete cytogenetic response (CCR) predict the duration of CCR in imatinib mesylate-treated patients with CML. *Blood*. 2006;107:4250–4256.
23. Baccarani M, Rosti G, Castagnetti F, et al. Comparison of imatinib 400 mg and 800 mg daily in the front-line treatment of high-risk, Philadelphia-positive chronic myeloid leukemia: A European Leukemia Net study. *Blood*. 2009;113:4497–4504.
24. Castagnetti F, Palandri F, Amabile M, et al. Results of high-dose imatinib mesylate in intermediate Sokal risk chronic myeloid leukemia in early chronic phase: A phase 2 trial of the GIMEMA CML Working Party.

Blood. 2009;113:3428–3434.

25. Talpaz M, Silver RT, Druker BJ, et al. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: Results of a phase 2 study. *Blood*. 2002;99:1928–1937.
26. Amadori S, Picardi A, Fazi P, et al. A phase II study of VP-16, intermediate-dose Ara-C and carboplatin (VAC) in advanced acute myelogenous leukemia and blastic chronic myelogenous leukemia. *Leukemia*. 1996;10:766–768.
27. Sawyers CL, Hochhaus A, Feldman E, et al. Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: Results of a phase II study. *Blood*. 2002;99:3530–3539.
28. Milojkovic D, Apperly J. Mechanisms of resistance to imatinib and second-generation tyrosine kinase inhibitors in chronic myeloid leukemia. *Clin Cancer Res.* 2009;15:7519–7527.
29. Nelson RP, Cornetta K, Ward KE, Ramanaju S, Fausel C, Cripe L. Desensitization to imatinib in patients with leukemia. *Ann Allergy Asthma Immunol.* 2006;97:216–222.
30. Talpaz M, Shah NP, Kantarjian H, et al. Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. *N Engl J Med.* 2006;354:2531–2541.
31. Hochhaus A, Kantarjian HM, Baccarani M, et al. Dasatinib induces notable hematologic and cytogenetic responses in chronic-phase chronic myeloid leukemia after failure of imatinib therapy. *Blood*. 2007;109:2303–2309.
32. Kantarjian HM, Pasquini R, Levy V, et al. Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia resistant to imatinib at a dose of 400 to 600 milligrams daily. *Cancer*. 2009;115:4136–4147.
33. Shah NP, Kantarjian HM, Kim DW, et al. Intermittent target inhibition with dasatinib 100 mg once daily preserves efficacy and improves tolerability in imatinib-resistant and -intolerant chronic-phase chronic myeloid leukemia. *J Clin Oncol.* 2008;26:3204–3212.
34. Apperley JF, Cortes JE, Kim DW, et al. Dasatinib in the treatment of chronic myeloid leukemia in accelerated phase after imatinib failure: The START A trial. *J Clin Oncol.* 2009;24:3472–3479.
35. Kantarjian HM, Cortes J, Kim DW, et al. Phase 3 study of dasatinib 140

mg once daily versus 70 mg twice daily in patients with chronic myeloid leukemia in accelerated phase resistant or intolerant to imatinib: 15-Month median follow-up. *Blood*. 2009;113:6322–6329.

36. Cortes J, Kim DW, Martinelli G, et al. Efficacy and safety of dasatinib in imatinib-resistant or -intolerant patients with chronic myeloid leukemia in blast phase. *Leukemia*. 2008;22:2176–2183.
37. Cortes J, Saglio G, Kantarjian HM, et al. Final 5-year results of DASISION: The dasatinib versus imatinib study in treatment-naïve chronic myeloid leukemia patients trial. *J Clin Oncol.* 2016;34:2333–2340.
38. Giles FJ, le Coutre PD, Pinilla-Ibarz J, et al. Nilotinib in imatinib-resistant or imatinib-intolerant patients with chronic myeloid leukemia in chronic phase: 48-Month follow-up results of a phase II study. *Leukemia*. 2013;27:107–112.
39. Le Coutre P, Ottmann OG, Giles F, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is active in patients with imatinib-resistant or -intolerant accelerated phase chronic myelogenous leukemia. *Blood*. 2008;111:1834–1839.
40. Hochhaus A, Saglio G, Hughes TP, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-Year update of the randomized ENESTnd trial. *Leukemia*. 2016;30:1044–1054.
41. Gambacorti-Passerini C, Kantarjian HM, Kim DW, et al. Long-term efficacy and safety of bosutinib in patients with advanced leukemia following resistance/intolerance to imatinib and other tyrosine kinase inhibitors. *Am J Hematol.* 2015;90:755–768.
42. Khoury HJ, Cortes JE, Kantarjian HG, et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib therapy failure. *Blood*. 2012;119:3403–3412.
43. Cortes JE, Gambacorti-Passerini C, Deininger MW, et al. Final 5-year study results of DASISION: The dasatinib versus imatinib study in treatment-naïve chronic myeloid leukemia patients trial. *J Clin Oncol.* 2018;36:231–237.
44. Cortes JE, Kantarjian H, Shah NP, et al. Ponatinib in refractory Philadelphia chromosome-positive leukemias. *N Engl J Med.* 2012;367:2075–2088.
45. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. A phase 2 trial of ponatinib in

Philadelphia chromosome-positive leukemias. *N Engl J Med.* 2013;369:1783–1796.

46. Ponatinib (Iclusig) prescribing information. 2016. Available at: http://iclusig.com/pi/. Accessed June 20, 2016.
47. Cortes JE, Nicolini FE, Wetzler M, et al. Subcutaneous omacetaxine mepesuccinate in patients with chronic-phase chronic myeloid leukemia previously treated with 2 or more tyrosine kinase inhibitors including imatinib. *Clin Lymphoma Myeloma Leuk.* 2013;13:584–591.
48. Cortes J, Lipton JH, Rea D, et al. Phase II study of subcutaneous omacetaxine mepesuccinate after tyrosine kinase inhibitor failure in patients with chronic phase chronic myeloid leukemia with the T315I mutation. *Blood.* 2012;120:2573–2580.
49. Etienne G, Guilhot J, Rea D, et al. Long-term follow-up of the French stop imatinib (STIM1) study in patients with chronic myeloid leukemia. *J Clin Oncol.* 2017;35:298–305.
50. Saussele S, Richter J, Guilhot J, et al. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): A prespecified interim analysis of a prospective, multicenter, non-randomised, trial. *Lancet Oncol.* 2018;19:747–757.
51. Gratwohl A, Brand R, Apperly J, et al. Allogeneic hematopoietic stem cell transplantation for chronic myeloid leukemia in Europe 2006: Transplant activity, long-term data and current results. An analysis by the Chronic Leukemia Working Party of the European Group for the Blood and Marrow Transplantation (EBMT). *Haematologica.* 2006;91:513–521.
52. van Rhee F, Szydlo RM, Hermans J, et al. Long-term results after allogenic bone marrow transplantation for chronic myelogenous leukemia in chronic phase: A report from the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant.* 1997;20:553–560.
53. Deininger M, Schleuning M, Greinix H, et al. The effect of prior exposure to imatinib on transplant-related mortality. *Haematologica.* 2006;91:452–459.
54. Porter D, Levine JE. Graft-versus host disease and graft-versus leukemia after donor leukocyte infusion. *Semin Hematol.* 2006;43:53–61.
55. Hallek M. Chronic lymphocytic leukemia: 2015 Update on diagnosis, risk stratification, and treatment. *Am J Hematol.* 2015;90:446–460.
56. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in

relapsed chronic lymphocytic leukemia. *N Eng J Med.* 2013;369:32–42.

57. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Eng J Med.* 2014;370:997–1007.
58. Landgren O, Albitar M, Ma W, et al. B-cell clones as early markers for chronic lymphocytic leukemia. *N Engl J Med.* 2009;360:659–667.
59. Dohner H, Stilgenbauer S, Benner A, et al. Genetic aberrations and survival in chronic lymphocytic leukemia. *N Engl J Med.* 2000;343:1910–1916.
60. Tam CS, Shanafelt TD, Wierda WG, et al. De novo deletion of 17p13.1 chronic lymphocytic leukemia shows significant clinical heterogeneity: The MD Anderson and Mayo Clinic experience. *Blood*. 2009;114:957–964.
61. Wang L, Lawrence MS, Wan Y, et al. SF3B1 and other novel cancer genes in chronic lymphocytic leukemia. *N Engl J Med.* 2011;365:2497–2506.
62. National Comprehensive Cancer Network. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Clinical Practice Guideline (Version 1.2020). 2019. Available at: http://www.nccn.org. Accessed September 20, 2019.
63. Tsimberidou AS, O'Brien S, Khouri I, et al. Clinical outcomes and prognostic factors in patients with Richter's syndrome treated with chemotherapy or chemoimmunotherapy with or without stem cell transplantation. *J Clin Oncol.* 2006;24:2343–2351.
64. Eisele L, Haddad T, Sellmann L, Durhsen U, Durig J. Expression of CD38 on leukemic B-cells but not on non-leukemic T-cells are comparably stable over time and predict the course of disease in chronic lymphocytic leukemia. *Leuk Res.* 2009;33:775–778.
65. Vroblova V, Smolej L, Vrbacky F, et al. Biological prognostic markers in chronic lymphocytic leukemia. *Acta Medica.* 2009;52:3–8.
66. Rassenti LZ, Huynh L, Toy TL, et al. ZAP-70 compared with immunoglobulin heavy-chain gene mutation status as a predictor of disease progression in chronic lymphocytic leukemia. *N Engl J Med.* 2004;351:893–901.
67. Zenz T, Mertens D, Kuppers R, Dohner H, Stilgenbauer S. From pathogenesis to treatment of chronic lymphocytic leukemia. *Nat Rev Cancer.* 2010;10:37–50.
68. Byrd JC, Jones JJ, Woyach JA, et al. Entering the era of targeted therapy

for chronic lymphocytic leukemia: Impact on the practicing clinician. *J Clin Oncol.* 2014;32:3039–3047.

69. Trialists CLL. Collaborative Group. Chemotherapeutic options in chronic lymphocytic leukemia: A meta-analysis of the randomized trials. *J Natl Cancer Inst.* 1999;91:861–868.
70. Robak T, Blonski JZ, Kasznicki M, et al. Cladribine with or without prednisone in the treatment of previously treated and untreated B-cell chronic lymphocytic leukaemia—updated results of the multicentre study of 378 patients. *Br J Haematol.* 2000;108:357–368.
71. Sorensen JM, Vena DA, Fallavollita A, et al. Treatment of refractory chronic lymphocytic leukemia with fludarabine phosphate via the group C protocol mechanism of the National Cancer Institute: Five-year follow-up report. *J Clin Oncol.* 1997;15:458–465.
72. Rai KR, Peterson BL, Appelbaum FR, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. *N Engl J Med.* 2000;343:1750–1757.
73. Eichhorst BF, Busch R, Schweighofer C, et al. Due to the low infection rates no routine anti-infective prophylaxis is required in younger patients with chronic lymphocytic leukemia during fludarabine-based first line therapy. *Br J Haematol.* 2007;136:63–72.
74. Keating MJ, O'Brien S, Kontoyiannis D, et al. Results of first salvage therapy for patients refractory to a fludarabine regimen in chronic lymphocytic leukemia. *Leuk Lymphoma.* 2002;43:1755–1762.
75. Cheson BD, Rummel MJ. Bendamustine: Rebirth of an old drug. *J Clin Oncol.* 2009;27:1492–1501.
76. Knauf WU, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. *J Clin Oncol.* 2009;27:4378–4384.
77. Hainsworth JD, Litchey S, Barton JH. Bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukaemia: Updated results of a randomized phase III trial. *Br J Haematol.* 2012;159:67–77.
78. Hillmen P, Skotnicki AB, Robak T, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. *J Clin Oncol.* 2007;35:5616–5623.
79. Osterborg A, Karlsson C, Lundin J, Kimby E, Mellstedt H. Strategies in

the management of alemtuzumab-related side effects. *Semin Oncol.* 2006;33(suppl 5):S29–S35.

80. Weirda WG, Kipps TJ, Mayer J, et al. Ofatumumab as a single agent CD20 immunotherapy in fludarabine refractory chronic lymphocytic leukemia: A phase I/II study. *J Clin Oncol.* 2010;28:1749–1755.
81. Byrd JC, Brown JR, O'Brien S; RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphocytic leukemia. *N Eng J Med.* 2014;371:213–223.
82. Byrd JC, Hillmen P, O'Brien SM, et al. Long-term efficacy and safety with ibrutinib (ibr) in previously treated chronic lymphocytic leukemia (CLL): Up to four years follow-up of the RESONATE study. *J Clin Oncol.* 2017;35(15_suppl):7510.
83. O'Brien S, Jones JA, Coutre SE, et al. Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukemia with 17p deletion (RESONATE-17): A phase 2, open-label, multicenter study. *Lancet Oncol.* 2016;17:1409–1418.
84. Barr P, Robak T, Owen CJ, et al. Sustained efficacy and detailed clinical follow-up of first-line ibrutinib treatment in older patients with chronic lymphocytic leukemia: Extended phase 3 results from RESONATE-2. *Haematologica.* 2018;103:1502–1510.
85. Ahn Ie, Underbayev C, Albitar A, et al. Clonal evolution leading to ibrutinib resistance in chronic lymphocytic leukemia. *Blood.* 2017;129:1469–1479.
86. Woyach JA, Ruppert AS, Guinn D, et al. BTKC481S-Mediated resistance to ibrutinib in chronic lymphocytic leukemia. *J Clin Oncol.* 2017;35:1437–1443.
87. Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. *N Engl J Med.* 2016;374:323–332.
88. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med.* 2018;378:1107–1120.
89. Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. *N Engl J Med.* 2016;374:311–322.
90. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: A

multicenter, open-label, phase 2 study. *Lancet Oncol.* 2016;17:768–778.

91. Hillmen P, Robak T, Janssens A, et al. Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with chronic lymphocytic leukemia (COMPLEMENT-1): A randomized, multicenter, open-label phase 3 trial. *Lancet.* 2015;385:1873–1883.
92. Keating MJ, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. *J Clin Oncol.* 2005;23:4079–4088.
93. Robak T, Dmoszynska A, Solal-Céligny P, et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. *J Clin Oncol.* 2010;28:1756–1765.
94. Halleck M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: A randomized, open-labeled, phase 3 trial. *Lancet.* 2010;376:1164–1174.
95. Assouline S, Buccheri V, Delmer A, et al. Pharmacokinetics, safety, and efficacy of subcutaneous versus intravenous rituximab plus chemotherapy as treatment for chronic lymphocytic leukemia (SAWYER): A phase 1b, open-label, randomized controlled non-inferiority trial. *Lancet Haematol.* 2016;3:e128–138.
96. Fischer K, Cramer P, Busche R, et al. Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia. A multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. *J Clin Oncol.* 2012;30:3209–3216.
97. Eichhorst B, Fink AM, Busch R, et al. Frontline chemoimmunotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) shows superior efficacy in comparison to bendamustine (B) and rituximab (R) in previously untreated and physically fit patients with advanced chronic lymphocytic leukemia(CLL): Final analysis of an international, randomized study of the German CLL Study Group (GCLLSG) (CLL10 Study). *Blood*. 2014;124. Abstract e19.
98. Fischer K, Cramer P, Busche R, et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia. A multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. *J Clin Oncol.* 2011;29:3559–3566.

99. Cartron G, deGuibert S, Dilhuydy MS, et al. Obinutuzumab (GA101) in relapsed/refractory chronic lymphocytic leukemia: Final data from the phase 1/2 GAUGUIN study. *Blood*. 2014;124:2196–2202.
100. Moreno C, Greil R, Demirkan F, et al. Ibrutinib + obinutuzumab versus chlroambucil + obinutuzumab as first-line treatment in patients with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL): Results from Phase 3 iLLUMINATE. 2018 ASH Annual Meeting Oral Presentation 691.
101. Delgado J, Milligan DW, Dreger P. Allogeneic hematopoietic cell transplantation for chronic lymphocytic leukemia: Ready for prime time? *Blood*. 2009;114:2581–2588.
102. Flinn IW, Hillmen P, Montillo M, et al. The phase 3 DUO trial: Duvelisib vs ofatumumab in relapsed and refractory CLL/SLL.. *Blood*. Dec 6, 2018;132(23):2446–2455. doi:10.1182/blood-2018-05-850461.
103. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med.* Jun 6, 2019;380(23):2225–2236. doi:10.1056/NEJMoa1815281.
104. Offner F, Robak T, Janssens A, et al. Long-term follow-up of previously untreated patients (pts) with chronic lymphocytic leukemia (CLL) treated with ofatumumab (OFA) and chlorambucil (CHL): Final analysis of the phase 3 COMPLEMENT 1 trial. *J Clin Oncol.* 2019;37(15_suppl):7528.
105. Ghia P, Pluta A, Wach M, et al. ASCEND phase 3 study of acalbrutinib vs investigator’s choice of rituximab plus idelalisib (IDR) or bendamustine (BR) in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) [abstract]. European Hematology Association Congress; 2019: Abstract LB2606.

153

Multiple Myeloma

Amy M. Pick and Kamakshi V. Rao

KEY CONCEPTS

1. Multiple myeloma (MM) is a cancer that develops in plasma cells, leading to excessive production of a monoclonal immunoglobulin.
2. Most patients have skeletal involvement at the time of diagnosis with associated bone pain and fractures. Anemia, hypercalcemia, and renal failure may also be present.
3. Initial therapy for patients with newly diagnosed MM should be personalized based on cytogenetics and tools such as the Mayo Stratification for Myeloma and Risk-Adapted Therapy (mSMART).
4. Primary treatment selection is based on the patient's eligibility for an autologous hematopoietic stem cell transplantation. Immunomodulatory agents and proteasome inhibitors are used over traditional chemotherapy because of higher response rates and survival. The increased response rate is at the expense of significant grade 3 and 4 toxicity, which may include myelosuppression, venous thromboembolism (VTE), and neuropathy depending on the regimen used.
5. Thalidomide, lenalidomide, and pomalidomide are immunomodulatory agents with antiangiogenic and anti-inflammatory activity. Lenalidomide is widely utilized compared to thalidomide due to increased potency and less adverse effects. Pomalidomide is currently only used in relapsed/refractory MM.
6. The proteasome inhibitors, bortezomib, carfilzomib, and ixazomib, are highly active in the treatment of MM, particularly in those with high-risk cytogenetics.
7. Autologous hematopoietic stem cell transplantation (HSCT) is used after induction in patients with reasonably good performance status to maximize

complete remissions and prolong survival. Combining autologous HSCT with allogeneic HSCT is investigational and should be performed within a clinical trial.

8 Maintenance therapies may be used in both transplant-eligible and ineligible patients. Current regimens usually include lenalidomide or bortezomib with the intent of increasing progression-free survival.

9 Bisphosphonates are used to treat bone disease associated with MM, which results in decreased pain and skeletal-related events and improved quality of life.

10 Salvage therapy for patients with relapsed or refractory MM can include any of the prior therapies and depends on the patient's performance status, risk category, and prior treatments used for induction.

Preclass Engaged Learning Activity

Watch the online YouTube video, "What is multiple myeloma" by Khan Academy Medicine. This 10-minute video provides an overview of multiple myeloma, highlighting classic myeloma disease presentation in the patient "Babs the CRAB", myeloma's pathogenesis, and diagnosis. This video increases the students' understanding regarding the COLLECT and ASSESS steps in the patient care process.

INTRODUCTION

1 Multiple myeloma (MM) is a malignancy of plasma cells or immunoglobulin-producing B lymphocytes.[1,2] The cancer is characterized by clonal proliferation and accumulation of a monoclonal immunoglobulin secreted from the plasma cell that can be measured in the plasma or urine. Patients with MM often have osteolytic bone lesions at the time of diagnosis, which is probably related to various bone-mobilizing cytokines secreted from the MM clone and bone marrow stromal cells. Other clinical manifestations include end-organ damage such as renal insufficiency, hypercalcemia, and anemia. The treatment of MM often consists of two- or three-drug combinations incorporating a proteasome inhibitor and immunomodulator. These regimens have improved response rates and outcomes compared to conventional

chemotherapeutic agents. Although therapy is not currently curative, MM continues to be a remarkable example of bench-to-bedside translation in new drug development.

EPIDEMIOLOGY AND ETIOLOGY

In the United States, it is estimated that 32,110 cases of MM were diagnosed in 2019, with 12,960 deaths.[3] It is a disease that affects older adults, with a median age of 69 years at diagnosis.[4] MM occurs more frequently in men and African Americans. Familial clusters of MM have been reported with emerging evidence suggesting a genetic predisposition toward the disease.[5]

Certain environmental factors have been implicated with MM. Radiation exposure has been historically linked to the development of MM with atomic bomb survivors having a five times higher risk of MM. Data suggest that low levels of radiation may also be a risk factor.[6] MM has been associated with exposure to various chemicals including pesticides, aromatic hydrocarbons, and petroleum products used in farming, cleaning works, mining, and other occupational groups working with these chemicals. Although the pathogenesis of MM has not been fully elucidated, multiple genetic mutations have been identified which are involved in the development and proliferation of MM. Research continues to increase our understanding of cellular changes and the supporting bone marrow microenvironment.

PATHOPHYSIOLOGY

MM is a genetically heterogeneous disease characterized by abnormal clonal plasma cell infiltration in the bone marrow. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (ie, asymptomatic) MM may precede active MM. These conditions do not require treatment but do require active monitoring. MGUS is associated with the presence of monoclonal immunoglobulin in the blood (≤3 g/dL [30 g/L]), less than 10% clonal plasma cells in the bone marrow, and the absence of clinical manifestations of MM (eg, end-organ damage).[7,8] The conversion rate of MGUS to MM is about 1% per year. The molecular changes associated with the conversion of MGUS to MM are not clear, but genome-wide studies have identified several candidate genes associated with disease progression.[2,8] Smoldering MM is an advanced premalignant stage that is clinically distinct from MGUS with criteria including

high monoclonal immunoglobulin in the blood (≥3 g/dL [30 g/L]) and 10% to 60% plasma cells in bone marrow with no clinical manifestations of MM. Although patients with smoldering MM have asymptomatic disease, the risk of progression to MM is about 10% per year for the first 5 years after diagnosis, about 3% per year for the next 5 years, and about 1% per year for the next 10 years.[9] Certain cytogenetic characteristics appear to be associated with a higher risk of transformation to active MM including translocation of 4 and 14 (t(4;14)) and deletion of 17p (del (17p)).[8,10] Multiple genetic changes may occur over time leading to more symptomatic disease. Understanding the clinical features of the disease may help clinicians identify which patients are at high-risk for progression from MGUS or smoldering MM to active MM.

MM is characterized by the accumulation of malignant plasma cells in the bone marrow. Both MM and normal plasma cells are produced from differentiated B cells after antigen stimulation. Normal plasma cells will die within days to weeks after differentiation, whereas MM plasma cells are long-lived, with low proliferative activity.[1] MM was thought to originate from a single tumor cells, but it is now believed MM is composed of genetically diverse clones and subclones that originate from one or more stem cells. The malignant plasma cell is involved in the unregulated production of a monoclonal antibody referred to as *M-protein.* MM cells are seldom seen in large quantities in the peripheral blood because of their close interaction with bone marrow stromal cells. MM cells are supported by a nurturing bone marrow microenvironment which promotes the further expansion of myeloma clones. Molecules such as interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF-1), and the transcriptional regulator nuclear factor kappa B (NF-κB) are part of the microenvironment and stimulate clonal growth, disease progression, and promote resistance to therapy (see **Fig. 153-1**).[11] Disruption of the microenvironment is an important strategy for therapy.

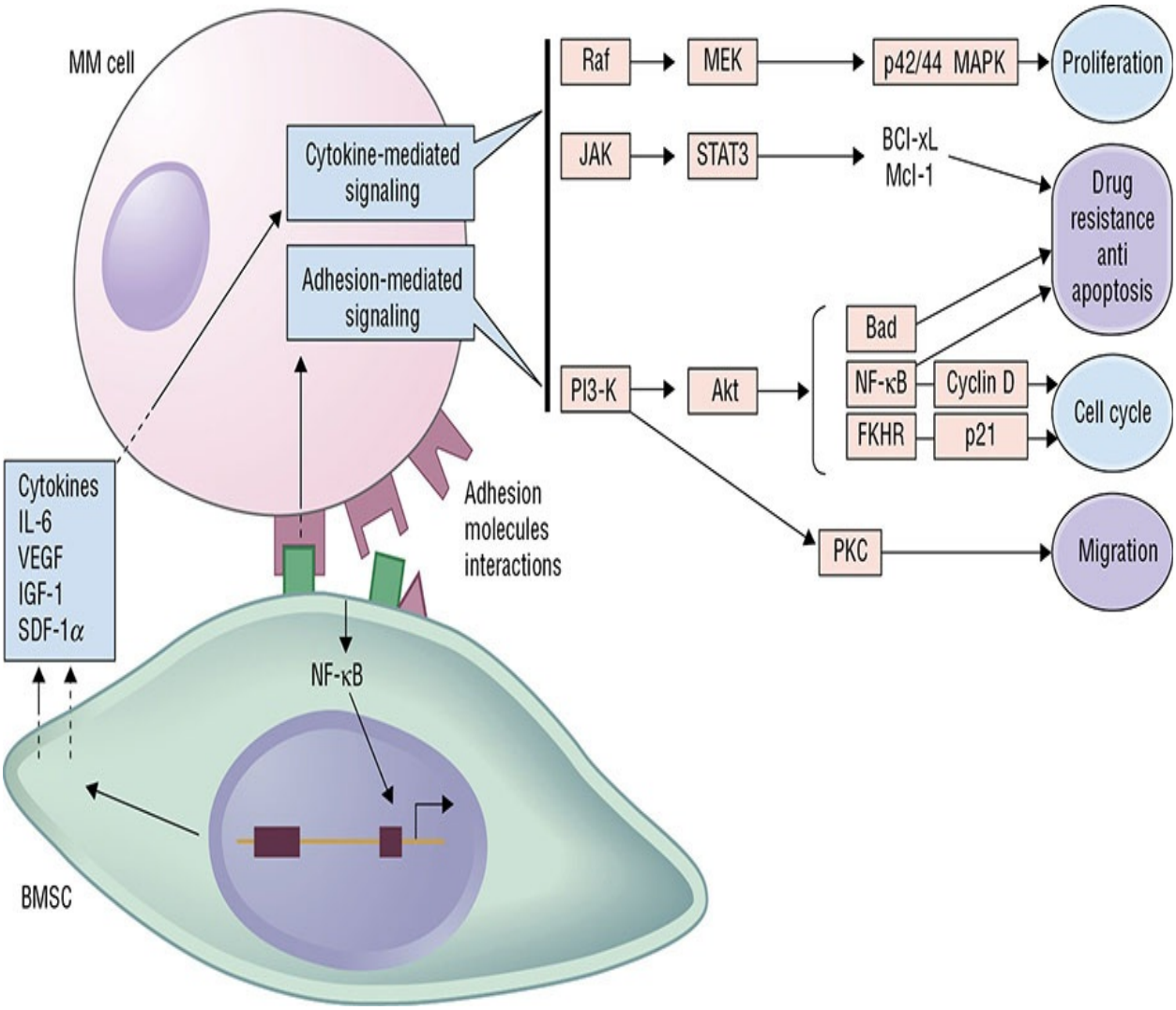


FIGURE 153-1 Pathogenesis of multiple myeloma. Multiple myeloma (MM) cells interact with bone marrow stromal cells (BMSCs) and extracellular matrix proteins via adhesion molecules, triggering adhesion-mediated signaling as well as cytokine production. This triggers cytokine-mediated signaling that provides growth, survival, and antiapoptotic effects as well as development of drug resistance. (*from JL Jameson, AS Fauci, DL Kasper, SL Hauser, DL Longo, J Loscalzo. Harrison's Principles of Internal Medicine, 20th ed. New York: McGraw-Hill; 2019.*)

CLINICAL PRESENTATION

2 The clinical manifestations are related to the effects of the myeloma cell on the bone microenvironment and the unregulated production of the M protein. Most patients with MM present with complaints of bone pain and fatigue at

diagnosis. Initial laboratory evaluation often reveals hypercalcemia, renal insufficiency, anemia, and other abnormalities including β_2-microglobulin that measures tumor burden. Skeletal evaluation shows gross abnormalities in most patients. Bone scans show abnormalities that often include lytic lesions, osteoporosis, and fractures. This group of findings—hyper**c**alcemia, **r**enal insufficiency, **a**nemia, and **b**one lesions—is often referred to by the acronym *CRAB*, and are considered myeloma-defining events and suggest end-organ damage.[1,7] A confirmed diagnosis is defined by a bone marrow biopsy with 10% or more plasma cells, one or more myeloma-defining events, or biomarkers of malignancy.[7,12] Both the National Comprehensive Cancer Network (NCCN) and International Myeloma Working Group (IMWG) have described criteria to diagnose MM.[7,12]

Following the diagnosis of MM, further workup involves analyzing and quantifying the isotype of M-protein present. M-protein is a surrogate marker used to assess treatment response and disease progression. Serum protein and urine electrophoresis and serum and urine immunofixation identify the M-protein isotype secreted.[1] About 60% of patients have intact monoclonal immunoglobulin G (IgG), 20% have monoclonal IgA, and the remaining 20% secrete only monoclonal light chains. Antibodies are composed of two light chains where antigen binds, and two heavy chains. Light-chain immunoglobulins, called Bence Jones proteins, can be secreted by the MM clone and excreted in the urine due to their low molecular weight, resulting in MM-associated renal failure. Serum-free light chains (SFC) may also be measured and these results may provide valuable information on the likelihood of disease progression.

CLINICAL PRESENTATION — Multiple Myeloma

General Criteria

- Most patients present with symptomatic disease

Signs and Symptoms

- Bone pain (fractures, lytic lesions)
- Fatigue (anemia)

- Infection (reduced polyclonal response)
- Neurologic symptoms (nerve compression)
- Polyuria (hypercalcemia)
- Nausea and vomiting (hypercalcemia)

Laboratory Parameters

- Elevated M-protein
  - Plasma electrophoresis
  - Urine electrophoresis
  - Immunofixation
- Elevated serum creatinine
- Hypercalcemia
- Low hemoglobin
- Low albumin
- Elevated β_2-microglobulin
- Elevated C-reactive protein

Bone Marrow

- More than or equal to 10% plasma cells

Imaging

- Skeletal survey with MRI or low-dose CT scan, as indicated

Cytogenetics

- Chromosome 13 deletion
- Translocations of t(4;14), t(11;14) and t(14;16)
- Del (17p)
- Chromosome 1 amplification

Most patients have bone involvement at the time of diagnosis.[7] The effects of

MM on the bone result from the abnormal production of cytokines, including IL-1, IL-6, tumor necrosis factor-α (TNF-α), and the receptor for activation of NF-κB ligand (RANK-L).[6] Bone involvement results from the activation of osteoclasts and inhibition of osteoblastogenesis, and leads to bone destruction and resorption predisposing the patient to pathologic fractures and lytic lesions. Patients with MM are frequently anemic due to infiltration of the bone marrow with the MM clone and poor erythropoietin response. Patients can have clinically important hypercalcemia, which results from calcium mobilization due to bone resorption. Renal failure can occur as a result of high protein load from the monoclonal protein secretion and dehydration.

STAGING AND PROGNOSTIC FACTORS

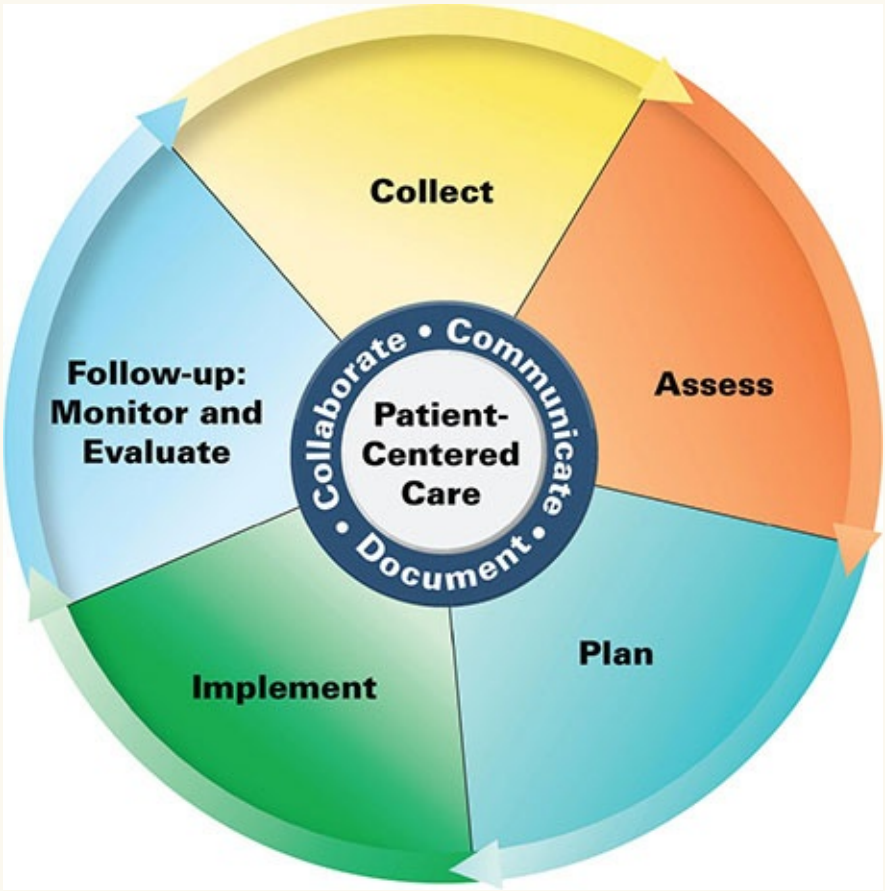
Several clinical staging systems for MM have been developed. The revised International Staging System (R-ISS) incorporates serum β_2-microglobulin, albumin, and lactate dehydrogenase levels, and high-risk chromosomal abnormalities to stage patients.[13] An older staging system, Durie-Salmon, may also be used. It uses hemoglobin, serum calcium, bone involvement, and M-protein to categorize patients into one of three stages. The Durie-Salmon system has variable accuracy in patients undergoing hematopoietic stem cell transplantation (HSCT) and with newer novel therapies.[6] **Table 153-1** shows the R-ISS and median survival times for each stage.

TABLE 153-1 International Staging System for Multiple Myeloma

Stage	Characteristics	Frequency (% of pts)	5-year survival (months)
I	Serum β_2-microglobulin <3.5 mcg/mL (mg/L) and Serum albumin ≥3.5 g/dL (35 g/L) No high-risk cytogenetics Normal LDH	28	82
II	Not stage I or stage III	62	62
III	Serum β_2-microglobulin ≥5.5 mcg/mL (mg/L) and High-risk cytogenetics [t(4;14), t(14;16), or del(17p)] or elevated LDH	10	40

Source: Reprinted, with permission, from Rajkumar SV. Updated Diagnostic Criteria and Staging System for Multiple Myeloma, American Society of Clinical Oncology Educational Book 36 (October 29, 2018) e418-e423.

3 Certain cytogenetic abnormalities have been identified as important prognostic factors. Shortened overall survival has been demonstrated in patients with chromosomal 13 deletion (del 13), translocation of 4 and 14 (t(4;14)), and deletion of 17p (del (17p)).[7] Recent data suggest that the translocation of 11 and 14 may be associated with increased survival. The Mayo Clinic developed a risk-adapted approach, known as the mSMART (Mayo Stratification for Myeloma and Risk-Adapted Therapy), that categorizes patients into three risk groups based on cytogenetics and gene expression profiling: high, intermediate, and standard risk.[14] Therapeutic options and treatment length are then recommended for each risk group. Additional prognostic factors generally represent the underlying pathologic changes associated with MM, including proinflammatory biomarkers (elevated C-reactive protein), tumor load (increased β_2-microglobulin), and dysregulated cellular growth (labeling index and marrow microvessel density).



Patient Care Process for Multiple Myeloma

Collect

- Patient characteristics (eg, age at diagnosis)
- Patient medical history (personal and family)
- Patient comorbidities
- Patient organ function
- Current medications including OTC agents
- Prior treatment history for myeloma, if any
- Objective data
    - Labs including CBC, comprehensive metabolic panel, β_2-microglobulin

- Results of bone scan

Assess

- Indication for therapy
- Impact of comorbidities on tolerance of therapy (eg, diabetes)
- Health literacy and adherence
- Emotional status (eg, presence of anxiety, depression)
- Ability/willingness to pay for antimyeloma treatment options (PO vs IV therapy)

Plan

- Drug therapy regimen (upfront therapy versus transplant versus relapse therapy)
- Supportive care regimen (treatment of anemia, renal dysfunction, use of bone modifying agents)
- Monitoring parameters including efficacy and safety; frequency and timing of follow-up
- Patient education (eg, goal of therapy, schedule of treatments, adherence, self-monitoring)

Implement*

- Provide patient education
- Assess steps needed for insurance approval for oral/at home agents
- Ensure follow-up appointments are scheduled for active and supportive therapy

Follow-up: Monitor and Evaluate

- Response (minimum residual disease, M-protein)
- Safety (skeletal-related events, adverse effects of anti-myeloma therapy)
- Address supportive care concerns
- Adherence

**Collaborate with patient, caregivers, and other healthcare professionals.*

TREATMENT

Desired Outcomes

The primary goal in the treatment of MM is to prolong the patient's survival and improve quality of life. Newly diagnosed MM patients who can tolerate chemotherapy will receive primary therapy where the goal is to achieve at least a major response. In transplant-eligible patients, primary therapy may be followed by transplant and maintenance therapy. The goals of these subsequent phases are to further improve response rates. With the integration of novel agents into therapy, progression-free survival and overall survival have steadily improved, and responses have increased in frequency, depth, and duration. Unfortunately, there is no convincing evidence that patients are cured of their disease.

General Approach

The decision to initiate treatment depends on whether the patient is experiencing symptoms of the disease. Early conventional treatment is not beneficial in patients with MGUS or smoldering MM.[8] Therefore, watchful waiting is the most common practice for patients with smoldering MM and is currently recommended by the NCCN guidelines.[7] However, this treatment paradigm is evolving with the availability of novel agents. Several small published studies, including a phase III randomized trial of 119 high-risk smoldering MM, suggest early treatment with novel agents in patients with high-risk smoldering MM may improve overall survival and delay time-to-progression.[8] Clinical trials are highly encouraged and close monitoring every 3 to 6 months should be considered for patients with high-risk smoldering MM.[7]

4 Initial therapy for symptomatic MM (refer to "Clinical Presentation") depends on whether the patient is a candidate for autologous HSCT (see **Fig. 153-2**). Eligibility for HSCT depends on patient age, renal function, performance status, and comorbidities. All patients with symptomatic MM are treated with primary therapy, with the selected regimen depending on transplant eligibility. Therapies that may compromise stem cell reserve are

avoided in transplant-eligible patients. The selected regimen will often be composed of agents from multiple, distinct classes. Triplet combination regimens are commonly utilized, and often include dexamethasone, a proteasome inhibitor, and an immunomodulatory drug.

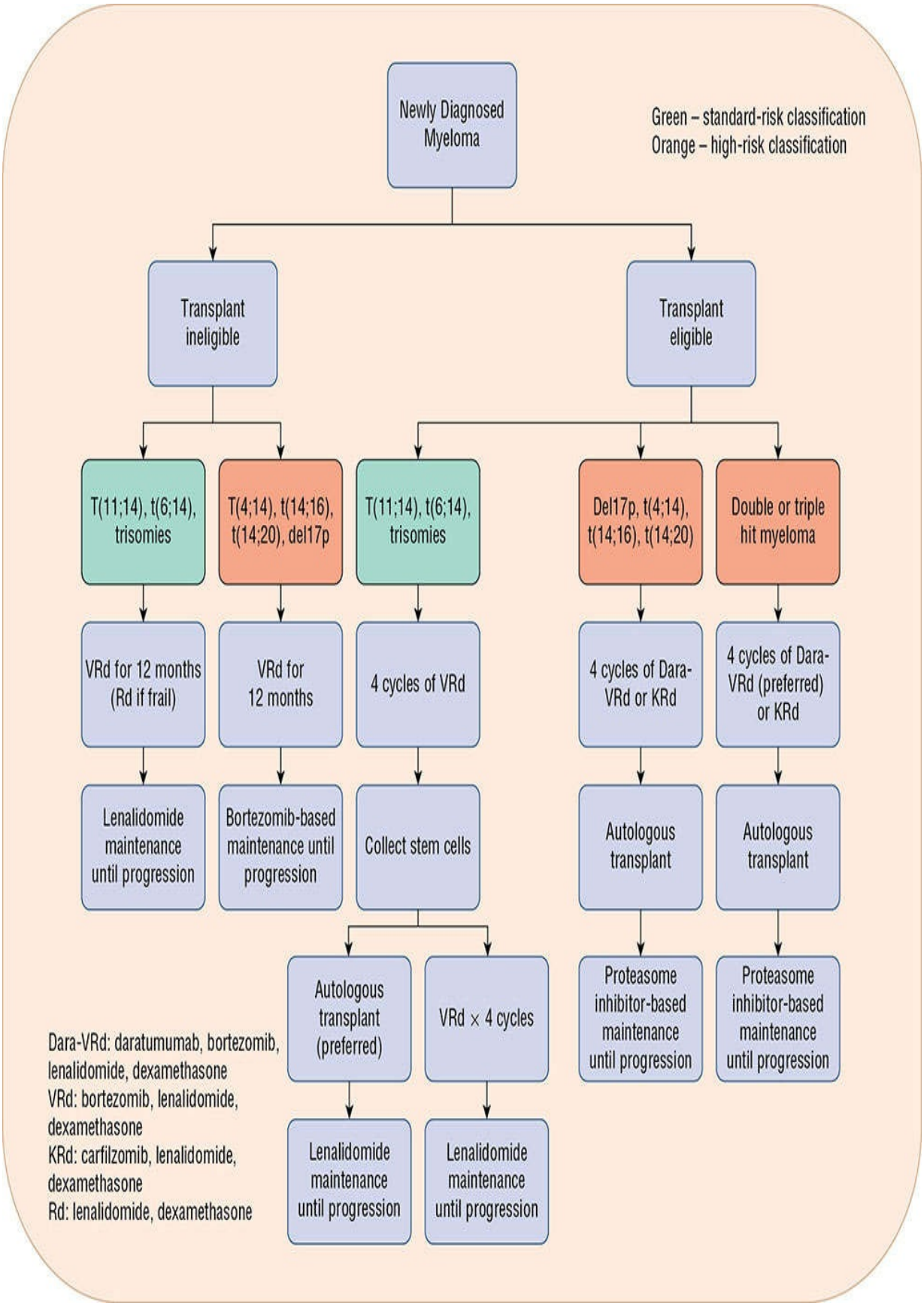

Newly Diagnosed Myeloma
Green – standard-risk classification
Orange – high-risk classification
Transplant ineligible
Transplant eligible
T(11;14), t(6;14), trisomies
T(4;14), t(14;16), t(14;20), del17p
T(11;14), t(6;14), trisomies
Del17p, t(4;14), t(14;16), t(14;20)
Double or triple hit myeloma
VRd for 12 months (Rd if frail)
VRd for 12 months
4 cycles of VRd
4 cycles of Dara-VRd or KRd
4 cycles of Dara-VRd (preferred) or KRd
Lenalidomide maintenance until progression
Bortezomib-based maintenance until progression
Collect stem cells
Autologous transplant
Autologous transplant
Autologous transplant (preferred)
VRd × 4 cycles
Proteasome inhibitor-based maintenance until progression
Proteasome inhibitor-based maintenance until progression
Lenalidomide maintenance until progression
Lenalidomide maintenance until progression
Dara-VRd: daratumumab, bortezomib, lenalidomide, dexamethasone
VRd: bortezomib, lenalidomide, dexamethasone
KRd: carfilzomib, lenalidomide, dexamethasone
Rd: lenalidomide, dexamethasone

FIGURE 153-2 Risk-adapted treatment of multiple myeloma based on eligibility for hematopoietic stem cell transplantation. (*Adapted from mSMART.org. http://www.msmart.org/mm-treatment-guidelines. Accessed 17 December 2019.*)

Primary therapy is usually continued until the desired response is achieved. Patients who are candidates for autologous HSCT will often receive four to six months of therapy before proceeding to hematopoietic stem cell collection, harvesting enough stem cells for two transplants.[7] Most patients undergo autologous HSCT immediately following collection, but some patients may decide to delay the transplant until first relapse. Patients who are not candidates for autologous HSCT usually continue their myeloma therapy or receive maintenance therapy, although the optimal duration of therapy after the desired response is achieved is unknown. Single-agent maintenance therapy, consisting of lenalidomide, may be given in both transplant-eligible and ineligible patients. Guidelines, such as the NCCN and IMWG Guidelines and mSMART treatment recommendations (see Fig. 153-2), may assist the clinician with drug therapy selection.

The IMWG has developed uniform response criteria to assess response to drug therapy in patients with MM.[15] Clinical response to therapy is generally defined by a reduction in serum and urine M-protein by immunofixation and electrophoresis and plasma cells in bone marrow. Numerous response types have been defined including a stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR) and stable disease (SD). The depth-of-response correlates with improved outcomes; a meta-analysis showed a correlation between a complete response and prolonged overall survival.[15,16] Since the depth of response is important, measurements of minimal residual disease with more sensitive assays such as qualitative polymerase chain reaction (Q-PCR) and next generation sequencing have been added to the IMWG Response Criteria. **Table 153-2** describes the most common types of clinical responses.[15]

TABLE 153-2 IMWG Response Criteria in Multiple Myeloma

Standard IMWG response criteria	
Stringent complete response	Complete response as defined below plus normal FLC ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas <5% plasma cells in bone marrow aspirates
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg/24hr
Partial response	≥50% reduction of serum M-protein plus reduction in 24 hours urinary M-protein by ≥90% or to <20 mg per 24 hours; If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein is unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is required
Minimal response	≥25% but ≤49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50% to 89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response or progressive disease
Progressive disease	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in one or more of the following criteria: Serum M-protein (absolute increase must be ≥0.5 g/dL [5 g/L]); Serum M-protein increase ≥1 g/dL (10 g/L), if the lowest M component was ≥ 5g/dL (5 g/L); Urine M-protein (absolute increase must be ≥200 mg/24hr); In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be ≥10 mg/dL [100 mg/L]); In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); Appearance of a new lesion(s), ≥50% increase from nadir in the size of >1 lesion, or ≥50% increase in the longest diameter of a previous lesions >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells/μL [0.2 x 10^9/L]) if this is the only measure of disease

Source: Data from reference 15.

Pharmacotherapy

Treatment of MM is based on the combination of novel agents from two classes of drugs, the immunomodulators and proteasome inhibitors. A three-drug regimen is commonly used in the treatment of MM and often incorporates dexamethasone and a drug from each class. The optimal regimen is not clear because of the lack of head-to-head comparative trials. Several highly active combination regimens are available. These regimens have improved response rates and survival with acceptable but different toxicity profiles compared to conventional regimens previously used in MM. **Tables 153-3** and **153-4** show dosing and monitoring parameters for the commonly used agents in the treatment of MM. Dose reductions in elderly patients and in patients experiencing adverse events are often required.[7]

TABLE 153-3 Dosing of Drugs Used in the Treatment of Multiple Myeloma

Drug (Brand Name)	Dosing	Comments/Special Population
Lenalidomide (Revlimid®)	Induction Therapy 25 mg/day PO on Days 1–21 of a 28-day cycle) Maintenance Therapy 10 mg/day, may be increased to 15 mg/day as tolerated	Adjust dose in renal impairment: 30-60 mL/min (0.5-1.0 mL/s) (10 mg every 24 hours) <30 mL/min (0.5 mL/s) (15 mg every 48 hours) <30 mL/min (0.5 mL/s) (dialysis) (5 mg every 24 hours) *Doses noted above are when used in combination therapy
Pomalidomide (Pomalyst®)	4 mg/day PO for 21 days (28-day cycle)	Mild-to-moderate hepatic impairment (Child-Pugh class A or B): 3 mg/day Severe hepatic impairment (Child-Pugh class C): 2 mg/day
Thalidomide (Thalidomide®)	200 mg/day	Start low in elderly adults; increase dose every 1-3 weeks
Bortezomib (Velcade®)	1.3 mg/m² SQ Days 1, 4, 8, and 11 Every 21 days	Reduce initial dose in hepatic impairment (serum bilirubin >1.5 x ULN) to 0.7 mg/m²
Carfilzomib (Kyprolis®)	20 mg/m2 on day 1 of cycle 1 and then 70 mg/m² on day 8; continue with 70 mg/m² for subsequent doses.	Dosing for relapsed/refractory disease. Alternate dosing when used in upfront treatment (off-label)
Ixazomib (Ninlaro®)	4 mg/day PO Days 1, 8, and 15 Every 28 days	Renal impairment <30 mL/min (0.5 mL/s): 3 mg PO Hepatic impairment serum bilirubin >3 x ULN: 3 mg PO
Daratumumab (Darzalex®)	16 mg/kg (actual body weight) IV weekly x 8 weeks then 16 mg/kg IV every other week x 8 weeks, then 16 mg/kg every 4 weeks until disease progression	
Elotuzumab (Empliciti®)	10 mg/kg IV weekly on days 1, 8, 15, 22 for cycles 1 and 2; dosing changes with subsequent cycles	
Panobinostat (Farydak®)	20 mg PO every other day for 3 doses per week (days 1, 3, 5, 8, 10, 12) of a 21-day cycle	Hepatic impairment serum bilirubin >1-1.5 x ULN: 15 mg PO serum bilirubin >1.5-3 x ULN: 10 mg PO serum bilirubin >3 x ULN: Not recommended

TABLE 153-4 Adverse Reactions and Monitoring Parameters for Drugs Used in the Treatment of Multiple Myeloma

Drug	Adverse Drug Reactions	Monitoring Parameters	Comments
Lenalidomide	Myelosuppression, rash, constipation, VTE, teratogenicity	CBC, LFTs, renal function, REMS Program (pregnancy testing), serum electrolytes and uric acid, thyroid function tests	Adjust dose in renal impairment VTE prophylaxis Secondary malignancies
Pomalidomide	Myelosuppression, rash, VTE, teratogenicity, infection	CBC, LFTs, renal function, REMS Program (pregnancy testing), serum electrolytes and uric acid	Adjust dose in hepatic impairment VTE prophylaxis
Thalidomide	Neuropathy, sedation, constipation, VTE, rash, neutropenia, teratogenicity	CBC, REMS Program (pregnancy testing), serum electrolytes and uric acid	Evening dose to decrease sedation Laxatives VTE prophylaxis
Bortezomib	Myelosuppression, neuropathy, infection including herpes zoster, gastrointestinal	CBC, LFTs, serum electrolytes and uric acid, neurologic examination	Antiviral prophylaxis
Carfilzomib	Myelosuppression, infection including herpes zoster, cardiac toxicity, infusion reactions, renal failure, neuropathy	CBC, LFTs, serum electrolytes and uric acid, renal function	Hydration to reduce risk of renal toxicity and TLS Dexamethasone premedication for infusion reactions Antiviral prophylaxis
Ixazomib	Myelosuppression, rash, neuropathy, infection including herpes zoster, gastrointestinal	CBC, LFTs, serum electrolytes and uric acid, renal function	Antiviral prophylaxis
Daratumumab	Severe infusion reactions, myelosuppression, infections, gastrointestinal,	CBC	Premedicate with acetaminophen, diphenhydramine, methylprednisolone for infusion reactions Oral corticosteroid for 2 days following infusion Inhaled corticosteroids and bronchodilators may be needed for patients with COPD Antiviral prophylaxis which is continued for 3 months after therapy
Elotuzumab	Severe infusion reactions, infections, hepatotoxicity, fatigue	LFTs	Premedicate with acetaminophen, H_1-receptor antagonist (ie, diphenhydramine), H_2-receptor antagonist (ie, ranitidine), dexamethasone for infusion reactions
Panobinostat	Severe gastrointestinal toxicity (vomiting/diarrhea) resulting in dehydration, cardiac toxicity including QTc prolongation, myelosuppression, infection, hepatotoxicity	CBC, LFTs, serum electrolytes and uric acid, ECG	Anti-diarrheals Anti-emetics

CBC, complete blood count; REMS, Risk Evaluation and Mitigation Strategy; VTE, venous thromboembolism.

Conventional Chemotherapy

Conventional chemotherapy incorporating a corticosteroid was once the mainstay for the treatment of MM. Today, these conventional drugs may be

combined with novel agents to improve overall survival. Melphalan and cyclophosphamide are two conventional chemotherapeutic drugs found in selected MM regimens. Newer regimens have largely replaced melphalan-based therapy due to inferior overall survival and melphalan's negative adverse effects on stem cell mobilization.[7] Cyclophosphamide continues to be incorporated in primary therapy for both transplant and nontransplant candidates with either bortezomib or carfilzomib and dexamethasone.

Corticosteroids are the cornerstone in MM therapy. Dexamethasone is incorporated into most treatment regimens, with the dosing being higher than used in the treatment of other diseases. High-dose dexamethasone is associated with a higher risk of infection and central nervous system toxicity so it should be used with caution, particularly in older patients.[17] In current regimens, proteasome inhibitors and immunomodulatory drugs are combined with dexamethasone to maximize initial response rates.[7]

Immunomodulatory Drugs (IMiD)

Immunomodulatory drugs are incorporated into most treatment regimens for MM. Three IMiDs, thalidomide, lenalidomide, and pomalidomide, are approved for the treatment of MM. These drugs are often used in combination with a proteasome inhibitor and dexamethasone for the treatment of primary and relapsed/refractory MM.

5 IMiDs have complex immune effects and appear to block several pathways that are involved in disease progression in MM.[18] While not fully understood, IMiDs have anti-angiogenic and anti-inflammatory properties that directly or indirectly affect the myeloma cell. IMiDs decrease the production of cytokines and growth factors such as IL-6, TNF-α, and VEGF which are believed to have a role in the pathogenesis of the disease. IMiDs may also inhibit nuclear factor-κB (NF-κB) activation, either directly or indirectly via TNF, which results in increased apoptosis of the MM clone.[6] Further discussion of NF-κB can be found in the proteasome inhibitors treatment section. IMiDs also induce IL-2 mediated T-cell proliferation including natural killer cell activity. Figure 153-1 shows the proposed involvement of cytokines on the myeloma cell.

Thalidomide Thalidomide was first used clinically in Europe in the late 1950s as a sedative and antiemetic, but its use was largely abandoned when teratogenicity was reported. Its immunomodulatory effects became evident in the treatment of Hansen disease (leprosy), and it continues to be used for this

rare indication. These clinical benefits are thought to be related to the anti-TNF activity of thalidomide. Recognizing that TNF may be involved in the pathophysiology of MM led researchers to study thalidomide as a treatment for refractory MM in 1999. The observation that thalidomide had activity against myeloma rejuvenated it as an important therapeutic agent.[18]

Although thalidomide was the initial immunomodulatory drug studied in MM, it has been largely replaced by lenalidomide due to increased potency and less adverse effects.[7] Thalidomide may be used in combination therapy for selected patients and circumstances where resources may limit access and affordability of other agents.[7] Adverse effects include dose-limiting peripheral neuropathy, constipation, sedation, fatigue, and rash. Although these toxicities can be problematic, they rarely require discontinuation of thalidomide treatment and can be managed.

A major concern with thalidomide and other IMiDs is the rates of VTEs. The risk of VTE is increased when thalidomide is combined with dexamethasone or anthracycline-based chemotherapy, with the risk of thrombosis reported between 10% and 22%.[19] The underlying mechanism for thrombosis in these patients is unknown, but appears to be multifactorial. The NCCN, American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO) and the IMWG have guidelines for VTE prevention. The guidelines list slightly different recommendations based on the patient's risk for a VTE. The most commonly used drugs used for VTE prophylaxis include aspirin, warfarin, and low-molecular-weight heparin (LMWH). Prophylactic aspirin may be an option for patients at low risk of VTE. High-risk patients, including myeloma patients receiving an IMiD with high-doses of dexamethasone (480 mg/month), should receive LMWH or therapeutic doses of warfarin.[7] Prospective studies are needed to examine the safety and efficacy of direct oral anticoagulants for VTE prophylaxis in MM patients.[20] Studies must also accurately identify which patients with MM are at high-risk for VTE and ensure aspirin alone is sufficient for VTE prophylaxis.[21]

5 **Lenalidomide** Lenalidomide is a potent thalidomide analog and shares a similar mechanism of action to other IMiDs by targeting the microenvironment. Lenalidomide can be used as primary therapy in transplant-eligible or -ineligible patients, in relapsed/refractory MM, and as maintenance therapy following transplant. Lenalidomide is preferred over thalidomide due to an improved toxicity profile. In phase I studies, patients

with relapsed, refractory MM were found to have a maximum tolerated dose of lenalidomide of 25 mg/day, with this dose being the most commonly used dose in subsequent phase II and III studies.[22]

Lenalidomide was FDA approved in 2006 for the treatment of relapsed or refractory MM based on the results of two randomized controlled trials. In both trials, patients were randomized to receive a combination of either lenalidomide (25 mg/day on days 1-21 of a 28-day cycle) and high-dose dexamethasone or an identical lenalidomide placebo and high-dose dexamethasone. In one trial, patients receiving lenalidomide and dexamethasone group had overall response and CR rates of 61% and 14%, respectively, compared with 20% and 0.6% in the dexamethasone alone group ($P < 0.001$).[23] These improved response rates translated into longer median overall survival time in the lenalidomide and dexamethasone group (29.6 vs 20.5 months). Similar results were reported in the second trial.[24] Since then, the combination of lenalidomide and dexamethasone with a third agent has been studied for relapsed/refractory MM. The triplet regimens of lenalidomide, dexamethasone and carfilzomib, ixazomib, elotuzumab, or daratumumab have demonstrated significant progression-free survival benefits resulting in the approval of these regimens for treatment of relapsed/refractory disease.[7,22]

Lenalidomide is also FDA approved for the treatment of newly diagnosed patients with MM. In this setting, the doublet of lenalidomide and dexamethasone was compared with dexamethasone alone. The trial was halted when a planned interim analysis showed the combination to be more active than dexamethasone alone, with increased progression-free survival and overall response rate in the combination arm.[22] Subsequent trials examined the addition of a third agent, bortezomib, to the lenalidomide-dexamethasone regimen. The phase III study reported increased median progression-free survival (43 vs 30 months) and increased overall survival (75 vs 62 months) with the triplet regimen compared to the doublet lenalidomide and dexamethasone.[25] The regimen of bortezomib, lenalidomide, and dexamethasone is a category 1 NCCN recommendation for the primary treatment of MM patients regardless of transplant eligibility.[7] Additional studies are examining lenalidomide-dexamethasone with other proteasome inhibitors and monoclonal antibodies.

The most appropriate dosing of dexamethasone with lenalidomide has also been evaluated. An open-label noninferiority phase III trial addressed this question in untreated patients with MM.[26] Patients were randomized to

lenalidomide plus high-dose dexamethasone (40 mg on days 1-4, 9-12, and 17-20 of each 28-day cycle) compared with lenalidomide plus low-dose dexamethasone (40 mg/week). Patients who received lenalidomide with low-dose dexamethasone had longer 2-year overall survival (87% vs 75%) and less toxicity than those who received lenalidomide with high-dose dexamethasone. This trial was halted after a second interim analysis and patients were allowed to cross-over to the low-dose arm.[26] Patients in the lenalidomide plus high-dose dexamethasone arm had a 26% incidence of VTE compared to a 12% rate in those randomized to the lenalidomide plus low-dose dexamethasone arm.[26] The improved survival in the low-dose dexamethasone arm is likely related to lower mortality from adverse events, particularly VTE. Deaths in the high-dose dexamethasone group usually occurred in the first 4 months and in elderly patients. The low risk of VTE in the lenalidomide plus low-dose dexamethasone arm may allow for VTE prophylaxis with low-dose aspirin, LWMH, or warfarin, depending on the patient's overall VTE risk.[22] Lenalidomide is better tolerated than thalidomide. Lenalidomide causes less neurotoxicity, somnolence, and constipation but more myelosuppression than thalidomide. Patients receiving lenalidomide are at an increased risk of secondary primary malignancies, with patients >74 years receiving maintenance lenalidomide having the highest risk of secondary malignancies at 3 years (17.3% vs 6.5% in the observation group).[27] When used as part of combination therapy, the risk of VTE with lenalidomide is similar to that observed with thalidomide, and VTE prophylaxis is recommended.[7,22] Multiple cycles of lenalidomide can impair stem cell mobilization. The IMWG recommends that transplant-eligible patients receiving lenalidomide have stem cells collected within the first four cycles of therapy.[7] Mobilization with chemotherapy or plerixafor may be utilized if stem cell collection is decreased.

Lenalidomide and other IMiDs are considered teratogenic based on the known teratogenicity of thalidomide. All of the IMiDs have black box warnings for the potential for severe birth defects and embryo-fetal death. The drugs are commercially available through restricted distribution programs and require enrollment into their respective Risk Evaluation and Mitigation Strategy (REMS) programs. The intent is to encourage safe use of the medication and minimize the risk of fetal exposure.

5 **Pomalidomide** Pomalidomide is a third-generation IMiD used in the treatment of myeloma. It is FDA approved in relapsed MM in patients who

have received at least two prior therapies, including lenalidomide and a proteasome inhibitor. Pomalidomide is not approved for first-line therapy. An open-label phase III trial compared pomalidomide and low-dose dexamethasone to pomalidomide and high-dose dexamethasone in patients with relapsed or refractory MM who were refractory to lenalidomide and bortezomib. The primary endpoint of progression-free survival was longer in the low-dose dexamethasone arm as compared with the high-dose dexamethasone combination (4 vs 1.9 months).[28] Median overall survival was also longer in the low-dose dexamethasone arm (12.7 vs 8.1 months).[7] Thus, the combination of pomalidomide and dexamethasone is a NCCN category 1 recommendation for relapsed and refractory MM.[7] Additional studies are examining pomalidomide triplet regimens including monoclonal antibodies and proteasome inhibitors.

Proteasome Inhibitors

Proteasome inhibitors are incorporated into most treatment regimens for MM. Three proteasome inhibitors, bortezomib, carfilzomib, and ixazomib, are approved for the treatment of MM. Bortezomib is the backbone of many regimens and the newer generation drugs seek to improve the toxicity profile, specifically lessening the degree of neuropathy. These drugs are often used in combination with an IMiD, previously discussed, and dexamethasone for the treatment of primary and relapsed/refractory MM.

Proteasome inhibitors inhibit the proteasome and NF-κB activation. The proteasome is a protease complex responsible for degrading cytosolic proteins that are conjugated to ubiquitin. Ubiquitin is an 8.5-kD polypeptide that tags various proteins for destruction.[29] By reversibly binding to the chymotrypsin site in the catalytic core of the 26S proteasome, bortezomib inhibits the degradation of these targeted proteins. Ixazomib is a reversible inhibitor while carfilzomib irreversibly binds to the chymotrypsin site, which explains the differences in pharmacokinetics among the drugs in this class.[30]

As discussed earlier, NF-κB activity is increased in MM. In the cytosol, NF-κB is bound to and is inhibited by IκB. The proteasome degrades IκB. When the proteasome is inhibited, cytosolic concentrations of IκB remain high, and NF-κB is retained in the cytosol as an inactive complex. The resulting inhibition of the NF-κB signal leads to a reduction in cytokine production and growth inhibition of the MM clone. Other proteins involved in cell-cycle regulation and apoptotic signaling that may be affected by proteasome inhibitors include p53 and caspase.[29]

Bortezomib Bortezomib was the first drug in the class of proteasome inhibitors and is the backbone of many regimens used in the treatment of MM. A 2016 Cochrane review concluded bortezomib treatment improves response rates, progression-free survival, and overall survival and should be considered standard of care for the treatment of MM.[31] Bortezomib is extensively studied and is approved as primary therapy for newly diagnosed and relapsed/refractory MM. Bortezomib was initially approved in 2003 under the FDA' accelerated approval process for relapsed or refractory MM in patients who had failed at least two prior therapies. The approval was based on a phase II trial in which refractory MM received 1.3 mg/m^2 of bortezomib twice weekly for 2 weeks followed by 1 week of rest. Patients received up to 8 cycles. The overall response rate was 35% (includes minor responses) with seven (3.6%) patients achieving a CR.[32] Subsequently, a large phase III study (Assessment of Proteasome Inhibition for Extending Remissions [APEX] trial) demonstrated that bortezomib had superior activity compared with high-dose dexamethasone in relapsed MM. Bortezomib-treated patients had higher CR and PR rates (38% vs 18%), longer median time-to-progression (6.2 vs 3.5 months), and improved 1-year overall survival (80% vs 66%) compared with patients receiving dexamethasone.[33] The differences in each of these end points were statistically significant. The results from this study led to expanded FDA approval in 2005 to include patients who had relapsed after one therapy. Numerous trials have examined bortezomib in combination with monoclonal antibodies, immunomodulatory drugs, and/or traditional chemotherapy for relapsed and refractory MM. Various triplet combinations include bortezomib and dexamethasone with lenalidomide, daratumumab, or bendamustine.[7]

6 Bortezomib is used extensively in the primary treatment of MM. As discussed earlier, the triple drug regimen of lenalidomide, bortezomib, and dexamethasone is the preferred treatment regimen for primary therapy in patients regardless of transplant eligibility. The inclusion of bortezomib in three- or four-drug combinations improves response rates and increases progression-free and overall survival. Bortezomib-based therapies may also be preferred in patients with high-risk disease, based on data which suggests that bortezomib may be able to overcome certain cytogenetic abnormalities, including the t(4;14) translocation.[34]

Bortezomib can cause significant toxicity. The most common adverse effects are mild-to-moderate fatigue and gastrointestinal toxicities. Neuropathy occurs frequently and is the most common cause of

discontinuation of therapy. Other important toxicities include thrombocytopenia, fever, neutropenia, and infection. An increased risk of shingles has been reported in bortezomib-treated patients, and the NCCN guidelines recommend herpes zoster prophylaxis.[7] Bortezomib-based therapy is an attractive option for those patients with renal dysfunction since renal dose modifications are not required. Unlike lenalidomide, bortezomib does not affect stem cell mobilization.

Neurotoxicity is a concern with bortezomib. The neurotoxicity may be decreased by modifying the route of administration and dosing schedule of bortezomib. In a phase III trial in relapsed MM, therapeutic equivalence was found between intravenous and subcutaneous routes of administration.[35] In addition, subcutaneous administration offers the potential advantage of administration in patients without IV access, is more convenient, and has a lower risk of peripheral neuropathy. Subcutaneous bortezomib administration is now the preferred route of administration.[7] Dose schedules have also been modified to decrease toxicity-related treatment delays. Once-weekly bortezomib has been compared with twice-weekly dosing with similar overall response rates demonstrated (93% vs 88%), respectively.[7] The once-weekly schedule was associated with fewer dose reductions and the risk of neuropathy was similar.

Carfilzomib Carfilzomib is a second-generation, irreversible proteasome inhibitor approved for patients with relapsed and refractory disease. Its mechanism, higher selectivity for the chymotryptic site of the 20S proteasome, and toxicity profile are distinct compared to bortezomib.[36] The dosing schedule is also different than bortezomib. Carfilzomib is more potent, yet tolerable with two consecutive daily doses or once weekly dosing. Collectively, clinical trials start with carfilzomib 20 mg/m^2 IV over 10 to 30 minutes on the first cycle/week and increase to 27 to 70 mg/m^2 depending on tolerability and dosing frequency.[36,37]

Numerous trials have examined carfilzomib in the treatment of progressive or relapsed myeloma. The ASPIRE trial showed the addition of carfilzomib to a lenalidomide-dexamethasone backbone improved progression-free survival (26.3 vs 17.6 months), median overall survival (48.3 vs 40.4 months), and health-related quality of life without any change in adverse effects.[36] The incidence of neuropathy was similar in both arms.[36] Carfilzomib-dexamethasone was compared to bortezomib-dexamethasone in relapsed/refractory MM in the head-to-head Phase III trial (ENDEAVOR).

The median progression-free survival was improved with carfilzomib as compared to the bortezomib groups (18 vs 9.4 months).[38] A second interim analysis showed that carfilzomib improved median overall survival as compared to bortezomib (47.6 vs 40.0 months).[39] Based on these data, carfilzomib in combination with lenalidomide-dexamethasone or dexamethasone is a NCCN category 1 recommendation for previously treated MM.[7] Additional studies are evaluating carfilzomib with traditional chemotherapy and other novel drugs.

The activity of carfilzomib in combination regimens as first-line treatment is also impressive. Two phase II trials have evaluated carfilzomib in combination with lenalidomide and low-dose dexamethasone and an additional trial has examined carfilzomib with cyclophosphamide and dexamethasone. The overall response rate (VGPR or higher) reported in these trials ranges from 74% to 88%.[7,40] The responses were rapid and increased in depth with additional cycles of therapy. The three-drug regimen containing lenalidomide did not adversely affect stem cell collection but was associated with peripheral neuropathy, which was usually grade 1 or 2 and observed in 23% of patients.[40] The Endurance trial is currently comparing bortezomib-lenalidomide-dexamethasone versus carfilzomib-lenalidomide-dexamethasone. According to the NCCN guidelines, certain carfilzomib-containing regimens may be used for primary therapy, but bortezomib-based regimens are often preferred.[7]

The most mature safety data for carfilzomib come from the compiled results of four phase II studies.[41] The most frequently reported adverse events included fatigue (55%), anemia (47%), nausea (45%), thrombocytopenia (36%), dyspnea (35%), diarrhea (33%), and pyrexia (30%). The most common grade 3 or greater adverse events were thrombocytopenia (23%), anemia (22%), lymphopenia (18%), pneumonia (11%), and neutropenia (10%). Most of these events were manageable. The incidence of peripheral neuropathy is less with the second-generation proteasome inhibitors. The incidence of grade 3 or higher neuropathy was less than 1% in the carfilzomib phase II clinical trials. The ENDEAVOR trial reported a lower risk of grade 2 or higher peripheral neuropathy in patients who received carfilzomib as compared with bortezomib (6% vs 32%).

Carfilzomib is associated with cardiac and pulmonary toxicities. The cardiovascular adverse events include congestive heart failure, hypertension, arrhythmias, and ischemia. A meta-analysis of 24 studies reported the rate of cardiovascular events as 18.1%, with higher doses of carfilzomib (≥45

mg/m^2) associated with higher rates of cardiovascular events.[42] The pulmonary adverse events of dyspnea, cough, respiratory tract infections, and pneumonia are also of concern.[43] Clinicians should monitor patients for carfilzomib-related cardiac and pulmonary symptoms and initiate symptom management when necessary.

Ixazomib Ixazomib is the first oral proteasome inhibitor approved for the treatment of MM. It is given once-weekly as second-line therapy in combination with lenalidomide and dexamethasone. The approval is based on the TOURMALINE-MM1 phase III trial, which showed the addition of ixazomib to lenalidomide and dexamethasone prolonged progression-free survival in patients with relapsed or refractory MM as compared with lenalidomide and dexamethasone alone (20.6 vs 14.7 months; HR 0.742; P = 0.012).[44] The safety profile was similar to the individual agents and included neutropenia, anemia, thrombocytopenia, pneumonia, diarrhea, cutaneous rash, and peripheral neuropathy. Unlike carfilzomib, cardiac toxicity with ixazomib is minimal.[45] A phase I/II trial also examined ixazomib with lenalidomide and dexamethasone in newly diagnosed patients with MM, with 58% of patients having a VGPR or better.[7] A phase III trial is evaluating this combination in newly diagnosed patients with MM. The approval of ixazomib is exciting because it allows for an orally administered triple-drug combination in the management of MM.

Monoclonal Antibodies

Two monoclonal antibodies are FDA approved for the treatment of MM. These monoclonal antibodies are added to a combination drug regimen, with most of the early studies showing efficacy in relapsed and refractory MM.

Daratumumab Daratumumab is an IgG1-κ fully human monoclonal antibody that targets CD38, a glycoprotein highly expressed on MM cells. Accelerated FDA approval for daratumumab in relapsed/refractory MM was granted after two open-label phase II trials of daratumumab showed single-agent activity (overall response rates of 29% and 36%).[46] Subsequent studies confirmed the role of daratumumab in combination therapy. The phase III trial of daratumumab, bortezomib, and dexamethasone reported a higher 12-month progression-free survival as compared to bortezomib and dexamethasone (60.7% vs 26.9%).[46] Similar findings were reported with daratumumab, lenalidomide, and dexamethasone, with a higher 12-month

progression-free survival as compared with lenalidomide and dexamethasone (83.2% vs 60.1%).[46] The combinations of daratumumab, bortezomib and dexamethasone, and daratumumab, lenalidomide and dexamethasone are NCCN category 1 recommendations for patients with relapsed and refractory MM.

Studies are also examining daratumumab combinations in front-line therapy for newly diagnosed MM. Daratumumab has received FDA approval for primary therapy when used in combination in transplant-eligible and -ineligible MM patients. The combination of daratumumab with bortezomib, melphalan, and prednisone was the first regimen approved for newly diagnosed patients with MM who are ineligible for transplant. This approval was based on the phase III trial which showed that the addition of daratumumab to the regimen resulted in a higher overall response rate and a lower risk of disease progression and death as compared to bortezomib, melphalan, and prednisone.[47] Since then additional studies have shown the benefits of daratumumab combination therapy. The three-drug regimen of daratumumab, lenalidomide, and dexamethasone is considered a NCCN category 1 preferred recommendation as primary therapy for nontransplant patients and the four-drug regimen of daratumumab, bortezomib, thalidomide, and dexamethasone may be used as primary therapy for transplant eligible candidates.[7]

Daratumumab is well-tolerated. Infusion-reactions are common, occurring in 48% of patients.[46] Patients should be pre-medicated with a corticosteroid, acetaminophen, and an antihistamine to reduce the risk of a severe infusion reaction. Since daratumumab can interfere with cross-matching and red blood cell antibody screening, blood typing should occur prior to starting therapy. Additional adverse effects include fatigue, thrombocytopenia, anemia, neutropenia and upper respiratory tract infections.

Elotuzumab Elotuzumab is a monoclonal antibody directed against signaling lymphocyte activation molecule family 7 (SLAMF7), which is expressed on myeloma cells.[48] The binding of elotuzumab to SLAMF7 results in cytotoxicity, through various mechanisms including antibody-dependent cellular cytotoxicity. Elotuzumab was evaluated in a phase III trial in combination with lenalidomide and dexamethasone in patients with relapsed and refractory MM. The elotuzumab combination showed improved progression-free survival (19.4 vs 14.9 months) and a higher overall response rate as compared to lenalidomide and dexamethasone.[48] The elotuzumab,

lenalidomide, and dexamethasone regimen is considered a NCCN category 1 recommendation for previously treated patients with MM.[7] Common adverse effects include hematologic toxicities, fatigue, pyrexia, constipation, and cough. Patients should be pre-medicated with dexamethasone, diphenhydramine, ranitidine, and acetaminophen to reduce the risk of an infusion reaction. Infusion reactions occurred in 10% of patients despite premedication, and most of the infusion reactions occurred with the first dose.[48] Patients receiving an elotuzumab-combination should be also monitored for infections because infections are the most common cause of nonrelated myeloma death.

Panobinostat

Panobinostat is an oral inhibitor of histone deacetylase enzymes and has shown activity in MM. Panobinostat was evaluated in a phase III trial in patients with refractory or relapsed MM who had received prior therapy with an IMiD and bortezomib.[49] Patients were randomized to receive bortezomib, dexamethasone, and panobinostat or bortezomib, dexamethasone, and placebo. The addition of panobinostat significantly improved the primary endpoint of progression-free survival by 3.9 months (11.99 vs 8.08 months).[49] No overall survival data has been reported. Serious adverse effects include thrombocytopenia, diarrhea, fatigue, and peripheral neuropathy. The regimen is considered a NCCN category 1 option for the treatment of relapsed/refractory MM who have received at least two prior therapies with an IMiD and bortezomib.[7]

Selinexor

Selinexor is the first in a new class of drugs that inhibits nuclear export of tumor suppressor proteins (TSPs) and exportin 1 (XPO1). The inhibition of XPO1 allows the cell to restore endogenous tumor suppressing proteins resulting in cancer cell apoptosis. Selinexor received accelerated FDA approval in 2019 for use with dexamethasone in patients with relapsed/refractory MM who have received at least four prior therapies, including an anti-CD38 monoclonal antibody (eg, daratumumab). Selinexor is dosed orally at 80 mg on days 1 and 3 of each week. Serious adverse reactions include thrombocytopenia, resulting in potentially fatal hemorrhage and requiring frequent monitoring of platelet counts, neutropenia, nausea, vomiting, diarrhea, weight loss, hyponatremia, and infections.

Initial Therapy

Initial therapy is guided by the NCCN, IMWG, and mSMART recommendations. The combination of bortezomib, lenalidomide, and dexamethasone is frequently used for primary therapy in both transplant eligible and ineligible patients. Daratumumab, carfilzomib and ixazomib-based therapy are additional treatment options for select patients. Treatment decisions are made based on physician preference, patient characteristics, and transplant eligibility. Some experts recommend a risk-adapted approach that personalizes treatment based on cytogenetics and gene expression profiling. The high cost of medications can pose a financial challenge for patients and clinicians must consider the financial implications when selecting a regimen.

Some clinicians may choose therapies based on risk (eg, mSMART). Bortezomib-containing induction regimens are recommended in patients with high-risk cytogenetics (see Fig. 153-2).[14] In this approach, high-risk patients receive a combination of bortezomib, lenalidomide, and dexamethasone as induction therapy. The combination of bortezomib, cyclophosphamide, and dexamethasone or lenalidomide and low-dose dexamethasone is recommended in intermediate- and standard-risk patients. These regimens are continued in transplant-eligible patients for four cycles before transplant, but transplant can be delayed depending on patient preference. Transplant-ineligible patients will receive therapy for about one year and then possibly maintenance therapy.

Autologous Hematopoietic Stem Cell Transplantation

Although MM is a chemosensitive tumor with significant response rates after treatment with conventional chemotherapy, the duration of response is usually short. To improve outcomes with chemotherapy, high-dose chemotherapy regimens with autologous stem cell support have been used after initial induction therapy. The intent of the induction therapy before transplant is to reduce tumor burden. With newer treatment regimens being used for induction, higher rates of quality responses (CR, VGPR, nCR) can be obtained. Recent data suggest that obtaining quality responses during induction improves the outcomes associated with autologous HSCT.[50]

7 Two pivotal, randomized, controlled trials have evaluated the role of high-dose chemotherapy followed by autologous HSCT. In these trials,

previously untreated patients were randomized to induction therapy alone versus the same induction therapy followed by high-dose chemotherapy and autologous HSCT. In 1996, the Intergroupe Francophone du Myelome (IFM) reported results of a trial demonstrating a survival advantage for high-dose chemotherapy with autologous HSCT compared with conventional chemotherapy.[51] In 2003, a second trial comparing chemotherapy alone to high-dose chemotherapy with autologous HSCT showed an increase in complete response rates and overall survival.[52] Since then, several other trials have confirmed the benefit of autologous HSCT when compared to conventional chemotherapy.[53,54] Some experts have questioned the potential value of upfront autologous HSCT in an era of novel induction therapies for myeloma. Four published trials have used myeloma induction regimens with newer or novel therapies.[55–58] Palumbo et al. evaluated an induction regimen of lenalidomide and dexamethasone followed by either chemotherapy (melphalan/prednisone/lenalidomide) or tandem melphalan-based autologous transplants.[55] Results of this trial showed a progression-free survival and overall survival benefit for the autologous transplant arm. In an IFM/DFCI trial, patients received induction therapy with bortezomib, lenalidomide, and dexamethasone, with either upfront or delayed consolidation with autologous HSCT, followed by lenalidomide maintenance therapy. Results of this trial showed that upfront transplant followed by maintenance resulted in significant improvements in progression-free survival.[56] Based on all available data, current recommendations support high-dose chemotherapy and autologous HSCT in patients with a first remission after induction as a level A recommendation.[59]

The optimal timing of autologous HSCT (early vs late) in MM was investigated in three trials. In a landmark trial, patients were randomized to early (within 12 months of diagnosis, $n = 91$) or late transplantation (>12 months after diagnosis, $n = 94$), and no significant difference in 5-year overall survival was observed between the groups.[60] Event-free survival, however, was significantly longer in the early transplantation group (39 vs 13 months). In an analysis that factors in the time without symptoms, treatment, or treatment toxicity (TWisTT), patients receiving early transplantation had a longer time in a state associated with a good quality of life (27.8 vs 22.3 months). The results of this study supported early autologous HSCT because of its effects on event-free survival and quality of life. Since then, two retrospective studies comparing early versus delayed autologous HSCT have been published.[61,62] These studies included MM patients who received either

lenalidomide or thalidomide-based induction regimen, or another novel-therapy based induction regimens. Both trials demonstrated similar time-to-progression and overall survival in the early (within 12 months) and delayed transplant groups. Most recently, the IFM-DFCI study that evaluated autologous HSCT early or late in patients with myeloma demonstrated that upfront autologous HSCT improved the response rates, median progression-free survival, and quality of life, but did not improve overall survival. The results of these evaluations may support the idea that, in the setting of novel therapy, delaying transplant may be feasible for certain low/standard-risk patients, but the lack of rigorous, prospective, randomized data prevents the uniform recommendation to delay transplant. For patients with high-risk disease, current data does not support delaying transplant. Enrollment in clinical trials is highly recommended for most patients when evaluating the appropriate timing of stem cell transplantation in MM.[7]

A specialized form of autologous HSCT, tandem transplantation, involves the use of two separate autologous HSCT procedures separated by a rest period of several months. It was hypothesized that this more intensive approach would lead to improvements in therapeutic outcomes. Since the initial evaluation showing a benefit to the tandem transplant approach, several trials have investigated this approach to therapy. Two large meta-analyses evaluated single versus tandem autologous HSCT in the setting of MM.[63,64] Combined, these meta-analyses included nine individual trials in their evaluations. Both analyses concluded that the use of tandem autologous HSCT was associated with an improvement in response rate but did not result in improvements in event-free survival or overall survival. Of note, though, is that none of the nine trials utilized currently used induction regimens, limiting the data's applicability to current practice. Three trials evaluated single versus tandem autologous HSCT utilizing newer induction regimens.[65–67] Investigators for the European Myeloma Network conducted a study evaluating upfront single versus double autologous HSCT for patients with newly diagnosed myeloma.[65] Patients received induction with bortezomib, cyclophosphamide, and dexamethasone, followed by single or tandem transplant. Results showed a significant improvement in median progression-free survival and 10-year overall survival in favor of tandem transplantation, with benefit clearly being greater in patients with high-risk disease. Conversely, the prospective phase III StaMINA trial from the Bone Marrow Transplant Clinical Trials Network randomized patients following first transplant to either second transplant or consolidative chemotherapy.[66] All

patients received lenalidomide as maintenance therapy. Results from this trial did not show improvement in outcomes associated with tandem transplantation, but there was significant variability in the induction regimens, duration of induction, and definitions of risk levels of disease. In summary, current data does not support the routine use of tandem transplant. Tandem autologous HSCT could be considered in selected patients with high-risk disease, but any such decision would be best evaluated in the context of a clinical trial.

The primary conclusion from the current data on autologous HSCT as consolidation therapy in MM is that it should be used in younger patients with good performance status. Before transplant, all patients should receive induction therapy to reduce tumor burden. A second autologous HSCT is not currently recommended because of higher transplant-related mortality. The Mayo Clinic mSMART guideline recommends autologous HSCT in transplant-eligible intermediate- and high-risk patients after bortezomib-based induction therapy. Standard-risk patients are given the option of autologous HSCT followed by maintenance therapy or continued induction followed by maintenance therapy (see Fig. 153-2).

Maintenance Therapy

8 Even with the advances in induction therapy and autologous HSCT, most patients will eventually progress within 3 to 5 years, suggesting that effective maintenance therapy could control or delay disease progression. The International Myeloma Working Group has published a consensus document on maintenance therapy in MM.[68]

Historically, variable efficacy and high toxicities have been reported with interferon-α (IFN-α) and dexamethasone maintenance, and neither drug can be recommended outside of a clinical trial.[23] IFN-α at one time was considered to be the maintenance drug of choice after autologous HSCT based on data from a randomized trial showing superior progression-free survival and overall survival following autologous HSCT.[69] A meta-analysis supports the benefit of IFN-α maintenance, but the benefit is limited by high toxicity and intolerance.[70] A randomized trial conducted by the Southwest Oncology Group evaluated the benefit of prednisone maintenance therapy in 125 patients.[71] Patients who received high-dose steroids had significantly longer progression-free survival and overall survival at the expense of high toxicity. Although IFN-α or corticosteroid maintenance has not been widely

adopted because of toxicity profile, these therapies served as proof of principle for maintenance therapy and led to trials evaluating thalidomide, lenalidomide, and bortezomib in this setting.

Thalidomide has been studied as maintenance after autologous HSCT. Six trials have evaluated the role of thalidomide maintenance therapy.[72] In all six trials, treatment with thalidomide was associated with improvements in overall response rate, progression-free survival, and event-free survival. Overall survival was improved in three of the six trials. Toxicity assessments showed that patients receiving thalidomide experienced significantly higher rates of clinically significant toxicities, leading to discontinuation of maintenance therapy in a large number of patients. Of note, three of these studies found that in patients who relapsed after transplant, survival after relapse was shorter if they had received prior thalidomide therapy. Additionally, follow-up from the MRC Myeloma IX trial demonstrated that in patients with adverse-risk cytogenetics, the use of maintenance thalidomide resulted in shorter overall survival.[73] Overall, the evidence shows that thalidomide maintenance significantly reduces disease progression and prolongs event-free survival, but the effect on overall survival is unclear. The toxicities associated with thalidomide also make it a less than optimal choice in the maintenance setting.

Lenalidomide has largely replaced thalidomide as maintenance therapy because of its more favorable toxicity profile. Three randomized, controlled trials have investigated the use of lenalidomide maintenance after autologous HSCT.[74–76] In the CALGB 100104 study, 460 patients with myeloma underwent autologous HSCT, after which subjects were randomized to receive placebo or lenalidomide maintenance.[74,75] Interim analysis of the data showed significant improvement in time-to-progression in the lenalidomide arm, which led to unblinding of the study. After unblinding, 86 of 128 patients receiving placebo crossed over to active treatment with lenalidomide. Updated results from the trial, with an average 91 month follow-up, showed sustained improvements in progression-free and overall survival. In the IFM-2005 trial, patients after autologous HSCT received two cycles of lenalidomide consolidation, followed by randomization to either further lenalidomide maintenance or placebo.[76] In this trial, lenalidomide treatment was associated with an improvement in progression-free survival, but overall survival was similar between groups. Finally, the Myeloma XI, in a part of its design, evaluated posttransplant lenalidomide compared to no maintenance therapy.[73] Maintenance therapy with lenalidomide was associated with

prolonged median progression-free survival in patients, regardless of risk stratification. One unique adverse effect noted in these trials was second primary malignancy, including solid tumors, hematologic malignancies, and nonmelanoma skin cancers. These second malignancies occurred at a significantly higher rate as compared to placebo or control arms. Based on these data, the FDA issued a safety announcement to be added to the warning section of the lenalidomide drug labeling. Some practitioners advocate limiting the duration of maintenance lenalidomide to 2 years after transplant in order to minimize risk.[77]

Bortezomib maintenance after autologous HSCT was evaluated in the Phase III HOVON-65/GMMG-HD4 trial.[78] In that study, 833 patients with newly diagnosed myeloma were randomized to receive induction therapy with vincristine/doxorubicin/dexamethasone (VAD) or bortezomib/doxorubicin/dexamethasone (PAD) followed by autologous HSCT. Maintenance for the VAD group consisted of thalidomide, while maintenance for the PAD group consisted of bortezomib. After 2 years of maintenance, CR rates and progression-free survival were improved in the PAD group. At the conclusion of the trial, progression-free survival was improved in the PAD arm. Of note, the improvement in progression-free survival was maintained even in patients with poor cytogenetic risks. Although the design of the trial makes it difficult to determine whether bortezomib inclusion as part of induction or maintenance had the greatest impact, it was thought bortezomib maintenance should be considered, particularly in patients with high-risk cytogenetics.

Ixazomib has recently been studied as maintenance therapy following autologous HSCT. The phase III TOURMALINE-MM3 trial randomized patients to oral ixazomib dosed on days 1, 8, and 15 in 28-day cycles or placebo as maintenance therapy for 2 years.[79] The trial demonstrated that ixazomib maintenance therapy prolonged progression-free survival in newly diagnosed patients who received a single autologous HSCT within 12 months of diagnosis. While lenalidomide is the preferred maintenance medication by the NCCN guidelines, the guidelines recently added ixazomib as an option. Since ixazomib is administered weekly, the convenient dosing may make it the preferred proteasome inhibitor for maintenance therapy. The lack of secondary malignancies and low risk of peripheral neuropathy may make ixazomib a desirable alternative to lenalidomide. Future comparative trials are needed to determine whether ixazomib or lenalidomide should be the preferred maintenance therapy, particularly in patients with high-risk MM.

Given the available data, NCCN and ASTCT do not recommend the use of dexamethasone or IFN-α in the maintenance setting.[7,59] As noted earlier, lenalidomide is the preferred maintenance agent by both the NCCN and ASTCT. Bortezomib and ixazomib are feasible maintenance options for patients with poor risk cytogenetics. The decision to use any of these agents in the maintenance setting must include careful consideration of the benefits and risks.

Allogeneic Hematopoietic Stem Cell Transplantation

Allogeneic HSCT uses a stem cell source other than the patient and is therefore a transplant across immunologic barriers. Unlike autologous HSCT, which is simply a method of increasing the dose intensity of chemotherapy, allogeneic HSCT is a form of immunotherapy. The interest in allogeneic transplantation for MM is based on the use of a stem cell source free of tumor, which may potentially offer longer disease control and possible cure. The major posttransplant complications associated with allogeneic transplants are acute and chronic graft-versus-host disease (GVHD). GVHD may be accompanied by a graft-versus-myeloma effect. The graft-versus-myeloma effect, which is mediated by antitumor effector cells from the GVHD reaction, reduces relapse risk and may offer the patient the best chance for long-term disease-free survival.[80]

Myeloablative allogeneic HSCT has traditionally been associated with a high rate of morbidity and mortality, between 20% and 50%.[81] Historically, allogeneic transplant has been used after patients have received and progressed after an autologous HSCT. Several trials have compared tandem autologous transplants to autologous followed by allogeneic stem cell transplant, although there is wide variability in trial design patient selection, and protocols for the prevention and treatment of GVHD.[59] In all trials to date, no consistent improvement in overall survival or progression-free survival has been reported. Meta-analyses show that allogeneic HSCT may result in a higher CR rate, but this comes at the cost of a higher rate of transplant-related mortality.[82,83]

Allogeneic HSCT may have a role in the management of patients with high-risk disease. Ongoing clinical trials are evaluating the role of allogeneic HSCT in patients with MM who have high-risk cytogenetic characteristics, who are likely to either respond poorly to upfront therapy or who relapse

quickly after upfront therapy or autologous HSCT. There is increasing interest in the use of reduced-intensity conditioning regimens. Based on the available data, upfront myeloablative allogeneic HSCT is not routinely recommended.

Supportive Care

Bone-Modifying Agents

9 Along with anti-MM therapy, supportive care measures are aggressively used to stabilize skeletal abnormalities. Patients with MM have a high rate of bone involvement of their disease. The mechanism of MM-associated bone disease is thought to be mediated through a number of pathways, including IL-6, IL-1, and TNF-α, but the most targeted pathway is that involving receptor activator factor kappa B ligand (RANK-L) and osteoprotegerin (OPG).[16] In normal bone, RANK-L and OPG are both produced by osteoblasts. RANK-L binds to RANK receptors on osteoclasts, to stimulate bone resorption, and to OPG, a “decoy receptor,” to inhibit bone resorption and stimulate bone formation. A balance between RANK-L and OPG is the basis for normal bone remodeling. In MM, an imbalance in normal bone homeostasis leads to increased osteoclast activity and the formation of osteolytic bone lesions which can lead to clinically significant skeletal-related events, including fracture, hypercalcemia, and bone pain. Based on the 2017 ASCO guidelines, clinical indications for bone modifying therapies include hypercalcemia, renal dysfunction, anemia, bone disease. In the absence of these features, patients with >60% plasma cells in the bone marrow or more than one site of bone disease are now recommended for treatment.[84]

Bisphosphonates (ie, zoledronic acid, pamidronate) bind to crystalline calcium in the bone, and are then phagocytized by osteoclasts, leading to osteoclast apoptosis.[85,86] In addition to osteoclast inhibition, bisphosphonates may also promote apoptosis in MM cells. In addition, other potential antimyeloma effects of bisphosphonates include modifying the cytokine microenvironment, inhibiting the adhesion of MM cells to bone marrow matrix cells, and inhibiting angiogenesis.[87]

Pamidronate and zoledronic acid, the two most commonly used bisphosphonates in MM, are usually well tolerated. Flu-like symptoms can occur after the administration of bisphosphonates. Acute renal impairment can occur with both agents and is related to both infusion time and dose. Patients with moderate renal impairment (creatinine clearance: 30-60 mL/min

[0.5-1.0 mL/s]) should have their dose of zoledronic acid adjusted downward by 25% (3 mg).[88] Osteonecrosis of the jaw (ONJ) is characterized by an area of exposed necrotic bone and often affects the mandible and the maxilla, but it can also affect the soft palate. The development of ONJ may be related to dental disease and tooth extraction and is more common with IV bisphosphonates (vs oral) and zoledronic acid (vs pamidronate). The incidence of ONJ is unknown but may be as high as 10% in MM patients receiving zoledronic acid for extended periods of time. A recent meta-analysis found no difference between the bisphosphonate used and the risk of ONJ.[89]

Denosumab is a first monoclonal antibody directed toward RANK-L. By binding to RANK-L, denosumab prevents binding of RANK-L to RANK, reducing osteoclast activity and allowing bone formation and osteoblast function to predominate. A phase III trial evaluated the efficacy and safety of denosumab compared to zoledronic acid in patients with newly diagnosed MM.[90] Results from this study showed denosumab to be noninferior to zoledronic acid in delaying time to first skeletal-related event. Rates of overall survival and ONJ were similar between groups. In an exploratory analysis, denosumab significantly improved median progression-free survival (46.1 vs 35.4 months), which suggests that denosumab may have antimyeloma activity. Of note, renal adverse effects occurred at a higher rate with zoledronic acid. Denosumab does not require dose adjustments for those with impaired renal function.

Relapsed or Refractory Disease

10 The most appropriate therapy for an individual who relapses depends on the type and duration of previous therapies, whether the patient received a transplant, presence or absence of adverse prognostic factors, toxicity of prior therapies (eg, peripheral neuropathy), organ dysfunction (eg, renal impairment), and how much time has elapsed from initial response to relapse.[7] The same drugs used to treat MM initially can also be used as salvage therapy in patients who have relapsed more than 6 months after initial induction therapy.[7] Patients with relapsed or refractory MM can be treated with active agents in combination or single agents used sequentially. With the growing number of highly active agents, combination therapy is more commonly given. The NCCN has twelve category 1 recommendations and lists many other additional regimens.[7] Bortezomib is widely used in relapsed and refractory MM because of its activity in patients with high-risk

cytogenetics. Bortezomib may be used as a single agent or in combination therapy. The addition of dexamethasone, liposomal doxorubicin, panobinostat, lenalidomide, or thalidomide to patients who progress on single-agent bortezomib has been shown to improve response.[50] Interestingly, prior use of IMiDs or high-dose chemotherapy does not appear to affect bortezomib activity in relapsed MM. A phase III trial reported that bortezomib with or without dexamethasone had activity in relapsed or refractory disease despite prior thalidomide therapy or autologous HSCT.[91] Several IMiD combination regimens may also be used in relapsed and refractory MM. Lenalidomide is the IMiD most commonly utilized and has received a category 1 recommendation in relapsed or refractory patients when combined with dexamethasone alone or with carfilzomib and dexamethasone.[7]

Treatment decisions for individual patients with relapsed disease should be personalized based on patient-specific information such as the type of previous therapies, adverse cytogenetics, and end-organ dysfunction. For example, in patients with relapsed MM, the addition of liposomal doxorubicin to bortezomib improves time-to-progression as compared with bortezomib alone, including in patients who had received prior anthracyclines, lenalidomide, and thalidomide.[92] Despite clear progress, most salvage therapies produce less than a 50% response rate, and new drugs and drug combinations are needed.

Questions remain on the optimal timing for autologous HSCT. For patients who are eligible for autologous HSCT and did not receive a transplant as part of initial therapy, autologous HSCT should be considered at first relapse. Although quality of life is higher when autologous HSCT was used as consolidation therapy, overall survival was not different based on the timing of transplant. Salvage autologous HSCT in patients who received a prior autologous HSCT appears to be most beneficial in patients who had a response of greater than 24 months after initial autologous HSCT.[93] In patients with relapsed or refractory MM, autologous HSCT followed by nonmyeloablative allogeneic HSCT has potential benefit but this approach should only be performed as part of a research protocol because of the increased transplant-related mortality.

EVALUATION OF THERAPEUTIC OUTCOMES

As MM is currently an incurable disease, the goals of therapy are to prolong

survival and improve quality of life. Patients with asymptomatic MM are usually followed and not treated. Asymptomatic patients are assessed every 3 to 6 months for disease progression, which would then warrant therapy. Assessment involves measurement of M protein in blood and urine and laboratory tests that include complete blood count, serum creatinine, and calcium. Patients are treated as the disease produces symptoms. Disease response is defined by a decline in M protein. After completion of the initial course of therapy and once a response is obtained, patients should be monitored every 3 months. Bone surveys are performed yearly or as required because of changes in symptoms. Various other tests, including bone marrow biopsy, magnetic resonance imaging, and positron emission tomography, or computed tomography scan, are performed as needed to evaluate disease status.

Postclass Engaged Learning Activity

Create a table with four columns that summarize the (1) anti-myeloma drug name, (2) mechanism of action, (3) major toxicities and counseling points and (4) monitoring parameters. Students should identify key differences among the antimyeloma drugs. This activity increases the students' understanding regarding the PLAN, IMPLEMENT, and MONITOR/EVALUATE steps in the patient care process.

ABBREVIATIONS

ASTCT	American Society for Transplantation and Cellular Therapy
ASCO	American Society of Clinical Oncology
CI	confidence interval
CR	complete remission

IκB	inhibitory factor kappa B
IFN	interferon
IGF-1	insulin-like growth factor
IL	interleukin
IL-6	interleukin-6
IMiD	immunomodulatory drug
HSCT	hematopoietic stem cell transplantation
IFM	Intergroupe Francophone du Myelome
IgG	intact monoclonal immunoglobulin
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
ISS	International Staging System
LMWH	low-molecular-weight heparin
MGUS	monoclonal gammopathy of undetermined significance
MM	multiple myeloma
mSMART	Mayo Stratification for Myeloma and Risk-adapted therapy
MUC-1	mucin-1
NCCN	National Comprehensive Cancer Network
NF-κB	nuclear factor kappa B
ONJ	osteonecrosis of the jaw
OPG	osteoprotegerin
PR	partial response
RANK	receptor activator of nuclear factor-κB
RANK-L	receptor for activation of NF-κB ligand
SFC	Serum free light chains
TNF-α	tumor necrosis factor-α
VEGF	vascular endothelial growth factor
VGPR	very good partial response
VTE	venous thromboembolism

REFERENCES

1. Röllig C, Knop S, Bornhäuser M. Multiple myeloma. *Lancet*. 2015;385: 2197–2208.
2. Morgan GJ, Walker BA, Davies FE. The genetic architecture of multiple myeloma. *Nat Rev Cancer.* 2012;12:335–348.

3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin.* 2019;69:7–34.
4. Surveillance, epidemiology, and end results (SEER) program. SEER stat facts sheets: Myeloma. Available at: http://seer.cancer.gov/statfacts/html/mulmy.html. Accessed December 15, 2019.
5. Landgren O, Kristinsson SY, Goldin LR, et al. Risk of plasma cell and lymphoproliferative disorders among 14621 first-degree relatives of 4458 patients with monoclonal gammopathy of undetermined significance in Sweden. *Blood*. 2009;114:791–795.
6. Munshi NC, Anderson KC. Plasma cell neoplasms. In: Devita VT, Hellman S, Rosenberg SA, eds. *Cancer Principles and Practice of Oncology*. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011:ebook.
7. National Comprehensive Cancer Network. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (Version 2.2020). Available at: http://www.NCCN.org. Accessed December 15, 2019.
8. Mateos MV, Landgren O. MGUS and smoldering multiple myeloma: Diagnosis and epidemiology. *Cancer Treatment and Research*. 2016;169:3–12.
9. Landgren O. Monoclonal gammopathy of undetermined significance and smoldering multiple myeloma: Biological insights and early treatment strategies. *Hematology Am Soc Hematol Educ Program.* 2013;2013:478–487.
10. Rajkumar SV, Gupta V, Fonseca R, et al. Impact of primary molecular cytogenetic abnormalities and risk of progression in smoldering multiple myeloma. *Leukemia*. 2013;27:1738–1744.
11. Ahn IE, Mailankody S, Korde N, Landgren O. Dilemmas in treating smoldering multiple myeloma. *J Clin Oncol.* 2015;33:115–123.
12. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International myeloma working group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol.* 2014;15:e538–e548.
13. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised international staging system for multiple myeloma: A report from International Myeloma Working Group. *J Clin Oncol.* 2015;33:2863–2869.
14. Mikhael JR, Dingli D, Roy V, et al. Management of newly diagnosed symptomatic multiple myeloma: Updated mayo stratification of myeloma

and risk-adapted therapy (mSMART) consensus guidelines 2013. *Mayo Clin Proc.* 2013;88:360–376.

15. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol.* 2016;17:e328–e346.
16. Hanbali A, Hassanein M, Rasheed W, Aljurf M, Alsharif F. The evolution of prognostic factors in multiple myeloma. *Adv Hematol.* 2017;2017:4812637.
17. Facon T, Mary JY, Pegourie BF, et al. Dexamethasone-based regimens versus melphalan-prednisone for elderly multiple myeloma patients ineligible for high-dose therapy. *Blood*. 2006;107:1292–1298.
18. Chang X, Zhu Y, Shi C, Stewart AK. Mechanism of immunomodulatory drugs' action in the treatment of multiple myeloma. *Acta Biochim Biophys Sin.* 2014;46:240–253.
19. Palumbo A, Palladino C. Venous and arterial thrombotic risks with thalidomide: Evidence and practical guidance. *Ther Adv Drug Saf.* 2012;3:255–266.
20. Man L, Morris A, Brown J, Palkimas S, Davidson K. Use of direct oral anticoagulants in patients on immunomodulatory agents. *J Thombo Thrombolysis.* 2017;128:1449.
21. Sanfilippo KM, Luo S, Carson KR, Gage BF. Aspirin may be inadequate thromboprophylaxis in multiple myeloma. *Blood*. 2017;44:298–302.
22. Holstein SA, Suman VJ, McCarthy PL. Update on the role of lenalidomide in patients with multiple myeloma. *Ther Advances Hematol.* 2018;9:175–190.
23. Weber DM, Chen CF, Niesvizky RF, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med.* 2007;347:2133–2142.
24. Dimopoulos M, Spencer AF, Attal MF, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med.* 2009;357:2123–2132.
25. Durie BG, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): A randomised, open-label, phase 3 trial. *Lancet*. 2017;389:519–527.
26. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-

dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: An open-label randomised controlled trial. *Lancet Oncol.* 2010;11:29–37.

27. Jones JR, Cairns DA, Gregory WM, et al. Second malignancies in the context of lenalidomide treatment: An analysis of 2732 myeloma patients enrolled to the myeloma XI trial. *Blood Cancer J.* 2016;6:e506–e506.
28. Miguel JS, Weisel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): A randomised, open-label, phase 3 trial. *Lancet Oncol.* 2013;14:1055–1066.
29. Shah JJ, Orlowski RZ. Proteasome inhibitors in the treatment of multiple myeloma. *Leukemia*. 2009;23:1964–1979.
30. Brayer J, Baz R. The potential of ixazomib, a second-generation proteasome inhibitor, in the treatment of multiple myeloma. *Ther Adv Hematol.* 2017;8:209–220.
31. Scott K, Hayden PJ, Will A, Wheatley K, Coyne I. Bortezomib for the treatment of multiple myeloma. *Cochrane Database Syst Rev.* 2016(4):CD010816.
32. Richardson PG, Barlogie BF, Berenson JF, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. *New Engl J Med.* 2003;348:2609–2617.
33. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *New Engl J Med.* 2005;352:2487–2498.
34. Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-risk cytogenetics: A consensus of the International Myeloma Working Group. *Blood*. 2016;127:2955–2962.
35. Arnulf B, Pylypenko HF, Grosicki SF, et al. Updated survival analysis of a randomized phase III study of subcutaneous versus intravenous bortezomib in patients with relapsed multiple myeloma. *Haematologica*. 2012;97:1925–1928.
36. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *New Engl J Med.* 2015;372:142–152.
37. Moreau P, Mateos MV, Berenson JR, et al. Once weekly versus twice weekly carfilzomib dosing in patients with relapsed and refractory multiple myeloma (A.R.R.O.W.): Interim analysis results of a randomised,

phase 3 study. *Lancet Oncol.* 2018;19:953–964.

38. Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): A randomised, phase 3, open-label, multicentre study. *Lancet Oncol.* 2016;17:27–38.
39. Dimopoulos MA, Goldschmidt H, Niesvizky R, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): An interim overall survival analysis of an open-label, randomised, phase 3 trial. *Lancet Oncol.* 2017;18:1327–1337.
40. Jakubowiak AJ, Dytfeld D, Griffith KA, et al. A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. *Blood*. 2012;120:1801–1809.
41. Siegel D, Martin TF, Nooka AF, et al. Integrated safety profile of single-agent carfilzomib: Experience from 526 patients enrolled in 4 phase II clinical studies. *Haematologica*. 2013;98:1753–1761.
42. Waxman AJ, Clasen S, Hwang W, et al. Carfilzomib-associated cardiovascular adverse events: A systematic review and meta-analysis. *JAMA Oncology*. 2018;4:e174519.
43. Lataifeh AR, Nusair A. Fatal pulmonary toxicity due to carfilzomib (Kyprolis™). *J Oncol Pharm Pract.* 2016;22:720–724.
44. Moreau P, Masszi T, Grzasko N, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med.* 2016;374:1621–1634.
45. Kumar S, Moreau P, Hari P, et al. Management of adverse events associated with ixazomib plus lenalidomide/dexamethasone in relapsed/refractory multiple myeloma. *Br J Haematol.* 2017;178:571–582.
46. Blair HA. Daratumumab: A review in relapsed and/or refractory multiple myeloma. *Drugs*. 2017;77:2013–2024.
47. Mateos M, Dimopoulos MA, Cavo M, et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. *N Engl J Med.* 2018;378:518–528.
48. Lamb YN. Elotuzumab: A review in relapsed and/or refractory multiple myeloma. *Drugs*. 2018;78:1481–1488.
49. San-Miguel JF, Hungria VT, Yoon SS, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: A

multicentre, randomised, double-blind phase 3 trial. *Lancet Oncol.* 2014;15:1195–1206.

50. Rosinol L, Oriol A, Teruel AI, et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pre-transplantation in multiple myeloma: A randomized Phase 3 PETHEMA/GEM study. *Blood*. 2012;120:1589–1596.
51. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. *N Engl J Med.* 1996;335:91–97.
52. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem cell rescue for multiple myeloma. *N Engl J Med.* 2003;348:1875–1883.
53. Blade J, Rosinol L, Sureda A, et al. High dose therapy intensification compared with continued standard chemotherapy in multiple myeloma patients responding to the initial chemotherapy: Long term results from a prospective randomized trial from the Spanish cooperative group PETHEMA. *Blood*. 2005;106:3755–3759.
54. Palumbo A, Bringhen S, Petrucci MT, et al. Intermediate-dose melphalan improves survival of myeloma patients aged 50 to 70: Results of a randomized controlled trial. *Blood*. 2004;104:3052–3057.
55. Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. *N Engl J Med.* 2014;371:895–905.
56. Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. *N Engl J Med.* 2017;376:1311–1320.
57. Gay F, Oliva S, Petrucci MT, et al. Chemotherapy plus lenalidomide versus autologous transplantation, followed by lenalidomide plus prednisone versus lenalidomide maintenance, in patients with multiple myeloma: A randomized, multicenter, phase 3 trial. *Lancet Oncol.* 2015;16:1617–1629.
58. Cavo M, Hajek R, Pantani L, et al. Autologous stem cell transplantation versus bortezomib-melphalan-prednisone for newly diagnosed multiple myeloma: Second interim analysis of the phase 3 EMN02/HO95 study. *Blood*. 2017;130(suppl 1):397.
59. Shah N, Callander N, Ganguly S, et al. Hematopoietic stem cell transplantation for multiple myeloma: Guidelines from the American

Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2015;21:1155–1166.

60. Fermand JP, Ravaud P, Chevaer S, et al. High dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: Up-front or rescue treatment? Results of a multicenter sequential randomized clinical trial *Blood*. 1998;92:3131–3136.
61. Kumar SK, Lacy MQ, Dispenzieri A, et al. Early versus delayed autologous transplantation after immunomodulatory agents based induction therapy in patients with newly diagnosed multiple myeloma. *Cancer*. 2012;118:1585–1592.
62. Dunavin NC, Wei L, Elder P, et al. Early versus delayed autologous stem cell transplant in patients receiving novel therapies for multiple myeloma. *Leuk Lymphoma.* 2013;54:1658–1664.
63. Kumar A, Kharfan-Dabaja MA, Glasmacher A, Djulbegovic B. Tandem versus single autologous hematopoietic cell transplantation for treatment of multiple myeloma: A systematic review and meta-analysis. *J Natl Cancer Inst.* 2009;101:100–106.
64. Neumann-Winter F, Greb A, Borchmann P, et al. First-line tandem high-dose chemotherapy and autologous stem cell transplant versus single high-dose chemotherapy and autologous stem cell transplant in multiple myeloma, a systematic review of controlled studies. *Cochrane Database Syst Rev.* 2012;10:CD004626.
65. Cavo M, Goldschmidt H, Rosinol L, et al. Double vs. single autologous stem cell transplantation for newly diagnosed multiple myeloma: Long-term follow-up (10 years) analysis of randomized phase 3 studies. *Blood*. 2018;132(suppl 1):124.
66. Stadtmauer EA, Pasquini MC, Blackwell B, et al. Autologous transplantation, consolidation, and maintenance therapy in multiple myeloma: Results of the BMT CTN 0702 trial. *J Clin Oncol.* 2019;37:589–597.
67. Cavo M, Gay FM, Patriarca F, et al. Double autologous stem cell transplantation significantly prolongs progression-free survival and overall survival in comparison with single autotransplantation in newly diagnosed multiple myeloma: An analysis of Phase 3 EMN02/HO95 Study. *Blood*. 2017;130(suppl 1):401.
68. Ludwig H, Durie BG, McCarthy P, et al. IMWG consensus on maintenance therapy in multiple myeloma. *Blood*. 2012;119:3003–3015.

69. Mandelli F, Avvisati G, Amadori S, et al. Maintenance treatment with recombinant interferon-alpha 2b in patients with multiple myeloma responding to conventional induction chemotherapy. *N Engl J Med.* 1990;322:1430–1434.
70. Fritz E, Ludwig H. Interferon-alpha treatment in multiple myeloma: Meta-analysis of 30 randomized trials among 3948 patients. *Ann Oncol.* 2000;11:1427–1436.
71. Berenson JR, Crowley JJ, Grogan TM, et al. Maintenance therapy with alternate-day prednisone improves survival in multiple myeloma patients. *Blood*. 2002;99:3163–3168.
72. Sengsayadeth S, Malard F, Savani JB, et al. Posttransplant maintenance therapy in multiple myeloma: The changing landscape. *Blood Cancer J.* 2017;7:e545.
73. Morgan GJ, Gregory WM, Davies FE, et al. The role of maintenance thalidomide therapy in multiple myeloma: MRC Myeloma IX results and meta-analysis. *Blood*. 2012;119:7–15.
74. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem cell transplantation for multiple myeloma. *N Engl J Med.* 2012;366:1770–1781.
75. Holstein SA, Jung SH, Richardson PG, et al. Updated analysis of CALGB (Alliance) 100105 assessing lenalidomide versus placebo maintenance after single autologous stem cell transplantation for multiple myeloma: A randomized, double-blind, phase 3 trial. *Lancet Haematol.* 2017;4:e431–e442.
76. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem cell transplant for multiple myeloma. *N Engl J Med.* 2012;366:1782–1791.
77. Rajkumar SV. Lenalidomide maintenance – perils of a premature denouement. *Nature Reviews*. 2012;9:372–373.
78. Sonneveld P, Schmidt-Wolf I, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: Results of the randomized Phase III Hovon-65/GMMG-HD4 trial. *J Clin Oncol.* 2012;30:2946–2955.
79. Dimopoulos MA, Gay F, Schjesvold F, et al. Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): A double-blind, randomised, placebo-controlled phase 3 trial. Lancet. 2019;393:253–264.

80. Laterveer L, Verdonck LF, Peeters T, et al. Graft-versus-myeloma may overcome the unfavorable effect of deletion of chromosome 13 in multiple myeloma. *Blood*. 2003;101:1201–1202.
81. Bruno B, Giaccone L, Sorasio R, Boccadoro M. Role of allogeneic stem cell transplantation in multiple myeloma. *Semin Hematol.* 2009;46:158–165.
82. Armeson KE, Hill EG, Costa LJ. Tandem autologous vs autologous plus reduced intensity allogeneic transplantation in the upfront management of multiple myeloma: Meta-analysis of trials with biological assignment. *Bone Marrow Transplant.* 2013;48:562–567.
83. Kharfan-Dabaja MA, Hanadani M, Reljic T, et al. Comparative efficacy of tandem autologous versus autologous followed by allogeneic hematopoietic cell transplantation in patients with newly diagnosed multiple myeloma: A systematic review and meta-analysis of randomized controlled trials. *J Hematol Oncol.* 2013;6:2.
84. Anderson K, Ismaila N, Flynn PJ, et al. Role of bone-modifying agents in multiple myeloma: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol.* 2018;36:812–818.
85. Russell RG. Bisphosphonates: From bench to bedside. *Ann N Y Acad Sci.* 2006;1068:367–401.
86. Papapoulos SE. Bisphosphonate actions: Physical chemistry revisited. *Bone*. 2006;38:613–616.
87. Neville-Webbe HL, Holen I, Coleman RE. The anti-tumor activity of bisphosphonates. *Cancer Treat Rev.* 2002;28:305–319.
88. Zometa [package insert]. East Hanover, NJ: Novartis Pharmaceutical Corporation; March 2016.
89. Mhaskar R, Redzepovic J, Wheatley K, et al. Bisphosphonates in multiple myeloma: A network meta-analysis. *Cochrane Database Syst Rev.* 2012;5:CD003188.
90. Raje N, Terpos E, Willenbacher W, et al. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: An international, double-blind, double-dummy, randomised, controlled, phase 3 study. *Lancet Oncol.* 2018;19:370–381.
91. Mikhael JR, Belch AR, Prince HM, et al. High response rates to bortezomib with or without dexamethasone in patients with relapsed or refractory multiple myeloma: Results of a global phase IIIb expanded access programs. *Br J Hematol.* 2009;144:169–175.

92. Rajkumar SV. Multiple Myeloma: 2014 Update on diagnosis, risk-stratification and management. *Am J Hematol.* 2014;89:998–1009.
93. Lemieux E, Hulin C, Caillot D, et al. Autologous stem cell transplant: An effective salvage therapy in multiple myeloma. *Biol Blood Marrow Transplant*. 2013;19:445–449.

Myelodysplastic Syndromes

Jill S. Bates

KEY CONCEPTS

1. Myelodysplastic syndromes (MDS) primarily affect elderly adults.
2. The exact cause of MDS is unknown and is probably multifactorial. MDS have been associated with host-specific characteristics, environmental, lifestyle, and therapeutic exposures.
3. Genomic instability drives MDS development and progression. The clonal population of cells manifested as MDS results from enhanced self-renewal of a hematopoietic stem cell or acquisition of self-renewal in a progenitor cell, increased proliferative capacity in the abnormal clone, impaired cell differentiation, evasion of immune regulation, and antiapoptotic mechanisms in the disease-sustaining cell.
4. Most patients with MDS present with fatigue, infection, bleeding/bruising, lethargy, or other symptoms related to cytopenias.
5. The prognosis of patients with MDS is variable and depends on the biology of the MDS and host characteristics. Overall survival time ranges from a few months to several years and is most accurately estimated with the International Prognostic Scoring System—Revised (IPSS-R).
6. The goals of therapy for MDS are to change the natural history of the disease, reduce the number of red blood cell transfusions, and improve quality of life.
7. Lenalidomide should be considered for patients with MDS that harbors a del(5q) clone and is particularly beneficial in those with symptomatic anemia.
8. Patients with lower-risk MDS and symptomatic anemia who have a serum erythropoietin level ≤500 mU/mL (U/L) are suitable candidates for an erythropoietin stimulating agent with or without growth factor support.

9. A subset of lower-risk MDS patients respond well to antithymocyte globulin (ie, immunosuppressive therapy), which is most effective in patients who have a hypocellular marrow, MDS that expresses HLA DR15 with trisomy 8 as the sole cytogenetic abnormality, refractory anemia, and are younger than 60 years old.
10. Further evaluation is required to determine optimal hypomethylating agent treatment regimens.
11. Allogeneic hematopoietic stem cell transplantation offers potentially curative therapy to patients with MDS who have a donor and are healthy enough for the procedure.

Preclass Engaged Learning Activity

Create a table. On the x-axis of the grid, create the following columns: name of drug, target, dosing, and top three counseling points. Beginning in row 2 and column 1, create the following y-axis labels in column 1: lenalidomide, antithymocyte globulin (equine), cyclosporine, azacitidine, and decitabine. Fill in the table.

Name of drug	Target	Dosing	Top 3 counseling points
Lenalidomide			
Antithymocyte globulin (equine)			
Cyclosporine			
Azacitidine			
Decitabine			

INTRODUCTION

Myelodysplastic syndromes (MDS) are a heterogeneous group of myeloid stem cell disorders, which are clonal in nature and characterized by ineffective hematopoiesis with morphologic dysplasia in hematopoietic cells and peripheral

cytopenia(s).[1] About one-third of patients with MDS will have a disease course that progresses to acute myeloid leukemia (AML).[1] The diagnostic criteria for MDS is the presence of bone marrow dysplasia in at least 10% of cells in one or more of three major bone marrow lineages.[1] Additionally, a diagnosis of MDS can be achieved if 5% to 19% blasts or an MDS-associated karyotype is noted in the bone marrow.[1–3] The clinical course of patients with MDS varies from a slowly progressing, indolent disease, to more aggressive disease characterized by excess bone marrow blasts and rapid progression to AML.[2,3]

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

Renal Cell Carcinoma

Daniel J. Crona and Amber B. Cipriani

KEY CONCEPTS

1. Renal cell carcinoma (RCC) predominantly occurs later in life, with about 70% of all cases diagnosed between the ages of 55 and 84 years.
2. Established risk factors for RCC include smoking, obesity, hypertension, and inherited susceptibility.
3. Inactivation of the von Hippel-Lindau tumor suppressor gene (*VHL*) is the hallmark of the most common type of RCC, the clear cell histologic subtype.
4. More than 50% of RCC cases are diagnosed by incidental findings on routine imaging for unrelated reasons.
5. The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) Criteria classifies patients into favorable-, intermediate-, and poor-risk groups based on five clinical factors, and can predict survival among both untreated patients and those treated with immunotherapy and/or targeted agents.
6. Surgical excision of the primary tumor, either by radical or partial nephrectomy, is the preferred treatment modality for patients with stage I-III RCC, but some patients with stage IV disease may also benefit from surgery.
7. Historically, immunotherapy (interleukin [IL]-2 and interferon [IFN]-α) were considered preferred first-line therapies for metastatic RCC (mRCC), but have largely been replaced by immune checkpoint inhibitors and targeted agents because of their improved efficacy and tolerability.
8. First-line treatment options for mRCC are chosen based on patient-specific factors and include small molecule tyrosine kinase inhibitors (sunitinib, pazopanib, axitinib, cabozantinib), an mTOR inhibitor (temsirolimus) and

immune checkpoint inhibitors (ipilimumab plus nivolumab and pembrolizumab plus axitinib).

9. In patients who progress after first-line treatment, the multikinase inhibitors sorafenib, cabozantinib, axitinib, and lenvatinib (in combination with everolimus) are the preferred options. Immunotherapy with nivolumab has also demonstrated clinical efficacy in the second-line setting, and combination immunotherapy with a multikinase inhibitor (eg, pembrolizumab plus axitinib) is an option.

Preclass Engaged Learning Activity

Create summary tables to show the appropriate treatment of advanced and metastatic renal cell carcinoma (RCC) in different patient groups. This first summary table should include factors included in the Memorial Sloan Kettering Cancer Center (MSKCC) prognostic scoring tool, and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) Criteria prognostic scoring tool. The summary table should also include how these respective prognostic tools stratify patients into favorable/low-, intermediate- and poor-risk categories. Next, create a summary table with first-line and second-line pharmacotherapeutic options for patients with advanced and metastatic RCC. This summary table should include both orally and intravenously administered pharmacotherapeutic options. The intent of this preclass learning activity is to help students practice their skills in the Collect and Assess steps of the patient care process and apply them to patients with advanced and metastatic RCC.

INTRODUCTION

Renal cell carcinoma (RCC) represents about 2% to 4% of all adult malignancies and is the most common type of malignancy of the kidney and renal pelvis. Until a decade ago, there were few treatment options, and those that were available had modest activity and were poorly tolerated by patients. However, treatment for the disease has been revolutionized by targeted agents and immunotherapies that were developed based on an increased understanding of RCC pathophysiology. Clear cell is the predominant histologic subtype of RCC (about 80% of all cases), and is characterized by the inactivation of the von Hippel-

Lindau (*VHL*) tumor suppressor gene located on chromosome 3p25. *VHL* inactivation leads to increased production of growth factors, such as vascular endothelial growth factor (VEGF), transforming growth factor (TGF), platelet-derived growth factor (PDGF), and others responsible for angiogenesis and cell growth.[1] Prior to 2005, the primary therapeutic option for patients with advanced or metastatic RCC (mRCC) after nephrectomy was immunotherapy (high-dose interleukin-2 or interferon-α), which induced few durable responses and caused high rates of severe toxicities. However, nine targeted drugs have been approved as first- or second-line therapy for RCC in recent years: axitinib, bevacizumab, cabozantinib, everolimus, lenvatinib (in combination with everolimus), pazopanib, sorafenib, sunitinib, and temsirolimus.[2–9] Each drug is an example of targeted therapy against growth factors important in the pathophysiology of RCC, and has yielded much needed progress in a disease with few therapeutic options. Additionally, immune checkpoint inhibitors, such as avelumab, ipilimumab, nivolumab and pembrolizumab, have emerged as treatment options with novel mechanisms of action and toxicity profiles. RCC serves as an example of the rational development of targeted agents based on knowledge of tumor biology and molecular signaling pathways for the treatment of other malignancies.

The complete chapter, learning objectives, and other resources can be found at **www.pharmacotherapyonline.com.**

156

Melanoma

Cindy L. O'Bryant, Jamie C. Poust, and Christina M. Davis

KEY CONCEPTS

1. Cutaneous melanoma is an increasingly common malignancy that can be cured if detected early. Public education about screening and early detection is one strategy to control the increase in incidence and the mortality associated with cutaneous melanoma.
2. Surgical resection can cure patients with early-stage melanoma.
3. Adjuvant therapy should be considered in patients with locally advanced disease; recommended options include IFN-α_{2b}, ipilimumab, nivolumab, pembrolizumab, BRAF/MEK inhibitors, and clinical trial.
4. Chemotherapy and biochemotherapy offers limited benefit in the treatment of metastatic melanoma.
5. Advances in immunotherapy with ipilimumab, nivolumab, the combination of ipilimumab/nivolumab and pembrolizumab have led to durable responses in patients with metastatic melanoma and have significantly influenced overall survival.
6. Immune-related toxicities associated with immunotherapy can be severe and life-threatening. Consequently, the use of these agents warrants appropriate patient selection, close monitoring and toxicity management by an experienced healthcare team.
7. As the biology of melanoma has been further delineated, a growing number of potential targets for drug therapy have been identified. BRAF mutations occur in up to 70% of melanoma patients. The use of combination BRAF and MEK inhibitors improves overall survival in patients with this mutation.
8. Treatment of melanoma is determined by many factors. As the number of treatment options for patients with metastatic melanoma grows, it will be

important to consider disease- and patient-related aspects when determining appropriate therapy.

Preclass Engaged Learning Activity

Review educational materials regarding skin self-exams created by at least two skin/cancer-related professional organizations. Assess the level of understanding and ease of use from a patient perspective for each. Then perform your own skin self-exam using the ABCDE rule to identify any new or suspicious spots on your skin. This activity will enhance student understanding regarding the COLLECT and ASSESS steps in the patient care process.

INTRODUCTION

Skin cancer is the most common malignancy worldwide and is associated with chronic ultraviolet (UV) exposure. The two types of skin cancer are nonmelanoma skin cancers (NMSCs) and melanoma. Although NMSCs are the most common malignancy of the skin, cutaneous melanoma accounts for up to 75% of all skin cancer-related deaths. Melanoma cases are increasing globally with the highest rates found in Australia, New Zealand, North America, and Northern Europe.[1] Melanoma is the fifth most common cancer in the United States.[2] The incidence of melanoma has rapidly increased in the United States over the last 30 years, and has increased an average of 1.5% each year over the last decade.[2] When detected early, patients generally have a good prognosis. Skin cancer prevention and screening have a major impact on public health, as well as the success of treatment for those individuals diagnosed with both NMSC and melanoma. Skin cancers tend to occur more frequently in older individuals with a median age of diagnosis 64 years old.[1] Therefore, as the population continues to age, effective strategies to prevent, detect, and treat individuals with these cancers are necessary. An understanding of the biology of melanoma has led to the development of therapies targeted toward somatic mutations and the immune response, which have shown improved outcomes in patients with advanced melanoma.

EPIDEMIOLOGY

In the United States, it is estimated that 100,350 cases of melanoma will be diagnosed in 2019, accounting for 6,850 deaths.[3] The overall incidence is greater in men than women, but rates are higher in women before the age of 50. Risk also varies with ethnicity, with most melanoma cases occurring in non-Hispanic whites.[3] Childhood and adolescent melanoma account for only 1% of new melanoma cases each year but is the most common skin cancer in individuals younger than 20 years old. Adolescents between the age of 15 and 19 have the highest rates of melanoma compared to younger children. The majority of childhood and adolescent melanoma occur in females and non-Hispanic white patients.[4] From the 1970s to the early 2000s, the incidence of melanoma in those younger than 20 years old increased by 2% to 3% per year, but data from 2004 to 2010 show a decrease of 11.6% per year.[2,4]

Survival rates for both adult and pediatric patients with melanoma have gradually increased over the past four decades. The 5-year relative survival rate is 91.8% for all stages of melanoma, but survival declines to 22.5% in patients with more advanced disease.[2] Over the last decade, the death rate from melanoma has been declining around 1% per year in adults greater than 50 years of age and 2.6% per year in adults younger than 50.[2,3]

A number of patient-specific and environmental factors have been identified (see **Table 156-1**), and it is likely these factors alone, or in combination, increase the risk of cutaneous melanoma.

TABLE 156-1 Risk Factors for Melanoma

Patient-Specific Risk Factors
Adulthood (age older than 15 years)
History of cutaneous melanoma
Dysplastic nevi
High density of common nevi and atypical nevi
Cutaneous melanoma in first-degree relative
Immunodeficiency or immunosuppression
High degree of freckling
Sunburns easily or tans rarely
Blonde or red hair
Blue, green, or gray eyes
Socioeconomic status (higher > lower)
Race (Caucasians > Hispanics > African Americans)
External Risk Factors
Intense, intermittent sun exposures
History of sunburn
More than four painful sunburns before age 15 years
Recreational sun exposure

Both UVB and UVA are known carcinogens and are related to the development of melanoma. Caucasians with fair-colored hair (red or blond), light-colored eyes (blue or green), high degrees of freckling, and those who have a tendency to burn, and rarely tan with sun exposure, appear to be especially at risk. Clinical and epidemiologic research shows a higher rate of melanoma in those who have extensive or repeated intense UV and sun exposure.[5] Intermittent, intense sun exposure, blistering sunburns, tanning bed use, and the time of life when exposed to the sun are critical factors for the development of cutaneous melanoma.[1,6] The risk of melanoma seems to be greater during childhood and adolescence and lower in adults who have had chronic sun exposure, without a history of burning, and those with occupational exposure. The risk with sunlight and UV radiation seems to be greatest during childhood and adolescence and is more hazardous than exposure during adult life.

A significant risk factor for melanoma is the number and size of melanocytic nevi (pigmented lesions or moles) on the body. The formation of these nevi has been shown to be directly related to cumulative sun exposure. The relative risk of developing melanoma increases with the number of typical nevi on an individual. A second risk factor is the presence of atypical melanocytic nevi. Atypical nevi may progress from a normal nevus or be dysplastic from the onset. Up to 20% of melanomas develop from atypical nevi. Congenital melanocytic nevi may be present at birth or within the first few months of life, and the associated risk of melanoma increases with size.[1,4]

Other risk factors in the development of melanoma include immunodeficiency (either inherited or acquired), a personal history of NMSC or melanoma skin cancer, and a diagnosis of xeroderma pigmentosum, a rare skin disorder. Patients with these risk factors often have more aggressive disease and have been shown to have a poor prognosis.[1,4,7]

It is estimated that up to 10% of cases of melanoma are associated with family history. Familial atypical multiple mole syndrome (FAMMM) or dysplastic nevus syndrome is a hereditary disease characterized by the presence of more than 50 combined common and atypical moles plus a first- or second-degree relative with melanoma. It is an autosomal dominant disease and accounts for about 1% of melanoma cases.[8] Patients with FAMMM syndrome are at considerable risk for developing melanoma which increases with age. FAMMM syndrome is associated with mutations in the *CDKN2A* gene.[4,8] *CDKN2A* encodes two distinct proteins: p16, an inhibitor of cyclin-dependent kinase 4 and 6, and p14ARF which inhibits p53 degradation. Mutations in *CDKN2A* result in increased proliferation and decreased apoptosis.[8] The frequencies of *CDKN2A* mutations vary in melanoma but are more commonly associated in individuals with familial inheritance patterns, young age at diagnosis, and pancreatic cancer.[8]

ETIOLOGY

Melanoma arises from the melanocytes in the basal layer of the epidermis. DNA damage, most commonly a result of UV radiation, leads to cellular mutations that transform the cell, uncontrolled proliferation, and the formation of tumors. The identification of these genetic alterations has led to the recognition of molecular subgroups of melanoma and more focused drug development for treatment.

One of the major signaling pathways associated with the development of melanoma is the mitogen-activated protein kinase pathway (MAPK), which mediates receptor tyrosine kinases, resulting in activation of RAS and downstream BRAF. Activating *BRAF* mutations are the most common somatic genetic event in human melanoma, occurring in 25% to 70% of melanoma patients and primarily noted by a single point mutation at residue V600. The V600E mutation, a valine is substituted for glutamic acid at codon 600 is the most common point mutation but the V600K mutation may also occur at this residue. *BRAF* mutations are associated with younger age at diagnosis, intermittent sun exposure, and superficial spreading melanoma.[1]

Upstream of BRAF, mutations in *NRAS,* and c-*Kit* have also been found as molecular drivers in the development of melanoma. Mutations in *NRAS* are found in up to 25% of patients. These tumors are associated with chronic sun exposure, more advanced disease at diagnosis, high-growth rates, and shorter survival times than those with *BRAF* mutations.[1] c-*Kit* is a transmembrane receptor tyrosine kinase which, when activated, signals the MAPK and phosphatidyl-inositol-3-OH kinase (PI3K) pathways, resulting in transcription and cell proliferation. Mutations in c-*Kit* are commonly found in acral and mucosal melanomas.[6]

Other genetic alterations involved in the development of melanoma include *MITF* (microphthalmia-associated transcription factor) and *MCIR* (melanocortin 1 receptor gene). *MITF* is a gene important to the survival of melanocytes and when mutated acts as an oncogene.[9] *MCIR* is prevalent in individuals with melanoma and signals through the MITF pathway. It is involved in melanin synthesis and is associated with the red hair and fair skin phenotype.

PATHOPHYSIOLOGY

Melanomas most often arise within epidermal melanocytes of the skin, although they can also arise from noncutaneous melanocytes. During fetal development, melanocytes migrate over a predictable route to a variety of sites within the body including the skin, uveal tract, meninges, and ectodermal mucosa. Melanocytes synthesize melanin to protect various tissues, such as the skin, from UV damage and reach the keratinocytes in the upper layers of the epidermis via dendrites. Primary melanoma can arise in any area of the body with melanocytes. Cutaneous melanoma is the most frequent site constituting 90% of all melanomas. Other sites of primary melanoma include the eye (uveal melanoma), the mucosa, and in some cases, as metastatic disease with an unknown primary site.[10]

The pathogenesis of human melanoma involves a series of morphologic stages: melanocytic atypia, atypical melanocytic hyperplasia, radial growth phase, vertical growth phase with or without in-transit metastasis, regional lymph node metastatic melanoma, and distant metastatic melanoma. Melanoma gains the potential for metastasis formation with the onset of a vertical growth phase. Therefore, the thickness of a primary melanoma is an important prognostic factor and is used in the staging classification of cutaneous melanoma. As the disease progresses, melanoma cells increase the production of certain growth factors and cytokines which, in turn, activate cellular growth and

survival pathways including the MAPK, PI3K/AKT, and mammalian target of rapamycin (mTOR). Understanding the biology of melanoma has provided targets for innovative drug therapy.

The role of the immune system in the development of melanoma is well documented and spontaneous cancer regressions associated with host immunity have been reported.[11] Melanoma cells evade the immune system by exploiting immune checkpoints. Immune checkpoint receptors such as cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed death-1 (PD-1) are found on the surface of activated T cells and when bound to a ligand inhibit the function of the T cell. In the case of PD-1, when interferon is released by T-cell recognition of the melanoma cell, janus-kinase (JAK) and signal-transducer-and-activator-of-transcription (STAT) are upregulated leading to increased expression of programmed cell death ligand 1 (PD-L1) on the melanoma cell surface. When PD-L1 binds PD-1, the T cell becomes inactivated and the antitumor immune response is inhibited.[1]

HISTOLOGIC SUBTYPES

Cutaneous melanomas are categorized by growth patterns. Four major histologic subtypes, or growth patterns of primary cutaneous melanoma, have been identified: superficial spreading melanoma (SSM), nodular melanoma, lentigo maligna melanoma (LMM), and acral lentiginous melanoma (ALM). While these subtypes do not directly correlate with clinical outcomes, it is important for diagnosis and histopathological identification.

SSM is the most common histological type of cutaneous melanoma, accounting for about 75% of all melanomas and is associated with intense, intermittent sun exposure. Early in lesion development, SSM is flat, growing radially before vertically. SSM evolves slowly, typically over 1 to 5 years. As the lesion progresses it may become raised or ulcerated. The borders are often irregular and asymmetrical as the lesion progresses and may vary in color (blue, black, brown, pink, or other colors). SSMs may occur at any anatomic site on the body but are more commonly seen on the back in men, and on the legs in women.[12] The average age of a diagnosis of SSM is 50 years old. These lesions can be linked to mutations in *BRAF*.

Nodular melanoma is the second most common growth pattern of melanoma, occurring in 15% to 30% of patients. Since nodular melanoma is a pure vertical growth phase disease, it is more aggressive and develops more rapidly than other subtypes.[12] Nodular melanomas are often dark blue–black and uniform in color

with a shiny surface, although a small percentage of nodular melanomas are amelanotic and have a fleshy appearance. Nodular melanomas are raised and often symmetric. Although they can occur at any age, they typically occur around 50 years of age and are most common on the trunk, head, and neck. Nodular melanomas are more common in men.

LMM represents 10% to 20% of melanomas and is commonly found on the head and neck. It is unique from other histologic subtypes; because of a prolonged radial growth phase, it does not have the same propensity to metastasize. LMM arises on chronically sun-exposed sites in older individuals and presents as a freckle-like lesion. LMMs are generally large flat, tan-colored lesions with shades of brown and black. The lesions gradually grow, develop, and begin to change in color.[12] Evolution into invasive melanoma is characterized by nodular development within the flat lesion. The median age at diagnosis is 65 years old. These lesions can be linked to mutations in *KIT*.

ALM makes up about 5% of melanomas and is not related to UV exposure. It presents commonly as melanoma on the palms of the hands or soles of the feet but may present as subungual melanoma, and mucosal melanoma. ALMs located on the soles of the feet appear as a large tan or brown stain. The lesions often have irregular convoluted borders and may be masked by thick skin on the feet. Suspicious lesions on the palms or soles of the feet should be evaluated. Subungual melanoma arises in the nail matrix or nail bed. The most common presentation is a brown or black line in the great toe or the thumbnail. Mucosal melanoma is rare and can occur in any mucosal surface. Most commonly is seen in the oropharyngeal mucosa followed by the anal and rectal, genital, and urinary mucosa. Unfortunately, mucosal melanoma often does not become clinically apparent until the mass is large or the lesion bleeds. ALM is the most common type of melanoma reported in individuals with a dark complexion (eg, African Americans, Asians, and Hispanics).[12] Similar to LMMs, this subtype is characterized by a protracted radial growth phase and is associated with mutations in *c-KIT*.

Uveal melanoma arises from the pigmented epithelium of the choroid. It is the most common primary intraocular malignancy seen in adults but is an uncommon tumor. Unlike cutaneous melanoma, the frequency and mortality rates of uveal melanoma have remained steady.[13] The risk of metastasis varies with the histologic type and size of the tumor as well as the location in the eye. The liver is the most frequent site of metastasis but uveal melanoma can spread to a variety of tissues.[14]

CLINICAL SUBTYPES

With the understanding of the role of genetic alterations in the treatment and outcomes of patients with melanoma, four distinctive clinical subtypes have emerged based on UV exposure and anatomic site. The four subtypes are divided into (1) nonchronic sun damage (non-CSD): melanomas on the skin without chronic sun-induced damage; (2) chronic sun damage (CSD): melanomas on the skin with chronic sun-induced damage characterized by the presence of solar elastosis; (3) acral; and (4) mucosal. A genomic analysis revealed differences in the activation of the MAPK and PI3K pathways between the different clinical subtypes. The results showed *BRAF* mutations predominantly occur in non-CSD and less commonly in the other groups. About 5% to 20% of all the subtypes contain *NRAS* mutations and these mutations occur independently of BRAF. Further studies showed *c-KIT* mutations are found in almost 40% of acral and mucosal subtypes, in almost a third of CSD melanomas and not at all in non-CSD melanomas.[6] As a result of the differences in presentation and outcomes, guidelines recommend uveal and mucosal melanoma be treated differently than CSD and non-CSD melanoma.[6] This further emphasizes the need for continued refinement of tumor classifications in melanoma based on genetic and biological features, which will lead to more personalized treatment options and improved outcomes for patients.

PREVENTION AND DETECTION

1 Skin cancer is a major health problem in the United States. In 2014, the US Surgeon General released a Call to Action to Prevent Skin Cancer which addressed the following goals to support skin cancer prevention: increase opportunities for sun protection in outdoor settings; provide individuals with the information they need to make informed, healthy choices about UV radiation exposure; promote policies to advance the national goal of preventing skin cancer; reduce harms from indoor tanning; and strengthen research, surveillance, monitoring, and evaluation related to skin cancer prevention.[15]

Both UVA and UVB exposure plays a major role in melanoma development and is the most preventable cause of melanoma. The incidence of melanoma has been associated with latitude and the intensity of solar exposure among susceptible populations. As such, the mainstay of melanoma prevention remains strategies to protect individuals from the harmful effects of the sun (see **Table 156-2**).

TABLE 156-2 Options for Sun Protection Sunscreens

	Sunscreens	
Behavioral	**Physical Blockers (Reflectants)**	**Chemical Absorbers**
Protective clothing and accessories Seek shade (avoid peak sun hours) Avoid tanning equipment	Zinc oxide Talc Titanium dioxide Red petrolatum	Ultraviolet B absorbers Salicylates Cinnamates Camphor derivatives Aminobenzoates Ultraviolet A absorbers Benzophenone-6 Dibenzoylmethanes

Strategies such as sun avoidance, especially during peak hours of sun intensity (10 AM–4 PM), seeking the shade when outdoors, and use of protective clothing are important education concepts for individuals who are in the sun for prolonged periods or who are at high risk for burning. In addition, the use of sunglasses, with both UVA and UVB protection, is important. Due to its correlation with the development of melanoma, the World Health Organization International Agency for Research on Cancer has declared UV light emitted from tanning beds a human carcinogen and the United States Food and Drug Administration (FDA) reclassified UV tanning devices to class II (moderate-to-high risk) devices.[16,17] As a result, 44 states have regulations in place to restrict minors' access to indoor tanning, including 19 which prohibit the use of indoor tanning for anyone younger than 18 years of age.

The use of sunscreen is another strategy to decrease UV exposure. A broad-spectrum sunscreen with both UVA and UVB protection and a SPF of 15 or higher used regularly as directed is recommended with other sun protective measures to prevent sunburn and reduce the risk of skin cancer. Of note, regulations limit the SPF value on sunscreen labels to 50+ because of the lack of evidence to show that products with SPF values greater than 50 provide greater protection.[18]

It is important to counsel patients about the appropriate use of sunscreen to optimize benefits from these products. Sunscreen should be applied 30 minutes before going into the sun and should be reapplied every 2 hours, after swimming or after perspiring heavily. About 1 ounce (30 mL) of sunscreen (a "palmful") should be used to cover the arms, legs, neck, and face of the average adult. Sun protection must be used regularly and not merely limited to times of recreation or anticipated "prolonged" exposure.

Currently, there are no consistent recommendations for the screening and early detection of melanoma. Early detection can play a large part in preventing a premalignant melanoma precursor from becoming melanoma and/or preventing a melanoma recurrence. It has been estimated about 50% of the initial melanoma lesions found are discovered by self-skin examination (SSE). Improved survival rates for melanoma have been attributed to the identification and treatment of disease at an early stage when the disease is limited and has not yet metastasized. High-risk patients with a strong family history should have additional clinical examinations, and in some cases, screening photography to document the size, shape, and location of moles. The entire cutaneous surface, including the scalp, should be examined. Both patients and clinicians need to be properly educated in the clinical features of the disease to ensure a more appropriate diagnosis.

Although the cost effectiveness of melanoma screening for all adults by a healthcare provider has never been demonstrated, many healthcare organizations and skin cancer groups recommend SSEs to serve as a mechanism for recognizing moles or marks on the skin that may be melanoma. In some cases, an individual may need the help of a partner or caregiver to perform a skin exam. This is especially important for elderly adults as they are more likely to develop and die from melamoma.[2] Barriers to successful SSEs in elderly adults, such as failing eyesight, lack of partners, and poor memory impact older adults in detecting new or changing lesions. These barriers, coupled with the higher incidence of melanoma in older adults, present challenges and opportunities for healthcare professionals to target education on this growing segment of our population.

Healthcare professionals who routinely work with the public have an opportunity to increase public awareness concerning the benefits and appropriate methods for SSE. Educational pamphlets describing SSE (see **Table 156-3**) for the public are widely available through the American Cancer Society, American Academy of Dermatology, and Skin Cancer Foundation. If a newly discovered pigmented lesion is identified on a SSE, or if a preexisting pigmented lesion changes, the individual should be immediately evaluated by a medical provider.

TABLE 156-3 Self-Examination of Suspicious Moles

1. Examine your body front and back in the mirror and then the right and left sides with the arms raised
2. Bend the elbows and look carefully at the forearms and upper arms and palms
3. Look at the backs of the legs and feet. Look specifically in the spaces between toes and at the soles of the feet
4. Examine the back of the neck and scalp with the help of a hand-held mirror; part the hair (or use a blow dryer) to lift the hair and give yourself a closer look
5. Check the back and buttocks with a handheld mirror

Derived from publications of the American Academy of Dermatology.

Benign nevi often occur in sun-exposed areas and are typically 4 to 6 mm in diameter (about the size of a pencil eraser), raised or flat, uniform in color and round in shape. Dysplastic nevi, an intermediate between benign nevi and melanoma, tend to be larger than common nevi (>5 mm), appear as flat macules with asymmetry, have a fuzzy or ill-defined shape, and vary in color.

CLINICAL PRESENTATION

The initial clinical presentation of melanoma is often a cutaneous lesion and depends on the histologic subtype and the stage of development of the lesion. The cardinal clinical feature of cutaneous melanoma is a pigmented skin lesion that changes over a period of time. Any changes in the skin surrounding a nevus, including redness or swelling, are important clinical signs. Uncommonly, the lesion may become itchy or tender and painful. Friability of the lesion, resulting in bleeding or oozing, is a danger sign. Perhaps the most important warning sign of danger is the evolution of any characteristic of a lesion. A biopsy of the lesion is critical to establish the diagnosis of melanoma. Subsequent pathologic interpretation of the biopsy will help provide information on prognosis and treatment options. An excisional biopsy, with a 1- to 3-mm margin of normal-appearing skin, is recommended for a suspicious lesion and should include a portion of underlying subcutaneous fat for microstaging. For larger lesions, an incisional or punch biopsy can be performed and should include a core of full-thickness skin and subcutaneous tissue. When excisional biopsies are not appropriate, as with the face or palmar surface of the hands, a full-thickness incisional or punch biopsy is preferred. A shave biopsy is never appropriate, because it can underestimate the thickness of the lesion, and may not fully remove it. Additionally, scarring may mask the remaining tumor.

Evaluation of any individual with a suspected melanoma includes a complete

history and total-body skin examination. The focus of the patient history is identifying potential risk factors including family history of melanoma, personal history of skin cancer or nevus excisions, immunosuppression or an immunosuppressive condition, sun exposure, tanning bed use, and phenotype. A total dermatologic examination is necessary to determine melanoma risk factors (eg, mole pattern, mole type, or freckling) and for staging. Since melanoma commonly spreads to the lymph nodes, individuals suspicious for advanced disease should be examined for lymphadenopathy. Lactate dehydrogenase (LDH) should be measured as elevated serum levels are an independent predictor of decreased survival.[19] In addition, any other signs or symptoms suggestive of metastatic disease should be completely evaluated.

CLINICAL PRESENTATION — Melanoma

General

- Any lesion that changes in appearance over time

Local Signs and Symptoms

- The clinical features used to describe questionable lesions are highlighted with the mnemonic “ABCDE”
  - Asymmetry: Melanoma lesions are often asymmetric
  - Border: Melanoma lesions have irregular borders
  - Color: Color is often variegated in a melanoma ranging from tan, blue-black, red, purple, or white
  - Diameter: Melanoma lesions are frequently greater than 6 mm
  - Enlargement or evolution: A sudden enlargement or change in lesion is concerning for melanoma
- Other signs of melanoma include a lesion that swells, bleeds, or oozes

Systemic Signs and Symptoms

- Palpable lymph nodes

- Depending on the site of metastasis, shortness of breath, abdominal pain, bone pain, headache, and mental status changes

Laboratory Tests

- In addition to a comprehensive metabolic panel, LDH should be evaluated

Other Diagnostic Tests

- Biopsy and pathology review for staging with molecular testing for *BRAF* and *c-Kit*
- When applicable, SLNB
- Systemic staging should include chest, abdomen, and pelvic CT scan or CT/PET bone scan, and brain MRI

CT, computed tomography; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PET, positron emission tomography; SLNB, sentinel lymph node biopsy.

STAGING AND PROGNOSTIC FACTORS

The size of a primary melanoma lesion is associated with the likelihood of metastasis. The Breslow tumor thickness of the lesion is commonly used as a prognostic factor to determine predicted outcomes.[20] Tumor thickness is quantified to the nearest 0.1 mm with an ocular micrometer, measuring from the top of the granular layer of the overlying epidermis to the deepest contiguous invasive melanoma cell. The correlation between tumor thickness and the risk of tumor metastasis is strong but does not include aspects such as tumor satellites, defined rather arbitrarily, as skin involvement within 2 cm of the primary lesion, and vascular invasion. Patients with satellitosis have a worse prognosis than patients with thick primary lesions (tumor thickness >4 mm), and the prognosis is more similar to that of patients with nodal metastasis. The American Joint Committee on Cancer (AJCC) developed an early staging system for melanoma which divides patients with localized melanoma into four stages according to the microstaging criteria of Breslow. Additionally, ulceration of the melanoma, satellite lesions of the primary tumor, and location of distant metastases must be

considered for accurate staging. As a result, the revised AJCC staging system for cutaneous melanoma was implemented in 2018.[19] It is important to carefully examine older clinical trials to determine which staging system was used to determine patient inclusion and exclusion criteria, as results may differ based on these patient criteria. Clinical staging includes microstaging of the primary melanoma with clinical, laboratory, and radiologic evaluation. It is used after complete excision of the primary melanoma along with clinical assessment to determine regional and distant metastasis. Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional nodes after partial or complete lymphadenectomy. At this time, it appears that patients with very limited disease (in situ, stage 0 or stage 1A) do not require pathologic evaluation of lymph nodes (see **Tables 156-4** and **156-5**).[6]

TABLE 156-4 Melanoma Tumor (T), Node (N), Metastasis (M) Classification

T Classification	Thickness	Ulcerative Status
T_X	Primary tumor cannot be addressed (eg, shave biopsy)	
T_0	No evidence of primary tumor	
T_{is}	Melanoma in situ	
T_1	≤1 mm	Unknown or unspecified
	0.8-1 mm	With or Without ulceration
	<0.8mm	A: Without ulceration
		B: With ulceration
T_2	>1-2 mm	Unknown or unspecified
		A: Without ulceration
		B: With ulceration
T_3	>2-4 mm	Unknown or unspecified
		A: Without ulceration
		B: With ulceration
T_4	>4 mm	Unknown or unspecified
		A: Without ulceration
		B: With ulceration
N Classification	**No. of Tumor Involved Nodes**	**Presence of In-Transit, Satellite, and/or Microsatellite Metastases**
N_X	Regional lymph nodes cannot be assessed	No
N_0	No regional lymph nodes	No
N_1	1 node	
N_{1a}	1 clinically occult node[a]	No
N_{1b}	1 clinically detected node	No
N_{1c}	No regional lymph node disease	Yes
N_2	2-3 nodes	
N_{2a}	2-3 clinically occult nodes	No
N_{2b}	2-3, with 1 clinically detected node	No
N_{2c}	1 clinically occult or detected node	Yes
N_3	≥4 nodes	
N_{3a}	≥4 clinically occult nodes	No
N_{3b}	≥4, with 1 clinically detected, or presence of any matted nodes	No
N_{3c}	≥2 clinically occult or detected and/or any matted nodes	Yes
M Classification	**Site**	**Serum Lactate Dehydrogenase**
M_0	No detectable distant metastasis	
M_{1a}	Distant skin, soft tissue, and/or nonregional lymph nodes	Not elevated Elevated: $M_{1a(1)}$
M_{1b}	Lung metastases	Not elevated Elevated: $M_{1b(1)}$
M_{1c}	Any distant metastasis visceral metastases	Not elevated Elevated: $M_{1c(1)}$
M_{1d}	Distant metastases to the CNS	Not elevated Elevated: $M_{1d(1)}$

M, metastasis; N, node; T, tumor.

[a]Clinically occult node detected by sentinel lymph node biopsy.

Data from Gershenwald JE, Scolyer RA, Hess, KR, et al. Melanoma Staging: Evidence-Based Changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual. CA: A Cancer Journal for Clinicians. 2017;67:472-492.

TABLE 156-5 American Joint Committee on Cancer Tumor (T), Node (N), Metastasis (M) Stage Grouping for Cutaneous Melanoma

Pathologic Stage	T	N	M	Clinical Stage	T	N	M
0	T_{is}	N_0	M_0	0	T_{is}	N_0	M_0
IA	T_{1a}	N_0	M_0	IA	T_{1a}	N_0	M_0
	T_{1b}	N_0	M_0	IB	T_{1b}	N_0	M_0
IB	T_{2a}	N_0	M_0		T_{2a}	N_0	M_0
IIA	T_{2b}	N_0	M_0				
	T_{3a}	N_0	M_0	IIA	T_{2b}	N_0	M_0
IIB	T_{3b}	N_0	M_0		T_{3a}	N_0	M_0
	T_{4a}	N_0	M_0	IIB	T_{3b}	N_0	M_0
	T_{4a}	N_0	M_0		T_{4a}	N_0	M_0
IIC	T_{4b}	N_0	M_0	IIC	T_{4b}	N_0	M_0
IIIA	$T_{1a/b}, T_{2a}$	N_{1a}, N_{2a}	M_0	III	Any T, TIS	$>N_1$	M_0
IIIB	T_0	N_{1b}, N_{1c}	M_0				
	$T_{1a/b}, T_{2a}$	$N_{2b/c}, N_{2b}$	M_0				
	T_{2b}, T_{3a}	$N_{1a-c}, N_{2a/b}$					
IIIC	T_0	$N_{2b/c}, N_{3b/c}$	M_0				
	$T_{1a-}T_{3a}$	N_{2c}, N_{3a-c}	M_0				
	T_{3b}, T_{4a}	Any N ≥ N1	M_0				
	T_{4b}	N_{1a-c}, N_{2a-c}	M_0				
IIID	T_{4b}	N_{3a-c}	M_0				
IV	Any T, T_{is}	Any N	M_1	IV	Any T	Any N	M_1

As with other solid tumors, the presence of regional lymph node involvement is a powerful predictor of tumor burden and patient outcome. Sentinel lymph node biopsy (SLNB) is a minimally invasive procedure that determines if a patient is a candidate for a complete lymph node dissection. The rationale for lymphatic mapping and subsequent SLNB is based on the observation that regions of the skin have patterns of lymphatic drainage to specific lymph nodes in the regional lymphatic basin. The sentinel lymph node is believed to be the first node in the lymphatic basin into which the primary melanoma drains. Unlike other solid tumors, melanoma appears to progress in an orderly nodal distribution. SLNB allows for the detection of micrometastases as a result of a

more thorough examination of a single sentinel node than is possible when examining multiple lymph nodes with a lymph node dissection. SLNB is associated with low false-negative rates and low complication rates.[21] SLNB may be most useful for melanomas located in ambiguous drainage sites such as the head and neck. Detection of clinically undetectable disease in a lymph node basin not directly adjacent to the primary lesion may allow for upstaging of patients who initially are believed to have node-negative disease. The American Society of Clinical Oncology and Society of Surgical Oncology joint clinical practice guidelines recommend SLNB for patient with any intermediate-thickness melanoma and may be considered for a thinner melanoma.[21]

Tumor thickness, ulceration, and mitotic rate, in addition to age and gender, are the primary indicators of the natural history of the disease and correlate with prognosis. Mitotic rate, defined as the number of mitosis per square millimeter, is an important prognostic factor for developing metastatic disease. Increasing mitotic rate, characterized as greater than ≥1 mitosis per mm^2, represents a more aggressive lesion and is associated with a poorer survival rate despite tumor size. Other factors such as tumor growth pattern, vertical growth phase, histological subtype, density of tumor-infiltrating lymphocytes (TILs) in the tumor tissue, elevated LDH level, satellite lesions, and angiolymphatic invasion also have been reported to influence survival (see **Table 156-6**). The location of the primary tumor on the skin is also important as tumors of the extremities have an increased survival compared with those with axial, neck, head, and trunk tumors. In addition, several additional prognostic factors have been identified in patients with advanced disease. The number of metastatic sites, involvement of the central nervous system, gastrointestinal tract, liver, pleura, or lung, Eastern Cooperative Oncology Group (ECOG) performance status of 1 or greater, male sex, and prior immunotherapy have all been associated with poor prognosis.[6,22]

TABLE 156-6 Prognostic Factors for Cutaneous Melanoma

Tumor-Related Factors
Tumor thickness
Level of tumor invasion
Ulceration
Histologic subtype
Anatomic site of primary tumor
Mitotic rate
Lymphangitic invasion
Occurrence of microsatellites
Presence of tumor-infiltrating lymphocytes
Patient-Related Factors
Age
Gender

TREATMENT

Desired Outcomes

Treatment of cutaneous melanoma depends on the stage of disease. Local disease is managed, and often cured, with surgical ablation. Regional disease is treated with surgical resection of the primary lesion and, depending on the risk of recurrence, adjuvant therapy in an effort to eradicate any residual disease and cure the patient. The role of interferon-α (IFN-α) and ipilimumab as adjuvant therapy after surgical resection is limited with BRAF/MEK inhibitors and PD-1 inhibitors now favored in this setting based on recent FDA approvals. Historically, metastatic melanoma has been a difficult disease to treat. The goals of treatment for metastatic disease are to slow tumor progression, prolong survival, relieve acute symptoms, and improve quality of life. After more than a decade of ineffective drug development, several new treatment options including molecular targeted agents (BRAF and MEK inhibitors) and immunotherapy (CTLA-4 and PD-1 inhibitors) are approved for the treatment of metastatic melanoma. Molecular targeted agents offer rapid and high-response rates with prolonged time to disease progression, while immunotherapy can induce durable responses. These new treatment options have increased survival expectations to an all-time high in the history of melanoma treatment.

Surgery

Patients who present with a suspicious pigmented lesion should undergo a full-thickness excisional biopsy, if possible. A full-thickness incisional or punch biopsy is preferred in cases where an excisional biopsy not possible, to provide microstaging and ultimately determine therapy.

2 Localized cutaneous melanoma can often be cured with surgical excision. The cure rates for melanomas smaller than 1 mm are as high as 98%. The extent of the excision margin is important in preventing local recurrence and ultimately survival. For melanoma in situ, excision of the visible lesion or biopsy site with a 0.5- to 1-cm border of clinically normal skin and a layer of subcutaneous tissue along with confirmation of histologically negative peripheral margins is recommended. The recommended clinical margin for invasive melanoma depends on tumor thickness. Excision with a 1-cm margin of clinically normal skin and underlying subcutaneous tissue is recommended for invasive melanomas 1-mm thick or smaller. Current guidelines recommend a 1- to 2-cm margin for melanoma with tumor thickness of 1.01 to 2 mm.[6] Lesions that are 2- to 4-mm thick should be excised with a 2-cm margin and primary tumors more than 4-mm thick require at least a 2-cm margin. Surgical management of lentigo maligna melanoma is problematic as subclinical extension of atypical junctional melanocytic hyperplasia may extend beyond the visible margins. Complete excision of these lesions is important.

When isolated regional lymph nodes in the absence of distant disease are detected via physical examination, a therapeutic lymphadenectomy is recommended. The extent of the therapeutic lymph node dissection is often modified according to the anatomic area of the lymphadenopathy. Selective regional lymphadenectomy performed after scintigraphic and dye lymphographic identification of the affected draining sentinel lymph node(s) is the standard of care for melanomas more than 1-mm thick. If the sentinel node is found to have micrometastatic melanoma, regional dissection of the involved nodal basin is performed. If the lesion is less than 0.8 mm in thickness with ulceration, 0.8 to 1 mm in thickness with or without ulceration, or <0.8 mm with other adverse features (very high mitotic index >2/mm^2, lymphovascular invasion) lymphatic mapping with SLNB should be discussed and considered.[23] The likelihood of detecting metastatic disease in the sentinel lymph node is <5% in thin melanomas that are less than 0.8 mm, but increases to more than 30% in tumors 4 mm thick.[23] The Multicenter Selective Lymphadenectomy Trial (MSLT-1) investigated the use of SLNB and immediate complete lymph node dissection (CLND) compared to nodal

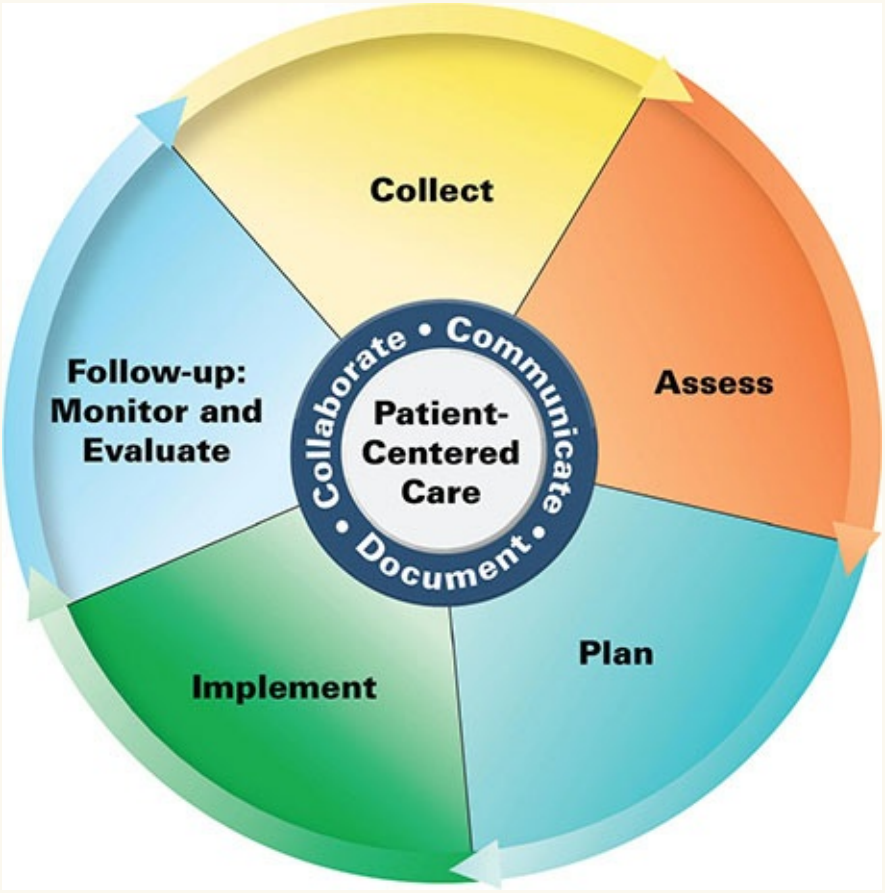
observation in patients with melanoma undergoing a wide local excision. Results demonstrated a significant improvement in disease-free survival but not melanoma-specific survival, supporting the staging value of SLNB.[24] The Multicenter Selective Lymphadenectomy Trial II (MSLT-II) then randomized sentinel lymph node-positive patients to either CLND or nodal observation. No difference in melanoma-specific survival was observed despite an increased rate of regional disease control.[25] As a result, the value of CLND in routine practice is limited.[6] However, SLNB results are important for accurate staging and aid in the decision to offer adjuvant treatment.[23]

One of the most important aspects of surgical management for cutaneous melanoma is patient follow-up.[6] Postsurgical follow-up of patients who have had a melanoma excised is essential to monitor for undetected metastatic disease and the development of a second primary cutaneous melanoma or nonmelanoma malignancy. Scheduled screening, in addition to routine surgical follow-up, is required for any patient with a melanoma; the recommended frequency and duration depend on the stage of melanoma. The optimal duration of follow-up remains controversial. Most patients who develop recurrent disease do so within the first 5 years after treatment but late recurrences (more than 10 years after surgery) have been observed. The increased lifetime risk of developing a second primary melanoma supports lifetime dermatologic surveillance for all patients.

A patient with stage III melanoma typically has lymph node involvement but intralymphatic metastases, including satellite metastases and in-transit metastases, may also occur. Satellite metastases are either clinically (visible) or pathologically (microscopic) detectable and occur within 2 cm of the primary site.[6] In-transit metastases are defined as regional metastases that occur more than 2 cm from the original lesion and are more common in individuals with thick, ulcerated lesions. Surgery may be used for the management of in-transit lesions with the goal of complete resection with clear margins. Unfortunately, this isn’t always feasible and subsequent recurrence in the same extremity often occurs after initial resection of an in-transit metastasis.

The role of surgery beyond that of cure is less clear, although surgery may offer palliation for patients with isolated metastasis.[23] Brain metastases occur in up to 50% of patients with metastatic melanoma. Surgical resection, with or without radiation, has been used in select individuals. More recently, high control rates of brain metastasis have been achieved with focal radiation therapy such as linear accelerator–based stereotactic radiosurgery or gamma-

knife technologies.[26] Appropriate resection or bypass may provide significant relief of symptoms in patients with a bowel obstruction due to metastasis. Despite the lack of controlled clinical trials, the impact of palliative surgery should be evaluated in the context of a patient's comfort and quality of life. In some cases, surgery may improve quality of life, result in long-term disease control and/or extend survival in select patients with metastatic disease.[23]



Patient Care Process for Melanoma

Collect

- Patient characteristics (eg, age, sex, physical features)
- Patient medical history (personal/family) including autoimmune diseases
- Social history (eg, history of blistering sunburns; intermittent, intense

sun exposure; tanning bed use)

- Current medications including OTC products, herbal products, dietary supplements, current or past use of immunosuppressants
- Objective data
  - Type of biopsy performed
  - Pathology report: Breslow thickness, presence or absence of ulceration, mitotic rate
  - Routine imaging and labs not recommended for early stage/localized disease. Perform for baseline staging in stage IIIB or higher (can be considered for stage IIIA)
  - Labs: serum creatinine (SCr), liver function (AST, ALT, total bilirubin), lactate dehydrogenase (LDH), complete blood count (CBC), thyroid function (TSH, free T4) for regional/metastatic disease

Assess

- Appropriate primary treatment (wide excision, need for sentinel lymph node biopsy)
- Status of sentinel lymph node biopsy, if performed; if positive sentinel lymph node, appropriateness of nodal basin ultrasound surveillance versus complete lymph node dissection
- Mutational analysis, if appropriate
- Presence of active autoimmune disease
- Ability/willingness to complete one year of adjuvant treatment, if recommended
- Ability/willingness to pay for treatment options
- Ability/willingness to obtain laboratory monitoring tests and imaging to evaluate signs and symptoms
- Emotional status (eg, presence of anxiety, depression)

Plan

- Wide excision for all stages. Consider sentinel lymph node biopsy for stage IB; offer to stage II

- Adjuvant treatment with either PD-1 inhibitor or BRAF/MEK inhibitor combination for patients with fully resected stage III or stage IV disease that are appropriate for therapy
- Drug therapy regimen including specific drug(s) dose, route, frequency, and duration (see Tables 156-8 and 156-9)
- Referral to neurosurgery for treatment of brain metastases (Gamma Knife stereotactic radiosurgery; resection by craniotomy)
- Monitoring parameters including efficacy (eg, CT and brain MRI as indicated) and safety (eg, signs and symptoms of immune-related adverse events [irAEs]); frequency and timing of follow-up
- Patient education (eg, purpose of treatment, drug-specific information, proper administration/storage/handling for targeted therapies, when to seek emergency medical attention (see Tables 156-8 to 156-11)
- Referrals to other providers when appropriate (eg, endocrinology, GI)

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- At least annual skin exam; self-exam of skin and lymph node
- Imaging to assess signs/symptoms and/or every 3 to 12 months to screen for recurrence
- Presence of adverse effects
- Patient adherence to treatment plan using multiple sources of information

** Collaborate with patient, caregivers, and other healthcare professionals.*

Adjuvant Therapy

3 The risk of relapse and death after resection of a local or regional cutaneous melanoma is the primary determinant for the use of adjuvant therapy. Adjuvant trials have focused on patients at intermediate or high risk for recurrence.

Historically, melanoma has shown resistance to traditional treatment modalities such as radiation and chemotherapy. However, melanoma is considered one of the most immunogenic solid tumors and lymphocyte infiltration in the tumor suggests that immunomodulation may impact the biology of the disease. Early work with nonspecific immunomodulators, such as levamisole and Bacillus Calmette-Guérin (BCG), resulted in tumor regression but many of these responses were limited and short-lived. In early trials, patients who showed the highest response to immunotherapy had minimal disease burden. The use of adjuvant immunotherapy to treat these patients has been investigated to prevent distant recurrence and improve long-term survival.

Interferon

One of the oldest and most controversial immunotherapy approaches for the treatment of melanoma is the use of IFNs. IFN*s* are a group of proteins with diverse immunomodulatory and antiangiogenic properties. Several studies have evaluated various doses and schedules of recombinant IFN for the treatment of metastatic melanoma. Response rates in metastatic melanoma range from 10% to 30%. In clinical trials of IFN therapy for patients with metastatic melanoma, response rates were highest in patients with limited disease. The activity of IFN in patients with minimal disease encouraged investigators to evaluate the role of adjuvant IFN. A large, multicenter cooperative group trial (E1684) randomized 287 patients with high-risk melanoma (stage IIB/III disease based on 1997 AJCC staging criteria) to adjuvant IFN-α_{2b} or observation following complete surgical resection. IFN-α_{2b} was given as induction therapy at a maximum tolerated dose of 20 million units/m^2 per dose given IV 5 days per week for 4 weeks followed by maintenance therapy of 10 million units/m^2 given subcutaneously three times per week for 48 weeks. This therapy now is often referred to as *high-dose interferon* (HDI). With a median follow-up period of 6.9 years, patients treated with HDI had significantly longer relapse-free and overall survival compared with patients who were observed after surgical resection (1.72 vs 0.98 years and 3.8 vs 2.8 years, respectively).[6] At 5 years, both the relapse-

free and overall survival rates remained higher in the HDI cohort. This data led to the 1995 FDA approval of HDI as the standard of care in the adjuvant setting. However, longer follow-up (median 12.6 years) demonstrated no significant difference in overall survival.[6]

Toxicities of IFN therapy in the adjuvant HDI trial were common and severe. About one-third of patients required a dose modification during induction and only half of the patients were able to complete the one year of therapy. One strategy for reducing toxicities associated with IFN is to modify the dose and duration. A subsequent ECOG trial (E1690) of low-dose IFN (3 million IU per dose given subcutaneously three times weekly [LDI]) for 24 months) as compared with the HDI regimen versus observation did not demonstrate an overall survival advantage of HDI versus observation.[6] At a median follow-up period of 52 months, the 5-year estimated relapse-free survival rates for HDI, LDI, and observation were 44%, 40%, and 35%, respectively.

For patients who receive IFN, it is important to effectively prevent and manage treatment-related toxicities. Patients commonly experience constitutional symptoms which can include acute symptoms such as fever, chills, myalgia, and fatigue, and can encompass some of the more chronic toxicities such as fatigue, anorexia, and depression.[27] Acetaminophen can be used to prevent or minimize acute dose-related symptoms such as fever, myalgia, and chills. Opiates, such as meperidine, are often used to manage severe chills or rigors, which are most common during the initial month of the HDI induction phase. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been used to manage IFN-related myalgia, but may have overlapping side effects with IFN, such as a decrease in renal blood flow. NSAIDs and acetaminophen may mask fevers that occur in patients who experience neutropenia while undergoing therapy. Additionally, NSAIDs may increase the risk of bleeding in the setting of thrombocytopenia caused by IFN. Hematologic, renal, and hepatic toxicities require monitoring and appropriate dose modification in patients treated with IFN. Fatigue is another frequently observed dose-limiting toxicity of IFN therapy, occurring in 70% to 100% of patients.[27] IFN-induced fatigue appears to be dose-related and may worsen with continued therapy. Pharmacologic (eg, methylphenidate) and nonpharmacologic (eg, exercise, psychosocial techniques, distraction, energy management, and dietary modifications) interventions may improve IFN-related fatigue in patients. Depression is common and should be fully evaluated. Contributing factors such as IFN-induced hypothyroidism or other

concomitant IFN symptoms (eg, nausea and fatigue) should be evaluated concurrently with depression symptoms to optimize treatment decisions. Antidepressants, such as selective serotonin reuptake inhibitors, have been studied in IFN-induced depression with notable benefit.[27] Anorexia is reported in about 70% of patients receiving adjuvant IFN therapy for melanoma and is mediated by direct effects on hypothalamic neurons, modification of normal hypothalamic neurotransmitters or neuropeptides, or effects from stimulation of other cytokines.[27] Taste alterations may also contribute to anorexia. Glucocorticoids should not be used for appetite stimulation or as part of an antiemetic therapy as they may adversely impact the immunomodulatory effects of IFN.

Pegylated IFN-α2b has also been evaluated in the adjuvant setting in patients with resected stage III melanoma with the hope that the change in formulation would improve the efficacy and toxicity profile. In the European Organization for Research and Treatment of Cancer (EORTC) 18991 trial patients were randomized to observation or pegylated IFN. Results demonstrated an improvement in relapse-free survival with pegylated IFN-α2b, but no difference in overall survival or distant metastasis-free survival.[6] Based on this data, the FDA approved pegylated IFN-α2b as an option for adjuvant treatment.

HDI and pegylated IFN-α_{2b} are both adjuvant treatment options for patients with completely resected stage III melanoma. However, the use of these agents is no longer recommended in this setting due to the lack of overall survival benefit and the development of newer, more effective immunotherapies.

CTLA-4 Inhibitor

It is well known that T cells play a crucial role in cell-mediated immunity. They are activated when the T-cell receptor (TCR) binds to its antigen in conjunction with the binding of CD28 on the T cell to the costimulatory molecule B7 on antigen-presenting cells (APCs). To prevent over activation of T cells, immune checkpoints such as CTLA-4 function as inhibitory receptors for the costimulatory molecule B7. Crosslinking of CTLA-4 by B7 inhibits T-cell activation, transcription, translation, and transduction. CTLA-4 blockade overcomes this inhibition and results in the activation and proliferation of T cells.[11] Ipilimumab, a monoclonal antibody against CTLA-4, has demonstrated efficacy in both the adjuvant and metastatic setting in the treatment of melanoma. The EORTC 18071 trial evaluated 475 patients

treated with high-dose ipilimumab (10 mg/kg IV every 3 weeks for 4 doses then every 3 months for up to 3 years) as compared to placebo in the adjuvant setting. Recurrence-free survival was 26.1 months in patients treated with high-dose ipilimumab as compared to 17.1 months in patients treated with placebo. Long-term data demonstrated significantly higher 5-year recurrence-free survival (40.8% vs 30.3%) and overall survival (65.4% vs 54.4%) with adjuvant ipilimumab as compared to placebo.

However, these results did not come without toxicity. CTLA-4 inhibitors produce immune-related adverse events (irAEs) that are distinct and different from adverse events associated with conventional cancer treatments (see **Table 156-7**). irAEs are the result of the activation of self-reactive T-cells. The incidence of irAEs with the high-dose ipilimumab in EORTC 18071 was 90% and up to 40% of patients experienced grade 3 or 4 irAEs.[28] The most common serious adverse effects observed in the EORTC 18071 adjuvant trial were autoimmune colitis and autoimmune hepatitis, consistent with known adverse effects of ipilimumab. Autoimmune endocrinopathies occurred at a higher frequency than in the metastatic disease trials. irAEs led to the discontinuation of treatment in 52% of patients who were treated with ipilimumab. Of concern, five deaths were attributed to drug-related adverse effects.[28]

TABLE 156-7 Management of Immune-Related Adverse Effects

Organ Toxicity	Signs/Symptoms	Management	Comments
Skin and Mucosa	Pruritus, rash, desquamation, mucositis	Grade 1 or 2 Topical corticosteroids (betamethasone 0.1%) Urea based creams Oral antipruritic as needed (diphenhydramine or hydroxyzine) Grade 3 or 4 Prednisone 0.5-2 mg/kg/day or equivalent	Rare cases of toxic epidermal necrosis and Stevens-Johnson syndrome have been reported with ipilimumab
Gastrointestinal	Diarrhea, hematochezia, abdominal cramping, nausea, and vomiting	Grade 1 Oral hydration Electrolyte repletion Loperamide Budesonide 9 mg daily Grade 2 Prednisone 1-2 mg/kg/day unless diarrhea is transient Grade 3 or 4 Methylprednisolone 1-2 mg/kg/day IV	Infliximab 5 mg/kg IV every 2 weeks may be given if symptoms do not improve with 48-72 hours of high-dose steroids. Bowel perforation and obstruction may occur in cases of severe colitis
Hepatic	Transaminitis, jaundice, sclera icterus	Grade 1 Monitor Grade 2 Consider prednisone 0.5-1 mg/kg/day Grade 3 or 4 Methylprednisolone 1-2 mg/kg/day or equivalent	Mycophenolate mofetil 500 mg IV/PO Q12 hours can be used in patients who do not respond to steroids within 48 hours
Neurologic	Muscle weakness, motor neuropathies, sensory neuropathies	Grade 1 Monitor Grade 2 Hold therapy, prednisone 0.5-1 mg/kg/day Grade 3 or 4 Prednisone 1-2 mg/kg/day or equivalent	Rare case reports of Guillain-Barre' syndrome and myasthenia gravis have been reported with ipilimumab
Endocrine	Headache, weakness, visual changes, behavioral changes, electrolyte imbalances	Grade 1 or 2 Appropriate hormone replacement therapy Grade 3 or 4 Consider prednisone/methylprednisolone 1-2 mg/kg/day for severe symptoms	Potential endocrinopathies include Addison's disease, pan-hypopituitarism, adrenal crisis, and hypophysitis (may be irreversible)
Ocular	Photophobia, eye dryness, blurred vision	Grade 1 or 2 Prednisolone acetate 1% topical Grade 3 or 4 Opthalmic steroids and Prednisone 1-2 mg/kg/day or equivalent	Rare cases of episcleritis and uveitis have been reported
Pulmonary	Dyspnea, new or worsened cough, chest pain, hemoptysis	Grade 1 Hold; monitor Grade 2 Prednisone 1-2 mg/kg/day or equivalent Grade 3 or 4 Methylprednisolone 1-2 mg/kg/day IV	Pneumonitis is more common with pembrolizumab and nivolumab than ipilimumab

Source: Data from references 31 and 32.

The irAEs with ipilimumab are dose-related and can follow a pattern: skin-related toxicities typically occur after the first dose; colitis tends to occur after the second dose; and hepatitis and endocrinopathies often occur after the third or fourth dose.[31] However, irAEs can occur at any time during treatment and even after treatment is complete. The development and time of onset of irAEs cannot be predicted because they result from the individual's immune system and not the treatment itself. Most irAEs are reversible with treatment and resolve after 6 to 8 weeks; the exception being endocrinopathies which may require lifelong hormonal treatment. Close monitoring for irAEs and early intervention is necessary while on therapy.[6] It is recommended that patients obtain a comprehensive metabolic panel (with liver function tests), complete blood count, and thyroid function tests at baseline, throughout treatment and for up to 6 months after treatment.[31]

Ipilimumab therapy should be held and high-dose systemic corticosteroids initiated for grade 2 irAEs that do not improve from withholding therapy or for any grade 3 or 4 irAE. Ipilimumab can be restarted when adverse events improve to grade 0 or 1 and systemic corticosteroid dose is less than prednisone 10 mg (or equivalent). In early studies, corticosteroids were discouraged due to the theoretical risk of blunting the desired immune response. However, studies have shown that the efficacy of ipilimumab is not compromised when corticosteroids are utilized for toxicity management.[32] For patients who develop steroid-refractory irAEs, defined as no response to high-dose steroids within 48 to 72 hours of initiation, other immunosuppressive agents have been utilized. Agents such as infliximab and mycophenolate can be used for patients who develop steroid-refractory colitis and hepatitis, respectively.[32] Due to case reports of hepatotoxicity with infliximab, this agent should be avoided as a secondary immunosuppressant in patients with autoimmune hepatitis. Published guidelines for the treatment of irAEs are available.[32] In cases of severe or life-threatening irAEs, permanent discontinuation of ipilimumab therapy is recommended. Patients who experienced grade 3 or 4 autoimmune toxicities were also the most likely to exhibit tumor regression and increased time to relapse in the metastatic setting.[32]

Based on recent data supporting the use of targeted therapy (dabrafenib/trametinib) and PD-1 inhibitors (nivolumab, pembrolizumab) in the adjuvant setting along with the high risk of toxicity with ipilimumab, ipilimumab is no longer recommended in the NCCN guidelines for the

adjuvant treatment of stage III melanoma.[6]

PD-1 Inhibitors

The inhibitor signal to suppress T-cell activation that results from the binding of PD-1 to its ligand (PD-L1 or PD-L2) physiologically prevents autoimmunity and recognition of self. However, melanoma cells can overexpress PD-L1, leading to T-cell exhaustion and the inability to mount an immune response against a tumor. Monoclonal antibodies directed against PD-1 block the binding of PD-L1, thus allowing T cells to remain stimulated.[1] PD-1 inhibitors have exhibited improved efficacy and reduced toxicity compared to ipilimumab.

Pembrolizumab and nivolumab are PD-1 checkpoint inhibitors initially approved for the treatment of metastatic melanoma but have recently been studied in the adjuvant setting. Checkmate-238 was the first in a series of published adjuvant studies that changed the treatment landscape of early-stage melanoma. A total of 906 patients with high-risk stage III or stage IV melanoma who underwent complete resection were randomized to receive either ipilimumab 10 mg/kg IV every 3 weeks for 4 doses then every 12 weeks or nivolumab 3 mg/kg IV every 2 weeks for up to one year. Results showed 12-month recurrence-free survival of 70.5% with nivolumab as compared to 60.8% with ipilimumab.[33] Long-term follow-up data including overall survival benefit are not mature. Additionally, the rate of grade 3 to 4 toxicities was significantly less in the patients receiving nivolumab (14.4%) versus ipilimumab (45.9%). Treatment discontinuation due to an adverse event occurred in 9.7% of patients treated with nivolumab versus 42.6% of patients treated with ipilimumab.[33]

A similar study of adjuvant pembrolizumab, Keynote-054, was conducted in patients with stage III melanoma undergoing complete resection. Patients were randomized to receive pembrolizumab 200 mg IV every 3 weeks or placebo for up to one year. The 1-year recurrence-free survival rate was 75.4% with pembrolizumab as compared to 61.0% with placebo. Grade 3 to 4 adverse events were reported in 14.7% of patients who received pembrolizumab.[34]

Based on these studies, both nivolumab and pembrolizumab are FDA approved for the adjuvant treatment of melanoma in patients who have undergone complete resection and both are recommended treatment options in the NCCN guidelines.[6] Based on the data for both nivolumab and

pembrolizumab, PD-1 inhibitors are now the mainstay of immunotherapy utilized for adjuvant treatment and are preferred over ipilimumab.

Targeted Therapy

Mutations in BRAF, found in up to 50% of melanomas, lead to the constitutive activation of the MAPK pathway and uncontrolled cell growth/differentiation.[1] BRAF-targeted therapies have shown an improvement in survival in patients with metastatic melanoma. However, resistance eventually develops, potentially caused by mutations in MEK. The use of MEK inhibitors in combination with BRAF inhibitors delays the development of acquired resistance and increases efficacy.

For patients with early-stage melanoma and molecular mutations identified in BRAF, the combination of BRAF and MEK inhibitors has been assessed in the adjuvant setting. The COMBI-AD trial investigated the use of adjuvant dabrafenib and trametinib in patients with completely resected, stage III melanoma and the presence of a BRAF V600E or V600K mutation. Patients were randomized to receive dabrafenib 150 mg twice daily plus trametinib 2 mg daily or placebo for up to one year. The 3-year relapse-free survival rate was 58% in the dabrafenib/trametinib group and 39% in the placebo group ($P < 0.001$), with a 53% lower risk of relapse at 2.8 years.[35] The rate of overall survival was also increased in the combination arm but this did not reach statistical significance in the first interim analysis. No new or unexpected side effects were observed in the adjuvant setting; major toxicities of BRAF/MEK inhibitor therapy will be discussed in the “treatment of metastatic melanoma” section. Based on this data, the combination of dabrafenib/trametinib received FDA approval for adjuvant treatment in patients with BRAF V600E or V600K melanoma following complete resection and is also recommended per NCCN guidelines for this population.[6]

Summary of Adjuvant Therapy

Although IFN is approved in the adjuvant setting, many experts question its use given the considerable treatment toxicities, uncertain survival advantage, and development of newer therapies. High-dose ipilimumab provides a treatment option for patients with high-risk disease, although it has fallen out of favor given its significant toxicities. Both IFN and ipilimumab have been removed from the list of recommended adjuvant treatment options in the NCCN guidelines.[6] The treatment of choice in this setting has become PD-1

inhibitors (nivolumab or pembrolizumab) or dabrafenib/trametinib for patients with BRAF V600-activating mutation due to improved efficacy and reduced toxicity.

Treatment of Metastatic Melanoma

Chemotherapy and Biochemotherapy

4 Although many chemotherapy drugs show in vitro activity against melanoma, only a few have consistently shown a response rate greater than 10% in individuals with metastatic melanoma. Dacarbazine and temozolomide, the oral prodrug of the active metabolite of dacarbazine, are alkylating agents studied in the treatment of metastatic melanoma. Dacarbazine is the only FDA-approved chemotherapeutic agent for treatment in this setting and at one time was the standard of care. Reported response rates with these two cytotoxic drugs is 10% to 25%, with an average duration of response of 5 to 7 months.[36] Common adverse effects with these agents include myelosuppression and severe nausea and vomiting. Carboplatin in combination with paclitaxel demonstrated activity in the second-line setting.[37] Response rates of 15% to 17% were seen in trials with single-agent paclitaxel.[36] A phase III trial comparing albumin-bound paclitaxel with dacarbazine in chemotherapy-naïve melanoma patients reported an increase in progression-free survival in patients receiving albumin-bound paclitaxel. Neuropathy and neutropenia were more common in the albumin-bound paclitaxel arm.[38] Due to their minimal benefit and added toxicity, these chemotherapy agents are not routinely used but are listed in the NCCN guidelines as potential cytotoxic regimens for treatment of metastatic disease.[6]

In an attempt to improve on the limited response rates with chemotherapy, the strategy of combining chemotherapy (dacarbazine, platinum agents, or vinca alkaloids) and cytokines (aldesleukin or IFN) often termed biochemotherapy has been evaluated for the management of metastatic melanoma and in the adjuvant setting. The primary rationale for this combination is to increase overall activity and response rates based on preclinical work suggesting potential synergistic interactions between cytokines and some chemotherapy agents. Results of clinical studies with biochemotherapy have not demonstrated a clear survival advantage and toxicities are additive and can be severe. The NCCN guidelines currently do

not recommend biochemotherapy in the adjuvant setting or in the metastatic setting and it should not be given in centers that do not have significant clinical experience and the infrastructure to manage toxicities.[6]

Immunotherapy

Significant attention has been given to immunotherapy as a treatment option in metastatic melanoma due to its general resistance to traditional treatment modalities. Over the past few years, advances in immunotherapy for the treatment of melanoma have significantly impacted survival in patients with metastatic disease.

Interleukin-2 *Interleukin-2* is a glycoprotein produced by activated lymphocytes. IL-2 was first identified as a T-cell growth factor, but IL-2 is also a growth factor for a variety of cells, including lymphocytes and natural killer (NK) cells. IL-2 also may be immunosuppressive.

The precise mechanism of cytotoxicity of IL-2 is unknown. In vitro and in vivo, IL-2 stimulates the production and release of many secondary monocyte-derived and T-cell–derived cytokines, including IL-4, IL-5, IL-6, IL-8, tumor necrosis factor (TNF)-α, granulocyte-macrophage colony-stimulating factor, and IFN-γ, which may have direct or indirect antitumor activity. In addition, IL-2 stimulates the cytotoxic activities of NK cells, monocytes, lymphokine-activated killer (LAK) cells, and cytotoxic T lymphocytes (CTLs). IL-2 also appears to activate endothelial cells, which results in increased expression of adhesion molecules.[39]

High-dose aldesleukin was evaluated in a series of trials with objective response rates around 16%. Of significance, 6% of those patients produced a complete response which was durable (median response, 70 months).[39] Responses were seen in a variety of metastatic sites such as the lung, liver, bone, lymph nodes, and subcutaneous tissue. The FDA-approved high-dose aldesleukin regimen for the treatment of metastatic melanoma is 600,000 IU/kg per dose every 8 hours for a maximum of 14 doses in a 5-day period given for two cycles, with a 10- to 14-day rest period between cycles. At these doses, cytokine-induced capillary leak syndrome is a common problem and often is accompanied by significant hypotension, visceral edema, dyspnea, tachycardia, and arrhythmias. Increased permeability of capillary walls allows for a fluid shift from the intravascular space into tissues. As the patient becomes intravascularly dehydrated, hypotension may occur, resulting in reflex tachycardia and arrhythmias. In addition, the decrease in blood

volume may result in decreased renal blood flow, manifesting as increases in blood urea nitrogen, serum creatinine, edema, and weight gain and a decrease in urine output (input greater than output). Visceral edema may result in pulmonary congestion, pleural effusions, and edema. The management of patients receiving high-dose aldesleukin requires extensive supportive care medications, careful monitoring, and staff trained in aspects of critical care such as hypotension management. Constitutional symptoms are a frequent complication of aldesleukin therapy and become more intense as therapy progresses. Additional side effects seen with aldesleukin include pruritus, eosinophilia, bone marrow suppression, increased liver function tests, neurologic disturbances, diarrhea, and nausea.

Careful patient selection for aldesleukin therapy is important. Pretreatment factors such as performance status, site of metastasis, and LDH may predict who will respond. Based on reports of long-term responses (>10 years) experienced by some patients, the benefit certainly exceeds the risk for those individuals. Unfortunately, at this time, it is difficult to determine which individuals will respond to aldesleukin therapy because no biologic or immunologic biomarkers have been found to correlate with response. The decision to treat an individual with high-dose aldesleukin should be based on an analysis of an individual patient's risk versus potential benefit. With newer agents now available on the market, and complexity of administration, the role of aldesleukin has diminished.

5 **CTLA-4 Inhibitors** CTLA-4 was the first immune checkpoint identified as a target for immunotherapy and ipilimumab was the first drug in this class to demonstrate efficacy in metastatic melanoma. Results from phase I and II trials with ipilimumab demonstrate up to 20% response rates in advanced disease.[6] In a phase III trial of 676 HLA-A*0201-positive patients with refractory metastatic melanoma, ipilimumab (3 mg/kg) plus a glycoprotein 100 (gp100) peptide vaccine was compared with ipilimumab (3 mg/kg) alone or gp100 alone.[40] The median overall survival time was significantly longer in patients treated with ipilimumab, alone or combined with gp100, as compared with patients treated with gp100 alone (10.0 or 10.1 vs 6.4 months, hazard ratio [HR] 0.66, $P = 0.003$). Another phase III trial compared a higher dose of ipilimumab (10 mg/kg) plus dacarbazine with dacarbazine alone in patients previously untreated for metastatic melanoma.[6] Ipilimumab plus dacarbazine demonstrated significantly longer median overall survival (11.2 vs 9.1 months, HR 0.72, $P < 0.001$) than dacarbazine alone. Based on these results, ipilimumab, dosed at 3 mg/kg IV every 3 weeks for 4 doses became

the first FDA-approved drug for the treatment of unresectable or metastatic melanoma with a survival benefit. With longer follow-up, the survival benefit was maintained in patients who had an initial response to ipilimumab. Five-year follow-up data demonstrates survival rates of 13% to 23% with survival durations of 13 to 16 months.[41] It is also important to note that the 3-year survival mark is noteworthy for patients treated with ipilimumab. Up to 85% of the patients who were alive at 3 years were alive at 4 years, suggesting that the 3-year survival mark may be a useful surrogate endpoint.[42] After a period of time, it is felt that the balance between immune response and tumor growth can shift leading to disease relapse after an extended duration of response. Retreatment can be an option for patients who had an initial clinical benefit and has been shown to re-induce a response; no additional toxicities have been observed with re-induction.[43]

One of the greatest lessons learned from early clinical trials with ipilimumab was the difference in the kinetics of response seen with immunotherapies. Patients appeared to have no regression of disease for many weeks after treatment initiation. Even more alarming was around 10% of patients initially experienced a significant increase in tumor burden which suggested disease progression. This pseudoprogression was then followed by a delayed response to the drug after about 12 weeks of therapy; some patients continued to have a steady reduction in tumor burden over time which eventually produced a durable clinical benefit.[44] It is hypothesized that the delayed response is related to the time needed to stimulate the immune system.[41] Due to this phenomenon, the Response Evaluation Criteria in Solid Tumors (RECIST) has developed immune-related response criteria irRECIST and more recently iRECIST to evaluate immunotherapies.[45]

6 The greatest challenge with the use of ipilimumab is the management of irAEs. Patients must be thoroughly educated on signs and symptoms of irAEs and when to seek medical attention. Providers should be familiar with the different types, timing and appropriate management of irAEs (see Table 156-7). As previously discussed, management of irAEs should follow established treatment guidelines.[32]

5 **PD-1 Inhibitors** These agents have demonstrated response rates of 40% with long-term clinical benefit in early phase I trials.[46] Results from clinical trials showed that PD-1 inhibitors had a more favorable safety profile with significantly fewer irAEs compared to ipilimumab. Additionally, benefits were seen in patients who had been previously treated with ipilimumab. The

KEYNOTE-001 trial evaluated the efficacy of pembrolizumab in patients who were previously treated with ipilimumab. The trial reported an overall response rate was 26%, progression-free survival at 24 weeks was 45%, and 1-year overall survival of 58%.[47] Treatment was well tolerated with grade 3 or 4 adverse events occurring in 12% of patients. In the CheckMate 037 randomized controlled trial of patients previously treated with ipilimumab, nivolumab produced higher response rates (32% vs 11%) with fewer irAEs when compared to chemotherapy.[48] An important observation from these studies is the lack of cross-resistance between ipilimumab and PD-1 inhibitors. As with ipilimumab, if patients are able to achieve a response to these agents, that response can be maintained for an extended duration. Both pembrolizumab 2 mg/kg IV every 3 weeks and nivolumab 3 mg/kg IV every 2 weeks was approved for the treatment of patients with advanced or unresectable melanoma who progressed on previous ipilimumab therapy and, if applicable, a BRAF inhibitor.

6 Like ipilimumab, the response to PD-1 inhibitors is delayed but the response to PD-1 inhibitors may be slightly faster than with ipilimumab. The irAE profile with PD-1 inhibitors is different, with the most common adverse effects with pembrolizumab and nivolumab being fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgias and diarrhea.[47,48] The risk of grade 3 or 4 irAEs is significantly lower as compared to ipilimumab. Specifically, the incidence of grade 3 or 4 diarrhea/colitis with PD-1 inhibitors is dramatically lower and occurs in only 1% to 2% of patients. However, a higher incidence of autoimmune pneumonitis (1%-2%) is seen with nivolumab and pembrolizumab as compared to ipilimumab.[31] Patients should be counseled to notify a provider if they notice new or worsening cough, chest pain or shortness of breath. Treatment of irAEs follows the same established treatment algorithms as ipilimumab (Table 156-7).[32]

First-line therapy with PD-1 inhibitors has been evaluated for the treatment of unresectable or metastatic melanoma. In the KEYNOTE-006 trial, pembrolizumab was compared directly to ipilimumab for first-line treatment. In this trial, 834 patients with unresectable or metastatic melanoma were randomized to receive pembrolizumab 10 mg/kg every 2 weeks or every 3 weeks or ipilimumab 3 mg/kg every 3 weeks for 4 doses. One-year overall survival rates were 75% for the pembrolizumab every 2 weeks, 68.4% for the pembrolizumab every 3 weeks and 58.2% for ipilimumab.[49] Treatment-related grade 3 or 4 adverse effects were lower in both pembrolizumab arms.

With better efficacy and less toxicity compared to ipilimumab, the FDA-approved pembrolizumab 2 mg/kg IV every 3 weeks as a first-line treatment option for metastatic melanoma. Similarly, in a randomized controlled trial comparing nivolumab with dacarbazine for first-line treatment of BRAF wild-type metastatic melanoma, nivolumab produced significantly better 1-year overall survival rates (73% vs 42%), median progression-free survival (5.1 vs. 2.2 months), and overall response rates (40% vs 14%), respectively.[50] The NCCN Guidelines recommend both pembrolizumab and nivolumab as preferred first-line treatment options for patients with unresectable or metastatic disease.[6] More recently, each agent has received FDA approval to be given as a flat dose (pembrolizumab 200 mg every 3 weeks; nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks) based on dose/exposure, efficacy, and safety relationships.

5 6 **Combination CTLA-4 and PD-1 Inhibitors** The combination of a CTLA-4 inhibitor, which exerts its immune inhibition at the central level in the priming phase of activated T cells, and a PD-1 inhibitor, which acts in the peripheral phase within the tumor microenvironment, can result in synergistic activity. Survival rates of 90% at 1 year and >80% at 2 years are unprecedented in the treatment of metastatic melanoma in early trials.[39] This combination was studied in 945 previously untreated patients with unresectable stage III or IV melanoma. Patients were randomized to nivolumab alone, nivolumab plus ipilimumab, or ipilimumab alone. The median progression-free survival was 11.5 months with nivolumab plus ipilimumab as compared to 2.9 months with ipilimumab.[51] One of the most significant concerns of combining two immune checkpoint inhibitors is the safety profile. Grade 3 and 4 treatment-related adverse events were significantly higher with the combination arm compared to the ipilimumab arm (55% vs 27.3%), with an increased risk of hepatotoxicity in the combination arm. A second trial, CheckMate-069 confirmed the benefits of this combination. In that double-blind trial, 142 untreated melanoma patients were randomized to receive ipilimumab 3 mg/kg and nivolumab 1 mg/kg or the same dose of ipilimumab with placebo once every 3 weeks for 4 doses. Ipilimumab was then discontinued and patients received nivolumab or placebo at the same dose every 2 weeks until disease progression or unacceptable toxicity.[52] The objective response rate was 61% for patients receiving the combination versus 11% for patients receiving ipilimumab alone. Complete responses were seen in 22% of the combination arm with

none in the ipilimumab arm. Responses were seen regardless of BRAF mutational status. Median progression-free survival was significantly longer in the combination arm. As with previous studies, the responses appeared to be durable, with 82% of responding patients in the combination arm maintaining their response. The risk of grade 3 or 4 drug-related adverse reactions was higher in the combination arm (54% vs 24%). As a result of data from these two trials, the FDA granted approval of combination therapy with nivolumab and ipilimumab in patients with unresectable or metastatic melanoma. While this combination is a preferred treatment option according to the NCCN guidelines, it offers higher response rates, careful monitoring and aggressive management of toxicities are important.

Summary of Immune Checkpoint Inhibitors Over the last decade, the advances in immunotherapy have provided new treatment options and offered new hope regarding survival to patients with metastatic melanoma. These benefits are realized with single-agent or combination immune checkpoint inhibitors. Despite advances in the treatment of melanoma, several questions still surround the use of immunotherapy. First, how do we identify which patients will benefit from immunotherapy treatment? Some clinicians are hesitant to treat elderly patients or those with autoimmune conditions with ipilimumab because of concern for toxicity. These unique patient populations require further investigation. Second, what are the biomarkers of response to immunotherapy? Immunologic markers and other biomarkers have been investigated without success.[53] Tumors that express PD-L1, regardless of the type of cancer, have demonstrated higher responses to PD-1/PD-L1 blockade. However, patients with tumors that do not express PD-1/PD-L1 may also benefit and should not be excluded from this treatment option. Additionally, it remains unclear as to the best approach for assessing PD-L1 expression, definition of positivity in the assay, and clinical application.[46] Lastly, what is the optimal sequencing of immunotherapeutic agents and with immunotherapy and other therapeutic options? Ongoing studies are looking at sequencing of CTLA-4 inhibitors, PD-1/PD-L1 inhibitors, BRAF/MEK inhibitors, chemotherapy, and other investigational agents.

Other Immunotherapy Approaches Vaccine therapy has been investigated for over a decade in metastatic melanoma. The rationale for vaccination is that antigens expressed on the surface of tumor cells differ from normal cells and a vaccine has the ability to induce effective tumor-specific immune responses with less toxicity than conventional chemotherapy or other

immunotherapies.

A variety of melanoma vaccines, based on whole tumor cells, peptides, and proteins have been evaluated for the treatment of patients with metastatic disease and for intermediate- and high-risk patients after surgical resection of disease. To date, no vaccine has shown a survival advantage.[11] Occasional clinical responses have been observed in trials of melanoma vaccines. Vaccines in combination with other biologic therapies have been evaluated. Although early efficacy signals have been seen with some combinations approaches, none have shown improvement in survival.[11] Clinical trials that incorporate vaccines into currently approved immunotherapeutic treatments are ongoing.

Oncolytic immunotherapy is currently being investigated for the treatment of metastatic melanoma. Talimogene laherparepvec (T-VEC) is a genetically modified oncolytic virus derived from herpes simplex-1. T-VEC works by two distinct mechanisms: (1) modification of attenuated HSV-1 to selectively replicate within the tumor environment causing death while sparing other cells and (2) secretion of GM-CSF to attract dendritic cells to the site for antigen presentation and T-cell activation. Activated T cells can then target the cancer cells systemically. In a phase III study, T-VEC demonstrated better response rates (including complete responses) and a trend toward improved survival compared to GM-CSF alone.[54] It was well tolerated with fatigue, chills, and fever being the most common adverse events with few severe events reported. T-VEC is FDA approved for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with recurrent melanoma after initial surgery. T-VEC is administered intratumorally (injected directly into the tumor) and therefore patients with internal visceral disease are not appropriate candidates for treatment. With its favorable toxicity profile, ongoing studies are evaluating T-VEC in combination with other immune-directed treatments.

Targeted Therapy

7 Oral kinase inhibitors have emerged as standard therapy for malignancies such as renal cell carcinoma, chronic myelogenous leukemia, subsets of lung cancer, and gastrointestinal stromal tumors. As our understanding of the biology of melanoma grows, there is increasing interest in developing therapies against molecular targets involved in the development and progression of melanoma. Several orally administered targeted therapies are FDA approved for the treatment of melanoma (see **Tables 156-8** and **156-9**).

TABLE 156-8 Dosing of BRAF Inhibitors in Melanoma

Drug	Brand Name	Dose	Dose Reductions for Adverse Reactions	Food–Drug Interaction	Drug–Drug Interactions
Dabrafenib	Tafinlar	• 150 mg BID • Missed dose may be taken up to 6 hours prior to next dose	• First: 100 mg BID • Second: 75 mg BID • Third: 50 mg BID • Subsequent: permanently discontinue if unable to tolerate 50 mg BID	• Take at least 1 hour before or 2 hours after a meal • High-fat meals decrease C_{max} and AUC	• Dabrafenib may decrease drug levels of CYP2B6, CYP2C19, CYP2C8, CYP2C9, and CYP3A4 substrates • Strong CYP2C8 and CYP3A4 inhibitors may increase dabrafenib drug levels • Concurrent use with antacids, H2-antagonists, and proton pump inhibitors may decrease dabrafenib concentrations • Concurrent use with St. John's wort may decrease dabrafenib concentrations • Monitor closely if dabrafenib is used concurrently with other drugs known to prolong QT interval
Encorafenib	Braftovi	• 450 mg daily • Missed dose may be taken up to 12 hours prior to next dose	• First: 300 mg daily • Second: 200 mg daily • Subsequent: permanently discontinue if unable to tolerate 200 mg daily	• Take with or without food • Avoid grapefruit juice	• Strong and moderate CYP3A4 inhibitors may increase encorafenib drug levels • Reduce encorafenib dose to one-third original dose if used concurrently with strong CYP3A4 inhibitor • Reduce encorafenib dose to one-half original dose is used concurrently with moderate CYP3A4 inhibitor • Strong or moderate CYP3A4 inducers may decrease encorafenib drug levels • Encorafenib may increase toxicity or decrease efficacy of sensitive CYP3A4 substrates • Coadministration with hormonal contraceptives can result in decreased concentrations and loss of efficacy • Avoid coadministration of encorafenib with medicinal products known to prolong QTc interval
Vemurafenib	Zelboraf	• 960 mg BID • Missed dose may be taken up to 4 hours prior to next dose	• First: 720 mg BID • Second: 480 mg BID • Subsequent: permanently discontinue if unable to tolerate 480 mg BID	• Take with or without food • Avoid grapefruit juice	• Avoid concomitant administration with CYP1A2 substrates with a narrow therapeutic window • Strong CYP3A4 inhibitors/inducers may increase/decrease vemurafenib levels and should be avoided • Vemurafenib may increase levels of CYP2D6 substrates • Avoid concurrent use with P-gp substrates known to have narrow therapeutic indices • Monitor closely if vemurafenib is used concurrently with other drugs known to prolong QT interval

AUC, Area under the curve; CYP, cytochrome P450.

TABLE 156-9 Dosing of MEK Inhibitors in Melanoma

Drug	Brand Name	Dose	Dose Reductions for Adverse Reactions	Food-Drug Interaction	Drug-Drug Interactions
Binimetinib	Mektovi	• 45 mg BID • Missed dose may be taken up to 6 hours prior to the next dose	• First: 30 mg BID • Subsequent: permanently discontinue if unable to tolerate 30 mg BID	• Take with or without food	• No known significant interactions
Cobimetinib	Cotellic	• 60 mg daily on days 1-21 of 28-day cycle	• First: 40 mg daily • Second: 20 mg daily • Subsequent: permanently discontinue if unable to tolerate 20 mg daily	• Take with or without food	• CYP3A4 inducers may decrease the serum concentration of cobimetenib • CYP3A4 inhibitors may increase the serum concentration of cobimetenib
Trametinib	Mekinist	• 2 mg daily • Store in the refrigerator (36-46°F [2-8°C]) • Missed dose may be taken up to 12 hours prior to the next dose	• First: 1.5 mg daily • Second: 1 mg daily • Permanently discontinue if unable to tolerate 1 mg daily	• Take at least 1 hour before or 2 hours after a meal • High-fat meals may decrease AUC	• May enhance the adverse effects of dabrafenib

AUC, Area under the curve; CYP, cytochrome P450.

Vemurafenib, an orally available BRAF inhibitor, has shown activity in patients with melanoma who harbor a V600E mutation. In a phase III trial comparing vemurafenib with dacarbazine in patients with unresectable, previously untreated stage IIIC or IV melanoma with a *BRAF* V600E mutation, vemurafenib significantly improved response rate (48% vs 5%) and overall survival.[29] Patients treated with vemurafenib had longer median progression-free survival (5.3 vs 1.6 months) and a higher overall survival rate at 6 months (84% vs 64%). The median time-to-response was also shorter with vemurafenib than dacarbazine (1.45 vs 2.7 months).

Dabrafenib, another oral selective *BRAF* inhibitor, demonstrated similar activity to vemurafenib in early-stage clinical trials in patients with previously untreated *BRAF* V6000E mutated melanoma. In a phase III study, dabrafenib 150 mg orally twice daily was compared to dacarbazine in patients with untreated stage IV or unresectable stage III melanoma. Patients in the dabrafenib arm had longer median progression-free survival (5.1 vs 2.7 months).[55] A follow-up analysis showed that overall survival at 12 months

was 70% with dabrafenib as compared to 63% with dacarbazine.[55] Both vemurafenib and dabrafenib have been studied in melanoma patients with CNS metastasis with some activity. Other drugs targeted toward mutated *BRAF*, such as sorafenib, have not reported encouraging results.

BRAF inhibitors are generally well tolerated (see **Table 156-10**). Skin complications, comprising of cutaneous squamous cell carcinoma or keratoacanthoma and photosensitivity reactions, are a major concern with the use of these agents. In clinical trials, the incidence of cutaneous squamous cell carcinoma or keratoacanthoma with vemurafenib was 18% and 6% with dabrafenib.[6] The development of these lesions is thought to result from the activation of the MAPK pathway in healthy skin cells lacking BRAF alterations. As a result, patients receiving a BRAF inhibitor should have dermatologic evaluations prior to starting therapy, every 2 months while on therapy and for up to 6 months following discontinuation of therapy. Cutaneous complications can be effectively managed by surgical resection and treatment with the BRAF inhibitor can continue without dose adjustment.[56]

TABLE 156-10 Monitoring of BRAF Inhibitors in Melanoma

Drug	Adverse Reactions		Monitoring Parameters	Comments
	Common	Rare but Serious		
Dabrafenib	• Pyrexia • Rash • Chills • Headache • Arthralgia • Fatigue • Hyperkeratosis • Nausea/vomiting/diarrhea • Alopecia • Palmar-plantar erythrodysesthesia • Increased LFTs • Hyperglycemia • Hypophosphatemia	• New primary malignancies (cutaneous and noncutaneous) • Hemorrhage • Uveitis • Pancreatitis • Interstitial nephritis	• CMP including serum phosphorus, albumin, glucose, and LFTs • CBC for myelosuppression • Dermatologic exams at baseline, every 2 months during treatment, then 6 months after discontinuation for secondary skin malignancies • ECG for QT prolongation • Signs/symptoms of uveitis (vision changes, photophobia, eye pain)	• Risk of secondary skin malignancies decreases when used in combination with MEK inhibitor • ECHO to assess LVEF when used in combination with MEK inhibitor • Patients with G6PD deficiency are at risk for hemolytic anemia
Encorafenib	• Fatigue • Nausea/vomiting • Abdominal pain • Arthralgia • Rash • Myopathy • Hyperkeratosis • Headache • Anemia • Increased LFTs • Pyrexia	• New primary malignancies (cutaneous and noncutaneous) • Hemorrhage • Uveitis • QTc prolongation	• Dermatologic evaluation prior to, while on therapy, and following discontinuation of treatment • CMP including serum phosphorus, magnesium, glucose, and LFTs • ECG for QT prolongation; electrolytes before and during treatment • Signs/symptoms of uveitis (vision changes, photophobia, eye pain)	• Only FDA approved in combination with binimetinib • If binimetinib is held, the encorafenib dose must be reduced to 300 mg daily
Vemurafenib	• Arthralgia • Rash • Alopecia • Fatigue • Nausea • Photosensitivity • Pruritus • Skin papilloma	• New primary malignancies (cutaneous and noncutaneous) • Uveitis • QTc prolongation • Severe dermatologic reactions (SJS, TEN) • Hypersensitivity reactions (including DRESS) • Renal failure	• LFTs at baseline and monthly or as clinically indicated • Serum creatinine at baseline and periodically during treatment • ECG and electrolytes (including potassium, magnesium, and calcium) at baseline, after 15 days, monthly for the first 3 months, then every 3 months or as clinically indicated • Dermatologic exams at baseline, every 2 months during treatment. Consider monitoring for 6 months following discontinuation • Signs/symptoms of uveitis (vision changes, photophobia, eye pain) • Monitor closely if administered concomitantly or sequentially with radiation treatment	• Off-label indication for BRAF V600K mutation • Associated with rare cases of pancreatitis; evaluate unexplained abdominal pain • Due to photosensitivity, patients should avoid sun, wear protective clothing, and wear sunscreen

LFT's, liver function tests; CMP, comprehensive metabolic panel; CBC, complete blood count; LVEF, left ventricular function; CPK, creatine phosphokinase; DVT, deep vein thrombosis; PE, pulmonary embolism; DRESS, drug reaction with eosinophilia and systemic symptoms.

Resistance to BRAF inhibitors is potentially caused by mutations in *MEK*, dependency on MEK/ERK antiapoptotic signaling, PI3K/AKT pathway involvement, *NRAS* mutation, or MAPK pathway reactivation. Concurrent treatment with a MEK inhibitor in combination with a BRAF can delay the development of acquired resistance.

7 MEK inhibitors have been studied in the treatment of metastatic melanoma and have shown modest activity as monotherapy. Trametinib is an oral small-molecule inhibitor of MEK1/2. These results were confirmed in a phase III trial that compared trametinib to chemotherapy (dacarbazine or paclitaxel). In this trial, median progression-free survival was 4.8 months versus 1.5 months in the trametinib and chemotherapy arms, respectively. Overall survival at 6 months was 81% for trametinib and 67% for chemotherapy (HR 0.54, $P = 0.01$), even with crossover at progression. Common adverse events seen with trametinib were rash, diarrhea, and peripheral edema (see **Table 156-11**). Interestingly, secondary skin neoplasms were not observed in this trial.[30]

TABLE 156-11 Monitoring of MEK Inhibitors in Melanoma

Drug	Adverse Reactions		Monitoring Parameters	Comments
	Common	Rare but Serious		
Binimetinib	• Fatigue • Nausea/vomiting • Abdominal pain • Diarrhea • Constipation • Rash • Increased LFTs • Anemia • Increased creatinine • Increased CPK • Hyponatremia	• VTE • Cardiomyopathy • Ocular toxicity (serous retinopathy/retinal pigment epithelial detachments, retinal vein occlusion) • Interstitial lung disease/ pneumonitis • New primary malignancies (cutaneous and noncutaneous) • Hemorrhage • Rhabdomyolysis	• LFTs at baseline, monthly during treatment, and as clinically indicated • CPK and serum creatinine at baseline, periodically during treatment, and as clinically indicated • Assess for visual symptoms at each visit. Perform ophthalmologic exam at regular interval and for any new/ worsening visual disturbances • Signs and symptoms of bleeding • LVEF at baseline, 1 month after therapy initiation, then at 2- to 3-month intervals for cardiomyopathy • Evaluate for signs/symptoms of pulmonary toxicity (cough, dyspnea, hypoxia, pleural effusions, infiltrates)	• If encorafenib is permanently discontinued, discontinue binimetinib • Serous retinopathy occurred in 20% of patients treated with binimetinib in combination with encorafenib • Elevation in LFTs can occur with combination; monitor prior to beginning treatment and monthly during treatment
Cobimetinib	• Nausea/vomiting • Diarrhea • Hypertension • Photosensitivity • Pyrexia • Hypophosphatemia • Electrolyte disturbances • Hypoalbuminemia • Lymphopenia • Anemia • Increased LFTs • Increased CPK • Increase in serum creatinine • Hyponatremia	• Cardiomyopathy • Hemorrhage • New primary malignancies (cutaneous and noncutaneous) • Ocular toxicity (serous retinopathy, retinal vein occlusion • Hepatotoxicity • Rhabdomyolysis	• CMP at baseline and monthly during treatment for hepatotoxicity, renal failure, and electrolyte replacement • CPK at baseline, periodically during treatment, and as clinically indicated • LVEF at baseline, 1 month after initiation of therapy, and every 3 months until discontinuation • Dermatologic exams at baseline, every 2 months during treatment, then 6 months after discontinuation for secondary skin malignancies • Ophthalmological evaluation at regular intervals and at any sign of new or worsening visual disturbances • Signs and symptoms of hemorrhage and rhabdomyolysis	• Due to photosensitivity, patients should avoid the sun, wear protective clothing, and wear sunscreen • Hypertension has been seen in combination with vemurafenib
Trametinib	• Dermatologic toxicity (rash, acneiform dermatitis, palmar-plantar erythrodysesthesia, erythema) • Diarrhea • Lymphedema (including edema, peripheral edema) • Pyrexia • Hypertension • Fatigue • Nausea/vomiting • Hyperglycemia • Increased LFTs • Anemia • Hypoalbuminemia	• VTE • Cardiomyopathy • Ocular toxicity (retinal pigment epithelial detachments, retinal vein occlusion) • Interstitial lung disease/ pneumonitis • New primary malignancies (cutaneous and noncutaneous) • Hemorrhage • Colitis/GI perforation • Rhabdomyolysis	• CBC and CMP at baseline and as clinically indicated • LVEF at baseline, 1 month after therapy initiation, then at 2- to 3-month intervals • Ophthalmological evaluation periodically and at any sign of visual disturbance • Evaluate for signs/symptoms of pulmonary toxicity (cough, dyspnea, hypoxia, pleural effusions, infiltrates) • Blood pressure • Signs and symptoms of bleeding • Dermatologic exams at baseline, every 2 months during treatment, then 6 months after discontinuation • Monitor closely for colitis and GI perforation	• Some hospitalizations required for severe skin toxicities • Intracranial hemorrhage reported to be fatal • Many adverse effects are increased when trametinib is used in combination with dabrafenib • Increase incidence of DVT/PE when used in combination with dabrafenib • Increase in serious febrile reactions when used in combination with dabrafenib

LFT's, liver function tests; CMP, comprehensive metabolic panel; CBC, complete blood count; LVEF, left ventricular function; CPK, creatine phosphokinase; DVT, deep vein thrombosis; PE, pulmonary embolism; DRESS, drug reaction with eosinophilia and systemic symptoms; VTE, venous thromboembolism.

In addition to delaying drug resistance, the combination of BRAF and MEK inhibitors shows additive efficacy in the treatment of melanoma. The combination of trametinib 2 mg orally once daily and dabrafenib 150 mg orally twice daily received accelerated approval for treatment in patients with unresectable or metastatic melanoma with BRAF V600 mutations based on higher objective response rates compared to either agent alone. Additional trials with this combination compared to BRAF inhibitors in the same patient population confirmed early findings and led to a full FDA approval. In a clinical trial that compared the combination to dabrafenib alone, patients randomized to the combination had longer median progression-free survival (9.3 vs 8.8 months), overall survival at 6 months (93% vs 85%) and higher overall response rates (66% vs 51%) as compared with dabrafenib alone.[57] In another phase III trial, the combination of dabrafenib and trametinib showed significantly longer median overall survival (not reached vs 17.2 months, HR 0.69, $P = 0.005$) and higher overall survival at 12 months (72% vs 65%). Median progression-free survival was also significantly longer (11.4 vs 7.3 months) and the overall response rate was higher (64% vs 51%) in patients treated with the combination.[58] The safety profile with the combination was similar to that observed with either drug given alone, with the notable exception of decreased incidence of skin complications in the combination arms.

Cobimetinib is another inhibitor of MEK1/2 approved in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation. The recommended dosing with this regimen is vemurafenib 960 mg orally twice daily on days 1 to 28 and cobimetinib 60 mg orally once daily on days 1 to 21 of a 28 day cycle. In a phase III trial, median progression-free survival was significantly improved with the combined regimen of cobimetinib and vemurafenib versus vemurafenib alone (12.3 vs 7.2 months). Median overall survival was also statistically significant in favor of the combination (22.3 vs 17.4 months). Overall response rates were 70% and 50% for the combination and single-agent arms, respectively. Adverse events were similar across the two groups and similar to the other MEK and BRAF combination, the number of secondary cutaneous cancer was decreased.[59]

After years of dabrafenib/trametinib and vemurafenib/cobimetinib as the only BRAF/MEK inhibitors on the market, a new combination was FDA approved in June 2018. The safety and efficacy of encorafenib/binimetinib

were established in the COLUMBUS trial, a phase III study where 577 patients were randomized to receive either encorafenib 450 mg daily plus binimetinib 45 mg twice daily, encorafenib 300 mg daily, or vemurafenib 960 mg twice daily. Median progression-free survival was significantly longer with the combination as compared with vemurafenib alone (14.9 vs 7.3 months). The overall response rate was higher with encorafenib/binimetinib (63%) as compared to BRAF inhibitor monotherapy (40% with vemurafenib). The median overall survival was 33.6 months for the combination of encorafenib/binimetinib as compared to 16.9 months with vemurafenib (HR 0.61, $P < 0.001$).[60] This is the longest overall survival seen of all studies conducted with BRAF/MEK inhibitors. The adverse events seen with encorafenib/binimetinib are similar to those of other BRAF/MEK inhibitor combinations.

Another agent of interest in the treatment of metastatic melanoma is imatinib mesylate, an oral agent that inhibits *KIT* and platelet-derived growth factor receptor. *KIT* is expressed primarily in acral and mucosal melanomas and treatment with imatinib showed activity against melanoma cell growth in preclinical studies. In clinical trials with unselected patients, imatinib did not show benefit in metastatic melanoma despite downregulation of phosphorylated *KIT*.[6] However, a phase II trial of imatinib in patients with *KIT* mutations reported that 23% had a partial response, 30% had stable disease, and progression-free survival was 3.5 months.[61] Responses in these patients were short, similar to what is seen with BRAF inhibitor monotherapy.

Other potential molecular targets in the treatment of melanoma include vascular endothelial growth factor and cyclin-dependent kinases. Studies with drugs that inhibit these pathways are currently ongoing. With the success of immunotherapy, combining targeted agents with immunotherapeutic agents is another area of research interest. Reports from a phase I trial combining vemurafenib and ipilimumab showed significant hepatotoxicity, thus reiterating the importance of patient selection to identify the best candidates for combined modality therapy.[62] KEYNOTE-022 is another ongoing study looking at the combination of immunotherapy (pembrolizumab) and targeted therapy (dabrafenib/trametinib).

Radiation

The role of radiation in the adjuvant treatment of melanoma has been investigated. Recent data from a prospective study suggest patients treated

with therapeutic lymphadenectomy for lymph node relapse benefit from postoperative radiation to the nodal basins as compared to observation. Lymph node recurrence was significantly less in the adjuvant radiation arm, but increased toxicity was noted. No difference in overall survival or relapse-free survival was observed between the groups.[63] Adjuvant radiation may be an acceptable option for selected patients. Radiation can also be used patients with in-transit metastasis, satellite metastasis or for extranodal tumor extension. For patients with metastatic melanoma, radiation is palliative to symptomatic areas of disease progression. Stereotactic radiosurgery (SRS), or stereotactic radiotherapy (SRT), is the preferred type of treatment for brain metastases. Adjuvant radiation, given after resection of brain metastases, can help with disease control. Whole brain radiation is associated with worse cognitive decline compared to SRS/SRT, and therefore should be used in situations when SRS/SRT is not achievable.[64] Whole brain radiation may be needed in situations that involve numerous brain metastasis or leptomeningeal disease.

Limb Perfusion and Limb Infusion

Isolated limb perfusion is a surgical procedure involving regional intravascular delivery of chemotherapy or biotherapy (or both) into an extremity with cutaneous melanoma.[65] When in-transit metastasis occurs in extremities, local therapy with isolated limb perfusion or isolated limb infusion has been used. Isolated limb perfusion is a method for escalating the dose of chemotherapeutic drugs to a specific region of the body while limiting the systemic toxicities of the agent. Most perfusions can be performed with drug exposures of less than 2%. The most significant side effect of isolated limb perfusion is regional toxicity because the skin, subcutaneous tissue, and tissue of the extremity receives the same dose and is subjected to the same perfusion conditions as the tumor located within the extremity. After regional perfusions, objective response rates greater than 50% in treated limbs have been reported, with overall response rates possibly as high as 80%. Although most clinical trials have used melphalan, it is not known whether the combination of melphalan with other agents may improve results.[66] A simplified form of isolated limb perfusion, called isolated limb infusion, is a low-flow isolated limb perfusion performed under hypoxic conditions via small-caliber arterial and venous catheters. It has been proposed that the hypoxia which develops during isolated limb infusion may

be beneficial with certain cytotoxic agents such as melphalan.

EVALUATION OF THERAPEUTIC OUTCOMES

The outcome of patients treated with melanoma depends on the stage of disease at presentation. The prognosis of patients with thin tumors (less than 1 mm in thickness) and localized disease is good with long-term survival in more than 90% of patients. The risk of regional nodal involvement rises with increasing tumor thickness and survival rates decrease in patients with nodal involvement. Long-term survival in patients with distant metastasis is even lower. Therefore, early diagnosis and appropriate treatment of early disease are essential. Patients with suspicious pigmented lesions should be evaluated and the lesion excised whenever possible. Treatment is determined by patient factors and stage of disease.

Clinical practice guidelines published by the NCCN and European Society of Clinical Oncology (ESMO) provide guidance for treatment and follow-up of patients with melanoma.[6,67] Intensive surveillance has the benefit of early detection of recurrent disease, which may lead to better options for surgical resection. Emphasis on the evaluation of locoregional areas is important. For patients with in situ melanoma, periodic skin examinations for life are recommended, with frequency determined based on patient risk factors. Local recurrence is associated with aggressive tumor biology and frequently is a manifestation of an aggressive primary tumor. If a local recurrence occurs after inadequate primary disease management, the patient should undergo a workup based on the lesion thickness of the original melanoma. Patients with nodal recurrence should be evaluated for lymph node metastasis. Patients with systemic recurrence should be evaluated and treated in a fashion similar to patients presenting with systemic disease.

CONCLUSION

Treatment of cutaneous melanoma is determined by both disease-related and patient-related issues. Treatment recommendations are based on stage of disease. Treatment of localized disease is surgical excision, with the extent of excision based on the tumor size. Wide excision is recommended for in situ melanoma and wide excision with SLNB for stage IA, IB, and II disease.

The addition of new immunotherapy and targeted agents has increased the number of adjuvant treatment options for patients with melanoma who are at

high risk of recurrence. Identifying which patients are appropriate candidates for treatment after resection of the primary tumor remains a challenge. When choosing an adjuvant treatment patient preference, age, comorbidities, and risk of recurrence should all be taken into account.[6]

8 Due to the rapid influx of effective therapies, the management of metastatic melanoma has become complex. The NCCN guidelines list a variety of preferred systemic therapies for advanced or metastatic melanoma, including ipilimumab, ipilimumab/nivolumab, pembrolizumab, nivolumab, combination BRAF/MEK inhibitor, high-dose aldesleukin and in certain cases chemotherapy.[6] The choice of drug therapy should be based on *BRAF* mutational status, the aggressiveness of the disease, and disease-related symptoms. Patients with a more indolent clinical picture may respond better to immunotherapy. Patients with a documented *BRAF* mutation are candidates for treatment with a BRAF/MEK inhibitor regimen. Best supportive care is also an option in some individuals. Data suggest that surgical treatment of metastatic melanoma should be considered in select individuals based on the extent and location of disease and performance status.

Postclass Engaged Learning Activity

Conduct a literature search and identify a primary research article published in the past 12 months regarding an immunotherapeutic agent or targeted agent used for the treatment of metastatic melanoma. Write a brief summary of the study methods, the major findings, and how this new information might change current practice. If the article discusses a new medication that is not described in the chapter, write a brief summary of the medication's mechanisms of action, how it is administered, and one potential advantage or disadvantage of this new medication compared to the current standard of care. This activity is intended to build your literature evaluation skills and the ability to critically appraise research articles.

ABBREVIATIONS

AJCC	American Joint Committee on Cancer
ALM	acral lentiginous melanoma
ARF	alternative reading frame
CSD	chronic sun damage
CTL	cytotoxic T lymphocyte
CTLA-4	cytotoxic T lymphocyte antigen 4
ECOG	Eastern Cooperative Oncology Group
EORTC	The European Organization for Research and Treatment of Cancer
ESMO	European Society of Clinical Oncology
FAMMM	familial atypical multiple mole syndrome
FDA	Food and Drug Administration
HR	hazard ratio
HDI	high-dose interferon
HLA	human leukocyte antigen
IFN	interferon
IL-2	interleukin-2
irAEs	immune related adverse effects
JAK	janus-kinase
LAK	lymphokine-activated killer
LDH	lactate dehydrogenase
LDI	low-dose interferon
LMM	lentigo maligna melanoma
MAPK	mitogen-activated protein kinase pathway
mTOR	mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
NK	natural killer
NMSC	nonmelanoma skin cancer

NSAID	nonsteroidal anti-inflammatory drug
PD-1	programmed death receptor 1
PET	positron emission tomography
PI3K	phosphatidyl-inosital-3-OH kinase
SLNB	sentinel lymph node biopsy
SPF	sun protection factor
SRS	stereotactic radiosurgery
SRT	stereotactic radiotherapy
SSE	skin self-examination
SSM	superficial spreading melanoma
STAT	signal-transducer-and-activator-of-transcription
TNF	tumor necrosis factor
TIL	tumor-infiltrating lymphocyte
UV	ultraviolet
UVA	ultraviolet A
UVB	ultraviolet B
VEGF	vascular endothelial growth factor

REFERENCES

1. Schadendof D, van Akkoo1 ACJ, Berking C, et al. Melanoma. *Lancet*. 2018;392:971–984.
2. SEER Cancer Statistics Factsheets: Melanoma of the Skin. Bethesda, MD: National Cancer Institute. Available at: http://seer.cancer.ogv/statfacts/html/melan/html. Accessed March 8, 2020.
3. American Cancer Society. *Cancer Facts & Figures 2020*. Atlanta, GA: American Cancer Society; 2020.
4. Saiyed FK, Hamilton EC, Austin MT. Pediatric melanoma: Incidence, treatment, and prognosis. *Pediatric Health Med Ther.* 2017;8:39–45.
5. Lin SW, Wheeler DC, Park Y, et al. Prospective study of ultraviolet radiation exposure and risk of cancer in the United States. *Int J Cancer*. 2012;131:E1015–E1023.
6. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Cutaneous Melanoma version 1.2020. Available at: http://www.nccn.org. Accessed March 8, 2020.
7. Kubica AW, Brewer JD. Melanoma in immunosuppressed patients. *Mayo Clin Proc.* 2012;87:991–1003.

8. Soura S, Eliades PJ, Shannon K, et al. Hereditary melanoma: Update on syndromes and management: genetics of familial atypical multiple mole melanoma syndrome. *J Am Acad Dermatol*. 2016;74:395–407.
9. Soura S, Eliades PJ, Shannon K, et al. Hereditary melanoma: Update on syndromes and management: Emerging melanoma cancer complexes and genetic counseling. *J Am Acad Dermatol*. 2016;74:411–420.
10. Gangadhar TC, Fecher LA, Miller CJ, et al. Melanoma. *Ableoff's Clinical Oncology*. 5th ed. Philadelphia, PA: Churchill Livingstone; 2014;1071–1091.
11. Zhu Z, Liu W, Gotlieb V. The rapidly evolving therapies for advanced melanoma: Towards immunotherapy, molecular targeted therapy, and beyond. *Crit Rev Oncol Hematol*. 2016;99:91–99.
12. Linares MA, Zakaria A, Nizran P. Skin Cancers. *Primary Care: Clinics in Office Practice*. 2015;42;645–659.
13. Lane Am, Kim IK, Gragoudas ES. Survival rates in patients after treatment for metastasis from uveal melanoma. *JAMA Ophthalmol*. 2018;136:981–986.
14. Goh AY, Layton CJ. Evolving systemic targeted therapy strategies in uveal melanoma and implications for ophthalmic management: A review. *Clin Experiment Ophthalmol*. 2016;44:509–519.
15. U.S. Department of Health and Human Services. *The Surgeon General's Call to Action to Prevent Skin Cancer*. Washington, DC: U.S. Dept of Health and Human Services, Office of the Surgeon General; 2014.
16. Wehner MR, Chren M, Nameth D, et al. International prevalence of indoor tanning: A systematic review and meta-analysis. *JAMA Dermatol*. 2014;150:390–400.
17. Ogden N. General and plastic surgery devices: Reclassification of ultraviolet lamps for tanning, henceforth to be known as sunlamp products and ultraviolet lamps intended for use in sunlamp products. Available at: https://www.federalregister.gov/articles/2014/06/02/2014-12546/general-and-plastic-surgery-devices-reclassification-of-ultraviolet-lamps-for-tanning-henceforth-to. Accessed March 8, 2020.
18. Department of Health and Human Services, Food and Drug Administration 21 CFR Parts 201 and 310, labeling and effectiveness testing; sunscreen drug products for over-the-counter human use. Available at: https://www.gpo.gov/fdsys/pkg/FR-2011-06-17/pdf/2011-14766.pdf. Accessed March 8, 2020.

19. Gershenwald JE, Scolyer RA. Melanoma staging: American Joint Committee on Cancer (AJCC) 8th edition and beyond. *Ann Surg Oncol*. 2018;25:2105–2010.
20. Breslow A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. *Ann Surg*. 1970;172: 1902–1908.
21. Wong SL, Farles MB, Kennedy EB, et al. Sentinel lymph node biopsy and management of regional lymph nodes in melanoma: American Society of Clinical Oncology and Society of Surgical Oncology clinical practice guideline update. *J Clin Oncol*. 2018;36:399–413.
22. Wisco OJ, Sober AJ. Prognostic factors for melanoma. *Dermatol Clin*. 2012;30:496–485.
23. Joyce KM. Chapter 7: Surgical management of melanoma. In: Ward WH, Farma JM, eds. *Cutaneous Melanoma: Etiology and Therapy* [Internet]. Brisbane (AU): Codon Publications; 2017.
24. Morton DL, Thompson JF, Cochran AJ, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *N Engl J Med.* 2014;370:599–609.
25. Faries MB, Thompson JF, Cochran AJ, et al. Completion dissection or observation for sentinel-node metastasis in melanoma. *N Engl J Med.* 2017;376:2211–2222.
26. Bernard ME, Wegner RE, Reineman K, et al. Linear accelerator based stereotactic radiosurgery for melanoma brain metastasis. *J Cancer Res Ther.* 2012;8:215–221.
27. Hauschild A, Gogas H, Tarhini A, et al. Practical guidelines for the management of interferon-alpha-2b side effects in patients receiving adjuvant treatment for melanoma. *Cancer*. 2008;112:982–994.
28. Eggermont AMM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): A randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2015;16:522–530.
29. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med.* 2011;364:2507–2516.
30. Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. *N Engl J Med.* 2012;367:107–114.
31. Weber JS, Yang JC, Atkins MB, Disis ML. Toxicities of immunotherapy

for the practitioner. *J Clin Oncol*. 2015:2092–2099.

32. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Management of Immunotherapy-Related Toxicites version 1.2020. Available at: http://www.nccn.org. Accessed March 8, 2020.
33. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. *N Engl J Med.* 2017;377:1824–1835.
34. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. *N Engl J Med.* 2018;378:1789–1801.
35. Long GV, Hauschild A, Santinami M, et al. Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. *N Engl J Med.* 2017;377:1813–1823.
36. Yang AS, Chapman PB. The history and future of chemotherapy for melanoma. *Hematol Oncol Clin North Am.* 2009;23:583–597.
37. Hauschild A, Agarwala SS, Trefzer U, et al. Results of a phase III randomized, placebo controlled study of sorafenib in combination with carboplatin and paclitaxel as second line therapy in patients with unresectable stage II or stage IV melanoma. *J Clin Oncol*. 2009;27:2823–2830.
38. Hersh E, Del Vecchio M, Brown M, et al. A randomized, controlled phase III trial of nab-paclitaxel versus dacarbazine in chemotherapy-naïve patients with metastatic melanoma. *Ann Oncol*. 2015;26:2267–2274.
39. Sim GC, Radvanyi L. The IL-2 cytokine family in cancer immunotherapy. *Cytokine Growth Factor Rev.* 2014;25:377–390.
40. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med.* 2010;363:711–723.
41. Delyon J, Maio M, Lebbé C. The ipilimumab lesson in melanoma: Achieving long-term survival. *Semin Oncol*. 2015;42:387–401.
42. McDermott D, Lebbe C, Hodi FS, et al. Durable benefit and the potential for long-term survival with immunotherapy in advanced melanoma. *Can Treat Review*. 2014;40:1056–1064.
43. Chiarion-Sileni V, Pigozzo J, Ascietro PA, et al. Ipilimumab retreatment in patients with pretreated advanced melanoma: The expanded access programme in Italy. *Br J Can.* 2014;110:1721–1726.

44. Weber JS, Kahler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol*. 2012;30:2691–2697.
45. Seymour L, Bogaerts J, Perrone A, et al. iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol*. 2017;18:e143–e152.
46. Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer. *J Clin Oncol*. 2015;33:1974–1982.
47. Ribas A, Hodi FS, Kefford R, et al. Efficacy and safety of the anti-PD-1 monoclonal antibody MK-3475 in 411 patients with melanoma. *J Clin Oncol*. 2014;32:5s.
48. Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): A randomised controlled, open-label, phase 3trial. *Lancet Oncol*. 2015;16:375–384.
49. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med.* 2015;372:2521–2532.
50. Roberts C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med.* 2015;372:320–330.
51. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med.* 2015;373:23–34.
52. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N Engl J Med.* 2015;372:2006–2017.
53. Eggermont AMM, Maio M, Robert C. Immune checkpoint inhibitors in melanoma provide the cornerstones for curative therapies. *Semin Oncol*. 2015;42:429–435.
54. Andtbacka RHI, Collichio FA, Amatruda T, et al. OPTiM: A randomized phase III trial of talimogene laherparepvec versus subcutaneous granulocyte-macrophage colony-stimulating factor for the treatment of unresected stage IIIB/C and IV melanoma. *J Clin Oncol*. 2015;58:3377.
55. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated melanoma: A muticentre, open-label, phase 3 randomised controlled trial. *Lancet*. 2102;380:358–365.
56. Muñoz-Couselo E, García JS, Pérez-García JM, et al. Recent advances in the treatment of melanoma with BRAF and MEK inhibitors. *Ann Transl*

Med. 2015;3:207.

57. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N Engl J Med.* 2014;371:1877–1888.
58. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med.* 2015;372:30–39.
59. Larkin J, Ascierto B, Dreno V, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med.* 2014;371:1867–1876.
60. Dummer R, Ascierto PA, Gogas HJ, et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): A multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2018;19:1315–1327.
61. Amaria RN, Gonzalez R. Updated approach to the patient with metastatic melanoma. *Emerg Cancer Ther.* 2012;3:583–602.
62. Ribas A, Hodi FS, Callahan M, et al. Hepatotoxicity with combination of vemurafenib and ipilimumab. *N Eng J Med.* 2013;368:1365–1366.
63. Burmeister BH, Ainslie J, et al. Adjuvant lymph-node field radiotherapy versus observation only in patients with melanoma at high risk for further lymph-node filed relapse after lymphadenectomy (ANZMTG 01.02/TROG02.01): 6-Year follow-up of a phase 3, randomised controlled trial. *Lancet Oncol*. 2015;16:1049–1060.
64. Brown PD, Ballman KV, Cerhan JH, et al. Postoperative stereotactic radiosurgery compared to whole brain radio-therapy for resected metastatic brain disease: A multicenter, randomized, controlled, phase 3 trial. *Lancet Oncol*. 2017;18:1049–1060.
65. Coleman A, Augustine CK, Beasely G, et al. Optimizing regional infusion treatment strategies for melanoma extremities. *Expert Rev Anticancer Ther.* 2009;9:1599–1609.
66. Sanki A, Kam PCA, Thompson JF. Long-term results of hyperthermic isolated limb perfusion for melanoma. *Ann Surg.* 2007;245:591–596.
67. Michieli O, van Akkooi ACJ, Ascierto PA, Dummer R, Keilholz U. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol*. 2019;30:1884–1901.

157

Hematopoietic Stem Cell Transplantation

Susanne Liewer and Janelle Perkins

KEY CONCEPTS

1. Hematopoietic stem cell transplantation (HSCT) is a process that involves intravenous infusion of hematopoietic stem cells from a donor into a recipient, after the administration of chemotherapy with or without radiation. The rationale is to increase tumor cell kill by increasing the dose of myelotoxic therapies and using donor hematopoietic stem cells to "rescue" the recipient from the hematologic toxicity. Immune-mediated effects also contribute to the tumor cell kill observed after allogeneic HSCT.
2. Hematopoietic stem cells used for transplantation can come from the recipient (autologous) or from a related or unrelated donor (allogeneic). If the related donor is a twin, the transplant is referred to as a syngeneic transplant.
3. Human leukocyte antigen (HLA) mismatching of allogeneic donor-recipient pairs at either class I or class II loci increases the risk of graft failure, graft-versus-host disease (GVHD), and worsens survival. The ideal donor is one that is matched at HLA-A, B, C, and DRB1.
4. Hematopoietic stem cells are found in the bone marrow, peripheral blood, and umbilical cord blood. Because of the rarity and similarity to other cells, hematopoietic stem cells are difficult to isolate and measure. These stem cells express the CD34 antigen, and measurement of the number of $CD34^+$ cells is a clinically useful measure of the number of hematopoietic stem cells.
5. Because of clinical and economic advantages, peripheral blood has replaced bone marrow as the source of hematopoietic stem cells in the autologous

and adult allogeneic HSCT setting.

6. The purpose of the preparative (or conditioning) regimen in traditional myeloablative transplants is twofold: (a) maximal tumor cell kill and (b) immunosuppression of the recipient to reduce the risk of graft rejection (allogeneic HSCT only).
7. Reduced-intensity conditioning regimens (including those that are nonmyeloablative) have been developed in order to reduce early posttransplant morbidity and mortality while maximizing the graft-versus-malignancy (GVM) effect. The advantage of this approach is that patients who would otherwise not be eligible for allogeneic HSCT can be offered a potentially curative therapy.
8. Transplant-related mortality associated with allogeneic HSCT ranges from 10% to 80% depending mostly on age, recipient performance status, donor source and degree of HLA matching, and disease status. Major causes of death include relapse, infection, organ toxicity, and GVHD. The most common cause of death after autologous HSCT is disease relapse; transplant-related mortality is usually less than 5%, depending on the conditioning regimen, age, and disease status.
9. Patients undergoing allogeneic HSCT are given prophylactic immunosuppressive therapy, which inhibits T-cell activation, proliferation, or both. The most commonly used GVHD prophylaxis regimens are cyclosporine or tacrolimus and methotrexate. Sirolimus or mycophenolate mofetil are often substituted for methotrexate.
10. Initial treatment of both acute and chronic GVHD consists of prednisone, either alone or combined with cyclosporine or tacrolimus. Treatment of patients with steroid-refractory GVHD is unsatisfactory.

Preclass Engaged Learning Activity

Watch the “What is GVHD?” video available on the YouTube website. This video gives a brief overview of graft-versus-host disease (GVHD) for the purposes of patient education. By watching the video, students can learn the basics about GVHD in preparation for a more in depth discussion provided by the chapter.

Next, watch the video “Ruxolitinib and ibrutinib: the future for GvHD treatment?” about two new drugs that have been used for the treatment of

GVHD.

INTRODUCTION

1 Hematopoietic stem cell transplantation (HSCT) is a process that involves intravenous infusion of hematopoietic stem cells from a compatible donor into a recipient, usually after administration of high-dose chemotherapy with or without radiation (called conditioning or preparative regimens). The original rationale for HSCT in the treatment of malignant disease is based on studies showing that many anticancer drugs and radiation have a steep dose–response relationship and that myelosuppression limits the chemotherapy dosage that can be safely administered. Although standard-dose chemotherapy can prolong survival in many cancer patients, most patients are not cured of their disease with this strategy alone. Infusion of hematopoietic stem cells allows the administration of very high doses of chemotherapy (as much as 10-fold higher) by reestablishing hematopoiesis. If tumor cells that are resistant to standard doses are sensitive to higher doses of chemotherapy, then tumor cell kill will be greatly increased, and the likelihood of cure would be higher with HSCT compared with standard-dose chemotherapy. However, the chemotherapy dose cannot be escalated indefinitely due to the risk of death caused by nonhematologic toxicity (see **Fig. 157-1**).

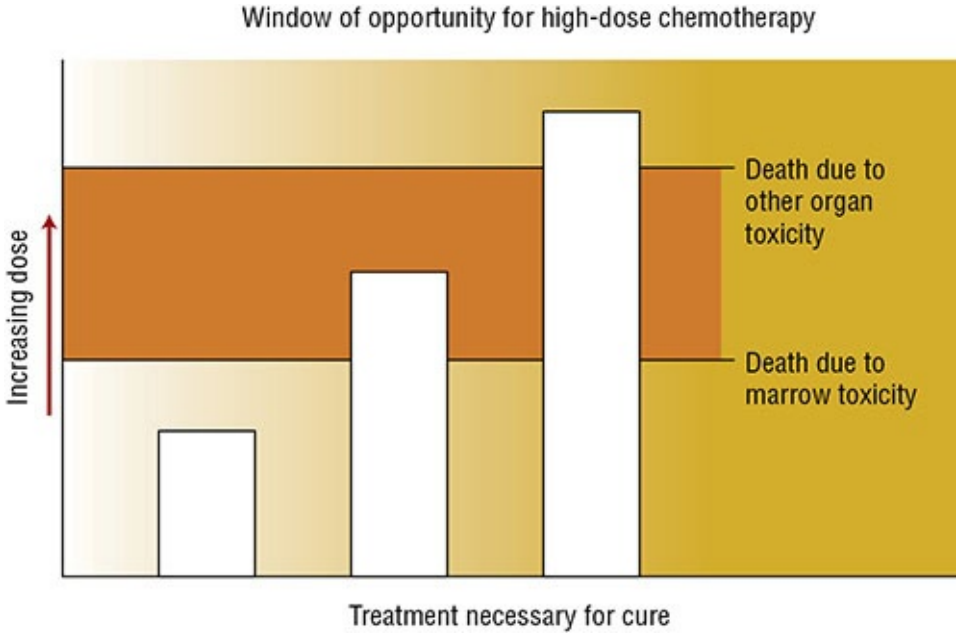


FIGURE 157-1 Patients represented by the middle column are the best

candidates for hematopoietic stem cell transplantation because the technique allows for administration of chemotherapy or radiation in doses that otherwise would be intolerable because of severe myelosuppression.

HSCT is an important modality for the treatment of a variety of malignant and nonmalignant diseases. Within the United States, about 23,000 transplants were performed in 2017, primarily for malignant diseases.[1] The most common malignancies treated with HSCT are multiple myeloma, lymphomas, and leukemias. The number of transplants has grown steadily over the past decade because of an increase in the number of patients receiving alternative donor transplants and an increase in the number of patients older than 60 years undergoing transplantation.

Although HSCT is most commonly used for treatment of malignant diseases, many nonmalignant hematologic disorders, including aplastic anemia, thalassemia, and sickle cell anemia; immunodeficiency disorders; and other genetic disorders are also potentially curable with allogeneic HSCT. Transplantation is also being investigated as a treatment modality for patients with life-threatening autoimmune diseases, such as rheumatoid arthritis, systemic and multiple sclerosis, and systemic lupus erythematosus.

This chapter summarizes the procedures involved in HSCT and the common complications associated with HSCT. More detailed information on HSCT can be found in published reviews and books.[2,3] Information on HSCT also can be found on several websites, including http://www.cibmtr.org (Center for International Blood and Marrow Transplant Research [CIBMTR]) and https://bethematch.org/ (National Marrow Donor Program [NMDP]).

HISTOCOMPATIBILITY TESTING AND DONOR SELECTION

2 Different types of donors are used in HSCT. The choice of donor depends on the diagnosis and disease status of the recipient as well as his or her age, concurrent comorbidities, and performance status. The role and indications for HSCT are discussed in detail within individual disease chapters of this text. In *autologous* transplants, patients receive their own hematopoietic stem cells, which were collected and stored before administration of the transplant conditioning regimen. In *syngeneic* transplants, an identical twin serves as the donor. In *allogeneic* transplants, the donor is genetically not identical to the

recipient but shares some common cell surface antigens called human leukocyte antigens (HLAs). These antigens are encoded by the major histocompatibility complex (MHC), a cluster of genes located on the sixth chromosome.[4] The MHC contains three distinct regions designated as class I, class II, and class III. Class I and class II genes encode for HLA; products of class III genes have other important roles in the immune system. Class I and class II HLA antigens differ in their tissue distribution, structure, and function. Their primary function is to aid the immune system in recognizing cells or tissues as "self" or "nonself." The genes (and the corresponding antigens they encode for) important in HSCT are the class I antigens, HLA-A, HLA-B, and HLA-C and the class II antigen, HLA-DRB1. Class II antigens also include HLA-DQ and –DP. Because of the polymorphism of the HLA system, there are many different HLA antigens within each different class of HLA. To reduce the chance of graft rejection and graft-versus-host disease (GVHD), a donor is chosen based on how many of these HLA antigens are the same as those of the recipient. Thus, an ideally matched donor would be an "8/8" match, matching at HLA-A, -B, -C, and –DRB1.

To identify a suitable allogeneic donor, both the recipient and potential donors are HLA typed (ie, specific HLA antigens are identified); the potential donor who is most closely matched is generally chosen to be the transplant donor. HLA typing is accomplished by DNA-based techniques that use polymerase chain reaction (PCR) amplification of specific HLA genes from genomic DNA. DNA typing methods are categorized by the level of discrimination they provide in defining the sequence of an HLA gene.[4] Low-resolution methods provide limited sequence information about a particular HLA gene and are typically used to identify sibling donors. However, low-resolution techniques cannot distinguish the extremely polymorphic nature of many of the HLA antigens. HLA antigens are characterized by thousands of genetic variations (alleles), and each allele may correspond to a unique HLA molecule. Different alleles can be distinguished only by high-resolution typing techniques; high-resolution methods are used to identify suitable unrelated donors.

3 The degree of HLA mismatching correlates with the risk of graft rejection, GVHD, and survival.[4] Mismatches at HLA-A, HLA-B, HLA-C, and HLA-DRB1 are similarly associated with increased risk of GVHD and mortality.[5] HLA-DQB1 and –DPB1 mismatching are less predictive of negative outcomes, which suggests an 8/8 match is as beneficial as a 10/10 match. As the number of mismatches increases, the risk of GVHD and transplant-related mortality also increases. In the search for an allogeneic donor, the patient's siblings are typed first. About 30% of Americans have an HLA-identical sibling.

In an effort to offer allogeneic HSCT to patients who lack an HLA-identical sibling donor, alternative donors are being used. The most common type of alternative donor is an individual unrelated to the recipient who is fully or closely HLA matched. To facilitate the identification of these donors, the NMDP (https://bethematch.org) was started in 1986 with initial funding from a US Navy contract. To date, the NMDP has registered more than 20 million donors in the United States and has facilitated more than 90,000 unrelated donor transplants. Donors outside the United States can also be accessed by the NMDP through agreements with international cooperative registries. Although it is the transplant center's responsibility to select the donor, the NMDP recommends that selected donor and recipient be matched at HLA-A, B, C, and DRB1 by high-resolution typing when possible for bone marrow or peripheral blood HSCT.[5] If more than one suitable HLA-matched unrelated donor is identified, other factors can be used to select the donor, such as younger age, being male or a nulliparous female, and negative cytomegalovirus (CMV) serostatus.

The likelihood of a recipient finding an HLA-matched unrelated donor ranges from 1 in 100 to 1 in 1,000,000 depending on the prevalence of the recipient's HLA type, race, and ethnic background. With the current size and racial make-up of the NMDP registry, the matching likelihood is higher for whites than for patients from other racial or ethnic groups. Agreements between NMDP and international registries may improve the likelihood of finding donors for these patients and NMDP has actively promoted participation among nonwhite donor volunteers. Another limitation is the time needed to search for a potential donor. While searches are generally done in an expeditious manner, some donor searches may take several weeks, and patients with acute leukemia can relapse while waiting for completion of the search. With improved HLA typing techniques and better supportive care, most reported outcomes with matched unrelated donors are not significantly different than those reported with related sibling donors.[6]

Unfortunately, not every patient who could benefit from an allogeneic donor transplant will have a matched related or matched unrelated donor available. Alternative donor options such as umbilical cord blood (discussed in the next section), mismatched unrelated donors, or related haploidentical donors have become feasible options.[7] Potentially useful HLA-mismatched unrelated donors are those who are mismatched at one or, at most, two HLA loci. If minimal mismatching is allowed, the chance of finding an unrelated donor increases significantly. Although mismatched unrelated donor transplants are inferior with respect to GVHD, transplant-related mortality and overall survival when

compared to matched unrelated donors, these transplants do offer a curative therapeutic option in select patients.[8] Research is focused on evaluating the relative effect of mismatches at specific loci to determine if some are less detrimental (permissive) than others in order to improve outcomes. In addition, NMDP recommends testing the recipient for donor-specific HLA antibodies as graft failure is more common when the antibodies are present.[4]

Related haploidentical donors are a 50% match to the recipient; the donor and recipient are matched at 3 of 6 or 4 of 8 HLA loci. Donors can be parents, children, or siblings of the recipients. Historically, haploidentical allogeneic transplants (Haplo-HSCT) resulted in poor outcomes because of high rates of graft failure and GVHD. Strategies to reduce the incidence of graft failure and GVHD have included various methods of T-cell depletion including administration of anti-thymocyte globulin (ATG), alemtuzumab, or posttransplant cyclophosphamide (PTCy).[8,9] Several retrospective studies have compared outcomes after Haplo-HSCT to those seen after traditional matched related and unrelated donor transplants and have shown that GVHD and survival outcomes were similar.[9,10] Two parallel prospective studies with identical objectives, eligibility criteria and clinical endpoints were conducted with reduced-intensity conditioning regimens in either Haplo-HSCT with PTCy or umbilical cord blood transplant (UCBT).[10] While the trials were not designed for results to be compared directly, patients receiving Haplo-HSCT had higher rates of engraftment, lower risk of acute and chronic GVHD and less nonrelapse mortality than reported in the UCBT trial. However, relapse rates were lower after UCBT leading to similar progression-free and overall survival between the two studies. These trials reproduce single-center results with Haplo-HSCT or UCBT and suggest that survival rates with these alternative donor sources are comparable to those observed after matched unrelated donors. Based on these results, a phase III study comparing the two alternative stem cell sources is currently underway (BMT-CTN 1101, NCT01597778). Until the results of that trial and other randomized controlled trials are available, choosing an alternative donor in the absence of an HLA-matched sibling or unrelated donor remains controversial and will depend on patient characteristics, physician preference and center experience.

HEMATOPOIETIC STEM CELLS

Hematopoietic stem cells serve as “mother” cells for all blood cells, including erythrocytes, leukocytes, and platelets (see Chapter e102). Stem cells have

varying degrees of “stemness.” True pluripotent stem cells are capable of replicating indefinitely and can give rise to stem and progenitor cells of all tissues. Multipotent stem cells, such as hematopoietic stem cells, have the capacity for self-renewal and can differentiate into more than one cell type in a particular tissue lineage. Because of their capacity for self-renewal, hematopoietic stem cells are capable of repopulating the recipient’s marrow, which has been “emptied” by the administration of high-dose chemotherapy, either alone or combined with radiation.

4 Hematopoietic stem cells are rare cells, comprising less than 0.01% of all bone marrow cells. Isolation and quantitative measurement of hematopoietic stem cells are extremely difficult because of their rarity and their similar appearance to other cells. For these reasons, surrogate markers are used to measure the number of stem cells. CD34 is an antigen expressed on hematopoietic stem cells and other early progenitor cells. The number of cells expressing the CD34 antigen ($CD34^+$ cells) can be determined by flow cytometry and has become the standard method of measuring hematopoietic stem cell content.

Hematopoietic stem cells are found in the bone marrow, peripheral blood, and umbilical cord blood (UCB). Hematopoietic stem cells from the bone marrow are obtained by multiple aspirations from the anterior and posterior iliac crests while the donor is under general anesthesia. The procedure takes about 1 hour and yields 200 to 1,500 mL, depending on the size of the donor. In allogeneic bone marrow transplantation (BMT), the marrow stem cells are given to the recipient 12 to 24 hours after harvest. In autologous BMT, the marrow is frozen and stored until needed. After intravenous infusion, the marrow stem cells enter the systemic circulation and find their way to the bone marrow cavity, where they reseed and grow in the bone marrow microenvironment. Although the donor experiences local soreness for a few days, the procedure usually is well tolerated, with no delayed complications resulting from the marrow aspiration. The major risk of serving as a marrow donor is the risk of undergoing general anesthesia.

Hematopoietic stem cells in peripheral blood (peripheral blood stem cells [PBSCs]) are found in the mononuclear fraction of white blood cells (lymphocytes and monocytes) and are collected by a procedure called leukapheresis (or apheresis). This is an outpatient procedure that involves withdrawal of blood from a vein (through a specialized IV catheter), selective removal of mononuclear cells (containing the hematopoietic stem cells) by an apheresis machine, and reinfusion of the unneeded blood components back to the

patient. During this process, about 10 to 15 L of blood is processed over several hours during each daily apheresis session. Most of the blood cells are returned to the donor, and each apheresis yields about 200 mL of cells. Leukapheresis is continued daily until a target number of $CD34^+$ cells (which include hematopoietic stem cells) are collected.

The number of hematopoietic stem cells that circulate in peripheral blood normally is too low for apheresis to be technically feasible. Without mobilization techniques, at least six aphereses are usually required to collect a sufficient number of PBSCs. Several methods have been used clinically to "mobilize" hematopoietic stem cells from the bone marrow into peripheral blood for use in autologous transplantation. **Figure 157-2** shows representative schemas for mobilization and collection of PBSCs. The most commonly used mobilization method in both donor populations (healthy donors and autologous donors) is the administration of a recombinant hematopoietic growth factor such as granulocyte colony-stimulating factor (G-CSF [filgrastim]) or granulocyte-macrophage colony-stimulating factor (GM-CSF [sargramostim]). Both agents are approved by the Food and Drug Administration (FDA) for this indication, but filgrastim is more commonly used. Head-to-head comparisons report superior outcomes with filgrastim in terms of the number of stem cells collected, and posttransplant patient outcomes such as hematopoietic recovery, transfusion, and antibiotic support.[11] Chemotherapy followed by a hematopoietic growth factor in the autologous transplant population increases the number of PBSCs to a greater extent than growth factor alone. This approach is more expensive and is associated with more adverse effects, but the number of aphereses is reduced, and the additional chemotherapy may further reduce the tumor burden before transplant. However, these benefits have not translated into improved transplant outcomes so this approach is generally not used.[11] Pegfilgrastim (pegylated filgrastim) has also been evaluated in the mobilization setting, either alone or after chemotherapy (6 and 12 mg doses). Its prolonged half-life of 33 hours allows for single-dose administration, increasing patient convenience. Studies of single agent pegfilgrastim are limited by small numbers and report varying degrees of success.[11] The combination of pegfilgrastim and chemotherapy mobilization has resulted in similar $CD34^+$ cell collections and transplant-related outcomes to chemotherapy and filgrastim mobilization.[11]

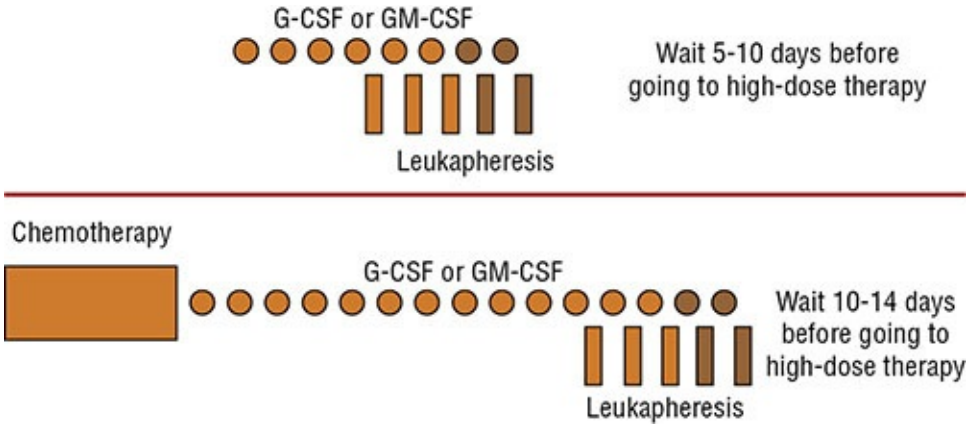


FIGURE 157-2 Schema for collection of peripheral blood progenitor cells after hematopoietic growth factor administration (top) or after chemotherapy and hematopoietic growth factor administration (bottom). Symbols with darker shading represent procedures performed only if adequate numbers of $CD34^+$ cells have not been collected. (G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor.)

The first colony-stimulating factor biosimilar was introduced in Europe in 2008. Professional organizations were initially reluctant to recommend the use of these agents for mobilization of stem cells due to a paucity of safety and efficacy data. However, more recent prospective trials comparing biosimilar products to the reference product have been published. A meta-analysis summarized the results in over 1,800 subjects that included healthy donors and patients with hematologic malignancies who used biosimilar agents to collect PBSCs. Mobilization with biosimilars resulted in expected $CD34^+$ stem cell yields with similar posttransplant engraftment and adverse effects to filgrastim, which suggests that biosimilars are an acceptable option in mobilization.[12]

Plerixafor is a novel inhibitor of the CXCR4 chemokine receptor that is FDA approved as a mobilizing agent in combination with filgrastim in autologous transplant candidates. Two phase III trials of plerixafor combined with filgrastim reported the combination was associated with higher $CD34^+$ cell yields, fewer apheresis sessions, increased likelihood of achieving $CD34^+$ target yields, and lower graft failure rates compared to single-agent filgrastim.[13,14] Based on the results of these trials, plerixafor is being routinely used to mobilize stem cells in autologous HSCT patients. However, because most patients are able to mobilize efficiently with filgrastim alone and plerixafor is expensive, transplant centers generally use a risk-adapted or preemptive approach to identify which patients are appropriate candidates for plerixafor. One approach is to give plerixafor to patients with certain characteristics that have been associated with a high risk of

poor mobilization (ie, risk-adapted approach). These characteristics include older age, diagnosis of non-Hodgkin lymphoma (NHL), extensive chemotherapy history, previous radiation therapy, previous exposure to lenalidomide or purine analogs, previous mobilization failure, and low preapheresis circulating peripheral blood $CD34^+$ ($PBCD34^+$) cell counts.[11] However, these characteristics lack sensitivity and specificity in predicting poor mobilization outcomes and thus patients may be either over or under treated.[15] Another approach is often referred to as a preemptive strategy, which identifies poor mobilizers based on $PBCD34^+$ cell counts on day 4 or 5 of filgrastim administration or on the first apheresis collection. Low numbers of $CD34^+$ cells after filgrastim administration have been associated with mobilization failure. Patients who do not have a minimal number of $CD34^+$ cells receive plerixafor.[11] Many transplant centers use these preemptive approaches to guide their mobilization strategies thereby limiting plerixafor use to patients at high risk for not obtaining the target $CD34^+$ yield. These algorithms have been reported to improve initial mobilization rates while efficiently managing resources.[11]

In about 20% to 30% of autologous transplant candidates, an optimal number of $CD34^+$ cells will not be obtained after the first attempt with standard mobilization regimens.[11] Several strategies for overcoming the obstacle of poor mobilization have been evaluated, including remobilization with the same or higher doses of the same hematopoietic growth factor, a combination of hematopoietic growth factors (ie, filgrastim and sargramostim), or a combination of chemotherapy and a hematopoietic growth factor. Each of these remobilization strategies has been used with varying success. Unfortunately, these strategies are associated with failure rates that exceed 70%.[11] Bone marrow harvest is also an option if other strategies fail.

Current consensus guidelines suggest that plerixafor be used in remobilization regimens for patients failing primary mobilization attempts, regardless of whether it was used in the primary mobilization.[11] When combined with filgrastim, plerixafor is associated with failure rates of less than 30%, which compares favorably with other secondary mobilization strategies but is also more costly, especially if multiple doses of plerixafor are required.[16] The use of plerixafor combined with chemotherapy and filgrastim may be a promising strategy, but further data are needed to better understand the appropriate timing and use of this regimen. The selection of a secondary mobilization regimen should be based on patient-specific factors and clinician judgment.

Several studies show that the number of $CD34^+$ cells infused correlates

significantly with the rate of neutrophil and platelet recovery after high-dose chemotherapy.[11] Rapid neutrophil recovery usually is observed in patients who receive at least 2×10^6 $CD34^+$ cells/kg (body weight of recipient). More rapid platelet recovery is observed when at least 5×10^6 $CD34^+$ cells/kg is transplanted compared with lower cell doses. As a result, consensus guidelines recommend 2×10^6 $CD34^+$ cells/kg as a minimum number to collect for autologous transplant, with an optimal target of 5×10^6 $CD34^+$ cells/kg.[11] The decision to use a collection yield of less than 2×10^6 $CD34^+$ cells/kg should be limited to those cases in which the potential benefit of a HSCT outweighs the risks of infusing a suboptimal $CD34^+$ cell dose. For patients with multiple myeloma undergoing tandem transplants, cells for both transplants are collected before the first transplant. A minimum of 4×10^6 $CD34^+$ cells/kg is required and generally the entire cell dose collected is divided into two equal aliquots, one for each transplant.

5 The use of peripheral blood instead of bone marrow as a source of hematopoietic stem cells offers several clinical and economic advantages. For autologous transplant patients, the most clinically important advantage is that patients who receive mobilized PBSCs experience more rapid hematopoietic engraftment. Although engraftment of all lineages is more rapid when PBSCs are used, the most significant effect is observed with platelet recovery. Patients who receive mobilized PBSCs experience platelet recovery as much as 2 to 3 weeks earlier and require fewer platelet transfusions than those who receive bone marrow stem cells. As a result, patients usually are discharged earlier from the hospital, so the overall cost of autologous HSCT is reduced with the use of PBSCs. PBSCs may be less likely to be contaminated with malignant cells compared with marrow stem cells. Finally, because PBSCs are collected from the mononuclear cell fraction, a fraction that also contains immunocompetent cells (eg, natural killer [NK] cells and T lymphocytes), some investigators believe that infusion of PBSCs represents a form of “adoptive immunotherapy.” In this model, NK cells and lymphocytes targeted against tumor cells help to kill residual tumor cells. As a result of these clinical and economic advantages, peripheral blood has replaced bone marrow as the source of stem cells in the autologous setting.

Peripheral blood has also become the predominant source of hematopoietic stem cells in adults undergoing allogeneic HSCT. About two-thirds of allogeneic HSCTs performed in adults currently come from PBSCs harvested from normal donors receiving filgrastim mobilization. Filgrastim is generally well tolerated in the normal donor population. Short-term effects are similar to those seen in

cancer patients receiving filgrastim (eg, bone pain, headache, fever, arthralgias, malaise). Although there are concerns about increased risk of acute myeloid leukemia (AML) in healthy subjects given filgrastim, no higher risk has been observed thus far.[17] Because of the long latent period of drug-related AML and the very low incidence of AML in the general population, longer follow-up of thousands of healthy donors will be required to definitively rule out an association between filgrastim and AML.

Randomized controlled trials and meta-analyses have shown that the stem cell source can influence posttransplant outcomes in allogeneic HSCT. Traditionally, matched related PBSCT have been associated with a more rapid hematopoietic recovery and required fewer transfusions compared with patients receiving bone marrow.[18] The difference in the rate of engraftment may be related to the threefold higher numbers of $CD34^+$ cells infused in recipients of PBSC transplants. Although an increased risk of acute GVHD or transplant-related mortality in patients receiving allogeneic PBSC transplants has not been reported, a higher risk of chronic GVHD has been observed in many retrospective studies and meta-analyses.[18] The Blood and Marrow Transplant Clinical Trials Network (CTN) reported results from a trial that randomized 551 patients to allogeneic PBSC or bone marrow from matched unrelated donors.[19] Two years after transplant, no differences in overall survival, relapse, acute GVHD or mortality not related to relapse were observed. However, a higher incidence of chronic GVHD was reported in patients who received PBSC transplants. Two-year survival is an early outcome and longer follow-up is needed to determine if these results are maintained over time. The published reports describing the impact of stem cell source on transplant-related outcomes has focused primarily on transplants using myeloablative conditioning (discussed below). The CIBMTR reported retrospective data of patients with hematologic malignancies who received reduced intensity unrelated donor transplants with either PBSCs or bone marrow. Time-to-engraftment, risks of acute or chronic GVHD, relapse, nonrelapse morality, and overall survival were not significantly different between the two groups. Subgroup analysis suggests that GVHD prophylaxis may impact survival in this patient population and warrants further evaluation.[20] The selection of the optimal source of hematopoietic stem cells for an individual patient should be based on the risk of relapse, chronic GVHD, graft failure, and donor preference.

Hematopoietic stem cells found in UCB are an attractive source for several reasons.[21] Because the stem cells are collected from placental blood, there is a very low risk of transmissible infectious diseases, no risk to the mother or the

baby, and the cells are immediately available. UCB initially was obtained from siblings, but now recipients of transplants from unrelated donors account for almost all patients who receive UCB transplants. More than 700,000 UCB grafts are available in more than 100 UCB banks, and more than 40,000 unrelated UCB transplants have been performed worldwide.[22] However, cord blood use as a stem cell source has decreased over the last three years in adults patients with just over 900 performed in 2015. This decline in cord blood source has been attributed to increasing costs, posttransplant infections and the need for multiple cord blood units to increase stem cell dose.[21]

Recipients of UCB transplants usually receive a $CD34^+$ cell dose more than 1 log lower than that given to recipients of BMT, and this difference in $CD34^+$ cell dose may explain the delayed engraftment in recipients of UCB transplants. The number of infused total nucleated and $CD34^+$ cells correlates with outcomes after UCB transplantation. The CIBMTR compared outcomes for adults with acute leukemia who were transplanted with unrelated bone marrow or PBSC versus UCB. Overall and leukemia-free survival was similar in all transplant groups. The risk of acute and chronic GVHD was lower in UCB recipients compared with PBSC, and the risk of chronic GVHD was lower in UCB compared with bone marrow. However, transplant-related mortality was higher after UCB as compared with other stem cell sources. A single-center experience of over 500 patients receiving myeloablative HSCT from UCB, HLA-matched unrelated donor or mismatched unrelated donors supported the use of UCB in patients with hematologic malignancies who still had minimal residual disease. Patients in the UCB group with minimal residual disease had a lower risk of relapse and death as compared to the other groups. Among patients who did not have minimal residual disease, the data also trended in favor of UCB.[23] These data support the use of UBCs as a source of stem cells when matched PBSCs or bone marrow are not immediately available.

A major limitation of UCB transplants is the small volume of blood collected, usually 60 to 150 mL with resultant low numbers of $CD34^+$ cells. The relatively low numbers of hematopoietic cells may limit its use for larger recipients. This has led to “pooling” two or more units of UCB for one recipient (referred to as double cord transplant). The Seattle and Minnesota groups published their experience in more than 500 patients older than 10 years of age who received a matched related donor, matched unrelated donor, mismatched unrelated donor, or double cord transplant. Leukemia-free survival was similar in all groups, but the double cord transplant recipients had a higher risk of transplant-related mortality.[8] Despite increasing $CD34^+$ cells doses through using double cord

products, there remains a significant time to engraftment. Additional interventions such as ex-vivo expansion of UCB stem cells prior to transplant have reported encouraging results but ongoing testing is needed to confirm long-term safety and efficacy.[21] Although the role of double cord transplantation has not yet been fully defined, pooled UCB units may provide an option for patients in which no other appropriate donors are available.

APPROACHES TO ERADICATE MALIGNANT CELLS

Conditioning Regimens

6 The purpose of the pretransplant conditioning regimen (also called the preparative regimen) depends on the type of transplant and the indication for its use. In the autologous setting, conditioning is used to eradicate malignant cells.[24] This is also the case in allogeneic HSCT for malignant diseases, but the conditioning regimen also serves a dual purpose to suppress the recipient's immune system to allow for donor cell engraftment. Conditioning regimens can be myeloablative or reduced intensity. Myeloablative conditioning (MAC) regimens contain very high doses of chemotherapy with or without radiation that would lead to life-threatening or fatal myelosuppression if hematopoietic stem cells were not infused.[25] Patients undergoing autologous HSCT receive only MAC regimens. Reduced-intensity conditioning (RIC) regimens are only used in allogeneic HSCT and consist of lower doses or different types of chemotherapy or lower doses of radiation than used in MAC regimens, resulting in less toxicity. RIC regimens were developed after the observation was made that some of the antitumor effect of the allogeneic transplant was mediated by a reaction between the donor's transplanted immune system and the recipient's cancer cells. This meant that very high doses of chemotherapy, radiation, or both may not be needed in all patients. Because RIC regimens use lower doses of chemotherapy or radiation or less toxic drugs, older patients and those with comorbidities can be offered potentially curative allogeneic transplants. Both types of regimens are discussed in detail below.

Myeloablative Conditioning Regimens

MAC regimens usually include at least one anticancer drug with a relatively steep dose-response curve and myelosuppression as their dose-limiting toxicity,

such as an alkylating agent. Cyclophosphamide, melphalan, busulfan, and carmustine are examples of chemotherapy agents commonly used in MAC regimens. Other agents are usually added that have additive or synergistic effects with these alkylating agents in specific types of cancers; other alkylating agents have also been used. **Table 157-1** lists chemotherapeutic agents that are frequently used in MAC regimens and the doses used and their dose-limiting toxicity in the transplant setting. Also listed are common regimens which include the agents listed.

TABLE 157-1 Dose-Limiting Nonhematologic Toxicities for Selected Chemotherapeutic Agents Included in Myeloablative Conditioning Regimens in Hematopoietic Stem Cell Transplantation and Examples of Commonly Used Conditioning Regimens

Drug	Conventional Dose[a] (mg/m^2)	HSCT Dose (mg/m^2)	Dose-Limiting Toxicity	Commonly Used Regimens
Busulfan (oral)	2	450	Hepatic	BuCy, BuFlu
Carboplatin	400	2,000	Hepatic, renal	Carboplatin + E + Cy or Mel
Carmustine (BCNU)	200	1,200	Pulmonary, hepatic	BEAM, BEAC, CBV
Cyclophosphamide	1,000	7,500	Cardiomyopathy	CyTBI, FluCy + TBI,
Etoposide	300-600	2,400	Mucositis	BEAM, BEAC
Melphalan	40	225	Mucositis	Single agent melphalan, BEAM
Thiotepa	20-50	750	Mucositis, central nervous system	BCNU + Thiotepa Thiotepa + Bu + Cy
Fludarabine	125	125-240	Neurotoxicity	FluMel, BuFlu

Doses for regimens are given in the body of the text

Bu - busulfan, Cy - cyclophosphamide, Flu - fludarabine, BEAM - BCNU, etoposide, cytarabine, melphalan, BEAC - BCNU, etoposide, cytarabine, cyclophosphamide, CBV - cyclophosphamide, BCNU, etoposide, TBI - total body irradiation, Mel - melphalan.

Total-body irradiation (TBI) is also used in some pretransplant conditioning regimens. In patients with malignant disease, the rationale of TBI is to eradicate malignant cells located in areas inaccessible to the systemic circulation and thus to the chemotherapeutic agents (eg, CNS and testicles). TBI also has significant immunosuppressive activity. TBI doses for MAC regimens range from 10 to 15 Gy (1,000-1,500 rads or cGy), which is more than twice the lethal myelosuppressive dose of radiation for a normal person. TBI in these doses is typically fractionated (split over several days, once or twice a day) rather than given as a single-dose. Fractionated TBI has an improved therapeutic ratio

compared with single-dose administration, that is, the destruction of more leukemic cells and marrow stem cells while sparing other normal tissues. The acute toxicities of TBI consist of fever, nausea, vomiting, diarrhea, mucositis, and tender swelling of the parotid gland. Long-term complications of TBI-containing regimens include cataract formation, growth retardation, carcinogenesis, permanent reproductive sterility, and secondary malignancies.

Based on its immunomodulatory and antineoplastic effects, cyclophosphamide (60 mg/kg/day for 2 days) is commonly combined with TBI (CyTBI). Other chemotherapy agents have been used with TBI but there is no evidence to suggest that any of these combinations are more effective than CyTBI.[26] Due to the toxicities seen with high-dose TBI, chemotherapy only regimens also have been developed. Many of these regimens contain busulfan due to its activity against a variety of malignancies. Busulfan can either be given IV or orally. The use of IV busulfan-containing regimens has been associated with improved survival compared to TBI-containing regimens in patients with myeloid malignancies.[27] At some transplant centers, plasma busulfan concentrations are monitored and doses adjusted as systemic exposure has been shown to correlate with both efficacy and toxicity and the use of preparative regimens with targeted busulfan may improve patient outcomes.[28,29] Busulfan is commonly combined with cyclophosphamide (BuCy) or fludarabine (BuFlu).

Several studies, both prospective and retrospective, have compared different allogeneic transplant MAC regimens.[26,27] In general, one regimen has not been shown to be superior over another, such that the choice of regimens before allogeneic HSCT generally is based on the experience of the transplant center, patient characteristics, diagnosis, and disease status.

Conditioning regimens used in autologous HSCT are exclusively myeloablative and generally include at least one alkylating agent with other agents added that may have specific activity against the tumor type being treated.[24,26] TBI is not commonly used and is not included in the conditioning regimen in patients who have received prior radiotherapy. MAC regimens commonly used in patients with lymphoma include BEAM (BCNU, etoposide, cytarabine, and melphalan), BEAC (BCNU, etoposide, cytarabine, and cyclophosphamide) or CBV (cyclophosphamide, BCNU, and etoposide).[30] In order to reduce BCNU-related toxicities and due to periodic shortages of BCNU, substitute agents such as bendamustine are being evaluated in these lymphoma regimens. Rituximab is commonly added in patients with CD20-positive lymphomas, although randomized controlled studies supporting the use of rituximab in this setting are lacking.[24] Studies have also evaluated the addition

of a radioimmunoconjugate (iodine-131 tositumomab or yttrium-90 ibritumomab tiuxetan) to conditioning regimens in patients with lymphoma. Only one randomized study has compared the addition of iodine-131 tositumomab to BEAM to rituximab plus BEAM in patients with diffuse large B cell lymphoma. Results showed a similar 2-year progression-free and overall survival.[30] Hence, these agents are not typically used as a part of conditioning outside the context of a clinical trial. Single-agent melphalan (200 mg/m^2) is the standard conditioning regimen for patients undergoing autologous HSCT for myeloma. The addition of other agents to melphalan has not been proven to be superior to melphalan alone.[24]

Reduced-Intensity Conditioning Regimens

7 Donor T cells contribute to the tumor cell kill and prevention of relapse observed after allogeneic HSCT, an effect referred to as the graft-versus-malignancy (GVM) effect. Evidence for the GVM effect is based on retrospective studies showing that patients who developed GVHD had a lower risk of leukemic relapse than those who did not develop GVHD. However, the overall survival rate was not different because of the increased nonrelapse mortality associated with GVHD. Other anecdotal evidence supporting a T cell–mediated GVM effect includes the increased risk of relapse found with T cell–depleted transplants compared with unmodified transplants and the efficacy of donor lymphocyte infusions (DLIs) in producing responses in patients who have relapsed after allogeneic HSCT.[26]

RIC regimens containing lower doses of chemotherapy or radiation or less toxic agents were developed to take advantage of the GVM effect but with a lower incidence of regimen-related toxicity than that of MAC regimens. Animal data showed that MAC was not required for engraftment of donor cells (the other important role of conditioning in allogeneic HSCT), thus paving the way for the evaluation of RIC in humans.[26] The major advantage of RIC is that potentially curative transplants can be offered to patients who typically would not be considered for allogeneic HSCT because of their unacceptably high risk of transplant-related complications due to increased age or moderately compromised organ function. The use of RIC regimens has steadily increased in patients aged 50 and older.[1] In addition, because of the lower rate of toxicity, allogeneic HSCT with RIC can be offered to patients who have relapsed after traditional myeloablative autologous or allogeneic transplants, provided they are healthy enough to tolerate a second transplant. Because RIC regimens may not

be completely myeloablative, host hematopoiesis can persist and lead to mixed chimerism (ie, blood cells from both donor and recipient are present) (see **Fig. 157-3**).[31] Several studies have reported significant correlations between donor T-cell chimerism levels and the risk of graft rejection, GVHD, and relapse. For example, a low percentage of donor T and NK cells present on day 14 has been associated with graft rejection, but high T-cell donor chimerism on day 28 has been associated with acute GVHD. Achievement of full donor chimerism was associated with better GVM effect and longer progression-free survival. These data suggest that monitoring donor chimerism after transplant may allow early interventions to prevent graft rejection or relapse.[31]

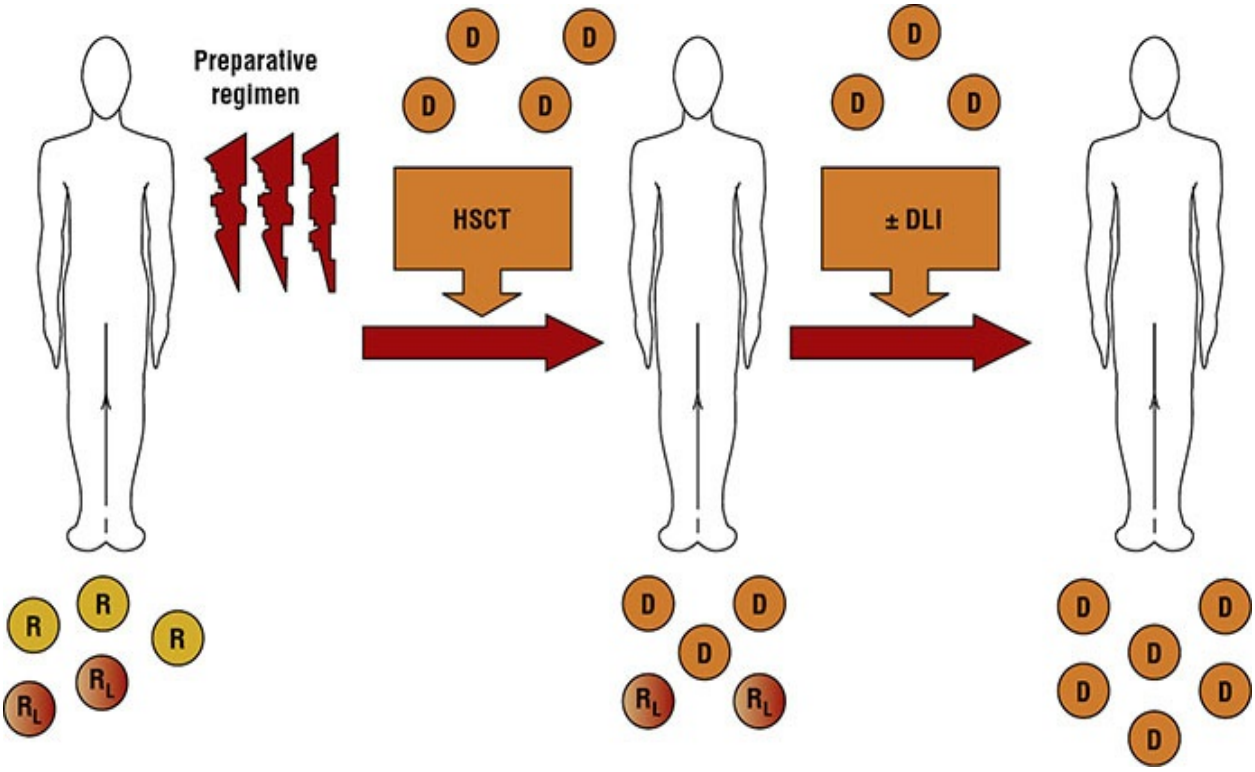


FIGURE 157-3 Schema for nonmyeloablative transplantation for hematologic malignancy. Recipients (R) receive a reduced-intensity conditioning regimen and an allogeneic hematopoietic stem cell transplant (HSCT). Initially, mixed chimerism is present with the coexistence of donor (D) cells and recipient-derived normal and leukemia/lymphoma (R_L) cells. Donor-derived T cells mediate a graft-versus-host hematopoietic effect that eradicates residual recipient-derived normal and malignant hematopoietic cells. Donor lymphocyte infusions (DLIs) can be administered to enhance graft-versus-malignancy effects.

Several RIC regimens that vary in their cytotoxic, myelosuppressive, and immunosuppressive activity have been developed.[26] Most regimens include fludarabine (125-240 mg/m^2) because of its potent immunosuppressive activity, combined with either low-dose TBI (at doses up to 8 Gy [800 rad]) or an alkylating agent, such as cyclophosphamide (2-3.6 g/m^2 or 120-200 mg/kg), busulfan (up to 10 mg/kg), or melphalan (up to 180 mg/m^2). ATG or alemtuzumab is sometimes given for additional immunosuppression, and other purine analogs (eg, pentostatin or clofarabine) are sometimes used instead of fludarabine. Rituximab has also been included in patients with CD20-positive lymphoid malignancies. Many of these regimens are myeloablative but are defined as RIC because of the lower doses of chemotherapy and the reduced toxicity associated with these regimens as compared to MAC regimens.[25]

Some RIC regimens are considered nonmyeloablative because they result in little to no myelosuppression and do not require hematopoietic cell support for the recovery of hematopoiesis. Nonmyeloablative regimens are associated with very little regimen-related toxicity but, similar to other RIC regimens, are sufficiently immunosuppressive to allow for full engraftment of important donor immune effector cells.[25] Two of the most common nonmyeloablative regimens are fludarabine (25 mg/m^2/day for 3-5 days) combined with cyclophosphamide (60 mg/kg/day × 2 days) or with TBI (less than or equal to 2 Gy [200 rad]). Although these regimens are clearly nonmyeloablative, the distinction may be more difficult with other regimens as definitions remain somewhat arbitrary.

Transplant-related outcomes, such as nonrelapse related mortality, relapse, overall and progression-free survival, vary depending on the specific RIC regimen, disease type and status at the time of transplant, donor type, and patient age, performance status, and comorbidities. Several large retrospective registry-based studies and meta-analyses have reported the results of RIC regimens either alone or in comparison to MAC regimens.[32,33] In general, regimen-related toxicity and nonrelapse mortality have been reported to be lower than that of historical or concurrent control participants receiving MAC regimens in these nonrandomized comparisons. This is remarkable considering the older age and higher incidence of comorbidities in patients receiving RIC transplants. Of concern, however, has been an increased rate of relapse in patients receiving RIC regimens in some comparisons, resulting in similar overall survival. This finding depends on the RIC regimen used, as well as patient and disease characteristics. Randomized trials comparing MAC versus RIC regimens to date have included only patients with AML or myelodysplastic syndrome (MDS) who were less than 65 years of age. In a long-term follow-up of their randomized trial in AML

patients comparing FluTBI (RIC) to CyTBI (MAC), German investigators reported no differences in the risk of relapse and disease-free or overall survival between the two regimen groups.[34] The European Society of Blood and Marrow Transplantation conducted a multicenter randomized trial comparing BuCy (MAC) versus BuFlu (RIC) in patients with MDS or secondary AML.[35] This study also reported no difference in nonrelapse mortality, risk of relapse, and relapse-free and overall survival between the two groups. The Blood and Marrow Transplant CTN also performed a large randomized trial comparing RIC versus MAC in patients with high-risk AML or MDS.[36] Eligibility criteria included age less than or equal to 65, disease in complete remission and minimal comorbidities. This trial was halted prematurely because a lower relapse rate in the MAC arm of the study was observed. This translated into a higher but nonsignificant increase in overall survival and a significantly higher relapse-free survival in the MAC arm as compared to the RIC arm. As expected, transplant-related mortality was higher in the MAC arm but was offset by the substantial difference in relapse rate. The investigators concluded that the data supported the use of MAC as the standard of care for fit patients with high-risk AML or MDS. Based on these results, elderly patients (>65 years of age) and younger patients with significant comorbidities who are at lower risk of relapse are more likely to receive transplants with a RIC regimen. For patients with diagnoses other than AML or MDS, clinicians will need to consider patient and disease characteristics and donor type when choosing an appropriate conditioning regimen.

Posttransplant Therapy

Relapse of primary disease remains the most common cause of death for both allogeneic and autologous HSCT patients. As a result, much research has been directed at both preventing and treating posttransplant relapse or progression of disease.[37–39] Posttransplant therapy can be categorized either as “maintenance (or consolidation) therapy” or “salvage therapy.” Maintenance/consolidation therapy is used to prevent relapse whereas salvage therapy is given to treat active relapse. Methods to identify relapsed disease for many hematologic malignancies have become quite sensitive, and often disease can be detected at the molecular level (ie, minimal residual disease) and used to direct posttransplant therapy. Several posttransplant therapies have been evaluated both in the maintenance and salvage settings, including immunotherapy, conventional chemotherapy, and targeted therapy. Relapse after autologous transplant can often be treated with standard doses of chemotherapy, a second autologous

transplant, chimeric antigen receptor (CAR) T-cell therapy, or an allogeneic transplant, depending on the diagnosis, disease status, side effects, response, and duration of response to the first transplant. Treatment options for most patients who relapse after allogeneic HSCT are more limited, and the prognosis is generally poor. Disease-specific chemotherapy and immunotherapy can be considered for some patients. A second allogeneic HSCT may be considered but is associated with a mortality rate of up to 45%.[38]

Immunotherapy

The rationale for posttransplant immunotherapy after allogeneic HSCT is based on the GVM effect. To take advantage of the GVM effect in patients who relapse after allogeneic HSCT, immunosuppressive therapy being used for GVHD is withdrawn as quickly as possible without inducing a serious GVHD flare. In rare cases, this is enough to reinduce a remission, but further therapy is usually required. This is not a viable option in patients with active GVHD.

The most commonly used form of posttransplant immunotherapy is DLI.[40,41] Lymphocytes are collected from the same donor who provided hematopoietic stem cells for the original allogeneic transplant, thus limiting this option to patients with available donors. Response to DLI is disease specific. More than 80% of patients with CML who are in cytogenetic or molecular relapse respond to DLI. The response rate of patients in more advanced phases is about 15% to 30%. Although the time-to-response is delayed (median, 3-4 months), patients often have a durable molecular remission to DLI. Response rates to DLI of patients with other myeloid malignancies, such as AML and MDS, are generally lower (15%-30%) than the rates of patients with CML. This may be related to the rapid proliferation of acute leukemia during the often prolonged time-to-response after DLI. Patients with relapsed AML after HSCT are more likely to achieve a complete response to DLI if they had a longer remission period after transplant and have some GVHD after the DLI; low tumor burden, remission at the time of DLI, and good-risk cytogenetics have also been shown to be favorable characteristics. Administration of induction chemotherapy or therapeutic agents such as 5-azacitidine before DLI administration may improve the antitumor activity of DLI in patients with AML or other rapidly proliferating malignancies. Retrospective data from 154 patients with myeloid malignancies (primarily AML or MDS) who received azacitidine and DLI was reported by the German Cooperative Transplant Study Group. The complete remission rate was 27% with a 2-year overall survival of 29%, which suggested benefit of 5-azacitidine prior to DLI. Posttransplant DLI has been shown to have little benefit

in patients with relapsed acute lymphoblastic leukemia (ALL).

The most serious complications of DLI are pancytopenia and GVHD, and DLI is not usually given to patients with active GVHD. The cytopenias generally are transient and can be treated with hematopoietic growth factors. Some patients may have a more prolonged course of aplasia with the associated risk of infection, bleeding, and anemia and these patients may benefit from another infusion of donor hematopoietic stem cells.

New strategies being evaluated to improve outcomes with DLI include infusion of selected subsets of T-lymphocytes to promote GVM, preemptive use of DLI based on the presence of minimal residual disease or evidence of molecular/cytogenetic relapse, or prophylactic DLI in patients who are at high risk of relapse.[40]

Tumor evasion may play a fundamental role in relapse after HSCT, which suggests that immune checkpoint inhibitors could be useful in this setting. Pembrolizumab is currently being studied in lymphoma patients who have relapsed after autologous HSCT. For patients who relapse after an allogeneic HSCT, the use of these immune checkpoint inhibitors may increase the risk of GVHD.

CAR T-cell therapy in patients with B-cell lineage ALL who relapse after allogeneic HSCT is being investigated as a salvage therapy or bridge to a second transplant. In a series of 21 pediatric patients receiving CAR T-cell therapy, including 8 who relapsed after allogeneic HSCT, a 67% complete remission rate was reported, with 60% achieving MRD-negative disease status. Cytokine release syndrome was reported in 76% of patients and 29% developed neurotoxicity.[40]

Monoclonal Antibodies

Although earlier studies showed potential benefit of rituximab as maintenance therapy for certain types of NHL patients after autologous HSCT, more recent randomized controlled trials with mature follow-up have not consistently demonstrated benefit.[42] Therefore, routine use of rituximab maintenance is not recommended. Rituximab may be useful in combination with other active agents for salvage therapy of posttransplant relapse.

Brentuximab vedotin (anti-CD30 antibody conjugated to monomethyl auristatin E, a microtubule-disrupting agent) was evaluated as maintenance therapy in a randomized placebo-controlled study in patients with Hodgkin lymphoma after autologous HSCT.[43] Progression-free survival at 5 years was

significantly improved in patients randomized to brentuximab (hazard ratio 0.52, 95% confidence interval 0.38-0.72). Consistent benefit was seen across all subgroups that were analyzed, but the benefit of brentuximab was more pronounced in patients at higher risk for relapse. The most frequent adverse events in the brentuximab group were peripheral sensory neuropathy and neutropenia. These results led to the FDA approval of brentuximab administration after autologous HSCT and has been increasingly adopted into clinical practice.

Chemotherapy or Targeted Therapy

Tyrosine kinase inhibitors (TKIs), such as imatinib, dasatinib, and nilotinib, are used to prevent and treat relapse after allogeneic HSCT in patients with CML and Philadelphia chromosome–positive (Ph+) ALL.[42,44] In patients with CML who experience hematologic relapse (presence of leukemic blasts in blood or bone marrow) after allogeneic HSCT, imatinib can induce complete hematologic responses (disappearance of leukemic blasts) and complete cytogenetic responses (disappearance of cytogenetic markers of disease) in most patients. Similar outcomes in patients with Ph+ ALL have been reported. TKIs may be given soon after transplant to prevent relapse.[42,44] Patients with Ph+ ALL and CML without evidence of disease after transplant who are treated with TKIs to prevent relapse appear to have sustained cytogenetic remissions (without evidence of cytogenetic markers of disease). TKIs are generally well tolerated after transplant. Commonly reported side effects include neutropenia, thrombocytopenia, liver function abnormalities, edema, and muscle pain, which may require dosage reductions or discontinuation. Large comparative studies will be required to define the benefit of TKIs after transplant, and the optimal dosing, timing, and duration of therapy.

Based on its activity in AML and MDS, hypomethylating agents such as 5-azacitidine and decitabine have been evaluated in the posttransplant setting to prevent relapse in patients with these diagnoses. The RICAZA trial assessed maintenance 5-azacitidine therapy in 37 patients after allogeneic HSCT. Twenty-one patients remained in remission, which suggests 5-azacitidine may have a role in preventing relapse in this setting. Treatment was well tolerated and did not induce excessive toxicities or chronic GVHD.[45] A phase II CALGB trial of maintenance 5-azacitidine after allogeneic HSCT was only able to initiate therapy in 42 of 66 patients enrolled and only 17 were able to complete the planned six cycles of treatment due to toxicities.[42] Decitabine given as maintenance therapy after allogeneic HSCT has also been evaluated. Two-year

overall survival was reported at 56% with a 28% relapse rate. Hematologic toxicities were common during decitabine maintenance therapy.[46]

Other therapies being investigated as maintenance therapy after allogeneic HSCT include panobinostat (deacetylase inhibitor) and the FLT3 tyrosine kinase inhibitors (sorafenib, quizartinib, and midostaurin).[42] Posttransplant therapy is also being evaluated in patients with multiple myeloma. Previous studies showed a potential benefit of thalidomide to prevent relapse after autologous transplant, but its use is limited by neurotoxicity and other bothersome adverse effects. When given after autologous transplant, lenalidomide has been shown to prolong progression-free survival compared with patients receiving placebo.[42] However, a small but significant increased risk of second primary cancers was reported in the lenalidomide-treated patients. Further study is needed to better define the risk of secondary malignancies. Patients should be informed of this potential safety issue when treatment with lenalidomide after autologous HSCT is considered. Bortezomib maintenance therapy after autologous HSCT has also been associated with prolonged progression-free survival, but a prospective randomized trial has not been reported.

TRANSPLANT-RELATED COMPLICATIONS

8 Although many patients with cancer treated with high-dose chemotherapy and autologous or allogeneic HSCT experience long-term survival and cure of their disease, this modality is associated with many serious and potentially life-threatening complications.[24,27] Despite the availability of improved broad-spectrum anti-infective agents, immunosuppressive drugs, and hematopoietic growth factors which has improved survival over the last four decades, transplant-related mortality rate after allogeneic HSCT with HLA-matched sibling and unrelated donors is 20% to 30%. The mortality rate is generally lower with the use of RIC regimens and higher when alternative donors are used. Causes of nonrelapse-related death are a result of transplant-related organ toxicity, GVHD, or immunosuppression. The risk of transplant-related mortality after autologous HSCT generally is less than 5%, depending on the patient population and conditioning regimen.[24] The mortality rate is lower with autologous transplants because of the lack of GVHD and associated complications of immunosuppression. Transplant-related mortality in autologous HSCT usually is caused by regimen-related toxicity or infection.

Table 157-1 lists the dose-limiting nonhematologic toxicities for several drugs that are commonly included in MAC regimens. These toxicities may be

uncommon or rare with the administration of conventional doses of specific drugs. When these agents are given in high doses, the toxicities seen with conventional doses (eg, mucositis, enteritis, nausea, vomiting, and hematuria) can be more frequent or severe. Several unusual and severe manifestations of regimen-related toxicities are discussed in this section.

Sinusoidal Obstruction Syndrome

Sinusoidal obstruction syndrome (SOS), formerly known as hepatic venoocclusive disease (VOD), occurs as a result of chemotherapy-induced damage to the sinusoidal endothelial cells of the liver, which leads to release of proinflammatory cytokines and further damage to the endothelium. Gaps develop between the endothelial cells, which allows cellular debris to accumulate and cause the sinusoids to narrow and eventually become occluded. In addition, injury to the endothelial cells produces fibrin deposition and clot formation, further narrowing the sinusoids.[47] These histologic changes can lead to obstruction of sinusoidal flow, reduced hepatic venous outflow, portal hypertension, and hepatic failure. Clinical signs of SOS include fluid retention (resulting in sudden weight gain and ascites), hepatomegaly (sometimes painful), and hyperbilirubinemia or jaundice. SOS usually occurs within the first 4 weeks after transplant, and the incidence of SOS ranges from 5% to 20% in most published series. Severe SOS is fatal in 50% to 75% of cases. Factors that have been reported to increase the risk of SOS include use of TBI-containing conditioning regimens (dose-dependent), use of sirolimus for the prevention of GVHD, increased systemic exposure to busulfan, oral administration of busulfan, individual variability in cyclophosphamide metabolism, chronic viral hepatitis, and elevated liver function test results before transplant. Pretransplant exposure to gemtuzumab ozogamicin (Mylotarg®) has been implicated in the development of SOS in patients undergoing allogeneic HSCT, especially when given within a few months of transplant.[47]

Prostaglandin E_1, unfractionated low-molecular-weight heparin, and ursodiol have been studied in the prevention of SOS.[27,47] Ursodiol has been found to not only reduce the risk of SOS in patients undergoing MAC allogeneic transplants but also reduce the risk of transplant-related mortality and GVHD. Defibrotide, a polydisperse oligonucleotide with fibrinolytic properties, reduced the risk of SOS in a randomized, open-label trial of pediatric patients who were at high risk of SOS and it is routinely being used in some European transplant centers.[47]

Treatment of SOS is generally supportive, including fluid and electrolyte

management. Hepato- and nephrotoxic drugs should be avoided. Mild-to-moderate disease generally resolves without specific therapy. Recombinant tissue plasminogen activator (tPA) has been given to patients with severe SOS because of the possible role of the coagulation cascade in the pathogenesis of SOS. Responses have been reported, but patients also experienced a higher risk of bleeding so tPA is generally not recommended.[47] Other studies have evaluated high-dose methylprednisolone or N-acetylcysteine in the treatment of SOS with varying success. These treatments are generally not recommended due to adverse effects or lack of clinical efficacy.[47] Defibrotide (Defitelio®) was approved by the FDA in 2016 based on prospective clinical trials in patients with SOS with advanced multi-organ dysfunction that showed improved response rates and lower mortality as compared with historical control participants. Adverse effects were not distinguishable from those commonly reported in this patient population. Post-hoc analysis showed that earlier initiation of defibrotide treatment was associated with significantly higher posttransplant day 100 survival rates and future research should focus on identification of factors (eg, biomarkers) that predict SOS onset.[47]

Pulmonary Complications

Pulmonary complications after HSCT can be categorized as infectious and noninfectious (see Chapter 140). Noninfectious complications can be caused by direct damage to the pulmonary tissue by chemotherapy or radiation used in the conditioning regimen, immune effects of the graft, or other causes not clearly understood. Early complications include diffuse alveolar hemorrhage, periengraftment respiratory distress syndrome, and idiopathic interstitial pneumonitis.[48] Diffuse alveolar hemorrhage is characterized by dyspnea, hypoxia, dry cough, and fever; chest radiography usually shows diffuse infiltrates in an alveolar pattern. It occurs in 5% to 12% of HSCT patients with mortality rates reported as high as 60% to 100%. Diffuse alveolar hemorrhage is diagnosed by examination of bronchoalveolar lavage fluid via bronchoscopy, which reveals progressively bloodier fluid with each instilled aliquot and negative findings on microbiologic analysis. Although the condition can be life-threatening or fatal, prompt treatment with high doses of corticosteroids (methylprednisolone 500-1000 mg daily for 5 days) is sometimes beneficial.[48]

Periengraftment respiratory distress syndrome is characterized by fever, erythrodermatous skin rash, and noncardiogenic pulmonary edema and can occur during neutrophil recovery after HSCT.[48] The incidence of engraftment

syndrome is not known because of the lack of uniform diagnostic criteria, although some series report that 5% to 10% of patients who receive autologous HSCT develop the syndrome. This syndrome can progress to life-threatening respiratory failure with or without multiple organ failure. Treatment consists of methylprednisolone 1 to 2 mg/kg/day for 3 days, followed by a rapid taper.

Idiopathic interstitial pneumonitis (also called idiopathic pneumonia syndrome) is defined as widespread alveolar injury in the absence of active lower respiratory tract infection, cardiac or renal dysfunction, or iatrogenic-induced circulatory overload after HSCT.[48] Patients with idiopathic interstitial pneumonitis are clinically indistinguishable from patients with interstitial pneumonitis related to infection. Idiopathic interstitial pneumonitis is postulated to have a multifactorial etiology, including toxic effects of MAC regimens, immunologic cell-mediated injury, inflammatory cytokine-induced lung damage, and occult pulmonary infections. The risk is similar in recipients of autologous or allogeneic HSCT but appears to be higher in patients who are conditioned with a TBI-containing regimen or who have acute GVHD. A mortality rate as high as 80% has been reported, and treatment consists of supportive care only as the efficacy of corticosteroids has not been consistently reported. Uncontrolled studies of etanercept showed some benefit when added to corticosteroid therapy, but a randomized controlled trial, which was closed early due to low accrual, failed to show a significant difference in response rates between patients receiving etanercept plus corticosteroids versus those receiving corticosteroids plus placebo.[49]

Late pulmonary complications cover a wide spectrum of disorders and include both obstructive and restrictive lung diseases.[48,50] The most common disorders are cryptogenic organizing pneumonia (COP; previously known as bronchiolitis obliterans with organizing pneumonia [BOOP]) and bronchiolitis obliterans syndrome (BOS). COP is an interstitial and airspace disease with symptoms that mimic classic pneumonia but biopsy reveals chronic alveolar inflammation and extensive granulation of the alveolar ducts and small airways.[48] COP is generally responsive to prednisone 1 mg/kg/day with an extended taper over several months. BOS is thought to be a result of chronic GVHD affecting the lungs and is generally thought to be irreversible with mortality rates as high as 40%.[48,50] Therapy consists of oral corticosteroids, which are about 50% effective, often in combination with inhaled fluticasone, azithromycin, and montelukast. Extracorporeal photopheresis may also provide benefit.[50]

Graft Failure

Initial engraftment of hematopoietic cells after high-dose chemotherapy conditioning regimens usually occurs in the first 2 to 4 weeks after transplant. Engraftment is evidenced by rising peripheral blood counts and the presence of hematopoietic precursor cells in the marrow; it is defined as an absolute neutrophil count of greater than 500 cells/mm^3 (0.5×10^9/L) and a platelet count of greater than 20,000 cells/mm^3 (20×10^9/L) on the first day of seven consecutive days without a platelet transfusion. In allogeneic HSCT, the presence of donor cells (ie, chimerism) is confirmed by PCR-based analysis of polymorphic DNA sequences of cells from the bone marrow and peripheral T cells. Full chimerism is defined as greater than 95% of cells of donor origin. In most patients, engraftment is sustained with complete recovery of hematopoiesis.

However, graft failure (loss of bone marrow function with resultant loss in peripheral blood counts) can occur after both allogeneic and autologous HSCT. It can be the result of heavy pretreatment with chemotherapy or radiation therapy (or both); infusion of insufficient numbers of hematopoietic stem cells; viral infection; recurrence of primary hematologic malignancy; drug reaction (eg, ganciclovir); development of a secondary myelodysplasia; or in the allogeneic setting, an immunologic reaction between the donor and recipient caused by inadequate immunosuppression of the recipient (ie, graft rejection). Two syndromes have been observed. Whereas early graft failure occurs when the rate of hematopoietic recovery is delayed greater than 28 days after transplant (later after UCB transplants) or does not occur at all (primary graft failure or delayed engraftment), late graft failure is characterized by a decline in peripheral blood counts after initial engraftment (secondary graft failure).[51] With widespread use of PBSCs and posttransplant growth factors, primary graft failure is rare after autologous and HLA-matched allogeneic HSCT but is not uncommon after UCBT. Graft failure that occurs after allogeneic HSCT, characterized by regrowth of immunocompetent recipient cells and a simultaneous loss of donor cells, is referred to as *graft rejection*. Graft rejection occurs rarely after HLA-matched allogeneic HSCT. An increased risk of graft rejection has been observed in recipients of hematopoietic stem cells from HLA-mismatched donors, recipients of T cell–depleted marrow, and patients with severe aplastic anemia or other nonmalignant disorders. In a large retrospective analysis of over 20,000 patients undergoing myeloablative allogeneic HSCT the incidence of primary graft failure was reported was 5.5%.[52] In this analysis, risk factors for primary graft failure included bone marrow (vs peripheral blood) grafts, RIC

regimens, diagnosis of a myeloproliferative disorder, HLA mismatched transplants, ABO incompatibility, and BuCy conditioning (compared with other MAC regimens).

The long-term prognosis of patients with persistent graft failure is poor. Despite supportive care and treatment with hematopoietic growth factors, death may result from infection or bleeding. In some patients with an allogeneic donor, a second infusion of stem cells can be attempted.[27] While this can be a viable alternative for some patients, many are not physically able to undergo a second transplant. Of those that do, nonrelapse mortality is high, despite the use of nonmyeloablative regimens.[51] Hematopoietic growth factors usually are given after transplant to patients who receive autologous HSCT, based on several benefits associated with their use including fewer antibiotic days and decreased length of stay. Decreasing resource utilization after transplant (total antibiotic days and length of stay) can help justify the cost of growth factors in this patient population. Growth factors can be initiated the day of, the day after, or as late as 7 days after the infusion of stem cells and are continued until neutrophil recovery to greater than an arbitrary number of neutrophils (500-1,000 cells/mm^3 [$0.5 \times 10^9 - 1.0 \times 10^9$/L]). Pegfilgrastim appears to be equally efficacious to filgrastim in this setting.

Hematopoietic growth factors also accelerate the rate of neutrophil recovery in patients undergoing allogeneic HSCT. However, filgrastim has not been shown to reduce infection rates, antibiotic days or length of stay in this population. The decision to whether or not to use filgrastim preemptively must be made by each institution and may be reserved for use in patients who are at risk for a prolonged rate of neutrophil recovery (eg, UCB transplants). If allogeneic HSCT patients develop graft failure, filgrastim can be given based on data that supports its use in this situation.[51]

Results of studies to improve platelet recovery posttransplant with thrombopoietin and interleukin-11 (IL-11) have been disappointing. Several case studies and case series have described the use of eltrombopag, an oral thromobopoietin receptor agonist, in allogeneic HSCT patients with persistent thrombocytopenia posttransplant.[51] Although additional data are needed, the reported response rates have been promising. Platelet transfusions remain the standard of care in patients with thrombocytopenia below a given threshold (eg, 10,000 cells/mm^3 [10×10^9/L]) and in patients with significant bleeding.

Anemia may be problematic in the posttransplant setting, especially in patients receiving allogeneic HSCT. The etiology is unclear and most likely is multifactorial. Although erythropoiesis-stimulating agents may reduce the need

for red blood cell transfusions, its use in cancer patients is associated with an increased risk of adverse events and is limited by FDA warnings and restrictions.

Graft-Versus-Host Disease

GVHD is caused by immunocompetent allogeneic donor T cells reacting against recipient/host antigens on the surface of antigen-presenting cells (APCs). In that setting, donor T cells recognize unmatched major or minor histocompatibility antigens of the host as genetically foreign, become activated, proliferate, and attack recipient tissue, thereby producing the clinical syndrome of GVHD.

Two different clinical syndromes of GVHD (acute and chronic) are recognized, each with two subcategories. Classic acute GVHD occurs within 100 days after transplant or DLI while persistent, recurrent or late-onset acute GVHD occurs beyond 100 days after transplant, withdrawal of immunosuppression or DLI.[53] Both subcategories of acute GVHD occur in the absence of chronic GVHD. Classic chronic GVHD usually occurs after day 100, with only clinical manifestations that can be attributed to chronic GVHD. Chronic GVHD may occur after the resolution of acute GVHD or de novo (no prior acute GVHD). Acute and chronic overlap syndrome is a newly defined entity in which features of both acute and chronic GVHD appear together. Chronic GVHD usually develops before the resolution of acute GVHD (also called progressive onset). The clinical manifestations of GVHD are distinct. Whereas acute GVHD usually is limited to the gastrointestinal tract, skin, and liver, signs and symptoms of chronic GVHD resemble an autoimmune disorder and can affect many organ systems.

A “hyperacute” form of GVHD may occur in patients with multiple HLA mismatches and in patients who receive T cell–replete transplants without adequate GVHD prophylaxis, especially after MAC regimens.[53] Descriptions of hyperacute GVHD vary but usually include fever, generalized erythroderma, desquamation, and edema. More severe forms with accompanying organ failure have been seen in haploidentical donors. Hyperacute GVHD typically occurs about 1 week after transplant before engraftment of neutrophils. The response rate to first-line therapy appears to be lower in patients with hyperacute GVHD compared with patients who develop GVHD later after transplant, but no difference in survival has been observed.

Acute Graft-Versus-Host Disease

Classically, the pathophysiology of acute GVHD has been described as a three-

step process and emphasized the role of mature T cells, newer studies highlight the importance of the intestinal epithelium and role of the microbiome.[53] In step 1, the conditioning regimen causes damage to the intestinal mucosa, leading to the release of lipopolysaccharides into the systemic circulation. This stimulates the secretion of inflammatory cytokines such as IL-1, IL-6 and tumor necrosis factor-α (TNF-α). These cytokines upregulate MHC gene products and host APCs such as dendritic cells, which play a critical role in this immune response. In step 2, donor T cells are activated, and secretion of other cytokines (IL-2 and interferon-γ) by activated T cells results in the recruitment of macrophages and alteration of target cells in the gastrointestinal tract and skin so that they are more susceptible to damage. In step 3, multiple cytotoxic effector cells (T cells and macrophages) are generated and contribute to target tissue injury by secreting more inflammatory cytokines that cause target cell apoptosis. The term "cytokine storm" is sometimes used to describe the critical role of inflammatory cytokines in this process. Three general approaches have been used to prevent GVHD in humans. The first is to reduce host tissue damage with the use of RIC regimens. The second and most widely used approach is to modulate donor T cells by reducing T-cell numbers (T-cell depletion), activation (most immunosuppressive agents), or proliferation (antiproliferative agents). The third approach is to block inflammatory stimulation and effectors (eg, TNF-α inhibition, IL-1 receptor blockade).

The principal target organs in acute GVHD are the skin, liver, and gastrointestinal tract.[53] Acute GVHD is classified into four grades, depending on the number of organs involved and the degree of involvement of each organ (see **Table 157-2**). Grade I disease involves only the skin. Grades II through IV involve the skin and the liver, gastrointestinal tract, or both. Acute skin GVHD usually is manifested as a generalized maculopapular rash that initially involves the face, ears, palms, soles, and upper trunk. The skin rash can spread to the rest of the body and, if untreated or refractory to treatment, will progress to bullae formation and desquamation similar to a burn injury. Gastrointestinal GVHD presents as secretory diarrhea but may progress to abdominal pain or cramping and ileus; hemorrhage may also occur. GVHD of the upper intestinal tract appears as persistent nausea, vomiting, anorexia, and dyspepsia. The diagnosis of gastrointestinal GVHD should be made by biopsy of the intestinal tract (stomach, duodenum, or rectum). Hepatic GVHD usually is asymptomatic, consisting of hyperbilirubinemia and elevated alkaline phosphatase levels; increases in serum transaminases occur less consistently. The diagnosis can be made by biopsy, if possible.

TABLE 157-2 Consensus Grading of Acute Graft-versus-Host Disease

Organ/Extent of Involvement			
	Skin	**Liver**	**Intestinal Tract**
Stage			
1	Rash on <25% of skin[a]	Bilirubin 2-3 mg/dL (34.2-51.3 µmol/L)[b]	Diarrhea >500 mL/day[c] or persistent nausea[d]
2	Rash on 25%-50% of skin	Bilirubin 3-6 mg/dL (51.3-102.6 µmol/L)	Diarrhea >1,000 mL/day
3	Rash on >50% of skin	Bilirubin 6-15 mg/dL (102.6-256.5 µmol/L)	Diarrhea >1,500 mL/day
4	Generalized erythroderma with bulla formation	Bilirubin >15 mg/dL (256.5 µmol/L)	Severe abdominal pain with or without ileus
Grade			
0	None	None	None
I	Stage 1-2	None	None
II	Stage 3	or Stage 1	or Stage 1
III	—	Stage 2-3	or Stage 2-4
IV[e]	Stage 4	or Stage 4	—

[a]Use the "rule of nines" to determine body surface area involvement.

[b]Range given as total bilirubin. Downgrade one stage if an additional cause of elevated bilirubin has been documented.

[c]Volume of diarrhea applies to adults. For pediatric patients, the volume of diarrhea should be based on body surface area.

[d]Persistent nausea with histologic evidence of graft-versus-host disease in the stomach or duodenum.

[e]Grade IV may include lesser organ involvement but with extreme decrease in performance status.

Reprinted from Semin Hematol, Vol. 43, Deeg HJ, Artin JH. The clinical spectrum of acute graft-verus-host disease, pp. 24-31. Copyright © Elsevier 2006 with permission from Elsevier.

The overall incidence of moderate-to-severe (grades II-IV) acute GVHD

ranges from 20% to more than 80%.[54] Mortality directly attributable to acute GVHD or its treatment occurs in about 20% of patients. The incidence of GVHD is related to the degree of histocompatibility, number of T cells in the graft, donor and recipient age and gender, intensity of the conditioning regimen, source of hematopoietic cells (bone marrow vs peripheral blood), and prophylactic regimen. The most severe acute GVHD is observed in allogeneic HSCT with non-HLA-identical donors. In this setting, the incidence of grades II to IV acute GVHD can exceed 50% despite aggressive GVHD prophylaxis. Severe acute GVHD is a major cause of mortality and the risk of death increases as the grade of GVHD increases. This risk is further increased if initial therapy is not effective.

Multiorgan acute GVHD and the drugs given to prevent or treat the disease are associated with delayed immunologic recovery and increased susceptibility to infections. Infection is often the primary cause of death in patients with GVHD. Patients with GVHD treated with an immunosuppressive regimen should receive prophylactic antiviral, antibacterial, and antifungal therapy and be monitored routinely for the occurrence of these infections.

Prevention of Acute Graft-Versus-Host Disease 9 Because treatment of established acute GVHD often is unsatisfactory, aggressive preventive measures usually are taken. The most common strategy used to prevent acute GVHD is to block the activation of T cells by administration of immunosuppressive agents.[53,54] Several immunosuppressive agents have been used, including methotrexate (MTX), cyclosporine (CSA), tacrolimus (TAC), sirolimus, mycophenolate mofetil, ATG, corticosteroids, and monoclonal antibodies directed at T cells. **Table 157-3** shows the doses, toxicities, and monitoring of immunosuppressive agents used to prevent or treat GVHD. Most GVHD prophylaxis regimens combine immunosuppressive agents that affect different stages of T-cell activation. The most commonly used GVHD prophylaxis regimens are CSA or TAC and MTX. Another strategy is removing or depleting most T cells from donor bone marrow ex vivo before transplant by physical separation or by treatment with monoclonal antibodies directed at T cells.

TABLE 157-3 Immunosuppression for the Prevention and Treatment of GVHD

Agent	Dose	Drug Monitoring
Prevention		
Tacrolimus[54]	0.02-0.03 mg/kg/day IV beginning 1-3 days before transplant; change to PO when able to tolerate	Check blood levels ~72 hours after start and then 2-3 times/week until stable (trough blood levels, 5-15 mcg/L [6.2-18.6 nmol/L]); serum creatinine for renal toxicity, CBC for hematologic toxicity, blood pressure for hypertension, and BMP for electrolyte abnormalities
Cyclosporine[54]	3-5 mg/kg/day IV beginning 1-3 days before transplant; change to PO when able to tolerate	Check blood levels ~72 hours after start and then 2-3 times/week until stable (trough blood levels, 150-450 mcg/L [125-374 nmol/L]); serum creatinine for renal toxicity, CBC for hematologic toxicity, blood pressure for hypertension, and BMP for electrolyte abnormalities
Sirolimus[56]	Loading dose 12 mg PO on day +1 followed by 4 mg PO daily starting on day +2	Check serum levels ~24 hours after start and then 2-3 times/week until stable (trough serum levels, 3-12 mcg/L [3-13 nmol/L]); serum creatinine for renal toxicity and CBC for hematologic toxicity
Methotrexate[54]	15 mg/m^2 IV on day +1 followed by 10 mg/m^2 IV on days +3, 6, and 11 or 5 mg/m^2 IV on days +1, 3, 6, and 11	Monitor for toxicity: mucositis, LFTs for hepatic dysfunction, serum creatinine for renal impairment, fluid retention, and CBC for hematologic toxicity; methotrexate levels are not routinely monitored unless the patient develops renal dysfunction or third spacing; doses may be omitted if severe mucositis or hepatotoxicity develops
Mycophenolate[58]	15 mg/kg/dose IV twice daily beginning on day 0; change to PO when able to tolerate	Monitor for toxicity: CBC for neutropenia and severe GI symptoms
Pentostatin[54]	1.5 mg/m^2 IV weekly × 4 doses beginning day +8	Monitor for toxicity: BMP for renal impairment and CBC for thrombotic thrombocytopenic purpura
Cyclophosphamide[59]	50 mg/kg/day IV on days +3 and +4	Monitor for toxicity: BMP for renal impairment, LFTs for hepatic toxicity (including SOS), urinalysis for hemorrhagic cystitis, vital signs and possible cardiac workup for pericarditis (only for symptomatic patients)
Rabbit anti-thymocyte globulin (ATG)[62]	2.5-6 mg/kg/day IV beginning 3 days before transplant	Monitor for toxicity: frequent vital signs during infusion for fever, rash, cardiovascular and GI dysfunction, anaphylaxis and serum sickness
Alemtuzumab[54]	10-20 mg/day IV daily beginning 4-5 days before transplant	Monitor for toxicity: fever, chills, infection, and anaphylaxis
Treatment		
Methylprednisolone[a] or Prednisone[a,54]	1-2 mg/kg/day	Monitor for toxicity: glucose for hyperglycemia, blood pressure for hypertension, labile mood, bone osteopenia, avascular bone necrosis, impaired wound healing, and adrenal insufficiency
Mycophenolate[54]	1.5-2 g PO daily in divided doses	As above
Sirolimus[54]	1-2 mg/day; then adjust based on levels	As above
Infliximab[54]	10 mg/kg/week for at least 4 doses	Monitor for toxicity: anaphylaxis (rare)
Etanercept[54]	0.4 mg/kg/dose (maximum dose, 25 mg) SC twice weekly for 8 weeks	Monitor for toxicity; generally well tolerated
Rabbit ATG[54]	0.5 mg/kg for first dose followed by 1-1.5 mg/kg for subsequent doses	As above
Pentostatin[54]	1.5 mg/m^2 IV on days 1-3 and 15-17	As above

[a]Considered first-line therapy.

BMP, basic metabolic panel; CBC, complete blood count; GI, gastrointestinal; LFT, liver function test; PO, orally; SC, subcutaneous; SOS, sinusoidal obstruction syndrome.

Initially, acute GVHD prophylaxis was single agent MTX administered on days 1, 3, 6, and 11 after transplant and then weekly. However, when a short course of MTX was combined with CSA, the two agents showed synergy and a survival benefit. The addition of a third agent, such as prednisone, to the CSA and MTX combination failed to improve overall outcomes. TAC, another calcineurin inhibitor, was shown to have similar results to CSA when combined with a short course of MTX. The combination of a calcineurin inhibitor with MTX remains a standard immunosuppressive regimen used today. Intravenous CSA or TAC is usually started a few days before or on the day of transplant. Patients are converted to oral formulations when they can be tolerated. CSA or TAC typically are given at full doses until days 50 to 100, gradually tapered in the absence of GVHD, and discontinued by day 180. MTX is still given IV on days 1, 3, 6, and 11 after transplant. About 70% of patients are able to receive all four doses of MTX. Elimination of one or more MTX doses may be associated with an increased risk of GVHD. However, toxicities such as severe mucositis, hepatotoxicity, or the development of conditions that may prolong MTX systemic exposure (eg, renal failure or third spacing) are common reasons to omit the day 11 dose of MTX. For patients who experience significant toxicity from MTX, monitoring of MTX levels with leucovorin rescue may be warranted.

Despite standard prophylaxis with CSA or TAC and MTX, grade II to IV acute GVHD still occurs in 30% to 50% undergoing allogeneic HSCT.[55] Because of the gastrointestinal and hematologic toxicities of MTX, and in an effort to improve prevention, other prophylactic regimens have been evaluated. Sirolimus, an mTOR inhibitor, has theoretical advantages when used as GVHD prophylaxis. This agent has been reported to promote immune tolerance through generation of regulatory T cells, has antiviral properties (CMV and Epstein-Barr virus), and has antitumor activity against some hematologic malignancies.[56] Several studies have shown encouraging results with sirolimus when combined with a calcineurin inhibitor (TAC or CSA) in the prevention of GVHD, and many clinicians believe that the combination of TAC and sirolimus is less toxic and more efficacious than CSA and sirolimus. A meta-analysis of sirolimus-based GVHD prophylaxis showed that when compared to TAC and either MTX or MMF, sirolimus-based regimens significantly decreased the incidence of grade II-IV acute GVHD (relative risk 0.65, 95% confidence interval 0.47-0.89). However, the incidence of grade III to IV acute and chronic GVHD was similar and no significant differences in event-free or overall survival were observed.[57]

Based on similar long-term outcomes, sirolimus-based prophylaxis regimens appear to be an effective and safe alternative to TAC and MTX.

Other MTX-sparing strategies have been evaluated for GVHD prophylaxis. Mycophenolate mofetil through its metabolite, mycophenolic acid, inhibits lymphocyte proliferation and is synergistic with calcineurin inhibitors. A Cochrane review showed that the combination of mycophenolate and TAC compared to a calcineurin inhibitor and MTX had no difference in risk of acute or chronic GVHD, overall survival, or median time-to-engraftment. The mycophenolate and TAC regimen has a more favorable toxicity profile, which makes it a reasonable option for a MTX-sparing GVHD prophylaxis regimen.[58]

Single-agent PTCy is another GVHD prophylaxis strategy that does not include a calcineurin inhibitor. Its immunosuppressive activity is related to its antiproliferative effects on rapidly dividing alloreactive T cells. Hematopoietic stem cells have high levels of aldehyde dehydrogenase, which spares them from the antiproliferative activity of Cy. Two trials of PTCy after myeloablative regimens showed that PTCy as the sole GVHD prophylaxis agent had reasonable rates of acute GVHD with low rates of chronic GVHD.[59] The use of posttransplant Cy combined with other immunosuppressive agents such as mycophenolate mofetil and a calcineurin inhibitor has shown to be effective immunosuppression for Haplo-HSCT patients.

Other novel agents, such are bortezomib and tocilizumab, have shown activity in preventing GVHD in phase I and II studies. The addition of bortezomib to standard regimens may improve efficacy or potentially provide an alternative to calcineurin inhibitor regimens.[60] IL-6 inhibition with tocilizumab was recently described in a phase I-II trial. The addition of tocilizumab to standard GVHD prophylaxis regimens in matched related donors resulted in a grade II to IV acute GVHD rate of 12%.[61] Although the addition of these novel agents is intriguing, the role of these agents in GVHD prophylaxis is not clear and ongoing trials will help to define their role.

Another strategy to prevent acute GVHD is to reduce the number of donor T cells in the stem cell donation. In vivo T-cell depletion may be incorporated into conditioning regimens with agents such as ATG. Uncontrolled trials of ATG with MAC regimens suggested that ATG could prevent GVHD, but may increase the risk of relapse and graft failure. However, three prospective trials showed that ATG decreased the incidence of chronic GVHD without increasing the risk of relapse or nonrelapse mortality.[62] The role of ATG with RIC transplantation has not been evaluated in a randomized controlled trial. The CIBMTR has reported that ATG recipients were more likely to have disease relapse and shorter overall

and disease-free survival.[63] However, another observational study of European patients receiving RIC regimens reported reduced risk of acute and chronic GVHD with similar relapse risk, nonrelapse mortality, and survival.[64] Results from that study also suggested a dose effect with ATG doses of less than 6 mg/kg associated with improved outcomes. Based on these conflicting data, the use of ATG in RIC transplants needs to be further evaluated through randomized studies.

The role of ex vivo T-cell depletion is controversial.[65] Earlier reports of this technique were associated with an increased risk of graft failure, delayed immune reconstitution, leukemic relapse, CMV reactivation, and Epstein-Barr virus–related lymphoproliferative disorders. Most of these studies occurred when bone marrow was the preferred stem cell source. In a comparative analysis of patients who received ex vivo T-cell depletion or the standard calcineurin inhibitor and MTX prophylaxis, T cell–depleted stem cells had lower rates of chronic GVHD. No differences in rates of graft rejection, leukemia relapse, treatment-related mortality, or overall survival rates were reported.[66]

Biomarkers that predict the development of GVHD could direct treatment before the patient develops severe disease. An ideal biomarker would be predictive of both disease onset and prognosis, inexpensive, and readily available in order to facilitate real-time clinical decision making. Many biomarkers have been studied including ST2, TNF-a receptor type 1, CD25 and microRNAs.[55] Although several biomarkers appear promising, they should not be used outside of a clinical trial.

Treatment of Acute Graft-Versus-Host Disease 10 Patients with mild skin-only acute GVHD (grade I) can be treated with topical corticosteroid preparations and counseled on the appropriate use of sunscreen. If a patient develops grades II to IV GVHD, prophylactic agents are continued, and high-dose corticosteroids in the form of IV methylprednisolone or oral prednisone are given.[54,67] The usual dosage is 1 to 2 mg/kg/day given in two divided doses; higher dosages have not been shown to be more efficacious. About 25% to 40% of patients with established acute GVHD respond to high-dose corticosteroids. If the patient responds, the corticosteroid dose is tapered gradually over several weeks to months, depending on response. In patients who experience a flare in GVHD during the taper phase, therapy consists of increasing the corticosteroid dose and then tapering more slowly. Oral beclomethasone dipropionate, a topically active corticosteroid, has been shown to reduce the frequency of gastrointestinal GVHD relapses when continued after prednisone taper.[67]

Administration of beclomethasone has been associated with a better survival at 200 days and 1 year after transplant. Budesonide, another nonabsorbable corticosteroid, has also been evaluated in uncontrolled studies and may also reduce the need for sustained use of high-dose systemic corticosteroid administration.[67]

GVHD-associated mortality is strongly correlated to response to initial treatment and ranges from about 25% in patients who had a complete response to about 80% in patients who had no response or progressive disease. Several randomized trials have evaluated other agents combined with methylprednisolone in an effort to improve response to initial therapy for acute GVHD. At this time, no agent when combined with methylprednisolone has demonstrated any additional benefit over steroids alone.[54,67] The use of glucocorticoid treatment with an additional agent for initial therapy of acute GVHD should only be done within the confines of a clinical trial.

The mortality rate of patients with steroid-refractory GVHD is high. Criteria and indications for initiating secondary therapy for steroid-refractory acute GVHD are not well defined. Although different centers may have varying criteria, in general, if the manifestations of acute GVHD in any organ worsen over 3 days of corticosteroid treatment or symptoms do not improve by 5 days, the patient likely will not respond to corticosteroids, and secondary therapy should be considered.[54] There is no standard treatment of patients with steroid-refractory acute GVHD because very few prospective comparative studies have been conducted to assess the efficacy of individual agents. Second-line therapy consists of continuation of corticosteroids with the addition of one or more of the following: ATG, tocilizumab, ruxolitinib, mycophenolate mofetil, sirolimus, infliximab, etanercept, alemtuzumab, or pentostatin.[54,68] One approach that has shown benefit as corticosteroid-sparing therapy is extracorporeal photopheresis. During this procedure, the patient's blood is exposed extracorporeally to 8-methoxypsoralen followed by ultraviolet A radiation and then returned to the patient. This process is thought to result in suppression of T-cell reactivity and induction of regulatory T cells. Clinical results have been positive, especially in patients with skin GVHD.[69] The choice of a second-line regimen for acute GVHD should be based on the risk of potential toxicities, interactions with other agents, convenience, and cost.

Chronic Graft-Versus-Host Disease

Chronic GVHD is the major determinant of late transplant-related morbidity and mortality. The pathophysiology of chronic GVHD is poorly understood but

appears to involve defects in immune tolerance combined with adaptive immune responses targeting autoantigens. This produces chronic tissue inflammation and damage, often resulting in fibrosis.[70,71] A three-phase model based on murine and human data has been proposed to explain the pathophysiology of chronic GVHD: tissue injury and inflammation secondary to a variety of insults (eg, conditioning regimen toxicity, infection, acute GVHD, sun exposure) (phase 1), chronic inflammation and dysregulated B-cell and T-cell immunity (phase 2), and tissue repair with fibrosis (phase 3).[71] Specific cellular and cytokine activity during these processes have become therapeutic targets for which pharmacologic agents are being evaluated and used in the prevention and treatment of chronic GVHD.

The incidence of chronic GVHD ranges from 30% to 70% and is increasing due to the increased use of alternative (mismatched and unrelated) donors, transplantation of older patients, and longer survival of transplant recipients. The risk of chronic GVHD increases with a previous history of acute GVHD, increasing donor and recipient age, patients who receive transplants from HLA-nonidentical donors and in patients who receive PBSC versus BM transplants (especially with higher $CD34^+$ cell doses).[71] Prophylaxis of chronic GVHD includes similar strategies used to prevent acute GVHD such as in vivo T-cell depletion with ATG or posttransplant cyclophosphamide.[70]

Unlike the acute form, chronic GVHD can affect many different organs and tissues including the skin, mouth, eyes, genitalia, GI tract, liver, lung, and joints.[71] The National Institutes of Health (NIH) Consensus Development Project developed standardized criteria for the diagnosis of chronic GVHD and proposed a clinical scoring system for the evaluation of patients with chronic GVHD based on the extent of organ damage and degree of functional impairment.[72] The Working Group recommends that the diagnosis of chronic GVHD be made with the presence of at least one diagnostic clinical sign of chronic GVHD (eg, poikiloderma or esophageal web) or a distinctive manifestation (eg, keratoconjunctivitis sicca) confirmed by biopsy or other test (eg, Schirmer test). In addition, the NIH Working Group recommends documenting all specific manifestations (acute and chronic) when establishing a diagnosis.[72]

The clinical scoring system categorizes chronic GVHD into mild, moderate, and severe, based on the scoring of individually involved organ systems.[72] Mild chronic GVHD involves only one or two organs or sites (except the lung) with no clinically significant functional impairment (no more than mild involvement in any one organ). Moderate chronic GVHD involves at least one organ or site

with clinically significant but no major disability (at least moderate involvement), three or more organs or sites with no clinically significant functional impairment (no more than mild involvement), or mild lung involvement. Severe chronic GVHD indicates major disability caused by chronic GVHD (at least one organ with severe involvement) or at least moderate lung involvement.

Patients with mild skin-only chronic GVHD can be treated with topical steroid preparations; lower potency steroids are preferred for the face, axillae, and groin whereas more potent preparations can be used for other areas. Topical calcineurin inhibitor products such as tacrolimus and pimecrolimus have also been used with some success.[73] Mild-to-moderate involvement of the mouth can also be managed with local therapy consisting rinsing with oral solutions of high potency steroids such as dexamethasone, budesonide, or clobetasol.[73] Artificial tears are usually recommended for mild ocular involvement; moderate-to-severe disease requires cyclosporine or steroid eye drops or punctal occlusion.[73]

Initial treatment of patients with moderate or severe chronic GVHD consists of prednisone 0.5 to 1 mg/kg/day with or without a calcineurin inhibitor. Although calcineurin inhibitors do not clearly improve response rates to prednisone, they are often used to reduce toxicities of prolonged steroid therapy by enabling the use of lower prednisone doses, especially in patients who may be at high risk for prednisone-related complications. The addition of other agents such as mycophenolate or thalidomide to first-line treatment with prednisione has not been shown to be beneficial.[70] Tapering of prednisone dosing is generally initiated after 1 to 2 weeks if signs and symptoms have improved or stabilized. The tapering schedule varies by institution. Patients with chronic GVHD may require prolonged immunosuppressive treatment for several years from the initial diagnosis.

In addition to treatment specifically for chronic GVHD, ancillary therapies and supportive care should be recommended to lessen the symptoms of chronic GVHD.[73,74] Patients should be educated on the avoidance of sun exposure and the use of sunscreens to reduce skin injury and exacerbation of GVHD skin lesions. Nonsclerotic skin lesions without erosions or ulcerations may respond well to emollients in addition to topical steroids. Patients should be advised to maintain good oral hygiene with routine dental care. Saliva substitutes can be given for mild dry mouth symptoms. Physical therapy is recommended to reduce functional loss as a result of steroid myopathy, joint contractures, and deconditioning.[73]

About one-third of patients respond to initial systemic steroid therapy; those

who do not respond have a very poor prognosis. Steroid-refractory chronic GVHD is defined as progression on 1 mg/kg/day for 2 weeks, stable disease on greater than or equal to 0.5 mg/kg/day of prednisone for 4 to 8 weeks, or inability to taper prednisone to less than 0.5 mg/kg/day due to a flare in symptoms. Patients with steroid-refractory disease require additional therapy to control progression and reduce systemic steroid exposure. Uncontrolled trials have investigated several therapies in this setting with varying degrees of success. To date, no consensus has been reached regarding the optimal choice for salvage therapy.[70,71] When choosing initial salvage therapy, clinicians should consider agents with documented activity and an adequate safety profile as well as agents that are steroid sparing. In addition, some therapies appear to be more effective in treating specific organ systems better than others. Agents with reported activity in refractory chronic GVHD include extracorporeal photophoresis, sirolimus, methotrexate, bortezomib, ruxolitinib, rituximab, ibrutinib, low-dose interleukin-2, imatinib, and others.[70,74,75] Of these agents, the only one that has received FDA approval in the treatment of steroid-refractory chronic GVHD is ibrutinib. Many patients will require third- and fourth-line therapies. In general, ineffective therapies should be discontinued prior to starting a new agent, except for steroid therapy, which is usually continued. Clinicians are encouraged to enroll patients with steroid-refractory chronic GVHD in clinical trials when available.

Monitoring for long-term drug toxicities and infectious complications is critical during long-term immunosuppression. Infection is the primary cause of death in patients with chronic GVHD, and antimicrobial prophylaxis is an important component of the care of patients being treated for chronic GVHD.[74,75] Patients should receive oral trimethoprim–sulfamethoxazole, penicillin, an antifungal azole agent, and acyclovir to prevent infections commonly seen in immunocompromised patients. Routine monitoring for CMV reactivation should be performed. Some HSCT centers also administer IV immunoglobulin to patients with low serum immunoglobulin G levels. Patients who remain on long-term steroids should be monitored for chronic corticosteroid toxicities, including osteoporosis, cataracts, hypertension, myopathies, and diabetes mellitus. Other chronic GVHD therapies have their own toxicity profiles and patients should be counseled and monitored accordingly.

Infection

Patients undergoing high-dose chemotherapy with autologous or allogeneic

HSCT are severely immunocompromised and therefore are at high risk for bacterial, fungal, and viral infections.[24,75] Management of these infections is discussed in detail in Chapters 139 and 140.

Late Complications

With the success of HSCT, the number of long-term survivors has grown. Many survivors experience delayed complications of transplantation and treatments used to prevent or treat those complications, including restrictive and obstructive pulmonary disease, bone and joint disease (including osteoporosis and avascular necrosis), cataract formation, endocrine dysfunction (including sterility and thyroid dysfunction), impaired growth and development, infections, cardiovascular disease, chronic renal and hepatic dysfunction, and secondary malignancies.[24,75,76] These effects are more frequent after allogeneic compared with autologous HSCT and among allogeneic HSCT patients, those with chronic GVHD tend to have a higher prevalence of multiple health conditions than those without chronic GVHD.[24,76] Physical recovery tends to occur earlier than psychological or work recovery. Full recovery usually takes several years, and about two-thirds of patients are without major limitations by 5 years. Both allogeneic and autologous HSCT is associated with a several-fold increase in the risk of premature death; relative mortality decreased with time but remained significantly elevated even 10 years after transplant. The leading cause of death is relapse of primary disease in both allogeneic and autologous HSCT patients. Allogeneic HSCT patients also continue to die from complications of chronic GVHD while autologous HSCT patients more frequently developed secondary malignancies.[24,76] Long-term monitoring of HSCT patients is required, both by transplant clinicians and primary care providers who are knowledgeable in the care of these patients, to screen for, prevent and treat late complications when such interventions are available. In 2012, the CIBMTR (in partnership with leading transplant organizations) published posttransplant care recommendations for adult and pediatric autologous and allogeneic HSCT recipients (www.cibmtr.org/posttransplant).

Postclass Engaged Learning Activity

Perform a literature search and find a study published in the past 24 months that evaluates treatment for GVHD. If it’s a drug that is discussed in the book

chapter, write a brief summary of the study methods, the major findings, and how this new information might change current practice. If the publication evaluates a new medication that is not described in the chapter, write a brief summary of the medication's mechanism of action, how it is administered, and one potential advantage or disadvantage of this new medication compared to the current standard of care.

ABBREVIATIONS

ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
APC	antigen-presenting cell

ASTCT	American Society for Transplantation and Cellular Therapy
ATG	anti-thymocyte globulin
BMT	bone marrow transplantation
BOS	bronchiolitis obliterans syndrome
CAR	chimeric antigen receptor
CIBMTR	Center for International Blood and Marrow Transplant Research
CML	chronic myeloid leukemia
CMV	cytomegalovirus
COP	cryptogenic organizing pneumonia
CSA	cyclosporine
CTN	Clinical Trials Network
DLI	donor lymphocyte infusion
EBMT	The European Bone Marrow Transplantation Association
G-CSF	granulocyte colony-stimulating factor; filgrastim
GM-CSF	granulocyte-macrophage colony-stimulating factor; sargramostim
GVHD	graft-versus-host disease
GVM	graft-versus-malignancy (effect)
Haplo-HSCT	haploidentical allogeneic transplant
HLA	human leukocyte antigen
HSCT	hematopoietic stem cell transplantation
MAC	myeloablative conditioning
MDS	myelodysplastic syndrome
MHC	major histocompatibility complex
MTX	methotrexate
NIH	National Institutes of Health
NHL	non-Hodgkin lymphoma
NK	natural killer (cells)
NMDP	National Marrow Donor Program
PCR	polymerase chain reaction
Ph+	Philadelphia chromosome–positive
PBSC	peripheral blood stem cell
PTCy	posttransplant cyclophosphamide
RIC	reduced-intensity conditioning
SOS	sinusoidal obstruction syndrome
TAC	tacrolimus
TBI	total-body irradiation
TKI	tyrosine kinase inhibitor
TNF-α	tumor necrosis factor-α
TKI	tyrosine kinase inhibitor
UCB	umbilical cord blood
UCBT	umbilical cord blood transplant
VOD	venoocclusive disease

REFERENCES

1. D'Souza A, Fretham C. Current uses and outcomes of hematopoietic cell transplantation (HCT): CIBMTR summary slides. Updated 2018.
2. Wingard J, Gastineau D, Leather H, Synder E, Szczepiorkowski Z. *Hematopoietic Stem Cell Transplantation: A Handbook for Clinicians*. 2nd ed. Bethesda, MD: AABB; 2015.
3. Forman S, Negris R, Antin JAF, eds. *Thomas' Hematopoietic Cell Transplantation*. 5th ed. Oxford, UK: Wiley-Blackwell; 2015.
4. Fung MK, Benson K. Using HLA typing to support patients with cancer. *Cancer Control*. 2015;22:79–86.
5. https://bethematchclinical.org/transplant-therapy-and-donor-matching/hla-typing-and-matching/. Accessed January 21, 2019.
6. Majhail NS, Chitphakdithai P, Logan B, et al. Significant improvement in survival after unrelated donor hematopoietic cell transplantation in the recent era. *Biol Blood Marrow Transplant*. 2015;21:142–150.
7. Eapen M, O'Donnell P, Brunstein CG, et al. Mismatched related and unrelated donors for allogeneic hematopoietic cell transplantation for adults with hematologic malignancies. *Biol Blood Marrow Transplant*. 2014;20:1485–1492.
8. Ballen KK, Koreth J, Chen YB, Dey BR, Spitzer TR. Selection of optimal alternative graft source: Mismatched unrelated donor, umbilical cord blood, or haploidentical transplant. *Blood*. 2012;119:1972–1980.
9. Kanakry CG, de Lima MJ, Luznik L. Alternative donor allogeneic hematopoietic cell transplantation for acute myeloid leukemia. *Semin Hematol*. 2015;52:232–242.
10. Barker JN, Kurtzberg J, Ballen K, et al. Optimal practices in unrelated donor cord blood transplantation for hematologic malignancies. *Biol Blood Marrow Transplant*. 2017;23:882–896.
11. Giralt S, Costa L, Schriber J, et al. Optimizing autologous stem cell mobilization strategies to improve patient outcomes: Consensus guidelines and recommendations. *Biol Blood Marrow Transplant*. 2014;20:295–308.
12. Schmitt M, Hoffmann JM, Lorenz K, Publicover A, Schmitt A, Nagler A. Mobilization of autologous and allogeneic peripheral blood stem cells for transplantation in haematological malignancies using biosimilar G-CSF.

Vox Sang. 2016;111:178–186.

13. DiPersio JF, Micallef IN, Stiff PJ, et al. Phase III prospective randomized double-blind placebo-controlled trial of plerixafor plus granulocyte colony-stimulating factor compared with placebo plus granulocyte colony-stimulating factor for autologous stem-cell mobilization and transplantation for patients with non-Hodgkin's lymphoma. *J Clin Oncol*. 2009;27:4767–4773.
14. DiPersio JF, Stadtmauer EA, Nademanee A, et al. Plerixafor and G-CSF versus placebo and G-CSF to mobilize hematopoietic stem cells for autologous stem cell transplantation in patients with multiple myeloma. *Blood*. 2009;113:5720–5726.
15. Costa LJ, Nista EJ, Buadi FK, et al. Prediction of poor mobilization of autologous $CD34^+$ cells with growth factor in multiple myeloma patients: Implications for risk-stratification. *Biol Blood Marrow Transplant*. 2014;20:222–228.
16. Perkins JB, Shapiro JF, Bookout RN, et al. Retrospective comparison of filgrastim plus plerixafor to other regimens for remobilization after primary mobilization failure: Clinical and economic outcomes. *Am J Hematol*. 2012;87:673–677.
17. Moalic V. Mobilization and collection of peripheral blood stem cells in healthy donors: Risks, adverse events and follow-up. *Pathol Biol (Paris)*. 2013;61:70–74.
18. Holtick U, Albrecht M, Chemnitz JM, et al. Comparison of bone marrow versus peripheral blood allogeneic hematopoietic stem cell transplantation for hematological malignancies in adults: A systematic review and meta-analysis. *Crit Rev Oncol Hematol*. 2015;94:179–188.
19. Anasetti C, Logan BR, Lee SJ, et al. Peripheral-blood stem cells versus bone marrow from unrelated donors. *N Engl J Med*. 2012;367:1487–1496.
20. Eapen M, Logan BR, Horowitz MM, et al. Bone marrow or peripheral blood for reduced-intensity conditioning unrelated donor transplantation. *J Clin Oncol*. 2015;33:364–369.
21. Dahlberg A, Milano F. Cord blood transplantation: Rewind to fast forward. *Bone Marrow Transplant*. 2017;52:799–802.
22. Ballen K. Update on umbilical cord blood transplantation. *F1000Res*. 2017;6:1556.
23. Milano F, Gooley T, Wood B, et al. Cord-blood transplantation in patients with minimal residual disease. *N Engl J Med*. 2016;375:944–953.

24. Hamadani M. Autologous hematopoietic cell transplantation: An update for clinicians. *Ann Med*. 2014;46:619–632.
25. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: Working definitions. *Biol Blood Marrow Transplant*. 2009;15:1628–1633.
26. Gyurkocza B, Sandmaier BM. Conditioning regimens for hematopoietic cell transplantation: One size does not fit all. *Blood*. 2014;124:344–353.
27. Arnaout K, Patel N, Jain M, El-Amm J, Amro F, Tabbara IA. Complications of allogeneic hematopoietic stem cell transplantation. *Cancer Invest*. 2014;32:349–362.
28. Gyurkocza B, Rezvani A, Storb RF. Allogeneic hematopoietic cell transplantation: The state of the art. *Expert Rev Hematol*. 2010;3:285–299.
29. Palmer J, McCune JS, Perales MA, et al. Personalizing busulfan-based conditioning: Considerations from the American Society for Blood and Marrow Transplantation practice guidelines committee. *Biol Blood Marrow Transplant*. 2016;22:1915–1925.
30. Zahid U, Akbar F, Amaraneni A, et al. A review of autologous stem cell transplantation in lymphoma. *Curr Hematol Malig Rep*. 2017;12:217–226.
31. Koreth J, Kim HT, Nikiforow S, et al. Donor chimerism early after reduced-intensity conditioning hematopoietic stem cell transplantation predicts relapse and survival. *Biol Blood Marrow Transplant*. 2014;20:1516–1521.
32. Pingali SR, Champlin RE. Pushing the envelope-nonmyeloablative and reduced intensity preparative regimens for allogeneic hematopoietic transplantation. *Bone Marrow Transplant*. 2015;50:1157–1167.
33. Weisdorf DJ. Reduced-intensity versus myeloablative allogeneic transplantation. *Hematol Oncol Stem Cell Ther*. 2017;10:321–326.
34. Fasslrinner F, Schetelig J, Burchert A, et al. Long-term efficacy of reduced-intensity versus myeloablative conditioning before allogeneic haemopoietic cell transplantation in patients with acute myeloid leukaemia in first complete remission: Retrospective follow-up of an open-label, randomised phase 3 trial. *Lancet Haematol*. 2018;5:e161–e169.
35. Kroger N, Iacobelli S, Franke GN, et al. Dose-reduced versus standard conditioning followed by allogeneic stem-cell transplantation for patients with myelodysplastic syndrome: A prospective randomized phase III study of the EBMT (RICMAC trial). *J Clin Oncol*. 2017;35:2157–2164.
36. Scott BL, Pasquini MC, Logan BR, et al. Myeloablative versus reduced-

intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. *J Clin Oncol*. 2017;35:1154–1161.

37. Avigan D, Hari P, Battiwalla M, et al. Proceedings from the National Cancer Institute's second international workshop on the biology, prevention, and treatment of relapse after hematopoietic stem cell transplantation: Part II. autologous transplantation-novel agents and immunomodulatory strategies. *Biol Blood Marrow Transplant*. 2013;19:1661–1669.
38. de Lima M, Porter DL, Battiwalla M, et al. Proceedings from the National Cancer Institute's second international workshop on the biology, prevention, and treatment of relapse after hematopoietic stem cell transplantation: Part III. prevention and treatment of relapse after allogeneic transplantation. *Biol Blood Marrow Transplant*. 2014;20:4–13.
39. Oran B. Is there a role for therapy after transplant? *Best Pract Res Clin Haematol*. 2015;28:124–132.
40. Dietz AC, Wayne AS. Cells to prevent/treat relapse following allogeneic stem cell transplantation. *Hematology Am Soc Hematol Educ Program*. 2017;2017:708–715.
41. Toprak SK. Donor lymphocyte infusion in myeloid disorders. *Transfus Apher Sci*. 2018;57:178–186.
42. Soiffer RJ, Chen YB. Pharmacologic agents to prevent and treat relapse after allogeneic hematopoietic cell transplantation. *Hematology Am Soc Hematol Educ Program*. 2017;2017:699–707.
43. Moskowitz CH, Walewski J, Nademanee A, et al. Five-year PFS from the AETHERA trial of brentuximab vedotin for Hodgkin lymphoma at high risk of progression or relapse. *Blood*. 2018;132:2639–2642.
44. Giebel S, Czyz A, Ottmann O, et al. Use of tyrosine kinase inhibitors to prevent relapse after allogeneic hematopoietic stem cell transplantation for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: A position statement of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Cancer*. 2016;122:2941–2951.
45. Craddock C, Jilani N, Siddique S, et al. Tolerability and clinical activity of post-transplantation azacitidine in patients allografted for acute myeloid leukemia treated on the RICAZA trial. *Biol Blood Marrow Transplant*. 2016;22:385–390.
46. Pusic I, Choi J, Fiala MA, et al. Maintenance therapy with decitabine after

allogeneic stem cell transplantation for acute myelogenous leukemia and myelodysplastic syndrome. *Biol Blood Marrow Transplant*. 2015;21:1761–1769.

47. Richardson PG, Grupp SA, Pagliuca A, Krishnan A, Ho VT, Corbacioglu S. Defibrotide for the treatment of hepatic veno-occlusive disease/sinusoidal obstruction syndrome with multiorgan failure. *Int J Hematol Oncol*. 2017;6:75–93.
48. Wieruszewski PM, Herasevich S, Gajic O, Yadav H. Respiratory failure in the hematopoietic stem cell transplant recipient. *World J Crit Care Med*. 2018;7:62–72.
49. Yanik GA, Horowitz MM, Weisdorf DJ, et al. Randomized, double-blind, placebo-controlled trial of soluble tumor necrosis factor receptor: Enbrel (etanercept) for the treatment of idiopathic pneumonia syndrome after allogeneic stem cell transplantation: Blood and Marrow Transplant Clinical Trials Network protocol. *Biol Blood Marrow Transplant*. 2014;20:858–864.
50. Williams KM. How I treat bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation. *Blood*. 2017;129:448–455.
51. Ozdemir ZN, Civriz Bozdag S. Graft failure after allogeneic hematopoietic stem cell transplantation. *Transfus Apher Sci*. 2018;57:163–167.
52. Olsson RF, Logan BR, Chaudhury S, et al. Primary graft failure after myeloablative allogeneic hematopoietic cell transplantation for hematologic malignancies. *Leukemia*. 2015;29:1754–1762.
53. Nassereddine S, Rafei H, Elbahesh E, Tabbara I. Acute graft-versus-host disease: A comprehensive review. *Anticancer Res*. 2017;37:1547–1555.
54. Martin PJ, Rizzo JD, Wingard JR, et al. First- and second-line systemic treatment of acute graft-versus-host disease: Recommendations of the American Society of Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2012;18:1150–1163.
55. Zeiser R, Blazar BR. Acute graft-versus-host disease—biologic process, prevention, and therapy. *N Engl J Med*. 2017;377:2167–2179.
56. Abouelnasr A, Roy J, Cohen S, Kiss T, Lachance S. Defining the role of sirolimus in the management of graft-versus-host disease: from prophylaxis to treatment. *Biol Blood Marrow Transplant*. 2013;19:12–21.
57. Wang L, Gu Z, Zhai R, et al. The efficacy and safety of sirolimus-based graft-versus-host disease prophylaxis in patients undergoing allogeneic

hematopoietic stem cell transplantation: A meta-analysis of randomized controlled trials. *Transfusion*. 2015;55:2134–2141.

58. Kharfan-Dabaja M, Mhaskar R, Reljic T, et al. Mycophenolate mofetil versus methotrexate for prevention of graft-versus-host disease in people receiving allogeneic hematopoietic stem cell transplantation. *Cochrane Database Syst Rev*. 2014;(7):CD010280.
59. Al-Homsi AS, Roy TS, Cole K, Feng Y, Duffner U. Post-transplant high-dose cyclophosphamide for the prevention of graft-versus-host disease. *Biol Blood Marrow Transplant*. 2015;21:604–611.
60. Al-Homsi AS, Feng Y, Duffner U, et al. Bortezomib for the prevention and treatment of graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. *Exp Hematol*. 2016;44:771–777.
61. Servais S, Beguin Y, Delens L, et al. Novel approaches for preventing acute graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. *Expert Opin Investig Drugs*. 2016;25:957–972.
62. Baron F, Mohty M, Blaise D, et al. Anti-thymocyte globulin as graft-versus-host disease prevention in the setting of allogeneic peripheral blood stem cell transplantation: A review from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Haematologica*. 2017;102:224–234.
63. Soiffer RJ, Lerademacher J, Ho V, et al. Impact of immune modulation with anti-T-cell antibodies on the outcome of reduced-intensity allogeneic hematopoietic stem cell transplantation for hematologic malignancies. *Blood*. 2011;117:6963–6970.
64. Baron F, Labopin M, Blaise D, et al. Impact of in vivo T-cell depletion on outcome of AML patients in first CR given peripheral blood stem cells and reduced-intensity conditioning allo-SCT from a HLA-identical sibling donor: A report from the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant*. 2014;49:389–396.
65. Holtan SG, Pasquini M, Weisdorf DJ. Acute graft-versus-host disease: A bench-to-bedside update. *Blood*. 2014;124:363–373.
66. Pasquini MC, Devine S, Mendizabal A, et al. Comparative outcomes of donor graft $CD34^+$ selection and immune suppressive therapy as graft-versus-host disease prophylaxis for patients with acute myeloid leukemia in complete remission undergoing HLA-matched sibling allogeneic hematopoietic cell transplantation. *J Clin Oncol*. 2012;30:3194–3201.

67. Dignan FL, Clark A, Amrolia P, et al. Diagnosis and management of acute graft-versus-host disease. *Br J Haematol*. 2012;158:30–45.
68. Roddy JVF. Tocilizumab for steroid refractory acute graft-versus-host disease. *Leuk Lymphoma*. 2016;57:81–85.
69. Schneiderman J. Extracorporeal photopheresis: Cellular therapy for the treatment of acute and chronic graft-versus-host disease. *Hematology Am Soc Hematol Educ Program*. 2017;2017:639–644.
70. Cutler CS, Koreth J, Ritz J. Mechanistic approaches for the prevention and treatment of chronic GVHD. *Blood*. 2017;129:22–29.
71. Zeiser R, Blazar BR. Pathophysiology of chronic graft-versus-host disease and therapeutic targets. *N Engl J Med*. 2017;377:2565–2579.
72. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 diagnosis and staging working group report. *Biol Blood Marrow Transplant*. 2015;21:389–401.
73. Carpenter PA, Kitko CL, Elad S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: V. The 2014 ancillary therapy and supportive care working group report. *Biol Blood Marrow Transplant*. 2015;21:1167–1187.
74. Flowers ME, Martin PJ. How we treat chronic graft-versus-host disease. *Blood*. 2015;125:606–615.
75. Socie G, Ritz J. Current issues in chronic graft-versus-host disease. *Blood*. 2014;124:374–384.
76. Bhatia S, Armenian SH, Landier W. How I monitor long-term and late effects after blood or marrow transplantation. *Blood*. 2017;130:1302–1314.

SECTION 20 NUTRITIONAL DISORDERS

158

Assessment of Nutrition Status and Nutrition Requirements

Katherine H. Chessman and Vanessa J. Kumpf

KEY CONCEPTS

1. *Malnutrition* encompasses both undernutrition and overnutrition (obesity), although the term is most often used to refer to undernutrition.
2. Nutrition screening is distinct from nutrition assessment; an effective screening process should be designed to quickly and consistently identify those with preexisting malnutrition or those at risk for malnutrition.
3. A comprehensive medical, surgical, and dietary history and a nutrition-focused physical examination (NFPE) are essential components of a comprehensive nutrition assessment.
4. Anthropometrics, physical measurements of the size, weight, and proportions of the human body, are important parameters used to assess nutrition status.
5. Laboratory assessment of nutrition status must be interpreted in the context of clinical status and acute and chronic inflammation.
6. Macronutrient or micronutrient deficiencies or toxicities or risk factors for these deficiencies or toxicities can be identified by a comprehensive nutrition assessment.
7. Evidence-based patient-specific goals should be established considering the patient's clinical condition and the need for maintenance or repletion in adults and continued growth and development in children.
8. Validated predictive equations are most often used to determine energy requirements; however, if available, indirect calorimetry is the most accurate bedside method to determine energy requirements.
9. Daily protein needs are based on age, sex, nutrition status, disease state, and

clinical condition.

10 Drug–nutrient interactions can affect response to drug therapy and nutrition status.

Preclass Engaged Learning Activity

Watch the video entitled “Malnutrition Matters: A Call to Action for Providers Caring for Adult Patients.” This 15-minute video, sponsored by the American Society for Parenteral and Enteral Nutrition, is useful to enhance student understanding of malnutrition, the etiology of malnutrition, and identification of malnourished patients. This will aid in the COLLECT and ASSESS steps in the patient care process.

INTRODUCTION

Nutrition care is an essential component of quality patient care. Nutrition screening and assessment are integral components of the nutrition care process. No single clinical or laboratory parameter is an absolute indicator of nutrition status, so information must be collected and analyzed from a number of sources. This chapter reviews tools most commonly used for accurate, relevant, and cost-effective nutrition screening and assessment, including various methods used to determine patient-specific macro- and micronutrient requirements, and potential drug–nutrient interactions.

CLASSIFICATION OF NUTRITION STATUS

1 *Malnutrition* encompasses both undernutrition and overnutrition (obesity), although the term is most often used to refer to undernutrition. Malnutrition is a consequence of nutrient imbalance. In general, deficiency states can be classified as those involving protein, energy, or single nutrients such as individual vitamins or trace elements. Many terms have been used to define malnutrition leading international nutrition experts to propose standardization of nomenclature for both adults and children.[1,2] Starvation-associated malnutrition, *marasmus*, results from prolonged inadequate intake, absorption, or utilization of protein and energy. It can occur in patients with an inadequate food supply, anorexia

nervosa, major depression, and malabsorption syndromes (**Fig. 158-1**). Somatic protein (skeletal muscle) and adipose tissue (subcutaneous fat) wasting occurs, but visceral protein (albumin [ALB] and transferrin [TFN]) production is usually preserved. Moderate weight loss of 10% of usual body weight (UBW; typical weight) over a 6-month period is prognostic of poor clinical outcomes. Severe weight loss (30% or more of UBW) is life-threatening.[3] Patients with starvation-associated malnutrition commonly have a prototypical wasted appearance. When starvation-associated malnutrition develops as a consequence of primarily inadequate protein intake as is seen in areas of famine or limited food supply, affected individuals may not appear malnourished because of relative adipose tissue sparing, especially with mild undernutrition, but visceral (and to some degree somatic) protein stores are depleted, resulting in severe hypoalbuminemia and edema in more advanced cases. In patients with starvation-related malnutrition, enhancing nutritional intake or bypassing impaired absorption with specialized nutrition support can reverse the condition. Careful nutritional resuscitation is required to avoid complications related to refeeding.[3]

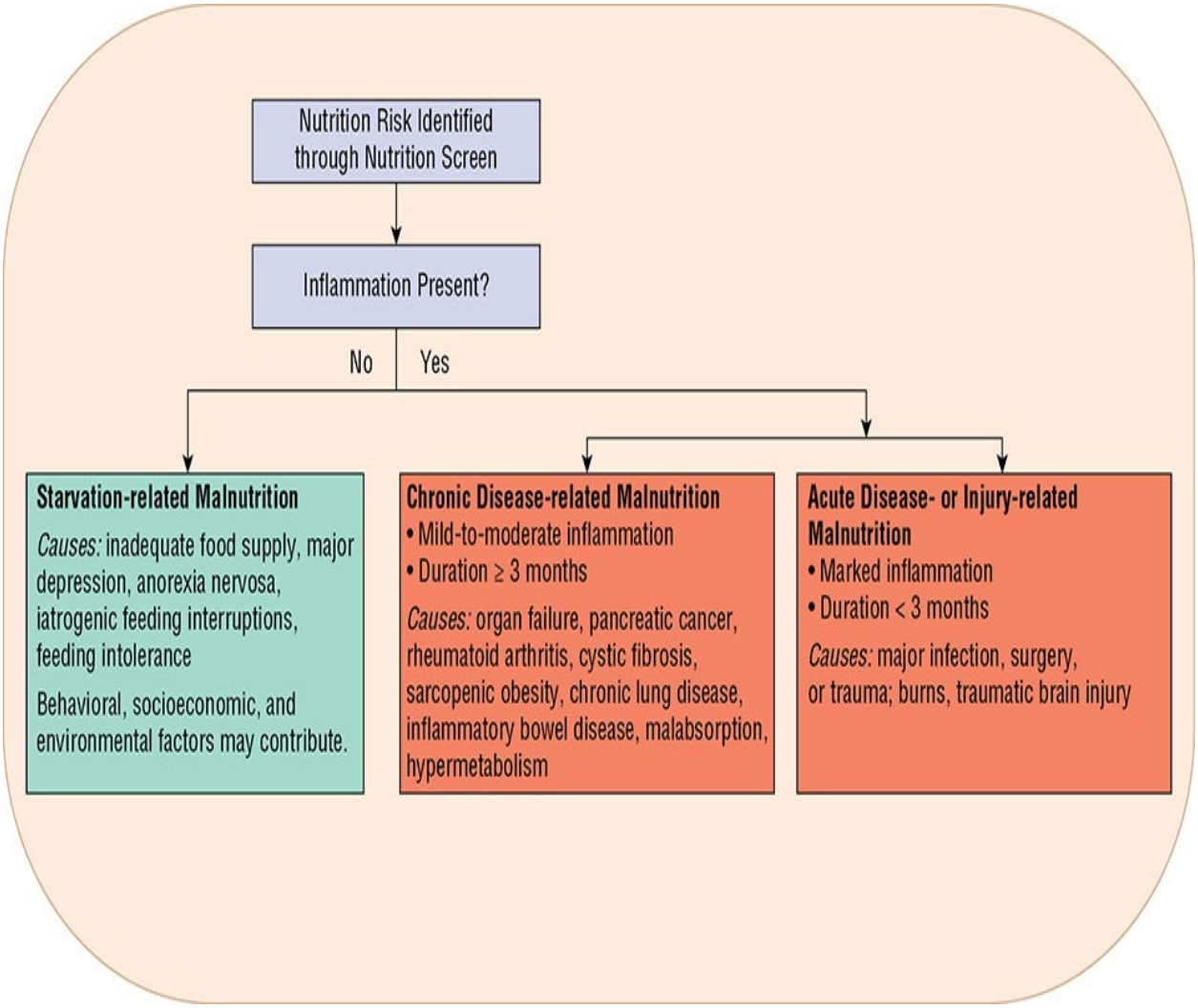
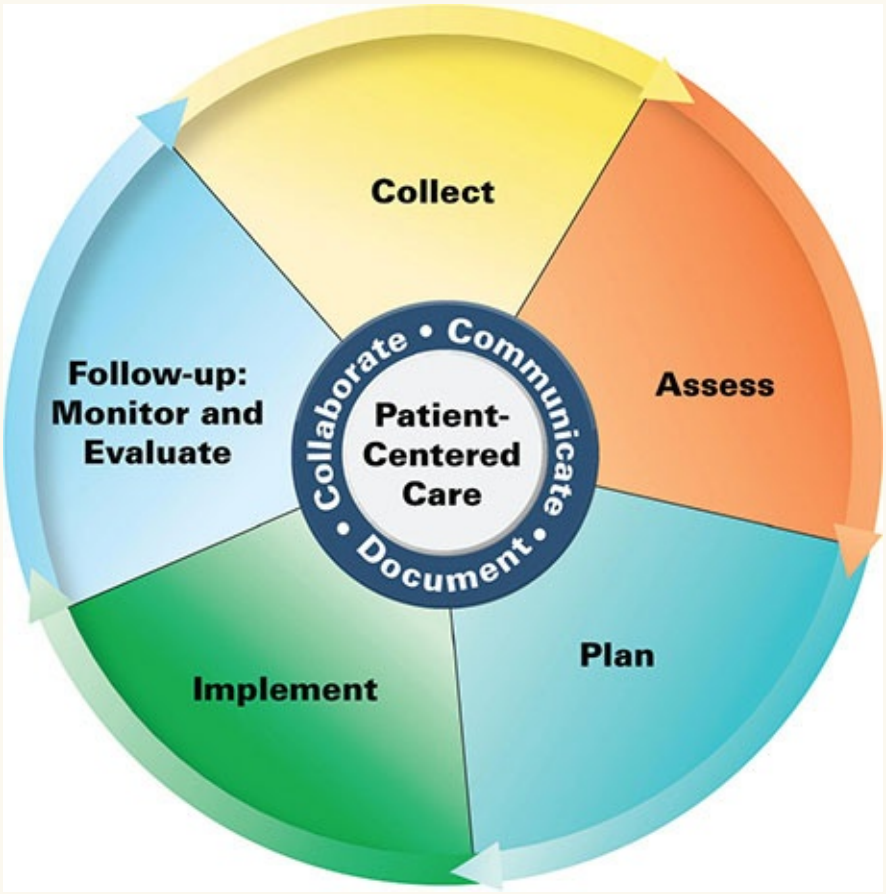


FIGURE 158-1 Etiologic basis for malnutrition diagnosis. (*Adapted from References 1 and 2*.)



Patient Care Process for Nutrition Screening and Assessment

Collect

- Patient characteristics (eg, age, sex, diagnosis)
- Patient history (eg, medical, surgical, diet, recent GI losses, environmental exposures, alcohol use; see Tables 158-1 and 158-2)
- Current medications, including nutrition supplements
- Objective data
  - Body weight (current and usual)
  - Stature, body mass index (BMI), head circumference
  - Recent dietary and fluid intake

- Nutrition-focused physical exam (see Table 158-3)
- Labs (eg, serum electrolytes; glucose; BUN/SCr; albumin, prealbumin; CRP; liver function tests; vitamin, mineral, and trace element concentrations)

Assess

- Nutrition status: presence of malnutrition, obesity (see Table 158-4)
- Risk of refeeding syndrome (eg, unintentional weight loss of more than 5%-10% of usual body weight, prolonged period with poor nutritional intake, BMI less than 18 kg/m^2, low visceral proteins with normal CRP, cachexia, muscle wasting)
- Signs and symptoms of micronutrient deficiencies or toxicities (see Tables 158-7 and 158-8)
- Determine nutrition requirements based on current clinical condition (see Tables 158-9 to 158-15)
- Conduct indirect calorimetry to estimate energy needs, if appropriate

Plan

- Develop a nutrition care plan to ensure delivery of estimated nutrition needs (energy, protein, fluid, vitamins, trace elements)
- Develop a plan to avoid or manage potential drug–nutrient interactions (see Table 158-16)
- Develop a plan to monitor nutritional recovery
- Make referrals to other providers, when appropriate (eg, dietitian, speech therapist, wound care nurse, lactation specialist)

Implement*

- Provide nutrition support using estimated goals
- Provide nutrient supplements to correct deficiencies
- Restrict nutrients to avoid toxicities
- Provide patient education regarding all elements of the nutrition care plan

Follow-up: Monitor and Evaluate

- Appropriate weight gain, loss, or maintenance
- Appropriate gains in length and head circumference in children
- Maintenance or return of function, including muscle strength
- Laboratory parameters, as indicated
- Monitor for side effects of nutrition care
- Monitor for patient adherence to nutrition care plan

** Collaborate with patient, caregivers, and other healthcare professionals.*

Malnutrition (undernutrition) may also develop as the result of an acute or chronic condition or disease, especially those associated with mild-to-severe inflammation (see Fig. 158-1).[1–4] Patients with severe acute disease or injury (major infections, burns, trauma) or with chronic inflammatory diseases (Crohn's disease, systemic lupus erythematosus), organ failure, or cancer can develop disease-related malnutrition because of increased metabolic demands despite seemingly adequate nutrition intake. Individuals with preexisting starvation-related malnutrition can develop pronounced malnutrition if they experience a severe injury or inflammatory process. In patients with disease-related, acute or chronic, malnutrition, simply providing nutrients in usual or even increased amounts may not be sufficient to reverse the nutrient imbalance due to the chronic inflammatory process. As a patient's clinical course progresses, they may change from one malnutrition classification to another.[3] Regardless of the cause, malnutrition (undernutrition and overnutrition) can result in changes in subcellular, cellular, or organ function that increase morbidity and mortality.

Nutrition screening is also used to identify overnutrition: overweight and obese individuals and those at risk of becoming overweight or obese. Obesity is a major global healthcare concern: during 2015 to 2016, approximately 69% of US adults were overweight (defined as a body mass index [BMI] of 25-29.99 kg/m^2) and 39.8% (82 million) were obese (BMI greater than or equal to 30 kg/m^2).[5] In all states, more than 20% of adults were obese. Obesity prevalence in 2017 was 20% to 24.99% only in Colorado, Hawaii, and the District of Columbia; and more than 35% in seven states (West Virginia, Arkansas, Mississippi, Alabama, Iowa, Louisiana, Oklahoma).[6] Additionally, 18.5% (12.7 million) of all US children and adolescents, aged 2 to 19 years, were obese (BMI

greater than or equal to the 95th percentile for age on the gender-appropriate BMI-for-age Centers for Disease Control and Prevention's [CDC] 2000 growth chart).[5,7] The prevalence of obesity in children varied by age group: 2 to 5 years, 13.9%; 6 to 11 years, 18.4%; and, 12 to 19 years, 20.6%.[5] Interestingly, there was no change in obesity prevalence among US adults or children from 2011 to 2014 compared with 2003 to 2004. After a steady increase in obesity prevalence since 1999, this leveling trend is encouraging. The consequences of obesity are numerous and include type 2 diabetes mellitus, cardiovascular disease, hypertension, and stroke. Obesity contributes significantly to all-cause mortality and decreased life expectancy.[8]

Because malnutrition is associated with higher morbidity and mortality rates in many settings, an effective nutrition screening program is essential to identify patients at nutrition-related risk, alerting clinicians to perform a comprehensive nutrition assessment to accurately characterize baseline nutrition status, estimate nutrition needs, and develop a patient-specific nutrition care plan. Diligent monitoring of ongoing nutrition status can ensure that nutrition-related goals are being met and improve patient outcomes.

NUTRITION SCREENING

2 Nutrition screening is distinct from nutrition assessment; an effective screening process should be designed to quickly and consistently identify those with preexisting malnutrition or those at risk for malnutrition.[9] It is not practical, expedient, cost-effective, nor clinically warranted to conduct a comprehensive nutrition assessment on every individual; thus, nutrition screening provides a reliable, systematic method to identify persons for whom a detailed nutrition assessment is warranted. A validated nutrition screening tool can be used to detect those who are overweight, obese, malnourished, or at risk for malnutrition; predict their health outcomes based on nutrition-related factors; and identify individuals who would benefit from nutritional intervention.[9–11]

The ideal nutrition screening tool is quick, simple, and noninvasive and can be done by lay and healthcare providers in homes, long-term care facilities, ambulatory care clinics, and hospitals. Since 1995, the Joint Commission has included nutrition screening and assessment in its performance standards for accredited healthcare institutions. Each entity must have written criteria that identify when nutrition screening and assessment will be performed. In critical access hospitals, a nutrition screen must be completed within 24 hours of

inpatient admission on all applicable patients.[12] In hospitals, most screens are done by nurses.[13] Periodic rescreening should occur at regular intervals determined by the institution and the patient population, usually every 3 to 7 days. For outpatients, nutrition screening should occur at the first visit with a new provider and thereafter as warranted by the patient's condition.

Risk factor identification is the foundation of appropriate nutrition screening. Risk factors for malnutrition include recent unintended weight loss; presence and severity of acute and chronic disease states; drugs and/or other treatments; socioeconomic factors that may result in a decreased nutrient intake; and altered nutrient absorption, metabolism, or utilization. Risk factors for obesity include a family history of obesity, certain medical diagnoses (eg, polycystic ovary syndrome, Prader-Willi syndrome, Cushing's syndrome), poor dietary habits, inadequate exercise, and some drug therapies. Various rating and classification systems have been proposed to screen for nutrition risk and guide subsequent interventions.[9] In general, checklists of varying complexity are used to quantify a person's food and alcohol consumption habits; ability to buy, prepare, and eat food; weight history; diagnoses; medical and surgical procedures; drug and supplement therapies; and history of specialized nutrition support (enteral or parenteral nutrition). Although no tool is 100% sensitive and specific for detecting malnutrition, the Mini-Nutritional Assessment–Short Form (MNA-SF) and the Malnutrition Screening Tool (MST) were found to have high sensitivity and specificity when compared to nine other tools.[14] The MNA-SF has been used extensively in geriatric patients and found to be useful in several care settings.[15] The Nutrition Risk Screening 2002 (NRS 2002) and the Nutrition Risk in the Critically Ill (NUTRIC) are tools recommended for use in critically ill adults.[16,17] Given the drawbacks with use of these tools, a more simple approach is to ask two questions: (1) Has there been a recent weight loss of at least 5% to 10%? (2) Has there been inadequate food intake for at least 1 to 2 weeks? If the answer to either question is Yes, then further assessment is warranted.[9] Nutrition screening for children generally is based on the evaluation of growth parameters against the World Health Organization (WHO; birth to 2 years of age) or CDC (2-19 years of age) growth charts (www.cdc.gov/growthcharts),[7,18] the presence of medical conditions known to increase nutrition risk, and recent changes in weight or food intake. Current estimates of the prevalence of in-hospital malnutrition for pediatric and adult patients range from 13% to 88% depending on the patient population, disease severity, and the criteria used.[13]

In any setting, patients screened to be nutritionally-at-risk should receive a

timely comprehensive nutrition assessment to verify nutrition-related risk and to formulate a complete nutrition care plan which includes monitoring parameters to ensure that desired outcomes are met. For patients who are screened to be *nutritionally-at-risk*, a comprehensive nutrition assessment ideally will be completed by a trained professional within 48 to 72 hours. Most nutrition assessments are completed by dietitians but may be completed by others including nurses, pharmacists, physicians, and physician assistants with training in nutrition support.[13]

NUTRITION ASSESSMENT

3 A comprehensive medical, surgical, and dietary history and a nutrition-focused physical examination (NFPE) are essential components of a comprehensive nutrition assessment. Goals of nutrition assessment include identification of risk factors associated with malnutrition, including disorders resulting from macro- or micronutrient deficiencies (undernutrition), obesity (overnutrition), or impaired nutrient absorption, metabolism or utilization; determination of the risk of nutrition-related complications; estimation of nutrition needs; and establishment of baseline nutrition parameters against which to measure nutrition therapy outcomes. Nutrition assessment should include a nutrition-focused medical, surgical, and dietary history, and an NFPE, including anthropometrics and laboratory measurements.[9]

Nutrition-Focused History and Physical Examination

The nutrition-focused medical, surgical, and dietary history serves to identify factors that predispose to malnutrition (eg, prematurity, chronic disease, gastrointestinal [GI] dysfunction, alcohol abuse, acute or chronic inflammation [cancer, surgery, trauma]) and overnutrition (eg, poor dietary habits, limited exercise, chronic disease, family history) (**Table 158-1**). The clinician should clarify any history of weight gain or loss (intended or unintended), anorexia, vomiting, diarrhea, decreased or restrictive food intake, and enteral or parenteral nutrition. Any conditions that suggest ongoing inflammation, including fever, hypothermia, tachycardia, or infection, should be documented (**Table 158-2**).[4]

TABLE 158-1 Pertinent Data from a Nutrition-Focused Medical, Surgical, and Dietary History

Nutrition intake and dietary habits
Anorexia
Unusual or absent taste
Diet, including vegetarianism
Specialized nutrition support (enteral or parenteral nutrition)
Supplemental vitamin, mineral, or herbal intake
Food allergies or intolerances
Underlying pathology with nutritional effects
Chronic infection or inflammatory state
Cancer
Endocrine disorders
Chronic illness (eg, lung disease, cirrhosis, kidney failure)
Hypermetabolic states (eg, trauma, burns, sepsis)
Digestive/absorptive disease (eg, short bowel syndrome, pancreatitis, cirrhosis)
Hyperlipidemia
End-organ effects
Weight changes
Skin or hair changes
Exercise intolerance or fatigue
Gastrointestinal tract symptoms (diarrhea, vomiting, constipation, abdominal pain)
Gastrointestinal surgery
Bariatric surgery
Small bowel or colon resection or diversion
Gastrectomy
Miscellaneous
Catabolic medications or therapies (eg, corticosteroids, immunosuppressive agents, radiation, chemotherapy)
Other medications (eg, diuretics, laxatives, antipsychotics, anabolic steroids)
Genetic background (eg, body habitus of parents, siblings, family)
Alcohol or drug abuse

TABLE 158-2 Assessment of Inflammation

Laboratory Assessment	Clinical Findings	Acute/Chronic Disease States
Decreased	Fever	Cancer
Albumin	Hypothermia	Celiac disease
Transferrin	Infection	Cystic fibrosis
Prealbumin	Urinary tract	Inflammatory bowel disease
Nitrogen balance	Pneumonia	Organ failure (eg, ARDS)
Elevated	Bacteremia	Pancreatitis
CRP	Wound/incision	Rheumatologic disorders (eg, RA, SLE)
Serum glucose	Abscess	Trauma (burns, major surgery, TBI)
% neutrophils		
Decreased or increased		
WBC		
Platelets		

ARDS, adult respiratory distress syndrome; CRP, C-reactive protein; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TBI, traumatic brain injury; WBC, white blood cell count.

The NFPE uses a system-based approach to assess for abnormal nutrition-related clinical and physical findings in each region of the body. Components of the NFPE include general inspection, vital signs, skin, nails, head/hair, eyes/nose, mouth, neck/chest, abdomen, and musculoskeletal.[17] The clinician completing an NFPE assesses for muscle and fat loss, fluid status, micronutrient deficiency/toxicity, functional status/hand grip strength, and, in children, mid-arm muscle circumference (MUMC).[19,20] The clinician completing an NFPE notes findings commonly associated with malnutrition such as muscle wasting, alopecia, dermatitis, glossitis, cheilosis, or jaundice (Table 158-3).

TABLE 158-3 Nutrition Focused Physical Examination Findings Suggestive of Malnutrition

General Inspection
Edema
Cachexia or obesity
Signs/symptoms of dehydration (poor skin turgor, sunken eyes, orthostasis, dry mucous membranes)
Muscle wasting or loss of subcutaneous fat

Vital Signs
Fever
Tachycardia

Skin
Thin, shiny, dry, or scaly skin
Dermatitis, rash
Decubitus ulcers, poorly healing wounds
Bruising, petechiae
Follicular hyperkeratosis
Pallor, cyanosis, jaundice

Nails
Spoon shape, clubbing
Transverse ridging/banding
Mottled, pale, poor blanching

Head/Hair
Dry, dull, brittle, sparse, easily pluckable hair
Corkscrew, coiled, or depigmented hair
Alopecia
Scaly, flaky scalp
Moon face
Bilateral temporal wasting

Eyes/Nose
Dull dry appearance to sclerae or inner lids
Dull milky appearance of cornea
Bitot spots[a]
Icteric sclerae
Pale conjunctiva
Cracked red corners of eyes

Mouth
Pale, red, or bleeding gums
Dry, cracked, red lips
Fissures at corners (angular stomatitis)
Vertical cracks of the lips (cheilosis)
Magenta or beefy red tongue (glossitis)
Atrophied papillae
Excessive dental caries

Neck/Chest
Enlarged thyroid
Distended neck veins
Prominent bony chest, visible ribs (muscle and fat wasting)

Abdomen
Scaphoid, concave, or protuberant abdomen
Hepatomegaly, ascites

Musculoskeletal
Ataxia (poor muscle control)
Numbness, tingling
Swollen or painful joints
Rickets, knock needs, bowleg

[a]Bitot spots are foamy spots on the surface of the eye.

The Subjective Global Assessment (SGA) and the tool described in the Academy of Nutrition and Dietetics (AND) and the American Society for Parenteral and Enteral Nutrition (ASPEN) consensus statement on the identification and documentation of adult malnutrition are representative examples of a relatively simple, reproducible, cost-effective, bedside approach to nutrition assessment.[1,9] The SGA assesses five aspects of the medical and dietary history: weight change in the previous 6 months, dietary changes, GI symptoms, functional capacity, and disease states known to affect nutrition status. Weight

loss of less than 5% of UBW is considered a “small” loss, 5% to 10% loss is “potentially significant,” and more than a 10% loss is “definitely significant.” Dietary intake is characterized as normal or abnormal, and the duration and degree of abnormal intake are noted. The presence of daily GI symptoms (anorexia, nausea, vomiting, diarrhea) for longer than 2 weeks is significant. Functional capacity assesses the patient’s energy level and whether the patient is active or bedridden. Finally, disease state impact on metabolic demands (no, low, moderate, or high stress) is documented. Four physical examination findings are rated as normal, mild, moderate, or severe: loss of subcutaneous fat (triceps and chest), muscle wasting (quadriceps and deltoids), edema (ankle and sacral), and ascites. The patient’s nutrition status is then rated as adequately nourished, moderately malnourished or suspected of being malnourished, or severely malnourished. Critics of the SGA find it time-consuming and complex. The AND/ASPEN consensus tool assesses six characteristics: insufficient energy intake, weight loss, loss of muscle mass, loss of subcutaneous fat, localized or generalized fluid accumulation, and diminished functional status measured by hand grip strength. The presence of two or more of these characteristics identifies malnutrition in an adult.

Anthropometric Measurements

4 Anthropometrics, physical measurements of the size, weight, and proportions of the human body, are important parameters used to assess nutrition status. Common measurements are weight, stature (standing height or recumbent length), head circumference (for children younger than 3 years of age), and waist circumference. Measurements of limb size, such as skinfold thickness, MUMC, and wrist circumference, may be useful in selected individuals. Bioelectrical impedance analysis (BIA) is also an anthropometric assessment tool. Body measurements can be compared with normative population standards to identify clinical concerns and may be repeated at various intervals to monitor response to a nutrition care plan. In adults, nutrition-related changes in anthropometric measurements tend to occur slowly; several weeks or more may be required before detectable changes are noted. In infants and young children, changes occur more quickly. Significant acute changes in weight and skinfold thickness usually reflect changes in hydration status, which must be considered when interpreting these parameters.

Accurate measurement of anthropometrics (weight, stature, head circumference) and not the use of self-reported values is critical for effective assessment, whenever possible. Measurement can be difficult in injured and

critically ill patients but should be conducted as soon as feasible.

Weight, Stature, and Head Circumference

Body weight is a nonspecific measure of body cell mass, representing skeletal mass, body fat, and the energy-using component, lean body mass (LBM). Fat-free mass includes skeletal muscle, bone, connective tissue, organs, and water while fat mass includes the subcutaneous fat beneath the skin and the visceral (internal) fat. Change in weight over time, particularly in the absence of edema, ascites, or voluntary losses, is an important indicator of altered LBM. Actual body weight (ABW) interpretation should include consideration of ideal weight-for-height, referred to as ideal body weight (IBW), UBW (typical weight), fluid status, and age (**Table 158-4**). Both acute and chronic changes in fluid status can affect the ABW; these changes often can be detected by monitoring the patient's daily fluid intake and output. Patients who are dehydrated will have a decreased ABW but not a loss of LBM. Once rehydrated, these patients must be reweighed to establish an appropriate baseline weight for nutrition evaluation. Edema and ascites increase total body water (TBW), thus increasing ABW but not LBM. The ABW of patients with severe edema and ascites should not be used for nutrition assessment, and practitioners often use an estimated "*dry weight*" to account for this increase in TBW.

TABLE 158-4 Evaluation of Body Weight and Waist Circumference

Parameter	Interpretation	NHLBI Obesity Classification	Waist Circumference	
ABW compared with IBW				
ABW <69% IBW	Severe malnutrition			
ABW 70%-79% IBW	Moderate malnutrition			
ABW 80%-89% IBW	Mild malnutrition			
ABW 90%-120% IBW	Normal			
ABW >120% IBW	Overweight			
ABW ≥150% IBW	Obese			
ABW ≥200% IBW	Morbidly obese			
ABW compared with UBW				
ABW 85%-95% UBW	Mild malnutrition			
ABW 75%-84% UBW	Moderate malnutrition			
ABW <75% UBW	Severe malnutrition			
BMI (kg/m^2)				
Adults				
<16	Severe malnutrition			
16-16.9	Moderate malnutrition			
17-18.9	Mild malnutrition			
19-24.9	Healthy		Disease risk above BMI-related risk[a]—Waist Circumference	
Older Adults				
22-30	Healthy		Women ≤89 cm (35 in) Men ≤102 cm (40 in)	Women >89 cm (35 in) Men >102 cm (40 in)
25-29.9	Overweight		Increased	High
30-40	Moderate obesity			
30-34.9		I	High	Very high
35-39.9		II	Very high	Very high
>40	Severe or morbid obesity	III	Extremely high	Extremely high
Children				
BMI for age <5th percentile	Underweight			
BMI for age 5th-84th percentile	Healthy			
BMI for age 85th-94th percentile	Overweight			
BMI for age ≥95th percentile	Obese			

[a]Increased risk for type 2 diabetes mellitus, hypertension, and cardiovascular disease.

ABW, actual body weight; BMI, body mass index; IBW, ideal body weight; NHLBI, National Heart, Lung, and Blood Institute; UBW, usual body weight.

The IBW is a population reference standard against which the ABW can be compared. IBW-for-height reference tables are available, and IBW can be calculated using mathematical equations based on sex and height. Using the Hamwi method, IBW is calculated as follows:

Adult men: IBW = 48 kg [106 lb] + 2.7 kg [6 lb] × [inches > 5ft]
Adult women: IBW = 45 kg [100 lb] + 2.3 kg[5 lb] × [inches > 5ft]

Using the Devine equations, IBW is calculated as follows:

Adult men: IBW = 50 kg + (2.3 × inches > 5ft)
Adult women: IBW = 45.5 kg + (2.3 × inches > 5ft)

For both equations, a range of ± 4.5 kg for large or small frame size can be used for interpretation purposes.

Adjusted body weight (AdjBW) has been suggested as a logical means to account for the percentage of the obese weight that is LBM (22%-38%). For obese adults, use of an AdjBW has been recommended for nutrition-related calculations, as follows:

$$\text{AdjBW} = ([\text{ABW} - \text{IBW}] \times [0.25 - 0.4]) + \text{IBW}$$

However, the use of AdjBW is generally not recommended; its use is not evidence-based because most of the metabolic rate equations were formulated using ABW in a mix of obese and nonobese individuals.[21] The IBW of a child younger than 18 years of age and 60 in or shorter can be calculated using the Traub equation:

$$\text{IBW} = [\text{height (cm)}]^2 \times 1.65)/1{,}000$$

The IBW-for-height can be determined by identifying the body weight corresponding to the same growth channel as the child's measured stature on the appropriate WHO or CDC growth chart. Using the 50th percentile weight-for-age has been suggested as the appropriate IBW, but this approach is misleading when the child's height is not also at the 50th percentile height-for-age.

Change in weight over time can be calculated as a percentage of UBW. Use of UBW as a reference point provides a more accurate reflection of clinically significant weight change over time (Table 158-4). The use of UBW avoids the

inherent problems with normative tables and documents comparative changes in body weight. However, unless documented in the medical record, determining UBW depends on patient or family recall, which is often inaccurate. All weight changes should be interpreted relative to time because unintentional weight loss, especially rapid weight loss (5% of UBW in 1 month or 10% of UBW in 6 months), increases the risk of nutrition-related poor clinical outcomes.[11,14]

Stature is determined by both genetics and nutrition. Accurate measurement of stature is critical to appropriate interpretation. In older children and adults, a standing height should be obtained. If a standing height cannot be measured using a wall-mounted stadiometer, recumbent length, knee height, and arm spam have been used. Each of these methods yields different results.[22] In infants and young children who are unable to stand, a recumbent length is measured using a *length board* which requires two people to obtain an accurate measurement.

Demispan is determined in a seated patient by measuring the distance from the sternal notch to the web between the middle and ring fingers along a horizontally outstretched arm, with the wrist in neutral rotation and zero extension or flexion. Demispan may more accurately assess stature in elderly adults, especially those with kyphosis or vertebral collapse. After the demispan is measured, height is estimated using the following equations:[23]

$$\text{Women: height (cm)} = (1.35 \times \text{demispan [cm]}) + 60.1$$
$$\text{Men: height (cm)} = (1.4 \times \text{demispan [cm]}) + 57.8$$

Knee height may also be used to estimate stature and is helpful in patients with limb contractures, such as patients with cerebral palsy[24] and the elderly. Knee height is measured from just under the heel to the anterior surface of the thigh just proximal to the patella. Using the average of two measurements rounded to the nearest 0.1 cm, height can be estimated using the following equations:[11]

$$\text{Women: height (cm)} = [1.83 \times \text{knee height (cm)}] - [0.24 \times \text{age (yr)}] + 84.8$$
$$\text{Men: height (cm)} = [2.02 \times \text{knee height (cm)}] - [0.04 \times \text{age (yr)}] + 64.9$$

Appropriate growth is predictable and the best indicator of adequate nutrition in a child. At each medical encounter, weight, stature, head circumference (until 3 years), and BMI (after 2 years) should be plotted on the WHO (younger than 2 years) or CDC gender- and age-specific growth curves.[7,18] The CDC charts were revised in 2000 from US data only and indicate how US children grow. The WHO charts developed in 2006 are preferred in those younger than 2 years

because they include data from infants from six industrialized countries including the United States who were predominantly breastfed for the first 4 months of life and who were receiving some breast milk at 12 months, conditions felt to ensure optimal growth.[18] Specialized charts are also available for assessment of growth of premature infants.[25,26] For premature infants with corrected postnatal age of 40 weeks or more, the WHO growth charts can be used; however, weight-for-age, length-for-age, and head circumference-for-age should be plotted according to corrected postnatal age until 2 years, 1.5 to 3 years, and 3 years of age, respectively.

Recommended intervals between measurements in young children are weight, 7 days; length, 4 weeks; height, 8 weeks; and head circumference, 7 days in infants and 4 weeks in children until 3 years of age. Daily weight fluctuations can occur with changes in fluid status. Growth velocity can be used to assess growth at intervals too close to plot accurately on a growth chart (**Table 158-5**). In newborns, average weight gain is 10 to 20 g/kg/day (24-35 g/day in term infants; 10-25 g/day in preterm infants depending on gestational age). The rate of weight gain declines considerably after 3 months of age; children 6 to 10 years of age gain about 2 to 3 kg/year. The adolescent "growth spurt" typically begins at 9 to 10 years in girls and 11 to 12 years in boys. During the 11- to 13-year-old-interval of maximum growth in height, girls will gain about 10 kg (22 lb) while boys gain 15.5 kg (33 lb). Length increases rapidly in infancy (see Table 158-5). In children 6 to 10 years of age, height increases by 2 to 3 in/year (approximately 5-7.5 cm/year) and continues until about 16 to 18 years of age in girls and 18 to 20 years of age in boys. Head growth (measured by head circumference), usually 0.5 cm/week (0.2 in/week) during the first year of life, can be compromised during periods of critical illness or malnutrition. Rapid head growth, at a rate faster than expected, suggests hydrocephalus which may be benign but must be further evaluated.

TABLE 158-5 Expected Growth Velocities in Term Infants and Children

Age	Weight (g/day)	Height (cm/month)[a]
0-3 months	24-35	2.8-3.4
4-6 months	15-21	1.7-2.4
7-12 months	10-13	1.3-1.6
1-3 years	5-9	0.6-1
4-6 years	5-6	0.5-0.6
7-10 years	7-11	0.4-0.5

[a]Growth velocity of 1 cm/month is equivalent to 0.4 in/month.

Example of growth assessment:

Age: 2 months; weight: 3.2 kg; weight at 1 month of age, 3.1 kg; time since last weight was obtained: 30 days.

Growth velocity = ([3.2 kg–3.1 kg] × 1,000 g/kg)/30 days = 3.3 g/day.

Interpretation: suboptimal growth; comprehensive nutrition assessment needed.

In the International Classification of Disease-10 (ICD-10), failure-to-thrive (FTT; growth faltering) in a child is defined as *lack of expected normal physical growth*, *failure to gain weight*, or *lack of growth*. Not all children with low weight have FTT, but it has been defined as weight-for-age, length-for-age, BMI-for-age, or weight velocity below the 2nd percentile or a weight deceleration crossing two or more major percentiles (major percentiles are defined as 97th, 95th, 90th, 75th, 50th, 25th, 10th, 5th, and 3rd), or if an infant is not gaining the expected daily weight.[27] In children, a significant weight loss is defined as: greater than 2% in 1 week; greater than 5% in 1 month; greater than 7.5% in 3 months; and greater than 10% in 6 months. Growth faltering is best defined by using z-scores for weight-for-length, BMI-for-age, or length- or height-for age: a z-score of −1 indicates mild malnutrition; −2 moderate malnutrition; and −3 severe malnutrition.[2] Weight-for-height evaluation is age-independent and helps differentiate a stunted child (chronic malnutrition) from a wasted child (acute malnutrition). Short stature can be associated with chronic undernutrition, but short stature in the absence of poor weight gain suggests another etiology, such as growth hormone deficiency or constitutional growth delay.[28]

Body Mass Index

Body mass index can be calculated as either body weight in kilograms divided by height in meters squared (kg/m^2) or body weight in pounds multiplied by 703 divided by height in inches squared (lb/in^2). The assessment of BMI is the first

step but not the sole criterion to judge potential health risk.[29] A BMI of 25 kg/m^2 or higher is considered a risk factor for premature death and disability. High BMI contributed to an estimated 4 million deaths worldwide in 2015.[30] Health risks increase with increasing BMI; however, individual variation, especially in very muscular persons, can lead to erroneous nutrition status classification when BMI alone is used. Thus, BMI must be interpreted based on characteristics such as sex, frame size, race/ethnicity, and age. For example, at the same BMI, a woman tends to have more body fat than a man, and an older adult will have more body fat than a younger one. Asian Americans may have more body fat than whites at a lower BMI; and health risks such as type 2 diabetes have been associated with lower BMIs in individuals of Asian descent.[31]

The National Institutes of Health obesity expert panel report classifies a BMI between 18.5 and 24.9 kg/m^2 as a healthy or normal weight, between 25 kg/m^2 and 29.9 kg/m^2 as overweight, between 30 kg/m^2 and 39.9 kg/m^2 as obese; and 40 kg/m^2 or higher as extreme obesity (see Table 158-4).[32] These BMI classifications may not be appropriate for adults older than 60 to 65 years.[33] The Centers for Medicaid and Medicare Services defines normal BMI for adults older than 65 years to be between 23 and 30 kg/m^2; the National Screening Initiative defined normal BMI for this age as 22 to 27 kg/m^2. The NIH classifies a BMI of less than 18.5 kg/m^2 as undernutrition, but this relationship is not as well established.[32] BMI values below 18.5 kg/m^2 have been associated with higher mortality rates in patients with cancer.[34] Children 2 years of age and older are considered overweight if their BMI is at or above the 85th percentile on the age- and gender-specific CDC BMI chart and obese if the BMI is at or above the 95th percentile.[7,18] Use of these charts at each medical encounter helps to heighten awareness of children whose BMI and family history put them at risk for adult obesity and its associated complications.

Waist Circumference

Body fat distribution is associated with health risk. Waist circumference is a simple measurement used to assess abdominal (visceral) fat. Waist circumference is determined by measuring the distance around the smallest area below the rib cage and the top of the iliac crest. Extra weight around the waist rather than peripheral (subcutaneous) fat confers a greater health risk than extra weight around the hips and thighs. The larger the waist circumference, the greater the risk of obesity-related complications, especially diabetes mellitus, cardiovascular disease, and all-cause mortality.[29,35] Men and women are

considered to have abdominal obesity and at increased risk (beyond their BMI-related risk) when the waist circumference is greater than 40 in (102 cm) and greater than 35 in (89 cm), respectively (Table 158-4). Children have abdominal obesity if the waist circumference is at the 90th percentile or greater according to CDC age- and sex-specific standards.[36]

Waist-to-Hip and Waist-to-Height Ratios

The waist-to-hip ratio is determined by dividing the waist circumference by the hip circumference (maximal posterior extension of the buttocks). In adults, a waist-to-hip ratio of greater than 0.9 in men and 0.85 in women is considered an independent risk factor for adverse health consequences.[35] Waist-to-height ratio (both measured in centimeters) has been used to evaluate children at risk for the metabolic syndrome because, unlike waist circumference, it is independent of age and sex. A child (aged 6-18 years) with a waist-to-height ratio of more than 0.5 is considered to have abdominal obesity and at risk for developing the metabolic syndrome. This cutoff may overestimate abdominal obesity in younger children (aged 2-5 years).[36]

Skinfold Thickness and Mid-Arm Muscle Circumference

More than 50% of the body's fat is subcutaneous; thus, changes in subcutaneous fat reflect changes in total body fat. Skinfold thickness measurement provides an estimate of subcutaneous fat, and MUMC, which is calculated using the skinfold thickness and mid-arm circumference, estimates skeletal muscle mass. Although simple and noninvasive, these anthropometric measurements are used most commonly in population analysis and long-term monitoring of individuals. Triceps skinfold thickness measurement is used most often, but reference standards also exist for subscapular and suprailiac measurements.[37] Consistent technique in the use of pressure-regulated calipers is essential for reproducibility and reliability in measuring skinfold thickness. Published standards do not account for variation in bone size, muscle mass, hydration, or skin compressibility, and they do not consider obesity, ethnicity, illness, and increased age. Results should be interpreted cautiously as these parameters change slowly in adults, often requiring weeks before significant alterations from baseline can be detected. They will change more rapidly in young children.

Bioelectrical Impedance

Bioelectrical impedance is a portable, simple, quick, noninvasive, and relatively inexpensive technique used to measure body composition.[38,39] When a weak, alternating electric current is applied to two appendages (wrist and ankle or both feet), impedance (resistance) to flow is measured as it passes through the body. This current is well conducted by water and electrolyte-rich tissues such as blood and muscle but poorly conducted by fat, bone, and air-filled spaces. Assessment of LBM, TBW, and water distribution can be determined with BIA. Increased TBW decreases impedance; thus, it is important to evaluate hydration status along with BIA. Other potential limitations of BIA include variability with electrolyte imbalance and interference by large fat masses, environment, ethnicity, menstrual cycle phase, and underlying medical conditions.[39] Although BIA equations have high validity when used in the population in which they were developed (mostly young healthy adults), BIA calculations are subject to considerable errors if applied to other populations where conditions are not identical (eg, electrode placement must be identical).[39] The use of BIA in clinical practice may be limited by the lack of reference standards that reflect variations in individual age, body size, and clinical conditions.[38]

OTHER NUTRITION ASSESSMENT TOOLS

Functional status is very dependent on nutrition, but the specific tools to assess it are not well defined. Muscle function is an end-organ response; thus, diminished skeletal muscle function can be a useful indicator of malnutrition. Muscle function may also recover more quickly in response to adequate nutrition support than anthropometric measurements. Simple functional assessments include the ability to perform activities of daily living, participate in physical and occupational therapy, and wean from the ventilator. Hand-grip strength (forearm muscle dynamometry), respiratory muscle strength, and muscle response to electrical stimulation also have been used. Measuring hand-grip strength is part of an NFPE and is a relatively simple, noninvasive, and inexpensive procedure that correlates well with patient outcome.[40–42] Normative standards supplied by the manufacturer of the specific dynamometer must be used for assessment. Hand-grip strength is an indirect measurement of LBM, making it a good parameter for assessment of undernutrition. However, some conditions will limit hand-grip strength, such as rheumatoid arthritis, stroke, neuromuscular disease, dementia, and heavy sedation. Ulnar nerve stimulation causes measurable muscle contraction and is used in most intensive care units to monitor neuromuscular blockade. In malnourished patients, increased fatigue

and a slowed muscle relaxation rate are noted, and these indices return to normal with refeeding.

Other methods have been used to determine body composition, including bioimpedance spectroscopy, dual energy x-ray absorptiometry (DXA), quantitative computed tomography (CT), air displacement plethysmography (BodPod®), three-dimensional photonic scanning, quantitative magnetic resonance imaging (MRI), ultrasonography, and positron emission tomography (PET).[16,39,43,44] These methods are often complex and expensive to perform. DXA, best known for its use in measuring bone density, is a promising method for routine clinical practice because it can quantify mineral, fat, and LBM compartments and is available in most hospitals and many outpatient facilities. A central body DXA scanner requires a fair amount of space, and the cost depends on the scanner's complexity. Portable (or peripheral) DXA devices can be used to measure bone density in peripheral bones, such as the wrist, fingers, or heel, and have also been used to assess subcutaneous fat. Portable DXA scanners are much less expensive than central scanners and can be used in community screenings. Further research is needed to determine how DXA can be used clinically in nutrition assessment. MRI and CT can measure subcutaneous, intra-abdominal, and regional fat distribution and thus also have the potential to be useful clinically.

Laboratory Assessment

5 Laboratory assessment of nutrition status must be interpreted in the context of clinical status and acute and chronic inflammation. Biochemically, LBM can be assessed by measuring the serum concentrations of the serum visceral proteins, ALB, TFN, and prealbumin (also known as transthyretin). C-reactive protein (CRP) can be useful as a marker of inflammation. Creatinine-height index has historically been calculated to assess LBM but is rarely used because of the lack of evidence to support its value.[11]

Serum Visceral Proteins

Visceral proteins synthesized by the liver with the greatest relevance for nutrition assessment are serum ALB, TFN, and prealbumin. It is assumed that in undernutrition states, a low serum protein concentration reflects diminished hepatic protein synthetic mass and indirectly reflects the functional protein mass of other organs (heart, lung, kidney, intestines). However, many factors other than nutrition can affect the serum concentrations of these proteins including

age; abnormal kidney (nephrotic syndrome), GI tract (protein-losing enteropathy) or skin (burns) losses; hydration (dehydration results in hemoconcentration, overhydration in hemodilution); liver function (synthesis); and metabolic stress and inflammation (eg, chronic disease, sepsis, trauma, surgery, infection). Thus, visceral protein concentrations must be interpreted relative to the individual's overall clinical condition (**Table 158-6**). The use of visceral protein concentrations for nutrition assessment is of greatest value in the presence of uncomplicated starvation and recovery but may be affected by other factors even in these states. The significant influence of inflammation on visceral protein concentrations is now well established; thus, these *negative acute-phase reactants* may be considered to reflect the extent of physiologic stress or inflammation more than the presence of undernutrition in many circumstances (Table 158-3).[11,45] During severe acute stress (trauma, burns, sepsis), these proteins are poor markers of nutrition status because the resultant increased vascular permeability can lead to dramatic fluid shifts, and the reprioritizing of liver protein synthesis increases the production of acute-phase reactants such as CRP, ferritin, fibrinogen, and haptoglobin.[9,45] CRP is a true acute-phase protein rising within 10 hours after major surgery or acute sepsis; it can be used to assess the degree of inflammation present.[45] If CRP is elevated, then inflammation is likely a major contributing factor to decreased visceral protein concentrations. Assessing individual patient trends, not comparison to normative standards, may be useful in these cases.

TABLE 158-6 Serum Proteins Used for Assessment of Lean Body Mass

Serum Protein	Half-Life (Days)	Function	Factors Resulting in Increased Values	Factors Resulting in Decreased Values
Albumin	18-20	Maintains plasma oncotic pressure; transports small molecules	Dehydration, anabolic steroids, insulin, infection	Fluid overload; edema; kidney dysfunction; nephrotic syndrome; poor dietary intake; impaired digestion; burns; heart failure; cirrhosis; thyroid, adrenal, or pituitary hormones; trauma; sepsis
Transferrin	8-9	Binds Fe in plasma; transports Fe to bone	Fe deficiency, pregnancy, hypoxia, chronic blood loss, estrogens	Chronic infection, cirrhosis, burns, enteropathies, nephrotic syndrome, cortisone, testosterone
Prealbumin (transthyretin)	2-3	Binds T_3 and, to a lesser extent, T_4; retinol-binding protein carrier	Impaired kidney function	Cirrhosis, hepatitis, stress, surgery, inflammation, hyperthyroidism, cystic fibrosis, burns, zinc deficiency

T_3, triiodothyronine; T_4, thyroxine.

Albumin, the most abundant serum protein, is involved in the maintenance of colloid oncotic pressure and binding and transport of numerous hormones, anions, drugs, and fatty acids. Although it has been widely used as a marker of chronic malnutrition, it is a relatively insensitive index of protein malnutrition because there is a large amount normally in the body (4-5 g/kg of body weight), it is extensively distributed in the extravascular compartment (60%), and it has a long half-life (18-20 days). However, chronic protein deficiency in the setting of adequate nonprotein calorie intake leads to marked hypoalbuminemia because of a net ALB loss from the intravascular and extravascular compartments. Serum ALB concentrations also are affected by moderate-to-severe calorie deficiency and liver, kidney, and GI disease. ALB is a negative acute-phase reactant, and serum concentrations decrease with inflammation, infection, trauma, stress, and burns. Serum ALB concentrations less than 2.5 g/dL (25 g/L) can be expected to exacerbate ascites and peripheral, pulmonary, and GI mucosal edema because of decreased colloid oncotic pressure. Hypoalbuminemia also affects the interpretation of serum concentrations of calcium and highly protein bound drugs (eg, phenytoin, valproic acid).

Transferrin is a glycoprotein that binds and transports ferric iron to the liver and reticuloendothelial system for storage. Because it has a shorter half-life (8-9 days) and there is less of it in the body (less than 100 mg/kg of body weight), TFN will decrease in response to protein and energy depletion before the serum ALB concentration decreases. If a direct measure of serum TFN is not available, TFN concentration can be estimated indirectly from measurement of total iron-binding capacity, as follows:

$$\text{TFN (in mg/dL)} = (\text{total iron-binding capacity [mcg/dL]} \times 0.8) - 43$$

Alternatively, TFN (mg/dL) = 0.7 × total iron-binding capacity (mcg/dL), or TFN (g/L) = 0.039 × total iron-binding capacity (µmol/L). TFN is also a negative acute-phase reactant, and its concentration is decreased in the presence of critical illness and inflammation.[11] Iron stores also affect serum TFN concentrations: in iron deficiency, hepatic TFN synthesis is increased, resulting in increased serum TFN concentrations.

Prealbumin (transthyretin) is the transport protein for thyroxine and a carrier for retinol-binding protein. Prealbumin stores are low (10 mg/kg of body weight), and it has a very short half-life (2-3 days); thus, the serum prealbumin concentration may be reduced quickly after a significant reduction in calorie and protein intake (NPO status) or in patients with metabolic stress (trauma, burns, sepsis). Prealbumin is most useful in monitoring the short-term, acute effects of

nutrition support or deficits, as it responds very quickly in both situations, but it too is an acute negative-phase reactant.[11] As with ALB and TFN, prealbumin synthesis is decreased in liver disease. Falsely elevated prealbumin concentrations may be seen in patients with kidney dysfunction because of impaired excretion.

Nitrogen Balance Study

Nitrogen is found only in protein and at a relatively constant ratio of 1 g nitrogen per 6.25 g of protein. This ratio may vary somewhat for enteral and parenteral feeding formulations, depending on the biologic value of the protein source. The adequacy of protein intake can be assessed clinically by a nitrogen balance study —measuring urinary nitrogen excretion and comparing it with nitrogen intake. Nitrogen balance indirectly reflects protein use or the protein catabolic rate, which increases with hypercatabolism. As the stress level increases, a concomitant increase in protein catabolism results in an increase in urinary nitrogen excretion. The amount of urine urea nitrogen (UUN) measured in a 24-hour urine collection in healthy individuals accounts for 80% to 90% of the total urine nitrogen (TUN) excreted. Nitrogen output (g/day) can be approximated as 24-hour UUN + 4, where 4 is a factor representing usual skin, fecal, and respiratory nitrogen losses.[11] Alternatively, nitrogen output can be estimated using the equation: 24-hour UUN + 2 + 20% of urinary urea losses.[46] At higher UUN values (30 g nitrogen or more), then the use of a factor of + 6 may yield a more accurate measure of nitrogen output.[47] Alternatively, if available, TUN can be measured and may be more accurate, especially in critically ill patients who excrete more nitrogen-containing substances such as 3-methylhistidine. If TUN is used, then the best estimate of nitrogen output is TUN + 1.05, where 1.05 is the average extraurinary nitrogen losses.[47] In patients with kidney failure, in which case neither UUN nor TUN accurately represents net protein degradation, nitrogen output can be approximated with equations based on urea nitrogen appearance.[48]

Immune Function Tests

Nutrition status affects immune function either directly, via actions on the lymphoid system, or indirectly by altering cellular metabolism or organs that are involved with immune system regulation. Immune function tests most often used in nutrition assessment are the total lymphocyte count and delayed cutaneous hypersensitivity (DCH) reactions. Both tests are simple, readily available, and

inexpensive. A lack of specificity, however, limits the usefulness of these tests as nutrition status markers.

Total lymphocyte count reflects the number of circulating T and B lymphocytes. Tissues that generate T cells are very sensitive to malnutrition, undergoing involution resulting in decreased T-cell production and eventually lymphocytopenia. A total lymphocyte count less than 1,200 cells/mm^3 (1.2×10^9 cells/L) is a nonspecific marker for nutrition depletion.[11] Total lymphocyte count is reduced in the presence of infection (eg, human immunodeficiency virus [HIV], other viruses, tuberculosis), immunosuppressive drugs (eg, corticosteroids, cyclosporine, tacrolimus, sirolimus, chemotherapy, antilymphocyte globulin), leukemia, and lymphoma.

Delayed cutaneous hypersensitivity is commonly assessed using recall antigens to which the patient was likely previously sensitized, such as mumps and *Candida albicans*. Although not specific for nutrition status, anergy is associated with severe malnutrition, and response can be restored with nutrition repletion.[11] Other immune function tests used in nutrition research include lymphocyte surface antigens (eg, CD4, CD8, CD4:CD8 ratio), T-lymphocyte responsiveness, and various serum interleukin concentrations. Factors affecting DCH include fever, viral illness, recent live-virus vaccination, critical illness, irradiation, immunosuppressive drugs, diabetes mellitus, HIV, cancer, and surgery. Nutrients such as arginine, omega-3 fatty acids, and nucleic acids given in pharmacologic doses may improve immune function. Monitoring efficacy of a nutrition care plan that includes these potentially immune-modulating nutrients may include these immune function assessments, although they are primarily used in research.

NUTRIENT DEFICIENCIES AND TOXICITIES

6 Macro- or micronutrient deficiencies or toxicities or risk factors for these deficiencies or toxicities may be identified by a comprehensive nutrition assessment. A comprehensive nutrition assessment should include an evaluation for possible trace element, vitamin, and essential fatty acid deficiencies (EFAD) or toxicities. Because of their key role in metabolic processes (coenzymes and cofactors), a deficiency of any of these nutrients may result in altered metabolism and cell dysfunction. An accurate history to identify symptoms and risk factors for a specific nutrient deficiency or toxicity is critical. An NFPE and biochemical assessment to confirm a suspected deficiency or toxicity should be done in all nutritionally at-risk patients. Ideally, biochemical assessment would

be based on the nutrient’s function (eg, metalloenzyme activity) rather than simply measuring the serum concentration. Unfortunately, few practical methods to assess micronutrient function are available; thus, the serum concentration is most often measured (**Table 158-7**).

TABLE 158-7 Assessment of Trace Element Status

Trace Element	Signs of Deficiency	Signs of Toxicity	Factors Associated with Altered Plasma Concentrations	Monitoring
Chromium	Impaired glucose/protein utilization, peripheral neuropathy, weight loss, increased LDL-C, increased free fatty acid concentrations	Industrial exposure: skin or nasal septum lesions, allergic dermatitis, increased incidence of lung cancer	**Decreased**: long-term inadequate intake **Increased**: kidney failure	Serum glucose, plasma chromium (unreliable)
Copper	Menkes' syndrome: progressive mental deterioration, vomiting, diarrhea, protein-losing enteropathy, hypopigmentation, bone and hair changes Deficiency: neutropenia, hypochromic anemia, pallor, dermatitis, neurological dysfunction, osteoporosis, myopathy, thrombocytopenia, decreased bone mineralization (children)	Wilson's disease: cirrhosis, Kayser-Fleischer rings,[a] kidney dysfunction, neurologic or psychiatric symptoms (tremors, slow speech, inappropriate behavior, personality changes) Mild chronic toxicity: fatigue, anemia, thrombocytopenia Acute toxicity: nausea, vomiting, diarrhea	**Decreased**: high zinc, iron, or vitamin C intake; corticosteroid use **Increased**: infection, rheumatoid arthritis, pregnancy, oral contraceptives, decreased biliary excretion	Serum copper and ceruloplasmin with CRP[b], CBC
Iodine	Hypothyroid goiter, neuromuscular impairment, deaf-mutism, increased embryonic and postnatal mortality, cognitive impairment, impaired fertility, congenital hypothyroidism (severe cases)	Thyrotoxicosis: nodular goiter, weight loss, tachycardia, muscle weakness, warm skin	**Decreased**: long-term inadequate intake	Serum T_3, T_4, TSH
Iron	Microcytic, hypochromic anemia (weakness, pallor, fatigue), glossitis, headache, dysphasia, nail changes, gastric atrophy, paresthesia, decreased cognitive function, pica	Cirrhosis, cardiomyopathy, pancreatic damage, skin pigmentation changes	**Increased**: blood transfusion **Decreased**: blood loss; long-term iron-free PN	Serum ferritin[c], iron, percent iron saturation, iron-binding capacity; CBC
Manganese	Nausea; vomiting; dermatitis; hair color changes; hypocholesterolemia; growth retardation; defective carbohydrate, lipid, and protein metabolism	Parkinsonian-like symptoms, hyperirritability, hallucinations, libido disturbances, ataxia, mental confusion, lack of attention, memory loss, weakness, seizures, facial nerve abnormalities, headache, dizziness, dystonia, peripheral neuropathy	**Increased**: decreased biliary excretion, high iron or vitamin C intake	Whole blood manganese, brain MRI
Molybdenum	Tachycardia, tachypnea, altered mental status, visual changes, headache, nausea, vomiting	Gout-like syndrome, increased urinary copper	**Decreased**: low-birth-weight, excessive GI losses	Urinary hypoxanthine, xanthine, and sulfite oxidase
Selenium	Muscle weakness or pain, cardiomyopathy, skin and hair pigmentation changes, macrocytosis, alopecia, growth retardation in infants	Nausea, vomiting, hair or nail loss, tooth decay, skin lesions, irritability, fatigue, peripheral neuropathy	**Decreased**: malignancy, liver failure, pregnancy, stress, infection **Increased**: reticuloendothelial-neoplasia	Plasma, serum, or whole blood selenium; RBC glutathione peroxidase; CBC
Zinc	Dermatitis (scaly, hyperpigmented skin lesions), stomatitis, glossitis, perioral and periungual ulceration, altered taste and smell, alopecia, diarrhea, apathy, depression, growth retardation, impaired wound healing, anorexia, confusion, immunosuppression, delayed sexual maturation, hypogonadism (decreased sperm count and function)	Acute: diarrhea, vomiting, nausea, dizziness, garlic-smelling breath; death with large IV doses Chronic: immunosuppression, decreased HDL-C, copper deficiency	**Decreased**: infection, burns, stress, hypoalbuminemia, corticosteroids, pregnancy, inflammation **Increased**: tissue injury, hemolysis, contaminated collection tube	Plasma or serum zinc with albumin and CRP, stool or ostomy output, serum copper

[a]Kayser-Fleischer rings are dark rings that appear to encircle the iris of the eye.

[b]If CRP > 4 mg/dL (40 mg/L), serum copper concentration will be falsely elevated. Ceruloplasmin increased with inflammation, pregnancy, liver disease, malignancy, and myocardial infarction.

[c]If ferritin low, iron deficiency; if high, inflammation.

CBC, complete blood count; CRP, C-reactive protein; GI, gastrointestinal; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol; MRI, magnetic resonance imaging; PN, parenteral nutrition; RBC, red blood cell; RQ, respiratory quotient; TSH, thyroid stimulating hormone.

Trace Elements

Trace elements considered essential in humans (at least one important role and a range of intakes within which homeostasis is maintained) are iron, zinc, selenium, copper, chromium, manganese, molybdenum, and iodine. A complete discussion of each of these elements is beyond the scope of this chapter.[49–53] Each trace element is involved in a variety of biologic functions and is necessary for normal metabolism, acting as a coenzyme or in other roles in hormonal metabolism or erythropoiesis. Toxicities can occur with excess intake of some trace elements. With the current interest in complementary medicine, clinicians must ask patients about their use of all dietary supplements.

Iron

Iron is the most abundant trace element and is an important component of hemoglobin, myoglobin, and cytochrome enzymes; it is also involved in oxygen transport and cellular energy production. Patients with iron-deficiency anemia typically present with fatigue, weakness, and pallor. Inadequate iron intake, malabsorption, and chronic blood loss are the principal causes of iron-deficiency anemia. Iron toxicity (overload) with possible organ damage can occur when chronic iron intake exceeds requirements, such as in patients receiving multiple blood transfusions over an extended period (1 unit of packed red blood cells provides 200-250 mg elemental iron [~1 mg elemental iron/mL]). Iron deficiency or overload is confirmed by assessment of iron stores, as reflected indirectly by measurement of hemoglobin, serum iron, total iron-binding capacity, and serum ferritin or directly by bone marrow staining or liver biopsy. Direct methods are the most accurate but are invasive and rarely necessary. Because indirect parameters such as ferritin are altered by acute or chronic inflammation independent of iron stores, concomitant illness must be considered in their interpretation. As with visceral protein assessment, CRP measurement simultaneously with iron assessments will help to determine the degree to which inflammation influences these parameters.[51]

Zinc

Zinc, the second-most abundant trace element, is a cofactor in many enzymatic reactions involved in protein, fat, and carbohydrate metabolism and is involved in the regulation of gene expression, immunity, growth, wound healing, and liver regeneration.[50,51,54] Most of the body’s zinc (85%) is found in muscle and bone;

less than 1% is found in the serum. Zinc is eliminated through the urine and the GI tract. Zinc deficiency develops with decreased intake or absorption, increased loss, or increased demand. Patients at risk for zinc deficiency include those with anorexia; alcohol dependence; excessive biliary, intestinal, or urinary losses; increased metabolic demands (sepsis, burns); or after bariatric surgery.[54] Urinary zinc losses are increased by thiazide diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and hemofiltration.[52] Zinc deficiency can develop in 14 days to 3 months with insufficient intake and is characterized by skin lesions (acrodermatitis enteropathica), a moist eczematous dermatitis that is most apparent in the nasolabial folds and around orifices, and other symptoms (Table 158-7).[50] Recovery is rapid with zinc supplementation; severe dermatitis can improve in as little as 4 to 5 days. Zinc deficiency can be documented by the presence of low serum zinc concentrations. However, serum zinc concentrations decrease during acute stress states and generally remain depressed until the stress resolves. Hair zinc analysis and urinary zinc excretion can also be used as biomarkers of zinc status.[54] Excess zinc intake is usually eliminated by the kidneys and GI tract; thus, zinc toxicity is uncommon except in overdoses or excessive parenteral supplementation.

Selenium

Selenium is not an antioxidant itself, but an integral part of selenoproteins. There are 25 genes coding for these selenoproteins, about half of which have a defined metabolic function. Important selenoproteins include selenoprotein P (antioxidant activity), glutathione peroxidase (antioxidant activity), iodothyronine deiodinase (thyroid hormone regulation), thioredoxin reductase (vitamin C), selenoprotein V (spermatogenesis), and selenoprotein S (inflammation, immune response).[51,55] A key metabolic function of selenium is its role in the enzymatic cofactor selenocysteine, the 21st proteinogenic amino acid.[55] Selenoprotein P is the major (60%) circulating form of selenium in serum. Prematurity, critical illness, burns, chronic GI losses, and long-term selenium-free parenteral nutrition are associated with low serum selenium concentrations and decreased glutathione peroxidase activity.[50] The clinical significance of reduced serum selenium concentrations is unclear, but low selenium concentrations may increase susceptibility to physiologic stressors. Low serum selenium concentrations in critically ill patients correlate with low triiodothyronine (T_3) concentrations.[56] Serum selenium concentrations reflect acute distribution between tissues rather than selenium stores. Selenium

deficiency is associated with muscle pain, wasting, and weakness (see Table 158-7), but severe biochemical deficiency is not always accompanied by these symptoms. Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase and can induce myopathy by interfering with synthesis of selenoproteins.[51] Fatal cardiomyopathy has been reported in several cases. Although critically ill patients require higher selenium intakes than normal, the optimal intake is unknown; current recommendations range from 20 to 1,000 mcg/day.[56]

Serum, erythrocyte, and whole-blood selenium, serum selenoprotein P, and serum, platelet, and whole-blood glutathione peroxidase activity respond to changes in selenium intake, but the response is heterogeneous.[57] Decreased serum selenium concentrations may indicate selenium deficiency, but reductions have also been observed in patients with malignancies, liver failure, pregnancy, alcoholism, and HIV; in patients receiving statins or corticosteroids; and in smokers. Selenium toxicity (selenosis) generally occurs only in those with long-term exposure to foods grown in selenium-rich soil (eg, US Great Plains area) but may occur when intake exceeds 200 mcg/day or 5 mcg/kg/day for prolonged periods.[51] Selenium toxicity results in hair and nail brittleness and loss, GI disturbance, skin rash, garlic breath odor, fatigue, irritability, nervous system abnormalities, and has been linked to type 2 diabetes mellitus.[55]

Copper

Copper is a cofactor in oxidative enzymes vital to the function of hematopoietic, vascular, and skeletal tissue, as well as structure and function of the nervous system.[48,49] It is a component of ceruloplasmin and key metalloenzymes involved in iron and manganese metabolism (ceruloplasmin), electron transfer and oxidation-reduction reactions (cytochrome c oxidase), connective tissue and collagen cross-linking (lysyl oxidase), dopamine conversion to norepinephrine (dopamine monooxygenase), and free radical scavenging (superoxide dismutase), and many others.[50,51] Copper is absorbed in the duodenum and excreted through the bile bound to bile salts. Most copper (67%) is found in bone and muscle, and 60% to 95% of serum copper is bound to ceruloplasmin.[58] Signs and symptoms of copper deficiency are listed in Table 158-7 and include anemia, neutropenia, thrombocytopenia, and neurologic dysfunction. In severe cases, such as in Menkes' syndrome, copper deficiency is further manifested as hypothermia, hair and skin depigmentation, progressive mental deterioration, and growth retardation. Factors predisposing to copper deficiency include generalized malabsorption, protein-losing enteropathy, nephrotic syndrome,

prematurity, and copper-free parenteral nutrition.[58,59] While long-term parenteral nutrition supplemented with copper increases the risk of copper toxicity, copper deficiency has been reported with copper-free parenteral nutrition most often resulting with removal of copper from the parenteral nutrition solution due to concern for accumulation with decreased biliary elimination due to a rising direct bilirubin concentration (cholestasis).[58] Patients undergoing bariatric surgery are also at risk for developing copper deficiency as early as 2 months after surgery. Resolution typically occurs within 1 to 3 weeks after initiation of copper supplementation (1 mg/day).[50]

Copper deficiency is assessed using serum copper concentrations along with CRP and ceruloplasmin, which appear to reflect changes in copper status in both copper-depleted and copper-replete individuals.[59] While they are reliable indicators of severe copper deficiency, serum copper and ceruloplasmin concentrations may not detect marginal copper deficiency because serum concentrations may be altered by a variety of conditions including inflammation (Table 158-7). Copper concentrations should be monitored every 2 to 6 months in patients receiving long-term parenteral nutrition. The chronic ingestion of excessive copper or inadequate elimination can result in cirrhosis as seen in Wilson's disease, an autosomal-recessive genetic disorder.

Chromium

Historically, trivalent chromium was thought to be essential for insulin function and maintenance of normal blood glucose concentrations. In fact, a low-molecular-weight chromium binding substance, *the glucose tolerance factor*, that may enhance insulin receptor response has been discussed. However, in 2014, the European Food Safety Authority (EFSA) determined that chromium is not an essential element in humans.[60] The United States and Canada have not re-evaluated chromium essentiality since 2001. Chromium is stored in the heart, muscle, kidney, and liver and excreted in the urine.[50,53] Chromium deficiency has been reported in four patients receiving long-term chromium-free parenteral nutrition; symptoms included hyperglycemia, weight loss, and neuropathy.[50] Urine and serum chromium concentrations reflect chromium absorption not stores.[60] Chromium toxicity varies depending on the valence; trivalent chromium used in parenteral nutrition solutions is generally not toxic. No chromium toxicity has been reported in patients receiving parenteral nutrition, even though intake may be 30 to 60 times higher than estimated requirements through chromium contamination, primarily Dextrose 70%, so additional

supplementation is rarely needed.[53] Chromium toxicity has been reported only with contaminated drinking water or industrial exposure with other forms of chromium. Chromium supplementation as an adjunct to aerobic exercise for weight loss or diabetes management is not effective.[60,61]

Manganese

Manganese is needed as a cofactor for several metalloenzymes, including isocitrate dehydrogenase (Krebs cycle), superoxide dismutase (mitochondrial antioxidant), glutamine synthetase (astrocytes), arginase (urea cycle), pyruvate carboxylase (carbohydrate metabolism), glycosyltransferases (bone formation), and prolidase (wound healing).[51,62] Excess manganese is rapidly and efficiently eliminated in bile as long as there is not cholestatic liver disease. Excretion may be compromised in newborns due to immature liver function. Manganese deficiency has only been reported in association with the ingestion of chemically defined manganese-deficient oral diets. Table 158-7 lists symptoms associated with manganese deficiency.

Manganese toxicity is more concerning and has been described in industrial exposures via inhaled manganese (welding) and in patients receiving long-term manganese-supplemented parenteral nutrition in the setting of chronic cholestasis. Toxicity has been reported in adults receiving more than 500 mcg/day and in children receiving more than 40 mcg/kg/day.[62] Manganese can accumulate in brain tissue; an intravenous dosage of 1.1 mg/day has been associated with brain deposition.[51] Because of its paramagnetic properties, manganese is detectable using MRI with increased signal intensity on T1-weighted images of the basal ganglia, especially in the striatum, globus pallidus, and substantia nigra. Manganese appears to target the dopaminergic neurons but may affect other neurotransmitters.[62] Whole-blood manganese concentrations are used to assess manganese status; serum concentrations do not correlate with either whole blood concentrations or MRI findings.[62] The neurodegenerative process induced by manganese is termed *manganism*. Lewy bodies, the hallmark of Parkinson's disease, are not seen in manganism.[62] Symptoms mimicking Parkinson's disease, including psychiatric symptoms, cognitive deficits, motor impairment, extrapyramidal symptoms, headache, dizziness, rigidity, tremors, ataxia, and facial muscle spasms.[50,62] Removing manganese from the parenteral nutrition solution resulted in resolution of neurologic symptoms with partial or total MRI normalization within 1 year.[62] The newborn brain may be more susceptible to the effects of manganese toxicity which has implications for

manganese supplementation in premature neonates receiving parenteral nutrition.[62]

Molybdenum

Molybdenum is a cofactor for enzymes involved in catabolism of sulfur-containing amino acids, purines, and pyrimidines (xanthine, aldehyde, sulfite oxidases).[50,51,63] Molybdenum deficiency is uncommon, but a rare genetic defect that prevents sulfite oxidase synthesis resulting in molybdenum deficiency has been identified. A case of molybdenum deficiency has been reported in a patient receiving long-term molybdenum-free parenteral nutrition who presented with symptoms that included tachycardia, tachypnea, headache, night blindness, nausea, vomiting, central scotomas, lethargy, disorientation, and ultimately coma (Table 158-7).[50,51,63] Symptoms were reversed when molybdenum was added to the parenteral nutrition solution. Because the brain contains sulfated compounds, a continuous supply of sulfated compounds is needed during brain development which puts young infants at risk if an adequate molybdenum supply is not available.[63] Plasma and serum molybdenum are very low and difficult to measure, and their concentrations do not reflect molybdenum status.[53] Biochemical abnormalities expected in molybdenum deficiency include very low serum and urine uric acid concentrations (low xanthine oxidase activity) and low urine inorganic sulfate concentrations with high urine inorganic sulfite concentrations (low sulfate oxidase activity).[50,51] Molybdenum toxicity has not been described.

Iodine

Iodine is found primarily in the thyroid gland (70%-80%), incorporated into thyroid hormones, and required for normal thyroid function which affects resting energy expenditure and growth. In iodine deficiency, there is a constant release of thyroid stimulating hormone (TSH), resulting in thyroid gland hyperplasia and goiter formation. However, not everyone with an iodine-deficient diet will develop a goiter. The most serious effects of iodine deficiency are seen during pregnancy and in childhood, including fetal death, cretinism, abnormal growth, and mental retardation.[50] Measurement of thyroxine (T_4), tri-iodothyronine (T_3), and TSH can be used to assess iodine status (Table 158-7). Iodine needs may be met by consumption of iodized salt or cutaneous iodine absorption from povidone–iodine, a topical antiseptic, used in catheter care.[51] Use of povidone–iodine for this indication has virtually been eliminated with the increased use of

chlorhexidine for catheter site care, putting long-term parenteral nutrition patients at higher risk. Intravenous iodine is no longer available as a separate entity, and no trace element combination product marketed in the United States contains iodine. Iodine excess is rarely a clinical concern when thyroid and kidney function are normal except in overdoses or too rapid correction of iodine deficiency.[51]

Vitamins

Vitamins act as both catalysts (cofactors) and substrates in essential metabolic reactions. They are needed for normal growth, metabolism, and cellular integrity. They facilitate energy-yielding chemical reactions; they do not contribute energy. A thorough review of vitamins and their complex effects on nutrition and metabolism is beyond the scope of this chapter.[51,53,64] A comprehensive nutrition-focused history and physical examination is a valuable means of assessing patients for vitamin deficiency or toxicity (**Table 158-8**). Generalized malnutrition is often associated with multiple vitamin deficiencies or increased needs; however, single vitamin deficiencies do occur. Thiamine (B_1) deficiency can result in early symptoms (dry or wet beriberi, GI symptoms) or advanced symptoms (lactic acidosis, Wernicke's encephalopathy, polyneuropathy, ataxia, mental confusion) due to impaired oxidative and energy metabolism often leading to serious and potentially irreversible neurological damage or death.[51,65] Macrocytic anemia, peripheral neuropathy, and neuropsychiatric sequelae may be caused by vitamin B_{12} (cyanocobalamin) deficiency which can occur after gastric or ileal resection due to the loss of intrinsic factor or absorption sites of the intrinsic factor-B_{12} complex, respectively. Vitamin B_{12} deficiency has been reported with increasing frequency in older adults, especially with prolonged gastric acid suppression with proton pump inhibitors.[66] There is a high prevalence of subclinical vitamin K deficiency in patients with chronic kidney disease, including those on hemodialysis or peritoneal dialysis. Vitamin K deficiency is a modifiable risk factor for cardiovascular disease and bone fracture in this patient population.[67]

TABLE 158-8 Assessment of Vitamin Status

Vitamin	Signs of Deficiency	Laboratory Assay	Comments
Water-Soluble Vitamins			
Thiamine (B_1)	Early: anorexia, fatigue, depression, impaired memory or concentration Late: paresthesia, nystagmus, GI beriberi (nausea, vomiting, abdominal pain, lactic acidosis), beriberi (heart failure, edema), Wernicke's encephalopathy, Korsakoff's psychosis, peripheral neuropathy	Whole blood or erythrocyte transketolase activation test Blood thiamine pyrophosphate Erythrocyte glutathione reductase activity coefficient	
Riboflavin (B_2)	Mucositis, dermatitis, cheilosis, glossitis, photophobia, corneal vascularization, lacrimation, decreased vision, impaired wound healing and growth, normocytic anemia	Urine riboflavin	
Pantothenic acid	Fatigue, malaise, headache, insomnia, vomiting, abdominal cramps	Serum pantothenic acid	
Niacin	Pellagra: dermatitis, dementia, glossitis, diarrhea, memory loss, headaches	Urine niacin and N_1-methylnicotinamide Erythrocyte NAD and NADP concentrations to determine "niacin number"	Flushing, nausea, and vomiting seen with hyperlipidemia treatment; increased need with hemo- and peritoneal dialysis
Pyridoxine (B_6)	Pellagra, dermatitis, glossitis, cheilosis, distal limb numbness or paresthesia, convulsions, microcytic anemia	Plasma pyridoxal 5-phosphate Urine 4-pyridoxic acid	Sensory neuropathy and seizures with very high doses (>2 g/day)
Folic acid	Macrocytic anemia, diarrhea, glossitis, cheilosis, angular stomatitis, fatigue, difficulty concentrating, irritability, headache, palpitations, shortness of breath, heart failure, tachycardia, postural hypotension, lactic acidosis, neural tube defects, impaired cellular immunity, paranoid behavior	Serum or plasma folate (acute) Red blood cell folate (chronic) Serum homocysteine	Decreased with increased cellular/tissue turnover (pregnancy, malignancy, hemolytic anemia); masks diagnosis of vitamin B_{12} deficiency; decreases risks of neural tube defects
Cyanocobalamin (B_{12})	Pernicious (megaloblastic) anemia, glossitis, spinal cord degeneration, peripheral neuropathy, paresthesias, pancytopenia, personality changes, dementia, depression, psychosis	Serum cobalamin Plasma homocysteine Urine or plasma methylmalonic acid[a] CBC	Decreased absorption in the elderly, distal ileal resection, loss of gastric intrinsic factor due to gastrectomy or long-term gastric acid suppression
Biotin	Dermatitis, depression, lassitude, somnolence	Urine biotin	
Ascorbic acid (C)	Enlargement or keratosis of hair follicles, impaired wound healing, anemia, lethargy, depression, bleeding, ecchymosis, scurvy	Plasma ascorbic acid Leukocyte ascorbate	GI disturbances, hyperoxaluria and kidney stones, excess iron absorption with excess intake; smokers need 35 mg/day more than nonsmokers; rebound scurvy with abrupt discontinuation after long-term high doses
Fat-Soluble Vitamins			
Vitamin A (includes retinol, retinal, retinoic acid, and retinyl esters)	Dermatitis, night blindness, xerophthalmia, Bitot spots,[b] pruritus, follicular hyperkeratosis, excessive deposition of periosteal bone, hair changes, poor growth and wound healing, impaired resistance to infection Irreversible: punctate keratopathy, keratomalacia, corneal perforation	Serum retinol Serum retinol-binding protein Serum retinyl esters (toxicity)	Teratogenic, liver toxicity with excessive intake; alcohol intake, liver disease, hyperlipidemia, and severe protein malnutrition increase susceptibility to adverse effects of high intake; β-carotene supplements recommended only for those at risk of deficiency (fat malabsorption); may reverse corticosteroid-induced poor wound healing
D	Rickets, osteomalacia, osteoporosis, muscle weakness, poor growth, hypocalcemia, immune dysfunction, cardiomyopathy	Serum 25(OH)D Serum 1,25$(OH)_2$D (kidney disease)	Elevated intake causes hypercalcemia, nephrocalcinosis, azotemia, poor growth; decreased in uremia, elderly (especially in winter), fat malabsorption
α-Tocopherol (E)	Hemolysis	Serum α-tocopherol Ratios of serum α-tocopherol to total lipids	Excess intake: hemorrhagic toxicity; increased risk of bleeding with anticoagulants; impaired leukocyte function
K	Bleeding (ecchymosis, petechiae, hematomas)	Prothrombin time INR	Anticoagulant therapy can be affected by supplements or diet

[a]Plasma methylmalonic acid concentrations increase with vitamin B_{12} deficiency.

[b]Bitot spots are spots which are oval, triangular, or irregular in shape and located superficially in the conjunctiva.

25(OH)D, 25-hydroxyvitamin D; CBC, complete blood count; GI, gastrointestinal; INR, international normalized ratio; NAD, nicotinamide adenine dinucleotide; NADP, nicotinamide adenine dinucleotide phosphate.

Patients with steatorrhea have an increased risk of fat-soluble vitamin (A, D, E, and K) deficiencies. However, the increasing prevalence of vitamin D deficiency is a worldwide concern, including all ages, genders, and racial/ethnic groups, especially children, pregnant women, obese or elderly adults, individuals with dark skin, invalids and shut-ins, patients on long-term parenteral nutrition, and those living in temperate and higher latitudes.[68] Laboratory assessment can confirm the clinical suspicion of a deficiency state. Vitamin D_2 (ergocalciferol from plant-based sources) and vitamin D_3 (cholecalciferol from conversion of cholesterol in the skin by ultraviolet light) are quickly converted to 25-hydroxyvitamin D (25[OH]D) via hydroxylation in the liver. The best marker for vitamin D deficiency is the serum concentration of 25(OH)D. Reference ranges for US laboratories are typically 20 to 100 ng/mL (50-250 nmol/L), but the optimal range is likely above 30 ng/mL (75 nmol/L) based on the concentration associated with parathyroid hormone (PTH) stimulation and calcium absorption efficiency.[68] The first indication of a deficiency is usually a decrease in circulating serum 25(OH)D. Subsequently, there is a decrease in urinary vitamin D excretion, which is followed by diminished tissue concentrations. Because the active form of vitamin D, $1,25(OH)_2D$, is produced only when needed, not stored, and dependent on kidney function, intact PTH concentration, and calcium and phosphorus supply, it is not a useful marker of vitamin D stores but may be helpful if assessing the kidney's ability to hydroxylate to the active form.

Vitamin toxicity can occur, especially with fat-soluble vitamins, which are stored in the body. Vitamin D toxicity can cause significant hypercalcemia, hypercalciuria, and soft tissue calcifications leading to kidney and cardiovascular damage.[51] Vitamin A toxicity is associated with many signs and symptoms including effects on bone.[51] Water-soluble vitamins, except cyanocobalamin (vitamin B_{12}), are not stored in the body; consequently, the toxicity risk is minimal unless ingested in very high doses. Recent evidence, however, suggests that even water-soluble vitamins may be associated with adverse events when taken chronically in high doses. Preconception folic acid supplementation is definitively associated with a reduction in neural tube defects.[69] Multivitamin supplementation containing folic acid does not prevent cardiovascular disease despite its effects on homocysteine concentrations.[70] With Americans consuming large amounts of nutrition supplements and spending over $130B for them each year, clinicians should be alert for signs of inappropriate vitamin use and hypervitaminosis (see Table 158-8) and be prepared to discuss rational

supplement use with all patients.

Essential Fatty Acids

The human body can synthesize all fatty acids except the essential fatty acids, linoleic acid (an omega-6 fatty acid) and α-linolenic acid (an omega-3 fatty acid). Essential fatty acid deficiency (EFAD) can be prevented if approximately 5% (linoleic acid) and 0.6% (linolenic acid) of total energy is ingested as these fatty acids.[71,72] EFAD is rare in adults and children but can occur with prolonged lipid-free parenteral nutrition, severe fat malabsorption, very low-fat enteral feeding formulations or diets, high-medium-chain-triglyceride–containing diets, and severe malnutrition, especially in stressed patients.[73] Although the time needed to develop EFAD is variable, symptomatic EFAD has been shown to occur after only 4 weeks of lipid-free parenteral nutrition, but biochemical evidence can occur within 1 week.[73] The brain grows rapidly during the last trimester of gestation and the first 2 years of life. Large amounts of essential fatty acids are needed for central nervous system myelin synthesis. Thus, newborns, especially those born prematurely, who have very limited fat stores, may develop EFAD more rapidly than adults and should generally receive a source of essential fatty acids within 72 hours after birth.[73] Symptoms reported with EFAD include dermatitis (dry, scaly skin), increased susceptibility to infection, impaired wound healing, poor growth and brain development, and immune dysfunction.[72,73]

Linoleic acid is converted to arachidonic acid (20:4ω-6; a tetraene fatty acid). When linoleic acid is unavailable, oleic acid (18:1ω-9) is the preferred substrate, resulting in production of eicosatrienoic acid (20:3ω-9; a triene fatty acid). Thus, EFAD is associated with decreased tetraene and increased triene production. The usual triene-to-tetraene ratio is less than 0.4; a ratio of greater than 0.2 indicates subclinical EFAD, but clinical symptoms of EFAD are generally only seen when the ratio is greater than 0.4.[72] EFAD diagnosis is generally made based on risk assessment and clinical findings with confirmation by measuring serum fatty acid concentrations.

Carnitine

Carnitine is a quaternary amine required for transport of long-chain fatty acids into the mitochondria for β-oxidation and energy production. Additionally, acyl compounds that are trapped within cells due to cell membrane impermeability

can be esterified with carnitine, forming acylcarnitine derivatives, which are transported out of the cell, preventing the acyl compounds from accumulating to toxic concentrations, aiding in detoxification. Carnitine is also important in the metabolism of intracellular acetyl coenzyme A.[74,75] The L isomer is the physiologic active form,

Carnitine is available from a wide variety of dietary sources (especially dairy products and meats) and can be synthesized when intake is low from lysine and methionine.[75] Carnitine is filtered by the kidney and reabsorbed in the proximal tubule.[76] Hepatic synthesis is decreased in premature infants, and low serum carnitine concentrations and overt carnitine deficiency have been documented in premature infants receiving carnitine-free parenteral nutrition or diets (secondary deficiency), as well as in those with inborn errors of carnitine metabolism (eg, defect in the OCTN2 transporter; primary deficiency).[75,76] Daily supplementation of neonatal parenteral nutrition solutions with 2 to 10 mg/kg carnitine is required when no enteral source is provided.[53] Higher doses are required for treatment of primary deficiency. Other predisposing factors for secondary carnitine deficiency include malabsorption, cystic fibrosis, short bowel syndrome, HIV, pregnancy, chronic kidney or liver disease,[76] chronic valproic acid, verapamil, or zidovudine use,[76,77] and a vegetarian diet.

The clinical presentation of carnitine deficiency varies but may include generalized skeletal muscle weakness, gross motor delay, hypotonia, failure-to-thrive, fasting hypoglycemia, seizures, encephalopathy, recurrent infections, cardiomyopathy, and coma.[75,76] Symptoms are typically more severe in those patients with primary deficiency. In clinical practice, carnitine status is assessed by measuring the serum total and free carnitine concentrations along with acylcarnitine, although carnitine is distributed primarily in the muscle. When only total and free concentrations are available, the free is subtracted from the total to give the acylcarnitine concentration. Serum and urine carnitine concentrations are most helpful in primary carnitine deficiency; acylcarnitine concentrations are more helpful in secondary deficiency.[76]

NUTRIENT REQUIREMENTS

7 Evidence-based patient-specific goals should be established considering the patient’s clinical condition and the need for maintenance or repletion in adults and continued growth and development in children. Individual nutrient requirements vary with age, sex, size, and clinical condition. Nutrition status,

physical activity, and the need for continued maintenance of adequate nutrition or repletion in those with ongoing metabolic stress or malnutrition dictate the nutrient requirements for an individual. For obese patients, usual nutrition requirements may be altered because of desired weight loss and after bariatric surgery. In children, sustaining or reestablishing normal growth and development is critical. Organ function (intestine, kidney, liver, pancreas) may affect nutrient utilization. Nutrient requirements can be estimated using various methods interpreted in the context of patient-specific factors.

Recommended Dietary Allowances

The Recommended Daily Allowances (RDAs) were first established in 1941; in 1997, the Food and Nutrition Board introduced a new designation for nutrition reference values, the Dietary Reference Intakes (DRIs). The four DRI categories are estimated average requirements (EARs), RDAs, adequate intakes (AIs), and tolerable upper intake levels (ULs). The nutrient intake that meets the needs of half of the healthy persons in a group (EAR) can be used for planning nutrient intakes for groups. The RDA, the nutrient intake that meets the needs of almost all persons in a designated group, is approximately two standard deviations above the EAR for nutrients for which the requirement is well defined and 1.2 times the EAR for other nutrients. To evaluate an individual's daily intake, the RDA is the most appropriate comparator. The AI, defined as the average intake for the designated group that appears to sustain growth or other indicator of health, is reserved for nutrients for which no EAR or RDA has been determined. Finally, the UL is the maximum nutrient intake unlikely to pose adverse effects in almost all persons in a designated group.[78]

DRIs have been established for six nutrient groups: calcium, phosphorus, magnesium, vitamin D, and fluoride; folate and other B vitamins; antioxidants (eg, selenium, vitamin C, vitamin E); trace elements; macronutrients (protein, fat, carbohydrates, fiber); and electrolytes and water. Because of the increased prevalence of vitamin D deficiency, calcium and vitamin D recommendations were revised in 2010.[79] An on-line Interactive DRI for Healthcare Professionals is available to calculate DRI-based nutrition needs for a generally healthy individual.[80]

In general, healthy adults and children older than 1 year of age should consume 45% to 65% of their total calories as carbohydrates. Recommended fat intakes vary by age: 1 to 3 years, 30% to 40%; 4 to 18 years, 25% to 35%; and adults, 20% to 35% of total calories. Infants, especially premature infants,

require a higher proportion of calories from fat (approximately 40%-50% of total calories) to ensure normal neurological development. Protein recommendations also vary by age: 1 to 3 years, 5% to 20%; 4 to 18 years, 10% to 30%; and, adults, 10% to 35% of total calories.

Energy

8 Validated predictive equations are most often used to determine energy requirements; however, if available, indirect calorimetry is the most accurate bedside method to determine energy requirements. The most appropriate method is determined by a variety of factors, including severity of illness and resource availability.

Estimating Energy Expenditure

Daily energy expenditure consists of the basal energy expenditure (BEE), diet-induced thermogenesis (10%), and energy used for physical activity. In sick or injured patients, the BEE is increased because of stress-related hypermetabolism, but the physical activity is usually greatly reduced. Continuous infusion enteral feeding, often used in critically ill patients, results in minimal diet-induced thermogenesis (not more than 5%) unless overfeeding. Failure to account for these changes can result in overfeeding.[21]

Numerous methods for determining an individual's daily energy requirement in a variety of settings have been published. These methods use population estimates of calories per kilogram of body weight (kcal/kg), equations that estimate energy expenditure (kcal/day or kJ/day; 1 kcal is equivalent to 4.184 kJ), or indirect calorimetry. The simplest and most convenient method to determine energy requirements is to use population estimates of calories required per kilogram of body weight. This method assumes standard values for health or the energy requirements associated with various disease states or clinical conditions, as well as the additional requirements for repletion of a malnourished individual. Most do not take into consideration age- or sex-related differences in energy needs. No stress or activity modifiers are used with these equations because the effect of the clinical condition (hypermetabolism) has been captured in the calculation. Daily adult requirements by this method can be estimated as shown below:[17,82]

Healthy, normal nutrition status, minimal illness severity: 20-25 kcal ABW/kg/day (84-105 kJ ABW/kg/day)

Illness, metabolic stress (BMI <30 kg/m^2): 25-30 kcal ABW/kg/day (105-126

kJ ABW/kg/day)

Illness, metabolic stress (BMI ≥30 kg/m^2): 11-14 kcal ABW/kg/day (46-59 kJ ABW/kg/day) or 22 to 25 kcal IBW/kg/day (92-105 kJ ABW/kg/day)

Major burn (≥50% total body surface area [TBSA]): 25 kcal/kg ABW (kg) + 40 kcal per % TBSA burned (adult) (which is equivalent to 105 kJ/kg ABW (kg) + 170 kJ per % TBSA burned [adult]) or 25-35 kcal/kg/day (105-146 kJ/kg/day) in nonobese patients and 21 kcal/kg/day (88 kJ/kg/day) in obese patients.[85]

When using the equations for individuals with a BMI over 30 kg/m^2, as the BMI increases, the number derived using ABW compared to IBW becomes quite disparate. Accuracy is improved by using the ABW recommendation for patients with BMI 30 to 50 kg/m^2 and the IBW recommendation when the BMI is greater than 50 kg/m^2. When these recommendations are used for patients with a BMI of 30 kg/m^2 or more, the calories provided allow for permissive underfeeding (provision of approximately 65% to 75% of estimated or measured energy needs), which decreases infection rates and hospital lengths of stay.[21] DRIs for energy for healthy infants and children are shown in **Table 158-9**.[71] These maintenance energy requirements are approximately 130% to 150% of the basal metabolic rate, with the additional calories provided to support usual activity and growth. For all ages, energy requirements may increase with fever, sepsis, major surgery, trauma, burns, and long-term growth failure and in the presence of chronic conditions such as bronchopulmonary dysplasia, congenital heart disease, and cystic fibrosis. Energy needs may decrease with obesity and neurologic disability (eg, cerebral palsy).

TABLE 158-9 Dietary Reference Intakes for Energy and Protein in Healthy Children

Age (Reference age/weight)	Estimated Energy Requirement (kcal/day)[a]		Protein RDA (g/kg/day)[b]
	Boys	Girls	
0-6 months (3 months/6 kg)	570	520	1.52[c]
7-12 months (9 months/9 kg)	743	676	1.5
1-2 years (24 months/12 kg)	1,046	992	
1-3 years (24 months/12 kg)			1.1
3-8 years (6 years/20 kg)	1,742	1,642	
4-8 years (6 years/20 kg)			0.95
9-13 years (11 years/M: 36 kg; F: 37 kg)	2,279	2,071	0.95
14-18 years (16 years/M: 61 kg; F: 54 kg)	3,152	2,368	0.85

[a]1 kcal is equal to approximately 4.18 kJ.

[b]Protein requirements in children with moderate-to-severe stress increase by 50% or more.

[c]Adequate intake.

F, female; M, male; RDA, recommended dietary allowance.

There are more than 200 equations available with an accuracy of approximately 40% to 77% to estimate energy expenditure in adults and children (**Tables 158-10** and **158-11**, respectively).[17,21,71,81–85] The Harris-Benedict equations, derived in 1919 from a study of 239 individuals, are still used by some clinicians for assessing energy requirements in adults. They have the advantage of incorporating the patient's age, height, weight, sex, and clinical condition. These equations were derived from oxygen consumption measurements made in normally nourished healthy individuals who were in a fasting and resting state. Although they are commonly referred to as the "BEE equations," they estimate resting energy expenditure (REE), the amount of energy expended at rest by a fasting, awake individual in a temperature-controlled environment performing only basal functions such as breathing, circulation, and metabolic processes.

TABLE 158-10 Estimates of Energy Expenditure in Adults[a]

Healthy Adults
Harris-Benedict[b] Equations (kcal/day)
Men: BEE = 66 + (13.75W + 5H [cm]) – (6.8A)
Women: BEE = 655 + (9.6W + 1.8H [cm]) – (4.7A)
DRI Equations (kcal/day)[c]
Men: EER = 662 – 9.53A + (PA × 15.91W) + 539.6H (m)
Women: EER = 354 – 6.91A + (PA × 9.36W) + 726H (m)
PA = 1 if sedentary; 1.12 if low active; 1.27 if active; and 1.45 if very active
Mifflin-St. Jeor Equations (kcal/day)
Men: 10W + 6.25H (cm) – 5A + 5
Women: 10W + 6.25H (cm) – 5A – 161
Critically Ill Adults
Penn State Equation (kcal/day): Mifflin(0.96) + T_{max}(167) + Ve(31) – 6212
Penn State Equation, modified (kcal/day) for age ≥60 yr with BMI ≥30 kg/m²: Mifflin(0.71) + T_{max}(85) + Ve(64) – 3085

A, age in years; BEE, basal energy expenditure; BMI, body mass index; DRI, dietary reference intakes; EER, estimated energy requirement; H, height in centimeters or meters, as indicated; PA, physical activity factor; T_{max}, maximum body temperature in the previous 24 hours in degrees centigrade; Ve, minute ventilation in L/min; W, actual body weight in kilograms; yr, years.

[a]No real consensus exists as to which formula is best in all situations. Many clinicians use more than one equation and calculate a range of acceptable intakes.

[b]The common practice of using an adjusted body weight for obesity in these calculations is not supported by the original data that used actual body weight in all cases up to a BMI of 56 kg/m² in men and 40 kg/m² in women.

[c]1 kcal is equal to approximately 4.18 kJ.

TABLE 158-11 Equations to Estimate Energy Expenditure in Children[a,b]

FAO/WHO/UNU 2001 (kcal/day)[b]
0-12 Months
Breastfed
TEE (kcal/day) = –152 + 92.8W
TEE (MJ[c]/day) = –0.635 + 0.388W
Formula fed
TEE (kcal/day) = –29 + 82.6W
TEE (MJ[c]/day) = –0.122 + 0.346W
Boys 1-17 Years
TEE (kcal/day) = 310.2 + 63.3W – 0.263W^2
TEE (MJ[c]/day) = 1.298 + 0.265W – 0.0011W^2
Girls 1-17 Years
TEE (kcal/day) = 263.4 + 65.3W – 0.454W^2
TEE (MJ[c]/day) = 1.102 + 0.273W – 0.0019W^2
DRI Equations (kcal/day)
Birth through 2 years of age
EER = (89W – 100) + GF
GF = 175 kcal if 0-3 months; 56 kcal if 4-6 months; 22 kcal if 7-12 months; 20 kcal if 13-35 months
3-18 years of age
Boys: EER = 88.5 – (61.9A) + PA (26.7W + 903H) + GF
Girls: EER = 135.3 – (30.8A) + PA (10W + 934H) + GF
GF = 20 kcal if 3-8 years; 25 kcal if 9-18 years
PA = 1 if sedentary; 1.13-1.16 if low activity; 1.26-1.31 if normal activity; and 1.42-1.56 if very active

A, age in years; DRI, dietary reference intakes; EER, estimated energy requirement; FAO/WHO/UNU, Food and Agriculture Organization/World Health Organization/United Nations University; GF, growth factor; H, height in meters; PA, physical activity factor; TEE, total energy expenditure; W, actual body weight in kilograms.

[a]No real consensus exists as to which formula is best in all situations. Many clinicians use more than one equation and calculate a range of acceptable intakes.

[b]Additional daily calories are needed for growth; about 2 kcal/g of weight gain desired.

[c]1 kcal is equivalent to approximately 4.18 kJ; 1 MJ = 1,000 kJ.

Because these equations approximate REE, the results have been modified by an activity or stress factor that adjusts for the individual's clinical condition. For

example, an individual who is confined to bed may require a calorie intake that is only 20% to 30% above the REE, while a person who has sustained a severe burn injury may require 150% to 200% of the calculated REE. Some clinicians multiply the calculated REE by both a stress factor and an activity factor. Because these equations overestimate REE by 6% to 15%, the calculated REE should be multiplied by either a stress factor or an activity factor to avoid further overestimation of the individual's energy needs. Stress factors used in adults and children are shown in Tables 158-12 and 158-13, respectively.[84]

TABLE 158-12 Stress Factors for Use in Adults

Condition	Factor
No Stress	
Confined to bed	1.2
Out of bed: normal activity	1.3
Mild Stress[a]	
Postoperative recovery: uncomplicated surgery	1-1.15
Trauma: mild (eg, long-bone fracture)	1.2
Moderate Stress[a]	
Sepsis (moderate)	1.2-1.4
Trauma: CNS (sedated)	1.3
Trauma: moderate to severe	1.3-1.4
Severe Stress[a]	
Sepsis (severe)	1.3
Trauma: CNS (severe)	Up to 1.3
Burns (proportionate to TBSA burned)[b]	Up to 2.0

CNS, central nervous system; TBSA, total body surface area.

[a]Assumes decreased activity during periods of stress.

[b]Formulas specifically for estimating energy needs in burned children and adults have been published and are likely to be more accurate.

TABLE 158-13 Stress Factors for Use in Children

Condition	Factor
Well-nourished child at bedrest with mild-to-moderate stress	REE × 1.3
Normally active child with mild-to-moderate stress OR inactive child with severe stress (eg, trauma, cancer) OR child with minimal activity and malnutrition requiring catch-up	REE × 1.5
Active child requiring catch-up growth OR an active child with severe stress	REE × 1.7

REE, resting energy expenditure.

It should also be noted that ABW (up to a BMI of 56 kg/m^2 in men and 40 kg/m^2 in women), not IBW or AdjBW, was used to generate the original data with these equations and thus should be used for these calculations. Overestimation of energy needs with the Harris-Benedict equations is well documented.[21,82] There is no individual method proven to accurately determine the energy needs of all critically ill patients (see Table 158-10). The Penn State equations appear to be most accurate in critically ill adults receiving mechanical ventilation. When compared to indirect calorimetry in mechanically ventilated patients, the accuracy of these equations has been shown to be about 34%.[86] The Penn State equations were found to have an accuracy rate of 77%, 70%, and 53% in older nonobese, younger obese (BMI ≥30 kg/m^2) and nonobese, and older obese patients, respectively. In older obese patients, use of the modified Penn State equation increased accuracy to 74%.[21,86] There is no consensus as to the best equation for critically ill adults who are not mechanically ventilated.

Measuring Energy Expenditure

The most accurate method to determine energy expenditure in clinical practice is to measure it using indirect calorimetry (metabolic gas monitoring), but capital and operational costs may limit its availability in many settings. Handheld calorimeters have been shown to be more accurate than predictive equations and may be a viable alternative to the more expensive equipment in both inpatient and outpatient settings.[87,88]

Indirect calorimetry methodology is based on pulmonary gas exchange: when a substrate (carbohydrate, fat, protein) is oxidized, heat is produced, oxygen is consumed, and carbon dioxide is expired in a constant amount depending on the substrate being oxidized. More carbon dioxide is produced when a gram of glucose is metabolized than either a gram of protein or a gram of fat. Indirect

calorimetry is a noninvasive procedure in which oxygen consumption (VO_2, mL/min) and carbon dioxide production (VCO_2, mL/min) are measured, and the measured resting energy expenditure (MREE; kcal/day) is calculated using the modified Weir equation, as follows:[87–89]

$$\text{MREE} = ([3.94\ VO_2 + 1.11\ VCO_2] + [2.17\ uN_2]) \times 1.44.$$

The urinary nitrogen component (uN_2) is often omitted when calculating energy expenditure because it accounts for less than 4% of the energy expenditure, and its omission results in an insignificant measurement error.[82,87] Excluding the nitrogen component obviates the need for a 24-hour urine collection, which can be difficult in some patients and delay the measurement in others.

The MREE represents the total energy expended during the period over which the measurements were taken extrapolated to a 24-hour period to approximate daily energy requirements. MREE reflects changes in energy requirements resulting from diseases or clinical conditions, but it does not include energy required for repletion of a malnourished individual or growth. No multiplier (activity/stress factor) should be used in critically ill adults.[82] Other factors may be used in other settings (eg, weight loss clinics). In children, the MREE should be multiplied by a factor for physical activity or stress (Table 158-13).[84]

Indirect calorimetry also can be used to determine the patient's respiratory quotient (RQ), calculated as VCO_2/VO_2, which reflects substrate utilization. RQ values for nutrient substrates are fat, 0.71; carbohydrate, 1; protein, 0.82; and mixed substrate (fat, carbohydrate, and protein), 0.85. An RQ value greater than 1 denotes either lipogenesis or hyperventilation; less than 0.7 may indicate a ketogenic diet, fat gluconeogenesis, or ethanol oxidation. Values outside the physiologic range of 0.67 to 1.3 suggest an invalid test. Clinically, the RQ is used to determine if a patient is being overfed, which is likely if the RQ value is greater than 1.[82] Increased carbon dioxide production with overfeeding leads to increased respiratory demand which can be decreased by reducing overall energy and carbohydrate administration.

Indirect calorimetry should be considered in any patient in whom uncertainty in estimating energy requirements needs to be minimized. These may include adults and children who are severely malnourished (BMI <18.5 kg/m^2) or obese (BMI ≥ 30 kg/m^2); patients who have unexplained high partial arterial pressure of carbon dioxide ($PaCO_2$) concentrations or minute ventilation; patients with spinal cord injuries; patients who experience weight loss despite apparently

receiving adequate protein and energy intakes; critically ill surgery patients receiving parenteral nutrition; patients with large total body surface area burns, and patients unable to be weaned from the ventilator.[20,88]

Indirect calorimetry may not be accurate in all clinical situations. Indirect calorimetry overestimates REE for patients with hyperventilation, metabolic acidosis, overfeeding, and if there is an air leak anywhere in the ventilator circuit. Underestimation of REE is likely with hypoventilation, metabolic alkalosis, underfeeding, and gluconeogenesis. Mechanically ventilated patients are technically easier to study because the indirect calorimeter can be integrated directly into the ventilator circuit. However, the patient must be at complete rest for 1 hour, must not receive bolus feedings either by feeding tube or orally for 4 hours, should have no changes in substrate delivery for 12 hours, and must be on a fraction of inspired O_2 (FiO_2) of less than 0.6 with a positive end-expiratory pressure (PEEP) less than 10 cm H_2O (1.0 kPa) and a peak airway pressure of less than 30 cm H_2O (2.9 kPa) to ensure an accurate steady-state reading.[82,84] Unfortunately, many of the patients who would benefit most from the use of indirect calorimetry will not meet these requirements.

Protein

9 Daily protein requirements are based on age, sex, nutrition status, disease state, and clinical condition. For individuals older than 18 years of age, the RDA for protein is 0.8 g/kg/day, which is significantly less than most Americans typically consume.[71] In adults older than 60 years of age, protein needs are increased to 1.5 g/kg/day to reduce the loss of LBM that occurs with aging, and 1.5 to 2 g/kg/day or more may be needed in states of metabolic stress.[17,71,90] Protein requirements are also higher in pregnant and lactating women (1.1 g/kg/day or 6-10 g protein per day above the usual RDA). Table 158-9 lists the RDAs for protein for children.[71]

Protein metabolism depends on both kidney and liver function. Critical illness results in a hypercatabolic state in which there is both increased protein synthesis and degradation. The goal of protein administration is to minimize catabolism by maximizing protein synthesis. Consequently, protein requirements are increased to 1.2 to 2 g/kg/day in critically ill patients. For obese critically ill patients, protein needs are 2 g/kg IBW or more if the BMI is between 30 and 40 kg/m^2 and 2.5 g/kg IBW or more if the BMI is greater than 40 kg/m^2.[17] Adults with significant burns have protein requirements of 2.5 to 3 g/kg ABW/day or more;

children with burns should receive between 20% and 25% of their energy needs as protein.[85] Large stool or ileostomy losses also increase protein requirements. Liver failure typically results in the need for protein restriction (0.5 g/kg/day) unless a hypercatabolic state is also present, which will increase requirements to 1.5 g/kg/day. Protein needs in patients with kidney failure are variable and affected by the various renal replacement therapies available. The application of these protein intake guidelines requires both clinical judgment and frequent monitoring of kidney and liver function, serum chemistries, clinical condition, and nutrition outcomes.

Fat

The daily AI for men and women for α-linolenic acid is 1.6 and 1.1 g, respectively; for linoleic acid, it is 14 to 17 g/day for men and 11 to 12 g/day for women.[71] Overall, for adults, fat should represent no more than 10% to 35% of total calories, with the recommendation that saturated fatty acids, *trans* fatty acids, and dietary cholesterol intake be kept as low as possible while a nutritionally adequate diet is consumed. Fat should constitute 30% to 40% of energy in children 1 to 3 years of age and 25% to 35% of energy in children 4 to 18 years of age.[71] Fat intake in children younger than 3 years of age is critical for proper central nervous system growth and development; generally, fat-restricted diets (skim milk) should not be imposed until after the age of 2 to 3 years except under medical supervision.

Fiber

Decreased serum cholesterol, improved glycemic control in patients with metabolic syndrome and type 2 diabetes, and maintenance of normal laxation have been attributed to dietary fiber intake, but only 5% of Americans consume the recommended amount of fiber daily.[91] Men and women 50 years of age and younger should ingest 38 g/day and 25 to 26 g/day of total fiber, respectively. For men and women older than 50 years of age, the AI is 30 and 21 g/day, respectively.[71] The AI for fiber has not been set for children younger than 1 year of age. Breast milk and infant formulas are essentially fiber-free. For older children, the recommended fiber intake is 19 g/day for children 1 to 3 years of age, 24 g/day for children 4 to 8 years of age, and 26 to 31 g/day for children 9 to 13 years of age.[71]

Fluid

The daily fluid requirement for an adult depends on many factors but is generally estimated to be 30 to 40 mL/kg.[92] Fluid requirements per kilogram of body weight are higher for children and even higher for preterm infants because of their higher percentage of TBW and basal energy needs. Additionally, premature neonates have increased fluid requirements because of greater insensible losses and decreased urine concentrating ability of the kidneys. The Holliday-Segar method is a commonly used, quick, and simple method for estimating minimum daily fluid needs of children and adults. Children weighing less than 10 kg should receive at least 100 mL/kg/day. An additional 50 mL/kg/day should be provided for each kilogram of body weight between 11 and 20 kg and 20 mL/kg/day for each kilogram above 20 kg.[93] Thus, the minimum fluid required for a child weighing 8 kg would be 800 mL/day, a 17-kg child would need 1,350 mL/day, and a 50-kg individual would need 2,000 mL/day.

Factors that may alter fluid needs in both adults and children are listed in Table 158-14. All sources of fluid intake should be considered (eg, vehicles for intravenous medications, intravenous or feeding tube flushes) when determining fluid requirements. Urine output and specific gravity as well as serum electrolytes and weight changes can be used to assess fluid status. A urine output of at least 1 mL/kg/hr (in children) and approximately 0.5 mL/kg/hr or 40 to 50 mL/hr (in adults) is considered adequate to ensure tissue perfusion. Urine output should be higher if large fluid volumes or high renal solute loads (eg, parenteral nutrition, concentrated enteral feeding formulations) are being administered. Urine specific gravity, however, depends on the kidneys' concentrating and diluting capabilities. Concomitant diuretic therapy, resulting in increased solute or water excretion, limits the usefulness of urine specific gravity as an assessment of fluid status.

TABLE 158-14 Factors That Alter Fluid Requirements

Increased Requirements	Decreased Requirements
Fever	Fluid overload
Radiant warmers	Heart failure
Diuretics	Decreased urine output
Vomiting	Heat shields
Nasogastric suction	Relatively high humidity
Ostomy or fistula drainage	Humidified air via endotracheal tube
Diarrhea	Kidney failure
Glycosuria	Hypoalbuminemia with starvation
Phototherapy	Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
Diabetes insipidus	
Increased ambient temperatures	
Hyperventilation	
Prematurity	
Excessive sweating	
Increased metabolism (eg, hyperthyroidism)	

Micronutrients

Requirements for micronutrients (electrolytes, minerals, trace elements, vitamins) vary with age, sex, and route of ingestion (**Table 158-15**).[49–53,64,79,94] Enteral and parenteral requirements vary due to bioavailability considerations. Micronutrients poorly absorbed via the GI tract usually are required in greater amounts when given by the enteral than parenteral route. However, many water-soluble micronutrients are excreted more rapidly via the kidneys when administered intravenously. In these situations, the intravenous dose is greater than the oral dose. Other factors that affect micronutrient requirements include GI losses through diarrhea, vomiting, or high-output fistula or ostomies; wound healing; and hypermetabolism or hypercatabolism. Cutaneous micronutrient losses (eg, zinc, copper, selenium) also may be significant after major burn injury. Sodium, potassium, magnesium, and phosphorus excretions are particularly dependent on kidney function, and in the setting of acute kidney injury or chronic kidney disease, intake will likely need to be restricted. Calcium needs, on the other hand, may be increased in these patients. Patients with moderate-to-severe malnutrition will have increased requirements during early refeeding owing to preexisting deficiencies and rapid intracellular uptake with anabolism. Failure to provide adequate electrolyte replacement, especially potassium and phosphorus, and vitamin supplementation (thiamine) before delivery of full calories during refeeding can result in significant morbidity and even death from refeeding syndrome.[95–97]

TABLE 158-15 Recommended Daily Electrolyte, Trace Element, and Vitamin Intake[a]

	Adult (≥19 Years of Age)		Pediatric	
Nutrient	**Enteral**	**Parenteral**	**Enteral**	**Parenteral**
Electrolytes and Minerals				
Acetate[b]	—	—	—	—
Calcium	1,000-1,200 mg	0-15 mEq (0-7.5 mmol)	0-12 months: 210-270 mg 1-3 years: 700 mg 4-8 years: 1,000 mg 9-18 years: 1,300 mg	Premature: 2-4 mEq/kg (1-2 mmol/kg) Other: 1-2.5 mEq/kg (0.5-1.25 mmol/kg)
Chloride[b]		—	—	2-6 mEq/kg (2-6 mmol/kg)
Magnesium	M: 400-420 mg W: 310-320 mg	10-20 mEq (5-10 mmol)	0-6 months: 30 mg 7-12 months: 75 mg 1-3 years: 80 mg 4-8 years: 130 mg 9-18 years: 240-410 mg	0.25-1 mEq/kg (0.12-0.5 mmol/kg)
Phosphorus	700 mg	20-45 mmol	0-6 months: 100 mg 7-12 months: 275 mg 1-8 years: 460-500 mg 9-18 years: 1,250 mg	Premature: 1-2 mmol/kg Others: 0.5-1 mmol/kg
Potassium[c,d]	4,700 mg	60-100 mEq (60-100 mmol) (1-2 mEq/kg [1-2 mmol/kg])	0-6 months: 400 mg 7-12 months: 700 mg 1-8 years: 3,000-3,800 mg 9-18 years: 4,500-4,700 mg	2-5 mEq/kg (2-5 mmol/kg)
Sodium[c,d]	1,200-1,500 mg	60-100 mEq (60-100 mmol) (1-2 mEq/kg [1-2 mmol/kg])	0-6 months: 120 mg 7-12 months: 370 mg 1-8 years: 1,000-1,200 mg 9-18 years: 1,500 mg	2-6 mEq/kg (2-6 mmol/kg)
Trace Elements				
Chromium[e] (mcg)	20-45 (varies with age and sex)	10-15 0.14-0.87[f]	0-6 month: 0.2 7-12 month: 5.5 1-8 year: 11-15 9-18 year: 21-35	0-6 month: 0.0006 mcg/kg[f] 7-12 month: 0.012 mcg/kg[f] 1-3 year: 0.22 mcg[f] 4-8 year: 0.3 mcg[f] 9-13 year: M 0.5 mcg; F 0.42 mcg[f] 14-18 year: M 0.7 mcg; F 0.48 mcg[f]
Copper[g] (mcg)	900 1,000 (pregnancy) 1,300 (lactation)	0.3-1.5 (increased with GI loss)	0-12 months: 200-220 1-8 years: 340-440 9-18 years: 700-890	20 mcg/kg (maximum, 300 mcg)
Fluoride (mg)	M: 4 W: 3	1	0-6 months: 0.01 mg 7-12 months: 0.5 mg 1-8 years: 0.7-1 mg 9-18 years: 2-3 mg	—
Iodine (mcg)	150 220 (pregnancy) 290 (lactation)	70-140 (not well defined)[h]	0-12 months: 110-130 1-8 years: 90 9-18 years: 120-150	1 mcg/kg[h]
Iron (mg)	M: 8 W (≤50 years): 18 27 (pregnancy) 9 (lactation) W (>50 years): 8	1 1.5 (blood loss)	0-6 months: 0.27 7 months-8 years: 7-11 M (9-18 years): 8-11 F (9-13 years): 8 F (14-18 years): 15	Varies
Manganese[g] (mg)	W: 1.8 2 (pregnancy) 2.6 (lactation) M: 2.3	0.15-1	0-6 months: 0.003 7-12 months: 0.6 1-8 years: 1.2-1.5 9-18 years: 1.6-2.2	1 mcg/kg (maximum, 50 mcg)
Molybdenum (mcg)	45 50 (pregnancy, lactation)	100-200	0-12 months: 2-3 1-8 years: 17-22 9-18 years: 34-43	0.25 mcg/kg (maximum, 5 mcg)

Selenium (mcg)	55 60 (pregnancy) 70 (lactation)	20-60[j] 100* with deficiency	0-12 months: 15-20 1-8 years: 20-30 9-18 years: 40-55	1.5-3 mcg/kg (maximum, 30 mcg)
Zinc[j] (mg)	W: 8 M, pregnancy: 11 Lactation: 12	2.5-5[j] (increased with GI loss)	0-12 months: 2-3 1-8 years: 3-5 9-18 years: 8-11	Premature: 300-400 mcg/kg Other: 50-250 mcg/kg
Vitamins				
Ascorbic acid (mg) (vitamin C)	75-90	100	0-12 months: 40-50 1-8 years: 15-25 9-18 years: 45-75	80
Biotin (mcg)	30	60	0-12 months: 5-6 1-8 years: 8-12 9-18 years: 20-25	20
Cobalamin (mcg) (vitamin B_{12})	2.4	5	0-12 months: 0.4-0.5 1-8 years: 0.9-1.2 9-18 years: 1.8-2.4	1
Folic acid (mcg)	400	400	0-12 months: 65-80 1-8 years: 150-200 9-18 years: 300-400	140
Niacin (mg NE)	14-16	40	0-12 months: 2-4 1-8 years: 6-8 9-18 years: 12-16	17
Pantothenic acid (mg)	5	15	0-12 months: 1.7-1.8 1-8 years: 2-3 9-18 years: 4-5	5
Pyridoxine (mg) (vitamin B_6)	1.3-1.7	4	0-12 months: 0.1-0.3 1-8 years: 0.5-0.6 9-18 years: 1-1.3	1
Riboflavin (mg)	1.1-1.3	3.6	0-12 months: 0.3-0.4 1-8 years: 0.5-0.6 9-18 years: 0.9-1.3	1.4
Thiamine (mg)	1.1-1.2	3	0-12 months: 0.2-0.3 1-8 years: 0.5-0.6 9-18 years: 0.9-1.2	1.2
Vitamin A (mcg RE) (retinol)	700-900	600-1,000 (3,300-5,500 international units)	0-12 months: 400-500 1-8 years: 300-400 9-18 years: 600-900	700 (2,300 international units)
Vitamin D (mcg)	≤70 years: 15 (600 international units) >70 years: 20 (800 international units)	5 (200 international units)[i]	All ages: 15 (600 international units)	5-10 (200-400 international units)[i]
Vitamin E (mg TE) (α-tocopherol)	15 (15 international units)	10 (10 international units)	0-12 months: 4-5 (4-5 international units) 1-8 years: 6-7 9-18 years: 11-15	7 (7 international units)
Vitamin K (mcg)	90-120	0.7-2.5 mg	0-12 months: 2-2.5 1-8 years: 30-55 9-18 years: 60-75	200

M, men; NE, niacin equivalents; RE, retinol equivalents; TE, tocopherol equivalent; W, women.

[a]Data represent either the recommended dietary allowance (RDA) or the adequate intake (AI) for each nutrient where established.

[b]Not established; as needed to maintain acid–base balance.

[c]Newborns and low-birth-weight or very-low-birth-weight infants or with concomitant disease (eg, necrotizing enterocolitis) may have higher requirements. Intake in nonhealthy children must be individualized.

[d]No RDA or AI has been established.

[e]An additional 20 mcg/day is recommended in patients with significant intestinal losses.

[f]ASPEN recommendations.

[g]May accumulate in cholestasis.

[h]Considered if on long-term total parenteral nutrition; no commercial intravenous iodine product is marketed in the United States; topical povidone iodine products may provide sufficient intake if used for central venous catheter dressing changes.

[i]Higher doses may be required in patients with short bowel syndrome receiving long-term parenteral nutrition.

[j]Additional intake needed with small bowel losses, which can be 12 mg zinc/L or 17 mg zinc/kg of stool or ileostomy output; an additional 2 mg/day needed for acute catabolic stress.

DRUG–NUTRIENT INTERACTIONS

10 Drug–nutrient interactions can affect response to drug therapy and nutrition status. A comprehensive discussion of drug–nutrient interactions is beyond the scope of this chapter.[98–102] Drug-induced nutrient deficiency, poor therapeutic response, enhanced drug toxicity, and failure to achieve desired nutrition outcomes can occur if either nutrition support or drug therapy is stopped because of adverse effects. Patient outcomes may be enhanced when an effective method to identify significant drug–nutrient interactions is coupled with a patient counseling program. An important part of the assessment process is to recognize risk factors that influence drug–nutrient interactions. The potential for drug–nutrient interactions is greatest in pediatric and elderly individuals, those who are critically ill, those receiving multiple drug therapies or enteral tube feedings, and those with existing comorbidities, such as intestinal dysfunction.

Mineral and electrolyte serum concentrations may change because of drug therapy. For example, with loop diuretics, urine sodium, potassium, calcium, and magnesium wasting may occur, causing a reduction in their respective serum concentrations. Alternatively, calcium excretion is reduced with thiazide diuretics. Serum electrolyte concentrations also may increase as a direct result of the drug's mechanism (potassium-sparing diuretics) or because of the drug's salt form (sodium piperacillin/tazobactam). Corticosteroids and cyclosporine are known to cause hyperglycemia; other drugs are prescribed to pharmacologically lower blood glucose concentrations (insulin, oral hypoglycemics).

Vitamin and trace element status also may be affected by drugs (**Table 158-16**). For example, sulfasalazine therapy causes a decrease in folic acid, isoniazid therapy causes pyridoxine deficiency, and furosemide therapy may result in decreased thiamine concentrations. Drug therapy outcomes also may be affected by vitamin intake. For instance, the ingestion of high folic acid doses may decrease the therapeutic effect of methotrexate, and changes in an individual's usual vitamin K or vitamin E intake may cause variability in the anticoagulant effects of warfarin.

TABLE 158-16 Drug and Nutrient Interactions

Drug	Effect
Angiotensin converting enzyme inhibitors	Increased urinary zinc losses
Angiotensin receptor blockers	Increased urinary zinc losses
Antacids	Thiamine deficiency
Antibiotics	Vitamin K deficiency
Aspirin	Folic acid deficiency; increased vitamin C excretion
Cathartics	Increased requirements for vitamins D, C, and B_6
Cholestyramine	Vitamins A, D, E, and K and β-carotene malabsorption
Colestipol	Vitamins A, D, E, and K and β-carotene malabsorption
Corticosteroids	Decreased vitamins A, D, and C
Diuretics (loop)	Thiamine deficiency
Diuretics (thiazides)	Increased urinary zinc losses
Efavirenz	Vitamin D deficiency caused by increased metabolism of 25(OH)D and $1,25(OH)_2D$
$Histamine_2$ antagonists	Vitamin B_{12} malabsorption (reduced acid results in impaired release of B_{12} from food)
Isoniazid	Vitamin B_6 and niacin deficiency
Isotretinoin	Vitamin A increases toxicity
Mercaptopurine	Niacin deficiency
Methotrexate	Folic acid inhibits effect
Orlistat	Vitamins A, D, E, and K malabsorption caused by fat malabsorption
Pentamidine	Folic acid deficiency
Phenobarbital	Increased vitamin D metabolism
Phenytoin	Increased vitamin D metabolism; decreased folic acid concentrations
Primidone	Folic acid deficiency
Protease inhibitors	Vitamin D deficiency (impaired renal hydroxylation)
Proton pump inhibitors	Decreased iron and vitamin B_{12} absorption (reduced acid results in impaired release of B_{12} from food)
Sulfasalazine	Folic acid malabsorption
Trimethoprim	Folic acid depletion
Warfarin	Vitamin K inhibits effect; vitamins A, C, and E may increase effect
Valproic acid	Zinc
Zidovudine	Folic acid and B_{12} deficiencies increase myelosuppression

Vehicles for drug-delivery also may contain nutrients. Most intravenous therapies (maintenance intravenous fluids, drugs, electrolyte replacements) are delivered using solutions of either dextrose (dextrose 5% or 10% in water) or sodium (0.9% NaCl). Lipid emulsion (10%) is used as the vehicle for the anesthetic agent propofol and the intravenous calcium channel blocker clevidipine and contributes fat calories (1.1 kcal/mL or 4.6 kJ/mL) when these continuous infusions are used. In these instances, nutrition support regimens must be adjusted to accommodate calories and other nutrients delivered through these therapies to avoid overfeeding and other complications.

PRACTICAL GUIDELINES

The value of any marker used for nutrition screening is only as good as its ability to accurately identify malnourished patients and to correlate with nutrition-related outcomes. The response of the various nutrition status markers to nutrition therapy and the correlation between improvement in these markers and decreased morbidity and mortality support their validity. However, when applied to an individual, most of these markers lack specificity and sensitivity, which makes the development of a clinically useful, cost-effective approach to nutrition screening challenging.

The importance of the nutrition-focused history and physical examination in both nutrition screening and assessment cannot be overemphasized. The minimum amount of objective data that can further substantiate the clinical impression and provide a baseline for subsequent monitoring is weight and the serum CRP and ALB concentrations. The cost effectiveness of other biochemical parameters is unknown. The assessment of other anthropometric measures is most useful in the setting of anticipated long-term nutrition support in which these measurements will serve as a longitudinal marker of response to the nutrition care plan.

Initially, nutrition requirements are determined based on assumptions made about the patient’s clinical condition and the nutrition needs associated with repletion or growth, if needed. After a nutrition intervention has been initiated, periodic reassessment of nutrition status is critical to determine the accuracy of the initial estimate. Nutrition requirements are dynamic in the setting of acute or critical illness—as the patient’s clinical status changes, so will protein and energy requirements, further emphasizing the need for continued reassessment.

Better markers of nutrition status and methods for determining patient-

specific nutrition requirements are needed to allow further refinement of estimates of an individual's nutrition needs. Functional tests and simple, noninvasive tests for body composition analysis hold promise for the future. However, until better methods of assessment become available and are demonstrated to be cost-effective, the currently available battery of tests will continue to be the mainstay of nutrition assessment.

Postclass Engaged Learning Activity

Conduct a literature search and identify a study that has been published within the last 24 months related to assessment of nutrition status or nutrition requirements. Write a brief summary of the study aims, methods, and findings, and specifically describe what impact, if any, the study may have on current practice. This activity is intended to build your experience with accessing and evaluating the primary biomedical literature and applying your knowledge to make evidence-based recommendations.

ABBREVIATIONS

ABW	actual body weight
AdjBW	adjusted body weight
AI	adequate intake
ALB	albumin
AND	Academy of Nutrition and Dietetics
ASPEN	American Society for Parenteral and Enteral Nutrition
BEE	basal energy expenditure
BIA	bioelectrical impedance analysis
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CRP	C-reactive protein
CT	computed tomography
DCH	delayed cutaneous hypersensitivity
DRI	Dietary Reference Intake
DXA	dual-energy x-ray absorptiometry
EAR	estimated average requirement
EFAD	essential fatty acid deficiency
FTT	failure-to-thrive
GI	gastrointestinal
HIV	human immunodeficiency virus
IBW	ideal body weight
LBM	lean body mass
MNA-SF	Mini-Nutritional Assessment–Short Form
MREE	measured resting energy expenditure
MRI	magnetic resonance imaging
MST	Malnutrition Screening Tool
MUMC	mid-arm muscle circumference
NFPE	nutrition-focused physical examination
RDA	recommended dietary allowance
REE	resting energy expenditure
RQ	respiratory quotient
SGA	Subjective Global Assessment
TBSA	total body surface area
TBW	total body water
TFN	transferrin
TUN	total urine nitrogen
UBW	usual body weight
UL	tolerable upper intake level
UUN	urine urea nitrogen
VCO_2	carbon dioxide production
VO_2	oxygen consumption
WHO	World Health Organization

REFERENCES

1. White JV, Guenter P, Jensen GL, et al. Consensus statement: Academy of Nutrition and Dietetics and the American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). *J Parenter Enteral Nutr*. 2012;36:275–283.
2. Mehta NM, Corkins MR, Lyman B, et al. Defining pediatric malnutrition: A paradigm shift toward etiology-related definitions. *J Parenter Enter Nutr*. 2013;37:460–481.
3. Jensen GL, Hsiao PY, Wheeler D. Adult nutrition assessment tutorial. *J Parenter Enteral Nutr*. 2012;36:267–274.
4. Malone A, Hamilton C. The Academy of Nutrition and Dietetics/The American Society for Parenteral and Enteral Nutrition Consensus Malnutrition Characteristics: Application in practice. *Nutr Clin Pract*. 2013;28:639–649.
5. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity among adults and youth: United States, 2015–2016. NCHS data brief, no 288. Hyattsville, MD: National Center for Health Statistics; 2017.
6. Centers for Disease Control and Prevention. Overweight and Obesity: Adult Obesity Facts. 2018. Available at: http://www.cdc.gov/obesity/data/adult.html. Accessed December 17, 2018.
7. Centers for Disease Control and Prevention. Growth Charts. Available at: http://www.cdc.gov/growthcharts/. Accessed December 18, 2018.
8. Bhaskaran K, dos-Santos-Silva I, Leon DA, et al. Association of BMI with overall and cause-specific mortality: A population-based cohort study of 3.6 million adults in the UK. *Lancet Diabetes Endocrinol*. 2018;6:944–953.
9. Correia MITD. Nutrition screening vs nutrition assessment: What's the difference? *Nutr Clin Prac*. 2018;33:62–72.
10. Cederholm T, Bosaeus I, Barazzoni R, et al. Diagnostic criteria for malnutrition: An ESPEN consensus statement. *Clin Nutr*. 2015;34:335–340.
11. Jensen GL, Hsiao PY, Wheeler D. Nutrition screening and assessment. In: Mueller C, ed. *The A.S.P.E.N. Adult Nutrition Support Core Curriculum*. 2nd ed. Silver Spring, MD: American Society for Parenteral and Enteral

Nutrition; 2012:155–169.

12. The Joint Commission. Standards FAQ Details. Available at: http://www.jointcommission.org/standards_information/jcfaq.aspx. Accessed December 18, 2018.
13. Patel V, Romano M, Corkins MR, et al. Nutrition screening and assessment in hospitalized patients: A survey of current practice in the United States. *Nutr Clin Pract*. 2014;29:483–490.
14. Skipper A, Ferguson M, Thompson K, et al. Nutrition screening tools: An analysis of the evidence. *J Parenteral Enteral Nutr*. 2012;36:292–298.
15. Cereda E. Mini-nutritional assessment. *Curr Opin Clin Nutr Metab Care*. 2012;15:29–41.
16. Lee Z-Y, Heyland DK. Determination of nutrition risk and status in critically ill patients: What are our considerations? *Nutr Clin Pract*. 2019;34(1):96–111.
17. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the critically ill adult patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *J Parenter Enter Nutr*. 2016;40:159–211.
18. Grummer-Strawn LM, Reinold C, Krebs NF, Centers for Disease Control and Prevention (CDC). Use of the World Health Organization and CDC growth charts for children aged 0-59 months in the United States. Recommendations and Reports. *MMWR*. 2010;59(RR-9):1–15.
19. Esper DH. Utilization of nutrition-focused physical assessment in identifying micronutrient deficiencies. *Nutr Clin Pract*. 2015;30:194–202.
20. Corkins KG. Nutrition-focused physical examination in pediatric patients. *Nutr Clin Pract*. 2015;30:203–209.
21. Frankenfield DC, Ashcraft CM. Estimating energy needs in nutrition support patients. *J Parenter Enteral Nutr*. 2011;35:563–570.
22. Froehlich-Grobe K, Nary DE, Van Sciver A, et al. Measuring height without a stadiometer: Empirical investigation of four height estimates among wheelchair users. *Am J Phys Med Rehabil*. 2011;90:658–666.
23. Hickson M, Frost G. A comparison of three methods for estimating height in the acutely ill elderly population. *J Hum Nutr Diet*. 2003;16:13–20.
24. Bell KL, Davies PS. Prediction of height from knee height in children with cerebral palsy and non-disabled children. *Ann Hum Biol*. 2006;33:493–

499.
25. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr*. 2013;13:59.
26. Olsen IE, Groveman SA, Lawson ML, et al. New intrauterine growth curves based on United States data. *Pediatrics*. 2010;125:e214–e224.
27. Cole SZ, Lanham JS. Failure to thrive: An update. *Am Fam Physician*. 2011;83:829–834.
28. Braun LR, Marino R. Disorders of growth and stature. *Pediatr Rev*. 2017;38:293–304.
29. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *J Am Coll Cardiol*. 2014;63(25 Pt B):2985–3023. Erratum in.
30. GBD Obesity 2015 Collaborators. Health effects of overweight and obesity in 195 countries over 25 years. *New Engl J Med*. 2017;377:13–27.
31. Hsu WC, Araneta MRG, Kanaya AM, et al. BMI cut points to identify at-risk Asian Americans for type 2 diabetes screening. *Diabetes Care*. 2015;38:150–158.
32. National Institutes of Health. Managing Overweight and Obesity in Adults. Systematic evidence review from the obesity expert panel, 2013. Available at www.nhlbi.nih.gov/health-topics/managing-overweight-obesity-in-adults. Accessed December 19, 2018.
33. DiMaria-Ghalili RA. Integrating nutrition assessment in the comprehensive geriatric assessment. *Nutr Clin Pract*. 2014;29:420–427.
34. Martin L, Senesse P, Gioulbasanis I, et al. Diagnostic criteria for the classification of cancer-associated weight loss. *J Clin Oncol*. 2015;33:90–99.
35. Ness-Abramof R, Apovian CM. Waist circumference measurement in clinical practice. *Nutr Clin Pract*. 2008;23:397–404.
36. Xi B, Mi J, Zhao M, et al. Trends in abdominal obesity among US children and adolescents. *Pediatrics*. 2014;134:e334–e339.
37. Fryar CD, Gu Q, Ogden CL, Flegal KM. Anthropometric reference data for children and adults: United States, 2011-2014. National Center for Health Statistics. *Vital Health Stat*. 2016;3(39). https://www.cdc.gov/nchs/data/series/sr_03/sr03_039.pdf. Accessed

December 17, 2018.

38. Mulasi U, Kuchnia AJ, Cole AJ, Earthman CP. Bioimpedance at the bedside: current applications, limitations, and opportunities. *Nutr Clin Pract*. 2015;30:180–193.
39. Earthman CP. Body composition tools for assessment of adult malnutrition at the bedside: a tutorial on research considerations and clinical applications. *J Parenter Enteral Nutr*. 2015;39:787–822.
40. Guerra RS, Fonseca I, Pichel F, et al. Handgrip strength and associated factors in hospitalized patients. *J Parenter Enteral Nutr*. 2015;39:322–330.
41. Flood A, Chung A, Parker H, et al. The use of hand grip strength as a predictor of nutrition status in hospital patients. *Clin Nutr*. 2014;33:106–114.
42. Whiting SJ, Cheng PC, Thorpe L, et al. Hand grip strength as a potential nutritional assessment tool in long-term care homes. *J Ageing Res Healthcare*. 2016;1:1–11.
43. Fields DA, Gunatilake R, Kalaitzoglou E. Air displacement plethysmograpy: cradle to grave. *Nutr Clin Pract*. 2015;30:219–226.
44. Baracos V, Caserotti P, Earthman CP, et al. Advances in the science and application of body composition measurement. *J Parenter Enteral Nutr*. 2012;36:96–107.
45. Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: pathogenesis and clinical significance. *J Parenter Enter Nutr*. 2019;43:181–193.
46. Young LS, Kearns LR, Schoepfel SL, Clark NC. Protein. In: Mueller C, ed. *The A.S.P.E.N. Adult Nutrition Support Core Curriculum*. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2012:83–97.
47. Velasco N, Long CL, Otto DA, et al. Comparison of three methods for the estimation of total nitrogen losses in hospitalized patients. *J Parenter Enteral Nutr*. 1990;14:517–522.
48. Wolk R, Foulks C. Renal disease. In: Mueller C, ed. *The A.S.P.E.N. Adult Nutrition Support Core Curriculum*. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2012:491–510.390.
49. Food and Nutrition Board, Institute of Medicine, National Academies. Dietary Reference Intakes (DRIs): Recommended dietary allowances and adequate intakes, elements. 2009. Available at: https://www.ncbi.nlm.nih.gov/books/NBK56068/table/summarytables.t3/?

report=objectonly.t8/?report=objectonly. Accessed January 19, 2019.

50. Fessler TA. Trace elements in parenteral nutrition: a practical guide for dosage and monitoring for adult patients. *Nutr Clin Pract*. 2013;28:722–729.
51. Clark SF. Vitamins and trace elements. In: Mueller C, ed. *The A.S.P.E.N. Adult Nutrition Support Core Curriculum*. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2012:121–154.
52. Jin J, Mulesa L, Rouillet MC. Trace elements in parenteral nutrition: considerations for the prescribing clinician. *Nutrients*. 2017;9:440.
53. Vanek VW, Borum P, Buchman A, et al. A.S.P.E.N. position paper: recommendations for changes in commercially available parenteral nutrition multivitamin and multi-trace element products. *Nutr Clin Pract*. 2012;27:440–491.
54. Livingstone C. Zinc: Physiology, deficiency, and parenteral nutrition. *Nutr Clin Pract*. 2015;30:371–382.
55. Steinbrenner H, Speckmann B, Klotz L-O. Selenoproteins: antioxidant selenoenzymes and beyond. *Arch Biochem Biophysics*. 2016;595:113–119.
56. Manzanares W, Langlois PL, Heyland DK. Pharmaconutrition with selenium in critically ill patients: what do we know? *Nutr Clin Pract*. 2015;30:34–43.
57. Ashton K, Hooper L, Harvey LJ, et al. Methods of assessment of selenium status in humans: a systematic review. *Am J Clin Nutr*. 2009;89(Suppl):2025S–2039S.
58. MacKay M, Mulroy CW, Street J. Assessing copper status in pediatric patients receiving parenteral nutrition. *Nutr Clin Pract*. 2015;30:117–121.
59. Harvey LJ, Ashton K, Hooper L, et al. Methods of assessment of copper status in humans: a systematic review. *Am J Clin Nutr*. 2009;89(Suppl):2009S–2024S.
60. Vincent JB. New evidence against chromium as an essential trace element. *J Nutr*. 2017;147:2212–2219.
61. Tian H, Guo X, Wang X, et al. Chromium picolinate supplementation for overweight and obese adults. *Cochrane Database Syst Rev*. 2013;11. CD010063.
62. Peres TV, Schettinger MRC, Chen P, et al. Manganese-induced neurotoxicity: a review of its behavioral consequences and neuroprotective strategies. *BMC Pharmacol Toxicol*. 2016;17:57.

63. Sardesai VM. Molybdenum: An essential trace element. *Nutr Clin Pract*. 1993;8:277–281.
64. Food and Nutrition Board, Institute of Medicine, National Academies. Dietary Reference Intakes (DRIs): Recommended dietary allowances and adequate intakes, vitamins. 2009. Available at: https://www.ncbi.nlm.nih.gov/books/NBK56068/table/summarytables.t2/?report=objectonly. Accessed January 19, 2019.
65. Frank LL. Thiamin in clinical practice. *J Parenter Enteral Nutr*. 2015;39:503–520.
66. Lam JR, Schneider JL, Zhao W, Corley DA. Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B_{12} deficiency. *JAMA*. 2013;310:2435–2442.
67. McCabe KM, Adams MA, Holden RM. Vitamin K status in chronic kidney disease. *Nutrients*. 2013;5:4390–4398.
68. Holick MF. The vitamin D deficiency pandemic: approaches for diagnosis, treatment, and prevention. *Rev Endocr Metab Disord*. 2017;18:153–165.
69. De-Regil LM, Peña-Rosas JP, Fernández-Gaxiola AC, Rayco-Solon P. Effects and safety of periconceptional oral folate supplementation for preventing birth defects (Review). *Cochrane Database Syst Rev*. 2015;12:CD007950.
70. Kim J, Choi J, Kwon SY, et al. Association of multivitamin and mineral supplementation and risk of cardiovascular disease: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004224.
71. Food and Nutrition Board, Institute of Medicine, National Academies. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. 2005. Available at: https://www.nap.edu/read/10490/chapter/1. Accessed January, 19 2019.
72. Hise M, Brown JC. Lipids. In: Mueller C, ed. *The A.S.P.E.N. Adult Nutrition Support Core Curriculum*. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2012:63–82.
73. Borum PR. Fats. In: Corkins MR, ed. *The A.S.P.E.N. Pediatric Nutrition Support Core Curricula*. 2nd ed. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2015:31–40.
74. Gramlich L, Meddings L, Alberda C, et al. Essential fatty acid deficiency in 2015: the impact of novel intravenous lipid emulsions. *J Parenter Enter Nutr*. 2015;39(Suppl 1):61S–66S.

75. Buist NRM. Historical perspective on clinical trials of carnitine in children and adults. *Ann Nutr Metab*. 2016;68(suppl 3):1–4.
76. Reuter SE, Evans AM. Carnitine and acylcarnitines: pharmacokinetic, pharmacological, and clinical aspects. *Clin Pharmacokinet*. 2012;51:553–572.
77. Scruggs ER, Dirks Naylor AJ. Mechanisms of zidovudine-induced mitochondrial toxicity and myopathy. *Pharmacology*. 2008;82:83–88.
78. Food and Nutrition Board, Institute of Medicine, National Academies. Dietary Reference Intakes (DRIs): the development of DRIs 1994-2004: lessons learned and new challenges. 2008. Available at: https://www.nap.edu/read/12086/chapter/1. Accessed January 19, 2019.
79. Food and Nutrition Board. Dietary Reference Intakes for Calcium and Vitamin D (2011). Available at:https://www.nap.edu/read/13050/chapter/2. Accessed January 19, 2019.
80. United States Department of Agriculture, National Agriculture Library. Interactive DRI for Healthcare Professionals. Available at: https://fnic.nal.usda.gov/fnic/dri-calculator/. Accessed January 19, 2019.
81. Frankenfield DC. Factors related to the assessment of resting metabolic rate in critically ill patients. *J Parenter Enter Nutr*. 2019;43:226–33.
82. Wooley JA, Frankenfield D. Energy. In: Mueller C, ed. *The A.S.P.E.N. Adult Nutrition Support Core Curriculum*. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2012:22–35.
83. Mehta NM, Skillman HE, Irving SY, et al. Guidelines for the provision and assessment of nutrition support therapy in the pediatric critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition. *J Parenter Enter Nutr*. 2017;41:706–742.
84. Sentongo T. Assessment of nutrition status by age and determining nutrient needs. In: Corkins MR, ed. *The A.S.P.E.N. Pediatric Nutrition Support Core Curricula*. 2nd ed. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2015:531–565.
85. Rollins C, Huettner F, Neumeister MW. Clinicians guide to nutritional therapy following major burn injury. *Clin Plas Surg*. 2017;44:555–566.
86. Cooney RN, Frankenfield DC. Determining energy needs in critically ill patients: equations or indirect calorimetry. *Curr Opin Crit Care*. 2012;18:174–177.
87. Hipskind P, Glass C, Charlton D, et al. Do handheld calorimeters have a role in assessment of nutrition needs in hospitalized patients? A systematic

review of literature *Nutr Clin Pract*. 2011;26:426–433.

88. Oshima T, Berger MM, De Waele E, et al. Indirect calorimetry in nutritional therapy. A position paper by the ICALIC study group. *Clin Nutr*. 2017;36:651–662.
89. McClave SA, Martindale RG, Kiraly L. The use of indirect calorimetry in the intensive care unit. *Curr Opin Clin Nutr Metab Care*. 2013;16:202–208.
90. Wolfe RR, Miller SL, Miller KB. Optimal protein intake in the elderly. *Clin Nutr*. 2008;27:675–684.
91. Lambeau KV, McRorie JWJr.. Fiber supplements and clinically proven health benefits: How to recognize and recommend an effective fiber therapy. *J Amer Assoc Nurse Pract*. 2017;29:216–223.
92. Langley G, Tajchman S. Fluids, electrolytes, and acid-base disorders. In: Mueller C, ed. *The A.S.P.E.N. Adult Nutrition Support Core Curriculum*. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2012:98–120.
93. Schmidt GL. Fluids and electrolytes. In: Corkins MR, ed. *The A.S.P.E.N. Pediatric Nutrition Support Core Curricula*. 2nd ed. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2015:107–128.
94. Greene HL, Hambidge KM, Schanler R, Tsang RC. Guidelines for the use of vitamins, trace elements, calcium, magnesium, and phosphorus in infants and children receiving total parenteral nutrition: Report of the Subcommittee on Pediatric Parenteral Nutrient Requirements from the Committee on Clinical Practice Issues of the American Society for Clinical Nutrition. *Am J Clin Nutr*. 1988;48:1324–1342.
95. Skipper A. Refeeding syndrome or refeeding hypophosphatemia: A systematic review of cases. *Nutr Clin Pract*. 2012;27:34–40.
96. Friedli N, Stanga Z, Sobotka L, et al. Revisiting the refeeding syndrome: Results of a systematic review. *Nutrition*. 2017;35:151–160.
97. Pulchini CD, Zettle S, Srinath A. Refeeding syndrome. *Pediatr Rev*. 2016;37:516–523.
98. Robien K, Oppeneer SJ, Kelly JA, Hamilton-Reeves JM. Drug–vitamin D interactions: A systematic review of the literature. *Nutr Clin Pract*. 2013;28:194–208.
99. Chen L-N. Drug-nutrient interactions. *Nutr Clin Pract*. 2013;37:450–459.
100. Boullata JI, ed. *Guidebook on Enteral Medication Administration*. Silver

Spring, MD: American Society for Parenteral and Enteral Nutrition; 2019.
101. Deng J, Zhu X, Chen Z, et al. A review of food-drug interactions on oral drug absorption. *Drugs*. 2017;77:1833–1855.
102. Heldt T, Loss SH. Drug-nutrient interactions in the intensive care unit: Literature review and current recommendations. *Rev Bras Ter Intensiva*. 2013;25:162–167.

Parenteral Nutrition

Todd W. Mattox and Catherine M. Crill

KEY CONCEPTS

1. Development and implementation of an appropriate, individualized nutrition care plan requires definition of nutrition goals, determination of nutrition requirements and appropriate route of nutrient delivery, and design of a monitoring plan to evaluate suitability of the nutrition regimen as a patient's clinical condition changes.
2. The appropriate route of nutrition support depends on the functional condition of the patient's gastrointestinal (GI) tract, risk of aspiration, expected duration of nutrition therapy, and clinical condition.
3. Suitable candidates for parenteral nutrition (PN) therapy can be identified on the basis of their age, nutrition status, expected duration of GI dysfunction, and potential risks of PN therapy.
4. PN formulations include injectable amino acids, dextrose, water, electrolytes, vitamins, trace elements, and other additives. Some formulations may include intravenous lipid emulsion (IVLE).
5. PN solutions may be appropriately formulated for administration by peripheral or central venous access.
6. PN formulations are available as standardized commercial premixed products or they may be compounded with an automated compounding device (ACD).
7. PN solutions may be infused continuously or intermittently.
8. Biochemical and clinical measurements for effective monitoring of patients receiving PN include serum chemistries, vital signs, body weight, total daily fluid intake and losses, and nutritional intake.
9. Non–catheter-related complications of PN therapy can be minimized by using age-appropriate nutrient dosing guidelines, frequent monitoring, and

implementing rational adjustments to the PN regimen when metabolic abnormalities occur.

10. Individualized PN therapy should be based on nutrition therapy goals determined from a patient-specific nutrition assessment, type of available IV access, and macronutrient and micronutrient requirements.
11. A patient's nutrient requirements are affected by age, degree of metabolic demand, organ function, drug therapy, exogenous losses, acid–base status, and enteral intake in patients with recovering GI function.

Preclass Engaged Learning Activity

Watch the video entitled "PN Appropriateness: The General Approach" at the American Society for Parenteral and Enteral Nutrition (ASPEN) website. This 13.5-minute video provides a brief overview regarding selection of appropriate PN candidates. The video is useful to enhance student understanding regarding the COLLECT and ASSESS steps in the patient care process.

INTRODUCTION

Maintenance of adequate nutrition status during illness has been recognized for more than 50 years as an integral part of the treatment plan for patients who are unable to attain and sustain oral nourishment. Successful techniques for providing IV nutrition support were introduced to clinical practice in adults and subsequently, infants in the late 1960s.[1] Use of central venous access was investigated to reduce risk of metabolic complications associated with IV fluid overload and electrolyte imbalances. The use of large central vessels permitted infusion of concentrated formulas, which decreased the fluid volume required and avoided the phlebitis that commonly occurred when hypertonic infusions were given peripherally.

Clinical experience and research fostered development of protocols that promoted better patient care and resulted in a decline in complications and costs associated with parenteral nutrition (PN) therapy.[2] The scope of practice for nutrition support clinicians has broadened as a result of increasing knowledge regarding the metabolic consequences associated with acute injury and chronic

disease states. The pharmacist's role in providing safe and effective nutrition-support care requires knowledge of the principles of patient selection, initial therapy design, outcome monitoring, and strategies for providing therapy during PN product shortages.[3–5] In addition, the pharmacist is uniquely prepared to take on the responsibility for PN order verification as well as compounding and dispensing of the PN admixture. The PN order must be verified by a pharmacist to ensure the order is clear, complete, and correctly transcribed. A clinical review should be performed to confirm appropriate indication, nutrient dosing, and non-nutrient medication dosing. A pharmaceutical review should be performed to confirm compatibility of ordered nutrients and any non-nutrient medications in addition to the expected stability of the formulation.[4,5] Other responsibilities of the nutrition support pharmacist may include development of policy and procedures as well as quality improvement activities for patient care and operational processes associated with providing parenteral and enteral nutrition.[4,5] The clinical role of other healthcare professionals may be similar because of the evolving interprofessional approach to nutritional support.[6–10] This chapter reviews indications for PN, components of PN formulations, routes of IV administration, practical aspects of regimen design, solution admixture, outcome monitoring, and management of complications for both adult and pediatric (neonates, infants, and children) patients.

>DESIRED OUTCOMES

1 The primary objective of nutrition support therapy is to promote positive clinical outcomes of an illness and improve a patient's quality of life. Four fundamental steps are key to providing optimal care for patients who require nutrition support. They are establishing patient-specific nutrition goals, determining nutrient requirements to achieve the nutrition goals, assuring delivery of the required nutrients, and subsequently assessing the nutrition regimen.[5–7]

A patient's nutrition goals can be established after a thorough nutritional assessment (see Chapter 158, "Assessment of Nutrition Status and Nutrition Requirements"). Nutrient requirements and an appropriate route for delivery of the required nutrients can then be determined. Nutrition support goals include correction of the patient's caloric and nitrogen imbalances and any fluid, electrolyte, vitamin, or trace element abnormalities. An additional goal is to lessen the metabolic response to injury by minimizing oxidant stress and favorably modulating immune response. These interventions should not cause or

worsen other metabolic complications.

2 The gastrointestinal (GI) tract is the optimal route for providing nutrients unless obstruction or other GI complications are present (see Chapter 160, "Enteral Nutrition").[11] Two other considerations that may impact selection of the optimal route for delivery of nutrition support include expected duration of nutrition therapy and risk of aspiration. Patients who have nonfunctional GI tracts or are otherwise not candidates for enteral nutrition may benefit from PN.

INDICATIONS FOR PARENTERAL NUTRITION SUPPORT

The association between malnutrition and development of complications and mortality is well documented for adult and pediatric patients.[7,11–13] Although improvement in various clinical nutrition markers has been reported for patients who received PN, the impact on clinical outcome has been difficult to demonstrate in many adult populations. Several investigations have reported a positive effect of PN on complications and mortality, but others have failed to confirm these findings.[11] Consensus guidelines for PN use for adults and pediatric patients are based on clinical experience and investigations in specific patient populations.[11–18] Unfortunately, conflicting data have resulted in a lack of consistency in published guidelines from different sources, which complicates identification of the patient who is most likely to benefit from PN. However, these published reports may serve as resources for development of institution-specific standards.

3 PN use should not be determined by medical diagnosis or disease state.[11] However, more detailed considerations for specific disease states have been reported.[11–18] The decision to initiate PN is based on the findings of an assessment performed after a patient demonstrates an inability to meet nutritional needs enterally for an extended time period (**Tables 159-1** and **159-2**). This assessment must include an evaluation of the patient's nutrition status, clinical status, age, and potential risks of initiating therapy (eg, infection and other metabolic abnormalities). The appropriate length of time to wait before starting PN therapy depends on patient age and clinical status.[11–18] PN therapy is not an emergent intervention and should not be initiated until the patient is hemodynamically and metabolically stable.[11]

TABLE 159-1 Time Frame for Initiating Parenteral Nutrition

1. Adults
   a. Previously well-nourished patients: Initiate PN after 7 days of oral intake or EN less than 50% of estimated requirements
   b. Nutritionally at risk patients (ie, involuntary loss of 10% or more of usual body weight within 6 months; involuntary loss of greater than or 5% or more of usual body weight in 1 month; involuntary loss or gain of 10 pounds within 6 months; BMI less than 18.5 kg/m^2; inadequate nutrition intake, including inadequate food or nutrition products for greater than 7 days): Initiate PN after 3-5 days of oral intake or EN less than 50% of estimated requirements
   c. Moderate or severely malnourished patients: Initiate PN as soon as feasible for those in whom oral intake or EN is not possible or sufficient.
   d. Delay PN in metabolically unstable patients until improvement in clinical condition.
2. Neonates
   a. Very low birth weight infant (birth weight less than 1,500 g): Begin PN promptly.
   b. Critically ill: Initiate PN when EN is unable to meet energy requirements for energy expenditure and growth.
3. Pediatrics
   a. Infant, child or adolescent with self-limited illness: Delay PN for up to 7 days.
   b. Infants: Initiate PN within 1-3 days when EN is unable to provide sufficient nutrients to support growth for an extended period.
   c. Older children and adolescents: Initiate PN within 4-5 days when EN is unable to provide sufficient nutrients to support growth for an extended period.

BMI, body mass index; EN, enteral nutrition; PN, parenteral nutrition.

Data from Reference 11.

TABLE 159-2 Indications for Parenteral Nutrition

1. Impaired absorption or loss of nutrients via the GI tract because of one or more of the following:
   a. Massive small bowel resection: Adult patients with less than 120 cm of small bowel distal to the ligament of Treitz without a colon or less than 60 cm of small bowel with an intact colon; neonates, infants and pediatric patients who are unable to meet nutrient, electrolyte, and fluid requirements regardless of intestinal length.
   b. High output GI fistulae: Greater than 500 mL/day; location precludes enteral access.
   c. High volume fistula output with EN.
   d. Neutropenic colitis: Typhlitis or opportunistic infection in an immunocompromised patient.
   e. Small bowel mucosal disease: Radiation- or chemotherapy-related enteritis, autoimmune enteropathy, intractable diarrhea of infancy.
   f. Intestinal atresia
   g. Gastroschisis
   h. Volvulus
   i. Meconium ileus
   j. Necrotizing enterocolitis
   k. Mesenteric thrombosis
2. Mechanical bowel obstruction: Intrinsic or extrinsic blockage of intestinal lumen.
   a. Stenosis or stricture
   b. Inflammatory disease
   c. Peritoneal carcinomatosis
   d. Severe adhesive disease
   e. Severe superior mesenteric artery syndrome
3. Restricted oral intake or EN necessary for bowel rest
   a. Ischemic bowel
      Mesenteric artery stenosis
      Abdominal compartment syndrome
      Low flow states
   b. Severe pancreatitis
      EN exacerbated pain
      Worsening serum lipase levels
      Infected pancreatic phlegmon/pseudocyst
      Complex pancreatic fistula
      Abdominal compartment syndrome
   c. Chylous fistula: High output with low-fat diet or elemental formula.
   d. Preoperative status: Severely malnourished patient with nonfunctional GI tract for 7-10 days prior to surgery.
4. Motility disorders
   a. Prolonged ileus
      Diffuse peritonitis
      Medical treatment-induced
      Other disease states
   b. Pseudo-obstruction
   c. Scleroderma
   d. Visceral organ myopathy
   e. Very long segment Hirschsprung's disease
   f. Severe adhesive disease
5. Inability to achieve or maintain enteral access or EN
   a. Hemodynamic instability
   b. Active GI bleeding
   c. Severe neutropenic fever
   d. Low birth weight infant

EN, enteral nutrition; GI, gastrointestinal.

Data from Reference 11.

COMPONENTS OF PARENTERAL NUTRITION

4 PN formulations include IV sources of protein, dextrose, fat, water, electrolytes, vitamins, trace elements, and other additives. PN solutions should provide the optimal combination of macro- and micronutrients to provide a patient's specific nutritional requirements. Macronutrients include water, protein, dextrose, and fat or lipid (**Table 159-3**). Micronutrients include vitamins, trace elements, and electrolytes. Both macronutrients and micronutrients are necessary for maintenance of normal metabolism. In general, macronutrients are used for energy (dextrose and lipid) and as structural substrates (protein and lipid). Micronutrients on the other hand support a variety of metabolic activities necessary for cellular homeostasis such as enzymatic reactions, fluid balance, and regulation of electrophysiologic processes.

TABLE 159-3 Macronutrient Components of PN Solutions

Nutritional Substrate	IV Source	Description
Fluid	Sterile water for injection USP	
Nitrogen	Crystalline amino acids Standard solutions	Contain a balanced profile of essential, semi-essential, and nonessential L-amino acids
	Hepatic encephalopathy	Amino acid profile includes higher BCAA concentrations and lower AAA and methionine concentrations
	Kidney Disease	Amino acid profile includes higher EAA and histidine concentrations
	Metabolic stress or trauma	Amino acid profile provides standard essential, semi-essential, and nonessential amino acids with higher BCAA concentrations
	Pediatrics	Amino acid profile includes standard essential, semi-essential, and nonessential amino acids with lower methionine, phenylalanine, and glycine concentrations; these solutions also contain taurine, glutamate, and aspartate
Energy		
Carbohydrate	Dextrose	
	Glycerol	Used in ProcalAmine (B. Braun Medical, Inc.)
Fat	IV lipid emulsion LCT emulsions Fish Oil emulsion Mixed lipid emulsions	Fatty acid source • Soybean • Fish oil • Soybean-olive oil • SMOF (soybean oil, MCT, olive, and fish oils)
	Alternative lipid emulsions (investigational)	• Olive oil • MCT-LCT • MSF (MCT, soybean, and fish oils)

AAA, aromatic amino acids (includes phenylalanine and tyrosine); BCAA, branched-chain amino acids (leucine, isoleucine, and valine); EAA, essential amino acids (leucine, isoleucine, valine, phenylalanine, tryptophan, methionine, threonine, and lysine); LCT, long-chain triglycerides; MCT, medium-chain triglycerides; MSF, MCT, soybean, and fish oils; PN, parenteral nutrition; SMOF, soybean oil, MCT, olive, and fish oils; USP, United States Pharmacopeia.

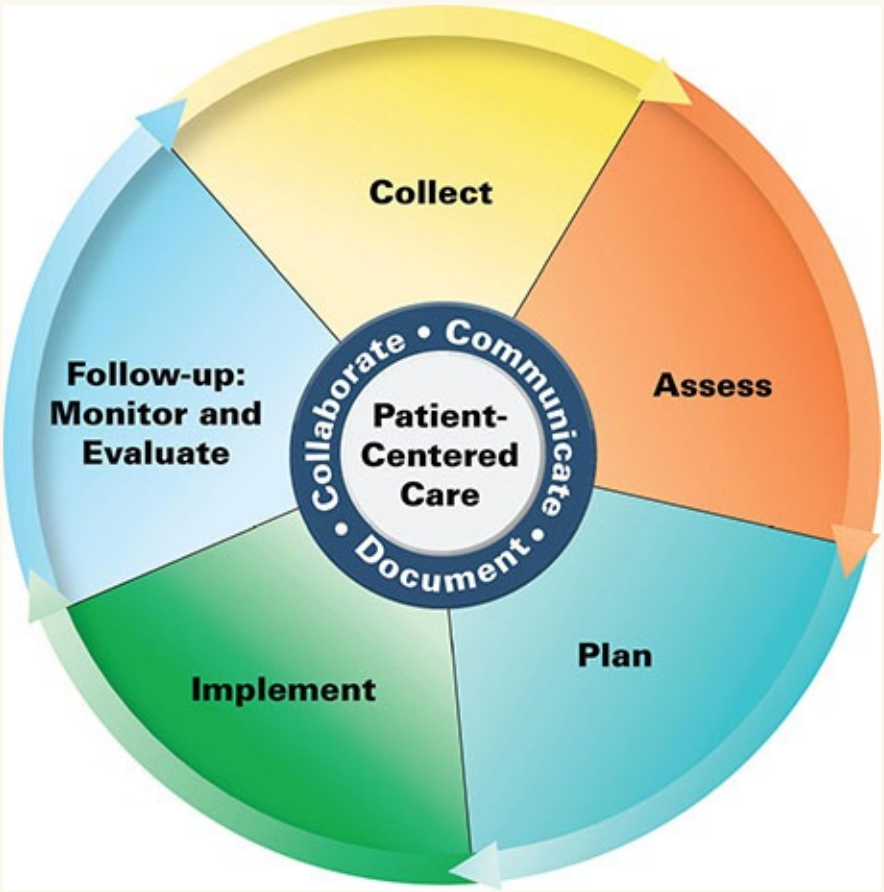
Over the past 5 to 10 years, shortages of all PN components have been reported.[3] The unavailability of these products has resulted in delays in PN therapy initiation, restricted or limited nutrient dosing, and negative effects on all steps of the PN process that have compromised patient health and safety. Providing safe therapy during PN product shortages can be challenging for PN patients and practitioners.[3,5] Conservation recommendations and alternative therapy measures may need to be employed to optimize quality of care and avoid patient harm.[3,5] In addition, the FDA may permit the temporary importation of PN products from foreign manufacturers that have been used safely and successfully in the foreign market. However, the products may have not received official FDA approval for routine use and distribution in the United States because the manufacturer has not sought FDA approval. Imported products have included PN components such as sodium glycerophosphate, multitrace element products, and amino acids.[3] If such products are imported and used in the United States, practitioners should thoroughly familiarize themselves with the prescribing information located in the product's package insert because of potential differences in product ingredients and concentration that may affect dosing. In addition, potential interactions resulting in stability or compatibility problems should be considered.

Amino Acids

Protein in PN solutions is provided in the form of crystalline amino acids (CAAs), which when oxidized for energy yield 4 cal or approximately 17 kJ/g of protein. However, including the caloric contribution from protein when calculating calories provided by the PN regimen is controversial.[19] While sufficient energy substrate should be provided to allow utilization of amino acids for protein synthesis rather than an energy source, oxidation of amino acids for energy has been demonstrated in critically ill patients and is thought to occur because of metabolic derangements seen during severe metabolic stress. Hence, some practice settings may differ in expressing calories provided by a PN regimen as total calories (protein, carbohydrate, and lipid calories) or nonprotein calories (carbohydrate and lipid calories).

Commercially available CAA solutions may be categorized as standard amino acid solutions or modified amino acid solutions. Standard CAA solutions are designed for patients with "normal" organ function and nutritional requirements (see Table 159-3). Although standard CAA solutions differ in the proportion of

specific amino acids, they contain a balanced profile of essential, semi-essential, and nonessential L-amino acids. Despite these differences, similar effects on markers of protein metabolism have been reported.[20] The protein concentration, total nitrogen, and electrolyte content may also differ among products. Because the nitrogen concentration of dietary protein is approximately 16%, 6.25 (100 g protein / 16 g nitrogen) is commonly accepted as the conversion figure for calculating the nitrogen amount provided by CAA protein. Differences in nitrogen content per gram of amino acids among CAA products may affect calculation of nitrogen amounts infused when determining nitrogen balance.[20,21] The clinical significance of these differences in determining nitrogen balance for routine clinical use is unknown.[21]



Patient Care Process for Use of Parenteral Nutrition

Collect

- Patient characteristics (eg, age, race, sex)
- Patient history (past medical, surgical, family, social—alcohol use)
- Nutrition history (dietary history, weight history)
- Current medications (including nutritional supplements)
- Age appropriate objective data (Fig. 159-3)

  Height/length, weight, BMI, head circumference

  Fluid balance (intake and output)

  Labs (eg, serum electrolytes, Scr, BUN, glucose, albumin)

  Vital signs (eg, temperature, pulse rate, respiration rate, blood pressure)

Assess

- Current nutrition status and time period of insufficient nutrient intake
- Clinical condition(s) preventing adequate oral nutrient intake
- Clinical condition(s) preventing use of enteral tube feeding to determine if an indication for parenteral nutrition (PN) therapy exists (Tables 159-1 and 159-2)
- Vascular access
- Current degree of metabolic instability (eg, hemodynamics, organ function, fluid/electrolyte status)
- Appropriate route of PN (central or peripheral)

Plan*

- Design an age-appropriate PN regimen that provides estimated nutrient requirements and minimizes risk of adverse effects or worsening current metabolic conditions (see Designing a Parenteral Nutrition Regimen; Figs. 159-1 and 159-2)
- Monitoring parameters for efficacy (Fig. 159-3)

Implement*

- Provide education regarding all elements of treatment plan to

patient/caregivers and other members of the healthcare team

- Use a standardized PN order form for ordering PN prescription to minimize risk of errors
- Verify the order to ensure that it is clear, complete, and correctly transcribed
- Confirm stability of formulation and compatibility of ordered nutrients and any non-nutrient medications
- Determine if PN solution will be provided as compounded sterile preparation according to United States Pharmacopoeia Chapter 797 standards or provided as a standardized, commercially available parenteral nutrition product
- Determine appropriate plan for patient-specific monitoring based on the patient's clinical condition to anticipate, prevent or treat mechanical/technical, metabolic/nutritional or infectious complications (Fig. 159-3)

Follow-up: Monitor and Evaluate

- Evaluate patient for mechanical, metabolic, and infectious complications (Fig. 159-3)
- Re-evaluate clinical condition(s) preventing adequate oral intake or precluding use of enteral tube feeding to anticipate either transition off of PN support or need for continuing PN therapy (Fig. 159-3)

**Collaborate with patient, caregivers, and other healthcare professionals.*

Electrolyte composition of standard CAA solutions varies from small, obligatory amounts to the provision of maintenance requirements of most electrolytes for an adult. Electrolytes provided by CAA solutions must be considered when determining a patient's individual requirements. CAAs are available in several different concentrations, which facilitate compounding of patient-specific PN regimens. Use of highly concentrated products (15%-20% amino acids) is attractive for critically ill patients who typically require fluid restriction but have large protein needs. Modified amino acid solutions are designed for patients who have altered protein requirements, such as those with hepatic encephalopathy, kidney disease, and metabolic stress or trauma, as well as for neonates and pediatric patients (see Table 159-3). These solutions tend to

be more expensive than standard CAA solutions. The rationale for and clinical efficacy of modified amino acids in disease-specific PN regimens is also controversial because of inconsistency in clinical outcomes reported in multiple clinical trials.[12,15,17,18,22]

Several commercially available CAA solutions are designed to provide conditionally essential amino acids, which are considered nonessential during health because they are produced from other amino acids. However, under certain physiologic conditions, such as prematurity or sepsis, these amino acids cannot be synthesized in sufficient quantities.[20,22] CAA solutions specifically designed for neonates and pediatric patients contain increased amounts of taurine, aspartic acid, and glutamic acid. Other conditionally essential amino acids, such as cysteine, carnitine, and glutamine, are not available in commercial CAA solutions in pharmacologic amounts because they are relatively unstable or poorly soluble.[20,22]

Consequently, PN solutions may need to be modified to provide the desired amount of supplemental conditionally essential amino acids. For example, cysteine is a conditionally essential amino acid for preterm and term infants because of their enzymatic immaturity of the trans-sulfuration pathway. Cysteine may be added to PN solutions at the time of compounding as a supplement to CAA solutions and to enhance calcium and phosphate solubility by decreasing solution pH.[23] Carnitine is a quaternary amine required for long-chain fatty acid transport into the mitochondria for β-oxidation and energy production. Newborns are at risk for carnitine deficiency because of their immature biosynthetic capacity. Decreased plasma carnitine concentrations have been reported in infants and children receiving PN without carnitine.[16] Supplemental carnitine may be added to the PN solution at the time of compounding. Although the benefit of carnitine supplementation in PN has not been clearly identified, positive effects on nutritional markers, including improved fatty acid oxidation, weight gain, and nitrogen balance, have been documented. In general, carnitine supplementation is reserved for neonates expected to receive PN support for 7 days or longer.[16]

Glutamine is the most abundant free amino acid in the body and is an important intermediate for many metabolic processes. Glutamine is reported to have an important role in maintaining intestinal integrity, immune function, and protein synthesis during conditions of metabolic stress[24] Investigations in humans and animals have reported positive effects on nutritional markers such as nitrogen balance, but others have reported significant improvement in other outcome markers, such as decreased length of hospitalization, incidence of

infections, and GI toxicities associated with chemotherapy or radiation.[24] Unfortunately, the best candidate for response to glutamine therapy has not been clearly identified.[22,24] Use of both intravenous and enteral glutamine in combination with a variety of antioxidant supplements in critically ill adult patients has been associated with increased mortality.[25] Although an association between increased brain volume and head circumference has been reported in school-aged children, who were premature at birth and received glutamine during the first year of life, the clinical usefulness of glutamine in neonates and infants is not clear.[24,26,27] Plasma glutamine concentrations increase with supplementation, but no beneficial effect on sepsis incidence or outcome, enteral feeding tolerance, necrotizing enterocolitis, growth, or mortality has been reported.[24,27,28] The clinical use of glutamine is further complicated because there is no parenteral glutamine formulation commercially available in the United States. Currently available CAA solutions do not contain glutamine because of poor solubility and instability. Use of parenteral glutamine requires special manufacturing techniques not readily available in many institutional pharmacies.[24] However, parenteral glutamine has been made available from several licensed pharmacies that extemporaneously compound glutamine crystalline powder under sterile conditions either as a separate parenteral solution or as a part of a CAA solution.

Recent Food and Drug Administration (FDA) mandated changes in conditions under which a human drug product that has no applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph or is not a component of an FDA-approved drug can be used to compound a prescription medication may create further obstacles to obtaining extemporaneously compounded glutamine-containing PN formulations in the future. The FDA's Pharmacy Compounding Advisory Committee, which provides advice on scientific, technical, and medical issues concerning drug compounding, has recommended to not allow the use of alanyl-L-glutamine in compounding due to insufficient information to fully assess safety related to impurities of the product.[29] However, the FDA issued the Interim Policy on Compounding Drugs Using Bulk Drug Substances in order to avoid unnecessary disruption to patient treatment while alanyl-L-glutamine and multiple other substances are undergoing evaluation for inclusion on the list of bulk drug substances that can be used to compound drug products.[29]

Dextrose

The primary energy source in PN solutions is carbohydrate, usually in the form of dextrose monohydrate, hereafter referred to as dextrose which is available in concentrations ranging from 5% to 70%. When oxidized, each gram of dextrose provides 3.4 kcal (14.2 kJ). The appropriate IV dextrose dose depends on the patient's age, estimated caloric requirements, and clinical condition. For example, minimum dextrose requirements for neonates are estimated to be approximately 6 to 8 mg/kg/min and infusion rates should not exceed 14 to 18 mg/kg/min for infants or 4 to 7 mg/kg/min for adults.[16,31,32] The recommended dextrose dose for routine clinical care rarely exceeds 5 mg/kg/min for adolescents and adults.[16,31,32] Maintaining an age-appropriate dextrose infusion rate is necessary to minimize risk of adverse effects. If the dextrose infusion rate exceeds the glucose oxidation rate, metabolically expensive pathways, such as glycogen repletion and lipid synthesis, are favored, resulting in increased energy expenditure, increased oxygen consumption, and increased carbon dioxide production. Excessive dextrose infusion rates also may contribute to the development of hyperglycemia and an increase in the concentration of biochemical markers indicative of fatty infiltration of the liver.[30,32]

Carbohydrate sources that are not insulin-dependent have been investigated as an alternative to dextrose to improve glycemic control for patients with impaired insulin secretion or activity who require PN. Glycerol, a sugar alcohol that provides 4.3 kcal/g (18 kJ/g), is the only dextrose alternative commercially available. It is available as an isotonic, 3% solution in combination with 3% amino acids and supplemental electrolytes (ProcalAmine, B. Braun Medical, Irvine, CA). Although the solution may be peripherally infused, a major disadvantage of this product is the dilute amino acid and carbohydrate concentrations. Most adult patients require up to 3 to 4 L/day of ProcalAmine solution together with intravenous lipid emulsion as a caloric source to meet minimum energy requirements.[33] IV glycerol use for catabolic adults is safe and effective, but similar data are not available for infants and children.[34]

Intravenous Lipid Emulsion

Intravenous lipid emulsion (IVLE) is used as a concentrated source of calories and essential fatty acids.[35–38] Commercially available IVLE products have traditionally contained soybean oil (SO) or a combination of SO and safflower oil. However, IVLE products containing safflower oil are no longer commercially available. SO-based IVLE may have negative effects on immune function and hepatic function, and this has led to approval of an alternative

mixed-oil IVLE for clinical use.[39] These products contain combinations of SO and olive oil, as well as SO, olive oil, medium chain triglyceride oil (MCT), and fish oil (FO), collectively known as SMOF.[36,37] An additional IVLE alternative containing 100% FO is also approved for clinical use (Table 159-3).[38]

As a caloric source, IVLE use may facilitate provision of adequate calories and minimize complications of nutrition therapy such as hyperglycemia, hepatotoxicity, or increased carbon dioxide production.[39] In the past, SO-based IVLE has been used for treatment or prevention of essential fatty acid deficiency (EFAD) in both adult and pediatric patients because of the higher linoleic and linolenic FA composition.[39] EFAD is the result of a biochemical deficiency of linoleic acid and arachidonic acid, which are considered essential for humans.[31,39] Linoleic acid, an omega-3 FA, and linolenic acid, an omega-6 FA, are important for a variety of functions such as cellular integrity, platelet function, postnatal brain development, and wound healing.[40] Both are polyunsaturated long chain triglycerides (LCT). Normally, linoleic acid is converted to the tetraene arachidonic acid. When linoleic acid is not present in sufficient amounts, oleic acid is converted to the tetraene 5,8,11-eicosatrienoic acid, a FA of lesser physiologic integrity, and as a result, EFAD develops. EFAD may be prevented by providing 2% to 4% of total calories as linoleic acid and 0.25% to 0.5% of total calories as linolenic acid. This may be achieved for most adult patients by giving approximately 100 g SO IVLE weekly.[31] However, larger amounts of mixed-oil IVLE may be necessary in adults with higher requirements. Neonates and infants require a minimum of 0.5 to 1 g/kg SO IVLE daily.[16] The SO-olive oil and SMOF products are not approved for use in pediatric patients because of their lower linoleic and linolenic acid content and inadequate provision of essential fatty acids to prevent or treat EFAD when used in recommended doses.[36,37] In general, the 100% FO product is not indicated for treating EFAD because of the relatively lower essential FA content.[39] This product is indicated for use in pediatric patients with PN-associated cholestasis.[38] However, EFAD prevention has been reported in PN-dependent infants who received FO IVLE as the sole source of fat calories for at least 1 month.[41]

IVLEs with SO as the lipid source have negative effects on immune function as the result of omega-6 PUFA influence on proinflammatory eicosanoid production through arachidonic acid metabolic pathways.[39,40] Mixed-oil IVLE may promote lower production of proinflammatory cytokines by providing lower amounts of omega-6 FA. Olive oil–based IVLEs provide essential fatty

acids, are a rich source of vitamin E, and appear to have a neutral effect on immune function because of the decreased amount of omega-6 PUFA linoleic acid.[39] MCTs may offer several advantages, especially for critically ill patients. MCTs are hydrolyzed and cleared more rapidly than LCTs, and they do not accumulate in the liver. In addition, MCTs do not require carnitine for entrance into mitochondria for oxidation. However, MCTs are not a source of essential fatty acids. IV MCT-LCT mixtures demonstrate safety and efficacy comparable with standard LCT emulsions.[39] FO-based IVLE contain predominantly omega-3 PUFAs, which are metabolized to cytokine mediators that may be less inflammatory and immunosuppressive than those derived from omega-6 PUFAs. The clinical effect of FO-containing IVLE administration on immune function, as well as on patient morbidity and mortality, is not clear.[39,42]

Phytosterols are sterols that are a natural component of plant-based oils used in IVLE formulations.[43] Animal and human studies have associated SO-based IVLE and phytosterol intake with cholestasis of PN-associated liver disease (PNALD). SO-based IVLE have a higher phytosterol content relative to the other mixed-oil IVLE products.[43] Recent investigations of mixed-oil or 100% FO IVLE in PN-dependent patients who developed cholestasis while receiving SO-based IVLE have reported improvement in or reversal of PNALD.[43]

Commercially available products are reviewed in Table 159-3. All commercially available IVLE formulations contain egg phospholipids as an emulsifying agent and glycerol to make the emulsion isotonic. Although the caloric contribution of fat is 9 kcal/g (38 kJ/g), the caloric content of 10% IVLE is 1.1 kcal/mL (4.6 kJ/mL), 2 kcal/mL (8.4 kJ/mL) for the 20% emulsion, and 3 kcal/mL (12.6 kJ/mL) for the 30% emulsion because of the caloric contribution of the egg phospholipid and glycerol. The concentrated SO IVLEs (20% and 30%) have a lower phospholipid-to-triglyceride ratio compared with 10% SO IVLE.[16] Because higher amounts of circulating phospholipids are associated with impaired triglyceride clearance in neonates and infants, 20% SO IVLE is the preferred product for this population.

Commercially available IVLE products may be administered by either the central or the peripheral route. They may be added directly to the PN solution as a total nutrient admixture (TNA), also referred to as a three-in-one system (lipids, protein, glucose, and additives), or they may be co-infused with the CAA-dextrose solution, commonly referred to as a two-in-one admixture.[5,35–38,44] However, 30% IVLEs are only approved for use in the preparation of TNA and are not intended for direct IV administration.

Plasma IVLE clearance is directly related to gestational age of infants and

appears to be influenced by the infusion rate and the patient's clinical status.[16] Rapid SO-IVLE infusions are reported to contribute to decreased oxygenation for neonates.[45] Adverse pulmonary effects are thought to be caused by polyunsaturated fatty acid (PUFA)–driven prostaglandin production, which results in altered vascular tone. Although the association between IVLE and pulmonary dysfunction is not clear, a boxed warning appears in the FDA product labeling for both SO, SO-olive oil and SMOF IVLE that acknowledges deaths in preterm infants associated with pulmonary fat accumulation thought to be related to IVLE infusions.[35–37] In addition, rapid infusion of long-chain fatty acid formulations may have a negative impact on immunocompetence by saturating the reticuloendothelial system.[31,46]

Although the frequency of acute adverse effects is reported to be less than 1% with current formulations, patients receiving their first IVLE dose should be monitored for dyspnea, chest tightness, palpitations, and chills. Headache, nausea, and fever also have been reported and might be associated with a rapid infusion rate. In general, IVLE use is contraindicated for patients with an impaired ability to clear fat emulsion, such as patients with pathologic hyperlipidemia, lipoid nephrosis, and hypertriglyceridemia associated with pancreatitis.[35–38] Patients should be evaluated for hypersensitivity to any of the product-dependent ingredients such as fish, egg, soybean, or peanut protein prior to initiating IVLE.[35–38]

Although IVLE products remain the most common source of parenteral fat, a number of drugs have been introduced that contain lipid either as a vehicle for delivery or as a portion of the drug formulation. Propofol, an IV anesthetic, is delivered in a soybean-oil-in-water emulsion that has essentially the same composition and caloric concentration as 10% SO-IVLE. This agent is used commonly for continuous sedation of mechanically ventilated patients and should be considered a potentially significant source of calories that may require adjustment of a patient's nutrition regimen.[31,47] Clevidipine is an injectable calcium channel blocker that contains 20% IVLE as a vehicle that may be a potentially clinically significant source of IV fat when used as a continuous infusion for multiple days of therapy.[48] The antifungal amphotericin B is available in several lipid-containing combinations such as liposomal and lipid complex formulations. The caloric contribution from these products when used in standard doses generally is small and is not clinically relevant.

Vitamins

The Nutrition Advisory Group of the American Medical Association (NAG-AMA) recommended in 1975 the daily parenteral supplementation of 13 essential (four fat-soluble and nine water-soluble) vitamins for pediatric and adult patients based on requirements for healthy people.[49]

Since these original recommendations, the NAG-AMA has revised the guidelines for children to primarily reflect changes for preterm infants requiring PN.[49] The FDA also mandated in 2000 changes in adult parenteral vitamin formulations (inclusion of vitamin K and higher doses of vitamins B_1, B_6, and C).[49] Vitamin K was not included in early multivitamin formulations due to the potential for drug-nutrient interactions in patients receiving anticoagulants. Although the NAG-AMA recommendation for vitamin K for adults is 2 to 4 mg weekly, only 150 mcg/day was mandated to be included in newer formulations by the FDA.[50] However, an investigation of adult patients receiving long-term SO-IVLE-containing PN with vitamin K–free parenteral multivitamins at home suggested that supplemental vitamin K may not be necessary to maintain normal prothrombin times and plasma vitamin K concentrations.[51] Indeed, SO used in IVLEs is a natural source of phylloquinone (vitamin K_1). However, the other commercially available mixed-oil IVLE formulations contain phylloquinone as well.[52] SO-IVLE formulations contain the highest amount of vitamin K and the concentration is generally dependent on the SO concentration in the IVLE.[50–52] Although current vitamin K-containing multiple-vitamin products should provide sufficient amounts to prevent adverse effects associated with vitamin K deficiency, supplemental vitamin K may be given intramuscularly or subcutaneously or added to the PN solution if needed.[50]

The 2012 A.S.P.E.N. recommendations advocate for the continued availability of multivitamin products with and without vitamin K so that clinicians have the ability to withhold vitamin K supplementation in patients receiving warfarin therapy. Most adult parenteral multiple-vitamin products which are available commercially contain vitamin K. MVI-12, multivitamin infusion without vitamin K is available from Hospira, Inc. Lake Forest, IL. Two parenteral multiple-vitamin products are commercially available for use for pediatric patients. MVI-Pediatric (Hospira Inc.) and Infuvite Pediatric (Baxter Healthcare Corporation) are formulated to meet the revised NAG-AMA guidelines for infants weighing less than 1 kg (2.2 lb) and children up to 11 years. However, there are no commercially available injectable multivitamin products designed to specifically meet the unique requirements of premature infants, including higher vitamin A and lower doses of vitamins B_1, B_2, B_6, and

B_{12}.

Vitamin requirements may be altered in malnutrition and other specific disease states or with certain drug therapies. Individual and combination products are available to provide additional or tailored supplementation, which may be necessary to prevent development of vitamin toxicities or deficiencies caused by altered metabolism or drug therapy.

The 2012 A.S.P.E.N. recommendations question whether the vitamin D content of parenteral multivitamins is adequate to meet current Recommended Dietary Allowances (RDA) and advocate for the addition of a parenteral vitamin D product for PN-dependent patients who are unresponsive to additional enteral vitamin D supplementation.[49] In addition, the recommendations support the continued production of adult injectable multivitamin products with and without vitamin K and for the supplementation of carnitine (2-5 mg/kg/day) in neonatal PN and choline in all patients receiving PN.[49]

Trace Elements

Many trace elements are an important part of metalloenzymes and function as cofactors in a variety of regulatory metabolic pathways.[53] Although 17 trace elements have demonstrated biologic importance, clear deficiency syndromes in humans have been described only for cobalt (as vitamin B_{12}), copper, iodine, iron, and zinc.[53–55] In 1979, the NAG-AMA recommended chromium, copper, manganese, and zinc supplementation for patients receiving PN.[49,53] Recommendations followed in 1984 to also supplement with selenium.[49,53] Although a clear deficiency syndrome for manganese has not been reported in humans, the NAG-AMA considered manganese essential based on case reports of patients receiving PN with metabolic complications that corrected after manganese supplementation. Reports of deficiency syndromes associated with selenium and molybdenum suggest that they also may be essential.[49,53,54] Although iodine deficiency has not been reported for patients receiving short-term PN, it has been observed in patients receiving long-term PN and may be related to the use of chlorhexidine for central-line care instead of povidone–iodine.[49,53,55]

Injectable trace elements are available as single-trace element solutions and as multiple-trace element combinations. The use of single-entity injectable products allows for individualization of trace mineral supplementation of chromium, copper, iodine, manganese, selenium, and zinc. Most combination

products for adults provide the daily requirements for the trace elements considered essential by the NAG-AMA (ie, chromium, copper, manganese, selenium, and zinc).[16] Combination products approved for use in the United States for neonates and pediatric patients contain only chromium, copper, manganese, and zinc; the addition of single-entity selenium is necessary to provide requirements considered essential by the NAG-AMA.[16]

Requirements for trace elements also vary on the basis of the patient's clinical condition. For example, higher doses of supplemental zinc likely are necessary for patients with high-output ostomies or diarrhea because the GI tract is the predominant excretion route for zinc. Whereas manganese and copper are excreted through the biliary tract, chromium, molybdenum, and selenium are excreted renally. Hence, these trace elements should be restricted or withheld from PN solutions for patients with cholestatic liver disease and kidney disease, respectively.

A.S.P.E.N. recommended formulation changes to the available injectable multiple-trace element preparations for PN patients.[49] The recommendations support overall decreased contamination of trace elements in large- and small-volume PN products.[49] The recommendations advocate for decreased copper and manganese, no (or decreased) chromium, and inclusion and increased dose of selenium in all injectable adult multiple-trace products.[49] The recommendations also support products with no chromium, decreased manganese, and the inclusion of selenium in all injectable pediatric multiple-trace products.[49]

Electrolytes

Electrolytes such as sodium, potassium, calcium, magnesium, phosphorus, chloride, and acetate are necessary PN components for the maintenance of many cellular functions. Electrolytes may be given to maintain normal serum concentrations or to correct deficits. Patients who have "normal" organ function and relatively normal serum concentrations of any electrolyte should receive "normal" maintenance electrolyte doses when PN is initiated and daily thereafter. Specific electrolyte requirements vary according to the patient's age, disease state, organ function, previous and current drug therapy, nutrition status, and extrarenal losses. Electrolytes are available commercially as single- and multiple-nutrient solutions. Multiple-electrolyte solutions are useful for stable patients with normal organ function who are receiving PN. Concentrated multiple-electrolyte solutions designed for addition to PN solutions generally contain only sodium, potassium, calcium, and magnesium. Phosphorus must be

added as a separate additive. Further information regarding metabolism and requirements of vitamins, trace elements, and electrolytes is given elsewhere.[56]

DESIGNING A PARENTERAL NUTRITION REGIMEN

5 Several factors, including the patient's venous access, fluid status, and macronutrient and micronutrient requirements, are important considerations when designing the PN regimen. A patient's venous access and fluid status determines the maximum PN osmolar concentration, which will impact the nutrient amount that may be provided. PN solutions may be administered by central or peripheral venous access. The patient's clinical condition determines which route is most appropriate.

Parenteral nutrition formulations may be provided as a two-in-one admixture that contains dextrose, CAA, and other necessary micronutrients or as a three-in-one admixture or TNA that contains dextrose, CAA, and IVLE, as well as other necessary micronutrients. Use of TNA solutions offers several potential advantages, including reduced inventory (infusion pumps, tubing, and other related supplies), decreased time for compounding and administration, a potential decrease in manipulations of the infusion line (which should correspond with a decreased risk of catheter contamination), and ease of delivery and storage for patients receiving home PN.[44] Potential disadvantages include increased risk of infections and stability and compatibility concerns. For example, the stability of TNA admixtures is less predictable than that of two-in-one admixtures, which makes their use less desirable in some patient populations such as neonates and infants.[44,57]

Routes of Parenteral Nutrition Administration

Peripheral Route

Peripheral parenteral nutrition (PPN) is an option for mild-to-moderately stressed patients in whom adequate GI tract function is expected to return within 10 to 14 days.[11] PPN may also be used as a temporary source of PN, or as a bridge therapy during transition periods where oral intake or EN is suboptimal or clinical circumstances do not justify placing a central venous catheter (CVC) access.[11] In general, potential PPN candidates should not be fluid-restricted or require large nutrient amounts. Lower concentrations of amino acids (3%-5%

final concentration), dextrose (5%-10% final concentration), and micronutrients compared with central parenteral nutrition (CPN) must be used for peripheral administration. Because PPN solutions are relatively dilute, larger volumes are usually necessary to provide nutrient requirements. Additionally, many patients who receive PPN likely will require IVLE to achieve the desired caloric intake at levels consistent with CPN regimens. The primary advantages of PPN include a potentially lower risk of infectious and technical complications associated with CVC access.[11] Patients who are likely to be poor candidates for PPN include those with poor venous access as the result of multiple courses of chemotherapy, malnutrition, illness of long duration that has required multiple venous accesses for fluid and medication administration, premature infants, and the elderly. PPN use is also limited by relatively poor peripheral vein tolerance to hypertonic solutions. Thrombophlebitis is a commonly reported complication for patients receiving PPN.[57] Although the risk of phlebitis is greater with solution osmolarities greater than 600 to 900 mOsm/L, peripherally administered TNA with much higher osmolarities to adults has been associated with low infusion-site complications in some centers.[57,58] Efforts to minimize development of phlebitis or infiltration sequelae for patients receiving PPN include addition of IVLE as a possible venous lumen protectant, subtherapeutic heparin doses (0.5-1 unit/mL) to prevent thrombus formation, or small doses of hydrocortisone (5 mg/L) to minimize access site inflammation.[57,58] However, the coinfusion of IVLE with PPN (ie, not provided as a TNA) has not been shown to reduce phlebitis. In addition, heparin has not been shown to reduce catheter-related thrombosis and is not compatible for use in TNAs.[57] Midline catheter use may offer some advantage and has been associated with a reduced risk of thrombophlebitis.[11,59] Although these catheters are not central venous access devices, they are longer and infuse into larger venous vessels that may dilute the PPN solution to a more tolerable osmolarity. The osmolarity of a PN solution may be estimated by using the guidelines for osmolarities of selected PN components in **Table 159-4**.

TABLE 159-4 Osmolarities of Selected Parenteral Nutrients

Nutrient	Osmolarity
Amino acid	100 mOsm/%
Dextrose	50 mOsm/%
Lipid emulsion (20%)	1.3-1.5 mOsm/g
Sodium (acetate, chloride)	2 mOsm/mEq
Sodium phosphate	3 mOsm/mEq sodium
Potassium (acetate, chloride)	2 mOsm/mEq
Potassium phosphate	1.7-2.7 mOsm/mEq potassium
Magnesium sulfate	1 mOsm/mEq
Calcium gluconate	1.4 mOsm/mEq

Central Route

CPN is the preferred route for PN delivery and is used predominantly for patients who require PN for periods of more than 7 to 14 days during hospitalization or indefinitely at home.[11,60] These patients may have large nutrient requirements; poor peripheral venous access; or fluctuating fluid requirements, such as metabolically stressed patients with extensive surgery, trauma, sepsis, multiple-organ failure, or malignancy. CPN solutions are highly concentrated hypertonic solutions that must be administered through a large central vein. Unlike peripheral veins, central veins have a higher blood flow, which quickly dilutes the hypertonic solutions. Disadvantages of CPN include risks associated with catheter insertion, routine catheter use, and care of the access site. Relative to peripheral venous access, CVC access is associated with a greater potential for infection. In addition, the risk of more serious catheter-induced trauma and related sequelae and other serious technical or mechanical problems is greater than that with peripheral access.

The choice of central venous access site depends on a number of factors, including the patient's age and anatomy. CVCs vary in composition, lumen size, number of injection ports, and other features that affect ease or convenience of care and maintenance. CVCs for short-term use for adults are commonly inserted percutaneously into the subclavian vein and advanced so that the tip is at the superior vena cava.[59] If this approach is not possible, the internal jugular vein can be used. Frequently, short-term central venous access is obtained for critically ill neonates via a catheter placed in the umbilical vein. Other sites for central venous access in infants and older children are similar to those in adults. When therapy is expected to last longer than 4 weeks, the catheter usually is

tunneled subcutaneously before entering the central vessel, secured initially with retaining sutures, and anchored in place with a felt cuff that promotes subcutaneous fibrotic tissue growth around the catheter. The injection port may remain external or may be concealed entirely beneath the skin. Implanted CVCs have a larger port or reservoir that is surgically placed beneath the skin surface and anchored in the chest wall muscle. Peripherally inserted central catheters (PICCs) are venous access devices that are inserted into a peripheral vein (basilic, cephalic, or brachial) and advanced so that the tip is at the superior vena cava.[59] PICCs are increasingly used for both short- and long-term central venous access in acute or home care settings because of ease and economy of bedside placement.[11,59]

Constructing a Parenteral Nutrition Regimen

After the route of delivery is chosen, the components of the PN regimen are determined based on the patient's nutritional assessment. Although not recommended due to increased potential for errors, some healthcare systems may require the entire PN order to be written in individual components and additives on traditional paper order forms without the use of a standard order form. Standardized electronic PN orders suitable for computerized prescriber order entry (CPOE) have been recommended for all patients to minimize risk of errors associated with the ordering process.[5,61] Standardized order forms or clinical decision support within electronic PN ordering systems promote education of practitioners by providing brief guidelines for initiating PN and foster cost-efficient nutrition support by minimizing errors in ordering, compounding, and administration.[5,57,60] Standardized order forms also may include options for ordering certain related procedures, laboratory tests, protocols for patient management, or consultations with other medical services related to the patient's nutrition support.

Adult Parenteral Nutrition Solutions

6 In general, there are two methods for ordering adult PN. The "standard formula approach" offers a variety of admixtures with a fixed nonprotein-calorie-to-nitrogen ratio. This method usually includes different formulas for mild-to-moderately stressed patients, and those who have kidney or liver failure or are fluid-restricted. Because the nonprotein-calorie-to-nitrogen ratio is fixed, the daily amount of nutrient delivered depends solely on the volume infused. Standard institutional PN formulations may be compounded; however,

standardized commercial PN products or “premixed” solutions are available from several manufacturers.[62] A standard institutional formula may promote clinician prescribing of a complete, balanced formulation and promote consistent provision of stable and compatible admixtures. However, efficiencies associated with use of the standard formula approach may be hindered if there is a frequent need to modify the PN formulation. Finally, standard PN formulations may be difficult to use in complicated patients, such as neonatal or pediatric patients, and those with severe malnutrition, organ failure, glucose intolerance, large GI losses, or critical illness.[62]

The “individualized formula approach” permits compounding of patient-specific admixtures. Compounding of the PN admixture is limited only by the concentrations of stock solutions and stability of the additives. The nutrient amount delivered depends on the daily volume of the PN solution infused and the nutrient amounts in the PN solution. The total daily amount of PN solution may be prepared in multiple bags or more cost-effectively in a single container.[44]

Traditionally, adult PN formulations have been ordered by expressing the final concentrations of each component in the solution. For example, CAA and dextrose are ordered commonly in final percentage, electrolytes in milliequivalents (or millimoles) per liter, and other additives in amount (milliliters or units) per day. This inconsistency may promote confusion and misinterpretation of PN admixture contents that may result in harm, especially when patients are transferred between health system environments. To ensure that PN labels in all health system environments clearly and accurately reflect the PN admixture contents, guidelines for standardized adult PN labeling have been recommended.[5,61] In addition to including a variety of other information on the label such as dosing weight and administration route, the guidelines recommend expressing PN ingredients in amounts per daily volume, which minimizes the need for pharmaceutical calculations to determine the nutrient value of the admixture. Commercially available computer software for calculating PN formulations include the recommended A.S.P.E.N. labeling guidelines (Baxter Healthcare, Deerfield, Il.; B. Braun Medical Inc., Bethlehem, PA).[5,61] Pharmaceutical calculations of an adult TNA PN regimen are briefly reviewed in **Fig. 159-1**.

Calculation of an Adult PN Regimen

Patient case: A patient's daily nutritional requirements have been estimated to be 105 g protein and 2,200 total kcal. The patient has central venous access and reports no history of diabetes, hyperlipidemia, or egg allergy. The patient is not fluid-restricted. The PN formulation will be compounded as an individualized regimen using a single-bag, 24-hour infusion of a TNA. Determine the total PN volume and administration rate by calculating the macronutrient solution volumes required to provide the desired daily nutrients. The PN products used for this regimen are 10% CAA, 70% dextrose, and 30% IVLE.

1. Determine the daily IVLE calories and volume.
   - 2,200 kcal/day × 30%–40% of total calories as fat = 660 – 880 kcal/day
   - Choose 660 kcal to minimize IVLE calories; calculate 30% IVLE volume

     660 kcal ÷ 3 cal/mL 30% IVLE = X mL X = 220 mL 30% IVLE

   - Calculate IVLE gram amount
     30 g/100 mL = X g/220 mL 30% IVLE X = 66 g IVLE

2. Determine the appropriate volume of 70% dextrose to deliver the desired dextrose calories

   - Dextrose calories = Total kcal – IVLE kcal – Protein kcal
     = 2,200 kcal – 660 kcal IVLE – (4 kcal × 105 g CAA) = 1,120 kcal

   - Calculate required dextrose (grams):

     1,120 kcal ÷ 3.4 kcal/g dextrose = 329 g dextrose

   - Determine 70% dextrose volume
     70 g/100 mL = 329 g/X mL 70% dextrose; X = 470 mL 70% dextrose

3. Determine the appropriate volume of 10% CAA
   10 g/100 mL = 105 g/X mL 10% CAA X = 1,050 mL 10% CAA

4. Determine the TNA PN volume and administration rate
   - Calculate CAA/dextrose/IVLE volume:
     470 mL 70% dextrose + 1,050 mL 10% CAA + 220 mL 30% IVLE = 1,740 mL
   - Add 100-200 mL for additives:
     Total TNA volume = approximately 1,840-1,940 mL/day
   - Calculate the administration rate:
     1,840 to 1,940 mL/day ÷ 24 h = 77 to 81 mL/h; round up to 80 to 85 mL/h

5. Choose final TNA regimen and determine final concentrations of CAA, dextrose, and IVLE
   - Final TNA regimen
     105 g CAA/329 g dextrose/66 g IVLE in 1,920 mL/d to infuse at 80 mL/h

   - Calculate final concentrations of CAA, dextrose, and IVLE

     - 105 g CAA/1,920 mL = X g/100 mL X = 5.5% CAA
     - 329 g dextrose/1,920 mL = X g/100 mL X = 17.1% dextrose
     - 66 g IVLE/1,920 mL = X g/100 mL X = 3.4% IVLE

FIGURE 159-1 Calculation of an adult PN regimen. To convert to energy units of kilojoules (kJ) multiply values with kilocalories as the numerator (kcal, kcal/mL, kcal/kg, kcal/g) by 4.18 to give the corresponding value in kilojoules (kJ, kJ/mL, kJ/kg, kJ/g). (CAA, crystalline amino acids; IVLE, intravenous lipid emulsion; PN, parenteral nutrition; TNA, total nutrient admixture.)

Several guidelines are available to help simplify calculation of a PN regimen after a patient's nutritional requirements have been decided. For example, adult patients receiving only PN therapy may need larger volumes of fluid to provide maintenance requirements and replace extrarenal losses. However, patients requiring other IV drug therapy may receive adequate fluid from an additional IV maintenance solution (eg, 0.45% NaCl in 5% dextrose) or co-infused medications (or both). Depending on individual institutional practices, maximally concentrating the PN admixture and using an inexpensive maintenance fluid to manage hydration may provide a cost-effective regimen that requires fewer adjustments. Another guideline that may be helpful in designing a PN regimen is to allow a volume of approximately 100 to 150 mL/L of base solution (approximately 200-300 mL/day) for electrolytes and other additives. PN regimens for patients who require very small amounts of additives, such as patients with kidney failure, may need further concentration.

Pediatric Parenteral Nutrition Solutions

Pediatric PN admixtures are typically ordered using an individualized approach because current safe clinical practice guidelines recommend nutrient intakes based on the patient's weight.[5] To simplify pediatric PN ordering, many institutions use a pediatric-specific PN order form that expresses daily nutrient amount based on weight. For example, protein and IVLE are ordered as grams per kilogram per day, dextrose as milligrams per kilogram per minute, and electrolytes as milliequivalents per kilogram per day. However, some institutions may order macronutrients by expressing the final concentration of each component in the solution. Current safe practice guidelines recommend ordering all PN ingredients based on weight as "amount per kilogram per day."[5] The PN bag label should accurately reflect the weight-based order as well. Calculations for determining a pediatric PN admixture are reviewed to illustrate fundamental concepts for ordering pediatric PN formulations (**Fig. 159-2**). Additional features of the pediatric PN label include the dosing weight, administration date and time, expiration date, infusion rate, and duration of infusion. Because infants and children generally receive daily maintenance fluid from the PN regimen,

supplemental IV solutions are rarely needed. Pediatric PN may be provided as a two-in-one admixture or TNA. However, the TNA system is not recommended for compounding neonatal and infant PN because of IVLE instability with the often-needed higher calcium and phosphorus concentrations.[41,57] The IVLE labeling guidelines for pediatric PN are similar to adult IVLE labeling recommendations.

Calculation of a Pediatric PN Regimen

The nutrition requirements for a 2-week-old preterm neonate (28 weeks gestation; weight 1.2 kg) have been estimated to be 3.5 g/kg/day protein, 3 g/kg/day IVLE, 100 nonprotein kcal/kg/day, and 150 mL/kg/day fluid. The neonate has central access and no prior history of hyperlipidemia or egg allergy. The PN regimen will be compounded as an individualized regimen using a single-bag, 24-hour infusion of a 2-in-1 solution with 20% IVLE co-infused into the PN infusion line. Determine the macronutrient calculations to deliver this neonate's nutrition goals; 10% pediatric CAA and 70% dextrose stock solutions will be used to compound the solution.

1. Determine the goal daily IVLE amount, volume, and administration rate
   - 3 g/kg/day IVLE × 1.2 kg = 3.6 g
   - Calculate 20% IVLE volume
     - 20 g/100 mL = 3.6 g/X mL
     - X = 18 mL/day of 20% IVLE (15 mL/kg/day)
   - Calculate the IVLE administration rate:
     - 18 mL 20% IVLE ÷ 24 hours = 0.75 mL/h (rate may need to be rounded up to 0.8 mL/h or down to 0.7 mL/h depending on precision capability of infusion pump)

2. Determine the goal 2-in-1 PN volume and administration rate
   - Total volume based on maintenance fluid requirements
     - 150 mL/kg/day (estimated fluid goal) – 15 mL/kg/day (20% IVLE) = 135 mL/kg/day for PN volume
     - 135 mL/kg/day × 1.2 kg = 162 mL/day
   - PN infusion rate is 162 mL/day ÷ 24 hours = 6.75 mL/h (rate may need to be rounded up to 6.8 mL/h or down to 6.7 mL/h depending on precision capability of infusion pump)

3. Determine the daily protein amount and the corresponding 10% CAA volume
   - Calculate the goal protein amount
     - 3.5 g/kg/day × 1.2 kg = 4.2 g/day
   - Calculate the 10% pediatric CAA stock solution volume
     - 10 g/100 mL = 4.2 g/X mL 10% pediatric CAA
     - X = 42 mL 10% pediatric CAA

4. Determine the daily dextrose amount, corresponding 70% dextrose volume, and final dextrose concentration in the 2-in-1 PN solution
   - Goal is to provide approximately 14 mg/kg/min dextrose
     - 14 mg x 1.2 kg × 1,440 minutes/day ÷ 1,000 mg/g = 24.2 g dextrose
   - Calculate the 70% dextrose volume
     - 70 g/100 mL = 24.2 g/X mL 70% dextrose
     - X = 34.6 mL 70% dextrose
   - Calculate the final dextrose concentration of the PN solution
     - 24.2 g dextrose/162 mL = X g/100 mL
     - X = 14.9% dextrose (round up to 15% dextrose final concentration)
     - 162 mL × 15% dextrose = 162 × 15 g/100 mL = 24.3 g dextrose

5. Determine the available volume for additives
   - 162 mL – 42 mL (10% pediatric CAA) – 34.6 mL (70% dextrose) = 85.4 mL
   - Depending on volume needed for additives, sterile water may be necessary to add to formulation to make final total volume of 162 mL

6. Determine the final PN regimen and provided nutrient amounts
   - Final PN regimen
     - 3.5 g/kg/day pediatric CAA and 15% dextrose to infuse at 6.75 mL/h
     - 3 g/kg/day (or 18 mL) 20% IVLE to infuse at 0.75 mL/h

   - Macronutrient calories

Dextrose:	24.3 g × 3.4 kcal/g	=	82.6 kcal
Protein:	4.2 g × 4 kcal/g	=	16.8 kcal
20% IVLE	18 mL × 2 kcal/mL	=	36 kcal
Total kcal (kcal/kg):			135.4 kcal (113 kcal/kg)
Nonprotein kcal (kcal/kg):			118.6 kcal (99 kcal/kg)

FIGURE 159-2 Calculation of a pediatric PN regimen. To convert to energy units of kilojoules, multiply values with kilocalories as the numerator (kcal, kcal/mL, kcal/kg, kcal/g) by 4.18 to give the corresponding value in kilojoules (kJ, kJ/mL, kJ/kg, kJ/g). (CAA, crystalline amino acids; IVLE, intravenous lipid emulsion.)

Administration Techniques

PN admixtures should be administered with an infusion pump. The IV administration line for CAA-dextrose solutions should include a 0.22-micron inline filter to remove particulate matter, air, and any microorganisms that may be present in the solution. IVLE's may be administered separately from the CAA-dextrose solution by co-infusion into the PN line. A port beyond the inline filter must be used because the average size of IVLE particles is approximately 0.5 microns.[5,57] However, co-infused IVLE should also be filtered with a 1.2-micron filter.[35–38,44] The FDA recommends use of a 1.2-micron filter with TNA solutions, which may be effective in preventing catheter occlusion caused by precipitates or lipid aggregates.[5,44] This filter size is also reported to remove *Candida albicans.*

INITIATING AND ADVANCING THE PARENTERAL NUTRITION INFUSION

Adult Parenteral Nutrition

The patient's nutrition status, current clinical status, history of glucose tolerance, and dextrose concentration in the formula will dictate the infusion rate at which the adult PN solution should be initiated. Stable patients with normal organ function and stable baseline serum glucose concentrations have demonstrated minimal effect on serum glucose concentrations when PN is abruptly initiated or discontinued.[5,63] However, another approach is to begin the PN infusion and increase the rate gradually over 12 to 24 hours to the desired rate. The infusion rate may likewise be reduced in a stepwise fashion, such as decreasing the rate by 50% for 1 hour before discontinuation.[5,63] This approach should prevent development of hyperglycemia and rebound hypoglycemia, respectively. Alternatively, the PN regimen may be initiated at the goal infusion rate but with a hypocaloric dextrose dose. The dextrose dose can be increased daily to the goal based on patient response. Tapered initiation and cessation should be considered

for patients receiving intermittent subcutaneous regular insulin; patients with severe kidney or liver disease; and patients with other disease states that have an increased risk for development of hyperglycemia or hypoglycemia, such as severe diabetes or pancreatic malignancy.

The SO-IVLE dose should not exceed 2.5 g/kg/day or 60% of total daily calories, lower doses of 1 g/kg/day not to exceed 30% of calories have been recommended to minimize negative effects associated with long-chain fatty acids.[12,35,39] Higher doses of mixed-oil IVLE up to 2.5 g/day may be necessary to prevent EFAD in patients with larger energy requirements. Manufacturer's dosing and administration recommendations differ depending on the product.[35–38] However, co-infusion over 12 hours as a separate infusion with 2-in-1 admixtures and infusion over no longer than 24 hours in a TNA formulation appears to be the best clinical strategy to promote IVLE clearance and minimize risk of negative effects on infection control and pulmonary and immune function.[5]

The manufacturer's guidelines recommend initiating SO-IVLE, SO-olive oil IVLE and SMOF IVLE with a test dose of 0.5 to 1 mL/min for the first 15 to 30 minutes because of the potential for an immediate hypersensitivity reaction.[35,37] For most adult patients, this is probably not necessary because of the relatively low incidence and benign nature of acute adverse reactions. In addition, infusion over 12 to 24 hours eliminates the need for a test dose because the infusion rate is within the range of the recommended test dose rates. Appropriate electrolytes should be provided to patients with normal organ function based on standard nutrient ranges adjustments may be necessary depending on the patient's clinical condition. Adults and children older than 11 years should receive daily amounts of trace elements and an adult vitamin formulation.

Pediatric Parenteral Nutrition

Pediatric PN solutions are typically initiated with a volume calculated to provide the patient's daily maintenance fluid requirements on the first day of therapy. Individual nutrient substrates are then advanced daily as tolerated with the goal PN regimen generally being achieved by day 3 of therapy. However, the PN formulation should be initiated with the goal of achieving the desired protein dose on day one. The initial dextrose dose for older infants and children is based on their previous glucose tolerance. Although practices may vary, one approach is to start with 10% dextrose and advance the concentration in 5% increments daily, as tolerated, to goals of 10 to 14 mg/kg/min in infants, 8 to 10 mg/kg/min

in children, or 5 to 6 mg/kg/min in adolescents.[16] Initial dextrose doses for premature infants should approximate fetal nutrient delivery rates of 5 to 6 mg/kg/min. Frequently, this results in a final PN dextrose concentration of 5% to 10%. The dextrose concentration for the neonatal PN should be advanced daily by 1% to 2.5% or by 2 to 4 mg/kg/min increments to a goal of 10 to 14 mg/kg/min (maximum, 14-18 mg/kg/min).[16] SO-IVLE is usually initiated at 0.5 g/kg/day for neonates and 0.5 to 1 g/kg/day for infants and children and increased daily by 0.5 to 1 g/kg/day. Incremental increases of SO-IVLE dose allow daily serum triglyceride evaluation and early detection of those with impaired fat clearance. The SO-IVLE dose should not exceed 60% of total daily calories for neonates and 30% of total calories for children, and the maximum SO-IVLE dose should not exceed 3 g/kg/day (approximately 30 kcal/kg/day [126 kJ/kg/day]) for infants and 2.5 g/kg/day for children.[16] The maximum dose for FO-IVLE is 1 g/kg/day.[38] The best clinical strategy for minimizing the risk of adverse effects associated with SO-IVLE administration and promoting IVLE clearance is to infuse SO-IVLE over 20 to 24 hours, not exceeding 1 g/kg in 4 hours. FO-IVLE may be infused over 8 to 12 hours.[38]

IV electrolytes, vitamins, and trace elements should be initiated on the first day of therapy and continued as a daily component of the PN solution.[5,16] Children younger than 11 years should receive a vitamin product formulated for pediatric patients. Two multivitamin dosing schemas have been suggested for infants and children.[16] One method recommends 2 mL/kg/day for infants weighing less than 2.5 kg (less than 5.5 lb) and 5 mL/day for infants and children weighing 2.5 kg (5.5 lb) or greater. The other suggests 30% of a vial (1.5 mL/day) for infants weighing less than 1 kg (less than 2.2 lb), 65% of a vial (3.25 mL/day) for infants weighing 1 to 3 kg (2.2-6.6 lb), and 100% of the vial (5 mL/day) for children weighing more than 3 kg (6.6 lb) (up to 11 years of age). Adult injectable vitamin products should not be used for infants because of potential neurotoxicity from accumulation of polysorbate and propylene glycol preservatives. Weight-based dosage recommendations for pediatric multiple trace element products are 0.3 mL/kg for children weighing less than 3 kg (less than 6.6 lb) and 0.2 mL/kg for children weighing 3 kg (6.6 lb) or greater (maximum, 5 mL/day). Children weighing more than 25 kg (55 lb) should receive an adult trace element product. Weight-based doses of the multiple trace element products do not provide the recommended daily intake for all trace elements, so additional supplementation or individual dosing with single-entity products may be necessary. Individualized dosing allows for dose adjustment based on serum trace element assessment, individual patient characteristics (eg,

cholestasis, stool losses, wounds), and the need to minimize administration of trace elements that accumulate in patients receiving chronic PN such as chromium and manganese. Pediatric patients receiving PN commonly transition from PN support to enteral nutrition gradually, over a period of days to weeks, by decreasing the PN infusion rate while increasing the enteral intake. The PN infusion rate should be reduced for 1 to 2 hours before stopping the infusion for neonates and infants because of their immature counter-regulatory mechanisms that contribute to an increased risk for developing rebound hypoglycemia.[5] Blood glucose concentrations should be measured within 15 to 60 minutes after the PN infusion ends.

Continuous versus Cyclic Infusions

7 Continuous infusions are attractive for patients with unstable fluid balance or glucose homeostasis. The intermittent or cyclic infusion of PN over less than 24 hours, usually for 12 to 18 hours each day, is useful for hospitalized patients with limited venous access in whom administration of multiple other medications requires interruption of the PN infusion.[63] Cyclic PN also may minimize the incidence or reverse the liver injury associated with continuous PN therapy. In addition, this delivery mode allows patients receiving PN at home the ability to resume a relatively normal lifestyle.[16,60,63] Various protocols have been reported that suggest incremental increases to the maximum infusion rate for a desired period of time followed by a gradual taper to discontinue the solution.[63] However, metabolically stable adults and children older than 2 years receiving IVLE–based PN regimens are likely candidates for abrupt initiation and discontinuation of their intermittent PN regimen.[5,63,64] Cyclic PN should be used with caution for those with severe glucose intolerance, diabetes, or unstable fluid balance.

EVALUATION OF THERAPEUTIC OUTCOMES

8 Thorough and consistent monitoring of patients who are receiving PN is necessary to ensure that the desired nutritional outcomes are achieved and to prevent the occurrence of adverse effects or complications. Routine evaluation should include the assessment of the patient's clinical condition with a focus on nutritional and metabolic effects of the PN regimen. Serial documentation of a patient's response to their PN regimen is a helpful guide for determining appropriate adjustments in fluid, electrolyte, and nutrient therapies.

Serum concentrations of electrolytes, hematologic indices, and biochemical markers for kidney and liver function, and nutrition status should be measured before PN initiation and periodically thereafter depending on the patient's age, nutrition status, and clinical condition. The frequency of blood laboratory measurements for neonates and infants tends to be more conservative because of their smaller blood volumes and, in some cases, lack of central vascular access. Other important clinical measurements include vital signs, weight, total fluid intake and output, and nutritional intakes. Weekly measurements of height, length, and head circumference are helpful for monitoring nutritional changes in neonates. Monitoring parameters considered important for patients receiving PN and the suggested frequency of measurement for each are outlined in **Fig. 159-3**. Appropriate assessment and evaluation of patient data can identify potential complications that may be avoided or treated early. Monitoring protocols should be developed and tailored for the patient population, medical practices, and resources of individual practice settings.

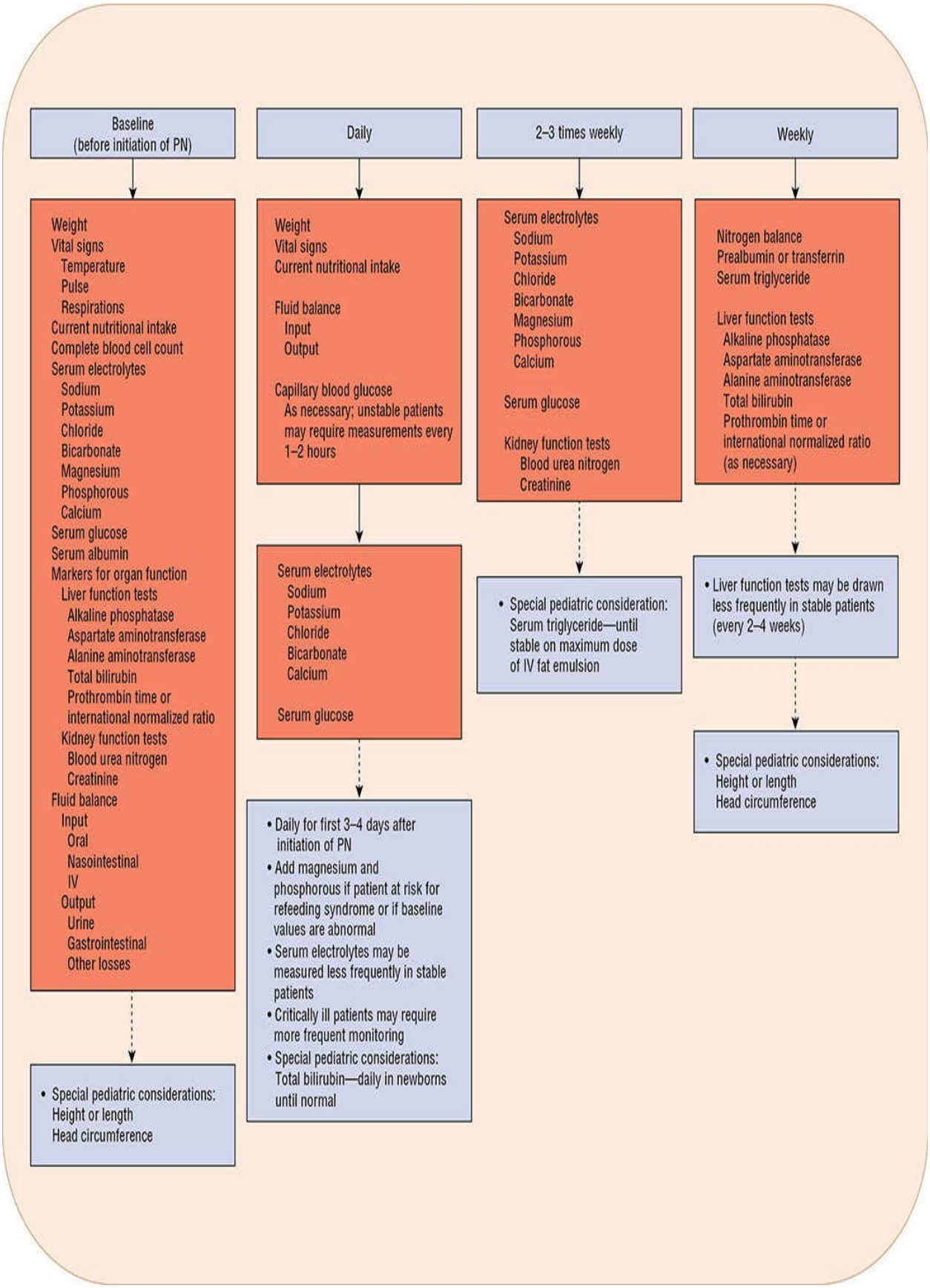

Baseline
(before initiation of PN)
Weight
Vital signs
Temperature
Pulse
Respirations
Current nutritional intake
Complete blood cell count
Serum electrolytes
Sodium
Potassium
Chloride
Bicarbonate
Magnesium
Phosphorous
Calcium
Serum glucose
Serum albumin
Markers for organ function
Liver function tests
Alkaline phosphatase
Aspartate aminotransferase
Alanine aminotransferase
Total bilirubin
Prothrombin time or international normalized ratio
Kidney function tests
Blood urea nitrogen
Creatinine
Fluid balance
Input
Oral
Nasointestinal
IV
Output
Urine
Gastrointestinal
Other losses
• Special pediatric considerations:
Height or length
Head circumference
Daily
Weight
Vital signs
Current nutritional intake
Fluid balance
Input
Output
Capillary blood glucose
As necessary; unstable patients may require measurements every 1–2 hours
Serum electrolytes
Sodium
Potassium
Chloride
Bicarbonate
Calcium
Serum glucose
• Daily for first 3–4 days after initiation of PN
• Add magnesium and phosphorous if patient at risk for refeeding syndrome or if baseline values are abnormal
• Serum electrolytes may be measured less frequently in stable patients
• Critically ill patients may require more frequent monitoring
• Special pediatric considerations:
Total bilirubin—daily in newborns until normal
2–3 times weekly
Serum electrolytes
Sodium
Potassium
Chloride
Bicarbonate
Magnesium
Phosphorous
Calcium
Serum glucose
Kidney function tests
Blood urea nitrogen
Creatinine
• Special pediatric consideration:
Serum triglyceride—until stable on maximum dose of IV fat emulsion
Weekly
Nitrogen balance
Prealbumin or transferrin
Serum triglyceride
Liver function tests
Alkaline phosphatase
Aspartate aminotransferase
Alanine aminotransferase
Total bilirubin
Prothrombin time or international normalized ratio (as necessary)
• Liver function tests may be drawn less frequently in stable patients (every 2–4 weeks)
• Special pediatric considerations:
Height or length
Head circumference

FIGURE 159-3 Monitoring strategy for patients receiving parenteral nutrition (PN).

COMPOUNDING, STORAGE, AND INFECTION CONTROL

The USP Chapter 797 details the procedures and requirements for compounding sterile preparations, including PN admixtures.[65] These standards apply to all healthcare settings in which sterile preparations are compounded and are used by boards of pharmacy, the FDA, and accreditation organizations such as The Joint Commission. Compounded sterile preparations (CSP) are defined by risk level (immediate use, low, low with 12-hour beyond-use date, medium and high) based on the probability of microbial, chemical, or physical contamination. PN solutions are classified as a medium-risk CSP. In general, PN solutions should be prepared using aseptic technique in a device or room that meets International Organization for Standardization (ISO) class 5 standards that is located in an ISO class 7 buffer area with an ISO class 8 ante area.[65] Preparation of PN formulations should be supervised by a pharmacist experienced in compounding IV solutions and knowledgeable about the stability, compatibility, and storage of PN admixtures. Quality assurance procedures should be developed to maintain safe and accurate admixture preparation. A standardized process for PN ordering, labeling, determining nutrient requirements, screening of the PN order, PN administration, and monitoring has been recommended to minimize risk of potentially life-threatening compounding errors.[5,62] The potential risk of infectious complications associated with PN solution contamination can be decreased greatly when pharmacy-based admixture programs follow specific guidelines developed to ensure proper compounding of PN solutions.[5,65] USP Chapter 797 is currently in the process of revision.[66] However, the published version of the chapter which became official on June 1, 2008 is currently official and enforcable.[66]

In general, the type of solution being prepared dictates the compounding, storage, and infusion methods. Currently, the two most commonly used types of PN solutions are two-in-one admixtures with or without IVLE co-infused into the PN line and TNAs. Methods for compounding PN admixtures vary based on a healthcare system's patient population and medical practices and the number of PN admixtures that need to be prepared. PN base admixtures may be prepared by using gravity-driven transfer of CAA stock solutions to partially filled bags of

concentrated dextrose stock solutions.[5,67] Other practice settings may use standardized commercial PN products with CAA and dextrose, and more recently, IVLE separated within a single bag that must be mixed before use.[5,44,62] Advances in compounding technology have facilitated the use of ACDs for preparing PN solutions. These devices are computer-based systems that perform the calculations necessary to determine volumes of nutrient-stock solutions for PN admixtures. In addition, most ACD systems include software that communicates the determined calculations directly to a transfer pump device that delivers fluid from the source container to the final container by either a volumetric or gravimetric fluid pumping system.[5,67] Advantages of ACDs include reduced personnel time and compounding materials and improved compounding accuracy. Disadvantages include the potential for equipment failure. Because of their acidic pH and hypertonicity, two-in-one PN admixtures are poor media for microbial growth.[5,44] However, several characteristics of IVLE, such as isoosmotic tonicity, near neutral to alkaline pH, glycerol content, and preservative-free formulations favor microbial growth, particularly at room temperature.[57] Other factors contributing to the potential for compromised IVLE stability or sterility include the container material, length of IVLE co-infusion with PN, length of time between administration set change, effect of infusion from the source container such as the original container, and infusion of IVLE transferred to a secondary container. When IVLEs are added to dextrose-CAA solutions to make TNAs, the growth potential is decreased, presumably because of the protective effects of the hypertonic dextrose-CAA solution and decreased pH.[44,57]

Because of the risk for microbial contamination, manufacturers recommend storage of PN solutions for as little time as possible after preparation. The USP 797 standards recommend storage times of not more than 30 hours at controlled room temperature (20°C-25°C [68°F-77°F]) and not more than 9 days at refrigerated temperatures (2°C-8°C [36°F-46°F]) for all medium-risk compounded CSPs, including PN admixtures.[65]

When co-infusing IVLE with PN (ie, not as a TNA), the appropriate IVLE dosage form (original packaging or re-packaged doses) and administration time to minimize risk of contamination is controversial. Unfortunately, the Centers for Disease Control and Prevention (CDC) guidelines offer no guidance for administration times.[59] Instead, the guidelines recommend administration tubing replacement every 24 hours for both IVLE infused separately or when given as part of a TNA. The guidelines also recommend administration tubing replacement no more frequently than at 96-hour intervals but at least every 7

days for tubing used continuously for infusion of IV solutions other than blood, blood products, or IVLE. More conservative recommendations have been presented.[5,57] The A.S.P.E.N. 2013 PN Safety Consensus suggests a 24-hour infusion time and administration tubing replacement every 24 hours for TNAs and 2-in-1 PN formulations and a 12-hour infusion time and administration tubing replacement every 12 hours for IVLE co-infused separately.[5]

Compliance with A.S.P.E.N. recommendations in pediatric patients is problematic. For example, an infant receiving 3 g/kg/day IVLE at the recommended infusion rate of 0.15 g/kg/hr to promote lipid clearance and minimize metabolic complications would require at least a 20-hour infusion.[16,68] To accommodate prolonged IVLE infusions, many institutions routinely infuse IVLE separately over 24 hours and change administration tubing for the IVLE and PN solution with each new bag because the use of TNA formulations is not recommended in neonates and infants. In addition, since commercially available IVLE products are not manufactured in unit volumes suitable for safe use in neonates and infants, institutions commonly transfer IVLE from the original container into another container to accommodate the smaller patient-specific volume to decrease risk of adverse events from infusion-related errors. A variety of methods have been utilized for repackaging IVLE. Syringe repackaging and aseptic transfer into sterile bags with the use of an ACD are not recommended because of higher contamination rates. Other methodologies such as aseptic withdrawal of an appropriate IVLE volume resulting in a patient-specific dose in the original manufacturer's container (drawing-down) have been recommended as a potential option.[57,68] These multifactorial concerns with providing IVLE to pediatric patients have been addressed by the A.S.P.E.N. Safety Consensus Recommendations.[5] When prolonged IVLE infusions are required in neonates and infants, the daily dose should be divided in two separate 12-hour infusions. The IVLE container and administration tubing should be replaced every 12 hours.[5] When utilizing repackaged IVLE, the infusion time should not exceed 12 hours per unit and the administration tubing should be changed with each new infusion.[5,57,68]

Stability and Compatibility

Comprehensive current information regarding compatibility and stability of PN solutions can be found in several reference sources such as *Handbook on Injectable Drugs*[69] and *King Guide to Parenteral Admixtures*.[70] In many cases, the answer to a compatibility question may not be readily available, and a review

of the primary literature may be necessary. When information is not available, clinical judgment and experience must be used to resolve the situation.

The stability of a PN formulation is determined by the rate or degree of component degradation and any resulting changes in chemical integrity or pharmacologic activity that may render the formulation unsuitable for safe administration. In general, the sterile combination of PN components accelerates the rate of physicochemical destabilization of all of the components in the formulation; certain amino acids, vitamins, and IVLE are the most susceptible nutrients.[5,23,31,49] When compounded and stored appropriately, the degree of degradation is usually not clinically relevant for most patients receiving short-term PN because many patients have sufficient stores of those susceptible nutrients to support any short-term periods of suboptimal intake. However, nutrient degradation that is more extensive may be problematic for patients with marginal nutrient stores who receive long-term PN. TNAs present additional stability challenges because of the presence of IVLE in the solution. IVLE stability in TNAs is affected by the amino acid and dextrose concentration, solution pH, order of mixing, electrolyte amounts, and final TNA volume as well as container material, storage conditions, and addition of non-nutrient drugs. Stability studies on the effect of specific electrolyte concentrations on TNA stability are limited. In general, IVLE stability is affected by the PN cation content. Divalent and trivalent cation additives such as calcium and magnesium have a greater destabilizing potential compared with monovalent cation additives such as sodium and potassium. However, when given in sufficiently high concentrations, monovalent cation additives may also increase instability. Cations act to reduce the surface potential of the emulsion droplet, thereby enhancing tendency to aggregate and ultimately, in some cases, destabilize the solution to coalescence or a “cracked” admixture.[5,23,44] When a cracked IVLE occurs, the oil phase separates from the water phase, resulting in the appearance of free oil fat globules. Early stages may appear as subtle changes in the uniformly white appearance of the TNA, which may progress to yellow oil streaks throughout the bag or development of an amber oil layer at the top of the admixture bag. TNA formulations with any visible free oil should be considered unsafe for parenteral administration because infusion of circulating fat globules may be of sufficient size to accumulate in the pulmonary vasculature and potentially compromise respiratory function. In general, the likelihood of preparing an unstable TNA formulation can be minimized by maintaining the final concentrations of CAA greater than 4%, dextrose greater than 10%, and IVLE greater than 2%.[5] Specific guidelines for compounding TNAs are

reviewed elsewhere.[2,5,23,35,37,38,57]

Because of differences in pH among various CAA products and phospholipid content among IVLE products, the manufacturer of each product should be consulted for compatibility and stability information before routinely admixing components. One approach to compounding TNAs manually is to combine CAA, dextrose, and sterile water (if necessary) followed by the addition of electrolytes, vitamins, and trace elements. Then the solution should be visually inspected for precipitate or other particulates. Finally, IVLE may be added and the solution should then be visually inspected again to ensure a uniform emulsion exists.[23,35,37,38] Mixing components in this specific order may not be possible with the use of ACDs. Although CAA, dextrose, and IVLE may be simultaneously transferred to an admixture container, the ACDs manufacturer should be consulted for the optimal mixing sequence to ensure safe compounding of TNA formulations.

The precipitation of calcium and phosphorus is a common interaction that is potentially life-threatening.[16,23,71] The risk of precipitate formation is greater with increased solution temperature and pH, higher concentrations of calcium and phosphorus, lower concentrations of amino acids and dextrose, use of the chloride salt of calcium, improper mixing sequence when adding calcium and phosphorus salts, and the presence of other additives (including IVLEs).[16,23,71] In general, steps to minimize risk of calcium and phosphate precipitation in PN admixtures include the use of calcium gluconate instead of calcium chloride because it is less reactive, adding phosphate salts early in the mixing sequence, adding calcium last or nearly last, and agitating the mixture throughout the admixture process to achieve homogeneity. PN admixtures with a lower final pH should be used when clinically appropriate. Higher final concentrations of dextrose and CAA and lower final concentrations of IVLE favor a lower admixture pH. CAA product-specific solubility curves that are available from the manufacturer or primary literature should be consulted to project calcium and phosphorous solubility. The calculation of a sum or product of calcium and phosphate concentrations should not be used as the sole criterion for determining solubility because the product of calcium and phosphate concentrations vary inconsistently as calcium concentration decreases and phosphate concentration increases.[71]

Electrolyte stability in TNA solutions is difficult to assess because of poor visualization of a precipitate if one occurs. PN solutions for neonates and infants tend to contain larger amounts of calcium and phosphorus, as well as other divalent cations, that limit the use of TNAs. Because of the limited amount of

published stability information, the use of a two-in-one admixture with separate administration of IVLEs is recommended for neonates and infants.[57] In general, alternative methods of delivering electrolytes or medications should be pursued in any clinical situation in which TNA compatibility information is lacking. Because the addition of bicarbonate to acidic PN admixtures may result in the formation of carbon dioxide gas and insoluble calcium and magnesium carbonates, sodium bicarbonate use in PN admixtures is not recommended. Use of a bicarbonate precursor salt such as acetate usually is preferred.

Vitamins may be affected adversely by changes in solution pH, presence of other additives, storage time, solution temperature, and exposure to light.[23,31] Because of variable stabilities of individual vitamins, IV vitamin solutions should be added to the PN solution as near to the time of administration as is clinically feasible and should not be in the PN solution longer than 24 hours.

Increased peroxide concentrations have been reported in IVLE and dextrose–amino acid solutions after addition of injectable multivitamins or exposure to air or light.[72] Multiple in vitro experiments have reported negative effects of peroxides and associated metabolites on organ and immune function. Peroxides are associated with neonatal hypoxic–ischemic encephalopathy, intraventricular hemorrhage, periventricular leukomalacia, chronic lung disease, retinopathy of prematurity, and necrotizing enterocolitis.[72] Neonates and infants are at increased risk for harmful effects of peroxides because they receive a higher daily peroxide load from PN solutions compared to adults and they have lower endogenous antioxidant levels. Protecting PN and IVLE solutions from light is therefore recommended to minimize peroxide formation.[5,72]

Many patients receiving PN also receive other IV medications. The compatibility of these medications with the PN solution is an important consideration for safe and effective drug delivery. Although some medications may be added directly to the PN solution and administered at the same rate as the PN infusion, most are administered as a separate admixture co-infused in the PN line. Several criteria should be considered before medications are added directly to the PN solution because of the potential for ineffective drug therapy or other complications associated with physiochemical incompatibility and stability of the PN solution.[57] First, the drug should be stable for at least 24 hours and should have pharmacokinetic properties appropriate for continuous infusion. Second, the chemical and physical compatibility of the medication with PN admixture components and other medications that may be co-infused concomitantly into the PN line should be verified. Advantages of using PN admixtures as drug vehicles include consolidation of dosage units, improved

pharmacodynamics for certain drugs, conservation of fluid in volume-restricted patients, fewer venous catheter violations, and decreased compounding and administration times. However, a major disadvantage to the use of PN solutions as drug-delivery vehicles is the lack of compatibility and stability data. Medications frequently added to PN solutions include regular insulin and histamine-2 receptor antagonists.[57]

COMPLICATIONS OF PARENTERAL NUTRITION

Mechanical and Technical Complications

Mechanical and technical complications include malfunctions in the system used for IV delivery of the solution, such as infusion pump failure, problems with administration sets or tubing, or the CVC. Although problems associated with infusion pumps and administration sets can be decreased by appropriate equipment selection and routine care and monitoring, CVC-related complications are potentially life-threatening. Pneumothorax, catheter misdirection or migration into the wrong vein or improper positioning within the cardiac chambers, arterial puncture, bleeding, and hematoma formation may occur during surgical placement of the catheter. Many of these complications, in addition to venous thrombosis and air embolism, can occur after insertion. CVCs occasionally occlude or break during use and if these problems cannot be rectified easily, the catheter may need to be surgically replaced.

Infectious Complications

Infectious complications can be a major hazard for patients receiving CPN because of the increased risk associated with the presence of an indwelling CVC. The source of a CVC infection may be skin organisms from the catheter insertion site, contamination of the catheter hub, or hematogenous seeding of the catheter from a distant site. In addition, patients receiving PN therapy are often predisposed to infection because of compromised immunity or concomitant infection. Frequent use of broad-spectrum antibiotic therapy and malnutrition are also predisposing factors for development of infection. The risk of catheter infection is increased for those who require multiple manipulations of the line used for PN administration as well as those who experience failure of in-line bacterial filter, poor catheter placement technique, and poor CVC and insertion

site care.[59]

Infection rarely develops secondary to solution contamination.[59] Strict adherence to protocols for preparation of PN admixtures should minimize this occurrence.[66,73] Catheter-related bloodstream infections (CRBSIs), defined as the presence of clinical manifestations of infection (eg, fever, chills, hypotension) associated with bacteremia or fungemia resulting from no apparent source other than the catheter, are common sources of systemic infection.[73] Before this diagnosis can be made, there should be evidence of more than one positive blood culture result obtained from the peripheral vein with growth of the same organism from a blood culture obtained from the catheter or catheter segment. When a CRBSI is suspected or confirmed, appropriate antimicrobial therapy should be initiated. Retention or removal of the central catheter depends on the patient's severity of illness, the suspected or identified pathogen, and the type of catheter involved. The catheter may be removed and replaced in the same site, the catheter may be removed and replaced at a different anatomic location, or it may not be replaced.[73] Filling the catheter with antimicrobials such as vancomycin or antiseptics such as 70% alcohol and allowing the solution to dwell for a period of time while the catheter is not in use is referred to as a catheter lock.[59] Antimicrobial catheter locks have been used to prevent and treat CRBSI in patients with long-term catheters such as those receiving home PN.[59,60]

Metabolic and Nutritional Complications

9 Metabolic and nutritional complications associated with PN therapy are numerous; frequently multifactorial in origin; and if left untreated, potentially fatal. Metabolic abnormalities related to substrate intolerance, fluid and electrolyte disorders, and acid–base disorders are summarized in multiple recent review articles and their management is briefly summarized in the following sections.[30–32,43,56,78–80]

Liver Disease

Parenteral nutrition–associated liver disease presents as elevations in total bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase. Both adult and pediatric patients who receive PN are at risk for developing PNALD; it is reported to occur in approximately 50% to 60% of children who receive long-term PN, with a higher incidence in premature

infants.[31,32,74] No single etiology has been identified, although several risk factors have been reported, such as degree of prematurity, sepsis, hypoxia, lack of enteral nutrition, small bowel bacterial overgrowth, GI conditions requiring surgical intervention, duration of PN therapy, and long-term administration of excessive calories.[32,43,74] PNALD in infants is characterized clinically by a serum direct bilirubin concentration greater than 2 mg/dL (more than 34.2 µmol/L).[32] Taurine deficiency has been proposed as an etiology of cholestasis for preterm infants and neonates.[32,43] Taurine is a conditionally essential amino acid that is not present in standard CAA solutions but is important for neonatal and infant bile metabolism. However, the preventative or therapeutic benefit of PN regimens with CAA solutions containing supplemental taurine is unclear. Recent studies have focused on the potential relationship between IVLE and the development of PNALD.[43] SO-based IVLEs contain large concentrations of plant sterols or phytosterols, which are inefficiently metabolized to bile acids by the liver. Experimental data suggest parenteral phytosterols may impair bile flow. Improvement or reversal of PNALD has been reported for patients who received FO-IVLE.[41,43] Other PNALD treatments that have been investigated include providing reduced doses of SO-based IVLE and use of enteral fish oil in patients with limited oral intake.[43,75]

Risk factors for PNALD in adults include pre-existing liver disease, sepsis, pre-existing malnutrition, extensive bowel resection, prolonged duration of PN therapy, lack of enteral intake, nutrient deficiencies such as choline deficiency, and long-term administration of excessive calories.[31,32,43,74] PNALD in adults typically presents as steatosis and steatohepatitis on biopsy. Clinically, PNALD is characterized by mild elevations in serum liver enzymes, usually less than three times the upper limit of normal, with peak enzyme levels usually occurring between 1 and 4 weeks after initiating PN. In many cases, the liver abnormalities improve or resolve with manipulation of substrate intake or discontinuation of PN therapy. However, in severe cases, liver dysfunction may progress to overt failure and death despite use of traditional therapies such as using cyclic PN, ursodiol, and oral antibiotics for bacterial overgrowth; maximizing enteral feeding; and avoiding sepsis and parenteral overfeeding.[31,32,74] Intestinal transplant with or without liver transplantation has become a treatment option for PN-dependent patients who have progressive PNALD.

Hypertriglyceridemia

Hypertriglyceridemia, defined as serum triglyceride concentrations greater than

400 mg/dL (4.52 mmol/L) for adults and 150 mg/dL (1.70 mmol/L) to 200 mg/dL (2.26 mmol/L) for preterm infants, neonates, and older pediatric patients, may occur in patients receiving IVLE-based PN. Risk factors include pre-existing liver or pancreatic dysfunction, sepsis, multiple-organ failure, degree of prematurity, IVLE infusion rate, and dose.

IVLE–associated hypertriglyceridemia is generally thought to be caused by defective lipid clearance or an excessive rate of IVLE administration.[31] Premature infants and neonates have relatively slower lipid clearance than do adults because of immature metabolic pathways, including decreased lipoprotein lipase activity.[16] Reducing the IVLE infusion rate or dose or withholding IVLE therapy should be considered when patients present with hypertriglyceridemia or lipemic serum.[31] Use of low-dose heparin (1 unit/mL of two-in-one PN formulation) to stimulate lipoprotein lipase activity has been suggested as a potential therapeutic intervention to treat IVLE–associated hypertriglyceridemia in neonates.[16] However, others have suggested that the risk associated with heparin delivery via PN outweighs the clinical benefits because of the potential for compounding errors associated with confusion between heparin and insulin doses.[76] The role of carnitine for treatment of IVLE–associated hypertriglyceridemia is not clear.[16,31]

Hyperglycemia

Hyperglycemia is one of the most common complications of PN administration and is associated with a history of diabetes, metabolic stress, adverse effects of medications such as glucocorticoids, and excessive carbohydrate administration. In the pediatric population, additional risks for hyperglycemia include prematurity and surgery. The optimal blood glucose concentration for acutely ill hospitalized patients receiving PN is not known. However, a target range of 140 to 180 mg/dL (7.8-10 mmol/L) has been suggested for adults, and less than 150 mg/dL (8.3 mmol/L) has been suggested for neonates.[77,78] Clinical management of PN patients with hyperglycemia has not been well studied and is largely empiric.[79,80] Blood glucose concentrations can be controlled with regular insulin, which may be given subcutaneously or added to the PN formulation. One approach for adult PN patients requiring insulin or oral hypoglycemic agents before starting PN therapy is to initiate PN with approximately 100 to 200 g of dextrose and add 0.05 to 0.1 units of regular insulin per gram of dextrose in the PN solution for those patients with mild hyperglycemia (140-180 mg/dL [7.8-10 mmol/L]). The insulin dose may be increased to 0.15 to 0.2 units/gram

of dextrose for patients with moderate hyperglycemia (181-200 mg/dL [10.0-11.1 mmol/L]).[31,79,80] Others have suggested continuing pre-admission basal insulin with long-acting insulin (detemir or glargine). Response to blood glucose monitoring prior to initiating PN therapy can be useful in determining initial insulin dosing. Blood glucose concentrations should be monitored every 4 to 6 hours. Blood glucose measurements above the goal range should be treated with short-acting insulin administered subcutaneously according to an appropriate sliding scale (see Chapter 91, "Diabetes Mellitus"). The insulin dose is modified daily by adding 60% to 100% of the sliding-scale insulin given over the previous 24 hours to the PN formulation daily until blood glucose concentrations are stable and within the target range. When blood glucose measurements are stable, the dextrose dose may be advanced to achieve the therapeutic goal and the frequency of monitoring blood glucose concentrations may be decreased after blood glucose concentrations are stable within the target range at the goal dextrose dose. Use of a separate IV insulin infusion is most commonly used for pediatric patients, but it may also provide better and safer glycemic control for patients with very large insulin requirements or those with unstable marked fluctuations in their blood glucose concentrations.

Refeeding Syndrome

Severe and rapid declines in serum phosphate, potassium, and magnesium concentrations; fluid retention; and other micronutrient deficiencies are common features of the refeeding syndrome.[81] Individuals at greatest risk for refeeding syndrome are severely malnourished patients with significant weight loss who receive aggressive nutritional supplementation. In addition, those who are unfed for 7 to 10 days with evidence of stress or nutritional depletion; those with chronic diseases causing undernutrition such as cancer, cardiac cachexia, chronic obstructive pulmonary disease, or cirrhosis; and individuals who were previously morbidly obese and have experienced massive weight loss are at heightened risk for this syndrome.[81] Electrolyte abnormalities appear to be related to acute provision of macronutrient substrates that promote anabolism in an environment of depleted total body stores of phosphorus, potassium, and magnesium. Recommendations for initiating PN in adults at risk for refeeding syndrome include providing 25% to 50% of the calculated nonprotein caloric requirements initially. The dextrose dose should be initiated at approximately 100 to 200 g/day. Calories should be advanced over 3 to 4 days to the desired goal. Because the metabolic abnormalities described with refeeding syndrome appear to be related primarily to acute provision of large amounts of dextrose, the goal

protein dose may be provided with the initial PN infusion. Pediatric PN regimens are usually advanced over several days as a general practice for all pediatric patients. Additional recommendations for minimizing the risk of refeeding syndrome for pediatric patients include provision of additional phosphorus and potassium above standard nutrient requirements at the time PN is initiated.[82]

Complications Associated with Long-Term Parenteral Nutrition

Other nutritional complications of PN therapy may develop over a prolonged course of therapy (weeks to months) as a result of inappropriate intake of a particular nutrient. Certain conditions, such as metabolic stress in a previously malnourished patient, may elicit symptoms of deficiency much earlier if a nutrient is not appropriately provided. For example, lactic acidosis and other life-threatening complications associated with severe thiamine deficiency have been reported in patients who received PN solutions without multivitamin supplementation.[49] Maintenance doses of vitamins, trace elements, and essential fatty acids should be provided to all patients with normal age-related organ function receiving PN.

Essential Fatty Acid Deficiency

Patients receiving PN regimens without IVLEs for weeks to months are at risk for development of EFAD. Clinical signs of EFAD include hair loss, desquamative dermatitis, thrombocytopenia, malabsorption, and diarrhea resulting from changes in intestinal mucosa.[31] EFAD also may be diagnosed by evaluating plasma fatty acid profiles. Although this assessment is not routinely available, it can be provided by several larger regional laboratories. Historically, a triene-to-tetraene ratio more than 0.4 has been considered biochemical evidence for EFAD; however, individual laboratory reference ranges should be used when evaluating patients for EFAD.[16] Although the time in which EFAD may develop depends on the patient’s nutrition status, disease state, and age, these manifestations may occur 2 to 4 weeks after initiation of fat-free PN in adults and within 48 hours in newborn infants.[41]

Metabolic Bone Disease

Metabolic bone disease has been reported for adults and children receiving long-

term home PN.[31,32] This disorder in adults is characterized by osteomalacia with or without osteoporosis that may present without associated clinical, radiologic, or biochemical abnormalities. The diagnosis may not be made for premature infants until after the development of bone fractures or overt rickets. The etiology is poorly understood and likely multifactorial. Treatment options include pharmacologic intervention, calcium and vitamin D supplementation, and exercise. Because excessive vitamin D has also been implicated in the development of metabolic bone disease, others have recommended removal of vitamin D from the PN for patients with a normal 25-hydroxyvitamin D concentration and low serum parathyroid hormone and 1,25-hydroxyvitamin D concentrations.[31,32]

Trace Element and Vitamin Complications

Clinical symptoms of trace element deficiencies, although rare, have been reported for patients receiving long-term PN. More commonly, decreased serum trace element concentrations have been reported in a variety of patient populations. However, the clinical significance of abnormally low concentrations of many trace elements is not known because serum concentrations often do not correlate with total body stores.[49] Occasionally, patients may develop clinical toxicities from elevated vitamin or trace element concentrations as the result of increased intake or decreased metabolism. These abnormalities are frequently associated with an underlying disease state such as severe kidney or hepatic failure and may necessitate reduction in vitamin and trace element intake.

Many trace elements are present in PN components as contaminants.[49,57] Some investigations of patients with normal organ function who were receiving PN supplemented with commercially available parenteral multiple trace element solutions have reported concern with elevated serum concentrations of trace elements such as chromium and manganese.[49,57] Aluminum is a common contaminant of many sterile IV solutions, including those used for compounding PN. Calcium and phosphorus solutions are among those components with the highest levels of aluminum contamination.[83,84] Aluminum accumulation may occur during long-term PN therapy, especially for patients with reduced kidney function, and is associated with abnormal neurologic and hematologic function and metabolic bone disease in adults and premature infants.[31,83,84] Preterm infants are at higher risk of aluminum toxicities because they receive larger doses (micrograms per kilogram) from PN solutions than adults.[84] Preterm infants are also more likely to retain aluminum because of immature kidney

function. Although the maximum safe level of IV aluminum intake is unknown, the FDA has reported that parenteral doses of 4 to 5 mcg/kg/day were associated with central nervous system and bone toxicity.[85] Even smaller amounts may result in tissue accumulation but no documented toxicity.

The FDA implemented a mandate in 2004 to restrict aluminum content in large-volume PN stock solutions (CAA, dextrose, sterile water for injection, IVLE) to a maximum of 25 mcg/L and for manufacturers to indicate the maximum aluminum concentration at expiration for both large- and small-volume parenteral products used for PN.[85] Investigations have determined actual aluminum concentrations in parenteral products to be lower than the amounts reported on the manufacturer's label; however, aluminum amounts in PN solutions still exceed FDA guidelines.[83,84] In addition, the aluminum content of parenteral products appears to vary considerably during the shelf life of the products and increases with time because of leaching from glass containers. The amount of aluminum contamination delivered to patients receiving long-term parenteral therapy, such as chronic PN patients or dialysis patients, can be substantially reduced if newer stock solutions are used to prepare their PN.[83,84]

HOME PARENTERAL NUTRITION

Advances in technology for the delivery of IV solutions have allowed medically stable patients who require extended PN therapy to be maintained indefinitely on IV nutrition. An increasing concern for cost containment of healthcare services has fostered use of sophisticated infusion devices to provide PN at home. Numerous programs are now available outside the traditional healthcare setting to support patients who require long-term or permanent PN. Standards have been developed to promote safe and effective care.[60] Home PN services may be coordinated and administered through a hospital or by a commercial home care company.[60]

Many factors are considered in selecting candidates for home PN therapy. Significant benefit must be expected from the therapy. Examples of patients who have been maintained successfully with home PN include those with intestinal failure secondary to Crohn's disease, ischemic bowel disease, severe GI motility disorders, extensive intestinal obstruction, and congenital bowel dysfunction.[60] The patient and the patient's caregiver must be willing to complete training and assume numerous responsibilities for managing the new daily routine. Other logistics such as funding, procurement of solutions and supplies, and clinical

management and follow-up must be individualized for each patient in order to achieve the desired outcomes.[60]

Patients commonly receive PN solutions from their home care provider. IV vitamins or other additives may be added daily by the patient or caregiver, depending on the arrangement with the home care provider. The solution generally is administered through the night by infusion pump over 8 to 20 hours.[60,63] A cycled regimen allows the patient time away from the pump during daylight hours and provides many patients with the freedom to have a reasonably normal daily routine. Clinical management and follow-up are performed periodically according to the needs of the patient and the protocol of the home care provider or the managing healthcare team. A coordinated effort among several healthcare professionals, including physicians, pharmacists, nurses, dietitians, social workers, and the patient and the patient's caregiver, as well as the suppliers, is paramount to providing safe and effective management. Home PN affords some patients the potential for an ambulatory lifestyle while maintaining an IV feeding regimen that was previously only available in the hospital setting. For others, home PN may contribute to a better quality of life in the comfort of their homes.[60]

PHARMACOECONOMIC CONSIDERATIONS

Determining the true cost of PN support is difficult because numerous variables affect the provision of PN and the clinical response to therapy. PN therapy cost variables include the underlying indication for treatment, the administration setting (home or acute care), timing of PN initiation, therapy associated complications, and the type of PN formulation provided (compounded or standardized commercial PN product).[60,86–91] Expenses associated with PN therapy may be categorized as direct and indirect costs.[89] Direct costs may be further categorized as fixed or variable costs. Fixed costs do not depend on the volume of patients receiving therapy. For example, an ACD and the tubing sets required to transfer volumes of stock solutions to the administration bag would be considered fixed costs in many practice settings. These costs per patient tend to be highest in low-volume environments. Variable costs such as PN administration bags or standard commercial PN products depend directly on the number of patients receiving PN. Other direct costs include ancillary services required by patients receiving PN and costs related to the management of PN associated complications.

Clinical benefits and other clinical effects of PN (ie, reduction in hospital

length of stay and frequency of complications) in specific patient populations have been evaluated but few investigations have reported a comprehensive economic assessment of PN therapy. Attempting to measure the cost or cost savings associated with reported benefits of PN therapy and other clinical effects based on results of controlled clinical trials is difficult.[87,88] Clinical outcome measurements and hence economic outcomes are influenced by multiple factors, including experimental design, sample size, and specific health system practices.[87,89,90,92,93] More recent cost analyses for PN therapy have focused on timing of initiating therapy in critically ill patients and choice of PN formulation (compounded or standard commercial PN product). In general, although individual investigations have reported cost savings with supplemental PN in critically ill patients unable to meet nutritional goals within 24 to 48 hours of intensive care unit (ICU) admission, others have reported no cost advantage with early PN intervention.[90] Similarly, while cost savings have been reported with use of standard commercial PN products compared to PNs compounded with an ACD, others have reported increased costs with other supportive care usually provided with compounded PN when standard commercial PN products were used.[92,94]

Although the results of economic analyses of PN remain controversial, similarities among several reports provide a basis for minimizing the costs of PN therapy:

1. Use PN only for the most appropriate patients as described by institution-specific criteria based on current consensus statements. Enteral nutrition should be used whenever feasible because the associated costs and complications are demonstrated to be less than those associated with PN.[91,95]
2. Reassess the need for routine laboratory monitoring measurements used for PN therapy. In general, the level of laboratory monitoring should decrease as a patient's clinical condition stabilizes.
3. Minimize the direct cost of PN by using efficient purchasing practices for PN solutions and compounding supplies through contract purchasing, streamlined compounding procedures, standardized administration times, single-bag PN solutions, and optimized monitoring plans. Some institutions may realize direct cost savings with use of standardized, commercial PN products depending on the usual daily PN census and patient population.[93,94] Others may reduce direct costs by outsourcing PN compounding to a third-party compounding pharmacy facility.

PHARMACOTHERAPY CONSIDERATIONS

10 11 Considerations for individualizing a patient's PN regimen include: goals determination based on a patient-specific nutrition assessment, selection of the optimal type of available vascular access, and macronutrient and micronutrient requirements. In general, both macronutrient and micronutrient doses are age and weights based but are also affected by the patient's degree of metabolic demand, organ function, other drug therapy, exogenous losses, and acid–base status. Nutrient amounts provided by the PN may also require adjustment based on enteral intake either orally or by feeding tube in patients with recovering GI tract function.

Patient-specific caloric goals include (a) adequate energy intake to promote normal growth and development in neonates, infants, and children; (b) energy equilibrium and preservation of fat calorie stores in well-nourished adults; and (c) positive energy balance in malnourished patients with depleted endogenous fat stores. Overweight patients with a body mass index above 30 kg/m^2 may require less caloric support than nonobese patients with the same clinical condition.[12] Critically ill adults may also benefit from a hypocaloric regimen.[12] Specific nitrogen goals are positive nitrogen balance or nitrogen equilibrium and improvement in the serum concentration of visceral protein markers such as transferrin or prealbumin in patients without systemic inflammation. Routine monitoring is necessary to ensure that the nutrition regimen is suitable for a given patient as the patient's clinical condition changes and to minimize or treat complications. The PN component doses usually require individualized adjustments as the patient's clinical condition affects further changes in metabolic stress, organ function, fluid and electrolyte balance, and acid–base status.

Appropriate patient selection, assessment, and monitoring are key to successful PN therapy and the prevention of unnecessary complications. Because pharmacists are actively involved in the provision of PN at many levels, including order verification, PN compounding and dispensing, direct patient care, education, and research, nutrition support is recognized as a pharmacy practice specialty.[96] In addition, as the interprofessional team–based approach to specialized nutrition support has evolved, standards of practice have been defined for pharmacists as well as for other healthcare professionals.[4,8–10] Standardized order forms and monitoring protocols are useful tools to ensure safe administration and monitoring of PN therapy. The future of PN therapy and the role of nutrition-support clinicians will be affected primarily by new insights

from clinical research and economic challenges in the evolving healthcare environment.

Postclass Engaged Learning Activity

Given a patient's anthropometric data and estimated daily nutritional requirements, create an appropriate order for an adult PN formulation and a pediatric PN formulation to be administered via central venous access. The order should be designed to comply with the A.S.P.E.N. Parenteral Nutrition Safety Consensus recommendations. The formulation should be patient-specific and suitable for compounding with an automated compounding device using the following macronutrient PN components: CAA 15%, Dextrose 70%, SO-IVLE 20%. Complete the pharmacist care plan by outlining appropriate monitoring and evaluation activities after implementation of therapy. This exercise is useful to enhance student understanding regarding the PLAN, IMPLEMENT, and FOLLOW-UP steps in the patient care process.

ABBREVIATIONS

AAP	American Academy of Pediatrics
A.S.P.E.N.	American Society for Parenteral and Enteral Nutrition
CAA	crystalline amino acid
CDC	Centers for Disease Control and Prevention
CSP	compounded sterile preparation
CPN	central parenteral nutrition
CRBSI	catheter-related bloodstream infection
CVC	central venous catheter
EFAD	essential fatty acid deficiency
FO	fish oil
FDA	Food and Drug Administration
GI	gastrointestinal
ICU	intensive care unit

IVLE	IV fat emulsion
LCT	long-chain triglyceride
MCT	medium-chain triglyceride
NAG-AMA	Nutrition Advisory Group of the American Medical Association
NF	National Formulary
PICC	peripherally inserted central catheter
PN	parenteral nutrition
PNALD	parenteral nutrition–associated liver disease
PPN	peripheral parenteral nutrition
PUFA	polyunsaturated fatty acid
SO	soybean oil
SMOF	soybean oil, medium chain triglyceride oil, olive oil, fish oil
TNA	total nutrient admixture
USP	United States Pharmacopeia

REFERENCES

1. Dudrick SJ, Palesty JA. Historical highlights of the development of total parenteral nutrition. *Surg Clin N Am*. 2011;693–717.
2. Delegge MH, Kelley AT. State of nutrition support teams. *Nutr Clin Pract*. 2013;28:691–697.
3. Holcombe B, Mattox TW, Plogsted S. Drug Shortages: Effect on Parenteral Nutrition Therapy. *Nutr Clin Pract*. 2018;33:53–61.
4. Tucker A, Ybarra J, Bingham A, et al. American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Standards of Practice for Nutrition Support Pharmacists. *Nutr Clin Pract*. 2015;30:139–146.
5. Ayers P, Adams S, Boullata J, et al. A.S.P.E.N. Parenteral Nutrition Safety Consensus Recommendations. *JPEN J Parenter Enteral Nutr*. 2014;38:296–333.
6. Ukleja A, Gilbert K, Mogensen KM, Walker R, Ward CT, et al. Standards for nutrition support: Adult hospitalized patients. *Nutr Clin Pract*. 2018;33:906–920.
7. Corkins MR, Griggs KC, Groh-Wargo S, et al. Standards for nutrition support: Pediatric hospitalized patients. *Nutr Clin Pract*. 2013;263–276.
8. Brantley SL, Russell MK, Mogensen KM, et al. American society for

parenteral and enteral nutrition and academy of nutrition and dietetics revised 2014 standards of practice and standards of professional performance for registered dietitian nutritionists (competent, proficient, and expert) in nutrition support. *Nutr Clin Pract*. 2014;29:792–828.

9. DiMaria-Ghalili RA, Gilbert K, Lord L, Neal T, Richardson D, et al. Standards of nutrition care practice and professional performance for nutrition support and generalist nurses. *Nutr Clin Pract*. 2016;31:527–547.
10. Mascarenhas MR, August DA, DeLegge MH, et al. ; Task Force on Standards for Nutrition Support Physicians; American Society for Parenteral and Enteral Nutrition Board of Directors; American Society for Parenteral and Enteral Nutrition. Standards of practice for nutrition support physicians. *Nutr Clin Pract*. 2012;27:295–299.
11. Worthington P, Balint J, Bechtold M, Bingham A, Chan LN, et al. When is parenteral nutrition appropriate? *JPEN J Parenter Enteral Nutr*. 2017;41:324–377.
12. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr*. 2016;40:159–211.
13. Mehta NM, Skillman HE, Irving SY, Coss-Bu JA, Vermlyea S, et al. Guidelines for the provision and assessment of nutrition support therapy in the pediatric critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition. *JPEN J Parenter Enteral Nutr*. 2017;41:706–742.
14. Arends J, Bachman P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr*. 2017;36:11–48.
15. Koretz RL, Avenell A, Lipman TO. Nutritional support for liver disease (Review). *Cochrane Database Syst Rev*. 2012 (May 16);5:CD008344.
16. Crill CM, Gura KM. Parenteral nutrition support. In: Corkins MR, ed. *The A.S.P.E.N. Pediatric Nutrition Support Core Curriculum*. 2nd ed. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.); 2015;593–614.
17. Brown RO, Compher C; American Society for Parenteral and Enteral Nutrition Board of Directors. A.S.P.E.N. clinical guidelines: Nutrition support in adult acute and chronic renal failure. *JPEN J Parenter Enteral*

Nutr. 2010;34:366–377.

18. Moyses HE, Johnson MJ, Leaf AA, Cornelius VR. Early parenteral nutrition and growth outcomes in preterm infants: As systematic review and meta-analysis. *Am J Clin Nutr*. 2013;97:816–826.
19. Skipper A, Tupesis N. Is there a role for nonprotein calories in developing and evaluating the nutrient prescription? *Nutr Clin Pract*. 2005;20:321–324.
20. Furst P, Stehle P. Are intravenous amino acid solutions unbalanced? *New Horizons*. 1994;2:215–223.
21. Dickerson RN. Using nitrogen balance in clinical practice. *Hosp Pharm*. 2005;40:1081–1085.
22. Yarandia SS, Zhaob VM, Hebbara G, Ziegler TR. Amino acid composition in parenteral nutrition: What is the evidence? *Curr Opin Clin Nutr Metab Care*. 2011;14:75–82.
23. American Hospital Formulary Service (AHFS). Amino Acids. In: McEvoy GK, ed. *Handbook on Injectable Drugs*. 20th ed. Bethesda, MD: American Society of Health-System Pharmacists; 2018:44–76.
24. Vanek VW, Matarese LE, Robinson M, et al. ; Novel Nutrient Task Force, Parenteral Glutamine Workgroup; American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. A.S.P.E.N. position paper: Parenteral nutrition glutamine supplementation. *Nutr Clin Pract*. 2011;26:479–494.
25. Heyland D, Muscedere J, Wischmeyer PE, et al. A randomized trial of glutamine and antioxidants in critically ill patients. *N Engl J Med*. 2013;368:1489–1497.
26. de Kieviet JF, Vuijk PJ, van den Berg A, et al. Glutamine effects on brain growth in very preterm children in the first year of life. *Clin Nutr*. 2014;33:69–74.
27. Moe-Byrne T, Wagner JV, McGuire W. Glutamine supplementation to prevent morbidity and mortality in preterm infants. *Cochrane Database Syst Rev*. 2012;(3):CD001457.
28. Brown JV, Moe-Byrne T, McGuire W. Glutamine supplementation for young infants with severe gastrointestinal disease. *Cochrane Database Syst Rev*. 2014;(12):CD005947.
29. Bulk Drug Substances Used in Compounding Under Section 503A of the FD&C Act. Available at: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Pl

Accessed December 3, 2018.

30. Btaiche IF, Khalidi N. Metabolic complications of parenteral nutrition in adults, part 1. *Am J Health Syst Pharm*. 2004;61:1938–1949.
31. Kumpf VJ, Gervasio J. Complications of parenteral nutrition. In: Mueller CM, ed. *The A.S.P.E.N. Adult Nutrition Core Curriculum*. 3rd ed. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.); 2017;345–358.
32. Btaiche IF, Khalidi N. Metabolic complications of parenteral nutrition in adults, part 2. *Am J Health Syst Pharm*. 2004;61:2050–2057.
33. Waxman K, Day AT, Stellin GP, et al. Safety and efficacy of glycerol and amino acids in combination with lipid emulsion for peripheral parenteral nutrition support. *JPEN J Parenter Enteral Nutr*. 1992;16:374–378.
34. ProcalAmine. *Product Information*. Irvine, CA: B. Braun Medical; 2015.
35. Intralipid. *Product Information*. Deerfield, IL: Baxter Healthcare Corporation; 2015.
36. Clinolipid. *Product Information*. Deerfield, IL: Baxter Healthcare Corporation; 2015.
37. Smoflipid. *Product Information*. Uppsala, Sweden: Fresenius Kabi; 2016.
38. Omegaven. *Product Information*. Graz, Austria: Fresenius Kabi; 2018.
39. Vanek VW, Seidner DL, Allen P, et al. ; Novel Nutrient Task Force, Intravenous Fat Emulsions Workgroup; American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. A.S.P.E.N. position paper: Clinical role for alternative intravenous fat emulsions. *Nutr Clin Pract*. 2012;27:150–192.
40. Calder PC. Functional roles of fatty acids and their effects on human. *JPEN J Parenter Enteral Nutr*. 2015;39(suppl 1):18S–32S.
41. de Meijer VE, Le HD, Meisel JA, Gura KM, Puder M. Parenteral fish oil as monotherapy prevents essential fatty acid deficiency in parenteral nutrition–dependent patients. *J Pediatr Gastroenterol Nutr*. 2010;50:212–218.
42. Kreymann KG, Heyland DK, de Heer G, Elke G. Intravenous fish oil in critically ill and surgical patients-historical remarks and critical appraisal. *Clin Nutr*. 2018;37:1075–1081.
43. Zaloga GP. Phytosterols, lipid administration, and liver disease during parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 2015;39(suppl 1):39S–60S.

44. Gervasio J. Total nutrient admixtures (3-in-1): Pros and cons for adults. *Nutr Clin Pract*. 2015;30:331–335.
45. Hicks RW, Becker SC, Chuo J. A summary of NICU fat emulsion medication errors and nursing services. Data from MEDMARX. *Adv Neonatal Care*. 2007;7:299–310.
46. Raman M, Almutairdi A, Mulesa L, Alberda C, Beattie C, Gramlich L. Parenteral nutrition and lipids. *Nutrients*. 2017;9:388. doi:10.3390/nu9040388. www.mdpi.com/journal/nutrients.
47. Diprivan. *Product Information*. Lake Zurich, IL: Fresenius Kabi USA LLC; 2014.
48. Cleviprex (clevidipine) injectable emulsion. *Product Information*. Graz, Austria: Fresenius Kabi Austria GmbH; 2017.
49. Vanek VW, Borum P, Buchman A, et al. ; Novel Nutrient Task Force, Parenteral Multi-Vitamin and Multi–Trace Element Working Group; American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. A.S.P.E.N. Position paper: Recommendations for changes in commercially available parenteral multivitamin and multi-trace element products. *Nutr Clin Pract*. 2012;27:440–491.
50. Helphingstine CJ, Bistrian BR. New food and drug administration requirements for inclusion of vitamin K in adult parenteral multivitamins. *JPEN J Parenter Enteral Nutr*. 2003;27:220–224.
51. Chambrier C, Lellerq M, Saudin F, et al. Is vitamin K_1 supplementation necessary in long-term parenteral nutrition? *JPEN J Parenter Enteral Nutr*. 1998;22:87–90.
52. Forchielli ML, Conti M, Motta R, Puggioli C, Germana B. Phytonadione content in branded intravenous fat emulsions: A comparative study of 6 products with different fat sources using liquid chromatography–mass spectrometry. *JPEN J Parenter Enteral Nutr*. 2017;41:489–495.
53. Greene HL, Hambidge KM, Schanler R, Tsang RC. Guidelines for the use of vitamins, trace elements, calcium, magnesium, and phosphorus in infants and children receiving total parenteral nutrition: Report of the Subcommittee on Pediatric Parenteral Nutrient Requirements from the Committee on Clinical Practice Issues of the American Society for Clinical Nutrition. *Am J Clin Nutr*. 1988;48:1324–1342.
54. Stehle P, Stoffel-Wagner B, Kuhn KS. Parenteral trace element provision: Recent clinical research and practical conclusions. *Eur J Clin Nutr*. 2016;70:886–893.

55. Zimmermann MB, Crill CM. Iodine in enteral and parenteral nutrition. *Best Pract Res Clin Endocrinol Metab*. 2010;24:143–158.
56. Kraft MD, Btaiche IF, Sacks GS, Kudsk KA. Treatment of electrolyte disorders in adult patients in the intensive care unit. *Am J Health Syst Pharm*. 2005;62:1663–1682.
57. Boullata JI, Gilbert K, Sacks G, et al. A.S.P.E.N. Clinical Guidelines: Parenteral nutrition ordering, order review, compounding, labeling, and dispensing. *JPEN J Parenter Enteral Nutr*. 2014;38:334–377.
58. Anderson ADG, Palmer D, MacFie J. Peripheral parenteral nutrition. *Br J Surg*. 2003;90:1048–1054.
59. O'Grady NP, Alexander M, Burns LA, Dellinger EP, et al. Healthcare Infection Control Practices Advisory Committee. Guidelines for the Prevention of Intravascular Catheter-Related Infections (2011). 2015. Available at: https://www.cdc.gov/infectioncontrol/guidelines/bsi. Accessed June 12, 2018.
60 Kirby DF, Corrigan ML, Speerhas RA, Emery DM. Home parenteral nutrition tutorial. *JPEN J Parenter Enteral Nutr*. 2012;36:632–644.
61. Vanek VW, Ayers P, Kraft M, Bouche JM, Do VT, et al. A call to action for optimizing the electronic health record in the parenteral nutrition workflow: Executive summary. *Nutr Clin Pract*. 2018;33:594–596.
62. Kochevar M, Guenter P, Holcombe B, et al. ; A.S.P.E.N. Board of Directors and Task Force on Parenteral Nutrition Standardization. A.S.P.E.N. Statement on Parenteral Nutrition Standardization. *JPEN J Parenter Enteral Nutr*. 2007;31:441–448.
63. Speerhas R, Wang J, Seidner D, Steiger E. Maintaining normal blood glucose concentrations with total parenteral nutrition: Is it necessary to taper total parenteral nutrition? *Nutr Clin Pract*. 2003;18:414–416.
64. Stout ST, Cober MP. Metabolic effects of cyclic parenteral nutrition infusion in adults and children. *Nutr Clin Pract*. 2010;25:277–281.
65. USP <797> Guidebook to Pharmaceutical Compounding—Sterile Preparations. Rockville, MD: United States Pharmacopeia Convention 2008.
66. General Chapter <797> Pharmaceutical Compounding-Sterile Preparations. Available at: http://www.usp.org/compounding/general-chapter-797. Accessed August 10, 2019.
67. American Society for Health-System Pharmacists. ASHP guidelines on the safe use of automated compounding devices for the preparation of

parenteral nutrition admixtures. *Am J Health Syst Pharm*. 2000;57:1343–1348.

68. Cober MP. Repackaging of intravenous fat emulsions: A clinical conundrum. *Nutr Clin Pract*. 2016;31:642–646.
69. *Handbook on Injectable Drugs*. 20th ed. Bethesda, MD: American Society of Health-System Pharmacists. Available at: https://www.ahfsdruginformation.com/handbook-on-injectable-drugs. Accessed June 12, 2018.
70. King JC, Catania PN. *King Guideto Parenteral Admixtures*. Napa, CA: King Guide Publications, Inc. https://kingguide.net.
71. Newton DW, Driscoll DF. Calcium and phosphate compatibility: Revisited again. *Am J Health-Syst Pharm*. 2008;65:73–80.
72. Hoff DS, Michaelson AS. Effects of light exposure on total parenteral nutrition and its implications in the neonatal population. *J Pediatr Pharmacol Ther*. 2009;14:132–143.
73. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;49:1–45.
74. Tillman EM. Review and clinical update on parenteral nutrition-associated liver disease. *Nutr Clin Pract*. 2013;28:30–39.
75. Tillman EM, Helms RA. Omega-3 long chain polyunsaturated fatty acids for treatment of parenteral nutrition-associated liver disease: A review of the literature. *J Pediatr Pharmacol Ther*. 2011;16:31–38.
76. ISMP Medication Safety Alert!® Acute Care. Action needed to prevent dangerous heparin-insulin confusion. May 3, 2007. Available at: www.ismp.org/Newsletters/acutecare/articles/20070503.asp. Accessed August 29, 2016.
77. McMahon MM, Nystrom E, Braunschweig C, et al. ; American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. A.S.P.E.N. Clinical guidelines: Nutrition support of adult patients with hyperglycemia. *JPEN J Parenter Enteral Nutr*. 2012;37(1):23–36.
78. Arsenault D, Brenn M, Kim S, et al. ; American Society for Parenteral and Enteral Nutrition Board of Directors, Puder M. A.S.P.E.N. Clinical Guidelines: Hyperglycemia and hypoglycemia in the neonate receiving parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 2012;36:81–95.
79. Vennard KC, Selen DJ, Gilbert MP. The management of hyperglycemia in

noncritically ill hospitalized patients treated with continuous enteral or parenteral nutrition. *Endocr Pract*. 2018;24:900–906.

80. Drincic AT, Knezevich JT, Akkireddy P. Nutrition and hyperglycemia management in the inpatient setting (meals on demand, parenteral, or enteral nutrition). *Curr Diab Rep*. 2017;17:59–71.
81. Boland K, Solanki D, O'Hanlon C, IrSPEN's Standards and Guidelines Committee. IrSPEN guideline document no. 1: prevention and treatment of refeeding syndrome in the acute care setting. November 2013. Available at: https://www.irspen.ie/wp-content/uploads/2014/10/IrSPEN_Guideline_Document_No1.pdf. Accessed December 6, 2018.
82. Schmidt GL. Fluid and electrolytes. In: Corkins MR, ed. *The A.S.P.E.N. Pediatric Nutrition Support Core Curriculum*. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.); 2010:87–102.
83. Gura KM. Aluminum contamination in products used in parenteral nutrition: Has anything changed? *Nutrition*. 2010;26:585–594.
84. Gura KM. Aluminum contamination in parenteral products. *Curr Opin Clin Nutr Metab Care*. 2014;17:551–557.
85. Food and Drug Administration. Aluminum in large and small volume parenterals used in total parenteral nutrition. *Fed Regist*. 2000;65:4103–4111.
86. Howard L. Home parenteral nutrition: Survival, cost, and quality of life. *Gastroenterology*. 2006;130:S52–S59.
87. Lipman TO. The cost of TPN: Is the price right? *JPEN J Parenter Enteral Nutr*. 1993;17:199–200.
88. Eisenberg JM, Glick HA, Buzby GP, et al. Does perioperative total parenteral nutrition reduce medical care costs? *JPEN J Parenter Enteral Nutr*. 1993;17:201–209.
89. Eisenberg JM, Glick H, Hillman AL, et al. Measuring the economic impact of perioperative total parenteral nutrition: Principles and design. *Am J Clin Nutr*. 1988;47:382–391.
90. Bost RBC, Tjan DHT, Van Zanten ARH. Timing of (supplemental) parenteral nutrition in critically ill patients: A systematic review. *Ann Intensive Care*. 2014;4:31.
91. DeLegge MH, Base MD, Bannister C, Budak AR. Parenteral nutrition (PN) use for adult hospitalized patients: A study of usage in a tertiary

medical center. *Nutr Clin Pract*. 2007;22:246–249.

92. Busch RA, Curtis CS, Leverson GA, Kudsk KA. Use of piggyback electrolytes for patients receiving individually prescribed vs premixed parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 2015;39:586–590.
93. Bozat E, Korubuk G, Abbasoglu O. Cost analysis of premixed multichamber bags versus compounded parenteral nutrition: Breakeven point. *Hosp Pharm*. 2014;49:170–176.
94. Alfonso JE, Berlana D, Ukleja A, Boullata J. Clinical, ergonomic, and economic outcomes with multichamber bags compared with (hospital) pharmacy compounded bags and multibottle systems: A systematic literature review. *JPEN J Parenter Enteral Nutr*. 2017;41:1162–1177.
95. Zaloga GP. Parenteral nutrition in adult inpatients with functioning gastrointestinal tracts: Assessment of outcomes. *Lancet*. 2006;367:1101–1111.
96. Mirtallo JM. Advancement of nutrition support in clinical pharmacy. *Ann Pharmacother*. 2007;41:869–872.

160

Enteral Nutrition

Vanessa J. Kumpf and Diana W. Mulherin

KEY CONCEPTS

1. The gastrointestinal (GI) tract defends the host from toxins and antigens by both immunologic and nonimmunologic mechanisms, collectively referred to as the gut barrier function. Whenever possible, enteral nutrition (EN) is preferred over parenteral nutrition (PN) because it is associated with a lower risk of metabolic and infectious complications and is less expensive and invasive.
2. Candidates for EN are those with a sufficiently functioning GI tract to allow adequate nutrient absorption who cannot or will not eat and in whom enteral access can be safely obtained.
3. Critically ill patients benefit from early initiation of EN. It is acceptable to deliver EN at low rates (eg, trophic feeds) for the first week in most ICU patients. However, this method may not be appropriate for severely malnourished patients who should have their EN advanced to goal as quickly as tolerated.
4. The most common route for both short- and long-term EN access is directly into the stomach. The method of delivery may be continuously via an infusion pump, intermittently via a pump or gravity drip, or bolus administration via gravity or syringe.
5. Patients unable to tolerate tube feeding into the stomach because of impaired gastric motility may benefit from feeding tube placement into the duodenum or jejunum. When feeding into the small bowel, the continuous method of delivery via an infusion pump is required to enhance tolerance.
6. Selection of the enteral feeding formulation depends on nutritional requirements, the patient's primary disease state and related complications, and nutrient digestibility and absorption. A standard polymeric formulation will be appropriate for the majority of adults.

7. Management of diarrhea in patients receiving EN should focus on identification and correction of the most likely cause(s). Tube feeding–related causes include too rapid delivery or advancement, intolerance to the formula composition, and occasionally formula contamination.
8. Medication administration through a feeding tube requires selection of an appropriate dosage form and verification of appropriate enteral access. Medications that should not be crushed and administered through a tube include enteric-coated or sustained-release capsules or tablets and sublingual or buccal tablets.
9. The coadministration of medications with EN can result in alterations in bioavailability and/or changes in the desired pharmacologic effects. Medications known to interact with EN include phenytoin, warfarin, levothyroxine, select antibiotics, antacids, and proton-pump inhibitors.

Preclass Engaged Learning Activity

Visit the "Feeding Tube Awareness Foundation" website and navigate to "Tube Feeding Basics." The webpage contains information on each type of feeding tube. The information is presented in a patient education format and is useful to enhance student understanding of the types of feeding tubes available, how these appear when inserted into a patient, and general clinical and patient considerations for each tube. This will aid in the COLLECT and ASSESS steps in the patient care process.

INTRODUCTION

Enteral nutrition (EN) is defined as the delivery of nutrients by tube or by mouth into the gastrointestinal (GI) tract. This chapter focuses on nutrient delivery through a feeding tube rather than oral food ingestion. The terms *enteral nutrition* and *tube feeding* are thus used interchangeably in this context. The goal of EN is to provide calories, macronutrients, and micronutrients to those patients who are unable to achieve these requirements from an oral diet. Increased recognition of malnutrition, along with improvements in enteral access techniques, feeding formulations, and methods to prevent and manage complications, have resulted in an increased use of EN across all healthcare settings. In this chapter, principles and practices related to the safe and

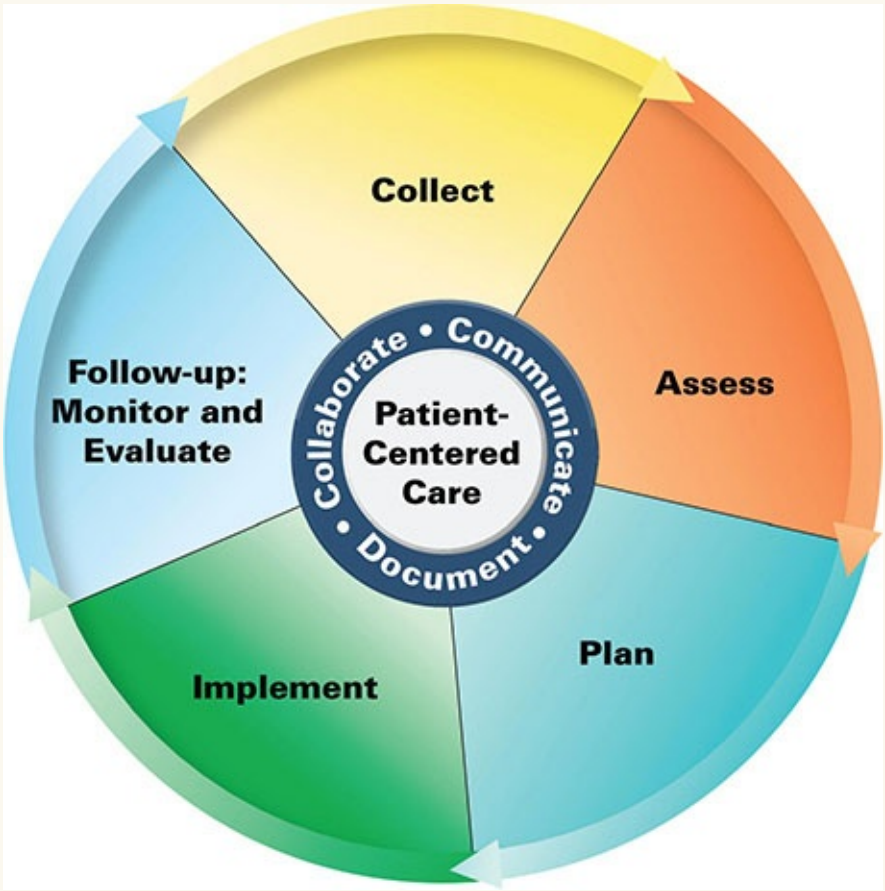
successful use of EN therapy are described.

GASTROINTESTINAL TRACT PHYSIOLOGY

The GI tract plays a key role in the processing of ingested foods. Many of the processes involved in digestion, absorption, and utilization of nutrients are modifiable by the presence of acute and chronic illnesses.

Digestion and Absorption

Digestion and absorption are GI processes that generate the body's usable fuels.[1,2] Ingested nutrients are primarily large polymers that cannot be absorbed across the intestinal cell membrane unless they are transformed into an absorbable molecular form. Digestion consists of the stepwise conversion of a complex chemical and physical nutrient into a molecular form that is absorbable by the intestinal mucosa. Absorption from the GI tract is a multistep process that includes the transfer of a nutrient across the intestinal cell membrane. The nutrient ultimately reaches the systemic circulation through the portal venous or splanchnic lymphatic systems, provided that the GI or biliary tract does not excrete it. In addition, a coordinated interplay of GI motility and neurohormonal secretion is required to facilitate adequate digestion and absorption.



Patient Care Process for the Use of Enteral Nutrition

Collect

- Patient characteristics (eg, age, race, sex)
- Patient history (past medical, surgical, family, social—alcohol use)
- Nutrition history (dietary history, weight history, dietary intolerance, prior enteral or parenteral nutrition therapy)
- Current medications (including nutritional supplements)
- Current diet and current nutrition support regimen
- Procedures related to enteral access placement
- Objective data

- Height, weight, BMI
- Fluid balance (intake and output)
- Labs (eg, serum electrolytes, Scr, BUN, glucose, albumin)
- Other diagnostic tests when indicated (eg, abdominal imaging, gastric emptying study, swallow study)

Assess

- Appropriate time to initiate enteral nutrition
- Presence of altered GI anatomy or function (eg, bariatric surgery, delayed gastric emptying, pancreatic insufficiency)
- Nutritional status and risk of refeeding syndrome (eg, unintentional weight loss, prolonged time period with poor nutritional intake, BMI 18, low visceral proteins, muscle wasting)
- Nutrition requirements (goal protein, calories, fluid, and micronutrient intake)
- Appropriate enteral access (see Table 160-3)

Plan

- Enteral nutrition regimen including specific enteral feeding formulation, method of administration (continuous, bolus), and initiation and advancement guidelines (see Table 160-5)
- Monitoring parameters for efficacy (weight, enteral intake), GI tolerance (stool output, nausea, vomiting, abdominal distension), and metabolic complications (serum electrolytes, Scr, BUN, glucose, LFTs; see Table 160-6)

Implement

- Initiate enteral nutrition when the oral route fails or is not possible, the GI tract is functional, and enteral access can be safely achieved
- Patient education when home enteral nutrition is indicated

Follow-up: Monitor and Evaluate*

- Determine nutrition goal attainment

- Provide adjustments to the enteral nutrition regimen when nutrition goals are not achieved and consider transition to parenteral nutrition if repeated adjustments fail or intolerance develops
- Transition off enteral nutrition when nutrition needs are safely met by oral dietary intake

Collaborate with patient, caregivers, and other healthcare professionals.

Nutrient digestion involves the complex coordination of multiple mechanical, enzymatic, and physiochemical processes.[1,2] Mechanical dissolution of food occurs by chewing, then mixing and grinding the stomach contents. Food stimulates secretion of numerous hormones and enzymes from the salivary glands, stomach, liver and biliary system, pancreas, and intestines (**Table 160-1**). As food traverses the gut lumen, these hormones modulate GI motility and the secretions from other organs of the digestive system. Nutrient absorption occurs within the gut lumen and is a specific function of the intestinal cell membrane, which is comprised of fingerlike projections called villi. Each individual villus is made up of epithelial cells called enterocytes. The enterocyte surface contains special luminal projections called microvilli, which provide an increased surface area that is referred to as the brush-border membrane.

TABLE 160-1 Gastrointestinal Enzymes and Hormones

Enzyme/Hormone	Site of Secretion	Main Actions
Amylase	Salivary glands, pancreas	Converts carbohydrates, starch, and glycogen to simple disaccharides
Cholecystokinin	Duodenum, jejunum	Stimulates pancreatic enzyme secretion and gallbladder contraction
Chymotrypsinogen	Pancreas	Breaks down proteins into peptides
Enteroglucagon	Duodenum, small intestine	Inhibits pancreatic enzyme secretion and bowel motility
Gastric inhibitory peptide	Small intestine	Decreases gastric motility and stimulates insulin secretion
Gastrin	Stomach, duodenum	Stimulates gastric acid secretion and mucosal growth
Glucagon	Pancreas	Stimulates hepatic glycogenolysis and inhibits motility
Lipase	Pancreas	Hydrolyzes dietary fat to release fatty acids
Pancreatic polypeptide	Pancreas	Inhibits gallbladder contraction and pancreatic and biliary secretion
Pepsinogen	Stomach	Converts large proteins into polypeptides
Secretin	Small intestine	Stimulates hepatic and pancreatic water and bicarbonate release
Trypsinogen	Pancreas	Breaks down proteins into peptides
Vasoactive inhibitory peptide	Small intestine, pancreas	Vasodilator; stimulates water and bicarbonate secretion, insulin and glucagon release, and small bowel secretions

The digestion and absorption of carbohydrate, fat, and protein within the small intestine are illustrated in **Fig. 160-1**. Carbohydrates are presented to the small intestine in either a digestible or a nondigestible form. Polysaccharides (starches) and oligosaccharides (sucrose and lactose) undergo enzymatic digestion to simple sugars. The simple sugars are absorbed via active and passive transport mechanisms and are eventually released into the portal vein. Polysaccharides, such as cellulose complexes and other fiber components, pass undigested to the colon, where they are digested by bacteria and enzymes to short-chain fatty acids. Colonic absorption of short-chain fatty acids stimulates sodium and water reabsorption. The short-chain fatty acids serve as a systemic energy source and they provide nourishment for the colonic mucosa cells.

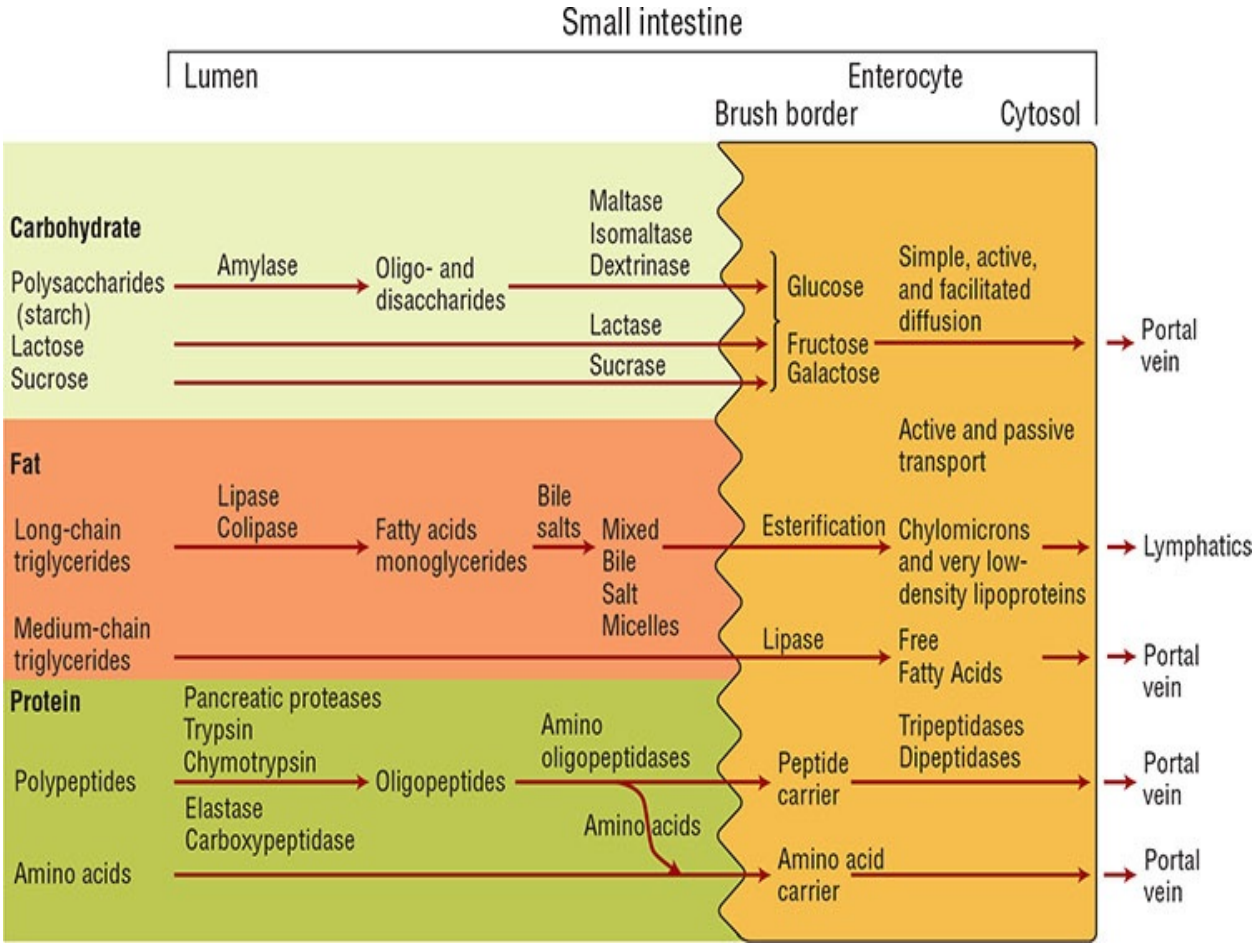


FIGURE 160-1 Schematic of carbohydrate, fat, and protein digestion.

Fat is most often presented to the small intestine as long-chain triglycerides. Fat digestion requires pancreatic lipase release and formation of mixed bile salt micelles, which are then absorbed across the intestinal enterocyte. Within the enterocyte, triglycerides are reesterified and packaged into chylomicrons that are then transported into the lymphatic system. Medium-chain triglycerides (MCTs) can be absorbed intact by the mucosal membrane and are acted on by intracellular lipase within the enterocyte to release free fatty acids that pass directly into the portal vein.[3]

Protein is presented to the small intestine primarily as large polypeptides and to a lesser extent as free amino acids because of protein denaturation in the stomach. Polypeptide digestion generates oligopeptides, which are further hydrolyzed to dipeptides and tripeptides. Peptide absorption occurs via a peptide transport system while free amino acids are absorbed via specific amino acid transporters. These peptide carriers are very efficient, whereas free amino acid absorption appears to be less efficient.[2]

Understanding the mechanisms involved in digestion and absorption can greatly enhance the rational use of EN in patients with normal or altered GI anatomy and/or function. Various circumstances may alter the efficacy of nutrient digestion and absorption. For example, pancreatic insufficiency may result in malnutrition associated with inadequate absorption of fat and fat soluble vitamins.

Gut Host Defense Mechanisms

1 Besides digesting and absorbing nutrients to maintain nutritional health, the GI tract is actively involved in defending the host from toxins and antigens by both immunologic and nonimmunologic mechanisms.[4] These gut host defense mechanisms are collectively referred to as the gut barrier function. The gut barrier acts to prevent the systemic spread of intraluminal bacteria and endotoxins to other organs and tissues. Hydrochloric acid secreted by the stomach kills most of the bacteria ingested with food. Under normal circumstances, a mucus layer coats the intestinal epithelium and thereby alters the adherence of bacteria to the cells of the GI tract but provides a favorable environment for anaerobic bacteria. Anaerobic bacteria, which normally colonize the mucus layer, aid in preventing tissue colonization by potential pathogens. Small bowel peristalsis further prevents bacterial stasis and overgrowth. The gut barrier function is also maintained by the intestinal immune system, known as the gut-associated lymphoid tissue (GALT). GALT regulates the local immune response to antigens within the GI tract. Specific immunoglobulins are secreted to kill the remaining organisms and neutralize any toxins they produce. The liver Kupffer cells help to maintain gut barrier function by clearing the portal blood of gut-derived bacteria and endotoxins. Gut barrier integrity may be affected negatively by numerous pathogenic insults, such as physiologic stress and ischemia, and a variety of drugs, including chemotherapeutic agents. The administration of certain probiotics can modify intestinal flora and may have beneficial effects in various disease states and patient populations by positively affecting the maintenance of gut barrier function and intestinal immune function.[5]

INDICATIONS FOR ENTERAL NUTRITION

2 The decision to initiate EN is based on a variety of factors. Suitable candidates are those who cannot or will not eat a sufficient amount to meet their

nutritional requirements, those who exhibit a sufficient functioning GI tract to allow for nutrient absorption, and those in whom a method of enteral access can be safely initiated.[6,7] Thus, EN may be indicated in a variety of conditions or disease states (Table 160-2). For example, patients who have difficulty swallowing due to stroke, altered mental status, or obstruction in the head, neck, or esophagus due to cancer may benefit from EN.

TABLE 160-2 Potential Indications for Enteral Nutrition

Neoplastic disease	**Neurologic impairment**
Chemotherapy	Comatose state
Radiation therapy	Cerebrovascular accident
Upper GI tumors	Demyelinating disease
Cancer cachexia	Severe depression
Organ dysfunction	Cerebral palsy
Liver disease/failure	**Other indications**
Kidney disease/failure	AIDS
Cardiac cachexia	Anorexia nervosa
ARDS/ALI	Complications during pregnancy
Bronchopulmonary dysplasia	Failure-to-thrive
Congenital heart disease	Geriatric patients with multiple chronic diseases
Organ transplantation	Inborn errors of metabolism
Hypermetabolic states	Cystic fibrosis
Closed head injury	
Burns	
Trauma	
Postoperative major surgery	
Sepsis	
GI disease	
Inflammatory bowel disease	
Short bowel syndrome	
Esophageal motility disorder	
Pancreatitis	
Fistulas	
Gastroesophageal reflux disease (severe)	
Esophageal or intestinal atresia	

AIDS, acquired immune deficiency syndrome; ALI, acute lung injury; ARDS, acute respiratory distress syndrome.

Critically ill patients who are endotracheally intubated represent a large percentage of hospitalized patients requiring EN. Traditionally, EN in the critically ill population was regarded as supportive care designed to provide nutrients during the period of time the patient was unable to maintain adequate oral dietary intake. Current evidence also supports the use of EN as a tool to modulate the stress response to critical illness and improve patient outcomes.

Nutrition guidelines support the initiation of EN in critically ill adults who are unable to maintain volitional intake.[8–10] Some of these patients may have reduced gastric emptying caused by sepsis, GI surgery, anesthetic agents, opioid analgesics, and underlying pathology, such as diabetic gastroparesis and burns. However, successful EN can often be achieved by advancing the tip of the feeding tube beyond the pylorus into the duodenum, or preferably into the jejunum. Small bowel feeding may also be appropriate for patients with gastric outlet obstruction, those with pancreatitis, those with moderate-to-severe gastroesophageal reflux, or those with high-aspiration risk.

Contraindications to EN use are distal mechanical intestinal obstruction, bowel ischemia, and necrotizing enterocolitis. Contraindications to tube placement include active peritonitis and uncorrectable coagulopathy.[1,11] Conditions that may result in significant challenges to EN use include severe diarrhea, protracted vomiting, enteric fistulas, severe GI hemorrhage, hemodynamic instability, and intestinal dysmotility.

BENEFITS OF ENTERAL NUTRITION

The importance of maintaining nutrient delivery through the GI tract in patients without a contraindication to its use is well supported. The beneficial effects of EN, specifically in the critically ill patient, are further enhanced if EN is initiated within 24 to 48 hours of admission to an intensive care unit (ICU).[8–10]

Enteral Versus Parenteral Nutrition

Clinical studies comparing EN and parenteral nutrition (PN) in the critically ill adult patient have historically demonstrated a decrease in infectious complications with the use of EN.[12] Infectious complications are thought to be less common with EN in part because EN supports functional gut integrity by stimulating bile flow and the release of endogenous trophic agents, such as cholecystokinin, gastrin, and bile salts. Provision of enteral nutrients appears to help maintain the intestinal mucosal villous height and support the mass of secretory immunoglobulin A (IgA)-producing immunocytes that comprise the GALT. In the setting of critical illness or severe injury, adverse changes in gut permeability and gut barrier function that result in increased risk for systemic infection and multiorgan dysfunction syndrome have been noted. By supporting gut integrity, the enteral feeding route is thought to lower infection risk and minimize organ failure.[8]

Use of EN in patients with abdominal trauma, burns, severe head injury, major surgery, and acute pancreatitis is generally thought to lower infectious complications compared to PN. This reduction in infectious complications is primarily associated with a lower incidence of pneumonia and catheter-related bloodstream infections and a decrease in abdominal abscess in trauma patients.[12] However, findings from recent studies challenge EN use as the preferred route for early nutritional support in critically ill patients.[13–15] Enteral nutrition is more physiologic than PN in terms of nutrient utilization and therefore is generally associated with fewer metabolic complications, such as glucose intolerance and elevated insulin requirements.[16] Enteral formulations contain both complex and simple carbohydrates, which results in slower carbohydrate absorption compared with the simple carbohydrate, dextrose, used in PN. In addition, enteral formulations that contain fiber and/or a high-fat content will further slow carbohydrate absorption and reduce blood sugar elevations by delaying gastric emptying, accounting for better blood glucose control when carbohydrates are given via the enteral route. An additional physiologic benefit of enteral feeding is that it stimulates bile flow through the biliary tract and thus reduces the risk of developing cholestasis, gallbladder sludge, and gallstones, conditions that have been associated with long-term PN and bowel rest.[17] EN avoids the potential infectious and technical complications associated with the placement and use of a central venous access device required for PN. Finally, EN is less costly than PN when all factors associated with the therapy are considered.

Timing of Initiation

The timing of initiation of EN in the critically ill patient is of clinical significance. Initiating EN in the first 24 to 48 hours following admission appears to attenuate the stress response and may reduce disease severity and infectious complications when compared with the initiation of feedings after 48 hours.[8–10] Early EN has also been associated with a decrease in the release of inflammatory cytokines and fewer effects on gut permeability. As previously mentioned, reductions in infectious complications with EN compared with PN have been reported in the critically ill patient when feeding was initiated within 24 to 48 hours of hospital admission.[8] The benefit of fewer infectious complications is not apparent when the initiation of EN is delayed. A review of available studies comparing early versus delayed EN in critically ill patients revealed a trend toward a reduction in infectious complications with early EN.[8–

[10] In addition, a trend toward reduction in mortality associated with early EN has been noted.[8–10]

In critically ill patients who are hemodynamically unstable, there is concern that EN may result in bowel necrosis because of poor gastric perfusion and increased oxygen demand. Even though well-designed trials are lacking, it is recommended that initiation of EN be delayed until the patient is fluid resuscitated and vasopressors are being withdrawn or are infusing at low, stable doses.[8] EN is well-tolerated in patients receiving lower doses of vasopressors, and early EN is associated with decreased mortality in patients receiving vasopressors.[18,19] Therefore, early EN (within 24-48 hours after hospital admission) can safely be initiated in most critically ill adult patients.[8–10] Early EN initiation is not warranted for previously well-nourished, mild-to-moderately stressed adult patients who are not critically ill. When oral intake is inadequate, it is reasonable to delay the initiation of EN for 5 to 7 days in these patients.[6] In the mild-to-moderately stressed adult patient who is moderately-to-severely malnourished, most clinicians would initiate EN sooner.

ENTERAL ACCESS

Advances in enteral access techniques have contributed to the expanded use of EN for conditions in which PN had previously been used. In particular, improved methods of achieving jejunal access for feeding have allowed the use of EN during the early postoperative and postinjury period when gastric motility is typically impaired. As outlined in **Table 160-3**, various factors influence the selection of enteral access site and device, including anticipated duration of use and whether to feed into the stomach or small bowel. **Figure 160-2** illustrates the predominant enteral access options.

TABLE 160-3 Options and Considerations in the Selection of Enteral Access

Access	EN Duration/Patient Characteristics	Tube Placement Options	Advantages	Disadvantages
Nasogastric or orogastric	Short term Intact gag reflex Normal gastric emptying	Manually at bedside	Ease of placement Allows for all methods of administration Inexpensive Multiple commercially available tubes and sizes	Potential tube displacement Potential increased aspiration risk
Nasojejunal	Short term Impaired gastric motility or emptying High risk of GER or aspiration	Manually at bedside Fluoroscopically Endoscopically	Potential reduced aspiration risk Allows for early postinjury or postoperative feeding Multiple commercially available tubes and sizes	Manual transpyloric passage requires greater skill Potential tube displacement or clogging Bolus or intermittent feeding not tolerated
Gastrostomy	Long term Normal gastric emptying	Surgically Endoscopically Radiologically Laparoscopically	Allows for all methods of administration Low-profile buttons available Large-bore tubes less likely to clog Multiple commercially available tubes and sizes	Attendant risks associated with each type of procedure Potential increased aspiration risk Risk of stoma site complications
Jejunostomy	Long term Impaired gastric motility or gastric emptying High risk of GER or aspiration	Surgically Endoscopically Radiologically Laparoscopically	Allows for early postinjury or postoperative feeding Potential reduced aspiration risk Multiple commercially available tubes and sizes Low-profile buttons available	Attendant risks associated with each type of procedure Bolus or intermittent feeding not tolerated Risk of stoma site complications

EN, enteral nutrition; GER, gastroesophageal reflux.

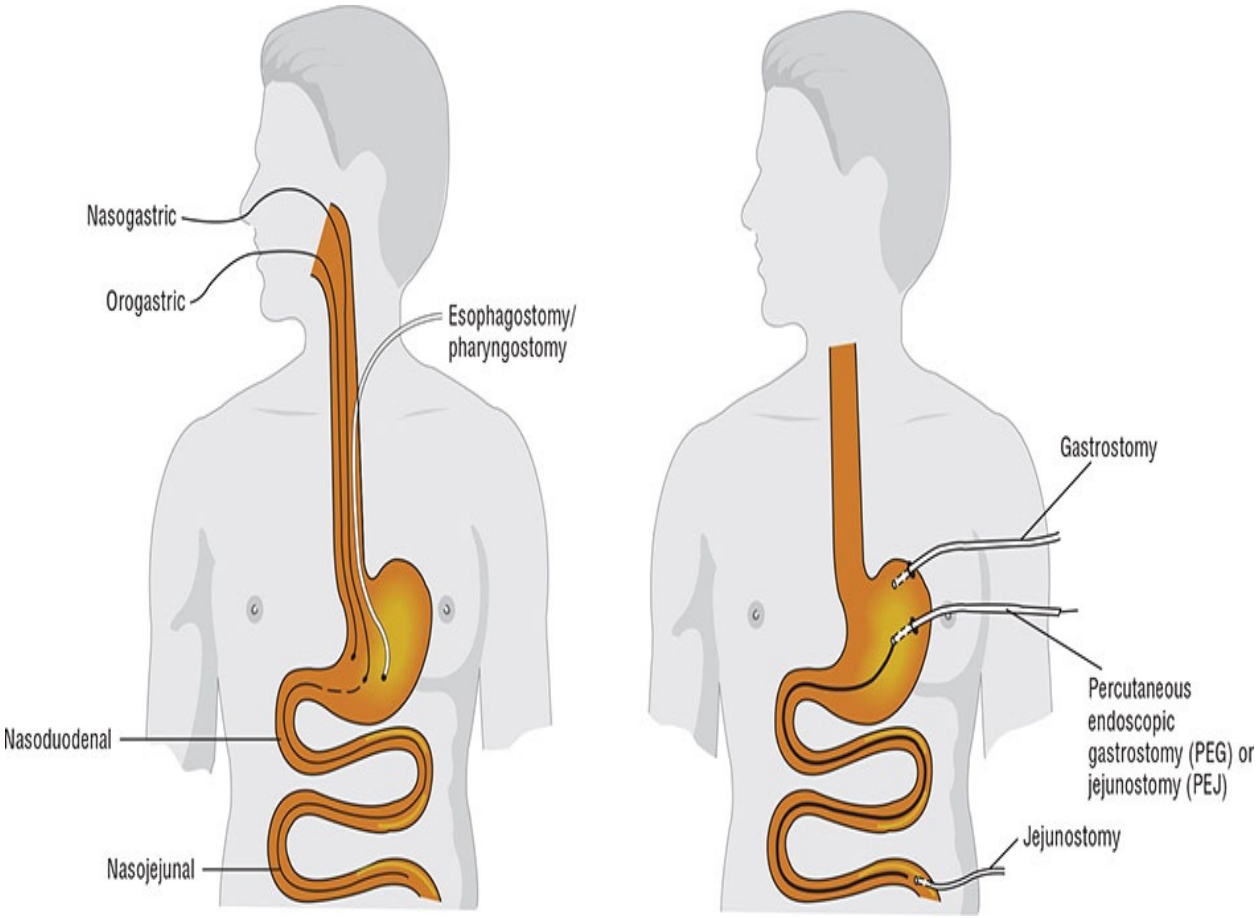


FIGURE 160-2 Access sites for tube feeding.

Short-Term Access

3 Short-term enteral access is easier to initiate, less invasive, and less costly than the establishment of long-term access.[20] The most frequently used routes for short-term enteral access are established by inserting a tube through the nose or mouth and passing the tip into the stomach (nasogastric [NG]; orogastric [OG]), or jejunum (nasojejunal [NJ]). In general, these tubes are used in the hospitalized patient when the anticipated tube feeding duration is less than 4 to 6 weeks. The orogastric route is generally reserved for patients in whom the nasopharyngeal area is inaccessible. Because these routes do not require surgical intervention, they are the least invasive options. The most common technique for placement is blind passage at the bedside by trained medical personnel. Several techniques have been described in the literature to help facilitate bedside placement, and greater skill is required to advance the tip of the feeding tube beyond the pylorus and into the small bowel.[11] Metoclopramide, a prokinetic agent, has been used with variable success to aid passage of the tube beyond the

pylorus. A bedside electromagnetic tube placement device has also been used to guide tip position into the small bowel by attracting a metal tip on the end of the tube.[21,22] Alternatively, a variety of endoscopic and fluoroscopic techniques have been described to insert tubes into the small bowel.[11,20] Radiographic confirmation of appropriate tip placement should be obtained prior to use for all bedside placed feeding tubes.[11,23]

Nasogastric tubes vary in diameter and stiffness. Large-bore (greater than or equal to 14F) rigid NG tubes are used primarily to decompress the stomach but can also be used for feeding. There is a low incidence of clogging with these tubes, and they provide a reliable way to measure gastric residual volumes (GRVs). The major disadvantage associated with the use of these tubes is patient discomfort. Small-bore nasal tubes designed solely for feeding are available in varying lengths (12-60 in. [30-152 cm]) and diameters (3.5F-12F) to accommodate both pediatric (including neonates) and adult patients. The tip of the tube can be placed into the stomach or into the duodenum or jejunum (also referred to as transpyloric placement). These tubes consist of a lightweight, pliable silicone or polyurethane material that is designed for patient comfort. A disadvantage of small-bore tubes is that they more easily occlude, often as a result of improper medication administration or flushing technique. The feeding tube is frequently held in place only by a piece of tape on the nose or face; therefore, it can be inadvertently dislodged relatively easily. Nasal bridles have been used with variable results to secure the nasoenteric tube in place.[11] A bridle involves passing a piece of thin tubing or suture into one nostril, then around the bony portion of the nose, and out the other nostril, and finally tying the tubing around the feeding tube.

4 In general, gastric feeding is the least expensive and the least labor-intensive method for enteral feeding; however, feeding into the stomach is not always tolerated. Patients with impaired gastric motility may be predisposed to aspiration and pneumonia when fed into the stomach. Many critically ill, injured, and postoperative patients exhibit delayed gastric emptying, which limits their ability to tolerate gastric feeding. In addition, patients with diabetic gastroparesis or patients with severe gastroesophageal reflux disease or intractable vomiting are at a higher risk for aspiration of gastric contents, which can result in pneumonia. In these patients, placing the tip of the tube into the duodenum or jejunum has been suggested as a method to decrease aspiration risk.[11] Transpyloric feeding has been associated with a lower rate of vomiting and ventilator-associated pneumonia when compared to NG feeding. However, the evidence to support the difference in aspiration and aspiration pneumonia risk

associated with gastric and small bowel feeding is inconclusive.[8] In general, small bowel feeding may be beneficial in patients who do not tolerate gastric feeding and offers an alternative option for EN prior to resorting to PN.[8–10]

Long-Term Access

Feeding tubes used for short-term enteral access are usually not optimal for long-term use because of patient discomfort, complications, and mechanical failures that develop over time. Long-term access should generally be considered when the need for EN is anticipated to be longer than 4 to 6 weeks. Many techniques can be used to establish long-term enteral access, including laparotomy, laparoscopy, endoscopic, and image guidance (eg, fluoroscopy and ultrasound).[11] The ability to perform the various techniques will be somewhat dependent on the expertise and facilities available within each institution. Long-term enteral access options include gastrostomy and jejunostomy tubes.

A gastrostomy is the most common type of long-term enteral access. It eliminates the nasal irritation and discomfort associated with nasoenteric feeding tubes and inadvertent removal is uncommon. In addition, because feeding gastrostomies use large-bore tubes, clogging is less of a problem. The most commonly placed is the percutaneous endoscopic gastrostomy (PEG). The technique is minimally invasive and can be performed safely and cost-effectively in an endoscopy suite or at the bedside using conscious sedation and local anesthesia in adult patients. Gastrostomy tubes are available in various sizes (12F-28F; 0.8-5 cm shaft lengths), material (eg, silicone and polyurethane), and have different retention mechanisms. Since smaller-diameter tubes are prone to more frequent occlusion and dysfunction, the largest diameter size possible is preferred. For patient convenience, comfort, and cosmetic appearance, a low-profile skin-level gastrostomy device may be used. It is typically placed as an exchange tube for a preexisting gastrostomy or jejunostomy once the tract has matured but can also be used at the time of initial tube placement. This “gastric button” consists of a short, silicone, self-retaining conduit with either a mushroom-type or a balloon-type tip at the internal end and a one-way valve and small flange at the skin surface. Because this averts the external tube presence, it tends to be preferred in children or ambulatory adults who are receiving intermittent feedings. The exit site of all gastrostomies requires general stoma care to prevent inflammation and infection. Routine replacement of the gastrostomy tube at defined intervals (usually 3-6 months) is a standard of practice of many clinicians to prevent failure of the retention mechanism that can

occur over time.[11]

In patients with a functional bowel but impaired gastric motility, pancreatitis, or who otherwise do not tolerate gastric feeding and require long-term enteral access, a jejunostomy may be an appropriate option.[20] Various endoscopic and fluoroscopic techniques are available for direct jejunostomy placement. A surgically placed jejunostomy may be an option if the patient requires a laparotomy or laparoscopy for other reasons. For patients who require small bowel feeding with simultaneous gastric decompression, a gastrojejunal tube may be placed utilizing various endoscopic, fluoroscopic, and surgical techniques.[20] Because jejunostomies use smaller-bore tubes, occlusion occurs more commonly than with gastrostomy tubes. Gastrojejunostomy tubes are often replaced every 3 to 6 months to prevent occlusion.

There are ethical implications regarding determination of appropriate candidates for long-term feeding tube placement.[11,24–26] Because a gastrostomy is relatively easy to place and many patients, families, and clinicians overestimate the benefits of EN, it is prone to inappropriate use. In certain patient populations, such as those with advanced dementia or other near end-of-life conditions, the placement of a gastrostomy is not recommended. Artificial nutrition and hydration (ANH) has not been shown to promote the healing of pressure ulcers, increase patient comfort or functional status, or prolong survival when compared to hand feeding in patients with advanced dementia.[24] From a clinical standpoint, ANH does not increase a patient’s comfort or improve nutrition parameters of most terminally ill individuals and can result in medical complications.[24] Studies consistently demonstrate that survival rates are not improved in older patients with advanced dementia who receive tube feedings and it is associated with substantial burden, including agitation, greater use of physical and chemical restraints, recurrent aspiration, and tube-related complications.[25,26] Evaluation by a multidisciplinary team is warranted for all patients near the end of life to establish whether the benefit of EN outweighs the risks of feeding tube placement.[24–26]

ADMINISTRATION METHODS

Enteral nutrition may be administered by continuous, cyclic (continuous rate over a portion of the day), intermittent (infused over 20-60 minutes), or bolus (generally given in 5-10 minutes) methods and may be accomplished by syringe, gravity, or pump-controlled techniques. The delivery method depends on the

location of the tip of the feeding tube, the patient's clinical condition and intestinal function, and the patient's tolerance to the tube feeding.

Continuous

Pump-assisted continuous administration of EN is generally the method of choice for most hospitalized patients, especially when initiating therapy. They may be candidates for transitioning to intermittent or bolus feeding for long-term use as their medical condition stabilizes, as described below. However, when EN is to be delivered into the small intestine, the continuous method is always preferred because it is associated with enhanced tolerance. The rapid delivery of feeding into the small intestine may contribute to abdominal distension, cramping, hyperperistalsis, and diarrhea. Therefore, conversion to intermittent or bolus administration is not recommended for those with jejunostomies.

The delivery system for continuous administration generally includes a feeding set with attached reservoir bag or spike set that connects to a feeding container. The feeding set is attached to a pump and then connected to the patient's enteral access tube with an adaptor. Continuous administration may increase nursing time because routine checks are needed, but this disadvantage is usually offset by the improved tolerance. For adults, target EN administration rates generally range from 50 to 125 mL/hr, although higher rates have been used without complications. The primary disadvantage to this method of administration is the cost and inconvenience associated with the pump and administration sets. In the home care setting, battery-operated ambulatory enteral pumps that fit into a backpack with the feeding bag are available to allow the patient greater mobility.

Cyclic

A patient who is not eating well during the day because of complaints of fullness and lack of appetite or who is not able to consume enough calories during the day to meet increased needs (eg, trauma and burns) may benefit from cyclic EN, in which the enteral feeding is administered by pump during part of the day—this typically occurs at night. In addition, nocturnal EN administration will free the patient from the pump during the day and allow for greater mobility. This increased mobility may be particularly useful for the home patient or patient requiring therapy for physical rehabilitation during the day. This method may be used in patients with either gastric or small bowel access.

Bolus

The bolus administration of EN is commonly used for patients in the home or long-term care setting who have a gastrostomy. This administration technique involves the delivery of the enteral feeding formulation over 5 to 10 minutes. Essentially, the only equipment needed is a syringe to instill the feeding volume into the tube. Depending on the patient's nutritional requirements, a feeding volume of 240 to 500 mL is generally used and repeated four to six times daily. From a convenience standpoint, it is generally preferable to adjust the bolus volume in increments of the feeding formulation container size (usually 240-250 mL). Bolus delivery is not appropriate for patients with duodenal or jejunal access, as it may result in cramping, nausea, vomiting, aspiration, and diarrhea. Bolus administration also should be avoided in patients with delayed gastric emptying and in patients who are at high risk of aspiration.

Intermittent

The intermittent method is used in patients with a gastric feeding tube who may be experiencing intolerance to bolus administration over 5 to 10 minutes. In this scenario, the prescribed volume is administered over a longer time period, generally 20 to 60 minutes every 4 to 6 hours. For this method, the desired volume of feeding formulation is emptied into a reservoir bag or container with attached tubing and administered by an enteral pump or via gravity drip using a roller clamp. The bolus and intermittent methods of administration are more consistent physiologically with normal eating patterns compared to the continuous method.

INITIATION AND ADVANCEMENT PROTOCOL

Guidelines for the initiation and advancement of enteral feeding formulations vary greatly and are primarily tailored to patient tolerance. The typical recommendation for continuous EN administration for adults is to start at 20 to 50 mL/hr and advance by 10 to 25 mL/hr every 4 to 8 hours until the desired goal is achieved. For intermittent administration, the typical recommendation is to start with 120 mL every 4 hours and advance by 30 to 60 mL every 8 to 12 hours.[6] Schedules for progression of tube feeding from initial to target rates are important and may influence tolerance. If the protocol is too conservative, it may take an excessively long period of time to reach nutrient goals. The practice of diluting enteral feeding formulations is not recommended due to increased risk

of microbial contamination.[23] The development of an EN protocol within an institution that outlines initiation and advancement criteria is recommended to optimize achievement of nutrient goals.[8,9] Due to frequent interruptions of EN, some institutions have implemented volume-based feeding protocols to improve success in meeting targeted goals. Such a protocol shifts the focus from an hourly rate target goal to a 24-hour volume goal and provides guidance on how to adjust the rate of administration when EN is interrupted for reasons unrelated to GI tolerance.[27,28]

The optimal dose of EN in critically ill adult patients is a subject of debate. The intentional use of permissive underfeeding (50%-80% of goal) or trophic EN (10-20 mL/hr) in critically ill adult patients requiring short ICU lengths of stay may result in improved GI tolerance and similar short-term outcomes when compared to full feeding.[8] However, the strategy of intentional underfeeding may not be appropriate for patients at high-nutrition risk as defined by validated scores accounting for nutrition status, disease severity, preexisting malnutrition, and comorbidities. Patients who are severely malnourished or at high-nutrition risk should have their EN advanced toward their energy goal over 24 to 48 hours while monitoring for refeeding syndrome. This is due to an association with lower mortality in critically ill patients at high-nutrition risk who receive adequate nutrition.[8,29]

WATER FLUSHES

All feeding tubes require routine flushing with water before and after administration of EN and medications.[23] Flushing may be done manually with a syringe or via the tube feeding pump. Feeding tubes should be flushed immediately before and after bolus or intermittent feedings and at standard intervals (eg, a minimum of 30 mL every 4 hours) with continuous feedings. Safe drinking water is an appropriate flushing source for most patients. Purified water is the preferred flushing source for immunocompromised or critically ill patients. Any fluid needs unmet by the tube feeding formula itself can be achieved via tube feeding water flushes.[23]

ENTERAL FEEDING FORMULATION SELECTION

Historically, enteral formulas were designed primarily to provide essential

nutrients. Over the years, enhancements have been made to meet specific patient needs and improve tolerance. For example, nutrient composition has been enhanced by changing the content of the amino acids (eg, glutamine and arginine), increasing the omega-3 polyunsaturated fatty acid content, and adding RNA to enhance immune function and improve therapeutic outcomes. These specific nutrients have been called pharmaconutrients or immunonutrients because of the intent to use them to modify the activity of the immune system and improve clinical outcomes.[30] Currently, enteral feeding formulations are categorized by the FDA as medical foods.[31] They are considered components of supportive care and are simply regulated to ensure sanitary manufacture. Unfortunately, they are not subject to rules governing health claims, and promotion of medical foods for therapeutic intent is currently not regulated by the FDA.[31]

The macronutrient content of enteral formulas (namely, protein, carbohydrate, and fat) varies in nutrient complexity (**Table 160-4**). Nutrient complexity refers to the amount of hydrolysis and digestion a substrate requires prior to intestinal absorption. Polymeric or intact substrates are of similar molecular form as the foods we eat. Enteral formulas that contain partially hydrolyzed or elemental substrates are characterized as elemental or defined-formula diets. The caloric contribution of each of the macronutrients is as follows: carbohydrates, 4 kcal/g (17 kJ/g); protein, 4 kcal/g (17 kJ/g); and fat, 9 kcal/g (38 kJ/g).

TABLE 160-4 Enteral Formula Nutrient Complexity

Nutrient	Polymeric or Intact	Partially Hydrolyzed or Elemental
Carbohydrate	Starches Fruit, vegetable, cereal solids Glucose polymers Corn syrup solids Polysaccharides	Oligosaccharides Maltodextrins Disaccharides Maltose, sucrose, lactose Monosaccharides Glucose Galactose
Fat	Long-chain triglycerides Polyunsaturated fatty acids Corn oil Safflower oil Soybean oil Canola oil Marine oils	Medium-chain triglycerides Coconut oil Palm kernel oil Free fatty acids Linoleic
Protein	Whole Egg, milk, wheat, whey Isolates Caseinate salts Lactalbumin	Oligopeptides Dipeptides Tripeptides L-amino acids

Protein Composition

The essential amino acid content of the protein source determines the quality of the protein, and most commercially available enteral feeding formulations contain proteins of high quality. The form of the protein source in enteral formulas will determine the amount of digestion that is required for absorption. Polymeric or intact protein sources require digestion to smaller peptides and free amino acids before absorption. Protein sources, such as meat, milk, eggs, and caseinates, require digestion by hydrochloric acid, specific protein enzymes, and pancreatic proteases. Enteral formulations may also contain protein sources that are partially hydrolyzed to peptides or L-amino acids. As the molecular form of protein is reduced in size, the osmotic load of the enteral formulation is increased. Many commercially available enteral feeding formulations contain combinations of intact and partially hydrolyzed protein sources. Most enteral formulations are gluten-free.

Conditionally Essential Amino Acids

Glutamine and arginine are generally considered nonessential amino acids. However, during periods of high-physiologic stress, the need for these nutrients may be increased beyond the body's synthetic ability; consequently, these amino acids are characterized as conditionally essential. Because they are usually present in low amounts in most enteral feeding formulations, formulations targeted for the critically ill may be supplemented with glutamine and/or arginine.

Glutamine serves as a key fuel for rapidly dividing cells, including enterocytes, endothelial cells, lymphocytes, and fibroblasts. The primary site of glutamine production is skeletal muscle. During critical illness, skeletal muscle catabolism provides an increased glutamine supply, but this may not be enough to meet the high rate of glutamine use by cells of the immune system and other cells involved in recovery and repair. Glutamine depletion may develop, particularly during prolonged periods of metabolic stress. Favorable outcomes have been documented in subtypes of critically ill patients when enteral formulations have been supplemented with glutamine.[8] Immune-modulating EN formulas containing glutamine are specifically recommended in patients with traumatic brain injury due to their association with decreased infections.[8] However, high-dose glutamine supplementation in critically ill patients with shock and multisystem organ failure should be avoided.[8,32]

Arginine has been added to some immune-modulating enteral formulations in concentrations that range from 4.5 to 14 g/L. Immune-modulating EN formulas containing arginine in combination with fish oil in perioperative patients in the surgical ICU is associated with decreased infections and decreased length of stay.[8] However, arginine supplementation remains controversial, especially in patients with sepsis.[30] Many of arginine's physiologic effects are mediated by its conversion to nitric oxide, which, in turn, modulates immune function, inflammation, and vasodilation. Some of these effects may be potentially harmful in the patient with sepsis, especially when higher arginine intakes are used.[8] Unfortunately, studies have not extensively evaluated the effects of individual immunonutrients, and they are criticized for significant patient heterogeneity and large range of nutrient dosing.

Carbohydrate Composition

The carbohydrate component of enteral feeding formulations usually provides the major source of calories. Polymeric or intact enteral formulations contain starches and numerous types of glucose polymers, which require digestion to

monosaccharides prior to intestinal absorption (see Fig. 160-1). As the extent of hydrolysis of carbohydrates increases within an enteral formulation, the osmolality of the formulation increases. Simple sugars, such as glucose and galactose, contribute significantly to the osmolality of enteral formulations. Consequently, polymeric entities, rather than elemental sugars, are preferred. Glucose polymers provide a useful carbohydrate source that is tolerated by most individuals (see Table 160-4). The polymers are large chains that provide minimal osmotic load, yet are absorbed easily in the intestine. The one shortcoming of glucose polymers and oligosaccharides is that they are not as sweet as simple glucose and thus may decrease the palatability of orally consumed products. Finally, almost all commercially available enteral feeding formulations used in adults and older children are lactose-free because disaccharidase production within the gut lumen is reduced during illness and periods of prolonged bowel rest. Additionally, there is a high incidence of lactose intolerance in those of certain ethnic descent.

Fat and Fatty Acid Composition

Fat is an important constituent in the diet because it provides a concentrated calorie source and serves as a carrier for fat-soluble vitamins. Sufficient linoleic acid is required to prevent essential fatty acid deficiency and should approximate at least 1% to 3% of total daily calories. The most common fat sources in enteral feeding formulations are vegetable oils (soy or corn) that are rich in polyunsaturated fatty acids. The fat concentration varies between less than 2% and 45% of total calories. High-dietary fat content is associated with delayed gastric emptying. Enteral feeding formulations can also contain fat in the form of MCTs derived from palm kernel or coconut oils. Because MCTs do not contain linoleic acid, enteral formulations that contain MCTs will also have a source of long-chain triglycerides to provide essential fatty acids. Potential advantages of MCTs compared to long-chain triglycerides are that they are more water soluble, undergo rapid hydrolysis, require no pancreatic lipase or bile salts for absorption, and do not require carnitine for transport into the mitochondria, where they are converted to energy. They also do not require chylomicron formation for small bowel enterocyte absorption and are not transported via the lymphatic system.

The source of long-chain fat within some enteral formulations has been modified from omega-6 to omega-3 fatty acids in an effort to modulate the inflammatory response in critically ill patients.[8] The omega-6 fatty acids are high in linoleic acid and are derived from vegetable oil, whereas the omega-3 fatty acids, derived from cold-water fish oils, are high in linolenic acid. Omega-6

fatty acids serve as precursors to certain arachidonic acid-derived cytokines that are potent inflammatory mediators and also decrease cell-mediated immune response; whereas omega-3 fatty acids are precursors for eicosapentanoic acid-derived cytokines which are less inflammatory. It has been proposed that if the dietary proportion of omega-3 fatty acids is increased and omega-6 fatty acids is decreased, less inflammation and immunosuppression may occur during metabolic stress. However, use of enteral formulas containing omega-3 fatty acids in patients with acute respiratory distress syndromes (ARDS) and acute lung injury (ALI) has fallen out of favor, specifically in the medical ICU population with ARDS or ALI. Thus, immune-modulating formulas containing fish oil (in combination with arginine) are reserved for patients requiring EN in the perioperative setting in the surgical ICU.[8]

Fiber Content

Fiber, in both soluble and insoluble forms, is added to several enteral feeding formulations in amounts ranging from 5.9 to 24 g/L. Fiber supplementation is common in clinical practice, primarily because fiber-free enteral formulations are implicated as a contributing factor to both diarrhea and constipation. Soluble fiber stimulates the growth of “healthy” bacteria such as *Bifidobacterium* and *Lacobacillus* species. It undergoes bacterial degradation within the colon to produce short-chain fatty acids, which in turn provide an energy source for colonocytes and trophic effects on the colonic mucosa by promoting sodium and water absorption. Insoluble fiber is undigested and may help decrease GI transit time by increasing fecal weight. Although beneficial effects of fiber supplementation have not been clearly demonstrated in clinical studies, there is evidence that fiber may play an integral role in regulating bowel function with minimal associated risk.[33] Fiber supplementation may be beneficial when long-term EN is required or in patients who experience diarrhea or constipation while receiving a fiber-free enteral formulation. Supplementation with a fermentable soluble fiber is recommended for routine use in all medical and surgical ICU patients who are on a fiber-free EN formula, particularly in the setting of diarrhea, due to possible benefits in maintaining a healthy gut microbiome. Both insoluble and soluble fiber should be avoided in critically ill patients who are at risk for bowel ischemia or severe dysmotility due to potential for bowel obstruction in surgical and trauma ICU patients.[8]

Osmolality and Renal Solute Load

The unit of measure of osmolality is milliosmoles per kilogram (mOsm/kg) or millimoles per kilogram (mmol/kg); iso-osmolar is considered to be approximately 300 mOsm/kg (mmol/kg). Osmolality and renal solute load can affect tolerance to enteral feeding formulations. The osmolality of a given enteral formulation is a function of the size and quantity of ionic and molecular particles, primarily related to the protein, carbohydrate, electrolyte, and mineral content within a given volume. Enteral formulations with greater amounts of partially hydrolyzed or elemental substrates have a higher osmolality than formulations containing polymeric or intact substrates. Therefore, formulations that contain sucrose or glucose, dipeptides and tripeptides, and amino acids are generally hyperosmolar. Increased caloric density also increases the osmolality of an enteral formulation. In general, the osmolality of commercially available enteral feeding formulations ranges from 280 to 875 mOsm/kg (mmol/kg).[31]

Symptoms of gastric retention, diarrhea, abdominal distension, nausea, and vomiting have been attributed to enteral formulations with a high osmolality based on the assumption that higher osmolality draws water into the gut lumen. However, clinical evidence to support this relationship between osmolality and GI tolerance is lacking. The practice of diluting hyperosmolar formulations has not been shown to enhance tolerance and should be discouraged.[16] Factors, such as concurrent antibiotic therapy, method of enteral feeding administration, and the formulation's composition, are likely to play a greater role in GI tolerance than the osmolality.

The renal solute load is determined by the protein, sodium, potassium, and chloride content of the enteral formulation. Formulations that contain a greater solute load increase the obligatory water loss via the kidney. It is estimated that 40 to 60 mL of water is the minimal amount necessary to excrete 1 g of nitrogen. Those receiving high-protein enteral formulations unable to ingest or tolerate supplemental water may be at risk for developing dehydration.

CLASSIFICATION OF ENTERAL FEEDING FORMULATIONS

5 Most patients' nutritional needs can be met using a standard enteral feeding formulation; however, certain disease states or clinical conditions may warrant the use of a specialty feeding formulation. Development of an evidence-based, enteral formulary should focus on clinically significant characteristics of available formulations and avoid duplication. Categorizing enteral feeding

formulations according to therapeutic class is necessary in developing a formulary system for adults (Table 160-5).

TABLE 160-5 Adult Enteral Feeding Formulation Classification System

Category	Features	Indications
Standard polymeric	Isotonic 1-1.2 kcal/mL (4.2-5 kJ/mL) NPC:N 125:1-150:1 May contain fiber	Designed to meet the needs of the majority of patients Patients with functional GI tract Not suitable for oral use
High protein	NPC:N <125:1 May contain fiber	Patients with protein requirements >1.5 g/kg/day, such as trauma patients and those with burns, pressure sores, or wounds Patients receiving propofol
High caloric density	1.5-2 kcal/mL (6.3-8.4 kJ/mL) Lower electrolyte content per calorie Hypertonic	Patients requiring fluid and/or electrolyte restriction, such as kidney insufficiency
Elemental	High proportion of free amino acids Low in fat	Patients who require low fat Use has generally been replaced by peptide-based formulations
Peptide-based	Contains dipeptides and tripeptides Contains MCTs	Indications/benefits not clearly established Trial may be warranted in patients who do not tolerate intact protein due to malabsorption
Disease specific		
Kidney	Caloric dense Protein content varies Low-electrolyte content	Alternative to high-caloric density formulations, but generally more expensive
Liver	Increased branched-chain and decreased aromatic amino acids	Patients with hepatic encephalopathy
Lung	High fat, low carbohydrate Anti-inflammatory lipid profile and antioxidants	Patients with ARDS and severe ALI
Diabetes mellitus	High fat, low carbohydrate	Alternative to standard, fiber-containing formulation in patients with uncontrolled hyperglycemia
Immune-modulating	Supplemented with glutamine, arginine, nucleotides, and/or omega-3 fatty acids	Patients undergoing major elective GI surgery, trauma, burns, head and neck cancer, and critically ill patients on mechanical ventilation Use with caution in patients with sepsis Select nutrients may be beneficial or harmful in subgroups of critically ill patients
Oral supplement	Sweetened for taste Hypertonic	Patients who require supplementation to an oral diet

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; MCT, medium-chain triglyceride; NPC:N, nonprotein calorie-to-nitrogen ratio.

Standard Polymeric

A large number of commercially available enteral feeding formulations fall into the standard polymeric formulation category. These formulations are approximately isotonic (300 mOsm/L [300 mmol/L]), provide 1 to 1.2 kcal/mL (4.2-5 kJ/mL), and are composed of intact nutrients in a nutritionally balanced mix of carbohydrate, fat, and protein. They may contain dietary fiber. The nonprotein calorie-to-nitrogen ratio of these products is approximately 125:1 to 150:1. This ratio is a useful parameter for assessing protein density in relation to calories provided (see Chapter 158). Certain feeding formulations in this category may be promoted as high nitrogen but actually fall within standard protein amounts. To maintain isotonicity, many products within this category are not sweetened, making them unpalatable and generally suited only for tube feeding; however, flavored products are available for oral supplementation. The nutrient requirements of the majority of adults receiving EN can generally be met using feeding formulations in this category.

High Protein

Enteral feeding formulations with a nonprotein calorie-to-nitrogen ratio less than 125:1 can be categorized as high protein. The lower the ratio, the higher the protein density in relation to calories provided. In patients with high-protein requirements, it is generally unacceptable to use a feeding formulation with standard protein amounts because the volume necessary to meet protein requirements will result in excessive calorie intake. Patients who may be candidates for a high-protein feeding formulation are critically ill patients and those with pressure sores, surgical wounds, and high-output enterocutaneous fistulas. In general, adult patients with estimated protein requirements exceeding 1.5 g/kg/day may benefit from a high-protein formulation. High-protein formulations may also be beneficial in mechanically ventilated patients who are receiving propofol for sedation. The vehicle for propofol is a soybean fat emulsion that contains 1.1 kcal/mL (4.6 kJ/mL). At therapeutic dosages, propofol intake can significantly contribute to caloric intake, and a high-protein formulation may be beneficial in allowing for the provision of protein requirements while minimizing overfeeding.

High-Caloric Density

High-caloric density formulations are concentrated to provide less fluid and

electrolyte intake in comparison to a standard polymeric formulation. They provide approximately 1.5 to 2 kcal/mL (6.3-8.4 kJ/mL) and similar calorie and protein intake can be achieved as a standard polymeric formulation, using less volume. High-caloric density formulations are often necessary for patients who require fluid and/or electrolyte restriction, such as those with heart, kidney, liver, or respiratory failure. Although specialty enteral formulations targeted for acute kidney injury and chronic kidney disease are available, many patients with kidney failure can be managed using a product in this category.

Elemental/Peptide-Based

Formulations in this category contain protein and/or fat components that are hydrolyzed into smaller, predigested forms. Traditionally, enteral formulations in this category were referred to as elemental and contained a high proportion of protein in the form of free amino acids and a low amount of fat. Many of these formulations have been reformulated to provide a portion of the protein in the form of dipeptides and tripeptides and fewer free amino acids because dipeptides and tripeptides are more readily absorbed than an equivalent intake of free amino acids.[34] These peptide-based formulations may be beneficial in patients with impaired digestion or absorption. Peptide-based formulations are generally higher in fat than the more elemental formulations and use MCTs in varying proportions as the fat source.

Evidence to support the use of elemental or peptide-based formulations is limited, and their routine use is generally not recommended. Patients who do not tolerate standard, intact nutrient formulations as a result of malabsorption or short-bowel syndrome might be candidates for a trial of a peptide-based formulation. In addition, elemental or peptide-based products that have higher percentages of MCTs and small amounts of long-chain triglycerides may be beneficial for patients with severe pancreatic insufficiency, such as chronic pancreatitis and cystic fibrosis; severe abnormalities of the intestinal mucosa, such as untreated celiac disease; biliary tract disease, such as biliary atresia or severe cholestasis; or chylothorax or chylous ascites.

Disease Specific

Enteral feeding formulations have also been designed to meet unique nutrient requirements and manage metabolic abnormalities associated with specific-disease states. Specialized enteral feeding formulations are marketed for use in adult patients with kidney and liver failure; lung disease, including ARDS;

diabetes mellitus; wound healing; and metabolic stress (see Table 160-5).

Specialized enteral formulations designed to modulate the inflammatory response in adult patients with severe metabolic stress have been referred to as immune-modulating formulations or immunonutrition. These formulations are supplemented with nutrients such as glutamine, arginine, antioxidants, nucleotides, and omega-3 polyunsaturated fatty acids, because of their potential role in regulating immune function. However, nutrition guidelines recommend against routine use of immune-modulating enteral formulations in the medical ICU population due to lack of benefit and potential harm. These formulas should be reserved for patients in the surgical ICU and in patients with traumatic brain injury where beneficial effects have been demonstrated.[8,35,36]

Diabetes-specific formulas are lower in carbohydrate and higher in fat and fiber compared to standard formulas.[37] They contain slowly digestible carbohydrates and their primary fat sources are omega-3 fatty acids and monounsaturated fatty acids. The rationale for this combination of ingredients is to slow gastric emptying and improve glycemic control. Use of diabetes-specific formulas in hospitalized patients may lead to an improvement in glycemic control and a decrease in total insulin requirements, but to date the supporting evidence is limited. Therefore, in hospitalized patients with diabetes or stress-induced hyperglycemia, a standard enteral formula in combination with pharmacologic management of hyperglycemia is appropriate.[37]

Enteral formulas with lower protein, higher amounts of branched-chain amino acids (BCAAs) (leucine, valine, and isoleucine), and lower amounts of aromatic amino acids (AAAs) have been marketed for use in patients with hepatic encephalopathy. However, these formulations may result in under-dosing protein in a population with a high prevalence of malnutrition. Additionally, they have not been shown to improve outcomes in patients with hepatic encephalopathy and are therefore not recommended for routine use in this patient population.[31]

Oral Supplements

In general, oral supplements are not intended for tube feeding but are taken by mouth to enhance an oral diet. They are sweetened to improve taste and therefore are hypertonic (approximately 450-700 mOsm/kg [mmol/kg]), but osmolality is rarely a problem in the patient with a functioning GI tract. However, in the tube-fed patient, a sweetened product is unnecessary and may contribute to GI intolerance, particularly diarrhea. Powder supplements that are mixed with milk should be avoided in lactose-intolerant patients. In addition to

liquid supplements, puddings, gelatins, bars, and milkshake-like supplements are available.

Modular Products

A module is a powder or liquid form of a single nutrient (eg, protein, carbohydrate, fat, and dietary fiber) that is used to supplement nutrition intake when the diet or commercially available enteral formulation does not fully meet a patient's needs.[31] Alternatively, formulations available in powder or concentrate can be mixed with less water than needed for the standard dilution to deliver more nutrients in less volume. The mixing process required for modular components increases the potential for bacterial contamination and incorrect preparation. Contamination is a particular concern with the use of blenders and reconstitution of powders.[23] Modular products used to supplement tube feedings should not be mixed with the EN formula but administered separately via feeding tube similar to the process required for medication administration.

Rehydration

Oral rehydration formulations are useful in maintaining hydration or treating dehydration in patients with high-GI output (eg, from frequent vomiting, diarrhea, or ostomy output). Such formulations are available commercially in powder or liquid form or can be extemporaneously compounded. They can be administered orally or given via a feeding tube. The glucose content of oral rehydration solutions is important because it stimulates active transport systems, which, in turn, stimulate passive glucose-coupled sodium and water uptake for rehydration. Therefore, oral or enteral administration of rehydration solutions may decrease fecal water loss and generate a positive fluid and electrolyte balance.[38]

FORMULARY AND DELIVERY SYSTEM CONSIDERATIONS

For an institution's enteral formulary, generally no more than one product per category is necessary, and it may be possible to omit certain categories based on the specific patient population cared for within a given institution. Additional selection criteria include container size and type, liquid or powder form, shelf life, ease of use, and cost.

Most enteral products are available as ready-to-use, prepackaged liquids, but a few are available in the powdered state and require reconstitution prior to use. Advantages of ready-to-use liquid formulations are convenience and reduced susceptibility to microbiologic contamination. One disadvantage is that more storage space may be required. The ease or convenience of a ready-to-use liquid is especially important for self-care patients, the disabled, and those who have difficulty reading or following printed instructions. Ready-to-use liquid enteral formulations are generally available in ready-to-hang rigid plastic containers or bags (*closed system*), cans, or bottles. Bolus administration of EN is usually achieved using formulas available in cans or bottles. However, when formula from a can/bottle is used for continuous or cyclic administration, it must first be poured into a feeding bag and attached to an administration set to allow for administration via a pump. This “open system” has a higher risk of microbial contamination than the ready-to-hang containers. The use of a powder formula is also considered an open-delivery system.

Contamination of enteral feeding formulations is a potential cause of diarrhea.[6,23] Contamination is caused by a lack of attention to proper handling techniques, inadequate cleaning and disinfection of preparation equipment, and the use of nonsterile or contaminated tube-feeding additives. Unlike liquid formulations, powdered products are not guaranteed by the manufacturer to be sterile because it is not possible to sterilize the powder without destruction of some of its components. Closed-system containers supply a ready-to-hang, prefilled, sterile supply of formula in volumes of 1 to 1.5 L. Most but not all enteral formulations intended for use in adults are available in the closed-administration system. The closed-administration system also offers the advantage of not requiring refrigeration and allowing hang times of 24 to 48 hours, whereas the conventional open-delivery system necessitates hang times of generally 4 to 8 hours.[23]

New enteral connectors are currently being integrated into the EN marketplace to prevent enteral misconnections and improve patient safety. An enteral misconnection occurs when a component of the enteral feeding system is inadvertently connected to a nonenteral site, such as a tracheostomy tube, peritoneal dialysis catheter, or other medical device or IV tubing. Misconnections are commonly attributed to the use of universal connectors that allow for misconnections between incompatible systems. Due to several reports of serious patient harm, including death, an international standard (ISO 80369) has been developed to guide the redesign of all small-bore connectors and the new enteral connectors, referred to as the ENFit™ system.[39] The ENFit™

connector provides a unique connection that is not compatible with any other device and has been specifically designed for all nutrition sources, enteral administration sets, enteral syringes, and all feeding tubes.[39] Filling and administration instructions for syringes used to deliver medications via feeding tubes will differ from oral syringes. Information about these processes and other resources is available at the Global Enteral Device Supplier Association (GEDSA) website (www.stayconnected.org).[40]

COMPLICATIONS AND MONITORING

The majority of complications associated with EN are metabolic, GI, or mechanical. The early detection and management of potential complications is necessary to allow for the safe and successful use of EN. In addition, measures to avoid complications should be incorporated into the management of all patients receiving EN (**Table 160-6**).

TABLE 160-6 Suggested Monitoring for Adult Patients on Enteral Nutrition

Parameter	During Initiation of EN Therapy	During Stable EN Therapy
Vital signs	Every 4-6 hours	As needed with suspected change (ie, fever)
Clinical assessment		
Weight	Daily	Weekly
Total intake/output	Daily	As needed with suspected change in intake/output
Tube-feeding intake	Daily	Daily
Enterostomy tube site assessment	Daily	Daily
GI tolerance		
Stool frequency/ volume	Daily	Daily
Abdomen assessment	Daily	Daily
Nausea or vomiting	Daily	Daily
Gastric residual volumes	Every 4-8 hours (varies)	As needed when delayed gastric emptying suspected
Tube placement	Prior to starting, then ongoing	Ongoing
Laboratory		
Electrolytes, blood urea nitrogen/ serum creatinine, glucose	Daily until stable, then 2-3 times/ week	Every 1-3 months
Calcium, magnesium, phosphorus	Daily until stable, then 2-3 times/ week	Every 1-3 months
Liver function tests	Weekly	Every 1-3 months
Trace elements, vitamins	If deficiency/toxicity suspected	If deficiency/toxicity suspected

EN, enteral nutrition.

Metabolic Complications

Metabolic complications associated with EN are similar to those associated with PN, but the incidence tends to be lower.[16] Critically ill patients, especially those with underlying organ dysfunction, are at risk of developing complications related to hydration and electrolyte imbalance and altered glucose control. Patients who present with a history of minimal dietary intake for an extended period of time and have experienced significant weight loss are at risk of developing refeeding syndrome which can be evidenced by hypophosphatemia, hypokalemia, hypomagnesemia, thiamine deficiency, and sodium retention.[41] The frequency of clinical and laboratory assessment to monitor hydration, electrolytes, organ function, and glucose adequately for a patient who is critically ill or at risk of developing refeeding syndrome is greater than for a stable hospitalized patient or patients residing in rehabilitation units or at home (see Table 160-6). Patients receiving long-term EN at home may require laboratory monitoring only every 2 to 3 months, depending on their clinical status. Besides macronutrient content, it is important to evaluate the actual water and micronutrient content provided by the enteral formulation, especially in critically ill patients. Supplemental fluid, electrolytes, and minerals may be required in some patients. Conversely, for patients who have fluid retention or elevated serum electrolytes, the enteral formulation may need to be changed to one that is more concentrated or provides less of a particular nutrient, if available.

Gastrointestinal Complications

6 The GI complications associated with tube feeding include nausea, vomiting, abdominal distension, cramping, aspiration, diarrhea, and constipation. GRV refers to the volume of contents in the stomach and is measured by using a syringe and aspirating from a large-bore NG or gastrostomy tube. Historically, GRV has been used to identify patients at risk of vomiting, aspiration, and/or ventilator-associated pneumonia. However, when GRV alone is used to assess tolerance to EN, it can lead to unnecessary holding of EN and prevent patients from meeting their EN goal.[42] Further, introducing stomach acid into feeding tubes may contribute to clogging. Current guidelines recommend against the use of GRV as part of routine monitoring for ICU patients receiving EN.[8,43] However, some argue that GRV monitoring remains a useful tool in patients at high risk for EN intolerance and it remains widely used.[43] For ICUs that continue to utilize GRV, it is suggested to avoid holding EN in response to any GRV less than 500 mL in the absence of other symptoms suggesting intolerance

(eg, nausea, abdominal pain, distension).[8]

If symptoms of intolerance are present, and GRVs are greater than 500 mL, a decrease in the tube feeding rate or discontinuation may be warranted. Unless GRVs are excessive (greater than 500 mL in adults), they are generally reinstilled through the tube to minimize nutrient, fluid, and electrolyte losses. In patients at high risk for aspiration, clinicians should implement other measures to reduce aspiration risk, including elevating the head of the patient's bed to a 30° to 45° angle, advancement of the feeding tube into the small bowel, and initiation of a prokinetic agent such as metoclopramide or erythromycin.[16,23] Other potential interventions include minimizing the use of narcotics, sedatives, or other agents that may slow gastric emptying and correcting underlying fluid and electrolyte imbalances that can impair GI motility.[44] Aspiration pneumonia is considered the most serious complication associated with tube feeding. Although aspiration is a fairly common event for critically ill patients receiving tube feeding, progression to aspiration pneumonia is difficult to predict. Risk factors for aspiration include a previous aspiration episode, decreased consciousness, neuromuscular disease, structural airway or GI tract abnormalities, endotracheal intubation, vomiting, persistently high GRVs, and prolonged supine positioning.[43] Historically, blue food coloring had been added to enteral formulations in an attempt to detect aspiration. However, because of its low sensitivity for detection and association with several serious adverse events, including death associated with mitochondrial toxicity, the addition of blue food dye to enteral formulations is not advised. There are currently no reliable methods available to detect aspiration in enterally fed patients.[8]

Diarrhea is the most common GI complication in patients receiving EN, but the actual incidence is unclear due to the lack of a standard definition and the large number of contributing factors.[6,16] When monitoring for diarrhea, stool frequency, consistency, and volume should be evaluated, and previous bowel habits should be considered. Diarrhea has been defined as more than three liquid stools daily or a stool volume of more than 250 to 500 mL/day for at least two consecutive days.[16] Therefore, the intermittent occurrence of one or two loose stools does not constitute diarrhea or require intervention.

7 Diarrhea in patients receiving tube feeding may be caused by a number of factors, and management should be directed at identifying and correcting the most likely cause(s).[16] Tube feeding-related factors that may contribute to diarrhea include too rapid delivery or advancement of formula, intolerance to the formula composition, administration of large volumes of feeding into the small bowel, and formula contamination. Thus, measures to prevent or manage

diarrhea related directly to the tube feeding should address these potential causes.[16] If diarrhea occurs when using a fiber-free formulation, a fiber-containing formulation or supplement may be considered in hemodynamically stable patients. If using a high-fat formulation, it may be beneficial to switch to a formulation lower in fat or having a higher proportion of the fat supplied as MCTs; however, a high-MCT concentration has also been associated with diarrhea. Finally, it is important to assess the risk of bacterial contamination of the formula and take steps to minimize any potential risk factors. If infectious etiologies have been excluded, severe diarrhea may require pharmacologic treatment with loperamide, diphenoxylate/atropine, or opioids (see Chapter 53).

Drug therapy, particularly the use of broad-spectrum antibiotics, is a common cause of diarrhea that is unrelated to tube feeding. Sorbitol, used as a sweetening agent in many liquid formulations to enhance palatability, is an osmotic laxative that can cause diarrhea. In addition, many drugs available in a liquid form are hyperosmolar, which may contribute to diarrhea, especially when these medications are not diluted properly before administration. Because many patients receiving tube feeding also receive medications in a liquid form, all medications should be evaluated for their potential contribution. Malabsorption, secondary to the underlying disease state or condition, may also cause diarrhea. Infectious causes, such as antibiotic-induced bacterial overgrowth by *Clostridioides difficile* or other intestinal flora, need to be considered when diarrhea develops. Certain probiotic strains may have a role in the prevention and treatment of infectious and antibiotic-associated diarrhea.[45] However, the value of adding probiotics to patients on EN in the ICU setting is unclear. The makeup of intestinal flora becomes disrupted in response to antimicrobial treatment and stress response of ICU patients. The use of probiotics has been associated with the reduction of ventilator-associated pneumonia, antibiotic-associated diarrhea, and overall infections in critically ill patients.[8,46] However, the existing evidence is limited by low-quality studies in heterogeneous patient populations. Further, increased risk of mortality has been shown when probiotics are used concomitantly with fiber and jejunal feeding in patients with severe acute pancreatitis. Therefore, the use of studied probiotic strains should be considered only for select ICU patient populations such as trauma, pancreatectomy, and liver transplantation.[8]

Mechanical Complications

Mechanical complications of EN are those associated with the feeding tube,

including tube occlusion or malposition, and inadvertent nasopulmonary intubation. Feeding tube occlusion usually results from improper medication administration and/or flushing. Kinking of the tube also may cause occlusion. Adult feeding tubes should be flushed with at least 15 to 30 mL of water before and after administering any medication. If more than one medication is scheduled for a given time, each should be administered separately, and the tube should be flushed with 5 to 15 mL of water between drugs.[23,47] The frequency of flushing should be at least every 8 hours during continuous feeding and before and after each intermittent feeding. If tube occlusion occurs, the tube should be irrigated with warm water. Other fluids such as carbonated beverages and cranberry juice have been used to irrigate occluded tubes but have not been shown to be any more effective than warm water. Further, the acid in these liquids may precipitate with protein in the enteral formula and lead to new or worsening of occlusions.[23] Pancreatic enzymes mixed with sodium bicarbonate may be used to reestablish patency in this situation.[47] Declogging devices that are specifically designed to unclog feeding tubes are available. They have been designed to either mechanically break through or remove the occlusion or provide an applicator and syringe prefilled with pancreatic enzymes and various powders targeted to restore patency.[6,47]

Inadvertent nasoenteric tube removal or displacement has been reported in approximately 40% of patients receiving EN.[48] An agitated or confused patient may pull at the feeding tube and cause its removal or malposition. Measures to decrease agitation and confusion should be attempted. Securing the tube with tape may be helpful, as well as marking the tube with permanent ink at the exit site to assess for position change. A nasal bridle that uses a magnetic retrieval system has proven to be a simple and effective method for securing nasoenteric feeding tubes and preventing accidental removal.[49]

When a feeding tube is inserted nasally or orally, there is a risk that the tube may inadvertently enter the tracheobronchial tree. The risk may be higher in patients who have an impaired cough or gag reflex and when a stylet is used for tube insertion. Proper positioning of the tube should always be confirmed by radiography prior to feeding initiation and routinely reassessed to avoid inadvertent administration of enteral formula into the lung.[23]

Other Complications

Infectious complications of feeding tube placement include sinusitis (with nasoenteric placement), exit site-related infections (eg, cellulitis, subcutaneous

abscess, and necrotizing fasciitis), and intra-abdominal infections (eg, peritonitis and abscess). Leaking and bleeding around the exit site can also occur.[11] Formation of excessive granulation tissue around the exit site is often the cause of leaking and bleeding and can be managed by applying silver nitrate and topical corticosteroids.[50]

NUTRITION CARE PLAN

A nutrition care plan that incorporates nutrition assessment and therapy goals should be developed for all patients who require EN (see Chapter 158). Desired outcomes of EN are to promote an adequate nutritional state while minimizing any associated metabolic complications. The EN goals are individualized and based on meeting estimated fluid, calorie, protein, and micronutrient requirements. The desired end point should be included in the care plan. The end point may be resolution of a disease or condition that impairs ability to eat, such as in a critically ill patient who is expected to transition back to an oral diet. EN may be considered a lifelong therapy for those with a permanent impairment that restricts or limits eating, such as gastroparesis.

Assessing the outcome of EN requires monitoring objective measures of body composition, protein and energy balance, and muscle function and wound healing. In addition to optimizing nutrition, the goal of EN is to reduce disease-related morbidity and mortality. Measures of disease-related morbidity include length of hospital stay, infectious complications, and the patient's functional status and sense of well-being. A target weight should be established for each patient and energy content from the EN regimen adjusted as needed to safely achieve or maintain the target weight. In general, in adults, no more than 1 to 2 lb (approximately 0.45-0.9 kg) per week should be gained or lost. EN may be used to supplement an oral diet when oral intake is inadequate and should be modified as needed based on changes in tolerance.

DRUG DELIVERY VIA FEEDING TUBE

Using enteral feeding tubes to deliver drugs is a common practice and offers an alternative for patients unable to take drugs by the oral route. However, in addition to tube occlusion, effects on drug bioavailability and other potential interactions need to be considered when using this route. Medications have been given as a concomitant bolus administration via the feeding tube or admixed with the enteral feeding formulation.

Concomitant Drug Administration

8 Concomitant administration of medications with enteral feedings can be extremely complicated and potentially deleterious. Depending on the indication for enteral nutrition (eg, inadequate oral intake), oral administration may still be the most appropriate route for medication administration.[23] Therefore, if it is feasible and appropriate, oral medications should be continued to be delivered orally whenever possible. If medication must be delivered through a feeding tube, then larger bore feeding tubes (eg, nasogastric or gastrostomy tubes) are preferred over small bore tubes. Delivering medications directly into the stomach allows for the normal process of drug dissolution. Medication delivery directly into the small bowel, however, may result in alterations in drug dissolution because the stomach is bypassed. In addition, therapeutic effects designed to occur within the stomach, such as with antacids and sucralfate, may not be achieved. Because many drugs are best absorbed in the fasting state, they should be administered on an empty stomach whenever possible. Patients on bolus gastric feeding must receive these medications appropriately spaced between feedings, and patients on continuous feeding will require feeding interruptions for drug administration.

Selecting the proper medication dosage form for coadministration with the tube feeding is another important consideration. If crushing a given solid dosage form results in changes to drug absorption, then it should be avoided. Medications in sublingual form, sustained-release capsules or tablets, and enteric-coated tablets should not be crushed and therefore should not be administered via enteral feeding tubes.[23,47] Solid dosage forms that are appropriate to crush should be prepared as a very fine powder and mixed with 15 to 30 mL of water or other appropriate solvent before administering through the tube. In addition, many capsules may be opened and the contents administered in the same manner. Pellets contained inside microencapsulated dosage forms should generally not be crushed. It may be acceptable to administer intact pellets through larger bore feeding tubes, provided that the pellets are small enough and drug absorption is not compromised.[51] To avoid the need to crush a solid dosage form, liquid dosage forms are commonly preferred for administration through feeding tubes. However, the risk of GI intolerance should be considered because of the hyperosmolality of many liquid formulations and possible sorbitol content.[47,52] Although the use of a liquid dosage preparation may be more convenient than a solid dosage form, it may not be the best choice if GI intolerance is an issue.

Admixture of Drugs with Enteral Feeding

Mixing liquid medications with certain enteral feeding formulations is associated with several types of physical incompatibilities, including granulation, gel formation, separation, and precipitation.[47,51] Not only can these physical incompatibilities inhibit drug absorption, but gel formation may clog small-bore feeding tubes. Physical incompatibility with medications is more common in formulations that contain intact protein than in those with hydrolyzed protein. Also, medication and enteral formula incompatibilities are more common with the use of acidic pharmaceutical syrups. The most prudent recommendation is to avoid the routine admixture whenever possible, especially for nonaqueous preparations and syrups. In the clinical setting, exceptions do exist, such as adding sodium or magnesium to enteral formulas to assist in maintaining or repleting electrolytes.

Drug–Nutrient Interactions

9 The most significant drug–nutrient interactions that can occur during continuous enteral feeding are those in which the drug's bioavailability is reduced, and the desired pharmacologic effect is not achieved (Table 160-7).[53] Unfortunately, limited clinical studies are available to document the extent of this problem with enteral feeding. Most of the observations are anecdotal case reports involving few patients. One of the well-documented interactions is between phenytoin and enteral feeding. Phenytoin serum concentrations may decrease by 50% to 75% when phenytoin is given concomitantly with EN, possibly as a result of the binding of phenytoin to calcium caseinates or protein hydrolysates in the enteral formulation. Management options include holding EN for one to two hours before and after drug administration in addition to flushing the tube with water before and after drug delivery. The dosing of phenytoin should be divided into two doses per day rather than three divided doses to minimize interruption of EN. If EN cannot be held around the administration of phenytoin suspension per tube, then patients will typically require higher than normal phenytoin doses.[47] The patient's clinical response and phenytoin serum concentrations should be monitored to assure that the desired therapeutic effects are achieved.

TABLE 160-7 Select Medications with Special Considerations for Enteral Feeding Tube Administration

Drug	Interaction	Comments
Phenytoin	Reduced bioavailability in the presence of tube feedings Possible phenytoin binding to calcium caseinates or protein hydrolysates in enteral feeding	To minimize interaction, holding tube feedings 1-2 hours before and after phenytoin has been suggested Adjust tube-feeding rate to account for time held for phenytoin administration Monitor phenytoin serum concentration and clinical response closely Consider switching to IV phenytoin or an alternative-treatment option if unable to reach therapeutic serum concentration
Fluoroquinolones Tetracyclines	Potential for reduced bioavailability because of complexation of drug with divalent and trivalent cations found in enteral feeding	Consider holding tube feeding 1 hour before and after administration Avoid jejunal administration of ciprofloxacin Monitor clinical response
Warfarin	Decreased absorption of warfarin because of enteral feeding; therapeutic effect antagonized by vitamin K in enteral formulations	Adjust warfarin dose based on INR Anticipate need to increase warfarin dose when enteral feedings are started and decrease dose when enteral feedings are stopped Consider holding tube feeding 1 hour before and after administration
Omeprazole Lansoprazole	Administration via feeding tube complicated by acid-labile medication within delayed-release, base-labile granules	Granules become sticky when moistened with water and may occlude small-bore tubes Granules should be mixed with acidic liquid when given via a gastric feeding tube An oral liquid suspension can be extemporaneously prepared for administration via a feeding tube

INR, International normalized ratio.

Decreased bioavailability of certain antibiotics, particularly quinolones, has been documented when coadministered with enteral feeding due to complexation with multivalent cations such as calcium, magnesium, and iron contained in the feeding.[47,51] Although the practice of holding tube feeding for 30 minutes before and 30 minutes after quinolone administration has been recommended, it has not been shown to improve drug absorption. Another option is to increase the quinolone dose when given concurrently with EN. Oral ciprofloxacin is absorbed primarily in the duodenum and early jejunum. There is evidence to suggest that ciprofloxacin bioavailability is significantly decreased when given via a jejunostomy tube due to bypassing the site of absorption, so this practice should be avoided.[47]

Warfarin resistance has been documented during enteral feeding, possibly as a consequence of decreased absorption, binding to protein in EN, or the antagonist effects of vitamin K in the feeding formulation. Before 1980, it was thought that the content of vitamin K (up to 1,330 mcg/1,000 kcal [317 mcg/1,000 kJ] of enteral feeding formula) was contributing to the pharmacologic interaction with warfarin. Subsequently, the vitamin K content within formulas intended for use in adults was reduced to less than 200 mcg/1,000 kcal (48 mcg/1,000 kJ).

However, warfarin resistance continues to be reported in patients on EN. Holding EN for one hour before and after warfarin administration along with close monitoring of the International Normalized Ratio is warranted to ensure therapeutic drug concentrations are maintained.[54] Conversely, when EN is discontinued, a reduction in warfarin dosage may be required.

Decreased absorption of levothyroxine has been described in patients receiving continuous EN.[51,55] This is thought to be due to the binding of the drug to the tube feeding formula and/or the binding of thyroid hormones to enteral nutrition during enterohepatic recirculation. Several recommendations have been described, including holding tube feedings for one hour before and after drug administration and increasing the dose of levothyroxine while continuous tube feedings are required. Thyroid function tests should be monitored closely (eg, every 7 days) during this time.[55]

CLINICAL BOTTOM LINE

Identifying appropriate candidates for EN and designing a personalized EN regimen and monitoring plan is a complex process that is often under-appreciated. The successful use of EN can minimize the need for PN in patients unable to meet nutrient requirements with an oral diet. Ultimately, no disease process can improve with prolonged starvation and malnutrition. ASPEN has identified safety issues related to the administration and management of EN and created practice recommendations based on evidence-based research and expert opinion.[23] Practice guidelines are also available to address the provision and assessment of nutrition support therapy, including EN, for adult critically ill patients.[8,9] A multidisciplinary team approach, either as a formal nutrition support service or as a team of caregivers within the practice setting, is recommended to optimize patient outcomes.

Postclass Engaged Learning Activity

Conduct a literature search and identify a manuscript that has been published within the last 24 months that focuses on an aspect of enteral nutrition in the adult critical care population. Write a brief summary of the study aims, methods, and its findings. Answer the following questions about the study: (1) what subgroup of ICU patients were included? (2) how are the study methods

similar to or different from standard practice? (3) what impact, if any, might the study results have on current practice? This activity is intended to build your experience with accessing and evaluating the primary biomedical literature and applying your knowledge to make evidence-based recommendations for the use of enteral nutrition.

ABBREVIATIONS

ALI	acute lung injury
ANH	artificial nutrition and hydration
ARA	arachidonic acid
ARDS	acute respiratory distress syndrome
DHA	docosahexaenoic acid
EN	enteral nutrition
GALT	gut-associated lymphoid tissue
GI	gastrointestinal
GRV	gastric residual volume
ICU	intensive care unit
IgA	immunoglobulin A
MCT	medium-chain triglyceride
NG	nasogastric
NJ	nasojejunal
NPO	nothing by mouth
OG	orogastric
OJ	orojejunal
PEG	percutaneous endoscopic gastrostomy
PN	parenteral nutrition

REFERENCES

1. Colaizzo-Anas T. Nutrient intake, digestion, absorption, and excretion. In: Mueller CM, ed. *The ASPEN Adult Nutrition Support Core Curriculum*. 3rd ed. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2017:3–25.
2. Abumrad NA, Nassir F, Marcus A. Digestion and absorption of dietary fat, carbohydrate, and protein. In: Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease:*

Pathophysiology/Diagnosis/Management. 10th ed. Philadelphia, PA: Saunders Elsevier; 2016:1736–1764.

3. Hise M, Brown JC. Lipids. In: Mueller CM, ed. *The ASPEN Adult Nutrition Support Core Curriculum*. 3rd ed. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2017:71–95.
4. Dotan I, Mayer L. Mucosal immunology and inflammation. In: Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management*. 10th ed. Philadelphia, PA: Saunders Elsevier; 2016:16–27.
5. Shanahan F, Dinan TG, Ross P, Hill C. Probiotics in transition. *Clin Gastroenterol Hepatol*. 2012;10:1220–1224.
6. Kozeniecki M, Fritzshall R. Enteral nutrition for adults in the hospital setting. *Nutr Clin Pract*. 2015;30:634–651.
7. Doley J, Phillips W. Overview of enteral nutrition. In: Mueller CM, ed. *The ASPEN Adult Nutrition Support Core Curriculum*. 3rd ed. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2017:213–225.
8. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr*. 2016;40(2):159–211.
9. Dhaliwal R, Cahill N, Lemieux M, Heyland DK. The Canadian critical care nutrition guidelines in 2013: An update on current recommendations and implementation strategies. *Nutr Clin Pract*. 2014;29:29–43.
10. Singer P, Blaser AR, Berger MM, et al. ESPEN guideline on clinical nutrition in the intensive care unit. *Clin Nutr*. 2019;38(1):48–79. doi:10.1016/j.clnu.2018.08.037.
11. Itkin M, DeLegge MH, Fang JC, et al. Multidisciplinary practical guidelines for gastrointestinal access for enteral nutrition and decompression from the Society of Interventional Radiology and American Gastroenterological Association (AGA) Institute, with endorsement by Canadian Interventional Radiological Association (CIRA) and Cardiovascular and Interventional Radiological Society of Europe (CIRSE). *Gastroenterology*. 2011;141:742–765.
12. McCleary EJ, Tajchman S. Parenteral nutrition and infection risk in the intensive care unit: A practical guide for the bedside clinician. *Nutr Clin*

Pract. 2016;31(4):476–489.

13. Doig GS, Simpson F, Sweetman EA, et al. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: A randomized controlled trial. *JAMA*. 2013;309(20):2130–2138.
14. Harvey SE, Parrott F, Harrison DA, et al. Trial of the route of early nutritional support in critically ill adults. *N Engl J Med*. 2014;371:1673–1684.
15. Reignier J, Boisramé-Helms J, Brisard L, et al. Enteral versus parenteral early nutrition in ventilated adults with shock: A randomized, controlled, multicenter, open-label, parallel-group study (NUTRIREA-2). *Lancet*. 2018;391(10116):133–143.
16. Malone AM, Seres DS, Lord LM. Complications of enteral nutrition. In: Mueller CM, ed. *The ASPEN Adult Nutrition Support Core Curriculum*. 3rd ed. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2017:265–283.
17. Kumpf VJ. Parenteral nutrition-associated liver disease in adult and pediatric patients. *Nutr Clin Pract*. 2006;21:279–290.
18. Mancl EE, Muzevich KM. Tolerability and safety of enteral nutrition in critically ill patients receiving intravenous vasopressor therapy. *JPEN J Parenter Enteral Nutr*. 2013;37(5):641–651.
19. Khalid I, Doshi P, DiGiovine B. Early enteral nutrition and outcomes of critically ill patients treated with vasopressors and mechanical ventilation. *Am J Crit Care*. 2010;19(3):261–268.
20. Fang JC, Kinikini M. Enteral access devices. In: Mueller CM, ed. *The ASPEN Adult Nutrition Support Core Curriculum*. 3rd ed. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2017:251–264.
21. Koopmann MC, Kudsk KA, Szotkowski MJ, Rees SM. A team-based protocol and electromagnetic technology eliminate feeding tube placement complications. *Ann Surg*. 2011;253:297–302.
22. Rivera R, Campana J, Hamilton C, et al. Small bowel feeding tube placement using an electromagnetic tube placement device: Accuracy of tip location. *JPEN J Parenter Enteral Nutr*. 2011;35(5):636–642.
23. Boullata JI, Carrera AL, Harvey L, et al. ASPEN safe practices for enteral nutrition therapy. *JPEN J Parenter Enteral Nutr*. 2017;41:15–103.
24. Barrocas A, Geppert C, Durfee SM, et al. A.S.P.E.N. ethics position paper.

Nutr Clin Pract. 2010;25:672–679.

25. Schwartz DB, Barrocas A, Wesley JR, et al. Gastrostomy tube placement in patients with advanced dementia or near end of life. *Nutr Clin Pract*. 2014;29:829–840.
26. American Geriatrics Society Ethics Committee and Clinical Practice and Models of Care Committee. American Geriatrics Society feeding tubes in advanced dementia position statement. *J Am Geriatr Soc*. 2014;62:1590–1593.
27. McClave SA, Saad MA, Esterle M, et al. Volume-based feeding in the critically ill patient. *JPEN J Parenter Enteral Nutr*. 2015;39:707–712.
28. Taylor B, Brody R, Denmark R, et al. Improving enteral delivery through the adoption of the "Feed early enteral diet adequately for maximum effect (FEED ME)" protocol in a surgical trauma ICU: A quality improvement review. *Nutr Clin Pract*. 2014;29:639–648.
29. Rahman A, Hasan RM, Agarwala R, et al. Identifying critically-ill patients who will benefit most from nutritional therapy: Further validation of the "modified NUTRIC" nutritional risk assessment tool. *Clin Nutr*. 2016;35(1):158–162.
30. McCarthy MS, Martindale RG. Immunonutrition in critical illness: What is the role? *Nutr Clin Pract*. 2018;33(3):348–358.
31. Roberts S, Kirsch R. Enteral nutrition formulations. In: Mueller CM, ed. *The ASPEN Adult Nutrition Support Core Curriculum*. 3rd ed. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2017:227–249.
32. Heyland D, Muscedere J, Wischmeyer PE, et al. A randomized trial of glutamine and antioxidants in critically ill patients. *N Engl J Med*. 2013;368:1487–1495.
33. Zaman MK, Chin K, Rai V, Majid HA. Fiber and prebiotic supplementation in enteral nutrition: A systematic review and meta-analysis. *World J Gastroenterol*. 2015;21:5372–5381.
34. Young LS, Kim DW. Protein. In: Mueller CM, ed. *The ASPEN Adult Nutrition Support Core Curriculum*. 3rd ed. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2017:97–112.
35. van Zanten AR, Sztark F, Kaisers UX, et al. High-protein enteral nutrition enriched with immune-modulating nutrients vs standard high-protein enteral nutrition and nosocomial infections in the ICU: A randomized clinical trial. *JAMA*. 2014;312:514–524.

36. Rice TW, Wheeler AP, Thompson BT, et al. Enteral omega-3 fatty acid, γ-linolenic acid, and antioxidant supplementation in acute lung injury. *JAMA*. 2011;306:1574–1581.
37. Walker R, Tucker AM, Birtcher KK. Diabetes mellitus. In: Mueller CM, ed. *The ASPEN Adult Nutrition Support Core Curriculum*. 3rd ed. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2017:675–700.
38. Limketkai BN, Hurt RT, Palmer LB. Short bowel syndrome. In: Mueller CM, ed. *The ASPEN Adult Nutrition Support Core Curriculum*. 3rd ed. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2017:587–601.
39. Guenter P. New enteral connectors: Raising awareness. *Nutr Clin Pract*. 2014;29:612–614.
40. Global Enteral Device Supply Associate (GEDSA). Stay Connected. Available at: www.StayConnected.org. Accessed November 25, 2018.
41. Skipper A. Refeeding syndrome or refeeding hypophosphatemia: A systematic review of cases. *Nutr Clin Pract*. 2012;27:34–40.
42. Marik PE. Enteral nutrition in the critically ill: Myths and misconceptions. *Crit Care Med*. 2014;42(4):962–969.
43. Elke G, Felbinger TW, Heyland DK. Gastric residual volume in critically ill patients: A dead marker or still alive? *Nutr Clin Pract*. 2015;30(1):59–71.
44. Btaiche IF, Chan LN, Pleva M, Kraft MD. Critical illness, gastrointestinal complications, and medication therapy during enteral feeding in critically ill adult patients. *Nutr Clin Pract*. 2010;25:32–49.
45. Guarino A, Guandalini S, Lo Vecchio A. Probiotics for prevention and treatment of diarrhea. *J Clin Gastroenterol*. 2015;49:S37–S45.
46. Manzanares W, Langlois PL, Wischmeyer PE. Restoring the microbiome in critically ill patients: Are probiotics our true friends when we are seriously ill? *JPEN J Parenter Enteral Nutr*. 2017;41(4):530–533.
47. Williams NT. Medication administration through enteral feeding tubes. *Am J Health Syst Pharm*. 2008;65:2347–2357.
48. Gunn SR, Early BJ, Zenati MS, Ochoa JB. Use of a nasal bridle prevents accidental nasoenteral feeding tube removal. *JPEN J Parenter Enteral Nutr*. 2009;33:50–54.
49. Bechtold ML, Nguyen DL, Palmer LB, et al. Nasal bridles for securing

nasoenteric tubes: A meta-analysis. *Nutr Clin Pract*. 2014;29(5):667–671.

50. Warriner L, Spruce P. Managing overgranulation tissue around gastrostomy sites. *Br J Nurs*. 2012;21(5):S14–S16.
51. Wohlt PD, Zheng L, Gunderson S, et al. Recommendations for the use of medications with continuous enteral nutrition. *Am J Health Syst Pharm*. 2009;66:1458–1467.
52. Klang M, McLymont V, Ng N. Osmolality, pH, and compatibility of selected oral liquid medications with an enteral nutrition product. *JPEN J Parenter Enteral Nutr*. 2013;37:689–694.
53. Chan LN. Drug-nutrient interactions. *JPEN J Parenter Enteral Nutr*. 2013;37:450–459.
54. Dickerson RN, Garmon WM, Kuhl DA, et al. Vitamin-K-independent warfarin resistance after concurrent administration of warfarin and continuous enteral nutrition. *Pharmacother*. 2008;28(3):308–313.
55. Dickerson RN, Maish GO, Minard G, Brown RO. Clinical relevancy of the levothyroxine-continuous enteral nutrition interaction. *Nutr Clin Pract*. 2010;25(6):646–652.

Obesity

Amy Heck Sheehan, Judy T. Chen, and Jack A. Yanovski

KEY CONCEPTS

1. Two clinical measures of excess body fat, regardless of sex, are the body mass index (BMI) and the waist circumference (WC). BMI and WC provide a better assessment of total body fat than weight alone and are independent predictors of obesity-related disease risk.
2. Excessive central adiposity increases risk for development of type 2 diabetes, hypertension, and dyslipidemia.
3. Weight loss of as little as 5% of total body weight can significantly improve blood pressure, lipid levels, and glucose tolerance in patients with overweight and obesity. Sustained, large weight losses (ie, after bariatric surgery) are associated with a lower risk of cardiovascular events and death and long-term improvements in many of the complications associated with obesity.
4. Clinicians should consider the weight-altering effects of medications used to treat comorbid conditions (eg, antidepressants, antipsychotics, antiepileptics, and antidiabetics) and select medications that promote weight loss or are weight-neutral.
5. Bariatric surgery is reserved for patients with extreme obesity having a BMI more than or equal to 40 kg/m^2 or BMI more than or equal to 35 kg/m^2 with a significant comorbidity.
6. Pharmacotherapy may be considered an adjunctive treatment in patients with a BMI more than or equal to 30 kg/m^2 or BMI of 27 to 30 kg/m^2 with a comorbidity if comprehensive lifestyle modifications (eg, diet, exercise, and behavioral modification) fail to achieve or sustain weight loss.
7. Weight regain occurs with a high probability when pharmacotherapy for obesity is discontinued.

8. Pharmacotherapy should be discontinued if weight loss of at least 5% is not achieved after 12 weeks of maximum-dose therapy with phentermine–topiramate or bupropion–naltrexone because significant weight loss is unlikely to be achieved despite continued therapy. Liraglutide should be discontinued if weight loss of at least 4% is not achieved after 16 weeks of therapy.
9. The Food and Drug Administration (FDA) does not regulate labeling of herbal and food supplement diet agents, and content is not guaranteed.

Preclass Engaged Learning Activity

Access the Centers for Disease Control and Prevention (CDC) Overweight & Obesity website found at https://tinyurl.com/w9847zx. Review the latest obesity statistics and recommended strategies to prevent and manage obesity. This website is useful to enhance student awareness of the significant public health impact of overweight and obesity and provides tools to assist in the IMPLEMENT step of the patient care process.

INTRODUCTION

Since 1975, the prevalence of obesity worldwide has nearly tripled.[1] It is now estimated that at least two out of every three adult women and three out of every four adult men are overweight or obese in the United States, and the number of women with obesity outnumbers those who are overweight.[2] While the rise in childhood obesity appears to have reached a plateau, the prevalence of obesity persistently increased among adults over the most recent decade between 1999-2000 and 2015-2016.[3,4] The presence of obesity and overweight is associated with a significantly increased risk for the development of many diseases (**Table 161-1**), poorer outcomes of comorbid disease states, compromised quality of life, and increased healthcare costs.[5–20] As of 2008, it was estimated that obesity accounted for 20.6% of total medical expenditures in the United States,[21] and the cost of treating obesity-related illnesses in adults approached a national health expenditure of $149.4 billion annually in 2014.[22] National and global initiatives to stem the obesity epidemic have been established through prevention strategies, consensus guidelines, and best practices.[6,7,23–26] This chapter reviews

the epidemiology, pathophysiology, and therapeutic approaches for the management of obesity. Although nonpharmacologic treatment modalities are discussed, the pharmacotherapy of obesity is highlighted, and the role of pharmacotherapy relative to the other therapeutic options is critically reviewed.

TABLE 161-1 Conditions More Prevalent Among Patients with Obesity

Cancer
- Biliary tract system cancer
- Breast cancer (postmenopausal)
- Colorectal cancer
- Endometrial cancer (premenopausal)
- Esophageal cancer
- Gallbladder cancer
- Kidney cancer
- Leukemia
- Liver cancer
- Multiple myeloma
- Non-Hodgkin's lymphoma
- Ovarian cancer
- Pancreatic cancer
- Prostate cancer
- Rectal cancer
- Thyroid cancer

Cardiovascular
- Atrial fibrillation
- Cerebral vascular accidents
- Congestive heart failure
- Coronary artery disease
- Cor pulmonale
- Hypertension
- Left ventricular hypertrophy
- Myocardial infarction
- Peripheral vascular disease
- Peripheral venous insufficiency
- Pulmonary embolism
- Sudden cardiac death
- Thrombophlebitis
- Varicose veins
- Venous thromboembolism
- Ventricular arrhythmias

Dermatologic
- Acanthosis nigricans
- Cellulitis
- Intertrigo, carbuncles
- Lymphedema
- Panniculitis
- Psoriasis (women)
- Skin tags
- Status pigmentation of legs
- Striae distensae (stretch marks)

Endocrine and Reproductive
- Amenorrhea and other menstrual disorders
- Congenital anomalies
- Fetal abnormalities
- Hirsutism
- Hyperandrogenism
- Hypogonadism (male)
- Infertility
- Precocious thelarche
- Polycystic ovarian syndrome
- Pregnancy complications
- Sexual dysfunction

Gastrointestinal
- Cholelithiasis
- Gastroesophageal reflux disease
- Hepatic cirrhosis
- Hernias
- Nonalcoholic fatty liver disease
- Pancreatitis

Genitourinary
- Chronic kidney disease
- End-stage renal disease
- Increased serum urate
- Obesity-related glomerulopathy
- Urinary stress incontinence

Metabolic
- Diabetes mellitus
- Hyperlipidemia
- Hyperinsulinemia
- Hypertriglyceridemia
- Impaired glucose tolerance
- Low high-density lipoprotein
- Metabolic syndrome

Musculoskeletal
- Degenerative joint disease
- Diffuse idiopathic skeletal hyperostosis
- Disc disease
- Fibromyalgia
- Flat feet
- Gait disturbance
- Gout and hyperuricemia
- Immobility
- Low back pain/back strain
- Osteoarthritis (knee, hips, ankles, feet)
- Plantar fasciitis

Neurologic
- Carpal tunnel syndrome
- Idiopathic intracranial hypertension
- Migraines
- Meralgia paresthetica
- Pseudotumor cerebri
- Stroke

Oral Health
- Dental caries
- Loss of teeth
- Periodontitis
- Xerostomia

Psychological
- Affective disorders
- Body image disturbance
- Depression
- Eating disorders
- Low self-esteem
- Social stigmatization

Respiratory
- Asthma
- Chronic obstructive pulmonary disease
- Dyspnea
- Hypoventilation syndrome
- Obstructive sleep apnea
- Pickwickian syndrome
- Pneumonia
- Pulmonary hypertension

Data from References 5–20.

EPIDEMIOLOGY

One of the global health targets set by the World Health Assembly is to halt the rise of diabetes and obesity.[24,27] Obesity in the United States has climbed since the 1960s.[28] The National Health and Nutrition Examination Survey (NHANES) II data estimated that the prevalence of obesity among adults in the United States was at 15% in 1976 to 1980.[29] By 2015 to 2016, the prevalence of obesity had increased over twofold and affected 39.8% of the adult population while severe obesity affected 7.7% of the adult population.[3,4] While the speed with which the prevalence of obesity has increased appears to have somewhat leveled off in recent years, prevention of obesity remains a public health priority due to its high prevalence. Children who are overweight are likely to remain overweight as adults.[30] Furthermore, children and adolescents who are overweight or obese have a higher risk of premature mortality and morbidity as adults.[30] Therefore, childhood and early adulthood are critical intervention periods for prevention of obesity in the next generation and require long-term commitment and investment from all stakeholders.[27] The prevalence of obesity using the 30 kg/m^2 cut point varies by sex and race/ethnicity within the United States. Non-Hispanic Asian men (10.1%) and women (14.8%) have the lowest prevalence of obesity compared to other ethnic groups, though they develop obesity-linked complications at lower BMI than other races/ethnicities.[3] The highest prevalence of obesity is observed among non-Hispanic black women at 54.8% compared with 36.9% for non-Hispanic black men.[3] This gender disparity is also associated with the level of education. Black women without a college degree are at greater risk of obesity compared with black men.[31] Educational achievement, which is linked to socioeconomic status, is also correlated with the fraction of people who are obese. The prevalence of obesity is greatest in those with high school education or less among non-Hispanic white women and men, non-Hispanic black women, and Hispanic women.[31]

ETIOLOGY

Obesity occurs when there is increased energy storage resulting from an imbalance between energy intake and energy expenditure over time. The specific etiology for this imbalance in the vast majority of individuals is multifactorial, with genetic and environmental factors contributing to various degrees. In a

small minority of individuals, excess weight may be attributed to an underlying medical condition or an unintended effect of a medication.

Genetic Influences

Genetics plays an important role in determining both obesity and distribution of body fat. In some individuals, genetic factors are the primary determinants of obesity, whereas in others, obesity may be caused primarily by environmental factors. The genetic contribution to the actual variance in body mass index (BMI) and body fat distribution is estimated to be between 40% and 70%.[32] A number of single-gene mutations producing extreme obesity have been identified, but such mutations are rare and account for a relatively small number of the total cases of obesity.[32] The total number and identity of contributing genes are still being determined, as is the means by which the many potential so-called “obesity” genes interact with each other and with the environment to produce the obese phenotype.

Environmental Factors

Many of the societal changes associated with economic development over the past 40 years have been implicated as potential causes for the increase in the prevalence of obesity.[33] These include an abundant and easily accessible food supply and the material comforts of modern life in Western civilizations, which have contributed to a reduction in physical activity. Advances in technology and automation have resulted in more sedentary lifestyles during both work and leisure time for most individuals. At the same time, there has been a significant increase in the availability and portion size of high-fat foods, which are aggressively marketed and are often more convenient and less expensive than healthier alternatives. This modern environment has been described by some as “obesogenic” because it is likely to result in a state of positive energy balance in many individuals (**Fig. 161-1**).[34] Obesity has also been reported more frequently among individuals within close social networks (eg, siblings, spouses, and friends), with a person’s risk of developing obesity increasing significantly if a friend in his or her social network is obese.[35] Cultural factors such as socioeconomic status and religious beliefs may influence eating habits and body weights. Obesity has also been linked to changes in gut microorganisms and lack of sleep.[33]

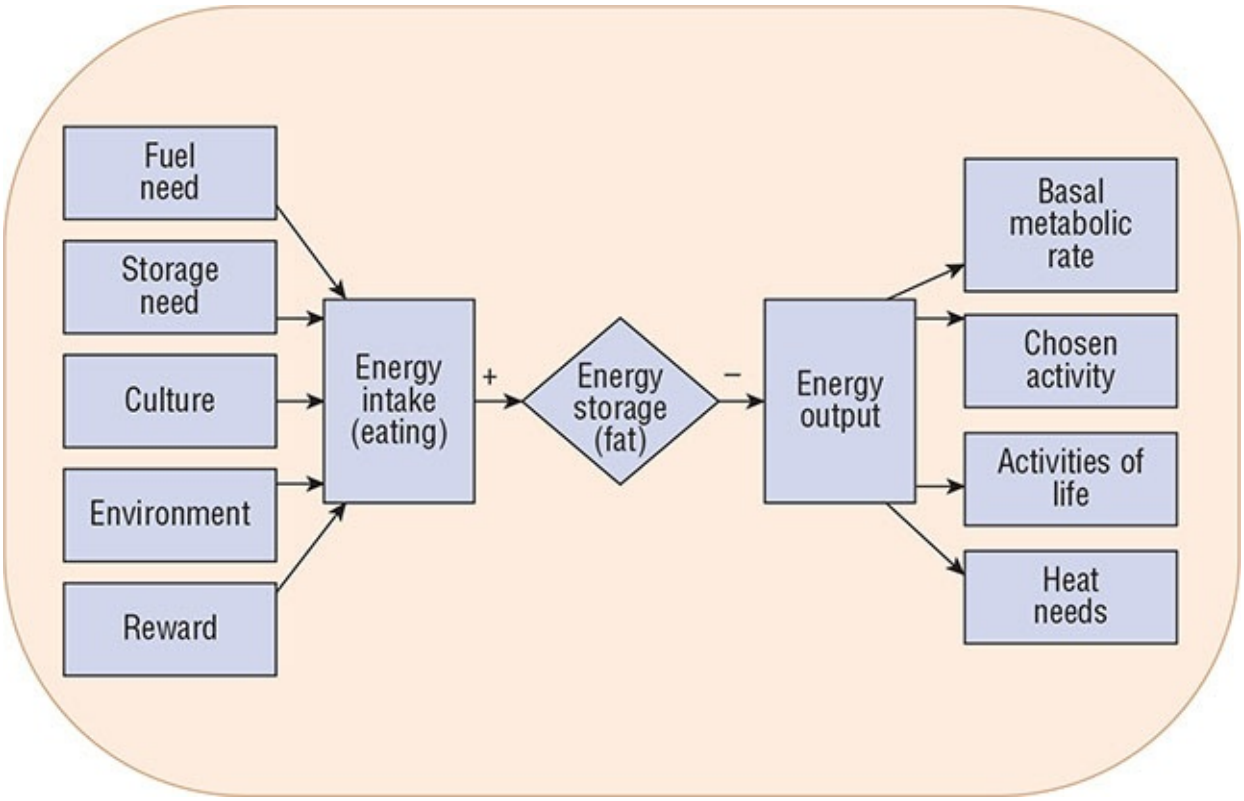


FIGURE 161-1 Net energy stores are determined by various inputs and outputs. Simply stated, obesity occurs when there is an imbalance between energy intake and expenditure.

Medical Conditions

Occasionally, patients present with obesity secondary to an identifiable medical condition. Conditions associated with weight gain include iatrogenic and idiopathic Cushing syndrome, growth hormone deficiency, insulinoma, leptin deficiency, and various psychiatric disorders, such as depression, binge-eating disorder, and schizophrenia. Hypothyroidism is often included in this list, but it mostly causes fluid retention (myxedema) and is generally not a cause of significant obesity. Genetic syndromes that have obesity as a major component are extremely rare and include Prader-Willi, Wilms' tumor, aniridia, genitourinary abnormalities or gonadoblastoma, and mental retardation (WAGR), Simpson-Golabi-Behmel, Cohen, Bardet-Biedl, Carpenter, Börjeson, and Wilson-Turner syndromes. The clinician evaluating a patient for obesity needs to be aware of these potential conditions. The physical examination of patients with obesity should always include an assessment for secondary causes of obesity, including genetic syndromes.

Medications

An increasing number of medications are associated with unintended weight gain.[36] These include several anticonvulsants (eg, carbamazepine, gabapentin, pregabalin, and valproic acid), antidepressants (eg, mirtazapine and tricyclic antidepressants), atypical antipsychotics (eg, clozapine, olanzapine, quetiapine, and risperidone), conventional antipsychotics (eg, haloperidol), and hormones (eg, corticosteroids, insulin, and medroxyprogesterone). Although the pharmacologic mechanism responsible for weight gain is usually drug-specific, in most cases the precise mechanism is unknown.

PATHOPHYSIOLOGY

The pathophysiology of obesity involves numerous factors that regulate appetite and energy balance.[26,37,38] Disturbance of these homeostatic functions results in an imbalance between energy intake and energy expenditure.

Appetite

Human appetite is a complex process that is the net result of many inputs within a neural network involving principally the hypothalamus, limbic system, brainstem, hippocampus, and elements of the cortex.[26,37,38] Within this neural network, many neurotransmitters and neuropeptides have been identified that can stimulate or inhibit the brain's appetite network and thereby affect total caloric intake. The first receptor systems found to alter food intake in animals and humans were the biogenic amines. Serotonin, also known as 5-hydroxytryptamine (5-HT), and cells known to respond to 5-HT are found throughout the central nervous system (CNS) and the periphery. Currently, two major noradrenergic receptor subtypes are recognized (α and β), each with multiple subtypes. Histamine and dopamine also demonstrate multiple receptor subtypes, but their role in the regulation of human eating behaviors and food intake is less well documented. **Table 161-2** summarizes the major effects of direct receptor stimulation, inhibition, and changes in synaptic cleft amine concentrations on food intake.

TABLE 161-2 Effects of Various Neurotransmitters, Receptors, and Peptides on Food Intake

Anatomic Region	Increased Eating	Decreased Eating
Arcuate nucleus of hypothalamus	NPY AgRP	α-MSH CART Leptin Insulin GLP-1 PYY
Paraventricular nucleus of hypothalamus	NPY AgRP	α-MSH, melanocortin CRH CCK
Lateral hypothalamus	Orexin MCH	
Hypothalamus	Norepinephrine α_2 Serotonin 5-HT_{1A}	Norepinephrine α_1 and β_2 Serotonin 5-HT_{1B} and 5-HT_{2C} Histamine H_1 and H_3
Nucleus accumbens	Dopamine	
Brainstem (hindbrain)	NPY AgRP Opioids (especially μ)	Leptin α-MSH, melanocortin CCK
Vagus nerve	Ghrelin	Leptin CCK GLP-1 PYY

AgRP, agouti-related protein; CART, cocaine-and-amphetamine-regulated transcript; CCK, cholecystokinin; CRH, corticotropin-releasing hormone; GLP-1, glucagon-like peptide-1; MCH, melanocyte concentration hormone; α-MSH, α-melanocyte-stimulating hormone; NPY, neuropeptide Y; PYY, peptide YY.

Data from References 37 and 38.

Many neuropeptides also influence appetite within the hypothalamus. Most research has focused on the neural projection between parts of the hypothalamus and the arcuate nucleus with signals to the paraventricular nucleus. The key peptides in this projection are thought to include neuropeptide Y and α-melanocyte–stimulating hormone. Neuropeptide Y is the most potent known stimulator of eating, and α-melanocyte–stimulating hormone action at the melanocortin 3 and 4 receptors is one of the crucial inhibitors of eating.[37] The lateral hypothalamus has been referred to as the “hunger” centered within the brain. The most prominent of the lateral hypothalamic peptides, orexin, increases food intake stimuli within the lateral hypothalamus.[33] Another important

neuropeptide stimulator of eating that principally originates in the lateral hypothalamus is melanocyte-concentrating hormone. Neurons in the lateral hypothalamus use orexin and melanocyte-concentrating hormone to communicate with other neurons throughout the brain and thereby affect a number of functions beyond appetite.[37] Table 161-2 summarizes the major effects of various neuropeptides on food intake. Although hunger and satiety functions are thought to be primarily regulated by the hypothalamus, humans eat in response to a broad set of stimuli, including reward, pleasure, learning, and memory.

Peripheral appetite signals also dramatically affect food intake.[37,38] Leptin, a hormone that is secreted by adipose cells, acts on the arcuate nucleus of the hypothalamus and elsewhere in the brain to decrease appetite and increase energy expenditure.[37,38] Studies conducted in leptin-deficient mice and humans revealed that exogenous leptin administration produced significant weight loss. However, recombinant leptin replacement therapy in humans with obesity who are not leptin deficient has not proved successful because most humans with obesity appear to be leptin resistant.[37] **Figure 161-2** shows the peripheral link that leptin appears to provide in signaling the CNS about the status of fat cell mass.

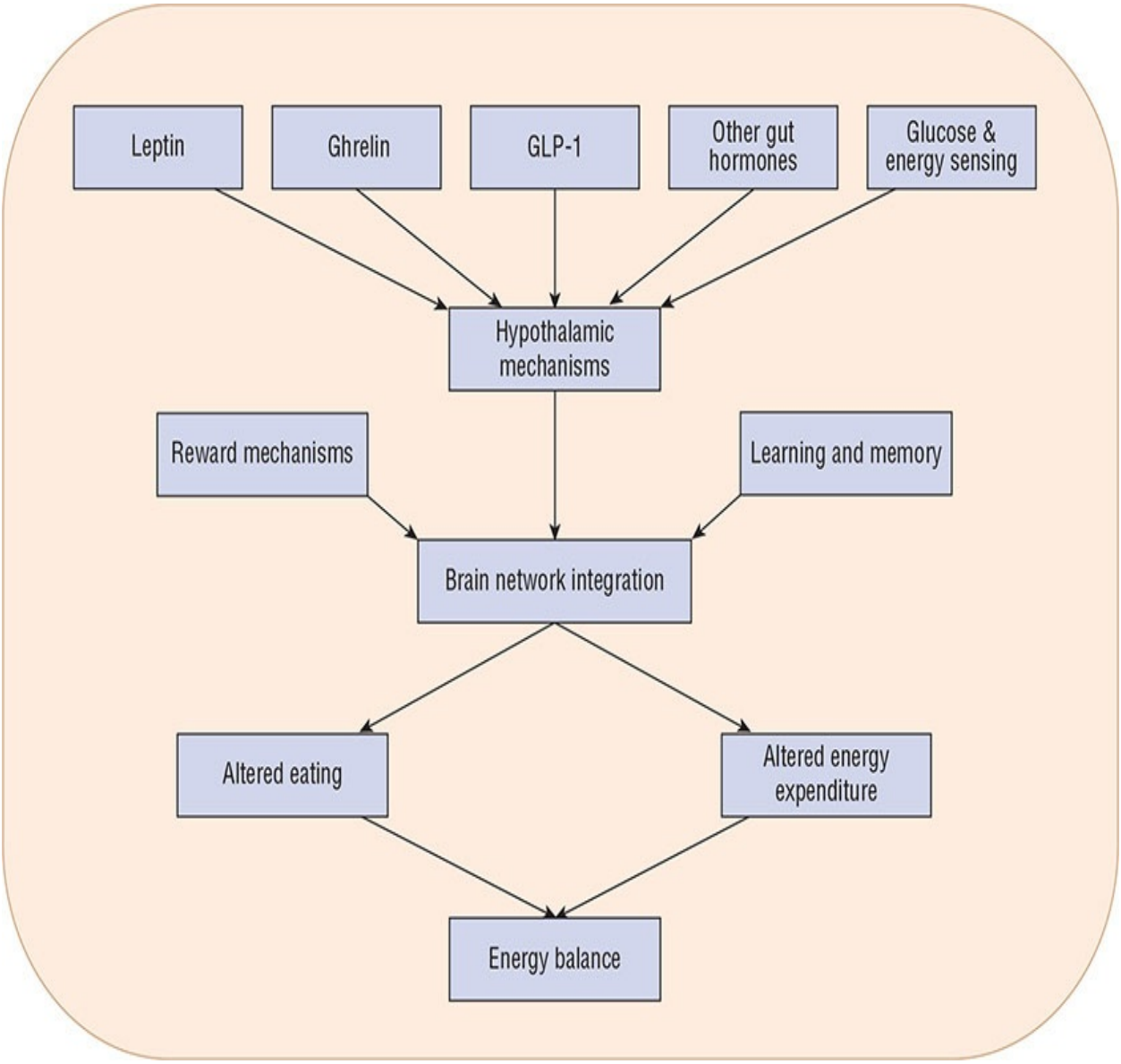


FIGURE 161-2 Intrinsic hypothalamic hunger and satiety mechanisms are modified by input from fat tissue via leptin, and from the gut via ghrelin, glucagon-like peptide-1 (GLP-1), and other hormones. Additional input is derived by direct sensing of prevailing glucose and other energy signals. The hypothalamus generates signals that are integrated within brain networks, which also receive additional signals. The brain network effects change in energy balance by modifying food intake and energy expenditure.

Other peripheral signals important to the brain's processing of appetite include several gut hormones, notably those released by the intestine in response to passage of digesting food such as glucagon-like peptide-1 (GLP-1), oxyntomodulin, and peptide YY.[38] Each of these hormonal signals suppresses

eating in animals and humans. GLP-1 has other effects, most importantly as an incretin, which facilitates release of insulin by pancreatic β cells in response to meal-related glucose. Ghrelin, another important gut hormone that is released from the distal stomach and duodenum, stimulates appetite. An understanding of the relationships among the brain, its many neurotransmitters and neuropeptides, environmental stimulation of brain activities, and other hormones is still evolving.

Energy Balance

The net balance of energy ingested relative to energy expended by an individual over time determines the degree of obesity (Fig. 161-1). An individual's metabolic rate is the single largest determinant of energy expenditure. Resting energy expenditure (REE) is defined as the energy expended by a person at rest under conditions of thermal neutrality. Basal metabolic rate (BMR) is defined as the REE measured soon after awakening in the morning at least 12 hours after the last meal. Metabolic rate increases after eating based on the size and composition of the meal. It reaches a maximum approximately 1 hour after the meal is consumed and returns to basal levels 4 hours after the meal. This increase in metabolic rate is known as the *thermogenic effect of food*. The REE measures the energy costs of the wakeful state and may include the residual thermogenic effect of a previous meal. Physical activity is the other major factor that affects total energy expenditure and is the most variable component. With regard to energy storage, there are two major types of adipose tissue, white and brown. The primary function of white adipose tissue is lipid manufacture, storage, and release. Brown adipose tissue, once believed to be found only in infants, is now recognized to exist in most adults.[39] It is more commonly identified in those who are lean than in those who are obese, but its importance for human obesity remains unclear. Whereas lipid storage occurs in response to insulin, lipid release is seen during periods of calorie restriction. Brown adipose tissue is notable for its ability to dissipate energy via uncoupled mitochondrial respiration.[39] Both white and brown adipose tissues are highly innervated by the sympathetic nervous system, and adrenergic stimulation via β-adrenergic receptors (β_1, β_2, and β_3) is known to activate lipolysis in fat cells as well as increase energy expenditure in adipose tissue and skeletal muscle.

CLINICAL PRESENTATION

Although obesity is readily apparent, most patients with obesity seek healthcare only when obesity-associated comorbidities become problematic. The National Institutes of Health (NIH) has established a stratification of weight excess based on associated medical risks.[40] These levels of excess weight are defined on the basis of BMI, a measure of total body weight relative to height. Using metric units, BMI (kg/m^2) is defined as weight in kilograms divided by height in meters squared (kg/m^2). Using pounds and inches, BMI (kg/m^2) is estimated as (weight [lb]/height [$inches^2$]) × 703. Adults with a BMI of 25 to 29.9 are considered "*overweight*"; the terms *obesity* and *extreme obesity* are reserved for those with a BMI of 30 to 39.9, and 40 and over, respectively. The Endocrine Society clinical practice guideline currently classifies children and adolescents older than 2 years of age with a BMI at 120% or above of the 95th percentile or BMI at 35 kg/m^2 or above as extreme obesity, BMI at the 95th percentile or above as obesity, and those with a BMI between the 85th and 94th percentiles as overweight.[41] Because BMI may overestimate the degree of excess body fat in some clinical situations (eg, edematous states, extreme muscularity, muscle wasting, hydration status, large tumor, and short stature), the assessment of body composition in such cases often requires clinical judgment.

1 BMI is an acceptable measure of obesity and is the practical method of defining obesity in the clinic and epidemiologic studies; however, it does not always correspond to excess fat. There are well-established differences in the relationship between BMI and obesity-related risks among disparate racial, sex, and ethnic groups. For example, the standard cut points for BMI underestimate risks among Asians and therefore utilizing a lower BMI value of 23 kg/m^2 or above to confirm excess body adiposity in this population is recommended.[7,42] Whites tend to have higher level of visceral adipose tissue than African Americans and males usually have greater visceral adipose tissues than females.[43] Central obesity reflects high levels of intra-abdominal or visceral fat, and this pattern of obesity is associated with an increased propensity for the development of hypertension, dyslipidemia, type 2 diabetes, and cardiovascular disease (sometimes referred to as the "metabolic syndrome") and an increased cardiometabolic disease risk. Thus, in addition to the absolute excess fat mass, the distribution of this fat regionally in the body has important clinical effects. Intra-abdominal fat is best estimated by imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) but can be approximated through measurement of waist circumference (WC). Clinically, WC is the narrowest circumference measured in the area between the last rib and the top of the iliac crest. Currently in the United States, Canada, and Europe, the

definition for high-risk WC is greater than 40 in. (102 cm) in men and greater than 35 in. (89 cm) in women.[8] Region- and ethnicity-specific WC thresholds should be used to assess abdominal obesity and disease risks in other populations.[7] Routine determination of WC should be implemented in those with BMIs between 25 and 34.9 kg/m^2 to assess additional metabolic risk. However, after a patient's BMI reaches 35 kg/m^2, it is not necessary to measure WC because it will likely be elevated and adds little in terms of risk prediction.[6]

2 Although BMI and WC are related, each measure independently predicts disease risk. Both measurements should be assessed and monitored during therapy for obesity.[6–8] The risks for development of type 2 diabetes, hypertension, or cardiovascular disease at various stages of obesity based on BMI or WC are outlined in **Table 161-3**. Note that increased WC confers increased risk even in normal-weight individuals. A higher prevalence of cardiometabolic abnormalities among normal weight individuals is particularly evident in racial/ethnic minority populations.[44]

TABLE 161-3 Classification of Overweight and Obesity by Body Mass Index, Comorbidity Risk, Waist Circumference, and Associated Disease Risk

				Disease Risk[a] (Relative to Normal Weight and Waist Circumference)	
				Men	
				≤40 in. (102 cm)	>40 in. (102 cm)
				Women	
	BMI (kg/m^2)	Obesity Class	Comorbidity Risk[7]	≤35 in. (89 cm)	>35 in. (89 cm)
Underweight	<18.5		Low but other problems	—	—
Normal weight[b]	18.5-24.9		Average	—	High
Overweight	25.0-29.9		Increased	Increased	High
Obesity	30.0-34.9	I	Moderate	High	Very high
	35.0-39.9	II	Severe	Very high	Very high
Extreme obesity	≥40	III	Very severe	Extremely high	Extremely high

[a]Disease risk for type 2 diabetes, hypertension, and cardiovascular disease.

[b]Increased waist circumference can also be a marker for increased risk even in persons of normal weight.

BMI, body mass index.

Adapted from Preventing and Managing the Global Epidemic of Obesity. Report of the World Health Organization Consultation on Obesity. Geneva: World Health Organization, 1997. Reprinted with permission from National Institutes of Health, National Heart, Lung, and Blood Institutes. 1997, http://www.nhlbi.nih.gov/guidelines/obesity/ob_home.htm.

Comorbidities

Obesity and overweight are associated with an increased risk of all-cause mortality and contribute to approximately 7.1% of total death globally.[45] A J-shaped association is noted between BMI and all-cause mortality; the greater the BMI, the greater the risk of cancer, cardiovascular diseases (CVD), type 2 diabetes, and respiratory diseases in both men and women.[46] For each standard deviation higher BMI there is an increased risk of type 2 diabetes by 67% and coronary artery disease by 20%.[47] While substantial reduction in life expectancy has been predicted in adults with BMIs greater than 35 kg/m^2, healthy life-years lost due to obesity is estimated to be two to four times greater than total years of life lost.[48] Excessive body fat affects virtually all organ systems. A plethora of evidence continues to link obesity with numerous disease states and health conditions (Table 161-1).[5–20] Therefore, current clinical practice guidelines recommend a "complication-centric approach" for management of obesity.[7,26] It is important for clinicians to assess presence and severity of weight-related complications to determine the appropriate treatment and intensity of weight loss therapy in all individuals with overweight and obesity (**Fig. 161-3**).[7] Because individuals with obesity are also at risk for developing many malignancies, adherence to routine age- and risk-appropriate cancer screening guidelines is recommended.[26] Furthermore, hypertension, hyperlipidemia, coronary heart disease, cerebrovascular accidents, insulin resistance, glucose intolerance, and diabetes are all known cardiac risk factors that tend to cluster in individuals with obesity. Aggressive management of these comorbid cardiovascular risk factors and other weight-related complications (eg, sleep apnea, major depression, osteoarthritis, nonalcoholic fatty liver disease) is warranted in an individual with obesity regardless of an individual's weight loss efforts.[7,8,26]

DIAGNOSIS AND MEDICAL MANAGEMENT OF OBESITY

DIAGNOSIS		COMPLICATION-SPECIFIC STAGING AND TREATMENT		
Anthropometric Component (BMI kg/m²)	**Clinical Component**	**Disease Stage**	**Chronic Disease Phase of Prevention**	**Suggested Therapy (based on clinical judgment)**
<25 <23 in certain ethnicities waist circumference below regional/ ethnic cutoffs		**Normal weight** (no obesity)	**Primary**	• **Healthy lifestyle:** healthy meal plan/ physical activity
25–29.9 23–24.9 in certain ethnicities	Evaluate for presence or absence of adiposity-related complications and severity of complications • Metabolic syndrome • Prediabetes • Type 2 diabetes • Dyslipidemia • Hypertension • Cardiovascular disease • Nonalcoholic fatty liver disease • Polycystic ovary syndrome • Female infertility • Male hypogonadism • Obstructive sleep apnea • Asthma/reactive airway disease • Osteoarthritis • Urinary stress incontinence • Gastroesophageal reflux disease • Depression	**Overweight stage 0** (no complications)	**Secondary**	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions
≥30 ≥25 in certain ethnicities		**Obesity stage 0** (no complications)	**Secondary**	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions • **Weight-loss medications:** Consider if lifestyle therapy fails to prevent progressive weight gain (BMI ≥27)
≥25 ≥23 in certain ethnicities		**Obesity stage 1** (1 or more mild-to-moderate complications)	**Tertiary**	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions • **Weight-loss medications:** Consider if lifestyle therapy fails to achieve therapeutic target or initiate concurrently with lifestyle therapy (BMI ≥27)
≥25 ≥23 in certain ethnicities		**Obesity stage 2** (at least 1 severe complication)	**Tertiary**	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions • **Add weight-loss medication:** Initiate concurrently with lifestyle therapy (BMI ≥27) • **Consider bariatric surgery:** (BMI ≥35)

a. All patients with BMI ≥25 have either overweight or obesity stage 0 or higher, depending on the initial clinical evaluation for presence and severity of complications. These patients should be followed over time and evaluated for changes in both anthropometric and clinical diagnostic components. The diagnoses of overweight/obesity stage 0, obesity stage 1, and obesity stage 2 are not static, and disease progression may warrant more aggressive weight-loss therapy in the future. BMI values ≥25 have been clinically confirmed to represent excess adiposity after evaluation for muscularity, edema, sarcopenia, etc.

b. Stages are determined using criteria specific to each obesity-related complication; stage 0 = no complication; stage 1 = mild to moderate; stage 2 = severe.

c. Treatment plans should be individualized; suggested interventions are appropriate for obtaining the sufficient degree of weight loss generally required to treat the obesity-related complication(s) at the specified stage of severity.

d. BMI ≥27 is consistent with the recommendations established by the US Food and Drug Administration for weight-loss medications.

FIGURE 161-3 Diagnosis and medical management of obesity. (*Reproduced with permission from Reference 7.*)

TREATMENT

Available treatment options for the chronic management of obesity include reduced caloric intake, comprehensive lifestyle intervention, pharmacotherapy, implantable medical devices, and bariatric surgery.

Desired Outcomes

Weight management is commonly considered successful when a predefined amount of weight has been lost such that a final goal is achieved. However, in the current "complication-centric approach" of obesity management, the primary goal is to ameliorate weight-related complications and ultimately improve the patient's health and quality of life rather than a preset decline in body weight.[7] An evidence-based guideline on the management of overweight and obesity was published by The Obesity Society (TOS), American Heart Association (AHA), and American College of Cardiology (ACC), which recommends the initial weight loss goal for adults to be approximately 5% to 10% of the baseline weight over a 6-month period.[6] In 2016, comprehensive clinical practice guidelines published by the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) outlined intervention and weight loss goals based on severity of obesity-related complications (see **Fig. 161-4**).[7] The AACE/ACE guideline further outlines the three-phase paradigm of chronic disease prevention and treatment: primary, secondary, and tertiary. The goal of the primary phase is to prevent overweight and obesity; the goal of the secondary phase is to prevent progressive weight gain or achieve weight loss to prevent complications; and the goal of the tertiary phase is to achieve sufficient weight loss to improve obesity-related complications and prevent further deterioration. Treatment selection and intensity of the obesity intervention varies depending on the phase of prevention and treatment in which the patient resides. If improvement in type 2 diabetes, dyslipidemia, hypertension, and polycystic ovary syndrome are primary goals, then the recommended weight loss goal is at least 5% to 15% or more.[7] For patients with steatohepatitis, the recommended weight loss goal is 10% to 40% in order to reduce inflammation and fibrosis of the liver.[7] Success may also include end points of decreasing the rate of weight gain or maintaining a weight-neutral

status. All too often patients expect to lose weight overnight, only to be disappointed. Thus, it is important to set a time course for the plan. A significant number of web-based resources for supporting both the patient and practitioner weight-management activities are available.[8,49,50]

TREATMENT GOALS BASED ON DIAGNOSIS IN THE MEDICAL MANAGEMENT OF PATIENTS WITH OBESITY

	DIAGNOSIS		TREATMENT GOALS	
	Anthropometric Component	**Clinical Component**	**Intervention/ Weight-Loss Goal**	**Clinical Goals**
PRIMARY PREVENTION				
Primordial Prevention	BMI ≤25 (≤23 in certain ethnicities)	Obesogenic environment	• Public education • Built environment • Access to healthy foods	Decreased incidence of overweight/obesity in populations
Primary Prevention	BMI ≤25 (≤23 in certain ethnicities)	High-risk individuals or subgroups based on individual or cultural behaviors, ethnicity, family history, biomarkers, or genetics	• Annual BMI screening • Healthy meal plan • Increased physical activity	Decreased incidence of overweight/obesity in high-risk individuals or identifiable subgroups
SECONDARY PREVENTION				
Overweight	BMI 25–29.9 (BMI 23–24.9 in certain ethnicities)	No clinically significant or detectable weight-related complications	• Prevent progressive weight gain or • Weight loss	• Prevent progression to obesity • Prevent the development of weight-related complications
Obesity	BMI ≥30 (≥25 in certain ethnicities)	No clinically significant or detectable weight-related complications	• Weight loss or • Prevent progressive weight gain	Prevent the development of weight-related complications
TERTIARY PREVENTION				
Overweight or Obesity	BMI ≥25 (≥23 in certain ethnicities)	Metabolic syndrome	10%	Prevention of T2DM
		Prediabetes	10%	Prevention of T2DM
		T2DM	5% to ≥15%	• Reduction in A1C • Reduction in number and/or doses of glucose lowering medications • Diabetes remission especially when diabetes duration is short
		Dyslipidemia	5% to ≥15%	• Lower triglycerides • Raise HDL-c • Lower non-HDL-c
		Hypertension	5% to ≥15%	• Lower systolic and diastolic BP • Reductions in number and/or doses of antihypertensive medications
		Nonalcoholic fatty liver disease: Steatosis	5% or more	Reduction in intrahepatocellular lipid
		Nonalcoholic fatty liver disease: Steatohepatitis	10% to 40%	Reduction in inflammation and fibrosis
		Polycystic ovary syndrome	5% to 15% or more	• Ovulation • Regularization of menses • Reduced hirsuitism • Enhanced insulin sensitivity • Reduced serum androgen levels
		Female infertility	10% or more	• Ovulation • Pregnancy and live birth
		Male hypogonadism	5% to 10% or more	Increase in serum testosterone
		Obstructive sleep apnea	7% to 11% or more	• Improved symptomatology • Decreased apnea-hypopnea index
		Asthma/reactive airway disease	7% to 8% or more	• Improvement in forced expiratory volume at 1 second • Improved symptomatology
		Osteoarthritis	• ≥10% • 5% to 10% or more when coupled with exercise	• Improvement in symptomatology • Increased function
		Urinary stress incontinence	5% to 10% or more	Reduced frequency of incontinence episodes
		Gastroesophageal reflux disease	10% or more	Reduced symptom frequency and severity
		Depression	Uncertain	• Reduction in depression symptomatology • Improvement in depression scores

FIGURE 161-4 Treatment goals based on diagnosis in the medical management of patients with obesity. (*Reproduced with permission from Reference 7.*)

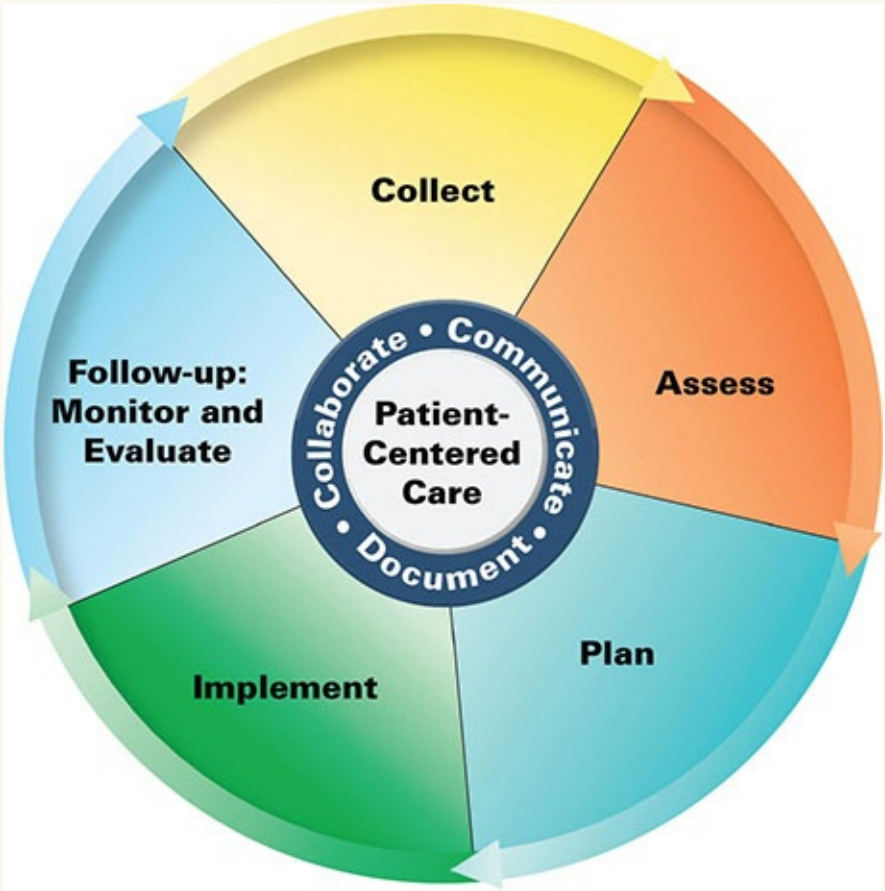
General Approach to Treatment

To achieve meaningful weight loss goals, successful obesity treatment plans require incorporation of comprehensive lifestyle interventions such as a healthy diet, adequate physical activity, and behavioral modifications as the cornerstone of weight management.[6,7,25,26] Once the need for weight loss has been determined, the clinician needs to assess a patient's readiness to engage in weight loss efforts and identify any potential barriers to success. They need to initiate a dialogue with each patient who is overweight or obese to ensure they understand the potential health consequences of excess body weight and the benefits of appropriate weight management. Specific weight goals should be established that are consistent with medical needs, weight-related complications, and the patient's personal desire.[7] Patients should not be allowed to attain an abnormally low body weight (ie, less than their estimated ideal body weight).

3 Patients seeking help for obesity do so for many reasons, including improvement in their quality of life, a reduction in associated morbidity, and increased life expectancy. Because weight stigma is prevalent in the western culture, numerous individuals seek therapy for obesity primarily for cosmetic purposes and often have unrealistic goals and expectations. Aggressive marketing of weight loss programs, therapies, and diets—parallel to the fashion industry's standards of desirable body profiles—has led many individuals to set impossible goals and expectations. In some cases, these individuals will go to extreme measures to achieve weight loss. Consequently, clinicians must be careful to fully discuss the risks of therapies and to clearly define the achievable benefits and magnitude of weight loss. Patients with obesity should be directed away from trying to achieve an "ideal weight" to a more realistic goal of modest (eg, loss of 5%-10% of body weight) but sustained, medically relevant weight loss. In practice, goals should be set based on many factors, including initial body weight, patient motivation and desire, presence of obesity-related comorbid conditions, and age. The Look Action for Health in Diabetes (AHEAD) study found that patients with diabetes who maintained weight loss of at least 7% with intensive lifestyle modifications for a period of almost 10 years did not experience a reduced incidence of cardiovascular events, but they did have a reduced need for diabetes medications and improvement in physical function, lipids, blood pressure, kidney disease, sleep apnea, fitness, and depression.[51]

Indeed, in patients with overweight and obesity with diabetes, lifestyle modification with sustained weight loss of greater than 5% improves HbA1c level and ameliorates hyperglycemia, hyperlipidemia, and hypertension within a year.[52] For individuals with obesity who have gastroesophageal reflux disease, a 10% or more weight reduction may be required to improve symptoms.[7] These data emphasize the importance of defining end points and measures of success in any weight-loss plan.

4 Weight-loss interventions must be founded on lifestyle changes, such as a modification in eating practices; complemented by drug therapy, if indicated; and in some cases, surgery. Before recommending any therapy, the clinician must evaluate the patient for the presence of secondary causes of obesity. If a secondary cause is suspected, then a more complete diagnostic workup and the initiation of appropriate therapy may be warranted. The next step in patient evaluation is to determine the presence and severity of other medical conditions that are either directly associated with obesity (eg, diabetes, cardiovascular diseases, uncontrolled hypertension) or that have an impact on therapeutic decision-making (eg, history of pancreatitis, cardiac arrhythmia, seizure disorders, concurrent medications).[7,26] The Endocrine Society Clinical Practice Guideline for the Pharmacological Management of Obesity emphasizes that clinicians should always consider the potential weight-altering effects of all medications a patient is receiving for the management of comorbid conditions and select medications that are weight-neutral or promote weight loss (strong recommendation with moderate-quality evidence).[26] For example, in patients with type 2 diabetes, antidiabetic agents that promote weight loss (eg, metformin, glucagon-like pepetide-1 analogs or sodium-glucose-linked transporter-2 inhibitors) are preferred. Appropriate laboratory tests to exclude or quantify the degree of specific conditions such as diabetes, liver dysfunction, and nephropathy should be performed as indicated by the history and physical examination. Based on the outcome of this medical evaluation, the patient should be counseled on treatment options, benefits, and risks. Ultimately, lifelong therapeutic goals should consist of maintenance of reduced body weight and prevention of weight gain.



Patient Care Process for Management of Obesity

Collect

- Patient characteristics (eg, age, race, sex)
- Patient history (past medical, family, social — dietary habits, tobacco use)
- Obesity-related conditions (see Fig. 161-1 and Table 161-1)
- Current medications including prescription, nonprescription, and herbal product use
- Weight loss history and prior attempts to lose weight
- Objective data
  - Height, weight, BMI, waist circumference, and blood pressure
  - Labs (eg, fasting glucose, hemoglobin A1c, lipid panel)

Assess

- Causes of secondary obesity (eg, insulinoma, Cushing syndrome)
- Current medications that may contribute to weight gain
- Presence of obesity-related comorbidities (eg, hypertension, dyslipidemia, coronary artery disease, type 2 diabetes mellitus, sleep apnea, increased waist circumference; see Fig. 161-3)
- Class of overweight and obesity determined by BMI, waist circumference, and obesity-related comorbidities (see Table 161-3)
- Readiness to engage in weight loss efforts and potential barriers to success
- Candidacy for treatment with implantable medical devices, bariatric surgery, or pharmacotherapy

Plan*

- Nonpharmacologic lifestyle intervention including low-calorie diet, physical activity, and behavioral modifications
- Pharmacotherapy (if appropriate) including specific medication, dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Table 161-5)
- Initial weight loss goal of 5% to 10% over a 6-month time period (see Fig. 161-4).
- Monitoring parameters including efficacy (weight loss) and tolerability (medication-specific adverse effects)
- Patient education (eg, purpose of dietary and lifestyle modification, drug therapy)
- Self-monitoring of weight—when and how to record results
- Referrals to other providers when appropriate (eg, physician, dietician, psychologist)

Implement*

- Educate patient regarding health risks associated with overweight and obesity
- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize

adherence

- Schedule follow-up (eg, monthly for first 3 months and every 3 months thereafter)

Follow-up: Monitor and Evaluate

- Determine weight loss goal attainment
- Presence of adverse effects
- Patient adherence to treatment plan using multiple sources of information

Collaborate with patient, caregivers, and other healthcare professionals.

Nonpharmacologic Therapy

Nonpharmacologic therapy including reduced caloric intake, increased physical activity, and behavioral modification is the mainstay of obesity management. This combination, also known as lifestyle therapy, is recommended for all patients with overweight and obesity by The Endocrine Society Clinical Practice Guidelines for the Pharmacological Management of Obesity (graded as strong recommendation with high-quality evidence)[26] and the AACE/ACE Guidelines for the Medical Care of Patients with Obesity (grade A recommendation with the best level of evidence).[7] Although the difference is subtle, it should be noted that the AHA/ACC/TOS Guidelines for the Management of Overweight and Obesity in Adults do not recommend weight-loss therapy for patients with BMI between 25 and 29.9, unless the patient has CVD risk factors.[6] Weight loss will require significant effort on the part of the patient to change their lifestyle and comply with the management plan. If the patient is not ready to meet these expectations, then early counseling will reduce the chance of frustration for the patient, clinician, and possibly other family members. Providing basic education can lead to a significant change in motivation and desire to lose weight and improved compliance.

Reduced Caloric Intake

Current adult guidelines recommend reduced caloric intake through adherence to a low-calorie diet (LCD).[6,7] The LCD should provide a daily caloric deficit of 500 to 750 kcal (2,092-3,138 kJ), which generally correlates to a total intake of 1,200 to 1,500 kcal/day (5,021-6,276 kJ/day) for women and 1,500 to 1,800

kcal/day (6,276-7,531 kJ/day) for men. Individuals with severe obesity will require more energy, at least at the start of dietary restriction. Adherence to the LCD results in an average weight loss of 8% after 6 months.[8]

Numerous diet and nutrition plans are available to aid patients in their pursuit of weight loss, and current guidelines allow for choice among many potential evidence-based diet plans.[6–8] Popular diets include moderate energy-deficient plans (eg, DASH [Dietary Approaches to Stop Hypertension], Mediterranean, Weight Watchers, LEARN [Lifestyle, Exercise, Attitude, Relationships, Nutrition], and Jenny Craig), vegetarian-based plans (eg, Ornish), and low carbohydrate plans (eg, Zone and Atkins). Short-term weight loss is significant for almost all diet plans. However, long-term weight loss and maintenance of weight loss are less promising, primarily because of difficulty with adherence. Therefore, the choice of diet plan should be determined based on patient-specific preferences, health status, and ability to consistently adhere to the specific recommendations of the diet.[6,7] A meta-analysis of 48 clinical trials assessing the efficacy of various diets concluded that differences in weight loss among popular named diets are not clinically significant,[53] highlighting the general consensus that macronutrient composition of the diet may not be as important as consistent adherence to reduced energy consumption.

Very-low-calorie diets, providing less than 800 kcal/day (3,349 kJ/day), are generally not recommended.[8] Although very-low-calorie diets can often result in early weight loss, long-term results have been disappointing because it is difficult for individuals to maintain compliance.[52] Additionally, very-low-calorie diets require intensive medical monitoring and should only be used in certain situations under the supervision of an experienced clinician. Regardless of the diet program, it is clear that energy consumption must be less than energy expenditure to achieve weight loss (see Fig. 161-1). The challenge is to develop a diet plan that leads to consistent adherence by the patient and sustained weight loss and maintenance.

Comprehensive Lifestyle Intervention

Comprehensive lifestyle intervention encompasses the combination of reduced-caloric intake, increased physical activity, and behavioral modification. Increased physical activity is an important component in achieving the state of greater energy expenditure than energy intake that is necessary to lose weight and maintain weight loss. Weight loss is modest when increased physical activity is attempted as monotherapy. However, when it is combined with reduced calorie intake and behavior modification, it can augment weight loss and

improve obesity-related comorbidities and cardiovascular risk factors.[6,8] Aerobic physical activity for at least 150 minutes per week, completed over three to five days is recommended for adults.[7,54] Greater levels (ie, 200-300 min/week) may be required to augment weight loss and maintain lost weight. Patients should be advised to start slowly and gradually increase intensity. All patients with obesity should receive a medical examination before embarking on a physical activity program.

Current adult guidelines recommend initiation of a comprehensive lifestyle program to help patients with overweight and obesity adhere to the prescribed LCD and increased physical activity (NHLBI Grade A; strong recommendation).[6,7] On-site, individual, or group behavioral counseling sessions offered by a trained clinician on at least 14 occasions during a 6-month time period are preferred.[6] However, electronic- or commercial-based programs may also be effective. For patients who have successfully lost weight during the first 6 months, long-term participation in a comprehensive lifestyle program is recommended. The primary aim is to help patients choose lifestyles that are conducive to safe and sustained weight loss. Most such programs use self-monitoring of diet and exercise to increase patient awareness of behavior and as a tool for the clinician to determine patient compliance as well as patient motivation. Clinical studies evaluating the efficacy of high-intensity comprehensive lifestyle interventions that include a reduced-calorie diet, increased exercise, and in-person behavioral counseling sessions have reported an average weight loss of 8 kg (17.6 lb) after 6 months.[8]

Bariatric Surgery

5 Consistent with the growing obesity epidemic, the demand for bariatric surgery has increased drastically over the past two decades. Surgery currently remains the most powerful and effective intervention for the treatment of obesity.[55] Current clinical practice guidelines recommend that surgical intervention be reserved for patients with extreme obesity (ie, BMI ≥40 kg/m^2 or BMI ≥37.5 kg/m^2 in Asian Americans) or BMI at 35 kg/m^2 or above (BMI 32.5-37.4 kg/m^2 in Asian Americans) with at least one or more significant comorbidities such as hypertension, type 2 diabetes, or obstructive sleep apnea (NHLBI Grade A; strong recommendation).[6,7,56,57] Surgery may also be advocated for patients with BMI between 30 and 34.9 kg/m^2 (27.5-32.4 kg/m^2 in Asian Americans) and diabetes or metabolic syndrome, as a similar efficacy and safety profile for improving type 2 diabetes and metabolic disorders is observed

among bariatric patients with a BMI below or above 35 kg/m^2.[6,56–58] This has led to use of the term “metabolic surgery” with focuses on treating metabolic diseases independent of body weight.[58]

Surgical weight-loss options should only be considered in patients who have met the eligibility criteria and have failed other recommended methods for weight loss. It is critical for bariatric surgical candidates to fully understand the surgical risks and be able to adhere to the extensive postoperative care plan, follow-ups, and necessary lifelong dietary and lifestyle adjustments to ensure the long-term success of the procedure.

The four available surgical procedures are (1) adjustable gastric banding, (2) sleeve gastrectomy, (3) biliopancreatic diversion with duodenal switch, and (4) conventional Roux-en-Y gastric bypass. The adjustable gastric banding and sleeve gastrectomy are designed to reduce the volume of the stomach and thus restrict the rate of nutrient intake. The biliopancreatic diversion with duodenal switch is primarily malabsorptive in nature, and the length of the diversion determines the extent of nutrient malabsorption. This hybrid procedure combines a restrictive approach with a degree of malabsorption induced by reducing the size of the stomach pouch and causing food to bypass parts of the small intestine. Techniques that involve redirection of the flow of nutrients have humoral and malabsorptive effects, generally yield greater and longer lasting weight loss than the purely restrictive methods.[55] The sleeve gastrectomy has increased in its popularity worldwide and is currently the most common procedure performed in the United States.[55] Resection of the gastric segment from sleeve gastrectomy also removes the endocrine cells, which alters neuro-humoral activity and results in earlier satiety and improvements in glucose metabolism.

The STAMPEDE trial demonstrated that after 5 years, patients with type 2 diabetes with BMI of 27 to 43 kg/m^2 who undergo gastric bypass surgery lose more (23%) of their initial body weight compared to patients who receive sleeve gastrectomy (19%) and patients who receive intensive medical therapy (5%).[59] The extent of weight loss and the potential for weight regain after bariatric surgery is multifactorial as metabolic, anatomic, and lifestyle changes can all impact the outcome of the procedure. Bariatric surgeries are now considered among the safest abdominal surgical procedures performed in the United States; the operative 30-day mortality rate reported for gastric bypass is 0.2% and sleeve gastrectomy is 0.1%.[55] Some of the most common early surgical complications are gastric and anastomotic leaks, bleeding, wound infections, and pulmonary emboli. Due to the disruption of the normal gastric anatomy and physiology,

postsurgical patients are often at risk for severe micronutrient deficiencies (eg, vitamin B_{12} and anemia) as well as deficiencies in fat-soluble vitamins such as vitamins A, D, E, and K due to fat malabsorption.[60] Therefore, empiric supplementation with daily adult multivitamin plus minerals, elemental calcium, vitamin D, folic acid, thiamine, elemental iron, and vitamin B_{12} is essential to prevent nutritional deficiencies in bariatric patients.[56] All bariatric surgical patients should undergo life-long monitoring of nutritional deficiencies after the procedure. Substantial weight loss resulting from bariatric surgery provides multitude of health benefits from head to toe, which are often accompanied by dramatic improvements, and sometimes complete resolution, of many obesity-related complications.[55] Significant reduction in risks of myocardial infarction and cardiovascular death, as well as the incidence of type 2 diabetes, hypertension, dyslipidemia, and cancer, has also been documented after bariatric surgery.[55,59,61,62] It has long been known that bariatric surgery improves microvascular diseases,[63] and it is now clear that it substantially reduces macrovascular disease and mortality in patients with type 2 diabetes and severe obesity.[61] Patients who underwent Roux-en-Y gastric bypass surgery experienced 40% decrease in all-cause mortality, 60% decrease in mortality due to cancer, 92% decrease in mortality due to diabetes, and 56% decrease in mortality due to coronary artery disease at 12 years.[62] Significant increase in life expectancy is also expected after bariatric surgery.[55]

After experiencing weight loss, many gastric surgery patients are able to discontinue pharmacotherapy for glucose lowering, dyslipidemia, hypertension, and reduce medication costs.[55,59] However, the need for use of proton-pump inhibitors or H_2-receptor antagonists is often increased.[60] It is imperative for clinicians to recognize that bariatric interventions not only alter nutrient absorption but also may impede drug absorption and can cause potential serious consequences.[60,64] Achlorhydria, reduced surface area for intestinal and gastric absorption, and alterations in drug metabolism via the intestinal metabolic pathways (eg, cytochrome P450 enzymes or efflux transporters) after bariatric surgery can lead to altered dissolution and/or absorption of many medications. Reduced bioavailability has been reported for some antimicrobials, immunosuppressives, anticonvulsants, highly lipophilic tricyclic antidepressants, SSRIs, and warfarin.[60,64] Furthermore, concurrent administration of proton-pump inhibitors may also alter bioavailability of weak basic drugs such as antifungals (eg, ketoconazole), certain antibiotics, and some cardiovascular medications (eg, digoxin), as well as hinder the absorption of micronutrients.[60,64]

Therefore, clinicians need to recognize that the standard dosage regimens recommended for presurgical patients may need to be adjusted. Switching from solid medications to liquid formulations for postsurgical patients would be beneficial for at least the first 2 months.[64] Long-term close therapeutic monitoring of all orally administered medications after surgery, particularly those with narrow therapeutic ranges, is highly recommended because dosage form selection, dose conversion, or therapeutic interchange may be necessary to avoid or minimize absorption problems and ensure optimal patient outcomes.

Implantable Medical Devices

Despite meeting the medical necessity for bariatric surgery, some individuals may not qualify as surgical candidates or may choose to not undergo the procedure. Implantable medical devices may fill the existing treatment gap in obesity management and may address the unmet needs in these individuals. Currently, there are five FDA-approved medical devices for weight reduction involving electrical stimulation, gastric emptying, or gastric balloon systems (**Table 161-4**).[65–69] Each of these devices are fully reversible and are designed to work in conjunction with prescribed diet and exercise programs. A patient's ability to provide appropriate follow-up is essential to enhance the safety and to avoid complications related to the devices. Unfortunately, once the device is removed, patients will often regain the lost weight.[65]

TABLE 161-4 FDA-Approved Medical Devices for Weight Loss

Device	Mechanism of Action	BMI Indication	Contraindications	Weight-Loss Outcomes	Adverse Events	Comments
Gastric Emptying System						
AspireAssist®[65-67]	An implanted percutaneous gastrostomy aspiration tube removes approximately 30% of the meal from stomach after ingestion	BMI 35-55 kg/m²	Uncontrolled hypertension Bulimia Binge eating disorder Night eating syndrome Previous abdominal surgery Inflammatory bowel disease Stomach ulcer History of serious pulmonary or cardiovascular disease Coagulation disorders Chronic abdominal pain Pregnancy or lactation, or desire to become pregnant	Percent total body weight loss (%TBWL) across trials after 1 year of therapy is 14.2%-21.4%	Abdominal pain Indigestion Nausea Vomiting Constipation Diarrhea Peristomal granulation tissue Peristomal irritation and inflammation	Patient must take extra time to chew thoroughly and drink sufficient liquid with each meal to ensure proper aspiration Frequent medical visits are also necessary to monitor device use and weight loss and to provide counseling on lifestyle therapies The device contains a safety feature to track the number of times the drain tube is connected to the port and automatically stops working after 115 cycles (approximately 5-6 weeks of therapy) to ensure proper use
Electrical Stimulation System						
Maestro® Rechargeable System[65]	A neurometabolic therapy, deliver via a place-maker like device that is implanted on the vagal trunk. The device is designed to intermittently block the communication with the vagus nerve (vBloc) through the delivery of electrical impulse to increase satiety and improve food-related cognitive restraints	BMI 40-45 kg/m² OR BMI 35-39.9 kg/m² with at least 1 comorbidity	Liver cirrhosis Portal hypertension Esophageal varices Hiatal hernia Planned MRI or diathermy Permanently implanted, electrical-powered medical device	Percent total body weight loss (%TBWL) after 1 year of therapy is 9.2%	Neuroregulator site pain Nausea Abdominal pain Heartburn Dyspepsia	The implanted neuroregulatory is controlled by the clinician with an external programming device to deliver at least 12 hours of intermittent nerve block Once the device is turn-off, patient often will regain the weight lost
Gastric Balloon System						
Obera Intragastric Balloon[65,69]	Endoscopically placed intragastric balloon device designed to occupy space in the stomach to reduce hunger and improve appetite control	BMI 30-40 kg/m²	Previous gastric surgery Hiatal hernia Coagulation disorder A potential bleeding lesion of the upper gastrointestinal tract Alcoholism or drug addiction Severe liver disease Pregnancy or lactation, or desire to become pregnant Any contraindication to endoscopy	Percent total body weight loss (%TBWL) after 1 year of therapy is 11.5%[4]	Abdominal pain Nausea Early explantation Migration Perforation	The device placement is intended to be temporarily. After 6 months, the balloon is punctured and removed through the mouth via a grasping device Patients who fail to remove the device after 6 months will be at increased risk of intestinal obstruction due to migration of the deflated balloon Aggressive symptoms control with anti-nausea medications and proton pump inhibitor in the early period after insertion Weight regain occurs after device removal

The ReShape Integrated Dual Balloon System[65,69]	Endoscopically placed intragastric balloon device designed to occupy space in the stomach to reduce hunger and improve appetite control	BMI 30-40 kg/m^2 with at least 1 comorbidity	Prior gastrointestinal or bariatric surgery Inflammatory intestinal or bowel disease Large hiatal hernia Delayed gastric emptying Upper gastrointestinal bleed Coagulation disorder Severe liver disease Active *Helicobacter pylori* infection A structural abnormality in the esophagus or pharynx Use of anticoagulants or anti-inflammatory agents Pregnancy or lactation, or desire to become pregnant Any contraindication to endoscopy	Percent total body weight loss (%TBWL) after 6 months of therapy is 15.4%	Abdominal pain Nausea Vomiting Heartburn Gastric ulcer Deflation Perforation Dysphagia Gastric bleeding	The device placement is intended to be temporarily and should be removed 6 months after insertion as the device will deflate over time Patients who fail to remove the device after 6 months will be at increased risk of intestinal obstruction due to migration of the deflated balloon Aggressive symptoms control with anti-nausea medications and proton pump inhibitor in the early period after insertion Patients currently taking selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs) should use this device with caution due to the potential for balloon rupture and release of methylene blue which with these concurrent therapies can increase risk of developing serotonin syndrome Weight regain occurs after device removal
Obalon Balloon System[65]	Sequentially swallowed balloon device designed to occupy space in the stomach to reduce hunger and improve appetite control. A total of 3 balloons are placed over 3 months	BMI 30-40 kg/m^2	Any structural or functional abnormality in the esophagus, pharynx, stomach, intestines, or any portion of the gastrointestinal tract Prior bariatric surgery Inflammatory and other conditions of the gastrointestinal tract Active *Heliocobacter pylori* infection Bulimia, binge eating or other eating disorders Use of gastric irritants such as NSAIDs and aspirin Use of antiplatelets or anticoagulants Irritable bowel syndrome or other inflammatory bowel disease Taking medications on specified hourly intervals that may be affected by changes in gastric emptying (eg, antiseizure or antiarrhythmic medications) Alcoholism or drug addiction Pregnancy or lactation, or desire to become pregnant	Percent total body weight loss (%TBWL) after 6 months of therapy is 6.8%	Abdominal pain Nausea Vomiting Heartburn Bloating Gastric ulcer	The only intragastric balloon that does not require endoscopic placement. The balloon is encapsulated, attached to a tube, and swallowed under provider supervision The device placement is intended to be temporarily and should be endoscopically removed after 3 to 6 months Aggressive symptoms control with anti-nausea medications and proton pump inhibitor in the early period after insertion Weight regain occurs after device removal

BMI, body mass index; TBWL, total body weight loss.

Pharmacologic Therapy

6 7 According to current guidelines, pharmacotherapy is an adjunct to comprehensive lifestyle intervention in adults who are motivated to lose weight, have failed to achieve or sustain weight loss with lifestyle changes alone, and have a BMI more than or equal to 30 kg/m^2 or a BMI more than or equal to 27 kg/m^2 with at least one weight-related comorbidity (graded as a strong recommendation with high-quality evidence).[7,26] Furthermore, patients who meet the BMI requirements and have a history of failed attempts to lose weight or maintain weight loss with comprehensive lifestyle intervention alone may also be candidates for pharmacotherapy.[26] Long-term pharmacotherapy may have a place in the treatment of obesity for patients who have no obvious contraindications to approved drug therapy, as the likelihood of weight regain after treatment discontinuation is quite high.[70] **Table 161-5** lists FDA-approved pharmacotherapeutic agents currently available for management of overweight and obesity.

TABLE 161-5 FDA-Approved Pharmacotherapeutic Agents for Weight Loss

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Comment
Gastrointestinal Lipase Inhibitor					
Orlistat	Xenical	120 mg three times daily with each main meal containing fat	120 mg three times daily with each main meal containing fat		Approved for long-term use Take during or up to 1 hour after the meal Omit dose if meal is occasionally missed or contains no fat
Orlistat	Allia	60 mg three times daily with each main meal containing fat	60 mg three times daily with each main meal containing fat		Same as Xenical
Phentermine–Topiramate Combination					
Phentermine and topiramate extended-release	Qsymia	3.75 mg of phentermine and 23 mg of topiramate once daily for 14 days; then increase to 7.5 mg of phentermine and 46 mg of topiramate once daily	7.5 mg of phentermine and 46 mg of topiramate once daily to a maximum dose of phentermine 15 mg and topiramate 92 mg once daily	Maximum dose for patients with moderate or severe renal impairment or patients with moderate hepatic impairment is 7.5 mg of phentermine and 46 mg of topiramate	Approved for long-term use Take dose in the morning to avoid insomnia Controlled substance: C–IV
Naltrexone–Bupropion Combination					
Bupropion and naltrexone extended-release	Contrave	8-mg naltrexone/90-mg bupropion (1 tablet) once daily in the morning for 1 week; then 8-mg naltrexone/90-mg bupropion twice daily (morning and evening) for 1 week; then 16-mg naltrexone/180-mg bupropion in the morning and 8-mg naltrexone/90-mg bupropion in the evening for 1 week; then 16-mg naltrexone/180-mg bupropion twice daily (morning and evening)	16-mg naltrexone and 180-mg bupropion (2 tablets) twice daily	Maximum dose for patients with moderate or severe renal impairment is 8-mg naltrexone/90-mg bupropion (1 tablet) twice daily Maximum dose for patients with hepatic impairment is 8-mg naltrexone/90-mg bupropion (1 tablet) once daily in the morning	Approved for long-term use Do not take dose with high-fat meal
Glucagon-Like Peptide-1 Antagonist					
Liraglutide	Saxenda	0.6 mg once daily for 1 week 1.2 mg once daily for 1 week 1.8 mg once daily for 1 week 2.4 mg once daily for 1 week 3.0 mg once daily for 1 week administered by subcutaneous injection	3 mg once daily	Use with caution in mild, moderate, and severe renal and hepatic impairment	Approved for long-term use Inject subcutaneously in the abdomen, thigh, or upper arm Administer at any time of day without regard to the timing of meals
Noradrenergic Agents					
Phendimetrazine	Bontril PDM; Bontril Slow-Release	Conventional tablet: start at 17.5 mg two or three times daily, given 1 hour before meals Extended-release capsule: 105 mg once daily 30-60 minutes before morning meal	70-105 mg/day	Use caution in patients with renal impairment	Approved for short-term monotherapy Controlled substance: C–III Prescriptions should be written for the smallest quantity to minimize possibility of overdose

Phentermine	Lomaira Adipex-P	8 mg three times daily, given half hour before meal Orally disintegrating tablet: 15 or 30 mg once every morning Phentermine hydrochloride: 15-37.5 mg/day given in one or two divided doses; administer before breakfast or 1-2 hours after breakfast	8 mg three times daily, given half hour before meal Orally disintegrating tablet: 15 or 30 mg once every morning Phentermine hydrochloride: 15-37.5 mg/day given in one or two divided doses; administer before breakfast or 1-2 hours after breakfast	Use with caution in patients with renal impairment	Approved for short-term monotherapy Controlled substance: C–IV Prescriptions should be written for the smallest quantity to minimize possibility of overdose Individualize to achieve adequate response with lowest effective dose
Diethylpropion	Tenuate, Tenuate Dospan	Immediate release: 25 mg three times daily administered 1 hour before meals Controlled release: 75 mg once daily administered at midmorning	75 mg/day	Use with caution in patients with renal impairment	Approved for short-term monotherapy Dose should not be administered in the evening or at bedtime Controlled substance: C–IV

A multidisciplinary team approach to the management of obesity is necessary to ensure long-term success. It is common for patients to use a combination of nonprescription, prescription, and other complementary and alternative therapies to attain the desired weight-loss goal. Therefore, clinicians should maintain a high degree of sensitivity toward the potential polypharmacy practices of patients with obesity. Finally, it is prudent to consider specific patient factors and characteristics along with the efficacy and safety profiles of individual therapies when determining if use of a pharmacologic intervention is warranted. (**Figure 161-5**) lists preferred weight-loss agents based on patient-specific comorbidities.

PREFERRED WEIGHT-LOSS MEDICATIONS: INDIVIDUALIZATION OF THERAPY

KEY: PREFERRED DRUG | USE WITH CAUTION | AVOID

CLINICAL CHARACTERISTICS OR COEXISTING DISEASES		MEDICATIONS FOR CHRONIC WEIGHT MANAGEMENT				
		Orlistat	Lorcaserin[a]	Phentermine/ topiramate ER	Naltrexone ER/ bupropion ER	Liraglutide 3 mg
Diabetes Prevention (metabolic syndrome, prediabetes)			Insufficient data for T2DM prevention		Insufficient data for T2DM prevention	
Type 2 Diabetes Mellitus						
Hypertension				Monitor heart rate	Monitor BP and heart rate. Contraindicated in uncontrolled HTN	Monitor heart rate
Cardiovascular Disease	CAD			Monitor heart rate	Monitor heart rate, BP	Monitor heart rate
	Arrhythmia		Monitor for bradycardia	Monitor heart rate, rhythm	Monitor heart rate, rhythm, BP	Monitor heart rate, rhythm
	CHF	Insufficient data	Insufficient data	Insufficient data	Insufficient data	Insufficient data
Chronic Kidney Disease	Mild (50–79 mL/min)					
	Moderate (30–49 mL/min)			Do not exceed 7.5 mg/46 mg per day	Do not exceed 8 mg/90 mg bid	
	Severe (<30 mL/min)	Watch for oxalate nephropathy	Urinary clearance of drug metabolites	Urinary clearance of drug	Urinary clearance of drug	Avoid vomiting and volume depletion
Nephrolithiasis		Calcium oxalate stones		Calcium phosphate stones		
Hepatic Impairment	Mild-Moderate (Child-Pugh 5–9)	Watch for cholelithiasis	Hepatic metabolism of drug	Do not exceed 7.5 mg/46 mg per day	Do not exceed 8 mg/90 mg in AM	Watch for cholelithiasis
	Severe (Child-Pugh >9)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Depression			Insufficient safety data Avoid combinations of serotonergic drugs	Avoid maximum dose: 15 mg/92 mg per day	Insufficient safety data Avoid in adolescents and young adults	
Anxiety				Avoid max dose: 15 mg/92 mg per day		
Psychoses		Insufficient data	Insufficient data	Insufficient data	Insufficient data	Insufficient data
Binge Eating Disorder			Insufficient data. Possible benefit based on reduction in food cravings	Insufficient data. Possible benefit based on studies with topiramate	Insufficient data. Possible benefit based on studies with bupropion Avoid in patients with purging or bulimia nervosa	Insufficient data
Glaucoma				Contraindicated, may trigger angle closure	May trigger angle closure	
Seizure Disorder				If discontinue at dose of 15 mg/92 mg, taper slowly	Bupropion lowers seizure threshold	
Pancreatitis		Monitor for symptoms				Monitor for symptoms Avoid if prior or current disease
Opioid Use					Will antagonize opioids and opiates	
Women of Reproductive Potential	Pregnancy	Use contraception and discontinue orlistat should pregnancy occur	Use contraception and discontinue lorcaserin should pregnancy occur	Use contraception and discontinue phentermine/topiramate should pregnancy occur (perform monthly pregnacy checks to identify early pregnancy)	Use contraception and discontinue naltrexone ER/bupropion ER should pregnancy occur	Use contraception and discontinue liraglutide 3mg should pregnancy occur
	Breast-feeding	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Age ≥65 years *		Limited data available	Insufficient data	Limited data available	Insufficient data	Limited data available
Alcoholism/ Addiction			Might have abuse potential due to euphoria at high doses	Insufficient data. Topiramate might exert therapeutic benefits	Avoid due to seizure risk and lower seizure threshold on bupropion	
Post-Bariatric Surgery		Insufficient data	Insufficient data	Limited data available	Insufficient data	Data available at 1.8 – 3.0 mg/day

*Use medications only with clear health-related goals in mind; assess patient for osteoporosis and sarcopenia.

[a] Lorcaserin was withdrawn from the US market in February 2020.

Abbreviations: BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; HTN = hypertension; T2DM = Type 2 Diabetes Mellitus.

FIGURE 161-5 Preferred weight-loss agents based on patient-specific comorbidities. (*Reproduced with permission from Reference 7.*)

Agents Approved for Long-Term Use

8 There are currently four products FDA approved in the United States for the chronic management of obesity. These include the lipase inhibitor orlistat (Xenical, Genentech USA, South San Francisco, CA; Alli, GlaxoSmithKline, Middlesex, UK), the combination product phentermine–topiramate extended-release (Qsymia, Vivus, Inc, Mountain View, CA), the combination product naltrexone–bupropion extended-release tablets (Contrave, Takeda Pharmaceuticals America Inc, Cambridge, MA), and the GLP-1 receptor agonist liraglutide (Saxenda, Novo Nordisk Inc, Plainsboro, NJ). Pharmacotherapy management guidelines recommend discontinuation of drug therapy in patients who fail to lose sufficient amounts of body weight after 3 months and in patients who experience significant adverse events, with consideration given to potential alternative weight-loss agents (strong recommendation with high-quality evidence).[26] **Table 161-6** lists clinical and economic considerations for use of the products approved for long-term use.[26,70]

TABLE 161-6 Clinical and Economic Considerations for Long-Term Pharmacotherapy Options

Drug	Brand Name	Weight Loss Above Diet and Exercise Alone (1 year)[35,59,73]	Cost for 30 days of Therapy[a]	Comments[35]
Orlistat	Xenical	2.9-3.4 kg (6.5-7.5 lb)	$685.81	Use may be limited by GI intolerance
Phentermine and topiramate extended-release	Qsymia	6.6-8.6 kg (14.5-18.9 lb)	$186.00, 7.5-46 mg $199.50, 15-92 mg	Limited distribution under FDA Risk Evaluation Mitigation Strategy (REMS)
Bupropion and naltrexone extended-release	Contrave	4.9 kg (10.8 lb)	$277.99	Lowers seizure threshold (bupropion) Rare reports of hepatotoxicity (naltrexone) Drug interactions with opioids, CYP2B6 inducers and CYP2D6 substrates
Liraglutide	Saxenda	5.8 kg (12.8 lb)	$1,242.00	Injectable Reduces HbA1c and fasting glucose Risk of medullary thyroid carcinoma and Multiple Endocrine Neoplasia syndrome type 2 Rare reports of pancreatitis, gall bladder disease, and suicidal ideation

[a]Cost of therapy based on maintenance dose using wholesaler acquisition cost (WAC) as of January 9, 2018.

Lipase Inhibitor: Orlistat Excessive intake of dietary fat is one of the contributing factors in the development of obesity. GI (gastric, pancreatic, and carboxyl ester) lipases are essential in the absorption of the long-chain triglycerides. Additionally, lipase is known to play a role in facilitating gastric emptying and secretion of other pancreaticobiliary substances. Orlistat (Xenical) is a synthetic derivative of lipstatin, a natural lipase inhibitor produced by *Streptomyces toxytricini*. The drug is minimally absorbed and induces weight loss by persistent lowering of dietary fat absorption through selective inhibition of the GI lipase. Furthermore, lower luminal free fatty acid concentrations result in malabsorption of cholesterol. Up to 30% reduction in fat absorption occurred with daily doses of 120 mg three times daily with meals.[70] A nonprescription formulation of orlistat (Alli) is approved in the United States at a reduced daily dose of 60 mg three times daily.[70] The drug must be taken within 1 hour of consuming foods that contain fat in order to exert its effect. If a meal is skipped or contains no fat, the dose of orlistat can be omitted.

Clinical studies using orlistat as an adjunct to diet therapy demonstrate dose-dependent reductions in fat absorption. Orlistat modestly increases the amount of weight lost and decreases the amount of weight regained during medically supervised weight-loss programs.[70–72] Improved glycemic control can be attained in patients with type 2 diabetes by inducing or increasing weight loss with orlistat in addition to diet management.[70] In some cases, dosages or the number of antidiabetic medications may be reduced or discontinued. Significant improvements in lipid profile (reduction in total and low-density lipoprotein [LDL] cholesterol), glucose control, and other markers of metabolism are seen when using orlistat in addition to the diet.[70,71] Orlistat is approved for the chronic treatment of obesity in adults and adolescents between ages 12 and 16 years. The recommended dose is 120 mg three times daily taken within 1 hour of consuming a fat-containing meal.

At least one GI complaint (soft stools, abdominal pain or colic, flatulence, fecal urgency, or incontinence) has been reported in up to 80% of individuals using prescription-strength orlistat. These complaints are most common in the first 1 to 2 months of therapy, are mild to moderate in severity, and tend to improve with continued orlistat use. Limiting dietary fat before initiation of orlistat therapy may be beneficial in decreasing initial GI complaints. Severe diarrhea secondary to orlistat use can affect the absorption of orally administered drugs, such as oral contraceptives, fat-soluble vitamins (A, D, E, and K), and β-carotene. Therefore, supplementation with a multivitamin should be considered during therapy. In the presence of severe diarrhea, women receiving oral

contraceptives should be advised of the need to use alternative backup methods because absorption of the oral contraceptive may be reduced. Although orlistat does not appear to alter the pharmacokinetic profiles of other agents, including digoxin, glyburide, metformin, phenytoin, fluoxetine, amitriptyline, phentermine, losartan, nifedipine, captopril, atenolol, furosemide, alcohol, or atorvastatin, reduced fat absorption can potentially affect the absorption of lipophilic drugs, such as lamotrigine, valproic acid, gabapentin, and amiodarone.[73,74] Decreased vitamin K absorption has also been noted and can alter the patient's warfarin dosage needs. Clinicians should also be aware that orlistat may directly interfere with the absorption of other narrow therapeutic range drugs, such as cyclosporine and levothyroxine.[74] In patients requiring concomitant therapies with orlistat, close monitoring is warranted to ensure an adequate therapeutic response. Separation of the administration times of the medications may minimize these potential drug interactions. Finally, there have been rare postmarketing reports of liver damage with the use of orlistat.[74] Although causality has not been definitively linked to orlistat, patients are advised to notify their healthcare providers if they notice signs and symptoms of liver injury, such as development of itching, yellow eyes or skin, dark urine, loss of appetite, or light-colored stools.

Serotonin Receptor Agonist Lorcaserin (Belviq) is a selective serotonin (5-HT_{2C}) receptor agonist, approved for chronic weight management in patients who have obesity (BMI of greater than or equal to 30 kg/m^2) or overweight (BMI of greater than 27 kg/m^2) with at least one weight-related comorbidity.[75] At the recommended dose of 10 mg twice daily, lorcaserin selectively activates central 5-HT_{2C} receptors on hypothalamic anorexigenic pro-opiomelanocortin neurons. Activation of central 5-HT_{2C} receptors results in appetite suppression, leading to reduced energy intake and enhanced satiety.

Clinical trials evaluating the efficacy of lorcaserin, used in combination with an LCD and exercise counseling, have reported a modest but significantly greater weight loss compared with placebo.[76,77] The Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) trial was a 2-year, randomized, placebo-controlled, double-blind, prospective trial that enrolled more than 3,000 patients with obesity and overweight.[76] Mean weight loss at 1 year was 5.8 kg (12.8 lb) in the lorcaserin group compared with 2.2 kg (4.8 lb) in the placebo group. Patients in the lorcaserin-treated group also experienced significant improvements in fasting glucose, insulin, total cholesterol, LDL cholesterol, and triglyceride concentrations at the end of the

first year. Although weight regain was observed during the second year of the trial, 68% of the patients who had previously achieved 5% weight loss during the first year were able to maintain this level of weight loss by the end of the second year. Lorcaserin is also effective in patients with type 2 diabetes, with an average weight loss of 4.5% and significant improvements in HbA_{1c} and fasting glucose after 1 year of treatment.[78] Lorcaserin therapy should be discontinued if 5% weight loss is not achieved by week 12 because it is unlikely that a benefit will be seen.[75]

The most common adverse effects associated with the use of lorcaserin in clinical trials were headache, dizziness, constipation, fatigue, and dry mouth.[76] Previous serotonergic agents (eg, dexfenfluramine) used for weight loss have been associated with cardiac valvulopathy.[73,79] The mechanism for this toxicity is thought to be related to stimulation of $5HT_{2B}$ receptors on cardiac cells. At therapeutic doses, lorcaserin is selective for central $5HT_{2C}$ receptors. During clinical trials, the incidence of cardiac valvulopathy was not significantly different between patients who received lorcaserin (2.4%) and those who received placebo (2%).[75] However, patients should be counseled to contact their healthcare providers if they experience signs or symptoms of cardiac valve disease such as dyspnea or edema. Lorcaserin should not be used in combination with other serotonergic and dopaminergic drugs because of the increased risk of serotonin syndrome or neuroleptic malignant syndrome–like reactions. Lorcaserin should be used cautiously in patients with congestive heart failure because these patients may be at an increased risk for cardiac valvulopathy. In February 2020, the FDA requested that the manufacturer of lorcaserin withdraw the drug from the U.S. market because of safety concerns related to increased risk of cancer (www.fda.gov/media/135189/download).

Phentermine–Topiramate Extended-Release A combination product containing phentermine and topiramate extended-release (Qsymia) is approved for chronic weight management in patients who have obesity (BMI of greater than or equal to 30 kg/m^2) or overweight (BMI of greater than 27 kg/m^2) with at least one weight-related comorbidity.[80] Phentermine is structurally similar to amphetamine, but it has less severe CNS stimulation and a lower abuse potential. Its mechanism of action centers on its ability to enhance norepinephrine (NE) and dopamine neurotransmission, resulting in appetite suppressing effects. Topiramate is an antiepileptic drug. Although the exact mechanism for its efficacy in weight management is not known, it may decrease appetite and increase satiety through multiple pathways, including effects on γ-

aminobutyrate, voltage-gated ion channels, excitatory glutamate receptors, or carbonic anhydrase.[80] The doses of phentermine (3.75-15 mg) and topiramate (23-92 mg) in this combination are significantly lower than the therapeutic doses of each separate product when used as monotherapy for obesity (37.5 mg) and epilepsy (400 mg), respectively. The recommended dosing strategy for phentermine–topiramate extended-release involves gradual titration, staring with 3.75 mg of phentermine and 23 mg of topiramate once daily for 14 days and then increasing the dose to 7.5 mg of phentermine and 46 mg of topiramate once daily.[80] After 12 weeks of therapy, the dose may be increased again to 11.25 mg of phentermine and 69 mg of topiramate for 14 days and then to a maximum dose of 15 mg of phentermine and 92 mg of topiramate daily. Likewise, when discontinuing therapy, the dose should be gradually decreased by taking a dose every other day for at least 1 week to prevent the possible precipitation of seizures.

Clinical trials evaluating the efficacy of phentermine–topiramate, when used as an adjunct to a reduced-calorie diet and lifestyle changes, have reported dose-dependent weight loss and significant reductions in blood pressure, total cholesterol, LDL cholesterol, triglycerides, fasting glucose, and HbA_{1c}.[81,82] The CONQUER trial was a randomized, placebo-controlled, double-blind, prospective trial of 2,487 patients with overweight or obesity and two or more obesity-related comorbidities.[81] After a 4-week dose titration phase, subjects were randomized to receive (a) placebo, (b) 7.5 mg of phentermine with 46 mg of topiramate, or (c) 15 mg of phentermine with 92 mg of topiramate daily. Weight loss at 1 year was significantly greater than placebo in both of the treatment groups, with a mean weight loss of 8.1 kg (17.8 lb) in the 7.5-mg phentermine and 46-mg topiramate group and a mean weight loss of 10.2 kg (22.4 lb) in the 15-mg phentermine and 92-mg topiramate group. The efficacy of phentermine–topiramate has also been documented in patients with class II and class III obesity (mean BMI, 42 kg/m^2), with a reported mean weight loss of 10.9% after 1 year of treatment.[82]

The most common adverse effects associated with the use of phentermine–topiramate in clinical trials were constipation, dry mouth, paraesthesia, dysgeusia, and insomnia.[81,82] Because topiramate is a known teratogen, this drug is contraindicated in pregnancy because fetal exposure in the first trimester increases the risk of cleft lip or cleft palate. To manage the potential risk of teratogenicity, the drug is only available through a limited distribution process under a risk evaluation and mitigation strategy (REMS).[80] All women of childbearing age must have a documented negative pregnancy test result before

beginning treatment and then monthly to continue therapy. Topiramate has been associated with acute myopia associated with secondary angle-closure glaucoma, and phentermine can cause mydriasis from adrenergic stimulation. Therefore, this product is also contraindicated in patients with glaucoma. The potential for hypertensive crisis with coadministration of phentermine and MAOIs exists; therefore, patients should have stopped an MAOI for at least 14 days before use of any adrenergic agent. Phentermine–topiramate is also contraindicated in patients with untreated hyperthyroidism.

Monitoring parameters and drug interactions that clinicians should be aware of include known issues related to both components of the formulation. Of note, increases in heart rate greater than 10 beats/min were observed in approximately 50% of patients receiving phentermine–topiramate during clinical trials.[80] In patients receiving the highest dose, 19% experienced increases in heart rate that were greater than 20 beats/min. Therefore, heart rate should be monitored in all patients, particularly those with preexisting CVD. Decreases in serum bicarbonate were also noted in clinical trials, which were generally mild with peak decreases observed after 4 weeks of therapy. Decreases in serum potassium and increases in serum creatinine were also reported. Therefore, monitoring of serum electrolytes and creatinine is recommended at baseline and during therapy. Clinicians should be aware that concomitant use of non–potassium-sparing diuretics may potentiate the risk for hypokalemia. Although pregnancy risk is not expected, use of phentermine–topiramate concomitantly with oral contraceptives may result in breakthrough bleeding because of increased exposure to progestin and decreased exposure to estrogen. Phentermine–topiramate is classified as a controlled substance in schedule IV because of the abuse potential of phentermine. Therapy should be discontinued if 5% weight loss is not achieved after 12 weeks.[80]

Naltrexone–Bupropion Extended-Release A combination product containing naltrexone and bupropion extended-release (Contrave) was approved in 2014 for chronic weight management in patients who have obesity (BMI of more than or equal to 30 kg/m^2) or overweight (of more than or equal to 27 kg/m^2) with at least one weight-related comorbidity.[83] Naltrexone and bupropion are both approved separately for treatment of alcohol and opioid dependence, and depression and smoking cessation, respectively.[84] Bupropion is a dopamine and norepinephrine reuptake inhibitor, and naltrexone is an opioid antagonist. Although the exact weight-loss mechanism of action is not known for this drug combination, stimulation of release of α-MSH in the hypothalamus by bupropion and inhibition of endogenous opioids by naltrexone are thought to contribute to a

decrease in appetite.[84] The recommended dosing strategy for naltrexone–bupropion extended-release involves gradual titration, starting with one tablet (8-mg naltrexone/90-mg bupropion) per day and slowly increasing the dose over a period of 4 weeks to a maintenance dose of two tablets twice daily. Doses greater than 32 mg of naltrexone and 360 mg of bupropion (ie, 4 tablets) per day are not recommended. Patients should be advised to not take their dose with a high-fat meal as this would result in increased systemic exposure to both naltrexone and bupropion.

Four randomized, placebo-controlled clinical trials evaluating the efficacy of naltrexone/bupropion, when used in combination with a reduced-calorie diet and lifestyle changes, have reported significantly more weight loss with naltrexone/bupropion compared to placebo, as well as improvements in high-density lipoprotein (HDL) cholesterol, triglycerides, glucose, and insulin.[85–88] The average total weight loss reported among the four studies was 7.3 kg (95% CI, 7.0-7.6 kg) following 1 year of treatment,[84] with the greatest amount of weight loss (9.7 kg [21 lb]) reported in nondiabetic subjects who were also receiving intensive behavior modification therapy.[87]

The most common adverse effects associated with the use of naltrexone/bupropion in clinical trials were nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, and diarrhea.[83] Approximately 24% of patients who received naltrexone–bupropion in clinical trials discontinued treatment due to adverse events, with nausea being the most frequently cited reason.[83] Statistically significant increases in heart rate (2.1 beats/min) and blood pressure (1.8-2.3 mm Hg systolic and 1.7-2.1 mm Hg diastolic) were observed in patients receiving naltrexone–bupropion compared with those who received placebo during the first 3 months of therapy. Although the clinical significance of these increases is unknown, blood pressure and pulse should be monitored at baseline and at regular intervals following initiation of therapy. Naltrexone–bupropion should not be used in patients with uncontrolled hypertension.[83] Naltrexone monotherapy has been associated with rare reports of hepatotoxicity, and patients receiving naltrexone–bupropion should be advised of the signs and symptoms of acute hepatitis. Bupropion lowers the seizure threshold in a dose-dependent manner, and has been associated with serious neuropsychiatric reactions and an increased risk of suicidal thoughts and behavior when used for smoking cessation and treatment of depression. Bupropion has also been reported to cause activation of mania, serious allergic reaction, and angle-closure glaucoma.

Clinicians should also be aware of potential drug interactions with

naltrexone–bupropion. Because of the opioid antagonist effects of naltrexone, naltrexone–bupropion is contraindicated in patients receiving chronic opioid or opiate agonist therapy, and also in patients undergoing abrupt withdrawal of chronic alcohol, benzodiazepine, barbiturate, or antiepileptics. Bupropion is metabolized by cytochrome P450 2B6 (CYP2B6) and inhibits cytochrome P450 2D6 (CYP2D6). Therefore, any medication that induces CYP2B6 (eg, rifampin, carbamazepine) could potentially reduce the effects of bupropion, and bupropion could increase the effects of medications that are CYP2D6 substrates (eg, SSRIs, tricyclic antidepressants, antipsychotics). Bupropion is also contraindicated with concomitant use of MAOIs. As with other long-term pharmacologic treatments for obesity, weight loss may increase the risk of hypoglycemia in patients with type 2 diabetes receiving antidiabetic medications. Finally, treatment with naltrexone–bupropion should be discontinued if 5% weight loss is not achieved after 12 weeks.

Glucagon-Like Peptide-1 Receptor Agonist Liraglutide Liraglutide (Saxenda), an analog of GLP-1, is the most recent medication approved in the United States for chronic weight management in patients who have obesity (BMI of more than or equal to 30 kg/m^2) or overweight (BMI of more than 27 kg/m^2) with at least one weight-related comorbidity.[89] Endogenous GLP-1 is released in response to food digestion and stimulates GLP-1 receptors in the brain to reduce appetite. GLP-1 also stimulates insulin secretion and reduces glucagon secretion. For that reason, several GLP-1 receptor agonists, including liraglutide, are currently approved for the treatment of type 2 diabetes at recommended doses of 1.2 mg or 1.8 mg daily far less than the maintenance dose for weight loss of 3 mg daily.[89] Liraglutide is administered subcutaneously and is available in prefilled, multidose pens. When used for weight loss, a 5-week dose escalation schedule is recommended to improve tolerability of GI adverse events. It should be initiated at a dose of 0.6 mg daily, and increased weekly by 0.6-mg increments to a final maintenance dose of 3 mg daily. If the patient cannot tolerate the GI adverse events at any point during the dose escalation phase, a dose increase may be delayed by a week. Patients should be instructed on the proper technique for subcutaneous injection into the abdomen, thigh, or upper arm.

The efficacy of liraglutide for the management of overweight and obesity has been studied in patients with and without diabetes.[89–91] In the SCALE Obesity and Prediabetes study, mean weight loss after 1 year of treatment was greater [8.4 kg (18.5 lb)] in the liraglutide group compared with placebo [2.8 kg (6.1 lb)]. As expected, patients who received liraglutide also experienced significant

improvements in HbA_{1c}, fasting glucose, and insulin, and had a lower prevalence of prediabetes. Similarly, in the SCALE Diabetes trial, average weight loss after 1 year of treatment was greater in patients receiving liraglutide compared to placebo, and response was dose-related (ie, patients who received the higher dose had greater weight loss than those receiving low dose). Significant improvements in fasting glucose and the number of subjects achieving HbA_{1c} targets were also observed.

The most common adverse effects associated with the use of liraglutide are nausea, diarrhea, constipation, vomiting, dyspepsia, hypoglycemia, and abdominal pain.[89–91] GI complaints are the most common reason for premature discontinuation of therapy, underscoring the importance of the slow dose-escalation schedule with initiation of therapy. Rare cases of acute pancreatitis (0.3%), potentially leading to fatal hemorrhagic or necrotizing pancreatitis, have been reported with the use of liraglutide.[89] Small increases in resting heart rate averaging 2 to 3 beats/min have been reported in clinical trials. However, in some cases increases were as high as 20 beats/min. Although the clinical significance of these increases is unknown, heart rate should be regularly monitored in all patients receiving liraglutide. Cholelithiasis (1.5%), cholecystitis (0.6%), and suicidal ideation (0.2%) have also been observed during clinical trials.[89] Liraglutide carries a boxed-warning about the risk of thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), and is contraindicated in patients with a personal or family history of MTC or multiple endocrine neoplasia syndrome type 2 (MEN2). Hypoglycemia may occur when liraglutide is used in combination with other antidiabetic agents (particularly sulfonylureas and insulin) in patients with type 2 diabetes. Therefore, dose adjustments of antidiabetic medications may be necessary. Because liraglutide increases gastric emptying time, clinicians should be aware that absorption of concomitantly administered oral medications may be altered. Liraglutide should be discontinued if weight loss of at least 4% is not achieved after 16 weeks of therapy.

Agents Approved for Short-Term Use Several noradrenergic agents are currently approved by the FDA for short-term weight loss. Because short-term therapy is not consistent with current national guidelines for the chronic management of obesity, these agents have limited clinical utility in practice.[6,7]

Phentermine Phentermine is available in both immediate-release and sustained-release formulations. However, the value of sustained-release formulations is questionable based on the reported phentermine plasma half-life of 12 to 24

hours. Phentermine is an effective adjunct to diet, exercise, and behavior modification for producing weight loss in excess of that seen with placebo.[92] Intermittent phentermine therapy appears to elicit comparable weight loss as that seen with continuous use. However, most individuals experience weight regains during therapy and generally always after discontinuing use.[92] A single dose of 30 mg once daily in the morning provides effective appetite suppression throughout the day. Divided doses of 8 mg immediately before meals, however, are common.[93] Evening or nighttime dosing should be avoided because of insomnia. Significant increases in blood pressure, palpitations, and arrhythmias can occur with phentermine administration. Use is not advisable in hypertensive patients. Pharmacotherapy management guidelines recommend against the use of sympathomimetic agents in patients with uncontrolled hypertension or a history of CVD (strong recommendation with high-quality evidence).[26]

The potential for hypertensive crisis with coadministration of phentermine and MAOIs is noted in the product labeling of each agent; therefore, patients should discontinue MAOI use for at least 14 days before use of any adrenergic agent to avoid excessive adrenergic stimulation syndromes.[94] Phentermine use is contraindicated in patients with hyperthyroidism or agitated states and in those who are abusers of substances such as cocaine, phencyclidine, and methamphetamine, again because of the potential for excessive adrenergic stimulation syndromes and abuse. Mydriasis from adrenergic stimulation can worsen glaucoma, and patients diagnosed with glaucoma should not receive phentermine. Patients with diabetes may experience altered insulin or oral hypoglycemic dosage requirements soon after beginning therapy and before any substantial weight loss. Phentermine remains the most widely prescribed weight management medication by obesity specialists despite product labeling that indicates short-term (a few weeks), monotherapy use only.[92] This usage pattern deviates from the current national recommendations that promote only long-term drug intervention when obesity pharmacotherapy is appropriate.[6,7] Some clinicians consider use of long-term phentermine to be reasonable in select patients given the low cost and a lack of serious long-term adverse events reported in the literature over the past 20 years. Select patients include those without evidence of CVD, psychiatric disease, or substance abuse; without clinically significant increases in blood pressure or heart rate while receiving phentermine; and documentation of significant weight loss while receiving phentermine.

Diethylpropion Diethylpropion stimulates NE release from presynaptic storage

granules. Increased adrenergic neurotransmitter concentrations activate hypothalamic centers, which result in decreased appetite and food intake. Diethylpropion can be taken in divided daily doses, generally 25 mg three times daily before meals. An extended-release formulation is also used by some clinicians, usually as 75 mg taken once daily in the morning or midmorning.[92] Both dosing regimens are effective in achieving short-term weight loss in excess of placebo. Complaints of insomnia increase if late afternoon dosing is used. Diethylpropion causes less stimulation of the CNS than mazindol and generally causes less insomnia than phentermine. Patients with severe hypertension or significant CVD should not receive diethylpropion. Patients with diabetes may experience decreased insulin or oral hypoglycemic dosage requirements soon after beginning therapy and before any substantial weight loss. More frequent blood glucose self-monitoring and medical follow-up are warranted when treating diabetic patients with diethylpropion.

Amphetamines Appetite suppressant effects of the amphetamines were well recognized in the 1930s. Amphetamines activate central noradrenergic receptor systems as well as dopaminergic pathways at higher doses by stimulating neurotransmitter release. Increases in blood pressure and mild bronchodilation are attributed to peripheral α- and β-receptor activation. Amphetamines are no longer widely used for the treatment of obesity because of their powerful stimulant effects and addictive potential.

Complementary and Alternative Therapies Many complementary and alternative therapy products are currently promoted for weight loss. A nationwide survey of US consumers reported that about 15.2% of adults had used “dietary supplements” specifically for the purposes of weight loss.[95] It is important for clinicians to be aware that the regulation of dietary supplements is less rigorous than that of prescription and over-the-counter drug products. As such, a manufacturer of a dietary supplement does not have to prove the safety or effectiveness of the product before it is marketed. Of concern, some herbal and food supplement diet agents contain pharmacologically active substances that should be used with caution or avoided in patients who have obesity and also have conditions such as diabetes, hypertension, and significant CVD. In addition, many marketed products have been reported to lack consistency in labeling versus actual product content, and a number of dietary supplements have been found to contain undeclared prescription drugs.[96] Common herbal and natural products that have been used for weight loss include hoodia, green tea, citrus aurantium, forskolin, caffeine, glucomannan, yohimbine, chitosan, guar

gum, hydroxycitric acid, and garcinia cambogia.[95,96]

PERSONALIZED PHARMACOTHERAPY

Genetic influences are estimated to contribute between 40% and 70% of the actual variance in body weight and fat distribution.[32] As such, identifying specific genes involved in the development of obesity is an area of extensive research. Several gene variants associated with the development of obesity have been identified through the use of genome-wide association studies.[97] However, the use of personalized pharmacotherapy to treat obesity has only been documented for rare cases of monogenic obesity in patients with congenital leptin deficiency[98] or proopiomelanocortin deficiency.[99] These are extremely rare conditions in which administration of recombinant human leptin or a melanocortin-4 receptor agonist results in significant improvement in body weight and other associated abnormalities. Recommendations regarding how currently available medications can be individualized to maximize patient benefit are not yet available.

EVALUATION OF THERAPEUTIC OUTCOMES

The evaluation and management of a patient with obesity requires careful clinical, biochemical, and, if necessary, psychological evaluation. This evaluation should include an assessment of the patient's current medical condition and medication regimen. A multidisciplinary team including, but not limited to, a physician, nutritionist, psychologist, behavioral expert, and pharmacist should be involved in the care of individuals with obesity.

Monitoring the Pharmaceutical Care Plan

Assessment of patient progress should be documented frequently.[6] Each encounter should document weight, WC, BMI, blood pressure, medical history, and patient assessment of obesity medication tolerability.[6] Chronic use of obesity medications should be consistent with the approved product labeling. According to current pharmacologic management guidelines, efficacy and tolerability of the medication should be assessed monthly for the first 3 months, followed by visits every 3 months thereafter (weak recommendation with low-quality evidence).[26] If the patient has failed to demonstrate weight loss or maintenance of prior

weight, medication therapy should be discontinued after 3 months (strong recommendation with high-quality evidence).[26]

To achieve optimal weight loss, patients should be instructed about the importance of adherence to prescribed medication and lifestyle changes. The Short Form 36 (SF-36) has been used as a quality-of-life evaluation tool for patients with obesity undergoing programmatic weight loss. Quarterly assessments of well-being and quality of life using validated assessment tools can be helpful in objectively quantifying the effectiveness of therapy. **Table 161-7** provides monitoring parameters and potential adverse reactions of medications used for long-term management of overweight and obesity.

TABLE 161-7 Drug Monitoring

Drug	Brand Name	Adverse Reactions	Monitoring Parameters	Comments
Gastrointestinal Lipase Inhibitor				
Orlistat	Xenical, Alli[a]	Soft stools, diarrhea, abdominal pain or colic, flatulence, fecal urgency, incontinence, liver damage (rare)	BMI; calorie and fat intake; serum glucose in patients with diabetes; thyroid function in patients with thyroid disease; liver function tests in patients exhibiting symptoms of hepatic dysfunction	Supplement with a multivitamin during therapy to prevent vitamin deficiency
Phentermine–Topiramate Combination				
Phentermine and topiramate extended-release	Qsymia	Constipation, dry mouth, paraesthesia, dysgeusia, insomnia, hypoglycemia in patients with diabetes	BMI; calorie and fat intake; serum glucose in patients with diabetes; pregnancy; depression or suicidal thoughts; mood or sleep disorders; heart rate; serum electrolytes and creatinine at baseline and during treatment	Discontinue or escalate dose if 3% weight loss not achieved by week 12 on phentermine 7.5 mg and topiramate 46 mg Discontinue if 5% weight loss not achieved by week 12 on phentermine 15 mg and topiramate 92 mg Gradually discontinue phentermine 15 mg and topiramate 92 mg to prevent possible seizure
Bupropion–Naltrexone Combination				
Bupropion and naltrexone extended-release	Contrave	Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth and diarrhea	BMI; calorie and fat intake; serum glucose in patients with diabetes; heart rate and blood pressure; signs and symptoms of hepatotoxicity, neuropsychiatric reactions, and suicidal thoughts or behavior	Discontinue if 5% weight loss not achieved by week 12
Glucagon-Like Peptide-1 Antagonist				
Liraglutide	Saxenda	Nausea, diarrhea, constipation, vomiting, dyspepsia, hypoglycemia, and abdominal pain	BMI; calorie and fat intake; serum glucose in patients with diabetes; signs and symptoms of pancreatitis; heart rate; signs and symptoms of gallbladder disease and suicidal ideation	Discontinue if 4% weight loss not achieved by week 16
Noradrenergic Agents				
Phendimetrazine Phentermine Diethylpropion	Bontril PDM; Bontril Slow-Release Adipex-P, Suprenza Tenuate, Tenuate Dospan	Increased blood pressure, ischemic events, palpitations, tachycardia, valvular disease, urticaria, agitation, dizziness, headache, insomnia, overstimulation, psychosis, restlessness, dry mouth, constipation, thirst, diarrhea	Baseline cardiac evaluation (for preexisting valvular heart disease, pulmonary hypertension); echocardiogram during therapy; weight, waist circumference; blood pressure	Approved as monotherapies only for short-term use (a few weeks) Discontinue if satisfactory weight loss has not occurred within the first 4 weeks of treatment or if tolerance develops Abrupt discontinuation after prolonged high doses may be associated with extreme fatigue and depression

[a]Available without a prescription.

BMI, body mass index.

Patients with diabetes receiving weight-loss medication require more intense medical monitoring and self-monitoring of blood glucose. Insulin therapy may need to be adjusted with the start of obesity medication therapy. Some patients with diabetes may require daily telephone contact with a healthcare provider to assist in adjusting their hypoglycemic therapy. Weekly patient visits to a healthcare setting may be necessary for 1 to 2 months until the effects of diet, exercise, and weight-loss medication become more predictable. As frequent as quarterly assessment of HbA_{1c} may be appropriate in patients with type 2 diabetes who lose weight to aid in adjustment of hypoglycemic therapy. Lipid profiles can normalize or improve with weight loss. Lipid status should be assessed semiannually or annually in patients with hyperlipidemia to determine the need for continued hyperlipidemia therapies. Weight loss also can result in normalization of blood pressure in hypertensive patients who have obesity. Assessment of appropriateness of antihypertensive therapy should occur with each follow-up visit.

CONCLUSION

Obesity is a complex chronic disease with a prevalence that has increased dramatically over the past 50 years. Increased body weight is a consequence of increased energy storage resulting from an imbalance between energy intake and energy expenditure over time, which is influenced by many factors, including genetics and the environment. Nonpharmacologic therapy, including reduced caloric intake, increased physical activity, and behavioral modification, is currently the mainstay of obesity management. Drug therapy may be considered as an adjunct for patients who fail to achieve adequate weight loss with comprehensive lifestyle modifications. Currently, four products—orlistat, phentermine–topiramate extended-release, naltrexone–bupropion extended-release, and liraglutide—are approved by the FDA for the long-term treatment of overweight and obesity. Bariatric procedures have evidence for long-term efficacy for weight reduction, but they also introduce surgical complications and, for the most efficacious procedures, may cause significant nutritional deficiencies. For patients who are not able to undergo bariatric surgery, implantable medical devices may also be considered. Treatment of obesity should be individualized, considering factors such as patient desires, age, degree and duration of obesity, and the presence and severity of medical conditions both directly related to obesity and those that may have an impact on the therapeutic

decisions. Regardless of the chosen treatment plan, the management of obesity is a lifelong process requiring patient support and careful monitoring for safety and efficacy.

Postclass Engaged Learning Activity

Conduct a literature search and identify a clinical trial evaluating the safety and efficacy of a currently available FDA-approved medication for the management of obesity. Write a brief summary of the study methods, the clinical significance of the findings, and implications for use of this medication in clinical practice. This activity is intended to build your experience with accessing the primary biomedical literature and critically appraising research manuscripts.

ABBREVIATIONS

5-HT	5-hydroxytryptamine (serotonin)
AHEAD	Action for Health in Diabetes
BMI	Body mass index
BMR	basal metabolic rate
CNS	central nervous system
CT	computed tomography
CVD	cardiovascular disease
FDA	Food and Drug Administration
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
HbA_{1c}	hemoglobin A_{1c}
HDL	high-density lipoprotein
LCD	low-calorie diet
LDL	low-density lipoprotein
MAOI	monoamine oxidase inhibitor
MEN2	multiple endocrine neoplasia syndrome type 2
MRI	magnetic resonance imaging
MTC	medullary thyroid carcinoma
NE	norepinephrine
NHANES	National Health and Nutrition Examination Survey
NIH	National Institutes of Health
REE	resting energy expenditure
REMS	risk evaluation and mitigation strategy
SCALE	Satiety and Clinical Adiposity-Liraglutide Evidence in Nondiabetic and Diabetic Individuals
SF-36	Short Form 36
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
WAGR	Wilms' tumor, aniridia, genitourinary abnormalities or gonadoblastoma, and mental retardation
WC	waist circumference
XENDOS	XENical in the prevention of Diabetes in Obese Subjects

ACKNOWLEDGMENT

Supported in part by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (ZIAHD00641 to J.A.Y.).

REFERENCES

1. World Health Organization. Obesity and overweight. Fact sheet No. 311, February 2018. Available at: http://www.who.int/mediacentre/factsheets/fs311/en/. Accessed October 29, 2018.
2. Yang L, Colditz GA. Prevalence of overweight and obesity in the United States, 2007-2012. *JAMA Intern Med*. 2015;175(8):1412–1413.
3. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity among adults and youth: United States, 2015-2016. NCHS Data Brief. No. 288, 2017. Available at: https://www.cdc.gov/nchs/data/databriefs/db288.pdf. Accessed December 23, 2018.
4. Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL. Trends in obesity and severe obesity prevalence in US youth and adults by sex and age, 2007–2008 to 2015–2016. *JAMA*. 2018:1723–1725.
5. U.S. Department of Health and Human Services. *National Heart Lung and Blood Institute. Obesity Initiative Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*. Washington, DC: U.S. Public Health Service; 1998.
6. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS Guideline for the Management of overweight and Obesity in adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation*. 2014;129(suppl 2):S102–S138.
7. Garvey WT, Mechanick JI, Brett EM, et al. American Association of Clinical Endocrinologist and American College of Endocrinology Comprehensive Clinical Practice Guidelines for medical care of patients with obesity. *Endocr Pract*. 2016;3:1–203.
8. National Heart, Lung, and Blood Institute. Managing Overweight and Obesity in Adults: Systemic Review from the Obesity Expert Panel, 2013. Available at: https://www.nhlbi.nih.gov/sites/default/files/media/docs/obesity-evidence-

review.pdf. Accessed December 27, 2018.
9. Upadhyay J, Farr O, Perakakis N, et al. Obesity as a disease. *Med Clin North Am*. 2018;102(1):13–33.
10. Chughtai M, Khlopas A, Newman JM, et al. What is the impact of body mass index on cardiovascular and musculoskeletal health? *Surg Technol Int*. 2017;30:379–392.
11. Sarwer DB, Hanson AJ, Voeller J, Steffen K. Obesity and sexual functioning. *Curr Obes Rep*. 2018;7(4):301–307.
12. Kyrgiou M, Kalliala I, Markozannes G, et al. Adiposity and cancer at major anatomical sites: Umbrella review of the literature. *BMJ*. 2017;356:j477.
13. Kushner RF, Roth JL. Assessment of the obese patient. *Endocrinol Metab Clin North Am*. 2003;32(4):915–933.
14. Ueda H, Yagi T, Amitani H, et al. The roles of salivary secretion, brain-gut peptides, and oral hygiene in obesity. *Obes Res and Clin Prac*. 2013;7:e321–e329.
15. Robinson PD. Obesity and its impact on the respiratory system. *Paediatr Respir Rev*. 2014;15(3):219–226.
16. Naguib MT. Kidney disease in the obese patient. *South Med J*. 2014;107(8):481–485.
17. Tobin AM, Ahern T, Rogers S, Collins P, O'Shea D, Kirby B. The dermatological consequences of obesity. *Int J Dermatol*. 2013;52(8):927–932.
18. Persson M, Cnattingius S, Villamor E, et al. Risk of major congenital malformations in relation to maternal overweight and obesity severity: Cohort study of 1.2 million singletons. *BMJ*. 2017;357:j2563.
19. Kinlen D, Cody D, O'Shea D. Complications of obesity. *QJM*. 2018;111(7):437–443.
20. Bhaskaran K, Santos-Silva I, Leon DA, Douglas IJ, Smeeth L. Association of BMI with overall and cause-specific mortality: A population-based cohort study of 3.6 million adults in the UK. *Lancet Diabetes Endocrinol*. 2018;6(12):944–953.
21. Cawley J, Meyerhoefer C. The medical care costs of obesity: An instrumental variable approach. *J Health Econ*. 2012;31(1):219–230.
22. Kim DD, Basu A. Estimating the medical care costs of obesity in the United States: Systemic review, meta-analysis, and empirical analysis.

Value Health. 2016;19(5):602–613.

23. Whitlock EP, O'Connor E, Williams SB, Beil TL, Lutz KW. *Effectiveness of Weight Management in Children and Adolescents*. Rockville, MD: Agency for Healthcare Research and Quality; 2008. AHRQ Publication 08-E014, Evidence Report/Technology Assessment 170. Available at: http://www.ahrq.gov/research/findings/evidence-based-reports/chwght-evidence-report.pdf. Accessed December 29, 2018.
24. World Health Organization. *Resolutions and decisions. Sixty-sixth World Health Assembly, May 20-27, 2013. WHA66/2013/REC/1*. Geneva: World Health Organizations; 2013.
25. US Preventative Services Task Force. Behavioral weight loss interventions to prevent obesity-related morbidity and mortality in adults: US Preventative Services Task Force Recommendation Statement. *JAMA*. 2018;320(11):1163–1171.
26. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2015;100:342–362.
27. World Health Organization. Report of the Commission on Ending Childhood Obesity: implementation plan. Seventieth World Health Assembly, March 2017. Available at: http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_31-en.pdf. Accessed December 20, 2018.
28. Hurby A, Hu FB. The epidemiology of obesity: A big picture. *Pharmacoeconomics*. 2015;33:673–689.
29. Ogden CL, Yanovski SZ, Carroll MD, Flegal KM. The epidemiology of obesity. *Gastroenterology*. 2007;132(6):2087–2102.
30. Kelsey MM, Zaepfel A, Bjornstad P, Nadeau KJ. Age-related consequences of childhood obesity. *Gerontology*. 2014;60(3):222–228.
31. Ogden CL, Fakhouri TH, Carroll MD, et al. Prevalence of obesity among adults, by household income and education – United States, 2011-2014. Center for Disease Control and Prevention. *Morbidity and Mortality Weekly Report: MMWR*. 2017;66(50):1369–1371. Available at: https://www.cdc.gov/mmwr/volumes/66/wr/mm6650a1.htm?s_cid=mm6650a1_w. Accessed December 27, 2018.
32. Waalen J. The genetics of human obesity. *Transl Res*. 2014;164:293–301.
33. Apovian CM. Obesity: Definition comorbidities, causes and burden. *Am J Manag Care*. 2016;22(suppl):s176–s185.

34. Berthoud HR. The neurobiology of food intake in an obesogenic environment. *Proc Nutr Soc*. 2012;71(4):478–487.
35. Powell K, Wilcox J, Clonan A, et al. The role of social networks in the development of overweight and obesity among adults: Scoping review. *BMC Public Health*. 2015;15:996.
36. Domecq JP, Prutsky G, Leppin A, et al. Clinical review: Drugs commonly associated with weight change: A systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2015;100(2):363–370.
37. Schneeberger M, Gomis R, Claret M. Hypothalamic and brainstem neuronal circuits controlling homeostatic energy balance. *J Endocrinol*. 2014;220:T25–T46.
38. Camilleri M. Peripheral mechanism in appetite regulation. *Gastroenterology*. 2015;148:1219–1233.
39. Sidossis L, Kajimura S. Brown and beige fat in humans: Thermogenic adipocytes that control energy and glucose homeostasis. *J Clin Invest*. 2015;125(2):478–486.
40. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: The Evidence Report. National Institutes of Health. *Obes Res*. 1998;6(suppl 2):51S–209S.
41. Styne DM, Arslanian SA, Conner EL, et al. Pediatric obesity—assessment, treatment, and prevention: An endocrine society clinical practice guideline. *Clin Endocrinol Metab*. 2017;102(3):709–757.
42. Echeverria SE, Mustafa M, Pentakota SR, et al. Socially and clinically-relevant cardiovascular risk factors in Asian American adults: NHANES 2011-2014. *Prev Med*. 2017;99:222–227.
43. Staiano AE, Broyles ST, Gupta AK, Katzmarzyk. Ethnic differences in visceral, subcutaneous, and total body fat in children and adolescents. *Obesity*. 2013;21(6):1251–1255.
44. Gujral UP, Vittinghoff E, Mongraw-Chaffin M, et al. Cardiometabolic abnormalities among normal-weight persons from five racial/ethnic groups in the United States: A cross-sectional analysis of two cohort studies. *Ann Intern Med*. 2017;166(9):628–636.
45. The GBD 2015 Obesity Collaborators. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. 2017;377:13–27.
46. Bhaskaran K, dos-Santos-Silva I, Leon DA, Douglas IJ, Smeeth L. Association of BMI with overall and cause-specific mortality: A population-based cohort study of 3.6 million adults in the UK. *Lancet*

Diabetes Endocrinol. 2018;6:944–953.

47. Riaz H, Khan MS, Siddiqi TJ, et al. Association between obesity and cardiovascular outcomes: A systemic review and meta-analysis of Mendelian randomization studies. *JAMA Netw Open*. 2018;1(7):e183788.
48. Grover SA, Kaouache M, Rempel P, et al. Years of life lost and healthy life-years lost from diabetes and cardiovascular disease in overweight and obese people: A modeling study. *Lancet Diabetes Endocrinol*. 2015;3(2):114–122.
49. Center for Disease Control and Prevention. Overweight and obesity: Strategies to prevent obesity. Available at: https://www.cdc.gov/obesity/strategies/index.html. Last accessed December 28, 2018.
50. Community Preventative Services Task Force (CPSTF). CPSTF findings for obesity. The Community Guide website available at https://www.thecommunityguide.org/content/task-force-findings-obesity. Accessed December 29, 2018.
51. Salvia MG. The Look AHEAD Trial: Translating lessons learned into clinical practice and further study. *Diabetes Spectr*. 2017;30(3):166–170.
52. Franz MJ, Boucher JL, Rutten-Ramos S, VanWormer JJ. Lifestyle weight-loss intervention outcomes in overweight and obese adults with Type 2 diabetes: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *J Acad Nutr Diet*. 2015;S2212-2672(15):00259–2.
53. Johnston BC, Kanters S, Bandayrel K, et al. Comparison of weight loss among named diet programs in overweight and obese adults: A meta-analysis. *JAMA*. 2014;312(9):923–933.
54. Piercy KL, Troiano RP, Ballard RM, et al. The physical activity guidelines for Americans. *JAMA*. 2018;320:2020–2028.
55. English WJ, Williams DB. Metabolic and bariatric surgery: An effective treatment option for obesity and cardiovascular Disease. *Prog Cardiovasc Dis*. 2018;61(2):253–269.
56. Mechanick JI, Youdim A, Jones DB, et al. American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic and Bariatric Surgery. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient—2013 update. *Endocr Prac*. 2013;19(2):337–372.
57. American Diabetes Association. Obesity management for the treatment of

type 2 diabetes: Standards of medical care in diabetes—2019. *Diabetes Care*. 2019;42:S81–S89.

58. Cummings DE, Cohen RV. Bariatric/metabolic surgery to treat type 2 diabetes in patients with a BMI <35 kg/m^2. *Diabetes Care*. 2016;39:924–933.
59. Schauer PR, Bhatt DL, Kirwan JP, et al. Bariatric surgery versus intensive medical therapy for diabetes: 5-Year Outcomes. *N Engl J Med*. 2017;376(7):641–651.
60. Stein J, Stier C, Raab H, Weiner R. Review article: The nutritional and pharmacological consequences of obesity surgery. *Aliment Pharmacol Ther*. 2014;40(6):582–609.
61. Fisher DP, Johnson E, Haneuse S, et al. Association between bariatric surgery and macrovascular disease outcomes in patients with type 2 diabetes and severe obesity. *JAMA*. 2018;320(15):1570–1582.
62. Adams TD, Davidson LE, Litwin SE, et al. Weight and metabolic outcomes 12 years after gastric bypass. *N Engl J Med*. 2017;377:1143–1155.
63. Sjöström L, Peltonen M, Jacobson P, et al. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. *JAMA*. 2014;311(22):2297–2304.
64. Azran C, Wolk O, Zur M, et al. Oral drug therapy following bariatric surgery: An overview of fundamentals, literature and clinical recommendations. *Obes Rev*. 2016;17(11):1050–1066.
65. Saunders KH, Igel LI, Saumoy M, et al. Devices and endoscopic bariatric therapies for obesity. *Curr Obes Rep*. 2018;7:162–171.
66. Nyström M, Machytka E, Norén E, et al. Aspiration therapy as a tool to treat obesity: 1- to 4-year results in a 201-patient multicenter post-market European registry study. *Obes Surg*. 2018;28:1860–1868.
67. Sullivan S. Aspiration therapy for obesity. *Gastrointest Endosc Clin N Am*. 2017;27(2):277–288.
68. Abu Dayeh BK, Kumar N, et al. Bariatric Endoscopy Task Force ASGE. Technology Committee ASGE. ASGE Bariatric Endoscopy Task Force systemic review and meta-analysis assessing the ASGE PIVI thresholds for adopting endoscopic bariatric therapies. *Gastrointest Endosc*. 2015;82(3):425–438.
69. Ali MR, Moustarah F, Kim JJ, American Society for Metabolic and

Bariatric Surgery Clinical Issues Committee. American Society for Metabolic and Bariatric Surgery position statement on intragastric balloon therapy endorsed by the Society of American Gastrointestinal and Endoscopic Surgeons. *Surg Obes Relat Dis*. 2016;12(3):462–467.

70. Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: A systematic and clinical review. *JAMA*. 2014;311(1):74–86.
71. Sahebkar A, Simental-Mendia LE, Reiner Z, et al. Effect of orlistat on plasma lipids and body weight: A systematic review and meta-analysis of 33 randomized controlled trials. *Pharmacol Res*. 2017;122:53–65.
72. Torgerson JS, Hauptman J, Boldrin MN, Sjostrom L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: A randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care*. 2004;27(1):155–161.
73. Halpern B, Halpern A. Safety assessment of FDA-approved (orlistat and lorcaserin) antiobesity medications. *Expert Opin Drug Saf*. 2015;14(2):185–189.
74. *Xenical® [package insert]*. South San Francisco, CA: Genetech USA, Inc.; 2018.
75. *Belviq® [package insert]*. Zofingen, Switzerland: Arena Pharmaceuticals; 2016.
76. Smith SR, Weissman NJ, Anderson CM, et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. *N Engl J Med*. 2010;363:245–256.
77. Fidler MC, Sanchez M, Raether B, et al. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: The BLOSSOM trial. *J Clin Endocrinol Metab*. 2011;96(10):3067–3077.
78. O'Neil PM, Smith SR, Weissman NJ, et al. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: The BLOOM-DM study. *Obesity*. 2012;20(7):1426–1436.
79. Greenway FL, ShanahanW, Fain R, Ma T, Rubino D. Safety and tolerability review of lorcaserin in clinical trials. *Clin Obes*. 2016;6:285–295.
80. *QsymiaTM [package insert]*. Mountain View, CA: Vivus Inc; 2018.
81. Gadde KM, Allison DB, Ryan DH, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): A randomized, placebo-controlled, phase 3 trial. *Lancet*. 2011;377:1341–

1352.
82. Allison DB, Gadde KM, Garvey WT, et al. Controlled-release phentermine/topiramate in severely obese adults: A randomized controlled trial (EQUIP). *Obesity*. 2012;20(2):330–342.
83. *Contrave® [package insert]*. Cambridge, MA: Takeda Pharmaceuticals America, Inc.; 2014.
84. Yanovski SZ, Yanovski JA. Naltrexone extended-release plus bupropion extended-release for treatment of obesity. *JAMA*. 2015;313(12):1213–1214.
85. Greenway FL, Fujioka K, Plodkowski RA, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR–I): A multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2010;376(9741):595–605.
86. Apovian CM, Aronne L, Rubino D, et al. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity*. 2013;21:935–943.
87. Wadden TA, Foreyt JP, Foster GD, et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: The COR–BMOD Trial. *Obesity (Silver Spring)*. 2011;19(1):110–120.
88. Hollander P, Gupta AK, Plodkowski R, et al. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. *Diabetes Care*. 2013;36:4022–4029.
89. *Saxenda [package insert]*. Plainsboro, NJ: Novo Nordisk Inc; 2014.
90. Pi-Sunyer X, Astrup A, Fujioka K, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med*. 2015;373:11–22.
91. Davies MJ, Bergenstal R, Bode B, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: The SCALE diabetes trial. *JAMA*. 2015;314(7):687–699.
92. Velazquez A, Apovian CM. Update on obesity pharmacotherapy. *Ann N Y Acad Sci*. 2018;1411:106–119.
93. Saunders KH, Umashanker D, Igel L, Kumar RB, Aronne LJ. Obesity pharmacotherapy. *Med Clin N Am*. 2018;102:135–148.
94. *Adipex-P [package insert]*. Horsham, PA: Teva Select Brands; 2017.

95. Bray GA, Heisel WE, Afshin A, et al. The science of obesity management: An Endocrine Society Scientific Statement. *Endocr Rev*. 2018;39:79–132.
96. Cohen PA. American roulette: Contaminated dietary supplements. *N Engl J Med*. 2009;361(16):1523–1525.
97. Yazdi FT, Clee SM, Meyre D. Obesity genetics in mouse and human: Back and forth, and back again. *Peer J*. 2015. doi:10.7717/peerj.856.
98. Farooqi IS, Matarese G, Lord GM, et al. Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. *J Clin Invest*. 2002;110(8):1093–1103.
99. Kühnen P, Clément K, Wiegand S, et al. Proopiomelanocortin deficiency treated with a melanocortin-4 receptor agonist. *N Engl J Med*. 2016;375(3):240–246.

Index

Page numbers followed by *f*, *t*, or *b* indicate figures, tables, or clinical presentation boxes, respectively.

A

Abacavir, 2150*t*, 2152*t*, 2153
Abacteriuria
  significant, 1958
  symptomatic, 1965–1966
Abaloparatide, 1552*t*, 1553*t*
Abatacept, 1463, 1525*t*, 1529, 1533*t*
Abciximab, 174*t*
Abemaciclib, 2185*t*, 2246*t*
Abiraterone, 2312*t*, 2315
Abnormal uterine bleeding with ovulatory dysfunction. *See* Uterine bleeding with ovulatory dysfunction
Abscess
  in brain, 1795–1796
  definition of, 1939
  intra-abdominal, 1940 (*See also* Intra–abdominal infection)
  in ulcerative colitis, 510
Absence seizure, 881. *See also* Epilepsy
Absolute neutrophil count (ANC), 1112
Academy of Nutrition and Dietetics, 2
Acalabrutinib, 2185*t*, 2402*t*, 2403*t*
Acamprosate, 1074*t*, 1075
Acarbose, 1242*t*, 1248
ACE inhibitors. *See* Angiotensin-converting enzyme inhibitors (ACEIs)
Acetaminophen. *See also* Nonsteroidal anti-inflammatory drugs (NSAIDs)
  adverse effects of, 1508
  dosing and administration of, 977*t*, 1504*t*, 1508
  drug-drug interactions, 1508

drug-food interactions, 1508
for migraine, acute, 995*f*
for osteoarthritis, 1506, 1508
for pain management, 965–966, 968*t*
pharmacology and mechanism of action, 1507*t*, 1508
Acetazolamide, 1600*t*
Acetic acid, 968*t*
Acetylsalicylic acid (ASA). *See* Nonsteroidal anti-inflammatory drugs (NSAIDs)
Acid pockets, 464, 477
Acid suppression therapy, 474–476
Acid-base chemistry, 813–814
Acid-base disorders, 813–831. *See also specific disorders*
acid-base disturbances in, 815–816, 816*t*
arterial blood gas analysis in, 816–817, 816*t*, 817*f*
bottom line, clinical, 830–831
buffers in, 814
chemistry of, 813–814, 814*t*
clinical assessment of acid-base status in, 816–817
diagnosis of, 817*t*
homeostasis and, 814–815
metabolic acidosis, 817–821 (*See also* Metabolic acidosis)
metabolic alkalosis, 824–825 (*See also* Metabolic alkalosis)
mixed, 830
metabolic acidosis and respiratory alkalosis, 830
metabolic alkalosis and respiratory acidosis, 830
respiratory acidosis and metabolic acidosis, 830
respiratory alkalosis and metabolic alkalosis, 830
patient care process for, 822*b*
renal regulation in, 815
respiratory, 827–828
respiratory acidosis, 828–829
respiratory alkalosis, 827–828
sodium chloride-resistant disorders, 826–827
sodium chloride-responsive disorders, 825–826
Acid-base homeostasis, 814–815
extracellular buffering in, 815

renal regulation in, 815, 815*f*
respiratory regulation in, 815
Acid-base management, in cardiac arrest, 334
Acid-base status, 816*t*
Acidemia, 815
Acidosis
lactic, 819–820, 819*t*
metabolic, 817–821 (*See also* Metabolic acidosis)
renal tubular, 818–819
respiratory, 828–829 (*See also* Respiratory acidosis)
Acinetobacter spp., 2008
Acitretin, 1662
Acne
comedonal, noninflammatory, 1632
maintenance therapy for, 1632
mild-to-moderate papulopustular inflammatory acne, 1632
nodular or conglobate acne, 1632
severe papulopustular or moderate nodular acne, 1632
Acne rosacea, 1626
Acne vulgaris, 1623–1628
clinical presentation of, 1626–1628, 1627*b*
definition of, 1623
diet and, 1624
differential diagnosis of, 1626–1628
drug-induced acne in, 1628
epidemiology of, 1623–1624
etiology of, 1624–1625
pathophysiology of, 1625–1626, 1625*f*
patient care process for, 1629*b*
psychosocial issues in, 1626
Acne vulgaris treatment, 1628–1646
in children, 1634–1635
drug class information in, 1635–1645
exfoliants (peeling agents), 1635
resorcinol, 1635
salicylic acid, 1635–1638

topical therapies in, 1635
general approach to, 1628
goals of, 1628
in infants, 1634
light therapy, 1644–1645
nonpharmacologic therapy in, 1628–1632
cleansing, 1629–1630
comedone extraction, 1630
cosmetic, prevention of, 1630–1631
dressings, 1632
psychologic approaches, hypnosis and biofeedback in, 1631
shaving, 1630
topical preparation use, 1631
ultraviolet light, 1630
vehicles, 1631
outcomes of
desired, 1628
therapeutic, evaluation of, 1646
personalized pharmacotherapy in, 1645–1646
pharmacologic therapy in, 1632–1646, 1632*f*
alternative
complementary and alternative medications, 1633–1634
glycolic acid, 1634
hydroquinone, 1634
antibacterial agents, 1639–1642
azelaic acid, 1642
bacterial resistance to, 1641
benzoyl peroxide, 1639–1640
dapsone, 1642
oral, 1641–1642
steroids, intralesional, 1642–1643
topical, 1640–1641
anti-sebum agents, 1643–1644
contraceptives, oral, 1643
corticosteroids, oral, 1643
cyproterone acetate, 1643

isotretinoin, oral, 1643–1644
spironolactone, 1643
cleansing, 1645
drug class information in, 1635–1645
efficacy and safety of, 1633
exfoliants (peeling agents), 1636*t*
resorcinol, 1635
retinoids, topical, 1638–1639
salicylic acid, 1635–1638
sulfur, 1638
first choice, 1632
guidelines on, 1632–1633, 1633*t*
monitoring of, 1636*t*–1637*t*, 1646, 1646*t*, 1647*t*
in pregnancy, 1635
of scarring, 1634
Acquired dislipidemia, 119
Acquired immunodeficiency syndrome (AIDS), 2143. *See also* Human immunodeficiency virus (HIV) infection
candidiasis in, 2032–2035
CNS infection in, 1797
concomitant disease states and, 1774
cryptococcosis in, 2057, 2058
diarrhea and, 544
histoplasmosis in, 2052, 2054
HIV encephalitis, 1797
melanoma and, 2430
non-Hodgkin lymphoma and, 2329, 2341–2342
onchomycosis in, 2039
tuberculosis in, 1902, 1905
Acquired resistance, 2046
Acral lentiginous melanoma (ALM), 2431
Activated partial thromboplastin time (aPTT), 1731*t*
Active community treatment, 1094
Acupuncture, 965*t*
Acute angle closure crisis (AACC), 1599
Acute bacterial rhinosinusitis, 1830–1834

clinical presentation of, 1831, 1831*b*
epidemiology of, 1831
etiology of, 1831
pathophysiology of, 1831
patient care process for, 1832*b*
treatment of
general approach to, 1831
nonpharmacologic therapy in, 1832
outcomes of
desired, 1831
therapeutic, evaluation of, 1834
pharmacologic therapy in, 1832–1834
Acute bronchitis, 1804–1805
clinical presentation of, 1804–1810
epidemiology of, 1804
etiology of, 1804
pathogenesis of, 1804
treatment of
desired outcome in, 1805
general approach to, 1805
pharmacologic therapy in, 1805
Acute chest syndrome, 1752, 1760
Acute coronary syndromes (ACSs), 161–185
cause of, 117
clinical presentation and diagnosis of, 165*b*
12-lead ECG, 164
biomarkers/cardiac enzymes in, 164–166
physical examination findings, 164
risk stratification in, 165*b*, 166–167, 167*t*
symptoms of, 164
epidemiology of, 162
etiology of, 162
evaluation and inital management, 166*f*
pathophysiology of, 162–167
clot formation in, 163
complications, 164

plaque rupture in, 163
ventricular remodeling after MI in, 164
"vulnerable plaque," 162–163
patient assessment in, 166*t*
Acute coronary syndromes (ACSs) treatment, 167–185
acute supportive care, 169–171, 170*t*
beta-blockers, 170–171, 170*t*
calcium channel blockers, 170*t*, 171
morphine, 169, 170*t*
nitroglycerin, 169, 170*t*
oxygen, 170, 170*t*
anticoagulants, 178–180
bivalirudin, 180
fondaparinux, 179–180
low-molecular-weight heparin, 179
oral, 180
unfractionated heparin, 178–179
antithrombotic therapy, 173–180
antiplatelet therapy, 173–178, 174*t*
aspirin, 173–175, 174*t*
P2Y12 inhibitors, 174*t*, 175–177
general approach to, 169, 170*t*
ischemia-guided approach, 173
nonpharmacologic therapy in
fibrinolysis, 172–173
percutaneous coronary intervention, primary PCI for STEMIs, 172
risk stratification in, 166–167
NSTE-ACS strategies, 173
outcomes of
desired, 167–169
evaluation of, 185
patient care process for, 168*b*
pharmacologic therapy in, 167–185
ACE inhibitors, 181*t*
aldosterone antagonists, 181*t*, 183–184
angiotensin receptor blockers, 181*t*, 183

angiotensin-converting enzyme inhibitors, 181*t*, 183, 184*t*
anticoagulants, 178–180
antiplatelet therapy, 173–178, 174*t*
aspirin, 173–175, 174*t*, 181*t*, 184*t*
beta-blockers, 170–171, 181*t*
calcium channel blockers, 171
cangrelor, 175*t*, 176–177
clopidogrel, 175–176, 175*t*
drug monitoring in, 184*t*
dual antiplatelet therapy, 182–183
fibrinolytic therapy, 172–173, 172*t*, 173*t*, 184*t*
glycoprotein IIb/IIIa receptor inhibitors, 174*t*, 177–178
lipid-lowering agents, 183
nitrates, 169
nitroglycerin, 181*t*, 184–185
P2Y12 inhibitors, 174*t*, 175–177, 181*t*, 182*f*, 184*t*
prasugrel, 175*t*, 176
statins, 181*t*, 183
ticagrelor, 175*t*, 176
secondary prevention following MI, 180–182, 182*f*, 182*t*
ACE inhibitors, 183
aldosterone antagonists, 183–184
cholesterol management, 183
dual antiplatelet therapy, duration of, 182–183
nitroglycerin, 184–185
STEMI strategies, 171–173
Acute decompensated heart failure (ADHF), 166–178
advanced therapies, 236–237
durable mechanical circulatory support, 236–237
heart transplantation, 237
clinical presentation of, 222–226, 223*b*
discharge, preparation for, 237–238
epidemiology of, 222
etiology of, 222
general management of, 224*f*
hemodynamic alterations in, 226*f*

hemodynamic measurements in, 226*t*, 228*f*
hospitalization, indications for, 224*f*
hospitalized patients, monitoring, 237*t*
invasive hemodynamic monitoring in, 225
laboratory evaluation of, 223–225
nonpharmacologic therapy in, 234–235
  hemodynamic monitoring, 235
  temporary mechanical circulatory support, 235–236, 235*f*
    extracorporeal membrane oxygenation, 235*f*, 236
    intra-aortic balloon pump, 235–236, 235*f*
    ventricular assist devices, 235*f*, 236
  ultrafiltration, 234–235
pathophysiology of, 222
patient care process for, 227*b*
pharmacologic therapy in, 229–236
  adjunct diuretics, 230
  diuretics, 229*t*
  inotropes, 232–234, 233*t*
    combined with vasopressor activity, 234
    dobutamine, 233
    milrinone, 233
    selection of, 234
  loop diuretics, 229–230
  vasopressin antagonists, 230–232
    nitroglycerin, 231–232
    sodium nitroprusside, 232
    vasodilators, 231, 231*t*
signs and symptoms of, 223
treatment of, 226–238
  general approach to, 226–229
    subset I (warm and dry), 228
    subset II (warm and wet), 228
    subset III (cold and dry), 228–229
    subset IV (cold and wet), 229
  outcomes of
    desired, 226

evaluation of, 237–238
Acute gouty arthritis
clinical presentation of, 1569–1571, 1570*b*, 1570*f*
diagnosis of, 1570–1571, 1571*t*
Acute gouty arthritis treatment. *See also* Gout and hyperuricemia
algorithm for, 1578*f*
nonpharmacologic therapy in, 1572
pharmacologic
colchicine, 1577*t*
corticosteroids, 1574*t*–1575*t*, 1577*t*
NSAIDs, 1574*t*, 1577*t*
pharmacologic therapy in, 1572–1578, 1574*t*–1576*t*
colchicine, 1576–1578
corticosteroids, 1576
NSAIDs, 1572–1576
Acute kidney injury (AKI), 625–633. *See also* Chronic kidney disease (CKD)
classification of, 625–626, 625*t*, 633*t*
clinical presentation of, 629–633
diagnostic considerations in, 632–633
markers of kidney damage
conventional, 630–632, 631*t*
novel, 632
patient assessment in, 630
continuum of, 625*f*
definition of, 625–626
epidemiology of, 627
etiology of, 627, 627*t*, 628*f*
pathophysiology of, 627–629
in intrinsic AKI, 629
glomerular damage, 629
interstitial damage, 629
renal vasculature damage, 629
tubular damage, 629
in postrenal AKI, 629
in prerenal AKI, 627–628
patient care process for, 636*b*

prevention of, 633–635
general approach to, 633
nonpharmacologic therapy in
electronic alert systems, 633
intravenous fluids, 633–634
remote ischemic preconditioning, 634
outcomes of, desired, 633
pharmacologic therapy in
ascorbic acid, 634
glycemic control, 634–635
N-acetylcysteine, 634
statins, 634
sepsis and, 2010
Acute kidney injury (AKI) treatment
continuous renal replacement therapy in, 637–639, 638*f*
diuretics in, 639–640, 639*f*
drug dosing in, 640
electrolyte management in, 635–636
general approach to, 635
intermittent hemodialysis, 637
intravenous fluids, 635
monitoring of, 642*t*
nutrition in, 636–637
outcomes of
desired, 635
therapeutic, evaluation of, 640–642
pharmacologic and nonpharmacologic therapies, 635–641
renal replacement therapy in, 637–640, 637*t*, 638*f*
Acute lymphoblastic leukemia, 2368–2375
initial response in, 2368
risk classification in, 2368–2370
treatment of, 2370–2375
in adolescents and young adults, 2373
in adults, 2373–2374
in Down syndrome, 2371
phases of, 2371–2373, 2371*f*

central nervous system prophylaxis in, 2372
consolidation therapy in, 2372
induction, 2371–2372
maintenance therapy in, 2373
reinduction in, 2372–2373
in Philadelphia chromosome positive ALL, 2373
in relapsed ALL, 2374–2375
supportive care issues in, 2381
therapeutic outcomes of, evaluation of, 2381–2382
Acute myeloid leukemia, 2375–2380
hematopoietic growth factors in, role of, 2380–2381
prognostic factors in, 2375
risk classification in, 2375, 2375*t*
treatment of
for acute promyelocytic leukemia, 2379–2380
in children, 2378–2379
outcomes of, desired, 2375–2376
phases of, 2376–2378
allogeneic hematopoietic stem cell transplantation in, 2377–2378
autologous hematopoietic stem cell transplantation in, 2378
induction, 2376–2377
postremission, 2377, 2378
in relapsed or refractory AML, 2379
supportive care issues in, 2381
therapeutic outcomes of, evaluation of, 2381–2382
Acute otitis media, 1827–1830
clinical presentation of, 1828, 1828*b*
epidemiology of, 1827
etiology of, 1827
pathophysiology of, 1827–1828
patient care process for, 1829*b*
treatment of, 1828–1830
general approach to, 1828
nonpharmacologic therapy in, 1828
outcomes of
desired, 1828

therapeutic, evaluation of, 1830*t*
pharmacologic therapy in, 1828–1830, 1830*t*
Acute pain, 961, 962*b*, 962*t*, 963, 982*t*
Acute pancreatitis, 580–584
clinical course and prognosis of, 584
clinical presentation of, 579, 582–584
complications of, 584
diagnosis of, 582–584, 583*t*
etiology of, 580–581, 581*t*
incidence of, 579
medications in, 581, 582*t*
pathophysiology of, 581, 582*f*
prevalence of, 579
prevention of, 583*t*
prognosis of, 584
signs and symptoms of, 582
Acute pancreatitis treatment, 584–585
abdominal pain relief in, 585
antimicrobials in, 587
fluid resuscitation in, 585
general approach to, 584–585, 584*f*
nonpharmacologic therapy in, 585
nutrition and probiotics in, 585
outcomes of
desired, 584
evaluation of, 592
pain management, 585
pancreatic necrosis prevention in, 585
pharmacologic therapy in, 585
systemic complication limitation in, 585
Acute pharyngitis, 1834–1838
clinical presentation of, 1834–1835, 1835*b*
definition of, 1834
epidemiology of, 1834
etiology of, 1834
pathophysiology of, 1834

patient care process for, 1837*b*
treatment of, 1835–1838
general approach to, 1835
nonpharmacologic therapy in, 1835
outcomes of
desired, 1835
therapeutic, evaluation of, 1838
pharmacologic therapy in, 1835–1838, 1836*t*
Acute promyelocytic leukemia
patient monitoring in, 2380
relapsed, 2380
treatment of, 2379–2380
phases of, 2379–2380
consolidation therapy in, 2380
induction, 2379–2380
maintenance therapy in, 2380
for relapsed APL, 2380
Acute pyelonephritis, 1964*t*
Acute respiratory distress syndrome, 2010
Acyclovir
dosing by age group, 1799*t*
for febrile neutropenia, 2093*t*
for genital herpes, 1988
for HSCT infections, 2102
for solid-organ transplant recipients, 2106
Adalimumab, 516, 516*t*, 519, 521, 522, 523*t*, 1525*t*, 1528, 1664–1665
Adamantanes, 1850
Adapalene, 1632, 1636*t*, 1639
Adaptive immune system, e1451
Adaptive pain, 960
Addiction, 981, 1046–1047, 1048. *See also* Substance-related disorders
Addison disease, 1305–1308
clinical presentation of, 1306*b*
diagnosis of, 1305–1306
etiology of, 1305*t*
treatment of, 1306–1308

Adefovir, 604
Adenocarcinoma, 2256–2257
Adenomas
  adrenal, 1301, 1301*t*
  pituitary, 1301
  toxic, 1270–1271
Adenovirus, 1925*t*
Adherence, medication
  in HIV infection treatment, 2155
  in hypertension treatment, 111–112
  in schizophrenia treatment, 1100–1104
Adhesion molecules, 375
Adjunct diuretics, 230
Adjuvant! (Internet-based tool), 2236
Adolescents. *See also* Pediatrics
  acute lymphoblastic leukemia in, 2373
  ADHD in, 1012
  amenorrhea in, 1338, 1341
  definition of, e61
  diabetes mellitus treatment, 1257
  dysmenorrhea in, 1348–1349
  endometriosis treatment in, 1360
  generalized anxiety disorder treatment, 1177
  hypertension treatment in, 100
  obsessive-compulsive disorder in, 1197
  social anxiety disorder in, 1183
Ado-trastuzumab ematansine, 2191*t*, 2207, 2243–2244
Adrenal adenoma, 1301, 1301*t*
Adrenal carcinoma, 1301
Adrenal gland
  anatomy of, 1291–1293, 1291*f*
  biochemistry of, 1291–1293, 1292*f*
  hormone production and metabolism in, 1292–1293, 1293*t*
  physiology of, 1291–1293
  regulation of hormone secretion in, 1293, 1293*f*
Adrenal gland disorders, 1291–1298. *See also specific disorders*

hyperaldosteronism, 1301–1305
hyperfunction, 1293–1298
Cushing syndrome, 1293–1298
hyperaldosteronism, 1301–1305
aldosteronism, primary, 1301
aldosteronism, secondary, 1304–1305
hypofunction, 1305–1309
Addison disease, 1305–1308
congenital adrenal hyperplasia, 1307, 1308*t*
hirsutism, 1307–1308
hypoaldosteronism, 1307
virilism, 1307
Adrenal gland disorders treatment
glucocorticoids in, 1308–1309, 1308*t*
for hyperfunction
Cushing syndrome, 1293–1301
hyperaldosteronism
primary, 1302–1305
secondary, 1304–1305
for hypofunction, 1305–1309
therapeutic outcomes of, evaluation of, 1309
Adrenal sufficiency
acute insufficiency, 1307
clinical presentation of, 1306*b*
diagnosis of, 1305–1306
etiology of, 1305
secondary, 1304–1305
treatment of, 1306–1308
Adrenergic blockers, 1277
Adrenolytic agents, 1300
Adrenoreceptor function, 350
Adriamycin, 2324–2328, 2325*t*
Adsorbents, 547, 549*t*
Adult-onset ADHD, 1012
Advanced cardiac life support, 329, 329*f*
Adverse drug events (ADEs), e69, e13

Aerophagia, 469
Afatinib, 2185*t*, 2200–2201, 2264*t*
Aflibercept, 1615, 1615*t*, 2360
Afrezza, 1240*t*
Agency for Healthcare Research and Quality (AHRQ), e9
Age-related macular degeneration. *See* Macular degeneration, age-related
Aging. *See also* Geriatrics
  epidemiology of, e67, e71
  mechanisms of, e67
Agitation. *See* Pain, agitation, delirium (PAD)
Agranulocytosis, 1112, 1119*t*
Airway smooth muscle, 376
Akathisia, 1110, 1119*t*
Akinesia, 947–948, 1110
Albumin, 565, 2467
Albuminuria, 717, 718
Albuterol, 453, 805*t*
Alcohol
  acute effects of, 1071
  cirrhosis and, 570–571
  pharmacokinetics of, 1070–1071
  poisoning with, 1071
Alcohol abuse, 1070–1076
  addiction disease model of, 1070
  clinical presentation of withdrawal in, 1072*b*
  colorectal cancer and, 2276
  effects of related to blood alcohol concentration, 1071*t*
  epidemiology of, 1070
  etiology of, 1070
  laboratory studies, 1071
  osteoporosis and, 1549
  pathophysiology of, 1070–1071
  patient care process for, 1076*b*
  prevalence, 1070
  risk factors for, 1070*t*
  screening for, 1071

Alcohol abuse treatment, 1071–1075
nonpharmacologic therapy in, 1074
outcomes of
desired, 1071
evaluation of, 1075–1076
pharmacologic therapy in, 1074–1075, 1074*t*
acamprosate, 1074*t*, 1075
anticonvulsants, 1074*t*
antidepressants, 1074*t*
disulfiram, 1074*t*, 1075
naltrexone, 1074*t*, 1075
for withdrawal, 1071–1072
nonpharmacologic therapy in, 1071
nutritional deficits and electrolyte abnormalities, 1073–1074
pharmacologic therapy in, 1071–1072, 1073*t*
seizures, 1072–1073
severe, 1072–1073
treatment regimens
fixed-schedule therapy, 1072
front-loading therapy, 1072
symptom-triggered therapy, 1072
Alcohol hypoglycemia, 1074
Alcohol poisoning, 1071
Alcohol Use Disorders Identification Test (AUDIT), 1071
Aldosterone, 197, 657, 1292
Aldosterone antagonists, 181*t*, 183–184, 184*t*, 204*t*, 207*t*, 208*t*, 213–214, 214*t*
Aldosteronism, primary
clinical presentation of, 1301–1302, 1302*b*
diagnosis of, 1302*b*, 1303*f*, 1304*t*
etiology of, 1301
therapeutic management, 1302–1305
for APA-dependent aldosteronism, 1304
for BAH-dependent aldosteronism, 1302–1304
for glucocorticoid-remediable aldosteronism, 1304
Aldosteronism, secondary, 1304–1305
Alectinib, 2184*t*, 2199, 2265*t*

Alefacept, 1664
Alemtuzumab, 2190*t*
  for celiac disease, 620
  for graft-versus-host disease, 2461*t*
  for multiple sclerosis, 863*t*, 866–867
  for solid-organ transplant recipients, 1489
Alendronate, 1551*t*
Alfuzosin, 1419, 1421*t*, 1424
Alginic acid, 472*t*, 474, 475*t*
Aliskiren, 107
Alitretinoin, 1686
ALK Inhibitors, 2184*t*, 2199
  alectinib, 2199
  brigatinib, 2199
  ceritinib, 2199
  crizotinib, 2199
  lorlatinib, 2199
Alkalemia, 815
Alkali replacement, alternatives for, 821*t*
Alkaline phosphatase and γ-glutamyl transpeptidase, 565
Alkalosis
  metabolic, 824–825 (*See also* Metabolic alkalosis)
  respiratory, 827–828 (*See also* Respiratory alkalosis)
Alkylating agents, 2195–2196. *See also specific agents*
  monitoring of, 2182*t*–2183*t*
  nitrogen mustards, 2195–2196
    bendamustine, 2195
    cyclophosphamide, 2195–2196
    ifosfamide, 2195–2196
  nitroureas, 2196
    carmustine, 2196
    lomustine, 2196
  nonclassical, 2196
    dacarbazine, 2196
    platinum analogs, 2196
    temozolomide, 2196

trabectedin, 2196
Allergens, e31. *See also specific types*
Allergic contact eczema, definition of, 1676*t*
Allergic drug reactions, e1471
Allergic interstitial nephritis, acute, 708–710
clinical presentation of, 697
drugs associated with, 709*t*
immune checkpoint inhibitors, 709
incidence of, 708
management, 710
NSAIDs and, 709
pathogenesis of, 709
prevention of, 710
proton pump inhibitors and, 709
risk factors for, 709
Allergic rhinitis treatment, e31
allergens in, e31
definition of, e31
epidemiology of, e31
etiology of, e31
in pregnancy, 1324, 1325*t*
Allogeneic hematopoietic stem cell transplantation. *See also* Hematopoietic stem cell transplantation (HSCT)
in acute myeloid leukemia treatment, 2377–2378
in multiple myeloma treatment, 2421
Allopurinol, 1575*t*, 1577*t*
Almotriptan, 995*f*, 998*t*
Alogia, 1093
Alogliptin, 1242*t*, 1246
Alopecia, 1691–1693
in cancer patients, 2214
clinical presentation of, 1694–1697
alopecia areata, 1695–1696, 1696*f*, 1696*t*
anagen hair loss, 1694, 1694*t*
androgenic alopecia, 1695
in children, 1696–1697, 1697*t*

dermatological disease, 1695, 1695*t*
male and female pattern hair loss, 1695*t*
scarring hair loss, 1695, 1695*t*
telogen hair loss, 1694, 1695*t*
complications of, 1697
diagnosis of, 1697, 1697*t*
genetic testing, 1697
hair follicle
anatomy and physiology of, 1691–1693, 1692*f*, 1693*f*
hair cycle, 1692–1693, 1693*f*, 1694, 1694*t*
hair stigma, 1702–1703
pathophysiology of, 1693–1694
genetic association, 1693–1694
hormones, 1693
inflammation, 1694
scarring, 1694
patient care process for, 1698*b*
treatment of, 1697–1702
Alopecia treatment
for alopecia areata, 1701–1702
biologic agents in, 1702
corticosteroids, 1701–1702
for androgenic alopecia, 1699–1701
in children, 1701
female hair loss, 1700–1701
male baldness
miscellaneous therapies, 1700
systemic therapy in, 1699–1700
topical therapy in, 1699
for autoimmune diseases, 1699
for chemotherapy-induced, 1697–1698
hair care in, 1702
for infectious causes, 1697
for iron deficiency, 1698
for nutritional deficiencies, 1698–1699
for trauma or stressors, 1699

Alosetron, 556–557
Alpelisib, 2188*t*
α_1-antitrypsin replacement therapy, 421
α_1-blockers, 106–107
α_2-adrenergic agonist, 1133*t*, 1601–1602
  for ADHD, 1019–1020
  adverse effects of, 1020
  for open-angle glaucoma, 1600*t*
  relative potencies, 1135*t*
α_2-agonist, central, 107
α-adrenergic antagonists, 1419–1420, 1421*t*
α-adrenergic receptor agonists, 1425
α-glucosidase inhibitors, 1248
Alprazolam, 1036, 1171*t*, 1175*t*, 1178*t*
Alprostadil, 1391*t*, 1398*t*, 1403–1406
  indications, 1403
  intracavernosal, 1403–1404
    adverse effects of, 1404–1405
    dosing and administration of, 1404, 1404*t*
    efficacy of, 1403
    pharmacokinetics of, 1403
  intraurethral, 1405–1406
    adverse effects of, 1405
    dosing and administration of, 1405, 1405*f*
    efficacy of, 1405
    pharmacokinetics of, 1405
  mechanism, 1403
  for multiple sclerosis, 870
Alteplase, 173*t*, 278–279, 278*t*, 685, 685*t*
Altretamine, 2358*t*
Aluminum salts, 668
Alveolar macrophages, 375
Alvimopan, 555
Alzheimer disease, 835–839
  clinical presentation of, 838–839, 838*b*

mild cognitive impairment in, 839
diagnosis of, 838–839
Down syndrome and
diagnosis of, 1219
pathophysiology of, 1219
risk factors for, 1219
treatment of
desired outcomes in, 1219
nonpharmacologic therapy in, 1219
pharmacologic therapy in, 1219–1220
therapeutic outcomes in, 1220
environmental factors in, 836
epidemiology of, 835–836
age in, 836
risk factors for, 836
survival rate, 836
etiology of, 836
genetics of, 836
history of, 836
pathophysiology of, 836–838
amyloid cascade hypothesis, 837
brain vascular disease and high cholesterol, 837
inflammatory mediators, 837
neurofibrillary tangles, 837
neurotransmitter abnormalities, 837
cholinergic hypothesis, 837
patient care process for, 841*b*
stages of, 838*t*
Alzheimer disease treatment, 839–848
brain vascular health, management of, 845
caregivers, resources for, 840*t*
effect on neurodegenerative processes, 845
general approach to, 840
nonpharmacologic therapy in, 840, 840*t*
memantine, for neuropsychiatric symptoms, 847
outcomes of

desired, 839–840
therapeutic, evaluation of, 848
pharmacologic therapy in, 840–848
for cognitive symptoms, 840–845, 842*t*, 843*t*, 844*t*
antiglutamatergic therapy, 843–844
antiinflammatory agents, 845
brain vascular health in, 845
cholinesterase inhibitors, 842–843, 843*t*
combination therapy, 844–845
in development, 846–847
dietary supplements, 845
effectiveness of, on neurodegeneration, 845
estrogen, 845
ginkgo biloba, 846
lipid-lowering agents, 845
medical foods, 846
omega-3 fatty acids, 846
vitamin B, 846
vitamin E, 845
for neuropsychiatric symptoms, 847–848
anticonvulsants, 848
antidepressants, 847
antipsychotics, 847–848
benzodiazepines, 848
cholinesterase inhibitors, 847
memantine, 847
selective serotonin reuptake inhibitors, 847
Amantadine, 869*t*, 870, 951–952, 952*t*, 953*t*
Ambrisentan, 442, 443*t*, 444*t*, 445*t*, 446*t*
Amenorrhea, 1336–1341
in adolescents, 1338, 1341
clinical presentation of, 1336*b*
definition of, 1336
epidemiology of, 1336
etiology of, 1336
pathophysiology of, 1336–1338, 1337*t*

hypothalamus in, 1338
ovaries in, 1336–1338, 1337*f*
pituitary gland in, 1338
uterus/outflow tract in, 1336
PCOS-related, 139*t*
treatment of, 1338–1341
algorithm for, 1341*f*
general approach to, 1338
nonpharmacologic therapy in, 1338
outcomes of
desired, 1338
therapeutic outcomes of, evaluation of, 1341
pharmacologic therapy in, 139*t*, 1338
bromocriptine, 1338
cabergoline, 1338
drug class in, 1338
progestin, 1338
American College of Physicians (ACP) Foundation, e9
American Nursing Association, 1
American Society of Health-System Pharmacists (ASHP), e13
America's Health Insurance Plans (AHIP), e9
Amides, 981*t*
Amikacin
adverse effects and monitoring of, 1919*t*
for cystic fibrosis, 454*t*
dosing of, 1914*t*
for febrile neutropenia, 2092*t*
for tuberculosis, 1913*t*
for UTIs, 1963*t*
Amiloride, 1304*t*
Amino acids
in enteral nutrition, 2520–2521
in parenteral nutrition, 2492–2495
Aminoglutethimide, 2305, 2315
Aminoglycosides. *See also specific agents*
adverse effects and monitoring of, 1777*t*

dosing of, 1819*t*
drug interactions, 1775*t*
for febrile neutropenia, 2090, 2095*t*
for intra-abdominal infection, 1947
nephrotoxicity, 699–700
clinical presentation of, 699
incidence of, 699
management of, 700
pathogenesis of, 699–700
prevention of, 700
risk factors for, 700, 700*t*
for peritoneal dialysis patients, 691*t*
for pneumonia, 1819*t*
for UTIs, 1963*t*
4-Aminopyridine, 869
Aminotransferases, 564–565
Amiodarone, 293, 293*t*
for arrhythmias, 292*t*, 293–294
for cardiac arrest, 332*t*
doses, 296*t*
electrophysiologic effects, 293*t*
monitoring, 294*t*
pharmacokinetics of, 295*t*
side effects of, 294*t*
thyrotoxicosis from, 1272–1273
Amitriptyline, 996*t*. *See also* Serotonin-norepinephrine reuptake inhibitors (SNRIs)
for chronic kidney disease, 670
for depression in Down syndrome, 1217
dosing and administration of, 996*t*
for headache in pregnancy, 1324
for major depressive disorder, 1133*t*
dosing, 1133*t*
for migraine headache prophylaxis, 996*t*
for multiple sclerosis, 869*t*
for pain management, 970*t*

pharmacokinetics of, 1138*t*
for posttraumatic stress disorder, 1191*t*, 1193*t*
relative potencies, 1135*t*
for sleep disorders, 1203
Amlodarone, 293*t*, 294*t*
Amlodipine, 94, 684
Ammonium chloride, 826
Amorolfine, 2040
Amoxicillin, 495
for acute otitis media, 1828–1830, 1830*t*
for acute pharyngitis, 1836, 1836*t*
for chronic bronchitis, 1811*t*
for peptic ulcer disease, 493
Amoxicillin-clavulanate
for acute bacterial rhinosinusitis, 1833–1834, 1833*t*
for acute otitis media, 1830*t*
for chronic bronchitis, 1811*t*
dosing and administration of, 1833*t*
for febrile neutropenia, 2092*t*
for UTIs, 1963*t*
Amphetamines, 1014–1019, 1059–1060, 1059*b*, 2549
Amphotericin B, 2069
for aspergillosis, 2068
for coccidioidomycosis, 2057
dosing by age group, 1799*t*
drug interactions, 1775*t*
for febrile neutropenia, 2095*t*
for histoplasmosis, 2054
for invasive fungal infections, 2070–2071
monitoring of, 2073*t*
nephrotoxicity, 702–703
clinical presentation of, 702–703
incidence of, 702
management of, 703
pathogenesis of, 703
prevention of, 703

risk factors for, 703
for oropharyngeal candidiasis, 2033*t*
for peritonitis, 692*t*
Ampicillin, 1793
for acute bacterial rhinosinusitis, 1833*t*
for chronic bronchitis, 1811*t*
dosing and administration of, 1833*t*
dosing by age group, 1799*t*
for febrile neutropenia, 2092*t*
for UTIs, 1963*t*
Amsler grid, 1607, 1610*f*
Amylase, 580, 2515*t*
Amylin analogs, 1248
Amyloid cascade hypothesis, 837
Amyloidosis, 1522
Anaerobic bacteria, 1814
Anagen phase, 1692, 1694, 1694*t*
Anakinra, 1525*t*, 1529, 1533*t*, 1575*t*
Anal warts, 1977*t*, 1991*t*
Analgesic nephropathy, 711
Analgesics. *See also specific types*
for chronic pancreatitis, 590
for migraine, acute, 995*f*
regional, 981
topical, 973, 974*t*
Anaphylaxis, 336, e1471
Anastrozole, 2248
for breast cancer, 2246*t*, 2248
for endometriosis, 1358*t*
ANCA-associated vasculitis, 733–734
clinical presentation of, 733
etiology and epidemiology of, 733
pathophysiology of, 733
treatment of, 733–734
Androgenic alopecia, 1695, 1697, 1699–1701
Androgens, 1292, 2246*t*, 2247*t*. *See also specific types*

for endometriosis, 1358*t*, 1359–1360
in menopause and perimenopausal/ postmenopausal hormone therapy, 1375
for prostate cancer, 2305
synthesis inhibitor, 2312*t*
Anemia, 1709–1720
aplastic, drug-induced, e1767
in cancer patients, 2212
classification of, 1710, 1710*f*
clinical presentation of, 1712*b*
diagnosis of, 1712
algorithm for, 1713*f*
general presentation in, 1712
laboratory evaluation of, 1712–1715
algorithm for, 1713*f*
folic acid, 1715
hematocrit, 1713
hemoglobin, 1713
homocysteine, 1715
methylmalonic acid, 1715
percentage transferrin situation, 1714
peripheral blood smear, 1714
red blood cell count, 1713
red blood cell distribution width, 1714
red blood cell indices, 1713–1714
Schilling test, 1715
serum ferritin, 1714
serum iron, 1714
soluble transferrin receptor, 1714–1715
total iron-binding capacity, 1714
total reticulocyte count, 1714
vitamin B12, 1715
in elderly, 1723–1724
epidemiology of, 1723
etiology of, 1723–1724
laboratory evaluation of, 1724
pathophysiology of, 1723

treatment of, 1724
of inflammation, 1721–1722 (*See also* Anemia of inflammation)
iron-deficiency, 1715–1718 (*See also* Iron-deficiency anemia)
macrocytic, 1710
megaloblastic, 1710, 1718–1720 (*See also* Megaloblastic anemia)
microcytic, 1710
nonmegaloblastic, 1710
patient care process for, 1717*b*
in pediatric populations, 1724–1725
epidemiology of, 1724
etiology of, 1724–1725
laboratory evaluation of, 1725
pathophysiology of, 1725
treatment of, 1725
in pediatrics, 1724–1725
prevalence of, 1709
red blood cells in, 1710–1711
erythropoiesis stimulation in, 1711
hemoglobin synthesis in, 1711
iron incorporation into heme in, 1711
normal destruction of, 1711, 1711*f*
treatment of
for anemia in elderly, 1724
anemia in pediatric populations, 1725
for anemia of inflammation, 1722–1723
for folic acid deficiency anemia, 1721
for iron-deficiency anemia, 1716–1718
outcome evaluation for, therapeutic, 1725–1726
for vitamin B12 deficiency anemia, 1720
Anemia of chronic disease, 1522
Anemia of chronic kidney disease, 651–652
diagnosis of, 654–655
treatment of, 658–664, 659*t*
algorithm for, 664*f*
erythropoiesis stimulating agents in, 659*t*
nonpharmacologic therapy, 659

outcomes of, desired, 658–659
pharmacoeconomic considerations in, 671
pharmacologic therapy, 659–664
erythropoiesis-stimulating agent therapy, 662–664, 662*t*
hypoxia-inducible factor inhibitors, 664–665
iron supplementation, 660–662, 661*t*
transfusions and adjunct therapies, 665
target hemoglobin in, 659
Anemia of inflammation, 1721–1722
causes of, 1722*t*
epidemiology of, 1721
etiology of, 1721–1722
laboratory evaluation of, 1722, 1722*t*
pathophysiology of, 1722
treatment of, 1722–1723
Anesthetics, inhaled, for refractory GCSE, 925
Anesthetics, local, 981*t*
Angina
in chronic heart failure, 217
differential diagnosis of, 141*t*
fixed threshold, 155–156
grading of, 141*t*
in ischemic heart disease, 140–142, 141*t*, 155–156
management of, 155–156
Prinzmetal's, 156
variable-threshold, 156
Angiogenesis, 2174
Angiogenesis inhibitors, 2295
Angiotensin converting enzyme inhibitors (ACEIs)
for acute coronary syndromes, 181*t*, 183, 184*t*
for chronic heart failure, 204*t*, 207*t*, 209–210
for hypertension, 95*t*, 96–97
monitoring of, 208*t*
nephrotoxicity of, 704–705
Angiotensin II (ATII), 196–197, 350–351, 364, 651, 2019
Angiotensin II receptor blockers/neprilysin inhibitor, 192–211

Angiotensin receptor blockers (ARBs), 656
for acute coronary syndromes, 181*t*, 184*t*
for chronic heart failure, 192, 207*t*, 211–212
for focal segmental glomerulosclerosis, 726
for glomerulonephritis, 721
for hypertension, 95*t*, 96–97
for immunoglobulin A nephropathy, 730
monitoring of, 208*t*
myocardial infarction and, 183
nephrotoxicity of, 704–705
in pregnancy, 100*t*
for resistant hypertension, 103
for stable ischemic heart disease, 147
Angiotensin-converting enzyme inhibitors (ACEIs), 146–148, 656
for chronic heart failure, 209–210
for focal segmental glomerulosclerosis, 726
for glomerulonephritis, 721
for immunoglobulin A nephropathy, 730
myocardial infarction and, 183
in pregnancy, 100*t*
for resistant hypertension, 102–103
Anidulafungin
for febrile neutropenia, 2093*t*
for oropharyngeal candidiasis, 2033*t*
Animal bites, 1856*t*, 1861*t*, 1878–1880
clinical presentation of, 1879*b*
epidemiology of, 1878
etiology of, 1878–1879, 1878*t*
pathophysiology of, 1879
physiology of, 1879
treatment of, 1879–1880
evidence-based, 1861*t*
nonpharmacologic therapy in, 1879–1880
outcomes of
desired, 1879
therapeutic, evaluation of, 1880

pharmacologic, 1862*t*
Ankle-branchial index (ABI). *See* Peripheral arterial disease (PAD)
Ankylosis, 1520*f*
Anorexia nervosa. *See also* Eating disorders
clinical presentation of, 1031–1032, 1031*b*
epidemiology of, 1029–1030
prognosis of, 1034
signs and symptoms of, 1031*f*
treatment of
nonpharmacologic therapy in, 1034–1036
pharmacologic therapy in
antidepressants, 1036
antipsychotics, 1036
therapeutic outcomes of, evaluation of, 1039
Anovulatory bleeding, 139*t*
Antacids, 472*t*, 474, 475*t*, 499–500, 533, 533*t*
Anthonisen criteria, 1808
Anthracyclines, 2195, 2236–2237, 2249–2250
Anthralin, 1660–1661
Antiandrogens, 2305, 2311*t*–2312*t*, 2313–2314
Anti-angiogenesis agents, 2360
Antiarrhythmics, 291–295. *See also* Arrhythmias
for cardiac arrest, 331–333
classification of, 292–293, 292*t*
class Ia, 291
class Ib, 291–292
class Ic, 292
class II, 292–293
class III, 293
class IV, 293
doses, 296*t*
electrophysiologic actions, 291
side effects of, 293, 294*t*
Antibacterial agents
for acne vulgaris, 1639, 1641–1642
adverse effects and monitoring of, 1636*t*–1637*t*

azelaic acid, 1642
bacterial resistance to, 1641
benzoyl peroxide, 1639–1640
dapsone, 1642
oral, 1641–1642
steroids, intralesional, 1642–1643
topical, 1640–1641
dosing by age group, 1799*t*
Antibiotic-associated diarrhea (AAD), 549
Antibiotics. *See also specific agents and infections*
for acute bacterial rhinosinusitis, 1832–1834, 1833*t*
for acute otitis media, 1828–1830, 1830*t*
for acute pancreatitis, 587
for acute pharyngitis, 1835–1838, 1836*t*
anxiety and, 1166*t*
for bite wounds, animal and human, 1879–1880
for chronic bronchitis, 1808–1810, 1811*t*
for Crohn's disease, 521
for cystic fibrosis, 454–455
for diabetic foot infections, 1872, 1873*t*
for gastrointestinal infections, 1930–1931, 1930*t*
for *H. pylori*-positive ulcers, 493
for HSCT infections, 2101–2102
for intra-abdominal infection, 1946–1951
for peritonitis, 690–691, 690*f*, 691*t*, 692*t*
pharmacodynamics of, 1821
pharmacokinetics of, 1821
for pneumonia, 1815–1821
for pressure sores, 1878
for prostatitis, 1971
resistance to, 1947, 2114
for sepsis and septic shock treatment, 2015–2016
for solid-organ transplant recipients, 2107
Antibodies
antidrug, 524
antinuclear, 1523

definition of, 2127
depleting, 1488–1489
nondepleting, 1489–1490
Antibody-drug conjugates, 2191*t*, 2207–2208
ado-trastuzumab ematansine, 2207
brentuximab vedotin, 2207
gemtuzumab ozogamicin, 2207
inotuzumab ozogamicin, 2207
polatuzumab vedotin, 2207–2208
Anticancer agents. *See also specific agents*
alkylating agents, 2182*t*–2183*t*, 2195–2196
nitrogen mustards, 2195–2196
bendamustine, 2195
cyclophosphamide, 2195–2196
ifosfamide, 2195–2196
nitroureas, 2196
carmustine, 2196
lomustine, 2196
nonclassical, 2196
dacarbazine, 2196
platinum analogs, 2196
temozolomide, 2196
antimetabolites, 2178–2179, 2180*t*, 2192–2194
folate antagonists, 2193–2194
methotrexate, 2193
pemetrexed, 2193
pralatrexate, 2193–2194
monitoring of, 2180*t*
purine analogs, 2193
cladribine, 2193
fludarabine, 2193
mercaptopurine, 2193
pentostatin, 2193
thioguanine, 2193
pyrimidine analogs, 2178–2179, 2192–2193
cytarabine, 2178–2179, 2180*t*

fluoropyrimidines, 2179, 2192
gemcitabine, 2192–2193
tipiracil, 2193
trifluridine, 2193
arsenic trioxide, 2197
asparaginase, 2197
bleomycin, 2197–2198
corticosteroids, 2197
endocrine therapies, 2196–2197
FLT3 inhibitors, 2201
hydroxyurea, 2198
lanreotide, 2198
lenalidomide, 2198
mechanism of action, 2179*f*
microtubule-targeting, 2180*t*–2181*t*, 2194
eribulin, 2194
estramustine, 2194
ixabepilone, 2194
taxanes, 2194
vinca alkaloids, 2194
mitomycin C, 2198
monitoring of, 2180*t*–2192*t*
omacetaxine mepesuccinate, 2198
pomalidomide, 2198
retinoids, 2198
targeted drugs in, 2198–2204
ALK inhibitors, 2199
BCR-ABL inhibitors, 2199–2200
BRAF inhibitors, 2200
BTK inhibitor, 2200
CDK inhibitors, 2200
EGFR pathway inhibitors, 2200–2201
FGFR inhibitor, 2201
IDH inhibitors, 2202
JAK inhibitor, 2202
thalidomide, 2198

therapeutic radiopharmaceuticals, 2197
ibitumomab tiuxetan, 2197
iobenguane I 131, 2197
lutetium Lu 177 dotatate, 2197
radium-233, 2197
topoisomerase inhibitors, 2181*t*–2182*t*, 2194–2195
anthracyclines, 2195
camptothecins, 2195
etoposide, 2195
teniposide, 2195
Anticholinergics. *See also specific agents*
for acute severe asthma, 389*t*, 397–398
for benign prostatic hyperplasia, 1421*t*–1422*t*, 1423*t*, 1424–1425
for COPD, 418
for diarrhea, 549
for Parkinson disease, 950–951, 952*t*
Anticipatory nausea and vomiting, 536, 537
Anticoagulants, 184*t*. *See also specific agents*
for acute coronary syndromes, 178–180
adverse effects of, 262–263
for atrial fibrillation and atrial flutter, 303–305
dosing and administration of, 263
efficacy of, 262
for glomerulonephritis, 722
indications and dosing for, 262*t*
interactions, 263
for ischemic stroke, 282
mechanism of action, 262
for NSTE-ACSs, 175–177
during pregnancy, 259*t*
for pulmonary arterial hypertension, 438
reversal agents, 263*t*, 283, 283*t*
for venous thromboembolism, 256, 261–263, 262*t*
Anticonvulsants. *See also specific agents*
for ADHD, 1020–1021
adverse effects of, 1157

for alcohol dependence, 1074*t*
anxiety and, 1166*t*
for bipolar disorder, 1157–1160
dosing and administration of, 996*t*, 1154*t*, 1157–1159
drug-drug interactions, 1157
for generalized anxiety disorders, 1171*t*
for migraine, acute, 996*t*
for migraine prophylaxis, 996*t*
oral contraceptives and, 49–50
for pain management, 966–970, 969*t*
for social anxiety disorder, 1183
Antidepressants, 1133*t*–1134*t*, 1203. *See also specific agents*
adverse drug reactions, 1144*t*
adverse effects of, 1196
for alcohol dependence, 1074*t*
for Alzheimer disease, 847
for anorexia nervosa, 1036
anxiety and, 1166*t*
augmentation with antipsychotics, 1196–1197
for bipolar disorder, 1160
for bulimia nervosa, 1036–1037
for children, 1197
cytochrome P450 enzymes and, 1139*t*
dosing and administration of, 996*t*, 1133*t*–1134*t*, 1193–1194, 1196
drug interactions, 1140*t*, 1141*t*
first-line treatments, 1132
for generalized anxiety disorders, 1171–1173, 1171*t*
adverse effects of, 1173
dosing and administration of, 1173
efficacy of, 1171–1173
mechanism of action, 1173
in irritable bowel syndrome, 557
for migraine, acute, 996*t*
for migraine prophylaxis, 996*t*, 1000
mixed serotonergic medications, 1133*t*, 1135–1136
monoamine oxidase inhibitors, 1133*t*, 1136

norepinephrine and dopamine reuptake inhibitor, 1133*t*, 1136
for obsessive-compulsive disorder, 1196, 1197*t*
for pain management, 970–971, 970*t*
pharmacodynamics of, 1137–1139
pharmacokinetics of, 1137–1139, 1138*t*, 1196
altered, 1138–1140
plasma concentration and clinical response of, 1139
for posttraumatic stress disorder, 1193–1194
relative potencies, 1135*t*
selective serotonin reuptake inhibitors, 1132, 1133*t*, 1138*t*, 1181
serotonergic, 1196
serotonin and α2-adrenergic antagonists, 1133*t*, 1136
serotonin-norepinephrine reuptake inhibitors, 1132–1135, 1133*t*
for social anxiety disorder, 1181–1183
tricyclic, 1132, 1133*t*, 1138*t*, 1174*t*, 1178*t*, 1209, 1342*t*
venlafaxine, 1182–1183
Antidiuretic hormone (ADH). *See* Vasopressin
Antidrug antibodies (ADAs), 524
Antiemetics. *See also* Nausea and vomiting
for CINV, 536
for CINV in children, 540
dosage recommendations for, 533*t*–534*t*
for gastroenteritis in children, 540
for geriatric patients, 540
for migraine headache, 999
in pregnancy, 539–540
Antiepileptics, 926, 999–1000, 1628, 2548. *See also specific agents*
Antiestrogens, 2247–2248, 2247*t*
Antifibrinolytic therapy, 1735
Antifungals
dosing by age group, 1799*t*
for peritoneal dialysis patients, 691*t*
for sepsis and septic shock treatment, 2016–2017
for solid-organ transplant recipients, 2107
Antigenic drift, 1841
Antigenic shift, 1841

Antigens, 2127
Anti-glomerular basement membrane glomerulonephritis, 734
Antiglutamatergic therapy, 843–844
Antihistamine-anticholinergic drugs, 533, 533*t*. *See also specific agents*
Antihistamines, 1203. *See also specific types*
  for atopic dermatitis, 1686
  for balance disorders, 539
  oral, 1686
Antihypertensives. *See also* Hypertension treatment; *specific types*
  anxiety and, 1166*t*
  chronic kidney disease and, 657*f*, 658
  diarrhea from, 546*t*
  dosing of, 95*t*–96*t*
  erectile dysfunction and, 1397, 1398*t*
  for glomerulonephritis, 720–721
  traumatic brain injury management and, 939
Anti-IgE. *See* Omalizumab
Antiinflammatory agents. *See* Nonsteroidal anti-inflammatory drugs (NSAIDs)
Antimalarials, 1461–1463
Antimetabolites, 2178–2179, 2192–2194. *See also specific types*
  folate antagonists, 2193–2194
    methotrexate, 2193
    pemetrexed, 2193
    pralatrexate, 2193–2194
  monitoring of, 2180*t*
  purine analogs, 2193
    cladribine, 2193
    fludarabine, 2193
    mercaptopurine, 2193
    pentostatin, 2193
    thioguanine, 2193
  pyrimidine analogs, 2178–2179, 2192–2193
    cytarabine, 2178–2179
    fluoropyrimidines, 2179, 2192
    gemcitabine, 2192–2193
    tipiracil, 2193

trifluridine, 2193
Antimicrobial pharmacotherapy, laboratory tests in, e1769
Antimicrobial prophylaxis in surgery
appropriate use of, 2122*t*
choice in, 2115
nonpharmacologic interventions, 2121–2122
scheduling in, 2114–2115
for specific surgery types, 2116–2121, 2117*t*–2118*t*
appendectomy, 2116
cardiothoracic surgery, 2118*t*, 2120–2121
cesarean section, 2117*t*, 2119–2120
colorectal surgery, 2116–2119
gastroduodenal surgery, 2116
gastrointestinal endoscopy, 2117*t*, 2119
gastrointestinal surgery, 2116
head and neck surgery, 2117*t*, 2120
hepatobiliary surgery, 2116
hysterectomy, 2117*t*
neurosurgery, 2118*t*, 2121
obstetric and gynecologic surgeries, 2117*t*, 2119–2120
orthopedic surgery, 2118*t*, 2121
urologic surgery, 2117*t*, 2119
vascular surgery, 2118*t*, 2121
therapeutic outcomes of, evaluation of, 2122
Antimicrobial regimen selection, 1771–1780, 1772*t*
antimicrobial stewardship in, 1779–1780
antibiotic formulary in, 1779–1780
confirming infection in, 1771–1772
fever, 1771–1772
local signs, 1772
white blood cell count, 1772
drugs for, first-choice, 1782–1783
for *Chlamydia pneumoniae*, 1783
for *Chlamydia trachomatis*, 1783
for gram-negative bacilli, 1782–1783
for gram-negative cocci, 1782

for gram-positive bacilli, 1782
for gram-positive cocci, 1782
for *Mycoplasma pneumoniae*, 1783
for spirochetes, 1783
failure of antimicrobials in, 1778–1779
drug selection in, 1779
host factors in, 1779
microorganisms in, 1779
monitoring response in, 1777*t*–1778*t*, 1778
pathogen identification in, 1772–1773
interpreting results in, 1773
microbiological studies in, 1772–1773
presumptive therapy in, 1773–1776
adverse drug reactions, 1777*t*–1778*t*
age in, 1774
allergy in, 1773–1774
antibiogram, 1773
breadening the spectrum of coverage, 1776
combination therapy in, 1776
disadvantages of, 1776
resistance prevention in, 1776
spectrum of coverage in, 1776
synergism in, 1776
concomitant disease states in, 1774
concomitant drugs in, 1774
drug factors in, 1775
pharmacodynamics in, 1775
pharmacokinetics in, 1775
drug toxicity in, 1776
host factors in, 1773
metabolic or genetic variation in, 1774
organ dysfunction in, 1774
patient history in, 1773
pregnancy in, 1774
tissue penetration in, 1775–1776
Antimicrobials. *See also specific agents*

for acne vulgaris, 1636*t*–1637*t*
for acute pancreatitis, 587
adverse effects and monitoring of, 1777*t*–1778*t*
for cystic fibrosis, 454–455, 454*t*
dosing by age group, 1799*t*
drug interactions, 1775*t*
for inflammatory bowel disease, 515, 516
penetration into CSF, 1791*t*
for peritonitis, 690–691, 690*f*, 691*t*, 692*t*
in pneumonia treatment, 1816–1821
in adults, 1817*t*
in children, 1818*t*
dosing of, 1819*t*
topical, 1636*t*
Antimotility agents, 549*t*, 1931
Antimuscarinic agents, 1441*t*, 1442*t*
Antimycobacterials, dosing by age group, 1799*t*
Antineoplastics. *See* Cancer treatment and chemotherapy
Antineutrophil cytoplasmic autoantibodies (ANCAs), 716
Antinuclear antibodies, 1523
Antioxidants
for acne vulgaris, 1643
for age-related macular degeneration, 1613–1614, 1614*t*, 1616
for Alzheimer disease, 845
for chronic obstructive pulmonary disease, 407, 1810
for pancreatitis, 591
for traumatic brain injury, 939
Antiparasitic drugs, 2095*t*. *See also specific types*
Antiphospholipid antibodies, 1465, 1466*t*
Antiplatelet agents
for acute coronary syndromes, 173–178, 174*t*
for ischemic stroke, 280
for stable ischemic heart disease, 144–146
Antiproteinuria agents, 721
Antiprotozoal agents, 2095*t*
Antipsychotics, 847–848. *See also specific agents*

for ADHD, 1021
adverse effects of, 1106–1113, 1107*t*, 1119*t*
cardiovascular system, 1108–1109
central nervous system, 1109–1112
dermatologic system, 1112–1113
endocrine system, 1106–1108
genitourinary system, 1112
hematologic system, 1112
ophthalmologic effects, 1112
for anorexia nervosa, 1036
augmentation with antidepressants, 1196–1197
for autism spectrum disorder, 1223–1224
for bipolar disorder, 1160
dosage ranges, 1096*t*
dosing and administration of, 1160
first-generation, 1095, 1096*t*, 1106*t*
long-acting injectable antipsychotics, 1099–1100, 1101*t*–1102*t*
mechanism of action, 1104
noncompliance, 1103*t*
pharmacokinetics of, 1104–1106, 1106*t*
for schizophrenia, 1096*t* (*See also* Schizophrenia treatment)
second-generation, 1106*t*, 1136–1137
Antireflux surgery, 473, 473*t*
Antiresorptives, for osteoporosis, 1554–1558. *See also specific agents*
bisphosphonates, 1555–1556
calcitonin, 1557–1558
calcium, 1554
denosumab, 1556–1557
estrogen, 1557
estrogen agonists antagonists, 1557
testosterone, 1558
vitamin D, 1554–1555
Antiretroviral therapy (ART), 2144, 2151–2155, 2152*t*–2153*t*, 2162–2163. *See also specific agents*
Anti-sebum agents, 1643–1644
adverse effects and monitoring of, 1637*t*

contraceptives, oral, 1643
corticosteroids, oral, 1643
cyproterone, 1643
isotretinoin, oral, 1643–1644
monitoring of, 1637*t*
spironolactone, 1643
Antisecretory agents, 547–549, 549*t*. *See also specific agents*
Antithrombotics, 173–180. *See also specific types*
antiplatelet therapy, 173–178, 174*t*
aspirin, 173–175, 174*t*
P2Y12 inhibitors, 174*t*, 175–177
Antithymocyte globulin, 1488–1489
Anti-tuberculosis drugs, primary, 1915–1918
ethambutol, 1911*t*, 1913*t*, 1914*t*, 1916
isoniazid, 1911*t*, 1913*t*, 1914*t*, 1915
pyrazinamide, 1911*t*, 1913*t*, 1914*t*, 1915
rifabutin, 1913*t*
rifampin, 1911*t*, 1913*t*, 1914*t*, 1915
rifapentine, 1913*t*
Anti-tuberculosis drugs, secondary, 1917–1918
amikacin/kanamycin, 1913*t*
Bacille Calmette-Guérin vaccine, 1918
bedaquiline, 1914*t*
capreomycin, 1913*t*
clofazimine, 1917
corticosteroids, 1918
cycloserine, 1913*t*, 1914*t*, 1917
ethionamide, 1913*t*, 1914*t*, 1917
levofloxacin, 1913*t*
macrolides/azalides, 1917
moxifloxacin, 1914*t*
new drugs and delivery systems in, 1917–1918
p-aminosalicylic acid, 1913*t*, 1914*t*, 1917
quinolones, 1917
streptomycin, 1913*t*, 1914*t*, 1917
Antiulcer agents, 497–500. *See also specific agents*

antacids, 499–500
bismuth preparations, 499
drug interactions, 498
H2-receptor antagonists, 499
long-term safety issues, 498–499
prostaglandins, 499
proton pump inhibitors, 497–499, 498*t*
sucralfate, 499
Antivirals, dosing by age group, 1799*t*
Anxiety
definition of, 1165
drug-induced, 1166
in Parkinson disease, 950*t*
Anxiety disorders, 1165–1168. *See also specific disorders*
clinical presentation of, 1167–1168, 1167*b*, 1168*b*
definition of, 1165
drug-induced, 1166*t*
epidemiology of, 1165–1166
etiology of, 1166
medical diseases, associated, 1166
psychiatric diseases, associated, 1166
drug-induced, 1166
medical diseases, associated, 1166*t*
drug-induced, 1166*t*
generalized anxiety disorder, 1168–1177
panic disorder (attack), 1168
pathophysiology of, 1166–1167
neurochemical theories, 1166–1167
noradrenergic model, 1166–1167
GABA receptor model, 1167
serotonin model, 1167
neuroimaging studies, 1167
patient care process for, 1170*b*
phobias, specific, 1168
social anxiety disorder, 1168
Anxiety disorders treatment

algorithm for, 1172*f*
drug choices for, 1169*t*
generalized anxiety disorder, 1169–1177
panic disorder (attack), 1178–1181
social anxiety disorder, 1181–1183
Apalutamide, 2311*t*, 2313
Apidra, 1240*t*
Aplastic crisis, 1760–1761
Apnea, drug-induced, e459
Apolipoproteins, 120
Apomorphine, 953*t*, 956
Appendectomy, antimicrobial prophylaxis in, 2116
Apraclonidine, 1600*t*
Apremilast, 1668
Aprepitant, 530*t*, 534*t*, 535, 537, 538–539, 539*t*
Arachidonic acid (ARA), 487, 488*f*, 2521
ARBs. *See* Angiotensin receptor blockers (ARBs)
Arginine monochloride, 826
Arginine vasopressin (AVP), 197, 757–758
Arhalofenate, 1583
Aripiprazole, 1115*t*. *See also* Antipsychotics
for ADHD, 1020*t*
adverse effects of, 1020*t*, 1107*t*
for autism spectrum disorder, 1223, 1224*t*
for bipolar disorder, 1160
dosing and administration of, 1154*t*
for major depressive disorder, 1133*t*
mechanism of action, 1104, 1105*t*
pharmacokinetics of, 1106*t*
for schizophrenia, 1096*t*, 1099, 1100, 1101*t*–1102*t*
Aristolochic acid, 710
Armodafinil, 869*t*, 870, 1209*t*
Aromatase inhibitors, 2247*t*
for breast cancer, 2246*t*, 2247*t*
for endometriosis, 1358*t*, 1360
Arrhythmias, 287–289

abnormal conduction, 290*f*
antiarrhythmic drugs, 291–295
bradyarrhythmias, 317–319
normal conduction in, 288–289
outcomes of
economic, 319
therapeutic, evaluation of, 319
paroxysmal supraventricular tachycardia, 306–310 (*See also* Paroxysmal supraventricular tachycardia (PSVT))
pathophysiology of, 288–291, 289*f*, 290*f*
abnormal conduction, 289–291
normal conduction in, 288–289
supraventricular, 295–309 (*See also* Supraventricular arrhythmias)
tachyarrhythmias (*See* Tachycardia)
treatment of
pharmacologic therapy in, 291–295
amlodarone, 293*t*, 294*t*
drug classification, 292*t*
IV dosing, 298*t*
maintenance doses, 296*t*
pharmacokinetics of, 295*t*
side effects of, 294*t*
ventricular, 310–317 (*See also* Ventricular arrhythmias)
Arsenic trioxide, 2183*t*, 2197
Arterial blood gas, 816–817, 816*t*
Arterial blood gas analysis, 817*f*
Arterial blood pressure, 85
cardiovascular risk and, 85–86
classification of, 85, 85*t*
diastolic, 85
systolic, 85
Arterial hypoxemia, 574
Arthritis
acute gouty, 1569–1571
gonococcal, 1996
infectious (*See* Infectious arthritis)

osteoarthritis, 1497–1513
septic, 1571, 1772, 1879, 1995–2005 (*See also* Septic arthritis)
Arthritis, rheumatoid, 1517–1523
clinical presentation of, 1519*b*
definition of, 1517
diagnostic criteria, 1523, 1523*t*
epidemiology of, 1517–1518
etiology of, 1518
extra-articular involvement in, 1521–1522
amyloidosis, 1522
cardiac involvement, 1522
Felty syndrome, 1522
laboratory findings in, 1522–1523
lymphadenopathy, 1522
ocular manifestations, 1522
pulmonary complications, 1522
rheumatoid nodules, 1521–1522
vasculitis, 1522
joint involvement in, 1519–1520, 1519*f*, 1520*f*–1521*f*
pathophysiology of, 1518–1519, 1518*f*
patient care process for, 1524*b*
Arthritis, rheumatoid, treatment of, 1523–1532
algorithm for, 1526*f*
assessment of, 1532*t*
biosimilars, 1532
comorbidity management in, 1531–1532
cardiovascular risk reduction, 1531
immunization in, 1532
osteoporosis and, 1531
future directions, 1532
general approach to, desired, 1523
heart failure in, 1531
hepatitis in, 1531
infections in, 1531
malignancy and, 1531
nonpharmacologic therapy in, 1523–1524

outcomes of
desired, 1523
therapeutic, evaluation of, 1532–1534
pharmacologic therapy in, 1524–1526, 1525*t*
abatacept, 1529
adalimumab, 1528
adverse effects of, 1533*t*
anakinra, 1529
biologic agents, 1527–1528
non-TNF, 1529–1530
TNF-a inhibitors, 1528–1529
certolizumab, 1528
DMARDs, 1530
etanercept, 1528
glucocorticoids, 1530
golimumab, 1528
hydroxychloroquine, 1527
infliximab, 1528–1529
leflunomide, 1527
methotrexate, 1526–1527
nonsteroidal anti-inflammatory drugs, 1530
rituximab, 1529
sarilumab, 1529–1530
sulfasalazine, 1527
tocilizumab, 1529
tofacitinib, 1530
pregnancy and lactation in, 1530–1531
Artificial tears, e25
Ascites, 563
pathogenesis of, 563*f*
treatment of, 570–571, 572*t*
diuretic therapy in, 571
Ascorbic acid, 634, 2480*t*
Asenapine, 1096*t*, 1105*t*, 1106*t*, 1107*t*, 1115*t*, 1154*t*. *See also* Antipsychotics
Asian influenza of 1957, 1841
Asparaginase, 2197, 2371–2372

Aspart, 1239
Aspergilloma, 2066–2067
Aspergillosis, 2066–2073
  aspergilloma, 2066–2067
  clinical presentation of, 2067–2068
  diagnosis of, 2067–2068
  diagnostic tests in, 2068
  epidemiology of, 2066
  invasive, 2067
  pathophysiology of, 2066
  signs and symptoms of, 2067
  treatment of, 2068–2073
    in non-HIV-infected patients, 2068
    secondary prophylaxis, 2069
    specific therapy in, 2068–2069
Aspergillus, 2046, 2048*t*, 2066–2073, 2082
Aspirin. *See also* Acetylsalicylic acid (ASA); Nonsteroidal anti-inflammatory drugs (NSAIDs)
  for acute coronary syndromes, 173–175, 174*t*, 181*t*, 184*t*
  allergic reactions to, e1471
  antiplatelet therapy, 144–146
  dosing and administration of, 977*t*, 1504*t*
  for ischemic stroke, 278*t*, 279
  for migraine, acute, 995*t*
  for NSTE-ACSs, 174
  peptic ulcer disease and, 485
  for vascular access thrombosis, 684
Asthma, 371–380, 400–401, 1324, 1325*t*
  cardiac arrest treatment in, 335
  clinical presentation of
    acute severe asthma, 379, 379*b*
    in chronic asthma, 378–379, 378*b*
    in exercise-induced bronchospasm, 379, 382*f*
    in nocturnal asthma, 380
  vs. COPD, 407*t*
  definition of, 371

epidemiology of, 371–372
etiology of, 372
pathophysiology of, 372–378, 373*f*
  acute inflammation in, 372–375
  airway remodeling in, 376
  airway smooth muscle in, 376
  chronic inflammation in, 372–375
    adhesion molecules, 375
    alveolar macrophages, 375
    eosinophils, 374
    epithelial cells, 373
    fibroblasts, 375
    inflammatory mediators, 375
    lymphocytes, 374
    mast cells, 375
    mediators in, 375
    myofibroblasts, 375
    neutrophils, 375
    Th1 and Th2 cell imbalance in, 374–375
  mucus production in, 375–376
  neural control in, 376
  neurogenic inflammation in, 376
  nitric oxide in, 376
patient care process
  for acute severe asthma, 385*b*
  for persistent asthma, 381*b*
protective factors for, 373*f*
risk factors for, 373*f*
severity of, factors in, 376–378, 377*t*
  chronic rhinosinusitis, 377
  classification of, 380*t*
  depression, 377
  environmental and occupational, 376–377
  environmental factors in, 376–377
  female hormones, 377
  foods, drugs, additives, and vitamins, 377–378

gastroesophageal reflux disease, 377
obesity, 378
occupational factors in, 376–377
psychosocial factors in, 377
stress, 377
tobacco smoke, exposure to, 378
viral respiratory infections, 376
in sickle cell disease, 1752
Asthma treatment, 380–401
in acute care facility, 388*f*
for acute severe asthma, 384–386
in children 5-years and younger, 386
in emergency department, 379, 388*f*
nonpharmacologic therapy in, 392
pharmacologic, 393–400
anticholinergics, 389*t*, 397–398
β_2-agonists, short-acting, 389*t*, 393–395, 393*t*
corticosteroids, 389*t*, 395–397, 395*t*, 396*t*
ketamine, 400
magnesium sulfate, 400
aerosol therapy in, 383*t*, 386–391, 389*t*, 391*t*
device determinants of delivery, 382*f*, 386–390, 390*t*
patient determinants of delivery, 390–391
alternative therapies, 400
biologic agents in, 398–399, 398*t*
for chronic asthma, 382–384
nonpharmacologic therapy in, 391–392
pharmacologic therapy in
b2-agonists, long-acting, 394–395
benralizumab, 399
corticosteroids, inhaled, 396–397, 397*t*
dupilumab, 399
leukotriene modifiers, 398
mepolizumab, 399
methylxanthines, 400

omalizumab, 399
reslizumab, 399
in special populations, 383–384
children 5-years and younger, 383–384
elderly, 384
pregnant women, 384
general approach to, 381–382
outcomes of
desired, 380–381
evaluation of, 400–401
patient education in, 392*f*, 393
self-management, 387*f*
stepwise approach to control and minimize future risk, 384*t*
Astrovirus, 1925*t*
Asymptomatic bacteriuria (ASB), 1958, 1966
Asystole
causes of, 333*f*
nonpharmacologic therapy in, 333
pharmacologic therapy in, 333–334
Atacicept, 1463
Atazanavir, 2150*t*, 2152*t*, 2154
Atenolol, 996*t*
Atezolizumab, 2191*t*, 2208, 2263*t*
Atherogenesis, 124*f*
Atherogenic cholesterol, 128–129
Atherosclerosis. *See also* Ischemic heart disease
C-reactive protein and, 140
detection of, 90
diabetic foot infections and, 1872
dyslipidemia and, 117
in hypertension, 90, 1492
pathogenesis of, 120–122
psoriasis and, 1654
in stable ischemic heart disease, 137, 142–143
systemic lupus erythematosus and, 1456
Atherosclerotic cardiovascular disease (ASCVD), 117, 120–122. *See also*

Dyslipidemia treatment
reducing risk of, 125*t*
Atomoxetine, 1038
for ADHD, 1019–1020
adverse effects of, 1019, 1020*t*
for autism spectrum disorder, 1224*t*
dosing, 1020*t*
for narcolepsy, 1209*t*
Atonic seizure, 881. *See also* Epilepsy
Atopic dermatitis, 1675–1680
in children, 1675
clinical presentation of, 1678–1680, 1679*t*
complications of, 1679–1680
definition of, 1676*t*
diagnosis of, 1679*t*
early onset, 1675
epidemiology of, 1676
etiology of, 1676–1677
genetic factors in, 1676
hygiene hypothesis and, 1676
lichenification in, 1678
outcomes of, evaluation of, 1688
pathophysiology of, 1677–1678
patient care process for, 1681*b*
predisposing factors in, 1677–1678
prevalence of, 1675
severity of, 1679, 1680*f*
signs and symptoms of, 1679*t*
skin features associated with, 1678*t*
Atopic dermatitis treatment, 1680–1687
information resources, 1682*t*
nonpharmacologic therapy in, 1680–1683
outcomes of, desired, 1680
patient considerations in, 1687
pharmacologic therapy in, 1683–1687
calcineurin inhibitors, topical, 1684–1685

coal tar, 1685
complementary and alternative therapies in, 1686–1687
immunotherapy, 1687
probiotics/prebiotics, 1686–1687
traditional Chinese herbal therapy, 1686
corticosteroids, topical, 1683–1684
phototherapy in, 1685–1686
selective phoshodiesterase 4 inhibitors, 1685
systemic therapies in, 1686
alitretinoin, 1686
antihistamines, oral, 1686
azathioprine, 1686
biologic agents in, 1686
corticosteroids, 1686
cyclosporine, 1686
infliximab, 1686
methotrexate, 1686
mycophenolate mofetil, 1686
recombinant interferon, 1686
stepwise treatment, 1683*f*
Atopic march, 1675
Atopic triad, 1675
Atovaquone, 2093*t*
Atrial fibrillation and atrial flutter, 295–298
acute treatment, 298–303
algorithm for, 299*f*
in chronic heart failure, 217
chronic treatment, 303–306
antiarrhythmic therapy, 305–306
anticoagulants, 303–305
clinical presentation of, 295–298, 296*b*
management, 298, 300*t*
acute treatment, 298–303
restoration of sinus rhythm, 300–303
mechanisms of, 296–297
patient care process for, 297*b*

pharmacologic therapy in, 300*t*
sinus rhythm, restoration of, 300–303
Atrioventricular (AV) block, 318–319, 318*t*
Atrioventricular (AV) node, 287
Attapulgite, 549*t*
Attention deficit/hyperactivity disorder (ADHD), 1009–1021
autism spectrum disorder and, 1224*t*
clinical presentation of, 1011–1012, 1011*b*
in adolescents, 1012
in adults, 1012
in preschoolers, 1012
in school-age children, 1012
comorbidities in, 1021–1023
autism spectrum disorder, 1021
bipolar disorder, 1021
epilepsy, 1021
ODD/conduct disorder, 1022
substance abuse disorders, 1021–1022
Tourette disorder, 1022–1023
dosing, 1020*t*
epidemiology of, 1010
etiology of, 1010–1011
nonpharmacologic therapy in, 1014, 1014*t*
behavioral interventions, 1014, 1014*t*
cognitive interventions, 1014, 1014*t*
dietary interventions, 1014
educational interventions, 1014, 1014*t*
outcomes of
desired, 1012–1014
therapeutic, evaluation of, 1023–1024
pathophysiology of, 1010–1011
patient care process for, 1013*b*
personalized pharmacotherapy in, 1023
pharmacokinetic and drug interactions in, 1023
pharmacologic therapy in, 1014–1021, 1015*t*, 1016*t*–1017*t*

α_2-adrenergic agonists, 1019–1020
anticonvulsants, 1020–1021, 1020*t*
antipsychotics, 1021
atomoxetine, 1019–1020
bupropion, 1020, 1020*t*
lithium, 1020–1021
nonstimulants, 1019–1021, 1020*t*
stimulants, 1014–1019
Atypical pneumonia, 1821. *See also* Pneumonia
Aura, migraine, 992
Autism spectrum disorder (ASD), 1220–1225
ADHD and, 1021
clinical presentation of, 1221–1222, 1221*b*
diagnosis of, 1221
epidemiology of, 1220
etiology of, 1220–1221
history of, 1220
pathophysiology of, 1221
screening for, 1222*t*
treatment of, 1222–1225
nonpharmacologic therapy in, 1223
outcomes of
desired, 1222–1223
therapeutic, evaluation of, 1225
pharmacologic therapy in, 1223–1224, 1224*t*
antipsychotics, 1223–1224
miscellaneous agents, 1225
psychostimulants, 1224
selective serotonin reuptake inhibitors, 1224
Autoimmune diseases, 616, 617. *See also specific types*
hypothyroidism and, 1327
membranous nephropathy and, 726
non-Hodgkin lymphoma and, 2329
psoriasis and, 1664
secondary, 867

Autoimmune polyendocrine syndrome (APS), 1305
Autoimmune thyroiditis, 1280–1281
Autologous hematopoietic stem cell transplantation. *See also* Hematopoietic stem cell transplantation (HSCT)
in acute myeloid leukemia treatment, 2378
in multiple myeloma treatment, 2419–2421
Automated peritoneal dialysis (APD), 688
Avanafil, 1390*t*, 1398*t*
Avelumab, 2191*t*, 2208
Avian influenza, 1841–1843
Avibactam, 2086
Axicabtagene ciloleucel, 2192*t*, 2209
Axitinib, 2187*t*, 2202
Axona, 846
Azacitidine, 2185*t*
Azalides. *See also specific agents*
adverse effects and monitoring of, 1778*t*
dosing of, 1819*t*
drug interactions, 1775*t*
for pneumonia, 1819*t*
for tuberculosis, 1917
Azapirone, 1171*t*
Azathioprine, 1702
for atopic dermatitis, 1686
for celiac disease, 620
for Crohn’s disease, 520
fetal deformities, association with, 522
for inflammatory bowel disease, 515, 516*t*, 519, 523*t*, 524
for minimal-change nephropathy, 724
for solid-organ transplant recipients, 1486–1487
adverse effects of, 1487
dosing and administration of, 1487
drug-drug interactions, 1487
drug-food interactions, 1487
pharmacokinetics of, 1487
pharmacology and mechanism of action, 1486–1487

for systemic lupus erythematosus, 1460, 1461*t*, 1462*t*
Azelaic acid, 1637*t*, 1642
Azithromycin
for acne vulgaris, 1641
for acute pharyngitis, 1836*t*
for chlamydial infections, 1984–1985, 1985*t*
for chronic bronchitis, 1811*t*
for COPD, 420
for gonorrhea, 1978, 2000*t*
Azoles. *See also specific agents*
for aspergillosis, 2069
for coccidioidomycosis, 2057
drug interactions, 1775*t*
for febrile neutropenia, 2094
for invasive fungal infections, 2071
Aztreonam, 1963*t*
for cystic fibrosis, 454*t*
dosing by age group, 1799*t*
for UTIs, 1963*t*

B

Bacille Calmette-Guérin vaccine, 1918
Bacillus anthracis, 1797–1798
Bacillus cereus, 1935*t*
Baclofen, 477, 868–869, 869*t*, 971, 972*t*
Bacteremia. *See also specific types*
catheter-related, 685–686
hemodialysis access infection, 686*t*
infective endocarditis and, 1884
MRSA, 685
persistent, 1889
S. aureus, 1894
transient, 1890
VRE, 2082
Bacterial meningitis, 1791*t*
acute, 1791–1794

Bacterial replacement, 549*t*
Bacterial rhinosinusitis, acute, 1830–1834
  clinical presentation of, 1831, 1831*b*
  epidemiology of, 1831
  etiology of, 1831
  pathophysiology of, 1831
  patient care process for, 1832*b*
  treatment of
    general approach to, 1831
    nonpharmacologic therapy in, 1832
    outcomes of
      desired, 1831
      therapeutic, evaluation of, 1834
    pharmacologic therapy in, 1832–1834
Bacteriostatic soaps, 1645
Bacteriuria
  asymptomatic, 1966
  significant, 1958, 1958*t*
Bacteroides fragilis, 1941, 1996, 2008
Baker's cyst, 1522
Balance disorders, 539
Balloon tamponade, 569
Balsalazide, 516*t*, 519
Balvaptan, 1224*t*
Bantu haplotype, 1748–1749
Bapineuzumab, 846
Barbiturates. *See also specific agents*
  high-dose therapy, 935–937
Bariatric surgery, 473, 2540–2541
Baricitinib, 1702
Basal ganglia, 946
Basal-bolus regimes, 1239–1240
Basic life support, 328–329, 328*f*
Basiliximab, 1489–1490
Basophils, 373
Bath salts (cathinones), 1060

Bazedoxifene, 1376, 1552*t*, 1553*t*, 1557
B-cell lymphoma-2 inhibitors, 2184*t*
B-cell lymphomas, 2321*t*
BCL-2 inhibitors, 2199
BCR-ABL inhibitors, 2184*t*, 2199–2200
  bosutinib, 2199–2200
  dasatinib, 2199–2200
  imatinib, 2199
  nilotinib, 2199–2200
  ponatinib, 2200
Beclomethasone, 383*t*
Becocalcidiol, 1660
Bed sores. *See* Pressure sores
Bedaquiline, 1914*t*, 1917, 1919*t*
Bee venom, 871*t*
Belimumab, 1461*t*, 1462*t*, 1463
Belinostat, 2186*t*, 2201
Belladonna, 1044
Bendamustine, 2182*t*, 2195, 2337–2338, 2401–2402
Benign prostatic enlargement (BPE), 1412
Benign prostatic hyperplasia (BPH), 1411–1427
  clinical presentation of, 1413–1414, 1414*b*
  diagnosis of, 1414–1415, 1415*t*
  epidemiology of, 1412
  etiology of, 1412–1413
  medication-related symptoms, 1413
  pathophysiology of, 1413
  patient care process for, 1416*b*
  peak incidence of, 1412
  prostate cancer and, 2302
Benign prostatic hyperplasia (BPH) treatment, 1415–1426, 1417*f*
  general approach to, 1417
  nonpharmacologic therapy in, 1417
  outcomes of
    desired, 1417
    evaluation of, 1426

pharmacologic therapy in, 1417–1426, 1418*t*
5 α-reductase inhibitors, 1420–1422, 1421*t*, 1423*t*
prostate cancer and, 1422–1423
α-adrenergic antagonists, 1419–1420, 1421*t*, 1423*t*
β-adrenergic agonists, 1422*t*
anticholinergic agents, 1421*t*–1422*t*, 1423*t*, 1424–1425
combination therapy in, 1425–1426
phosphodiesterase inhibitors, 1421*t*, 1423*t*, 1424
phytotherapy in, 1426
surgical interventions in, 1426
β-adrenergic agonists, 1423*t*
Benign prostatic obstruction (BPO), 1412
Benin haplotype, 1749
Benralizumab, 398*t*, 399
Benzathine penicillin G, 1982, 1983*t*
Benzocaine, e35
Benzodiazepine-receptor agonists, 1203–1204, 1205*t*
Benzodiazepines. *See also specific agents*
adverse effects of, 1174*t*
for alcohol withdrawal, 1071–1072, 1073*t*
for Alzheimer disease, 848
for anorexia nervosa, 1036
for bipolar disorder, 1160
for generalized anxiety disorders, 1171*t*, 1173–1176
adverse effects of, 1175
discontinuation, 1176
dosing and administration of, 1176
drug interactions, 1176
efficacy of, 1175
misuse, dependence, withdrawal, and tolerance, 1175–1176
pharmacokinetics of, 1173–1175, 1175*t*
pharmacology and mechanism of action, 1173
for nausea and vomiting, 533–534, 533*t*
for panic disorder (attack), 1178*t*, 1180
for refractory GCSE, 923–924
for sleep-wake disorders, 1204–1205

for social anxiety disorder, 1182*t*, 1183
for status epilepticus, 920
withdrawal, treatment for
clinical presentation of, 1057*t*
general approach to, 1057
nonpharmacologic therapy in, 1057
pharmacologic therapy in, 1057
Benzoyl peroxide, 1636*t*, 1639–1640
Benztropine, 953*t*
Berger's disease. *See* Immunoglobulin A nephropathy
Beta carotene, 1616
β_3-adrenergic agonists, 1422*t*, 1423*t*, 1441*t*, 1442*t*
β-adrenergic antagonists (beta blockers), 170*t*, 575*t*, 995*f*. *See also specific agents*
for acute coronary syndromes, 170–171, 181*t*, 184*t*
for arrhythmias, 292–293, 292*t*
for chronic heart failure, 211–212
for cirrhosis, 569
diabetes mellitus and, 1231*t*
vs. first-line agents, 97
for hypertension, 96*t*, 105–106
for ischemic heart disease, 149
for migraine, acute, 996*t*
for migraine prophylaxis, 996*t*, 1000
monitoring of, 208*t*
myocardial infarction and, 170–171
for NSTE-ACSs, 182*f*
for open-angle glaucoma, 1599–1601, 1600*t*
in pregnancy, 100*t*
for resistant hypertension, 105–106
for social anxiety disorder, 1183
for thyrotoxicosis, 1277
for traumatic brain injury, 938
β-agonists, 389*t*, 1808
long-acting, 394–395
short-acting, 394

β-lactam, 1772. *See also specific agents*
allergic interstitial nephritis and, 709, 709*t*
bactericidal effects of, time-dependent, 1775
for cellulitis, 1868
for febrile neutropenia, 2086–2090, 2090*t*
for infective carditis, 1890
for intra-abdominal infections, 1947
for sepsis and septic shock treatment, 2015
for streptococcal endocarditis, 1890
for surgical site infections, 2116, 2122
synergistic activity, 1776
for syphilis, 1982
β-lactam-β-lactamase inhibitor, 1868
Betamethasone, 1308*t*
Betaxolol, 383*t*, 1600*t*
Bethanechol, 476
Bevacizumab, 1615, 1615*t*, 2190*t*, 2206–2207, 2263*t*, 2290*t*, 2291*t*, 2294*t*, 2356*t*, 2359–2360, 2359*t*
Bexarotene, 2183*t*
Bicalutamide, 2311*t*, 2313
Bictegravir, 2150*t*, 2152*t*, 2154
Bifidobacterium, 495, 514
Bifidobacterium lactis, 1687
Biguanides, 1241–1243, 1242*t*
Bile acid sequestrants, 1242*t*, 1248
Biliary tract, 580*f*, 1940
Bilirubin, 565, 565*t*, 1711
Bimatoprost, 1600*t*
Bind ligation, endoscopic, 568–569
Binge-eating disorder. *See also* Eating disorders
clinical presentation of, 1032, 1033*b*
epidemiology of, 1030
prognosis of, 1034
treatment of
nonpharmacologic therapy in, 1037
pharmacologic therapy in, 1037–1039

therapeutic outcomes of, evaluation of, 1039
Binimetinib, 2187*t*, 2202, 2443*t*, 2445*t*
Bioavailability, e15, 209
Bioelectrical impedance, 2474
Biofeedback, 553, 965*t*, 1631
Bioflavonoids, 846
Biologic agents, 398–399, 398*t*, 1463. *See also specific agents*
for atopic dermatitis, 1686
for inflammatory bowel disease, 515, 516
for rheumatoid arthritis, 1527–1528
Biomarkers
of acute coronary syndromes, 164–166
of stable ischemic heart disease, 142
Biotin, 1700, 2480*t*
Bipolar disorder, 1149–1152
clinical presentation of, 1150, 1151*b*
course of, 1151–1152
definition of, 1149
diagnosis of, 1150, 1150*t*
diagnostic difficulty, 1150–1151
epidemiology of, 1149
etiology of, 1149–1150
mania, secondary causes of, 1150*t*
mood disorders defined by episodes, 1150, 1150*t*
pathophysiology of, 1149–1150
patient care process for, 1156*b*
prevalence of, 1149
Bipolar disorder treatment, 1152–1161
algorithm for, 1153*t*
in children, 1161
general approach to, 1152, 1152*t*
nonpharmacologic therapy in, 1152
outcomes of
desired, 1152
therapeutic, evaluation of, 1161
personalized pharmacotherapy in, 1161

pharmacologic therapy in, 1152–1161, 1154*t*–1155*t* (*See also specific agents*)
anticonvulsants, 1157–1160
antidepressants, 1160
antipsychotics, 1160
benzodiazepines, 1160
carbamazepine, 1159*t*
general principles of, 1152–1161
lamotrigine, 1159–1160
lithium, 1153–1157
monitoring of, 1158*t*
oxcarbazepine, 1159*t*
pregnant women, 1160–1161
Bisacodyl, 554*t*
Bismuth salicylate, 495
Bismuth subcitrate potassium (biskalcitrate), 499
Bismuth subsalicylate, 499, 547, 549*t*
Bispecific T-cell engagers, 2191*t*, 2207
Bisphosphonates, 1555–1556, 2421
adverse events, 1555–1556
dosing and administration of, 1551*t*, 1556
drug interactions, 1556
efficacy of, 1555
for hypercalcemia, 784–785
monitoring of, 1553*t*
pharmacokinetics of, 1555
pharmacology of, 1555
Bite wounds, animal and human, 1856*t*, 1861*t*, 1878–1880
clinical presentation of, 1879*b*
epidemiology of, 1878
etiology of, 1878–1879, 1878*t*
pathophysiology of, 1879
physiology of, 1879
treatment of, 1879–1880
evidence-based, 1861*t*
outcomes of
desired, 1879

therapeutic, evaluation of, 1880
pharmacologic, 1862*t*
pharmacologic and nonpharmacologic, 1879–1880
Bivalirudin, 178*t*, 180
Black cohosh, 1377
Bladder outlet obstruction, 1413
Bladder overactivity. *See* Overactive bladder; Urinary incontinence
Blastocyst, 1316
Blastomyces braziliensis, 2054
Blastomyces dermatitidis, 2054
Blastomycosis, 2054–2056
acute pulmonary, 2055
chronic pulmonary, 2055
clinical presentation of, 2055
definition of, 2054
epidemiology of, 2054
laboratory and diagnostic tests, 2055
North American, 2054
pathophysiology of, 2055
South American, 2054
sporadic (nonepidemic) pulmonary, 2055
treatment of, 2055*t*
in HIV patients, 2056
in non-HIV-infected patients, 2055–2056
Blatchford score, 501
Bleeding risk, scoring, 284
Bleomycin, 2183*t*, 2197–2198, 2324–2328, 2325*t*, 2334
Blinatumomab, 2191*t*, 2207, 2374
Blisibimod, 1463
Blood alcohol concentration (BAC), 1070–1071, 1071*t*
Blood glucose dysregulation, 2215
Blood pressure, 85. *See also* Hypertension
cardiovascular risk and, 85–86
classification of, 85*f*
diastolic, 85
management of, 279–280, 282–283

measurement of, e81, 88–89
ambulatory and self-monitoring in, 89
cuff, 88–89
pathophysiology of
humoral mechanisms in
natriuretic hormone, 87
renin-angiotensin-aldosterone system, 86–87, 86*f*
reduction of, 148
systolic, 85
treatment guidelines in stroke, 276*t*
Blood products, for shock, 357, 357*t*
Blood transfusions, in chronic kidney disease, 665
Blood-brain barrier/blood-CSF barrier, 1787, 1787*f*
B-lymphocyte stimulator, 1463
Body mass index, 2472*t*, 2473, 2535
Body weight, 1371
Bone and joint infection, 1995–1999
clinical presentation of
infectious arthritis, 1998–1999, 1998*t*
osteomyelitis, 1998
epidemiology of, 1995–1996
infectious arthritis, 1996
osteomyelitis, 1995–1996
etiology of, 1996
infectious arthritis, 1996
osteomyelitis, 1996
pathophysiology of, 1996–1998
infectious arthritis, 1998
osteomyelitis, 1996–1998
chronic, 1998
contiguous, 1998
direct inoculation, 1997–1998
hematogenous, 1996–1997, 1997*f*
patient care process for, 2000*b*
radiologic and laboratory tests in, 1999
infectious arthritis, 1999

osteomyelitis, 1999
Bone and joint infection treatment, 1995–2005
general approach to, 2001
home antibiotic therapy in, 2004
individualized therapy, 2004
outcomes of
desired, 1999–2000
therapeutic, evaluation of, 2004–2005
pharmaceutical care plan monitoring in, 2004–2005, 2005*t*
pharmacologic therapy in, 2001–2004
antibiotic bone concentration in, 2002
antibiotic joint space concentration in, 2004
antibiotic selection in, 2001–2002, 2004
antibiotics, doses of, 2003*t*
duration of antibiotics in, 2002
for IV drug users, 2002
oral antibiotics in, 2002
for sickle cell hemoglobinopathies, 2002–2004
Bone health, cystic fibrosis and, 452
Bone-modifying agents, 2421
Borrelia burgdorferi (Lyme disease), 1798
Bortezomib, 1490, 2188*t*, 2203–2204, 2417
Bosentan, 443*t*, 444*t*, 445*t*, 446*t*
Bosutinib, 2184*t*, 2199–2200, 2392*t*, 2394*t*, 2395
Botulinum toxin, 869*t*, 1001, 1444–1445, 1935–1936
for multiple sclerosis, 869, 869*t*
Bradyarrhythmias, 317–319
atrioventricular block, 318–319, 318*t*
sinus bradycardia, 317–318
Bradycardia, 171
Bradykinesia, 947–948
BRAF inhibitors, 2185*t*, 2200, 2442*t*, 2443, 2444*t*
Brain
abscesses in, 1795–1796
cerebral hemispheres, 276*f*
insulin resistance in, 846

posterior circulation, 276*f*
Brain injury management, acute, 929–941. *See also* Traumatic brain injury (TBI)
algorithm for, 933*f*
for complications, treatment and prophylaxis, 939–940
clinical pathways/guideline implementation in, 940
investigational therapy, 940
for posttraumatic seizures, 939
supportive care in, 939–940
epidemiology of, 929
general principles of, 932, 933*f*
initial resuscitation, 932
postresuscitative care, 934–935
for intracranial hypertension, 935–940
barbiturates, 935–937
corticosteroids, 937
general strategies in, 935–938
hyperventilation, 937
hypothermia in, 937–938
investigational therapies, 938–939
osmotic agents in, 938
outcomes of
desired, 932
therapeutic, evaluation of, 940, 940*t*
patient care process for, 934*b*
personalized pharmacotherapy in, 940
Breakthrough nausea and vomiting, 536, 537
Breast, anatomy of, 2226*f*
Breast cancer, 2221–2230
advanced, 2230
clinical presentation of, 2225, 2226*f*, 2227*b*
from combined hormonal contraceptives, 53
diagnosis of, 2225–2226
epidemiology and etiology of, 2222–2223
age in, 2222
endocrine factors in, 2222
environmental and lifestyle factors in, 2223

gender in, 2222
genetic factors in, 2222–2223
incidence rates, 2221
in menopausal hormone therapy, 1370
metastatic, 2230
mortality rates, 2221
pathology of, 2226–2228
in invasive carcinoma, 2226–2228
in noninvasive carcinoma, 2228
patient care process for, 2231*b*
prevention and early detection of, 2223–2225
mammography in, 2224
other radiologic imaging methods, 2224
screening in, 2224, 2225*t*
prognostic factors in, 2228–2230
racial and ethnic groups, 2221
risk assessment in, 2222*t*
staging and prognosis in, 2229*t*–2230*t*, 2230, 2232*t*–2233*t*
Breast cancer treatment, 2230–2250
for early breast cancer (stage I and II), 2230–2242
locoregional therapy, 2231–2234
outcomes of, desired, 2230–2231
postmastectomy radiation therapy, 2234
sentinel lymph nodes in, 2234
systemic adjuvant therapy, 2234–2242
benefits, 2235, 2235*t*
biologic therapy, 2238–2240
chemotherapy in, 2236–2238, 2237*t*
dose density and intensity in, 2237–2238
endocrine therapy, 2240–2242, 2242*f*
guidelines, 2235–2236, 2235*f*
neoadjuvant (primary), preoperative, 2236
for HER2 metastatic, 2246*t*–2247*t*
for locally advanced breast cancer (stage III), 2242
for metastatic breast cancer (stage IV), 2242–2250
biologic or targeted therapy, 2243–2245

anti-HER2 agents, 2239*t*, 2243–2244, 2244*t*
cyclin-dependent kinase inhibitors, 2244–2245
mTOR pathway inhibitors, 2245
Poly (ADP-ribose) polymerase (PARP), 2245
chemotherapy in, 2248–2250, 2249*t*
endocrine therapy, 2245–2248, 2247*t*
outcomes of, desired, 2243
radiation therapy, 2250
outcome evaluation for, therapeutic, 2250–2251
Breastfeeding, inflammatory bowel disease and, 522
Brentuximab vedotin, 2191*t*, 2207
Brexanolone, 1138
Brexpiprazole, 1096*t*, 1115*t*–1116*t*
adverse effects of, 1107*t*
for major depressive disorder, 1133*t*
mechanism of action, 1104
pharmacokinetics of, 1106*t*
Brigatinib, 2184*t*, 2199, 2265*t*
Brimonidine, 1600*t*
Brinzolamide, 1600*t*
Brivaracetam, 894*t*–895*t*
Brodalumab, 1666–1667
Bromocriptine, 953*t*, 1242*t*
for amenorrhea, 1338
for menstruation-related disorders, 1342*t*
for Parkinson disease, 953*t*
Bronchiolitis, 1810–1811
clinical presentation of, 1810, 1811*t*
epidemiology of, 1810
etiology of, 1810
treatment of, 1810–1811
desired outcome in, 1810
general approach to, 1810–1811
Bronchitis, 1804–1805
acute, 1804–1805
clinical presentation of, 1804–1805

epidemiology of, 1804
etiology of, 1804
pathogenesis of, 1804
treatment of
desired outcome in, 1805
general approach to, 1805
pharmacologic, 1805
chronic, 1805–1810
clinical presentation of, 1806–1807, 1808*t*
epidemiology of, 1805–1806
etiology of, 1805–1806
pathogenesis of, 1806
treatment of, 1807–1810
desired outcome in, 1807
general approach to, 1807
pharmacologic therapy in, 1807–1810, 1809*f*, 1811*t*
Bronchodilators, 414–420, 424, 453, 1166*t*
long-acting, 417–418
short-acting, 415–417
Bronchospasm, 1119*t*
Brudzinski's neck signs, 1788*f*
BTK inhibitor, 2200
Budesonide, 383*t*, 515, 516*t*, 521
Buffers, 814
Bulimia nervosa. *See also* Eating disorders
clinical presentation of, 1032, 1032*b*
epidemiology of, 1030
prognosis of, 1034
signs and symptoms of, 1031*f*
treatment of, 1038*f*
nonpharmacologic therapy in, 1036
pharmacologic therapy in
antidepressants, 1036–1037
combination therapy in, 1037
selective serotonin reuptake inhibitors, 1037
therapeutic outcomes of, evaluation of, 1039

Bulk-forming laxatives, 553, 554*t*
Bumetanide, 207*t*
Bupivacaine, 981*t*
Buprenorphine, 976*t*, 978*t*, 980, 1051*t*
  for opioid use disorder, 1051–1054, 1053*t*, 1054*t*
  patient education for, 1055*t*
Bupropion, 1135*t*, 1136
  for ADHD, 1020
  adverse drug reactions, 1144*t*
  adverse effects of, 1020, 1020*t*
  dosing, 1020*t*
  drug interactions, 1140*t*
  for major depressive disorder, 1133*t*
  for nicotine cessation, 1081*t*, 1082
  pharmacokinetics of, 1138*t*
Burn wounds, 1856*t*
Buspirone, 1133*t*, 1171*t*, 1174*t*, 1176–1177, 1182*t*
Busulfan, 2182*t*, 2454*t*
Butoconazole, for vulvovaginal candidiasis, 2027*t*
Butorphanol, 976*t*, 978*t*
Butyrophenones, 533*t*, 534

C

Cabazitaxel, 2180*t*, 2194, 2314*t*, 2315
Cabergoline, 1298*t*
  for amenorrhea, 1338
  for Cushing syndrome, 1298*t*
  for menstruation-related disorders, 1342*t*
Cabotegravir, 2154
Cabozantinib, 2187*t*, 2202–2203
Cafergot, 995*f*
Caffeine use and abuse, 1084–1087
  clinical presentation of, 1085–1086
  clinical presentation of intoxication in, 1085*b*
  clinical presentation of withdrawal in, 1086*b*, 1086*t*
  differential diagnosis of, 1086, 1086*t*
  energy drinks and, 1085
  epidemiology of, 1085
  headaches and, 1086
  osteoporosis and, 1549
  pathophysiology of, 1085
  in pregnancy, 1086
  sleep effects of, 1086
  treatment of, 1086–1087
    nonpharmacologic therapy in, 1086–1087
    outcomes of
      desired, 1086
      evaluation of, 1087
  withdrawal, 1086, 1086*t*
Caffeinism, 1084, 1086
CAGE questionnaire, 1071
Calcifediol, 669*t*
Calcimimetics, 670–671
  adverse effects of, 670
  dosing and administration of, 671
  drug-drug interactions, 670–671
  drug-food interactions, 670–671

efficacy of, 670
pharmacokinetics of, 670
pharmacology and mechanism of action, 670
Calcineurin inhibitors, 733, 1231*t*, 1661. *See also specific agents*
for atopic dermatitis, 1684–1685
for focal segmental glomerulosclerosis, 725–726
for membranous nephropathy, 727–728
for minimal-change nephropathy, 724
for solid-organ transplant recipients, 1481–1485
efficacy of, 1482
pharmacokinetics of, 1482
pharmacology and mechanism of action, 1482
adverse effects of, 1482–1483
concomitant drugs in, 1482*t*
nephrotoxicity of, 1483–1484
adverse effects of, 1483*t*
nephrotoxicity of, 1483*t*
dosing and administration of, 1484
drug-drug interactions, 1484, 1485
drug-food interactions, 1484
drug monitoring in, 1484–1485
therapeutic concentrations, 1484*t*
topical, 1684–1685
Calcipotriol, 1660
Calcitonin, 784, 1552*t*, 1553*t*, 1557–1558
Calcitonin gene-related peptide antagonists, 1000
Calcitriol, 653, 668, 669–670, 669*t*, 1660
Calcium, 1547–1548, 1549*t*
administration of, 1554
adverse events, 1554
dosing and administration of, 1551*t*
efficacy of, 1554
hyperkalemia and, 805*t*
KDIGO monitoring of, 665*t*
monitoring of, 1553*t*
supplementation, 1554

Calcium carbonate, 472*t*, 475*t*, 533, 666
Calcium channel blockers, 657–658, 1001. *See also specific agents*
for acute coronary syndromes, 170*t*, 171, 184*t*
for chronic hearth failure, 204*t*
for heart failure with reduced ejection fraction, 215–216
for hypertension, 95*t*, 96–97
for ischemic heart disease, 150
myocardial infarction and, 171
for NSTE-ACSs, 182*f*
in pregnancy, 100*t*
for pulmonary arterial hypertension, 443–444
for resistant hypertension, 103–104
Calcium citrate, 666
Calcium homeostasis, 1544
Calcium homeostasis disorders, 779–780. *See also specific disorders*
hypercalcemia, 780–785
hypocalcemia, 785–789
Camptothecins, 2195
Campylobacter jejuni, 1925*t*
Campylobacter spp., 1925, 1930*t*, 1935*t*, 2159*t*
Camustine, 2196
Canagliflozin, 1242*t*, 1247
Canakinumab, 1575*t*
Cancer, 2167–2216. *See also specific types*
carcinogenesis in, 2167–2169, 2170*t*
in children, 2176*t*
classification of, by tissue type, 2175*t*
clinical presentation of, 2174–2175
diagnosis of, 2174–2175
screening in, 2174, 2176*t*
staging in, 2175
epigenetic alternations in, 2171, 2172*f*
etiology of, 2167–2171
febrile neutropenia in, 2082–2083
genetic alterations in, 2169–2171
accumulation of, 2170–2171

DNA repair genes, 2170
oncogenes, 2169, 2171*t*
tumor suppressor genes, 2170, 2171*t*
incidence of, 2167, 2169*f*
oncogenes in, 2169, 2171*t*
pain and, 962 (*See also* Pain management)
pain management, 966*f*
pathology of, 2171–2174
cancer growth, 2173–2174
cell cycle in, 2171–2173, 2172*f*
defense systems in, 2173
immune evasion, 2173
invasion and metastasis in, 2174
rheumatoid arthritis treatment in, 1531
seven warning signs of, 2176*t*
in solid-organ transplant recipients, 1494
tumor suppressor genes in, 2170, 2171*t*
Cancer treatment and chemotherapy. *See also* Chemotherapy-induced nausea and vomiting (CINV)
anticancer agents
alkylating agents, 2182*t*–2183*t*, 2195–2196
nitrogen mustards, 2195–2196
nitroureas, 2196
nonclassical, 2196
antimetabolites, 2178–2179, 2192–2193
folate antagonists, 2193–2194
purine analogs, 2193
pyrimidine analogs, 2178–2179, 2192–2193
arsenic trioxide, 2197
asparaginase, 2197
bleomycin, 2197–2198
corticosteroids, 2197
endocrine therapies, 2196–2197
hydroxyurea, 2198
lanreotide, 2198
lenalidomide, 2198

microtubule-targeting, 2180*t*–2181*t*, 2194
eribulin, 2194
estramustine, 2194
ixabepilone, 2194
taxanes, 2194
vinca alkaloids, 2194
mitomycin C, 2198
monitoring of, 2180*t*–2192*t*
omacetaxine mepesuccinate, 2198
pomalidomide, 2198
retinoids, 2198
targeted drugs in, 2198–2204
CDK inhibitors, 2200
thalidomide, 2198
therapeutic radiopharmaceuticals, 2197
ibritumomab tiuxetan, 2197
iobenguane I 131, 2197
lutetium Lu 177 dotatate, 2197
radium-233, 2197
topoisomerase inhibitors, 2181*t*–2182*t*, 2194–2195
anticancer agents, systemic, 2177–2178
antimetabolites, 2178–2179, 2192–2194
biologic therapies in
fusion proteins, 2208
monoclonal antibodies, 2204–2208
chemotherapy, 2178–2198 (*See also* Anticancer agents)
combination therapy in, 2178
dosing and administration of, 2211
goals of, 2176
immunotherapy in, 2208–2209
modalities in, 2175–2176
combined, 2175–2176
monoclonal antibodies
antibody-drug conjugates, 2207–2208
ado-trastuzumab ematansine, 2207
brentuximab vedotin, 2207

gemtuzumab ozogamicin, 2207
inotuzumab ozogamicin, 2207
polatuzumab vedotin, 2207–2208
fusion proteins
moxetumomab pasudotox, 2208
ziv-aflibercept, 2208
targeting B-lymphocyte antigen CD20, 2204–2205
targeting CD38, 2205
targeting CD52, 2205
targeting chemokine receptors, 2205
targeting EGFR
cetuximab, 2206
necitumumab, 2206
panitumumab, 2206
targeting GD2, 2205
targeting PDGFR-α, 2205–2206
targeting SLAMF7, 2206
targeting VEGF
bevacizumab, 2206–2207
ramucirumab, 2207
response criteria in
factors affecting treatment response, 2210–2211
dose intensity, 2210
drug resistance, 2210
molecular biomarkers, 2210–2211
patient-specific factors, 2211
for hematologic malignancies, 2210
for solid tumors, 2209–2210
safety and handling issues in, 2211
supportive care issues in, 2211–2216
cytokine release syndrome, 2215
dermatologic, 2214–2215
alopecia, 2214
extravasation, 2214–2215
hand-and-foot syndrome, 2215
hand-foot skin reaction, 2215

rash, 2215
endocrine
blood glucose dysregulation, 2215
hypothyroidism, 2215
gastrointestinal, 2214
hematologic, 2212–2214
anemia, 2212
neutropenia, 2212–2214
thrombocytopenia, 2214
hypertension, 2215–2216
immune-related adverse events, 2215
ocular, 2216
survivorship, 2216
infertility, 2216
secondary malignancies, 2216
thrombosis, 2216
systemic therapies in, 2177–2178
chemotherapy in, 2177
combination therapy in, 2178
immunotherapy in, 2178
targeted drugs in, 2177–2178
targeted drugs in, 2177–2178
ALK Inhibitors, 2199
alectinib, 2199
brigatinib, 2199
ceritinib, 2199
crizotinib, 2199
lorlatinib, 2199
BCL-2 inhibitors, 2199
BCR-ABL inhibitors, 2199–2200
bosutinib, 2199–2200
dasatinib, 2199–2200
imatinib, 2199
nilotinib, 2199–2200
ponatinib, 2200
BRAF inhibitors, 2200

BTK inhibitor, 2200
DNA methyltransferase inhibitors, 2200
EGFR pathway inhibitors, 2200–2201
  afatinib, 2200–2201
  dacomitinib, 2200–2201
  erlotinib, 2200
  gefitinib, 2201
  lapatinib, 2201
  neratinib, 2201
  osimertinib, 2201
FGFR inhibitor, 2201
FLT3 inhibitors, 2201
HDAC inhibitors
  belinostat, 2201
  panobinostat, 2201
  romidepsin, 2201
  vorinostat, 2201
Hedgehog pathway inhibitors, 2201–2202
IDH inhibitors, 2202
JAK inhibitor, 2202
lanreotide, 2198
lenalidomide, 2198
MEK inhibitor, 2202
mTOR pathway inhibitors, 2202
  everolimus, 2202
  temsirolimus, 2202
multikinase inhibitors, 2202–2203
  axitinib, 2202
  cabozantinib, 2202–2203
  lenvatinib, 2203
  pazopanib, 2202
  regorafenib, 2203
  sorafenib, 2202
  sunitinib, 2202
  vandetanib, 2203
PARP inhibitor, 2203

PI3K inhibitor, 2203
pomalidomide, 2198
proteasome inhibitors, 2203–2204
bortezomib, 2203–2204
carfilzomib, 2204
ixazomib, 2204
TRK inhibitor, 2203
Candida albicans, 2008, 2026, 2047*t*, 2049, 2061, 2082. *See also* Endocarditis, infective
Candida glabrata, 2047*t*, 2049
Candida guilliermondii, 2049
Candida krusei, 2047*t*, 2049
Candida lusitaniae, 2047*t*
Candida parapsilosis, 2047*t*
Candida spp. infections, 2008–2009, 2026, 2046, 2047*t*, 2082
acute hematogenously disseminated candidiasis, 2061–2065
candidemia, 2061–2065
pathophysiology of, 2061
Candida tropicalis, 2047*t*, 2049
Candidal leukoplakia, 2031*t*
Candidemia, 2061–2065
clinical presentation of, 2061–2062
epidemiology of, 2061
laboratory tests for, 2061–2062
pathophysiology of, 2061
patient care process for, 2051*b*
risk factors for, 2062*t*
treatment of, 2062–2065
antifungal therapy for specific Candida species, 2063
antifungal therapy in non-neutropenic patients, 2063, 2064*t*–2065*t*
empirical therapy for febrile neutropenic patients, 2064–2065
empirical therapy in, 2063
hematogenous candidiasis, 2062
in immunocompromised patients, 2063–2064
in nonimmunocompromised patients, 2062–2063
prophylaxis, 2062–2064

specific therapy in, 2065
Candidiasis. *See also specific types*
mucosal, 2033*t*
oropharyngeal and esophageal, 2028–2036 (*See also* Oropharyngeal and esophageal candidiasis)
vulvovaginal, 2025–2028
Candidosis. *See* Oropharyngeal and esophageal candidiasis
Candiduria, 2065–2066
Cangrelor, 174*t*, 175*t*, 176–177
Canker sores, e35
Cannabidiol, 894*t*–895*t*
Cannabinoid hyperemesis syndrome, 1062
Cannabinoids, 533*t*, 534–535, 1061
Cannabinoids, synthetic, 1061–1062
Cannabis, 871*t*, 973, 1044
Cannabis extract, 870
Cannabis use disorder, 1062
Cap-dependent endonuclease inhibitors, 1850
Capecitabine, 2179, 2180*t*, 2249*t*, 2288, 2290*t*, 2358*t*
Capreomycin
adverse effects and monitoring of, 1919*t*
dosing of, 1914*t*
for tuberculosis, 1913*t*, 1914*t*
Capsaicin, 1507
adverse effects of, 1511
dosing and administration of, 1504*t*, 1511
for osteoarthritis, 1507*t*, 1511
pharmacology and mechanism of action, 1511
topical, 974*t*
Capsid inhibitors, 2154
Capsule colonography, 2281
Carbachol, 1600*t*, 1603
Carbamazepine, 969*t*
adverse effects of, 891*t*, 1159*t*
for bipolar disorder, 1159*t*
dosing and administration of, 1154*t*, 1159*t*

drug interactions, 891*t*, 1159*t*
for epilepsy, 889, 897
for ischemic heart disease, 152
mechanism of action, 890*t*
for multiple sclerosis, 869*t*
pharmacokinetics of, 890*t*–891*t*
Carbanilides, 1645
Carbapenems. *See also specific agents*
adverse effects and monitoring of, 1777*t*
for cellulitis, 1868
dosing of, 1819*t*
for pneumonia, 1819*t*
for UTIs, 1963*t*
Carbidopa/L-Dopa, 952–955, 952*t*, 953*t*
Carbohydrates, in enteral nutrition, 2521
Carbonic anhydrase inhibitors, 1600*t*, 1602
Carboplatin, 2182*t*, 2196, 2249*t*, 2263*t*, 2356*t*, 2358*t*, 2359*t*, 2454*t*
Carbuncles, 1857–1859
clinical presentation of, 1857*b*
definition of, 1857
etiology of, 1857
treatment of, 1859
evidence-based, 1860*t*
outcomes of
desired, 1857–1858
therapeutic, evaluation of, 1859
pharmacologic, 1859, 1862*t*
Carcinogenesis, 2167–2169. *See also* Cancer
Carcinoma, adrenal, 1301
Cardiac arrest, 325–328
clinical presentation of, 326*b*
drug administration for, 337
epidemiology of, 325
etiology of, 326–327
pathophysiology of, 326
patient care process for, 327*b*

postcardiac arrest syndrome, 334*t*
postresuscitative care in, 334–335
treatment of, 326–337
acid-base, 334
advanced cardiac life support, 329, 329*f*
in anaphylaxis, 336
in asthma, 335
basic life support, 328–329, 328*f*
cardiocerebral resuscitation, 330
cardiopulmonary resuscitation, 326–327
in drowning, 337
in electrocution/lightning, 337
evidence-based, 332*t*
general approach to, 326–330
in hypothermia, 336
outcome of
desired, 326
evaluation of, 337–338
in pregnancy, 336
for pulseless electrical activity and asystole, 333–334, 333*f*
nonpharmacologic therapy in, 333
pharmacologic therapy in, 333–334
in trauma, 336–337
for ventricular fibrillation/pulseless ventricular tachycardia, 27–32 (*See also* Ventricular fibrillation), 330–333
antiarrhythmics, 331–333
magnesium, 332*t*, 333
nonpharmacologic therapy in, 330
pharmacologic therapy in, 330–333
sympathomimetics, 330–331
thrombolytics, 333
vasopressin, 331
Cardiac catheterization, e81
Cardiac device infective endocarditis (CDIE). *See also* Endocarditis, infective
definition of, 1883
epidemiology of, 1883–1884

etiology of, 1883–1884
pathophysiology of, 1885
Cardiac enzymes, 164–166
Cardiac output, 85
Cardiac remodeling, 195, 196*f*
Cardiocerebral resuscitation, 330
Cardiomyopathy, 1108–1109
Cardiopulmonary exercise testing, e369
Cardiopulmonary resuscitation, 326–327
Cardiothoracic surgery, antimicrobial prophylaxis in, 2118*t*, 2120–2121
Cardiovascular disease (CVD), e81
in chronic kidney disease, 671–672, 672*f*
death rate of, 137
epidemiology of, 137
in menopausal hormone therapy, 1369–1370
solid-organ transplant recipients, infections in, 1492–1493
Cardiovascular testing, e81
cardiac catheterization in, e81
computed tomography in, e81
echocardiography in, e81 (*See also* Echocardiography)
electrocardiography in, e81 (*See also* Electrocardiography (ECG))
exercise stress testing in, e81
magnetic resonance imaging, e81
stress testing, e81
Care plan
development of, 4–5, 5*t*
implementation of, 5, 6*t*
Carfilzomib, 2188*t*, 2204, 2417–2418
Cariprazine, 1096*t*, 1106*t*, 1107*t*, 1115*t*, 1154*t*
Carisoprodol, 971, 972*t*
Carmustine, 2454*t*
Carnitine, 2481
Carteolol, 1600*t*
Cartilage
normal, 1499–1500
osteoarthritic, 1500, 1500*f*

Carvedilol, 684
Caspofungin
  for aspergillosis, 2069
  for febrile neutropenia, 2093*t*
  for oropharyngeal candidiasis, 2033*t*
  for peritonitis, 692*t*
Catagen phase, 1692, 1694*t*
Cataplexy, 1208
Catecholamine vasopressors, 349*f*
Catecholamines, 289
Cathine, 1060
Cathinones, synthetic (bath salts), 1060
Cattechol-*O*-Methyltransferase inhibitors. *See* COMT inhibitors
CDK inhibitors, 2185*t*, 2200
Cefaclor, 1963*t*
Cefadroxil, 1836*t*, 1869
Cefazolin, 1947*t*
Cefdinir, 1869
  for acute otitis media, 1830*t*
Cefepime
  for cystic fibrosis, 454*t*
  dosing by age group, 1799*t*
  for febrile neutropenia, 2092*t*
  for UTIs, 1963*t*
Cefotaxime, 1799*t*
  for acute bacterial rhinosinusitis, 1833*t*
  dosing and administration of, 1833*t*
  for intra-abdominal infection, 1947*t*
Cefoxitin, 1947*t*
Cefpodoxime, 1830*t*
Cefpodoxime-proxetil, 1869, 1963*t*
Cefprozil, 1869
Ceftaroline, 1792, 1867, 1869, 2092*t*
Ceftazidime, 1963*t*, 2086
  for cystic fibrosis, 454*t*
  dosing by age group, 1799*t*

for febrile neutropenia, 2092*t*
for UTIs, 1963*t*
Ceftazidime-avibactam, 2092*t*
Ceftolozane, 2086
Ceftolozane-tazobactam, 2092*t*
Ceftozolane, 1963*t*
Ceftriaxone, 1760, 1799*t*, 1963*t*
for acute bacterial rhinosinusitis, 1833*t*
for acute otitis media, 1830*t*
dosing and administration of, 1833*t*
for gonorrhea, 1978, 1980*t*
for intra-abdominal infection, 1947*t*, 1949
for syphilis, 1982
Cefuroxime
for acute otitis media, 1830*t*
for intra-abdominal infection, 1947*t*
Celecoxib, 1504*t*, 1509, 1574*t*. *See also* Cyclooxygenase 2 (COX-2) selective inhibitor
Celiac disease, 615–618
classification of, 618
clinical presentation of, 617–618
common misdiagnoses, 618*t*
definition of, 615
diagnosis of, 617–618
epidemiology of, 616
etiology of, 616
gluten and, 616
history of, 615
mnemonic for, 618*t*
pathophysiology of, 616–617, 617*t*
patient care process for, 619*b*
prevalence of, 615
signs and symptoms of, 617, 617*t*
Celiac disease treatment, 618–620
general approach to, 618
nonpharmacologic therapy in, 618–620

outcomes of
desired, 618
evaluation of, 620
pharmacologic therapy in, 620
Celiac sprue. *See* Celiac disease
Cell cycle, 2171–2173, 2172*f*
Cellulitis, 1856*t*, 1866–1869
clinical presentation of, 1867*b*
etiology of, 1866
nonpurulent, 1867
purulent, 1867
treatment of
algorithm for, 1868*f*
evidence-based, 1860*t*
nonpharmacologic therapy in, 1866–1869
outcomes of
desired, 1866
therapeutic, evaluation of, 1869
pharmacologic therapy in, 1862*t*, 1866–1869
Cemiplimab, 2191*t*, 2208
Center for Medicare and Medicaid Services (CMS), 7
Centers for Disease Control and Prevention (CDC), e9
opioid prescribing guidelines, 1046*t*
Central nervous system (CNS)
anatomy and physiology of, 1786–1787, 1786*f*
blood-brain barrier/blood-CSF barrier, 1787, 1787*f*
cerebrospinal fluid, 1787, 1787*t*
meninges, 1786
antipsychotics, adverse effects of, 1109–1112
extrapyramidal system, 1109, 1110*t*
akathisia, 1110
dystonia, 1109
pseudoparkinsonism, 1110
tardive dyskinesia, 1110–1111
neuroleptic malignant syndrome, 1111–1112
psychiatric, 1112

seizures, 1111
thermoregulation, 1111
pathophysiology of, 1787–1788, 1788*f*
Central nervous system (CNS) infection, 1785–1789
brain abscess in, 1795–1796
clinical presentation and diagnosis of, 1788–1789
laboratory tests, 1789
signs and symptoms of, 1788–1789
epidemiology of, 1786
etiology of, 1786
patient care process for, 1790*b*
Central nervous system (CNS) infection treatment, 1789–1800
acute bacterial meningitis, 1791–1794
bacterial brain abscess, 1795–1796
by causative organisms, 1791–1794, 1797–1800
Acinetobacter, 1795
Bacillus anthracis, 1797–1798
Borrelia burgdorferi (Lyme disease), 1798
Haemophilus influenzae type b, 1793
Listeria monocytogenes, 1794
Lyme disease, 1798
Mycobacterium tuberculosis (tuberculous meningitis), 1798
Neisseria meningitidis, 1793
nocardia, 1798
primary amoebic meningoencephalitis, 1798–1800
Pseudomonas aeruginosa, 1794
Streptococcus agalactiae, 1793–1794
Streptococcus pneumoniae, 1791–1793, 1792*t*
Toxoplasma gondii, 1799–1800
Treponema pallidum (neurosyphilis), 1797
dexamethasone as adjunct in, 1798
general approach to, 1789–1791, 1791*t*
health-care associated ventriculitis and meningitis, 1794–1795
nonpharmacologic therapy in, 1789–1791
outcomes of
desired, 1789

therapeutic, evaluation of, 1800
pharmacologic therapy in
antimicrobial agent CSF penetration in, 1789, 1791*t*
drug dosing by age group in, 1799*t*
first- and alternative-choice agents in, 1792*t*
supportive therapy, 1789–1791
viral encephalitis, 1796–1797
Central papillary atrophy, 2031*t*
Central sleep apnea, 1206, 1207
Central α_2-agonists, 107
Cephalexin, 1811*t*, 1836*t*
Cephalosporins, 1793, 1963*t*. *See also specific agents*
adverse effects and monitoring of, 1777*t*
allergic reactions to, e1471
dosing of, 1819*t*
drug interactions, 1775*t*
for febrile neutropenia, 2086
for intra-abdominal infection, 1949
for peritoneal dialysis patients, 691*t*
for pneumonia, 1819*t*
resistance to, 2114
Ceramide, 1682
Cerebrospinal fluid, 1787, 1787*t*
CerefolinNAC, 846
Ceritinib, 2184*t*, 2199
Certolizumab, 516*t*, 519, 521, 523*t*, 1525*t*, 1528
Certolizumab pegol, 516
Cervical cap, 42*t*, 44, 45
Cervical ripening, 1329
Cervicitis, 1977*t*
Cesarean section, antimicrobial prophylaxis in, 2117*t*, 2119–2120
Cetuximab, 2190*t*, 2206, 2291*t*, 2294*t*
Challenging behaviors, 1216, 1218–1219
Chancroid, 1991*t*
Chemokine receptors, 2205

Chemoprevention, 2258
Chemoreceptor trigger zone, 529–530
Chemotherapy-induced nausea and vomiting (CINV), 536–537
  categories, 536
  in children, 540
  prophylaxis of
    for acute CINV, 536–537
    for anticipatory CINV, 537
  treatment of
    antiemetic use, principles of, 536
    for breakthrough CINV, 537
    for refractory CINV, 537
    for multi-day chemotherapy, 537
Chest pain, in ischemic heart disease, 140–142, 141*t*
Child-Pugh scoring system, 564, 565, 565*t*
Children. *See also* Pediatrics
  acne vulgaris in, 1634–1635
  alopecia in, 1696–1697, 1697*t*
  alopecia treatment in, 1701
  bipolar disorder treatment in, 1161
  chemotherapy-induced CINV in, 540
  cholesterol classifications in, 124*t*
  cystic fibrosis in, 457
  definition of, e61
  dehydration in, 1928*t*
  depressive disorders in, 1142
  diabetes mellitus, screening for, 1236
  diabetes mellitus treatment, 1257
  epilepsy treatment in, 906
  gastroenteritis in, 540
  generalized anxiety disorder treatment, 1177
  with GERD, 478, 478*t*
  hypertension treatment in, 100
  obsessive-compulsive disorder in, 1197
  pain management in, 981
  posttraumatic stress syndome in, 1194

psoriasis and, 1669
social anxiety disorder treatment in, 1183
thyrotoxicosis treatment in, 1279
tuberculosis treatment in, 1912
venous thromboembolism and, 259–261
Chills, 682*t*
Chimeric antigen receptor therapies, 2192*t*, 2209, 2374
Chinese herbal therapy, 1686
Chlamydia, 1322, 1323*t*
Chlamydia pneumoniae, 1751, 1783
Chlamydia trachomatis, 1983–1985
clinical presentation of, 1984, 1984*t*
diagnosis of, 1984
epidemiology of, 1983–1984
etiology of, 1983–1984
pathophysiology of, 1984
treatment of, 1984–1985, 1985*t*
outcomes, evaluation of, 1985
Chlamydia trachomatis, 1783
Chlamydophila pneumoniae, 1820*t*
Chloracne, 1628
Chlorambucil, 724, 2182*t*
Chloramphenicol
adverse effects and monitoring of, 1777*t*
drug interactions, 1775*t*
Chlordiazepoxide
for alcohol withdrawal, 1072, 1073*t*
for generalized anxiety disorders, 1171*t*, 1175*t*, 1177
Chlorhexidine, 1645
Chloroprocaine, 981*t*
Chloroquine, 1461–1463
Chlorpromazine, 534*t*, 999, 1096*t*, 1105*t*, 1106*t*, 1107*t*. *See also* Antipsychotics
Chlorpropamide, 1242*t*, 1243
Chlorthalidone, 94
Chlorzoxazone, 971–972, 972*t*
Cholecalciferol, 668, 669*t*

Cholecystitis, 1753
Cholecystokinin (CCK), 2515t, 580
Cholelithiasis, 1753
Cholera, 1924. *See also* Gastrointestinal infection
Cholesterol, 119. *See also* Lipoproteins
  absorption and transportation of, 118*f*
  biosynthetic pathway, 120*f*
  brain vascular disease and, 837
  classification of, 124*t*
  synthesis of, 119
Cholesterol emboli, 712
Cholinergic agents, 869
Cholinergic agonists, for open-angle glaucoma, 1600*t*
Cholinergic hypothesis, 837
Cholinergics, 1603
Cholinesterase inhibitors, 842–843, 844, 844*t*, 847, 1600*t*. *See also specific agents*
Chondroitin, 1512
Choroidal neovascularization, 1607
Chromium, 2477*t*, 2478
Chronic autoimmune thyroiditis, 1280–1281
Chronic bronchitis, 406, 1805–1810
  clinical presentation of, 1806–1807, 1808*t*
  epidemiology of, 1805–1806
  etiology of, 1805–1806
  pathogenesis of, 1806
  treatment of, 1807–1810
    desired outcome in, 1807
    general approach to, 1807
    pharmacologic therapy in, 1807–1810, 1809*f*, 1811*t*
Chronic diseases, in older adults, e67
Chronic heart failure. *See* Heart failure (HF), chronic
Chronic hyperglycemia, e33
Chronic inflammatory disorders, 133
Chronic kidney disease (CKD), 647–655
  anemia of, 651–652, 654–655

classification of, 647, 649*f*
clinical presentation of, 654–655, 654*b*
complications in hemodialysis, 683
complications of, 648–649, 649*t*, 671–673
cardiovascular disease, 671–672, 672*f*
hyperlipidemia, 132–133, 672
definition of, 647
diagnosis of, 654–655
for anemia of CKD, 654–655
for CKD-MBD, 655
epidemiology of, 649–650
etiology of, 650–651
diabetes mellitus, 651
hypertension, 651
obesity, 651
proteinuria, 651
smoking, 651
mineral and bone disorder in, 652–654, 653*f*, 655
osteoporosis treatment and, 1560–1561
pathophysiology of, 651–654, 652*f*
patient care process for, 648*b*
pharmacokinetic changes in, 740–741
prevalence of, 650, 650*f*
prognosis of, 647–648
risk factors for, 650–651, 650*t*
Chronic kidney disease (CKD) treatment, 739–751
for anemia of CKD, 658–664, 659*t*
algorithm for, 664*f*
erythropoiesis stimulating agents in, 659*t*
nonpharmacologic therapy, 659
outcomes of, desired, 658–659
pharmacoeconomic considerations in, 671
pharmacologic therapy, 659–664
erythropoiesis-stimulating agent therapy, 662–664, 662*t*
hypoxia-inducible factor inhibitors, 664–665
iron supplementation, 660–662, 661*t*

transfusions and adjunct therapies, 665
target hemoglobin in, 659
for CKD-MBD, 665–673
nonpharmacologic therapy, 666
dialysis, 666
dietary phosphorus restriction, 666
parathyroidectomy, 666
outcomes of, desired, 665–666
pharmacoeconomic considerations in, 671
pharmacologic therapy, 666–671
calcimimetics, 670–671
phosphate-binding agents, 666–668, 667*t*
vitamin D therapy, 668–670
general approach to, 655–656
hypertension treatment in, 98–99
KDIGO guidelines in, 656*t*, 659*t*, 665*t*
nonpharmacologic therapy in, 656
outcomes of
desired, 655
therapeutic, evaluation of, 658, 665
pharmacologic therapy in, 656
for diabetes, 658
for hypertension, 657*f*, 658
for proteinuria, 656–658
statins in, 672–673
recommendations, 655*t*
Chronic kidney disease (CKD) treatment, drug individualization therapy in, 739–751
drug dosing regimen in, 744–747, 744*t*, 745*t*, 746*f*, 746*t*, 747*t*
information resources in, 744
in renal replacement therapy, 747–750
hemodialysis, 748–750, 749*b*
peritoneal dialysis, 748
kidney function evaluation in, 743–744
pharmacodynamics of, 743–747
pharmacokinetic changes in CKD, 740–741

drug absorption, 740
drug distribution, 740–741, 740*t*
altered tissue binding in, 741
plasma protein binding in, 741
V_D calculation method, 741
drug elimination, 741–743
CYP 450 enzyme activity, 741–743
metabolite accumulation, 743
nonrenal clearance, 742–743, 742*t*
renal clearance, 741–742
Chronic lymphocytic leukemia, 2396–2404
clinical presentation of, 2398*b*
epidemiology of, 2396
etiology of, 2396
pathophysiology of, 2396–2398
patient care process for, 2397*b*
staging and prognosis in, 2398
treatment of, 2398–2404, 2399*f*, 2400*t*
biologic therapy in, 2399–2400
combination therapy in, 2401–2404
cytotoxic chemotherapy in, 2399
alkylating agents, 2399
purine analogs, 2399
dosing of, 2402*t*
hematopoietic stem cell transplantation, 2404
intramuscular immunoglobulin in, 2138
monitoring of, 2403*t*
outcomes of
desired, 2398–2399
therapeutic, evaluation of, 2404
targeted therapy in, 2400–2401
Chronic myeloid leukemia, 2387–2396
clinical presentation of, 2389–2390
criteria for phases of, 2389*t*
epidemiology of, 2388

etiology of, 2388
pathophysiology of, 2388, 2388*f*
patient care process for, 2391*b*
prognosis of, 2390
treatment of, 2390–2396, 2392*t*
chemotherapy in, 2390
hematopoietic stem cell transplantation, 2396
imatinib mesylate, 2391–2393
accelerated phase/blast crisis, 2393
adverse effects and drug interactions, 2393
chronic phase, 2391–2393
monitoring, 2393
resistance to, 2393
interferon alfa, 2390–2391
omacetaxine, 2396
outcomes of
desired, 2390
therapeutic, evaluation of, 2396
tyrosine kinase inhibitors, 2393–2395
discontinuation, 2396
dosing and administration of, 2392*t*
monitoring of, 2394*t*
Chronic obstructive pulmonary disease (COPD), 405–410
vs. asthma, 407*t*
classification based on severity, 410
clinical presentation of, 408–409, 409*b*, 410*t*
definition of, 405
differential diagnosis of, 407
economic impact of, 410
epidemiology of, 406, 406*f*
etiology of, 406–407, 408*t*
etiology of airflow limitation in, 408*t*
incidence of, 406
mortality rate, 406
pathogenesis of, 408*f*
pathophysiology of, 407–410

pathophysiology of exacerbation in, 408
patient care process for, 411*b*
postbronchodilator testing, 409*t*
prognosis of, 410, 412*t*
risk factors for, 406–407, 407*t*
spirometric grades, 409*t*
Chronic obstructive pulmonary disease (COPD) treatment, 410–422
complications of, 421–422
cor pulmonale, 421–422
polycythemia, 422
pulmonary hypertension, 421
surgical interventions in, 422
discharge, preparation for, 424–426, 425*t*
end-of-life care in, 426
for exacerbations, 422–424, 422*t*, 424*t*
assessment of, 423*t*
classification of, 423*t*
clinical presentation of, 422*b*
nonpharmacologic therapy in
controlled oxygen therapy, 423
noninvasive mechanical ventilation, 423–424
outcomes of, desired, 423
pharmacologic therapy in
antimicrobial therapy in, 424, 425*t*
bronchodilators, 424
corticosteroids, 424
prognosis, 422–423
staging, 422*t*
general approach to, 411
goals of, 412*t*
monitoring of, 658*t*
nonpharmacologic therapy in, 411–414
adjunctive, 414
immunizations, 414
immunotherapy in, 414
oxygen therapy, long-term, 413–414

pulmonary rehabilitation, 413
smoking cessation, 412–413, 413*t*
outcomes of
desired, 410–411
therapeutic, evaluation of, 426
palliative care, 426
pharmacologic therapy in, 414–421, 415*t*, 416*t*–417*t*
α_1-antitrypsin replacement therapy, 421
azithromycin, 420–421
bronchodilators, 414–420
long-acting, 417–418
short-acting, 415–417
corticosteroids, 419–420
expectorants, 421
investigational drugs, 421
methylxanthines, 418–419
mucolytics, 421
opioids, 421
phosphodiesterase inhibitors, 420
Chronic pain, 961–962, 962*b*, 962*t*, 963, 1046*t*
Chronic pancreatitis, 587–589
clinical course and prognosis of, 588–589
clinical presentation of, 579, 587
diagnosis of, 588, 588*t*
etiology of, 587, 588*t*
incidence of, 579
pathophysiology of, 587
prevalence of, 579
risk factors for, 588*t*
signs and symptoms of, 588*t*
stages of, 587
Chronic pancreatitis treatment, 589–592
analgesics in, 590
general approach to, 589, 589*f*
nonpharmacologic therapy in, 589

outcomes of
desired, 589
evaluation of, 592
pharmacologic therapy in, 589–592, 590*t*
abdominal pain relief in, 590–591
analgesics in, 590
enzyme therapy, adjuncts to, 592
malabsorption treatment in, 590*f*, 591–592
pancreatic enzymes, 590, 591, 591*t*
recommendations, 589–590, 590*t*
Chronic urinary retention, 1435*b*
Chymotrypsinogen, 2515*t*
Ciclesonide, 383*t*
Ciclopirox, 2039
Cigarette smoking. *See* Smoking
Cimetidine, 472*t*, 473*t*, 475*t*, 476, 494*t*, 499, 502, 502*t*, 534*t*
Cinacalcet, 785
Ciprofloxacin
for acne vulgaris, 1641
for chronic bronchitis, 1811*t*
for cystic fibrosis, 454*t*
dosing by age group, 1799*t*
drug interactions, 1775*t*
for febrile neutropenia, 2092*t*
for inflammatory bowel disease, 515
for intra-abdominal infection, 1947*t*
for peritonitis, 692*t*
for urinary tract infections, 1963*t*
for UTIs, 1963*t*
Circadian rhythm disorders, 1209–1211
jet lag, 1209–1210
periodic limb movements of sleep, 1211
restless legs syndrome, 1210, 1210*t*, 1211*t*
shift work sleep disorder, 1210
treatment of, 1210–1211
pharmacologic therapy in, 1210–1211

Circulating recombinant forms, 2145
Cirrhosis, 561–566
anatomic and physiologic effects of, 563–564
ascites, 563
coagulation defects, 564
hepatic encephalopathy, 563–564
portal hypertension and varices, 563
associated conditions, 561
causes of, 561
clinical presentation of, 564–566, 564*b*
endoscopic and radiographic abnormalities, 566
liver biopsy, 566
liver chemistries, 564–566
albumin and coagulation factors, 565
alkaline phosphatase and γ-glutamyl transpeptidase, 565
aminotransferases, 564–565
bilirubin, 565
biopsy, 566
Child-Pugh classification, 565, 565*t*
imaging, 566
MELD score, 565
thrombocytopenia, 566
complications in, systemic, 573–574
complications of, 562
definition of, 561
epidemiology of, 561–562
etiology of, 562*f*
in hepatitis B, 601, 601*t*
in hepatitis C, 606
hepatopulmonary syndrome in, 574
hepatorenal syndrome in, 574
pathophysiology of, 562–563, 562*f*
patient care process for, 568*b*
prevalence of, 561
in sickle cell disease, 1753
Cirrhosis treatment, 566–574

altered drug pharmacokinetics and pharmacodynamics, 574
for ascites and spontaneous bacterial peritonitis, 570–572
ascites treatment in, 570–571
diuretic therapy in, 571
peritonitis treatment in, 571
recommendations, 571–572, 572*t*
drug monitoring in, 575*t*
general approach to, 566
for hepatic encephalopathy, 572–573, 573*t*
drugs and neurotransmission in, 573
grading in, 572, 573*t*
hyperammonemia, 572–573
recommendations in, 573
recurrent, 572
liver transplantation in, 574
outcomes of
desired, 566
evaluation of, 574
for portal hypertension and variceal bleeding, 566–567
systemic complications in, 573–574
for variceal hemorrhage, acute, 567–570
drug therapy in, 569–570
endoscopic interventions, 568–569
interventional and surgical, 569
octreotide, 567–568
sclerotherapy and bind ligation, endoscopic, 568–569
secondary prophylaxis, 569, 570
secondary prophylaxis in variceal bleeding, 569–570
somatostatin, 567
spontaneous bacterial peritonitis, prevention of, 568
Cisplatin, 2182*t*, 2196, 2356*t*, 2358*t*, 2359*t*
nephrotoxicity, 702
clinical presentation of, 702
incidence of, 702
management, 702
pathogenesis of, 702

prevention of, 702
risk factors for, 702
Citalopram, 1037, 1133*t*, 1135*t*, 1138*t*, 1140*t*, 1144*t*, 1178*t*. *See also* Selective serotonin reuptake inhibitors (SSRIs)
in menopause and perimenopausal/postmenopausal hormone therapy, 1376*t*
for obsessive-compulsive disorder, 1197*t*
for social anxiety disorder, 1182*t*
Cladribine, 2180*t*, 2193
Clarithromycin, 493, 495, 1811*t*, 1836*t*
Clearance, e15
Clevidipine, 110*t*, 111
Clindamycin, 1645, 1869
for acne vulgaris, 1636*t*, 1641
for acute bacterial rhinosinusitis, 1833*t*
for acute otitis media, 1830*t*
for acute pharyngitis, 1836*t*
adverse effects and monitoring of, 1778*t*
dosing and administration of, 1833*t*
for febrile neutropenia, 2094*t*
Clinical breakpoints, 2046, 2047*t*, 2049*t*
Clinical coding systems, 7*t*
Clinical Opiate Withdrawal Scael (COWS), 1048
Clinical resistance, 2046
Clobazam
advantages and disadvantages of, 890*t*
adverse effects of, 891*t*, 895*t*
drug interactions, 891*t*, 895*t*
for epilepsy, 894*t*–895*t*
mechanism of action, 890*t*, 894*t*
Clofarabine, 2180*t*, 2374
Clofazimine, 1917
Clomipramine
for menstruation-related disorders, 1342*t*
for obsessive-compulsive disorder, 1196, 1197*t*, 1198*t*
Clonazepam, 869*t*, 890*t*–891*t*, 1171*t*, 1175*t*, 1178*t*, 1182*t*
drug interactions, 891*t*

for epilepsy, 889
Clonic seizure, 881. *See also* Epilepsy
Clonidine
for ADHD, 1019–1020
adverse effects of, 1020*t*
for autism spectrum disorder, 1224*t*
dosing, 1020*t*, 1073*t*
in menopause and perimenopausal/postmenopausal hormone therapy, 1376*t*
for nicotine cessation, 1083
in pregnancy, 100*t*
Clopidogrel, 174*t*, 175*t*
in acid suppression therapy, 476
for acute coronary syndromes, 175–176, 175*t*
co-administration of NSAIDs, 486
for ischemic stroke, 280
for peptic ulcer disease, 498
proton pump inhibitors and, 498
Clorazepate, 1171*t*, 1175*t*
Clostridial myonecrosis, 1870
Clostridium botulinum, 1935*t*
Clostridium difficile infection, 1932–1933. *See also* Gastrointestinal infection
clinical presentation of, 1932
epidemiology of, 1932
etiology of, 1930
pathophysiology of, 1932
patient care process for, 1929*b*
treatment of, 1932–1933, 1933*t*
Clostridium perfringens, 1935*t*
Clostridium spp., 2008
Clotrimazole
for febrile neutropenia, 2092*t*
for oropharyngeal candidiasis, 2033*t*
for vulvovaginal candidiasis, 2027, 2027*t*
Clozapine, 1096*t*, 1103. *See also* Antipsychotics
adverse effects of, 1107*t*
drug interactions, 1116*t*

mechanism of action, 1105*t*
pharmacokinetics of, 1106*t*
Cluster headache, 1002–1003. *See also* Cluster headache treatment
clinical presentation of, 1002
diagnosis of, 992*t*
epidemiology of, 1002
pathophysiology of, 1002
Cluster headache treatment, 1002–1003
abortive therapy in, 1002–1003
ergotamine derivatives, 1003
oxygen, 1002
triptans, 1002–1003
outcomes of
desired, 1002
therapeutic, evaluation of, 1003–1004
prophylactic therapy, 1003
corticosteroids, 1003
lithium, 1003
verapamil, 1003
CMV hyperimmune globulin, 2093*t*
CNS depressants. *See* Substance-related disorders; *specific drugs*
Coagulation disorders, 1729–1743. *See also* Hemophilia
complications of replacement therapy in, 1743
diagnosis of, 1729
hemophilia, 1729–1739
clinical presentation of, 1731–1732, 1732*b*
diagnosis of, 1731–1732, 1731*t*
treatment of (*See* Hemophilia treatment)
hemophilia C, 1743
other congenital factor deficiencies, 1743
patient care process for, 1730*b*
von Willebrand disease, 1739–1743, 1739*t*
classification of, 1739–1740, 1740*f*
clinical presentation of, 1740–1741, 1740*b*
diagnosis of, 1740–1741, 1740*f*, 1741*t*
treatment of, 1741–1743, 1742*f*

gene therapy in, 1743
outcomes, evaluation of, 1743
pharmacologic therapy in, 1742–1743
replacement therapy in, 1741–1742, 1742*t*
Coagulation factors, 565, 1729
Coal tar, 1661, 1685
Co-analgesics, 964–965, 969*t*, 970*t*
Cobicistat, 2150*t*
Cobimetinib, 2187*t*, 2202, 2443, 2443*t*, 2445*t*
Cocaethylene, 1059
Cocaine, 1058–1059, 1058*b*
Coccidiodes, 2048*t*
Coccidioides immitis, 2056–2058
Coccidioidomycosis, 2056–2058
clinical presentation of, 2056
CNS infection in, 2056
disseminated, 2056
epidemiology of, 2056
pathophysiology of, 2056
primary, 2056
risk factors for, 2056*t*
signs and symptoms of, 2056–2057
treatment of, 2057–2058
for extrapulmonary (disseminated) disease, 2057–2058
general guidelines in, 2057
goals of, 2057
in HIV patients, 2159*t*
for meningeal disease, 2058
for nonmeningeal disease, 2057–2058
for primary respiratory infection, 2057
for pulmonary cavity infections, 2057
specific agents in, 2057
Codeine. *See also* Opioids
for chronic pancreatitis, 590*t*
dosing and administration of, 977*t*
for pain management, 975*t*, 980

Cognition, lithium toxicity and, 1155
Cognitive behavioral therapy (CBT)
for generalized anxiety disorders, 1169–1170
for obsessive-compulsive disorder, 1195
Cognitive impairment, 950*t*
Cognitive remediation, 1094
Colchicine, 1574*t*, 1576–1578, 1577*t*, 1579*t*
Cold sores, e35
Colectomy, 514
Colesevelam, 1242*t*, 1248
Colipase, 580
Colistimethate, 454*t*
Colistin, dosing by age group, 1799*t*
Colloid carcinoma, 2227
Colonoscopy, 2281
Colorectal cancer, 2273–2284
clinical presentation of, 2282–2284, 2283*b*
diagnosis of, 2282–2284
signs and symptoms in, 2282
workup and imaging in, 2282–2283
epidemiology of, 2274–2275, 2274*f*
etiology and risk factors for, 2275–2277
dietary intake and nutrients, 2276–2277
calcium and vitamin D, 2276
fiber, fruits, and vegetables, 2276
folate and other micronutrients, 2276–2277
red meat, processed meat, and fat, 2276
family history and inherited genetic risk, 2275
adenomatous polyps, 2275
enzyme polymorphism, 2275
hereditary syndromes, 2275
lifestyle factors, 2275–2277, 2276*t*
alcohol use, 2276
NSAID and aspirin use, 2275–2276
obesity and physical inactivity, 2276
postmenopausal hormone replacement therapy, 2276

tobacco use, 2276
personal medical history, 2275
adenomatous polyps, 2275
age, 2275
inflammatory bowel disease, 2275
type 2 diabetes mellitus, 2275
incidence of, 2273
mortality rate, 2273
pathophysiology of, 2277–2280
anatomy and bowel function in, 2277–2278, 2277*f*
genomic instability in, 2278–2279, 2279*t*
growth factor signaling pathways in, 2279–2280
histology in, 2280
oncogenes and tumor suppressor genes in, 2279
tumorigenesis in, 2278, 2278*f*
patient care process for, 2286*b*
prevention of, 2280–2282
chemoprevention in, 2280
surgical resection in, 2280–2281
prognosis in, 2284
screening for, 2281–2282
capsule colonography, 2281
colonoscopy, 2281
computed tomography colonography, 2281
fecal occult blood tests, 2281
flexible sigmoidoscopy, 2281
guidelines for, 2282*t*
serology test, 2281
stool DNA screening tests, 2281
stool DNA screening tests, staging and classification in, 2283, 2284*t*, 2285*f*
Colorectal cancer treatment, 2284–2286
for metastatic disease, initial therapy, 2289–2293
resectable or potentially resectable, 2289–2290
chemotherapy, neoadjuvant and adjuvant, 2288–2289
hepatic-directed therapies, 2289–2290
surgery, 2289

selection of, 2293
unresectable, 2290–2293
chemotherapy, 2290–2292
immunotherapy in, 2290*t*–2291*t*, 2293
targeted therapy, 2292–2293
for metastatic disease, second-line and subsequent therapy, 2293–2296, 2294*t*
chemotherapy, systemic, 2293–2295
immunotherapy in, 2296
targeted therapy, 2295–2296
angiogenesis inhibitors, 2295
BRAF inhibitors, 2295
EGFR inhibitors, 2295
HER2 inhibitors, 2295
MEK inhibitor, 2295
for operable disease, 2285–2289
adjuvant and neoadjuvant therapy for rectal cancer in, 2288–2289
adjuvant therapy for colon cancer in, 2285–2286
chemotherapy, systemic, 2285–2286, 2287*t*
radiation, 2285
selection of, 2288
surgery in, 2285
outcomes of
desired, 2284
therapeutic, evaluation of, 2296
Colorectal carcinoma
risk factors for, 510
screening for, 510
Colorectal surgery, antimicrobial prophylaxis in, 2116–2119
Combined androgen blockade, 2313–2314
Combined hormonal contraceptives (CHCs), 46–58
adverse effects of, 52, 1358*t*
breast cancer from, 53
classification of, 50*t*
diabetes mellitus from, 53
dyslipidemia from, 53
for endometriosis, 1357, 1358*t*

estrogens, 46
hypertension from, 53
migraine headaches from, 53
with obesity, 54
progestins, 46
selection of, 46–48
smoking and, 52–53
STDs and, 51
with systemic lupus erythematosus, 54
thromboembolism from, 53–54
in women older than 35 years, 52
Community-acquired pneumonia, 1813, 1813*t*, 1816
Community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA), 1856
Complementary and alternative medicine (CAM)
for acne vulgaris, alternative, 1633–1634
for multiple sclerosis, 870, 871*t*
for psoriasis, 1668–1669
for systemic lupus erythematosus, 1464–1465
Computed tomography colonography, 2281
Computed tomography (CT), in cardiovascular testing, e81
COMT inhibitors, 952*t*, 953*t*, 955–956
Condoms, 42*t*, 44
Conduct disorder (CD), 1022
Congeners, 976–980
Congenital adrenal hyperplasia, 1307, 1308*t*
Congenital hypothyroidism, 1281, 1286
Congenital syphilis, 1981
Conjugated estrogens, 1342*t*, 2246*t*
Constipation, 550–552
causes of, 550, 550*t*
clinical presentation of, 551–552, 552*t*
definition of, 550
disordered defecation in, 550
drug-induced, 550–551, 551*t*
epidemiology of, 550

incidence of, 550
normal transit, 550
in Parkinson disease, 950*t*
pathophysiology of, 550
patient care process for, 551*b*
prevalence of, 550
prevention of, 555
primary, 550
Rome criteria, 551
secondary, 550
slow transit, 550
Constipation treatment, 552–556
general approach to, 552, 553*f*
nonpharmacologic therapy in, 552–553
biofeedback in, 553
dietary modification in, 552
electrical stimulation in, 553
surgery in, 553
outcomes of
desired, 552
evaluation of, 556
pharmacologic therapy in, 553–554, 554*t*
alvimopan, 555
bulk-forming agents, 553, 554*t*
emollient laxatives, 553–554
glycerin, 554
hyperosmolar agents, 554
intestinal secretagogues in, 554, 555
lactulose, 554
linaclotide, 554, 555
lubiprostone, 555
magnesium salts, 554
methylnaltrexone, 555
naldemedine, 555
naloxegol, 555
opioid receptor antagonists, 554, 554*t*, 555

plecanatide, 554, 555
polyethylene glycol, 554
probiotics, 555
prucalopride, 555
sorbitol, 554
stimulant laxatives, 554
Contact dermatitis, e1707
Contact eczema, definition of, 1676*t*
Continuous ambulatory peritoneal dialysis (CAPD), 687–688
Continuous renal replacement therapy (CRRT), 637–639, 638*f*
Continuous venovenous hemodiafiltration (CVVHDF), 637, 638*f*
Continuous venovenous hemodialysis (CVVHD), 638*f*
Continuous venovenous hemofiltration (CVVH), 637, 638*f*
Contraception, 41–58. *See also specific types*
clinical presentation of, 44
emergency, 57
epidemiology of, 41
etiology and pathophysiology of, 42–44
etiology of, 42–44
failure rates, 41, 42*t*
menstrual cycle in, 42–43, 43*f*
follicular phase, 43
luteal phase, 44
ovulation, 44
nonhormonal, 42
nonpharmacologic therapy in, 42*t*, 44–45
barrier techniques, 44–45
fertility awareness-based methods, 44
periodic abstinence, 44
outcomes of
desired, 44
therapeutic, evaluation of, 58
pathophysiology of, 42–44
patient care process for, 45*b*
personalized pharmacotherapy in, 58
pharmacologic therapy in, 45–58

hormonal, 46–58 (*See also* Combined hormonal contraceptives (CHCs))
depo-medroxyprogesterone acetate, 54–55
long-acting reversible, 55
oral contraceptives, 46–51
progestins, injectable, 54
subdermal progestin implants, 55–56
transdermal contraceptives, 51–52
vaginal rings, 52
intrauterine devices, 56–57
pregnancy and continuation rates in, 42*t*
spermicide-implanted barrier techniques, 45–46
spermicides, 45–46
unintended pregnancies and, 41
Contrast nephrotoxicity, 701*t*
Coordination, lithium toxicity and, 1155
Copanlisib, 2188*t*
Copper, 2477*t*, 2478
Cor pulmonale, 421–422
Corbicistat, 2150*t*
Coronary artery bypass graft surgery (CABG), 154–155
internal mammary artery in, 154
pharmacotherapy with, 155
saphenous vein graft in, 154
Coronary heart disease (CHD)
diabetes mellitus and, 1255–1256
epidemiology of, 138
hypertension and, 90
hypertension treatment in, 97–98
mortality rate of, 138
Coronavirus-like particles, 1925*t*
Corticosteroid-binding globulin (CBG), 1292
Corticosteroids
for acne vulgaris, 1643
for acute gouty arthritis, 1574*t*–1575*t*, 1576
for acute severe asthma, 389*t*, 395–397, 395*t*
adverse effects of, 523–524, 1511, 1533*t*, 1577*t*

for alopecia areata, 1701–1702
antenatal, 1328
anxiety and, 1166*t*
for asthma, 383*t*
for atopic dermatitis, 1683–1684, 1686
for bronchiolitis, 1811
in cancer treatment, 2197
for celiac disease, 620
for cluster headache, 1003
for COPD, 419–420, 424
for Crohn's disease, 520, 521
for hypercalcemia, 785
for inflammatory bowel disease, 515, 519, 522, 523*t*
inhaled, 396–397, 397*t*
intra-articular, 1506, 1510–1511
  adverse effects of, 1511
  dosing and administration of, 1511
  pharmacology and mechanism of action, 1510–1511
for intracranial hypertension, 937
intralesional, 1701
for membranous nephropathy, 727
for migraine, acute, 999
for nausea and vomiting, 534*t*, 535
oral, 1643
for osteoarthritis, 1507*t*, 1510–1511
peptic ulcer disease and, 486
for psoriasis, 1658–1660, 1659*t*
for sepsis and septic shock treatment, 2014*t*
for solid-organ transplant recipients, 1485
  adverse effects of, 1485
  dosing and administration of, 1485
  drug-drug interactions, 1485
  drug-food interactions, 1485
  efficacy of, 1485
  pharmacokinetics of, 1485
  pharmacology and mechanism of action, 1485

systemic, 1701–1702
for systemic lupus erythematosus, 1380t, 146–141
topical, 1683–1684, 1701
for tuberculosis, 1918
Corticotropin, 1575*t*, 1577*t*
Corticotropin-releasing factor (CRF), 1188–1189
Cortisol, 350–351, 1292, 1295–1298
Cortisone, 1308*t*
Corynebacterium jeikeium, 2082
Costimulatory signal inhibitor, 1488
Cough, e29
COX-2 inhibitors, 1509
C-reactive protein (CRP), 120–122, 1522
Crisaborole, 1668
Critical care, e73, e75, e77
Critical care, neonatal, e65
Critical illness
dynamic trajectory of, e77
epidemiology of, e77
Crizotinib, 2184*t*, 2199, 2264*t*
Crohn's disease, 510–511. *See also* Inflammatory bowel disease (IBD)
clinical presentation of, 512, 512*t*
mild to moderate active disease, 520
moderate to severe active disease, 520–521
pathophysiology of, 509*t*, 510–511
recurrence of, 520
remission maintenance for, 521
severe or fulminant disease, 521
treatment of, 518*t*, 520–521, 520*f*
Crohn's Disease Activity Index (CDAI), 512
Crossing the Quality Chasm (Institute of Medicine), 2
Cryptococcal meningitis, 2061, 2159*t*
Cryptococcosis, 2058–2061
clinical presentation of, 2058
definition of, 2058
epidemiology of, 2058

laboratory tests, 2058
treatment of, 2058–2061, 2059*t*
in HIV patients, 2060
in immunocompromised patients, 2060
in nonimmunocompromised patients, 2058–2060
in organ transplant patients, 2060
outcome evaluation for, therapeutic, 2060–2061
suppressive therapy for cryptococcal meningitis, 2060
Cryptococcus, 2048*t*
Cryptococcus neoformans, 2046, 2058
Crystal nephropathy, 707
CTLA-4 checkpoint inhibitor, 2208, 2437–2439, 2440
Cultural competency, e11
Current procedure terminology (CPT), 7*t*
Cushing syndrome, 1293–1301
clinical presentation of, 1294–1297, 1296*b*
diagnosis of, 1294–1297, 1295*f*, 1296*t*
etiology of, 1294, 1294*t*
history of, 1293–1294
Cushing syndrome treatment, 1297–1301
nonpharmacologic therapy in, 1301
adrenal adenoma, 1301, 1301*t*
adrenal carcinoma, 1301
ectopic adrenocorticotropic hormone syndrome, 1301
pituitary adenoma, 1301
surgery, 1301
outcomes of, desired, 1297
patient care process for, 1299*b*
personalized pharmacotherapy in, 1297
pharmacologic therapy in, 1297–1301
adrenolytic agents, 1298*t*, 1300
based on etiology, 1298*t*
dosing, 1298*t*
glucocorticoid-receptor blocking agents, 1300
monitoring of, 1298*t*
neuromodulatory agents, 1300

steroidogenesis inhibitors, 1297–1300
Cyanocobalamin, 2480*t*
Cyclic adenosine monophosphate (cAMP), 1926
Cyclin-dependent kinase inhibitors, 2244–2245
Cyclobenzaprine, 972, 972*t*
Cyclooxygenase, 485*t*
Cyclooxygenase 2 (COX-2) selective inhibitor
nephrotoxicity of, 705
peptic ulcer disease and, 485*t*, 486, 487, 488*f*, 497
Cyclophosphamide, 724, 1461*t*, 1462*t*, 2182*t*, 2195–2196, 2336*t*, 2356*t*, 2359*t*, 2454*t*, 2461*t*
Cycloserine, 1913*t*, 1914*t*, 1917
Cyclosporine
for atopic dermatitis, 1686
for celiac disease, 620
chronic interstitial nephritis and, 710
for Crohn’s disease, 521
for focal segmental glomerulosclerosis, 725
for graft-versus-host disease, 2460, 2461*t*
for inflammatory bowel disease, 515–516, 516*t*, 519, 522
for minimal-change nephropathy, 724
nephrotoxicity of, 705–706, 710
for psoriasis, 1662
Cyclothymic disorder, 1150*t*
CYP3A, 2154, 2155
Cyproheptadine, 1300
Cyproterone, 1643, 2313
Cyproterone acetate, 1701
Cystic fibrosis, 449–451
in children, 457
clinical presentation of, 450–451
definition of, 449
in diabetes, 455–456
diagnosis of, 450–451
for screened newborns, 450
epidemiology of, 449

etiology of, 449
gastrointestinal system presentation in, 450
genetic mutations, 456*f*, 456*t*
incidence of, 449
nutritional assessment, 451*t*
pathophysiology of, 449–450, 450*f*
patient care process for, 452*b*
pregnancy in, 457
reproduction with, 455
reproductive presentation in, 450
sinus and pulmonary presentation in, 450
in transplant patients, 457
Cystic fibrosis treatment, 451–457
antimicrobial agents in, 454*t*
bone health and vitamin supplementation in, 452
diabetes, 455–456
gastrointestinal, 457
general approach to, 451
nonpharmacologic therapy in, 451
nutrition in, 451, 451*t*
outcomes of
desired, 457
gastrointestinal, 457
psychosocial, 457
pulmonary and sinus, 457
evaluation of, 457
pharmacologic therapy in, 451–457
pancreatic enzyme replacement therapy, 451–452, 453*t*
transmembrane conductance regulator modulators, 456–457, 456*f*, 456*t*
psychosocial, 457
pulmonary and sinus, 457
pulmonary health and treatment, 452–453
airway clearance in, 452–453, 453*t*
anti-inflammatory therapies in, 454
infectious disease in, 454–455
pharmacokinetics in, 455

reproduction, 455
special populations
children, 457
pregnant women, 457
transplant patients, 457
Cystitis, uncomplicated, acute, 1962–1965, 1964*t*
Cytarabine, 2178–2179, 2180*t*
Cytochrome P450 enzymes, e15, 1139*t*
CYP3A, 2154, 2155
Cytokine release syndrome, 2215
Cytokines. *See also specific types*
interferons, 2208
interleukin-2, 2208–2209
monitoring of, 2191*t*
in systemic lupus erythematosus, 1455
Cytomegalovirus, 1796, 2160*t*
Cytoprotection, 487
Cytotoxic agents, 2237
for focal segmental glomerulosclerosis, 725
for immunoglobulin A nephropathy, 730
for minimal-change nephropathy, 724
Cytotoxic therapy
for hepatitis B, 604–605
for membranous nephropathy, 727

D

Dabrafenib, 2185*t*, 2442–2443, 2444*t*
Dacarbazine, 2196
Daclizumab, 862*t*, 863*t*, 867
Dacominitinb, 2185*t*, 2200–2201
Dactylitis, 1750
Dalbavancin, 1868
Dalfampridine, 869, 869*t*
Danazol, 1358*t*
Dantrolene, 869, 869*t*, 971, 972*t*
Dapagliflozin, 1242*t*, 1247

Dapsone, 1637*t*, 1642, 2094*t*, 2095*t*
Daptomycin, 1792, 1867, 2092*t*
Daratumumab, 2190*t*, 2418
Darifenacin, 869*t*, 1421*t*, 1425, 1443
Darolutamide, 2311*t*, 2313
Darunavir, 2150*t*, 2152*t*, 2154
Dasatinib, 2184*t*, 2199–2200, 2392*t*, 2393–2395, 2394*t*
Daunorubicin, 2181*t*
Daytime sleepiness, 950*t*
D-dimer, 245–246
Debridement, 1877
Decitabine, 2185*t*
Decongestants. *See specific types*
Decubitus ulcer. *See* Pressure sores
Deep vein thrombosis (DVT), 247*b*
Deep-brain stimulation (DBS), 950
Definitive hosts, e1955
Degarelix, 2312*t*
Degludec, 1239, 1240*t*
Dehydroepiandrosterone (DHEA), 1375–1376, 1464
Delafloxacin, 1868, 2092*t*
Delamanid, 1917
Delavirdine, 2152*t*, 2154
Delirium. *See* Pain, agitation, delirium (PAD)
Delpazolid, 1918
Dematologic conditions, minor, e37
Demeclocycline, 765
Dementia, 836*t*, 1371. *See also* Alzheimer disease
Denileukin diftitox, 2192*t*
Denosumab, 1556–1557, 2191*t*, 2421
  adverse events, 1557
  dosing and administration of, 1552*t*, 1557
  drug interactions, 1557
  efficacy of, 1556–1557
  for hypercalcemia, 785
  monitoring of, 1553*t*

pharmacokinetics of, 1556
pharmacology of, 1556
Dental caries, e33, e35
Denture stomatitis, 2031*t*
Dependence, 1047. *See also* Substance-related disorders; *specific substances*
alcohol, 1070–1076 (*See also* Alcohol abuse)
benzodiazepine, 1175–1176
caffeine, 1084–1087 (See also Caffeine use and abuse)
nicotine, 1076–1084 (*See also* Nicotine use and dependence)
opioid, 981
physical, 1047
Depo-medroxyprogesterone acetate, 54–55
Depression
asthma and, 377
in multiple sclerosis, 870
in Parkinson disease, 950*t*
postpartum, 1331
in pregnancy, 1326–1327
Depressive disorder, 1125–1130
biomarkers of, 1127
clinical presentation of, 1127–1130, 1128*b*
depression rating scales in, 1129
DSM-5 criteria in, 1128–1129, 1129*t*
emotional symptoms in, 1129
intellectual or cognitive symptoms in, 1128*b*
physical symptoms in, 1129
psychomotor disturbances in, 1128*b*
definition of, 1125
epidemiology of, 1125
etiology of, 1126
medications associated with, 1128*t*
pathophysiology of, 1126–1127
patient care process for, 1131*b*
prevalence of, 1125
suicide risk evaluation and management in, 1129–1130
Depressive disorder treatment, 1130–1143

alternative pharmacotherapy in, 1141
folate, 1141
omega-3 fatty acids, 1141
S-adenosyl-l-methionine (SAMe), 1141
St. John's wort, 1141
in children, 1142
in elderly, 1141–1142
general approach to, 1130
nonpharmacologic therapy in, 1130
outcomes of
desired, 1130
therapeutic, evaluation of, 1144–1145
personalized pharmacotherapy in, 1143
pharmacologic therapy in, 1130–1143
adverse drug reactions, 1144*t*
adverse effects of, 1137
antipsychotics, second-generation, 1136–1137
dosing of, 1133*t*–1134*t*
drug interactions, 1139–1141
pharmacodynamic, 1139–1141, 1141*t*
pharmacokinetic, 1139, 1140*t*
investigational drugs, 1137
mixed serotonergic medications, 1133*t*, 1135–1136, 1138*t*
monoamine oxidase inhibitors, 1133*t*, 1136, 1137*t*
norepinephrine and dopamine reuptake inhibitor, 1133*t*, 1136, 1138*t*
pharmacodynamics of, 1137–1139
pharmacokinetics of, 1137–1139, 1138*t*
plasma concentration and clinical response of, 1139
relative potencies, 1135*t*
selective serotonin reuptake inhibitors, 1132, 1133*t*, 1138*t*
serotonin and a2-adrenergic antagonists, 1133*t*, 1136, 1138*t*
serotonin-norepinephrine reuptake inhibitors, 1132–1135, 1133*t*, 1138*t*
tricyclic antidepressants, 1132, 1133*t*, 1138*t*
in pregnancy and lactation, 1142–1143
for treatment-resistant depression, 1143
Dermatitis, atopic, 1675–1680

in children, 1675
clinical presentation of, 1678–1680, 1679*t*
complications of, 1679–1680
definition of, 1676*t*
diagnosis of, 1679*t*
early onset, 1675
epidemiology of, 1676
etiology of, 1676–1677
genetic factors in, 1676
hygiene hypothesis and, 1676
outcomes of, evaluation of, 1688
pathophysiology of, 1677–1678
patient care process for, 1681*b*
predisposing factors in, 1677–1678
prevalence of, 1675
severity of, 1679, 1680*f*
signs and symptoms of, 1679*t*
skin features associated with, 1678*t*
Dermatitis, atopic, treatment of, 1680–1687
information resources, 1682*t*
nonpharmacologic therapy in, 1680–1683
outcomes of, desired, 1680
patient considerations in, 1687
pharmacologic therapy in, 1683–1687
calcineurin inhibitors, topical, 1684–1685
coal tar, 1685
complementary and alternative therapies in, 1686–1687
immunotherapy, 1687
probiotics/prebiotics, 1686–1687
traditional Chinese herbal therapy, 1686
corticosteroids, topical, 1683–1684
phototherapy in, 1685–1686
selective phoshodiesterase 4 inhibitors, 1685
systemic therapies in, 1686
alitretinoin, 1686
antihistamines, oral, 1686

azathioprine, 1686
biologic agents in, 1686
corticosteroids, 1686
cyclosporine, 1686
infliximab, 1686
methotrexate, 1686
mycophenolate mofetil, 1686
recombinant interferon, 1686
Dermatitis herpetiformis, 617, 618
Dermis, e37
Desiccated thyroid, 1284
Designer drugs, 1061
Desipramine, 970*t*, 1133*t*, 1135*t*, 1138*t*
Desmopressin, 683, 1446, 1735, 1741
Desvenlafaxine, 1133*t*, 1138*t*, 1140*t*, 1144*t*, 1376*t*. *See also* Serotonin-norepinephrine reuptake inhibitors (SNRIs)
Detemir, 1239, 1240*t*
Determinants of health, social, e11
Detrusor (bladder) overactivity, 1433
Detrusor hyperactivity with impaired contractility, 1433
Dexamethasone, 530*t*, 531*t*, 534*t*, 535, 537, 538, 539*t*, 1296, 1794
Dexlansoprazole, 474, 475*t*, 476, 494*t*, 497, 498*t*
Dexmedetomidine, 1073*t*
Dexmethylphenidate, 1017
Dextroamphetamine, 869*t*, 870, 1017, 1209*t*
Dextromethorphan, 870, 1049
Dextrose, 805*t*, 2495
Diabetes insipidus, 769
causes of, 768*t*
central, 771, 772*t*
nephrogenic, 771–772, 772*t*
Diabetes mellitus (DM), 1229–1236
celiac disease and, 617
in chronic heart failure, 217
in chronic kidney disease, 651, 658
classification of, 1230–1231, 1231*t*

gestational, 1231
maturity onset diabetes of youth, 1231
medication-induced, 1231*t*
type 1, 1230–1231
type 2, 1231
clinical presentation of, 1235–1236, 1235*b*
from combined hormonal contraceptives, 53
cystic fibrosis in, 455–456
definition of, 1230
diagnosis of, 1235, 1236*t*
epidemiology of, 1230–1231
gestational diabetes mellitus, 1231*t*
maturity onset diabetes of youth, 1231*t*
type 1, 1231*t*
type 2, 1231*t*
etiology of, 1231–1235
gestational, 1316*b*
hyperglycemia
type 1, injectable medications, 1252*f*
type 2
AACE guidelines, 1252
injectable medications, 1251–1252
pharmacotherapy for, 1251*t*
management of, 145*t*
in menopausal hormone therapy, 1371
pathophysiology of, 1231–1235
gestational, 1234
maturity onset diabetes of youth, 1234–1235
sodium-glucose cotransporters, 1233
type 1, 1231–1232
clinical course of, 1232*f*
type 2, 1232–1234, 1233*f*
impaired insulin secretion, 1233–1234, 1233*f*
incretin hormone deficiency/resistance, 1233–1234
insulin resistance in, 1233–1234
risk factors for, 1232*t*

patient care process for, 1250*b*
in pregnancy, 1324, 1325*t*
screening for, 1235–1236
in adults, 1236
in children and adolescents, 1236
gestational diabetes, 1236, 1237*t*
type 1, 1236
type 2, 1236
in solid-organ transplant recipients, 1493
stable ischemic heart disease in, 145*t*
Diabetes mellitus (DM) treatment
in acutely ill patients, 1259
in adolescents, 1257
in children, 1257
clinical trials on
ACCORD, 1255
ADVANCE, 1243
United Kingdom Prospective Diabetes Study, 1237
Veterans Affairs Diabetes Trial, 1237
complications and comorbidities, 1254–1257
coronary heart disease, 1255–1256
diabetic ketoacidosis, 1254
foot ulcers, 1255
hyperosmoslar hyperglycemia state, 1254–1255
hypertension, 1256
macrovascular complications, 1255–1256
microvascular complications, 1256–1257
nephropathy, 1256
neuropathy, 1256–1257
retinopathy, 1256
general approach to, 1236–1238
in HIV patients, 1258
in hospitalized patients, 1258–1259
hyperglycemia
type 1, 1252–1253
adjunctive therapies in, 1253

glucose monitoring, 1253
type 2, 1249–1252
initial therapy, 1249
stepwise addition of medications, 1249
hypertension treatment in, 98
hypoglycemia, 1253–1254
initial evaluation in, 1236
nonpharmacologic therapy in, 1238–1239
diabetes self-management education and support, 1239
medical nutrition therapy in, 1238
medical therapy in, 1249
physical activity in, 1239
in older adults, 1257–1258
outcomes of
desired, 1236–1238
evaluation of, 1259–1260
medication adherence in, 1260
therapeutic inertia, 1260
pharmacologic therapy in, 1239–1248, 1242*t*
α-glucosidase inhibitors, 1242*t*, 1248
amylin analogs, 1248
biguanides, 1241–1243, 1242*t*
bile acid sequestrants, 1242*t*, 1248
combination products, 1261*t*
dipeptidyl peptidase 4 inhibitors, 1242*t*, 1246–1247
dopamine agonists, 1242*t*, 1248
dosing of, 1242*t*
glucagon-like peptide 1 receptor agonists, 1244–1246, 1245*t*
insulin, 1239–1241, 1240*t*
meglitinides, 1242*t*, 1248
sodium-glucose cotransporter-2 inhibitors, 1242*t*, 1247–1248
sulfonylureas, 1242*t*, 1243
thiazolidinediones, 1242*t*, 1243–1244
for type 1 DM, 1252–1253
for type 2 DM, 1249–1252, 1251*t*
preconception care for women in, 1258

prediabetes, 1257
in pregnancy, 1258
prevention of type 2, 1257
therapy goals, 1236–1238
glycemic control and, 1236–1237
glycemic targets, 1237–1238, 1238*t*
Diabetes self-management education and support (DSME/S), 1239
Diabetic dyslipidemia, 132
Diabetic foot infections, 1856*t*, 1871–1875
clinical presentation of, 1872, 1872*b*
epidemiology of, 1871
etiology of, 1856*t*, 1871, 1871*t*
pathophysiology of, 1872
treatment of, 1872–1875, 1873*t*
algorithm for, 1874*f*, 1875*f*
evidence-based, 1861*t*
outcomes of
desired, 1872
pharmacologic, 1862*t*
pharmacologic therapy in, 1872–1875, 1873*t*
therapeutic, evaluation of, 1875
types of, 1871
Diabetic ketoacidosis (DKA), 1254
Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), 1010, 1046, 1047*t*, 1070, 1085, 1086*t*, 1125
Dialysis, 677–683. *See also* Hemodialysis; Peritoneal dialysis
for CKD-MBD, 666
costs of, 677
indications for, 678–679
morbidity and mortality in, 677, 678
statistics on, 677
videos, patient-related, 693*t*
Diaphragm (contraception), 42*t*, 44
Diarrhea, 543–550. *See also* Gastrointestinal infection
acute, 549
causes of, 544, 564*t*

clinical presentation of, 545, 564*t*
definition of, 543, 1923
dysenteric, 1925*t*, 1930*t*
epidemiology of, 544
inflammatory, 1926
oral contraceptives and, 51
pathophysiology of, 544
patient care process for, 545*b*
physiology of, 544
prevention of, 545
severe, 550
stool examination in, 544
traveler's, 1930*t*, 1933–1934
watery, 1925*t*, 1930*t*
Diarrhea treatment, 545–550
for acute diarrhea, 547*f*
for chronic diarrhea, 548*f*
nonpharmacologic management, 545–546
electrolytes, 564
water and, 564
outcomes of
for acute diarrhea, 549
desired, 545
evaluation of, 549–550
for severe diarrhea, 550
pharmacologic therapy in, 546–549, 549*t*
adsorbents, 547, 549*t*
antimotility agents in, 549*t*
antisecretory agents, 547–549, 549*t*
enzymes, 549*t*
opiates, 546–547
oral rehydration solutions, 548*t*
vaccine, 549
vaccines, 549
Diastolic blood pressure, 85
Diazepam, 869, 920, 921*t*, 922*t*, 971, 972*t*, 1073*t*. *See also* Benzodiazepines

for alcohol withdrawal, 1072
for generalized anxiety disorders, 1171*t*, 1175*t*
for multiple sclerosis, 869*t*
for panic disorder (attack), 1178*t*
Diazoxide, 1231*t*
Dichloroacetate, 824
Diclofenac, 974*t*, 995*t*, 1504*t*
Dicyclomine, 869*t*
Didanosine, 2150*t*, 2152*t*, 2153
Diet, peptic ulcer disease and, 486
Dietary Approaches to Stop Hypertension (DASH), 92
Dietary supplements, 845
Diethylpropion, 2545*t*, 2549, 2550*t*
Dietician, standards of care, 1*t*
Difenoxin, 547, 549*t*
Diflunisal, 1504*t*
Digoxin, 289
for chronic heart failure, 214–215
drug interactions, 216*t*
for heart failure with preserved ejection fraction, 214–215
monitoring of, 208*t*
for pulmonary arterial hypertension, 441
toxicity, 216*t*
Dihydroergotamine, 995*t*, 999
Dihydropyridine, 94, 103–104
Dihydropyrimidine dehydrogenase (DPD), 2179
1,25-Dihydroxyvitamin D, 653*f*
Diiodotyrosine (DIT), 1266
Diltiazem, 292*t*, 293, 295*t*. *See also* Calcium channel blockers
Dimenhydrinate, 533*t*, 539*t*
Dimethyl fumarate, 862*t*, 863*t*, 866
Dimethyltryptamine (DMT), 1060, 1061
Dimorphic fungi, 2046
Dinutuximab, 2190*t*
Dipeptidyl peptidase 4 inhibitors (DPP-4 inhibitors), 1242*t*, 1246–1247
Diphenhydramine, 533*t*

Diphenoxylate, 546, 549*t*
Diphenylheptanes, 975*t*
Diphenylmethane, 1171*t*
Diphtheria toxoid adsorbed, 2131
Dipivefrin, 1598
Dipyridamole, 280
Direct arterial vasodilator, 107–108
Disease modification, 955
Disease-modifying antirheumatic drugs (DMARDs), 1530
Disopyramide, 291, 292*t*, 294*t*, 295*t*, 296*t*
Disruptive mood dysregulation disorder (DMDD), 1022
Disseminated intravascular coagulation, 2010
Distal ileum, 1941
Distributive shock
  fluid resuscitation in, 357–358
  vasopressors and inotropes in, 359–364
Disulfiram, 1074*t*
Diuretics. *See also specific agents*
  for acute decompensated heart failure, 229–230, 229*t*
  for acute kidney injury, 639–640, 639*t*
  characteristics of, 774*t*
  for chronic heart failure, 204*t*, 205–209, 207*t*
  for cirrhosis, 775*f*
  diabetes mellitus and, 1231*t*
  for edema, 773–775, 774*f*
  for hypertension, 95*t*, 104–105
  monitoring of, 208*t*
  for nephrotic syndrome, 775*f*
  for pulmonary arterial hypertension, 438
  for resistant hypertension, 102, 104–105
Divalproex sodium
  for bipolar disorder, 1157
  dosing and administration of, 996*t*, 1154*t*
Dizziness, 539
DNA methyltransferase inhibitors, 2185*t*, 2200
DNA repair genes, 2170

Dobutamine
for acute decompensated heart failure, 233, 233*t*
for septic shock, 2018
for shock, 363–364
Docetaxel, 2181*t*, 2194, 2249*t*, 2263*t*, 2314*t*, 2315, 2356*t*, 2358*t*
Docosahexaenoic acid (DHA), 684
Dofetilide, 293
for arrhythmias, 292*t*
doses of, 296*t*
pharmacokinetics of, 295*t*
side effects of, 294*t*
Dog bites, 1878–1879
Dolasetron, 530*t*, 531*t*, 539*t*
Dolutegravir, 2150*t*, 2152*t*, 2154
Domperidone, 477
Donabedian, Avedis, 6
Donepezil, 842, 843*t*
Donor lymphocyte infusion, 2455
Dopamine
for acute decompensated heart failure, 233*t*
eating disorders and, 1030
metabolism of, 946*f*
for septic shock, 2018, 2018*t*
for shock, 363
synthesis and metabolism, 954*f*
Dopamine agonists. *See also specific agents*
anxiety and, 1166*t*
for circadian rhythm disorders, 1210
for diabetes mellitus, 1242*t*, 1248
for menstruation-related disorders, 1342*t*
for Parkinson disease, 952*t*, 953*t*, 956
Dopamine D2 -receptor agonists, 1300
Doravirine, 2152*t*, 2154
Doripenem, 1963*t*, 2092*t*
Dornase alfa, 453
Dorzolamide, 1600*t*

Dose density, 2237–2238
Dose intensity, 2237–2238
Down syndrome, 1216–1219
  Alzheimer disease and, 1219–1220
    clinical presentation of, 1219
    etiology of, 1219
    risk factors for, 1219
    treatment of, 1219–1220
      desired outcomes in, 1219
      nonpharmacologic therapy in, 1219
      pharmacologic therapy in, 1219–1220
      therapeutic outcomes in, 1220
  clinical presentation of, 1217, 1217*b*
  diabetes mellitus and, 1231*t*
  diagnosis of, 1216
  epidemiology of, 1215–1216
  etiology of, 1216
  treatment of, 1217–1219
    general approach to, 1217
    nonpharmacologic therapy in, 1217
      depressive symptoms, 1217
    outcomes of
      desired, 1217
      therapeutic, evaluation of, 1220
    pharmacologic therapy in, 1217–1219, 1224*t*
      challenging behaviors, 1218–1219
      depressive disorders in, 1217–1218
      sleep disorders, 1219
Doxazosin, 94, 1419, 1421*t*, 1424
Doxepin, 1133*t*, 1135*t*, 1138*t*, 1203
Doxercalciferol, 668, 669–670, 669*t*
Doxorubicin, 2181*t*, 2324–2328, 2325*t*, 2334, 2336*t*, 2359
Doxycycline, 495, 1641
  for acne vulgaris, 1637*t*, 1641
  for acute bacterial rhinosinusitis, 1833*t*
  for chlamydial infections, 1984–1985

for chronic bronchitis, 1811*t*
for cystic fibrosis, 454*t*
dosing of, 1833*t*
for gonorrhea, 1978
for syphilis, 1982
Dronabinol, 533*t*, 535
Dronedarone, 292*t*, 293, 294*t*, 295*t*, 296*t*
Drooling, in Parkinson disease, 950*t*
Droperidol, 533*t*, 534, 539*t*
Drowning, cardiac arrest treatment in, 337
Droxidopa, 683
Drug abuse. *See* Substance-related disorders
Drug reaction with eosinophilia and systemic symptoms (DRESS), 1112
Drug-induced disorders
acne vulgaris, 1628
fever, 1772
glaucoma, 1595, 1595*t*
gout and hyperuricemia, 1569*t*
hypokalemia, 798–799, 799*t*
kidney disease, 697–712 (*See also* Kidney disease, drug-induced)
liver disease, e577 (*See also* Drug–induced liver disease (DILD))
ophthalmic disorders, e1621
Drug-induced liver disease (DILD), e577
Drug-nutrient interactions, 2485, 2488*t*
Drusen, 1607, 1609*f*, 1610*f*
Dry eye disease, e25, e1621
Dry powder inhaler, 390*t*
Dual antiplatelet therapy, 182–183, 281–282
Ductal carcinoma in situ (DCIS), 2228
Dulaglutide, 1244, 1245*t*
Duloxetine, 970*t*, 971, 1133*t*, 1135*t*, 1138*t*, 1140*t*, 1144*t*, 1171*t*, 1196, 1445–1446, 1507
for multiple sclerosis, 869*t*
for osteoarthritis, 1512
Dupilumab, 398*t*, 399, 1702
Durvalumab, 2191*t*, 2208

Dutasteride, 1421*t*, 1699–1701
Duvelisib, 2188*t*, 2402*t*, 2403*t*
Dyshidrotic eczema, definition of, 1676*t*
Dyskinesias, 954*t*, 955
Dyslipidemia, 117–133. *See also specific types*
  acquired, 119
  classification of cholesterols, 124*t*
  clinical presentation of, 122*b*
  from combined hormonal contraceptives, 53
  epidemiology of, 118–119
  etiology of, 119
  lipoprotein metabolism and transport in, 118*f*, 119–120, 120*f*
  pathophysiology of, 119–122
    atherosclerotic cardiovascular disease, 120–122
    familial hypercholesterolemia, 120
    lipid metabolism and transport, 119–120
    lipoproteins and cholesterol synthesis, 119
  patient evaluation in, 123
Dyslipidemia treatment, 122–133
  atherosclerotic cardiovascular disease (ASCVD)
    nonstatin therapies, 126*t*
    reducing risk of, 125*t*
  in children, 131–132
  clinical trials on, 125–126, 126*t*
  in concurrent diseases, 132–133
  for diabetic dyslipidemia, 132
  for familial hypercholesterolemia, 128
  general approach to, 122–126
  for hypertriglyceridemia, 128
  lifestyle factors, 122
  for low HDL cholesterol, 128
  nonpharmacologic, 126–127
    dietary supplementation in, 127
    lifestyle modifications in, 126–127
  in older adults, 131
  outcomes of

desired, 122
therapeutic, evaluation of, 133
patient care process for, 123
pharmacologic, 127
cholesterol absorption inhibitors, 129–130
fibrates, 130
niacin, 131
omega-3 polyunsaturated fatty acids, 131
proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, 130
statins, 125, 128–129, 129*t*
in women, 132
Dysmenorrhea, 1347–1349
in adolescent females, 1348–1349
clinical presentation of, 1347*b*
definition of, 1347
epidemiology of, 1347
etiology of, 1347
pathophysiology of, 1347
primary, 1347
secondary, 1347
treatment of, 1347–1349
algorithm for, 1348*f*
general approach to, 1347–1348
nonpharmacologic therapy in, 1348
outcomes of
desired, 1347
evaluation of, 1349
pharmacologic therapy in, 139*t*, 1348
combined estrogen-progestogens, 1348
NSAIDs, 1348
progestogens in, 1348
Dysphagia, in Parkinson disease, 950*t*
Dyspnea
in COPD, 408–409
treatment of, e79
Dysthymia, 1150*t*

Dystonia, 955, 1109

E

Early empirical therapy, 2050
Eating disorders, 1029–1033
  anorexia nervosa
    clinical presentation of, 1031–1032, 1031*b*
    signs and symptoms of, 1031*f*
  assessment of, physical and laboratory, 1033*t*
  binge-eating disorder, clinical presentation of, 1032, 1033*b*
  bulimia nervosa
    signs and symptoms of, 1031*f*
    clinical presentation of, 1032, 1032*b*
  clinical presentation of, 1030–1032
  definition of, 1029
  epidemiology of, 1029–1030
  etiology of, 1030
  medical complications of, 1032–1033
  pathophysiology of, 1030
  patient care process for, 1035*b*
Eating disorders treatment, 1034–1039
  general approach to, 1034, 1034*t*
  nonpharmacologic therapy in
    for anorexia nervosa, 1034–1036
    for bulimia nervosa, 1036
    for binge eating disorder, 1037
  outcomes of
    desired, 1034
    therapeutic, evaluation of, 1039
  pharmacologic therapy in
    for anorexia nervosa
      antidepressants, 1036
      antipsychotics, 1036
    for bulimia nervosa
      antidepressants, 1036–1037
      selective serotonin reuptake inhibitors, 1037
      combination therapy in, 1037

for binge eating disorder, 1037–1039
prognosis of, 1034
Ebstein's anomaly, 1160–1161
Echinocandins
for invasive fungal infections, 2071
monitoring of, 2073*t*
for oropharyngeal candidiasis, 2033*t*
for sepsis and septis shock, 2016
Echocardiography, e81
Echothiophate, 1600*t*, 1603
Eclampsia, 100
Ecstasy, 1060
Ectopic adrenocorticotropic hormone syndrome, 1301
Eczema (dermatitis), types of, 1676*t*
Edelman's equation, 757
Edema, 772–775. *See also specific agents*; *specific types*
clinical presentation of, 772–773
definition of, 772
overfill hypothesis of, 772
physiology of, 772
treatment of, 773–775
diuretics, 773–775, 774*f*, 774*t*
general approach to, 773
loop diuretics, 773–775
underfill hypothesis of, 772
Efavirenz, 1916*t*, 2150*t*, 2152*t*, 2154
Effective osmoles, 756
Eflornithine, 1308
EGFR pathway inhibitors, 2185*t*–2186*t*, 2200–2201, 2206, 2295
afatinib, 2200–2201
cetuximab, 2206
dacomitinib, 2200–2201
erlotinib, 2200
gefitinib, 2201
lapatinib, 2201
necitumumab, 2206

neratinib, 2201
osimertinib, 2201
panitumumab, 2206
Eicosapentaenoic acid (EPA), 684
Elagolix, 1358*t*
Elbasvir, 609
Elderly patients
depressive disorders in, 1141–1142
diabetes mellitus treatment, 1257–1258
generalized anxiety disorder treatment, 1177
with GERD, 478–479
pain management in, 981
panic disorder (attack) treatment, 1180
Electrical stimulation, and constipation, 553
Electrocardiography (ECG), e81
in cardiovascular testing, 164
use of, 164
Electrocution, cardiac arrest treatment in, 337
Electrolyte disorders. *See* Acid-base disorders
Electrolytes, 87
in parenteral nutrition, 2497
Electronic nicotine delivery systems (ENDS), 1082
Eletriptan, 995*f*, 998*t*
Elevated anion gap metabolic acidosis, 819–820
Elotuzumab, 2190*t*, 2206, 2418
Eluxadoline, 557
Elvitegravir, 2150*t*, 2152*t*, 2154
Emboli, 1886
Embryo, 1316
Emergency contraception, 57
Emollient laxatives, 553–554
Emollients, 554*t*, 1682
Empagliflozin, 1242*t*, 1247
Emphysema, 406
Emtricitabine, 2150*t*, 2151, 2151*t*, 2152*t*
Enalaprilat, 110*t*

Enasidenib, 2187*t*
Encephalitis. *See also* Central nervous system (CNS) infection
  HIV, 1797
  meningoencephalitis, 1798–1800, 2059*t*, 2060
  toxoplasmic, 2159*t*
  viral, 1796–1797
Encorafenib, 2185*t*, 2442*t*, 2444*t*
Endocarditis, infective, 1883–1888
  clinical presentation of, 1885–1886, 1885*t*, 1886*b*
  definition of, 1883
  diagnosis of, 1887–1888, 1887*t*
  epidemiology of, 1883–1884
  etiology of, 1883–1884, 1884*t*
  pathophysiology of, 1884–1885
  peripheral manifestations of, 1885–1886
  prevention of, 1897, 1898*t*
  risk factors for, 1884
Endocarditis, infective, treatment of, 1888–1896
  general approach to, 1888–1889
  for native valve, 1889*t*
  nonpharmacologic therapy in, 1889
  outcomes of
    desired, 1888
    evaluation of, 1896–1897
      blood cultures, 1897
      inflammatory markers, 1897
      microbiologic tests, 1897
      serum drug concentrations, 1897
      signs and symptoms, 1896–1897
  pharmacologic therapy in, 1889–1896
    atypical microorganisms, 1896
    culture-negative endocarditis, 1892*t*, 1896
    drug dosing, 1892*t*–1893*t*
    drug monitoring in, 1893*t*
    enterococcal endocarditis, 1895–1896
    HACEK group endocarditis, 1896

staphylococcal endocarditis, 1893–1894
IV drug abuser, 1894
prosthetic valves, 1894–1895
streptococcal endocarditis, 1890–1893
Endocrine therapies, 2196–2197
End-of-lilfe care, e79
Endometrial cancer, 1370–1371
Endometriosis, 1353–1360
clinical presentation of, 1354–1355, 1355*b*
definition of, 1353
diagnosis of, 1354
epidemiology of, 1353
etiology of, 1353–1354
pathophysiology of, 1354
patient care process for, 1356*b*
staging, 1355
Endometriosis treatment, 1355–1360, 1355*t*
general approach to, 1355–1356
nonpharmacologic therapy in, 1356–1357
outcomes of
desired, 1355
therapeutic, evaluation of, 1360
pharmacologic therapy in
in adolescents, 1360
adverse effects of, 1358*t*
alternative drugs, 1359–1360
dosing and administration of, 1358*t*
first choice, 1357–1359
combined estrogen-progestogens, 1357
first-line treatments, progestins in, 1357–1359
monitoring, 1358*t*
Endoscopic variceal ligation, 566
Endoscopy, e461
Endothelin, 651
Endothelin receptor antagonists, 442, 444*t*
Endothelium, 715

End-stage renal disease (ESRD). *See also* Hemodialysis; Peritoneal dialysis
costs of, 677
glomerulonephritis in, 716
statistics on, 677
Energy drinks, 1085
Enflurane, 400
Enfuvirtide, 2153*t*, 2154
Enoxaparin, 178*t*, 179
Entacapone, 953*t*
Entecavir, 603
Enteral nutrition, 2513–2527
access in, 2517–2519, 2518*t*
long-term, 2518–2519
selection of, 2517*t*
short-term, 2517–2518
administration methods, 2519
bolus, 2519
continuous, 2519
cyclic, 2519
intermittent, 2519
benefits of, 2516–2517
bottom line in, clinical, 2527
complications of, 2524–2526
gastrointestinal, 2525
infections, 2525
mechanical, 2525–2526
metabolic, 2524
definition of, 2513
drug delivery via feeding tube in
concomitant drug administration, 2526
drug admixture with feeding formulations, 2526
drug-nutrient interactions, 2526–2527, 2527*t*
formulation classification in, 2522–2523, 2522*t*
disease specific, 2522*t*, 2523
elemental/peptide based, 2522*t*, 2523
formulary and delivery system in, 2523–2524

high protein, 2522–2523, 2522*t*
high-caloric density, 2522*t*, 2523
modular products, 2522*t*, 2523
oral supplements, 2522*t*, 2523
rehydration, 2522*t*, 2523
standard polymeric, 2522, 2522*t*
formulation selection in, 2520–2521, 2520*t*
amino acids, conditionally essential, 2520–2521
carbohydrates, 2521
fat and fatty acids, 2521
fiber, 2521
nutrient complexity, 2520*t*
osmolality and renal solute load, 2521
protein composition, 2520
gastrointestinal tract physiology in, 2513–2516
digestion and absorption, 2513–2515, 2515*f*, 2515*t*
gut host defense mechanisms, 2515–2516
indications for, 2516, 2516*t*
initiation and advancement protocol in, 2519–2520
monitoring of, 2524*t*
nutrition care plan in, 2526
vs. parenteral, 2516
patient care process for, 2514*b*
water flushes, 2520
Enteroaggregative *E. coli* (EAEC), 1924, 1925*t*
Enteroclysis, e461
Enterococcal endocarditis, 1895–1896
Enterococcus faecalis, 1947
Enteroglucagon, 2515*t*
Enterohemorrhagic *E. coli*, 1924–1925, 1925*t*
Enteroinvasive *E. coli*, 1924, 1925*t*
Enteropathogenic *E. coli*, 1924, 1925*t*, 1935*t*
Enterotoxigenic *E. coli* (ETEC), 1925*t*, 1924, 1930*t*, 1935*t*
Enterotoxigenic poisonings, 1934–1936
botulinum toxin in, 1935–1936
epidemiology of, 1935*t*

etiology of, 1924–1926, 1935*t*
Enterovirus, 1925*t*
Entry inhibitors, 2153*t*, 2154
Enuresis, 1753
Environmental tobacco smoke, 406
Enzalutamide, 2311*t*, 2313
Enzymes, 2192*t*
Eosinophils, 374
Epidermal growth factor receptor (EGFR), 2278*f*
Epidermis, e37
Epidermophyton, 2036
Epididymitis, 1977*t*
Epilepsy, 877–882
ADHD and, 1021
classification of, 880*f*, 881–882, 882*f*
clinical presentation of, 879–882, 880*b*
focal seizures, 879–881
generalized onset, 881
unknown onset, 881
definition of, 877
diagnosis of, 882
epidemiology of, 877–878
epileptic syndromes, 881–882
etiology of, 878
genetic, 878
infectious, 878
metabolic, immune, and unknown, 878
risk factors for, 878
seizure triggers, 878
structural, 878
pathophysiology of, 879
patient care process for, 883*b*
in pregnancy, 1324–1325, 1325*t*
risk factors for, 878
seizures
focal onset, 879–881

generalized onset, 881
triggers of, 878
Epilepsy treatment, 882–908
algorithm for, 887*f*
in children, 906
in elderly, 906
general approach to, 882–885
nonpharmacologic therapy in, 886–888
ketogenic diet in, 887
surgery, 888
vagus nerve stimulation, 887–888
outcomes of
desired, 882
therapeutic, evaluation of, 908–909
pharmacologic therapy in (*See also specific agents*)
antiseizure drugs, 889–906, 890*t*–897*t*
adverse effects of, 888–889, 890*t*–897*t*
dosage, optimizing, 885–886, 886*t*
drug-drug interactions, 897
efficacy and effectiveness of, 888
efficacy and tolerability for refractory epilepsy, 902*t*–903*t*
elimination pathways, 885*t*
first-generation, 889, 896–900
mechanism of action, 889
pharmacokinetics of, 884*t*, 889, 896–897
second-generation, 900–904
selection of, 884*t*
third-generation, 904–906
in Asians and South Asians, 907–908
carbamazepine, 890*t*–891*t*
first-generation antiseizure drugs, 889, 896–900
advantages and disadvantages of, 900
adverse effects of, 900
drug-drug interactions, 900
efficacy, effectiveness, and tolerability, 898*t*–901*t*
mechanism of action, 889

pharmacokinetics of, 889, 896–897
in pregnancy and breastfeeding, 906–907
second-generation antiseizure drugs, 900–904
advantages and disadvantages of, 904
adverse effects of, 903–904
drug-drug interactions, 901–903
mechanism of action, 900–901
pharmacokinetics of, 901
serum concentration monitoring in, 886*t*
third-generation antiseizure drugs, 904–906
advantages and disadvantages of, 905–906
adverse effects of, 905
drug-drug interactions, 905
pharmacokinetics of, 904–905
mechanism of action, 90
in women (and men), 906
Epinephrine
for cardiac arrest, 325, 332*t*
for priapism, 1760
for septic shock, 2018, 2018*t*
for shock, 362–363
Epirubicin, 2181*t*
Epithelial cells, 373, 715
Epithelium, 715
Eplerenone, 1304*t*
Epoprostenol, 441, 443*t*, 444*t*
Epstein-Barr virus (EBV), 1454
Eptifibatide, 174*t*
ErbB family of receptors, 2178
Erdafitinib, 2186*t*
Erectile dysfunction, 1383–1407
benign prostatic hyperplasia and, 1426
clinical presentation of, 1367*b*
definition of, 1383
diagnosis of, 1387–1388
epidemiology of, 1383–1384

etiology of, 1386
hypertension treatment and, 101
incidence of, 1383
medication-induced, 1386*t*
organic, 1366
pathophysiology of, 1386
patient care process for, 1369*b*
penile erection physiology in, 1384–1386
prevalence of, 1384
psychogenic, 1366
types of, 1364*t*
Erectile dysfunction treatment, 1388–1406
algorithm for, 1393*f*
alprostadil, 1403–1406
general approach to, 1368, 1373
outcomes of
desired, 1388
therapeutic, evaluation of, 1407
phosphodiesterase inhibitors, 1394–1400, 1395*f*
testosterone replacement regimens, 1400–1403
unapproved agents, 1406
papaverine, 1406
penile prostheses, 1406, 1406*f*
phentolamine, 1406
yohimbine, 1406
vacuum erection device in, 1393–1394, 1394*f*
Ergocalciferol, 668, 669*t*
Ergotamine tartrate, 999
for cluster headache, 1003
for migraine, acute, 995*t*
Eribulin, 2181*t*
Erlotinib, 2185*t*, 2200, 2264*t*
Ertapenem, 692*t*, 1947*t*, 1963*t*
Ertugliflozin, 1242*t*, 1247
Erwinia asparaginase, 2371
Erysipelas, 1856*t*, 1859

clinical presentation of, 1859*b*
definition of, 1859
etiology of, 1859
treatment of, 1859
evidence-based, 1860*t*
outcomes of
desired, 1859
therapeutic, evaluation of, 1859
pharmacologic, 1859, 1862t
Erythrocyte sedimentation rate (ESR), 1522
Erythromycin
for acne vulgaris, 1637*t*, 1641
for chlamydial infections, 1985
for chronic bronchitis, 1811*t*
for febrile neutropenia, 2092*t*
for gonorrhea, 1979, 1980*t*
Erythropoiesis, stimulation of, 1711
Erythropoiesis stimulating agents, 662–664, 662*t*
adverse effects of, 663
dosing and administration, 663–664
drug-drug interactions, 663
efficacy of, 663
pharmacodynamics of, 663
pharmacokinetics of, 663
pharmacology and mechanism of action, 663
Escherichia coli, 1808*t*, 1924, 1935*t*, 2008
Escitalopram, 1133*t*, 1135*t*, 1138*t*, 1140*t*, 1171*t*, 1178*t*. *See also* Selective serotonin reuptake inhibitors (SSRIs)
in menopause and perimenopausal/postmenopausal hormone therapy, 1376*t*
for obsessive-compulsive disorder, 1197*t*
for social anxiety disorder, 1182*t*
Eslicarbazepine
adverse effects of, 895*t*
drug interactions, 895*t*
for epilepsy, 894*t*–895*t*
mechanism of action, 894*t*

Esmolol hydrochloride, 110*t*
Esomeprazole, 472*t*, 474, 475*t*, 476, 494*t*, 497, 498*t*, 502*t*
Esophageal candidiasis. *See also* Oropharyngeal and esophageal candidiasis
  clinical presentation of, 2031*t*
  treatment of
    in HIV patients, 2034–2035
    in non-HIV patients, 2035
Esophageal clearance, 465
Essential fatty acid deficiency (EFAD), 2479–2481, 2507
Essential hypertension, 84
Estazolam, 1205*t*
Esters, 981*t*
Estrogen agonists/antagonists, 1552*t*, 1553*t*, 1557
Estrogens, 46, 1412, 2246*t*, 2247*t*
  for Alzheimer disease, 845
  in menopause and perimenopausal/ postmenopausal hormone therapy, 1371–1372, 1373*t*
    adverse effects of, 1371
    dosage and administration of, 1372
    oral, 1372
    other routes of administration in, 1372
  for osteoporosis, 1557
Eszopiclone, 1057, 1205, 1205*t*
Etanercept, 1525*t*, 1528, 1533*t*, 1664–1665, 2461*t*
Ethambutol
  adverse effects and monitoring of, 1919*t*
  for CNS infection, 1798
  dosing by age group, 1913*t*
  dosing of, 1914*t*
  for tuberculosis, 1911*t*, 1914*t*, 1916
Ethinyl estradiol, 2246*t*
Ethinyl estradiol transdermal patch, 1342*t*, 1358*t*
Ethionamide, 1913*t*, 1914*t*, 1917
Ethosuximide
  adverse effects of, 891*t*
  drug interactions, 891*t*

for epilepsy, 889, 897
mechanism of action, 890*t*
Etodolac, 1504*t*, 1574*t*
Etomidate, 1298*t*
Etonogestrel, for endometriosis, 1358*t*
Etoposide, 2181*t*, 2195, 2358*t*, 2454*t*
Etravirine, 2151*t*, 2152*t*, 2154
Euglobulin clot lysis time (ECLT), 1731*t*
Everolimus, 2187*t*, 2202, 2245, 2247*t*
Exemestane, 2246*t*
Exenatide, 1244, 1245*t*
Exercise-induced bronchospasm, 379, 382*f*. *See also* Asthma
Exfoliants (peeling agents), 1635–1638
adverse effects and monitoring of, 1636*t*
resorcinol, 1635
retinoids, topical, 1638–1639
salicylic acid, 1635–1638
sulfur, 1638
Exogen phase, 1692
Exogenous thyroid hormone, 1272
Expectorants, 421
Extended-spectrum β-lactamases (ESBL), 1947
Extracorporeal membrane oxygenation (ECMO), 235*f*, 236
Extraesophageal GERD, 477–478
Extrapulmonary tuberculosis, 1905. *See also* Tuberculosis
Extravasation, 2214–2215
Extreme obesity, 2535, 2535*t*
Eye
anatomy of, 1592*f*
optic disk, 1589, 1591
visual field, 1591

F

Factor IX concentrate replacement, 1735
Factor VIII, 564
Factor VIII concentrate replacement, 1733–1734

Falling, and Parkinson disease, 950*t*
False hyperkalemia, 798
False hypokalemia, 798
Famciclovir, 1988
Familial dyslipidemia, 119
Familial hypercholesterolemia, 120, 128
Famotidine, 472*t*, 473*t*, 475*t*, 476, 494*t*, 496, 499, 502*t*, 534*t*
Fat
  daily requirements, 2484
  in enteral nutrition, 2521
  intravenous lipid emulsion, 2495–2496
Fatigue
  in multiple sclerosis, 870
  in Parkinson disease, 950*t*
Fatty acids, in enteral nutrition, 2521
Febrile neutropenia, in cancer patients, 2082–2083
  clinical presentation of, 2083, 2085*b*
  etiology of, 2082–2083
Febrile neutropenia treatment, in cancer patients
  antibacterial agents, 2095*t*
  antibiotic therapy in, after initiation of empirical therapy, 2090*t*, 2091–2094
  antifungal therapy in, 2094–2096, 2095*t*
  antimicrobials therapy in, duration of, 2096
  antiviral therapy in, 2095*t*, 2096
  approach to, 2083–2086, 2086*t*
  β-lactam, 2086–2090, 2090t
    plus aminoglycosides, 2090
  colony-stimulating factors in, 2096, 2098*t*
  drug dosing regimen in, 2092*t*–2094*t*
  evaluation tools for, 2089*t*
  evidence-based, 2087*t*–2088*t*
  fluoroquinolones in, 2090
  infectious complications in, 2097*t*
  initial management, 2086*f*
  oral antibiotics in, 2091
  outcomes of

desired, 2083
outcome evaluation for, therapeutic, 2099
prophylaxis in, 2097, 2098*t*
for bacterial infections, 2097–2099
for fungal infections, 2099
for other infections, 2099
subsequent management, 2087*f*
vancomycin in, 2090–2091
Febuxostat, 1575*t*, 1577*t*
Fecal occult blood tests, 2281
Felbamate
adverse effects of, 893*t*
drug interactions, 893*t*
for epilepsy, 892*t*–893*t*
mechanism of action, 892*t*
Felty syndrome, 1522
Fenamates, 968*t*
Fenoldopam mesylate, 110*t*, 111
Fenoprofen, 1504*t*, 1574*t*
Fentanyl, 1044
dosing and administration of, 977*t*–978*t*
for pain management, 975*t*
for substance-related disorders, 1049
Ferrell, Deen, e37
Ferric carboxymaltose, 661*t*
Ferric citrate, 668
Ferritin, serum, 1714
Fertility awareness-based methods of contraception, 44
Ferumoxytol, 661*t*
Fesoterodine, 1421*t*
Fesoterodine fumarate, 1442–1443
Fetal hemoglobin, 1749
Fetus, 1316
Fever, e21. *See also specific disorders*
definition of, 1771
drug-induced, 1772

false-positives, 1772
hemodialysis complications, 682*t*
infection and, 1771–1772
Feverfew, 996*t*
Fevipiprant, 398*t*
FGFR inhibitor, 2201
Fiasp, 1239, 1240*t*
Fiber, 2484, 2521
Fibrillation. *See specific types*
Fibrinolysis, 564
Fibrinolytic therapy, 172–173, 172*t*, 173*t*, 184*t*
Fibroblast growth factor receptor (FGFR) inhibitor, 2186*t*
Fibroblasts, 375
Finasteride, 1421*t*, 1699–1700
Fingolimod, 862*t*, 863*t*, 865–866
Fish oil, 127, 684, 730
Fixed-schedule therapy, 1072
Flakka, 1061
Flecainide, 292, 292*t*, 294*t*, 295*t*, 296*t*
Flexible sigmoidoscopy, 2281
FLG gene, 1676
FLT3 inhibitors, 2201
Fluconazole
for coccidioidomycosis, 2057–2058
dosing by age group, 1799*t*
for febrile neutropenia, 2092*t*
for fungal infections, 2049*t*
for histoplasmosis, 2054
for HSCT infections, 2103
for invasive fungal infections, 2072
monitoring of, 2073*t*
for onychomycosis, 2041
for oropharyngeal candidiasis, 2032, 2033*t*
for peritonitis, 692*t*
for vulvovaginal candidiasis, 2027, 2027*t*, 2028
Flucytosin, for febrile neutropenia, 2093*t*

Flucytosine
dosing by age group, 1799*t*
for febrile neutropenia, 2095*t*
for invasive fungal infections, 2071
monitoring of, 2073*t*
for peritonitis, 692*t*
Fludarabine, 2180*t*, 2193, 2338, 2401, 2454*t*
Fludrocortisone, 683, 1306
Fluid, 2484, 2485*t*
Fluid resuscitation
for distributive (septic) shock, 357–358
for hypovolemic shock, 358
Flumazenil, 573, 1063
Flunisolide, 383*t*
Fluoride, e35
Fluoropyrimidines, 2179, 2192
Fluoroquinolones, 1963*t*
for acne vulgaris, 1641
adverse effects and monitoring of, 1778*t*
dosing of, 1819*t*
for febrile neutropenia, 2090
for HSCT infections, 2101
for pneumonia, 1819*t*
for prostatitis, 1971
for UTIs, 1963*t*
Fluorouracil, 2180*t*, 2286–2288, 2290*t*
Fluoxetine, 1036, 1037, 1133*t*, 1135*t*, 1138*t*, 1140*t*, 1144*t*, 1178*t*. *See also* Selective serotonin reuptake inhibitors (SSRIs)
for multiple sclerosis, 869*t*
for narcolepsy, 1209*t*
for obsessive-compulsive disorder, 1197*t*
for postpartum depression, 1331
for posttraumatic stress disorder, 1191*t*, 1193*t*
Fluoxymesterone, 1401, 2246*t*
Fluphenazine. *See also* Antipsychotics
adverse effects of, 1107*t*

for schizophrenia, 1096*t*, 1099, 1100, 1101*t*–1102*t*
Flurazepam, 1205*t*
Flurbiprofen, 846, 1504*t*
Flutamide, 1701, 2311*t*, 2313
Fluticasone furoate, 383*t*
Fluticasone propionate, 383*t*
Fluvoxamine, 1037, 1133*t*, 1138*t*, 1140*t*, 1178*t*. *See also* Selective serotonin reuptake inhibitors (SSRIs)
for obsessive-compulsive disorder, 1197*t*
for social anxiety disorder, 1182*t*
FMS-Like Tyrosine Kinase-3 (FLT3) Inhibitors, 2186*t*
Focal onset seizures, 879–881
Focal segmental glomerulosclerosis, 708, 725–726
clinical presentation of, 725
epidemiology of, 725
etiology of, 725
pathophysiology of, 725
prognosis of, 726
steroid-resistant, 726
treatment of, 725–726
angiotensin receptor blockers, 726
angiotensin-converting enzyme inhibitors, 726
calcineurin inhibitors, 725–726
cytotoxic agents, 725
mycophenolate mofetil, 726
steroids, 725
Focal seizures, 879–881. *See also* Epilepsy
Folate, 1141, 2276–2277
Folate antagonists, 2193–2194
methotrexate, 2193
pemetrexed, 2193
pralatrexate, 2193–2194
Folic acid, 1715, 2480*t*
Folic acid deficiency anemia, 1720–1721
epidemiology of, 1720
etiology of, 1720–1721

laboratory evaluation of, 1721
pathophysiology of, 1721
treatment of, 1721
Follicle-stimulating hormone (FSH), 2305
Follicular phase, in menstrual cycle, 43
Folliculitis, 1626, 1857–1859
clinical presentation of, 1857*b*
definition of, 1857
etiology of, 1857
treatment of, 1859
evidence-based, 1860*t*
outcomes of
desired, 1857–1858
therapeutic, evaluation of, 1859
pharmacologic, 1859, 1862*t*
Fondaparinux
for acute coronary syndromes, 178*t*, 179–180
adverse effects of, 264
dosing and administration of, 265
efficacy of, 264
interactions, 265
mechanism of action, 264
for venous thromboembolism, 257, 264–265
Food, thermogenic effect of, 2534
Food poisoning, 1934–1936, 1935*t*
botulinum toxin in, 1935–1936
etiology of, 1935*t*
pathogens in, 1935*t*
treatment of, 1935–1936
Foot ulcers, 1255
Fosamprenavir, 2153*t*, 2154
Fosaprepitant, 530*t*, 534*t*, 535
Foscarnet
dosing by age group, 1799*t*
drug interactions, 1775*t*
for febrile neutropenia, 2093*t*, 2095*t*

Fosfomycin trometamol, 1963*t*
Fosphenytoin, 922*t*
for epilepsy, 889
for status epilepticus, 921*t*, 923
Fournier gangrene, 1870
Front-loading therapy, 1072
Frovatriptan, 995*f*, 996*t*, 998*t*
Fructose, 557
Fulvestrant, 2246*t*, 2248
Functional incontinence, 1433–1434. *See also* Urinary incontinence
Functional residual capacity (FRC), 408
Fungal infections, invasive, 2045–2073. *See also specific infections*
aspergillosis, 2066–2073
blastomycosis, 2054–2056
Candida infections, 2061
candidemia, 2061–2065
candiduria, 2065–2066
coccidioidomycosis, 2056–2058
cryptococcosis, 2058–2061
diagnosis of, 2050
histoplasmosis, 2050–2054
mycology of, 2045–2050, 2046*f*
antifungal agent resistance in, 2049, 2049*f*
antifungal agent susceptibility in, 2046–2049
clinical *vs.* microbial resistance, 2046
pathogenesis and epidemiology of, 2049–2050
risk factors for, 2050
sepsis and, 2008–2009
treatment of, 2050
antifungal therapy in, 2070–2073
adverse effects of, 2070*f*
amphotericin B, 2069, 2070–2071
azoles, 2071
drug interactions, 2072–2073
drug monitoring in, 2073, 2073*t*
echinocandins, 2071

fluconazole, 2072
flucytosine, 2071
isavuconazole, 2072
itraconazole, 2071–2072
posaconazole, 2072
voriconazole, 2072
for emerging pathogens, 2069
Fusarium, 2069
mucor infections, 2069
Scedosporium, 2069
Fungal infections, superficial, 2025–2041. *See also specific infections*
oropharyngeal and esophageal candidiasis, 2028–2036
prevalence of, 2025
skin, hair, and nail mycotic infections, 2036–2041
vulvovaginal candidiasis, 2025–2028
Furosemide, 207*t*, 575*t*, 805*t*
Furuncles, 1857–1859
clinical presentation of, 1857*b*
definition of, 1857
etiology of, 1857
treatment of, 1859
evidence-based, 1860*t*
outcomes of
desired, 1857–1858
therapeutic, evaluation of, 1859
pharmacologic, 1859, 1862*t*
Fusarium, 2048*t*, 2069
Fusion proteins, 2192*t*
moxetumomab pasudotox, 2208
ziv-aflibercept, 2208
Fusobacterium varium, 1942

G

GABA type B agonists, 477
Gabapentin, 969*t*
adverse effects of, 893*t*

for chronic pancreatitis, 590
drug interactions, 893*t*
for epilepsy, 892*t*–893*t*
mechanism of action, 892*t*
in menopause and perimenopausal/postmenopausal hormone therapy, 1376*t*
for multiple sclerosis, 869, 869*t*
for pain management, 967
for social anxiety disorder, 1182*t*
Gait
deep brain stimulation and, 950
festinating, 948
hyponatremia and, 761
multiple sclerosis and, 857*b*
osteoporosis and, 1550
propulsive, 948
pseudoparkinsonism and, 1110
spasticity and, 868–869
Galantamine, 842, 843*t*, 844*t*
Gallbladder disease, in menopausal hormone therapy, 1371
Gallstones, 1753
Gamma-aminobutyric acid (GABA)
satus epilepticus and, 915
in schizophrenia, 1093
Gamma-hydrobutyric acid (GHB), 1044
Ganciclovir
dosing by age group, 1799*t*
for febrile neutropenia, 2093*t*, 2095*t*
for HSCT infections, 2102
for solid-organ transplant recipients, 2106
Gas gangrene, 1870
Gastric emptying, 465–466
Gastric inhibitory peptide, 2515*t*
Gastric perforation, 488
Gastrin, 2515*t*
Gastrin-releasing peptide (GRP), 580
Gastritis, *vs.* peptic ulcer, 483

Gastroduodenal surgery, antimicrobial prophylaxis in, 2116
Gastroenteritis
in children, 540
clinical presentation of, 1926–1927
pathophysiology of, 1926
Gastroesophageal reflux disease (GERD), 463–468
asthma and, 377
in children, 478, 478*t*
clinical presentation of, 466–468, 467*b*
definition of, 463
diagnosis of, 466–468, 468*f*
in elderly, 478–479
epidemiology of, 464
extraesophageal, 477–478
foods and medications that affect, 465*t*
incidence of, 464
pathophysiology of, 464–466
lower esophageal sphincter pressure in, 465
anatomic factors in, 465
esophageal clearance in, 465
mucosal resistance in, 465
gastric emptying in, 465–466
increased intra-abdominal pressure in, 465–466
refluxate composition in, 466
complications of, 466
patient care process for, 470*b*
risk factors for, 464
symptoms of, 463–464
Gastroesophageal reflux disease (GERD) treatment, 469–479
evidence-based, 471*t*
general approach to, 469
nonpharmacologic therapy in, 469–474
antireflux surgery, 471*t*, 473
endoscopic therapies, 473–474
interventional approaches, 473–474
lifestyle modifications in, 469–473, 471*t*, 473*t*

magnetic sphincter augmentation, 473
radiofrequency ablation, 473–474
outcomes of
desired, 469
evaluation of, 479
pharmacologic therapy in, 474–477
acid suppression therapy, 471*t*, 474–476
antacid-alginic acid products, 474
antacids, 474
clinical controversies in, 477
combination therapy in, 477
drug monitoring in, 475*t*
H2-receptor antagonists, 473*t*, 476, 477
H_2-receptor antagonists, nonprescription, 472*t*, 474
maintenance therapy, 471*t*, 477
H2-receptor antagonists, 477
proton pump inhibitors, 477
mucosal protectants, 477
patient-directed therapy, 472*t*, 474
antacids and antacid-alginic products, 474
H2-receptor antagonists, nonprescription, 474
proton pump inhibitors, 474–476
promotility agents, 471*t*, 476–477
bethanechol, 476
metoclopramide, 476
proton pump inhibitors, 472*t*, 474–476, 477, 478*t*
in special populations, 477–479
in children, 478, 478*t*
in elderly, 478–479
extraesophageal GERD, 477–478
refractory GERD, 479
therapeutic approach, 472*t*–473*t*
Gastrointestinal endoscopy, antimicrobial prophylaxis in, 2117*t*, 2119
Gastrointestinal enzymes and hormones, 2515*t*
Gastrointestinal infection, 1923–1927

in children, 1928*t*
clinical presentation of, 1926–1927
Clostridium difficile, 1932–1933
complications of, 1927
epidemiology of, 1923–1924
etiology of, 1924–1926, 1924*t*, 1925*t*
food poisoning, 1934–1936
pathophysiology of, 1926
prevention of, 1931–1932
traveler's diarrhea, 1933–1934
Gastrointestinal infection treatment, 1927–1931
for *Clostridium difficile* infection, 1932–1933, 1933*t*
general approach to, 1927
rehydration therapy in, 1927–1929, 1928*t*
antimicrobial therapy in, 1930–1931, 1930*t*
antimotility agents in, 1931
oral zinc supplementation in, 1931
probiotics in, 1931
outcomes, evaluation of, 1932
for traveler's diarrhea, 1933–1934
Gastrointestinal surgery, antimicrobial prophylaxis in, 2116
Gastrointestinal tract evaluation, e461
Gatifloxacin, 1231*t*
Gefitinib, 2185*t*, 2201
Gemcitabine, 2180*t*, 2192–2193, 2249*t*, 2358*t*, 2359, 2359*t*
Gemella morbillorum, 1890
Gemtuzumab ozogamicin, 2191*t*, 2207
Gene therapy. *See specific disorders*
Generalized anxiety disorder (GAD), 1168–1177. *See also* Anxiety disorders
clinical presentation of, 1168*b*
etiology of, 1166
pathophysiology of, 1166–1167
prevalence of, 1165
treatment of, 1169–1177
algorithm for, 1172*f*
children and adolescents, 1177

drug choices for, 1169*t*
elderly, 1177
general approach to, 1169
hepatic disease patients, 1177
nonpharmacologic therapy in, 1169–1170
outcomes of
desired, 1169
therapeutic, evaluation of, 1177
pharmacologic therapy in, 1170–1177
adverse effects of, 1174*t*–1175*t*
alternative drugs, 1177
antidepressants, 1171–1173
benzodiazepines, 1171*t*, 1173–1176
buspirone, 1176–1177
nonbenzodiazapines, 1171*t*
pregnant women, 1177
Generalized onset seizures, 881
Genital herpes, 1323*t*, 1985–1988
clinical presentation of, 1986, 1986*t*
complications of, 1986
diagnosis of, 1986–1987
epidemiology of, 1985
etiology of, 1985
pathophysiology of, 1985–1986
in pregnancy, 1323
treatment of, 1987–1988, 1987*t*
first-episode infections, 1987
in immunocompromised patients, 1988
outcomes, evaluation of, 1988
recurrent infections, 1987–1988
Genital ulcers, 1977*t*
Genital warts, 1977*t*, 1990
Gentamicin
for cystic fibrosis, 454*t*
dosing by age group, 1799*t*
for febrile neutropenia, 2092*t*

for intra-abdominal infection, 1947
for UTIs, 1963*t*
Gentian violet, 2032
Geographic atrophy, 1607
Geriatrics, e67. *See also* Aging
antiemetic use in, 540
chronic diseases in, e67
epidemiology of aging in, e67
health, assessment of, e71
healthcare, delivery of, e71
mechanisms of aging, e67
Germline mutation, 2279*t*
Gestational age, 1316
Gestational diabetes mellitus (GDM), 1231*t*
patient care process for, 1316*b*
screening for, 1236, 1237*t*, 1319, 1320*t*
Gestational hypertension, 100
Gestational transient thyrotoxicosis (GTT), 1321
Gilteritinib, 2186*t*
Ginkgo biloba, 846, 871*t*
Glandular tissue, 1412
Glargine, 1239, 1240*t*
Glasdegib, 2186*t*
Glasgow Coma Scale, 931*t*
Glatiramer acetate, 862*t*, 863*t*, 864*t*, 865
Glaucoma, 1589–1595
classification of, 1589, 1590*t*
clinical presentation of, 1594*b*
closed-angle, 1589
definition of, 1589
drug-induced, 1595, 1595*t*
epidemiology of, 1591–1592
normal-tension, 1591
ocular hypertension in, 1591–1592
epidemiology of, 1591–1592
open-angle, 1589

clinical presentation of, 1593–1594
epidemiology of, 1591–1592
etiology of, 1592–1593
pathophysiology of, 1593
prognosis of, 1594
patient care process for, 1596*b*
physiology of
aqueous humor dynamics in, 1589–1591, 1590*f*
genetics in, 1591
intraocular pressure in, 1589–1591
optic disk and visual fields in, 1591, 1592*f*, 1592*t*
primary-angle closure, 1589
clinical presentation of, 1595
epidemiology of, 1594
etiology of, 1594–1595
pathophysiology of, 1595
suspects, 1589, 1591–1592
Glaucoma treatment, 1595–1604
for acute angle closure crisis, 1599
for glaucoma suspects, 1595–1597
for ocular hypertension, 1595–1597
for open-angle glaucoma, 1597–1599, 1597*b*
pharmacologic therapy in, 1599–1603, 1600*t*–1601*t*
α2-adrenergic agonists, 1601–1602
β-blockers, 1599–1601
carbonic anhydrase inhibitors, 1602
dipivefrin, 1598
future drugs, 1603
parasympathomimetic agents, 1602–1603
prostaglandin analogs, 1599, 1600*t*
rho kinase inhibitors, 1602
Glecaprevir, 609–610
Gleevec. *See* Imatinib mesylate
Gliadins, 616
Glimepiride, 1242*t*, 1243
Glipizide, 1242*t*, 1243

Glomerular basement membrane (GBM), 715
Glomerular disease treatment, 719–722
  for focal segmental glomerulosclerosis, 725–726
  general approach to, 719
  for immunoglobulin A nephropathy, 729–731
  for membranoproliferative glomerulonephritis, 728–729
  for membranous nephropathy, 726–728
  for minimal-change nephropathy, 722–724
  nonpharmacologic therapy in, 719
  pharmacologic therapy in, 719–722
    angiotensin receptor blockers, 721
    angiotensin-converting enzyme inhibitors, 721
    anticoagulants, 722
    antihypertensives, 720–721
    antiproteinuria agents, 721
    diuretics, 719–720
    immunosuppressive agents, 719
    nonsteroidal anti-inflammatory drugs, 721
    outcomes of, evaluation of, 722, 722*t*
    statins, 721
Glomerular diseases, 650, 708, 715–735. *See also specific types*
  ANCA-associated vasculitis, 733–734
  anti-glomerular basement membrane glomerulonephritis, 734
  clinical bottomline for, 735
  clinical presentation of, 717–719, 717*b*
    glomerulonephritis, 719*f*
    nephritic syndrome, 717*b*, 717*t*
    nephrotic syndrome, 718
  diagnostic considerations in, 718–719, 718*t*
  epidemiology of, 716
  etiology of, 716
  focal segmental glomerulosclerosis, 708, 725–726
  histology of, 716–717
  immunoglobulin A nephropathy, 729–731
  lupus nephritis, 731–733
  membranoproliferative glomerulonephritis, 728–729

membranous nephropathy, 708, 726–728
minimal change, 708
minimal-change nephropathy, 722–725
outcomes of, therapeutic, evaluation of, 1603
pathophysiology of, 716–717
patient care process for, 720*b*
poststreptococcal glomerulonephritis, 734–735
Glomerular filtration rate (GFR), e623
Glomerulonephritis. *See* Glomerular diseases
Glomerulus, 715–716, 716*f*
Glossitis, median rhomboid, 2031*t*
Glucagon, 1233, 2515*t*
Glucagon-like peptide 1 receptor agonists, 1244–1246, 1245*t*, 2544*t*, 2548–2549, 2550*t*
liragrutide, 2548–2549
Glucarpidase, 2193
Glucocorticoid-receptor blocking agents, 1300–1301
Glucocorticoids, 1231*t*, 1292. *See also* Corticosteroids
for acute chest syndrome, 1760
for adrenal gland disorders, 1308–1309, 1308*t*, 1309*t*
adverse effects of, 396*t*
for nausea and vomiting, 540
for rheumatoid arthritis, 1530
for systemic lupus erythematosus, 1461*t*, 1462*t*
Glucosamine, 1512
Glucose, 1252*f*
Glucose intolerance, 1119*t*
Glucose transporter 9 (GLUT9), 1583
α-Glucosidase inhibitors, 1248, 1258
Glulisine, 1239, 1240*t*
Glutamine, 1758, 2495
γ-Glutamyl transpeptidase, 565
Gluten, 616
Gluten intolerance. *See* Celiac disease
Gluten-sensitive enteropathy. *See* Celiac disease
Glyburide, 1242*t*, 1243

Glycemia, normal and abnormal, 1236*t*
Glycemic control, 634–635, 1236–1237
Glycemic goals, 1237–1238, 1238*t*
Glycerin, 554
Glycolic acid, 1634
Glycopeptides, adverse effects and monitoring of, 1777*t*
Glycoprotein IIb/IIIa receptor inhibitors
  for acute coronary syndromes, 174*t*, 177–178, 184*t*
  for NSTE-ACSs, 177–178
Glycosaminoglycan, 1959
Glycyrrhetinic acid, 804–805
Goiters, multinodular, 1271
Golimumab, 516, 516*t*, 519, 521, 522, 523*t*, 1525*t*, 1528
Gompertzian growth curve, 2173, 2173*f*
Gonadotropin-releasing hormone (GnRH)
  for adrenal gland disorders, 1307
  agonists, for endometriosis, 1358*t*, 1359
  antagonists, 1358*t*, 1359, 2312*t*, 2313
Gonococcal arthritis, 1996
Gonococcal ophthalmia, 1979
Gonorrhea, 1322, 1323*t*, 1976–1980
  clinical presentation of, 1977–1978, 1977*t*
  diagnosis of, 1978
  epidemiology of, 1976–1977
  etiology of, 1976–1977
  pathophysiology of, 1977
  patient care process for, 1979*b*
  in pregnancy, 1978–1979
  treatment of, 1978–1980, 1980*t*
    outcomes, evaluation of, 1979–1980
Goserelin, 2312*t*
  for breast cancer, 2246*t*
  for endometriosis, 1358*t*
Gout and hyperuricemia, 1567–1585
  associated conditions, 1569*t*
  clinical presentation of, 1569–1572, 1570*b*, 1570*f*

gouty nephropathy, 1572
tophaceous gout, 1572, 1572*f*
uric acid nephrolithiasis, 1571–1572
definition of, 1567
diagnosis of, 1571*t*
drug-induced, 1569*t*
epidemiology of, 1567–1568
etiology and pathophysiology of, 1568–1569
overproduction of uric acid, 1568–1569
underexcretion of uric acid, 1569
patient care process for, 1573*b*
Gout and hyperuricemia treatment, 1572–1585
for acute gouty arthritis, 1572–1578, 1574*t*–1575*t*
antiinflammatory prophylaxis for urate-lowering therapy in, 1582–1583
for hyperuricemia in gout, 1578–1582
outcomes of, therapeutic, evaluation of, 1584–1585
pharmacologic therapy in
investigational drugs, 1583
arhalofenate, 1583
interleukin-1 inhibitors, 1583
for nephrolithiasis, 1583–1584
pharmacotherapy considerations for, 1584, 1585*t*
uric acid lowering in absence of gout, 1584
for uric acid nephrolithiasis, 1583–1584
Gouty arthritis, acute, 1569–1571
clinical presentation of, 1569–1571, 1570*b*, 1570*f*
diagnosis of, 1570–1571, 1571*t*
treatment of, 1502–1508
algorithm for, 1578*f*
nonpharmacologic therapy in, 1572
pharmacologic therapy in, 1574*t*–1576*t*
colchicine, 1576–1578, 1579*t*
corticosteroids, 1575*t*–1576*t*, 1576, 1577*t*
NSAIDs, 1572–1576, 1574*t*, 1577*t*
Gouty nephropathy, 1572
Graft-versus-host disease, 2459–2463

acute, 2459–2460
consensus grading of, 2460*t*
incidence of, 2459
pathophysiology of, 2459
prevention of, 2460–2462, 2461*t*
principal target organs in, 2459
treatment of, 2462
chronic, 2459, 2462–2463
clinical manifestations of, 2459
definition of, 2459
hyperacute, 2459
Gram-negative bacilli, 1782–1783
Gram-negative bacteria, 1867, 1892*t*
enteric, 1814
nonenteric, 1814
sepsis, 2008
treatment of, 1820–1821
Gram-negative cocci, 1782
Gram-positive bacilli, 1782
Gram-positive bacteria, 1857
Gram-positive cocci, 1782
Gram-positive pathogens, 1819–1820
Granisetron, 530*t*, 531*t*, 538, 539*t*
Graves' disease, 1269–1270, 1269*f*, 1273*t*
treatment of, 1278–1279
Gravidity, 1316
Gray baby syndrome, e61
Grazoprevir, 609
Griseofulvin, 2041
Group A β-hemolytic Streptococcus (GABHS) pharyngitis, 1834–1838. *See also* Pharyngitis, acute
clinical presentation of, 1834–1835, 1835*b*
definition of, 1834
epidemiology of, 1834
etiology of, 1834
pathophysiology of, 1834

treatment of, 1835–1838
general approach to, 1835
nonpharmacologic therapy in, 1835
outcomes of, desired, 1835
pharmacologic therapy in, 1835–1838, 1836*t*
Group B *Streptococcus* infection, 1328–1329
Guanfacine
for ADHD, 1019–1020
adverse effects of, 1020*t*
for autism spectrum disorder, 1224*t*
dosing, 1020*t*
Guanylate cyclase stimulator, 443, 444*t*
Guideline-directed medical therapy, 97
Guillian-Barré syndrome, 1927
Guselkumab, 1667

H

H_2-receptor antagonists, 534*t*, 535, 474, 475*t*, 476, 477, 494*t*, 496, 502. *See also specific agents*
H3N2v variant of influenza A virus, 1843–1844
HACEK group endocarditis, 1896. *See also* Endocarditis, infective
Haemophilus influenzae, 1751, 1804, 1808*t*, 1820*t*, 1827
type b, 1793, 1996
Haemophilus influenzae type B (Hib), 2131–2132
Hair cycle, 1692–1693, 1693*f*, 1694, 1694*t*
Hair follicles, 1691–1693, 1692*f*, 1693*f*
Hair loss. *See* Alopecia
Hair restoration surgery, 1700
Hair transplantation, 1701
Half-life, e15
Hallucinations, in Parkinson disease, 950*t*
Hallucinogens, 1060–1062
Halogenated hydroxyphenols, 1645
Haloperidol. *See also* Antipsychotics
adverse effects of, 1020*t*, 1107*t*
dosing, 1020*t*, 1073*t*, 1096*t*

mechanism of action, 1105*t*
for nausea and vomiting, 533*t*, 534, 539*t*
pharmacokinetics of, 1106*t*
for schizophrenia, 1096*t*, 1099, 1101*t*–1102*t*, 1116*t*
Halothane, 400
Hand-and-foot syndrome
in cancer patients, 2215
clinical presentation of, 1750
Hand-foot skin reaction, 2215
Harvard Medical Practice Study, e13
Harvey-Bradshaw Index (HBI), 512
Hashimoto's disease, 1280–1281
Hay fever. *See* Rhinitis, allergic
HDAC inhibitors
belinostat, 2201
panobinostat, 2201
romidepsin, 2201
vorinostat, 2201
Head and neck surgery, antimicrobial prophylaxis in, 2117*t*, 2120
Headache disorders, e23, 989–1004
anatomy of, e23
classification of, 989, 990*t*
cluster headache, 1002–1003 (*See also* Cluster headache treatment)
clinical presentation of, 1002
epidemiology of, 1002
pathophysiology of, 1002
treatment of, 1002–1003
epidemiology of, e23
etiology of, e23
hemodialysis complications, 682*t*
mechanism of disease, e23
migraine headache, 989–992
clinical presentation of, 991*b*, 992
diagnosis of, 992*t*
epidemiology of, 989–990
etiology of, 990

pathophysiology of, 990–992, 991*f*
treatment of, 992–1001 (*See also* Migraine headache treatment)
patient care process for, 993*b*
in pregnancy, 1323–1324
prevalence of, 989
tension-type headache, 1001–1002
clinical presentation of, 1001
epidemiology of, 1001
pathophysiology of, 1001
treatment of, 1001–1002
nonpharmacologic therapy in, 1001–1002
outcomes of, desired, 1001
pharmacologic therapy in, 1002
Health literacy, e9
Health Resources and Services Administration's Vaccine Injury Table, 2131
Healthcare, delivery of, e71
Healthcare Common Procedural Coding System (HCPCS), 7*t*
Healthcare-associated pneumonia. *See* Hospital-acquired pneumonia
Healthy People 2020, e9
Heart
electrical property of, 287
mechanical property of, 287
Heart disease, hypertension and, 90
Heart failure (HF), chronic, 191–199. *See also* Acute decompensated heart failure (ADHF)
causes of, 192–193, 192*t*
clinical presentation of, 198–199, 199*b*
diagnosis in, 198–199
signs and symptoms in, 198
definition of, 191–192
epidemiology of, 192
etiology of, 192–193
incidence of, 192
pathophysiology of, 193–198, 195*f*
cardiac function, normal, 193–194, 193*f*
compensatory mechanisms in, 194–196, 194*t*

fluid retention and increased preload, 194
tachycardia and increased contractility, 194
vasoconstriction and increased afterload, 194–195
ventricular hypertrophy and remodeling, 195–196, 196*f*
heart failure with preserved ejection fraction, 193–194
neurohormonal model and therapy, 196–197
aldosterone, 197
angiotensin II, 196–197
arginine vasopressin, 197
natriuretic peptides, 197
norepinephrine, 197
precipitating/exacerbating factors in, 197–198, 198*t*
patient care process for, 201*b*
Heart failure (HF), chronic, treatment of, 200–217
functional classification of, 200*t*
general approach to, 201–204, 204*t*
for heart failure with preserved ejection fraction, 202*t*, 204*t*
for stage A, 202, 203*f*
for stage B, 202, 203*f*
for stage C, 202–204, 203*f*
for stage D, 204
nonpharmacologic, 204
outcomes of, desired, 200–201
pharmacologic, 204–217
ACE inhibitors, 209–210
aldosterone antagonists, 213–214
angiotensin II receptor blockers/ neprilysin inhibitor, 210–211
angiotensin receptor blockers, 210
β-blockers, 211–212
calcium channel blockers, 215–216
for concomitant disorders
angina, 217
atrial fibrillation, 217
diabetes, 217
hypertension, 216–217
digoxin, 214–215

diuretics, 205–209
for heart failure with preserved ejection fraction, 204–205
ivabradine, 214
nitrates and hydralazine, 214
for selected patients, 214–216
calcium channel blockers, 215–216
digoxin, 214–215, 216*t*
ivabradine, 214
nitrates and hydralazine, 214
for special populations, 216–217
staging system, 200*f*
therapeutic outcomes, evaluation of, 217–218
Heart failure with preserved ejection fraction (HFpEF), 193–194
causes of, 192
clinical presentation of, 198–199
clinical trials on, 205*t*
patient care process for, 201*b*
targeted approach to, 202*t*
treatment of
pharmacologic therapy, 204–205, 204*t*
diuretics, 204*t*
ACE inhibitors, 204*t*
angiotensin receptor blockers, 204*t*
aldosterone antagonists, 204*t*
calcium channel blockers, 204*t*
clinical trials on, 205*t*
aldosterone antagonists, 213–214
nitrates and hydralazine, 214
Heart failure with reduced ejection fraction (HFrEF), 191, 192
patient care process for, 206*b*
treatment of
pharmacologic therapy, 205–210, 207*t*–208*t*
ACE inhibitors, 209–210
aldosterone antagonists, 207*t*
angiotensin converting enzyme inhibitors, 207*t*
angiotensin II receptor blockers, 192–211

angiotensin receptor blockers, 207*t*
β-blockers, 211–212
calcium channel blockers, 215–216
digoxin, 214–216, 216*t*
diuretics, 205–209, 207*t*
nitrates and hydralazine, 214
Heart transplantation. *See also* Transplantation, solid-organ
acute cellular rejection in, 1479
for acute decompensated heart failure, 237
chronic rejection in, 1479
epidemiology and etiology of, 1475
physiologic consequences of, 1476–1477
Heavy menstrual bleeding, 1341–1345
clinical presentation of, 1343*b*
definition of, 1341
epidemiology of, 1341
etiology of, 1341
pathophysiology of, 1337*t*, 1341
treatment of, 1341–1345
evaluation of, 1345
general approach to, 1343
nonpharmacologic therapy in, 1343
outcomes of, desired, 1341
pharmacologic therapy in, 139*t*, 1343–1344
algorithm for, 1344*f*
LNG-IUS, 1344
medroxyprogesterone acetate, 1344
NSAIDs, 1344
tranexamic acid, 1344
for special populations, 1344–1345
Hedgehog pathway inhibitors, 2186*t*, 2201–2202
Helicobacter pylori infection
drug regimens for, 493*t*
eradication after initial treatment failure, 495
factors that predict eradication outcome, 495–496
peptic ulcer disease and, 484–485, 485*f*, 487, 492–493, 493*t*

tests for, 489, 490*t*
Hematemesis, 501
Hematogenous osteomyelitis, 1996
Hematologic disorders, drug-induced, e1767
aplastic anemia, e1767
incidence of, e1767
Hematopoietic stem cell transplantation (HSCT), 2099–2101, 2338, 2449–2463, 2450*f*
allogeneic, 2377–2378, 2421
autologous, 2378, 2419–2421
for chronic lymphocytic leukemia, 2404
for chronic myeloid leukemia, 2396
complications of, 2457–2463
graft failure, 2458–2459
graft-versus-host disease, 2459–2463
infections, 2463
late, 2463
pulmonary, 2458
sinusoidal obstruction syndrome, 2457–2458
definition of, 2449
donor selection in, 2450–2451
hematopoietic stem cells in, 2451–2453
histocompatibility testing in, 2450–2451
immunization in, 2130
infections in, 2099–2101
etiology and clinical presentation of, 2099–2101, 2100*f*
prophylaxis of, 2101
bacterial infections, 2101–2102
fungal infections, 2103
viral infections, 2102–2103
treatment of, 2101–2103
outcome evaluation for, therapeutic, 2103
outcomes of, desired, 2101
malignant cell eradication in, 2453–2457
conditioning regimens, 2453–2454
myeloablative, 2454

reduced-intensity, 2454–2456
posttransplant therapy in, 2456–2457
chemotherapy in, 2457
donor lymphocyte infusion, 2455
immunotherapy in, 2456
monoclonal antibodies, 2456–2457
targeted therapy in, 2457
Hematuria, 717, 1961
Heme, iron incorporation into, 1711
Hemochromatosis, 1231*t*
Hemocrit, 1713
Hemodiafiltration, 680–681
Hemodialysis, 679–686
access in, 679, 680*f*
arteriovenous fistula, 679, 680*f*
synthetic arteriovenous forearm graft, 679, 680*f*
adequacy of, 681
advantages and disadvantages of, 678*t*
complication management in
hypertension, 684
for hypotension, 682*t*, 683
for infection, 685–686, 686*t*
for muscle cramps, 684, 684*t*
for vascular access thrombosis, 684–685, 685*t*
complications of, 681–683, 682*t*
CKD complications, 683
intradialytic hypotension, 683
drug dose regimen in, 681
in renal replacement therapy, 748–750, 749*b*
hyperkalemia and, 805*t*
morbidity and mortality in, 678
nocturnal, 750
principles of, 679
procedure complications, 682
procedures of, 679–681, 680*f*
short-daily, 750

statistics on, 677
vascular access complications, 682–683
Hemodynamic monitoring, 235
Hemoglobin
laboratory evaluation of, 1713
mean cell hemoglobin, 1714
mean cell hemoglobin concentration, 1714
synthesis of, 1711
Hemoglobin A, 1749
Hemophilia, 1729–1739
clinical manifestations of, 1731*t*
clinical presentation of, 1731–1732, 1732*b*
diagnosis of, 1731–1732, 1731*t*
epidemiology of, 1730–1731
etiology of, 1730–1731
incidence of, 1729
Hemophilia treatment, 1732–1739
algorithm for, 1738*f*
on demand therapy in, 1735–1736
factor concentrates, 1733*t*
gene therapy in, 1737–1738
for hemophilia A, 1733–1735
antifibrinolytic therapy, 1735
desmopressin, 1735
factor replacement therapy, 1734*t*
factor VIII concentrate replacement, 1733–1734
pharmacologic therapy in, 1734–1735
plasma-derived factor VIII products, 1733
recombinant factor VIII, 1733
for hemophilia B
factor IX concentrate replacement, 1735
factor replacement therapy, 1734*t*
plasma-derived factor IX products, 1735
recombinant factor IX, 1735
history of, 1732–1733
for inhibitors, 1736–1737

outcome evaluation for, therapeutic, 1738–1739
outcomes, evaluation of, 1738–1739
pain management, 1738
prophylaxis *vs.* on-demand therapy, 1735–1736
surgery in, 1738
Hemorrhagic shock. *See* Hypovolemic shock treatment
Hemorrhagic stroke, 273
etiology of, 273–274
pathophysiology of, 275
treatment of, nonpharmacologic therapy in, 278
Heparin
low-molecular-weight, 1321
for acute coronary syndromes, 179
adverse effects of, 263–264
dosing and administration of, 264
efficacy of, 263
interactions, 264
mechanism of action, 263, 264*f*
for venous thromboembolism, 256, 256*t*
unfractionated, 684, 1321
for acute coronary syndromes, 178–179, 178*t*
adverse effects of, 265
dosing and administration of, 266
efficacy of, 265
interactions, 265
for ischemic stroke, 280
mechanism of action, 265
for venous thromboembolism, 257, 257*t*
Hepatic encephalopathy, 563–564
drugs and neurotransmission in, 573
episodic, 572
grading in, 572, 573*t*
persistent, 572
recurrent, 572
Hepatic lobule, 562*f*
Hepatitis, rheumatoid arthritis treatment in, 1531

Hepatitis A, 595–597
cirrhosis in, 601
clinical presentation of, 596–597, 596*t*
diagnosis of, 596
epidemiology of, 595–596
etiology of, 596
hepatocellular carcinoma in, 602
with HIV, 2160*t*
pathophysiology of, 596
prevention of, 597
immunoglobulin, 599
risk factors for, 596
symptoms of, 596*t*
treatment of, 597–599
general approach to, 597
immunoglobulin, 599
outcomes of, desired, 597
vaccines, 597–598, 597*t*
Hepatitis B, 599–605
chronic, 600
cirrhosis and, 601, 601*t*
clinical presentation of, 600–602
epidemiology of, 599
etiology of, 599
hepatocellular carcinoma in, 602
infection phases in, 600–602, 601*t*
pathophysiology of, 599–600
phases of, 601*t*
risk factors for, 600*t*
symptoms of, 596*t*
vaccine prevention of, 602, 602*t*
virus mutations in, 605
Hepatitis B treatment, 602–605
in children, 604
in cirrhosis, 604
general approach to, 602–603

with hepatitis C, 604
with hepatitis D, 604
with HIV, 604, 2160*t*
with immunosuppressive or cytotoxic therapy, 604–605
mutations, 605
nonpharmacologic therapy in, 603
outcomes of, desired, 602
patient counseling in, 603
pharmacologic therapy in, 603–604
adefovir, 604
combination therapy in, 604
entecavir, 603
interferon, 603
lamivudine, 604
telbivudine, 604
tenofovir, 603–604
in pregnancy, 604
resistance concerns in, 605
in special populations, 604–605
Hepatitis C, 605–611
cirrhosis in, 606
clinical presentation of, 606–607
epidemiology of, 605–606
etiology of, 606
pathophysiology of, 606
patient care process for, 598*b*
prevention of, 611
screening for, 606*t*
symptoms of, 596*t*
transmission of, 605
Hepatitis C treatment, 607–610
in acute exposures, 610
in alcoholism, 610
in children, 611
counseling in, 607
in DAA-experienced patients, 610

with decompensated cirrhosis, 610
in end-stage renal disease, 610
general approach to, 607
with HCV GT3, 610
in HIV, 610–611
in intravenous drug users, 610
in liver transplant, 611
nonpharmacologic therapy in, 607
outcomes of, desired, 607
in persons who inject drugs, 610
pharmacologic, 607–610
pharmacologic therapy in, 608*t*
elbasvir, 609
glecaprevir, 609–610
grazoprevir, 609
ledipasvir, 609
pibrentasvir, 609–610
ribavirin, 610
sofosbuvir, 608–609, 610
velpatasvir, 609, 610
voxilaprevir, 610
post-organ transplant, 611
in special populations, 610–611
in treatment-experienced patients, 610
Hepatobiliary surgery, antimicrobial prophylaxis in, 2116
Hepatocellular carcinoma, 602
Hepatomegaly, 1753
Hepatopulmonary syndrome, 574
Hepatosplenic T-cell lymphoma (HSTCL), 524
Hepcidin, 651–652
HER2 inhibitors, 2206, 2295–2296
pertuzumab, 2206
trastuzumab, 2206
HER2/neu gene, 2229
Herbal medicines, 557
Herbal products, 1166*t*, 1686

Hereditary nonpolyposis colorectal cancer (HNPCC), 2275
Hereditary persistence of fetal hemoglobin (HPFH), 1749
Heroin, 1048–1049
Herpes simplex virus (HSV), 2159*t*
Hexachlorophene, 1645
Hiatal hernia, 465
High-density lipoproteins (HDL), 117, 119, 124*t*
High emetogenic chemotherapy, 536–537
Hip osteoarthritis. *See* Osteoarthritis
Hirsutism, 1307–1308
Histamine, 996*t*
Histone acetyltransferases (HATs), 2358
Histone deacetylase (HDAC) inhibitors, 2186*t*
Histone deacetylases (HDACs), 2358
Histoplasma, 2048*t*
Histoplasma capsulatum, 2046, 2050–2054, 2160*t*
Histoplasmosis, 2050–2054
  clinical presentation of, 2052, 2053*t*
  diagnosis of, 2052–2054
  disseminated, 2052
  epidemiology of, 2050–2051
  in HIV patients, 2052
  pathophysiology of, 2051–2052
  pulmonary, acute, 2052
  pulmonary, chronic, 2052
  treatment of, 2054
    in HIV patients, 2054, 2159*t*
    in non-HIV-infected patients, 2054
    outcome evaluation for, therapeutic, 2054
Hodgkin lymphoma, 2320–2329. *See also* Non-Hodgkin lymphoma
  classification of, 2321*t*
  clinical presentation of, 2321, 2321*b*
  diagnosis of, 2321–2322
  epidemiology of, 2320
  etiology of, 2320
  pathophysiology of, 2320

prognosis factors in, 2321–2322
prognosis of, 2324*t*
staging in, 2321–2322, 2324*t*
Hodgkin lymphoma treatment, 2322–2329
chemotherapy in, 2324–2328, 2325*t*
combination regimens, 2325*t*
restaging during therapy and risk adaptive therapy, 2326
for classical Hodgkin lymphoma, 2326–2327
for advanced-stage disease, 2327
for early stage-disease
favorable, 2326
unfavorable, 2326
complications of, long-term, 2329
general approach to, 2322–2324
for nodular lymphocyte-predominant Hodgkin lymphoma, 2327–2328
outcomes of, desired, 2322
for refractory or relapsed disease, 2328
Home parenteral nutrition, 2508
Homeostasis
acid-base
extracellular buffering in, 815
renal regulation in, 815, 815*f*
respiratory regulation in, 815
calcium, 1544
potassium, 797–798
sodium and water, 755–758
Homeostasis disorders, 755–775 (*See also* specific disorders)
calcium
hypercalcemia, 780–785
hypocalcemia, 785–789
magnesium, 807–811
hypermagnesemia, 809–811
hypomagnesemia, 807–809
phosphorus, 789–790
hyperphosphatemia, 790–791
hypophosphatemia, 791–795

potassium, 797–811 (*See also* Hyperkalemia; Hypokalemia)
sodium
edema, 772–775
hyponatremia, 758–767
water
edema, 772–775
hyponatremia, 758–767
Homocysteine, 1715
Hong Kong influenza of 1968, 1841
Hormone therapy. *See* Menopause and perimenopausal/postmenopausal hormone therapy
Hormones, 377, 1337*f*, 1701
Hospice, e79, 426. *See also* Palliative care
Hospital-acquired pneumonia, 1813–1814, 1813*t*, 1816–1818
Host-parasitic relationship, e1955
Humalog, 1240*t*
Human bites, 1856*t*, 1878–1880
clinical presentation of, 1879*b*
epidemiology of, 1878
etiology of, 1878–1879, 1878*t*
pathophysiology of, 1879
physiology of, 1879
treatment of, 1879–1880
evidence-based, 1861*t*
nonpharmacologic therapy in, 1879
outcomes of
desired, 1879
therapeutic, evaluation of, 1880
pharmacologic therapy in, 1862*t*, 1879–1880
Human chorionic gonadotropin (hCG), 1316
Human immunodeficiency virus (HIV) infection, 2143–2149. *See also* Acquired immunodeficiency syndrome (AIDS)
clinical presentation of, 2148, 2148*t*
diabetes mellitus treatment, 1258
diagnosis of, 2147
epidemiology of, 2144–2145, 2145*t*

etiology of, 2145–2146
histoplasmosis in, 2052
pathogenesis of, 2146–2147
patient care process for, 2149*b*
pneumonia and, 1814, 1814*t*
in pregnancy, 1325–1326, 1325*t*
surrogate markers of progression, 214
tuberculosis coinfection in, 1902
vaccines, 2132
Human immunodeficiency virus (HIV) infection treatment, 2148–2157
complications of, 2158–2163
in ART era, 2162–2163
epidemiology of, 2158
opportunistic pathogens in, 2159*t*–2160*t*
Pneumocystis *jirovecii pneumonia* in, 2159*t*, 2160*t*
dyslipidemia and, 133
esophageal candidiasis and, 2034–2035
general approach to, 2148–2151, 2150*t*–2151*t*
oropharyngeal candidiasis andnd, 2032–2034
outcomes of
desired, 2148
outcome evaluation for, therapeutic, 2157–2158
pharmacologic therapy in, 2151–2157
adherence to, 2155
antiretroviral agents in, 2151–2155, 2152*t*–2153*t*
as chemoprophylaxis, 2157
drug interactions, 2155
efficacy of, 2156
evolution of, 2155
failure of, 2157–2158
in pregnancy, 2156–2157
resistance to, 2156
Pneumocystis jiroveci pneumonia and, 2161–2162
research, 2158
Human milk, e63
Human papillomavirus, 1990–1992

clinical presentation of, 1990
diagnosis of, 1990
epidemiology of, 1990
etiology of, 1990
with HIV, 2160*t*
pathophysiology of, 1990
treatment of, 1990–1992
vaccines, 1990–1992
Humectants, 1682
Humulin, 1240*t*
Hungry bone syndrome, 786
Hyaluronic acid, 1507, 1507*t*, 1512
Hydralazine, 110*t*, 208*t*, 214, 1760
Hydration, 633–634
Hydrochloric acid, 825–826
Hydrochlorothiazide, 94
Hydrocodone
dosing and administration of, 977*t*, 1504*t*
for pain management, 975*t*
Hydrocortisone, 1308*t*
Hydromorphone
dosing and administration of, 975*t*, 977*t*
for pain management, 975*t*, 980
Hydroquinone, 1634
Hydroxychloroquine, 733, 1461–1463, 1461*t*, 1462*t*, 1525*t*, 1527, 1533*t*
5-Hydroxyindoleacetic acid (5-HIAA), 1030
Hydroxylase, 1308*t*
Hydroxysteroid dehydrogenase, 1308*t*
5-Hydroxytryptamine, 990
5-Hydroxytryptamine-3 receptor antagonists, 530*t*, 531*t*, 534*t*, 535, 537, 540
Hydroxyurea, 1668, 2183*t*, 2198
for sickle cell disease, 1755–1758, 1756*t*, 1757*f*
Hydroxyzine, 533*t*, 1171*t*
Hygiene hypothesis, 1676
Hyoscyamine, 869*t*
Hyperaldosteronism, 1301–1305

aldosteronism, primary, 1301–1305
clinical presentation of, 1302, 1302*b*
diagnosis of, 1302, 1303*f*, 1304*t*
etiology of, 1301
therapeutic management, 1302–1305, 1304*t*
for APA-dependent aldosteronism, 1304
for BAH-dependent aldosteronism, 1302–1304
for glucocorticoid-remediable aldosteronism, 1304
aldosteronism, secondary, 1304–1305
Hyperalgesia, 981
Hyperammonemia, 572–573
Hyperandrogenemia, 1307
Hypercalcemia, 780–785
clinical presentation of, 781–782, 781*b*
epidemiology of, 780
etiology of, 780, 780*t*
nephrolithiasis in, 782
pathophysiology of, 780–782, 780*f*
patient care process for, 783*b*
Hypercalcemia treatment, 782–785
general approach to, 782–783
with nephrolithiasis, 785, 786*t*
outcomes of, desired, 782
pharmacoeconomic considerations in, 785
pharmacologic therapy in, 782*f*
asymptomatic management in, 784–785
bisphosphonates, 784–785
calcitonin, 784
cinacalcet, 785
corticosteroids, 785
denosumab, 785
symptomatic management in, 783–784, 784*t*
Hypercalcuria, 785
Hyperchloremia, 633
Hyperchloremic metabolic acidosis, 817–818
Hypercholesterolemia, 118. *See also* Hyperlipidemia

familial, 120
secondary causes, 121*t*
Hypercoagulability disorders, inherited and acquired, 245
Hypercortisolism, 1294
Hyperglycemia, 2020, 2506–2507
in type 1 diabetes, 1252–1253
in type 2 diabetes, 1249–1252
Hyperkalemia, 802–807
acute kidney injury and, 635
aldosterone antagonists and, 214*t*
clinical presentation of, 803*b*
definition of, 802
epidemiology of, 802–803
etiology and pathophysiology of, 803–804, 803*f*
potassium excretion in, decreased, 803–804
potassium intake in, increased, 803
potassium redistribution into extracellular space in, 804
tubular unresponsiveness to aldosterone, 804
false, 798
moderate, 804
severe, 804
treatment of, 804–807
general approach to, 804, 804*f*
nonpharmacologic therapy in, 804–805
outcomes, desired, 804
outcomes, evaluation of, 807
pharmacologic therapy in, 805–807
therapeutic alternatives, 805*t*
Hyperlipidemia, 672, 1119*t*
familial, 119
in solid-organ transplant recipients, 1492–1493
Hypermagnesemia, 809–811
causes of, 809, 810*t*
clinical presentation of, 810
epidemiology of, 809
etiology and pathophysiology of, 809–810

treatment of, 810–811
nonpharmacologic therapy in, 810
outcomes, desired, 810
outcomes, evaluation of, 810–811
pharmacologic therapy in, 810
Hypernatremia, 767–772
acute kidney injury and, 635
causes of, 768*t*
characteristics of, 768*t*
clinical presentation of, 768–770, 769*b*
diabetes insipidus in, 769
osmotic diuresis in, 769
sodium overload in, 770
diabetes insipidus in, 769
epidemiology of, 767–768
etiology of, 767–768
osmotic diuresis in, 769
pathophysiology of, 768
sodium overload in, 770
treatment of, 770–772
algorithm for, 770*f*
for central diabetes insipidus, 771, 772*t*
for euvolemic hypernatremia, 771
for hypervolemic hypernatremia, 771, 772
for nephrogenic diabetes insipidus, 771–772, 772*t*
outcomes, desired, 770
outcomes, evaluation of, 775
for sodium overload, 770
Hyperosmolality, 798
Hyperosmolar agents, 554
Hyperparathyroidism, 652
Hyperphosphatemia, 652, 667*t*
clinical presentation of, 790–791, 791*b*
definition of, 790
pathophysiology of, 790
acid-base disorders in, 790

exogenous phosphate loads in, 790
rapid tissue catabolism in, 790
treatment of
outcomes of, desired, 791
pharmacologic, 791
Hyperpigmentation, 1305
Hyperprolactinemia, 1119*t*
amenorrhea from, 1338
medication-induced, 138*t*
Hypersensitivity reactions. *See* Allergic drug reactions
Hypertension, 83–90. *See also* Blood pressure
in cancer patients, 2215–2216
in chronic heart failure, 216–217
in chronic kidney disease, 651, 657*f*, 658
clinical presentation of, 88–90, 88*b*
clinical evaluation of, 89–90
diagnostic considerations in, 88–89
natural course of disease in, 90
from combined hormonal contraceptives, 53
complications, associated, 90
in diabetes mellitus, 1256
epidemiology of, 84
etiology of, 84–85
essential hypertension, 84
secondary hypertension, 84–85, 84*f*
gestational, 100
glomerular diseases and, 717–718
in hemodialysis, 684
hemodialysis complications, 682*t*
masked, 89
pathophysiology of, 85–88, 85*t*
arterial blood pressure in, 85
humoral mechanisms in, 86–87
neuronal regulations, 87
peripheral autoregulatory components in, 87–88
electrolytes, 87–88

vascular endothelial mechanism, 87
patient care process for, 91*b*
in pregnancy, 1325*t*, 1326
prevalence of, 84
pseudohypertension, 89
secondary causes of, 89–90
in solid-organ transplant recipients, 1492
white coat, 89
Hypertension treatment, 90–111
algorithm for, 93*f*
angiotensin converting enzyme inhibitors, 102–103
angiotensin receptor blockers, 103
calcium channel blockers, 103–104
dihydropyridine, 103–104
nondihydropyridine, 103–104
in chronic kidney disease, 98–99
clinical inertia in, avoiding, 92
with coexisting conditions, 101
erectile dysfunction, 101
metabolic syndrome, 101
peripheral arterial disease, 101
pulmonary disease, 101
in coronary artery disease, 97–98
in diabetes mellitus, 98
general approach to, 92
in heart failure with preserved ejection fraction, 97
in heart failure with reduced ejection fraction, 97
hypertensive emergency in, 110–111, 110*t*
hypertensive urgency in, 109–110
nonpharmacologic therapy in, 92–94
lifestyle modifications in, 94*t*
outcome evaluation for, therapeutic, 111–112
combination therapy in, 108
fixed-dose products in, 108, 109*t*
optimal use of, 108
pharmacotherapy monitoring in, 111–112, 111*t*

adherence and persistence, 111–112
disease progression, 111
efficacy in, 111
side effects of, 111
toxicity, 111
outcomes of, desired
diabetes mellitus and, 92
goal blood pressure, 91*b*
overall goal in, 90
surrogate targets in, 90–92
pharmacoeconomic considerations in, 108–111
pharmacologic therapy in, 94–101
in adolescents, 100
in African Americans, 100–101
aliskiren, 107
α_1-blockers, 106–107
α_2-agonist, central, 107
alternative drug treatments, 96*t*, 99
angiotensin converting enzyme inhibitors, 95*t*, 96–97
angiotensin receptor blockers, 95*t*, 96–97
antihypertensive and lipid lowering treatment, 94
β-adrenergic antagonists (beta blockers), 96*t*
β-adrenergic antagonists (beta blockers) *vs.* first-line agents, 97
β-blockers, 105–106
calcium channel blockers, 95*t*, 96–97
in children, 100
combination therapy in, 108, 108*t*, 109*t*
direct arterial vasodilator, 107–108
diuretics, 95*t*, 104–105
in elderly, 99–100
in erectile dysfunction, 101
first-line and common agents in, 95*t*–96*t*, 96–97
individual drug classes, indications for, 93*f*
in metabolic syndrome, 101
orthostatic hypotension and, 100

in peripheral arterial disease, 101
in pregnancy, 100, 100*t*
in pulmonary disease, 101
thiazides, 94, 104–105
for resistant hypertension, 101–108
alternative drugs, 106–108
aliskiren, 107
α_1-blocker, 106–107
central α_2-agonists, 107
direct arterial vasodilator, 107–108
angiotensin receptor blockers, 103
angiotensin-converting enzyme inhibitors, 102–103
β-adrenergic antagonists (beta blockers), 105–106
calcium channel blockers, 103–104
causes of, 101*t*
diuretic therapy in, 102, 104–105
first-line antihypertensive agents, 102–108
thiazides, 104–105
in stable ischemic heart disease, 97–98
for stroke prevention, recurrent, 99
team-based collaborative care in, 109
Hypertensive crises, 85
Hypertensive disorders of pregnancy, 1320–1321, 1320*t*
Hypertensive emergency, 85
Hypertensive urgency, 85
Hyperthermia, 916
Hyperthyroidism, 1268. *See also* Thyrotoxicosis
neonatal, 1279
patient care process for, 1275*b*
pediatric, 1279
in pregnancy, 1327
treatment of, 1273*t*, 1274*t*
TSH-induced, 1271
Hypertonic hyponautremia, 758–759
Hypertonic saline, 453

Hypertriglyceridemia, 117–118, 121*t*, 128, 2506
Hyperuricemia in gout, 1567–1585
  associated conditions, 1569*t*
  asymptomatic management in, 1584
  clinical presentation of, 1569–1572
    acute gouty arthritis, 1569–1571
    gouty nephropathy, 1572
    tophaceous gout, 1572, 1572*f*
    uric acid nephrolithiasis, 1571–1572
  definition of, 1567
  drug-induced, 1569*t*
  epidemiology of, 1567–1568
  etiology and pathophysiology of, 1568–1569
    overproduction of uric acid, 1568–1569
    underexcretion of uric acid, 1569
  patient care process for, 1573*b*
  treatment of, 1575*t*–1576*t*, 1578–1582
    algorithm for, 1580*f*
    nonpharmacologic therapy in, 1578–1579
    pharmacologic therapy in, 1579–1581
      lesinurad, 1582
      lipid-lowering agents, 1582
      pegloticase, 1582
      probenecid, 1581–1582
      uricosuric drugs, 1581
      xanthine oxidase inhibitors, 1581
Hyperventilation, 937
Hypnosis, 1631
Hypoalbuminemia, 718
Hypoaldosteronism, 1307
Hypocalcemia, 652, 785–789
  clinical presentation of, 787*b*
  critical illness and, 787
  definition of, 785
  drug-induced, 787–788
  epidemiology of, 785

hungry bone syndrome in, 786
hypomagnesemia in, 786–787
hypoparathyroidism, 786
pathophysiology of, 785
vitamin D deficiency in, 785–786
treatment of, 788–789
outcomes of, desired, 788
pharmacologic therapy in, 788–789
acute, 788
adverse effects of, 789
algorithm for, 789*f*
chronic, 788–789
Hypoglycemia, 1074, 1240, 1253–1254
Hypogonadism, 1383
Hypokalemia, 798–802
clinical presentation of, 799*b*
definition of, 798
drug-induced, 798–799, 799*t*
epidemiology of, 798
etiology of, 798–799
false, 798
pathophysiology of, 798–799
treatment of, 799–802
alternative therapies, 802
bottom line, clinical, 802
general approach to, 799–800, 801*t*
nonpharmacologic therapy in, 800
outcomes, desired, 799
outcomes, evaluation of, 802
pharmacologic therapy in, 800–802
oral supplements, 801–802, 801*t*
Hypokinesia, 947–948
Hypomagnesemia, 799, 807–809
causes of, 807, 808*t*
clinical presentation of, 809*b*
epidemiology of, 807

etiology and pathophysiology of, 807–808
hypocalcemia and, 786–787
magnesium content in common products, 808*t*
treatment of, 808–809
bottom line, clinical, 809
general approach to, 808
nonpharmacologic therapy in, 808
outcomes, desired, 808
outcomes, evaluation of, 809
pharmacologic therapy in, 808–809
Hypomania, 1150, 1151*b*, 1153*t*
Hyponatremia, 758–767
acute or severely symptomatic hypotonic, sodium chloride infusion in, 763–764
assessment of, 759*f*
causes of, 761*t*
clinical presentation of, 725, 761–762, 761*b*
epidemiology of, 758
etiology of, 758
isotonic, 758
pathophysiology of, 722, 758–761
in euvolemic hypotonic hyponatremia, 760
in hypertonic hyponatremia, 758–759
in hypervolemic hypotonic hyponatremia, 760–761
in hypotonic hyponatremia, 759, 760*t*
in hypovolemic hypotonic hyponatremia, 759–760
in isotonic hyponautremia, 758
treatment of, 762–767
acute or severely symptomatic hypotonic, 762–764
NcCl infusion regimen, 763–764
outcomes, evaluation of, 764
algorithm for, 759*f*
euvolemic, 763*t*
general approach to, 762*t*
guidelines for, 763*t*
hypotonic hypovolemic, 764*t*

nonemergent euvolemic hypotonic, 764–766
demeclocycline, 765
outcomes, evaluation of, 766
vasopressin receptor antagonists, 765–766
nonemergent hypervolemic hypotonic, 766–767
nonemergent hypovolemic hypotonic, 764
outcomes, desired, 762
Hypoparathyroidism, 786
Hypophosphatemia, 791–795
acute kidney injury and, 635
clinical presentation of, 793–794, 793*b*
decreased gastrointestinal absorption in, 791–792
decreased tubular reabsorption in, 792
definition of, 791
incidence of, 791
internal redistribution in, 792–793
pathophysiology of, 791, 792*t*
treatment of
clinical bottomline for, 795
outcomes of, desired, 794
pharmacologic therapy in, 794, 794*t*
adverse effects of, 794–795
mild-to-moderate hypophosphatemia, 794
severe hypophosphatemia, 794
Hypophysis. *See* Pituitary gland
Hypoproteinemia, 718
Hypotension
hemodialysis complications, 682*t*, 683
intradialytic, 683
orthostatic, 1132
antipsychotics and, 1119*t*
definition of, 100
in Parkinson disease, 950*t*
schizophrenia and, 1108
Hypothalamic disease, 1281
Hypothalamus, e1313, 1338

Hypothermia
cardiac arrest treatment in, 336
in intracranial hypertension, 937–938
in status epilepticus (SE) treatment, 926
Hypothyroidism, 1279–1286
bipolar disorder treatment and, 1155
in cancer patients, 2215
causes of, 1281*t*
clinical presentation of, 1280*b*
congenital, 1281, 1286
definition of, 1280
epidemiology of, 1280
etiology of, 1280
iodine excess and deficiency in, 1281
neonatal screening for, 1281
pathophysiology of, 1280–1281
autoimmune thyroiditis, 1280–1281
chronic autoimmune thyroiditis, 1280–1281
hypothalamic disease, 1281
iatrogenic, 1281
pituitary disease, 1281
patient care process for, 1282*b*
Hypothyroidism treatment, 1281–1286
of congenital hypothyroidism, 1286
general approach to, 1281–1283, 1283*t*
of myxedema coma, 1286
outcomes of
desired, 1281
therapeutic, evaluation of, 1286
pharmacologic therapy in, 1283–1286
pharmacokinetics of, 1284
adverse effects of, 1284
drug-drug and drug-food interactions in, 1284–1285
drug and food interactions, 1284–1285
dosing and administration of, 1284–1286
in pregnancy, 1286

thyroid preparations in, 1282*t*
Hypovolemic shock treatment
fluid resuscitation in, 358
vasopressors and inotropes in, 361
Hypoxia-inducible factor (HIF) inhibitors, 664–665
Hysterectomy, antimicrobial prophylaxis in, 2117*t*, 2120

I

Iatrogenic hypothyroidism, 1281
Ibalizumab-uiyk, 2153*t*
Ibandronate, 1551*t*
Ibritumomab tiuxetan, 2189*t*, 2197
Ibrutinib, 2185*t*, 2402*t*, 2403*t*
Ibuprofen, 1504*t*. *See also* Nonsteroidal anti-inflammatory drugs (NSAIDs)
  antiplatelet therapy and, 144
  for gout and hyperuricemia, 1574*t*
  for migraine, acute, 995*t*
  for migraine prophylaxis, 996*t*
  for osteoarthritis, 1509
Ibutilide, 292*t*, 293, 294*t*, 295*t*
Idarubicin, 2181*t*
Idelalisib, 2188*t*, 2338, 2402*t*, 2403*t*
IDH inhibitors, 2202
Idiopathic interstitial pneumonitis, 2458
Idiopathic pneumonia syndrome (IPS), 2458
Ifosfamide, 2182*t*, 2195–2196
Ileal pouch anal anastomosis (IPAA), 514
Iloperidone, 1096*t*, 1104, 1105*t*, 1106*t*, 1107*t*, 1115*t*, 1116*t*. *See also* Antipsychotics
Iloprost, 443*t*, 444*t*, 446*t*
Imatinib, 2184*t*, 2199
Imatinib mesylate, 2391–2393, 2392*t*, 2394*t*, 2444
Imipenem, 454*t*, 640, 1963*t*
Imipenem-cilistatin, 1963*t*, 2092*t*, 2095*t*
Imipramine, 869*t*, 970*t*, 1133*t*, 1135*t*, 1138*t*, 1171*t*, 1178*t*, 1191*t*, 1193*t*, 1209*t*
Immune checkpoint inhibitors, 709, 2191*t*, 2208
Immune function tests, 2475–2476
Immune reconstitution inflammatory syndrome (IRIS), 865
Immune system
  definition of, e1451
  discrimination in, e1451
  diversity in, e1451

evaluation of, e1451
function of, e1451
memory of, e1451
mobility of, e1451
redundancy in, e1451
replication of, e1451
specificity of, e1451
Immune thrombocytopenia, 2138
Immunizations. *See also* Vaccines
contraindications and precautions in, 2130
in COPD treatment, 414
definition of, 2127
factors affecting response to, 2128
history in, obtaining, 2130–2131
in immunocompromised hosts, 2130
hematopoietic stem cell transplant patients, 2130
solid organ transplant patients, 2130
in infants, 2129
in pregnancy and postpartum, 2129–2130
products used in, 2127–2128
rheumatoid arthritis and, 1532
in sickle cell disease treatment, 1754–1755
Immunobiologics, 2127–2139. *See also* Immunoglobulin; Vaccines; *specific types*
toxoids, 2127–2128
Immunocompromised, 1848–1849
infections in, 2079–2083
febrile neutropenia in cancer, 2082–2083
hematopoietic stem cell transplantation, 2099–2101
patient care process for, 2084*b*
risk factors and epidemiology of, 2080–2081, 2080*t*
environmental contamination/microbial flora alteration, 2081
immune system defects, 2081
neutropenia, 2080–2081
protective barrier destruction, 2081
solid-organ transplant recipients, 2103–2105

influenza treatment in, 1851
Immunoglobulin, 599, 2138–2139, 2138*t*
definition of, 2128
rabies, 2135–2136
Rho(D), 2139
tetanus, 2136–2137
varicella-zoster, 2137–2138
Immunoglobulin A nephropathy, 729–731
clinical presentation of, 729
epidemiology of, 729
etiology of, 729
pathophysiology of, 729
prevalence of, 729
prognosis of, 731
treatment of, 729–731
algorithm for, 730*f*
general approach to, 729
nonpharmacologic therapy in, 729
low-gluten diet, 729
tonsillectomy, 729
pharmacologic therapy in, 729–731
alternative therapeutic agents, 731
angiotensin receptor blockers, 730
angiotensin-converting enzyme inhibitors, 730
cytotoxic agents, 730
fish oil, 730
mycophenolate mofetil, 730
steroids, 729–730
Immunologic memory, 2127
Immunomodulating therapies, for refractory GCSE, 925
Immunomodulators, 521
Immunosuppressive agents
for hepatitis B, 604–605
for inflammatory bowel disease, 515
Immunotherapy. *See also specific agents*
for atopic dermatitis, 1687

for cancer treatment, 2178, 2208–2209
chimeric antigen receptor T-cell therapies, 2209
for colorectal cancer, 2293, 2296
cytokines, 2208–2209
immune checkpoint inhibitors, 2208
for ovarian cancer, 2361
for prostate cancer, 2314*t*, 2315
therapeutic vaccines, 2209
Impetigo
clinical presentation of, 1865*b*
etiology of, 1856*t*, 1865
treatment of, 1865
evidence-based, 1860*t*
pharmacologic, 1862*t*
therapeutic, evaluation of, 1865
Implantable cardioverter-defibrillator (ICD), 313–315, 313*f*
Impulse control disorder, 950*t*
Incontinence, urinary. *See* Urinary incontinence
Incretin, 1233–1234
Indinavir, 2153*t*, 2154
Indomethacin, 1504*t*, 1574*t*. *See also* Nonsteroidal anti-inflammatory drugs (NSAIDs)
Infant mortality, e61
Infants, definition of, e61
Infections. *See also specific types*
bone and joint, 1999–2005
confirming, 1771–1772
fever, 1771–1772
local signs, 1772
white blood cell count, 1772
in solid-organ transplant recipients, 1493–1494
Infectious arthritis
clinical presentation of, 1998–1999, 1998*t*
epidemiology of, 1996
etiology of, 1996
incidence of, 1996

pathophysiology of, 1998, 1998*t*
radiologic and laboratory tests in, 1999
treatment of, 1999–2004
outcomes of, desired, 2000–2001
general approach to, 2001
pharmacologic
antibiotic joint space concentration in, 2004
antibiotic selection in, 2004
Infective endocarditis, 1883–1885
clinical presentation of, 1885–1886, 1885*t*, 1886*b*
definition of, 1883
diagnosis of, 1887–1888, 1887*t*
epidemiology of, 1883–1884
etiology of, 1883–1884, 1884*t*
pathophysiology of, 1884–1885
peripheral manifestations of, 1885–1886
prevention of, 1897, 1898*t*
risk factors for, 1884
Infective endocarditis treatment, 1888–1896
general approach to, 1888–1889
for native valve, 1889*t*
nonpharmacologic therapy in, 1889
outcomes of
desired, 1888
evaluation of, 1896–1897
blood cultures, 1897
inflammatory markers, 1897
microbiologic tests, 1897
serum drug concentrations, 1897
signs and symptoms, 1896–1897
pharmacologic therapy in, 1889–1896
atypical microorganisms, 1896
culture-negative endocarditis, 1892*t*, 1896
drug dosing, 1892*t*–1893*t*
drug monitoring in, 1893*t*
enterococcal endocarditis, 1895–1896

HACEK group endocarditis, 1896
staphylococcal endocarditis, 1893–1894
IV drug abuser, 1894
prosthetic valves, 1894–1895
streptococcal endocarditis, 1890–1893
Infertility, 2216
Infiltrating ductal carcinoma, 2226–2227
Infiltrating lobular carcinoma, 2226–2227
Inflammation
acute, in asthma, 372–375
anemia of, 1721–1722
assessment of, 2470*t*
chronic, in asthma, 372–375
mediators of, 375
neurogenic, in asthma, 376
Inflammatory bowel disease (IBD), 507–512
clinical presentation of, 511–512
in Crohn's disease, 512, 512*t*
in ulcerative colitis, 511–512, 511*t*
epidemiology of, 507–508
etiology of, 508–509
genetic factors in, 508
immunologic mechanisms in, 508–509
infectious factors in, 508
lifestyle, dietary, and drug-related causes in, 509
psychological factors in, 509
forms of, 507
incidence of, 507–508
pathophysiology of, 509–511, 509*t*
complications of, 510–511
dermatologic, 511
hematologic, coagulation, and metabolic, 511
hepatobiliary, 510
joint, 510
mucocutaneous, 511
ocular, 510–511

in Crohn's disease, 510–511
dermatologic complications of, 511
extraintestinal manifestations, 510
hematologic, coagulation, and metabolic abnormalities in, 511
hepatobiliary complications of, 510
joint complications of, 510
mucocutaneous complications of, 511
ocular complications of, 510–511
in ulcerative colitis, 510
patient care process for, 513*b*
prevalence of, 508
Inflammatory bowel disease (IBD) treatment, 512–525
for complications
extraintestinal manifestations, 521–522
toxic megacolon, 521
for Crohn's disease, 520–521, 520*f*
general approach to, 512–514
nonpharmacologic therapy in, 514
nutritional support in, 514
surgery, 514
outcomes of
desired, 512
evaluation of, 525
pharmacologic therapy in, 514–519, 515*f*, 516*t*
adverse drug effects, 522–525
agents for, 516*t*
in breastfeeding, 522
for Crohn's disease, 518*t*, 520–521
drug monitoring in, 523
levels of evidence for therapeutic interventions, 518*t*
in pregnancy, 522
for remission maintenance, 519
for ulcerative colitis, 517–519, 517*f*, 518*t*
for remission maintenance, 519, 521
Inflammatory cells, asthma and, 373–375, 374*f*
Inflammatory demyelinating polyneuropathy, 2138

Inflammatory mediators, 375
Infliximab
adverse effects of, 1533*t*
for atopic dermatitis, 1686
for celiac disease, 620
for graft-versus-host disease, 2461*t*
for inflammatory bowel disease, 516, 516*t*, 517, 519, 522, 523*t*, 524
for psoriasis, 1664–1665
for rheumatoid arthritis, 1525*t*, 1528–1529
Influenza, 1839–1849
clinical presentation of, 1842*b*–1843*b*
diagnosis of, 1842*b*–1843*b*
etiology and epidemiology of, 1840–1844
antigenic drift and antigenic shift, 1841
Asian influenza of 1957, 1841
avian influenza, 1841–1843
H3N2v variant virus, 1843–1844
Hong Kong influenza of 1968, 1841
influenza viruses A, B, and C, 1840–1841
Spanish influenza of 1918, 1841
swine influenza of 2009, 1843
with HIV, 2160*t*
mortality rate, 1840
pandemic preparedness for, 1851
pathogenesis of, 1844
patient care process for, 1849*b*
prevention of, 1844–1849
in immunocompromised hosts, 1848–1849
post-exposure prophylaxis in, 1847–1848, 1848*t*
in pregnancy, 1848–1849
vaccination in, 1844, 1845–1849
for different age groups, 1845*t*
live-attenuated, 1846–1847, 1846*t*
rates and goal by patient population, 1844*t*
trivalent and quadrivalent vaccine, 1845–1846
vaccines, 149

Influenza treatment, 1849–1851
general approach to, 1850
in immunocompromised hosts, 1851
nonpharmacologic therapy in, 1850
outcome evaluation for, therapeutic, 1851
pharmacologic therapy in, 1850–1851
adamantanes, 1850
cap-dependent endonuclease inhibitors, 1850
neuraminidase inhibitors, 1839–1851
in pregnancy, 1851
Inhalants, 1062–1063
Innate immune system, definition of, e1451
Inotropes. *See also specific types*
for acute decompensated heart failure, 232–234, 233*t*
for shock, 358–364, 359*t*
Inotuzumab ozogamicin, 2191*t*, 2207, 2374
Insomnia, 1202
chronic, 1202
differential diagnosis of, 1202
epidemiology of, 1202
etiologies of, 1202*t*
in Parkinson disease, 950*t*
primary, 1202
treatment of, 1202–1206
general approach to, 1203
nonpharmacologic therapy in, 1203, 1203*t*
outcomes of
desired, 1202–1203
therapeutic, evaluation of, 1205–1206
pharmacologic therapy in, 1203–1205
antidepressants, 1203
antihistamines, 1203
benzodiazepine-receptor agonists, 1203–1204, 1205*t*
benzodiazepines, 1204–1205
nonbenzodiazepine GABAA agonists, 1205
Institute of Medicine, 2, e9

Insulin, 1239–1241, 1240*t*
glucose and, 1252*f*
hyperkalemia and, 805*t*
impaired secretion of, 1233–1234, 1233*f*
pharmacodynamics of, 1239, 1240*t*
pharmacokinetics of, 1239, 1241*f*
resistance, 1233–1234
Insulin resistance, 846
Insulin-like growth factor-binding protein 7 (IGFBP7), 698
Integrin antagonists, 521
Integumentary system, e37
Intellectual disability disorders, 1215–1225. *See also specific disorders*
autism spectrum disorder, 1220–1225
challenging behaviors, 1216
clinical presentation of, 1217
definition of, 1215
Down syndrome, 1216–1219
epidemiology of, 1215–1216
patient care process for, 1218*b*
self-injurious behaviors, 1216
Interferon, 603, 2437
Interferon-alfa, 2191*t*
Interferon-β_{1a}, 860–865, 862*t*, 863*t*, 864*t*
Interferon-β_{1b}, 860–865, 862*t*, 863*t*, 864*t*
Interferon-γ release assays (IGRA), 1906
Interferons, 2208
Interleukin-1 inhibitors, 1575*t*, 1577*t*, 1583
Interleukin-2, 2191*t*, 2208–2209, 2440
Interleukin-2 receptor antagonists, 1488–1489
Intermediate hosts, e1955
Intermittent hemodialysis, 637
Internal mammary artery (IMA), 154
International Classification of Disease (ICD), 7*t*
International Headache Society (IHS), 989
Interstitial nephritis, chronic, 710–711

aristolochic acid, 710
cyclosporine, 710
lithium, 710
tacrolimus, 710
Intestinal microbiota, 514
Intestinal secretagogues, 555
Intoxication, 1048
Intra-abdominal infection, 1939–1943. *See also specific types*
clinical presentation of, 1942–1943
definition of, 1939
epidemiology of, 1939–1940
etiology of, 1940–1941, 1946*t*
microflora in
female genital tract, 1940–1941
gastrointestinal tract, 1940–1941, 1940*t*
pathophysiology of, 1941–1942
bacterial synergism in, 1942
microbiology of, 1942, 1942*t*
patient care process for, 1944*b*
Intra-abdominal infection treatment, 1943–1951
in appendicitis, 1949
general approach to, 1944–1945
nonpharmacologic therapy in, 1945
drainage procedures in, 1945
fluid therapy in, 1945
outcomes of
desired, 1943
therapeutic, evaluation of, 1951
pharmacologic therapy in, 1946–1951
antimicrobial therapy in, 1946–1951
recommendations for, 1946–1951
acute intra-abdominal contamination, 1950
community-acquired complicated infection, 1947*t*
for complicated infections, 1948*t*–1949*t*
empiric antimicrobial agents for, 1950*t*
enterococci, 1947–1948

evidence-based, for complicated infections, 1948*t*–1949*t*
guidelines, 1950*t*
Intra-abdominal pressure, 465–466
Intra-aortic balloon pump (IABP), 235–236, 235*f*
Intracellular signaling pathways, 2177*f*
Intracranial hypertension, 935–941
anesthetics, analgesics, and sedatives for, 935–938
corticosteroids, 937
hyperventilation, 937
hypothermia, 937–938
management of, 936*f*
osmotic agents in, 938
Intradialytic hypotension, 683
Intrauterine devices, 56–57
Intravenous fluids
for shock, 354–358, 355*t*
alternative fluid treatments, 355–357
blood products, 357, 357*t*
crystalloid solutions, 354–355
plasma expanders, 355*t*
Intravenous lipid emulsion, 2495–2496
Intrinsic resistance, 2046
Invasive hemodynamic monitoring, 225, 226*t*, 228*f*
Invasive lobular carcinoma, 2226–2228
Iobenguane, 2189*t*
Iobenguane I 131, 2197
Iodides, 1277
Iodine, 1272–1273, 2477*t*, 2479
Iodothyronine 5’-deiodinase isoforms, 1267*t*
Ipilimumab, 2191*t*
Irinotecan, 2181*t*, 2293, 2294*t*
Iron, 2476, 2477*t*
deficiency in, signs of, 2477*t*
incorporation into heme, 1711
serum, 1714
toxicity of, signs of, 2477*t*

Iron deficiency, 1709
Iron dextran, 661*t*
Iron sucrose, 661*t*
Iron supplementation, 660–662
  adverse effects of, 660–662
  dosing and administration of, 662
  drug interactions, 662
  therapeutic options, 660
Iron-deficiency anemia, 1715–1718. *See also* Anemia
  epidemiology of, 1715
  etiology of, 1715–1716
  iron balance in, 1715
  laboratory evaluation of, 1716, 1722*t*
  pathophysiology of, 1716
  treatment of, 1716–1718
    dietary supplementation in, 1716–1718, 1717*t*
    oral iron preparations in, 1716–1718, 1717*t*
    outcomes of, desired, 1716
    parenteral iron therapy in, 1718
Irritable bowel syndrome (IBS), 556–558
  clinical presentation of, 556, 556*t*
  definition of, 556
  epidemiology of, 556
  Manning criteria, 556
  pain in, 558
  pathophysiology of, 556
  Rome criteria, 556
  symptom-based criteria for, 556*t*
Irritable bowel syndrome (IBS) treatment, 556–558
  antidepressants in, 557
  for constipation-predominant disease, 557
  for diarrhea-predominant disease, 557
  general approach to, 556–557, 557*f*
  outcomes of, evaluation of, 558
Isavaconazonium, 2093*t*
Isavuconazole, 2069, 2072

Ischemic heart disease, 137–142
biomarkers in, 142
clinical presentation of, 140–142
coronary vasospasm, 140
death rate of, 138
diagnostic and prognostic testing of, 142
epidemiology of, 137–138
etiology and pathophysiology of, 138–140
fixed-threshold angina, management of, 155–156
grading in, 144*t*
myocardial oxygen demand in, 138
myocardial oxygen supply in, 138–140
coronary blood flow, 138–139, 139*f*
coronary collateral circulation, 140
heart rate and systole, 139
oxygen extraction and oxygen carrying capacity, 139–140
nonpharmacologic therapy (revascularization)
percutaneous coronary intervention, 153–154
vs. medical management, 154
pharmacotherapy with, 153–154
patient care process for, 143*b*
Prinzmetal's angina, 140
risk factor modification in, 145*t*–146*t*
alcohol consumption, 146*t*
blood pressure management, 145*t*
diabetes management, 145*t*
lipid management, 145*t*
physical activity in, 145*t*
psychological factors in, 145*t*–146*t*
smoking cessation, 145*t*
weight management, 145*t*
treatment of, 144–156
algorithm for, 147*f*
blood pressure management, 148
diabetes management, 149
influenza vaccine, 149

nonpharmacologic therapy (revascularization), 152–155, 153*t*
coronary artery bypass graft surgery, 154–155
percutaneous coronary intervention, 153–154
outcomes, evaluation of, 156
outcomes of, 144
pharmacologic therapy in, 146*t*
angiotensin-converting enzyme inhibitors, 146–148
antiplatelet therapy, 144–146
b-blockers, 149
calcium channel blockers, 150
lipid management, 148
nitrates, 150–152, 151*t*
with percutaneous coronary intervention, 153–154
ranolazine, 152
smoking cessation, 148
variable-threshold angina, management of, 156
Ischemic stroke, 273
etiology of, 273–274
pathophysiology of, 274–275, 274*f*
treatment of, nonpharmacologic therapy in, 276–278
Isocarboxazid, 1133*t*
Isocitrate dehydrogenase (IDH) inhibitors, 2187*t*
Isoflavones, 1549
Isoflurane, 400
Isolated systolic hypertension, 86
Isoniazid
adverse effects and monitoring of, 1919*t*
for CNS infection, 1798
dosing by age group, 1913*t*
dosing of, 1914*t*
drug interactions, 1775*t*
for tuberculosis, 1910*t*, 1911*t*, 1914*t*, 1915
Isosporiasis, 2159*t*
Isotonic hyponautremia, 758
Isotretinoin
monitoring of, 1636*t*

oral, 1643–1644
Itraconazole
for blastomycosis, 2055–2056
dosing by age group, 1799*t*
for febrile neutropenia, 2093*t*
for invasive fungal infections, 2071–2072
monitoring of, 2073*t*
for onychomycosis, 2040–2041
for oropharyngeal candidiasis, 2033*t*
Ivabradine, 208*t*, 214
Ivosidenib, 2187*t*
Ixabepilone, 2181*t*
Ixazomib, 2189*t*, 2204, 2418
Ixekizumab, 1666–1667

J

JAK inhibitor, 2187*t*, 2202
JAK-STAT signaling pathway, 2178
Janeway's lesions, 1885
Janus kinase inhibitors, 1490, 1702
Jarisch-Herxheimer reaction, 1982
Jet lag, 1209–1210
Jet nebulizer, 390*t*
John Cunningham virus (JCV) infection, 865
Joint Commission for Pharmacy Practitioners (JCPP), 1
Joints
infection of, 1995–2005 (*See also* Bone and joint infection)
inflammatory bowel disease complications of, 510
in rheumatoid arthritis, 1519–1520, 1519*f*, 1520*f*–1521*f*
Juxtaglomerular cells, 86

K

Kanamycin
adverse effects and monitoring of, 1919*t*
dosing of, 1914*t*
for tuberculosis, 1913*t*, 1914*t*

Kaolin-pectin mixture, 549*t*
Kawasaki disease, 2138
Keratoconjunctivitis sicca, e25
Kernicterus, e61
Kernig's sign, 1788*f*
Ketamine, 1060, 1138
  for acute severe asthma, 400
  for major depressive disorder, 1137
  for pain management, 973
  for refractory GCSE, 924*t*
Ketoconazole, 1298*t*, 2041
  for alopecia, 1700
  for coccidioidomycosis, 2057
  for Cushing syndrome, 1297–1299, 1298*t*
  for oropharyngeal candidiasis, 2032
  for peptic ulcer disease, 498
  for prostate cancer, 2305, 2315
Ketogenic diet
  for epilepsy, 887
  in status epilepticus (SE) treatment, 920
Ketoprofen, 996*t*, 1505*t*, 1574*t*
Ketorolac, 968*t*
Khat, 1060
Kidney disease, and dyslipidemia, 132–133
Kidney disease, drug-induced, 697–712
  acute phosphate nephropathy, 707–708
  cholesterol emboli, 712
  clinical presentation of, 698, 698*b*
  crystal nephropathy, 707
  epidemiology of, 697–698
  glomerular disease, 708
    focal segmental glomerulosclerosis, 708
    membranous nephropathy, 708
    minimal change, 708
  hemodynamically mediated injury in, 703–707, 703*f*
    ACE inhibitors and angiotensin II receptor blockers, 704–705, 704*f*

clinical presentation of, 704
cyclosporine, 705–706
incidence of, 704
management of, 705
NSAIDs and selective COX-2 inhibitors, 705
pathophysiology of, 704, 704*f*
prevention of, 705
risk factors for, 704–705
SGLT-2 inhibitors, 706–707
tacrolimus, 705–706
incidence of, 697
nephrocalcinosis, 707–708
nephrolithiasis, 708
nephrotoxicity, incidence of, 699
obstructive nephropathy, 707
pharmacoeconomic considerations in, 712
prevention of, 699, 700
renal vasculitis, 711
structural-functional alterations, 699*t*
thrombotic microangiopathy, 711–712
tubular epithelial cell damage in, 699–703
acute tubular necrosis, 699–703
aminoglycoside, 702–703
amphotericin B, 702–703
cisplatin, 702
radiographic contrast media, 700–702
osmotic nephrosis, 703
clinical presentation of, 703
risk factors for, 703
tubulointerstitial nephritis, 708–711
allergic interstitial nephritis, 708–710
chronic interstitial nephritis, 710–711
aristolochic acid, 710
cyclosporine, 710
lithium, 710
tacrolimus, 710

papillary necrosis, 711
Kidney function evaluation, e623. *See also* Anemia
Kidney transplantation. *See also* Transplantation, solid-organ
acute cellular rejection in, 1478–1479
chronic rejection in, 1479
epidemiology and etiology of, 1475
physiologic consequences of, 1476
Klinefelter's (XXY) syndrome, 1231*t*, 1454
Kyphoplasty, 1550

L

Labetalol, 100*t*, 110*t*
Lacosamide
adverse effects of, 895*t*
drug interactions, 895*t*
for epilepsy, 894*t*–895*t*
mechanism of action, 894*t*
for refractory GCSE, 924*t*
Lactase, 549, 549*t*
Lactation
drug use in, 1330–1331
schizophrenia treatment in, 1113–1114
Lactic acidosis, 819–820, 819*t*
Lactobacillus, 495
Lactobacillus acidophilus, 549, 549*t*, 1687
Lactobacillus bulgaricus, 549, 549*t*
Lactobacillus rhamnosus GG, 1687
Lactobacillus rhamnosus HN001, 1687
Lactulose
adverse effects of, 575*t*
for constipation, 554, 554*t*
for hepatic encephalopathy, 573
Lamivudine, 604, 1916*t*, 2151, 2151*t*, 2152*t*
Lamotrigine, 969*t*
adverse effects of, 893*t*, 1159–1160
for bipolar disorder, 1159–1160

dosing and administration of, 1154*t*, 1160
drug interactions, 893*t*, 1160
for epilepsy, 892*t*–893*t*
mechanism of action, 892*t*
for multiple sclerosis, 869*t*
oral contraceptives and, 50
Lanreotide, 549, 2189*t*, 2198
Lansoprazole, 472*t*, 474, 475*t*, 476, 494*t*, 497, 498*t*, 502*t*
Lanthanum carbonate, 668
Lantus, 1240*t*
Lapatinib, 2185*t*, 2201, 2243–2244
Larotrectinib, 2188*t*
L-asparaginase, 2192*t*
Latanoprost, 1600*t*
Latrepirdine, 846
Laxatives, 553–554
bulk-forming, 553
emollient, 554
stimulant, 554
L-Dopa, 952–955
"delayed-on" or "no-on" response, 954–955, 954*t*
dyskinesias in, 954*t*, 955
dystonias in, 955
end-of-dose wearing off, 954, 954*t*
freezing, 954*t*, 955
motor complications of, 954, 954*t*
pharmacokinetics of, 953–954
Leflunomide, 1525*t*, 1527, 1533*t*
Legionella pneumophila, 1815, 1820*t*
Lenalidomide, 2189*t*, 2198, 2338, 2416
Lentigo maligna melanoma, 2431
Lenvatinib, 2187*t*, 2203
Lesinurad, 1575*t*, 1577*t*, 1582
Letermovir, 2093*t*
Letrozole, 2358*t*
for abnormal uterine bleeding with ovulatory dysfunction, 1346–1347

for breast cancer, 2246*t*
for endometriosis, 1358*t*
Leucovorin, 1800, 2288, 2290*t*
Leukemia, acute, 2365–2382. *See also specific types*
acute lymphoblastic, 2368–2375
acute myeloid, 2375–2380
classification of, 2365–2366, 2368, 2368*t*
clinical presentation and diagnosis of, 2368, 2369*b*
epidemiology of, 2367
etiology of, 2367, 2367*t*
pathophysiology of, 2367–2368
Leukemia, chronic, 2387–2404. *See also specific types*
chronic lymphocytic leukemia, 2396–2404
chronic myeloid leukemia, 2387–2396
Leukotriene modifiers, 398
Leuprolide, 2312*t*
for breast cancer, 2246*t*
for endometriosis, 1358*t*
for menstruation-related disorders, 1342*t*
for premenstrual syndrome, 1350
Levamisole, 724
Levemir, 1240*t*
Levetiracetam, 921*t*
adverse effects of, 893*t*
drug interactions, 893*t*
for epilepsy, 892*t*–893*t*
mechanism of action, 892*t*
for refractory GCSE, 923
for traumatic brain injury, 937*t*
Levobunolol, 1600*t*
Levocarnitine, 683
Levofloxacin
for acute bacterial rhinosinusitis, 1833*t*
for chronic bronchitis, 1811*t*
for CNS infection, 1792
dosing and administration of, 1833*t*

dosing by age group, 1799*t*
dosing of, 1914*t*
for febrile neutropenia, 2092*t*
for intra-abdominal infection, 1947*t*
for peptic ulcer disease, 495
for peritonitis, 692*t*
for tuberculosis, 1913*t*, 1914*t*
for urinary tract infections, 1963*t*
Levomilnacipran, 1132, 1133*t*, 1135*t*, 1138*t*, 1140*t*
Levonorgestrel-releasing intrauterine system (LNG-IUS), 1342*t*
for endometriosis, 1358*t*, 1359
Levorphanol, 975*t*, 977*t*
Levothyroxine, 1283–1284
adverse effects of, 1284
dosing and administration of, 1284–1286
drug-drug and drug-food interactions of, 1284–1285
for hypothyroidism, 1281
pharmacokinetics of, 1284
Levotofisopam, 1583
Lewy bodies, 947
Lichenification, 1678
Lidocaine, 922*t*, 981*t*
for arrhythmias, 291–292, 292*t*
for cardiac arrest, 332*t*
for migraine, acute, 1003
pharmacokinetics of, 295*t*
for refractory GCSE, 924*t*
side effects of, 294*t*
topical, 974*t*
Life support
advanced, 329, 329f
basic, 328–329, 328f
Light therapy, for acne vulgaris, 1644–1645
Lightning, 337
Linaclotide, 554*t*, 555
Linagliptin, 1242*t*, 1246

Linezolid
for cellulitis, 1867
for CNS infection, 1792
dosing by age group, 1799*t*
for febrile neutropenia, 2092*t*, 2095*t*
for peritonitis, 692*t*
Linguistic competency, definition of, e11
Liothyronine, 1281, 1283–1284
Liotrix, 1284
Lipase, 2515*t*
Lipid amphotericin B, dosing by age group, 1799*t*
Lipid-associated amphotericin B, 2093*t*
Lipid-lowering agents, 845, 1582. *See also specific agents*
Lipopeptides, adverse effects and monitoring of, 1777*t*
Lipoprotein disorders, 117–118, 121*t*
Lipoproteins
apolipoproteins, 120
cholesterol synthesis, 119
chylomicrons, 119
composition of, 120
high-density, 117, 119
low-density, 117, 119
metabolism and transport of, 119–120
metabolism of, 121*f*
structure of, 118*f*
types of, 117, 119
very-low density, 117, 119
Liraglutide, 1244, 1245*t*, 2544*t*, 2547*t*, 2548–2549, 2550*t*
Lisdexamfetamine, 1017, 1038, 1209*t*
Lisinopril, 94
Lispro, 1239, 1240*t*
Listeria monocytogenes, 1794
Literacy, e9
Lithium
for ADHD, 1020–1021
adverse effects of, 1155

for bipolar disorder, 1153–1157
chronic interstitial nephritis and, 710
for cluster headache, 1003
dosing and administration of, 1154*t*, 1156–1157
drug interactions, 1156
efficacy of, 1155
for major depressive disorder, 1133*t*
nephrotoxicity of, 710
during pregnancy, 1160–1161
toxicity, 1155–1156
Live-attenuated influenza vaccine, 1846–1847, 1846*t*
Liver disease
drug-induced, e577
parenteral nutrition complications, 2506
Liver transplantation. *See also* Transplantation, solid-organ
acute cellular rejection in, 1479
chronic rejection in, 1479
epidemiology and etiology of, 1475
physiologic consequences of, 1476, 1476*t*
Lixisenatide, 1244, 1245*t*
Lobular carcinoma in situ (LCIS), 2228
Lofepramine, 871*t*
Lofexidine, 1050
Logical Observation Identifiers Names and Codes, 7*t*
Lomustine, 2196
Long-acting γ-receptor agonist (LABA), 1807, 1808
Long-acting muscarinic antagonists (LAMAs), 1808
Long-acting reversible contraception, 55
Loop diuretics
for acute decompensated heart failure, 229–230, 229*t*
characteristics of, 774*t*
for edema, 773–775, 774*t*
for heart failure with preserved ejection fraction, 206–209
for heart failure with reduced ejection fraction, 207*t*
infusion rates, 774*t*
for pulmonary arterial hypertension, 438

Loperamide, 546, 549*t*, 557, 1049–1050
Lopinavir, 2153*t*, 2154
Lorazepam, 533*t*, 920, 921*t*, 922*t*, 1036, 1073*t*, 1171*t*, 1175*t*, 1178*t*
Lorcaserin (serotonin receptor agonist), 2545–2547
Lorlatinib, 2184*t*, 2199
Losartan, 1582
Low emetogenic chemotherapy, 537
Low-density lipoprotein cholesterol (LDL-C), 117
Low-density lipoproteins (LDL), 117, 119, 124*t*
Lower esophageal sphincter (LES), 464*f*, 465
Lower respiratory tract infections, 1803–1822. *See also specific infections*
  bronchiolitis, 1810–1811
  bronchitis, 1804–1810
  pneumonia, 1812–1822
Lower urinary tract symptoms (LUTS), 1414
Low-level laser light (LLLL) therapy, 1700, 1701
Low-molecular-weight heparin (LMWH), 1321
Loxapine, 1096*t*
Lubiprostone, 554*t*, 555
Lung cancer
  patient care process for, 2260*b*
  staging of, non-small cell lung cancer, 2259*t*
Lung cancer treatment, 2255–2270
  clinical presentation of, 2257–2258, 2257*b*
  complication and supportive care in, 2269–2270
  diagnosis of, 2258
  epidemiology of, 2255–2256
  etiology of, 2256
  histologic classification of, 2256–2257, 2256*t*
  incidence of, 2255
  in menopausal hormone therapy, 1371
  mortality rate, 2255
  non-small cell lung cancer, 2259–2268, 2261*t*
    for advanced and relapsed disease, 2261–2268, 2263*t*–2265*t*
      in elderly and poor-performance status patients, 2268
      nonbiomarker driven, 2266–2267

with PD-L1+ tumors, 2262
relapses disease, 2267–2268
with targetable genetic mutation, 2262–2266
for local disease (advanced and relapsed), algorithm for, 2262*f*
for local disease (stages I-II), 2259–2260
for locally advanced disease (stage IIIA/ IIIB), 2260–2261
outcome evaluation for, therapeutic, 2268
outcomes of, desired, 2259
screening and prevention of, 2258
small cell lung cancer, 2268–2269, 2269*t*
extensive disease in, 2268–2269
limited disease in, 2268
outcome evaluation for, therapeutic, 2269
relapsed disease, 2269
staging of, 2258–2259
non-small cell lung carcinomas, 2258
small cell lung carcinomas, 2258–2259
Lung transplantation
acute cellular rejection in, 1479
chronic rejection in, 1480
epidemiology and etiology of, 1475, 1477
Lupus. *See* Systemic lupus erythematosus (SLE)
Lupus nephritis, 731–733
clinical presentation of, 731
epidemiology of, 731
etiology of, 731
pathophysiology of, 731
prognosis of, 733
treatment of, 731–733
algorithm for, 732*f*
alternative therapeutic agents, 733
chronic maintenance
calcineurin inhibitors, 733
hydroxychloroquine, 733
general approach to, 731–732
induction treatment, 732

mycophenolate mofetil, 731
steroids, 731
maintenance treatment, 732–733
calcineurin inhibitors, 733
cytotoxic agents, 732
hydroxychloroquine, 733
Lurasidone. *See also* Antipsychotics
adverse effects of, 1107*t*
dosing and administration of, 1154*t*
dosing of, 1096*t*
drug interactions, 1114, 1117*t*
mechanism of action, 1105*t*
pharmacokinetics of, 1106*t*
Luteal phase, in menstrual cycle, 44
Luteinizing hormone (LH), 2305
Luteinizing hormone-releasing hormone (LHRH), 2240–2242, 2245, 2248, 2304–2305, 2310–2313
Luteinizing-hormone agonists, 2312*t*
Lutetium, 2189*t*
Lutetium Lu 177 dotatate, 2197
Lyme disease, 1798
Lymphadenopathy, 1522
Lymphangitis, 1865–1866
clinical presentation of, 1866*b*
etiology of, 1856*t*
treatment of, 1866
outcomes of
desired, 1865–1866
therapeutic, evaluation of, 1866
pharmacologic, 1862*t*
Lymphoblastic leukemia, acute, 2368–2375
initial response in, 2368
patient care process for, 2366*b*
patient characteristics in, 2369
prognostic factors in, 2370
risk classification in, 2369*t*

in children, 2370*f*, 2370*t*
treatment of, 2370–2375
in adolescents and young adults, 2373
in adults, 2373–2374
in Down syndrome, 2371
phases of, 2371–2373, 2371*f*
central nervous system prophylaxis in, 2372
consolidation therapy in, 2372
induction, 2371–2372
maintenance therapy in, 2373
reinduction in, 2372–2373
in Philadelphia chromosome positive ALL, 2373
in relapsed ALL, 2374–2375
supportive care issues in, 2381
therapeutic outcomes of, evaluation of, 2381–2382
Lymphocytes, 374
Lymphocytic leukemia, chronic, 2396–2404
clinical presentation of, 2398*b*
epidemiology of, 2396
etiology of, 2396
pathophysiology of, 2396–2398
patient care process for, 2397*b*
staging and prognosis in, 2398
treatment of, 2398–2404, 2399*f*, 2400*t*
biologic therapy in, 2399–2400
combination therapy in, 2401–2404
cytotoxic chemotherapy in, 2399
alkylating agents, 2399
purine analogs, 2399
dosing of, 2402*t*
hematopoietic stem cell transplantation, 2404
intramuscular immunoglobulin in, 2138
monitoring of, 2403*t*
outcomes of, therapeutic, evaluation of, 2404
summary of options, 2404
targeted therapy in, 2400–2401

Lymphogranuloma venereum, 1991*t*
Lymphoma, 2319–2342. *See also specific types*
  Hodgkin, 2320–2329
  non-Hodgkin lymphoma, 2329–2342
  patient care process for, 2323*b*
Lysergic acid diethylamide (LSD), 1044, 1060

M

M. genitalium, 1992
M protein, 2410
Macitentan, 442, 443*t*, 445*t*, 446*t*
Macozinone, 1918
Macrocytic anemia, 1710
Macrolides
  for acne vulgaris, 1641
  adverse effects and monitoring of, 1778*t*
  dosing of, 1819*t*
  drug interactions, 1775*t*
  for pneumonia, 1819*t*
  for tuberculosis, 1917
Macular degeneration, age-related, 1607–1617
  Amsler grid, 1607, 1610*f*
  classification of, 1612, 1612*t*
    advanced AMD, 1612
    early AMD, 1612
    intermediate AMD, 1612
  clinical presentation of, 1612, 1613*b*
  definition of, 1607
  epidemiology of, 1607–1611, 1608*f*, 1609*f*, 1610*f*
    diet, 1610
    genetic factors in, 1608–1610
    risk factors for, 1608, 1610–1611, 1610*f*
    smoking, 1610
  etiology of, 1611
  eye, anatomy of, 1608*f*
  outcomes, evaluation of, 1617

pathophysiology of, 1611–1612
dry AMD, 1611
web AMD, 1611–1612
patient care process for, 1613*b*
prevention of, 1616–1617
treatment of, 1612–1617
antioxidant vitamins and minerals, 1613–1614, 1614*t*
smoking cessation, 1612–1613
for wet AMD, 1614–1616, 1615*t*
antioxidant vitamins and minerals, 1616
photodynamic therapy, 1616
statin therapy, 1616
surgical therapy, 1616
VEGF inhibitors, 1614–1616, 1615*t*
types of, 1607
Magnesium
for cardiac arrest, 332*t*, 333
in foods, 811*t*
functions of, 807
for migraine headache, 996*t*
recommended daily intake of, 807
Magnesium citrate, 554*t*
Magnesium homeostasis disorders, 807–811
hypermagnesemia, 809–811
hypomagnesemia, 807–809
patient care process for, 800*b*
Magnesium hydroxide, 475*t*
Magnesium salts, 554
Magnesium sulfate, 400, 554*t*
Magnetic resonance imaging, e81
Magnetic sphincter augmentation, 473*t*
Magnetic therapy, 871*t*
Major depressive disorder, 1125–1130
biomarkers of, 1127
clinical presentation of, 1127–1130, 1128*b*
depression rating scales in, 1129

DSM-5 criteria in, 1128–1129, 1129*t*
emotional symptoms in, 1129
intellectual or cognitive symptoms in, 1128*b*
physical symptoms in, 1129
psychomotor disturbances in, 1128*b*
definition of, 1125
epidemiology of, 1125
etiology of, 1126
medications associated with, 1128*t*
pathophysiology of, 1126–1127
patient care process for, 1131*b*
prevalence of, 1125
suicide risk evaluation and management in, 1129–1130
Major depressive disorder treatment, 1130–1143
algorithm for, 1134*f*
alternative pharmacotherapy in, 1141
folate, 1141
omega-3 fatty acids, 1141
S-adenosyl-l-methionine (SAMe), 1141
St. John's wort, 1141
in children, 1142
clinical presentation of, 1151*b*
in elderly, 1141–1142
general approach to, 1130
nonpharmacologic therapy in, 1130
outcomes of
desired, 1130
therapeutic, evaluation of, 1144–1145
pathophysiology of, 1126*f*, 1127*f*
personalized pharmacotherapy in, 1143
pharmacologic therapy in, 1130–1143
adverse drug reactions, 1144*t*
antipsychotics, second-generation, 1136–1137
dosing of, 1133*t*–1134*t*
drug interactions, 1139–1141
pharmacodynamic, 1139–1141, 1141*t*

pharmacokinetic, 1139, 1140*t*
investigational drugs, 1137
mixed serotonergic medications, 1133*t*, 1135–1136, 1138*t*
monoamine oxidase inhibitors, 1133*t*, 1136, 1137*t*
norepinephrine and dopamine reuptake inhibitor, 1133*t*, 1136, 1138*t*
pharmacodynamics of, 1137–1139
pharmacokinetics of, 1137–1139, 1138*t*
plasma concentration and clinical response of, 1139
relative potencies, 1135*t*
selective serotonin reuptake inhibitors, 1132, 1133*t*, 1138*t*
serotonin and α2-adrenergic antagonists, 1133*t*, 1136, 1138*t*
serotonin-norepinephrine reuptake inhibitors, 1132–1135, 1133*t*, 1138*t*
tricyclic antidepressants, 1132, 1133*t*, 1138*t*
in pregnancy and lactation, 1142–1143
for treatment-resistant depression, 1143
Malabsorption, 591–592
Maladaptive (pathologic) pain, 960
Malassezia furfur, 2036
Malignancy. *See* Cancer
Malnutrition
alcohol withdrawal and, 1074
causes of, 2467–2468
in chronic pancreatitis, 587
contraindications and precautions in, 2130
definition of, 2467
hypophosphatemia and, 793
in inflammatory bowel disease, 514
in peritonitis, 688
physical examination in, 2471*t*
surgical site infections and, 2112
Mammography, 2224
Manganese, 2477*t*, 2478
Mania, 1070, 1150*t*, 1151, 1151*b*, 1153*t*. *See also* Bipolar disorder
Manipulation, 965*t*
Manning criteria, 556
Mannitol, 557, 937*t*

Mantoux test, 1906
MAPK signaling pathway, 2178
Marasmus, 2467
Maraviroc, 2153*t*, 2154
Marijuana, 1061
  medical, 1061
  potency of, 1062
  synthetic, 1061–1062
Masked hypertension, 89
Massage, 965*t*
Mast cells, 375
Mastectomy, 2233
Mastitis, 1331
Maturity onset diabetes of youth (MODY), 1231, 1234–1235
Maxacalcitol, 1660
Mean cell hemoglobin, 1714
Mean cell hemoglobin concentration, 1714
Mean cell volume, 1713–1714
Mean corpuscular hemoglobin concentration (MCHC), 1749
Measles, vaccines, 2132–2133
Mechanical acne, 1624
Mechanical circulatory support (MCS)
  durable, 236–237
  temporary, 235–236, 235*f*
Mechlorethamine, 2182*t*, 2324–2326, 2325*t*
Meclizine, 533*t*
Meclofenamate, 1505*t*
Median eminence, e1313
Medical errors, e13
Medical foods, 846
Medical nutrition therapy, 1238, 1249
Medication adherence
  in HIV infection treatment, 2155
  in hypertension treatment, 111–112
  in schizophrenia treatment, 1100–1104
Medication errors (MEs), e13

Medication Therapy Problem Categories Framework, 5*t*
Medication-overuse headache, 994
Medicinal marijuana, 535
Meditation, 965*t*
Medroxyprogesterone
  for breast cancer, 2246*t*
  for endometriosis, 1358*t*, 1359
  for heavy menstrual bleeding, 1344
  for menstruation-related disorders, 1342*t*
Medullary carcinoma, 2227
Mefenamic acid, 1505*t*
Megaloblastic anemia, 1710, 1718–1720
  folic acid deficiency anemia, 1720–1721
  vitamin B12 deficiency anemia, 1719–1720
Megestrol, 2305
Megestrol acetate, 2246*t*
Meglitinides, 1242*t*, 1248
MEK inhibitor, 2187*t*, 2202, 2295, 2443, 2443*t*, 2445*t*
Melanoma, 2429–2434
  acral lentiginous, 2431
  clinical presentation of, 2432–2433, 2433*b*, 2434*t*
  definition of, 2429
  epidemiology of, 2429–2430
  etiology of, 2430
  incidence of, 2429
  lentigo maligna, 2431
  nodular, 2431
  pathophysiology of, 2430–2431
  patient care process for, 2436*b*
  prevention and detection of, 2431–2432, 2432*t*
  risk factors for, 2430*t*
  staging and prognostic factors in, 2433–2434, 2435*t*
  subtypes of
    clinical, 2431
    histologic, 2431
  superficial spreading, 2431

uveal, 2431
Melanoma treatment, 2434–2446
adjuvant therapy in, 2436–2439
CTLA-4 checkpoint inhibitor, 2437–2439
interferon, 2437
PD-1 inhibitors, 2439
targeted therapy in, 2439
for metastatic melanoma, 2439–2444
biochemotherapy in, 2439
chemotherapy in, 2439
immunotherapy in, 2440–2442
combination CTLA-4 and PD-1 checkpoint inhibitors, 2441
CTLA-4 checkpoint inhibitor, 2440, 2441
interleukin-2, 2440
PD-1 and PD-L1 checkpoint inhibitors, 2440–2441
vaccines, 2441
targeted therapy in, 2442–2444, 2442*t*
outcomes of, desired, 2434
surgery in, 2434–2436
Melatonin, 1224*t*
MELD score, 565
Melena, 501
Meloxicam, 1505*t*, 1574*t*
Melphalan, 2454*t*
Memantine, 843–844, 843*t*, 844*t*, 847
Membrane transport proteins, e15
Membranoproliferative glomerulonephritis, 728–729
clinical presentation of, 728
epidemiology of, 728
etiology of, 728
pathophysiology of, 728
treatment of, 728–729
cytotoxic agents, 728–729
steroids, 728–729
Membranous nephropathy, 708, 726–728
clinical presentation of, 726–727

epidemiology of, 726
etiology of, 726
nephrotic syndrome relapse in, 728
pathophysiology of, 726
prognosis of, 728
treatment of, 727–728
algorithm for, 727*f*
alternative options, 728
calcineurin inhibitors, 727–728
cytotoxic agents, 727
immunosuppresive therapy, 727–728
rituximab, 728
steroids, 727
Meninges, 1786
Meningitis, 1787. *See also* Central nervous system (CNS) infection
health-care associated, 1794–1795
tuberculous, 1912
vaccines, 2133
Meningoencephalitis, 1798–1800, 2059*t*, 2060
Menopause and perimenopausal/postmenopausal hormone therapy
benefits and risks of, 1368–1371, 1368*t*
body weight effects, 1371
breast cancer, 1370
cardiovascular disease, 1369–1370
diabetes, 1371
endometrial cancer, 1370–1371
gallbladder disease, 1371
lung cancer, 1371
mood, cognition, and dementia, 1371
osteoporosis, 1371
ovarian cancer, 1371
venous thromboembolism, 1370
bioidentical hormones, compounded, 1375
clinical trials on, 1368–1369
combined estrogen-progestogens, 1374–1375, 1374*t*
complementary and alternative medicine in, 1377

phytoestrogens, 1377
estrogens in, 1371–1372, 1373*t*
adverse effects of, 1371–1372
dosage and administration of, 1372
oral, 1372
other routes of administration in, 1372
evidence-based, 1379*t*
indications and contraindications for, 1365*t*
other treatments in, 1375–1376, 1376*t*
androgens, 1375
selective estrogen receptor modulators, 1376–1377
tibolone, 1377
outcomes of, desired, 1365
patient care process for, 1366*b*
personalized pharmacotherapy in, 1377–1378
pharmacologic therapy in, 1367–1377
progestogens in, 1372–1374, 1374*t*
therapeutic outcomes of, evaluation of, 1378, 1379*t*
Menopause and perimenopause, 1363–1379
clinical presentation of, 1364–1365, 1364*b*
epidemiology of, 1363
etiology of, 1363
genitourinary symptoms of, 1368
pathophysiology of, 1364–1365
vasomotor symptoms of, 1368
Menopause and perimenopause treatment, 1365–1378
general approach to, 1365–1367, 1367*f*
nonpharmacologic therapy in, 1367
outcomes of, desired, 1365
for perimenopausal women, 1367
pharmacologic therapy in
first choice, 1367
guidelines for, 1367*f*
Menopenem-vaborbactam, 2092*t*
Menorrhagia. *See* Heavy menstrual bleeding
Menstrual cycle, 42–43, 43*f*

follicular phase, 43
luteal phase, 44
ovulation, 44
Menstruation-related disorders, 1335–1350. *See also specific disorders*
abnormal uterine bleeding with ovulatory dysfunction, 1345–1347
amenorrhea, 1336–1341
dysmenorrhea, 1347–1349
heavy menstrual bleeding, 1341–1345
hormonal fluctuations, 1337*f*
pathophysiology of, 1337*t*
patient care process for, 1340*b*
premenstrual dysphoric disorder, 1349–1350
premenstrual syndrome, 1349–1350
therapeutic agents for, 139*t*–140*t*
Menthol/methyl salicylate, 974*t*
Meperidine, 980
dosing and administration of, 977*t*
for pain management, 975*t*
Mephedrone, 1060
Mepivacaine, 981*t*
Mepolizumab, 398*t*, 399
Mercaptopurine, 515, 516*t*, 520, 522, 524, 2180*t*, 2193, 2373
Meropenem
for CNS infection, 1792
for cystic fibrosis, 454*t*
dosing by age group, 1799*t*
for febrile neutropenia, 2092*t*
for UTIs, 1963*t*
Mesalamine, 515, 516*t*, 517–519, 521, 522, 523, 523*t*
Mesangium, 715
Mescaline, 1060
Mesotherapy, 1700, 1701
Metabolic acidosis, 817–821
causes of, 818*t*
clinical presentation of, 820, 821*b*
compensation in, 820–821, 820*t*

elevated anion gap, 819–820
hyperchloremic, 817–818
lactic, 819–820, 819*t*
pathophysiology of, 817
renal tubular acidosis, 818–819
treatment of, 821–827, 821*t*
for acute severe metabolic acidosis, 823–824
sodium bicarbonate in, 823–824
dichloroacetate in, 824
tromethamine in, 824
Metabolic alkalosis, 824–825
clinical presentation of, 825
compensation in, 825
pathophysiology of, 824
treatment of, 825–827, 826*f*
Metabolic bone disease, 2507
Metabolic syndrome, 1109
hypertension treatment and, 101
Metastatic melanoma, 2439–2444
Metastatic melanoma treatment, 2439–2444
biochemotherapy in, 2439
chemotherapy in, 2439
immunotherapy in, 2440–2442
combination CTLA-4 and PD-1 checkpoint inhibitors, 2441
CTLA-4 checkpoint inhibitor, 2440, 2441
interleukin-2, 2440
oncolytic, 2441–2442
PD-1 and PD-L1 checkpoint inhibitors, 2440–2441
vaccines, 2441
limb infusion in, 2445–2446
limb perfusion in, 2445–2446
outcomes of, therapeutic, evaluation of, 2446
radiation in, 2444–2445
targeted therapy in, 2442–2444, 2442*t*
Metaxalone, 972, 972*t*
Metered-dose inhalers (MDIs), 386, 390*f*, 390*t*, 392*f*

Metformin, 152, 658, 1241–1243, 1242*t*, 1343*t*
Methadone, 980, 1048
  dosing and administration of, 978*t*
  for pain management, 975*t*
  for substance-related disorders, 1048, 1050–1051, 1051*t*
Methamphetamine, 1059–1060, 1209*t*
Methaqualone, 1044
Methazolamide, 1600*t*
Methicillin-resistant Staphylococcus aureus (MRSA), 1820*t*, 1866, 1871, 1873*t*, 1894, 2114
Methicillin-sensitive Staphylococcus aureus (MSSA), 1820*t*, 1894
Methimazole, 1274–1277
  adverse effects of, 1276–1277
  dosing and administration of, 1275–1276
  mechanism of action, 1274
  pharmacokinetics of, 1274–1275
Methocarbamol, 972*t*, 973
Methotrexate, 58, 1462*t*, 2334
  for acute lymphoblastic leukemia, 2373
  adverse effects of, 1533*t*
  for atopic dermatitis, 1686
  for cancer treatment, 2180*t*, 2193
  for Crohn's disease, 520, 521
  for graft-versus-host disease, 2460, 2461*t*
  for inflammatory bowel disease, 515, 516, 516*t*, 522, 523*t*, 524
  for psoriasis, 1662–1663
  for rheumatoid arthritis, 1525*t*, 1526–1527
  for systemic lupus erythematosus, 1460, 1461*t*
Methylcellulose, 554*t*
Methyldopa, 100*t*
Methylenedioxypyrovalerone (MDPV), 1060
Methylmalonic acid, 1715
Methylnaltrexone, 554*t*, 555, 980
Methylone, 1060
Methylphenidate, 869*t*, 870, 1014–1019, 1016*t*, 1209*t*, 1224*t*
Methylprednisolone, 519, 538, 539*t*, 540, 860, 1308*t*, 1504*t*, 2461*t*

Methyltestosterone, 1391*t*, 1399*t*
Methylxanthines, 400, 418–419
Metipranolol, 1600*t*
Metoclopramide, 476, 477, 534*t*, 535, 537, 538, 540, 995*f*, 997, 999, 1036
Metronidazole, 495, 573, 575*t*
  adverse effects and monitoring of, 1778*t*
  for Crohn's disease, 520, 521
  drug interactions, 1775*t*
  for inflammatory bowel disease, 515, 524
  for intra-abdominal infection, 1947*t*, 1949
  for peptic ulcer disease, 493, 495
  for trichomoniasis, 1989
Metyrapone, 1298*t*
Mexiletine, 291, 292*t*, 294*t*, 295*t*, 296*t*
Micafungin
  for febrile neutropenia, 2093*t*
  for oropharyngeal candidiasis, 2033*t*
Miconazole
  for oropharyngeal candidiasis, 2033*t*
  for vulvovaginal candidiasis, 2027, 2027*t*
Microalbuminuria, 1753
Microbial resistance, 2046
Microcytic anemia, 1710
Micrographia, 932*f*
Micronutrients, 2485, 2486*t*–2487*t*. *See also specific types*
Microsporum, 2036
Microtubule-targeting drugs, 2180*t*–2181*t*, 2194
  eribulin, 2194
  estramustine, 2194
  ixabepilone, 2194
  monitoring of, 2180*t*–2181*t*
  taxanes, 2194
  vinca alkaloids, 2194
Midazolam, 920, 921*t*, 923, 924*t*
Midodrine, 683
Midostaurin, 2186*t*

Midstream clean-catch method, 1960
Mifepristone, 57–58, 1298*t*, 1300
MIG-99, 996*t*
Miglitol, 1242*t*, 1248
Migraine headache, 989–992. *See also* Migraine headache treatment
  aura, 992
  clinical presentation of, 991*b*, 992
  from combined hormonal contraceptives, 53
  diagnosis of, 992*t*
  epidemiology of, 989–990
  etiology of, 990
  pathophysiology of, 990–992, 991*f*
  phases of, 992
  premonitory symptoms of, 992
  triggers of, 994–995, 997*t*
Migraine headache treatment, 992–1001
  algorithm for, 997*f*
  general approach to, 994
  goals of, 994*t*
  nonpharmacologic therapy in, 994–996
  outcomes of, desired, 992–994
  pharmacologic
    analgesics, 996–998
    antidepressants, 996*t*
    antiemetics, 999
    β-adrenergic antagonists, 996*t*
    ergot alkaloids, 999
    nonsteroidal anti-inflammatory drugs, 996–998
    opiate analgesics, 999
    serotonin receptor agonists (triptans), 998–999, 998*t*
  pharmacologic therapy in
    abortive treatments, 996–998
    antidepressants, 1000
    antiepileptic drugs, 999–1000
    β-adrenergic antagonists (beta blockers), 1000
    calcitonin gene-related peptide antagonists, 1000

dosing and administration of, 995*f*
NSAIDs, 1000
petasites, 1000–1001
prophylactic agents, 999–1001
triptans, 1000
Miliary tuberculosis, 1905. *See also* Tuberculosis
Milnacipran, 970*t*, 971
Milrinone, 233, 233*t*
Mindfulness, 965*t*
Mineralocorticoid, 1306
Minimal-change nephropathy, 722–725
clinical presentation of, 722
epidemiology of, 722
etiology of, 722
histology of, 722
prognosis of, 724–725
steroid-resistant nephritic syndrome, 724
treatment of, 722–725
algorithm for, 723*f*
pharmacologic therapy in
calcineurin inhibitors, 724
cytotoxic agents, 724
levamisole, 724
mycophenolate mofetil, 724
rituximab, 724
steroids, 722–724
Minocycline, 1637*t*, 1641, 1811*t*
Minoxidil, 1699, 1700
Mirabegron, 869*t*, 1422*t*, 1425, 1443–1444
Mirtazapine, 1133*t*, 1144*t*
drug interactions, 1140*t*
for posttraumatic stress disorder, 1191*t*, 1193, 1193*t*
relative potencies, 1135*t*
Misoprostol, 494*t*, 496, 499
Mitomycin C, 2183*t*, 2198
Mitotane, 1298*t*, 1300

Mitoxantrone, 862*t*, 863*t*, 864*t*, 867, 2181*t*
Mixed incontinence, 1433–1434. *See also* Urinary incontinence
Mixed serotonergic medications, 1133*t*, 1135–1136, 1135*t*, 1138*t*, 1140*t*, 1144*t*
Modafinil, 869*t*, 870, 1208, 1209*t*
Model for end-stage liver disease (MELD) score, 565
Moderate emetogenic chemotherapy, 537
Mogamulizumab-kpkc, 2190*t*
Molds, 139, 2046*f*
Molybdenum, 2477*t*, 2479
Mometasone furoate, 383*t*
Monitoring the Future Study (MFS), 1044
Monoamine hypothesis, 1127*f*
Monoamine neurotransmitter, 1126*f*
Monoamine oxidase B inhibitors, 952*t*, 953*t*, 955
Monoamine oxidase inhibitors, 1133*t*, 1136, 1137*t*, 1178*t*
  for posttraumatic stress disorder, 1193*t*
  for social anxiety disorder, 1182*t*
Monoarticular infection, 1996
Monobactams
  adverse effects and monitoring of, 1777*t*
  dosing of, 1819*t*
Monoclonal antibodies, 2204–2208, 2456–2457
  antibody-drug conjugates, 2207–2208
    ado-trastuzumab ematansine, 2207
    brentuximab vedotin, 2207
    gemtuzumab ozogamicin, 2207
    inotuzumab ozogamicin, 2207
    polatuzumab vedotin, 2207–2208
  biosimilars, 2204
  bispecific T-cell engagers, 2207
  fusion proteins
    moxetumomab pasudotox, 2208
    ziv-aflibercept, 2208
  monitoring of, 2189*t*–2190*t*, 2191*t*
  for multiple myeloma, 2418
  targeting B-lymphocyte antigen CD20

obinutuzumab, 2205
ofatumumab, 2205
rituximab, 2204–2205
targeting CD38, 2205
targeting CD52, 2205
targeting cell surface receptors, alemtuzumab, 2205
targeting chemokine receptors, 2205
targeting EGFR
cetuximab, 2206
necitumumab, 2206
panitumumab, 2206
targeting GD2, 2205
targeting HER2
pertuzumab, 2206
trastuzumab, 2206
targeting PDGFR-α, 2205–2206
targeting SLAMF7, 2206
targeting VEGF
bevacizumab, 2206–2207
ramucirumab, 2207
Monocyte chemoattractant protein-1 (MCP-1), 651
Monoiodotyrosine (MIT), 1266
Montelukast, for chronic asthma, 384, 398
Mood, 1371
Mood disorders, by episodes, 1150*t*
Mood stabilizer, 1152
Moraxella catarrhalis, 1804, 1808*t*, 1827
Morning sickness, 1317
Morphine, 976–980
for acute coronary syndromes, 169, 170*t*, 184*t*
dosing and administration of, 977*t*
for intracranial hypertension, 935
metabolism of, 979–980
for NSTE-ACSs, 169
for pain management, 975*t*, 976–980
side effects of, 976–978

Morphine-3-glucuronide (M3G), 979
Morphine-6-glucuronide (M6G), 979
Motion sickness, 539
Motivational interviewing, 1079
Motoprolol, 996*t*
Moxetumomab pasudotox, 2192*t*, 2208
Moxifloxacin
  for acute bacterial rhinosinusitis, 1833*t*
  adverse effects and monitoring of, 1919*t*
  for chronic bronchitis, 1811*t*
  for CNS infection, 1792
  dosing by age group, 1799*t*
  dosing of, 1833*t*
  for febrile neutropenia, 2092*t*
  for intra-abdominal infection, 1947*t*
  for peritonitis, 692*t*
  for tuberculosis, 1914*t*
mTOR pathway inhibitors, 2187*t*, 2202
  everolimus, 2202
  temsirolimus, 2202
Mucinous carcinoma, 2227
Mucolytics, 421
Mucor infections, 2069
Mucosal candidiasis, 2033*t*
Mucosal defense, 487
Mucosal protection, 487, 494*t*
Mucus
  in asthma, 375–376
  mucosal protectants, 477
  mucosal resistance, 465
Multifocal motor neuropathy, 2138
Multikinase inhibitors, 2187*t*–2188*t*, 2202–2203
  axitinib, 2202
  cabozantinib, 2202–2203
  lenvatinib, 2203
  pazopanib, 2202

regorafenib, 2203
sorafenib, 2202
sunitinib, 2202
vandetanib, 2203
Multinodular goiters, 1271
Multiple myeloma, 2409–2412
clinical presentation of, 2410–2411, 2410*b*
epidemiology of, 2409–2410
etiology of, 2409–2410
pathophysiology of, 2410, 2411*f*
patient care process for, 2412*b*
staging and prognostic factors in, 2411–2412, 2411*t*
Multiple myeloma treatment, 2412–2422
allogeneic hematopoietic stem cell transplantation in, 2421
autologous hematopoietic stem cell transplantation in, 2419–2421
clinical response definitions in, 2414*t*
general approach to, 2412–2414, 2413*f*
initial therapy in, 2419
maintenance therapy in, 2420–2421
outcomes of
desired, 2412
therapeutic, evaluation of, 2422
pharmacologic therapy in, 2414–2419, 2415*t*
chemotherapy, 2414, 2415*t*
immunomodulatory drugs, 2414–2416
lenalidomide, 2416
pomalidomide, 2416
thalidomide, 2414–2416
monoclonal antibodies, 2418
daratumumab, 2418
elotuzumab, 2418
panobinostat, 2418–2419
protease inhibitors, 2417–2418
bortezomib, 2417
carfilzomib, 2417–2418
ixazomib, 2418

selinexor, 2418–2419
for relapsed or refractory disease, 2421–2422
supportive care in, 2421
bisphosphonates, 2421
bone-modifying agents in, 2421
denosumab, 2421
pamidronate, 2421
zoledronic acid, 2421
Multiple sclerosis, 853–858
clinical presentation and course of, 857*b*
clinical presentation of, 858
definition of, 853
diagnosis of, 858
differential diagnosis of, 858
epidemiology of, 853–854
etiology of, 854
laboratory evaluation of, 858
pathogenesis of, 856*f*
pathophysiology of, 854–858, 855*f*
autoimmune theory of, 856*f*
course of, 856–858
T-cell differentiation, 855*f*
patient care process for, 859*b*
primary-progressive, 854
prognostic indicators of, 858, 858*t*
secondary-progressive, 854
Multiple sclerosis treatment, 858–871
algorithm for, 861*f*
complementary and alternative therapies in, 870, 871*t*
general approach to, 859–860
nonpharmacologic therapy in, 860
outcomes of
desired, 859
therapeutic, evaluation of, 871–872
personalized pharmacotherapy in, 870–871
pharmacologic therapy in, 860–871

adverse drug reactions, 863*t*
disease-modifying therapy in, 860–868, 862*t*, 863*t*, 864*t*
alemtuzumab, 862*t*, 863*t*, 866–867
daclizumab, 862*t*, 863*t*, 867
dimethyl fumarate, 862*t*, 863*t*, 866
fingolimod, 862*t*, 863*t*, 865–866
glatiramer acetate, 862*t*, 863*t*, 864*t*, 865
interferon-β_{1b}, 860–865, 862*t*, 863*t*, 864*t*
interferon-β_{1a}, 860–865, 862*t*, 863*t*, 864*t*
mitoxantrone, 862*t*, 863*t*, 864*t*, 867
natalizumab, 862*t*, 863*t*, 864*t*, 865
ocrelizumab, 862*t*, 863*t*, 864*t*, 867
rituximab, 867
teriflunomide, 862*t*, 863*t*, 866
exacerbation in, 860
recommendations, 868*t*
symptomatic management in, 868–870, 869*t*
bowel and bladder, 869
cognition, 870
depression, major, 870
fatigue, 870
gait difficulties and spasticity, 868–869
pseudobulbar palsy, 870
sensory, 870
sexual dysfunction, 870
tremor, 869
vaccine recommendations in, 870
Multiple-organ dysfunction syndrome (MODS), 2007
Mumps, vaccine for, 2133
Muscle cramps, 682*t*, 684, 684*t*
Muscle relaxants. *See* Skeletal muscle relaxants
Mycobacterium avium, 2160*t*
Mycobacterium ovium, 2159*t*
Mycobacterium tuberculosis, 1798, 1814, 1901, 1996, 2160*t*. *See also* Tuberculosis

Mycophenolate mofetil, 724, 1668
for atopic dermatitis, 1686
for focal segmental glomerulosclerosis, 726
for graft-versus-host disease, 2461*t*
for immunoglobulin A nephropathy, 730
for systemic lupus erythematosus, 1460, 1461*t*, 1462*t*
Mycophenolic acid (MPA), 1464
Mycoplasma pneumoniae, 1751, 1760, 1783, 1804, 1820*t*
Mycoplasma tuberculosis, 1814
Mycotic infections of skin, hair and nails, 2036–2041. *See also specific infections*
onychomycosis, 2038–2039
pityriasis versicolor, 2038
tinea barbae, 2038
tinea capitis, 2038
tinea corporis, 2038
tinea cruris, 2038
tinea manuum, 2038
tinea pedis, 2037–2038
treatment of, 2037*t*
Myelodysplastic syndromes (MDS) treatment, e2425
Myeloid leukemia, acute, 2375–2380
hematopoietic growth factors in, role of, 2380–2381
prognostic factors in, 2375
risk classification in, 2375, 2375*t*
treatment of
for acute promyelocytic leukemia, 2379–2380
in children, 2378–2379
outcomes of, desired, 2375–2376
phases of, 2376–2378
allogeneic hematopoietic stem cell transplantation in, 2377–2378
autologous hematopoietic stem cell transplantation in, 2378
induction, 2376–2377
postremission, 2377, 2378
in relapsed or refractory AML, 2379
supportive care issues in, 2381

therapeutic outcomes of, evaluation of, 2381–2382
Myeloid leukemia, chronic, 2387–2396
clinical presentation of, 2389*b*
criteria for phases of, 2389*t*
epidemiology of, 2388
etiology of, 2388
pathophysiology of, 2388, 2388*f*
patient care process for, 2391*b*
prognosis of, 2390
treatment of, 2390–2396, 2392*t*
chemotherapy in, 2390
hematopoietic stem cell transplantation, 2396
imatinib mesylate, 2391–2393
accelerated phase/blast crisis, 2393
adverse effects and drug interactions, 2393
chronic phase, 2391–2393
monitoring, 2393
resistance to, 2393
interferon alfa, 2390–2391
omacetaxine, 2396
outcomes of
desired, 2390
therapeutic, evaluation of, 2396
tyrosine kinase inhibitors, 2393–2395
discontinuation, 2396
dosing and administration of, 2392*t*
monitoring of, 2394*t*
Myephenolic acid, 1485–1486
adverse effects of, 1486
dosing and administration of, 1486
drug-drug interactions, 1486
drug-food interactions, 1486
efficacy of, 1486
pharmacokinetics of, 1485–1486
pharmacology and mechanism of action, 1485
Myocardial infarction

secondary prevention following, 180–182
aldosterone antagonists, 183–184
angiotensin receptor blockers, 183
angiotensin-converting enzyme inhibitors, 183
aspirin, 182*f*
beta-blockers, 170–171
calcium channel blockers, 171
nitrates, 169
P2Y12 inhibitorss, 182*f*
statins, 183
in sickle cell disease, 1753
ventricular remodeling after, 164
Myocardial oxygen demand (MVO2), 138
Myocardial oxygen supply, 138–140
Myocarditis, 1108–1109
Myoclonic seizure. *See* Epilepsy
Myofibroblasts, 375
Myopathy, acute, e459
Myxedema coma, 1286

N

Nabilone, 534*t*, 535
Nab-paclitaxel, 2181*t*
Nabumetone, 1505*t*
N-acetylcysteine (NAC), 634, 1807
Nadifloxacin, 1641
Nadolol, 996*t*
Nafarelin, for endometriosis, 1358*t*
Nafcillin, 1799*t*, 2092*t*, 2095*t*
Nalbuphine, 976*t*, 978*t*
Naldemedine, 554*t*, 555
Naloxegol, 554*t*, 555, 980
Naloxone
for acute drug intoxications and withdrawals, 1063
delivery options, 1056*t*
dosing and administration of, 978*t*

for opioid use disorder, 1054–1056
for substance-related disorders, 1063
Naltrexone, 980, 1051, 1051*t*, 1054*t*, 1075
Naltrexone-bupropion ER, 2544*t*, 2547*t*, 2548, 2550*t*
Naproxen, 144, 995*t*, 996*t*, 1505*t*, 1574*t*. *See also* Nonsteroidal anti-inflammatory drugs (NSAIDs)
Naratriptan, 995*f*, 996*t*, 998*t*
Narcolepsy, 1207–1209
cataplexy, 1208
clinical presentation of, 1208*b*
definition of, 1207
prevalence of, 1207
tetrad, 1208
treatment of, 1208–1209
nonpharmacologic therapy in, 1208
outcomes, evaluation of, 1209
outcomes of, desired, 1208
pharmacologic, 1209*t*
pharmacologic therapy in, 1208–1209
Nasal spray, 995*f*, 998*t*
Natalizumab, 516*t*, 517, 521, 522, 523*t*, 862*t*, 863*t*, 864*t*, 865
Nateglinide, 1242*t*, 1248
National Action Plan to Improve Health Literacy, e9
National Childhood Vaccine Injury Act of 1986, 2131
National Health Interview Study, e23
National Institutes of Health, e9
National Survey on Drug Use and Health (NSDUH), 1044
National Vaccine Injury Compensation Program, 2131
Native valve infective (NVE) endocarditis, 1889, 1891*t*
Natriuretic hormone, 87
Natriuretic peptides, 197. *See also specific types*
Nausea and vomiting, 529–540
balance disorders, 539
in cancer patients
chemotherapy-induced (*See* Chemotherapy-induced nausea and vomiting (CINV))

nonchemotherapy, 536
clinical presentation of, 531, 531*t*
definitions of, 529
etiology of, 529, 530*t*, 532
etiology of in cancer patients, 536*t*
hemodialysis complications, 682*t*
pathophysiology of, 529–530, 531*f*
patient care process for, 532*b*
postoperative, 538–539, 539*t*
radiation-induced, 537–538
Nausea and vomiting treatment, 531–536
chemotherapy-induced, 536–537, 540
in children, 540
general approach to, 532
in geriatrics, 540
nonpharmacologic management, 532–533
outcomes of
desired, 531–532
evaluation of, 540
pharmacologic therapy in, 533–536, 533*t*–534*t*
antacids, 533
antihistamine-anticholinergic drugs, 533
benzodiazepines, 533–534
butyrophenones, 534
cannabinoids, 534–535
corticosteroids, 535
H2-receptor antagonists, 535
5-hydroxytryptamine-3 receptor antagonists, 535
metoclopramide, 535
neurokinin 1 receptor antagonist, 535–536
olanzapine, 536
phenothlazines, 536
during pregnancy, 539–540
Necitumumab, 2190*t*, 2206
Necrotizing fasciitis, 1870
etiology of, 1856*t*

treatment of, evidence-based, 1860*t*–1861*t*
types of, 1870
Necrotizing soft-tissue infections, 1869–1871
clinical presentation of, 1870*b*
definition of, 1870
treatment of, 1870–1871
debridement in, 1870
outcomes of
desired, 1870
therapeutic, evaluation of, 1871
pharmacologic therapy in, 1871
types of, 1870
Nefazodone, 1133*t*, 1135–1136, 1135*t*, 1138*t*, 1144*t*, 1191*t*, 1193*t*
Neisseria gonorrhoeae, 1979*b*, 1996
Neisseria meningitidis, 1751, 1792*t*, 1793
Nelfinavir, 2153*t*, 2154
Neomycin, 573, 575*t*
Neonatal critical care, e65
Neonates, e61
Nephritic syndrome, 718
Nephrocalcinosis, 707–708
Nephrolithiasis, 708, 782, 785, 786*t*, 1571–1572, 1583–1584
Nephropathy, 1256
analgesic, 711
crystal, 707
membranous, 708
obstructive, 707
phosphate, acute, 707–708
Nephrotic syndrome, 718
Neratinib, 2186*t*, 2201
Netarsudil, 1601*t*, 1602
Netupitant/palonosetron, 530*t*, 534*t*, 535–536
Neural tube defects, 1161, 1318
Neuraminidase inhibitors, 1850–1851
Neurodermatitis, definition of, 1676*t*
Neurohormonal model and therapy, 196–197

aldosterone, 197
angiotensin II, 196–197
arginine vasopressin, 197
natriuretic peptides, 197
norepinephrine, 197
Neurokinin 1 receptor antagonist, 534*t*, 535–536
Neuroleptic malignant syndrome (NMS), 1111–1112
Neurologic disorders, signs and symptoms of, e833
Neuromodulatory agents, 1300
Neuropathy, 1256–1257
Neuropeptide Y (NPY), 1189
Neurosurgery, antimicrobial prophylaxis in, 2118*t*, 2121
Neurosyphilis, 1797, 1981
Neurotrophic receptor tyrosine kinase (NTRK) Inhibitor, 2188*t*
Neutropenia
in cancer patients, 2212–2214
in immunocompromised hosts, 2080–2081
Neutrophils, 375
Nevirapine, 1916*t*, 2151*t*, 2152*t*, 2154
Newborn, e61
Niacin, 2480*t*
Nicardipine, 110*t*, 111
Nicotine replacement therapy, 1080–1083, 1081*t*
duration of, 1082
gum, 1080, 1081*t*
instruction to patients, 1082
lozenge, 1080, 1081*t*
nasal spray, 1080, 1081*t*
vs. non-nicotine options, 1083
oral inhaler, 1080
patch, 1080, 1081*t*
side effects of, 1082
Nicotine use and dependence, 1076–1084
assessment of, 1078, 1079*t*
clinical presentation of withdrawal in, 1078*b*
economic impact of, 1077

epidemiology of, 1077–1078
health risks of, 1077–1078
pathophysiology of, 1078
Nicotine use and dependence treatment, 1078–1083, 1079*t*
AHRQ guidelines in, 1078
behavioral interventions, 1079*t*
electronic nicotine delivery system, 1079*t*, 1082
general approach to, 1079*f*
nonpharmacologic therapy in, 1078–1079
outcomes of
desired, 1078
evaluation of, 1083
patient care process for, 1084*b*
pharmacologic therapy in, 1079*t*, 1080–1083
bupropion, 1081*t*, 1082
clonidine, 1083
combination therapy in, 1083
nicotine replacement therapy in, 1080–1083, 1081*t*
gum, 1080, 1081*t*
lozenge, 1080, 1081*t*
nasal spray, 1080, 1081*t*
oral inhaler, 1080
patch, 1080, 1081*t*
nortriptyline, 1083
second-line treatments, 1083
varenicline, 1081*t*, 1082–1083
smoking cessation strategy in, 1078–1079
treatment model, 1077*f*
Nicotinic acid, 1231*t*
Night eating syndrome, 1030
Nigrostriatal pathway, 946
Nil disease. *See* Minimal-change nephropathy
Nilotinib, 2184*t*, 2199–2200, 2392*t*, 2393–2395, 2394*t*
Nilutamide, 2311*t*, 2313
Niraparib, 2188*t*
Nitazoxanide, 495

Nitrates
for chronic heart failure, 214
for heart failure with reduced ejection fraction, 214
monitoring of, 208*t*
myocardial infarction and, 169
for NSTE-ACSs, 182*f*
for stable ischemic heart disease, 150–152, 151*t*
Nitric oxide, asthma and, 376
Nitrofurantoin, 1963*t*
Nitrogen balance study, 2475
Nitrogen mustards, 2195–2196
bendamustine, 2195
cyclophosphamide, 2195–2196
ifosfamide, 2195–2196
Nitroglycerin, 110*t*
for acute coronary syndromes, 169, 170*t*, 181*t*, 184–185, 184*t*
for acute decompensated heart failure, 231–232, 231*t*
for ischemic heart disease, 151*t*
Nitrosoureas, 2183*t*
Nitroureas, 2196
carmustine, 2196
lomustine, 2196
Nivolumab, 2191*t*, 2208, 2263*t*, 2291*t*, 2296
Nizatidine, 472*t*, 473*t*, 475*t*, 476, 494*t*, 534*t*
NMDA hypofunction, 1093
N-methyl-D-aspartate (NMDA)
receptor antagonist, 843–844, 843*t*
in schizophrenia, 1092
Nocardia, 1798
Nociceptors, 960, 961*f*
Nocturia, 1446
Nocturnal asthma, 380. *See also* Asthma
Nocturnal hemodialysis, 750
Nodular melanoma, 2431
Nonadrenergic agents, 2550*t*
Nonbacterial rhinosinusitis, 1832

Nonbenzodiazepine GABAA agonists, 1205
Nondepleting antibodies, 1489–1490
Nondihydropyridine, 98, 103–104
Nongonococcal urethritis (NGU), 1991*t*, 1992
Non-Hodgkin lymphoma, 2329–2342. *See also* Hodgkin lymphoma
  clinical presentation of, 2331–2332, 2331*b*, 2332*t*
  diagnosis of, 2332–2334
  epidemiology of, 2329–2330
  etiology of, 2329–2330
  molecular abnormalities in, 2330
  pathology and classification of, 2330–2331, 2330*t*
    disease entities in, 2330–2331
    immunology in, 2330
    morphology in, 2330
  prognosis factors in, 2332–2334, 2333*t*
  risk factors for, 2333*t*
  staging in, 2332–2334, 2332*t*
Non-Hodgkin lymphoma treatment, 2334–2342
  in AIDS, 2341–2342
  for diffuse large B-cell lymphoma, 2338–2341
    for advanced disease, 2339–2340
    in elderly, 2340
    for localized disease, 2339
    for refractory or relapsed disease, 2340–2341
  for follicular lymphomas, 2335–2338
    for advanced disease, 2335–2338
      bendamustine, 2337–2338
      chemotherapy, 2336, 2336*t*
      fludarabine, 2338
      hematopoietic stem cell transplantation, 2338
      lenalidomide, 2338
      obinutuzumab, 2337
      PI3K inhibitor, 2338
      radioimmunotherapy, 2337
      rituximab, 2336–2337
      watch-and-wait approach, 2336

for localized disease, 2335
general approach to, 2334
for mantle cell lymphoma, 2341
outcomes of
desired, 2334
therapeutic, evaluation of, 2342
Noninflammatory acne, 1626
Nonmegaloblastic anemia, 1710
Nonmelanoma skin cancers, 2429
Nonnucleoside/nucleotide reverse transcriptase inhibitors (NNRTIs), 2151, 2154
Nonopioid agents, 965–973, 968*t*
Nonpurulent cellulitis, 1867
Nonsalicylates, 485*t*
Non-small cell lung cancer, 2256–2257, 2256*t*, 2258. *See also* Lung cancer; Small cell lung cancer
staging of, 2259*t*
treatment of, 2259–2270, 2261*t*
for advanced and relapsed disease, 2261–2268, 2263*t*–2265*t*
nonbiomarker driven, 2266–2267
with PD-L1+ tumors, 2262
relapses disease, 2267–2268
with targetable genetic mutation, 2262–2266
for advanced-stage disease (stage IIIB and IV), in elderly and poor-performance status patients, 2268
for local disease (advanced and relapsed), algorithm for, 2262*f*
for local disease (stages I-II), 2259–2260
for locally advanced disease (stage IIIA/ IIIB), 2260–2261
outcome evaluation for, therapeutic, 2268
Non-ST-elevation acute coronary syndromes (NSTE-ACS)
pharmacologic therapy in
morphine, 169
aspirin, 174, 174*t*
P2Y12 inhibitors, 174*t*
glycoprotein IIb/IIIa receptor inhibitors, 174*t*
P2Y12 inhibitors, 175
fibrinolytic therapy, 177–178

glycoprotein IIb/IIIa receptor inhibitors, 177–178
anticoagulants, 178–180, 178*t*
beta-blockers, 182*f*
calcium channel blockers, 182*f*
nitrates, 182*f*
Nonsteroidal anti-inflammatory drugs (NSAIDs), 845
for acute gouty arthritis, 1572–1576, 1574*t*, 1577*t*
for acute pancreatitis, 587
adverse effects of, 1358*t*, 1508–1510, 1533*t*, 1577*t*
cardiovascular risk, 1509
gastrointestinal, 1508–1509
other toxicities, 1509
allergic interstitial nephritis and, 709
allergic reactions to, e1471
anxiety and, 1166*t*
dosing and administration of, 977*t*, 1504*t*–1505*t*, 1510
drug interactions, 1510
for dysmenorrhea, 1348
for endometriosis, 1358*t*
for glomerulonephritis, 721
for headache disorders, e23
for heavy menstrual bleeding, 1344
for inflammatory bowel disease, 509
for menstruation-related disorders, 1343*t*
for migraine, acute, 995*f*, 996–998
for migraine prophylaxis, 996*t*, 1000
nephrotoxicity of, 705
oral, 1505*t*, 1506, 1508–1510
adverse effects of, 1508–1510
cardiovascular, 1509
gastrointestinal, 1508–1509
dosing and administration of, 1510
drug-drug interactions, 1510
pharmacology and mechanism of action, 1508
for osteoarthritis, 1507*t*, 1508–1510
for pain management, 965–966

peptic ulcer disease and, 484, 485–486, 485*t*, 486*t*, 487, 488*f*, 496–497, 496*t*
pharmacology and mechanism of action, 1508, 1509*f*
for rheumatoid arthritis, 1530
for systemic lupus erythematosus, 1460, 1461*t*, 1462*t*
for tension-type headache, 1002
topical, 1506, 1510
adverse effects of, 1510
dosing and administration of, 1510
drug interactions, 1510
pharmacoeconomic impact of, 1510
pharmacology and mechanism of action, 1510
Non-STsegment elevation myocardial infarction (NSTEMI), 162
Nontyphoid Salmonella, 1925*t*
Noradrenergic agents, 2544*t*–2545*t*
Noradrenergic-serotonergics. *See specific types*
Norelgestromin, 1358*t*
Norepinephrine
for chronic hearth failure, 197
eating disorders and, 1030
for septic shock, 2018, 2018*t*
for shock, 362
Norepinephrine and dopamine reuptake inhibitor, 1133*t*, 1135*t*, 1136, 1138*t*, 1140*t*, 1144*t*
Norethindrone acetate, for endometriosis, 1358*t*, 1359
Norfloxacin, drug interactions, 1775*t*
Normal weight, 2535*t*
Noroviruses, 1924, 1924*t*
Nortriptyline, 970*t*, 1083, 1133*t*, 1135*t*, 1138*t*, 1203, 1209*t*, 1331
Nosocomial infections, 2111
Novel psychoactive substances (NPS), 1061
Novolin, 1240*t*
Novolog, 1240*t*
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), 2151–2153, 2152*t*
Nummular eczema, definition of, 1676*t*
Nutrient deficiencies and toxicities, 2476–2481

carnitine, 2481
essential fatty acids, 2479–2481
trace elements, 2476–2479, 2477*t*
vitamins, 2479
Nutrient requirements, 2481–2485
energy
estimating energy expenditure in, 2481–2483, 2482*t*
for children, 2482*t*
measuring energy expenditure in, 2483–2484
estimating energy expenditure in, 2483*t*
fat, 2484
fiber, 2484
fluid, 2484, 2485*t*
micronutrients, 2485, 2486*t*–2487*t*
protein, 2484
recommended dietary allowances, 2481
stress factors, 2483*t*
Nutrition, oral, in infants and children, e63
Nutrition assessment, 2470–2474
anthropometric measurements, 2471–2474
bioelectrical impedance, 2474
body mass index, 2472*t*, 2473
head circumference, 2471–2473
mid-arm muscle circumference, 2474
skinfold thickness, 2474
stature, 2471–2473
waist circumference, 2472*t*, 2473
waist-to-height ratio, 2473–2474
waist-to-hip ratio, 2473–2474
weight, 2471–2473
classification of nutrition status, 2467–2469
growth velocities in infants and children, 2473*t*
guidelines for, 2485
history and physical exam in, 2470–2471, 2470*t*
immune function tests, 2475–2476
laboratory

immune function tests, 2475–2476
nitrogen balance study, 2475
visceral proteins, 2474–2475, 2475*t*
patient care process for, 2468*b*
Nutrition disease, 1103*t*
Nutrition screening, 2469–2470
Nystatin
for febrile neutropenia, 2092*t*
for oropharyngeal candidiasis, 2032, 2033*t*
for vulvovaginal candidiasis, 2027, 2027*t*

O

Obesity
classification of, 2535, 2535*t*
diagnosis of, 2537*f*
patient care process for, 2538*b*
Obesity treatment, 2531–2551
asthma and, 378
bariatric surgery in, 2540–2541
chronic kidney disease and, 651
clinical presentation of, 2535–2536
from combined hormonal contraceptives, 54
comorbidities in, 2531, 2532*t*, 2535–2536
costs of, 2531
epidemiology of, 2531–2532
environmental factors in, 2532
genetic influences in, 2532
medical conditions in, 2532–2533
medications in, 2533
etiology of, 2532–2533
general approach to, 2535–2537, 2537*f*
GERD and, 469
goals of, 2539*f*
implantable medical devices in, 2541, 2542*t*–2543*t*
medical expenditures in, 2531
morbid, tuberculosis in, 1912–1915

nonpharmacologic therapy in, 2538–2540
caloric intake in, reduced, 2540
lifestyle intervention in, comprehensive, 2540
outcomes of
desired, 2535
therapeutic, evaluation of, 2550–2551
pathophysiology of, 2533–2535, 2533*t*, 2534*f*
appetite in, 2533–2534
energy balance in, 2533*t*, 2534–2535
personalized pharmacotherapy in, 2550
pharmaceutical care plan monitoring in, 2551
pharmacologic therapy in, 2541–2549, 2544*t*–2545*t*
based on comorbidities, 2546*f*
complementary and alternative therapies in, 2549
drug monitoring in, 2550*t*
long-term, 2541–2549
clinical and economic considerations, 2547*t*
liraglutide (glucagon-like peptide 1 receptor agonist), 2548–2549
lorcaserin (serotonin receptor agonist), 2545–2547
naltrexone-bupropion ER, 2548
orlistat (lipase inhibitor), 2541–2545, 2544*t*
phentermine-topiramate ER, 2547–2548
serotonergic agents, off-label use of, 2547
short-term, 2549
amphetamines, 2549
diethylpropion, 2549
phentermine, 2549
prevalence of, 2531–2532
Obinutuzumab, 2189*t*, 2205, 2337, 2402
Obsessive-compulsive disorder (OCD)
clinical presentation of, 1190–1191, 1190*b*
definition of, 1188
epidemiology of, 1188
etiology of, 1188
pathophysiology of, 1188–1189
neurochemical theories, 1189

neuroimaging studies, 1189
patient care process for, 1192*b*
Obsessive-compulsive disorder (OCD) treatment, 1195–1198
in children and adolescents, 1197
general approach to, 1195, 1195*t*
monitoring of, 1198*t*
nonpharmacologic therapy in, 1195–1196
outcomes of
desired, 1195
therapeutic, evaluation of, 1197–1198
personalized pharmacotherapy in, 1197
pharmacologic therapy in, 1196–1197
alternative drugs, 1196–1197
antidepressants, 1196, 1197*t*
antipsychotics, 1196–1197
pregnancy in, 1197
Obstetric and gynecologic surgeries, antimicrobial prophylaxis in, 2117*t*, 2119–2120
Obstructive lung disease, e369. *See also specific types*
Obstructive nephropathy, 707
Obstructive sleep apnea, 1206
causes of, 1206
risk factors for, 1202
signs and symptoms of, 1206
treatment of, 1207
nonpharmacologic therapy in, 1207
positive airway pressure, 1207
surgery, 1207
weight reduction, 1207
outcomes of
desired, 1207
therapeutic, evaluation of, 1207
pharmacologic therapy in, 1207
Occlusives, 1682
Ocrelizumab, 862*t*, 863*t*, 864*t*, 867
Octreotide, 547–548, 549*t*, 567–568, 575*t*

Ocular hypertension, 1591–1592
Ocular surface disease (OSD), 1598
Ofatumumab, 2189*t*, 2205
Olanzapine, 536, 1036. *See also* Antipsychotics
  for ADHD, 1020*t*
  adverse effects of, 1020*t*, 1107*t*
  for bipolar disorder, 1161
  dosing, 1020*t*, 1096*t*
  dosing and administration of, 1154*t*
  drug interactions, 1116*t*
  for major depressive disorder, 1133*t*
  mechanism of action, 1105*t*
  for nausea and vomiting, 530*t*, 534*t*, 537
  pharmacokinetics of, 1106*t*
  for schizophrenia, 1096*t*, 1099, 1100, 1101*t*–1102*t*
Olaparib, 2188*t*, 2249*t*, 2358*t*
Olaratumab, 2190*t*
Older adults
  health, assessment of, e71
  healthcare, delivery of, e71
  prescribing in, e69
    adverse drug reactions, e69
Olsalazine, 516*t*
Omacetaxine, 2183*t*, 2396
Omacetaxine mepesuccinate, 2198
Omalizumab, 398*t*, 399
Omega-3 fatty acids, 131, 846, 871*t*, 1141
Omeprazole, 472*t*, 474, 475–476, 475*t*, 494*t*, 495, 497, 498*t*, 502*t*
Oncogenes, 2169, 2171*t*
Ondansetron, 530*t*, 531*t*, 538, 539*t*, 540
Onychomycosis, 2037*t*, 2038–2039
  definition of, 2038
  differential diagnosis of, 2039*t*
  treatment of, 2039–2041, 2039*t*
    response and recurrence, 2041
    systemic therapy in, 2040–2041

topical therapy in, 2039–2040
Open-angle glaucoma, 1589
clinical presentation of, 1593–1594
epidemiology of, 1591–1592
etiology of, 1592–1593
pathophysiology of, 1593
prognosis of, 1594
treatment of, 1597–1598, 1597*f*
algorithm for, 1597*f*
nonpharmacologic therapy in, 1598–1599
pharmacologic therapy in, 1598
Ophthalmic disorders
drug-induced, dry eye disease, e1621
minor, dry eye disease, e25
Opiates, 546–547, 999, 1045–1046. *See also specific agents*
Opioid receptor antagonists, 554, 554*t*, 555
Opioid use disorder, treatment of, 1050–1063
nonpharmacologic therapy in, 1050
outcomes of, desired, 1050
pharmacologic therapy in, 1050–1057
buprenorphine, 1051–1054, 1051*t*, 1053*t*, 1054*t*, 1055*t*
extended release, 1054*t*
methadone, 1050–1051, 1051*t*
naloxone, 1054–1056, 1056*t*
naltrexone, 1051, 1051*t*, 1054*t*
in pregnancy, 1056–1057
Opioids, 1045–1046. *See also specific agents*
addiction to, 981
adverse effects of, 979*t*, 1511–1512
agonist-antagonist derivatives, 975*t*, 980
allergies to, 974
antagonists, 975*t*, 980–981
central and peripheral antagonists, 979*t*
central-acting, 980
for chronic pancreatitis, 590, 590*t*
for COPD, 421

for diarrhea, 546–547
for dyspnea, e79
hyperalgesial, 981
intoxication, 1047*b*
intraspinal, 979*t*
meperidine and congeners, 980
methadone and congeners, 980
morphine and congeners, 976–980
for osteoarthritis, 1506–1507, 1507*t*, 1511–1512
for pain management, 973–981, 975*t*–976*t*
physical dependence to, 981
prescribing guidelines for chronic pain, 1046*t*
pseudoaddiction, 981
tolerance to, 981
withdrawal, 1047*b*, 1048–1050
Opium tincture, 549*t*
Oppositional defiant disorder (ODD), 1022
Optic disk, 1591, 1592*f*, 1592*t*
Oral contraceptives, 46–51, 1307
for acne vulgaris, 1637*t*, 1643
choice of, 46–58
commonly prescribed, 47*t*–48*t*
composition of, 47*t*–48*t*
discontinuing, 51
drospirenone-containing, 1342*t*
drug interactions of, 48–51, 49*t*
initiating, 46
for menstruation-related disorders, 1342*t*
missed doses of, 51
monophasic *vs.* multiphasic, 46
patient instructions with, 51
postpartum use of, 54
side effects of, 48, 49*t*
vomiting and diarrhea while on, 51
Oral disorders, minor, e35
Oral health, e33

Oral hygiene, e35
Oral nutrition, for infants and children, e63
Oral rehydration solutions, 548*t*
Organ transplantation. *See* Transplantation, solid-organ
Oritavancin, 1868
Orlistat (lipase inhibitor), 1039, 2541–2545, 2544*t*, 2547*t*, 2550*t*
Oropharyngeal and esophageal candidiasis, 2028–2036
  classification of, 2031*t*
  clinical presentation of, 2029–2030
  diagnosis of, 2029–2030
  epidemiology of, 2028–2030
  etiology of, 2028–2030
  host defenses, 2029
  pathogenesis of, 2029
  patient counseling in, 2036*t*
  risk factors for, 2029, 2029*t*
  treatment of, 2031–2036
    anti-fungal prophylaxis, 2035–2036
    anti-fungal refractory, 2035
    general approach to, 2032, 2033*t*
    in HIV patients, 2032–2034, 2159*t*
    in non-HIV patients, 2034
    outcomes of
      desired, 2031–2032
      therapeutic, evaluation of, 2036
    pharmacologic, 2033*t*
Orphenadrine, 972*t*, 973
Orthopedic surgery, antimicrobial prophylaxis in, 2118*t*, 2121
Orthostatic hypotension
  antipsychotics and, 1119*t*
  definition of, 100
  in Parkinson disease, 950*t*
  schizophrenia and, 1108
Osimertinib, 2186*t*, 2201, 2264*t*
Osler’s nodes, 1885
Osmolality, 755, 2521

Osmotic agents, 938. *See also specific agents*
Osmotic diuresis, 769
Osmotic nephrosis, 703
Ospemifene, 1376–1377
Osteoarthritis, 1497–1501
clinical presentation of, 1501, 1501*b*
diagnosis of, 1501
definition of, 1497
diagnosis of, 1501
epidemiology of, 1497–1498
etiology of, 1498–1499
genetic factors in, 1499
obesity in, 1498
occupation and sports in, 1498–1499
trauma in, 1498–1499
incidence of, 1498
pathophysiology of, 1499–1500
normal cartilage, 1499–1500, 1499*f*
osteoarthritic cartilage, 1500, 1500*f*
patient care process for, 1502*b*
prevalence of, 1498
prognosis for, 1501
Osteoarthritis treatment, 1501–1512
drug class information in, 1507
dosing and administration in, 1504*t*–1505*t*
first-line treatments, 1506–1507
acetaminophen, 1506, 1508
capsaicin, 1507, 1511
corticosteroids, intra-articular, 1506, 1510–1511
NSAIDs, oral, 1506, 1508–1510
NSAIDs, topical, 1506, 1510
tramadol, 1506, 1507, 1511
monitoring, 1507*t*
second-line treatments, 1506–1507, 1511–1512
chondroitin, 1512
duloxetine, 1507, 1512

glucosamine, 1512
hyaluronic acid injections, 1512
hyaluronic acid, intra-articular, 1507
opioid analgesics, 1506–1507, 1511–1512
nonpharmacologic therapy in, 1503–1505, 1503*t*
exercise in, 1503
patient education in, 1503
surgery in, 1503–1505
weight loss in, 1503
outcomes of, 1504*t*–1505*t*
desired, 1501–1502
general approach to, 1502–1503, 1505*f*
therapeutic, evaluation of, 1512–1513
pharmacologic therapy in, 1505–1512
dosing, 1504*t*–1505*t*
for hand OA, 1507
first-line treatments, 1507
for hip and knee OA, 1506–1507
first-line treatments, 1506–1507
second-line treatments, 1506–1507
Osteochondritis, 1996
Osteomalacia, 1555
Osteomyelitis, 1871
chronic, 1998
clinical presentation of, 1998, 1998*t*
contiguous, 1996, 1998
direct inoculation, 1997–1998
epidemiology of, 1995–1996
etiology of, 1996
hematogenous, 1996–1997, 1998
pathophysiology of, 1996–1998
radiologic and laboratory tests in, 1999
treatment of, 1999–2004
general approach to, 2001, 2001*t*
outcomes of, desired, 1999–2000
pharmacologic therapy in, 2001–2004

antibiotic bone concentration in, 2002
antibiotic selection in, 2001–2002
duration of antibiotics in, 2002
for IV drug users, 2002
oral antibiotics in, 2002
for sickle cell hemoglobinopathies, 2002–2004
types of, 1997*t*
Osteonecrosis, 1753
Osteoporosis, 1537–1547
clinical presentation of, 1545, 1545*t*
consequences of, 1545
definition of, 1538
diagnosis of, 1547
epidemiology of, 1539
etiology of, 1539–1540, 1539*f*
bone density in, low, 1539–1540
bone quality in, impaired, 1540
falls in, 1540
medical conditions in, 1540*t*
medications in, 1541*t*
risk factors in, 1540*t*
glucocorticoid-induced, 1561–1562, 1561*t*
in menopausal hormone therapy, 1371
pathophysiology of, 1540–1544
age in, 1544–1545
bone physiology, 1540–1544
bone remodeling cycle, 1542*f*–1543*f*
calcium homeostasis, 1544
in males, 1544
parathyroid hormone, 1544
postmenopausal, 1544
secondary causes, 1545
vitamin D, 1544
patient assessment in, 1545–1547
bone turnover markers, 1547
central dual-energy x-ray absorptiometry, 1546–1547

laboratory tests, 1547
risk factors, 1546
screening, DXA or pDXA, 1546
patient care process for, 1538*b*
prevalence of, 1538
rheumatoid arthritis treatment in, 1531
Osteoporosis prevention and treatment, 1547–1562
in cancer treatment-related bone loss, 1562
in children and adolescents, 1559–1560
in chronic kidney disease, 1560–1561
in elderly, 1560
general approach to, 1547, 1548*f*
in glucocorticoid-induced disease, 1561–1562, 1562*t*
nonpharmacologic therapy in, 1547–1550
diet, 1547
alcohol, 1549
caffeine, 1549
calcium, 1547–1548, 1549*t*
isoflavones (phytoestrogens), 1549
vitamin D, 1548–1549, 1549*t*
exercise, 1549–1550
fall prevention, 1550
kyphoplasty, 1550
smoking, 1549
vertebroplasty, 1550
outcomes of
desired, 1547
therapeutic, evaluation of, 1562–1563
pharmaceutical care plan monitoring in, 1562–1563
pharmacologic therapy in, 1550–1559
anabolic therapies (teriparatide), 1558
antiresorptive therapies, 1554–1558
bisphosphonates, 1555–1556
calcitonin, 1557–1558
calcium, 1554
denosumab, 1556–1557

estrogen agonists antagonists, 1557
vitamin D, 1554–1555
dosing of, 1551*t*–1552*t*
first-choice drugs, 1552–1554
formation and antiresorptive medications, romosozumab, 1559
formation medications, parathyroid hormone analogs, 1558
fracture and bone mineral density effects of, 1550*t*
hormone therapies
estrogen, 1558
testosterone, 1558
monitoring of, 1553*t*
sequential and combination therapy, 1559
in premenopausal women, 1560
services for, 1563
Otic disorders, minor, e27
Otitis externa, acute, e27
epidemiology of, e27
etiology of, e27
Otitis externa, chronic, e27
Otitis media, acute, 1827–1830
clinical presentation of, 1828, 1828*b*
epidemiology of, 1827
etiology of, 1827
pathophysiology of, 1827–1828
patient care process for, 1829*b*
treatment of, 1828–1830
general approach to, 1828
nonpharmacologic therapy in, 1828
outcomes of
desired, 1828
therapeutic, evaluation of, 1830*t*
pharmacologic therapy in, 1828–1830, 1830*t*
Ovarian cancer, 2347–2350
chemoprevention in, 2349
clinical presentation of, 2350, 2350*b*
definition of, 2347

diagnosis of, 2350
epidemiology of, 2347–2348
etiology of, 2348
genetic screening for, 2350
in menopausal hormone therapy, 1371
pathophysiology of, 2348–2349
patient care process for, 2352*b*
prevention of, 2349–2350
prophylactic surgery in, 2349–2350
screening for, 2349
staging in, 2353*f*
survival rate, 2347
Ovarian cancer treatment, 2351–2361
biologic and targeted agents in, 2359–2361
aflibercept, 2359–2360
anti-angiogenesis agents, 2360
bevacizumab, 2359–2360
immunotherapy in, 2361
other targeted agents, 2360–2361
PARP inhibitor, 2360
poly(adenosine diphosphate [ADP]-ribose) polymerase, 2360
tyrosine kinase inhibitors, 2359–2360
chemotherapy in
first-line, 2353–2357, 2355*f*, 2356*t*
maintenance, 2357
neoadjuvant, 2357
consolidation therapy in, 2357
general approach to, 2351
outcomes of
desired, 2351
therapeutic, evaluation of, 2361
radiation in, 2353
for recurrent disease, 2357–2359, 2358*t*
platinum-resistant, 2359
platinum-sensitive, 2358–2359, 2359*t*
staging in, 2351*f*

surgery in, 2351–2354
Overactive bladder, 1433. *See also* Urinary incontinence
clinical presentation of, 1435*b*
in Parkinson disease, 950*t*
pharmacologic treatment of, 1440*t*, 1441*t*, 1442*t*
adverse effects of, 1444*t*
botulinum toxin A, 1444–1445
catheterization combined with medications, 1445
darifenacin, 1443
fesoterodine fumarate, 1442–1443
mirabegron, 1443–1444
oxybutynin extended-release, 1441
oxybutynin immediate release, 1440–1442
oxybutynin topical gel, 1443
solifenacin succinate, 1443
tolterodine immediate release, 1442
tolterodine long acting, 1442
trospium chloride extended release, 1443
trospium chloride immediate release, 1443
Overflow incontinence, 1433, 1435*b*. *See also* Urinary incontinence
Overnutrition, 2468–2469
Overweight, 2535, 2535*t*
Ovulation, 44
Oxacillin, dosing by age group, 1799*t*
Oxaliplatin, 2183*t*, 2196, 2286–2288, 2293, 2294*t*
Oxaprozin, 1505*t*
Oxazepam, 1073*t*, 1171*t*, 1175*t*
Oxazolidinones, adverse effects and monitoring of, 1777*t*
Oxcarbamazepine, 969*t*
Oxcarbazepine, 969*t*
adverse effects of, 893*t*, 1159*t*
for bipolar disorder, 1159*t*
dosing and administration of, 1154*t*, 1159*t*
drug interactions, 893*t*, 1159*t*
for epilepsy, 892*t*–893*t*
mechanism of action, 892*t*

for pain management, 966–967
Oxybutynin, 1425
for benign prostatic hyperplasia, 1421*t*
extended-release, 1442
immediate release, 1440–1442
for multiple sclerosis, 869*t*
topical gel, 1443
transdermal system, 1441–1442
Oxycodone, 980
for chronic pancreatitis, 590*t*
dosing and administration of, 977*t*, 1504*t*
for pain management, 975*t*
Oxygen
for acute coronary syndromes, 170, 170*t*
for cluster headache, 1002
for COPD, 413–414
for pulmonary arterial hypertension, 438, 441
Oxymorphone, 975*t*, 977*t*
Oxytocin, 1224*t*

P

P. aeruginosa, 2008
$P2Y_{12}$ inhibitors, 182*f*
  for acute coronary syndromes, 174*t*, 175–177, 181*t*, 184*t*
  for NSTE-ACSs, 175
Paclitaxel, 2181*t*, 2194, 2249*t*, 2263*t*, 2356*t*, 2358*t*
Pain, 959–963
  acute, 961, 962*b*, 962*t*, 963, 982*t*
  adaptive, 960
  cancer, 962, 963
  chronic, 961–962, 962*b*, 962*t*, 963, 1046*t*
  classification of, 961–962
  clinical presentation of, 962–963, 962*b*
  conduction of, 960
  definition of, e75, 959
  epidemiology of, 959
  in irritable bowel syndrome, 558
  maladaptive (pathologic), 960
  modulation of, 960
  nociceptive, 961*f*
  in Parkinson disease, 950*t*
  pathophysiology of, 959–960
  perception of, 960
  sickle cell, 1752
  signalling, immune system impact on, 960
  transduction of, 960
  transmission of, 960
Pain, agitation, delirium (PAD), e75
Pain management, 959–983
  for acute pain, 982*t*
  for cancer pain crisis, 966*f*
  in cancer patients, 981
  in children, 981
  in elderly, 981

in hemophilia, 1738
nonpharmacologic therapy in, 963, 963*t*
complementary and alternative therapies in, 965*t*
outcomes of
desired, 963
therapeutic, evaluation of, 983
patient care process for, 964*b*
personalized pharmacotherapy in, 981–982
pharmacologic therapy in
anticonvulsants, 969*t*
antidepressants, 970–971, 970*t*
co-analgesics, 964–965, 969*t*, 970*t*
dosing guidelines, 977*t*–978*t*
emerging agents, 973
local anesthetics, 981*t*
multimodal therapy, 981
nonopioid agents, 965–973, 968*t*
acetaminophen, 965–966
anticonvulsants, 966–970
NSAIDs, 965–966
opioid agents, 973–981, 975*t*–976*t*
adverse effects of, 979*t*
dosing and administration of, 977*t*–978*t*
intraspinal, 979*t*
morphine and congeners, 976–980
opioids, 975*t*–976*t*
equianalgesic opioid calculation, 967*t*
prescribing guidelines, 967*t*
patient selection in, 963
regional analgesia, 981
skeletal muscle relaxants, 971–973, 972*t*
topical analgesics, 974*t*
topical therapies in, 973
risk mitigation strategies, 964
sickle cell pain, acute, 1761–1762, 1761*t*
in special populations, 981

Painless thyroiditis, 1272
Palbociclib, 2185*t*, 2245, 2246*t*
Paliperidone, 1105*t*
  for schizophrenia, 1096*t*
Paliperidone palmitate. *See also* Antipsychotics
  adverse effects of, 1107*t*
  drug interactions, 1117*t*
  pharmacokinetics of, 1106*t*
  for schizophrenia, 1099, 1100, 1101*t*–1102*t*
Palliative care, e79
  end-of-life care in, 426
  hospice in, e79
Palonosetron, 530*t*, 531*t*, 539*t*
Pamidronate, 2421
p-Aminosalicylic acid (PAS), 1913*t*, 1917
  adverse effects and monitoring of, 1919*t*
  dosing of, 1914*t*
  for tuberculosis, 1913*t*, 1914*t*, 1917
Pancolitis, 511
Pancreas
  exocrine physiology of, 580, 580*f*
  proteolytic enzymes in, 580
Pancreatic enzyme replacement therapy, 451–452, 453*t*
Pancreatic polypeptide, 2515*t*
Pancreatitis, 579–592
  acute, 580–584
    clinical course and prognosis of, 584
    clinical presentation of, 579, 582–584
    complications of, 584
    diagnosis of, 582–584, 583*t*
    etiology of, 580–581, 581*t*
    incidence of, 579
    medications in, 581, 582*t*
    pathophysiology of, 581, 582*f*
    prevalence of, 579
    prevention of, 583*t*

prognosis of, 584
signs and symptoms of, 582
chronic, 587–589
clinical course and prognosis of, 588–589
clinical presentation of, 579, 587
diagnosis of, 588, 588*t*
etiology of, 587, 588*t*
incidence of, 579
pathophysiology of, 587
prevalence of, 579
risk factors for, 588*t*
signs and symptoms of, 588*t*
stages of, 587
definition of, 579
epidemiology of, 579–580
patient care process for, 586*b*
postERCP, 587
Pancreatitis treatment
for acute disease, 584–587
abdominal pain relief in, 585
antimicrobials in, 587
fluid resuscitation in, 585
general approach to, 584–585, 584*f*
nonpharmacologic therapy in, 585
nutrition and probiotics in, 585
outcomes of
desired, 584
evaluation of, 592
pain management, 585
pancreatic necrosis prevention in, 585
pharmacologic therapy in, 585
systemic complication limitation in, 585
for chronic disease, 589–592
analgesics in, 590
diagnosis of, 588
general approach to, 589, 589*f*

malabsorption treatment in, 590*f*
nonpharmacologic therapy in, 589
outcomes of
desired, 589
evaluation of, 592
pharmacologic therapy in, 589–592, 590*t*
abdominal pain relief in, 590–591
analgesics in, 590
enzyme therapy, adjuncts to, 592
malabsorption treatment in, 591–592
pancreatic enzymes, 590, 591, 591*t*
Panic disorder (attack). *See also* Anxiety disorders
clinical presentation of, 1168, 1168*b*
etiology of, 1166
pathophysiology of, 1166–1167
Panic disorder (attack) treatment, 1168, 1178–1181
algorithm for, 1179*f*
drug choices for, 1169*t*
in elderly, 1180
elderly, 1180
general approach to, 1178
nonpharmacologic therapy in, 1178
outcomes of
desired, 1178
therapeutic, evaluation of, 1180–1181
pharmacologic therapy in, 1178–1180, 1178*t*
selective serotonin reuptake inhibitors, 1179
serotonin-norepinephrine reuptake inhibitors, 1179
tricyclic antidepressants, 1179–1180
algorithm for, 1179*f*
resistance to, 1180
benzodiazepines, 1180
alternative drugs, 1180
phases of therapy in
acute, 1180
maintenance, 1180

discontinuation, 1180
pregnant women, 1180
treatment resistance, 1180
Panitumumab, 2190*t*, 2206, 2291*t*, 2294*t*
Panobinostat, 2186*t*, 2201, 2418–2419
Pantoprazole, 474, 475*t*, 494*t*, 497, 498*t*, 502*t*
Pantothenic acid, 2480*t*
Papaverine, 1406
Papillary necrosis, 711
Para-aminophenol, 968*t*
Parasitic disease treatment, e1955. *See also specific types*
Parasitism, e1955
Parasomnias, 1211
Parasympathomimetic agents, 1602–1603
Parathyroid hormone, 665*t*, 1544
Parathyroid hormone analogs, 1558
Parathyroidectomy, 666
Paregoric, 547, 549*t*
Parenteral iron therapy, 1718
Parenteral nutrition, 2491–2509
complications of, 2505–2508
infectious, 2505–2506
mechanical and technical, 2505
metabolic and nutritional, 2506–2508
essential fatty acid deficiency, 2507
hyperglycemia, 2506–2507
hypertriglyceridemia, 2506
liver disease, 2506
with long-term use, 2507
metabolic bone disease, 2507
refeeding syndrome, 2507
of trace elements and vitamins, 2507
components of, 2492–2497, 2493*t*
amino acids, 2492–2495
dextrose, 2495
electrolytes, 2497

intravenous lipid emulsion, 2495–2496
trace elements, 2497
vitamins, 2496–2497
compounding of, 2502–2505
vs. enteral, 2516
home, 2508
indications for, 2492, 2493*t*
in adults, 2492
in children, 2492
infection control in, 2502–2505
initiating and advancing, 2499–2502
in adults, 2499–2501
in children, 2502
continuous *vs.* cyclic, 2502
monitoring of, 2503*f*
outcomes of
desired, 2492
therapeutic, evaluation of, 2502
patient care process for, 2494*b*
personalized pharmacotherapy in, 2508–2509
pharmacoeconomic considerations in, 2508
regimen design in, 2497–2499
construction of, 2498–2499
administration in, 2499
for adults, 2499, 2500*f*
for children, 2499, 2501*f*
routes, 2498
central, 2498
peripheral, 2498
stability and compatibility of, 2504–2505
storage in, 2502–2505
time frame for initiating, 2492*t*
timing of initiation, 2516–2517
Paricalcitol, 668, 669–670, 669*t*
Parity, 1316
Parkinson disease, 945–948

clinical presentation of, 947*b*
definition of, 945
diagnosis of, 945
epidemiology of, 945
etiology of, 945–946, 946*f*
nonmotor symptoms of, 950*t*
pathophysiology of, 946–948, 946*f*
patient care process for, 949*b*
Parkinson disease treatment, 948–956
general approach to, 948–950, 951*f*, 952*t*
dosing and administration of, 952*t*
for nonmotor symptoms, 950*t*
nonpharmacologic (surgical), 950
outcomes of
desired, 948
therapeutic, evaluation of, 956–957, 957*t*
pharmacologic therapy in, 950–956
adverse effects of, monitoring for, 953*t*
amantadine, 951–952, 952*t*, 953*t*
anticholinergics, 950–951, 952*t*
carbidopa/L-Dopa, 952–955, 952*t*, 953*t*
COMT inhibitors, 952*t*, 953*t*, 955–956
dopamine agonists, 952*t*, 953*t*, 956
monoamine oxidase B inhibitors, 952*t*, 953*t*, 955
Paroxetine. *See also* Selective serotonin reuptake inhibitors (SSRIs)
adverse drug reactions, 1144*t*
drug interactions, 1140*t*
for generalized anxiety disorders, 1171*t*
for major depressive disorder, 1133*t*
in menopause and perimenopausal/postmenopausal hormone therapy, 1376*t*
for obsessive-compulsive disorder, 1197*t*
for panic disorder (attack), 1178*t*
pharmacokinetics of, 1138*t*
for postpartum depression, 1331
for posttraumatic stress disorder, 1191, 1191*t*, 1193*t*
relative potencies, 1135*t*

for social anxiety disorder, 1182*t*
Paroxysmal supraventricular tachycardia (PSVT), 306–310
clinical presentation of, 296*b*
general approach to treatment, 308–310, 309*f*
mechanism of, 307*f*
PARP inhibitor, 2188*t*, 2203, 2360
Partial mastectomy, 2233
Pasireotide, 1298*t*
Patet's disease, 2227
Patient care process, 1–7
for acid-base disorders, 822*b*
for acne vulgaris, 1629*b*
for acute bacterial rhinosinusitis, 1832*b*
for acute coronary syndromes, 168*b*
for acute decompensated heart failure, 227*b*
for acute ischemic stroke, 277*b*
for acute kidney injury, 636*b*
for acute otitis media, 1829*b*
for acute pharyngitis, 1837*b*
for acute severe asthma, 385*b*
for adult lymphoblastic leukemia, 2366*b*
for age-related macular degeneration, 1613*b*
for alcohol use disorder, 1076*b*
for Alzheimer disease, 841*b*
for androgenic alopecia, 1698*b*
for anemia, 1717*b*
for anxiety disorders, 1170*b*
for atopic dermatitis, 1681*b*
for atrial fibrillation and atrial flutter, 297*b*
for attention deficit/hyperactivity disorder, 1013*b*
for benign prostatic hyperplasia, 1416*b*
for bipolar disorder, 1156*b*
for bone and joint infections, 2000*b*
for brain injury, acute, 934*b*
for breast cancer, 2231*b*
for candidemia, 2051*b*

for cardiac arrest, 327*b*
for celiac disease, 619*b*
for central nervous system infection, 1790*b*
for chronic kidney disease, 648*b*
for chronic lymphocytic leukemia, 2397*b*
for chronic myeloid leukemia, 2391*b*
for cirrhosis, 568*b*
for *Clostridium difficile* infection, 1929*b*
for coagulation disorders, 1730*b*
for colorectal cancer, 2286*b*
for constipation, 551*b*
for contraception, 45*b*
for COPD, 411*b*
for Cushing syndrome, 1299*b*
for cystic fibrosis, 452*b*
for depressive disorders, 1131*b*
for diabetes mellitus, 1250*b*
for diarrhea, 545*b*
for dyslipidemias, 123
for eating disorders, 1035*b*
for endometriosis, 1356*b*
for enteral nutrition, 2514*b*
for epilepsy, 883*b*
for erectile dysfunction, 1369*b*
for gastroesophageal reflux disease (GERD), 470*b*
for gestational diabetes, 1316*b*
for glaucoma, 1596*b*
for glomerular disease, 720*b*
for gonorrhea, 1979*b*
for gout and hyperuricemia, 1573*b*
for headache disorders, 993*b*
for heart failure with preserved ejection fraction, 201*b*
for heart failure with reduced ejection fraction, 206*b*
for hepatitis C, 598*b*
for HIV patients, 2149*b*
for hormone therapy in women, 1366*b*

for hypercalcemia, 783*b*
for hypertension, 91*b*
for hyperthyroidism, 1275*b*
for hypothyroidism, 1282*b*
immunocompromised host, infection in, 2084*b*
importance of, 2–3
for inflammatory bowel disease, 513*b*
for influenza, 1849*b*
for intellectual disability disorders, 1218*b*
for intra-abdominal infection, 1944*b*
for ischemic heart disease, 143*b*
for lung cancer, 2260*b*
for lymphoma, 2323*b*
for melanoma, 2436*b*
for menstruation-related disorders, 1340*b*
for multiple myeloma, 2412*b*
for multiple sclerosis, 859*b*
for nausea and vomiting, 532*b*
for nutrition assessment, 2468*b*
for obesity, 2538*b*
for obsessive-compulsive disorder, 1192*b*
opioid use disorder, 1052*b*
to optimize pharmacotherapy, 3–6
  information collection, 4
  information assessment, 4
  medication therapy problem list, 4
  information collection, 4
  information assessment, 4
  medication therapy problem list, 4
  care plan development, 4–5
  information collection, 4*t*
  care plan implementation, 5
  patient follow-up, 5–6
  information assessment, 5*t*
  care plan development, 5*t*
  information assessment, 5*t*

care plan development, 5*t*
quality metrics, 6
workflow, documentation, and information systems, 6–7
care plan implementation, 6*t*
patient follow-up, 6*t*
documentation, attribution, and payment, 7
for osteoarthritis, 1502*b*
for osteoporosis, 1538*b*
for ovarian cancer, 2352*b*
for pain management, 964*b*
for pancreatitis, 586*b*
for parenteral nutrition, 2494*b*
for Parkinson disease, 949*b*
for peptic ulcer disease, 491*b*
for persistent asthma, 381*b*
for pneumonia, 1812*b*
for posttraumatic stress disorder, 1192*b*
for potassium and magnesium disorders, 800*b*
for prostate cancer, 2307*b*
for psoriasis, 1656*b*
for pulmonary arterial hypertension, 437*b*
for rheumatoid arthritis, 1524*b*
for schizophrenia, 1095*b*
for sepsis and septic shock, 2013*b*
for shock syndromes, 353*b*
for skin and soft-tissue infections, 1857*b*
for sleep-wake disorders, 1204*b*
for smoking cessation, 1084*b*
for solid-organ transplant recipients, 1474*b*
for status epilepticus, 918*b*
for systemic lupus erythematosus, 1457*b*
for tuberculosis, 1909*b*
for urinary incontinence, 1437*b*
for urinary tract infections, 1966*b*
for vasoocclusive episodes, 1754*b*
for venous thromboembolism, 248*b*, 260*b*

for vulvovaginal candidiasis, 2028*b*
for water and sodium homeostasis disorders, 756*b*
Patient Protection and Affordable Care Act of 2010, e9
Patiromer, 805*t*, 806
Pazopanib, 2187*t*, 2202
PD-1 and PD-L1 checkpoint inhibitors, 2439
PD-1 checkpoint inhibitors, 2208, 2440–2441
PD-L1 checkpoint inhibitors, 2208, 2440–2441
Pediatrics, e61
infant mortality in, e61
neonatal critical care, e65
oral nutrition, e63
poisonings in, e19
rehydration, e63
Peeling agents (exfoliants), 1635–1638
adverse effects and monitoring of, 1636*t*
resorcinol, 1635
retinoids, topical, 1638–1639
salicylic acid, 1635–1638
sulfur, 1638
Pegaptanib, 1615, 1615*t*
Pegloticase, 1576*t*, 1577*t*, 1582
Pegylated interferon, 610
Pegylated interferon-b1a, 862*t*
Pembrolizumab, 2191*t*, 2208, 2263*t*, 2291*t*, 2294*t*, 2296, 2439
Pemetrexed, 2180*t*, 2193, 2263*t*
Penicillin G, 1793
dosing by age group, 1799*t*
Penicillins. *See also specific types*
for acute pharyngitis, 1836*t*
adverse effects and monitoring of, 1777*t*
dosing of, 1819*t*
drug interactions, 1775*t*
for peritoneal dialysis patients, 691*t*
for pneumonia, 1819*t*
for sickle cell disease, 1755

for syphilis, 1982, 1983*t*
for UTIs, 1963*t*
Penile prostheses, 1406, 1406*f*
Penis
hormonal system of, 1384–1386
nervous system and psychogenic stimuli of, 1384
vascular system of, 1384, 1385*f*
Pentamidine, 1231*t*, 2093*t*, 2095*t*
Pentazocine, 975*t*, 978*t*
Pentobarbital, 922t, 924t, 937, 937t
for refractory GCSE, 924–925
Pentostatin, 2193, 2461*t*
Pepsin, 487
Pepsinogen, 487, 2515*t*
Peptic ulcer disease (PUD), 483–490
causes of, 484*t*
clinical course and prognosis of, 489
clinical presentation of, 488–489, 489*t*
common forms of, 484*f*, 484*t*
complications of, 488
diagnosis of, 489, 490*t*
endoscopy in, 489, 490*t*
tests for *H. pylori*, 489, 490*t*
epidemiology of, 484
H. pylori, 484
H. pylori, 484
NSAIDs, 484
etiology of, 484–486
cigarette smoking and, 486
dietary factors, 486
H. pylori, 484–485, 485*f*
NSAIDs, 485–486, 485*t*, 486*t*
psychological stress, 486
vs. gastritis and erosions, 483
locations of, 484*f*
pathophysiology of, 486–488, 488*f*

H. pylori, 487
NSAIDs, 487
Peptic ulcer disease (PUD) treatment, 490–503, 492*f*
general approach to, 490, 500*t*
lifestyle modifications in, 490
nonpharmacologic therapy in, 490
outcomes of
desired, 490
evaluation of, 500
patient care process for, 491*b*
pharmacologic therapy in, 491–495
antiulcer agents in, 497–500
antacids, 499–500
bismuth preparations, 499
drug interactions, 498
H2-receptor antagonists in, 499
long-term safety issues, 498–499
prostaglandins, 499
proton pump inhibitors, 493*t*, 497, 498*t*
sucralfate, 499
bismuth-based four-drug regimens, 495
drug dosing regimen in, 494*t*
drug monitoring in, 494*t*
for *H. pylori*-positive ulcers, 492–493, 493*t*, 500*t*
bismuth-based four-drug regimens, 493*t*, 495
eradication after initial treatment failure, 495
factors in eradication outcome, 495–496
non-bismuth quadruple therapy, 493*t*, 497
PPI-based three-drug regimens, 494–495
probiotics, 495
recommendations, 500*t*
sequential therapy, 493*t*, 495
levofloxacin-based therapy, 493*t*, 495
long-term maintenance of ulcer healing in, 497
non-bismuth quadruple therapy, 495
for non-H. pylori, non-NSAID ulcers, 497

for NSAID-induced ulcers, 496–497, 500*t*
COX-2 inhibitors *vs.* NSAID plus PPI, 497
cyclooxygenase-2 Inhibitors, 497
H2-receptor antagonists co-therapy, 496
misoprostol co-therapy, 496
prevention of, 496, 496*t*
proton pump inhibitor co-therapy, 496–497
recommendations, 500*t*
PPI-based three-drug regimens, 494–495
probiotics, 495
recommendations, 490–491
for refractory ulcers, 497
sequential therapy, 495
prognosis of, 489
Peptic ulcer-related bleeding, 501
Perampanel
adverse effects of, 897*t*
drug interactions, 897*t*
for epilepsy, 896*t*–897*t*
mechanism of action, 896*t*
Percentage transferrin situation, 1714
Percutaneous coronary intervention, 153–154
vs. medical management, 154
pharmacotherapy with, 153–154
primary, for STEMIs, 172
Perianal warts, 1991*t*
Perimenopausal/postmenopausal hormone therapy
benefits and risks of, 1368–1371, 1368*t*
body weight effects, 1371
breast cancer, 1370
cardiovascular disease, 1369–1370
diabetes, 1371
endometrial cancer, 1370–1371
gallbladder disease, 1371
lung cancer, 1371
mood, cognition, and dementia, 1371

osteoporosis, 1371
ovarian cancer, 1371
venous thromboembolism, 1370
bioidentical hormones, compounded, 1375
clinical trials on, 1368–1369
combined estrogen-progestogens, 1374–1375, 1374*t*
complementary and alternative medicine in, 1377
phytoestrogens, 1377
estrogens in, 1371–1372, 1373*t*
adverse effects of, 1371–1372
dosage and administration of, 1372
oral, 1372
other routes of administration in, 1372
evidence-based, 1379*t*
indications and contraindications for, 1365*t*
other treatments in, 1375–1376, 1376*t*
androgens, 1375
selective estrogen receptor modulators, 1376–1377
tibolone, 1377
personalized pharmacotherapy in, 1377–1378
progestogens in, 1372–1374, 1374*t*
therapeutic outcomes of, evaluation of, 1378, 1379*t*
Perimenopause, 1363–1365
clinical presentation of, 1364–1365, 1364*b*
epidemiology of, 1363
etiology of, 1363
genitourinary symptoms of, 1368
pathophysiology of, 1364–1365
vasomotor symptoms of, 1368
Perimenopause treatment, 1365–1378. *See also* Menopause and perimenopausal/postmenopausal hormone therapy
Periodic limb movements of sleep, 1211
Periodontal disease, e33
Perioral dermatitis, 1626
Peripheral arterial disease (PAD), e189
definition of, e189

epidemiology of, e189
hypertension treatment and, 101
Peripheral blood smear, 1714
Peripheral vascular disease, 1248
Peritoneal dialysis, 686–693
access in, 687, 687*f*
adequacy of, 688
advantages and disadvantages of, 679*t*
complications of, 688–689, 689*t*
catheter-site infections, 689, 691–692
exit-site infections, 692*f*
peritonitis, 689–691, 689*t*
antibiotic therapy for, 690–691, 690*f*, 691*t*, 692*t*
fungal, 691
prevention of, 692–693
recommendations, 691*t*
drug dosage regimen in renal replacement therapy, 748
history of, 686
principles of, 686–687
procedures of, 687–688
automated peritoneal dialysis, 688
continuous ambulatory peritoneal dialysis, 687–688
solutions, 688
Peritonitis, 571. *See also* Intra-abdominal infection; Intra-abdominal infection treatment
bacterial
spontaneous, 1939
causes of, 1940*t*
clinical presentation of, 1942–1944, 1943*t*
complications in hemodialysis, 689–691, 689*t*
definition of, 1939
primary, 1939
secondary, 1939
tertiary, 1939
Perphenazine, 538, 1096*t*. *See also* Antipsychotics
adverse effects of, 1107*t*

drug interactions, 1117*t*
pharmacokinetics of, 1106*t*
Persistent depressive disorder, 1150*t*
Pertussis, vaccines, 2133
Pertuzumab, 2190*t*, 2206, 2243–2244
Pervasive developmental disorders (PDDs), 1220
Pestivirus, 1924*t*
Petasites, 996*t*, 1000–1001
Petasites hybridus, 1000–1001
Petechiae, 485, 1885
Pharmaceutical care, 2
Pharmacist's Patient Care Process, 1, 2*f*
Pharmacodynamics, clinical, e15. *See also* Pharmacokinetics, clinical
Pharmacogenetics, e17
Pharmacogenomics, e17. *See also* Pharmacogenetics
Pharmacokinetics, clinical, e15. *See also* Pharmacodynamics, clinical; *specific agents and disorders*
clearance in, e15
half-life in, e15
Pharmacy Health Information Technology (HIT), 7
Pharmacy Quality Alliance, 4
Pharyngitis, acute, 1834–1838, 1977*t*
clinical presentation of, 1834–1835, 1835*b*
definition of, 1834
epidemiology of, 1834
etiology of, 1834
pathophysiology of, 1834
patient care process for, 1837*b*
treatment of, 1835–1838
general approach to, 1835
nonpharmacologic therapy in, 1835
outcomes of
desired, 1835
therapeutic, evaluation of, 1838
pharmacologic therapy in, 1835–1838, 1836*t*
Phenanthrenes, 975*t*

Phencyclidine (PCP), 1060
Phendimetrazine, 2544*t*, 2550*t*
Phenelzine, 1133*t*, 1176*t*–1177*t*, 1178*t*, 1182*t*, 1191*t*, 1193*t*
Phenethylamines, 1061
Phenobarbital, 921*t*, 922*t*
  adverse effects of, 891*t*
  for alcohol withdrawal, 1073*t*
  drug interactions, 891*t*
  for epilepsy, 889, 897
  for ischemic heart disease, 152
  mechanism of action, 890*t*
  monitoring of, 890*t*
  for status epilepticus, 921, 923
Phenothiazines, 534*t*, 536, 1113
Phentermine, 2545*t*, 2549, 2550*t*
Phentermine-topiramate ER, 2544*t*, 2547–2548, 2547*t*, 2550*t*
Phentolamine, 1406
Phenylephrine, 1760
  for septic shock, 2018, 2018*t*
  for shock, 363
Phenylpiperidines, 975*t*, 980
Phenylpropanolamines, 975*t*
Phenytoin, 921*t*, 922*t*
  adverse effects of, 891*t*
  drug interactions, 891*t*
  for epilepsy, 889, 890*t*–891*t*, 896–897
  for ischemic heart disease, 152
  mechanism of action, 890*t*
  for multiple sclerosis, 869*t*
  for status epilepticus, 92, 923
  for traumatic brain injury, 937*t*
Philadelphia chromosome positive ALL, 2373
Phobias, specific, 1165, 1168, 1183. *See also* Anxiety disorders
Phosphate, 789
Phosphate nephropathy, acute, 707–708
Phosphate-binding agents, 666–668, 667*t*. *See also specific agents*

adverse effects of, 668
dosing and administration of, 668
drug-drug interactions, 668
drug-food interactions, 668
efficacy of, 666–668
pharmacology and mechanism of action, 666
Phosphodiesterase 4 inhibitors (PDE-4), 1808
Phosphodiesterase inhibitors, 442–443
for benign prostatic hyperplasia, 1421*t*, 1423*t*, 1424
for COPD, 420
for erectile dysfunction, 1394
adverse effects of, 1397, 1398*t*–1400*t*
dosing and administration of, 1390*t*–1392*t*, 1396–1397
drug interactions, 1397–1400
drug-food interactions, 1396
efficacy of, 1395–1396
mechanism of, 1394, 1395*f*
monitoring for, 1398*t*–1400*t*
pharmacodynamics and pharmacokinetics of, 1395*t*
selectivity of, 1394–1400
for multiple sclerosis, 870
for pulmonary arterial hypertension, 444*t*
Phospholipids, 117
Phosphorus, 665*t*, 666
Phosphorus homeostasis disorders, 789–790. *See also specific disorders*
hyperphosphatemia, 790–791
hypophosphatemia, 791–795
Photochemotherapy, 1661
Photodynamic therapy, 1616
Phototherapy, 1661, 1685–1686
Physical activity, 1239
Physical dependence, 1047
Physical therapists, standards of care, 1*t*
Phytoestrogens, 1377, 1549
Phytosterols, 127
Phytotherapy, 1426

PI3K inhibitor, 2188*t*, 2203, 2338
PI3K signaling pathway, 2178
Pibrentasvir, 609–610
Picornaviridae, 596
Pilocarpine, 1600*t*, 1602–1603
Pioglitazone, 1242*t*, 1243–1244, 1257
Piperacillin-tazobactam, 1963*t*, 2092*t*
Piperazines, 1061
Piroxicam, 1505*t*, 1574*t*
Pituitary adenomas, 1301
Pituitary adenomas, TSH-secreting, 1271
Pituitary disease, 1281
Pituitary gland
  amenorrhea and, 1338
  anatomy and physiology of, e1313
Pituitary gland disorders, e1313
Pityriasis versicolor, 2037*t*, 2038
Plain Writing Act of 2010, e9
Plasma expanders, adverse effects of, 355*t*
Plasma-derived factor IX products, 1735
Plasma-derived factor VIII products, 1733
Plateau iris, 1595
Platelet aggregation, 1731*t*
Platelet count, 1731*t*
Platelet function analyzer, 1731*t*
Platelet-rich plasma (PRP) therapy, 1700
Platinum analogs, 2196
Plecanatide, 554*t*, 555
Pneumocystis jiroveci, 2083, 2159*t*, 2160*t*, 2161–2162
Pneumonia, 1812–1822
  atypical, 1821
  classification of, 1813*t*
  clinical presentation of, 1814–1815, 1815*t*
  common pathogens of, 1813
    anaerobic bacteria, 1814
    gram-negative bacteria

enteric, 1814
nonenteric, 1814
gram-positive bacteria, 1819–1820
gram-negative bacteria, 1820–1821
community-acquired, 1813, 1813*t*
epidemiology of, 1812
etiology of, 1813–1814
in HIV patients, 1814, 1814*t*
hospital-acquired, 1813–1814, 1813*t*
in neutropenic host, 1814
pathogenesis of, 1813–1814
patient care process for, 1812*b*
prevention of, 125.20
risk factors for, 1813*t*
ventilator-associated, 1813*t*, 1814
Pneumonia treatment, 1815–1821
general approach to, 1815–1816
goals of, 1815
patient monitoring in, 1821–1822
pharmacologic therapy in, 1816–1821
antibiotic concentrations in, 1821
antimicrobial agents in, 1816–1821
in adults, 1817*t*
in children, 1818*t*
dosing of, 1819*t*
pharmacodynamics of, 1821
pharmacokinetics of, 1821
for atypical pneumonia, 1821
for common pathogens, 1820*t*
for community-acquired pneumonia, 1816
duration of, 1821–1822
for gram-negative pathogens, 1820–1821
for gram-positive pathogens, 1819–1820
for hospital-acquired pneumonia, 1816–1818
modification of, 1821–1822
pathogen-directed, 1818–1819

for ventilator-associated pneumonia, 1816–1818
Podagra. *See* Gout and hyperuricemia
Podocytes, 715
Poikilothermia, 1111
Polatuzumab vedotin, 2191*t*, 2207–2208
Poliovirus, vaccines, 2134–2135
Poly (ADP-ribose) polymerase (PARP), 2245
Poly(adenosine diphosphate [ADP]-ribose) polymerase, 2360
Polycarbophil, 547, 549*t*, 554*t*
Polycystic ovarian syndrome (POS), 1307
in adolescents, 1346
progesterone in, 1346
Polycythemia, 422
Polydipsia, 1155
Polyethylene glycol, 554, 554*t*
Polyhexanide, 693
Polymerase chain reaction (PCR), 1789
Polymorphonuclear leukocytes (PMNs), 1959
Polymyxins
adverse effects and monitoring of, 1778*t*
dosing by age group, 1799*t*
dosing of, 1819*t*
for pneumonia, 1819*t*
Polypharmacy, e69
Polyphenols, 846
Pomalidomide, 2189*t*, 2198, 2416
Ponatinib, 2184*t*, 2200, 2392*t*, 2394*t*, 2395
Portal hypertension, 563
clinical features of, 564
clinical presentation of, 564
management of, 566
treatment of, 566–567, 570*t*
Portal venous system, 562*f*
Posaconazole, 2072
dosing by age group, 1799*t*
for febrile neutropenia, 2093*t*, 2095*t*

for fungal infections, 2049*t*
for HSCT infections, 2103
monitoring of, 2073*t*
for oropharyngeal candidiasis, 2033*t*
for peritonitis, 692*t*
Postcardiac arrest syndrome, 334*t*
PostERCP pancreatitis, 587
Postinjection delirium/sedation syndrome (PDSS), 1100, 1119*t*
"Post-intensive care syndrome," e77
Postoperative nausea and vomiting (PONV), 538–539
prophylaxis of, 538–539, 539*t*
risk factors for, 538, 538*t*
treatment of, 539, 539*t*
Postpartum depression, 1331
Postpartum thyroiditis (PPT), 1272, 1321
Postresuscitative care, 334–335
Poststreptococcal glomerulonephritis, 734–735
clinical presentation of, 734–735
epidemiology of, 734
etiology of, 734
pathophysiology of, 734
prognosis of, 735
treatment of, 735
Posttraumatic stress disorder (PTSD)
clinical presentation of, 1189, 1190*b*
definition of, 1187–1188
epidemiology of, 1188
etiology of, 1188
pathophysiology of, 1188–1189
neuroendocrine theories, 1188–1189
neurochemical theories, 1189
neuroimaging studies, 1189
patient care process for, 1192*b*
Posttraumatic stress disorder (PTSD) treatment
algorithm for, 1194*f*
in children, 1194

general approach to, 1191, 1193*t*
nonpharmacologic therapy in, 1191
outcomes of
desired, 1191
therapeutic, evaluation of, 1194–1195
personalized pharmacotherapy in, 1194
pharmacologic therapy in, 1191–1194
antidepressants, 1191*t*
alternative drugs, 1193
antidepressants, 1193–1194
maintenance and discontinuation, 1194
Potassium, 797–798
in foods, 801*t*
Potassium chloride, 801
Potassium homeostasis, 797–798
Potassium homeostasis disorders, 797–811
hyperkalemia, 802–807 (*See also* Hyperkalemia)
hypokalemia, 798–802 (*See also* Hypokalemia)
patient care process for, 800*b*
Practitioners, 2
Pralatrexate, 2193–2194
Pramipexole, 953*t*, 956
Pramlintide, 1248
Prasugrel, 174*t*, 175*t*, 176
Prazosin, 869*t*, 1193, 1193*t*, 1419, 1421*t*
Prealbumin, 2474
Prebiotics, 1686–1687
Prediabetes, 1257
Prednisolone, 1575*t*. *See also* Corticosteroids
Prednisone, 521, 522, 724, 1308*t*, 1575*t*, 2324–2328, 2325*t*, 2336*t*, 2461*t*. *See also* Corticosteroids
Preeclampsia, 100, 1320–1321, 1320*t*
Pregabalin, 590*t*, 869, 969*t*, 1175*t*
adverse effects of, 897*t*
drug interactions, 897*t*
for epilepsy, 896*t*–897*t*

for generalized anxiety disorders, 1171*t*
mechanism of action, 896*t*
in menopause and perimenopausal/postmenopausal hormone therapy, 1376*t*
for multiple sclerosis, 869, 869*t*
for social anxiety disorder, 1182*t*
Pregnancy, 1315–1331
acne vulgaris in, 1635
acute care issues in, 1321–1324
bacterial vaginosis and trichomoniasis, 1322
chlamydia, 1322
genital herpes, 1323
gonorrhea, 1322
headaches, 1323–1324
sexually-transmitted infections, 1322, 1323*t*
syphilis, 1322
urinary tract infections, 1321–1322, 1964*t*, 1969
anticoagulants in, 259*t*
antiemetic use during, 539–540
bipolar disorder treatment in, 1160–1161
caffeine use in, 1086
cardiac arrest treatment in, 336
characteristics of, 1316–1317
chlamydia trachomatis treatment in, 1985
chronic illnesses in, 1324–1327, 1325*t*
allergic rhinitis, 1324, 1325*t*
ashthma, 1324, 1325*t*
diabetes, 1324, 1325*t*
epilepsy, 1324–1325, 1325*t*
HIV infection, 1325–1326, 1325*t*
hypertension, 1325*t*, 1326
mental health conditions, 1326–1327
thyroid disorders, 1325*t*, 1327
cystic fibrosis and, 457
depressive disorders in, 1142–1143
diabetes mellitus treatment, 1258
drug safety in, 1317–1318

drug selection during, 1317–1318
epilepsy treatment in, 906–907
generalized anxiety disorder treatment in, 1177
genital herpes treatment in, 1988
gonorrhea treatment in, 1978–1979
hepatitis B treatment in, 604
HIV treatment in, 2156–2157
hypertension treatment in, 100, 100*t*
hypothyroidism treatment in, 1286
immunization in, 2129–2130
inflammatory bowel disease and, 522
influenza prevention in, 1848–1849
influenza treatment in, 1851
issues in, 1319–1321
  gastrointestinal tract, 1319
  gestational diabetes, 1319–1320 (*See also* Gestational diabetes mellitus (GDM))
  hypertensive disorders of pregnancy, 1320–1321, 1320*t*
  thromboembolism, 1321
  thyroid abnormalities, 1321
labor and delivery in, 1327–1330
  antenatal corticosteroids, 1328
  cervical ripening, 1329
  drug therapies, 1327–1328
  group B *Streptococcus* infection, 1328–1329
  labor analgesia, 1329–1330
  labor induction, 1329
  postpartum hemorrhage, 1330
  preterm labor, 1327, 1328
  tocolytic therapy, 1327–1328
nausea and vomiting in, 539–540
obsessive-compulsive disorder in, 1197
opioid use disorder in, 1056–1057
panic disorder (attack) treatment, 1180
pharmacokinetic changes during, 1317
physiology of, 1315–1317

postpartum issues in, 1330–1331
depression, 1331
drug use in lactation, 1330–1331
mastitis, 1331
preconception planning for, 1318–1319, 1318*t*
psoriasis treatment in, 1669
rheumatoid arthritis treatment in, 1530–1531
schizophrenia treatment in, 1113–1114
sickle cell disease in, 1754
syphilis treatment in, 1982
systemic lupus erythematosus (SLE) treatment, 1465
termination of, 57–58
thyrotoxicosis treatment in, 1278–1279
transplacental drug transfer, 1317
tuberculosis in, 1912
venous thromboembolism and, 259
Pregnenolone, 2305
Premature babies, e61
Premature ventricular complexes, 310
Premenstrual dysphoric disorder, 139*t*, 1349–1350, 1349*b*
Premenstrual syndrome, 1349–1350
diagnosis of, 1349*t*
epidemiology of, 1349
etiology of, 1349
pathophysiology of, 1349
treatment of, 1349–1350
general approach to, desired, 1350
nonpharmacologic therapy in, 1350
outcomes of
desired, 1349
therapeutic, evaluation of, 1350
pharmacologic
GnRH agonist, 1350
monophasic OCs, 1350
selective serotonin reuptake inhibitors, 1350
venlafaxine, 1350

pharmacologic therapy in, 1350
Pressure sores, 1856*t*, 1875–1878
classification of, 1876*t*
clinical presentation of, 1877*b*, 1877*f*
complications of, 1875
epidemiology of, 1875
etiology of, 1876
pathophysiology of, 1876
treatment of, 1876–1878
evidence-based, 1861*t*
nonpharmacologic therapy in, 1876–1878
outcomes of
desired, 1876
therapeutic, evaluation of, 1878
pharmacologic therapy in, 1876–1878
Pretomanid, 1917–1918
Priapism, 1112, 1752, 1760
Prilocaine, 981*t*
Primaquine, 2094*t*, 2095*t*
Primary amoebic meningoencephalitis (PAM), 1798–1800
Primary care, standards of care, 1*t*
Primary dyslipidemia, 119
Primary immunodeficiency states, 2138
Primary resistance, 2046
Primary-angle closure glaucoma, 1589
clinical presentation of, 1595
epidemiology of, 1594
etiology of, 1594–1595
pathophysiology of, 1595
with pupillary block, 1595
without pupillary block, 1595
Primidone
adverse effects of, 891*t*
drug interactions, 891*t*
for epilepsy, 889, 890*t*–891*t*
mechanism of action, 890*t*

Prinzmetal's angina, 140, 156
Probenecid, 1575*t*, 1577*t*, 1581–1582
Probiotics. *See also specific types*
  for atopic dermatitis, 1686
  for constipation, 555
  for diarrhea, 549, 549*t*
  for gastrointestinal infections, 1931
  for pancreatitis, 585
  for peptic ulcer disease, 495
Procainamide, 291, 292*t*
  pharmacokinetics of, 295*t*
  side effects of, 294*t*
Procaine, 981*t*
Procalcitonin, 1789
Procarbazine, 2183*t*, 2324–2326, 2325*t*
Prochlorperazine, 534*t*, 995*f*, 999
Proctitis, 511, 1977*t*
Proctocolectomy, 514
Proctosigmoiditis, 511
Progesterone
  for dysmenorrhea, 1348
  for polycystic ovarian syndrome, 1346
  for traumatic brain injury, 938
Progestin, 46, 2246*t*, 2247*t*, 2248
  adverse effects of, 1358*t*
  for amenorrhea, 1338
  for endometriosis, 1357–1359, 1358*t*
  injectable, 54
  subdermal implants, 55–56
Progestogens, 1372–1374, 1374*t*. *See also specific types*
Progressive multifocal leukoencephalopathy (PML), 865
Proliferation signal inhibitors, 1487–1488
  adverse effects of, 1487–1488
  dosing and administration of, 1487
  drug-drug interactions, 1488
  drug-food interactions, 1488

efficacy of, 1487
pharmacokinetics of, 1487
pharmacology and mechanism of action, 1487
Promethazine, 534*t*, 539*t*, 540
Promotility agents, 476–477. *See also specific agents*
bethanechol, 476
metoclopramide, 476
other investigative, 477
Promyelocytic leukemia, acute
patient monitoring in, 2380
relapsed, 2380
treatment of, 2379–2380
phases of, 2379–2380
consolidation therapy in, 2380
induction, 2379–2380
maintenance therapy in, 2380
for relapsed APL, 2380
Propafenone, 292, 292*t*, 294*t*, 295*t*, 296*t*
Propantheline, 869*t*
Propionibacterium acnes, 1624, 1625
Propionic acid, 968*t*
Propofol
for refractory GCSE, 924*t*, 925
for status epilepticus, 922*t*
for traumatic brain injury, 935, 937*t*
Propofol infusion syndrome, 935
Propranolol, 171, 996*t*
Propylthiouracil, 1274–1277
Prostacyclin and prostacyclin analogs, 441–442, 444*t*
Prostacyclin IP recpetor agonist, 442, 444*t*
Prostaglandin analogs, 1599, 1600*t*
Prostaglandin E1. *See* Alprostadil
Prostaglandin F_2 analogues, 1700
Prostaglandins, 499
Prostate, physiology of, 1412, 1413*f*

Prostate cancer, 2301–2306
chemoprevention of, 2303
classification of, 2306*t*
clinical presentation of, 2305, 2305*b*
diagnosis and staging workup for, 2306, 2306*t*
epidemiology of, 2301
etiology of, 2301–2302, 2302*t*
benign prostatic hyperplasia in, 2302
diet in, 2302
family history in, 2302
race and ethnicity in, 2301–2302
smoking in, 2302
pathophysiology of, 2304–2305, 2305*t*
patient care process for, 2307*b*
risk factors for, 2302*t*
screening for, 2303–2304
survival rates, 2308*t*
Prostate cancer treatment, 2306–2315
general approach to, 2306–2309, 2308*t*, 2309*f*
nonpharmacologic therapy in, 2310
observation in, 2310
orchiectomy in, 2310
radiation therapy in, 2310
radical prostatectomy in, 2310
outcomes of
desired, 2306
therapeutic, evaluation of, 2315
pharmacologic therapy in, 2310–2315, 2311*t*–2312*t*
alternative drugs, 2314–2315
chemotherapy, 2314*t*, 2315
immunotherapy, 2314*t*, 2315
nuclear medicine, 2315
secondary hormonal manipulations, 2314–2315
first-choice, 2310–2314
antiandrogens, 2311*t*–2312*t*, 2313–2314
combined androgen blockade, 2313–2314

gonadotropin-releasing hormone antagonists, 2312*t*, 2313
luteinizing hormone-releasing hormone agonists, 2310–2313, 2312*t*
Prostate gland, 2304*f*, 2305
Prostatism, 1413
Prostatitis, 1969–1971
clinical presentation of, 1970–1971, 1970*b*
etiology of, 1970
pathogenesis of, 1970
treatment of, 1964*t*, 1971
antibiotic therapy in, 1971
evidence-based, 1964*t*
goals of, 1971
Prosthetic valve endocarditis. *See* Endocarditis, infective
Prosthetic valve endocarditis (PVE)
definition of, 1883
epidemiology of, 1883–1884
etiology of, 1883–1884
pathophysiology of, 1885
treatment of, 1890*t*, 1891*t*
Protease inhibitors, 1231*t*, 2152*t*–2153*t*, 2154, 2417–2418
Proteasome inhibitors, 2188*t*–2189*t*, 2203–2204
bortezomib, 2203–2204
carfilzomib, 2204
ixazomib, 2204
Protein
daily requirements, 2484
in enteral nutrition, 2520
Proteinuria, 651, 708, 724, 1961
in chronic kidney disease, 651
treatment of, 656–658
Prothrombin complex concentrates, 357*t*
Prothrombin time, 568, 1731*t*
Proton pump inhibitors, 474–476. *See also specific agents*
adverse effects of, 475
allergic interstitial nephritis and, 709
for children, 478, 478*t*

dosing, 494*t*
drug interactions, 475, 498
long-term safety issues, 498–499, 498*t*
for maintenance therapy, 477
monitoring of, 475*t*, 494*t*
for peptic ulcer disease, 493, 494–495, 496–497, 498*t*
potential risks, 475, 498–499
for Zollinger-Ellison syndrome, 503
Protriptyline, 1209*t*
Prucalopride, 555
Pruritus, 682*t*, 1679
Pseudoaddiction, 981
Pseudoallergy. *See* Allergic drug reactions
Pseudobulbar palsy, 870
Pseudohypertension, 89
Pseudomonas aeruginosa, 1794, 1820*t*
Pseudoparkinsonism, 1110
Pseudopolyps, 510
Psilocybin, 1044, 1060
Psoriasis, 1653–1655
clinical presentation of, 1655*t*
comorbidities in, 1654–1655
definition of, 1653
diagnosis of, 1655
epidemiology of, 1653–1654
etiology of, 1654
genetic factors in, 1654
pathophysiology of, 1654–1655
patient care process for, 1656*b*
plaque in, 1655
precipitating factors in, 1654
predisposing factors in, 1654
types of, 1655, 1655*t*
Psoriasis treatment, 1656–1670
algorithm for, 1658*f*
in children, 1669

combination therapies in, 1667–1668
complementary and alternative therapies in, 1668–1669
in elderly, 1669–1670
general approach to, 1657
goals of, 1656–1657
nonpharmacologic therapy in, 1657
outcomes of
  desired, 1656–1657
  therapeutic, evaluation of, 1657
personalized pharmacotherapy in, 1669
pharmacoeconomic considerations in, 1670
pharmacologic therapy in, 1657–1670
  apremilast, 1668
  crisaborole, 1668
  first choice, 1657–1658
  guidelines on, 1657–1658
  hydroxyurea, 1668
  mycophenolate mofetil, 1668
  topical therapies in, 1658–1661
    anthralin, 1660–1661
    calcineurin inhibitors, 1661
    coal tar, 1661
    corticosteroids, 1658–1660, 1659*t*
    retinoids, 1660
    salicylic acid, 1661
    Vitamin D3 analogs, 1660
photochemotherapy in, 1661
phototherapy in, 1661
in pregnancy, 1669
with solid tumor theory, 1670
systemic therapies in, 1661–1663
  acitretin, 1662
  cyclosporine, 1662
  methotrexate, 1662–1663
systemic therapy with biologic response modifiers, 1663–1667
  alefacept, 1664

brodalumab, 1666–1667
general concerns and precautions, 1663–1664
guselkumab, 1667
ixekizumab, 1666–1667
place in therapy and transition from other therapies, 1664
risankizumab, 1667
secukinumab, 1666–1667
selection of, 1664
switching between biologics, 1667
tildrakizumab, 1667
tofacitinib, 1667
tumor necrosis factor-a inhibitors, 1664–1665
adalimumab, 1664–1665
etanercept, 1664–1665
infliximab, 1664–1665
ustekinumab, 1665–1666
Psychiatric disorders evaluation, e1007
Psychosis. *See also* Antipsychotics
in Parkinson disease, 950*t*
Psychostimulants, 1224
Psychotherapy, 1169–1170
Psyllium hydrophilic colloids, 554*t*
Pulmonary arterial hypertension, 431–436
classes of recommendations, 436*t*
classification of, 431, 432*t*
clinical presentation of, 434*b*
definition of, 431
diagnosis of, 434, 435*f*
epidemiology of, 432
etiology of, 432
functional classification of, 434*t*
levels of evidence, 436*t*
pathophysiology of, 432–434, 433*f*
patient care process for, 437*b*
risk assessment, 436*t*
signs and symptoms of, 433–434

vasodilator testing, agents for, 436*t*
Pulmonary arterial hypertension treatment, 436–447
follow-up, assessment and timing for, 438*t*
general approach to, 438
nonpharmacologic therapy in, 438
outcomes of
desired, 436–438
evaluation of, 446
pharmacologic therapy in, 438–446, 439*f*–440*f*, 443*t*
adverse drug reactions, 444*t*
calcium channel blockers, 443–444
combination therapy in, 444–446, 445*t*, 446*t*
conventional, 435–441
drug interactions, 445*t*
endothelin receptor antagonists, 442, 444*t*
guanylate cyclase stimulator, 443, 444*t*
phosphodiesterase inhibitors, 442–443, 444*t*
prostacyclin and prostacyclin analogs, 441–442, 444*t*
prostacyclin IP receptor agonist, 442, 444*t*
targeted, 441–446
in pregnancy, 446
risk assessment in, 436*t*
Pulmonary disease, 101
Pulmonary diseases, drug-induced, e459
Pulmonary embolism
clinical presentation of, 247*b*
diagnosis of, 246*f*
treatment of, outpatient, 254*t*
Pulmonary hypertension
COPD and, 421
in sickle cell disease, 1752, 1753*t*
Pulmonary rehabilitation, 413
Pulse pressure, 85
Pulseless electrical activity (PEA)
causes of, 333*f*
nonpharmacologic therapy in, 333

pharmacologic therapy in, 333–334
Pulseless ventricular tachycardia, 330–333
antiarrhythmics for, 331–333
nonpharmacologic therapy in, 330
pharmacologic therapy in, 330–333
sympathomimetics, 330–331
vasopressin, 331, 332*t*
Purging disorder, 1030
Purine analogs, 2193
cladribine, 2193
fludarabine, 2193
mercaptopurine, 2193
pentostatin, 2193
thioguanine, 2193
Purulent cellulitis, 1867
Pyelonephritis, acute, 1966–1967
Pyranocarboxylic acid, 968*t*
Pyrazinamide
adverse effects and monitoring of, 1919*t*
for CNS infection, 1798
dosing by age group, 1913*t*
dosing of, 1914*t*
for tuberculosis, 1911*t*, 1914*t*, 1915
Pyrazoles, 968*t*
Pyridoxine, 534*t*, 539, 2480*t*
Pyrimethamine, 1800, 2094*t*, 2095*t*
Pyrimidine analogs, 2178–2179, 2192–2193
cytarabine, 2178–2179, 2180*t*
fluoropyrimidines, 2179, 2192
gemcitabine, 2192–2193
tipiracil, 2193
trifluridine, 2193
Pyrovalerone, 1060
Pyrrolizine carboxylic acid, 968*t*
Pyuria, 1961

Q

Quadrivalent influenza vaccine, 1845–1846
Quality metrics, 6
Quaternary ammonium compounds, 1645
Quazepam, 1205*t*
Quetiapine. *See also* Antipsychotics
  for ADHD, 1020*t*
  adverse effects of, 1020*t*, 1107*t*, 1175*t*
  for bipolar disorder, 1161
  dosing, 1020*t*, 1073*t*
  dosing and administration of, 1154*t*
  drug interactions, 1117*t*
  for generalized anxiety disorders, 1171*t*
  for major depressive disorder, 1133*t*
  mechanism of action, 1104, 1105*t*
  pharmacokinetics of, 1106*t*
  for schizophrenia, 1096, 1096*t*
  for social anxiety disorder, 1182*t*
Quinidine, 291, 292*t*
  doses of, 296*t*
  pharmacokinetics of, 295*t*
  side effects of, 294*t*
Quinine, 684
Quinolones, 1917
  drug interactions, 1775*t*
  for peritoneal dialysis patients, 691*t*

R

Rabbit anti-thymocyte globulin (ATG), 1488, 2461*t*
Rabeprazole, 474, 494*t*, 497, 498*t*
Raberprazole, 475*t*
Rabies, 1879
  vaccines, 2135–2136
Radiation-induced nausea and vomiting (RINV), 537–538
  prophylaxis of, 538

risk groups, 538
Radioactive iodine, 1277–1278
Radiofrequency ablation, 473–474
Radiographic contrast media nephrotoxicity, 700–702
clinical presentation of, 700
incidence of, 700
management of, 702
pathogenesis of, 700–701
prevention of, 701
risk factors for, 701
Radioimmunotherapy, 2337
Radionuclide imaging, e461
Radiopharmaceuticals, 2189*t*
Radium Ra 223 dichloride, 2189*t*
Radium-223, 2197, 2315
Raloxifene, 1376, 1552*t*, 1553*t*, 1557, 2224
Raltegravir, 1916*t*, 2150*t*, 2152*t*, 2154
Ramelteon, 1203
Ramosetron, 530*t*, 531*t*
Ramucirumab, 2190*t*, 2207, 2263*t*, 2294*t*
Ranibizumab, 1615, 1615*t*
Ranitidine, 472*t*, 473*t*, 475*t*, 476, 477, 494*t*, 496, 499, 502*t*, 534*t*
Ranolazine, 152
Rasagiline, 953*t*, 955
Rash, 2215
Rebound headache, 994
Receptor pharmacology, 347–350, 348*t*
Recombinant factor IX, 1735
Recombinant factor VIII, 1733
Recombinant interferon, for atopic dermatitis, 1686
Recommended dietary allowances, 2481
Red blood cells
destruction of, 1711, 1711*f*
distribution width, 1714
erythropoiesis stimulation in, 1711
hemoglobin synthesis in, 1711

indices, 1713–1714
mean cell hemoglobin, 1714
mean cell hemoglobin concentration, 1714
mean cell volume, 1713–1714
iron incorporation into heme in, 1711
maturation and development of, 1710–1711, 1711*f*
total reticulocyte count, 1714
Red yeast rice, 127
5a-reductase inhibitors, 1420–1422, 1421*t*, 1423*t*
alopecia and, 1700
prostate cancer and, 1422–1423
Refeeding syndrome, 2507
Reflexology, 871*t*
Refractory GERD, 479
Refractory nausea and vomiting, 536, 537
Refractory ulcers, 497
Refuxate, composition of, 466
Regional analgesia, 981
Regorafenib, 2188*t*, 2203, 2294*t*
Rehydration therapy, e63, 1927–1929, 1928*t*
REM sleep behavior disorder, 950*t*
Remote ischemic preconditioning, 634
Renal cancer carcinoma (RCC), e2427
definition of, e2427
subtypes and pathophysiology of, e2427
clear cell RCC and VHL gene, e2427
survival rate, e2427
Renal osteodystrophy, 652
Renal replacement therapy, 635, 637–640, 638*f*. *See also specific types*
for acute kidney injury, 637–640, 637*t*, 638*f*
continuous renal replacement therapy in, 637–639
diuretics, 639–640, 639*t*
drug dosing in, 640–641
intermittent hemodialysis, 637
prolonged intermittent, 639
drug dosage regimen in, 747–750

hemodialysis, 748–750, 749*b*
peritoneal dialysis, 74
Renal solute load, 2521
Renal tubular acidosis, 818–819
Renal vasculitis, 711
Renin-angiotensin-aldosterone system (RAAS), 86–87, 86*f*, 195*f*, 721
Repaglinide, 1242*t*, 1248
Replacement therapy, complications of, 1743
Resistant hypertension, 101–108
causes of, 101*t*
diuretic therapy in, 102
Reslizumab, 398*t*, 399
Resorcinol, 1635, 1636*t*
Respiratory acidosis, 828–829
causes of, 827*t*, 828*t*
clinical presentation of, 829, 829*b*
compensation in, 829
pathophysiology of, 828–829
treatment of, 829–830
for acute respiratory acidosis, 829
in compensated chronic respiratory acidotic patients, 830
Respiratory alkalosis, 827–828
causes of, 824*t*
clinical presentation of, 827, 828*b*
compensation in, 827–828
definition of, 824
pathophysiology of, 827
treatment of, 828–829
Respiratory function, evaluation of, e369
Respiratory infections, viral, 376
Respiratory symptoms, nonspecific, e29
epidemiology of, e29
etiology of, e29
Respiratory tract infections, lower, 1803–1822. *See also specific infections*
bronchiolitis, 1810–1811
bronchitis, 1805–1810

pneumonia, 1812–1822
Respiratory tract infections, upper, 1827–1838. *See also specific infections*
acute bacterial rhinosinusitis, 1830–1834
acute otitis media, 1827–1830
acute pharyngitis, 1834–1838
Resting membrane potential (RMP), 288
Restless legs syndrome, 950*t*, 1210, 1210*t*, 1211*t*
Restrictive lung disease, e369. *See also specific types*
Retching, definition of, 529
Reteplase, 173*t*, 685, 686
Reticulocytes, 1714
Retinoic acid, 1635, 1636*t*, 1638
Retinoids, 2198
for acne vulgaris, 1638–1639
adverse effects and monitoring of, 1636*t*
monitoring of, 2183*t*–2184*t*
for psoriasis, 1660
Retinopathy, 1256
Revascularization, 152–155, 153*t*
Reverse remodeling, 196
Reverse transcriptase inhibitors, 2151–2153
Rheumatic heart disease, 1884–1885
Rheumatoid arthritis, 1517–1523
clinical presentation of, 1519–1523
definition of, 1517
diagnostic criteria, 1523, 1523*t*
epidemiology of, 1517–1518
etiology of, 1518
extra-articular involvement in, 1521–1522
amyloidosis, 1522
cardiac involvement, 1522
Felty syndrome, 1522
laboratory findings in, 1522–1523
lymphadenopathy, 1522
ocular manifestations, 1522
pulmonary complications, 1522

rheumatoid nodules, 1521–1522
vasculitis, 1522
joint involvement in, 1519–1520, 1519*f*, 1520*f*–1521*f*
pathophysiology of, 1518–1519, 1518*f*
patient care process for, 1524*b*
Rheumatoid arthritis treatment, 1523–1532
algorithm for, 1526*f*
assessment of, 1532*t*
biosimilars, 1532
comorbidity management in, 1531–1532
cardiovascular risk reduction, 1531
immunization in, 1532
osteoporosis and, 1531
future directions, 1532
general approach to, desired, 1523
heart failure in, 1531
hepatitis in, 1531
infections in, 1531
malignancy and, 1531
nonpharmacologic therapy in, 1523–1524
outcomes of
desired, 1523
therapeutic, evaluation of, 1532–1534
pharmacologic therapy in, 1524–1526, 1525*t*
abatacept, 1529
adalimumab, 1528
adverse effects of, 1533*t*
anakinra, 1529
biologic agents, 1527–1528
non-TNF, 1529–1530
TNF-a inhibitors, 1528–1529
certolizumab, 1528
DMARDs, 1530
etanercept, 1528
glucocorticoids, 1530
golimumab, 1528

hydroxychloroquine, 1527
infliximab, 1528–1529
leflunomide, 1527
methotrexate, 1526–1527
nonsteroidal anti-inflammatory drugs, 1530
rituximab, 1529
sarilumab, 1529–1530
sulfasalazine, 1527
tocilizumab, 1529
tofacitinib, 1530
pregnancy and lactation in, 1530–1531
Rheumatoid nodules, 1521–1522
Rhinitis, allergic, e31
allergens in, e31
definition of, e31
epidemiology of, e31
etiology of, e31
Rhinosinusitis, acute bacterial, 1830–1834
clinical presentation of, 1831, 1831*b*
epidemiology of, 1831
etiology of, 1831
pathophysiology of, 1831
patient care process for, 1832*b*
treatment of
general approach to, 1831
nonpharmacologic therapy in, 1832
outcomes of
desired, 1831
therapeutic, evaluation of, 1834
pharmacologic therapy in, 1832–1834
Rhinosinusitis, chronic, 377
Rho kinase inhibitors, 1601*t*, 1602
Rho(D) immunoglobulin, 2139
Ribavirin, 610, 1811
Ribociclib, 2185*t*, 2246*t*
Riboflavin, 996*t*, 2480*t*

Rifabutin
adverse effects and monitoring of, 1919*t*
for stable ischemic heart disease, 152
for tuberculosis, 1913*t*
Rifampin, 49, 1915
adverse effects and monitoring of, 1919*t*
for CNS infection, 1798
dosing by age group, 1913*t*
dosing of, 1914*t*
drug interactions, 1775*t*
for peritonitis, 692*t*
for stable ischemic heart disease, 152
for tuberculosis, 1910*t*, 1911*t*, 1914*t*
Rifamycin, 1777*t*
Rifapentine
adverse effects and monitoring of, 1919*t*
for stable ischemic heart disease, 152
for tuberculosis, 1910*t*, 1913*t*
Rifaximin, 557, 573, 575*t*
Rilonacept, 1575*t*
Rilpivirine, 2150*t*, 2152*t*, 2154
Riociguat, 443, 443*t*, 444*t*, 445*t*, 446*t*
Risankizumab, 1667
Risedronate, 1551*t*
Risperidone. *See also* Antipsychotics
for ADHD, 1021
adverse effects of, 1020*t*, 1107*t*
for autism spectrum disorder, 1223, 1224*t*
dosing, 1020*t*
dosing and administration of, 1154*t*
drug interactions, 1117*t*
for major depressive disorder, 1133*t*
mechanism of action, 1104, 1105*t*
pharmacokinetics of, 1106*t*
for schizophrenia, 1096*t*, 1099–1100, 1101*t*–1102*t*
Ristocetin cofactor activity (RCo), 1739*t*

Ritalin. *See* Methylphenidate
Ritodrine, 1327–1328
Ritonavir, 2150*t*, 2153*t*, 2154
Rituximab, 728, 867, 1461*t*, 1462*t*, 1490, 1529, 1743, 2189*t*–2190*t*, 2204–2205, 2336–2337
  adverse effects of, 1533*t*
  for chronic lymphocytic leukemia, 2401–2403
  for minimal-change nephropathy, 724
  for rheumatoid arthritis, 1525*t*
Rivastigmine, 843*t*, 844*t*
Rizatriptan, 995*f*, 998*t*
Rockall Score, 501
Rolapitant, 530*t*, 534*t*, 535
Rome criteria, 551, 556
Romidepsin, 2186*t*, 2201
Romosozumab, 1552*t*, 1553*t*, 1559
Ropinirole, 953*t*, 956
Ropivacaine, 981*t*
Rosiglitazone, 846, 1242*t*, 1243–1244, 1257
Rotavirus, 1924, 1925*t*
Roth's spots, 1885
Rotigotine, 953*t*, 956
Rubella vaccine, 2136
Rucaparib, 2188*t*, 2358*t*
Rufinamide
  adverse effects of, 897*t*
  drug interactions, 897*t*
  for epilepsy, 896*t*–897*t*
  mechanism of action, 896*t*
Ruxolitinib, 1702, 2187*t*, 2202
RxNorm, 7*t*

S

Saccharomyces boulardii, 514
Sacubitril, 208*t*
S-adenosyl-l-methionine (SAMe), 1141

Safflower oil, 2495
Safinamide, 955
Salicylanilides, 1645
Salicylates, 485*t*, 968*t*
Salicylic acid, 1635–1638, 1636*t*, 1641, 1661
Salmonella enterica, 1926
Salmonella infection, 1930*t*, 1935*t*, 2159*t*. *See also* Gastrointestinal infection
Salpingitis, 1977*t*
Salsalate, 1505*t*
Saphenous vein graft, 154
Saquinavir, 2153*t*, 2154
Sarilumab, 1525*t*, 1529–1530, 1533*t*
Sativex oromucosal spray, 871*t*
Saxagliptin, 1242*t*, 1246
Scedosporium, 2048*t*
Scedosporium, 2069
Schilling test, 1715
Schizoaffective disorder, 1150
Schizoid, 1093
Schizophrenia, patient care process for, 1095*b*
Schizophrenia treatment, 1091–1118. *See also* Antipsychotics
  adverse effects of, 1106–1113, 1107*t*
  assessment of, 1118*t*
  chronic phase of, 1093
  clinical presentation of, 1093–1094, 1094*b*
  epidemiology of, 1091
  etiology of, 1091–1092
  guidelines, 1096–1098
  maternal stress in, 1092
  mechanism of action of, 1104
  nonpharmacologic, 1095*t*
  nonpharmacologic therapy in, 1094
    active community treatment in, 1094
    cognitive remediation in, 1094
    recovery-based system of care in, 1094
    social media in, 1094

outcomes of
desired, 1094
evaluation of, 1118–1120
pathophysiology of, 1092–1093
personalized pharmacotherapy in, 1114–1118
pharmacokinetics of, 1106*t*
pharmacologic therapy in, 1094–1118 (*See also* Antipsychotics)
algorithm for, 1097*f*
antipsychotics, 1096*t*
drug interactions, 1114, 1115*t*–1118*t*
first- *vs.* second-generation antipsychotics in, 1095, 1096*t*
initial treatment of acute psychotic episode in, 1098–1099
in lactation, 1113–1114
long-injectable antipsychotics in, 1099–1100, 1101*t*–1102*t*
maintenance therapy in, 1099
patient adherence in, 1100–1104
predictors of response to, 1098
in pregnancy, 1113–1114
stabilization therapy in, 1099
for treatment-resistant disease, 1103–1104
augmentation and combination strategies in, 1103–1104
clozapine, 1103
for violent patients, 1104
prodromal phase of, 1093
symptoms of, 1093, 1094
violence in, 1104
Schizophrenic lesion, 1092
Sclerotherapy, 568–569
Scopolamine, 533*t*, 538, 539, 539*t*
Seborrheic eczema, definition of, 1676*t*
Secondary dislipidemia, 119
Secondary hypertension, 84–85, 84*f*
Secondary malignancies, 2216
Secondary prophylaxis, 2050
Secondary resistance, 2046
Secondhand smoke, 406

Secretin, 2515*t*
Secukinumab, 1666–1667
Sedation, 1119*t*
Sedative-hypnotics, 1057. *See also specific agents*
Segmental mastectomy, 2233
Seizures, 1111
  alcohol withdrawal, 1072–1073
  antipsychotics and, 939
  epileptic
    triggers of, 878
    focal onset, 879–881
    classification of, 880*f*
    generalized onset, 881
    classification of, 881–882
  posttraumatic, 939
Selective estrogen receptor downregulators (SERD), 2248
Selective estrogen receptor modulators (SERMs), 1376–1377, 2224
  adverse effects of, 1377
  dose and administration of, 1377
  efficacy of, 1376
Selective serotonin reuptake inhibitors (SSRIs), 1209
  adverse drug reactions, 1144*t*
  adverse effects of, 1174*t*
  for Alzheimer disease, 847
  for autism spectrum disorder, 1224
  for bulimia nervosa, 1037
  for chronic pancreatitis, 590, 590*t*
  dosing and administration of, 1181
  dosing of, 1133*t*
  drug interactions, 1140*t*
  efficacy of, 1181
  for major depressive disorder, 1132
  for menstruation-related disorders, 1343*t*
  for obsessive-compulsive disorder, 1197*t*, 1198*t*
  for panic disorder (attack), 1178*t*, 1179
  pharmacokinetics of, 1138*t*

for posttraumatic stress disorder, 1191*t*, 1193, 1193*t*
for premenstrual dysphoric disorder, 1350
relative potencies, 1135*t*
for schizophrenia, 1103
for social anxiety disorder, 1181, 1182*t*
Selegiline, 953*t*, 955, 1133*t*, 1209*t*. *See also* Monoamine oxidase inhibitors
Selenium, 2476–2478, 2477*t*
Selexipag, 442, 443*t*, 444*t*, 445*t*, 446*t*
Self-injurious behaviors, 1216
Selinexor, 2418–2419
Semaglutide, 1244, 1245*t*
Senna, 554*t*, 557
Sepsis and septic shock, 2007–2012
clinical presentation of, 2011–2012
complications of, 2009–2011
acute kidney injury, 2010
acute respiratory distress syndrome, 2010
disseminated intravascular coagulation, 2010
hemodynamic effects, 2010
septic shock, 2010–2011
definitions of, 2007–2008, 2008*t*
diagnosis of, 2011–2012
high-risk patients, assessment of, 2011–2012
organ failure assessment, 2012*t*
pathogens, identification of, 2011
epidemiology of, 2008
etiology of, 2008–2009
anaerobic bacteria, 2008
fungi, 2008–2009
gram-negative bacteria, 2008
gram-positive bacteria, 2008
pathogens in, 2008
risk factors for, 2008
infection sites in, 2008
mortality rate, 2011*f*
pathophysiology of, 2009, 2009*f*

cascade of sepsis, 2009
cellular components for initiating inflammatory process in, 2009
pro- and antiinflammatory mediators in, 2009
patient care process for, 2013*b*
prognosis of, 2011
Sepsis and septic shock treatment, 2012–2017
adjunctive therapies in, 2019–2020
antifungals, 2016–2017
antimicrobial therapy in, 2014*t*
antimicrobials, 2015–2016, 2016*t*
pharmacodynamics of, 2017
pharmacokinetics of, 2017
selection of, 2015–2016
de-escalation, 2017
definitions of, 2007–2008
duration of, 2017–2018
fluid therapy, 2012–2014, 2014*t*, 2015
glucose control, 2014*t*
hemodynamic support
fluid therapy, 2012–2014
vasopressor and inotropic therapy, 2018*t*
vasopressors, 2018–2019
infection source control, 2014–2015
initial resuscitation in, 2012
outcomes of
desired, 2012
evaluation of, 2017–2020
performance improvement bundle, 2019, 2019*t*
pharmacologic therapy in
corticosteroids, 2014*t*
vasopressors, 2014*t*, 2018–2019, 2018*t*
recommendations, 2014*t*
stress ulcer prophylaxis, 2014*t*
venous thromboembolism prophylasix, 2014*t*
Sepsis-induced hypotension, 2007
Septic arthritis

animal bites and, 1879
epidemiology of, 1996
etiology of, 1996
incidence of, 1996
pathogen identification in, 1772
radiologic and laboratory tests in, 1999
Septic emboli, 1885
Septic shock, 2010–2011. *See also* Sepsis and septic shock
definition of, 2007–2008
fluid resuscitation in, 357–358
vasopressors and inotropes in, 359–364
Sequestrum, 1997
Serology test, 2281
Serotonergic agents, 2547
Serotonergic antidepressants, 1196
Serotonin, 990, 1030
Serotonin agonists, 995*f*, 995*t*, 996*t*
Serotonin and α2-adrenergic antagonists, 1133*t*, 1136, 1138*t*, 1140*t*, 1144*t*
Serotonin receptor agonists, 998–999, 998*t*
Serotonin syndrome, 1137
Serotonin-norepinephrine reuptake inhibitors (SNRIs), 970*t*, 971, 1132–1135, 1133*t*, 1209. *See also* Tricyclic antidepressants (TCAs)
adverse drug reactions, 1144*t*
adverse effects of, 1174*t*
drug interactions, 1140*t*
for panic disorder (attack), 1178*t*, 1179
pharmacokinetics of, 1138*t*
for posttraumatic stress disorder, 1193, 1193*t*
relative potencies, 1135*t*
for social anxiety disorder, 1182*t*
Sertraline, 683, 1133*t*. *See also* Selective serotonin reuptake inhibitors (SSRIs); Serotonin and α2-adrenergic antagonists
for depression
in children, 1142
in pregnancy, 1142–1143
drug interactions, 1140*t*

for generalized anxiety disorders, 1171*t*, 1177
for hypotension, 683
for obsessive-compulsive disorder, 1197*t*
for panic disorder (attack), 1178, 1178*t*
pharmacokinetics of, 1138*t*
for postpartum depression, 1331
for posttraumatic stress disorder, 1191, 1191*t*, 1193*t*
for psoriasis, 1662
relative potencies, 1135*t*
for social anxiety disorder, 1181, 1182*t*
Sevelamer, 666
Severe sepsis, 2007. *See also* Sepsis and septic shock treatment
Sexual dysfunction, 1119*t*
in multiple sclerosis, 870
Sexually transmitted diseases (STDs), 1975–1992, 1976*t*. *See also specific diseases*
age-specific rates of, 1975–1976
Chlamydia trachomatis, 1983–1985
combined hormonal contraceptives and, 51
genital herpes, 1985–1988
gonorrhea, 1976–1980
human papillomavirus in, 1990–1992
pathogens, 1976*t*
in pregnancy, 1322, 1323*t*
prevalence of, 1975
prevention of, 1976
risk factors for, 1976
syndromes, associated, 1977*t*
syphilis, 1980–1983
treatment of, 1991*t*
trichomoniasis, 1988–1990
SGLT-2 inhibitors, 706–707
Shift work sleep disorder, 1210
Shigella, 1925*t*, 1926, 1927, 1930*t*, 1935*t*, 2159*t*
Shigellosis, 1926
Shock syndromes, 343–352

angiotensin II, 350–351
clinical presentation of, 351–352, 351*f*, 352*b*
cortisol, 350–351
epidemiology of, 343
etiology of, 343–344
pathophysiology of, 344–351, 344*f*
receptor pharmacology, 347–350, 348*t*
adrenoreceptor functions, 350
patient care process for, 353*b*
signs and symptoms of, 365*f*
vasopressin, 350–351
Shock treatment, 352–356. *See also* Sepsis and septic shock treatment
general approach to, 352–354
nonpharmacologic therapy in, 354
outcomes of, evaluation of, 364–366
pharmacologic therapy in, 354–364
angiotensin II, 364
dobutamine, 363–364
dopamine, 363
epinephrine, 362–363
intravenous fluids, 354–358, 355*t*
alternative fluid treatments, 355–357
blood products, 357, 357*t*
crystalloid solutions, 354–355
fluid resuscitation in, 357–358
plasma expanders, 355*t*
norepinephrine, 362
phenylephrine, 363
vasopressin, 364
vasopressors and inotropes in, 358–364, 359*t*
Short-daily hemodialysis, 750
Sialorrhea, 1113, 1119*t*
Sickle cell anemia, clinical presentation of, 1750*t*
Sickle cell b-thalassemia, clinical presentation of, 1750*t*
Sickle cell disease (SCD), 1747–1753
clinical presentation of, 1750, 1750*t*

complications of
acute, 1750–1752, 1751*t*
acute chest syndrome, 1752
fever and infection, 1750–1751
neurologic, 1751
priapism, 1752
sickle cell pain, 1752
splenic sequestration, 1752
venous thromboembolism, 1752
chronic, 1752–1753
cardiac diseases, 1753
growth and development, 1754
hepatobiliary diseases, 1753
ocular manifestations, 1753
pregnancy and, 1754
pulmonary, 1752, 1753*t*
renal diseases, 1753
skeletal and skin diseases, 1753
definition of, 1747
epidemiology of, 1748
etiology of, 1748–1749, 1749*f*
incidence of, 1748
pathophysiology of, 1749–1750, 1749*f*
prevalence of, 1748
types of, 1750*t*
Sickle cell disease (SCD) treatment, 1753–1762
allogeneic hematopoietic stem cell transplantation in, 1759
for complications, 1759–1762
acute chest syndrome, 1760
aplastic crisis, 1760–1761
cerebrovascular accidents, 1760
infection and fever, 1760
priapism, 1760
sickle cell pain, acute, 1761–1762, 1761*t*
sickle cell pain, chronic, 1762
splenic sequestration, 1761

transfusions, episodic, 1759–1760
disease-modifying therapy in, 1758
glutamine, 1758
hydroxyurea, 1755–1758, 1756*t*, 1757*f*
outcomes of
desired, 1753–1755
therapeutic, evaluation of, 1762
routine health maintenance in, 1754–1755, 1755*t*
immunizations in, 1754–1755
penicillin prophylaxis, 1755
transfusion therapy in, chronic, 1758–1759
Sickle cell hemoglobin, clinical presentation of, 1750*t*
Sickle cell syndromes, 1747
Sickle cell trait, 1747, 1750*t*
Significant abacteriuria, 1958
Significant bacteriuria, 1958, 1958*t*
Sildenafil, 442–443, 443*t*, 444*t*, 445*t*, 446*t*, 1390*t*, 1398*t*
Silodosin, 1420, 1421*t*, 1424
Siltuximab, 2191*t*
Single-nucleotide polymorphisms (SNPs), 1092
Sinoatrial (SA) node, 288
Sinus bradycardia, 317–318
Sinusitis
in asthma, 377
chronic, 377
definition of, 1830
Sinusoidal obstruction syndrome, 2457–2458
Sipuleucel-T, 2192*t*, 2209, 2314*t*, 2315
Sirolimus, 2460, 2461*t*
Sitagliptin, 1242*t*, 1246
Skeletal muscle relaxants, 971–973, 972*t*
Skin and soft-tissue infections (SSTIs), 1855–1880. *See also* Cellulitis; *specific infections*
animal and human bite wounds, 1878–1880
carbuncles, 1857–1859
cellulitis, 1866–1869

classification of, bacterial, 1856*t*
diabetic foot infections, 1871–1875
epidemiology of, 1856–1857
erysipelas, 1859
etiology of, 1857
folliculitis, 1857–1859
furuncles, 1857–1859
impetigo, 1859–1865
lymphangitis, 1865–1866
necrotizing soft-tissue infections, 1869–1871
pathophysiology of, 1857
patient care process for, 1857*b*
pressure sores, 1875–1878
treatment of
evidence-based recommendations, 1860*t*–1861*t*
oral drugs in, 1862*t*
drug dosing in, 1862*t*–1863*t*
drug monitoring in, 1864*t*
Skin cancers
age in, 2429
types of, 2429
Skin care, e37
Skin disorders, common, e1707
Skin reactions, drug-induced, e1707
Sleep
circadian rhythm, 1201
cycles, 1201
neurochemistry of, 1201–1202
polysomnography of, 1202
Sleep apnea, 1206–1207
central, 1206, 1207
definition of, 1206
obstructive, 1206–1207
Sleep disorders, Down syndrome and, 1219
Sleep terrors, 1211
Sleep-wake disorders, 1201–1211. *See also specific types*

algorithm for, 1206*f*
apnea
central, 1206
obstructive, 1206–1207
central, 1207
circadian rhythm disorders, 1209–1211
classification of, 1202
insomnia, 1202–1206 (*See also* Insomnia)
narcolepsy, 1207–1209
parasomnias, 1211
patient care process for, 1204*b*
prevalence of, 1201
sleep apnea, 1206–1207
Sleepwalking, 1211
Small cell lung cancer, 2256–2257. *See also* Lung cancer; Non-small cell lung cancer
staging of, 2258–2259
treatment of, 2268–2269, 2269*t*
extensive disease in, 2268–2269
limited disease in, 2268
outcome evaluation for, therapeutic, 2269
relapsed disease, 2269
Small molecule inhibitors, 2189*t*
Smoking
cessation, 145*t*, 148, 412–413, 413*t*, 1078–1079, 1612–1613
chronic kidney disease and, 651
chronic obstructive pulmonary disease and, 406–407
colorectal cancer and, 2276
combined hormonal contraceptives and, 52–53
economic impact of, 1077
epidemiology of, 1077–1078
GERD and, 469, 473
health risks of, 1077–1078
osteoporosis and, 1549
peptic ulcer disease and, 486
prostate cancer and, 2302

systemic lupus erythematosus and, 1454
Smooth muscle tissue, 1412
SOAP (Subjective, Objectives, Assessment, and Plan) note format, 7
Social anxiety disorder, 1168. *See also* Anxiety disorders
clinical presentation of, 1168, 1169*b*
etiology of, 1166
pathophysiology of, 1166–1167
prevalence of, 1165
Social anxiety disorder treatment, 1181–1183
in adolescents, 1183
in alcohol use disorder, 1183
algorithm for, 1182*f*
in children, 1183
drug choices for, 1169*t*
general approach to, 1181
nonpharmacologic therapy in, 1181
outcomes of
desired, 1181
therapeutic, evaluation of, 1183
pharmacologic therapy in, 1181–1183, 1182*t*
anticonvulsants, 1183
antidepressants, 1181–1183
benzodiazepines, 1183
β-adrenergic antagonists (beta blockers), 1183
resistance to, 1183
Social determinants of health, e11
Sodium bicarbonate, 497, 805*t*, 806, 823–824
Sodium chloride-resistant disorders, 824
Sodium chloride-responsive disorders
ammonium chloride for, 826
arginine monochloride for, 826
definition of, 825
hydrochloric acid for, 825–826
Sodium ferric gluconate, 661*t*
Sodium glucose cotransporter-2 inhibitors, 656–657, 1247–1248
Sodium homeostasis, 755–758

Sodium homeostasis disorders, 755–775. *See also specific disorders*
edema, 772–775
hypernatremia, 767–772
hyponatremia, 758–767
patient care process for, 756*b*
Sodium nitroprusside, 110*t*, 232
Sodium overload, 770. *See also* Hypernatremia
Sodium oxybate, 1209*t*
Sodium polystyrene sulfonate, 805*t*, 806
Sodium valproate, 1157
Sodium zirconium cyclosilicate, 805*t*, 806
Sodium-glucose cotransporters-2 inhibitors, 1233, 1242*t*, 1247–1248
Sofosbuvir, 608–609, 610
Soft-tissue infections. *See* Skin and soft-tissue infections (SSTIs)
Solanezumab, 846
Solid-organ transplant recipients
immunization in, 2130
infections in, 2103–2105
clinical presentation of, 2105, 2106*b*
etiology of, 2104
prevention of, 2105–2107
risk factors for, 2103–2104
timing of, 2105
treatment of, 2105–2107
outcomes of, desired, 2105
types of, 2105
Solid-organ transplantation (SOT), 1473–1494
epidemiology and etiology of, 1475
heart, 1475
kidney, 1473
liver, 1475
lung, 1475
patient care process for, 1474*b*
physiologic consequences of, 1476–1478
in heart transplantation, 1476–1477
in kidney transplantation, 1476

in liver transplantation, 1476, 1476*t*
in lung transplantation, 1477
rejection pathophysiology in, 1477–1480
acute cellular rejection, 1478–1479
antibody-mediated rejection, 1479
chronic rejection in, 1479–1480
general concepts of, 1477, 1478*f*
hyperacute rejection, 1477–1478
statistics on, 1473
survival rates, 1475*t*
treatment of rejection in, 1480–1490
bottom line, clinical, 1494
general approach to, 1480–1481, 1481*f*
in acute rejection, 1480–1481
induction therapy in, 1480
generic substitution in, 1492
immunosuppression-related complications in, 1492–1494
cardiovascular disease, 1492–1493
diabetes, new-onset, 1493
infection, 1493–1494
malignancy, 1494
laboratory monitoring, 1491*t*
maintenance therapy in, 1481–1490
alemtuzumab, 1489
antibody agents, 1488–1489
antimetabolites, 1485–1487
antithymocyte globulin, 1488–1489
azathioprine, 1486–1487
calcineurin inhibitors, 1481–1485
corticosteroids, 1485
costimulatory signal inhibitor, 1488
depleting antibodies, 1488–1489
interleukin-2 receptor antagonists, 1489–1490
investigational agents, 1490
mycophenolic acid derivatives, 1485–1487
nondepleting antibodies, 1489–1490

proliferation signal inhibitors, 1487–1488
outcomes of
desired, 1480
therapeutic, evaluation of, 1490
personalized pharmacotherapy in, 1490–1492
Solifenacin, 869*t*, 1422*t*, 1443
Soluble transferrin receptor, 1714–1715
Somatic mutation, 2279*t*
Somatostatin, 567
Somatostatin analogs. *See specific agents*
Sonidegib, 2186*t*
Sorafenib, 2188*t*, 2202
Sorbitol, 554, 554*t*, 557, 806
Sotalol, 292*t*, 293, 294*t*, 295*t*, 296*t*
Souvenaid, 846
Soybean oil, 2495–2496
Spanish influenza of 1918, 1841
Speciality nursing, standards of care, 1*t*
Spermicides, 42*t*, 44
Spirochetes, 1783
Spironolactone, 575*t*, 802, 1304*t*, 1637*t*, 1643, 1701
Splenic flexure, 511
Splenic sequestration, 1752, 1761
Splenomegaly, 1885
Splinter hemorrhages, 1885
Sponge (contraception), 42*t*, 45–46
Spontaneous bacterial peritonitis, treatment of, 568, 570, 571–572, 572*t*
Sprue, celiac. *See* Celiac disease
Squamous cell carcinoma (SCC), 2257
St. Anthony's fire. *See* Erysipelas
St. John's wort, 152, 1141
Stable ischemic heart disease (SIHD), 137–142
biomarkers in, 142
clinical presentation of, 140–142
coronary vasospasm, 140
death rate of, 138

diagnostic and prognostic testing of, 142
epidemiology of, 137–138
etiology and pathophysiology of, 138–140
fixed-threshold angina, management of, 155–156
grading in, 144*t*
myocardial oxygen demand in, 138
myocardial oxygen supply in, 138–140
  coronary blood flow, 138–139, 139*f*
  coronary collateral circulation, 140
  heart rate and systole, 139
  oxygen extraction and oxygen carrying capacity, 139–140
patient care process for, 143*b*
Prinzmetal's angina, 140
risk factor modification in, 145*t*–146*t*
  alcohol consumption, 146*t*
  blood pressure management, 145*t*
  diabetes management, 145*t*
  lipid management, 145*t*
  physical activity in, 145*t*
  psychological factors in, 145*t*–146*t*
  smoking cessation, 145*t*
  weight management, 145*t*
treatment of, 144–156
  algorithm for, 147*f*
  blood pressure management, 148
  diabetes management, 149
  influenza vaccine, 149
  medical therapy in
    calcium channel blockers, 150
    nitrates, 150–152, 151*t*
  nonpharmacologic therapy (revascularization), 152–155, 153*t*
    coronary artery bypass graft surgery, 154–155
    percutaneous coronary intervention, 153–154
  outcome of, 144
  outcomes, evaluation of, 156
  pharmacologic therapy in, 146*t*

angiotensin-converting enzyme inhibitors, 146–148
antiplatelet therapy, 144–146
b-blockers, 149
lipid management, 148
with percutaneous coronary intervention, 153–154
ranolazine, 152
smoking cessation, 148
variable-threshold angina, management of, 156
Standardization, 2–3
Standards of Care, 1*t*. *See also* Patient care process
Staphylococcal endocarditis, 1893–1894
IV drug abuser, 1894
prosthetic valves, 1894–1895
Staphylococcus aureus infections, 1751, 1813, 2008
atopic dermatitis in, 1677
enterotoxigenic poisonings, 1935*t*
skin and soft-tissue infections, 1856–1857
surgical site infections, 2113–2114
treatment of, 1819
Staphylococcus epidermidis, 2008, 2114
Staphylococcus pneumoniae, 1808*t*, 1819, 1820*t*, 2008
Stasis dermatitis, definition of, 1676*t*
Statins, 128–129
for acute coronary syndromes, 181*t*, 184*t*
for age-related macular degeneration, 1616
in chronic kidney disease, 672–673
for glomerulonephritis, 721
intensity of, 129*t*
for ischemic stroke, 282
myocardial infarction and, 183
Status epilepticus (SE), 913–917
classification of, 914*t*
clinical presentation of, 916–917, 917*b*
definition of, 914
diagnosis of, 916
epidemiology of, 914–915

etiology of, 915
morbidity and mortality in, 915*t*, 916
pathophysiology of, 915–916
patient care process for, 918*b*
Status epilepticus (SE) treatment, 917–926
general approach to, 919*f*
nonpharmacologic therapy in, 917–920
ketogenic diet in, 920
stabilization phase, 917–920
vagus nerve stimulation in, 920
outcomes of
desired, 917
therapeutic, evaluation of, 926
pharmacologic therapy in, 920–926, 921*t*
benzodiazepines, 920
drug monitoring in, 922*t*
fosphenytoin, 921*t*
initial therapy phase, 920–921, 921*t*
phenytoin, 923
for refractory GCSE, 923, 924*t*
benzodiazepines, 923–924
immunomodulating therapies, 925
inhaled anesthetics, 925
ketamine, 924*t*
lacosamide, 924*t*
levetiracetam, 923
lidocaine, 924*t*
midazolam, 924*t*
pentobarbital, 924–925, 924*t*
propofol, 924*t*, 925
topiramate, 924*t*, 925
valproate, 923
for second-therapy stage, 922–923
for super-refractory GCSE, 925–926
Stavudine, 2150*t*, 2151, 2151*t*, 2152*t*
Stem cell transplantation, hematopoietic, 2338, 2449–2463, 2450*f*

allogeneic, 2377–2378, 2421
autologous, 2378, 2419–2421
for chronic lymphocytic leukemia, 2404
for chronic myeloid leukemia, 2396
complications of, 2457–2463
graft failure, 2458–2459
graft-versus-host disease, 2459–2463
infections, 2463
late, 2463
pulmonary, 2458
sinusoidal obstruction syndrome, 2457–2458
definition of, 2449
donor selection in, 2450–2451
hematopoietic stem cells in, 2451–2453
histocompatibility testing in, 2450–2451
immunization in, 2130
infections in, 2099–2101
etiology and clinical presentation of, 2099–2101
prophylaxis of, 2101
bacterial infections, 2101–2102
colony-stimulating factors in, 2103
fungal infections, 2103
protozoal infections, 2103
viral infections, 2102–2103
treatment of, 2101–2103
outcome evaluation for, therapeutic, 2103
outcomes of, desired, 2101
malignant cell eradication in, 2453–2457
conditioning regimens, 2453–2454
myeloablative, 2454*t*
reduced-intensity, 2454–2456
posttransplant therapy in, 2456–2457
chemotherapy in, 2457
donor lymphocyte infusion, 2455
immunotherapy in, 2456
monoclonal antibodies, 2456–2457

targeted therapy in, 2457
Stenosis, fluid mechanics of, 140
Stenotrophomonas maltophilia, 2082
Steroidogenesis inhibitors, 1297–1300
Steroid-resistant nephrotic syndrome, 724
Steroids. *See also* Corticosteroids
for focal segmental glomerulosclerosis, 725
for immunoglobulin A nephropathy, 729–730
intralesional, 1642–1643
for membranoproliferative glomerulonephritis, 728–729
for membranous nephropathy, 727
for minimal-change nephropathy, 722–724
relapsed, 723
frequent relapse, 724
Stimulant laxatives, 554
Stimulants, 1058–1060. *See also specific agents*
for ADHD, 1014–1019, 1016*t*–1017*t*
adverse effects of, 1017–1019, 1018*t*
cardiac, 1018–1019
on growth, 1019
psychiatric, 1017–1018
amphetamine, 1059–1060
anxiety and, 1166*t*
cathinones, synthetic (bath salts), 1060
cocaine, 1058–1059
dosing and administration of, 1016*t*–1017*t*
ecstasy and methamphetamine analogs, 1060
methamphetamine, 1059–1060
substance abuse disorders, 1058–1060
Stool DNA screening tests, 2281
Streptococcal endocarditis, 1890–1893. *See also* Endocarditis, infective
Streptococcal gangrene, 1870
Streptococcus agalactiae, 1793–1794
Streptococcus gallolyticus, 1890
Streptococcus mutans, 1890
Streptococcus oralis, 1890

Streptococcus pneumoniae, 1751, 1791–1793, 1792*t*, 1804, 1827, 1890, 2160*t*
diagnosis of, 1814–1815
Streptococcus pyogenes, 1856, 2114
Streptococcus salivarius, 1890
Streptococcus sanguinis, 1890
Streptococcus thermophilus, 514
Streptomycin
adverse effects and monitoring of, 1919*t*
dosing of, 1914*t*
for tuberculosis, 1913*t*, 1914*t*, 1917
Stress
asthma and, 377
peptic ulcer disease and, 490, 486
Stress testing, e81
Stress ulcers, prevention of, 2014*t*
Stress urinary incontinence, 1432–1433, 1435*t*. *See also* Urinary continence
clinical presentation of, 1435*b*
pharmacologic treatment of, 1445–1446
duloxetine, 1445–1446
estrogens, 1445
venlafaxine, 1446
α-adrenergic agonists, 1445
Stress-related mucosal bleeding, 501–502
epidemiology of, 501
prevention of, 501–502, 502*t*
risk factors for, 501
treatment of, 501–502, 502*t*
Stress-related mucosal damage (SRMD), 500
Stroke, 273–275
clinical presentation of, 275, 275*b*
epidemiology of, 273–274
etiology of, 273–274
pathophysiology of
in ischemic stroke, 274–275, 274*f*
in hemorrhagic stroke, 275
patient care process for, 277*b*

risk factors for, 274, 274*t*
Stroke treatment, 275–283
bleeding risk, scoring, 284*t*
blood pressure treatment guidelines, 276*t*
general approach to, 276
nonpharmacologic
for ischemic stroke, 276–278
for hemorrhagic stroke, 278
outcomes of
desired, 275–276
therapeutic, evaluation of, 283–284
pharmacologic therapy in
alteplase, 278–279
for ischemic stroke, 278–282, 278*t*
secondary prevention, 278*t*
aspirin, 279
blood pressure management, 279–280
alteplase, 279*t*
heparin, 280
secondary prevention, 280
antiplatelet agents, 280
clopidogrel, 280
extended-release dipyridamole plus aspirin, 280
ticagrelor, 280–281
dual antiplatelet therapy, 281–282
secondary prevention, 281*t*
oral anticoagulants, 282
blood pressure management, 282
statins, 282
for hemorrhagic stroke, 282–283
blood pressure management, 282–283
anticoagulation reversal, 283, 283*t*
in hospitalized patients, 283*t*
temperature management, 278
Stromal tissue, 1412
Struma ovarii, 1273

ST-segment elevation myocardial infarction (STEMI), 162
nonpharmacologic therapy in, primary PCI, 172
pharmacologic therapy in
fibrinolytic therapy, 172–173, 172*t*
aspirin, 173–175
antiplatelet therapy, 173–178
fibrinolytic therapy, 173*t*
antiplatelet therapy, 174*t*
beta-blockers, 174*t*
nitrates, 174*t*
statins, 174*t*
P2Y12 receptor, 175
clopidogrel, 175–176
P2Y12 receptor, 175*t*
clopidogrel, 175*t*
prasugrel, 175*t*
cangrelor, 175*t*
prasugrel, 176
ticagrelor, 176
cangrelor, 176–177
glycoprotein IIb/IIIa receptor inhibitors, 177–178
anticoagulants, 178–180, 178*t*
treatment strategies, 171–173
Subacute thyroiditis, 1271–1272
Subcutaneous fat, e37
Subdermal progestin implants, 55–56
Substance P, 535
Substance-related disorders, 1043–1050
acute *vs.* chronic, 1047–1050
addiction in, 1046–1047
ADHD and, 1021–1022
alcohol, 1070–1076
caffeine, 1084–1087
clinical presentation of, 1046–1047
CNS depressants, opiates and opioids, 1045–1046
dextromethorphan, 1049

diagnosis of, 1047*t*
economic impact of, 1045
epidemiology of, 1044–1045
  economic impact of, 1045
  Monitoring the Future Study, 1044
  National Survey on Drug Use and Health, 1044
etiology of, 1045
fentanyl, 1049
hallucinogens, 1060–1062
  cannabinoids, 1061
    cannabinoid hyperemesis syndrome, 1062
    cannabis use disorder, 1062
  cannabinoids, synthetic, 1061–1062
  designer drugs, 1061
  LSD, 1061
  novel psychoactive substances, 1061
heroin, 1048–1049
history of, 1044
inhalants, 1062–1063
loperamide, 1049–1050
marijuana, 1061
methadone, 1048
nicotine, 1076–1084
opioid use disorder
  clinical presentation of, 1047*b*
  patient care process for, 1052*b*
  pharmacologic therapy in
    buprenorphine, 1051–1054, 1051*t*, 1053*t*, 1054*t*, 1055*t*
    extended release, 1054*t*
    methadone, 1050–1051, 1051*t*
    naloxone, 1054–1056, 1056*t*
    naltrexone, 1051, 1051*t*, 1054*t*
    in pregnancy, 1056–1057
  withdrawal, 1048–1050
pathophysiology of, 1045–1046
  opiates and opioids, 1045–1046

physical dependence in, 1047
prevalence rates, 1044
stimulants, 1058–1060
amphetamine, 1059–1060
cathinones, synthetic (bath salts), 1060
cocaine, 1058–1059
ecstasy and methamphetamine analogs, 1060
methamphetamine, 1059–1060
terminology, 1046
tolerance in, 1047
Substance-related disorders, treatment of, 1050–1063
for acute drug intoxications and withdrawals, 1063
benzodiazepines, 1063
dextromethorphan, 1049
fentanyl, 1049
flumazenil, 1063
heroin, 1048–1049
loperamide, 1049–1050
methadone, 1048
naloxone, 1063
pharmacologic therapy in, 1063
flumazenil, 1063
naloxone, 1063
benzodiazepine withdrawal
clinical presentation of, 1057*t*
general approach to, 1057
nonpharmacologic therapy in, 1057
pharmacologic therapy in, 1057
cannabinoids, general approach to, 1058
hallucinogens, general approach to, 1058
inhalants, general approach to, 1058
opioid use disorder
general approach to, 1050
nonpharmacologic therapy in, 1050
outcomes of, desired, 1050
pharmacologic therapy in, 1050–1057

outcomes of, evaluation of, 1063
stimulants, 1058–1060
amphetamine, 1059–1060
clinical presentation of, 1059*b*
cathinones, synthetic (bath salts), 1060
cocaine, 1058–1059
clinical presentation of, 1058*b*
ecstasy and methamphetamine analogs, 1060
general approach to, 1058
methamphetamine, 1059–1060
Substantial nigra, 946
Sucralfate, 494*t*, 499, 501–502
Sucroferric oxyhydroxide, 668
Sudden cardiac death, 310, 313–315, 314*f*, 1109
Suicide risk, 1129–1130
Sulfadiazine, 1800, 2094*t*
Sulfamethoxazole, 454*t*
Sulfasalazine, 515, 516*t*, 519, 520, 522, 523*t*, 1525*t*, 1527, 1533*t*
Sulfonamides
adverse effects and monitoring of, 1778*t*
drug interactions, 1775*t*
Sulfonylureas, 1242*t*, 1243
Sulfur, 1636*t*, 1638
Sulindac, 1574*t*
Sumatriptan, 995*f*, 995*t*, 998*t*
Sunitinib, 2188*t*, 2202
Superficial spreading melanoma (SSM), 2431
Super-refractory GCSE, 925–926
Suppressive therapy, 2050
Supraventricular arrhythmias, 295–309
atrial fibrillation, 295–298 (*See also* Atrial fibrillation and atrial flutter)
clinical presentation of, 296*b*
paroxysmal supraventricular tachycardia, reentry, 306–310
antidromic, 307
mechanisms of, 307
orthodromic, 307

mechanisms of, 307*t*
management, 308–310, 309*f*
Surgical site infections (SSIs)
antimicrobial prophylaxis in, 2111–2112
choice in, 2115
scheduling in, 2114–2115
for specific surgery types, 2116–2121, 2117*t*–2118*t*
appendectomy, 2116
cardiothoracic surgery, 2118*t*, 2120–2121
cesarean section, 2117*t*, 2119–2120
colorectal surgery, 2116–2119
gastroduodenal surgery, 2116
gastrointestinal endoscopy, 2117*t*, 2119
gastrointestinal surgery, 2116
head and neck surgery, 2117*t*, 2120
hepatobiliary surgery, 2116
hysterectomy, 2117*t*, 2120
neurosurgery, 2118*t*, 2121
obstetric and gynecologic surgeries, 2117*t*, 2119–2120
orthopedic surgery, 2118*t*, 2121
urologic, 2119
urologic surgery, 2117*t*
vascular surgery, 2118*t*, 2121
antimicrobial resistance in, 2114
bacteriology of, 2113–2114
classification of, 2112*t*, 2113*t*
incidence of, 2113*t*
major pathogens in, 2113*t*
risk factors for, 2112–2113, 2112*t*
identification of, 2112*t*, 2113
inherent patient, 2112–2113
Sustained low-efficiency dialysis (SLED), 639
Sutezolid, 1918
Suvorexant, 1203
Swine influenza of 2009, 1843
Symbiosis, e1955

Sympathomimetics, 330–331, 1166*t*. *See also specific agents*
Symptomatic abacteriuria, 1965–1966
Symptom-triggered therapy, 1072
Syphilis, 1322, 1323*t*, 1980–1983
clinical presentation of, 1980–1981, 1981*t*
congenital, 1981
diagnosis of, 1981–1982
epidemiology of, 1980
etiology of, 1980
latent, 1981
neurosyphilis, 1981
primary, 1981
secondary, 1981
tertiary, 1981
treatment of, 1982–1983, 1983*t*
outcomes, evaluation of, 1983
in pregnancy, 1982
Systematic Nomenclature of Medicine—Clinical Terms (SNOMED-CT), 6, 7*t*
Systemic adjuvant therapy, 2234–2242
benefits, 2235, 2235*t*
biologic therapy, 2238–2240
dose density and intensity in, 2237–2238
endocrine therapy, 2240–2242, 2242*f*
guidelines, 2235–2236, 2235*f*
Systemic lupus erythematosus (SLE), 1453–1456
cigarette smoking and, 1454
classification of, 1456*t*
from combined hormonal contraceptives, 54
definition of, 1453
environmental triggers of, 1454
epidemiology of, 1453–1454
ethnicity factor in, 1453
etiology of, 1454
incidence of, 1453
pathophysiology of, 1454–1455, 1454*f*
patient care process for, 1457*b*

prevalence of, 1453
in women, 1454
Systemic lupus erythematosus (SLE) treatment, 1456–1457
algorithm for, 1458*f*, 1459*f*
clinical presentation of, 1455–1456, 1455*b*
complementary and alternative therapies in, 1464–1465
with drug-induced lupus, 1466–1467
general approach to, 1458
immunizations, 1467
nonpharmacologic therapy in, 1458
outcomes of
desired, 1456–1457
therapeutic, evaluation of, 1467–1468
pharmacologic therapy in, 1458–1464, 1461*t*, 1462*t*
antimalarials, 1461–1463
biologic agents, 1463
corticosteroids, 1460–1461
cyclophosphamide, 1460
dehydroepiandrosterone, 1464
immunosuppressive agents, 1463–1464
nonsteroidal anti-inflammatory drugs, 1460
vitamin D supplements, 1465
pregnancy and contraception in, 1465
with SLE-antiphospholipid syndrome overlap, 1465–1466
Systolic blood pressure, 85

T

Tacalcitol, 1660
Tachyarrhythmias, mechanisms of, 289
Tachycardia, 171
  automatic, 289
  contractibility and, 194
  reentrant, 289–290, 290*f*
Tacrolimus
  for celiac disease, 620
  chronic interstitial nephritis and, 710
  for graft-versus-host disease, 2460, 2461*t*
  for inflammatory bowel disease, 519
  for minimal-change nephropathy, 724
  nephrotoxicity of, 705–706, 710
Tadalafil, 443, 443*t*, 444*t*, 445*t*, 446*t*, 1390*t*, 1398*t*, 1421*t*, 1424
Tafluprost, 1601*t*
Tai chi, 965*t*
Talazoparib, 2188*t*
Talimogene laherparepvec, 2192*t*, 2209
Talk-down therapy, 1063
Tamm-Horsfall protein, 1959
Tamoxifen, 1376, 2224, 2240–2242, 2242*f*, 2246*t*, 2247, 2248, 2358*t*
Tamsulosin, 869*t*, 1421*t*
Tanacetum parthenium, 1001
Tapentadol, 980
  dosing and administration of, 978*t*
  for pain management, 975*t*
Tardive dyskinesia, 1110–1111, 1119*t*
Targeted drugs, for cancer, 2177–2178. *See also specific agents*
  ALK Inhibitors, 2199
    alectinib, 2199
    brigatinib, 2199
    ceritinib, 2199
    crizotinib, 2199
    lorlatinib, 2199

BCL-2 inhibitors, 2199
BCR-ABL inhibitors, 2199–2200
  bosutinib, 2199–2200
  dasatinib, 2199–2200
  imatinib, 2199
  nilotinib, 2199–2200
  ponatinib, 2200
BRAF inhibitors, 2200
BTK inhibitor, 2200
CDK inhibitors, 2200
DNA methyltransferase inhibitors, 2200
EGFR pathway inhibitors, 2200–2201
  afatinib, 2200–2201
  dacomitinib, 2200–2201
  erlotinib, 2200
  gefitinib, 2201
  lapatinib, 2201
  neratinib, 2201
  osimertinib, 2201
FGFR inhibitor, 2201
FLT3 inhibitors, 2201
HDAC inhibitors
  belinostat, 2201
  panobinostat, 2201
  romidepsin, 2201
  vorinostat, 2201
Hedgehog pathway inhibitors, 2201–2202
IDH inhibitors, 2202
JAK inhibitor, 2202
lanreotide, 2198
lenalidomide, 2198
MEK inhibitor, 2202
mTOR pathway inhibitors, 2202
  everolimus, 2202
  temsirolimus, 2202
multikinase inhibitors, 2202–2203

axitinib, 2202
cabozantinib, 2202–2203
lenvatinib, 2203
pazopanib, 2202
regorafenib, 2203
sorafenib, 2202
sunitinib, 2202
vandetanib, 2203
PARP inhibitor, 2203
PI3K inhibitor, 2203
pomalidomide, 2198
proteasome inhibitors, 2203–2204
bortezomib, 2203–2204
carfilzomib, 2204
ixazomib, 2204
thalidomide, 2198
TRK inhibitor, 2203
Taxanes, 2194, 2249–2250. *See also specific agents*
Tazarotene, 1636*t*, 1640, 1660
Tazobactam, 2086
T-cell lymphomas, 2321*t*
Tedizolid, 1867
Tegaserod, 557
Telavancin, 1867
Telbivudine, 604
Telogen phase, 1692, 1694, 1694*t*
Temazepam, 1205*t*
Temozolomide, 2196
Temperature management
for cardiac arrest, 332*t*
in stroke, 278
Temsirolimus, 2187*t*, 2202
Tenecteplase, 173*t*, 685
Teniposide, 2195
Tenofovir, 603–604, 1916*t*, 2150*t*, 2152*t*, 2153
Tension-type headache, 1001–1002

clinical presentation of, 1001
epidemiology of, 1001
pathophysiology of, 1001
treatment of, 1001–1002
nonpharmacologic therapy in, 1001–1002
outcomes of, desired, 1001
pharmacologic therapy in, 1002
Terazosin, 869*t*, 1419, 1421*t*
Terbinafine, 2040–2041
Terbutaline, 1327–1328, 1760
Terconazole, for vulvovaginal candidiasis, 2027*t*
Teriflunomide, 862*t*, 863*t*, 866
Teriparatide, 1552*t*, 1553*t*, 1558
Testosterone, 1384, 1391*t*–1392*t*, 1399*t*–1400*t*, 1412, 2305
for erectile dysfunction, 1400–1403
adverse effects of, 1402–1403
dosing and administration of, 1402, 1402*t*
efficacy of, 1401
indications for, 1400–1401
mechanism, 1400
pharmacokinetics of, 1401–1402
for osteoporosis, 1558
Tetanus, 1879
immunoglobulin, 2136–2137
vaccines, 2136–2137, 2136*t*
Tetanus toxoid adsorbed, 2136–2137
Tetracaine, 981*t*
Tetracyclines
for acne vulgaris, 1637*t*, 1641
adverse effects and monitoring of, 1777*t*
for chronic bronchitis, 1811*t*
dosing of, 1819*t*
drug interactions, 1775*t*
for peptic ulcer disease, 493, 495
for pneumonia, 1819*t*
for syphilis, 1982

Tetrahydrocannabinol (THC), 871*t*
Texepelumab, 398*t*
Th_1 and Th_2 cell imbalance, 374–375
Thalidomide, e61, 2189*t*, 2198, 2414–2416
Theophylline, 399*t*, 400*f*
Therapeutic radiopharmaceuticals, 2197
  ibritumomab tiuxetan, 2197
  iobenguane I 131, 2197
  lutetium Lu 177 dotatate, 2197
  radium-233, 2197
Therapeutic vaccines, 2209
Thermogenic effect of food, 2534
Thermoregulation, 1111
Thiabendazole, 2094*t*
Thiamine, 2480*t*
Thiazides, 94
  characteristics of, 773*t*
  for edema, 773–775, 773*t*
  for heart failure with preserved ejection fraction, 205–206
  for hypertension, 94, 104–105
  in pregnancy, 100*t*
  for resistant hypertension, 104–105
Thiazolidinediones, 1242*t*, 1243–1244
Thioguanine, 520, 2193
Thionamide drugs, 1274–1277
  adverse effects of, 1276–1277
  dosing and administration of, 1275–1276
  mechanism of action, 1274
  pharmacokinetics of, 1274–1275
Thiopurine methyltransferase (TPMT), 524, 1464
Thiopurines, 521
Thioridazine. *See also* Antipsychotics
  adverse effects of, 1107*t*
  dosing of, 1096*t*
  for schizophrenia, 1096*t*

Thiotepa, 2183*t*, 2454*t*
Thiothixene, 1096*t*
  adverse effects of, 1107*t*
Thrombin time, 1731*t*
Thrombocytopenia
  in cancer patients, 2214
  in cirrhosis, 564, 566
  drug-induced, e1767
  glycoprotein IIb/IIIa receptor inhibitors and, 177
Thrombocytosis, 1522
Thromboembolism, 1109
  from combined hormonal contraceptives, 53–54
  in pregnancy, 1321
Thrombolysis, 259*t*
Thrombolytics, for cardiac arrest, 332*t*, 333. *See also specific agents*
Thrombotic microangiopathy, 711–712
Thrush. *See* Esophageal candidiasis
Thyroglobulin, 1266–1267
Thyroid cancer, 1273
Thyroid disorders, 1265–1273
  hyperthyroidism, 1268
  hypothyroidism, 1279–1286
  in pregnancy, 1325*t*, 1327
  thyrotoxicosis, 1268–1279
Thyroid hormones, 1266
  anxiety and, 1166*t*
  coupling reactions, 1266, 1266*f*
  exogenous, 1272
  pituitary resistance to, 1271
  regulation and action of, 1267
  structure of, 1266*f*
  synthesis of, 1266–1267, 1266*f*, 1266*t*
Thyroid storm, 1279, 1279*t*
Thyroiditis
  autoimmune, 1280–1281
  painless, 1272

postpartum, 1272
subacute, 1271–1272
Thyrotoxicosis
causes of, with elevated RAIU, 1269–1271
Graves' disease, 1269–1270, 1269*f*
multinodular goiters, 1271
toxic adenoma, 1270–1271
causes of, with suppressed RAIU, 1271–1273
exogenous thyroid hormone, 1272
medications containing iodine, 1272–1273
painless thyroiditis, 1272
struma ovarii, 1273
subacute thyroiditis, 1271–1272
thyroid cancer, 1273
clinical presentation of, 1268*b*
differential diagnosis of, 1268*t*
in elderly, 1278
epidemiology of, 1268
etiology of, 1268–1273
pathophysiology of, 1268–1273
radioiodine thyroid scans, 1270*f*
thyroid function tests, 1270*t*
Thyrotoxicosis factitia, 1272
Thyrotoxicosis treatment, 1273–1279
in children, 1279
general approach to, 1273
in Graves' disease, 1273*t*, 1278–1279
neonatal hyperthyroidism, 1279
nonpharmacologic therapy in, 1273
outcomes of
desired, 1273
therapeutic, evaluation of, 1279
pharmacologic therapy in, 1274–1278
antithyroid medications, 1274–1278
adrenergic blockers, 1277
iodides, 1277

radioactive iodine, 1277–1278
thionamide drugs, 1274–1277
iodides, 1277
methimazole, 1274–1277
propylthiouracil, 1274–1277
radioactive iodine, 1277–1278
thionamide drugs, 1274–1277
in pregnancy, 1278–1279
thyroid storm, 1279, 1279*t*
Thyrotropin, 1267
Thyroxine, 1266
Tiagabine
adverse effects of, 895*t*
drug interactions, 895*t*
for epilepsy, 894*t*–895*t*
mechanism of action, 894*t*
for multiple sclerosis, 869, 869*t*
Tibolone, 1376*t*, 1377
Ticagrelor, 174*t*, 175*t*, 176, 280–281
Ticonazole, for vulvovaginal candidiasis, 2027*t*
Tildrakizumab, 1667
Timolol, 996*t*, 1600*t*
Tinea barbae, 2037*t*, 2038
Tinea capitis, 2037*t*, 2038
Tinea corporis, 2037*t*, 2038
Tinea cruris, 2037*t*, 2038
Tinea manuum, 2037*t*, 2038
Tinea pedis, 2037–2038, 2037*t*
Tinidazole, for trichomoniasis, 1989
Tipiracil, 2180*t*, 2193, 2293–2295, 2294*t*
Tipranavir, 2153*t*, 2154
Tiratricol, 1272
Tirofiban, 174*t*
Tisagenlecleucel, 2192*t*, 2209
Tissue inhibitor of metalloproteinase 2 (TIMP-2), 698
Tissue transglutaminase (tTG), 617

Tizanidine, 869, 869*t*, 971, 972*t*
Tobacco use. *See* Smoking
Tobramycin
  for cystic fibrosis, 453, 454*t*
  dosing by age group, 1799*t*
  for febrile neutropenia, 2092*t*
  for intra-abdominal infection, 1947
  for UTIs, 1963*t*
Tocilizumab, 1529, 1533*t*
Tocolytics, 1327–1328
Tofacitinib, 516*t*, 517, 522, 523*t*, 524, 1525*t*, 1530, 1533*t*, 1667, 1702
Tolazamide, 1242*t*, 1243
Tolbutamide, 1242*t*, 1243
Tolcapone, 953*t*, 956
Tolerance, 1047
Tolerodine, 869*t*
Tolterodine
  for benign prostatic hyperplasia, 1422*t*, 1425
  immediate release, 1442
  long acting, 1442
Tonic seizure, 881. *See also* Epilepsy
Tonic-clonic seizure, 881. *See also* Epilepsy
Tophaceous gout, 1572, 1572*f*
Topiramate, 922*t*, 924*t*, 969*t*
  adverse effects of, 895*t*
  for binge eating disorder, 1038
  drug interactions, 895*t*
  for epilepsy, 894*t*–895*t*
  mechanism of action, 894*t*
  for migraine prophylaxis, 996*t*
  for refractory GCSE, 925
Topoisomerase inhibitors, 2194–2195
  anthracyclines, 2195
  camptothecins, 2195
  etoposide, 2195
  monitoring of, 2181*t*–2182*t*

teniposide, 2195
Topotecan, 2181*t*, 2358*t*, 2359
Toremifene, 2246*t*, 2247, 2248
Torsade de pointes, 315–317, 316*f*, 317*t*
Torsemide, 207*t*
Total iron-binding capacity, 1714
Total peripheral resistance, 85
Total reticulocyte count, 1714
Toujeo, 1240*t*
Tourette disorder, 1022–1023
Toxic adenoma, 1270–1271
Toxic megacolon, 510, 521
Toxicology, clinical, e19
death rates, e19
epidemiology of, e19
poisoning in, e19
Toxoids, 2127–2128
Toxoplasma gondii, 1799–1800, 2083, 2160*t*
Toxoplasmic encephalitis, 2159*t*
Trabectedin, 2183*t*, 2196
Trace elements, 2477*t*. *See also specific types*
chromium, 2477*t*, 2478
copper, 2477*t*, 2478
deficiencies and toxicities of, 2476–2479
iodine, 2477*t*, 2479
iron, 2476, 2477*t*
manganese, 2477*t*, 2478
molybdenum, 2477*t*, 2479
in parenteral nutrition, 2497
parenteral nutrition complications, 2507
selenium, 2476–2478, 2477*t*
zinc, 2476, 2477*t*
Tramadol, 980
adverse effects of, 1511
for chronic pancreatitis, 590*t*
dosing and administration of, 978*t*, 1504*t*, 1511

drug interactions, 1511
for osteoarthritis, 1506, 1507, 1507*t*, 1511
for pain management, 975*t*
pharmacology and mechanism of action, 1511
Trametinib, 2187*t*, 2202, 2443, 2443*t*, 2445*t*
Tramiprosate, 846
Tranexamic acid
for heavy menstrual bleeding, 1344
for menstruation-related disorders, 1343*t*
Tranilast, 1583
Transdermal contraceptives, 51–52
Transesophageal echocardiography (TEE), 1887
Transferrin, 2467
Transient ischemic attack (TIA). *See* Stroke
Transjugular intrahepatic portosystemic shunt (TIPS), 569, 569*f*
Transplant patients, cystic fibrosis in, 457
Transplantation, high-dose chemotherapy with, 537
Transplantation, solid-organ, 1473–1494
epidemiology and etiology of, 1475
heart, 1475
kidney, 1475
liver, 1475
lung, 1475
physiologic consequences of, 1475–1477
in heart transplantation, 1476–1477
in kidney transplantation, 1476
in liver transplantation, 1476, 1476*t*
in lung transplantation, 1477
rejection pathophysiology in, 1477–1480
acute cellular rejection, 1478–1479
antibody-mediated rejection, 1479
chronic rejection in, 1479–1480
general concepts of, 1477, 1478*f*
hyperacute rejection, 1477–1478
statistics on, 1473
survival rates, 1475*t*

treatment of rejection in, 1480–1490
bottom line, clinical, 1494
general approach to, 1480–1481, 1481*f*
in acute rejection, 1480–1481
induction therapy in, 1480
generic substitution in, 1492
immunosuppression-related complications in, 1492–1494
cardiovascular disease, 1492–1493
diabetes, new-onset, 1493
infection, 1493–1494
malignancy, 1494
laboratory monitoring, 1491*t*
maintenance therapy in, 1481–1490
alemtuzumab, 1489
antibody agents, 1488–1489
antimetabolites, 1485–1487
antithymocyte globulin, 1488–1489
azathioprine, 1486–1487
calcineurin inhibitors, 1481–1485
corticosteroids, 1485
costimulatory signal inhibitor, 1488
depleting antibodies, 1488–1489
interleukin-2 receptor antagonists, 1489–1490
investigational agents, 1490
mycophenolic acid derivatives, 1485–1487
nondepleting antibodies, 1489–1490
proliferation signal inhibitors, 1487–1488
outcomes of
desired, 1480
therapeutic, evaluation of, 1490
personalized pharmacotherapy in, 1490–1492
Transthoracic echocardiography (TTE), 1887
Transthyretin, 2474
Transurethral incision of the prostate (TUIP), 1426
Tranylcypromine, 1133*t*, 1136. *See also* Monoamine oxidase inhibitors
Trastuzumab, 2190*t*, 2206, 2238, 2243–2244, 2294*t*

Trauma. *See also specific types*
cardiac arrest treatment in, 336–337
Traumatic brain injury (TBI), 932–935
clinical presentation of, 931*b*
drug dosing and monitoring, 937*t*
epidemiology of, 929
pathophysiology of, 930–932, 930*f*
pharmacologic management of, 932*t*
primary and secondary, 930–932
Traumatic shock. *See* Hypovolemic shock treatment
Travel health, e39
pretravel preparation in, e39
in immunocompromised travelers, e39
in pregnant travelers, e39
pretravel consultation, e39
Traveler's diarrhea, 1930*t*, 1933–1934
Travoprost, 1601*t*
Trazodone, 1133*t*, 1135–1136, 1135*t*, 1138*t*, 1144*t*, 1203
Tremor, in multiple sclerosis, 869
Treponema pallidum, 1797, 1981–1982
Treprostinil, 441–442, 443*t*, 444*t*, 446*t*
Tresiba, 1240*t*
Tretinoin, 1635, 1639, 2184*t*
Triamcinolone, 1308*t*, 1504*t*
Triazenes, 2183*t*
Triazolam, 1205*t*
Trichomoniasis, 1322, 1323*t*, 1988–1990
clinical presentation of, 1988, 1988*t*
diagnosis of, 1989
epidemiology of, 1988
etiology of, 1988
outcome evaluation for, therapeutic, 1989–1990
pathophysiology of, 1988
treatment of, 1989
Trichophyton, 2036
Trichophyton mentagrophytes, 2038

Trichophyton rubrum, 2038
Trichosporon, 2048*t*
Trichotillomania, 1699
Tricyclic antidepressants (TCAs), 970–971, 970*t*, 1132, 1133*t*, 1209
  adverse effects of, 1174*t*
  for menstruation-related disorders, 1342*t*
  for panic disorder (attack), 1178*t*, 1179–1180
  pharmacokinetics of, 1138*t*
  for posttraumatic stress disorder, 1193*t*
  relative potencies, 1135*t*
Trifluoperazine, 1096*t*
Trifluridine, 2180*t*, 2193, 2293–2295, 2294*t*
Triglycerides, 124*t*, 130–131
Trihexyphenidyl, 953*t*
Triiodothyronine, 1133*t*, 1266
Trimester, 1316
Trimethobenzamide, 533*t*
Trimethoprim, 2094*t*
  adverse effects and monitoring of, 1778*t*
  for cystic fibrosis, 454*t*
  for prostatitis, 1971
Trimethoprim-sulfamethoxazole, 2093*t*, 1963*t*
  for acne vulgaris, 1641
  for chronic bronchitis, 1811*t*
  dosing by age group, 1799*t*
  for febrile neutropenia, 2095*t*
  for HSCT infections, 2103
  for peritonitis, 692*t*
Triple Aim, 2, 3*f*
Triptans. *See also specific agents*
  for cluster headache, 1002–1003
  for migraine headache, 995*f*, 998–999, 998*t*
  for migraine prophylaxis, 1000
Triptorelin, 2312*t*
  for breast cancer, 2246*t*
  for endometriosis, 1358*t*

Trivalent influenza vaccine, 1845–1846
TRK inhibitor, 2203
Trolamine salicylate, 974*t*
Tromethamine, 824
Trophoblastic diseases, 1271
Tropisetron, 530*t*, 531*t*
Trospium, 869*t*
Trospium, for benign prostatic hyperplasia, 1422*t*, 1425
Trospium chloride
  extended release, 1442
  immediate release, 1442
Trypsinogen, 2515*t*
Tryptamines, 1061
TSH-induced hyperthyroidism, 1271
TSH-secreting pituitary adenomas, 1271
Tuberculosis, 1901–1908
  clinical presentation of, 1905–1906, 1905*b*
    in children, 1906
    in elderly, 1906
    extrapulmonary, 1905–1906
    HIV in, 1905
  definition of, 1901
  diagnosis of, 1906–1908
    criteria for, 1907*t*
    culture and staining in, 1906–1908
    tests in, 1906, 1907*f*
      interferon-γ release assays (IGRA), 1906
      Mantoux test, 1906
  epidemiology of, 1901–1902
  etiology of, 1902–1903
    culture and susceptibility testing, 1903
    transmission in, 1903
  incidence of, 1902*f*
  pathophysiology of, 1903–1905
    extrapulmonary and miliary tuberculosis in, 1905
    HIV infection and, 1905

immune response in, 1903–1904
primary infection in, 1904
reactivated disease in, 1904–1905
patient care process for, 1909*b*
pneumonia and, 1814
risk factors, 1902
for disease, 1902
for infection, 1902
age in, 1902
coinfection with HIV, 1902
ethnicity in, 1902
location and place of birth in, 1902
race in, 1902
Tuberculosis treatment, 1908–1918
general approaches to, 1908
nonpharmacologic therapy in, 1908
outcomes of
desired, 1908
therapeutic, evaluation of, 1918–1919
pharmacologic therapy in, 1909–1918
in active disease, 1910–1912
in children, 1912, 1913*t*–1914*t*
in concomitant HIV, 1916*t*
drug monitoring in, 1918–1919, 1919*t*
in extrapulmonary disease, 1912
in hepatic failure, 1912
in HIV patients, 1912
in latent infection, 1908, 1909–1910
in morbid obesity, 1912–1915
newer drugs and delivery systems, 1917–1918
om tuberculous meningitis, 1912
in pregnancy, 1912
in renal failure, 1912
secondary anti-TB drugs in (*See* Anti-tuberculosis drugs, secondary)
in tuberculous meningitis, 1912
principles for, 1908

Tuberculous meningitis, 1912
Tubular carcinoma, 2227
Tubular epithelial cell damage, 699–703
Tubular necrosis, acute, 699–700
  aminoglycoside, 699–700
  amphotericin B, 702–703
  cisplatin, 702
  radiographic contrast media, 700–702
Tumor necrosis factor-α
  for Crohn's disease, 521
  for inflammatory bowel disease, 509, 519
  inhibitors, 521–522, 524–525
  for lupus arthritis, 1455
  for psoriasis, 1664–1665
  for rheumatoid arthritis, 1528–1529
Tumor suppressor genes, 2170, 2171*t*
Turner's (XO) syndrome, 1231*t*, 1454
Type 1 diabetes. *See* Diabetes mellitus (DM)
Type 2 diabetes. *See* Diabetes mellitus (DM)
Tyrosine kinase inhibitors, 2359–2360, 2393–2395, 2396

U

Ulcer, decubitus. *See* Pressure sores
Ulcerative colitis. *See also* Inflammatory bowel disease (IBD)
  abscesses in, 510
  clinical presentation of, 511–512, 511*t*
  colonic dysplasia in, 510
  complications of, 510
  mild to moderate active disease, 517–519
  moderate to severe active disease, 519
  pathophysiology of, 509*t*, 510
  pharmacologic therapy for, 517–519, 517*f*, 518*t*
  remission maintenance for, 519
  severe or fulminant disease, 519
  toxic megacolon in, 510
Ulipristal, 57

Ulodesine, 1583
Ultrafiltration, 234–235
Ultrasonic nebulizer, 390*t*
Underweight, 2535*t*
Unfractionated heparin (UFH), 684, 1321
  for acute coronary syndromes, 178–179, 178*t*
Unstable angina (UA), 162
Upper airway obstruction. *See specific types*
Upper gastrointestinal bleeding, 500
Upper respiratory tract infections, 1827–1838. *See also specific infections*
  acute bacterial rhinosinusitis, 1830–1834
  acute otitis media, 1827–1830
  acute pharyngitis, 1834–1838
Urate-lowering agents, 1582–1583
Urea reduction ratio, 681
Urethra, 1431
Urethral meatus warts, 1991*t*
Urethral underactivity, 1432–1433
  clinical presentation of, 1434–1436
  pharmacologic treatment of, 1445–1446
    duloxetine, 1445–1446
    venlafaxine, 1446
    estrogens, 1445
    α-adrenergic agonists, 1445
Urethritis, 1977*t*
Urge urinary incontinence, 1433. *See also* Urinary continence
  clinical presentation of, 1435*t*
  pharmacologic treatment of, 1440–1445, 1441*t*, 1442*t*
    adverse effects of, 1444*t*
    botulinum toxin A, 1444–1445
    catheterization combined with medications, 1445
    darifenacin, 1443
    fesoterodine fumarate, 1442–1443
    mirabegron, 1443–1444
    oxybutynin extended-release, 1441
    oxybutynin immediate release, 1440–1442

oxybutynin topical gel, 1443
solifenacin succinate, 1443
tolterodine immediate release, 1442
tolterodine long acting, 1442
trospium chloride extended release, 1443
trospium chloride immediate release, 1443
Uric acid
cardiovascular risk and, 1584
lowering in absence of gout, 1584
overproduction, 1568–1569
underexcretion of, 1569
Uric acid nephrolithiasis, 1571–1572, 1583–1584
Uricosurics, 1575*t*, 1581
Uridine triacetate, 2192
Urinary continence, 1432–1434
Urinary incontinence, 1112, 1431–1447
clinical presentation of, 1434*b*
with bladder overactivity, 1435*b*
with overflow incontinence, 1435*b*
prior medical or surgical illness in, 1436
symptoms in, 1435–1436, 1435*t*
with urethral underactivity, 1434*b*
urine leakage in, 1434–1436
definition of, 1431
epidemiology of, 1431–1432
etiology of, 1432–1434
mechanisms of, 1432–1434
bladder overactivity (urge urinary incontinence), 1433
urethral overactivity and/or bladder underactivity (overflow incontinence), 1433
urethral underactivity (stress urinary incontinence), 1432–1433
medication-related, 1434*t*
pathophysiology of, 1432–1434
patient care process for, 1437*b*
prevalence of, 1431
Urinary incontinence treatment, 1436–1446

general approach to, 1436–1437
nonpharmacologic therapy in, 1437–1440
nonsurgical treatment, 1437–1439, 1438*t*–1439*t*
surgical treatment, 1439–1440
outcomes of
desired, 1436
therapeutic, evaluation of, 1447
personalized pharmacotherapy in, 1446–1447
pharmacologic therapy in, 1440–1446
for nocturia, 1446
for overflow incontinence, 1446
for urethral underactivity, 1445–1446
duloxetine, 1445–1446
estrogens, 1445
venlafaxine, 1446
α-adrenergic agonists, 1445
for urge urinary incontinence, 1440–1445, 1441*t*, 1442*t*
adverse effects of, 1444*t*
antimuscarinic agents, 1441*t*, 1442*t*
b3-adrenergic agonist, 1441*t*, 1442*t*
botulinum toxin A, 1444–1445
catheterization combined with medications, 1445
darifenacin, 1443
fesoterodine fumarate, 1442–1443
mirabegron, 1443–1444
oxybutynin extended-release, 1441
oxybutynin immediate release, 1440–1441
oxybutynin topical gel, 1442
solifenacin succinate, 1443
tolterodine immediate release, 1442
tolterodine long acting, 1442
trospium chloride extended release, 1443
trospium chloride immediate release, 1443
Urinary tract infections (UTIs), 1957–1961
abacteriuria
significant, 1958*t*

symptomatic, 1965–1966
bacteriuria, asymptomatic, 1966
in catheterized patients, 1969
classification of, 1957
clinical presentation of, 1960–1961, 1960*b*
bacterial count, 1960
chemistry in, 1961
culture in, 1961
hematuria in, 1961
infection site in, 1961
proteinuria in, 1961
pyuria in, 1961
urine collection in, 1960
complicated, 1957–1958, 1964*t*
acute pyelonephritis, 1966–1967
recurrent infections, 1964*t*, 1967–1969
UTI in males, 1967, 1968*f*
definition of, 1957
diagnosis of, 1958*t*
in elderly, 1958
epidemiology of, 1958
etiology of, 1958
in females, 1958
pathophysiology of, 1959
bacterial virulence factors in, 1959
host defenses mechanisms in, 1959
infection route in, 1959
patient care process for, 1966*b*
predisposing factors to, 1959–1960
in pregnancy, 1321–1322, 1964*t*, 1969
prevalence of, 1958
recurrent, 1958
treatment of, 1961–1969
evidence-based, 1964*t*
in females, 1965*f*
for lower tract infections, 1964*t*

management of, 1961–1962
outcomes of, desired, 1960
pharmacologic therapy in, 1962–1965
for acute uncomplicated cystitis, 1962–1965
antimicrobial agents in, 1963*t*
uncomplicated, 1957–1958, 1964*t*
Urologic surgery, antimicrobial prophylaxis in, 2117*t*, 2119
Urothelium, 1432
Ustekinumab, 516*t*, 517, 521–522, 523*t*, 524, 1665–1666
Uterine bleeding with ovulatory dysfunction, 1345–1347
clinical presentation of, 1346*b*
definition of, 1345
epidemiology of, 1345
etiology of, 1345
pathophysiology of, 1337*t*, 1345
in special populations, 1347
treatment of, 1345–1347
general approach to, 1346
nonpharmacologic therapy in, 1346
outcomes of
desired, 1345–1346
therapeutic, evaluation of, 1347
pharmacologic therapy in, 1346–1347
hormonal contraceptives, 1346
Uveal melanoma, 2431

V

Vaccine Adverse Event Reporting System (VAERS), 2131
Vaccines, 2127–2139. *See also* Immunobiologics
administration of, 2128, 2129*t*
components of, 2127–2128
diarrhea, 549
diphtheria toxoid adsorbed, 2131
Haemophilus influenzae type B (Hib), 2131–2132
hepatitis A, 597–598
hepatitis B, 602, 602*t*

human papilloma virus, 1990–1992, 2132
inactivated, 2127
influenza, 149, 1844–1849, 1845*t*, 1846*t*
for different age groups, 1845*t*
live-attenuated, 1846–1847, 1846*t*
quadrivalent, 1845–1846
rates and goal by patient population, 1844*t*
trivalent, 1845–1846
information resources, 2139
live attenuated, 2127
measles, 2132–2133
meningococcal polysaccharide and conjugate, 2133
meningococcal serogroup B (MenB), 2133
monitoring of, 2192*t*
multiple sclerosis, 870
mumps, 2133
pertussis, 2133
pneumococcal, 1792–1793, 2134
conjugate, 2134
polysaccharide, 2134
poliovirus, 2134–2135
rabies, 2135–2136
rubella, 2136
storage of, 2128
systemic lupus erythematosus and, 1467
tetanus, 2136–2137, 2136*t*
therapeutic, 2209
use of, 2131
varicella, 2137
zoster, 2137
Vaginal rings, 52
Vaginal warts, 1991*t*
Vaginosis, bacterial, 1322, 1323*t*
Vagus nerve stimulation
for epilepsy, 887–888
in status epilepticus (SE) treatment, 920

Valacyclovir
for febrile neutropenia, 2093*t*
for genital herpes, 1988
for HSCT infections, 2102
for solid-organ transplant recipients, 2106
Valerian, 1203
Valganciclovir, 2093*t*, 2106
for HSCT infections, 2103
Valproate, 921*t*
for ADHD, 1021
adverse effects of, 893*t*
drug interactions, 893*t*
for epilepsy, 889, 892*t*–893*t*, 896, 897
mechanism of action, 892*t*
for refractory GCSE, 923
Valproate sodium, 1154*t*, 1157
Valproic acid
adverse effects of, 1157
for alopecia, 116.10
for bipolar disorder, 1157
dosing and administration of, 1154*t*, 1157–1159
drug interactions, 1157
for migraine prophylaxis, 996*t*
Valsartan, 208*t*
Vancomycin
for cystic fibrosis, 454*t*
dosing by age group, 1799*t*
for febrile neutropenia, 2090–2091, 2092*t*, 2095*t*
for intra-abdominal infection, 1947
Vandetanib, 2188*t*, 2203
Vapreotide, 549
Vardenafil, 1390*t*, 1398*t*
Varenicline, 1081*t*, 1083–1083
Variceal bleeding
endoscopic variceal ligation for, 566
prophylaxis

primary, 566–567
secondary, 569–570
treatment recommendations, 570*t*
Variceal hemorrhage, 567–570
drug therapy for, 569–570
endoscopic variceal ligation for, 566
prophylaxis, secondary, 569–570
recommendations, 569
treatment of, 567–570, 567*f*
clinical controversies in, 569
interventional and surgical, 569
octreotide, 567–568
sclerotherapy and bind ligation, endoscopic, 568–569
somatostatin, 567
Varicella vaccine, 2137
Varicella zoster virus, 2159*t*, 2160*t*
Vascular access thrombosis, 684–685, 685*t*
Vascular cell adhesion molecule 1 (VCAM-1), 865
Vascular surgery, antimicrobial prophylaxis in, 2118*t*, 2121
Vasculitis, 1522
Vasoactive inhibitory peptide, 2515*t*
Vasoactive intestinal peptide (VIP), 580
Vasoconstrictors, 1760
Vasodilators. *See also specific agents*
for acute decompensated heart failure, 231, 231*t*
for priapism, 1760
Vasooclusive episodes, 1754*b*
Vasopressin, 718
for autism spectrum disorder, 1224*t*, 1225
for cardiac arrest, 325, 331, 332*t*
for cirrhosis, 567
for sepsis and septic shock treatment, 2018*t*
for shock, 350–351, 364
Vasopressin antagonists, 230–232, 765–766
Vasopressors. *See also specific types*
comparative studies of, 361–362

for sepsis and septic shock treatment, 2014*t*, 2018–2019, 2018*t*
for shock, 358–364, 359*t*
Vedolizumab, 516*t*, 517, 519, 521, 523*t*, 524
VEGF inhibitors, 1614–1616, 1615*t*, 2206–2207
bevacizumab, 1615, 1615*t*, 2206–2207
ramucirumab, 2207
ranibizumab, 1615, 1615*t*
Velpatasvir, 609, 610
Vemurafenib, 2185*t*, 2442, 2442*t*, 2443, 2444*t*
Venetoclax, 2184*t*, 2199, 2402–2403, 2402*t*, 2403*t*
Venlafaxine, 971, 996*t*, 1038, 1376*t*. *See also* Serotonin-norepinephrine reuptake inhibitors (SNRIs)
adverse effects of, 1182
dosing and administration of, 1183
drug interactions, 1140*t*
efficacy of, 1182
for generalized anxiety disorders, 1171*t*
for major depressive disorder, 1132, 1133*t*
for menstruation-related disorders, 1343*t*
for narcolepsy, 1209*t*
for obsessive-compulsive disorder, 1196
for pain management, 970*t*
for panic disorder (attack), 1178*t*
pharmacokinetics of, 1138, 1138*t*
for posttraumatic stress disorder, 1191*t*, 1193, 1193*t*
relative potencies, 1135*t*
for social anxiety disorder, 1182–1183, 1182*t*
for urinary incontinence, 1446
Venous thromboembolism (VTE), 241–247, 2020
clinical presentation of, 245–247, 247*b*
definition of, 241
diagnosis of, 245–247, 246*f*
D-dimer in, 245–246
radiographic contrast in, 246
epidemiology of, 241
etiology of, 241–243, 242*f*

blood stasis in, 241
hypercoagulability in, 241–243
vascular injury in, 241
hypercoaulability disorders in, inherited and acquired, 245
in menopausal hormone therapy, 1370
pathophysiology of, 243–245, 243*f*, 244*f*
patient care process for, 248*b*, 260*b*
prevention of, 247–249
duration of therapy in, 251
general approach to, 248–249
guidelines for, 250*t*
nonpharmacologic therapy in, 249
pharmacologic therapy in
in medical patients, 249
in surgical patients, 249–251
prophylaxis of, 2014*t*
risk factors for, 242*t*
sickle cell disease and, 1752
Venous thromboembolism (VTE) treatment, 249–261
acute, decision algorithm for, 251*f*
in cancer patients, 261
in children, 259–261
drug class information, 261–269, 262*t*
direct oral anticoagulants, 261–263, 262*t*, 263*t*
fondaparinux, 264–265
low-molecular-weight heparin, 263–264
unfractionated heparin, 265–266
warfarin, 266–267
general approach to, 251–256, 251*f*, 252*f*
guidelines for, 253*t*
in invasive procedures, 261
outcomes of, desired, 248
outpatient, 254*t*, 255*t*
patient education for, 255*t*
personalized pharmacotherapy in, 267–268
drug interactions, 268

pharmacogenomics in, 268
prevention *vs.* treatment, 267–268
renal function in, 268
response to previous therapy in, 268
weight in, 268
pharmacologic (*See also specific agents*)
alternative treatment, 257–258
direct oral anticoagulants, 256
fondaparinux, 257
low-molecular-weight heparin, 256, 256*t*
unfractionated heparin, 257, 257*t*
warfarin, 257, 258*f*
in pregnancy, 259, 259*t*
prevention of, desired outcome in, 248
in renal insufficiency, 261
special populations
cancer patients, 261
in invasive procedures, 261
pediatric patients, 259–261
pregnancy, 259, 259*t*
in renal insufficiency, 261
therapeutic outcomes of, evaluation of, 268–269
thrombolysis, 259*t*
treatment of, outpatient, 254*t*, 255*t*
Ventilator-associated pneumonia, 1813*t*, 1814, 1816–1818
Ventricular arrhythmias, 310–317. *See also specific types*
clinical presentation of, 311*b*
general approach to treatment, 310–311
monomorphic, 315
premature ventricular complexes, 310
torsades de pointes, 315–317, 316*f*, 317*t*
Ventricular assist devices (VAD), 235*f*, 236
Ventricular fibrillation, 317, 330–333
antiarrhythmics for, 331–333
definition of, 317
management, 317

nonpharmacologic therapy in, 330
pharmacologic therapy in, 330–333
prevention of, 317
sympathomimetics, 330–331
vasopressin, 331, 332*t*
Ventricular hypertrophy, 195–196
Ventricular proarrhythmia, 315–317
Ventricular remodeling, 195–196, 196*f*
Ventricular tachycardia, 311–317. *See also specific types*
general approach to treatment, 312
management, 312–317
implantable cardioverter-defibrillator in, 313–315
sudden cardiac death, prevention of, 313–315
implantable cardioverter-defibrillator in, 313*f*
sudden cardiac death, prevention of, 314*f*
Ventriculitis, health-care associated, 1794–1795
Verapamil, 292*t*, 293, 295*t*, 1001, 1003, 1159*t*. *See also* Calcium channel blockers
Vertebroplasty, 1550
Vertigo, 539
Very low-density lipoproteins (VLDL), 117
Very-low density lipoproteins (VLDL), 117, 119
Vibrio cholerae, 1925*t*, 1926, 1930*t*, 1935*t*
Vibrio parahaemolyticus, 1935*t*
Vigabatrin
adverse effects of, 897*t*
drug interactions, 897*t*
for epilepsy, 896*t*–897*t*
mechanism of action, 896*t*
Vilazodone, 1133*t*, 1135–1136, 1135*t*, 1138*t*, 1140*t*, 1144*t*, 1171*t*
Vinblastine, 2181*t*, 2194, 2324–2327, 2325*t*, 2334
Vinca alkaloids, 2194
Vincristine, 2181*t*, 2194, 2324–2328, 2325*t*, 2336*t*
Vinorelbine, 2181*t*, 2194
Viral encephalitis, 1796–1797
Viral hepatitis, 595–602

hepatitis A, 595–597
clinical presentation of, 596–597, 596*t*
epidemiology of, 595–596
etiology of, 596
pathophysiology of, 596
prevention of, 597
treatment of, 597–599
general approach to, 597
immunoglobulin, 599
outcomes of, desired, 597
vaccines for, 597–598, 597*t*
hepatitis B, 599–605
chronic, 600
cirrhosis and, 601, 601*t*
clinical presentation of, 600–602
epidemiology of, 599
etiology of, 599
hepatocellular carcinoma in, 602
pathophysiology of, 599–600
phases of, 601*t*
risk factors for, 600*t*
symptoms of, 596*t*
treatment of, 602–605
general approach to, 602–603
nonpharmacologic therapy in, 603
outcomes of, desired, 602
patient counseling in, 603
pharmacologic therapy in, 603–604
in special populations, 604–605
vaccine prevention of, 602, 602*t*
hepatitis C, 605–611
clinical presentation of, 606–607
epidemiology of, 605–606
etiology of, 606
pathophysiology of, 606
prevention of, 611

screening for, 606*t*
symptoms of, 596*t*
treatment of, 607–610
counseling in, 607
general approach to, 607
nonpharmacologic therapy in, 607
outcomes of, desired, 607
pharmacologic therapy in, 607–610, 608*t*
in special populations, 610–611
Viral pneumonia. *See specific types*
Virilism, adrenal, 1307
Visceral adipose tissue, 1234
Visceral proteins, 2474–2475, 2475*t*
Vismodegib, 2186*t*
Visual field, 1591, 1592*f*, 1592*t*
Vitamin A acid, 1638
Vitamin A toxicity, 2480*t*
Vitamin B, 846
Vitamin B12, 1715
Vitamin B12 deficiency anemia, 1719–1720
etiology of, 1719
laboratory evaluation of, 1720
pathophysiology of, 1719–1720
treatment of, 1720
Vitamin C, 684
Vitamin D, 669*t*
administration of, 1555
adverse effects of, 670
for CKD-MBD, 668–670
colorectal cancer and, 2276
deficiency in, 785–786
dosing and administration of, 670, 1551*t*
drug interactions, 1555
drug-drug interactions, 670
drug-food interactions, 670
efficacy of, 669–670, 1555

metabolism of, 653*f*
monitoring of, 1553*t*
osteoporosis and, 1544, 1548–1549, 1549*t*
pharmacokinetics of, 669
pharmacology and mechanism of action, 668–669
supplementation, 1554–1555
for systemic lupus erythematosus, 1465
Vitamin D3 analogs, 1660
Vitamin E, 684, 845, 2480*t*
Vitamin K, 267*t*
Vitamins. *See also specific types*
cystic fibrosis and, 452
deficiencies and toxicities of, 2479, 2480*t*
fat soluble, 2480*t*
in parenteral nutrition, 2496–2497
parenteral nutrition complications, 2507
water soluble, 2480*t*
Vomiting. *See also* Nausea and vomiting
definition of, 529
etiology of, 529, 530*t*
oral contraceptives and, 51
pathophysiology of, 529–530
Vomiting center, 529–530
von Hippel-Lindau gene, e2427
von Willebrand disease, 1739–1743, 1739*t*
classification of, 1739–1740, 1740*f*
clinical presentation of, 1740–1741, 1740*b*
diagnosis of, 1740–1741, 1740*f*, 1741*t*
treatment of, 1741–1743, 1742*f*
desmopressin, 1741
gene therapy in, 1743
outcomes, evaluation of, 1743
pharmacologic therapy in, 1742–1743
replacement therapy in, 1741–1742, 1742*t*
rituximab, 1743
von Willebrand factor antigen (vWF:Ag), 1739*t*, 1740

von Willebrand factor (vWF), 564, 1739, 1739*t*
Voriconazole
  for aspergillosis, 2069
  dosing by age group, 1799*t*
  for febrile neutropenia, 2093*t*, 2095*t*
  for fungal infections, 2049*t*
  for invasive fungal infections, 2072
  monitoring of, 2073*t*
  for oropharyngeal candidiasis, 2033*t*
  for peritonitis, 692*t*
Vorinostat, 2186*t*, 2201
Vortioxetine, 1133*t*, 1135–1136, 1135*t*, 1138*t*, 1140*t*, 1144*t*, 1171*t*
Voxilaprevir, 610
Vulvovaginal candidiasis, 2025–2028
  antifungal-resistant, 2028
  classification of, 2025
  clinical presentation of, 2026, 2026*t*
  complicated, 2027
  definition of, 2025
  epidemiology of, 2025–2026
  pathophysiology of, 2026
  patient care process for, 2028*b*
  recurrent, 2027–2028
  risk factors for, 2026
  treatment of, 2026–2028
    general approaches to, 2026–2027
    goals of, 2026
    pharmacologic, 2027–2028
  uncomplicated, 2027
Vulvovaginitis, 1977*t*

W

Waist circumference, 2535
Warfarin
  adverse effects of, 266
  for atrial fibrillation and atrial flutter, 294–295

dosing and administration of, 266–267
efficacy of, 266
interactions, 266
mechanism of action, 266
for vascular access thrombosis, 684
for venous thromboembolism, 257, 258*f*, 266–267
Water homeostasis, 755–758
Water homeostasis disorders, 755–775. *See also specific disorders*
edema, 772–775
hypernatremia, 767–772
hyponatremia, 758–767
patient care process for, 756*b*
Wernicke-Korsakoff syndrome, 1074
Wernicke's encephalopathy, 917
White coat hypertension, 89
Willis-Ekborn syndrome, 1210
Women's Health Initiative, 1368, 1368*t*

X

Xanthine oxidase inhibitors, 1575*t*, 1581
Xerostomia, e35

Y

Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), 1195
Yeasts, 2083
Candida infections, 2061
isovuconazole for, 2072
morphology, 2046, 2046*f*
susceptibility testing, 2046
unicellular, 2046, 2046*f*
Yersinia enterocolitica, 1926, 1935*t*
Yersinia pseudotuberculosis, 1926
Yersinia spp., 1926, 1930*t*
Yersinia spp., 1925*t*
Yoga, 965*t*
Yohimbine, 1406

Z

Zafirlukast, 398
Zaleplon, 1057, 1205, 1205*t*
Zidovudine, 1916*t*, 2151, 2151*t*, 2152*t*
Zileuton, 398
Zinc, 573, 1616, 1931, 2476, 2477*t*
Ziprasidone. *See also* Antipsychotics
  for ADHD, 1021
  adverse effects of, 1020*t*, 1107*t*
  for bipolar disorder, 1161
  dosing, 1020*t*
  dosing and administration of, 1154*t*
  drug interactions, 1117*t*
  mechanism of action, 1105*t*
  pharmacokinetics of, 1106*t*
  for schizophrenia, 1096*t*
Ziv-aflibercept, 2192*t*, 2208
Zoledronic acid, 1551*t*, 2421
Zollinger-Ellison syndrome, 502–503
  clinical presentation of, 502–503
  diagnosis of, 502–503
  incidence of, 502
  pathophysiology of, 502
  treatment of, 503
Zolmitriptan, 995*f*, 996*t*, 998*t*
Zolpidem, 1057, 1205, 1205*t*
Zonisamide
  adverse effects of, 895*t*
  drug interactions, 895*t*
  for eating disorders, 1037
  for epilepsy, 894*t*–895*t*
  mechanism of action, 894*t*
Zoster, vaccines, 2137
Zygomycetes, 2048*t*